

## Anticonvulsant activity of Schiff bases of isatin derivatives

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Schiff bases of *N*-methyl and *N*-acetyl isatin derivatives with different aryl amines have been synthesized and screened for anticonvulsant activities against maximal electroshock (MES) and subcutaneous metrazole (ScMet). *N*-methyl-5-bromo-3-(*p*-chlorophenylimino) isatin (**2**) exhibited anticonvulsant activity in MES and ScMet with  $LD_{50} > 600 \text{ mg kg}^{-1}$ , showing better activity than the standard drugs phenytoin, carbamazepine and valproic acid. Thus, compound **2** may be chosen as a prototype for development of new anticonvulsants.

*Keywords:* Schiff base, isatin, anticonvulsant

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Epilepsy is a disease of complex nature and of different etiology (1). A large number of populations of different age groups and sex are affected by this disease. Mainly, two kinds of epilepsy have been identified, one with grand mal and the other with petit mal. Anticonvulsant drugs with MES (maximal electroshock) activity are generally useful in grand mal, while ScMet (subcutaneous metrazole) antagonists are effective in petit mal. Many drugs have been marketed recently for the treatment of epilepsy (2–4). These include miconazole, zonisamide, lamotrigine, felbamate and tiagabine. Recently, semicarbazones are emerging as novel anticonvulsant drugs. 4-Bromobenzaldehyde semicarbazone and 4-bromophenyl semicarbazones have shown promising activities (5–9). The proposed pharmacophoric requirements in the semicarbazone molecules are:

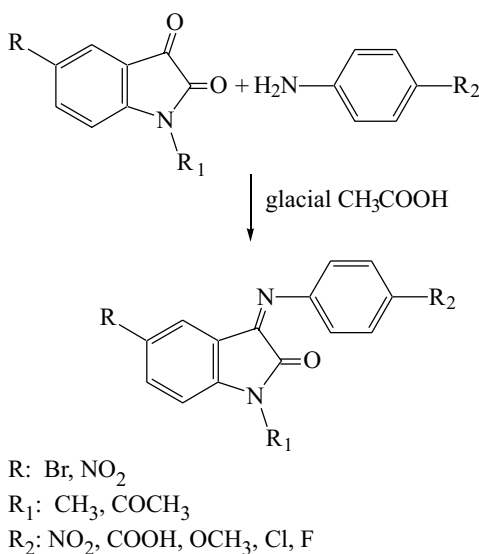
- (i) aryl binding site with a hydrophobic group;
- (ii) hydrogen bonding domain exemplified by the presence of the -NHCO- grouping;
- (iii) two electron donor system;
- (iv) hydrophobic binding site whose size determines the type of activity.

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The objective of the present work was to test this hypothesis and as a result, a new series of compounds have been prepared by reacting *N*-methyl or *N*-acetyl isatins with different aryl amines (Scheme 1):

- (i) Isatin has been selected because during initial screening it has shown activity in the MES test (10–14). In the isatin molecule, bromo substituent has been selected because of its high potency. Further, an electron withdrawing group, such as NO<sub>2</sub>, has also been included for SAR studies (15).
- (ii) Schiff bases of aromatic amines have been prepared because they contain a two electron donor system.
- (iii) The *N*-methyl and *N*-acetyl groups have been incorporated to increase the lipophilicity of the molecules.



Scheme 1

## EXPERIMENTAL

The melting point of the compounds was measured in an open capillary and was uncorrected. The purity of the compounds was confirmed by thin layer chromatography using silica gel glass plates as the stationary phase and benzene and ethanol (9:1) as the mobile phase. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer, Japan. NMR spectra were run on a JEOL FT-NMR spectrometer FX-90Q (Japan) with TMS as internal reference. Isatin derivatives were prepared by the literature methods (16). They were characterized by melting point, elemental analysis and spectral data.

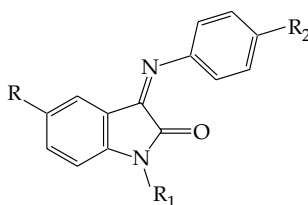
The aryl amines were procured from Aldrich (USA) and were used as received.

*Synthesis of Schiff bases. General procedure*

Equimolar quantities of 5-substituted *N*-methyl/*N*-acetyl isatin (0.003 mol) and aromatic amine (0.003 mol) were added into 20 mL of absolute ethanol containing a few drops of glacial acetic acid in a 250-mL round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol (99.5%) and characterized by elemental analysis, IR and <sup>1</sup>H NMR.

The physical and spectral data of the synthesized compounds are listed in Tables I and II, respectively.

Table I. Physical properties of isatin Schiff bases



Compd. No.	R	R <sub>1</sub>	R <sub>2</sub>	M.p. (°C)	Yield (%)	Molecular formula (M <sub>r</sub> )	R <sub>f</sub> <sup>a</sup>	Elemental analysis (%) (Calcd./found)		
								C	H	N
1	Br	CH <sub>3</sub>	OCH <sub>3</sub>	210	77	C <sub>16</sub> H <sub>13</sub> BrN <sub>2</sub> O <sub>2</sub> (345.19)	0.361	55.67 55.59	3.80 4.00	8.11 7.95
2	Br	CH <sub>3</sub>	Cl	243	79	C <sub>15</sub> H <sub>10</sub> ClBrN <sub>2</sub> O (349.61)	0.400	51.53 51.24	2.88 2.73	8.01 8.10
3	Br	CH <sub>3</sub>	NO <sub>2</sub>	104	89	C <sub>15</sub> H <sub>10</sub> BrN <sub>3</sub> O <sub>3</sub> (360.16)	0.545	50.02 50.11	2.80 2.52	11.67 11.58
4	Br	CH <sub>3</sub>	COOH	153	91	C <sub>16</sub> H <sub>11</sub> BrN <sub>2</sub> O <sub>3</sub> (359.17)	0.219	53.50 53.39	3.08 2.89	7.79 7.62
5	Br	CH <sub>3</sub>	F	231	70	C <sub>15</sub> H <sub>10</sub> FBrN <sub>2</sub> O (333.15)	0.250	54.08 54.84	3.02 3.33	8.41 8.80
6	Br	COCH <sub>3</sub>	OCH <sub>3</sub>	86	90	C <sub>17</sub> H <sub>13</sub> BrN <sub>2</sub> O <sub>3</sub> (373.20)	0.473	54.71 54.68	3.51 3.31	7.51 7.74
7	Br	COCH <sub>3</sub>	Cl	211	44	C <sub>16</sub> H <sub>10</sub> ClBrN <sub>2</sub> O <sub>2</sub> (377.62)	0.318	50.89 50.69	2.67 2.32	7.42 7.24
8	Br	COCH <sub>3</sub>	NO <sub>2</sub>	115	44	C <sub>16</sub> H <sub>10</sub> BrN <sub>3</sub> O <sub>4</sub> (388.17)	0.461	49.51 49.31	2.59 2.33	10.83 10.52
9	Br	COCH <sub>3</sub>	COOH	230	56	C <sub>17</sub> H <sub>11</sub> BrN <sub>2</sub> O <sub>4</sub> (387.19)	0.315	52.73 53.42	2.86 2.54	7.23 7.45
10	Br	COCH <sub>3</sub>	F	117	50	C <sub>16</sub> H <sub>10</sub> FBrN <sub>2</sub> O <sub>2</sub> (361.17)	0.550	53.21 53.01	2.79 2.52	7.76 7.60
11	NO <sub>2</sub>	COCH <sub>3</sub>	OCH <sub>3</sub>	98	91	C <sub>17</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub> (339.31)	0.277	60.18 60.41	3.86 4.26	12.38 12.60

Table I. Continued

12	NO <sub>2</sub>	COCH <sub>3</sub>	Cl	111	49	C <sub>16</sub> H <sub>10</sub> ClN <sub>3</sub> O <sub>4</sub> (343.66)	0.421	55.92	2.91	12.22
13	NO <sub>2</sub>	COCH <sub>3</sub>	NO <sub>2</sub>	55	57	C <sub>16</sub> H <sub>10</sub> N <sub>4</sub> O <sub>6</sub> (354.21)	0.270	54.22	2.82	15.81
14	NO <sub>2</sub>	COCH <sub>3</sub>	COOH	78	49	C <sub>17</sub> H <sub>11</sub> N <sub>3</sub> O <sub>6</sub> (353.29)	0.375	57.79	3.13	11.89
15	NO <sub>2</sub>	COCH <sub>3</sub>	F	178	64	C <sub>16</sub> H <sub>10</sub> FN <sub>3</sub> O <sub>4</sub> (327.28)	0.275	58.72	3.05	12.84
								58.50	3.00	12.67

<sup>a</sup> Mobile phase: benzene/ethanol 9:1

Table II. Spectral data of isatin Schiff bases

Compd. No.	IR (KBr), $\nu(\text{cm}^{-1})$	<sup>1</sup> H-NMR ( $\delta$ , ppm)
1	3349, 1700, 1702, 1268, 1050, 846, 600	2.8 (s, 3H, N-CH <sub>3</sub> ), 3.73 (s, 3H, OCH <sub>3</sub> ), 6.3–7.7 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
2	3450, 1672, 1603, 821, 708, 504	2.8 (s, 3H, N-CH <sub>3</sub> ), 6.3–7.0 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
3	3364, 1750, 1613, 1470, 1294, 845, 577	2.8 (s, 3H, N-CH <sub>3</sub> ), 6.3–7.9 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
4	3383, 3000, 1749, 1701, 1610, 844, 609	2.8 (s, 3H, N-CH <sub>3</sub> ), 6.3–7.9 (m, 7H, Ar-H), 11.0 (s, 1H, COOH), 8.4 (s, 1H, CH=N)
5	3451, 1673, 1605, 1388, 823, 506	2.8 (s, 3H, N-CH <sub>3</sub> ), 6.3–6.7 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
6	3349, 1700, 1702, 1268, 1050, 846, 600	2.4 (s, 3H, COCH <sub>3</sub> ), 3.7 (s, 3H, OCH <sub>3</sub> ), 6.3–8.0 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
7	3252, 1687, 1672, 1603, 821, 708, 503	2.4 (s, 3H, COCH <sub>3</sub> ), 3.7 (s, 3H, OCH <sub>3</sub> ), 6.3–8.0 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
8	3362, 1746, 1631, 1601, 1539, 1302, 841, 534	2.4 (s, 3H, COCH <sub>3</sub> ), 6.3–8.0 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
9	3000, 1739, 1682, 1604, 1535, 760, 519	2.4 (s, 3H, COCH <sub>3</sub> ), 6.3–7.9 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N), 11.0 (s, 1H, COOH)
10	3451, 1710, 1673, 1605, 1388, 823, 506	2.4 (s, 3H, COCH <sub>3</sub> ), 6.3–8.0 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
11	3348, 1700, 1702, 1570, 1340, 1268, 1050, 846	2.4 (s, 3H, COCH <sub>3</sub> ), 3.7 (s, 3H, OCH <sub>3</sub> ), 6.7–8.7 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
12	3253, 1689, 1670, 1605, 1573, 1333, 820, 710	2.4 (s, 3H, COCH <sub>3</sub> ), 6.4–8.7 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
13	3364, 1747, 1633, 1601, 1539, 1302, 845	2.4 (s, 3H, COCH <sub>3</sub> ), 6.7–8.7 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)
14	3000, 1710, 1684, 1607, 1564, 1332, 762	2.4 (s, 3H, COCH <sub>3</sub> ), 6.7–8.7 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N), 11.0 (s, 1H, COOH)
15	3453, 1711, 1672, 1608, 1568, 1390, 1351, 825	2.4 (s, 3H, COCH <sub>3</sub> ), 6.4–8.7 (m, 7H, Ar-H), 8.4 (s, 1H, CH=N)

### *Anticonvulsant screening*

All the compounds were screened for anticonvulsant properties adopting the anticonvulsant drug development (ADD) program protocol (17, 18). The mice used were Carworth Farms No. 1, weighing from 19 to 25.5 g, either sex and 22–33 days old. Accommodation conditions were maintained at 20 °C and the number of animals used was 1, 3, 5 and 8 in different experiments. Methyl cellulose was used for dissolving the test compounds in ScMet and Rotorod Test, while polyethylene glycol was used for MES. The control experiments were performed with solvents alone. Three animals were used in the control test. The compounds were administered intraperitoneally (0.01 mL g<sup>-1</sup> body mass) to mice, at doses of 30, 100 and 300 mg kg<sup>-1</sup> to 1 to 4 mice. The activities of the compounds in maximum electroshock (MES) and subcutaneous metrazole (ScMet) test along with their neurotoxicity are presented in Table III.

*Electroshock method.* – Maximal seizures were induced by the application of electrical current to the brain via corneal electrodes. The stimulus parameters for mice were 50 mA in a pulse of 60 Hz for 200 ms. The mice were given the test drug dissolved in polyethylene glycol. Abolition of the hind limb tonic extensor spasm was recorded as a measure of anticonvulsant activity.

*Subcutaneous metrazole seizure pattern test.* – A metrazole dose of 85 mg kg<sup>-1</sup> administered subcutaneously to mice causes seizures in more than 97% of the animals. This is called the convulsive dose 97 (CD<sub>97</sub>). The test was carried out by giving the metrazole injection approximately 10 minutes before the anticipated time of the peak anticonvulsant drug action. The animals were observed during the following 4 hours for the occurrence of seizures. A threshold convulsion is defined as one episode of clonic spasms which persists for at least 5 seconds. Absence of even a threshold convulsion during the period of observation is taken as the endpoint in this test.

*Rotorod test.* – The mice were trained to stand on an accelerating rotorod rotating at 10 rev min<sup>-1</sup>. The rod diameter was 3.2 cm. Trained animals were given the test compounds intraperitoneally at doses of 30, 100 and 300 mg kg<sup>-1</sup> in methyl cellulose after 30 minutes and up to 24 hours. The mice were placed on the rotorod to measure the effect of the drug on their motor performance. The dose at which animals fell off the rotorod was determined.

The compounds were also screened at an oral dose of 30 mg kg<sup>-1</sup> and the MES activity was noted at different time intervals up to 4 hours.

Some compounds with OCH<sub>3</sub>/Cl substituent in phenyl, N-COCH<sub>3</sub> and a substituent Br/NO<sub>2</sub> at the 5<sup>th</sup> position in the isatin moiety (compounds **6**, **7**, **11** and **12**) and the compound with fluoro substituent in the phenyl ring, N-COCH<sub>3</sub> and a substituent Br at the 5<sup>th</sup> position in the isatin structure (compound **10**) were screened at 6 Hz shock in mice at a dose of 100 mg kg<sup>-1</sup> up to 4 hours. The compounds were dissolved in methyl cellulose, introduced via the *i.p.* route and the mice were given a current shock of 32 mA.

## RESULTS AND DISCUSSION

The results of anticonvulsant screening are given in Table III. The two primary screens MES and ScMet were performed in mice at doses of 30, 100, 300 mg kg<sup>-1</sup> (intraperitoneally). As compared to isatin, the 5-Br, N-CH<sub>3</sub> isatin derivatives **2**, **3**, **4** with Cl, NO<sub>2</sub>, COOH groups, respectively, in the phenyl ring, require a lower dose in MES while the 5-Br, N-COCH<sub>3</sub> isatin derivatives **9**, **10** with F, COOH groups, respectively, in the phenyl ring and 5-NO<sub>2</sub>, N-COCH<sub>3</sub> isatin derivative **12** with NO<sub>2</sub> group in the phenyl ring showed activity in ScMet. In general, compounds with N-CH<sub>3</sub> were active in the MES test whereas those having N-COCH<sub>3</sub> group showed activity in the ScMet test. The *N*-methyl-5-bromo-3-(*p*-nitrophenylimino) isatin **3** and *N*-acetyl-5-bromo-3-(*p*-chlorophenylimino) isatin **10** have shown activity at a dose of 100 mg kg<sup>-1</sup> in MES and ScMet,

Table III. Anticonvulsant and neurotoxicity screening of isatin Schiff bases

Compd. No.	Concentration (mg kg <sup>-1</sup> body mass) <sup>a</sup>			
	MES <sup>a,b</sup>	ScMet <sup>a,b</sup>	Neurotoxicity <sup>a,b</sup>	LD <sub>50</sub> (mg kg <sup>-1</sup> )
<b>1</b>	–	–	30 (25 %)	27
<b>2</b>	300 (100%)	300 (20%)	–	> 600
<b>3</b>	100 (33.3%)	–	100 (50%)	100
<b>4</b>	300 (100%)	–	300 (50%)	> 300
<b>5</b>	–	–	300 (50%)	> 300
<b>6</b>	–	–	–	> 300
<b>7</b>	–	–	30 (25%)	27
<b>8</b>	–	–	300 (25%)	> 300
<b>9</b>	–	300 (60%)	100 (12.5%)	200
<b>10</b>	–	100 (20%)	–	> 300
<b>11</b>	–	–	–	> 300
<b>12</b>	–	300 (80%)	–	27
<b>13</b>	–	–	100 (25%)	150
<b>14</b>	–	–	30 (50%)	42
<b>15</b>	–	–	30 (50%)	28
Isatin	400 (100%)	–	–	> 400
Phenytoin	30 (100%)	–	100	170 ± 13
Carbamazepine	30 (100%)	100 (100%)	100	350
Valproic acid	–	300 (100%)	–	> 1000

MES – maximal electroshock seizure, ScMet – subcutaneous metrazole seizure

– No activity.

<sup>a</sup> The two primary screens of MES, ScMet and toxicity were performed by intraperitoneal injection in mice at doses of 30, 100, 300 mg kg<sup>-1</sup>.

<sup>b</sup> Values in parentheses in the MES and ScMet tests indicate the number of animals protected against the number of animals tested and in the neurotoxicity test they indicate the number of animals exhibiting toxicity against the number of animals tested. No protection of the solvent in control experiments was observed.

respectively. Compound **2** with bromo substituent in the isatin ring and chloro substituent in the phenyl ring showed activity both in MES and ScMet tests and no toxicity at the stipulated doses. In 6 Hz excitation, the *N*-acetyl-5-nitro-3-(*p*-chlorophenylimino) isatin **12** protected mice (25%) at a dose of 100 mg kg<sup>-1</sup> after 15 minutes of drug administration. In the oral test, *N*-methyl-5-bromo-3-(*p*-carboxyphenyl imino) isatin **4** showed 25% activity after half an hour at the dose of 30 mg kg<sup>-1</sup> and *N*-acetyl-5-nitro-3-(*p*-nitrophenylimino) isatin **13** showed 25% activity after 2 hours at the dose of 50 mg kg<sup>-1</sup>. *N*-methyl-5-bromo-3-(*p*-nitrophenylimino) isatin (**3**) showed activity in MES (100 mg kg<sup>-1</sup> with 33.3% protection) as well as *N*-methyl-5-bromo-3-(*p*-aminophenylimino) isatin (**4**) (300 mg kg<sup>-1</sup> with 100% protection). *N*-methyl-5-bromo-3-(*p*-bromophenylimino) isatin (**2**) showed activity both in MES (300 mg kg<sup>-1</sup> with 100% protection) and ScMet (300 mg kg<sup>-1</sup> with 20% protection). The reference compound, valproic acid, was active only in ScMet (300 mg kg<sup>-1</sup> with 100% protection) whereas phenytoin was active in MES only. Another reference compound, carbamazepine, was however active both in MES (30 mg kg<sup>-1</sup> with 100% protection) and in ScMet (100 mg kg<sup>-1</sup> with 100% protection). It is worthwhile to mention that the compound **2**, being active both MES and ScMet, had *LD*<sub>50</sub> > 600 mg kg<sup>-1</sup> as compared to carbamazepine with the *LD*<sub>50</sub> of 350 mg kg<sup>-1</sup>. Thus, compound **2** could be chosen as a lead compound for further modification aimed at improving the anticonvulsant activity.

## CONCLUSIONS

Compound **2** with bromo substituent in the isatin ring and chloro substituent in the phenyl ring exhibited a broad-spectrum activity with no neurotoxicity at the stipulated dose and can hence be chosen as a prototype for the development of new anticonvulsants.

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## S A Ž E T A K

### Antikonvulzivno djelovanje Schiffovih baza – derivata isatina

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Schiffove baze *N*-metil i *N*-acetil derivata izatina s različitim aromatskim aminima sintetizirane su i ispitane na sposobnost suzbijanja konvulzija uzrokovanih elektrošokom (MES) i subkutanom primjenom metrazola (ScMet). *N*-metil-5-bromo-3-(*p*-klorofenilimino) izatin **2** pokazao je nisku neurotoksičnost i jače antikonvulzivno djelovanje nego standardni antikonvulzivi fenitoin, karbamazepin i valproična kiselina. Zbog toga se spoj **2** može smatrati prototipom za razvoj novih antikonvulziva.

*Ključne riječi:* Schiffova baza, izatin, antikonvulziv

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