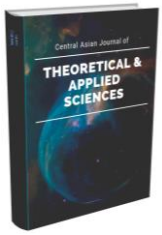

CENTRAL ASIAN JOURNAL OF THEORETICAL AND APPLIED SCIENCE

https://cajotas.centralasianstudies.org/index.php/CAJOTAS

Volume: 06 Issue: 01 | January 2025 ISSN: 2660-5317

Article

Synthesis and Identification of Novel 1,3-Oxazepane-7,4-Dione Compounds via the Reaction of Succinic Anhydride with Schiff's Base and Assessment of Biological Activity

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Abstract: This research showed how to use a cycloaddition method to make and describe new cyclic compounds, mainly oxazepine derivatives. Terephthalaldehyde and substituted aniline reacted with each other in an ethanol solvent under acidic conditions. Glacial acetic acid was used as a catalyst in this reaction. The final product was 1,1'-(1,4-phenylene)bis(N-substituted-methenamine) (H1-H6). We subsequently subjected these azomethines to pericyclic production in dry benzene using succinic anhydride, resulting in the production of 2,2'-(1,4-phenylene)bis(3-(substituted)-1,3-oxazepane-4,7-dione) (H7-H12). We employed the FT-IR, 1H-NMR, and 13C-NMR spectra to investigate the physicochemical properties of the produced compounds (H1 to H12). We tested the oxazepine compounds (H7, H8, H9, H10, H11, and H12) against different types of bacteria, such as gram-positive (Staphylococcus aureus) and gram-negative (E. coli), to see how well they worked against bacteria compared to common antibiotics like ciprofloxacin and norfloxacin. We employed three concentrations in DMSO: (0.01, 0.001, and 0.0001) mg/ml. The compounds They exhibited the most potent antibacterial activity against Staphylococcus aureus and Escherichia coli. This implies their potential for use as antimicrobials.

Keywords: Heterocyclic compounds, Schiff bases, oxazepane, biological activities

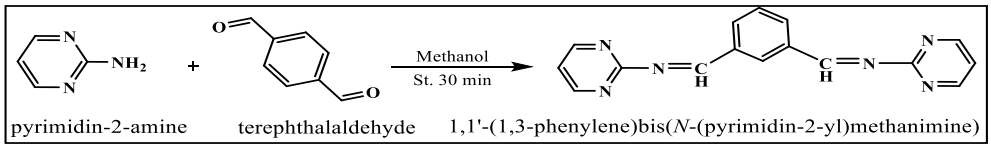
Citation: M. M.Al- Tufah. "Synthesis, Identification, and Biological Activity of Novel 1,3-Oxazepane-7,4-Dione Compounds. Central Asian Journal of Theoretical and Applied Science 2025, 6(1), 34-51.

Received: 10th Dec 2024
Revised: 22th Dec 2024
Accepted: 4th Jan 2025
Published: 18th Jan 2025

1. Introduction

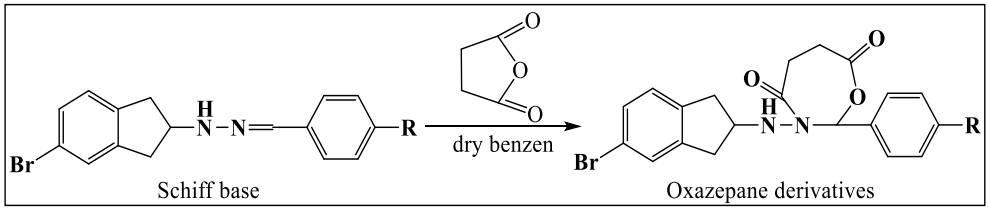
Cyclic organic compounds that contain at least one heteroatom are known as heterocyclic compounds. Among the heteroatoms, nitrogen (N), oxygen (O), and sulfur are the most prominent (S)[1]. Heterocycles with five- or six-membered rings are the most prevalent [2]. Contemporary medicinal chemistry widely uses heterocyclic compounds due to their broad applicability in drug design and discovery. [3]. Heterocycles are found in many medicines, most vitamins, natural products, biomolecules, and biologically active substances. They are antibacterial, antimicrobial, antidepressant, herbicidal, antifungal, anti-HIV, antibiotic, antitumor, antimalarial, antiviral, anti-inflammatory, fungicidal, and insecticidal.[4-8]. The term Schiff's base derives from the German scientist Hugo Schiff, that, in 1864, was the first person to clarify the products formed by the reaction of primary amines with carbonyl compounds.[9]. It is an extensive group of compounds that are distinguished by a double bond between carbon and nitrogen atoms. [10]. This chemical compound is the product of the condensation reaction between amines and aldehydes or ketones, resulting in the formation of imine groups (-N = CH) [11]. Through a 1:2 molar ratio reaction between terephthalaldehyde and a methanol solution of 2-aminopyrimidine,

Schiff bases have been synthesized. [12]. Scheme 1, There are biological activities associated with Schiff bases; their most significant uses in medicine include antimalarials [13] anti-fungal [14], antiviral [15], antitumor [16, 17], anti-inflammatory [18], antibacterial [19], and anticancer [20, 21].



Scheme 1: Synthesis of Schiff Base

The ring of oxazepanes is composed of seven parts, each of which contains one nitrogen atom and one oxygen atom. They are fascinating heterocyclic compounds. [22]. The seven-membered ring resembles oxazepane derivatives (1,2), (1,3), and (1,4).[23, 24]. Schiff base reacts with succinic anhydride to produce oxazepane compounds. [25]. Scheme 2. Oxazepane and its derivatives have significant biological pharmacological activity, including antibacterial properties[26], antioxidant [27], anti-depressant [28], and anti-fungal [29].



Scheme 2: Synthesis of Oxazepane derivatives

2.Experimental

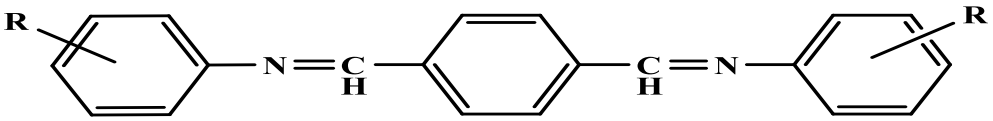
Terephthaldehyde, substituted aniline, succinic anhydride, ethanol, glacial acetic acid, and benzene are supplied from Fluka and Aldrich with the highest purity. We used the Electro-Thermal 9300 melting point apparatus from Engineering, Ltd., U.K. to determine the melting point of the produced compounds. We then used the Shimadzu FTIR-8400 Fourier transform infrared spectrophotometer to analyze the compounds using KBr pellets. We used Bruker 300 MHz spectrometers and tetramethylsilane (TMS) as an internal standard to get their 1H NMR and 13C NMR spectra in DMSO-d6. We conducted measurements in organic materials privately at the University of Kashan, Iran.

2. Materials and Methods

Preparation of Schiff base derivatives (H1-H6).[30]

In absolute ethanol (50 ml), a mixture of terephthaldehyde (0.0075 mol, 1.0 g) and substitute aniline (0.015 mol) was agitated prior to the addition of a few droplets of the glacial acetic acid. The mixture was then refluxed for 6 hours. After this, we concentrated the reaction mixture, cooled it, and then added it to crushed ice. Recrystallization of the solid product from ethanol was carried out. Table 1 provides the physical attributes of the compounds (H1–H6).

Table 1: The physical characteristics for compounds (H1-H6)

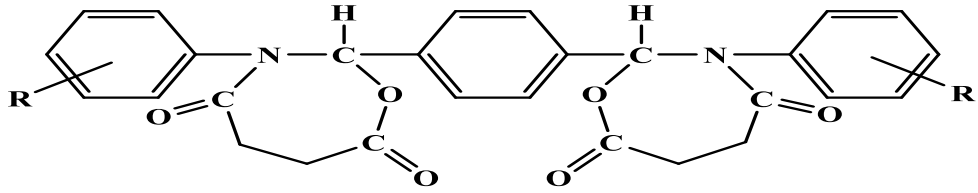


Comp. No.	R	Compound Name	Molecular formula	M.P (C°)	Yield (%)	Color
H_1	4- Br	1,1'-(1,4-phenylene)bis(N-(4-bromophenyl)methenamine)	$C_{20}H_{14}Br_2N_2$	212-214	69	Yellow
H_2	4- Cl	1,1'-(1,4-phenylene)bis(N-(4-chlorophenyl)methenamine)	$C_{20}H_{14}Cl_2N_2$	181-183	77	White
H_3	4- OCH_3	1,1'-(1,4-phenylene)bis(N-(4-methoxyphenyl)methenamine)	$C_{22}H_{20}N_2O_2$	224-226	59	Brown
H_4	4- NO_2	1,1'-(1,4-phenylene)bis(N-(4-nitrophenyl)methenamine)	$C_{20}H_{14}N_4O_4$	271-273	71	Brown
H_5	4-OH	4,4'-((1,4- phenylene bis(methaneylylidene))bis (azaneylylidene))diphenol	$C_{20}H_{16}N_2O_2$	23333-235	66	Yellow
H_6	4-$N(CH_3)_2$	4,4'-((1,4-phenylenebis(methaneylylidene)) bis(azaneylylidene))bis(N,N-dimethylaniline)	$C_{24}H_{26}N_4$	170-172	68	Yellow

3.2.Preparation of 1,3-oxazepane derivatives (H7-H12).[31]

A mixture of compounds (H1-H6) (0.015 mol) and succinic anhydride (0.030 mol, 3.0 g) in 20 ml of dry benzene. The product of the reaction was refluxed for 8 hours, then cooled, filtered, and crystallized in ethanol to get the H7-H12 compounds. The physical characteristics have been listed in Table 2.

Table 2: The physical characteristics for compounds (H7-H12).



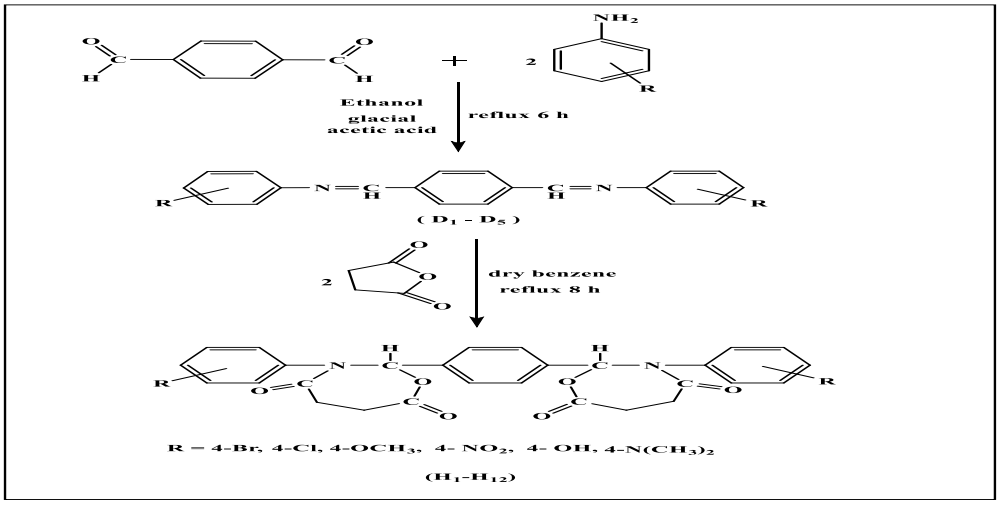
Comp. No.	R	Compound Name	Molecular formula	M.P (C°)	Yield (%)	Color
H_7	4- Br	2,2'-(1,4-phenylene)bis(3-(4-bromophenyl)-1,3-oxazepane-4,7-dione)	$C_{28}H_{18}Br_2N_2O_6$	236-238	88	Yellow
H_8	4- Cl	2,2'-(1,4-phenylene)bis(3-(4-chlorophenyl)-1,3-oxazepane-4,7-dione)	$C_{28}H_{22}Cl_2N_2O_6$	209-211	87	White
H_9	4- OCH_3	2,2'-(1,4-phenylene)bis(3-(4-methoxyphenyl)-1,3-oxazepane-4,7-dione)	$C_{30}H_{28}N_2O_8$	257-259	83	Brown
H_{10}	4- NO_2	2,2'-(1,4-phenylene)bis(3-(4-nitrophenyl)-1,3-oxazepane-4,7-dione)	$C_{28}H_{22}N_4O_{10}$	291-293	91	White
H_{11}	4-OH	2,2'-(1,4-phenylene)bis(3-(4-hydroxyphenyl)-1,3-oxazepane-4,7-dione)	$C_{28}H_{24}N_2O_8$	255-257	75	Yellow
H_{12}	4- $N(CH_3)_2$	2,2'-(1,4-phenylene)bis(3-(4-(dimethylamino)phenyl)-1,3-oxazepane-4,7-dione)	$C_{32}H_{34}N_4O_6$	196-198	81	Yellow

Biological activity measurement

The synthesized compounds (H7-H12) were assessed for their antibacterial properties against two bacterial strains: one Gram-positive (Staphylococcus aureus) and one Gram-negative (Escherichia coli) at concentrations of 0.01, 0.001, and 0.0001 mg per milliliter. To evaluate the biological activity, we employed the propagation technique. The biological activity was measured using the Kirby-Bauer technique. Muller-Hinton agar plates are inoculated with 0.1 milliliters of bacterial solution, and the suspension is allowed to absorb for 5 min[32]. After the plates were incubated at 37°C for 24 hours, the inhibition areas were measured and compared to the standard antibiotics (Ciprofloxacin and Norfloxacin) as control samples. DMSO served as a negative control. Each dish was punctured with a 5 mm cork auger. [33].

3. Results

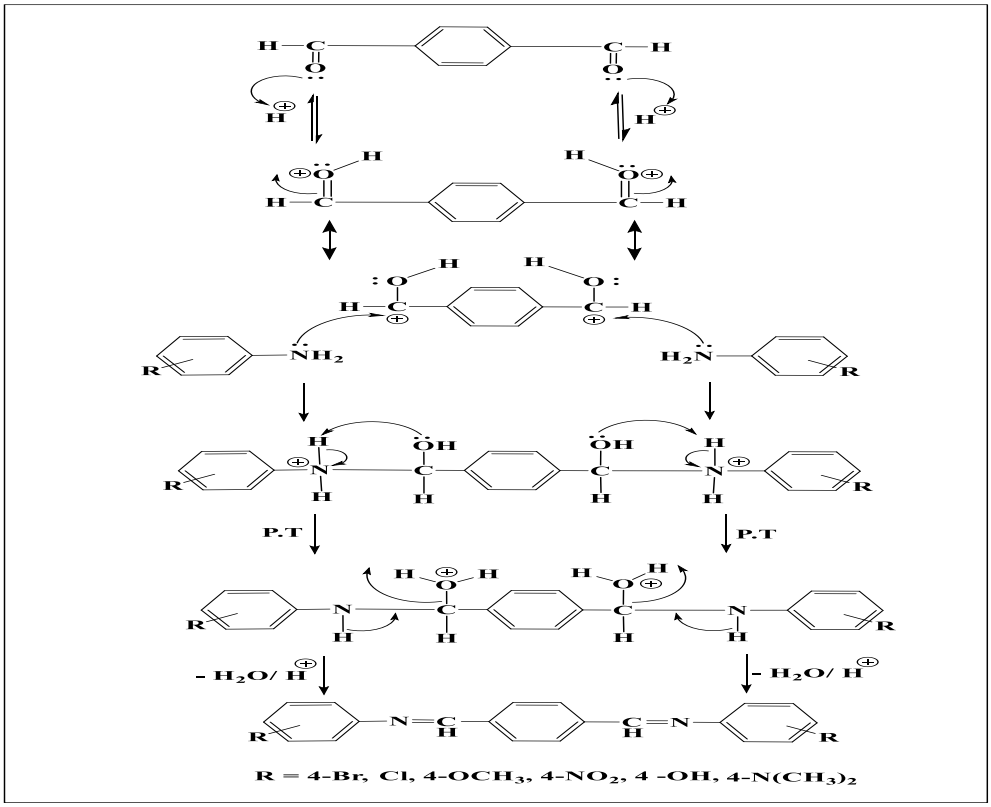
The compounds were produced in the order shown in scheme 3.



Scheme 3: Synthesis of compounds **(H_1-H_{12})**.

Characterization of Schiff base derivatives (H1-H6).

The synthesis of the compounds (H1-H6) was produced through the reaction of terephthalaldehyde with substituted aniline in ethanol, under acidic. The process included a nucleophilic assault by the amine group on the carbonyl carbon of terephthalaldehyde, resulting in unstable intermediates, which subsequently eliminated a water molecule to provide an imine product. [34], as shown in Scheme 4.



Scheme 4: The stages in the mechanism for the formation of compounds (H1–H6)

FT-IR was used to characterize compounds (H1-H6). The NH_2 group, both symmetric and asymmetric, disappeared at 3424 cm^{-1} in these spectra, and the υ (CH=N) group was responsible for the appearance of bands. [35]. The FT-IR spectra of compounds (H1–H6) showed the following absorption bands: C-H stretching (aromatic) at 3022 and 3072 cm^{-1}; C=N stretching at 1630-1658 cm^{-1}; C=C (aromatic ring) at 1479 and 1604 cm^{-1}; and C-N vibration at 1272-1354 cm^{-1}. The bands are shown in Table 3 and Figures 1, 2, and 3.

Table 3. Some spectral data for compounds (H1- H6)

I.R., ν (cm^{-1}), KBr Comp.No.	R	ν (C-H) Aromatic	ν (C=N)	ν (C=C) Aromatic	ν(C-N)	Others
H_1	4- Br	3053	1649	1593,1492	1340	νC-Br, 694

H_2	4- Cl	3062	1622	1519,1479	1354	νC-Cl, 842
H_3	4- OCH_3	3022	1658	1604,1571	1272	νCH_3, sy 2862 asy 2925
H_4	4- NO_2	3072	1634	1579,1512	1313	ν NO sy, 1340, asy 1473
H_5	4-OH	3066	1654	1598,1560	1326	ν OH, 3390
H_6	4- $N(CH_3)_2$	3043	1609	1598,1563	1307	νCH_3, sy 2873 asy 2935

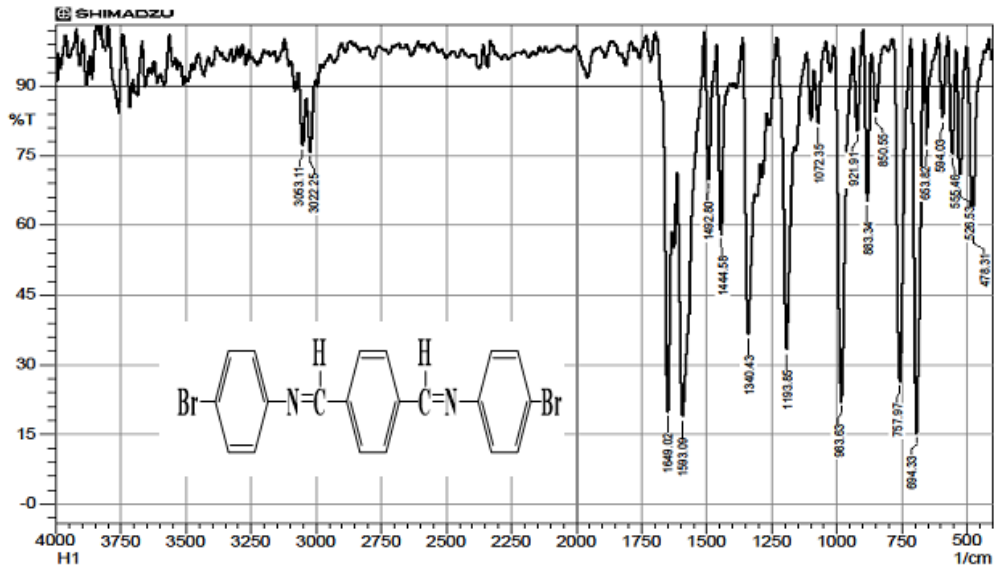


Figure 1: Show the IR for compound (H1)

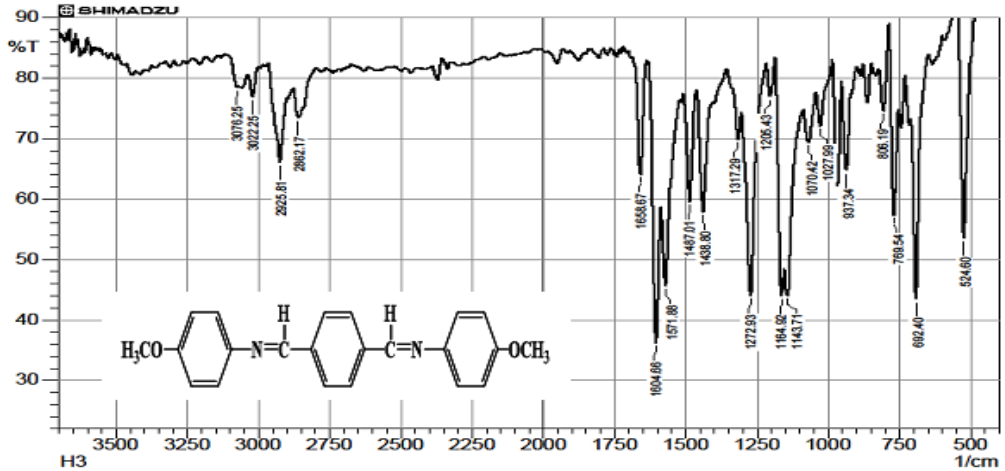


Figure 2: Show the IR for compound (H3)

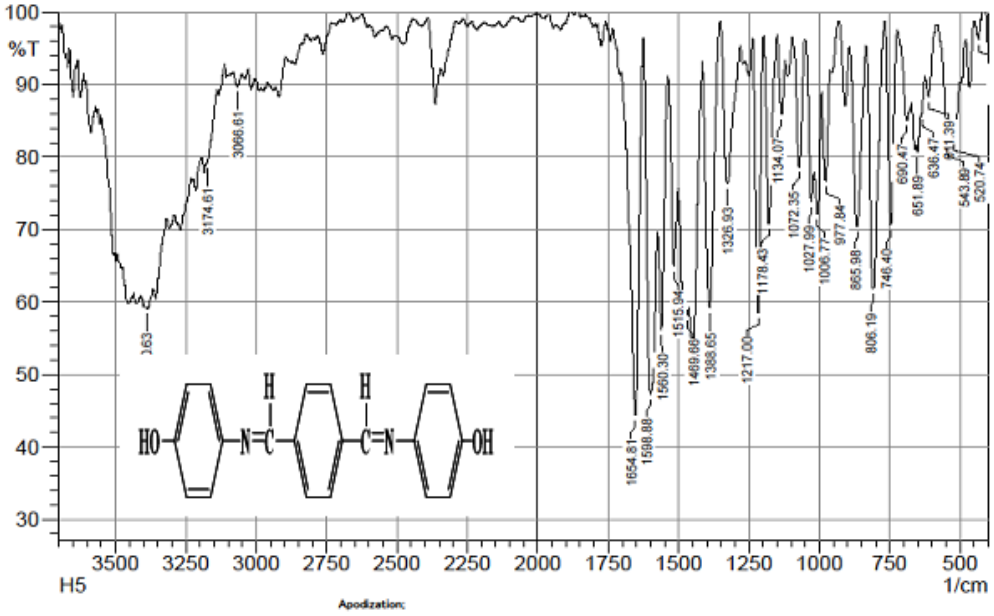
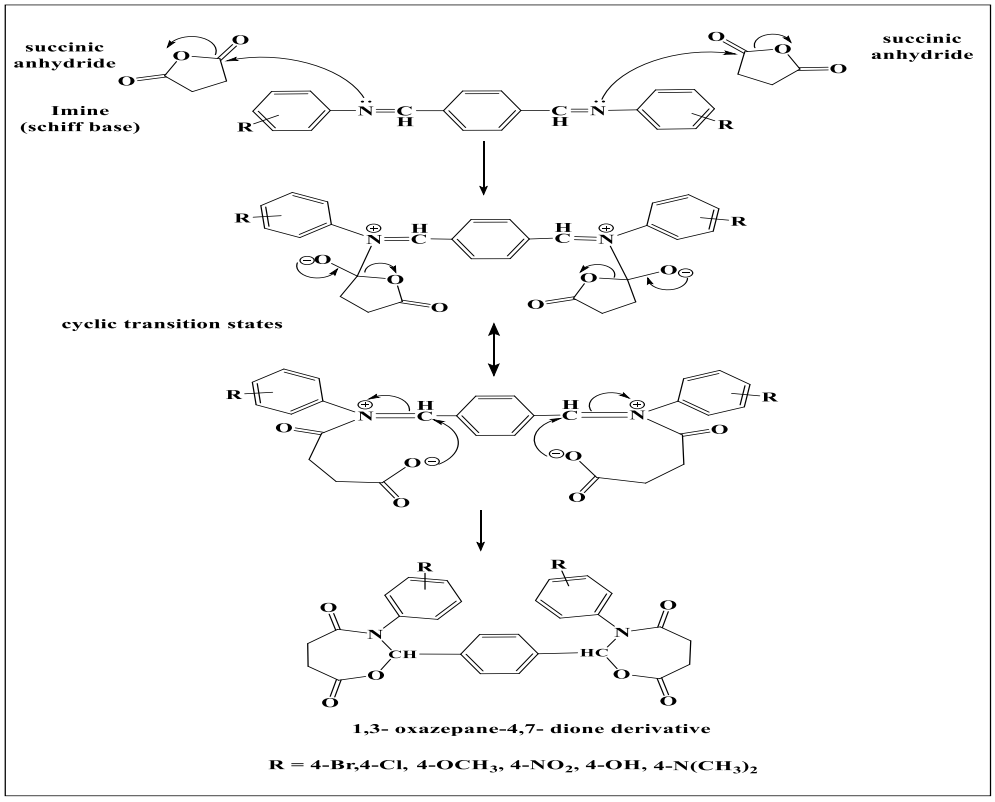


Figure 3: Show the IR for compound (H5)

Characterization of 1,3-oxazepane derivatives (H7-H12)

The new 1,3-oxazepane (H7-H12) was synthesized by the cycloaddition reaction of compound (H1-H6) with succinic anhydride in dry benzene as a solvent. The suggested mechanism is shown in Scheme 5.



Scheme 5: Mechanism steps of 1,3-oxazepane derivatives synthesis (H7-H10)

The FT-IR characterization of the synthesized compounds (H7-H12) revealed the absence of the imine absorption band at 1609–1656 cm^{-1} and the emergence of new bands

for absorption at 1709–1737 cm^{-1} and 1648–1677 cm^{-1}, respectively. These bands correspond to lactam (N-C=O) and lactone (O-C=O) within the oxazepine ring [36], Showing an absorption band at (3031–3078) cm^{-1}, indicative of aromatic (C-H) vibrations. A broad absorption band in the range of 2923-2982 cm^{-1} is attributed to aliphatic compounds. The (C=C) aromatic band is seen at (1568–1595) cm^{-1}, while the (C-N) vibration absorption band is noted at (1350–1366) cm^{-1}, as shown in Table 4 and Figures 4, 5, and 6.

Table 4. Some spectral data for compounds (H7- H12)

I.R., v (cm^{-1}), KBr Comp.No.	R	(C-H) Aliph.	(C-H) Arom.	(C=O) Lactone.	(C=O) Lactame.	(C=C) Arom.	(C-N)	Others
H_7	4-Br	2982, 2900	3031	1728	1656	1587	1326	C-Br 528
H_8	4- Cl	2956, 2845	3053	1705	1648	1568	1277	C-Cl 842
H_9	4- OCH_3	2937, 2833	3047	1737	1662	1596	1249	-
H_{10}	4-NO_2	2974, 2834	3061	1712	1657	1584	1314	NO sy 1340 asy 1473
H_{11}	4-OH	2923, 2852	3058	1714	1677	1595	1269	O-H 3427
H_{12}	4-$N(CH_3)_2$	2968, 2847	3078	1709	1658	1579	1322	-

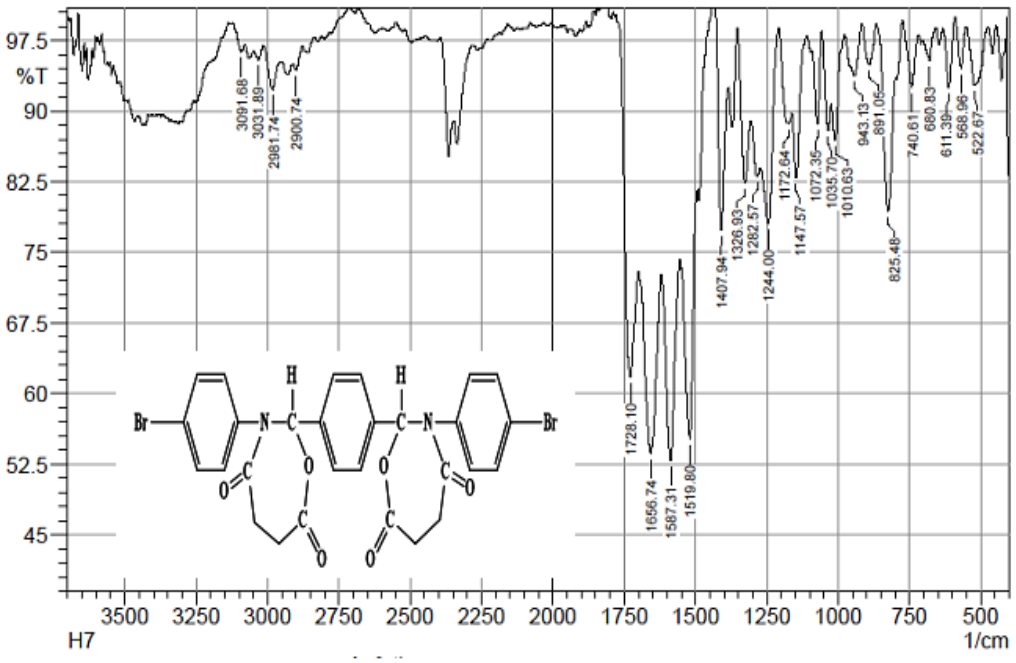


Figure 4: Show the IR for compound (H7)

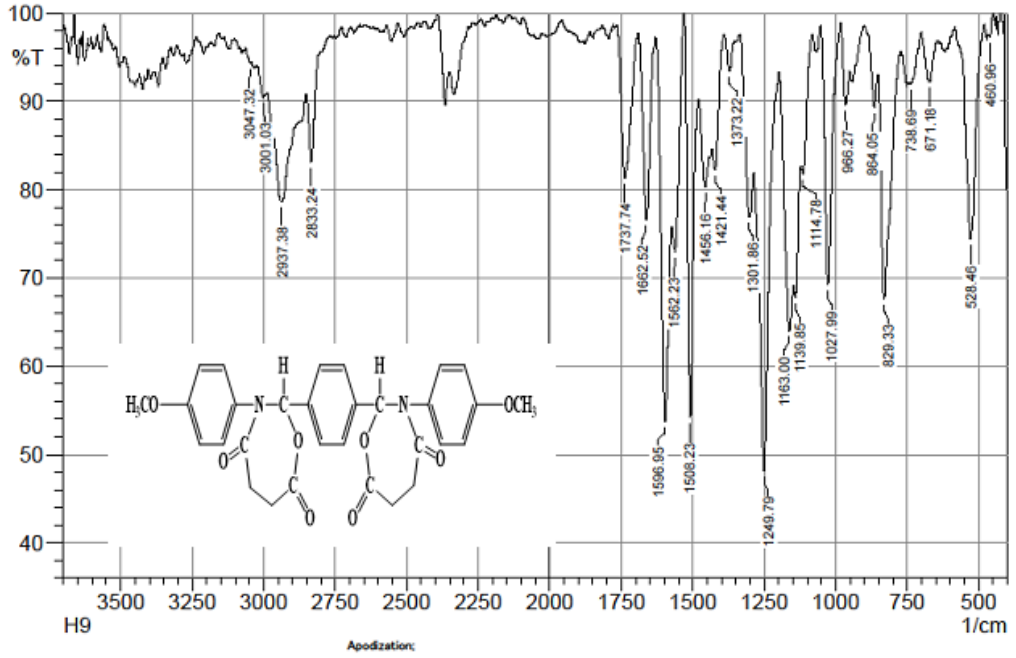


figure 5: Show the IR for compound (H9)

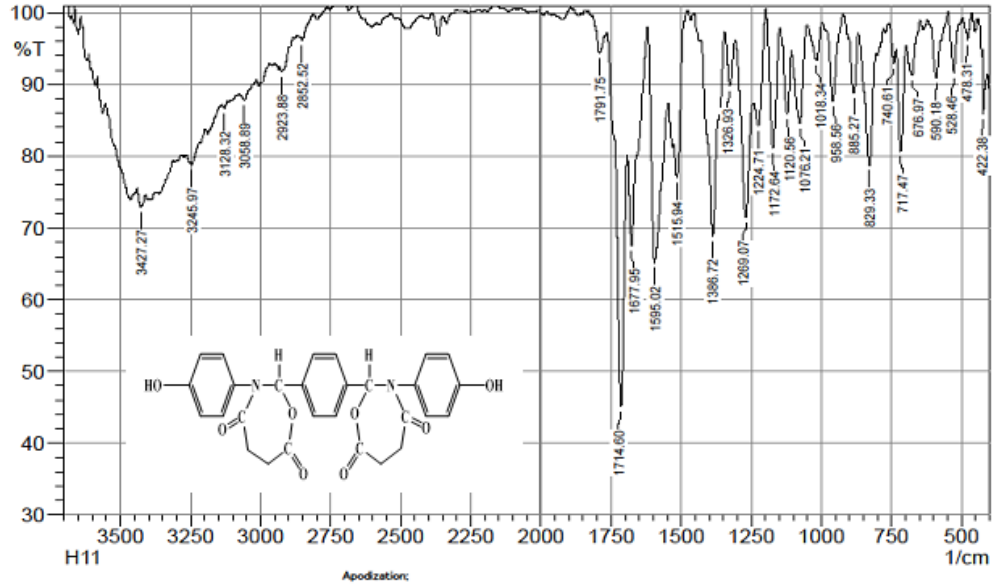


Figure 6: Show the IR for compound (H11)

4. Discussion

Discussion of (1H-NMR) spectra.

The compound H1 in the 1H-NMR spectra has a singlet at 8.16 ppm, corresponding to the proton in the N=CH band.[37], as well as several signals between 7.60 and 8.01 ppm, These are the protons of the aromatic ring. Additionally, we detect a solvent (DMSO) signal at (2.54) ppm, as shown in Figure 7. The chemical (H3) had a single signal at 8.29 ppm, which was assigned to the proton group (N=CH), as well as several signals ranging from 7.52 to 7.99 ppm, which were assigned to the protons in the aromatic ring. Also, a signal was observed at 3.37 ppm for the -OCH_3 group. As seen in Figure 8. The compound(H5) 1H-NMR spectra exhibited a singlet spectrum signal at 8.20 ppm, corresponding to the proton in the N=CH group. The protons of the aromatic ring exhibited several signals between 7.54 and 7.94 pp, Furthermore, Figure 9 displays a signal for the OH group at 10.90 ppm. The 1H-NMR spectra of compound H7 exhibited two distinct signals at 2.40 ppm and 2.53 ppm, which relate to the lactone (O-C=O) and lactam (N-C=O) moieties, respectively, linked to the protons of the CH2 group. Phenyl rings provide many signals (7.30–8.66 ppm), while the proton group (-CH) in the cyclic structure produces a signal at 9.99 ppm, shown in Figure 10.

Figure 11 showed two binary signals at 2.43 ppm and 2.84 ppm, relating to the lactone (O-C=O) and lactam (N-C=O) groups, accordingly linked to the protons of the CH2-CH2 moiety. The cyclic closed proton group (-CH) signaled at 9.79 ppm, while a singular signal at 3.76 ppm related to the methylene groups. Phenyl rings provide many signals between 6.73 and 8.73 ppm. The 1H-NMR spectra of compound H11 revealed two distinct signals at 2.48 ppm and 2.82 ppm, which were attributed to the lactone (O-C=O) and lactam (N-C=O) functionalities, respectively linked to the protons of the CH2-CH2 moiety. Phenyl rings produce many signals (7.22–8.04 ppm); the cyclic closed proton group (CH) displays a signal at 8.68 ppm; and the proton (OH) appears at 10.05 ppm, as seen in Figure 12.

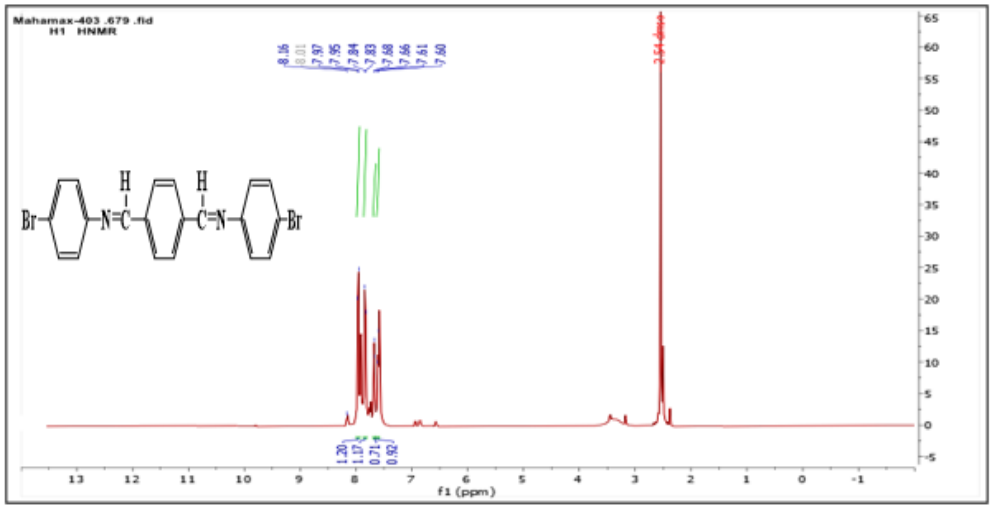


Figure 7 :Show the 1HNMR for compound (H1)

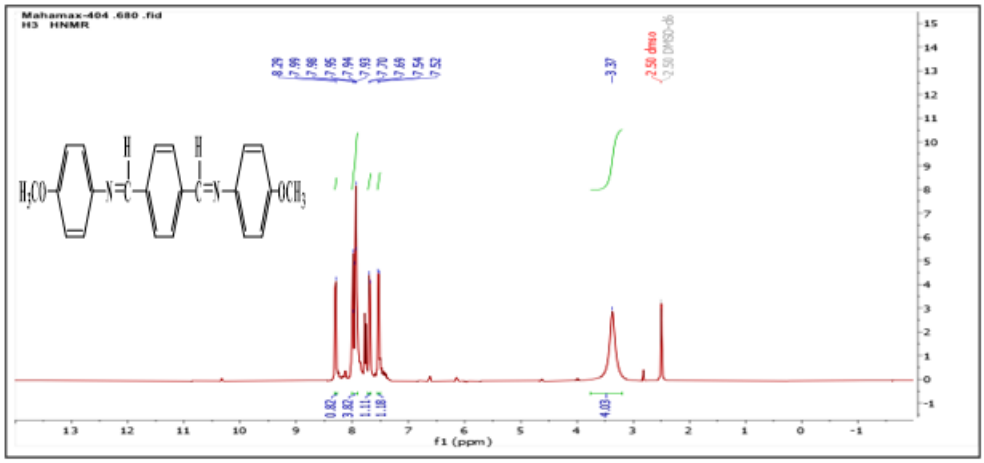


Figure 8 :Show the 1HNMR for compound (H3)

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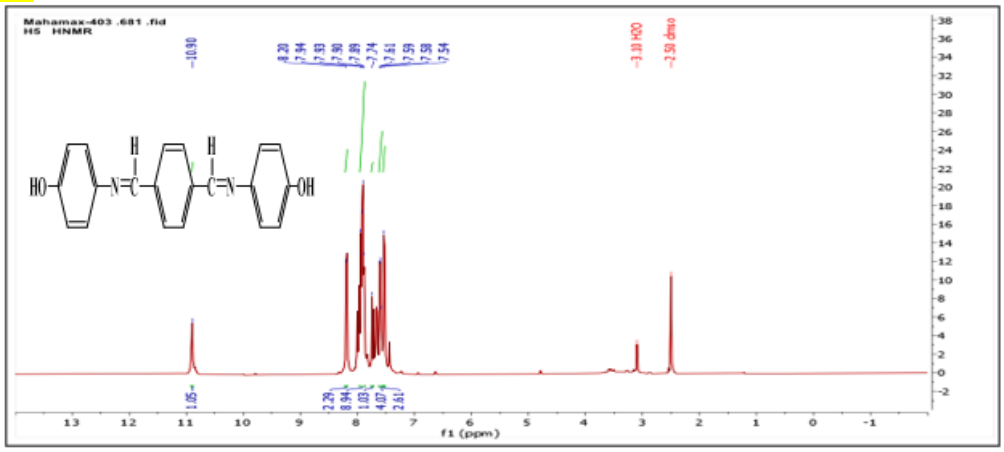


Figure 9 :Show the 1HNMR for compound (H5)

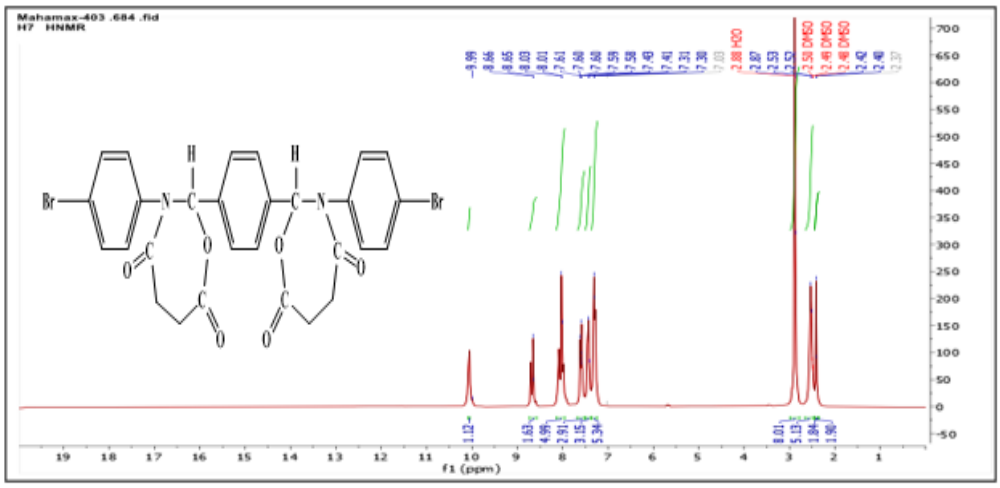


Figure 10 :Show the 1HNMR for compound (H7)

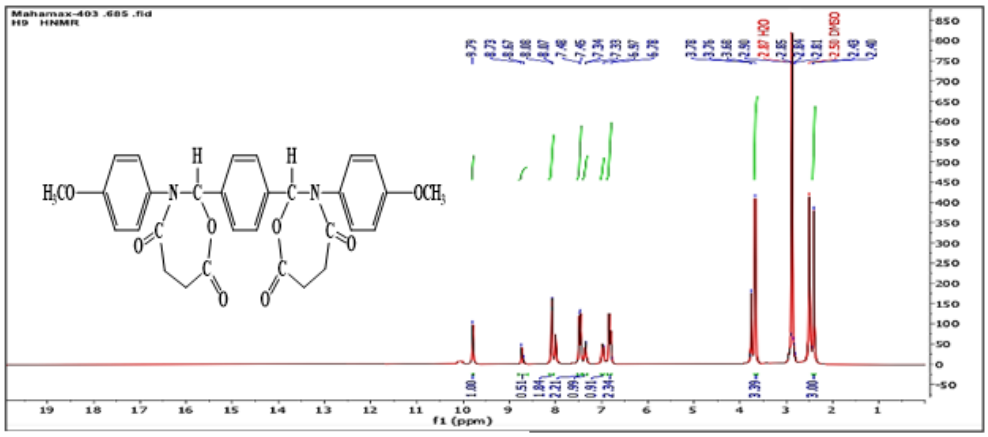


Figure 11 :Show the 1HNMR for compound (H9)

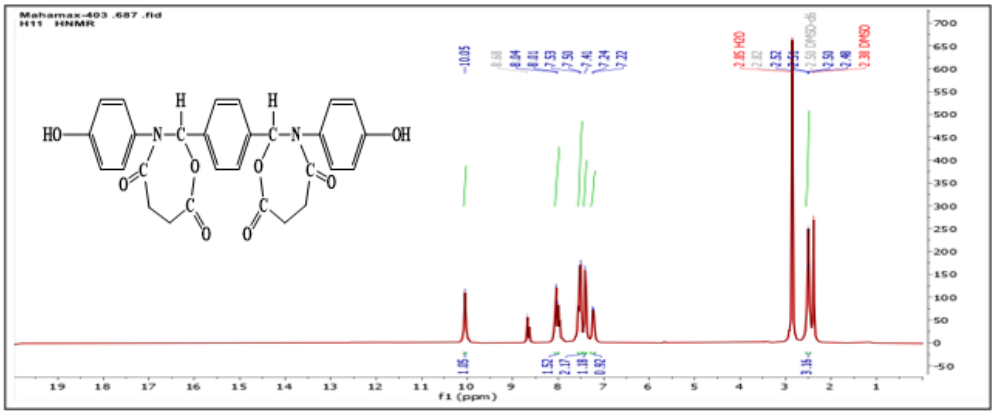


Figure 12:Show the 1HNMR for compound (H11)

Discussion of (13C-NMR) spectra.

The 13-C NMR spectrum of substance (H3) was obtained in DMSO-d6. The -CH=N signal of the imine group was seen at 161.72 ppm, whereas signals at 55.83 ppm corresponded to methyl (CH_3) groups. Aromatic carbon signals were seen at 114.87–144.56 ppm and 40 ppm, contingent upon the solvent, as seen in Figure 13. The 13C-NMR spectra of chemical H5 demonstrated a signal at 161.34 ppm related to the -CH=N band. Figure 14 shows the presence of aromatic carbon signals at (116.2–150.5) ppm. The chemical (H9), 13C-NMR spectrum showed signals at 29.55 ppm for the methyl (CH3) groups, at 29.25 and 31.34 ppm for the (CH_2-CH_2) group of the oxazepane ring, and at 64.32 ppm for the

(CH) group of the oxazepane ring. Both carbonyl (C=O) groups of the lactamase and lactone displayed two signals at 170 ppm and 174 ppm, respectively. The phenyl aromatic rings exhibit many signals between 112.55 and 143.31 ppm, as seen in Figure 15. Figure 16 shows a signal at (29.20, 31.29) ppm due to the (CH2-CH2) group of the oxazepane ring, a signal at (55.51) ppm corresponding to the (CH) group of the oxazepane ring, and two signals at (169.98) ppm and (173.55) ppm, which are given to the carbonyl (C=O) groups of the lactam and lactone, respectively. The phenyl aromatic rings manifest as multiple signals within the range of 114.19 to 132.95 ppm.

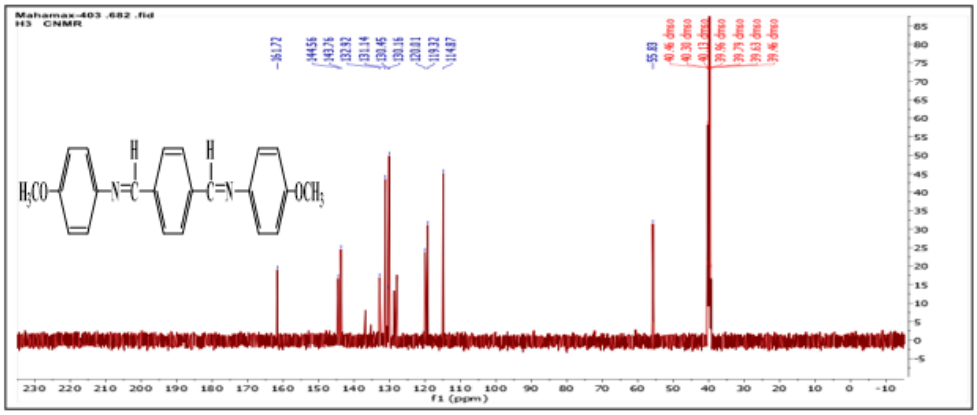


Figure 13 :Show the ^{13}C-NMR for compound (H_3)

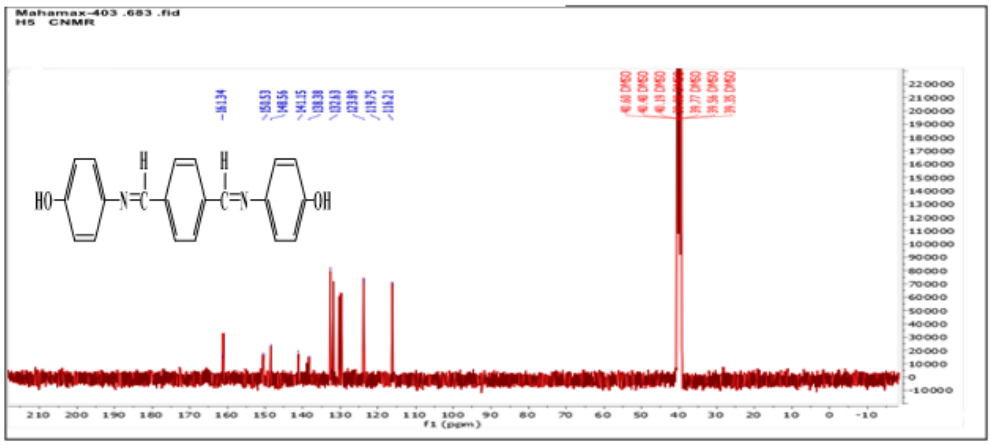


Figure 14 :Show the ^{13}C-NMR for compound (H_5)

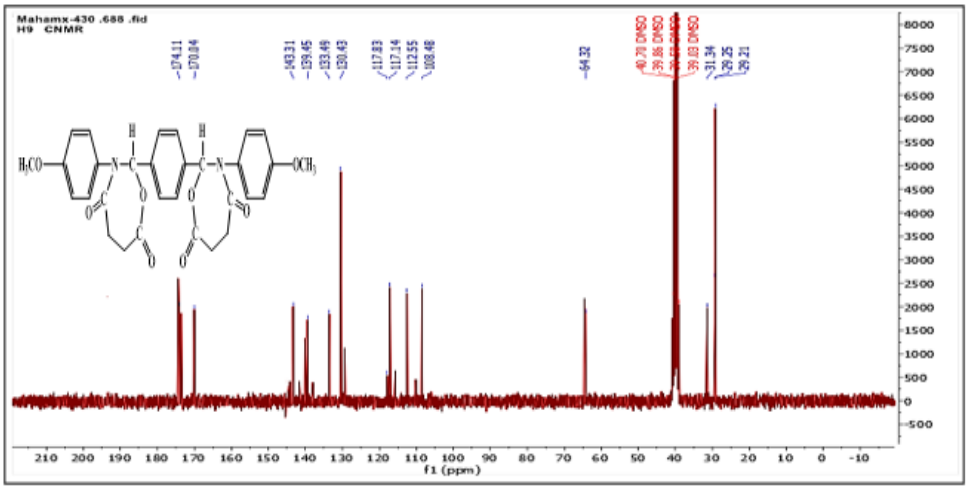


Figure 15 :Show the ^{13}C-NMR for compound (H_9)

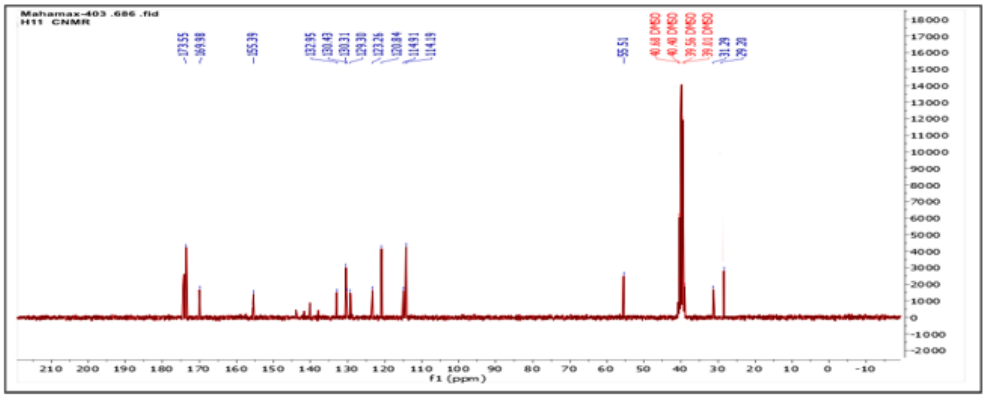
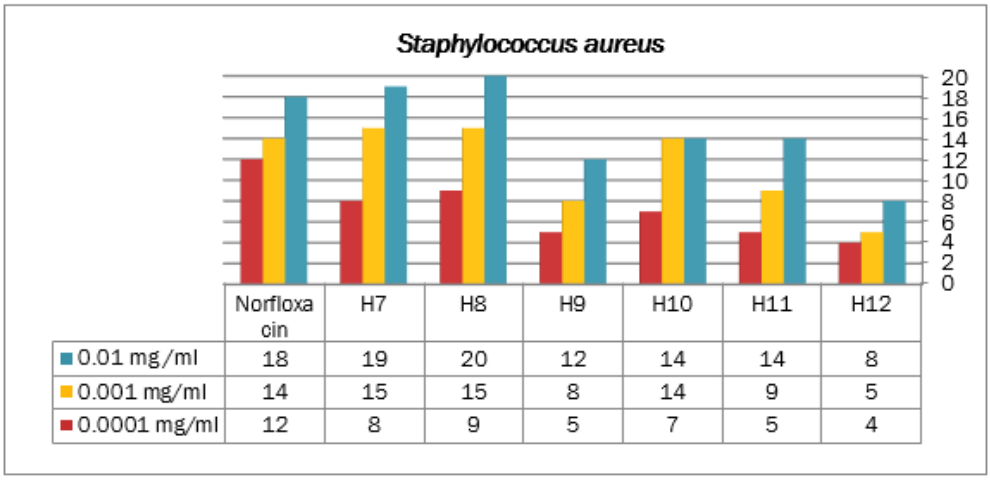


Figure 16 :Show the 13C-NMR for compound (H11)

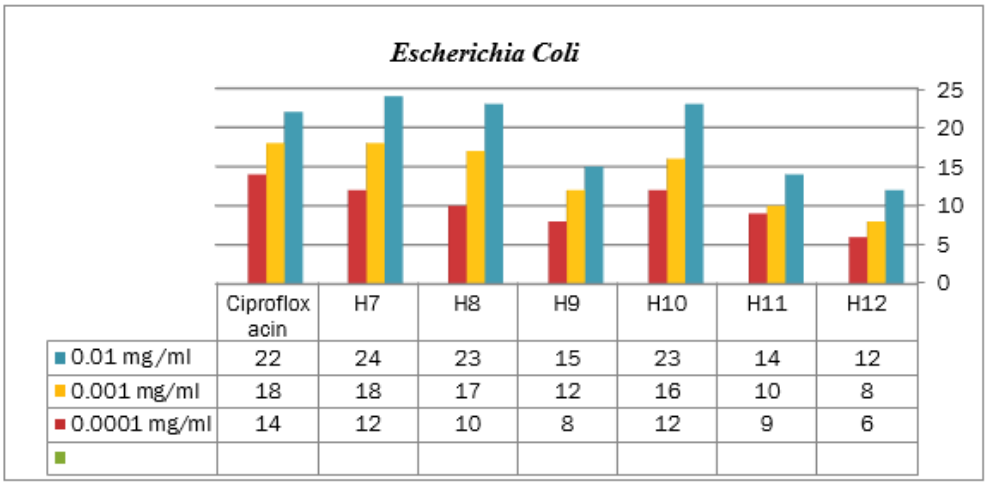
Antibacterial effectiveness.

Escherichia coli is a type of gram-negative bacteria, and it also includes gram-positive bacteria. Staphylococcus aureus constitutes two bacterial genotypes that are employed to investigate the biological activities of H7-H12. Compounds H7 and H10 were highly efficacious against E. coli, with a potency consistent with the medications used for comparison. In close proximity to the pharmaceuticals, compounds H8 and H11 exhibited activity against E. coli, while compounds H7, H8, and H10 exhibited activity against S. aureus. The activities of the other compounds that were produced were comparable to those of norfloxacin and ciprofloxacin, ranging from mild to medium. Gram-positive bacteria are robust and lack this membrane, in contrast to Gram-negative bacteria, which have reduced layers of peptidoglycan and an external lipid wall [38]. The substances have the potential to affect the peptidoglycan wall and outer lipid membrane of the bacteria [39]. This is shown in Figures 17, 18, 19, and 20.



	Norfloxacin	H7	H8	H9	H10	H11	H12
0.01 mg/ml	18	19	20	12	14	14	8
0.001 mg/ml	14	15	15	8	14	9	5
0.0001 mg/ml	12	8	9	5	7	5	4

Figure 17. Differential effect and different concentrations of compounds (H7-12) studied against bacteria (S. aureus).



	Ciproflox acin	H7	H8	H9	H10	H11	H12
0.01 mg/ml	22	24	23	15	23	14	12
0.001 mg/ml	18	18	17	12	16	10	8
0.0001 mg/ml	14	12	10	8	12	9	6

Figure 18. Differential effect and different concentrations of compounds (H7-12) studied against bacteria (E.Coli).

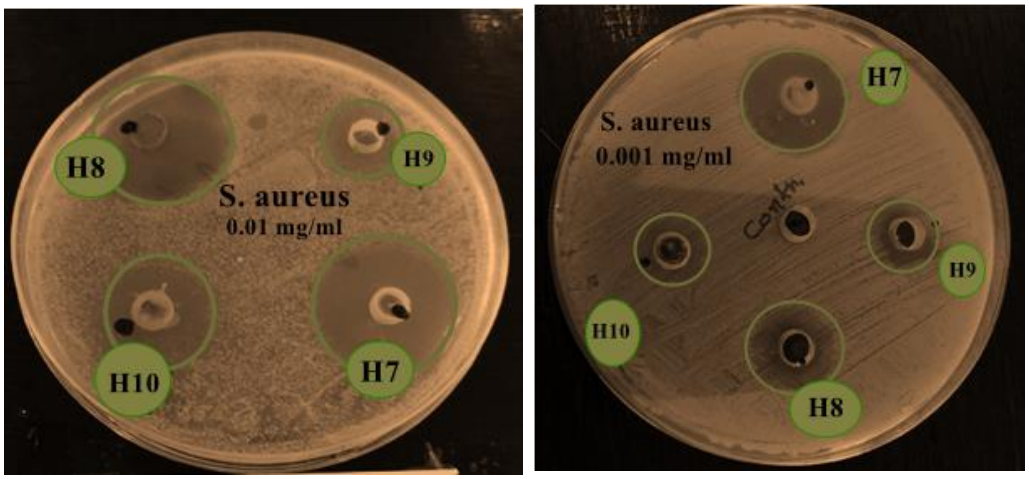


Figure 19: The biological efficacy of compounds H7, H8, H9 and H10 against S. aureus becteral.

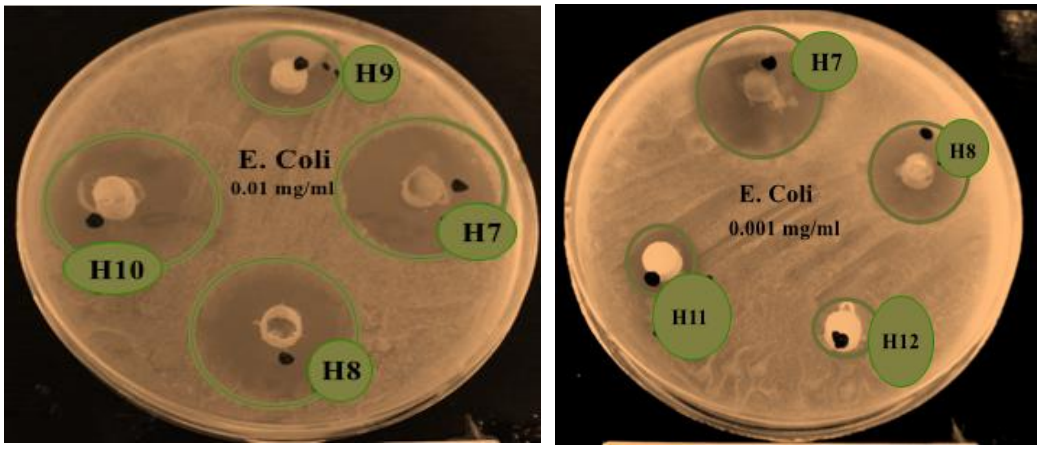


Figure 20: The biological efficacy of compounds H7, H8, H9 and H10 against E.Coli becteral.

5. Conclusion

In conclusion, novel chemical compounds were synthesized from derivatives of 1,3-Oxazepane-7,4-Dione based on the preceding findings. We accomplish this via two initial steps: Terephthalaldehyde reacts with substituted aniline to synthesize new compounds

with two azomethine groups. The subsequent step: The azomethine compounds synthesized in the preceding step were reacted with succinic anhydride in varying molar ratios (1:2). FT-IR, 1H-NMR, and 13C-NMR spectra were used to meticulously identify the compounds (H1 to H12). Many of the compounds, like H7, H8, and H10, were tested for their antibacterial activity and found to be very effective against both Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacterial strains.

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