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Synthesizing Novel Vanillin-Based Di-Schiff Compounds and Evaluating Their Antibacterial Properties

Running title: Novel Vanillin-Based Di-Schiff Compounds and Their Antibacterial Properties

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Abstract

Vanillin, a phenolic aldehyde, plays a crucial role as an antimicrobial agent and holds significance in medicinal applications. This study aims to synthesize a novel vanillin compound and investigate its potential as an antibacterial agent.

New di-Schiff compounds were synthesized through the reaction of vanillin with benzocaine, followed by the conversion of the ester group into a hydrazide through a reaction with hydrazine hydrate. The resulting hydrazide was involved in reactions with various carbonyl compounds to produce di-Schiff bases. Characterization of the new di-Schiff base compounds were conducted using FTIR, ^{1}H-NMR, and ^{13}C-NMR techniques. Subsequently, their biological activities against two types of bacteria, namely gram-positive and gram-negative, were studied.

The results revealed the synthesis of five di-Schiff base compounds, confirmed through FTIR, ^{1}H-NMR, and ^{13}C-NMR analyses. The antibacterial activity of these compounds demonstrated high efficacy against *Staphylococcus aureus* and *E. Coli*, with inhibition zones ranging from 15 to 21 mm for both bacterial types. In conclusion, this study highlights the significant antibacterial properties of the five new di-Schiff base compounds.

Keywords: di-Schiff base; vanillin; phenolic aldehyde; antibacterial activity

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Introduction:

Primary amines and the compounds with the carbonyl groups can react to form the Schiff bases, which are substances with the (C=N) group.[1,2]. They comprise the (C=N) group, recognized as a significant category playing a crucial role in coordination chemistry and finding widespread applications in both industrial and biological contexts [3,4]. In addition these class of compounds have a role as catalysts in the hydrogenation of olefins and their potential applications as antibacterial, antifungal, and anti-tumor drugs [5,6]. The nitrogen atom, which gives back electrons and delivers electrons to the metal surface, several Schiff bases are used as anticorrosion agents, This gives these compounds their unique properties [7,8].

Vanillin a phenolic aldehyde generated from biomass, due to its anti-oxidant and anti-microbial qualities, is frequently employed as a flavoring ingredient in foods, drinks, and medications [9]. The primary source of vanillin extraction is vanilla beans, primarily obtained from the Vanilla planifolia orchid. To potentially create a renewable feedstock chemical, vanillin can be synthesized from abundant lignin through metal-catalyzed air oxidation [10,11]. The study aim to synthesis new schiff bases with vanillin and hydrazide moieties, determine structures of the schiff bases using FTIR, H-NMR and C-NMR also study their physical properties and antibacterial activity against two type of Bacteria (positive and negative gram).

Experimental Details:

All chemicals were supplied from Merck, CDH and Aldrich Chemicals Co. the study were confirmed in period from April 2021- to Jule 2023 in labs of al Muthanna university, Samawah, Iraq.

FTIR spectra were logged using KBr discs on (8400s Shimadzu) FTIR spectrophotometer.^{1}HNMR and ^{13}C-NMR spectra were carried out by Bruker 400 MHz, DMSO served as the solvent, and TMS was utilized as an internal standard. The measurements were conducted at the Chemistry Department of Al-Basra University, Iraq. Melting points were determined using the Gallen Kamp melting point apparatus.

1- Synthesis of ethyl 4-((4-hydroxy-3-methoxybenzylidene)amino)benzoate (a)

mixture of primary amine compounds (benzocaine) (0.01 mol), vanillin (0.01 mol) , absolute ethanol (15 mL) and 2-3 drops of glacial acetic acid were refluxed for 4hrs. The solvent was evaporated under vaccum and the residue solid crystallized from THF [12].

2- Synthesis of 4-((4-hydroxy-3-methoxybenzylidene)amino)benzohydrazide (b)

A title compound was prepared by the reaction of compound (a) (0.01 mol) with hydrazine hydrate (99%) (0.01 mol) in ethanol (25 mL) as solvent, the reaction refluxed for six hours on water bath. The resulted precipitate was filtered then washed with cooled absolute ethanol then dried [13].

3- Synthesis of Schiff bases

Schiff bases were synthesized by reaction of hydrazide compound (b) (0.01 mol) with different carbonyl compounds (4-nitrobenzadehyde, 4-nitroacetophenone, 4-hydroxybenzaldehyde, 2-hydroxybenzaldehyde, 4-aminoacetophenone) (0.01 mol), in absolute ethanol (25 mL) and 2-3 drops of glacial acetic acid, the mixture was refluxed for 6 hrs. The solvent was evaporated under vacuum and the residue crystallized from suitable solvent[13] as illustrated in scheme No 1.

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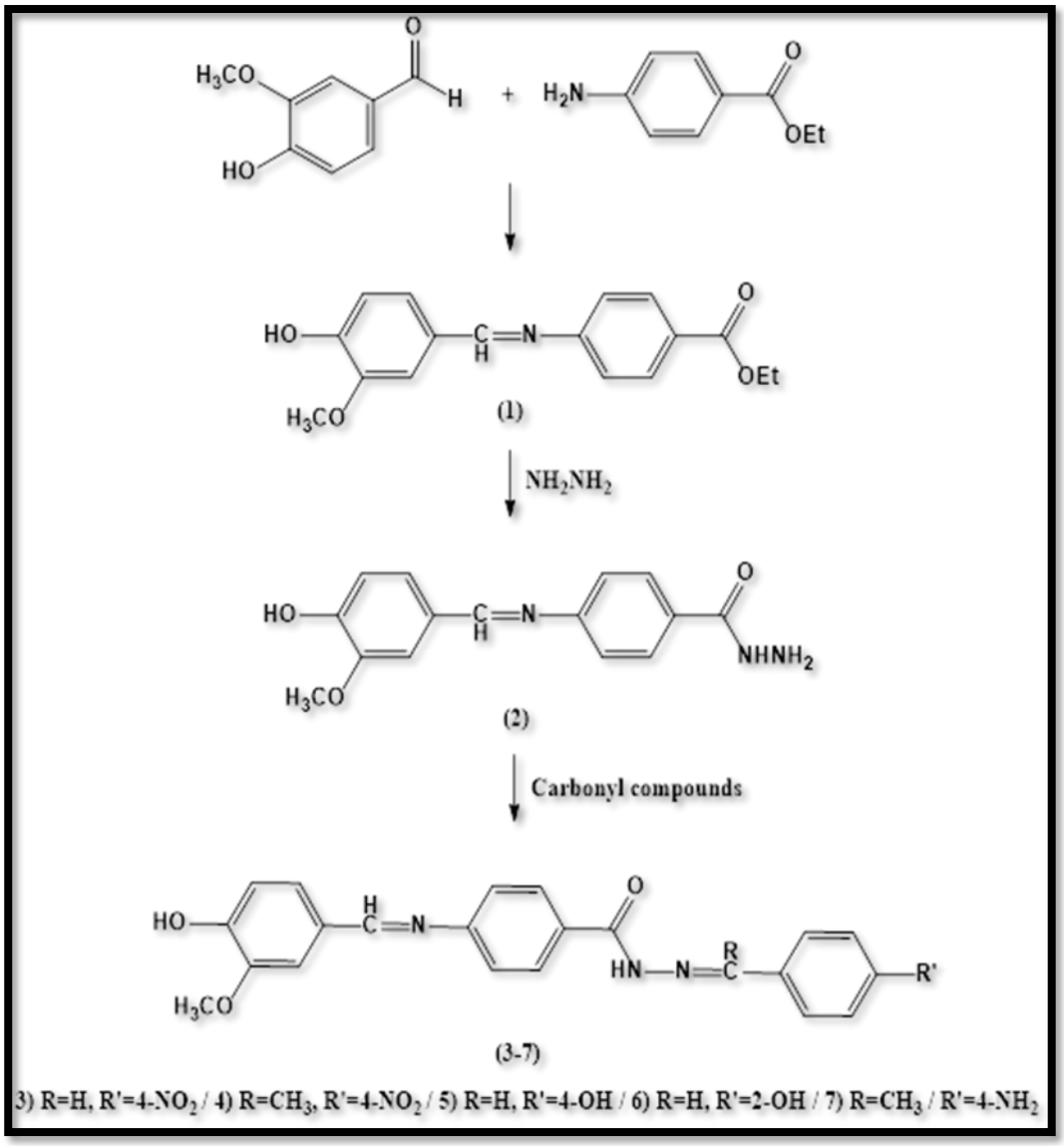

Scheme 1. Route for synthesis compounds

Antibacterial activity study

Antibacterial activity of synthesized di-Schiff compounds was studied against two types of bacteria (*S.aureus* and *E.coli*) by using the cup plate technique. DMSO solvent was used as solvent. Sample volume and sample solution for all of the inspected compounds were retitled (0.1 ml). The bacteria were incubated in sterilized cup. The inspection was done in the cups, (0.1 mL) of compounds solution was added in small holes in agar, and the petri dishes were incubated for (24 hr. at 37 C°). Inhibition zones were measured in millimetersfor polymers solution and the solvent (DMSO) diameter was determined by the same method [14].

Result and discussion

New molecules were synthesized containing vanillin with Schiff base moieties, because of the properties of these compounds. Therefore, present work involved synthesis of new compounds by three simple steps. first step involved reaction of vanillin with benzocaine to producing compound (a) (ethyl 4-((4-hydroxy-3-methoxybenzylidene)amino)benzoate) the product was pale yellow crystal; yield 87%; mp 143-145 °C; FTIR (KBr): ν, cm^{-1}: 1582 (C=N), 1705 (C=O), 2965-2980 (CH_3), 3427 (OH) as showed in Figures 1a, 2a and 3a [15].

In the second step reaction of compound (a) with hydrazine hydrate produce (4-((4-hydroxy-3-methoxybenzylidene)amino)benzohydrazide) (b) and the product was white needle crystals; yield

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83%; mp 180-182 °C; FTIR (KBr): ν, cm^{-1}: 1543 (C=N), 1622 (C=O), 2852-2922 (CH_3), 3232-3348 ($NHNH_2$), 3427 (OH) as in Figures 1b , 2b and 3b [16].

The product yielded in second step in turn was presented in third step in reaction with different carbonyl compounds producing the target di-Schiff base compounds (c,d,e,f and g).

4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(4-nitrobenzylidene) benzohydrazide (c); Orange crystal; yield 86%; mp 239-242 °C; FTIR (KBr): ν, cm^{-1}: 1535 and 1650 (C=N), 1622 (C=O), 2985-2973 (CH_3), 3219-3339 (NH), 3428 (OH) as in Figure 1c. ^{1}H-NMR (DMSO-d_6): δ, ppm: 3.82 (m, 3H, OCH_3), 5.87 (s, OH), 6.56-7.96 (s, 11H, ArH), 8.30, 8.49 (s, 2H, HC=N), 11.78 (s, 1H, NHCO) as in Figure 2c. ^{13}C-NMR (DMSO-d_6): δ, ppm: 56.51 (s, CH_3), 113.09-130.13 (s, 13C, Ar), 141.61-153.07 (s, 4C, Ar and 2C, C=N), 163.77 (s, C=O) and showed in Figure 3c [17].

4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(1-(4-nitrophenyl)ethylidene) benzohydrazide (d) Yellow crystal; yield 82%; mp 210-212 °C; FTIR (KBr): ν, cm^{-1}: 1567 and 1637 (C=N), 1602 (C=O), 2865-2945 (CH_3), 3231-3390 (NH), 3483 (OH) as in Figure 1d. ^{1}H-NMR (DMSO-d_6): δ, ppm: 1.977 (m, 3H, CCH3), 3.82 (m, 3H, OCH3), 5.58 (s, OH), 6.52-8.05 (s, 11H, ArH), 8.28 (s, HC=N), 10.50 (s, 1H, NHCO) in Figure 2d. ^{13}C-NMR (DMSO-d_6): δ, ppm: 14.37 (s, N=CCH_3), 56.1 (s, OCH_3), 112.97-130.62 (s, 13C, Ar), 145.08-152.90 (s, 4C, Ar and 2C, C=N), 166.93 (s, C=O) as showed in Figure 3d [17].

4-(((E)-4-hydroxy-3-methoxybenzylidene)amino)-N'-(4-hydroxybenzylidene) benzohydrazide (e) Yellow crystal; yield 82%; mp 210-212 °C; FTIR (KBr): ν, cm^{-1}: 1562 and 1562 (C=N), 1620 (C=O), 2855-2948 (CH_3), 3234-3348 (NH), 3431 (OH) as in Figure 1e. ^{1}H-NMR (DMSO-d_6): δ, ppm: 3.83 (m, 3H, OCH3), 5.59 and 5.76 (s, 2H, OH), 6.52-7.67 (s, 11H, ArH), and 8.30 (s, HC=N), 11.28 (s, 1H, NHCO) as in Figure 2e. ^{13}C-NMR (DMSO-d_6): δ, ppm: 55.98 (s, OCH_3), 113.08-129.68 (s, 13C, Ar), 146.84-163.30 (s, 4C, Ar and 2C, C=N), 166.94 (s, C=O) in Figure 3e [18].

4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(2-hydroxybenzylidene) benzohydrazide (f) Pale yellow crystal; yield 85%; mp 158-160 °C; FTIR (KBr) as in figure 1f: ν, cm^{-1}: 1543 and 1658 (C=N), 1621 (C=O), 2852-2920 (CH_3), 3232-3350 (NH), 3452 (OH). ^{1}H-NMR (DMSO-d_6): δ, ppm: 3.82 (m, 3H, OCH3), 5.58, 5.84 (s, 2H, OH), 6.51-7.93 (s, 11H, ArH), 8.56, 9.28 (s, 2H, HC=N), 11.55 (s, 1H, NHCO) as showd in Figure 2f. ^{13}C-NMR (DMSO-d_6): δ, ppm: 56 (s, OCH_3), 113.07-131.38 (s, 13C, Ar), 147.04-163.12 (s, 4C, Ar and 2C, C=N), 166.93 (s, C=O) as in Figure 3f [19].

N'-((4-aminobenzylidene)-4-((4-hydroxy-3-methoxybenzylidene)amino) benzohydrazide (g) Pale yellow crystal; yield 78%; mp 153-155 °C; FTIR (KBr) in Figure 1g: ν, cm^{-1}: 1548 and 1566 (C=N), 1624 (C=O), 2872-2971 (CH_3), 3211-3346 (NH), 3432 (OH). ^{1}H-NMR (DMSO-d_6): δ, ppm: 3.81 (m, 3H, OCH3), 5.44, (s, OH), 4.37, (m, NH), 6.51-7.64 (s, 11H, ArH), 8.33, 9.27 (s, 2H, HC=N), 10.07 (s, 1H, NHCO) as showed in Figure 2g. ^{13}C-NMR (DMSO-d_6): δ, ppm: 56.55 (s, OCH_3), 113.00-129.94 (s, 13C, Ar), 150.54-152.33 (s, 4C, Ar and 2C, C=N), 166.93 (s, C=O)as in Figure 3g [20].

Synthesized compounds were identified by using spectral data (FTIR, ^{1}H-NMR and ^{13}C-NMR), where vanillin reacts with benzocaine to produce Schiff base with imine group have FTIR absorption band at 1582 cm^{-1}, and the main absorption band at 1705 belong to C=O ester group that will disappear in the second step when the compound (1) convert to hydrazide (2), the hydrazide give new absorption band at 1622 cm^{-1} and 3232-3348 cm^{-1}belong to C=O hydrazide and NH respectively.

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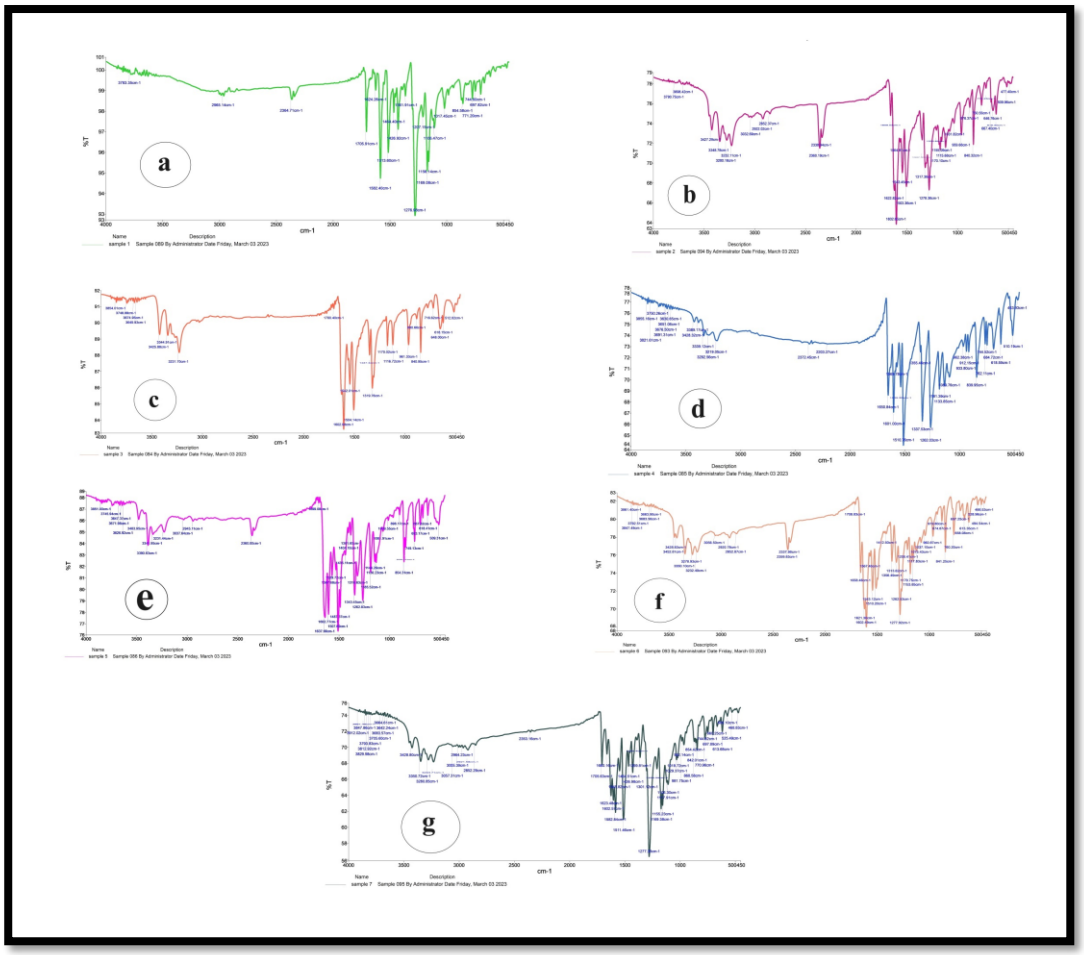

Figure (1): FTIR spectrum of: a: ethyl 4-((4-hydroxy-3-methoxybenzylidene)amino)benzoate. b: 4-((4-hydroxy-3-methoxybenzylidene)amino) benzohydrazide. c: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(4-nitrobenzylidene) benzohydrazide. d: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(1-(4-nitrophenyl)ethylidene) benzohydrazide. e: 4-(((E)-4-hydroxy-3-methoxybenzylidene)amino)-N'-(4-hydroxybenzylidene) benzohydrazide. f: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(2-hydroxybenzylidene) benzohydrazide. g: N'-((4-aminobenzylidene)-4-((4-hydroxy-3-methoxybenzylidene)amino) benzohydrazide.

The di-Schiff base compounds (c, d, e,f, g) synthesized by reaction of hydrazide with different carbonyl compounds (4-nitrobenzadehyde, 4-nitroacetophenone, 4-hydroxybenzaldehyde, 2-hydroxybenzaldehyde, 4-aminoacetophenone), this compounds give new absorption band for new imine bond at 1650 cm^{-1}, also these compounds gives the ^{1}HNMR spectra displayed a multiple signal at δ (1.9-3.8) ppm is attributed to (CH_3) protons, also gives signal at δ (5.58, 5.84) ppm belong to OH protons, and aromatic protons gives signals at δ (6.5-8.05) ppm. Important imine protons give signals at δ (8.28 and 9.28) ppm. The ^{13}C-NMR spectrum also gives the signals of main carbons in molecules; the signal at δ (56.1-56.5) and δ (14.37) ppm belong to methyl groups. The signal at δ (113.07-131.38) ppm belongs to the aromatic ring carbons. The imine group carbons and aromatic carbon bonded to oxygen and nitrogen atoms give signals at δ (141.61-163.12). The last signal at range δ (163.77-163.93) belong to C=O amide carbon group [21,22].

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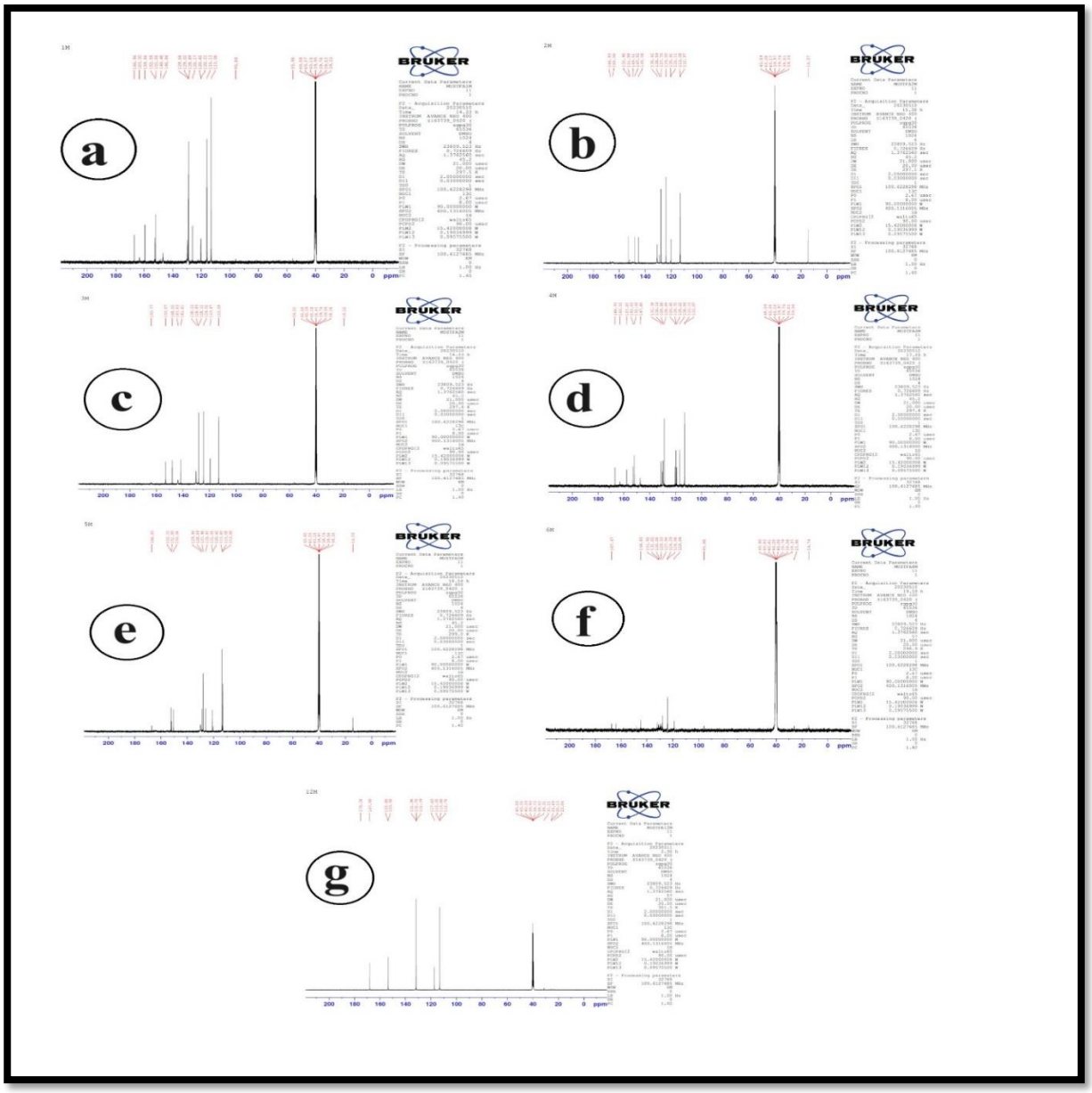

Figure (2): H-NMR spectrum of: a: ethyl 4-((4-hydroxy-3-methoxybenzylidene)amino)benzoate. b: 4-((4-hydroxy-3-methoxybenzylidene)amino) benzohydrazide. c: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(4-nitrobenzylidene) benzohydrazide. d: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(1-(4-nitrophenyl)ethylidene) benzohydrazide. e: 4-(((E)-4-hydroxy-3-methoxybenzylidene)amino)-N'-(4-hydroxybenzylidene) benzohydrazide. f: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(2-hydroxybenzylidene) benzohydrazide. g: N'-((4-aminobenzylidene)-4-((4-hydroxy-3-methoxybenzylidene)amino) benzohydrazide.

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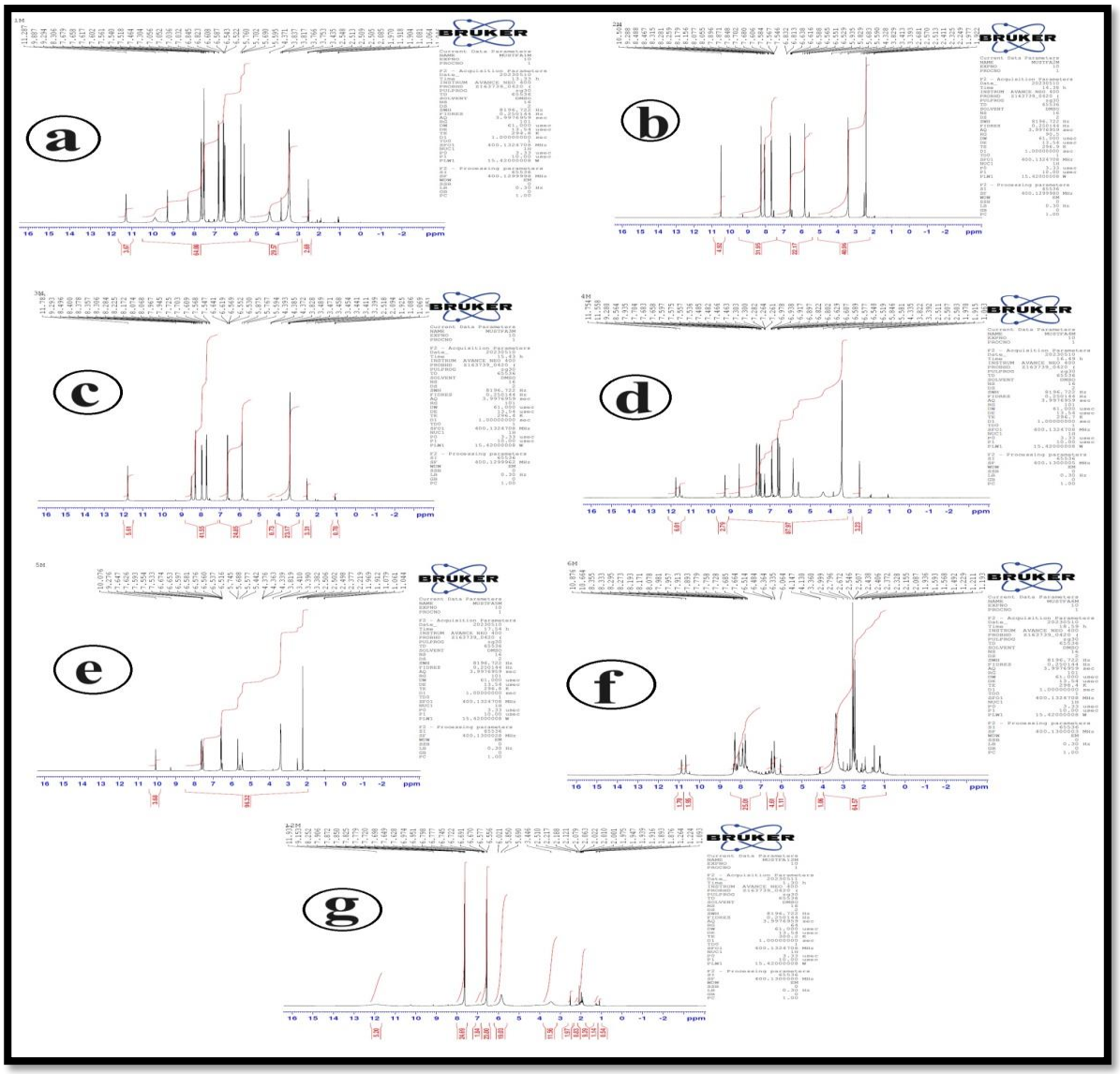

Figure 3: C-NMR spectrum of: a: ethyl 4-((4-hydroxy-3-methoxybenzylidene)amino)benzoate. b: 4-((4-hydroxy-3-methoxybenzylidene)amino) benzohydrazide. c: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(4-nitrobenzylidene) benzohydrazide. d: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(1-(4-nitrophenyl)ethylidene) benzohydrazide. e: 4-(((E)-4-hydroxy-3-methoxybenzylidene)amino)-N'-(4-hydroxybenzylidene) benzohydrazide. f: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(2-hydroxybenzylidene) benzohydrazide. g: N'-((4-aminobenzylidene)-4-((4-hydroxy-3-methoxybenzylidene)amino) benzohydrazide.

Antibiotics for Schiff base compounds are widely used to eliminate a wide range of bacteria and microorganisms, as is the case for compounds containing lipid groups, as they are included in the composition of many compounds that are used as treatments against a wide range of diseases and their causes. The synthesized compounds give good activities against two types of micro-organisms (*S.aureus* and *E.coli*) and the result listed in Table 1 and Figure 4.

Table 1; biological activity of synthesized compounds.

Comp.	Inhibition zone (mm) of *Staphylococcus aureus*	Inhibition zone (mm) of *E.coli*

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C	20	15
D	21	20
E	17	18
F	18	15
G	17	19

* C: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(4-nitrobenzylidene) benzohydrazide. D: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(1-(4-nitrophenyl)ethylidene) benzohydrazide.
E: 4-(((E)-4-hydroxy-3-methoxybenzylidene)amino)-N'-(4-hydroxybenzylidene) benzohydrazide.
F: 4-((4-hydroxy-3-methoxybenzylidene)amino)-N'-(2-hydroxybenzylidene) benzohydrazide.
G: N'-((4-aminobenzylidene)-4-((4-hydroxy-3-methoxybenzylidene)amino) benzohydrazide.

Figure (4): Anti-Bacterial activity of the five synthsis di Schiff compunds against *E. Coli* and *S. aureus.*

The inhibition of bacteria by Schiff- bases, including di-Schiff-bases, can be attributed to various important factors. It's important to note that the specific mechanism of inhibition can vary based on the structural characteristics of the Schiff base and the target bacteria [23]. Schiff bases may disrupt bacterial cell membranes [24]. The lipophilic nature of some Schiff bases allows them to interact with the lipid components of the bacterial cell membrane, leading to membrane disruption and increased permeability [25]. also Schiff bases might interact with bacterial DNA, affecting replication and transcription processes [25]. This interference with genetic material can lead to cell death [26]. The specific mode of action can depend on the chemical structure of the Schiff base, the bacterial species, and the experimental conditions. It's important to conduct detailed studies, including mechanistic investigations, to understand how a particular Schiff base inhibits E. coli or any other bacterial species. This might involve techniques such as molecular docking, spectroscopic analyses, and biochemical assays.

Conclusion:

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The conclusion of this study including synthsis of five new di Schiff base compounds which confirmed using FT-IR, H^1 NMR and C^{14} NMR, also the study showed high antibacterial activity of synthsis di Schiff compunds against *E. Coli* and *S. aureus.*

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