(Aryloxy)aryl Semicarbazones and Related Compounds: A Novel Class of Anticonvulsant Agents Possessing High Activity in the Maximal Electroshock Screen

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A number of (aryloxy)aryl semicarbazones and related compounds were synthesized and evaluated for anticonvulsant activities. After intraperitoneal injection to mice, the semicarbazones were examined in the maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ), and neurotoxicity (NT) screens. The results indicated that greater protection was obtained in the MES test than the scPTZ screen. Quantitation of approximately one-third of the compounds revealed an average protection index (PI, i.e. TD_{50}/ED_{50}) of approximately 9. After oral administration to rats, a number of compounds displayed significant potencies in the MES screen (ED_{50} of 1−5 mg/kg) accompanied by very high protection indices. In fact over half the compounds had PI figures of greater than 100, and two were in excess of 300. The compounds were essentially inactive in the scPTZ and NT screens after oral administration to rats. Various compounds displayed greater potencies and PI figures in the mouse intraperitoneal and rat oral screens than three reference clinically used drugs. The data generated supported a binding site hypothesis. Quantitative structure−activity relationships indicated a number of physicochemical parameters which contributed to activity in the MES screen. X-ray crystallography of five compounds suggested the importance of certain interatomic distances and bond angles for activity in the mouse and rat MES screens.

Introduction

A previous study revealed that a number of aryl semicarbazones possessed anticonvulsant activity in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screens when administered by the intraperitoneal route to mice.[1] These two test systems have been claimed to detect compounds affording protection to generalized tonic-clonic seizures and generalized absence convulsions respectively.[2] Nevertheless the compounds displayed neurotoxicity when given by this route and the protection indices (PI viz. TD_{50}/ED_{50} where TD_{50} and ED_{50} refer to the doses eliciting neurotoxicity and anticonvulsant activities respectively in 50% of the animals) of 10 representative compounds were low, i.e. in general less than 4. However an oral administration to rats, two interesting features were observed. First, marked activity in the MES screen was noted whereby some of the compounds had ED_{50} figures in the 20−25 mg/kg range while activity in the scPTZ test was virtually abolished. Second, neurotoxicity was diminished, and PI figures of approximately 25 were detected in some of the compounds.[1] A subsequent study of the anticonvulsant activities of a number of related aryl semicarbazones confirmed these general trends.[3]

If the aryl semicarbazones displaying activity in the MES screen interact at a specific binding site, it is likely that the semicarbazono group and the aryl ring align at complementary areas on a macromolecular complex *in vivo*; these areas have been referred to as the hydrogen bonding area and the aryl binding site, respectively.[4] These possible interactions are represented in Figure 1. The principal aim of the present study was to investigate the area around the postulated aryl binding site, which is shown in Figure 1 as the auxiliary binding area. Additional groups placed on the aryl ring could strengthen attachment at the binding site and increase potency, or alternatively, steric interactions, for example, may exert a dystherapeutic effect. From these investigations a clearer picture of the nature of the postulated binding site may emerge. A second goal of this investigation was the preparation of orally active compounds with approximately 10-fold greater potency than the semicarbazones synthesized previously, i.e. they should possess ED_{50} figures in the 2−3 mg/kg range while still retaining favorable PI values. If this objective was realized, structure−activity rela-

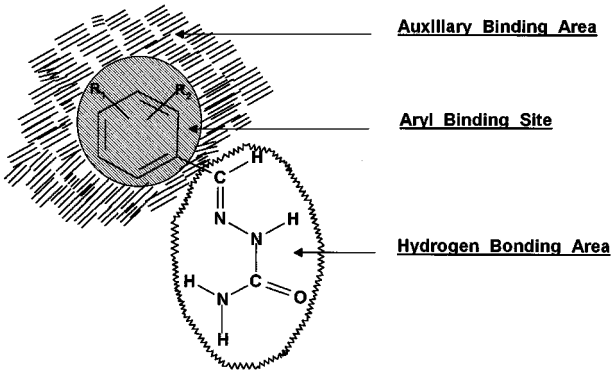

Figure 1. Proposed binding site of aryl semicarbazones.

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tionships in this new group of potent anticonvulsants would be sought using various physicochemical and computational techniques.

Initially the attachment of a second aryl group, designated the distal ring, to the proximal aromatic ring located nearest to the semicarbazono group was considered, i.e. the preparation and anticonvulsant evaluation of 4-phenylbenzaldehyde semicarbazone. This compound could increase the van der Waals bonding at a binding site and increase potency. However it displayed no bioactivity in the MES, scPTZ, and neurotoxicity screens when doses up to and including 300 mg/kg were given intraperitoneally to mice.[3] Nevertheless oral administration to rats revealed that neurotoxicity was absent at a dose of 500 mg/kg and activity in the MES screen was displayed, although the results were ambiguous, i.e. 0/8, 2/8, 3/8, and 0/16 animals were protected using doses of 20, 40, 80, and 160 mg/kg respectively. No oral activity in rats was noted in the scPTZ screen at a dose of 250 mg/kg. The conclusion reached was that the presence of a distal aromatic ring did not induce neurotoxicity and MES activity, while weak, was retained when the compound was administered orally. Thus the realignment of the distal ring at a distance from the proximal ring greater than is found with this compound was considered, i.e. the placement of a spacer group between the two aryl rings.

These considerations led to the decision to synthesize the three structural isomers **1**, **2**, and **58**, whereby a phenoxy group was placed in different locations of the proximal aryl ring, i.e. an oxygen atom was used as the spacer group. The structures of the compounds may be ascertained from Scheme 1 and Table 1. While the ortho (**58**) and meta (**1**) isomers were either inactive or demonstrated weak anticonvulsant properties in the mouse and rat screens (Table 1), the para analog **2** afforded good protection in both tests. From this observation, molecular modification of **2** proceeded in several directions with a view to defining more clearly the nature of the binding site for these compounds.

It is conceivable that while the phenoxy groups can align at different places on the auxiliary binding site, the presence of a distal ring in the location "para" to the proximal aromatic ring is preferable. In other words, favorable interaction of the distal ring and an area designated the distal binding site may occur (Figure 2). Early in this study, the marked activities of **5** and **23** were observed; hence the aryl substitution pattern in this series was developed using principally halogens and in particular fluorine (**3**−**20**) as well as alkyl groups (**21**−**38**). These aryl substituents were also used in other series of compounds in order that comparisons of their bioactivities could be made with these semicarbazones. The preparation and bioevaluation of the semicarbazones **3**−**48** may permit discernment of the structural and electronic requirements at the distal binding site. In addition, replacement of the methine proton by small alkyl groups leading to **49**−**57** was considered since the alkyl groups could interact at a hydrophobic pocket by forming van der Waals bonds, thereby assisting alignment at the binding site and leading to an increase in anticonvulsant activity. Alternatively unfavorable steric interactions between the alkyl groups in **49**−**57** and a place on the binding site could occur, resulting in a lowering of potency.

Table 1 reveals that the semicarbazone **58** was inactive in the mouse intraperitoneal screen and afforded only weak protection when given orally to rats in the MES test. Compounds **59**−**66** were proposed since reduction or abolition of anticonvulsant properties in these analogs would confirm the limitations as to the places on the auxiliary binding site at which interactions with the substituted aryl ring occurs. The semicarbazones prepared previously had an oxygen atom between the two aryl rings. Compounds **67**−**72** were designed that incorporated different spacer groups which could affect not only the distances between the two aryl rings but also their orientation in relation to each other. In other words, a lack of coplanarity between the proximal and distal rings may vary among the compounds **67**−**72**, and hence the biodata generated would afford some insight into the structure of the distal binding site. Likewise the preparation of **73**−**83** was considered whereby isosteric replacement of the oxygen atom of representative semicarbazones among the compounds **2**−**57** by sulfur was planned. In order to gain an improved understanding of the steric and electronic requirements of the hydrogen bonding area, the decision was made to prepare compounds **84**−**92** whose anticonvulsant activity could be compared to certain oxo analogs in the semicarbazones **2**−**48** and **73**−**83**. The R^1 groups in **84**−**92** would have sizes and hydrogen-bonding capabilities different than the oxo and amino groups found in the analogous semicarbazones. Furthermore, the question of whether replacement of the phenyl ring of **2** by β-naphthyl and 4-pyridyl groups producing compounds **93** and **94** would lead to compounds which would align at the distal binding site was posited. Finally, the possibility exists that by having two semicarbazono and two phenoxyaryl groups in one molecule a significant increase in anticonvulsant properties may be obtained since two rather than one parts of the molecule may align at the binding site. On the other hand, should **95** display little or no anticonvulsant activity, the result may indicate steric impendance at the binding site, i.e. the molecule has too large a group at the 4′-position of a phenoxyaryl group to be accommodated.

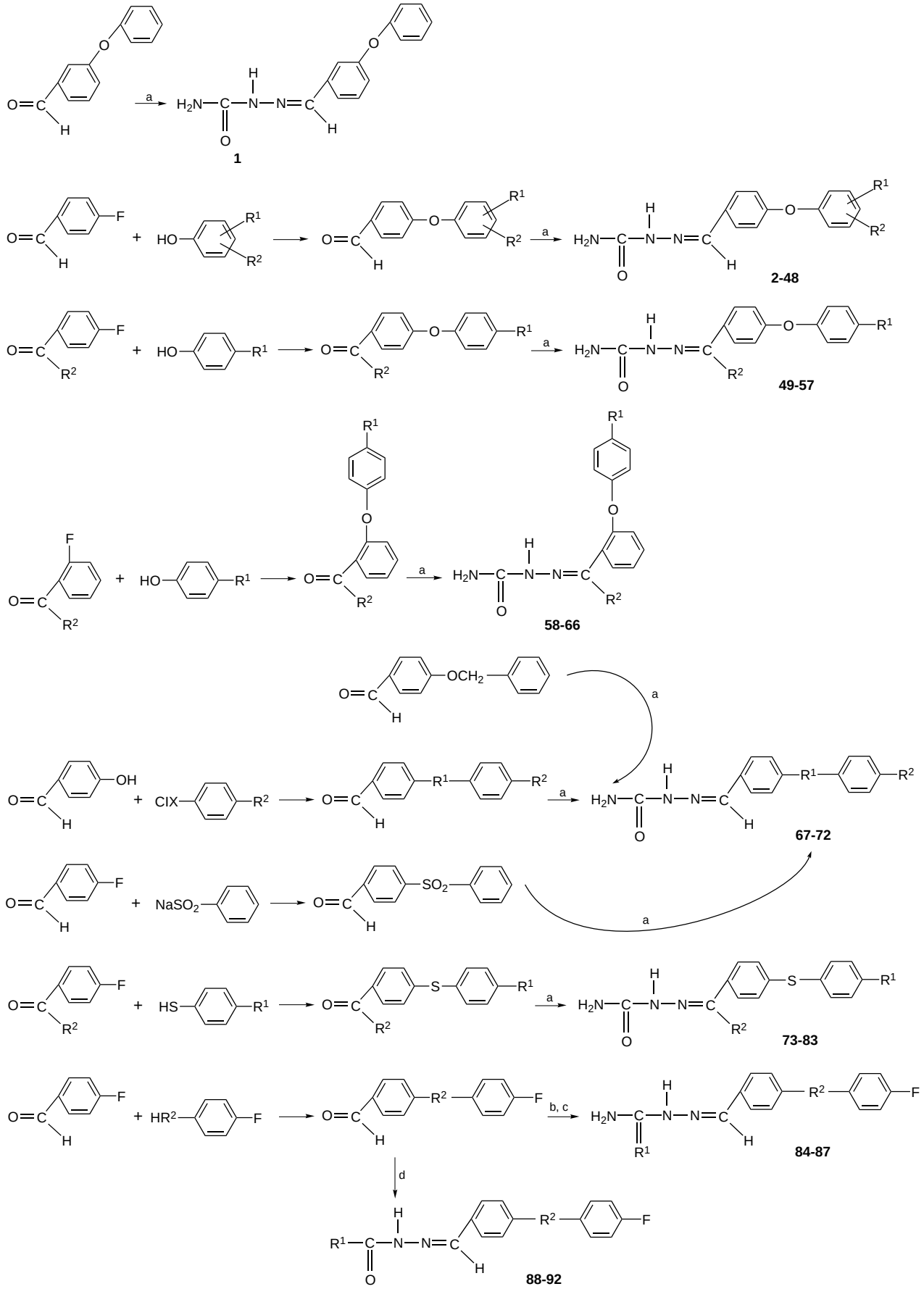
In summary, the principal aim of this study was to prepare a number of (aryloxy)aryl semicarbazones and related compounds for evaluation as candidate anticonvulsants with a view to understanding their chemical features which contribute to interactions at a binding site.

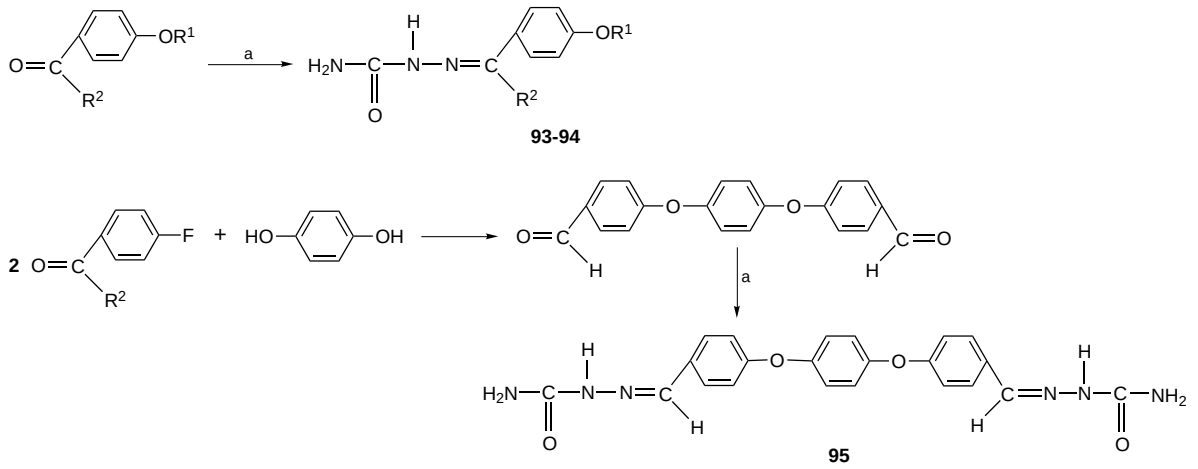
Results

The compounds were synthesized using the methodologies outlined in Scheme 1.

All of the compounds were examined in the MES, scPTZ, and NT screens after intraperitoneal injection into mice and these data are presented in Table 1. Quantitation of some of the compounds was undertaken, and the results are summarized in Table 2. After oral administration to rats, various semicarbazones and related compounds were evaluated for activity principally in the MES screen, and the results are given in Tables 1 and 3. X-ray crystallography of **1**, **2**, **5**, **23**, and **73** was undertaken in order to obtain further information pertaining to the structural features of a putative binding site.

Scheme 1. Preparation of (Aryloxy)aryl Semicarbazones and Related Compounds **1**–**95**[a]





[a] a = semicarbazide, b = thiosemicarbazide, c = aminoguanidine, d = various hydrazides possessing the general formula $RCONHNH_2$, X = CO or SO_2.

Discussion

A major aim of this study was to evaluate the viability of the binding site hypothesis (Figure 2). The method followed involved first the synthesis and anticonvulsant examination of different series of aryloxyaryl semicarbazones and related compounds. Second, an evaluation was made of the data using structure−activity relationships (from both a qualitative and quantitative viewpoint) and X-ray crystallography.

The syntheses of compounds **1**−**95** were accomplished successfully. The anticonvulsant examination of these compounds in the mouse intraperitoneal screen will be reviewed initially; subsequently the evaluation of most of these compounds in the rat oral test will be discussed. The data in Table 1 indicate the evaluation of all of these molecules in the MES, scPTZ, and NT screens after intraperitoneal injection in mice using doses of 30, 100, and 300 mg/kg. The following observations may be made. First, in general, the compounds demonstrated a selective protection in the MES screen rather than the scPTZ test which may be noted by comparing not only the percentage of compounds which were active in both screens but the fact that lower doses were required to afford protection. Thus the percentage of compounds which were active at minimum doses of 30, 100, and 300 mg/kg or were inactive were 56, 18, 15, and 11, respectively, in the MES screen whereas in the scPTZ test, the comparable figures were 16, 18, 25 and 41 respectively. Second, the percentage of compounds causing neurological deficit at minimum doses of 30, 100, and 300 mg/kg or were not neurotoxic at the maximum dose utilized were 5, 30, 35, and 30 respectively. Thus in the 30−100 mg/kg dose range, while 65% of the compounds did not display neurotoxicity, 74% demonstrated activity in the MES screen which suggested that favorable PI values may be displayed in this group of compounds. Third, a comparison of the bioactivity found in compounds **2**−**48** with the groups of analogs in which four or more compounds were present was made in order to discern the general effects of structural modifications of the series comprising the semicarbazones **2**−**48** on anticonvulsant activity. The percentage of compounds in this series which displayed activity in the MES, scPTZ, and NT screens was 96, 58, and 75, respectively. The comparable figures for the analogs were as follows: 100, 78, 89 (**49**−**57**); 33, 22, 56 (**58**−**66**); 83, 33, 17 (**67**−**72**); 100, 82, 82 (**73**−**83**); 100, 100, 100 (**84**−**87**); and 80, 80, 100 (**88**−**92**). These figures indicate that, in the MES screen, the percentage of active compounds was similar to **2**−**48** except in the case of the group of semicarbazones **58**−**66**. The data for the scPTZ test showed that in comparison to **2**−**48**, activity was greater in the series **49**−**57**, **73**−**83**, **84**−**87**, and **88**−**92** and lower in the analogs **58**−**66** and **67**−**72**. In contrast to **2**−**48**, neurotoxicity was more widely detected in the series **49**−**57**, **84**−**87**, and **88**−**92**; similar in **73**−**83**; and lower in **58**−**66** and **67**−**72**. Thus, in general, activity was retained by molecular modification of **2**−**48** except for **58**−**66**, suggesting that placement of aryloxy groups in the para position of the proximal ring is preferable to the ortho position.

Quantitative evaluations of the anticonvulsant efficacy and neurotoxicity of approximately one-third of the compounds were undertaken, and the results are presented in Table 2. Some of the features of interest are as follows. First, the selective efficacy of these anticonvulsants in reducing seizures in the MES rather than the scPTZ screen was confirmed. Thus all of the compounds displayed activity in the MES test, whereas ED_{50} figures were obtained in only 38% of these analogs for the scPTZ screen. In the remaining cases, the dose was elevated substantially above the ED_{50} figure in the MES screen. Furthermore, a comparison of the PI values in 12 cases where ED_{50} figures were available in both the MES and scPTZ screens revealed that higher figures were always obtained from MES screening. In fact the average PI value of the MES screen was 5.2 times the ED_{50} figures generated in the scPTZ test. The PI values of **32** and **82** which are approximately 22 and 21, respectively, are particularly noteworthy. Subsequent discussion will therefore revolve around the MES screening. Second, a comparison was made with the three reference drugs phenytoin, carbamazepine, and valproate in terms of potency and PI values. The ED_{50} figures in the mouse MES screen for compounds **18**, **25**, **52**, **57**, and **81** were lower than for phenytoin and carbamazepine; in addition those of **35**, **49**, **53**, **56**, and **82** were less than that of carbamazepine. Furthermore, the percentage of compounds which had PI values greater than phenytoin and carbamazepine were 63 and 78, respectively. All of the compounds listed in Table 2 were considerably more potent and had PI values higher than that of valproate. Hence a number of these (aryloxy)aryl semicarbazones and related compounds

Table 1. Aryl Substituents, Physical Data, and Anticonvulsant Evaluation after Intraperitoneal Injection into Mice and Oral Administration to Rats of the Compounds **1**−**95**

					intraperitoneal injection in mice[a]						oral administration to rats:[b] MES screen					
	aryl substituents				MES screen		scPTZ screen		toxicity screen							
compd	R^1	R^2	mp (°C)	yield (%)	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	dose (mg/kg)	0.25 h	0.5 h	1 h	2 h	4 h
1	---	---	224−225	70	−	300	−	−	−	−	50	−	−	−	−	−
2	H	H	224−225	60	100	300	−	−	−	−	50	−	3	4	4	4
3	2-F	H	228−230	42	100	300	300	−	−	−	50	2	4	4	4	4
4	3-F	H	209	42	30	300	100	−	300	300	50	4	4	4	4	4
5	4-F	H	233−234	65	30	100	−	−	−	−	50	2	4	4	4	4
6	2-F	3-F	225	50	100	100	300	−	−	−	12.5	−	3	4	4	4
7	2-F	4-F	229−230	42	30	30	100	−	−	−	50	3	4	4	4	4
8	2-F	5-F	230	65	100	300	100	−	300	300	12.5	−	1	1	4	1
9	2-F	6-F	232	27	30	30	300	300	300	300	12.5	−	2	4	4	4
10	3-F	4-F	212−213	86	100	30	30	300	−	−	50	2	4	4	4	4
11	3-F	5-F	177	46	30	30	−	−	300	300	12.5	1	3	4	4	4
12	2-Cl	H	207−208	42	30	30	100	300	300	−	50	3	4	4	4	4
13	3-Cl	H	185−186	35	30	100	30	300	300	100	50	−	4	4	4	4
14	4-Cl	H	225−226	40	30	30	30	−	300	30	50	4	4	4	4	4
15	3-Cl	4-Cl	216−217	45	300	30	−	−	−	300	50	−	2	4	4	4
16	4-Br	H	225−226	60	30	30	−	−	300	30	50	1	4	4	4	4
17	4-I	H	221−222	71	30	30	100	300	300	100	50	3	4	4	4	4
18	2-F	4-Cl	225−226	60	30	30	−	−	100	30	12.5	2	4	4	4	4
19	2-Cl	4-F	209−210	59	30	30	−	−	100	300	50	4	4	4	4	4
20	2-Br	4-F	203−205	40	100	100	300	−	300	300	50	4	4	4	4	4
21	2-CH_3	H	205	25	30	100	100	100	300	300	12.5	−	4	3	4	4
22	3-CH_3	H	205−206	35	30	100	−	−	100	300	12.5	−	4	4	3	2
23	4-CH_3	H	219−221	50	30	100	−	−	−	−	50	3	4	4	4	4
24	2-CH_3	3-CH_3	222−223	52	−	100	−	−	−	−	12.5	−	−	1	−	1
25	2-CH_3	4-CH_3	193−195	63	30	30	30	30	300	100	12.5	1	4	4	4	4
26	2-CH_3	5-CH_3	210−211	70	100	100	30	300	−	300	12.5	1	−	1	−	−
27	2-CH_3	6-CH_3	190	25	30	100	30	100	300	300	30	1	4	4	4	4
28	3-CH_3	4-CH_3	216−218	60	100	30	300	−	−	300	12.5	−	2	4	4	4
29	3-CH_3	5-CH_3	209−210	62	30	300	300	−	−	−	12.5	−	4	3	2	−
30	4-C_2H_5	H	210	40	30	30	300	−	300	100	12.5	−	2	4	4	4
31	2-$C_3H_7{}^n$	H	175−177	48	100	30	−	−	300	−	12.5	3	3	4	4	4
32	4-$C_3H_7{}^n$	H	215	53	100	100	300	−	−	300	12.5	−	1	2	4	2
33	4-$C_4H_9{}^n$	H	215	63	300	100	−	−	−	300	12.5	−	−	−	1	2
34	4-$C_4H_9{}^s$	H	192−193	38	100	30	−	100	300	100	12.5	−	2	2	3	4
35	4-$C_4H_9{}^t$	H	200−202	48	100	30	−	100	100	100	12.5	−	−	4	4	4
36	4-$C_5H_{11}{}^t$	H	198−200	61	300	3	−	−	−	−	15	−	−	2	3	4
37	4-$C_8H_{17}{}^n$	H	218−220	40	−	300	−	−	−	−	x	x	x	x	x	x
38	4-$C_8H_{17}{}^t$	H	190	30	−	−	−	−	−	300	x	x	x	x	x	x
39	2-CH_3	4-Cl	196−197	60	30	30	30	30	300	100	12.5	−	3	4	4	4
40	2-CH_3	4-I	156−157	41	30	30	−	−	300	100	12.5	2	4	4	4	4
41	3-CH_3	4-F	224	63	30	30	−	−	300	−	12.5	2	4	4	4	4
42	3-CH_3	4-Cl	220	58	30	30	300	−	300	100	12.5	1	4	4	4	4
43	4-C_6H_5	H	280	72	−	300	−	300	−	300	12.5	−	−	−	3	1
44	4-OCH_3	H	218−220	60	100	100	−	−	−	300	50	−	4	4	4	4
45	4-$OC_4H_9{}^n$	H	203	35	300	100	300	300	300	300	12.5	−	−	−	−	2
46	4-$OC_7H_{15}{}^n$	H	204−206	20	−	−	−	−	300	−	x	x	x	x	x	x
47	4-OC_6H_5	H	209−210	55	−	300	−	−	−	−	50	−	−	−	1	1
48	4-CN	H	218−220	40	30	30	30	30	300	100	12.5	2	4	4	4	4
49	H	CH_3	169−171	60	30	100	−	−	100	100	30	4	4	4	4	4
50	H	C_2H_5	154−156	58	30	100	−	−	100	100	30	1	4	3	3	−
51	F	CH_3	182−184	74	30	30	100	−	300	100	12.5	−	4	4	4	4
52	F	C_2H_5	170−172	72	30	30	100	−	300	100	12.5	−	2	4	4	4
53	Cl	CH_3	192−194	60	30	30	−	30	30	100	30	3	4	4	4	4
54	Cl	C_2H_5	186−188	38	30	−	300	−	300	100	30	−	1	4	4	4
55	Br	CH_3	195−197	30	30	30	300	−	300	100	12.5	1	3	4	4	4
56	Br	C_2H_5	184−186	38	30	30	100	−	300	100	12.5	−	2	4	4	4
57	CH_3	CH_3	205	62	30	100	30	−	−	−	12.5	−	1	2	4	4
58	H	H	198−199	40	−	−	−	−	−	−	50	−	−	2	1	1
59	H	CH_3	136−138	14	300	−	300	−	300	−	x	x	x	x	x	x
60	F	H	210−212	48	−	−	−	−	−	−	30	−	−	1	2	1
61	F	CH_3	154−157	27	−	−	−	−	−	−	30	1	1	3	3	2
62	F	C_2H_5	156−158	55	−	−	−	−	−	300	12.5	−	−	−	−	−
63	Cl	CH_3	167−169	32	300	300	300	300	300	300	x	x	x	x	x	x
64	Cl	C_2H_5	136−138	15	300	300	−	−	−	−	x	x	x	x	x	x
65	Br	CH_3	183−186	28	−	−	−	−	300	−	x	x	x	x	x	x
66	Br	C_2H_5	155−157	5	−	−	−	−	−	300	x	x	x	x	x	x
67	OCH_2	H	212−213	52	300	300	−	100	−	−	12.5	−	−	1	1	−
68	OCO	H	237−238	70	−	300	−	−	−	−	12.5	−	−	−	−	−
69	OCO	Cl	245−246	80	−	300	−	−	−	−	12.5	1	−	1	−	2
70	SO_2	H	254	40	−	300	−	−	−	−	x	x	x	x	x	x
71	OSO_2	H	146	40	30	30	30	−	300	300	12.5	1	2	2	4	3
72	OSO_2	CH_3	205−207	70	−	−	−	−	−	−	x	x	x	x	x	x

Table 1 (Continued)

					intraperitoneal injection in mice[a]						oral administration to rats:[b] MES screen					
	aryl substituents			yield	MES scrren		scPTZ screen		toxicity screen		dose					
compd	R^1	R^2	mp (°C)	(%)	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	(mg/kg)	0.25 h	0.5 h	1 h	2 h	4 h
73	H	H	226−227	40	30	30	−	−	−	300	50	−	4	4	4	4
74	H	CH_3	208−210	60	100	100	300	−	−	−	30	−	4	4	4	4
75	H	C_2H_5	131−133	16	30	30	100	100	100	100	30	−	3	4	3	4
76	F	H	230−231	52	30	30	30	−	300	100	12.5	1	3	4	4	4
77	F	CH_3	204−207	91	100	30	−	300	300	300	30	3	4	4	4	4
78	F	C_2H_5	150−152	18	30	100	−	−	100	100	30	−	−	2	3	3
79	Cl	H	216	40	100	30	300	−	−	100	50	1	4	4	4	4
80	Br	H	212−213	30	100	30	−	300	−	300	12.5	−	1	3	4	4
81	Br	CH_3	214−216	46	100	30	300	−	−	300	12.5	1	3	4	4	4
82	CH_3	H	225−227	32	30	30	100	100	300	100	12.5	−	−	4	4	4
83	CH_3	CH_3	222−224	60	100	100	100	−	−	−	12.5	−	−	−	3	4
84	S	O	156−158	56	30	30	30	30	100	30	12.5	−	2	2	3	1
85	S	S	171−172	62	100	100	100	100	−	100	12.5	−	1	2	1	1
86	NH	O	181−183	50	300	30	30	−	100	100	12.5	−	−	−	1	2
87	NH	S	172−173	40	300	−	30	30	100	100	12.5	−	−	−	1	−
88	H	O	176−178	60	300	300	−	300	−	300	x	x	x	x	x	x
89	H	S	146−148	80	100	100	−	300	−	300	30	1	−	−	−	1
90	CH_3	O	160	83	30	30	100	100	100	100	12.5	1	4	2	2	1
91	H_2NNH	O	220	80	300	100	−	300	−	300	30	−	−	−	−	−
92	H_2NCO	O	253	75	−	−	−	−	300	300	x	x	x	x	x	x
93	$C_{10}H_7$[c]	H	240−242	61	100	100	−	300	−	−	12.5	1	−	3	4	4
94	C_5H_4N[d]	H	300	15	−	300	−	−	−	−	12.5	−	−	−	−	2
95	---	---	342−344	50	−	−	−	−	−	−	x	x	x	x	x	x
phenytoin					30	30	−	−	100	100	x	x	x	x	x	x
carbamazepine					30	100	100	300	100	300	x	x	x	x	x	x
valproic acid					−	−	300	−	−	−	x	x	x	x	x	x

[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 lines − indicate an absence of anticonvulsant activity and neurotoxicity at the maximum dose administered (300 mg/kg). [b] The figures in the screen indicate the number of rats out of four which were protected. The line − means that no activity was demonstrated and the designation × indicates that the compound was not screened. [c] β-Naphthyl group. [d] 4-Pyridinyl group.

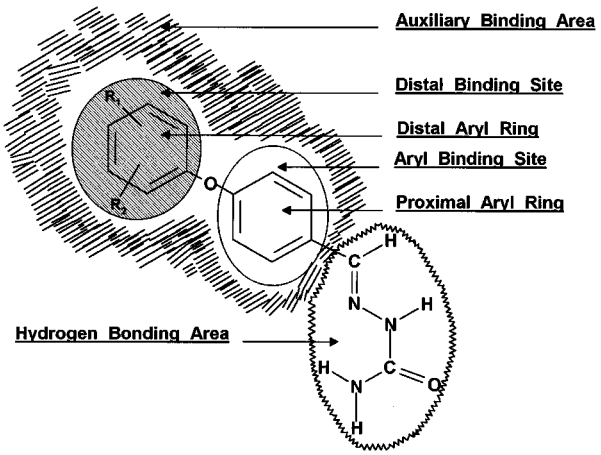


Figure 2. Proposed binding site of (aryloxy)aryl semicarbazones.

compare favorably with these three reference drugs. Third, with the exception of the data for **71**, the compounds listed in Table 2 are found in three series of compounds, namely **2**−**48**, **49**−**57**, and **73**−**83**. Since the substituents in the aryl ring were not constant in each of these three series, a strict comparison between the potencies and PI values cannot be made. However the following general observations may be of value in subsequent drug design. The average ED_{50} figures in the MES screen for the compounds in series **2**−**48**, **49**−**57**, and **73**−**83** were 15.90, 8.90, and 13.64 mg/kg, respectively, i.e. the highest potency was found in series **49**−**57**. It is conceivable therefore that replacement of the methine proton by alkyl groups may indicate a hydrophobic bonding area on the binding site. However the average PI values for the compounds in series **2**−**48**, **49**−**57** (based on seven of the eight compounds for which both ED_{50} and TD_{50} figures were available), and **73**−**83** were 8.95, 7.80, and 9.85, respectively, indicating that neurotoxicity was lower in series **73**−**83**. The data recorded in Table 2 do not conflict with the hypothesis that these compounds align at the binding site represented in Figure 2.

In order to evaluate the effects of different substituents in the distal aryl ring on anticonvulsant activity and neurotoxicity, various linear and semilogarithmic plots were made. The relatively few ED_{50} figures in the scPTZ test precluded their consideration; hence comments will be confined to activities in the MES screen. The physicochemical constants chosen reflected the electronic (σ,σ*), hydrophobic (π), steric (MR, i.e. molar refractivity), and topological (SA, i.e. surface area) characteristics of the aryl substituents. A correlation coefficient of 0.8 was chosen arbitrarily as indicating a relationship between the physicochemical constants and bioactivity, and when observed, the specific *r* values are indicated in the Experimental Section.

Plots were made between the σ,σ*, π, MR, and SA constants of the aryl substituents in the distal ring against the MES ED_{50} figures of (i) all members of series **2**−**48** listed in Table 2; (ii) **49**, **51**, **53**, **55**, and **57**; (iii) **52**, **54**, and **56**; and (iv) **73**, **76**, **79, 80**, and **82**. In addition, in order to obtain some insight into the importance of the size and shape of the group attached to the azomethine carbon atom and also at the para position of the distal aryl ring, the ED_{50} figures of (v) **5, 51**, and **52** and (vi) **5**, **23**, **30**, **32**, **34**, and **35** were plotted against the MR and SA values.

Table 2. Evaluation of Selected Compounds in the MES, scPTZ, and Neurotoxicity Screens after Intraperitoneal Injection in Mice

	MES screen			scPTZ screen			neurotoxicity screen			PI[a]	
compd	*t* (h)	ED_{50} (mg/kg) (95% CI)	slope (SE)	*t* (h)	ED_{50} (mg/kg) (95% CI)	slope (SE)	*t* (h)	TD_{50} (mg/kg) (95% CI)	slope (SE)	MES	scPTZ
3	0.5	20.7 (18.7−22.1)	18.6 (5.63)	0.5	>220 –	– –	2	170 (147−192)	12.4 (3.80)	8.22	–
5	1	12.9 (10.5−17.1)	8.28 (3.00)	1	>54 –	– –	1	108 (71.5−158)	3.69 (0.96)	8.40	–
6	1	45.8 (41.4−52.2)	15.5 (5.71)	1	>350 –	– –	2	293 (210−379)	5.78 (1.77)	6.39	–
7	0.25	11.4 (6.68−19.2)	2.78 (0.86)	0.25	57.9 (30.1−94.0)	1.70 (0.54)	1	96.8 (77.6−114)	11.5 (4.08)	8.61	1.67
9	2	11.3 (8.31−12.9)	10.9 (4.27)	2	>200 –	– –	2	125 (81.1−175)	3.92 (1.10)	11.1	–
10	1	14.5 (9.53−18.9)	4.62 (1.35)	0.5	72.8 (49.0−99.1)	4.27 (1.34)	2	94.8 (59.9−156)	3.17 (1.09)	6.55	1.30
11	0.5	12.3 (8.24−18.4)	3.86 (1.11)	0.5	>100 –	– –	1	68.8 (64.5−72.7)	35.0 (11.9)	5.58	–
13	0.5	27.7 (20.4−36.1)	6.01 (2.08)	0.5	41.2 (27.0−56.7)	3.53 (0.91)	2	64.5 (42.0−84.7)	4.54 (1.36)	2.33	1.57
18	2	3.31 (2.23−4.17)	3.55 (1.00)	2	>45 –	– –	1	36.3 (32.1−40.0)	13.3 (4.31)	11.0	–
19	1	13.1 (8.70−20.1)	3.12 (1.03)	1	>68 –	– –	1	62.5 (55.6−67.9)	15.5 (4.84)	4.76	–
23	1	14.7 (10.4−19.2)	5.59 (1.91)	1	88.6 (45.5−174)	1.87 (0.57)	2	204 (132−271)	4.29 (1.31)	13.9	2.30
25	0.5	4.60 (3.27−5.75)	6.22 (1.78)	0.25	33.6 (21.4−57.7)	2.80 (1.02)	1	37.0 (30.7−45.7)	11.9 (4.76)	8.04	1.10
26	1	34.7 (27.1−43.0)	7.29 (2.28)	0.25	>350 –	– –	2	356 (242−547)	4.04 (1.52)	10.3	–
30	2	10.3 (8.90−11.4)	15.8 (4.90)	2	>100 –	– –	2	34.0 (20.7−51.6)	2.75 (0.75)	3.32	–
32	1	11.0 (9.27−12.7)	10.3 (3.12)	1	79.6 (44.2−139)	2.16 (0.65)	4	243 (172−305)	6.02 (2.04)	22.0	3.05
34	4	13.4 (10.4−16.3)	6.95 (2.05)	1	86.9 (71.5−109)	11.4 (4.49)	4	131 (111−159)	6.47 (1.70)	9.83	1.51
35	4	8.87 (7.70−9.96)	13.1 (3.83)	4	>150 –	– –	4	106 (85.1−143)	6.31 (1.98)	11.9	–
49	0.25	9.08 (6.45−11.3)	6.21 (1.91)	0.25	43.3 (18.4−112)	1.54 (0.57)	1	73.5 (64.3−86.4)	10.5 (3.08)	8.09	1.70
51	1	11.6 (11.0−12.5)	22.7 (9.34)	0.25	>80 –	– –	2	60.7 (58.9−63.8)	45.2 (14.5)	5.22	–
52	1	5.46 (4.57−6.46)	11.6 (3.74)	2	12.8 (8.25−18.6)	3.34 (1.16)	2	35.3 (25.0−43.4)	6.78 (2.05)	6.45	2.75
53	2	9.14 (7.42−11.1)	8.17 (2.06)	2	34.4 (24.2−48.2)	4.38 (1.45)	2	76.5 (68.9−92.5)	10.5 (3.10)	8.37	2.23
54	4	11.1 (10.4−12.6)	20.3 (6.83)	4	>70 –	– –	2	<100[b]	–	<9.02	–
55	2	12.5 (9.47−15.2)	4.76 (1.34)	2	>110 –	– –	2	104 (100−113)	26.9 (8.99)	8.37	–
56	4	6.71 (5.56−7.98)	6.73 (2.39)	4	>75 –	– –	4	52.5 (45.0−63.7)	8.47 (2.46)	7.82	–
57	1	5.62 (3.67−8.30)	3.68 (1.06)	1	18.7 (12.6−31.1)	4.26 (1.47)	1	57.9 (43.9−75.3)	6.43 (2.23)	10.3	3.09
71	0.5	25.3 (21.5−29.9)	9.52 (3.00)	0.5	>100 –	– –	1	113 (103−123)	17.4 (5.73)	4.47	–
73	1	15.6 (10.5−20.6)	4.50 (1.36)	1	>46 –	– –	2	181 (123−251)	4.59 (1.27)	11.6	–
76	1	12.4 (9.25−16.1)	6.37 (1.92)	1	>120 –	– –	2	88.0 (83.3−94.9)	24.0 (6.85)	7.11	–
79	1	16.2 (14.6−17.6)	23.2 (8.59)	1	>120 –	– –	2	53.2 (41.4−72.5)	5.90 (1.89)	3.28	–
80	2	24.4 (18.5−30.9)	5.92 (1.72)	2	>200 –	– –	2	123 (102−150)	6.92 (2.10)	5.03	–
81	1	3.82 (2.91−4.84)	5.66 (1.73)	0.5	41.9 (34.6−50.9)	7.72 (2.56)	1	43.2 (32.5−58.9)	6.26 (1.80)	11.3	1.03
82	1	9.46 (6.35−13.0)	3.68 (0.99)	1	>300 –	– –	4	197 (174−227)	12.8 (3.96)	20.8	–
phenytoin	1	6.32 (5.44−7.23)	11.2 (3.52)	1	>50 –	– –	0.5	41.2 (36.9−46.1)	14.4 (4.82)	6.52	–
carbamazepine	0.25	9.85 (8.77−10.7)	20.8 (7.15)	0.25	>50 –	– –	0.25	47.8 (39.2−59.2)	7.98 (2.37)	4.85	–
valproate	0.25	287 (237−359)	7.31 (2.48)	0.25	209 (176−249)	8.51 (2.69)	0.25	483 (412−571)	12.3 (4.01)	1.68	2.31

[a] PI indicates the protection index, i.e. TD_{50}/ED_{50}. [b] Toxicity was displayed in 0/8, 3/8, and 8/8 mice using doses of 50, 70, and 100 mg/kg, respectively.

Table 3. Evaluation of Selected Compounds in the MES and Neurotoxicity Tests after Oral Administration to Rats

	MES screen					neurotoxicity screen					
compd	*t*	ED_{50}	95% CI	slope	SE	*t*	TD_{50}	95% CI	slope	SE	PI[a] (MES)
5	2	1.59	1.01−2.25	3.17	0.84	0.25−24[b]	>500	−	−	−	>315
6	4	6.15	3.69−9.17	2.55	0.69	−	−	−	−	−	−
8	2	11.4	7.61−15.8	4.12	1.32	−	−	−	−	−	−
9	4	5.53	3.18−8.75	2.44	0.66	0.25−24	>500	−	−	−	>90
10	4	2.37	1.54−3.62	3.18	0.81	0.25−24	>500	−	−	−	>210
18	4	1.13	0.71−2.01	2.66	0.95	2	>90	−	−	−	>79
21	2	5.65	3.79−7.81	3.65	0.98	0.25−24	>500	−	−	−	>88
22	1	3.07	2.58−3.94	7.11	2.29	0.25−24	>500	−	−	−	>163
23	2	3.43	2.28−4.73	4.12	1.32	0.25−24	>500	−	−	−	>146
30	6	6.48	2.97−15.5	1.98	0.75	−	−	−	−	−	−
32	2	2.63	1.69−3.93	3.21	0.82	0.25−24	>500	−	−	−	>190
34	4	3.21	2.25−4.64	3.58	1.02	0.25−24	>322	−	−	−	>100
35	4	1.68	1.15−2.44	4.44	1.28	0.25−24	>500	−	−	−	>297
45	4	45.8	19.5−316	1.33	0.52	*c*	>100	−	−	−	>2.18
49	4	9.73	6.44−14.1	3.84	1.30	−	−	−	−	−	−
50	0.5	23.1	14.3−36.6	3.14	0.92	−	−	−	−	−	−
51	2	3.37	2.37−4.72	5.74	1.80	2	109	80.3−178	4.82	1.82	32.3
52	2	4.25	2.89−5.97	3.67	1.04	4	>72	−	−	−	>16.9
53	4	2.92	2.20−3.46	5.77	1.60	4	<500[d]	−	−	−	−
54	2	2.89	1.57−5.29	2.04	0.59	0.25−24	>500	−	−	−	>173
55	4	1.52	0.99−2.30	3.60	1.02	0.25−24	>500	−	−	−	>328
56	4	4.39	2.67−5.83	4.21	1.28	−	−	−	−	−	−
61	2	43.4	25.1−66.3	2.29	0.57	−	−	−	−	−	−
73	4	4.29	3.20−5.24	6.02	2.00	0.25−24	>496	−	−	−	>116
74	1	16.6	13.7−18.9	11.8	4.49	−	−	−	−	−	−
75	2	18.6	14.2−25.0	5.24	1.67	−	−	−	−	−	−
76	2	4.98	3.24−7.01	3.92	1.10	4	183	101−338	2.49	0.86	36.8
77	2	9.11	6.19−11.7	5.29	1.50	−	−	−	−	−	−
82	2	3.65	2.42−5.30	3.84	1.30	0.25−24	>500	−	−	−	>137
90	0.5	18.7	12.4−27.6	3.93	1.11	2	>125	−	−	−	>6.70
phenytoin	2	23.2	21.4−25.4	15.1	4.28	0.25−24	>500	−	−	−	>21.6
carbamazepine	1	3.57	2.41−4.72	3.84	1.15	1	361	319−402	11.4	2.96	101
valproate	0.5	395	332−441	8.13	2.76	0.5	859	719−1148	6.57	2.17	2.17

[a] PI indicates the protection index, i.e. TD_{50}/ED_{50}. [b] The compound was examined 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after administration except for **22**, in which case observation at the end of 8 h was omitted. [c] No toxicity was noted at the end of 0.25, 0.5, 1, 2, and 4 h after administration. [d] Toxicity was observed in 0, 0, 0, 3, 5, 2, 1, and 0 rats out of 8 animals 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after administration.

A positive correlation between the MES activity of the compounds in point v, i.e. **5**, **51**, and **52** was noted with both the MR and SA constants, i.e. activity increased as the size of these physicochemical constants rose. One may conclude therefore that the hypothesis whereby a hydrophobic area on the binding site exists with which the alkyl groups of **51** and **52** interact is strengthened. In the case of point vi, the *r* values for the linear plots of the MES ED_{50} figures against the MR and SA constants were 0.693 and 0.709, which shows a general trend whereby activity increased as the MR and SA constants were elevated. In the remaining cases, no correlations were noted.

With few exceptions, the compounds were administered orally to rats and examined in the MES screen. These data are portrayed in Table 1. Initially a dose of 50 mg/kg was employed. However under these circumstances, virtually all of the compounds afforded complete protection, and hence the dose was reduced principally 4-fold in order to detect candidate anticonvulsants with marked potencies. The data in Table 1 reveal that in most cases complete protection was displayed by the rats which received 12.5 mg/kg of the compounds. Using principally the doses listed in Table 1, 18 compounds were examined in the scPTZ screen of which half were inactive, and in general the remaining analogs had marginal potencies whereby 25% of the rats were protected against seizures. With the exception of **19**, which caused neurological deficit in one of four rats, using the doses listed in Table 1, all of the compounds in Table 1 which were examined in the MES screen were bereft of neurotoxicity.

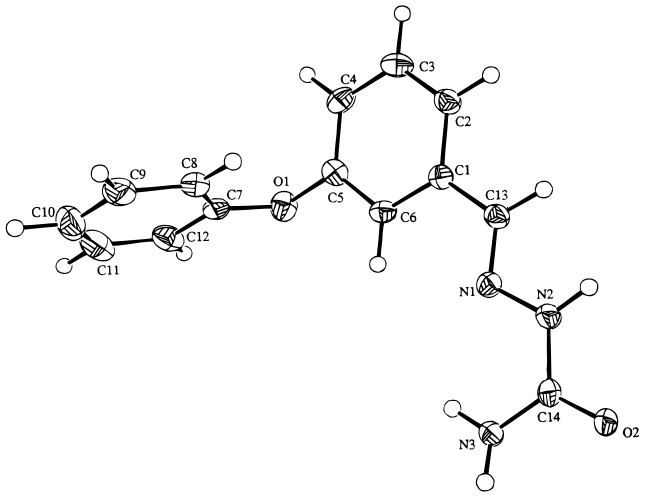


Figure 3. ORTEP diagram of **1**.

In addition, this qualitative examination revealed that complete protection was demonstrated in either all or the majority of the compounds in the series **2**−**48**, **49**−**57**, **73**−**83**, and **93**, **94**, suggesting that these molecules are accommodated well at the binding site. On the other hand, the diminished activity of the compounds in the series **58**−**66** reinforces the belief that alignment at the binding site is reduced when the aryloxy group is placed in the ortho position

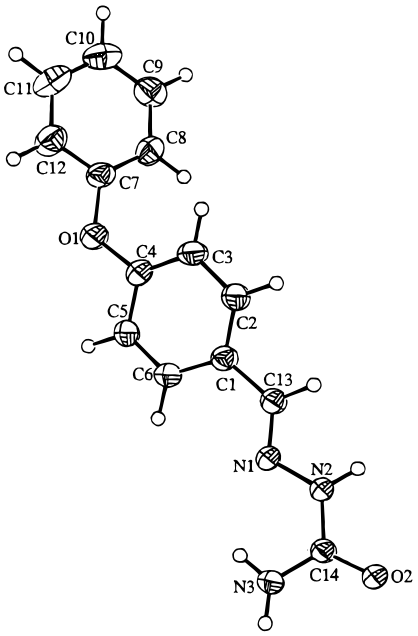


Figure 4. ORTEP diagram of **2**.

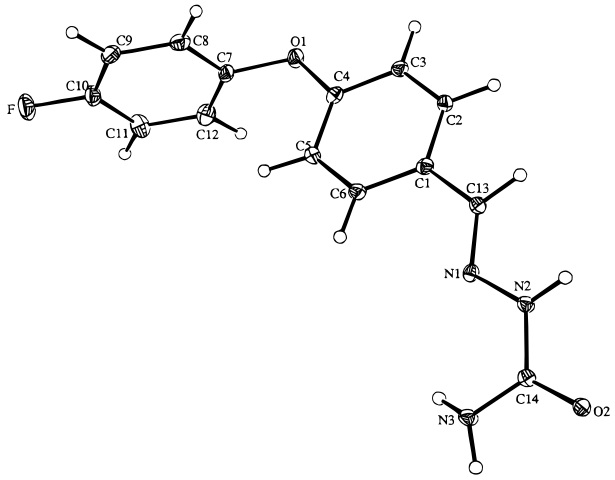


Figure 5. ORTEP diagram of **5**.

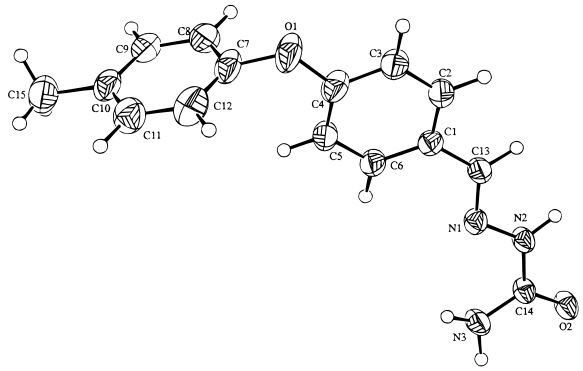


Figure 6. ORTEP diagram of **23**.

of the distal aryl ring. Other structural alterations whereby the size of the spacer group was greater than oxygen and sulfur atoms **67**−**72** or replacements of the oxygen and primary amino groups of the semicarbazono functions **84**−**87**, **88**−**92** appeared to be detrimental.

Quantitation in the rat oral MES screen was undertaken with approximately one-third of the compounds described in this study, principally from the series **2**−**48**, **49**−**57**, and **73**−**83**. The data are summarized in Table 3. Evaluation in the scPTZ screen was undertaken with 63% of the semicarbazones and related compounds which are listed in Table 3. At the maximum doses administered, the majority of the compounds were inactive while a few demonstrated very marginal anticonvulsant properties. The only exception was **21**, which afforded protection in 50% of the rats using a dose of 50 mg/kg. The marked MES selectivity displayed by these compounds is thus reinforced, and further discussion will refer to their evaluation in the MES screen only. Neurotoxicity was absent in virtually all compounds at the highest doses employed. The data in Table 3 revealed the very high potencies of many of these compounds in the rat oral MES screen. In fact the desired goal of an ED_{50} figure of 2−3 mg/kg or less was achieved with **5**, **10**, **18**, **32**, **35**, and **53**−**55**. The potential importance of these compounds as anticonvulsants is further emphasized by the following two considerations. First, bearing in mind that the preferred route of administration of drugs is oral, especially for long-term therapy, the extremely high PI values displayed by most of these compounds suggests a wide margin of safety. Second, a comparison with three established drugs was made. The data reveal that 93% of the compounds listed in Table 3 had ED_{50} figures lower than and 84% had PI values greater than those of phenytoin; the analogous figures for carbamazepine were 40 and 53%, respectively. All of the compounds were more potent than valproic acid and had higher PI values.

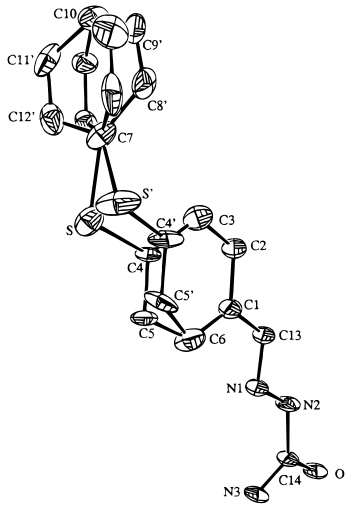


Figure 7. ORTEP diagram of **73**.

The marked increases in potencies of **5** and **51** compared to **90** and **61**, respectively, indicated the importance of both the primary amino group and also the position of the aryloxy function in the proximal aryl ring in conferring anticonvulsant activity. One of the earliest compounds to be evaluated in the rat oral MES screen was **5**, and currently it is undergoing extensive bioevaluation, details of which will be presented elsewhere.

Linear and semilogarithmic plots were made between the ED_{50} figures in the MES screen and the σ,σ*, π, MR, and SA figures of (i) all of the compounds in series **2**−**48** listed in Table 3; (ii) **49**, **51**, **53**, and **55**; (iii) **50**, **52**, **54**, and **56**; and (iv) **73, 76**, and **82**. In addition, an evaluation of the importance of the size and shape of the groups attached to the azomethine carbon atom and

the para position of the distal aryl ring were found by plotting the MES ED_{50} figures against the MR and SA constants found in (v) **5**, **51**, and **52** and (vi) **5**, **23**, **30**, **32**, **34**, **35**, and **45**.

The compounds in cases ii and iv correlated positively with the σ, π, MR, and SA constants, except a negative correlation was noted between the σ values and MES ED_{50} figures in iv. The potencies of the semicarbazones listed in iii correlated positively with the σ and SA constants. A plot of the MR and SA constants of **5**, **51**, and **52** (v) against the MES ED_{50} figures in Table 3 somewhat surprisingly revealed a negative correlation. No correlations were observed in the remaining cases. Thus relationships were noted with various compounds in the series **49**−**57** and **73**−**83** but not **2**−**48**. In general, increases in the σ, π, MR, and SA constants in **49**−**57** and **73**−**83** caused an increase in activity, and this observation can be utilized in subsequent drug design. However the exception to this general trend is the group of compounds **5**, **51** and **52** (v) whereby activity was diminished with increasing size and shape of the substituents. Hence future work should be directed to placing various groups on the azomethine carbon atom in order to evaluate further the structural requirements for interaction at the binding site.

Since bioactivity is considered to be influenced by the rate and extent of the passage of a drug to its site of action,[5] the partition coefficients between 1-octanol and buffer, pH 7.4, of 10 representative compounds and carbamazepine were determined. The log *P* values of these compounds are indicated in parentheses, viz. **1** (2.07), **2** (2.66), **5** (1.91), **10** (2.76), **44** (1.29), **47** (1.92), **51** (2.03), **76** (2.80), **90** (1.96), **91** (2.06), and carbamazepine (2.20). The data support the concept that the compounds align at a specific binding site and are not structurally nonspecific.[6] First, **1,** which is either very weakly active or inactive in the mouse intraperitoneal and rat oral MES screens (Table 1) has a partition coefficient similar to that of **5**, **51**, **90**, or **91**, which demonstrated marked anticonvulsant activity. Second, linear and semilogarithmic plots between the partition coefficients and mouse intraperitoneal ED_{50} figures of **5**, **10**, **51**, and **76** did not show any correlation ($r < 0.8$). Similarly no relationship was established between the partition coefficients of **5**, **10**, **51**, **76**, and **90** and the ED_{50} rat oral data. Third, the mouse and rat data for **90** and **91** in Table 1 indicated the greater anticonvulsant activity of **90**, yet both have similar partition coefficients. Fourth, in the MES screens, the isosteres **5** and **76** had the same activity in the mouse intraperitoneal test and both compounds are highly potent when given orally to rats, yet their partition coefficients are markedly divergent. Finally it is of interest to note that the average log *P* value for all of the active compounds was 2.15, which is similar to the figure for carbamazepine.

In solution, semicarbazones are capable of displaying *E*/*Z* isomerization pertaining to the carbimino double bond. The ratio of isomers could be influenced by the sizes of the groups on the carbimino carbon atom,[7] and hence the three representative compounds chosen, namely **5**, **51**, and **52**, reflected this possibility. Due to the very low aqueous solubilities of the compounds prepared in this study, 10 mM solutions were prepared in deuterated dimethyl sulfoxide. The data in Tables 2 and 3 reveal that the times of peak effect of **5**, **51**, and **52** in the mouse and rat MES screens were 1 and 2 h, respectively. Hence ^{1}H NMR spectra were recorded at dissolution and 3 h after incubation of the solutions at 37 °C. No changes in the spectra were noted. Since the stereochemistry of the carbimino group in different semicarbazones was shown by X-ray crystallography to have the *E* configuration (*vide infra*), the compounds were considered to retain this stereochemistry *in vivo*.

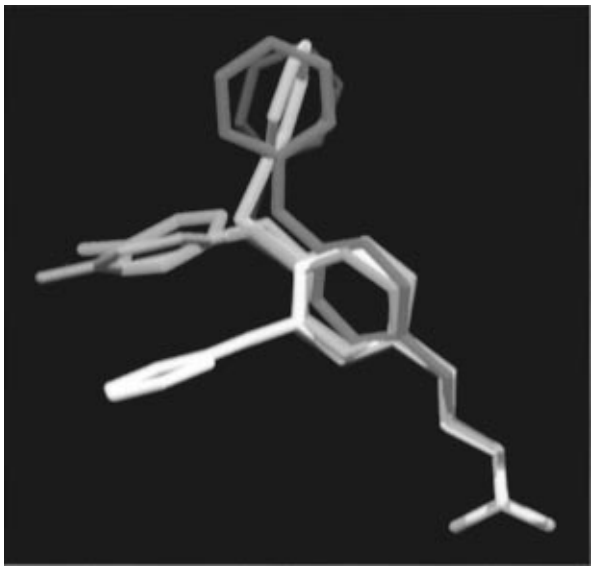


Figure 8. Orientations of the proximal and distal aryl rings of **1** (colorless), **2** (red), **5** (green), **23** (orange), **73A** (blue), and **73B** (yellow) when the N3, C14, (O2 or O), and N2 atoms of each molecule are superimposed.

The second phase of the study was an evaluation of the binding site hypothesis using X-ray crystallography. Examination of the shapes of molecules under nonbiological conditions does not necessarily reflect *in vivo* situations. In the case of X-ray crystallography, the structures were solved when the compounds were solids, and their flexibilities may permit various orientations to occur. Nevertheless, the data obtained may afford insight into their likely shapes *in vivo*. Results were obtained for four compounds which displayed activity in the MES mouse intraperitoneal and rat oral screens (**2**, **5**, **23**, **73**) and one semicarbazone which was very weakly active or inactive at the doses employed in both tests (**1**). The ORTEP diagrams of **1**, **2**, **5**, **23**, and **73** are portrayed in Figures 3−7, respectively. In the case of **73**, the C5, C4, S, C8, C9, C11, and C12 atoms occupy two different positions, each with an occupancy of 0.5. These two molecules are referred to as **73A** and **73B**. The carbimino group had the *E* configuration in all five compounds.

In order to compare the shapes of the five compounds, four atoms in the semicarbazono group, namely the N3−C14−(O2 or O)−N2 atoms, were superimposed (Figure 8). The results show that in the crystal state while the proximal ring occupies a similar position in all five compounds, the distal aryl rings are found in three distinct locations which may be designated as location A (**2** and **73**), location B (**5** and **23**), and location C (**1**). The determination of the precise positions of the aryl rings from the X-ray crystallographic data of all five compounds was undertaken in order to obtain further information pertaining to the nature of the binding site. The distances between the C14 atom and the centers of

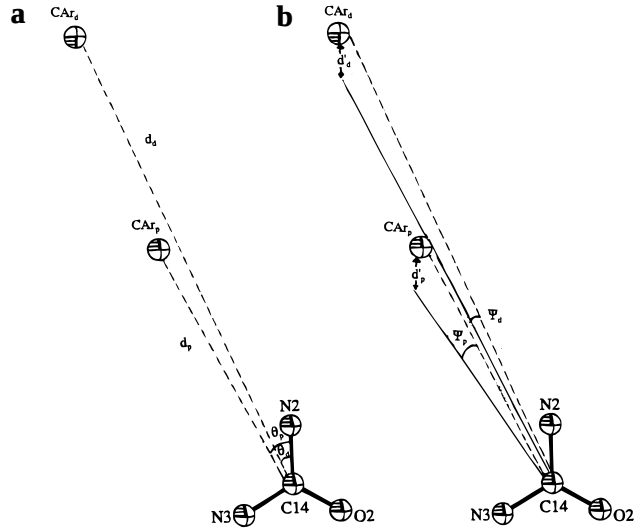


Figure 9. (a) Distances and θ angles between the C14 atom and centers of both the proximal (CAr_p) and distal (CAr_d) rings in **2**. (b) Displacement and ψ angles of the centers of the proximal (CAr_p) and distal (CAr_d) rings from the N3−C14−(O2)−N2 plane in **2**.

both aryl rings were measured. In addition, the angles θ between the centers of the aromatic rings and the C14−N2 bonds were obtained. Furthermore the displacements of the aryl rings above or below the N3−C14−(O2 or O)−N2 plane were calculated for each compound in terms of both distances and angles ψ. The determination for a representative compound **2** is illustrated in Figure 9.

The results revealed that the distances between the C14 atom and the centers of the proximal aryl rings (d_p) are similar for all compounds, namely in the range 6.0−6.1 Å. On the other hand, the d_d figures for the compounds in locations A−C are 10.9−11.1, 10.1−10.2, and 8.5 Å, respectively. If these spatial arrangements are the ones which align at the binding site, the fact that the MES figures in both the mouse ip and rat oral screens of **5** and **23** are lower than **73** may indicate that the d_d distances affect anticonvulsant activities. Thus the preparation of rigid analogs of the (aryloxy)aryl semicarbazones in which the distal aryl ring is confined to location B may lead to compounds with increased potencies.

The θ_p angles were between 29° and 34°. The synthesis and anticonvulsant evaluation of analogs in which this angle is altered, such as by replacing the hydrogen atom of the carbimino group by different functions, may reveal the importance of this angle in conferring anticonvulsant activity. The θ_d angles of **1**, **2**, **5**, **23**, **73A**, and **73B** were 64°, 25°, 51°, 51°, 28°, and 28°, respectively, and hence the θ_d figures for **5** and **23** in location B are approximately twice those for **2** and **73** in location A. However a further increase in the θ_d angle from approximately 51° to that found in **1** is detrimental to activity.

The data obtained from the measurements indicated in Figure 9b indicated the displacement of the proximal and distal aryl rings from the N3−C14−(O2 or O)−N2 plane. The proximal rings are nearly coplanar with the ureido group as revealed by the d'_p and ψ_p figures. The d'_d figures for **1**, **2**, **5**, **23**, **73A**, and **73B** were 2.3, 0.02, 0.71, −0.82, −1.4, and −1.4 Å, respectively, the negative figures indicating that the ring was below the N3−Cl4−(O2 or O)−N2 plane. Thus with the exception of **2**, there was a greater displacement of the distal than the proximal rings from the ureido group in **1**, **5**, **23**, and **73**. The distal aryl ring in **5**, which had the lowest ED_{50} figures in both the quantitative MES screens, was located above the N3−C14−(O2)−N2 plane while the marginally less active compounds **23** and **73** had distal rings below this plane. This observation may indicate that there is a pocket at location B and the distal ring of **5** could interact with the top of this cavity. The X-ray data have therefore provided further insight into the putative binding site of these novel anticonvulsants.

Conclusions

This study has revealed that many (aryloxy)aryl semicarbazones and related compounds have marked potency in the rat oral MES screen and did not demonstrate neurotoxicity at the highest doses administered. From the QSAR data, the size and shape of various groups in these molecules correlated positively with activity in the MES screen while the use of π constants, as well as partition coefficient determinations, indicate that in general the hydrophobicity of the molecules did not influence anticonvulsant activity. The X-ray crystallographic data suggested that the distal aryl ring occupied different positions at the distal binding site and that certain interatomic distances and bond angles affected potency. The deductions from the screening and X-ray crystallographic results suggest that the putative binding site at which MES-active compounds interact is a valid hypothesis which will be scrutinized carefully as additional data is generated.

Experimental Section

A. Chemistry. Melting points are uncorrected. ^{1}H NMR spectra were recorded routinely using a Varian T-60 spectrometer (60 MHz) while the stability studies used a Bruker AM 300FT instrument (300 MHz). Partition coefficients were determined using a Gilford UV/vis spectrophotometer. Thin layer chromatography (TLC) was performed using silica gel sheets with a fluorescent indicator. Elemental analyses (C, H, N) were undertaken by Mr. K. Thoms, Department of Chemistry, University of Saskatchewan, and in most cases were within 0.4% of the calculated values. For the following compounds, despite having sharp melting points and displaying homogeneity by TLC, repeated recrystallizations and submission for elemental analyses revealed that the figure for one element deviated slightly from ±0.4%, namely (element, difference between the calculated and found values expressed as a percentage) **4** (H, 0.48), **8** (N, 0.46), **11** (C, 0.63), **21** (N, 0.65), **37** (C, 0.84), **58** (N, 0.47), **59** (C, 0.55), **71** (N, 0.53), **81** (C, 0.66), and **95** (N, 0.55). In all cases except **11** and **81**, the values determined were lower than the calculated figures, which may have been due to a problem of incomplete combustion.

Synthesis of Compounds in the Series 1, 2−48, 49−57, 58−66, 73−83, 93, 94, and 95. 3-Phenoxybenzaldehyde required in the synthesis of **1** was obtained from the Aldrich Chemical Co., Milwaukee, WI. The intermediate (aryloxy)-aryl and (arylthio)aryl aldehydes required in the synthesis of the other compounds were prepared as follows.

Anhydrous potassium carbonate (0.12 M) was added to a solution of the appropriate phenol or thiophenol (0.15 M) and 4-fluorobenzaldehyde, 4-fluoroacetophenone, or 4-fluoropropiophenone (0.14 M) in dimethylacetamide (100 mL). For **95**, 4-fluorobenzaldehyde (0.28 M) was taken. The mixture was heated under reflux at 155 °C under nitrogen, and the progress of the reaction was monitored by TLC using a solvent system of benzene:methanol (9:1). After ∼5−10 h, the mixture was cooled and water (100 mL) was added. The reaction mixture

was extracted with chloroform (2 × 100 mL), and the combined organic extracts were washed with aqueous sodium hydroxide solution (4% w/v) and water. After the mixture was dried over anhydrous magnesium sulfate, the solvent was removed *in vacuo* and the resultant oil was distilled under reduced pressure to give the appropriate (aryloxy)aryl or (arythio)aryl aldehyde or ketone. The purity of the distillate was checked by TLC using benzene:methanol (9:1) as the solvent. The ^{1}H NMR spectral data (300 MHz) of a representative intermediate, namely 4-phenoxybenzaldehyde, were as follows: δ ($CDCl_3$) 9.94 (s, 1H, CHO), 7.82−7.88 (2t, 2H, ortho H of proximal aryl ring), 7.38−7.46 (m, 2H, meta H of proximal aryl ring), 7.20−7.27 (m, 1H, para H of distal aryl ring), 7.03−7.12 (m, 4H, ortho and meta H of distal aryl ring).

A mixture of semicarbazide hydrochloride (0.01 M), sodium acetate (0.01 M), and water (10 mL) was added slowly to a stirring solution of the (aryloxy)- or (arylthio)aryl aldehyde (0.01 M) in ethanol (95%, 30 mL). The reaction mixture was stirred at room temperature for 1−2 h, and the precipitate was collected, washed with ether, and dried. Most of the compounds were recrystallized from ethanol (95% v/v), except for compounds **2**, **3**, **5**, **9**−**16**, **44**, **45**, **47**, and **48** (absolute ethanol) and compound **23** (methanol). The ^{1}H NMR spectral data (300 MHz) of a representative compound **5** in dimethyl-d_6 sulfoxide were as follows: 9.40 (s, 1H, NH), 6.94 (s, 1H, CH), 6.82−6.88 (2t, 2H, meta H of distal aryl ring), 6.33−6.42 (m, 2H, ortho H of distal aryl ring), 6.05−6.30 (m, 4H, ortho and meta H of proximal aryl ring), 5.60 (s, 2H, NH_2). The literature melting points (°C) of **1**, **2**, and **58** were 217,[8] 219−220,[9] and 219−220,[10] respectively. The percentage yields are based on the last reaction between the (aryloxy)aryl or (arylthio)aryl carbonyl compounds and semicarbazide.

Synthesis of Compounds in the Series 67−72. 4-(Benzyloxy)benzaldehyde required in the synthesis of **67** was obtained from the Aldrich Chemical Co., Milwaukee, WI. The other intermediate aldehydes were prepared as follows.

Benzoyl chloride or 4-chlorobenzoyl chloride (0.05 M) was added to a solution of 4-hydroxybenzaldehyde (0.04 M) in pyridine (100 mL). After standing overnight at room temperature, the reaction mixture was poured onto acetic acid (2 N, 100 mL). The precipitate was collected, washed with water, and recrystallized from water−methanol to give 4-(benzoyloxy)benzaldehyde and 4-[(4-chlorobenzoyl)oxy]benzaldehyde required in the synthesis of **68** and **69**, respectively. 4-(Phenylsulfonyl)benzaldehyde used in the synthesis of **70** was prepared as follows. A mixture of sodium benzenesulfinate (0.11 M) and 4-fluorobenzaldehyde (0.1 M) in dry dimethyl sulfoxide (75 mL) was stirred at 100 °C for 18 h under nitrogen and then poured onto ice (∼200 g). The precipitate was collected, washed with water, and recrystallized from ethanol (95% v/v). Finally, benzenesulfonyl chloride or 4-methylbenzenesulfonyl chloride (0.20 M) was added dropwise to a stirred solution of 4-hydroxybenzaldehyde (0.16 M) in dichloromethane (90 mL) and trimethylamine (3−5 mL) at 0−10 °C over a period of 10 min. After a further 15 min, the reaction mixture was diluted with dichloromethane and successively extracted with water, hydrochloric acid (10% w/v), saturated sodium bicarbonate solution, and saturated sodium chloride solution. After the organic extract was dried, the solvent was removed, affording the products required in the syntheses of **71** and **72**. The compounds were homogeneous by TLC using a solvent system of benzene:methanol (7:3), and the melting points of **68**, **70** − **72** were in accord with literature values.

These intermediate aldehydes were reacted with semicarbazide as described previously.

Synthesis of Compounds in the Series 84−87 and 88−92. These compounds were prepared from the appropriate (aryloxy)aryl and (arylthio)aryl aldehydes using literature methodologies.[11,12] The time of heating the reactants under reflux was 6 h (**84**−**87**), while the times of stirring the reactants at room temperature were 8 (**88**), 10 (**89**, **91**), and 14 (**92**) h. In the case of **90**, the reaction mixture was heated at 60 °C for 0.5 h. All compounds were recrystallized from ethanol (95% v/v).

Determination of log *P* values. The log *P* figures were determined by a previously reported procedure[13] except that solutions were made using 1-octanol to which buffer was added. The λ_{max} and ϵ values of the compounds were obtained in 1-octanol and not phosphate-buffered saline, pH 7.4, due to the low aqueous solubilities of the compounds. The log *P* values (error in parentheses) were as follows: **1**, 2.07 (0.08); **2**, 2.66 (0.11); **5**, 1.91 (0.08); **10**, 2.76 (0.11); **44**, 1.29 (0.05); **47**, 1.92 (0.08); **51**, 2.03 (0.08); **76**, 2.80 (0.11); **90**, 1.96 (0.08); **91**, 2.06 (0.08); and carbamazepine, 2.20 (0.09).

Statistical Analyses. The σ, π, and MR constants were taken from the literature,[14] and the Taft σ^* values were obtained from a reference source.[15] The solvent accessible surface areas calculated with a probe radius of 1.4 Å were obtained using a MacroModel Version 4.5 program[16,17] and a Silicon Graphics Indigo Extreme workstation. The MES figures recorded in Tables 2 and 3 which were used in the statistical analyses were converted to μmol/kg. The correlations observed were summarized as follows: group of compounds (refer to discussion), physical constant, and linear (r_l) and semilogarithmic (r_{sl}) correlation coefficients. For the mouse intraperitoneal screen (Table 2) the following correlations were established: (v) MR, $r_l = 0.955$, $r_{sl} = 0.931$; (v) SA, $r_l = 0.919$, $r_{sl} = 0.899$. In the case of the rat oral test, the data summarized refer to the group of compounds, physical constant, r_l and r_{sl} figures: (ii) σ, 0.808, 0.825; (ii) π, 0.786, 0.851; (ii) MR, 0.692, 0.819; (ii) SA, 0.899, 0.926; (iii) σ, 0.765, 0.817; (iii) SA, 0.834, 0.861; (iv) σ, 0.998, 1.000; (iv) π, 0.847, 0.865; (iv) MR, 0.956, 0.966; (iv) SA, 0.778, 0.799; (v) MR, 0.971, 0.947; and (v) SA, 0.990, 0.975.

X-ray Crystallography of 1, 2, 5, 23, and 73. The compounds were crystallized from ethanol:dimethyl sulfoxide (**1**), ethyl acetate:cyclohexane (**2**), acetone:methanol (**23**), and hexane:methanol (**73**) by vapor diffusion while **5** was crystallized from hot ethanol. An Enraf-Nonius CAD-4 diffractometer with an ω scan was used for data collection, and the structure was solved by direct methods using NRCVAX.[18] Atomic scattering factors were taken from the literature.[19] All non-hydrogen atoms were found on the E-map and refined anisotropically. Hydrogen atom positions were calculated and not refined. In the case of **73**, the atoms S, C3, C4, C8, C9, C11, and C12 occupied two different positions, each with an occupancy of 0.5.

The data for **1** were as follows: $C_{14}H_{13}N_3O_2$, $M_r = 255.27$, $a = 11.809(3)$ Å, $b = 7.1862(20)$ Å, $c = 15.4816(20)$ Å, $\beta = 109.220(20)$, $Z = 4$, space group = $P2_1/a$, monoclinic, $D_x = 1.367$ g cm^{-3}, λ(Mo Kα) = 0.7093 Å, $T = 123$ K. Merging R is based on intensities 0.012 for 480 replicate reflections, $R(F) = 0.046$, $R_w = 0.049$, $S = 3.82$. A total of 2652 reflections were measured, 2172 of which were independent. The refinement of the structure used 1728 observed reflections [$I > 2\sigma(I)$]. Parameters refined = 172 [$w = 1/\sigma^2(F)$]. $\Delta\rho$ in the final difference map was within +0.25 and −0.240 e Å^{-3}.

The data for **2** were as follows: $C_{14}H_{13}N_3O_2$, $M_r = 255.27$, $a = 12.4637(15)$ Å, $b = 7.6840(22)$ Å, $c = 12.9457(15)$ Å, $\beta = 91.321(10)$, $Z = 4$, space group = $P2_1/c$, monoclinic, $D_x = 1.368$ g cm^{-3}, λ(Mo Kα) = 0.7093 Å, $T = 287$ K. Merging R is based on intensities 0.007 for 316 replicate reflections, $R(F) = 0.039$, $R_w = 0.044$, $S = 2.33$. A total of 2489 reflections were measured, 2173 of which were independent. The refinement of the structure used 1670 observed reflections [$I > 2\sigma(I)$]. Parameters refined = 172 [$w = 1/\sigma^2(F) + 0.0001$]. $\Delta\rho$ in the final difference map was within +0.24 and −0.260 e Å^{-3}.

The data for **5** were as follows: $C_{14}H_{12}N_3O_2F$, $M_r = 273.27$, $a = 12.7066(19)$ Å, $b = 7.7389(15)$ Å, $c = 13.2838(23)$ Å, $\beta = 103.965(15)$, $Z = 4$, space group = $P2_1/a$, monoclinic, $D_x = 1.432$ g cm^{-3}, λ(Mo Kα) = 0.7093 Å, $T = 123$ K. Merging R is based on intensities 0.017 for 301 replicate reflections, $R(F) = 0.038$, $R_w = 0.051$, $S = 2.15$. A total of 2508 reflections were measured of which 2207 were independent. The refinement of the structure used 1750 observed reflections [$I > 2\sigma(I)$]. Parameters refined = 181 [$w = 1/\sigma^2(F) + 0.0002$]. $\Delta\rho$ in the final difference map was within +0.17 and −0.260 e Å^{-3}.

The data for **23** were as follows: $C_{15}H_{15}N_3O_2$, $M_r = 269.30$, $a = 13.0692(6)$ Å, $b = 7.8606(4)$ Å, $c = 13.5724(6)$ Å, $\beta = 101.857(4)°$, $Z = 4$, space group = $P2_1/a$, monoclinic, $D_x = 1.311$ g cm^{-3}, λ(Mo Kα) = 0.7093 Å, $T = 287$ K. Merging R is based on intensities 0.006 for 119 replicate reflections, $R(F) = 0.041$,

R_w = 0.056, S = 2.51. A total of 2513 reflections were measured, 2394 of which were independent. The refinement of the structure used 1858 observed reflections [$I > 2.5\sigma(I)$]. Parameters refined = 181 [$w = 1/\sigma^2(F) + 0.0002$]. $\Delta\rho$ in the final difference map was within +0.22 and −0.25 e Å^{-3}.

The data for **73** were as follows: $C_{14}H_{13}N_3OS$, M_r = 271.32, a = 12.9365(15) Å, b = 5.3111(11) Å, c = 19.061(4) Å, β = 98.46(3), Z = 4, space group = $P2_1/a$, monoclinic, D_x = 1.391 g cm^{-3}, λ(Mo Kα) = 0.7093 Å, T = 123 K. Merging R is based on intensities 0.012 for 118 replicate reflections, $R(F)$ = 0.062, R_w = 0.078, S = 2.95. A total of 2394 reflections were measured, 2276 of which were independent. The refinement of the structure used 1519 observed reflections [$I > 2.5\sigma(I)$]. Parameters refined = 235 [$w = 1/\sigma^2(F)$]. $\Delta\rho$ in the final difference map was within +0.31 and −0.31 e Å^{-3}.

B. Pharmacology. The anticonvulsant evaluations were undertaken by the National Institute of Neurological Disorders and Stroke, National Institutes of Health, using their reported procedures.[20]

(i) Intraperitoneal Injection in Mice. All compounds were examined initially in the MES, scPTZ, and NT screens, and these data are presented in Table 1. Side effects were noted in the scPTZ screen for the following compounds at various doses (mg/kg) and time intervals. Continuous seizure activity (CSA) was noted in the case of **11** (300, 0.5 h, 4 h), **13** (300, 0.5 h), **14** (300, 0.5 h, and 100, 300, 4 h), **16** (100, 300, 0.5 h, 4 h), **18** (300, 0.5 h, and 100, 300, 4 h), **19** (100, 300, 0.5 h, and 300, 4 h), **22** (100, 300, 0.5 h), **25** (100, 300, 0.5 h, and 100, 300, 4 h), **31** (100, 300, 0.5 h), **35** (300, 4 h), **39** (30, 100, 300, 0.5 h, and 100, 300, 4 h), **40** (300, 0.5 h, and 100, 300, 4 h), **41** (300, 0.5 and 4 h), **42** (100, 300, 4 h), **48** (100, 300, 0.5 h, 4 h), **50** (30, 0.5 h, and 300, 4 h), **51** (100, 300, 4 h), **52** (100, 300, 4 h), **53** (30, 100, 300, 0.5 h, and 100, 300, 4 h), **54** (30, 100, 0.5 h, and 100, 300, 4 h), **55** (100, 0.5 h), **56** (300, 0.5 h, and 100, 4 h), **57** (100, 300, 0.5 h), **71** (300, 0.5 h), **76** (300, 0.5 h), **78** (300, 0.5 h, 4 h), **79** (300, 4 h for three of five mice), and **84** (300, 0.5 h, 4 h). Myoclonic jerks were observed in the following compounds, namely **9** (100, 300, 0.5 h), **14** (30, 100, 0.5 h), **42** (300, 0.5 h), **55** (300, 0.5 h), **56** (100, 0.5 h), **71** (100, 0.5 h for one of five mice), **79** (300, 4 h for two of five mice). Death following CSA was caused by the following compounds, namely **22** (300, 4 h), **56** (300, 4 h), **76** (100, 0.5 h, and 300, 4 h). Tonic extension was observed during the evaluation of **33** (30, 0.5 h). The mice died during the test without having seizure in the case of **49** (300, 0.5 h), **71** (300, 4 h), **86** (100, 300, 0.5 h), and **87** (100, 0.5 h for one of five mice, 300, 0.5 h for all mice and 30, 4 h for two of five mice). Stretching and rolling were noted for mice caused by **75** (300, 4 h), and tremors resulted from the administration of **85** (300, 4 h). Death occurred after injections of **86** (100, 300, 4 h) and **87** (100, 300, 4 h).

In the NT screen, mice were unable to grasp the rotorod after administration of the following compounds, viz. **9** (300, 4 h), **13** (300, 4 h), **14** (100, 300, 4 h), **16** (100, 300, 4 h), **18** (100, 300, 4 h), **19** (300, 4 h in one of two mice), **22** (100, 300, 0.5 h, and 300, 4 h), **25** (100, 300, 4 h), **30** (300, 4 h), **32** (300, 4 h), **35** (300, 4 h), **39** (300, 0.5 h, and 100, 300, 4 h), **40** (300, 0.5 and 4 h), **42** (300, 4 h), **49** (300, 0.5 h, 4 h), **50** (300, 0.5 h, 4 h), **51** (300, 4 h), **52** (300, 4 h), **53** (300, 0.5 h, and 100, 300, 4 h), **54** (300, 4 h), **55** (300, 4 h), **56** (100, 300, 4 h), **59** (300, 0.5 h), **71** (300, 4 h), **75** (300, 4 h), **76** (300, 0.5 h, and 300, 4 h), **78** (300, 4 h), **84** (300, 4 h), **85** (300, 4 h), **86** (300, 0.5 h), and **90** (300, 4 h). A loss of righting reflex was noted with **87** (300, 0.5 h).

The quantitative evaluation of the effect of selected compounds after intraperitoneal injection in mice in the MES, scPTZ, and NT screens is summarized in Table 2.

(ii) Oral Administration to Rats. Most of the compounds described in this study were examined for oral activity in the MES and NT screens. The results are presented in Table 1. In addition, a number of semicarbazones were evaluated in the scPTZ screen using the doses specified in Table 1 (except for **27** and **42** *vide infra*), and the results are as follows. Compounds **4**, **7**, **10**, **13**, **26**, **32**, **71**, **84**, and **85** were devoid of activity in the scPTZ screen. On the other hand, the following compounds had activity (number of rats protected out of 4, time of activity), viz. **12** (1, 4 h), **17** (1, 0.5, 1, 4 h), **21** (1, 0.5, 1, 2 h), **25** (1, 0.25, 4 h), **27** (1, 0.25, 1, 4 h, and 4, 2 h), **34** (1, 0.25, 1, 4 h, and 2, 2 h), **52** (1, 0.5, 1 h), **67** (1, 1 h), and **87** (1, 4 h). Using the doses indicated in Table 1, no neurological deficit was noted except for **19**, whereby one of four rats demonstrated neurotoxicity 1, 2, and 4 h after administration. In the case of **27** and **42**, the dose in both the scPTZ and NT screens was 50 mg/kg.

Quantitative evaluation of selected compounds in the rat oral MES and NT screens was undertaken, and the data are presented in Table 3. The following compounds were examined in the rat oral scPTZ test, and the results are as follows (ED_{50} at the maximum dose in mg/kg, time of administration in hours): **5** (>250, 2), **9** (>250, 4), **10** (>250, 4), **18** (>250,4), **22** (>250, 1), **23** (>125, 2), **32** (>250, 2), **34** (>161, 4), **35** (>250, 4), **51** (>250, 2), **52** (>250, 2), **53** (>250, 4), **54** (>250, 2), **55** (>250, 4), **73** (>248, 4), **76** (>250, 2), **82** (>250, 2), and **90** (>250, 0.5). In the case of **21**, the number of rats protected (out of four) at the end of 0.25, 0.5, 1, 2, and 4 h were 0, 0, 0, 1, and 2. The semicarbazones **6**, **8**, **30**, **45**, **49**, **50, 56**, **61**, **74**, **75**, and **77** were not evaluated in the rat oral scPTZ and NT screens. The figures for three reference drugs in the rat oral scPTZ screen were as follows: phenytoin (>250, 2 h), carbamazepine (>250, 1 h), and valproic acid (620, 0.5 h). For the latter compound, the 95% CI and slope were 469−985 mg/kg and 3.17, respectively.

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Supporting Information Available: Atomic anisotropic displacement parameters, hydrogen positional and isotropic displacement parameters, atomic positional and equivalent isotropic displacement parameters, and bond distances and angles for **1**, **2**, **5**, **23**, and **73** and tables of the measurements indicated in Figure 9 (19 pages). Ordering information is given on any current masthead page.

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