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Synthesis and Spectral Characterization of a New Series of N-4-Chlorobenzamide-5- phenylthiazolidin-3-one

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ABSTRACT

A new series of 4-thiazolidinones (4a-j) has been synthesized by cyclocondensation of various acid hydrazones with thioglycolic acid. The intermediate hydrazones (3a-j) were synthesized by the condensation of various substituted benzaldehydes with 4-chlorobenzohydrazide (2). The starting compound 4-chlorobenzohydrazide was prepared from the reaction of ethyl 4-chlorobenzoate and hydrazine hydrate. The structures of the new synthesized compounds had been confirmed by spectral data (FTIR, PP^{1}H-NMR, ^{13}C-NMR, and ^{13}C-NMR –DEPT and ESIMS). Some of the synthesized compounds (4a-j) were evaluated for their antibacterial activity against Gram-positive bacteria *staphylococcus aureus* and Gram – negative *psedomonas aeruginosa*

Keywords: Acid hydrazone, 4-Thiazolidinone.

تحضير و تشخيص طيفي لسلسلة جديدة من مركبات N-4-Chlorobenzamide-5- phenylthiazolidin-3-one

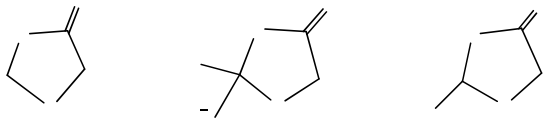
الملخص

تضمن هذا البحث تحضير سلسلة جديدة من مركبات الثايازولودينون(4a-j) من تفاعل الغلاق الحلقي لسلسلة من مركبات الهايدرازون الحامضي مع α- ميركبتو حامض الخليك. وقد تم تحضير المركبات الوسطية (3a-j) من التفاعل التكثيفي لسلسلة من البنزالديهايدات المعوضة مع 4-كلوروبينزوهيدرازايد المحضرة من التفاعل التعويضي لايثايل4-كلوروبنزوات مع الهيدرازين المائي. كما تم تشخيص التركيب الكيميائي للمواد المحضرة بواسطة الطرائق الطيفية مثل طيف الأشعة تحت الحمراء FTIR والرنين النووي المغناطيسي بأنواعه الثلاثة^{1}H-NMR, ^{13}C-NMR,^{13}C -NMR –DEPT و طيف الكتلة ESIMS. وقد استخدم قسم من المركبات المحضرة في اختبار الفعالية البايولوجية ضد بكتريا صبغة غرام الموجبة (+)*staphylococcus aureus* وبكتريا صبغة غرام السالبة (-)*psedomonas aeruginosa*.

INTRODUCTION

Hydrazones have been demonstrated to possess antimicrobial, anticonvulsant, analgesic, anti-inflammatory, antitubercular and antitumoral activities.

Acid hydrazones are not only intermediates, they are very effective organic compounds when used as intermediates in the synthesis of different biologically active compounds via different reagents. 4-Thiazolidinone is the most important product when acid hydrazones react with thioglycolic acid and thialactic acid (Rollas and Küçükgüzel, 2007). Thiazolidinones are the derivatives of thiazolidine, which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five membered ring. 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at the position (4)(I). Substitution is possible at 2,3 and 5 position(II,III), (Singh *et al.,* 1981), Verna and Saraf, 2008).



I II III

X = O, S,NR, NN=CR,R`

Many research on thiazolidinones has been carried out in the past. Various optical and geometrical isomers were reported in some works. Several methods for synthesis are available in the literature, (Tatar *et al.,* 2008), which involve conventional, either one pot three component condensation or two step process synthesis, and microwave as well as combinational synthetic methods, (Rao *et al*., 2004), Sanghani *et al.,* 2008). 4-Thiazolidinone derivatives are reported to show a variety of biological activities depending on the substituents.Thiazolidin-4-ones can induce different pharmacological properties (Singh *et al*., 1981), Abhinit *et al*., 2009), such as antibacterial, antifungal, antidiabetic, anticonvulsant activities, cyclooxygenase and lipoxygenase inhibitory, (Tatar *et a.,* (2008), Satetigeri *et al*., 2005), Rawal and Kumar (2006)).The synthesis of 4-thiazolidinone derivatives used as antibiotic to combat resistant organisms which inhibit many steps in cell wall synthesis, peptidoglycan is an essential component of the cell wall of both Gram-positive and Gram-negative bacteria (Silver, 2003; Andres *et al*., 2000) and tested for their ability of inhibition of the bacterial enzyme Murb. (Nagarajan *et al*., 2009).

MATERIALS AND METHODS

Melting points were determined by a capillary method on an elecrothermal melting point apparatus.IR were recorded on a thermo mattson IR 300 spectrophotometer as KBr disk and Bio-rad Merlin FTIR spectrophotometer Mod FTS 3000. The ^{1}H-NMR and ^{13}C-NMR spectra were measured with a Brucker (300 MH_Z) spectrometer in DMSO-d_6 at Al-Albayt University-Jordan. Mass spectra were recorded on High resolution mass Bruker Daltonics Data Analysis 3.4, and the GC-MS(EI),Shimatzu.by using ESI(+)/ ESI(-) method(where ESI=Electron Spray Ionization) at Al-Albayt University-Jordan. Chemical reagents used in the synthesis were purchased from Riedel-De haen AG, Scharlau and Fluka Company.

Thin layer chromatography (TLC) was carried out using DC-Aloufoline 20 x 20 Kieseigel 60 F_{254} pre-coated Germany Merck.

EXPERIMENTAL

1. **Synthesis of ethyl 4-chlorobenzoate,** (Jasim *et al*., (2008), Williamson (1964)).

The ester was prepared by refluxing a mixture of (0.1 mole) of 4-chlorobenzoic acid and (25 ml) absolute ethanol in the presence of 3-4ml concentrated sulfuric acid for 5 hrs.

2. Synthesis of *4*- chlorobenzohydrazide, (Ali (2007)).

To a solution of (9.225 g ,0. 05mole) of ethyl 4-chlorobenzoate in 10 ml of ethanol a (5 ml, 0.1 mole) of hydrazine hydrate was added and the mixture was refluxed for 2 hrs, then left to cool at room temperature to give white needle precipitate, which was filtered off , washed with cold ethanol and dried recrystallized from mixture ethanol/ water 3:1 (m.p 158-160Cº, yield 90%).

3. Synthesis of N`-Substituted benzylidine- 4-chlorobenzohydrazide (3a-j), (Jasim *et al*., 2008)).

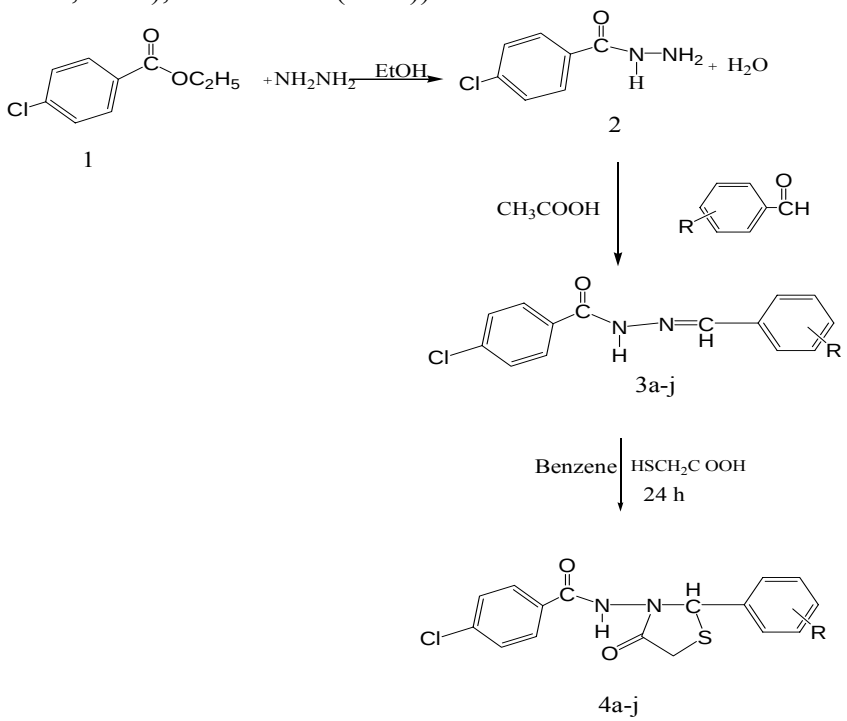
To a solution of (1.705 g, 0.01mole) *4*- chlorobenzohydrazide in 20 ml absolute ethanol, (0.01 mole) of substituted benzaldehyde was added followed by addition of some drops of glacial acetic acid, the reaction mixture was refluxed on a water bath for two hrs. Cooled, filtered off recrystallized from absolute ethanol. The physical properties with percentage of yield were listed in Table (2).

4. Synthesis of N-4-Chlorobenzamide-2-(Substituted phenyl) 4-thiazolidinone3-yl(4a-j), (Shah and Desia, 2007; Verna and Saraf, 2008).

To a solution of compounds (3-a-j) (0.005 mol) in 30ml benzene, (0.006, mol) of thioglycolic acid was added slowly with stirring. The mixture was refluxed for 28 hours. The solvent removed under vacuum, and the reaction mixture was neutralized with cold saturated of sodium bicarbonate solution, the product was kept at room temperature for 24 hours. The formed products were filtered off, washed three times with distilled water, and recrystallized from the appropriate solvent to give the desired compounds. Percentage of yields and the physical properties of the synthesized thiazolidinone derivatives were listed in Table (3).

RESULTS AND DISCUSSION

The synthetic pathway followed in the preparation of the compounds was outlined in scheme (1). The starting material ethyl 4-chlorobenzoiate (1) was obtained by previously described method[PP,] **(**Jasim *et al*., 2008), Williamson (1964)).



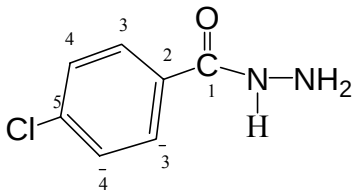
(R = *p*-NO_2, *p*-CH_3, *p*-OCH_3 , *p*-Cl, *p*-Br ,*o*-Br, m-OH , *o*-OH)

Scheme (1): Synthetic pathway for the preparation of 4(a-j)

The versality of the reaction is well demonstrated by the fact that a variety of aryl aldehydes with electron-releasing and withdrawing substituents afforded their corresponding compounds 4 a-j in a good yields. The structures of all the newly synthesized compounds were confirmed by elemental analysis, IR, ^{1}H-NMR,^{13}C-NMR and MS spectral and by their physical properties, (Tables 2- 9).

Compound (2) was also characterized by IR spectrum, ^{1}H-NMR and ^{13}C-NMR data. Its IR spectrum showed the appearance of new three bands at 3308- 3192 cm^{-1} with the two bands of amide (I) and amide (II) at 1667 and 1616 respectively which indicated the formation of the product. 4- Chlorobenzohydrazide was also identified by the ^{1}H-NMR through the appearance of one proton at δ (10) ppm and a singlet of two protons at δ (4.5) ppm which belongs to both NH and NH_{BB2} respectively (Patel and Patel (2010)).The presence of 4 protons as a two doublet at 7.5-7.8 ppm belong to the p-disubstituted aromatic rings.

The[PP13]C-NMR spectrum of 4-chlorobenzo hydrazide four signals in the aromatic region and one for amide carbonyl group (C=O), C_{BB1}(165.2), C_2(132.51), $C_{3,3'}$(129.31), $C_{4,4'}$(128.87), C_5(136.32) ppm. The disappearance of non protonated carbons C_1, C_2,C_5 was very clear in ^{13}C-NMR-DEPT spectrum, while the remaining protonated carbons were observed as a two signals at $C_{3,3'}$(129.31),$C_{4,4'}$(128.87) ppm.



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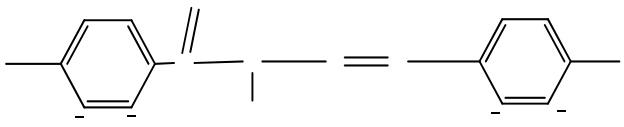
The structure of acid hydrazones derivatives (3a-j) were also assigned on the bases of the analysis of spectral data, their IR spectrum showed the absence of stretching vibration of amino group of compound (2) with observation of new bands due to the stretching vibration of characteristic azomethine bond C-H, HC=N and C=O at (2838-2890 cm^{PP-1}), (1594-1639) cm^{-1} (1644-1677) cm^{-1} respectively, and observation of new bands due to aromatic CH str. at (3024-3085)cm^{-1}, and C=C str. at (1549-1607cm^{-1}) (Table 4) (Küçükgüzel *et al.,* 2006; Pate and Shaik ,2010), Fig.(1). Moreover ^{1}H-NMR Spectra showed clear changes in splitting pattern of aromatic region that showed multiple signals for 8 protons at δ (6.7-8.1) ppm with two singlet at δ (8.3 -8.6) ppm and at δ (10.8-12.2) ppm which attribute to N=CH,CO-NH protons respectively Fig. (2) (3a), (Shah and Desia (2007), Palekar *et al*., 2009), Sharanabasappa *et al*., 2010), (Table 5).

The ^{13}C-NMR of compounds (3a-j) provide evidence for the formation of acid hydrazones, the appearance of 8 signals due to aromatic carbons and a signal for azomethine carbon with one signal for amide carbonyl C=O, in the case of the aldehydic ring with substituent at para position, as in compounds (3a, e): showed 10 signal for 10 carbon with signals due to 4- OCH_3 and 4-CH_3 carbons at 55.7 and 21.48 respectively, Fig. (3). While in hydrazones substituted aldehydic ring at o-position exhibited 12 singlets for 12 carbons, (Table 6). From ^{13}C-NMR-DEPT spectrum the conversion of compound 2 to 3a-j was proved from the absence of non-protonated carbons, the^{13}C-NMR-DEPT spectrum for example of compound (3a) showed six signals for six protonated carbon with odd number, OCH_3 : 55.76, $C_{2,2'}$: 114.03, $C_{9,9'}$:129.01, $C_{8,8'}$:129.23, $C_{3,3'}$: 129.96, C_5: 148.49 with disappearance of C_4 at 127.23, C_7 at 136.91, C_{10} ; 136.91,C $_6$: 162.33 and C_1: 161.33 ppm, Fig. (4).



3a

The molecular weight of some products was established by ESI mass spectrometer, the molecular weight of compound (3a) was obtained from the mass spectrum, Fig. (5), that determined by molecular ion $[M+23]^{+\cdot}$ at m/z 311 (5.8%).

The IR spectra of compounds 4b,4d showed two isomers of substituted 4-thiazolidinone and they are separated according of their R_f values using TLC aluminum silica gel plate using (Ethyl acetate: n-hexane 2:3). Formation of compounds 4a-j were characterized from the physical properties and analytical data, the IR spectra of 4-thiazolidinones showed the characteristic str. vibration of C=O bands in the region of 1667- 1717 cm^{-1}(Shah and Desia , 2007), Palekar *et al*., 2009), Aydogan *et al*., 2001), with the absence of C=N str. band Fig. (6), (Table 7).

The ^{1}H-NMR spectra also showed the characteristic signal for 4-thiazolidinone at δ (3.7-4.7) ppm as two doublet [while in some of the prepared compounds were observed as singlet], due to non equivalent geminal methylene protons assigned for S—CH_2 protons, (Shah and Desia (2007)), with a single signal at δ (6-6.7) attributed to (C-H) protons of the heterocyclic ring, while N-H amide exhibited at δ (8.3-12) Fig. (7), (Table 8).

The ^{13}C-NMR spectra of this series showed 12 different carbons for thiazolidinone and substituted benzaldehyde in para position,14 different carbons in thiazolidinone with substituted benzaldehyde in ortho position, (Table 9). The formation of new compounds were supported by ^{13}C- NMR spectra with the appearance of a new signal due to carbon atoms which were absent in the ^{13}C-NMR spectrum of the Schiff bases (disappearance of azomethines carbon), the carbons related to thiazolidinone moiety were observed at (C_5) δ(66.7-61), (C_6) δ (29.7 – 38.4) and C=O at (169-170) ppm respectively. The structure of 4-thiazolidinone derivatives were also established from their ^{13}-C-NMR-DEPT spectra, the disappearance of non protonated carbon atoms and appearance of carbons which have odd number of protons, and those bearing an even protons of thiazolidinone moiety observed at opposite side of the spectrum.

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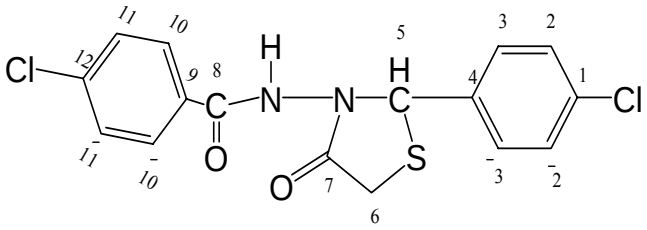


4d

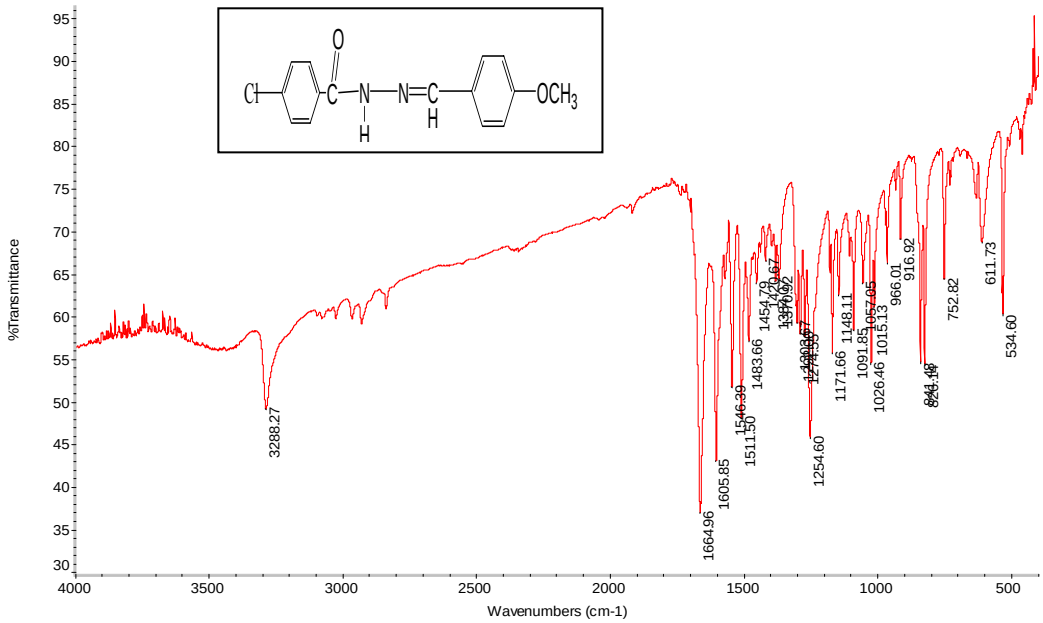


Fig. 1 : IR spectrum of compound (3a)

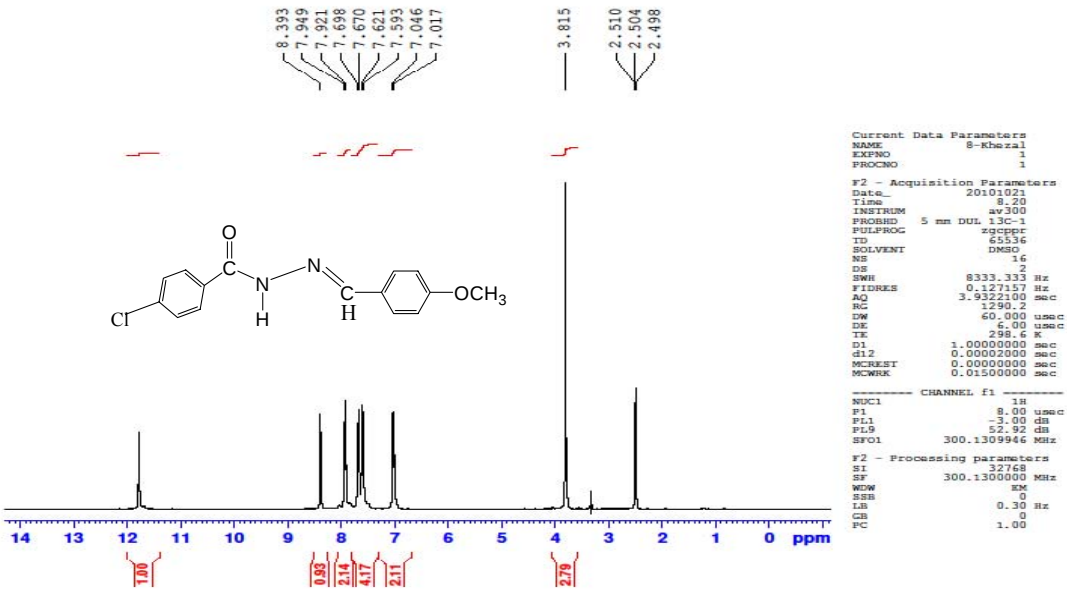


Fig. 2: 1H-NMR spectrum of compound (3a)

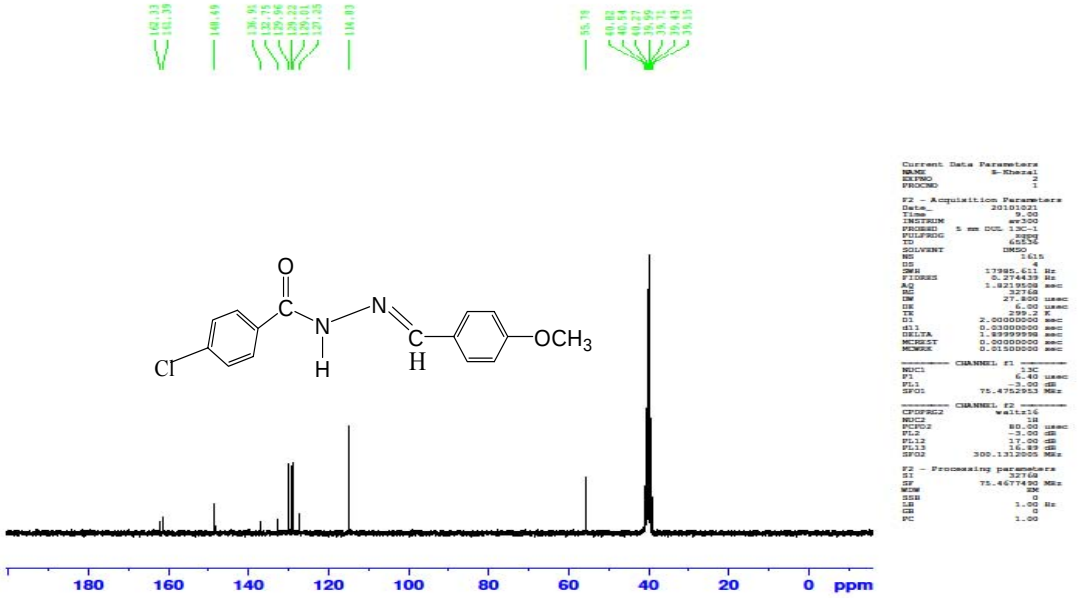


Fig. 3: ^{13}C-NMR spectrum of compound (3a)

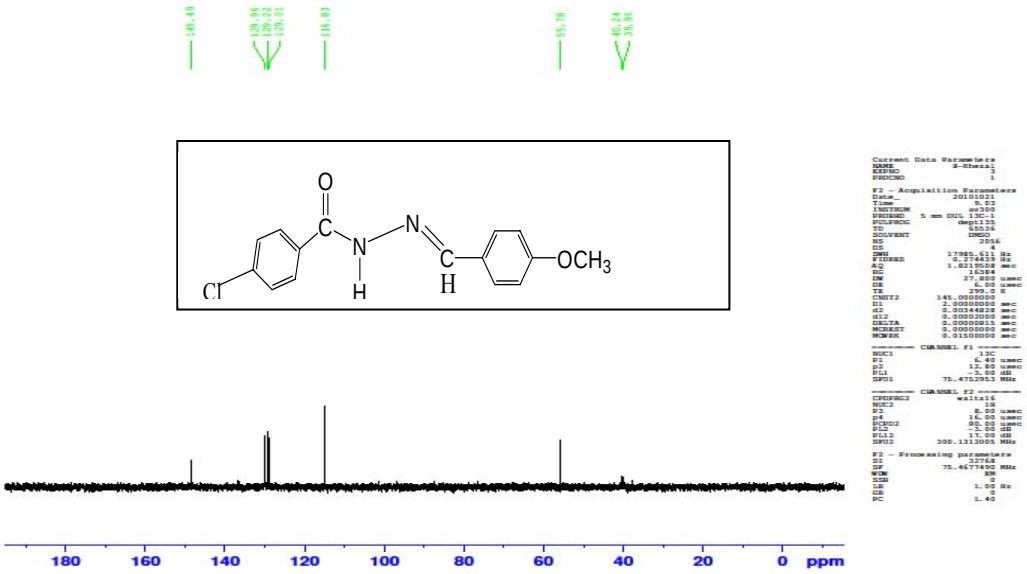
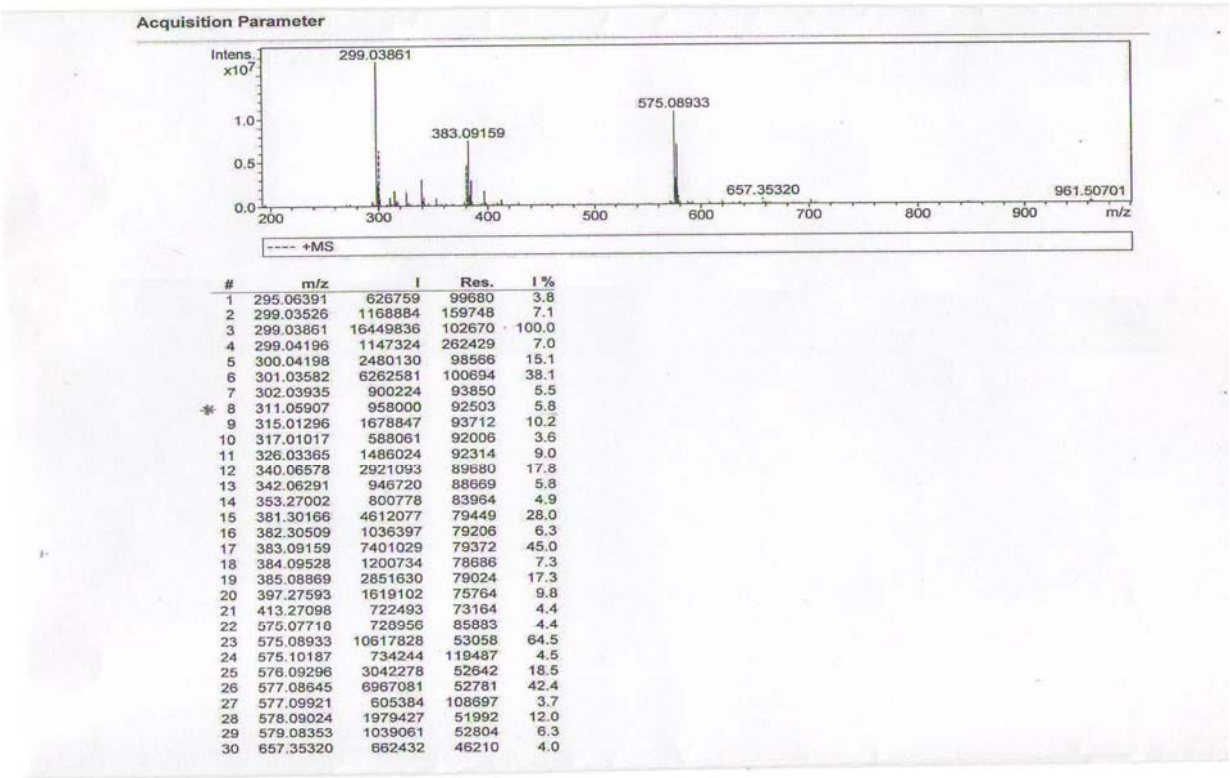


Fig. 4: Dept^{13}C-NMR spectrum of compound (3a)



#	m/z	I	Res.	I %
1	295.06391	626759	99680	3.8
2	299.03526	1168884	159748	7.1
3	299.03861	16449836	102670	100.0
4	299.04196	1147324	262429	7.0
5	300.04198	2480130	98566	15.1
6	301.03582	6262581	100694	38.1
7	302.03935	900224	93850	5.5
8	311.05907	958000	92503	5.8
9	315.01296	1678847	93712	10.2
10	317.01017	588061	92006	3.6
11	326.03365	1486024	92314	9.0
12	340.06578	2921093	89680	17.8
13	342.06291	946720	88669	5.8
14	353.27002	800778	83964	4.9
15	381.30166	4612077	79449	28.0
16	382.30509	1036397	79206	6.3
17	383.09159	7401029	79372	45.0
18	384.09528	1200734	78686	7.3
19	385.08869	2851630	79024	17.3
20	397.27593	1619102	75764	9.8
21	413.27098	722493	73164	4.4
22	575.07716	728956	85883	4.4
23	575.08933	10617828	53058	64.5
24	575.10187	734244	119487	4.5
25	576.09296	3042278	52642	18.5
26	577.08645	6967081	52781	42.4
27	577.09921	605384	108697	3.7
28	578.09024	1979427	51992	12.0
29	579.08353	1039061	52804	6.3
30	657.35320	662432	46210	4.0

Fig. 5: Mass spectrum of compound (3a)

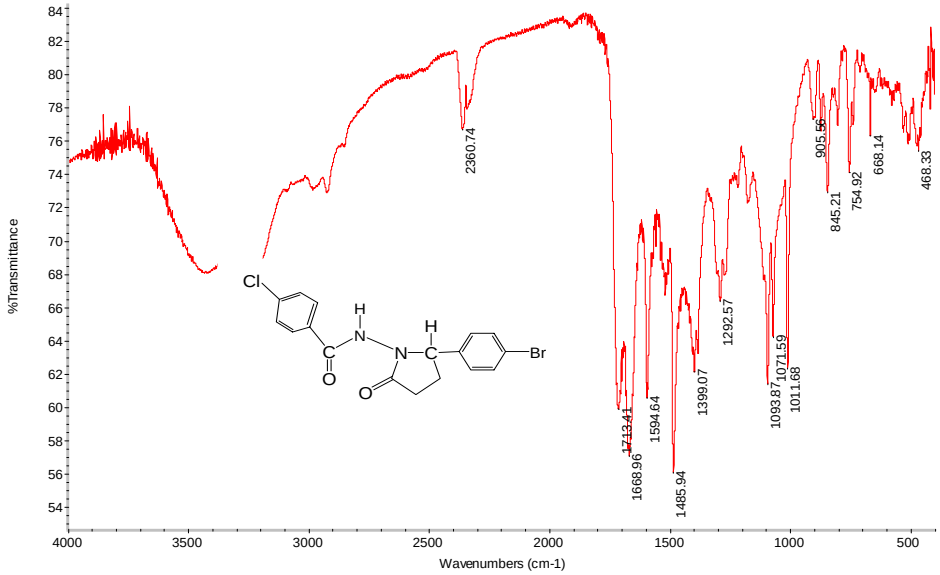


Fig. 6: IR spectrum of compound (4c)

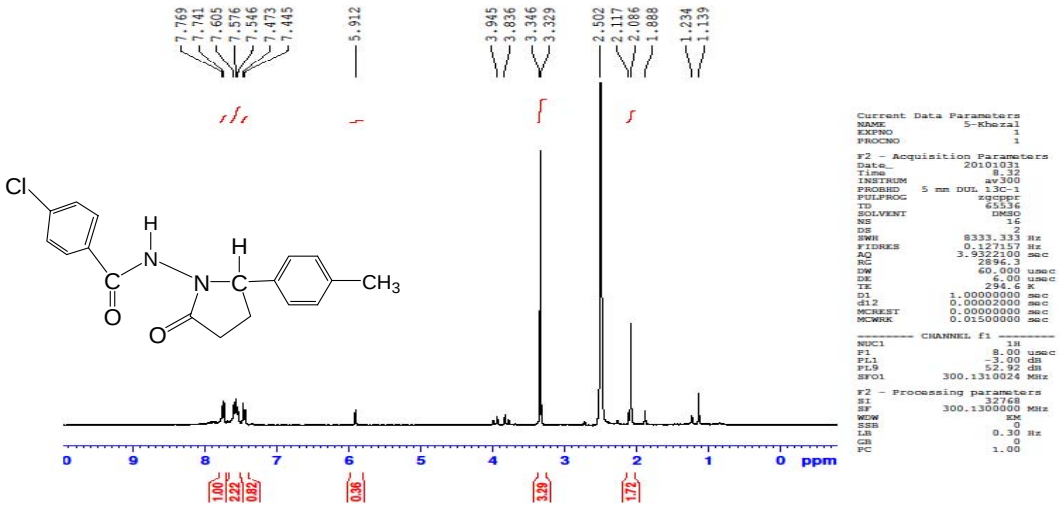


Fig. 7: ^{1}H-NMR spectrum of compound (4 e)

BIOLOGICAL ACTIVITY

The antibacterial activities for some of the synthesized thiazolidinone derivatives were carried out using disk agar diffusion method and the antibacterial activity was determined by measuring the diameter of inhibition zone.

The investigation of antibacterial screening data (Table 1) revealed that compounds (4 a-j) have different activity against *S.aureus* G (+ve) and *psedomonas aeruginosa* G(-ve).

Compounds (4a, d, f) were showed higher sensitivity than the others against *S.aureus* G (+ve), it might be due to the substituent on the aromatic ring by substituent such as $–OCH_3$,$-NO_2$ can form hydrogen bond with peptidoglycan causes inhibition of MurB enzyme which is an enzyme unique to prokaryotic cells. While they almost were active towards the *psedomonas aeruginosa* G (-ve)usually this type of bacteria has a high resistance against most of the drugs.

Table 1: Sensitivity of *Staphylococcus-aureus* and *pseudomonas aerginosa* against some prepared thiazolidinones

Compound	*S-aureus* G+ve	*Pseudomonas aeruginosa* G-ve
4a	+++	++++
4c	-	++++
4d	++++	++++
4e	-	++++
4f	++++	++++
4g	-	+++

Key to symbols:

High reactive	++++	(inhibition zone 24mm)
Active	+++	(inhibition zone 20- 24mm)
Moderately active	++	(inhibition zone 16- 20mm)
Slightly active	+	(inhibition zone 12- 16mm)
Inactive	–	(inhibition zone 12mm)

Table 2: Physical properties of the synthesized compounds (3a-j)

Compound	R	Yield%	M.P ˚C	Color	R_f 40% Ethylacetate-n-hexane
3a	4-OCH_3	82	179-180	Beige	0.58
3b	4-F	78	182-184	White	0.6
3c	2-Br	87	220-222	Beige	0.746
3d	4-Cl	75	218-221	White	0.47
3e	4-CH_3	68	202-203	Chalky	0.714
3f	4-NO_2	74	224-228	Yellow	0.68
3g	4-N$(CH3)_2$	82	184-185	Orange	0.28
3h	4-Br	69	218-220	Beige	0.43
3i	2-NO_2	68	210-212	Yellow	0.62
3j	2-OH	78	204-206	Bright green	0.48

Table 3: Physical properties of the prepared thiazolidinone compounds (4a-j).

Compd.	R	Yield%	M.P ˚C	Color	R_f 40%Ethylacetate-n-hexane
4a	4-OCH_3	48	159-160	White	0.85
4b	4-F	62	90-93 97-98	White	0.92 0.79
4c	2-Br	56	198-200	White	0.46
4d	4-Cl	68	206-208 135-138	White	0.88 0.369
4e	4-CH_3	58	188-192	White	0.5
4f	4-NO_2	65	202-204	Creamy	0.76
4g	4-$N(CH_3)_2$	80	239-240	Green	0.66
4h	4-Br	58	221-224	Brown	0.277
4i	2-NO_2	58	218-220	Yellow	0.56
4j	2-OH	68	18o-183	Green	0.48

Table 4: Assignment of characteristics frequencies ύ (cm^{-1}) of I.R. spectra for the prepared compounds (3a-j):

Compound	R	N—H	C—H Aromatic aliphatic	C—H Azomethine	C=O amide	N=CH Azomethine	C=C	Asym.NO2 Sym.	C—X
3a	4-OCH_3	3287	3024 2964	2838	1664	1636	1606		748 1256
3b	4-F	3194	3033	2845	1646	1603	1558		756 1065
3c	2-Br	3214	3052	2875	1651	1591	1549		514 749
3d	4-Cl	3230	3070	2875	1655	1596	1556		713
3e	4-CH_3	3285	3027 2965	2875	1665	1635	1607		750
3f	4-NO_2	3275	3085	2880	1677	1642	1593	1517 1347	745
3g	4N(CH_3)$_2$	3175	2994	2880	1644	1611	1596		755
3h	4-Br	3250	3075	2800	1667	1639	1594		748 514
3i	2-NO_2	3193	3066	2880	1652	1593	1550	1519 1341	747
3j	2-OH	3215 3376(OH)	3040	2890	1651	1623	1606		743

X = Cl, Br , F, O

Table 5: ^{1}H-NMR data (chemical shift δ) of some prepared compounds (3a-j) in DMSO (d6)

Compound	N-H$_{amide}$ ppm s,1H	N═CH azomethin ppm s,1H	CH aromatic ppm m,8H	OCH$_3$ ppm s,3H	CH$_3$ ppm s,3H
3a	11.8	8.39	7-7.9	3.8	
3d	12	8.4	7.5-7.9		
3e	10.8	8.4	7.2-7.97		2.3
3f	12.1	8.5	7.6-8.1		
3g	11.8	8.3	6.7-7.9		2.97
3h	12	8.45	7.5-7.97		
3i	12.2	8.6	7.6-8.1		

Table 6: Chemical Shift (δppm)^{13}C-NMR data for some prepared Hydrazide-Hydrazones (3 a-j) Solvent:DMSO d$_6$

Compound	CH$_3$ ppm	OCH$_3$ ppm	C$_{aromatic}$ Ppm	C$_{azomethin}$ Ppm	C=O Ppm
3a		55.78	114.83- 161.39	148. 49	162.33
3b			116.251-161.94	147.44	165.278
3d			129 .04- 137.124	147.262	162.587
3e	21.479		127.578- 140.454	148.695	162.471
3f			124.5-1 488.4	146.o5	162.82
3g	40.787		112.256-152.031	149.031	162.020
3i			125.128 - 148.731	143.765	162.726

Table 7: Assignment of characteristic frequencies ύ (cm^{-1})of IR spectra for the synthesized 4-thiazolidinone (4a-j)

Compound	N-H	C=O cyclic	C=O amide	N-H$_{bend.}$ C=C aromatic	N=O Sym. Asym.
4a	3220	1666	1635	1566	
4b	3433 3258	1717 1716	1651 1655	1602 1596	
4c	3214	1716	1651	1596	
4d	3257 3193	1717 1705	1653 1657	1596 1597	
4e	3217	1705	1655	1549 1606	1367 1549
4f	3216	1738	1641	1600 1590	
4g	3270	1673	1641	1598 1558	
4h	3264	1713	1668	1594	
4i	3367	1699	1652	1496	1346 1520
4j	3450(br.OH)	1733	1639	1616 1574	

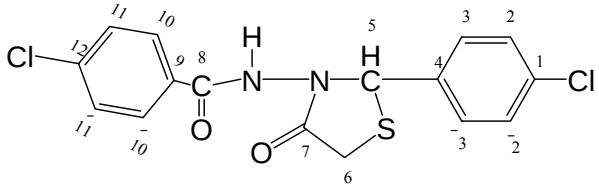
Table 8: The Chemical shift ^{1}H-NMR data of some synthesized 4-thiazolidinone (4a-j)DMSO (d6).

Compound	δ N-H_{amide} ppm(s, 1H)	δ $CH_{aromatic}$ ppm (m,8H)	δ CH thiazolidinone ppm(s,1H)	δ CH_2 thiazolidinone ppm(d,2H)
4a	12	7.3-8.4	7.2	4.7(s)
4b	10.6	7-8.4	6	3.8-4.7
	11	7-8.4	6	3.9-4.2
4d	11	7.4-8.4	6	3.3 – 4
4e		7.4-7.7	6	3.8-3.9
4f	12.2	7.6-8.5	7.2	4.7(s)
4i	9.4	7-8.3	7	4-4.3
4j	8.3	7.8-8.2	6.9	4-4.4

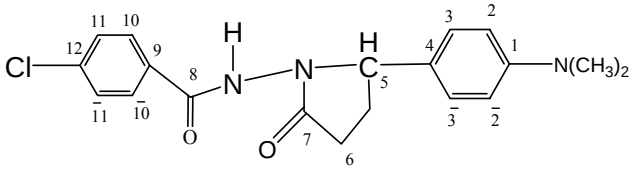
Table 9: Chemical Shift (δppm)^{13}C-NMR data for some of 4-thiazolidinones (4a-j). Solvent: DMSO d_6

Compound	CH_3	C_6 thiazolidinon	C_5 thiazolidinon	C_1	$C_{2,2^-}$	$C_{3,3^-}$	C_4
4d		29.7	61.3	134	129.2	130.1	137
4e	22.32	31.57	61.45	132,93	130.65	128.61	139.63
4f		22.16	63	146	124.56	129.13	148.3
4g	40	38.4	66.7	152	112.26	121.9	137

Compound	C_7 C=O	C_8 C=O	C_9	$C_{10,10^-}$	$C_{11,11}$	C_{12}
4d	169.5	164.68	133.65	129	128.5	137.91
4e	169.54	167.7	134.56	131.35	128.5	141
4f	170	162	137	130.15	128.53	140.9
4g	170	167	135	129.88	128.97	149



4d



4g

CONCLUSION

From the result of the reaction of acid hydrazones with thioglycolic acid, it has been showed that they are depended on the reaction medium (solvent), so the reaction in benzene has more effect than in ethanol. The times of the reactions also were affected by the type of substituent on the azomethines bond and this type of reactions can be done without using catalyst.

(+) The biological effect showed the activity of this type of thiazolidinone derivatives against the Grame–negative bacteria *psedomonas aeruginosa* is more than the Gram-positive one *staphylococcus aureus*.

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