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Synthesis New Hetrocyclic compounds Derived from Fouroic acid

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Abstract:

This paper including the preparation of new comounds starting from acid (furoic). The acid was converted to five membered ring (oxadiazole).The acid was reacted with ethanol in presence of sulfuric acid then converted to hydrazide compound by reacting it with htdrazine hydrate .The hydrazide also reacted with CS_2 carbon disulfide to obtain oxadiazole ring.

Then the oxadiazole ring reacted with hydrazine hydrate to give hydrazino oxadiazole .Derivatives of oxadiazole obtained from the reaction of different aldehydes with hydrazine oxadiazole to have Schiffs' bases and the diazonium salts was prepared from the reaction of hydrazino oxadiazole with derivatives of phenols then the (OH)group of phenols was reacted with acid chloride to obtain ester compounds. The prepared compounds were characterized by FT-IR,H-NMR)spectra and the melting points were recorded and the purity was checked besides the biologically activity was evaluated.

Key Words: Heterocyclic compounds, diazonium salt.

INTRODUCTION:

Heterocyclic compounds are considered an important branch of organic compounds due to their application in drugs and industrial studies [1]. They are major class of organic chemical compounds characterized by the fact that the atoms in their molecules are joined into rings containing at least one hetero atom[2].

The most common heterocyclic are those with five- or six-membered rings, containing nitrogen (N), oxygen (O), or sulfur (S) [3]. Among the five member heterocyclic compounds,1,3,4-oxadiazoles have became an important synthon for the development new therapeutic agents, compounds with 1,3,4-oxadiazole core substantiate for broad spectrum of biological activities including antimicrobial, antifugal, and anti-inflammatory, so, Muralikrishna et.al., have synthesized 2-((4-acetyl-5-methyl-5-(trifluoromethyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3yl)-3-(***p***-tolyl)thiazolidine-4-one and studied its antifungal activity[4].

Also, Muhanned et.al.,have synthesized 5-alkyl 1,3,4-oxadiazole 2-thion derivatives and converted it to Mannich base[5]. These Manich bases were synthesized from the reaction of oxadiazole derivatives with different primary amines and with terephthaldehyde . The oxadiazole chemistry has been developed extensively and still developed continuously.

Hydrazide and thiosemicarbazide derivatives attracted a lot of attention because they are considered as intermediates to synthesize several compounds such as Schiff bases, oxadiazole, thiadiazole,triazole, pyridazine and pyrazole derivatives which all were reported to posses biological activities. The structural formula of this type of compound is (RCONHNH-).

Hydrazide derivatives are considered biologically active; many hydrazide compounds were used in treatment of tuberculosis [6].

Aromatic Diazonium Salts Reactions of nucleophiles at nitrogen

Nucleophiles react with diazonium ions to give covalent diazo-compounds. For example, phenol via phenoxide ion couples with diazonium salt at pH 9-10 to afford para-azophenols in good yield SN1 Reaction Diazonium salts decompose on warming into nitrogen and aryl cation which is highly reactive and could be attacked by any nucleophile in its vicinit. SN1 Reaction Diazonium salts decompose on warming into nitrogen and aryl cation which is highly reactive and could be attacked by any nucleophile in its vicinit [7].

MATERIALS AND METHODS EXPERIMEMTAL:

All melting points are uncorrected. The FT-IR spectra were measured on perkin-Elmer spectrophotometer. The ^{1}H-NMR spectra were recorded on 300MHz instrument using $DMSd_6$ as solvent and TMS as internal reference.

1- Melting points are recorded using hot stage Gallen Kamp melting point apparatus and they were uncorrected.

2- Infrared spectra are recorded using Fourier Transform infrared *SHIMADZU* (8300) (F.T.IR) infrared spectrophotometer, KBr disc was performed by Chemistry Department, Baghdad University and using Fourier Transform infrared *SHIMADZU* (8400) (F.T.IR) infrared spectrophotometer, KBr disc was performed by Al-Mustansryia Univrsity.

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

Fuoroic acid, hydrazine hydrate, CS_2, P-hydroxybanzaldehyde ,soduim nitrite, two kinds of substituted phenols , two kinds of acid chloride were used.

Synthesis compounds:

1-Synthesis of Furan-2-carboxylic acid ethyl acetate / M1

A mixture of Fuoroic acid (0.001 mol) with 40ml absolute ethanol, then (5ml) of concentrated sulfuric acid was added, the mixture was refluxed for (6h.), the end of reaction was checked by TLC, the resulted ester was separated by extracted it with water M1[8].

2-Synthesis of Furan-2-carboxylic acid Hydrazied M2 [9]**.**

A mixture of M1 (0.01 mole) with (0.14 mole) of Hydrazine hydrate 80% in (10) ml of absolute ethanol was refluxed for 3h. at 75^{0}C. After cooling, the formed solid was filtered off and re crystallized .

3-Synthesis of xanthat salt M3 and 1-Furan-2-yl-ethanone; compound with [1,3,4]oxadiazole-2-thiol M4 [(10)]:

A mixture of M2 (0.015 mol) and10ml absolute ethanol,then (1.5 ml) of carbon disulfide CS_2 with (0.6 gm) NaOH was added. This mixture was refluxed in water bath for 10h. The resulted crude (M3) was dissolved in distilled water and acidified with hydrochloric acid, the solid product finally filtered off M4 .

4-Synthesis of 1-Furan-2-yl- [1,3,4]oxadiazol-2-yl-hydrazino M5[(11)]:

1,3,4-oxadiazole compound (0.01mol) (M4) was reacted with (10 ml) hydrazine hydrate 80% ,5ml in absolute ethanol, the mixture was refluxed for 8h., after that, the reaction mixture was cooled and precipitated by ethanol, the precipitate was filtered.

5-Synthesis of 4-([1,3,4]Oxadiazol-2-yl-hydrazinomethyl)-phenol 1-furan-2-yl-ethanone (Schiff's bases) M6 [(12)]:

The reaction of (o.oo6 mol) from (M5) with (10 ml) ethanol and added (0.006 mol)from ***p***- hydroxy benzaldehyde with 3drops of glacial acetic acid , the mixture was refluxed for 3h.,after completing the reaction, the solid filtered (M6) then re crystallized by suitable solvent [6]

6-Synthesis of Acetic acid 4-([1,3,4]oxadiazol-2-yl-hydrazonomethyl)-phenyl ester 1-furan-2-yl-ethanone M12[(13)].

M6 (0.001mol) was dissolved in pyridine and added the same mol of acetyl chloride and continuing the stirring in bath water at (0-5 ^{0}C) for 1h., after that the stirring was continuing at room temperature for 24h., at the end of this reaction ,the mixture was poured in ice water acidified with HCl acid. The product was filtered M12.

7-Synthesis of M7(diazonium salt).

In bath water (0-5 ^{o}C) first solution (1ml HCL with 1ml distilled water) was adding 0.66gm from M5 with stirring, the second solution (0.25gm of $NaNO_2$ with 1.5 water) ,was added to the first one, the solid product was filtered .

8-Synthesis of M8 (M9)

In ice bath water (0-5 ^{o}C) solution of (1gm NaOH with 5ml distilled water) was added to a solution of (0.01mol) of ***p***-nitro phenol (2,5 dimethyl phenol) with stirring gradually. Then solution of M7 was added. The solid product was filtered M8(M9).

9-Synthesis of M10 (M13)

In ice bath water (0-5 ^{o}C) solution of (0.3gm M8 with pyridine) was added\ 0.001mol from acetylchloride (or banzoylchloride) by dropwise with stirring 2h.,at the end of reaction, the mixture was poured in ice water with HCl ,the solid product was filtered (M10 ,M13).

Synthesis of M11 (M14)

The same procedure in (9) was used to prepare M10 (M13) by reaction of acetylchloride and benzoyl chloride with (0.3gm) M9.

RESULTS AND DISCUSSION:

The prepared compounds were characterized by FT-IR ,HNMR spectra and the melting points were recorded besides the purity was checked.

The FT-IR of compound M1(ethyl furoate)exhibited the main band (C=O)for ester at 1735cm^{-1}. While compound M2 showed the bands at 1665cm^{-1} attributed to carbonyl group and at 3378, $^{-1}$due to $NHNH_2$. Also, the HNMR spectrum for this compound exhibited the expected protons, figure (11), at 7.23ppm for NH besides the peak at 2.76ppm for NH_2.

In compound (M3) the xanthate salt was prepared from the reaction of hydrazide with CS_2 and KOH in presence of ethanol.(Scheme 1).

The FTIR spectrum of compound (M4) , figure (1) shows the band at 3435cm^{-1} due to (N-H)group, and at 1631cm^{-1} attributed to (C=N) besides the band at 1500,1446cm^{-1} due to (C=C) stretching frequency. The frequency appears a new one for (C=S) at 744cm^{-1}.

The FTIR spectrum of compound (M5), figure (2) shows the band of(N-H) stretching frequency at 3317cm^{-1}. The frequency of the NH_2 group appeared at 3265-3194cm^{-1}. While the band of (–SH) was disappeared. The FTIR spectrum of compound (M6), figure (3) shows the band at 3346cm^{-1} stretching frequency for (O-H). The frequency of the C=N group appeared at 1600cm^{-1}. While the frequency of (–NH_2) was disappeared.

The FTIR spectrum of compound (M12) ,figure (4) shows the disappearance of (O-H) band. Besides the frequency of the (C=N) group appeared at 1643cm^{-1} and 1774 cm^{-1} for carbonyl group and disappearing of(–OH).

The FTIR spectrum of compound (M8) ,figure (5) shows the band of (O-H) stretching frequency at 3240cm^{-1}. The frequency of the (C=N) group appeared at 1610cm^{-1}. While the frequency of (–N=N) for diazenium salt and a band appeared at 1473 ,the frequency of NO_2 appeared at (1444,1369). The FTIR spectrum of compound (M9) ,figure (8) shows the band (O-H) stretching frequency near 3223cm^{-1}.The frequency band of –N=N for diazonium salt appeared at 1496 cm-^{1} ,the band of NO_2 appeared at 1444,1369 cm^{-1}.

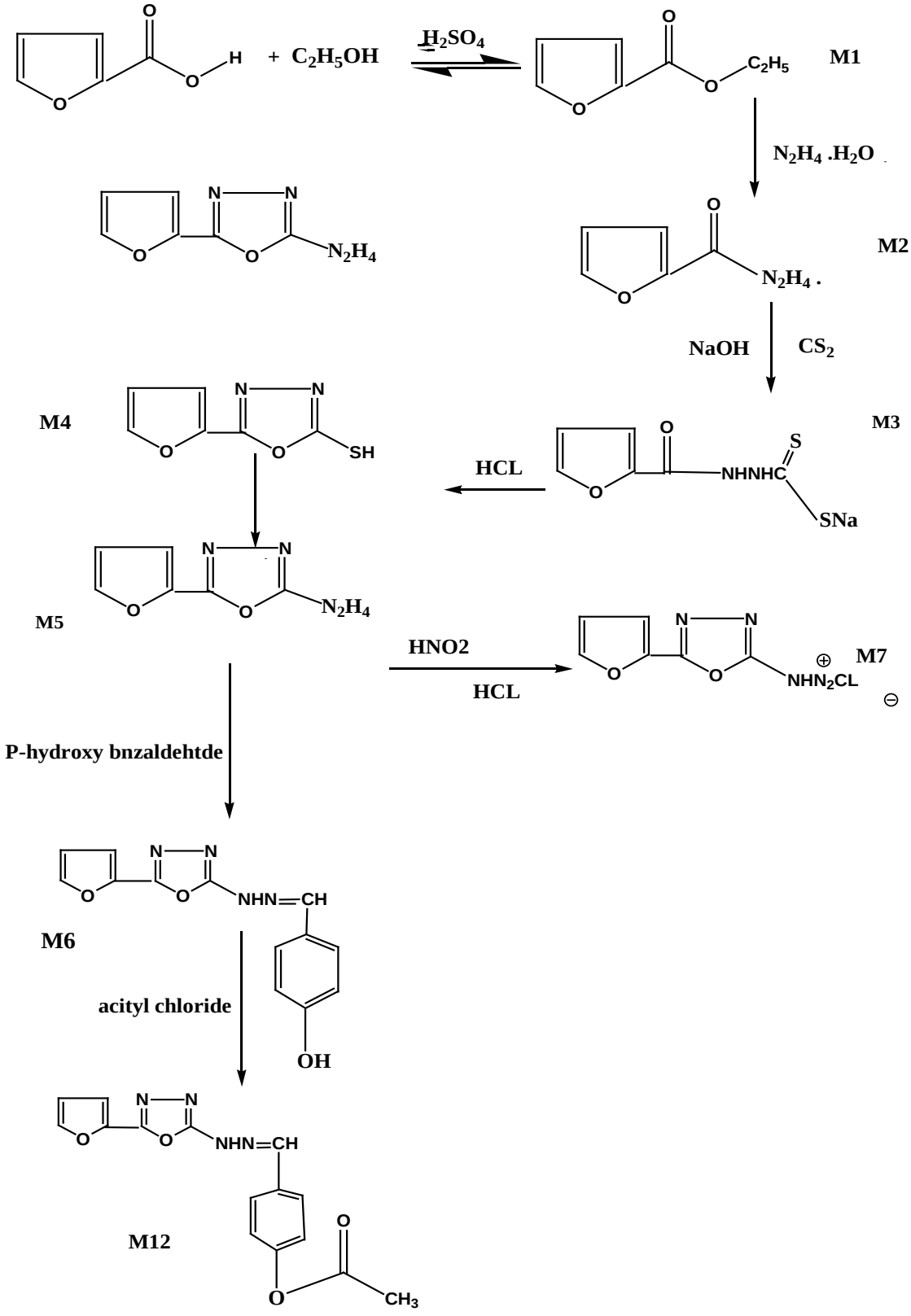
So , HNMR spectrum for compound M9,showed the expected protons.

Compound (M10) exhibited the disappearance of (O-H) frequency band, figure (6) . so the frequency of (–N=N) was appeared at 1450 cm^{-1} and at 1739 cm^{-1}for the frequency of C=O. HNMR spectrum also confirmed the proposed structure, figure (13).

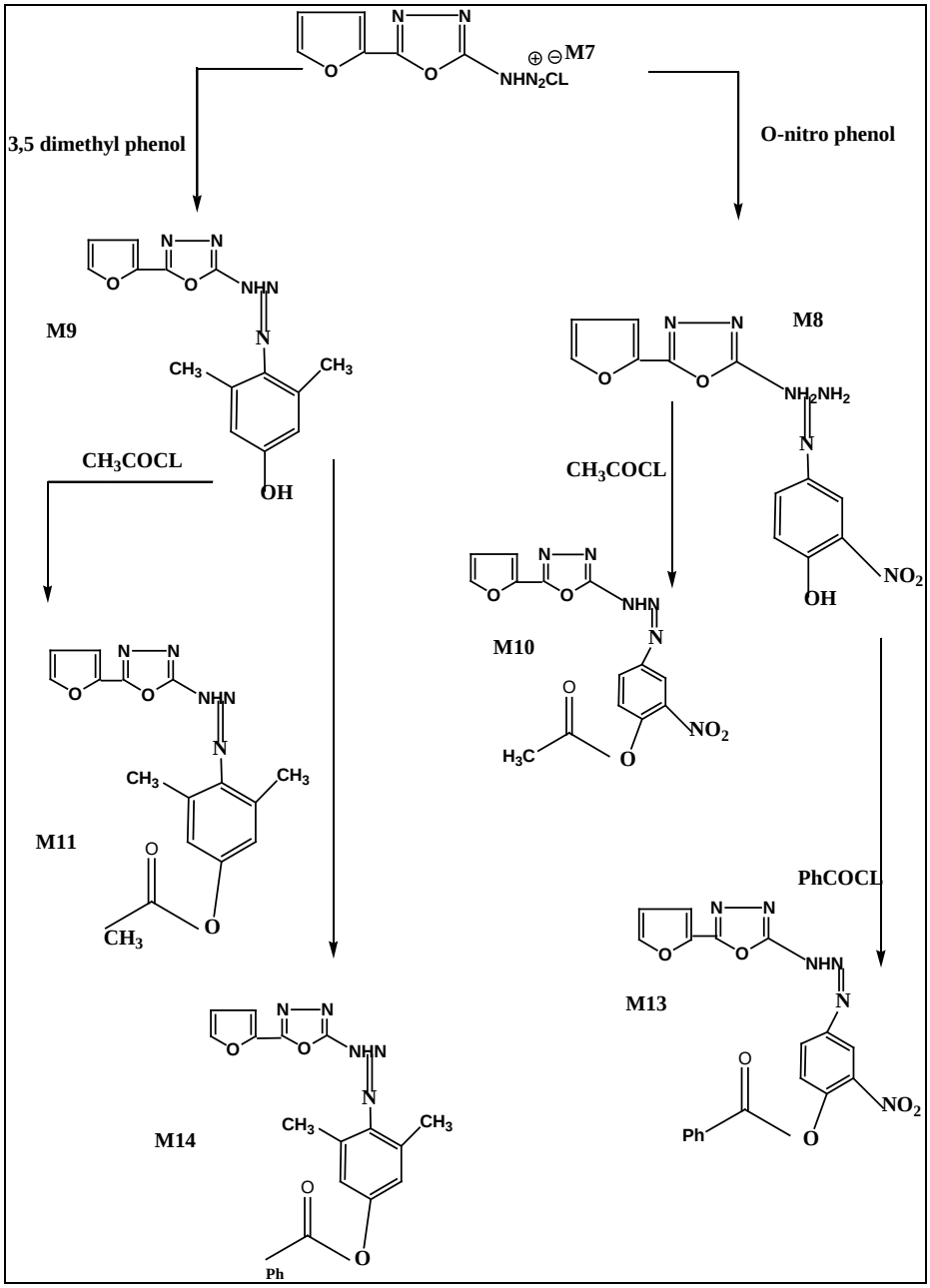
The FTIR spectrum of compound (M11), figure (9) shows the band of (C=O) stretching frequency near 1701cm^{-1}. The frequency band of the N=N group appears at 1465cm^{-1}.HNMR spectrum, figure (14), proved the structure.

The FTIR spectrum of compound (M13), figure (7) showed the disappearance of band (O-H) frequency was disappeared and the band of –N=N was appeared at 1531cm^{-1} also,the frequency of C=O appeared at1747 cm^{-1}.

The FTIR spectrum of compound (M14) ,figure (10) shows the band of (C=O) frequency was appeared at 1732 cm^{-1} . While the frequency band of (–N=N) appeared at 1381 cm^{-1}. Also ,the HNMR spectrum of compound (M14),figure (15), showed the suggested structure[(14)].


+ C2H5OH
H2SO4
M1
N2H4 .H2O
M2
N2H4 .
NaOH
CS2
M3
NHNHC
S
SNa
HCL
M4
SH
M5
N2H4
HNO2
HCL
M7
NHN2CL
P-hydroxy bnzaldehtde
M6
NHN=CH
OH
acityl chloride
M12
NHN=CH
CH3

Scheme No. 1



Scheme No. 2

Table No.(1) : Physical properties of the compounds

Comp.No.	Yield %	Melting Points°c	Color
M2	79	88	Brown
M3	80	172	Brown
M4	152	69	Yellow
M5	185	77	White
M6	70	210	Yellow
M7	65	190	Yellow
8M	78	40	Phosphorous
9M	56	45	Brown
M10	63	152	Yellow
M11	64	122	Brown
M12	78	132	Brown
M13	70	45	White
M14	53	62	White

Table (2) : FT-IR spectral data (cm⁻¹) for the prepared compounds.

Comp.No.	υC=O	υNH	υC=Car.	υC=N	υN-N	Others
M1	1735	-	-	-	-	-
M2	1665	3156,3378	1550	-	-	-
M4	-	3435	1500,1446	1631	1047	C=S 744
M5	-	3317		1647-1593	1089	$\upsilon NH_{2klinkmn}$ 3265-3194
M6	-	-	-	1600	-	OH 3346
M7	-	-	-	-	-	-
M8		3115		1610-1585	1078	N=N NO_2 1473 1444-1369 OH 3240
M9		3223		1608-1585	1020	N=N **OH** 1496 3223
M10	1739	3398		1600-1585	1026	N=N 1450
M11	1701	3271		1585	1111	N=N 1465
M12	1774	3421		1643-1608	1087	-
M13	1747	3240		1689-1616	1026	N=N 1327
M14	1732	3479		1651-1596	1018	N=N 1381

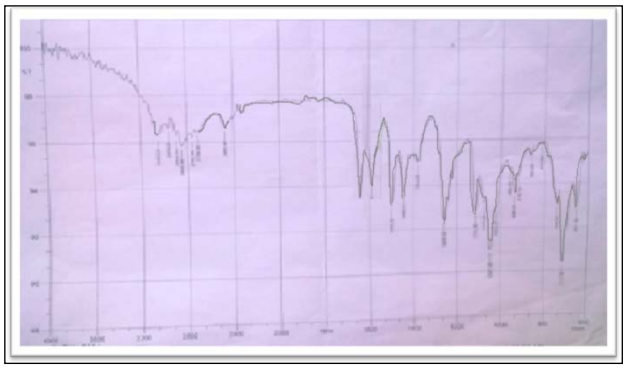
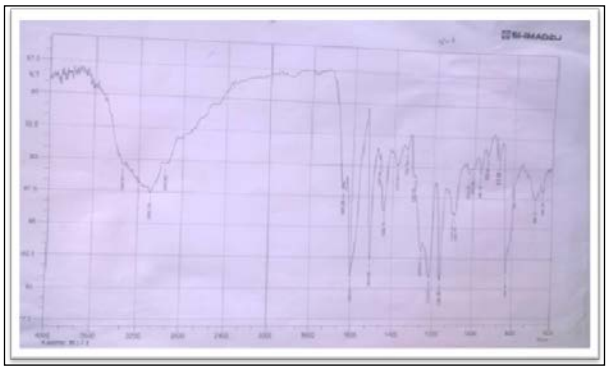
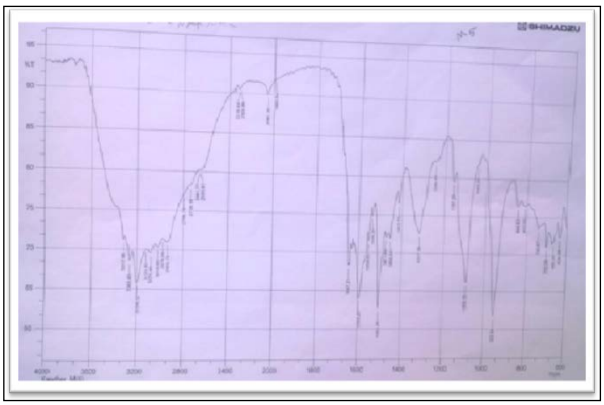


Figure (1): FTIR spectrum of compound [M4].



Figure(3): FTIR spectrum of compound [M6].



Figure(2):FTIR spectrum of compound [M5].

Figure(4): FTIR spectrum of compound [M12].

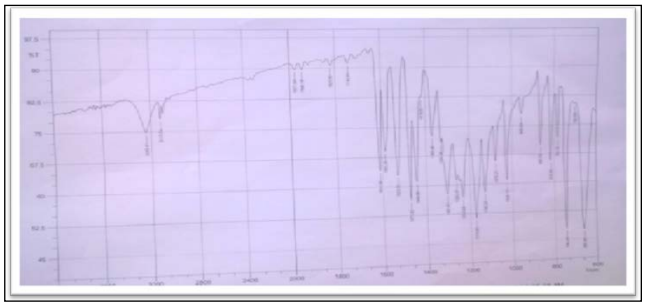
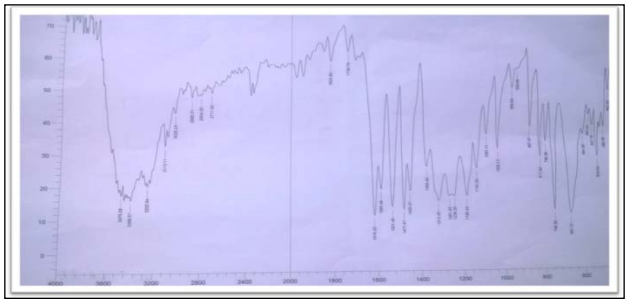
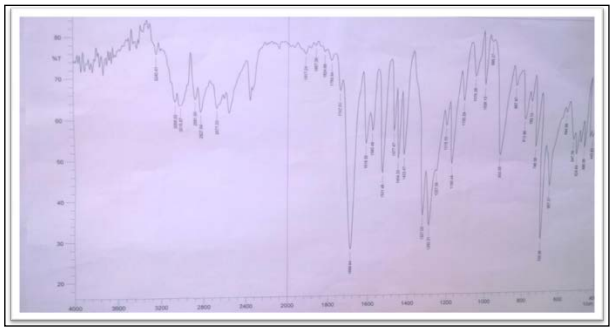


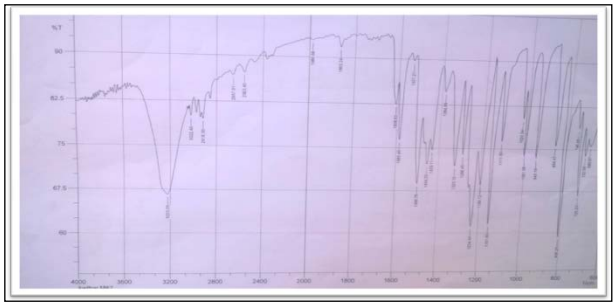
Figure (5): FTIR spectrum of compound [M8] .



Figure(6): FTIR spectrum of compound [M10].



Figure(7): FTIR spectrum of compound [M13].



Figure(8): FTIR spectrum of compound [M9] .

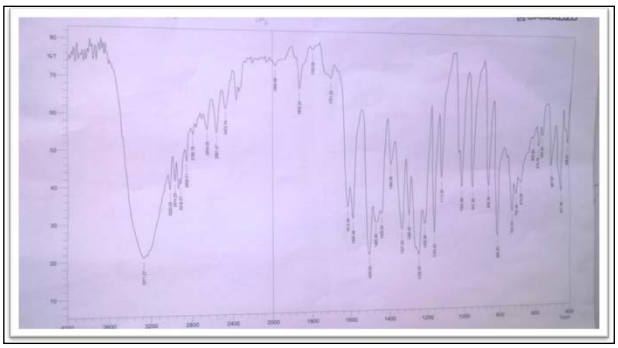


Figure (9):FTIR spectrum of compound [M11] .

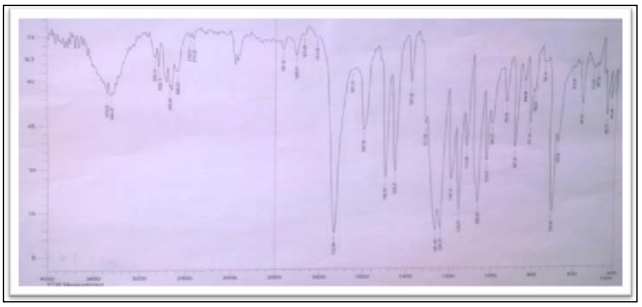


Figure (10): FTIR spectrum of compound [M14] .

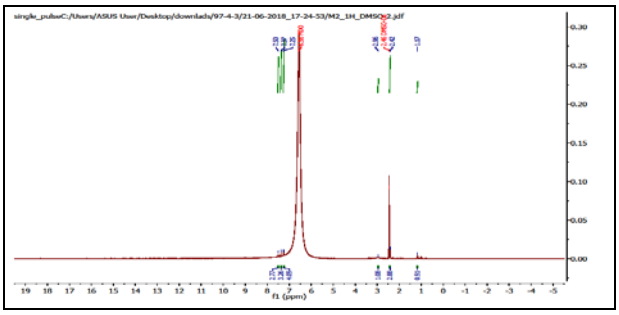


Figure (11): HNMR spectrum of compound [M2] .

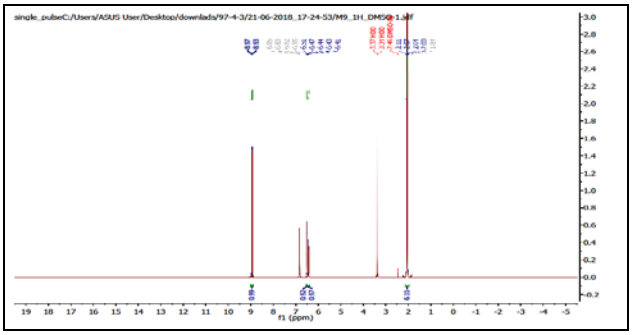


Figure (12): HNMR spectrum of compound [M9].

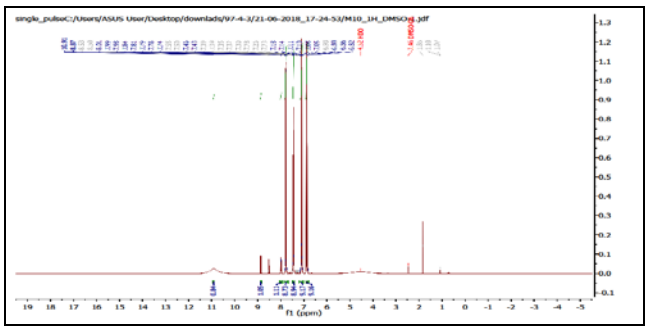


Figure (13):The HNMR spectrum of compound [M10].

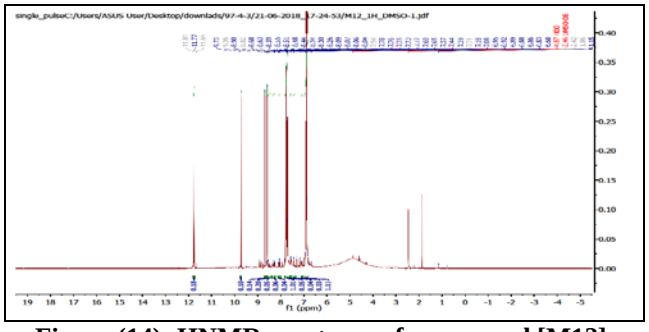


Figure (14): HNMR spectrum of compound [M12].

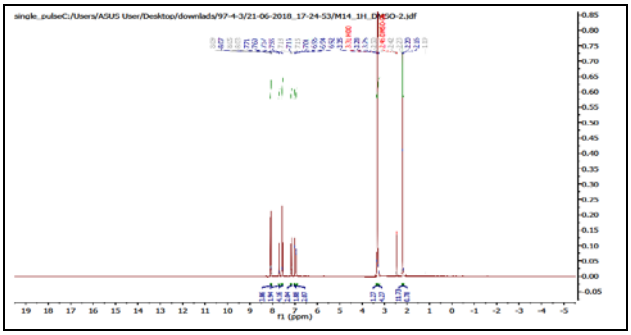


Figure (15):HNMR spectrum of compound [M14].

Biological activity:

The study of anti-bacterial activity for some of the synthesized compounds was determined in vitro using well diffusion method against three types of pathogenic strains bactria *staphylococcus aureus (G+), E.coli* and *Pseudomonas (G-).* The obtained results revealed that some at these compounds showed measurable activity, as shown in Table (3).

Table (3): Antibacterial activities for some of the prepared compounds.

Comp. No.	E.coli (G-)	Pseudomonas (G-)	Staphylococcus (G+)
M13	+ +	+ +	+ +
M12	+ +	+ +	+ + +
M11	+ +	+	+ +
M10	+ +	+ +	+ + +
M9	+ +	+ +	+ +
M6	+ +	+ +	+ + +

Key to symbols:

Highly active = +++ (inhibition zone > 20 mm).
Moderately active = ++ (inhibition zone 11-20 mm).
Slightly active = + (inhibition zone 5-10 mm).
Inactive = - (inhibition zone <5 mm).

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