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

Salwa Abd Al-Satar Jabbar

Department of Chemistry, College of Education for Women, Tikrit University , Tikrit , Iraq

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Corresponding Author:

Name:

Salwa Abd Al-Satar Jabbar

E-mail: Drsalwa85@yahoo.com

Tel:

Abstract

This study includs the synthesis of some new Amic acid and Imides, starting from the esters [S_1] of Terephthalic acid which then converted to its hydrazide [S_2] then to amic acid derivatives [S_3-S_7] and finally with imides [S_8-S_{12}]. Preparing of ester [S_1] by usual esterification of terephthalic acid with absolute ethanol in acidic medium, then has converted to its hydrazide [S_2] by reacting it with hydrazine hydrate. The amic acid derivatives [S_3-S_7] have been synthesized by the reaction of hydrazide [S_2] with anhydrides (2,3-dimethyl malic anhydride, 3-nitro phthalic anhydride, hexahydro phthalic anhydride, Diphenic anhydride, tetra Phenyl phthalic anhydride) in diethyl ether. Imides [S_8-S_{12}] 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 H^1-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. aurous* 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 cystene-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. H^1-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 [S_1] [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 [S_1] was white colored, M.P. (113-115) ^{0}C, yield 72%, Rf 0.62 and re-crystallized with ethanol as a solvent.

Synthesis of hydrazide [S_2] [6]:

Dissolved ester prepared [S_1] (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 [S_2] was white colored, M.P. (43-45) ^{0}C, yield 79%, Rf 0.81 and re-crystallization solvent ethanol.

Synthesis of amic acid derivatives [S_3-S_7] [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 [S_2] 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 Rf of these derivatives were given in table (1).

Table (1): physical properties, yield and Rf of compounds [S_3-S_7].

Comp. No.	Molecular Formula	Color	M.P ^oC	Yield %	R.f	Crystalline solvent
$_3$**S**	$C_{20}H_{22}N_4O_8$	light Yellow	128-130	65	0.82	Acetone
$_4$**S**	$C_{24}H_{30}N_4O_8$	White	300>	74	0.87	Acetone
$_5$**S**	$C_{24}H_{16}N_6O_{12}$	White	138-140	63	0.70	Ethanol
$_6$**S**	$C_{36}H_{26}N_4O_8$	light Yellow	165-167	72	0.85	Ethanol
$_7$**S**	$C_{72}H_{50}N_4O_8$	White	138-140	63	0.75	Ethanol

Synthesis of imide derivatives [S_8-S_{12}] [8,9]:
(0.01mol) of compounds [S_3-S_7] 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 Rf of these derivatives were given in table (2).

Table (2): physical properties, yield and Rf of compounds [S_8-S_{12}].

Comp. No.	Molecular Formula	Color	M.P ^oC	Yield %	R.f	Crystalline solvent
$_8$**S**	$C_{20}H_{18}N_4O_6$	White	300>	76	0.65	Acetone
$_9$**S**	$C_{24}H_{26}N_4O_6$	Yellow	230-232	65	0.81	Ethanol
S_{10}	$C_{24}H_{16}N_6O_{10}$	White	290-291	79	0.60	Ethanol
$_{11}$**S**	$C_{36}H_{22}N_4O_6$	Yellow	200-203	74	0.87	Dioxane
$_{12}$**S**	$C_{72}H_{46}N_4O_6$	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 ^{0}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 ^{0}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 ^{0}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):

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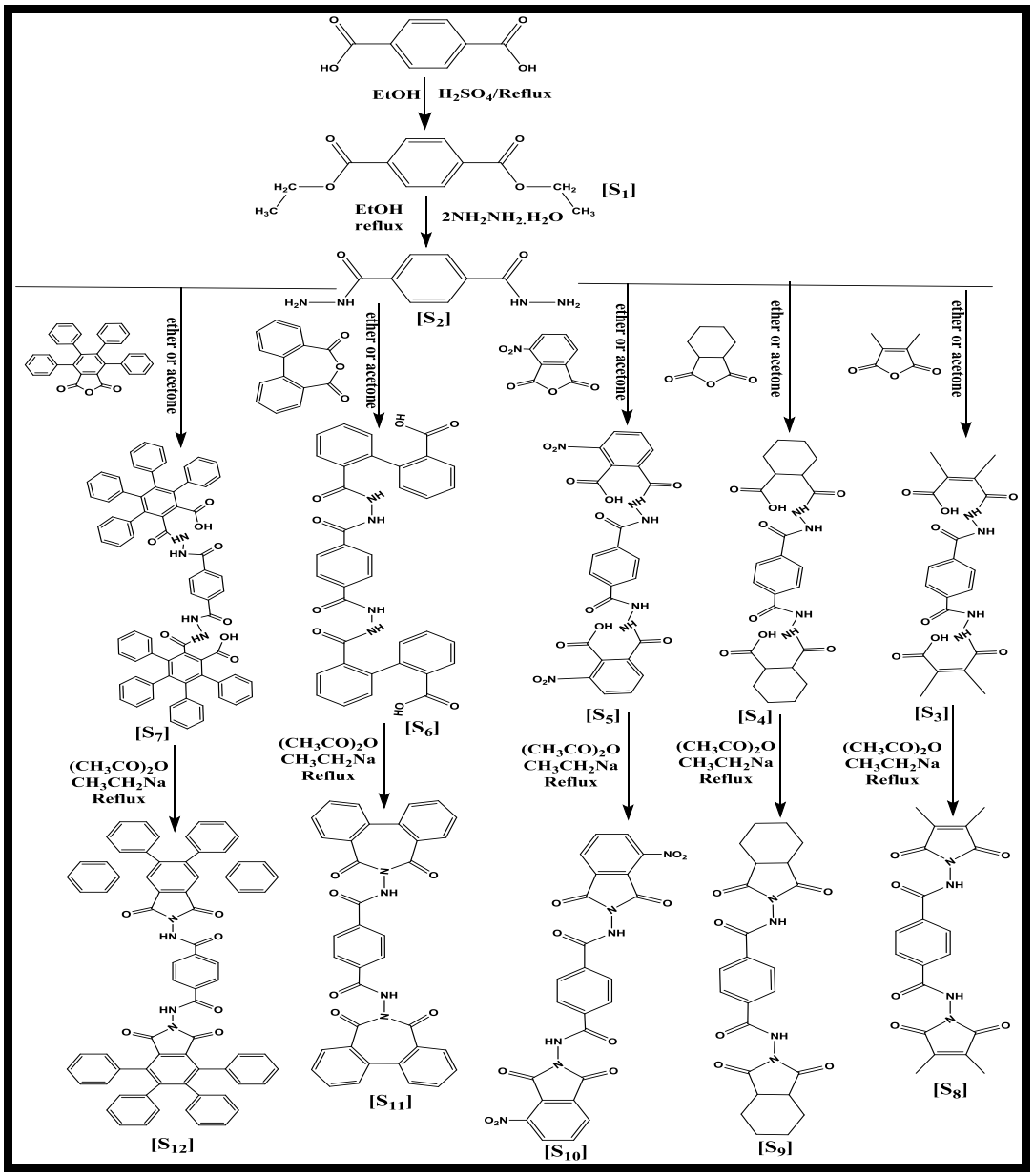

Scheme (1): synthesis of compounds [S_1 – S_{12}].

Results and Discussion:

Characterization of amic acid derivatives:

Amic acid derivatives have synthesized from the reaction of compound [S_2] with deferentes anhydride. Beside UV spectra showed the transions n→π* and π→π* 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).

^{1}H-NMR spectrum of compound (S_5) showed singlet signal at δ= (2.50) ppm due to DMSO-d^6 solvent, multiple signal (8.20 - 9.02) ppm due to aromatic rings, singlet signal at δ= (10.01) ppm due to N-H amic acid, and singlet signal (13.03) ppm due to O-H carboxylic acid. ^{1}H-NMR spectrum of compound [S_5] is given in fig (7).

Table (3): UV/Vis and FT-IR of the prepared compounds [S_3-S_7].

Comp. No.	λ_1 max $_2\lambda$ 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)
$_3$S	270 337	3332	3269	3053 2958	1749 1659	1473 1588
$_4$S	261 393	3400	3213	3003 2937	1728 1656	1429 1573
$_5$S	248 398	3568	3199	3043 -	1730 1681	1487 1597
$_6$S	217 342	3359	3277	3035 -	1722 1673	1455 1561
$_7$S	239 305	3446	3282	3091 -	1719 1667	1482 1545

Characterization of imide derivatives:

Imide derivatives have synthesized by dehydration of compounds [S_3-S_7] using acetic anhydride with sodium acetate anhydrous. Beside UV spectra which showed the transions n→π* and π→π* 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).

^{1}H-NMR spectrum of compound (S_{12}) showed singlet signal at δ= (2.51) ppm due to DMSO-d^6 solvent, multiple signal (7.08 - 8.48) ppm due to aromatic rings and singlet signal at δ= (15.46) ppm due to N-H imide. ^{1}H-NMR spectrum of compound [S_{12}] is given in fig (8).

Table (4): UV/Vis and FT-IR of the prepared compounds [S_8-S_{12}].

Comp. No.	λ_1 max $_2\lambda$ max	IR (KBr) cm^{-1}			
		ν (N-H)	ν(C-H) Arom. ν(C-H) Aliph.	ν(C=O) Imide	ν (C=C)
$_8$S	240 388	3259	3037 2945	1675	1460 1583
$_9$S	229 368	3238	3071 2928	1669	1488 1580
$_{10}$S	209 249	3213	3030 -	1689	1465 1598
$_{11}$S	237 367	3204	3066 -	1690	1476 1591
$_{12}$S	246 392	3225	3005 -	1653	1446 1573

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

Comp. No.	Molecular Formula	Found				Calculated			
		C%	H%	N%	O%	C%	H%	N%	O%
S_3	$C_{20}H_{22}N_4O_8$	53.81	4.97	12.55	28.67	53.98	4.88	12.75	28.47
S_5	$C_{24}H_{16}N_{6O12}$	49.66	2.78	14.48	33.08	49.41	2.50	14.44	32.97
S_7	$C_{72}H_{50}N_4O_8$	78.67	4.59	5.10	11.64	78.49	4.50	5.04	11.69
S_8	$C_{20}H_{18}N_4O_6$	58.54	4.42	13.65	23.39	57.82	4.48	13.57	23.18
S_{10}	$C_{24}H_{12}N_6O_{10}$	52.95	2.22	15.44	29.39	52.79	2.11	15.37	29.28
S_{12}	$C_{72}H_{46}N_4O_6$	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[S_1-S_{12}] were examined by the agar diffusion method using four different bacterial species ***Escherichia coli, Pseudomonas ariginosa, Staphylococcus aurous*** and ***Staphylococcus pyogenes***. The results indicated that all the assayed compounds showed a microbial activity against the used bacterial. Antibacterial activity of compounds [A_6, A_7, A_8, A_{12}] 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	*E. coil*	*P. ariginosa*	*S. aureus*	*S. pyogenes*	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
$_{10}S$	25	-	-	-	-	0
	50	-	-	+	_	0-1
	100	-	+	+	-	1-2
$_{11}S$	25	-	-	-	-	0
	50	+	+	++	++	1-4
	100	++	+	++	+++	1-5
$_{12}S$	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*	*E. Coil*	*S. pyogenes*	*S. aureus*	*P. ariginosa*
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

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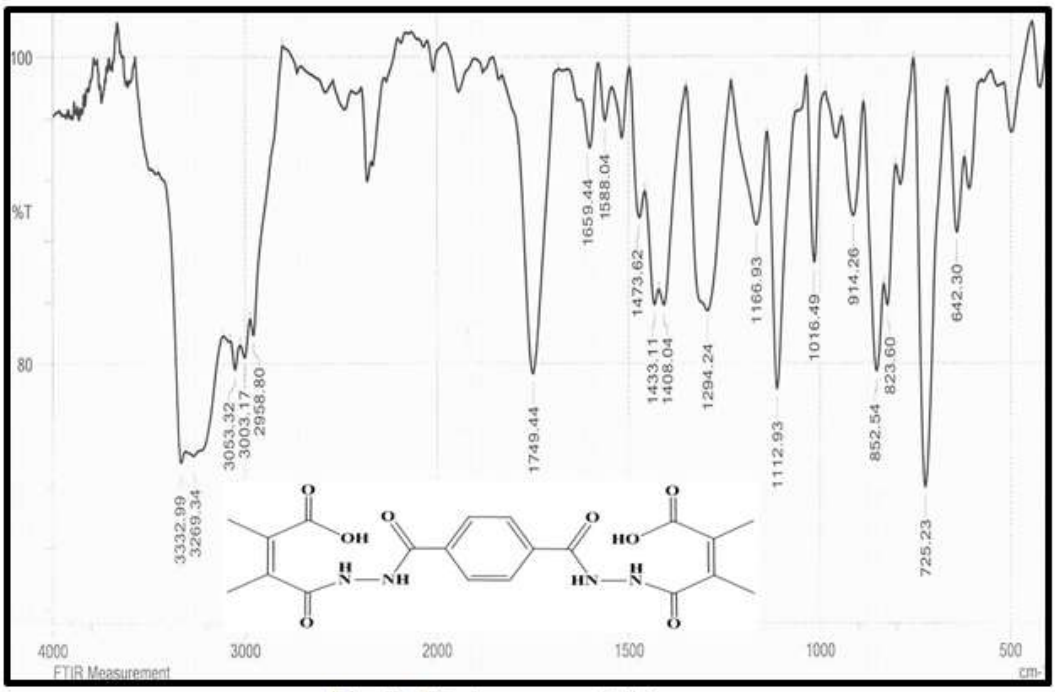

Fig. (1): FTIR spectrum of [S_3].

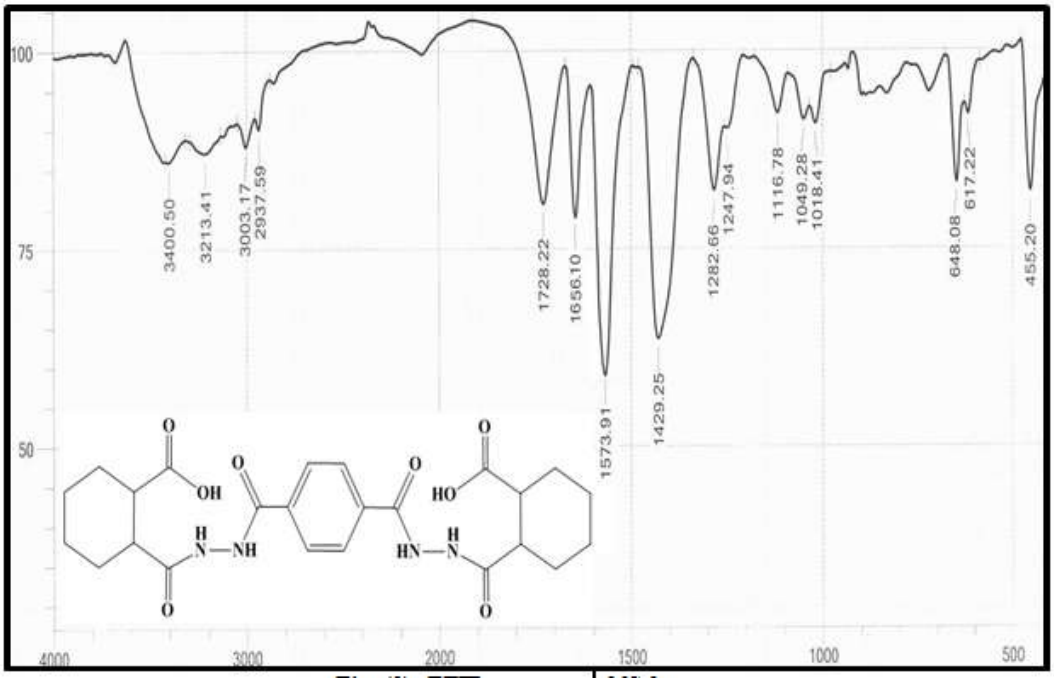

Fig. (2): FTIR spectrum of [S_4].

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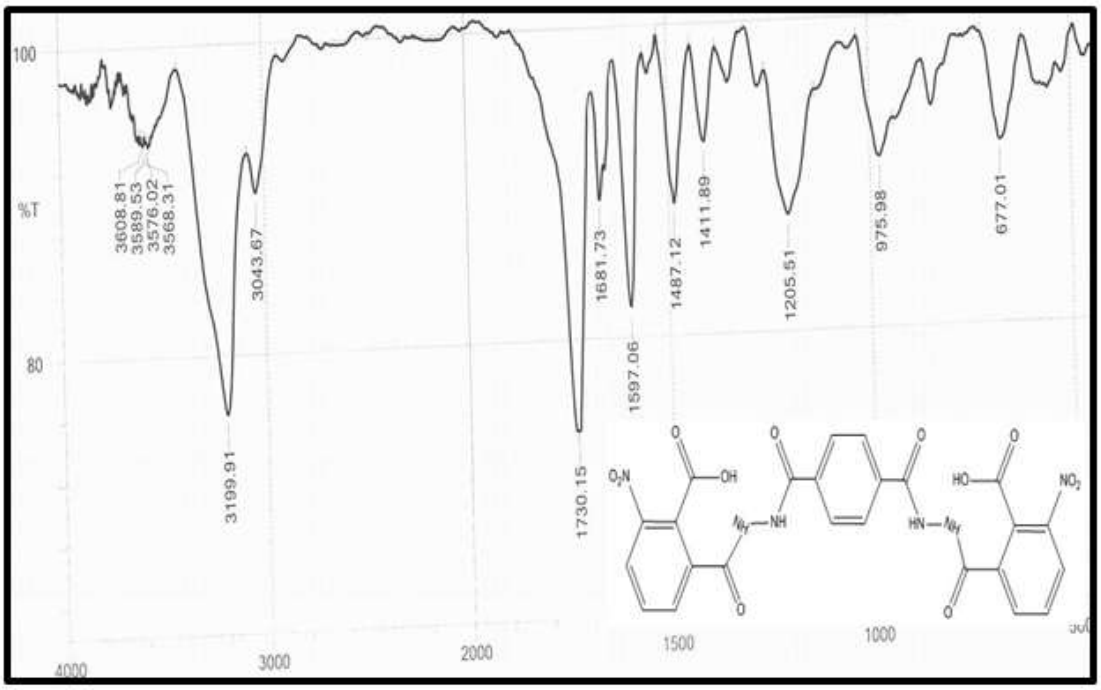

Fig. (3): FTIR spectrum of [S_5].

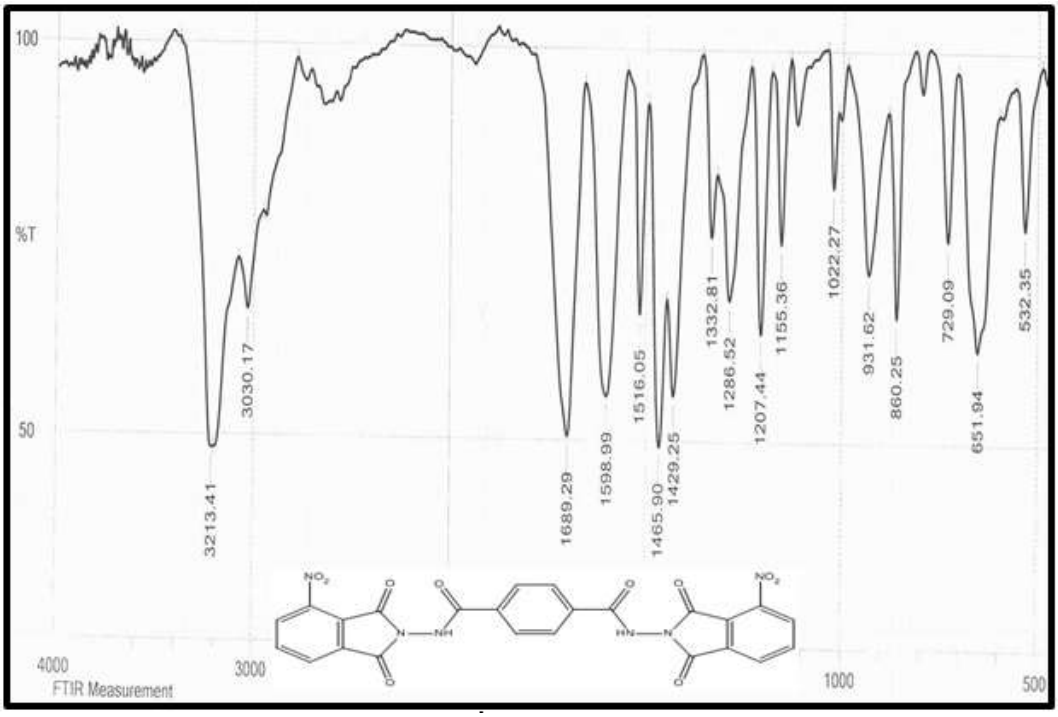

Fig. (4): FTIR spectrum of [S_{10}].

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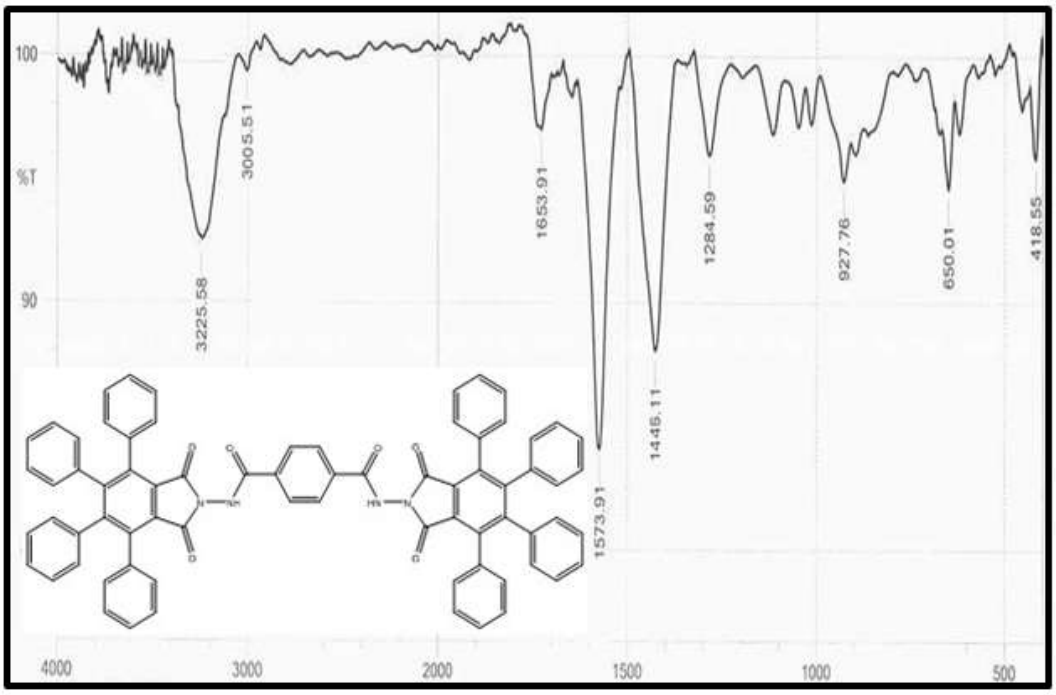

Fig. (5): FTIR spectrum of [S_{12}].

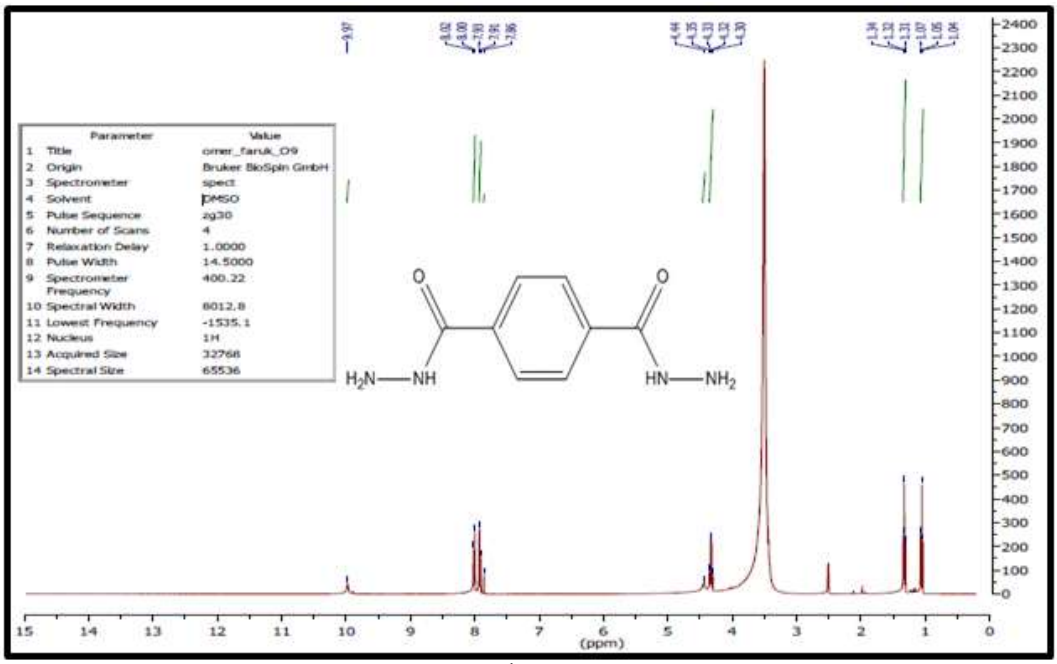

Fig. (6): H^1-NMR of [S_2].

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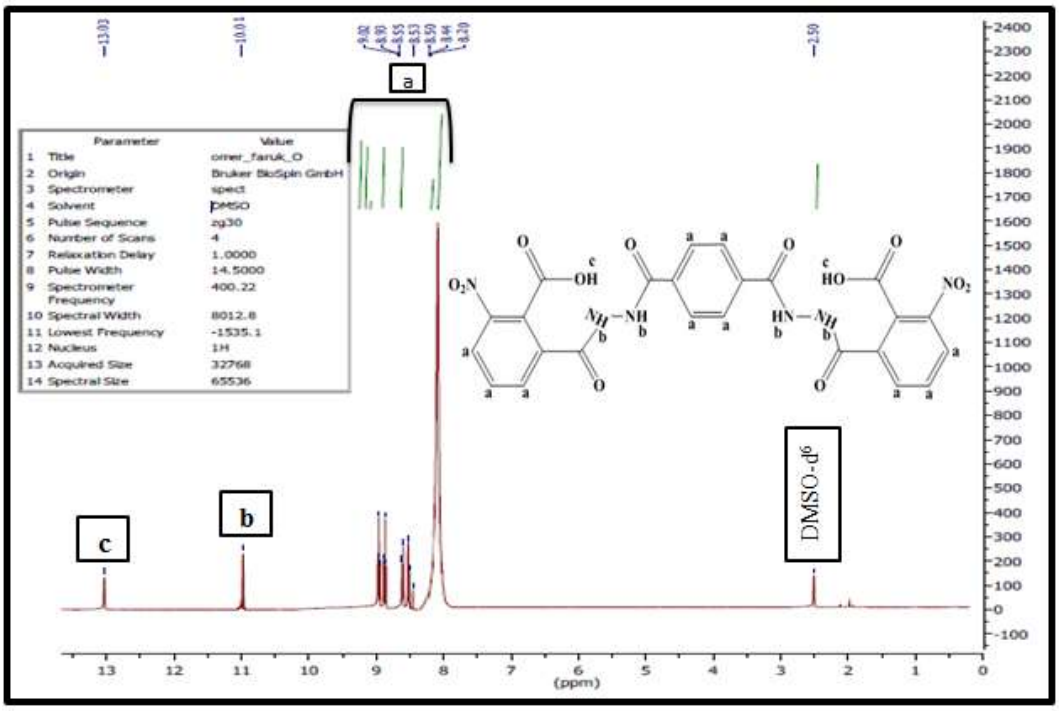

Fig. (7): H^1-NMR of [S_5].

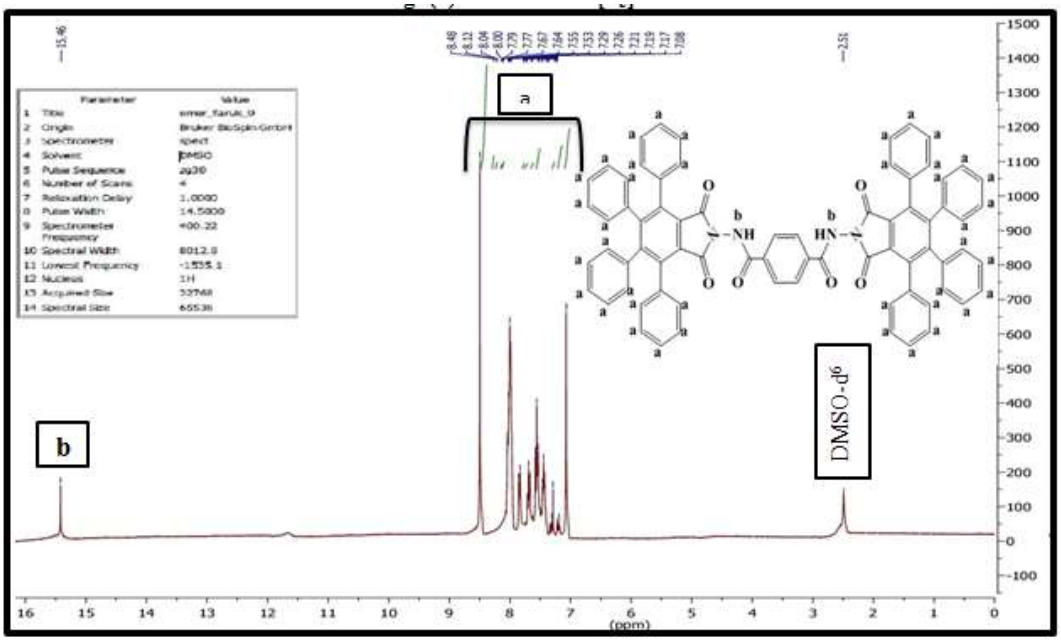

Fig. (8): H^1-NMR of [S_{12}].

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Fig. (9): Antibacterial activity of compound [S_7] against for *Escherichia coli.*

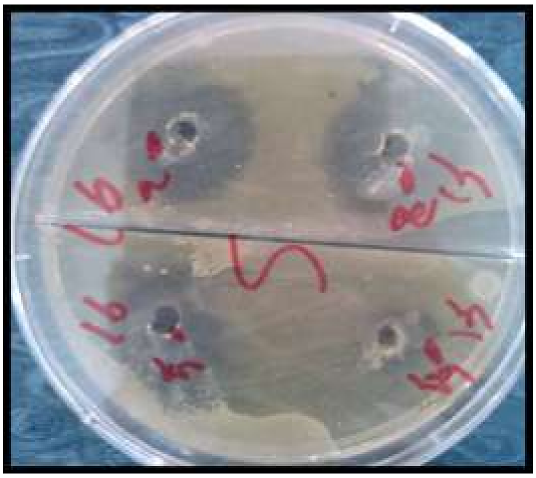

Fig. (11): Antibacterial activity of compound [S_{12}] against for *Staphylococcus aureus.*

Fig. (10): Antibacterial activity of compound[S_8] against for *Pseudomonas ariginosa.*

Fig. (12): Antibacterial activity of compound [S_6] against for *Staphylococcus pyogenes.*

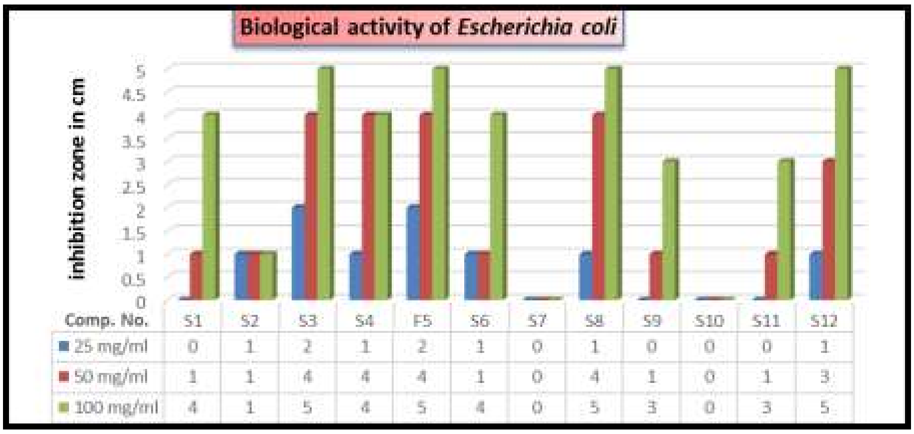

Fig. (13): Evaluation of inhibitory activity of compounds prepared for *Escherichia coli.*

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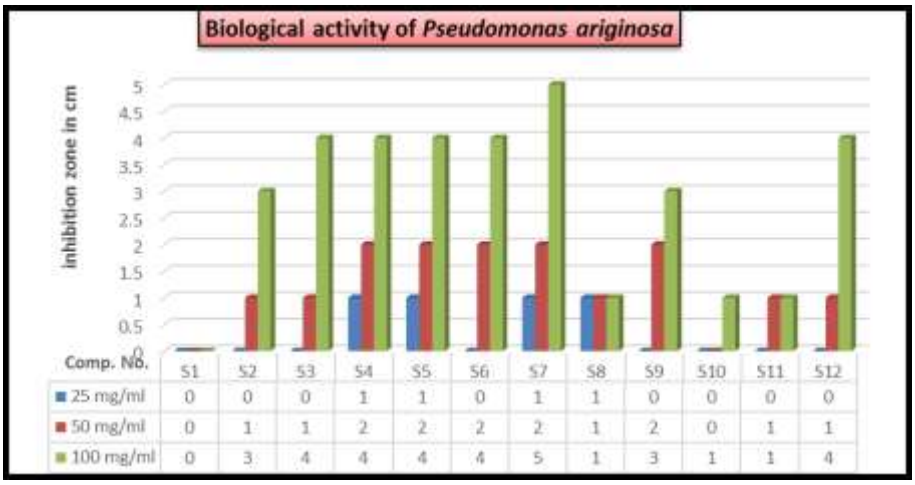

Fig. (14): Evaluation of inhibitory activity of compounds prepared for *Pseudomonas ariginosa*

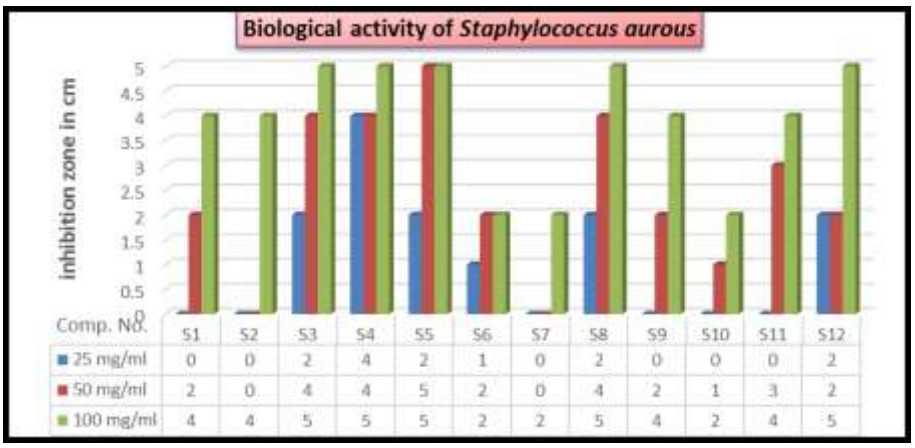

Fig. (15): Evaluation of inhibitory activity of compounds prepared for *Staphylococcus aureus*

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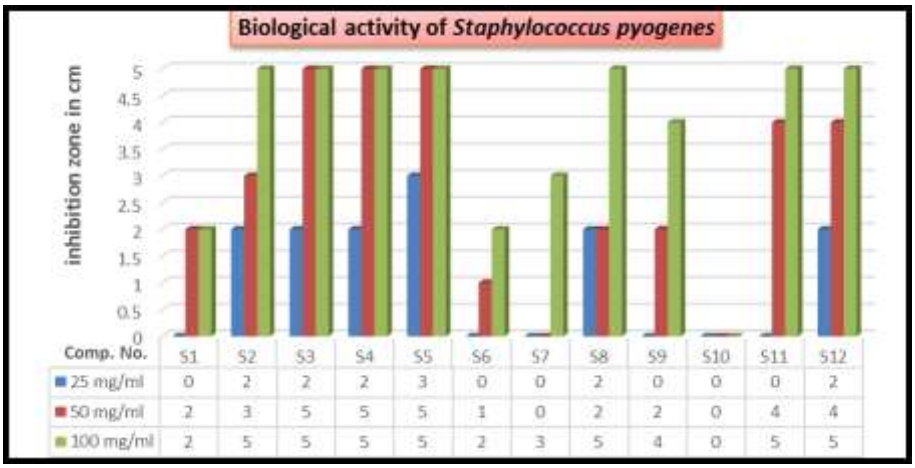

Fig. (16): Evaluation of inhibitory activity of compounds prepared for *Staphylococcus pyogenes.*

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تحضير وتشخيص بعض حوامض الأميك والإيميدات الجديدة ودراسة الفعالية البايولوجية لها

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

الملخص

تضمن هذا البحث تحضير بعض حوامض الأميك والإيميدات الجديدة، ابتداءاً من استرة حامض التيرفيثاليك [S_1] مروراً بالهيدرازايد [S_2] ومن ثم مشتقات حوامض الأميك [S_3-S_7] وإنتهاءاً بالإيميدات المقابلة [S_8-S_{12}]. حضر الاستر بعملية الاسترة الإعتيادية للحامض التيرفيثاليك مع الإيثانول المطلق في وسط حامضي والتي تم تحويلها إلى الهيدرازايد المقابل [S_2] من خلال تفاعلها مع الهيدرازين المائي، حضرت مشتقات حوامض الأميك من مفاعلة الهيدرازايد مع الإنهيدريدات (3,2- ثنائي مثيل ماليك إنهيدريد، 3- نايترو فثاليك إنهيدرايد، سداسي هيدرو فثاليك إنهيدرايد، دايفينك إنهيدرايد، رباعي فنيل فثاليك إنهيدرايد) 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 [^{1}H – 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.