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RESEARCH PAPER

Synthesis and Characterization of a New Series of [1, 3]-Oxazepine Compounds from Heterocyclic Schiff Bases

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A B S T R A C T:

In this study a new Series of aromatic heterocyclic [1, 3]-oxazepine have been synthesized by two steps. The first-step included synthesis of imine derivatives (1–7) using glacial acetic acid as a catalyst in the condensation reaction of 4-(6-methylbenzothiazol-2-yl)aniline with various substituted aromatic aldehydes. While in a second step, a series of seven-membered heterocyclic ring derivatives (8-14) obtained from Schiff base derivatives with phathalic anhydride in dry benzene. A variety of experimental techniques were used to characterize the new derivatives, including melting point, FT-IR, ^{1}H-NMR, and ^{13}C-NMR. Finally, the synthesized compounds were screened against two types of bacteria both Staphylococcus aureus Gram (+ve) and Escherichia coli Gram (-ve) microorganisms. The results revealed that slightly active to good active against both types of test organisms of bacteria.

KEY WORDS: Heterocyclic compounds, Schiff bases, [1, 3]-Oxazepine, antibacterial activity.
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1. INTRODUCTION:

Schiff bases are compounds with an azomethine group (-C=N-), which are formed by the condensation of an amine and an active carbonyl group (Mohammad, et al., 2019). They have important applications in chemistry as well as bioactivities such as anti-bacterial, antimicrobial, inhibitors, and anti-cancer (Zagade and Senthilkumar, 2011; Ahir, et al., 2005; Warad, et al., 2020). [1, 3]-Oxazepine is a seven-member ring compound that has two hetero atoms, an oxygen atom at position 1 and a nitrogen atom at position 3. Oxazepine and its derivatives have some important biological and pharmacological activities (Sindhu, et al., 2013) such as enzyme inhibitors (Sawant, et al., 2012), antibacterials and anti-fungi (Adnan and Ghafli, 2021) (Mosa, et al., 2019), antimicrobial (Mohammad Al-Janaby and Mustafa Al-Jobory, 2014), anticorrosion (Hamak and Eissa, 2013), and psychoactive drugs (Bera and Roy, 2009).

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There are only a few methods for preparing [1, 3]-oxazepine rings. Many studies have used the cycloaddition reaction to form various [1, 3]-oxazepine rings (Abood and Hussein, 2014). In this type of cycloaddition, a two-membered imine group was added to a five-membered of phthalic anhydrides, to form a seven-membered heterocyclic ring, (Abood, et al., 2013).

The aim of this work is synthesis of some Shiff bases and their 1,3-oxazepines, derived from phthalic anhydride by many steps of reaction and study biological activity for [1, 3]-oxazepines.

2.EXPERIMENTAL

2.1 The chemicals and materials

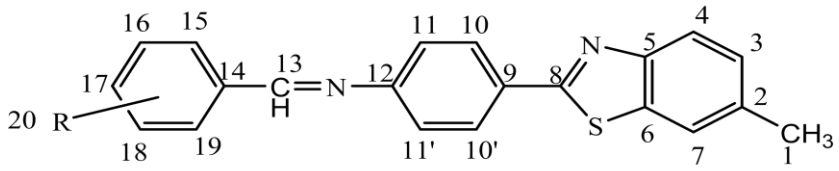
4-(6-Methylbenzothiazol-2-yl)aniline: BATCH NO. 2013120901 (95%); 4-Nitrobenzaldehyde: Riedel-de Haen AG (98%); 3-Nitrobenzaldehyde: Riedel-de Haen (97%); 4-Bromobenzaldehyde: Fluka AG (97%); 3-Hydroxybenzaldehyde: Riedel-de Haen (98%) and Phthalic anhydride: SDFCL (98%), Benzaldehyde: ROTH (99.5%); Anisaldehyde: SHBC (98%); p-Tolualdehyde: Fluka AG (97%); Ethanol: Scharlau (99.9%);

Glacial acetic acid: GCC (98%); Benzene: EMPLURA (99.5%) and Toluene: J.T.Baker (98%). All substances were employed without further purification.

2.2 Methods of preparing compounds

2.2.1 Synthesis of N-(4-(6-methylbenzothiazo-2-yl) phenyl)-1-(substituted phenyl)methanimine (Hanoon, 2011)

0.01 mole of 4-(6-methylbenzothiazol-2-yl)aniline placed in 50 mL absolute ethanol. After that 0.01 mole substituted aromatic aldehyde with a few drops of glacial acetic acid were added and then reflexed in a round bottom flask (4-8 hrs.). Thereafter allowing the reaction mixture to cool to room temperature, the solid product was filtered and recrystallized from ethanol to yield colored imine compounds. The yields, melting point, and time of reaction were assembled in **Table** 1.



R= H, 4-NO_2, 3-OH, 4-OCH_3, 3-NO_2, 4-Br, 4-CH_3

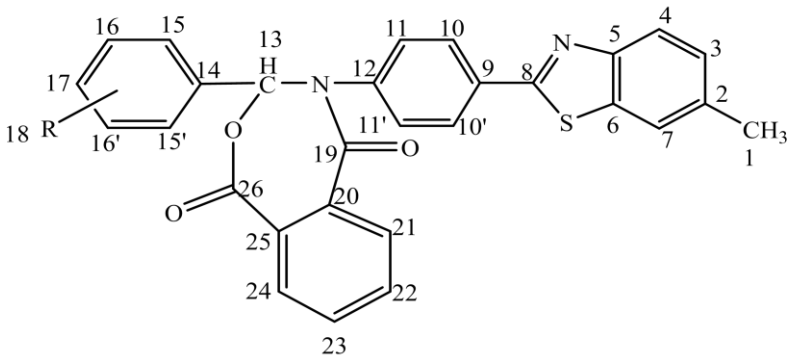
N-(4-(6-methylbenzothiazol-2-yl)phenyl)-1-(substituted phenyl)methanimine

Table 1: Some physiochemical properties of synthesized of N-(4-(6-methylbenzothiazo-2-yl) phenyl)-1-(substituted phenyl)methanimine (Siddiqui, et al., 2006)

No.	Compounds	M.F	Yield %	Time of Reaction (hrs.)	M.P ^{o}C
1.	N-(4-(6-methylbenzothiazol-2-yl)phenyl)-1-phenylmethanimine	$C_{21}H_{16}N_2S$	80	4	188-190
2.	N-(4-(6-methylbenzothiazol-2-yl)phenyl)-1-(4-nitrophenyl)methanimine	$C_{21}H_{15}N_3O_2S$	68	8	224-226
3.	N-(4-(6-methylbenzothiazol-2-yl)phenyl)-1-(3-hydroxyphenyl)methanimine	$C_{21}H_{16}N_2OS$	75	6	244-246
4.	N-(4-(6-methylbenzothiazol-2-yl)phenyl)-1-(4-methoxyphenyl)methanimine	$C_{22}H_{18}N_2OS$	73	5	185-187
5.	N-(4-(6-methylbenzothiazol-2-yl)phenyl)-1-(3-nitrophenyl)methanimine	$C_{21}H_{15}N_3O_2S$	70	8	198-200
6.	N-(4-(6-methylbenzothiazol-2-yl)phenyl)-1-(4-bromophenyl)methanimine	$C_{21}H_{15}N_2SBr$	80	5	241-243
7.	N-(4-(6-methylbenzothiazol-2-yl)phenyl)-1-(4-methylphenyl)methanimine	$C_{22}H_{18}N_2S$	72	5	191-193

2.2.2 Synthesis of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-phenyl)-3,4-dihydrobenzo[1, 3]oxazepine-1,5-dione (Abbas, et al., 2021)

2 mmole from prepared Schiff bases reacted with (2 mmoles, 0.0296 gm) of phthalic anhydride in 20 mL dry benzene was refluxed in a water bath at (85^{o}C) for (7-9 hrs) by the reaction of cycloaddition, as showen in **Scheme 1**. After that, the mixture was allowed to cool to room temperature. The product was filtered and recrystallized from toluene or ethanol. The yields, melting point, and time of reaction of the synthesized [1, 3]-oxazepines are showen in **Table 2**.



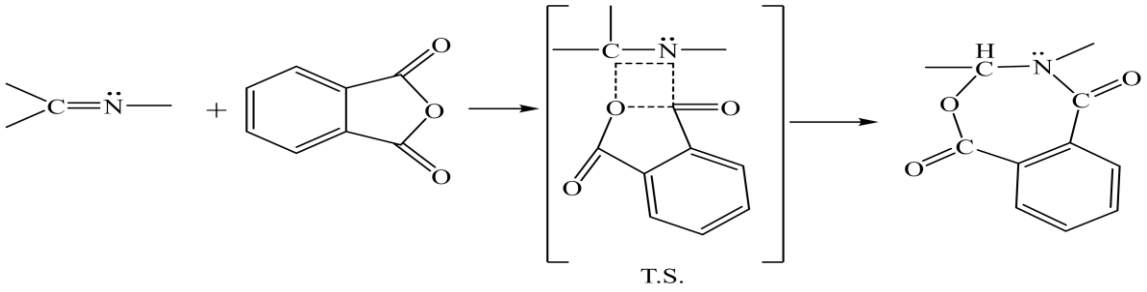
R= H, 4-NO_2, 3-OH, 4-OCH_3, 3-NO_2, 4-Br, 4-CH_3

4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(substituted phenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione

Table 2: Some physiochemical properties of synthesized of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(substituted phenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione (Abood and Hussein , 2014)

No.	Compounds	M.F	Yield %	Time of Reaction (hrs.)	M.P ^{o}C
8.	4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-phenyl-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione	$C_{29}H_{20}N_2O_3S$	72	7	295-297
9.	4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(4-nitrophenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione	$C_{29}H_{19}N_3O_5S$	63	9	228-230
10.	4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(3-hydroxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione	$C_{29}H_{20}N_2O_4S$	70	8	253-255
11.	4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(4-methoxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione	$C_{30}H_{22}N_2O_4S$	70	8	194-196
12.	4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(3-nitrophenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione	$C_{29}H_{19}N_3O_5S$	68	8	204-206

13.	4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(4-bromophenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione	$C_{29}H_{19}N_2O_3SBr$	75	8	250-252
14.	4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(4-tolylphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione	$C_{30}H_{22}N_2O_3S$	67	8	198-200



Scheme 1: Mechanism Synthesis of [1, 3]-Oxazepine-4,7-dione by using Phthalic Anhydride (Sallal and Ghanen, 2018)

2.3 Antibacterial activity

The antibacterial activity of all [1, 3]-oxazipine compounds against *Staphylococcus aureus* Gram (+ve), *Escherichia Coli* Gram (-ve) was examined using sterile discs from 0.3 g of each sample dissolved in 3 mL $CHCl_3$ were absorbed on the small filter paper (5 mm diameter) discs impregnated with stock solutions of each samples in the incubator at 37 °C for 1 hour to dry them.

The bacterial suspension was spread on the surface of Mueller Hinton Agar (MHA) plates by using cotton swab, and then the sample was left at room temperature (25 °C) to dye it, after that sample pleats or discs were gently pressed on the surface of the agar. All plates were incubated at 37 °C for 18-24 hours. In this invistagation $CHCl_3$ employed as a control. The antibacterial action of all [1, 3]-oxazipine compounds were estimated by measuring the inhibition zone (mm), and the data of antibacterial activities are illustrated in **Table 3** (Abood and Hussein, 2014).

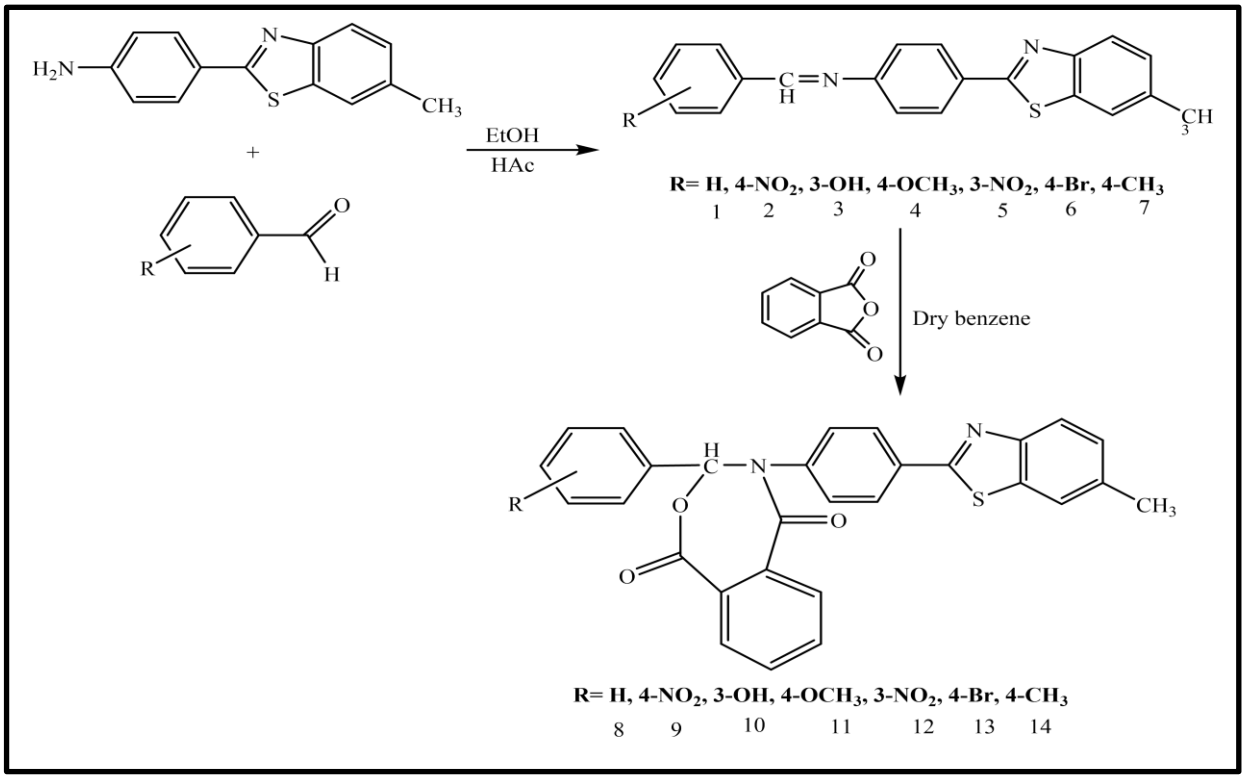
2.4 Instrumentals

BUCHI B-540 electrothermal melting point (M.P) apparatus was used to determine melting points. Fourier transform infrared (FTIR) spectroscopy for synthesized samples was recorded using the potassium bromide KBr disc method , with spectra in the range 400-4000 cm^{-1}a Bio-Rad Merli, FT-IR spectroscopy Mod FTS 3000, in Salahaddin University-Erbil. At Tehran Central Lab ^{1}H-NMR (Proton Nuclear Magnetic Resonane) and ^{13}C-NMR (Carbon Thirteen Nuclear Magnetic Resonance) spectra were obtained using a Varian-INOVA (500 MHz), by using those solvents DMSO and $CHCl_3$.

3. RESULTS AND DISCUSSION

Spectroscopic study of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(substituted phenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione

When the various substituted Schiff bases were cyclized with phthalic anhydride, they yielded a series of [1, 3]-oxazepines (8-14)**, as showen in scheme 2,** (Abbas, et al., 2021). The formation of new oxazepines was recognized using spectral methods such as FT-IR, ^{1}H-NMR, and ^{13}C-NMR.



Scheme 2: [1, 3]-Oxazepine synthesis from Schiff bases

3.1 FT-IR study

The functional groups of samples were investigated via the FTIR technique, **Figure (1)** exhibits the spectrum of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-phenyl-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione (8) (Abbas, 2002). From this figure, the appearance of a broad band at 1678.07 cm^{-1} for (O=C-O and O=C-N vibration coupling), during the peaks of thiazole ring appear at 1541.12 cm^{-1}, and disappearance of a sharp peak at 1624.06 cm^{-1}, it is agood evidence to form the product. For the IR spectrum of compound 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(3-hydroxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione (10), which is shown in **Figure 2**, there is a broad band at 1685.79 cm^{-1} related to (O=C-O and O=C-N vibration coupling). In case of the IR spectrum of compound 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(4-methoxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione (11) **Figure 3**, the broad band located at 1683.86 cm^{-1}, which related to (O=C-O and O=C-N vibration coupling), that is regarded as proof of the desired product's formation.

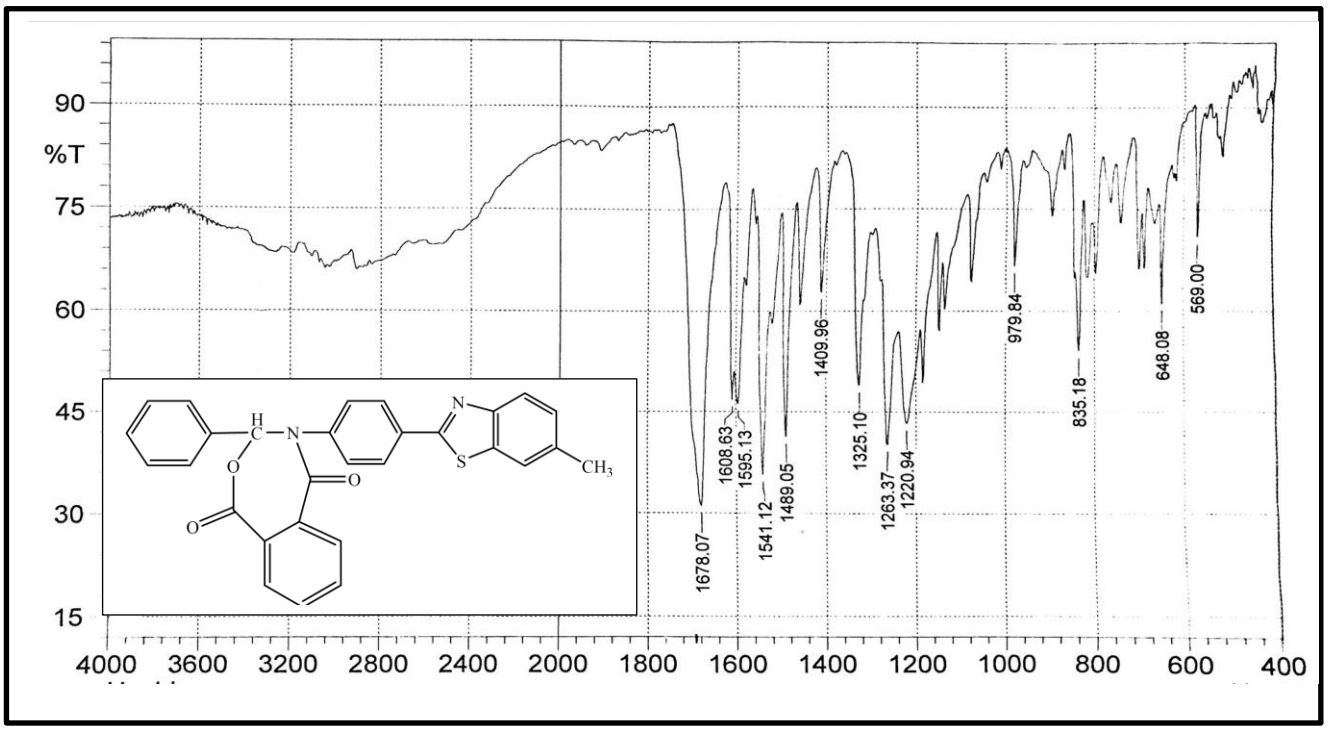
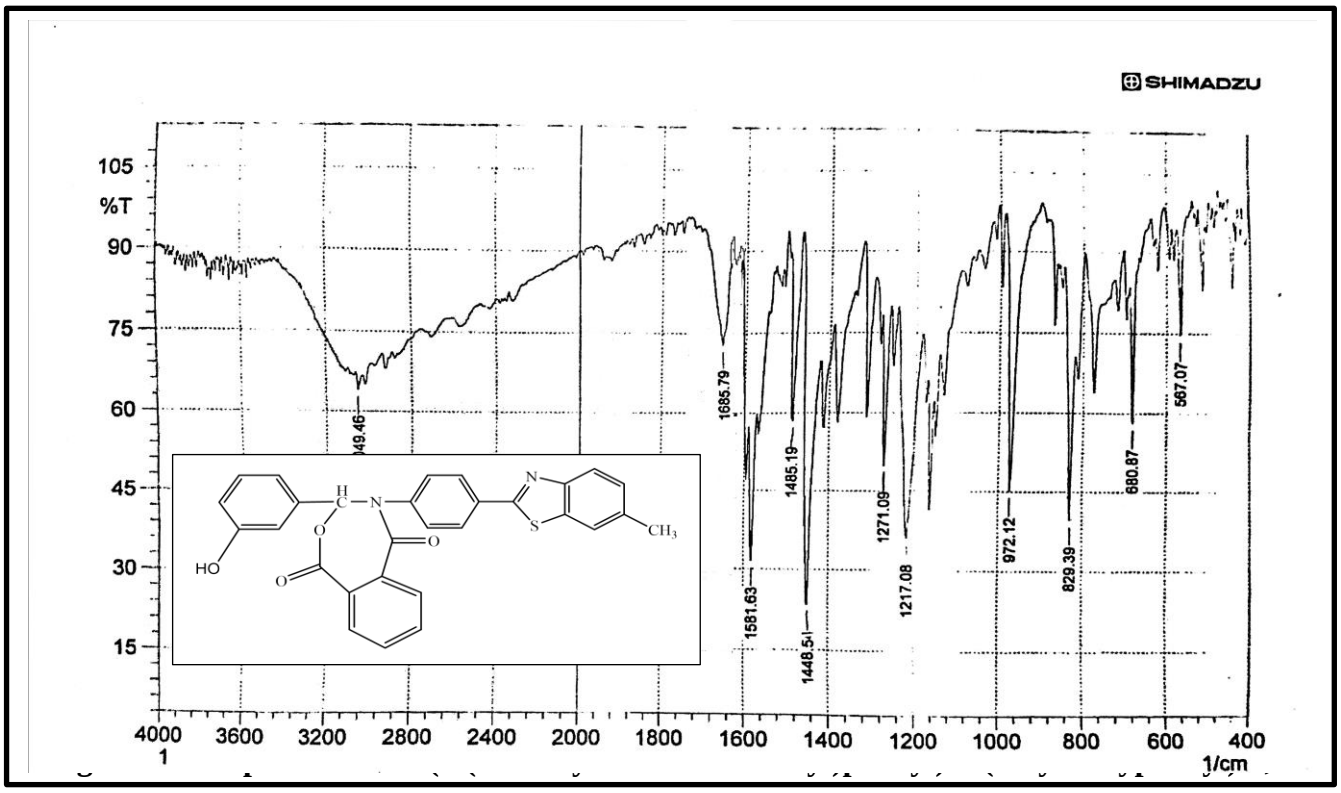


Figure 1: IR Spectrum of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-phenyl-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione



dihydrobenzo[1,3]oxazepine-1,5-dione

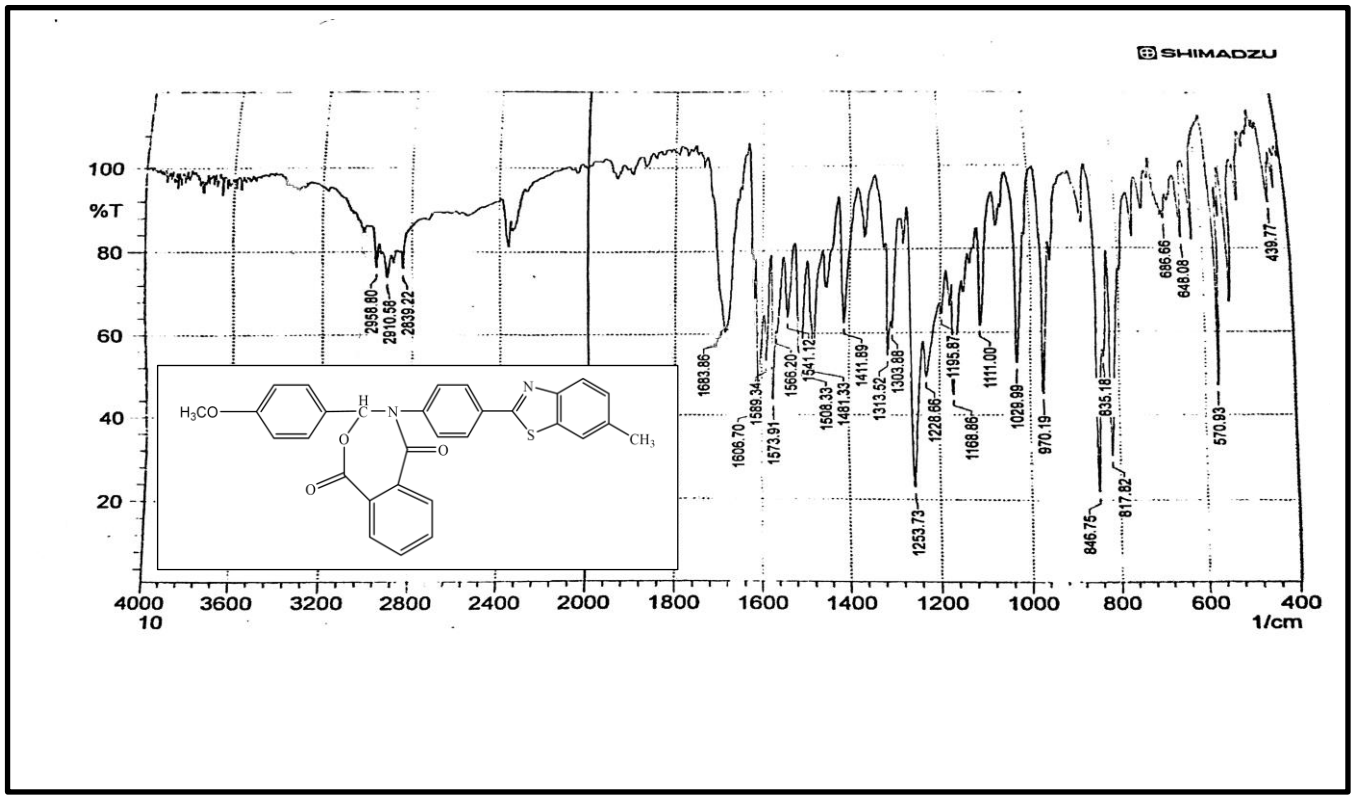


Figure 3: IR Spectrum of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(4-methoxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione

3.2 ^{1}H-NMR study

The functional groups of samples were investigated via the ^{1}H-NMR technique of a single signal at 2.24 ppm of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-phenyl-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione (8) (Azeez and Qadir, 2017; Abdulameer, et al., 2019) corresponds to the three protons of the (CH_3) group, multiple signals at (6.48-7.85) ppm connected to (16 H, aromatic rings), and another singlet signal at δ 9.95 ppm connected to one proton of (CH) oxazepine. The ^{1}H-NMR data of compound 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(3-hydroxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione (10), show a singlet signal at 2.21 ppm associated with the three protons of the (CH_3) group, and multiple signals at (6.48-7.84) ppm connected to (15 H, aromatic rings), and two another singlet signals at δ (8.95 and 9.66) ppm related to two protons of (OH) group and (CH) oxazepine ring respectively. ^{1}H-NMR data of compound 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(4-methoxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione (11) show a singlet signal at 2.04 ppm associated with the three protons of the (CH_3) group, and a singlet signal at 3.45 ppm associated with the (OCH_3) group, multiple signals at (6.30-7.68) ppm connected to (15 H, aromatic rings), and another singlet signal at δ 9.44 ppm related to one proton of (CH) oxazepine ring, that is measured as evidence for the formation of the desired product, also disappearance a strong singlet signal at the range (8.45-8.55) of (CH=N) Schiff base group. Were showen in **Figures (4-6).**

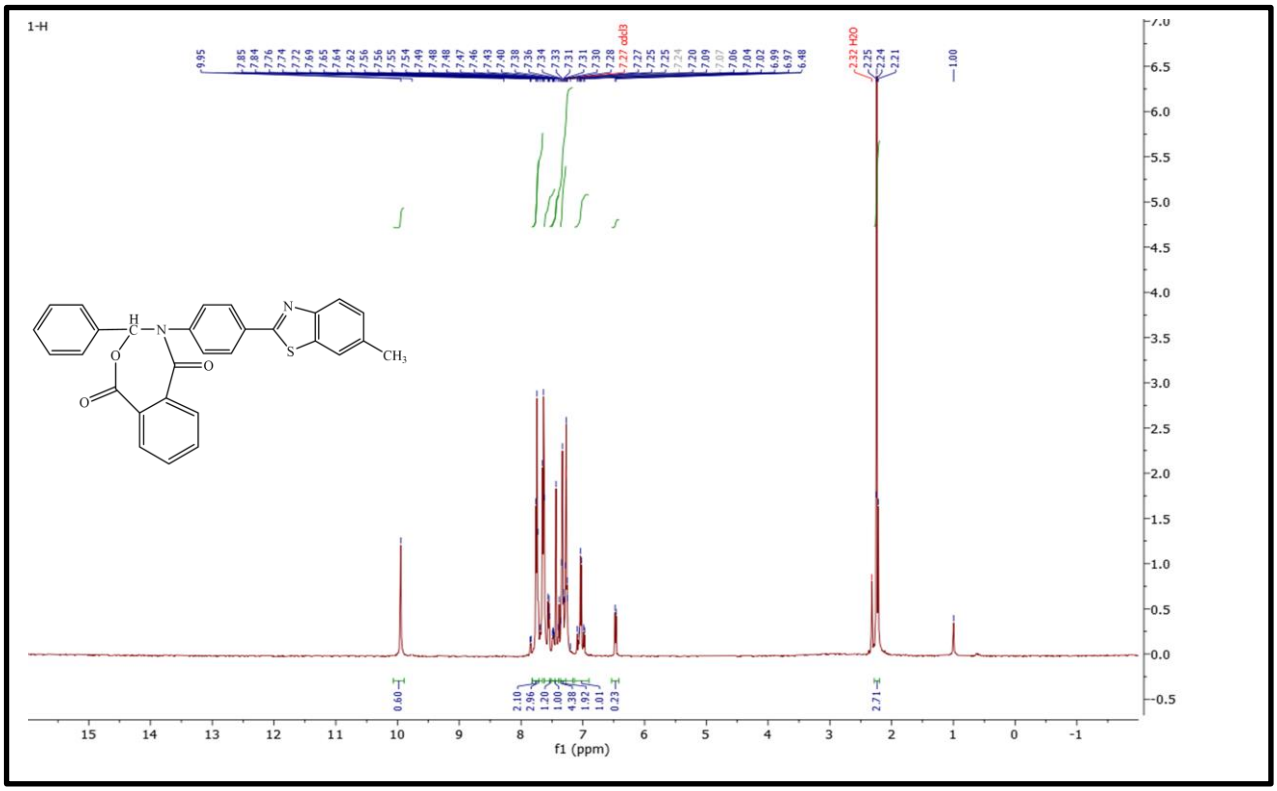


Figure 4: ^{1}H-NMR spectrum of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-phenyl-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione

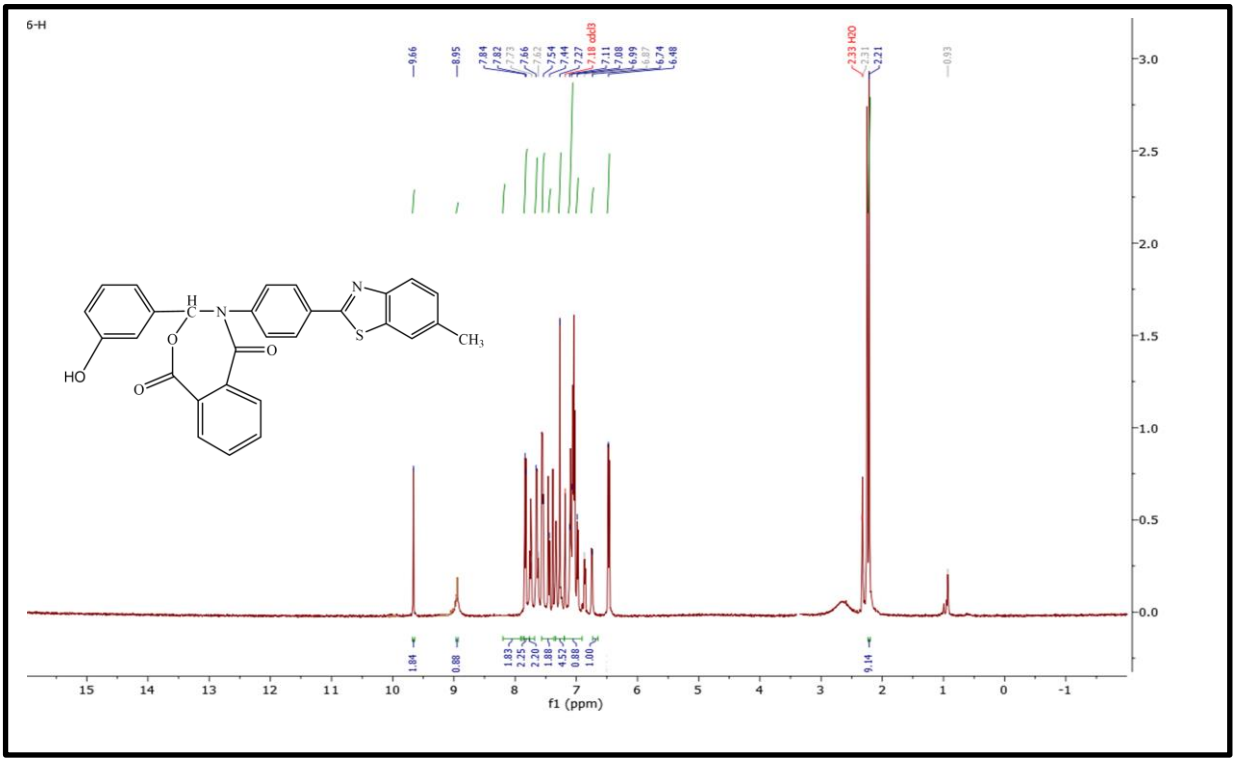


Figure 5: ^{1}H-NMR spectrum of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(3-hydroxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione

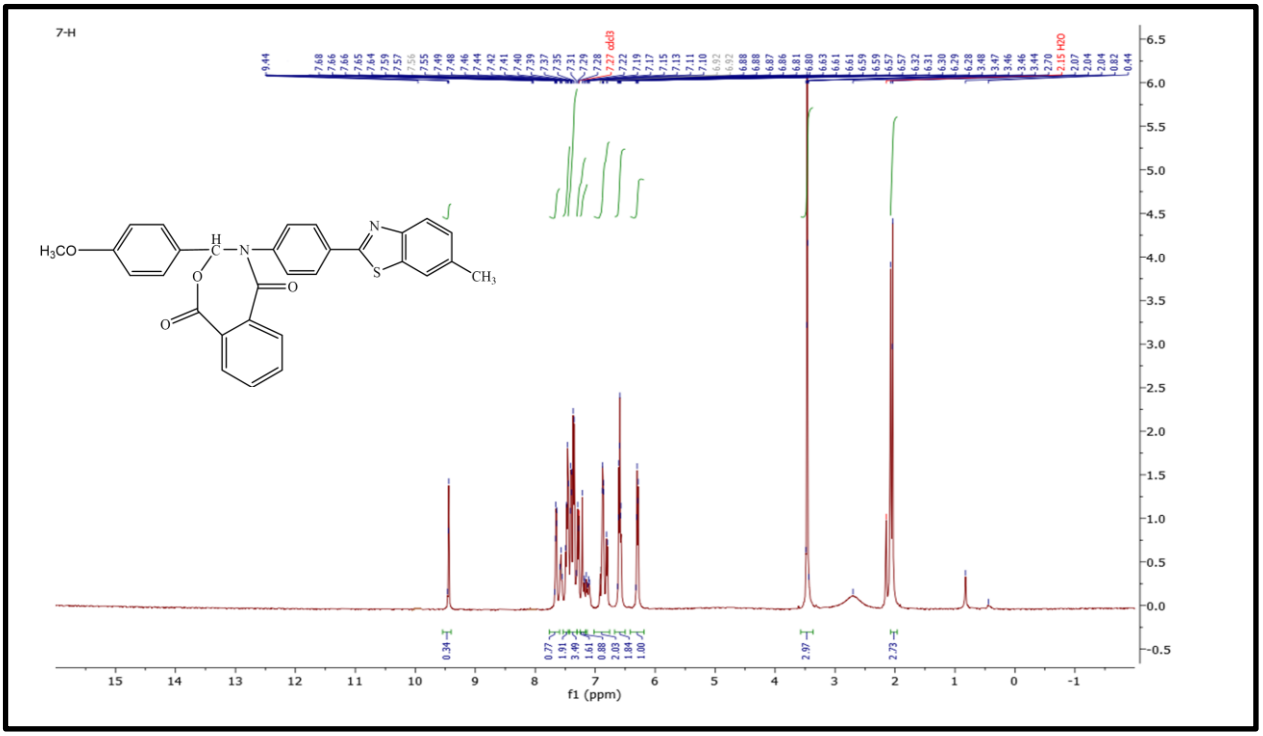


Figure 6: ^{1}H-NMR spectrum of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(4-methoxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione.

3.3 ^{13}C-NMR study

In this research, ^{13}C-NMR spectroscopy was employed to further study the functional groups of synthesized samples, as shown in **Figures 7-9** . In case of compound 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-phenyl-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione (8) **in Figure 7** (Azeez and Qadir, 2017; Dawood, et al., 2019), the CH_3 group appears at 21.33 ppm and at 114.28 having a relationship to C_{13} (CH) in the oxazepine ring, display seventeen lines for seventeen types of carbon in different chemical shifts as follows: $C_{4,7}$ (119.87); C_{21} (121.07); $C_{11,11'}$ (121.19); C_3 (121.55); $C_{15,15',9}$ (122.13); $C_{16,16'}$ (127.36); $C_{10,10',24}$ (127.69); C_{17} (128.42); C_{20} (128.63); C_{25} (129.23); C_{23} (129.92); C_{22} (131.50); C_2 (134.77); C_6 (134.91); C_{12} (138.83); C_{14} (141.86); C_5 (152.04). Two peaks at (166.41 and 167.76) ppm for (N-C=O and O-C=O) respectively, also at 168.19 related to C_8 of thiazole ring. From ^{13}C-NMR spectrum of compound 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(3-hydroxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione (10), **Figure 8**, that have the CH_3 group appear at 21.35 ppm and at 114.27 having a relationship to C_{13} (CH) in the oxazepine ring, exhibit nineteen lines for nineteen types of carbon in different chemical shifts as follows: $C_{15'}$ (114.93); C_{17} (115.12); C_{15} (119.22); $C_{4,7}$ (120.43); $C_{11,11'}$ (121.07); C_{21} (121.23); $C_{3,9}$ (121.34); C_{24} (121.55); $C_{10,10'}$ (121.95); C_{16} (122.28); C_{20} (127.35); $C_{23.25}$ (127.69); C_{22} (127.77); C_2 (128.12); C_6 (128.62); C_{12} (129.62); C_{14} (129.83); C_5 (134.15); C_{16}-OH (154.08). Two peaks at (158.22 and 162.18) ppm for (N-C=O and O-C=O) respectively, also at 166.14 related to C_8 of thiazole ring. The ^{13}C-NMR results benefit in the formation of the synthesized [1, 3]-oxazepine of compound 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(4-methoxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione (11) are shown in **Figure 9**, herein, the C_1 of (CH_3) group appears at 21.11 ppm, at 55.31 quality to the C_{18} (OCH_3) group and at 113.96 connected to C_{13} (CH) in the oxazepine ring, also the appearance of nineteen lines of nineteen carbon types in various chemical shifts, as shown: $C_{16,16'}$ (119.67); C_7 (120.95); C_4 (121.14); $C_{11,11'}$ (121.25); C_{21} (121.32); $C_{3,9}$ (121.88); C_{24} (121.98); $C_{15,15'}$ (122.09); $C_{10,10'}$ (127.21); C_{20} (127.50); C_{25} (127.64); C_{23} (127.95); C_{14} (128.43); C_{22} (130.43); C_2 (131.56); C_6 (133.91); C_{12} (134.92); C_5 (150.50); C_{17} (154.12). And appears

two peaks at (160.01 and 162.18) ppm for (N-C=O and O-C=O) respectively, also at 167.22 related to C_8 of thiazole ring. In NMR study used the solvents $CHCl_3$ and DMSO to dissolve them

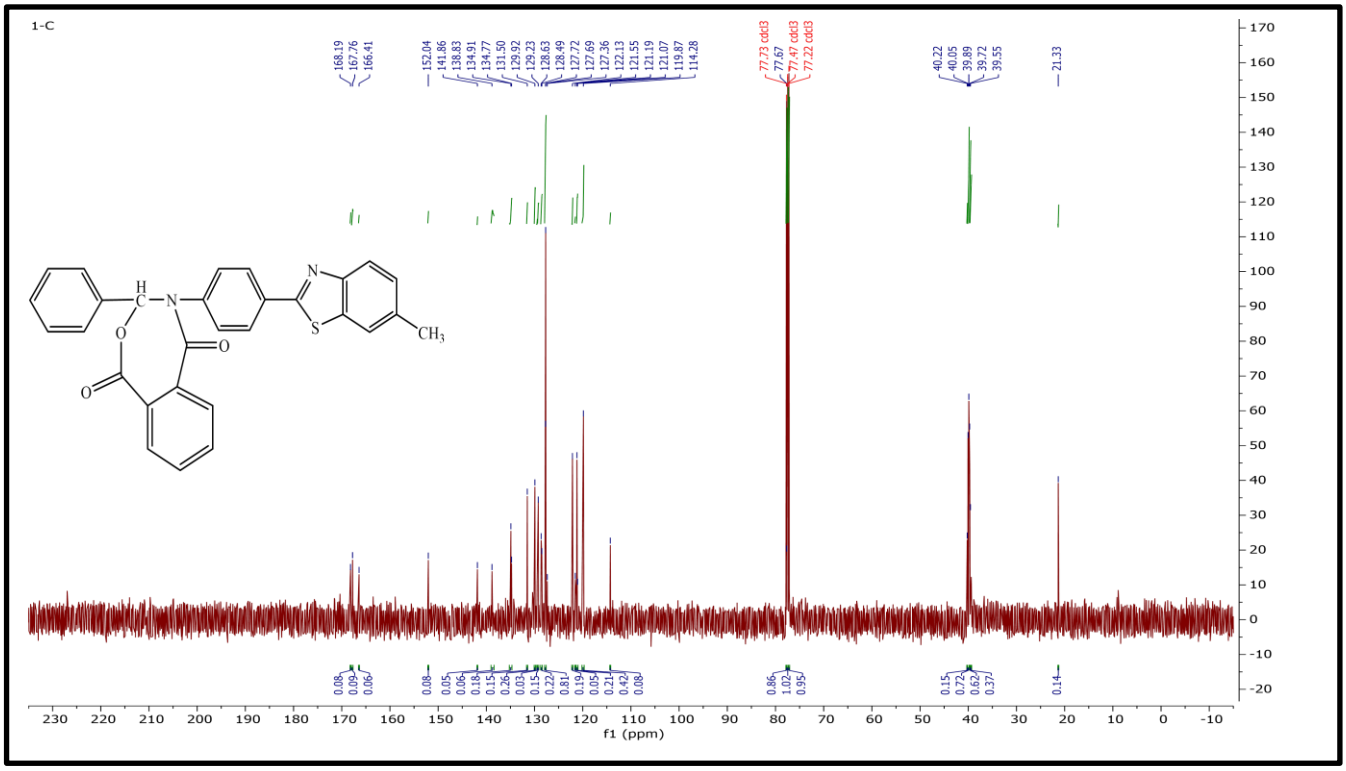


Figure 7: ^{13}C-NMR spectrum of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-phenyl-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione

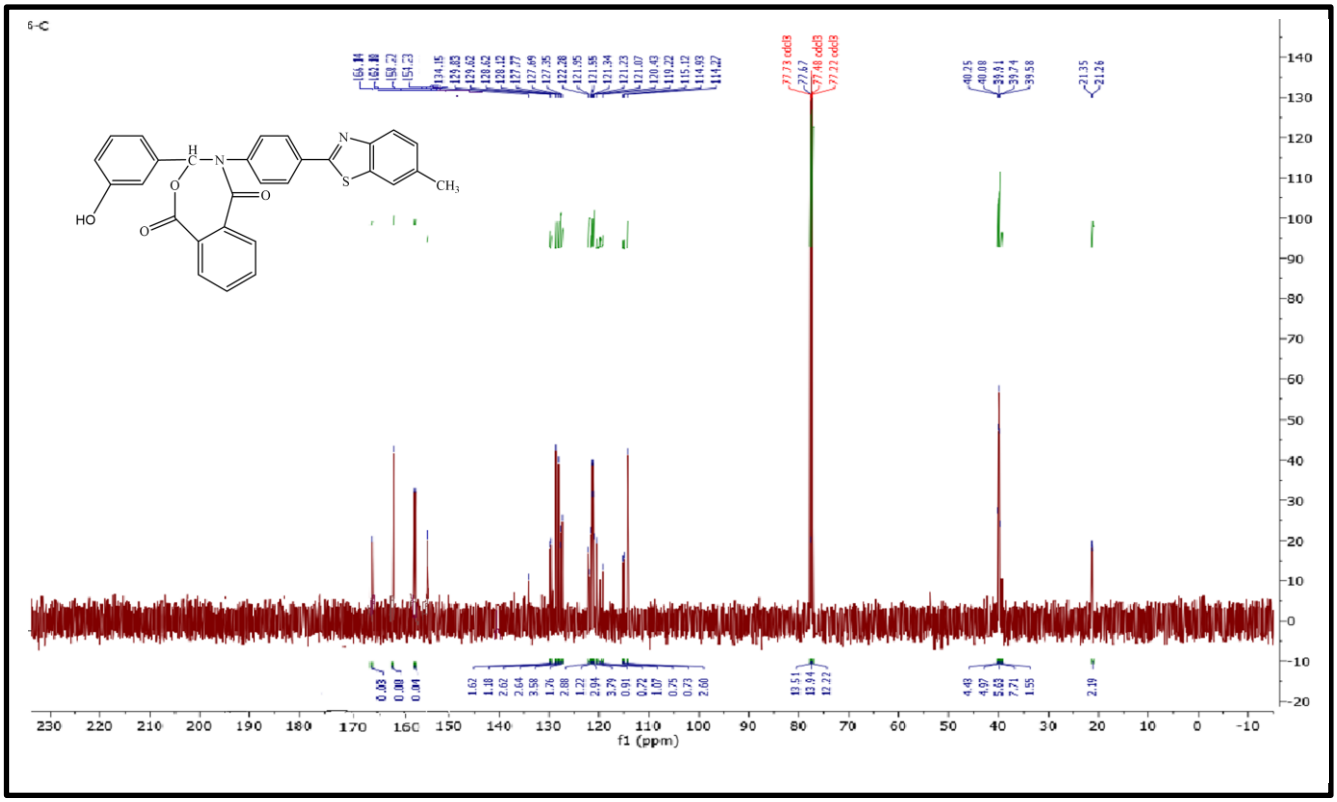


Figure 8: ^{13}C-NMR spectrum of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(3-hydroxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione

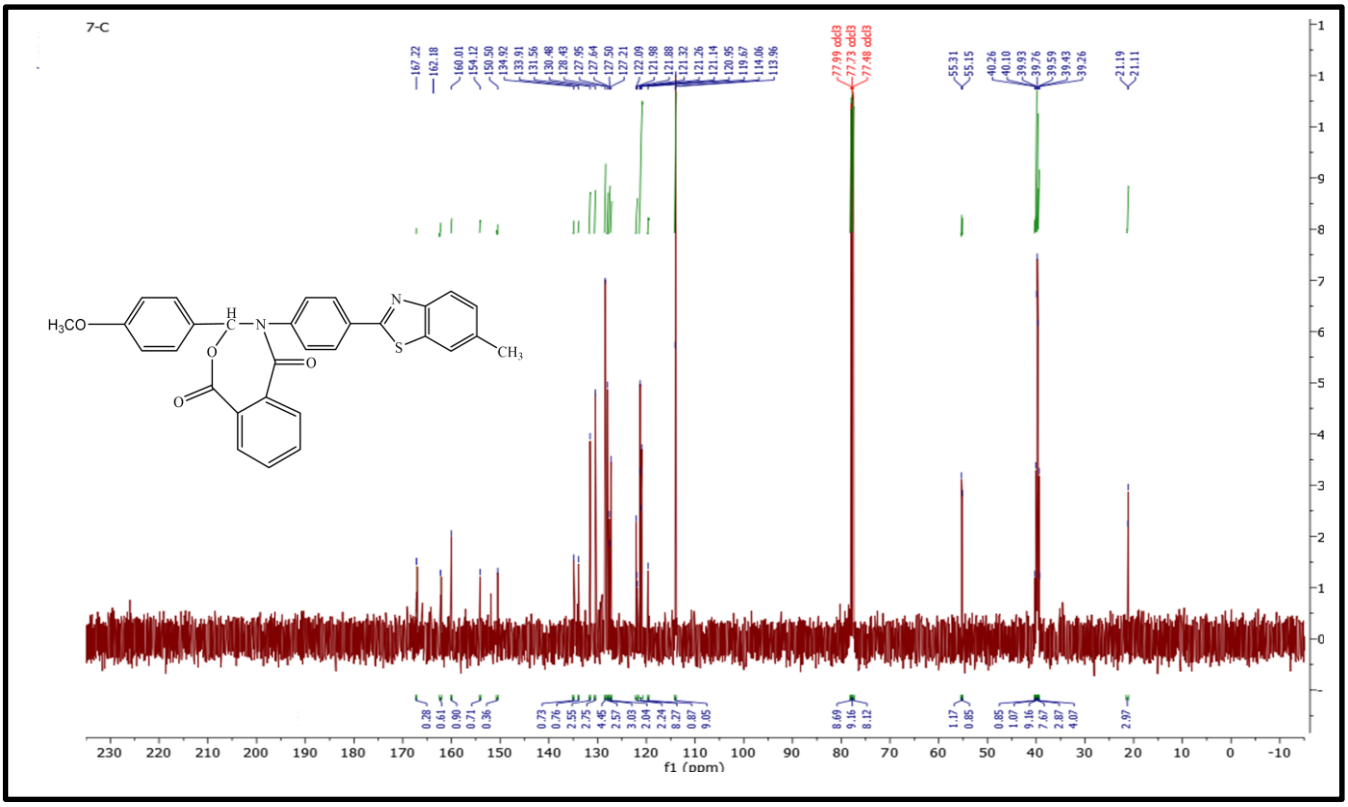


Figure 9: ^{13}C-NMR spectrum of 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(4-methoxyphenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione

3.4 Biological activity study

The screening of the synthesized 4-(4-(6-methylbenzothiazol-2-yl)phenyl)-3-(substituted phenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione compounds for their antibacterial activity against two strains of bacteria was studied. The synthesized compounds were screened for their antibacterial activity against two types of bacteria ***Staphylococcus aureus Gram (+ve)*** and ***Escherichia* coli *Gram (-ve)***, as showen in **Figures (10 and 11).** During this study, it was cleared that the prepared compounds have antibacterial activity and their results were mentioned in (+) assignment **Table 3**

Table 3: Results of the antibacterial activity for (8-14) products

Compounds	Microorganism	
	Staphylococcus aurous +ve	***Escherichia coli –ve***
8	+ + +	+ + +
9	+ +	+ +
10	+ +	+
11	+ + +	+ +
12	+	+
13	+	+
14	+ +	+

According to the reported procedure (Adnan and Ghafli, 2021) good active + + + (inhibition zone ≥ 20 mm); moderately + + (inhibition zone 11-20 mm); slightly active + (inhibition zone 5-10 mm) and inactive – less than (5 mm).

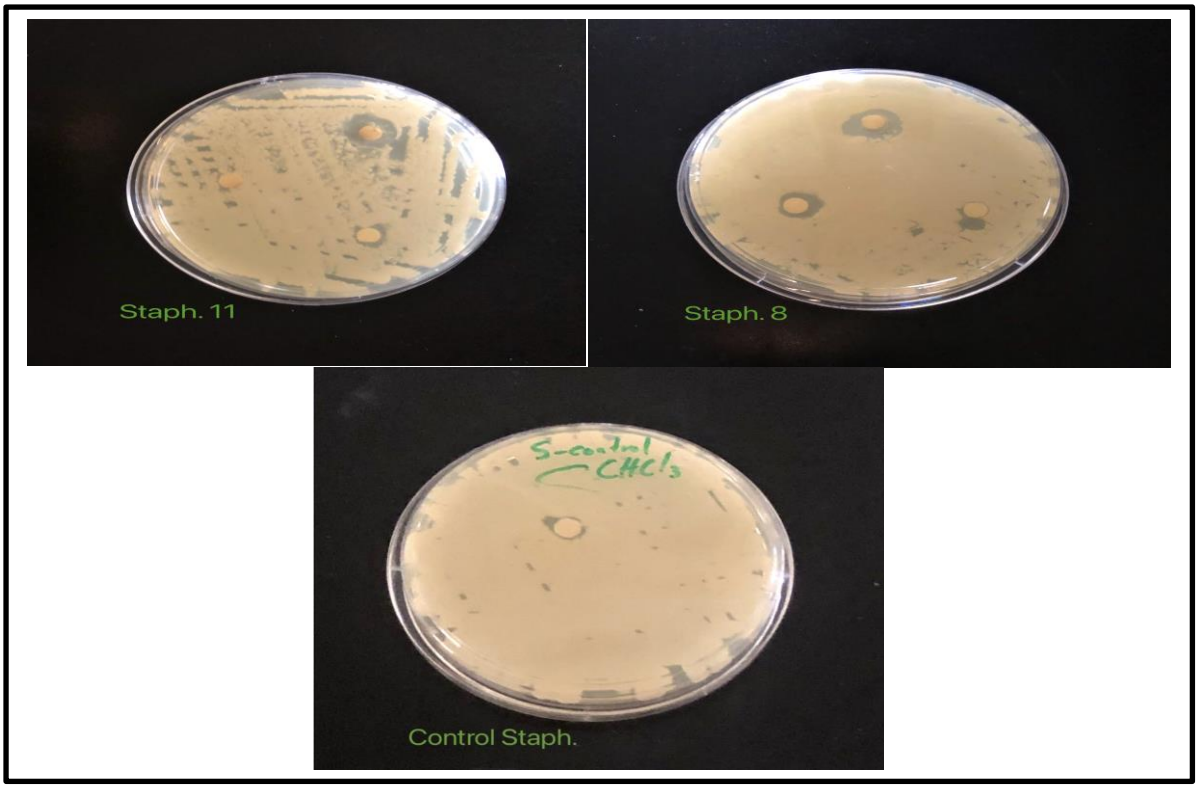


Figure 10: Anti-bacterial activities of the synthesized products against *Staphylococcus-aureus Gram (+ve)*

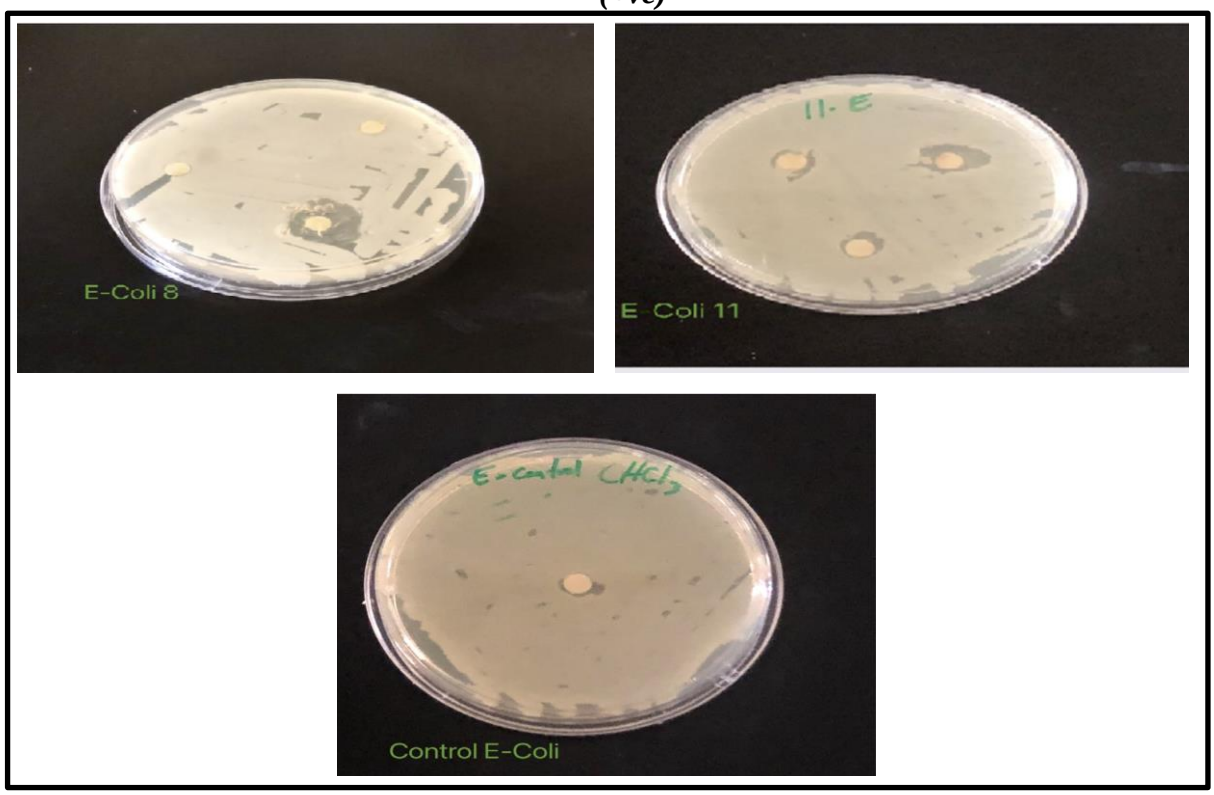


Figure 11: Anti-bacterial activities of the synthesized products against *Escherichia coli Gram (-ve)*

4- CONCLUSION

This work deduced that an easy and simple procedure for the synthesis of Schiff base from 4-(6-Methylbenzothiazol-2-yl)aniline in absolute ethanol with substituted aromatic aldehyde by using some drops of glacial acetic acid was

performed. The Schiff base reacted with phthalic anhydride in dry benzene to yield the desired product of [1, 3]-oxazepine derivatives. The materials were structurally characterized via melting point, FTIR and NMR techniques. The products can be obtained in high purity and a good yield from the reaction mixture. The screening results showed that all the products of (8-14) exhibt significant antibacterial activities against ***Staphylococcus aureus as Gram (+ve) and Escherichia coli as Gram (–ve).***

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