

## Synthesis , Characterization and antibacterial activity of Several New Schiff Bases Linked to Phthalimide Moiety

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### Abstract

Some novel Schiff bases linked to phthalimide moiety have been synthesized via multistep synthesis. The first step involved reaction of phthalic anhydride with aniline producing N-phenyl phthalamic acid which was subsequently dehydrated to the corresponding N-phenyl phthalimide via treatment with acetic anhydride and anhydrous sodium acetate. The synthesized imide was treated with chlorosulfonic acid in the third step producing 4-(N-phthalimidyl)phenyl sulfonyl chloride which on amination with hydrazine hydrate in the fourth step afforded 4-(N-phthalimidyl)phenyl sulfonyl hydrazine and this in turn when introduced in condensation reaction with various aromatic aldehydes and ketones afforded the desirable new Schiff bases.

Structures of the prepared compounds were elucidated on the basis of FTIR, <sup>1</sup>HNMR and <sup>13</sup>CNMR spectral data which agreed with the proposed structures.

The synthesized compounds were screened for their antibacterial activity against two microorganisms *Staphylococcus aureus* and *Escherichia Coli* and they were found to exhibit good to moderate antibacterial activity.

**Keywords:** Phthalic anhydride, phthalimide, Schiff bases.

### تحضير وتشخيص مع تقدير الفعالية المضادة للبكتريا لعدد من قواعد شيف الجديدة المرتبطة بمكونة الفثال ايميد

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### الخلاصة

تم في هذا البحث تحضير عدد من قواعد شيف الجديدة المرتبطة بمكونة الفثال ايميد وذلك من خلال انجاز التحضير المتعدد الخطوات حيث تم في الخطوة الاولى اجراء تفاعل بين انهيدريد الفثاليك والانيلين للحصول على حامض N- فنيل اميك الذي سحب منه الماء في الخطوة الثانية من خلال معاملته مع انهيدريد الخليك وخلات الصوديوم اللامائية للحصول على N- فنيل فثال ايميد. اما في الخطوة الثالثة فقد تم معاملة N- فنيل فثال ايميد المحضر مع كلورو حامض السلفونيك للحصول على 4- (N- فثال ايميديل) فنيل كلوريد السلفونيك والذي بدوره ادخل في تفاعل مع الهيدرازين في الخطوة الرابعة لانتاج 4- (N- فثال ايميديل) فنيل سلفونيل هيدرازين والذي تم ادخاله في الخطوة الخامسة في تفاعل تكاثف مع الديهايدات و كيتونات مختلفة لانتاج قواعد شيف الجديدة. تم اثبات صحة تراكيب المركبات المحضرة من خلال الاعتماد على مطيافية الاشعة تحت الحمراء FTIR والرنين النووي المغناطيسي بنوعيه <sup>1</sup>HNMR و <sup>13</sup>CNMR حيث كانت النتائج المستحصلة مطابقة للتراكيب المقترحة. كذلك تضمن البحث دراسة الفعالية البيولوجية لعدد من قواعد شيف المحضرة ضد انواع البكتريا وقد اظهرت النتائج بان لقواعد شيف المحضرة فعالية جيدة ضد انواع البكتريا قيد الدراسة.

## **Introduction**

Nitrogen heterocycle is an important part of the chemical structures of many natural and synthetic products with a variety of properties and applications in medicine<sup>(1)</sup>. Among the bicyclic non-aromatic nitrogen heterocycles, phthalimides are an interesting class of compounds with a large range of applications<sup>(2)</sup>. Phthalimides have served as starting materials and intermediates for the synthesis of many types of alkaloids and pharmacophores<sup>(3)</sup>. Recently, phthalimide and some of its derivatives have proved to have important biological effects similar or even higher than known pharmacological molecules and so their biological activity is being a subject of biomedical research<sup>(4-7)</sup>. On the other hand Schiff bases belong to a widely used group of organic intermediates important for production of specially chemicals like pharmaceuticals or rubber additive<sup>(8)</sup>. They also have uses in many fields including analytical<sup>(9)</sup>, inorganic<sup>(10)</sup>, medicinal<sup>(11,12)</sup> and polymer chemistry<sup>(13)</sup>. Moreover Schiff bases are also known to have biological activities such as antimicrobial<sup>(14)</sup>, antifungal<sup>(15)</sup>, antitumor<sup>(16)</sup> and as herbicides<sup>(17)</sup>. Keeping in view the facts mentioned we thought it is worthwhile to synthesize new Schiff bases containing phthalimide moiety which were predicated to have useful biological activities.

## **Experimental**

Melting points were determined on Thomas Hoover apparatus and were uncorrected. FTIR spectra were recorded on SHIMADZU FTIR-8400 Fourier Transform Infrared spectrophotometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on Bruker 300MHz instrument in Al-Albata University in Jordan using

tetramethylsilane (TMS) as an internal standard and DMSO-d<sub>6</sub> as a solvent.

### **1. Synthesis of N-Phenylphthalamic acid [1]**

Literature procedures<sup>(18)</sup> were used in preparation of the titled compound with minor modification. To a solution of (0.01 mole) of phthalic anhydride in (25 mL) of acetone, (0.01 mole) of aniline was added dropwise with stirring and cooling. Stirring was continued for two hours at room temperature then the resulted precipitate was filtered, dried then purified by recrystallization from ethanol.

### **2. Synthesis of N-Phenylphthalimide [2]**

A mixture of (0.01 mole) of N-phenylphthalamic acid in (25 mL) of acetic anhydride and (5%) by weight of anhydrous sodium acetate was refluxed for two hours with stirring<sup>(19)</sup>. The resulted homogenous solution was cooled to room temperature before pouring into crushed ice then the obtained precipitate was filtered, dried and purified by recrystallization from acetone.

### **3. Synthesis of 4-(N-phthalimidyl)phenylsulfonyl Chloride [3]**

Chlorosulfonic acid (4 mL) was added dropwise to (0.01 mole) of N-phenylphthalimide during two hours with stirring and keeping temperature at zero°C<sup>(19)</sup>. Stirring was continued for ten hours at room temperature then the resulted mixture was poured into crushed ice carefully with stirring. The obtained precipitate was filtered, washed thoroughly with cold water, dried and purified by recrystallization from acetone.

### **4. Synthesis of 4-(N-phthalimidyl)phenylsulfonyl hydrazine [4]**

To a solution of (0.01 mole) of compound [3] in (5 mL) of absolute

ethanol, (0.01 mole) of hydrazine hydrate was added dropwise with stirring and keeping temperature at (zero)°C. The resulted mixture was refluxed for 6 hours then cooled to room temperature before pouring on crushed ice with stirring. The resulted precipitate was filtered, washed with cold water, dried and finally recrystallized from ethanol. Physical properties of compounds [1-4] are listed in Table (1).

#### **5. Synthesis of Schiff Bases [5-18]**

A mixture of 4-(N-phthalimidyl)phenylsulfonyl hydrazine (0.01 mole), aromatic aldehyde or ketone (0.01 mole) and (2-3) drops of glacial acetic acid in absolute ethanol (20 mL) was refluxed for 6 hours<sup>(20)</sup>. After cooling the obtained precipitate was filtered then washed with cold ethanol, dried and recrystallized from a suitable solvent. Physical properties of compounds [5-18] are listed in Table (2).

#### **6. Biological study**

The cup plate method using nutrient agar medium was employed in studying the antibacterial activity of the prepared imides against two types of bacteria, *Staphylococcus aureous* (Gram positive) and *Escherichia Coli* (Gram negative). DMF was used as sample solution and sample size for all the compounds was fixed at (0.1 mL). Using a sterilized cork borer cups were scooped out of agar medium contained in a petridish which was previously inoculated with the microorganisms. The tested compound solution (0.1 mL) was added in the cups and the Petridishes were subsequently

incubated at 37°C for 48 hrs. Zones of inhibition produced by each compound was measured in mm and the results are listed in Table (5).

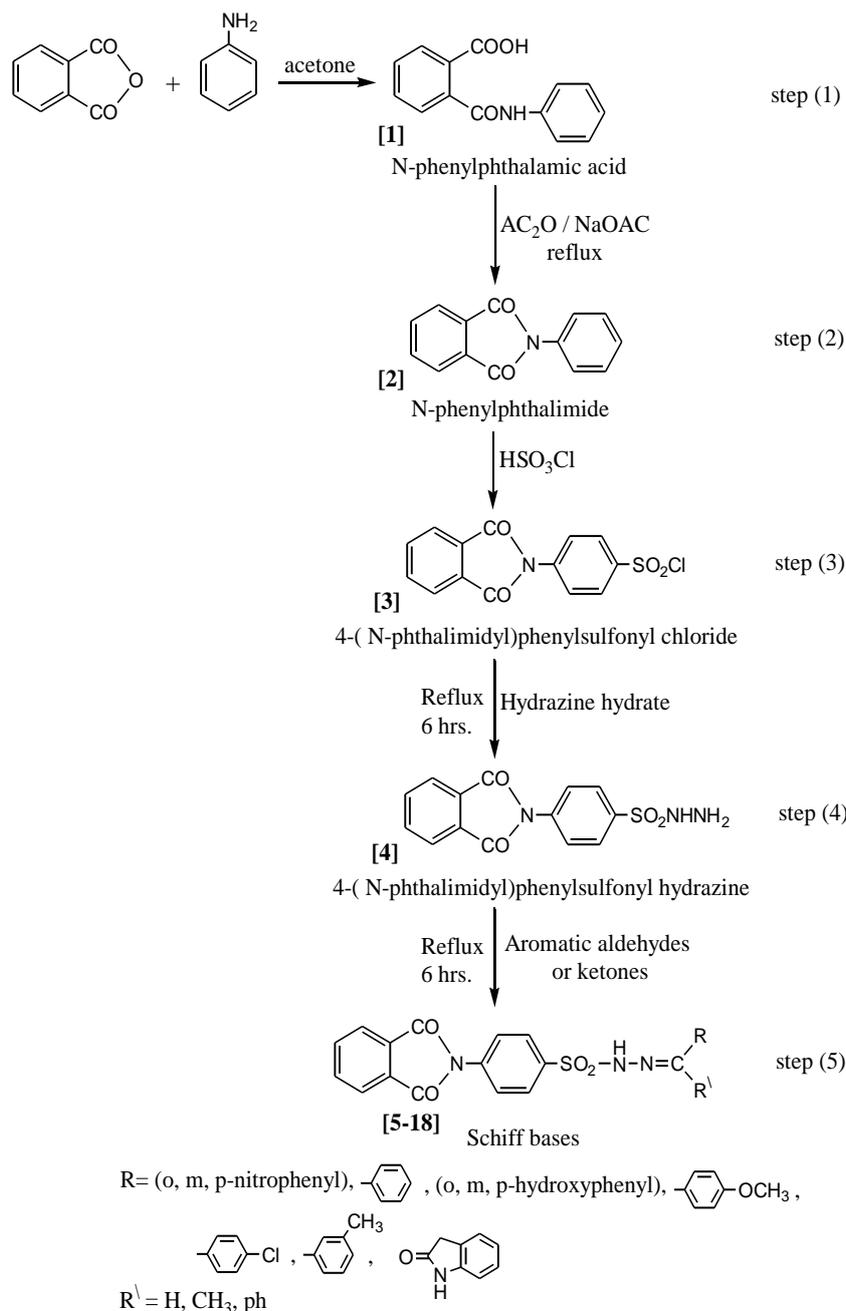
#### **Results and Discussion**

Since both N-substituted phthalimides and Schiff bases are known biologically active compounds having wide spectrum of various applications, the target of the present work has been directed toward building of new molecules containing these two active moieties (phthalimide and Schiff base) with expected biological activity.

Performing this target was made by multistep synthesis described in Scheme (1).

The first step involved synthesis of N-phenyl phthalamic acid via reaction of equimolar amounts of phthalic anhydride and aniline<sup>(18)</sup>. The prepared phthalamic acid was introduced in dehydration reaction in the second step via treatment with acetic anhydride and anhydrous sodium acetate as dehydrating agent.

This step involved both dehydration and cyclization under the influence of acetic anhydride and the catalyst NaOAC producing N-phenyl phthalimide [2]. In the third step the prepared imide was introduced in chlorosulfonation reaction via treatment with chlorosulfonic acid producing compound [3] which in turn was introduced subsequently in reaction with hydrazine hydrate producing phthalimidyl phenylsulfonyl hydrazine [4]. In the final step of this work the prepared hydrazine derivative [4] was introduced in condensation reaction with different aldehydes and ketones producing the desirable Schiff bases [5-18].



Scheme(1)

The strategy which we depend on in building the new Schiff bases involved introducing of sulfonyl chloride group in para position of phenyl ring attached to phthalimide moiety followed by nucleophilic replacement of chloride with hydrazine moiety which created a suitable position represented by amino group which in turn was ready for condensation with different aldehydes

and ketones producing the desirable Schiff bases.

Structures of the prepared compounds were confirmed by FTIR, <sup>1</sup>HNMR and <sup>13</sup>CNMR spectral data.

FTIR spectrum of compound [1] showed strong absorption bands at 3325 cm<sup>-1</sup> and at 3136 cm<sup>-1</sup> due to ν(O-H) carboxylic and ν(N-H) amide. Other absorption bands appeared at 1720, 1643 and at 1600 cm<sup>-1</sup> belong to

$\nu(\text{C}=\text{O})$  carboxylic,  $\nu(\text{C}=\text{O})$  amide and  $\nu(\text{C}=\text{C})$  aromatic respectively. FTIR spectrum of compound [2] showed disappearance of  $\nu(\text{O}-\text{H})$  and  $\nu(\text{N}-\text{H})$  absorption bands proving success of dehydration reaction and appearance of two bands at  $1735\text{ cm}^{-1}$  and  $1708\text{ cm}^{-1}$  due to asym., and sym., bands of  $\nu(\text{C}=\text{O})$  imide.

FTIR spectrum of compound [3] showed two clear bands at  $1365\text{ cm}^{-1}$  and  $1188\text{ cm}^{-1}$  due to  $\nu(\text{SO}_2)$  asym., and  $\nu(\text{SO}_2)$  sym., respectively indicating success of introducing sulfonyl chloride moiety in phenyl phthalimide molecule.

Finally FTIR spectrum of compound [4] showed two strong absorption bands at  $3359\text{ cm}^{-1}$  and  $3265\text{ cm}^{-1}$  respectively which belong to  $(-\text{NH}-\text{NH}_2)$  group and this is an excellent proof for the success of hydrazine compound formation. FTIR spectra of the prepared Schiff bases [5-18] showed disappearance of the two characteristic absorption bands at  $(3359\text{ and }3265)\text{ cm}^{-1}$  which belong to  $(-\text{NH}-\text{NH}_2)$  group in hydrazine compound [4] and appearance of new clear absorption band at  $(1608-1658)\text{ cm}^{-1}$  due to  $\nu(\text{C}=\text{N})$  imine. These two points are excellent proofs for the success of Schiff base formation<sup>(21)</sup>.

Besides FTIR spectra of Schiff bases [5-18] showed also clear absorption bands at  $(1735-1743)\text{ cm}^{-1}$  and  $(1706-1720)\text{ cm}^{-1}$  which were attributed to asym., and sym.,  $\nu(\text{C}=\text{O})$  imide.

Other absorptions appeared at  $(1573-1604)\text{ cm}^{-1}$ ,  $(1373-1388)\text{ cm}^{-1}$ ,  $(1157-1170)\text{ cm}^{-1}$  and  $(1315-1348)\text{ cm}^{-1}$  which belong to  $\nu(\text{C}=\text{C})$  aromatic, asym.,  $\nu(\text{SO}_2)$  sym.,  $\nu(\text{SO}_2)$  and  $\nu(\text{C}-\text{N})$  imide respectively.

Moreover FTIR spectra of Schiff bases [6, 8, 12, 15] showed clear absorption band at  $(3429-3479)\text{ cm}^{-1}$  belong to  $\nu(\text{O}-\text{H})$  phenolic, while compound [7] showed two absorption

bands at  $(1234\text{ and }1126)\text{ cm}^{-1}$  belong to  $(\text{C}-\text{O}-\text{C})$  ether and finally compound [14] showed strong absorption band at  $(1091)\text{ cm}^{-1}$  due to  $\nu(\text{C}-\text{Cl})$ .

All details of FTIR spectral data of compounds [1-4] and [5-18] are listed in Table (3) and (4) respectively.

On the other hand  $^1\text{H}$ NMR and  $^{13}\text{C}$ NMR spectra of the prepared compounds showed characteristic clear signals thus  $^1\text{H}$ NMR spectrum of compound [1] showed signals at  $\delta=(7.04-7.89)$  ppm belong to aromatic protons and NH proton. A clear signal appeared at  $\delta = 10.33$  ppm belong to  $(\text{OH})$  carboxylic proton.  $^{13}\text{C}$ NMR spectrum of compound [1] showed signals at  $\delta = (119.9-140)$  ppm,  $167.8$  and  $167.92$  ppm which belong to aromatic ring carbons,  $(\text{C}=\text{O})$  amide and  $(\text{C}=\text{O})$  carboxyl respectively<sup>(21)</sup>.

$^1\text{H}$ NMR spectrum of compound [2] N-phenyl phthalimide showed disappearance of  $(\text{OH})$  carboxyl proton signal and appearance of two multiplet signals at  $\delta = (7.44-7.56)$  and  $(7.89-7.97)$  ppm belong to protons of two aromatic rings.  $^{13}\text{C}$ NMR spectrum of compound [2] showed signals at  $\delta=(123.8-135.1)$  ppm and at  $\delta = 167.4$  ppm which belong to aromatic ring carbons and  $(\text{C}=\text{O})$  imide respectively.

$^1\text{H}$ NMR spectrum of compound [4] 4-(N-phthalimidyl) phenyl sulfonyl hydrazine showed signals at  $\delta=(3.5\text{ and }3.8)$  ppm which belong to  $\text{NH}_2$  and NH of hydrazine moiety while signals of aromatic protons appeared at  $\delta=(7.39-7.99)$  ppm.

$^{13}\text{C}$ NMR spectrum of compound [4] showed signals at  $\delta = (124-137.9)$  and  $(167)$  ppm which belong to aromatic ring carbons and  $(\text{C}=\text{O})$  imide respectively.

$^1\text{H}$ NMR spectrum of Schiff base [5] showed signal at  $\delta = 1.4$  ppm belong to  $(\text{CH})$  protons, multiplet signals at  $\delta = (7.39-8.34)$  ppm belong to aromatic

protons and signal at  $\delta = 8.97$  ppm belong to imine (-CH=N-) proton.

$^{13}\text{C}$ NMR spectrum of compound [5] showed signals at  $\delta = 24.97$ , (123.8-134.4), 135.3 and 159.1 ppm which belong to CH<sub>3</sub>, aromatic ring carbons, (C=N) and (C=O) imide respectively.

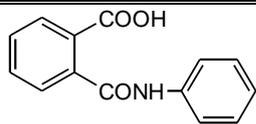
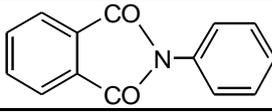
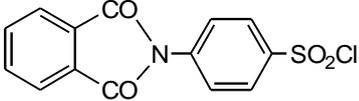
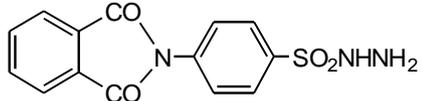
$^1\text{H}$ NMR spectrum of Schiff base [7] showed signal at  $\delta = 3.51$  ppm due to OCH<sub>3</sub> protons and four multiplet signals at  $\delta = (6.89-7.96)$  ppm belong to aromatic protons.

$^{13}\text{C}$ NMR spectrum of Schiff base [7] showed signal at  $\delta = 57$  ppm belong to OCH<sub>3</sub> group and signals at  $\delta = (123.9-127.1)$ , 135.1 and 168 ppm belong to aromatic carbons, (C=N) and (C=O) imide respectively.

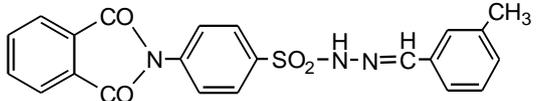
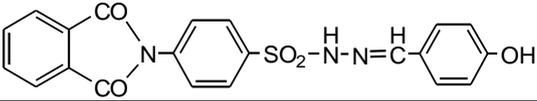
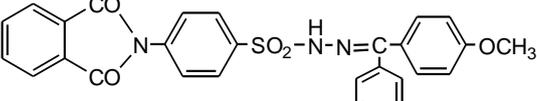
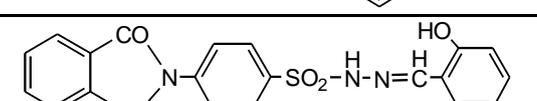
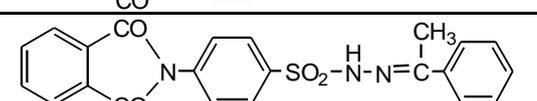
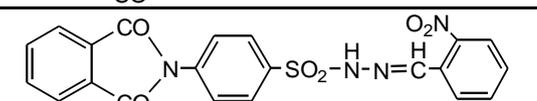
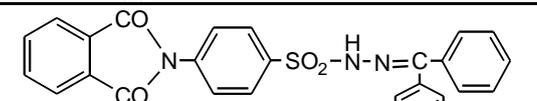
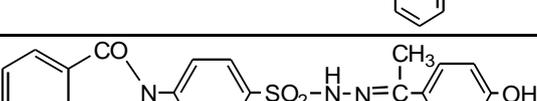
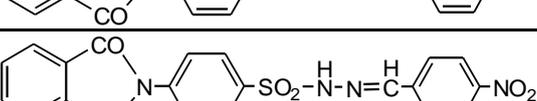
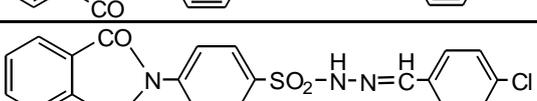
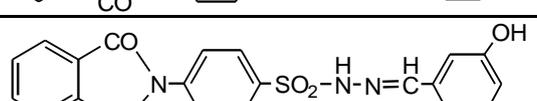
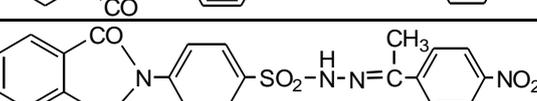
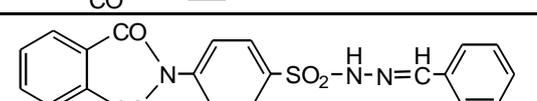
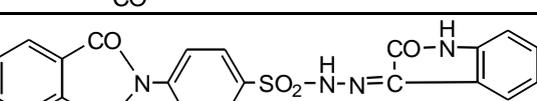
### **Biological activity**

Antibacterial activities for some of the prepared Schiff bases against two types of bacteria were evaluated and the results which are listed in Table (5) indicated that compounds [6,7,12] showed very high activity against *S.aureus*, compounds [5,17,18] showed high activity against this bacteria while compounds [10,14,16] showed moderate activity and compound [11] showed no activity against this bacteria. On the other hand compounds [7,18] showed very high activity against *E.coli*, compounds [10,14,16] showed high activity against this bacteria while compounds [5,11,12,17] showed moderate activity and compound [6] was found not active against this bacteria.

**Table (1): Physical properties of prepared compounds [1-4]**

Comp. No.	Compound structure	color	Melting points °C	Yield %	Solvent of Recrystallization
1		White	170-172	88	Ethanol
2		Off white	204-205	85	Acetone
3		Brown	200 dec.	72	Acetone
4		White	210 dec.	95	Ethanol

**Table (2): Physical properties of Schiff bases [5-18]**

Comp. No.	Compound structure	color	Melting points °C	Yield %	Solvent of Recrystallization
5		Pale yellow	119-120	85	Acetone
6		Orange	168-170	87	Acetone
7		Off white	192-193	81	Ethanol
8		Deep yellow	196-198	54	Acetone
9		White	179-181	80	Ethanol
10		Off white	138-139	66	Ethanol
11		Off white	200 dec.	72	Acetone
12		Off white	174-175	63	Ethanol
13		Pale yellow	130-132	91	Ethanol
14		White	226 dec.	77	Ethanol
15		Off white	135-136	83	Acetone
16		Pale yellow	> 220	93	Ethanol
17		White	187-188	90	Acetone
18		Yellow	198 dec.	86	Ethanol

**Table (3): FTIR spectral data of compounds [1-4]**

Comp. No.	FTIR spectral data $\text{cm}^{-1}$						
	$\nu(\text{O-H})$ carboxylic	$\nu(\text{N-H})$ amide	$\nu(\text{C-H})$ aromatic	$\nu(\text{C=O})$ carboxylic	$\nu(\text{C=O})$ amide	$\nu(\text{C=C})$ aromatic	
1	3325	3136	3062	1720	1643	1600	
Comp. No.	$\nu(\text{C-H})$ aromatic	$\nu(\text{C=O})$ imide		$\nu(\text{C=C})$ aromatic		$\nu(\text{C-N})$ imide	
2	3074	1735 1708	1593	1384			
Comp. No.	$\nu(\text{C-H})$ aromatic	$\nu(\text{C=O})$ imide	$\nu(\text{C=C})$ aromatic	$\nu(\text{SO}_2)$ asym.	$\nu(\text{SO}_2)$ sym.	$\nu(\text{C-N})$ imide	
3	3101	1743 1720	1585	1365	1188	1300	
Comp. No.	$\nu(-\text{NH-NH}_2)$ hydrazine	$\nu(\text{C-H})$ aromatic	$\nu(\text{C=O})$ imide	$\nu(\text{C=C})$ aromatic	$\nu(\text{SO}_2)$ asym.	$\nu(\text{SO}_2)$ sym.	$\nu(\text{C-N})$ imide
4	3359 3265	3097	1743 1718	1595	1390	1170	1338

**Table (4): FTIR spectral data of the prepared Schiff bases [5-18]**

Comp. No.	FTIR spectral data $\text{cm}^{-1}$							
	$\nu(\text{N-H})$ amide	$\nu(\text{C=O})$ imide	$\nu(\text{C=N})$	$\nu(\text{C=C})$ aromatic	$\nu(\text{SO}_2)$ asym.	$\nu(\text{SO}_2)$ sym.	$\nu(\text{C-N})$ imide	others
5	3221	1739 1712	1627	1589	1373	1165	1338	-
6	3221	1739 1716	1608	1589	1373	1165	1338	$\nu(\text{O-H})$ phenolic 3440
7	3417	1743 1716	1651	1597	1377	1168	1315	$\nu(\text{C-O-C})$ 1234 1126
8	3221	1739 1716	1616	1589	1377	1165	1338	$\nu(\text{O-H})$ Phenolic 3479
9	3043	1716	1624	1573	1388	1157	1330	-
10	3030	1741 1706	1610	1595	1386	1166	1340	$\nu(\text{NO}_2)$ 1498
11	3151	1735 1716	1654	1593	1377	1168	1319	-
12	3097	1739 1716	1627	1604	1377	1168	1342	$\nu(\text{O-H})$ Phenolic 3460

Table (4): Continued

Comp. No.	FTIR spectral data cm-1	Comp. No.	FTIR spectral data cm-1	Comp. No.	FTIR spectral data cm-1	Comp. No.	FTIR spectral data cm-1	Comp. No.
13	3221	1739 1716	1651	1589	1373	1165	1338	v(NO <sub>2</sub> ) 1496
14	3377	1741 1716	1625	1595	1375	1170	1330	v(C-Cl) 1091
15	3221	1739 1716	1627	1589	1373	1165	1338	v(O-H) Phenolic 3429
16	3232	1740 1716	1658	1593	1373	1165	1342	v(NO <sub>2</sub> ) 1469 1300
17	3147	1741 1720	1625	1593	1375	1170	1338	-
18	3400	1741 1718	1620	1593	1380	1170	1348	v(C=O) Amide 1701

Table (5): Antibacterial activity for some of the prepared schiff bases

Comp. No.	Gram positive bacteria	Gram negative bacteria
	Staphylococcus aureus	Escherichia Coli
5	+++	++
6	++++	-
7	++++	++++
10	++	+++
11	-	++
12	++++	++
14	++	+++
16	++	+++
17	+++	++
18	+++	++++

Key to symbols = Inactive = (-) inhibition Zone < 6 mm

Slightly active = (+) = inhibition Zone 6-9 mm

Moderately active = (++) inhibition Zone 9-12 mm

Highly active = (+++) inhibition Zone 13-17 mm

Very high activity = (++++) inhibition Zone > 17 mm

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