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Synthesis and Characterization of Some New Oxazepines from Triazoles Amines Derivatives

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ABSTRACT

In this work, four new Schiff bases and their derivatives (Oxazepine) were synthesized in two steps. The fiarst step was prepared a new Schiff bases from the reaction of heterocyclic and aromatic aldehyde and amines. The second step included the reaction of prepared Schiff bases derivatives with malic anhydride using few drops of glacial acetic acid as a catalyst to obtain derivatives of seven-membered heterocyclic rings. The newly synthesized compounds 1,3- oxazepine derivatives (a_1-a_4) were prepared by malic anhydride with new imines (S1-S4).by using microwave at 50W for (2–3 hours).The new derivatives were confirmed by demanding a variety of experimental techniques including ^{1}HNMR and IR

Keywords: *1,3-Oxazepine; Microwave; Schiff bases; Maleic anhydride; Heterocyclic compounds*

1. INTRODUCTION

Recently, the synthesis of heterocyclic organic compounds with a seven-membered ring is an important class and has diverse applications in medicinal chemistry[1]. Furthermore, heterocyclic compounds can also be classified into different groups based on their different structural variations [2]. Various heterocyclic compounds have been synthesized in Dimensions using Schiff's rule interactions with different Re Agents such as oxazepines [3]. Shiff bases are synthetically accessible and structurally diverse compounds, usually prepared from condensation reactions of primary amines with an aliphatic or aromatic aldehyde or ketone[4,5]. These are commonly used for industrial purposes and also exhibit a wide range of biological activities. These are the most widely used organic compounds[6]. Schiff's bases have emerged as promising antibacterial agents. For example, Mycobacterium can be effectively treated with N- (salicylidene) -2- hydroxyaniline[7]. Schiff bases contain an azomethine bond (–C=N–) that can assemble two or more biologically active aromatic/heterocyclic scaffolds to form various molecular hybrids with interesting biological properties[8]. 1,3- oxazepine derivatives can be prepared by added maleic or phthalic anhydride to the double bond (C=N) of Schiff bases[9]. Oxazepines are heterocyclic Unsaturated compounds containing two heteroatoms Oxygen and nitrogen. Generally, heterocyclic contain nitrogen atoms in the structures of most compounds of medical importance for pharmacological activities ranging from antibacterial to anticancer [10,11]. The development of resistance of microorganisms to most existing antimicrobial drugs constitutes a global health problem. To overcome this problem, there is an increasing need to synthesize new antimicrobials [12]. 1,3-oxazepine has various therapeutic applications and many members of this family are widely used as sedatives, antidepressants, and hypnotic agents as well as anticonvulsants, anti-anxiolytics, analgesics [13,16]. This study's main objective is to design new drugs with lower toxicity and cost and a significant activity profile.

2. EXPERIMENTAL

2.1 General: Equipment, chemical materials and applied techniques

The chemicals (3-Amino- 1,2,4- triazol (99%); 4-Imidazole carboxaldehyde(99%); p-methoxy aniline(98%); p-toluidine(99%); 4-chloroaniline(99%); and 4-bromobenzaldehyde(99%); were purchased from companies Hyperchem, and Sigma Aldrich. Panasonic Company purchased the Microwave Oven power supply: 220-240V~ 50Hz used in the experiments. (TLC) was purchased from Merk. TLC spots were visualized using iodine. Fourier transform infrared spectroscopy (FTIR) spectra for the synthesized compounds were recorded on a KBr disk in the

region (600–4000) cm-1 using "Perkin Elmer, tensor 27 (Bruker)" at the University Thi-Qar, Science College, Labs. from the chemistry department. Proton Nuclear Magnetic Spectra The 1HNMR spectra were recorded on Bruker by the college of Education for Pure Sciences at Basra University.

2.2 The Procedure for Preparation of Schiff base (S1-S4).

The preparation of imines (S1-S4) included, a mixture of an appropriate amine (0.001 mol) and aldehyde (0.001 mol), in 25 mL of absolute ethanol observed and (7-10) drops of accompanying with glacial acetic acid as catalyst. The reaction was heated by reflux for (4-10) hours with stirring under dry conditions. The evolution of the reaction was followed by TLC. Then, the ethanol was evaporated under vacuum. Finally, the solid compound was purified repeatedly by using absolute ethanol and suitable solvent to obtain a pure product (S1-S4) [14,5].

2.3 Characterization of Schiff Bases (S_1-S_4).

(Z)-5-(((1H-1,2,4-triazol-3-yl)imino)methyl)-2-methoxyphenol

(S1). Orange solid, yield (80%); IR ,ν 3620 (O-H), ν 3460 (N-H)Str. , ν 3079 (C-H aromatic), ν 2983,2873(C-H alphatic)symmetric asymmetric,1675 (ν C=N) imine, ν1581 (C=C aromatic), ν 1484 (N-H) Bending, ν1284-1182 (C-O-C) cm–1. Shown in figure (1)

6,6̃-((E,1'E)-((1,4phenylenebis(azanylylidene))bis(methanylylidene))bis(2-methoxyphenol)

(S2). Red, yield (75%); IR ν 3412 and 3333 (O-H), ν 3115-3106 (C-H Aromatic), ν2955-2914 (C-H alphatic),1595-1523(ν C=N) imine, ν 1467-1439 (C=C Aromatic), ν1212 (C-O-C) cm–1. Shown in figure (2).

(E)-N-(4-chlorophenyl)-1-(1H-imidazol-4-yl)methanimine

(S3). Yellow, yield (85%); IR ν 3397 (N-H)Str., ν 3144 (C-H Aromatic), ν 3053 (=C-H) diazol, ν 2984,2819 (C-H alphatic) symmetric asymmetric, 1630 (ν C=N) imine, ν 1581 (N-H) Bending, ν-1550-1530 (C=C Aromatic), ν 620 (C-Cl) cm–1. Shown in figure (3)

(E)-1-(4-bromophenyl)-N-(1H-1,2,4-triazol-3-yl)ethan-1-imine

(S4). Off White, yield (70%); IR ν 3494 (N-H)Str., ν3137 (C-H Aromatic), ν 3087 (=C-H) trezol, ν 2995,2832 (C-H alphatic)symmetric asymmetric, ν1685 (C=N) imine, ν 1617 (N-H) Bending, ν1577-1477 (C=C Aromatic), ν 820 (C-Br) cm–1. Shown in figure (4)

2.4 General Procedure for Preparation oxazepine compounds (a_1-a_4)

A mixture Schiff base (S1-S4) (0.001 mol), maleic anhydride (0.001 mol), and 7 drops of glacial acetic acid in DMF (15 mL) were subjected to microwave at 50W for (2–3 hours). The progress of the reaction was followed by TLC. After completion of the reaction, the solvent has been evaporated and the product was recrystallized in a suitable solvent to obtain a pure product[15]. The physical data of 1,3-oxazepines (a1-a4) are given in Table(2).

2. 5 Characterization of oxazepines (a1-a4).

2-(2-hydroxy-3-methoxyphenyl)-3-(1H-1,2,4-triazol-3-yl)-2,3-dihydro-2l3-1,3-oxazepine-4,7dione

(a1) (C14H12O5N4). Light nutty, yield (65%);IR (ATR) ,ν 3498 (O-H), ν 3389 (N-H)Str. , ν 3151 (C-H Aromatic), ν 3095 (=C-H) Oxazepine, ν 2974,2856 (C-H alphatic) symmetric asymmetric , ν 1792 (C=O lactone), ν1744 (C=O lactam), ν 1611 (C=N) triazol, ν 1525 (C=C Oxazepine), ν 1492 and1466 (C=C Aromatic), ν1254(C-O-C)cm–1. ^{1}H-NMR (DMSO-d6, 500 MHz): δ=(s, 3.84, 3H, OCH3)ppm, δ =9.43 ppm (s, 1H, NH), δ =14.59 ppm (s, 1H, OH), , δ =8.77 ppm (s, 1H, O-CH-N ppm, oxazpine ring), , δ = (6.94-7.19) ppm, (*d*,2H, J= 8.0MHz, CH=CH olefin protons), (7.37-8.02) ppm (m,4H, Ar-Aromatic).

2-(2-hydroxy-3-methoxyphenyl)-3-(4-(2-(2-hydroxy-3-methoxyphenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2H)-yl)phenyl)-2,3-dihydro-2l3-1,3-oxazepine-4,7-dione

(a2). Red, yield (75%); IR (ATR) ν 3497 (O-H), ν 3360 (N-H)Str. , ν 3151 (C-H Aromatic), ν 3095 (=C-H) Oxazepine, ν 2974,2856 (C-H alphatic) symmetric asymmetric , ν 1792 (C=O lactone), ν1744 (C=O lactam), ν 1611 (C=N) triazol, ν 1525 (C=C Oxazepine), ν 1492-1466 (C=C Aromatic), ν1254-1184(C-O-C) cm–1. **^{1}H-NMR (DMSO**-d6, 500 MHz): δ = 3.81 ppm, (s, 6H, OCH3), δ =9.00 ppm (s, 1H, NH), 13.07 ppm (s, 2H, OH), (7.53-7.96) ppm (d,4H, J = 24MHz, CH=CH olefin protons).

2,3-(4-chlorophenyl)-2-(4,5-dihydro-1H-imidazol-4-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione

(a3).(C14H12ClN3O3) Yellow, yield (85%); IR (ATR) , ν 3398 (N-H)Str. , ν 3063 (=C-H Aromatic), ν 3034 (=C-H) Oxazepine, ν 2979,2878 (C-H alphatic) symmetric asymmetric, ν 1789 (C=O lactone), ν1767-1714 (C=O lactam), ν1611 (C=N) triazol, ν1581(C=C Oxazepine), ν 1496-1466 (C=C Aromatic), ν 1222-1121(C-O-C), ν 790 (C-CI) cm–1: 1HNMR (DMSO-d6, 500 MHz): δ =8.71 ppm (s, 1H, NH), 7.93 ppm (s, 1H, O-CH-N, Oxazpine ring), (7.41-7.51) ppm (d,2H, J =

8.0 ppm MHz, CH=CH olefin protons), (7.61-8.00) ppm (d,4H, J =4.0 MHz , Ar-Aromatic), (6.62-7.38) ppm (m,4H, Ar-Aromatic).

2-(4-bromophenyl)-3-(1H-1,2,4-triazol-3-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione

(a4).(C13H9BrN4O3) Off White, yield (70%);IR (ATR) ν 3493 (N-H)Str. , ν 3095 (=C-H Aromatic), ν 2979,2878 (C-H alphatic) symmetric asymmetric , ν 1792 (C=O lactone), ν1770-1744 (C=O lactam), ν 1610 (C=N) trezol, ν 1526 (C=C Oxazepine), ν 1492-1466 (C=C aromatic), ν 1232-1184(C-O-C), ν 718 (C-Br) cm–1. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ =14.51 ppm (s, 1H, NH), 8.75 ppm (s, 1H, O-CH-N, oxazpine ring), (7.93-7.96) ppm (d,2H, J = 4MHz, CH=CH olefin protons); (8.00-8.02) ppm (d,4H, J = 4.0 MHz , Ar-Aromatic), δ =7.96 ppm (s, 1H, CH=N) ;

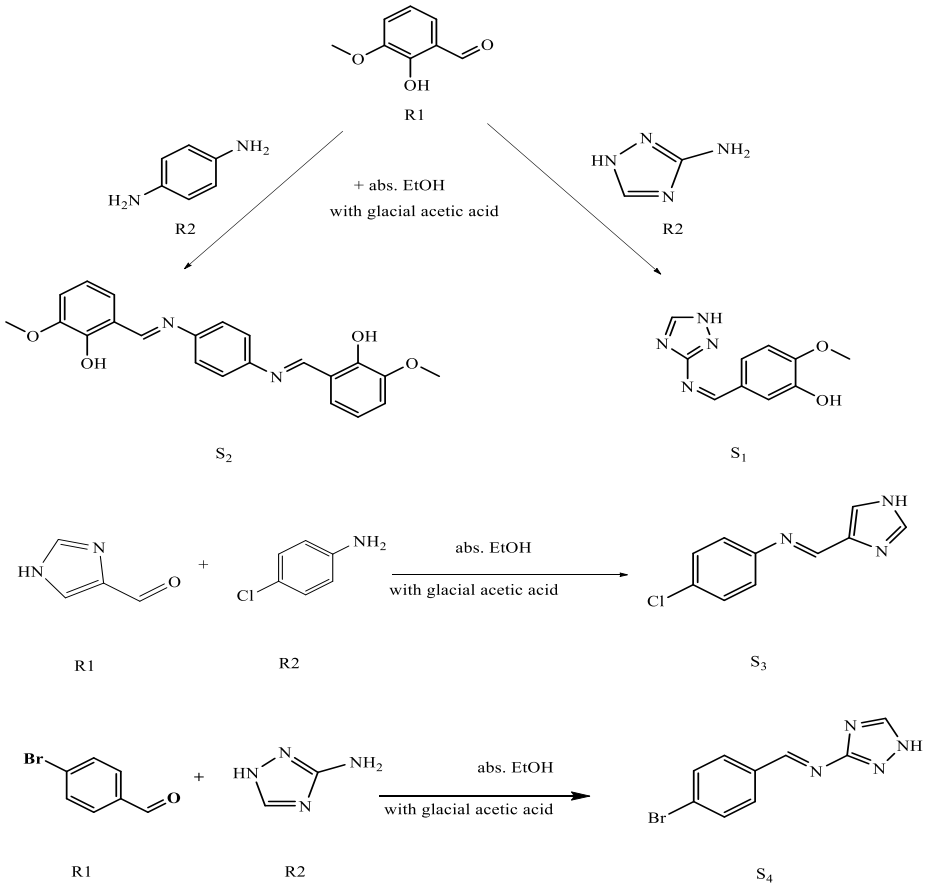
3. RESULTS AND DISCUSSION

Several 1,3-oxazepine derivatives were synthesized. All the prepared compounds were purified by recrystallization from an appropriate solvent. The synthesized compounds were identified via their physical properties and some spectral analyses such as FT-IR and ^{1}H-NMR spectrum. For ^{1}H-NMR, dimethyl sulfoxide (DMSO-d_6) was used as a solvent.

3.1: Preparation of Schiff base (S1-S4).

Different new imines (S1-S4) were prepared by reaction of heterocyclic and aromatic aldehyde and amines in absolute ethanol with 5 drops of glacial acetic acid are shown in Scheme 1

No.	R1	R2
S_1	2-Hydroxy-3-methoxy Benzaldehyde	3-Amino-1,2,4-triazole
S_2	2-Hydroxy-3-methoxy Benzaldehyde	1,4-phenylene diamine
S_3	4-Imidazole carboxaldehyde	p-chloroaniline
S_4	p-Bromobenzaldehyde	3-Amino-1,2,4-triazole



Scheme 1. Synthesis of Preparation of Schiff base (S1-S4).

3.2: IR spectra of Schiff base (S1-S4)

The IR spectra of the Schiff base (S1-S4) appear in the figures below. The IR spectra of the imine are characterized by multiple bands corresponding to the stretching vibrations of the aromatic (C-H), aliphatic (C-H), azomethine (C=N), aromatic (C=C) and (C-N) bands. These bands are in the cm-1 range as shown in Table (3-1)

The FT-IR spectra of Schiff's bases compounds (S1-S4) showed the absence of peak of carbonyl but a new peak was appeared at (1595-1685) cm^{-1} which is assigned to a new imines (C=N) group [16].

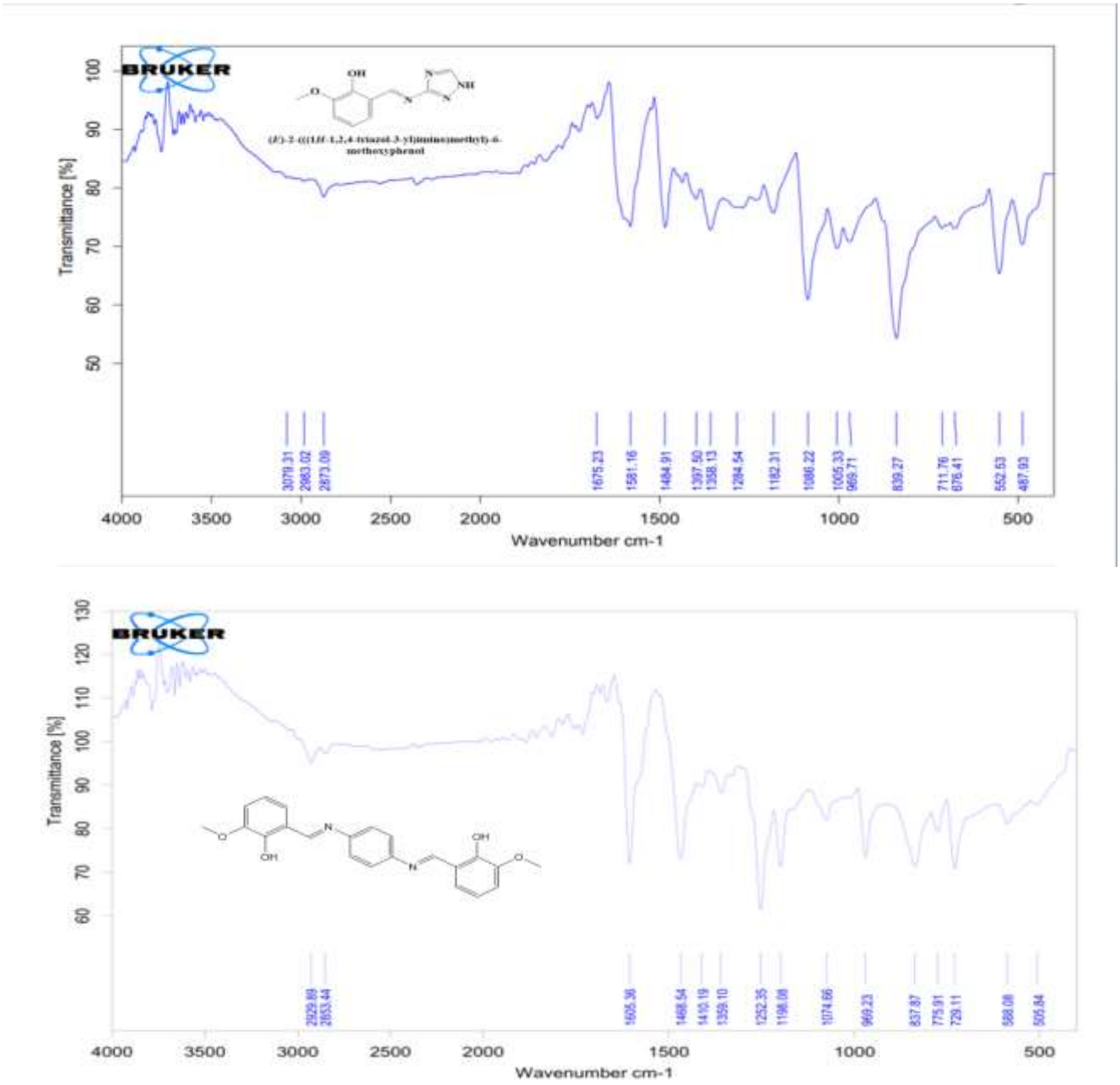


Fig (1): IR spectrum of the compound (S1)

Fig (2): IR spectrum of the compound (S2)

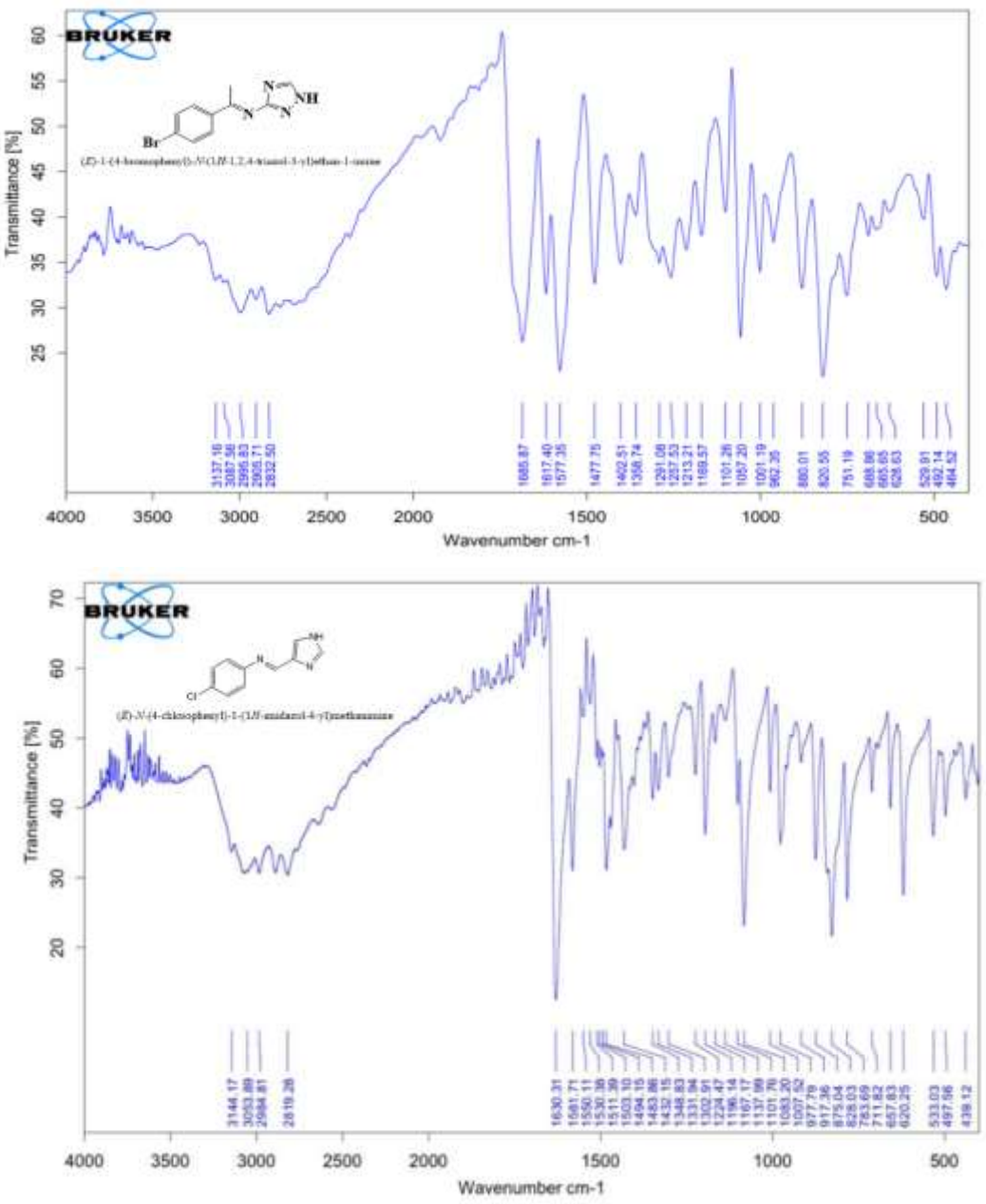
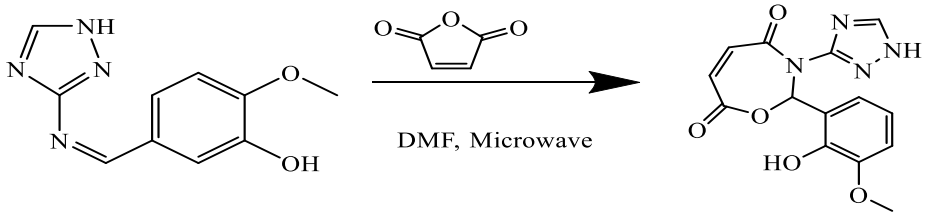


Fig (3): IR spectrum of the compound (S_3)

Fig (4): IR spectrum of the compound (S4)

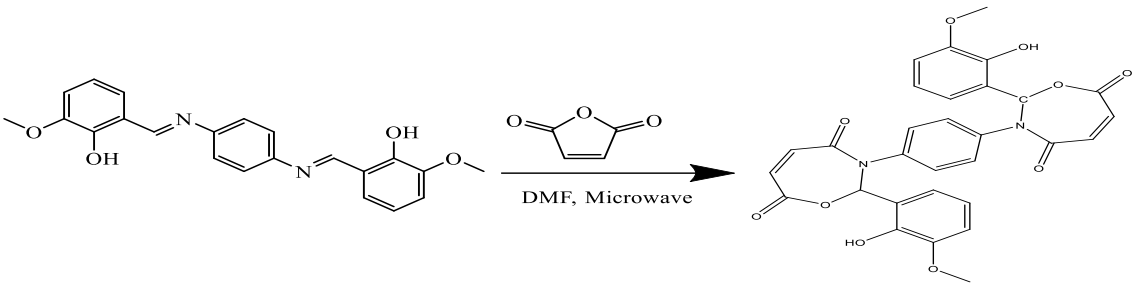
:Preparation of 1,3- Oxazepine derivatives (a1-a5)3 .3

1-3 Oxazepine derivatives (a1-a5) were prepared by the reaction Schiff- base with maleic anhydride and phthalic anhydride in DMF in the presence of some drops of glacial acetic acid in the microwave as shown in the Scheme (3-3).



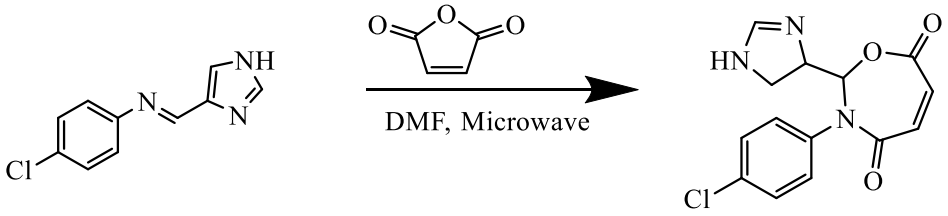
S_1 a_1

Scheme 2. synthesis of 1,3- oxazepine compounds 5



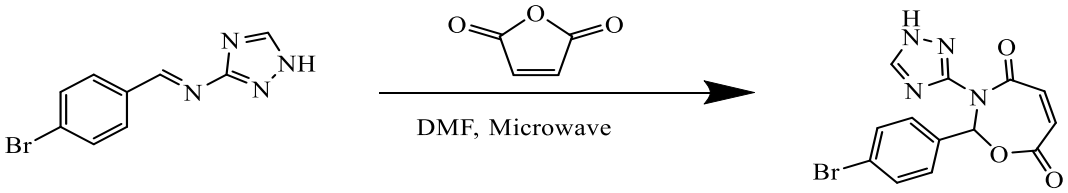
S_2 a_2

Scheme 3. Synthesis of 1,3- oxazepine compounds 6



S_3 a_3

Scheme 4. Synthesis of 1,3- oxazepine compounds 7



S_4 a_4

Scheme 5. Synthesis of 1,3- oxazepine compounds 8.

1,3- Oxazepines derivatives (a1- a4) are synthesized from the reaction of Schiff bases (S1-S4) with maleic anhydride were dissolved in DMF (15ml) with 5 drops of glacial acetic acid were subjected to Microwave at 50W for 2-3 hours. The FT-IR spectra of 1,3- Oxazepines derivatives compounds (a1-a4) showed the absence of peak imines of (C=N) group but a new peak was appeared of the absorption band at (1789-1792) cm^{-1} due to carbonyl group of lactone (O-C=O) and absorption band at (1744-1767) cm^{-1} due to carbonyl group of lactam (N-C=O), when the anhydride became part of the 7-membered ring of compounds showed by table (1-3) below:

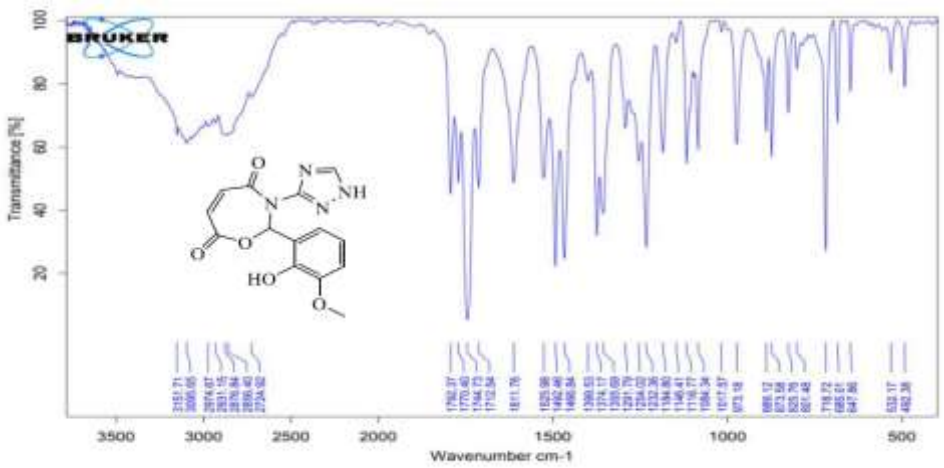


Fig (5): IR spectrum of the compound (a1)

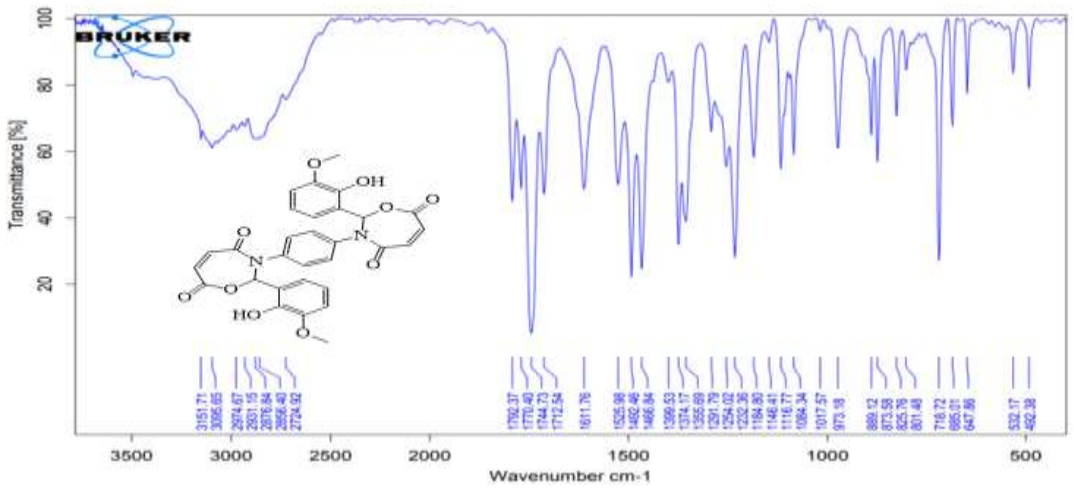


Fig (6): IR spectrum of the compound (a2)

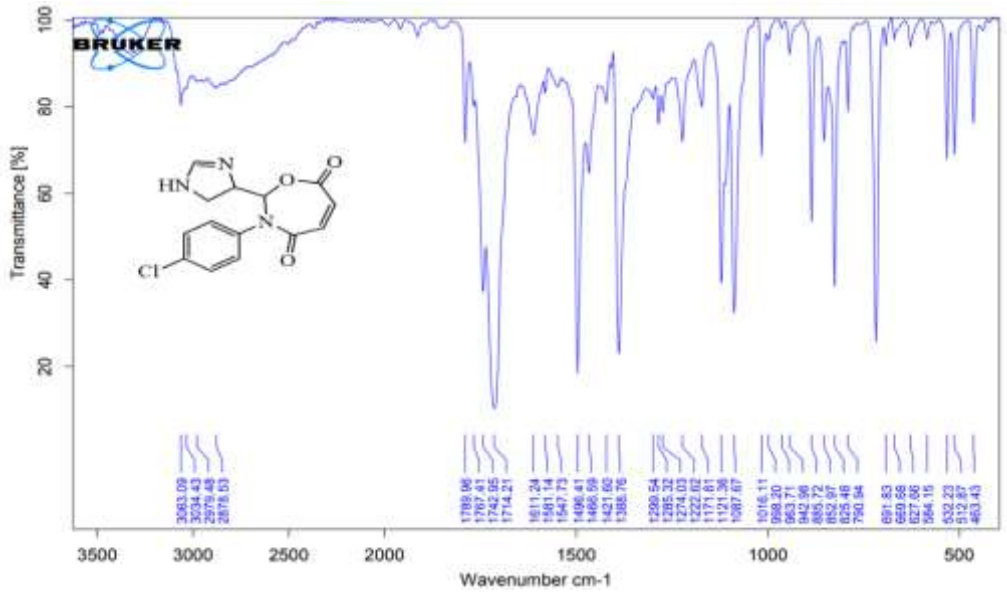


Fig (7): IR spectrum of the compound (a3)

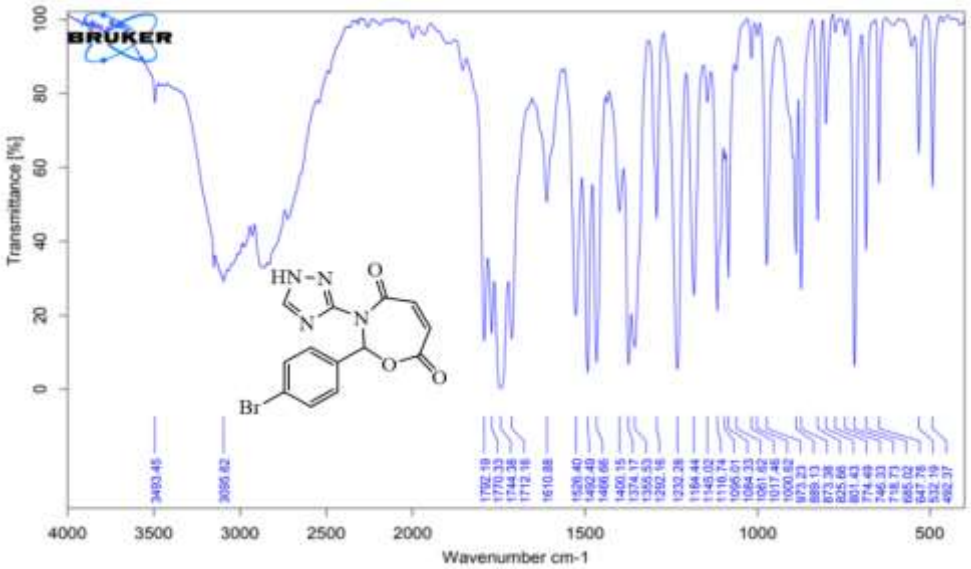


Fig (8): IR spectrum of the compound (a4)

In the ^{1}H-NMR spectrum for compounds a1 and a2 showed two singlet peaks at δ (14.59,13.07) ppm and at δ (3.84, 3.81) ppm were attributed to the phenolic (-OH) and methoxy (-OCH3) protons. The protons of aromatic ring (H-C=C-H) has appeared at δ (6.94-7.19) ppm and δ (7.53-7.96) ppm. The disappearances of the azomethine proton (CH=N) while the new peak formed at , δ 8.77 (O-CH-N) ppm and (7.53-7.96) ppm CH=CH olefin protons that confirm the obtained of 1,3 oxazepine. 1H NMR spectrum for compounds a3 and a4 showed the new peak formed at δ 7.93 ppm , δ 8.75 ppm (O-CH-N) and δ (7.41-7.51) ppm, δ (7.93-7.96) ppm CH=CH olefin protons that confirm the obtained of new 1,3 oxazepine.

Table (3-1) FT-IR spectrum data of Schiff base (S1-S5) and 1,3- Oxazepine derivatives (a1-a5)

COMP. NO.	**ν (OH)cm^{-1}**	Imine **ν(C=N)cm^{-1}**	**ν(N-H) cm^{-1}**	**Lactone ν (C=O)cm^{-1}**	**Lactam ν(C=O)cm^{-1}**	**ν (C=C) cm^{-1}**	**Aromatic ν (C-H)cm^{-1}**	**ν (C-H) alphatic asymmetric and symmetric**	**ν (C-O-C) cm^{-1}**	**ν Another**
S_1	3520	1675	3460	_	_	1581	3079	2983,2873	1284-1182	1484 **(N-H) Bending**
S_2	3412	1595	3313	-	-	1467-1439	3115	2955-2814	1212	-
S_3	**-**	1630	3397	-	-	1550-1530	3144	2984,2819	1273	3053 (=C-H) diazol,1581 (N-H) Bending
S_4		1685	3494	-	-	1577-1477	3137	2995,2832	1282	3087 (=C-H) trezol,1617 (N-H) Bending, 820 (C-Br)
a_1	3498	_	3389	1792	1744	1492-1466	3151	2974,2856	1254	1611(C=N) triazol,3095 (=C-H) and 1525 (C=C) Oxazepine
a_2	3497	_	3360	1792	1744	1492-1466	3151	2974,2856	1254-1184	1611(C=N) triazol,3095 (=C-H) and 1525 (C=C) Oxazepine
a_3	-	-	3360	1789	1767	1496-1466	3063	2979,2878	1222-1121	1611(C=N) triazol,3034 (=C-H) and 1581 (C=C) Oxazepine
a4	-	-	3493	1792	1770	1492-1466	3095	2979,2878	1232-1184	1610(C=N) triazol, 1526 (C=C) Oxazepine,718 (C-Br)

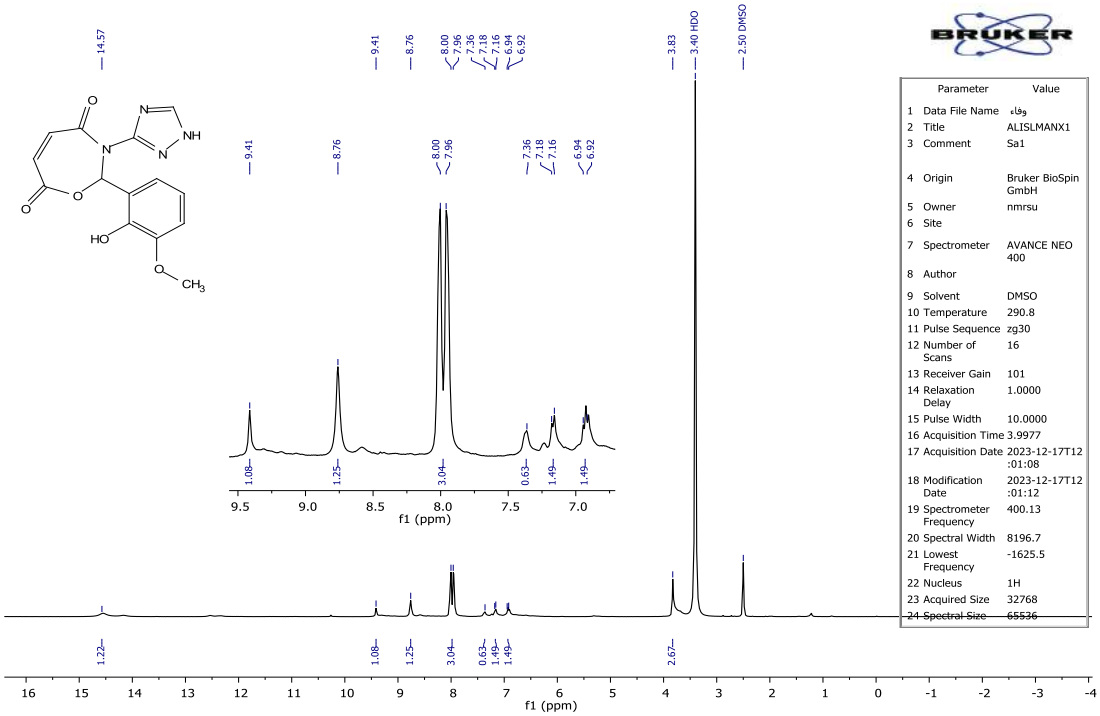


Figure 5: 1H-NMR spectrum of compound (a1)

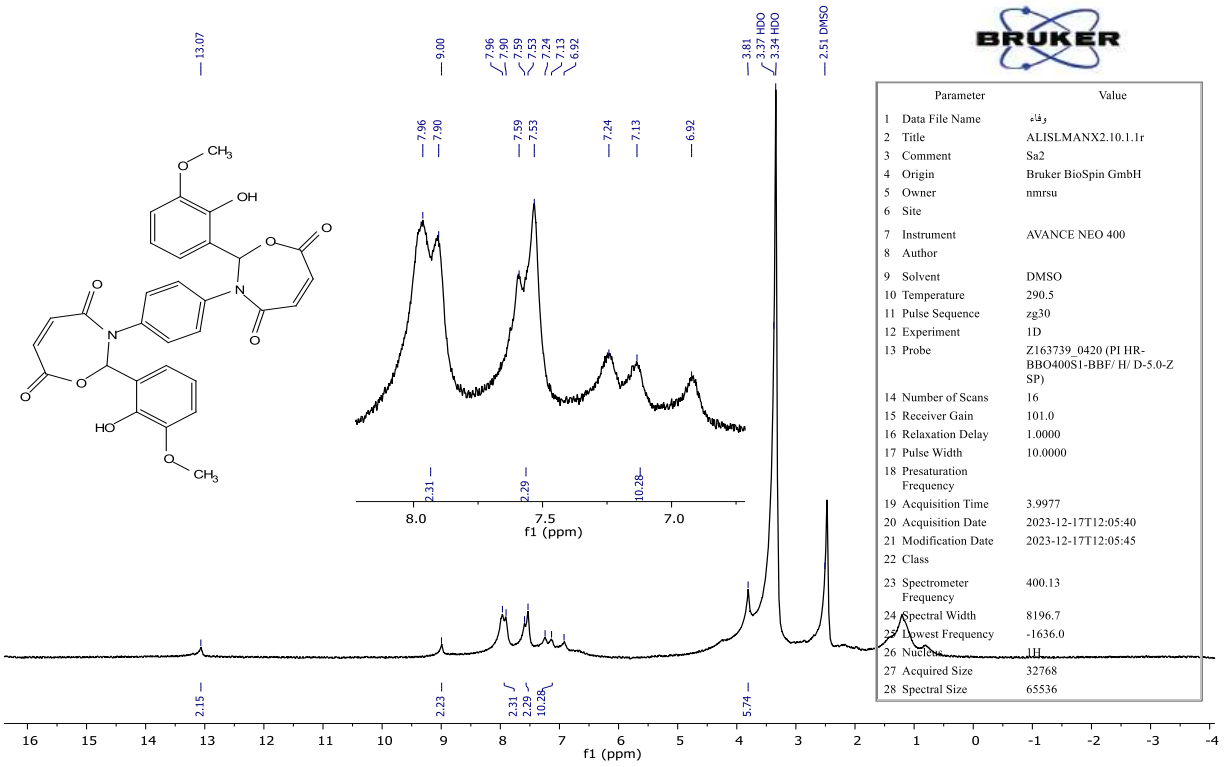


Figure 6: 1H-NMR spectrum of compound (a2)

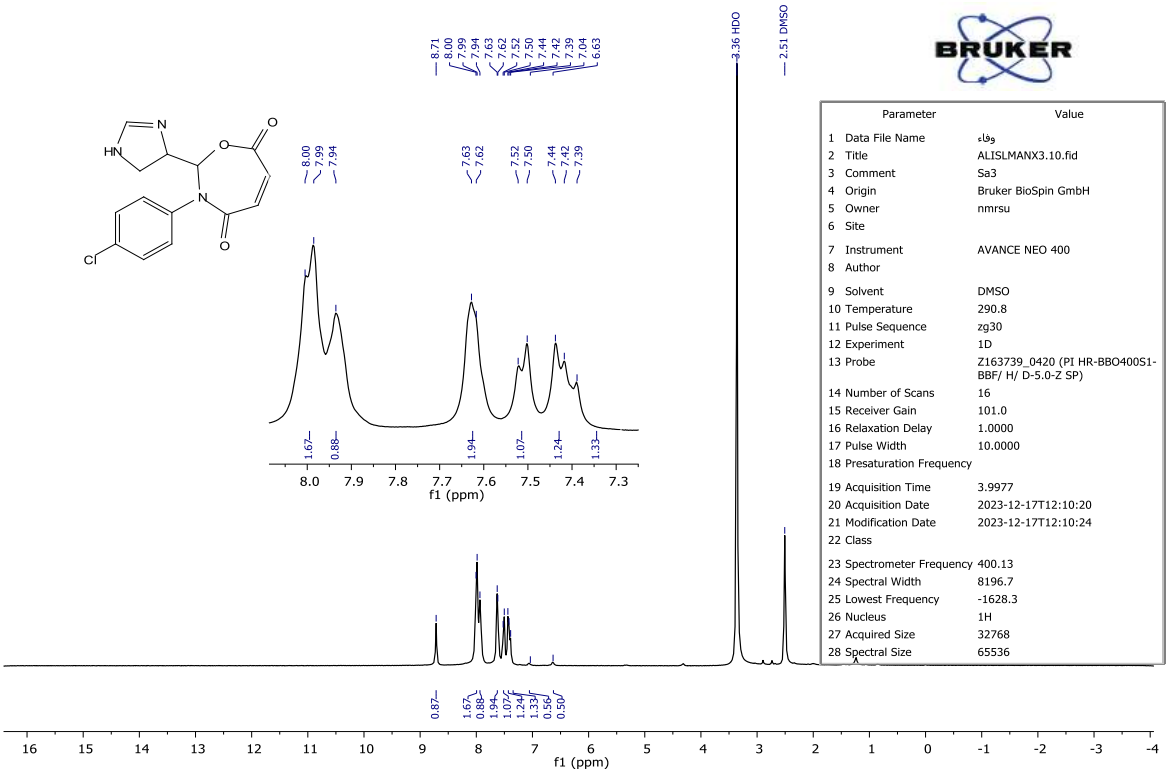


Figure 7: 1H-NMR spectrum of compound (a3)

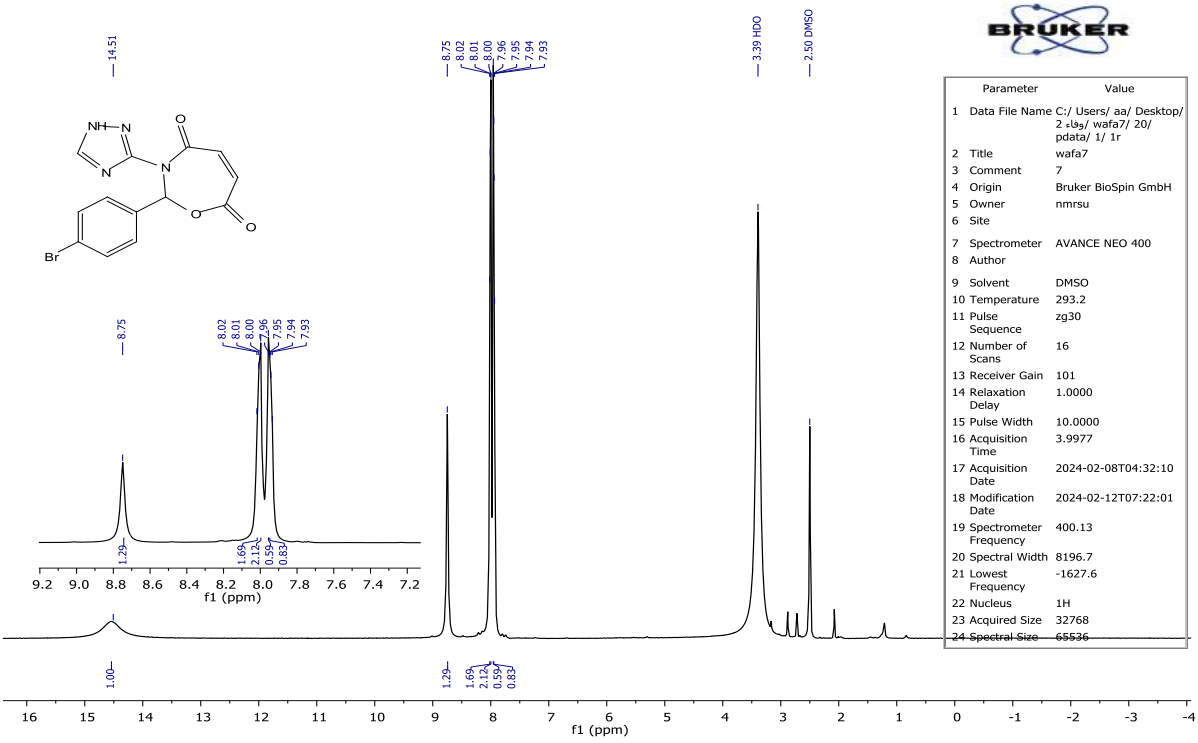


Figure 8: 1H-NMR spectrum of compound (a4)

4. CONCLUSIONS

In this work, the novel seven-membered heterocyclic compounds (1,3-oxazepines) were successfully synthesized, involving the direct cyclic addition of maleic anhydride, with double bond (C=N) of new Schiff bases compounds. Their structure

were confirmed by FTIR and 1HNMR spectroscopic analysis.

5. ACKNOWLEDGMENT

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