SYNTHESIS AND IDENTIFICATION OF SCHIFF BASES AND BILOGICAL ACTIVITY NEW STUDY

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Abstract

In this work we focused on the synthesis of new Open Schiff bases which were prepared by condensation of salicylaldehyde with both 4,4'-diaminodiphenyl methane,4,4'-diamino diphenyl sulphide,and by condensation of O-vanilin with diethyl ester of terephthalic acid respectively.Also new macrocyclic Schiff Bases were prepared by condensation of 1,6-bis(2-formylphenyl)hexane with thiocarbohydrazid.The Schiff bases were checked by different spectral technique (LC-MS, ^{1}H-NMR, IR). The work was extended to study the effect of the prepared compounds on four different bacteria in order to test there biological activity

Keywords: *Open Schiff base,Macrocyclic, Salicylaldehyde, Spectral Technique, Antimicrobial Activity.*

تحضير وتشخيص قواعد شيف جديدة ودراسة فعاليتها الحيوية

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الملخص

يركز هذا البحث على تحضير قواعد شيف مفتوحة جديدة حضرت من تكاثف السالیسل الدهيد مع كلاً من 4,4'- ثنائي امينو ثنائي فينيل الميثان،و4,4'- ثنائي امينو ثنائي فينيل سلفيد،ومن تكاثف الاورثو فانيلين مع ثنائي ايثيل استر لحمض التيرفثاليك، وايضاً حضرت قاعدة شيف حلقية كبيرة من تكاثف 6,1- بس(2 – فورميل فينيل)هكسان مع ثيوكربوهيدرازيد. وشُخصت هذه المركبات بالتقنيات الطيفية المختلفة(LC-MS, ^{1}H-NMR, IR). كمادرس تأثير المركبات المصنعة على أربع سلالات بكتيرية لمعرفة فعاليتها الحيوية.

الكلمات المفتوحة:قواعد شيف مفتوحة،حلقية كبيرة ، ساليسل الدهيد،تقنيات طيفية، فعالية بكتيرية.

1. Introduction

Azomethine group (–C=N–) containing compounds typically known as Schiff bases have been synthesized by the condensation of primary amines with active carbonyls. Schiff bases form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial,[1-6] antifungal[3-6] and antitumor activity.[7-8] They have been studied extensively as a class of ligands[9-11] and are known to coordinate with metal ions through the azomethine nitrogen atom. Schiff base complexes play a vital role in designing metal complexes related to synthetic and natural oxygen carriers. [12] Metal complexes make these compounds effective as stereospecific catalysts towards oxidation, reduction, hydrolysis, biological activity and other transformations of organic and inorganic chemistry.[13] In organic compounds the presence of –C=N– along with other functional groups form more stable complexes compared to compounds with only –C=N– coordinating moiety. Similarly coumarin derivatives have a great interest because of their role in natural and synthetic organic chemistry. Many products which contain a coumarin subunit exhibit biological activity such as molluscicides,[14] anthelmintic,hypnotic, insecticidal [15] activity and some are serving as anticoagulant agents[16] and fluorescent brighteners. So coumarins containing a Schiff base are expected to have enhanced antitumor and other biological activities. It is well established that the biological activity associated with the hydrazone compounds attributed to the presence of the active pharmacophore (-CONH-N=C-). Hence many hydrazone compounds containing this active moiety showed good anticancer bioactivities according to the literature [17].

Hence, in this paper, we are reporting the synthesis of new open and macrocyclic Schiff bases from condensation of salicylaldehyde derivatives with 4, 4'-diamino diphenyl methane,4,4'-diaminodiphenyl sulphide, and their characterization by spectral data such as IR, ^{1}H NMR and LC-Mass spectra was studied. Their antimicrobial activity was also evaluated. [18].

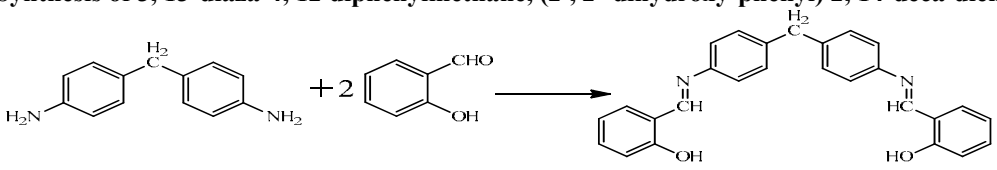
2. EXPERIMENTAL

2.1.Materials and method

Ethanol, dimethyl formamide, salicylealdehyde, 1,6-dibromohexane, diethylether,4,4'-diamino diphenyl methane, 4,4'-diamino diphenyl sulphide, hydrazine hydrate, diethyl ester of terephthalic acid,K_2CO_3,Nutrient agar,Filter paper discs (Whatman No.1 filter paper,5mm diameter).all materials obtained from Sigma Aldrich Company.

IR spectra were recorded on Jusco 300 FT-IR Spectrometer using compressed KBr discs. Mass spectra of the compounds were measured on a micro mass Quattro LC-MS/MS Spectrometer. ^{1}H- NMR spectra were recorded at ambient Broker DT-400 Spectrometer using $CDCl_3$ with DMSO- DMF as the internal standard, M.P Apparatus Digital (32-300 ^{O}C).

2.2. Synthesis of 3, 13-diaza-4, 12 diphenylmethane, (2', 2'-dihydroxy-phenyl) 2, 14-deca-diene.(I)



(I)

Scheme 1

Procedure:

The compound was prepared by a usual[19] Schiff's base condensation in methanol (50mL) of salicylaldehyde (2.44 g , 0.02 mol) with bridging diamine (4, 4'-diamino diphenylmethane(1.98 g, 0.01mol) . The solutions were stirred and refluxed for 6 h. Gold Yellow(scheme 1) precipitate was obtained, filtered then washed by a small amount of methanol and dried in vacuum . Yield:(87%), m.p>300^{0}C), Empirical formula: ($C_{27}H_{22}N_2O_2$), M.Wt: (406).

Mass spectrum (m/z): 406$[C_{27}H_{22}N_2O_2]^+$.

IR (KBr disk): 3415cm^{-1} (-OH), 3066.2 cm^{-1} (C-H ar), 2850.8cm^{-1}(C-H alkanes), 1637.5 cm^{-1} (HC=N), 1284.6cm^{-1}(C-O), 1497.2 cm^{-1} (C=C),. (Figure 1)

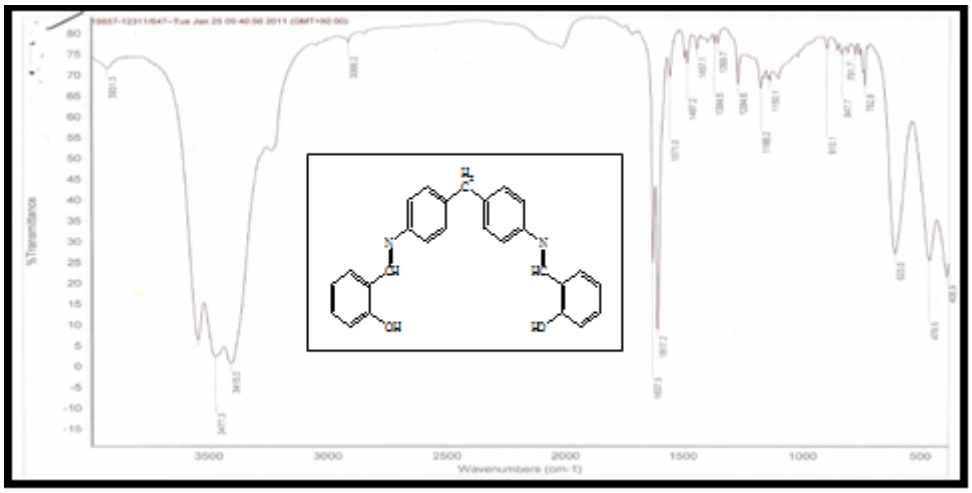


Figure 1: IR spectrum of Schiff base(I)

^{1}H-NMR(DMSO-$d_6$vs.TMS)δ=13.339 (s,2H,OH), 8.65 (s,2H,C=NH), 6.660-7.422 (m,16H,ar), 3.926-4.068 (2H, -CH_2-). (Figure 2).

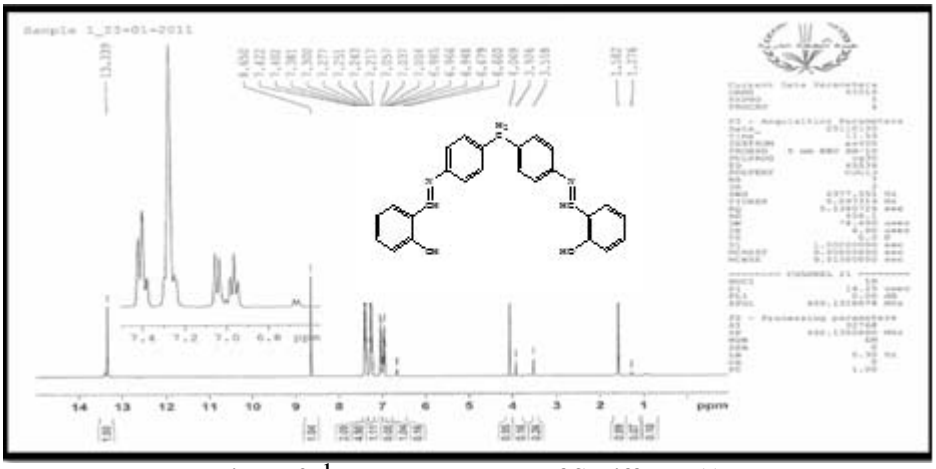
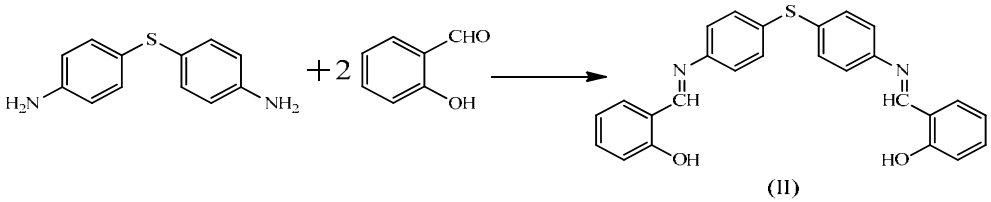


Figure 2. ^{1}H NMR spectrum of Schiff base(I)

2.3. Synthesis of 3, 13-diaza-4, 12 diphenyl sulphide, (2', 2'-dihydroxy phenyl)2, 14-deca-diene (II).



(II)

Scheme 2

A hot ethanolic solution (50ml) of salicylaldehyde(4.88 g,0.04 mol) was added to a hot ethanolic solution (50ml) of 4, 4'-diamino diphenyl sulphide(3.68 g ,0.02 mol) and the reaction mixture was refluxed on a water bath for 5 h. A solid mass (Scheme 2) seprated out on cooling[19].It was suction filtered ,washed with ethanol, diethyl ether and subsequently dried over anhydrous $CaCl_2$ in a disiccator. The Schiff base is soluble in organic solvents.viz., N,N'-dimethylformamide and dimethylsulfoxide.

Yield: (75%), m.p>300^{0}C), Empirical formula: ($C_{26}H_{20}N_2O_2S$), M.Wt:(424).

Mass spectrum(m/z) :424[$C_{26}H_{20}N_2O_2S$]$^+$

IR (KBr disk): 3414.8 cm^{-1}(-OH), 3052 cm^{-1} (C-H ar), 1616.4 cm^{-1} (C=N), 1456.3-1496.7cm^{-1} (C=C), 1284.2cm^{-1} (C-O). (Figure3).

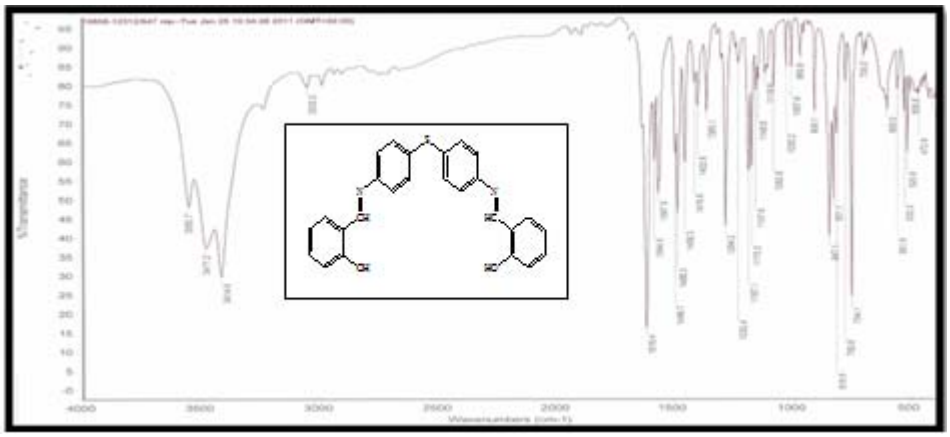


Figure 3: IR spectrum of Schiff base(II)

^{1}H-NMR(DMSO-$d_6$vs.TMS)δ=13.147 (s,2H,OH),8.617-8.657 (s, 2H, CH=N), 6.960-7.451 (m, 16H, ar), (Figure4).

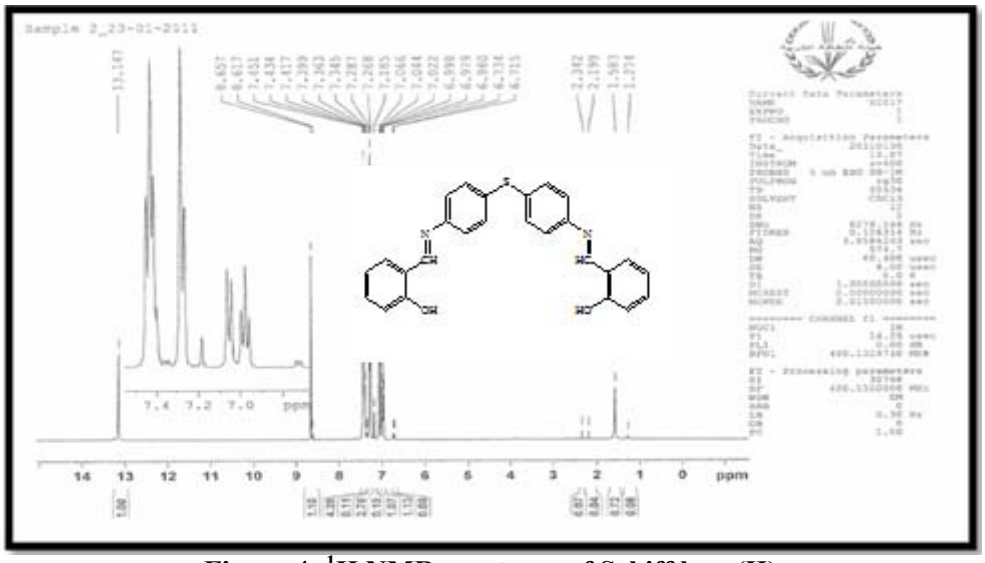
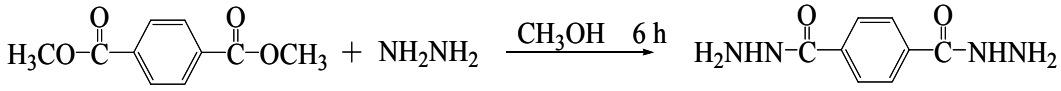
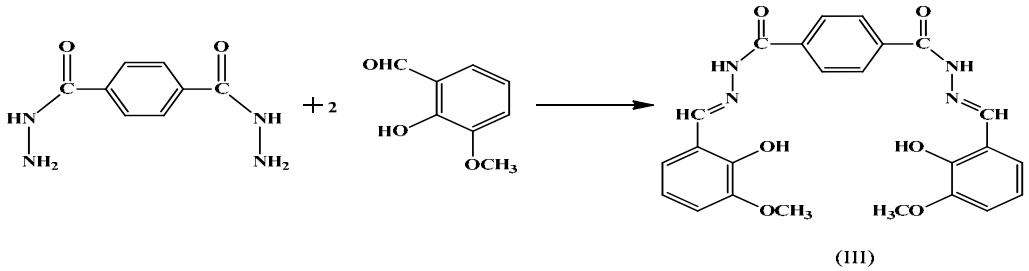


Figure 4: ^{1}H NMR spectrum of Schiff base(II)

2.4. Synthesis of 3, 12-diaza-4, 11-dicarbonyl phenyl dihydrazide, (2', 2'-dihydroxy,3',3'-methoxyphenyl)2, 14-decadiene.(III).



Scheme 3



Scheme 4

Synthesis of dihydrazide of terephthalic acid.[20]

A mixture of dimethyl ester of terephthalic acid (1.66 g , 0.01 mol) and hydrazine hydrate(98% 2 cc) in ethanol was refluxed for 5 h. The reaction mixture was allowed to cool to room temperature, then the cooled solution was poured onto ice cold water. The dihydrazide of

terephthalic acid (Scheme 3) thus obtained was filtered and recrystallized from ethanol .

Yield:(88%),m.p>300^{0}C),
Empirical formula:($C_8H_{10}N_4O_2$) , M.Wt:(194).
Mass spectrum(m/z) :194$[C_8H_{10}N_4O_2]^+$

IR(KBr disk):3314.66cm^{-1} (NH_2), 3197.08 (NH),3097.45cm^{-1},(ar-CH), 1698.7, 1614.9cm^{-1} (C=O),1488.43-1434.90cm^{-1} (C=C),734.38 cm^{-1} (substituted benzene). (Figure 5)

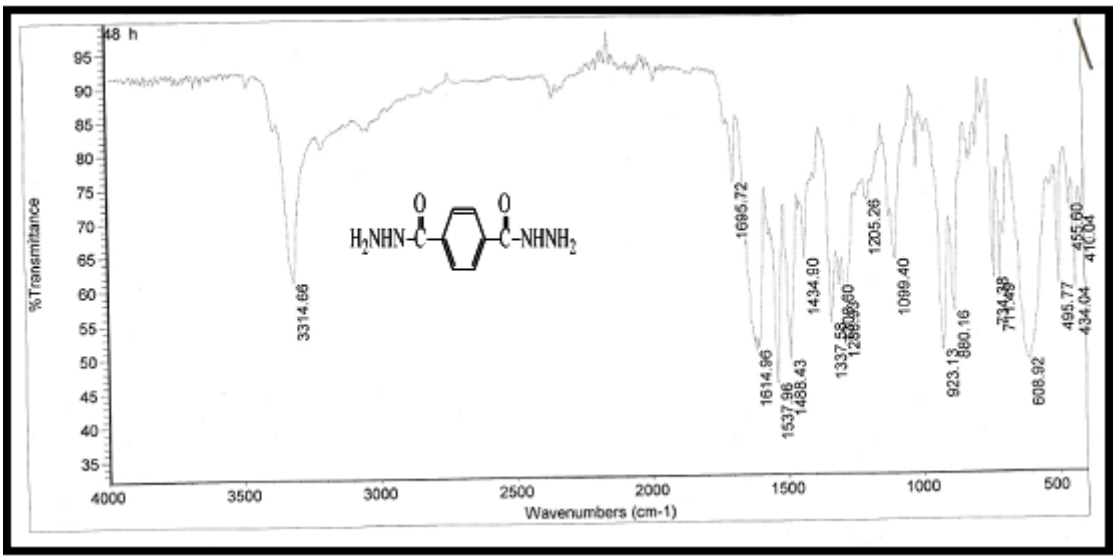


Figure 5: IR spectrum of 1, 4-dicarbonyl phenyl dihydrazide

^{1}H-NMR(DMSO-$d_6$vs.TMS)δ=8.213 (s,4H,ar),8,04(s,-NH-),2.431(s,-NH_2).

Synthesis of Shiff base (III)

o-Vanilin (3.04 g, 0.02 mol) in ethanol (50 mL) was added to an ethanolic solution of 1,4-dicarbonyl phenyl dihydrazide (1.94 g,0.01 mol) in 30 mlof ethanol containing a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h. The mixture was cooled to room temperature .The solid product(Scheme 4) was formed filtered and washed with cold ethanol and dried under vacuum.
Yield: (65%), m.p>300 ^{0}C) , Empirical formula: ($C_{24}H_{22}N_4O_6$), M.Wt:(462).
Mass spectrum (m/z): 462$[C_{24}H_{22}N_4O_6]^+$
IR (KBr disk): 3432.5 cm^{-1} (-OH), 3230.8cm^{-1} (C-NH-), 3000 cm^{-1}(C-H ar), 2950 cm^{-1} (C-H alk), 1645.5cm^{-1} (C=O), 1601.9 cm^{-1} (C=N), 1285.7cm^{-1}(C-O), 1451.5 cm^{-1} (C=C), (Figure 6).

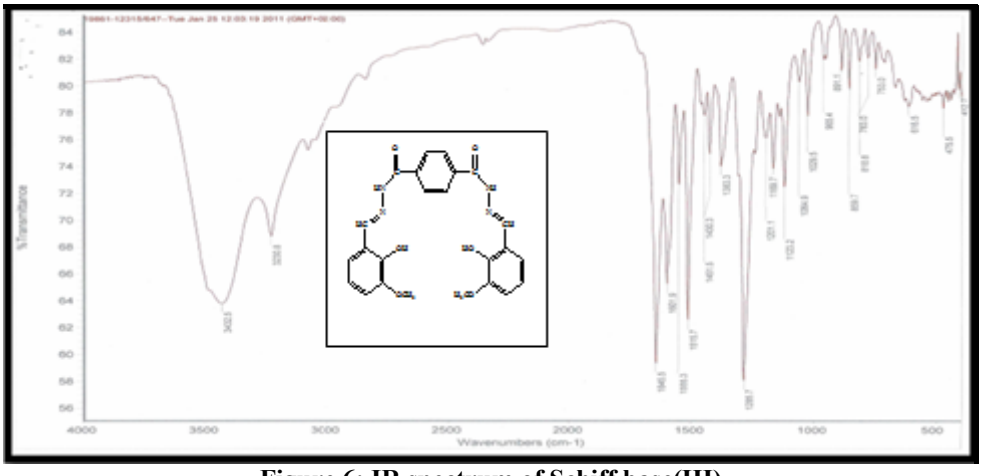


Figure 6: IR spectrum of Schiff base(III)

^{1}H-NMR (DMSO-$d_6$vs.TMS)δ = 13.327 (s,2H,OH), 9.845(NH-C=O), 7.285-8.285 (m,12H,ar), 8.601 (s,2H,C=NH), 3.713-3.763 (s,6H,O-CH_3) (Figure 7).

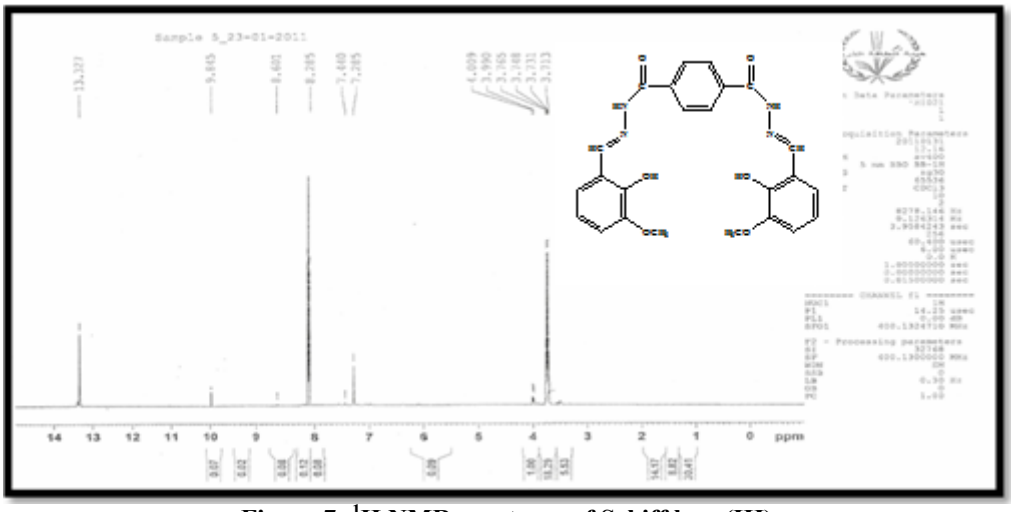
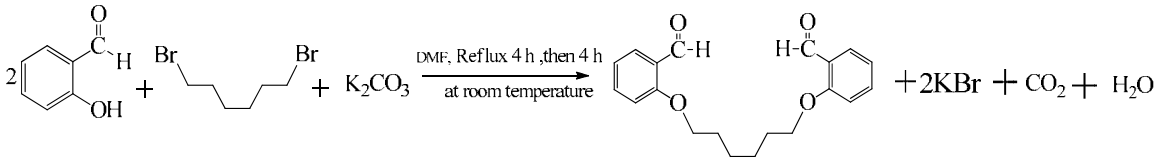
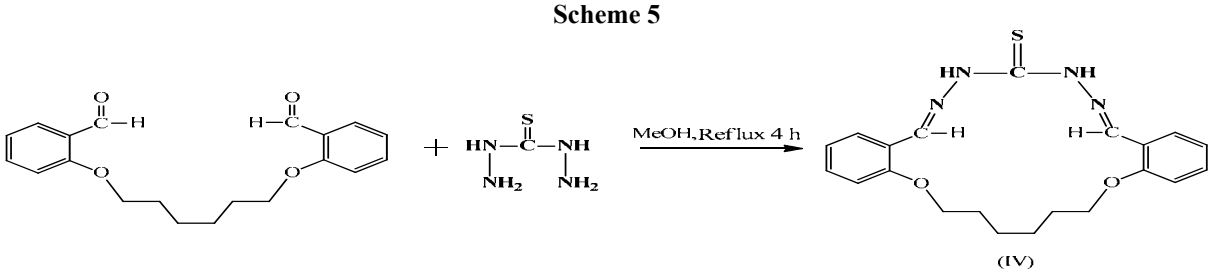


Figure 7: ^{1}H NMR spectrum of Schiff base(III)

2.5.Synthesis of 1, 16-diaza-(3,4;13,14-dibenzo)-17, 19- thiourea -5, 8, 11, 14-Tetra-oxacyclo heptacosine-1, 15-diene(IV).



Scheme 5



Scheme 6

Synthesis of 1, 6- bis (2- formyl phenel) hexane .[21]

To a stirred solution of salicylaldehyde (12.2 g ,0.1 mol) and K_2CO_3(6.9 g, 0.5 mol) in DMF (50ml) 1,6-dibromohexane (12.2 g , 0.5 mol) in DMF(10ml) was added dropwise, the reaction was continued with stirring for 10h at 150-155^{0}C and then 5h at room temperature. After the addition was completed, 20ml distilled water was added it was cooled in a refrigerator, 1h later the precipitate (Scheme 5) was filtered washed by 500 ml water , dried in air, recrystallized from ethanol.

Yield:(88%),m.p=75^{0}C), Empirical formula: ($C_{20}H_{22}O_4$), M.Wt:(326).

Mass spectrum (m/z):326$[C_{20}H_{22}O_4]^+$.

IR(KBr disk): 2951.56-2930.91 cm^{-1} (ar-CH), 2852.22 cm^{-1}(alk.-CH) , 1681.49cm^{-1} (C=O), 1486.90-1455 cm^{-1} (ar-C=C) ,1285.22-1245.16cm^{-1} (Ar-O),1189.96-1074.42 cm^{-1} (R-O), 756 cm^{-1} (substituted benzene).(Figure 8).

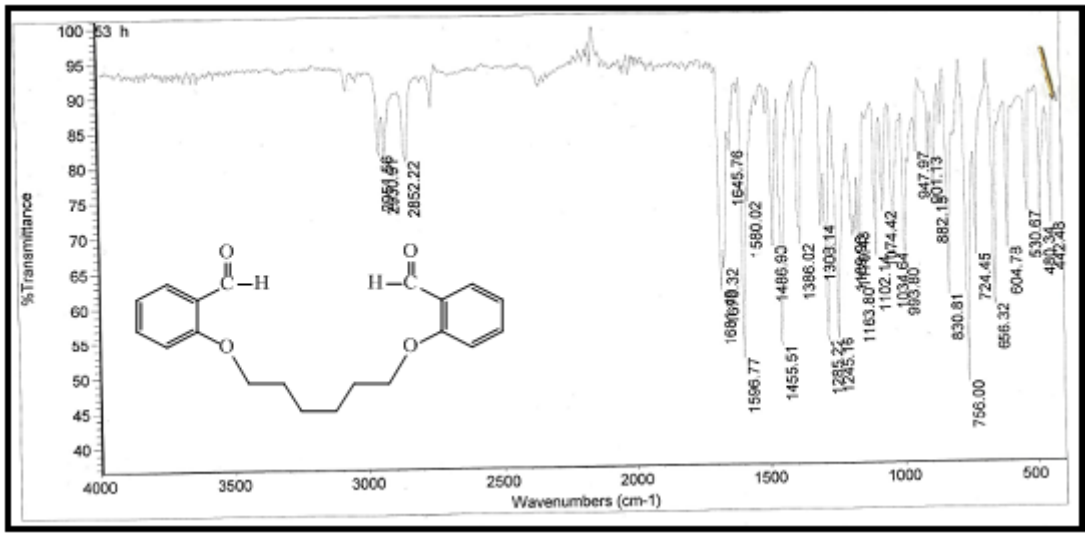


Figure 8: IR spectrum of 1, 6-bis (2-formylphenyl)hexane

^{1}H-NMR(DMSO$d_6$vs.TMS)δ=1.49 (t,4H,J=7.6, $CH_2CH_2CH_2$:),1.78(p,4H,J=6.2,CH_2CH_2O), 4,11 (t,4H,J=6.4,CH_2CH_2O),7.13-7.89 (m,8H,ar-H) , 10.37(S,2H,HC=O).

2.6.Synthesis of the macrocyclic Schiff base(IV):

The macrocyclic ligand (IV) was prepared by dropwise addition of a solution of the thiocarbohydrazide(2.12 g , 0.02 mol)in methanol(40 ml) to a stirred solution of 1,6-bis(2-formylphenyl) hexane(6.52 g ,0.02 mol) in methanol (60 ml). After the addition was completed, stirring was continued for 4 h. yellow colored precipitate was filtered and washed with methanol. Yield: (65%), m.p>300^{0}C),Empirical formula: ($C_{21}H_{24}N_4O_2$), M.Wt:(396).

Mass spectrum (m/z) :396$[C_{21}H_{24}N_4O_2]^+$

IR (KBr disk): 3414.3-3477 cm^{-1} (H_2O), 3236.8 (C-NH-),2939.3 cm^{-1} (C-H ar), 2869cm^{-1}(C-H alkanes), 1637.2cm^{-1},1616.8 (C=N), , 1455.3-1486.2 cm^{-1}(C=C), ,1245.2cm^{-1} (C-O),1106.5-1160.5(R-O),752.7cm^{-1} (C=S).(Figure9).

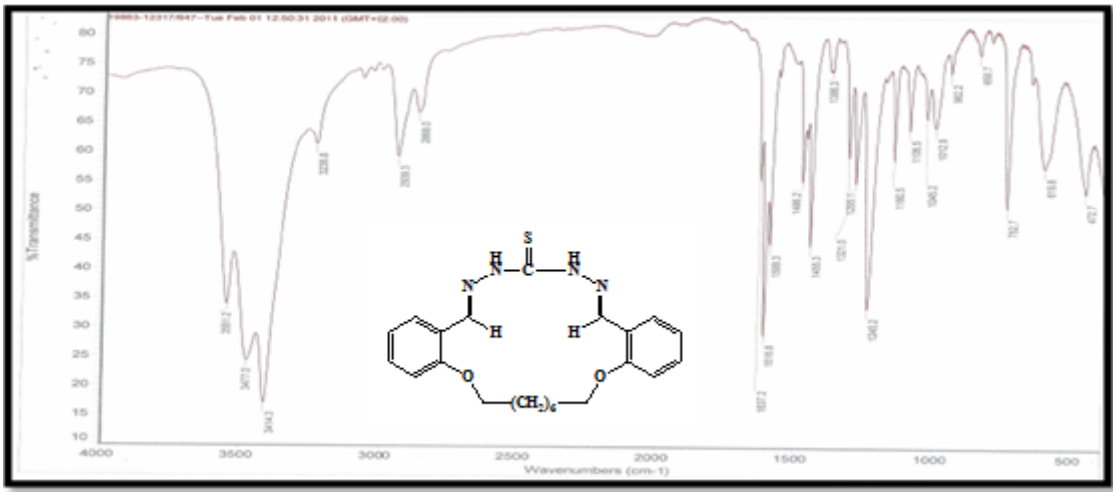


Figure 9: IR spectrum of Schiff base(IV)

^{1}H-NMR(DMSO$d_6$vs.TMS)δ= 1.908-2.103 (8H,CH_2CH_2),6.987-7.663 (m,8H,ar-H) , 3.262-3.491(4H,O-CH_2) 8.3(2H,HC=N),2.95(-NH-) (Figure 10).

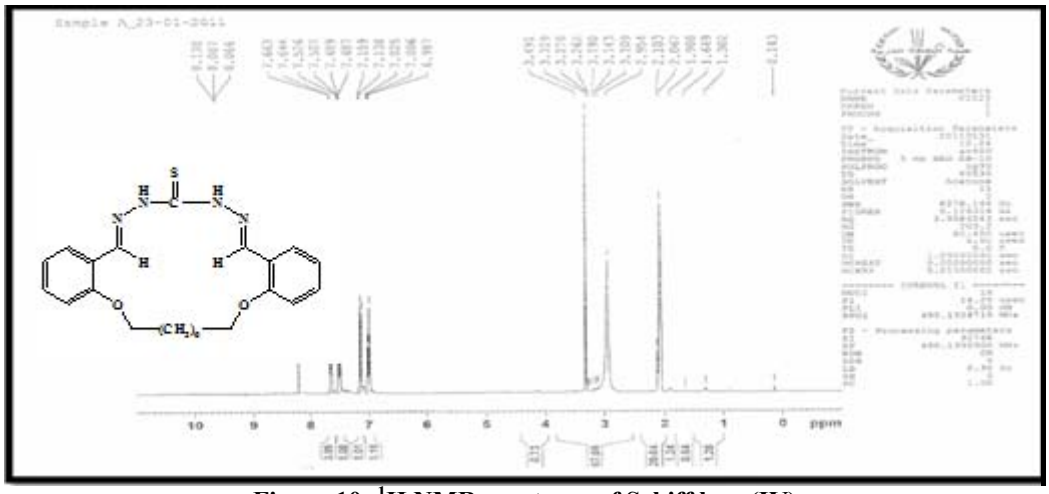


Figure 10: ^{1}H NMR spectrum of Schiff base(IV)

2.7.Biological Activity

The prepared compounds were tested for their antimicrobial activity against four speices of bacteria (klebcella, Escherichia coli ، Staphylococcus aureus ، Salmonella typhi) using filter paper disc method[22].The screened compounds were dissolved individually in DMSO (dimethyl sulfoxide) in order to make up a solution of 1000 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. Ampicillin 25 µg/ml was used as reference substance for bacteria.[22].

3.Result and Discussion :

The prepared organic compounds(I, II, III, IV) were soluble in DMF, DMSO and partially soluble in acetone, chloroform, carbon tetra chloride. All the compounds are characterized by LC-MS, IR, ^{1}H-NMR spectra, which help in elucidating their empirical formula (Table 3.1)

Table 3.1: Color, molecular weight, melting point of (I, II, III, IV).

Shiff base	Color	M.Wt	Melting point^{0}C
I	Gold Yellow	406	> 300 ^{0}C dec.
II	Brown	424	> 300 ^{0}C dec.
III	Yellowish white	462	> 300 ^{0}C dec.
IV	yellow	396	> 300 ^{0}C dec.

dec = decomposition

3.1. IR Spectra

Table 3.2: IR spectral data (cm^{-1}) of Schiff bases (I, II, III, IV)

Shiff base	v(C=N)	v(C-O)	v(OH)	v(CH-ar)	v(NH)	v(CH-alka)	v(C=O)
I	1637.5	1284.6	3415-3551.7	3066.2	-	2850.8	-
II	1616.4	1284.2	3414.8-3550.7	3052	-	-	-
III	1601.9	1285.7	3432.5	3000	3230.8	2950	1723.88
IV	1637.2	1245.2	-	2939	3236.8	2869	-

The IR Spectral data are shown in table (3.2) of the preponed schiff bases. The four bands at 1637.5, 1616.4, 1601.9 ,1637.2 cm^{-1} are attributed to imine group (-HC=N-) for (I, II, III, IV) (Figures 1, 3, 6, 9), respectively. The bands in the spectra at 1497.2, 1456.3-1496.7, 1451.5 and 1455.3-1486.2 is due to (C=C) of aromatic rings , The v(OH) stretching frequencies bands are observed at 3415, 3414.8, 3432.5 cm^{-1} for (I , II, III), respectively. Also, a strong v(H_2O) band of compound (IV) at 3414-3477 was also observed.The IR spectra of (III, IV) show characteristic absorption bands at 3230.8 and 3236.8 cm^{-1} due to v(-NH-) stretching vibrations,respectively.The bands which observed for all compounds at 1284.6,1284.2, 1285.7 and 1245.2 cm^{-1} due to v(C-O) vibration.while the bands at 2850.8,2950 and 2869-2939 cm^{-1} are attributed to (C-H alkanes) for(I,III,IV) respectively .Also, the bands at 3066.2, 3052, 2939 and 3000 $cm^{-1}$are attributed to (C-H ar) for (I, II, IV, III) respectively.[16]

3.2. ^{1}H-NMR Spectra of Ligands (I, II, III, IV)

The data of ^{1}H-NMR Spectra of prepared compounds are shown in table (3.3).The ^{1}H-NMR spectra of (I,II,III,IV) ligands in d_6-DMSO (Figures 2, 4, 7, 10) shows a singlet signal at 13.339,13.147 and 13.327ppm assigned to the protons OH groups of the Ligands (I, II , III) respectively.The multiplet signals 6.660-7.422, 6.960-7.451,7.285-8.285and6.987-7.663ppm are due to the aromatic protons for (I,II,III,IV) respectively.Also the signals at 8.65, 8.617, 8.601 and 8.3 ppm are assigned to the 2H, (HC=N) protons of the Ligands (I, II, III), respectively.

Table 3.3: ^{1}H-NMR Spectra of Ligands (I, II, III, IV)

Shiff base	(s,2H,OH)	(m,H,ar)	(s,2H,C=NH)
I	13.339	6.660-7.422	8.65
II	13.147	6.960-7.451	8.617
III	13.327	7.285-8.285	8.601
IV	-	6.987-7.663	8.3

3.3. Biological Activity

During the last two or three decades, attention has been increasingly paid to the synthesis of Schiff bases which exhibits various biological activities including antibacteria, fungicidal, tuberculostatic and plant growth regulative properties [22]. It was judicious to investigate the synthesis of various new types of Schiff bases and studied their antibacterial activity against four strains of bacteria (klebcella, Escherischa coli, Staphylococcus aureus, Salmonella typhimurium).The concentration used for the screened compounds is 1000 µg/ml. Control discs were preformed using DMSO solvent and inhibition zones are measured in mm.The results of antibacterial activity were compared with 25µg/ml Ampcilline [23].The results of the antibacterial activity are summarized in (Table 3.4)

Table 3.4: Effect of the compounds (I, II, III, IV) on the growth of Bacteria (Zone of inhibition in mm)

Bacteria				Schiff base (1000 µg/ml)
Gram-positive	Gram- negative			
Staphyllococcus aureus	klebcella	Salmonella typhi	Escherichia coli	
++	+	+	+	I
+++	+	++	++	II
+++	+	+	+	III
++	-	-	-	IV
+	+	+	+	Ampicillin (25 µg/ml)

(-)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.

The compounds (I,III) show moderate activity against the gram-negative bacteria,except (II) against Escherichia coli , Salmonella typhi show high activity.Also, the Shiff bases (I,IV) show

moderate a ctivity against the gram- positive bacteria,except (II,III) against Staphyllococcus aureus show high activity.
The compound (IV) don't have significant activity against the gram-negative bacteria.

4.conclusion

1- The (I, II, III, IV) compounds are new and were prepared for the first time.
2- The new compounds were identified by ^{1}H-NMR, IR, LC-MS spectral methods.
3-Some of the prepared compounds have been biologically screened i.e. studying their effects against gram-positive,three gram-negative bacteria. The results show that their activities were found to vary from moderate to very strong.

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