Synthesis and Characterization of New Azo isoxazole and pyrozole derivatives and Studies the biological activity

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Abstract:-

Aseries of new substituted phenyl azo isoxazoline-5-one (d-f) and substituted phenyl azo pyrozoline-5-one (g-i) have been synthesized from the substituted phenyl azo pentan 2,4-dion (a-c).The Structure of all new compounds (a-i) were fullyidentifed by elemental analysis and FT.IR spectra but som of new compounds were chaarecterized by HNMR spectra,for the new compounds biological activity.

Key word:isoxazoline-5-one,pyrozoline-5-one synthesis

الخلاصة:-

يتضمن البحث تحضير سلسلة جديدة من مركبات ازو-ايزواوكسازولين-5-اون (d-f) ومركبات فنيل ازوبايروزولين-5-اون (g-i)، وحضرت هذه المركبات من معوضات مركبات فنيل ازو بنتان 2,4-دايون (a-c)، جميع هذه المركبات شخصت بطيف الاشعة تحت الحمراء والتحليل الدقيق للعناصر وبعضها شخص بوساطة طيف الرنين النووي المغناطيسي، كما تمت دراسة الفعالية البايلوجية للمركبات المحضرة.

Introdaction:-

Azo compounds constitatafe one of the largest classes of industrially synthesized organic compounds.aliphatic azo compounds like azo bisisobutylonitrile (ALBN), can be used as radical initiators in polymerization of alkenes to make plastics(1) .Aromatic azo compounds are used as acid base indicators such as methyl red ,methyl orange and congo red(2) .Mkpenie et al(3) .have prepared 1-(4-methyl phenyl azo)-2-naphthal and study its in hibition effect on the biological activity activities of some bacteria like E.coli and S.aureus .Hetrocylic compound containing nitrogen,carbon and oxygen such as pyrazole derivatives(4-6) and isoxazol derivatives(7-11) ,have been reported to have devieres biological activities are antiviral(12-17) .This paper reports the synthesis of som new isoxazole and pyrazole derivatives.

Experimantal Section

Meterials:-

The necessary chemical were purch ased form merck and fluka :ethanol absolute, methanol absolute,hydrochloric acid ,m-Amino acetophenone,2,4-dichloro aniline ,m-methoxy aniline ,sodium nitrite,ethyl aceto acetate ,benzene,hydrazine hydrite,hydroxyl amine hydrochloride.

Measurments:-

Melting point was determined by stuart melting points apparatus.T.L.C. was run silica gel plates using Methanol :Benzeen (4:2) as developing solvent for the puring of the compounds .FT.IR spectra were recorded on SHIMDAZU FT.IR 8000 serises spectro photometer by using KBr pellet tectique H^1-NMR Spectra were recorded on Bruker,Ultra Shield 300 MHz,Switzerland .the elemental analysis were performed by Euro EAElemental Analyser the micro analytical univ.Kufa.

Methods:-

Synthesis of substituted azo ethyl aceto acetate compounds(18)

The compounds(a,b,c) were prepared by coupling substitute aniline with acetoacetate in alkaline alcoholic solution .Adiazonium solution was prepared by taking (0.01mole) of (4-amino acetophenon or methoxy aniline or 2,4dichloro aniline) in 20 ml of distilled water and 10 ml of concentration hydrochloric acid ,then adding sodium nitrite solution at (0-5) c° with stirring over mixture of ethyl aceto acetate (0.01)mol in ethanol (20ml) and 10 ml of sodium hydroxide solution (10%) at (0-5) c°.The mixture was allowed to stand for 24hr .The precipitate was filtered off washed ,dried and recrystallized ,scheme1.

Synthesis of substituted phenyl azo isoxazol-5-ones compounds(d-f)

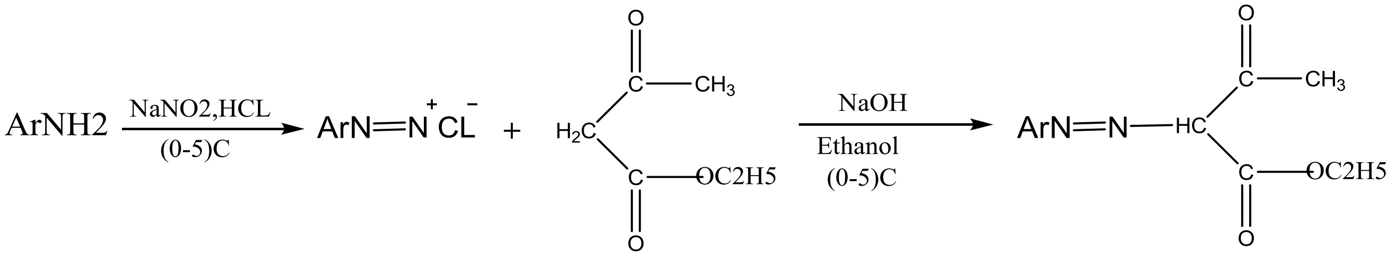
In the second step of this study ,Adyes of (a-c) ,(0.015 mole)in 30 ml of ethanol and hydroxyl amine hydrochloride (0.015) mole in the presence ammonium acetate was heated under reflux for 4 hr ,then coold at room temperature .The precipitate was then filtered off,washed with water ,dried at 70 c° in an oven to give substituted phenyl azo isoxazol-5-ones (d-f), scheme 2.

Synthesis of substituted phenyl azo pyrozoline-5-ones compounds(g-i)

Hydrizine hydrate (0.015mol) was added portion wise to adyes of (a-c) in 40 ml ethanol .The reaction was carried out in reflux for 5hrs .The formed solid was filtered off washed and dried to give substituted phenyl azo pyrozoline -5-ones (g-i), scheme(3).

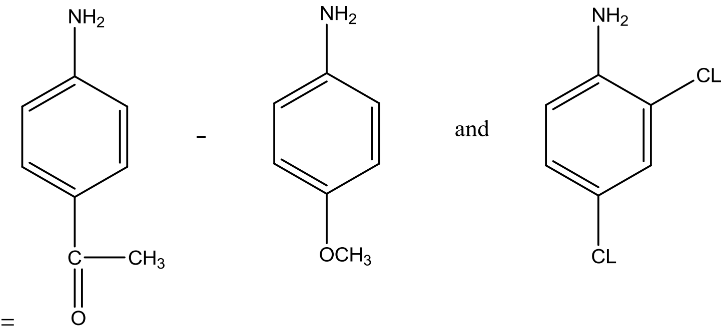
Checlcing of Biological activity of compounds make by method by paper disc.

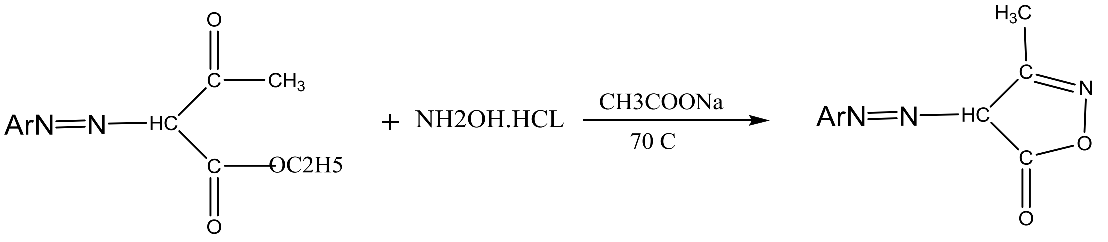
Paper discx made by flter paper whiteman number one after cutting it into smaller discs ,then sterilized by A utoglave for 15 mints ,concentration of $1*10^{-3}$M for compounds for which B.activity wanted to be measured by dissolving the Suitable weight of each compounds in 1ml of ethanol ,then the paper disc emerged in 10 ml .100 disc in 10 ml of the test solution ,then dried away from air in electrical oven at 37 cº



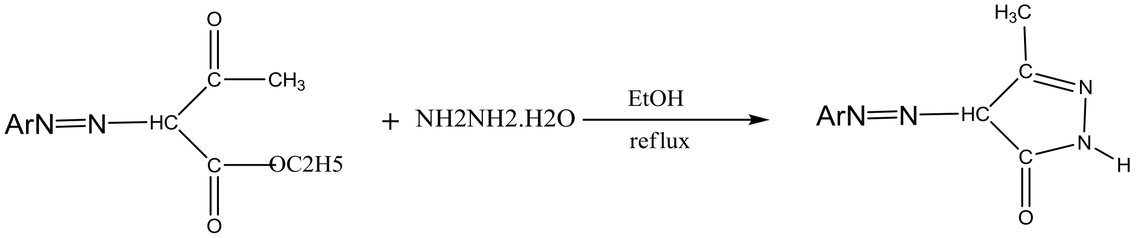
Scheme 1.Synthesis of the compounds (a-c)

Where Ar=





Scheme 2.Synthesis of the compounds (d-f)



Scheme 2.Synthesis of the compounds (g-i)

Results and Discussion.

a:Ethyl-2-[(3-acetyl phenyl) diazenyl]-3-oxo butanoate

Orange crystals,yield(66%),m.p(142-143)c^{o},R$_{f}$ (Benzen:methanol)(2:4)=0.62, FT.IRcm^{-1},1700-1720(C=O,ketone ,1715(C=O,ester)(19),1520(-N=N-),3000-3020 (C-H,aromatic)2800-2840(C-H,aliphatic)1320(C-O,ester) (19) 1550(C=C,aromatic)

Analysis :$C_{14}H_{16}N_2O_4$(288) calc. C:26.50 H:5.55 N:9.72
Found C:26.11 H:5.11 N:9.43

b:Ethyl-2-[(methoxy phenyl)diazenyl]-3-oxo butanoate

Red crystals,yield(59%),(Benzen:methanol)(2:4)=0.81, m.p(135-136) c^{o}, FT.IR cm^{-1}**:**1710-1715 (C=O,ketone)1730(C=O,ester) 1660(N=N,azo), 1500(C=C,aromatic),1250(C-OCH_3,ether),3000-3010(C-H,aromatic).Analysis: $C_{13}H_{16}N_2O_4$(264),calc. C:59.09 H:6.06 N:10.60
Fond: C:59.01 H:6.01 N:10.23

c:Ethyl-2-[(2,4dichloro phenyl) diazenyl]-3-oxo butanoate

Orange crystals,yield(67%),(Benzen:methanol)(2:4)=0.75, m.p(183-184) c^{o}, FT.IR cm^{-1}**:**1710-1720 (C=O,ketone)1735(C=O,ester) 1620(N=N,azo), 1580(C=C,aromatic), 3040-3070(C-H,aromatic),2890(C-H,aliphatic),600-800(C-Cl),HNMR^{1},C:(7.3-7.3) ppm,m, (3H,arom), (1.2-1.4)ppm,q, (3H) methyl ,2.3ppm ,S, (3H) acetyl,3.3ppm (1H) methane,and (4.3-4.4) ppm,t ,2H
Analysis: $C_{12}H_{15}N_2O_3Cl_2$(290),calc. C:58.77 H:4.13 N:9.65
Fond: C:58.23 H:4.04 N:9.13

d:4-[(3-acetyl phenyl)diazenyl]-3-methyl isoxazol-5-(4H)-one

Brown crystals,yield(61%),(Benzen:methanol)(2:4)=0.71, m.p(159-160) c^{o}, FT.IR cm^{-1}**:**1700-1720 (C=O,ketone)1735(C=O,ester) 1620-1640(N=N,azo), 1600(C=C,aromatic),1540(C=N,Isoxazole ring)$^{(18)}$, 3100-3150(C-H,aromatic)$^{(20)}$,2850-2900(C-H,aliphatic),600-800(C-Cl),HNMR^{1}, (1.9-2.4) ppm,d,3H,proton of acetyl group ,6.3 ppm S,protons of methyl group of isoxazole , (7.2-8.1) ppm,m,prpton of phenyl group,2.7 ppm ,s,proton of methaine group Analysis: $C_{12}H_{11}N_3O_3$(245),calc. C:58.77 H4.48 N:17.14,found C:58.18 H:4.11 N:17.13

e:4-[(3-methoxy phenyl)diazenyl]-3-methyl isoxazol-5-(4H)-one

Orange crystals,yield(64%),(Benzen:methanol)(2:4)=0.64, m.p(167-168) c^{o}, FT.IR cm^{-1}**:** 1730(C=O,ester) 1640(N=N,azo), 1620(C=C,aromatic),1520(C=N,Isoxazole ring) , 3100-3120(C-H,aromatic)$^{(19)}$,2840-2900(C-H,aliphatic),600-800(C-Cl), Analysis: $C_{11}H_{11}N_3O_3$(233),calc. C:65.65 H:4.72 N:18.02,found C:65.32 H:4.52 N:18.01

f:4-[(2,4-di chloro phenyl)diazenyl]-3-methyl isoxazol-5-(3H)-one

Orange crystals,yield(57%),(Benzen:methanol)(2:4)=0.83, m.p(179-180) c^{o}, FT.IR cm^{-1}**:** 1730(C=O,ester) , 152 0(N=N,azo), 1600(C=C,aromatic),1545(C=N,Isoxazole ring), 3070(C-H,aromatic), 2980(C-H,aliphatic),600-800(C-Cl),HNMR^{1},
Analysis: $C_{10}H_7N_3O_2Cl_2$(271),calc. C:44.28 H:2.58 N:15.49,found C:44.12 H:2.12 N:15.12

g:4-[(3-acetyl phenyl)diazenyl]-5-methyl 2,4-dihydro -3H-pyrozol-3-one

Orange crystals,yield(58%),(Benzen:methanol)(2:4)=0.66, m.p(165-164) c^{o}, FT.IR cm^{-1}**:**1720 (C=O,ketone),1500(N=N,azo), 1600(C=C,aromatic),3290 (N-H,pyrozole ring) $^{(18)}$,, 1640(C=N,pyrozole ring), 3070 (C-H,aromatic) 2980(C-H,aliphatic)
Analysis: $C_{12}H_{12}N_4O_2$(244),calc. C:59.01 H:4.91 N:22.95, found C:59.00 H:4.21 N:22.65

h:4-[(3-methoxy phenyl)diazenyl]-5-methyl 2,4-dihydro -3H-pyrozol-3-one

yellow crystals,yield(62%),(Benzen:methanol)(2:4)=0.82, m.p(186-187) c^{o}, FT.IR cm^{-1}**:**3290-3330(N-H),1710 (C=O,ketone) ,1620(O-CH_3)1625(N=N,azo), 1520(C=C,aromatic),3290 (N-H,pyrozole ring) $^{(18)}$, 1620(C=N,pyrozole ring), ,3080 (C-H,aromatic) 2980(C-H,aliphatic), HNMR^{1}, (7.1-7.9)ppm,m,4H aromatic

protone ,6.6 ppm,s,protone of metheine,3.8 ppm,s,proton of NH,3.4ppm ,s,protone of methoxy group ,2.5 ppm ,s, proton of solvent and 2.2 ppm ,s, proton of methyl group
Analysis: $C_{11}H_{12}N_4O_2$ (232),calc. C:56.89 H:5.17 N:24.17, found C:56.43 H:5.08 N:24.06

i:4-[(2,4-dichloro phenyl)diazenyl]-5-methyl 2,4-dihydro -3H-pyrozol-3-one
Orange crystals,yield(55%),(Benzen:methanol)(2:4)=0.68, m.p(162-163) c°, FT.IR cm^{-1}:3200-3400(N-H),1715 (C=O,ketone) , 1600(N=N,azo), 1520(C=C,aromatic), 1625(C=N,pyrozole ring), ,3080 (C-H,aromatic) 2980(C-H,aliphatic),1530(C=C,aromatic),600-800(C-Cl).
Analysis: $C_{10}H_8N_4OCl_2$ (270),calc. C:44.44 H:2.96 N:20.64, found C:44.20 H:2.14 N:20.12

Biological Activity :

According to the Results obtained from the table 4 ,we used four type of Bacteria 2 cram positive and 2 cram negative,at concentration 1*10-3,we founed that compounds (i,g,f,d,c,a) had weak resistance 6-9 mm of bacteria type S.aureus,other types of bacteris,all these compounds have no restance against it.

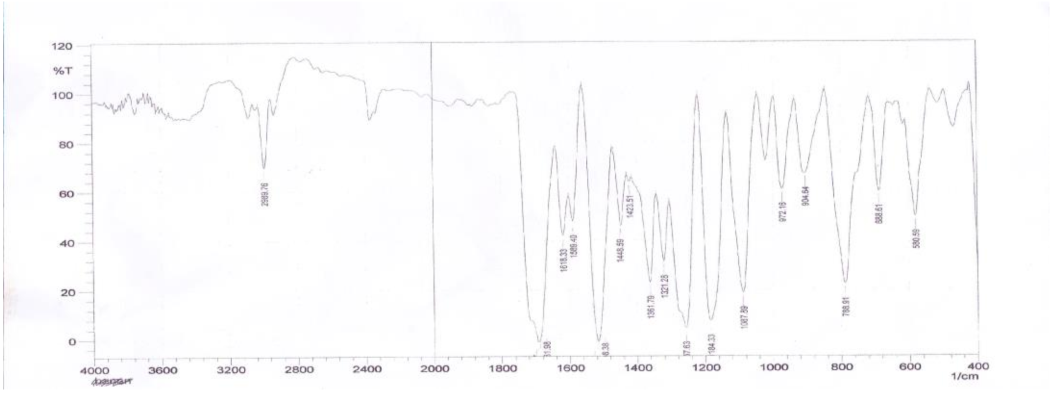


Fig.(1) FT.IR spectra for comp.(a)

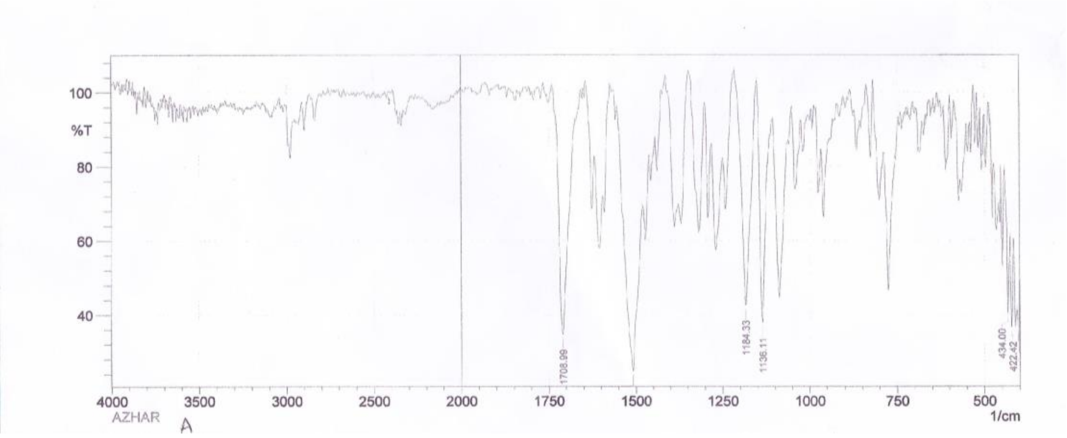


Fig.(2) FT.IR spectra for comp.(b)

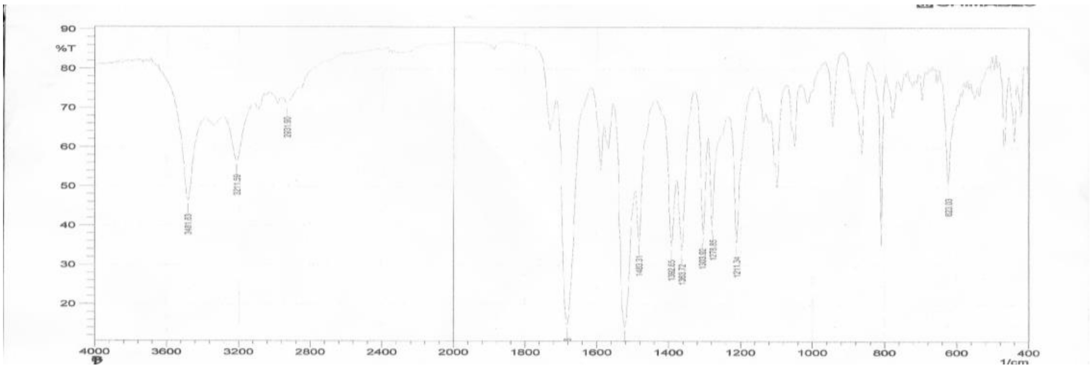


Fig.(3) FT.IR spectra for comp.(c)

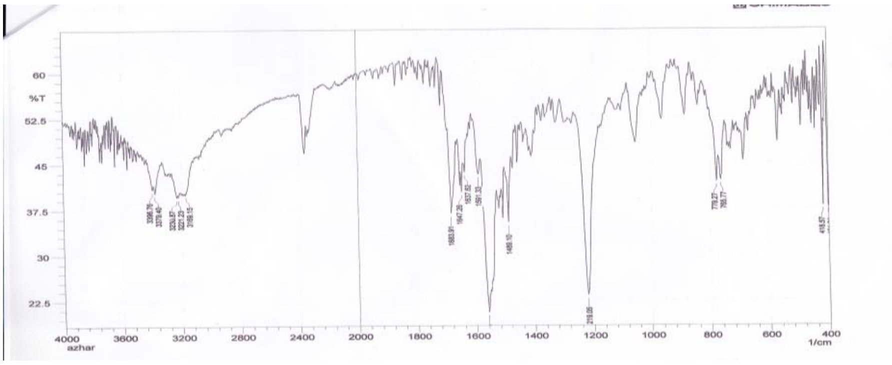


Fig. (4) FT.IR spectra for comp.(d)

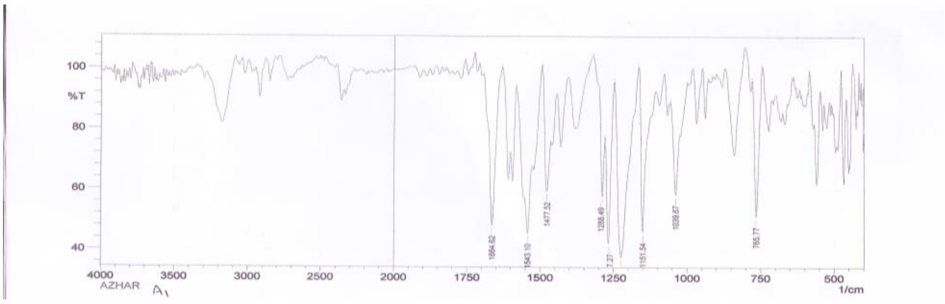


Fig.(5) FT.IR spectra for comp.(e)

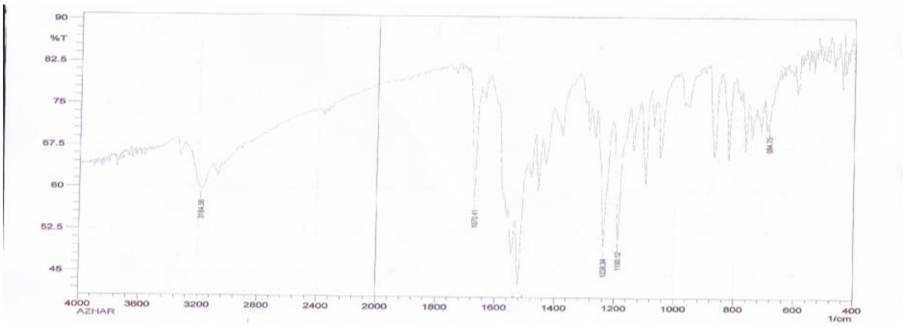


Fig.(6) FT.IR spectra for comp.(f)

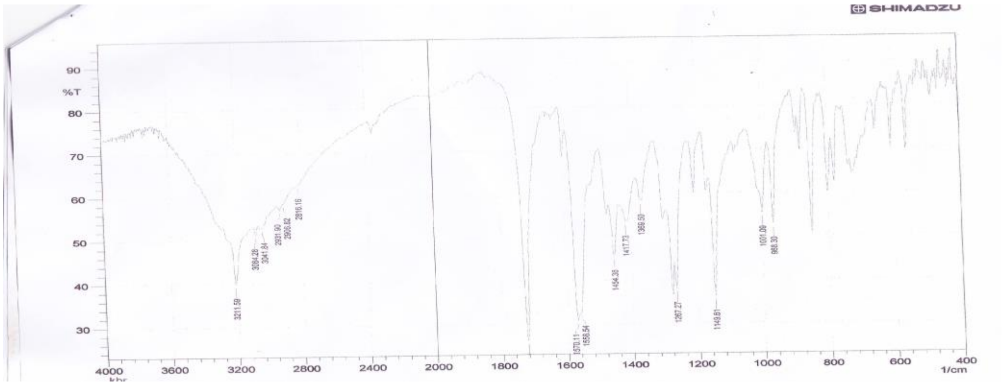


Fig.(7) FT.IR spectra for comp.(g)

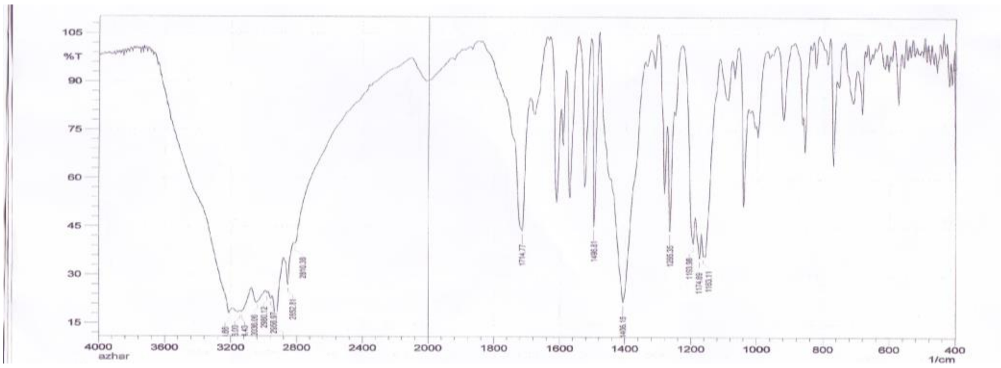


Fig.(8) .FT.IR spectra for comp.(h)

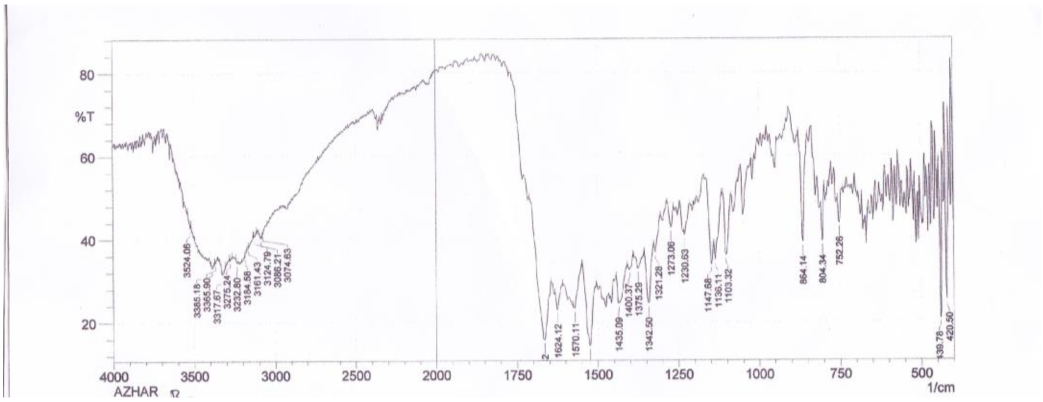
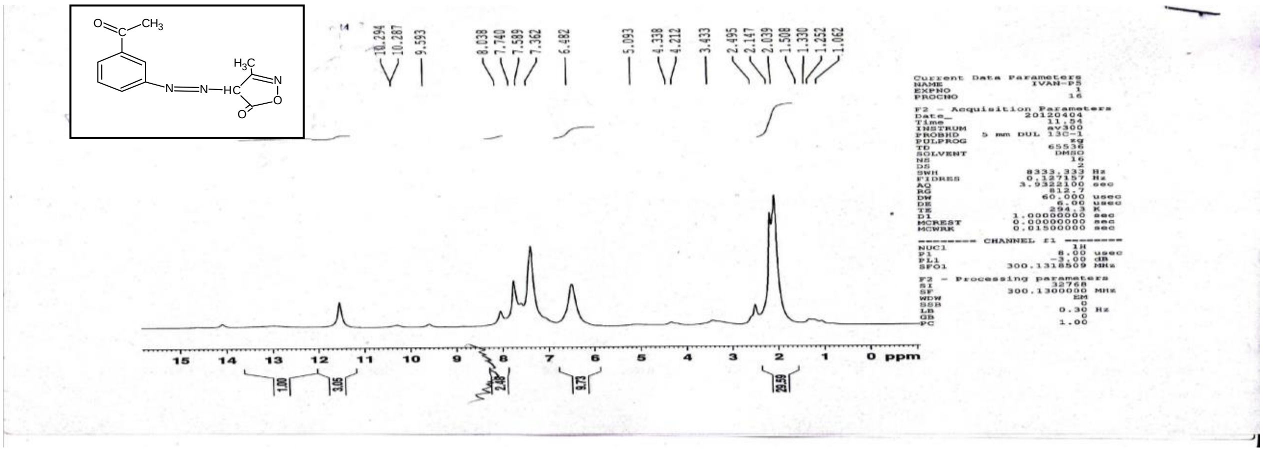


Fig.(9) FT.IR spectra for comp.(i)



Fig(10) HNMR Spectrum for compound (d)

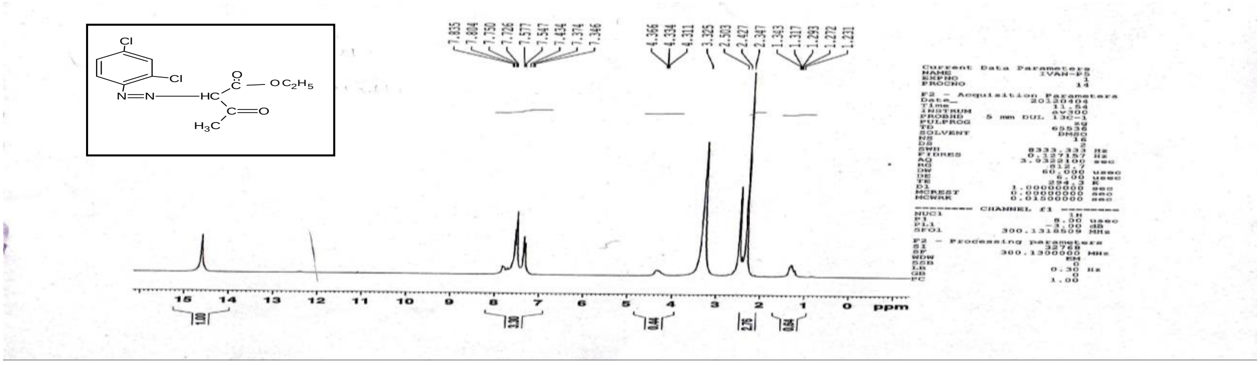
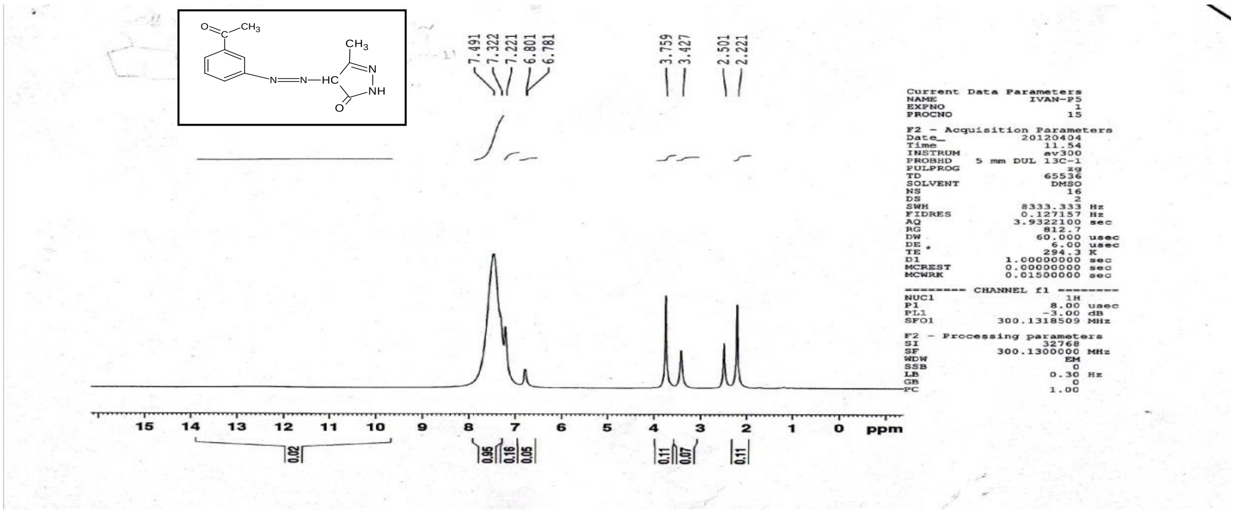


Fig (11) HNMR Spectrum for compound (c)



No.	M.F	M.wt Gm\mol	Yield %	M.P c^{o}	R_F(4:2) Benzene:Methanol	Color
a	**$C_{14}H_{16}N_2O_4$**	**288**	**66**	**142- 143**	**0.62**	**Orange**
b	**$C_{13}H_{16}N_2O_4$**	**264**	**59**	**-135 136**	**0.81**	**Red**
c	**$C_{12}H_{15}N_2O_3Cl_2$**	**290**	**67**	**-183 184**	**0.75**	**Orange**
d	**$C_{12}H_{11}N_3O_3$**	**245**	**61**	**-159 160**	**0.71**	**Brown**
e	**$C_{11}H_{11}N_3O_3$**	**233**	**64**	**-167 168**	**0.64**	**Orange**
f	**$C_{10}H_7N_3O_2Cl_2$**	**271**	**57**	**-179 180**	**0.83**	**Orange**
g	**$C_{12}H_{12}N_4O_2$**	**244**	**58**	**-164 165**	**0.66**	**Orange**
h	**$C_{11}H_{12}N_4O_2$**	**232**	**62**	**186- 187**	**0.82**	**Yello**
i	**$C_{10}H_8N_4OCl_2$**	**270**	**55**	**-162 163**	**0.68**	**Orange**

Fig (12) HNMR Spectrum for compound(h)

Table(1) physical and analytical data of compound(a-i)

Table 2 H-NMR Spectra of compounds (c,d,h)

No.	M.F	C% Calcul. Found	H% Calcul Found	N% Calcul Found
a	$C_{14}H_{16}N_2O_4$	26.50 26.10	5.55 5.11	9.72 9.43
b	$C_{13}H_{16}N_2O_4$	59.09 59.01	6.06 6.01	10.60 10.23
c	$C_{12}H_{15}N_2O_3\,Cl_2$	58.77 58.23	4.13 4.04	9.65 9.13
d	$C_{12}H_{11}N_3O_3$	58.77 58.18	4.48 4.11	17.14 17.13
e	$C_{11}H_{11}N_3O_3$	65.65 65.32	4.72 4.52	18.02 18.01
f	$C_{10}H_7N_3O_2Cl_2$	44.28 44.12	2.58 2.11	15.49 15.12
g	$C_{12}H_{12}N_4O_2$	59.01 59.00	4.91 4.21	22.95 22.65
h	$C_{11}H_{12}N_4O_2$	56.89 56.43	5.17 5.08	24.13 24.06
i	$C_{10}H_8N_4OCl_2$	44.44 44.20	2.96 2.14	20.74 20.12

Table 3 Elemental analysis of (a-i) compounds

No	
c	7.3-7.9ppm,m,3H,aromatic,1.2-1.4ppm,q,3H methyl,2.3ppmm,s,3H,actyl,3.3 ppm,1H,methane and 4.3-4.4ppm,t,2H
d	1.9-2.4ppm,d,3H,acetyl group ,6.3ppm,s,methyl group of isoxazol,7.2-8.1ppm ,m,proton of phenyl group,2.7ppm,s,methaine group
h	7.1-7.9ppm,m,4H,aromatic proton ,6.6ppm methane,3.8ppm ,s,NH,3.4ppm,methoxy ,2.5ppm,s,solvent,2.2ppm,s,methyl group,

Table 4 the FT-IR Spectral data of the compounds (a-c)

Comp.	Keton νC=O	Azo νN=N	Ester νC=O	Ester νC-O	Aromat. νC=C	Aromat. δC-H	Aliphat. δC-H
a	1720	1520	1715	1320	1550	-2800 2840	1320
b	1710- 1715	1660	1730	1315	1500	-3000 3010	2890
c	1715	1620	1735	1320	1580	-3040 3070	=

Table 5 the FT-IR Spectral data of the compounds (d-f)

Comp.	Ester νC=O	Azo νN=N	Ester νC-O	Aromat. νC=C	Aromat. δC-H	Aliphat δC-H	Isoxazol C=Nν
d	1735	-1620 1640	1330	1600	-2850 2900	-3100 3150	1540
e	1730	1640	1335	1620	-2840 2900	-3100 3120	1520
f	=	1500	1320	1600	2070	2980	1540

Table 6 the FT-IR Spectral data of the compounds (g-i).

Comp.	Keton νC=O	Azo νN=N	Aromat. νC=C	Aromat. δC-H	Aliphat δC-H	Pyrazole N-H	Pyrazole νC=N
g	1720	1500	1600	2980	3070	3290	1640
h	1710	1625	1520	=	3080	=	1620
i	1715	1600	=	=	=	=	1625

Table7.The Biological activity of the compounds(a-i)

NO. Comp.	S.aureus	E.coli	k.pneumonia	P.aeruginosa
a	+	-	-	-
b	-	-	-	-
c	+	-	-	-
d	+	-	-	-
e	-	-	-	-
f	+	-	-	-
g	+	-	-	-
h	-	-	-	-
i	+	-	-	-

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