SYNTHESIS AND SPECTROSCOPIC IDENTIFICATION OF A NEW SERIES OF BIOLOGICALLY ACTIVE 2-IMINOTHIAZOLIDINE-4-ONE DERIVATIVES

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Abstract

A series of 2-amino-5-(substituted phenyl) 1,3,4- thiadiazol have been synthesized through the reaction of thiosemicarbazide with substituted benzoic acids in the presence of phosphoroxy chloride readily undergo nucleophilic addition – elimination reaction with chloroacetyl chloride in benzene as a solvent to afford 2-chloro acetamido compounds. The prepared compounds were subjected cyclization reaction and results in the formation of a series of 2- imino-3-(substituted phenyl) 1,3,4- thiadiazol-2yl-thiazolidinone -4 one .

The IR ,^{1}H and ^{13}C- NMR spectra of the prepared compounds were confirmed to their proposed structures . Finally antimicrobial activity of the newly obtained compounds were tested against *Klepsilla pneumonia* (gram -ve) and *Staphylococcusaurous* (gram + ve) and the results showed that most of the prepared compounds are sensitive against both types of test organisms in different activities .

Key words: *iminothiazolidin-4-one, antimicrobial, addition–elimination*

1. Introduction

A heterocyclic compound (Morrison and Boyd ,1992) is one that contains a ring made up of more than one kind of atom. Heterocyclies (Chavan and Pai, 2007) bearing nitrogen, sulfur, and thiazole moieties constitute the core structure of a number of biological interesting compounds. The chemistry of thiazolidin-4-one ring system is one of considerable interesting as it is a core structure in various synthetic pharmaceuticals that displaying a broad spectrum of biological activities .Also 2-iminothiazolidin-4-ones have been found to have antifungal activity.

Design (Saeed et al. 2007) of general, simple and efficient methods for rapid synthesis of thiazolidinone would be greatly valuable and could warrant further investigations in drug discovery. Among (Turget et. al,2007) these types of molecules , 4-thiazolidinones have been shown to have various important biological activities such as bacterial antifungal and antiviral. Quantitative structure – activity relationship (QSAR) studies have also been performed on the basis of the fact that the biological activity of a compound is a function of it is physicochemical properties(Sharma et.al.,2009).

4-Thiazolidinones (Jubi et.al.,2009) are derivatives of thiazolidine with carbonyl group at the (4) position and formed by the attack of sulfur nucleophile on imine carbon followed by intramolecular cyclisation with the elimination of water. The derivatives of 4-thiazolidinone nucleus has occupied a unique place in the field of medicinal chemistry .

The synthesis of 2- iminothiazolidine -4-one has been (Singh et.al,1981) reported by using thiourea and sodium salt of the labled monochloroacetic acid .

2-Imino thiazolidinone were synthesized (Banday and Rauf,2009) from fatty acid hydrazides, firstly acylthiosemicarbazide was obtained which on cyclization of the latter compound with chloroacetyl chloride in chloroform give the desired 2-iminothiazolidinone .the aim of the our work is synthesize and spectroscopic identification of a new series of biologically active 2-iminothiazolidinone compounds.

2- Experimental

Instruments:

1- Melting points were determined by using electro thermal melting point apparatus from Stuart Scientific uncorrected.
2- IR spectrum were taken by Bio-rad Merlin FTIR spectroscopy ,Mod FTS 3000 .
3- The Nuclear Magnetic Resonance (300 MHz ^{1}H-NMR and 75MHz^{13}C-NMR) spectra were recorded on a Brucker using TMS as internal standard at Al-Albayat University-Jordon.

2.1 Synthesis of 2-amino-5-(substituted phenyl) 1,3,4-thiadiazols (1 a- h). (Jumaa,2005)

A mixture 0.02 mole of substituted benzoic acids, 0.02mole thiosemicarbazide and 10 mL of phosphoroxy chloride was placed in a 100 mL round bottom flask and refluxed for 0.5 h , the resulting reaction mixture cooled and followed by adding 24 mL of cooled water slowly. The obtained solution was further refluxed (4h). After completion of the reaction , the product was separated and washed with sodium carbonate solution (2.5 %) and water 2- times , then subject to dryness at r.t and recrystallized from (DMSO + H_2O) .The yields and melting points were summarized in Table (1) .

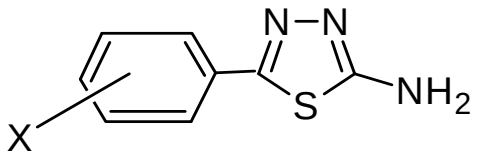
2.2 Synthesis of 2-chloro acetamido-5-(substituted phenyl) 1,3,4- thiadiazols (2 a-h).(Liu et. al,2000).

In a (100 mL) round bottom flask equipped with a dropping funnel and condenser,(0.01 mole) of 2-amino-5-(substituted phenyl) 1,3,4-thiadiazol was dissolved in benzene (30 mL) .The solution was cooled to (0-5C˚). After cooling, 0.01 mole of chloroacetyl chloride was added slowly to the mixture with vigorous stirring . After completion the addition , the reaction mixture was refluxed for 3h , and benzene removed under vaccuo . The residue was washed with 5% $NaHCO_3$,and subsequently with water, then dried and recrystallized from DMSO and water .The percentage of yields and melting points of the synthesized amides are shown in Table (2).

2.3 Synthesis of 2-imino-3-(substituted phenyl) 1,3,4-thiadiazol-2yl- thiazolidine-4ones (3 a-h)):(Liu et. al,2000).

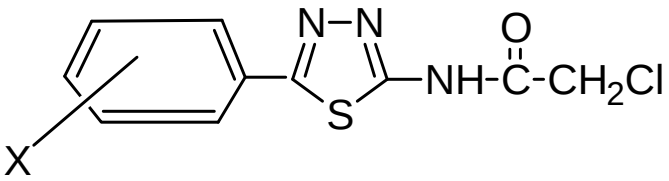
In a (50 mL) round bottom flask a mixture of 2- chloroacetatemido 5- (substituted phenyl) 1,3,4-thiadiazol (0.01 mole) and KSCN (0.01 mole) in acetone (33mL) was refluxed for 3 h. The excess of acetone removed under vacuum .The solid product was recrystallized from toluene. The percentage of yields and melting points of synthesized products are shown in Table (3)

Table (1): some physiochemical properties of prepared amines (2-amino-5-(substituted phenyl) 1,3,4-thiadiazols (1 a-h):



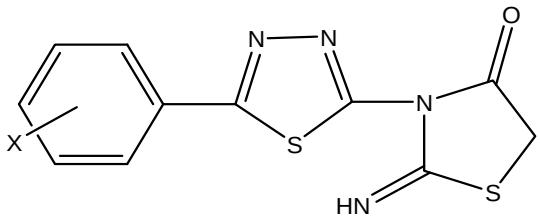
Compound	X	M .F	Yield %	M.P ˚C
1 a	4-CH_3	$C_9H_9N_3S$	62	214-216
1 b	4-OCH_3	$C_9H_9N_3OS$	85	228-230
1 c	3-Cl	$C_8H_6ClN_3S$	85	212-214
1 d	4-NO_2	$C_8H_6N_4SO_2$	83	226-230
1 e	3-NO_2	$C_8H_6N_4O_2S$	82	220-222
1 f	4-Br	$C_8H_6BrN_3S$	82	231-233
1 g	3-Br	$C_8H_6BrN_3S$	82	220-222
1 h	H	$C_8H_7N_3S$	83	174-176

Table (2): Some physiochemical properties of prepared amides (2-chloroacetamido-5-(substituted phenyl) 1,3,4-thiadiazols (2 a-h):



Compound	X	M.F of amides	Yield %	M.P ˚C
2 a	4-CH_3	$C_{11}H_{10}ClOS$	79	194-196
2 b	4-OCH_3	$C_{11}H_{10}ClN_3O_2S$	84	253-255
2 c	3-Cl	$C_{10}H_7Cl_2N_3OS$	83	174-176
2 d	4-NO_2	$C_{10}H_7ClN_3O_3S$	81	142-144
2 e	3-NO_2	$C_{10}H_7ClN_4O_3S$	81	190-192
2 f	4-Br	$C_{10}H_7BrClN_3OS$	83	190-192
2 g	3-Br	$C_{10}H_7BrClN_3OS$	83	194-196
2 h	H	$C_{10}H_8ClN_3OS$	83	228-230

Table (3): some physiochemical properties of prepared (2-imino-3-(substituted phenyl)1,3,4-thiadiazol-2yl thiazoilidin-4-ones(3 a-h) :

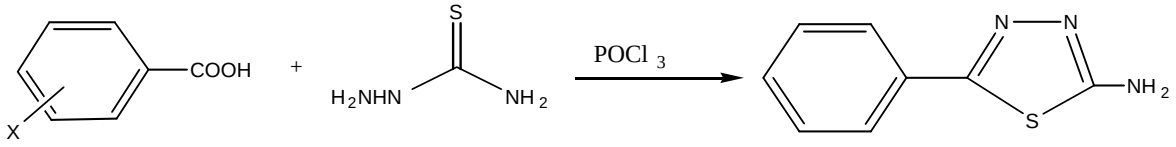


Compound	X	M.F	Yield %	M.P ˚C
3 a	4-CH_3	$C_{10}H_{10}N_4OS_2$	63	192-194
3 b	4-OCH_3	$C_{12}H_{10}N_4O_2S_2$	63	185-187
3 c	3-Cl	$C_{11}H_7ClN_4OS_2$	50	210-212
3 d	4-NO_2	$C_{11}H_7N_5O_3S_2$	44	190-192
3 e	3-NO_2	$C_{11}H_7N_5O_3S_2$	43	164-166
3 f	4-Br	$C_{11}H_7BrOS_2$	37	230-232
3 g	3-Br	$C_{11}H_7BrN_4OS_2$	35	98-100
3 h	H	$C_{11}H_8N_4OS_2$	35	200-202

Results and discussion

3.1 Synthesis of 2-amino -5-(substituted phenyl) 1, 3,4-thiadiazol (1 a-h) (Jumaa,2005) .

The reaction of substituted benzoic acids with thiosemicarbazide in the presence of phosphoroxy chloride gives 2- amino-5-(substituted phenyl) 1,3,4-thiadiazole. The products were identified by IR,[1] H-NMR, and ^{13}C-NMR .

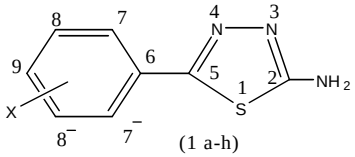


(1 a-h)

IR spectrum of 2-amino -5- (p-methyl phenyl) 1,3,4- thiadiazol (1 a) , Fig (1) (Table 4), observed several characteristic absorption bands at (3281 and 3081) cm^{-1} due to NH_2 group and at 2960 cm $^{-1}$ due to C-H str. of the methyl group (Madkoub , 2004) at para position of the benzene ring and the disappearance of carbonyl group band for substituted benzoic acids is a good evidence for the elucidation of expected structure . The ^{1}H-NMR data(Table5),showed a signal at 2.3 ppm for methyl and amino groups at 7.4ppm . In addition , the aromatic protons were resonated in the aromatic region between 7.2-7.7 ppm(Chavan and Pai, 2007) .

The ^{13}C-NMR spectrum of compounds (1a) (Table 6),revealed the expected signal at 21.3 ppm (Moghaddam and Hojabri,2007) due to methyl carbon atom , and also two signals at (169 ,156) due to C_2 and C_5 of the thiadiazol ring , respectively .

Table (4): Assignments of characteristic frequencies (cm^{-1}) of IR spectra for the prepared amines (1a-h).



(1 a-h)

Compound	N-H Str.	C-H Aromatic Str.	C-H Aliphatic Str.	C=N str.	C=C Str.	NO_2 Str.
1 a	3281 , 3081	3040	2960	1637	1515	-------
1 b	3254 , 3101	3030	2950	1609	1513	-------
1 c	3400 , 3150	-------	--------	1622	1525	-------
1 d	3427 , 3230	3093	---------	1639	1595	1352,1525
1 e	3407 , 3280, 3159	3100	---------	1635	1527	1345,1535
1 f	3461 , 3290	3100	---------	1681	1599	--------
1g	3380 , 3180	-------	---------	1620	1523	------
1 h	3275 , 3100	3060	---------	1634	1514	-------

Table (5): ^{1} H –NMR data of prepared substituted amines (1a,b)

Compound	δ NH ppm	δ CH_3 ppm	δ OCH_3 ppm	δ Aromatic protons ppm
1 a	7.4(s,2H)	2.3(s,3H)		7.7 d (2H, 7,7¯), 7.2 d (2H, 8,8 ¯)
1 b	7.3(s,2H)		3.79(s,3H)	7.0 d (2H, 7,7¯) 7.7 d (2H, 8,8¯)

Table (6): ^{13}C -NMR data of compound (1a,b) :

Compound	C_2	C_5	C_6	$C_{7,7}$ ¯	$C_{8,8}$ ¯	C_9	CH_3	OCH_3
1 a	169	156	130.3	129.5	129.7	21.3	21.3	
1 b	168	161	156.7	130	115	160.7		56

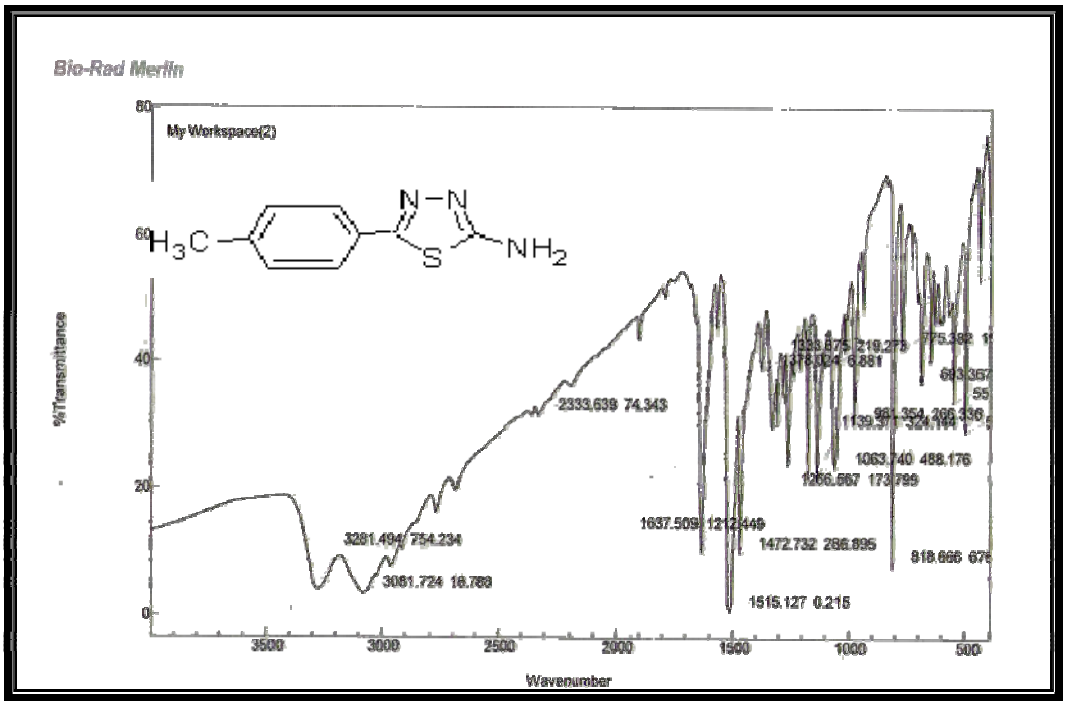
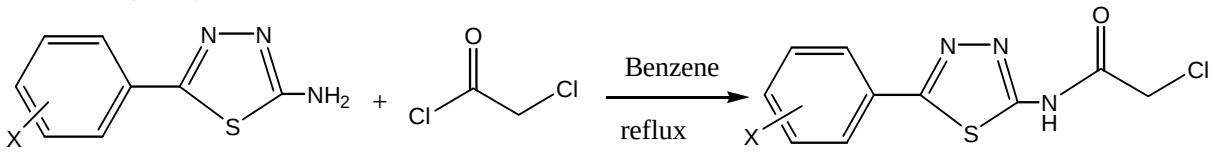


Fig (1): IR spectrum of compound (1a)

3.2 Synthesis of 2-chloro acetamido-5-(substituted phenyl)1,3,4- thiadiazols (2a-h) (Liu et.al.2000)

The most frequently used method for the preparation of amides is the reaction of amines and acylchlorides. In similar way , we focused on the synthesis of a series of 2-chloroacetamido 1,3,4-thiadiazol (2a-h) .



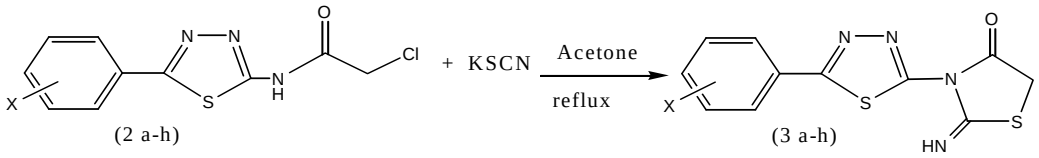
(1 a-h) (2 a-h)

2-Chloroacetamido-5-(p-methyl phenyl)-1,3,4-thiadiazol (2 a) was prepared from the reaction of 2-amino -5-(p-methyl phenyl) -1,3,4- thiadiazol and chloroacetyl chloride under reflux condition in benzene .

The infrared spectrum of 2-chloroacetamodo -5-(p-methyl phenyl) -1,3,4- thiadiazol (2 a) is shown in Fig. (2) and the most important feature of this spectrum is carbonyl stretch of the 2-chloroacetamido moiety at (1708) cm^{-1}(Chavan and Pai,2007) , Yadav(2005).The ^1H- NMR spectrum of (2a)(Fig 3) supported the expected structure by showing two singlet signals at (13) ppm(Chavan and Pai,2007) , due to N-H and at (2.3) ppm(Madkoub,2004) ,(Moghaddam and Hojabri,2007) (for methyl group , on the other band , the ^{13}C-NMR spectrum confirmed the ^1H-NMR finding by presenting two signals at (44) and (42.8) due to the 2-chloacetamido moiety.

3.3 Synthesis of 2-imino-3-(substituted phenyl)-1,3,4-thiadiazol-2-yl thiazolidin-4-ones (3 a-h) Jumaa,2005).

Since the nucleophilic substitution reaction of alkyl halides with potassium thiocyanate was successful especially in polar aprotic solvent , we decided to followed the same condition for carrying out reaction between (2 a) with potassium thiocyanate in acetone under reflux condition . In this reaction the in situ generated substitution product readily undergoes cyclization reaction to yield 2-imino -3-(p-methyl phenyl) -1,3,4 –thiadiazol-2-yl thiazilidin-4-ones (3 a) .



(2 a-h) (3 a-h)

The general feature of the IR spectrum of for compound (3a) exhibits a strong band at 1726 cm^{-1} (Table7) which belong to carbonyl groups of the 2-imino thiazolidin -4-ones structure(Sharma et al.2009;Abhinit et.al.2009) ,that is considered as evidence for the formation of the desired product , and strong band at 3253 cm^{-1} corresponding to NH str.(Abhinit et.al.2009 ; Makdoub 2004).

The Fig. (4) shows the ^{1}H-NMR data for some 2-iminothiazolidin-4-ones (3b) .The protons of CH_3 group are observed as a singlet signal at 3.85ppm (Jumaa 2005) , In addition the proton of (NH) group in thiazolidinone ring appears at (7.2) ppm (Yadav et.al.2005 ; Moghaddam and Hojabri,2007) , while the protons of aromatic rings appear at (7.06-7.92) ppm,(Makdoub 2004) and cyclic CH_2 appears as singlet signal at (4.27) ppm (Singh et.al.1981) . It seem from ^{13}C-NMR of some 2-iminothiazolidinones(3b), Fig. (5) , that the carbonyl of thiazolidinone compound (3b) appear at (174.5) ppm (Moghaddam and Hojabri,2007) which is the strong evidence for the forming of products. In addition to signal for(C=NH) carbon group appears (169.7) ppm(Singh et.al.1981;Aziz et.al.2009) and aromatic carbons appear at (114-161.8) (Aziz et.al.2009: Moghaddam and Hojabri,2007) .

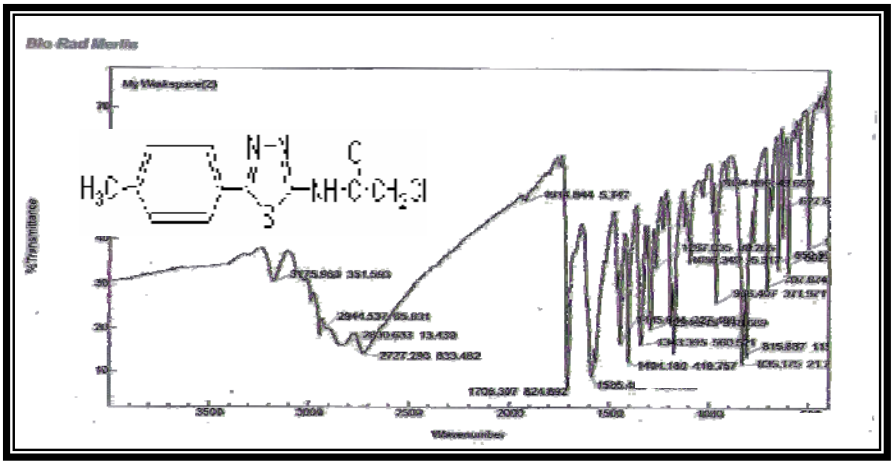
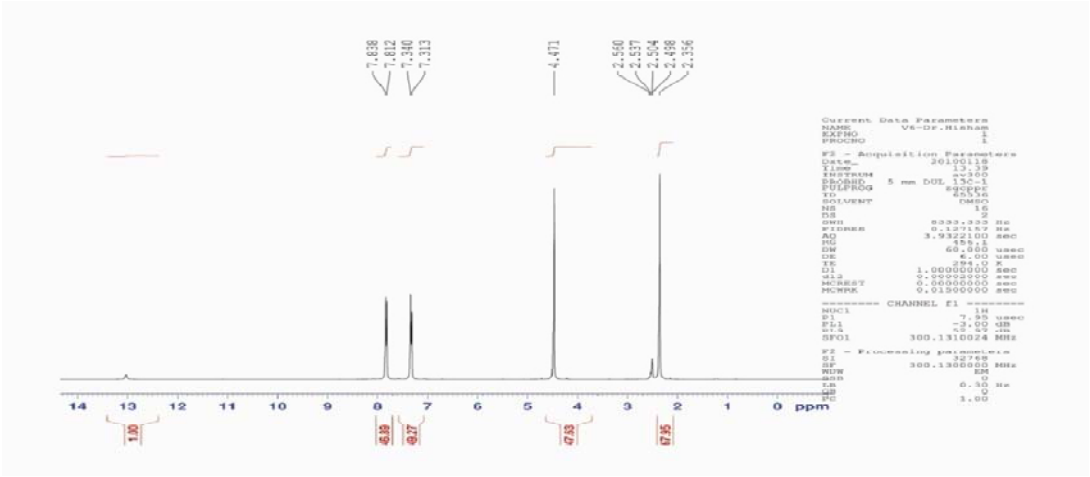
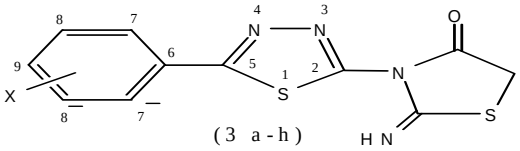


Fig (2): IR spectrum of compound (2 a)



Fig(3): ^{1}H-NMR spectrum of compound(2a)

Table (7): Assignments of characteristic frequencies (cm $^{-1}$) of IR spectra of the new 2-iminothiazolidin-4-ones (3 a-h).



Compound	N-H str.	C-H str. Aliphatic	C=O str.	C=N str.	C=C ring str.
3 a	3252	2924	1726	1632	1450
3 b	3437	2834	1736	1598	1580
3 c	3212	2987	1679	1501	1480
3 d	3200	2800	1679	1550	1590
3 e	3281	2987	1731	1614	1690
3 f	3200	-------	1700	1500	1550
3 g	3211	2981	1720	1570	1540
3 h	3440	2920	1715	1580	1540

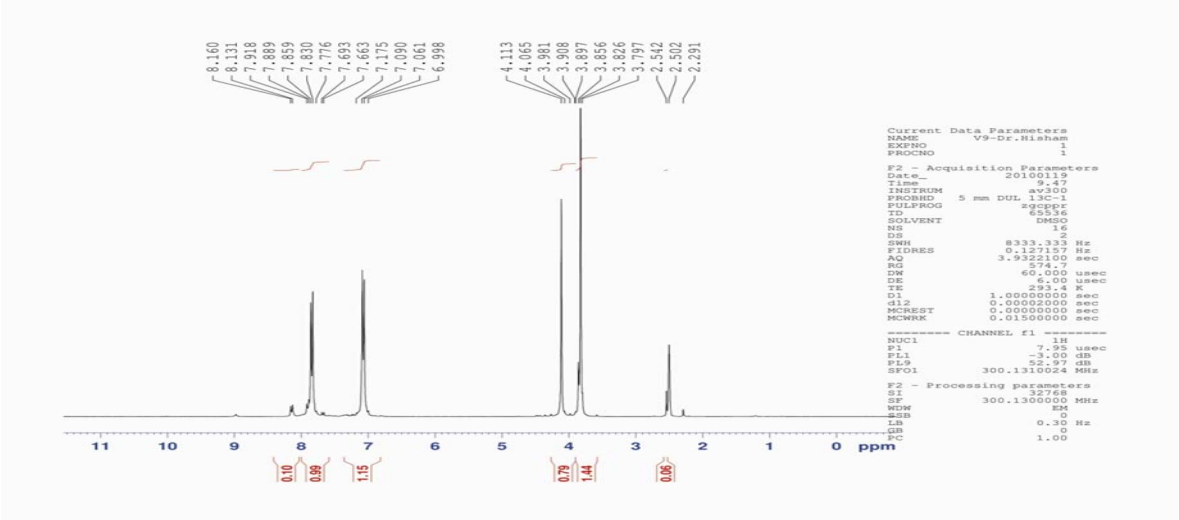


Fig (4): ^{1}H-NMR spectrum of compound(3 b)

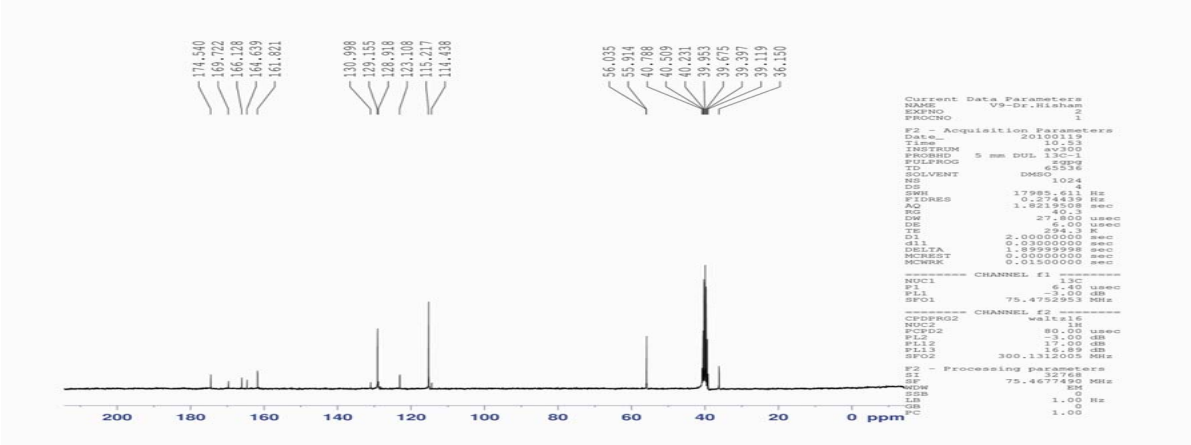


Fig (5) : C^{13} – NMR spectrum of compound (3b)

3.4. Anti-bacterial activities of the prepared compounds:

Some of the prepared compounds were screened for their antibacterial activity against two types of bacteria **Staphylococcus aurous** (gram positive) and **Kllepsilla pneumonia** (gram negative) using the cape late agar diffusion method . The prepared KBr discs of compounds(1:3) (the mixture was pressed under pressure to form discs) were placed on the surface of the cultured media and incubated for 24 hours at 37□C .Culturing the bacteria on nutrient agar, reading the zone inhibition: the larger zone of inhibition represents by more +ve but un effected by national committed for clinical laboratory.

During this study , it was found that the prepared compounds has anti-bacterial activity and their results were mentioned in (+) assignment (Table 8) .

Table(8): Anti-bacterial activities of some prepared compounds:-

Compounds	Microorganism	
	KIlebsilla pneumonia *–ve*	***Staphylococcus aurous*** *+ve*
1 a	+++	+++
1 c	+++	+++
1 d	++++	+++
1 e	++++	+++
2 a	++++	++++
2 f	+++	+++
3 a	+++	+++
3 b	+++	+++

Inhabitation zone (+) 7-10 mm , (++) 11-15 mm , (+++) 16-21mm, (++++) 22-28mm (Yadav et.al.2005)

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الخلاصة

يتضمن هذا البحث تحضير سلسلة من ٢-أمينو ١،٣،٤ ثايودايزول من خلال تفاعل ثايوسيمي كارباز ايد مع حامض البنزويك المعوض بوجود حامض فوسفوروكسي كلورايد والتي تعاني تفاعلات الاضافة والحذف مع كلورواسيتايل كلورايد في البنزين للحصول على 2- chloroacetamido 1,3,4- thiadiazol وبنتائج جيدة .

وفي مجال اخر في هذا البحث تم تحويل المركبات المحضرة بسهولة الى نظام حلقي لتعطي سلسلة جديدة من مركبات ٢- امينوثايزوليدين -٤- أون .

أخذت التحليل الطيفي (NMR, IR) للمركبات المحضرة لتاكد صحةالتراكيب المقترحة . و أخيرآ أختبرت الفعالية البيولوجية ضد نوعين مختلفين من البكتريا *Klebsiella pneumonia(gram –ve), Staphylococcusaurou*(gram +ve)و اظهرت النتائج بان معظم المركبات المحضرة لها حساسية ضد هذين النوعين من البكتريا و بفعاليات مختلفة .

پوختە

لەم توێژینەوە زانستی یە دا , زنجیرەیەك لە ٢- ئەمینۆ ٤,٣,١- سایەدایەزۆلّی ئامادە کراو لە کارلیّك کردنی سایۆسیمی کارباز اید لەگەلّ بەرخراوی ترشی بەنزویك بە بوونی فوسفورۆکسی کلۆراید لە جۆری کارلیّکی خستنە سەری و لیّکردنەوە بە ئاسانی لە گەلّ کلۆرۆئەسیتایل کلۆراید لە بەنزین بۆ بەدەست کەوتنی ٢-کلۆرۆئەسیتەمیدۆ کلۆراید بە بەرهەمێکی زۆرباش .

دواتر ئەمایدە ئامادەکراوەکان خرانە ناو کارلیّکی بەئەلقەبوون بۆ بەدەست هیّنانی زنجیرەیەکی نویّ لە ٢- ئیمینۆ سایۆزۆلیدین -٤-ئۆن .

شەبەنگی IR, ^{1}H-NMR, ^{13}C-NMR وەرگیرا بۆ ئاویّتە ئامادە کراوەکان وە راستی بەرهەمە ئامادەکراوەکانی دەرخست . لە کۆتایدا چالاکی دژە بەکتریا بۆ ئاویّتە بە دەست کەوتووەکان تاقی کرانەوە لە دژی *Klepsilla pneumonia*(-ve)و *staphylococcus aurous* (+ve)لە ئەنجامدا پیشانی دا کە زۆربەی ئاویّتە ئامادە کراوەکان هەستیارن بەرامبەر هەردوو جۆری بەکتریا یەکە بەلاّم بە چالاکی جیاواز.