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(RESEARCH ARTICLE)

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Preparation, characterization and biological activity of some new seven-membered heterocyclic compounds

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Abstract

Introduction: The synthesis of Schiff base has huge importance to prepare a lot of heterocyclic compounds, Oxazepines can be prepared by reaction of imine compounds with anhydrides to obtain seven-membered heterocyclic compound.

Materials and Methods: A series of 1, 3-oxazepine derivatives were prepared, firstly preparation of the imines (S1-S2) from reaction of 2-chlorobenzaldehyde with each of p-toluidine and 4, 4'-Methylenedianiline and using glacial acetic acid as a catalyst. The second step involves the reaction of prepared Schiff bases (S1-S2) with both 3-nitrophthalic anhydride and Itaconic anhydride in dry benzene to produce 1,3-oxazepine derivatives (OX1-OX4), The antibacterial activity determined by using Agar well diffusion procedure method, against two types of bacteria, which it gram-positive (Staphylococcus aureus) and gram-negative (*Escherichia coli*).

Results and Discussion: Oxazepine compounds are formed through Pericyclic reactions which are concerted processes that pass through a single cyclic transition state structure involving simultaneously breaking and formation of bonds. The compounds were identified by using FT-IR and NMR technology.

Conclusions: The possibility of preparing some mono-chelating and bi-chelating Schiff bases derived from the reaction of 2-chlorophenzaldehyde with different aromatic primary amines and preparing some of the new oxazepine compounds through the reaction of the Schiff bases with different anhydrides in benzene, which can be used to extract metal ions from their solutions. The biochemical efficacy of compounds demonstrated that their ability to inhibit Staphylococcus aureus was greater compared with the ability to inhibit *Escherichia coli*.

Keywords: 1, 3-Oxazepine; Schiff base; Cycloaddition; Antibacterial activity

1. Introduction

Heterocyclic compounds have been of great importance in the synthesis of many pharmaceutical drugs [1]. This has increased its importance in the field of biology[2], due to its participation in important biochemical processes and the formation of basic substances such as DNA and RNA, in living cells[3]. Heterocyclic compounds have been associated with many anaesthetics and sedatives as basic materials for many biomolecules, anti-inflammatories [4], antibacterial [5], antivirals [6], antiepileptics, and others. One of these important compounds is the heterocyclic oxazepine ring.

For many years, 1,3- and 1,4-oxazepine have been synthesized through two classic types of reactions, the first one is called Valence bond isomerism, which is happened by irradiating N-polypyridine oxides, leading to the expansion of the

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ring to 1,3-oxazepine[7]. The second reaction is called Enamines condensation which is accomplished by the reaction of erythro-1,2-diphenyl-2-phenylaminoethanol with dimethylacetylene dicarboxylate in methanol at room temperature to give a mixture of the Michael adduct and tetrahydro-1,4-oxazepine-7-one[8]. Oxazepine is an unsaturated and heterogeneous seven-member ring, which exists in three isomers depending on the location of the nitrogen atom for the oxygen atom[9]. 1.3-oxazepine ring consists of an oxygen atom at position 1 and a nitrogen atom at position 3, plus five carbon atoms as shown below in figure 1.

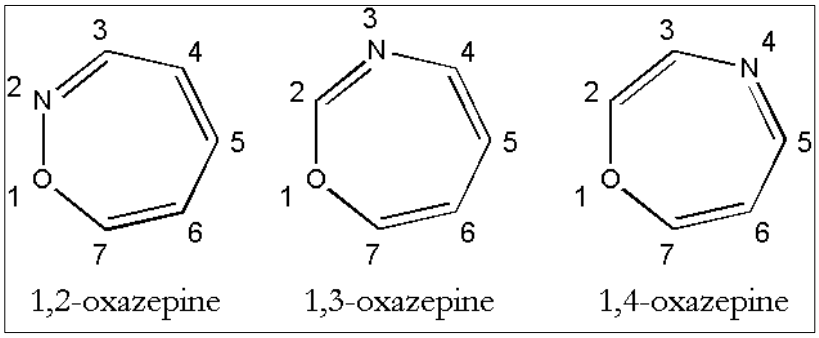


Figure 1 The structures of oxazepine isomers

The presence of N and O atoms and the stability of the oxazepane ring due to the lone paired electrons and double bonds gives these compounds an advantage in using them in the medicinal and pharmaceutical industries (10), and therefore this encouraged researchers to find new and different preparation methods and prepare more effective oxazepine compounds in the biological field. Oxazepine derivatives showed a wide range of applications, characterized by hypotonic muscle relaxation (11), antagonistic (12), anti-inflammatory (13), anticancer (14), antiallergic, and antihistaminic (15). These compounds are also used as psychoactive drugs (16), enzyme inhibitors (17), and analgesics (18).

For example, figure 2 shows some known oxazepane derivatives such as dibenzoxazepine (CR gas) which is used as a chemical weapon in tear gas grenades and is developed by the British Ministry of Defense as a riot-control agent in the late 1950s and early 1960s(19). Asendin is another important dibenzoxazepine derivative which is an antidepressant with a mild sedative component to its action. Diazepam (valium) is introduced in 1964 as a benzodiazepine derivative that is used in anxiety control, tension states, muscle relief, and acute induction during alcohol withdrawal (20).

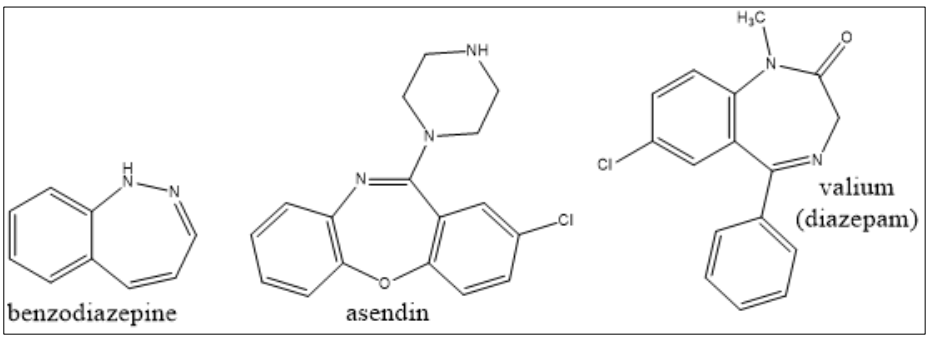


Figure 2 Chemical structures of some well-known oxazepine derivatives

In our research, we aim to prepare some of the 1, 3-oxazepine-4, 7-dicarbonyl ring derivatives from the cycloaddition reaction between Schiff bases and anhydrides and evaluate the biological activity of these compounds against two types of bacteria, which it gram-positive (Staphylococcus aureus) and gram-negative (*Escherichia coli*).

2. Material and methods

2.1. General information

All chemicals used were of commercial, AR and LR grades that are supplied by either Merck, RDH, H&W, BDH, SCH, Fluka or Aldrich. All solvents and other chemicals were dried and purified wherever necessary. The melting points were determined by Electrothermal Melting Point Apparatus BÜCHI B-510 – 400°C (Switzerland) in open capillary tubes and

were uncorrected. The melting points of all the solid chemicals used were verified by measuring them with the same apparatus. Thin-layer chromatography (TLC) was used for monitoring the reaction and to check the purity of prepared compounds by using Aluminum silica 60f. Fluorescent indicator from CHMLAB GROUP. The FTIR spectra in the range (400-4000) cm^{-1} were recorded as KBr disc on FTIR Shimadzu FTIR-8400S – JAPAN spectrophotometer, and ^{1}H-NMR spectra were scanned using Bruker model ultra-shield 400MHz (Switzerland) by using TMS as an internal standard reference in DMSO-d6 as solvent.

2.2. General procedure for the preparation of Schiff Bases [39]

N-(2-chlorobenzylidene)-p-tolylamine (S1)

Bis-N-(2-chlorobenzylidene)-4, 4'-Methylenedianiline (S2)

Schiff bases (S1, S2) were prepared from the gradual addition of a 10 ml ethanolic solution from the p-toluidine 0.002 mol for (S1) and 4, 4'-Methylenedianiline 0.001 mol for (S2), to another ethanolic solution 10 ml of 2-chlorobenzaldehyde 0.002 mol with two or three drops glacial acetic acid as a catalyst, and the mixture is refluxing and continuous stirring for 1-3 hrs. At 78 ℃. The reaction completion is tracked by using the thin layer chromatography technique TLC from a mixture of hexane & ethyl acetate (1:3) and then leaving the solution to cool down. The precipitate in the mixture can be formed either by adding cool distilled water (S1) or spontaneously (S2). The obtained precipitate is filtered and washed several times with cold water or ethanol, and performed recrystallization by using a mixture of ethanol/water for (S1) & ethanol only for (S2). Finally, we dry the precipitate, weigh it and find the percent yield. The physical properties of these compounds were summarized in table 1.

Table 1 Melting point, molecular weight and other properties of compounds (S1, S2)

Co.	M.wt	M.F	M.P	color	Reaction time hr.	Yield %
S1	229.71	$C_{14}H_{12}ClN$	61	light olive	3	70
S2	443.37	$C_{27}H_{20}ClN_2$	131	Yellow to white	1	90

2.3. General procedure for the preparation of Oxazepine compounds [32, 33]

- 2-(2-chlorophenyl)-3-(4-tolyl)-5-nitro-benzo[e]-1,3-oxazepine-4,9-dione (OX 1)
- 2-(2-chlorophenyl)-3-(4-tolyl)-5-methylene-1,3-oxazepane-4,7-dione (OX 2)
- 4,4'-methylenebis[N-[(2-chlorophenyl)-5-nitro-benzo[e]-1,3-oxazepine-4,9-dion]aniline] (OX 3)
- 4,4'-methylenebis[N-[(2-chlorophenyl)-5-methylene-1,3-oxazepane-4,7-dione]aniline] (OX 4)

The synthesis happened by taking equal amounts of prepared Schiff bases 0.0008 mol for (S1) and 0.0004 mol for (S2) with an excessive amount of different anhydrides 0.0008 mol (3-nitrophthalic anhydride, Itaconic anhydride) in 20 ml of dry benzene, and the mixture is refluxing and continuous stirring for 1-2 hrs. At 60 ℃. The reaction completion is tracked by using the thin layer chromatography technique TLC and using a mixture of methanol & benzene (1:2) to give a colored precipitate of oxazepine derivatives. It is left to cool down a little and the obtained precipitate is filtered and washed several times with benzene and achieve the recrystallization by using 1,4-dioxane or chloroform. Finally, we dry the precipitate, weigh it and find the percent yield. The physical properties of these compounds were listed in table 2.

Table 2 Melting point, molecular weight and other properties of compounds (OX1-OX4)

Co.	M.wt	M.F	M.P	color	Reaction time hr.	Yield%
OX1	422.82	$C_{25}H_{15}ClN_2O_5$	192-193	White	2	50
OX2	341.79	$C_{19}H_{16}ClNO_3$	164-165	White	2	53
OX3	829.60	$C_{43}H_{26}ClN_4O_{10}$	158	Yellow	1	41
OX4	667.54	$C_{37}H_{28}Cl_2N_2O_6$	203	Light yellow	1	58

2.4. Biological Activity

In this study, two types of bacteria were used, which are gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli*, and the agar well diffusion method was used to calculate the inhibitory effect of the prepared chemical compounds.

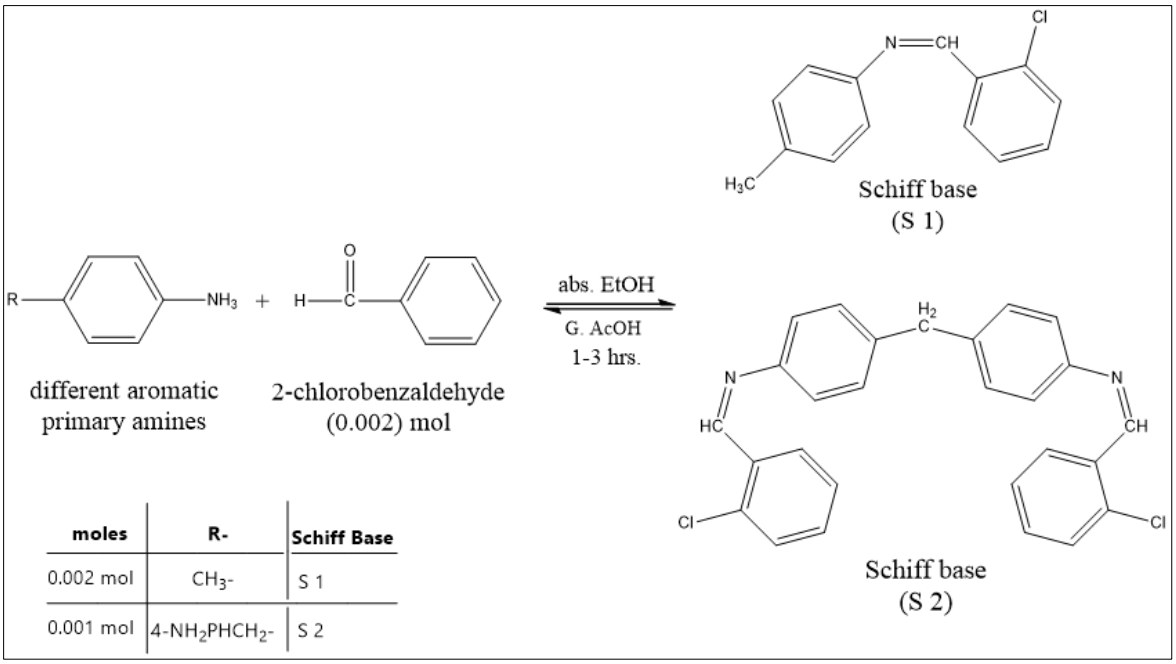
These nutrient agar cultivars were prepared and sterilized according to previous literature by dissolving 28 g of nutritious media in a liter of distilled water and mixing well in a conical flask and heating the solution until the agar is dissolved. After that, the agricultural medium is placed in an autoclave for 15-20 minutes at 120 °C to sterilize it. After sterilization, we took (20 ml) of the medium in glass dishes and cultured the small growing isolates for 24 hours in the prepared agar broth [21].

The diffusion method was used to spread the bacterial isolate onto the feeding medium using a cotton swab, and the dishes were incubated for 24 h at a temperature of 36 °C ± 1 °C. Agricultural circles were punctured with pure cork with a diameter of about 7 mm and 50 µL were added from the solutions of the prepared compounds that were dissolved in DMSO. Bacterial plates were incubated for 24 h at 36 °C ± 1 °C in an incubator. After that, these plates were removed from the autoclave and the diameters of the inhibition zones for the prepared compounds were measured by using a ruler (measured in millimeters) [22].

3. Results and discussion

Two types of primary aromatic amines were used in the preparation of Schiff bases, which are (p-toluidine) and (4,4'-Methylenedianiline) compound, by reacting them with 2-chlorobenzaldehyde and using glacial acetic acid as a catalyst. All reactions were carried out under conditions away from moisture. Scheme 1 is illustrated the reaction of synthesis of each of Schiff bases S1, S2.

The Schiff Base S1 preparation reaction takes only 1 hour to complete, while Schiff Base S2 takes 3 hr. to form. This indicates that bidentate Schiff bases are more easily to form more than monodentate Schiff bases. Most Schiff bases are less polar compounds and they usually dissolve in polar solvents like ethanol and methanol, and for that S1 is obtained by adding cold water (strong polarity) to the reaction mixture, while S2 is formed spontaneously without adding water. Also using a polar solvent such as ethyl acetate in TLC and using ethanol in recrystallization of both compounds.



moles	R-	Schiff Base
0.002 mol	CH_3-	S 1
0.001 mol	4-NH_2PHCH_2-	S 2

Figure 3 The reaction of synthesis each of Schiff base S1, S2

Oxazepine compounds are formed through Pericyclic reactions which is a concerted process pass-through a single cyclic transition state structure involving simultaneously breaking and formation of bonds[23], so these reactions never take place via generation of intermediate[23,24]. Process-based on the principle of conservation of molecular orbital

symmetry between the reaction components during the reaction proceeding which is leading to a cyclic transition state corresponding with the arrangement of participating orbitals [25]. The type of cycloaddition reaction that was used to synthesise of 1, 3-oxazepine ring was classified as [2+5] → 7 cycloaddition reaction in which two atoms of imine group as two membered components were added to a five-membered component such as maleic anhydrides to give a seven-membered heterocycle [26-29].

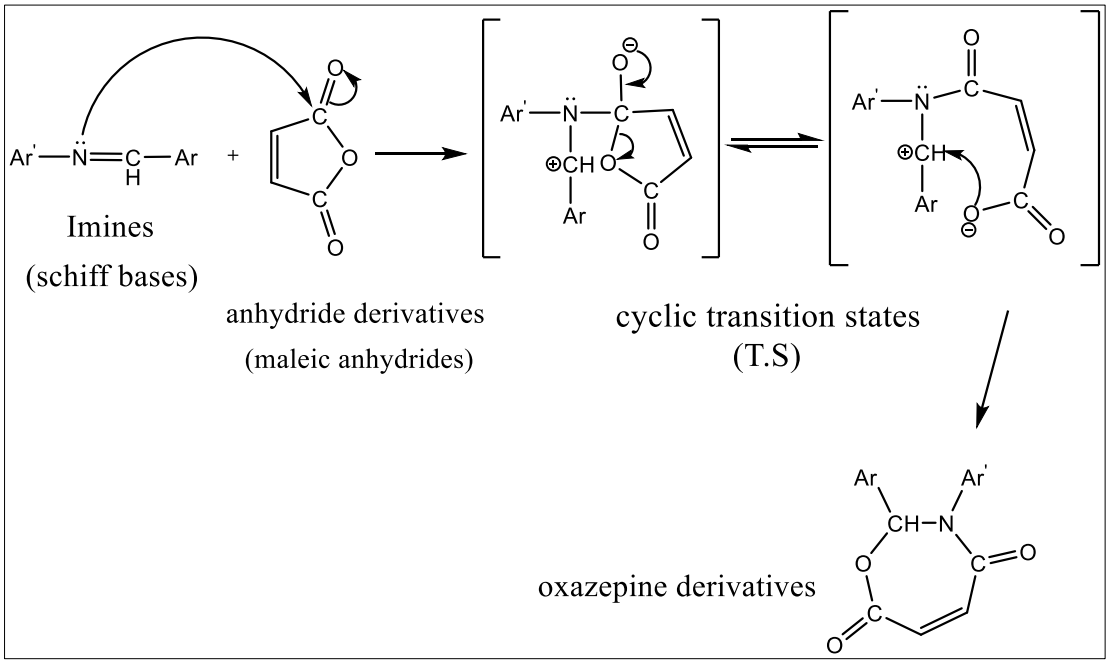


Figure 4 Mechanism of oxazepines synthesis

Scheme 2 illustrates the mechanism of oxazepines synthesis which can be interpreted in two phases. First, the nucleophilic attack is carried out by the azomethine group (π-bond), which contains a pair of electrons not involved in the nitrogen atom and a polarized double bond between the carbon and nitrogen atoms as a result of a difference in the electrolysis between them on the carbon atom The group of carbonyl of the anhydride of the presence of polarization in this group as well as a result of this attack, the anhydride ring opens up a polar compound consisting of positive and negative charge[31, 32]

Oxazepine compounds are synthesized through the reaction of prepared Schiff base compounds with two types of anhydrides which are (3-nitrophthalic anhydride) and (Itaconic anhydride) compounds. As shown in Scheme 3.

The reaction took place by using benzene as a solvent for the reaction where the Schiff bases were dissolved with dry benzene after heating, and co-solvent of ethanol and benzene to dissolve the anhydrides. The temperature of the reaction mixture should not exceed 50 ℃ in order to obtain a precipitate easy to separate and dry and with a high yield. Toluene can be us as a reaction mixture but it has a high boiling point of 110 ℃ and it takes so long time to evaporate from the precipitate.

All reactions happened under conditions away from moisture and light, by using dry solvents and saving anhydrides in inlet gas and making sure that anhydrides are not decomposed to carboxylic acids after absorbing water from the air can be done by measuring the melting point of anhydrides before any reaction. The anhydrides and prepared oxazepine were stored in dark containers to prevent exposure to light. The crystallization is carried out by using highly polar solvent 1, 4-Dioxane.

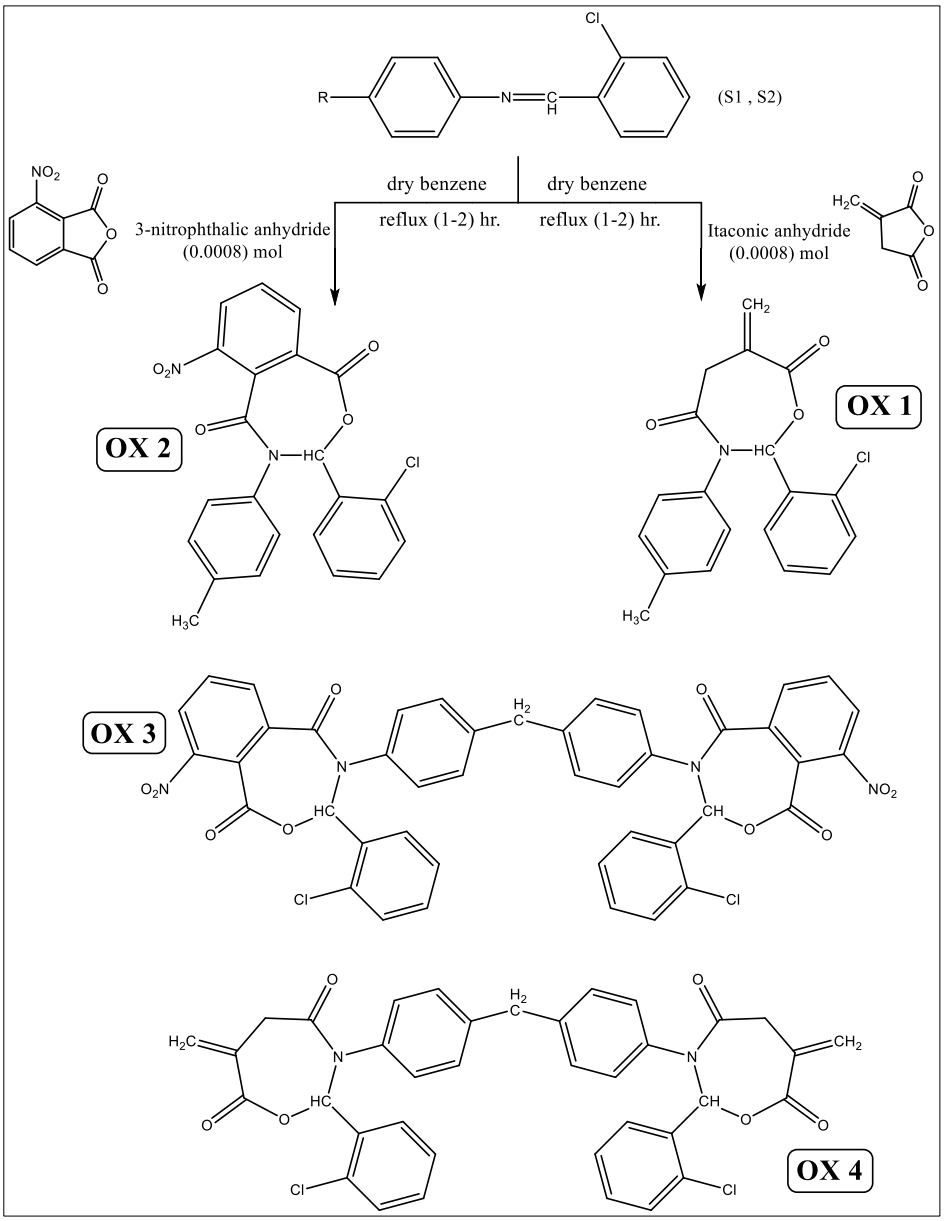


Figure 5 The reaction of synthesis each of oxazepines (OX1-OX4)

3.1. IR Spectra

Table (3), fig (3) and fig (4) are represents the IR absorption regions and FTIR spectra respectively of the prepared Schiff bases, as their spectra showed stretching vibration band of the Azomethine group (C=N) at (1614) cm^{-1} and the disappearance of the stretching vibration band (C=O) of the aldehyde as evidence of Schiff base formation[32].

IR spectra also showed strong vibration bands for the aromatic stretching band (C-N) within the range (1270-1275) cm^{-1} [32] The spectra of prepared Schiff bases were characterized by medium stretching bands in the range (3000-3100) cm^{-1} and strong bending broad bands in the range (680-900) cm^{-1} for aromatic (C-H) bond vibration [34]. While there are medium stretching bands in the range (3000-3100) cm^{-1} and strong bending broad bands in the range (680-900) cm^{-1} for aliphatic (C-H) bond vibration [34]in the azomethine group.

Also, there are medium to strong vibration bands at the range (1450-1600) cm^{-1} due to vibration of aromatic bond (C=C), and the spectra of the Schiff base showed a strong stretching band vibration of (C-Cl) bond within the range (600-800) cm^{-1} [35]

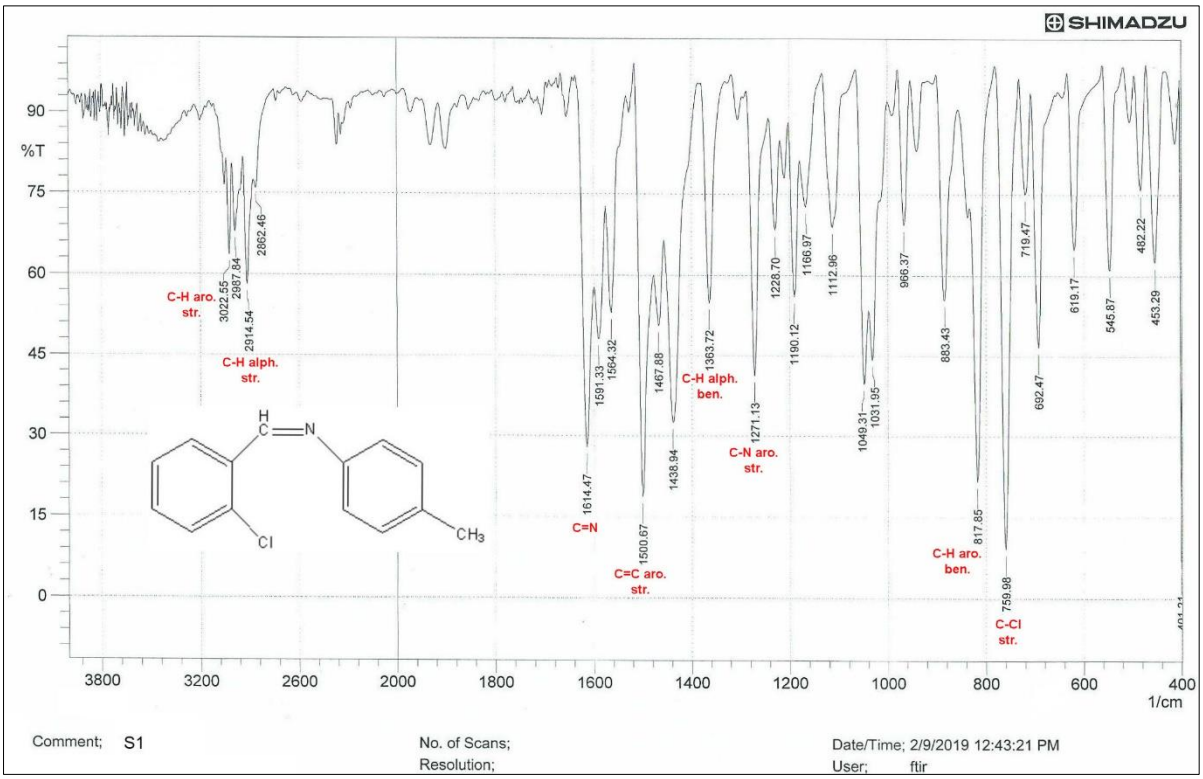


Figure 6 FT-IR spectrum of compound (S1)

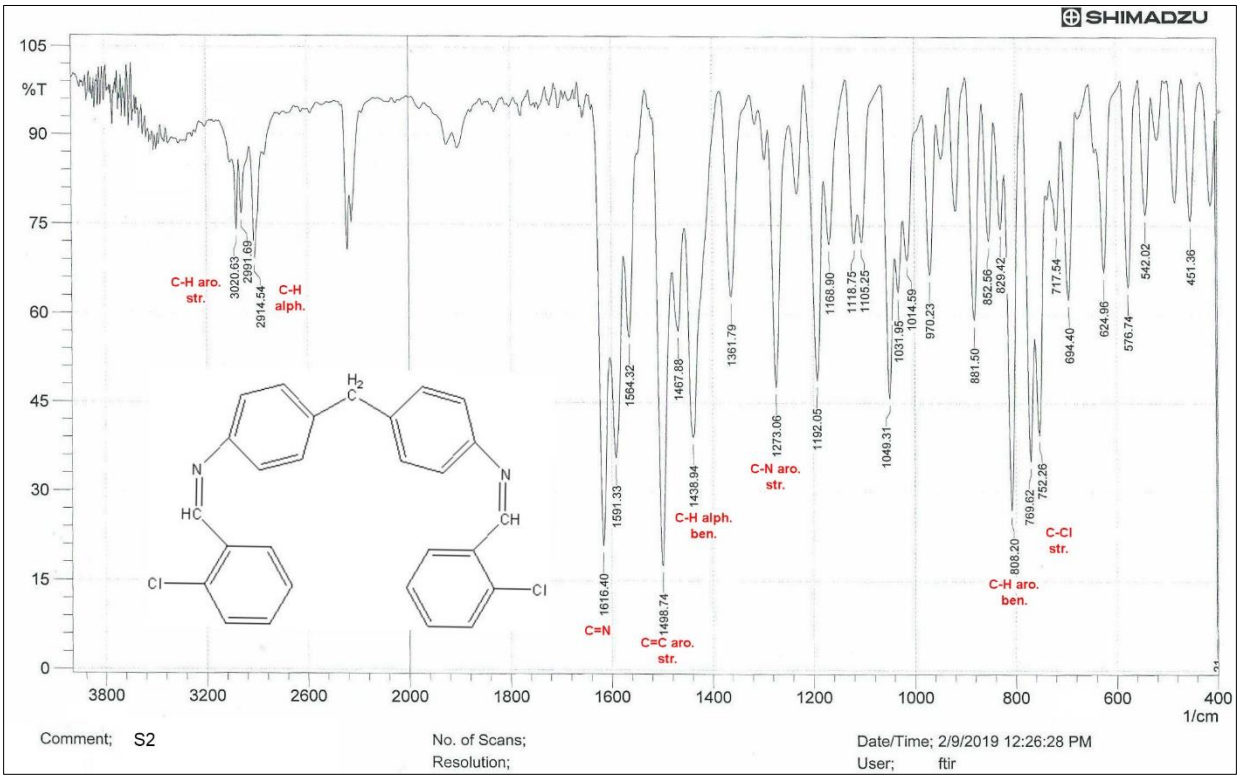


Figure 7 FT-IR spectrum of compound (S2)

Oxazepine compounds (OX1-OX4) were characterized at first by using IR spectroscopy. Table (4) and Figures (5-8) show the locations of the bands and the IR spectra of the prepared oxazapine compounds.

Table 3 FT.IR data of Schiff bases compounds (S1, S2)

COM. NO.	Characteristics bands FT-IR spectra $\bar{\nu}$ = cm-1							
	C-H Arom. Str.	C-H Arom. ben.	C-H Aliph. str.	C-H Aliph. ben.	C=N imine	C-N Arom. str.	C-Cl Str.	C=C Ar. Str.
S1	3022 (w)	817 (s)	2914 (m)	1363 (m)	1614 (m)	1271 (s)	759 (s)	1500 (m)
S2	3020 (w)	808 (s)	2914 (m)	1438 (m)	1616 (m)	1273 (s)	769 (s)	1498 (s)

All spectra of the prepared compounds showed strong absorption bands in the range (1700-1715) cm^{-1} due to the stretching vibration of the (C=O) Lactone [34] and the medium absorbency at the range (1650-1670) cm^{-1} due to the stretching vibration of the (C=O) Lactam [34]and common bands of all spectra at range (1000-1180) cm^{-1} and the range (1200-1270) cm^{-1} are due to the symmetric and asymmetric the (C-O) Lactone [36] as respectively. Also, common absorption stretching bands for OX1, OX3 in the range (1530-1540) cm^{-1} and at (1350) cm^{-1} are due to symmetric and asymmetric (N-O) respectively [35], and medium stretching absorption bands in all compounds which it belongs to (C-N) Lactam at range (1260-1330) cm^{-1} [37].

The spectrum of all oxazepine compounds was characterized by the presence of weak stretching bands in the range (3000-3100) cm^{-1} and medium broad bending bands in the range (680-900) cm^{-1}, which are the vibration of the aromatic (C-H) bond[23,24], and there are moderate to strong vibration bands (1450-1610) cm^{-1} for all compounds and weak to strong vibration bands (1630-1660) cm^{-1} for OX1, OX4 for aromatic & aliphatic (C=C) bond vibration as respectively [38], and also strong stretching vibration bands for C-Cl at range (600-800) cm^{-1} for all compounds [34,35].

Table 4 FT.IR data of prepared Oxazepine compounds (OX1-OX4)

COM. NO.		OX1	OX2	OX3	OX4
Characteristics bands FT-IR spectra $\bar{\nu}$ = cm^{-1}	C-O Lactone sy & asy	1072 & 1269	1165 & 1230	1145 & 1203	1161 & 1230
	N-O Arom. Str. sym	1533 (s)	N.F	1535 (s)	N.F
	N-O Arom. Str. asy	1350 (m)	N.F	1350 (s)	N.F
	C-H Arom. Str.	3055 (m)	3036 (w)	3039 (w)	3039 (w)
	C-H Arom. ben.	810 (m)	813 (m)	779 (m)	817 (w)
	C-H Aliph. str.	2983 (w)	2920 (w)	2874 (m)	2912 (w)
	C-H Aliph.ben. alkane & alkene	1384 (w)	1438 (m) 979 (m)	1465 (m)	1438 (m)
	C=O str. lactone	1705 (s)	1712 (s)	1712 (s)	1705 (m)
	C=O str. lactam	1668 (m)	1658 (m)	1654 (s)	1662 (m)
	C-N str. lactam	1298 (m)	1323 (m)	1269 (m)	1327 (m)
	C-Cl Str.	754 (m)	729 (m)	698 (s)	767 (w)
	C=C Ar. & Al. Str.	1527 (s) 1658 (s)	1464 (s) N.F	1604 (m) N.F	1519 (s) 1631 (w)
N.F = NOT FOUND					

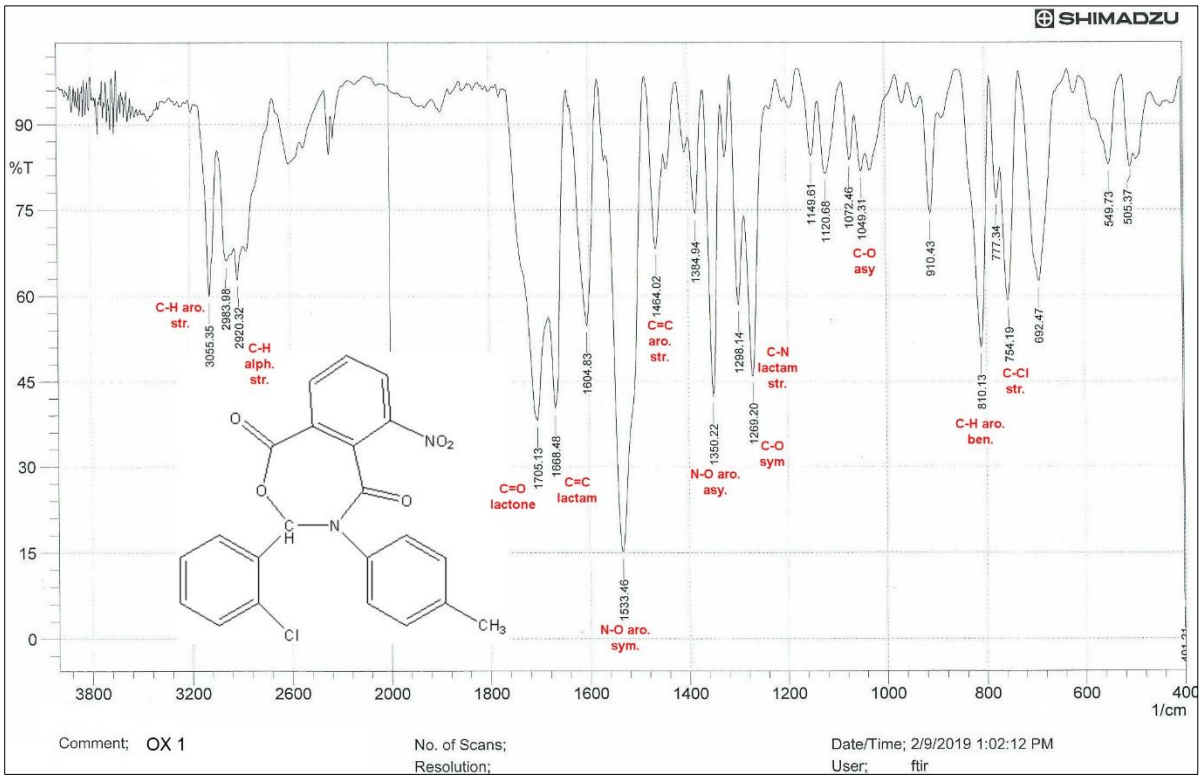


Figure 8 FT-IR spectrum of compound (OX 1)

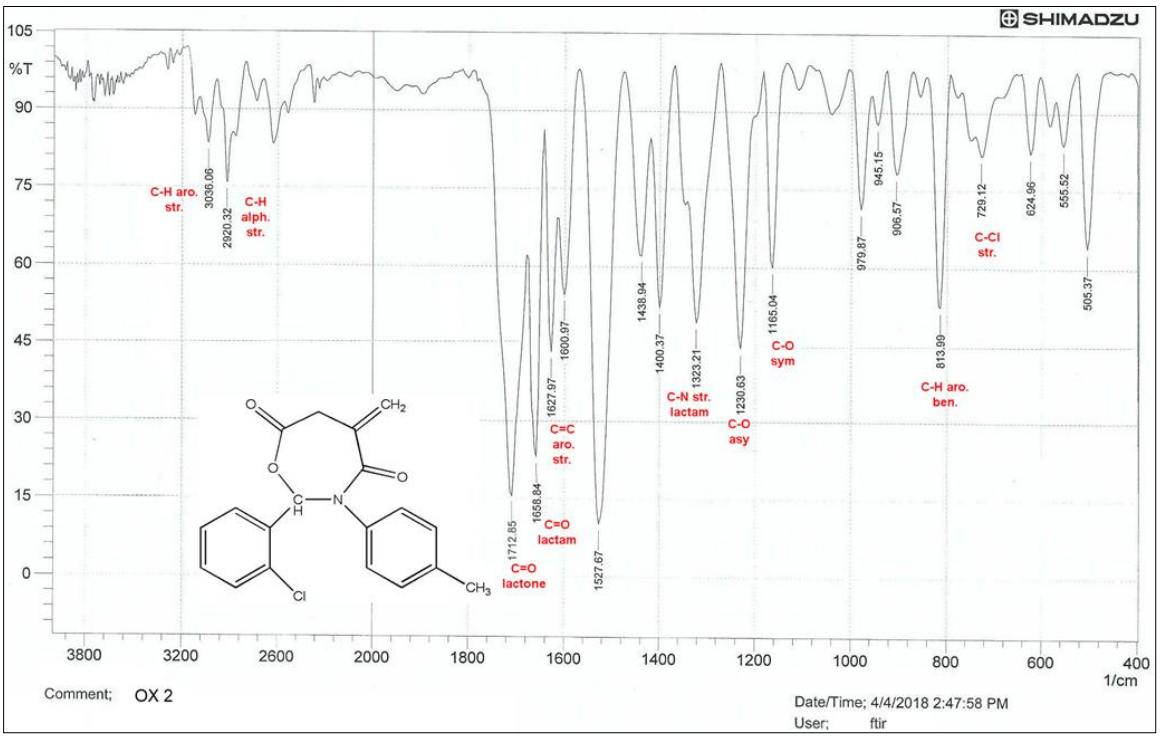


Figure 9 FT-IR spectrum of compound (OX 2)

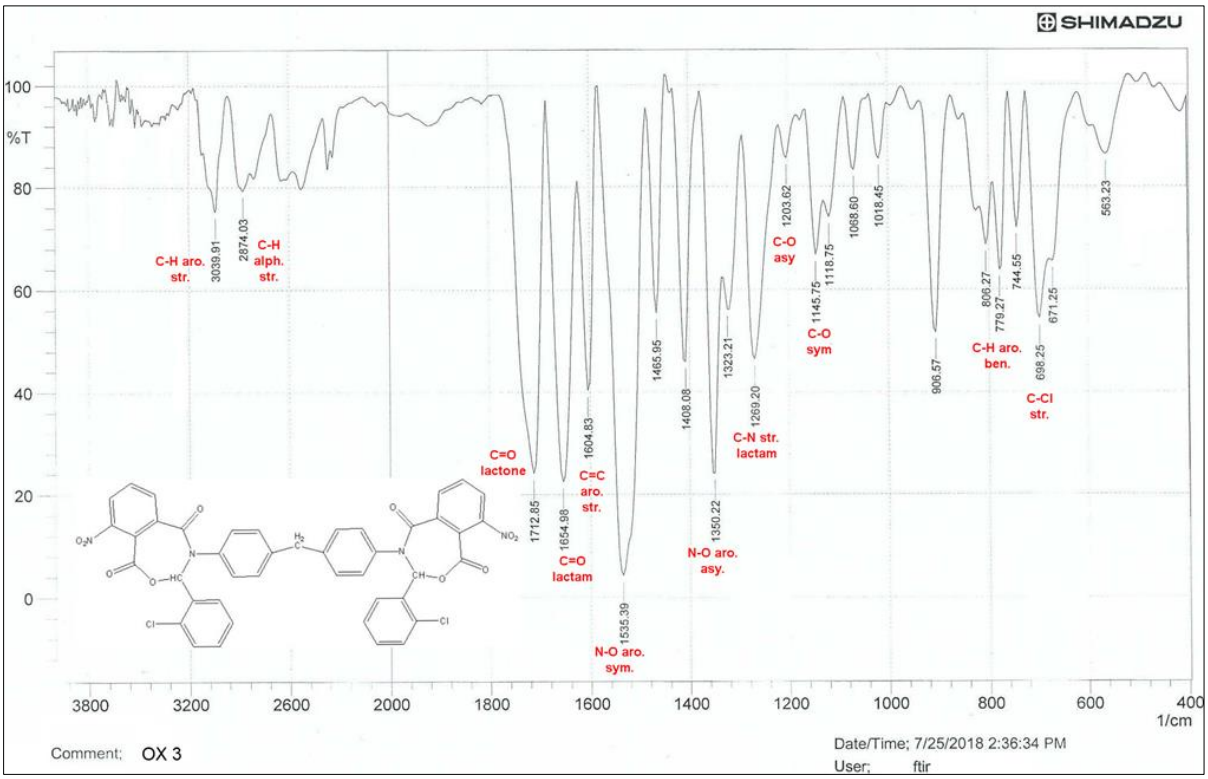


Figure 10 FT-IR spectrum of compound (OX 3)

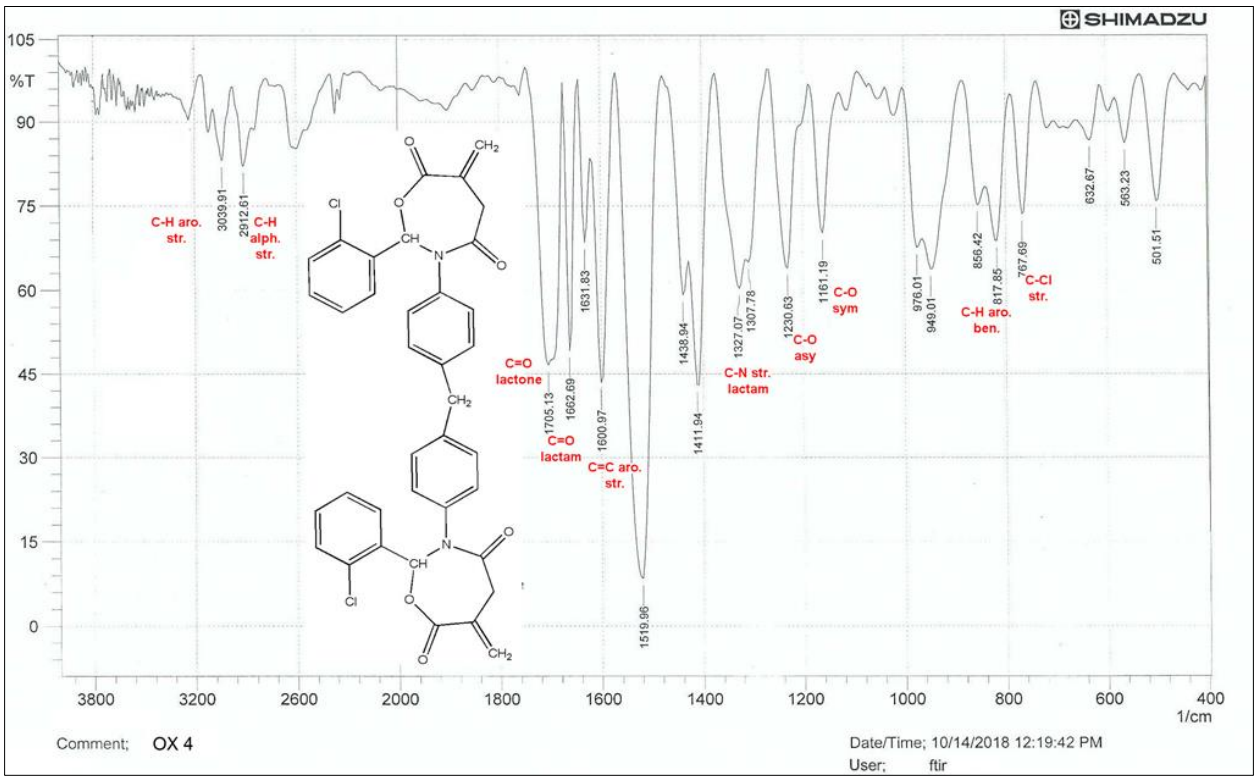


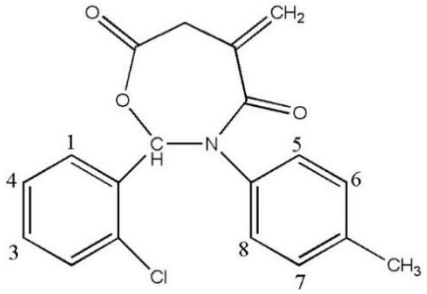
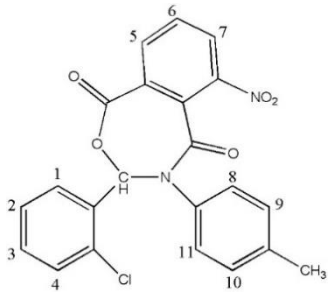
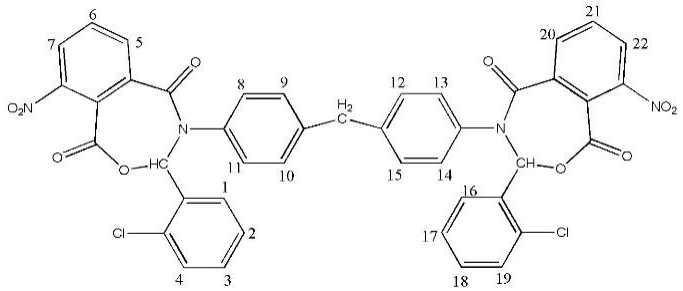
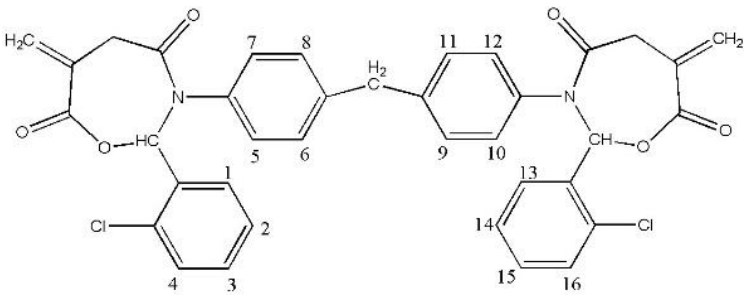
Figure 11 FT-IR spectrum of compound (OX 4)

3.2. ^{1}H-NMR Spectra

Table (5) and figures (9-12) show spectra and results for prepared oxazepines, also all showed singlet signals at 6.60-6.80 ppm due to the proton in (O-CH-N) and multiple signals at 7.0-8.5 ppm for protons in phenyl rings. Compounds (OX1, OX2) showed a sharp singlet signal at 2.2 ppm belonging to protons of the methyl group [40, 41].

Also, compounds (OX1, OX4) showed doublet signals at 3.2-3.4 ppm and doublet signals at 5.6-6.3 ppm due to the protons of aliphatic saturated (CH_2) and unsaturated (=CH_2) respectively on oxazepane rings. Both (OX3, OX4) showed singlet signals at 3.43 ppm due to proton in (Ph-CH_2-Ph) [42, 43].

Table 5 ^{1}H-NMR data of prepared compounds (OX1-OX4)

NO.	Structure	Chemical Shift (ppm) TMS = 0 ppm
OX1		2.20 (s, 3H, CH3) 3.24 (d, 1H, CH2) 3.26 (d, 1H, CH2) 5.64 (d, 1H, =CH2) 6.22 (d, 1H, =CH2) 6.71 (s, 1H, O-CH-N) 7.09-7.65 (m, 8H, H1-H8)
OX2		2.20 (s, 3H, CH3) 6.62 (s, 1H, O-CH-N) 7.09-8.44 (m, 11H, H1-H11)
OX3		3.43 (s, 2H, Ph-CH2-Ph) 6.63 (s, 2H, O-CH-N) 7.13-8.22 (m, 22H, H1-H22)
OX4		3.27 (d, 2H, CH2) 3.35 (d, 2H, CH2) 3.43 (s, 2H, Ph-CH2-Ph) 5.64 (d, 2H, =CH2) 6.22 (d, 2H, =CH2) 6.71 (s, 2H, O-CH-N) 7.13-7.65 (m, 16H, H1-H16)

The following figures for ^{1}H-NMR spectra show the peaks and signals for the protons of the prepared oxazapine compounds, as follows:

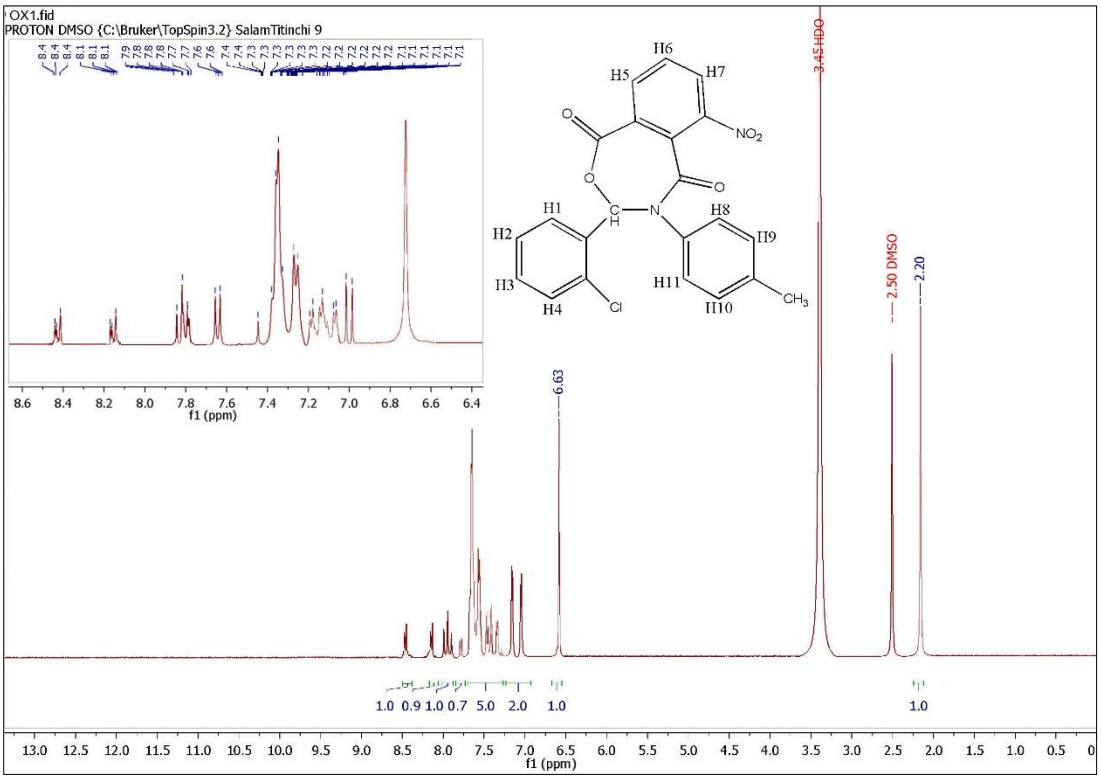


Figure 12 ^{1}H-NMR spectrum of compound (OX1)

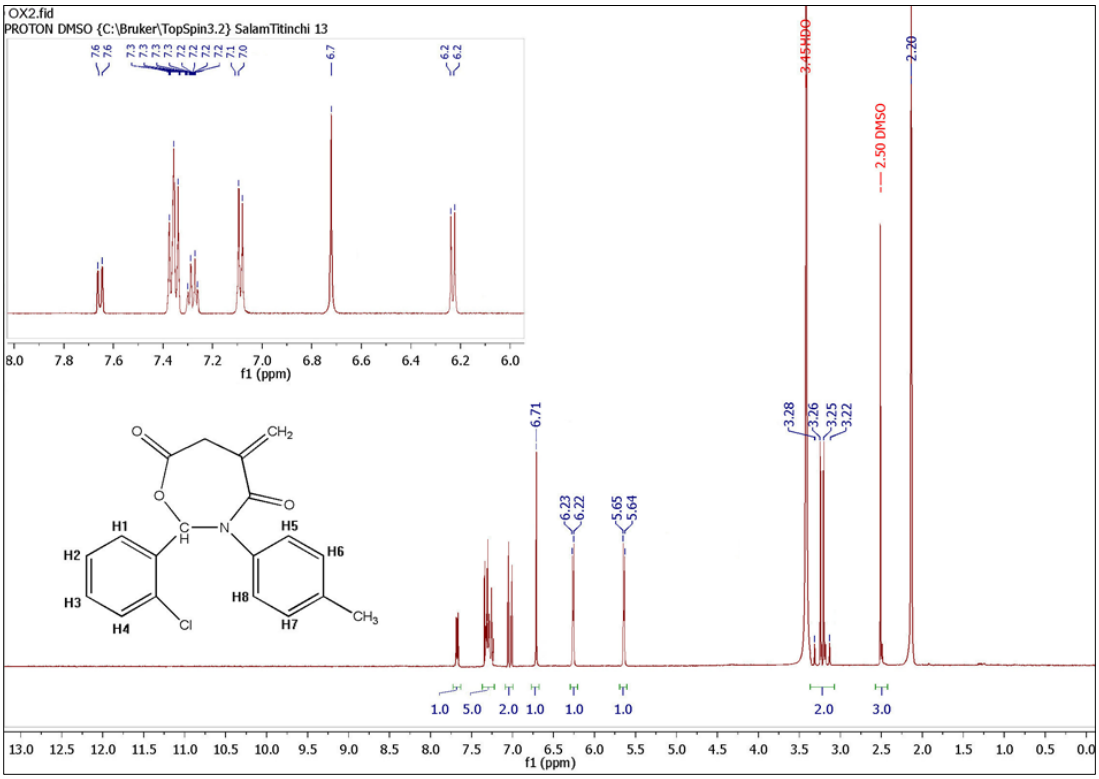


Figure 13 The ^{1}H-NMR spectrum of compound (OX2)

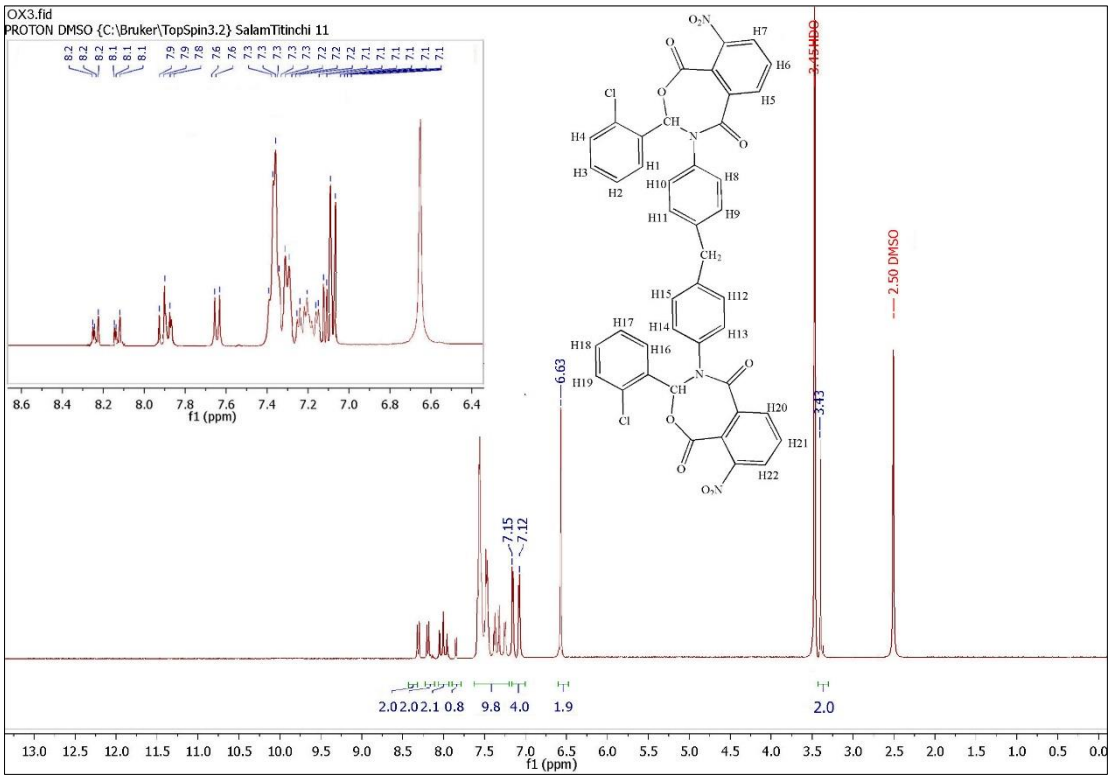


Figure 14 The ^{1}H-NMR spectrum of compound (OX3)

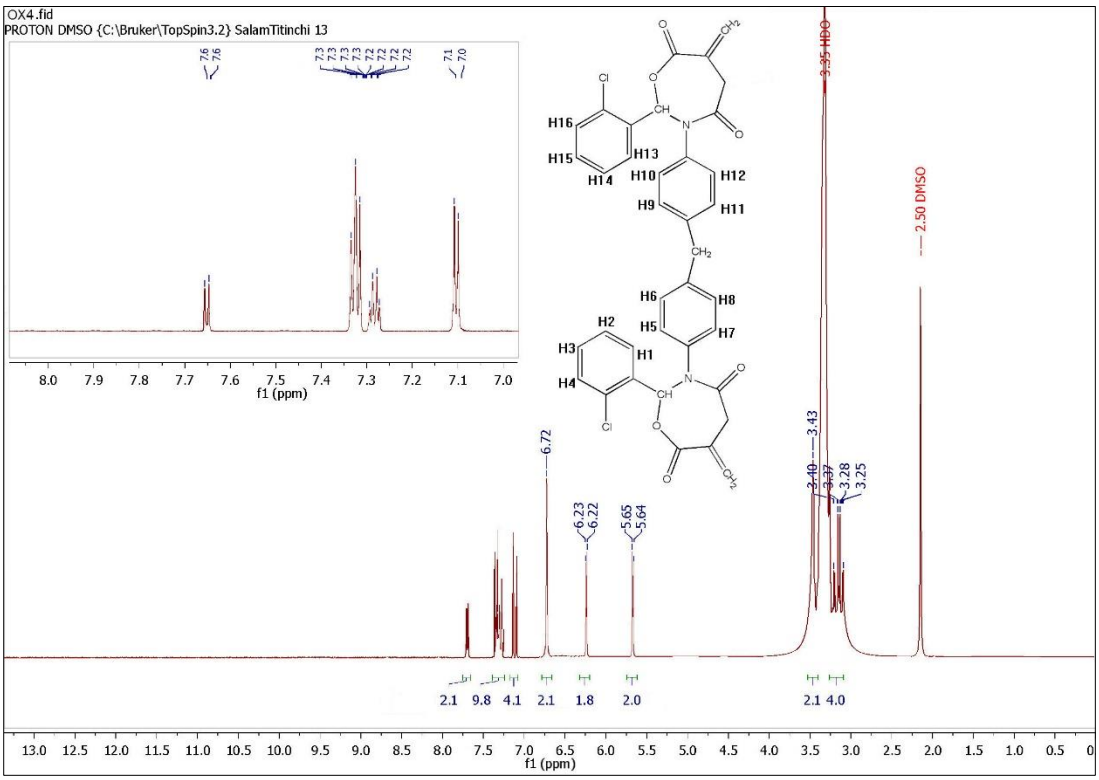


Figure 15 The ^{1}H-NMR spectrum of compound (OX4)

3.3. Antibacterial activity

Two types of bacteria have been used to study the biological activity of OX1-OX4 which is gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus*, A concentration of these compounds was obtained by dissolving (0.05 g) of the compounds in 1 ml of DMSO. The dishes were injected after being punctured by these solutions and incubated for 24 hr. at 37°C. The dishes were extracted and the diameters of the inhibition zones (mm). Table (6) and Figures (13) and (14) illustrate the results and effects of the prepared compounds. It showed that compound OX4 have high inhibition against *Staphylococcus aureus* and OX3 does not have any effect on bacteria, on the other hand, OX1 showed a good effect against *Escherichia coli* while OX2 did not show any inhibition on bacteria.

Table 6 Biological results of compounds (OX1-OX4)

No.	Conc. mg/ml	Inhibition zone(mm)	
		*S. aureus	*E. coli
OX1	50	11	12
OX2	50	16	zero
OX3	50	zero	10
OX4	50	20	9
Control		Zero	Zero

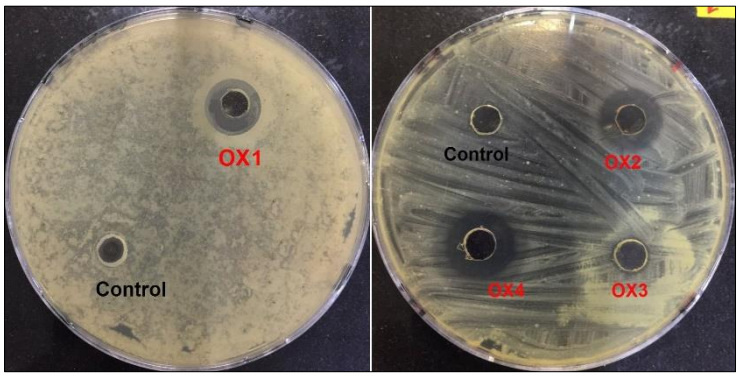


Figure 16 Biological activity of (OX1-OX4) against Staphylococcus aureus

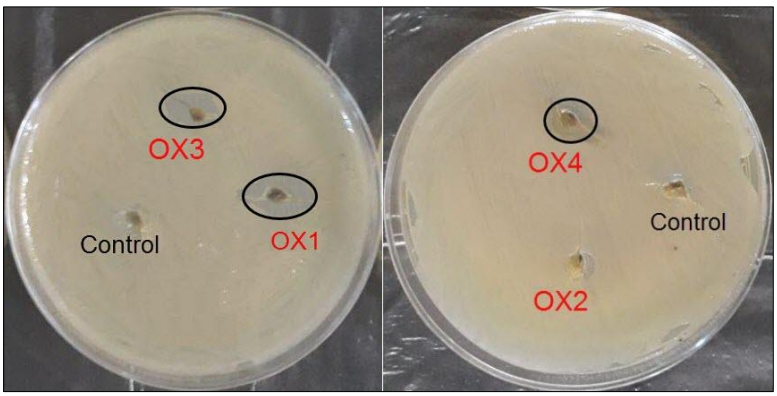


Figure 17 Biological activity of (OX1-OX4) against *Escherichia coli*

4. Conclusion

The possibility of preparing some mono-chelating and bi-chelating Schiff bases derived from the reaction of 2-chlorophenzaldehyde or another aldehyde with a different primary amine in ethanol solvent and with the presence of glacial acetic acid as a catalyst, with a reaction yield of 70 to 90%.

The possibility of preparing some of the new oxyazepine compounds through the reaction of the Schiff bases with different anhydrides in dry benzene or dry toluene solvents, and the yield of a reaction between 40 to 60%.

The possibility of preparation of complexes for some of the compounds oxyazepine prepared by the reaction of the oxazepine compound with metals ions salts and using ethanol as solvent to give a precipitate with a yield of a reaction between 35 to 87%.

The oxazepine compounds can decompose if they are not stored well far from light, heat, and moisture. And that is what we discover from our experiences inside our laboratory.

The results of the biochemical efficacy of oxyazepine and some of its complexes against the bacterial growth of two Gram-negative bacteria *Escherichia coli* and Gram-type Staphylococcus aureus demonstrated their ability to inhibit the growth of Staphylococcus aureus was greater compared with the ability to inhibit the growth of gram-negative bacteria *Escherichia coli*.

Recommendations

- Prepare new Schiff bases derived from different types of aldehydes and amines, using environmentally friendly catalysts and solvents, and using different reaction conditions.
- Prepare other heterocyclic compounds such as the thiazolidinedione, tetrazole and imidazolidinone rings by reacting of Schiff base with each thioglycolic acid, sodium azide and glycine, respectively, and under different reaction conditions and with the presence of oxazapine rings in the composition.
- Prepare new complexes derived from our or another oxazapine compounds with different types of positively charged mono or di-valence transition elements and their use as a method for extracting impurities such as metal ions from solutions.
- The reaction of oxazapine compounds with the dye 4, 4`,4``,4``-tetraamino copper phthalocyanine through the carbonyl group.
- Toxicological study of the prepared compounds.
- The possibility of studying the biological activity of oxazapine and its complexes against other types of bacteria and studying their effectiveness against types of fungi and using other drugs as references other than amoxicillin to be compared.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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