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Short communication

3-Chloro-2-methylphenyl-substituted semicarbazones: synthesis and anticonvulsant activity

Perumal Yogeeswari [a,*], Rathinasabapathy Thirumurugan [a], Ramkumar Kavya [a], Jayakar Selwyn Samuel [a], James Stables [b], Dharmarajan Sriram [a]

[a] *Medicinal Chemistry Research Laboratory, Pharmacy group, Birla Institute of Technology and Science, Pilani 333031, India*
[b] *Preclinical Pharmacology Section, Epilepsy Branch, National Institute of Health, Bethesda, USA*

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Abstract

A series of 3-chloro-2-methylphenyl substituted semicarbazones (**3–33**) was synthesized and evaluated for anticonvulsant and CNS activities. After intraperitoneal injection to mice or rats, the semicarbazone derivatives were examined in the maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), and subcutaneous strychnine (scSTY)-induced seizure and neurotoxicity screens. The aryl urea (**1**) and the semicarbazide (**2**) showed anticonvulsant activity in the MES and scPTZ screens with acute neurotoxicity, whereas the semicarbazone derivatives showed good anticonvulsant potency in the scSTY screen with moderate activity against MES and scPTZ screens. Compound **21** exhibited anticonvulsant potency against all the three screens with lesser neurotoxicity. Some titled compounds exhibited lesser CNS depression and neurotoxicity compared to phenytoin or carbamazepine as was evident from the CNS studies.

Keywords: Aryl semicarbazones; 3-Chloro-2-methyl substituted phenyl semicarbazones; Anticonvulsants; CNS depressants

1. Introduction

Epilepsy, one of the most frequent neurological disorders, is a major public health issue, affecting about 4% of individuals over their lifetime [1]. About 20–30% of the patients have seizures that are resistant to the available medical therapies. This fact warrants the search for new anticonvulsant drugs.

In recent years, aryl and heteroaryl semicarbazones and thiosemicarbazones [2–12] have emerged as structurally novel anticonvulsants. Aryl semicarbazides have also been reported to display excellent anticonvulsant activity in mice and rats [13]. In terms of interaction at the binding site, as proposed previously by Dimmock et al. [14,15], the pharmacophoric elements were thought to be a lipophilic aryl ring and hydrogen bonding semicarbazone moiety. The attachment of a second aryl ring designated as the distal ring to the proximal aryl ring to increase the van der Waal's bonding at the binding site and to increase potency have also been reported. Substitutions in the aryl ring by halogens have been found to increase potency in the MES screen [7–10,16] and our recent results with 3-bromo substituted phenyl semicarbazones [17] have given an impetus to the present investigation. In continuation to our work on aryl semicarbazones, the present work focuses on synthesis and anticonvulsant evaluation of 3-chloro-2-methylphenyl substituted semicarbazones, since substitution in the 2-position of the phenyl ring with electron-donating groups was generally beneficial to activity as reported elsewhere [18] and the importance of the ortho-methyl group for anticonvulsant activity had been depicted in many studies [19–23] including the recently marketed drug tiagabine.

2. Chemistry

The synthesis of 3-chloro-2-methyl phenyl semicarbazones was accomplished as presented in Scheme 1. 3-Chloro-2-methyl aniline was treated with sodium cyanate in the presence of glacial acetic acid according to the known urea preparation method, to yield 3-chloro-2-methyl phenyl urea (**1**). The urea derivative (**1**) on condensation with hydrazine hydrate in ethanol in presence of sodium hydroxide gave the semicarbazide (**2**). The semicarbazone derivatives (**3–33**) were prepared by reaction of the appropriate aryl/alkyl alde-

* Corresponding author. Tel.: +91-1596-244684; fax: +91-1596-244183.
E-mail address: pyogee@bits-pilani.ac.in (P. Yogeeswari).

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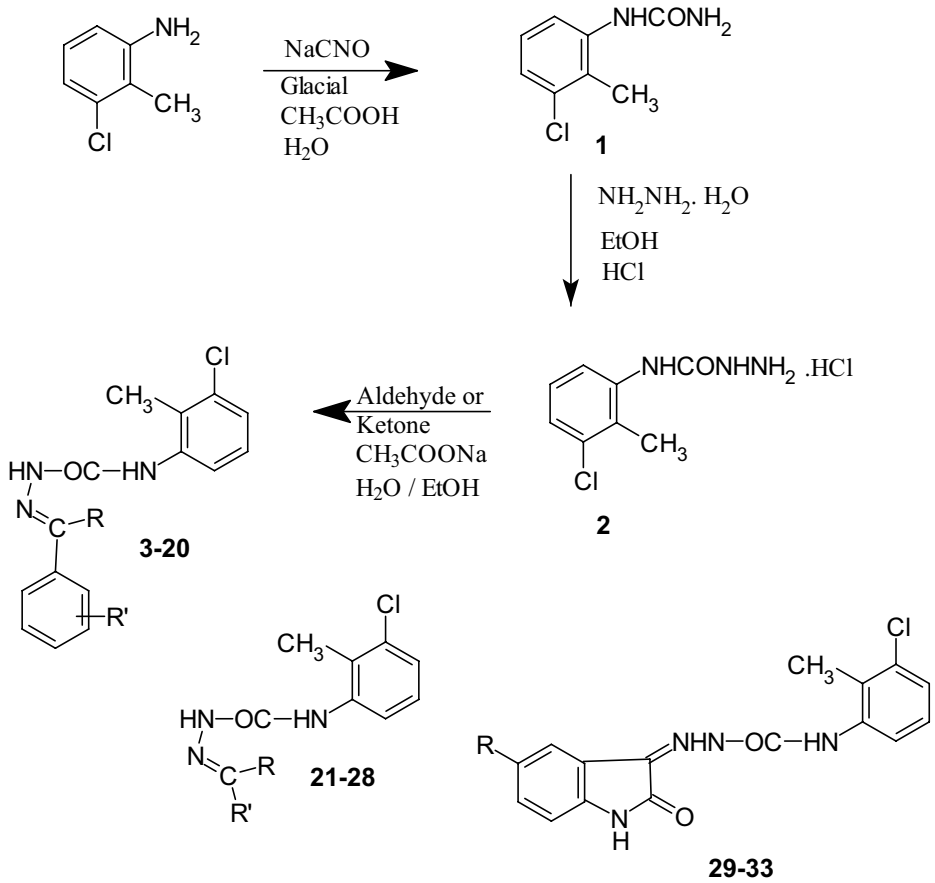

	R	R’
3	H	H
4	H	2-Cl
5	H	2-OH
6	H	2-NO_2
7	H	3-NO_2
8	H	4-NO_2
9	H	4-OH
10	H	4-CH_3
11	H	4-OCH_3
12	H	4-$N(CH_3)_2$
13	H	3-OCH_3, 4-OH
14	CH_3	H
15	CH_3	2-OH
16	CH_3	3-NH_2
17	CH_3	4-Cl
18	CH_3	4-OH
19	CH_3	4-NO_2
20	CH_3	4-NH_2

	R	R’
21	CH_3	CH_3
22	CH_3	CH_2COCH_3
23	Ph-CH_2-	Ph-CH_2-
24	CH_3	C_2H_5
25	CH_3	i-Butyl
26	H	2-furanyl
27	CRR’ = Cyclopentylene	
28	CRR’ = Cyclohexylene	

	R
29	H
30	Br
31	Cl
32	F
33	CH_3

Scheme 1. Synthetic protocol of the title compounds.

hyde or ketone or isatin derivatives with (**2**). Thin layer chromatography (TLC) was run throughout the reactions to optimize the reactions for purity and completion. The physical and chemical data for the newly synthesized compounds are presented in Table 1.

3. Pharmacology

The new derivatives (**1–33**) obtained from the reactional sequence were injected intraperitoneally into mice and evaluated in the maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine threshold test (scSTY) and neurotoxicity screens, using doses of 30, 100 and 300 mg/kg at two different time intervals. These data are presented in Table 2. Very few compounds were evaluated orally in rats for activity in MES test at several time points (Table 3). Some selected compounds were studied for their CNS behavioral activity in mice using actophotometer and Porsolt’s swim pool test in rats and the results are presented in Tables 4 and 5.

Table 1
Physical data of the aryl semicarbazones

Compound	Yield (%)	m.p. (°C)	Molecular formula[a]	R_f [$CHCl_3$:CH_3OH (9:1)]	Log P[b]
1	61	201	$C_8H_9N_2OCl$	0.58	0.87
2	80	163	$C_8H_{10}N_3OCl$	0.53	0.96
3	75	193	$C_{15}H_{14}N_3OCl$	0.91	2.53
4	80	209	$C_{15}H_{13}N_3OCl_2$	0.90	2.90
5	86	224	$C_{15}H_{14}N_3O_2Cl$	0.74	2.19
6	84	211	$C_{15}H_{13}N_4O_3Cl$	0.81	2.83
7	71	214	$C_{15}H_{13}N_4O_3Cl$	0.82	2.81
8	86	257	$C_{15}H_{13}N_4O_3Cl$	0.85	2.78
9	53	239	$C_{15}H_{14}N_3O_2Cl$	0.81	1.88
10	83	199	$C_{16}H_{16}N_3OCl$	0.88	2.71
11	83	187	$C_{16}H_{16}N_3O_2Cl$	0.92	1.98
12	79	216	$C_{17}H_{19}N_4OCl$	0.87	2.17
13	62	232	$C_{16}H_{16}N_3O_3Cl$	0.75	1.39
14	63	220	$C_{16}H_{16}N_3OCl$	0.92	2.54
15	37	215	$C_{16}H_{16}N_3O_2Cl$	0.77	2.15
16	61	184	$C_{16}H_{17}N_4OCl$	0.64	1.87
17	66	227	$C_{16}H_{15}N_3OCl_2$	0.90	2.63
18	54	191[c]	$C_{16}H_{16}N_3O_2Cl$	0.85	1.84
19	52	265	$C_{16}H_{15}N_4O_3Cl$	0.93	2.72
20	34	189	$C_{16}H_{17}N_4OCl$	0.83	2.03
21	57	166	$C_{11}H_{14}N_3OCl$	0.88	2.03
22	46	251	$C_{13}H_{16}N_3O_2Cl$	0.74	2.14
23	78	160	$C_{23}H_{22}N_3OCl$	0.90	2.57
24	74	175	$C_{12}H_{16}N_3OCl$	0.95	2.34
25	53	144	$C_{14}H_{20}N_3OCl$	0.87	2.70
26	51	186	$C_{13}H_{12}N_3O_2Cl$	0.89	2.42
27	75	191	$C_{13}H_{16}N_3OCl$	0.72	2.30
28	82	182	$C_{14}H_{18}N_3OCl$	0.77	2.40
29	77	266	$C_{16}H_{13}N_4O_2Cl$	0.78	1.28
30	41	231[c]	$C_{16}H_{12}N_4O_2ClBr$	0.80	1.68
31	42	255	$C_{16}H_{12}N_4O_2Cl$	0.88	1.65
32	56	271[c]	$C_{16}H_{12}N_4O_2ClF$	0.69	1.75
33	71	267[c]	$C_{17}H_{15}N_4O_2Cl$	0.79	1.35

[a] Elemental analyses for C, H, N were within ±0.4% of the theoretical values.
[b] Log P was generated using Alchemy 2000 and SciLog P softwares.
[c] Melting point of the compounds at their decomposition.

4. Results and discussions

Candidate anticonvulsants are often evaluated initially in the MES and scPTZ screens [24]. The intermediate compounds of the reactional sequence like urea (**1**) and semicarbazide (**2**) derivatives were also included in the anticonvulsant study. The compounds **1** and **2** showed anti-MES potency better than the semicarbazone derivatives (**3–33**), but for a shorter duration (0.5 h). The compounds except **1, 2, 6, 10** and **21** did not show protection in the scPTZ screen. In the MES screen, the compounds that showed mild protection at 100 mg/kg include **2, 4, 16, 21** and **32**, and in the scPTZ screen, **5, 6** and **31** (Table 2). Some selected compounds were also subjected to scSTY threshold test in mice, in which all the tested compounds showed protection in both time periods of 0.5 and 4 h. The anti-scSTY activity profile of compounds **4, 5, 6, 8, 16** and **21** were better than the standard drug ethosuximide. In the acute neurological toxicity screen, the compounds except **3, 5, 10, 16, 24, 25, 28** and **32** showed neurotoxicity. When compared with phenytoin, compounds **6, 21** and **31** showed lesser neurotoxicity. All the other compounds did not exhibit anticonvulsant activity and neurotoxicity. The acetone semicarbazone derivative (**21**) exhibited anticonvulsant activity in all the three screens and emerged as the most active compound in this series.

Some selected compounds were further tested in oral MES screen using rats at 30 mg/kg (Table 4) in which none of the compounds showed good protection when compared with phenytoin. Compound **2** exhibited anti-MES protection throughout the time period.

In the behavioral study using actophotometer, the compound **4** showed no behavioral despair effect when compared to phenytoin as represented in Table 4. Compounds **5** and **6** did show decreased locomotor activity in the 30 min interval but did not show any significant behavior despair effect in 1 h time period. All other compounds were found to decrease behavioral activity of the animal. In a similar study using swim pool test, the immobility time after administration of the test compounds were compared with carbamazepine (Table 5). The compounds **8** and **16** were found to show no

Table 2
Anticonvulsant activity and minimal motor impairment of aryl semicarbazones

Compound	Intraperitoneal injection in mice[a]							
	MES screen		scPTZ screen		scSTY screen[b]		Neuro-toxicity screen	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
1	100	–	300	–	x	x	100	–
2	100	–[c]	300	–	x	x	300	100
3	–	300	–	–	x	x	–	–
4	–	300[c]	–	–	100	300	300[f]	300
5	–	–	–[d]	–[d]	100	300	–	–
6	–	–	300	–[d]	100	100	300	300
8	–	300[c]	–	–	100	100	100	300
10	–	–	300	–	300[e]	–	–	–
16	–	300[c]	–	–	100	300	–	–
21	300[c]	300	300	–	100	100	300	300
24	–	300	–	–	300[e]	300	–	–
25	–	300	–	–	–[e]	–	–	–
27	–	300	–	–	x	x	–	–[f]
28	–	300	–	–	x	x	–	–
31	–	–	–[d]	–	x	x	300	–
32	–	–[c]	–	–	x	x	–	–
Phenytoin[g]	30	30	–	–	–	–	100	100
Ethosuxi-mide[g]	–	–	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. The animals were examined 0.5 and 4 h after injections were made. The dash (–) indicates an absence of activity at max dose administered (300 mg/kg) and (x) indicates not tested.

[b] In the scSTY screen compounds **11** and **29** showed protection at 300 mg/kg for 0.5 h.

[c] In the MES screen, at 30 mg/kg compound **8** (1/4, 4 h) and at 100 mg/kg compounds **2** (1/3, 4 h), **4** (1/3, 4 h), **16** (1/3, 4 h), **21** (2/3, 1 h) and **32** (1/7, 4 h).

[d] In the scPTZ screen, at 100 mg/kg, compounds **5** (1/5, 4 h), **6** (1/5, 4 h) and **31** (1/5, 0.5 h), and at 300 mg/kg compound **5** (1/5, 0.5 and 4 h).

[e] In the scSTY screen, mild clonic jerks were observed with compounds **10** and **24** (300 mg/kg, 1/3). Compound **25** caused loss of righting reflex and death (2/2, 300 mg/kg).

[f] In the neurotoxicity screen, at 100 mg/kg, compounds **4** (2/3, 2 h) and **27** (2/3, 2 h).

[g] Data from Refs. [7,17].

Table 3
Evaluation of some compounds in the MES test after oral administration (30 mg/kg) to rats

Compound	Oral administration to rats[a]				
	0.25 h	0.5 h	1 h	2 h	4 h
1	1	0	0	0	0
2	2	1	1	1	1
6	1	0	1	0	0
16	0	0	0	0	0
21	0	1	0	1	0
Phenytoin	1	4	3	3	3

[a] The figures indicate the number of rats out of four which were protected.

Table 4
Behavioral study on some selected compounds using actophotometer

Compound[a]	Activity score[b]		
	Control (24 h prior)	Post-treatment	
		0.5 h after	1 h after
4	320 ± 27.73	531 ± 17.22	343 ± 21.11 NS
5	519 ± 13.38	421 ± 26.78 *	359 ± 29.87 *
6	180 ± 30.22	61 ± 9.69 *	164 ± 11.02 NS
8	154 ± 10.90	113 ± 10.30 **	159 ± 6.77 NS
10	408 ± 32.96	48 ± 9.66	33 ± 2.11
16	303 ± 22.66	41 ± 2.21	27 ± 1.02
21	373 ± 32.75	20 ± 6.12	12 ± 2.35
24	247 ± 15.66	11 ± 7.25	12 ± 7.35
Phenytoin[c]	267 ± 31.12	44 ± 4.56	46 ± 2.44

[a] The compounds were tested at a dose of 30 mg/kg (i.p.).

[b] Each score represents the mean ± SEM of six mice, significantly different from the control score at $P < 0.0001$, * $P < 0.008$, ** $P < 0.02$ and NS at $P < 0.02$ denotes not significant (Student's *t*-test).

[c] Tested at 5 mg/kg p.o.

Table 5
CNS study on selected compounds in forced swim pool test

Compound[a]	Immobility time[b] (s)	
	Control (24 h prior)	Post-treatment (60 min after)
PEG	164.67 ± 11.69	168.53 ± 12.32 NS
3	125.67 ± 11.89	190.30 ± 12.45
4	57 ± 12.16	130.3 ± 11.25
6	134 ± 12.70	205.00 ± 11.63
8	78.65 ± 12.62	104.00 ± 12.94 NS
10	200 ± 11.63	137.30 ± 12.49
16	115.67 ± 12.05	150.60 ± 12.06 NS
24	104.33 ± 13.29	187.3 ± 13.09
Carbamazepine[a]	138.4 ± 17.3	240.60 ± 14.10

[a] The compounds were tested at a dose of 30 mg/kg (i.p.).

[b] Each value represents the mean ± SEM of six rats significantly different from the control at $P < 0.004$ and NS denotes not significant at $P < 0.004$ (Student's *t*-test).

significant CNS depression compared with the control at $P < 0.004$. All other compounds tested were found to emerge as CNS depressants as they increased the immobility time.

The conclusions drawn from the study are as follows. Generally these aryl semicarbazones exhibited good protection against scSTY-induced seizures and hence could act through inhibitory glycine receptors [25]. The present study showed the increase in immobility time by the anticonvulsant compounds and hence indicating facilitation of depression. These compounds facilitated depression in the doses of 30 mg/kg i.p. These doses are lower than the anticonvulsant dose, which suggest that the mechanism involved in the anticonvulsant action and in the facilitation of depression could be different. However, to confirm this fact, further studies are required to be carried out.

5. Experimental protocols

5.1. Chemistry

Melting points were determined in one end open capillary tubes on a Büchi 530 melting point apparatus and are uncor-

rected. Infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded for the compounds on Jasco IR Report 100 (KBr) and Brucker Avance (300 MHz) instruments, respectively. Chemical shifts are reported in parts per million (ppm) using tetramethyl silane (TMS) as an internal standard. All exchangeable protons were confirmed by addition of D_2O. Elemental analyses (C, H, and N) were undertaken with Perkin-Elmer model 240C analyzer. The homogeneity of the compounds was monitored by ascending thin layer chromatography (TLC) on silicagel-G (Merck) coated aluminium plates, visualized by iodine vapor. Developing solvents were chloroform–methanol (9:1). The log *P* values were determined using Alchemy-2000 and Scilog P softwares (Tripos Co.).

*5.1.1. Synthesis of 3-chloro-2-methyl phenyl urea (**1**)*

3-Chloro-2-methyl aniline (0.1 mol, 14.1 g, 11.8 ml) was dissolved in 20 ml of glacial acetic acid and 10 ml of water. To this, 0.1 mol of sodium cyanate (6.5 g) in 80 ml of warm water was added with stirring. Allowed to stand for 30 min, then cooled in ice and filtered with suction, and dried. Recrystallized from boiling water to yield **1** with m.p. 201 °C, IR (KBr) ν_{max} 3450, 1650, 840 cm^{-1}, ^{1}H-NMR (DMSO-d_6) δ 2.4 (s, 3H, CH_3), 7.2–7.4 (m, 3H, ArH) 8.28 (s, 1H, ArNH, D_2O exchangeable), 9.33 (s, 2H, $CONH_2$, D_2O exchangeable).

*5.1.2. Synthesis of 3-chloro-2-methyl phenyl semicarbazide (**2**) hydrochloride*

Equimolar quantities (0.05 mol) of **1** (9.2 g) and hydrazine hydrate (2.5 ml) in ethanol were refluxed for 24 h with stirring. The two-third volume of alcohol was distilled by vacuum distillation unit and then poured into ice. The resultant precipitate was filtered, washed with water and dried. The solid was recrystallized from 50 ml of 90% alcohol to which 25 ml of concentrated hydrochloric acid was added. The precipitate of **2**, hydrochloride, was filtered by vacuum and dried. IR (KBr) ν_{max} 3450, 3269, 1640, 840 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.33 (s, 3H, CH_3), 5.56 (s, 2H, NH_2, D_2O exchangeable), 7.2–7.45 (m, 3H, ArH), 8.34 (s, 1H, ArNH, D_2O exchangeable), 9.6 (bs, 1H, $NHNH_2$, D_2O exchangeable).

*5.1.3. General method for the synthesis of 3-chloro-2-methyl phenyl semicarbazones (**3–33**)*

The title compounds were synthesized following procedures reported earlier [7]. To a solution of **2** (0.005 mol, 1.175 g) in 25 ml of water was added sodium acetate (0.005 mol, 0.41 g) in 2 ml water. About 25 ml of ethanol was added to clear turbidity. This solution mixture was added to an equimolar quantity of the appropriate aldehyde or ketone in alcohol. Stirring was done if needed. Immediate precipitation occurred and the solids were filtered, dried and recrystallized from hot ethanol. The physical data of the semicarbazones are given in Table 1. The IR spectra of the semicarbazone derivatives were identical in the following aspects; 3450, 3300–3250, 1650, 1595, 840 cm^{-1}. ^{1}H-NMR (300 MHz, δ) spectra of some representative compounds are as follows:

5 (DMSO-d_6): 2.28 (s, 3H, $ArCH_3$), 6.81–7.8 (m, 7H, ArH), 8.25 (s, 1H, imine H), 8.67 (s, 1H, ArNH, D_2O exchangeable), 10.71 (s, 1H, CONH, D_2O exchangeable), 10.06 (s, 1H, ArOH, D_2O exchangeable); **8** (DMSO-d_6): 2.35 (s, 3H, $ArCH_3$), 7.20–8.31 (m, 7H, ArH), 8.10 (s, 1H, imine H), 9.01 (s, 1H, ArNH, D_2O exchangeable), 11.19 (s, 1H, CONH, D_2O exchangeable); **15** (DMSO-d_6): 2.18 (s, 3H, CH_3), 2.30 (s, 3H, $ArCH_3$), 6.74–7.78 (m, 7H, ArH), 8.62 (s, 1H, ArNH, D_2O exchangeable), 10.01 (s, 1H, ArOH, D_2O exchangeable), 10.64 (s, 1H, CONH, D_2O exchangeable); **19** (DMSO-d_6): 2.24 (s, 3H, CH_3), 2.37 (s, 3H, $ArCH_3$), 7.24–8.41 (m, 7H, ArH), 8.98 (s, 1H, ArNH, D_2O exchangeable), 11.05 (s, 1H, CONH, D_2O exchangeable); **21** (DMSO-d_6): 2.21 (s, 6H, CH_3), 2.34 (s, 3H, $ArCH_3$), 7.12–7.30 (m, 3H, ArH), 8.58 (s, 1H, ArNH, D_2O exchangeable), 10.54 (s, 1H, CONH, D_2O exchangeable); **24** (DMSO-d_6): 1.32–1.36 (t, 3H, CH_3, J = 7.6 Hz), 1.82–1.88 (q, 2H, CH_2, J = 7.6 Hz), 2.20 (s, 3H, CH_3), 2.32 (s, 3H, $ArCH_3$), 7.08–7.24 (m, 3H, ArH), 8.62 (s, 1H, ArNH, D_2O exchangeable), 10.61(s, 1H, CONH, D_2O exchangeable); **30** (DMSO-d_6): 2.30 (s, 3H, $ArCH_3$), 6.94–8.28 (m, 6H, ArH), 9.32 (s, 1H, ArNH, D_2O exchangeable), 10.88 (s, 1H, NH isatinyl, D_2O exchangeable), 10.92 (s, 1H, CONH, D_2O exchangeable); **31** (DMSO-d_6): 2.31 (s, 3H, $ArCH_3$), 6.88–8.14 (m, 6H, ArH), 8.74 (s, 1H, ArNH, D_2O exchangeable), 10.82 (s, 1H, NH isatinyl, D_2O exchangeable), 10.90 (s, 1H, CONH, D_2O exchangeable).

5.2. Pharmacology

The anticonvulsant evaluations were undertaken using reported procedures [26–28]. Male albino mice (CF-1 strain or Swiss, 18–25 g) and rats (Sprague–Dawley or Wistar, 100–150 g) were used as experimental animals. The tested compounds were suspended in 0.5% methyl cellulose/water mixture or in polyethylene glycol (PEG).

5.2.1. Anticonvulsant screening

Initially all the compounds were administered i.p. in a volume of 0.01 ml/g body weight for mice and 0.004 ml/g body weight for rats at doses of 30, 100 and 300 mg/kg to one to four animals. Activity was established using the MES, scPTZ and scSTY tests and these data are presented in Table 2. Some selected derivatives described in this study were examined for oral activity in the MES screen. The results are presented in Table 3.

5.2.2. Neurotoxicity screening

Minimal motor impairment was measured in mice by the rotorod test. The mice were trained to stay on an accelerating rotorod that rotates at six revolutions per minute. The rod diameter was 3.2 cm. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials.

5.2.3. Behavioral testing

The titled compounds (30 mg/kg) were screened for their behavioral effects using actophotometer [29] at 30 min and

1 h after injection. The behavior of animals inside the photocell was recorded as a digital score. Increased scores suggest good behavioral activity. The control animal was administered PEG. The observations are tabulated as Table 4.

5.2.4. CNS depressant study

The forced swim pool method described earlier was followed [30], Wistar rats were placed in a chamber (diameter: 45 cm, height: 20 cm) containing water up to a height of 15 cm at 25 ± 2 °C. Two swim sessions were conducted, an initial 15 min pre-test, followed by a 5 min test session 24 h later. The animals were administered an i.p. injection (30 mg/kg) of the test compounds 30 min before the test session. The period of immobility (passive floating without struggling, making only those movements which are necessary to keep its head above the surface of water) during the 5 min test period were measured. The results are presented in Table 5.

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