Synthesis and Structure-Activity Relationship on Anticonvulsant Aryl Semicarbazones

P. Yogeeswari[1], J.V. Ragavendran[1], R. Thirumurugan[1], S. Induja[1], D. Sriram[1,*], J. P. Stables[2]

[1]*Medicinal Chemistry Research Laboratory, Pharmacy Group, Birla Institute of Technology & Science, Pilani-333031, India;* [2]*Preclinical Pharmacology Section, Epilepsy Branch, National Institutes of Health, Bethesda 20892-9020, USA*

Abstract: Seven series of various substituted aryl semicarbazones were synthesized and evaluated for anticonvulsant activity in the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure threshold tests. A comprehensive structure-activity relationship was derived comparing the substituents on the aryl ring and in the carbimino terminal. Generally the order of activity was 4-F > 2-Br = 3-Br = 4-Cl > 4-CH_3 > 4-Br > 3-Cl > 3-CH_3 with respect to the primary aryl group. Most of the compounds exhibited activity both in the MES and scPTZ screens. The 4-fluorophenyl substituted semicarbazones (**5a-5y**) emerged as the most potent compounds exhibiting anticonvulsant activity in mouse intraperitoneal (i.p.) and rat per oral (p.o.) MES, scPTZ and psychomotor seizure (6 Hz) screens.

Key Words: Aryl semicarbazones, anticonvulsant activity, 4-fluorophenyl, maximal electroshock seizure.

INTRODUCTION

Aryl semicarbazones have documented consistent advances in the design of novel anticonvulsant agents [1-12]. These novel compounds were structurally dissimilar from many common monocyclic anticonvulsants containing the dicarboximide function (CONRCO), which may contribute to toxic side effects [13]. 4-Bromobenzaldehyde semicarbazone a prototype molecule demonstrated high anticonvulsant potency and very low neurotoxicity [14]. In these works, the importance of the terminal amino group of semicarbazone was implicated in hydrogen bonding [15]. Pandeya *et al*. [16] reported anticonvulsant aryl semicarbazones with a 4-bromo substituted phenyl group attached at the terminal amino function of the semicarbazone in contrast to the compounds synthesized by Dimmock *et al*. These 4-bromophenyl substituted semicarbazones compounds emerged with low neurotoxicity and showed greater protection than sodium valproate. Further recently, we had reported the synthesis of 3-bromophenyl substituted semicarbazones [17] in which 4-methoxybenzaldehyde *N*-(3-bromophenyl) semicarbazone demonstrated to have anticonvulsant activity in the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole seizure (scPTZ) tests, with ED_{50} of 32.35 mg/kg and < 45 mg/kg respectively. As there is a need for development on aryl semicarbazones as anticonvulsants, we have attempted to present a comprehensive structure-activity relationship (SAR) on aryl semicarbazones reported from our lab. In this report we describe the anticonvulsant profiles of some unreported 2-, 3-, and 4-halo and alkyl substituted aryl semicarbazones and derived the SAR by comparing with our earlier reported works.

*Address correspondence to this author at the Medicinal Chemistry Research Laboratory, Pharmacy Group, Birla Institute of Technology & Science, Pilani-333031, India; Tel: 91 (0159) 7644684; Fax: 91 (0159) 7644183; E-mail: dsriram@bits-pilani.ac.in

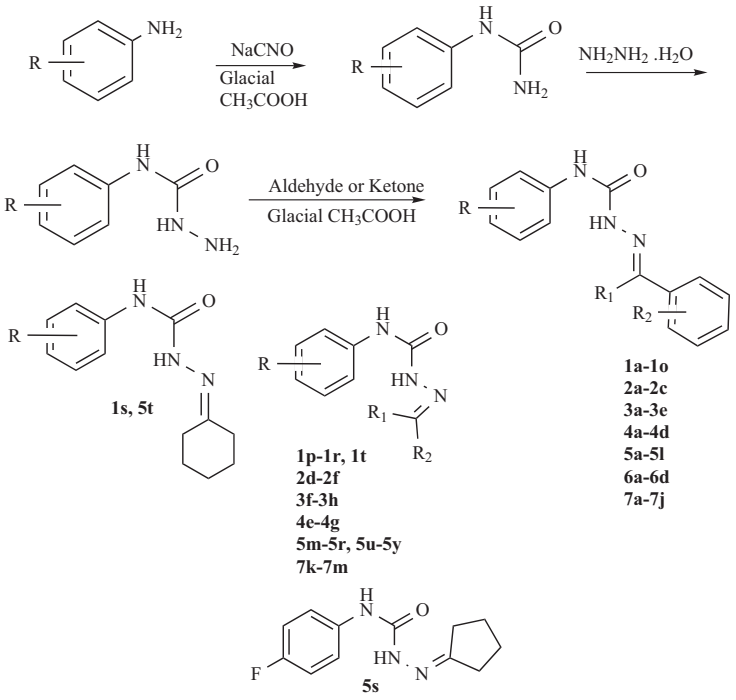
CHEMISTRY

The synthesis of 2-/3-/4-substituted phenyl semicarbazones was accomplished as presented in Scheme **1**. 2-/3-/4-substituted aniline was treated with sodium cyanate in the presence of glacial acetic acid according to the previously known urea preparation method [17-19], to yield 2-/3-/4-substituted phenyl urea. The urea derivatives on condensation with hydrazine hydrate in ethanol in presence of sodium hydroxide gave the 2-/3-/4-substituted phenyl semicarbazide. The semicarbazone derivatives (**1a-1t, 2a-2f, 3a-3h, 4a-4g, 5a-5x, 6a-6d, 7a-7m**) were prepared by reaction of the appropriate aryl/alkyl/cycloalkyl aldehyde or ketone or isatin derivatives with the corresponding semicarbazide. 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**-**5**.

PHARMACOLOGICAL ACTIVITY

As with any other class of drugs, the preclinical discovery and development of a new chemical entity for the treatment of epilepsy relies heavily on the use of predictable animal models. At the present time, there are three *in vivo* models that are routinely used by most antiepileptic drug discovery programs. They include the MES, the subcutaneous pentylene tetrazole (scPTZ) and the kindling model [20]. Of these, the MES and scPTZ seizure models represent the two animal seizure models most widely used in the search for new AEDs [21, 22]. All the titled compounds were evaluated initially in the MES and scPTZ seizure models. The acute neurological toxicity (NT) was determined in the rotorod test. The obtained results are listed in Table **1**-**5**. After intraperitoneal (i.p.) injection in mice using doses of 30, 100 and 300 mg/kg, the following observations may be made. In the MES screen, except **1b-d**, **1f**, **1i**, **1n**, **3a**, **3d**, **5a**, **5c**, **5e-f**, **5r**, **5y**, **6c-d**, all compounds exhibited protection indicative of their ability to prevent seizure spread. Compounds

1573-4064/06 $50.00+.00



Scheme 1. Synthetic protocol of aryl semicarbazones.

Table 1. Physical and Biological Results of 2-Bromophenyl Semicarbazones

Compd	R	R_1	R_2	Yield %	M.p. (°C)	Intraperitoneal injection in mice [a]					
						MES Screen		scPTZ Screen		Neurotoxicity Screen	
						0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
1a	2-Br	H	2-OH	65	188	300	-	300	-	300	-
1b	2-Br	H	2-Cl	64	204	-	-	-	-	300	-
1c	2-Br	H	2-CH_3	61	195	-	-	-	-	300	-
1d	2-Br	H	2-NO_2	55	188	-	-	-	-	300	-
1e	2-Br	H	3-NO_2	56	178	300	-	-	-	-	-
1f	2-Br	H	4-NO_2	90	185	-	-	-	-	300	-
1g	2-Br	H	4-CH_3	50	183	300	-	-	-	300	-
1h	2-Br	H	4-OCH_3	54	184	100	-	-	-	300	-
1i	2-Br	H	3-OCH_3, 4-OH	55	183	-	-	-	-	-	-
1j	2-Br	CH_3	H	50	184	300	300	300	-	300	300
1k	2-Br	CH_3	4-OH	57	189	100	-	300	-	300	-
1l	2-Br	CH_3	4-CH_3	56	182	300	-	300	-	300	-
1m	2-Br	CH_3	4-NH_2	52	187	300	-	-	-	300	-

(Table 1. Contd….)

Compd	R	R_1	R_2	Yield %	M.p. (°C)	Intraperitoneal injection in mice [a]					
						MES Screen		scPTZ Screen		Neurotoxicity Screen	
						0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
1n	2-Br	CH_3	4-NO_2	52	206	-	-	-	-	100	-
1o	2-Br	C_6H_5	H	70	163	300	-	-	-	300	-
1p	2-Br	CH_3	CH_3	67	177	100	300	-	-	300	300
1q	2-Br	CH_3	CH_2-CH_3	58	187	100	-	-	-	300	-
1r	2-Br	CH_3	CH_2COCH_3	55	182	100	-	-	-	300	-
Phenytoin	-	-	-	-	-	30	30	-	-	100	100
Ethosuximide	-	-	-	-	-	-	-	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 dash (-) indicates an absence of activity at maximum dose administered (300 mg/kg).

Table 2. Physical and Biological Results of 2-Bromo/-3-/4-Chlorophenyl Semicarbazones

Compd	R	R_1	R_2	Yield %	M.p. (°C)	Intraperitoneal injection in mice [a]					
						MES Screen		scPTZ Screen		Neurotoxicity Screen	
						0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
1s	2-Br	R_1-R_2 = Cyclohexanyl		54	167	100	-	300	-	300	-
1t	2-Br	R_1-R_2 = Isatinyl		72	164	100	300	300	-	300	300
2a	3-Br	CH_3	2-OH	59	199	100	300	100	300	100	300
2b	3-Br	CH_3	3-NH_2	80	189	100	300	300	300	300	300
2c	3-Br	CH_3	4-NH_2	72	145	100	-	300	-	300	-
2d	3-Br	CH_3	CH_3	82	170	100	-	100	-	100	300
2e	3-Br	CH_3	CH_2-CH_3	76	205	100	300	100	300	100	300
2f	3-Br	CH_3	CH_2COCH_3	71	167	100	300	100	300	100	300
3a	3-Cl	H	2-Cl	70	107	-	-	-	-	-	-
3b	3-Cl	H	2-OH	63	84	100	300	-	-	300	-
3c	3-Cl	H	4-CH_3	53	186	100	300	100	-	100	300
3d	3-Cl	H	4-OCH_3	76	159	-	-	-	-	-	-
3e	3-Cl	CH_3	4-NH_2	55	49	100	-	-	-	300	-
3f	3-Cl	CH_3	CH_3	52	184	100	300	300	-	300	-
3g	3-Cl	CH_3	CH_2-CH_3	51	178	100	100	30	100	300	-
3h	3-Cl	R_1-R_2 = Isatinyl		54	180	100	300	-	-	300	-
4a	4-Cl	CH_3	3-Cl	65	172	100	300	300	300	300	300
4b	4-Cl	H	3-NO_2	66	165	100	300	100	300	300	300
Phenytoin	-	-	-	-	-	30	30	-	-	100	100
Ethosuximide	-	-	-	-	-	-	-	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 dash (-) indicates an absence of activity at maximum dose administered (300 mg/kg).

Table 3. Physical and Biological Results of 4-Chloro/ 4-Fluorophenyl Semicarbazones

Compd	R	R_1	R_2	Yield %	M.p. (°C)	Intraperitoneal injection in mice [a]					
						MES Screen		scPTZ Screen		Neurotoxicity Screen	
						0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
4c	4-Cl	CH_3	3-NH_2	56	123	100	300	30	300	100	300
4d	4-Cl	H	4-CH_3	55	132	100	300	-	300	300	300
4e	4-Cl	CH_3	CH_3	70	156	100	100	-	-	300	300
4f	4-Cl	CH_3	CH_2-CH_3	62	120	100	300	-	-	300	300
4g	4-Cl	CH_3	CH_2-$CH(CH_3)_2$	71	162	100	100	100	300	300	300
5a	4-F	H	2-Cl	60	173	-	-	-	-	-	-
5b	4-F	H	2-OH	52	159	300	300	300	-	300	300
5c	4-F	H	2-NO_2	63	196	-	-	-	-	-	-
5d	4-F	H	3-NO_2	68	216	300	-	30	-	-	-
5e	4-F	H	4-NO_2	90	218	-	-	-	-	100	-
5f	4-F	H	3-OCH_3, 4-OH	82	77	-	-	-	-	-	-
5g	4-F	CH_3	2-OH	72	169	100	300	300	-	300	-
5h	4-F	CH_3	3-NH_2	74	172	300	-	300	-	-	-
5j	4-F	CH_3	4-NO_2	75	65	300	-	300	-	300	-
5k	4-F	CH_3	4-OH	72	166	300	300	300	100	300	-
5l	4-F	C_6H_5	H	63	51	300	-	300	-	300	-
5m	4-F	CH_3	CH_3	66	164	300	-	300	300	300	-
5n	4-F	CH_3	CH_2-CH_3	65	168	100	-	300	300	300	-
Phenytoin	-	-	-	-	-	30	30	-	-	100	100
Ethosuximide	-	-	-	-	-	-	-	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 dash (-) indicates an absence of activity at maximum dose administered (300 mg/kg).

Table 4. Physical and Biological Results of 4-Fluoro/ 3-Methylphenyl Semicarbazones

Compd	R	R_1	R_2	Yield %	M.p. (°C)	Intraperitoneal injection in mice [a]					
						MES Screen		scPTZ Screen		Neurotoxicity Screen	
						0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
5o	4-F	CH_3	CH_2COCH_3	84	176	100	300	300	300	300	300
5p	4-F	CH_3	CH_2-$CH(CH_3)_2$	54	170	300	300	300	-	300	300
5q	4-F	CH_2-C_6H_5	CH_2-C_6H_5	65	127	300	-	300	-	300	-
5r	4-F	H	2-Furyl	50	149	-	-	-	-	-	-
5s	4-F	R_1-R_2 = Cyclopentanyl		56	173	300	300	300	-	300	-
5t	4-F	R_1-R_2 = Cyclohexanyl		58	169	300	300	300	-	300	-

(Table 4. Contd….)

Compd	R	R_1	R_2	Yield %	M.p. (°C)	Intraperitoneal injection in mice [a]					
						MES Screen		scPTZ Screen		Neurotoxicity Screen	
						0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
5u	4-F	R_1-R_2 = Isatinyl		63	129	300	300	300	-	300	-
5v	4-F	R_1-R_2 = 5-Chloroisatinyl		56	141	300	-	300	-	300	300
5w	4-F	R_1-R_2 = 5-Bromoisatinyl		65	121	300	-	300	-	-	-
5x	4-F	R_1-R_2 = 5-Fluoroisatinyl		66	116	300	-	-	-	300	-
6a	3-CH_3	H	2-Cl	63	115	100	-	-	-	300	-
6b	3-CH_3	H	2-OH	89	63	300	-	300	-	300	-
6c	3-CH_3	H	3-NO_2	65	67	-	-	-	-	-	-
6d	3-CH_3	H	4-NO_2	47	68	-	-	300	-	300	-
Phenytoin	-	-	-	-	-	30	30	-	-	100	100
Ethosuximide	-	-	-	-	-	-	-	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 dash (-) indicates an absence of activity at maximum dose administered (300 mg/kg).

Table 5. Physical and Biological Results of 4-Methylphenyl Semicarbazones

Compd	R	R_1	R_2	Yield %	M.p. (°C)	Intraperitoneal injection in mice [a]					
						MES Screen		scPTZ Screen		Neurotoxicity Screen	
						0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
7a	4-CH_3	H	H	58	193	100	-	100	-	300	300
7b	4-CH_3	H	2-OH	54	185	300	-	300	-	300	-
7c	4-CH_3	H	4-NO_2	65	187	300	-	-	-	300	-
7d	4-CH_3	H	4-CH_3	58	195	300	-	300	-	300	-
7e	4-CH_3	H	4-OCH_3	55	175	300	300	300	-	300	-
7f	4-CH_3	CH_3	H	75	187	100	-	-	-	300	-
7g	4-CH_3	CH_3	4-Cl	72	192	100	-	-	-	300	-
7h	4-CH_3	CH_3	4-OH	69	172	300	-	-	-	300	-
7i	4-CH_3	CH_3	4-NH_2	66	177	100	-	300	100	300	-
7j	4-CH_3	CH_3	4-CH_3	63	189	300	300	-	-	300	-
7k	4-CH_3	CH_3	CH_3	56	156	300	-	300	-	300	-
7l	4-CH_3	CH_3	CH_2-CH_3	86	163	300	-	300	-	300	-
7m	4-CH_3	CH_3	CH_2-$CH(CH_3)_2$	65	169	300	-	300	-	300	-
Phenytoin	-	-	-	-	-	30	30	-	-	100	100
Ethosuximide	-	-	-	-	-	-	-	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 dash (-) indicates an absence of activity at maximum dose administered (300 mg/kg).

effective at 100mg/kg include **1h**, **1k**, **1p-t**, **2a-f**, **3b-c**, **3e-h**, **4a-g**, **5g**, **5n-o**, **6a**, **7a**, **7f-g** and **7i**. Generally the 3-bromo and 4-chlorophenyl semicarbazones showed higher potency than other compounds. In the scPTZ screen, all the compounds except **1b-i**, **1m-o**, **1q-r**, **3a**, **3d**, **5a**, **5c**, **5e-f**, **5r**, **5x-y**, **6a**, **6c**, **7f**, **7g-h** and **7i** showed protection. Compounds **3g**, **4c** and **5d** emerged as most potent compounds against scPTZ-induced seizures when compared to Ethosuximide. Generally comparing structures of all the compounds including the ones reported earlier [16-18], the 4-halo substituted phenyl semicarbazones were found to exhibit a broad spectrum of activity in both grand mal (MES) and petit mal (scPTZ) seizure models.

The neurotoxicity screen was established using rotorod model in mice. Compounds **1i**, **3a**, **3d**, **5a**, **5c-5d**, **5f**, **5h**, **5r**, **5w**, **5y**, and **6c** were found to be devoid of any neurotoxicity. But the compounds **1b-1d**, **1f**, **1n**, and **5e** despite having no anticonvulsant activity were found to be neurotoxic. The compounds that showed no or lesser neurotoxicity compared to the minimum anticonvulsant dose included **1e**, **1k**, **1p-1t**, **2b-2c**, **3b**, **3e-3h**, **4a-4b**, **4d-4g**, **5d**, **5g**, **5n-5o**, **5w**, **6a**, **7a**, **7f-7g**, and **7i**.

Some selected compounds (**5b**, **5d**, **5i**, **5m**, **5o**, **5u**, and **5x**) were examined for activity in the rat oral MES screen and the data are presented in Table **6**. A dose of 30mg/kg was employed in this test. All the compounds tested showed protection in all the time points except **5d** and **5m**. All the compounds exhibited activity with no neurotoxicity. The compound **5i** emerged as the most potent compound in the rat oral MES screen.

The MES and scPTZ tests, albeit extremely effective in identifying new antiepileptic drugs that may be useful for the treatment of human generalized tonic-clonic and generalized myoclonic seizures respectively, may miss novel antiepileptic drugs that may be useful for the treatment of therapy resistant partial seizures. Results obtained with levetiracetam in the 6Hz test suggest that it may identify a compound, which is not active by either the MES or scPTZ test and thus may detect active substances that would have been missed by the more traditional identification procedure [23, 24]. In the present study, some selected compounds (**5b** and **5c**) were screened in 6Hz psychomotor seizure model (Table **7**). The compounds **5b** and **5c** showed protection in 50% or more mice at 100mg/kg at 0.25h, 0.5h, 1h, and 1h respectively. The compound **5b** showed promising activity in this psychomotor seizure screen**.** Recent studies completed by the anticonvulsant screening program at NIH, have found that 6Hz seizures appear to be somewhat resistant to phenytoin and other sodium channel blockers.

STRUCTURE-ACTIVITY RELATIONSHIP

The difference in bioactivity of aryl semicarbazones could be related to the substituents at the aryl ring and at the carbimino terminal. First with respect to the aryl substituents the order of potency has been found to be 4-fluoro > 2-bromo equivalent to 3-bromo and 4-chloro > 4-methyl > 4-bromo >3-chloro > 3-methylphenyl semicarbazones.

At the carbimino terminal, there are two substituents that could be varied, one at the carbimino hydrogen end and another at the carbimino aryl / alkyl end. Generally the anticonvulsant activity was greater when the carbimino hydrogen was substituted with methyl group.

At the carbimino aryl end, 2- / 4-position when substituted with electron donating groups, the compounds exhibited anticonvulsant activity in both MES and scPTZ screens. But in the 3-bromophenyl [17] and 4-bromophenyl [16] series, 2-nitro substitution in the carbimino phenyl ring has shown activity in both MES and scPTZ tests exceptionally. At 3-position of the carbimino aryl ring, nitro group was beneficial with respect to 2-bromophenyl (**1e**), 4-chloro-phenyl (**4b**), and 4-fluorophenyl (**5d**) series, whereas 3-amino group was beneficial with respect to 3-bromophenyl (**3b**), 4-chlorophenyl (**4c**), and 4-fluorophenyl (**5h**). Replace-ment of the carbimino aryl group with isatinyl group was generally beneficial with the 2-/ 3-/ 4-halophenyl semi-carbazones. Generally at the carbimino end the order of anticonvulsant activity was methyl or ethyl > phenyl or substituted phenyl > cycloalkyl > heteroaryl.

Table 6. Rat p.o. Identification of some Selected Compounds in the MES Test (30mg/kg)

Compound	Oral administration to rats[a]				
	0.25h	0.5h	1h	2h	4h
5b	1	3	3	1	1
5d	0	1	0	1	2
5i	1	3	3	1	2
5m	0	2	0	0	0
5o	0	2	1	1	1
5u	1	2	0	1	2
5x	1	0	1	1	2
Phenytoin	1	4	3	3	3

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

Table 7. Mice i.p. Identification of some Selected Compounds in the 6Hz Test (100mg/kg)

Compound	0.25h	0.5h	1.0h
5b	3	2	2
5c	0	0	2
Levetiracetam[b]	0	2	4

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

[b] Tested at 30 mg/kg (i.p).

To conclude the present study has yielded a variety of anticonvulsant semicarbazones whose potency was comprehensively discussed. The 4-fluorophenyl semicarbazones emerged as the most potent among all the derivatives being active in different models of seizures like i.p. and oral MES, scPTZ, and psychomotor model (6 Hz) screens.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR-spectra were recorded on a JASCO IR Report 100 spectrometer in KBr. ^{1}H-NMR spectra were recorded on a JEOL Fx 90Q Fourier Transform-NMR spectrometer employing TMS as the internal standard. Elemental analyses were performed on a Perkin Elmer Model 240C analyser. The homogeneity of the compounds was monitored by thin layer chromatography (TLC) on silica-G (Merck) coated glass plates, visualized by iodine vapour.

Synthesis of 2-/ 3- / 4- Substituted Phenyl Urea

The 3-bromo-, 4-chloro-, and 4-fluorophenyl ureas were synthesized according to the procedures reported earlier [17-19]. Similarly the synthesis of 2-bromo, 3-chloro, 3-methyl, and 4- methylphenyl urea was achieved following the above-mentioned procedure. Briefly the 2-bromo, 3-chloro, 3-methyl, and 4- methylaniline was dissolved in 20 ml of glacial acetic acid and 10 ml of water. To this, equimolar amount of sodium cyanate 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 the respective phenyl ureas.

2-Bromophenyl Urea

M.p. 172°C; Yield: 65%; ($C_7H_7N_2OBr$) C, H, N.

3-Chlorophenyl Urea

M.p. 182°C; Yield: 68%; ($C_7H_7N_2OCl$) C, H, N.

3-Methylphenyl Urea

M.p. 156°C; Yield: 77%; ($C_8H_{10}N_2O$) C, H, N.

4-Methylphenyl Urea

M.p. 175°C; Yield: 68%; ($C_8H_{10}N_2O$) C, H, N.

Synthesis of 2-/ 3- / 4- Substituted Phenyl Semicarbazide

The 3-bromo, and 4-chlorophenyl semicarbazides were prepared according to the procedure reported earlier [17, 18]. Following the similar procedure, the 2-bromo, 3-chloro, 3-methyl, 4-methyl and 4-fluorophenyl semicarbazides were prepared by treating equimolar quantities of the phenyl urea and hydrazine hydrate in ethanol under reflux for 24h 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 phenyl semicarbazide obtained was recrystallized from 50ml of 90% alcohol.

2-Bromophenyl Semicarbazide

M.p. 165°C; Yield: 70%; ($C_7H_8N_3OBr$) C, H, N.

3-Chlorophenyl Semicarbazide

M.p. 134°C; Yield: 65%; ($C_7H_8N_3OCl$) C, H, N.

3-Methylphenyl Semicarbazide

M.p. 197°C; Yield: 76%; ($C_8H_{11}N_3O$) C, H, N.

4-Methylphenyl Semicarbazide

M.p. 212°C; Yield: 76%; ($C_8H_{11}N_3O$) C, H, N.

4-Fluorophenyl Semicarbazide

M.p. 185°C; Yield: 76%; ($C_7H_8N_3OF$) C, H, N.

General Method for the Synthesis of 2-/ 3- / 4- Substituted Phenyl Semicarbazones

The 2-/ 3- / 4- substituted phenyl semicarbazones were synthesized following procedures reported earlier [16-18]. To a solution of the required phenyl semicarbazide in 25 ml of water was added 25 ml of ethanol 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 **1-5**. 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, DMSO d_6) spectra of some representative compounds are as follows:

1a: 6.35 (s, 1H, ArNH, D_2O exchangeable), 6.80 (s, 1H, Carbimino H), 7.30–7.70 (m, 8H, ArH), 10.02 (s, 1H, ArOH, D_2O exchangeable), 9.50 (s, 1H, CONH, D_2O exchangeable).

1k: 1.85 (s, 3H, Carbimino CH_3), 2.30 (s, 3H, ArCH3), 6.30 (s, 1H, ArNH, D_2O exchangeable), 7.24–7.60 (m, 8H, ArH), 9.65 (s, 1H, CONH, D_2O exchangeable).

1o: 1.70–1.90 (m, 6H, $2CH_3$), 6.45 (s, 1H, ArNH, D_2O exchangeable), 7.20–7.50 (m, 4H, ArH), 9.50 (s, 1H, CONH, D_2O exchangeable).

2a: 6.40 (s, 1H, ArNH, D_2O exchangeable), 6.70 (s, 1H, Carbimino H), 7.20–7.60 (m, 8H, ArH), 9.55 (s, 1H, CONH, D_2O exchangeable), 10.11 (s, 1H, ArOH, D_2O exchangeable).

2d: 5.25 (s, 2H, $ArNH_2$, D_2O exchangeable), 6.40 (s, 1H, ArNH, D_2O exchangeable), 7.30–7.70 (m, 8H, ArH), 9.60 (s, 1H, CONH, D_2O exchangeable).

2e: 1.32-1.36 (t, 3H, CH_3 of ethyl), 1.82-1.88 (q, 2H, CH_2 of ethyl), 2.20 (s, 3H, Carbimino CH_3), 6.35 (s, 1H, ArNH, D_2O exchangeable), 7.26–7.50 (m, 4H, ArH), 9.55 (s, 1H, CONH, D_2O exchangeable).

3d: 6.50 (s, 1H, ArNH, D_2O exchangeable), 6.60 (s, 1H, Carbimino H), 7.10–7.40 (m, 8H, ArH), 3.30 (s, 3H, $ArOCH_3$), 9.60 (s, 1H, CONH, D_2O exchangeable).

3e: 1.75 (s, 3H, Carbimino CH_3), 5.17 (s, 2H, $ArNH_2$, D_2O exchangeable), 6.40 (s, 1H, ArNH, D_2O exchangeable), 7.24–7.60 (m, 8H, ArH), 9.50 (s, 1H, CONH, D_2O exchangeable).

4b: 6.30 (s, 1H, ArNH, D_2O exchangeable), 6.50 (s, 1H, Carbimino H), 7.30–7.70 (m, 8H, ArH), 9.40 (s, 1H, CONH, D_2O exchangeable).

5a: 6.30 (s, 1H, ArNH, D_2O exchangeable), 6.60 (s, 1H, Carbimino H), 7.20–7.60 (m, 8H, ArH), 9.50 (s, 1H, CONH, D_2O exchangeable).

5g: 1.85 (s, 3H, Carbimino CH_3), 6.25 (s, 1H, ArNH, D_2O exchangeable), 7.24–7.70 (m, 8H, ArH), 9.40 (s, 1H, CONH, D_2O exchangeable), 10.02 (s, 1H, ArOH, D_2O exchangeable).

5l: 6.35 (s, 1H, ArNH, D_2O exchangeable), 7.40–7.80 (m, 14H, ArH), 9.30 (s, 1H, CONH, D_2O exchangeable).

5t: 2.54-2.55 (m, 4H, o-position of cyclohexane ring), 3.26–3.40 (m, 6H, m- and p-positions of cyclohexane ring), 5.90 (s, 1H, ArNH, D_2O exchangeable), 7.21–7.43 (m, 4H, ArH), 8.91 (s, 1H, CONH, D_2O exchangeable).

6d: 2.30 (s, 3H, $ArCH_3$), 6.25 (s, 1H, ArNH, D_2O exchangeable), 6.70 (s, 1H, Carbimino H), 7.20–7.60 (m, 8H, ArH), 9.33 (s, 1H, CONH, D_2O exchangeable).

7e: 2.20 (s, 3H, $ArCH_3$), 3.30 (s, 3H, $ArOCH_3$), 6.35 (s, 1H, ArNH, D_2O exchangeable), 6.60 (s, 1H, Carbimino H), 7.20–7.50 (m, 8H, ArH), 9.40 (s, 1H, CONH, D_2O exchangeable).

7g: 1.85 (s, 3H, Carbimino CH_3), 2.20 (s, 3H, $ArCH_3$), 6.40 (s, 1H, ArNH, D_2O exchangeable), 7.20–7.60 (m, 8H, ArH), 9.30 (s, 1H, CONH, D_2O exchangeable).

Pharmacological Tests

Male albino mice (CF-1 strain, 18-25g) and male albino rats (Sprague-Dawley, 100-150g) were used as experimental animals. The semicarbazone derivatives were suspended in 0.5% methylcellulose /water mixture or in polyethylene glycol (PEG). The anticonvulsant evaluation [25, 26] was established by maximal electroshock seizure, subcutaneous pentylenetetrazole seizure threshold, and neurotoxicity screens. Table **1-5** lists the results obtained from the initial anticonvulsant evaluation compared with the clinically proven antiepileptics like Phenytoin, Phenobarbital, Carbamazepine and valproate. Some compounds of the 4-fluorophenyl semicarbazones were administered orally to rats and examined in MES screen and the data are presented in Table **6**. Two (**5b** and **5c**) compounds were challenged in the 6Hz, 32mA current for 3 seconds to examine antipsychomotor seizure activity in mice.

Received: 07 August, 2005 Revised: 28 September, 2005 Accepted: 29 September, 2005

ACKNOWLEDGEMENTS

This work was supported by the Department of Science and Technology (DST) under the SERC Fast track scheme for young scientists (No. SR./FT/L-84/2003).

REFERENCES

[1] Dimmock, J.R.; Sidhu, K.K.; Thayer, R.S.; Mack, P.; Dutty, M.J.; Reid, R.S.; Quail, J.W. *J. Med. Chem.,* **1993**, *36*, 2243.
[2] Pandeya, S.N.; Aggarwal, N.; Jain, J.S. *Pharmazie*, **1999**, *54*, 300.
[3] Dimmock, J.R.; Sidhu, K.K.; Tumber, S.D.; Basran, S.K.; Chen, M.; Quail, J.W.; Yang, J.; Rozas, I.; Weaver, D.F. *Eur. J. Med. Chem.,* **1995**, *30*, 287.
[4] Pandeya, S.N.; Ponnilavarasan, I.; Pandey, A.; Lakhan, R.; Stables, J.P. *Pharmazie*, **1999**, *54*, 923.
[5] Dimmock, J.R.; Puthucode, R.N.; Smith, J.M.; Hetherington, M.; Quail, J.W.; Pugazhenthi, U.; Lechler, T.; Stables, J.P. *J. Med. Chem.,* **1996**, *39*, 3984.
[6] Dimmock, J.R.; Semple, H.A.; John, S.; Beazely, M.A.; Abrams, G.D. *Pharmazie,* **1999**, *54*, 260.
[7] Dimmock, J.R.; Vashishtha, S.C.; Stables, J.P. *Eur. J. Med. Chem.,* **2000**, *35*, 241.
[8] Pandeya, S.N.; Manjula, H.; Stables, J.P. *Pharmazie,* **2001**,*56*, 121.
[9] Yogeeswari, P.; Thirumurugan, R.; Kavya, R.; Samuel, J.S.; Stables, J.P.; Sriram, D. *Eur. J. Med. Chem.,* **2004**, *39*, 729.
[10] Yogeeswari, P.; Sriram, D.; Pandeya, S.N.; Stables, J.P. *Farmaco,* **2004**, *59*, 609.
[11] 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.
[12] Yogeeswari, P.; Sriram, D.; Thirumurugan, R.; Ragavendran, J.V.; Sudhan, K.; Kuamr, R.; Stables, J. *J. Med. Chem.,* **2005**, *48*, 6202.
[13] Kadaba, P.K. *J. Pharm. Sci.,* **1984**, *73*, 850.
[14] Dimmock, J.R.; Baker, G.B. *Epilepsia,* **1994**, *35*, 648.
[15] Dimmock, J.R.; Puthucode, R.N.; Lo, M.S.; Quail, J.W.; Yang, J.; Stables, J.P. *Pharmazie,* **1996**, *51*, 83.
[16] Pandeya, S.N.; Yogeeswari, P.; Stables, J.P. *Eur. J. Med. Chem.,* **2000**, *35*, 879.
[17] Yogeeswari, P.; Sriram, D.; Brahmandam, A.; Sridharan, I.; Thirumurugan, R.; Stables, J.P. *Med. Chem. Res.,* **2003**, *12*, 57.
[18] Pandeya, S.N.; Mishra, V.; Ponnilavarasan, I.; Stables, J.P. *Pol. J. Pharmacol.,* **2000**, *52*, 283.
[19] Dimmock, J.R.; Vashishtha, S.C.; Stables, J.P. *Pharmazie*, **2000**, *55*, 490.
[20] White, H.S. *Epilepsia,* **2003**, *44*, 2.
[21] White, H.S.; Woodhead, J.H.; Franklin, M.R.; Swinyard, E.A.; Wolf, H.H. In *Antiepileptic drugs*, Levy, R.H.; Mattson, R.H.; Meldrum, B.S. Eds.; Raven Press, Ltd: New York, **1995**; pp. 99-110.
[22] White, H.S.; Woodhead, J.H.; Wilcox, K.S.; Stables, J.P.; Kupferberg, H.J.; Wolf, H.H. In *Antiepileptic drugs*, Levy, R.H.; Mattson, R.H.; Meldrum, B.S.; Perucca, E. Eds.; Lippincott: Philadelphia, **2002**; pp. 36-48.
[23] Loscher, W.; Fassbender, C.P.; Nolting, B. *Epilepsy Res.,* **1991**, *8*, 79.
[24] Piredda, S.G.; Woodhead, J.H.; Swinyard, E.A. *J. Pharmacol. Exp. Ther.,* **1985**, *232*, 741.
[25] Krall, R.L.; Penry, J.K.; White, B.G.; Kupferberg, H.J.; Swinyard, E.A. *Epilepsia*, **1978**, *19*, 409.
[26] Porter, R.J.; Cereghino, J.J.; Gladding, G.D.; Hessie, B.J.; Kupferberg, H.J.; Scoville, B.; White, B.G. *Cleveland Clin. Quart.,* **1984**, *51*, 293.