Synthesis ,characterization and investigation of biological activity of new heterocyclic compounds

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Abstract

A new compounds of 2-amino-5-(***m***-nitro phenyl)-1,3,4-oxadiazole [1] and 2-amino -5- phenyl-1,3,4-oxadiazole[2], N[(***o***-hydroxy benzylidene-5-(phenyl-2-yl)-1,3,4-oxadiazole-2-amine][3] or N[(***m***-nitro benzylidene-5-(***m***-nitro phenyl-2-yl)-1,3,4-oxadiazole-2-amine][4], 2-(***m***-nitro phenyl) -3 (5-***m***-nitrophenyl)1,3,4-oxadiazole]-2-yl-thiazolidin-4-one [5], 2-(***m***-nitro phenyl) –tetrazolo-1-yl)- 5-(***m***-nitrophenyl)1,3,4-oxadiazole] [6] , 5-(***m***-nitro phenyl)-2′-(***m***-nitrophenyl)-2-yl-2,3-dihydro-1,3-oxazpine-4,7-dione [7] , 4-hydrazino nicotinic acid [8], 1-phenyl-4-(nicotinoyl) thiosemicarbazide [9], and 3-hydrazino-5- (pyridyl)-1,2,4- Triazole-4-phenyl [11], 3-(***p***-N,N′ dimethyl amino benzylidene)- hydrazino -5- (pyridyl)-1,2,4- Triazole-4-phenyl [12], 4-(3-methyl pyrazol-5-one)- hydrazino -5- (pyridyl)-1,2,4- Triazole-4-phenyl [13], 4-(3,5-dimethyl pyrazol)- hydrazine-5- (pyridyl)-1,2,4- Triazole-4-phenyl [14], ethyl 4-bromo-phenoxy acetate [15], ***p***-bromo pheno -aceto thiosemicabazone [16] ,2- amino-5-[(***p***-bromp phenoxymethylene)-1,3,4-thiadiazole [17], 2N(***p***-nitro benzylidene)-1,3,4-Thiadiazole -5- (***p***-bromo phenoxy methyl [1 8], 5 -(***p***-bromo phenoxy methyl) 2′-(***p***-nitro phenyl- 2-yl)-5,6-dimethyl-1,3-oxazpine-4,7-dione [19] or5-(***p***-bromo phenoxy methyl) 3-(***p***-nitro phenyl- 2-yl)-2,3-dihydro-1,3-oxazpine-4,7-dione [20] and imidazoline[21].

The chemical structures of these compounds were identified by FT-IR,H-NMR , Uv spectroscopy and the reaction time ,purity was checked by TLC with determining the melting points. Some of the new compounds were tested against four strains of bacteria (*Klebsiella Pneumoniae* ,*Pseudomonas aeuroginosa* ,*Staphylococcus Aureus* and *Bacillus subtilus*) comparing these activities with that of starting material

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Key word: heterocyclic compounds , oxazepine ,imidazoline.

تحضير وتشخيص ودراسة الفعالية الحيوية لمركبات غير متجانسة الحلقة.

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الخلاصة

تضمن البحث تحضير 2-امينو-5-ميتانايترو فنيل-1,3,4-اوكسادايزول (1), 2-امينو-5-فنيل-1,3,4-اوكسادايزول(2), ن (اورثوهيدروكسي بنزليدين-5-فنيل-2-يل)-1,3,4-اوكسادايزول-2-امينو(3), (ميتانايتروبنزيلدين-5-(ميتانايترو فنيل-2-يل)-1و3و4-اوكسادايزول-2-امينو(4) او 2-ميتانايترو اريل-5-(ميتانايتروفنيل)1,3,4--اوكسادايزول-2-يل ثايزوليدين-4 اون (5), 2-(ميتانايتروفنيل)-تترازولو-1-يل)-5-(ميتانايتروفنيل)1,3,4--اوكسادايزول(6),2-(ميتانايتر وفنيل)-3-(ميتتانايتروفنيل)-2-يل-2و3-ثنائي هيدرو-1و3-اوكسازبين-4و7-اون(7), 4-هيدراز ينوحامض النيكوتنك(8), 1-فنيل-4-(نيكوتنيل) ثايوسيميكاربازايد(9), و3-هيدرازينو-5-(بري ديل)-1و2و4-ترايزول-4-فنيل(11), 3-(بارا داي مثيل امينو بنزليدين)هيدرازينو-5-(بريديل)-1,2,4--ترايزول-4-فنيل (12), و4-(3-مثيل بايرازول-5-5-اون)-هيدرازينو-5-(بريديل)-1,2,4-ترايزول (13), 4-(3-مثيل بايرازول-5-اون)-هيدرازين -5-(بريديل)1,2,4-ترايزول -4-ثايادايزول(14)واثيل 4-بروموفينوكسي اسيتيت (15) وكذلك بارا برومو فينو اسيتو ثايو سيميكاربازون(16)و2-امينو-5-(بارابروموفينوكسي مثيلين)-1,3,4-ثايادايزول(17) بالاضافة الى2ن – (بارانايتروبنزايلدين)-1,3,4-ثايادايزول-5-(بارابرومو فينوكسي مثيل(18)و 2-(بارا بروموفينوكسي مثيل)-3-(بارانايترو فنيل-2-يل)-5,6-ثنائي مثيل-1,3-اوكسازبين-4,7-داي اون(19), أو 2-(بارابرومو فينوكسي مثيل)-3-(بارانايترو فنيل)-2-يل-2و3-داي هيدرو-1و3-اوكسازبين-4,7-داي اون(20), واخيرا5-(بارانايتروفنيل)3/- (5-بارابروموفينوكسي مثيل)-1,3,4-ثايادايزول-2-يل)اميدازولين-4-اون (21).
تم تشخيص التراكيب الكيمياوية للمركبات المحضرة بوسطة اطياف الاشعة تحت الحمراء , فوق البنفسجية واطياف الرنين النووي المغناطيسي كما تم تحديد زمن التفاعل ونقاوة المركبات بواسطة كراموتوكرافيا الطبقة الرقيقة وتم اختبار الفعالية الحيوية للمركبات ضد اربعة انواع من البكتريا.

Introduction

The derivatives of 1,3,4-oxadiazol constitute an important family of heterocyclic compounds[1-5],since many of them display a remarkable biological activity[6]. antifungal [6],analgesic[7]and anti-inflammatory[8]and hypoglycemic activity[9].

A triazolo-thiadiazole system may be viewed as a cyclic analogue of two very important components[10].

Heterocyclic compounds play an important role in biochemical process [11-15] because the side groups of the most typical and essential constituents of living cells are based on aromatic heterocycles.

Between them ,sulfur and nitrogen containing heterocyclic compounds have maintained the interest of researchers through the development of organic synthesis[16].

Oxazepine belongs taking non homlogous structure which has 7-homologous atoms (oxygen and nitrogen)[17].

Pyrazole derivatives constitute an important family of compounds due to their applications as pharmaceuticals (analgesics, anti-inflammatory, anti-bacterial, and antidepressant), agrochemicals (insecticides) and dyestuffs [18- 20] .

Accordingly, we wish to report herein the synthesis of compound which possesses a chemically important nitrogen heterocyclic nucleus with a view to achieve better antimicrobial activity. Some of the prepared compounds were screened for their in vitro antimicrobial activity against different strains of bacteria.

Experimental part

1- Melting points were measured using hot stage ***Gallen Kamp*** melting point apparatus and were uncorrected.

2- The FTIR spectra in the range (4000-600) cm^{-1} were recorded using KBr disk on a ***SHIMADZU*** F.T.IR 8300 spectrophotometer Japan.

3- Uv/vis spectra were recorded on Uv/vis varian Uv-Cary-100 spectrophotometers in (ISSC).

4-^{1}H-NMR spectra were recorded a BRUKER-400 MHz operating at 300 MHZ with tetra methyl silane as internal standard in $CDCl_3$ and DMSO-d_6 as a solvent, measurements were made at Chemistry Department, AL-Baath University-Syria.

5-Elemental Analysis (C.H.N) was carried out with : Euroea Elemental Analyzer Italia by Chemistry 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 vapor.

7- The biological activity was performed by biology department/ college of Science ,Tikrit University.

1-Synthesis of 2-amino-5-m-nitro phenyl-1,3,4-oxadiazole [1] and 2-amino -5 phenyl-1,3,4-oxadiazole[2][21].

An equimolar of semicarbazide hydrochloride and benzaldehyde or ***m***-nitro benzaldehyde were dissolved in ethanol in presence of fused sodium acetate. The mixture was refluxed for one hour, then cooled and precipitated by water, filtered to obtain phenyl semicarbazone or ***m***-nitro phenyl semicarbazone. Phenyl semicarbazone or ***m***-nitro phenyl semicarbazone dissolved in glacial acetic acid and fused sodium acetate, bromine (in acetic acid) (0.5ml) was added to this mixture (2g) contained in flat flask. The mixture became warm and rapidly became colorless. This mixture was poured in water, filtered and dried. Re crystallized from mixture of ethanol and acetic acid.

2-Synthesis of Schiff bases N[(m-nitrobenzylidene-5-(m-nitrophenyl-2-yl)-1,3,4-oxadiazole-2-amine][4] or N[(o-hydroxy benzylidene-5-(phenyl-2-yl)-1,3,4-oxadiazole-2-amino][3][22] .

A mixture of 2-amino-5-(***m***-nitro phenyl)1,3,4-oxadiazole [2] or [3] 2-amino-5- phenyl)1,3,4-oxadiazole (0.01mol)and ***m***-nitro benzaldehydes (0.01mol) or ***o***-hydroxy benzaldehyde was refluxed in absolute ethanol (15ml) containing few drops of glacial acetic acid for 3hrs. After cooling to room temperature the precipitate was filtered and dried. The products were re-crystallized from ethanol. Yield 80%,FT IR (cm^{-1}),3100(C-Harm.),2923 and 2868 (C-Haliph.), 1602(C=N) ,780,720(C-NO_2 m-substituted).

3- Synthsis of 2-m-nitro phenyl)-3- (5-m-nitrophenyl)1,3,4-oxadiazole]-2-yl-thiazolidin-4-one [5][23]*:*

A (0.01) mole of 2- mercptoacetic acid was added dropwise to(0.01)mole of Schiff base in(20 ml)of dry benzene ,the mixture was refluxed for (24) hours then the solvent was evaporated and the formed precipitate was re crystallized from ethylacetate and benzene,m.p (160) °C,yield (75%).

4-Synthesis of 2-(m-nitro phenyl) –tetrazolo-1-yl)- 5-(m-nitrophenyl)1,3,4-oxadiazole] [6][24]*:*

A mixture of (0.01mol) of Schiff bases [4], tetrahydrofuran (THF) (15ml) and sodium azide (0.01mol,0.67gm) was heated on a water bath, the temperature of the water bath was controlled between (50-55)°C. The end of the reaction was checked by (TLC) which showed the disappearance of the starting material.

5- Synthesis of 5-(m-nitro phenyl)-2′-(m-nitrophenyl)-2-yl-2,3-dihydro-1,3-oxazpine-4,7-dione [7][25].

A mixture of compound [4] (0.01) mole of Schiff base and (0.01) mole of maleic anhydride in (20 ml) of benzene was refluxed for (24) hours then the solvent evaporated and the formed precipitate was re crystallized from appropriate solvents ,m.p (210) °C,yield (75%).

6-Synthesis of 4-hydrazino nicotinic acid [8]:

A mixture of nicotinamide (0.01 mol) and (99%) (0.32 g, 0.317 ml, 0.01 mol) of hydrazine hydrate was dissolved in ethanol, and the mixture was refluxed for 5 hours, excess solvent was distilled off. The resulting solid was separated out on cooling filtered and re crystallized from ethanol [(22)], m.p. (203-205 ^{o}C), yield (80%).

7- Synthesis of 1-phenyl-4-nicotinoyl thiosemicarbazide[(26)] [9]:

A mixture of nicotinic acid hydrzide (0.01mol) and phenyl iso thio cyanate (0.01mol,10ml) in(20 ml) absolute ethanol was refluxed for (7) hours .The solid material obtained on cooling was filtered off ,and re crystallized by using ethanol ,m.p (200) °C,yield (75%).

8-Synthesis of -5- (pyridyl)-1,2,4-Triazole-4-phenyl -3- thiol [10]:

A stirring mixture of compound [9] (0.01 mol) and (10 ml) of 2N sodium hydroxide solution was refluxed for 4 hours after cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered, the precipitate was re crystallized to give compound [10] , m.p (230) °C,yield (68%).

9-Synthesis of 3-hydrazino-5-(pyridyl)-1,2,4- Triazole-4-phenyl [11]:

A mixture of compound [10] (0.01 mol) and (99%) (0.32 g, 0.317ml,0.01 mol) of hydrazine hydrate was dissolvedin ethanol,and the mixture was refluxedfor 6hours,excess solvent was distilled off. The resulting solid then separated out on cooling filtered and re crystallized from ethanol[(22)],m.p (267^{0}C),yield (80%).

10--*Synthesis of 3-(p-N,N\ dimethyl amino benzylidene)-hydrazino -5- (pyridyl)-1,2,4-Triazole-4-phenyl [12]:*

The same procedure in (2) was used.

11- Synthesis of 4-(3-methyl pyrazol-5-one)- hydrazino -5-(pyridyl)-1,2,4- Triazole-4-phenyl [13].

A mixture of carbohydrazide [5] (0.01 mol) and methyl aceto acetate (0.01mol) in absolute ethanol was heated under reflux temperature for 5 hours. The reaction mixture cooled and the formed precipitate was filtered off to give the product,m.p190 C, yield (79%).

12 -Synthesis of 4-(3,5-dimethyl pyrazol-5-one)- hydrazine-5-(pyridyl)-1,2,4- Triazole-4-phenyl [14].

A mixture of compound [17] (0.01mol) and acetylacetone (0.01mol) in absolute ethanol (15ml) was heated at reflux temperature for 5 hours. The reaction mixture cooled and the formed precipitate was filtered off to give the product,m.p200^{0}C, yield (65%).

13--Synthesis of ethyl 4-bromo-phenoxy acetate [15]:

p-bromo phenol (0.01mole) was dissolved in absolute ethanol (100ml) with (0.01mol)of (K_2CO_3) and heated in a water bath. The hot solution was cooled. Ethyl chloro acetate (0.01mole ,10ml) was added to the mixture. The addition was performed dropwise with stirring for 1 hr.,the stirring and refluxing continued for 4hrs. The reaction mixture was filtered and evaporated to give a white crystals,which were re crystallized from ethanol to give the ester [15]. Physical properties of the products are listed in Table (1).

14- Synthesis of p-bromo pheno -aceto thiosemicarbazone [16].

A mixture of ethyl ***p***-bromo ethyl phenoxy acetate (0.01mol) and thiosemicabazide (0.01mol) in ethanol (20ml) was refluxed for 3hrs. The reaction mixture was filtered and poured on ice water. The precipitate was filtered and re-crystallized from chloroform petroleum to give white crystal of the thiosemicabazone derivative. Physical properties of the products are listed in table (1).

15-Synthesis of 2- amino-5-[(p-bromo phenoxymethylene)-1,3,4-thiadiazole [17].

A mixture of ethyl ***p***-bromo pheno acetothiosemicarbazone (0.01mole)and (10 ml) phosphorous oxy chloride was refluxed for 5 hrs. The cold reaction mixture was poured on crushed ice and neutralized by adding sodium hydroxide solution. The resulting solid was filtered and re crystallized from chloroform to give a white crystals of amino thiadiazole [17].

16- Synthesis of 2-(p-nitro benzylidene)-1,3,4-Thiadiazole -5-(p-bromo phenoxy methyl [18].

A mixture of compound [17] (0.01mol) and ***p***-nitro benzaldehyde (0.01mol) was refluxed in absolute ethanol (15ml) containing few drops of glacial acetic acid for 3hrs. After cooling to room temperature the precipitate was filtered and dried. The product was re-crystallized from ethanol. Yield 80%.

17 - *Synthesis of 5-(p-bromo phenoxy methyl) 2′-(p-nitro phenyl)- 2-yl-5,6-dimethyl-1,3-oxazpine-4,7-dione [19]or5-(p-bromo phenoxy methyl) 2′-(p-nitro phenyl)- 2-yl-2,3-dihydro-1,3-oxazpine-4,7-dione [20] .*

A mixture of (0.01) mole of Schiff base[18] and (0.01) mole of 2,3-dimethyl maleic anhydride or maleic anhydride in (20 ml) of benzene was refluxed for (24) hours then the solvent evaporated and the formed precipitate was re crystallized from appropriate solvents ,m.p (130-132, 157-159) °C,yield (75%).

18-Synthysis of 5-(p-nitro phenyl)-3′-[5-(p-bromo phenoxy

methyl)- 1,3,4-thiadizol-2-yl)imidazolidine-4-one[21]:

A mixture of Schiff base[18] (0.01) mole and glycine (0.01) mole in (15 ml) of THF was refluxed for (12) hours then cold to room temperature and the formed precipitate was filtrated and re crystallized from ethanol and THF,m.p (165-168) °C,yield (70%).

Table (1): physical properties of the prepared compounds.

Comp. No.	***Molecular formula***	***Molecular Weight***	***Yield (%)***	***M.P (^oC)***	***colour***
1	$C_8H_6N_4O_3$	206	68	107-109	Yellow
2	$C_8H_7N_3O$	161	82	220	Pale yellow
3	$C_{15}H_9N_5O_5$	339	73	85-87	White
4	$C_{15}H_{11}N_3O_2$	265	83	146-148	Pale yellow
5	$C_{19}H_{13}N_5O_8$	439	75	160	Yellow
6	$C_{15}H_{10}N_8O_5$	382	-	-	Brown
7	$C_{17}H_{11}N_5O_6S$	413	75	210	White
11	$C_{13}H_{12}N_6$	252	80	267	Yellow
12	$C_{22}H_{21}N_7$	385	76	200	Yellow
13	$C_{17}H_{14}N_6O$	318	79	190	Yellow
14	$C_{16}H_{16}N_6$	292	80	230	Yellow
17	$C_9H_8N_3OSBr$	289	75	245	White
18	$C_{16}H_{11}N_4O_3SBr$	419	87	230	Yellow
19	$C_{22}H_{17}N_4O_6SBr$	545	75	130-132	White
20	$C_{20}H_{13}N_4O_6SBr$	517	75	157-159	White
21	$C_{18}H_{12}N_5O_4SBr$	474	70	165-168	White

Table (2): Re-crystallization solvents and C.H.Nanalysis for some compounds.

Comp.No.	**Re-crystallization solvents**	**C.H.N.cal./found analysis**		
17	EtOH	37.76/37.6	2.79/2.7	14.68/13.99
3	EtOH+AcOH	53.09/53.0	2,65/2.4	20.64/20.33
6	MeOH	47.12/47.1	2.61/2.4	29.31/29.01
12	EtOH	68.57/68.33	5.45/5.24	25.45/25.20
18	EtOH	45.82/45.6	2.62/2.3	13.36/13.21
19	EtOH	48.44/48.32	3.11/3.0	10.27/10.14

Results and Discussion

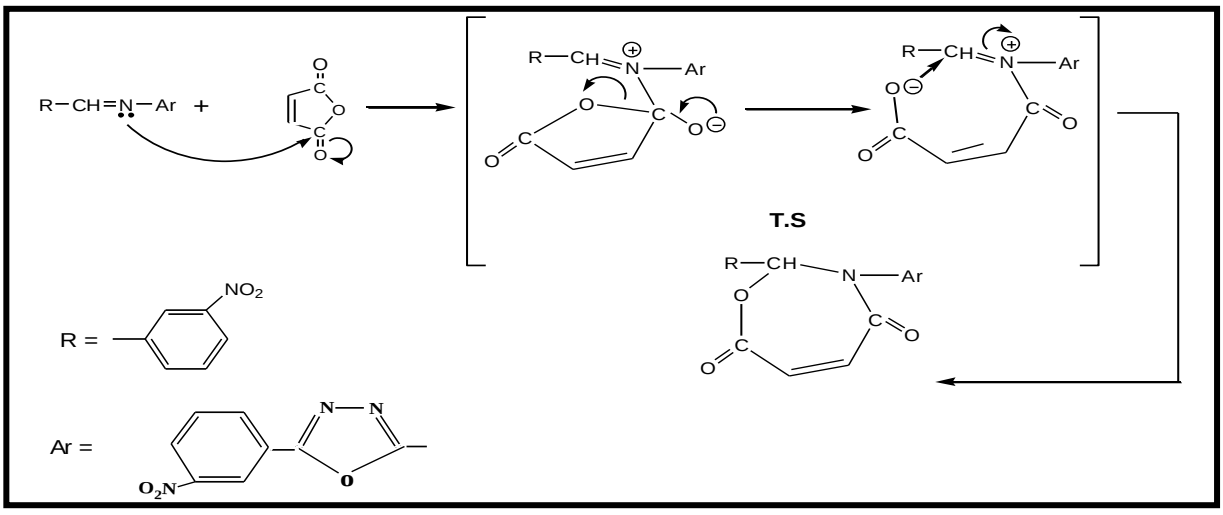
The first step in scheme (1) involved the synthesis of phenyl amino oxadiazole and substituted phenyl amino oxadiazole by the reaction of benzaldehyd or substituted benzaldehyde with semicarbazide hydrochloride and bromine in presence of sodium acetate in acetic acid.
These compounds were characterized through the FT-IR, ^{1}H-NMR spectra and other physical properties.

The FT-IR spectrum of compound [1], showed the appearance of stretching band of (NH_2) group at (3430-3600) cm^{-1} and at (1630) $cm^{-1}$for (C=N) group. The ^{1}H-NMRspectrum of compound [1],fig., (1), showed the peaks at (3.47) ppm due to (CH) group and (7.43-8.54) ppm(m,Ar-H).

Compounds [3] and [4] were prepared from the reaction of compounds [1or2] with ***m***-nitro benzaldehyde or benzaldehyde. The structure of compound [3] was confirmed through the disappearance of absorption bands of (NH_2) group at (3430-3600) cm^{-1} and appearance of band sym., and asym., at (1612) cm^{-1}which attributed to (C=N) azomethine group while the ^{1}H-NMR spectrum of this compound fig.,(2),showed singlet signal at (2.7) ppm due to (CH) group , singlet signal at (5.0) ppm due to (OH) group and multiplet signals at (7.4-8.2) ppm due to aromatic protons, besides the melting points ,colours and T.LC and C.HN analysis.

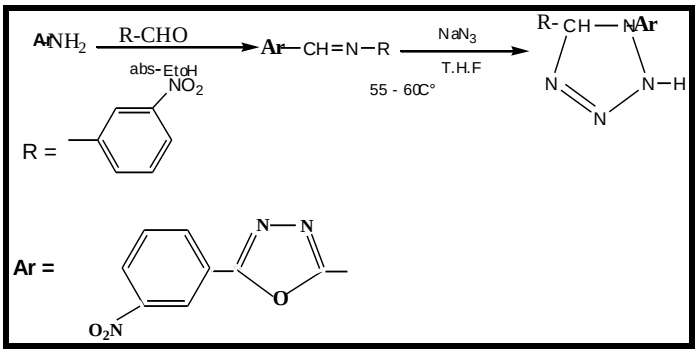
Thiazolidinone derivative (5) was prepared by the reaction of Schiff base[4] and mercaptoacetic acid in dry benzene ,the product was characterized by FT-IR spectroscopy and the melting point ,TLC were determined . The FT-IR spectrum of compound (7) showed the appearance of the (C=N) group in 1600 $cm^{-1}$and the disappearance of (O-H) broad band stretching vibration at 3500-3000 $cm^{-1}$of mercapto acetic acid.

The suggested mechanism[19] of the reaction is shown in scheme (below):



Scheme 1, Mechanism steps for the prepared compounds [7,19 and 20].

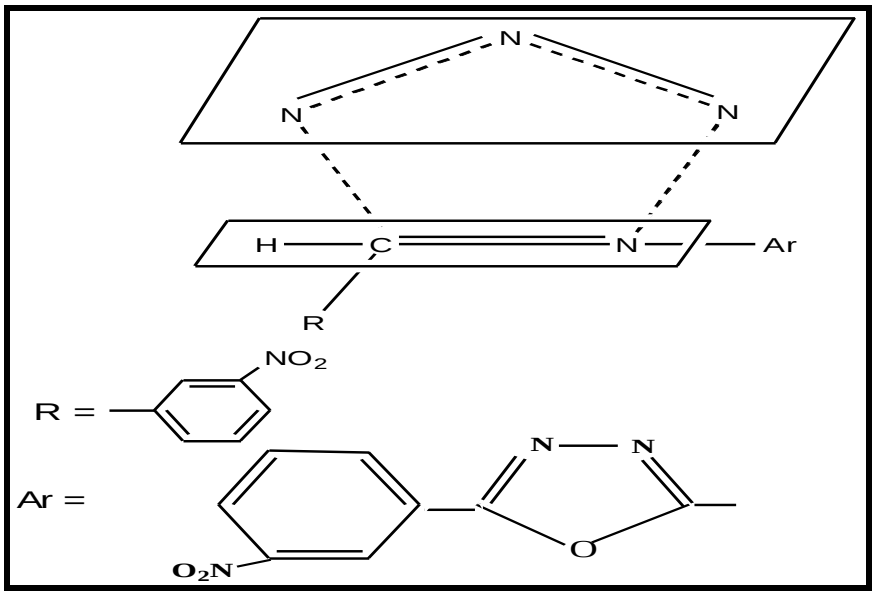
The compound [3] Schiff base was heated in water bath at (55 - 60°C) with sodium azide, to give the desired product [6]. The titled compound was characterized by their melting point, FT-IR table (3), or Uv/vis. spectra and checked by T.L.C also C.H.N analysis.



Scheme 2: Regents and conditions of the preparation of tetrazole.

The mechanism of the reaction systematically investigated as [3+2] cyclo additions which christened as a 1,3 -dipolar cycloadditions[28]. It involved the addition of unsaturated systems, dipolarphiles, to 1,3-dipoles, , a molecule possessing resonance contributors in which a positive and negative charge are located in 1,3-position relative to each other .The addition results in a five –member ring. Azides are a prominent class of 1,3-dipoles and azide 1,3-dipolar cycloadditions. They are of great synthetic value and have been studied mechanistically in great detail[2 The common features of this type of reactions is best accommodated by a T.S. geometry in which the dipolarphile and its ligands lies in one plane, and the azide lies in a parallel plane above or below, so that the orbitals perpendicular to the planes interact to form bonds, scheme below.

[9].



Scheme 3: Approximate transition state geometry for azide addition.

(1612 cm^{-1}), attributed to (C=N) (imine group) stretching frequency is good evidence for the success of this step of reaction. It also, the FT-IR spectra for these compounds were devoid of a strong band at (2120–2160)cm^{-1} attributed stretching frequency of a zide group. A band at (1531 cm^{-1}) was due to the cyclic (N=N) stretching of tetrazole ring. The characteristic data are reported in Table (3).

The FT-IR spectrum of compound [7] was confirmed from the appearance of carbonyl group band at (1720 cm-^{1} and (C-H)aliphatic band at (2924-2854)$cm^{-1(27)}$,besides the (C=N) band of oxadiazole ring at (1610cm^{-1}) and bands at (1239 and 1118cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band. All the spectral data for other compounds are listed in table (3).

The FT-IR absorption bands, was utilized to characterize the specific structure of the synthesized compounds. The disappearance of band at The compound [1,3]oxazepine-4,7-dione [7] was synthesized from the reaction of compound [1] with maleic anhydride in dry benzene[17,18]. This compound was characterized by its melting point,colour,and FT-IR,Uv/vis spectroscopy table (3), and checked by T.L.C .

The FTIR spectrum for hydrazide derivatives (4-hydrazino nicotinic acid) [8] show the appearance of the characteristic absorption bands in the regions (3332-3276) cm^{-1} due to asymmetric and symmetric stretching vibration of the (NH-NH_2) group, while a new band appeared at (1677) cm^{-1} and (1620) cm^{-1} due to the stretching vibration of amide I and appearance of amide II bending vibration band at (1523) and (1510) cm^{-1} respectively.

The triazole [10] was characterized using FT-IR spectrum which showed the disappearance of band of carbonyl at the region (1677) cm^{-1}due to amide II bending

and the appearance of bands in the region (1643-1612) cm^{-1} due to stretching vibration of (C=N) group, a band appeared in the region (2534)cm^{-1} due to ν(C=S)) stretching vibration. The analytical and spectral data are in accordance with the structures assigned.

Treatment of 3-mercapto- 4- phenyl-5- pyridyl-1,2,4- Triazole with hydrazine hydrate in ethanol afford 3-hydrazino-4-phenyl-5-pyridyl-1,2,4-Triazole [11]. The structure of the hydrazine -phenyl-5- pyridyl-1,2,4-Triazole was confirmed from its melting point,colour and F.T.IR spectrum.

The F.T.IR spectrum of compound [11] indicates the disappearance of the thiol bond at (2534 cm^{-1}) and appearance of doublet bands of NH_2 group asymmetric and symmetric at (3313, 3201 and ν NH stretching band at 3128 cm^{-1}).

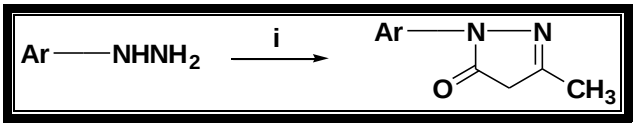
The title compound [12] was synthesized from the reaction between compound [11] and ***p***-N,N\-dimethyl amino aldehyde in absolute ethanol and glacial acetic acid.

This compound [12] was characterized by the melting point ,its colour and FT-IR spectrum. The FT-IR spectrum, shows the disappearance of the two absorption bands due to (-NH_2) stretching of hydrazino triazole [11], showed all the suggested bonds for (C=C) aromatic, endocyclic (C=N) and exocyclic imine group.

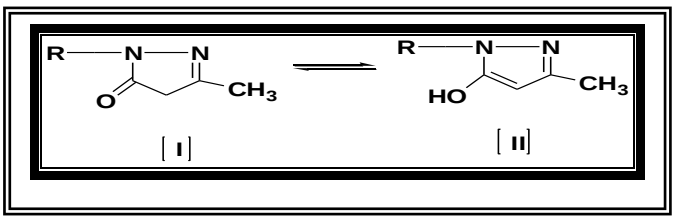
Stretching vibrations in addition to out of plane bending of substituted aromatic ring.. All the spectral data for other compounds are listed in table (3).

The pyrazol derivatives [13,14] were prepared through the reaction of hydrazine derivatives [11] with acetyl acetone or methyl aceto acetate.

The FTIR spectrum of compound [13] shows the disappearance of NH_2 and NH bands in the region (3332-3276) cm^{-1} and appearance of (OH) band at (3200) cm^{-1} of enol form and C=O band at (1740) cm^{-1} and (1720) cm^{-1} respectively of the keto form. From the above mentioned facts,we can indicate compound [13] can exist in equilibrium between keto [I] and enol [II] forms:



Reagents: i-$CH_3COCH_2COCH_3$, abs. EtOH, reflux (5) hrs.



The ***p***-bromo phenol was treated with ethyl chloroacetate in presence of potassium carbonate in absolute ethanol to give the ester [15].

The structure of compound [15] was confirmed by physical properties which are listed in table (2). FT-IR spectrum shows the band at 1720 $cm^{-1}$for (C=O) of ester, 2920 $cm^{-1}$for (C-H) aliphatic and disappearance of (O-H) absorption band.

For the product [16] ,FT-IR spectrum showed absorption band at (3460) cm^{-1} asy.,and sym.,for (-NH_2) group which overlap with absorption of (-NH) group, and aband appeared at(1662) cm^{-1} for (C=O)amid group. The band appeared at(1161) cm^{-1}due to (C=S) weak band while the ^{1}H-NMR spectrum fig.,(3), of compound (16) δppm showed the peak at 2.5(s, 2H,-CH_2); 6.9-7.4(m,4H,Ar-H) and at 4.34(s,2H,NH). The thiosemecarbazone derivative was refluxed with $POCl_3$ to give thiadiazole [17] . The FT-IR spectrum of this compound showed the band at (3600-3200) cm^{-1} broad for (-NH_2) ; at (1631) cm^{-1} for (C=N) and the ^{1}H-NMR spectrum fig., (4), of this product δppm sho

The FT-IR spectrum of compound [19] as example was confirmed from the appearance of carbonyl group band at (1710 cm^{-1}) and (C-H) aromatic band at (3090 cm^{-1}) and (C-H) aliphatic band at 2850cm^{-1}) and bands at (1273 and 1080 cm^{-1})

belong to asymmetric and symmetric (C-O-C) band. All the spectral data for other compounds are listed in table (3) while the ^{1}H-NMR spectrum for wed the peak at 2.35(S,2H,-CH_2); 4.39 (broad,2H,-NH_2); and at 6.6-7.9(m,4H, Ar-H) . Compounds (18) was prepared from the reaction of (17) and ***p***-nitro benzaldehydes in presence of glacial acetic acid and characterized by melting point, colour ,FT-IR ,^{1}H-NMR spectroscopy and checked by TLC techniuq.

The FT-IR spectrum of compound (18) exhibited the stretching band at 1610 cm^{-1}due to C=N bond besides the disappearance of C=O band of the aldehyde and disappearance of NH_2 bond at 3600-3200 cm^{-1}. The ^{1}H-NMR spectrum of compound (18) fig., (5), exhibited δppm the peaks showed the peak at 5.2(s, 1H,-CH); 6.9-8.1(m,8H,2Ar-H) and at 7.4(s,2H,-CH_2).

These compounds [19,20] were synthesized from the reaction of compounds [18] with 2,3-dimethyl maleic anhydride or maleic anhydride in dry benzene. These compounds were characterized by their melting points, FT-IR, H-NMR spectroscopy and they checked by T.L.C.

compound (19), fig.,(6) exhibited the peaks δppm at 2.12(s,3H,CH_3) ,at 5.4(s,2H,CH_2) and at 7.2(s,1H,CH) also at 6.9-7.4(m,8H,2Ar-H).

Imidazolidine derivative (21) was prepared by the heating of Schiff base derivative with glycine (α –amino acetic acid)in THF ,the product was identified by the FT-IR spectrum which shows the appearance of NH

vibration in 3320 $cm^{-1}$and the disappearance of C=N band in 1600 cm^{-1}.

Table (3):FT-IR and Uv/Vis spectral data for compounds .

Comp. No.	UV,λmax (nm),DMSO	vas. CH_2 vs CH_2	ν=C-H Ar.	ν C=C Ar.	ν C=N	ν C=O	N-H	Others
1	260	2950 2880	3080	1569,1480	1630	-	3430-3600	NO_2 1550,1350
3	250	2900 2870	3097	1470	1612	-		-
5	269	2924 2854	3100	1600,1490	1610	1720	3350	C-O-C1239,1118
6	295	2900 2870	3092	1590,1480	-	-	-	N=N1531
7	274	2940 2870	3099	1600,1490	1600	-	-	-
8	269	2960 2860	3095	1600,1495	-	1677,1620	3332-3276	-
10	270,350	2940 2860	3100	1598,1485	1643,1612	-	-	C=S 2534
11	296	2945 2875	3090	1550,1478	1610	1596	3460	-
13	250	2980	3090	1500	-	1740,1720	-	-
15	260	2920,2880	3100	1530	-	1720	-	-
16	260	2900,2980	3090	1500	-	1662	3460	C=S1161
17	267	2980	3100	1500	1600	-	3600,3200	-
18	280	2980	3090	1560	1620	-	-	-
19,20	250	2850	3090	1580	-	1710	-	C-O-C 1273,1080
21	270	2900	3100	1560	-	-	3320	

Biological activity

The biological activity of compounds was determined by measuring the diameter of the empty region around the well (Inhibition zone). The results of preliminary screening tests are listed in table (4).

Table (4) : Antibacterial activities of the synthesized compound

Comp. No.	*Klebsiella Pneumoniae*	*Pseudomonas aeuroginosa*	*Staphylococcus aureus*	*Bacillus subtilus*
3	++	++	++	-
4	+	+	-	-
7	++	-	+	++
8	+	++	-	++
9	-	++	+	+
11	++	-	+	+

Note:

- = No inhibition = inactive

+ = (5-10) mm = slightly active
++ = (11-20) mm = moderately active

The biological activity test showed that compound [3] with free (-NH_2) and (SH) groups having a biological effect more than other compounds.

Conclusion

1. For *Klebsiella Pneumonia*e (G^-), compounds [3,7,11] showed highest activity, while compounds [9] showed no active on this bacteria.
2. For *Pseudomonas aeuroginosa* (G^-), some compounds have no effect on this bacteria because this bacteria is highly resistant to a wide range of antibiotic because of the slim poly saccharides in cell wall which blocked antibiotics from bacteria and also there are genetic factor.
3. For *Staphylococcus aureus* (G^+), some compounds have moderate effect on this bacteria.

For *Bacillus subtilus* (G^+), all compounds have moderate effect except compounds [3,4] has no effect on these bacteria.

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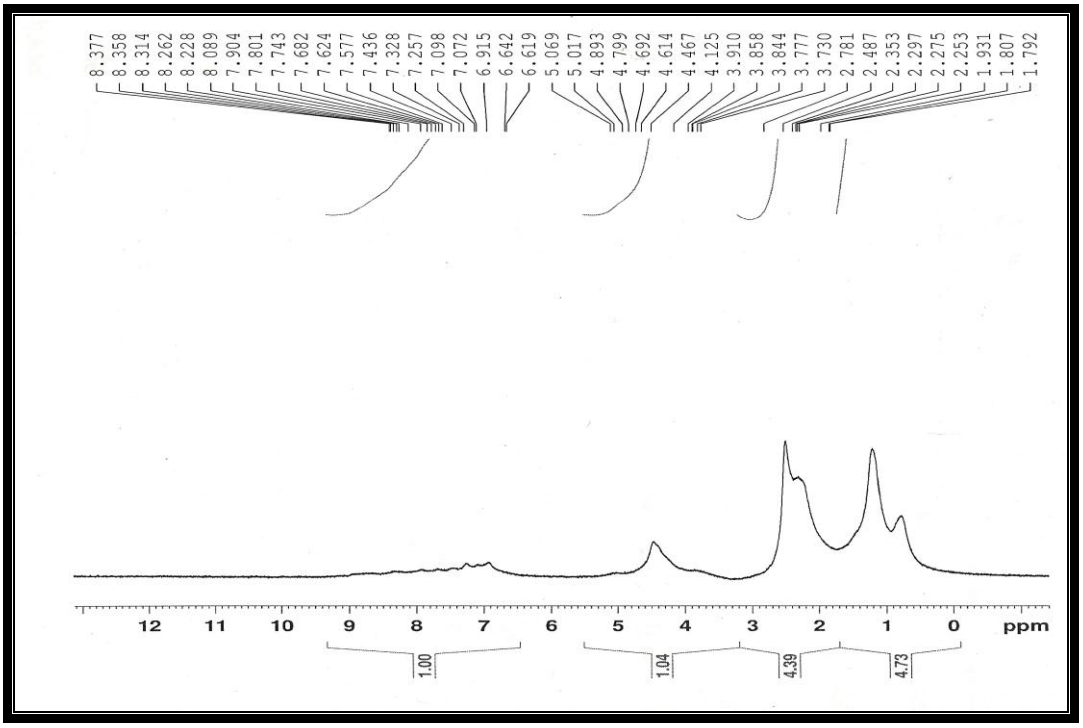


Fig.(3):H-NMRfor compound [16].

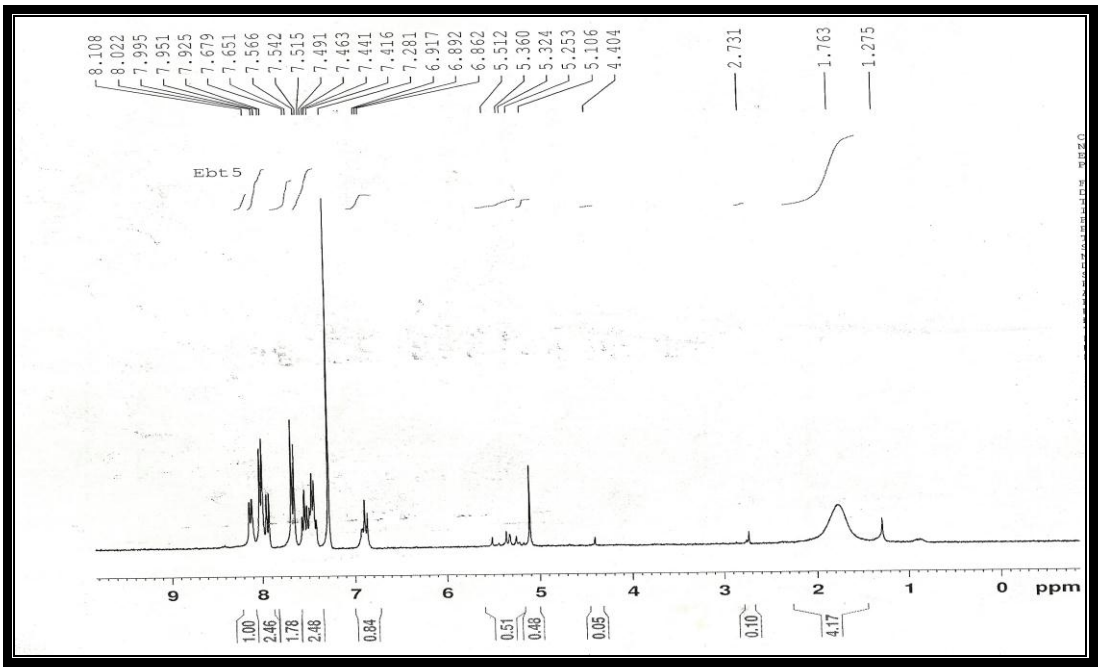


Fig.(5):H-NMR for compound[18].

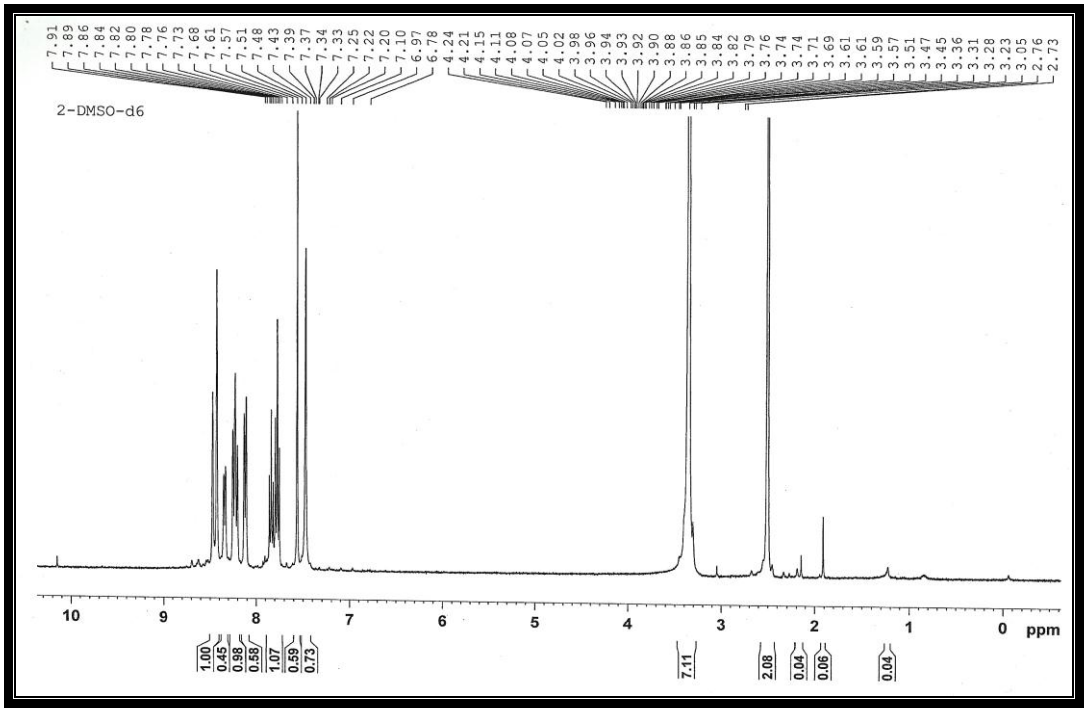


Fig.(1):H-NMRfor compound[1].

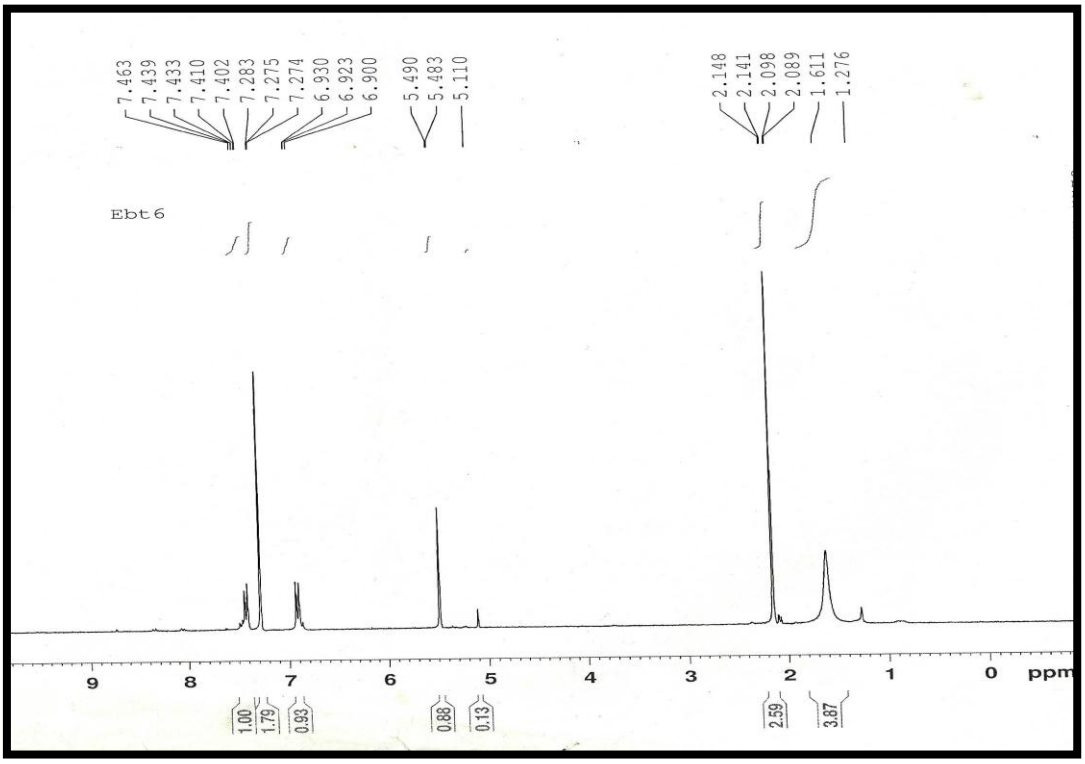


Fig.(6):H-NMR for compound [19].

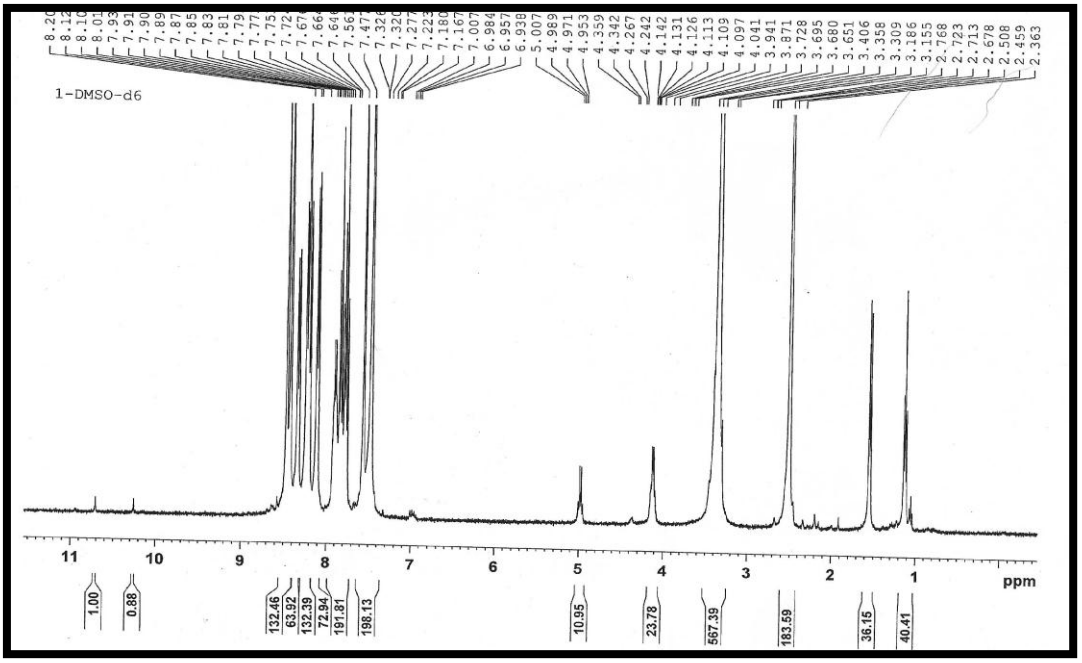


Fig.(2):H-NMRfor compound [3].

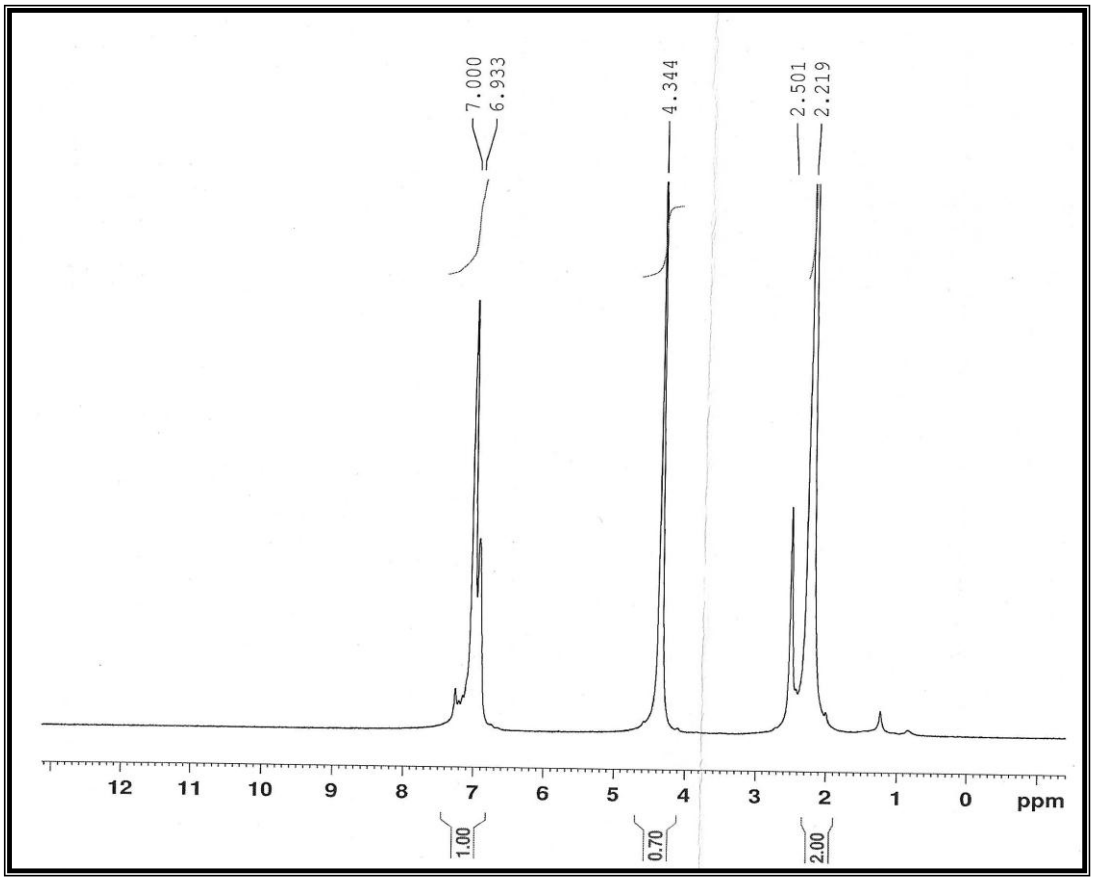
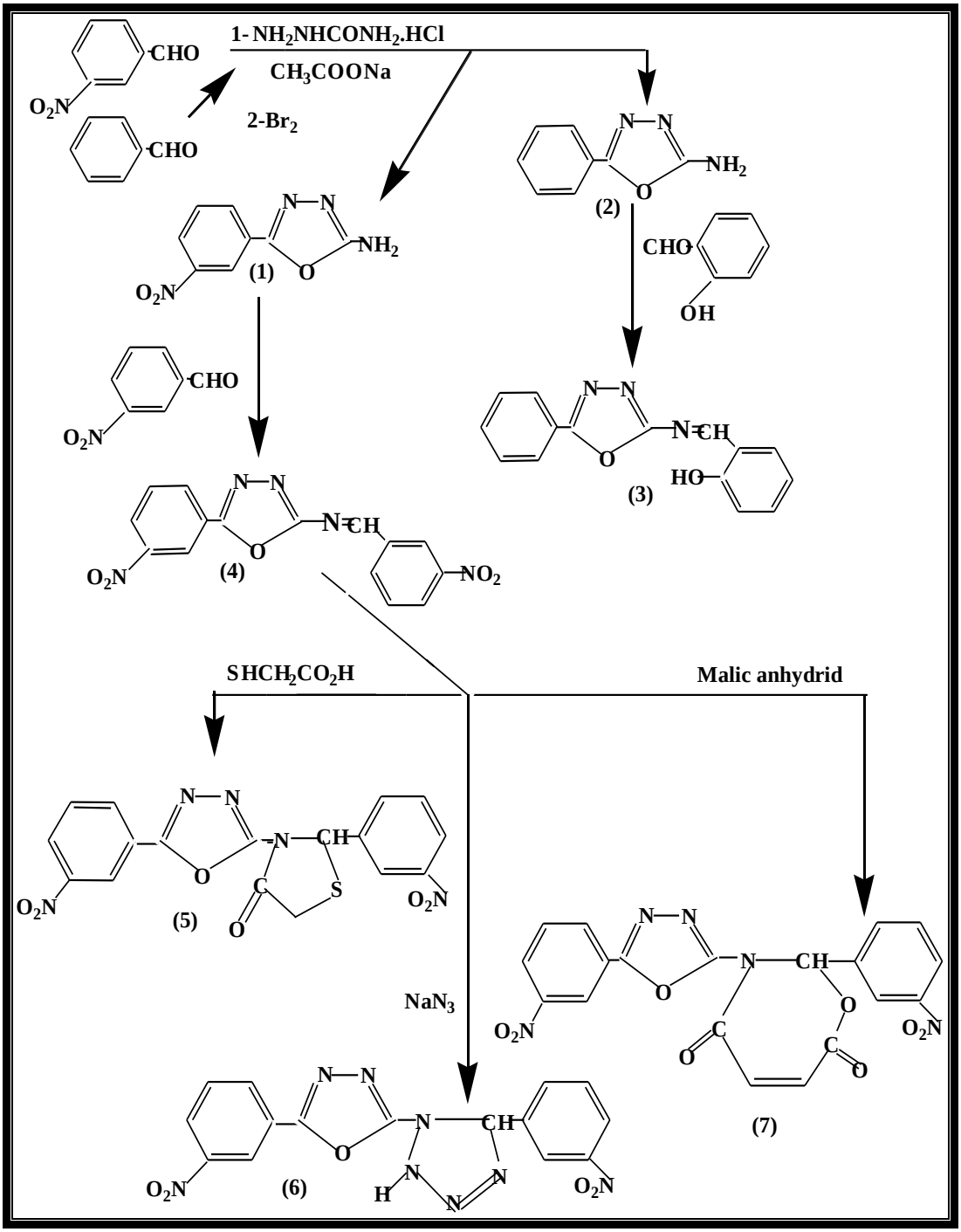
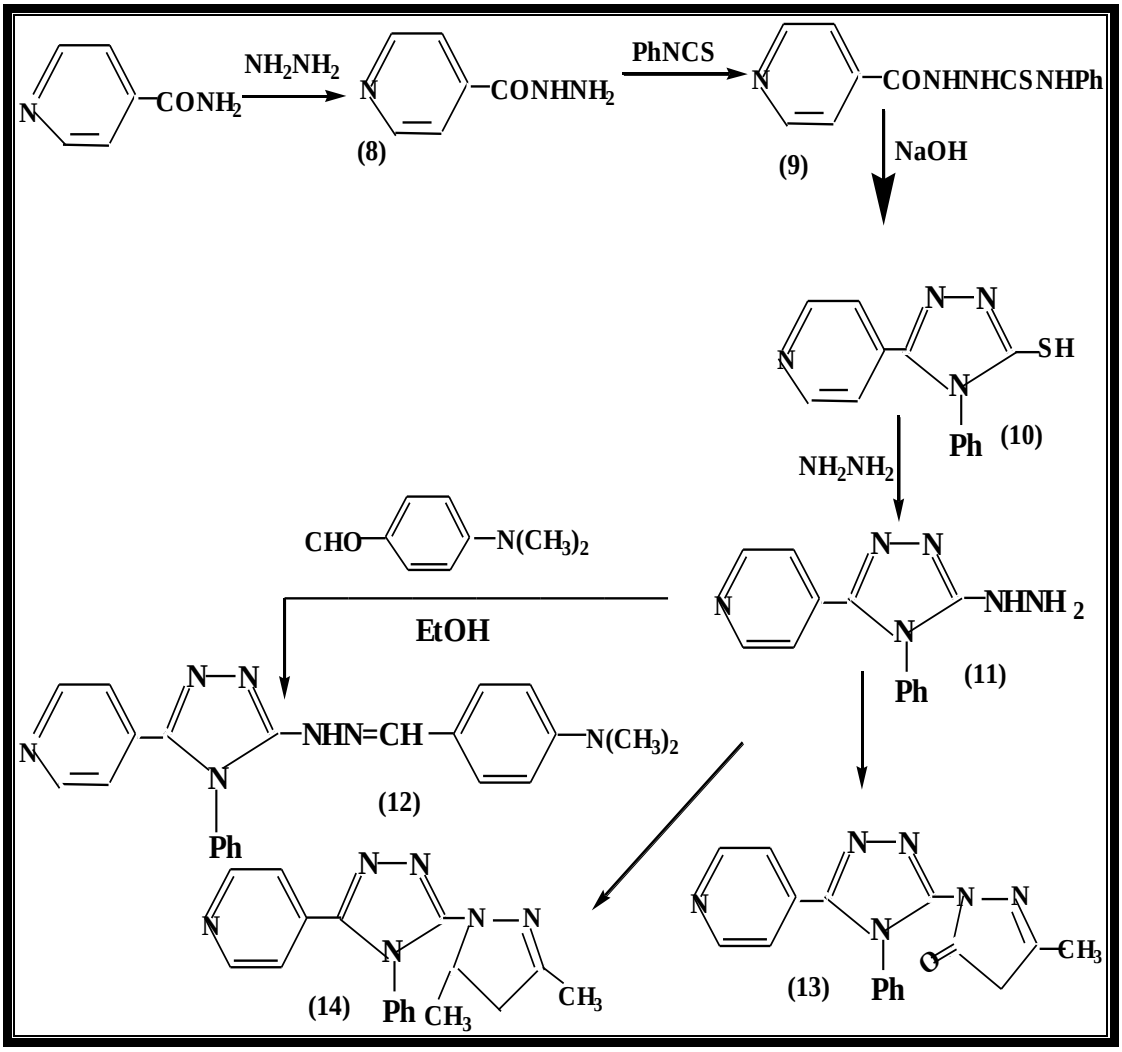


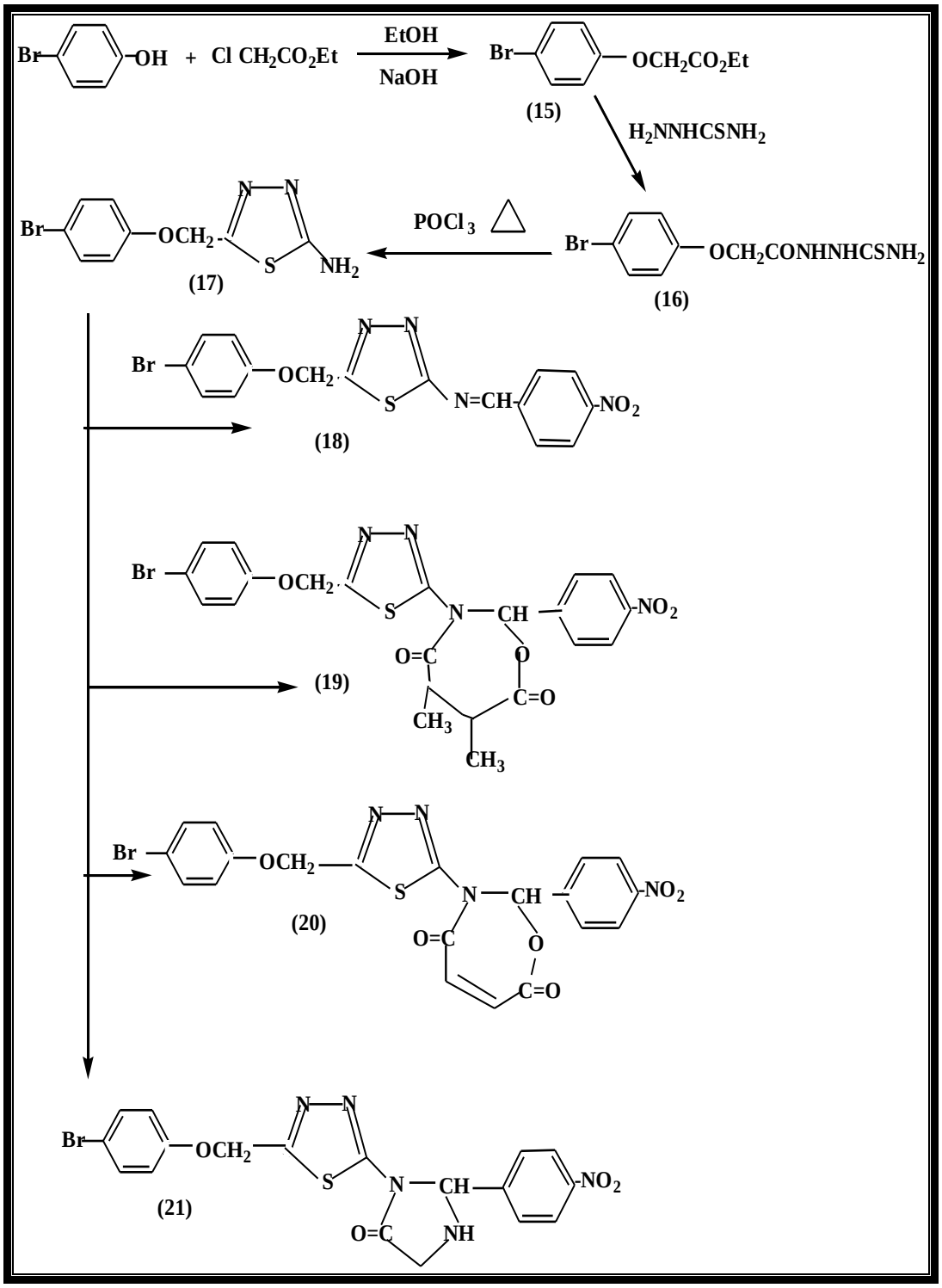
Fig.(4):H-NMRfor compound [17].


1- NH2NHCONH2.HCl
CH3COONa
2-Br2
(1)
(2)
(3)
(4)
(5)
(6)
(7)
SHCH2CO2H
Malic anhydrid
NaN3

Scheme 1


NH2NH2
CONH2
CONHNH2
(8)
PhNCS
CONHNHCSNHPh
(9)
NaOH
SH
Ph
(10)
NH2NH2
CHO
N(CH3)2
EtOH
NHNH 2
(11)
NHN=CH
N(CH3)2
(12)
Ph
CH3
(13)
(14)
Ph CH3
CH3

Scheme 2


Br
OH + Cl CH2CO2Et
EtOH
NaOH
Br
OCH2CO2Et
(15)
H2NNHCSNH2
Br
OCH2CONHNHCSNH2
(16)
POCl3
Br
OCH2
N
N
S
NH2
(17)
Br
OCH2
N
N
S
N=CH
NO2
(18)
Br
OCH2
N
N
S
N
CH
NO2
O=C
O
C=O
CH3
CH3
(19)
Br
OCH2
N
N
S
N
CH
NO2
O=C
O
C=O
(20)
Br
OCH2
N
N
S
N
CH
NO2
O=C
NH
(21)

Scheme (3)