Synthesis and Characterization of Oxazepine and Diazepine Derivatives from 1-Methyle Imidazole and Study Biological Activity for Them

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Abstract
This research included the preparation of heterocyclic compounds with a seven-membered ring (1,3 oxazepine) and (1,3 diazepine). the first step was included preparation of azo compound (1) from coupling of diazonium salt of p-phenylenediamine with 1-methyl imidazole in an alkaline alcoholic medium, then followed by the reaction of azo compound (1) with 2-hydroxy-5-nitro benzaldehyde to form a azo compound(2) then it react with 4-methoxy aniline in absolute ethanol and in the presence of glacial acetic acid as a catalyst to get Schiff bases (3) then Schiff bases reacted with (maleic anhydride, succinic anhydride) in dry benzene to get heterocyclic seven-membered compounds (4,5) and the last step react between oxazepine deritives (4,5) with phenyl hydrazine and aniline in absolute ethanol to get diazepine derivatives (6,7) from phenyl hydrazine and (8,9) from aniline, respectively, all these prepared compounds were characterized by FT-IR and 1H-NMR, and the reaction was followed up by RF and TLC technology, and melting points were measured, and then the biological activity of them was studied using two types of positive and negative bacteria.
Keywords: Azo compound, Schiff base, Oxazepine, diazepine

1. Introduction

Azo compound widespread compounds used as dyes in addition to their uses in the pharmaceutical industry(1). azo compound can be differentiated by functional group –N=N– the azo group which can be carry on both ends alkyl or aryl group(2) . aromatic azo compounds used widely in the chemical industries as dyes, food additives, and as initiators in free radical reaction and in drugs industry(3).Schiff bases are formed by the condensation reaction between primary amines with carbonyl compounds (R-CH=N-R、) the general formula of Schiff base that show the functional group (CH=N) which called azomethine group R and R、 refers to alkyl, aryl group(4).

Hugo Schiff was the first to report Schiff base in 1864[5]Anils, imines, azomethine are all the names for these compounds it was proposed that the C=N relationship in[6]. Schiff base play a crucial role in demonstrating biological activity this because of the existence of a lone pair of electrons in a sp^2 hybridized orbital of the nitrogen atom of the azomethine group was further investigated for its chemical and biological significance[7]. Heterocyclic compound are cyclic organic compounds that include at least one heteroatom in addition to carbon atoms , The most frequent heteroatoms are nitrogen, oxygen, and sulfur but the heterocyclic ring can also contain other hetero atoms[8].heterocyclic compounds have high activity as a biological disciplines such as anti-fungal , anti-inflammatory , anti-bacterial , anti-oxidant , anticonvulsant , anti-allergic , enzyme inhibitors , anti-HIV , anti-cancer activity[9].Oxazepine is a seven-membered unsaturated compound with heteroatoms oxygen in position 1 and nitrogen in position (2,3,4) as well as five carbon atoms[10].Oxazepine can synthesis by pericyclic cycloaddition of Schiff bases with anhydride[11]. oxazepine and derivatives are important medically and biologically as well as having medicinal and pharmacological applications[12] . specially as enzyme inhibitors, analgesic, anti-depressant, and psychoactive drugs[13].Diazepine is an organic heterocyclic molecule with seven-atom ring which contain two nitrogen atoms as well five carbon atoms [14]. there are three isomer of diazepine according to nitrogen atoms position which is (1,2-diazepine, 1,3-diazepine, 1,4-diazepine)[15]. when diazepine bind with benzene ring they form compounds known as benzodiazepine denoted by (BZD) , benzodiazepine are the most commonly medicines which it belongs to class of drugs called as secondary nerve sedatives[16]. benzodiazepine one of the most important substances in medical chemistry with application as an anti-microbial, anti-cancer, anti-anxiety, and anti-depressant[17].

2. Materials

(FT-IR) Spectra (400-4000 cm^{-1}) in KBr disk were recorded on a SHIMADZU FTIR - 8400S Fourier transform. Melting points were measured using Stuart, UK. H^1-NMR were recorded on Fourier transformation Bruker spectrometer operating at (400MHz) with (DMSO - de) measurements were made at Department of Chemistry, Basra University, Iraq.

doi.org/10.31838/hiv23.02.4 Received: 26.10.22, Revised: 12.11.22, Accepted: 14.12.22

Synthesis of Azo Derivative (1) (18)

The diazonium salt was prepared by dissolving (0.01 mol 1.0814 g) of the amino compound P-phenylene diamine in a solution consisting of 60 ml of distilled water and 4 ml of concentrated HCl. The solution was cooled to (0-5) °C in an ice bath add to it a solution of 20 mL Distilled water (0.01 mol ,0.7 g) of sodium nitrite (NaNO2), gradually added with continuous stirring, left for (20) minutes at a temperature of (0-5) °C to complete the dizoziation process. Then gradually add the formed diazonium salt to the component solution From (0.01 mol ,0.797 ml) of N-methylimidazole and 1 g of sodium hydroxide dissolved in 130 ml of distilled water and left the mixture for two hours with continuous stirring at PH = 6 to get a black precipitate that is washed with distilled water and then recrystallized with ethyl alcohol.

Synthesis of Diazo Derivative (2) (19)

The diazonium salt was prepared by dissolving 0.005 mol 1 g compound (1) in a solution consisting of 60 ml of distilled water and 4 ml of concentrated HCl. The solution was cooled to (0-5) °C in an ice bath add to it a solution of 20 mL Distilled water (0.01 mol, 0.7 g) of sodium nitrite ($NaNO_2$), gradually added with continuous stirring, left for (20) minutes at a temperature of (0-5) C° to complete the dizoziation process. Then gradually add the formed diazonium salt to the component solution from (0.005 mol, 0.835 g) of 2-hydroy-5- nitro benzaldehyde and 1 g of sodium hydroxide dissolved in 130 ml of distilled water and left the mixture for two hours with continuous stirring at PH = 6 to get a brown precipitate that is washed with distilled water and then recrystallized with ethyl alcohol.

General Method of synthesis Compound (3) (20)

The compound (3) Schiff base was prepared by reacting (1 g , 0.0026 mol) of compound (2) dissolved in 10 ml ethanol absolute and add 3 drops of glacial acetic acid with (0.3201 g, 0.0026 mol) of (4-methoxy aniline) in (10 ml) of ethanol absolute and reflux at (78 ^{0}C) for (28 hours) , after which the solution is left to cool at room temperature for (24) hours, and the precipitate are recrystallized With methanol.

Synthesis of Oxazepine Derivative (4,5) (21)

(4,5) derivatives (Oxazepine) were prepared by reacting (0.002 mol, 1g) of compound (3) with each of (0.002mol, 0.2 g) (succinic anhydride), (0.002 mol, 0.196 g)) (maleic anhydride) each dissolve in (25 ml) of dry benzene. The reflux was done from (26,32) hours at a temperature of (80 C°) after that the solution is left for a period of (24 hours), then, it is filtered and recrystallized with ethanol.

Synthesis of Diazepine Derivative (6,7) (22)

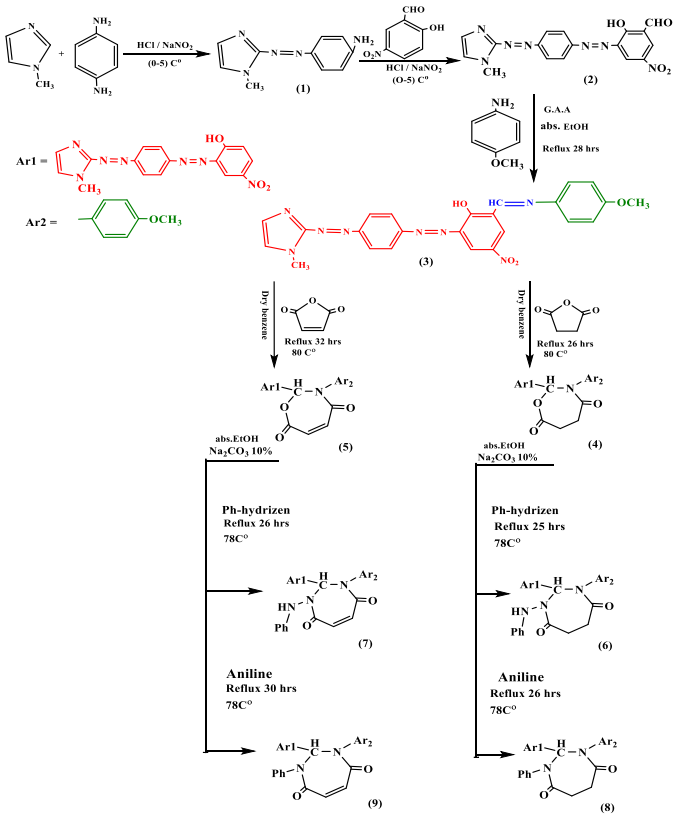
The diazepine derivatives (6,7) were prepared by dissolving (0.001mole) of the derivatives (6,7) (0.57, 0.58 g) dissolved in 20 ml of absolute ethanol and dissolve (0.001 mole, 0.098 ml) of phenyl hydrazine in 10 ml of absolute ethanol, mix the two solutions with addition of sodium carbonate (solution 10%) was refluxed for (25,26) hours. The solvent was evaporated, and the formed precipitate was washed with ethyl ether and recrystallized by absolute ethanol.

synthesis of Diazepine Derivative (8,9) (22)

The diazepine derivatives (8,9) were prepared by dissolving (0.001mole) of the derivatives (6,7) (0.57,0.58 g) dissolved in 20 ml of absolute ethanol and dissolve (0.001 mole 0.091 mL) of aniline in 10 ml of absolute ethanol, mix the two solutions with addition of sodium carbonate (solution 10%) was refluxed for (24-30) hours. The solvent was evaporated, and the formed precipitate was washed with ethyl ether and recrystallized by absolute ethanol.

Preparation of Microbiology Culture Media (23)

38 g of nutrient agar is dissolved in (1L) of distill water, after that place it in an autoclave for 15 minutes at 121 C° for the purpose of sterilizing. After the media reached 37 C°, it is poured into petri dishes made ready for bacteria streaking. It was acquiring isolated bacteria (*Escherichia coli*) and (*Staphylococcus aurous*) from hospital. It was cultivated, and the plates were incubated at 37 C° for 24 hours for both type of bacteria, DMSO was used as a solvent to prepare solution of the various compounds were tested (0.02 g of compounds in 5 ml DMSO) after that the inhibition zones were calculated for each compound.



Scheme (1): synthesis of some heterocyclic compound's

derivatives

3. Result and Discussion

Compound (1): 4-((1-methyl-1H-imidazol-2-yl)diazenyl)aniline

The infrared spectrum data of the compound (1) showed band at (3209.33-3332.76 cm-1) broad for (N-H) band in NH2 group, (1589.23 cm-1) for (C=N) for imidazole ring, (2846.74-2923.88 cm-1) for (C-H) in (CH3), (3031.89 cm-1) for (C-H) aromatic, (1388.65 cm-1) for (N=N) and 1512.09 cm-1 due to aromatic (C=C). The 1H-NMR (DMSO) spectrum data of compound (1) show δ: 6.6, 7.5 (m,6H, Ar-H), 5.7 (S, 2H, NH2) , 3.7 (S,3H,CH3).

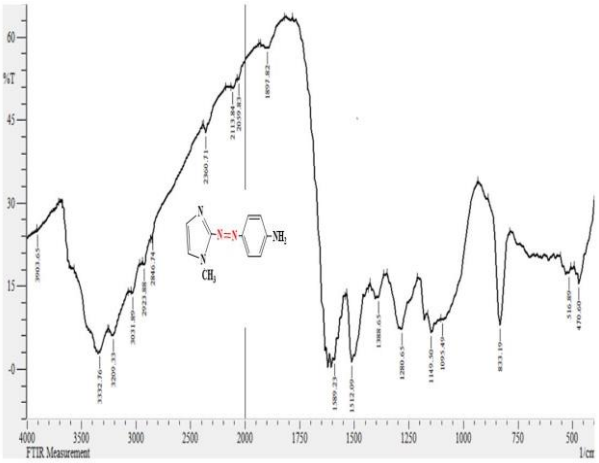


Fig. 1: FT-IR spectrum of compound (1)

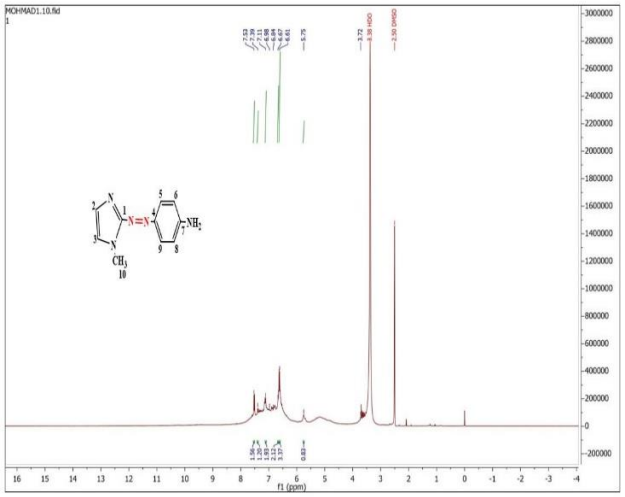


Fig. 2: 1H-NMR spectrum of compound (1)

Compound (2): 2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl)phenyl)diazenyl)-5-nitrobenzaldehyde

The infrared spectrum data of the compound (2) showed band at (3070.46 cm^{-1}) for (Ar-H) ,and the (N-H) band disappear in the chart of compound (1),(3394.48 cm^{-1}) for (OH) band, (1666.38 cm^{-1}) for (C=O benzaldehyde), (2738.73 cm^{-1}) for (C-H aldehyde), (1581.52 cm^{-1}) for (C=N) for imidazole ring, (2977.89cm^{-1}) for (C-H) in (CH_3), (1473.51 cm^{-1}) for (N=N) and (1542.95cm^{-1}) due to aromatic (C=C) and (1527.52 ,1342.36 cm^{-1}) for (NO_2) band. ^{1}H-NMR (DMSO) spectrum data of compound (2) show δ: 7.1-8.5 (m,8H, Ar-H), 12 (S, 1H, CH Aldehyde) , 1.2(S,3H,CH_3), 10.3(S,1H,OH).

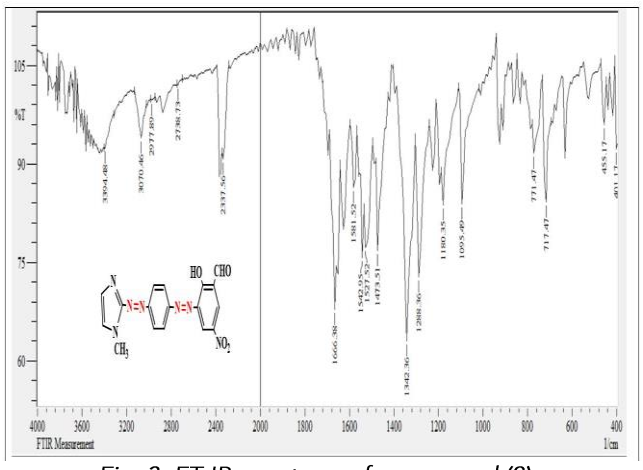


Fig. 3: FT-IR spectrum of compound (2)

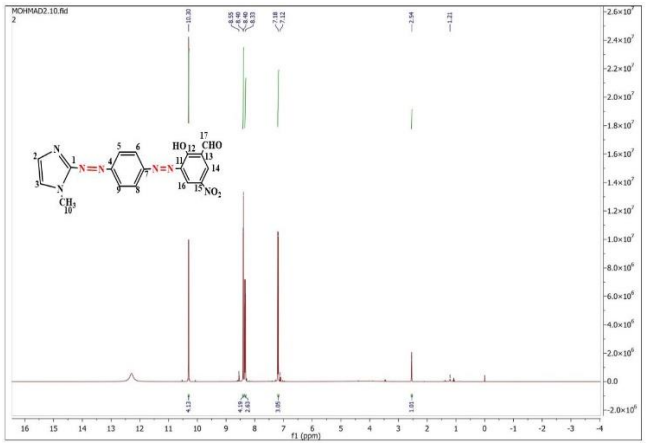


Fig. 4: ^{1}H-NMR spectrum of compound (2)

Compound (3) 2-(((4-methoxyphenyl) imino) methyl)-6-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-4-nitrophenol

The infrared spectrum data of the compound (3) showed band at (1620.09 cm-1) for azomethine group(C=N), (3271.05 cm-1) for (OH) band, (2916.17 cm-1) for (C-H) in (CH3), (3062.75 cm-1) for (C-H) aromatic, (1512.09 cm-1) for (C=C) and (1488.94 cm-1) due to aromatic (C=N), (2839.02 cm-1) for (OCH3), (1442.66,1342.36 cm-1) for (NO2). 1H-NMR (DMSO) spectrum data of compound (3) show δ: 6.7-8.6 (m,12H, Ar-H), 9.1 (S, 1H, OH) , 1.9(S,3H,CH3), 3.8(S, 3H, OCH3).

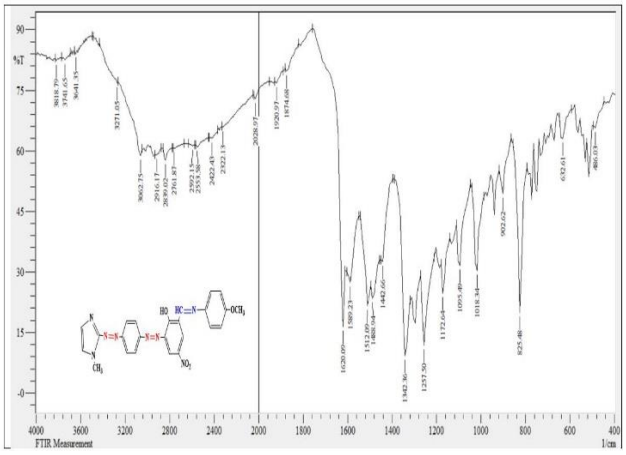


Fig. 5: FT-IR spectrum of compound (3)

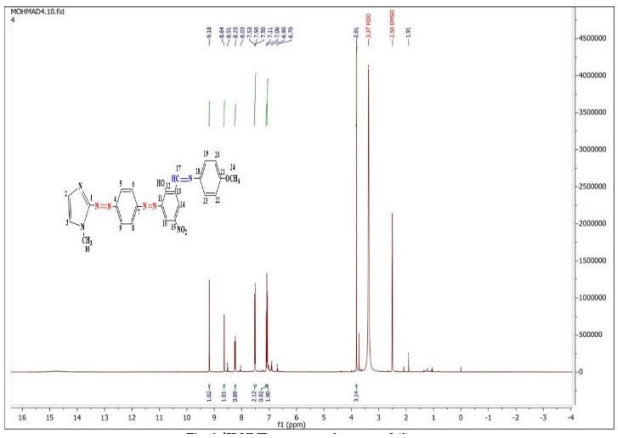


Fig. 6: 1H-NMR spectrum of compound (3)

Compound (4): 2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-3-(4-methoxyphenyl)-1,3-oxazepane-4,7-dione

The infrared spectrum data of the compound (4) showed band at (3024.18 -3062.75 cm1) for (Ar-H), (1596.95 cm-1) for (C=N) for imidazole ring, (2931.60 cm-1) for (C-H) in (CH3), (3332.76 cm-1) for (OH) band , (1419.51 cm-1) for (N=N) and (1512.09 cm-1) due to aromatic (C=C), (1697.24 cm-1) for amide carbonyl group(N-C=O) and (1774.39 cm-1) for ester carbonyl group (O-C=O) and (1342.36 cm-1) for (C-N) group inside oxazepine ring, (2846.74 cm-1) for (OCH3), (1257.50 cm-1) for (C-O-C) group. 1H-NMR (DMSO) spectrum data of compound (4) show δ: 9.1 (S,1H, OH), 0.85(S,3H,CH3), 1.2(S, 3H, OCH3), 2.4(S, 1H, CH), 3.07(t, 2H, (CH2)19), 3.8(t, 2H, (CH2)20).

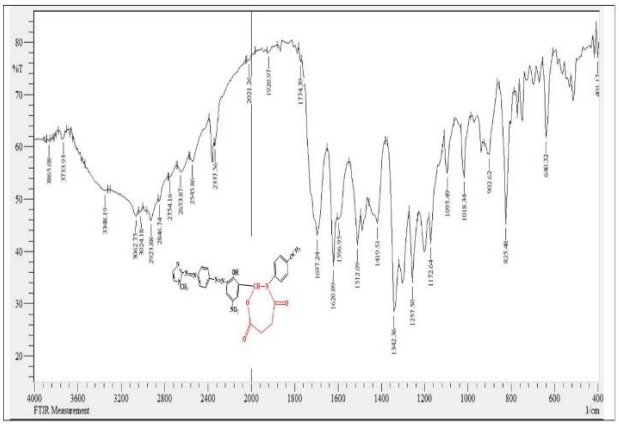


Fig. 7: FT-IR spectrum of compound (4)

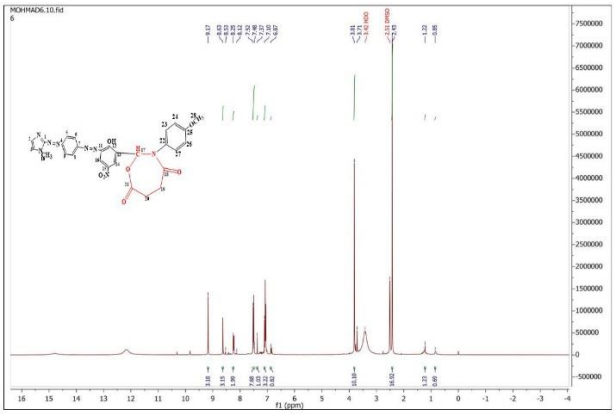


Fig. 8: [1]H-NMR spectrum of compound (4)

Compound(5):2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl) -5-nitrophenyl)-3-(4-methoxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione

The infrared spectrum data of the compound (4) showed band at (3062.75 cm-1) for (Ar-H), (1589.23 cm-1) for (C=N) inside imidazole ring, (2923.88 cm-1) for (C-H) in (CH3), (3379.09 cm-1) for (OH) , (1404.08 cm-1) for (N=N) and (1512.09 cm-1) due to aromatic (C=C), (1620.09 cm-1) for amide carbonyl group(N-C=O) and (1774.39 cm-1) for ester carbonyl group (O-C=O) and (1342.36 cm-1) for (C-N) group inside oxazepine ring, (1249.79 cm-1) for (C-O-C) group. 1H-NMR (DMSO) spectrum data of compound (5) show δ: 6.8-8.6(m,12H, Ar-H) 3.5(S, 3H, OCH3), 1.2(S,3H, CH3), 4.1(S, 1H, CH), 6.2(d, 1H, (CH)19), 6.5(d, 1H, (CH)20), 9.1(S, 1H, OH).

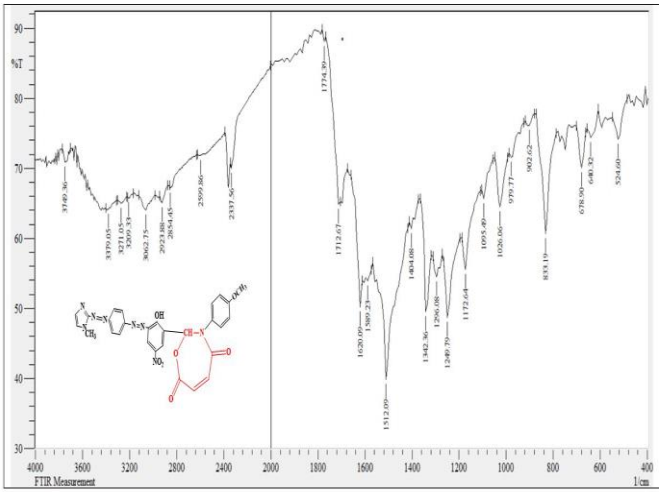


Fig. 9: FT-IR spectrum of compound (5)

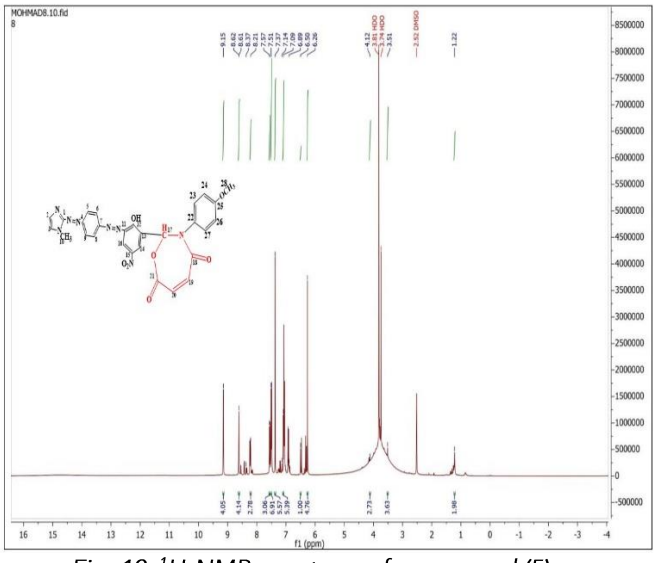


Fig. 10: [1]H-NMR spectrum of compound (5)

Compound (6): 2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-(4-methoxyphenyl)-3-(phenylamino)-1,3-diazepane-4,7-dione

The infrared spectrum data of the compound (6) showed band at (3039.60 cm-1) for (Ar-H), (1560 cm-1) (C=N) for imidazole ring, (2977.89 cm-1) for (C-H) in (CH3), (3286.48 cm-1) for (OH) , (1542.95cm-1) due to aromatic (C=C), and the band of ester carbonyl(O-

C=O) is disappear , (1650.95 cm-1) for amide carbonyl group(N-C=O) and (1485.08 cm-1) for N=N and (1242.07 cm-1) for (C-N) group inside oxazepine ring, (3379.05 cm-1) for (NH), (1172.64 cm-1) for (N-N). 1H-NMR (DMSO) spectrum data of compound (6) show δ: 6.1-8.7(m,17H, Ar-H) , 10.08 (S, 1H, OH) , 1.2(S,3H,CH3), 4.57(S, 1H, NH), 3.7(S, 1H, CH), 1.6 (S, 3H,OCH3), 2.2-2.3(t, 4H, CH2).

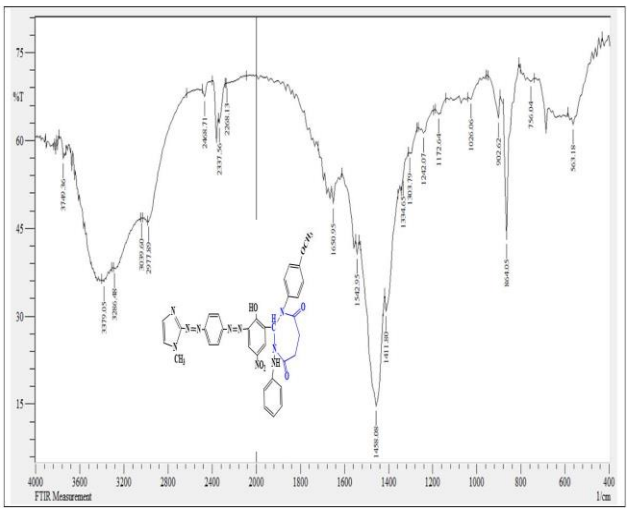


Fig. 11: FT-IR spectrum of compound (6)

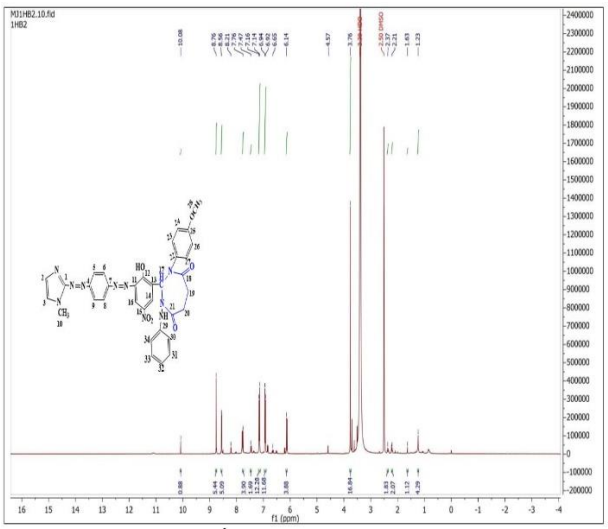


Fig. 12: 1H-NMR spectrum of compound (6)

Compound (7): 2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-(4-methoxyphenyl)-3-(phenylamino)-2,3-dihydro-1H-1,3-diazepine-4,7-dione

The infrared spectrum data of the compound (7) showed band at (3008.75-3062.75 cm-1) for (Ar-H), (1596.95 cm-1) (C=N) for imidazole ring, (2900.74cm-1) for (C-H) in (CH3), (3309.62 cm-1) for (OH) , (1488.08 cm-1) for (N=N) and (1512.09 cm-1) due to aromatic (C=C), and the band of ester carbonyl(O-C=O) is disappear , (1650.95 cm-1) for amide carbonyl group(N-C=O) and (2839.02cm-1) for OCH3, (1296.08 cm-1) for (C-N) group inside oxazepine ring, (3440.77 cm-1) for (NH), (1033.77 cm-1) for (N-N). 1H-NMR (DMSO) spectrum data of compound (7) show δ: 6.1- 8.7(m,17H, Ar-H), 10.03 (S, 1H, OH), 5.6(S, 1H, NH), 3.6(S,3H,CH3), 3.76(S, 1H, CH), 3.71(S, 3H, OCH3), 6.04 (d, 1H, CH).

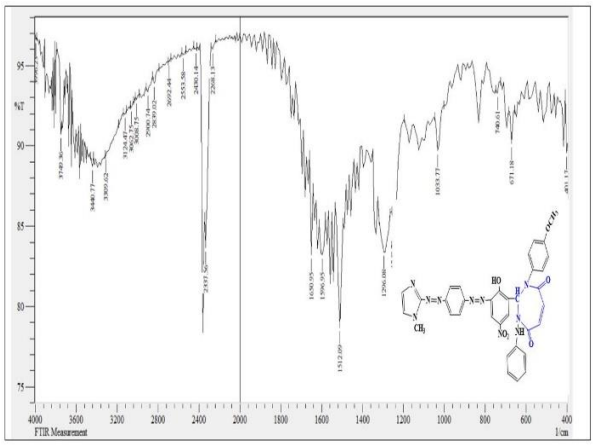


Fig. 13: FT-IR spectrum of compound (7)

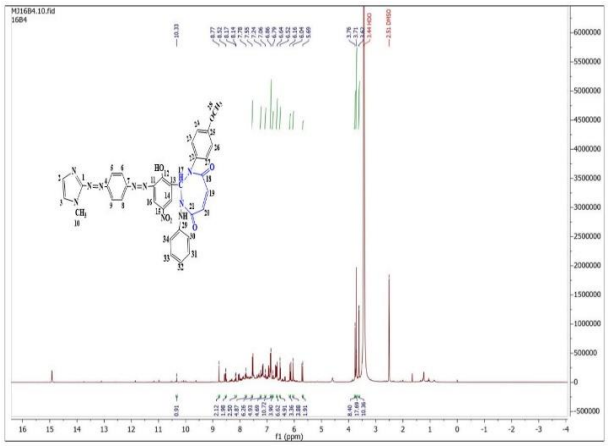


Fig. 14: ^{1}H-NMR spectrum of compound (7)

Compound (8): 2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl) -5-nitrophenyl) -1-(4-methoxyphenyl)-3-phenyl-1,3-diazepane-4,7-dione

The infrared spectrum data of the compound (9) showed band at (3379.05 cm-1) for (OH), (1580 cm-1) for (C=N) inside imidazole ring, (1458.08cm-1) for (N=N) and (1542.95 ccm-1) due to aromatic (C=C), (1666.38cm-1) due to (N-C=O amide) in diazepine ring , (1320 ,1411.80 cm-1) for (NO2) band, (1296.08 cm-1) for (C-N) in diazepine ring . 1H-NMR (DMSO) spectrum data of compound (8) show δ: 6-8.7(m,18H, Ar-H), 10.01 (S, 1H, OH) , 1.2(S,3H,CH3), 2.2(S, 1H, CH), 1.7(S, 3H, OCH3), 3.6-3.7(t, 4H, CH2).

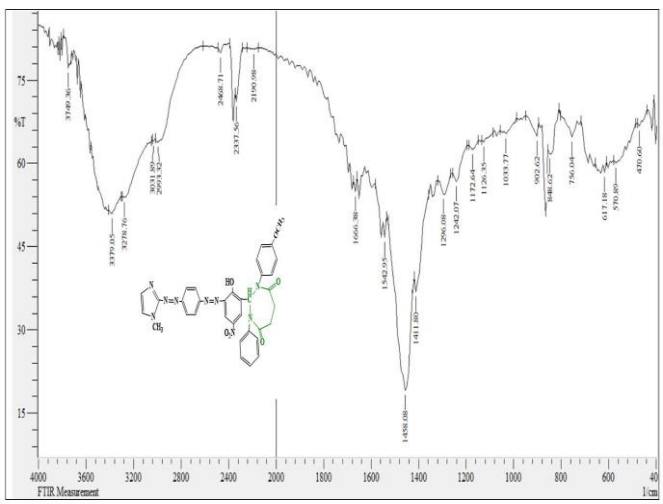


Fig. 15: FT-IR spectrum of compound (8)

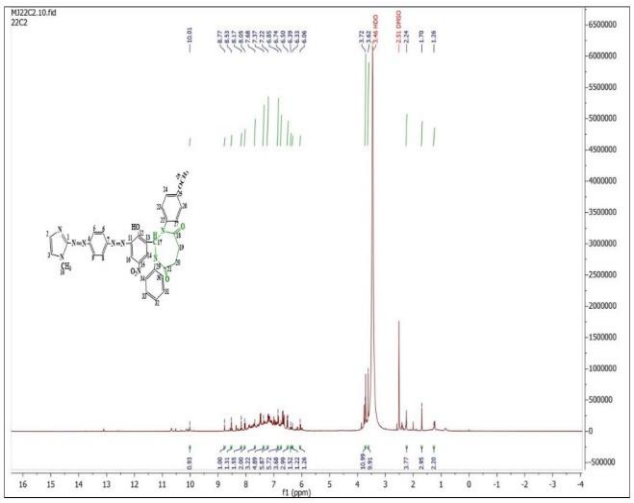


Fig. 16: [1]H-NMR spectrum of compound (8)

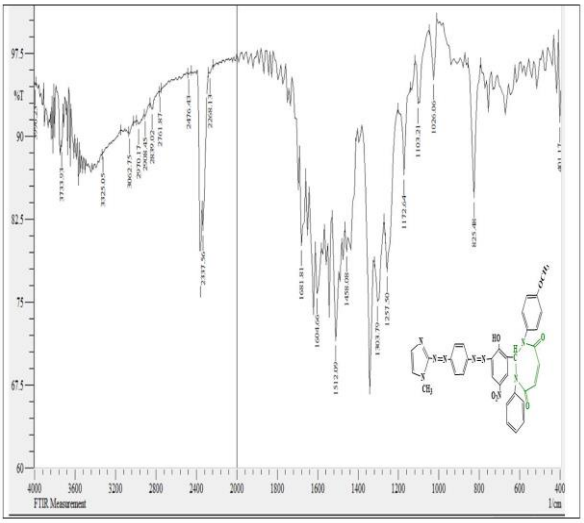


Fig. 17: FT-IR spectrum of compound (9)

Compound (9): 2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1H-1,3-diazepine-4,7-dione

The infrared spectrum data of the compound (9) showed band at (3062.75 cm-1) for (Ar-H) ,(3325.05 cm-1) for (OH), (1604.66 cm-1) for (C=N) inside imidazole ring, (2970.17-2908.45 cm-1) for (C-H aliphatic) in (CH3), (1458.08 cm-1) for (N=N) and (1542.95) cm-1 due to aromatic (C=C), (1681.18 cm-1) due to (N-C=O amide) in diazepine ring , (1303.79 cm-1) for (C-N) in diazepine ring. 1H-NMR (DMSO) spectrum data of compound (9) show δ: 7.1-8.7(m,18H, Ar-H), 10.07 (S, 1H, OH) , 1.2(S,3H,CH3), 3.7(S, 1H, CH), 3.6(S, 3H, OCH3) 6.03-6.11(d, 2H, CH).

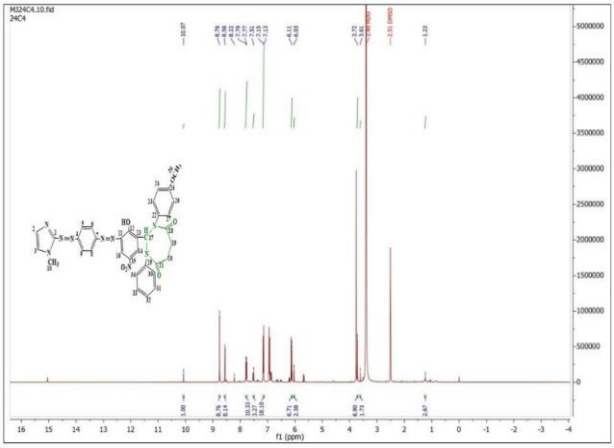


Fig. 18: 1H-NMR spectrum of compound (9)

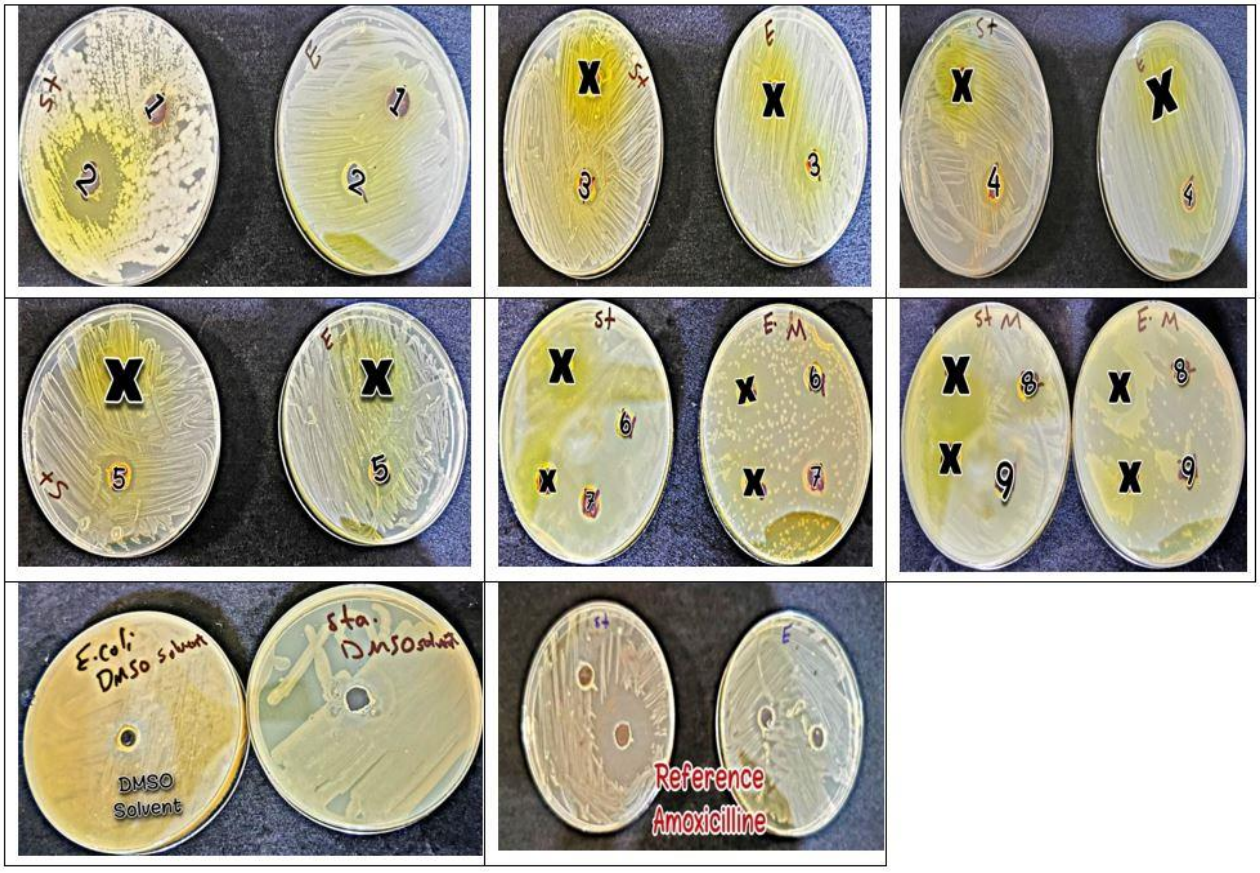


Fig. 19: Biological activity of compounds prepared against (St aureas, E Coli) bacteria

Table 1: Show Biological activity for compounds (1-9)		
Compounds No.	Bacterial species	
	E. Coli	Staph. Aureus
1	-	-
2	+	++
3	-	-
4	-	-
5	++	+
6	+	+
7	++	++
8	++	++
9	++	++
Ref. Amoxicillin	+	+++
DMSO Solvent	-	-
- = No inhibition = inactive, + = (5-10) mm = slightly active , ++= (11-20) mm = moderately active , +++ = (more than 20) mm = Good active		

Table 2: Physical properties of compounds (1-9)							
No.	Name of comp.	M.F	M.W	M.P(C°)	R.f	Color	%
1	4-((1-methyl-1H-imidazol-2-yl) diazenyl)anilin	$C_{10}H_{11}N_5$	201.23	More than 340	-	Black solid	67
2	2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrobenzaldehyde	$C_{17}H_{13}N_7O_4$	379.34	131-133	-	Dark brown	79
3	2-(((4-methoxyphenyl) imino) methyl)-6-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-4-nitrophenol	$C_{24}H_{20}N_8O_4$	484.48	175-178	0.27	Light brown	64
4	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-3-(4-methoxyphenyl)-1,3-oxazepane-4,7-dione	$C_{28}H_{24}N_8O_7$	584.55	214-216	0.45	brown powder	67
5	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-3-(4-methoxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione	$C_{28}H_{22}N_8O_7$	582.53	152-154	0.41	Light brown powder	70
6	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-(4-methoxyphenyl)-3-(phenylamino)-1,3-diazepane-4,7-dione	$C_{34}H_{30}N_{10}O_6$	674.68	294-296	0.52	Luminous shade of orange	84
7	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-(4-methoxyphenyl)-3-(phenylamino)-2,3-dihydro-1H-1,3-diazepine-4,7-dione	$C_{34}H_{28}N_{10}O_6$	672.66	265-267	0.6	Dark shade of orange	73
8	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-(4-methoxyphenyl)-3-phenyl-1,3-diazepane-4,7-dione	$C_{34}H_{29}N_9O_6$	659.66	288-290	0.031	Antique white	83
9	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1H-1,3-diazepine-4,7-dione	$C_{34}H_{27}N_9O_6$	657.65	266-268	0.55	Light Beige	88

4. Conclusions

Based on the above studies, we can conclude that the synthesized compounds appear crucial antibacterial activity against bacteria *S. aureus* and *E. coli*. The compounds that show good activity are (2,7,8,9) against (*St. aureus*), and (5,7,8,9) show good activity against (*E. coli*). The result of antibacterial activity is shown in Figure (19).

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