Synthesis and Spectroscopic analysis of Schiff bases of Isatin and Imesatin derivatives

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Abstract

Some Schiff bases are considered to be good candidates for various pharmaceutical and material applications attributable to the presence of different functional groups in their structures. Thus, a series of Schiff bases of Isatin and Imesatin derivatives were synthesized by the reaction of hydrazine monohydrate, p-phenylenediamine and 4,4’-diaminodiphenylmethane with Isatin and further condensation of products formed with different aromatic aldehydes giving moderate to excellent yields of 55.3 – 89.3%. The chemical structures of the synthesized compounds were investigated using Infrared, \(^1\)H and \(^13\)C Nuclear Magnetic Resonance Spectroscopy. The Infrared spectra of all synthesized compounds indicate the presence of significant bands at 3245 – 3500 cm\(^{-1}\), 1680 – 1720 cm\(^{-1}\) and 1580 – 1630 cm\(^{-1}\), which can be attributed to N-H, C=O and C=N (azomethine linkage) vibrations of the Isatin ring. In all the Schiff base derivatives, the bonds due to N-H and C=O of Isatin ring remain almost at the same position which support the non-involvement of the groups in the bonds formation of subsequent derivatives. In \(^1\)H NMR, a signal appears at \(\delta 8.32 – 10.68 \) ppm in the spectra of Imesatin and their corresponding Schiff base derivative as a result of the N-H group of the Isatin ring. Multiplet signal also appears for the aromatic ring at \(\delta 6.46 – 7.90 \) ppm while another signal appears at \(\delta 8.03 – 8.74 \) ppm in all the derivatives because of N=CH and the absence of the same signal in the initial Imesatin indicates the formation of Schiff base through the remaining primary amines group of Imesatin ring.

Keywords: Isatin, Schiff bases, Spectroscopic analysis, synthesis.
1. Introduction

Isatin (1H-indole-2, 3-dione) was first obtained by Erdman [1] and Laurent in 1841 [2] as a product from the oxidation of indigo by nitric and chromic acids. The synthetic versatility of Isatin has led to the extensive use of this compound in organic synthesis which in turn, has stemmed the interest in the biological and pharmacological properties of its derivatives [3]. Numerous Schiff bases of Isatin and its derivatives have been synthesized and they exhibit various biological activities like; antimicrobial [4,5,6], CNS depressant [7,8,9], anti-HIV [10,11,12], anti-inflammatory [13,14,15], analgesic [16], anticancer [17,18] and many other activities however, little research has been done on the synthesis, characterization and biological activities of different Schiff bases of Imesatin derivatives. In this study, we report the synthesis and spectroscopic analysis of some Isatin and Imesatin Schiff base derivatives with the use of Infrared, $^1$H and $^{13}$C NMR spectroscopic data.

2. Proposed methodology

![Scheme 1: General reaction scheme for Isatin and Imesatin Schiff base derivatives synthesis](image)

* i = CH$_3$OH  
  ii = CH$_3$COOH  
  iii = reflux  
  iv = CH$_3$CH$_2$OH, reflux 8 hrs  
  v = RCHO

2.1 Chemicals and reagents

Chemicals and reagents used in this research were purchased from Sigma-Aldrich via Capital lab supplies, South Africa. They include Isatin 98%, p-Phenylenediamine free base, Hydrazine monohydrate, 4,4'-
Diaminodiphenylmethane, 2,4-Dimethoxybenzaldehyde 99%, and 2-Hydroxy-4-methoxybenzaldehyde 98%.

Solvents like include methanol and ethanol were redistilled before use.

2.2 Synthesis

Equimolar quantities of Isatin 98% and \( p \)-Phenylenediamine free base, Hydrazine monohydrate, 4,4′-Diaminodiphenylmethane were dissolved respectively in 30 ml methanol in 15 ml glacial acetic acid and refluxed for two hours, then kept for few hours at room temperature, resulting in the formation of the respective Imesatins which were subsequently recovered after filtration and drying in a desiccator. Equimolar quantities of the Imesatins and various substituted aromatic aldehydes were dissolved in 30 ml ethanol and refluxed for 8 hours. After standing for four days at room temperature, the products which are Imesatin Schiff base derivatives were filtered off and dried.

The purity of the compounds was confirmed by thin layer chromatography (TLC) using silica gel F\(_{254}\) plates Germany, and solvent system of benzene:ethanol (9:1). The spots were developed and subsequently visualized under ultraviolet lamp. All compounds gave single spots on TLC plates with \( R_f \) values different from those of the starting mixture. Solubility tests and melting point determination were carried out on all synthesized compounds. Melting points were determined in open capillary tubes in a Gallen Kamp scientific melting point apparatus and were recorded uncorrected at room temperature (25°C).

2.3 Spectroscopic analysis

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with universal attenuated total reflectance (ATR) 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\(_3\))\(_2\)SO and CDCl\(_3\) in 5.0mm NMR tube using 400.22MHz and 100.63MHz 9.4T Bruker, Germany NMR spectrometers respectively.

The digital digitizer resolution was set at 22 for both \(^1\)H and \(^{13}\)C NMR experiments. Chemical shifts (\(\delta\)) were reported in ppm and coupling constants (\(J\)) in Hz. The \(^1\)H NMR chemical shifts of the deuterated solvents were at 2.50 and 7.26 for (CD\(_3\))\(_2\)SO and CDCl\(_3\) respectively while \(^{13}\)C NMR chemical shifts for them were at 39.52 and 77.16 respectively, referenced to the internal standard Tetramethysilane.

3.0 Results and discussion

Physical properties of synthesized Schiff base of Isatin and Imesatin derivatives are as shown below. Most of these compounds were soluble in Dimethylsulphoxide with moderate to good yields of 55.3 – 89.3%.
3.1 Physical properties of synthesized Schiff base of Isatin and Imesatin derivatives

Table 1: Physical properties of synthesized Schiff base of Isatin and Imesatin derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Yield</th>
<th>Rf Value</th>
<th>Soluble in</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-(4′-aminophenylimino)indoline-2-one</td>
<td>89.3</td>
<td>0.12</td>
<td>Ethanol, Acetone and Dimethylsulphoxide</td>
<td>349 – 351</td>
</tr>
<tr>
<td>3-hydrazono-indoline-2-one</td>
<td>77.9</td>
<td>0.24</td>
<td>Ethanol, Acetone and Dimethylsulphoxide</td>
<td>226 – 228</td>
</tr>
<tr>
<td>3-((4′′-aminobenzyl)phenylimino)indoline-2-one</td>
<td>81.6</td>
<td>0.10</td>
<td>Ethanol, Acetone and Dimethylsulphoxide</td>
<td>321 – 323</td>
</tr>
<tr>
<td>3-((4′′-6''-dimethoxybenzylideneamino)indoline-2-one)</td>
<td>57.4</td>
<td>0.14</td>
<td>Methanol and Dimethylsulphoxide</td>
<td>343 – 345</td>
</tr>
<tr>
<td>3-((4′′-hydroxy-4''-methoxybenzylideneamino)indoline-2-one)</td>
<td>55.3</td>
<td>0.47</td>
<td>Methanol and Dimethylsulphoxide</td>
<td>321 – 323</td>
</tr>
<tr>
<td>3-(6’-hydroxy-4'-methoxybenzylidenehydrazono)indoline-2-one</td>
<td>69.4</td>
<td>0.28</td>
<td>Chloroform</td>
<td>203 – 205</td>
</tr>
<tr>
<td>3-(6'-hydroxy-4'-methoxybenzylidenehydrazono) indoline-2-one</td>
<td>84.7</td>
<td>0.32</td>
<td>Methanol, Acetone and Dimethylsulphoxide</td>
<td>176 – 178</td>
</tr>
<tr>
<td>3-((4′-4''-((2''',4''')-dimethoxybenzylideneamino)(benzyl)phenylimino)indoline-2-one</td>
<td>65.4</td>
<td>0.16</td>
<td>Chloroform</td>
<td>351 – 353</td>
</tr>
<tr>
<td>3-(6'-hydroxy-4'-methoxybenzylidenehydrazono) indoline-2-one</td>
<td>69.4</td>
<td>0.28</td>
<td>Chloroform</td>
<td>203 – 205</td>
</tr>
</tbody>
</table>

3.2 Spectroscopic data of synthesized Isatin Schiff base derivatives

3-hydrazono-indoline-2-one: IR(KBr): 3350 (N-H), 3143 (N-H Isatin), 1655 (C=O), 1583 (C=N) cm⁻¹; ¹H-NMR (DMSO- d₆): δ ppm 10.68 (s, 1H, -N=CH), 10.55 (d, J=14.2 Hz, 1H, -NH₂), 9.55 (d, J=14.2 Hz, 1H, -NH₂), 6.85 – 7.37 (m, 4H, H-4, H-5, H-6, H-7, Ar-H); ¹³C NMR (DMSO): δ ppm 110 – 138 (Ar-C), 162 (C=O).

3-(4’,6’’-dimethoxybenzylidenehydrazono)indoline-2-one: IR(KBr): 3141 (N-H Isatin), 3070 (Aromatic H), 1709 (C=O), 1665 (C=C), 1577 (C=N), 1268 (C-O-C) cm⁻¹; ¹H-NMR (CDCl₃): δ ppm 8.92 (s, 1H, -N=CH), 6.46-7.87 (m, 7H, H-2', H-3', H-5', Ar-H), 3.81 (t, J=4.5 Hz, 3H); ¹³C NMR (CDCl₃): δ ppm 55 (-OCH₃), 110 – 164 (Ar-C), 166 (C=N), 188 (C=O).

3-(6'-hydroxy-4'-methoxybenzylidenehydrazono) indoline-2-one: IR(KBr): 3350 (O-H), 3150 (N-H Isatin), 1743 (C=O), 1685 (C=C), 1592 (C=N), 1286 (C-O-C) cm⁻¹; ¹H-NMR (DMSO- d₆): δ ppm 9.98 (s, 1H, -NH₂), 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), 3.81 (t, J=4.5 Hz, 3H); ¹³C NMR (DMSO): δ ppm 55 (-OCH₃), 110 – 164 (Ar-C), 165 (C=N), 191 (C=O).
3-((4'-4''-aminobenzyl)phenyl)imino)indoline-2-one: IR(KBr): 3231 (N-H), 1739 (C=O), 1652 (C=C), 1609 (C=N) cm⁻¹; ¹H-NMR (DMSO- d₆): δ ppm 9.89 (d, J=7.8 Hz, 2H, -NH₂), 6.42 – 7.41 (m, 12H, Ar-H), 4.03 (s, 2H, Ar-CH₂-Ar).

3-((4'-4''-dimethoxybenzylideneamino)benzyl)phenyl)imino)indoline-2-one: IR(KBr): 3181 (N-H), 1738 (C=O), 1653 (C=C), 1607 (C=N) 1287 (C-O-C) cm⁻¹; ¹H-NMR (CDCl₃): 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-Hs), 3.88 (s, 3H, -OCH₃), 3.86 (s, 3H, -OCH₃).

3-((4'-4''-((2''',4'''-dimethoxybenzylideneamino)benzyl)phenyl)imino)indoline-2-one: IR(KBr): 3190 (N-H), 1739 (C=O), 1609 (C=N), 1289 (C-O-C) cm⁻¹; ¹H-NMR (CDCl₃): δ ppm 8.53 (s, 1H, -N=CH), 6.49 – 7.29 (m, 15H, Ar- Hs), 4.04 (s, 2H, Ar-CH₂-Ar); ¹³C NMR (CDCl₃): δ ppm 40 (CH₂), 55 (OCH₃), 101 – 148 (Ar-Cs), 161 (C=N), 163 (C=O).

3-(4'-aminophenylimino)indoline-2-one: IR(KBr): 3085 (Ar-H), 1724 (C=O), 1650 (C=C), 1609 (C=N) cm⁻¹; ¹H-NMR (DMSO- d₆): δ ppm 8.32 (s, 1H, -N-H), 6.63 – 7.61 (m, 8H, Ar-Hs); ¹³C NMR (DMSO): δ ppm 111 – 155 (Ar-Cs), 158 (C=N), 163 (C=O).

3-(4'-(4'',6''-dimethoxybenzylideneamino)imino)indoline-2-one: IR(KBr): 3148 (N-H), 3085 (Ar-H), 1721 (C=O), 1651 (C=C), 1608 (C=N) 1290 (C-O-C) cm⁻¹; ¹H-NMR (DMSO- d₆): 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-Hs), 3.89 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃); ¹³C NMR (DMSO): δ ppm 55 (OCH₃), 111-147 (Ar-Cs), 155 (C=N), 163 (C=O).

3-(4'-6''-hydroxy-4''-methoxybenzylideneamino)imino)indoline-2-one: IR(KBr): 3125 (C=O), 1594 (C=C), 1569 (C=N), 1289 (C-O-C) cm⁻¹; ¹H-NMR (DMSO- d₆): δ ppm 8.91 (s, 1H, -N-H), 8.74 (s, 1H, -N=CH), 6.48-7.62 (m, 11H, Ar-Hs), 3.79 (t, J=2.4 Hz, 3H, OCH₃); ¹³C NMR (DMSO): δ ppm 115 – 147 (Ar-Cs), 155 (C=N), 163 (C=O).

The IR spectra of all synthesized compounds show bands at 3141 – 3350 cm⁻¹, 1709 – 1743 cm⁻¹ and weak bands at 1569 – 1609 cm⁻¹ which could be assignable to N-H, C=O and C=N (azomethine linkage) vibrations of the Isatin ring respectively [19]. In all the Schiff base derivatives, both the bands due to N-H and C=O of Isatin ring remain almost at similar positions, indicating their non-involvement in the bond formation.

The proton magnetic resonance spectrum of Isatin and Imesatin Schiff base derivatives were recorded and the following deductions could be made by examining the spectral data (a) The signal because of N-H group of the Isatin ring appears at δ 8.77 – 10.68 (b) Multiplets for the aromatic ring protons at δ 6.42 – 7.87 (c) A signal because of -N=CH appear between δ 7.79 – 8.97 in all the final compounds and absence of the same signal in the Imesatins indicates the formation of Schiff base through their primary amino group [19,20].
13C-NMR data showed signals at δ 154 – 166, 110 – 167 and 162 – 188 ppm assignable to C=N, aromatic and C=O carbons for all compounds [21].

4.0 Conclusion

This research reports a series of Schiff bases of 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 and were obtained in moderate to excellent yields of 55.3 – 89.3%.

Physical characterization using melting points, Thin-layer chromatography, Infrared, \(^1\)H and \(^{13}\)C Nuclear Magnetic Resonance was employed in the elucidation of the structures of synthesized derivatives.

The Infrared data obtained for all synthesized derivatives showed a weak band at 1580 – 1630 cm\(^{-1}\) attributed C=N vibration which suggests the formation of azomethine linkage. Similarly, \(^1\)H and \(^{13}\)C Nuclear Magnetic resonance spectroscopy showed chemical shifts at δ 7.60 – 8.40 and 155 – 165 ppm respectively in all synthesized derivatives which are attributed to the azomethine function in congeniality with literature data.

References


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Iloka Gabriel Sunday has received his Bachelor of Science degree in Pure Chemistry from University of Jos in the year 2010 and his Masters of Science degree in Chemistry from University of Ilorin in the year 2015. His area of interest lies in Organic Synthesis of chemical compounds.

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