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Synthesis and anticonvulsant and neurotoxicity evaluation of N^4-phthalimido phenyl (thio) semicarbazides

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Abstract

The phenyl (thio) semicarbazide derivatives of phthalimido pharmacophore were synthesized and evaluated for their anticonvulsant and neurotoxic properties. Initial anticonvulsant screening was performed using intraperitoneal (i.p.), maximal electroshock-induced seizure (MES), subcutaneous pentylenetetrazole (scPTZ) and subcutaneous strychnine (sc STY)-induced seizure threshold tests in mice. Compound **2c** afforded protection in all the three screens. Compounds except **1d**, **2a** and **2d** showed no neurotoxicity up to 300 mg/kg. Compounds **1a**, **1b**, **2c**, **2d**, **2g** and **2i** were found to show oral MES activity. The compounds exhibited CNS depression and behavioral despair side effects, lesser than the conventional antiepileptic drugs.

Keywords: Phthalimides; Semicarbazides; Thiosemicarbazides; Anticonvulsants; CNS depressants

1. Introduction

In recent years, aryl semicarbazones (Dimmock et al., 1993; Pandeya et al., 1999a, 2000; Puthucode et al., 1998) and thiosemicarbazones (Dimmock et al., 1990; Karali and Gursoy, 1994; Yogeeswari et al., 2002) have emerged as structurally novel anticonvulsants. Aryl semicarbazides are reported to display excellent anticonvulsant activity in mice and rats compared to that of phenytoin (Andurkar et al., 2001). The aryl semicarbazones were believed to interact at locations on the putative binding site designated as aryl binding site, a hydrogen bonding domain and an auxiliary aryl binding site (Dimmock et al., 1995a). The aryl binding site can be phenyl or other hydrophobic moieties with retention of the anticonvulsant activity (Dimmock et al., 1995b; Pandeya et al., 2001). *N*-Phenyl phthalimide derivatives were also found to possess anticonvulsant potency associated with a phenytoin-like profile (Bailleux et al., 1994a, 1994b, 1995; Poupaert et al., 1995). More recently a variety of substituted *N*-phenyl pthalimide derivatives have emerged as potent anticonvulsants (Vamecq et al., 1998, 2000).

In view of these data, we have undertaken the synthesis and pharmacological evaluation of hybrids of aryl (thio) semicarbazides and *N*-phenyl phthalimides (Fig. 1). In the present work, synthesis of N^4-phthalimido phenyl semicarbazide and thiosemicarbazide derivatives was accomplished. The compounds were evaluated for their antiepileptic and neurotoxic properties through the antiepileptic drug development (ADD) program developed by the National Institute of Health (Kupferberg and Stables, 1998; Stables and Kupferberg, 1997; White et al., 1995a, 1995b). The compounds were also evaluated for other CNS activities.

2. Experimental

2.1. Chemistry

The melting points were determined in open capillary tubes in a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Jasco IR Report 100 Spectrophotometer. The ^{1}H NMR

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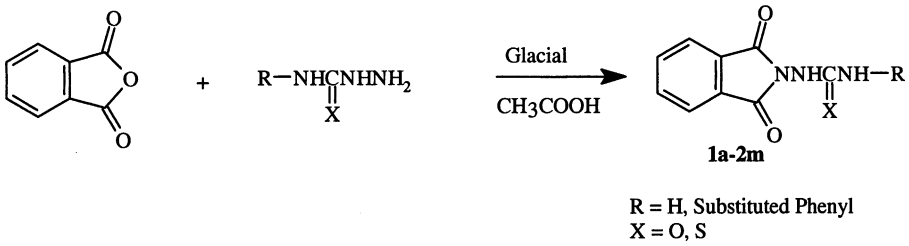


Fig. 1. Synthetic protocol of the target compounds.

spectra were taken on a Jeol Fx 90Q Fourier transform NMR spectrometer. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane (TMS) as an internal standard. Elemental analyses were realized on a Perkin-Elmer model 240c analyzer and were within ±0.4% of the theoretical values. The homogeneity of the compounds was checked by TLC on silica gel.

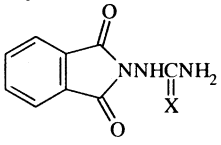
2.1.1. Synthesis of aryl semicarbazides

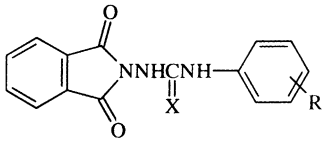
Aryl semicarbazides were prepared from the respective anilines according to the procedures reported earlier (Pandeya et al., 1999b). Briefly aryl ureas were prepared from anilines by reacting with equimolar quantities of sodium cyanate in the presence of glacial acetic acid. The urea thus obtained was refluxed with equimolar amounts of hydrazine hydrate and sodium hydroxide in ethanol as the solvent.

2.1.2. Synthesis of aryl thiosemicarbazides

Aryl thiosemicarbazides were prepared from the respective anilines in a similar manner as reported earlier (Pandeya et al., 1999c). Anilines on treatment with carbon disulphide in the presence of potassium hydroxide in tetrahydrofuran gave potassium salt of the corresponding dithiocarbamate, which on reaction with hydrazine hydrate yielded the respective thiosemicarbazide.

Table 1
Physical constants of the synthesized compounds


1a, 2a


1b-1h, 2b-2m

Compound	X	R	Yield (%)	Melting point (°C)	Molecular formula[a]	R_f[b]	R_m[c]
1a	O	–	32	244	$C_9H_7N_3O_3$	0.73	−0.44
1b	O	2-Cl	46	139	$C_{15}H_{10}N_3O_3Cl$	0.77	−0.54
1c	O	4-Cl	41	184	$C_{15}H_{10}N_3O_3Cl$	0.40	0.18
1d	O	4-NO_2	64	206	$C_{15}H_{10}N_4O_5$	0.37	0.23
1e	O	4-OCH_3	61	149	$C_{16}H_{13}N_3O_4$	0.40	0.18
1f	O	4-SO_3H	89	268	$C_{15}H_{11}N_3O_6S$	0.66	−0.29
1g	O	4-$NHCOCH_3$	62	264	$C_{17}H_{14}N_4O_4$	0.75	−0.48
1h	O	4-N=N–Ph	95	246	$C_{21}H_{15}N_5O_3$	0.72	−0.42
2a	S	–	51	249	$C_9H_7N_3O_2S$	0.67	−0.31
2b	S	2-Cl	60	273	$C_{15}H_{10}N_3O_2SCl$	0.71	−0.40
2c	S	4-Cl	99	159	$C_{15}H_{10}N_3O_2SCl$	0.74	−0.46
2d	S	2-NO_2	54	194	$C_{15}H_{10}N_4O_4S$	0.68	−0.33
2e	S	4-NO_2	46	169	$C_{15}H_{10}N_4O_4S$	0.52	−0.68
2f	S	2-OCH_3	59	137	$C_{16}H_{13}N_3O_3S$	0.45	0.09
2g	S	4-OCH_3	61	154	$C_{16}H_{13}N_3O_3S$	0.75	−0.48
2h	S	4-CH_3	56	193	$C_{16}H_{13}N_3O_2S$	0.62	−0.21
2I	S	4-OH	55	279	$C_{15}H_{11}N_3O_3S$	0.58	−0.14
2j	S	4-COOH	56	275	$C_{16}H_{11}N_3O_4S$	0.54	−0.07
2k	S	4-COOEt	70	151	$C_{18}H_{15}N_3O_4S$	0.72	−0.42
2l	S	4-SO_2NH_2	89	164	$C_{15}H_{12}N_4O_4S_2$	0.36	0.25
2m	S	4-N=N–Ph	61	251	$C_{21}H_{15}N_5O_2S$	0.90	−0.96

[a] Elemental analyses for C, H, N were within ±0.4% of the theoretical values.
[b] Eluants used in TLC were petroleum ether:ethyl acetate (7:3) for all compounds except **1a**, **1c**, **1g**, **1h**, **2a**, **2e**, **2h** and **2l** for which chloroform:methanol (9:1) was used.
[c] $R_m = \log(1 - 1/R_f)$.

2.1.3. General Method for the synthesis of N^4-phthalimido phenyl (thio) semicarbazides

The titled compounds were synthesized as per the reported procedure for *N*-phenyl pthalimides (Hearn and Lucas, 1984; Vamecq et al., 2000). An equimolar mixture of the respective aryl (thio) semicarbazide and phthalic anhydride in acetic acid was stirred and heated under reflux for 5 h. The product of this reaction was precipitated by the addition of water, filtered, dried and recrystallized from 95% ethanol. The physical data of the titled compounds are presented in Table 1. IR spectra (ν, cm^{-1}) of some representative compounds were as follows:

1c: 3500 (amino), 3300 (CONH), 1780–1720 (C=O of phthalimide), 1635, 1450 (phenyl), 1620 (C=O), 1100 (C–Cl).

1d: 3420 (amino), 3346 (CONH), 1765, 1705 (C=O of phthalimide), 1635, 1490 (phenyl), 1650 (C=O), 1350 (nitro).

2h: 3426, 3340, 1633 (amino), 1780, 1711 (imide), 1500 (C=S), 1660, 1470 (phenyl), ^{1}H NMR (90 MHz, δ ppm) spectra of some representative compounds were as follows:

1e ($CDCl_3$): 3.65 (s, 3H, OCH_3), 5.85 (s, 1H, ArNH, D_2O exchangeable), 7.7–8.4 (m, 8H, ArH), 8.77 (s, 1H, CONH, D_2O exchangeable).

2h ($CDCl_3$): 2.30 (s, 3H, CH_3), 6.75 (s, 1H, ArNH, D_2O exchangeable), 7.65–8.22 (m, 8H, ArH), 9.55 (s, 1H, C_3NH, D_2O exchangeable).

2.2. Pharmacological evaluation

The anticonvulsant evaluation was carried out using reported procedures (Löscher and Schmidt, 1994; Krall et al., 1978; Porter et al., 1984). Male albino mice (CF-1 strain, 18–25 g) and male albino rats (Sprague–Dawley, 100–150 g) were used as experimental animals. The test compounds were suspended in 0.5% methyl cellulose–water mixture or in polyethylene glycol (PEG).

2.2.1. Anticonvulsant screening

In the preliminary screening, each compound was administered as an i.p. injection at three dose levels (30, 100 and 300 mg/kg) and the anticonvulsant activity assessed after 30 min and 4 h intervals of administration. The anticonvulsant efficacy was evaluated by the maximal electroshock-induced seizure (MES), subcutaneous pentylenetetrazole (scPTZ) and subcutaneous strychnine (scSTY)-induced seizure threshold tests and the data are presented in Table 2. Some selected derivatives described in this study were examined for oral activity in the rat MES screen (Brodie, 1992) and the results are presented in Table 3.

Table 2
Anticonvulsant and neurotoxicity screening results of the titled compounds

Compound	Intraperitoneal injection in mice[a]							
	MES screen		scPTZ screen		scSTY screen[b]		Toxicity screen	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
1b	100	–	–	–	X	X	–	–
1c	–	300[c]	–	100	X	X	–	–
1d	–	–	300	–	X	X	–[d]	–
1f	–	–	30	–	X	X	–	–
1g	–	300	–	–	X	X	–	–
2a	–	–	–	–	300	–	300	–
2c	–[e]	300	300	300	300	300	300	100
2d	–	–	–	–	300	–	–	–
2e	–	–	–	–	300	300	–	–
2g	300	–	–	–	–	–	–	–
2I	–	–	–	–	300	–	–	–
2j	–	–	300	–	–	–	–	–
2m	–	300	–	–	300	–	–	–
Phenytoin[f]	30	30	–	–	X	X	100	100
Carbamazepine[f]	30	100	100	300	X	X	100	300
Sodium valproate[f]	–	–	300	–	X	X	–	–
Ethosuximide[f]	–	–	300	–	X	X	–	–
Phenobarbital[f]	100	30	30	30	X	X	100	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 animal. The animals were examined 0.5 and 4 h after administration. The dash (–) indicates an absence of activity at maximum dose administered (300 mg/kg) and 'X' mark indicates not tested.

[b] Rats were used as experimental animals.

[c] At 100 mg/kg, 1/6.

[d] At 100 mg/kg, 1/4.

[e] At 100 mg/kg after 2 h, 2/3 and at 30 mg/kg, 1/5.

[f] Data from references (Dimmock et al., 1996; Porter et al., 1984; Flaherty et al., 1996).

Table 3
Evaluation of selected compounds in the MES test after oral administration (30 mg/kg) to rats

Compound	Oral administration to rats[a]				
	0.25 h	0.5 h	1 h	2 h	4 h
1a	0	0	0	2	2
1b	1	4	2	3	1
2c	X	1	0	2	2
2d	3	0	0	1	2
2g	1	3	2	1	0
2I	0	0	0	2	0
Phaenytoin	1	4	3	3	3

[a] The figures indicate the number of rats out of four, which were protected. The mark 'X' indicates not tested.

2.2.2. Neurotoxicity screen

Minimal motor impairment was measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod that rotates at 10 revolutions/min. The rod diameter was 3.2 cm. Trained animals were given i.p. injection of the test compounds in doses of 30, 100 and 300 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials.

Table 4
Behavioral study on the titled compounds using actophotometer

Compound[a]	Score[b] (time span 5 min)
Control	275 ± 31.11**
1a	410 ± 13.58**
1b	216 ± 15.74**
1c	111 ± 32.75**
1d	155 ± 10.25**
1e	173 ± 23.69**
1f	141 ± 10.46**
1g	38 ± 22.35**
1h	115 ± 12.00**
2a	108 ± 12.37**
2b	294 ± 13.54*
2c	276 ± 15.57 NS
2d	210 ± 16.15**
2e	409 ± 22.32**
2f	204 ± 20.33**
2g	217 ± 10.22**
2h	207 ± 10.12**
2I	286 ± 24.44 NS
2j	330 ± 27.73**
2l	285 ± 20.22 NS
2m	60 ± 6.32**
Phenytoin[c]	44 ± 4.56**
Phenobarbital[c]	346 ± 7.22**
Sodium valproate[c]	30 ± 3.66**

[a] The compounds were tested at a dose of 30 mg/kg (i.p.).
[b] Each score represents the mean ±S.E.M. of six rats significantly different from the control and NS, insignificant (Student's *t*-test).
[c] Tested at 5 mg/kg p.o. and for sodium valproate at 100 mg/kg p.o.
* $P < 005$.
** $P < 0.005$.

Table 5
CNS depressant study on selected N^4-pthalimido phenyl semicarbazides in forced swim pool test

Compound[a]	Immobility time[b] (min)	
	Control (24 h prior)	Post-treatment (60 min after)
PEG	136.3 ± 6.3	l21.2 ± 9.6
1a	132.8 ± 8.4	152.4 ± 9.3
1c	127.4 ± 7.3	147.6 ± 8.7
1d	137.3 ± 8.1	146.4 ± 4.1
1e	133.5 ± 4.3	131.2 ± 2.5 NS
1f	132.2 ± 2.2	123.6 ± 2.6
1g	143.9 ± 8.1	150.6 ± 5.1 NS
1h	128.3 ± 7.7	132.6 ± 4.2 NS
Carbamazepine	138.4 ± 7.3	240.6 ± 4.l
Sodium valproate	125.8 ± 8.9	265.8 ± 4.3
Imipramine	135.3 ± 9.7	87.6 ± 4.6

[a] The compounds were tested at a dose of 30 mg/kg (i.p.).
[b] Each value represents the mean ±S.E.M. of six rats significantly different from the control at $P < 0.005$, and NS, denotes not significant at $t_{99.5\%}$ (Student's *t*-test).

2.2.3. Behavioral test

The titled compounds (30 mg/kg) were screened for their behavioural effects using actophotometer (Boissier and Simon, 1965). Albino mice were placed inside the actophotometer after 30 min of drug injection. The behaviour of animals inside the photocell was recorded as a digital score. Increased scores suggest good behavioural activity. The control animal was administered PEG. The observations are tabulated (Table 4).

2.2.4. CNS depressant study

The forced swim pool method described earlier was followed (Porsolt et al., 1978). Albino mice were placed in a chamber (diameter: 45 cm; height: 20 cm) containing water up to a height of 15 cm at 25 ± 2 °C. Two swim sessions were conducted, an initial 15 min pre-test, followed by a 5 min test 24 h later. The animals were administered an i.p. injection (30 mg/kg) of the test compounds after the pre-test session. The period of immobility (passive floating without struggling and making only those movements which are necessary to keep its head above the surface of water) during the 5 min test period were measured. The results are presented in Table 5.

3. Results and discussion

Initial anticonvulsant activity and neurotoxicity data for the titled compounds are reported in Table 2 along with the literature data on phenytoin, carbamazepine, sodium valproate, phenobarbital and ethosuximide (Porter et al., 1984; Dimmock et al., 1996; Flaherty et al., 1996). The MES and subcutaneous pentylenetetrazole (scPTZ) tests have become the most widely employed seizure models for the early identification and high throughput screening of

investigational antiepileptic drugs. At the three doses (30, 100 and 300 mg/kg) tested, compounds **1a**, **1e**, **1h**, **2b**, **2f**, **2h**, **2k** and **2l** were found to be devoid of activity in both MES and scPTZ tests and presented no neurotoxicity in any of the doses administered. Compounds that exhibited anti-MES activity include **1b**, **1c**, **1g**, **2c**, **2g** and **2m** showing their ability to prevent seizure spread and the mechanism may involve blockade of neuronal voltage-dependent Na+ channels as exhibited by the *N*-phenyl phthalimides (Vamecq et al., 2000). Among these **2c** exhibited protection against all the screens with neurotoxicity. In the MES screen, 2-chioro phenyl semicarbazide, **1b** was more potent than 4-chioro derivative, **1c** but with thiosemicarbazides it was the opposite. The nitro derivatives (**1d**, **2d** and **2e**) were found to be ineffective in this screen. The 4-methoxy phenyl thiosemicarbazide (**2g**) did show activity and the semicarbazide analog did not. Similar results were obtained with the 4-diazo compounds (**1h** and **2m**). The compounds **1c**, **1d**, **1f**, **2c** and **2j** showed anti-scPTZ activity indicating their ability to elevate seizure threshold. Compound **1f** was more potent than sodium valproate and ethosuximide. In the PTZ screen, the 4-chloro phenyl compound (**1c** and **2c**) showed protection at 100 and 300 mg/kg but the 2-chioro derivative (**1b** and **2b**) did not show any protection. The 4-phenyl sulfonic acid (**1f**) derivative showed more potency than other compounds. Among the thiosemicarbazide derivatives, compounds that showed protection against subcutaneous strychnine induced seizure threshold test (scSTY) include **2a**, **2c**–**2e** and **2i** which indicate that N^4-pthalimido phenyl thio semicarbazides could also act through inhibitory glycine receptors. In the neurotoxicity screen, all the compounds except **2a** and **2c** were devoid of toxicity at doses up to 300 mg/kg.

Some selected compounds (**1a**, **1b**, **2c**, **2d**, **2g** and **2i**) were examined for activity in the rat oral screen at 30 mg/kg dose to study their activity profiles. The compounds which were inactive or showed moderate activity in the mice i.p. screen were selected randomly. The data are presented in Table 3. Compound **2c** did not show much activity as it had been found with mice i.p. MES screen where at 300 mg/kg at 4 h it showed 100% protection. The 2-chioro phenyl semicarbazide derivative (**1b**) afforded protection against seizures with a peak time of activity at 0.5 h (100%) and 2 h (75%) compared to phenytoin. It is found that these compounds exhibit activity differences between mice and rats. The compound **1b** may undergo some oral activation in the gut to an active metabolite. This needs some more experimentation to confirm the hypothesis. There was no apparent toxicity observed in rats at the dose level of 30 mg/kg.

In the behavioral despair test the compounds except **1a**, **2b**, **2e**, **2i** and **2j** showed decreased motor activity as indicated by the actophotometer scores (Table 4). The compounds with acetamido group (**1g**) showed the maximum motor impairment with the lowest actophotometer score of 38 ± 22.35. The N^4-pthalimido phenylsemicarbazide derivatives were studied for CNS depressant effect by Porsolt's forced swim pool test and compared with Imipramine. The present study showed an increase in the immobility time by all the compounds (except **1e** and **1f**) but not as much as the standard antiepileptic drugs carbamazepine and sodium valproate, indicating lesser CNS depression effects than that of conventional drugs.

In conclusion the present results have revealed that a number of phthalimido phenyl (thio) semicarbazides exhibit a range of activities in anticonvulsant screens, with compound **1b** showing anti-MES activity comparable with phenytoin.

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