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Synthesis and Characterization of Some Derivatives 1,2,3,4- Tetra Hydro Pyrimidine by Using Three Components Reactions and study the Biological Activity

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Abstract

This paper includes a preparation of a number of heterogeneous ring compounds through a three-component reaction methods. The work started with the synthesis of derivatives 1,2,3,4-tetrahydropyrimidine-5-carboxylate [K1-K6] through the reaction of three substances together and at the same time; ethyl acetoacetate, urea, thiourea and benzaldehyde substitutes. Then synthesis of substituted 1,2,3,4-tetrahydropyrimidine-5-carboxylic acid compounds [K7-K12] through the aqueous base hydrolysis reaction of the compounds [K1-K6] with 5% KOH aqueous solution following by neutralize the product with HCl solution. The synthesized compounds were identified by spectral methods: UV, FT-IR and H1- NMR beside melting point and the purity was determined by using (TLC). Some of these compounds are tested against four strains of bacteria (P. aeruginosa and S. aurous).

تحضير وتشخيص عدد من معوضات 4,3,2,1- رباعي هيدروبايريميدين باستخدام التفاعلات ثلاثية المكونات وتقييم الفعالية البايولوجية لبعض منها

كمال ياسين علي محمد غازي عبد الكريم

الخلاصة

يتضمن هذا البحث تحضير عدد من المركبات الحلقية غير المتجانسة من خلال طرائق التفاعلات ثلاثية المكونات حيث حضرت معوضات 4,3,2,1–رباعي هايدروبايريميدين –5– كاربوكسيليت [K_6-K_1] (نواة بجنيلي) من مفاعلة ثلاث مواد معاً وفي آنٍ واحد وهي اثيل أسيتو استيت ويوريا (أو ثايو يوريا) وأحد معوضات البنزالديهايد، ثم تحضير مشتقات 4,3,2,1– رباعي هايدروبايريميدين–5–حامض الكاربوكسيل [K_{12}-K_7] من مفاعلة مشتقات نواة بجنيلي [K_6-K_1] مع محلول 5% من هيدروكسيد الصوديوم، وكما في المخطط رقم (1). وشخصت المركبات المحضرة بالطرائق الطيفية المتوفرة مثل طيف الأشعة فوق البنفسجية وطيف الأشعة تحت الحمراء وأطياف الرنين النووي المغناطيسي للبروتون والتحليل الكمي للعناصر وتعيين درجات الانصهار، ومتابعة سير التفاعلات بكروماتوغرافيا الطبقة الرقيقة، وتقييم الفعالية البايولوجية لبعض المركبات المحضرة على نمو نوعين من العزلات البكتيرية وهي ***الزائفة الزنجارية والمكورات العنقودية الذهبية.***

الكلمات المفتاحية: التفاعلات الثلاثية المكونات، تفاعل بجنيلي، مشتقات 4,3,2,1–رباعي هيدروبايريميدين.

Introduction

Multicomponent reaction (MCR) is a synthetic methodology in which three or more reactants come together in a one reaction vessel to form a new product [1]. The characteristic aspect of MCRs is that the final products contain almost all portions of substrates, generating almost no by-products. That makes MCRs an extremely ideal and eco-friendly reaction system [2]. Target compounds can be obtained in one pot with much fewer steps [3]. Therefore, MCRs have been paying much attention in various research fields, such as detection of lead compounds in medicinal chemistry, or combinatorial chemistry [4]. There have been a number of reports on MCRs so far, and typical example are described as following [5]. In 1891, an Italian chemist, P. Biginelli had reported the three components MCR using B-keto esters such as ethyl acetoacetate, aromatic aldehydes such as benzaldehyde, and ureas (or theories) in the presence of an acid catalyst (Brönsted or Lewis acids), affording dihydropyrimidinone derivatives [6]. Dihydropyrimidinones have been paying much attention because of their various bioactivities such as anti-inflammatory or anti-bacterial activities [7].

Experimental

Material: All chemicals were used in this work had purchased from Fluka, Aldrich.

Devices used: Melting points were recorded using a measuring device melting point type: Automatic melting point\SMP40 and were uncorrected. Thin layer chromatography (TLC) was carried out using sheet Polygram silica- gel as the stationary phase, the spots were enhanced using UV rays. UV-Vis. Spectra were recorded with spectrophotometer type: SHIMADZU UV spectrophotometer -1800 using Ethanol as a solvent. Infrared spectra

were recorded using FT-IR-600 Fourier-Transform infrared (FT-IR) Spectrophotometer by KBr disc. ^{1}H-NMR spectra were recorded on Fourier Transform Varian spectrophotometer operating at 400 MHz with DMSO-d^6. Quantitative analysis of the elements.

Methods of preparation

Synthesis of substituted -1,2,3,4-tetrahydropyrimidine-5-carboxylate compounds (K_1-K_6) [8]:

Mix (0.01 mole 1.3 gm) of ethyl acetoacetate and (0.01 mole) of one of benzaldehyde substitutes and (0.01 mole) of urea or thiourea and (0.0014 mole) of nickel chloride water hexa ($NiCl_2.6H_2O$). Then add (6-5) a drop of hydrochloric acid. In a ceramic mortar mix and then grind the mixture for (2-5) minutes. The mixture turns into a sticky material within (5-20) minutes. Then the solution keep for the next day on the bench, the following day, the precipitate form add of by cold distilled water is washed and then recrystallized with ethanol. Some physical properties and yield are given in Table (1).

Table (1):- Some physical properties and yield of (K_1-K_6).

Comp. No.	R	X	Molecular Formula/ M.Wt g/mol	Color	M.P. (^{0}C)	Yield (%)
K_1	NO_2	S	$C_{14}H_{15}N_3O_4S$ 321.35	Yellow	88-90	79
K_2	$N(CH_3)_2$	S	$C_{16}H_{21}N_3O_2S$ 319.42	Yellow	122-123	86
K_3	H	S	$C_{14}H_{16}N_2O_2S$ 276.35	Green	105-107	71
K_4	Br	O	$C_{14}H_{15}N_2O_3Br$ 339.19	Light green	166-168	69
K_5	Cl	O	$C_{14}H_{15}N_2O_3Cl$ 294.74	Brown	191-193	70
K_6	OH	O	$C_{14}H_{16}N_2O_4$ 276.29	Yellow	218-220	82

Synthesis of substituted 1,2,3,4- tetrahydropyrimidine -5- carboxylic acid compounds (K_7-K_{12}) [9]:

Mix (0.007 mole) one of substituted -1,2,3,4- tetrahydropyrimidine-5-carboxylate compounds (K_1-K_6) with 5% sodium hydroxide solution, then reflux the mixture for (5-8) hours, then cool and neutralize the mixture with 5% hydrochloric acid solution. Filter the precipitate and recrystallize with ethanol. Some physical properties and yield are given in Table (2).

Table (2): some physical properties and yield of (K_7-K_{12}).

Comp. No.	R	X	Molecular Formula/ M.Wt g/mol	Color	M.P. (^{0}C)	Time Reflux (h.)	Yield (%)
K_7	NO_2	S	$C_{12}H_{11}N_3O_4S$ 293.30	Orange	177-179	8	80
K_8	$N(CH_3)_2$	S	$C_{14}H_{17}N_3O_2S$ 291.37	Green	141-143	8	57
K_9	H	S	$C_{12}H_{12}N_2O_2S$ 248.30	Black	89-91	7	88
K_{10}	Br	O	$C_{12}H_{11}N_2O_3Br$ 311.14	Red	200-202	6	76
K_{11}	Cl	O	$C_{12}H_{11}N_2O_3Cl$ 266.68	Yellow	125-127	6	91
K_{12}	OH	O	$C_{12}H_{12}N_2O_4$ 248.24	Dark yellow	132-134	5	78

The biological activity [10]:

The bacteria species used are listed in table (5). All strains were obtained from the College of Education for Women, Tikrit University. They were grown up to the stationary phase 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.

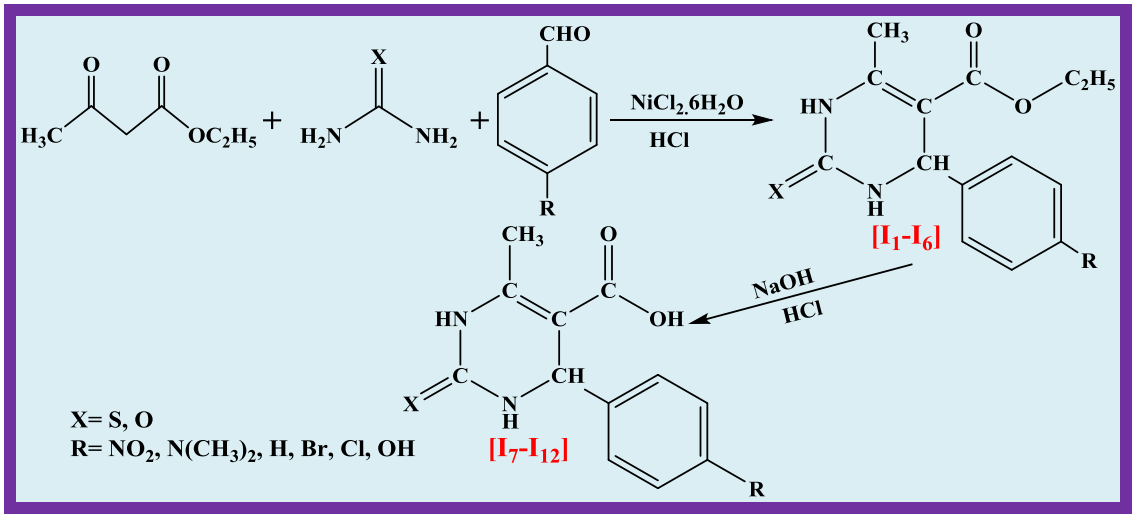
Antibacterial assay [11]:

DMSO was used as a solvent for compounds (K_1, K_3, K_5, K_8, K_{10}, K_{12}). The same solvent was used for antibiotics (Amoxicillin, Ampicillin). The inoculated plates are incubated at 37C$_0$ for 24 hrs. And the inhibition zone (cm) was measured. In all experiments the mean of each triplicate was measured

Results and Discussion

In this work, compounds were synthesized (K_1-K_{12}) as in the following Scheme:

Scheme (1): synthesis of compounds (K_1-K_{12}).



Characterization of substituted -1,2,3,4- tetrahydropyrimidine-5-carboxylate compounds (K_1-K_6):

The UV spectra of 1,2,3,4-tetrahydropyrimidine-5- carboxylate derivatives (K_1-K_6) in general showed the

transitions n→π* and π→π* which have confirmed the presences of the un-bonded electrons pair on nitrogen, oxygen atoms and aromatic system (double bond). The FT-IR spectra of substituted 1,2,3,4-tetrahydropyrimidine -5-carboxylate compounds (K_1-K_6) in general showed disappearance of (NH_2) absorption band and appearances of (NH) absorption band in (3278-3127) cm^{-1}, and appearances of (C=O) absorption band for ester in (1730-1720) cm^{-1}, and appearances of (C=O) absorption band for amid carbonyl in (1676-1660) cm^{-1} for (K_4-K_6), and appearances of (C=S) absorption band in (1101-1027) cm^{-1} for (K_1-K_3). UV and IR absorbance spectra are given in table (3) see fig (1) and (2) [12,13]. ^{1}H-NMR spectrum of compound (K_3) showed singlet signal at δ= (10.14) ppm due to (NH), singlet signal at δ= (8.47) ppm due to (NH), multiple signal (7.55-7.41) ppm due to proton of aromatic ring, singlet signal (7.40) ppm due to chloroform solvent, singlet signal at δ= (4.89) ppm due to (CH) for aliphatic ring, quartic signal at δ= (3.60-3.55) ppm due to (CH_2),), singlet signal at δ= (2.38) ppm due to (CH_3), and triple signal (1.18, 1.19, 1.21) ppm due to (CH_3), see fig (5) [14].

Table (3):- FT-IR and UV/Vis. data of the prepared compounds (K_1-K_6).

Comp. No.	R	X	λ_1 max λ_2 max	IR (KBr) cm^{-1}						
				ν (N-H)	ν(C-H) Arom. Aliph.	ν(C=O) Ester Amide	ν (C=C) Arom.	ν (C-O)	ν (C=S)	Others
K_1	NO_2	S	244 336	3200 3144	3066 2974	1730	1591 1475	1317	1065	ν (NO_2). *asy*.(1538) *sym*.(1370)
K_2	$N(CH_3)_2$	S	231 342	3257 3155	3019 2932	1725	1586 1480	1295	1101	-----
K_3	H	S	204 362	3278 3172	3068 2956	1722	1552 1496	1330	1027	-----
K_4	Br	O	213 387	3243 3127	3010 2989	1731 1676	1579 1473	1329	-----	ν (C-Br) 790
K_5	Cl	O	219 340	3211 3150	3036 2964	1720 1666	1599 1481	1300	-----	ν (C-Cl) 751
K_6	OH	O	225 369	3247 3176	3062 2977	1728 1660	1600 1481	1280	-----	ν (O-H) 3461

Characterization of substituted 1,2,3,4- tetrahydropyrimidine -5- carboxylic acid compounds (K_7-K_{12}):

The UV spectra of 1,2,3,4-tetrahydropyrimidine-5- carboxylic acid derivatives (K_7-K_{12}) in general showed the transitions 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), and the FT-IR spectra1,2,3,4- tetrahydropyrimidine-5-carboxylic acid derivatives (K_7-K_{12}) in general showed disappearance of (C=O) absorption band for ester in (1730-1720) cm^{-1} and appearances of (OH) absorption band for carboxylic acid in (3487-3409) cm^{-1}, (NH) absorption band in (3264-3135) cm^{-1}, appearances of (C=O)

absorption band for carboxylic acid in (1735-1721) cm^{-1}, appearances of (C=O) absorption band for amide in (1672-1668) cm^{-1}, and appearances of (C=S) absorption band in (1097-1071) cm^{-1}. UV and IR absorbance spectra are given in table (4) see fig (3) and (4) [15, 16]. ^{1}H-NMR spectrum of compound (K_8) showed singlet signal at δ= (13.51) ppm due to (OH), singlet signal at δ= (8.64) ppm due to (NH), singlet signal at δ= (8.25) ppm due to (NH), multiple signal (7.55-7.11) ppm due to aromatic rings, singlet signal at δ= (4.52) ppm due to (CH) for aliphatic ring, singlet signal at δ= (3.39) ppm due to ($N(CH_3)_2$), singlet signal at δ= (2.51) ppm due to DMSO-d^6 solvent and singlet signal (2.50) ppm due to (CH_3), see fig (6) [17]

Table (4): FT-IR and UV/Vis. data of the prepared compounds (K_7-K_{12}).

Comp. No.	R	X	λ_1 max λ_2 max	IR (KBr) cm^{-1}							
				ν (O-H)	ν (N-H)	ν(C-H) Arom. Aliph.	ν(C=O) Ester Amide	ν (C=C) Arom.	ν (C-O)	ν (C=S)	Others
K_7	NO_2	S	211 325	3409	3264 3156	3048 2976	1729	1597 1484	1336	1088	ν (NO_2). *asy*.(1550) *sym*.(1310)
K_8	$N(CH_3)_2$	S	246 373	3446	3249 3153	3083 2974	1735	1596 1471	1319	1097	-----
K_9	H	S	258 305	3459	3220 3135	3082 2933	1722	1581 1470	1324	1071	-----
K_{10}	Br	O	219 318	3460	3217 3156	3069 2941	1721 1670	1595 1478	1321	-----	ν (C-Br) 615
K_{11}	Cl	O	252 321	3423	3236 3170	3033 2945	1724 1672	1622 1483	1313	-----	ν (C-Cl) 715
K_{12}	OH	O	229 334	3487	3231 3142	3092 2919	1731 1668	1593 1477	1342	-----	ν (C-OH) 3404

Table (4):- Elemental analysis of some of the prepared compounds.

Comp. No.	Molecular Formula	Found					Calculated				
		C%	H%	N%	O%	S%	C%	H%	N%	O%	S%
K_1	$C_{14}H_{15}N_3O_4S$	52.49	4.66	12.87	20.05	9.90	52.33	4.71	13.08	19.91	9.98
K_5	$C_{14}H_{15}N_2O_3Cl$	57.24	5.08	9.39	16.45	---	57.05	5.13	9.50	16.28	---
K_9	$C_{12}H_{12}N_2O_2S$	57.85	4.90	11.33	13.01	12.78	58.05	4.87	11.28	12.89	12.91
K_{12}	$C_{12}H_{12}N_2O_4$	57.83	4.80	11.47	25.60	---	58.06	4.87	11.29	25.78	---

Biological activity [18]:

The antimicrobial activity of the synthesized compounds [K_1, K_3, K_5, K_8, K_{10}, K_{12}] were examined by the agar diffusion method by using two different bacterial species ***Pseudomonas aeruginosa*** and ***Staphylococcus aurous***.

The results indicated that some of the assayed compounds showed a microbial activity against the used bacterial. As in the figures (7) and (8) and in the Table (5) show Antibacterial activity of some of the prepared compounds.

Table (5): Antibacterial activity of some of the prepared compounds.

Comp. No.	Conc. mg/ml	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	Inhibition distance
K_1	0.0001	-	-	0
	0.001	-	+	1
	0.01	-	++	3
K_3	0.0001	-	-	0
	0.001	+	+	2
	0.01	+	+	2
K_5	0.0001	-	+	1
	0.001	+	+	3
	0.01	+++	+	4
K_8	0.0001	-	-	0
	0.001	+	-	1
	0.01	++	-	3
K_{10}	0.0001	-	-	0
	0.001	+	+	1
	0.01	+	+++	5
K_{12}	0.0001	+	+	1
	0.001	+	+	3
	0.01	+	+++	4

(-) = No inhibition **(+) = Inhibition zone (1-2) cm**
(++) = Inhibition zone (2-4) cm **(+++) = Inhibition zone (4-5) cm**

Table (6): 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*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
1	Amoxicillin	2.7	3.0
2	Ampicillin	2.5	2.5
3	Blank disk	0	0

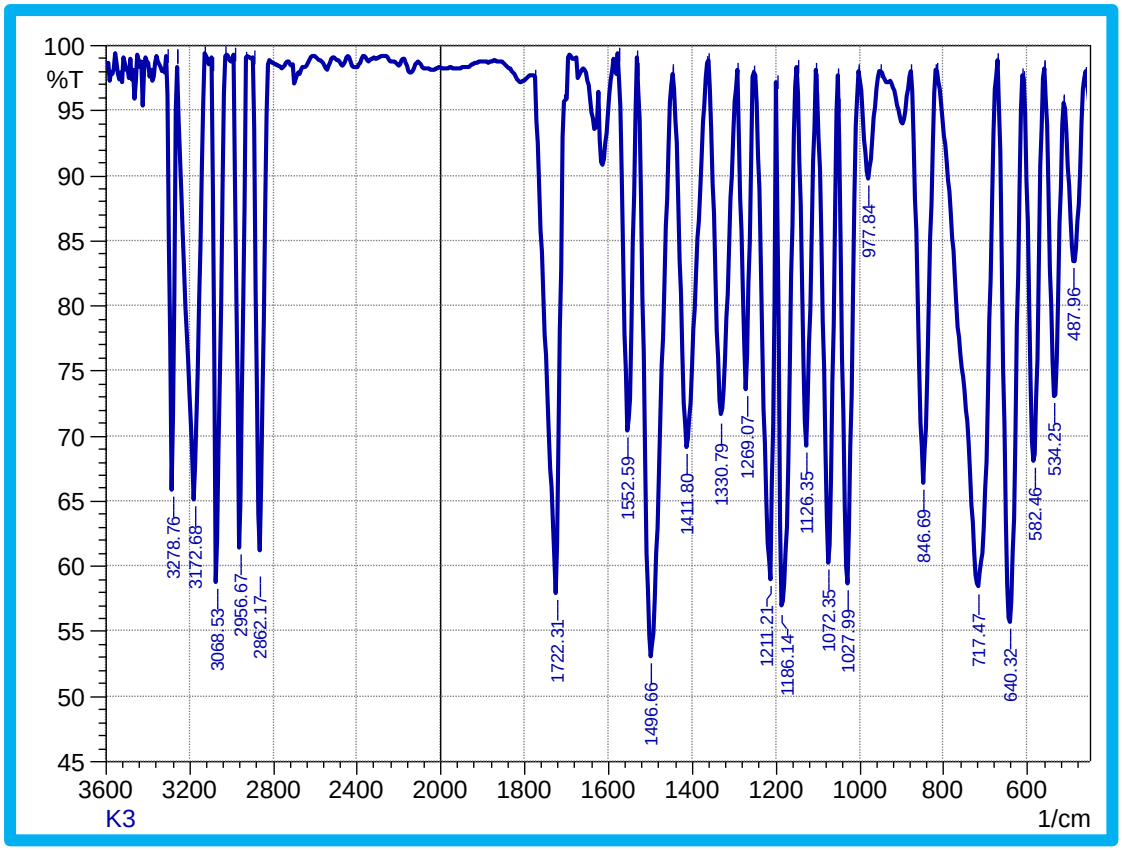


Fig. (1): FT-IR spectrum of compound [K_3].

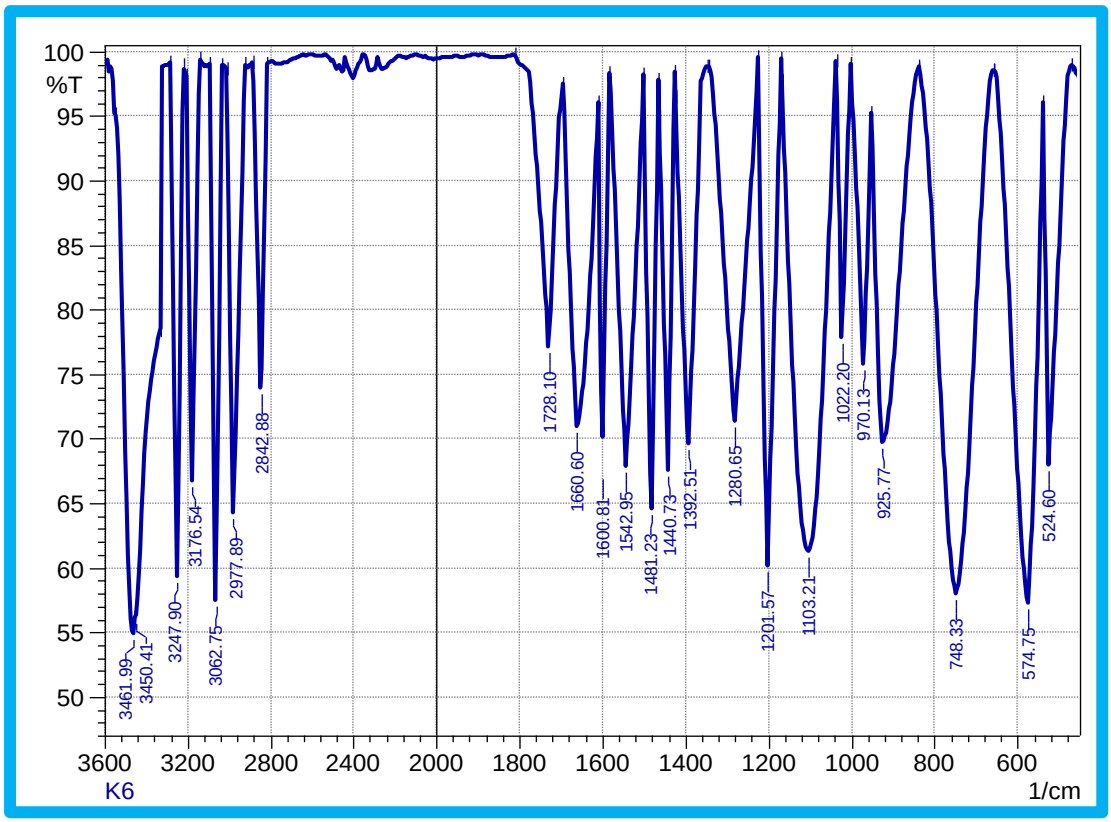


Fig. (2): FT-IR spectrum of compound [K_6].

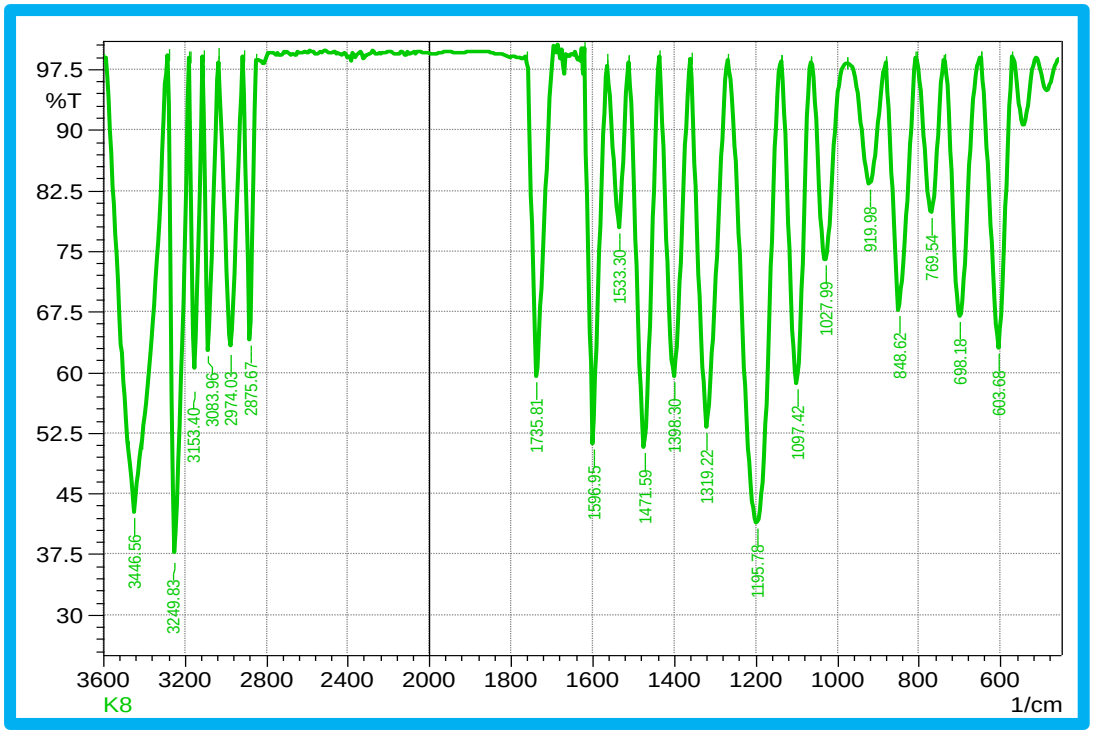


Fig. (3): FT-IR spectrum of compound [K_8].

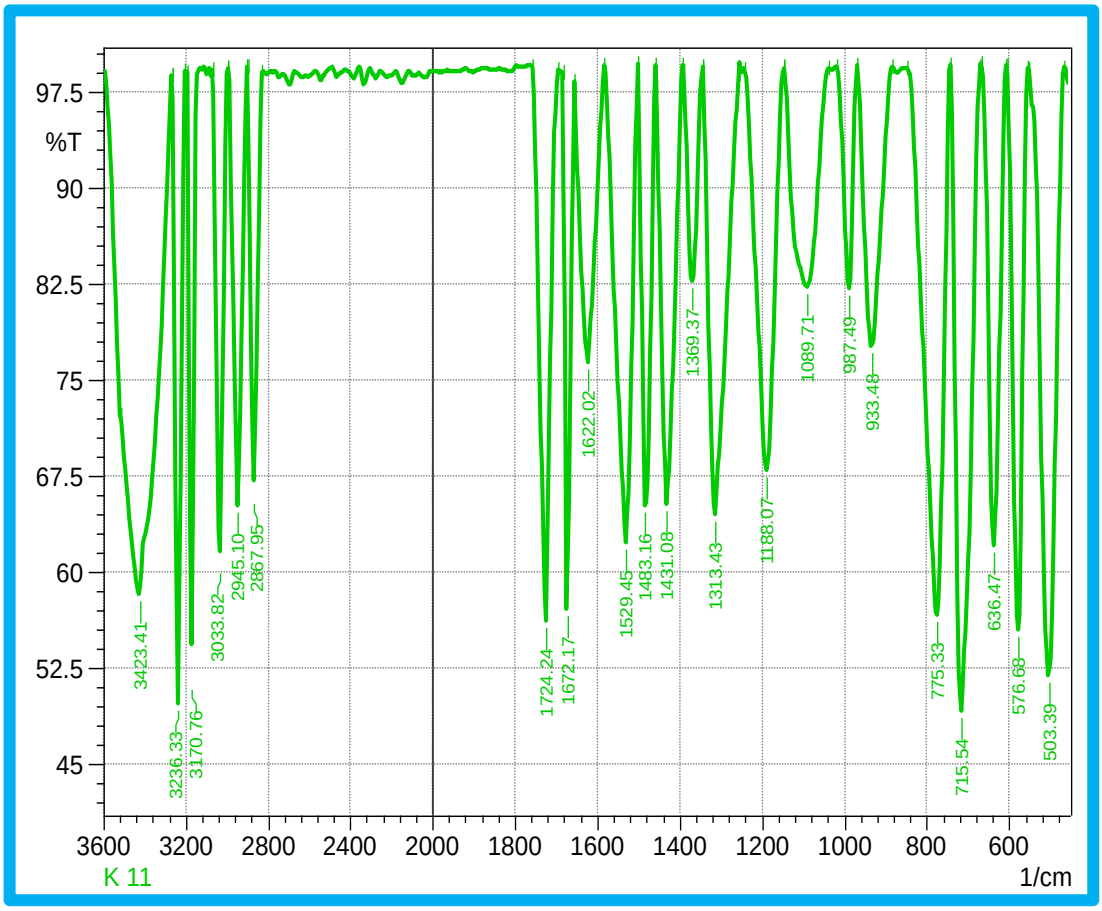


Fig. (4): FT-IR spectrum of compound [K_{11}].

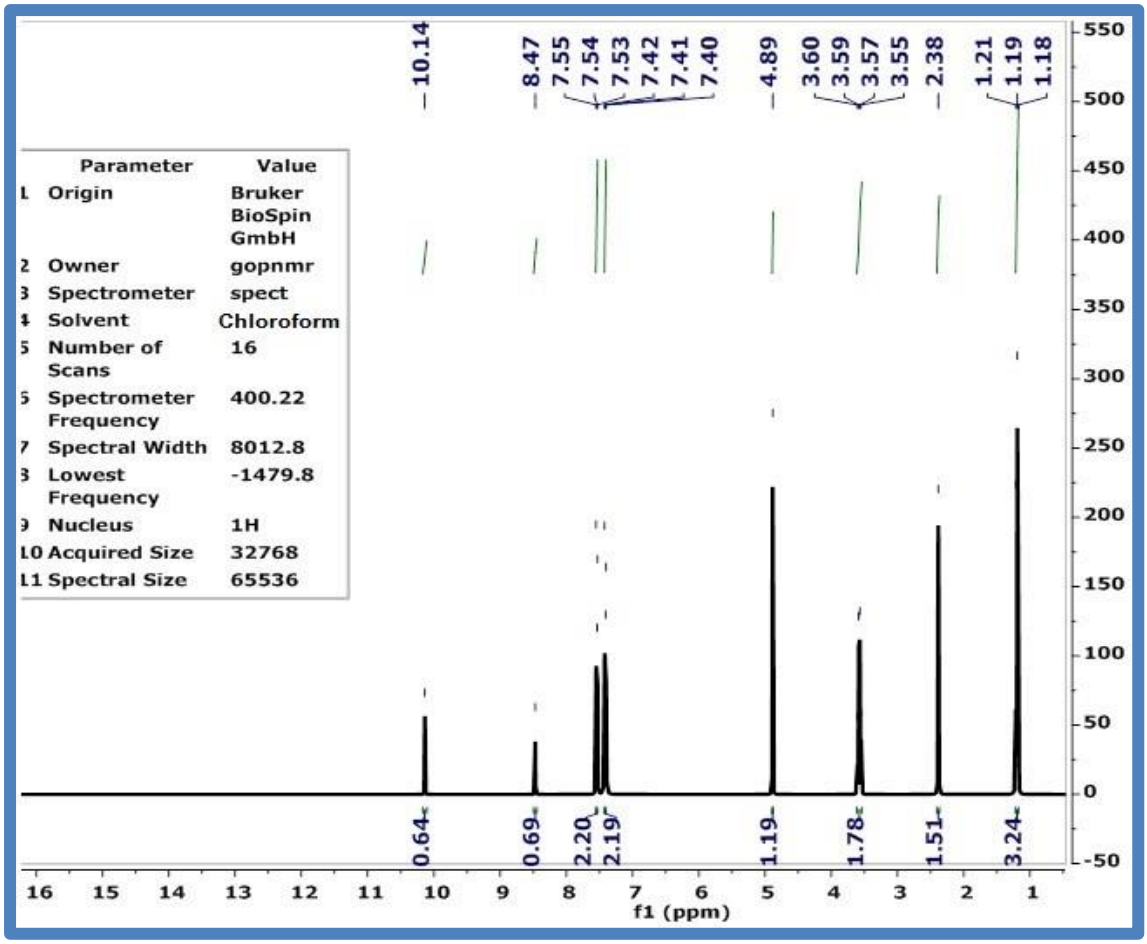


Fig. (5): ^{1}H-NMR spectrum of compound [K_3].

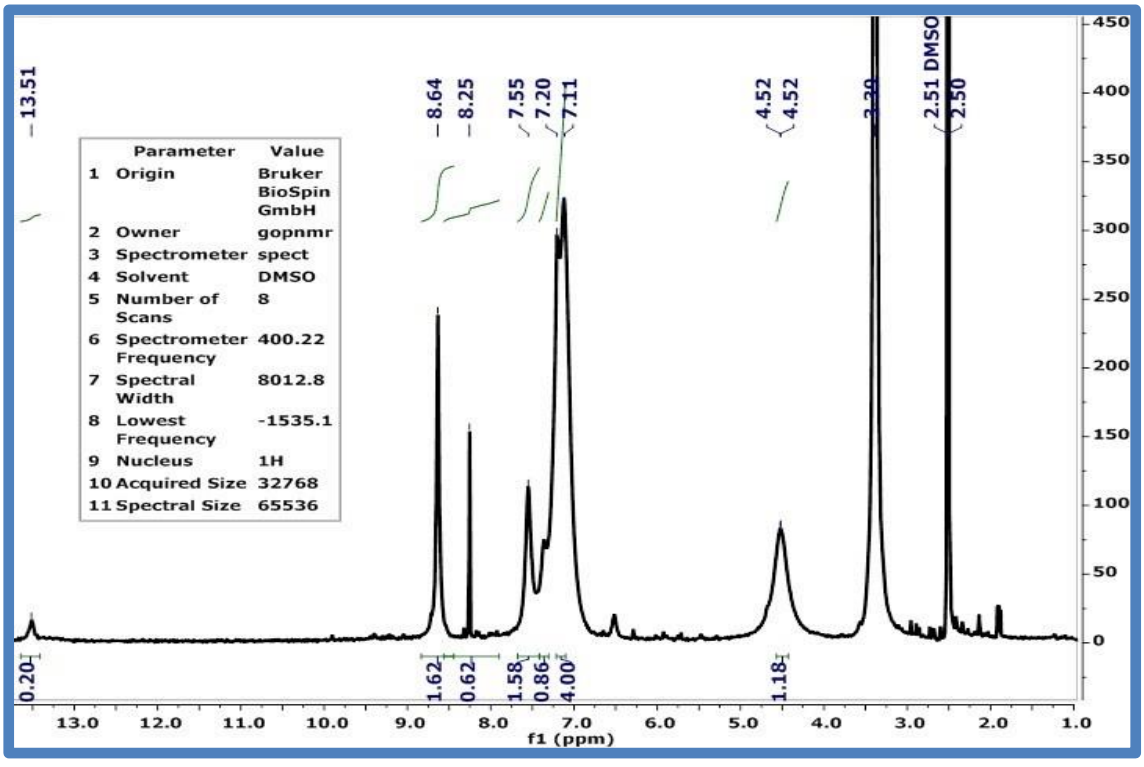


Fig. (6): ^{1}H-NMR spectrum of compound [K_8].

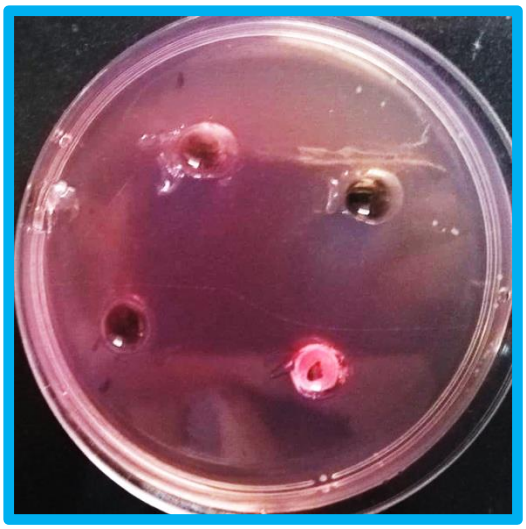


Fig. (7): Antibacterial activity of compounds [K_1] against *Pseudomonas* aeruginosa

Fig. (8): Antibacterial activity of compounds [K_{12}] against *Staphylococcus aurous*.

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