Synthesis and Characterization of some Heterocyclic Compounds from Indole Derivatives

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ABSTRACT:

This research involves preparation of heterocyclic compounds from indole -2- carboxylic acid. The first step synthesized of ester compound from indole -2- carboxylic acid and prepared hydrazinamide from ester.Then prepared Schiff bases from hydrazinamide derivatives with benzaldehyde derivatives. The last step preparedoxazepine and oxazepane derivatives from Schiff bases with(malice, phthalic and succinic)inhydride .These compounds were characterized by melting point ,FT.IR,^{1}HNMRand^{13}C-NMRKey words: indole -2-carboxylic acid,Schiff bases,Oxazepine , 1,3-oxazepane, biological activity.

الخلاصة:

يتضمن البحث تحضير مركبات حلقية غير متجانسة عن طريق استعمال 2- كاربوكسياندول كمادة أولية ,تتضمن الخطوة الاولى تحضير الأستر من 2- كاربوكسياندول وتحضير الهايدرازاينامايد من الاستر ومن ثم تحضير قواعد شف من الهايدرازاينامايدبأستعمال مشتقات البنزالديهايد.الخطوة الأخيرة تتضمن تحضير مشتقات الاوكسازبينوالاوكسازبان معانهدريد (المالك ,الفثالكوالسكسنك) بعدها يتم التأكد من صحة المركبات المحضرة بوساطة درجة الانصهار وتقنية ^{13}C-NMR , ^{1}HNMR ,FT.IR.

INTRODUCTION

Indoles and substituted indoles are the basic skeleton ofseveral biologically active organic scaffolds such as Turbomycin, BVibrindoles,Arsindoles, Arundine, Ajamalicine.[(1)]All indole compounds have a bicyclic structure,consisting of a sixmembered benzene ring fused toa five-membered nitrogen-containing pyrrole ring.[(2)]Indole derivatives are one of the most promising heterocyclicMoieties[(3)], which have active sites in treating various diseases.[(4)]its pharmacological significance providestremendous opportunities to discover novel drugswith different modes of action.[(5)]Indole-2-carboxylic acid is a versatile intermediate in the preparation of many pharmaceuticallyactive agents[(6)] showed significant structural and biological diversity through several methods of these compounds. The conventional method is the Hemetsberger-Knittel indole synthesis[(7)] Here the five atom involved in the synthesis of oxazepinedionederivative component is the anhydride nucleus of phthalic anhydrideand the two atom comgroup is C=N of schiff base or imine[(8)]its symbol (R-N=CH-R1) [(9)].They are the result of mixing the aromatic primary amines with the carbonyl compounds (aldehydes or ketones)[(10)]Azomethine (C=N). These are known as "Schiff's bases", named after the German scientist (Hugo Schiff)[(11)] , and which are famous for their biological importance and for its uses as anti-dioxides, anti-viruses (antibacterial, antiproliferative , anti – inflammatory, antiviral, antipyretic properties [(12)], and for the curing of tumors as well[(13)].The

stability of the resulting Schiff bases depends on the type of amine and the used carbonyl compounds[14]. It depends on the ringing state [15]

EXPERIMENTAL SECTION

Materials

Chemicals used during the current work are indole -2- carboxylic acid ,H_2SO_4, Phathilic anhydride , maleic anhydride and succinic anhydride,produced by (sigma and Aldrich) company, In addition to use of ethanol, dry benzene and methanol as a solvent .

.Instrumentation

Recorded melting point by hot stage Gallen Kamp. To ensure the purity of the resulting compounds used techniqueThin layer chromatography (TLC)was carried out, the presence of iodine an aspect of the spot. F.T.I.Ras spectroscopy was used KBr disc,^{1}HNMR and^{13}C-NMR Bruker-UItra Shield-300MHz spectra was used DMSO-d6 as solvents.

EXPERIMANTAL

Synthesis of ester derivative compound (M $_1$: Ethyl 1H-indole-2-carboxylate)

The compound (M1) was prepared by reactionindole-2-carboxylic acid taking(2g,0.01mol) of compound is dissolved in (50ml) of ethanol absolute. Then added 6 drops of H_2SO_4concentrate. Esterification for (6hrs), follow up the reaction by (TLC). After cooling the mixture was neutralized. The titled product was achieved by evaporating the solution under reduced pressure.

Synthesis of hydrazineamide derivative (M2: 1H−indole−2−carbohydrazide).

Compound (M1) (2g,0.01mol) was dissolved in refluxed ethanol (50ml), hydrazine hydrate (1ml) was slowly added to the mixture. The solution was refluxed for (13hrs) the solvent was removed by evaporating, the residue was cooled .The product was recrystallized from absolute ethanol to give titled compound.

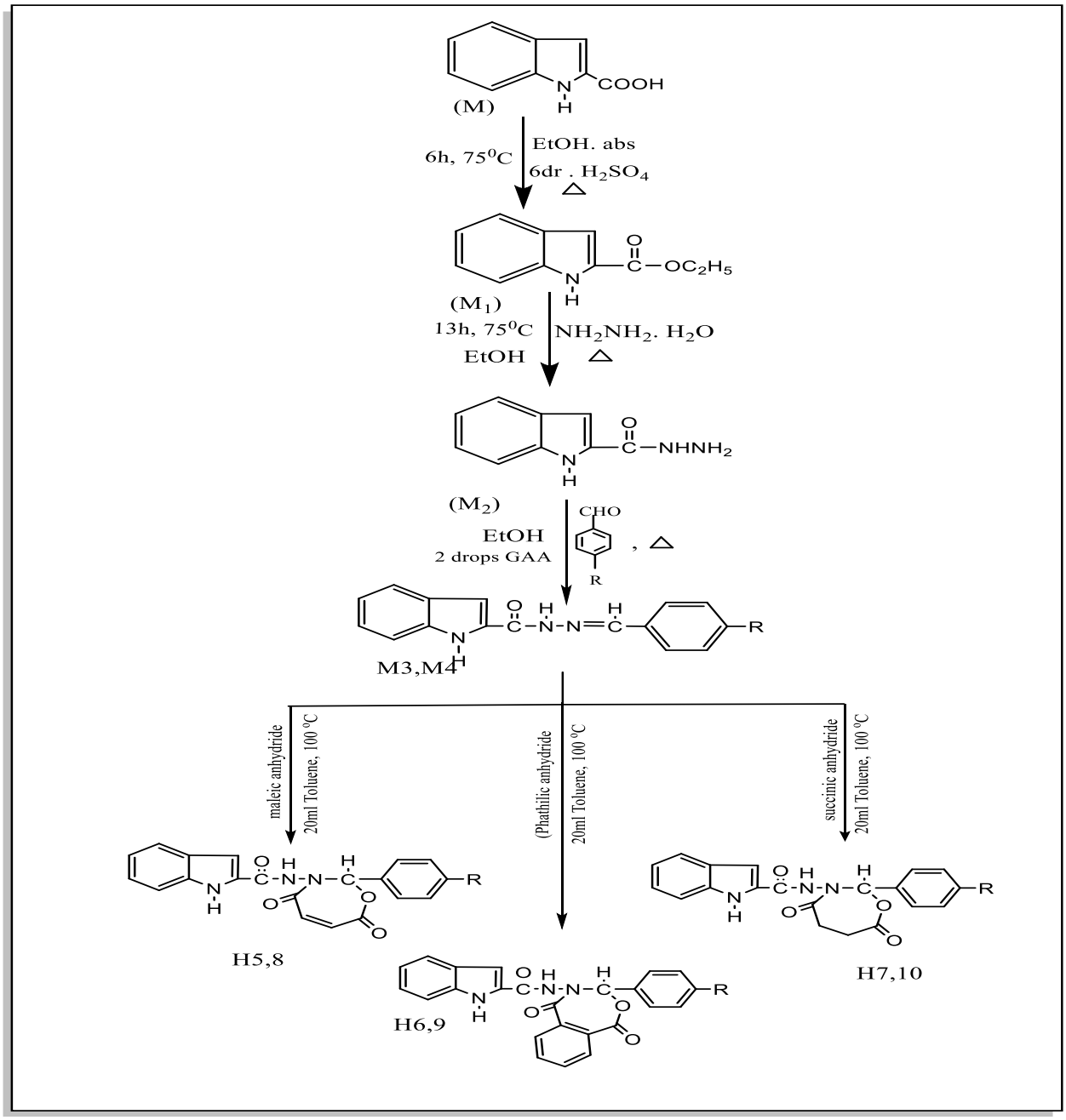
Synthesis of Schiff bases (M3:N'-(4-chlorobenzylidene)-1H-indole-2-carbohydrazide,

M4:N'-(4-Florobenzylidene)-1H-indole-2-carbohydrazide).

Amixtuer of (0.4g and 0.7g) of aromatic benzaldehyde derivatives and compound (M2) was refluxed for (7-10)hrs in (20ml) of absolute ethanol,The reaction mixture was cooled and kept for (24hrs), The crystals found were filtered,dried and recrystallized from absolute ethanol to give derivatives (M3,M4).

procedure synthesis of 1,3 oxazepine and 1,3 oxazepane[18] (H5-H10)

Amixtuer of Schiff bases (M3,M4) (0.3g,0.001mol) dissolved inToluene(20ml) and (malice, phthalic and succinic)anhydride (0.11g, 0.001mol) and refluxed for (8-10)hrs. The reaction was then cooled and the resulting final(H5-H10), recrystallized from absolute ethanol and ether. Scheme(1).



R= F ,Cl

Scheme(1):synthesis of 1,3 oxazepine and 1,3 oxazepane

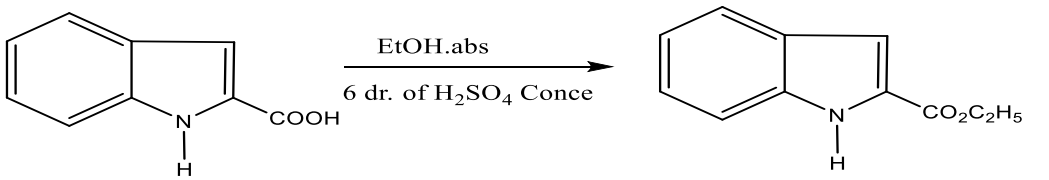
Table (1): Physical properties and other characteristics for the synthesizedcompounds (M1-M4,H5-H10)

NO.	Molecular Formula	M.wt g/mol	m.p °C	Color	Rf	Solvent	Reflex Time
M	$C_9H_7NO_2$	161.16	209 -211	White	0.57	EtOH	-----
M1	$C_{11}H_{11}NO_2$	189	191 – 193	Light Yellow	0.55	EtOH	6hrs
M2	$C_9H_9N_3O$	175	158 – 161	Brown	0.75	EtOH	13hrs
M3	$C_{16}H_{12}N_3OCl$	297.5	211 – 213	DarkYellow	0.52	EtOH	7hrs
M4	$C_{16}H_{12}N_3OF$	281	177 – 179	Brown	0.48	EtOH	7hrs
H5	$C_{20}H_{14}FN_3O_4$	379	245 – 248	Yellow	0.42	Toluene	7hrs
H6	$C_{24}H_{16}FN_3O_4$	429	203 – 206	Brown	0.46	Toluene	8hrs
H7	$C_{20}H_{16}FN_3O_4$	381	199 – 201	Yellow	0.57	Toluene	7hrs
H8	$C_{20}H_{14}ClN_3O_4$	395.80	171 – 174	Yellow	0.48	Toluene	7hrs
H9	$C_{24}H_{16}ClN_3O_4$	445.86	179 – 181	Yellow	0.45	Toluene	8hrs
H10	$C_{20}H_{16}ClN_3O_4$	397	186 – 189	Light Yellow	0.40	Toluene	9hrs

RESULTS AND DISCUSSION

Synthesis derivatives (M1:Ethyl 1H-indole-2-carboxylate)

The reaction between Indole-2-carboxylic acid (M) and absolute ethanol in the presence concentration H_2SO_4 to synthesis ester derivative(M1)



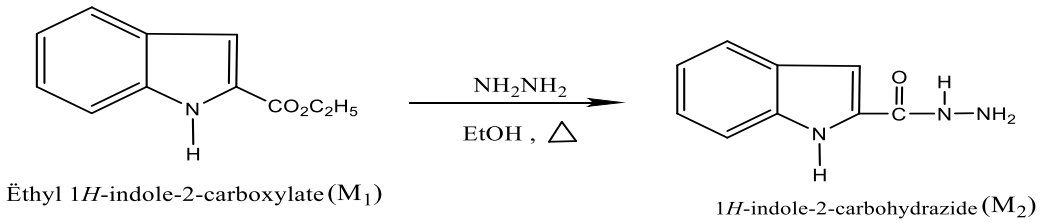
1*H*-indole-2-carboxylic acid Ethyl 1*H*-indole-2-carboxylate (M_1)

The FT-IR spectrum of Indole-2-carboxylic acid dye (M) fig(1), show stretching vibration bond of (OH) group of carboxylic acid is broad at (2500-3400cm^{-1}), the ($CH_{aromatic}$) group at (3051cm^{-1}), the stretching vibration band of (N-H)occur at 3421cm-1 .

The FT-IR spectrum of ester derivative (M1), fig(2) show the stretching vibration band of (NH) group occur at (3356cm^{-1}), the carbonyl group of ester at (ν 1708 cm^{-1}),($CH_{aromatic}$) ν3055, ν2999($CH_{aliphatic}$), $(C=C)_{aromatic}$ ν1523 and disappearance the stretching vibration of(OH) of carboxylic acid at (2500-3400cm^{-1}) .

Synthesis of hydrazineamide derivative (M2:1H−indole−2−carbohydrazide)

The reaction between ester derivative (M1) with hydrazine hydrate in the presence absolute ethanol as solvent at 70^{0}C .to prepare the hydrazine derivative (M2).



Ëthyl 1*H*-indole-2-carboxylate (M_1)

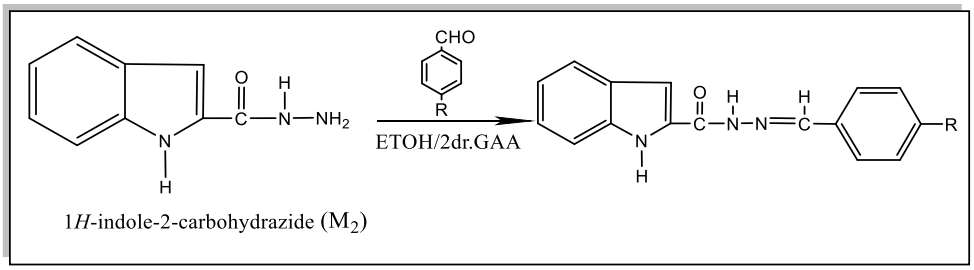
1*H*-indole-2-carbohydrazide (M_2)

The FT-IR spectrum of hydrazide derivative (M2), fig(3) show the stretching vibration band of (NH_2) group at (3454&3425)cm^{-1}, the stretching vibration band of (NH) group at (3332cm^{-1}) the carbonyl group of amide at(1691cm^{-1}) .

Synthesis Schiff bases (M3:N'-(4-chlorobenzylidene)-1H-indole-2-carbohydrazide,

M4:N'-(4-Florobenzylidene)-1H-indole-2-carbohydrazide)

The reaction between hydrazineamide derivative (M2) and benzaldehyde derivatives(4-chlorobenzaldehydeand4-floro benzaldehyde)respectivly in the presence(GAA 2 drops)as catalyst reagent to synthesisschiff



1*H*-indole-2-carbohydrazide (M_2)

R= F ,Cl

bases(M3,M4).

M_3 :N'-(4-chlorobenzylidene)-1H-indole-2-carbohydrazide

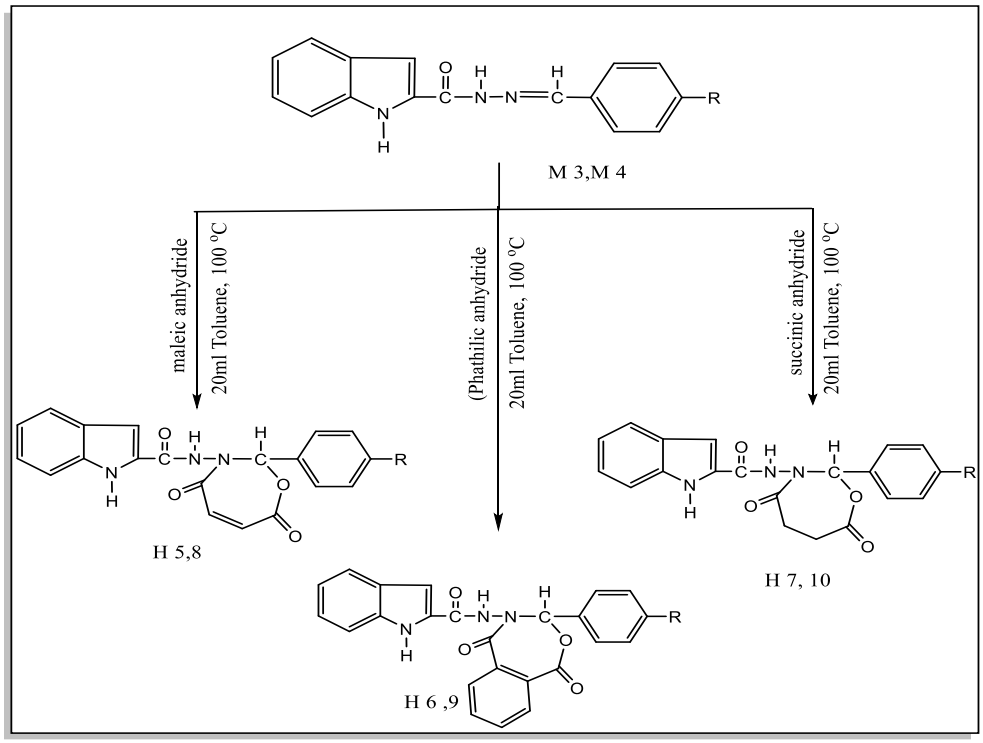
FT-IR(KBr) cm^{-1} ,ν3448(NHindole),ν3047($CH_{aromatic}$) , ν2995-2850($CH_{aliphatic}$), ν1624(C=ONH), ν1589($C=N_{imine}$),ν1566$(C=C)_{aromatic}$, ,(C-Cl)at(721.38)cm-1.

M_4 :N'-(4-Florobenzylidene)-1H-indole-2-carbohydrazide

FT-IR(KBr) cm^{-1} ,ν3419(NHindole),ν3059 ($CH_{aromatic}$) , ν2709 ($CH_{aliphatic}$), ν1631(C=ONH), ν1600($C=N_{imine}$),ν1508$(C=C)_{aromatic}$

Synthesis derivatives (H5-H10).

These compounds were synthesized according to the sequence in scheme(2)



R= F, Cl

scheme(2)Synthesis derivatives (H5-H10)

The Schiff bases (M3,M4) were reacted with (Phathilic anhydride, maleic anhydride and succinic anhydride) respectively to synthesis (H5-H10) .

These compounds were characterized by their melting points, FT.IR, ^{1}HNMR , ^{13}C-NMR and checked by TLC.

H_5:N-(2-(4-fluorophenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2H)-yl)-1H-indole-2-carboxamide

FT-IR(KBr)cm^{-1}Fig(4) ν3406(NHindole),ν3070($CH_{aromatic}$),2978 ($CH_{aliphatic}$),ν 1724(C=O)lactone ,1674(C=O)lactam.

^{1}H-NMR(DMSO), fig(11) 6.9-7.4(m,aromatic ring), 8.976(d,1H,N-CH), 9.310 (s,1H,NH_{amide}), 10.926 (s,1H,NH_{indol}) , ^{13}C-NMR(DMSO) ,fig(12)δ 107-124ppm C for C=C ring ,, δ130ppm C for N-CH_{ring}, δ177.788,169.308 ppm C for lactone and lactam respectively.

H_6:N-(3-(4-fluorophenyl)-1,5-dioxo-1,5-dihydrobenzo[e][1,3]oxazepin-4(3H)-yl)-1H-indole-2-carboxamide

FT-IR(KBr) cm^{-1}fig(6)ν3396(NHindole)ν3020($CH_{aromatic}$),2899($CH_{aliphatic}$),ν1697(C=O)lactone ,1664(C=O)lactam, ^{1}H-NMR(DMSO),fig(13)6.8-7.8(m,aromatic ring), 8.750(d,1H,N-CH), 9.740 (s,1H,NH_{amide}), 10.300 (s,1H,NH_{indol}) , ^{13}C-NMR(DMSO) ,fig(14) δ 125-133ppm C for C=C ring ,, δ155ppm C for N-CH_{amide}, δ 169.091 ,160.510 ppm C for lactone and lactam respectively.

. **H_7**:N-(2-(4-fluorophenyl)-4,7-dioxo-1,3-oxazepan-3-yl)-1H-indole-2-carboxamide

FT-IR(KBr) cmfig(7)v3211 (NHindole)v3051 ($CH_{aromatic}$),2943 ($CH_{aliphatic}$),v 1693(C=O)lactone ,1623(C=O)lactam, ^{1}H-NMR(DMSO),fig(15)6.8-7.9(m,aromatic ring), 8.880(d,1H,N-CH), 9.870 (s,1H,NH_{amide}), 10.335(s,1H,NH_{indol}) , ^{13}C-NMR(DMSO) fig(16), δ 107-135ppm C for C=C ring , δ153ppm C for N-CH_{ring}, δ 173.971 ,170.354 ppm C for lactone and lactam respectively..

H_8:N-(2-(4-chlorophenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2H)-yl)-1H-indole-2-carboxamide

FT-IR(KBr)cm^{-}
^{1}fig(8)v3354(NHindole),v3049(CHaromatic),2995(CHaliphatic),v1705(C=O)lactone ,1624(C=O)lactam, 1H-NMR(DMSO),fig(17)6.2-7.2(m,aromatic ring), 8.663(d,1H,N-CH), 9.773(s,1H,NHamide), 10.103 (s,1H,NHindol) , , ^{13}C-NMR(DMSO) ,fig(18) δ 128-134ppm C for C=C ring ,δ160ppm C for N-CHring, δ 176.112,168.140 ppm C for lactone and lactam respectively.

H_9:N-(3-(4-chlorophenyl)-1,5-dioxo-1,5-dihydrobenzo[e][1,3]oxazepin-4(3H)-yl)-1H-indole-2-carboxamide

FT-IR(KBr) cmfig(9)v3446 (NHindole)v3028 ($CH_{aromatic}$),2997 ($CH_{aliphatic}$),v 1697(C=O)lactone ,1625(C=O)lactam, ^{1}H-NMR(DMSO),fig(19)7.0-8.0(m,aromatic ring), 8.708 (d,1H,N-CH), 9.868 (s,1H,NH_{amide}), 10.317 (s,1H,NH_{indol}) , ,^{13}C-NMR(DMSO) ,fig(20) δ 128-1301ppm C for C=C ring ,, δ133ppm C for N-CH_{ring}, δ 178.199 ,169.109 ppm C for lactone and lactam respectively.

H_{10}:N-(2-(4-chlorophenyl)-4,7-dioxo-1,3-oxazepan-3-yl)-1H-indole-2-carboxamide

FT-IR(KBr)cm^{-1}fig(10)v3442(NHindole),v3051($CH_{aromatic}$),2995 ($CH_{aliphatic}$),v 1703(C=O)lactone ,1645(C=O)lactam, ^{1}H-NMR(DMSO),fig(21)7.0-7.8(m,aromatic ring), 8.697(d,1H,N-CH), 9.764 (s,1H,NH_{amide}), 10.006 (s,1H,NH_{indol}) , , ^{13}C-NMR(DMSO) ,fig(22) δ 105-132ppm C for C=C ring ,, δ164ppm C for N-CH_{ring}, δ 183.258 ,172.472 ppm C for lactone and lactam respectively. .

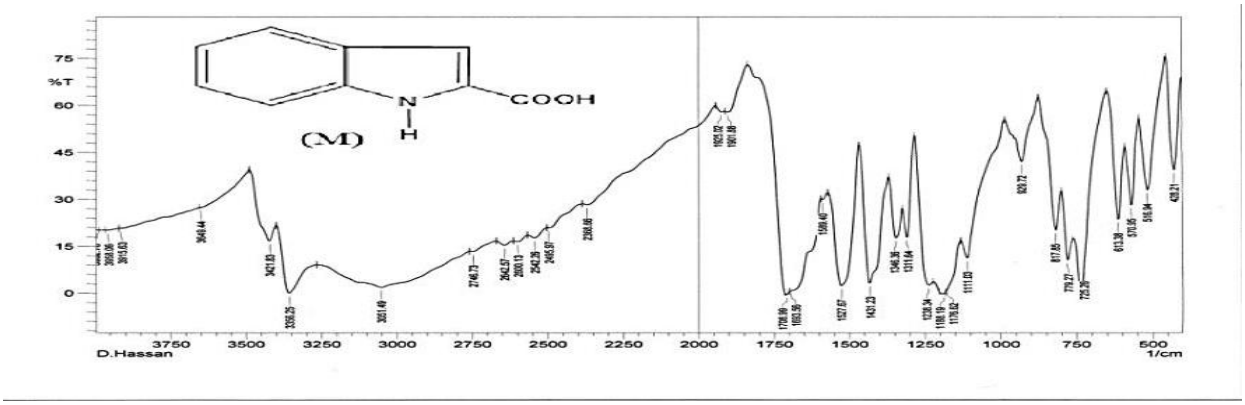


Figure 1: FT.IR spectrum of Indole-2-carboxylic acid compound (M)

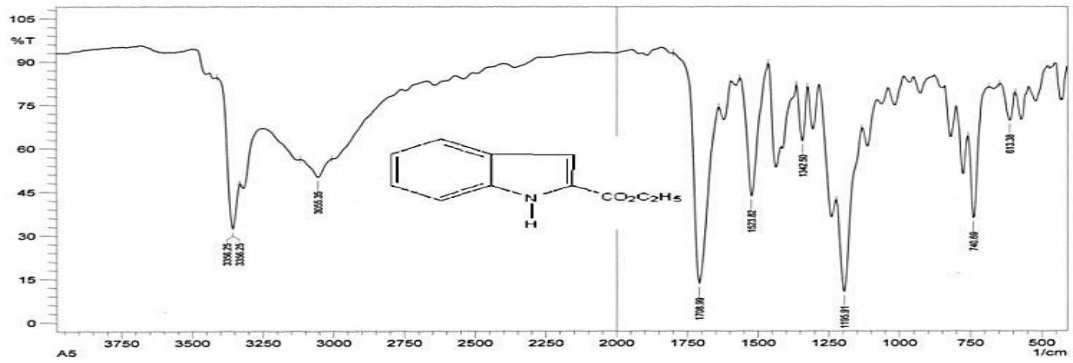


Figure 2: FT.IR spectrum of ester compound (M1)

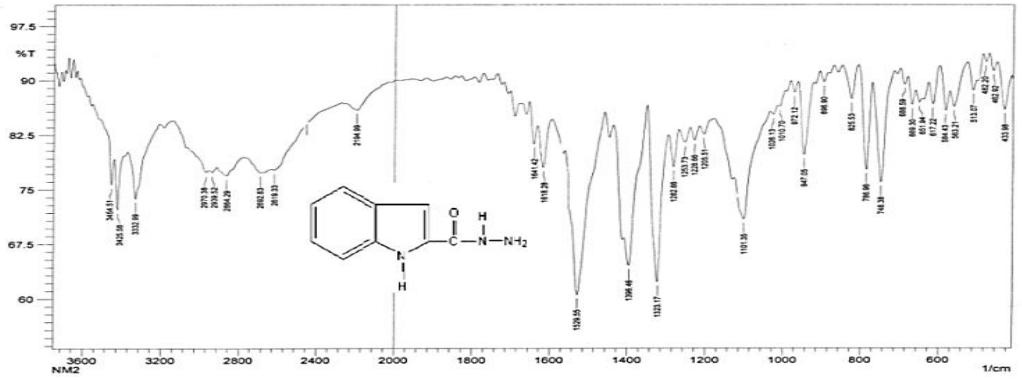


Figure 3: FT.IR spectrum of hydrazide compound (M2)

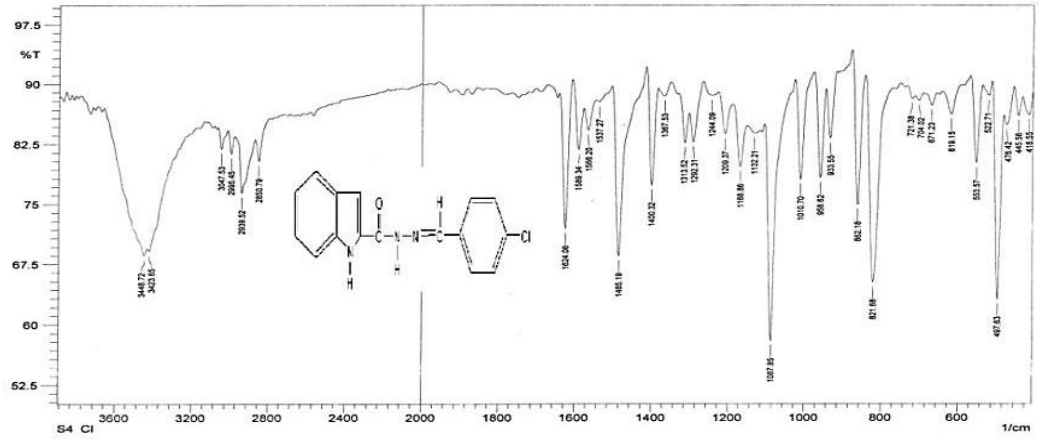


Figure 4: FT.IR spectrum of Schiff base compound (M3)

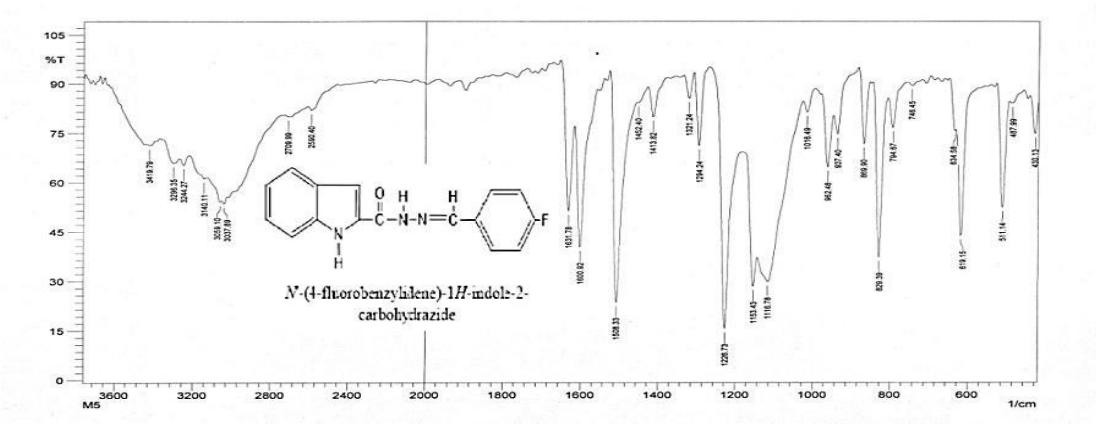
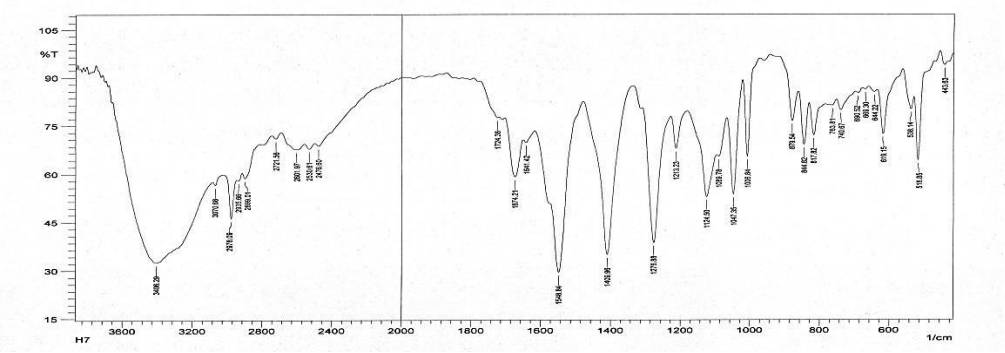


Figure 4: FT.IR spectrum of Schiff base compound (M4)



5 Figure:FT.IR spectrum of the compound (H5)

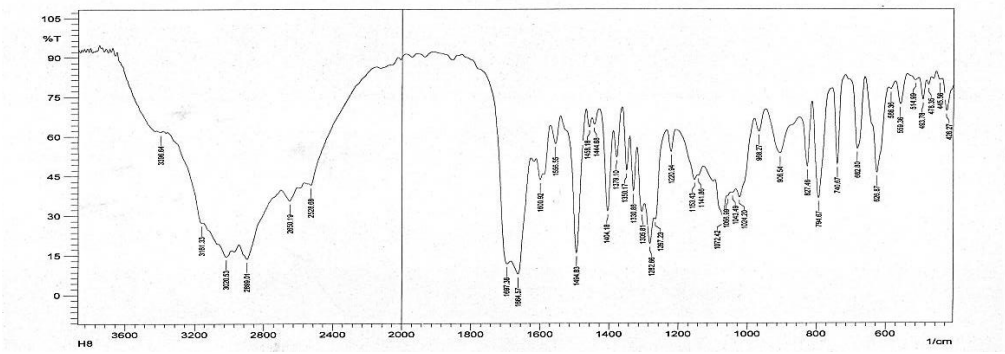


Figure6:FT.IR spectrum of the compound (H6)

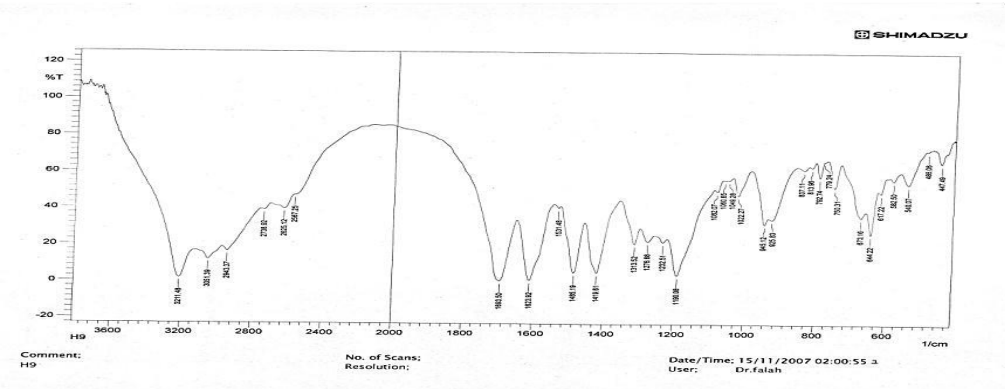


Figure 7:FT.IR spectrum of the compound (H7)

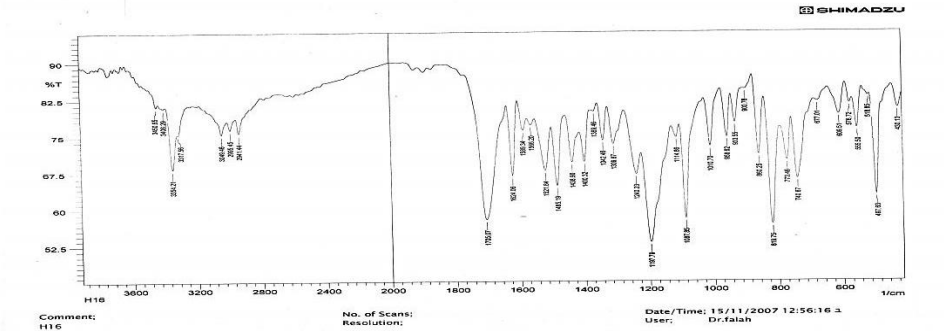


Figure8 :FT.IR spectrum of the compound (H8)

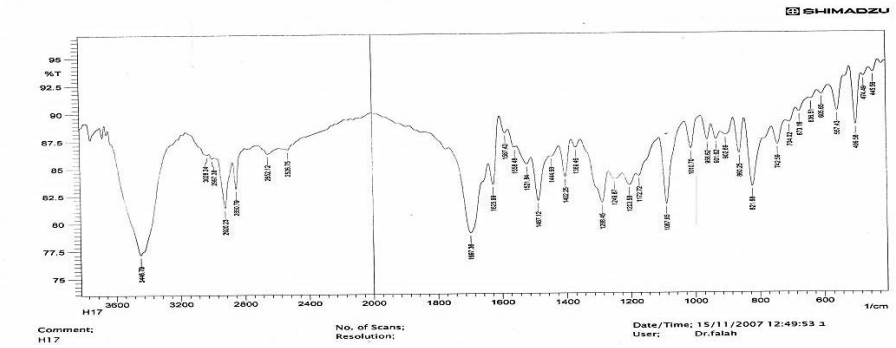


Figure9:FT.IR spectrum of the compound (H9)

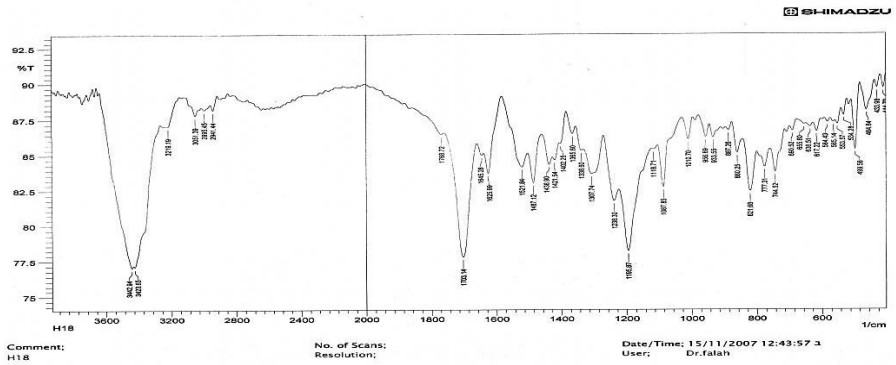
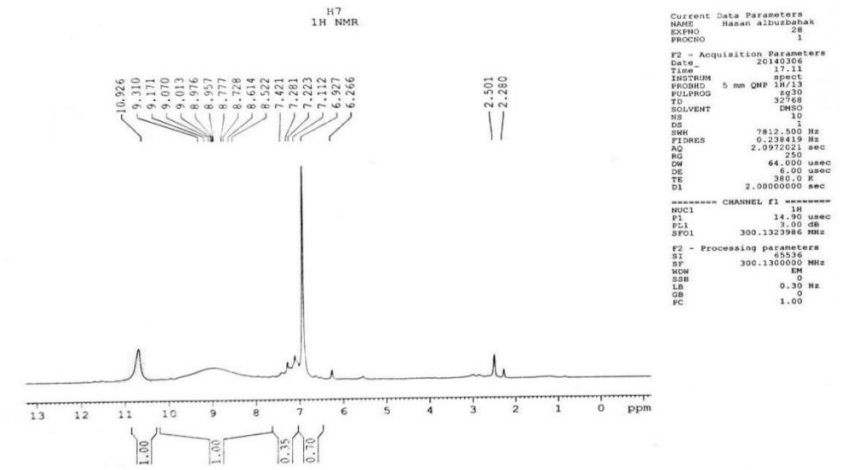
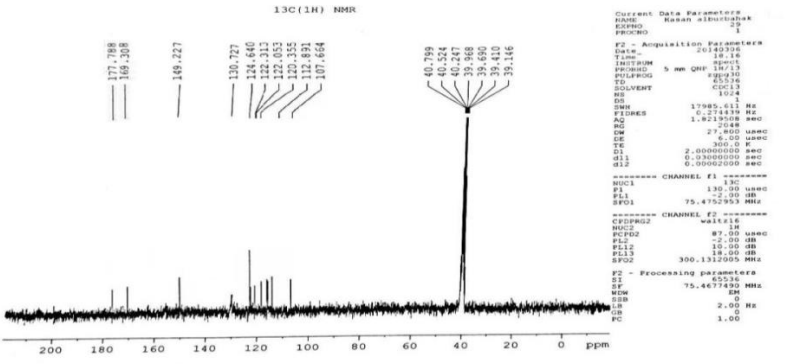


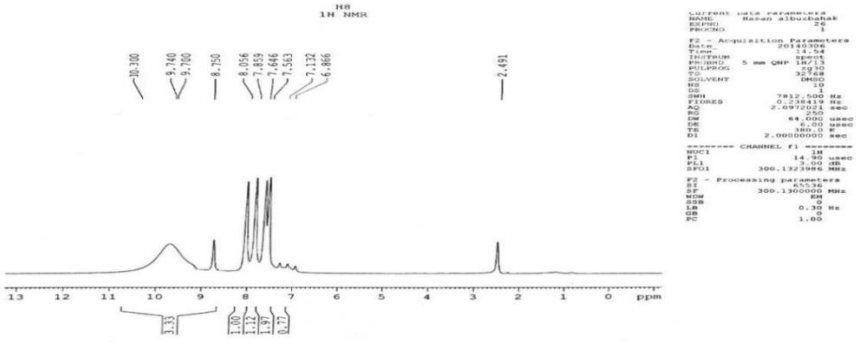
Figure10 :FT.IR spectrum of the compound (H10)



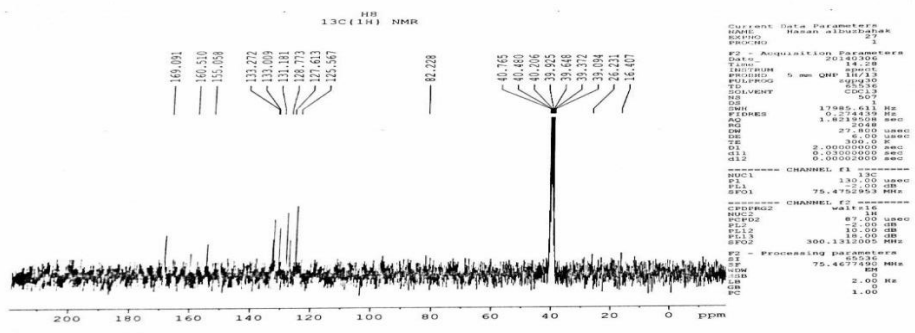
Fig(11): [1]HNMR spectrum of the compound H5



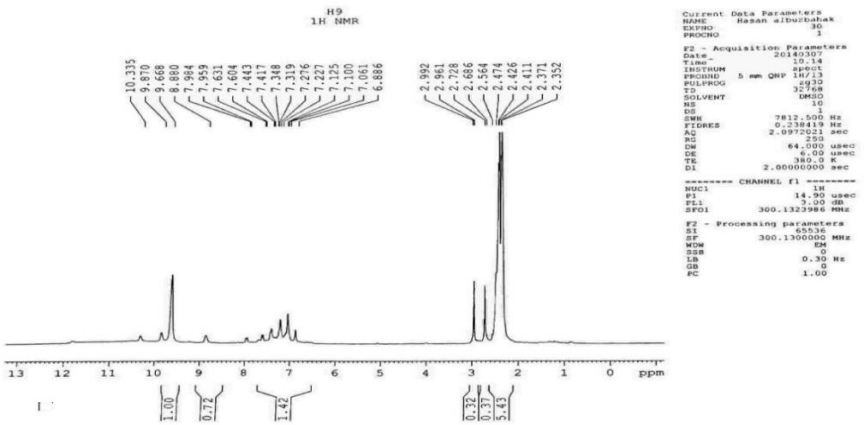
Fig(12) :[13]CNMR spectrum of the compound (H5)



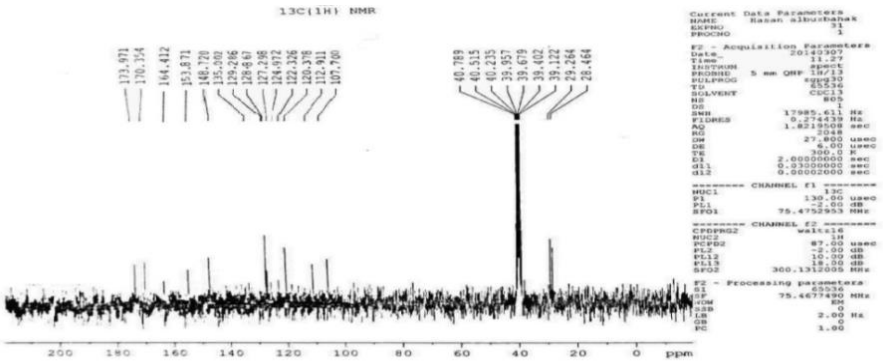
Fig(13):[1]HNMR spectrum of the compound(H6)



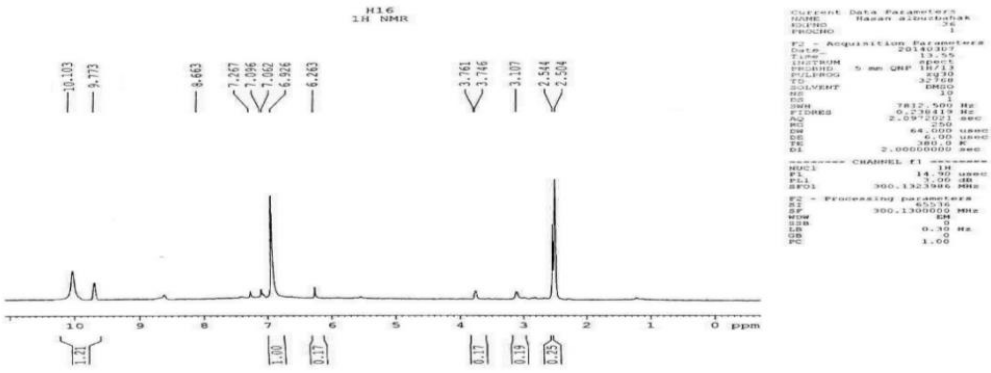
Fig(14) : [13]CNMR spectrum of the compound (H6)



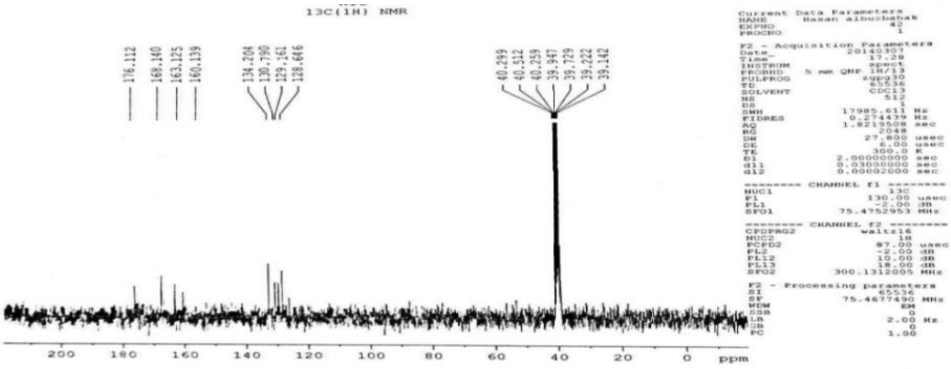
Fig(15):[1]HNMR spectrum of the compound(H7)



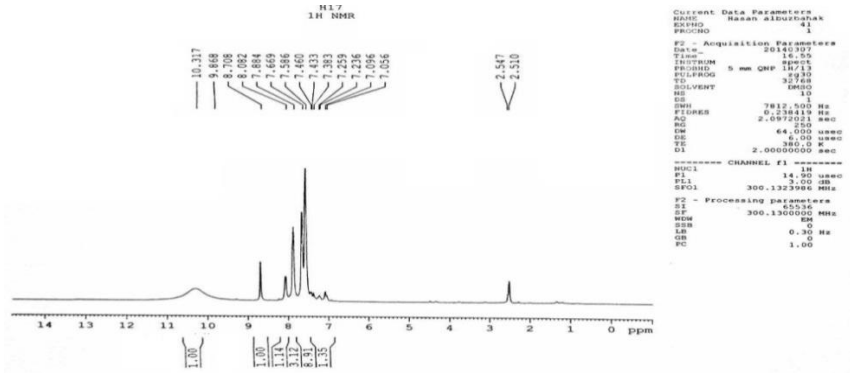
Fig(16) : [13]CNMR spectrum of the compound (H7**)**



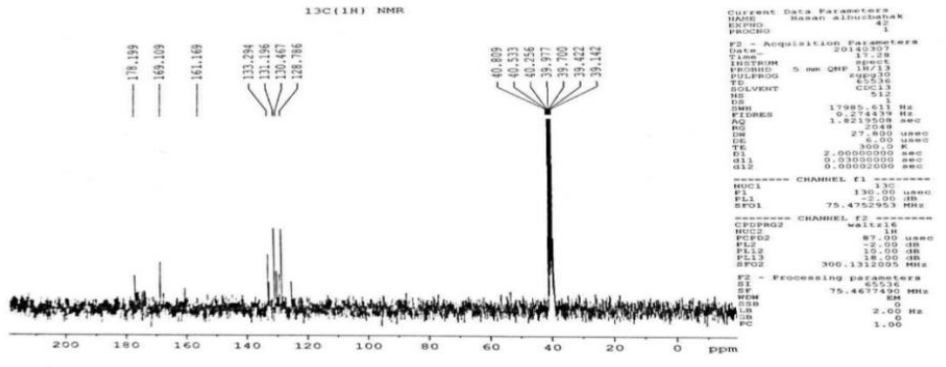
Fig(17):[1]HNMR spectrum of the compound H8



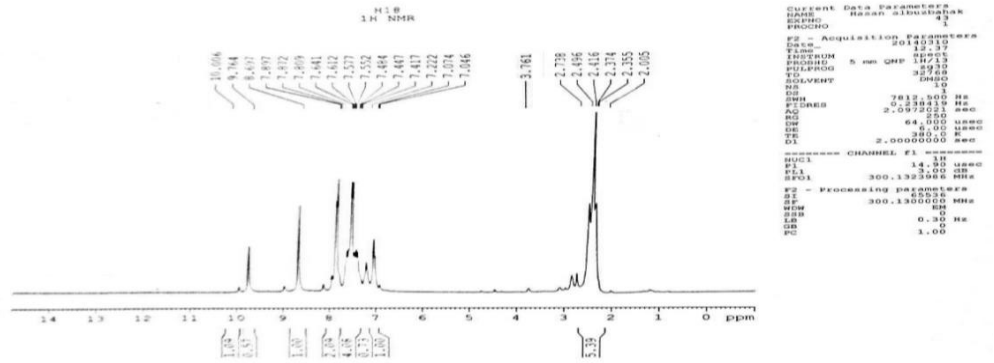
Fig(18) : [13]CNMR spectrum of the compound (H8)



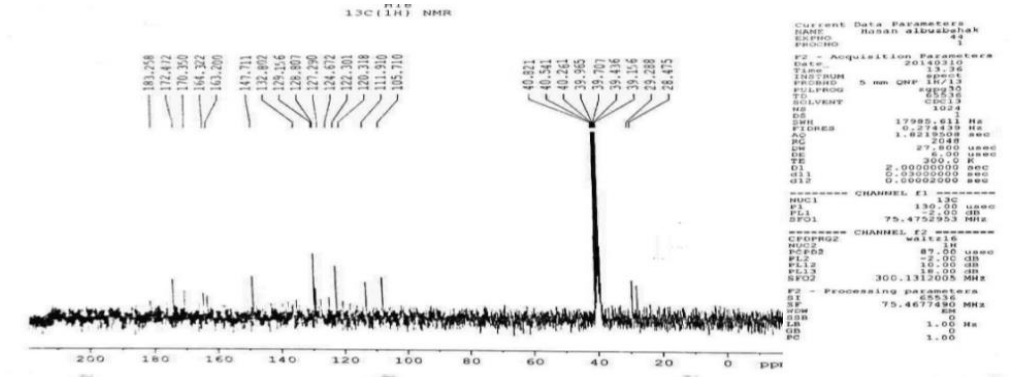
Fig(19) [1]HNMR spectrum of the compound(H9)



Fig(20) : ^{13}CNMR spectrum of the compound (H9)



Fig(21):^{1}HNMR spectrum of the compound(H10)



Fig(22) : ^{13}CNMR spectrum of the compound (H10)

Study of the biological activity of the compounds by paper technique disks.

Antibacterial activity has been conducted according to Kirby bauer[16] method, by using filter paper type (Whiteman NO.1) to prepared (200) pills, after that ,the pills put in the test tube with average of (5) pills for every tube then added (1 mml) from syntheses solution .

Preparing the nutrient agar:

The nutrient agar was prepared by 37 gm from agar and dissolved in one liter of distilled water and heating the mixture, the resulting agar was sterilized by the autoclave at $121C^0$ for 15 minutes .the surface of the agar was left for dryness and then used in the following work.

Preparing the bacterial inoculums

Four type of isolated and diagnosed bacterial inoculum .these bacteria were cultivated and incubated overnight at $37C^0$,then isolated by the gram stain and separated to gram positive and gram negative bacteria, in clued

1-staphylococcus :gram positive

2- Enterococcus faecalis : gram positive

3- Proteus mirabilis:gram negative

4 -klebsiella pneumonia :gram negative

Antimicrobial Activity

An antibacterial activity has been managed according to Kirby Bauer method ,the prepared compounds were projected for their antibacterial activity against gram negative bacteria(*klebsiella pneumonia, Proteus mirabilis)* , gram positive (*staphylococcus, Enterococcus faecalis,)* ,the result are given in table (2) ,The compound H_5 was given high inhibition against Proteus mirabilis*: gram negative*, staphylococcus.

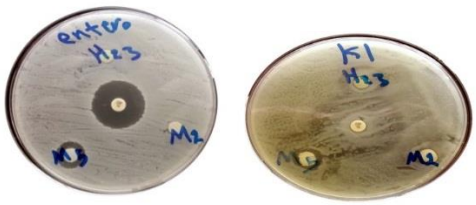
Table (2):

Type of bacteria / Comp.NO.	inhibition zone(mm) $1x10^{-5}$M ,$1x10^{-4}$M ,$1x10^{-3}$M			
	klebsiella pneumonia	***Staphylococcus***	***Enterococcus faecalis***	***Proteus mirabilis***
M_1	-	-	-	-
M_2	-	-	-	-
M_3	-	-	-	-,-,5
M_4	-, -, 5	-, -, 8	-,-,5	-,-,4
H_5	-,-,4	-,-,8	-	5,12,18
H_6	-	-,-,5	-	-,-,5
H_7	-	-,-,5	-	-,-,6
H_8	-	-,-,6	-	-
H_9	-	-	-	-
H_{10}	-	-,-,9	-,-,5	-

*Staphylococcus*Proteus mirabilis

H7:N-(2-(4-fluorophenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2H)-yl)-1H-indole-2-carboxamide

H12:N-(2-(4-chlorophenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2H)-yl)-1H-indole-2-carboxamide



Enterococcus faecalis-klebsiell a pneumonia

M5: N'-(4-Florobenzylidene)-1H-indole-2-carbohydrazide

CONCLUSION

In the present study preparation of Some Heterocyclic compounds From Indole Derivative, which arecharacterized by the spectral measurements (IR ,^{1}H NMR ,^{13}C NMR). We conclude that it is possible to be Indole derivative antibiotics effectiveness of the compounds is vital in the futurecompared with drugs that contain derivatives.

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