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SYNTHESIS, IDENTIFICATION AND BIOLOGICAL ACTIVITY OF NEW HETEROCYCLIC COMPOUNDS FROM REACTION OF NEW SCHIFF-BASES WITH PHATHALIC ANHYDRIDE

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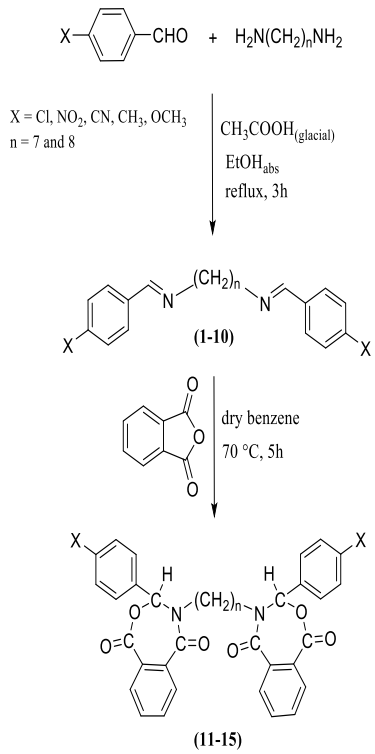
ABSTRACT:
Series of new Schiff bases and their derivatives (Oxazepine) have been synthesized during two steps. The first step synthesis of imines derivatives (1-10) by the condensation reaction of 1, 7-diaminohepatane and 1,8-diaminooctane with different substituted aromatic aldehydes by using glacial acetic acid as catalyst. The second step includes reaction of the prepared Schiff bases derivatives with phathalic anhydride in dry benzene to obtain seven-membered heterocyclic ring derivatives (11-15). The biological activities of some prepared compounds were also studied against different kinds of bacteria. The new derivatives were confirmed by suing a range of experimental techniques including ^{1}HNMR, ^{13}C NMR, IR and Mass spectra.

KEYWORDS: Oxazepine, Schiff bases, 1, 7-diaminoheptane, 1, 8-diaminooctane, Antibacterial activity, Phathalic anhydride.

1. INTRODUCTION

The chemistry of the imine group is considered to be a significant part in the progress of chemistry science (Yang et al, 2002; Al-Jeboori et al, 2008). Schiff bases which characterizing by a double bond (-CH = N-) are generally prepared by condensation method of aromatic aldehyds or ketones with primary amines (Celik et al, 2009; Saeed, 2005). Schiff-bases showed different biological activities such as antibacterial, antifungal and antitubercular (Wadher et al, 2009; Mohammed et al, 2019). Many heterocyclic compounds were prepared from the Schiff bases, for example oxazepines derivative which indicate a seven membered ring involving oxygen and nitrogen atoms in addition to five carbon atoms (Khattar et al, 2004; Aljamali et al, 2014). Over the years, the synthesis of oxazepine has been studied and attested. The oxazepine is prepared from addition of Schiff bases with maleic, phthalic and succinic anhydrides (Hanoon, 2011; Abood, 2010; Sadiq, 2017; Taha, 2017; Abdul-Wahid et al, 2016; Abdullah et al, 2016; Hamak and Eissa, 2013; Abood, 2013; Abdulqahar and Jaber, 2016; Aljamali, 2013) and also by green chemistry method (Verma et al, 2015; Hameed, 2012). A vast variety of biological activities were found to show of Oxazepine derivatives such as antibacterial (Agirbas et al, 2011), antifungal (Serrano-Wu et al, 2002), hypnotic muscle relaxant (Abedel-Hahez and Abdel-Wahab, 2008), antagonistic (Hallinan et al, 1996), inflammatory (Kubota et al, 2011) and antiepileptic (Bajajt et al, 2003).

Because of the biological importance of these compounds, the aim of this work is to synthesize some new Schiff bases and oxazepine derivatives as shown in Scheme 1 and investigate their biological activities against different kinds of bacteria.



Scheme1: Synthetic rout of preparation of schiff bases and oxazepine derivatives.

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2. EXPERIMENTAL DATA

2.1 General: Equipments, Chemical Materials and Applied Techniques

All reactions were carried out with dry in solvents under anhydrous conditions. Commercial reagents were used without purification. Ethanol was used as absolute solvent. ^{1}H-NMR and ^{13}C-NMR were recorded on Bruker DPX-300FT (^{1}H: 300 MHz, ^{13}C: 75.5 MHz). All NMR spectra present in this work were measured in $CDCl_3$ solution. All chemical shifts are given in ppm. The chemical shifts (δ) is expressed in ppm. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High resolution mass spectra were recorded on a Micro-mass ZABSpec TOF, on a Q-Tof Applied Biosystems and on Waters Q-Tof 2 apparatus. IR spectra were recorded on a Perkin-Elmer 1710 spectrophotometer or on a Perkin-Elmer Aragon 1000 FT-IR spectrophotometer. Thin Layer Chromatography (TLC) Merck Kiese gel 60 F254 on aluminum foil from Macherey-Nagel. Melting points were determined by electrothermal apparatus and are uncorrected.

2.2 General Procedure for Preparation N, N'- (alkane-1,7-diyl) and (alkane-1,8-diyl) bis(1-(4-substituted phenyl) methanimine (1-10)

A mixture of aromatic aldehydes (1.6 mmol, 2 eq.), 1,7-diaminoheptane, 1,8-diaminooctane (0.8 mmol, 1 eq.), and 5 drops of glacial acetic acid in 50 ml of dry ethanol were heated by reflux for (2-3) hours under dry conditions. Then ethanol was evaporated by vacuum. Finally, the solid compound was purified twice using absolute ethanol to obtain a pure product (1-10) (Ghosh et al, 2006; Aljamali, 2013) as shown in Table 1.

Table 1. The physical properties and Mass spectroscopy of N, N'-(Naphthaline-1, 5-diyl) bis Ketone Derivatives (1-10).

Comp. No.	Substrate	Name of Compound	Color	M.P (°C)	Yield (%)	HRMS (ESI)
1		(*1E,1'E*)-*N, N'*-(heptane-1,7-diyl bis(1-(4-methoxy phenyl)	Pale-yellow	60-63	78	Calcd. 357.2307 Found 357.2307
2		(*1E,1'E*)-*N, N'*-(heptane-1,7-diyl)bis(1-p-tolylmethanmine)	Deep-yellow	70-72	75	Calcd. 389.2205 Found 389.2206
3		(*1E,1'E*)-*N, N'*-(heptane-1,7-diyl)bis(1-(nitrophenylmethanimine	Pale-brown	108-110	79	Calcd. 419.1695 Found 419.1697
4		(*1E,1'E*)-*N, N'*-(heptane-1,7-diyl) bis(1-(4-chlorophenylmethanimine)	Pale-yellow	79-80	77	Calcd. 397.1214 Found 397.1212
5		4,4'-((*1E,1'E*)-(heptane-1,7-diylbis(azanylylidene))bis(methanylylidene))dibenzonitrile	White	81-84	88	Calcd. 379.1899 Found 379.1900
6		N-(8-(((*E*)-4-methoxy benzylidene) amino)octyl)-1-((4methoxyphenyl) methanimine	Pale-brown	110-112	85	Calcd. 403.2361 Found 403.2359
7		N-(8-(((*E*)-4-methyl benzylidene) amino)octyl)-1-(ptoly)methanimine	White	95-98	72	Calcd. 371.2463 Found 371.2463
8		4-(((8-(((*E*)-4 isocyano benzylidene amino)octylimino)methyl)benzonitrile	White	75-77	91	Calcd. 393.2055 Found 393.2053
9		*N*-(8-(((*E*)-4-nitrobenzylideneamino) octyl)-1-(4-nitrophenyl) methanimine	White	101-104	82	Calcd. 433.1852 Found 433.1852
10		*N*-(8-(((*E*)-4-chlorobenzylidene) amino) octyl)-1-(4-chlorophenylmethanimine	White	88-90	71	Calcd. 411.1371 Found 411.1369

2.3 Preparation of oxazepine compounds (11-15)

Schiff base derivatives (1-10) (1.2 mmol, 1eq.) and phthalic anhydride 18 (2.5 mmol, 1eq.) were dissolved in (20 mL) dry benzene. The mixture was heated for 5 hours in water bath at (70 °C). The mixture was then allowed to cool down at room temperature; a formed precipitate was filtered and recrystallized from ethanol to obtain a pure product. (Hamak and Eissa, 2013; Al-juburi, 2012) as shown in Table 2.

Table 2. The physical properties of oxazepane derivatives (11-15).

Comp. No.	Name of Compound	Color	M.P (°C)	Yield (%)
11	4,4'-(octane-1,8-diyl)bis(3-(4-nitrophenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5 -dione)	White	143-145	80
12	4,4'-(heptane-1,7-diylbis(1,5-dioxo-1,3,4,5 -tetrahydrobenzo[e][1,3]oxazepine-4,3-diyl)) dibenzonitrile	White	104-107	78
13	4,4'-(heptane-1,7-diyl)bis(3-(p-tolyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione)	White	169-173	70
14	4,4'-(heptane-1,7-diyl)bis(3-(4-methoxy phenyl)-3,4- dihydrobenzo[e][1,3] oxazepane -1,5-dione	White	171-174	75
15	4,4'-(octane-1,8-diylbis(1,5-dioxo-1,3,4, 5-tetrahydrobenzo[e][1,3] oxazepine-4,3-diyl)) dibenzonitrile	White	120-124	85

2.4 Preliminary Biological Study

All newly synthesized compounds were tested against two types of bacterial groups including Gram-negative, *E. coil* and Gram-positive *Staphylococcus aureus* as shown in Table 3. Of each bacterial kind a loopful was maintained in a nutrient broth and incubated at 37 °C for 14-16 hours. Finally, bacterial spread on nutrient agar using a sterilized swab. For comparison, Tetracycline, Lincomycine and Nalidixic acid were used as controls. The dishes were incubated for 18-24 hours at 37 °C. Prescott method was used to clarify the sensitivity of the studied compounds (Prescott et al, 1996). The results interpreted according to the report of W.H.O. The resistance R explains the diameter of inhibition zone < 11 mm, while the sensitive S was over 16 mm, but moderately sensitive MS was involved when the inhibition zone is 12-16 mm.

2. RESULTS AND DISCUSSION

The first part in this work was the synthesis of ten Schiff bases (1-10) from the reaction of (4-substituted benzaldehydes) with primary aliphatic amines in the presence of glacial acetic acid as catalyst in absolute ethanol. The IR spectra of Schiff base compounds (1-10) appeared the medium bands at 1640-1651 cm $^{-1}$ assigned to the stretching vibration of imine group (C=N), and the disappearance of stretching band of (C=O) group. The absorption bands showed in the range of (1560-1606) cm^{-1}, (3020-3089) cm^{-1}, (2920-2935) cm^{-1}, related to the stretching vibrations of (C=C) aromatic, (C-H) aromatic, (C-H) aliphatic respectively as shown in Table 3.

The ^{1}H-NMR spectra of the Schiff bases (Figure 1) exhibited a singlet peak for the proton of CH=N group at (8.26-8.36) ppm. A triplet signal at (3.26-3.63) ppm related to methylene proton of $CH=N-CH_2$, while methylene protons displayed as multiplet signal at (1.21-1.72) ppm. Aromatic protons appeared as doublet signal at the region (6.92-8.13) ppm Table 4. In the ^{13}C–NMR spectra (Figure 2) of compounds (2-4, 6, 7 and 10), the signal for carbon of CH=N groups of compounds showed at (166.1) ppm. A signal appeared at 59 ppm attributed to methylene carbon of $CH=N-CH_2$, while the signals of methylene carbons exhibited at (27.2-55.6) ppm. The signals of aromatic carbons exhibited at (114.2 – 184.9) ppm Table 5.

Table 3. Spectral data (FT-IR) of N, N'- (alkane-1,7-diyl) and (alkane-1,8-diyl) bis(1-(4-substituted phenyl) methanimine (1-10) :

Comp.No.	FT-IR(KBr) υ cm^{-1}			
	C-H Arom.	C-H Alipha.	C=N Imine	C=C Arom.
1	3024	2926	1649	1606
2	3020	2920	1651	1606
3	3030	2933	1643	1602
4	3049	2933	1639	1596
5	3089	2935	1643	1560
6	3047	2920	1645	1606
7	3055	2922	1647	1606
8	3055	2933	1643	1608
9	3062	2935	1643	1604
10	3053	2924	1645	1593

Table 4. Spectral data (^{1}H-NMR) of N, N'- (alkane-1,7- diyl) and (alkane-1,8-diyl) bis(1-(4-substituted phenyl) methanimine (1- 10):

Comp. No.	^{1}H-NMR δ ppm					
	CH_2	C=N-CH_2	CH=N	Ar-H	OCH_3	CH_3
1	1.29-1.68 m, 10H	3.4 t, 4H	8.29 s, 2H	7.23 d, 8H	3.81 s, 6H	
2	1.25-1.61 m, 10H	3.26 t, 4H	8.71 s, 2H	7.33 d, 8H		2.38 s, 6H
3	1.21-1.68 m, 10H	3.43 t, 4H	8.32 s, 2H	7.98 d, 8H		
4	1.25-1.69 m, 10H	3.44 t, 4H	8.28 s, 2H	7.42 d, 8H		
5	1.33-1.72 m, 10H	3.63 t, 4H	8.30 s, 2H	7.66 d, 8H		
6	1.27-1.70 m, 12H	3.37 t, 4H	8.26 s, 2H	7.24 d, 8H	3.81 s, 6H	
7	1.28-1.70 m, 12H	3.60 t, 4H	7.32 s, 2H	7.31 d, 8H		2.35 s, 6H
8	1.28-1.66 m, 12H	3.51 m, 4H	8.36 s, 2H	7.64 m, 8H		
9	1.30-1.69 m, 12H	3.36 t, 4H	8.31 s, 2H	7.95 d, 8H		
10	1.26-1.68 m, 12H	3.38 m, 4H	8.28 s, 2H	7.42 d, 8H		

Table 5. Spectral data (^{13}C-NMR) of N, N'- (alkane-1,7-diyl) and (alkane-1,8-diyl) bis (1-(4-substituted phenyl) methanimine:

Comp. No.	^{13}C-NMR δ ppm					
	CH_2	CH=N-CH_2	Ar-H	CH=N	OCH_3	CH_3
2	27.2-31.0 5C	59.0 2C	128.9-142.5 12C	166.1 2C	-	21.1 2C
3	27.2-31.0 5C	59.0 2C	124.7-151.2 12C	166.1 2C	-	-
4	27.2-31.0 5C	59.0 2C	129.4-137.1 12C	166.1 2C	-	-
6	27.2-55.6 6C	59.0 2C	114.2-184.9 12C	166.1 2C	56.0 2C	-
7	27.2-31.0 6C	59.0 2C	128.9-142.5 12C	166.1 2C	-	21.1 2C
10	27.2-31.0 6C	59.0 2C	129.4-137.1 12C	166.1 2C	-	-

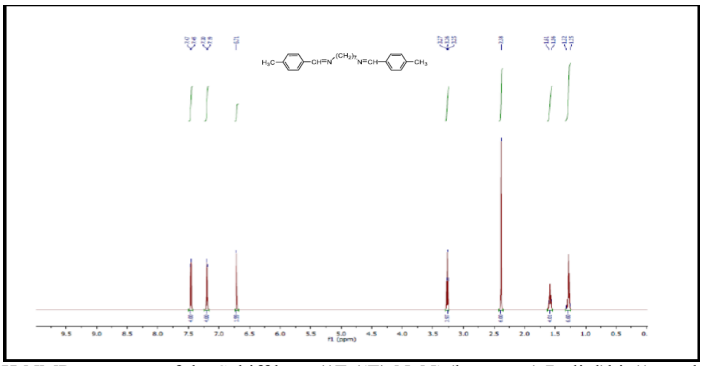


Figure 1. 1H-NMR spectrum of the Schiff base (1E,1'E)-N, N'-(heptane-1,7 -diyl)bis(1-p-tolylmethanmine) (1)

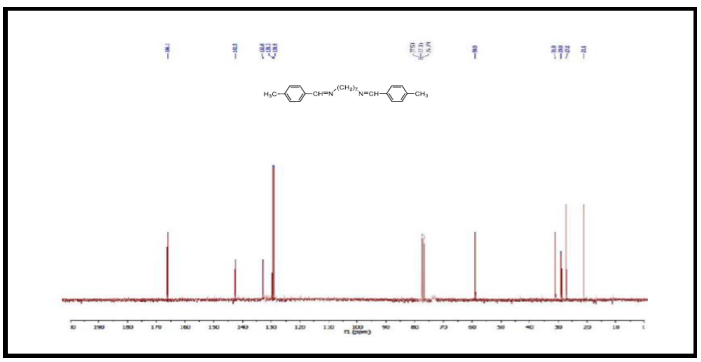
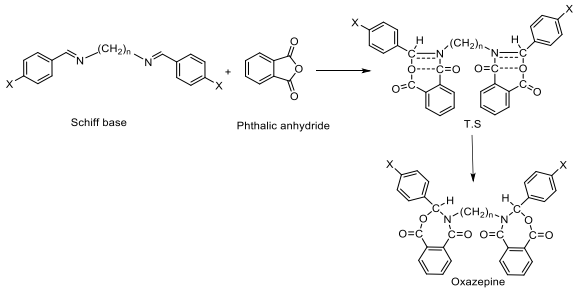


Figure 2. ^{13}C-NMR spectrum of the Schiff base (*1E,1'E*)-*N, N'*-(heptane-1,7-diyl)bis(1-p-tolylmethanmine) (1)

The second part focused on the synthesis of five oxazepine derivatives (11-15) by reaction between imine groups of Schiff bases (1-10) and cyclic acid anhydride [phthalic anhydride] in dry benzene as shown in the Scheme 2. The general feature of the I.R spectra of oxazepine derivatives showed the band at (1705-1782) cm^{-1} belongs to (C=O) groups in oxazepane structure and disappearance of (C=N) group. Also appeared a strong band which belongs to the formation of (C-O-C) at 1280-1185 cm^{-1}, this evidence confirmed the formation of the described products Table 6.

The ^{1}HNMR spectra for oxazepine compounds (11-15) observed a triplet signal of methylene proton attached to nitrogen atom at (3.09-4.04) ppm and showed the proton of the CH-N group with protons of aromatic ring as multiplet signals at (6.90-8.23) ppm, which is a good evidence of obtaining the products Table 7. Furthermore, the appearance of the new extra different carbon peaks in the aromatic at δ (109.5–160.2) and carbonyl groups at (166.4 and 170.6) ppm regions in the ^{13}C-NMR spectra, provided further support to the structures of the oxazepine products Table 8.



Scheme 2: Mechanism of synthesis 1,3-oxazepine

Table 6. Spectral data (FT-IR) of oxazepine compounds (11-15):

Comp.No.	FT-IR(KBr)cm^{-1}		
	C=O	C=C	C-O-C
11	1727	1615	1185
12	1705	1607	1261
13	1782	1615	1259
14	1717	1585	1280
15	1726	1616	1272

Table 7. Spectral data (^{1}H-NMR) of oxazepane compounds (11-15):

Comp. No.	**^{1}H-NMR δ ppm**				
	CH_2	C-N-**CH_2**	Ar-**H** & C-**H**	**OCH_3**	**CH_3**
11	1.28-1.66 m, 12H	3.70 t, 4H	7.55-8.23 m, 18H	-	-
12	1.23-1.63 m, 10H	3.55 t, 4H	7.45-8.06 m, 18H	-	-
13	1.23-1.59 m, 10H	3.69 t, 4H	7.17-8.06 m, 18H	-	2.34 s, 6H
14	1.37-1.70 m, 10H	3.78 m, 4H	6.90-8.05 m, 18H	3.42 s, 6H	-
15	1.21-1.64 m, 12H	3.57 t, 4H	7.47-8.07 m, 18H	-	-

Table 8. Spectral data (^{13}C-NMR) of oxazepane compounds (11-15):

Comp. No.	^{13}C-NMR δ ppm						
	CH_2	C-N-CH_2	Ar-H & C-H	C=O	OCH_3	CH_3	CN
11	27.5-29.0 6C	42.1 2C	123.7-147.2 26C	166.4,170.6 4C	-	-	-
12	27.5-29.0 5C	42.1 2C	109.5-142.9 26C	166.4,170.6 4C	-	-	119.5 2C
13	27.5-29.0 5C	42.1 2C	126.1-139.2 26C	166.4,177.6 4C	-	21.1 2C	-
14	27.5-29.0 5C	42.1 2C	112.9-160.2 26C	166.4,170.6 4C	56.0 2C	-	-
15	27.5-29.0 6C	42.1 2C	126.1-147.2 24C	166.4,170.6 4C	-	-	123.7 2C

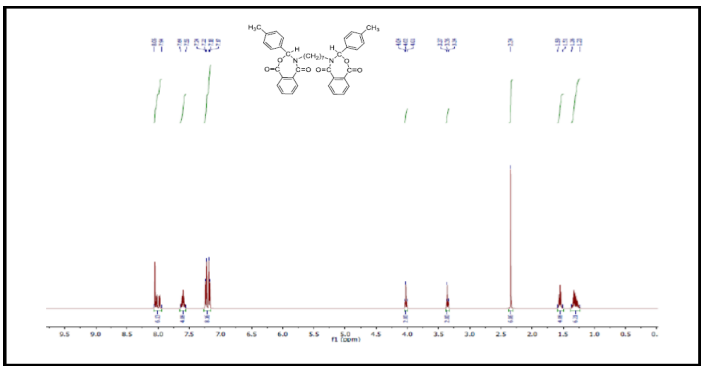


Figure 3. ^{1}H-NMR spectrum of the oxazepine 4,4'-(heptane-1,7-diyl)bis (3-(p-tolyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione)

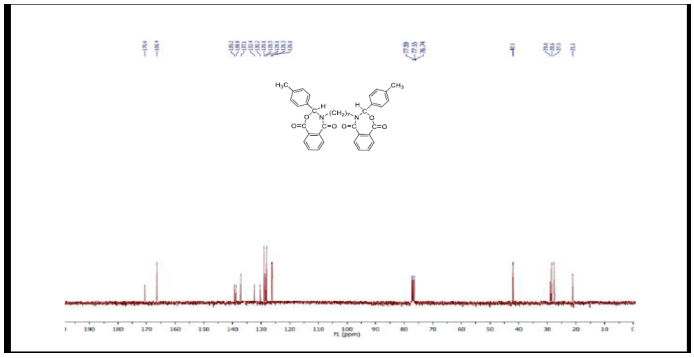


Figure 4. ^{13}C-NMR spectrum of the oxazepine 4,4'-(heptane-1,7-diyl)bis (3-(p-tolyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione)

The results of such preliminary biological study exhibited that most of new compounds have good antibacterial activity Table 9. The compounds 1, 3, 5, 6, 8, 9, 11, 12 and were sensitive against *Escherichia Coli* bacteria which represent Gram-negative type. Inhibition of these compounds was similar to that one in
Tetracycline and Nalidixic acid and opposite to the influence of the compounds 2, 7, and 13 which were similar to Lincomycine. The compounds 4, 10 and 14 were a moderately sensitive against the type of bacteria. Otherwise, the compounds 2, 4 and 13 have resistant against the *Staphylococcus aureus* bacteria which represent Gram-positive type and this inhibition were the same as Lincomycine. Furthermore, the compounds 3, 5, 7, 9, 11, 14 and 15 showed sensitive against these bacteria and the result was agreed with that one in Tetracycline and Nalidixic acid. While the compounds 1, 6, 8, 10 and 14 were moderately sensitive with this kind of bacteria.

Table 9. Inhibition Effect of certain of products on growth of *staphylococcus* arueus and *Escherichia coil*.

Compound no.	Test organism			
	E.coli		*Sta. aureus*	
	GIZ in mm	Mode	GIZ in mm	Mode
1	23	S	15	MS
2	11	R	11	R
3	22	S	20	S
4	15	MS	10	R
5	23	S	21	S
6	23	S	16	MS
7	10	R	20	S
8	21	S	14	MS
9	22	S	21	S
10	13	MS	16	MS
11	21	S	19	S
12	22	S	20	S
13	10	R	9	R
14	15	MS	14	MS
15	22	S	20	S
Control				
Tetracycline	25	S	26	S
Lincomycine	11	R	24	S
Nalidixic acid	22	S	10	R

4.Conclusion

A series of new Schiff bases and 1,3 -oxazepine derivatives containing imine group were synthesized successfully using pericycliccyclo addition of Schiff bases with phthalic anhydrides, besides using a small amount of solvents, shorter reaction times and good yield. Some of these compounds shown good antibacterial activity against the bacterial pathogens.

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