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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 1HNMR 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.

Keywords: N-benzylisatins, Schiff bases, antimicrobial activitiy.

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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.[1] Isatin and its derivatives possess numerous biological properties like antibacterial, antifungal,[2-4] anti-HIV, [5,6] antiviral, [7] anticonvulsant, [8, 9] anti-tubercular, [10, 11] and anticancer. [12, 13]

Sulfonamides are one of the organic sulfur compounds containing the – SO_2NH_2 group, which have attracted attention for their better medicinal activity [14]. 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. [15-17] 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. [18] Moreover, Schiff bases of sulfonamides 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. [19,20]

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. [21] 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. [22]

Many other studies reported that Schiff bases of isatin derivatives demonstrate a variety of biological activities, such as anti-inflammatory, anticonvulsant, anti- HIV, anti-bacterial, anti-fungal, and anti-depressant activities. [23,24] Schiff bases are an important class of compounds due to their structural similarities with natural biological substances[25], 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. [26]

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. Sulfanilamide obtained from BDH chemicals, England, 4- methyl sulfonyl aniline, from Hawn, China. Potassium carbonate (K_2CO_3) 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. ^{1}HNMR 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[27] 2(a-c):

(6 mmol) isatin **1a**, 5-methoxyisatin **1b**, and 5-fluoroisatin**1c,** separately, was added to a flask containing acetonitrile (15 mL)**,** K_2CO_3 (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, scheme1.

1-benzylindoline- 2,3-dione(2a)

(0.88 g, 6mmol) of isatin (**1a**) was added in a flask containing 15 mL of acetonitrile, then K_2CO_3 (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, R_f =0.913, yield 79%, m.p. 127-130 ^{0}C, FT-IR (υ, cm^{-1}): 3032 and 3086(C-H) asym. and sym. str. of the aromatic ring, 2970 and 2960 (C-H) aliphatic asym. and sym. str. of CH_2 (benzyl group), 1728 and 1608 of carbonyl groups (two C=O) str., 1492 and 1465 str. of C=C (aromatic ring), 850 (out of plane C-H bending of the aromatic ring), 690 (C=C)of aromatic ring bending.

1-benzyl-5-methoxyindoline-2,3-dione (2b)

(1.06gm, 6mmol) of 5-methoxyisatin (**1b**) was added in a flask containing 15 mL of acetonitrile, then K_2CO_3 (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, R_f = 0.84, yield 90%, m.p. 115-117 ^{0}C, FT-IR (υ, cm^{-1}): 3070 (C-H) str. of aromatic ring, 2962 and 2943 (C-H) aliphatic asym. and sym. str. of CH_2 (benzyl group), and 1720 and 1620 str. (two C=O) carbonyl groups, 1600 and 1492 str. of C=C (aromatic ring), 850 (out of plane C-H bending of the aromatic ring), 690 (C=C)of aromatic ring bending.

1-benzyl 5- fluoroindoline- 2,3-dione (2c)

(1.02g, 6mmol) of fluoroisatin (**1c**) was added in a flask containing 15 mL of acetonitrile then K_2CO_3 (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, R_f = 0.75 yield 70%, m.p 126-128 ^{0}C, FT-IR (υ, cm^{-1}): 3066 (C-H) str. of aromatic ring, 2974 and 2885 asym. and sym. (C-H) str. of CH_2 (benzyl group), 1724 and 1620 str. of (two C=O) carbonyl groups, 1608 and 1485 str. of C=C (aromatic ring), 887 cm^{-1} 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 (3(a-c) and 4(a-c))

(2 mmol) of compounds **2(a-c)**, separately, was dissolved in 15 mL dried absolute ethanol and 3 drops of glacial acetic acid, stirring for 1 hour then an equimolar amount of amine (2mmol) of sulphanilamide for compounds **3(a-c)** and (2 mmol) of 4-(methyl sulphonyl) aniline for compounds **4(a-c)** were added. After another three hours of refluxing a colored precipitate appeared, this is for **3(a-c)** compounds, while for compounds **4(a-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)amino)benzenesulfonamide(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 sulphanilamide added as the procedure shown above. Orange powder; R_f =0.8; yield 79.7%; m.p 224-227 C; FT-IR(υ, cm^{-1}): 3294 and 3205 (N-H) asym. and sym. str. of SO_2NH_2, 3085 and 3079 (C-H) asym. and sym. str. of aromatic rings, 2927 and 2850 (C-H) asym. and sym. str. of aliphatic CH_2 (benzyl group), 1604 and 1585 asym. and sym. str. st. of (C=C) aromatic ring, 1651 str. of (C=N) of the imine, 1334 and 1165 asym. and sym. 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. ^{1}HNMR (δ, ppm): 5.0 (2H, s, C<u>H</u>$_2$ benzyl group), 6.4 (2H, s, N<u>H</u>$_2$ of sulphanilamide) and 6.8-7.5 (9H, m, of Ar-<u>H</u>), 7.45(2H,dd, Ar-<u>H</u>, para substituted sulfonamide group), 7.9 (2H,dd, Ar-<u>H</u> para 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; R_f =0.79, m.p 252-254 ^{0}C; yield 75%. FT-IR (υ, cm^{-1}): 3363 and 3232 (N-H str.of sulfonamide group), 2970 and 2935 (C-H asym. and sym. str. of aliphatic C<u>H</u>$_2$ of benzyl group), 3089 and 3020 (C-H) asym. and sym. str. of aromatic rings, 1674 (C=N imine) str., 1585 and 1481 str. of (C=C) aromatic ring, 1334 and 1165 asym. 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. ^{1}HNMR (δ, ppm): 5.01 (2H, s, C<u>H</u>$_2$ benzyl group), 5.9 (2H, s, of N<u>H</u>$_2$ of sulfonamide group), 6.9- 7.3 (8H, m, of Ar-<u>H</u>), 7.42 (2H, dd, Ar-<u>H</u>, para substituted sulfonamide group), 8.0 (2H, dd, Ar-<u>H</u>, para substituted sulfonamide group).

4-((1-benzyl-5-fluoro-2-oxoindolin-3-ylidene)amino)benzenesulfonamide (3c)

(0.5 gm, 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 sulphanilamide added as the procedure above. Yellow powder, R_f =0.83, m.p 258-260 ^{0}C, yield 78%. FT-IR(υ, cm^{-1}): 3305 and 3228 (N-H asym. and sym. str. of SO_2<u>N</u>H$_2$), 3093 and 3062 (C-H) asym. and sym. str. of aromatic rings, 2940 and 2920 (C-H asym. and sym. str. of CH_2 benzyl group),1616 and 1589 asym. and sym. str. of C=C of aromatic ring, 1674 (C=N Imine) str., 1334 and 1165 asym. 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. ^{1}HNMR (δ, ppm): 5.0 (2H, s, C<u>H</u>$_2$ benzyl group), 6.3(2H, s, SO_2<u>N</u>H$_2$), (6.8 - 7.5) (8H, m, of Ar-<u>H</u>), 7.48 (2H, dd, Ar-<u>H</u> para substituted sulfonamide group), 7.9 (2H, dd, Ar-<u>H</u> para substituted sulfonamide group).

1-benzyl-3-((4-(methylsulfonyl)phenyl)imino)indolin-2-one (4a)

(0.474gm, 2 mmol) of compound**(** **2a**) was added in 15 mL absolute ethanol with 3 drops of glacial acetic acid and (0.5 gm, 2mmol)of 4-(methyl sulphonyl) aniline added as the procedure above**.** Orange powder, R_f = 0.84, m.p 172-175^0 C, yield 55%. FT-IR (υ, cm^{-1}): 3062 (C-H) str. of aromatic ring, 2924 and 2850 (C-H) asym. and sym. str. of CH_2 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. ^{1}HNMR: (δ, ppm) show peaks at 3.2 (3H of C<u>H</u>$_3$S<u>O</u>$_2$), 5.0 (2H, s, <u>CH</u>$_2$, benzyl group), 6.7- 7.5 (9 H,m, of Ar-<u>H</u>), 7.3 (2H,dd, Ar-<u>H</u>, para substituted methyl sulfonyl benzene ring), 8.0 (2H,dd, Ar-<u>H</u>, para substituted methyl sulfonyl benzene ring).

1-benzyl-5 - methoxy-3-((4 (methylsulfonyl)phenyl)imino)indolin-2-one(4b)

(0.53gm , 2 mmol) of compound(**2b**) was added in 15 mL absolute ethanol with 3 drops of glacial acetic acid and (0.5 gm ,2mmol)of 4-(methyl sulphonyl) aniline added as the procedure above. Yellow powder, R_f =0.82, m.p. 160-162^0 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_3SO_2), 3.31 (3H of CH_3O), and at 4.9 (2H, s, CH_2 Benzyl), and 6.9- 7.5 (8H, m, of Ar-H), 7.4 (2H,dd, Ar-H, para substituted methyl sulfonyl benzene ring), 8.05 (2H,dd, Ar-H, para substituted methyl sulfonyl benzene ring).

1-benzyl-5 – fluoro -3-((4 (methylsulfonyl)phenyl)imino)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 sulphonyl) aniline added as the procedure above. Orange powder/ R_f =0.88, m.p 192-194^0 C / yield 50%. FT-IR (υ, cm^{-1}): 3078 (C-H) st. of aromatic ring, 2931and 2850 (C-H) asym. and sym. str. of CH_2 group , 1681(C=N)str. of imine,1608 and 1585 str. (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-H, para substituted methyl sulfonyl benzene ring), 8.04(2H,dd, Ar-H, para substituted methyl sulfonyl benzene ring).

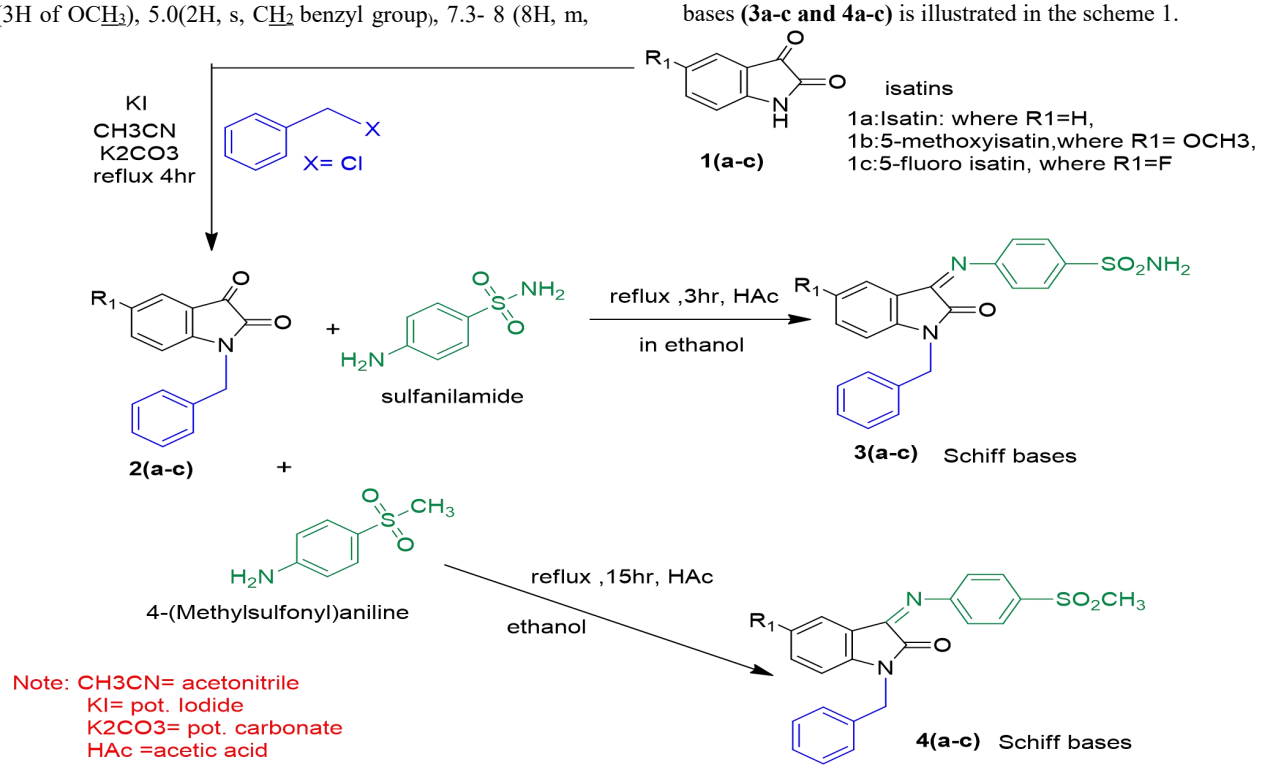
Antimicrobial study

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 (*Staphyllococcus aureus, streptococcus pyogens, enterococcus fecalis* as Gram-positive bacteria) and (*Pseudomonas aeruginosa, Klebsiella pneomonae, and Eschericia coli)* as a Gram-negative bacteria), (*Candida albicans* and as fungi), 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

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 RI > RBr > RCl. The N-Alkylation of isatin is usually carried out generating the highly conjugated isatin anion with a base like K_2CO_3 shown in (Figure 2), followed by treatment with appropriate alkylating agents, generally alkyl halides. [30]

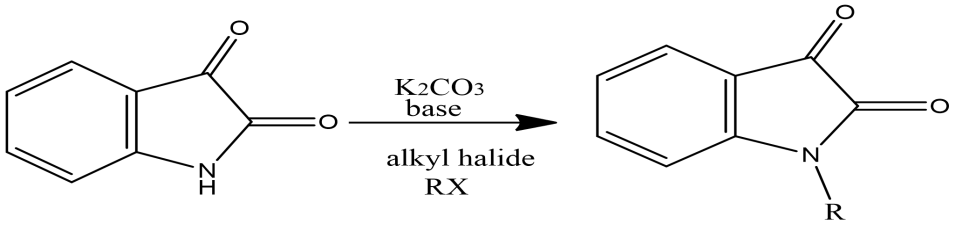


Figure 1: General reaction of isatin alkylation

Figure 2: Mechanism of isatin alkylation

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]

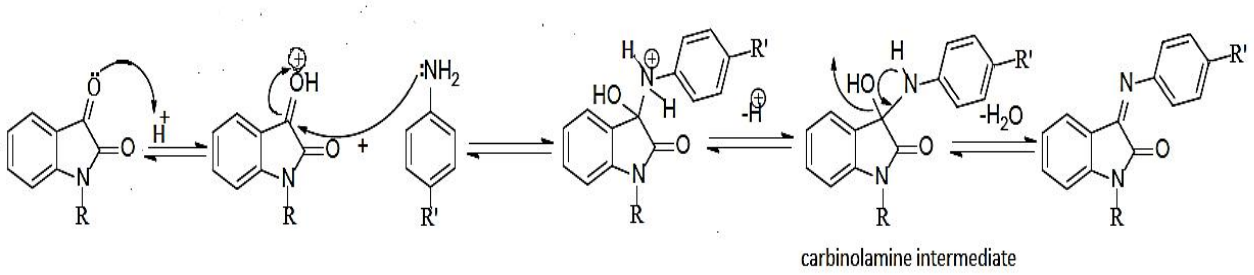


Figure 3: Mechanism of isatin Schiff base synthesis

All the derivatives were analyzed using FT- IR and ^{1}H 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 benzylic CH_2 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 NH_2 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 CH_3 group of methyl sulfonyl benzene moiety in these compounds.

In ^{1}HNMR the presence of peaks for the compounds **3 (a-c)** and **4(a-c)** at around 5 ppm indicate the presence of CH_2 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 NH_2 of sulphonamide group ($SO_2\underline{NH_2}$) for compounds **3 (a-c)**, and around 3ppm indicate presence of alkyl groups of $O\underline{CH_3}$ of methoxyisatin groups and CH_3 of $SO_2\underline{CH_3}$ of amine (4-methyl (sulphonyl aniline)).

Antimicrobial study

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

Table 1: Antimicrobial activities of the synthesized Schiff bases in two concentrations (1.6 and 5 mg/mL)

Microorganism		**G +ve bacteria**			**G –ve bacteria**			**fungi**
Compound	**Conc. mg/mL**	***S. aurues***	***S. pyogenes***	***E. fecalis***	***K. pneumoniae***	***E. coli***	***P. aeruginosa***	***C. albicans***
		Inhibition zone (IZ) in mm						
3a	1.6	-	-	-	-	-	-	-
	5	-	-	-	-	10	5	-
3b	1.6	-	-	-	-	-	-	-
	5	-	-	-	-	-	-	-
3c	1.6	-	-	-	-	-	-	-
	5	-	-	-	-	-	-	-
4a	1.6	-	-	-	-	-	-	-
	5	-	13	13	-	13	5	-
4b	1.6	-	-	-	-	-	-	-
	5	-	13	14	-	13	5	-
4c	1.6	-	-	-	-	-	-	-

	5	10	14	14	-	14	5	-
Amoxicillin	1.6	25	17	29	24	12	21	-
	5	30	20	29	24	18	21	
Ciprofloxacin	1.6	28	28	25	2	21	28	-
	5	30	30	28	15	28	30	
Fluconazole	1.6	-	-	-	-	-	-	18
	5							24
DMSO	-	-	-	-	-	-	-	-

(-) = 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)[34]

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. fecalis*, 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.[35]

CONCLUSION

In this research, the new six Schiff bases of N-benzyl isatins derivatives have been synthesized with good yields. All the synthesized compounds were characterized by IR and ^{1}H 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.

REFERENCES

1. Grewal AS. Isatin derivatives with several biological activities. International Journal of Pharmaceutical Research. 2014 Jan;6(1):1-7.
2. Pandeya SN, Sriram D, Nath G, De Clercq E. Synthesis, antibacterial, antifungal and anti-HIV evaluation of Schiff and Mannich bases of isatin and its derivatives with triazole. Arzneimittelforschung. 2000 Jan;50(01):55-9.
3. Patel A, Bari S, Telele G, Patel J, Sarangapani M, Synthesis and antimicrobial activity of some new Isatin derivatives, Iran. J. Pharm. Sci., 2006; 5(4): 249- 254
4. Meenakshi K, Gopal N, and Sarangapani M Synthesis, Characterization and Antimicrobial Activity of Some Novel Schiff and Mannich Bases of Isatin, Int. J. Pharm Pharm. Sci., 2014; 6(6): 318-322.
5. Bal TR, Anand B, Yogeeswari P, Sriram D, Synthesis and Evaluation of AntiHIV Activity of Isatin β-thiosemicarbazone Derivatives, Bio-org Med Chem. Let., 2005; 15(20): 4451-4455.
6. Sriram D, Bal TR, and Yogeeswari P, Aminopyrimidino Isatin Anlogues: Design of Novel Non-nucleoside HIV-1 reverse Transcriptase Inhibitors with Broad Spectrum Chemotherapeutic Properties. J. Pharm. Pharmaceut. Sci.,2005; 8(3): 565-577.
7. Selvam P, Murgesh N, Chandramohan M, De Clercq E, Keyaerts E, Vijgen L, et al, In vitro Antiviral Activity of Some Novel Isatin Derivative against HCV and SARS-Co V Viruses. Ind. J. Pharm. Sci.,2008; 70(1): 91-94.
8. Verma M, Pandeya SN, Singh KN, Stables JP Anticonvulsant Activity of Schiff Bases of Isatin Derivatives. Acta Pharm.,2004; 54: 49-56.
9. Smitha S, Pandeya S, Stables J, Ganapathy S, Anticonvulsant and Sedative-Hypnotic Activities of Nacetyl/methyl Isatin Derivatives. Sci. Pharm.,2008; 76: 621-636.
10. Aboul-Fadl T, Bin-Jubair FA, Antitubercular activity of Isatin derivatives, Int. J. Res Pharm. Sci.,2010; 1(2): 113-126.
11. Hussein MA, Aboul-Fadl T, and Hussein A, Synthesis and Anti-tubercular Activity of Mannich Bases Derived from Isatin Isonicotinic acid hydrazine, Bull Pharm. Sci. Assiut. Univ.,2005; 28: 131-136.
12. Karali N, Gürsoy A, Kandemirli F, Shvets N, Kaynak FB, Özbey S, et al, Synthesis and Structure Antituberculosis Activity Relationship of 1H-indole-2,3- dione Derivatives, Bio-org Med. Chem., 2007; 15(17): 5888-5904.
13. Vine KL, Locke JM, Ranson M, Pyne SG, Bremner JB, In vitro Cytotoxicity Evaluation of Some Substituted Isatin Derivatives, Bio org Med. Chem.,2007; 15(2): 931-938.
14. Sławinski J, Szafranski K, Vullo D, Supuran CT. Carbonic anhydrase inhibitors. Synthesis of heterocyclic 4-substituted pyridine- 3-sulfonamide derivatives and their inhibition of the human cytosolic isozymes I and II and transmembrane tumor-associated isozymes IX and XII. European Journal of Medicinal Chemistry, 2013;**69**:701
15. Pingaew R, Prachayasittikul V, Mandi P, Nantasenamat C, Prachayasittikul S, Ruchirawat S, et al., Synthesis and molecular docking of 1,2,3-triazole-based sulfonamides as aromatase inhibitors, Bioorganic & Medicinal Chemistry, 2015;**23**:3472.
16. Wang XL, Wan K, Zhou CH.,Synthesis of novel sulfanilamide derived1,2,3-triazoles and their evaluation for antibacterial and antifungal activities, European Journal of Medicinal Chemistry, 2010;**45**:4631.
17. Suhair Q. Al-Sultan and Mohamed H. Mohammed, Synthesis of New Sulfonamide Derivatives as Possible Antibacterial Agents, Der Pharmacia Lettre, 2016; 8(21): 86-93.
18. Sonu, B Rabiya Parveen, Sabiya Praveen and Himanshu Pal, A short review on Sulphonamides with antimicrobial activity, International Journal of Pharmaceutical Chemistry, 2017; 07(05): 70-73.
19. L. Bouissane, S. El Kazzouli, S. Léonce, B. Pfeiffer, E. M. Rakib, M. Khouili, G. Guillaumet, Synthesis and biological evaluation of N-(7-indazolyl)

benzenesulfonamide derivatives as potent cell cycle inhibitors, Bioorg. Med. Chem.,2006; 14: 1078-1088.
20. G. Melagraki, A. Afantitis, H. Sarimveis, O. Igglessi-Markopoulou, C. T. Supuran, QSAR study on para-substituted aromatic sulfonamides as carbonic anhydrase II inhibitors using topological information indices, Bioorg. Med. Chem.,2006; 14:1108-1114.
21. Garima Kumari , Ramendra K. Singh, Synthesis and in vitro antibacterial activity of schiff bases of N-substituted isatins as effective scaffolds, Medicinal Chemistry Research,2013; **22**:927–933.
22. Yogeeswari P, Sriram D, Kavya R, Tiwari S, Synthesis and In vitro Cytotoxicity Evaluation of Gatifloxacin Mannich Bases, Biomed and Pharmacother,2005; 59 (9): 501-510.
23. Adnan A. Kadi, Nasser S. Al-Shakliah, and A. F. M. Motiur Rahman ,Synthesis and Fragmentation Behavior Study of N -alkyl/benzyl Isatin Derivatives Present in Small/Complex Molecules: Precursor for the Preparation of Biological Active Heterocycles, Mass Spectrometry Letters,2015; 6(3):65-70.
24. May Mohammed Jawad Al-Mudhafar, Rana A. Kamoon, Synthesis, Characterization, and Antimicrobial Activity of New Schiff's and Mannich Bases of Isatin and Isatin Derivatives, Journal of Global Pharma Technology, 2020; 12(01): 529-536.
25. Anwar A. Tamer,1 and Ahlam J Qassir, Synthesis of Acetylenic Derivatives of a Substituted 1, 3, 4-Thiadiazole as Antibacterial Agents, Iraqi J Pharm Sci,2019;28(1):125-132.
26. R. Selwin Joseyphus and M. Sivasankaran Nair, Antibacterial and Antifungal Studies on Some Schiff Base Complexes of Zinc(II), Mycobiology, 2008;36(2) : 93-98.
27. Kamaleddin Haj Mohammad Ebrahim Tehrani a , Maryam Hashemi a , Maryam Hassan b , Farzad Kobarfard c,d, Shohreh Mohebbi , Synthesis and antibacterial activity of Schiff bases of 5-substituted isatins, Chinese Chemical Letters, 2016; 27 ; 221–225.
28. Mohammed Hadi Al-Douh, Hasnah Osman, Shafida Abd Hamid, Efficient Benzylation of o–Vanillin using TBAI as Catalyst and the crystal structure of the product, Univ. Aden J. Nat. and Appl. Sci.,2008;12(1):79-91.
29. Anton Mastitski*, Aleksander Abramov, Anneli Kruve, and Jaak Järv, Potassium iodide catalysis in the alkylation of protected hydrazines,chemistry, 2017; 66, 1: 10–17.
30. María Sol Shmidt, Ana María Reverdito, Lautaro Kremenchuzky, Isabel Amalia Perillo and María Mercedes Blanco, Simple and Efficient Microwave Assisted N-Alkylation of Isatin,molcules,2008;13:831-840.
31. John McMurry, organic chemistry, seventh edition published by physical science, David Harris in USA, 2008; 710-711.
32. Alsryfy, A.H., Mosaa, Z.A., Alrazzak, N. "Synthesis and characterization of new schiff base derived from 1,2-Di (indol-2-yl) - 2-hydroxyethanon" Research Journal of Pharmaceutical, Biological and Chemical Sciences, (2015); 6 (2), pp. 798-802.
33. Alrazzak, N.A.B.D., Saad, S.T., Aljamali, N.M. "Synthesis, characterization and thermal analysis for new amoxil ligands" Asian Journal of Chemistry, 2019: 31 (5), pp. 1022-1026.
34. Halah A. Sahib, and Mohammed H. Mohammed, Synthesis and Preliminary Biological Activity Evaluation of New N- Substituted Phthalimide Derivatives, Iraqi J Pharm Sci,2020; 29(1) :247-252
35. Ruchi Shrivastava, Premlata Gupta, Significant Antimicrobial Activity of some Schiff Bases, Juni Khyat,2020;10(6):273-278.