Article

Synthesis and characterization of heterocyclic derivatives from azo-azomethine compounds and evaluation of biological activity

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ABSTRACT

This investigation encompasses the synthesis of various heterocyclic derivatives, initiated by the reaction of 5-aminotetrazole with 2-hydroxy-4-methoxybenzaldehyde, resulting in the formation of Azo compound (1). Subsequently, Azo compound (1) undergoes a reaction with 4-methoxyaniline, yielding a Schiff base derivative (2). The derivative (2) is then reacted with various reagents including Glycine, Alanine, Thioglycolic acid, Phthalic anhydride, Malic anhydride, and Succinic anhydride, leading to the production of Imidazolidine (3), Thiazolidine (4), Oxazepine and Oxazepane derivatives (5-7) respectively. These compounds are characterized through Fourier Transform Infrared Spectroscopy (FTIR) ^{1}HNMR, , and^{13}CNMR. Following their synthesis, the biological activity of all synthesized heterocyclic derivatives was evaluated against two distinct bacterial strains.

Keywords:- Schiff bases, Heterocyclic ,Tetrazole

INTRODUCTION

Members of an important category of organic compounds are distinguished by the unique feature where some or all atoms within their molecular structures are organized into ring formations that incorporate at least one non-carbon element. The term "heterocyclic" in these compounds signifies the presence of one or more ring structures, with "hetero" denoting the inclusion of non-carbon atoms, also known as heteroatoms, within these rings. Structurally, heterocyclic compounds are analogous to cyclic organic compounds that exclusively contain carbon atoms in their ring structures. However, the incorporation of heteroatoms imparts distinct

physical and chemical characteristics to heterocyclic compounds, markedly differentiating them from their all-carbon-ring counterparts[1, 2].

Heterocyclic chemistry, a prominent field, encompasses heterocyclic compounds that represent approximately sixty-five percent of the published literature in organic chemistry. These compounds are not only ubiquitous in nature but also fundamental to life, playing a crucial role in the metabolic processes of all living cells. The genetic blueprint of life, DNA, is constituted of heterocyclic bases, specifically pyrimidines and purines. A significant array of heterocyclic compounds, both naturally occurring and synthetically produced, exhibit pharmacological activity and have found applications in clinical settings[3, 4].

Heterocyclic compounds boast a broad spectrum of applications. They are predominantly utilized in pharmaceuticals, serving as active ingredients in numerous drugs. Additionally, their use extends to agrochemicals and veterinary products. Beyond the medical and agricultural fields, these compounds are employed in various industrial processes and products. They are integral in the formulation of sensitizers, developers, antioxidants, and corrosion inhibitors. Furthermore, they play a role in the manufacturing of copolymers and dyestuffs. Heterocyclic compounds are also crucial as intermediaries or catalysts in the synthesis of other organic compounds, underlining their versatile and pivotal role in both science and industry[5, 6] .

Materials

Spectra from Fourier Transform Infrared (FTIR) Spectroscopy, ranging between 400 and 4000 cm^{-1}, were obtained using a SHIMADZU FTIR-8400S instrument, employing KBr disks for sample preparation. Proton Nuclear Magnetic Resonance (^{1}HNMR) and Carbon-13 Nuclear Magnetic Resonance (^{13}CNMR) analyses were performed on a Varian Agilent instrument, operating at a frequency of 500 MHz, with samples prepared in Deuterated Dimethyl Sulfoxide (DMSO-d_6). These measurements were conducted at the Department of Chemistry, Al-Basra University, Iraq.

Methods

Preparation of azo derivative (1)[7, 8]

(0.0058777 moles) of (5-aminotetrazole) were dissolved in a mixture containing (4 ml) of hydrochloric acid (HCl) and (30 ml) of distilled water. The solution was then cooled to a temperature within the range of (0-5) ^{o}C. Subsequently, a solution of sodium nitrite ($NaNO_2$) (0.4 g) (equivalent to 0.0058777 moles), dissolved in (10 ml) of distilled water, was introduced into the cooled mixture. The resulting mixture was allowed to cool further and was stirred for a duration of (20 minutes) to ensure completion of the diazotization process, maintaining a temperature within the range of (0-5) ^{o}C.

Next, the resulting brown-colored solution was combined with a solution of (0.005877 moles) of (2-hydroxy-4-methylbenzaldehyde), along with (1 g) of sodium hydroxide (NaOH), all of which were dissolved in a mixture containing (20 ml) of distilled water and (5 ml) of ethanol. The combined solution was then cooled to a temperature of 0 to 5 degrees Celsius.

The completion of the addition process, it was observed that a precipitate of the azo compound, with a brown color, formed. The entire procedure was conducted at a pH of 5, and the resulting solutions were left of 24 hours. After this duration, the precipitate was separated by filtration, and it underwent subsequent steps including washing with distilled water, drying, and re crystallized using absolute ethanol . With a melting point of 120-122^{O}C.

Preparation of Schiff bass(2) [9, 10]

Equal molar quantities of an azo derivative and 4-methoxyaniline (0.01 mole) were dissolved in 30 mL of ethanol, followed by the addition of three drops of glacial acetic acid. The solution was then subjected to reflux for 3 hours. After cooling, the solution was allowed to stand for 24 hours, afterward filtered, and the product was re crystallized using absolute ethanol. . With a melting point of 107-111^{O}C.

Preparation of Imidazolidine Derivative(3,4)[11, 12]

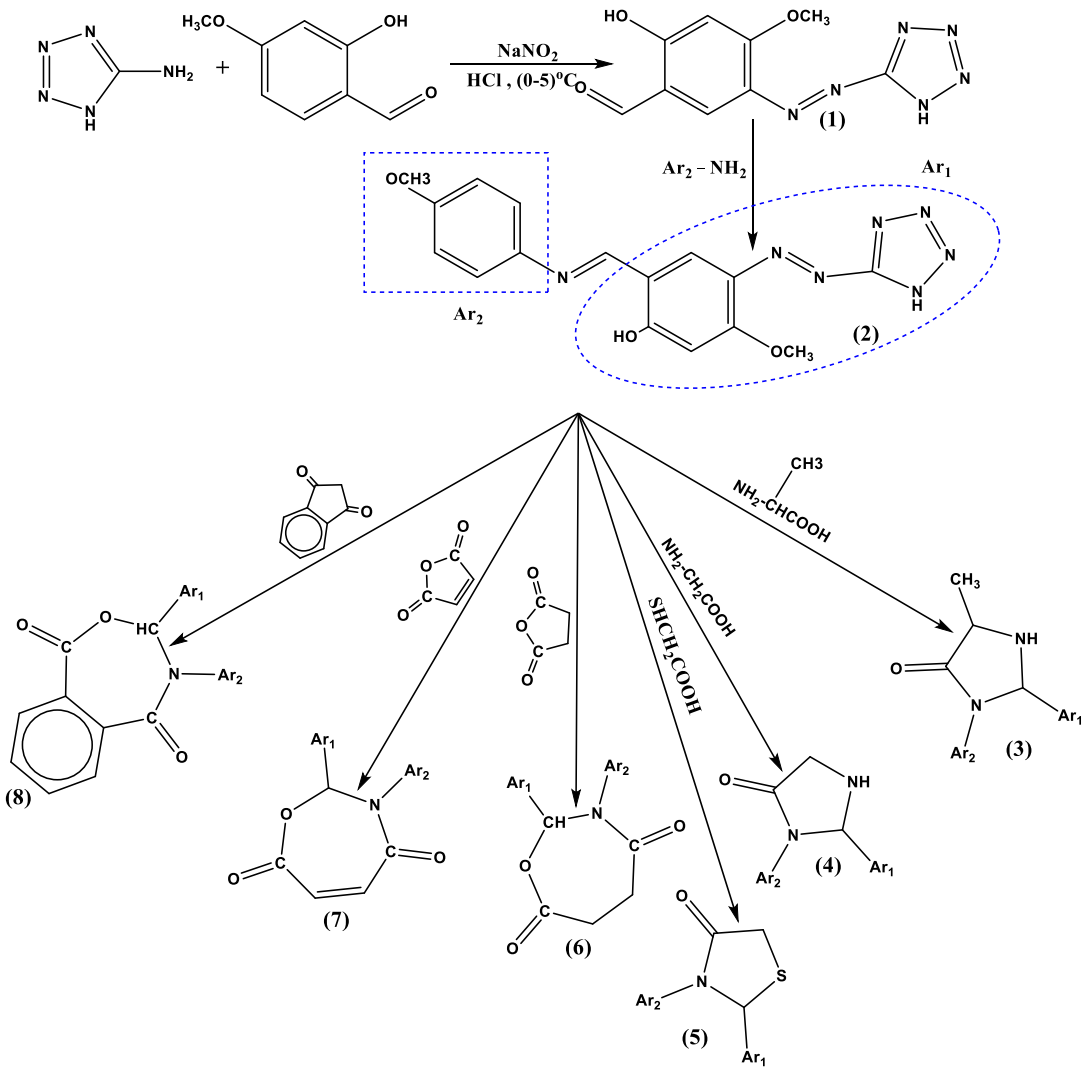
Compound (2) (0.001 mol) was dissolved in 20 mL of tetrahydrofuran (THF), and mixed with 0.02 mol of Galycin and Alanin respectively , each also dissolved in 20 mL of THF. The mixture was then refluxed for 27 hours. After cooling, it was allowed to stand for 40 hours, and subsequently, the product was re crystallized using absolute ethanol.With a melting point of 133- 135^{O}C.

Preparation of Thiazolidine Derivative (5)[13, 14]

Compound (2) 0.001 mol was combined with 0.003mol of dissolved (thioglycolic acid) in 30 mL of 1,4-dioxane, followed by the addition of 0.4 g of anhydrous zinc chloride. This mixture experienced an increase in precipitation over a period of 24 hours. Afterward, it was allowed to stand for 72 hours, then filtered, and the resultant product was re crystallized using absolute ethanol. With a melting point of 119- 121^{O}C.

Preparation of Oxazepine and Oxazepane Derivatives(6-8)[15, 16]

In this procedure, 0.001mol (compound (2)) was dissolved in (25 mL) of benzene. Subsequently, 0.001 mol of each of phthalic anhydride, maleic anhydride, and succinic anhydride were added to the solution. After that, this mixture was refluxed for 30 hours at 80°C. The solution was left to stand uninterrupted for 24 hours after the reflux process was finished. After filtering the solution, the result re crystallized using absolute ethanol. With a melting points of 132- 1134^{O}C, 140-142^{O}C, 131- 133^{O}C



Schem1: Synthesis of some heterocyclic derivatives

RESULTS AND DISCUSSION

Derivative(1)5-((1H-tetrazol-5-yl)diazenyl)-2-hydroxy-4-methoxybenzaldehyde

The FT-IR spectrum data for derivative (1) exhibit disappearing the two bands that due to the primary amine and appearing several peaks:3300 cm^{-1} corresponding to the -OH bond,3101cm^{-1}(Ar-H) bonds, 2993 cm^{-1}(-CH) bonds in -CH_3 groups, 1620 cm^{-1} indicating a C=N endo (tetrazole ring) bond, 1700 cm^{-1}suggesting a -C=O aldehyde, and 1570 cm^{-1} representing a C=C bond, The data can be found in Figure (1).

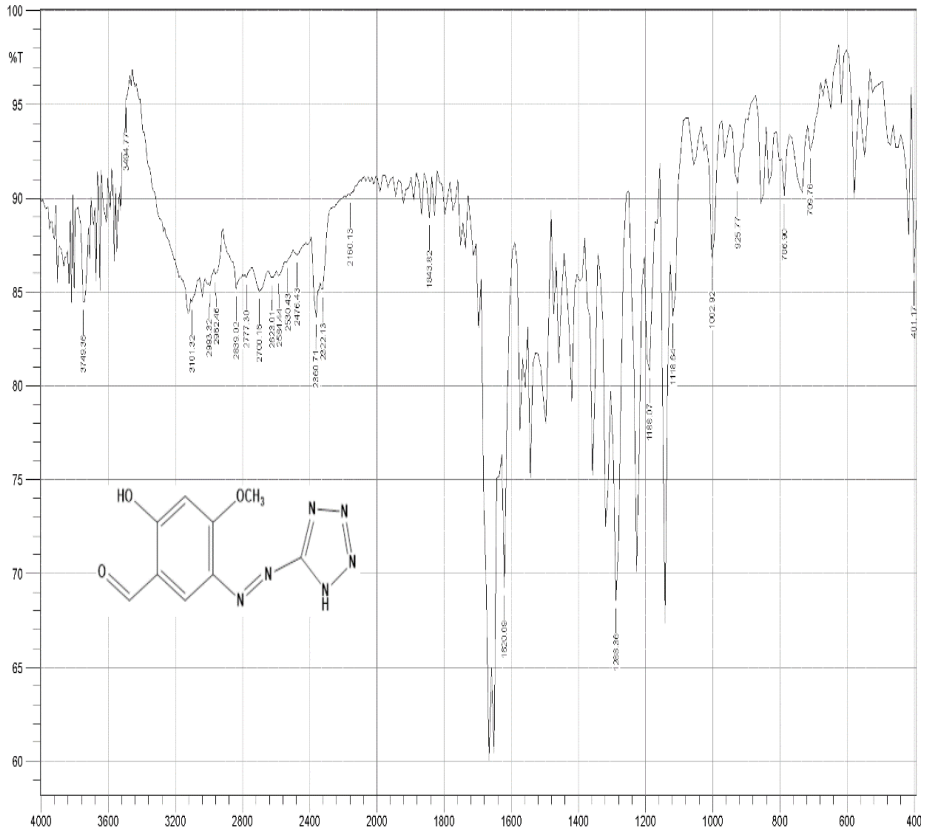


Figure 1: FTIR spectrum of compound (1)

Derivative(2)4-(-(1H-tetrazol-5-yl)diazenyl)-5-methoxy-2-(-((4-methoxyphenyl)imino)methyl)phenol

The FT-IR spectrum data for derivative (2) reveal disappearing the band that due to the carbonyl aldehyde and appearing several peaks: 3487 cm^{-1} for the O-H bond, 3263 cm^{-1} for N-H bond, 3047 cm^{-1} for C-H aromatic bonds, 2923 cm^{-1} for C-H aliphatic bonds in CH_3 groups,1666 cm^{-1} indicating a C=N bond,1600 cm^{-1} N=N, and 1553 cm^{-1} representing a C=C bond ,The data can be found in Figure (2).

In the ^{1}H-NMR spectrum data of derivative (2), the following chemical shifts were observed: a peak at 2.50 ppm (DMSO), a singlet at 8.8 ppm for 1H corresponding to N-H group, a singlet at 9 ppm for 1H representing OH group, a singlet at 4 ppm for 6H to OCH_3 group, and a range of 6.4-8 ppm indicating a multiplet for 6H corresponding to Ar-H bonds ,The data can be found in Figure (3).

The ^{13}C-NMR spectrum data for compound (2) in DMSO revealed several chemical shifts: 177 ppm for C_9, 55 ppm for C_8,C_{16},158 ppm for C_1,and a range of 101-134 ppm indicating carbon atoms in aromatic region ,The data can be found in Figure (4).

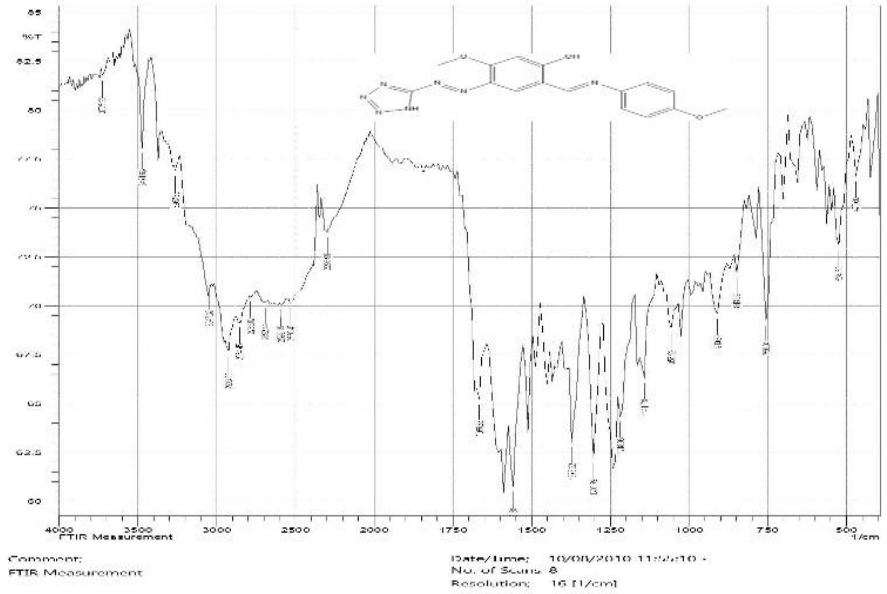


Figure 2: FTIR spectrum of compound (2)

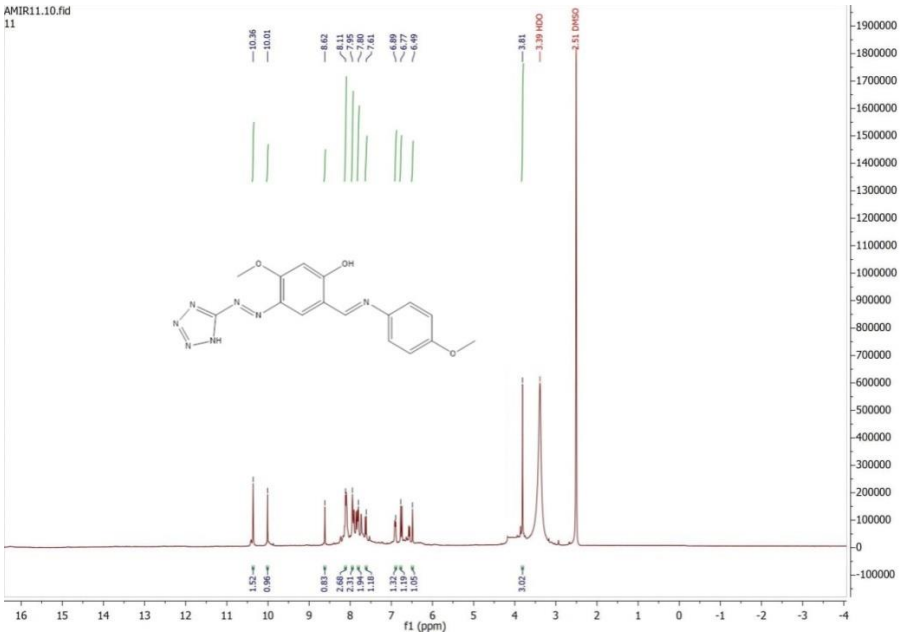


Figure 3: ^{1}H-NMR spectrum of compound (2)

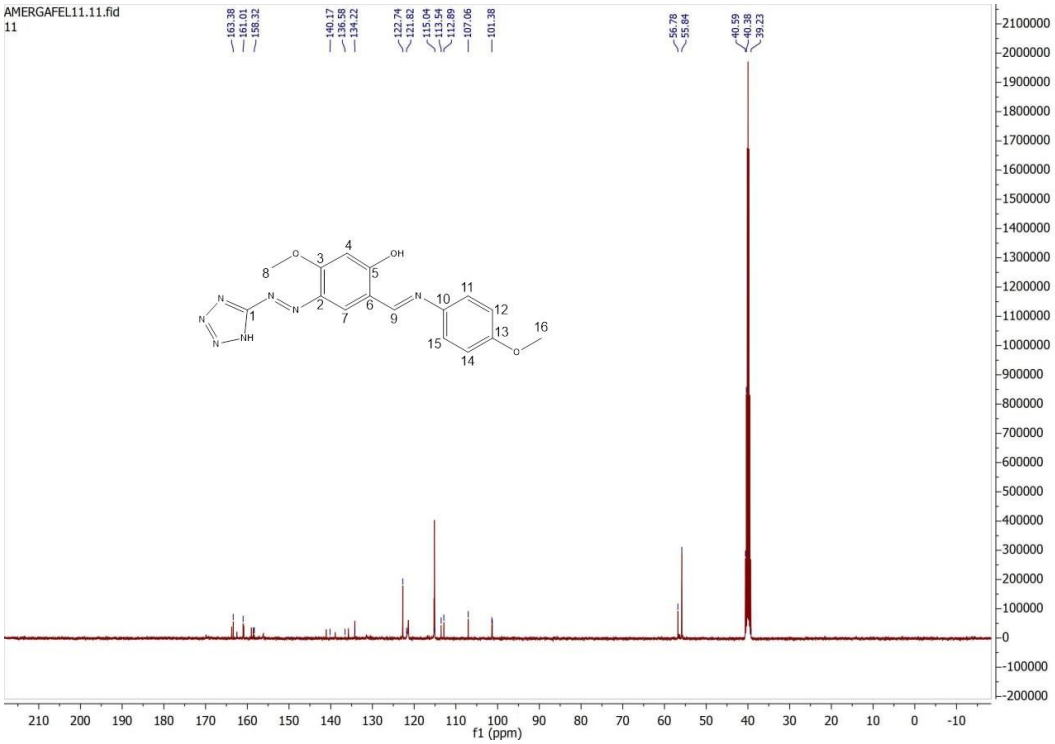


Figure 4: ^{13}C-NMR spectrum of compound (2)

Derivative(3)2-(5-((1H-tetrazol-5-yl)diazenyl)-2-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)-5-methylimidazolidin-4-one

The Fourier Transform Infrared (FT-IR) spectrum of derivative (3) displays distinctive peaks, including a peak at 3278 cm^{-1} attributed to the O-H bond, 3193 cm^{-1} for Ar-H bonds, 2923 cm^{-1} associated with C-H bonds in CH_3 groups, 1650 cm^{-1} indicative of a C=O bond, 1598 cm^{-1} for a C=N endo cyclic bond, and 1512 cm^{-1} denoting a N=N bond. These observations are detailed in Figure (5).In the Proton Nuclear Magnetic Resonance (^{1}HNMR) spectrum of derivative (3), measured in DMSO-d_6, the following shifts were noted: a peak at 2.50 ppm DMSO , a singlet at 10.2 ppm for 1H related to the OH group, singlets at 8.8 and 8.2 ppm for 2H corresponding to NH groups, a doublet at 1.2 ppm for 3H associated with the CH_3 group, singlets at 4 and 3.9 ppm for 6H linked to the -OCH_3 group, a quartet at 2.3 ppm for 1H pertaining to a CH group, a singlet at 1.2 ppm for 1H also corresponding to a CH group, a singlet at 6.4 ppm for 1H of H=N related to a CH group, and a multiplet ranging from 6.5-7.5 ppm for 6H indicative of Ar-H bonds. This data is presented in Figure (6).The Carbon-13 Nuclear Magnetic Resonance (^{13}CNMR) spectrum of compound (3) in DMSO elucidated various

chemical shifts: 164 ppm for C12, 55 and 56 ppm for C8 and C19, respectively, 8 ppm for C9, 58 ppm for C10, 16 ppm for C11, 161 ppm for C1, and a spectrum ranging from 101-158 ppm, highlighting the carbon atoms in aromatic regions. This information can be found in Figure (7).

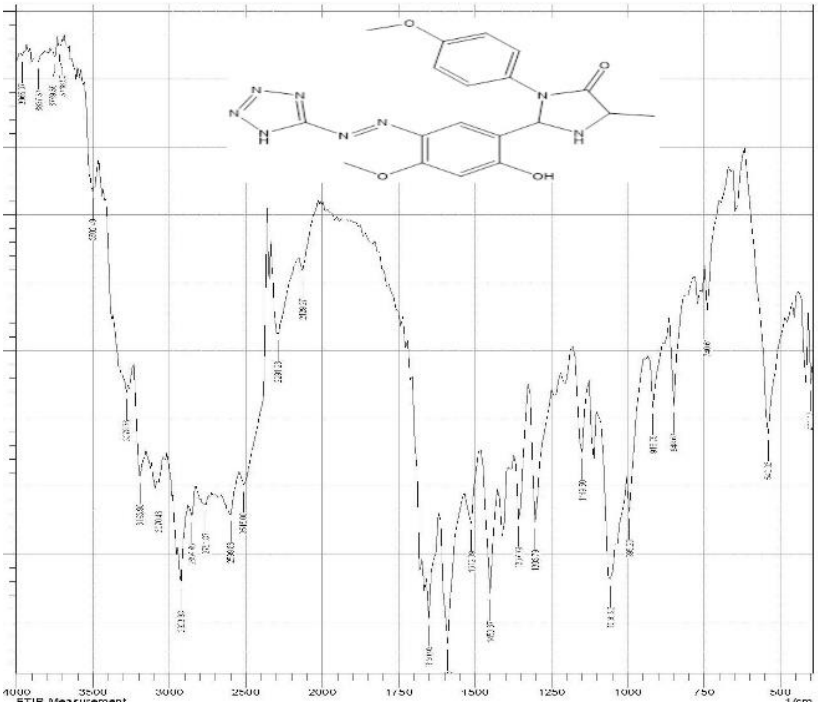


Figure 5: FTIR spectrum of compound (3)

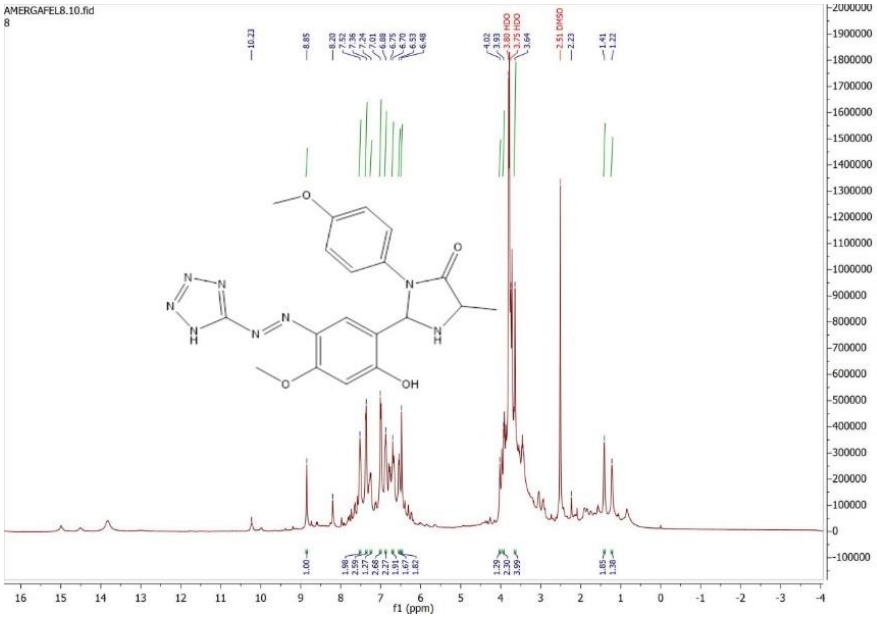


Figure 6: ^{1}H-NMR spectrum of compound (3)

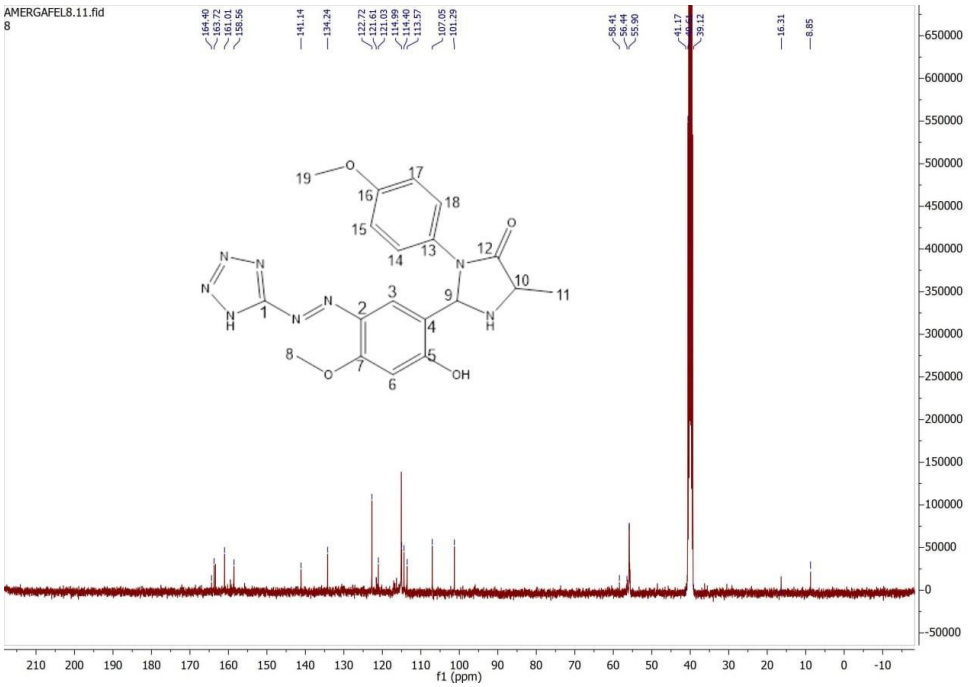


Figure 7: ^{13}C-NMR spectrum of compound (3)

Derivative(4)2-(5-((1H-tetrazol-5-yl)diazenyl)-2-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)imidazolidin-4-one

The FT-IR spectrum data for derivative (4) reveal several peaks: 3278 cm^{-1} for the O-H bond, 3070 cm^{-1} for Ar-H bonds, 2928 cm^{-1} for C-H bonds in CH_3 groups, 1650 cm^{-1} indicating a C=O bond, 1586 cm^{-1} indicating a C=N endo cyclic bond, and 1512 cm^{-1} representing a N=N bond ,The data can be found in Figure (8).

In the ^{1}H-NMR spectrum data of derivative (4), the following chemical shifts were observed: a peak at 2.50 ppm (DMSO), a singlet at 10 ppm for 1H corresponding to OH group, a singlet at 8.8,8.2 ppm for 2H representing NH groups, a singlet at 6.4 ppm for 1H representing H-C=N group, a singlet at 1.2 ppm for 1H corresponding to CH group, singlet at 3.5ppm for 2H corresponding to CH_2 group,singlet at 3.9,4 ppm for 6H corresponding to OCH_3 group, and a range of 6.7-7.6 ppm indicating a multiple for 6H corresponding to Ar-H bonds ,The data can be found in Figure (9).

The ^{13}C-NMR spectrum data for compound (4) in DMSO revealed several chemical shifts: 163 ppm for C_{11}, 66 ppm for C_{10},8.9 ppm for C_9 , 45,55 ppm for C_8,C_{18} , 161 ppm for C_1, and a range of 101-115 ppm indicating carbon atoms in aromatic regions ,The data can be found in Figure (10).

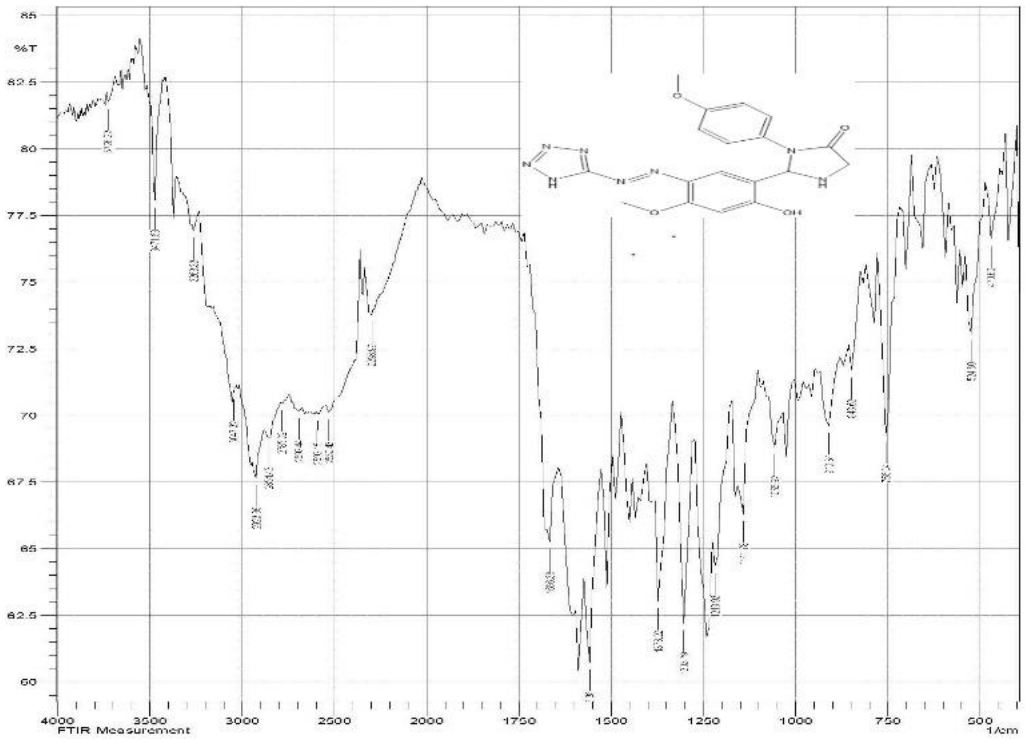


Figure 8: FTIR spectrum of compound (4)

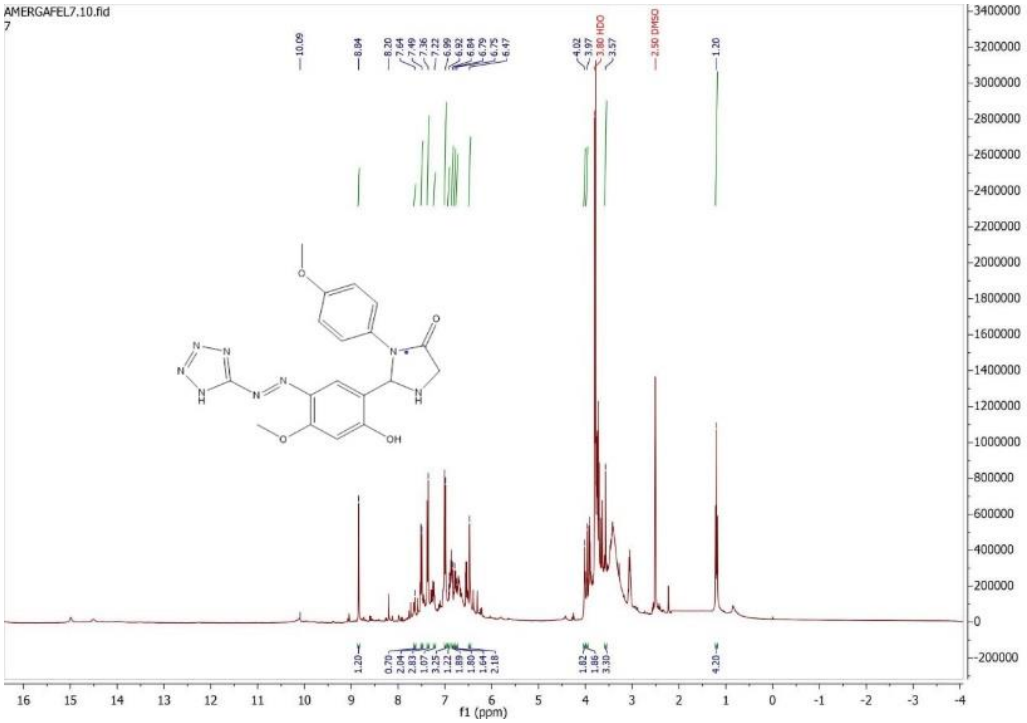


Figure 9: ^{1}H-NMR spectrum of compound (4)

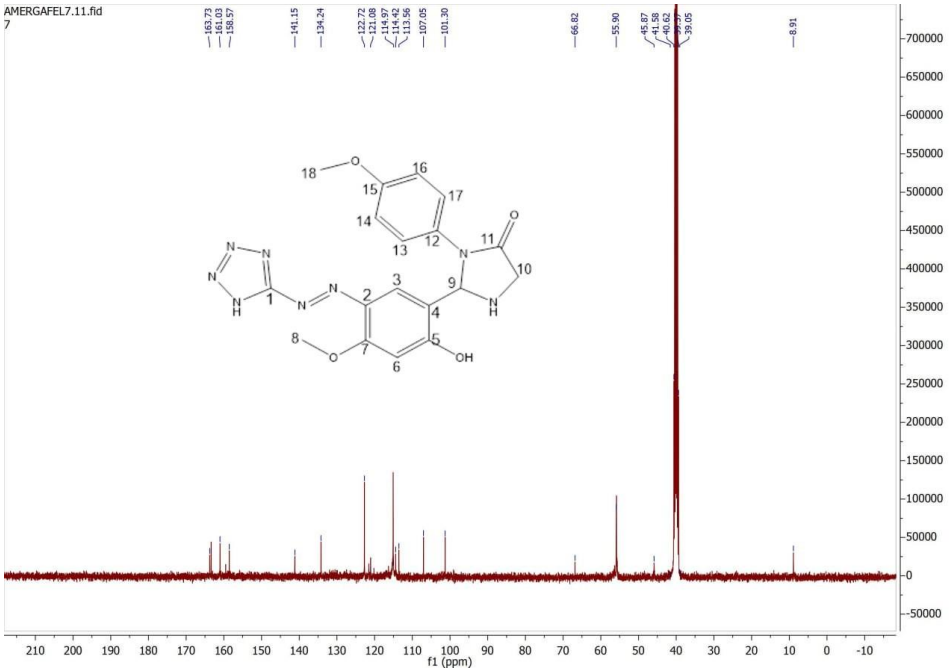


Figure 10: ^{13}C-NMR spectrum of compound (4)

Derivative(5)2-(5-((1H-tetrazol-5-yl)diazenyl)-2-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)thiazolidin-4-one

The FT-IR spectrum data for derivative (5) reveal several peaks: 3325 cm^{-1} for the O-H bond, 3178 cm^{-1} for Ar-H bonds, 2985 cm^{-1} for C-H bonds in CH_3 groups, 1623 cm^{-1} indicating a C=O bond, 1573 cm^{-1} indicating a C=N bond, and 1518 cm^{-1} representing a N=N bond ,The data can be found in Figure (11).

In the ^{1}H-NMR spectrum data of derivative (5), the following chemical shifts were observed: a peak at 2.50 ppm (DMSO), a singlet at 9.3 ppm for 1H corresponding to OH group, a singlet at 8.8 ppm for 1H representing NH group, a singlet at 1.1 ppm for 1H representing CH group, a singlet at 3.7-3.9 ppm for 6H corresponding to OCH_3 groups, a singlet at 3 ppm for 2H corresponding to CH_2 group, a singlet at 6 ppm for 1H corresponding to thiazoliden ring , and a range of 6.2-7.5 ppm indicating a multiplet for 6H corresponding to Ar-H bonds ,The data can be found in Figure (12).

The ^{13}C-NMR spectrum data for compound (5) in DMSO revealed several chemical shifts: 170 ppm for C_{11}, 55 ppm for C_{10} , 9 ppm for C_9 , 46,43 ppm for C_8,C_{18} , 142 ppm for C_1, 137 ppm for C_5, and a range of 114 -124 ppm indicating carbon atoms in aromatic regions ,The data can be found in Figure (13).

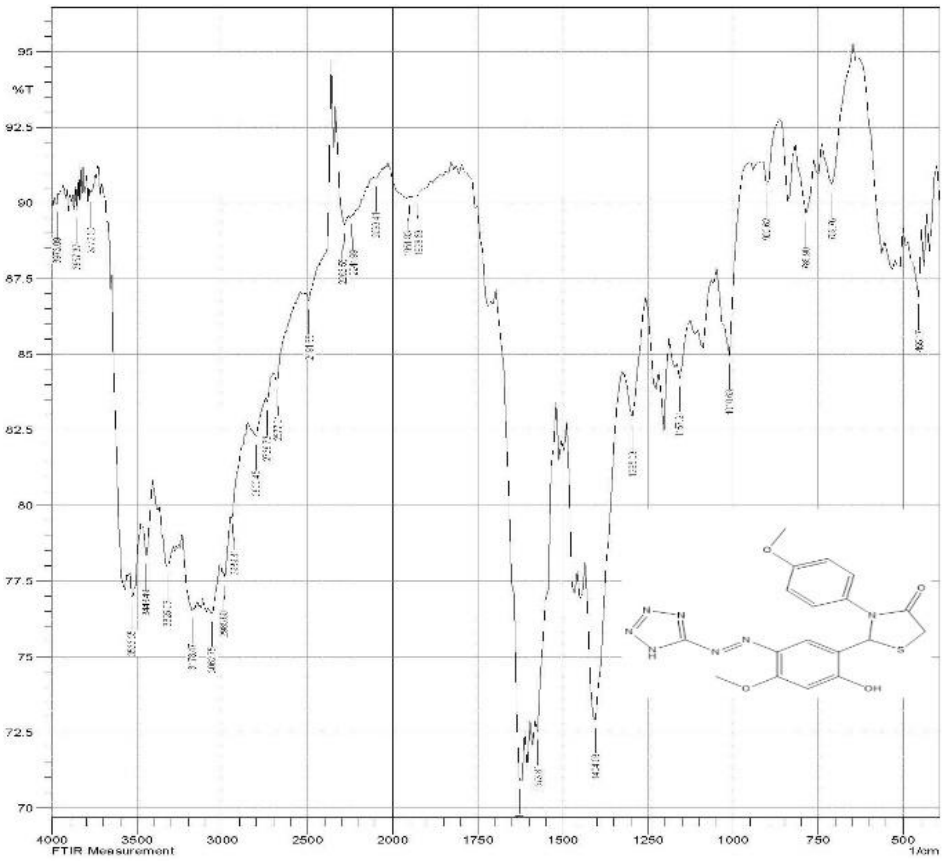


Figure 11: FTIR spectrum of compound (5)

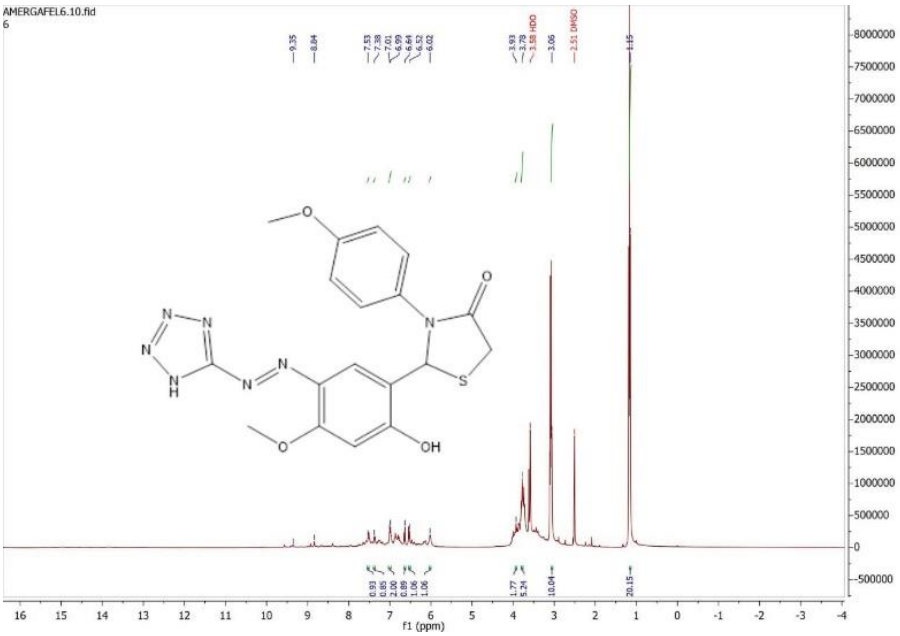


Figure 12: ^{1}H-NMR spectrum of compound (5)

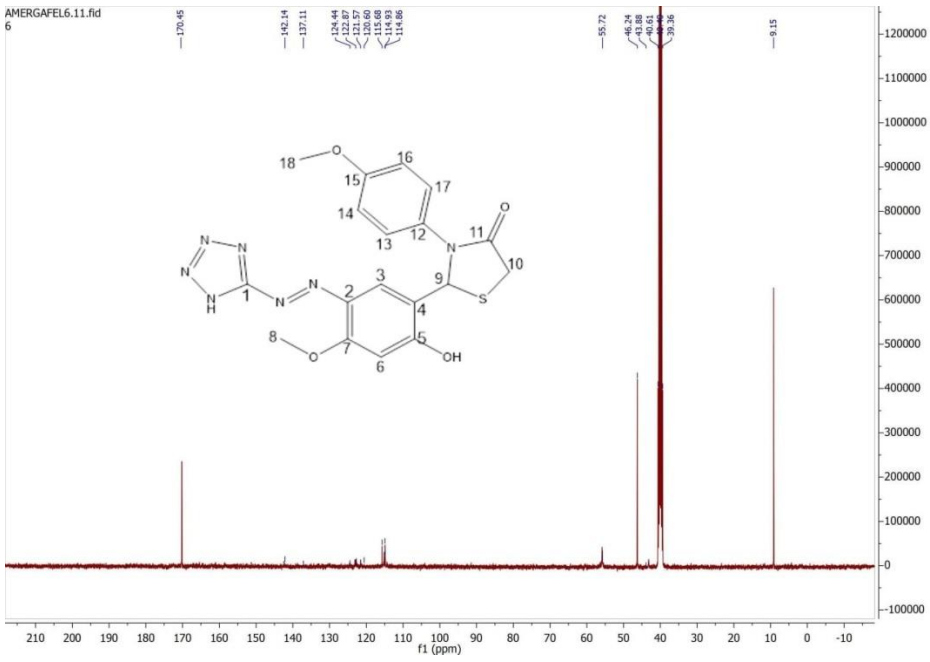


Figure 13: ^{13}C-NMR spectrum of compound (5)

Derivative(6)2-(5-((1H-tetrazol-5-yl)diazenyl)-2-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)-1,3-oxazepane-4,7-dione

The FT-IR spectrum data for derivative (6) reveal several peaks: 3271 cm^{-1} for the O-H bond, 3193 cm^{-1} for Ar-H bonds, 2910 cm^{-1} for C-H bonds in CH_3 groups, 1712 cm^{-1} indicating a C=O Lacton, , 1666 cm^{-1} indicating a C=N bond, and 1550 cm^{-1} representing a N=N bond ,The data can be found in Figure (14).

In the ^{1}H-NMR spectrum data of derivative (6), the following chemical shifts were observed: a peak at 2.50 ppm (DMSO), a singlet at 12 ppm for 1H corresponding to OH group, a singlet at 9.9 ppm for 1H representing NH group, a singlet at 1.2 ppm for 1H corresponding to CH group, a singlet at 2.4,3 ppm for 1H corresponding to CH_2 group, a singlet at 3.9,4 ppm for 6H corresponding to OCH_3 group , 6.5 ppm for 1H corresponding to oxazipen ring , and a range of 6.7-7.5 ppm indicating a multiplet for 6H corresponding to Ar-H bonds ,The data can be found in Figure (15).

The ^{13}C-NMR spectrum data for compound (6) in DMSO revealed several chemical shifts: 174,169 ppm for C_{10},C_{13} , 155 ppm for C_1, 10 ppm for C_9, 29,31 ppm for C_{11},C_{12}, 55,56 ppm for $C_{8,}$ C_{20} , 135 ppm for C_5 , and a range of 101-127 ppm indicating carbon atoms in aromatic regions ,The data can be found in Figure (16).

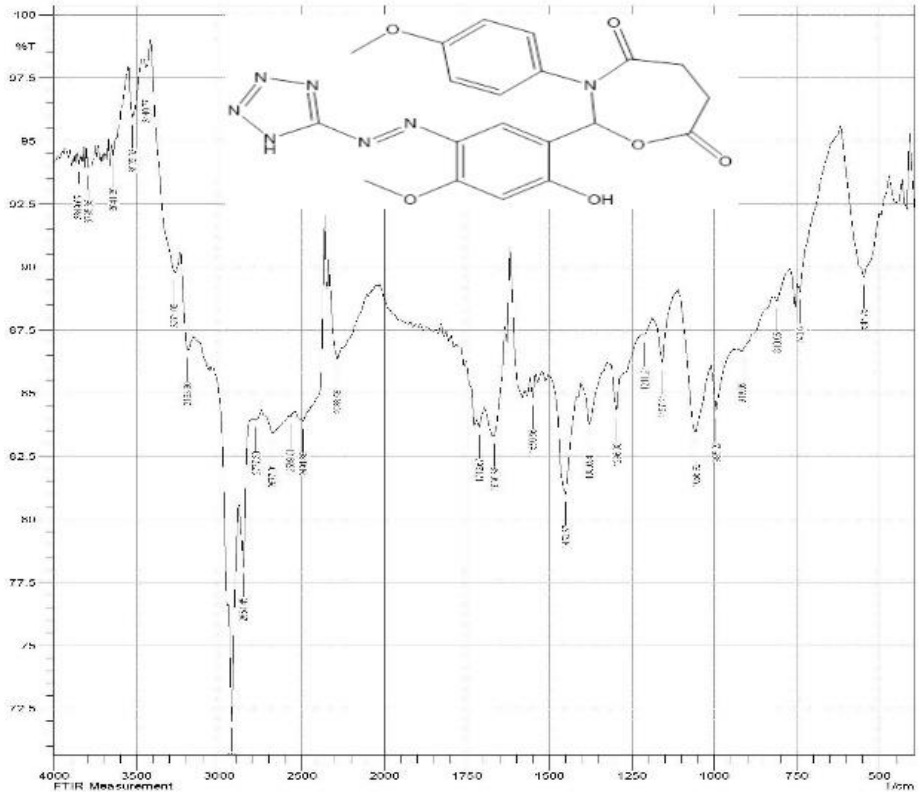


Figure 14: FTIR spectrum of compound (6)

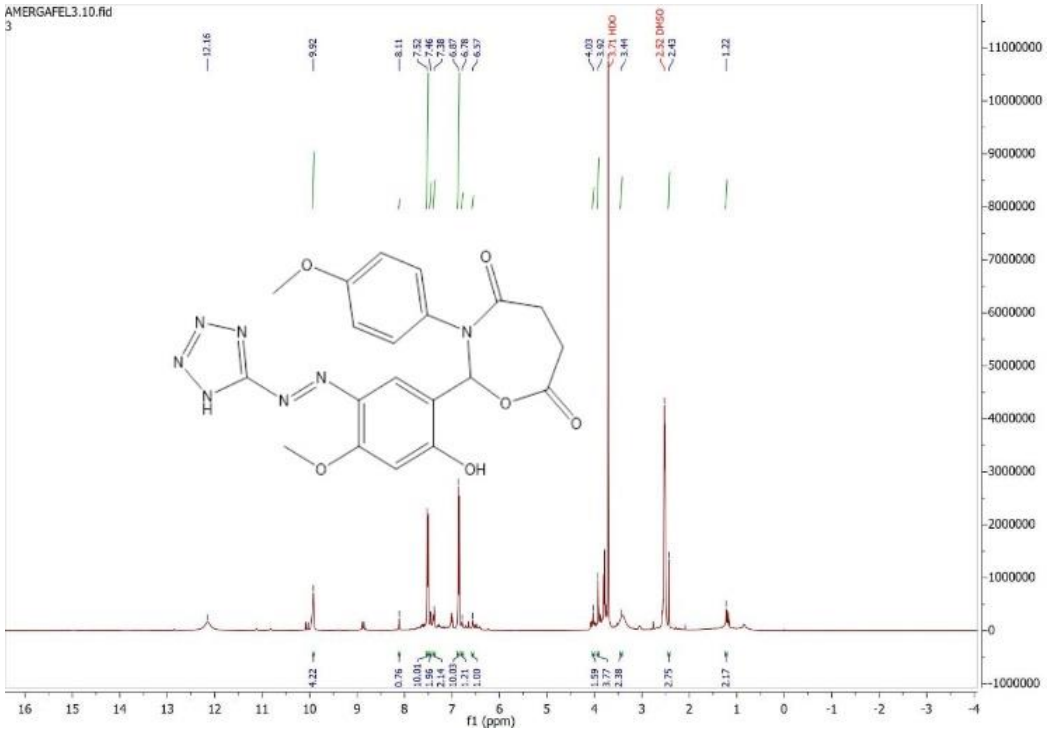


Figure 15: ^{1}H-NMR spectrum of compound (6)

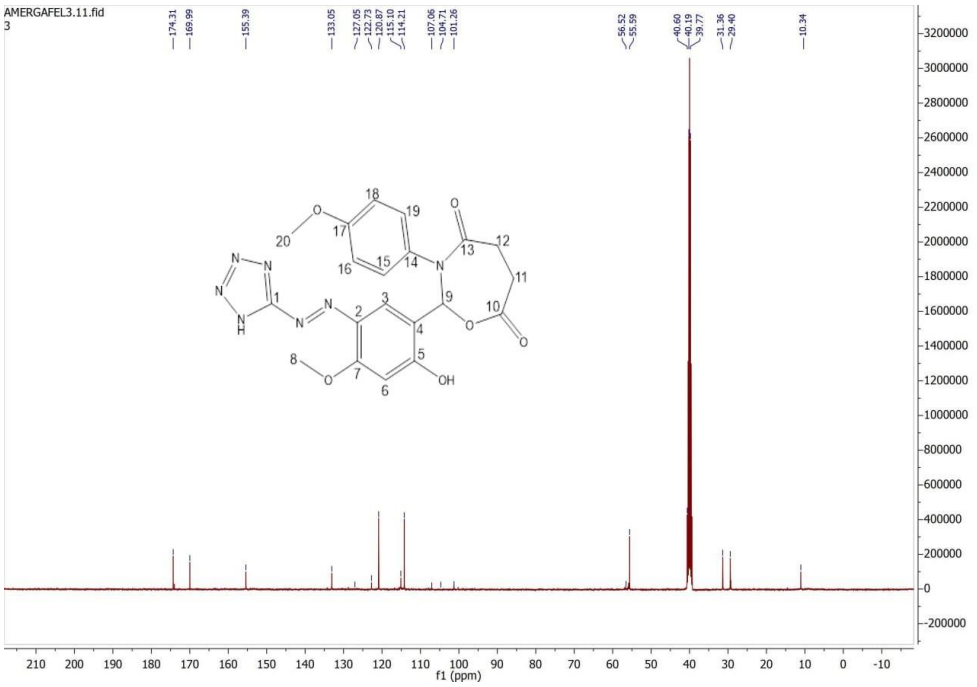


Figure 16: ^{13}C-NMR spectrum of compound (6)

Derivative(7) 2-(5-((1H-tetrazol-5-yl)diazenyl)-2-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione

The FT-IR spectrum data for derivative (7) reveal several peaks: 3271 cm^{-1} for the O-H bond,3178 cm^{-1} for Ar-H bonds, 2908 cm^{-1} for C-H bonds in CH_3 groups, 1650 cm^{-1} indicating a C=O Lactam bond, 1550 cm^{-1} indicating a C=N bond, and 1458 cm^{-1} representing a N=N bond ,The data can be found in Figure (17).

In the ^{1}H-NMR spectrum data of derivative (7)the following chemical shifts were observed: a peak at 2.50 ppm (DMSO), a singlet at 10.7 ppm for 1H corresponding to OH group, a singlet at 8.8 ppm for 1H representing NH group, a singlet at 1.2 ppm for 1H corresponding to CH group, a singlet at 4,3 ppm for 1H corresponding to CH_2 group, Aromatic , 6 ppm for 1H corresponding to oxazipen ring , and a range of 6.7-7.5 ppm indicating a multiple for 6H corresponding to Ar-H bonds,The data can be found in Figure (18).

The ^{13}C-NMR spectrum data for compound (7) in DMSO revealed several chemical shifts: : 167,166 ppm for C_{10},C_{13} , 163 ppm for C_1, 8 ppm for C_9, 156,154 ppm for C_{11},C_{12} , 45,55 ppm for $C_{8,}$ C_{20} , 135 ppm for C_5 , and a range of

101-132 ppm indicating carbon atoms in aromatic regions,The data can be found in Figure (19).

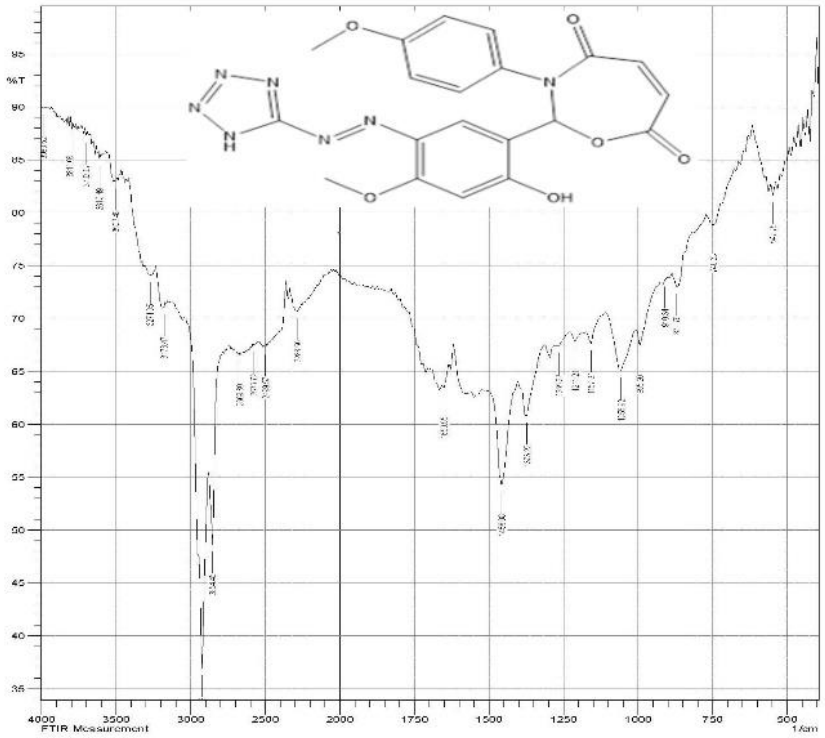


Figure17: FTIR spectrum of compound (7)

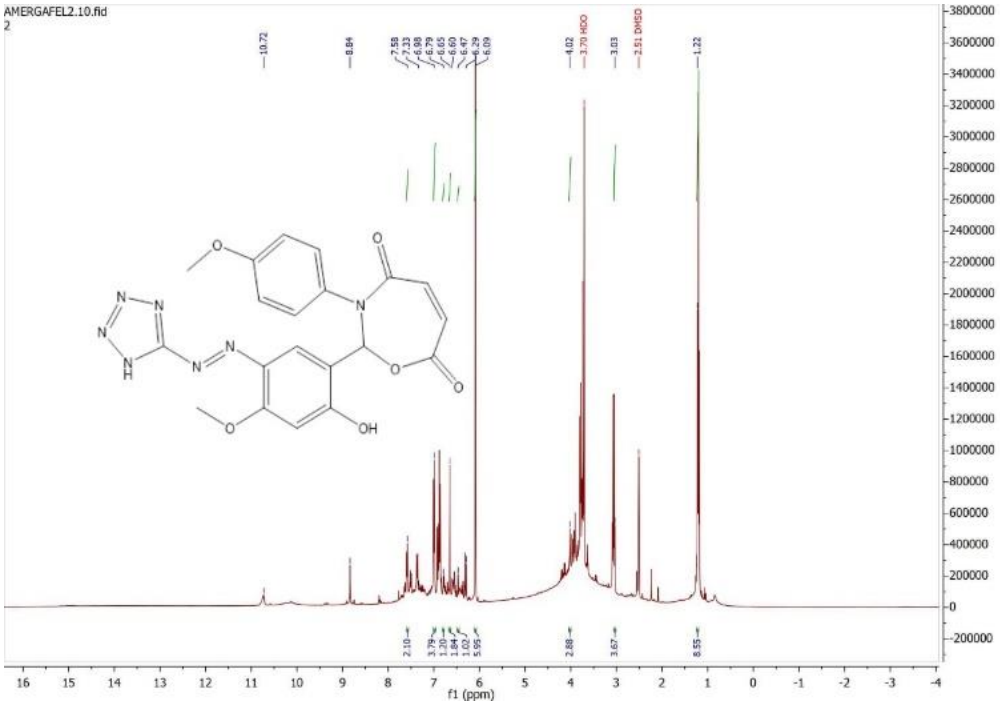


Figure18: ^{1}H-NMR spectrum of compound (7)

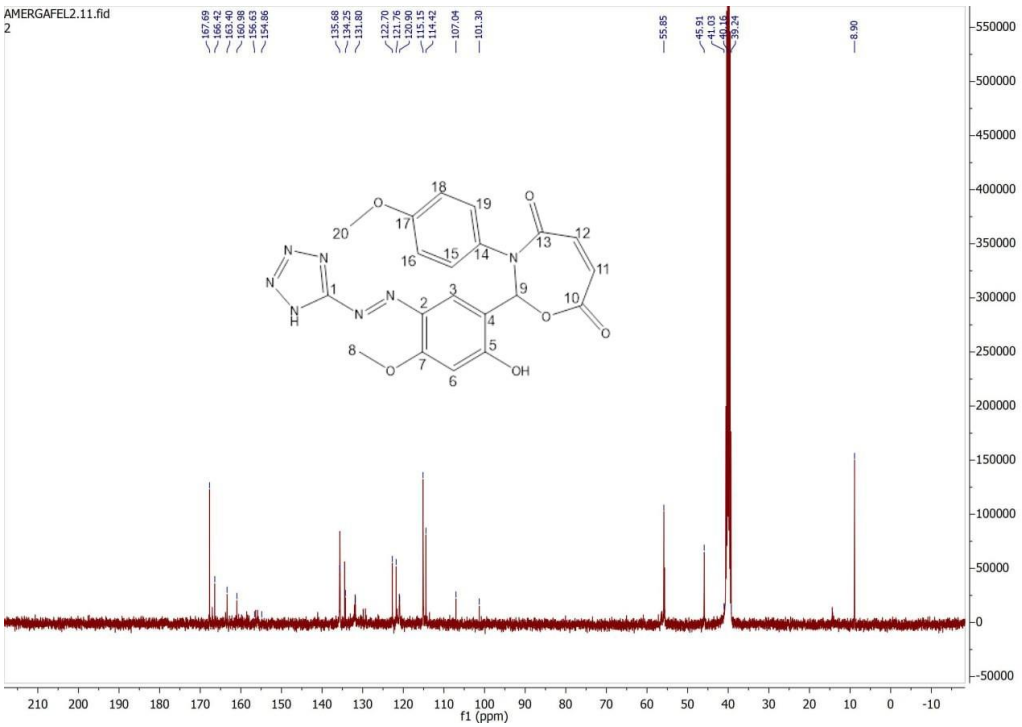


Figure 19: ^{13}C-NMR spectrum of compound (7)

Derivative(8) 3-(5-((1H-tetrazol-5-yl)diazenyl)-2-hydroxy-4-methoxyphenyl)-4-(4-methoxyphenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione

The FT-IR spectrum data for derivative (8) reveal several peaks: 3271 cm^{-1} for the -OH bond, NH bond 3040cm^{-1} for Ar-H bonds, 2908cm^{-1} for -CH bonds in -CH_3 groups, 1720cm^{-1} indicating a -C=O Lacton bond, 1650cm^{-1} indicating a N -C=O Lactam bond, and 1550 cm^{-1} representing a N=N bond,The data can be found in Figure (20).

In the ^{1}H-NMR spectrum data for the derivative (8)the following chemical shifts were observed: a peak at 2.50 ppm (DMSO), a singlet at 13.8 ppm for 1H corresponding to OH group, a singlet at 8.8 ppm for 1H representing NHgroup, a singlet at 1.2 ppm for 1H corresponding to CH group, a multiple at 3.9,3.0 ppm for 6H corresponding to OCH_3 group , 6.5 ppm for 1H corresponding oxazipen ring, and a range of 6.7-7.5 ppm indicating a multiple for 10H corresponding to Ar-H bonds,The data can be found in Figure (21).

The ^{13}C-NMR spectrum data for compound (8) in DMSO revealed several chemical shifts: : 167.7 ppm for C_{17} , 167.6 ppm for C_{10} , 8 ppm for C_9, 159 ppm

for C_1 , 145,155 ppm for $C_{24,}$ C_8 , 135 ppm for C_5 , and a range of 101-132 ppm indicating carbon atoms in aromatic regions,The data can be found in Figure (22).

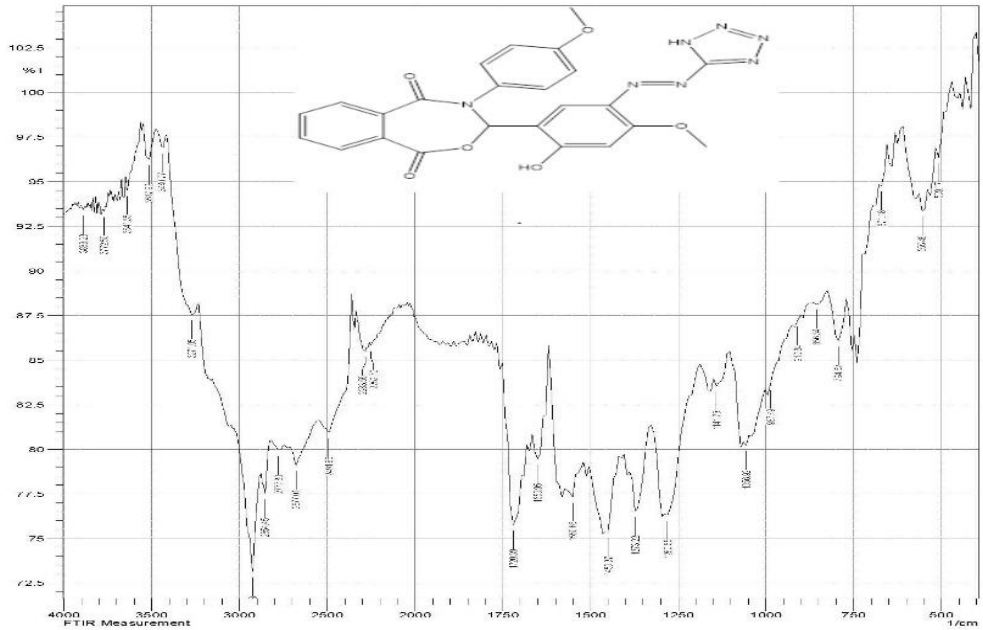


Figure 20: FTIR spectrum of compound (8)

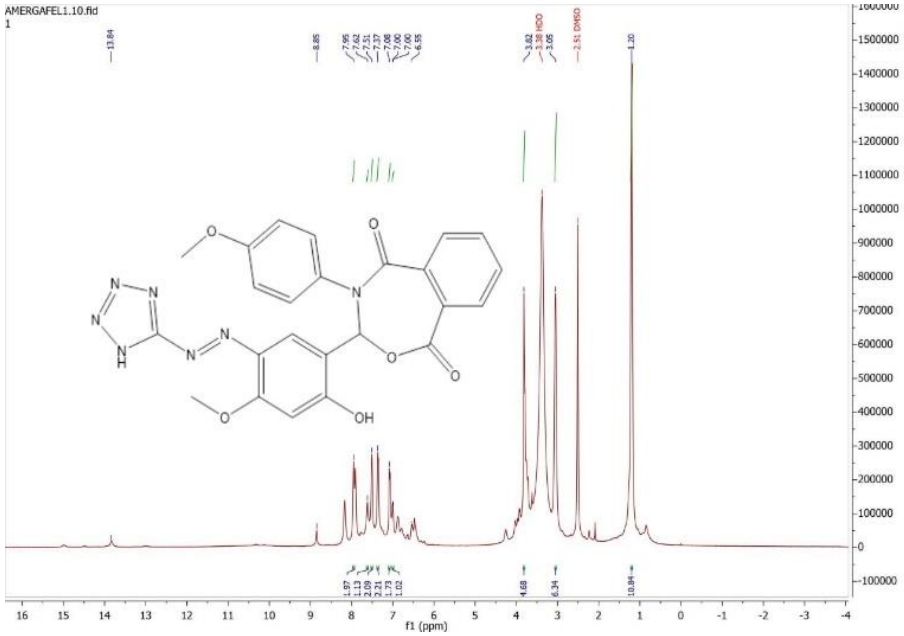


Figure 21: ^{1}H-NMR spectrum of compound (8)

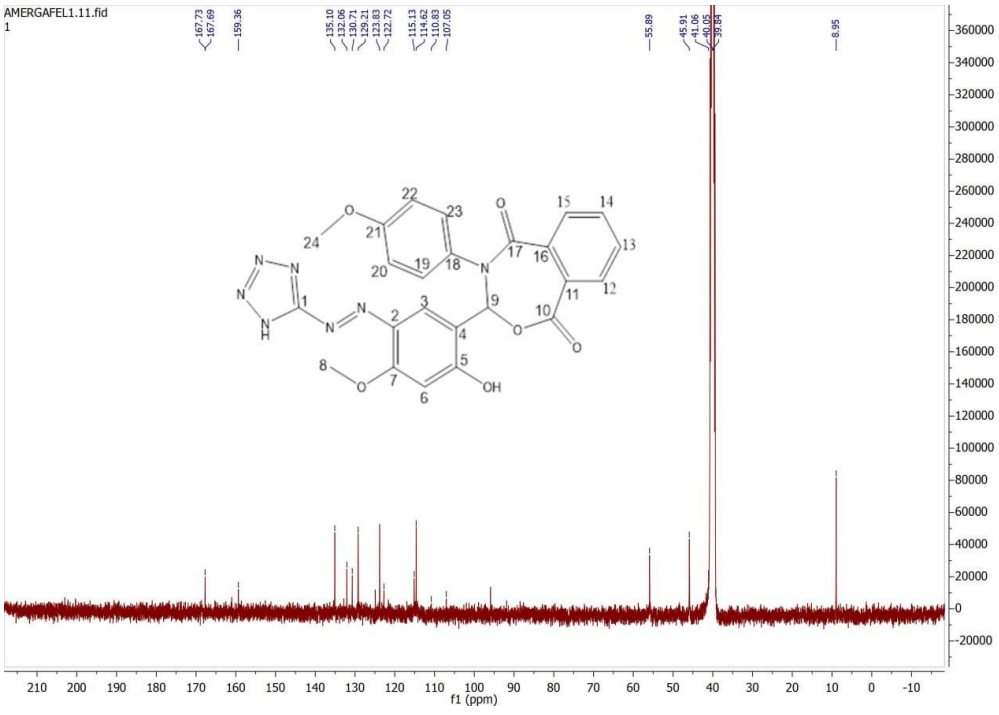


Figure 22: ^{13}C-NMR spectrum of compound (8)

Biological Activity(antibacterial)

The results show that derivatives reduce significant antibacterial effectiveness against bacteria "*staphylococcus aurous* and *Escherichia coli*." the compounds that show moderately activity are (4,7) against (*Escherichia coli*) the antibacterial activity are shown in the Figure (23) and Table (1)

Table 1: Results of the antibacterial activity for 1-6 derivatives

Comp NO	Staph Aureus	Mm	E.Coli	Mm
1	-	2	-	0
2	-	3	+	5
3	-	0	-	3
4	+	5	+	6
5	+	5	-	2
6	-	2	+	5
7	+	5	+	6
8	-	0	-	2

"+= (5-10)mm =slightly active, ++= (11-20)mm moderately +++ = More than 20, good active"

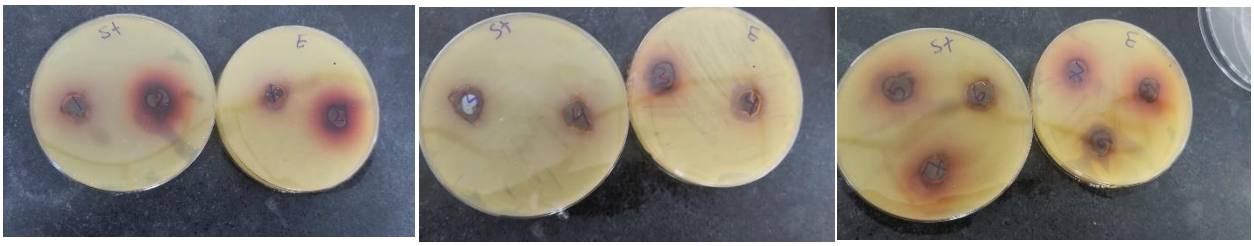


Fig. 23: Biological activity of compound prepared *E. Coli*and *S. Aureus*

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