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Synthesis, Characterization and Antibacterial Activity of Macrocyclic Schiff Bases Based on 1,3-Docarbonyl Phenyl Dihydrazide, 1,4-Docarbonyl Phenyl Dihydrazide

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Abstract

Three new Macrocyclic Hydrazone Schiff bases were synthesized by condensation of intermediate compounds: 1,6- bis (2-formylphenyl) hexane and glutaraldehyde with both dihydrazide of isophthalic acid and dihydrazide of terephthalic acid. Identification of these macrocyclic Schiff bases ligands (V, VI, VII). The Schiff bases were checked by different spectral technique (LC-MS, ^{1}H-NMR, IR, elemental analyses). The new Macrocyclic Hydrazone Schiff Bases were studied for antibacterial activities against Gram positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram negative (*Salmonella typhi* and *Escherichia coli*). The compound ligands exhibited a variable activity of inhibition on the growth of the bacteria.

Keywords: Macrocyclic Hydrazone; Dihydrazide of isophthalic acid; Dihydrazide of terephthalic acid; Antibacterial activity

Introduction

Schiff bases are widely studied and used in the fields of organic synthesis and metal ion complex [1,2] for a number of reasons: their physiological and pharmacological activities [3-5] their use in ion selective electrodes [6-11], in the determination of heavy metals ions in environmental samples [12], in the extraction of metals ions [13,14] and their many catalytic applications e.g. for epoxidation of olefins, alkene cyclopropanation [15,16] trimethylsily-lcyanation of ketones [17] asymmetric oxidation of methyl phenyl sulfide enantioselective epoxidation of silylenol [18] and ring-opening Polymerization of lactide [19]. Hydrazones are special group of compounds in the Schiff bases family. They are characterized by the presence of (C=N-N=C). the presence of two inter-linked nitrogen atoms was separated from imines, oximes etc. Hydrazone Schiff bases of acyl, aroyl and heteroacroyl compounds have additional donor sites like C=O. The additional donor sites make them more flexible and versatile. This versatility has made hydrazones good polydentate chelating agents that can form a variety of complexes with various transition and inner transition metals and have attracted the attention of many researchers. Various hydrazones are obtained depending on the experimental conditions; which have application as biologically active compounds [20] and as analytical reagents [21]. As biologically active compounds, hydrazones find applications in the treatment of diseases such as anti-tumor [22], tuberculosis [22], leprosy and mental disorder [23]. Tuberculostatic activity is attributed to the formation of stable chelates with transition metals present in the cell. Thus many vital enzymatic reactions catalyzed by these transition metals cannot take place in the presence of hydrazones [24,25]. Hydrazones also act as herbicides, insecticides, nematocides, rodenticides and plant growth regulators.

Experimental

Reagents and apparatus

All the chemicals used were of Analytical grade and procured from Sigma-Aldrich and Fluka. Metal salts were purchased from E. Merck and were used as received. The elements C, H, and N were analyzed on a Carlo-Erba 1106 elemental analyzer. The IR spectra were recorded on Jusco 300 instrument in KBr pellets. ^{1}H NMR spectra of ligands in $CDCl_3$ solution were recorded on a Bruker DT-400 MHz spectrometer, and chemical shifts are reported in ppm. Mass spectra were recorded using a KRATOS MS50TC spectrometer.

AA 929 Unicam Spectrometer was used for FAAS measurements with an air-acetylene flame. A pH meter (Metrohm –691 pH Meter) was also used. All extraction experiments were performed by using a mechanical flask agitator in 50 cm^3 stoppered glass flasks, M.P Apparatus Digital (32-300°C).

Method

Synthesis of Dimethyl isophthalate (I): Isophthalic acid (1.66 gm, 0.1 mmol) in super dry methanol (60 mL) containing 2-3 drops of concentrated H_2SO_4 (AR) was refluxed till it dissolved. Then, the reaction mixture was poured onto ice cold water, immediately a solid started separating from the clear solution. To this a solution of sodium bicarbonate was added till the effervescence seized. The ester thus obtained was filtered and washed with water for several times (M.P: 64-67°C) [26].

Synthesis of dihydrazide of isophthalic acid (II): A mixture of dimethyl ester of isophthalic acid (2.22 gm) and hydrazine hydrate (98%, 2 cc) in methanol was refluxed for 4-5 hours. The reaction mixture was allowed to cool to room temperature then, the cooled solution was poured on to ice cold water. The dihydrazide of isophthalic acid thus obtained was filtered and recrystallized from ethanol [27].

Yield: (85%), M.P=241°C, Empirical formula: ($C_8H_{10}N_4O_2$), M.Wt: (194 gm) (Scheme 1).

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Synthesis of Dimethyl terephthalate (III): Terephthalic acid (1.66 gm, 0.1 mmol) in super dry methanol (60 mL) containing 2-3 drops of concentrated H_2SO_4 (AR) was refluxed till it dissolved. Then, the reaction mixture was poured onto ice cold water, immediately a solid started separating from the clear solution. To this a solution of sodium bicarbonate was added till the effervescence seized. The ester thus obtained was filtered and washed with water for several times (M.P: 138-140ºC) [26].

Synthesis of dihydrazide of terephthalic acid (IV): A mixture of dimethyl ester of terephthalic acid (2.22 gm) and hydrazine hydrate (98%, 2 cc) in methanol was refluxed for 4-5 hours. The reaction mixture was allowed to cool to room temperature then the cooled solution was poured on to ice cold water. The dihydrazide of terephthalic acid thus obtained was filtered and recrystallized from ethanol [28].

Yield: (80%), M.P>300ºC, Empirical formula: ($C_8H_{10}N_4O_2$), M.Wt: (194 gm) (Scheme 2).

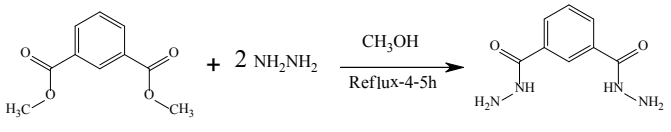
Synthesis of 1,6-bis (2-formylphenyl)hexane (V): To a stirred solution of salicylaldehyde (24.4 gm, 0.2 mol) and K_2CO_3 (13.8 gm, 0.1 mol) in DMF (100 mL), was added drop wise 1,6-dibromo hexane (12.2 gm, 0.01 mol) in DMF (40 mL). The reaction was continued for 4 hours at 150- 155ºC and then for 4 hours at room temperature. Then, 200 mL distilled water was added and the mixture was kept in refrigerator. After 1 hour, the precipitate was filtered and washed with 500 ml water. It was dried in air and recrystallized from EtOH and filtered under vacuum [29].

Yield: 85%, M.P: 75ºC, Empirical formula: ($C_{20}H_{22}O_4$), M.Wt: (326 gm) (Scheme 3).

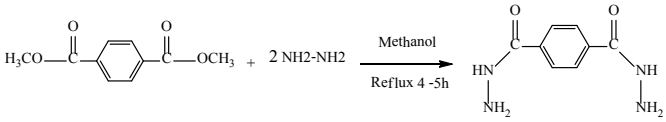
Synthesis of 1,7,8,14,15,21,22-hepta aza-10,12,24,26-di phenyl-9,13,23,27-tetra oxo-cyclo hepta icozane-1,6,15,20-tetriene (VI): The macrocyclic Schiff base (VI) was prepared by drop wise addition of a solution of the dihydrazide of isophthalic acid (II) (0.388 gm, 0.002 mol) in DMF (40 mL) to a stirred solution of glutaraldehyde (0.200 gm, 0.002 mol) in DMF (60 mL) containing a few drops of concentrated HCl. The reaction mixture was heated to reflux for 5 hours, where yellow precipitate was formed after cooling. On cooling, 200 ml distilled water was added and the mixture was kept in a refrigerator. After 2 hours, the precipitate was filtered and washed with 200 mL water. The solid obtained was collected and recrystallized from mixture DMF, EtOH (9:1) as white crystals. A white colored precipitate was washed with water, ethanol, $CHCl_3$ and diethyl ether, respectively. Then the precipitate was dried in air (Scheme 4).

Yield: 80%, M.P >300ºC, Anal. Calc. ($C_{26}H_{28}N_8O_4$): C: 60.45, H: 5.46, N: 21.69, O: 12.39, Found: C: 60.42, H: 5.29, N: 22.02, O: 12.27%, Mass spectrum (LCMS): m/z= 516 ($C_{26}H_{28}N_8O_4$), IR (KBr disk): 3431.4 cm^{-1} (CO-NH-), 2946.0 cm^{-1} (C-H, aliphatic), 1727.5 cm^{-1} (C=O), 1688.4 cm^{-1} (C=N), 1599.2-1619.6 cm^{-1} (C=C, aromatic), 1227.2 cm^{-1}(C-O, aromatic).

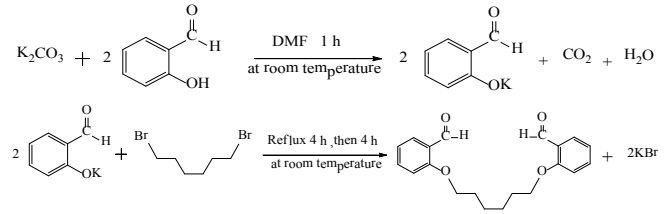
^{1}H-NMR($CDCl_3$-400MHz) δ=11.213 (s,2H,CO-NH-), 8.813 (s,2H,CH=N), 7.165-8.043 (m,8H,Ar), 1.274-2.981 (m,12 ,-$CH_2CH_2CH_2$), 4.459 (Solvent organic).



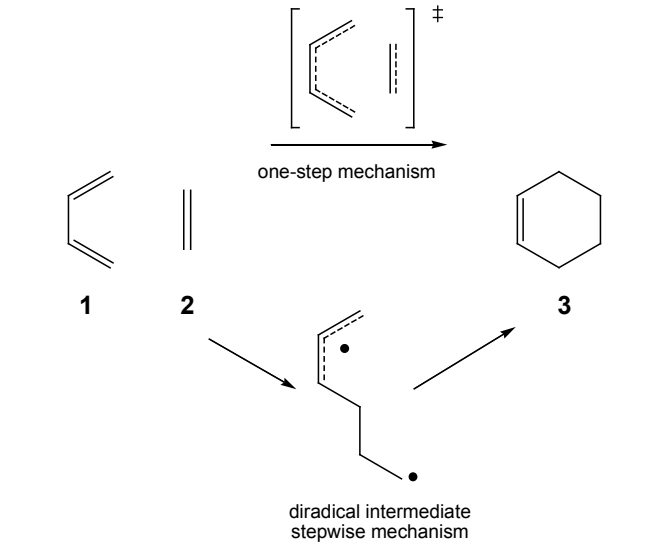
Scheme 1: Synthesis of dihydrazide of isophthalic acid(II).



Scheme 2: Synthesis of dihydrazide of terephthalic acid.



Scheme 3: Synthesis of 1,6-bis (2-formylphenyl)hexane(V).



Scheme 4: Synthesis of 1,7,8,14,15,21,22-hepta aza-10,12,24,26-di phenyl-9,13,23,27-tetra oxo-cyclo hepta icozane-1,6,15,20-tetriene.

Synthesis of 1,16-di aza-3,4,13,14,19,22-tri phenyl-18,23-di oxo-5,12-di oxa-cyclo tetra icozane-1,15-diene (VII): The macrocyclic Schiff base (VII) was prepared by drop wise addition of a solution of the dihydrazide of terephthalic acid (IV) (0.388 gm, 0.002 mol) in DMF (40 mL) to a stirred solution of 1,6-bis (2-acetylphenyl) hexane (V) (0.652 gm, 0.002 mol) in DMF (60 mL) containing a few drops of concentrated HCl. The reaction mixture was heated to reflux for 5 hours, where yellow precipitate was formed after cooling. On cooling, 200 ml distilled water was added and the mixture was kept in a refrigerator. After 2 hours, the precipitate was filtered and washed with 200 mL water. The solid obtained was collected and recrystallized from mixture DMF, EtOH (9:1) as white crystals. A white colored precipitate was washed with water, ethanol, $CHCl_3$ and diethyl ether, respectively. Then the precipitate was dried in air (Scheme 5).

Yield: 85%, M.P >300°C, Anal. Calc. ($C_{28}H_{28}N_4O_4$): C: 69.41, H: 5.82, N: 11.56, O: 13.21, Found: C: 69.51, H: 5.76, N: 11.53, O: 13.20%, Mass spectrum (LCMS): m/z= 484 ($C_{28}H_{28}N_4O_4$).

IR (KBr disk): 3237.1-3476.7 cm^{-1} (CO-NH-), 2867.0-2942.7 cm^{-1} (C-H, aliphatic), 1723.2 cm^{-1} (C=O), 1635.64 cm^{-1} (C=N), 1600.5 cm^{-1}(C=C, aromatic), 1281.7-1249.7 cm^{-1} (C-O, aromatic).

^{1}H-NMR($CDCl_3$-400 MHz) δ =12.513 (s,2H,CO-NH-), 8.901 (s,2H,CH=N), 7.021- 8.126 (m,12H, Ar-H), 4.336-4.345 (s,4H ,-O-CH_2-), 2.508-3.361 (m,8H,-CH_2-CH_2-CH_2-CH_2-).

Synthesis of 1,18-di aza-3,5,14,16,21,24-tri phenyl-20,25-di oxo-6,13-di oxa-cyclo hexa icozane-1,17-diene (VIII): The macrocyclic Schiff base (VIII) was prepared by drop wise addition of a solution of the dihydrazide of terephthalic acid (IV) (0.388 gm, 0.002 mol) in DMF (40 mL) to a stirred solution of 1,6-bis (2-acetylphenyl) hexane (V) (0.692 gm, 0.002 mol) in DMF (60 mL) containing a few drops of concentrated HCl. The reaction mixture was heated to reflux for 5 hours, where yellow precipitate was formed after cooling. On cooling, 200 ml distilled water was added and the mixture was kept in a refrigerator. After 2 hours, the precipitate was filtered and washed with 200 mL water. The solid obtained was collected and recrystallized from mixture DMF, EtOH (9:1) as white crystals. A white colored precipitate was washed with water, ethanol, $CHCl_3$ and diethyl ether, respectively. Then the precipitate was dried in air (Scheme 6).

Yield: 82%, M.P =241°C, Anal. Calc. ($C_{30}H_{24}N_4O_4$): C: 69.41, H: 5.82, N: 11.56, O: 3.21, Found: C: 69.67, H: 5.68, N: 11.48, O: 13.17%, Mass spectrum (LCMS): m/z= 484 ($C_{28}H_{28}N_4O_4$).

IR (KBr disk): 3140.11- 3278.99 cm^{-1} (CO-NH-), 3072.7 cm^{-1}, 2843.07-2993.52 cm^{-1} (C-H, aliphatic), 1705.07 cm^{-1} (C=O), 1600.92 cm^{-1} (C=N), 1577.77 cm^{-1} (C=C, aromatic), 1242.16 cm^{-1} (C-O, aromatic).

^{1}H-NMR ($CDCl_3$-400 MHz) δ=10.509 (s,2H,CO-NH-), 8.940-8.977 (s,2H,CH=N), 6.958-8.138 (m,12H, Ar-H), 4.009-4.018 (s,4H ,-O-CH_2-),1.276-2.198 (m,8H,-CH_2-CH_2-CH_2-CH_2-), 2.383-3.743 (Solvents organic).

Biological activity

The prepared compounds were tested for their antimicrobial activity against four species of bacteria (*Bacillus subtilis, Escherichia coli, Staphylococcus aureus, Salmonella typhi*) using filter paper disc method [38]. The screened compounds were dissolved individually in DMSO (dimethyl sulfoxide) in order to make up a solution of 50, 100, and 200 µg/ml concentration for each of these compounds. Filter paper discs (Whitman No.1 filter paper, 5 mm diameter) were saturated with the solution of these compounds. The discs were placed on the surface of solidified Nutrient agar dishes seeded by the tested bacteria. The diameters of inhibition zones (mm) were measured at the end of an incubation period, which was 24 hours at 37°C for bacteria. Discs saturated with DMSO are used as solvent control. Ciprofloxacin 100 µg/ml was used as reference substance for bacteria [30].

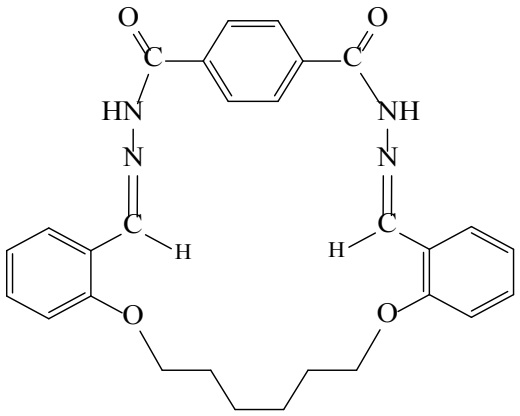
Result and Discussion

Synthesis

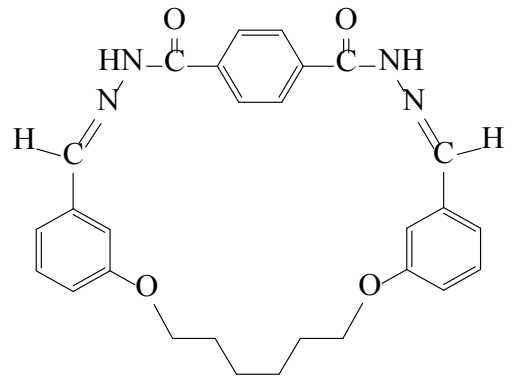
The prepared macrocyclic hydrazone (VI, VII, VIII) were synthesized by condensation of intermediate compounds: 1,6- bis (2-formylphenel) hexane, and glutaraldehyde with both dihydrazide of isophthalic acid and dihydrazide of terephthalic acid in the molar ratio (2:2) in DMF. The reactions proceeded smoothly, producing the corresponding Schiff bases ligands in good yield. The ligands are soluble in common organic solvent but insoluble in water. The structures of the ligands were elucidated by elemental analyses, MS, FTIR, electronic absorption, and ^{1}H- NMR spectra, which help in elucidating their empirical formula (Table 1).

Elemental analyses of macrocyclic hydrazone (VI, VII, VIII)

The results of elemental analyses macrocyclic hydrazone (VI, VII,VIII), as shown in Table (2), are in good agreement with those required by the proposed formulae.



Scheme 5: Synthesis of 1,16-di aza-3,4,13,14,19,22-tri phenyl-18,23-di oxo-5,12-di oxa-cyclo tetra icozane-1,15-diene.C



Scheme 6: Synthesis of 1,18-di aza-3,5,14,16,21,24-tri phenyl-20,25-di oxo-6,13-di oxa-cyclo hexa icozane-1,17-diene.

Schiff base	Color	M.Wt	Melting point °C	Yield %	Crystallization Solvent
VI	White	516	>300	80	DMF, EtOH (9:1)
VII	White	484	>300	85	DMF, EtOH (9:1)
VIII	White	484	241	82	DMF, EtOH (9:1)

Table 1: Color, molecular weight and melting point of macrocyclichydrazone (V, VI, VII).

Schiff base	Elemental analysis Calculated (Found %)				
O	C	H	N	S	O
VI	60.42 (60.45)	5.29 (5.46)	22.02 (21.69)	-------	12.27 (12.39)
VII	69.51 (69.41)	5.76 (5.82)	11.53 (11.56)	-------	13.20 (13.21)
VIII	69.47 (69.41)	5.78 (5.82)	11.48 (11.56)	-------	13.27 (13.21)

Table 2: Elemental analysis data ofmacrocyclichydrazone (VI, VII,VIII).

IR spectra analysis

Compound (VI): A strong band at 1688.4 and 1727.5 cm^{-1} in the IR spectrum of the Schiff base (Figure (1)) are assigned to υ(C=N) of azomethine and carbonyl υ(C=O) vibrations, respectively. An intense band at 3431.4 cm^{-1} is due to the -NH- vibrations of the hydrazine group. The band in the spectra at 1619.6 - 1599.2 cm^{-1} is due to (C=C) of aromatic rings, while the band at 2946.0 cm^{-1} is attributed to (C-H, aliphatic). Also, the band at 3051.39 cm^{-1} is attributed to (C-H, aromatic) [31-35].

Compound (VII): A strong band at 1637.9 and 1723.2 cm^{-1} in the IR spectrum of the Schiff base (Figure (2)) are assigned to υ(C=N) of azomethine and carbonyl υ(C=O) vibrations, respectively. An intense band at 3476.7 -3237.1 cm^{-1} is due to the -NH- vibrations of the hydrazine group. The band in the spectra at 1600.5 cm^{-1} is due to (C=C) of aromatic rings, while the band at 2942.7 - 2867 cm^{-1} are attributed to (C-H, aliphatic). Also, the band at 3027.1 cm^{-1} is attributed to (C-H, aromatic) [31-35].

Compound (VIII): A strong band at 1600.92 and 1705.07 cm^{-1} in the IR spectrum of the Schiff base (Figure (3)) are assigned to υ(C=N) of azomethine and carbonyl υ(C=O) vibrations, respectively. An intense band at 3278.99-3140.11 cm^{-1} is due to the -NH- vibrations of the hydrazine group. The band in the spectra at 1577.77 cm^{-1} is due to (C=C) of aromatic rings, while the band at 2993.52-2843.07 cm^{-1} are attributed to (C-H, aliphatic). Also, the band at 3055.24 cm^{-1} is attributed to (C-H, aromatic) [26-30]. However, in the IR spectra of Schiff bases this bands (C=O) disappears and a new vibration bands for azomethine (-HC=N-), indicating that complete condensation takes place [36,37] (Table 3).

^{1}H-NMR Spectra of macrocyclic hydrazone (VI, VII, VIII)

Compound (VI): The ^{1}H-NMR spectrums (Figure (4)) of the Schiff base (VI) showed that in the region 2.981-1.274 ppm was assigned to protons of methyl groups in two different environments [38]. The signals at 11.213 and 8.813 ppm were assigned to the protons of amide CONH and imine -CH=N groups respectively. Signals in the region 8.043-7.165 ppm were assigned to the aromatic protons.

Compound (VII): The ^{1}H-NMR spectrums (Figure (5) of the Schiff base (VII) showed that in the region 2.449 - 1.278 ppm was assigned to protons of methyl groups in two different environments [38]. The

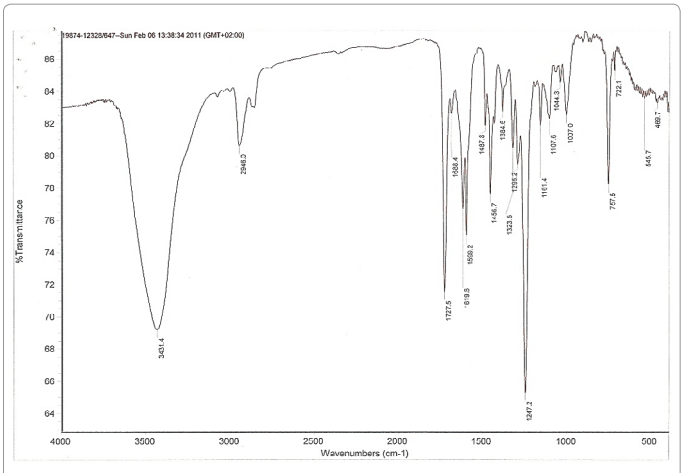


Figure 1: IR spectrum ofSchiff base(VI).

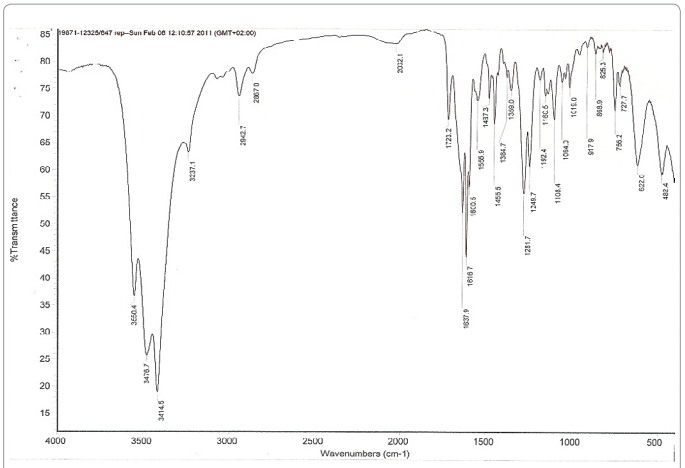


Figure 2: IR spectrum ofSchiff base(VII).

signals at 10.510 and 8.901 ppm were assigned to the protons of amide CONH and imine -CH=N groups respectively. Signals in the region 8.126-7.021 ppm were assigned to the aromatic protons. While the singlet signals at 4.345 - 4.336 ppm were assigned to the protons (-O-CH_2-) group.

Compound (VIII): The ^{1}H-NMR spectrums (Figure (6)) of the Schiff base (VIII) showed that in the region 2.198 - 1.276 ppm was assigned to protons of methyl groups in two different environments [38]. The signals at 10.509 and 8.977 ppm were assigned to the protons of amide CONH and imine -CH=N groups respectively. Signals in the region 8.138-6.958 ppm were assigned to the aromatic protons. While the singlet signals at 4.018-4.009 ppm assigned to the protons (-O-CH_2-) group.

The other obtained values for ^{1}H-NMR chemical shifts of the compounds are given in the experimental section.

The ^{1}H-NMR spectral data of the new compounds are in good agreement with those previously reported for similar compounds. These results strongly suggest that the proposed compounds have been formed [36,37].

Biological activity

During the last two or three decades, attention has been increasingly paid to the synthesis of macrocyclic hydrazone (VI, VII, VIII), which exhibits various biological activities including antibacterial, fungicidal, tuberculostatic and plant growth regulative properties [39]. It was judicious to investigate the synthesis of various new types of Schiff base and studied their antibacterial activity against four strains of bacteria (*Bacillus subtilis, Escherichia coli, Staphylococcus aureus, and Salmonella typhi*). The concentrations used for the screened compounds are 50, 100, and 200 µg/ml. Ciprofloxacin was used as reference standard while DMSO as control and inhibition zones is measured in mm. The new compounds were tested against one strain each of a gram positive and two gram negative. The test results presence in Table 4, a new compound was active against tested and another compound are no active.

All compounds are not active when used in the concentration of 50, 100 µg/ml but active in the concentration of 200 µg/ml (Table 5 and Figure 7).

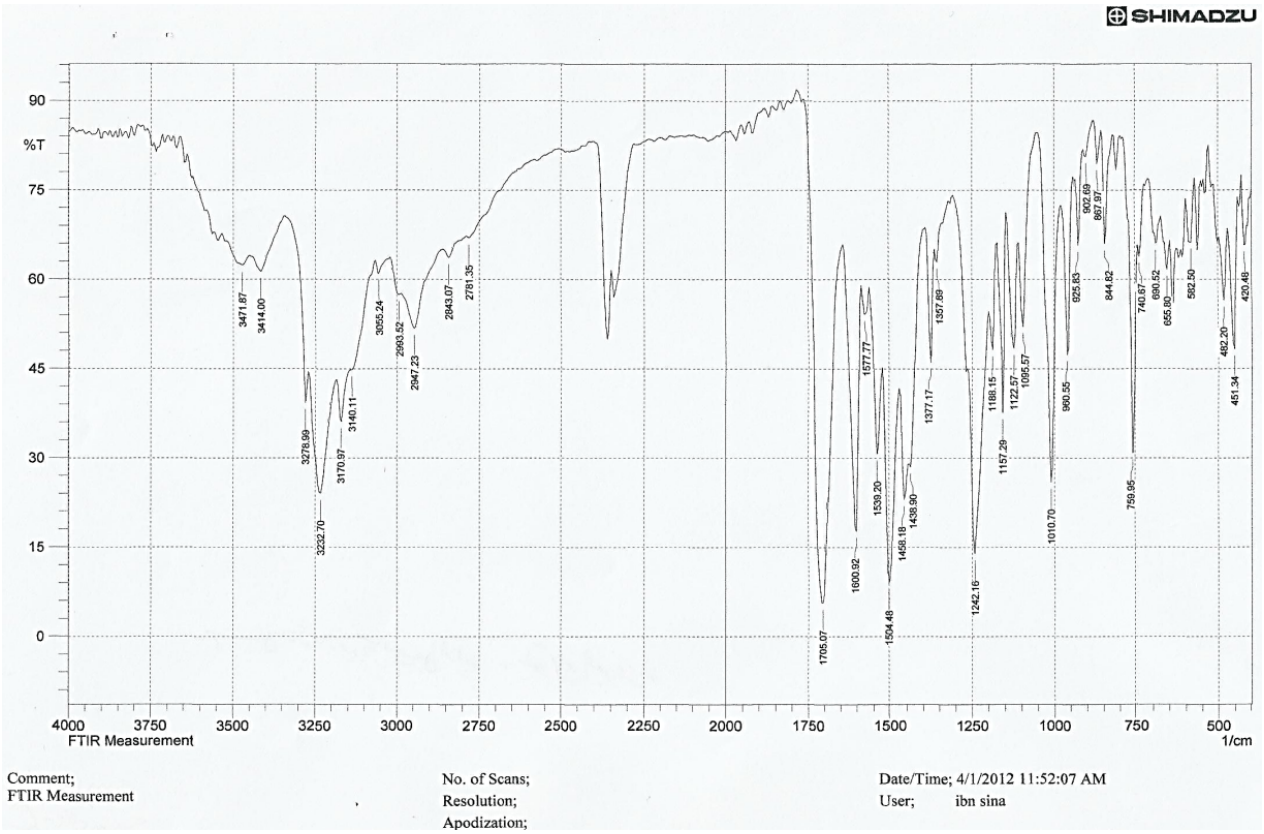


Figure 3: IR spectrum ofSchiff base(VIII).

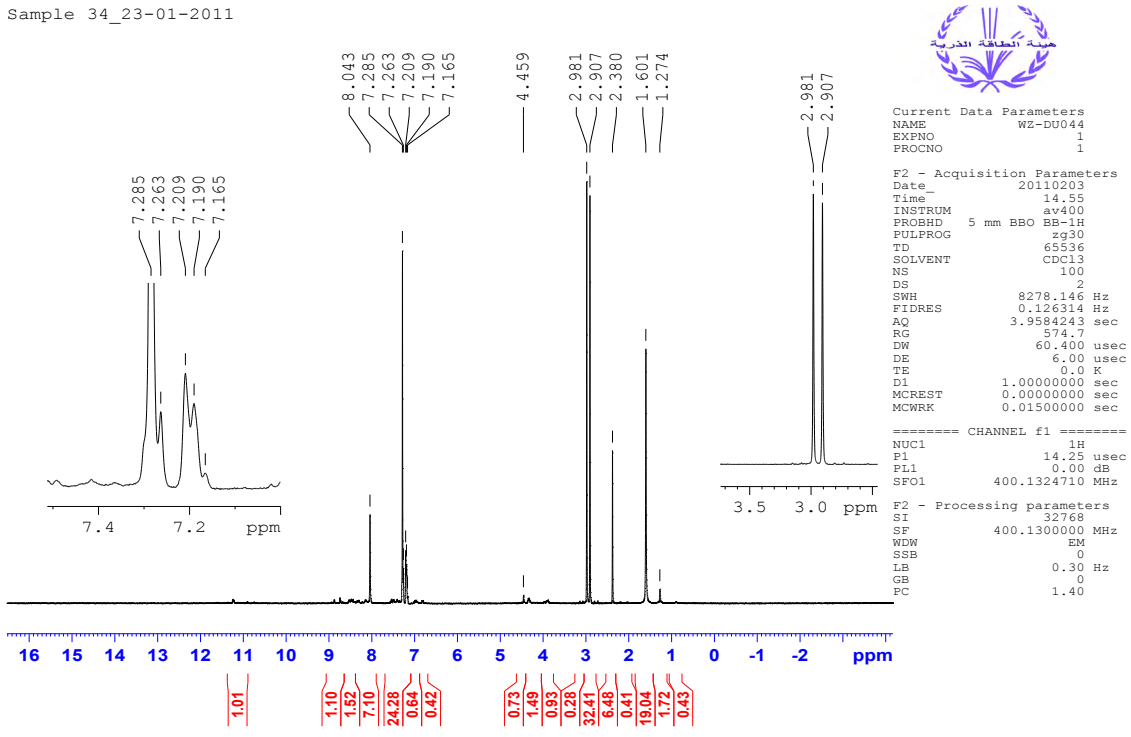


Figure 4: ^{1}H-NMR spectrum ofSchiff base(VI).

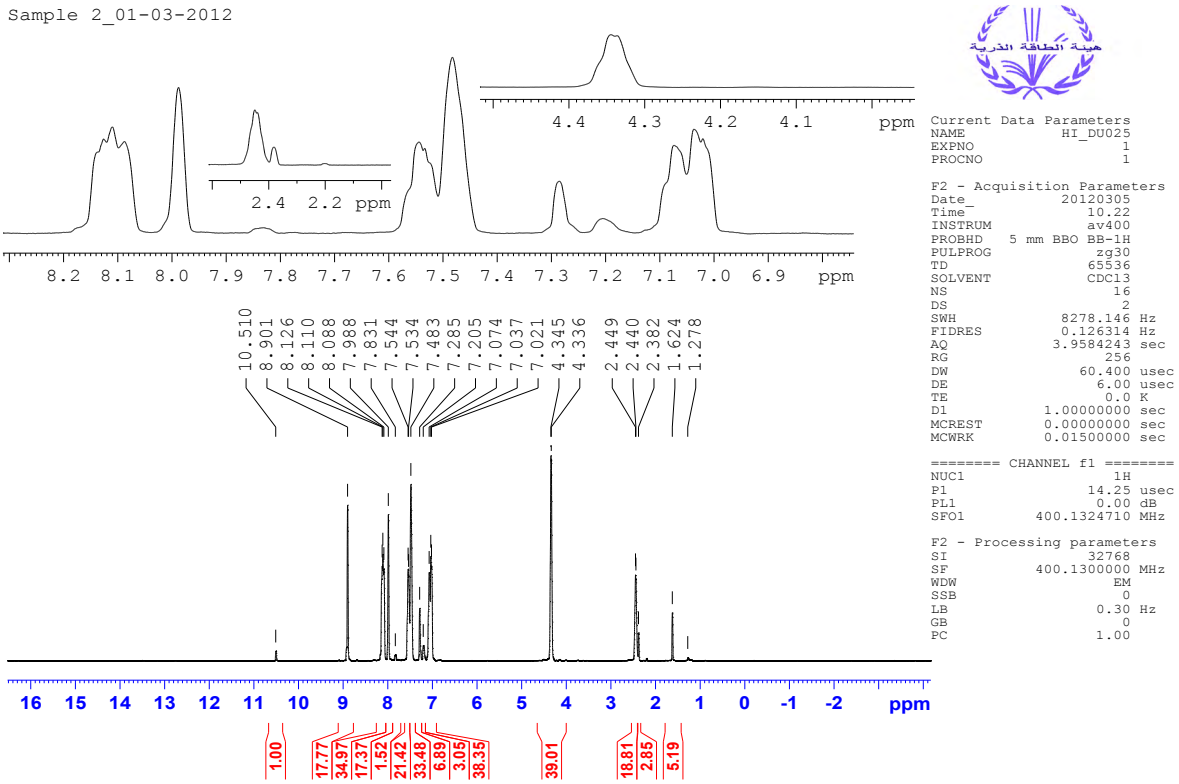


Figure 5: ^{1}H-NMR spectrum ofSchiff base(VII).

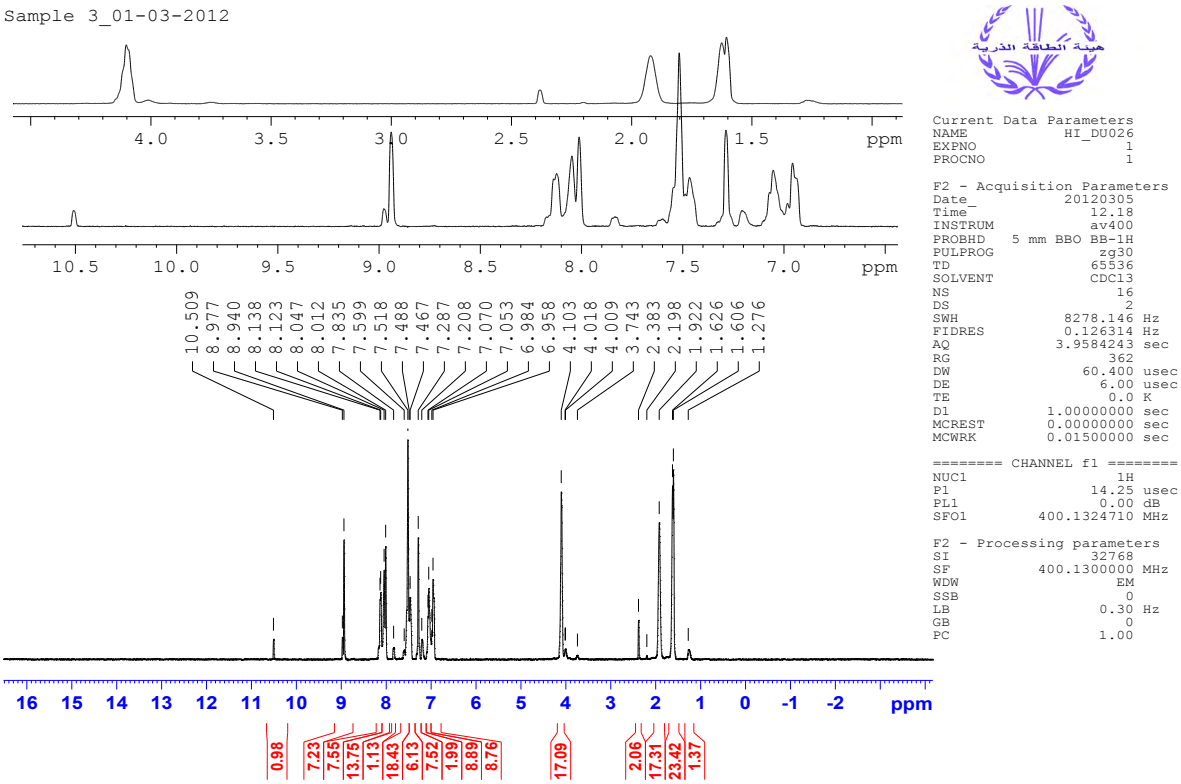


Figure 6: ^{1}H-NMR spectrum ofSchiff base(VIII).

Schiff bases	v(C-O)	v(C=C)	v(C=N)	v(C=O)	C-H aliph	C-H aromatic	-CO-NH-
VI	1227.2	1619.6 - 1599.2	1688.4	1727.5	2946.0	3051.39	3431.4
VII	1281.7-1249.7	1600.5	1637.9	1723.2	2942.7 - 2867.0	3027.1	3476.7 -3237.1
VII	1242.16	1577.77	1600.92	1705.07	2993.5-2843.07	3055.24	3278.99-3140.1

Table 3: IR spectral data (cm^{-1}) of macrocyclichydrazone (VI, VII, VIII).

Shiff base	Bacteria			
	Gram negative		Gram positive	
	B. subtilis	S. aureus	E.coli	S. typhi
VI	17 mm	18 mm	15 mm	18 mm
VII	18 mm	16 mm	16 mm	19 mm
VIII	18 mm	15 mm	12 mm	17 mm
Control	00 mm	00 mm	00 mm	00 mm
Ciprofloxacin	20 mm	20 mm	20 mm	20 mm

Table 4: Effect of new macrocyclichydrazone (VI, VII,VIII) on the growth of tested bacteria (conc.200 µg/ml).

Schiff base	Chemical Shiftsδppm				
	$(CH_2-CH_2-)_n$	$-O-CH_2-$	C-H aromatic	CH=N	-CO-NH-
VI	2.981 - 1.274(m,12H)	----------	8.043 - 7.165 (m,8 H)	8.813 (s,2H)	11.213 (s,2H)
VII	2.449 - 1.278(m,8H)	4.345 -4.336 (s,4H)	8.126 - 7.021 (m,12 H)	8.901 (s,2H)	10.510 (s,2H)
VIII	2.198 - 1.276(m,8H)	4.018 -4.009(s,4H)	8.138 - 6.958(m,12 H)	8.977 (s,2H)	10.509 (s,2H)

Table 5: ^{1}H-NMR Spectra ofmacrocyclichydrazone (VI, VII,VIII).

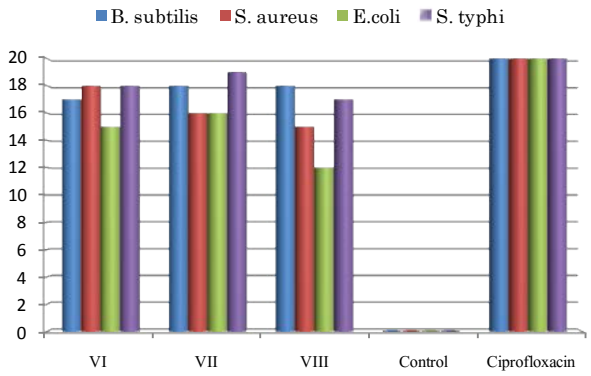


Figure 7: Antibacterial activity (Gram positive, negative) of synthesized compounds.

Conclusion

The compounds are new and were prepared for the first time. The new compounds were identified by melting point, elemental analyses ^{1}HNMR, IR, LC-MS, spectral methods. The prepared compounds have been biologically screened i.e. studying their effects against two gram-positive, two gram-negative bacteria. The results show that their activities were found to vary from moderate to very strong.

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