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Synthesis and Spectroscopic Analysis of Schiff Bases of Imesatin and Isatin Derivatives

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ABSTRACT: A series of new Schiff bases of Imesatin and Isatin derivatives which have been previously prepared from the reaction of Hydrazine monohydrate, *p*-phenylenediamine and 4,4-diaminodiphenylmethane with Isatin were reported. The compounds were characterized by elemental analyses, UV-visible, Infrared and Nuclear Magnetic Resonance (^{1}H NMR and ^{13}C NMR) spectroscopic analyses. The synthesized Schiff bases were obtained in moderate to excellent yields between 55.3 – 89.3%. Infrared spectra of all synthesized compounds contain the characteristic azomethine linkage (-CH=N) between 1580 – 1630 cm^{-1} and the N–H of the Isatin ring signals between δ 8.32 – 10.68 ppm in their ^{1}H NMR spectra. The present work affords reaction pathway that is efficient and operational simplicity for the synthesis of Schiff bases derivatives. @JASEM

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Keywords: Schiff bases, isatin, imesatin, spectroscopic analysis, biological activity

Isatin (1H-indole-2, 3-Dione) was first synthesized by Erdman, 1840 and established by Laurent, 1841 as a product from the oxidation of indigo by nitric and chromic acids. The synthetic versatility of Isatin has led to the wide applications of this compound in organic synthesis with medical and pharmacological properties of its derivatives extensively studied (Da Silva *et al*., 2001). A number of Schiff bases derived from Isatin and Imesatin derivatives have been reported with various biological properties such as, antimicrobial (Bari *et al*., 2008; Kumar *et al*., 2010; Chaluvaraju and Zaranappa, 2011), Central nervous system (CNS) depressant (Pandeya and Raja, 2002; Singh *et al.,*2004; Smitha *et al*., 2008), anti-HIV (Teitz *et al*., 1994; Pandeya *et al*., 1998; Pandeya *et al*., 1999), anti-inflammatory (Khan *et al*., 2006; Babu *et al*., 2010; Panneerselvam *et al*., 2010), analgesic (Reddy, 2008) and as anticancer agents (Vine *et al*., 2007; Aboul-Fadi *et al*., 2012). These class of compounds have also been variously applied in a number of other applications such as, identification, detection and determination of aldehydes or ketones; purification of carbonyl or amino compounds and for protection of these groups during complex or sensitive reactions (Raman *et al*., 2007). In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds and serve as important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate (Daniel *et al*., 2003).

The condensation of a primary amine in an enzyme, usually that of a lysine residue, with a carbonyl group of the substrate to form Schiff base or Imesatin is one of the most important types of catalytic mechanism in biochemical processes (Kaura and Kaura, 2012; Eissa, 2015).

In the light of different applications of Schiff bases derived from Isatin, we hereby report the synthesis of new Schiff bases derived from Isatin and Imesatin derivatives, investigation of biological and catalytic activities of these compounds is a subject of an ongoing research in our laboratory.

MATERIALS AND METHOD

All the chemicals used were analytical grade obtained from Sigma-Aldrich via Capital lab supplies, South Africa. All the solvents were redistilled and dried according to standard procedures (Glikbery and Marcus, 1985; Wheet, 2011).

Melting points were determined in open capillary tube and are uncorrected using Gallen Kamp scientific melting point apparatus GKI05. The progress of the reaction were routinely checked by Thin-layer chromatography on Merck pre-coated Silica gel 60F_{254} plates, 0.25mm, Germany using solvent system of Benzene/ethanol (9:1), developed and visualized under UV lamp at 254 and 366 nm. UV-Visible spectrometric data of the synthesized compounds were recorded on Beckman Coulter DU 730 UV-Visible Spectrophotometer. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with universal attenuated total reflectance

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(ATM) sampling accessory. ^{1}H and ^{13}C NMR spectra were recorded at 298K with 5.0-10.0 mg of samples dissolved in 0.75ml $(CD_3)_2SO$ and $CDCl_3$ in 5.0 mm NMR tube using 400.22 MHz and 100.63 MHz 9.4T Bruker, Germany NMR spectrometers respectively. Gradient heteronuclear single quantum coherence (HSQC), gradient heteronuclear multiple-bond correlation (HMBC) and nuclear over hauser effect spectroscopy (NOESY) spectra were all recorded using 376.58 MHz on the same NMR spectrometer. The digital digitizer resolution was set at 22 for both ^{1}H and ^{13}C NMR experiments. Chemical shifts (δ) were recorded against an internal standard, tetramethylsilane (TMS) for ^{1}H and ^{13}C NMR. Elemental analyses were carried out on a Perkin-Elmer CHN Analyser 2400 Series II.

*Preparation of Derivatives***:** *Synthesis of Schiff bases of Imesatin and Isatin:* The compounds were prepared by a slight modification of literature procedures (Ibrahim *et al*., 2006; Chaluvaraju and Zaranappa, 2011; Kaura and Kaura, 2012). Isatin (1.47 g, 1 mmol), was separately added to equimolar quantity of *p*-Phenylenediamine (1.08 g, 1 mmol), Hydrazine monohydrate (0.51 g, 1 mmol) and 4,4'-Diaminodiphenylmethane (0.20 g, 1 mmol) in 30 ml of methanol containing 5 ml of glacial acetic acid inside a 100 ml round bottomed flask. The reaction mixture was heated to reflux for 2 h at the refluxing temperature. The solvent was then distilled off to obtain precipitates which were cooled, filtered and washed with distilled water (2 x 10 ml). Recrystallization from ethanol afforded the pure Imesatin derivatives.

Equimolar quantity of purified Imesatin derivatives and various substituted aromatic aldehydes were dissolved in 30 ml ethanol and the mixtures heated to reflux for 8 h. The resulting solution was cooled and the solvent was removed on a Buchi R-215 rotary evaporator. The solid residue was washed with distilled water to obtain the crude product. The crude product was purified by recrystallization in ethanol to afford Schiff base of Isatin derivatives.

RESULTS AND DISCUSSION

Spectroscopic and analytical data of synthesized Schiff base of Imesatin and Isatin derivatives

3-hydrazono-indoline-2-one: Yield (%): 77.9; **m.pt. (°C):** 226-228; **UV** λ_{max}(nm): 238 (π→π*), 303 (n→σ*); **IR** ν_{max} (cm^{-1})**:** 3350 (N-H), 3143 (N-H Isatin), 1655 (C=O), 1583 (C=N); **^{1}H NMR (DMSO-d_6)**: δ ppm 10.68 (s, 1H, -N-H), 10.55 (d, J=14.2 Hz, 1H, -NH_2), 9.55 (d, J=14.2 Hz, 1H, -NH_2), 6.85 – 7.37 (m, 4H, H-4, H-5, H-6, H-7, Ar-H); **^{13}C NMR (DMSO–d_6)**: δ ppm 110 – 138 (Ar-C), 164 (C=N), 162 (C=O); Anal. Calcd. for $C_8H_7N_3O$; C, 59.62; H, 4.38; N, 26.07; O, 9.93; Found C 59.68; H, 4.36; N, 26.01; O, 9.95.

3-(2',4'-dimethoxybenzylidenehydrazono)indoline-2-one: Yield (%): 69.4; **m.pt. (°C):** 203-204; **UV** λ_{max}(nm): 210 (π→π*), 300 (n→σ*); **IR** ν_{max} (cm^{-1})**:** 3141 (N-H Isatin), 3070 (Ar, H), 1709 (C=O), 1665 (C=C), 1577 (C=N), 1268 (C-O-C); **^{1}H NMR ($CDCl_3$):** δ ppm 8.92 (s, 1H, N-H), 8.27 (d, J=7.5 Hz, 1H, -N=CH-), 6.46-7.87 (m, 7H, H-4, H-5, H-6, H-7, H-2', H-3', H-5', Ar-H), 3.8 (s, 6H, OCH_3); **^{13}C NMR ($CDCl_3$):** δ ppm 55 (-OCH_3), 97 – 98 (C-O), 110 – 164 (Ar-C), 166 (C=N), 163 (C=O); Anal. Calcd.for $C_{17}H_{15}N_3O_3$; C, 66.01; H, 4.89; N, 13.58; O, 15.52; Found C 66.08; H, 4.65; N, 13.12; O, 16.15.

3-(2'-hydroxy-4'-methoxybenzylidenehydrazono) indoline-2-one: Yield (%): 84.7; **m.pt. (°C):** 176-177; **UV** λ_{max}(nm): 246 (π→π*), 470 (n→σ*); **IR** ν_{max} (cm^{-1})**:** 3350 (O-H), 3150 (N-H Isatin), 1743 (C=O), 1685 (C=C), 1592 (C=N), 1286 (C-O-C); **^{1}H NMR (DMSO-d_6):** δ ppm 9.98 (s, 1H, N-H), 8.03 (d, J=7.32 Hz, 1H, -N=CH-), 6.46-6.64 (m, 3H, H-2', H-3', H-5', Ar-H), 6.85-7.62 (m, 7H, H-4, H-5, H-6, H-7, Ar-H), 3.81 (t, J=4.5 Hz, 3H); **^{13}C NMR (DMSO-d_6):** δ ppm 55 (-OCH_3), 110 – 164 (Ar-C), 165 (C=N), 160 (C=O); Anal. Calcd.for $C_{16}H_{13}N_3O_3$; C, 65.08; H, 4.44; N, 14.23; O, 16.25; Found C 65.12; H, 4.23; N, 14.12; O, 16.53

3-((4'-(4''-aminobenzyl) phenyl)imino)indoline-2-one: Yield (%): 81.6; **m.pt. (°C):** 321-322; **UV** λ_{max}(nm): 203 (π→π*), 309 (n→σ*); **IR** ν_{max} (cm^{-1})**:** 3231 (N-H), 1739 (C=O), 1652 (C=C), 1609 (C=N); **^{1}H NMR (DMSO-d_6)**: δ ppm 9 .89 (d, J =7.8 Hz, 2H, -NH_2), 6.42 – 7.41 (m, 12H, Ar-H), 4.03 (s, 2H, Ar-CH_2-Ar); **^{13}C NMR ($CDCl_3$)**: δ ppm 40 (CH_2), 101 – 158 (Ar-C), 163 (C=N), 161 (C=O); Anal. Calcd.for $C_{21}H_{17}N_3O$; C, 77.04; H, 5.23; N, 12.84; O, 4.89; Found C 77.08; H, 5.23; N, 12.75; O, 4.94

3-((4-4'-((2'', 4''-dimethoxybenzylideneamino) benzyl) phenyl)imino)indoline-2-one: Yield (%): 65.4; **m.pt. (°C):** 351-352; **UV** λ_{max}(nm): 218 (π→π*), 335 (n→σ*); **IR** ν_{max} (cm^{-1})**:** 3181 (N-H), 1738 (C=O), 1653 (C=C), 1607 (C=N), 1287 (C-O-C); **^{1}H-NMR ($CDCl_3$):** δ ppm 10.27 (s, 1H, -N-H), 7.79 (d, J=8.7 Hz, 1H, -N=CH), 6.42 – 7.24 (m, 15H, Ar-H), 3.88 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3); **^{13}C NMR ($CDCl_3$)**: δ ppm 40 (CH_2), 56 (OCH_3), 101 – 160 (Ar-C), 163 (C=N), 161 (C=O); Anal. Calcd.for $C_{30}H_{25}N_3O_3$; C, 75.77; H, 5.30; N, 8.84; O, 10.09; Found C 75.54; H, 5.28; N, 8.56; O, 10.62

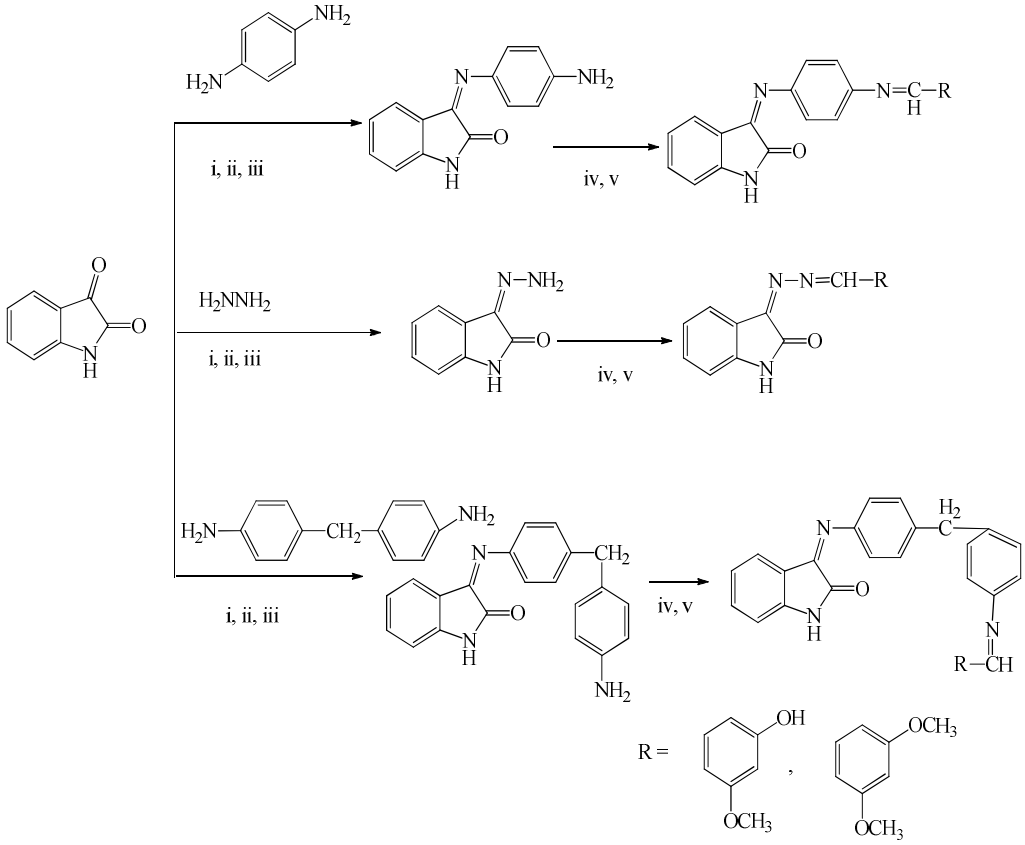
3-((4-4'-((2'',-hydroxy-4''-methoxybenzylideneamino) benzyl) phenyl)imino)indoline-2-one: Yield (%): 71.5; **m.pt. (°C):** 324-325; **UV** λ_{max}(nm): 232 (π→π*), 315 (n→σ*); **IR** ν_{max} (cm^{-1})**:** 3190 (N-H), 1739 (C=O), 1609 (C=N), 1289 (C-O-C); **^{1}H NMR ($CDCl_3$)**: δ ppm 8.53 (s, 1H, -N=CH), 6.49 – 7.29 (m, 15H, Ar-Hs), 4.04 (s, 2H, Ar-CH_2-Ar); **^{13}C NMR ($CDCl_3$)**: δ ppm 40 (CH_2), 55 (OCH_3), 101 – 159 (Ar-C), 163 (C=N), 161 (C=O); Anal.

Calcd.for $C_{29}H_{23}N_3O_3$; C, 75.47; H, 5.02; N, 9.10; O, 10.40; Found C 75.50; H, 4.98; N, 9.00; O, 10.52

3-(4'-aminophenylimino) indoline-2-one: Yield (%): 89.3; **m.pt. (°C):** 349-350; **UV** λ_{max}(nm): 238 ($\pi\rightarrow\pi^*$), 303 ($n\rightarrow\sigma^*$);**IR** ν_{max} (cm^{-1})**:** 3085 (Ar-H), 1724 (C=O), 1650(C=C), 1609 (C=N); **^{1}H NMR (DMSO-d_6):** δ ppm 8.32 (s, 1H, -N-H), 6.63 – 7.61 (m, 8H, Ar-H); **^{13}C NMR (DMSO-d_6):** δ ppm 111 – 155 (Ar-C), 163 (C=N), 158 (C=O); Anal. Calcd.for $C_{14}H_{11}N_3O$; C, 70.87; H, 4.67; N, 17.71; O, 6.74; Found C 70.88; H, 4.56; N, 17.81; O, 6.75.

3-(4'-(2'',4''-dimethoxybenzylideneamino) phenylimino) indoline-2-one: Yield (%): 57.4; **m.pt. (°C):** 343-344; **UV** λ_{max}(nm): 227 ($\pi\rightarrow\pi^*$), 328 ($n\rightarrow\sigma^*$);**IR** ν_{max} (cm^{-1})**:** 3148 (N-H), 3085 (Ar-H), 1721 (C=O), 1651 (C=C), 1608 (C=N) 1290 (C-O-C); **^{1}H NMR (DMSO-d_6):** δ ppm 8.77 (s, 1H, -N-H), 7.97 (d, J=8.3 Hz, 1H, -N=CH), 6.67 – 7.62 (m, 11H, Ar-H), 3.89 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); **^{13}C NMR (DMSO-d_6):** δ ppm 55 (OCH_3), 111-150 (Ar-C), 158 (C=N),158 (C=O); Anal. Calcd.for $C_{23}H_{19}N_3O_3$; C, 71.68; H, 4.97; N, 10.90; O, 12.45; Found C 71.56; H, 4.85; N, 10.86; O, 12.73.

3-(4'-(2'-hydroxy-4''-methoxybenzylideneamino) phenylimino) indoline-2-one: Yield (%): 55.3; **m.pt. (°C):** 321-322; **UV** λ_{max}(nm): 212 ($\pi\rightarrow\pi^*$), 306 ($n\rightarrow\sigma^*$); **IR** ν_{max} (cm^{-1})**:** 1725 (C=O), 1594 (C=C), 1569 (C=N), 1289 (C-O-C); **^{1}H NMR (DMSO-d_6):** δ ppm 8.91 (s, 1H, -N-H), 8.74 (s, 1H, -N=CH), 6.48-7.62 (m, 11H, Ar-H), 3.79 (t, J=2.4 Hz, 3H, OCH_3); **^{13}C NMR (DMSO):** δ ppm 56 (OCH_3), 115 – 160 (Ar-C), 163 (C=N), 158 (C=O); Anal. Calcd.for $C_{22}H_{17}N_3O_3$; C, 71.15; H, 4.61; N, 11.31; O, 12.92; Found C 71.02; H, 4.50; N, 11.20; O, 13.28.



Scheme 1: Synthesis of the Schiff bases of Isatin and Imesatin derivatives (i) CH_3OH; (ii) CH_3COOH; (iii) reflux 2 h (iv) CH_3CH_2OH, RCHO and reflux 8 h.

The reaction pathways for the syntheses of the new compounds are shown in Scheme 1. The elemental analysis data and the sharp melting points obtained for these compounds are indication of the purity of the synthesized Schiff base derivatives. Most of the compounds were soluble in dimethylsulphoxide while the others were soluble in chloroform but insoluble in other common organic solvents. As shown in the experimental data, all the compounds were obtained in moderate to excellent yield and purity.

The IR spectra of all synthesized compounds show prominent strong bands in the range 1569 – 1609 cm^{-1} attributable to the presence of the characteristic

azomethine –CH=N linkage in all the compounds. This is a direct evidence of the formation of the desired Schiff bases. The presence of strong bands between 3141 – 3350 cm^{-1} and weak bands in the region 1709 – 1743 cm^{-1} assignable to N–H and C=O vibrations of Imesatin and Isatin rings respectively (Manjusha *et al*., 2004). In all the Schiff base derivatives, bands due to N–H and C=O of Imesatin or Isatin ring which remain almost at similar positions, indicating their non-involvement in the bond formation. Proton magnetic resonance spectra of the Schiff base of Imesatin and Isatin derivatives were assigned using different chemical shifts (δ). Signals due to the N–H group of the Isatin ring appears at δ 8.77 – 10.68 and multiplets peaks observed for the aromatic ring protons between δ 6.42 – 7.87. The characteristic -N=C–H signal appears between δ 7.79 – 8.97 in all the synthesized compounds and absence of the same signal in the Imesatin structures indicates the formation of Schiff base derivatives through their primary amino group (Manjusha *et al*., 2004; Aliasghar *et al*., 2007; Prakash *et al*., 2010; Eissa, 2015). The ^{13}C-NMR results are consistent with the ^{1}H-NMR results.

Conclusion: This research reports a series of Schiff base of Imesatin and Isatin derivatives synthesized by the reaction of hydrazine monohydrate, *p*-phenylenediamine and 4, 4'-diaminodiphenylmethane with Isatin and further condensation of the products (Imesatin) with different aromatic aldehydes. The synthesized derivatives are all coloured compounds, mostly soluble in dimethylsulphoxide. Physical characterization using spectroscopic techniques was employed in the elucidation of the structures of the synthesized derivatives. This class of compounds might have some important biological activity and can be effectively utilized as lead molecules for drug development. Further studies on this class of compounds are in progress for getting more information on their pharmacological and toxicological importance.

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