DOI: https://doi.org/10.31351/vol32issSuppl.pp156-163

Synthesis, Characterization, and Preliminary Antimicrobial Evaluation of New Schiff Bases and Mannich Bases of Isatin

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2nd Scientific Conference for Postgraduate Students Researches.

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Abstract

Till now, isatin derivatives have received a lot of interest in organic and medicinal chemistry due to their significant biological and pharmacological activities. Schiff's and Mannich bases of isatins are an effective group of heterocyclic derivatives that play a significant role in medicinal chemistry as antimicrobial agents. In light of these facts, new Schiff bases and Mannich bases of isatin were synthesized. The monomer Mannich bases; **3(a-e)** have been synthesized by reacting isatin with different secondary amines including piperidine, morpholine, pyrrolidine, dimethylamine, diphenylamine, separately, and formaldehyde, while the dimer Mannich base **(5)** formed by reacting isatin with piperazine and formaldehyde.

the synthesized Mannich bases then react separately with phenylhydrazine to form new monomer Schiff bases **4(a-e)**, and dimer Schiff base **(6)** as final products. The structures of the newly synthesized compounds were identified using two spectroscopic methods; (Fourier- transform infrared) FTIR and proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) analysis. The preliminary *in vitro* antibacterial and antifungal screening results of new isatin derivatives [**4(a-e)** and **6**] reported moderate to potent antimicrobial activity, the compound **4c** exhibited moderate broad-spectrum antibacterial and antifungal activities compared to other derivatives. Moreover, compounds **4c** and **6** have a good inhibitory effect against *B. subtilis* while amoxicillin (standard drug) shows no activity. For antifungal activity compounds (**4a-c** and **4e**) have considerable activity towards *C. albicans*, whereas compound **4d** exhibits slight activity and **6** of no activity.

Keywords: Isatin, Secondary amines, Mannich bases, Schiff bases, antimicrobial activity.

تخليق، تشخيص وتقييم أولي لمضادات الميكروبات لقواعد شيف وقواعد مانخ الجديدة للإيزاتين#

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الخلاصة

حتى الآن، حظيت مشتقات isatin باهتمام كبير في الكيمياء العضوية والطبية بسبب أنشطتها البيولوجية والدوائية الهامة. تعتبر قواعد شيف والمانخ من isatins مجموعة فعالة من المشتقات الحلقية غير المتجانسة التي تلعب دورًا مهمًا في الكيمياء الطبية كعوامل مضادة للميكروبات. في ضوء هذه الحقائق، تم تصنيع قواعد شيف وقواعد مانخ جديدة من isatin. قواعد مانخ الأحادية؛ **3 (a-e)** تم تصنيعها عن طريق تفاعل isatin مع الأمينات الثانوية المختلفة وتشمل البيبيريدين، المورفولين، والبيروليدين، ثنائي ميثيل أمين، ديفينيل أمين، بشكل منفصل، مع الفورمالديهايد، بينما يتكون المانخ الثنائي (**5**) بتفاعل isatin مع البيبرازين والفورمالديهايد والذي يتفاعل بعد ذلك كلاً على حدة مع فينيل هيدرازين لتشكيل قواعد احادية شيف جديدة **4 (a-e)** ، وقاعدة ثنائي شيف (**6**) كمنتجات نهائية. تم تحديد هياكل المركبات المصنعة حديثًا باستخدام طريقتين طيفية؛ (الأشعة تحت الحمراء) تحليل FTIR وطيف الرنين المغناطيسي النووي (^{1}H-NMR). أظهرت نتائج الفحص الأولي المضاد للبكتيريا والفطريات في المختبر لمشتقات isatin الجديدة [**4 (a-e)** و **6**] نشاطًا متوسطًا إلى قويًا لمضادات الميكروبات، أظهر المركب **4c** أنشطة معتدلة واسعة الطيف مضادة للبكتيريا ومضادة للفطريات مقارنة بالمشتقات الأخرى. علاوة على ذلك، فإن المركبين **4c** و**6** لهما تأثير مثبط جيد ضد *B. subtilis* بينما لا يظهر أموكسيسيلين (عقار قياسي) أي نشاط. بالنسبة للمركبات ذات النشاط المضاد للفطريات (**4a-c** و**٤e**) لها نشاط كبير تجاه *C. albicans*، بينما يظهر المركب **4d** نشاطًا طفيفًا والمركب **6** لا يظهر أي نشاط.

الكلمات المفتاحية: إيزاتين، امين ثانوي، قواعد مانخ، قواعد شيف، الفعالية المضادة للميكروبات.

Introduction

Indoles and their related derivatives, indolines, have attracted the attention of synthetic chemists since they are common in biologically active compounds and natural products [1,2]. Indolines; also known as isatin, are well-known for serving as the building blocks for a variety of chemicals that are synthesized to create specific medicines that target particular tissues and cells [3]. Isatin, 2,3-dioxoindoline, is an indole derivative containing a keto group at positions 2 and 3 of the ring. The isatin ring system consists of a pyrrole ring fused with a benzene ring. Isatin was first synthesized by Erdman and Laurent in 1841 [4]. This compound is found in many plants, such as *Isatis tinctoria*, *Couroupita guianensis*, and *Calanthe discolor* [5].

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Received: 4/4 /2023
Accepted: 8/6 /2023

Isatin is used to produce a wide variety of heterocyclic compounds. Positions 2 and 3, in particular, the keto groups, can participate in condensation and addition processes at the C=O bond. Compounds from different isatin types can enter Mannich and Michael processes, N-alkylation, and N-acylation through the amide group. [6-8]. Over the past decade years, the Schiff's and Mannich bases of isatins have gained a considerable degree of interest due to their facile chemical synthesis as well as their numerous pharmacological features, including antibacterial and antifungal activities [9], antiprotozoal, [10], anthelminthic activities [11] and antiviral, anti-HIV. [12]. Many halogenated compounds especially fluorine-containing aromatic compounds have received a lot of attention because of their biological activities [12]. Semaxanib and indirubin, two isatin-based compounds illustrated in figure 1, are already employed to treat a variety of disorders in clinics or during clinical studies [13,14].

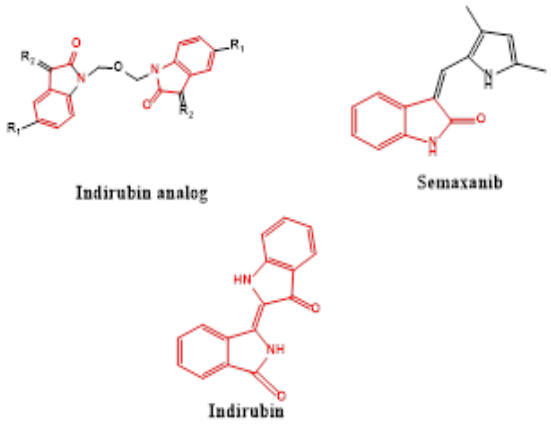


Figure 1. Different compounds containing isatin moiety.

Banerjee et al. [15] synthesized sixty isatin-thiosemicarbazone derivatives in an effort to produce efficient drugs for the treatment of HIV-TB coinfection; some of the compounds show promising efficacy against the multiplication of HIV-1 cells. Hydrazide Schiff bases (hydrazones) and 2,5-disubstituted-1,3,4-oxadiazole derivatives exhibit various biological activities that include anticancer, antibacterial, antifungal, antiviral, anti-tubercular, anti-inflammatory, and analgesia [16]. Hydrazine–derived isatins were found to be active against carcinosarcoma [17,18].

Dimerization is a prospective method for developing new medications since it can broaden the biological range, improve activity, overcome drug resistance, and enhance pharmacological, pharmacokinetic, and physicochemical properties [19]. The isatin dimers have a wide range of biological features, and some of these characteristics, as shown by the antibacterial and antiprotozoal activity of indirubin and its analogs (Figure 1), which can be used to attack drug-resistant infections like Methicillin-resistant Staphylococcus aureus (MRSA) and Methicillin-Resistant Staphylococcus epidermidis (MRSE) [20]. Additionally, dimers may have less effect on healthy cells' metabolic pathways than monomers [21]. These findings and continued attempts led the researchers to synthesize Schiff and Mannich bases of isatin with different amines, which then tested for antibacterial and antifungal properties.

Materials And Methods

General

Chemicals commercially supplied by hyper-chem (China) were used in chemical synthesis. Thin-layer chromatography (TLC) was used to evaluate the purity and the formation of synthesized chemical compounds and follow the progress of reactions on aluminum sheets covered with Silica gel GF254 (type 60) and exposed to UV-254 nm. Two solvent systems (S_1 and S_2) were used: S_1(ethanol: ethyl acetate: toluene (0.5:2:2)) and S_2 (ethanol: ethyl acetate (1:3)) [22]. The melting points were uncorrected and detected by using the Stuart 1SMP3 melting point apparatus in open capillary tubes. Spectroscopic data were recorded on the following instruments: Fourier-1transform Infrared (FT-IR) which was performed at the University of Baghdad/ College of Pharmacy, and proton 1Nuclear Magnetic Resonance (^{1}H-NMR) spectrum was recorded by NMR ultra-shield spectrophotometer 500 MHz, Bruker- Avance III (1Switzerland).

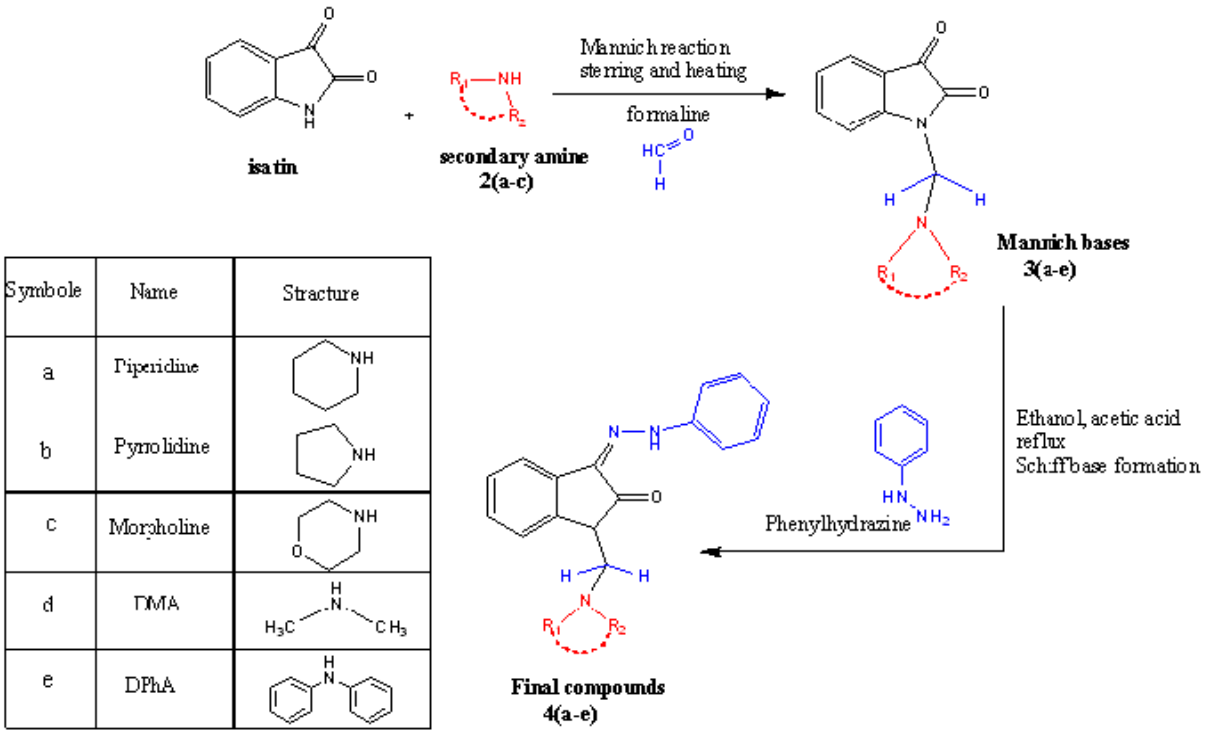
Chemical synthesis

Synthesis of Mannich bases (3a-e)

By dissolving (0.147 gm, 0.001 moles) of isatin in 35 ml tetrahydrofuran, then 0.001 moles of secondary amine were added (the weight of each sec. amines was given in table 1), then 1 ml of aqueous formaldehyde solution was added. The reaction mixture was allowed to stand for 1hr, followed by heating in a steam bath for 15 minutes then keeping the reaction mixture at 4 °C for 48hrs, as shown in Scheme 1. The collected products (3a-e) were recrystallized from an ethanol and chloroform mixture.

Table 1. The names of secondary amines and their weights

Secondary amines symbol	Secondary amines Name	Weight in grams	Mannich bases symbol
a	Piperidine	0.077	3a
b	Pyrrolidine	0.063	3b
c	Morpholine	0.079	3c
d	Dimethylamine (DMA)	0.043	3d
e	Diphenylamine (DPhA)	0.167	3e



Scheme 1. Synthesis of Schiff's and Mannich bases of isatin (monomers).

Analytical data for compounds 3(a-e):

1-(piperidin-1-ylmethyl) indoline-2,3-dione (3a)
Chemical formula; ($C_{14}H_{16}N_2O_2$), color and appearance: orange powder, percent of yields 59%, m.p: (165-166˚C). FT-IR (υ, cm^{-1}): 3050 C-H $_{aromatic}$ str., 2935, 2854 CH_2 Asymmetric and symmetric str., 1728 C=O $_{ketone}$ str., 1608 C=O $_{amide}$ str., 1469, 1408 C=C $_{aromatic}$ str..

1-(pyrrolidin-1-ylmethyl) indoline-2,3-dione (3b)
Chemical formula; ($C_{13}H_{14}N_2O_2$), color and appearance: orange powder, percent of yields 52%, m.p: (131-134˚C). FT-IR (υ, cm^{-1}): 3043 C-H $_{aromatic}$ str., 2966, 2800 CH_2 Asymmetric and symmetric str., 1728 C=O $_{ketone}$ str., 1621C=O $_{amide}$ str., 1481, 1458 C=C $_{aromatic}$ str..

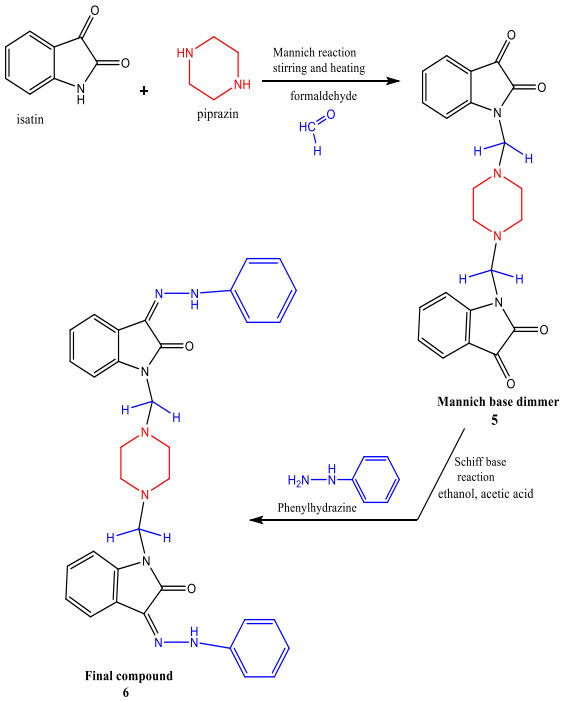
1-(morpholino ethyl) indoline-2,3-dione (3c)
Chemical formula; ($C_{13}H_{14}N_2O_3$), color and appearance: orange powder, percent of yields 64%, m.p: (126-128˚C). FT-IR (υ, cm^{-1}): 3051 C-H $_{aromatic}$ str., 2954, 2858 CH_2 Asymmetric and symmetric str., 1728 C=O $_{ketone}$ str., 1608 C=O $_{amide}$ str., 1465, 1435 C=C $_{aromatic}$ str..

1-((dimethylamino)methyl)indoline-2,3-dione (3d)
Chemical formula; ($C_{11}H_{12}N_2O_2$), color and appearance: orange powder, percent of yields 68%, m.p: (120-122˚C). FT-IR (υ, cm^{-1}): 3059 C-H $_{aromatic}$ str., 2962, 2910 CH_2 and CH_3 Asymmetric and symmetric str., 1724 C=O $_{ketone}$ str., 1604 C=O $_{amide}$ str., 1469, 1423 C=C $_{aromatic}$ str..

1-((diphenylamino)methyl) indoline-2,3-dione(3e)
Chemical formula; ($C_{21}H_{16}N_2O_2$), color and appearance: orange powder, percent of yield 66%, m.p: (138-140˚C). FT-IR (υ, cm^{-1}): 3054 C-H $_{aromatic}$ str., 2962, 2832 CH_2 Asymmetric and symmetric str., 1732 C=O $_{ketone}$ str., 1597 C=O $_{amide}$ str., 1492, 1469 C=C $_{aromatic}$ str..

Synthesis of Mannich bases dimers (5)
The procedure is applied by dissolving (0.294 gm, 0.002mole) of isatin in 40 ml tetrahydrofuran, then (0.078 gm, 0.001 moles) of piperazine was added then an excess amount of 3ml of aqueous

formaldehyde solution was added. The reaction mixture was allowed to stand for 1hr, followed by heating in a steam bath for 15 minutes then keeping the reaction mixture at 4 ℃ for 48hrs, as shown in Scheme 2. The collected solid product (**5**) was recrystallized from an ethanol and chloroform mixture.



Scheme 2: Dimer synthesis of Schiff's and Mannich bases of isatin

Analytical data:

1,1'-(piprazine-1,4-diylbis(methylene)) bis(indoline-2,3-dione) (5)

Chemical formula; ($C_{22}H_{20}N_4O_4$), color and appearance: orange powder, yield 38%, m.p: (190-192˚C). FT-IR (υ, cm^{-1}): 3050 C-H $_{aromatic}$ str., 2958, 2835 CH_2 Asymmetric and symmetric str., 1735 C=O $_{ketone}$ str., 1608 C=O $_{amide}$ str., 1496, 1400 C=C $_{aromatic}$ str..

The general procedure for the synthesis of target compounds

Mannich base derivatives of **3(a-e)**, (0.002 moles, the weight of each derivative was given in table 2) were added, separately, to Phenylhydrazine (0.002 moles, 0.1g) which dissolved in 20ml absolute ethanol in a round bottom flask, then 1 ml of glacial acetic acid was added as a catalytic agent and refluxed for 3hrs to obtain final compounds 4(a-e) (Scheme 1), while in the case of dimer derivative synthesis, the amount of phenylhydrazine added was (0.004 moles, 0.2 g) to dimer Mannich base derivative (**5**), then starting the reflux for 3hrs as shown in Scheme 2. Usually, the reaction was monitored by TLC, and after the reaction was completed, the solvent was removed under vacuum then the product recrystallized from the chloroform-petroleum ether.

Table 2. The weight of each Mannich base derivatives required in the final step

Mannich base derivatives symbol	The chemical name of Mannich base derivatives	Weight in grams
3a	1-(piperidin-1-ylmethyl) indoline2,3-dione	0.233
3b	1-(pyrrolidin-1-ylmethyl) indoline2,3-dione	0.221
3c	1-(morpholino ethyl)indoline2,3-dione	0.237
3d	1-((dimethylamino)methyl) indoline-2,3-dione	0.201
3e	1-((diphenylamino)methyl) indoline-2,3-dione	0.328
5	1,1'-(piprazine-1,4-diylbis(methylene)) bis(indoline-2,3-dione)	0.393

Analytical data for final compounds:

3-(2-phenylhydrazineylidene)-1-(piperidin-1-ylmethyl)indolin-2-one(4a)

Chemical formula; ($C_{20}H_{22}N_4O$), color and appearance: pale yellow powder, yield 71%, m.p: (187-189˚C). FT-IR (υ, cm^{-1}): 3209 N-H $_{amine}$ str., 3051 C-H $_{aromatic}$ str., 2924, 2850 CH_2 Asymmetric and symmetric str., 1674 C=O $_{amide}$ str., 1597 C=N $_{imine}$ str., 1558, 1516 C=C $_{aromatic}$ str.. ^{1}H-NMR δ ppm: 12.74 (1H, s, NH), 7.56-7.07 (9H, m, Ar-H), 4.50 (2H, s, CH_2), 1.50-1.44(4H, t, CH_2), 1.36-1.32 (6H, m, CH_2).

3-(2-phenylhydrazineylidene)-1-(pyrrolidin-1-ylmethyl)indolin-2-one(4b)

Chemical formula; ($C_{19}H_{20}N_4O$), color and appearance: pale yellow powder, yield 74%, m.p: (244-246˚C). **FT**-IR (υ, cm^{-1}): 3212 N-H $_{amine}$ str., 3051 C-H $_{aromatic}$ str., 2978, 2873 CH_2 Asymmetric and symmetric str., 1705 C=O $_{amide}$ str., 1600 C=N $_{imine}$ str., 1554, 1485 C=C $_{aromatic}$ str.. ^{1}H-NMR δ ppm: 12.74 (1H, s, NH), 7.53-7.07 (9H, m, Ar-H), 4.68 (2H, s, CH_2), 2.64-2.59 (4H, t, CH_2), 1.68-1.65 (4H, m, CH_2).

1-(morpholinomethyl)-3-(2-phenylhydrazineylidene)indolin-2-one(4c)

Chemical formula; ($C_{19}H_{20}N_4O_2$), color and appearance: yellow powder, yield 76%, m.p: (195-

197˚C). FT-IR **(υ,** cm^{-1}): 3162 N-H $_{amine}$ str., 3055 C-H $_{aromatic}$ str., 2885,2827 CH_2 Asymmetric and symmetric str., 1681 C=O $_{amide}$ str., 1597 C=N $_{imine}$ str., 1554, 1519 C=C $_{aromatic}$ str.. ^{1}H-NMR δ ppm: 12.76 (1H, s, NH), 7.57-7.01 (9H, m, Ar-H), 4.39 (2H, s, CH_2), 3.83-3.78(4H, t, CH_2), 2.59-2.56 (4H, t, CH_2).

1-((dimethylamino)methyl)-3-(2-phenylhydrazineylidene)indolin-2-one(4d)

Chemical formula; ($C_{17}H_{18}N_4O$), color and appearance: yellow powder, yield 72%, m.p: (190-192˚C). FT-IR (υ, cm^{-1}): 3136 N-H $_{amine}$ str., 3059 C-H $_{aromatic}$ str., 2997, 2897 CH_2 and CH_3 Asymmetric and symmetric str., 1670 C=O $_{amide}$ str., 1597 C=N $_{imine}$ str., 1550, 1516 C=C $_{aromatic}$ str.. ^{1}H-NMR δ ppm: 12.70 (1H, s, NH), 7.58-7.03 (9H, m, Ar-H), 4,50 (2H, s, CH_2), 1.43 (6H, s, CH_3).

1-((diphenylamino)methyl)-3-(2-phenylhydrazineylidene)indolin-2-one (4e)

Chemical formula; ($C_{27}H_{22}N_4O$), color and appearance: yellow powder, yield 82%, m.p: (226-228˚C). FT-IR (υ, cm^{-1}):3128 N-H $_{amine}$ str., 3055 C-H $_{aromatic}$ str., 2974, 2827 CH_2 Asymmetric and symmetric str., 1681 C=O $_{amide}$ str., 1597 C=N $_{imine}$ str., 1554, 1514 C=C $_{aromatic}$ str.. ^{1}H-NMR δ ppm: 12.69 (1H, s, NH), 7.62-6.91 (19H, m, Ar-H), 5.19 (2H, s, CH_2).

1,1'-(piperazine-1,4-diylbis(methylene))bis(3-(2-phenylhydrazineylidene) indolin-2-one (6)

Chemical formula; ($C_{34}H_{32}N_8O_2$), color and appearance: pale yellow powder, yield 66%, m.p: (231-233˚C). FT-IR (υ, cm^{-1}): 3215 N-H $_{amine}$ str., 3054 C-H $_{aromatic}$ str., 2943, 2877 CH_2 Asymmetric and symmetric str., 1666 C=O $_{amide}$ str., 1597 C=N $_{imine}$ str., 1558, 1512 C=C $_{aromatic}$ str.. ^{1}H-NMR δ ppm: 12.75 (2H, s, NH) 7.57-6.92 (18H, m, Ar-H) 4.44(4H, s, CH_2) 2.53 (8H, s, CH_2).

In vitro antimicrobial estimation

By employing the well-diffusion approach[23], the synthesized Schiff's and Mannich bases were screened for their ability to inhibit the growth of gram-positive (*Staphylococcus aureus*, and *Bacillus subtilis*) and gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Proteus mirabilis*) bacteria as well as fungus (*Candida albicans*). The inhibition zone (IZ) was measured in millimeters and matched with the inhibition zones of the common medications amoxicillin, ciprofloxacin, and fluconazole. Dimethyl sulfoxide (DMSO) was used to dissolve all of the investigated substances and standard medications, giving a concentration of 350 mg/ml. Aljazeera Company Medical Laboratory assessed the *in vitro* antimicrobial activities.

Results And Discussion

Chemistry

The designed Schiff's and Mannich bases monomers (**4a-e**) and dimer **(6)** which are six final compounds were described in Scheme 1 and 2. The Mannich bases (**3a-e**) and **(5)** were formed by heating the acidic imino group of (isatin) with different sec. amines in the presence of aqueous formaldehyde. This reaction involved the formyl carbonyl's carbon atom being attacked by the amine nitrogen of the secondary amine in a nucleophilic method, which was followed by water being eliminated and this, in turn, was reacted with the isatin molecule. This resulted in Mannich base compounds being condensed separately with phenylhydrazine to obtain new Schiff bases as final compounds, the proposed mechanism; involved the nucleophilic attack of the amine nitrogen of phenylhydrazine on the carbon atom of the keto group of isatin followed by water elimination. [24]

The chemical structures of the newly synthesized Schiff bases and Mannich bases were confirmed by FTIR and ^{1}H-NMR analysis. The FTIR results for all Mannich bases showed the disappearance of the N-H str. band of Isatin which is about 3200 cm^{-1} while the Schiff bases result shows the formation of a new imine band at about 1650 cm^{-1}.

The ^{1}H-NMR results for the final compounds show two peaks between (1.5-4.0) (except the diphenylamine which appears at (7.0-8.0) and piperazine in the case of dimer which has only a single peak at (2.53)) ppm of secondary amine protons and peak in (4.0-5.5) ppm of the formaldehyde protons these two peaks illustrate the formation of Mannich base products. A peak between (12-13) ppm indicates the connection between Mannich base products and Phenylhydrazine which contains the N-H group that appears in this region.

In vitro antimicrobial evaluation

From the results illustrated in Table 3, all the synthesized compounds showed moderate to potent antibacterial activity against *E. coli*, except compound **4b**, which had no effect at 350 mg/mL, compared to standard medications (amoxicillin and ciprofloxacin) at the same concentration, and compounds **4a** and **6** demonstrate potent activity against *S. aureus*. Furthermore, the dimer (**6**) also exhibits potent effectiveness against some pathogens; *S. aureus* and *E. coli*. Moreover, compounds 4c and 6 showed good activities toward *B. subtilis* while standard amoxicillin has no effect.

Among the other synthesized derivatives, compound **4c** is the only derivative that demonstrates moderate activity toward *P. aeruginosa*. For the bacterial strains; *P. mirabilis* and *K. pneumonia* displayed no response to any of these derivatives.

For antifungal activity, fluconazole was used as the reference for inhibitory activity against fungi; only compounds (**4a-c** and **4e**) have considerable activity towards *C. albicans*, whereas compound **4d** exhibits slight activity and **6** of no

activity. These findings make sense given that a prior study found that the *N*-Mannich bases of isatin analogs were effective in increasing their antimicrobial activity [25].

Table 3. Antimicrobial activities of the final derivatives (4a-e) and 6 in a concentration of (350 mg/mL)

Compound no.	Inhibition Zone (IZ)						
	Strains of Bacteria						Fungi
	Gram-positive		Gram-negative				
	S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coil*	*K. pneumoniae*	*P. mirabilis*	*C. albicans*
4a	25	-	-	15	-	-	10
4b	10	-	-	-	-	-	16
4c	-	11	15	13	-	-	13
4d	12	-	-	14	-	-	8
4e	16	-	-	10	-	-	16
6	20	10	-	18	-	-	-
Amoxicillin	30	-	30	20	10	-	-
Ciprofloxacin	52	28	50	30	16	40	-
Fluconazole	-	-	-	-	-	-	35
Control (DMSO)	-	-	-	-	-	-	-

(-) = No activity, slightly active (IZ =5-10 mm), moderately active (IZ= 10-15 mm), highly active (IZ= more than 15 mm).

Conclusion

Five monomer derivatives of Schiff's and Mannich bases of isatin and one dimer containing piperazine (sec. amine) of isatin Schiff base were synthesized in acceptable yields and examined by FT-IR and ^{1}HNMR spectroscopy. The preliminary *in vitro* antibacterial and antifungal screening results of new isatin derivatives [**4**(**a-e**) and **6**] reported moderate to potent antimicrobial activity. The compound **4c** exhibited moderate broad-spectrum antibacterial and antifungal activities compared to other derivatives. The dimer **6** exhibits potent activity toward the bacterial stains; *S. aureus* and *E. coli*, with no activity toward the fungus *C. albicans.* Moreover, compounds **4c** and **6** have a good inhibitory effect against *B. subtilis* while amoxicillin (standard drug) shows no activity.

Acknowledgment

The continuous support of the University of Baghdad is greatly acknowledged.

Conflict of interest

The authors have declared there is no conflict of interest.

Funding

This research did not receive any specific funding.

Ethics Statements

The authors state that as this was an *in-vitro* investigation, no ethics committee permission was required for the synthesis and evaluation of new compounds.

Author contributions

The first author; (Mustafa) contributed to the synthesis of final compounds; IR and ^{1}H-NMR data analysis, discussion of the antimicrobial activity, drafting of the manuscript; and critical revising of the manuscript. The second author; (May) contributed to the design of the study, discussed the final results, and approved the final version of the manuscript.

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