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Synthesis , Identification And Evaluation Of Antibacterial Activity For Some New Heterocyclic Derivatives From 4-Methoxy-2-Nitroaniline

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Synthesis , identification and evaluation of antibacterial activity for some new heterocyclic derivatives from 4-methoxy-2-nitroaniline

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ABSTRACT

This research involved synthesis. novel heterocyclic derivatives (quinazoline and thiazinone) derivatives , this compounds prepared from starting react (4-methoxy-2-nitroaniline) with 2,4-dimethoxyacetophenone to gate azo derivative (A) , (A) interact with aromatic amine derivatives to produce imine compounds (B1-B2), imine derivatives interact with (anthranilic acid , 2-mercaptobenzoic) to get heterocyclic derivatives quinazoline (C1-C2) and thiazinone (D1-D2) . All these compound characterized by13 C-NMR , FT-IR , 1HMNR . Then that,we studies the,biological,properties for,all heterocyclic derivatives,to,ward.two different kindof bacteria.

1.Introduction

Heterocyclic,compounds that,have (N,S) as hetero atoms,are very,important because,of,the applications[1]Heterocyclic compounds forms a part of large number,of pharmaceutical relevant molecule andhave major biological significance [2]Organic heterocyclic compounds currently account for about 70 % of all clinically used drugs [3] Azo,compounds,or.dyes are,characterized, by,the,presenc of the,Azo,moiety (–N=N–).)in their,structure,conjugated with two,distinct or,identical,,mono- or,poly-cyclic.aromatic.or heteroaromatic. systems[4].Thebiological,importance of,Azo,compounds is,well,known due to their use as inflammatory[5] , antibacterial[6], anti-diabetic[7],and antifungal[8]. Schiff bases are condensation products of primary amines and carbonyl compounds and they were discovered by Hugo Schiff in 1864.[9] . A,Schiff base,is the nitrogen,analogue of,aldehyde in,which the

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C=O group,is replaced,by a,C=N group [10].There are numbers,of,biologically. important,Schiff,bases have,been noted in,previous,study possessin,,antibacterial, antifungal,antimicrobial,,anticonvulsant.,antitumor.,,anti-inflammatory,and,anti,HIV,activities[11]. Quinazolines,and,thiazine,derivatives,have,six-.membered,containing,(N,and,S),respectively such as antitubercular, anti-inflammatory, antimicrobial , antipyretic. , anti-HIV , analgesic , antitumor , and calcium channel modulatory activities[12], thiazine derivatives,that exhibit,various,biological,activities,such,as anti-tubercular,,anti-fungal[13]insecticidal,and,pesticidal[14]. ,Studies,of,heterocycles,containing,hetero,atoms, such as Sulphur and Nitrogen,,are definitel,one of,the supreme,targeted areas,in heterocyclic,chemistry. They,are extensively,used in,several studies,of natural,products,and pharmaceutical,agent's,synthesis Thiazine ring,systems are,considered a,significant,heterosystem in,heterocyclic,chemistry[15],Quinazoline nucleus,is an,interesting molecule,among the,most important,classes of,an aromatic,bicyclic,compounds with two,nitrogen atoms in,their structure,It is,consisting of,aromatic,benzopyrimidine,system,Synthesis[16] made up,of two,fused six member simple,aromatic rings,benzene,and pyrimidine,ring[17]. ,Researchers,have already,determined,many,therapeutic,activities,of,quinazoline,derivatives,,including,,nticancer[18], antiviral[19`),"antiviral ,antimalarial[20] ,,.

2. Materials

"(FTIR.),Spectra,(400., -4000 .cm-1), in KBr,,disk,were,recorded,on,SHIMADZU.FTIR-,8400S,Fourier transform. ^{13}C-NMR,and ^{1}HNMR were recorded on varian agilant USA at (500.MHz) with.(DMSO.-d6) measure.ement were.made at Department ofChemistry,Tehran University,,Iran."

2.1 Preparation of compound A[21]

(0.01) (1.68 g) of 4-methoxy-2-nitro aniline,was dissolved in a solution consisting of (10 ml),hydrochloric acid with the mixture cooled,to.(0,-5) °C and..then added sodiumnitrite (0.8g) $NaNO_2$ with a brown color drop as a drop to a solution consisting of (1.8g) (0.01mol) of 2,4-dimethoxyacetophenone and (2 g) of NaOH dissolved in (130ml) distilled and cooled water to (20 ^{o}C) and (10ml) ethanol was,observed The Azo composite deposit is dark brown color after completing the addition process. This process was carried out in PH = 5and the solution is left for ,(24 hours) after which the precipitate was filtered and then the precipitate was collected after filtering and washed with distilled water,and dried and recrystallized with ethanol.

2.2 Preparation of compound (B1-B2)[22]-

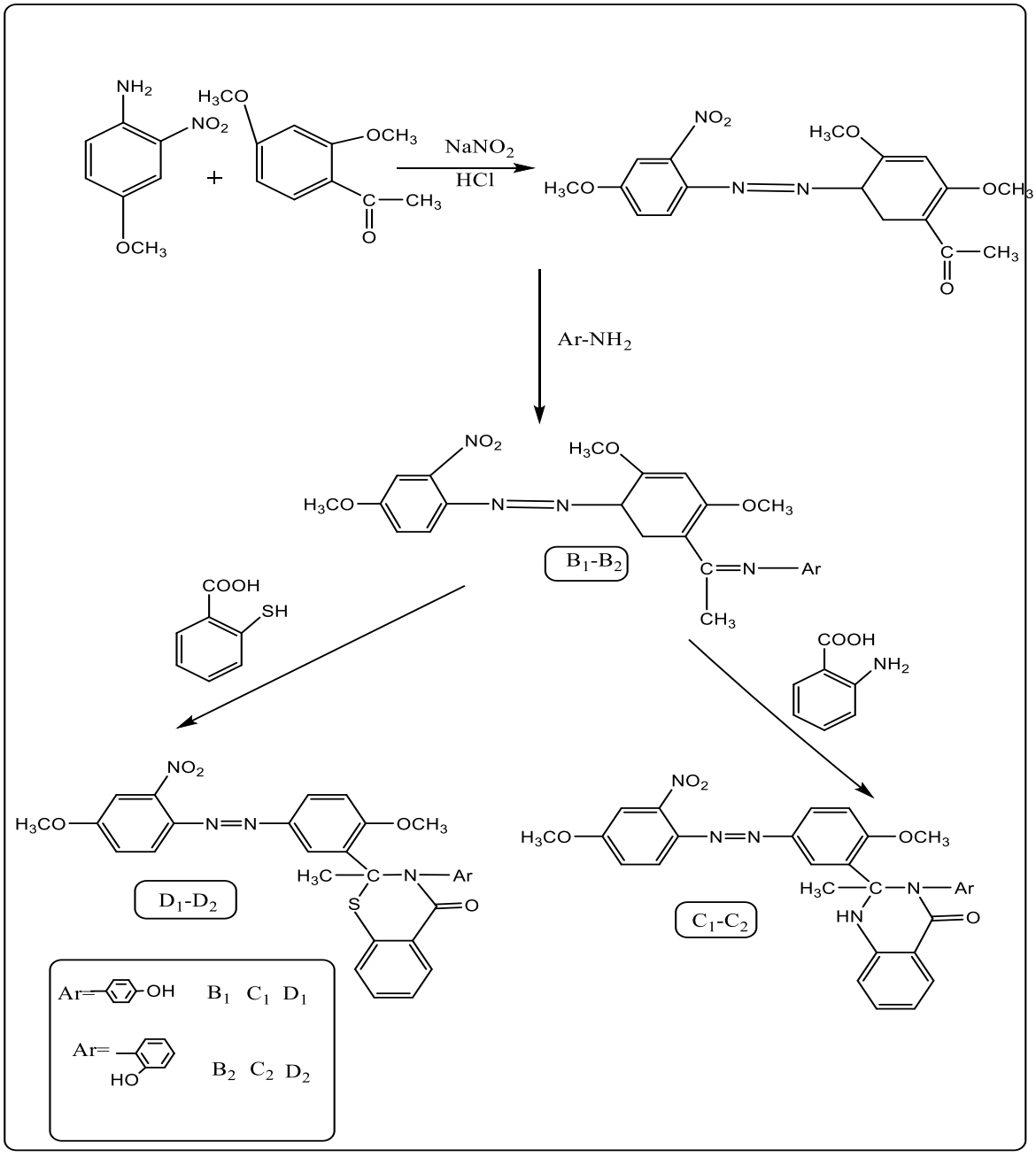
In a double-beaker flask,(1g) (0.00278mol) of derivative(A) was mixed with(0.303g) (0.00278mol) of p-amino phenol ,(0.303g) of,2-amino phenol, compound with (20ml) of ethyl alcohol added to it (three drops) of,glacial.acetic.acid and the,.mixture up .and ,left For a period of two hours,at a,temperature ,(78 oC) and then cool the mixture and leave it for (24 hours) and then re-crystallize it with absolute ethyl alcohol.

2.3 Preparation of compound (C1-C2):-

(0.00150mol) (0.7 g) of dissolved schiff base B1and B2 compound was mixed in (1-4-dioxane (20ml) with (0.213g) of (anthranilic acid) or (0.00150mol)(0.7 g) of Schiff base B2 ,was mixed in (1-4-dioxane (20ml) with (0.205g) of (anthranilic acid) was mixed in (1-4-dioxane (20ml) with (0.213g) of (anthranilic acid) then add drops of (DMF) and reflex of (36 Hour) and then re-crystallized the product with absolute ethanol .

2.4 Preparation of compound (D1-D2):-

(0.7g) (0.00155mol) of Schiff baseB1,B2 compound was mixed in (22ml) of benzene with (0.239g) of 2-mercapto benzoic acid (3ml) of DMF then add drops of triethylamine to the reaction mixture and from Then reflex of (10 hours) , then the product was filtered and re-crystallized with absolute ethanol .



Scheme(1,) prepare ofsome,.heterocyclic, compounds

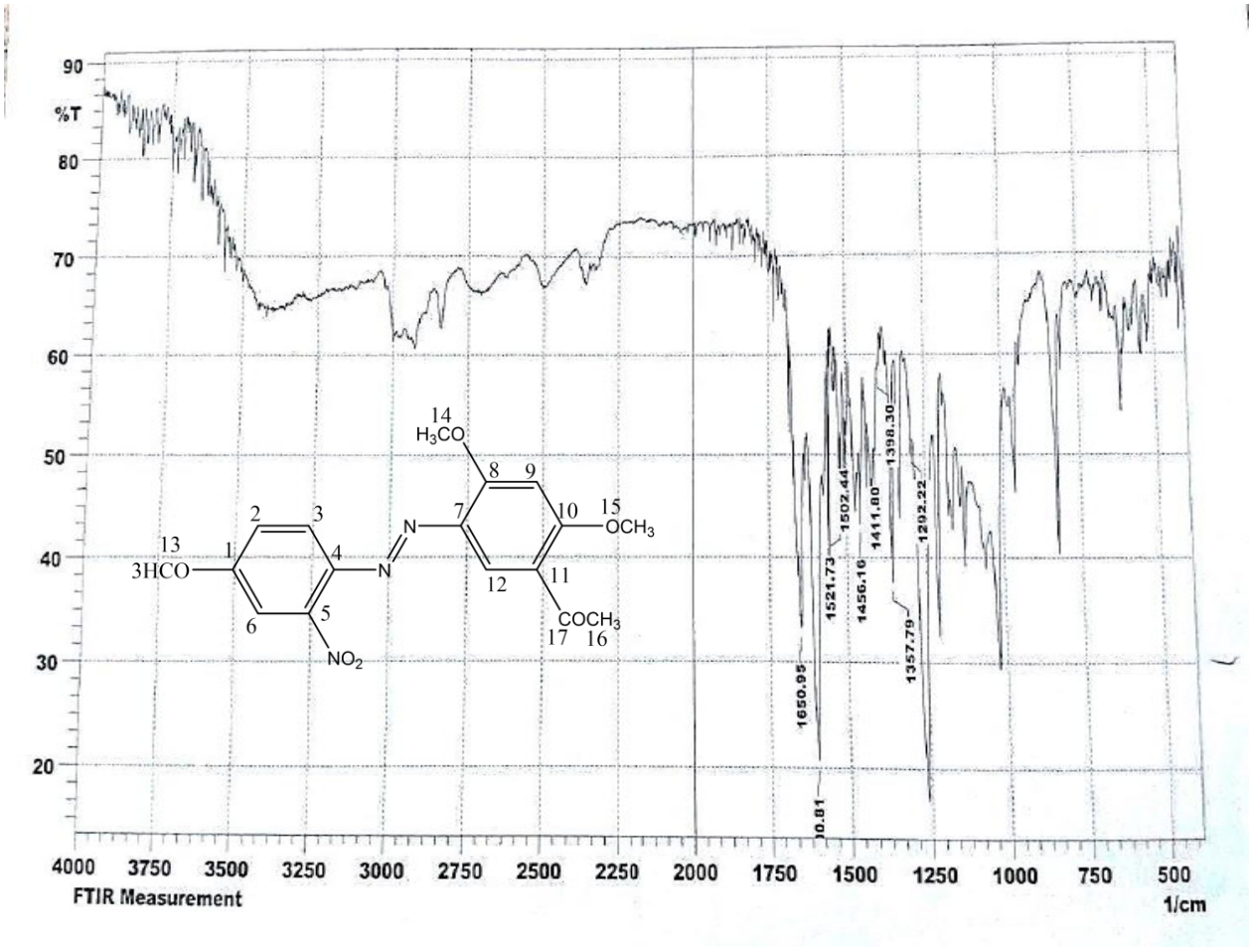
3. Results and Discussion

Derivative (A)

(E)-1-(2,6-dimethoxy-3-((E)-(4-methoxy-2-nitrophenyl)diazenyl)phenyl)-N-(4-nitrophenyl)ethan-1-imine C4,C

FT-.IR,spectrum,data for,.derivative (A), show.peak at 3000 for (Ar – H) , 2980cm^{-1} for(,C- H) in CH_3 , 1700 cm^{-1}for(C=O), 1650 cm$^{-1,}$ for ,(C=C) ,(1521-1357)cm^{-1}for(NO_2). ^{1}HMNR spectrum data of derivative (A) show 2.52ppm (DMSO) , 3.78ppm (S ,3H, $(OCH_3)_{13}$), , 3.87ppm (S ,3H, $(OCH_3)_{14}$), 3.98ppm (S ,3H, $(OCH_3)_{15}$), 3.9ppm (s, 1H, CH_3) ,6.3-7.6ppm (M, 5H , Ar-H) , 9.4PPm.The C13-NMR

spectrum data (DMSO) compound (A) show :197ppm (C_{17}) ,79ppm(C_{16}) 56ppm (C_{15}) , 55ppm (C_{14}) , 31ppm (C_{13}) , 164ppm(C_3) ,161ppm(C_4,C_7), 98-132ppm (CArom)).



Fig(1) FTIR spectrum of compound(A)

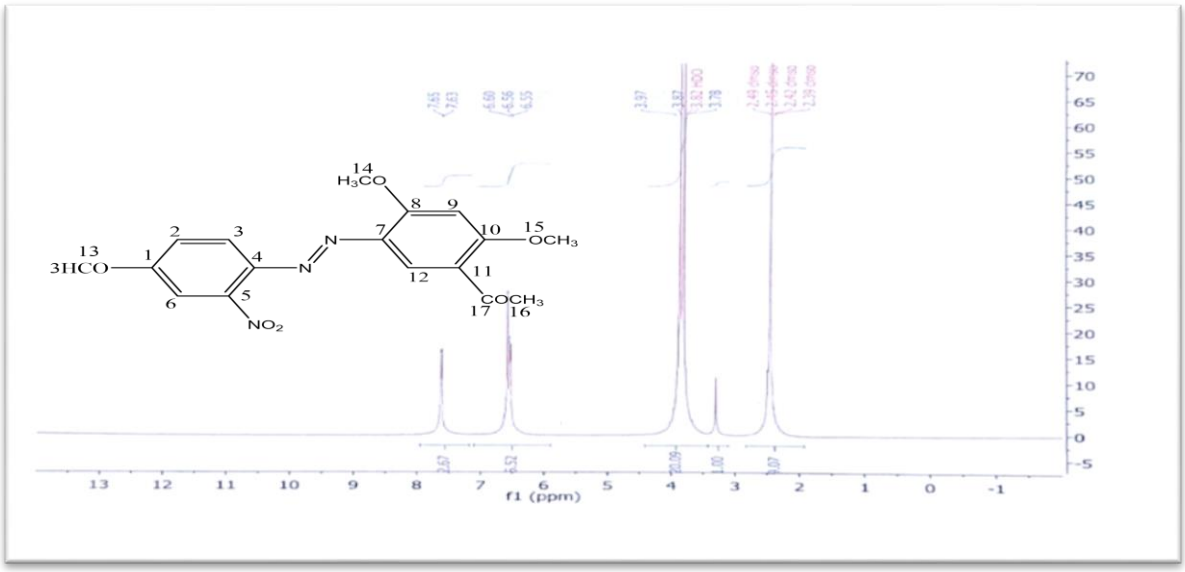


Fig.(2)(^{1} HNMR),spectrum,of.compound(A)

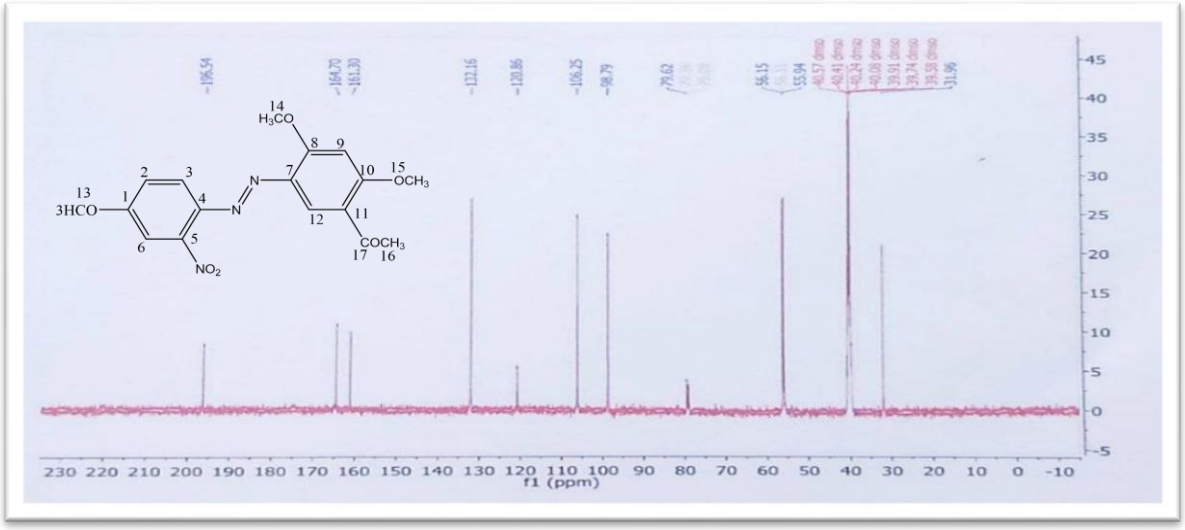
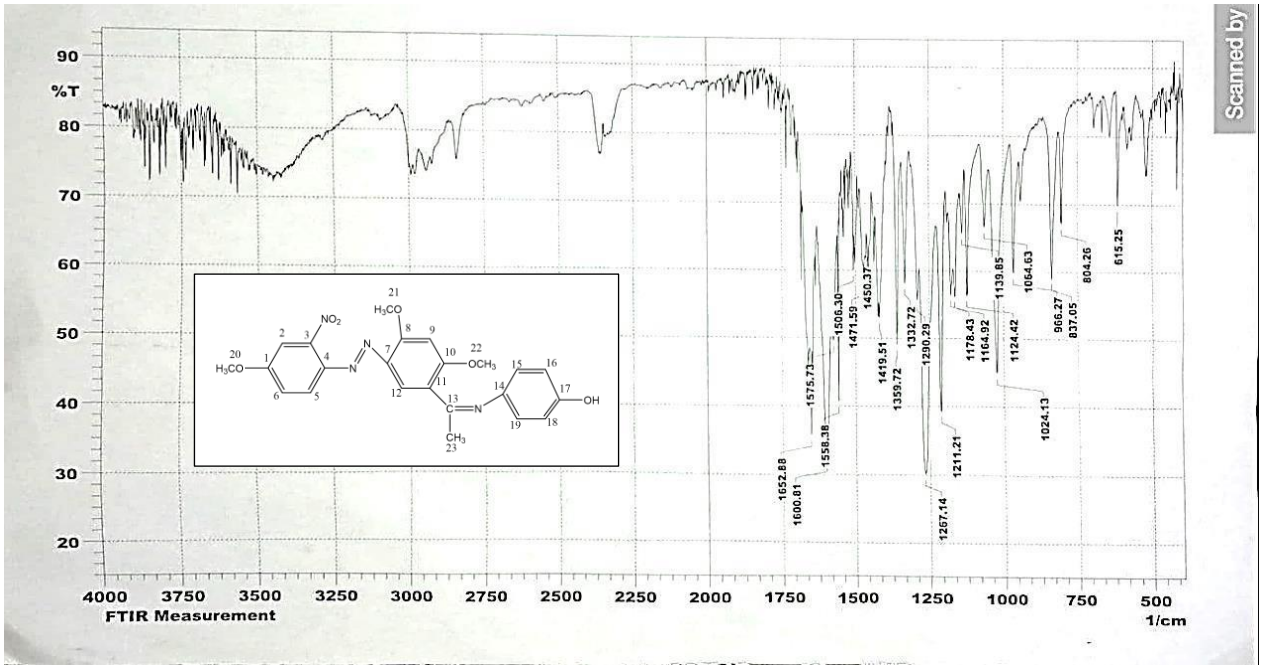


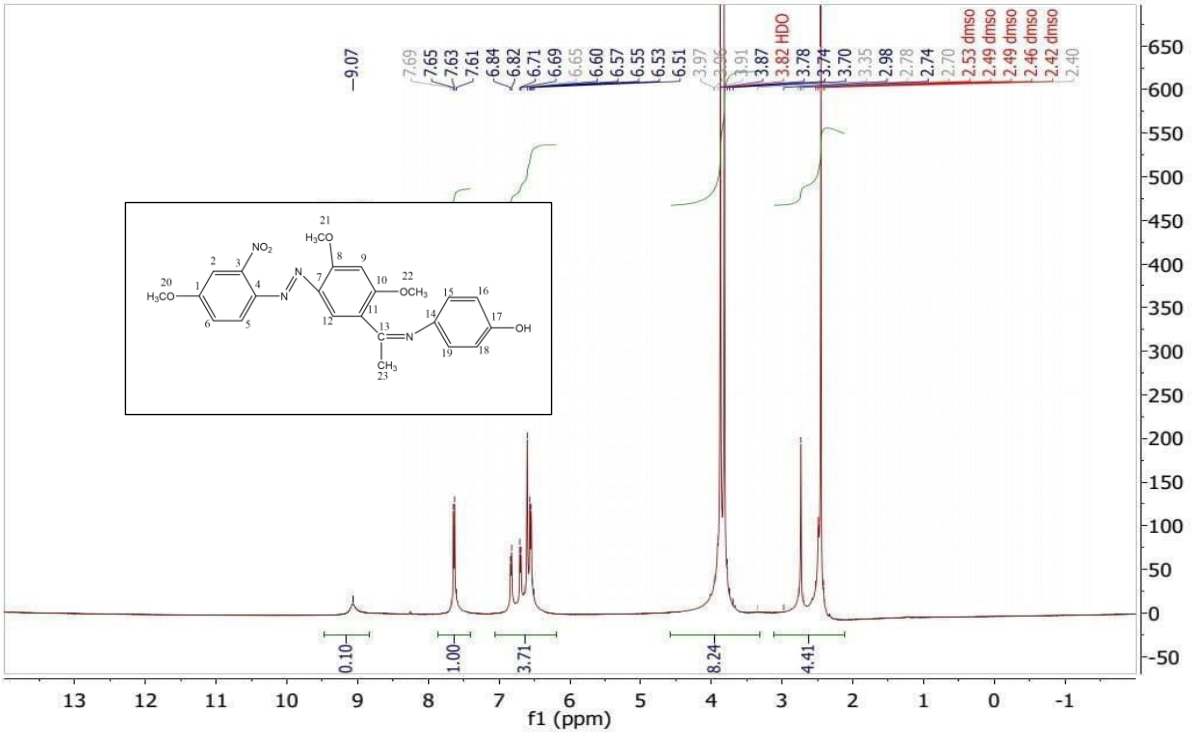
Fig.(3) (13CNMR)spectrum of,compound(A)

Derivative (B1) 4-(((Z)-1-(2,4-dimethoxy-5-((E)-(4-methoxy-2-nitrophenyl)diazenyl)phenyl) ethylidene) amino)phenol

FT-IR spectrum data for derivative (B1) show peak at, 3025 for (Ar – H) , 2988cm^{-1} for (C- H) in CH_3 , 1456 forN=N, 1652 cm^{-1},for C.=N, , 1500,1350 cm^{-1},for.NO_2 ,1650Cm^{-1}(C=C)arom . ^{1}HMNR spectrum data of derivative (B1) show 2.52ppm (DMSO) , 2.9 (S,,.3H,,$(OCH_3)_{19}$) , 3.9 (S, ,3H,,$(OCH_3.)_{21}$) ,3.7 (S ,3H, $(OCH_3)_{22,}$) ,3.8ppm (s,, 1H, CH) , (,6.5-7.6)ppm (m , 9H ,, (Ar-H) ,., The C13-NMR spectrum data (DMSO) compound,(B1),show :79ppm (C_{21}) , 55ppm (C_{20}) , 79ppm (C_{21}) , 31ppm(C_{22}) ,161ppm (C_{13}),164ppm(C_4,C_7),196ppm(C_{17}),34 ppm (C_{19}).



Fig(4) FT-IR,spectrum of,compound,(B1)



Fig(5).(^{1}, H-NMR,)spectrum,of,compound,(B1)

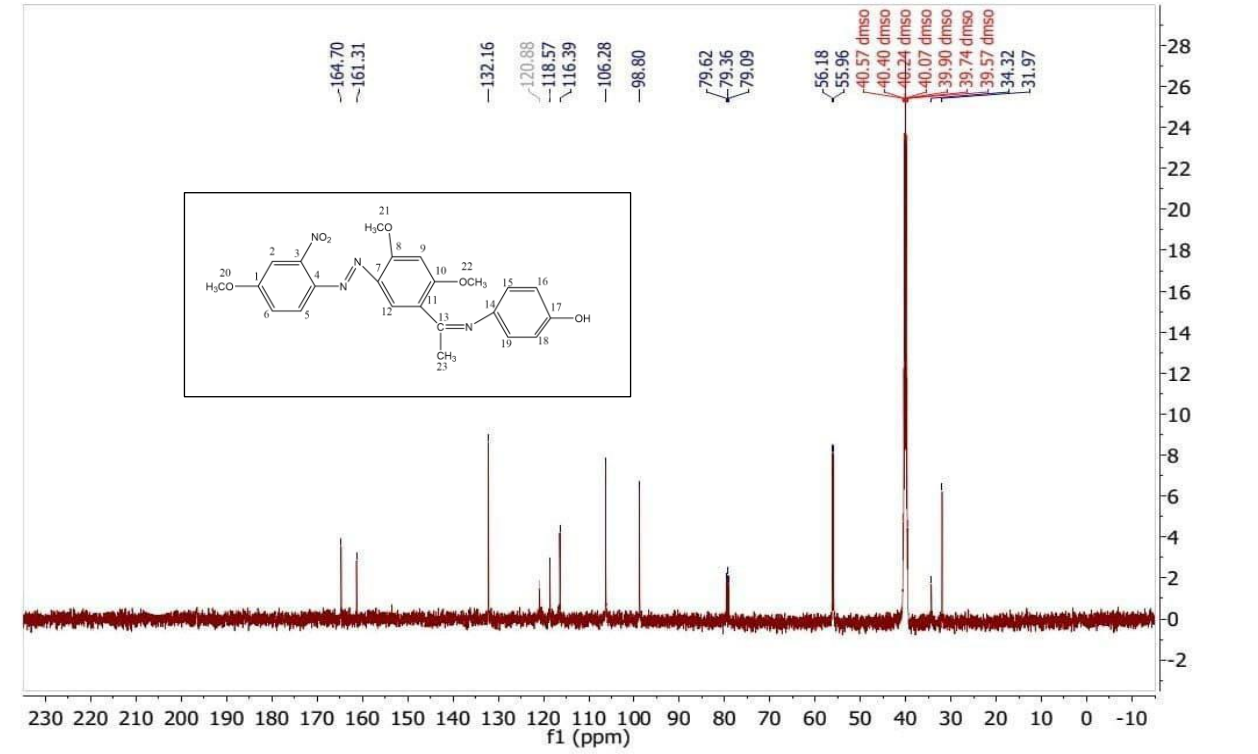
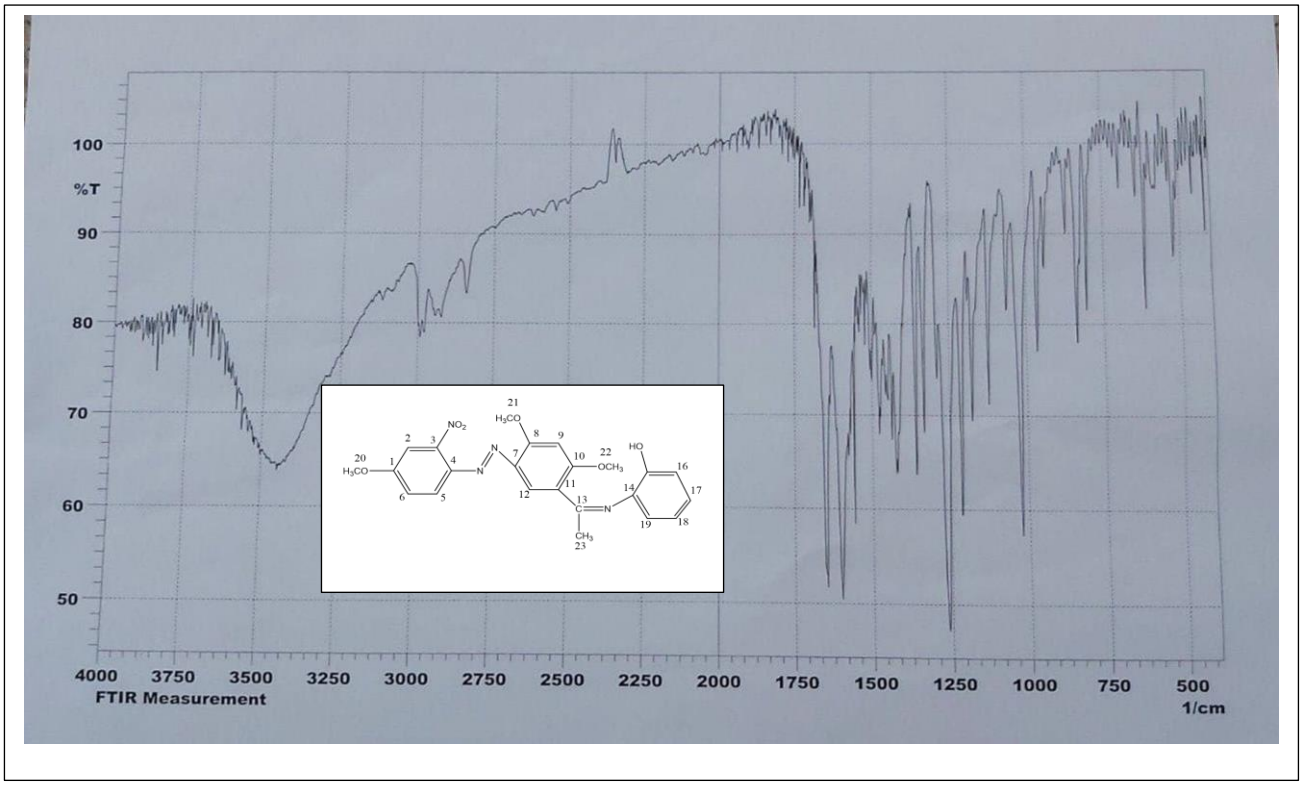


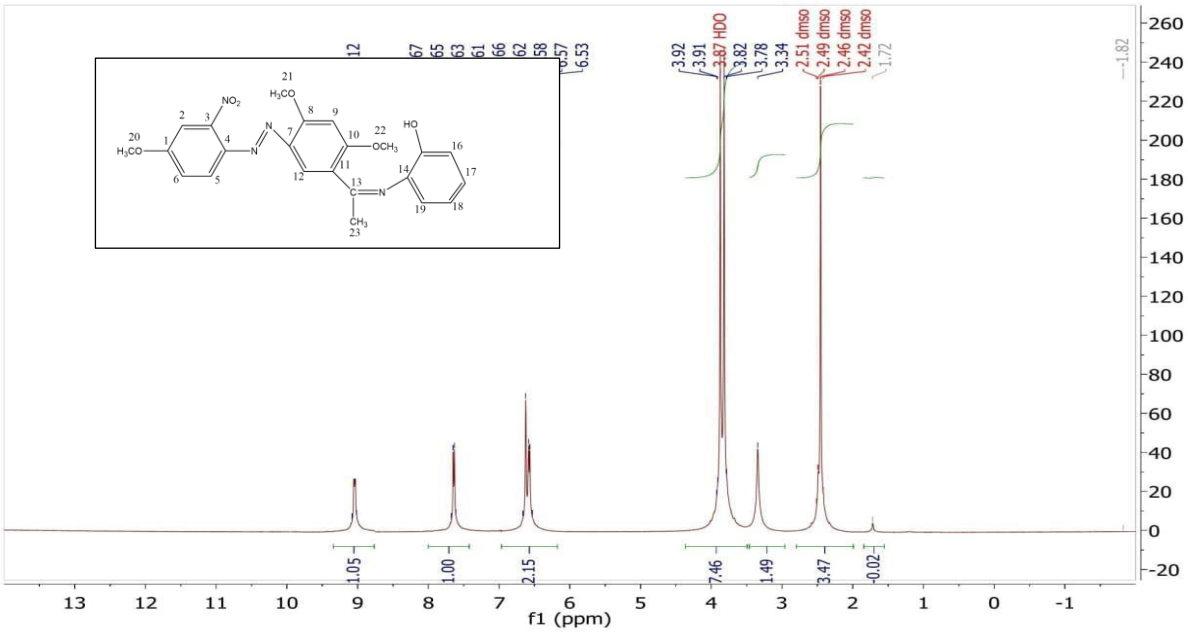
Fig.(6)(^{13}C,-NMR).spectrum,of compound.(B1)

Compound,(B2) 2-(((Z)-1-(2,4-dimethoxy-5-((E)-(4-methoxy-2-nitrophenyl)diazenylphenyl) ethylidene)amino)phenol

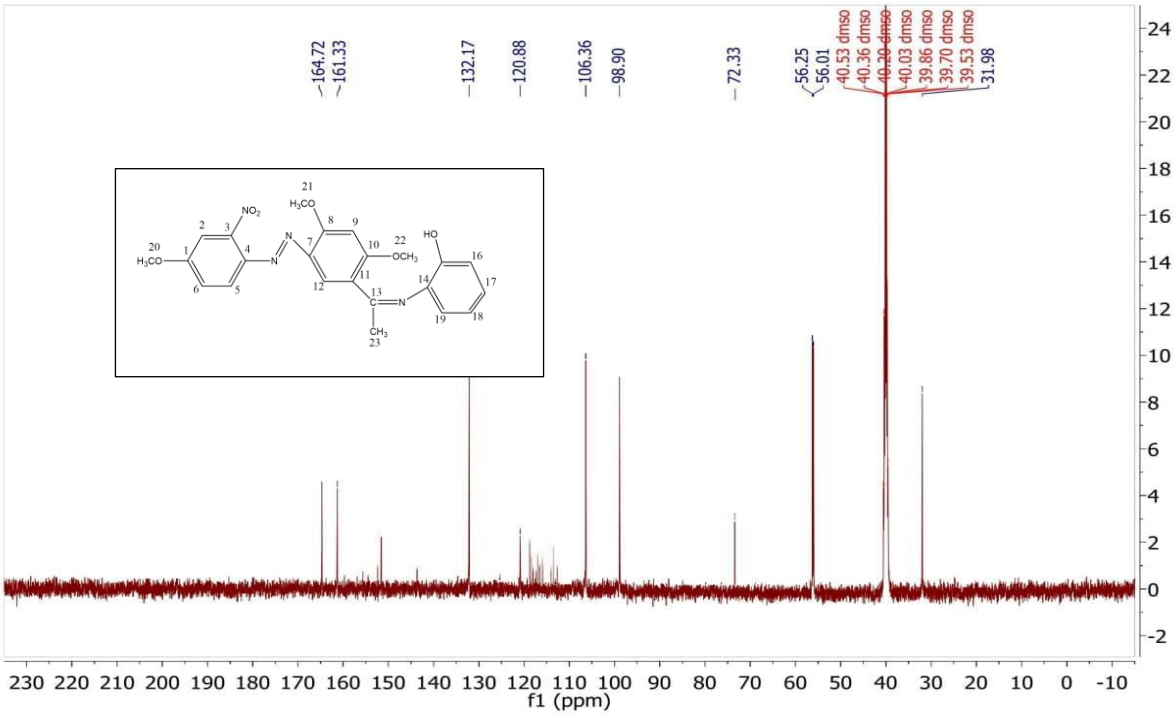
FT-IR,spectrum,data for, derivative ,(B2) show,band,at 3300 $cm^{-1,}$ for (O – H) 3080for (Ar – H) , 2985cm^{-1} for(C- H) inCH_3 ,1600 cm^{-1}or (C=N), 1593 cm^{-1},for .(C=C),1470cm^{-1} forN=N, ^{1}HMNR spectrum data of derivative (B2) show 2.52ppm (DMSO) , 1.9 (S ,3H, $(OCH_3)_{22}$) , 3.9 (S ,3H,. $(CH_3)_{21}$), 3.8 (S ,3H, $(OCH_3)_{20}$, 3.7,(S .,,3H, (,$OCH_3)_{19}$), 2.01 (S ,3H, .,$(OCH_3)_{18}$),9.1(S,1H(OH), 6.5-7.6ppm (m ,9H, , Ar-H). The C13-NMR spectrum data (,DMSO),compound (B1) show :79ppm (C_{21}) , 72ppm (C_{20}) , 56ppm (C_{21}) , 161ppm(C_{22}) ,31ppm (C_{23}),164ppm(C_4,C_7),196ppm(C_{17}),



Fig(7) FT-.IR spectrum of.compound (B2) .



Fig(8) (^{1} H-NMR).spectrum,of.:compound (B2)



Fig,(9) (^{13} C-NMR,) spectrum,of,compound (B2)

Compound,(C1) و ((E)-2-(2,6-dimethoxy-3-((4-methoxy-2-nitrophenyl)diazenyl)phenyl)-3-(4-hydroxyphenyl)-2-methyl-2,3-dihydroquinazolin-4(1H)-one

FT-IR:,spectrum,data:,for derivative ,(C1) show,peak at ,1420 for (N=N), 3078 for (Ar – H) , 2947cm-1 for (C- H) in CH3 ,1670cm-1 for(C=O) , 1620.cm-1 for(C=C),3425cm-1for(N-H).1HMNR.spectrum;,data,of derivative (C1) show 4.0ppm (s, 1H , NH) , 2.6.ppm (S ,3H, OCH3)30 , 3.8.ppm (S ,3H, OCH3)28) , 2.8.ppm (S,,3H,OCH3)29,1.2.ppm (S ,3H, OCH3)27, (s, 1H, CH) , 1.8ppm (s, 2H, CH2) , 6.5-7.8ppm 13H , (Ar-H) ,8.4 ppm.(s,1H,OH),4.1ppm 9s,1H NH). C13_NMR spectrum data (DMSO) compound (C1) show :79ppm (C27) ,56ppm(C28), 56.2ppm (C29) , 32ppm (C30) , 31ppm (C19) ,164ppm(C3) ,63ppm (C13) 196ppm(C14), 164-,98ppm (CArom) .

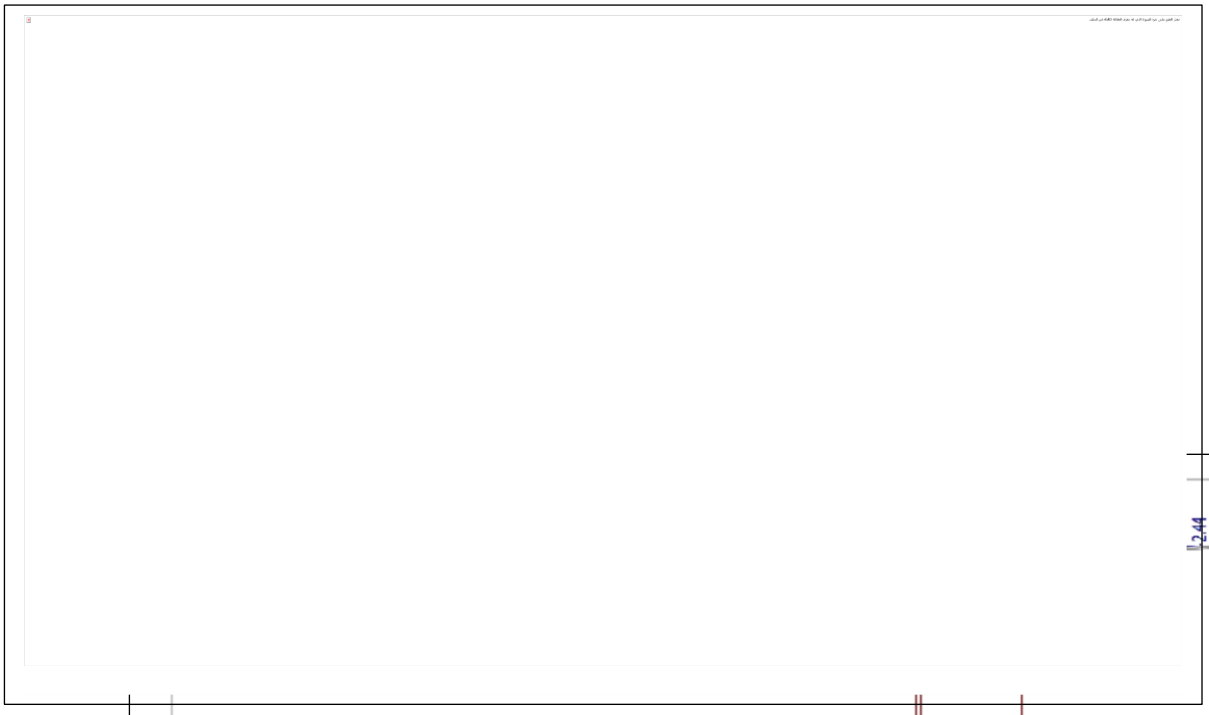
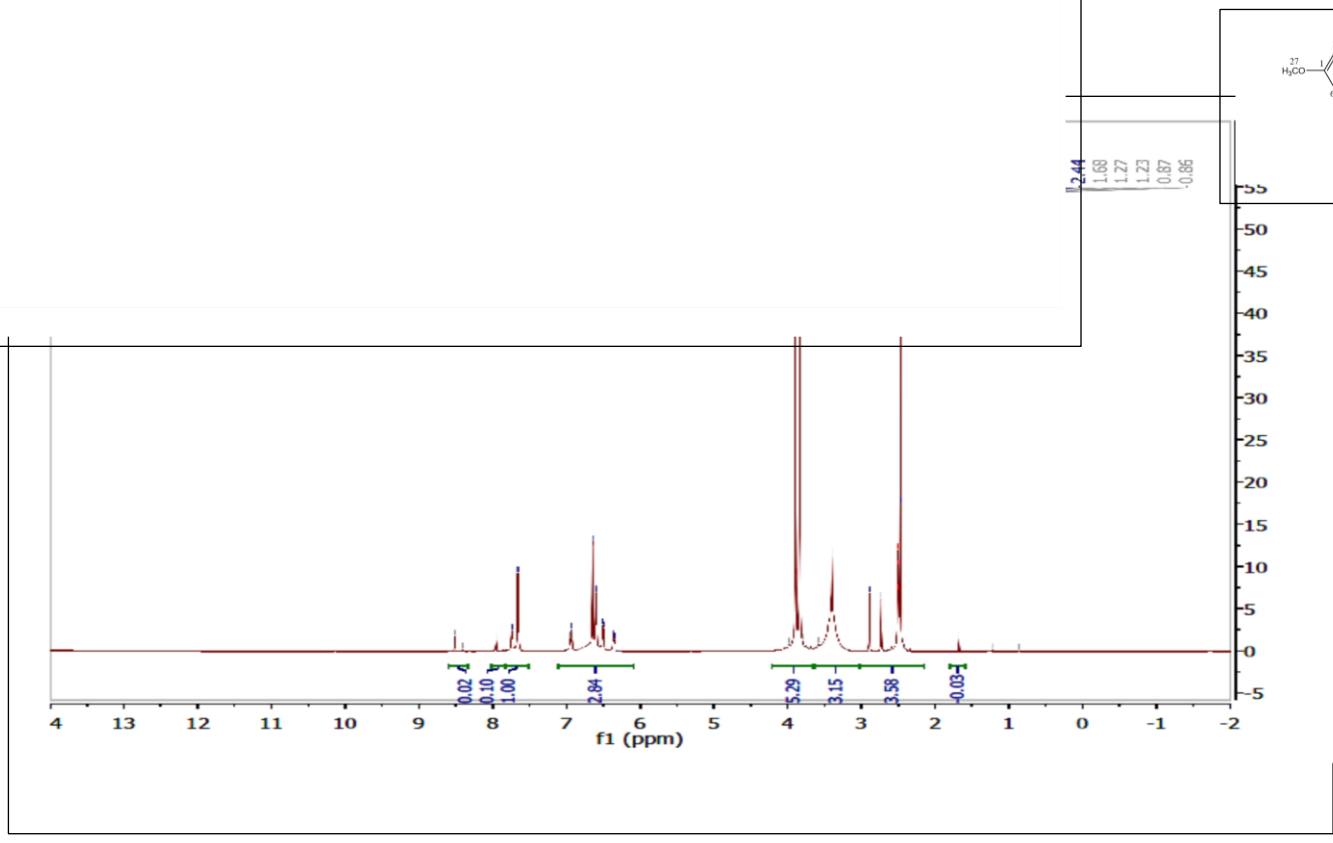
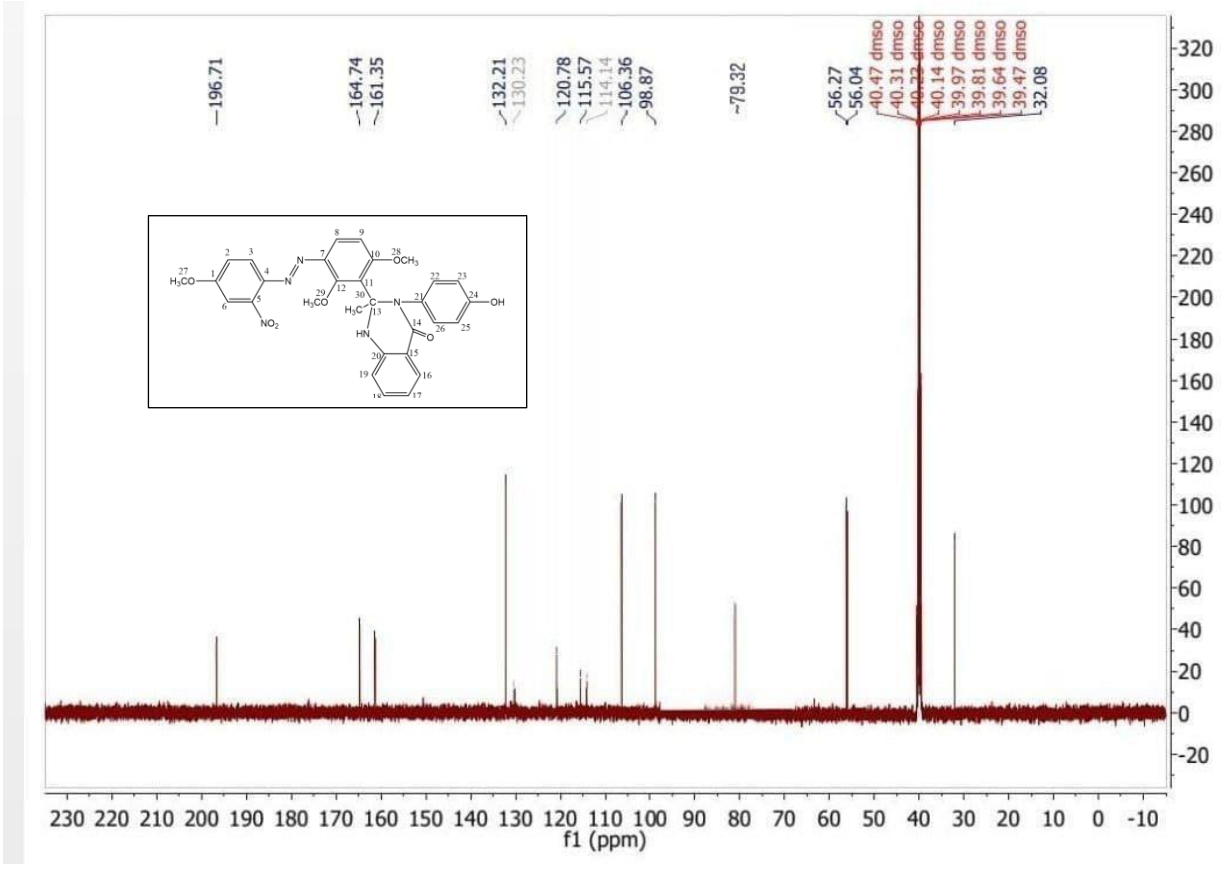


Fig.(10) :-(FT-IR)spectrum:of :compound (C1)



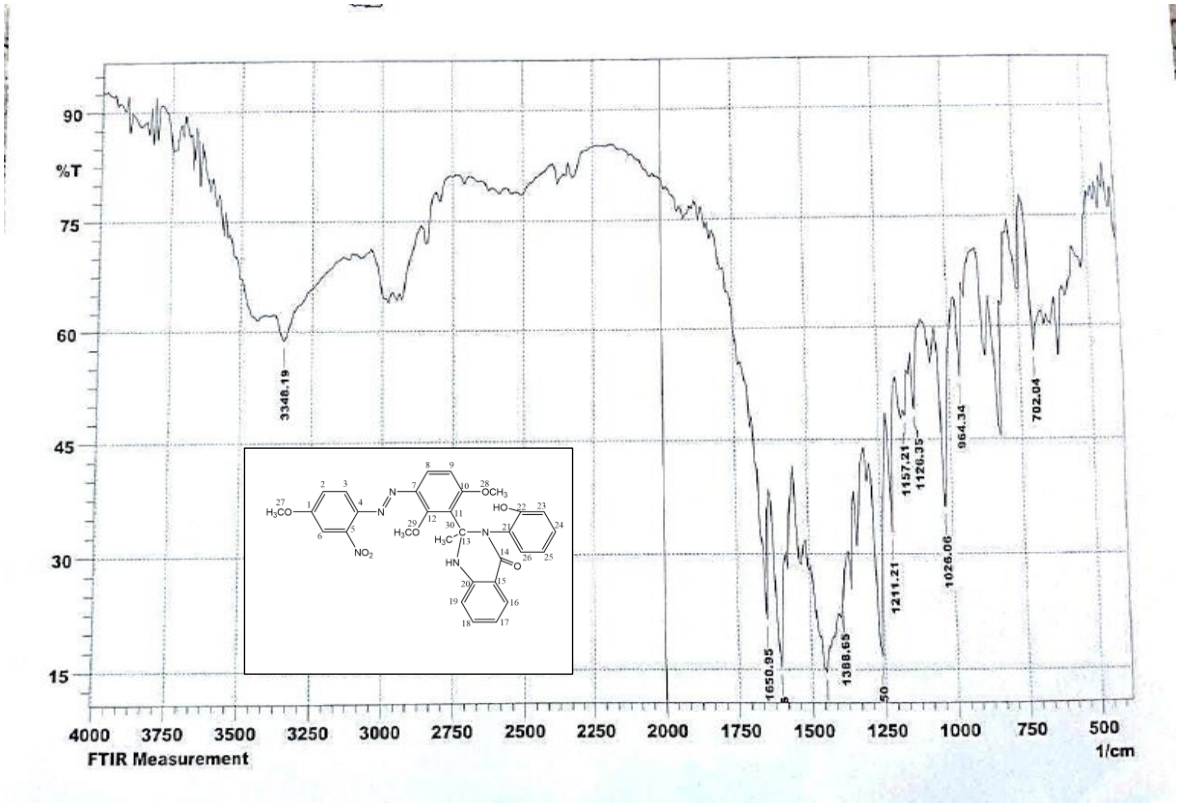
Fig(11), (1H NMR) spectrum,of,compound (C1)



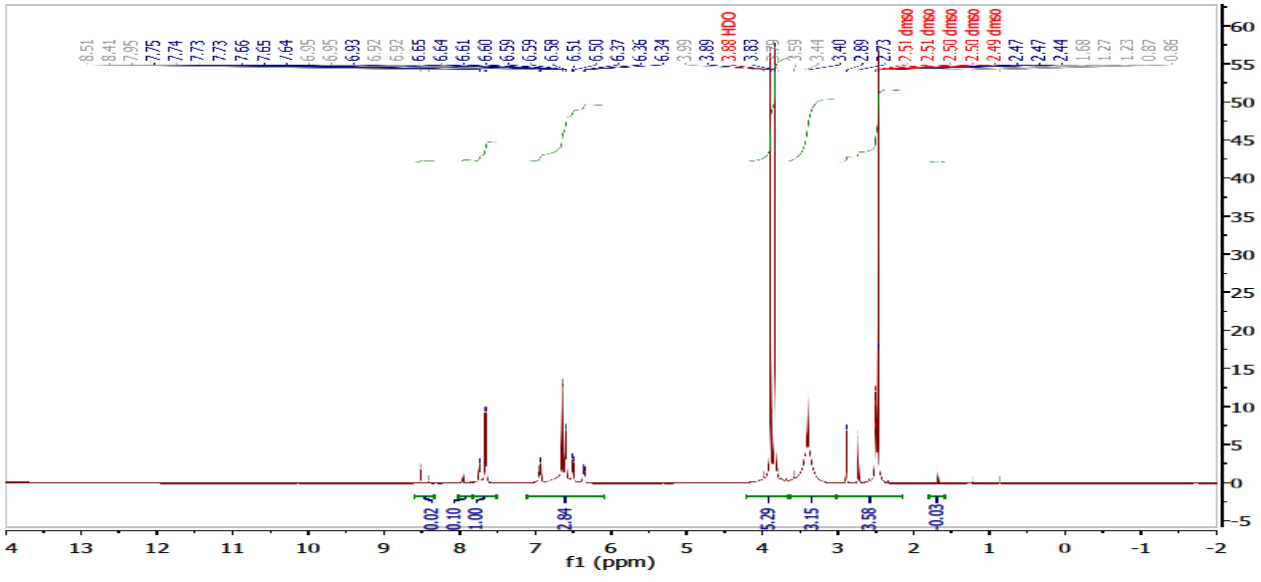
Fig(12):,-(^{13} C1-NMR),spectrum,.of.compound(C1)

Compound (C2 (E)-2-(2,6-dimethoxy-3-((4-methoxy-2-nitrophenyl)diazenyl)phenyl)-3-(2-hydroxyphenyl)-2-methyl-2,3-dihydroquinazolin-4(1H)-one

FT-,.IR spectrum,:data for,derivative,(C2) show,peak at 3325 cm-1 for,(O – H), , ,3060 for (Ar – H) , 2920cm-1 for (C- H) in CH3 , 1680,cm-1,for,(C=O) , 1600cm-1,for (C=C),1550cm-1,(C=N),(1500-1360)cm-1NO2 . 1HMN, spectrum,data of,:compound (C2) show,,2.8ppm(S ,3H, OCH3)27) 2ppm (S ,3H, OCH3)26) ,3.9ppm (S ,3H, OCH3)25),0.8ppm (s, 3H, CH3)29) , 1.2ppm (s,3H, CH3)28), 6.3 -8.4ppm (m , 13H , Ar-H) ,.4ppm (s,1H,N-H). The C13_NMR spectrum, data (DMSO). compound (C2) show :31ppm (C29), , 32ppm (C28) , 56.05ppm (C27).,36ppm (C26),,56.28ppm(C25) 167ppm(C23),162,ppm(C21),164ppm,(C5-C7)),164-96 ppm(CArom),196(C=O).



Fig(13):-(FT-IR)spectrum of:compound. (C2)



Fig(.14):-(^{1} H-NMR),spectrum,:of:compound (C2)

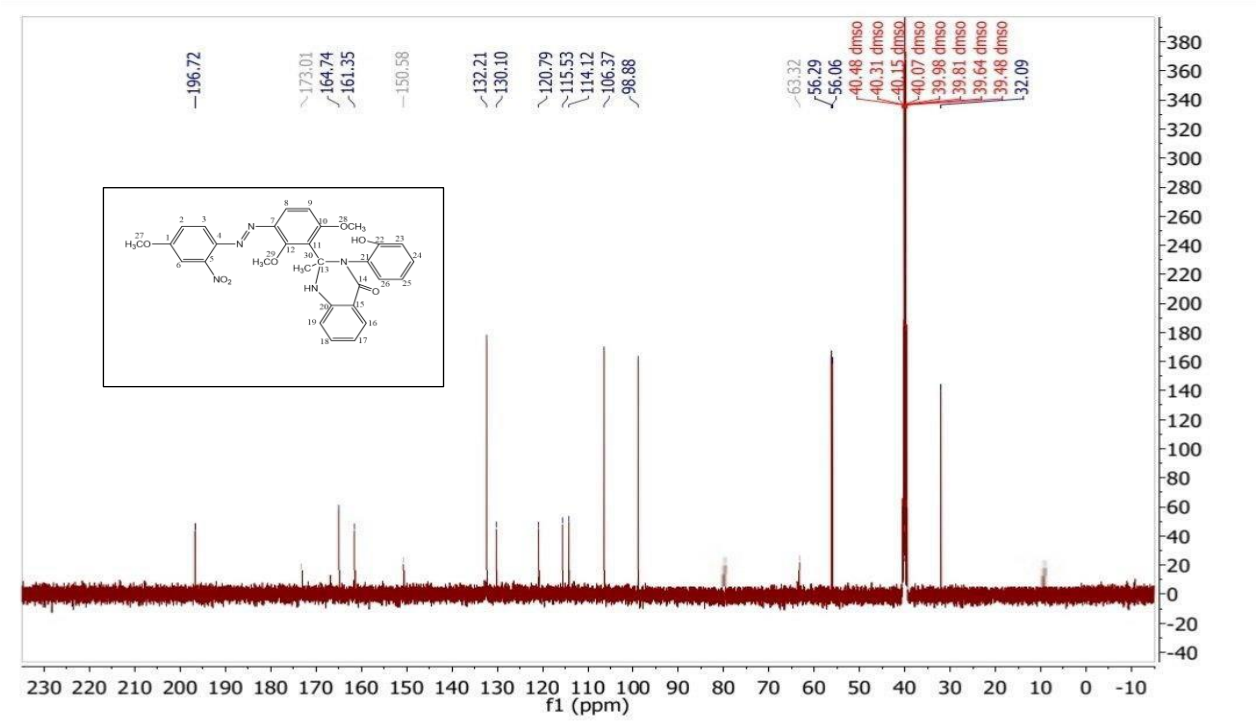
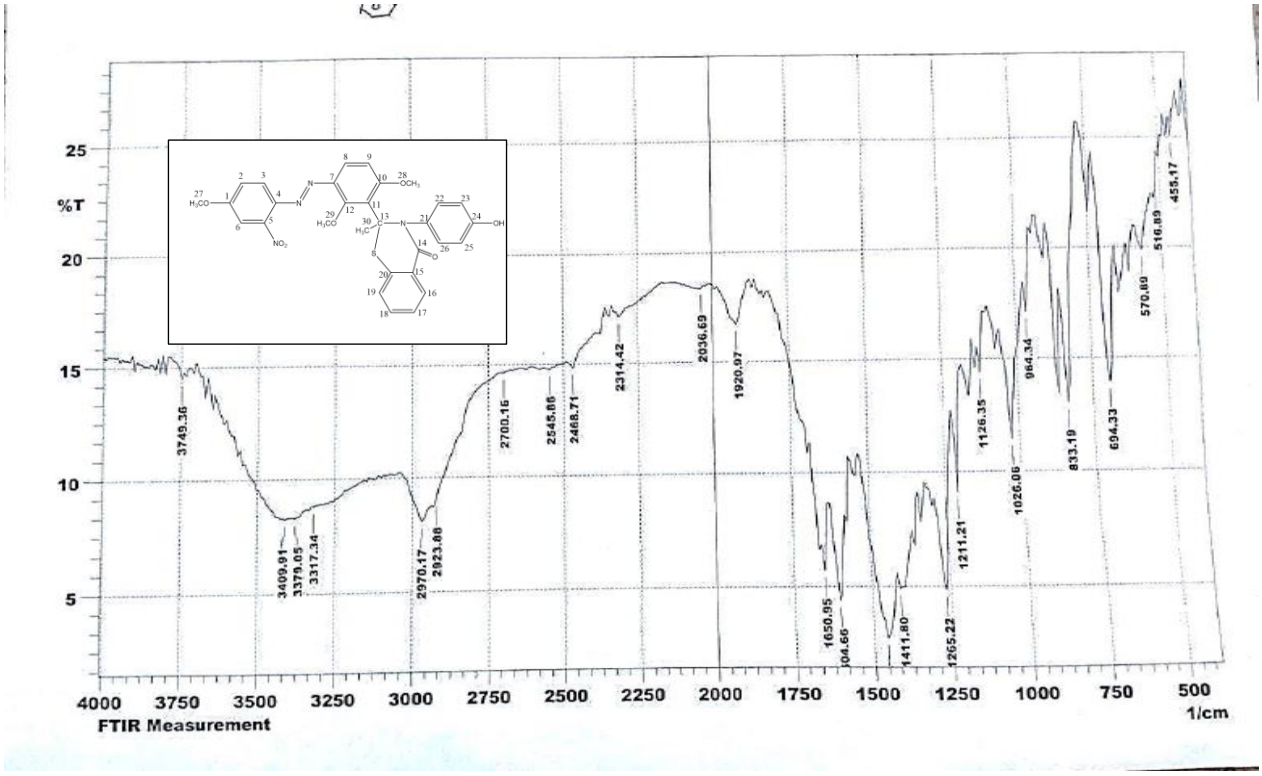


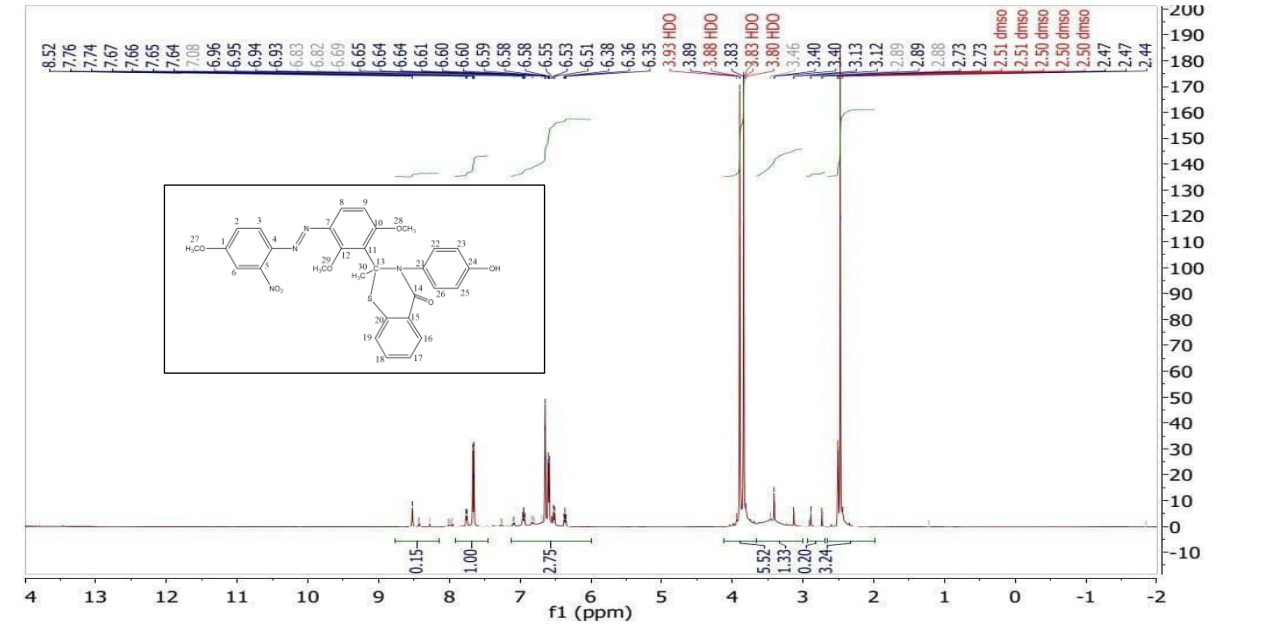
Fig:(15):- (^{13}C1-NMR) spectrum: of: compound (C2)

Compound (D1):- ((E)-2-(2,6-dimethoxy-3-((4-methoxy-2-nitrophenyl)diazenyl)phenyl)-3-(4-hydroxyphenyl)-2-methyl-2,3-dihydro-4H-benzo[e][1,3]thiazin-4-one

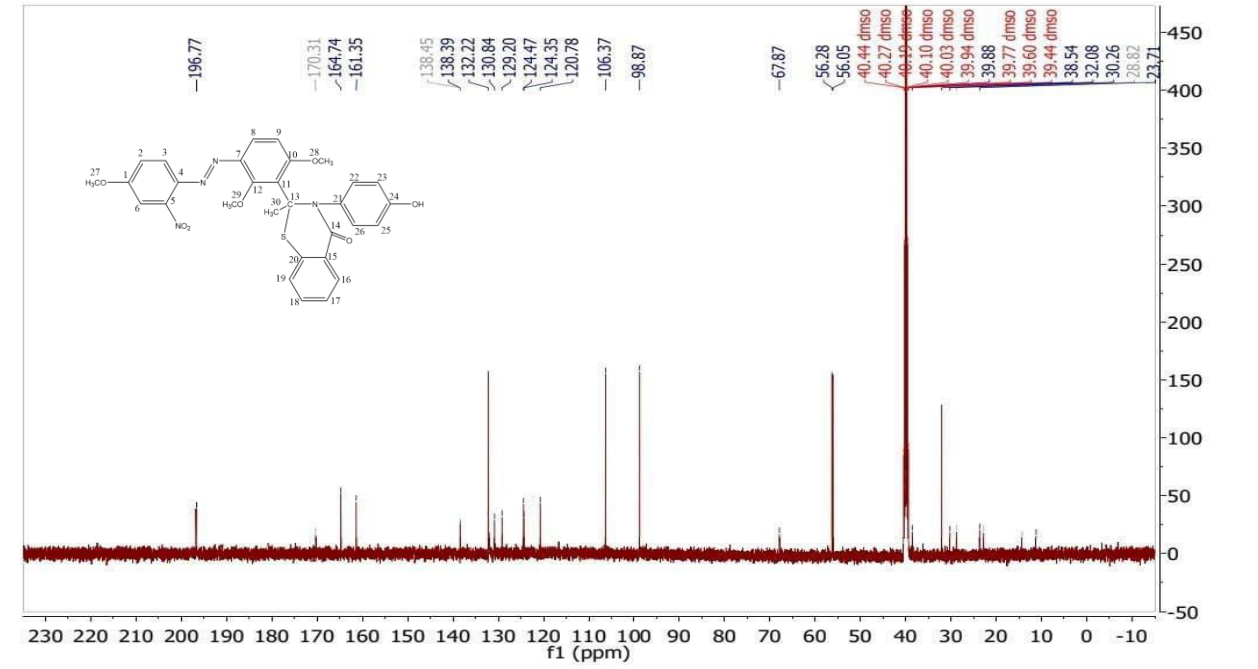
FT-IR spectrum:data for derivative (D1) show: peak at, 3090 for (Ar – H) , 2910cm^{-1} for (C- H) in CH_3 , 1680cm^{-1} for (C=O) , 1412 cm^{-1} for (N=N) ,1600 cm^{-1}:for (C=C),(1550-1396) Cm^{-1} for(NO2).^{1}HMNR spectrum:data of:compound (D1) show, 1.2ppm (S ,3H, $OCH_3)_{28}$) ,0.8ppm (s, 3H, $CH_3)_{29}$) 1.2ppm (S ,3H, $OCH_3)_{28}$) ,, 3.8ppm (s , 3H , $OCH3_{(29)}$, 2.4ppm (S ,3H, $OCH_3)_{30}$) ,(6.5-7.9)ppm(s,13H,Ar-H). The C^{13}-NMR spectrum data (DMSO) compound (D1) show :16.6ppm (C_{28} , 56ppm (C_{30}) , 153ppm (C_4,C_{14},C_{17}) 191ppm (C_{31}) , 111-134ppm (C_{Arom}).



Fig(16):-(FT:-IR): spectrum of compound (D1)



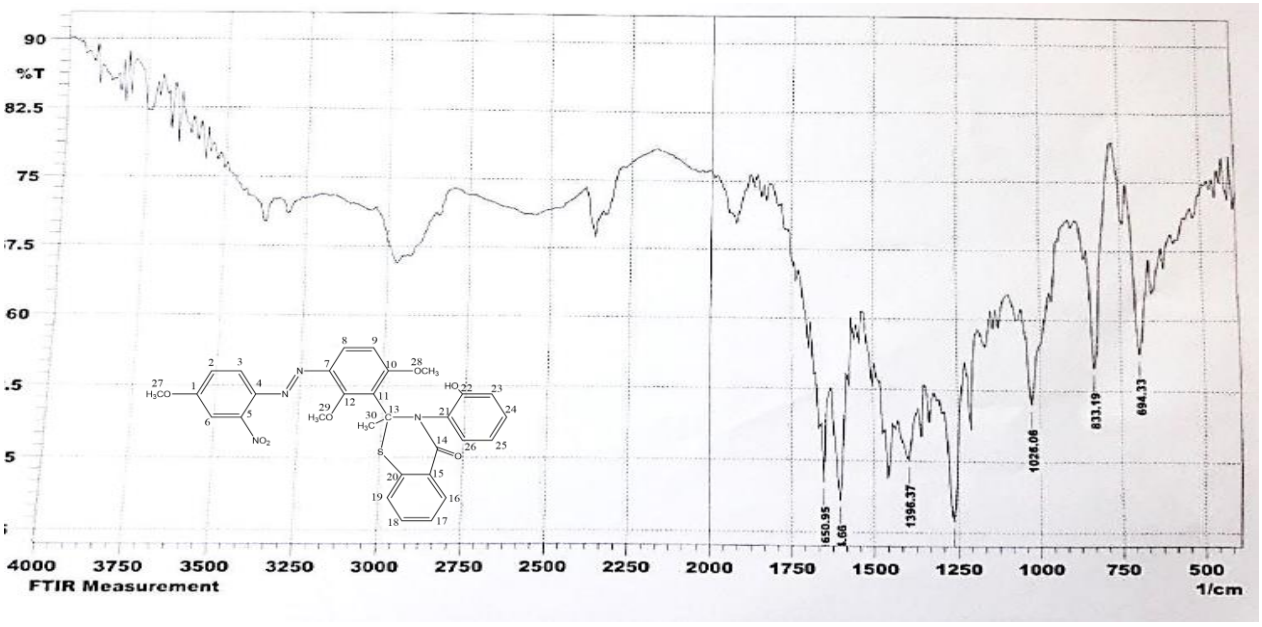
Fig(17):-H NMR, spectrum, of,compound (D1)



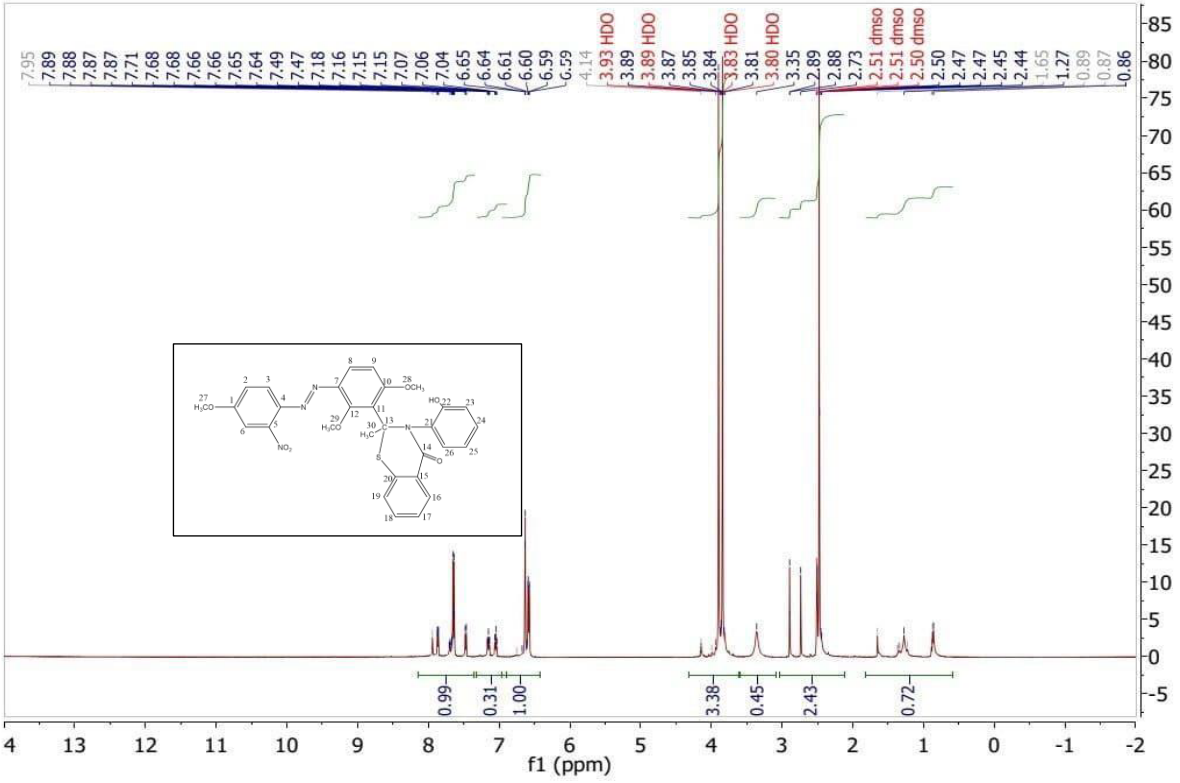
Fig(18):-(^{13}C-NMR), spectrum, of compound (D1)

Compound (D2) (E)-,2-(2,6-dimethoxy-3,-((4-methoxy,-2-nitrophenyl)diazenyl)phenyl)-3-(5-hydroxy-4-methylpyrimidin-2-yl)-2-methyl-:2,3-dihydro:-4H-benzo[:e][1,3]thiazin-4-:one

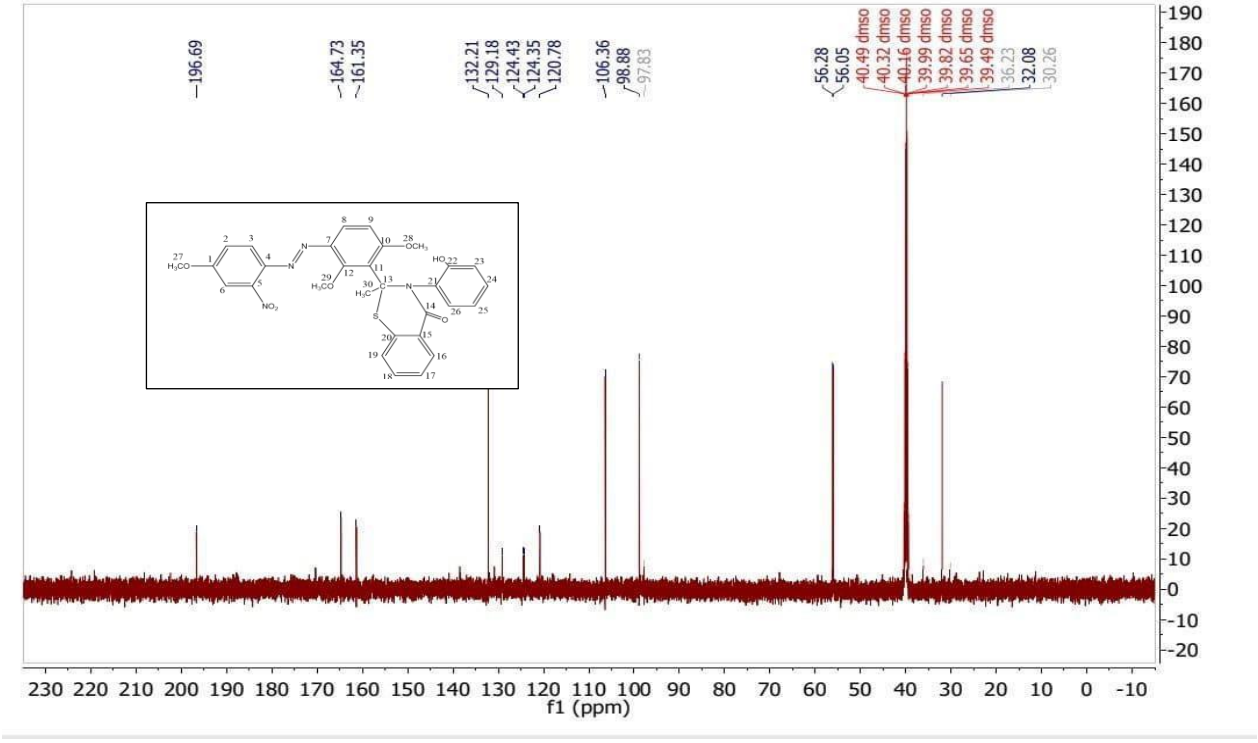
FT-IR:spectrum data for,derivative (D2),show:,band at 3332 $cm^{-1,}$ for (O –H) ,,,3080 for ,((Ar –H) , 2931cm^{-1} for(C- H) in CH_3 , 1700 cm^{-1} for (C=O), ,,1458 cm^{-1} for (N=N) , 1600,cm^{-1} for(C=C) ,1650cm^{-1} for(C=N),(1535-1357)$cm^{-1}$for(NO_2). ^{1}HMNR spectrum,data,of:compound (D2) show 0.8ppm(s, 3H , $CH_3)_{28}$) , 1.2ppm (S ,3H, $OCH_3)_{26}$) ,2.4ppm (s, 3H, $OCH_3)_{27}$) , 3.8ppm (s, 3H, $OCH_3)_{25}$)8.4 ppm (s,1H,OH), 6.5-7.6ppm (m , 10H , Ar-H) The C^{13}–NMR spectrum data (DMSO) compound (D2) show :196ppm (C_{14}) , 36ppm (C_{29}) , 32ppm (C_{28}) ,32ppm(C_{26})38ppm(C_{27}),56ppm(C_{25}),67 ppm (C_{13}) 30ppm(C_{30}),164ppm(C_4,C_7).



Fig(19):- (FT-IR) spectrum of: compound (D2)



Fig(20):- (^{1}H-NMR) spectrum ,of,compound (D2)

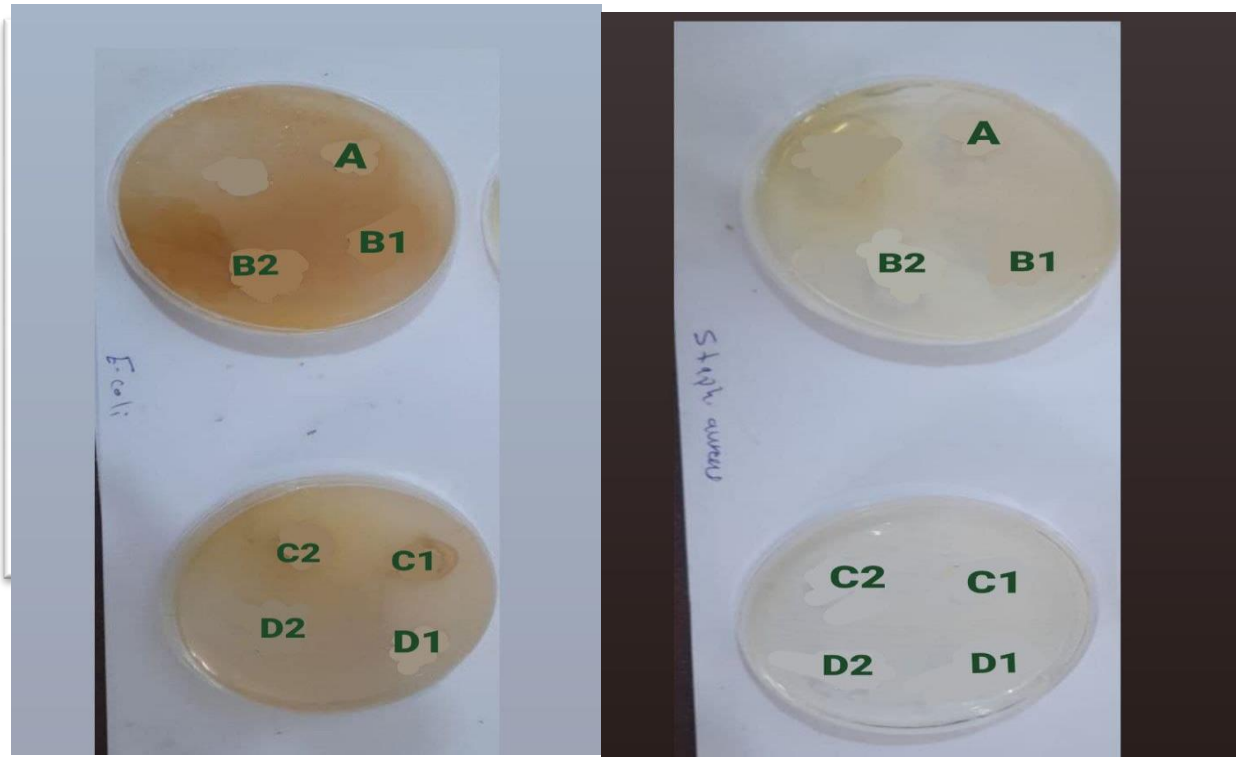


Fig(21):-(^{13} C-NMR:)spectrum:,of::compound (D2)

4. Biological activity

4.1 antibacterial

The results,show that,derivetives,reduce significant,antibacterial,effectiveness against bacteria "staphylococcus"aurous:and Escherichia:coli" . the compounds that show good:activity,are (A,B1,C1,C2, ,D1) against (staphylococcus aurous) , and compound that show very good activity are (A-D1),against.(Escherichia coli:,):,the results,of the antibacterial,activity are,shown:in,the fig (6). The results show that derivetives reduce significant antibacterial effectiveness against bacteria "staphylococcus aurous and Escherichia, coli",the compounds that show good activity are (A,B1,B2,C1,C2,D1,D1) against (staphylococcus aurous) , and compound that show very good activity are (A-D1) against, (Escherichia coli) , the results of the antibacterial activity are shown in the fig (6).



Fig, (30) effect: componds :(Staph Aureus) aginst and (E.Coli) aginst

Table (1) the results of the antibacterial activity for (A-D3) derivatives

Comp No	Staph aureus	Mm	E.Coli	Mm
A	+++	37	+++	40
B1	+++	45	+++	30
B2	-	0	-	Zero
C1	-	Zero	+++	45
C2	-	Zero	-	Zero
			-	
D1	++	22.3	+++	30
D2	+++	30.5	-	Zero

(-)No discouragementl

"+= (5-10)mm ,=slightly,:active, ++=, (11-20)mm moderately +++= More,than ,20: good,active"

Table:(2) Proaratese of derivtive (A-D3)derivetives

Comp	M.F M.wat	m.p	R*f*	Colour	%
A	**$C_{17}H_{17}N_4O_6$ 359.11**	**45**	**0.5**	**Brown**	**72**
B1	**$C23H_{22}N_4O_6$450.5**	**120**	**0.47**	**Black**	**90**
B2	**$C23H_{22}N_4O_6$ 450.5**	**115**	**0.5**	**Brown**	**93**
C1	**$C_{30}H_{27}N_5O_7$ 569.6**	**180**	**0.4**	**Black**	**90**
C2	**$C_{30}H_{27}N_5O_7$ 569.6**	**134**	**0.3**	**Brown**	**87**
D1	**$C_{30}H_{25}N_5O_8S$ 615.6**	**160**	**0.2**	**Black**	**79**
D2	**$C_{29}H_{26}N_6O_7S$ 602.6**	**182**	**0.29**	**Black**	**85**

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