Synthesis and biological activity evalution of some new 1,3 –oxazine and 1,3 –thiazinederivedfrom (5-amino-1,3,4-thiadiazole-2-thiol).

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Abstract :.

The thiosemicarbazid was reacted with carbon disulfide .the result of their reaction was 5-amino 1,3,4 thiadiazol [1] .then the resulted compound was retreated with acetic anhydride to optain 5- mercapto 1,3,4 thiadiazol-2-yl acetamaied [2] to synthese 5 amino 1,3.4 thiadiazole-2- thiol [3].

This compound was allowed to react with aromatic aldehyde in precense of sodium hydroxide the resulted of the reaction -5- (2- amino-4-methyl thio1,3,4 thiadiazol (2H) yl -6-(1,3) oxazine 1,3 thiazine(4-6)(7-12)through reaction with urea and thio urea .the chemical structures of the products were characterized by (FT-IR) and (^{1}H-NMR) (10,11) and melting points apparatus.

Key words:. (5-2amino -4- 5- methyl thio 1,3,4 thaidiazol -3- (2H) yl 1,3 thiazine 1,3 oxazine , Antibacterial .)

(تحضير وتقييم الفعالية البايولوجية لبعض مشتقات الجديدة لمركبات 1,3اوكسازين و 1,3ثايازينالمشتقة من (5-امينو 1,3,4ثاياديازول-2- ثايول)

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الملخص:

تم مفاعلة الثايوسيمكاربازيد مع ثنائي كبريتيد الكاربون والحصول على المركب 5- امينو 1,3,4ثاياديازول2-ثايول المركب (1)ثم مفاعلة المركب (1) مع انهيدريد حامض الخليك والحصول على 5- مركبتو1,3,4ثاياديازول – 2-يل اسيتدامايد.ثم مفاعلة المركب (٢) مع المثيل كلوراید للحصول على المركب (٣) ثم مفاعلة المركب (٣) مع الديهايداتاروماتية بوجود هيدروكسيد الصوديوم والحصول على المشتقات (٤-٦)ومن ثم تفاعل المركبات الاخيرة مع اليوريا والثايوريا للحصول على المركبات (12 -7) . تم تشخيص المركبات باستخدام الأشعة تحت الحمراء وقياس درجة الانصهار ومطيافية الرنين النووي المغناطيسي البروتون (10،11) .

الكلمات الدالة :- الفعالية البايولوجية ، ١ ، ٣ – اوكسوزين ، مشتقا ١ ، ٣ - ثايوزين

Introduction

1,3oxazines exhibit awide range of biological activity (1-11) , such as bactericidal, fungicidal , antitumor , and anthelmintic effects , therefore the synthesis of these compound has attracted great interest .several elegant method for the preparation of these compound have been documented in literature(12-20) .burke and co – workers disclosed Mannich – type condensation of phenol with amines and formaldehyde to provide 2- unsubstituted 3,4-dihydro -2H -1,3 benzoxazine[4,5,6] . condensations of 2- aminomethyl phenol with aromatic aldehydes another route to 3,4- dihydro-2H-1,3- benzoxazine(21).

1,3 thiazine is active core of cephalosporinswhich are more the wiedly used in various biological activities such as antimicrobial and anticancer (22-23) . inhabition of chemical mediators release activity of various substituted

pyrimididines as biological agent(24-25).

The ability of thiazine to exhibiteantitubercular(26).which is inactivate in biological activities , itappeared of interest to synthesis some new amimo guanidine pyrimidines and thiazine derivatives (27) . some 1,3 thiazine and 1,3 oxazine have been also prepared using amino acid glacine as astarting material.(28) .

Experimental Part:

2-1 :Synthesis of 5- amino -1,3,4 thiadiazol-2-thiol(1) The compound was prepared from thiosemicarbazid and carbon disulfide according to previcone method[(29).]

2-2: Synthesis of N- (5- Mercapto -1,3,4- thiadiazol - 2- yl) acetamide (2) (30 ml) of acetic anhydride was added to solution of 2- amino-5-mercapto-1,3,4- thiadiazol (1) (20ml) absolute ethanol and the resulting mixture was refluxed for(6 hours) (30)The solid compound separated on cooling was filtered off and dried .

2-3: Synthesis of N- (5-methylthiol -1,3,4 thiadiazol – 2-yl)acetamide Mixture of(0.02 mol) (3.7g)from compound (2 precense methyl chloride .compound separated cooling was filtered off and dried .

2-4: Synthesis of (4-6) 5- (2- amino -4- (5- methythio)- 1,3,4 thiadiazol-3- (2H) –yl – 6H)1,3,4 – oxazine -6- yl) -2- benzaldehyde .

To Mixture of the N- (5-methylthiol- 1,3,4 thiadiazol – 2-yl)acetamide [5.8gm](0.04 mol) substitedbenzaldhyde(0.02 mol))(1g)NaoH)and (20ml) absolute ethanol.the Mixture refluxed for(4 hour)these compound filtered , washed with cold water dried and crystallized from absolute ethanol.

2-5: Synthesis of 1,3 – oxazines derivatives (7-12).

AMixture of compound (4-6) (0.01) mol and urea (0.01) mol were dissolved in ethanolic sodium hydroxide (10) ml.the Mixture was refluxed for(6 hours). cold and poured into cold water with continuous stirring for(1hours) . theprecipitatd obtained was obtained was filtered , washed and crystallized . the procedure was used to Synthesis1,3 thiazine derivatives (10-12) from compound(4-6) and thiourea. [31] ,[32].

2-6:Biological activity.

BacterialisolatesofStaphylococcusaureus, E,coli , Klebseillapneumonia,andpseudomonasaeruginosa , wereobtained from department of Microbiology Tikrit University – Collegeofveterinary, Medicine.

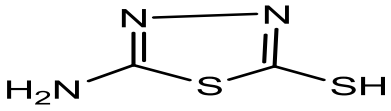
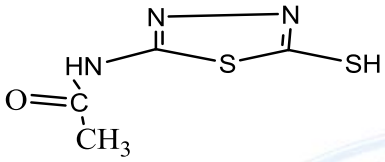
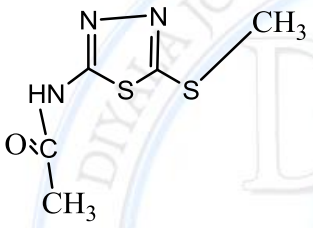
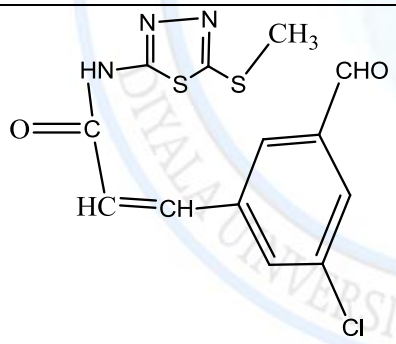
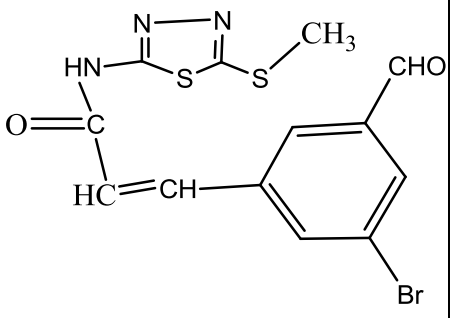
These isolates werecultured on to nutrient agar plates and incubated at(37^{o}C)

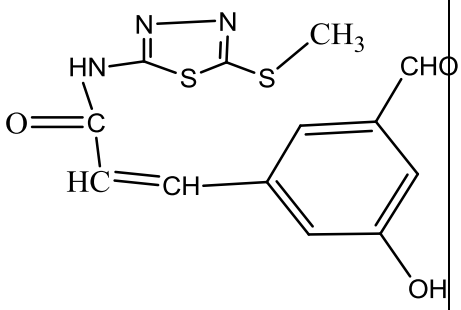
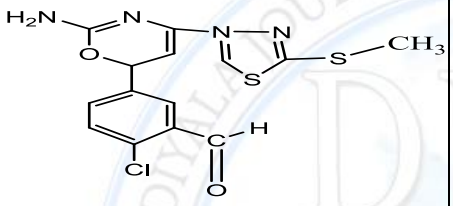
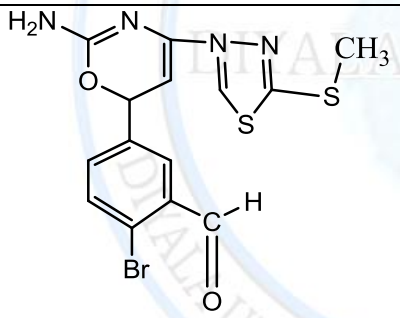
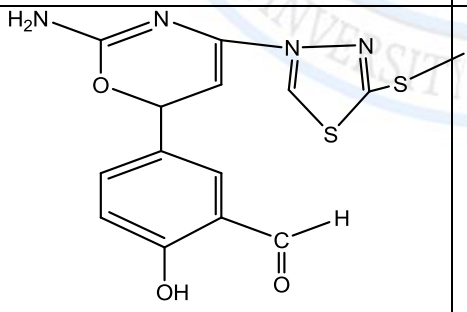
for(24 hours). Theantibacterialactivityofdimethylsulfoxide(DMSO).

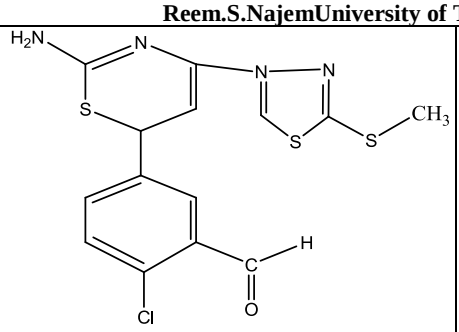
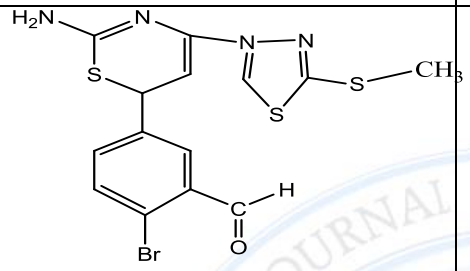
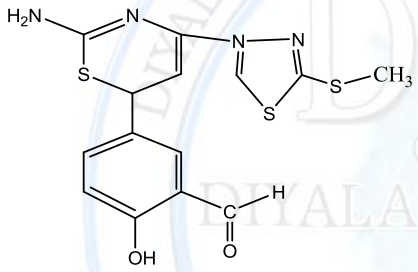
Was evaluated using the concentrations (50,100,150) mg\ml. agar diffusionMethodonmueller Hinton Agar.which prepared and sterilized by autoclave, then poured in petri dishes, left to solidify and three wells were done.In each plate.these plates were cultured with bacterialisolatesby streaking and Concentrationsto be test were the wells then plates were incubated at(37^{o}C)for 24 hours.

Inhibition zones around the wells were measuredwhich represent the antibacterial activity of DMSO. [33

Table (1) physical properties of prepared compound (1-12)

Comp NO	Chemical structure	m.p°C	Color	Yeild %	Name of Compound
1		225-227	White	75	5- amino -1,3,4-thiadiazol -2-thiol
2		220-210	White	61	N- (5- mercapto – 1,3,4 thiadiazol– 2- yl)acetamide
3		218-219	Yellow	50	N- (5-methylthiol -1,3,4 thiadiazol– 2-yl) acetamide
4		143-141	Yellow	50	(E)-3-(3-chloro-5-formylphenyl)-N-(5-(methylthio)-1,3,4-thiadiazol-2-yl)acrylamide
5		153-155	Grey	43	(E)-3-(3-Bromo-5-formylphenyl)-N-(5-(methylthio)-1,3,4-thiadiazol-2-yl)acrylamide

6		186-187	Yellow	77	(E)- 3- (3-fomyl)-5-hydroxyl phenyl) –N -5- methythio) 1,3,4 thiadiazol -2- yl)) acryl amide
7		152-154	Yellow	64	5- (2- amino -4-(5 methylthio)1,3,4 thiadiazol -3(2H) –yl) -6H -1,3 oxazine -2 – chlorobenzaldehyde
8		162-164	Yellow	35	5- (2- amino -4-(5 methylthio)1,3,4 thiadiazol -3(2H) –yl) -6H -1,3 oxazine -2- bromobenzaldehyde
9		176- 178	Yellow	44	5- (2- amino -4-(5 methylthio)1,3,4 thiadiazol -3(2H) –yl) -6H -1,3 oxazine -6- yl) - 2- hydroxyl benzaldehyde

10		216-218	White	65	5(-2- amino -4- (5- methylthio 1,3,4 thiadiazo -3-) (2H) –yl)1,3 thiazine -6 yl) -2- chlorobenzaldehyde
11		233-235	White	45	5(-2- amino -4- (5- methylthio 1,3,4 thiadiazo -3-) (2H) –yl)1,3 thiazine -6 yl) -2- bromobenzaldehyde
12		229-231	White	57	5(-2- amino -4- (5- methylthio 1,3,4 thiadiazo -3-) (2H) –yl)1,3 thiazine -6 yl) -2- hydroxyl benzaldehyde

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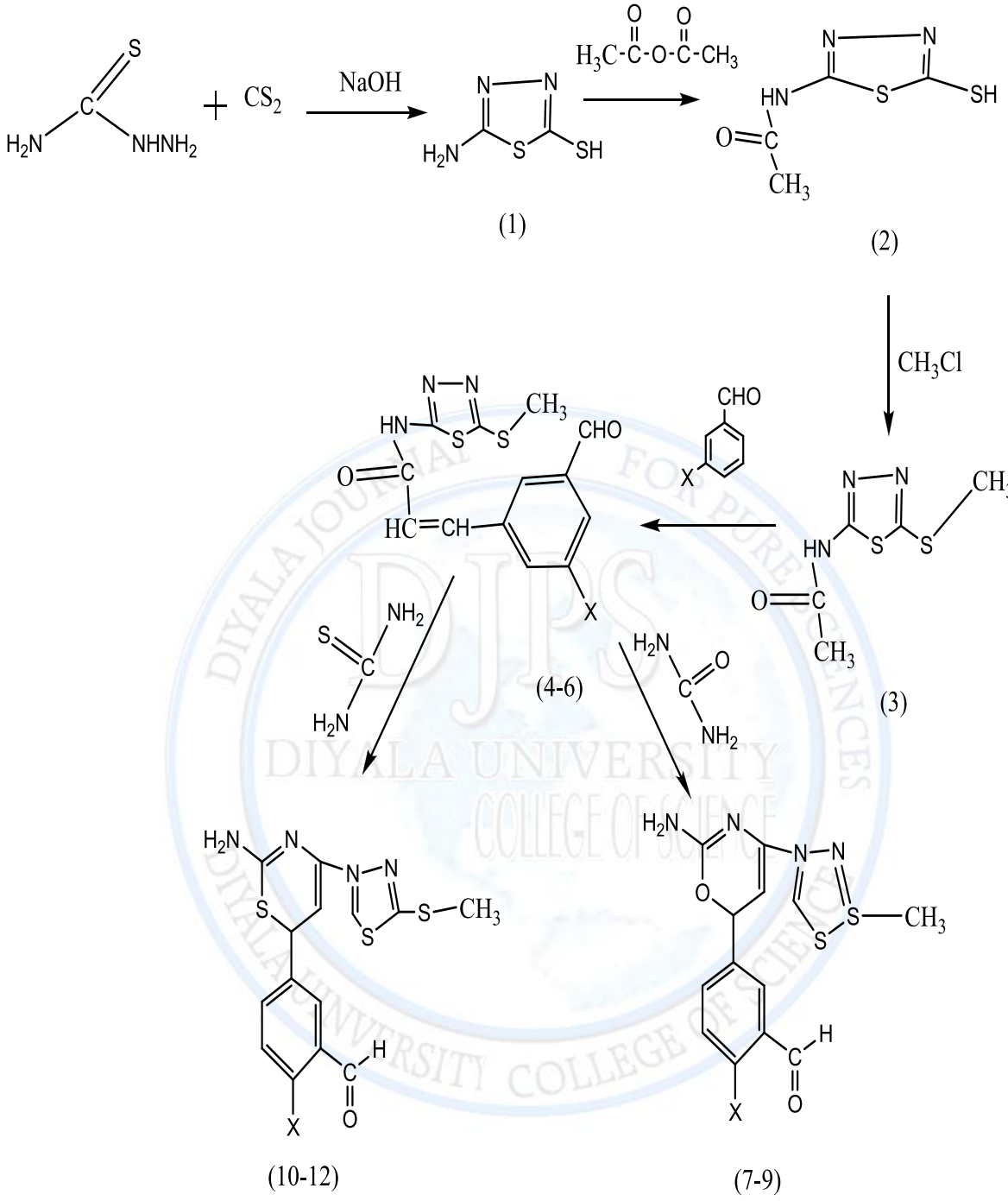

Scheme (1)

Resuits and discussion :

The thiolgroup in 2- amino -5- mercapto -1,3,4,- thiadiazol (1) was converted into acetic anhydride derivative (2) by heating under reflux with an ethanolicsolution .The later compound was allowed to react with methyl chlorid to synthesize 1,3,4-thiadiazol -2-yl acetamide (3) respectively The acetamide group in these compound was converted to benzaldehydegroup.and these compound(4-6) reactionwith urea and thio urea give compound (7-12). FT-I.R spectra showed (NH) band for compound (1) absorbedat (3390-2230) $cm^{-1}$for , (NH_2) band absorbedat (3200cm^{-1}) , (1348cm^{-1}) for C=S.I.R spectraalso showed that the(CH_3) band absorbedat (3300-3195)cm^{-1} forcompound (3). (C-H aromatic) absorbedat 3075 cm-1 and (C=O) at (1700) cm-1 for compounds (4-12).
I.R spectra also showed that (aromatic C- H)at 3100 cm-1 and . (C=N) at 1625 cm-1
H^1-N.M.R data for compound (10) showed that protons ring at(9.915) ppm for (NH_2) and CH (7.4-7.090) ppm (CH_3) (3.361) ppm for compound (11) CH (7.702-7.673)ppm CH_3 (3.3-3.04) ppm NH_2 (9.673) in the area (2.5-3.5) ppm The figures (1-2) showedthe assigned.

Resuits and discussion

Table (2)resuitobsorption data of I.R spectra and H: N.M:R data

I.Rspectr data cm			H^1-N.M.R		
Comp.No	vC-H Ar	vC=O	C-H	$C-H_3$	NH_2
[10]	3075	1700	1610	3.361	9.915
[11]					9.673
[10]				3.3-3.04	2.5-3.5

Biological activity:.

The results of the antibacterial screening.the some compound at a concentration of

(50,100,150) mg/ml against all bacterialhave been found. The inhibition zones were measured in mmand results are shown in Table (3).The results ofantimicrobialscreening, The compounds prepared invitro effective inhibition towards our high four types of bacteria, namely: Staphylococcusaureus,E.coli,Klebesill_pneumoniaPseudomonasaeruginosa._ Two compounds showed high inhibition. values of (1.2)and these values are (27.35, 22and 30 , 35).

,Toward the four types of bacteria, and this goes back to the two compounds contain

[1,2] the effective range a group secretary It is that play an important roletowardsbacteria.

It also showed the effectivenessof the compound (4) inhibitiontowards high1- bacteria–1-Staphylococcusaureus2 - E. coli 3- Klebseillpneumonia did not appear effective inhibition towards our bacteria. Pseudomonasaeruginosaand this goes back to the compound (4) containing oneffective range a group aldehydic a group(chlorinegroup)Interfe with bacterial.Showed the compound (6) and high effective inhibition of these values are(28, 43, 38, 30 , 39, 31, 22, and 23, 44)towardthefour types of bacterial.

and this goes back to the containment of the compound (6)aldehydic group of (Bromo group) which plays , an important roletowards our bacteria because it contains rules(1,3,4 -oxazine 6- yl -2- Bromobenzaldehyde). Compound(9) also showed high inhibition

values and these values are (38, 33, 27 and .35, 22 and37 ,.29) toward the four types of bacteria a group (1,3 oxazine) play an important role towards bacteria.

Compound(11,12) also showed highinhibitionvalues and these values are(40,42,44, and33,38) toward the four types of bacteria because 1,3 thiazine group play an important role towards bacteria.

Antibacterial activity of these compoundsshow ascending order. When we increase concentration, area of inhibited growth alsoincreased. .[34]

Table (3)(Hits inhibitory compounds prepared in thegrowthof the number of negativeand positive bacteria. (diameter of the circleinhibitory measured by Malam)

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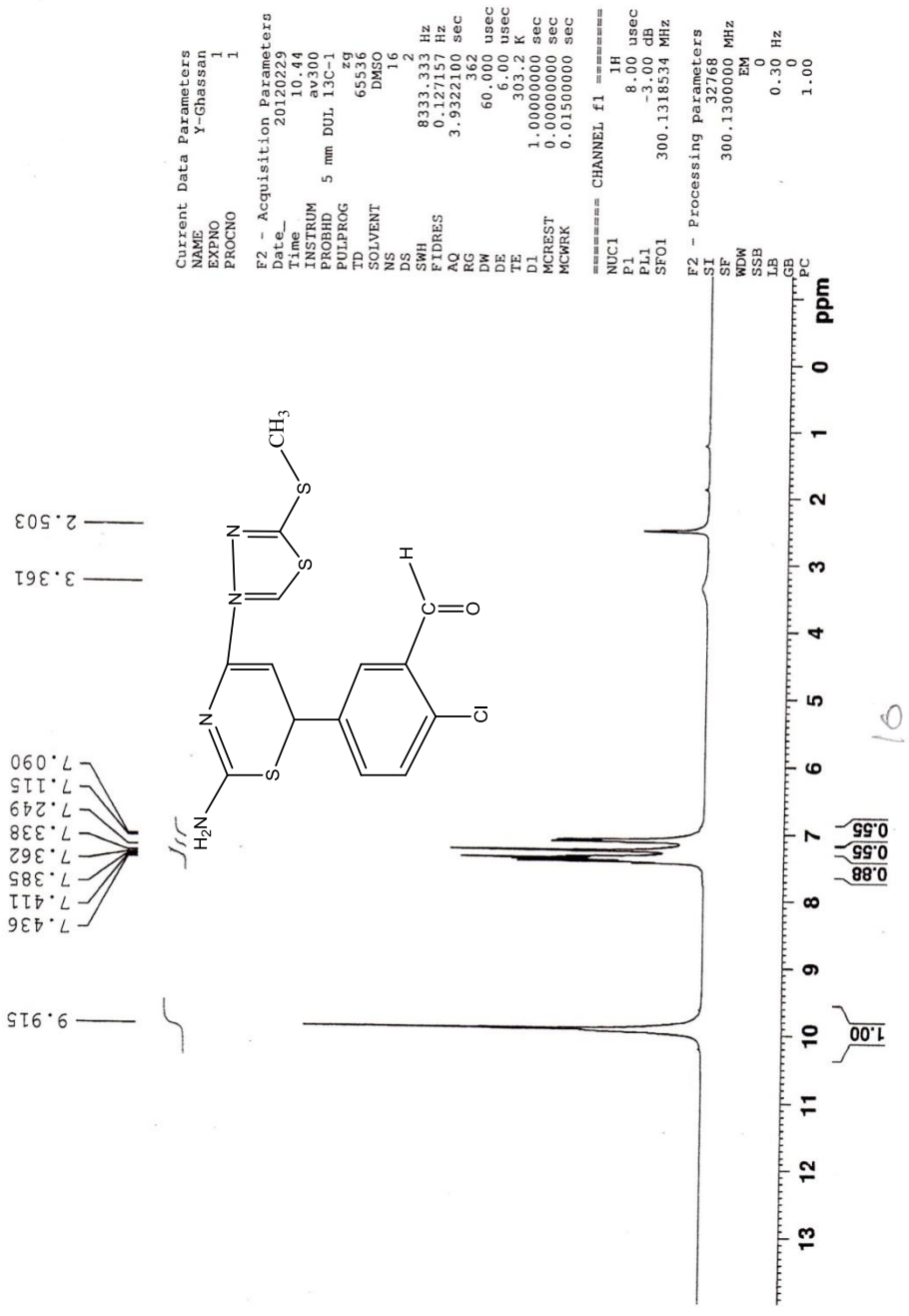
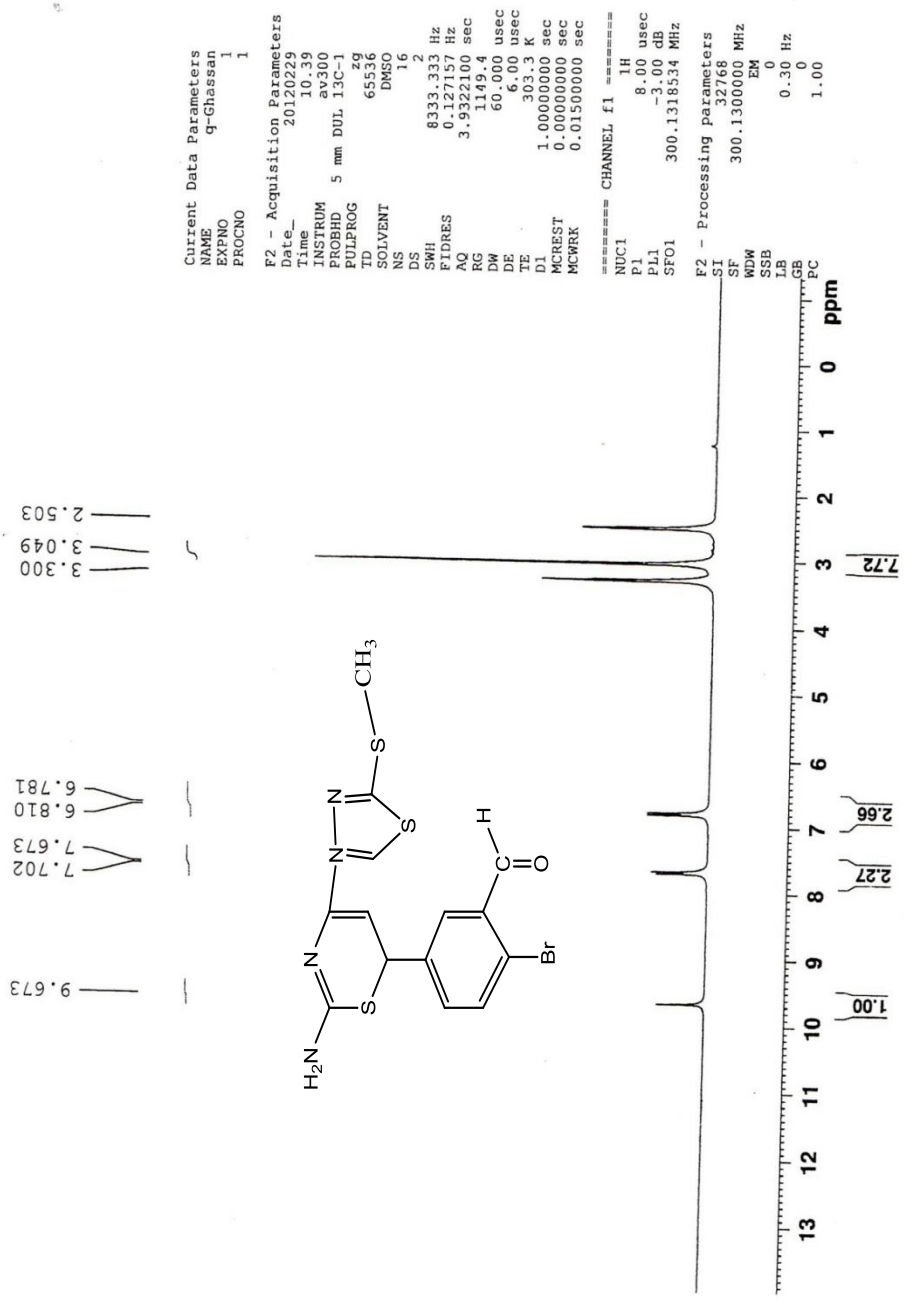
Comp. No.	Conc. Mg/ml	*Staphylococcus aureus*	*E. coli*	*Klebseill pneumonia*	*Pseudomonas aeruginosa*
1	50	29	35	30	25
	100	30	35	35	25
	150	22	35	27	25
2	50	35	48	33	40
	100	30	38	38	44
	150	22	41	30	45
4	50	40	42	33	-
	100	44	36	36	-
	150	45	38	32	-
6	50	28	33	44	35
	100	43	36	31	22
	150	38	39	30	23
9	50	38	22	35	22
	100	33	37	37	33
	150	27	32	29	35
11	50	44	38	48	37
	100	42	40	42	36
	150	40	42	40	40
12	50	33	44	40	44
	100	35	38	42	40
	150	38	45	44	42



شكل رقم (1) يمثل طيف H^1.N.M.R للمركب رقم (10)



شكل رقم (2) يمثل طيف H^1.N.M.R للمركب رقم (11)

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