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Anticonvulsant and Sedative-Hypnotic Activities of *N*-Substituted Isatin Semicarbazones

A series of *N*-methyl/acetyl, 5-(un)-substituted isatin-3-semicarbazones were screened for anticonvulsant and sedative-hypnotic activities. The results revealed that protection was obtained in all the screens i.e., MES, scPTZ, and scSTY. Compounds **2**, **4**, **6**, **10** but not **1** and **3** showed low neurotoxicity when compared to clinically used drugs. Compounds **5**, **7**, **8** and **9** were completely non-toxic. Compound **6** showed good activity in the rat oral MES screen. Among all the compounds, **3** and **6** emerged as the most active compounds as indicated by the protection they exhibit in MES, scSTY, and scPTZ screens. All the compounds showed significant sedative-hypnotic activity.

Keywords: Epilepsy; Anticonvulsants; Sedative-hypnotic activity; Isatin semicarbazones

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Introduction

Approximately 50,000,000 persons worldwide have epilepsy, and at least 25% of those afflicted have seizures that are resistant to available medical therapies [1]. Antiepileptic drug discovery has made enormous progress from the serendipity and screening process of earlier days to the rational drug development of today. Our interest in developing semicarbazones rests upon the need for alternative new drugs because of the well-established side effects of phenytoin, which include sedation or irritability [2]. Recently Dimmock and co-workers have been synthesizing semicarbazones as candidate anticonvulsants. In one of his papers [3], he proposed a binding site to account for the way in which these compounds elicited anti-MES (maximal electroshock) activity whereby the aryl ring and the semicarbazono group ($H_2NCONHN=$) were considered to interact at both an aryl binding site and a hydrogen bonding area, respectively. They have further proposed an additional hydrophobic binding area. In order to test this hypothesis we have prepared certain aryl semicarbazones with two hydrophobic centres. Isatin has been reported to possess anti-MES activity [4]. We therefore selected isatin as one hydrophobic centre. In order to increase the lipophilicity of the =NH of the isatin we have alkylated and acetylated it, because several *N*-methyl and acetyl indole derivatives have exhibited anticonvulsant property [5, 6]. The choice of the second hydrophobic group was taken from our observation with *p*-nitrophenyl substituted semicarbazones [7]. The major difference between Dimmock's and our compounds has been that an aryl substitution on the terminal $–CONH_2$ group which is also proposed to be a hydrogen bonding area [8]. Thus a series of *N*-methyl/acetyl substituted isatin-3-semicarbazones were synthesized according to Scheme 1.

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Synthesis

The *N*-methyl/acetyl isatin and 5-nitro-*N*-acetyl isatin were prepared starting from isatin [10–13]. The *p*-substituted phenyl semicarbazides were prepared from appropriate anilines according to the method reported earlier [7, 9, 14–16]. The semicarbazones (compounds **1**–**10**) were prepared by the condensation of *N*-substituted-5-(un)-substituted isatin with appropriate phenyl semicarbazides (2-Cl, 3-Cl, 4-Cl, 4-Br, 4-NO2, and 4-SO_2NH_2). The compounds were identified by IR and ^{1}H-NMR data. The homogenity of the compounds was monitored by thin layer chromatography (TLC) on silica-G (Merck) coated glass plates, visualised by iodine vapour. The physical data of the compounds are presented in Table 1.

Pharmacological evaluation

The initial anticonvulsant evaluation of *N*-methyl/acetyl isatin (**1**–**8**) and 5-nitro N-acetyl isatin-3-semicarbazones (**9**, **10**) was undertaken by following the Anticonvulsant Drug Development (ADD) program protocol [17–19]. All compounds were administered intraperitoneally (ip) to mice. Table 2 lists the results obtained from the initial anticonvulsant evaluation compared to the clinically proven antiepileptics such as phenytoin, carbamazepine, and isatin. They include one electrical test, i.e. maximal electroshock (MES), and two chemical tests

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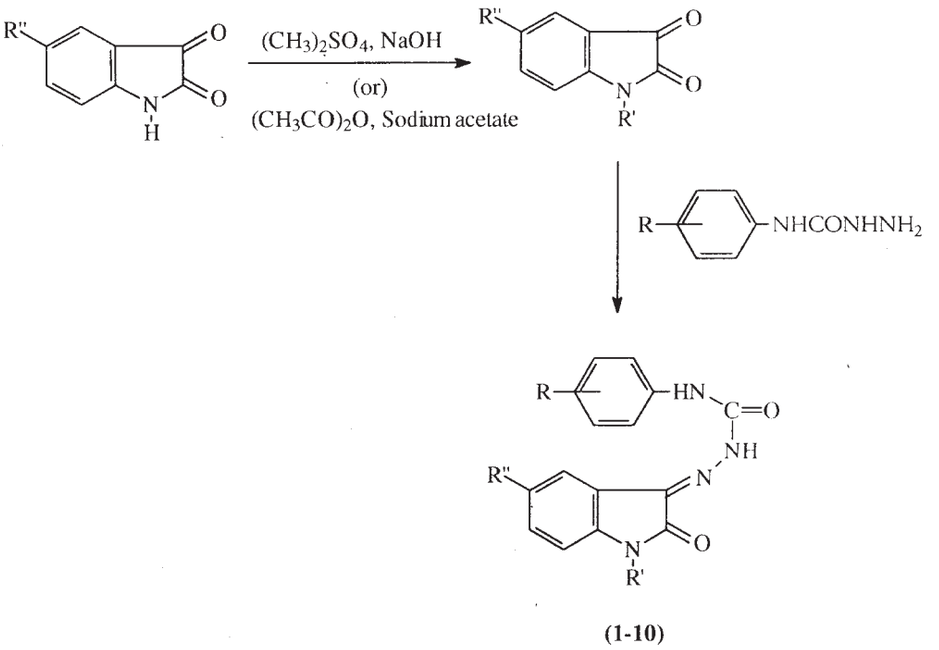

(1-10)

R = 2-Cl, 3-Cl, 4-Cl, 4-Br, 4-NO_2, 4-SO_2NH_2

R' = CH_3, $COCH_3$

R'' = H **(1-8)** R'' = NO_2 **(9,10)**

Scheme 1. Synthetic protocol of *N*-methyl/acetyl-5-(un)-substituted isatin-3-semicarbazones

Table 1. Physical data of *N*-methyl/acetyl isatin-3-semicarbazones and its 5-nitro derivatives (compounds **1**–**10**).

Compound	R´	R´´	R	Yield (%)	Mp [°C]	R_f	Mol. formula (Mol. mass)
1	CH_3	H	2-Cl	72	173	0.63	$C_{16}H_{13}N_4O_2Cl$ (328.59)
2	CH_3	H	4-Cl	74	191	0.76	$C_{16}H_{13}N_4O_2Cl$ (328.59)
3	CH_3	H	4-Br	68	250	0.65	$C_{16}H_{13}N_4O_2Br$ (373.04)
4	CH_3	H	4-NO_2	84	97	0.84	$C_{16}H_{13}N_5O_4$ (339.12)
5	CH_3	H	4-SO_2NH_2	76	186	0.82	$C_{16}H_{15}N_5O_4S$ (373.18)
6	$COCH_3$	H	2-Cl	66	134	0.67	$C_{17}H_{13}N_3O_3Cl$ (356.59)
7	$COCH_3$	H	4-Br	70	147	0.42	$C_{17}H_{13}N_4O_3Br$ (401.04)
8	$COCH_3$	H	4-SO_2NH_2	68	139	0.67	$C_{17}H_{15}N_5O_5S$ (401.04)
9	$COCH_3$	5-NO_2	2-Cl	66	127	0.51	$C_{17}H_{12}N_5O_5Cl$ (401.57)
10	$COCH_3$	5-NO_2	4-NO_2	60	119	0.54	$C_{17}H_{12}N_6O_7$ (412.10)

Table 2. Anticonvulsant profile of *N*-methyl/acetyl isatin-3-semicarbazones and its 5-nitro derivatives.

	Intraperitoneal injection in mice[a]							
	MES screen[c]		scPTZ screen[d]		scSTYscreen		NT	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
1	100	–	300	–	300	–	100	100
2	100	300	100	300	–	–	100	–
3	100	100	300	300	300	–[b]	100	100
4	–	–	–	–	–	–	100	–
5	–	–	–	–	300	–	–	–
6	100	300	–	300	300	–	100	–
7	–	–	100	–	300	–	–	–
8	–	–	100	–	300	–	–	–
9	100	300	–	–	–	–	–	–
10	300	–	300	–	–	–	100	–
Phenytoin	30	–	–	–	NOT	–	100	100
Carbamazepine	30	–	100	–	NOT	–	100	300
Isatin	400	–	–	–	–	–	–	–
4-(4-Fluoro-phenoxy)-benzaldehyde semi-carbazone		30	100	–	–	–	–	–

[a] Doses of 10, 30, 100, and 300 mg/kg were administered. The figures in the table reveal the minimum dose at which bioactivity was demonstrated in half or more of the animals. The lines (–) indicate the absence of activity at maximum dose administered. NOT denotes not tested.

[b] In the scSTY screen, compound **3** showed protection at a dose of 300 mg/kg for up to 1 h.

[c] In the MES screen, at a dose of 300 mg/kg, compounds that showed protection were **10** (0.5 h) **2**, **6**, **9** (4 h), at a dose of 100 mg/kg compounds that showed protection were **1**, **2**, **3**, **6**, **9**, (0.5 h), **3** (1 h).

[d] In the scPTZ screen, at a dose of 300 mg/kg, compounds that showed protection were **1**, **3**, **10** (0.5 h) **2**, **3**, **6** (4 h) and at a dose of 100 mg/kg **2**, **7**, **8** (0.5 h).

Table 3. Rat po identification of compound 6 in the MES test (30 mg/kg).

Compound	15 min	30 min	1 h	2 h	4 h	Toxicity
6	+++	++++	++	++	+++	–
Phenytoin (30 mg/kg)	++++	–+++	+++–	++++	+	–
4-(4-Fluoro-phenoxy)-benzaldehyde semicarbazone (50 mg/kg)	+++	++++	++++	++++	++++	–

Symbols are as follows: ++++ activity in 75–100 % of administered animals, +++, in 50–75 % of animals, ++, in 25–50 % of animals +, 0–25 % of animals, and –, no activity or toxicity.

strychnine (scSTY) and pentylene tetrazole (scPTZ). Minimal motor impairment was measured by the rotorod (neurotoxicity) (NT) test. Compound **6** was administered orally to rats and examined in MES screen and the data are presented in Table 3. The compounds were also evaluated for their sedative-hypnotic activity by the method reported by Pandeya et al. [20] and presented in Table 4.

Results

Table 2 provides screen data for the activity of compounds in animal testing against seizures induced by electroshock (MES test), pentylene tetrazole (scPTZ test), strychnine (scSTY test), and neurotoxicity (NT). Compounds were administered to mice by the intraperi-

Table 4. Evaluation of compounds for sedative-hypnotic activity[a].

Compound	Mean sleeping time[b] [min]
1	75.00 ± 3.00
2	232.67 ± 4.04
3	177.33 ± 2.08
4	212.67 ± 2.51
5	231.33 ± 2.08
6	103.00 ± 5.56
7	111.67 ± 2.08
8	69.66 ± 2.51
9	0.66 ± 0.57
10	237.3 ± 0.57
Pentobarbitone (Control)	182.3 ± 1.15

[a] Compounds were tested at a dose of 30 mg/kg (ip) in rats for the potentiation or antagonism of pentobarbitone induced narcosis.

[b] Each value represents the mean (SEM of 6 rats significantly different from the control ($P < 0.005$) in Student's t-test.

toneal route 30 min before evaluation of the activities in these tests. Comparison with data recorded under the same conditions with phenytoin, carbamazepine, and isatin. The reference prototyped antiepileptic drugs.

MES and rotorod test

At the doses tested (10, 30, 100, and 300 mg/kg), compounds **1**, **2**, **3**, **6**, and **9** possessed anti-MES activity at 100 mg/kg and only compound **10** was potent at 300 mg/kg .Compounds **4**, **5**, **7**, and **8** were found to be devoid of activity in the MES test and also presented no neurotoxicity at any of the doses administered except compound **4** at 100 mg/kg after 30 min. Compounds **2**, **3**, **6**, and **9** were potent in the MES test after 4 h at a dose of 300 mg/kg, except for **3** (100 mg/kg).

scPTZ test

Some activity was recorded in the scPTZ for compounds **2**, **7**, and **8** potent at 100 mg/kg at 30 min. **1**, **3**, and **10** (potent at 300 mg/kg) at 30 min. Compounds **2**, **3**, and **6** were potent at 300 mg/kg at 4 h.

scSTY test

Most of the compounds were potent in this test at 300 mg/kg after 30 min. Only one compound **3** was potent after 1 h.

Anticonvulsant and neurotoxic properties of compound in rats dosed orally

Compound **6** was selected for oral evaluation of anti-MES and neurotoxic activity in rats. The compound was administered per os, and its effect in rats was studied at 15, 30, 60, 120, and 240 min after ingestion of 30 mg/kg of experimental drug.

Sedative-hypnotic activity

All the compounds were tested for the sedative-hypnotic activity at 30 mg/kg for pentobarbitone induced narcosis in rats. All the compounds were found to have significant sedative-hypnotic activity.

Discussion

From the studies it is evident that the compounds of this series are potential anticonvulsants. Compound **2**, **3**, and **6** have shown anticonvulsant properties in various tests and some of them have advantages over phenytoin in the scPTZ test also. Compounds **2**, **7**, and **8** are equipotent with carbamazepine in the scPTZ test. They only show neurotoxicity at 100 mg/kg equal to phenytoin and carbamazepine. There is a considerable increase in anticonvulsant activity over isatin. Introduction of *N*-acetyl group which could be easily hydrolysed to the putative =NH group and also the *N*-methyl containing compounds have increased the activity due to lipophilicity of this centre at the other end of the hydrophobic group. *p*-Bromophenyl substituted derivative (**3**) was considered to be more active in MES (100 mg/kg) screen. This is in accordance with the observation for *p*-bromophenyl substituted semicarbazone [8]. All the compounds were less active than Dimmock's compound (4-(4-fluorophenoxy)-benzaldehyde semicarbazone) [21]. However compound **3** was equipotent in the MES screen after 4 h. Further compounds in the present series showed activity in the scPTZ screen and Dimmock's compound did not exhibit any activity in this test. Therefore compounds of this series may have a broad spectrum activity as compared to Dimmock's compound. In conclusion, two compounds (**3** and **6**) could be the lead compounds for further beneficial modification in the design of semicarbazones as anticonvulsants.

Experimental part

Mp: Thomas Hoover apparatus, uncorrected; IR-spectra: JASCO FT/IR 5300 (KBr); ^{1}H-NMR-spectra: JEOL FX 90 Q (Fourier Transform), TMS internal standard.

N-Substituted isatin

N-Methyl/acetyl isatin were synthesized from isatin according to the earlier reported methods [10, 11]. *N*-methyl isatin: Yield:

77%. Mp 131°C (lit. 134°C); *N*-acetyl isatin: Yield: 75%. Mp 140°C (lit. 141°C).

5-Nitro-N-acetylisatin

5-Nitro-*N*-acetyl isatin was synthesized according to the earlier reported methods [12, 13]. Yield: 62%. Mp 192°C (lit. 193–194°C).

m-Chlorophenylsemicarbazide

Equimolar quantities of (0.1 mol) *m*-chloro phenyl urea (17 g) and hydrazine hydrate (5 mL) in ethanol were refluxed and kept in ice. The precipitate formed was filtered off, dried, and recrystallised from 95% ethanol to give *m*-chlorophenylsemicarbazide. Yield: 58%. Mp 152°C.

IR (KBr): 3454, 3262 (N–H), 1632 (C=O), 1586 (C=N), 840 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ (ppm): 5.5 (s, 2H, NH_2, D_2O exchangeable), 6.2 (s, 1H, ArNH, D_2O exchangeable), 7.3–7.85 (m, 4H, ArH), 9.8 (bs, 1H, $NHNH_2$, D_2O exchangeable).

Substituted phenylsemicarbazides [7, 9, 14–16]

Other phenylsemicarbazides (2-Cl, 4-Cl, 4-Br, 4-NO_2 and 4-SO_2NH_2) were synthesized according to earlier reported methods.

o-Chlorophenylsemicarbazide: Yield: 68%. Mp 172°C (lit. 179°C); *p*-Chlorophenylsemicarbazide: Yield: 72%. Mp 232°C (lit. 234°C); *p*-Bromophenylsemicarbazide: Yield: 74%. Mp 268°C (lit. 270°C); *p*-Nitrophenylsemicarbazide: Yield: 78%. Mp 185°C (lit. 191°C); *p*-Sulfamoylphenylsemicarbazide: Yield: 67%. Mp 192°C (lit. 195°C).

General method for the synthesis of N-substituted-5-(un)-substituted isatin semicarbazones (**1**–**10**)

To a solution of 2/3/4-substituted phenylsemicarbazide in ethanol was added an equimolar quantity (0.003 mol) of the *N*-methyl/acetyl/5-nitro-*N*-acetyl isatin in ethanol. The pH of the reaction mixture was adjusted between 5–6 by adding glacial acetic acid. The reaction mixture was refluxed for 1–3 h. The product obtained after cooling was filtered off, dried, and recrystallised from 95% ethanol. The purity of the compounds was determined by TLC and the eluants used were chloroform: methanol (9:1) for all the compounds.

The spectral data of the synthesized compounds are as follows:

Compound **1**

UV (methanol): (λ_{max}) (nm) 276, 238.5. IR (KBr): 3427 (2^0 NH), 3319 (N–H), 2926 (–CH_3), 1650 (C=O), 1585 (C=N), 1612, 1466 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.5 (s, 3H, N-CH_3), 5.7 (s, 1H, –CONH, D_2O exchangeable), 7.1–7.9 (m, 8H, Ar-H), 8.6 (s, 1H, =N–NH, D_2O exchangeable).

Compound **2**

UV (methanol): (λ_{max}) (nm) 243.5. IR (KBr): 3420 (2^0 NH), 3314 (N–H), 2922 (–CH_3), 1655 (C=O), 1587 (C=N), 869 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.4 (s, 3H, N-CH_3), 5.4 (s, 1H, –CONH, D_2O exchangeable), 7.1–7.8 (m, 8H, Ar-H), 8.7 (s, 1H, =N-NH, D_2O exchangeable).

Compound **3**

UV (methanol): (λ_{max}) (nm) 245.5. IR (KBr): 3425 (2^0 NH), 3406 (N–H), 2953 (–CH3), 1653 (C=O), 1590 (C=N), 869 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.4 (s, 3H, N-CH_3), 5.8 (s, 1H, –CONH, D_2O exchangeable), 7–7.7 (m, 8H, Ar-H), 8.6 (s, 1H, =N-NH, D_2O exchangeable).

Compound **4**

UV (methanol): (λ_{max}) (nm) 371, 242. IR (KBr): 3476 (2^0 NH), 3319 (N–H), 2926 (–CH_3), 1685 (C=O), 1595 (C=N), 1520, 1350 (C-NO_2), 842 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.5 (s, 3H, N-CH_3), 5.8 (s, 1H, –CONH, D_2O exchangeable), 7.3–8.1 (m, 8H, Ar-H), 8.7 (s, 1H, =N-NH, D_2O exchangeable).

Compound **5**

UV (methanol): (λ_{max}) (nm) 326.5, 264, 262. IR (KBr): 3462 (2^0 NH), 3373 (N–H), 2926 (–CH_3), 1637 (C=O), 1597 (C=N), 1311, 1147 (S=O), 825 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.2 (s, 3H, N-CH_3), 5.6 (s, 1H, –CONH, D_2O exchangeable), 6.8–7.7 (m, 8H, Ar-H), 9.7 (s, 1H, =N-NH, D_2O exchangeable), 10.6 (bs, 2H, SO_2NH_2, D_2O exchangeable).

Compound **6**

UV (methanol): (λ_{max}) (nm) 294, 240.5. IR (KBr): 3433 (2^0 NH), 3315 (N–H), 2922 (–CH_3), 1728 (acetyl C=O), 1637 (C=O), 1597 (C=N), 940 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.7 (s, 3H, N-$COCH_3$), 5.8 (s, 1H, –CONH, D_2O exchangeable), 7.2–7.9 (m, 8H, Ar-H), 8.7 (s, 1H, =N-NH, D_2O exchangeable).

Compound **7**

UV (methanol): (λ_{max}) (nm) 322, 270, 247, 242. IR (KBr): 3433 (2^0 NH), 3310 (N–H), 2952 (–CH_3), 1728 (acetyl C=O), 1650 (amide C=O), 1545 (C=N), 1460, 860 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.6 (s, 3H, N-$COCH_3$), 5.4 (s, 1H, –CONH, D_2O exchangeable), 7–7.8 (m, 8H, Ar-H), 8.6 (s, 1H, =N-NH, D_2O exchangeable).

Compound **8**

UV (methanol): (λ_{max}) (nm) 325, 226. IR (KBr): 3479 (2^0 NH), 3375 (N–H), 3275 (SO_2NH_2 N–H), 2922 (–CH_3), 1728 (acetyl C=O), 1630 (amide C=O), 1595 (C=N), 1315, 1147 (S=O), 825 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.5 (s, 3H, N-$COCH_3$), 5.8 (s, 1H, –CONH, D_2O exchangeable), 7.1–7.9 (m, 8H, Ar-H), 8.7 (s, 1H, =N-NH, D_2O exchangeable), 10.5 (bs, 2H, SO_2NH_2, D_2O exchangeable).

Compound **9**

UV (methanol): (λ_{max}) (nm) 294, 246, 241. IR (KBr): 3427 (2^0 NH), 3314 (N–H), 2922 (–CH_3), 1730 (acetyl C=O), 1653 (amide C=O), 1585 (C=N), 1540, 1340 (C-NO_2), 804 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.5 (s, 3H, N-$COCH_3$), 5.9 (s, 1H, –CONH, D_2O exchangeable), 7.1–7.9 (m, 7H, Ar-H), 8.9 (s, 1H, =N-NH, D_2O exchangeable).

Compound **10**

UV (methanol): (λ_{max}) (nm) 374, 368.5, 247, 241.5. IR (KBr): 3472 (2^0 NH), 3369 (N–H), 2928 (–CH_3), 1728 (acetyl C=O), 1650 (amide C=O), 1586 (C=N), 1525, 1317 (C-NO_2), 840 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.6 (s, 3H, N-$COCH_3$), 5.7 (s, 1H, –CONH, D_2O exchangeable), 7.1–8 (m, 7H, Ar-H), 8.6 (s, 1H, =N-NH, D_2O exchangeable).

Pharmacological tests

The anticonvulsant evaluation [17–19] was performed by maximal electroshock seizure, subcutaneous pentylene tetrazole seizure threshold, subcutaneous strychnine seizure threshold, and neurotoxicity screens. The sedative-hypnotic activity of the compounds was also evaluated by using pentobarbitone induced narcosis method [20]. Male albino mice (CF-1 strain,

18–25 g) and male albino rats (Sprague-Dawley, 100–150 g) were used as experimental animals. The semicarbazone derivatives were suspended in 0.5% methylcellulose/water mixture or in polyethylene glycol (PEG).

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