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Synthesis, Characterization of Schiff's and Mannich bases of 5-Fluoroisatin and Preliminary Antimicrobial Evaluation

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ABSTRACT

With the aim of developing potential antimicrobials, a series of new 5-fluoroisatin derivatives incorporated with different secondary amines (piperidine, morpholine, pyrrolidine, dimethylamine, and diphenylamine) for monomer, and (piperazine) in case of dimer Mannich bases, separately in presence of formaldehyde to obtain Mannich bases of 5-fluoroisatin derivatives, which then each Mannich derivatives reacts with phenylhydrazine to form Schiff bases as final products. The resulting compounds were characterized by two spectroscopic analyses; (Fourier- transform infrared) FT-IR and proton nuclear magnetic resonance spectroscopy (^{1}H-NMR). In addition, the *in vitro* antibacterial and antifungal activities were tested against some human pathogenic microorganisms by employing the well-diffusion technique. The majority of these derivatives showed activity against several microorganisms. The relationship between the functional group variation and the biological activity of the evaluated compounds is discussed. From the comparison, the resulting compounds, (**4b** and **4d**) were determined to be the most potent compounds. Dimer **6** exhibits an acceptable activity toward the bacterial stain; *P. mirabilis.*

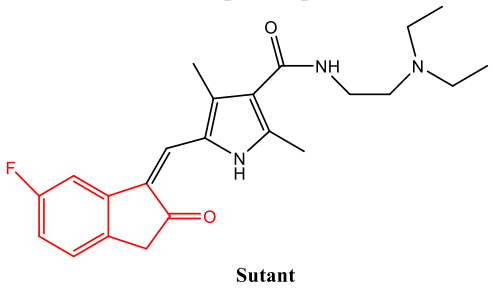
Keywords: *5-Fluoroisatin, Secondary amines, Mannich bases, Schiff bases, Antimicrobial activity.*

INTRODUCTION

Isatin (2,3-dioxindole), an indole derivative, is among the substrates used as raw material in medication treatment. It is also a synthetic substance that can be utilized for obtaining some other derivatives [1,2]. The isatin moiety also exhibits significant chemical reactions like aldol condensation, Friedel-Crafts reaction, ring expansion, and oxidation. As a result of these reactions, several biologically active substances are generated, including indirubins, tryptanthrin, and 2-oxindoles[3]. Isatins and their derivatives like Schiff bases and Mannich bases have been reported to possess a wide range of activities involving antibacterial [4, 7], antiviral [6], antifungal, anti-HIV [5, 8], antiprotozoal [9, 10], and anthelminthic activities [11, 12].

A variety of halogenated compounds particularly fluorine-containing aromatic compounds have drawn much attention because used as precursors for the synthesis of biologically active compounds [13]. The incorporation of one or more fluorine atoms into an organic molecule can improve their pharmacokinetic and pharmacodynamic properties. Many of these compounds containing a fluorine atom have a significant therapeutic impact [14, 15].

Fluorinated isatin derivatives have become a focus in the development of new biologically active compounds [16]. Many of them are used as biologically active compounds, in 2006, SU11248 (Sutent); 5-fluoro-3-substituted-2-oxindole, illustrated in Figure 1, was approved by the US FDA for the treatment of gastrointestinal stromal tumors [17] and advanced renal-cell carcinoma [18]. Moreover, hydrazine-derived isatins were found to be active against carcinosarcoma [19-20].



Sutant

FIGURE 1: A biologically active compound containing 5-fluoroisatin moiety

Many studies demonstrated the activity of fluorinated isatin derivatives. Ganim Ramadan *et. al* [21] synthesized four compounds containing 5-fluoroisatin thiosemicarbazone derivatives bearing a methoxyphenyl group in different positions and were evaluated based on their biological activities, It was found that 5-fluoroisatin 3-((N-2-methoxyphenyl)-thiosemicarbazone) was the most potent compound affecting gram-negative bacteria *P. vulgaris, E. coli,* and *S. marcescens* and better than Levofloxacin (standard drug).

Abbas *et. al* [22] synthesized new compounds of hydrazones, thiosemicarbazones, thiazoles, and thiocarbohydrazones containing 5-fluoroisatin motif, the antiviral evaluation of these derivatives showed good inhibitory activities as antiviral agents, among these tested derivatives; 5-fluorinated isatin thiocarbohydrazone and 5-fluorinated isatin hydrazine carbothioamide derivatives were the most active ones that possess antiviral activity.

Other researchers designed different Mannich bases by reacting hydrazone derivative named 5-fluoro-3-((thiophen-2-ylmethylene)hydrazono)indolin-2-one, with many secondary amines and they found that all of the resulting compounds had moderate activity against *E. coli* and *K. pneumonia,* and more active as antifungal agents toward *C. albicans* in an *in vitro* antimicrobial evaluation [23].

A series of 14 derivatives of 3-imino –[(4-Benzylidene-2-phenyl-imidazole- 5-one-1-(4-bezoylhydrazono)]-indole-2-ones synthesized by Patel *et. al* [24], these compounds were tested for *in vitro* antimicrobial activity, the results are summarized that the halogenated derivatives showed moderate to potent activity against *S. aureus* and *E. coli* and *S. typhi* compared to reference compound (Gentamicin). The antifungal activity of the compounds was studied against *C. albicans* and *A. niger* fungi, the (Amphotericin B) was used as reference compound. It was observed that halogenated derivatives are more reactive, especially the fluorinated derivative as antimicrobial agents.

In 2019 Zhang *et. al* [25] reported that dimerization of 5-fluoroisatin derivatives through position N-1 of the molecule will give different derivatives that showed different ranges of activity toward the examined microorganisms, the majority of them were more potent against methicillin-resistant *S. aureus* (MRSA)) and methicillin-resistant *S. epidermidis* (MRSE).

Besides, the isatin analog dimers have already been employed in clinical practice or are undergoing clinical trials, indicating the potential of isatin dimers as prospective medications.

Researchers have given much interest in designing novel Mannich and Schiff bases, due to their suitability in preparation and structural flexibility, and according to the previous investigations of different studies on the activity of isatin analogs the researchers in this study are encouraged to continue the research for screening antimicrobial activity of new derivatives of 5-fluoroisatin.

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**)) [26]. 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).

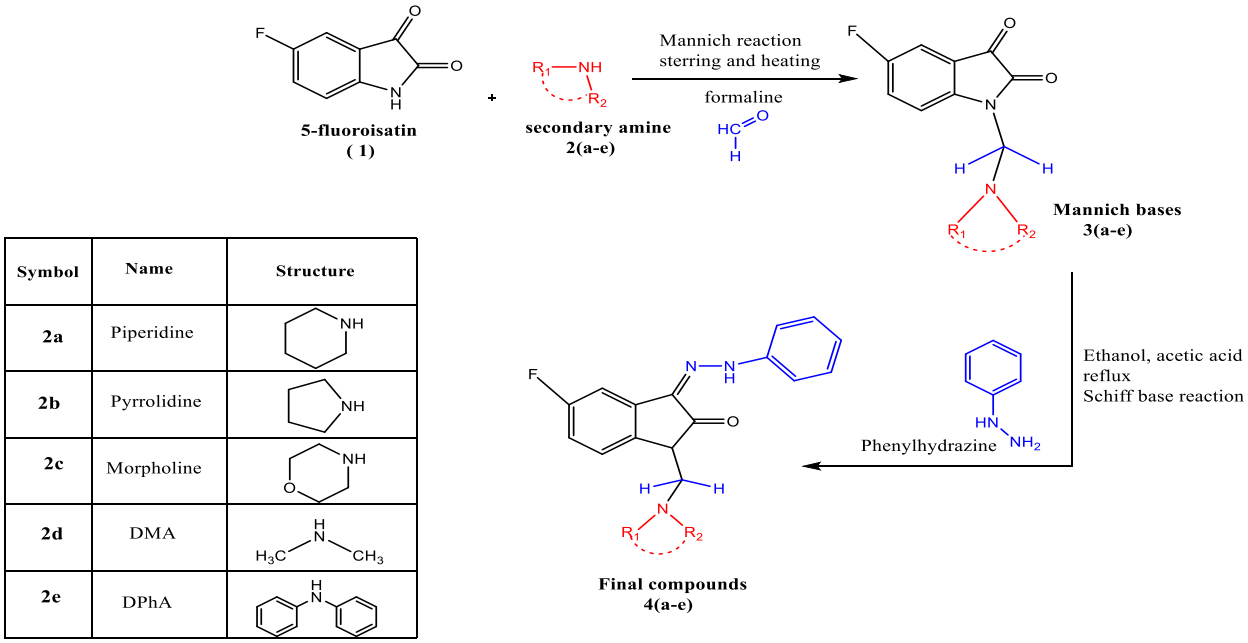
Chemical synthesis

Synthesis of Mannich bases (4a-e):

By dissolving (0.165 gm, 0.001 moles) of 5-fluoroisatin, 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 an 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 1. The collected products **4(a-e)** were recrystallized from an ethanol and chloroform mixture.

TABLE 1. Secondary amines name's used and their weights

Secondary amines symbol	Secondary amines name	Weight in grams	Mannich bases symbol
a	Piperidine	0.077	4a
b	Pyrrolidine	0.063	4b
c	Morpholine	0.079	4c
d	Dimethylamine(DMA)	0.045	4d
e	Diphenylamine(DPhA)	0.167	4e



Symbol	Name	Structure
2a	Piperidine	
2b	Pyrrolidine	
2c	Morpholine	
2d	DMA	
2e	DPhA	

Scheme 1: Synthesis of Schiff's and Mannich bases of 5-fluoroisatin (monomers)

Analytical data:

5-fluoro-1-(piperidin-1-ylmethyl)indoline-2,3-dione(4a)

Chemical formula; ($C_{14}H_{15}FN_2O_2$), color and appearance: red powder, yield 63%, m.p: (175-177˚C). **FT-IR** (υ, cm^{-1}): C-H $_{aromatic}$, str. at 3057, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2951, 2877, C=O $_{ketone}$: str. at 1732, C=O $_{amide}$: str. at 1616, C=C $_{aromatic}$: str. at 1481&1408, C-F $_{halide}$: str. at around 1000.

5-fluoro-1-(pyrrolidin-1-ylmethyl)indoline-2,3-dione(4b)

Chemical formula; ($C_{13}H_{13}FN_2O_2$), color and appearance: red powder, yield 57%, m.p: (168-170˚C). **FT-IR** (υ, cm^{-1}) C-H $_{aromatic}$: str. at 3066, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2962, 2908, C=O $_{ketone}$: str. at 1728, C=O $_{amide}$: str. at 1600, C=C $_{aromatic}$: str. at 1469& 1400, C-F $_{halide}$: str. at around 1000.

5-fluoro-1-(morpholino ethyl)indoline-2,3-dione(4c):

Chemical formula; ($C_{13}H_{13}FN_2O_3$), color and appearance: red powder, yield 67%, m.p: (144-146˚C). **FT-IR** (υ, cm^{-1}): C-H $_{aromatic}$, str. at 3051, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2951, 2854, C=O $_{ketone}$: str. at 1728, C=O $_{amide}$: str. at 1620, C=C $_{aromatic}$: str. at 1481& 1435, C-F $_{halide}$: str. at around 1000.

1-((dimethylamino)methyl)-5-fluoroindoline-2,3-dione(4d):

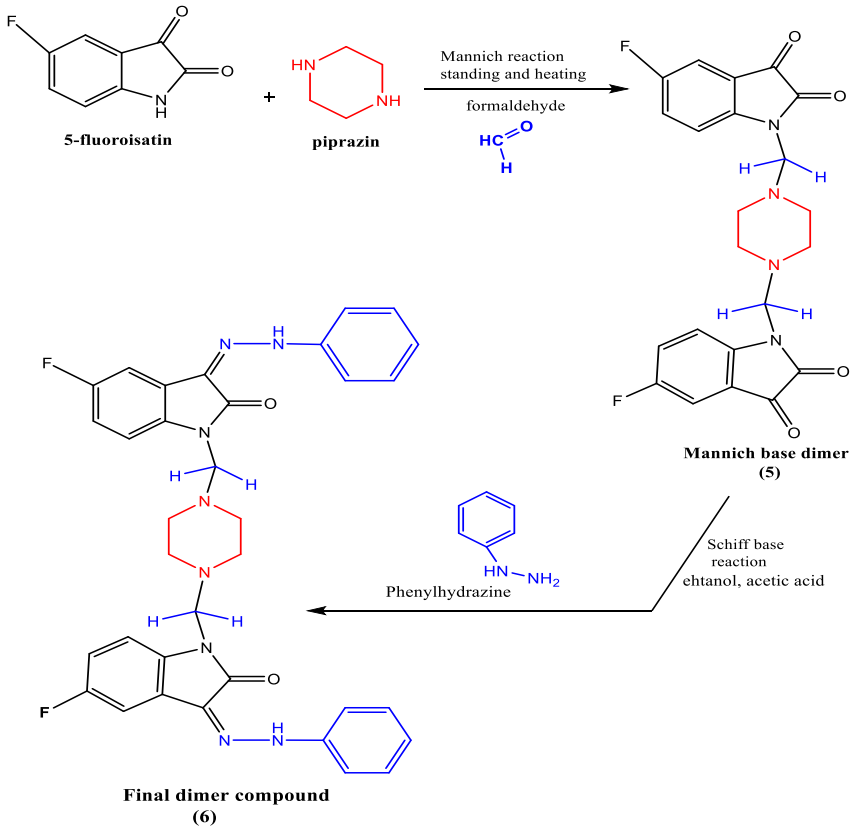
Chemical formula; ($C_{11}H_{11}FN_2O_2$), color and appearance: red powder, yield 63%, m.p: (141-143˚C). **FT-IR** (υ, cm^{-1}): C-H $_{aromatic}$, str. at 3066, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2996, 2862, C=O $_{ketone}$: str. at 1735, C=O $_{amide}$: str. at 1616, C=C $_{aromatic}$: str. at 1485 & 1454, C-F $_{halide}$: str. at around 1000.

1-((diphenylamino)methyl)-5-fluoroindoline-2,3-dione(4e):

Chemical formula; ($C_{21}H_{15}FN_2O_2$), color and appearance: red powder, yield 70%, m.p: (152-155˚C). **FT-IR** (υ, cm^{-1}): C-H $_{aromatic}$, str. at 3066, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2990 and 2866, C=O $_{ketone}$: str. at 1732, C=O $_{amide}$: str. at 1616, C=C $_{aromatic}$: str. at 1485&1458, C-F $_{halide}$: str. at around 1000.

Synthesis of Mannich bases dimer (5):

The procedure is applied by dissolving (0.33gm, 0.002mole) of 5-fluoroisatin in 30 ml tetrahydrofuran, then (0.078 gm, 0.001 moles) of piperazine, then an excessive 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: Synthesis of Schiff's and Mannich base of 5-fluoroisatin (dimer)

Analytical data:

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

Chemical formula; ($C_{22}H_{18}F_2N_4O_4$), color and appearance: red powder, yield 40%, m.p: (187-189˚C). **FT-IR** (υ, cm^{-1}) C-H $_{aromatic}$: str. at 3048, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2881, 2850, C=O $_{ketone}$: str. at 1712, C=O $_{amide}$: str. at 1612, C=C $_{aromatic}$: str. at 1562, 1512, C-F $_{halide}$: str. at around 1000 cm^{-1}.

The synthetic procedure of target compounds:
By adding 0.002 moles of **3(a-e)** compounds, the weight of each derivative was given in Table 2, separately, to phenylhydrazine (0.002 moles, 0.1g) dissolved in 20ml dried ethanol in a 250 ml round bottom flask, then 1 ml of glacial acetic acid was added as a catalytic agent to obtain final compounds **4(a-e)** (Scheme 1), 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, TLC is used to monitor the reaction, and after the reaction is completed the solvent is removed under vacuum then the product recrystallization from the chloroform-petroleum ether.

TABLE 2: The weight of each Mannich base derivative required in the final step

Mannich base derivatives symbol	Chemical Name of Mannich base derivatives	Weight in grams
4a	5-fluoro-1-(piperidin-1-ylmethyl)indoline2,3-dione	0.251
4b	5-fluoro-1-(pyrrolidin-1-ylmethyl)indoline2,3-dione	0.239
4c	5-fluoro-1-(morpholinoethyl)indoline2,3-dione	0.255
4d	1-((dimethylamino)methyl)-5-fluoroindoline-2,3-dione	0.220
4e	1-((diphenylamino)methyl)-5-fluoroindoline-2,3-dione	0.347
6	1,1'-(piprazine-1,4-diylbis(methylene))bis(5-fluoroindoline-2,3-dione)	0.429

Analytical data:

5-fluoro-3-(2-phenylhydrazineylidene)-1-(piperidin-1-ylmethyl)indolin-2-one(4a)
Chemical formula; ($C_{20}H_{21}FN_4O$), color and appearance: pale orange powder, yield 80%, m.p: (215-218˚C). **FT-IR** (υ, cm^{-1}) N-H $_{amine}$: str. at 3128, C-H $_{aromatic}$: str. at 3055, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2889, 2823, C=O $_{amide}$: str. at 1681, C=N $_{imine}$: str. at 1597, C=C $_{aromatic}$: str. at 1550 & 1519, C-F $_{halide}$: str. at around 1000 cm^{-1}. **^{1}H-NMR δ ppm:** 12.68 (1H, s, N-H), 7.61-7.05 (7H, m, Ar-H), 6.40 (1H, s, Ar-H), 4.54 (2H, s, CH_2), 3.56-3.54 (4H, d, CH_2), 2.68-2.55 (6H, t, CH_2).

5-fluoro-3-(2-phenylhydrazineylidene)-1-(pyrrolidin-1-ylmethyl)indolin-2-one(4b)
Chemical formula; ($C_{19}H_{19}FN_4O$), color and appearance: orange powder, yield 79%, m.p: (219-222˚C). **FT-IR** (υ, cm^{-1}) N-H $_{amine}$: str. at 3209, C-H $_{aromatic}$: str. at 3059, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2954, 2846, C=O $_{amide}$: str. at 1689, C=N $_{imine}$: str. at 1597, C=C $_{aromatic}$: str. at 1558 &1492, C-F $_{halide}$: str. at around 1000 cm^{-1}. **^{1}H-NMR δ ppm:** 12.70 (1H, s, N-H), 7.61-7.04 (8H, m, Ar-H), 4.69 (2H, s, CH_2), 2.65-2.59 (4H, d, CH_2), 1.70-1.63 (4H, t, CH_2).

5-fluoro-1-(morpholinomethyl)-3-(2-phenylhydrazineylidene)indolin-2-one(4c)
Chemical formula; ($C_{19}H_{20}N_4O_2$), color and appearance: dark yellow powder, yield 85%, m.p: (213-216˚C). **FT-IR** (υ, cm^{-1}) N-H $_{amine}$: str. at 3163, C-H $_{aromatic}$: str. at 3047, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2954, 2819, C=O $_{amide}$: str. at 1678, C=N $_{imine}$: str. at 1597, C=C $_{aromatic}$: str. at 1550 &1519, C-F $_{halide}$: str. at around 1000 cm^{-1}. **^{1}H-NMR δ ppm:** 12.72 (1H, s, N-H), 7.55-7.05 (7H, m, Ar-H), 6.41 (1H, s, Ar-H), 4.54 (2H, s, CH_2), 3.56-3.54 (4H, d, CH_2), 2.57-2.55 (4H, d, CH_2).

1-((dimethylamino)methyl)-5-fluoro-3-(2-phenylhydrazineylidene)indolin-2-one(4d):
Chemical formula; ($C_{17}H_{17}FN_4O$), color and appearance: orange powder, yield 86%, m.p: (215-217˚C). **FT-IR** (υ, cm^{-1}) N-H $_{amine}$: str. at 3201, C-H $_{aromatic}$: str. at 3055, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2962, 2908, C=O $_{amide}$: str. at 1678, C=N $_{imine}$: str. at 1597, C=C $_{aromatic}$: str. at 1554&1519, C-F $_{halide}$: str. at about 1000. **^{1}H-NMR δ ppm:** 12.72 (1H, s, N-H), 7.53-7.08 (7H, m, Ar-H), 6.43 (1H, s, CH), 4.49 (2H, s, CH_2), 1.43 (6H, s, CH_3).

1-((diphenylamino)methyl)-5-fluoro-3-(2-phenylhydrazineylidene)indolin-2-one (4e):
Chemical formula; ($C_{27}H_{21}FN_4O$), color and appearance: orange powder, yield 84%, m.p: (237-239˚C). **FT-IR** (υ, cm^{-1}) N-H $_{amine}$: str. at

3147, C-H $_{aromatic}$: str. at 3032, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2958, 2819, C=O $_{amide}$: str. at 1674, C=N $_{imine}$: str. at 1593, C=C $_{aromatic}$: str. at 1546 &1519, C-F $_{halide}$: str. at about 1000. **^{1}H-NMR δ ppm:** 12.76 (1H, s, N-H), 7.62-6.92 (17H, m, Ar-H), 6.42 (1H, s, CH), 5.19 (2H, s, CH_2).

1,1'-(piperazine-1,4-diylbis(methylene))bis(5-fluoro-3-(2-phenylhydrazineylidene)indolin-2-one (10)

Chemical formula; ($C_{34}H_{30}F_2N_8O_2$), color and appearance: orange powder, yield 72%, m.p: (252-255˚C). **FT-IR** (υ, cm^{-1}) N-H $_{amine}$: str. at 3147, C-H $_{aromatic}$: str. at 3035, C-H $_{aliphatic}$: symmetric and asymmetric str. at 2889,2823, C=O $_{amide}$: str. at 1667, C=N $_{imine}$: str. at 1593, C=C $_{aromatic}$: str. at 1546 &1519, C-F $_{halide}$: str. at around 1000 cm^{-1}. **^{1}H-NMR δ ppm:** 12.79 (2H, s, N-H), 7.47-7.05 (14H, m, Ar-H), 6.46 (2H, s, CH), 4.53 (4H, s, CH_2), 2.68-2.55 (8H, d, CH_2).

In vitro antimicrobial assessment

Determination of anti-microbial activity for the synthesized final products was done with the assistance of Aljazeera Company Medical Laboratory using gram-positive (*Staphylococcus aureus*, and *Bacillus subtilis*) and gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumonia*, and *Proteus mirabilis*) bacteria as well as fungus (*Candida albicans*). The technique used is the well-diffusion method [27], which involved handling these compounds to generate discs containing 350 mg/ml of each used component and standard medications dissolved in DMSO. The inhibition zone (IZ) was measured in millimeters (mm) and matched with the inhibition zones of the standard medications; amoxicillin, ciprofloxacin, and fluconazole, the obtained results were presented in Table 3.

RESULT AND DISCUSSION

Chemistry

The designed Schiff's and Mannich bases monomers (**4a-e**) and dimer **(6)** which are six final compounds were obtained through 2 steps reaction as described in Scheme 1 and 2. The Mannich bases (**3a-e**) and **(5)** were formed by heating the acidic amine group of (5-fluoroisatin) with different sec. amines in 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 5-fluoroisatin molecule. Then resulted in Mannich base compounds being condensed separately with phenylhydrazine with the aid of reflux and an acidic catalyst 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 5-fluoroisatin followed by water elimination [28].

The chemical structures of the newly synthesized Schiff bases and Mannich bases were confirmed by FTIR and ^{1}H-NMR analysis. The FT-IR results for all Mannich bases (**3a-e** and **5**) revealed the disappearance of the N-H stretching vibrations band of 5-fluoroisatin which is about 3200 cm^{-1}, as well as new IR bands around 2881-2990 cm^{-1} for asymmetric vibration of aliphatic $–CH_2$, and the symmetric vibration, appeared in 2850-2908cm^{-1} for the same aliphatic($-CH_2$), which confirmed the formation of Mannich bases. While the Schiff bases final compounds (**4a-e** and **6**) showed new bands due to the C=N stretching vibrations at regions 1597-1593 cm^{-1}.

The ^{1}H-NMR results for the final monomer compounds (**4a-e**) displayed characteristic >N-CH_2-N< signals at around (5.19-4.49) ppm (s, 2H, CH_2), while dimer compound **6** the signals appeared at 4.53 ppm (4H, s, CH_2), another characteristic singlet one proton band were detected for (**4a-e**) at (12.79- 12.68) ppm, whereas, the dimer **6** shows singlet two protons at 12.79 ppm band, which indicate the Schiff bases formation and presence of NH group of phenylhydrazine.

In vitro antimicrobial evaluation

Table 3 provides the antimicrobial activity of the final compounds. All synthesized derivatives showed moderate to potent antibacterial activity against *E. coli,* at 350 mg/mL, compared to standards (amoxicillin and ciprofloxacin) at the same concentration, the compound **4d** demonstrates potent activity against *S.1aureus*. The dimer (**6)** also exhibits good effectiveness against two pathogens; *E. coli* and *P.1mirabilis*. Moreover, all compounds showed no activity toward *B. subtilis* except compound **4d** of good activity, even the standard drug (amoxicillin) has no effect. Compounds **6** and **4b** demonstrate low to moderate activity toward *P. aeruginosa,*

respectively. Both compounds **4c** and **6** demonstrate acceptable activity against *P. mirabilis*, while all synthesized compounds showed no activity toward *K. pneumonia*.

For the antifungal effect, fluconazole was used as the standard for inhibitory activity against fungi; only compounds (**4a, 4b,** and **4e**) have considerable activity towards *C. albicans*. These results make sense given that a prior study found that the *N*-Mannich bases of isatin analogs were effective in increasing their microbial activity [29]. These differences in the efficacy of different new derivatives towards various microbes depend either on the impermeability and/ or variations in the ribosomes of the cell's pathogen.

TABLE 3: Antimicrobial activities of the final derivatives (5a-c), (6a-c), and (9, 10) in a concentration of (350 mg/mL)

Compound no.	1Inhibition Zone (IZ) in mm						
	Bacterial Strains						Fungi
	Gram-positive		Gram-negative				
	S. 1aureus	*B. 1subtilis*	*P. 1aeruginosa*	*E. 1coli*	*K. 1pneumoniae*	*P. 1mirabilis*	*C. 1albicans*
4a	-	-	-	13	-	-	12
4b	-	-	12	16	-	-	14
4c	-	-	-	12	-	8	-
4d	16	6	-	12	-	-	-
4e	12	-	-	14	-	-	12
6	-	-	5	10	-	10	-
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

A new series of 5-fluoroisatin Schiff's and Mannich bases derivatives were synthesized; five monomers containing different secondary amines (piperidine, morpholine, pyrrolidine, dimethylamine, and diphenylamine), and one dimer containing piperazine (sec. amine) in acceptable yields and characterized by FT-IR and ^{1}HNMR spectroscopy. The antimicrobial evaluation of the target compounds was performed against Gram-positive and Gram-negative bacteria, as well as fungi using the well-diffusion technique. The antimicrobial screening of synthesized compounds indicated good inhibitory activities. The new 5-fluoroisatin compounds [**4(a-e)** and **6**] showed moderate to high antibacterial effects in the preliminary antibacterial screening results. The compound **4d** exhibited moderate antibacterial activity compared to other derivatives. Dimer **6** exhibits acceptable activity toward the bacterial stains; *P. aeruginosa*, *E. coli*, and *P. mirabilis* with no activity toward the fungus *C. albicans.* Moreover, only compound **4d** has a low inhibitory effect against *B. subtilis.* For antifungal activity, only compounds (**4a, 4b,** and **4e**) have considerable activity towards *C. albicans.* This study's results might help to develop new bioactive 5-fluoroisatin derivatives as antimicrobial agents.

ACKNOWLEDGMENT

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