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SYNTHESIS AND ANTICONVULSANT ACTIVITIES OF 4-N-SUBSTITUTED ARYLSEMICARBAZONES

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A series of 4-N-substituted arylsemicarbazones with increased lipophilicity were synthesized and evaluated for anticonvulsant activity. The compounds provided significant protection against maximal electroshock induced seizures (MES) and seizures indicated by *sc* pentetrazole administration (*sc* PTZ) at 300 mg/kg after 0.5 h. The compounds **8** and **4** were active in MES and *sc* PTZ indicated seizure. The study has shown that introduction of alkyl (ethyl) at the terminal amino group and alkoxy (methoxy) moiety at the distal aryl ring led to increased activity and decreased toxicity.

Key words: *anticonvulsant, 4-N-substituted arylsemicarbarones, sedative-hypnotic, synthesis*

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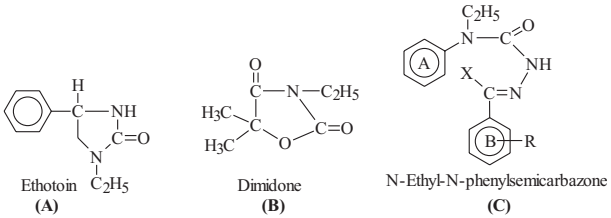
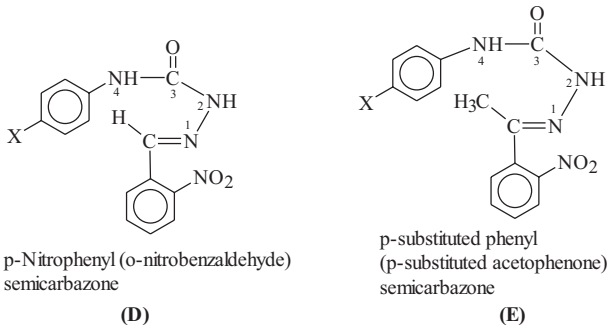
INTRODUCTION

Epilepsy is a central nervous system (CNS) malfunction that leads either to generalized hyperactivity involving essentially all parts of the brain or to hyperactivity of only a portion of the brain [7]. It has been estimated that adequate control of seizures could not be obtained in up to 20% of the patients with epilepsy using first generation of antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, sodium valproate and diazepam) [15]. A group of new drugs including felbamate, gabapentin, lamotrigine, oxacarbazepine, topiramate, milacemide, vigabatrin and zonisamide are entering into clinical practice [2, 9]. The convulsions of approximately 25% of epileptics are inadequately controlled by current clinically available drugs [16]. Current drug therapy is accompanied by numerous side effects including drowsiness, ataxia, gastrointestinal disturbances, gingival hyperplasia, hirsutism and megaloblastic anemia [4].

The past decade has witnessed a resurgence of interest in the development of anticonvulsant drugs. Consistent advances have been documented in the design of novel anticonvulsant agents based on semicarbazones, through the work of Dimmock et al. [6]. A number of aryl semicarbazones elicited anti-MES activity, as a result of interaction of aryl ring and the semicarbazone group (HNCONHN=) at aryl binding site and a hydrogen bonding area respectively [5]. Various p-substituted (Cl, Br, NO_2) phenylsemicarbazones were synthesized by Pandeya et al. to confirm the role of primary amino group in hydrogen bonding at the receptor site [12–14]. These studies have shown that p-NO_2 phenyl (o-nitrobenzaldehyde) semicarbazone (D) has an ED_{50} of 83 mg/kg in maximal electroshock test at a dose of 30 mg/kg. The aim of the present study was to synthesize lipophilic derivatives of arylsemicarbazones. The lipophilicity was increased by substituting alkyl (ethyl) moiety at the terminal nitrogen (4-N) of arylsemicarbazones. The selection of N-ethyl moiety in N-ethyl-N-phenylsemicarbazones (C) was considered because of its structural similarity with that of standard anticonvulsant drugs (A and B), i.e. ethotoin and dimidone. In another approach, the lipophilic character was increased by synthesizing alkoxy (methoxy) derivatives at the distal aryl ring of arylsemicarbazones. These compounds were assumed to be dealkylated after metabolism and the alkyl (ethyl) and alkoxy (methoxy) groups were replaced by H, which is considered to be essential for activity (Scheme 1 and 2).



Scheme 1



Scheme 2

CHEMISTRY

The preparation of 4-N-substituted arylsemicarbazones was initiated by treating required aniline with nitrourea or sodium cyanate to form arylureas. The arylureas were treated with hydrazine hydrate to form arylsemicarbazides, which were further converted to semicarbazones by reaction with aromatic aldehydes or aromatic ketones. The synthesized semicarbazones exhibited characteristic amide band at 3100–3250 cm^{-1} and 1700–1600 cm^{-1}. The presence of N-ethyl group was evident at 2850–2980 cm^{-1}. The stretching peak of C=N, appeared at 1590 cm^{-1}. The absorption band at 800–850 cm^{-1} was characteristic of phenyl ring. The ^{1}H-NMR spectrum also revealed that the hydrazine (=N-NH-) proton attached to the phenyl ring at δ 8.5–8.9, singlet was D_2O exchangeable, was presented in all synthesized compounds. The N-ethyl moiety was confirmed by the presence of a triplet at δ 2.5–3.0 of CH_3 and multiplet at δ 3.3–3.6 of -CH_2. The characteristic amide -NH proton showed singlet at δ 5.8–6.0 and D_2O exchange-

able, in p-substituted phenyl (p-methoxyacetophenone) semicarbazones.

MATERIALS and METHODS

Chemistry

Melting points are uncorrected. All the compounds were subjected to elemental analysis (CHN) and the measured values agreed within ± 0.4% with the calculated ones. The purity of the compounds was confirmed by thin layer chromatography using silica gel glass plates and a solvent system of benzene : ethanol (90:10). The spots were developed in iodine chamber and visualized with an ultraviolet lamp. ^{1}H-NMR spectra were recorded on a Jeol FX 90Q Fourier Transform. spectrometer and the IR spectra were recorded on a Jasco infrared spectrophotometer. The R_m values of the synthesized compounds were determined. The data were statistically analyzed using Student's *t*-test.

Synthesis of 4-N-substituted arylsemicarbazones

Step I: synthesis of arylureas

(a) Synthesis of N-ethyl-N-phenylurea

To a saturated aqueous solution of nitrourea (excess), one molecular equivalent (0.1 mol) of N-ethylaniline was added slowly. The solution was stirred and kept in ice. Dark brown precipitate was formed.

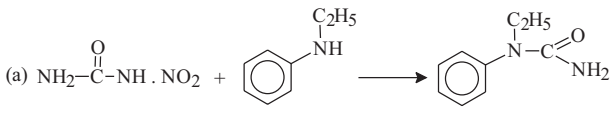
(m.p. = 60°C (charred)) [1].

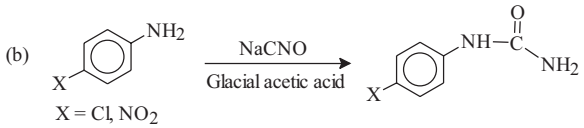
(b) Synthesis of p-substituted phenylurea

0.1 mol of p-substituted aniline was dissolved in 10 ml of glacial acetic acid and diluted to 100 ml with water. To this solution an equimolar (0.1 mol) quantity of sodium cyanate in 50 ml of warm water was added with stirring. The reaction mixture was allowed to stand for 30 min, then it was filtered, washed with water and dried after recrystallization from boiling water.

(m.p. = p-chlorophenylurea and p-nitrophenylurea: 200–205°C, 140°C, respectively).

Step I:



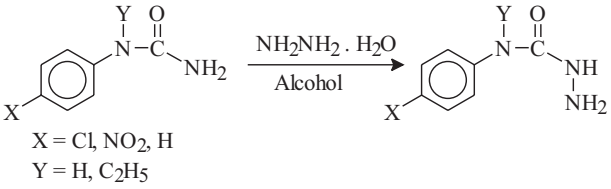


Step II: synthesis of 4-N-substituted arylsemicarbazides

To an aqueous solution of (0.1 mol) of arylureas; an equimolar quantity of hydrazine hydrate was added. Few ml of ethanol was added. The reaction mixture was refluxed for 30 min and cooled in ice. For p-substituted phenylsemicarbazides, 4 g of NaOH were added to make the reaction mixture alkaline, before refluxing. The product was filtered under suction and recrystallized from ethanol.

(m.p. = N-ethyl-N-phenylsemicarbazide: 240°C)
(m.p. = p-chloroarylsemicarbazide: 303–308°C) [12]
(m.p. = p-nitroarylsemicarbazide: 180–185°C) [13].

Step II:



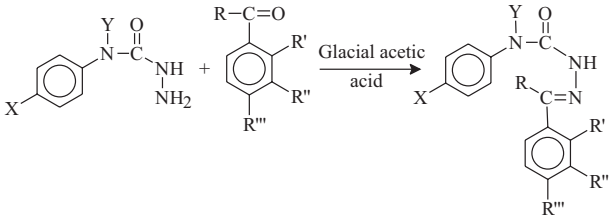
Step III: synthesis of 4-N-substituted arylsemicarbazones

To a solution of required arylsemicarbazide (0.01 mol) in water, 1–2 ml of glacial acetic acid was added, to maintain pH between 5–6. To this solution, an equimolar quantity of aromatic carbonyl compounds (aromatic aldehydes and ketones) in alcohol were added. The reaction mixture was refluxed for 30 min. The resulting product obtained after cooling was filtered and recrystallized from ethanol. Melting points and percent yields are presented in Table 1.

Animals

Adult male albino mice (#/FCM, 20–25 g) and adult male albino rats (Sprague-Dawley strain,

Step III:



Compound No.	Y	X	R	R'	R''	R'''
1	$-C_2H_5$	H	H	-OH	H	H
2	$-C_2H_5$	H	H	H	H	OCH_3
3	$-C_2H_5$	H	H	-Cl	H	H
4	$-C_2H_5$	H	CH_3	H	H	-OH
5	$-C_2H_5$	H	CH_3	H	H	NO_2
6	$-C_2H_5$	H	H	H	OCH_3	OH
7	$-C_2H_5$	H	H	H	OCH_3	OCH_3
8	-H	-Cl	CH_3	H	H	OCH_3
9	-H	$-NO_2$	CH_3	H	H	OCH_3

100–140 g) procured from NIH, were used as experimental animals. The animals were maintained on an adequate diet and allowed free access to food and water except during the short time they were removed from their cages for testing. The animals were maintained at room temperature (25–30°C). Number of animals was from five to eight depending upon the nature of test.

Anticonvulsant screening

Electroshock-induced seizures (MES test)

The albino mice (20–25 g) were used in this test. The test animals were stimulated through corneal electrodes to 50 mA current at a pulse of 60 Hz alternating current (AC) applied for 300 ms (0.25). The mice were previously administered *ip* with the test drug solution in polyethylene glycol. The abolition of hind limb tonic extensor spasm was recorded as a measure of anticonvulsant activity [8].

Pentetrazole-induced seizures (PTZ test)

Pentetrazole (PTZ) was obtained from Boehringer Mannheim, Germany. Aqueous solution of PTZ at a dose of 85 mg/kg administered *sc* in mice caused seizures in more than 97% of the animals. This dose is called convulsive dose 97 (CD_{97}). The test was carried out by PTZ injection half an hour before the injection of test compounds and observing the animals during the following 0.5 h and 4 h for the occurrence of seizures. A threshold convulsion was defined as one episode of clonic convulsions which persisted for at least 5 s. Absence of even a threshold convulsion during the period of observation was taken as the end point in this test [3].

Neurotoxic effects

Rota-rod test

Albino mice (25–30 g) were trained to stay on an accelerating rota-rod that rotated at 10 rev/min. The rod diameter was 3.2 cm. The trained animals were injected with the test compounds and were tested at TPE (time of peak drug effect) to measure the effect of the drug on motor performance. The dose at which 50% of the animals fell off the rota-rod was determined [10].

Sedative-hypnotic activity

This test was performed using the test substance at a dose of 30 mg/kg only. The drug was administered to a group of six animals. The animals were injected with a solution of pentobarbitone sodium (in PEG 200) at a dose of 30 mg/kg, after 30 min. The animals were then placed on their back and the loss of righting reflex was taken as the onset of sleep. The time taken by the animals to awake was noted. A control was also performed after pretreatment with test substance vehicle (PEG-200) [11].

RESULTS and DISCUSSION

Anticonvulsant activity

The pharmacological evaluation of the compounds was carried out under the Anliepileptic Drug Development (ADD) Programme, Epilepsy Branch, NIH, Rockville, Maryland. The methods employed have been previously described. The compounds were initially screened in the mouse MES test and the test involving *sc* PTZ administration (Tab. 2). Minimal motor impairment was measured by the rota-rod test (Tox) (Tab. 2). The compounds were evaluated for the potentiation or antagonism of pentobarbitone-induced narcosis (Tab. 3). The compounds have been tested at 30, 100, 300 mg/kg for 30 min, 4 h and 4.25 h. In MES test, the compounds were inactive at 30 mg/kg, while one compound (**8**) showed 33.33% protec-

Table 1. Physical and spectral properties of the tested compounds (**1**–**9**)

Comp.	M.P. (°C)	Percent yield	Mol. formula*	R_m value**	^{1}H NMR (DMSO-d_6) δ(ppm)	IR (cm^{-1})
1	193	52.8	$C_{16}H_{17}N_3O_2$	–0.60	2.9–3.3 (t, 3H, CH_3), 3.4–3.7 (m, 2H, CH_2), 6.7 (s, 1H, carbimino H), 7.0–7.3 (m, 5H, Ar-H), 7.4–7.7 (m, 4H, Ar-H), 8.0–8.2 (s, 1H, CONH, D_2O exchangeable), 8.9–9.0 (s, 1H, OH)	3250 (N-H), 2930, 2854 (C-H, C_2H_5), 1680 (C=O), 1600 (C=N), 820 (aromatic –C-H)
2	152	78.0	$C_{17}H_{19}N_3O_2$	–0.41	3.0–3.3 (t, 3H, CH_3), 3.4–3.9 (m, 5H, 3H of OCH_3 and 2H of CH_2 of N-ethyl), 6.8 (s, 1H, carbimino H), 7.1–7.3 (m, 5H, AR-H), 7.8–8.0 (m, 4H, Ar-H), 8.8 (s, 1H, CONH, D_2O exchangeable)	3100 (N-H), 2930, 2856 (C-H; C_2H_5), 1620 (C=O), 1590 (C=N), 830 (aromatic –CH)
3	119	65.7	$C_{16}H_{16}N_3Cl$	–0.72	3.1 (t, 3H, CH_3), 3.6 (q, 2H, CH_2), 7.1–7.5 (m, 5H, phenyl), 7.6–7.8 (m, 4H, chlorosubstituted phenyl), 8.9 (s, 1H, CONH, D_2O exchangeable), 9.8 (s, 1H, N=C-H)	3100 (N-H), 2856, 2930 (C-H, C_2H_5), 1680 (C=O), 1614 (C=N), 820 (aromatic –C-H)
4	85	68.7	$C_{17}H_{19}N_3O_2$	0.091	2.4 (s, 3H, CH_3), 3.2 (t, 3H, CH_3), 3.5 (q, 3H, CH_2), 5.4 (bs, 1H, OH), 6.9–7.2 (m, 5H, phenyl), 7.3–7.5 (m, 4H, phenyl with OH group), 8.8 (s, 1H, CONH, D_2O exchangeable)	3200 (N-H), 2930 (C-H, C_2H_5), 1645 (C=O), 1585 (C=N), 835 (aromatic –C-H)
5	140	59.0	$C_{17}H_{18}N_4O_3$	–0.50	2.4 (3H, CH_3), 3.2 (t, 3H, CH_3), 3.6 (q, 2H, CH_2), 6.9–7.2 (m, 5H, phenyl), 7.3–7.6 (m, 4H, phenyl with NO_2 group), 8.9 (s, 1H, CONH, D_2O exchangeable)	3200 (N-H), 2924, 2850 (-CH, C_2H_5), 1690 (C=O), 1593 (C=N), 825 (aromatic –C-H-);
6	155	81.2	$C_{17}H_{19}N_3O_3$	–0.09	2.9–3.4 (t, 3H, CH_3), 3.5–3.8 (m, 5H, 3H of OCH_3 and 2H of CH_2 of N-ethyl), 5.6 (bs, 1H, OH, D_2O exchangeable), 7.0–7.2 (m, 5H, phenyl), 7.3–7.5 (m, 3H, phenyl), 9.0 (s, 1H, CONH, D_2O exchangeable), 9.5 (s, 1H, aldehydic)	3200 (N-H), 2935, 2856 (C-H, C_2H_5), 1656 (C=O), 1601 (C=N), 818 (aromatic –C-H)
7	183	61.0	$C_{18}H_{21}N_3O_3$	0.03	2.8 (t, 3H, CH_3), 3.1–3.5 (s, m, 8H, 2x OCH_3 and CH_2), 7.0–7.3 (m, 5H, phenyl), 7.4–7.6 (m, 3H, substitutes phenyl), 9.0 (s, 1H, CONH, D_2O exchangeable), 9.6 (s, 1H, N=C-H)	3100 (N-H), 2854, 2924 (C-H, C_2H_5), 1630 (C=O), 1602 (C=N), 815 (aromatic –C-H-)
8	133	40.0	$C_{16}H_{16}O_2N_3$	–0.86	2.3–2.5 (s, 3H, CH_3), 3.3–3.5 (s, 3H, OCH_3), 5.8–6.0 (s, 1H, ArNH, D_2O exchangeable), 7.1–7.3 (m, 4H, Ar-H), 7.5–7.9 (m, 4H, Ar-H), 8.7 (s, 1H, CONH, D_2O exchangeable)	3425, 3310 (N-H), 2856 (-C-H, CH_3), 1680 (C=O), 1595 (C=N), 850 (aromatic –C-H-)
9	120	67.0	$C_{16}H_{16}N_4O_4$	–0.41	2.8 (t, 3H, CH_3), 3.5 (s, 3H, OCH_3), 5.9 (bs, 1H, D_2O exchangeable), 6.9–7.6 (8H, two phenyl rings), 8.8 (bs, 1H, CONH, D_2O exchangeable)	3420, 3310 (N-H), 2856 (C-H, CH_3), 1685 (C=O), 1594 (C=N), 1520 and 1350 (NO_2), 855 (aromatic –CH-)

***** The values established by elemental analysis were within = 0.4% in comparison to calculated values; ****** solvent system benzene : ethanol (90:10)

Table 2. Anticonvulsant profile and rota-rod toxicity of the examined compounds (**1**–**9**) in mice

Comp.	Percent protection (after 0.5 h)			Percent protection (after 4 h)			Dose (mg/kg)	Percent toxicity (unable to grasp rota-rod)	
	MES dose (mg/kg)		*sc* PTZ dose (mg/kg)	MES dose (mg/kg)		*sc* PTZ dose (mg/kg)			
	100	300	300	100	300	300		0.5 h	4 h
3	0.0	0.0	20.0 ± 19.1	0.0	0.0	0.0			
							100	25.0	0.0
4	0.0	100.00 ± 0.0	100.00 ± 0.0	0.0	0.0	0.0	300	100.0	0.0
							100	0.0	0.0
5							300	75.0	0.0
							100	25.0	50.0
6							300	0.0	0.0
							100	37.5	75.0
7	0.0	0.0	0.0	0.0	100.00 ± 0.0	0.0	300	75.0	50.0
							100	50.0	25.0
8	33.33 ± 19.2	100.00 ± 0.0	100.00 ± 0.0	0.0	0.0	0.0	300	100.0	100.0
							100	62.5	25.0
9	0.0	100.00 ± 0.0	0.0	0.0	0.0	0.0	300	100.0	0.0

Compounds **4**, **8**, **9** showed 100% protection at 30 mg/kg after 0.5 h. Values are means ± SEM of 5.8 mice/group. Compounds **1**, **2**, **5** and **6** were inactive. All the compounds were tested at 30 mg/kg and showed no toxicity except **8** and **9**, which showed 25% and 100% toxicity, respectively. Number of animals used were 4 at dose of 30 and 300 mg/kg and 8 at a dose of 100 mg/kg. Compounds **1**, **2**, **3** did not exhibit any neurotoxicity at a dose of 100 mg/kg and 300 mg/kg

tion at 100 mg/kg. Compounds (**4**, **8**, **9**) showed 100% protection at dose of 300 mg/kg for 0.5 h. Compound (**7**) showed protection against MES at 300 mg/kg after 4 h. This delayed activity of the compound could be due to delayed metabolic dealkylation of the ethyl group. The p-substituted derivatives (**8**, **9**) were found to possess more beneficial activity. In *sc* PTZ test, compounds (**4**, **8**) showed 100% protection at 300 mg/kg while compound (8) showed 60% protection at 100 mg/kg. Compound (**4**) exhibited 20% protection for 0.5 h at 300 mg/kg. However, no drug was found to be active at 300 mg/kg after 4 h. Compounds (**1**, **2**, **3**) exhibited no toxicity at 0.5 and 4 h. Compound (**3**) showed activity in *sc* PTZ at 300 mg/kg with negligible toxicity. Compound (**4**) exhibited 25% and 100% toxicity at 100 mg/kg and 300 mg/kg, respectively, at 0.5 h, but no toxicity was observed at 4 h. The p-substituted derivatives exhibited toxicity at 100 mg/kg and 300 mg/kg at 0.5 and 4 h.

All the synthesized compounds were evaluated in sedative and hypnotic test at a dose of 30 mg/kg.

Table 3. Sedative-hypnotic activity of the tested compounds (**1**–**9**)

Compound	Mean sleeping time (min)
1	36.0 ± 16.37
2	78.3 ± 20.20
3	30.3 ± 4.50
4	52.3 ± 12.50
5	10.6 ± 1.15
6	117.0 ± 8.18
7	41.0 ± 21.28
8	298.0 ± 8.18
9	220.0 ± 2.57
Pentobarbitone (control)	187.6 ± 2.08

All the compounds were tested at 30 mg/kg and significantly varied with control at $p < 0.005$ except compound **2** which significantly varied at $p < 0.05$ (Student's *t*-test)

All the compounds showed significant variation (99%) from control except **2**. Compounds **8** and **9** resulted in elongation of mean sleeping time confirming that these drugs potentiate narcosis induced by barbiturates. However, compounds **3**, **4**, **5**, showed antagonistic properties to barbiturates. The compounds were compared with control, injected with pentobarbitone at a dose of 30 mg/kg. The broad spectrum activity of compound **4** with least toxicity and lack of sedative side effect may be due to N-ethyl moiety (causing increased lipophilic character) which undergoes metabolic dealkylation. The p-substituted derivatives were found to possess more beneficial activity.

CONCLUSIONS

1. The ethyl group at the terminal amino group of semicarbazones results in least toxicity and increased activity.
2. The presence of methoxy group in ring B causes more lipophilic character of the molecule.
3. The p-substitution with electron withdrawing groups at the terminal phenyl ring (A) is beneficial for anticonvulsant activity.

Thus, the present study has demonstrated that new compounds can be synthesized, in which both the p-substitution of electron withdrawing moiety (Cl, Br, NO_2 at ring A and an alkyl (ethyl, methyl) derivative at the terminal amino (N-4) moiety with potent anticonvulsant activity.

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