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Anticonvulsant 4-Aryl Semicarbazides & Thioureas†

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Among a series of anticonvulsant 1-aryl semicarbazides, 1-(3-5-bistrifluoromethyl)phenylsemicarbazide, C 3884-Go (**11**) and its 4-methyl derivative, C 3165-Go (**12**) showed good activity of long duration in the electroshock test in mice and rats. Quantitative structure activity analysis indicates that σ and π values are respectively important for the aromatic and side chain substituents respectively. N-Acetyl-N'-(3,5-bistrifluoromethyl)phenyl hydrazine (**20**) is highly anticonvulsant but causes ataxia. 4-Aryl thiosemicarbazides show weak to moderate activity. Among N-(3,5-bistrifluoromethyl)phenyl thiocarbamoyl derivatives, the product **33** from N-benzyl piperazine is potent in the electroshock test. Compounds **11** and **12** have been compared with standards such as phenytoin, phenurone and carbamazepine.

The treatment of epilepsy requires newer cost-effective drugs that would possess (i) activity profiles comprising improved efficacy and tolerability as well as positive psychotropic and nootropic effects and (ii) a longer duration of the anticonvulsant effect, so that dosage frequency could be minimised and compliance increased. In the course of the general pharmacological profiling of the antiimplantation agent, C 2696-Go, 1-(3,5-bistrifluoromethyl)phenylthiosemicarbazide (**28**)[1], we observed that **28** had considerable anticonvulsant activity in the test for electroshock-induced seizures. Although this property was not exhibited by a large number of analogous thiosemicarbazides, it was found that the corresponding semicarbazide, C 3165-Go (**12**) was very potent with a long duration of action, as also the thiocarbonyl derivative **33**. We report in this paper our limited studies on the two series with respect to structure-activity relationships, with the former being treated quantitatively. A brief account is also given of the profiles of **12** and its desmethyl derivative **11** in relation to standard antiepileptic drugs.

Chemistry

All the semicarbazides of Table 1 were prepared by reaction of aryl hydrazine with the appropriate isocyanate, except for **11** which arose by the interaction of 3,5-bistrifluoromethylphenyl hydrazine with cyanic acid. Compound **20** (Table 2) was obtained from hydrazine and acetic anhydride and the others from relevant carbamoyl chloride and hydrazine. The synthesis of thiosemicarbazides of Table 3 has been published[1]. Thioureas of Table 4 resulted from the action of 3,5-bistrifluoromethylphenyl isothiocyanate with piperazines (**31-35**), piperidine (**36**), morpholine (**37**) or 2,6-dimethylthiamorpholine (**38**). Compound **39** (Table 4) was obtained by the action of 3,5-bistrifluoromethylphenylisocyanate on N-methyl-piperazine.

Biological screening

Compounds were administered orally (p.o.) in 0.2% agar suspension to CF male mice and CW rats for evaluation of anticonvulsant activity. Protection against electroshock-induced seizures was determined in graded doses upto 500 mg/kg p.o., routinely 3 hr post drugging. ED_{50} and ED_{100} doses were estimated and used as basis of comparison[2]. The results are shown in Tables 1-4. Protection against strychnine and metrazol induced seizures in mice was also studied[2] as well as efficacy in the psychomotor electroshock test in the same species[3]. C 3165-Go, phenytoin and carbamazepine were also examined in the monkey model of focal motor seizures[4].

Qualitative structure-activity relationships

Anticonvulsant activity in the electroshock test in mice is widespread among the 1-aryl-4-methylsemicarbazides, the parent **1** having an ED_{50} of about 140 mg/kg p.o. at the 3rd hour. Substitution by two chlorine atoms at positions 3 and 4 (**9**) or by a CF_3 group alone at position-3 (**3**) or position-4 (**5**) improves the potency considerably. The activity of **3** is diminished nearly three-fold by an adjacent Cl atom (**8**), but slightly enhanced by a *para*-placed Cl atom (**7**). Further enhancement occurs with a CF group in the *meta* position. Compound **12**, (C 3165-Go), thus has an ED_{50} of about 30 mg/kg p.o. Among these compounds, replacement of a methyl group by an ethyl

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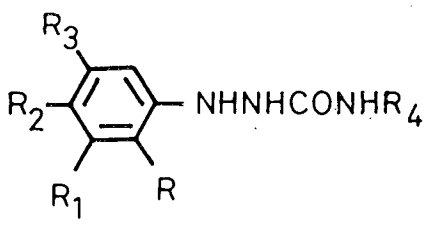
Table 1 – Arylsemicarbazides



Compd	R	R_1	R_2	R_3	R_4	Mol. formula	Crystallised from*	m.p. (°C)	Antielectroshock activity†	
									ED_{100} mg/kg p.o.	ED_{50} mg/kg p.o.
1	H	H	H	H	Me	$C_8H_{11}N_3O$	A+F	150-52	250	139±15.8
2	CF_3	H	H	H	Me	$C_9H_{10}F_3N_3O$	A+F	144-45	>500[a,c]	387.3±19.6
3	H	CF_3	H	H	Me	$C_9H_{10}F_3N_3O$	J+G	129-31	100[b,c]	46.9±6.7
4	H	CF_3	H	H	n-Bu	$C_{12}H_{16}F_3N_3O$	F	81-83	>500	318.8±22.9
5	H	H	CF_3	H	Me	$C_9H_{10}F_3N_3O$	A+F	161-63	250[b,c]	71.1±10
6	CF_3	H	Cl	H	Me	$C_9H_9ClF_3N_3O$	A+F	155-57	250	
7	Cl	H	H	CF_3	Me	$C_9H_9ClF_3N_3O$	A+F	169-71	60[b]	38.0±3.2
8	H	CF_3	Cl	H	Me	$C_9H_9ClF_3N_3O$	A+F	196-99	250	127.7±17.7
9	H	Cl	Cl	H	Me	$C_8H_9Cl_2N_3O$	A+F	194-95	250	70.2±6.6
10	H	Cl	Cl	H	Et	$C_9H_{11}Cl_2N_3O$	A+F	173-75	>250	159.4±22.9
11	H	CF_3	H	CF_3	H	$C_9H_7F_6N_3O$	A+F	205-06	100[b,c]	27.2±2.2
12	H	CF_3	H	CF_3	Me	$C_{10}H_9F_6N_3O$	E+F	212-14	100	30.3±1.7
13	H	CF_3	H	CF_3	Et	$C_{11}H_{11}F_6N_3O$	D+F	184-86	>100	48.2±5.8
14	H	CF_3	H	CF_3	n-Pr	$C_{12}H_{13}F_6N_3O$	B+F	150-52	300[a]	129.3±13.4
15	H	CF_3	H	CF_3	n-Bu	$C_{13}H_{15}F_6N_3O$	A+F	130-31	>100	65.2±8.5
16	H	CF_3	H	CF_3	n-C_5H_{11}	$C_{14}H_{17}F_6N_3O$	C+F	132-34	>300	165.6±18.9
17	H	CF_3	H	CF_3	Cyclo-hexyl	$C_{15}H_{17}F_6N_3O$	A+F	142-43	>400	226.5±11.4
18	H	CF_3	H	CF_3	$(CH_2)_2Cl$	$C_{11}H_{10}ClF_6N_3O$	A+F	166-67	250	112.2±22.9
19	H	CF_3	H	CF_3	$(CH_2)_3Cl$	$C_{12}H_{12}ClF_6N_3O$	A+F	106-8	250	75.9±3.9

* Solvents for Tables 1, 2 and 4: (A) acetone; (B) benzene; (C) chloroform; (D) ether; (E) ethyl acetate; (F) hexane; (G) methanol; (H) methylene chloride; (I) tetrahydrofuran; (J) water; and (K) ethanol.
† At 3 hours postdose.
[a] sedation; [b] hypotonia; [c] ataxia; [d] dyspnoea.

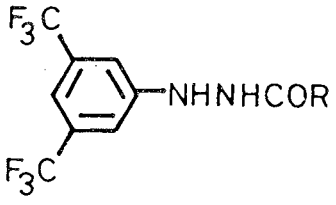
(**9**→**10**; **12**→**13**) or a butyl group (**3**→**4**) in active molecules reduces their efficacy by 50-700%.

A systematic variation of the substituent at position-4 has been attempted on C 3165-Go (**12**) since it is very potent. Replacement of a methyl group by hydrogen results in a slightly more potent preparation (**11**), while ethyl or longer alkyl or cycloalkyl group causes a decrease in potency. An extra methyl group at position-4 in **12** again gives a weaker preparation (**21**), as also substitution of methylamino by piperidino or morpholino moiety (**22**/**23**). The acetyl derivative **20** of 3,5-bistrifluoromethylphenyl hydrazine has good activity against electroshock in mice but causes ataxia and dyspnoea at 40 mg/kg.

1-Aryl-4-alkylthiosemicarbazides have some anticonvulsant activity, but the best of them, **28**[1] (C 2696-Go) which differs from **12** in having S instead of O atom is not even half as active.

Among 3,5-bistrifluoromethylphenylthiocarbamoyl derivatives (Table 4), the situation is reverse, since the thiourea (**31**) is twice as active as the urea (**39**). Anticonvulsant activity is found for some thiocarbamoyl derivatives of piperazines (**31**-**33**), morpholine (**37**) and thiamorpholine (**38**). The best of these, 1-(3,5-

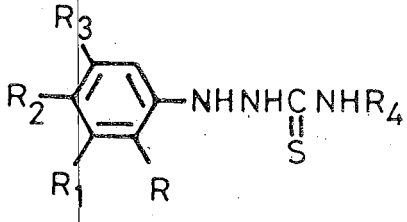
Table 2 – Acetyl and Carbamoyl Derivatives of 3,5-Bistrifluoromethyl Phenylhydrazine



Compd	R	Mol. formula	Crystallised from*	m.p. °C	Antielectroshock activity	
					ED_{50} mg/kg p.o.	ED_{100} mg/kg p.o.
20	Me	$C_{10}H_8F_6N_2O$	I+D	200-1	18.3±1.5	40[c,d]
21	NMe_2	$C_{11}H_{11}F_6N_3O$	E+F	205-8	55.4±4.8	100
22	piperidino	$C_{14}H_{15}F_6N_3O$	D+F	210-12		250
23	morpholino	$C_{13}H_{13}F_6N_3O_2$	D+F	175-78		250

*See Table 1 for solvents of crystallisation.

Table 3 – 1-Arylthiosemicarbazides



[R = R_2 = H for **24**, **26-30**; R = Cl, R_2 = H for **25**]

Compd	R_1	R_3	R_4	Antielectroshock activity	
				ED_{50} mg/kg p.o.	ED_{100} mg/kg p.o.
24	H	H	Me		250
25	H	H	Me	200	>250
26	Cl	H	Me		250
27	Cl	Cl	Me		>250
28	CF_3	CF_3	Me	66.8±5.4	100
29	CF_3	CF_3	Et		>250
30	CF_3	CF_3	$Ph(CH_2)_2$		>250

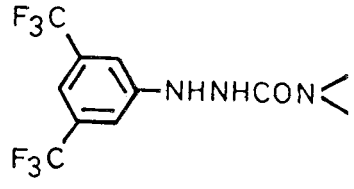
bistrifluoromethyl)phenylthiocarbamoyl-4-benzyl piperazine (**33**) is quite active in the electroshock test in mice with an ED_{50} of about 28 mg, while **31**, the next best, has a value of 53 mg. The former causes hypotonia and ataxia in mice and has not been studied further. The latter is found to exhibit activity in the electroshock test in the rat as well with an ED_{50} of 22.8 mg/kg p.o.

Quantitative structure activity relationships in the C3165-Go (**12**) series

Compounds of Table 1 represent a systematic variation of nuclear and side chain substitution and hence were well-suited for a Hansch analysis. Seventeen compounds from Table 1 and **21** from Table 2 were chosen for analysis. **2** and **6** of Table were omitted since they had very weak activity. Actually ED_{50} for **6** could not be properly determined. Table 5 incorporates data used in the Hansch analysis. π values for aromatic substituents were taken from the data bank[5]; σ values for *meta* and *para* substituents from Tute[6] and the apparent σ-value for *ortho*-Cl was again from literature[7]. ED_{50} values obtained (mg/kg) for protection against electroshock in mice at the third hour after p.o. administration were converted into log $\frac{1}{C}$ (c = mol/kg body weight). Both linear and quadratic regression analyses were carried out with the following results:

Linear regression analysis

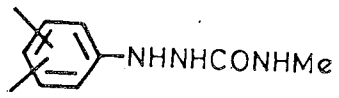
Set 1



compounds 11-19, 21
(n = 10)

$\log \frac{1}{C} = K_0 + K_1\pi$
$K_0 = 4.863$; $K_1 = -0.276 \pm (0.137)$
SD = 0.1512; $r = 0.86$; $F_{1,8} = 21.75$*** (very highly significant)

Set 2



compounds 1,3,5,7,8,9,12 (n = 7)

$\log \frac{1}{C} = K_0 + K_1\pi$ where $\pi = \pi_1 + \pi_2$
$F_{1,5} = 5.52 < 6.61$ (insignificant)

For the benzene substituents π is not the dominating factor.

Multiple regression: Factorisation of π into π_1 and π_2

$\log \frac{1}{C} = K_0 + K_1\pi_1 + K_2\pi_2 + K_3\sigma$
(all compounds of Table 5; $n = 18$)
$K_0 = 3.161$; $K_1 = -0.026 \pm (0.258)$
$K_2 = -0.235 \pm (0.138)$; $K_3 = 0.971 \pm (0.856)$
SD = 0.1913; $r = 0.83$
$F_{3,14} = 10.43$***; $F_{1,14}$ for $K_1 = 0.05$; for $K_2 = 13.46$*** and $K_3 = 5.92$**.

Thus the regression $\log \frac{1}{C}$ on π_1 is insignificant but significant on π_2 and σ.
Thus π_2 and σ would be sufficient for predicting $\log \frac{1}{C}$.

Use of π_2 and σ

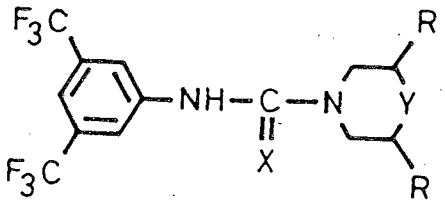
$\log \frac{1}{C} = K_0 + K_2\pi_2 + K_3\sigma$
(all compounds of Table 5; $n = 18$)
$K_0 = 3.159$; $K_2 = -0.240 \pm (0.125)$;
$K_3 = 0.896 \pm (0.388)$; $r = 0.83$
$F_{2,15} = 16.68$***; $F_{1,15}$ for $K_2 = 16.76$*** and for $K_3 = 24.20$***

Both regression coefficients together or alone are highly significant.

Conclusion

We tested quadratic relationship, but it was much less satisfactory than the linear regression which adequately explained the structure-activity observations. The linear regression analysis revealed clearly that the π component of the aromatic substituents need not be included in the regression equation. The σ-values for the aromatic substituents and the π-values of the N-alkyl groups were sufficient for predicting 1/C.

Table 4 – N-(3,5-Bistrifluoromethylphenyl)thiocarbamoyl and Carbamoyl Azacyclics



[X = S for **31-38** and X = O for **39**. R = H for **31-37**, **39** and R = Me for **38**]

Compd	Y	Mol. formula	Crystallised from*	m.p. °C	Antielectroshock activity	
					ED_{50} mg/kg p.o.	ED_{100} mg/kg p.o.
31	N – Me	$C_{14}H_{15}F_6N_3S$	H + F	160-1	53.3 ± 3.9	100
32	$N(CH_2)_2OH$	$C_{15}H_{17}F_6N_3SO$	A + F	142-4	80.7 ± 7.3	250
33	NCH_2Ph	$C_{20}H_{19}F_6N_3S$	A + F	140-2	28.3 ± 5	100[b,c]
34	NPh	$C_{19}H_{17}F_6N_3S$	A + F	177-9		φ
35	NCO_2Et	$C_{16}H_{17}F_6N_3O_2S$	A + F	167-70°		φ
36	CH_2	$C_{14}H_{14}F_6N_2S$	A + F	182-4		φ
37	O	$C_{13}H_{12}F_6N_2OS$	A + F	158-60°	94.7 ± 4.6	250
38	S	$C_{15}H_{16}F_6N_2S_2$	A + F	134-7		>250
39	N – Me	$C_{14}H_{15}F_6N_3O$	A + F	158-60	118.0 ± 12.0	250

*See Table 1 for solvents of crystallisation
φ – no effect upto 250 mg/kg p.o.

Table 5 – QSAR Data for 1-Aryl semicarbazides

Compd	π_1	π_2	$\pi=\pi_1+\pi_2$	σ	ED_{50}	$\log\frac{1}{C}$
1	0	0.52	0.52	0	139.0	3.075
3	1.49	0.52	2.01	0.43	46.88	3.697
4	1.49	2.02	3.51	0.43	318.8	2.936
5	1.05	0.52	1.57	0.54	71.06	3.516
7	2.18	0.52	2.70	1.10	38.02	3.847
8	2.42	0.52	2.94	0.66	127.7	3.321
9	1.97	0.52	2.49	0.60	70.2	3.523
10	1.97	1.02	2.99	0.60	159.4	3.192
11	2.98	0	2.98	0.86	27.2	4.023
12	2.98	0.52	3.50	0.86	30.27	3.998
13	2.98	1.02	4.00	0.86	48.19	3.815
14	2.98	1.52	4.50	0.86	129.3	3.406
15	2.98	2.02	5.00	0.86	165.22	3.721
16	2.98	2.52	5.50	0.86	165.6	3.334
17	2.98	2.62	5.60	0.86	226.5	3.212
18	2.98	1.41	4.39	0.86	112.20	3.493
19	2.98	1.91	4.89	0.86	75.86	3.681
21	2.98	0.87	3.85	0.86	55.3	3.756

Table 6 – Anticonvulsant Profile of **11** and **12** in Relation to Standard Drugs

Compd	Efficacy against electroshock in mice		Rota Rod test AT_{50}	Protective index AT_{50}/ED_{50}	Efficacy against electroshock in rat		Efficacy against Psychomotor electric-shock seizure in mice	
	Postdose hr	ED_{50}	mg/kg p.o.		Postdose hr	ED_{50}	Postdose hr	ED_{50}
	3	27.2±2.2			3	6.5±1.7		
11	6	23.6±1.3	42.7	1.8	6	5.9±0.9	3	100.0
	24	22.6±1.4	30.0	1.3	24	3.4±1.4		
					48	6.5±1.7		
					3	11.8±2.4		
	3	30.3±1.7			6	8.8±1.7	3	71
12	6	26.9±2.3	110.3	4.1	24	5.8±0.8		
	24	25.8±1.6	158.5	6.1	48	15.8±4.0		
	3	11.0±0.7	53.0	4.8	3	34.9±10.9		
Phenytoin	6	10.6±0.7	53.0	4.9	6	20.6± 5.2		φ
	24	φ			24	85.2±13.0		(upto 200 mg)
	1	62.5±3.9	67	1.08	1	22.1±3.8		
Phenurone	3	60.6±5.0	—		3	22.4±4.4	1	89
					6	45.1±10		
	1	11.0±0.4	165	15	1	10.0±2.4		
Carba-	3	10.0±0.2			4	10.0±0.7	3	20
mazepine	16	>30			16	>50		

The negative value for the regression coefficient of π_2 probably reflected higher rate of metabolic destruction with increase in chain length. The very poor activity of **4** becomes easily understandable because σ has been decreased while π_2 has been tremendously increased, both tending to reduced $\log\frac{1}{C}$.

Anticonvulsant profile of C 3884-*Go* (**11**) *and C* 3165-*Go* (**12**)

Compounds **11** and **12** having high anticonvulsant efficacy in the electroshock test at 3 hr were chosen for detailed studies in comparison with standards such as phenytoin, phenurone and carbamazepine. Results are presented in Table 6.

Compounds **11** and **12** did not antagonize metrazol or strychnine induced seizures upto 1000 mg/kg p.o. Against psychomotor seizures, both were about equiactive with phenurone, but only one-fourth to one-fifth as potent as carbamazepine.

In the electroshock test in mice, **11** and **12** were highly active at the ED_{50} doses even 24 hr post drugging, unlike phenytoin and carbamazepine which

required much higher doses. The protective index of **12**, defined as the ratio of ataxic dose in the rota rod test to the ED_{50} in the electroshock test was about the same for **12** and phenytoin for 3 and 6 hr: it was very poor for **11** and phenurone whereas it was superior for carbamazepine. In the rat again, both **11** and **12** had a long duration of action, with low ED_{50} values even at 48 hr, **11** and **12** being respectively 13 and 7.5 times more potent than phenytoin.

Phenytoin and carbamazepine, 50 mg/kg/day and **12**, 25 mg/kg/day given orally for 10 days to chronically epileptic monkeys completely abolished the seizures, without any side effects. Following discontinuation of medication, there were no withdrawal seizures in the three treated groups.

In acute toxicity studies, C 3165-Go (**12**) was relatively nontoxic, LD_{50} in mice and rats being respectively 1096 ± 297 and 2148 ± 278 mg/kg p.o. However, in four-week toxicity studies, rats could not tolerate 30 mg/kg/day, indicating a very high degree of cumulative toxicity. When administered 80 mg/kg p.o. at intervals of 4 days, rats showed good tolerance for a period of 3 months[8].

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