Synthesis and Characterization of (Azo-Oxazepane and Azo-Diazepine) Derivatives and Study their Biological Activity

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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 the prepared compound is condensed with 2-aminothiazole in absolute ethanol and in the presence of glacial acetic acid as a catalyst to get Schiff bases (3) respectively Schiff bases then reacted with (maleic anhydride, succinic anhydride) in dry benzene to get heterocyclic seven-membered compounds (4,5) and the last step the react between oxazepine derivatives(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 H1NMR, 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 bacteria.
Keywords: Azo compound, Schiff base, Oxazepine, diazepine

1. Introduction

Azo compounds are distinguished by the presence of azo group (-N=N-) in its composition, this group act as a chromophore which give these compound coloring properties in the field of dyes and pigments[1]. Azo compounds have a wide range of uses including antifungal, antibacterial[2], anti-inflammatory, anticancer, and antioxidant properties[3]. Schiff bases are by react of primary amine with carbonyl compounds such as (aldehyde and ketone) condensation[4]. These compounds are the most widespread distributed organic compounds, were first discovered by Hugo Schiff in 1864 the German chemist who won the Nobel prize. Schiff bases are generally distinguished by the presence of an imine group (–N=CH-)[5], this group give these compounds important rule in medicinal field such as biological activities , a lot of theme play role as antibacterial, antifungal, and antitumor [6], [7].Heterocyclic compounds are one of the most important areas of research in organic chemistry[8], these compounds are a cyclic compounds contain at least one heteroatom contrast to carbon the most common heteroatoms are oxygen, nitrogen and sulfur, other elements also can participate[9] Heterocyclic compounds make numerous contributions to industry, agriculture, polymers, drugs and other fields. The heterocyclic compounds play an important role in medicine application as anti-viral, anti-bacterial[10], anti-inflammatory, anti-fungal and anti-tumor drugs[11]. 1,3-oxazepine is a seven-member ring that has two hetero atoms in their structure, an oxygen atom at position one and a nitrogen atom at position three[12]. Oxazipine derivatives have a variety of biological activity including anti-bacterial, enzyme inhibitors[13],painkillers, antidepressant, anti-contraction, anti-cancer and antipsychotics[14]. Diazepine are a type of heterocyclic compounds with seven-membered ring which contain two nitrogen atoms in different position such as (1,2), (1,3) and (1,4) in heptane ring[15] Diazepine are bioactive with wide range of biological application, the diazepine scaffold is found in a number of drugs that have been used for anxiolytics, sedative and anticonvulsants [16]. The diazipine derivatives were discovered to suppress the acetyl-lysine bonding action of bromodomain-comprising proteins, which is important for gene transcriptional activation in both inflammation and cancer[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 – d6) measurements were made at Department of Chemistry, Basra University, Iraq.

preparation of the compound (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 (0.7 g) (0.01 mol) of

doi.org/10.31838/hiv22.02.555 Received: 14.07.22, Revised: 26.08.22, Accepted: 31.08.22

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.

preparation of the compound (2) [19]

The diazonium salt was prepared by dissolving (0.005 mole, 1g) 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 (0.7 g) (0.01 mol) 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 mole, 0.835 g) of 2-hydroy-5- nitro benzeldehyde 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.

Preparation of Schiff Base [20]

The compound (3) Schiff base was prepared by reacting (1 g, 0.0026 mole) of compound (2) dissolved in 10 ml ethanol absolute and add 3 drops of glacial acetic acid with (0.2603 g, 0.0026 mole) of (2-amino thiazole) in (10 ml) of ethanol absolute and reflux at (78 C°) for (24 hours), after which the solution is left to cool at room temperature for (24) hours, and the precipitate are recrystallized with methanol.

Preparation of Oxazepine Derivatives (4,5) [21]

The four derivatives (Oxazepine) were prepared by reacting (0.0021 mole, 1g) of compound (3) with each of (0.0021mole, 0.21 g) (succinic anhydride), (0.0021 mole, 0.206 g)) (maleic anhydride) each dissolve in (25 ml) of dry benzene. The reflux was done from (24-36) hours at a temperature of (80 C°) after that the solution is left to cool for (24 hours), then filtered and recrystallized with ethanol.

Preparation of Diazepine Derivatives (6,7) [22]

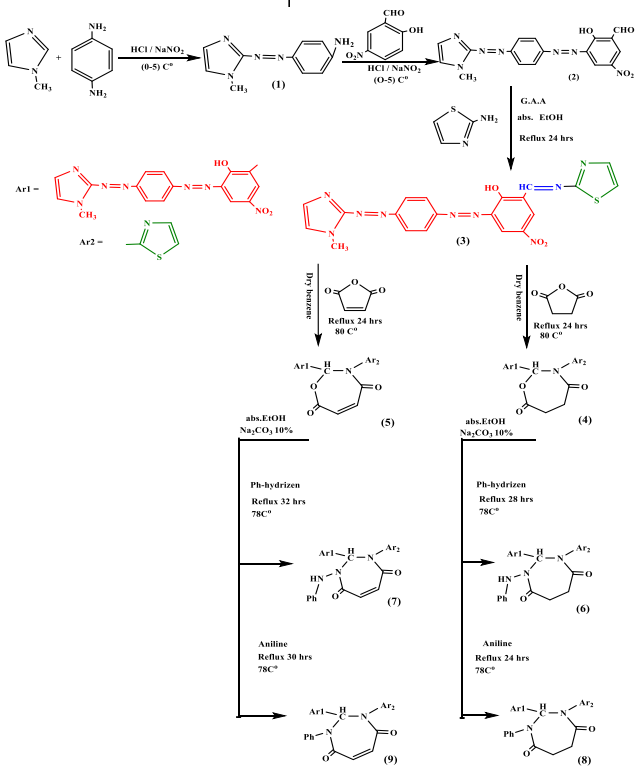
The diazepine derivatives (6,7) were prepared by dissolving (0.001mole) of the derivatives (4,5) (0.547,0.559 g) dissolved in 20 ml of absolute ethanol and dissolve (0.001 mole, 0.098 ml) of phenyl hydrazine in 10 ml of absolute ethanol, mix the two solutions with addition of sodium carbonate (solution 10%) was refluxed for (28-32) hours. The solvent was evaporated, and the formed precipitate was washed with ethyl ether and recrystallized by absolute ethanol.

Preparation of Diazepine Derivatives (8,9 22])[

The diazepine derivatives (8,9) were prepared by dissolving (0.001mole) of the derivatives (4,5) (0.547,0.559 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 (Eschericia coli) and (Staphylococcus aurous) from hospital. It was cultivated, and the plates were incubatd 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 Seven-membered heterocyclic compounds 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 NH_2 group, (1589.23 cm^{-1}) for (C=N) for imidazole ring, (2846.74-2923.88 cm^{-1}) for (C-H) in (CH_3), (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 ^{1}H-NMR (DMSO) spectrum data of compound (1) show δ: 6.6, 7.5 (m,6H, Ar-H), 5.7 (S, 2H, NH_2), 3.7 (S,3H, CH_3).

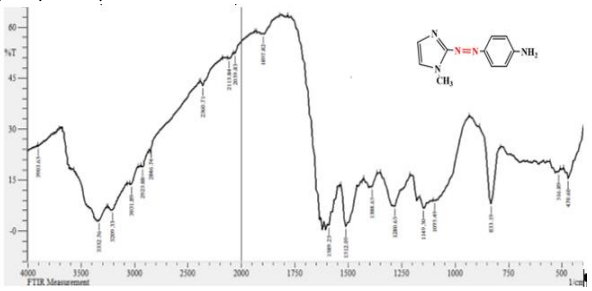


Fig. 1: FT-IR spectrum of compound (1)

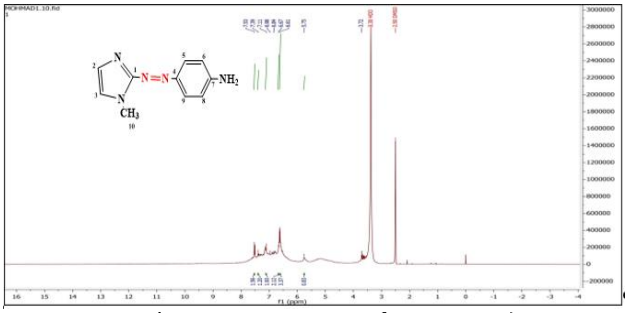


Fig. 2: ^{1}H-NMR spectrum of compound (1).

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 benzeldehyde), (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 (1342.36 ,1527.52 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).

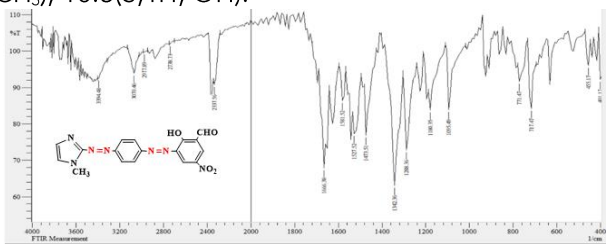


Fig. 3: FT-IR spectrum of compound (2)

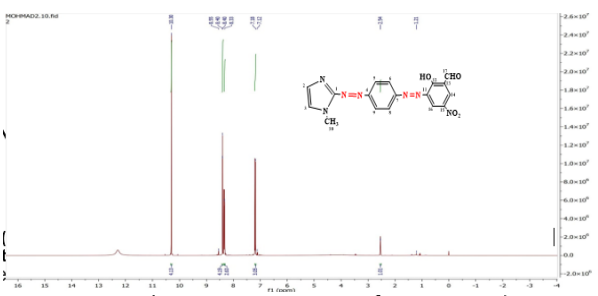


Fig. 4: ^{1}H-NMR spectrum of compound (2)

Compound(3):2-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-4-nitro-6-((thiazol-2-ylimino) methyl) phenol

The infrared spectrum data of the compound (3) showed band at (1596.95 cm^{-1}) for azomethine group(C=N), (3271.05 cm-1) for (OH) band, (2896.74 cm-1) for (C-H) in (CH3), (3070.46 cm-1) for (C-H) aromatic, (1481.23 cm-1) for (N=N) and (1512.09 cm-1) due to aromatic (C=C), (1442.66 cm-1) for (N-O) . 1H-NMR (DMSO) spectrum data of compound (3) show δ: 6.3-8.7 (m,10H, Ar-H), 9.3 (S, 1H, OH), 1.91(S,3H, CH3).

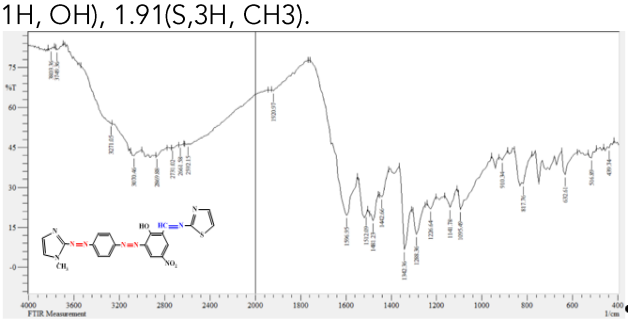


Fig. 5: FT-IR spectrum of compound (3)

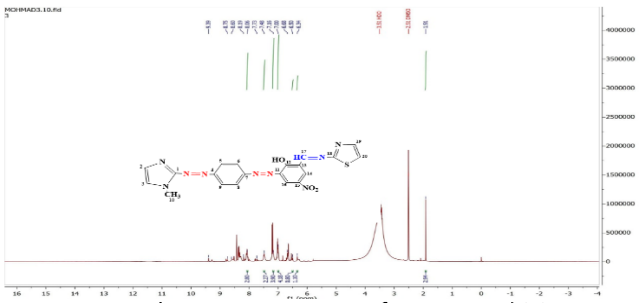


Fig. 6: ^{1}H-NMR spectrum of compound (3)

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

The infrared spectrum data of the compound (4) showed band at (3031.89 -3070.46 cm-1) for (Ar-H), (1519.80 cm-1) for (C=N) inside imidazole ring, (2931.60 cm-1) for (C-H) in (CH3), (3332.76 cm-1) for (OH) band , (1596.95 cm-1) for (N=N) and (1419.51 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 (1334.65 cm-1) for (C-N) group inside oxazepine ring, (1288.36 cm-1) for (C-O-C) group . 1H-NMR (DMSO) spectrum data of compound (4) show δ: 6.8-8.4 (m,10H, Ar-H), 10.3 (S, 1H, OH), 1.2(S,3H, CH3), 2.4(S, 1H, CH), 1.3(t, 2H, (CH2)19), 1.9(t, 2H, (CH2)20).

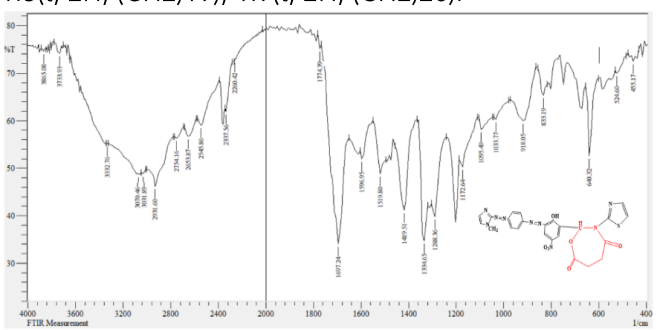


Fig. 7: FT-IR spectrum of compound (4)

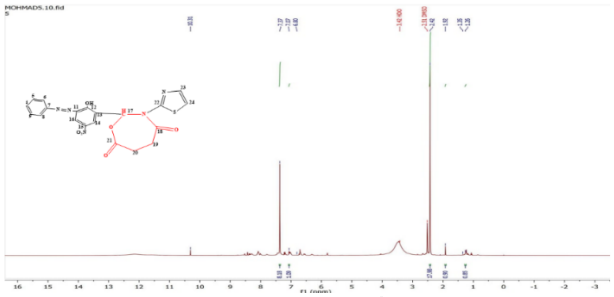


Fig. 8: [1]H-NMR spectrum of compound (4)

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

The infrared spectrum data of the compound (4) showed band at (3031.89 -3070.46 cm-1) for (Ar-H), (1589.23 cm-1) for (C=N) inside imidazole ring, (2931.60 cm-1) for (C-H) in (CH3), (3332.76 cm-1) for (OH) band , (1473.51 cm-1) for (N=N) and (1519.80 cm-1) due to aromatic (C=C), (1712.67 cm-1) for ester carbonyl group(O-C=O) and (1666.38cm-1) for C=O imide (N-C=O) and (1342.36 cm-1) for (C-N) group inside oxazepine ring, (1226.64 cm-1) for (C-O-C) group. 1H-NMR (DMSO) spectrum data of compound (5) show δ: 6.9-8.5(m,10H, Ar-H), 10.3 (S, 1H, OH), 1.2(S,3H, CH3), 4.1(S, 1H, CH), 6.2(d, 1H, (CH)19), 6.3(d, 1H, (CH)20).

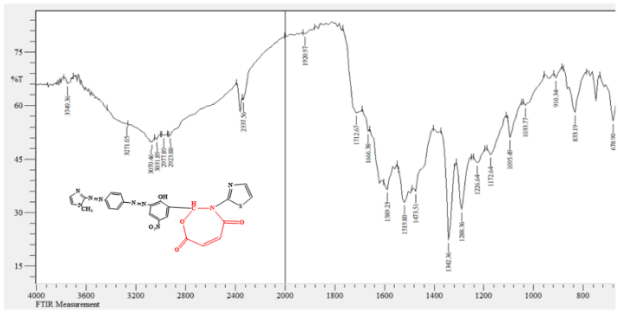


Fig. 9: FT-IR spectrum of compound (5)

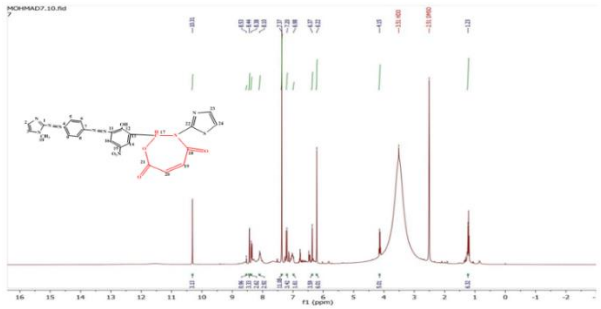


Fig. 10: [1]H-NMR spectrum of compound (5)

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

The infrared spectrum data of the compound (6) showed band at (3078.18 cm-1) for (Ar-H), (1650.95 cm-1) for (C=N) for imidazole ring, (2908.45 cm-1) for (C-H) in (CH3), (3263.33 cm-1) for (OH) , (1458.08 cm-1) for (N=N) and (1558.38 cm-1) due to aromatic (C=C), and the band of ester carbonyl(O-C=O) is disappear , (1681.81,1690 cm-1) for amide carbonyl group(N-C=O) and (1280.56 cm-1) for (C-N) group inside oxazepine ring, (3471.63 cm-1) for (NH), (1126.35 cm-1) for (N-N).1H-NMR (DMSO) spectrum data of compound (6) show δ: 6.4-8.4(m,15H,Ar-H) , 10.09 (S, 1H, OH) , 1.2(S,3H,CH3), 5.9(S, 1H, NH), 3.5(S, 1H, CH), 1.6-2.2(t, 4H, CH2).

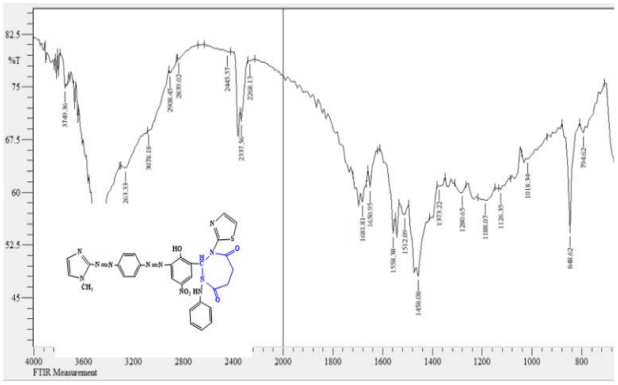


Fig. 11: FT-IR spectrum of compound (6)

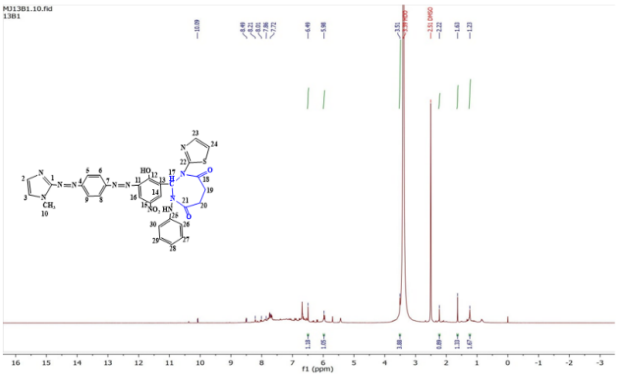


Fig. 12: 1H-NMR spectrum of compound (6)

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

The infrared spectrum data of the compound (7) showed band at (3016.46 cm^{-1}) for (Ar-H), (1596.95 cm^{-1}) for (C=N) for imidazole ring, (2962.46 cm^{-1}) for (C-H) in (CH_3), (3209.33 cm^{-1}) for (OH) , (1488.95 cm^{-1}) for (N=N) and (1519.80 cm^{-1}) due to aromatic (C=C), and the band of ester carbonyl(O-C=O) is disappear , (1670 ,1681.81 cm^{-1}) for amide carbonyl group(N-C=O) and (1288.36 cm^{-1}) for (C-N) group inside oxazepine ring, (3394.48 cm^{-1}) for (NH), (1072.35 cm^{-1}) for (N-N). [1]H-NMR (DMSO) spectrum data of compound (7) show δ: 6- 8.4(m,13H, Ar-H), 10.08 (S, 1H, OH), 1.2(S,3H, CH_3), 1.6(S, 1H, CH).

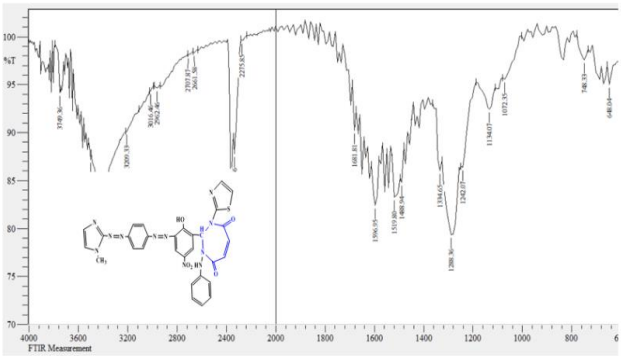


Fig. 13: FT-IR spectrum of compound (7)

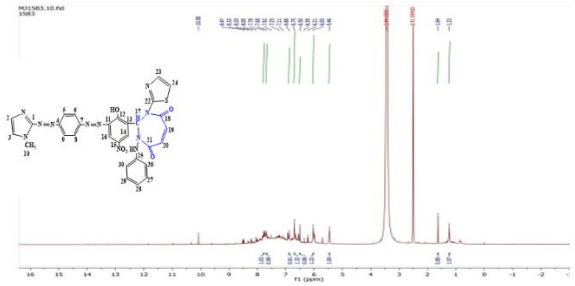


Fig. 14: [1]H-NMR spectrum of compound (7)

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

The infrared spectrum data of the compound (9) showed band at (3394.48 cm^{-1}) for (OH), (1558.38 cm^{-1}) for (C=N) for imidazole ring, (1458.08 cm^{-1}) for (N=N) and (1542.95) cm^{-1} due to aromatic (C=C), (1650.95,1680 cm^{-1}) due to (N-C=O amide) in diazepine ring , (1442.07 cm^{-1}) for (N-O) band, (1342.36 cm^{-1}) for (C-N) in diazepine ring.[1]H-NMR (DMSO) spectrum data of compound (8) show δ: 6.1-8.5(m,10H,Ar-H) , 10.08 (S, 1H, OH) , 1.2(S,3H,CH_3), 1.6(S, 1H, CH), 2.2(t, 4H, CH_2).

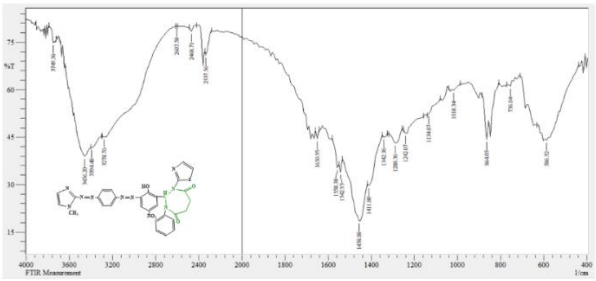


Fig. 15: FT-IR spectrum of compound (8)

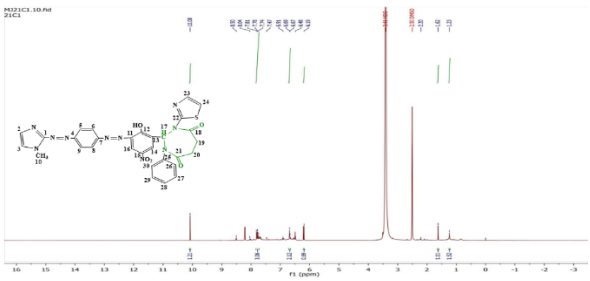


Fig. 16: 1H-NMR spectrum of compound (8)

Compound (9): 2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl)diazenyl)-5-nitrophenyl)-1-phenyl-3-(thiazol-2-yl)-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) ,(3394 cm^{-1}) for (OH), (1596.95 cm^{-1}) for (C=N) inside imidazole ring, (2977.89-2908.45 cm^{-1}) for (C-H aliphatic) in (CH_3), (1434.94 cm^{-1}) for (N=N) and (1542.95) cm^{-1} due to aromatic (C=C), (1666.38, 1697.24 cm^{-1}) due to (N-C=O amide) in diazepine ring , (1434.94 cm^{-1}) for (N-O) band, (1334.65 cm^{-1}) for (C-N) in diazepine ring. [1]H-NMR (DMSO) spectrum data of compound (9) show δ: 6.2- 8.5(m,15H, Ar-H), 10.07 (S, 1H, OH), 1.2(S,3H, CH_3), 1.6(S, 1H, CH), 6.02(d, 2H, CH).

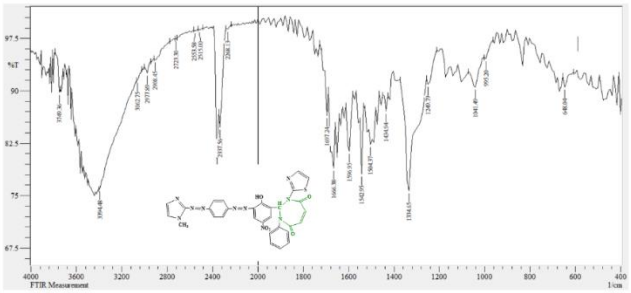


Fig. 17: FT-IR spectrum of compound (9)

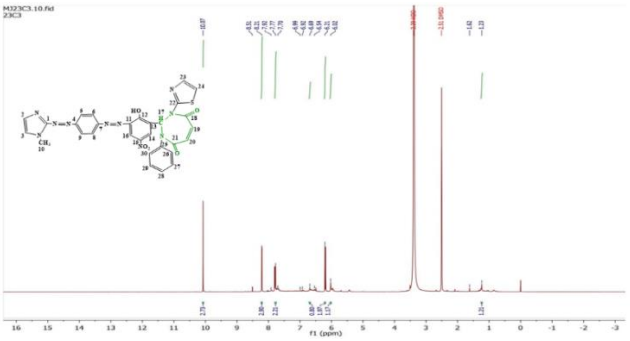


Fig. 18: [1]H-NMR spectrum of compound (9)

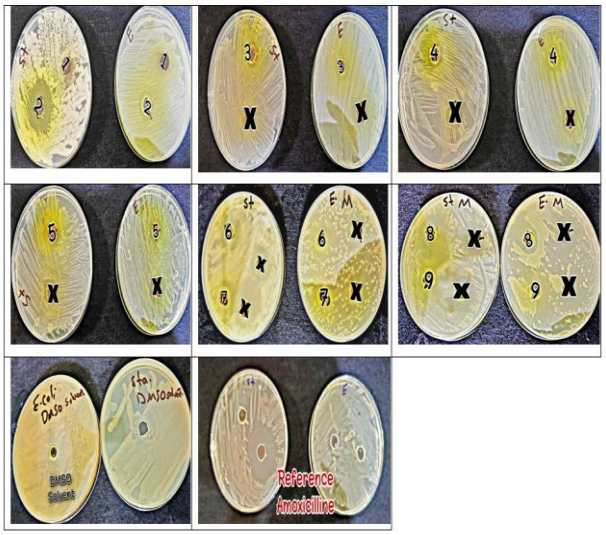


Fig. 19: Biological activity of compounds prepared against (St areas, E Coli) bacteria

Table 1: Show Biological activity for compounds (1-9)		
Compounds No.	Bacterial species	
	E.Coli	***S.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-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-4-nitro-6-((thiazol-2-ylimino) methyl) phenol	$C_{20}H_{15}N_9O_3S$	461.46	176-178	0.3	black	64
4	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-3-(thiazol-2-yl)-1,3-oxazepane-4,7-dione	$C_{24}H_{19}N_9O_6S$	561.53	198-200	0.45	Dark brown powder	68
5	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-3-(thiazol-2-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione	$C_{24}H_{17}N_9O_6S$	559.52	201-204	0.5	Black powder	82
6	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-(phenylamino)-3-(thiazol-2-yl)-1,3-diazepane-4,7-dione	$C_{30}H_{25}N_{11}O_5S$	651.66	232-234	0.44	Pale brown powder	88
7	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-(phenylamino)-3-(thiazol-2-yl)-2,3-dihydro-1H-1,3-diazepine-4,7-dione	$C_{30}H_{23}N_{11}O_5S$	649.65	110-112	0.32	Dark brown crystal	75
8	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-phenyl-3-(thiazol-2-yl)-1,3-diazepane-4,7-dione	$C_{30}H_{24}N_{10}O_5S$	636.65	293-295	0.33	Dark brown	85
9	2-(2-hydroxy-3-((4-((1-methyl-1H-imidazol-2-yl) diazenyl) phenyl) diazenyl)-5-nitrophenyl)-1-phenyl-3-(thiazol-2-yl)-2,3-dihydro-1H-1,3-diazepine-4,7-dione	$C_{30}H_{22}N_{10}O_5S$	634.63	272-275	0.42	Pale green (olive)	80

4. Conclusions

According to the above studies it can be concluded that the synthesized compounds have substantial antibacterial activity against bacteria Staphylococcus aureas and Escherichia Coli, the compounds that appeared good activity are (2,5,6,7,8,9) against (Staphylococcus aureas) on other hand, compounds (6,7,8,9) show good activity against (Escherichia Coli), the results of the antibacterial activity are shown in the Fig. (19)

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