



Synthesis and Characterization of some New Amic acid and Imides and study the Biological Activity

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Abstract

This study includes the synthesis of some new Amic acid and Imides, starting from the esters [S₁] of Terephthalic acid which then converted to its hydrazide [S₂] then to amic acid derivatives [S₃-S₇] and finally with imides [S₈-S₁₂]. Preparing of ester [S₁] by usual esterification of terephthalic acid with absolute ethanol in acidic medium, then has converted to its hydrazide [S₂] by reacting it with hydrazine hydrate. The amic acid derivatives [S₃-S₇] have been synthesized by the reaction of hydrazide [S₂] with anhydrides (2,3-dimethyl malic anhydride, 3-nitro phthalic anhydride, hexahydro phthalic anhydride, Diphenic anhydride, tetra Phenyl phthalic anhydride) in diethyl ether. Imides [S₈-S₁₂] were also synthesized by cyclization of amic acids derivatives using acetic acid anhydride and anhydrous sodium acetate. The synthesized compounds were identified by spectral methods UV, FT-IR and H¹-NMR beside melting point and the purity was determined using (TLC) and some of its physical properties were measured. Some of these compounds were tested against four strains of bacteria (*E. coli*, *P. ariginosa*, *S. aureus* and *S. pyogenes*).

Introduction

In organic chemistry, an imide is a functional group consisting of two acyl groups bound to nitrogen. These compounds are structurally related to acid anhydrides, although imides are less reactive. In terms of commercial applications, imides are best known as components of high-strength polymers. These are an important part of organic chemistry[1]. The N-substituted imides and their derivatives were important high performance engineering plastic [2]. It has been shown that imide derivatives of the anticancer drugs doxorubicin to the cysteine-34 position of circulating albumin after intravenous administration [3-5].

Experimental part

Materials:

All chemicals which have been used of reagent grade supplied by (Merck, Fluka, BDH and Aldrich). The melting point were determined by electro thermal melting Apparatus 9300. Thin layer chromatography (TLC) was used for monitoring the reaction and to check purity. The FT-IR spectra in the rang (400-4000) cm⁻¹ were recorded as KBr disk on FT-IR 8300 Shimadzu spectrophotometer. The UV-Visible spectra were measured in ethanol using Shimadzu

UV propel version 1.11 in range (200-400) nm. H¹-NMR spectra were recorded on Fourier Transform Varian spectrophotometer operating at 400 MHz with DMSO-d₆ with TMS as internal standard. Quantitative analysis of the elements.

Synthesis Methods:

Synthesis of ester [S₁] [6]:

A mixture of terephthalic acid (0.1 mol) in excess of absolute ethanol and concentrated sulfuric acid (5ml) was refluxed for 6 hrs., after that the solvent was distilled under vacuum, the product washed by sodium bicarbonate solution then with diethyl ether (40 ml). The physical properties of ester prepared [S₁] was white colored, M.P. (113-115) °C, yield 72%, R_f 0.62 and re-crystallized with ethanol as a solvent.

Synthesis of hydrazide [S₂] [6]:

Dissolved ester prepared [S₁] (0.1mol) and hydrazine hydrate 98% (0.2mol) mixture in absolute ethanol (40ml) and refluxed for 6hrs., after cooling to room temperature, the precipitate was filtered, washed, recrystallized from ethanol and dried. The physical properties of hydrazide [S₂] was white colored, M.P. (43-45) °C, yield 79%, R_f 0.81 and re-crystallization solvent ethanol.

Synthesis of amic acid derivatives [S₃-S₇] [7]:

A solution of (2,3-dimethyl malic anhydride, 3-nitro phthalic anhydride, hexahydro phthalic anhydride, diphenic anhydride, tetra phenyl phthalic anhydride) (0.02mol) in diethyl ether was added drop wise with stirring to a suspension of (0.01mol) compound [S₂]

in diethyl ether. The mixture was stirred overnight at room temperature. The precipitated was filtered, washed with water and recrystallized from ethanol. The physical properties, yield and R_f of these derivatives were given in table (1).

Table (1): physical properties, yield and R_f of compounds [S₃-S₇].

Comp. No.	Molecular Formula	Color	M.P °C	Yield %	R.f	Crystalline solvent
3S	C ₂₀ H ₂₂ N ₄ O ₈	light Yellow	128-130	65	0.82	Acetone
4S	C ₂₄ H ₃₀ N ₄ O ₈	White	300>	74	0.87	Acetone
5S	C ₂₄ H ₁₆ N ₆ O ₁₂	White	138-140	63	0.70	Ethanol
6S	C ₃₆ H ₂₆ N ₄ O ₈	light Yellow	165-167	72	0.85	Ethanol
7S	C ₇₂ H ₅₀ N ₄ O ₈	White	138-140	63	0.75	Ethanol

Synthesis of imide derivatives [S₈-S₁₂] [8,9]:

(0.01mol) of compounds [S₃-S₇] was dissolved in acetic anhydride (10-20) % from the weight of acid sodium acetate anhydrous was added then refluxed until the color of solution, was changed then cooled and added ice after strongly stirring, precipitated

imide derivatives which was filtered, washed with water then by dilute sodium bicarbonate and finally by ethanol and recrystallized from ethanol + acetone (1:1). The physical properties, yield and R_f of these derivatives were given in table (2).

Table (2): physical properties, yield and R_f of compounds [S₈-S₁₂].

Comp. No.	Molecular Formula	Color	M.P °C	Yield %	R.f	Crystalline solvent
8S	C ₂₀ H ₁₈ N ₄ O ₆	White	300>	76	0.65	Acetone
9S	C ₂₄ H ₂₆ N ₄ O ₆	Yellow	230-232	65	0.81	Ethanol
S₁₀	C ₂₄ H ₁₆ N ₆ O ₁₀	White	290-291	79	0.60	Ethanol
11S	C ₃₆ H ₂₂ N ₄ O ₆	Yellow	200-203	74	0.87	Dioxane
12S	C ₇₂ H ₄₆ N ₄ O ₆	Yellow	249 d	80	0.74	Acetone

The biological activity [10]:

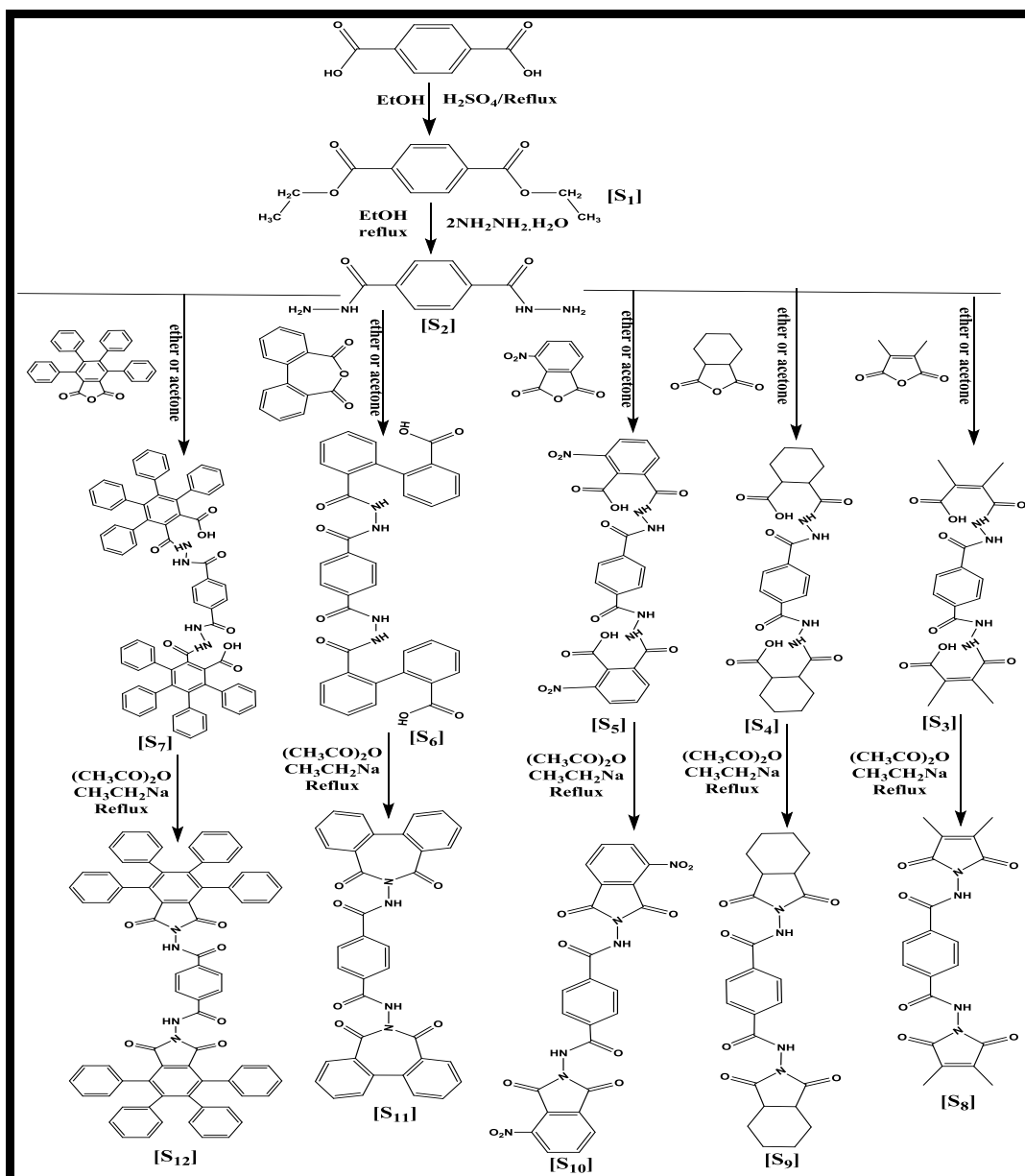
The bacteria species used are listed in tables (7). All strains were obtained from College of Education for Women, Tikrit University. They were grown up to the stationary phase in nutrient bath at 37 °C and a sample of 0.5 ml of each bacteria was spread over a surface of a nutrient agar plate.

Antibacterial assay [11]:

Disc of filter paper (6 mm diameter) is sterilized at 140 °C for 1hr., and impregnated with the germs.

DMSO was used as a solvent for all compounds. The same solvent was used for antibiotics. Blank paper discs of DMSO was used as control. The inoculated plates are incubated at 37 °C for 24 hrs., and the inhibition zone (cm) were measured [12].

In this work many compounds were synthesized including ester, hydrazide, amic acid and imide as in the following Scheme (1):

Scheme (1): synthesis of compounds [S₁ – S₁₂].**Results and Discussion:****Characterization of amic acid derivatives:**

Amic acid derivatives have synthesized from the reaction of compound [S₂] with deferentes anhydride. Beside UV spectra showed the transions $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ which have confirmed the presences of the un-bonded pair electrons on nitrogen, oxygen atoms and aromatic system (double bond). UV absorbance spectra is given in table (3).

The FT-IR spectra of amic acid derivatives in general showed disappearance of (NH₂) absorption of primary amine and appearances of (NH) absorption

band in (3282-3199) cm^{-1} . Besides bands in (1749-1719) cm^{-1} , (1681-1656) cm^{-1} are due to (C=O) acid and (C=O) imide, and band at (3568-3332) cm^{-1} due to (OH) acid. IR spectra is given in table (3) see fig. (1), fig. (2) and fig. (3).

¹H-NMR spectrum of compound (S₅) showed singlet signal at $\delta = (2.50)$ ppm due to DMSO- d_6 solvent, multiple signal (8.20 - 9.02) ppm due to aromatic rings, singlet signal at $\delta = (10.01)$ ppm due to N-H amic acid, and singlet signal (13.03) ppm due to O-H carboxylic acid. ¹H-NMR spectrum of compound [S₅] is given in fig (7).

Table (3): UV/Vis and FT-IR of the prepared compounds [S₃-S₇].

Comp. No.	λ_1 max λ_2 max	IR (KBr) cm ⁻¹				
		ν (O-H)	ν (N-H)	ν (C-H) Arom. ν (C-H) Aliph.	ν (C=O) acid ν (C=O) imide	ν (C=C)
₃S	270	3332	3269	3053	1749	1473
	337			2958	1659	1588
₄S	261	3400	3213	3003	1728	1429
	393			2937	1656	1573
₅S	248	3568	3199	3043	1730	1487
	398			-	1681	1597
₆S	217	3359	3277	3035	1722	1455
	342			-	1673	1561
₇S	239	3446	3282	3091	1719	1482
	305			-	1667	1545

Characterization of imide derivatives:

Imide derivatives have synthesized by dehydration of compounds [S₃-S₇] using acetic anhydride with sodium acetate anhydrous. Beside UV spectra which showed the transitions $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ which confirmed the presence of the un-bonded pair of electrons on nitrogen, oxygen and aromatic system (double bond). UV absorbance spectra was given in table (4).

The FT-IR spectrum of imide derivatives showed disappearance of (OH) acid and (NH) imide

absorption bands and appearance of (C=O) imide at (1690-1653) cm⁻¹. IR spectra is given in table (4). See fig. (4) and fig. (5).

¹H-NMR spectrum of compound (S₁₂) showed singlet signal at $\delta =$ (2.51) ppm due to DMSO-d⁶ solvent, multiple signal (7.08 - 8.48) ppm due to aromatic rings and singlet signal at $\delta =$ (15.46) ppm due to N-H imide. ¹H-NMR spectrum of compound [S₁₂] is given in fig (8).

Table (4): UV/Vis and FT-IR of the prepared compounds [S₈-S₁₂].

Comp. No.	λ_1 max λ_2 max	IR (KBr) cm ⁻¹			
		ν (N-H)	ν (C-H) Arom. ν (C-H) Aliph.	ν (C=O) Imide	ν (C=C)
₈S	240	3259	3037	1675	1460
	388		2945		1583
₉S	229	3238	3071	1669	1488
	368		2928		1580
₁₀S	209	3213	3030	1689	1465
	249		-		1598
₁₁S	237	3204	3066	1690	1476
	367		-		1591
₁₂S	246	3225	3005	1653	1446
	392		-		1573

Table (5): Elemental analysis of some prepared compounds.

Comp. No.	Molecular Formula	Found				Calculated			
		C%	H%	N%	O%	C%	H%	N%	O%
S₃	C ₂₀ H ₂₂ N ₄ O ₈	53.81	4.97	12.55	28.67	53.98	4.88	12.75	28.47
S₅	C ₂₄ H ₁₆ N ₆ O ₁₂	49.66	2.78	14.48	33.08	49.41	2.50	14.44	32.97
S₇	C ₇₂ H ₅₀ N ₄ O ₈	78.67	4.59	5.10	11.64	78.49	4.50	5.04	11.69
S₈	C ₂₀ H ₁₈ N ₄ O ₆	58.54	4.42	13.65	23.39	57.82	4.48	13.57	23.18
S₁₀	C ₂₄ H ₁₂ N ₆ O ₁₀	52.95	2.22	15.44	29.39	52.79	2.11	15.37	29.28
S₁₂	C ₇₂ H ₄₆ N ₄ O ₆	81.34	4.36	5.27	9.03	81.25	4.26	5.33	9.15

Biological activity:

The antimicrobial activity of the synthesized compounds [S₁-S₁₂] were examined by the agar diffusion method using four different bacterial species *Escherichia coli*, *Pseudomonas ariginosa*, *Staphylococcus aureus* and *Staphylococcus pyogenes*. The results indicated that all the assayed

compounds showed a microbial activity against the used bacterial. Antibacterial activity of compounds [A₆, A₇, A₈, A₁₂] is given in fig (9), (10), (11), and (12). The figures (13), (14), (15) and (16) show the inhibitory activity values of compounds prepared against the bacteria used.

Table (6): Antibacterial activity of some of the prepared compounds.

Comp. No.	Conc. mg/ml	<i>E. coil</i>	<i>P. ariginosa</i>	<i>S. aureus</i>	<i>S. pyogenes</i>	Inhibition Distance
S ₁	25	-	-	-	-	0
	50	+	-	+	+	1-2
	100	++	-	++	+	1-4
2S	25	+	-	-	+	1-2
	50	+	+	-	++	1-3
	100	+	++	++	+++	2-5
3S	25	+	-	+	+	1-2
	50	++	+	++	+++	1-5
	100	+++	+++	+++	+++	4-5
4S	25	+	+	++	+	1-4
	50	+++	++	++	+++	2-5
	100	+++	+++	+++	+++	4-5
5S	25	+	+	+	++	1-3
	50	+++	++	+++	+++	2-5
	100	+++	+++	+++	+++	4-5
6S	25	+	-	+	-	0-1
	50	+	++	+	+	1-2
	100	++	++	+	+	1-4
7S	25	-	+	-	-	0-1
	50	-	++	-	-	0-2
	100	-	+++	+	++	0-5
8S	25	+	+	+	+	1-2
	50	++	+	++	+	1-4
	100	+++	+	+++	+++	-51
9S	25	-	-	-	-	0
	50	+	+	+	+	1-2
	100	++	++	++	++	3-4
10S	25	-	-	-	-	0
	50	-	-	+	-	0-1
	100	-	+	+	-	1-2
11S	25	-	-	-	-	0
	50	+	+	++	++	1-4
	100	++	+	++	+++	1-5
12S	25	+	-	+	+	1-2
	50	++	+	+	++	1-4
	100	+++	+++	+++	+++	4-5

(-) = No inhibition

(+) = Inhibition zone (1-2) cm

(++) = Inhibition zone (2-4) cm

(++) = Inhibition zone (4-5) cm

Table (7): Antibacterial efficacy of control treatments in the growth of a number of negative and positive bacteria (diameter of the inhibition circuit measured by cm).

Comp. No.	Name	<i>E. Coil</i>	<i>S. pyogenes</i>	<i>S. aureus</i>	<i>P. ariginosa</i>
1	Amoxicillin	2.9	2.6	3.2	2.5
2	Ampicillin	3.6	2.7	2.8	2.6
3	Blank disk	0	0	0	0

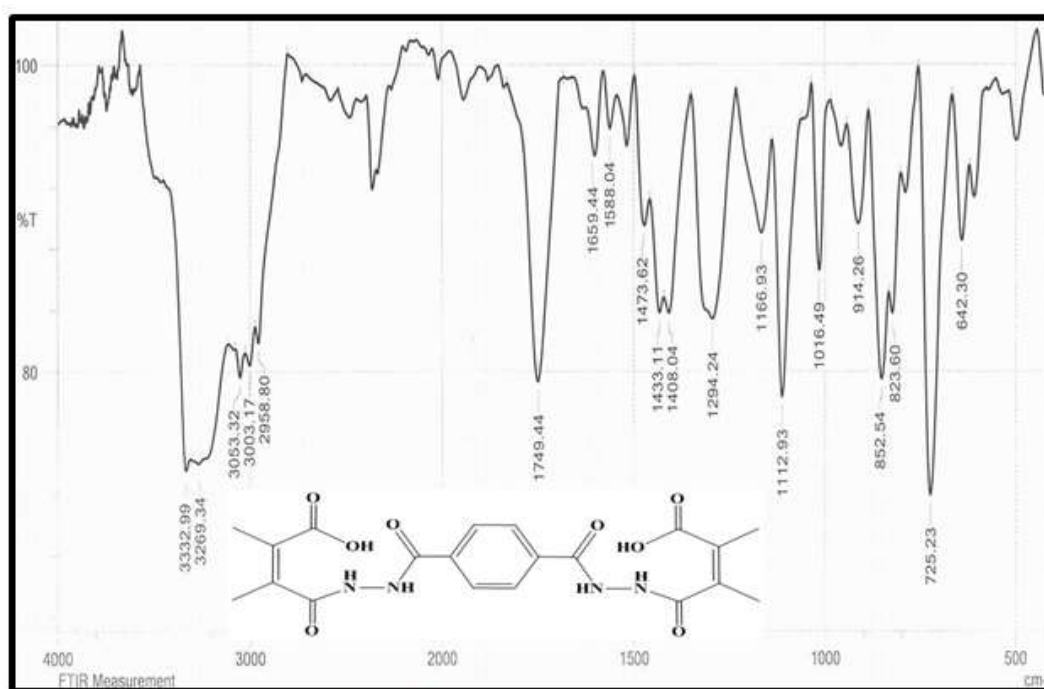


Fig. (1): FTIR spectrum of [S₃].

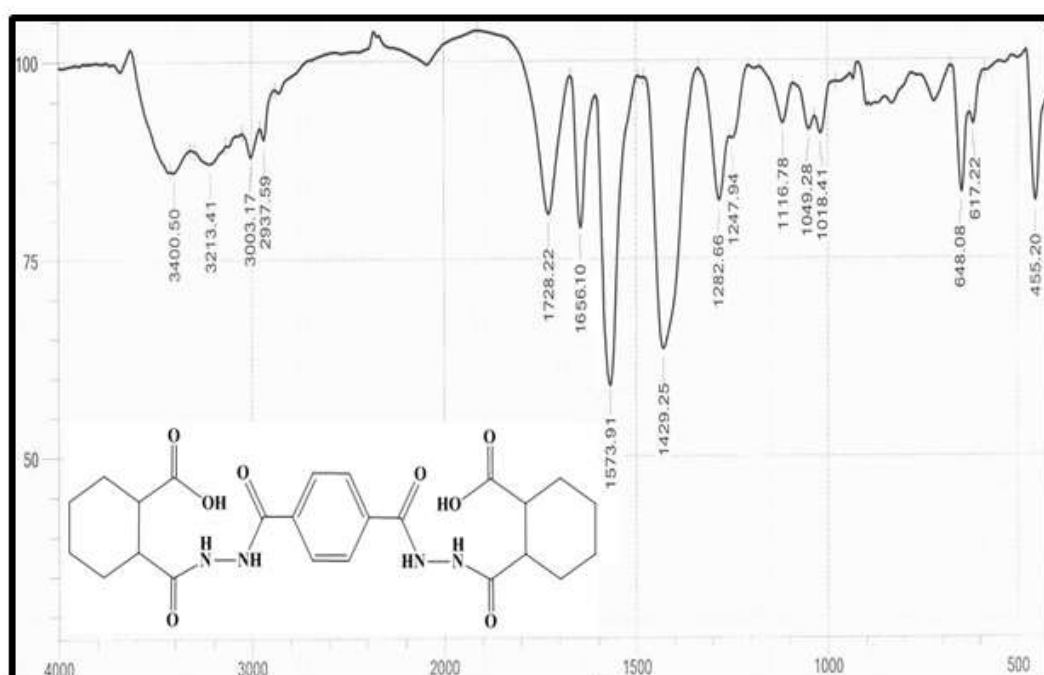


Fig. (2): FTIR spectrum of [S₄].

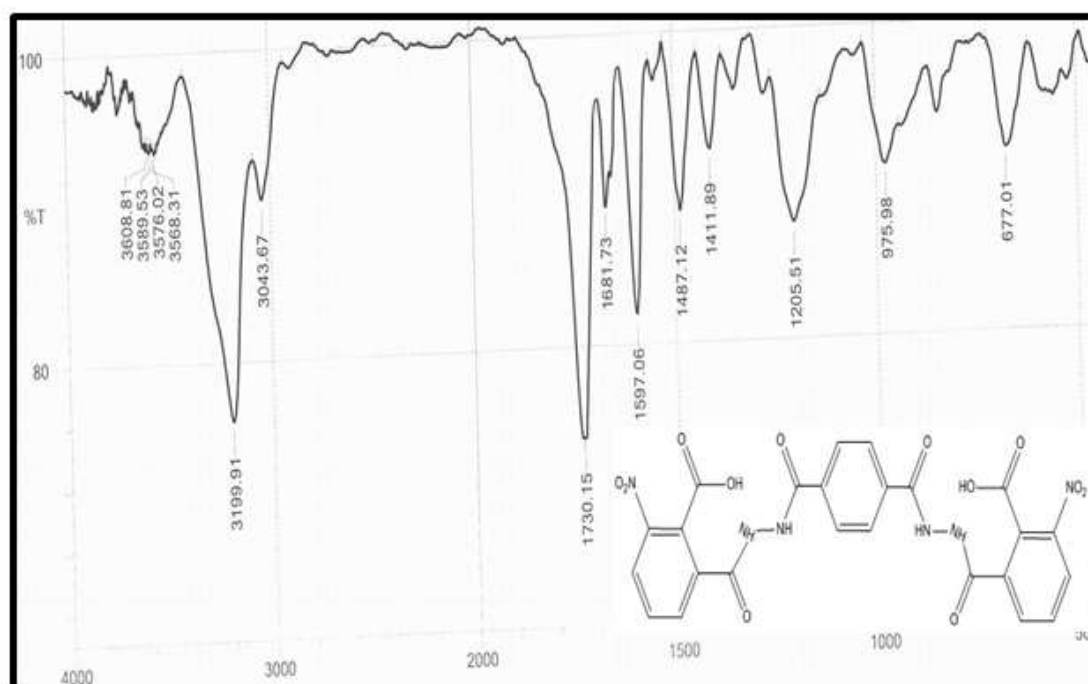


Fig. (3): FTIR spectrum of [S₅].

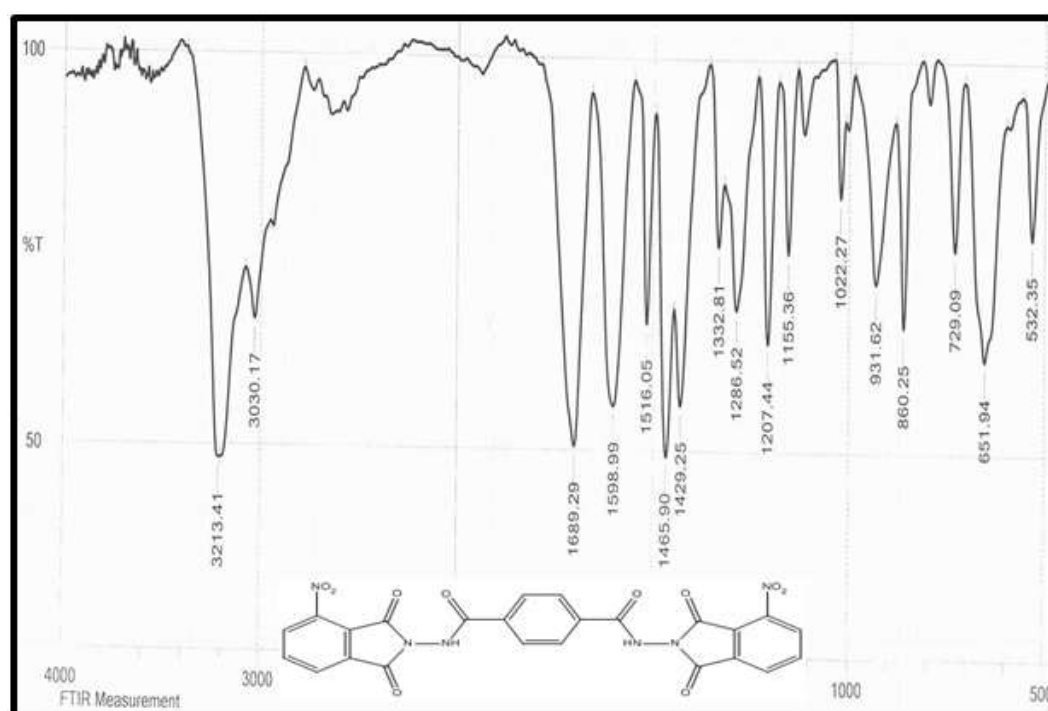
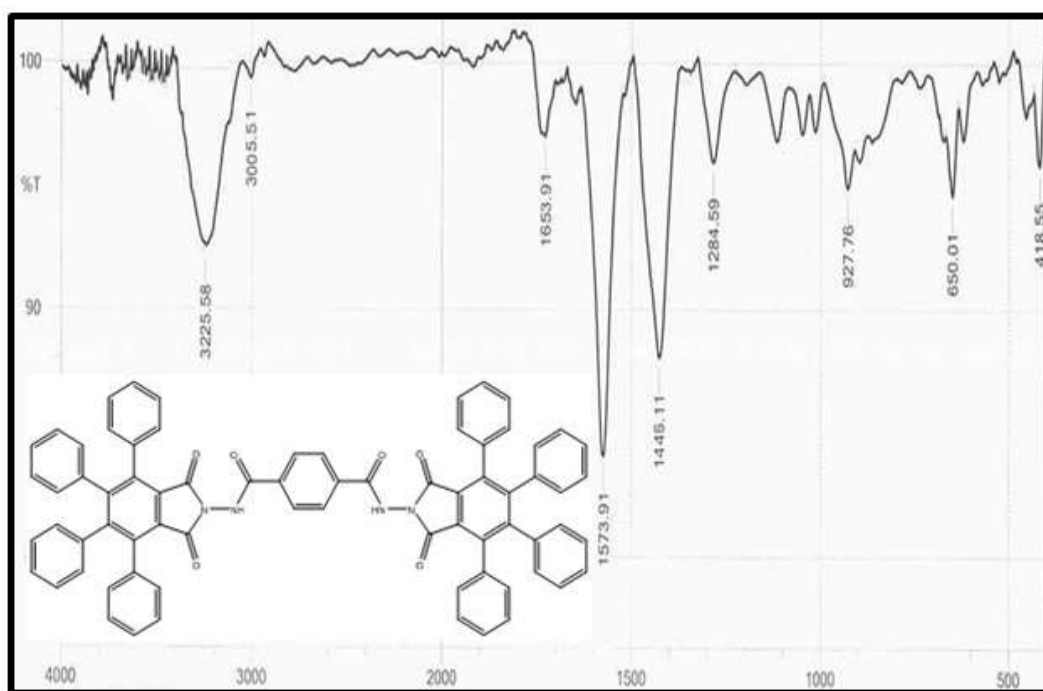
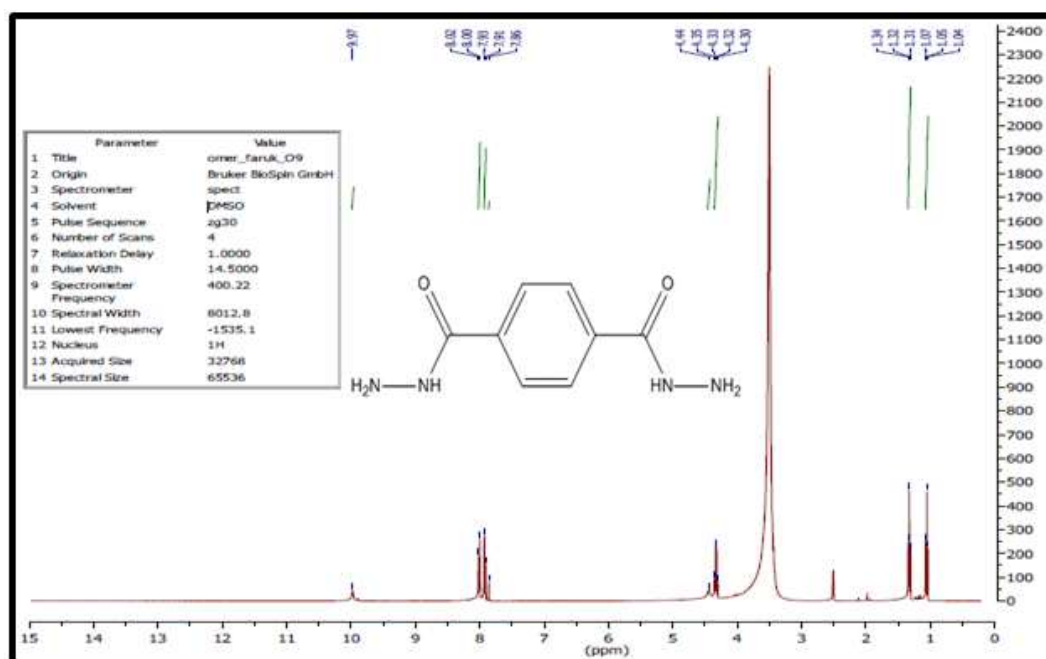


Fig. (4): FTIR spectrum of [S₁₀].

Fig. (5): FTIR spectrum of [S₁₂].Fig. (6): ¹H-NMR of [S₂].

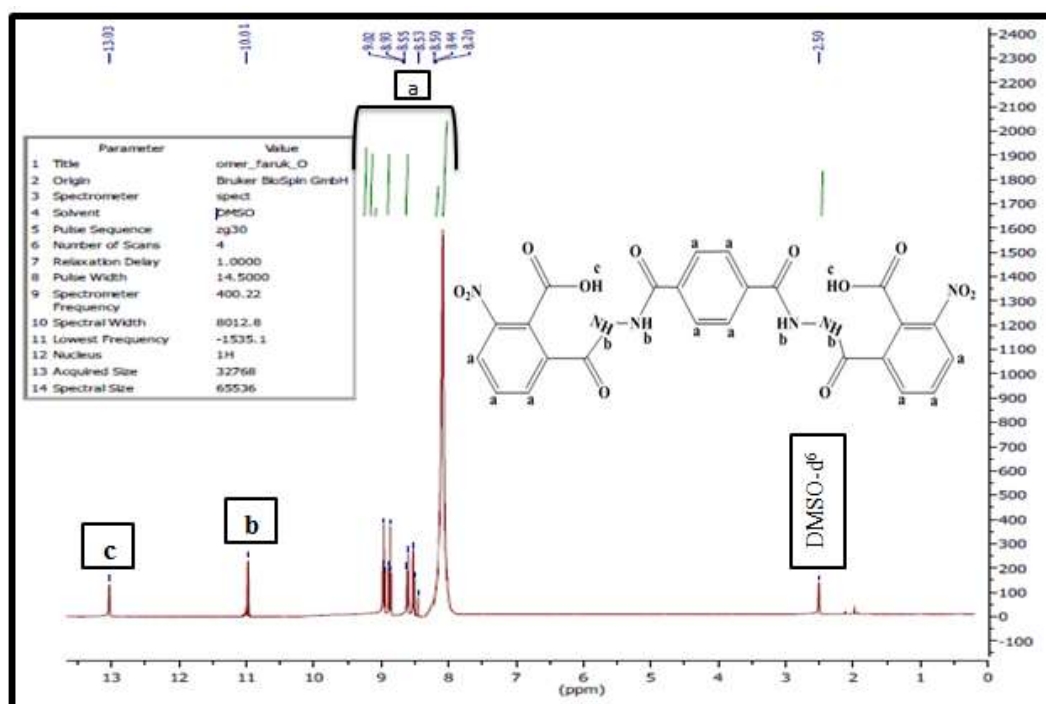
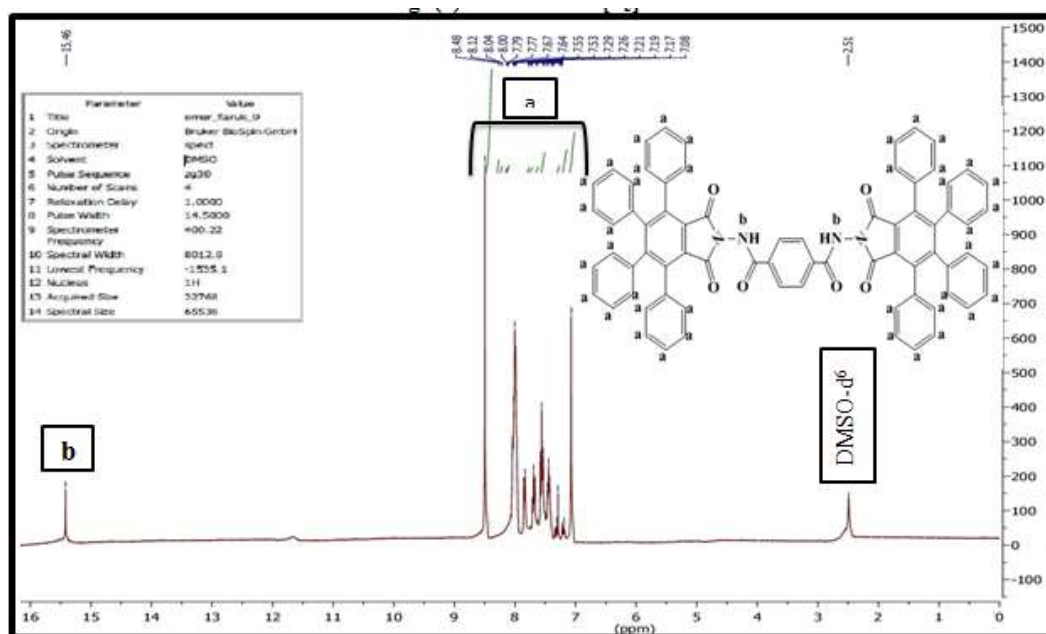
Fig. (7): ^1H -NMR of $[\text{S}_5]$.



Fig. (9): Antibacterial activity of compound [S₇] against for *Escherichia coli*.



Fig. (11): Antibacterial activity of compound [S₁₂] against for *Staphylococcus aureus*.



Fig. (10): Antibacterial activity of compound [S₈] against for *Pseudomonas ariginosa*.



Fig. (12): Antibacterial activity of compound [S₆] against for *Staphylococcus pyogenes*.

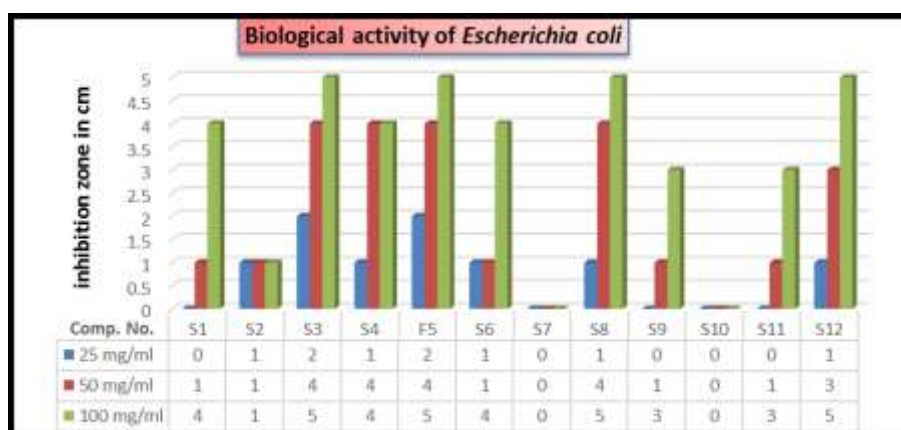
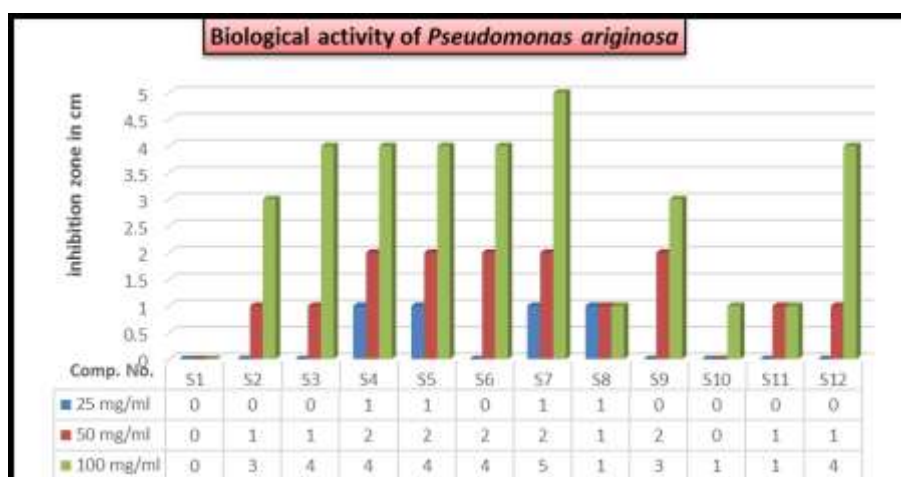
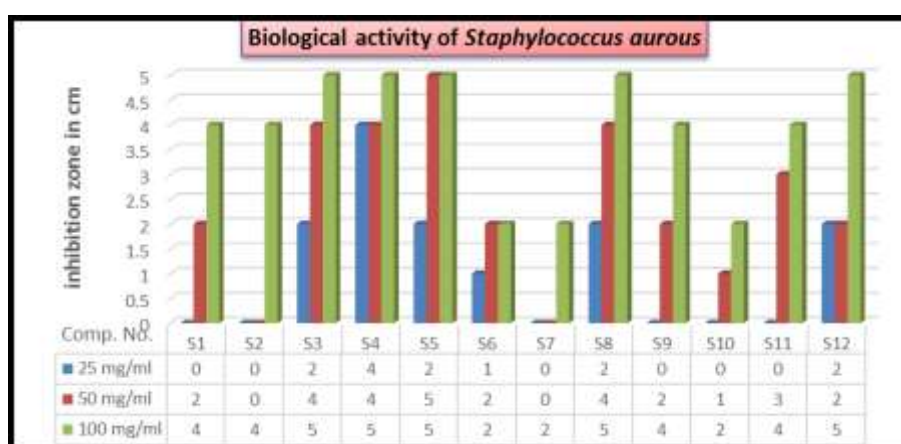
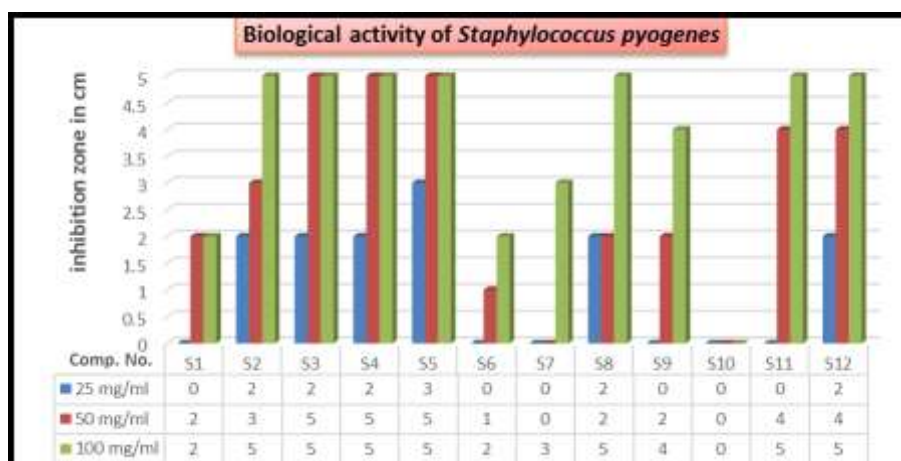


Fig. (13): Evaluation of inhibitory activity of compounds prepared for *Escherichia coli*.

Fig. (14): Evaluation of inhibitory activity of compounds prepared for *Pseudomonas ariginosa*Fig. (15): Evaluation of inhibitory activity of compounds prepared for *Staphylococcus aureus*Fig. (16): Evaluation of inhibitory activity of compounds prepared for *Staphylococcus pyogenes*.

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تحضير وتشخيص بعض حوامض الأميك والإيميدات الجديدة ودراسة الفعالية البايولوجية لها

سلوى عبد الستار جبار

قسم الكيمياء ، كلية التربية للبنات ، جامعة تكريت ، تكريت ، العراق

الملخص

تضمن هذا البحث تحضير بعض حوامض الأميك والإيميدات الجديدة، ابتداءً من استرة حامض التيريفيثاليك [S₁] مروراً بالهيدرازيد [S₂] ومن ثم مشتقات حوامض الأميك [S₃-S₇] وإنهاءً بالإيميدات المقابلة [S₈-S₁₂]. حضر الاستر بعملية الاسترة الإعتيادية للحامض التيريفيثاليك مع الإيثانول المطلق في وسط حامضي والتي تم تحويلها إلى الهيدرازيد المقابل [S₂] من خلال تفاعلها مع الهيدرازين المائي، حضرت مشتقات حوامض الأميك من مفاعلة الهيدرازيد مع الإنهيدريدات (2,3- ثنائي مثيل ماليك إنهيدريد، 3- نايثرو فثاليك إنهيدريد، سداسي هيدرو فثاليك إنهيدريد، دايفينيك إنهيدريد، رباعي فنيل فثاليك إنهيدريد) في ثنائي أثيل إيثر، وكما حضرت الإيميدات من خلال الغلق الحلقي لمشتقات حوامض الأميك بوجود حامض الخليك اللامائي وخلات الصوديوم. ثم شخصت المركبات المحضرة بالطرائق الطيفية مثل طيف الأشعة فوق البنفسجية [UV] وطيف الأشعة تحت الحمراء [FT-IR] وأطياف الرنين النووي المغناطيسي [¹H – NMR] والتحليل الكمي للعناصر (C.H.N.) وتعيين درجات الانصهار، ومتابعة سير التفاعلات بكروماتوغرافيا الطبقة الرقيقة TLC، وتقييم الفعالية البايولوجية لبعض المركبات المحضرة على نمو أربعة أنواع من العزلات البكتيرية وهي أشريشيا القولون والزائفة الزنجارية والمكورات العنقودية الذهبية والعقدية المقيحة.