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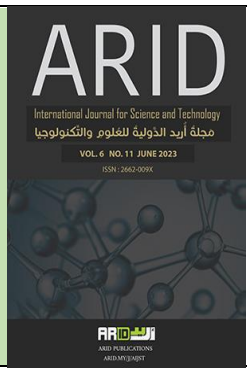

مَجلةُ أُريد الدَّوليةُ للعُلومِ والتِّكنولوجيا

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Preparation and Analysis of Heterocyclic Rings Made from (Thioxanthone) Derivatives Methods of Biological Activity, Thermal Analysis

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تحضير وتحليل الحلقات الهيدرولية المصنوعة من مشتقات (ثايوكزانثون) وطرق النشاط البيولوجي والتحليل الحراري

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ABSTRACT

In this study heterocyclic compounds were prepared from thioxanthone derivatives and determined their structure by measuring melting point (M.P) and infrared spectrum (FTR) and ^{1}HNMR for each one. These derivatives used for testing antibacterial activity *Streptococcus mutans*, *Staphylococcus saprophyticus*, *Enterococcus faecalis* (Gram positive bacteria) *Haemophilus influenzae* (Gram negative bacteria). Prepared compounds I,II,III,IIV showed clear antibacterial activity against all tested bacteria either as solutions or powder. Solutions with DMSO have antibacterial activity greater than those with distilled. Compound I showed greater antibacterial activity than other compounds. On the other hand, Gram-positive bacteria showed higher sensitivity than Gram-negative ones to all solutions. The results of thermal analysis of the prepared derivatives showed stability at high temperatures (DSC and TG curves).

Key words: Thioxanthone, Schiff bases, antibacterial activity , imidazolidin-4-one , Oxazepine .

الملخص

في هذه الدراسة تم تحضير المركبات الحلقية غير المتجانسة من مشتقات الثايوكزانثون، وتم تحديد تركيبها عن طريق قياس درجة الانصهار (M.P) وطيف الأشعة تحت الحمراء (FTR)و ^{1}HNMR لكل منها. استخدمت هذه المشتقات لاختبار النشاط المضاد للبكتيريا *Streptococcus mutans*، *Staphylococcus saprophyticus*، *Enterococcus faecalis* (بكتريا موجبة الجرام) *Haemophilus influenzae* (بكتريا سالبة الجرام). أظهرت النتائج أن المركب المحضر أظهر نشاطًا مضادًا للبكتيريا واضحًا ضد جميع أنواع البكتيريا المختبرة. أظهرت نتائج التحليل الحراري للمشتقات المحضرة لها استقرار في درجات الحرارة المرتفعة من منحنيات (DSC)و(TG).

الكلمات المفتاحية: ثايوكزانثون ، حلقية غير متجانسة، قواعد شيف، نشاط مضاد للجراثيم اميدازولدين-4-اون، الاوكزازبين.

1. INTRODUCTION:

Heterocyclic rings are cyclic compounds (organic) have contain one or more hetero atoms in structures, are (nitrogen, oxygen and sulphur) [1]. Most drugs are derivatives from heterocyclic compounds played widely role in living cells, DNA and RNA, hemoglobin and vitamins as (β-Lactams and Imidazole) [2]. All show has applications in different diseases as urinary antiseptics, antimicrobial herbicides and anti-inflammatory[3]. Schiff bases have more of application in multiplies fields such as, antibacterial, antifungal, anti-inflammatory, ant proliferative and antimalarial, [4] . Antiviral, antidepressant, antipyretic properties , ant tubercular, analgesic-anti-inflammatory , anticancer, anticonvulsant, antioxidant, anthelmintic, antiglycation, activities [5] . Four-membered rings (β-lactams) used as antibiotics, this involves penicillin derivatives, cephamycins, cephalosporins, monobactams and carbapenems. Beta-lactams one of the drugs which have clinical indications as (penicillin)[6]. Five (Imidazole) and seven (Oxazepine) - membered rings have (N,O) atoms in structural therefore spreads in nature, their heterocyclic exhibit a high spectrum in biological activity,anti-biotic, anticancer, anti-inflammatory and antimicrobial activity [7,8]. This study included preparation heterocyclic compounds as(imidazole,oxazepine and β-Lactam) from Schiff bases reactions by used Thioxanthone derivative as a principle material.

2. MATERIALS AND METHODS:

2.1. Chemical study :

2.1.1. Synthesis of 2-((4-hydroxy-3-methoxybenzylidene)amino)-9H-thioxanthen-9-one (I):

To prepare the mixture for recrystallization from 100% ethanol, vanillin (0.02 mole) was dissolved in (25 ml) of absolute ethanol, condensed with (0.02 mole) of (2-amino-9H-thioxanthen-9-one), and then added 1-2 drops of glacial acetic acid. This process was carried out while the mixture

was continuously shaken for 20-25 min on a magnetic stirrer at 65-70 °C. The mixture was evaporated and dried by Rotary evaporator to give compound (**I**). as displayed in **Scheme 1.**

2.1.2. Synthesis of 2-(4-hydroxy-3-methoxyphenyl)-3-(9-oxo-9H-thioxanthen-2-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione (II):

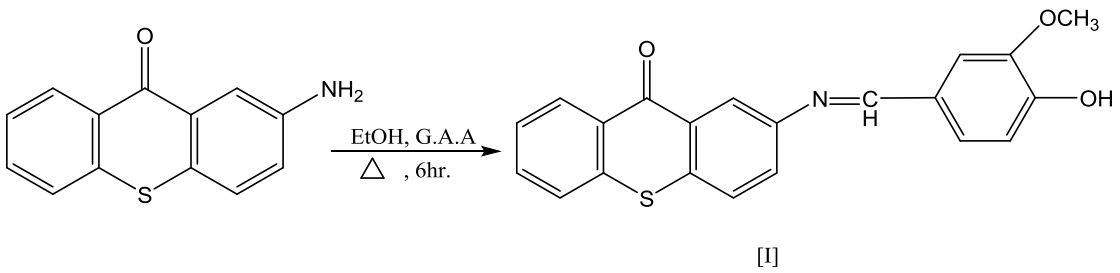
Maleic anhydride (0.02 mole) was added progressively after (0.02 mole) of compound (I) had been dissolved in (20 mL) of dry benzene to complete the reaction at 60–65 °C in 15 hours. For the purpose of preparing the mixture for recrystallization from 100% ethanol to provide compound (**II**) **Scheme 1**, the mixture was evaporated and dried using a Rotary evaporator.

2.1.3. Synthesis of 3-chloro-4-(4-hydroxy-3-methoxyphenyl)-1-(9-oxo-9H-thioxanthen-2-yl)azetidin-2-one (III):

In order to complete the reaction at 10°C in 9 hours, (0.02 mole) of compound (I) was dissolved in 20 mL of dioxin before (0.02 mole) of triethylamine and (0.05 mole) chloroacetyl chloride were added progressively. In order to prepare the mixture for recrystallization from 100% ethanol to yield compound (**III**) **Scheme 1**, the mixture was evaporated and dried using a Rotary evaporator.

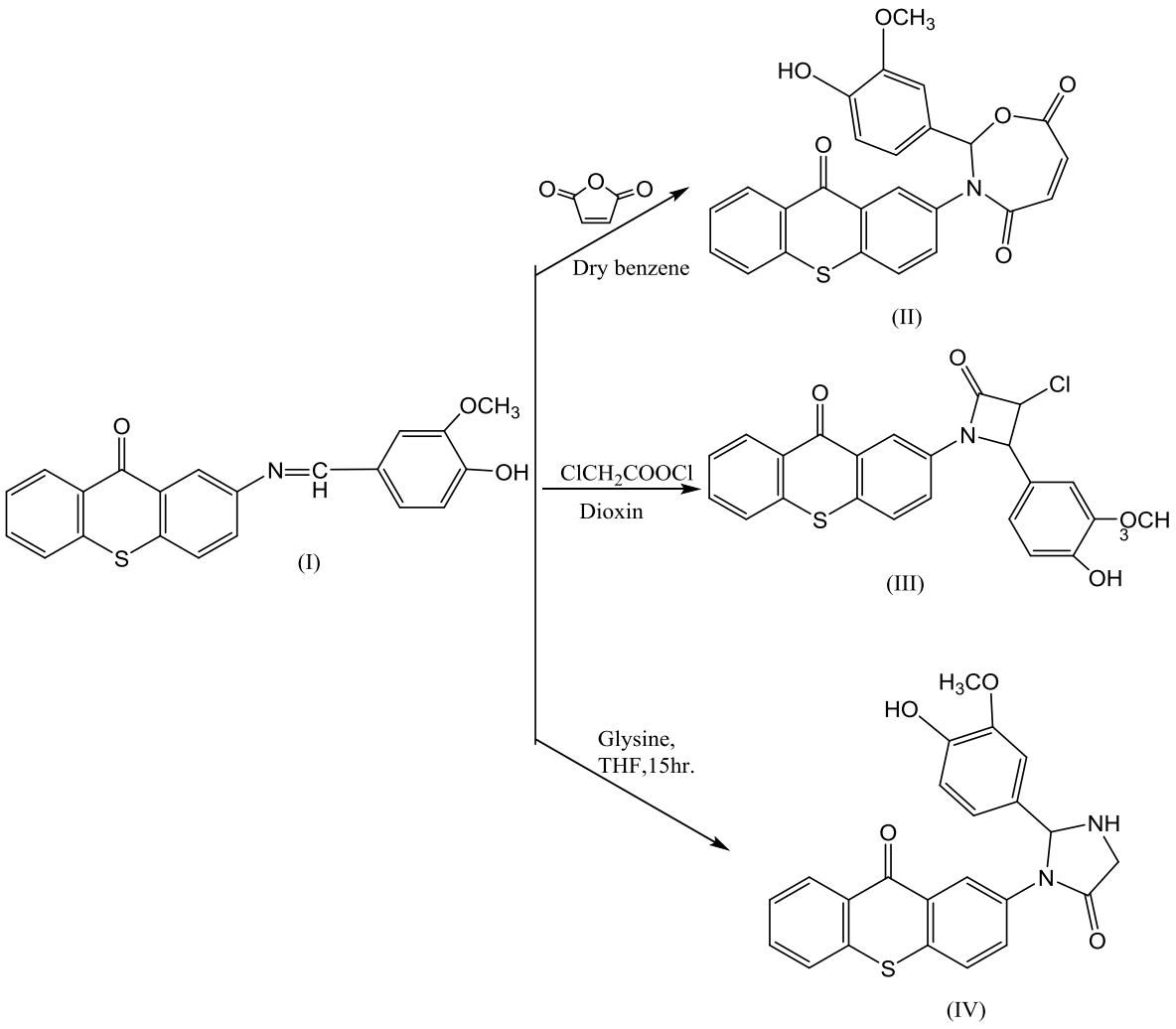
2.1.4. Synthesis of 2-(4-hydroxy-3-methoxyphenyl)-3-(9-oxo-9H-thioxanthen-2-yl) imidazolidin-4-one (IV):

(0.02mole) of compound (I) was dissolved in 20 mL of THF, and (0.02mole) of (Glysine) was added gradually to complete the reaction at(10°C) in 15 hours. The mixture was then evaporated and dried by a Rotary evaporator to prepare it for recrystallization from absolute ethanol to yield compound (**IV**). [9] **Scheme 1**. TLC was used on the finished result, and Table 1 has a list of all the compounds' physical characteristics .



[I]

Scheme(1)



Scheme(2)

Table (1): physical properties of synthesized compounds [I-IV].					
Compound No	**M.P (°C)**	**Color**	**Yield**	**Rf**	**Solvents (TLC)**
[I]	**187**	**Yellow**	**72**	**0.58**	**Ethanol:Toluene**
[II]	**193**	**Deep Yellow**	**76**	**0.68**	**Ethanol:Toluene**
[III]	**210**	**Orange**	**80**	**0.60**	**Ethanol:Toluene**
[IV]	**223**	**Yellowish Orange**	**82**	**0.64**	**Ethanol:Toluene**

2.2. Antibacterial Activity Test:

The bacterial inoculum was prepared by 2–3 pure colonies (of already diagnosed bacterial isolates) were added into 5 ml of BHI (brain heart infusion broth), which is sterile. After incubation (at 37ºC for 18 hrs), this broth culture was diluted with sterile normal saline in order to produce a standard bacterial suspension (turbidity equal to a standard McFarland tube). Bacterial suspention was used in the antibacterial activity test. The antibacteriall activity test was performed by agar well diffusion method as detailed in Al-Sa'ady and Hussein[10] by using four bacterial isolates included *Streptococcus mutans, Staphylococcus saprophyticus, Enterococcus faecalis* (Gram positive bacteria) and *Haemophilus influenzae* (Gram negative bacteria). The compound solutions were prepared by using DMSO and Distilled Water as solvents for preparing two concentrations (125 mg/ml, 250 mg/ml) for each. Inoculum from the bacterial suspension was streaked on a Muller Hinton agar. On the streaked medium, four holes (6 mm) have been punched by a sterile cork borer(No.6), about 200 µl of each solution has been introduced in each hole. in addition to the powder (500 mg/ml) was used in this test. After incubation period (at 37ºC for 18 hrs),diameter of inhibition zone was measured in millimeter.

3. RESULTS AND DISCUSSION :

3.1. Spectral Investigation :

Typically, melting points and FT-IR spectroscopy were used to study Schiff base (**I**) (**fig. 1**). With the appearance of a new stretching vibration at 1661 cm-1, which is assigned to the azomethine group (CH=N), peak at 1677 cm-1 due to the C=O group, peak at 787 cm-1 due to the C-S group, the FT-IR spectrum revealed the elimination of absorption peaks induced by NH2 and C=O groups. By adding azomethine C=N and maleic anhydrides in dry benzene, the (**II**) was created (**fig. 2**). New bands generated at 1558 as a result of the cyclic amid group (CO-N) in lactam. A lactone created a band at 1698 cm-1, while OH was responsible for the band at (3330-3442) cm-1. The most recognizable proof of compound (**III**)'s FT-IR absorption bands is shown in **figure 3**. revealed that bands at 1776 cm-1 due to N-C=O and 3462 cm-1 due to hydroxyl were among the other bands. [11-12] . The chemical [**IV**]'s FT-IR spectra is shown in **Figure 4**. displays absorption bands at 1541 cm-1 caused by the endocycle of (C=N) and an absorption band at 1608 cm-1 caused by (C=O) Amide.

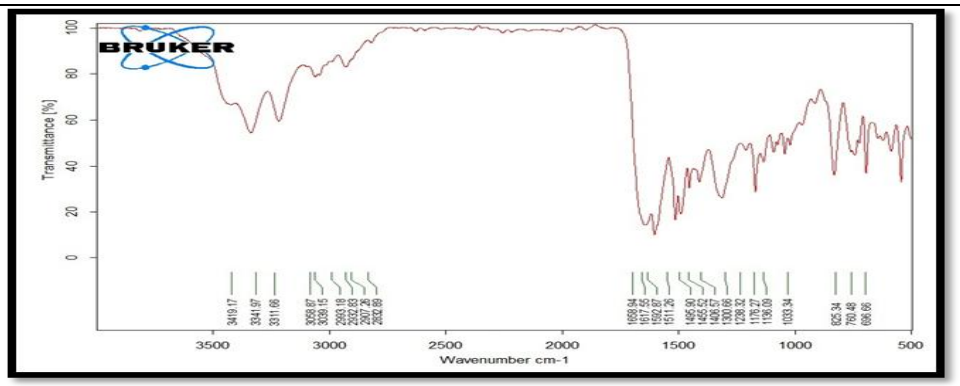


Fig.(1): FT-IR Spectrum for[I]

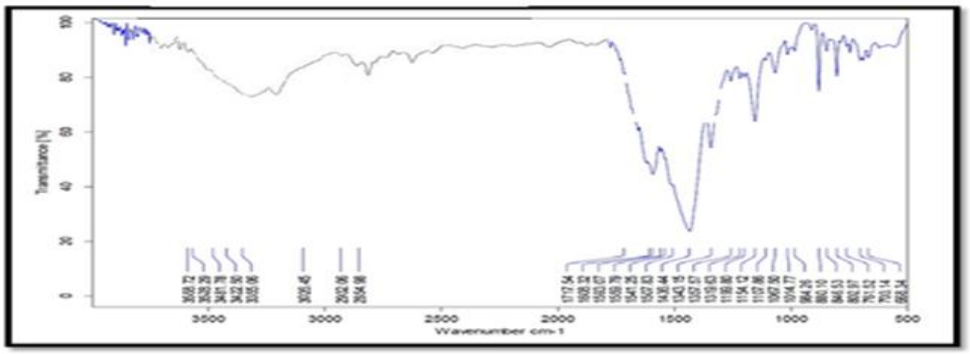


Fig.(2): FT-IR Spectrum for[II]

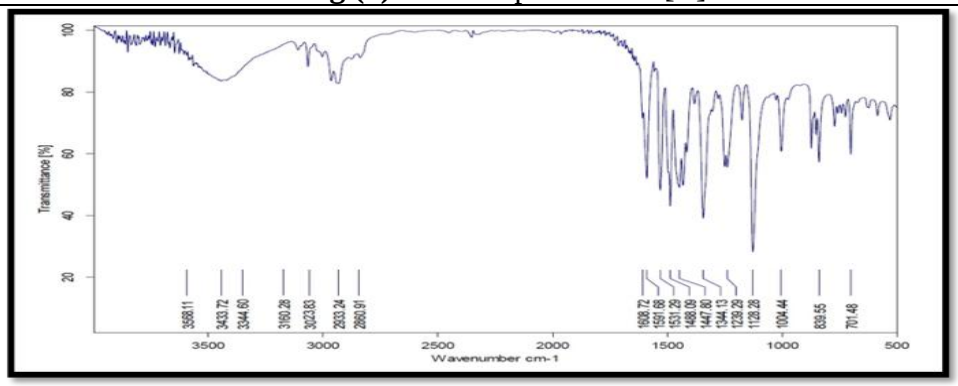


Fig.(3): FT-IR Spectrum for[III]

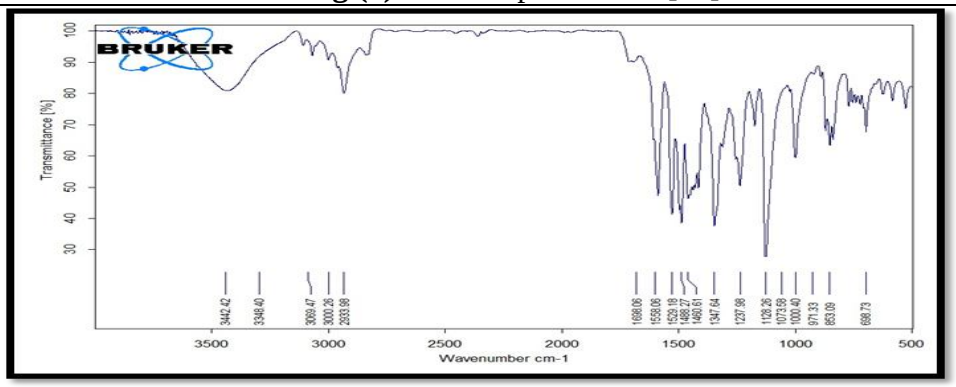


Fig.(4): FT-IR Spectrum for [IIV]

3.2. 1H-NMR spectral identification

Compound [**I**],(fig.5) A singlet signal was found in the (1H-NMR) spectrum (DMSO-d6) for the proton of CH=N., Many signals indications at δ6.9 – 7.4(ppm) resulting from aromatic protons. Last but not least, the 1H-NMR spectrum exhibits a signal peak at 13.4 of OH and an apparent

peak at 2.5 of solvent (DMSO-d6) protons. The (1H-NMR) spectrum of compound [**II**] (DMSO-d6) revealed a sharp signal at 8.6 ppm for one proton of the N-CH-O oxazepine group and bands at 7.83–7.54 ppm that were identical to the CH=CH ring of the oxazepine ring and aromatic protons. Additionally, a singlet signal of methoxy group proton absorption at 4.2 PPm. Finally, the 1H-NMR spectrum reveals peaks at δ10.2-13.0 to OH. Compound [**IV**]'s (1H-NMR) spectra (DMSO-d6) (**fig. 7**) revealed singlet signals for one proton of the NH endo cycle of the imidazole ring at 8.7 ppm and 3.0 3.5 ppm for the OCH3 and CH2 group rings. Finally, the 1H-NMR spectrum shows an OH group band at 11.1 PPm and several signals indicative of aromatic protons between(6.6 and 7.6) PPm. [13-14].

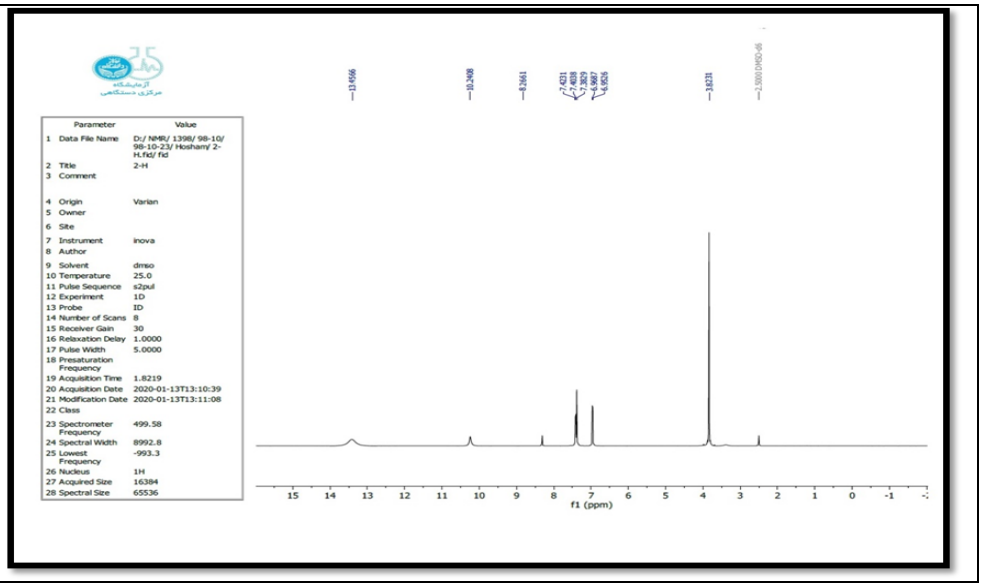


Fig.(5): 1H-NMR of [I] Compound

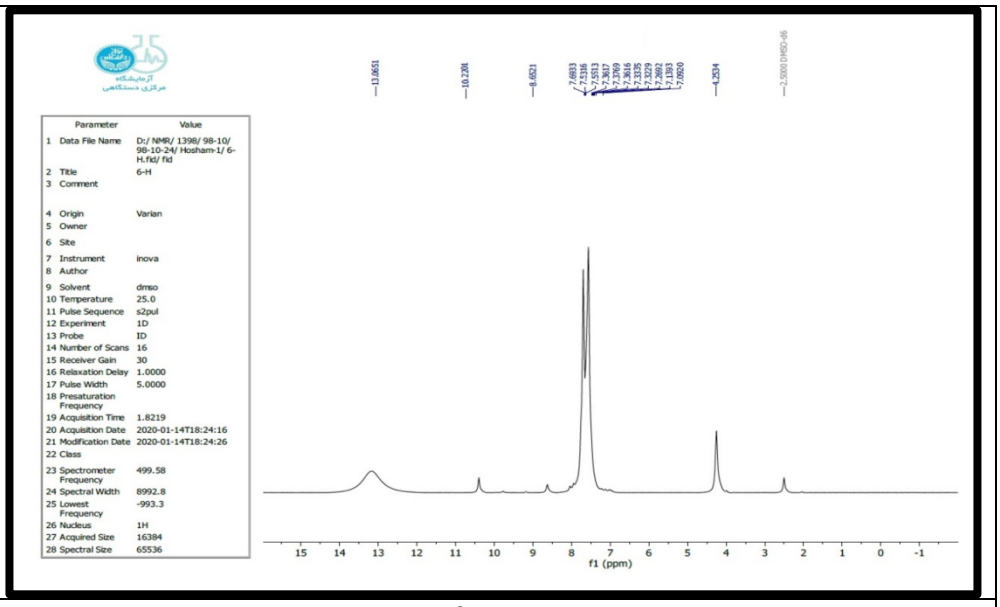


Fig.(6): 1H-NMR of [II] Compound

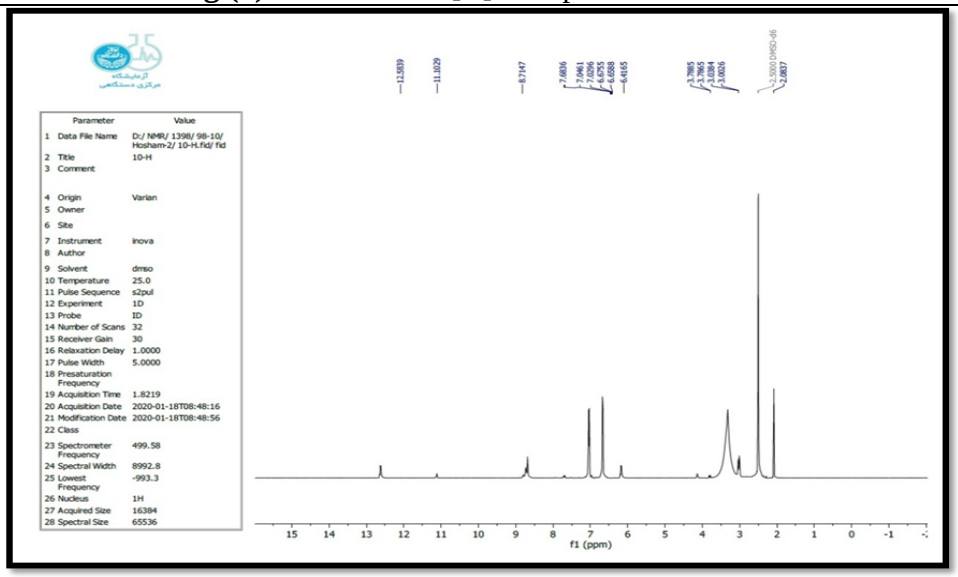
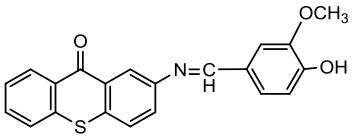
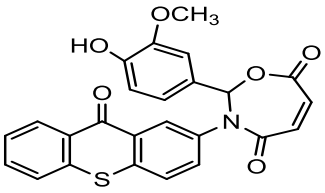
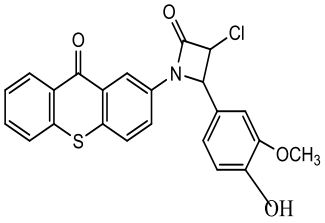
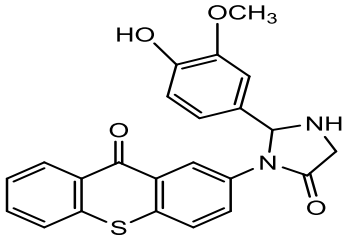


Fig.(7): 1H-NMR of [IV] Compound

3.3.Thermal stability study of the synthesised compounds [I- IV].

These days, thermal analysis is a crucial instrument for researching the thermal stability of crucial goods including medications, polymers, and organic chemicals. TG and DSC techniques were used in the current investigation to examine thermal stability. One of the most fundamental and practical analytical techniques for thermal analysis is DSC, which is used to measure the weight loss of a tested sample as a function of temperature or of the amount of time it spends in a heated environment. The mass loss across the same temperature range is exactly proportional to the peak area of the DSC curve's ($T_{initial}$, T_{final}), and the peak height of the DSC curve at any temperature provides the mass loss rate. Because of this, understanding the DSC curve makes it possible to directly apply the rate function of the change in target sample weight to the study of derivatives that occur during differential scanning calorimetry analysis. shown in Fig. 8 , Table 2 The next step was completed for all compounds. Sometimes mechanical treatment can also produce metastable forms following ethanol crystallization, materials were ground in a mortar and pestle, compressed, and a DSC experiment was conducted [15]. The TG measurements were also performed to confirm the lack of solvates or breakdown. Figure 9 displays the DSC scans and TG for compounds. The melting of these compounds is observed for all runs due to their endothermic thermal impact. The temperatures are (462) K for ethanol crystallization, (462) K for toluene crystallization, and 462 K for post grinding and pressing. A shock cooling period was followed by the second measurement. DSC traces without solvate only display an endothermic peak at 462 K. In the inquiry temperature range, no mass loss in the TG analysis for any sample has suggested a decomposition process.

Table(2): DSC data of compounds [I-IV]				
Compound No	**Structure**	**Decomposition temperature range °C**		**Losing weight%**
[I]		260	397	35.8
[II]		205	410	25.2
[III]		279	358	24.6
[IV]		280	350	25.2

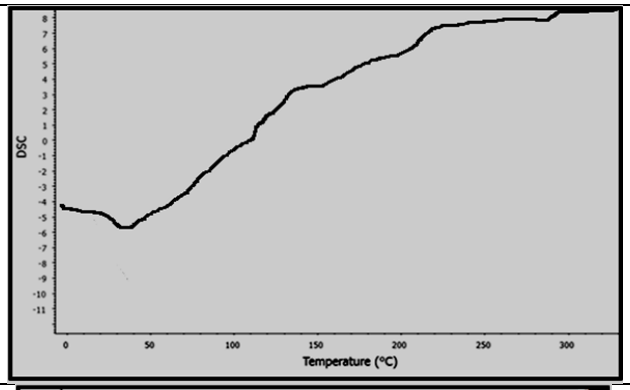
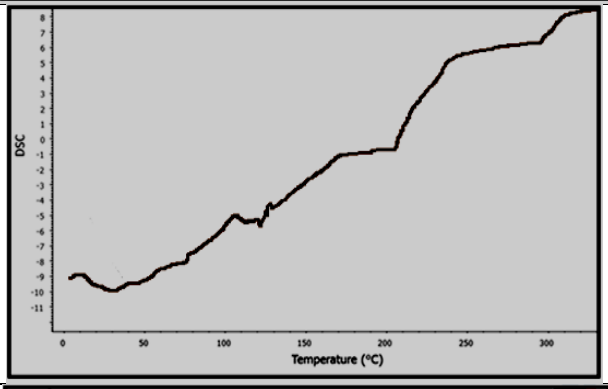
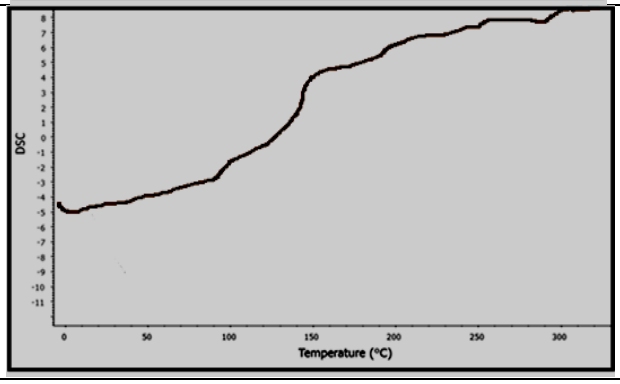
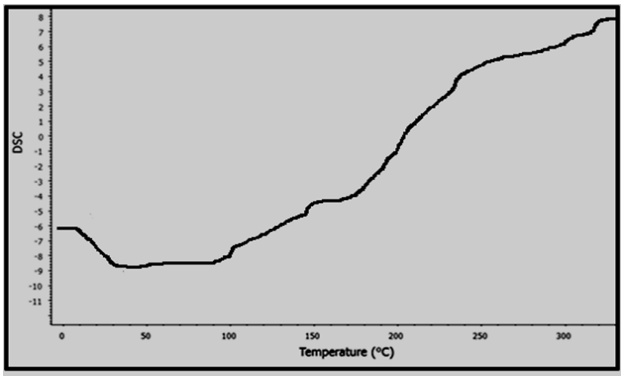
	**Compound I**
	**Compound II**
	**Compound III**
	**Compound IV**

Fig.(8): DSCcurves for compounds [I-IV]

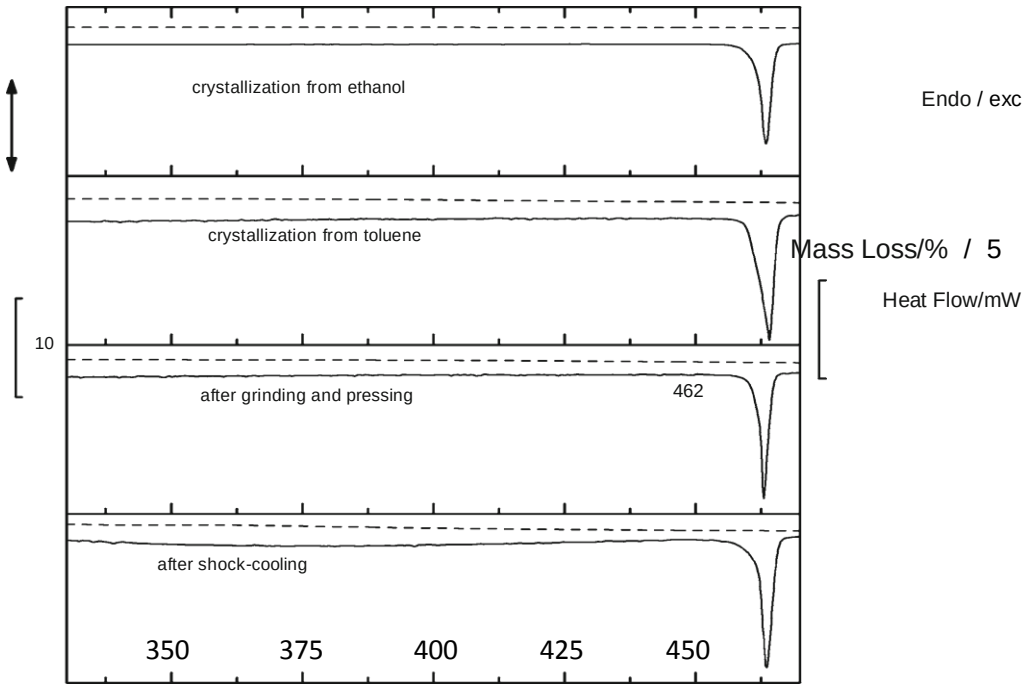


Fig.(9): (DSC and TG) traces for compounds [I–IV] at 5 K min-1

3.4. Antibacterial Activity Test

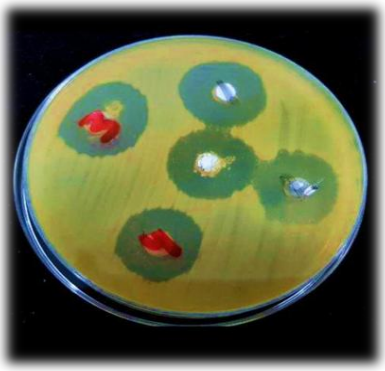
Recently, scientists and specialists have tended to search for more effective and safe alternatives compared to antibiotics due to the excessive increase in bacterial resistance to the most common antibiotics, which has become a major challenge for individuals and health institutions [16]. In the present study, prepared compounds I,II,III,IIV showed clear antibacterial activity against all tested bacterial species either as solutions or powder (DMSO and DW as solvents). Solutions with DMSO (as a solvent) have antibacterial activity greater than those with distilled water (table 3, figure 10), May be because DMSO is considered better solvent than DW which restrict the spread through agar resulting in less inhibition zone [17]. As detailed in table 3, Compound I showed greater antibacterial activity than other compounds II, III, and IIV and the powder. against microorganisms that are both(Gram-positive and Gram-negative). On the other hand, (

Gram-positive) bacteria displayed greater sensitivity to all solutions examined in this study than Gram-negative ones.

This finding is consistent with the published studies that have shown that thioxanthones have *potential* antimicrobial activities In addition. It plays a unique part in boosting the effectiveness of antibiotics against bacteria that are multidrug resistant.This activity may be intributed of isons of xanthones which have been reported as inhibitors of the Bacterial efflux pumps and their rings contain (N, S, and O) atoms in their structures., which causes damage of the cell wall, inhibition of protein synthesis and RNA synthesis. In general. most of a drug's activity depends on the balance of hydrophilic and lipophilic characteristics, as well as substituent-dependent solubility, which improves a drug's lipophilicity, which could explain why nitrogen compounds have increased activity. [18,19,20]. In a study by Durães *et al.,* [21] The thioxanthone derivatives were suggested as potential bacterial efflux pump inhibiter, consequently, reduce the bacterial ability for antibiotic resistance.

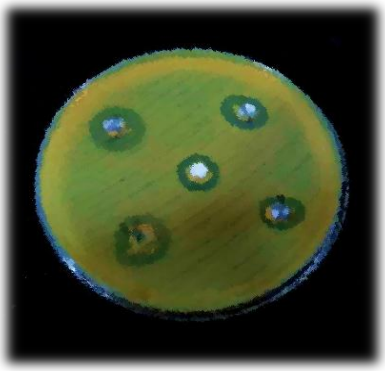
Table(3): Antibacterial activity test of compounds I,II,III,IIV prepared in the current study against Gram positive bacteria and Gram negative bacteria

Solvent	**Compound number**	**DMSO**		**Distilled Water**		**Powder**
Conc. (mg/ml)		**125**	**250**	**125**	**250**	**500 mg**
Streptococcus mutans	I	26	28	22	25	15
	II	23	26	22	25	15
	III	23	24	18	22	9
	IIV	20	21	15	19	9
Staphylococcus saprophyticus	I	25	27	19	23	14
	II	25	27	18	23	15
	III	23	25	18	23	9
	IIV	21	22	14	20	10
Enterococcus faecalis	I	26	28	18	22	11
	II	23	25	15	20	9
	III	23	25	15	20	9
	IIV	22	25	14	20	10
Haemophilus influenza	I	22	24	18	20	9
	II	21	24	17	21	9
	III	21	24	16	22	9
	IIV	20	23	15	21	8
The data in this table represent the diameter of inhibition zone by mm						



Haemophilus influenzae

Streptococcus mutans



Enterococcus faecalis

Staphylococcus saprophyticus

Fig.(10) : Antibacterial activity by agar well diffusion method in the prese study

4. CONCLUSION

This research suggests that all rings synthesized have a strong antibacterial activity, suggesting that they could be used to combat a wide range of diseases in the future To characterize solid states, differential thermal analysis (DSC) has been employed. Additionally, calculations using the Density Functional Theorem (DFT) were carried out. Controlling crystal clarity is crucial for the pharmaceutical sector. Our study's objective was to identify the existence of different solid-state forms. Theoretical calculations indicate that all chemicals are capable of forming hydrogen bonds with ethanol as a solvent.. . Since it is stable at high temperatures, it can be used as a ligand in inorganic chemistry to create complexes. The byproducts of the processes can also be

used as activators or sensitizers in the photo-polymerization of ethylenically unsaturated monomers or in the preparation of pharmaceutical products for use in the field of psychotherapy.

Table 4 List of abbreviations

DMSO	**Dimethyl sulfoxide**
DSC	**Differential scanning calorimetry**
DW	**Distill Water**
M.P	**Melting point**
Rf	**Retention factor**
TG	**Thermogravimetric**
TLC	**Thin layer Chromatography**
THF	**Tetra Hydro Furan**

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