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Original article

Synthesis and anticonvulsant activity of 4-bromophenyl substituted aryl semicarbazones

Surendra N. Pandeya[a]*, Perumal Yogeeswari[a], James P. Stables[b]

[a]Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-221005, India
[b]Preclinical Pharmacology Section, Epilepsy Branch, National Institutes of Health, Bethesda, MD 20892-9020, USA

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Abstract – A number of 4-bromophenyl semicarbazones were synthesised and evaluated for anticonvulsant and sedative–hypnotic activities. After intraperitoneal injection to mice, the semicarbazone derivatives were examined in the maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY) and neurotoxicity (NT) screens. All the compounds showed anticonvulsant activity in one or more test models. Compound **12** showed greatest activity, being active in all the screens with very low neurotoxicity and no sedative–hypnotic activity. All the compounds except **7** had lower neurotoxicity compared to phenytoin. Three compounds (**6, 11** and **14**) showed greater protection than sodium valproate. The essential structural features responsible for interaction with receptor site are established within a suggested pharmacophore. © 2000 Éditions scientifiques et médicales Elsevier SAS

semicarbazones / electroshock / pentylenetetrazole / strychnine / neurotoxicity / pentobarbitone

1. Introduction

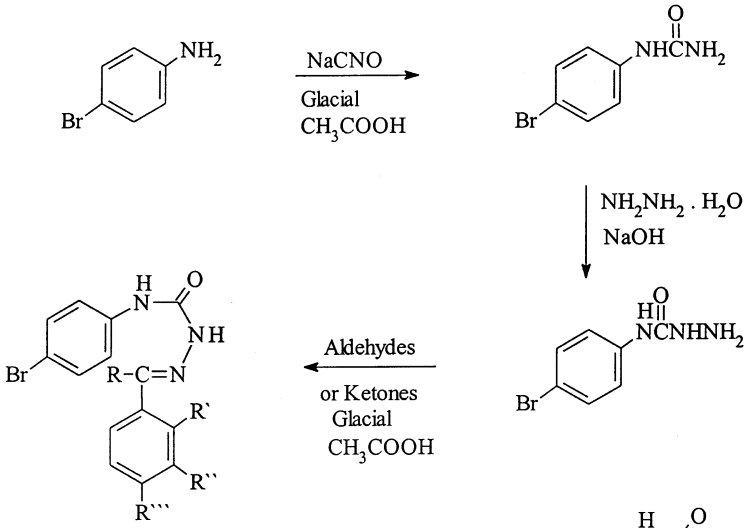
More than half of a century has elapsed since the anticonvulsant properties of phenytoin were first evidenced in laboratory animal models [1] with successful therapeutic administration in epileptic patients [2, 3]. Current drug therapy for epilepsy suffers from a number of disadvantages including the fact that the convulsions of approximately 25 % of epileptics are inadequately controlled by medication [4]. In recent years, the field of antiepileptic drug development has become quite dynamic, affording many promising research opportunities. Mechanistic approaches are increasingly being facilitated by 'the new wave of research in the epileptics' [5]. Semicarbazones have documented consistent advances in the design of novel anticonvulsant agents, through the work of Dimmock and his colleagues [6]. A number of (aryloxy)aryl semicarbazones possessed greater protection in the maximal electroshock seizure (MES) screen [7]. If the aryl semicarbazones displaying activity in the MES screen interact at a specific binding site, it is likely that the semicarbazone group and the aryl ring align at complimentary areas on a macromolecular complex in vivo; these areas have been referred to as the hydrogen bonding area and the aryl binding site, respectively [8]. In the initial studies on aryl semicarbazones, it was found to possess potent anticonvulsant activity and the importance of the terminal amino group of semicarbazone was implicated in hydrogen bonding [9–11]. The presence of electron-rich atom/group attached at the *para* position of the aryl ring showed increased potency in the MES screen. Substitution in the aryl ring by halogens led to a number of semicarbazones with low ED_{50} values in the rat oral MES screen accompanied by high protective index values [12]. In the present study, 4-bromophenyl group was considered an important aryl group. In a study of 3-aminopyrroles for anticonvulsant activity, 4-(4-bromophenyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester proved to be the most active compound with an oral ED_{50} of 2.5 mg/kg in MES screen and with no neurotoxicity up to

* Correspondence and reprints:
E-mail address: snpande@banaras.ernet.in (S.N. Pandeya).

500 mg/kg [13]. Moreover 4-bromobenzaldehyde semicarbazone displayed high potency in the MES test with very low neurotoxicity resulting in high protective index [14]. Thus the aim of the present study was to prepare a series of 4-bromophenyl semicarbazones with a view to confirm their chemical features which contribute to interactions at a binding site. The 4-bromophenyl group has been attached at the terminal amino function of the semicarbazone in contrast to the compounds synthesised by Dimmock et al. [7]. The 4-bromo derivatives have shown significant anticonvulsant activity in the MES screen, which would serve as prototypic molecule for subsequent molecular modification. The compounds were also tested against subcutaneous strychnine (scSTY) test, a test that throws light for the interaction with glycine receptors.

2. Chemistry

The preparation of 4-bromophenyl semicarbazones was achieved as depicted in *figure 1*. 4-Bromoaniline was treated with sodium cyanate in presence of glacial acetic acid according to the known urea preparation method, to yield 4-bromophenyl urea. The urea derivative on condensation with hydrazine hydrate in ethanol in the presence of sodium hydroxide gave the 4-bromophenyl semicarbazide. The semicarbazones were prepared by reaction of the appropriate aldehyde or ketone with 4-bromophenyl semicarbazide. The products (*table II*) were identified by spectral data. In general, IR spectra showed the C=N peak at 1610–1590 cm^{-1} and the NH streching vibrations at 3450 cm^{-1}. The semicarbazone derivatives exhibited char-



1 R` = Cl; R = R`` = R``` = H
2 R` = NO_2; R = R`` = R``` = H
3 R = R` = R`` = H; R``` = $N(CH_3)_2$
4 R = R` = H; R`` = OCH_3; R``` = OH
5 R = R` = H; R`` = R``` = OCH_3
6 R = CH_3; R` = R`` = R``` = H
7 R = CH_3; R` = R`` = H; R``` = OH
8 R = CH_3; R` = R`` = H; R``` = CH_3
9 R = CH_3; R` = R`` = H; R``` = NH_2
10 R = CH_3; R` = R`` = H; R``` = NO_2
11 R = C_6H_5; R` = R`` = R``` = H

12 R = R` = CH_3
13 R = H; R` = cinnamyl
14 R = H; R` = piperanyl
15 R = H; R` = 2-furyl
16 R = R` = cyclohexanyl
17 R = R` = 2-CH_3-6-isopropyl cyclohexanyl

Figure 1. Synthetic protocol of the 4-bromophenyl semicarbazones.

acteristic amide bonds at 3300–3240 cm^{-1} and 1700–1670 cm^{-1} and absorption band at 820 cm^{-1} was characteristic of a *para*-substituted phenyl ring. The ^{1}H-NMR spectrum revealed that the hydrazino (=N–NH) proton attached to the phenyl ring at 9.1–9.8 and the aryl NH proton which showed a singlet at 5.7–6.9 were D_2O exchangeable.

3. Pharmacology

Initial anticonvulsant evaluation of the 4-bromophenyl semicarbazones was undertaken by following the anticonvulsant drug development (ADD) program protocol [15, 16]. The profile of anticonvulsant activity was established after i.p. injections by one electrical and two chemical tests. The electrical test employed was the MES pattern test. The chemical tests employed were the subcutaneous pentylenetetrazole (scPTZ) seizure threshold test and scSTY seizure threshold test. Minimal motor impairment was measured by the rotorod (neurotoxicity, NT) test. Some compounds were administered orally to rats and examined in the MES screen. The compounds were also evaluated for the sedative hypnotic activity by using pentobarbitone induced narcosis in rats.

4. Results

The evaluations of the semicarbazones in the mouse i.p. MES, scPTZ, scSTY and NT screens are summarised in *table IV* along with the literature data on phenytoin, carbamazepine, sodium valproate, pentobarbital and ethosuximide [7, 16, 17]. All of the 4-bromo substituted phenyl semicarbazones were active in the MES test at a dose of 300 mg/kg, indicative of their ability to prevent seizure spread. At a dose of 100 mg/kg, compounds that showed protection in half or more of the tested mice were **2** (2 h), **3** (0.25 h, 1 h), **4** (2 h), **12** (1 h) and **17** (1 h). Compound **8** did not show any protection at 0.5 h interval but showed protection at 4 h at a dose of 300 mg/kg. All of the compounds except **1**, **5**, **9** and **17** were active in the scPTZ test, a test used to identify compounds that elevate seizure threshold. The most active compound in scPTZ test was **12**, which showed activity comparable with carbamazepine and potency greater than sodium valproate. Compounds **2**, **3**, **10**, **11**, **15** and **16** showed activity only at 0.5 h and compounds **7** and **14** showed activity only at 4 h. The activity of compounds **2, 6** and **9–15** in scSTY test showed that semicarbazones could also act through inhibitory glycine receptors. The compounds **2** and **6** were found to possess activity at 100 mg/kg. In the NT screen, all the compounds showed neurotoxicity at a higher dose level (300 mg/kg) except **7** (100 mg/kg). Compounds **1**, **2**, **3**, **11** and **15** showed neurotoxicity only up to 0.5 h and not at 4 h. All compounds were less neurotoxic than phenytoin except compound **7**. Mice were unable to grasp rotorod after administration of the following compounds, viz. **3** (300, 0.5 h), **4** (300, 0.5 h), **5** (300, 0.5 h, 4 h), **6** (300, 0.5 h, 4 h), **8** (300, 0.5 h, 4 h), **10** (300, 0.5 h), **11** (300, 0.5 h), **12** (300, 0.5 h), **13** (300, 0.5 h, 4 h), **15** (300, 0.5 h) and **17** (300, 0.5 h).

Some selected compounds (**2**, **4**, **6**, **7**, **12** and **17**) were examined for activity in the rat oral MES screen and these data are presented in *table I*. Initially a dose of 30 mg/kg was employed. Compounds afforded complete protection against seizures confirming their potential utility as prototypic molecules and compounds **2**, **6** and **7** emerged as the most active compounds in the oral MES screen. In the sedative hypnotic evaluation (*table V*), compounds **1**, **3**, **4**, **8**, **9**, **13**, **15** and **16** were found to potentiate the pentobarbitone induced narcosis and compounds **2** and **6** did not induce sleep. Compounds **6**, **10**, **11**, **12** and **14** hence emerged as the most promising anticonvulsant agents with low neurotoxicity and no sedative activity.

Table I. Evaluation of selected 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
2	2	1	3	4	4
4	1	3	2	2	3
6	2	2	3	4	3
7	1	3	3	3	4
12	1	2	–	3	2
17	1	–	2	3	3

[a] The figures indicate the number of rats out of four which were protected. The dash (–) means that no activity was demonstrated.

5. Discussion

The bioevaluation led to an understanding of the importance of the size of the group at the carbimino

Table II. Elemental analyses for reviewers[a].

Compound	Molecular formula	Found (%) (calc. %) C H N		
		C	H	N
1	$C_{14}H_{11}N_3OBrCl$	47.57 (47.68)	3.12 (3.14)	11.98 (11.92)
3	$C_{16}H_{17}N_4OBr$	53.23 (53.19)	4.78 (4.74)	15.49 (15.51)
5	$C_{16}H_{16}N_3O_3Br$	50.84 (50.81)	4.32 (4.26)	11.16 (11.11)
6	$C_{15}H_{14}N_3OBr$	54.36 (54.23)	4.29 (4.25)	12.71 (12.65)
8	$C_{16}H_{17}N_3OBr$	55.43 (55.34)	4.91 (4.94)	12.13 (12.10)
11	$C_{20}H_{16}N_3OBr$	61.10 (60.92)	4.11 (4.09)	10.35 (10.66)
12	$C_{10}H_{12}N_3OBr$	44.58 (44.46)	4.48 (4.47)	15.64 (15.56)
13	$C_{16}H_{14}N_3OBr$	55.78 (55.83)	4.16 (4.10)	12.21 (12.21)
15	$C_{12}H_{10}N_3O_2Br$	46.83 (46.77)	3.30 (3.27)	13.59 (13.64)
17	$C_{17}H_{24}N_3OBr$	55.94 (55.74)	6.64 (6.60)	11.50 (11.47)

[a] Elemental analyses were determined with Perkin Elmer model 240C analyser.

carbon atom. Replacement of the proton on the carbimino carbon atom by methyl (**6**–**10**) or phenyl (**11**) or cinnamylidene (**13**) leading to increase in the size of the group at this position of the molecule has shown variation in activity. This modification might increase the anticonvulsant activity due to additional van der Waals bonding or alternatively steric impedance to alignment at a binding site leading to a reduction or abolition of activity [18]. The introduction of a third phenyl group led to compound **11** which was active in MES, scPTZ and showed moderate activity in scSTY screens.

In terms of interaction at the binding site, as proposed previously by Dimmock et al. [7, 18], the pharmacophoric descriptors were thought to be a lipophilic aryl ring and a 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 Waals bonding at binding site and to increase potency have been studied [12]. In all these studies, the terminal amino function was found to be free. In our approach, 4-bromophenyl group has been attached at the terminal amino function in contrast to Dimmock's study, to reveal the importance of the terminal amino function for anticonvulsant activity. It is conceivable from our study that the structural features essential to interact at the binding site were a lipophilic moiety (4-bromophenyl ring) and a hydrogen bonding domain (amide function, NHCO) as proposed by Cook and co-workers [19]. The distal aryl ring at the carbimino terminal (benzylidene ring) may be essential for the pharmacokinetic properties of the compounds since variation in the substituents at the distal aryl ring was found to affect the biological activity. The distal aryl ring is expected to get *p*-hydroxylated during metabolism. Introduction of *o*-nitro group (**2**) showed protection in all the screens compared to the *o*-chloro substituted compound (**1**) or a *p*-*N*,*N*-dimethyl substituted compound (**3**). Replacement of the phenyl ring with furyl (**15**) or cyclohexanone derivatives (**16**, **17**) showed less or no activity in scSTY screen. 3,4-Methylenedioxyphenyl compounds like stiripentol [20] and 7,8-methylenedioxy-2,3-benzodiazepines [21] were found to possess longer-lasting anticonvulsant activity. Likewise, compound **14** showed higher protection in the scSTY screen compared to the standard drugs. Since bioactivity is considered to be influenced by the rate and extent of the passage of a drug to its site of action, the partition coefficients between chloroform and buffer pH 7.4 of all the compounds were determined (*table III*). The data support the concept that the compounds align at a specific binding site and are not structurally non-specific. The pharmacophore model of these aryl semicarbazones resemble that of the standard anticonvulsants as depicted in *figure 2* and the 4-bromophenyl semicarbazones largely resemble the structure of desmethyl diazepam. Hence these semicarbazones could emerge as bioisosteres of desmethyl diazepam (CH_2 replaced with NH).

In conclusion, the present results indicate that the terminal amino function of the semicarbazone is not essential for activity and can be substituted with a lipophilic aryl ring. This is a new aspect, which led to prototypic molecules with potential activity in the preliminary studies.

Table III. Physical data of the semicarbazone derivatives.

Compound	Yield (%)	Mp (°C)	Molecular formula[a]	R_f[b]	P[c]
1	62	210	$C_{14}H_{11}N_3OBrCl$	0.66	0.51
2	52	183	$C_{14}H_{11}N_4O_3Br$	0.67	0.72
3	74	172	$C_{16}H_{17}N_4OBr$	0.71	0.86
4	69	253	$C_{15}H_{14}N_3O_3Br$	0.48	2.10
5	88	144	$C_{16}H_{16}N_3O_3Br$	0.73	0.94
6	85	229	$C_{15}H_{14}N_3OBr$	0.61	2.15
7	55	200	$C_{15}H_{15}N_3O_2Br$	0.58	2.95
8	59	222	$C_{16}H_{17}N_3OBr$	0.64	0.43
9	55	196	$C_{15}H_{15}N_4OBr$	0.78	0.77
10	65	167	$C_{15}H_{14}N_4O_3Br$	0.63	1.23
11	55	179	$C_{20}H_{16}N_3OBr$	0.72	1.05
12	57	201	$C_{10}H_{12}N_3OBr$	0.77	2.26
13	68	158	$C_{16}H_{14}N_3OBr$	0.83	1.48
14	83	184	$C_{15}H_{12}N_3O_3Br$	0.50	0.59
15	52	112	$C_{12}H_{10}N_3O_2Br$	0.51	1.82
16	59	193	$C_{13}H_{16}N_3OBr$	0.68	0.46
17	56	245	$C_{17}H_{24}N_3OBr$	0.42	2.53

[a] Elemental analyses for C,H,N were within 0.4 % of the theoretical values.
[b] Eluants for TLC were benzene–ethanol (9.8:0.2) for all compounds except **3–5, 9, 11–15** and **17** for which only benzene was used.
[c] Partition coefficient at 25 °C [chloroform–phosphate buffer system, pH 7.4].

6. Experimental protocols

6.1. Chemistry

Melting points were determined in open capillary tubes on a Thomas Hoover melting point apparatus and are uncorrected. Infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded for the compounds on Jasco IR Report 100 (KBr) and JEOL Fx 90Q (Fourier Transform) instruments, respectively. Chemical shifts are reported in ppm (δ) using tetramethylsilane (TMS) as internal standard. All exchangeable protons were confirmed by addition of D_2O. Elemental analyses (C,H,N) undertaken with Perkin Elmer Model 240C analyser on compounds **1**, **3**, **5**, **6**, **8**, **11**–**13**, **15** and **17** were within 0.4 % of the calculated values. The homogeneity of the compounds was monitored by ascending thin layer chromatography (TLC) on silica-G (Merck) coated glass plates, visualised by iodine vapour. Developing solvents were either benzene or benzene–ethanol (9.8:0.2). The partition coefficients were determined using a chloroform–phosphate buffer (pH 7.4) system by UV method.

6.1.1. Synthesis of 4-bromophenyl semicarbazide

The 4-bromophenyl urea was prepared from *p*-bromoaniline by a reported procedure [22] and converted into 4-bromophenyl semicarbazide by a method which has been described previously [10]. Equimolar quantities (0.1 mol) of 4-bromophenyl urea (21.5 g) and hydrazine hydrate (5 mL) in ethanol were refluxed for 3 h in the presence of 0.1 mol sodium hydroxide. The resultant precipitate was filtered, dried and recrystallised from 95 % ethanol to give 4-bromophenyl semicarbazide, mp 278–280 °C in 78 % yield. ^{1}H-NMR ($CDCl_3$) 5.6 (s, 2H, NH_2, D_2O exchangeable), 6.15 (s, 1H, ArNH, D_2O exchangeable), 7.2–7.46 (m, 4H, ArH), 9.6 (bs, 1H, $NHNH_2$).

6.1.2. Synthesis of 4-bromophenyl semicarbazones

To a solution of 4-bromophenyl semicarbazide (0.69 g, 0.003 mol) in ethanol was added an equimolar quantity of the appropriate aldehyde or ketone. The pH of the reaction mixture was adjusted between 5 and 6 by adding glacial acetic acid. The reaction mixture was refluxed for 1–2 h. The product obtained after cooling was filtered and recrystallised from 95% ethanol. The physical data of the semicarbazones are presented in *table III*. The IR spectra of the compounds were identical in the following aspects: 3450 (NH), 3300–3240 (CONH), 1640 (C=O), 1590 (C=N) and 840 cm^{-1} (Ar–CH); ^{1}H-NMR (90 MHz, δ) spectra of some representative compounds were as follows: **1** (DMSO-d_6): 5.8 (s, 1H, ArNH, D_2O exchangeable), 6.84 (s, 1H, Carbimino H) 7.2–7.6 (m, 8H, Ar–H), 8.89 (s, 1H, CONH, D_2O exchangeable); **3** ($CDCl_3$): 3.0 (s, 6H, N $(CH_3)_2$),

Table IV. Anticonvulsant activity and minimal motor impairment of 4-bromophenyl semicarbazone derivatives.

Compound	Intraperitoneal injection in mice[a]							
	MES screen		scPTZ screen		scSTY screen[b]		Toxicity screen	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
1	300	300	–	–	–	–	300	–
2	300	300[c]	300	–	300	300	300	–
3	300[c]	–[c]	300	–	–	–	300	–
4	300	300[c]	300	300	–	–	300	300
5	300	300	–	–	–	–	300	300
6	100	300	300	300	100	100	300	300
7	300	300	–	300	–	–	100	300
8	–	300	300	300	–	–	300	300
9	300	300	–	–	300	300	300	300
10	300	300	300	–	300	300	300	300
11	300	300	300	–	100	300[d]	300	–
12	300	300[c]	100	300	300	300	300	300
13	300	300	300	300	100	300	300	300
14	300	300	–	300	100	100	300	300
15	300	300	300	–	300	300	300	–
16	300	300	300	–	–	–	300	300
17	300	300[c]	–	–	–	–	300	300
Phenytoin[e]	30	30	–	–	–	100	100	100
Carbamazepine[e]	30	100	100	300	–	–	100	300
Na. Valproate[e]	300	–	300	–	300	–	—	—
Phenobarbital[f]	100	30	30	30	–	100	100	300
Ethosuximide[f]	–	–	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 maximum dose administered (300 mg/kg).
[b] In scSTY screen, rats were used.
[c] In the MES screen, at a dose of 100 mg/kg, compounds that showed protection were **2** (2 h), **3** (0.25, 1 h), **4** (2 h), **12** (1 h) and **17** (1 h).
[d] Compound **11** showed protection at a dose of 100 mg/kg up to 1 h in the scSTY screen.
[e] Data from references [7, 16].
[f] Data from reference [17].

5.9 (s, 1H, ArNH, D_2O exchangeable), 6.91 (s, 1H, Carbimino H), 7.2–7.5 (m, 4H, *p*-bromophenyl), 7.6–7.8 (m, 4H, *p*-dimethylaminophenyl), 8.75 (s, 1H, CONH, D_2O exchangeable); **4** ($CDCl_3$): 3.63 (s, 3H, OCH_3), 5.89 (s, 1H, ArNH, D_2O exchangeable), 6.94 (s, 1H, Carbimino H), 7.23–7.43 (m, 7H, ArH), 9.66 (s, 1H, CONH, D_2O exchangeable), 10.95 (s, 1H, OH); **8** ($CDCl_3$): 2.3 (s, 3H, CH_3), 2.35 (s, 3H, N=C(CH_3)), 6.1 (s, 1H, ArNH, D_2O exchangeable), 7.3–7.6 (m, 8H, ArH), 8.71 (s, 1H, CONH, D_2O exchangeable); **11** ($CDCl_3$): 5.82 (s, 1H, ArNH, D_2O exchangeable), 7.2–8.12 (m, 14H, ArH), 8.88 (s, 1H, CONH, D_2O exchangeable); **12** ($CDCl_3$): 2.29 (s, 6H, $2 \times CH_3$), 5.81 (s, 1H, ArNH, D_2O exchangeable), 7.2–7.56 (m, 4H, ArH), 8.75 (s, 1H, CONH, D_2O exchangeable); **14** ($CDCl_3$): 5.88 (s, 1H, ArNH, D_2O exchangeable), 6.05 (m, 2H, OCH_2O), 6.77 (s, 1H, Carbimino H), 7.18–7.62 (m, 7H, ArH), 8.86 (s, 1H, CONH, D_2O exchangeable); **15** ($CDCl_3$): 5.83 (s, 1H, ArNH, D_2O exchangeable), 6.75 (s, 1H, Carbimino H), 6.46–7.49 (m, 7H, ArH), 8.82 (s, 1H, CONH, D_2O exchangeable); **16** ($CDCl_3$): 2.54 (m, 4H, *o*-position of cyclohexane ring), 3.26–3.4 (m, 6H, *m*- and *p*-positions of cyclohexane ring), 5.9 (s, 1H, ArNH, D_2O exchangeable), 7.21–7.43 (m, 4H, ArH), 8.91 (s, 1H, CONH, D_2O exchangeable).

6.2. Pharmacology

The anticonvulsant evaluations were undertaken by the National Institute of Neurological Disorders and

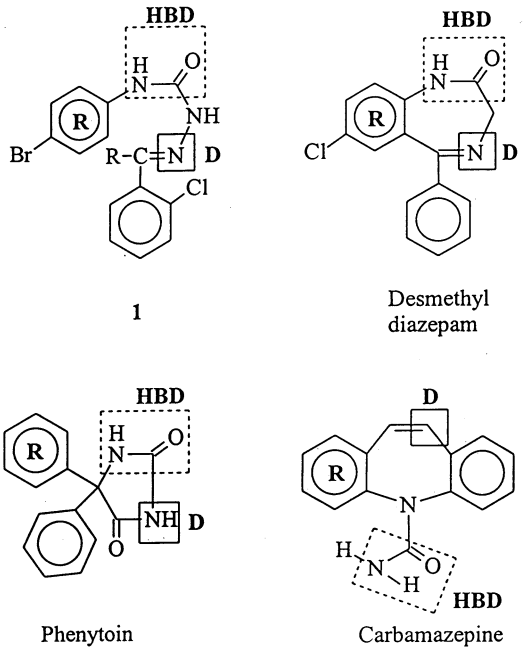


Figure 2. Development of a pharmacophore model. **R**-hydrophobic unit; **HBD**-hydrogen bonding domain; **D**-electron donor.

Table V. Evaluation of compounds for the potentiation or antagonism of pentobarbitone induced narcosis[a].

Compounds[b]	Mean sleeping time[c] (min)
1	196.6 ± 49.80
3	141.16 ± 15.75
4	147.30 ± 4.67
5	23.60 ± 7.18
7	34.60 ± 4.25
8	160.40 ± 10.78
9	69.40 ± 8.02
10	23.60 ± 2.82
11	34.16 ± 7.82
12	20.33 ± 6.18
13	107.60 ± 27.84
14	14.30 ± 1.55
15	132.09 ± 6.26
16	182.7 ± 11.95
17	28.00 ± 10.74
Pentobarbitone (control)	49.30 ± 1.36

[a] Compounds were tested at a dose of 30 mg/kg (i.p.).
[b] Compounds **2** and **6** did not induce sleep in rats.
[c] Each value represents the mean SEM of six rats significantly different from the control ($P<0.5$) (student's t-test).

Strokes, NIH (USA) using their reported procedures [15, 16, 23]. Male albino mice (CF-1 strain, 18–25 g) and male albino rats (Sprague–Dawley, 100–150 g) were used as experimental animals. The semicarbazones were suspended in 0.5 % methylcellulose/water mixture or in polyethylene glycol (PEG).

6.2.1. 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 IV*. Some selected semicarbazone derivatives described in this study were examined for oral activity in the MES screen. The results are presented in *table I*.

6.2.2. Neurotoxicity (NT) screen

Minimal motor impairment was measured in mice by the rotorod test. The mice were trained to stay on an accelerating rotorod that rotates at 10 revolutions per minute. The rod diameter was 3.2 cm^{-1}. Trained animals were given i.p. injection of the test compounds in doses of 30, 100 and 300 mg/kg. 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 trails.

6.2.3. Sedative–hypnotic activity

This test was performed with the test substances in a dose of 30 mg/kg only by the method reported previously [10]. The compounds in PEG were administered i.p. to a group of six rats. After 30 min, rats were injected i.p. with a solution of pentobarbitone (in PEG) in a dose of 30 mg/kg. The rats were then placed on their back and loss of righting reflex was taken as onset of sleep. The time taken by rats to awake was noted. A control was also performed after pre-treatment with test substance vehicle (PEG) and injected pentobarbitone.

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