Synthesis And Preliminary Antimicrobial Evaluation Of Schiff Bases Of N-Benzyl Isatin Derivatives

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ABSTRACT
Isatin (1H-indole-2,3-dione) and its analogs are an important class of heterocyclic compounds. N-benzyl isatins and Schiff bases of isatin analogs have been reported to demonstrate a variety of biological activities. This work illustrates the synthesis of new N-benzylisatin Schiff bases and studies their biological activity. Firstly, isatin and its analogs; 5-methoxyisatin, 5-fluoroisatin reacted with benzyl iodide to obtain N-benzylated derivatives of isatins 2(a-c). Secondly, these compounds were reacted with different amines (sulphanilamide and 4-methyl sulphonyl aniline) separately, to obtain Schiff bases compounds 3(a-c) and 4(a-c), respectively. The synthesized compounds were characterized by using FT-IR and 1H NMR spectroscopy. The synthesized Schiff bases 3(a-c) and 4(a-c) were examined for their in vitro antimicrobial activity using different Gram-positive bacteria, Gram-negative bacteria, and Candida albicans as fungi. The obtained results were compared with standard drugs: amoxicillin, ciprofloxacin, and fluconazole. All the compounds show no antifungal activity at any concentrations used, while most of them show moderate antibacterial activity at concentration 5mg/ml toward most bacteria except Klebsiella pneumonia.

INTRODUCTION
Isatin (2, 3-dioxindole), an indole derivative, is an important class of heterocyclic compounds. Isatin derivatives are synthetically important substrates, which can be used for the synthesis of a large variety of heterocyclic compounds, and as raw material for drug synthesis. In the last decade, isatin derivatives have attracted great interest in organic and pharmaceutical chemistry due to their potent biological and pharmacological activities. Isatin and its derivatives possess numerous biological properties like antibacterial, antifungal, antihIV, antiviral, anticonvulsant, antitubercular, and anticancer.

Sulphonamides are one of the organic sulfur compounds containing the – SO₂NH₂ group, which have attracted attention for their better medicinal activity. It is interesting to note that the organic sulfur-containing moiety is known to have many biological and pharmaceutical properties, such as antitumor, antibacterial, and antifungal activities. The sulfa drugs competitively inhibit folic acid synthesis in microorganisms and subsequently inhibit the multiplication of bacteria. They have been used against most Gram-positive and many Gram-negative bacteria, and some fungi. Moreover, Schiff bases of sulphonamides are a potential class of compounds, which have been found to possess a wide range of medicinal properties as carbonic anhydrase II inhibitors, anti-infectious, and anticancer agents.

The introduction of the benzyl group into bioactive molecules such as isatin and its analogs will enhance their therapeutic efficacy, this effect might be due to the increasing penetration of the cell membrane, and there is a clear connection between lipophilicity and activity. N-alkyl/benzyl isatins have shown various biological activities, such as cytotoxicity, antiviral, caspase inhibition, and cannabinoid receptor 2 agonists for the treatment of neuropathic pain.

Many other studies reported that Schiff bases of isatin derivatives demonstrate a variety of biological activities, such as anti-inflammatory, anticonvulsant, anti-HIV, antibacterial, anti-fungal, and anti-depressant properties. Schiff bases are an important class of compounds due to their structural similarities with natural biological substances, and their pharmacological activity may be attributed to the formation of hydrogen bonds with the active center of cell constituents of microorganisms by the azomethine group (C= N), resulting in interference with the normal process of the cell.

From the previous studies, the N-alkylation and Schiff base formation of isatin molecules will enhance their antimicrobial, analgesic, and anti-inflammatory activities. The goal of the present work was to synthesize different Schiff bases of N-benzyl isatins with two different amines: sulphanilamide and 4-methyl sulphonyl aniline and predict their antimicrobial activity.

MATERIAL AND METHODS
Chemicals and solvents used during synthesis as follows: Isatin (1a) purchased from Hi-Media Laboratories, India, 5-methoxyisatin (1b), 5-fluoroisatin (1c), from Hangzhou Hyper Chemicals Limited, China. Sulphanilamide obtained from BDH chemicals, England, 4-methyl sulfonyl aniline, from Hawn, China. Potassium carbonate (K₂CO₃) and potassium iodide(KI) obtained from Sigma Aldrich, Germany, benzyl chloride from laboratory chemicals, India. Monitoring of the reaction and checking the purity of the products were determined by Thin-layer chromatography (TLC), using silica gel pre-coated aluminum sheets, Merck (Germany) exposed to UV-254nm light. Chromatograms were eluted by using solvent systems: A /ethanol: ethyl acetate: toluene (0.5:2:2) and B /ethanol: ethyl acetate (1:3). Melting points were measured by using Stuart SMP3 melting point apparatus in open capillary tubes, and are uncorrected. The Infrared spectra were performed using the FT-IR spectrophotometer, Shimadzu, Japan. ¹H NMR spectra were recorded on the NMR-500 spectrometer model with tetramethylsilane as an internal standard; chemical shifts (δ) were expressed as ppm.

Synthesis
General procedures for the Synthesis of N-benzyl isatins (2a-c):
(6 mmol) isatin 1a, 5-methoxyisatin 1b, and 5-fluoroisatin 1c, separately, was added to a flask containing acetonitrile (15 mL), K₂CO₃ (0.99g, 7.2 mmol), and KI (0.99g, 1.2 mmol)
were then added. The stirring was started after 5 minutes; benzyl chloride (1.29 g, 9 mmol) was then added dropwise. After 4 hours of reflux, the mixture cooled to room temperature and then filtered. The filtrate dried under a vacuum then dissolved in ethyl acetate in a separatory funnel and extracted with hot water many times until clear solution achieved indicative clearance of isatins, then dried the product in the oven at 60 °C then recrystallized from hot ethanol, scheme 1.

1-benzylindoline- 2,3-dione (2a)
(0.88 g, 6 mmol) of isatin (1a) was added in a flask containing 15 mL of acetonitrile, then K₂CO₃ (0.99g, 7.2 mmol) and KI (0.99g, 1.2 mmol) were added, and after 5 minutes of stirring, benzyl chloride (1.29 g, 9 mmol) was added dropwise as the procedure shown above. Orange crystals, Rₛ =0.913, yield 79%, m.p. 127-130 °C; FT-IR (ν, cm⁻¹): 3032 and 3086 (C-H) asymmetric and sym. str. of the aromatic ring, 2970 and 2960 (C-H) aliphatic asymmetric and sym. str. of CH₃ (benzyl group), 1728 and 1608 of carbonyl groups (two C=O), 1492 and 1465 str. of C=C (aromatic ring), 850 (out of plane C-H bending of the aromatic ring), 690 (C=C=O) of aromatic ring bending.

1-benzyl-5-methoxyindoline-2,3-dione (2b)
(1.06gm, 6mmol) of 5-methoxysatin (1b) was added in a flask containing 15 mL of acetonitrile, then K₂CO₃ (0.99gm, 7.2 mmol) and KI (0.99g, 1.2 mmol) were added, and after 5 minutes of stirring, benzyl chloride (1.29 g, 9 mmol) was added dropwise as the procedure mentioned above. Dark violet crystals, Rₛ = 0.84, yield 90%, m.p. 115-117 °C; FT-IR (ν, cm⁻¹): 3070 (C-H) str. of aromatic ring, 2962 and 2943 (C-H) aliphatic asymmetric and sym. str. of CH₃ (benzyl group), and 1720 and 1620 str. (two C=O) are carbonyl groups, 1603 and 1492 str. of C=C (aromatic ring), 850 (out of plane C-H bending of the aromatic ring), 690 (C=C=O) of aromatic ring bending.

1-benzyl 5- fluoroindoline-2,3-dione (2c)
(1.02g, 6mmol) of fluoroosatin (1c) was added in a flask containing 15 mL of acetonitrile then K₂CO₃ (0.99g, 7.2 mmol) and KI (0.99g, 1.2 mmol) were added, and after 5 minutes of stirring, benzyl chloride (1.29 g, 9 mmol) was added dropwise as the procedure mentioned above. Red crystals, Rₛ = 0.75 yield 72%, m.p 126-128 °C; FT-IR (ν, cm⁻¹): 3066 (C-H) str. of aromatic ring, 2974 and 2885 symmetric and symmetric str. of CH₃ (benzyl group), 1724 and 1620 str. of (two C=O) are carbonyl groups, 1608 and 1485 str. of C=C (aromatic ring), 887 cm⁻² out of a plane (C-H) bending of the aromatic ring, 694 cm⁻¹ (C=C) of aromatic ring bending.

General procedure for Synthesis of Schiff bases of N-benzyl isatins (3a-c) and 4(a-c)
(2 mmol) of compounds 2a-e, separately, was dissolved in 15 mL of dried absolute ethanol and 3 drops of glacial acetic acid, stirring for 1 hour then an equimolar amount of amine (2mmol) of sulfanilamide for compounds 3a-c (and) and (2 mmol) of 4-(methyl sulfonyl) aniline for compounds 4a-c were added. After another three hours of refluxing a colored precipitate appearing, this is for 3a-c compounds, while for compounds 4a-c more time was needed about 15 hours, and then filtered the mixture of reaction while is hot and the precipitate was washed with hot ethanol two times, then final colored precipitate recrystallized from hot ethanol and dried again. (Scheme 1)

4-(1-benzyl-2-oxoindolin-3-ylidene)aminobenzenesulfonamide(3a)
(0.474g, 2 mmol) of compound (2a) was added to 15 mL of absolute ethanol with 3 drops of glacial acetic acid and (0.5 g, 2mmol) of (methyl sulfonyl) aniline added as the procedure above. Orange powder, Rₛ = 0.8, yield 79.7%; m.p 224-227 C; FT-IR(ν, cm⁻¹): 3294 and 3205 (N-H) asymmetric and sym. str. of SO₂H, 3085 and 3079 (C-H) asymmetric and sym. str. of aromatic rings, 2927 and 2850 (C-H) asymmetric and sym. str. of aliphatic CH₂ (benzyl group), 1604 and 1585 asymmetric and sym. str. of (C=C) aromatic ring, 1651 str. of (C=N) of the imine, 1334 and 1165 asymmetric and str. of (S-O), 871 cm⁻¹ out of plane (C-H) bending of aromatic ring, 694 cm⁻¹ (C=C) of aromatic ring bending. ¹HNMR (δ, ppm): 5.0 (2H, s, CH₂ benzyl group), 6.4 (2H, s, NH₂ of sulphanilamide) and 6.8-7.5 (9H, m, of Ar-H), 7.45(2H,dd, Ar-H, for substituted sulfonamide group), 7.9 (2H,dd, Ar-H, for substituted sulfonamide group).

4-[[1-benzyl-5-methoxy-2-oxoindolin-3-ylidene)amino]benzenesulfonamide (3b)
(0.53 g, 2 mmol) of compound (2b) was added to 15 mL absolute ethanol with three drops of glacial acetic acid and (0.5 g, 2mmol) of sulphanilamide added as the procedure shown above. Red- violet crystals; Rₛ =0.79, m.p 252-254 °C; yield 75%. FT-IR (ν, cm⁻¹): 3363 and 3232 (N-H str.of sulfonamide group), 2970 and 2935 (C-H asymmetric and sym. str. of aromatic rings, 1674 (C=N imine) str., 1585 and 1481 str. of (C=C) aromatic ring, 1334 and 1165 asymmetric and sym. str. of (S-O), 894 cm⁻¹ out of plane (C-H) bending of aromatic ring, 694 cm⁻¹ (C=C) of aromatic ring bending. ¹HNMR (δ, ppm): 5.01 (2H, s, CH₂ benzyl group), 5.9 (2H, s, of NH₂ of sulphonamide group), 6.9-7.3 (8H, m, of Ar-H), 7.42 (2H, dd, Ar-H, for substituted sulfonamide group), 8.0 (2H, dd, Ar-H, for substituted sulphonamide group).

4-(1-benzyl-5-fluoro-2-oxoindolin-3-ylidene)amino]benzenesulfonamide (3c)
(0.5 g, 2 mmol) of compound (2e) was added in 15 mL absolute ethanol with 3 drops of glacial acetic acid and (0.5 g, 2mmol) of sulphanilamide added as the procedure above. Yellow powder, Rₛ =0.83, m.p 258-260 °C, yield 78%. FT-IR(ν, cm⁻¹): 3305 and 3228 (N-H asymmetric and sym. str. of SO₂HN₃) 3093 and 3062 (C-H) asymmetric and sym. str. of aromatic rings, 2940 and 2920 (C-H) asymmetric and sym. str. of CH₃ benzyl group),1616 and 1589 asymmetric and sym. str. of C=C of aromatic ring, 1674 (C=N imine) str., 1534 and 1165 asymmetric and sym. str. of (S-O), 898 cm⁻¹ out of plane (C-H) bending of aromatic ring, 694 cm⁻¹ (C=C) of aromatic ring bending. ¹HNMR (δ, ppm): 5.0 (2H, s, CH₂ benzyl group), 6.3(2H, s, SO₂HN₃), (6.8 - 7.5) (8H, m, of Ar-H), 7.48 (2H, dd, A-H, for substituted sulphonamide group), 7.9 (2H, dd, Ar-H, for substituted sulfonamide group).

1-benzyl-3-[(4-(methylsulfonyl)phenyl)limino]indolin-2-one (4a)
(0.474g, 2 mmol) of compound (2a) was added in 15 mL absolute ethanol with 3 drops of glacial acetic acid and (0.5 g, 2mmol) of (4- methyl sulphonyl) aniline added as the procedure above. Orange powder, Rₛ = 0.84, m.p 172-175 °C, yield 55%. FT-IR(ν, cm⁻¹): 3062 (C-H) str. of aromatic ring, 2924 and 2850 (C-H) asymmetric and sym. str. of CH₃ benzyl group, 1681 (C=N) imine str., 1600 and 1585 str. (C=C) aromatic ring 1334 and 1165 str. of (S-O), 898 cm⁻¹ out of plane (C-H) bending of aromatic ring , 694 cm⁻¹ (C=C) of aromatic ring bending. ¹HNMR (δ, ppm) show peaks at 3.2 (3H of CH₃SO₃), 5.0 (2H, s, CH₂ benzyl group), 6.7-7.5 (9 Hm, of Ar-H), 7.3 (2H,dd, Ar-H, for substituted methyl sulfonyl benzene ring), 7.0 (2H,dd, Ar-H, for substituted methyl benzene ring).

1-benzyl-5- methoxy-3-[4 (methylsulfonyl)phenyl)limino]indolin-2-one (4b)
(0.53g , 2 mmol) of compound (2b) was added in 15 mL absolute ethanol with 3 drops of glacial acetic acid and (0.5 g ,2mmol) of (4- methyl sulphonyl) aniline added as the procedure above. Yellow powder, Rₛ =0.82, m.p. 160-162 °C,
yield 30%. FT-IR (υ, cm\(^{-1}\)): 3062 (C-H) str. of aromatic rings, 2927 and 2835 (C-H) asym. and sym. str. of CH\(_2\) benzyl group, 1674 (C=N) imine str., 1627 and 1593 str. (C=C) aromatic ring, 1334 and 1165 str. asym. and sym. of (S=O), 898 cm\(^{-1}\) out of plane (C-H) bending of aromatic ring, 694 cm\(^{-1}\) (C-C) of aromatic ring bending. \(^{1}\)HNMR: (δ, ppm) show peaks at 3.26 (3H of CH\(_3\)SO), 3.31 (3H of CH\(_2\)O), and at 4.9 (2H, s, CH\(_2\) benzyl), and 6.9- 7.5 (8H, m, of Ar-\(\text{H}\)), 7.4 (2H, dd, Ar-\(\text{H}\), para substituted methyl sulfonyl benzene ring), 8.05 (2H, dd, Ar-\(\text{H}\), para substituted methyl sulfonyl benzene ring).

1-benzyl-5-fluoro-3-((4-methylsulfonyl)phenyl)iminio)indolin-2-one (4c)

(0.5gm, 2 mmol) of compound (2c) was added in 15 mL absolute ethanol with 3 drops of glacial acetic acid and (0.5 gm, 2mmol) of 4- (+ methyl sulphenyl) aniline added as the procedure above. Orange powder R\(_t\) = 0.88, m.p 192-194ºC / yield 50%. FT-IR (υ, cm\(^{-1}\)): 3078 (C-H) st. of aromatic ring, 2933 and 2850 (C-H) asym. and sym. str. of CH\(_2\) group , 1585 (C=O) str., 1618 (C=O) str, 1608 cm\(^{-1}\) (C=C) aromatic ring, 1334 and 1165 str. asym. and sym. of (S=O), 894 out of plane (C-H) bending of aromatic ring, 698 cm\(^{-1}\) (C-C) of aromatic ring bending. \(^{1}\)HNMR: (δ, ppm) show peak at 3.3 (3H of OCH\(_3\)), 5.0(2H, s, CH\(_2\) benzyl group), 7.3- 8 (8H, m, of Ar-H), 7.4(2H, dd, Ar-\(\text{H}\), para substituted methyl sulfonyl benzene ring), 8.04(2H, dd, Ar-\(\text{H}\), para substituted methyl sulfonyl benzene ring).

**Antimicrobial study**

The antimicrobial activity of the final compounds was evaluated using the well-diffusion method. The synthesized compounds were examined their antimicrobial activity in vitro against three types of tested microorganisms (Staphylococcus aureus, streptococcus pyogenes, enterococcus fecalis as Gram-positive bacteria) and (Pseudomonas aeruginosa, Klebsiella pneumoniae, and Eschericia coli) as a Gram-negative bacteria, (Candida albicans and as fung), they were clinically activated and maintained on nutrient agar for examining antibacterial activity, and Amoxicillin and ciprofloxacin were used as antibacterial standard drugs for Gram-positive bacteria and Gram-negative bacteria, respectively. Fluconazole was used as a standard drug for antifungal activity.

**RESULT AND DISCUSSION**

**Chemistry**

The synthetic pathway of the targeted N-benzylated Schiff bases (3a-c and 4a-c) is illustrated in the scheme 1.

![Scheme 1: Stepwise synthesis of targeted compounds](image)

First step, N-alkylated derivatives of isatin are commonly formed from the reaction of the sodium salt or potassium salt of isatin with alkyl halides \(^{(28)}\) (Figure1). The possibility of alkylation by generating alkyl iodides from less reactive alkyl halogenides (alkyl chloride) in situ in the presence of catalytic amounts of inorganic iodides such KI. The reactive alkyl iodide molecules were generated in situ from less reactive halogens, which significantly accelerated the alkylation reaction. \(^{(29)}\) Alkyl halides reactivity generally decreases in the series R1 > RBr > RCI. The N-Alkylation of isatin is usually carried out generating the highly conjugated isatin anion with a base like K\(_2\)CO\(_3\) shown in (Figure 2), followed by treatment with appropriate alkylation agents, generally alkyl halides. \(^{(30)}\)
Second step, to synthesize the Schiff bases (imines) an equimolar amount of N-benzylisatin and amine were mixed using acidic media. The Schiff base formation is an acid-catalyzed process that begins with the nucleophilic addition of the primary amine to the carbonyl group, followed by transfer of a proton from nitrogen to oxygen to yield neutral amino alcohol or carbinolamine. Finally, protonation of the carbinolamines’ oxygen by an acid catalyst then converts the -OH into a better-leaving group (–OH2) as described in Figure 3, and loss of water produces an imine compound as final product. [31-33]

All the derivatives were analyzed using FT-IR and 1H NMR spectrometry. The FT-IR spectra of 2(a-c) demonstrated the disappearance of the N-H stretching of isatins band in (3151-3186) cm⁻¹ and the appearance of new band C=H stretching of benzyl CH₂ group at (2885-2970) cm⁻¹. The appearance of C=N stretching in FT-IR in the range of (1681-1674) cm⁻¹ indicates the formation of a new band of Schiff base for the compounds 3(a-c) and 4 (a-c). The presence of new bands around 3300 to 3200 cm⁻¹ indicate the presence of NH₂; group of sulfanilamide for compounds 3(a-c), while the bands around 2930-2924 cm⁻¹ of compounds 4(a-c) indicate the presence of CH₃ group of methyl sulfonyl benzene moiety in these compounds.

In ¹H NMR the presence of peaks for the compounds 3 (a-c) and 4(a-c) at around 5 ppm indicate the presence of CH₃ of benzylic group, while the presence of peaks from (7.1-8) ppm indicate the presence of aromatic rings, and the presence of peaks at around 6 ppm indicate presence of NH₂ of sulphonamide group (SO₂NH₂) for compounds 3 (a-c), and around 3 ppm indicate presence of alkyl groups of OCH₃ of methoxysatin groups and CH₃ of SO₂CH₃ of amine (4-methyl (sulphonyl aniline)).

**Antimicrobial study**

All the synthesized compounds were screened for their antimicrobial activity, (Table 1).

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Conc. mg/mL</th>
<th>G +ve bacteria</th>
<th>G −ve bacteria</th>
<th>fungi</th>
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</thead>
<tbody>
<tr>
<td><strong>Compound</strong></td>
<td></td>
<td>S. aureus</td>
<td>S. pyogenes</td>
<td>E. fecalis</td>
</tr>
<tr>
<td>3a</td>
<td>1.6</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3b</td>
<td>1.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3c</td>
<td>1.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>4a</td>
<td>1.6</td>
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<td>5</td>
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<td>13</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>-</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>4c</td>
<td>1.6</td>
<td>-</td>
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<td>-</td>
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</tbody>
</table>

**Table 1: Antimicrobial activities of the synthesized Schiff bases in two concentrations (1.6 and 5 mg/mL)**
Synthesis And Preliminary Antimicrobial Evaluation Of Schiff Bases Of N -Benzy1 Isatin Derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>5</th>
<th>10</th>
<th>14</th>
<th>14</th>
<th>-</th>
<th>14</th>
<th>5</th>
<th>-</th>
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</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>1.6</td>
<td>25</td>
<td>17</td>
<td>29</td>
<td>24</td>
<td>7</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>5</td>
<td>20</td>
<td>29</td>
<td>25</td>
<td>21</td>
<td>28</td>
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</tr>
<tr>
<td>Fluconazole</td>
<td>1.6</td>
<td>30</td>
<td>28</td>
<td>28</td>
<td>26</td>
<td>30</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</table>

(-) = No activity- slightly active (zone of inhibition between 5-10 mm), moderately active (zone of inhibition between 10-20 mm), highly active (zone of inhibition more than 20 mm).

All the synthesized compounds showed no activity at 1.6 mg/mL concentration, whereas, at 5 mg/mL concentration showed only no antifungal activity. For the antibacterial results: at 5 mg/mL concentration regarding the 3(a-c) Schiff bases, the compounds 3a showed antibacterial low activity against two G-ve bacteria (E. coli and P. aeruginosa). At the same concentration, Schiff bases 4 (a-c) displayed moderate activity against most of tested bacteria, the compounds 4a and 4b showed moderate activity against E. coli, E. fæcalis, and S. pyogenes, while compound 4c showed moderate activity against S. aureus beside the three previous bacteria. The results in Table 1 displayed that the compound 4c is the most active one among 4-methyl sulfonyl phenyl Schiff bases (4a-c). The reason that Schiff bases 4(a-c) showed better activity than 3(a-c) is related to the lipophilic feature of the molecules facilitated their penetration to the lipid membrane of the bacterial cell wall and enhances the activity of the molecules.

CONCLUSION

In this research, the new six Schiff bases of N-benzy1 isatins derivatives have been synthesized with good yields. All the synthesized compounds were characterized by IR and 1H NMR spectroscopy. The in vitro antimicrobial activity of the compounds was determined by the well-diffusion method. The newly synthesized Schiff bases 4 (a-c) are more active than 3(a-c) ones against most of the tested bacteria. Compound 4c among the test new compounds is a more active one with moderate activity.

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