# Synthesis and Identification of some 1,3-oxazepine derivatives containing *p*-methoxy phenyl and studying their anti bacterial activity

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**Key words**: seven heterocyclic rings,oxazepine,*p*-methoxy phenyl
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**Abstract**

This search includes preparation *p*-methoxy benzoyl hydrazine ($II_2$) from the reaction between *p*-methoxy ethyl benzoate ($I_1$) with hydrazine haydrate with the existence of ethanol absolute , then they were converted to hydrazine derivatives with different substituents ($III_{3-6}$) through the reaction with aromatic benzaldehyde with out using a solvent under thermal fussion . Compounds of 1,3-oxazepine-4,7-dione ($IV_{7-10}$) have also been prepared by ring closer reaction through the treatment of the prepared hydrazones ($III_{3-6}$) and maleic anhydride ,The structure of the synthesis compounds was confirmed by FT-IR and $^1$HNMR spectral data , as the physical means ,the biological activity was studied againt two types of bacteria.

## تحضير وتشخيص بعض مشتقات 1، 3-اوكسازبين الحاوية على بارا ميثوكسي فنيل ودراسة فعاليتها البكتيرية

**بشرى عبد المرتاح خير الله / كلية التربية للعلوم الصرفة / قسم الكيمياء / تكريت ـ العراق**

مفتاح الكلمات:حلقات غير متجانسة سباعية,اوكسازبين,باراميثوكسي فنيل .

**الخلاصة :**

تضمن هذا البحث تحضير بارا-ميثوكسي بنزوايل هيدرازين ($II_2$) من تفاعل بارا- ميثوكسي بنزوات الاثيل ($I_1$) مع الهيدرازين المائي بوجود الايثانول المطلق ، ومن ثم يتم تحويلها إلى مشتقات هيدرازونات مختلفة التعويض ($III_{3-6}$) من خلال التفاعل مع بعض البنزالديهايدات الاروماتية وبدون استخدام مذيب تحت تأثير الصهر الحراري، كما حضرت مركبات 3، 1- اوكسازبين-7، 4- دايون المقابلة ($IV_{7-10}$) بتفاعل غلق الحلقة الناتج من خلال معاملة الهيدرازونات المحضرة ($III_{3-6}$) مع انهيدريد الماليك , ثم شخصت المركبات المحضرة بالطرق الطيفية المتضمنة أطياف الأشعة تحت الحمراء(FT-IR) والرنين النووي المغناطيسي ($^1$HNMR) ، فضلاً عن الطرق الفيزياوية مثل اللون ودرجات الانصهار ، كما تمت دراسة الفعالية البايولوجية لبعض المركبات المحضرة ضد نوعين من البكتريا.

## Introduction:

Hydrazides are from important compounds which are used in the synthesis of different heterocyclic organic compounds from which are thiadiazole [(1)],oxadiazole[(2).] Triazole [(3)] and Schiff bases (hydrozone)[(4)],and study their biological activities against some strains of bacteria and fungi[(5)],and also as Anti-inflammatory, Anti-hypersensitivity[(6)] .

Hydrazones are important compounds used in the organic synthesis of different organic compounds such as heterocyclic compounds[(7)] . Hydrazones have large important in medical and Pharmaceutical, they used as anti cancer, and schezofrenic disease, Meninginitis[(8)]. In industrial hydrazone used in fixing of polymers and started in polymer processes and anti oxidant[(9)], in agriculture hydrazones used as insecticide and anti parasite and against rodents and in improvement of vegetation.of plants[(10)].

Heterocyclic compounds has important and high uses in medical , agricultural and industrial from these heterocyclic that contains nitrogen atom in it's structure , which specialized in good properties as adrugs and insecticides , dyes and polymers. There for some important pharmaceuticals which contains oxazepine used as convulsant with depression and schezofrenic diseases and anti spasmodic, anti throb[(11-13)] .

**Experimental:**

**Materials :**

Melting points were determined by using (Electro Thermal) melting apparatus- Gallenkamp- and remain uncorrected .

The FT-IR spectra were recorded on ashimadzu infra- red spectrophotometer in KBr discs (δ $cm^{-1}$) .

Melting points , boiling points crystallization solvents of percentage yields are listed in a Tables (1).

$^{1}$HNMR spectra (DMSO) were recorded on Bruker 500 MHZ – Avance instrument university of Jordan , faculty of science , Department of Chemistry .

Someof the chemicals used are from (Fluka ,BDHm Aldrich ,Merck) and used directly without purification . .

**Synthesis Processes :**

**1-Preparation of ester *p*-methoxy ethyl benzoate [14] ($I_1$) :**

(0.001mol .0.152g) of *P*-methoxy benzoic acid dissolved in enough amount of absolute ethanol (50mL) and (2mL) of Concentration $H_2SO_4$ added and the mixture was refluxed for (4-5) hrs , cooled to (25) $^{0}$C and then filtered and purified by recrystallization using absolute ethanol .

**2- Preparation of hydrazide 4-methoxy benzohydrazide [15] ($II_2$) :**

(0.01mole ,10mL) of 99% hydrazine hydrate added to (0.001mol ,0.180 g) ester in (50mL)of absolute ethanol ,the mixture of compounds was refluxed for 2hrs after cooling , the precipitate was filtered and washed with some quantity of cooled ethanol , then recrystallized from ethanol

**3-Preparation of hydrazones derivatives of N-benzylidene -4-methoxy benzohydrazide [16] (.$III_{3-6}$):**

(0.001mol) of hydrazide with (0.001mol) of one of benzaldehyde derivatives was mixed and the mixture heated till starting to fused , the time of this operation between (5-10) minutes till the colour of fusion materials fixed , let recrystalized by appropriate solvent .

**4- Preparation of oxazepines derivatives of (S)-N-(4,4-dioxo-2-phenyl-1,3-oxazepin-3(2H,4H,7H)-yl)-4-methoxy benzamide[17]( $IV_{7-10}$):**

(0.001mol) of one derivatives of hydrazones with (0.001mol)of maleic anhydride mixed very good and the mixure heated for (5-10) minutes till fused with changing in colour and naturality of the reaction materials , mixture was left to cool , then washed , dried and then recrystallized from suitable solvent .

**Biological testing :**

Antimicrobial activity of the Compounds ($II_2$, $III_4$, $III_5$,$III_6$,$IV_7$,$IV_8$,$IV_9$, $IV_{10}$) was examined by modifical agar diffusion method[18](Kerby-Bauer method) , using different species l.e (*Escherichia Coli , Staphylococus aureus*) . The zone of inhibition was measuring in mm , the diameter zone of inhibition was measured in mm and are represented by ( –), (+),(++),(±) depending upon the diameter , the antimicrobial screening data are recorded in Table (4) .

The results indicated that some of the assayed compounds have activity against the tested organism , but with different effects of sensitivity , but some of the assayed compounds have no activity against the tested organism .

Using two antibiotics (Gentamycine , Tetracycline) to compare between the different species activity used (reference) (*Escherichia Coli , Staphylococus aureus*) .

**Results and discussions :**

**a. F.T. I.R. Spectra :**

**1-Preparation and identification of ester 4-methoxy ethyl benzoate ($I_1$) :**

Esterification operation of 4-methoxy benzoic acid is applied by using absolute ethanol in the

presence of concentration $H_2SO_4$ by reflux .

The preparing ester was identified by FT-IR Spectral data shouled absorption in the range of ($1730cm^{-1}$) belong to stretching of carbonyl group , the band of symmetric and asymmetric stretching for (C-H) aliphatic group at ($2920,2889cm^{-1}$) and appearing of band at ($1250cm^{-1}$) belong to stretching band of alone (C-O),and disappearing of stretching band of (O-H) group which belong to carboxylic acid and increasing the value of stretching for carbonyl group in ester comparing with it's value in carboxylic acid[19].

**2- Preparation and identification of hydrazide *p*-methoxy benzohydrazide ($II_2$):**

This compound was prepared by reaction of ester with hydrazine hydrate in absolute ethanol using reflux .

The prepared hydrazide was identified by IR spectra , the band seen at ($1650cm^{-1}$) is belongs to amide carbonyl group stretching , so that absorption of carbonyl group shifted to low vibration in comparing with absorption of ester carbonyl group and this is due to the presence of resonance in case of hydrazide which work to minimize the properties of double bond (C=O) , and stretching bands observed at ($3350-3188cm^{-1}$) which belong to (N-H) group stretching (Amines and amide) . also the stretching of (=C-H) aromatic group in the region ($3075cm^{-1}$) and bands in the region ($1504-1573cm^{-1}$) belongs to (C=C) stretching in the aromatic ring[20] .

**3- Preparation and identification of hydrazone derivatives of N-benzylidene-4-methoxy benzohydrazide ($III_{3-6}$) :**

These derivatives were prepared by the fusion method without using solvent , so that a mixture of hydrazide and one of benzaldehyde derivative were fused together .

The prepared compounds are identified by IR spectral , so that absorption bands in the region ($1600-1606cm^{-1}$) belongs to (C=N) stretching band and absorption bands in the region ($1637-2649cm^{-1}$) which belong to (C=O) stretching band with observed two absorption bands in the region ($1457-1544cm^{-1}$) and ($1548-1585cm^{-1}$) belong to (C=C) aromatic stretching band , and also band observed for (C-H) aromatic stretching band in the region ($3053-3067cm^{-1}$)[20] as listed in table (2) Figure (1) .

**4- Preparation and identification of oxazepines derivatives of (S) –N-(4,4-dioxo-2-Phenyl-1,3-Oxazepim-3(2H.4H,7H)-Yl)-4-methoxy benzamide ($IV_{7-10}$) :** These compounds were prepared by fusion method without solvent (fusion reaction) , a mixture of one of hydrazones derivatives with maleic anhydride .

The prepared compounds were identified by IR spectra , it is obvious that the absorption bands in the range of ($1165-1180cm^{-1}$) which belongs to (C-N) stretching bond , and other in the rang ($1651-1694cm^{-1}$) belong to (C=O) stretching bands in addition to two bands of absorption in the region ($1512-1546cm^{-1}$) , ($1554-1606cm^{-1}$) belong to (C=C) aromatic stretching band with observed absorption band in the region ($1255-1289cm^{-1}$) belong to (C-O) stretching, as listed in table (3) diagrams (2,3).

**b. $^1$H.N.M.R.spectra**:

The ($^1$HNMR) spectra of the compounds prepared were studying with using DMSO-$d_6$ solvent and TMS (Tetramethylsilane) and using standard δ(ppm):

**1-Compound ($II_2$)**

Singlet signal of the compound observed at (3.35 ppm) with integration corresponds to three protons due to methoxy group (O-$CH_3$)with singlet signal observed at (4.4ppm) with integration corresponds to two protons which belongs to ($NH_2$), also two doublet signals the first one (6.79-6.99ppm), the second one (7.80-7.82ppm) to every one integration corresponds to with two protons the first belong to proton of *ortho* position of (C=O), the 2$^{nd}$ one for *ortho* methoxy proton and that is due to high electro negativity of oxygen atom[21], also singlet signal at (9.6ppm) observed which opposite one proton due to secondary amine (NH) as in figure (4).

**2-Compound.($III_3$):**

Singlet signal of the compound observed at (3.82ppm) with integration corresponds to three protons due to methyl group (O-$CH_3$), with two doublet signal one of them at (7.08-7.06ppm) and the second at (7.53-7.51ppm) with integration corresponds to two protons and this is due to the protons of the 1-4-phenyl ring which is connected to chlorine atom , also two doublet signal the first one (7.76-7.47ppm) and the second one at (7.91-7.93ppm) every one with integration corresponds to two protons due to phenyl ring which connected with methoxy group in addition to appear another singlet signal at (8.49ppm) with integration corresponds to one proton belong to imine group (-N=C-H) and another singlet signal at (11.80ppm) with integration corresponds to one proton also belong to amide group (-CO-NH) as in the figure (5) .

**3-Compound($III_4$):**

. Singlet signal of the compound observed at (2.9ppm)with integration corresponds to six protons due to N($CH_3$)$_2$ group with appearance another singlet signal at (3.8ppm) with integration corresponds to three protons related to (O-$CH_3$) group, also two secondary signals the first one at (6.77-6.75ppm), the second at (7.06-7.04ppm) every one of them with integration corresponds to two protons due to 1-4-substituted phenyl ring which connected with nitrogen atom , also two secondary signalappear in the region (7.55-7.53ppm) and (7.91-7.89ppm) belong to protons of aromatic substituted ring with methoxy group , everyone with integration corresponds to two protons and thin due to high electrical negativity of oxygen comparing with nitrogen atom in addition to appear of singlet signal at (8.31ppm) with integration corresponds to one proton belong to immine group and another singlet signal at (11.43ppm) with integration corresponds to one proton also due to (NH) group .

**4-Compound ($IV_9$) :**

Singlet signal of the compound at (3.8ppm) with integration corresponds to three protons belong to methyl group with appearing one secondary signal for (H-C=C-H) group at (6.37-6.32ppm) corresponds to proton in addition to appear multiple signals in the range of (7.92-7.08ppm) belong to the protons of the two aromatic rings also singlet signal appear (8.49ppm) with integration corresponds to one proton belong to (N-CH-O) group , also two single signals for hydroxyl group every one of them corresponds to one proton the first appear at (9.9ppm) due to *P*-hydroxyl group and the second at (11.8ppm) with integration corresponds to one proton for amine group, figure (6).

**5-Compound.($IV_{10}$):**

Singlet signal of the compound at (3.9ppm) with integration corresponds to three protons belongs to methyl group with appearing of doublet signals at (7.08-7.06ppm) belong to (HC=CH) group with integration corresponds to two protons in addition to multiple signals in arrange of (7.93-7.ppm) belong to (Ar-C-H) protons , also two singlet signals appears , the first at (8.43ppm) and the second at (11.8ppm) every one of them with integration corresponds to one proton and belong to (N-CH-O) and (N-H) respectively figure (7).

**Antibacterial activity of the compounds prepared :**

In the figure (7) some of the prepared compounds shows low activity of inhibition against negative *Escherichia Coli* , but we see high activity inhibition against positive *Staphylococcus aureus* , so that the compound ($IV_8$) have high activity of inhibition and high selectivity between the prepared compounds against *staphylococcus aureus*.

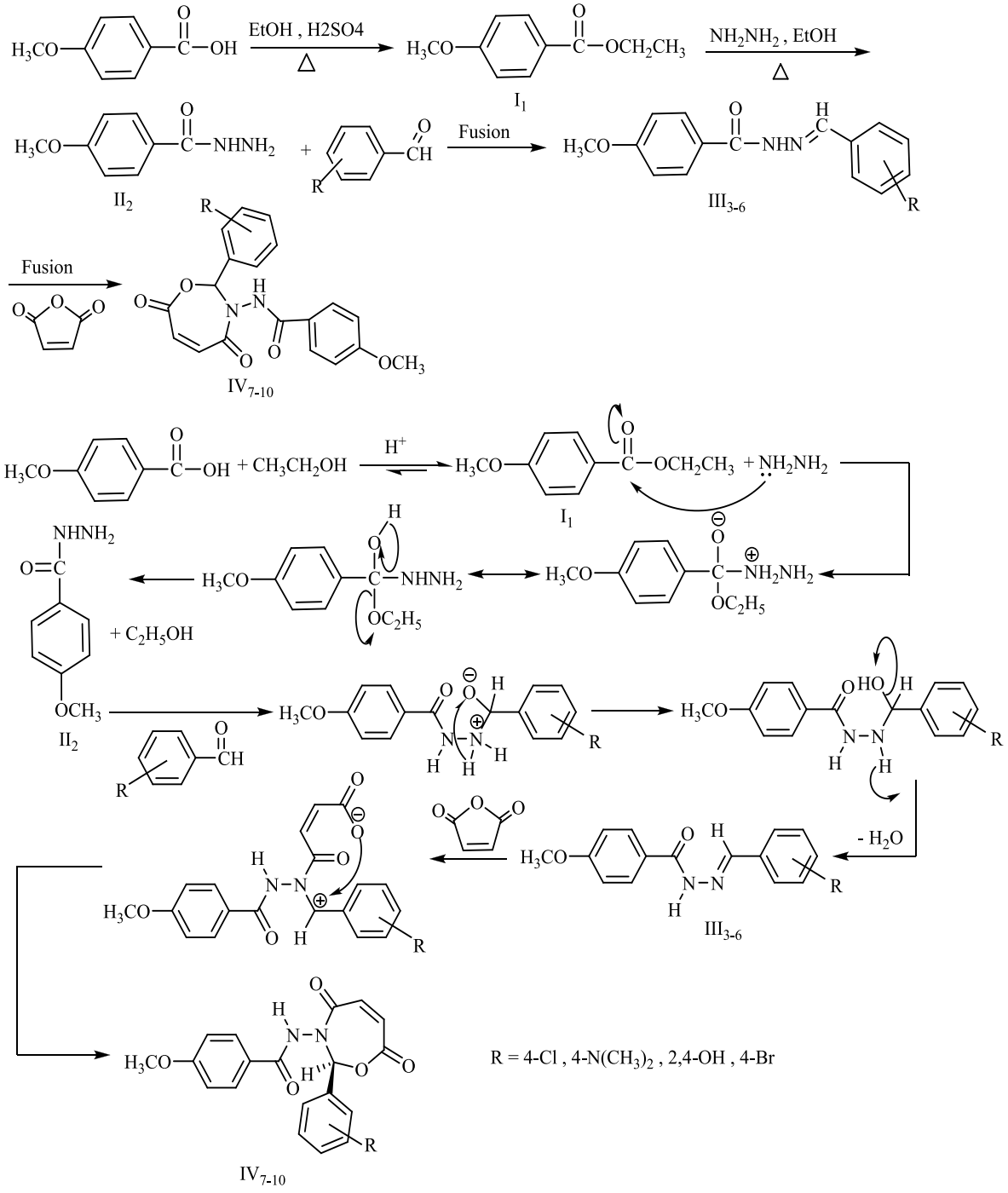

EtOH , H2SO4
NH2NH2 , EtOH
Fusion
Fusion
H+
+ C2H5OH
- H2O
R = 4-Cl , 4-N(CH3)2 , 2,4-OH , 4-Br

Table (1) :Some Physical properties of derivative of the synthesized compounds[1-10]

| Comp. No. | R | Molecular formula | Color | b.P($^0$C) | Yield (%) | Recryst. Solvent |
|---|---|---|---|---|---|---|
| $I_1$ | 4-$CH_3$OPh | $C_{10}H_{12}O_3$ | White | 263 | 70 | Ethanol |
| $II_2$ | 4-$CH_3$OPh | $C_8H_{10}N_2O_2$ | white | 135-137 | 64 | Ethanol |
| $III_3$ | 4-Cl | $C_{15}H_{13}N_2O_2Cl$ | Yellowish green | 190-192 | 63 | Ethanol |
| $III_4$ | 4-N($CH_3$)$_2$ | $C_{17}H_{19}N_3O_2$ | Orange | 226-227 | 90 | Ethanol |
| $III_5$ | 2,4-OH | $C_{15}H_{14}N_2O_4$ | Yellowish white | 279-280 | 83 | Methanol |
| $III_6$ | 4-Br | $C_{15}H_{13}N_2O_2Br$ | pale Yellowish | 168-170 | 87 | Methanol |
| $IV_7$ | 4-Cl | $C_{19}H_{15}N_2O_5Cl$ | Pale Yellow | 218-220 | 66 | Ethanol |
| $IV_8$ | 4-N($CH_3$)$_2$ | $C_{21}H_{21}N_3O_5$ | Brown | 198-200 | 52 | Dioxane |
| $IV_9$ | 2,4- OH | $C_{19}H_{17}N_2O_7$ | Dark Yellow | 285 dec. | 60 | Dioxane |
| $IV_{10}$ | 4-Br | $C_{19}H_{15}N_2O_5Br$ | white | 206-208 | 71 | Ethanol |

Table (2) : FT-IR spectral data for the synthesized compounds[3-6 ]

| Comp. No. | R | ν C=O | ν(C-H)Ar | ν(C=C)Ar | νC-N | νC=N | Others |
|---|---|---|---|---|---|---|---|
| $III_3$ | 4-Cl | 1637 | 3061 | 1550 1536 | 1176 | 1602 | νC-Cl 759 |
| $III_4$ | 4-N($CH_3$)$_2$ | 1645 | 3052 | 1548- 1457 | 1176 | 1600 | ν($CH_3$)$_2$ 2941,2867 |
| $III_5$ | 2,4- OH | 1649 | 3060 | 1585- 1544 | 1178 | 1606 | νOH 3373 |
| $III_6$ | 4-Br | 1639 | 3067 | 1550- 1485 | 1142 | 1601 | νC –Br611 |

Table (3) : FT-IR spectral data for the synthesized compounds[7-10 ]

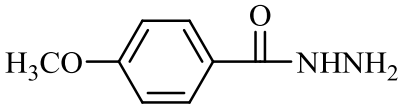
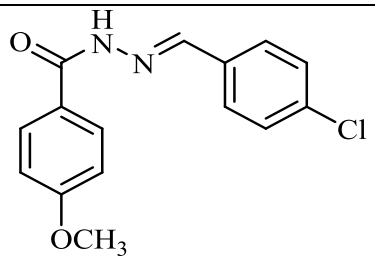
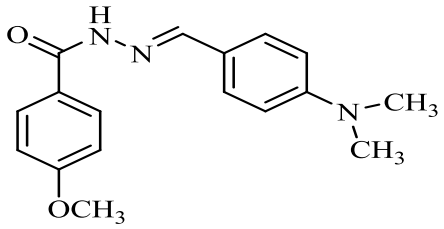
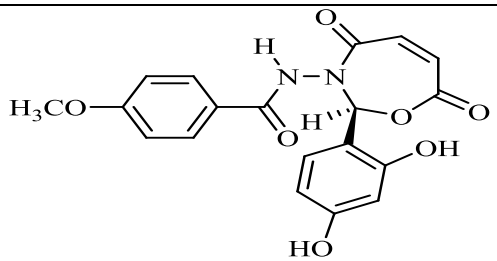
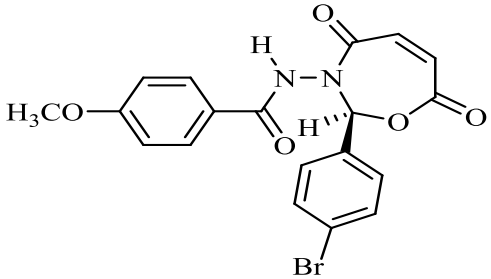
| Comp. No. | R | νC-O | ν C=O | ν(C-H)Ar | ν(C=C)Ar | νC-N | Others |
|---|---|---|---|---|---|---|---|
| $IV_7$ | 4-Cl | 1284 | 1664 | 3070 | 1606- 1543 | 1178 | νC-Cl761 |
| $IV_8$ | 4-N($CH_3$)$_2$ | 1289 | 1694 | 3103 | 1590- 1531 | 1177 | ν($CH_3$)$_2$ 2915,2820 |
| $IV_9$ | 2,4- OH | 1255 | 1686 | 3095 | 1554- 1512 | 1165 | νOH 3402 |
| $IV_{10}$ | 4-Br | 1284 | 1651 | 3093 | 1589- 1546 | 1180 | νC –Br613 |

Table.(4) Biological activity for some prepared compound

| Comp. No. | R | *Escherichia coli* | *Staphylococcus aureus* |
|---|---|---|---|
| $II_1$ | 4- $OCH_3$ | ± | ± |
| $III_4$ | 4-$N(CH_3)_2$ | ± | - |
| $III_5$ | 2,4-OH | + | + |
| $III_6$ | 4-Br | - | + |
| $IV_7$ | 4-Cl | + | - |
| $IV_8$ | 4-$N(CH_3)_2$ | - | ++ |
| $IV_9$ | 2,4-OH | + | + |
| $IV_{10}$ | 4-Br | - | + |

The symbols : (-) no inhibition , (±) = 5-9mm , (+) =10-14mm , (++)=15-22 mm

Table (5) : $^1$HNMR for some prepared compounds

| Comp. No. | Structure | $^1$HNMR Spectrum ،δppm,500$MH_z$ |
|---|---|---|
| $II_2$ |  | 3.35ppm(S,3H,$OCH_3$),4.4ppm(dd,2H,$NH_2$),6.99-6.97(dd,2H,Ar-H,----),7.82-780(dd,2H,Ar-H-$OCH_3$),9.6(S,1H,NH). |
| $III_3$ |  | 3.81ppm(2,3H,$OCH_3$),7.53-7.06ppm(dd,4H,Ar-H-Cl),7.93-7.74(dd,4H,Ar-H,-$OCH_3$),8.9(S,1H,N=CH),11.80 (S,1H,NH). |
| $III_4$ |  | 2.9ppm(S,6H,N($CH_3$)$_2$),3.8ppm(S,3H,$OCH_3$),7.06-6.75(dd,4H,Ar-H,N($CH_3$)$_2$,),7.91-753(dd,4H,Ar-H-$OCH_3$),8.31(S,1H,N=CH),11.43(S,1H,NH). |
| $IV_9$ |  | 3.84ppm(S,1H,$OCH_3$),6.37-6.32(dd,2H,HC=CH),7.92-7.08(m,8H,Ar-H),8.50(S,1H,-O-CH-N),9.9(S,1H,p-OH),11.5(S,1H,m-OH),11.81(S,1H,NH). |
| $IV_{10}$ |  | 3.9ppm(S,3H,$OCH_3$),7.08-7.06ppm(dd,2H,HC=CH),7.93-7.67(m,8H,Ar-H),8.43(S,1H,-O-CH-N),11.5(S,1H,m-OH),11.81(S,1H,NH). |

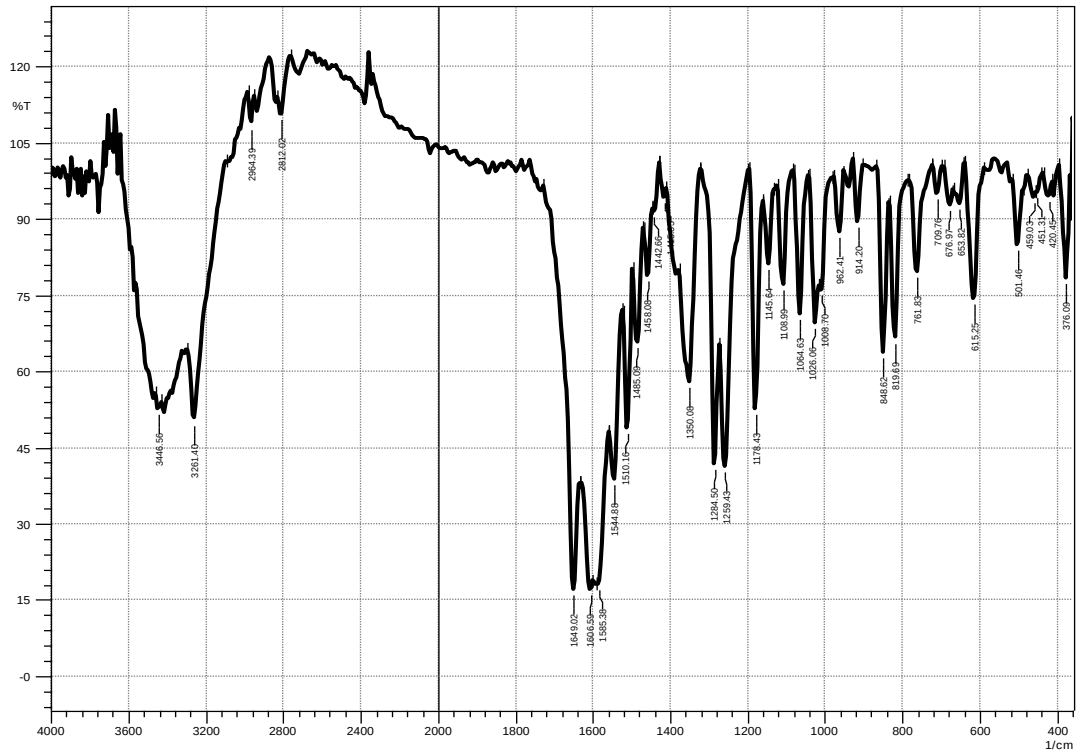



Figure.(1) IR spectral for compound($III_5$)

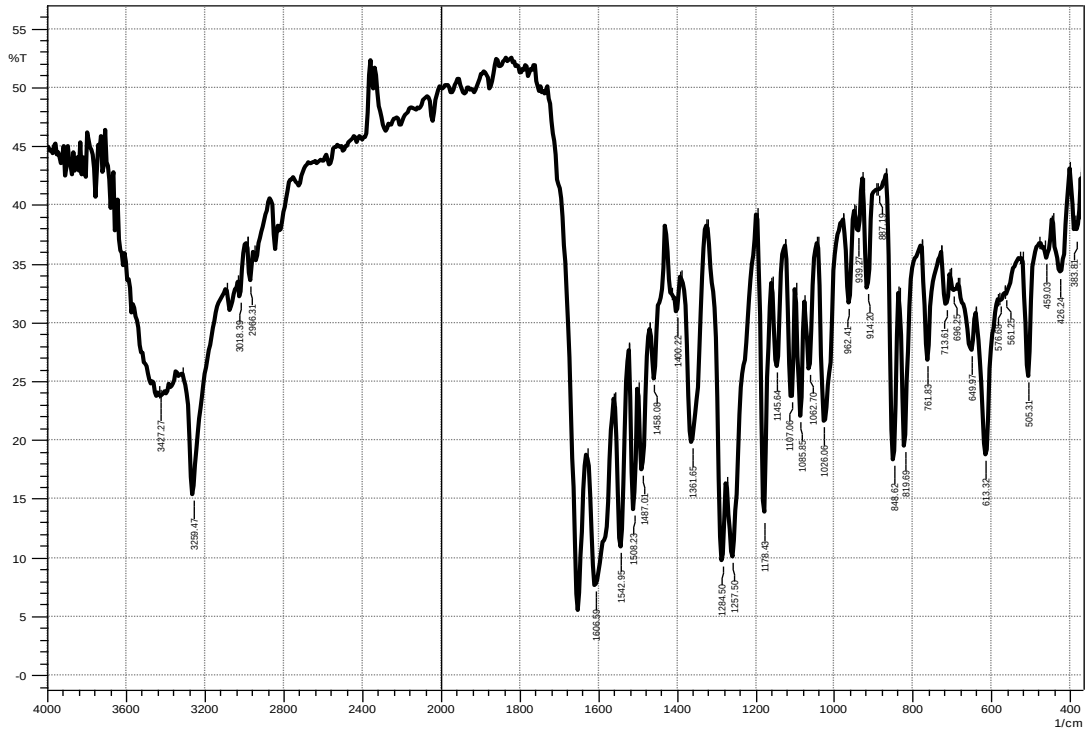



Figure.(2) IR spectral for compound ($IV_7$)

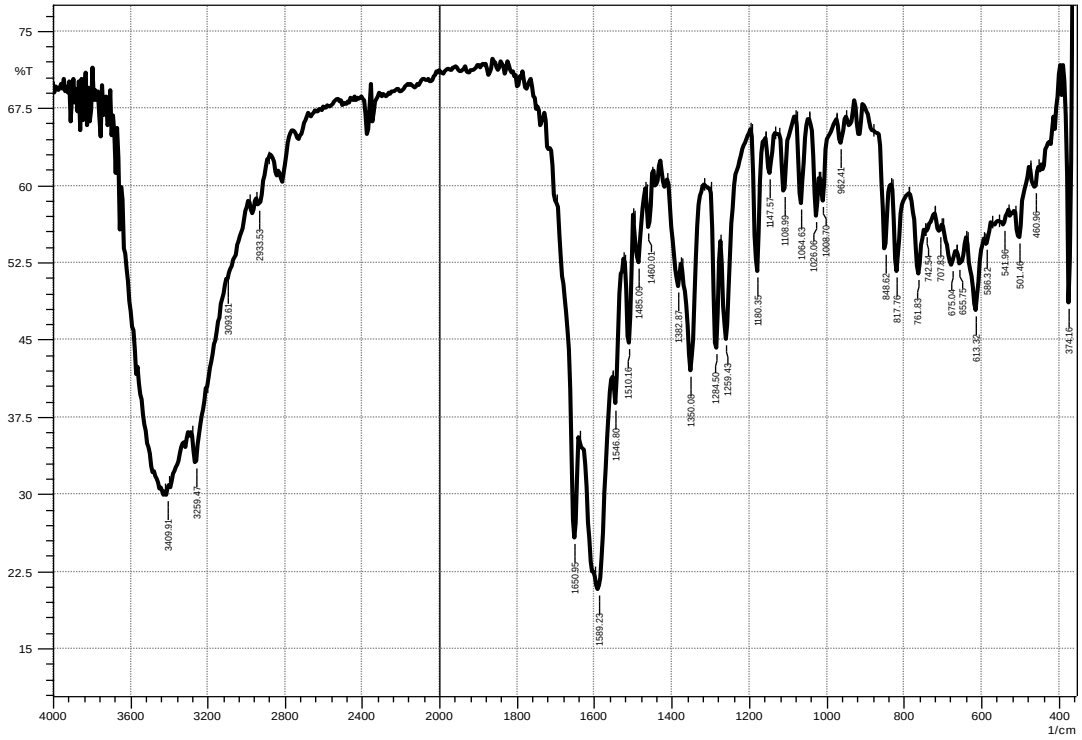



Figure.(3) IR spectral for compound ($IV_{10}$)

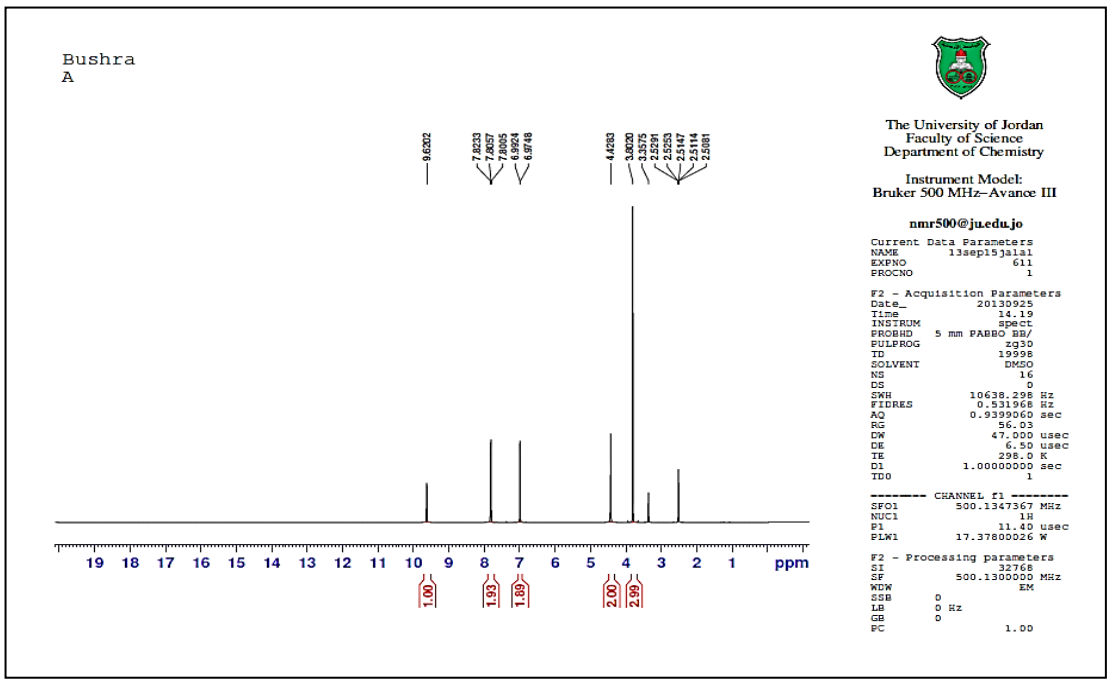



Figure.(4) $^{1}$HNMR for compound($II_2$)

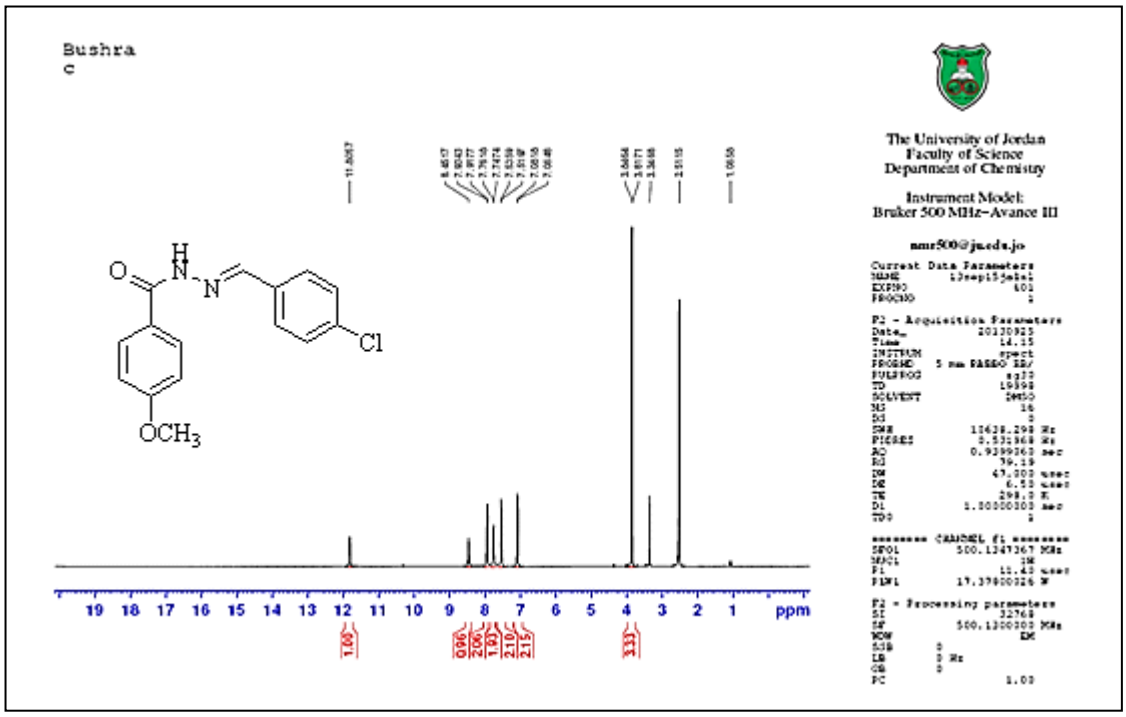



Figure.(5) $^{1}$HNMR for compound($III_3$)

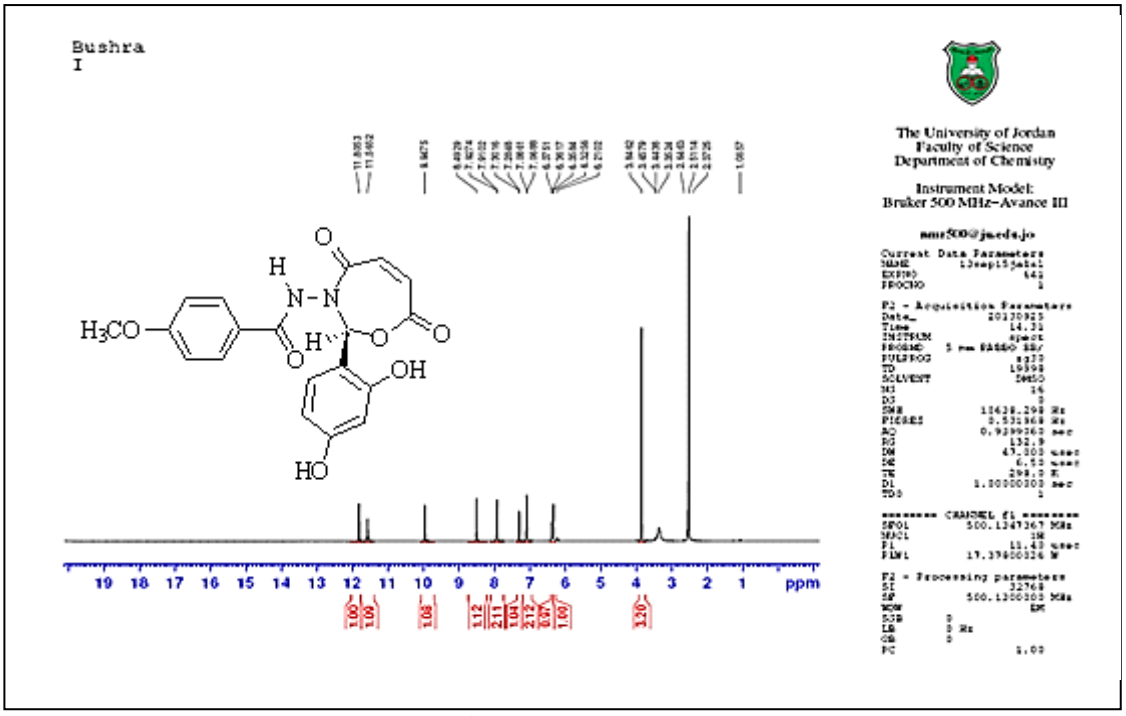



Figure.(6) $^{1}$HNMR for compound($IV_9$)

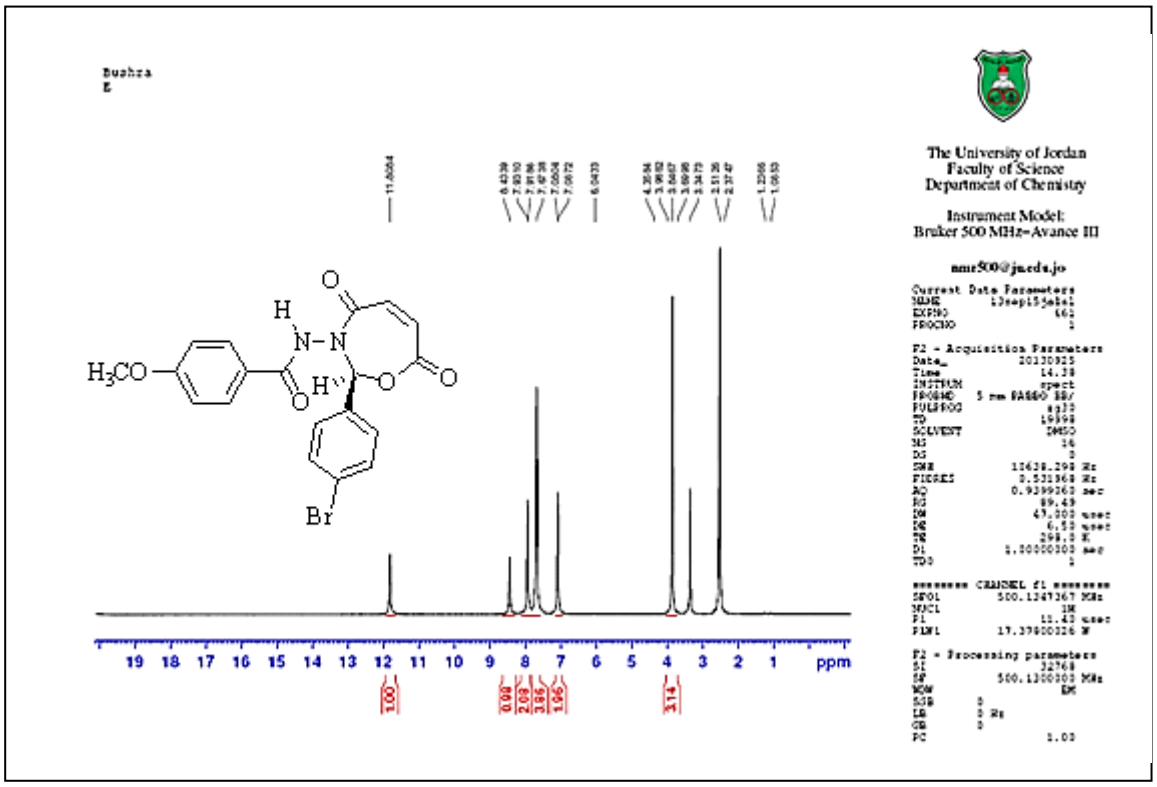



Figure.(7) $^{1}$HNMR for compound($IV_{10}$)

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