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Research Article

SYNTHESIS , CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF MACROCYCLIC SCHIFF BASES BASED ON 1,3-DOCARBONYL PHENYL DIHYDRAZIDE

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Abstract

Four new Macrocyclic Hydrazone Schiff bases were synthesized by condensation of intermediate compounds: 1,6- bis (2-formylphenel) hexane(III),1,6-bis (2-acetylphenyl)hexane(IV), α,α'-bis(2-carboxyaldehyde phenoxy) xylene(V), and isophthal aldehyde with dihydrazide of isophthalic acid. Identification of these macrocyclic Schiff bases ligands (VI, VII, VIII, IX).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 (Bacillus subtilis and Staphylococcus aureus) are Gram positive and (Salmonella typhi and Escherichia coli) are Gram negative. The compounds ligands were exhibited a variable activity of inhibition on the growth of the bacteria.

Keywords: Macrocyclic Hydrazone, dihydrazide of isophthalic acid , spectral technique, antibacterial activity.

Introduction

Schiff bases are widely studied and used in the fields of organic synthesis and metal ion complexation [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] and 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 enantioselectiveepoxidation 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.

In the context of the above applications we have reported here the synthesis and characterization of novel macrocyclic hydrazone Schiffbases. All these compounds have been characterized byelementa analyses, LC-MS, IR, ^{1}H NMR spectra data.A Survey of

the literature reveal that no work has been carried outon the synthesis of mcrocyclic hydrazone Schiff bases derived from1,3-Docarbonyl phenyl dihydrazide, and in the present study, we synthesized hydrazone Schiff bases and used it in studying antibacterial activity

2.Experimental

2.1.Reagents and Apparatus.

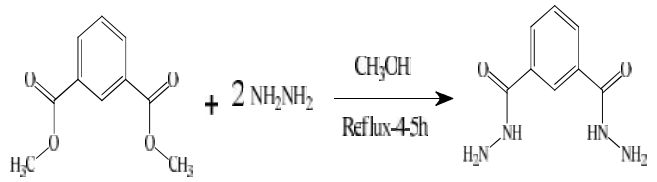
All the chemicals used were of AnalaR grade and procured from Sigma-Aldrich and Fluka. Metal salts were purchased from E. Merck and were used as received. The C, H, and N were analyzed on a Carlo-Erba 1106 elemental analyzer. The IR spectra was recorded on Jusco 300 instrument in KBr pellets. ^{1}H NMR spectra of ligands in $CDCl_3$ solution were recorded on a Bruker DT-400 MHz spectrometer, and chemical shifts are indicated in ppm relative to tetra methyl silane. Mass spectra were recorded using a KRATOS MS50TC spectrometer.
, M.P Apparatus Digital (32-300 ^{0}C).

2.2.1.Synthesis of Dimethyl isophthalate(I)

Isophthalic acid (1.66 g, 0.1mmol) 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 (mp 64-67°C) [26].

2.2.2. Synthesis of dihydrazide of isophthalic acid(II).

A mixture of dimethyl ester of isophthalic acid (2.22 g) and hydrazine hydrate (98% 2 cc) in methanol was refluxed for 4-5h. 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.[27-28].
Yield:(85%), m.p=241 C^{0}, Empirical formula:($C_8H_{10}N_4O_2$),M.Wt:(194 g).

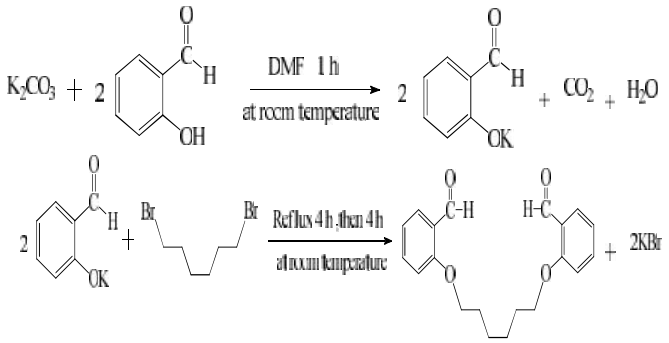


(II)

2.2.3.Synthesis of 1,6-bis (2-formylphenyl)hexane(III)

To a stirred solution of salicylaldehyde (24.4 g, 0.2 mol) and K_2CO_3 (13.8 g, 0.1 mol) in DMF (100mL), was added drop wise 1,6-dibromo hexane (12.2 g, 0.01 mol) in DMF (40 mL). The reaction was continued for 4 h at 150- 155°C and then for 4 h at room temperature. Then, 200 mL distilled water was added and the mixture was kept in refrigerator. After 1 h, 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%, mp75 °C, Empirical formula:($C_{20}H_{22}O_4$),M.Wt:(326 g).

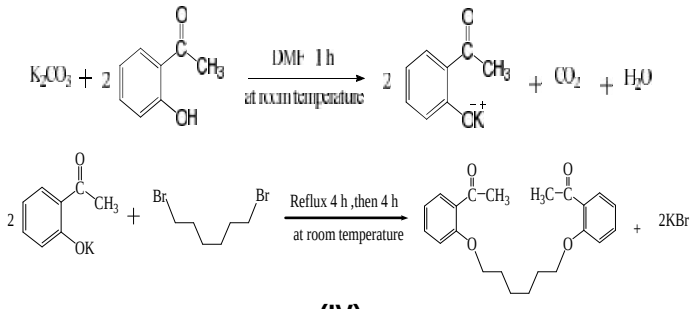


(III)

2.2.4.Synthesis of 1,6-bis (2-acetylphenyl)hexane(IV).

To a stirred solution of 2- hydroxyl acetophenone (13.6 g, 0.1 mol) and K_2CO_3 (6.9 g, 0.05mol) in DMF (50 mL), was added drop wise 1,6-dibromo hexane (6.1 g, 0.05 mol) in DMF (20 mL). The reaction was continued for 4 h at 150- 155°C and then for 4 h at room temperature. Then, 100 mL distilled water was added and the mixture was kept in refrigerator. After 1 h, the precipitate was filtered and washed with 250 ml water. It was dried in air and recrystallized from EtOH and filtered under vacuum..[29].

Yield: 80%, mp122 °C, Empirical formula:($C_{22}H_{26}O_4$),M.Wt:(354 g).



(IV)

2.2.5.Synthesis of α,α'-bis(2-carboxyaldehyde phenoxy) xylene(V)

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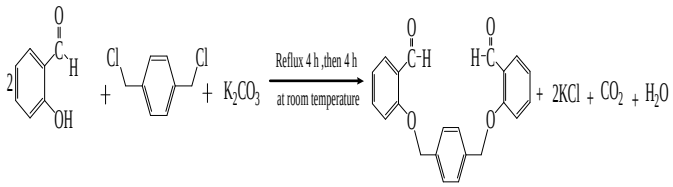
To a stirred solution of salicylaldehyde (24.4 g, 0.2 mol) and K_2CO_3 (13.8 g, 0.1 mol) in DMF (100 mL), was added drop wise α,α'-Dichlor-p-xylene (17.4 g, 0.1mol) in DMF (40 mL). The reaction was continued for 4 hrs at 150-155°C and then for 4 h at room temperature. Then, 200 mL distilled water was added and the mixture was kept in refrigerator. After 1 h, the precipitate was filtered and washed with 500 mL water. It was dried in air and recrystalized from EtOH and filtered under vacuum..[29].

Yield: 75%, mp 107 ^{0}C, Empirical formula:($C_{22}H_{18}O_4$),M.Wt:(346 g).



(V)

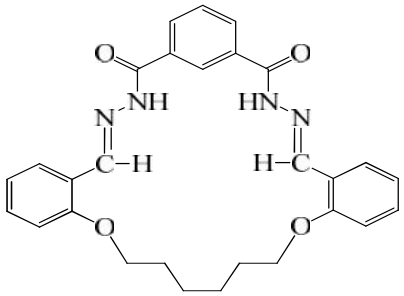
2.2.6.Synthesis of 1,16-di aza-3,4,12,13,14,18,21-tri phenyl-17,22-di oxo-5,12-di oxa-cyclo tri icozane-1,15-diene. (VI):

The macrocyclic Schiff base (VI) was prepared by dropwise addition of a solution of the dihydrazide of isophthalic acid (II)(0.388 g, 0.002 mol) in DMF (40 mL) to a stirred solution of 1,6-bis (2-formylphenyl)hexane(I) (0.652 g, 0.002 mol) in DMF (60 mL) containing a few drops ofconcentrated HCl. The reaction mixture was heated to reflux for 5 h, 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 h, 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 withwater, ethanol, CHCl3 and diethyl ether, respectively. Then dried in air.

Yield: 85 %. mp>300 ^{0}C. Anal. Calc. for $C_{28}H_{28}N_4O_4$: C: 69.41, H: 5.82, N: 11.56, O: 13.21. Found: C: 69.34, H: 5.91, N: 11.62, O: 13.13%, Mass spectrum (LCMS): m/z=488 ([$C_{28}H_{28}N_4O_4$]).**(figure 1)**

IR (KBr disk): 3236.8 - 3414.3 cm^{-1} (CO-NH-), 3072.2 cm^{-1}(C-H), aromatic), 2866.0 - 2939.3 cm^{-1}(C-H), aliphatic), 1637.2 cm^{-1} (C=O), 1616.8cm^{-1} (C=N), 1599.3 cm^{-1} (C=C, aromatic), 1245.2 cm^{-1}(C-O). **(figure 2)**

^{1}H-NMR($CDCl_3$-400MHz) δ =12.511 (s,2H, CO-NH-), 8.954 (s,2H,CH=N) , 7.121 - 8.391 (m,12, Ar), 4.147 (s,4H,-O-CH_2), 1.873 – 2.223 (m,8H ,-$CH_2CH_2CH_2CH_2$). **(figure 3)**



(VI)

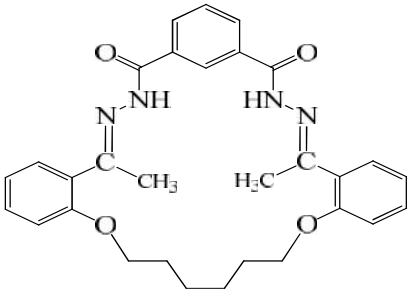
2.2.7.Synthesis of 1,16-di aza-3,4,13,14,18,21-tri phenyl-17,22-di oxo-5,12-di oxa-2,15-di methyl-cyclo tri icozane-1,15-diene.. (VII):

The macrocyclic Schiff base (VII) was prepared by dropwise addition of a solution of the dihydrazide of isophthalic acid(II) (0.388 g, 0.002 mol) in DMF (40 mL) to a stirred solution of 1,6-bis (2-acetylphenyl)hexane (IV) (0.708 g, 0.002 mol) in DMF (60 mL) containing a few drops of concentrated HCl. The reaction mixture was heated to reflux for 5 h, 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 h, 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, CHCl3 and diethyl ether, respectively. Then dried in air.

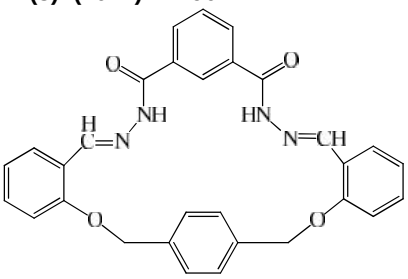
Yield: 85 %. mp>300 ^{0}C. Anal. Calc. for $C_{30}H_{32}N_4O_4$: C: 70.29; H, 6.29; N, 10.93; O, 12.48. Found: C:70.34, H:6.12, N:11.0, O:12.51 %, Mass spectrum (LCMS): m/z= 512 ([$C_{30}H_{32}N_4O_4$]). **(figure 4)**

IR (KBr disk): 3224.3 - 3415.9 cm^{-1} (CO-NH-), 3066.2 cm^{-1}(C-H), aromatic), 2866.0 - 2939.3 cm^{-1}(C-H), aliphatic), 1726.6cm^{-1} (C=O), 1651.0 cm^{-1}(C=N), 1599.0 – 1578.5 cm^{-1} (C=C, aromatic), 1267.0 cm^{-1}(C-O). **(figure 5)**

^{1}H-NMR($CDCl_3$-400MHz) δ =10.923 (s,2H, CO-NH-), 6.978 - 7.664 (m,12, Ar), 4.126 – 4.211 (s,4H,-O-CH_2), 3.942(N=C-CH_3), 1.305 – 2.868 (m,8H ,-$CH_2CH_2CH_2CH_2$). **(figure 6)**



VII



VIII

2.2.8.Synthesis of 1,16-di aza-3,4,13,14,19,21-tri phenyl-18,22-di oxo-5,12-di oxa-cyclo tri icozane-1,15-diene(VIII).

The macrocyclic Schiff base (VIII) was prepared by dropwise addition of a solution of the dihydrazide of isophthalic acid (II) (0.388 g, 0.002 mol) in DMF (40 mL) to a stirred solution of α,α'-bis(2-carboxyaldehyde phenoxy) xylene (V) (0.692 g, 0.002 mol) in DMF (60 mL) containing a few drops of concentrated HCl. The reaction mixture was heated to reflux for 5 h, 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 h, 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, CHCl3 and diethyl ether, respectively. Then dried in air.

Yield: 85 %. mp>300 ^{0}C. Anal. Calc. for $C_{30}H_{24}N_4O_4$: C: 71.42 , H: 4.79 , N: 11.10 , O: 12.68. Found: C: 71.37 ,H: 4.82 ,N: 11.16 ,O: 12.65%, Mass spectrum (LCMS): m/z= 504 ([$C_{30}H_{24}N_4O_4$]). **(figure 7)**

IR (KBr disk): 3414.7 - 3477.0 cm^{-1} (CO-NH-),3072.7 cm^{-1}, 2871.4-2950.4cm^{-1}((C-H), aliphatic), 1663.6cm^{-1} (C=O), 1637.6 cm^{-1} (C=N), 1594.9 – 1617.5cm^{-1} (C=C, aromatic), 1244.3 cm^{-1} ((C-O),aromatic). **(figure 8)**

^{1}H-NMR($CDCl_3$-400MHz) δ =13.133 (s,2H, CO-NH-), 9.035 (s,2H,CH=N) , 76.079 - 7.923 (m,16H, Ar-H), 3.723 – 3.982 (s,4H ,-O-CH_2-),2.179 – 3.400 (Solvents organic).

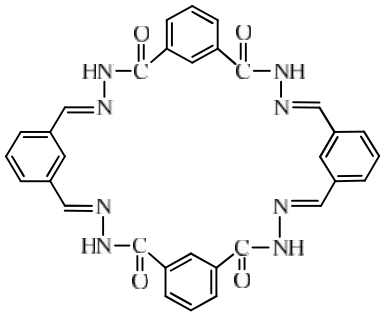
^{13}C-NMR($CDCl_3$-400MHz) δ= 187.35 (2C,CO-HN), 163.00 (2C,CH=N), 124.64 -138.81 (24C, Ar-C), 94.18 (2C, -O-CH_2-).**(figure 9)**

2.2.9.Synthesis of 1,7,8,14,15,21,22-hepta aza-3,5,10,12,17, 19, 24,27-tetra phenyl-9,13,23,27-tetra oxo-cyclohepta icozane-1,6,15,20-tetriene. (IX):

The macrocyclic Schiff base (IX) was prepared by dropwise addition of a solution of the dihydrazide of isophthalic acid (II) (0.388 g, 0.002 mol) in DMF (40 mL) to a stirred solution of isophthal aldehyde (0.268 g, 0.002 mol) in DMF (60 mL) containing a few drops of concentrated HCl. The reaction mixture was heated to reflux for 5 h, 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 h, 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, CHCl3 and diethyl ether, respectively. Then dried in air. Yield: 75 %. mp>300 ^{0}C. Anal. Calc. for $C_{32}H_{24}N_8O_4$: C: 65.75, H: 4.14, N: 19.17, O: 10.95. Found: C: 65.80, H:4.12, N:19.23, O:10.85 %, Mass spectrum (LCMS): m/z= 584 ([$C_{32}H_{24}N_8O_4$]). **(figure 10)**

IR (KBr disk): 3192.1 - 3439.9 cm^{-1} (CO-NH-),3052.3cm^{-1}((C-H), aromatic), 1672.3 cm^{-1} (C=O), 1588.6cm^{-1} (C=N), 1522.70 cm^{-1} (C=C, aromatic), 1268.9 cm^{-1} ((C-O),aromatic). **(figure 11)**.

^{1}H-NMR($CDCl_3$-400MHz) δ =10.128 (s,2H, CO-NH-), 8.596 (s,2H,CH=N) , 6.711 - 8.200 (m,16H, Ar-H). **(figure 12)**



(IX)

Biological Activity

The prepared compounds were tested for their antimicrobial activity against four speices of bacteria (Bacillus subtilis, Escherichia coli , Staphylococcus aureus, Salmonella typhi) using filter paper disc method [30]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,5mm 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 h at 37C for bacteria. Discs saturated with DMSO are used as solvent control. Ciprofloxacin 100 µg/ml was used as reference substance for bacteria.[30].

3.Result and Discussion :

3.1.1. Synthesis

The prepared macrocyclichydrazone (VI,VII,VIII, IX) were synthesized by condensation of intermediate compounds: : 1,6- bis (2- formylphenel) hexane(III),1,6-bis (2-acetylphenyl)hexane(IV), α,α'-bis(2-carboxyaldehyde phenoxy) xylene(V), with dihydrazide of isophthalic acidin the molar ratio (1:1) in DMF.Andcondensation ofisophthal aldehyde with dihydrazide of isophthalic acidin 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 formulaas in Table 1.

3.1.2. Elemental analyses of macrocyclic hydrazone (VI,VII,VIII, IX).

he results of elemental analyses macrocyclichydrazone (VI,VII,VIII, IX), as shown in Table 2, are in good agreement with those required by the proposed formulae

IR spectra analysis

Compound(VI): A strong band at 1616.8 and 1637.2 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 3414.3 - 3236.8 cm^{-1} is due to the -NH- vibrations of the hydrazine group The band in the spectra at 1599.3cm^{-1} is due to (C=C) of aromatic rings. while the band at 2939.3 – 2868 cm^{-1} are attributed to (C-H aliph) .Also, the band at 3072.2cm^{-1} are attributed to (C-H ar).[31-35].

Compound (VII): A strong band at 1651.0and 1726.6cm^{-1} in the IR spectrum of the Schiff base**(figure 5)** are assigned to υ(C=N) of azomethine and carbonyl υ(C=O) vibrations, respectively. An intense band at 3415.9 - 3224.3cm^{-1} is due to the -NH- vibrations of the hydrazine group The band in the spectra at 1599.0 – 1578.5cm^{-1} is due to (C=C) of aromatic rings. while the band at 2939.3 - 2866.0 cm^{-1} are attributed to (C-H aliph). Also, the band at 3066.2cm^{-1} are attributed to (C-H ar). [31-35].

Compound (VIII): A strong band at 1637.6and 1663.6cm^{-1} in the IR spectrum of the Schiff base **(figure 8)**are assigned to υ(C=N) of azomethine and carbonyl υ(C=O) vibrations, respectively. An intense band at 3477.0 - 3414.7cm^{-1} is due to the -NH- vibrations of the hydrazine group The band in the spectra at 1617.5 - 1594.9cm^{-1} is due to (C=C) of aromatic rings. while the band at 2950.4 - 2871.4cm^{-1} are attributed to (C-H aliph) .Also, the band at 3072.7cm^{-1} are attributed to (C-H ar). [31-35].

Compound (IX):A strong band at 1588.6and 1672.3cm^{-1} in the IR spectrum of the Schiff base**(figure 11)** are assigned to υ(C=N) of azomethine and carbonyl υ(C=O) vibrations, respectively. An intense band at 3439.9 - 3192.1cm^{-1} is due to the -NH- vibrations of the hydrazine group The band in the spectra at 1522.70cm^{-1} is due to (C=C) of aromatic rings.Also, the band at 3052.3cm^{-1} are attributed to (C-H ar).[31-35]

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.All IR spectral data of the synthesized compounds showed in theTable 3[36-37].

3.1.3. ^{1}-H-NMR Spectra of macrocyclic hydrazone (VI,VII,VIII, IX).

Compound (VI): The ^{1}H NMR spectrum**(figure 3)**of the Schiff base (VI), showed that in the region 2.223 - 1.873 ppm were assigned to protons of methyl groups in two differentenvironments [38]. The signals at 12.511 and 8.954ppm were assigned to the protons of amide CONH and imine -CH=N groups respectively. Signals in the region 8.391 - 7.121 ppm were assigned to the aromatic protons.While the singlet signal at 4.147 ppm assigned to the protons (-O-CH_2-) group.

Compound (VII): The 1H NMR spectrum **(figure 6)**of the Schiff base (VII), showed that in the region 2.868 - 1.305ppm were assigned to protons of methyl groups in

Table 1. Physical and chemical properties of the synthesized compounds[VI]-[IX]

Schiff base	Color	M.Wt	Melting point ^{0}C	Yield %	Crystallization Solvent
VI	White	484	> 300	85	DMF , EtOH (9:1)
VII	White	512	> 300	62	DMF , EtOH (9:1)
VIII	White	504	> 300	80	DMF , EtOH (9:1)
IX	White	584	> 300	87	DMF , EtOH (9:1)

Table 2. Elemental analysis data of the synthesized compounds[VI]-[IX].

Schiff base	Elemental analysis Calculated (Found %)				
	C	**H**	**N**	**S**	**O**
VI	69.34 (69.41)	5.91 (5.82)	11.62 (11.56)	-------	13.13 (13.21)
VII	70.34 (70.29)	6.12 (6.29)	11.03 (11.93)	-------	12.51 (12.48)
VIII	71.37 (71.42)	4.82 (4.79)	11.16 (11.10)	-------	12.65 (12.68)
IX	65.80 (65.75)	4.12 (4.14)	19.2 (19.17)	-------	10.85 (10.95)

Table 3. IR spectral data of the synthesized compounds[VI]-[IX].

Schiff bases	v(C-O)	v(C=C)	v(C=N)	v(C=O)	C-H aliph	C-H aromatic	-CO-NH-
VI	1245.2	1599.3	1616.8	1637.2	2939.3 - 2868.0	3072.2	3414.3 - 3236.8
VII	1267.0	1599.0 – 1578.5	1651.0	1726.6	2939.3 - 2866.0	3066.2	3415.9 - 3224.3
VIII	1244.3	1617.5 - 1594.9	1637.6	1663.6	2950.4 - 2871.4	3072.7	3477.0 - 3414.7
IX	1268.9	1522.70	1588.6	1672.3	-------	3052.3	3439.9 -3192.1

Table4. ^{1}H-NMR Spectra of the synthesized compounds[VI]-[IX]

Schiff base	Chemical Shifts δ ppm				
	$(CH_2-CH_2-)_n$	$-O-CH_2-$	C-H aromatic	CH=N	-CO-NH-
VI	2.223 - 1.873 (m,8H)	4.147 (s,4H)	8.391 - 7.121 (m,12 H)	8.954 (s,2H)	12.511 (s,2H)
VII	2.868 - 1.305 (s,8H)	4.126 – 4.211 (s,4H)	7.664 - 6.978 (m,12 H)	----------	10.923 (s,2H)
VIII	----------	3.982 - 3.723 (s,4H)	7.923 - 6.079 (m,16 H)	9.035 (s,2H)	13.133 (s,2H)
IX	----------	----------	8.200 - 6.711 (m,12 H)	8.596 (s,2H)	10.128 (s,2H)

Table 5. Antibacterial activity of the synthesized compounds[VI]-[IX]

Shiff base	Bacteria			
	Gram negative		Gram positive	
	B. subtilis	S. aureus	E.coli	S. typhi
VI	15 mm	13 mm	19 mm	14 mm
VII	16 mm	12 mm	18 mm	18 mm
VIII	20 mm	18 mm	17 mm	18 mm
IX	16 mm	17 mm	15mm	16 mm
Control	00 mm	00 mm	00 mm	00 mm
Ciprofloxacin	20 mm	20 mm	20 mm	20 mm

(-)No zones of inhibition were observed.
Moderately sensitive,(+)Inhibition zones of 7-10mm.
Sensitive,(++)Inhibition zones of 11-14mm.
High sensitive,(+++)Inhibition zones of 15-20mm.

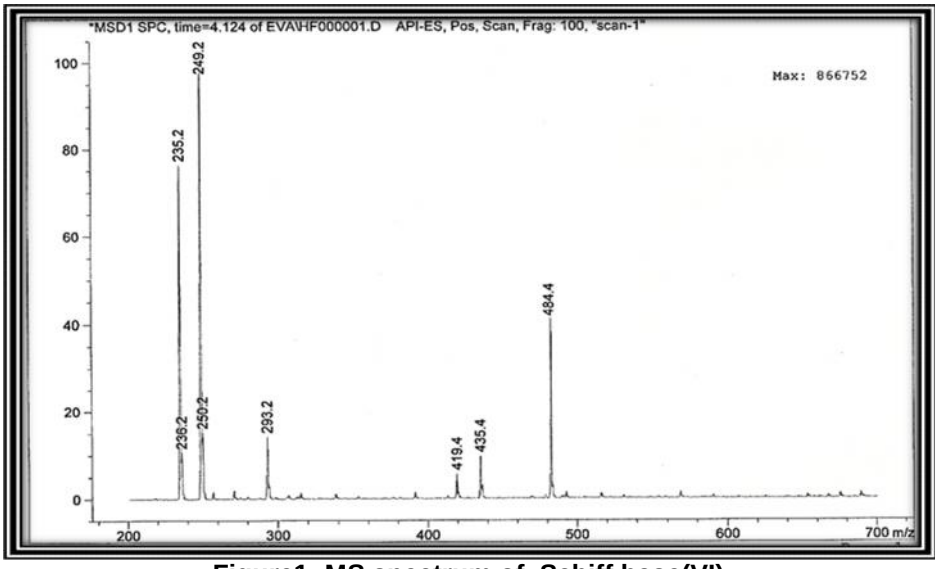


Figure1: MS spectrum of Schiff base(VI)

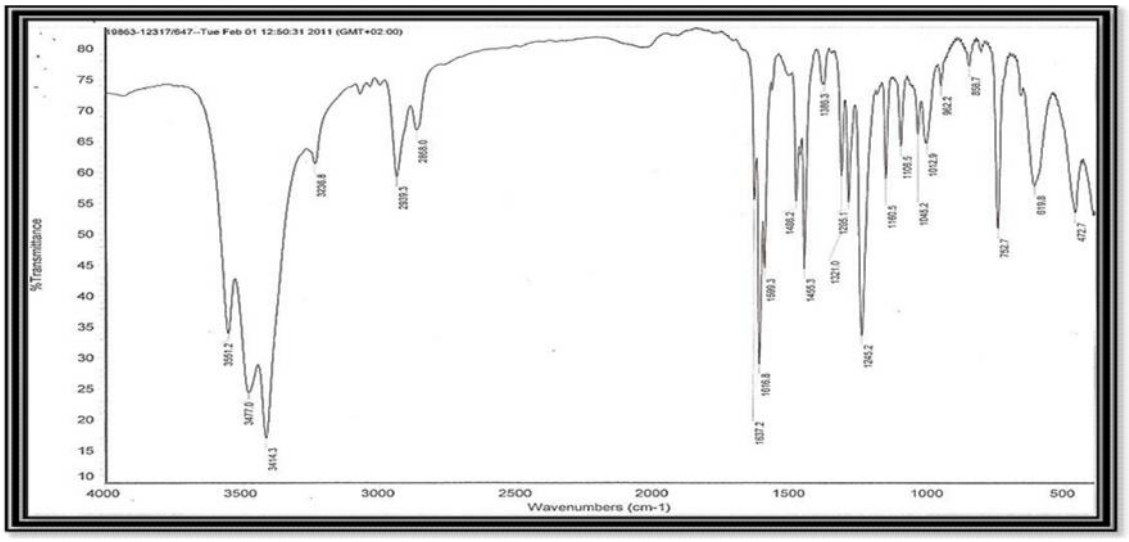


Figure 2: IR spectrum of Schiff base(VI)

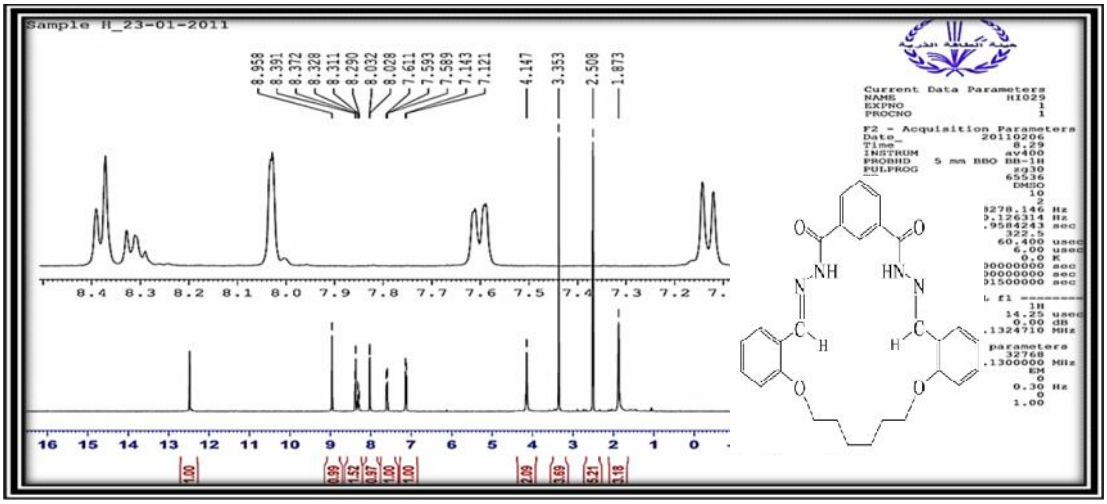


Figure 3: ^{1}HNMR spectrum of Schiff base(VI)

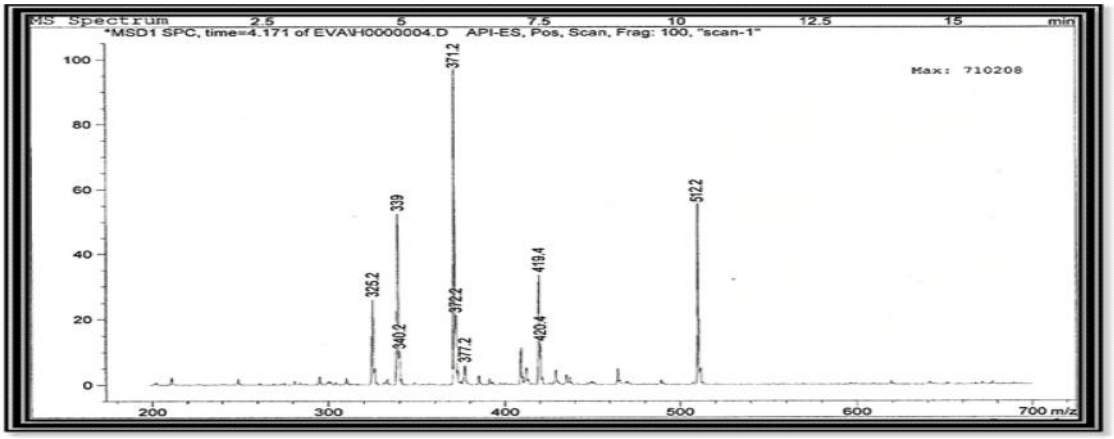


Figure 4: MS spectrum of Schiff base(VII)

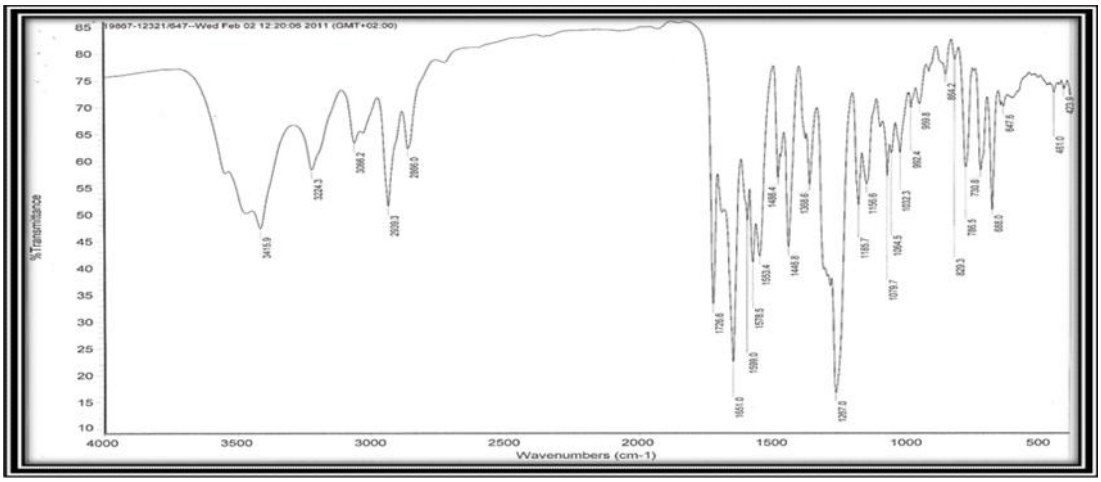


Figure 5: IR spectrum of Schiff base(VII)

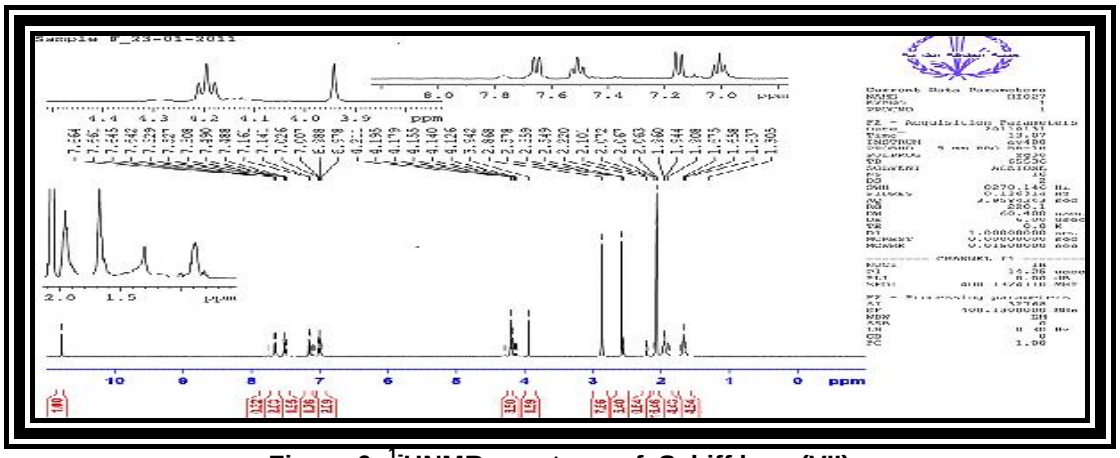


Figure 6: ^{1}HNMR spectrum of Schiff base(VII)

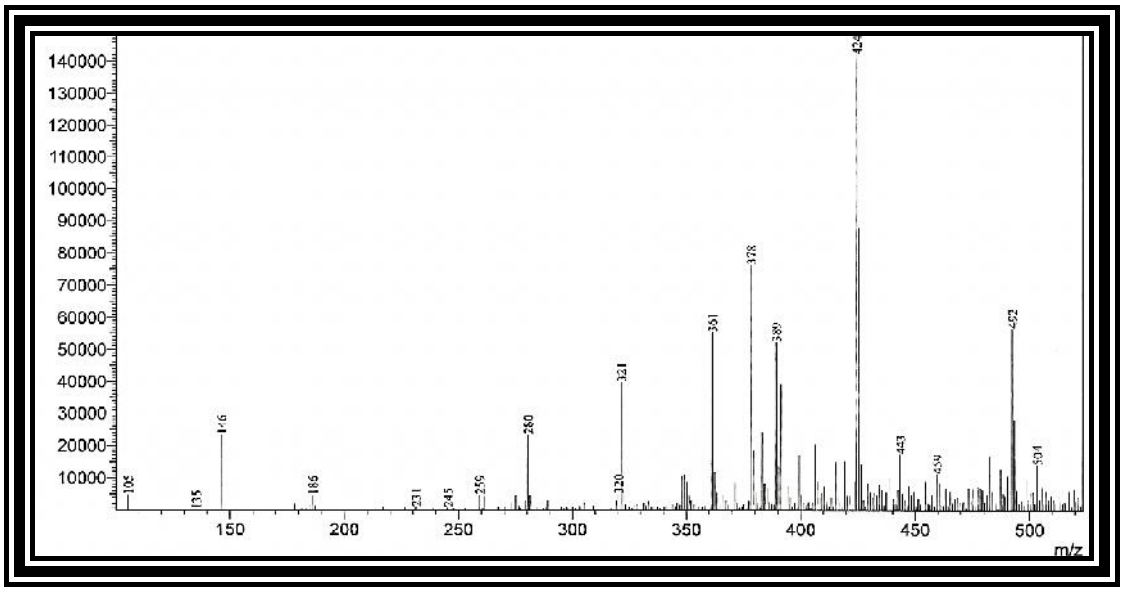


Figure 7: MS spectrum of Schiff base(VIII)

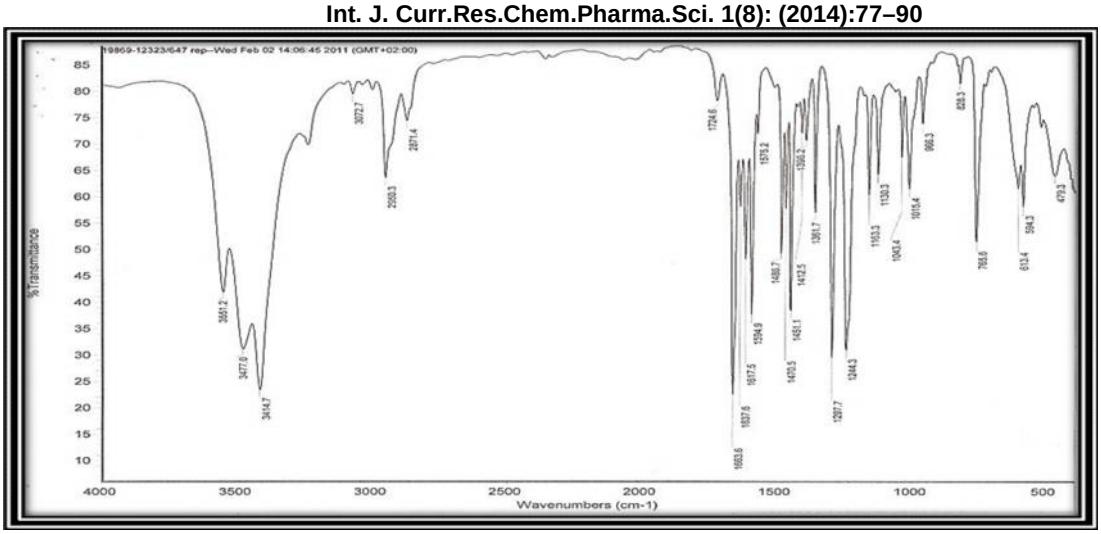


Figure 8 : IR spectrum of Schiff base(VIII)

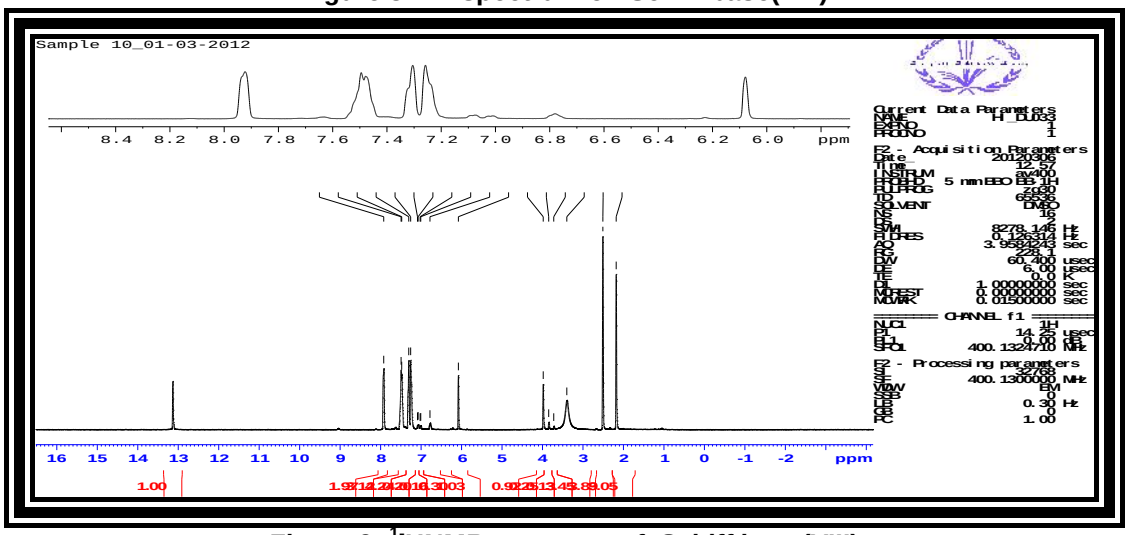


Figure 9: ^{1}HNMR spectrum of Schiff base(VIII)

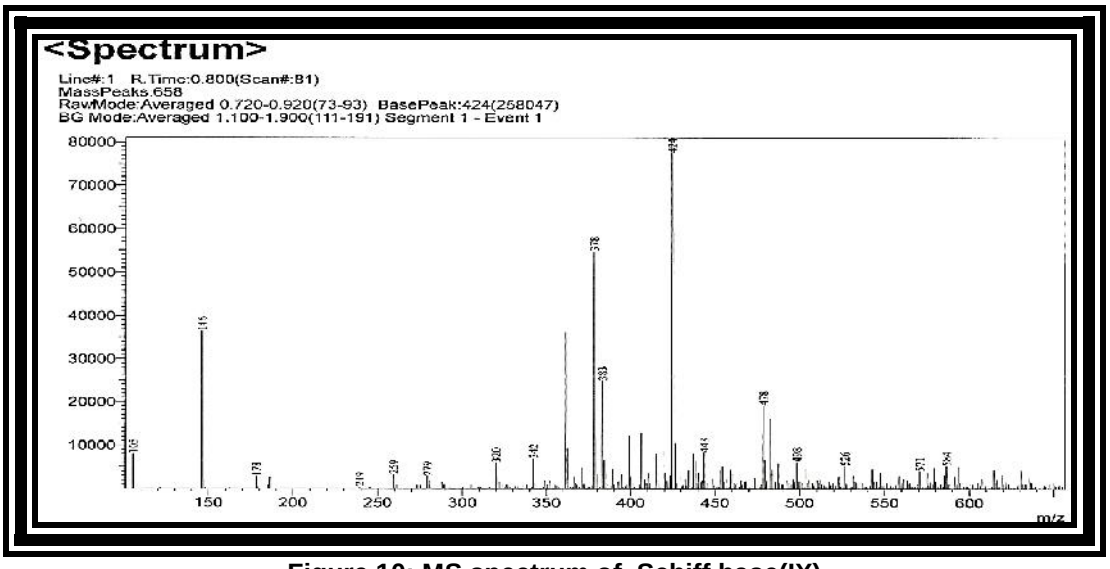


Figure 10: MS spectrum of Schiff base(IX)

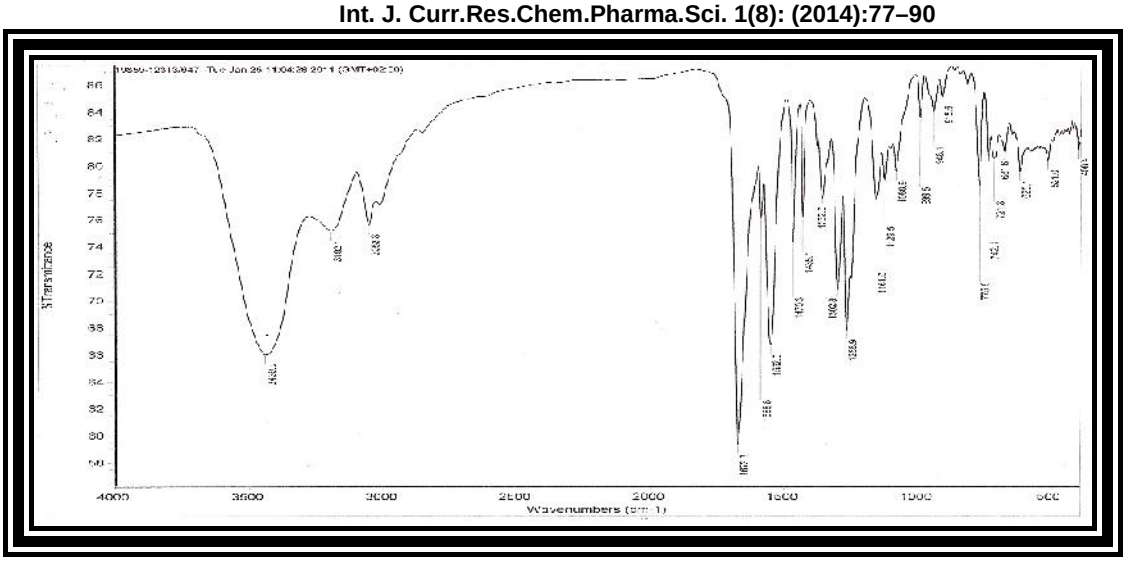


Figure 11: IR spectrum of Schiff base(IX)

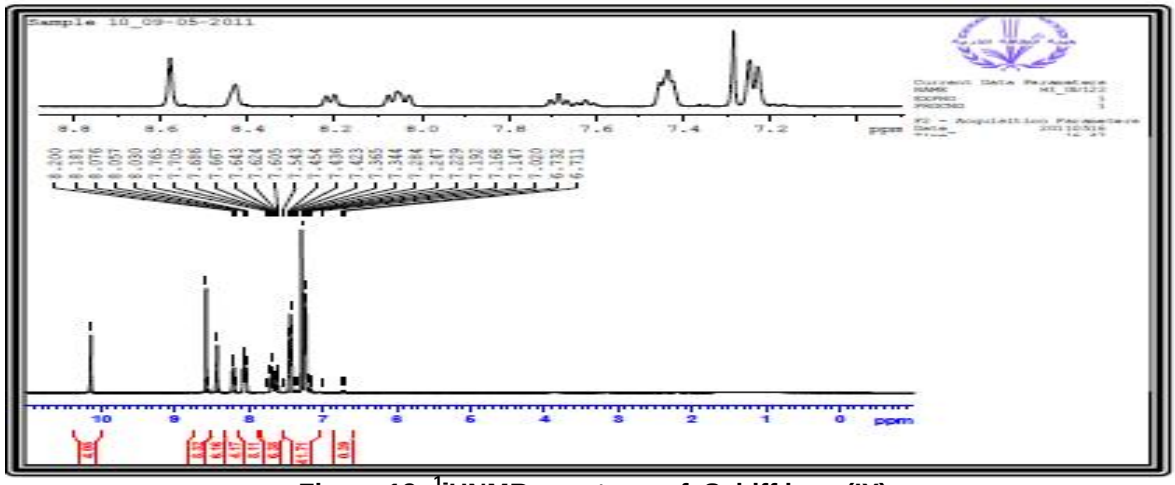


Figure 12: ^{1}HNMR spectrum of Schiff base(IX)

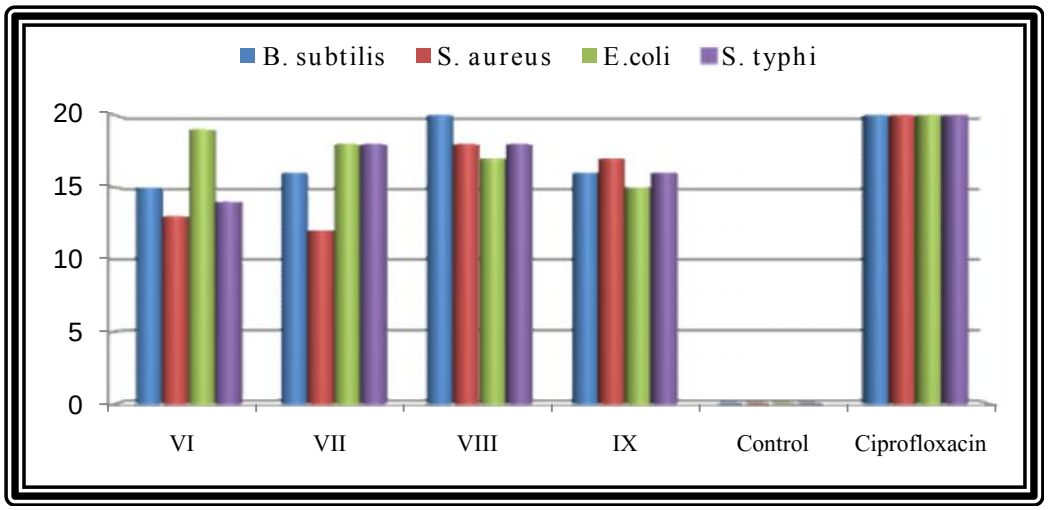


Figure 13.Antibacterial activity of synthesized compounds[VI]-[IX].

two differentenvironments [38]. The signals at 10.923ppm were assigned to the protons of amide CONH. Signals in the region 7.664 - 6.978ppm were assigned to the aromatic protons.While the singlet signal at 4.126 – 4.211 ppm assigned to the protons (-O-CH_2-) group.

Compound (VIII): The ^{1}H NMR spectrum **(figure 9)**of the Schiff base (VIII), showed that in the signals at 13.133 and 9.035 ppm were assigned to the protons of amide CONH and imine -CH=N groups respectively. Signals in the region 7.923 - 6.079 ppm were assigned to the aromatic protons.While the singlet signal at 3.982 - 3.723 ppm assigned to the protons (-O-CH_2-) group..[38]

Compound (IX): The ^{1}H NMR spectrum **(figure 12)** of the Schiff base (IX), showed that in the signals at 10.128 and 8.596 ppm were assigned to the protons of amide CONH and imine -CH=N groups respectively. Signals in the region 8.200 - 6.711 ppm were assigned to the aromatic protons.[38]

The other obtained values for $^{1-}$H-NMR chemical shifts of the compounds are given in the experimental section.
The $^{1-}$HNMR spectral data of the new compoundsshowed in theTable 4. These data are in good agreement with those previously reported for similar compounds. These results strongly suggest that the proposed compounds have been formed**.[36-37]**

3.3 Biological Activity

During the last two or three decades, attention has been increasingly paid to the synthesis of macrocyclic hydrazone (VI,VII,VIII, IX), 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, 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 are 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 (3.11), a new compound was active against tested and another compounds are no active.
All compounds are no active where used 50, 100 µg/ml but active in the concentrations 200 µg/ml see Table 5.

Conclusion

1- The compounds are new and were prepared for the first time.
2- The new compounds were identified by melting point, elementalanalyses^{1}HNMR, IR, LC-MS, spectral methods.
3-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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References

1. Layer RW (1963) The Chemistry of Imines. Chem Rev 63: 489-499.
2. Renaud J. L, Brueau. C, Demerseman B (2003) Ruthenium-Bisimine: A New Catalytic Precursor for RegioselectiveAllylic Alkylation. Synlett 408-412.
3. Correa W. H, Papadopoulos . C, Radnidge P, Roberts BA, Scott JL (2002) Direct, efficient, solvent-free synthesis of 2-aryl-1,2,3,4 tetrahydroquin-azolines. GreenChem 4: 245-251.
4. Johnson C. P, Atwood J. L, Steed J. W, Bauer C. B, Rogers R. D (1996) Transition Metal Complexes of *p*-Sulfonatocalix[5] arene. InorgChem 35: 2602-2610.
5. Sprung MM (1940) A summary of the reactions of aldehydes with amines. Chem Rev 26: 297-338.
6. Naeimi H, Safari J, Heidarnezhad A (2007) Synthesis of Schiff base ligands derived from condensation of salicylaldehyde derivatives and synthetic diamine. Dyes Pigments 73: 251-253.
7. Ambroziak K, Pelech R, Milchert E, Dziembowska T, Rozwadowski Z (2004) New dioxomolybdenum(VI) complexes of tetradentate Schiff base as catalysts for epoxidation of olefins. J MolCatal A Chem 211: 9-16.
8. Suga H, Fudo T, Ibata T (1998) Cu(I)-Binaphthyldiimine Catalyzed Asymmetric Cyclopropanation of Olefin with Diazoacetate. Synlett 8: 933-935.
9. Yang ZH, Wang LX, Zhou ZH, Zhou QL, Tang CC (2001) Synthesis of new chiralSchiff bases and their application in the asymmetric

trimethylsilylcyanation of aromatic aldehydes. Tetrahedron: Asymmetry 12: 1579-1582.
10. Tony KM Shing, Yong-Li Zhong (2001) Ring-selective synthesis of O-heterocycles from acyclic 3-O-allyl-monosaccharides via intramolecular nitrone–alkene cycloaddition. Tetrahedron: Asymmetry 12: 1573-1579.
11. Kim GJ, Shin JH (1999) Application of new unsymmetrical chiral Mn(III), Co(II,III) and Ti(IV) salen complexes in enantioselective catalytic reactions. CatalLett 63: 83-90.
12. Sasaki C, Nakajima K, Kojima M (1991) Preparation and Characterization of Optically Active Quadridentate Schiff Base-Titanium(IV) Complexes and the Catalytic Properties of These Complexes on Asymmetric Oxidation of Methyl Phenyl Sulfide with Organic Hydroperoxides. Bull ChemSocJpn 64: 1318-1324.
13. Casella L, Ibers JA (1981) Synthesis, characterization, and reactivity of copper(I) and copper(II) complexes of N,N'-bis(3-(2-thenylideneimino)propyl) piperazine (tipp) and N,N'-bis(3-(2-thenylamino)propyl)piperazine (tapp). Crystal structure of [Cu(tapp)][ClO4]2. InorgChem 20: 2438-2448.
14. Al zoubi W, Kandil F, Khaled Chebani M (2011) The synthesis of ($N_2O_2S_2$)- Schiff base ligands and investigation of their ion extraction capability from aqueous media. SpectrochimActa A MolBiomolSpectrosc 79: 1909-1914.
15. Waldemar A, Rainer RS (1998) Synthesis of Optically Active α-Hydroxy Carbonyl Compounds by the Catalytic, Enantioselective Oxidation of SilylEnol Ethers and Ketene Acetals with (Salen)manganese(III) Complexes. Am ChemSoc 120: 708-714.
16. Schmeyers J, Toda F, Boy J, Kaupp G (1998) Quantitative solid–solid synthesis of azomethines. J ChemSoc Perkin Trans 2: 989-994.
17. Tanaka K (2003) Solvent-free Organic Synthesis; Wiley-VCH: Weinheim.
18. Sans D, Perona A, Claramunt RM, Elquero J (2005) Synthesis and spectroscopic properties of Schiff bases derived from 3-hydroxy-4-pyridinecarboxaldehyde. Tetrahedron 61: 145-154.
19. Fernandez-G JM, Del Rio-Portilla F, Quiroz-Garcia B, Toscano RA, Salcedo R (2001) The structures of some ortho-hydroxy Schiff base ligands. J MolStruct 561: 197-207.
20. Sclatani J. A, Maranto M. T, Sisk T. M, Arman SAV (1996) Terminal Alkylation of Linear Polyamines. J Org Chem 61: 3221-3222.
21. Corhnelissen J. P, Van Diemen J. H, Groeneveld L. R, Haasnoot J. G, Spek AL (1992) Synthesis of Co(II), Ni(II) and Cu(II) Complexes from Schiff base. J ReediskInorgChem 31:198-202.
22. Richardson D. R, Bernhardt P. V (1999) Crystal and molecular structure of 2-hydroxy-1-naphthaldehyde isonicotinoyl hydrazone (NIH) and its iron(III) complex: an iron chelator with anti-tumour activity. J BiolInorgChem 4: 266- 273.
23. Yadawe M. S, Patil S. A (1997) Synthesis, characterization and biological studies of cobalt(II) and nickel(II) complexes with new Schiff bases. Transition Met Chem 22: 220-224.
24. Darnell G, Richardson DR (1999) The potential of iron chelators of the pyridoxalisonicotinoyl hydrazone class as effective antiproliferative agents III: the effect of the ligands on molecular targets involved in proliferation. Blood 94: 781-92.
25. Murukan B, Mohanan K (2007) Synthesis, characterization and antibacterial properties of some trivalent metal complexes with [(2-hydroxy-1- naphthaldehyde)-3-isatin]-bishydrazone. J Enzyme Inhib Med Chem 22: 65-70.
26. Ziyadonogullari B, Topal G, Erdogan S (2001) Effect of structural modificationsof diaza-18-crown-6 on the extractability and selectivity of univalent metal picrates. Talanta 53: 1083-1087.
27. Avaji P. G, VinodKumar C. H, Shivananda N. K, Nagaraju C (2009) Synthesis, spectral characterization, in-vitro microbiological evaluation and cytotoxic activities of novel macrocyclicbis hydrazone. Eur J med Chem 44: 3552-3559.
28. Ahmad .R, Ehsan. Z, Masoud. S.; 2007,Effect of anionic surfactant on transport of copper(II) through liquid membrane containing a new synthesis Schiff base, Separation and Purification Technology 54 (2007) 28–33.
29. Kenneth R. A, Darren S. B, Paul A. D, Leonard F. L, Mary M.P, Alan B, Harold R. P. and Peter A. T., 1995, Macrocyclic ligand design. Effect of donor-set and ringsize variation on silver(I)/lead(II) discrimination within an extended series of dibenzo substituted rings, J. Chem. Soc., Dalton Trans., 1127-1131
30. Ibrahim.U.H.;Basaran.I.;Kilic.T.;Cakir U.;2006-Synthesis, complexation andanti- fungal, antibacterial activity studies of a new

Macrocyclic Schiff Base,J. Hetrocyclic Chem.,**43**,1679.

31. Machacek M, Lebvoua M, Hrbata J, Drsata J (1988) Quantitative relations between chemical structure and hepatotoxicity of thiobenzamides. J Collect Czech ChemCommun 53: 2957-2961.
32. Emara AA, El-Sayedand BA, Ahmed AE (2008) Syntheses, spectroscopic characterization and thermal behavior on novel binuclear transition metal complexes of hydrazones derived from 4,6-diacetylresorcinol and oxalyldihydrazine. pectrochimActa A MolBiomolSpectrosc 69: 757-769.
33. Robert M, Francis XS, David J (2005) Spectrometric Identification of Organic Compounds, John Wiley & Sons Inc.
34. Donald L, Pavia Gary M, Lampman S (2001) Introduction to Spectroscopy. (3rd edn), Thomson Learning Inc..
35. Pretsch E, Buhlmann P, Affolter C (2001) Structure Determination of Organic Compounds. (3rd edn) Springer, Verlag Berlin Heidelberg, New York.
36. Pathak P., Jolly. V. S. & Sharma. K. P. (2000).Synthesis and biological activities of some new substituted arylazo Schiff bases. Orient. J. Chem., 16, 161-162
37. Rajaa.A.G.; "Preparation of Some New Azo-Schiff Bases Compounds and Studing Their Biological Activity". M.Sc. Thesis, College of education for Women, University of Kufa, (2008).
38. Chandra S, Kumar Sharma A (2009) Nickel(II) and copper(II) complexes with Schiff base ligand 2,6-diacetylpyridine bis(carbohydrazone): Synthesis and IR, mass, 1H NMR, electronic and EPR spectral studies. SpectrochimActa A MolBiomolSpectrosc 72: 851-857.
39. Jarraphour; A.; Motamedifar; M.;Pakshir; K.; Hadi; N.; and Zarei; M.; "Synthesis of Novel Azo Schiff Bases and Their Antibacterial and Antifungal Activites". Molecules, 9, 815-824 (2004).

