Synthesis and characterization of new heterocyclic compounds with studying its biological activity.

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Abstract :

Reaction of malonic acid di hydrazide (1) with CS_2 / KOH then with hydrazine hydrate gave 1,2,4-triazole (2) which was reacted with different substituted benzaldehyde to give Schiff bases derivatives (3-8) respectively. Schiff bases (3-8) were reacted with thioglycolic acid to give thiazolidenones (9-13). Also ,Schiff bases were reacted with glycine to give imidazolidenone (14-18). The prepared compounds were characterized by FT-IR ,^{1}H-NMR ,Uv/vis spectra ,melting points were recorded and the purity was checked through T.L.C.technique. Some of the synthesized compounds were screened for antibacterial activity.

تحضير وتشخيص بعض المركبات الغير متجانسة الحلقة مع دراسة فعاليتها الحيوية.

هلال مسعود عبدالله وابتسام خليفة جاسم وملاك نبيل صافي.*

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الكلمات المفتاحية : ترايزولات ،ايميدازولات ، ثايازوليدين .

الملخص :

ان تفاعل حامض المالونك ثنائي الهيدرازايد (2) مع ثنائي كبريتيد الكاربون وهيدروكسيد البوتاسيوم ثم مع هيدرازين هيدريت مرة اخرى اعطى المركب (2) 1,2,4-ترايزول والذي تمت مفاعلته مع مختلف المعوضات للبنزلديهايد ليعطي قواعد شف 03-8).ثم تمت مفاعلة قواعد شف هذه مع حامض ثايوكلايكولك لتعطي مشتقات الثايازوليدين اون(9-13).كذلك فوعلت قواعد شف مع الكلايسين لتعطي مشتقات الايميدازوليدين اون (14-18).شخصت المركبات المحضرة عن طريق اطياف الاشعة تحت الحمراء والرنين النووي المغناطيسي والفوق البنفسجية –المرئية ودرجات الانصهار وتم تحديد نقاوتها بواسطة تقنيةالطبقة الرقيقة الكروماتوكرافية . كما تم اختبار الفعالية المضادة للبكتريا للبعض منها

Introduction :

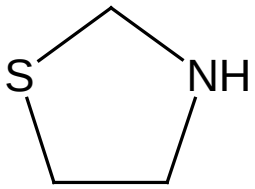
Heterocyclic systems are widespread occurrence in nature, particularly in such natural products as nucleic acids, plant alkaloids and chlorophyll [(1)]. Heterocyclic compounds are considered one of an important type of organic compounds due to their application in drugs and industrial studies. A variety of atoms, such as N, O, S, P, Si and As can be incorporated into the ring structures [(2)] The **triazoles** are two isomers, namely 1,2,3-triazole or 1,2,4-triazole, with the formula $C_2H_3N_3$. They are aromatic ring compounds similar to the azoles pyrazole and

imidazole, but with an additional nitrogen atom in the ring structure. Like the azoles, triazoles are used in many antifungal drugs and fungicides, and the triazole-based drugs are more selective for fungi than mammalian cells than the azole-based antifungal compounds. Today, most substituted triazoles are produced by so-called click chemistry pioneered by K. Barry Sharpless and others. Synonyms for both of these triazoles sometimes denote that a proton is attached in the 1-position, as for example, the naming 1H-1,2,3-triazole or 1,2,3-1H-triazole [3].

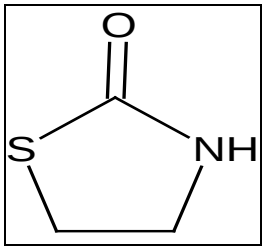
Pyrimidines[4] also known as *m*-daizine, is the parent substance of large group of heterocyclic compounds which has attracted much attention for a longtime. These compounds which belong to this group where known as breakdown products of uric acid at a very early date of the history of organic chemistry , but systematic study of this ring system began with work pinner. who first applied the name pyrmidine to the unsubstantiated parent body.

Pyrimidine derivatives play an important role in many biological processes the ring being present in nucleic acid, several vitamin coenzymes, uric acid and other purine. Many drugs (barbituric acid derivatives) and chemotherapeutic agents (Sulfadiazine) contain pyrimidine ring. Pyrimidine can be regarded as cyclic amidine and the chemical behavior of its derivatives is dominated by this fact.

Thiazolidines and thiozolidinones are five member ring heterocyclic compounds [5]contain sulfur and nitrogen atoms and three carbon atoms these compounds are not aromatic they have the below structure

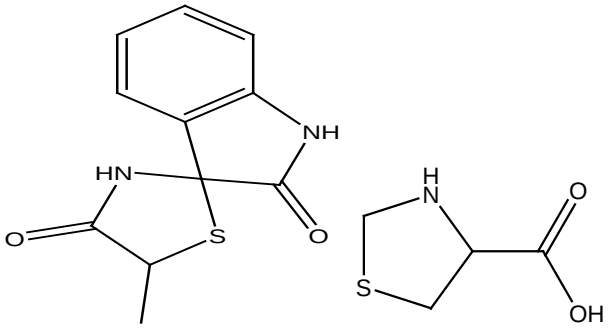


Thiazolidine



Thiazolidinone

The best method of preparation of thiazaolidinone by the reaction of mercaptoacetic acid with imines (Schiff bases) [6,7] . **Milind, and Frank** [8] prepared 5'-Methylspiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-diones by the cyclocondensation of thiolactic acid with isatin-3-imines



D Chiarino et,al [9] prepared number of-substituted-4-thiazolidin carboxylic acid derivatives by cyclocondensation of L-cysteine or its esters with various aldehydes, with anti- inflammatory properties

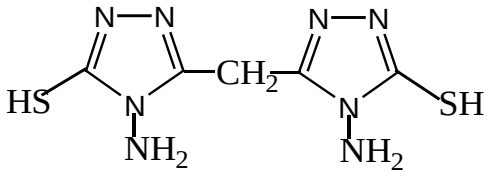
Experimental / Techniques :

1. Melting points were recorded with Stuart Melting point apparatus and were uncorrected.
2. Infra red spectra (FT-IR) were recorded on Shimadzu FT-IR-8300 spectrophotometer in Ibn – Al-Haitham college **.**
3. Uv/vis spectra were recorded on Uv/vis varian Uv-Cary-100 spectrophotometer in (ISSC).
4. ^{1}H-NMR spectra were recorded on a BRUKER-400 MHz operating at 300 MHZ with tetra methyl silane as internal standard in DMSO-d_6 as a solvent, measurements were made at Chemistry Department, AL-Bayt University-Jordon.

5. Elemental Analysis (C.H.N.S.) was carried out with: Euroea Elemental Analyzer Italia by Chemical Department College of Science, Babylon University.

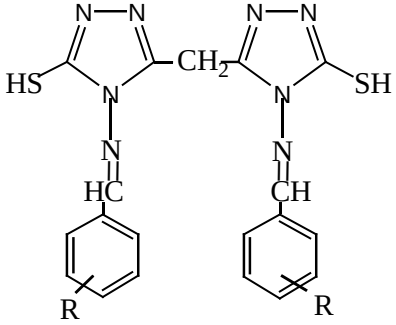
6. Thin layer chromatography (TLC) was carried out using Fertigfollen precoated sheets type polygram Silg, and the plates were developed with iodine vapour.

1-Synthesis of bis 3-mercapto -4-amino - 5-methylene 5-yl -1,2,4-triazole[10] [2].



A mixture of malonic acid dihydrazide (21g, 0.01mole) and (25ml)of carbon disulfide and potassium hydroxide (2.23g,0.01mole) was dissolved in (50ml)of absolute ethanol and refluxed with stirring for (5 hours).After That ,The excess of ethanol was removed by rotary evaporator .Hydrazine hydrate (20ml)was added to the crude and refluxed for (4 hours), cooled and diluted with (20ml) distilled water and acidified with diluted HCL to produce a white precipitate , Yield (85 %).

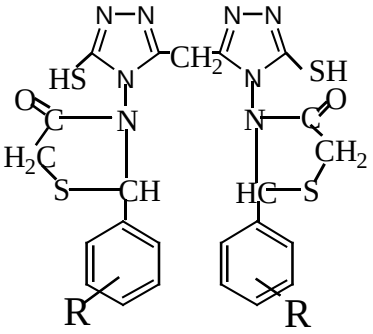
2-Synthesis of Schiff Bases [3-8] [11].



R = 3-NO_2 , *4*-$N(CH_3)_2$, 2-Chloro ,*4*-NO_2 , *4*-OH and Vaniline .

A mixture of equimolar amounts (0.09 mol) of appropriate aldehyde and the triazole in absolute ethanol (15 ml) with (3) drops of glacial acetic acid was refluxed in water bath for 3 hours. The reaction mixture was then allowed to cool at room temperature, the precipitate was filtered, dried and re crystallized from ethanol to give yellow crystals.

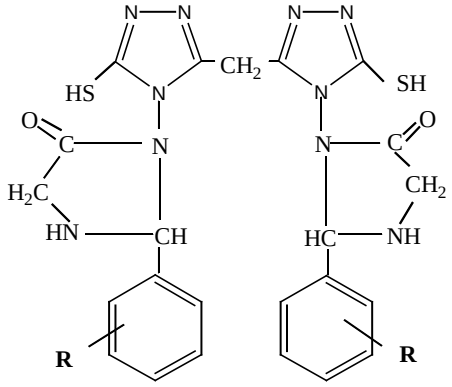
3-Synthesis of Compounds [9-13] [(12)].



R = 3-NO_2 , *4*-$N(CH_3)_2$, *4*-NO_2 , *4*-OH and Vaniline .

Mercapto acetic acid (0.002 mol) in dry benzene (7.5 ml) was added slowly to (0.001 mol) of Schiff bases [3]. The addition continued about (10 second) with stirring then the mixture was refluxed for 10 hours. Excess solvent was evaporated and the residue was treated with sodium bicarbonate to produce compounds [9-14] as solid precipitate and re- crystallized from ethanol.

4-Synthesis of bis [3-mercapto-2-methylene-2yl)-4- imidazolin-4-one (14-18) [(13)]:



R= 3-NO_2 , *4*-$N(CH_3)_2$, *4*-NO_2 , *4*-OH and Vaniline .

A mixture of Schiff base (0.01mol) and glycine (0.02mol) in 20 ml THF was refluxed for 24 h then cooled to room temperature, the precipitate was filtered and recrystallized from ethanol and THF (25/75).

Table (1). Yields and physical data of the synthesized compounds.

Compound No.	R_f	Yield %	Color	Recryst. Solvent
1	0.68-0.78	73	White	Ethanol
2	-	71	White	Ethanol/H_2O
3	-	65	Yellow	Ethanol
4	-	72	red	Ethanol
5	-	74	Orange	Ethanol
6	-	73	Orange	Ethanol/H_2O
7	-	66	Pale yellow	Ethanol
8	-	70	Yellow	Ethanol
9	-	75	Yellow	Ethanol/H_2O
10	-	79	Yellow	Ethanol
11	-	60	Yellow	Ethanol
12	-	92	Yellow	Benzene
13	-	70	Yellow	Ethanol/H_2O
14	-	81	Yellow	Ethanol/H_2O
15	-	65	Yellow	Ethanol

16	-	83	Yellow	Ethanol
17	-	90	Yellow	Ethanol
18	-	60	White	Benzene

Table (2) : C.H.N.S. analysis for some prepared compounds.

Comp. No.	C.H.N .S .analysis Calc /Found.
2	24.59 /24.1 3.27/3.00 45.90/45.4 26.22/26.00
3	44.70/44.30 2.74/2.40 27.45/27.00 12.54/12.00
9	46.46/46.00 3.03/3.0 23.56/23.10 10.77/10.20
14	44.23/44.00 3.20/3.00 26.92/26.30 10.25/10.0
4	45.61/45.01 5.13/4.80 27.66/26.10 12.64/12.01
10	54.91/54.30 5.08/4.90 23.72/23.40 10.84/10.20
15	52.25/52.00 5.16/4.90 27.09/26.09 10.32/10.00

Table (3). Spectral data for the newly synthesized compounds.

Compound No.	Spectral data FT-IR /Uv λmax
1	IR (KBr. cm^{-1}). 3309, 3221 (NH-NH_2 asym. sym-stretch) and 1660 (C=O) amide I.
2	IR (KBr. cm^{-1}). 1610 (C=N), and 2470 (S-H). 3363, 3309, 3174 (NH_2 asym. sym-stretch and NH), 1608 (C=N), 1568 (C=C) /276,624
3	IR (KBr. cm^{-1}). 1608 (C=N), 1568 (C=C) .
4	IR (KBr. cm^{-1}). 1706 (C=N cyclic stretch of triazole ring) and 1601(C=N).

5	IR (KBr. cm^{-1}). 2528 (S-H), 3055 (C-H) aromatic and 1616 (C=N)
6	IR (KBr. cm^{-1}). 1612 (C=N) and 3020 (C-H) aromatic.
7	IR (KBr. cm^{-1}). 3113 (NH), 3080 (C-H) aromatic and 1610 (C=N).
8	IR (KBr. cm^{-1}).3305, 3221, 3149 three groups of (N-H), 1240 (C=S) and 1643 (C=O).
9	IR (KBr. cm^{-1}).1602 (C=N), 3395 (N-H) and 700 (C-S-C)./ λmax 276,236,283.
10	IR (KBr. cm^{-1}).1600 (C=N), 3400 (N-H) and 1240 (C=S)/ λmax 412,276,238,352,240.
11	IR (KBr. cm^{-1}). 3627 (O-H), 3369, 3128 (NH-NH) and 698 (C-S-C).
12	IR (KBr. cm^{-1}). 3300 (N-H), 1670 (C=O), 1645 (C=O) amide I and 3090, 3060 (C-H) aromatic.
13	IR (KBr. cm^{-1}).1602 (C=N), 3375 (N-H) and 1240, 1026 (C-O-C asym. sym-stretch).
14	IR (KBr. cm^{-1}). 1608 (C=N) and 3433 (O-H)./ λmax 310,340,283.
15	IR (KBr. cm^{-1}). 3431 (O-H), 3300, 3210 (NH-NH). /λmax 276,212,224.
16	IR (KBr. cm^{-1}). 3274 (O-H), 1737 (C=O) pyrazole ring, 1661 (C=O) amide I and 2979 (C-H) aliphatic.
17	IR (KBr. cm^{-1}). 3215 (N-H), 1641 (C=O) and 3064 (C-H) aromatic.
18	IR (KBr. cm^{-1}). 3192 (N-H), 1676 (C=O), and 1600 (C=N) .

Results and Discussion:

In this work, malonic acid di hydrazide (1), was used as the key intermediate for further synthesis. Thus, when compound (1) was treated with carbon disulfide and potassium hydroxide then with hydrazine hydrate according to reported method of **Young** and **Wood**[14], (2) was obtained, (scheme I. Table 3). The IR spectrum of this compound shows the bands at 3363,3309,3174 $cm^{-1}$for (NH_2 asymmetric and symmetric stretching and NH. Band at 1608 $cm^{-1}$for (C=N) , a band at 1568 $cm^{-1}$for (C=C) . The ^{1}H-NMR spectrum of compound [2], shows the following characteristic chemical shifts (DMSO-d_6) ppm. (δ 9.25) due to protons of (N-

H)toutomeric of triazole ring and protons of (CH_2) appeared at (δ 4.4). Also ,the protons at (δ 9.78,7.60) due to NH_2 (amino group).

Condensation of compound (2) with different substituted of benzaldehydes in absolute ethanol afforded the corresponding ***Schiffs*** bases (3-8) (scheme I. Table 3).

2-Synthesis and characterization of 4N[substitutedbenzylidene]-5-mercapto -2-methyl-2yl-1,2,4-triazole [3-8].

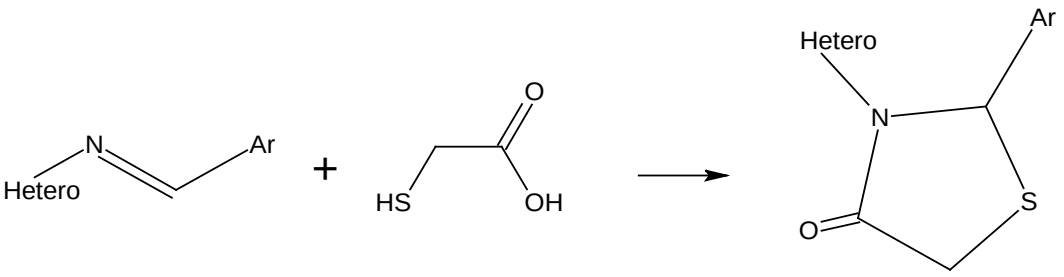
The titled compounds were synthesized from the reaction between compound [2] and appropriate aldehydes in absolute ethanol and glacial acetic acid [11].

Compounds [3-8] containing imine bond have been synthesized for preparing another derivatives like thiazolidin, and imidazolines because these derivatives have a wide range of biological activity[15] and industry[16]. The condensation reaction of equimolar quantity of primary amine with the appropriate aromatic aldehydes is the major method to prepare series of Schiff bases. The titled compounds were characterized by their melting points, FT-IR spectra and C.H.N.S. analysis for some of them.

The FT-IR spectra, show the disappearance of the two absorption bands due to (-NH_2) [17] stretching of amino triazole [2] ,derivative [3] as example, showed all the suggested bonds for (C=C) aromatic, endocyclic (C=N) and exocyclic imine group. All the prepared compounds (Schiff bases) exhibited the stretching band near the region (1219-1250) cm^{-1} this due to (=N-N=C-) cyclic group. All the spectral data for other compounds are listed in table (1).

^{1}H-NMR spectrum of compound [4], shows the following characteristic chemical shifts (DMSO-d_6) ppm. protons of (C-H) appeared at δ (2.9-3.7) and (N-H) proton appeared at (δ 13.5) and S-H proton at 11.36). Protons of *p*-substituted, aromatic rings (2 rings) appeared at the range δ (6.7–8.3) as a multiplet peaks.

3-Synthesis and characterization of 4N[(substituted aminophenyl)]-4'-oxo-1̀,3̀-thiazolidin-2-yl]-3-mercapto-2-methyl-1,2,4-triazole [9-13].

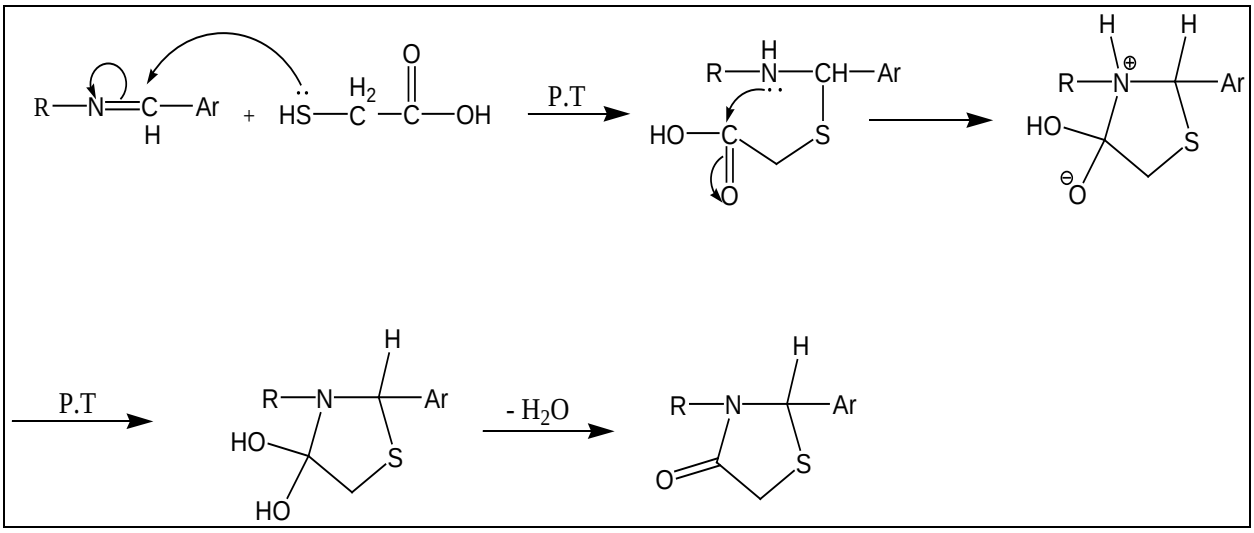


Hetero = triazole (2) , Ar = substituted phenyl.

Thiazolidinones play a vital role due to their wide range of biological activity and industrial importance as stabilizer for polymeric material[18]. For a long time imines have been used successfully in the synthesis of nitrogen contaning hetrocycles. The 4-thiazolidinone derivatives [9-13] were synthesized by refluxing equimolar amounts from the imine [3-8] with thioglycolic

acid in dry benzene. The synthesized compounds were characterized by their m.p. and FT-IR, ^{1}H-NMR besides the C.H.N.S. analysis and TLC.

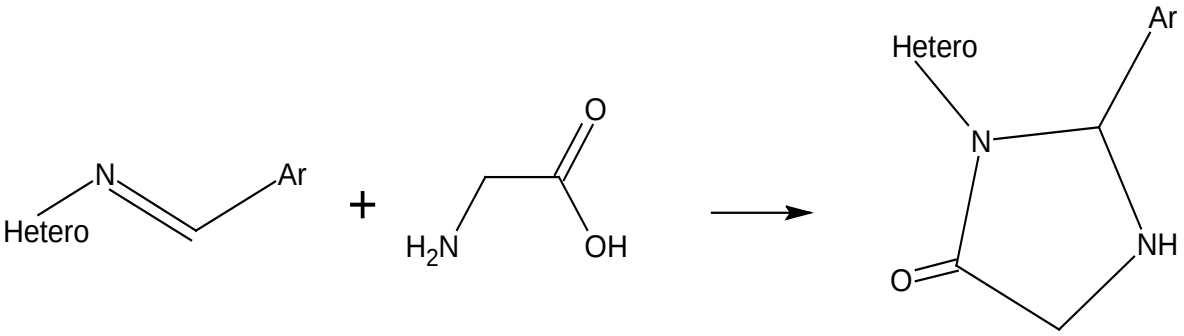
The C.H.N.S. analysis table (3) agree with the suggested structure. The FT-IR spectrum of compound [9], shows the appearance of stretching band of carbonyl group at (1710 cm^{-1}) due to thiazolidinone ring and this was the most characteristic evidence for the success of cyclization step. Fig. (3), also shows bands at (3089 cm^{-1}), (2924 and 2854 cm^{-1}) are attributed to υ(C-H) aromatic, and (C-H) aliphatic stretching vibrations of (C-H) group. Other characteristic bands of aromatic system is the appearance of υ(C=C) at about (1512 cm^{-1}) besides the band at (1600 cm^{-1}) due to (C=N) of triazole ring. Besides the disappearance of the C=N group in 1600cm^{-1} (for Schiff base) and the disappearance of O-H broad band stretching vibration at 3500-3000cm^{-1} of mercaptocetic acid . The proposed mechanism of this reaction is shown below :



The ^{1}H-NMR spectrum of compound [9], shows the following characteristic chemical shifts (DMSO-d_6) ppm. Protons of (CH_2) of thiazolidinone appeared at (δ 4.22). Proton of (NH) group appeared at(δ 9.2). Protons of *m*-substituted aromatic rings appeared at the range δ (7.2-8.1) as a multiplate peaks and signal at δ 3.54 belong to (CH_2) between triazole rings.

The ^{1}H-NMR spectrum of compound [13] fig.(6), shows the proton of (CH_2) at (δ 4.5) ppm and protons of aromatic rings appeared at (δ 7.7-8.5), proton of (NH) appeared at (δ 13.94) and proton of (OH) group appeared at (δ 10.3).

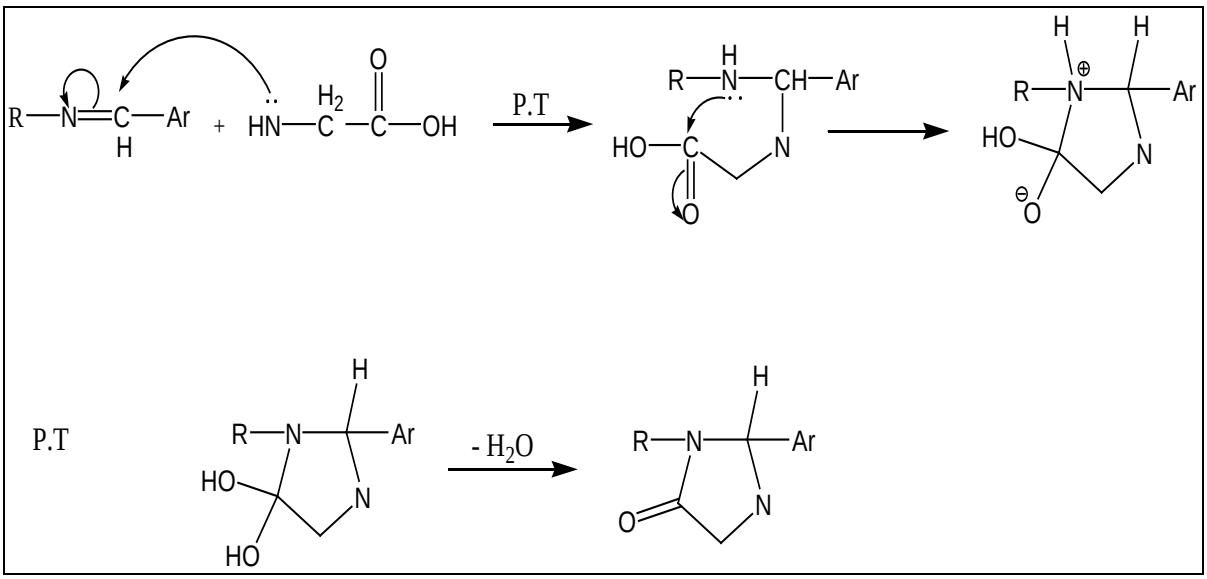
4-Characterization of bis [3-mercapto-2-methylene-2yl)-4- imidazolin-4-one (14-18) :

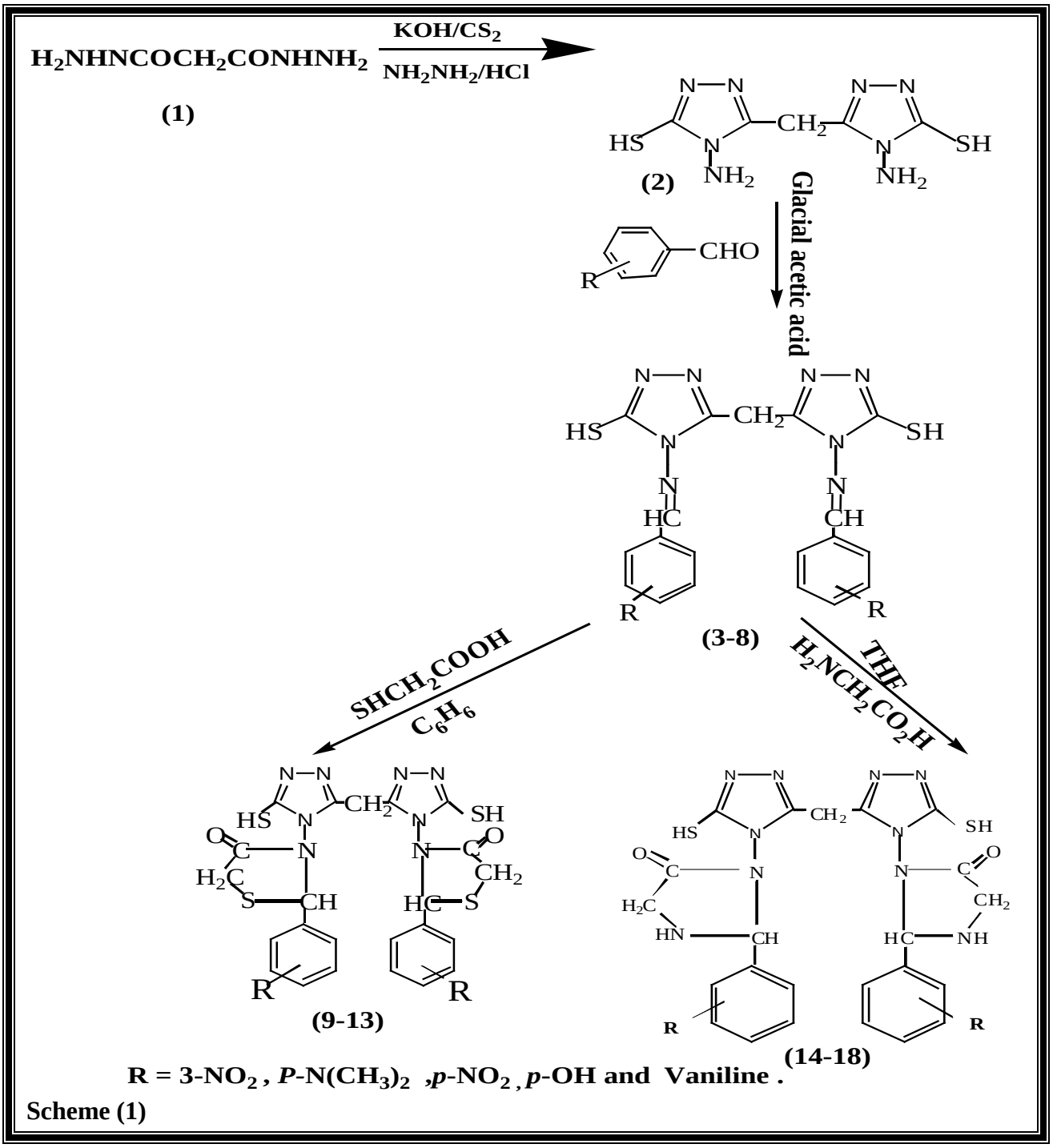


Imidazolidine derivatives prepared by the heating of Schiff base derivatives with glycine(α-amino acetic acid) in THF the product were identified by the FTIR spectrum which show the appearance of NH vibration in 3320 cm^{-1} and the disappearance of C=N band in 1600cm^{-1}.

The product is also identified by the ^{1}H-NMR spectrum which shows the protons at (δ 6.7-7.6) ppm due to aromatic protons. Proton of (N-H) of imidazole ring appeared at δ (8.59) and the proton of (N-H) toutomeric appeared at (δ 9.5)ppm .

The proposed mechanism of this reaction described below.




H2NHNCOCH2CONHNH2
KOH/CS2
NH2NH2/HCl
(1)
(2)
Glacial acetic acid
CHO
R
(3-8)
SHCH2COOH
C6H6
THF
H2NCH2CO2H
(9-13)
(14-18)
R = 3-NO2 , P-N(CH3)2 ,p-NO2 , p-OH and Vaniline .

Scheme (1)

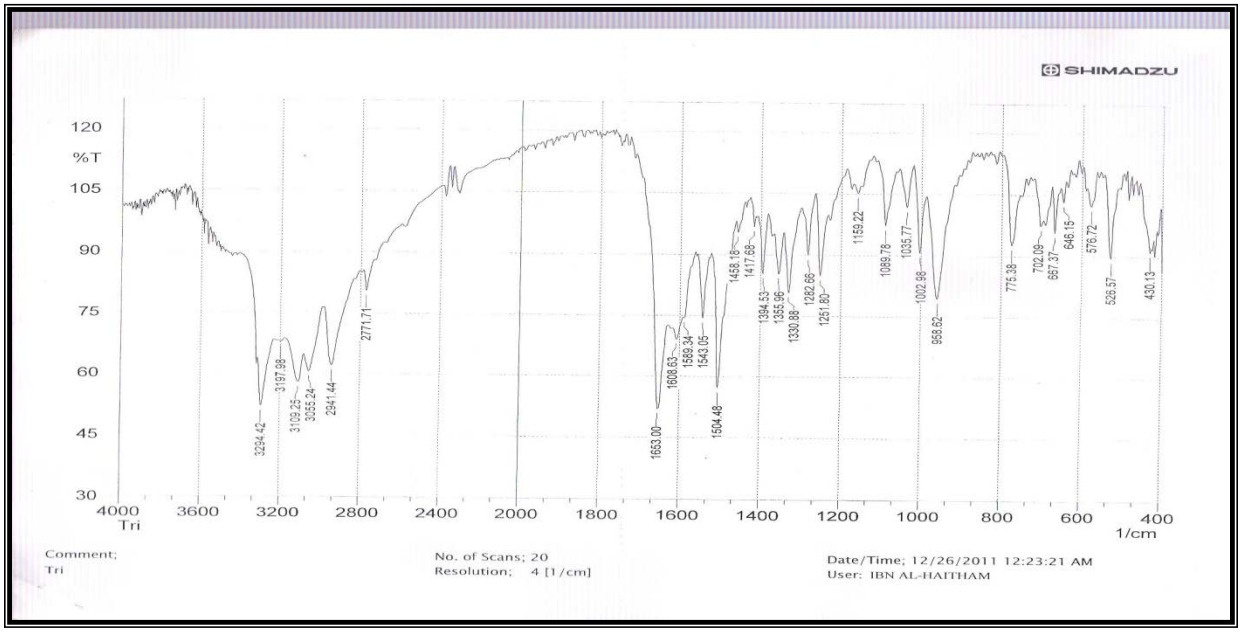


Fig.(1): FT-IR spectrum of compound 2.

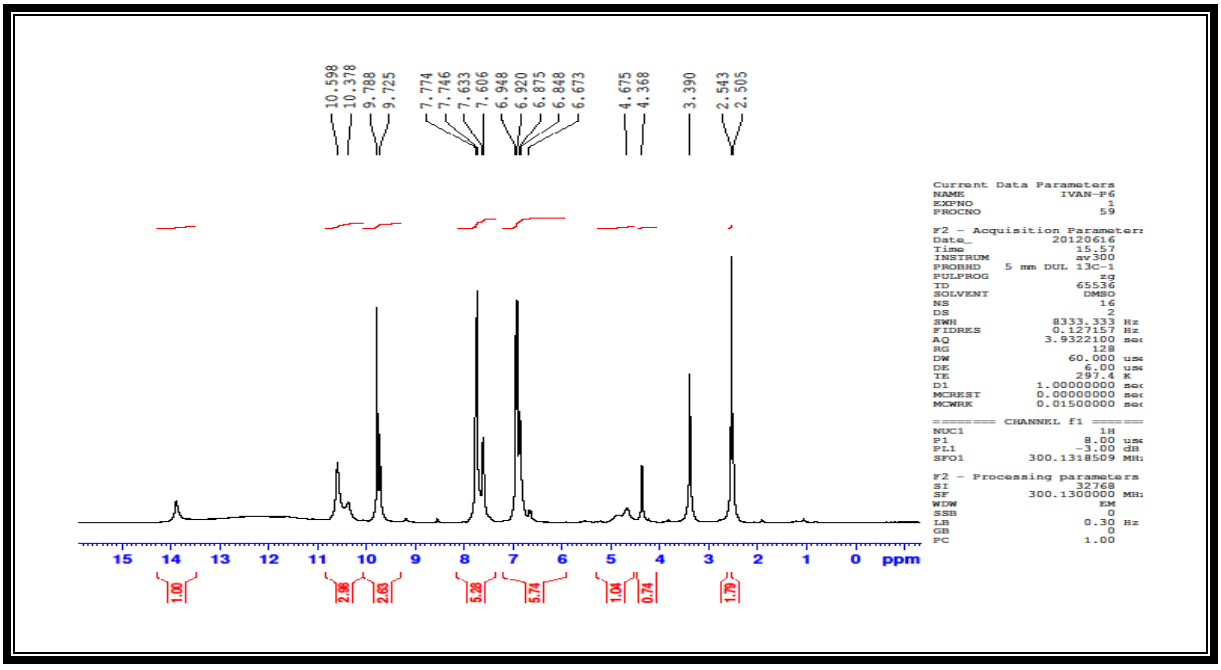


fig.(2): ^{1}H-NMR spectrum of compound (2).

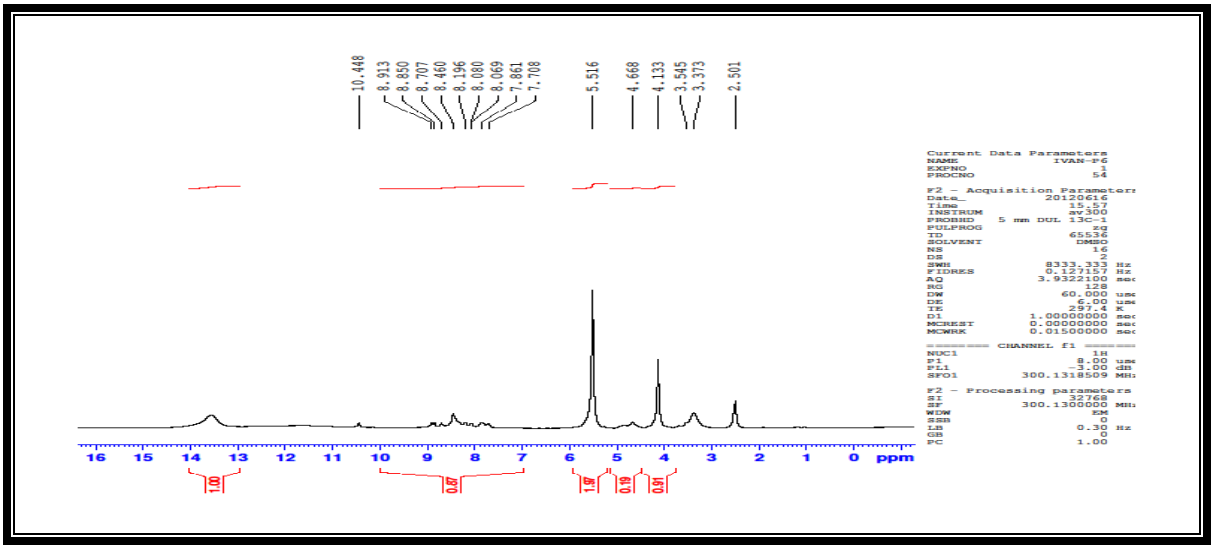


Fig.(3): ^{1}H-NMR spectrum of compound (3).

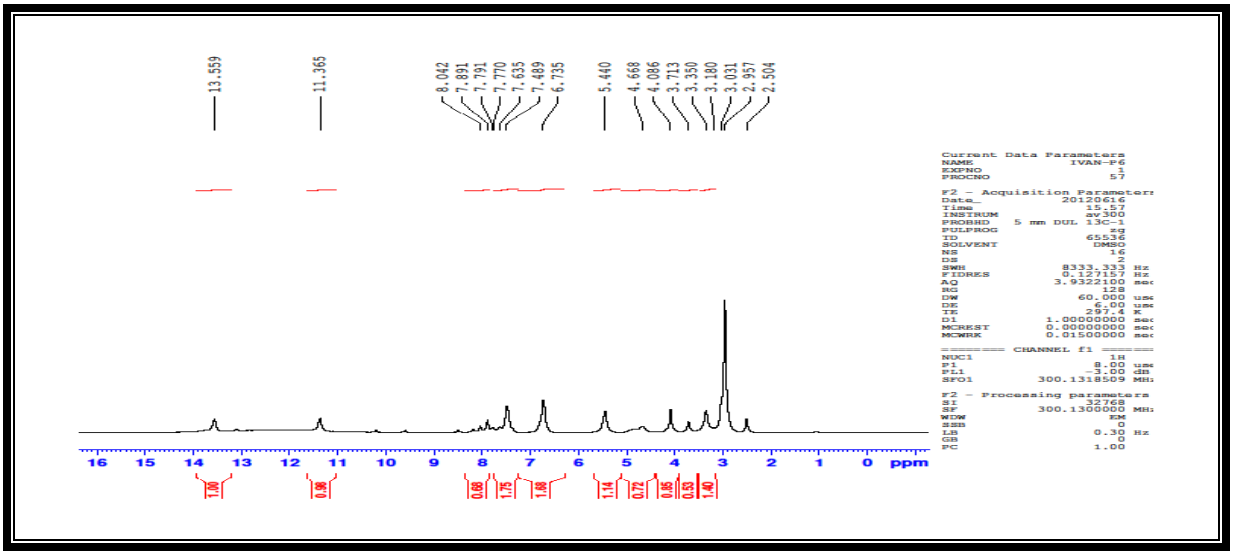


Fig.(4): H-NMR spectrum of compound (4).

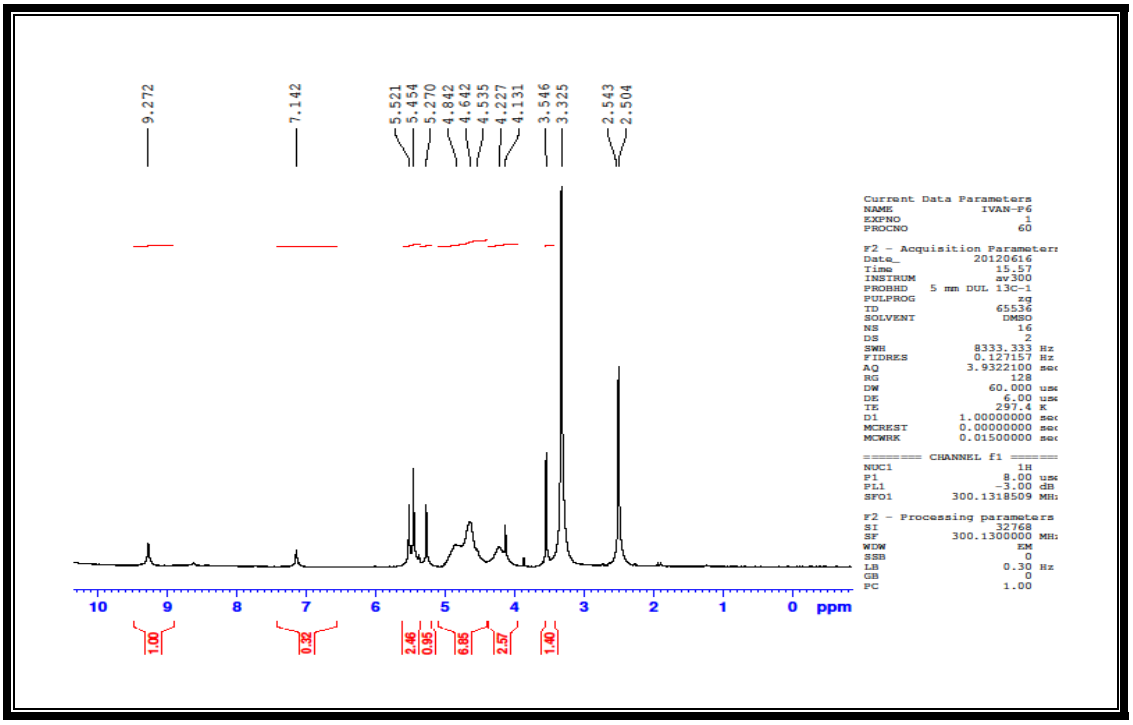


Fig. (5): H-NMR spectrum of compound (9).

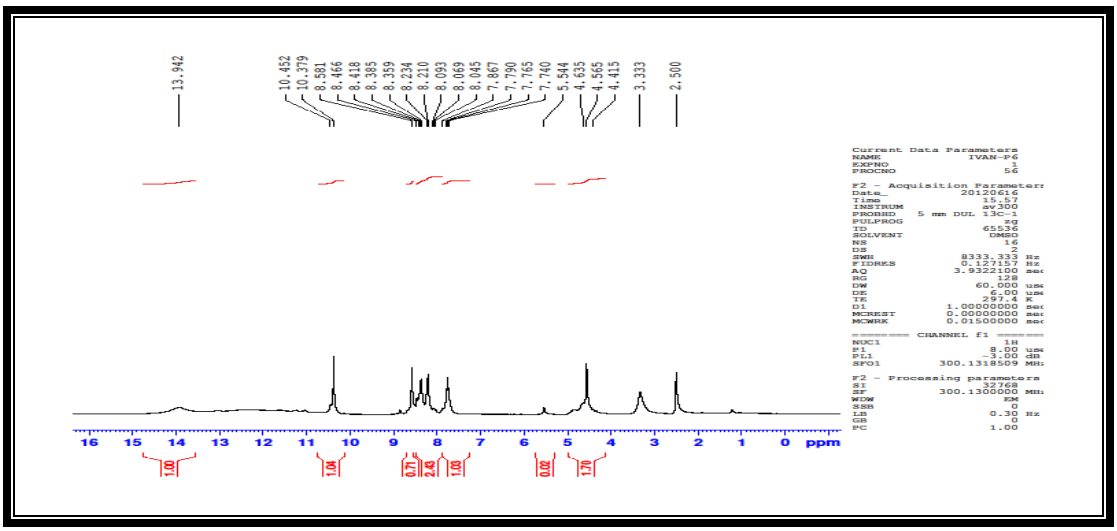


Fig . (6): H-NMR spectrum of compound (13).

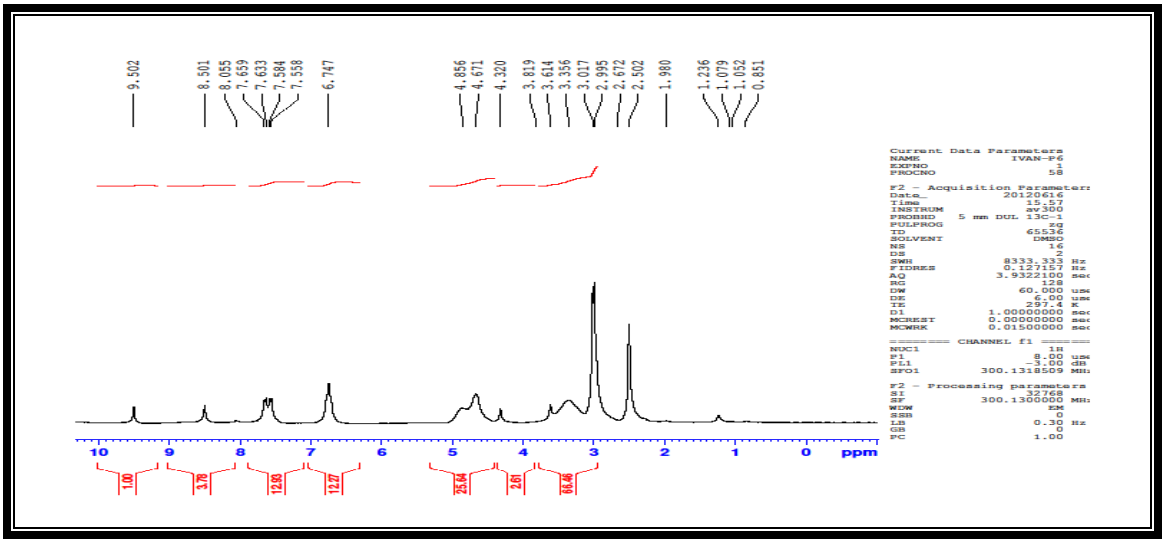


Fig. (7):^{1}H-NMR spectrum of compound (14).

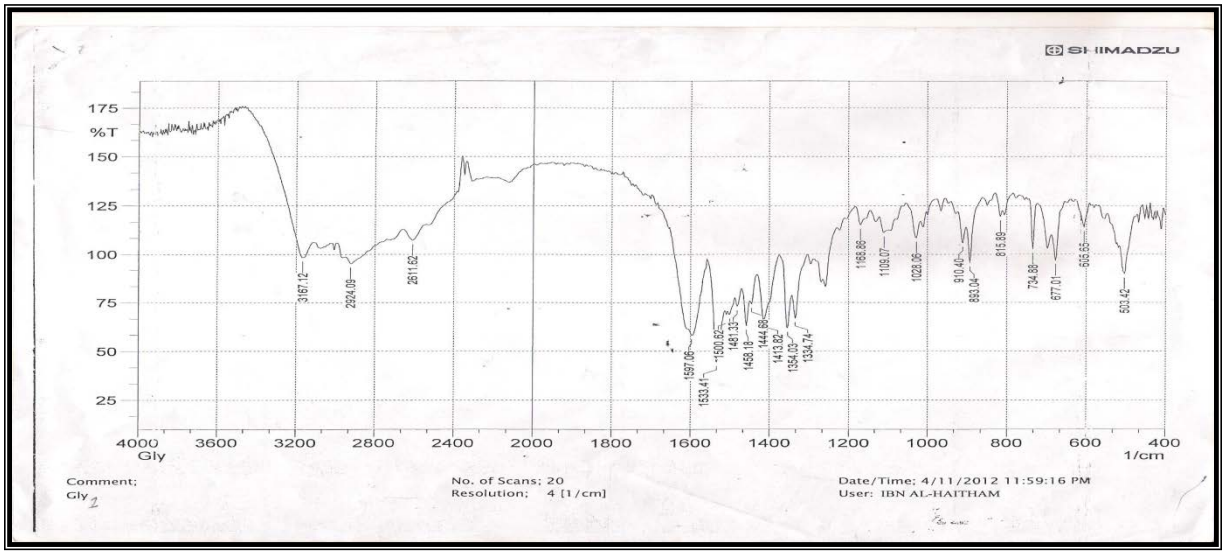


Fig. (8): FT-IR spectrum of compound (13).

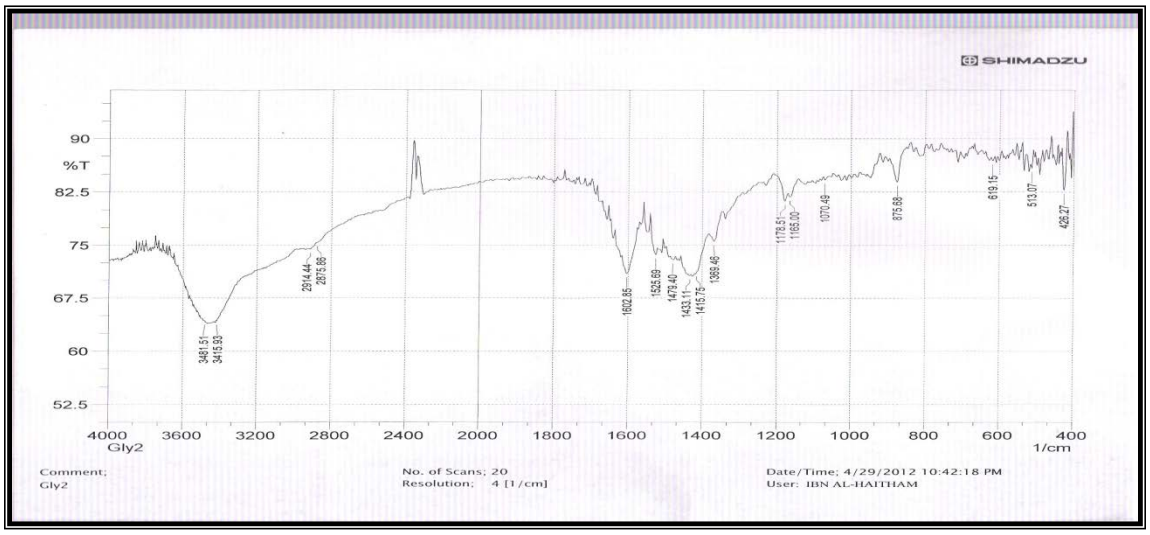


Fig.(9): FT-IR spectrum of compound (9).

Biological screening: Antibacterial activity test.

In this work, the antibacterial test was performed according to the disc diffusion method. Compounds ([1], [4], [10], [17] and [18]) were assayed for their antimicrobial activity *in vitro* against three strains of Gram negative bacteria (***Escherichia Coli, Klebsiella Pneumonia*** and ***Proteus Vulgaris)***. Prepared agar and Petri dishes were sterilized by autoclaving for 15min. at 121 ºC. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all 6mm in diameter. These holes were filled with 0.1 ml of the prepared compounds (10mg of the compound dissolved in 1ml of DMSO solvent), DMSO was used as a solvent. These plates were incubated at 37 ºC for 24hr for bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are listed in Table (4).

Table (4): Results of antibacterial activity of the tested compounds.

compound No.	*Escherichia Coli*	*Klebsiella Pneumonia*	*Proteus Vulgaris*
[1]	+	+	-
[4]	-	-	+
[10]	++	+	-
[17]	-	++	-
[18]	++	++	+

Note: - = No inhibition = inactive ., + = (5-10) mm = slightly active., ++ = (11-20) mm = moderately active .

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