International Journal of Pharmacy and Pharmaceutical Sciences
ISSN- 0975-1491 Vol 2, Issue 4, 2010

Research Article

SYNTHESIS, CHARACTERIZATION AND ANTICONVULSANT ACTIVITY OF NOVEL SCHIFF BASE OF ISATIN DERIVATIVES

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Received: 23 May 2010, Revised and Accepted: 24 Jun 2010

ABSTRACT

In the present study, a series of novel Schiff bases of isatin [5a-5l] were synthesized by condensation of imesatin with different aromatic aldehydes. The imesatins were synthesized by reaction of isatin with *p*-phenylenediamine. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, Mass spectroscopy and Elemental analysis. All the synthesized compounds screened for anticonvulsant activities against maximal electroshock (MES) and subcutaneous metrazole (ScMet).Among the compounds synthesized 3-(4-(3, 4, 5,-trimethoxy benzylideneamino) phenylimino) indoline-2-one [5h] showed excellent anticonvulsant activity with lower dose in MES as well as in ScMet methods. Thus, compound 5h may be chosen as a prototype for development of new anticonvulsants.

Keywords: Schiff base, Isatin, Anticonvulsant

INTRODUCTION

Epilepsy, a ubiquitous disease characterized by recurrent seizures, inflicts more than 60 million people worldwide according to epidemiological studies[1]. For epilepsy treatment, nearly 95% of clinically available drugs were approved before 1985 and they could provide satisfactory seizure control for 60–70% of patients. These drugs, however, also cause notable adverse side effects such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anemia[2-4], and even life threatening conditions[5]. Research to find more effective and safer antiepileptic drugs are, therefore, imperative and challenging in medicinal chemistry. Among the important pharmacophores responsible for anticonvulsant activity, the isatin scaffold is still considered a viable lead structure for the synthesis of more efficacious anticonvulsant activity. Isatin was reported to possess proconvulsant and anticonvulsant activities[6] apart from other pharmacological properties[7-8]. 3-Hydroxy-3-substituted oxindoles[9-12] derived from isatin, 3-(4-thiazolidone-2-hydrazono)-isatin[13], 1-morpholino-methyl-3-(aryloxy-arylthio-acetyl hydrazone)-isatin[14], isatin based spiroazetidinones[15] and recently isatin-5-Sulphonamide derivatives[16] were reported to possess anticonvulsant activity. Therefore, it was envisaged that Schiff bases of isatin would also exhibit significant anticonvulsant activity; we hereby report the anticonvulsant activity of Schiff bases of isatin by maximal electroshock method (MES) and metrazol-induced convulsions (MET). The neurotoxicity of the compounds was also assessed for the compounds at the experimental dose levels.

MATERIALS AND METHODS

General procedure

In the present work a novel series of various 3-substituted isatin compounds were synthesized. Aniline and chloral hydrate were used as starting materials to produce Schiff bases of substituted isatin via the intermediate imesatin (4) through condensation reaction. The condensation proceeds selectively on the carbonyl group in position 3 of the isatin ring. Reactions of imesatin with different aromatic aldehydes have been carried out in ethanol in the presence of glacial acetic acid, and a variety of Schiff base derivatives have been isolated according to the synthetic scheme - 1. The method used for the preparation and isolation of the compounds gave materials of good purity as evidenced by their spectral analyses and thin layer chromatography.

Aniline 1 was treated with chloral hydrate to form isonitrosoacetanilide 2. Then this intermediate undergoes cyclization with sulphuric acid to form isatin 3[17]. Equimolar quantities of (0.01 mol) of isatin 3 and *p*–phenylenediamine were dissolved in sufficient quantity of methanol (30 mL) in the presence of acetic acid and refluxed for 1 h, then kept for 2 h at room temperature (37^{0}C), resulting in the formation of imesatin 4. Equimolar quantities (0.01 mol) of imesatin 4 and various aromatic aldehydes were dissolved in ethanol and refluxed for 8 h. After standing for one to two days at room temperature, the product of different substituted derivatives of isatin (5a-5l) separated out as a mixture of E and Z isomers were filtered, dried and recrystallised from absolute ethanol. The Schiff base derivatives are found to be soluble in chloroform, dimethylsulphoxide and dimethylformamide. The spectral data IR, 1H NMR, mass spectroscopy and elemental analyses were used to ascertain the structures of all the compounds. Other characteristic data for compounds are given in Table 1.

Melting points were determined in open capillary tubes in a Thomas Hoover melting point apparatus and are uncorrected. The purity of the compounds was confirmed by thin layer chromatography using silica gel glass plates and solvent system of benzene:ethanol (9:1). The spots were developed in iodine chamber and visualized under ultraviolet lamp. Infrared (IR) and ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were recorded for the compounds in Testcan Shimadzu FTIR 8000 (KBr) ^{13}C Avance Bruker 300 MHz spectrophotometer, respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Elemental analysis (N and S) was undertaken with Perkin Elmer-2400 instrument and the measured values agreed within 0.4% with the calculated. Mass spectra were obtained on Joel SX 102/M-6000 mass spectrometer applying FAB method.

3-(4-(benzylideneamino) phenylimino) indoline-2-one [5a]. IR: 3177 (N-H), 3050 (Ar-CH), 1690 (C=O), 1597 (C=N), 1580 (C=C) cm^{-1}; ^{1}H-NMR (DMSO): δ 8.29 (s, 1H, -N=C<u>H</u>-), 8.02 (s, 1H, -N<u>H</u>-), 7.01-7.68 (m, 13H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6', H-2'', H-3'', H-4'', H-5'', H-6'', Ar-H); EI-MS (m/z, %): 325(M$^+$, 21), 235(14), 120(100), 105(24), 69(44); (Calcd. for $C_{21}H_{15}N_3O$: 325.36); Anal. Calcd. for $C_{21}H_{15}N_3O$: C, 74.35; H, 4.82; N, 11.82; Found: C, 74.30; H, 4.84; N, 11.78.

3-(4-(4-chlorobenzylideneamino) phenylimino) indoline-2-one [5b].IR : 3130 (N-H), 2988 (Ar-CH), 1613 (C=N), 1700 (C=O), 1599 (C=C), 744 (C-Cl) cm^{-1}; ^{1}H-NMR (DMSO): δ 8.25 (s, 1H, -N=C<u>H</u>-), 7.92 (s, 1H, -N<u>H</u>-), 7.03-7.60 (m, 12H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6', H-2'', H-3'', H-5'', H-6'', Ar-H); EI-MS (m/z, %): 362(M+2), 360(M$^+$, 20), 264(22), 91(100), 77(22), 69(44); (Calcd. for $C_{21}H_{14}ClN_3O$: 359.80); Anal. Calcd. for $C_{21}H_{14}ClN_3O$: C, 70.10; H, 3.92; N, 11.68; Found: C, 70.15; H, 3.95; N, 11.72.

3-(4-(4-hydroxybenzylideneamino) phenylimino) indoline-2-one [5c]. IR : 3529 (Ar-OH), 3130 (N-H), 3011 (Ar-CH), 1680 (C=O), 1615 (C=C), 1591 (C=N) cm^{-1}; ^{1}H-NMR (DMSO): δ 8.28 (s, 1H, -N=CH-), 8.01 (s, 1H, -NH-), 7.01-7.48 (m, 8H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6', Ar-H), 7.42 (d, J=7.2 Hz, 1H, C-2'' Ar-H), 7.47 (d, J=6.5 Hz,1H, C-6'' Ar-H), 6.62 (d, J=5.9 Hz,1H, C-3'' Ar-H), 6.67 (d, J=7.8 Hz, 1H, H-5'' Ar-H), 5.14 (s, 1H, Ar -OH); EI-MS (m/z, %): 341(M^+, 26), 222(66), 149(74), 121(100), 57(74), 69(44); (Calcd. for $C_{21}H_{15}N_3O_2$: 341.36); Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31; Found: C, 73.91; H, 4.46; N, 12.28.

3-(4-(4-methoxybenzylideneamino) phenylimino) indoline-2-one [5d]. IR: 3146 (N-H), 3079 (Ar-CH), 1688 (C=O), 1647 (C=C), 1567 (C=N), 1270 (C-O-C) cm^{-1}; ^{1}H-NMR (DMSO): δ 8.39 (s, 1H, -N=CH-), 8.01(s, 1H, -NH-), 7.51(d, J=6.3 Hz, 1H, C-6'' Ar-H), 7.47 (d, J=5.9 Hz, 1H, C-2'' Ar-H), 6.99-7.31 (m, 8H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6' Ar-H), 6.81 (d, J=7.2 Hz, 1H, H-5'' Ar-H), 6.77(d, J=6.5 Hz, 1H, H-3'' Ar-H), 3.70 (s, 3H, -OCH_3); EI-MS (m/z, %): 355(M^+, 18), 282(20), 121(100), 91(42), 55(94); (Calcd. for $C_{22}H_{17}N_3O_2$: 355.38); Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82; Found: C, 74.36; H, 4.80; N, 11.78.

3-(4-(4-nitrobenzylideneamino) phenylimino) indoline-2-one [5e]. IR : 3132 (N-H), 3012 (Ar-CH), 1690 (C=O), 1603 (C=C), 1590 (C=N), 1515 & 1310 (N=O) cm^{-1}; ^{1}H-NMR (DMSO): δ 8.29 (s, 1H, -N=CH-), 8.21 (d, J=7.1 Hz, 1H, H-5'' Ar-H), 8.17 (d, J=6.8 Hz, 1H, H-3'' Ar-H), 8.10 (s, 1H, -NH-), 7.77(d, J=7.5 Hz, 1H, H-2' Ar-H), 7.69 (d, J=6.2 Hz, 1H, H-6'' Ar-H), 6.99-7.70 (m, 8H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6' Ar-H); EI-MS (m/z, %): 370(M^+, 58), 324(18), 235(100), 120(18), 77(42). (Calcd. for $C_{21}H_{14}N_4O_3$: 370.36); Anal. Calcd. for $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.81; N, 15.13; Found: C, 68.12; H, 3.78; N, 15.15.

3-(4-(2-hydroxybenzylideneamino) phenylimino) indoline-2-one [5f]. IR : 3467(Ar-OH), 3210 (N-H), 3065 (Ar-CH), 1678 (C=O), 1649 (C=C), 1575 (C=N) cm^{-1}; ^{1}H-NMR (DMSO): δ 8.22 (s, 1H, -N=CH-), 7.06-7.67 (m, 8H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6' Ar-H), 6.75-7.40 (m, 4H, H-3'', H-4'', H-5'' and H-6'' Ar-H), 6.01 (s, 1H, -NH-), 5.20 (s,1H, Ar-OH); EI-MS (m/z, %): 341(M^+, 36), 282(6), 242(34), 131(100), 89(26), 77(30). (Calcd. for $C_{21}H_{15}N_3O_2$: 341.36); Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31; Found: C, 73.91; H, 4.45; N, 12.35.

3-(4-(4-methylbenzylideneamino) phenylimino) indoline-2-one [5g]. IR: 3198 (N-H), 3144 (Ar-CH), 1696 (C=O), 1618 (C=C), 1518 (C=N) cm^{-1}; ^{1}H-NMR(DMSO): δ 8.21 (s, 1H, -N=CH-), 8.01 (s, 1H, -NH-), 7.01-7.50 (m, 12H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6', H-2'',H-3'', H-5'', H-6'' Ar-H), 2.30 (s, 3H, -CH_3); EI-MS (m/z, %): 339(M^+, 28), 235(40), 222(80), 104(92), 55(100). (Calcd. for $C_{22}H_{17}N_3O$: 339.38); Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38; Found: C, 77.84; H, 5.09; N, 12.34.

3-(4-(3, 4, 5,-trimethoxy benzylideneamino) phenylimino) indoline-2-one [5h]. IR: 3186 (N-H), 3061 (Ar-CH), 1682 (C=O), 1672 (C=C), 1574 (C=N), 1283 (C-O-C) cm^{-1}; ^{1}H-NMR(DMSO): δ 8.35 (s, 1H,-N=CH-), 7.99 (s, 1H, -NH-), 6.99-7.29 (m, 8H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6' Ar-H), 6.51 (s, 1H, H-2'' Ar-H), 6.58 (s, 1H, H-6'' Ar-H), 3.70 (s, 9H, [OCH_3]$_3$); EI-MS (m/z, %): 415(M^+, 28), 324(18), 263(8), 167(100), 125(58), 69(30); (Calcd. for $C_{24}H_{21}N_3O_4$: 415.44); Anal. Calcd. for $C_{24}H_{21}N_3O_4$: C, 69.39; H, 5.10; N, 10.11; Found: C, 69.41; H, 5.12; N, 10.14.

3-(4-(4-hydroxy-3-methoxylbenzylideneamino) phenylimino) indoline-2-one [5i]. IR: 3523 (Ar-OH), 3210 (N-H), 3023 (Ar-CH), 1698 (C=O), 1631 (C=C), 1595 (C=N), 1127 (C-O-C) cm^{-1}; ^{1}H-NMR(DMSO): δ 8.29 (s, 1H, -N=CH-), 8.02 (s, 1H, -NH-), 7.03-7.68 (m, 8H, H-4, H-5, H-6, H-7, H-2', H-3', H-5' , H-6' Ar-H), 7.00 (d, J=7.8 Hz 1H, H-6'' Ar-H), 6.95-6.97 (s, 1H, H-2'' Ar-H), 6.64 (d, J=6.6 Hz 1H, H-5'' Ar-H), 5.06 (s, 1H, Ar-OH), 3.73 (s, 3H, OCH_3); EI-MS (m/z, %): 371(M^+, 72), 324(8), 242(28), 235(100), 177(28), 95(12); (Calcd. for $C_{22}H_{17}N_3O_3$: 371.38); Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31; Found: C, 71.19; H, 4.59; N, 11.36.

3-(4-(3-nitrobenzylideneamino) phenylimino) indoline-2-one [5j]. IR: 3175 (N-H), 3055 (Ar-CH), 1686 (C=O), 1650 (C=N), 1652 (C=C), 1491 & 1373 (C-NO_2) cm^{-1}; ^{1}HNMR(DMSO): δ 8.55 (s,1H, H-2'' Ar-H), 8.23(d, J=8.1 Hz, 1H, H-4'' Ar-H), 8.19(s,1H, -N=CH-), 8.10 (s, 1H, -NH-), 8.03 (d, J=6.5 Hz, 1H, H-6'' Ar-H), 7.54 (dd, J=7.3, Hz, 1H, H-5'' Ar-H), 7.01-7.30(m, 8H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6' Ar-H); EI-MS (m/z, %): 370(M^+ , 40), 324(16), 242(38), 173(72), 122(100), 77(22); (Calcd. for $C_{21}H_{14}N_4O_3$: 370.36); Anal. Calcd. $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.81; N, 15.13; Found: C, 68.12; H, 3.83; N, 15.10.

3-(4-(4-dimethylaminobenzylideneamino) phenylimino) indoline-2-one [5k]. IR : 3150 (N-H), 3055 (Ar-CH), 3019 (C-H), 1698 (C=O), 1613 (C=C), 1568 (C=N) cm^{-1}; ^{1}H-NMR(DMSO): δ 8.21 (s, 1H, -N=CH-), 8.02 (s, 1H, -NH-), 7.42 (dd, J=5.9 Hz, 2H, H-2'' and H-6'' Ar-H), 7.03-7.68 (m, 8H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6' Ar-H), 6.61 (dd, J=7.2 Hz, 2H, H-3'' , H-5'' Ar-H), 2.85 (s, 6H, -N[CH_3]$_2$); EI-MS (m/z, %): 368(M^+, 6), 324(14), 242(38), 133(100), 91(20). (Calcd. for $C_{23}H_{20}N_4O$: 368.43); Anal. Calcd. $C_{23}H_{20}N_4O$: C, 74.98: H, 5.47; N, 15.21; Found: C, 74.95; H, 5.49; N, 15.22.

3-(4-(3-phenylallylideneamino) phenylimino) indoline-2-one [5l]. IR : 3168 (N-H), 3090 (Ar-CH), 1700 (C=O), 1591 (C=N), 1498 (C=C) cm^{-1}; ^{1}H-NMR (DMSO): δ 8.01 (s, 1H, -NH-), 7.51 (s, 1H, -N=CH-), 6.99-7.32 (m, 13H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', H-6', H-2'', H-3'', H-4'', H-5'', H-6'' Ar-H), 6.62 (d, 1H, J=7.1 Hz; C_6H_5-CH=CH-), 5.63 (d, 1H, J=8.2 Hz, C_6H_5-CH=CH-); EI-MS (m/z, %): 351(M^+,26), 300(24), 243(10), 221(8), 179(18), 109(100), 60(32); (Calcd. for $C_{23}H_{17}N_3O$: 351.40); Anal. Calcd. for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96; Found: C, 78.59; H, 4.85; N, 11.90.

Anticonvulsant activity

All the compounds were screened for anticonvulsant properties adopting the anticonvulsant drug development (ADD) program protocol[18-19]. 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 body mass) to mice, at doses of 30, 100 and 300 mg kg^{-1} 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 2**.

Subcutaneous metrazole seizure pattern test

A metrazole dose of 85 mg kg^{-1} administered subcutaneously to mice causes seizures in more than 97% of the animals. This is called the convulsive dose 97 (*CD*97). 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.

Neurotoxicity screen rotorod test

The test is used to evaluate the activity of drugs interfering with motor coordination. The skeletal muscle relaxation induced by a test compound could be evaluated by testing the ability of mice or rats to remain on a revolving rod. Minimal motor impairment was measured in mice by the rotorod test. The mice were trained to stay on an accelerating rotorod 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^{-1}. 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.

RESULTS AND DISCUSSION

Chemistry

IR, ^{1}H-NMR, mass spectra and elemental analyses of the synthesized compounds are in accordance with the assigned structures. The IR

spectra of all synthesized compounds show bands at 3150-3245 cm^{-1}, 1680-1700 cm^{-1} and weak band at 1600-1630 cm^{-1} which can be assignable to N-H, C=O and C=N (azomethine linkage) vibrations of the isatin ring respectively. In all the Schiff base derivatives, both the bands due to N-H and C=O of isatin ring remain almost at the same position, indicating non-involvement of the groups in the bond formation. IR spectrum of 3-[4-(4-hydroxy benzylideneamino) phenylimino] indoline-2-one was shown absorption band in the region of 3350-3400 cm^{-1} which may be assigned to O-H stretching. The proton magnetic resonance spectrum of imesatin and their corresponding Schiff base derivatives were recorded in DMSO-d_6. The following conclusions can be derived by comparing the spectra of imesatin and their corresponding Schiff base. (a) The signal because of N-H group of the isatin ring appears at δ 8.0 in the spectra of imesatin and their corresponding Schiff base derivative. (b) Imesatin and their corresponding Schiff base derivatives show a multiplet for the aromatic ring at δ 6.99-7.70. (c) A signal because of N=CH appear at δ 7.51-8.39 in all the final compounds and absence of the same signal in imesatin clearly indicates the formation of Schiff base through primary amino group of imesatin The EI - mass spectra of compounds showed molecular ions of different intensity which confirmed their molecular weight. The major fragmentation pathway is supported by the formation of two fragments such as C_8H_7NO (m/z 133) and C_6H_5N (m/z 91) in all the synthesized compounds. The fragment C_6H_5N was obtained from C_8H_7NO, through cleavage of the endocyclic NH-CO bond of isatin ring.

Table 1: Formula and physical constants of compounds 5a-l

Compounds	M.P (^{0}C)	Yields	Molecular formula	Molecular weight
5a	322-324	80	$C_{21}H_{15}N_3O$	325
5b	346-348	75	$C_{21}H_{14}ClN_3O$	360
5c	334-336	68	$C_{21}H_{15}N_3O_2$	341
5d	326-328	79	$C_{22}H_{17}N_3O_2$	355
5e	338-340	68	$C_{21}H_{14}N_4O_3$	370
5f	318-320	73	$C_{21}H_{15}N_3O_2$	341
5g	320-322	77	$C_{22}H_{17}N_3O$	339
5h	316-318	71	$C_{24}H_{21}N_3O_4$	415
5i	340-342	65	$C_{22}H_{17}N_3O_3$	371
5j	314-316	72	$C_{21}H_{14}N_4O_3$	370
5k	322-324	80	$C_{23}H_{20}N_4O$	368
5l	310-312	67	$C_{23}H_{17}N_3O$	351

Anticonvulsant activity

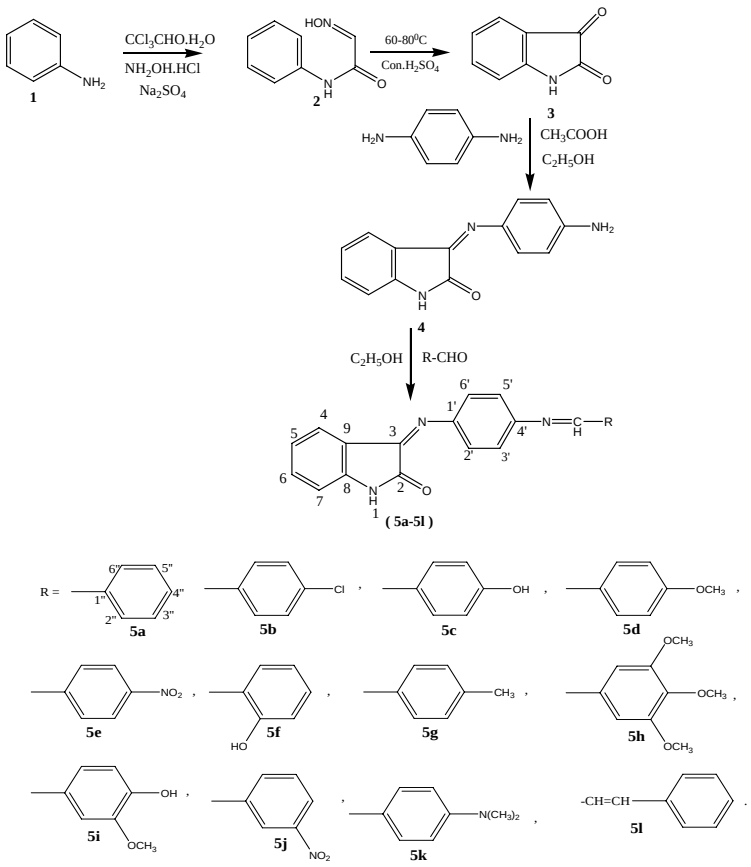
The results of anticonvulsant screening are given in Table 2. The two primary screens MES and ScMet were performed in mice at doses of 30, 100, 300 mg kg^{-1} (intraperitoneally).As compared to unsubstituted phenyl ring on isatin, compounds bearing substituents like 3,4,5 trimethoxy 5h showed excellent anticonvulsant activity with lower dose in MES as well as in ScMet methods. Whereas the phenyl ring bearing 4-hydroxy-3-methoxy substituents 5i showed excellent activity only in MES method. Moreover the phenyl ring substituted with groups like 4-hydroxy 5c, 4-methoxy 5d and 4-N-dimethylamino 5k exhibited moderate anticonvulsant activity in MES and ScMet methods, Whereas phenyl ring having groups like 4-methyl 5g and 4-hydroxy-3-methoxy 5i derivatives showed moderate activity only in ScMet methods. Compound 5l 3-(4-(3-phenylallylideneamino) phenylimino) indoline-2-one showed anticonvulsant activity only in MES method but no activity in ScMet method upto 300 mg kg^{-1} bodyweight. Among the compounds synthesized the phenyl ring bearing substituents like 4-nitro and 3-nitro derivatives showed no anticonvulsant activity up to the maximum dose tested (300 mg kg^{-1} body weight) both in MES and ScMet methods. In the Neurotoxicity screening the results showed compounds having 4-nitro 5e and 3-nitro 5j substituent showed neurotoxicity at 30 mg kg^{-1} bodyweight. Compound 5l substituted with allyl group showed no neurotoxicity up to the maximum dose used in this model 300 mg kg^{-1} bodyweight.

Table 2: Anticonvulsant and neurotoxicity screening of isatin Schiff bases

Compounds	Concentration (mg kg^{-1} body mass) [a]		
	MES[a]	ScMet[a]	Neurotoxicity[a]
5a	300	300	100
5b	-	300	100
5c	100	100	>300
5d	100	100	>300
5e	-	-	30
5f	300	-	>300
5g	300	100	300
5h	30	30	100
5i	30	100	>300
5j	-	-	30
5k	100	100	>300
5l	100	-	-
Phenytoin	30	-	100
Carbamazepine	30	100	100

MES – maximal electroshock seizure, ScMet – subcutaneous metrazole seizure – No activity.

[a] The two primary screens of MES, ScMet and toxicity were performed by intraperitoneal injection in mice at doses of 30, 100, 300 mg kg^{-1}.



Scheme 1: Synthesis of Schiff bases (5a-5l)

CONCLUSION

In conclusion, the present study highlights the importance of the structural features responsible for the anticonvulsant activity. Compounds bearing electron donating groups like methoxy, methyl, hydroxy and dimethyl amino exhibited good anticonvulsant activity. While compounds with electron withdrawing substituent like nitro and chloro showed less activity in both the models with high neurotoxicity even at low dose level. Considering the structural activity relationships for this class of compounds and analyzing the contribution of different groups at C-3 position to the anticonvulsant efficacy we could speculate that both the size and the nature of the substituents modulate the activity.

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