SYNTHESIS AND BIOLOGICAL EVALUTION OF 3-CHLORO 2-METHYL PHENYL CARBAMOYL SUBSTITUTED SEMICARBAZONE DERIVATIVES AS POTENTIAL ANTICONVULSANT AGENTS

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ABSTRACT

A series of 3- chloro 2- methyl phenyl carbamoyl substituted semicarbazones (4-21) was synthesized and evaluated for anticonvulsant and CNS activities. The anticonvulsant activity of the synthesized compounds was established after intraperitoneal administration in three seizure models in mice which include maximal electroshock seizure, subcutaneous pentylenetetrazole, and subcutaneous strychnine-induced seizure screens. All the test compounds were administered at doses of 30, 100, and 300 mg/kg body weight and the anticonvulsant activity was noted at 0.5 and 4 h time intervals after the drug administration . . Aryl semicarbazides have also been reported to display excellent anticonvulsant activity in mice and rats . In terms of interaction at the binding site, as proposed previously by Dimmock et al. the pharma-cophoric elements were thought to be a lipophilic aryl ring and hydrogen bonding semicarbazone moiety. The attach- ment 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 .

KEYWORDS – 3- Chloro 2-methyl phenyl carbamoyl substituted semicarbazone derivatives ,Neurotoxicity ,Electroshock ,Phentylenetetrazole ,Anticonvulsant activity

INTRODUCTION

Epilepsy, one of the most frequent neurological disorders, is a major public health issue, affecting about 4% of individuals over their lifetime Epilepsy is characterized by unprovoked seizures, and affects at least 50 million people worldwide. There is a continuing demand for new anticonvulsant agents as it hasnot been possible to control every kind of seizure with the currently available antiepileptic drugs. There is currently a need for improved agents for the treatment of seizure disorders, since available drugs are effective in only 60–80% of epileptic patients. During the past decade, several new drugs have been approved (Rufinamide, Retigabine, Pregabaline,Remacemide, etc.). Despite advances in the drug treatment of epilepsy, a number of limitations of antiepileptic drug therapy continue to exist . In recent years, aryl and heteroaryl semicarbazones and thiosemicarbazones have emerged as structurally novel anticonvulsants . the present work focuses on synthesis and anticonvulsant evaluation of 3-chloro-2-methylphenyl carbamoyl substituted semicarbazones, since substitution in the 2-position of the phenyl ring with electron-donating groups was generally beneficial to

activity as reported elsewhere and the importance of the ortho-methyl group for anticonvulsant activity had been depicted in many studies .

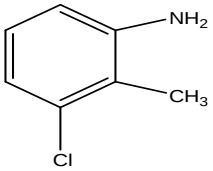
MATERIAL AND METHODS

Chemicals : 3-chloro 2-methyl aniline ,sodium cynate ,water ,Triethylamine, Hydrazine hydrate Dichloromethane,Glacial acetic acid , Ethanol, Phenylchloroformate

Animal : Animals used in this study were whister rat and albino mice of different weight.

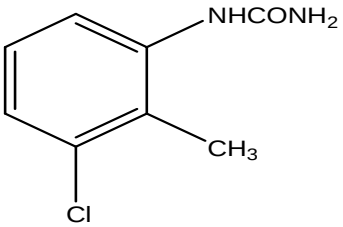
Preparation of scheme

Scheme - 1



$NaCNO, H_2O$

CH_3COOH

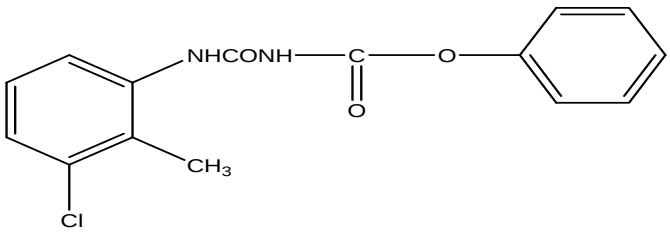


(1)

3-Chloro 2-methyl phenyl urea

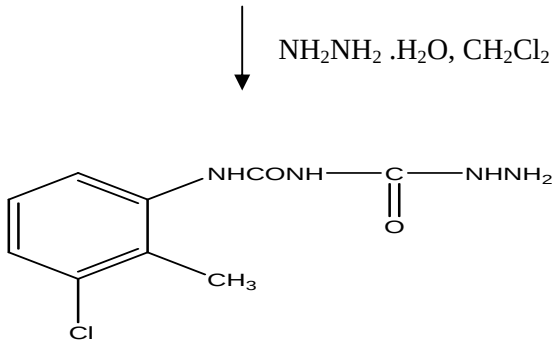
$(C_2H_5)_3N$, $CHCl_3$

Phenylchloroformate



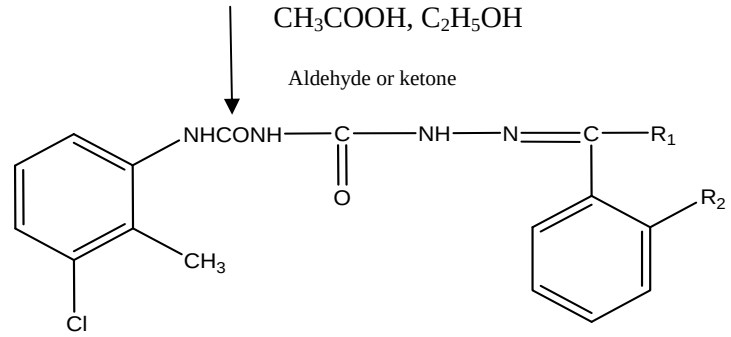
(2)

Phenyl 3-chloro-2-methylphenylcarbamoylcarbamate



(3)

4-(3-chloro-2-methyl phenyl carbamoyl)semicarbazide



(4)

4-(3-Chloro-2-methyl phenyl carbamoyl) substituted semicarbazone

Table 1 -Substitution at the position of R_1 and R_2

Compound	Substituent	
	R_1	R_2
4	H	H
5	H	3- NO_2
6	H	2- OH

7	H	4 – OH
8	H	2- Cl
9	H	4- OCH_3
10	H	4- CH_3
11	CH_3	H
12	CH_3	2-OH
13	CH_3	CH_3
14	CH_3	C_2H_5
15	CH_3	4- Cl
16	CH_3	4- NH_2
17	CH_3	4- NO_2

Table – 2 Physical data of the synthesized compound

Compound	Yield	Molecular formula	m.p^{0}c	R_f
4	61	$C_{16}H_{15}N_4O_2Cl$	203	0.89
5	57	$C_{16}H_{14}N_5O_4Cl$	189	0.83
6	60	$C_{16}H_{15}N_4O_3Cl$	174	0.78
7	59	$C_{16}H_{15}N_4O_3Cl$	201	0.86
8	52	$C_{16}H_{14}N_4O_2Cl_2$	217	0.80
9	74	$C_{17}H_{17}N_4O_3Cl$	198	0.90
10	80	$C_{17}H_{17}N_4O_2Cl$	185	0.83
11	67	$C_{17}H_{17}N_4O_2Cl$	200	0.91
12	63	$C_{16}H_{18}N_4O_3Cl$	177	0.79
13	65	$C_{18}H_{20}N_4O_2Cl$	172	0.81
14	70	$C_{19}H_{22}N_4O_2Cl$	180	0.80
15	56	$C_{17}H_{17}N_4O_2Cl_2$	208	0.72
16	64	$C_{17}H_{19}N_5O_2Cl$	193	0.88
17	58	$C_{17}H_{17}N_5O_4Cl$	210	0.85

Method for the determination of melting point

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

Method for the estimation of synthesized compound: Infrared (IR) and proton nuclear magnetic resonance (1H-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 D2O.

Method for the determination of peurity: 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).

Synthesis

Method for the 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**

Method for the synthesis of Phenyl 3-chloro-2-methylphenylcarbamoylcarbamate(2)

The urea derivative (**1**)treated with phenylchlorophoroformate (0.1 mol ,12.6 ml) was dissolved in 40 ml of chloroform and 3- chloro 2- methyl phenyl urea gave the phenyl [(3- chloro 2-methyl)carbamayl] carbamate (2)

Method for the synthesis of 4-(3-chloro-2-methyl phenyl carbamoyl)semicarbazide (3) was dissolved in dichloromethane.To this solution hydrazine hydrate added and formed 1(3-chloro-2-methyl phenyl)-3-[hydrazinyloxy carbonyl]urea.(3)

Method for the synthesis of 4-(3-Chloro-2-methyl phenyl carbamoyl) substituted semicarbazone.(3-33)

In the last step (3) is react with the glacial acetic acid and ethanol and equimoler quantity of appropriate aldehyde and ketone . and formed 3-chloro 2-methyl phenyl carbamoyl substituted smicarbazone.(4).The semicarbazone derivatives (**4-21**) were prepared by reaction of the appropriate aryl/alkyl alde- hyde or ketone or isatin derivatives with (3).

Biological evalution of the synthesized compound

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).

. 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 . Some selected derivatives described in this study were examined for oral activity in the MES screen. The

results are presented in **Table 3.**

. **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 ,observation are tabulated as **Table - 3**

Behavioral testing

The titled compounds (30 mg/kg) were screened for their behavioral effects using actophotometer at 30 min and 1 h after injection. The behavior of animals inside the photocell was recorded as digital score. Increased scores suggest good behavioral activity. The control animal was administered PEG. The observations are tabulated as **Table 4.**

CNS depressant study

The forced swim pool method described earlier was followed 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**.

RESULT AND DISCUSSION

Synthesis

The synthesis of 3-chloro-2-methyl phenyl carnonyl substituted 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**)treated with phenylchlorophoroformate (0.1 mol ,12.6 ml) was dissolved in 40 ml of chloroform and 3- chloro 2- methyl phenyl urea gave the phenyl [(3- chloro 2-methyl)carbamayl] carbamate (2).was dissolved in dichloromethane.To this solution hydrazine hydrate added and formed 1(3-chloro-2-methyl phenyl)-3-[hydrazinyloxy carbonyl]urea.(3). In the last step (3) is react with the glacial acetic acid and ethanol and equimoler quantity of appropriate aldehyde and ketone . and formed 3-chloro 2-methyl phenyl carbonyl substituted smicarbazone.(4).The semicarbazone derivatives (**4-21**) were prepared by reaction of the appropriate aryl/alkyl alde- hyde or ketone or isatin derivatives with (3). Thin layer chromatography (TLC) was run throughout the reactions to optimize the reactions for purity and completion.

Pharmacological activity

The new derivatives (4–21) 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, and observation carried out at two different time intervals (0.5 and 4 h). These data are presented in **Table 3**

FOR MES

Compound 1,2, showed antiMES potency better then the MES activity of semicarbazide derivatives (4-21) but for shorter duration of action (0.5 h) All the compounds except **5,7,11, 14, 18**, showed anti-MES activity indicative of their ability to prevent seizure spread. Compounds that showed protection against MES model at 100 mg/ kg include **4,6,9,10,13(0.25),20(0.25),.** The compounds **4, 9, 10, 12, 15 19**, showed activity both at 0.5 h and 4.0h periods. Most of the compounds showed activity only at 0.5 h, indicating that they have rapid onset and shorter duration of action.

FOR scPTZ

Compounds **1, 2,3,5,9,10,13,16,17,19,20,21**, were found to be active in the scPTZ test, a test used to identify compounds that elevate seizure threshold. Compounds **3,10,20** showed activity at a dose of 100 mg/kg comparable with Ethosuximide. Compounds that showed moderate protection at a dose of 100 mg/kg include **5 (0.25 h, 1/5),9 (0.25 h, 2/5), 17 (0.25 h, 1 h, 1/5),** . All these compounds showed 100% protection at a dose of 300 mg/kg at 0.5 h. So these compounds have quick onset of action but for shorter duration.

FOR scPTY

The compounds were also screened in the scSTY pattern test. All the compounds except **10,13,17,20** showed protection against scSTY-induced seizure threshold test, indicative of their ability to prevent seizure. Compounds **1,5,6,12,18,15,21**, showed activity at 100 mg/kg at 0.5 h in which compound **15,21** showed activity up to 4.0 h. Compounds that showed activity at 300 mg/kg include **2,3,4(4.0),7,8(4.0),11,14,16,19,(4.0)**

IN NEUROTOXICITY SCREEN

. In the neurotoxicity screen, compounds 5,6,9,13,16 did not show neurotoxicity in the maximum administered dose (300 mg/kg) and the compounds 2,8,11,17,20,19, were less neurotoxic compared to Phenytoin. On the other hand, compounds 3,7,12 14,21 were neurotoxic at the anticonvulsant dose and compounds . Compounds 5 exhibited neither anticonvulsant activity nor neurotoxicity. Among the compounds, the unsubstituted aryl derivative (2 and 13) exhibited activity against MES and scSTY models

Table – 3 Anticonvulsant activity and minimal motor impairment of synthesized semicarba-zones

Compound	Intraperitoneal injection in mice[a]							
	MES screen		$_{sc}$PTZ screen		$_{sc}$STY screen		Neuro-toxicityScreen	
	0.5h	4.0	0.5h	4.0	0.5h	4.0h	0.5h	4.0h
1	100	-	300	-	100	300	100	-
2	100	-	300	-	300	-	300	-
3	300	-	100	300	300	300	100	100
4	100	-	-	-	300	300	100	-
5	-	-	300[c]	-	100	300	-	-
6	100	300	-	-	100	300	-	-
7	-	-	-	-	300	300	100	100
8	300[b]	-	-	-	300	300	300	-
9	100	-	300[c]	300	-	-	-	-
10	100	100	100	-	-	-	100	-
11	-	-	-	-	300	-	300	-
12	300	-	-	-	100	300	100	100
13	300[b]	-	300	-	-	-	-	-
14	-	-	-	-	300	-	100	100
15	100	100	-	-	100	100	100	-
16	100	300	300	-	300	-	-	-
17	-	-	300[c]	-	-	-	300	-
18	300	300	-	-	100	300	100	-
19	300[b]	-	300	300	300	300	300	-
20	100	100	100	-	-	-	300	-
21	300	-	100	-	100	100	100	100
Phenytopine	30	30	-	-	-	-	100	100
Ethoxamide	-	-	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. The animals were examined 0.5 and 4.0 h (scSTY test, 0.5 and 2.0 h period study) after injections were administered. The dash (—) indicates the absence of activity at maximum dose administered (300 mg/kg)

[b] In the MES screen at a dose of 100 mg/kg, compounds that showed protection were 8 (0.25 h, 1/3), 13(0.25h,1/3), and 19 (0.25 h, 1/3).

[c] In the scPTZ screen, at a dose of 100 mg/kg, compounds that showed protection were 5 (0.25 h, 1/5), 9 (0.25 h, 2/5), 17 (0.25, 1 h, 1/5),

FOR – ORAL ADMINISTRATION

Four compounds (1, 7 18, and 21) were evaluated orally in rats for activity in scPTZ test at several time points **(Table 4).** The compounds were tested at 30 mg/kg and compared with standard drug Ethosuximide. Compounds 15, 17, and 18 showed better protection than the standard drug Ethosuximide. These compounds did not exhibit neurotoxicity at the tested dose of
30 mg/kg

Table -4 Evaluation of some compounds in the MES test after oral administration (30 mg/kg) to rats

compound	Oral administration to rat [a]				
	0.25h	0.5h	1.0h	2.0h	4.0h
1	1	2	0	0	0
7	2	1	1	1	1
18	0	1	1	1	0
21	3	3	2	1	1
Phenytoin	1	4	2	2	1

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

FOR CNS BEHAVIOR SCREEN BY ACTOPHOTOMETER

Some selected compounds (4, 5,6,8,10,16,21,24) were studied for the CNS behavioral activity in mice using actophotometer the results are presented in Table 5 In the behavioral study, using actophotometer, the compounds 4 and 19 showed no behavioral despair effect after 1.0 h when compared to Phenytoin.

Table 5 CNS Behavioral study on some selected compounds using actophotometer

Compound	Activity score[b]		
	Control (24 h before)	Post-treatment (60 mint after	
		0.5 h after	1 h after
4	322± 29.71	533 ± 18.28	345 ± 23.11 NS
5	517 ± 11.38	419 ± 24.78 *	357 ± 25.87*
6	184 ± 31.29	65±8.69	168 ± 11.02
8	151 ± 21.91	110 ± 12.38**	156 ± 6.77
10	410 ± 22.99	50± 99.66	35 ± 23.11
16	309 ± 21.67	50 ± 22.28	33 ± 19.02
21	372 ± 32.74	19 ± 16.12	11 ± 2.35
24	250 ± 13.69	14 ± 27.29	15 ± 79.35
Phenytoin[c]	33.11	41 ± 34.57	43± 21.44

[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 diffe- rent from the control score at $P < 0.0001$, * $P < 0.008$, ** $P < 0.02$ and NS at $P<0.02$denotesnotsignificant(Student'st-test).

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

FOR CNS BEHAVIOR SCREEN BY FORCE SWIM POOL TEST

All other compounds were found to decrease the activity of the animals. In a similar study using Porsolt's swim test, the immobility time after the administration of the test compounds was compared with that of Carbamazepine. The compound 20 was found to show no significant CNS depression and all other compounds tested were found to emerge as CNS depressants as they increased the immobility time

Table 6 CNS study on selected compounds in forced swim pool test

Compound[a]	Immobility time[b]	
	Control (24 h prior)	Post-treatment (60 mi after)
PEG	174.67 ± 9.69	178.53 ± 15.32
3	128.67 ± 11.78	193.30 ± 10.45
4	64 ± 10.14	137.3 ± 11.27
6	131 ± 18.75	203.00 ± 14.83
8	80.65 ± 19.65	106.00 ± 11.94 NS
10	208 ± 17.69	145.30 ± 12.59
16	125.67 ± 13.05	160.60 ± 16.06 NS
24	124.33 ± 13.29	207.3 ± 13.09
Carbamazepine[a]	137.4 ± 18.30	239.60 ± 17.11

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

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

Experimental protocol of ^{1}H-NMR of synthesized compound

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) mmax 3450, 1650, 840 cm–1, 1H-NMR (DMSO-d6) d 2.4 (s, 3H, CH3), 7.2–7.4 (m, 3H, ArH) 8.28 (s, 1H, ArNH, D2O exchangeable), 9.33 (s, 2H, CONH2, D2O exchangeable).

4-(3-chloro-2-methyl phenyl carbamoyl)semicarbazide (3)

To the solution of 2(0.05 mol) was dissolved in 100 ml of dichloromethane .To this solution 4.85 ml of hydrazine hydrate (0.1mol) was added and refluxed with stirring for 24 hous.The precipitate was separated by vaccum filtration and washed with dichloromethan and dried .

IR (KBr) mmax 3450, 3269, 1640, 840 cm–1; 1H-NMR (CDCl3) d 2.38 (s, 3H, CH3), 6.16 (s, 2H, NH2, D2O exchangeable), 7.12–7.14 (m, 3H,ArH), 8.04 (s, 1H,ArNH,D2O exchangeable), 9.60 (bs, 1H, NHNH2, D2O exchangeable).

General method for the synthesis of 3-chloro-2-methyl phenyl carbamoyl semicarbazones (4-21)

The title compounds were synthesized following procedures reported earlier To a solution of 3 (0.003 mol),in 25 ml of ethanol,an equimolar quantity of appropriate aldehyde or ketone in 5ml ethanol and glacial acetic acid (1-2 drop) was added .The mixture was stirred with heating for 1-4 hours until the completion of the reaction and the resultant precipitate was filtered and dried .The product was recrystallized from 95% ethanol. The IR spectra of the semicarbazone derivatives were identical in the following aspects; 3450, 3300–3250, 1650, 1595, 840 cm–1. 1H-NMR (300 MHz, d) spectra of some representative compounds are as follows:

Compaund	**1H-NMR**
5	(DMSO-d_6): 2.38 (s, 3H, $ArCH_3$), 7.23-8.29 (m, 7H, ArH), 8.12(s, 1H, imine H), 9.06 (s, 1H, ArNH, D_2O exchangeable), 11.09 (s, 1H,CONH, D_2O exchangeable);
6	(DMSO-d_6): 2.25 (s, 3H, $ArCH_3$), 6.83-7.2 (m, 7H, ArH), 8.19 (s, 1H, imine H), 8.62(s, 1H, ArNH, D_2O ex- changeable), 10.76 (s, 1H, CONH, D_2O exchangeable), 10.11 (s, 1H, ArOH, D_2O exchangeable
12	(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
15	DMSO-d_6): 2.24 (s, 3H, CH_3), 2.36(s, 3H, $ArCH_3$), 7.21-8.14 (m, 7H, ArH), 8.60 (s, 1H, ArNH, D_2O exchangeable), 10.17 (s, 1H, ArOH, D_2O exchangeable), 9.64 (s, 1H, CONH, D_2O exchangeable
17	(DMSO-d_6): 2.11(s, 3H, CH_3), 2.34(s, 3H, $ArCH_3$), 6.72-7.74 (m, 7H, ArH), 8.60 (s, 1H, ArNH, D_2O exchangeable), 10.14 (s, 1H, ArOH, D_2O exchangeable), 10.60 (s, 1H, CONH, D_2O exchangeable
19	DMSO-d_6): 2.37 (s, 3H, CH_3), 2.30 (s, 3H, $ArCH_3$), 7.12-7.38 (m, 7H, ArH), 6.62 (s, 1H, ArNH, D_2O exchangeable), 8.62 (s, 1H, ArOH, D_2O exchangeable), 10.64 (s, 1H, CONH, D_2O exchangeable

CONCLUSION : Generally these aryl semicarbazones exhibited good protection against scSTY-induced seizures and hence could act through inhibitory glycine receptors 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.

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REFERENCES

[1] 1 . Dimmock, J. R.; Vashishtha, S. C.; Stables, J. P. Eur. J. Med. Chem. 2000, 35, 241.

[2] 2. Dimmock, J. R.; Vashishtha, S. C.; Stables, J. P. Pharmazie 2000, 55, 490.

[3] 3. Pandeya, S. N.; Yogeeswari, P.; Stables, J. P. Eur. J. Med. Chem. 2000, 35, 879.

[4] 4. Yogeeswari, P.; Sriram, D.; Suniljit, L. R. J.; Kumar, S. S.; Stables, J. P. Eur. J. Med. Chem. 2002, 37, 231.

[5] 5. Yogeeswari, P.; Sriram, D.; Brahmandam, A.; Sridharan,I.; Thirumurugan, R.; Stables, J. P. Med. Chem. Res. 2003,12, 57.

[6] 6. Yogeeswari, P.; Thirumurugan, R.; Kavya, R.; Samuel, S.J.; Stables, J. P.; Sriram, D. Eur. J. Med. Chem. 2004, 39,729.

[7] 7. Yogeeswari, P.; Sriram, D.; Pandeya, S. N.; Stables, J. P.Farmaco 2004, 59, 609.

[8] 8. Yogeeswari, P.; Sriram, D.; Veena, V.; Kavya, R.;Rakhra, K.; Mehta, S.; Ragavendran, J. V.; Thirumurugan,R.; Stables, J. P. Biomed. Pharmacother. 2005, 59,51.

[9] 9. Yogeeswari, P.; Sriram, D.; Thirumurugan, R.; Ragavendran,J. V.; Sudhan, K.; Kuamr, R.; Stables, J. J. Med.Chem. 2005, 48, 6202.

[10] 10. Jones, G. L.; Woodbury, D. M. Drug Dev. Res. 1982, 2,333.

[11] 11.S.J. Hays, M.J. Rice, D.F. Ortwine, G. Johnson, R.D. Schwarz,D.K. Boyd, et al., Substituted 2-benzothiazolamines as sodium flux inhibitors: quantitative structure–activity relationships and anticonvulsant activity, J. Pharm. Sci. 83 (1994) 1425.

[12] 12. J. Mizoule, B. Meldrum, M. Martine, M. Croucher, C. Ollat, A. Uzar, et al., 2-Amino-6-trifluoromethoxy benzothiazole, a possible antagonist of excitatory amino acid neurotransmission-I. Anticonvulsant properties, Neuropharmacology 24 (1985) 767.

[13] 13.R.S. Chopade, R.H. Bahekar, P.B. Khedekar, K.P. Bhusari, A.R. Rao,Synthesis and anticonvulsant activity of 3-(5-substitutedbenzothiazol- 2-yl)-6-phenyl- [1,3]-oxazinane-2-thiones, Arch.Pharm. (Weinheim) 335 (2000) 881.

[14] 14. S.N. Pandeya, D. Sriram, P.Yogeeswari, J.P. Stables, Anticonvulsants and neurotoxicity evaluation of 5-(un)-substituted isatiniminoderivatives,Pharmazie56(2001)875