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Preparation of Heterocyclic Seven-Membered Compounds and the Reaction with Schiff Bases and study the biological activity

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Abstract

This study involved the synthesis of heterocyclic compounds containing a seven-membered ring, specifically 1,3-oxazepine. The initial step comprised the preparation of an azo compound (1) through the coupling of the diazonium salt of 2-amino-4-hydroxy-6-methylpyrimidine with 4-bromoacetophenone in an alkaline alcoholic medium. Subsequently, azo compound (1) was reacted with 4-methoxylaniline and 2-amino-4-hydroxy-6-methylpyrimidine in absolute ethanol, with glacial acetic acid serving as a catalyst, resulting in the formation of Schiff base derivatives (2) and (3) respectively. Furthermore, Schiff base (2) was subjected to reaction with maleic anhydride, succinic anhydride, and phthalic anhydride in dry benzene, leading to the formation of heterocyclic seven-membered compounds (4), (5), and (6) respectively. Similarly, Schiff base (3) was reacted with maleic anhydride, succinic anhydride, and phthalic anhydride in dry benzene, yielding heterocyclic seven-membered compounds (7), (8), and (9) respectively. All the synthesized compounds were characterized using FT-IR and 1H-NMR spectroscopy, and the progress of the reactions was monitored through Rf and TLC analysis. Additionally, melting points were measured, and the biological activity of these compounds was evaluated against both positive and negative bacteria strains.

keywords: Schiff bases, oxazepine, azo compounds

introduction

Heterocyclic compounds are classified as cyclic compounds incorporating one or more heteroatoms within their structures. The heteroatoms typically involved are oxygen, nitrogen, and sulfur, among others[1-2]. Azo compound widespread compounds used as dyes in addition to their uses in the pharmaceutical industry[3]. azo compound can be differentiated by functional group –N=N– the azo group which can be carry on both ends alkyl or aryl group [4]. aromatic azo compounds used widely in the chemical industries as dyes, food additives, and as initiators in free radical reaction and in drugs

industry[5]. Schiff bases play a significant role in coordination chemistry as they are widely recognized and important mixed donor systems. The pioneering work on the synthesis of imines, including Schiff bases, was reported by Schiff in the 19th century (Schiff, 1884). These compounds are obtained through the condensation reaction between primary amines and aldehydes or ketones under specific reaction conditions. Due to their ease of preparation, synthetic versatility, and unique properties of the C=N group, Schiff bases are highly regarded as excellent chelating agents. Moreover, their metal complexes have demonstrated notable biological activities. [6-7]. ring to 1,3-oxazepine. 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.

Materials

The FTIR spectra covering the range of 400-4000 cm-1 were acquired using a SHIMADZU FTIR-8400S Fourier transform spectrometer. To prepare the samples for analysis, KBr disks were utilized. The melting points of the compounds were determined using a Stuart instrument from the United Kingdom. For the acquisition of 13C-NMR and 1H-NMR spectra, a Fourier transformation Bruker spectrometer operating at a frequency of 400 MHz was employed. The measurements were carried out using DMSO-d6 as the solvent. All of these measurements were conducted at the Department of Chemistry, Kashan University, located in Iran.

Methods

Azo Derivative (1) Synthesis (10):

The synthesis of the diazonium salt was executed by dissolving 1.0814 g (0.01 mol) of 2-amino-4-hydroxy-6-methylpyrimidine in a solution comprising 60 ml of distilled water and 4 ml of concentrated HCl. This solution was subsequently chilled to a temperature between 0-5 °C. Following this, a solution of 0.7 g (0.01 mol) sodium nitrite (NaNO2) in 20 ml of distilled water was incrementally introduced to the diazonium salt solution under continuous stirring. The reaction was allowed to proceed for 20 minutes within the temperature range of 0-5 °C, facilitating the diazotization process. The produced diazonium salt was then carefully introduced to a solution comprising 0.797 ml (0.01 mol) of 4-methoxylaniline and 1 g of sodium hydroxide in 130 ml of distilled water. The mixture was persistently stirred at pH 6 over a

period of two hours, leading to the generation of a black precipitate. This precipitate was then purified by washing with distilled water and recrystallization with ethyl alcohol.

Schiff Base 2 Synthesis (11):

Schiff base compound (2) was prepared by dissolving 1 g (0.0026 mol) of compound (1) in 10 ml of absolute ethanol. To this solution, 0.3201 g (0.0026 mol) of 4-methoxylaniline was added along with 3 drops of glacial acetic acid in 10 ml of absolute ethanol. The reaction mixture was refluxed at 78°C for 12 hours. After completion of the reaction, the solution was allowed to cool at room temperature for 24 hours, resulting in the formation of a precipitate. The precipitate was recrystallized using methanol.

Schiff Base 3 Synthesis (12):

The Schiff base compound (3) was synthesized by dissolving 1 g (0.0026 mol) of compound (1) in 10 ml of absolute ethanol. Subsequently, 0.3201 g (0.0026 mol) of 2-amino-4-hydroxy-6-methylpyrimidine was introduced into this solution, supplemented with 3 drops of glacial acetic acid in 10 ml of absolute ethanol. The reaction mixture was then subject to reflux at 78°C over a period of 12 hours. Upon completion of the reaction, the solution was permitted to cool to room temperature over a 24-hour duration, which resulted in the generation of a precipitate. This precipitate was subsequently recrystallized using methanol.

Oxazepine Derivatives (4, 5, 6) Synthesis (13):

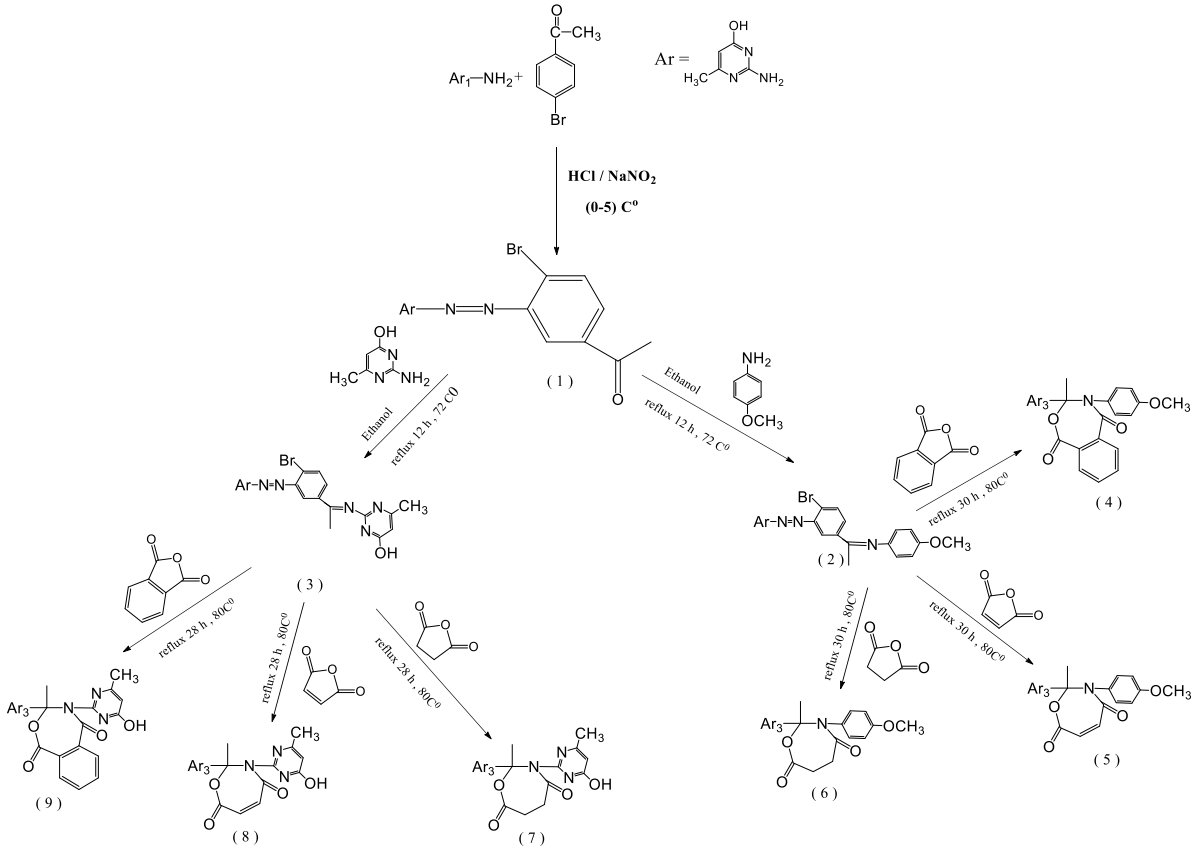
The reaction commenced with the preparation of a solution consisting of 0.001 mol of compound (2) in 25 ml of benzene, to which 0.001 mol each of phthalic anhydride, maleic anhydride, and succinic anhydride were added. The reaction mixture was then subjected to reflux at 80°C for a duration of 30 hours. Following this, the solution was allowed to stand undisturbed for 24 hours before being filtered and the precipitate recrystallized using ethanol.

Oxazepine Derivatives (7, 8, 9) Synthesis (14):

To a solution of 0.001 mol of compound (3) in 25 ml of benzene, 0.001 mol of phthalic anhydride, maleic anhydride, and succinic anhydride were added. The reaction mixture was refluxed at 80°C for 28 hours. Afterward, the solution was left for 24 hours, filtered, and recrystallized using ethanol.

Preparation of Microbiology Culture Medium (15):

A nutrient agar medium was prepared through the dissolution of 10 g of nutrient agar in 250 mL of distilled water. This mixture was subsequently subjected to autoclaving at 170°C for 25 minutes to ensure its sterility. Following the medium's cooling to a temperature of 37°C, it was dispensed into Petri dishes in preparation for inoculation with bacteria. Bacterial cultures of Staphylococcus aureus and Escherichia coli, which were isolated from a hospital setting, were streaked onto the plates. These plates were then incubated at a constant temperature of 37°C over a period of 24 hours to promote bacterial growth.



Results and Discussion

Compound 1

FT-IR spectrum data for compound (1) show band at 3440cm^{-1} for (OH), 1681 cm^{-1} for (C=O) ,1620 cm^{-1} for (C=C) ,3008cm^{-1} for(Ar-H) ,2954 cm^{-1} for (C-H) of (CH_3) ,1504 cm^{-1} for (N=N) . ^{1}H NMR (DMSO) spectrum data of compound (1) show 2.42 ppm (S , 3H , CH_3) , 2.49 ppm (S , 3H , $COCH_3$) , 12.5 ppm (S, 1H ,OH) , 6.7-7.8 ppm (M ,4H , Ar-H) . The ^{13}C- NMR (DMSO) spectrum data of compound (1) show : 27ppm (C_{13}) , 47ppm (C_{12}) , 197ppm (C_{22}) , 137ppm (C_1) , 135ppm (C_5) , 113-132ppm (C_{Arom}) .

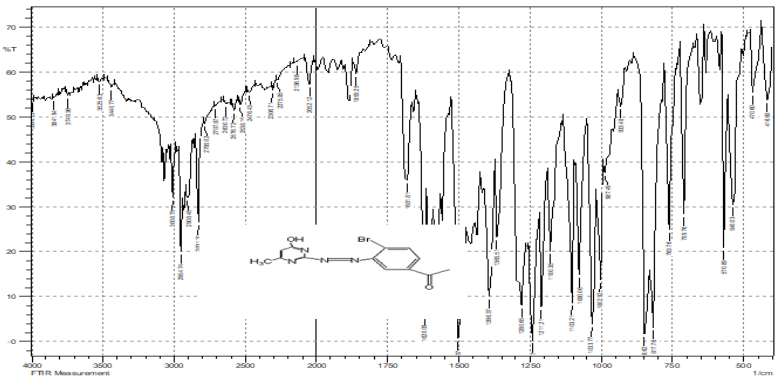


Fig.1: FT-IR of compound 1

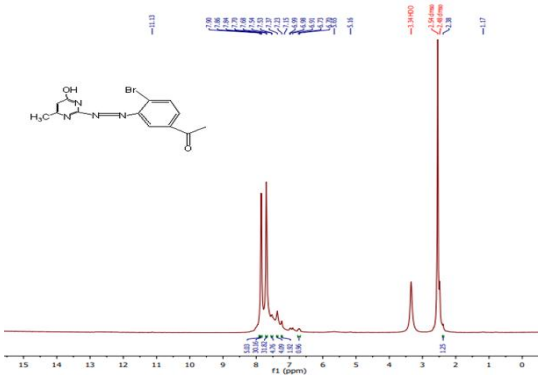


Fig. 2: ^{1}HNMR of compound 1

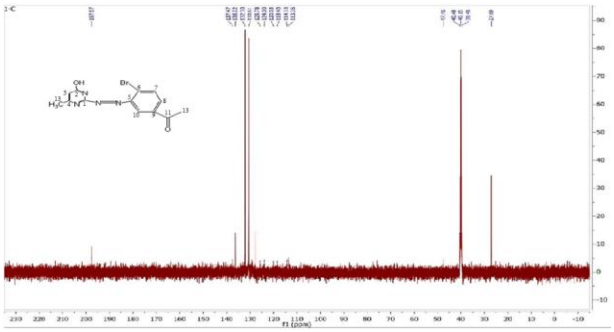


Fig. 3: ^{13}CNMR OF Compound 1

Compound 2

FT-IR spectrum data for compound (2) show band at 1658 cm^{-1} for (C=N) , 3400cm^{-1} for (OH) , 1666 cm^{-1} for (C=C) ,3100cm^{-1} for(Ar-H) ,2916 cm^{-1} for (C-H) of (CH_3) ,1589 cm^{-1} for (N=N) . ^{1}H NMR (DMSO) spectrum data of compound (2) show 2.1 ppm (S , 3H , CH_3) , 3.6 ppm (S , 3H , CH_3 in pyrimidine) , 3.7 ppm (S , 3H , $COCH_3$) , 9.8 ppm (S, 1H ,OH) , 6.5-7.8 ppm (M ,8H , Ar-H) . The ^{13}C- NMR (DMSO) spectrum data of compound (1) show : 47ppm (C_{13}) , 17ppm (C_{12}) , 55ppm (C_{20}) , 156ppm (C_1) , 144ppm (C_5) , 138ppm (C_{14}) , 164ppm (C_{11}) , 114-144ppm (C_{Arom}) .

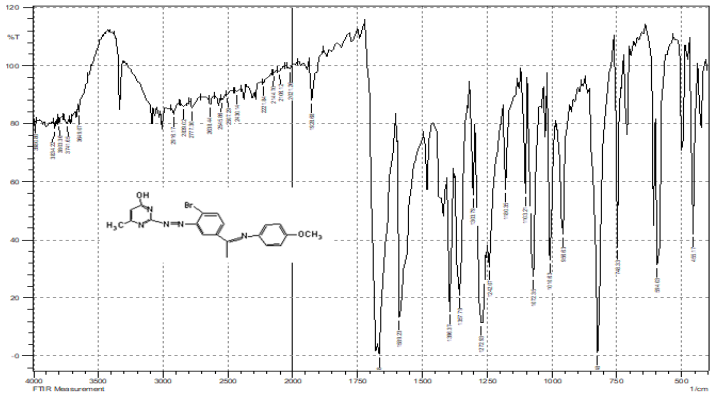


Fig. 4: FT-IR of compound 2

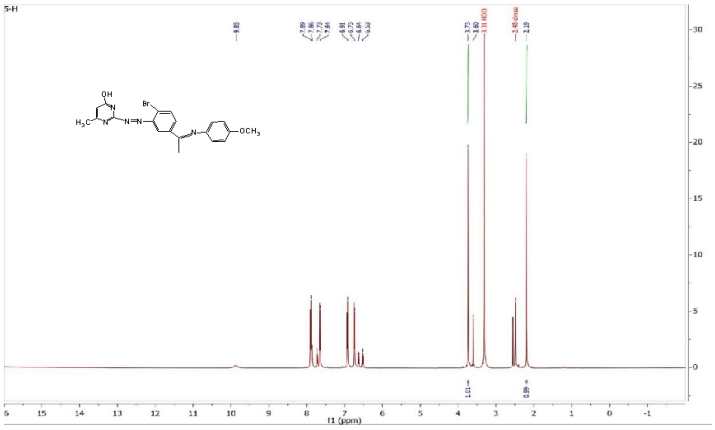


Fig. 5: ^{1}HNMR OF Compound 2

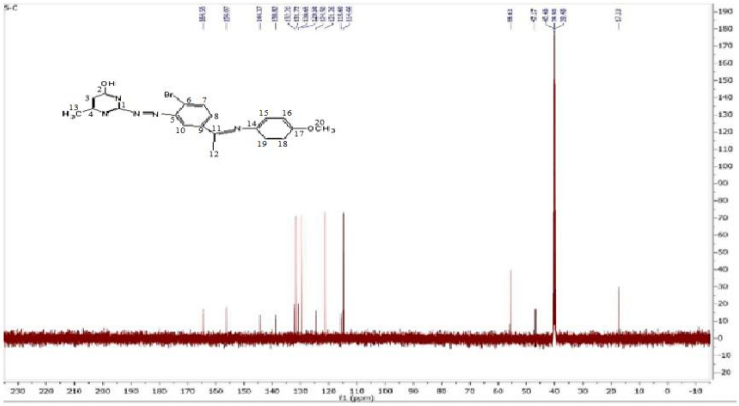


Fig. 6: ^{13}CNMR OF Compound 2

Compound 3

FT-IR spectrum data for compound (2) show band at 1658 cm^{-1} for (C=N) , 3332cm^{-1} for (OH) , 1600 cm^{-1} for (C=C) ,3085cm^{-1} for(Ar-H) ,2931 cm^{-1} for (C-H) of (CH_3) ,1465 cm^{-1} for (N=N) . ^{1}H NMR (DMSO) spectrum data of compound (3) show 2.56 ppm (S , 6H , CH_3 in pyridine) , 1.9 ppm (S , 3H ,

CH_3) , 3.7 ppm (S , 3H , $COCH_3$) , 10.7 ppm (S, 1H ,OH) , 6.5-7.8 ppm (M ,5H , Ar-H) . The ^{13}C- NMR (DMSO) spectrum data of compound (1) show : 27ppm ($C_{13,18}$) , 16ppm (C_{12}) , 55ppm (C_{20}) , 147ppm ($C_{1,14}$) , 144ppm (C_5) , 155ppm (C_{11}) , 100-145ppm (C_{Arom})

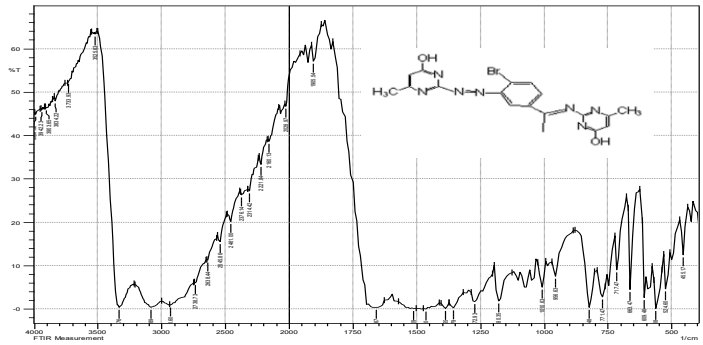


Fig. 7: FT-IR of compound 3

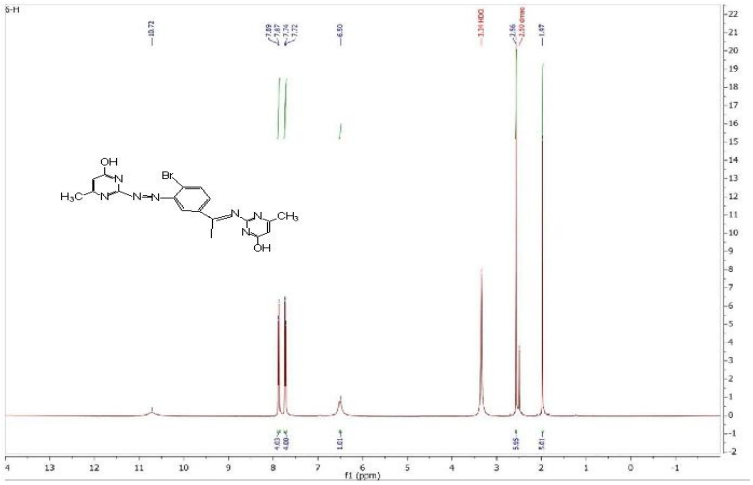


Fig. 8: ^{1}HNMR OF Compound 3

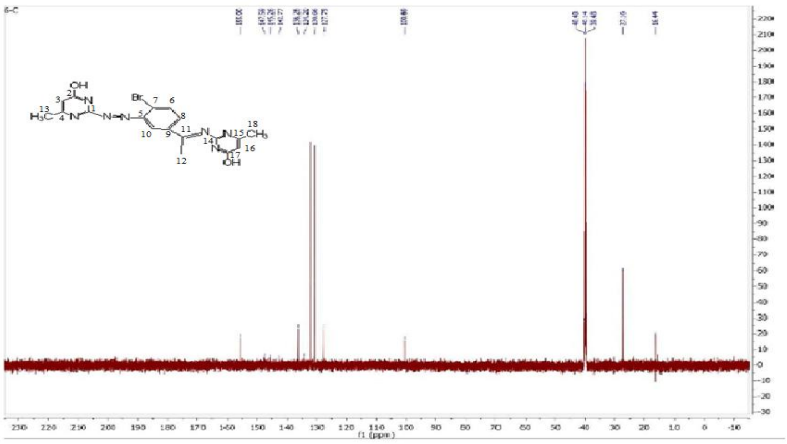


Fig. 9: ^{13}CNMR OF Compound 3

Compound 4

FT-IR spectrum data for compound (4) show band at 3024cm^{-1} for(Ar-H) , 3440cm^{-1} for (OH) , 2916 cm^{-1} for (C-H) of (CH_3) , 1704 cm^{-1} (C=O) amid , 1658 cm^{-1} for (C=C) , (1172) cm^{-1} for (C-O-C) and 1257 cm^{-1} for (C-N) of oxazepine . ^{1}H NMR (DMSO) spectrum data of compound (4) show 3.72 ppm (S, 3H, CH_3 in pyridine) , 1.2 ppm (S , 3H , CH_3) , 3.79 ppm (S , 3H , $COCH_3$) , 10.1 ppm (S, 1H ,OH) , 6.5-7.9 ppm (M ,5H , Ar-H) . The ^{13}C- NMR (DMSO) spectrum data of compound (1) show : 22ppm (C_8) , 28ppm (C_{13}) , 46ppm (C_{28}) , 55ppm (C_{11}) , 167.7ppm (C_{14}) , 167.2ppm (C_{14}) , 159ppm (C_1) , 114-145ppm (C_{Arom})

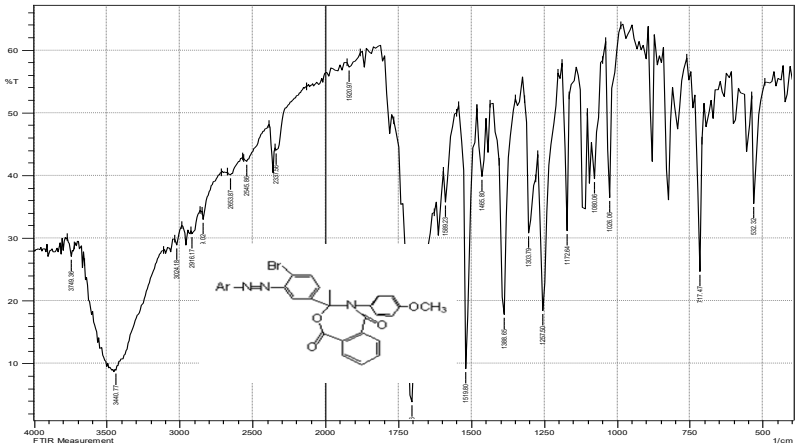


Fig. 10: FT-IR of compound 4

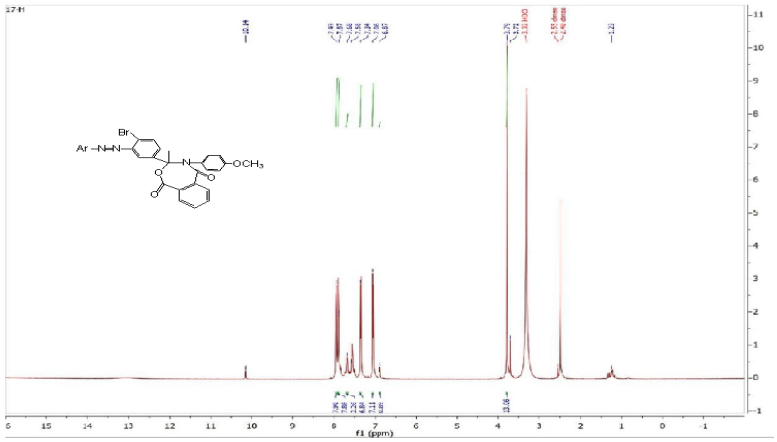


Fig. 11: ^{1}HNMR OF Compound 4

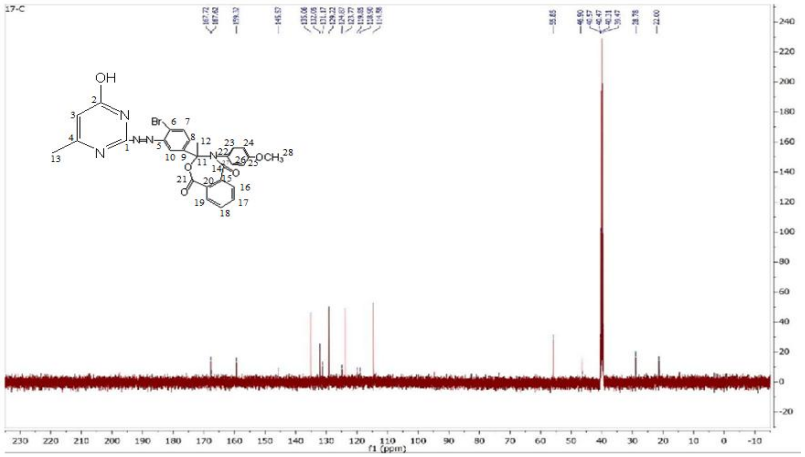


Fig. 12: ^{13}CNMR OF Compound 4

Compound 5

FT-IR spectrum data for compound (4) show band at 3024cm^{-1} for(Ar-H) , 3300cm^{-1} for (OH) , 2931 cm^{-1} for (C-H) of (CH_3) , 1681 cm^{-1} (C=O) amid , 1620 cm^{-1} for (C=C) , (1180) cm^{-1} for (C-O-C) and 1257 cm^{-1} for (C-N) of oxazepine . ^{1}H NMR (DMSO) spectrum data of compound (5) show 2.5 ppm (S, 3H, CH_3 in pyridine) , 1.2 ppm (S , 3H , CH_3) , 3.3 ppm (S , 3H , $COCH_3$) , 9.9 ppm (S, 1H ,OH) , 6.4-7.2 ppm (M ,5H , Ar-H) , 7.7-7.8 (d ,2H , CH=CH) ppm . The ^{13}C- NMR (DMSO) spectrum data of compound (5) show : 15.6ppm (C_{12}) , 16.3ppm (C_{13}) , 27ppm (C_{24}) , 55ppm (C_{11}) , 169ppm (C_{14}) , 170ppm (C_{17}) , 135,138ppm ($C_{15,16}$) , 114-130ppm (C_{Arom})

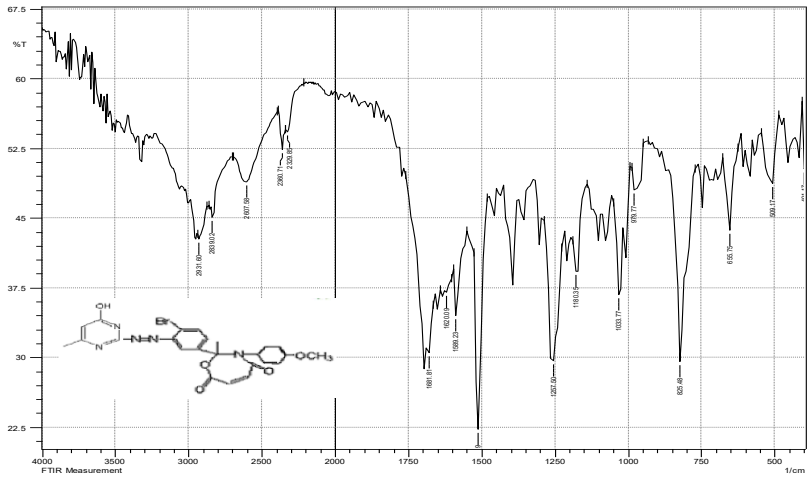


Fig. 11: FT-IR of compound 5

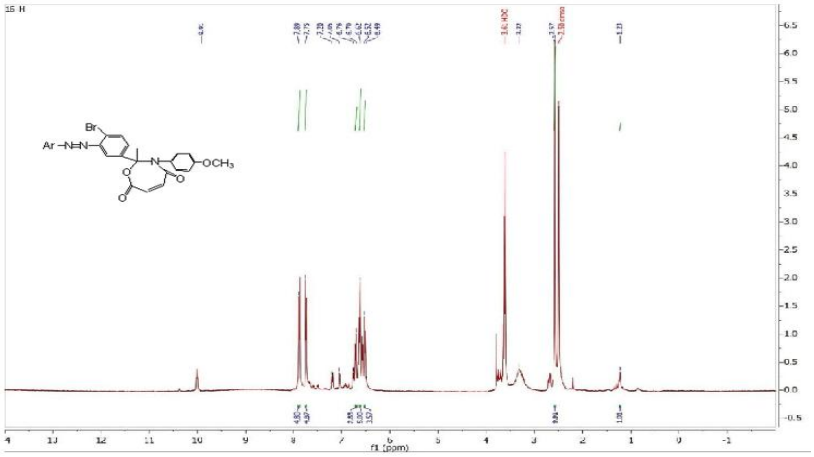


Fig.12: ^{1}HNMR OF Compound 5

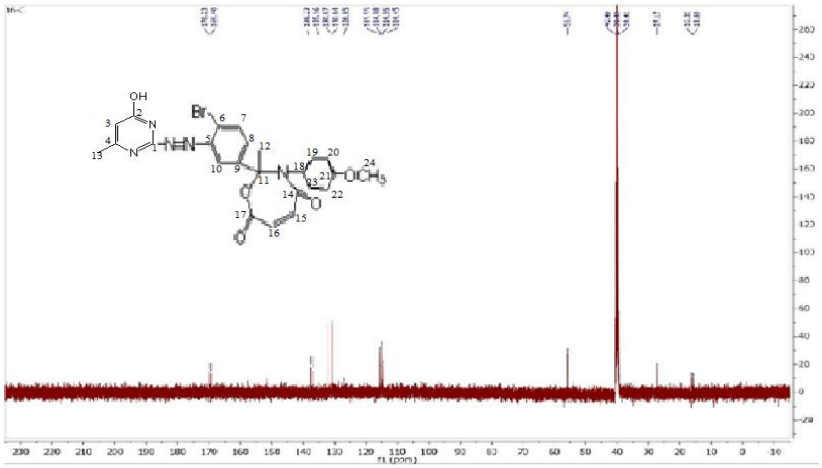


Fig. 13: ^{13}CNMR OF Compound 5

Compound 6

FT-IR spectrum data for compound (4) show band at 3000cm^{-1} for(Ar-H) , 3448cm^{-1} for (OH) , 2931 cm^{-1} for (C-H) of (CH_3) , 1700 cm^{-1} (C=O) amid , 1650 cm^{-1} for (C=C) , 1172 cm^{-1} for (C-O-C) and 1249 cm^{-1} for (C-N) of oxazepine . ^{1}H NMR (DMSO) spectrum data of compound (6) show 2.4 ppm (S , 3H , CH_3 in pyridine) , 2.2 ppm (S , 3H , CH_3) , 2.7 ppm (S , 3H , $COCH_3$) , 9.7 ppm (S, 1H ,OH) , 6.5-7.9 ppm (M ,8H , Ar-H) , 3.6-3.7 (t ,4H , CH_2-CH_2) ppm . The C13- NMR (DMSO) spectrum data of compound (6) show : 15ppm (C_{12}) , 16ppm (C_{13}) , 27ppm (C_{23}) , 29ppm (C_{11}) , 55ppm (C_{14}) , 64ppm (C_{16}) , 173,174ppm ($C_{14,17}$) , 114-151ppm (C_{Arom}) .

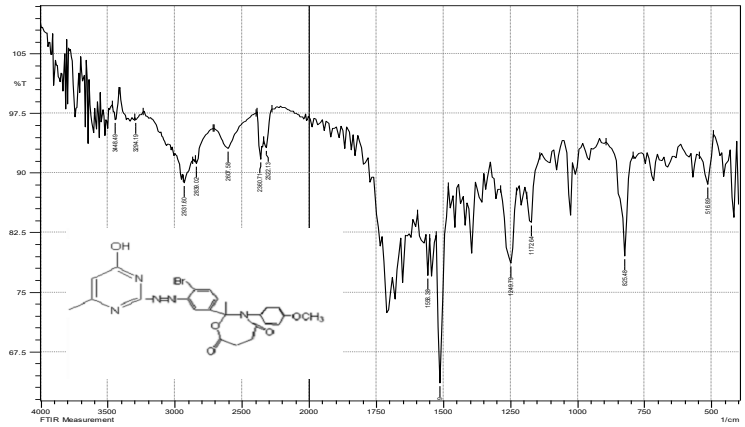


Fig. 14: FT-IR of compound 6

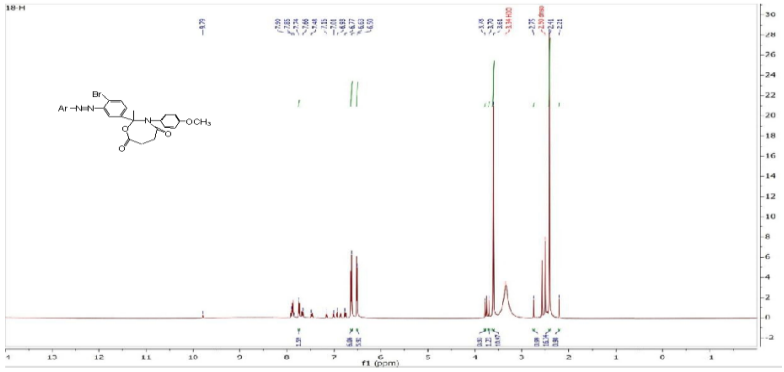


Fig. 15: ^{1}HNMR OF Compound 6

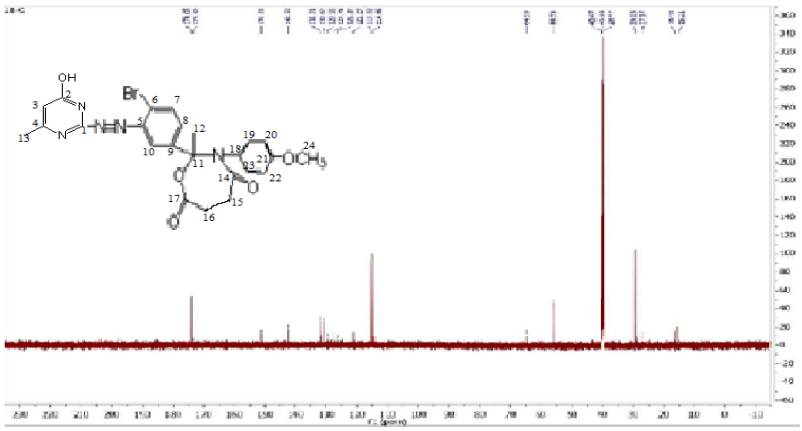


Fig. 16: ^{13}CNMR OF Compound 6

Compound 7

FT-IR spectrum data for compound (4) show band at 3085cm^{-1} for(Ar-H) , 3440cm^{-1} for (OH) , 2931 cm^{-1} for (C-H) of (CH_3) , 1681 cm^{-1} (C=O) amid , 1650 cm^{-1} for (C=C) , 1080 cm^{-1} for (C-O-C) and 1195 cm^{-1} for (C-N) of oxazepine . ^{1}H NMR (DMSO) spectrum data of compound (7) show 1.2 ppm (S ,

3H , CH_3) , 1.99 ppm (S , 3H , CH_3) , 9.9 ppm (S, 1H ,OH) , 6.6-7.8 ppm (M ,8H , Ar-H) , 2.4-2.56 (t ,4H , CH_2-CH_2) ppm . The ^{13}C- NMR (DMSO) spectrum data of compound (7) show : 16ppm (C_{12}) , 23ppm (C_{13}) , 29ppm (C_{11}) , 42ppm (C_{15}) , 43ppm (C_{16}) , 174,169ppm ($C_{14,17}$) , 100-164ppm (C_{Arom})

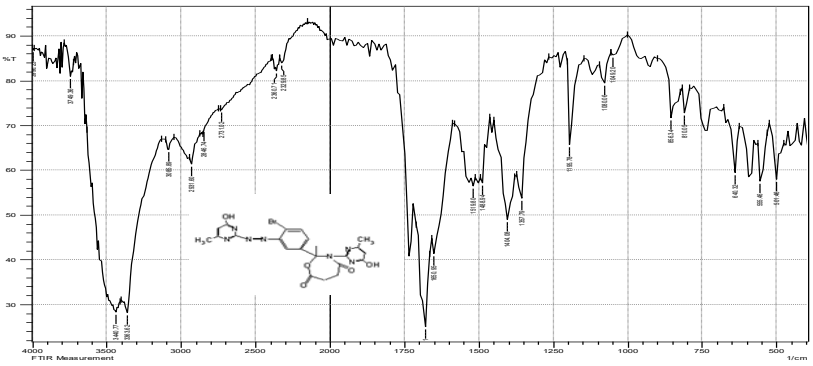


Fig. 17: FT-IR of compound 7

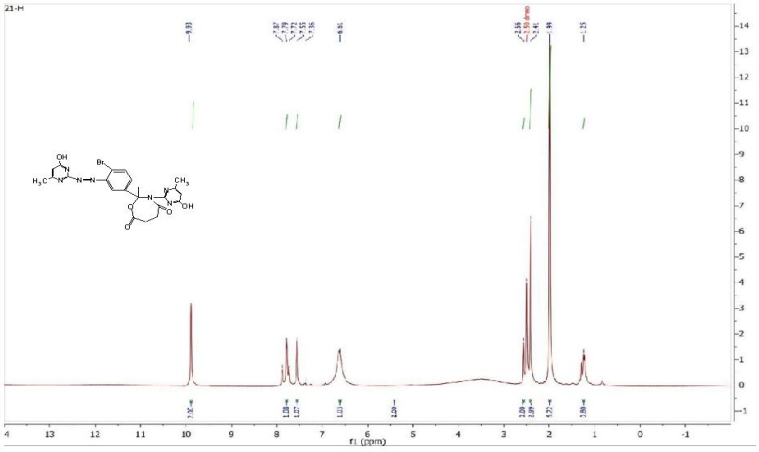


Fig. 18: ^{1}HNMR OF Compound 7

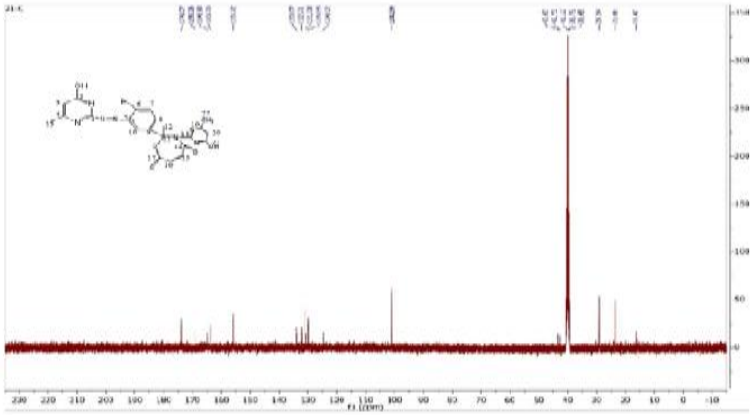
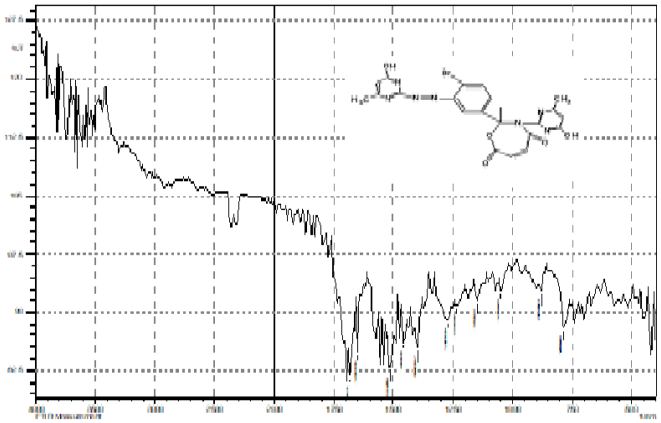


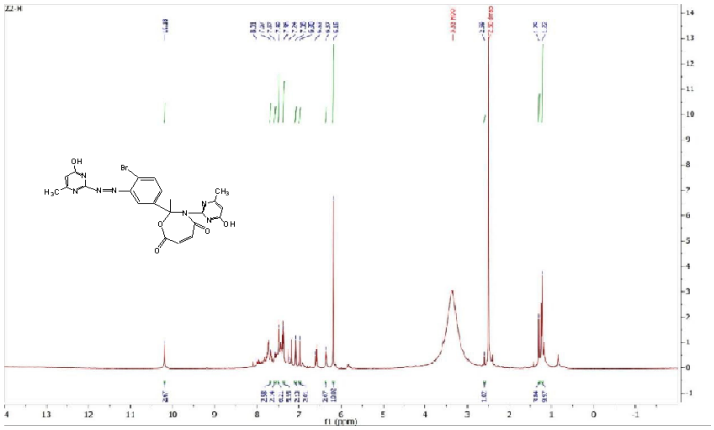
Fig. 19: ^{13}CNMR of Compound 7

Compound 8

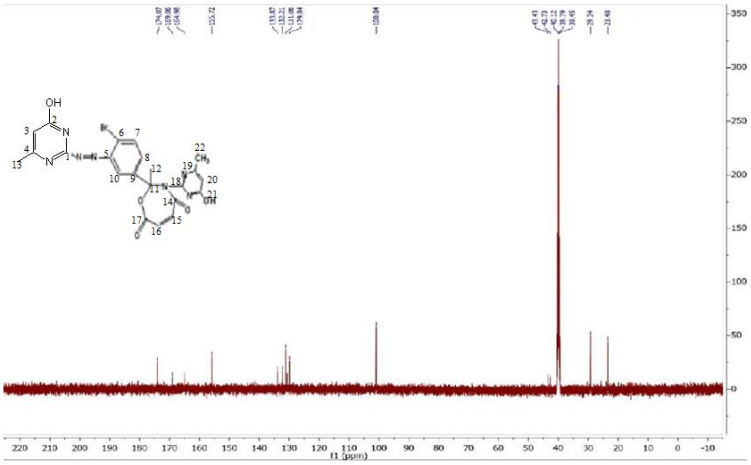
In the compound (4), the FT-IR spectrum data demonstrate a band at 3062cm^{-1} attributable to (Ar-H), at 3448cm^{-1} correlated with (OH), at 2931 cm^{-1} associated with (C-H) of (CH_3), at 1712 cm^{-1} for (C=O) amid, at 1635 cm^{-1} linked to (C=C), at 1049 cm-1 related to (C-O-C), and at 1180 cm^{-1} assigned to (C-N) of oxazepine. As for compound (8), 1H NMR (DMSO) spectrum data reveal signals at 1.2 ppm (S, 3H, CH_3), 2.5 ppm (S, 6H, CH3), 10.1 ppm (S, 1H, OH), 6.3-8 ppm (M ,8H , Ar-H), and 6.1 (d ,2H , CH=CH) ppm. In the case of 13C-NMR (DMSO) spectrum data for the same compound (8), findings indicate signals at 23ppm (C13), 29ppm (C11), 42ppm (C15), 43ppm (C16), 174,169ppm (C14,17), and within a range of 100-164ppm for (CArom). This data interpretation provides a valuable framework for understanding the structure of these compounds.



Fig(20) FT-IR of compound 8



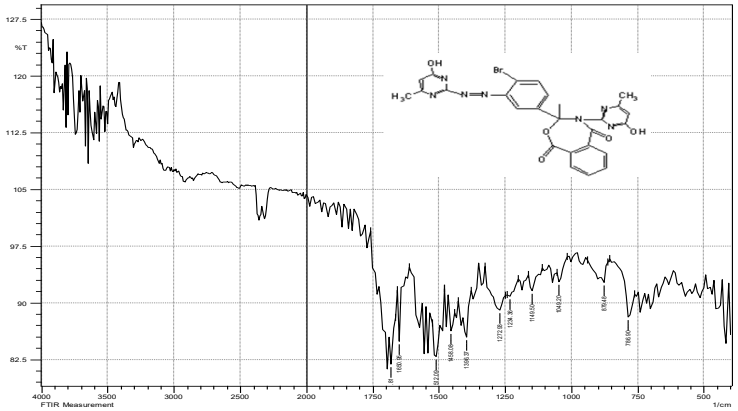
Fig(21) ^{1}HNMR OF Compound 8



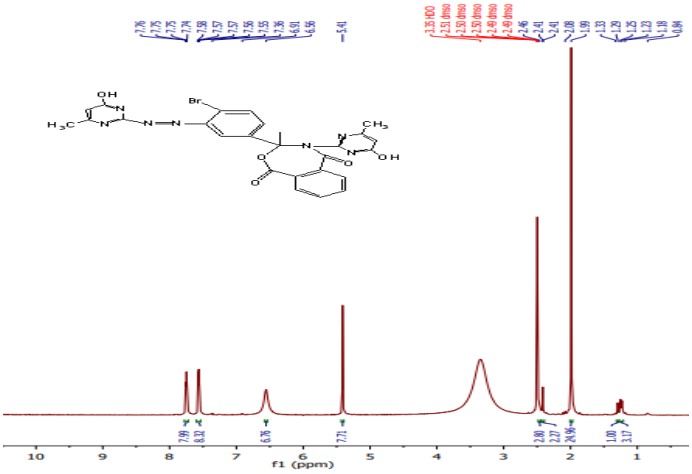
Fig(22) ^{13}CNMR OF Compound 8

Compound 9

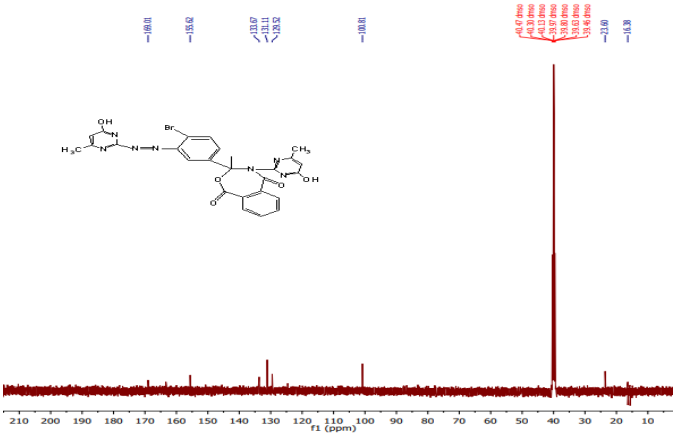
For compound (4), the FT-IR spectrum data reveals a band at 3000cm^{-1} ascribed to (Ar-H), at 3300cm^{-1} connected to (OH), at 2931 cm^{-1} linked to (C-H) of (CH3), at 1681 cm^{-1} indicative of (C=O) amid, at 1650 cm^{-1} associated with (C=C), at 1149 cm^{-1} correlated with (C-O-C), and at 1272cm^{-1} related to (C-N) of oxazepine. In reference to compound (9), the 1H NMR (DMSO) spectrum data presents signals at 1.2 ppm (S , 3H , CH3), 1.3 ppm (S , 6H , CH3), 10.1 ppm (S, 1H ,OH), and within the range of 7.2-7.9 ppm (M ,9H , Ar-H). Furthermore, the 13C-NMR (DMSO) spectrum data for the compound (9) displays signals at 16ppm (C12), 23ppm (C13), 29ppm (C11), 42ppm (C15), 43ppm (C16), 174,169ppm (C14,17), and a range of 100-164ppm for (CArom). These observations provide important insights into the molecular configuration of these compounds.



Fig(23) FT-IR of compound 9



Fig(24) ^{1}HNMR OF Compound 9



Fig(25) ^{13}CNMR OF Compound 9

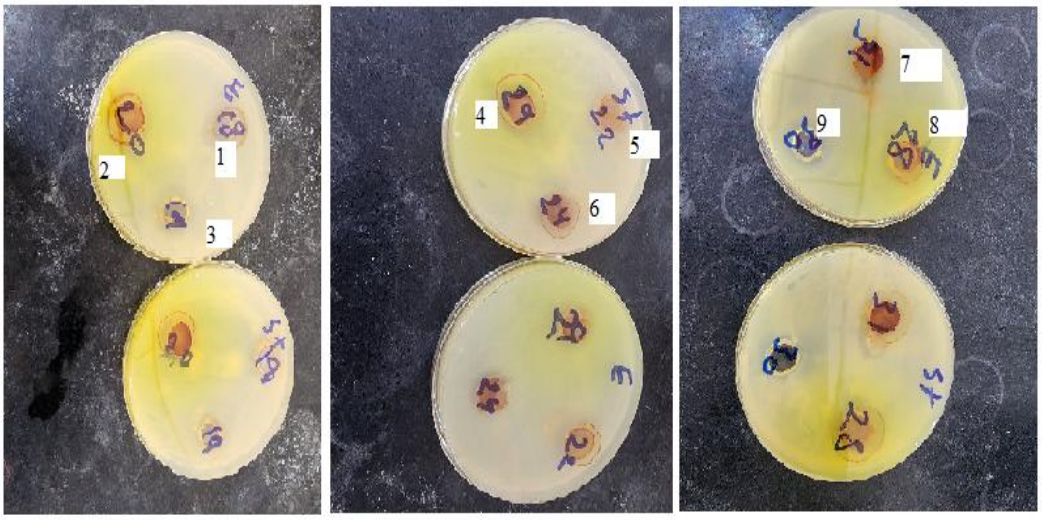


Fig 26: Biological activity of compound prepared Escherichia and staphylococcus aurou

Compounds NO.	Bacterial species	
	Staph.aureus	E. coli
1	++	+
2	++	_
3	+	+
4	+++	+++
5	_	+
6	_	+
7	-	-
8	++	++
9	-	-

- =No inhibition = in active ,+= (5-10)mm =slightly active, ++= (11-20)mm moderately active
+++ = More than 20 , good active

Scheme 1 : prepare of some oxazepine derivatives

No.	Name of comp.	M.F	M.W	M.P(C°)	R.f	Color	%
1	1-(4-bromo-3-((4-hydroxy-6-methylpyrimidin-2-yl)diazenyl)phenyl)ethan-1-one	$C_{13}H_{11}BrN_4O_2$	335.16	95	-	white	67
2	2-((2-bromo-5-(2-((4-methoxyphenyl)imino)-2l5-propan-2-yl)phenyl) diazenyl)-6-methylpyrimidin-4-ol	$C_{21}H_{21}BrN_5O_2$ 455.34	379.34	97	-	Light brown	77
3	2-((2-(4-bromo-3-((4-hydroxy-6-methylpyrimidin-2-yl)diazenyl)phenyl)-2l5-propan-2-ylidene)amino)-6-methylpyrimidin-4-ol	$C_{21}H_{17}BrN_5O_4$	484.48	97	0.52	Light brown	64
4	3-(4-bromo-3-((2,3-dichlorophenyl)diazenyl)phenyl)-4-(4-methoxyphenyl)-3-methyl-3,4-dihydrobenzo[e] [1,3]oxazepine-1,5-dione	$C_{29}H_{20}BrCl_2N_3O_4$	625.30	140	0.13	Light brown	77
5	2-(4-bromo-3-((2,3-dichlorophenyl)diazenyl)phenyl)-3-(4-methoxyphenyl)-2-methyl-2,3-dihydro-1,3-oxazepine-4,7-dione	$C_{25}H_{18}BrCl_2N_3O_4$	575.24	130	0.51	Light brown	90
6	2-(4-bromo-3-((2,3-dichlorophenyl)diazenyl)phenyl)-3-(4-methoxyphenyl)-2-methyl-1,3-oxazepane-4,7-dione	$C_{34}H_{30}N_{10}O_6$	577.26	145	0.31	Light brown	88
7	3-(4-bromo-3-((2,3-dichlorophenyl)diazenyl)phenyl)-4-(4-hydroxy-6-methylpyrimidin-2-yl)-3-	$C_{27}H_{18}BrCl_2N_5O_4$	627.28	160	0.51	Dark brown	87

	methyl-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione						
8	2-(4-bromo-3-((2,3-dichlorophenyl)diazenyl)phenyl)-3-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-2,3-dihydro-1,3-oxazepine-4,7-dione	$C_{25}H_{18}BrCl_2N_3O_4$	577.22	145	0.033	Dark brown	77
9	2-(4-bromo-3-((2,3-dichlorophenyl)diazenyl)phenyl)-3-(4-methoxyphenyl)-2-methyl-1,3-oxazepane-4,7-dione	$C_{25}H_{20}BrCl_2N3O_4$	577.26	143	0.12	Dark brown	85

Conclusion

Based on the aforementioned studies, it can be concluded that the synthesized compounds demonstrate substantial antibacterial activity against bacteria, namely Escherichia coli and Staphylococcus aureus. Notably, compounds (3,4,6,9) exhibit potent activity against Staphylococcus aureus, while compounds (9,10) are particularly effective against Escherichia coli. The data pertaining to the antibacterial activity are depicted in Figure 31.

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