

Synthesis, Characterization and Investigation the Antibacterial Activity of New Heterocyclic Compounds Derived From 4-(4'-methoxy benzoyloxy) benzaldehydethiosemicarbazone

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Abstract

4-Thiazolidinone were synthesized by three steps,the reaction of ansoyl chloride with 4-hydroxy benzaldehyde to give 4-(4'-methoxy benzoyloxy) benzaldehyde[I].The reaction of later compound with thiosemicarbazideled to formation thiosemicarbazon [II] and the reacted thiosemicarbazone with chloro acetic acid in $\text{CH}_3\text{CO}_2\text{Na}$ medium to yield 4- thiazelidinone compound[III].The 4-thiazolidinone [III]was used as a key intermediates to synthesis new compounds, compound[IV] synthesized from the reaction [III] with acetic anhydride, while the reaction of compound [III] with amines to yield azo compound[V]_{a,b,c}. The azo compound reacted with benzoyl chloride or anisole chloride in basic medium to get a new esters compound[VI]_{a,b}. Also, synthesis oxazepine compound[VII],[VIII] and [IX]_{a,b,c} from heating schiff bases [III],[IV][V]_{a,b,c} with phthalic anhydride in dry benzene in cyclo-addition reaction. The compounds were characterized by FTIR and ¹HNMR (of some of them), the synthesized compounds have been screened for their six species of bacteria were used in this study as tested organisms. These are *pseudomonas aeruginosa*, *klebseilla*, *providencea*, *Serratiamarcescens*(Gram negative) and *staphylococcus epidermidis*, *Bacillus*(Gram positive).

Keywords: thiazolidinone, Schiff bass, azo compound, 1,3-oxazepine and antibacterial activity.

Introduction

1,3-Thiazolidin-4-one is five heterocyclic system that has two heteroatoms sulfur and nitrogen at position 1,3 respectively, beside a carbonyl group at position 4 [1]. Thiazolidin-4-ones are usually synthesized from thiourea, thiosemicarbazides or azomethine group [2]. Thiazolidine ring is of considerable interest as it is a structure in various synthetic pharmaceuticals have a broad spectrum of biological activities [3-5]. Oxazepine is unsaturated non-homologous seven membered heterocyclic (containing oxygen at position 1 and nitrogen at position 3 in addition to the five carbon atoms. It is prepared by the pericyclic cycloaddition reaction of schiff bases with a suitable cyclic anhydride carboxylic acid) [6,7]. Oxazepine derivatives was found to exhibit a good variety of biological activities [8] like, anticancer [9], antifungal [10], antibacterial [11] and anticorrosion [12]. Azo linkage is considered biological active moiety [13], The most important method for preparing azo compounds via the coupling reaction between diazonium salts and phenols [14].

The aim of this work is synthesis of some new oxazepine and thiazolidin-4-ones derivatives containing the biologically active azo group, as attempt for increasing the biological activity and its variety. [15]

Experimental

Chemicals: All chemicals were supplied by fluka, GCC, merk and Aldrich chemicals Co. and used as received.

Techniques

FTIR spectra were recorded by using KBr disc on a Shimadzo (Ir prestige -21) ¹H NMR spectra were examined by company : Bruker, model: ultra shield 300 MHz, origin : Switzerland and are reported in DMSO as a solvent, ppm(δ), uses TMS as an internal standard were made at chemistry department, Al-Bayt University, Jordan. Hot-Stage, Gallen Kamp melting point apparatus was used for determined uncorrected melting points. **Synthesis**

New compounds are synthesized according to scheme 1.

Preparation of [4-(4'-methoxy benzyloxy) benzaldehyde] [I]

Ansoyl chloride (0.17g, 0.001mol) was added to a stirred solution of 4-hydroxy benzaldehyde (0.12g, 0.001mol), dry pyridine (1mL) in dimethyl formamide (DMF) (10 mL) at (5-10°C). Stirring was continued for 3hrs (at the same temperature). The resulting mixture was poured onto 20 mL of 10% hydrochloric acid. The precipitate was filtered, washed with solution of 10% NaHCO₃ and water for several times, dried and recrystallized from ethanol. m.p 76-78°C, yield 86%.

Synthesis of 4-(4'-methoxybenzyloxy) benzaldehyde thiosemicarbazone [II]

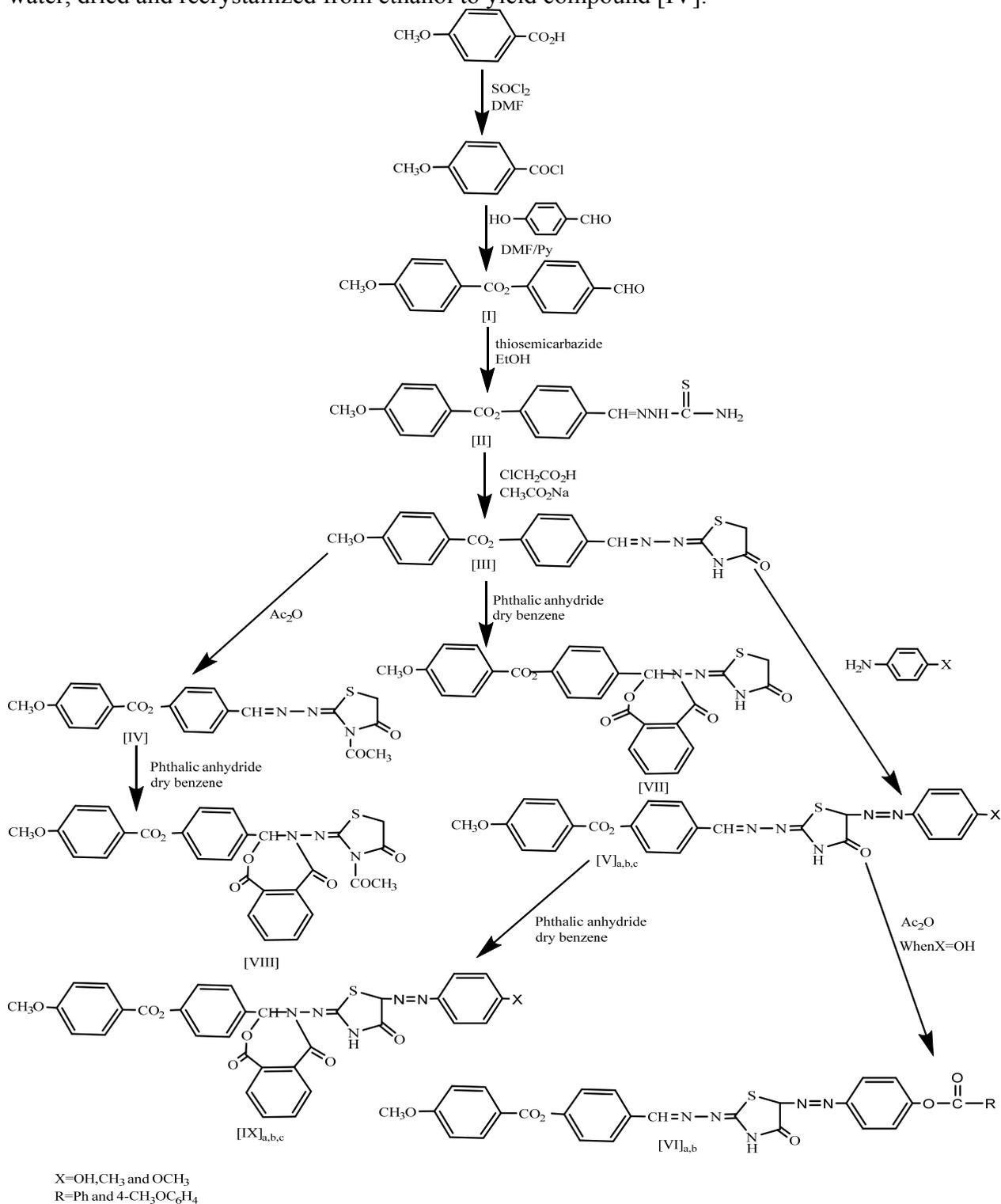
A mixture of a suitable aromatic aldehyde [I] (0.256g, 0.001mole), thiosemicarbazide (0.091g, 0.001mole) in ethanol (5mL) was heated under reflux for 4hrs, then cooled. The off white solid formed was filtered, dried and recrystallized from ethanol to give compound [II]. m.p 200-202°C, yield 97%.

Synthesis of 4-(((4-oxothiazolidin-2-ylidene)hydrazono)methyl)phenyl 4-methoxybenzoate [III]

A mixture of thiosemicarbazone [II] (0.01mol), chloroacetic acid (0.01mol, 0.945g) and fused sodium acetate (0.03mol, 2.46g) in absolute ethanol (10 mL) was heated for 6 hrs. The mixture of reaction was poured onto (100 mL) cold water and the precipitate was filtered, washed with water (for many times), recrystallized by ethanol.

Synthesis of 4-(((3-acetyl-4-oxothiazolidin-2-ylidene)hydrazono)methyl)phenyl 4-methoxybenzoate[IV]

A solution of compound [III] (3.67g ,0.01mole) in acetic anhydride (25mL) was refluxed for 4hrs, afterward cooled and poured onto ice-water. The resulting was filtered off, washed with water, dried and recrystallized from ethanol to yield compound [IV].



Scheme (1)

Synthesis of azo derivatives [V]_{a, b, c}

This compound was prepared by two main steps:

A-Azofization: Into flask was placed in the ice bath (2.1g, 0.02mole) of compound amine dissolved in 12mL of concentrated hydrochloric acid (50%) and the mixture was cooled at (0-5) °C then added 8mL of a solution contains sodium nitrite(20%) drop by drop to the reaction , that led to formation of diazonium salt in solution.

B-Coupling :A mixture of solution (3.67g, 0.01 mole) from compound [III] in 50mL of aqueous solution NaOH (10%) was put into a 250 mL two necked round bottom flask and fitted with thermometer and a dropping funnel and placed in ice bath to be cooled at(0-5) °C. The cold diazonium solution (step A) was added to the solution (of step B) drop by drop with stirring during two hrs. At the same temperature, we add a solution of HCl 30% to the mixture to form a precipitated compound, which was filtered, washed by cold water and re-crystallized from chloroform.

Synthesis of 4-(((5-((4-(benzoyloxy)phenyl)diazenyl)-4-oxothiazolidin-2-ylidene)hydrazono)methyl)phenyl 4-methoxybenzoate and 4-((2-((4-(4-methoxybenzoyloxy)benzylidene)hydrazono)-4-oxothiazolidin-5-yl)diazenyl)phenyl 4-methoxybenzoate [VI]_{a, b}

To a stirred solution of compound [V]_c (0.47g, 0.001mol), triethylamine(0.2g,0.002mol)in dried mixture of (5mL DMF:10Ml THF), was added drop wise carboxylic acid chloride(0.001mol) at(0-4) °C. After the addition had been completed the resulting suspension was stirred at the same temperature for 3hrs. The triethylaminehydrochloride salt was precipitate. It was filtered and the filtrate was poured with stirring into 100mL ice-water, then resulting solid was filtered and recrystallized from ethanol.

Synthesis of 1,3-oxazepine derivatives [VII],[VIII] and [IX]_{a, b, c}

A mixture of compound [III],[IV] or [V]_{a, b, c} (0.48g, 0.001mole) and phthalic acid anhydrides (0.14g, 0.001mol) in dry benzene (3mL) was heating for 6 hrs. The solvent was removed and the resulting colored crystalline solid recrystallized from ethanol. The physical properties for the synthesized compounds are given in Table1.

Determination of antibacterial activity

Antibacterial activity were detected by agar well diffusion method [16] . Fresh bacterial cultures suspension equivalent of 0.5 tube McFarland turbidity standards (10⁸cfu/ml) were spread on Muller-Hinton agar plates using sterile cotton swabs. Wells of 6mm diameter were cut in solidified agar and filled with 50µl Of each concentration. The dimethyl sulfoxide was also used as control. The plates were incubated aerobically at 37 ° C for 24 hours, then inhibition zones diameter (mm) around wells were measured by rule. All testes were applied as double.

Results and Discussion

4-(4'-methoxybenzoyloxy) benzaldehyde [I] was prepared from reaction of 4-n-alkoxybenzoyl chloride with 4-hydroxy benzaldehyde in dry pyridine and DMF. The FT-IR spectrum of compound [I] showed many bands in the region (2981-2950) cm⁻¹ due to νC-H aliphatic stretching, two sharp bands of carbonyl stretching (of ester and aldehyde groups) around 1728 cm⁻¹ and 1685 cm⁻¹, respectively, besides two stretching bands at 2846 cm⁻¹ and 2744 cm⁻¹ due to CH aldehydic. Finally, a sharp peak around 1269 cm⁻¹ is attributed of ν C-O stretching of ether (OR) group.

Thiosemicarbazone [II] is synthesized by condensation of 4-(4'-methoxy benzoyloxy) benzaldehyde [I] and thiosemicarbazide in ethanol under reflux.

FTIR absorption-spectrum of this compound [II] exhibited the disappearance of aldehydic (C=O) and CH absorption bands together with appearance of new absorption stretching band at 1695 cm^{-1} which is assigned to $\nu\text{C}=\text{N}$ stretching [17]. The spectrum showed many peaks in the region $3441\text{-}3088\text{ cm}^{-1}$ which could be attributed to asym. and sym. stretching vibration of NH and NH_2 groups [18] besides to two sharp peaks at 1732 cm^{-1} and 1195 cm^{-1} due to ester and thion bonds, respectively.

Compound [III] was synthesized from the condensation of compound [II] with chloroacetic acid (in presence of sodium acetate). The FTIR spectrum showed the appearance of new stretching band due to a carbonyl group of thiazolidinone at 1690 cm^{-1} [19] and stretching band appears at 698 cm^{-1} due to C-S group. While $^1\text{H NMR}$ spectrum (in DMSO-d as a solvent), Figure (1) showed the following signals: singlet signal at δ (12.28) ppm [20] for one proton of CO- NH (amide) group. Many signals at δ (7.36-8.68) ppm that could be assigned to the eight aromatic protons, but signal at δ (8.1) ppm for a proton of imine, also a singlet signal at δ (3.59) ppm [21] for two protons at C-5 thiazolidinone ring. Finally a singlet signal appeared at δ (4.14) ppm for three protons of OCH_3 group.

The reaction of thiazolidinone [III] with acetic anhydride yielded a new compound [IV]. This compound is identified by FTIR spectroscopy. The FTIR spectrum of compound [IV] showed disappearance absorption band due to NH group and the appearance of a new band at 1699 cm^{-1} due to stretching vibration carbonyl for amide group (COCH_3).

While, the compounds $[\text{V}]_{\text{a,b,c}}$ were synthesized by the reaction of one mole of compound [III] with two moles of amine with HNO_2 at $0\text{-}4\text{ }^\circ\text{C}$ to get diazonium salt, The FTIR spectrum of this compounds $[\text{V}]_{\text{a,b,c}}$ showed a stretching band at $(1546\text{-}1504)\text{ cm}^{-1}$ [22] due to the N=N group, as in Figure (2) of compound $[\text{V}]_{\text{c}}$.

$^1\text{H NMR}$ spectrum of compound $[\text{V}]_{\text{b}}$ (in DMSO) Figure (3) showed the following characteristics chemical shifts: a singlet signal at δ (3.99) ppm one protons at C-5 thiazolidinone ring, also a singlet signal at δ (4.12) ppm for three protons of OCH_3 group and signals in the region δ (7.2-8.3) ppm that due to the eight aromatic protons, another singlet signal appeared at δ (8.35) ppm for a proton of imine, Also a singlet was observed at δ (12.28) ppm for one proton of CO- NH (amide) group.

The azo compound $[\text{V}]_{\text{c}}$ was first converted to ester compounds $[\text{VI}]_{\text{a,b}}$ by using benzoyl chloride or ansoylchloride in THF and triethyl amine. The ester was identified by FTIR spectra which showed the disappearance of a wide peak around $(3442)\text{ cm}^{-1}$ which belongs to stretching vibration of the (-OH) group. The FT-IR spectra also, showed the appearance of the characteristic absorption band at $(1732\text{-}1724)\text{ cm}^{-1}$ [23] due to the stretching vibration of the (C=O) of the forming new ester group.

The 1,3-oxazepines $[\text{VII}]$, $[\text{VIII}]$, $[\text{IX}]_{\text{a,b,c}}$ were obtained by addition reaction of Schiff bases with naphthalic anhydride in dry benzene. The FTIR absorption bands of these compounds were confirmed from the disappearance of stretching band due to $\text{CH}=\text{N}$ of Schiff bases with the appearance of two bands characteristic of two carbonyl groups of oxazepine ring in region $(1760\text{-}1740)\text{ cm}^{-1}$ and $(1697\text{-}1674)\text{ cm}^{-1}$ [24], as in Figure (4) of compound $[\text{IX}]_{\text{b}}$.

The $^1\text{H NMR}$ spectrum of compound $[\text{VIII}]$, Figure (5) showed twenty aromatic ring protons appear as multiplet in the range (δ 7.01-8.44) ppm, a singlet signal of N-CH proton of oxazepine absorbed at δ 6.87 ppm and two singlet signal at δ (2.3 and 2.2) ppm for two protons at C-5 thiazolidinone ring and COCH_3 group, respectively. Furthermore, a singlet signals at δ 4.14 ppm for OCH_3 protons absorbed.

Biological activity

These compounds stabilizer is reasonable biological activity due to presence of either NH or C=O and OH group sinits structure [25]. The cell wall structural nature of gram negative enteric bacteria may be responsible for the observed susceptibility. For instance, (the cell wall of gram negative bacteria contains 15-20% poly saccharides and 10-20% lipid, where gram positive bacteria contain 35-60% poly saccharides and only 0-2% lipid [26]. The poly saccharides and lipid contents of the cell wall affect the permeability of allicin and porrum constituents) [27, 28]. The effect of the prepared compounds was due to interfering with the structure of bacteria cell wall or by stopping bacteria multiplying [29]. All the oxazepine derivatives [X]_{a-c} which were containing azo group show a moderate antibacterial activity against serratiamarcescens, while did not showed any antibacterial activity towards the other types Table (4).

Figures (6) exhibited the effect of the synthesized compounds on six types of bacteria.

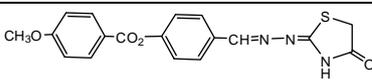
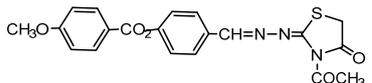
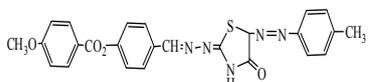
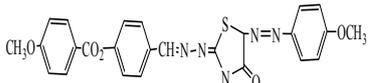
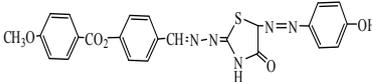
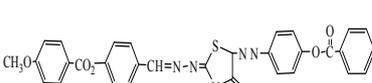
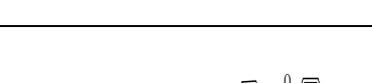
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Table (1) The physical data of compounds [III]-[IX]

| Comp No. | Nomenclature | Structural formula | Molecular formula | M.P °C | Yield % | Color |
|-------------------|--|--|---|---------|---------|-----------|
| [III] | 4-[(4-oxothiazolidin-2-ylidene)hydrazono-methyl]phenyl 4-methoxybenzoate |  | C ₁₈ H ₁₅ N ₃ O ₄ S | 230-232 | 96 | White |
| [IV] | 4-[(3-acetyl-4-oxothiazolidin-2-ylidene)hydrazono-methyl]phenyl 4-methoxybenzoate |  | C ₂₀ H ₁₇ N ₃ O ₅ S | 210-212 | 92 | Off white |
| [V] _a | 4-[(4-oxo-5-(4-tolylidiazonyl)thiazolidin-2-ylidene)hydrazono-methyl]phenyl 4-methoxybenzoate |  | C ₂₅ H ₂₁ N ₅ O ₄ S | 195-197 | 91 | Orange |
| [V] _b | 4-[(5-((4-methoxyphenyl)diazonyl)-4-oxothiazolidin-2-ylidene)hydrazono-methyl]phenyl 4-methoxybenzoate |  | C ₂₅ H ₂₁ N ₅ O ₅ S | 206-208 | 99 | Brown |
| [V] _c | 4-[(5-((4-hydroxyphenyl)diazonyl)-4-oxothiazolidin-2-ylidene)hydrazono-methyl]phenyl 4-methoxybenzoate |  | C ₂₄ H ₁₉ N ₅ O ₅ S | 220-222 | 95 | Black |
| [VI] _a | 4-[(5-((4-(benzoyloxy)phenyl)diazonyl)-4-oxothiazolidin-2-ylidene)hydrazono-methyl]phenyl 4-methoxybenzoate |  | C ₃₁ H ₂₃ N ₅ O ₆ S | 170-172 | 96 | Black |
| [VI] _b | 4-[(2-(4-(4-methoxybenzoyloxy)benzylidene)hydrazono)-4-oxothiazolidin-5-yl]diazonyl]phenyl 4-methoxybenzoate |  | C ₃₂ H ₂₅ N ₅ O ₇ S | 198-200 | 95 | Brown |

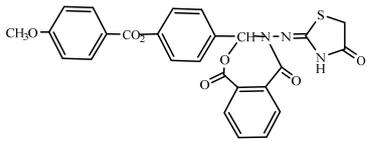
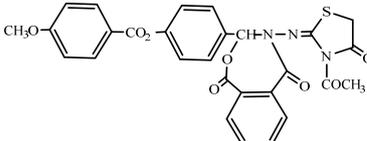
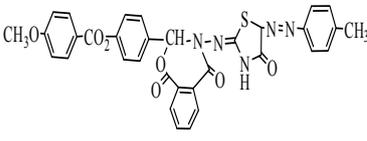
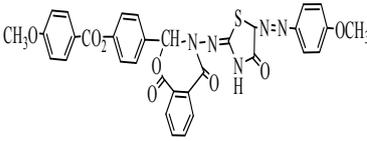
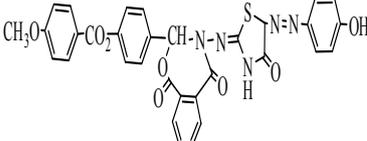
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|-------------------|---|--|-----------------------|---------|----|------------|
| [VII] | 2-[4-(4-methoxybenzoyloxy)phenyl]-3-4-oxothiazolidin-2-ylideneamino)-2,3-dihydrobenz [1,2e][1,3]oxazepin-4,7-diones |  | $C_{26}H_{19}N_3O_7S$ | 175-177 | 64 | White |
| [VIII] | 2-[4-(4-methoxybenzoyloxy)phenyl]-3(3-acetyl-4-oxothiazolidin-2-ylideneamino)-2,3-dihydrobenz [1,2e][1,3]oxazepin-4,7-diones |  | $C_{28}H_{21}N_3O_8S$ | 169-170 | 63 | Off white |
| [IX] _a | 2-[4-(4-methoxybenzoyloxy)phenyl]-3-[4-oxo-5(4-tolyl) diazenyl]thiazolidin-2-ylidene amino)-2,3-dihydrobenz [1,2e] [1,3]oxazepin-4,7-diones |  | $C_{33}H_{25}N_5O_7S$ | 252-254 | 58 | Pal brown |
| [IX] _b | 2-[4-(4-methoxybenzoyloxy)phenyl]-3-[4-oxo-5(4-methoxyphenyl)- diazenyl] thiazolidin-2-ylidene amino]-2,3-dihydrobenz [1,2e] [1,3]oxazepin-4,7-diones |  | $C_{33}H_{25}N_5O_8S$ | >290 | 42 | Gray |
| [IX] _c | 2-[4-(4-methoxybenzoyloxy)phenyl]-3-{5[(4-hydroxyphenyl) diazenyl]-4-oxo thiazolidin-2-ylidene amino)-2,3-dihydrobenz [1,2e] [1,3]oxazepin-4,7-diones |  | $C_{32}H_{23}N_5O_8S$ | 178-180 | 58 | Dark brown |

Table (2) Characteristics FTIR absorption bands of compounds[V]_{a,b,c}-[VI]_{a,b}

| Comp.N | Characteristics bands FTIR spectra(cm^{-1}) | | | | | |
|-------------------|---|---------------------|-----------|--------------------|-----------|-------------------------------|
| | ν NH | ν C-H aliphatic | ν C=O | ν C=C aromatic | ν N=N | Other |
| [V] _a | 3275 | 2980-2819 | 1722,1695 | 1600 | 1506 | δ CH ₃ 1371 |
| [V] _b | 3257 | 2997-2837 | 1730,1700 | 1600 | 1505 | |
| [V] _c | 3296 | 2983-2810 | 1739,1718 | 1600 | 1546 | ν OH: 3442 |
| [VI] _a | 3290 | 2980-2850 | 1732-1680 | 1603 | 1504 | |
| [VI] _b | 3280 | 2970-2820 | 1724-1675 | 1598 | 1510 | |

Table (3) Characteristics FTIR absorption bands of compounds[VII],[VIII] and [IX]_{a,b,c}

| Comp.No. | Characteristics bands FTIR spectra(cm ⁻¹) | | | | | |
|-------------------|---|-------------------|--------------------|----------------|-------------------|-------|
| | ν NH | ν C-H aromatic | ν C-H aliphatic | ν C=O | ν C=C aromatic | ν C-N |
| [VII] | 3323 | 3076 | 2966-2848 | 1755,1720,1693 | 1595 | 1356 |
| [VIII] | - | 3070 | 2962-2833 | 1760,1728,1693 | 1604 | 1365 |
| [IX] _a | 3320 | 3090 | 2960-2840 | 1756,1724,1695 | 1595 | 1355 |
| [IX] _b | 3328 | 3080 | 2968-2820 | 1760,1722,1697 | 1597 | 1345 |
| [IX] _c | 3310 | 3060 | 2895-2810 | 1740,1710,1674 | 1589 | 1340 |

Key of symbols :

1. active (slightly) = + 5 – 10mm, 2. active (Moderately) = ++ 11 – 15mm

3. active (Highly) = +++ more than 15mm .

Con: DMSO

Table (4) Antibacterial activity for synthesized compounds

| Comp. No. | Serratiamarcescens | Staphylococcus-epidermidis | Bacillus | Pseudomonas-aeruginosa | klebseilla | providencia |
|-------------------|--------------------|----------------------------|----------|------------------------|------------|-------------|
| [III] | ++ | - | ++ | - | ++ | - |
| [IV] | - | - | - | - | - | - |
| [V] _a | - | - | - | - | - | - |
| [V] _b | - | - | - | - | - | - |
| [V] _c | - | +++ | - | - | ++ | - |
| [VI] _a | - | - | - | - | - | - |
| [VI] _b | - | - | - | - | - | - |
| [VII] | - | - | - | - | - | - |
| [VIII] | - | - | - | - | - | ++ |
| [IX] _a | ++ | - | - | - | - | - |
| [IX] _b | ++ | - | - | - | - | - |
| [IX] _c | ++ | - | - | +++ | ++ | - |
| Con. | - | - | - | - | - | - |

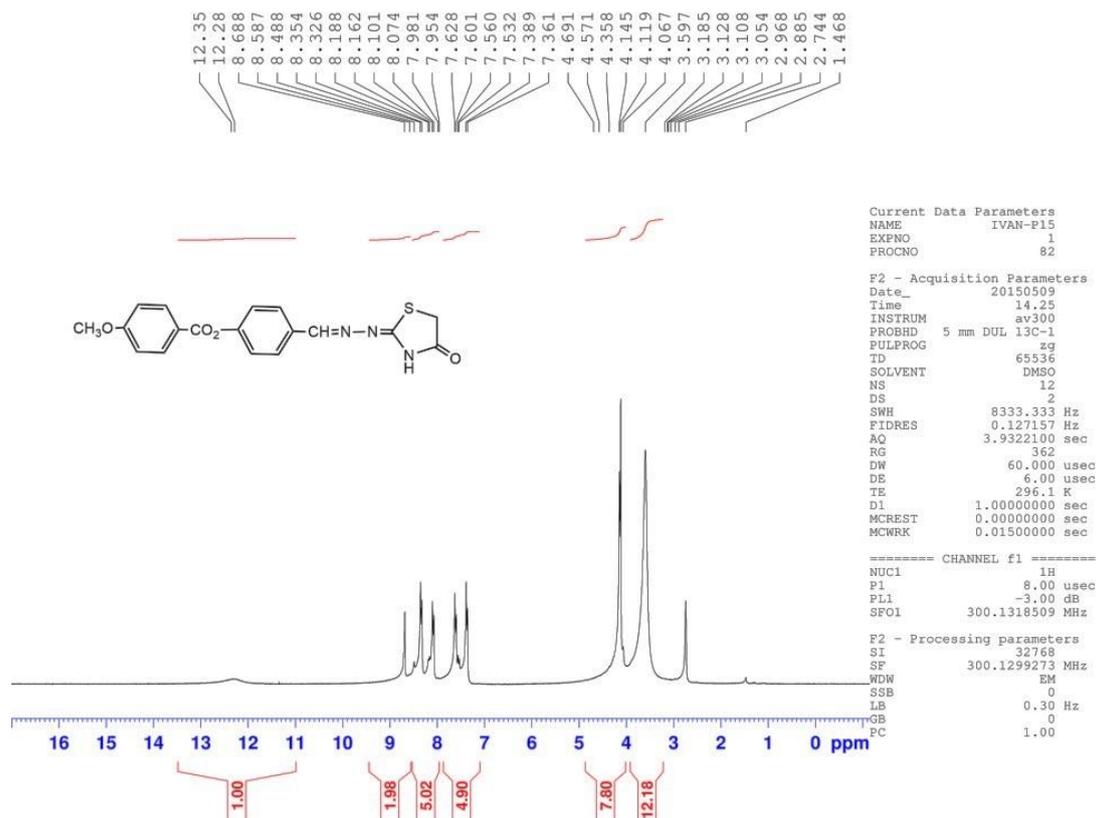
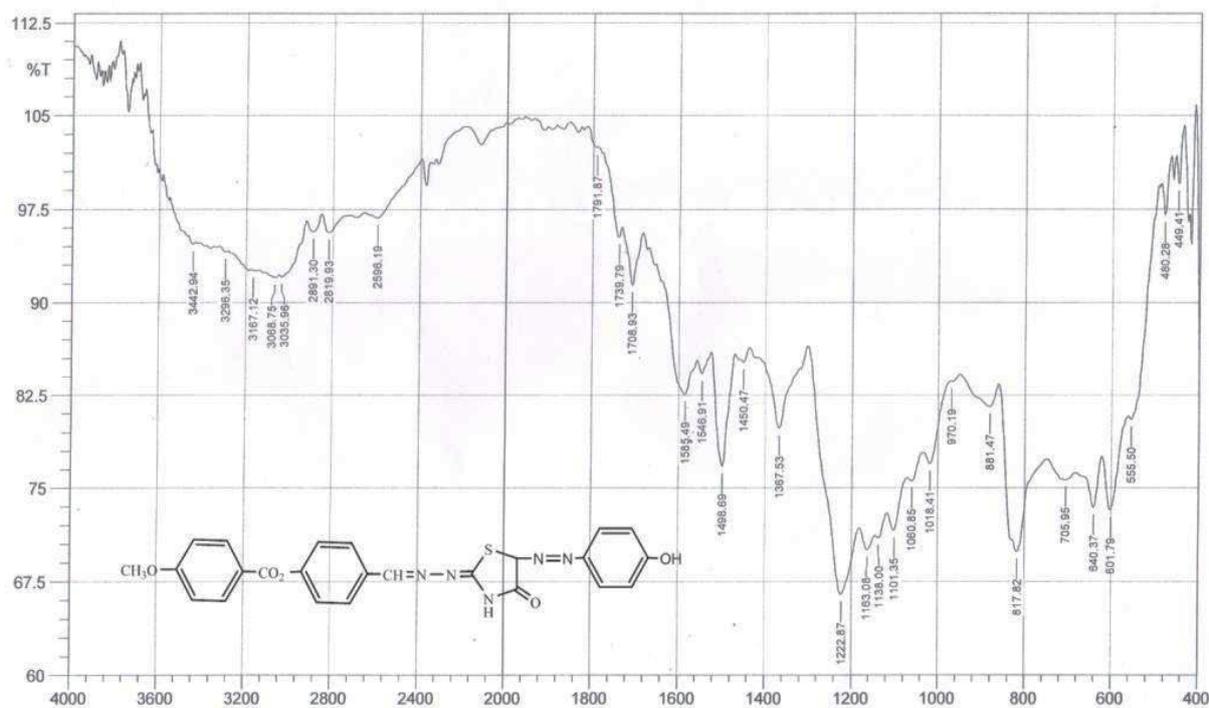
Figure (1) ¹H NMR-Spectrum of compound [III]

Figure (2) FTIR-Spectrum of compound [V]

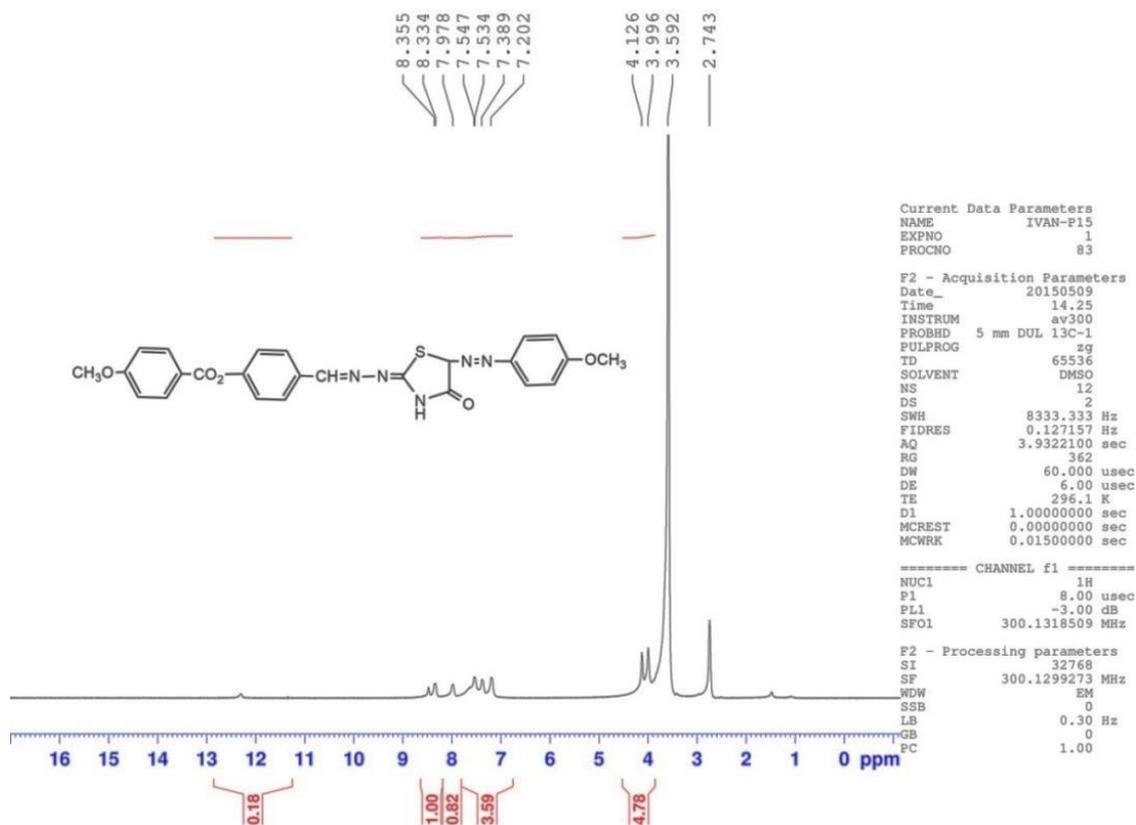


Figure (3) ¹HNMR-Spectrum of compound [V]_b

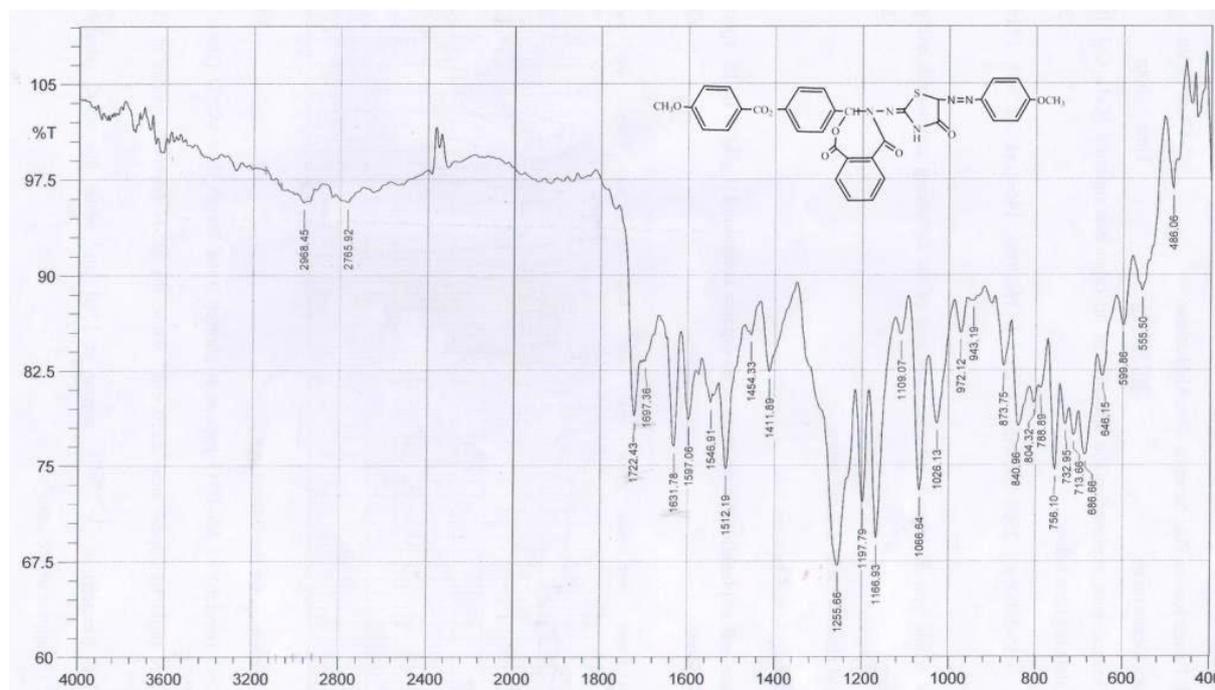


Figure (4) FTIR-Spectrum of compound [IX]_b

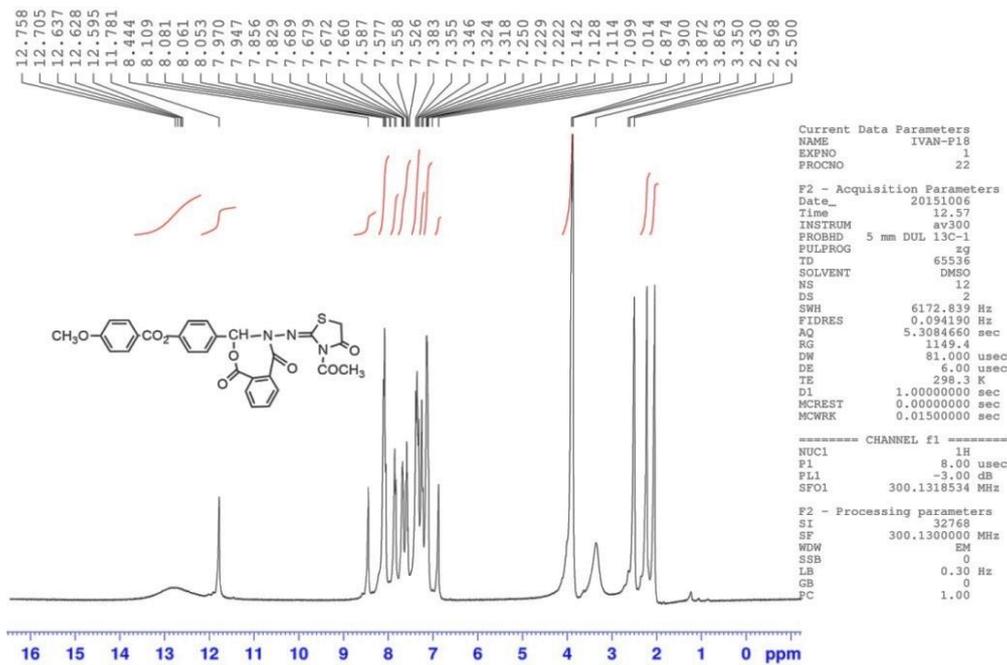


Figure (5) ¹H NMR-Spectrum of compound [VIII]



Figure (6) effect of compounds:[III]-[IX] on bacteria

تحضير وتشخيص وفحص الفعالية البكتيرية للمركبات الحلقية غير المتجانسة الجديدة والمشتقة من 4 (4-ميثوكسي بنزويلوكسي) بنزالديهايد ثايوسيمكياريزون

نبراس مظفر جميل

رجاء كاظم باقر

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استلم في: 15/أيار/2016، قبل في: 28/حزيران/2016

الخلاصة

حضر 4- ثايوزولدنون بثلاث خطوات من تفاعل انيسول كلورايد مع 4-هيدروكسي بنزالديهايد في خطوة يتكون خلالها الديهايد اروماتي [4- (4-ميثوكسي بنزويل) بنزائل الديهايد [I] ومن ثم مفاعلة المركب الأخير مع ثايوسيمكياريزايد ليعطي ثايوسيمكياريزون [II] وبتفاعل ثايوسيمكياريزون مع كلورو حامض الخليك بوجود خلاص الصوديوم يحضر مركب 4- ثايوزولدنون [III] الذي يستعمله مركب وسطي لتكوين مركبات جديدة حضر مركب [IV] من تفاعل [III] مع انهيديد الخليك بينما مع الامينات ينتج مركب الازو [V]_{a,b,c} وعند مفاعلة مركبات الازو مع انيسول كلورايد وبنزويل كلورايد في وسط قاعدي نحصل على مركبات استيرية جديدة [VI]_{a,b}. حضرت مركبات اوكسوزيين [VII], [VIII] و [IX]_{a,b,c} من تفاعل الاضافة لقواعد شف [IV], [III], [V]_{a,b,c} مع انهيديد نفتالك في البنزين الجاف. شخصت المركبات المحضرة باستعمال مطيافية FTIR و¹HNMR (للبيعض منها). تم فحص المركبات المحضرة ضد ستة انواع من البكتريا وهي *pseudomonas aeruginosa*, *klebseilla*, *aphylococcusepidermidis*, و *providencea*, *Serratiamarcescens* (Gram negative) و *Bacillus* (Gram positive).

الكلمات المفتاحية: ثايوزولدنون, قواعد شف, مركبات الازو, 1,3- اوكسوزيين والفعالية البكتيرية.