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Original article

Anticonvulsant and neurotoxicity evaluation of some 6-chlorobenzothiazolyl-2-thiosemicarbazones

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Abstract

Ten 6-chlorobenzothiazolyl-2-thiosemicarbazones were synthesised and screened for anticonvulsant and neurotoxic properties. Most of the compounds showed anticonvulsant activity against both maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole screens. Eight compounds have shown good protection in the rat p.o. MES test at 30 mg kg^{-1}. Compound **1** [4-(6-chlorobenzothiazol-2-yl)-1-(3-isatinimino)thiosemicarbazone] emerged as the most promising one with an ED_{50} of 17.86 and 6.07 mg kg^{-1} in mice i.p. and rat p.o., respectively. Compound **1** showed a weak ability to block the expression of fully kindled seizures. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Benzothiazolylthiosemicarbazones; Electroshock; Pentylenetetrazole; Neurotoxicity; Fully kindled

1. Introduction

The conditions grouped under the term epilepsy constitute an area of continuing medical need. It has been estimated that about 20% of the patients with epilepsy using the first generation of antiepileptic drugs (Phenobarbital, Phenytoin, Carbamazepine, Sodium valproate and Diazepam) were not able to acquire adequate control of seizure [1]. In recent years, aryl semicarbazones have emerged as structurally novel anticonvulsants [2–4]. 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 [5]. The aryl group can be replaced by other hydrophobic moieties with retention of anticonvulsant activity [6]. In 1985, Riluzole [6-(trifluoromethoxy)-2-benzothiazolamine] was reported to be a potent anticonvulsant agent [7]. Various 2-benzothiazolamine derivatives were investigated as anticonvulsants and the 6-chloro compound possessed anticonvulsant activity in MES with no ataxia [8]. In our earlier report thiosemicarbazone derivatives have shown moderate anticonvulsant activity [9]. Thus in the present study 6-chlorobenzothiazolyl thiosemicarbazones, bioisoster of semicarbazones have been synthesised to understand their potential as anticonvulsants. Isatin derivatives were reported to possess anticonvulsant properties [3,9–11], and hence considered important in the present study to investigate the effect of the auxiliary heteroaryl ring. Epilepsy, particularly temporal lobe epilepsy with complex partial seizures, is often associated with disturbance of cognitive function and behaviour, and it has been suggested that a drug combining cognition enhancing and antiepileptic activity would be a benefit in the treatment of epileptic patients [12]. In the present study one compound has been tested in the preliminary hippocampal-kindling screen. The 6-chlorobenzothiazolyl thiosemicarbazones have shown activity in the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) screens, which would serve as structurally novel class for subsequent molecular modifications.

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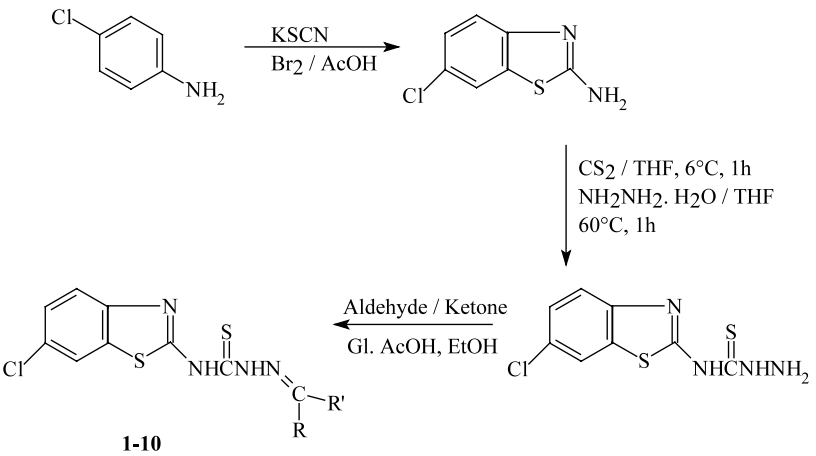

Compound	CRR'
1	3-isatinyl
2	5-chloro-3-isatinyl
3	5-bromo-3-isatinyl
4	5-fluoro-3-isatinyl
5	5-methyl-3-isatinyl
6	2-chlorophenyl
7	2-hydroxyphenyl
8	4-N,N-dimethylaminophenyl
9	4-hydroxyacetophenone
10	4-nitroacetophenone

Fig. 1. Synthetic protocol of the title compounds.

2. Chemistry

The synthesis of 6-chlorobenzothiazolyl-2-thiosemicarbazones was accomplished as shown in the Fig. 1. 6-Chlorobenzothiazolyl-2-thiosemicarbazone was synthesised from 4-chloroaniline via a one-pot procedure. In this method the thiourea is produced in situ and then oxidatively cyclised to the desired heterocycle. Thus when **4**-chloroaniline was treated with potassium thiocyanate and bromine in glacial acetic acid, the expected intramolecularly cyclised 6-chloro-2-benzothiazolamine product was isolated. This benzothiazolamine derivative on treatment with carbon disulphide in the presence of potassium hydroxide in tetrahydrofuran (THF) gave potassium salt of the corresponding benzothiazolyl dithiocarbamate, which on reaction with hydrazine hydrate yielded 6-chloro-2-benzothiazolyl thiosemicarbazide. The thiosemicarbazones were prepared by reaction of the appropriate aldehyde or ketone or isatin derivatives. The thiosemicarbazones (Table 1) were identified by spectral data.

3. Pharmacology

All the compounds were injected intraperitoneally into the mice and evaluated in the initial anticonvulsant screening with at least three dose levels (30, 100 and 300 mg kg^{-1}), following the anticonvulsant drug development (ADD) program protocol [13,14]. The profile of anticonvulsant activity was established by MES pattern test and scPTZ seizure threshold test. Minimal motor impairment was measured by the rotorod (neurotoxicity, NT) test.

Some compounds were administered orally to rats and examined in the MES screen. Experiments in fully kindled rats were carried out for one compound as described earlier [15,16].

Table 1
Physical data of 6-chloro-2-benzothiazolyl thiosemicarbazones

Compound	Yield (%)	M.p. (°C)	Molecular formula [a]	Molecular weight
1	69	135	$C_{16}H_{10}N_5OS_2Cl$	387.45
2	62	116 [b]	$C_{16}H_9N_5OS_2Cl_2$	421.90
3	52	135 [b]	$C_{16}H_9N_5OS_2BrCl$	466.45
4	74	159 [b]	$C_{16}H_9N_5OS_2FCl$	405.45
5	56	162	$C_{17}H_{12}N_5OS_2Cl$	401.89
6	59	141	$C_{15}H_{10}N_4S_2Cl_2$	381.29
7	83	125 [b]	$C_{15}H_{11}N_4OS_2Cl$	362.85
8	68	138	$C_{17}H_{16}N_5S_2Cl$	389.92
9	57	177	$C_{16}H_{13}N_4OS_2Cl$	376.45
10	65	154	$C_{16}H_{12}N_5O_2S_2Cl$	405.45

[a] Elemental analyses for C, H, N were within 0.4% of the theoretical values.
[b] With decomposition.

Table 2
Anticonvulsant activity and minimal motor impairment of 6-chloro-2-benzothiazolyl thiosemicarbazones

Compound	Intraperitoneal injection in mice [a]					
	MES screen		scPTZ screen		Toxicity screen	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
1	30	100	100	– [b]	30	100
2	30	100	300 [c]	–	300 [d]	–
3	100	300	300 [c]	–	300	300
4	30	100	30 [c]	100	30	100
5	30	100	100	100	30	100
6	100	–	100	300	300 [e]	300
7	100	300	300 [f]	300	100	300 [e]
8	–	–	– [g]	–	–	–
9	10	100	30 [c]	30 [c]	30	30
10	100	100	100	300	100 [e]	100
Phenytoin [h]	30	30	–	–	100	100
Carbamazepine [h]	30	100	100	300	100	300
Sodium valproate [h]	–	–	300	–	–	–
Ethosuximide [h]	–	–	300	–	–	–
Phenobarbital [h]	100	30	30	30	100	300

[a] Doses of 30, 100 and 300 mg kg^{-1} were administered. The figures in the table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 and 4 h after injections were made. The dash (–) indicates an absence of activity at maximum dose administered (300 mg kg^{-1}).
[b] Died during test at 300 mg kg^{-1} without seizure.
[c] Myoclonic jerks.
[d] Neurotoxicity at 100 mg kg^{-1} (0.25 h, 1 h).
[e] Loss of righting reflex.
[f] At 100 mg kg^{-1}, after 0.25 h, 3/5 and after 1 h 4/5 mice were protected.
[g] Death following tonic extension.
[h] Data from Refs. [14,17,18].

4. Results and discussion

Initial anticonvulsant activity and neurotoxicity data for the 6-chlorobenzothiazolyl thiosemicarbazones are reported in Table 2, along with the literature data on Phenytoin, Carbamazepine, Sodium valproate, Phenobarbital and Ethosuximide [14,17,18]. All the 6-chloro-2-benzothiazolyl thiosemicarbazone derivatives except **8** were active in both MES and scPTZ tests. In the earlier reports it was highlighted that presence of electron rich atom/group attached at the *para* position of the aryl ring showed increased potency in the MES screen [5,19]. Replacement of the aryl ring with heteroaryl ring was found to show good activity. In the MES screen, compound **9** showed potency greater than the standard drugs at 10 mg kg^{-1} dose with neurotoxicity at 30 mg kg^{-1}. Compound **2** showed anti-MES activity similar to Carbamazepine, but showed low neurotoxicity compared to Phenytoin, Carbamazepine and Phenobarbital. Compound **6** displayed activity in the MES screen after 0.5 h (100 mg kg^{-1}) while it was active at both 0.5 (100 mg kg^{-1}) and 4 h (300 mg kg^{-1}) in the scPTZ test. The most active compounds in the scPTZ test, a test used to identify compounds that elevate seizure threshold, were **4** and **9**. The bioevaluation led to the understanding of the importance of the size of aryl ring at the carbimino carbon atom. Generally isatinimino derivatives (**1**–**5**) were more potent than benzylidene/acetophenone derivatives (**6**–**10**). In the neurotoxicity test, isatinimino and acetophenone derivatives were more toxic than benzylidene derivatives. Among the isatinimino compounds, 5-fluoro derivative (**4**) was more active against both the screens, but showed neurotoxicity at the active dose. The 5-chloro/bromo derivatives, compounds **2** and **3**, respectively, were less neurotoxic. The 2-chloro arylidene compound (**6**) emerged as an anticonvulsant compound with low neurotoxicity. It was earlier reported by Pavia et al. [20] that 2-substitution in the phenyl ring with electron-donating groups was generally beneficial. The 4-hydroxyacetophenone compound (**9**) showed potential anti-MES activity with high neurotoxicity. Compounds that showed myoclonic jerks in the scPTZ test include **2**, **3** (300 mg kg^{-1}) and **9** (30 mg kg^{-1}). Mice were unable to grasp rotorod after administration of the following compounds, viz. **2** (100, 0.25 h, 1 h), **6** (300, 0.5 h), **7** (300, 4 h) and **10** (100, 0.5 h).

Selected compounds (except **3** and **8**) were examined for activity in the rat oral MES screen and the data are presented in Table 3. Initially a dose of 30 mg kg^{-1} was

Table 3
Evaluation of selected compounds in the MES test after oral administration (30 mg kg^{-1}) to rats

Compound	Oral administration to rats [a] (h)				
	0.25	0.5	1	2	4
1	4	4	4	4	4
2	3	4	3	4	1
4	2	4	4	3	1
5	4	4	3	4	3
6 [b]	4	2	3	2	3
7	3	3	2	4	X
9	4	4	4	4	4
10	4	4	4	4	4
Phenytoin	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.
[b] Compound **6** in the rat p.o. scPTZ test at 50 mg kg^{-1} gave protection profile as 1, 2 and 1 at 0.5, 1 and 2 h, respectively.

employed. All the compounds tested afforded complete protection against seizures confirming their potential utility as prototypic molecules and compounds **1**, **5**, **9** and **10** emerged as the most active compounds in the oral MES screen. Compound **6** tested for the rat oral scPTZ screen at 50 mg kg^{-1} showed 50% protection at 1 h.

Compound **1** was carried on to a phase II evaluation for quantification of activities (ED_{50} and TD_{50}) against MES and scPTZ-induced seizures. These pharmacological parameters are presented in Table 4 along with the standard anticonvulsant drugs Phenytoin, Phenobarbital, Valproate and Ethosuximide [14]. The ED_{50} value confirmed the phase I findings that compound **1** was effective than the reference drug against both the MES and scPTZ-induced seizures. Compound **1** was more potent than Valproate against MES and scPTZ tests and more effective than Ethosuximide against MES-induced seizure. The compound showed protective index (PI) value of 8.77 in the rat p.o. identification in the MES screen.

Table 5
Preliminary hippocampal-kindling screen of compound **1** in rats, i.p. at 100 mg kg^{-1}

	Seizure score		ADD [a] (s)	
	Predrug	Drug	Predrug	Drug
Rat #1	5	4	50–77	77
Rat #2	5	3	41–88	97

[a] ADD = after discharge duration (time of maximum effect: 135 min).

In the preliminary hippocampal-kindling screen in rats (i.p.), compound **1** was administered at a single dose of 100 mg kg^{-1} and the after discharge threshold (ADT) was determined either at 30, 60, 90 min or more after administration. Seizure score and after discharge (AD) duration in seconds were recorded and the result is tabulated in Table 5. The seizure severity was classified behaviourally according to Racine [15] as: (1) immobility, eye closure, twitching of vibrissae, sniffing and facial clonus; (2) head nodding associated with more severe facial clonus; (3) clonus of one of the fore limbs; (4) rearing, often accomplished by bilateral forelimb clonus; and (5) all of the above plus loss of balance and falling, accomplished by generalised clonic seizures. The AD duration was the duration of limbic (stage 1–2) and/or motor seizures (stage 3–5). Behavioural alterations after administration of compound **1** were determined at different times after injection up to 2 min before amygdala stimulation. Results suggest only a weak ability to block the expression of fully kindled seizures. However, further testing would be

Table 4
Quantitative anticonvulsant testing data

Compound	Test animals	Route	ED_{50} (mg kg^{-1}) [95% CI]		TD_{50} (mg kg^{-1}) [95%m CI]	PI (TD_{50}/ED_{50})	
			MES	scPTZ		MES	scPTZ
1	Mice	i.p.	17.86 (14.96–20.06)	>40	20.81 (16.62–26.99)	1.17	<0.520
	Rats	p.o.	6.07 (3.72–8.33)	>250	53.23 (41.71–67.29)	8.77	<0.213
Phenytoin	Mice	i.p.	9.5 (8–10)	– [a]	65 (52–72)	6.9	<0.22
	Rats	p.o.	30 (22–39)	– [b]	– [c]	>100	–
Phenobarbital	Mice	i.p.	22 (15–26)	13 (5.9–16)	69 (63–73)	3.2	5.2
	Rats	p.o.	9.1 (7.6–12)	12 (7.7–15)	61 (44–96)	6.7	5.3
Valproate	Mice	i.p.	272 (247–338)	149 (123–177)	426 (369–450)	1.6	2.9
	Rats	p.o.	490 (351–728)	180 (147–210)	280 (191–353)	0.57	1.6
Ethosuximide	Mice	i.p.	>1000	130	441 (383–485)	<0.44	3.4
	Rats	p.o.	– [d]	54 (46–61)	1010 (902–1110)	<0.84	19

[a] No protection up to 300 mg kg^{-1}.
[b] No protection up to 800 mg kg^{-1}.
[c] No ataxia up to 3000 mg kg^{-1}.
[d] No protection up to 1200 mg kg^{-1}.

required before any definite conclusion regarding efficacy against focal seizures could be drawn.

The potency and spectrum of activity of these compounds were comparable to that of standard drugs. In this respect, it should be noted that only few standard anticonvulsants exhibit such a broad spectrum of activity in these threshold models. It is important to note that several clinically effective drugs, including Primidone and Vigabatrin are not capable of blocking seizures in both the MES and scPTZ test [21,22].

5. Experimental protocols

5.1. Chemistry

Melting points were determined in open capillary tubes in a Thomas Hoover melting point apparatus and are uncorrected. Infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded for the compounds in Jasco IR Report 100 (KBr) and JEOL Fx 90Q (Fourier transform) instruments, respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. All exchangeable protons were confirmed by addition of D_2O. Elemental analysis (C, H, N) was undertaken with Perkin–Elmer Model 240C analysis.

5.1.1. Synthesis of 6-chloro-2-benzothiazolyl thiosemicarbazones

6-Chloro-2-benzothiazolamine was synthesised from 4-chloroaniline by a reported procedure [8]. 6-Chloro-2-benzothiazolyl thiosemicarbazide was synthesised from the 2-amino derivative in a similar manner as reported earlier [23].

To a solution of 6-chloro-2-benzothiazolyl thiosemicarbazide (0.02 mol) in ethanol was added an equimolar quantity of the appropriate isatin derivative or other aryl aldehyde or ketone. The pH of the reaction mixture was adjusted between 5 and 6 by adding glacial acetic acid. The reaction mixture was refluxed for 24 h. The product obtained after pouring into ice was filtered, and recrystallised from 95% ethanol. The physical data of the semicarbazones are presented in Table 1. The IR spectrum of a representative compound **1** was as follows (cm^{-1}): 3200 (CONH), 1700 (C=O), 1640 (C=N) and 1015 (C=S). ^{1}H-NMR (90 MHz, δ) spectra of some representative compounds were as follows: **1** ($CDCl_3$): 7–7.5 (m, 7H, Ar–H), 9.6 (s, 2H, 2 × NH, D_2O exchangeable), 10.4 (s, 1H, NH of isatin, D_2O exchangeable); **2** ($CDCl_3$): 7.2–7.7 (m, 6H, Ar–H), 9.45 (s, 2H, 2 × NH, D_2O exchangeable), 10.0 (s, 1H, NH of isatin, D_2O exchangeable); **6** ($CDCl_3$): 6.74 (s, 1H, Carbimino H), 7.2–7.6 (m, 7H, Ar–H), 9.89 (s, 2H, 2 × NH, D_2O exchangeable); **7** ($CDCl_3$): 6.87 (s, 1H, Carbimino H), 7.2–7.66 (m, 7H, Ar–H), 7.78 (s, 1H, OH), 9.61 (s, 2H, 2 × NH, D_2O exchangeable); **10** ($CDCl_3$): 2.4 (s, 3H, N=C(CH_3)), 7.1–7.46 (m, 7H, Ar–H), 9.56 (s, 2H, 2 × NH, D_2O exchangeable).

5.2. Pharmacology

The anticonvulsant evaluation was carried out using reported procedures [12,13]. 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).

5.2.1. 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^{-1}) with anticonvulsant activity and neurotoxicity assessed at 30 min and 4 h intervals after administration. Anticonvulsant efficacy was measured by MES and scPTZ 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. The results are presented in Table 2.

The pharmacological parameters estimated in the preliminary screening were quantified for compound **1** (Table 4). Anticonvulsant activity was expressed in terms of the median effective dose (ED_{50}), and NT was expressed as the median toxic dose (TD_{50}). For determination of the ED_{50} and TD_{50}, groups of 6–12 mice were given a range of i.p. doses of the test drug until at least three points were established in the range of 10–90% seizure protection or minimal observed NT. From the plot of this data, the respective ED_{50}, TD_{50} values, 95% confidence intervals, slope of the regression line, and the standard error of the slope were calculated by means of a computer program written at NINDS, NIH.

5.2.2. Preliminary hippocampal-kindling screen

The kindling procedure for drug experiments in fully kindled rats was according to Löscher and Honack [24]. Briefly, the rats were anaesthetised with chloral hydrate (360 mg kg^{-1} i.p.) for implantation of a bipolar electrode into the right hemisphere aimed at the basolateral amygdala. Electrical stimulation of the amygdala was initiated after a recovery period of 2 weeks after surgery. Threshold for induction of amygdala after discharge (prekindling ADT) was determined and constant current stimulations (500 μA, 1 ms, monophasic square-wave pulse, 50 s^{-1} for 1 s) were delivered to the amygdala at intervals of 1 day until at least ten consecutive fully kindled seizures were elicited. The compound **1** was administered at a single dose of 100 mg kg^{-1} i.p. and ADT was determined either 30, 60, 90 min or more after administration. Seizure score and AD duration (ADD) in seconds were recorded and presented in Table 5. Behavioural alterations after administration of

test compound were determined at different times after injection up to 2 min before amygdala stimulation.

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