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Synthesis of new quinoline -2-one derivatives

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Abstract

Series of new derivatives of quinoline-2-one were synthesized ,*m*-cresol was chosen as the starting material which was reacted with ethyl acetoacetate in presence of conc.sulphuric acid to give 4,7-dimethyl coumarin (I) which treated with nitric acid in the presence of sulpharic acid afforded 4,7-dimethyl-6-nitrocumarin (II) and 4,7-dimethyl-8-nitrocumarin (III) and then the compound (II) was treated with hydrazine hydrate80% to give a new compound 1-amino-4,7-dimethyl-6-nitroquinoline-2(1H)-one (IV).The latter compound was used to synthesize different compounds via the reaction with aldehydic azo compounds (V-VII) by Schiff base reaction to prouduce compounds(VIII-X), these azo compounds were prepared by reaction of different aromatic amines with salicyladehyde. in the other hand the compound (IV) was converted to diazonium salt compound and coupling it with either salicyladehyde to produce compound (XI) or with ethyl acetoacetate to produce compound (XII).These synthesized compounds were characterized by the available physical and spectral methods UV-Visible, FTIR, ^{1}H-NMR.and ^{13}C-NMR spectra.

Keywords: Quinoline-2-one, 4, 7-dimethyl coumarin, Schiff base, azo

تحضير مشتقات جديده للكوينولين-2-اون

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الخلاصه

يشمل هذا البحث تحضير مشتقات جديده للكوينولين 2-اون تم اختيار ميتا كريسول كمادة اولية بمفاعلتها مع اثيل اسيتو اسيتيت بوجود حامض الكبريتيك المركز ليعطي مركب 4،7-ثنائي مثيل كومارين (I) تم مفاعله المركب الناتج مع حامض النتريك بوجود حامض الكبريتيك المركزلينتج مزيج من مركبين ،7,4- ثنائي مثيل-6-نايترو كومارين (II) و4،7- ثنائي مثيل-8-نايترو كومارين(III)بعدها تم مفاعله المركب رقم (II) مع الهيدرازين المائي 80% نتج عنه المركب الجديدN -امينو-3,4-ثنائي مثيل-6-نايترو-كوينولين-2-اون (IV) بعدها تم مفاعله المركب الاميني الناتج مع مركبات ازوالديهايديه مختلفه لينتج مشتقات لقواعد الشف بيس (VIII- X) حضرت صبغات الازوعن طريق مفاعله مركبات اروماتيه امينيه مختلفه مع حامض HCl و $NaNO_2$ لتكوين املاح الدايزونيوم التي اضيفت الى مزيج السلسلديهايد في الماء (VII-V). من ناحيه اخرى تم تحويل المركب الاميني (S4) الى ملح الدايازانيوم وازدواجه مره مع مركب السلسلديهايد لينتج مركب XI ومره مع مركب الاثيل اسيتو اسيتت لينتج مركب XII تم تشخيص المركبات المحضرة بالطرائق الفيزيائية والطيفية المتيسرة UV-visible و FTIR وطيف الرنين النووي المغانطيسي,^{1}H-NMR ^{13}C-NMR

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Introduction

Quinoline derivatives are interesting series of heterocyclic compounds which have been shown to possess a variety of biological a activities such as anticonvulsant[1], antitumor[2] , anti-malarial [3], anti-platelet [4], antidepressant [5], antiulcer [6] and cardiac stimulant[7]. There are several reports on the synthesis of quinoline -2-one, which include many biological activities for example, quinoline-2- etc. one have been synthesized by the reaction of coumarin with amine, hydrazine, phenyl hydrazine, proceed through ring opening of the pyrone ring of coumarin and recyclized to form N-substituted quinoline-2-one derivatives. [8]Schiff bases are well known to have pronounced biological activities, and a form a class of important compounds in medicinal and pharmaceutical field [9]. Some azo compounds have been shown to possess good antibacterial activity[10] The main objective of this work is preparing a series of derivatives of quinoline -2-one .The basic ring was designed to 4,7-dimethyl -6-nitro quinoline -2-one with additional derivatives as diazo and Schiff base schemes-1.

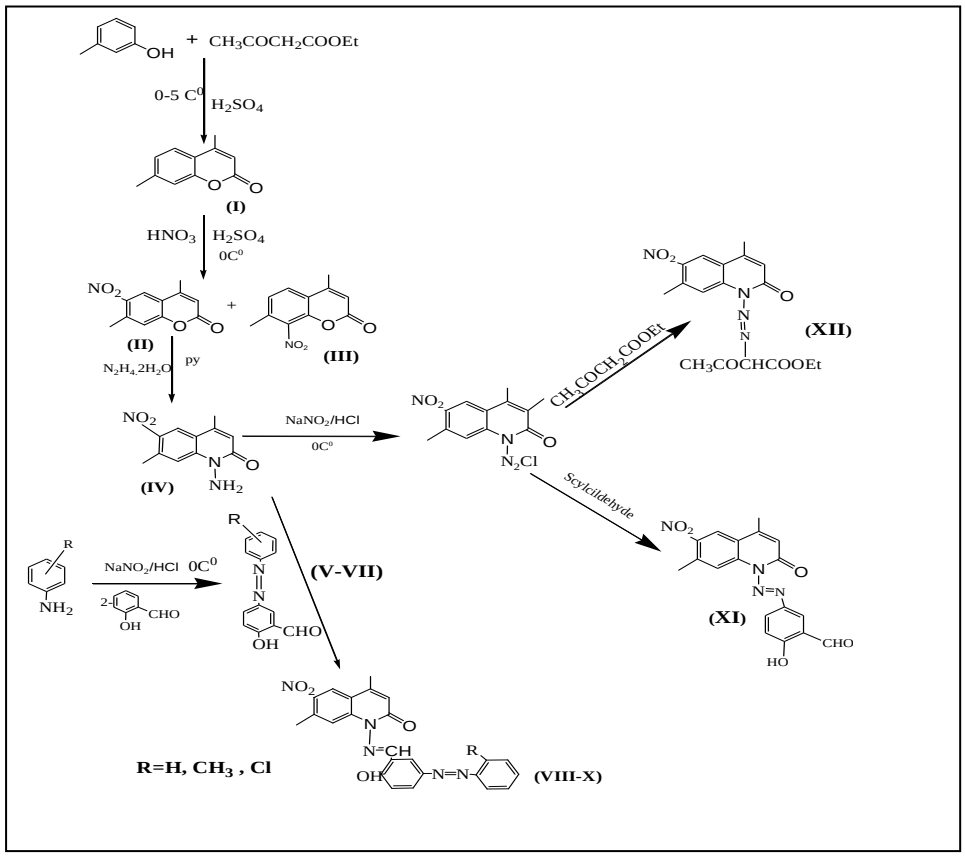
Experimental

A-Instruments:

All chemical used were of reagent grade (supplied by either Merck or Fluka) and used as supplied. The FTIR spectra in the range (4000–400) cm-1 were recorded whithout KBr disc on FTIR 8300 Shimadzu Spectrophotometer ^{1}HNMR and ^{13}C NMR spectrum (solvent DMSO) was recorded on Bruker-DPX 400 MHz spectrometer with TMS as internal standard in Isfahan University. The UV-Visible spectra were measured in DMF as solvent using Shimadzu UV-Vis. 160 A spectrophotometer in the range (200-1000) nm.Melting points were determined on Gallen-kamp MFB-600 melting point apparatus. Analytical thin layer chromatography (TLC) in (hexane: ethyl acetate)7:3 as mobile phase was performed on plates precoated with silica gel (Merck 60 F254,0.25 mm) visualizing with ultraviolate light.

B-Chemicals:

All chemicals used were of high purity as the manufactures supplied starting chemical compounds were obtained from BDH, Sigma Aldrich, fluka and used as received.



Scheme1-Synthesis of new quinoline -2-one derivatives

Synthesis of 4,7-dimethyl coumarin (I)[11]

Mixture of (0.1 mol) 12.18 ml from *m*-cresol and (0.1 mol)12.634ml of ethyl acetoacetate was cooled down below (0-4)C^{o} ,46ml of conc. Sulphuric acid was added drop wise in such a way that the temperature does not rise above $8C^{O}$ and the stirring was continued for one hour at room temperature then heating at (60-70C^{O}) for 6 an hour after that the mixture was cooled then poured into ice /cold water ,the solid product was filtered and wash with cold water, dried at room temperature, then recrystallized from mixture EtOH:H_2O (1:1) the resultant yield 80% ,m.p 131-133C^{O}

Synthesis of 4,7- dimethyl -6-nitro coumarin and4,7- dimethyl -8-nitro coumarin :(II and III) [12,13]

A mixture of 4,7-dimethylcoumarin(I) (0.004mole) and conc. Sulphuric acid (75ml) was stirred at $0C^{O}$ for 20minutes .then a mixture conc.sulphuric acid (1.25ml,98%)and conc.nitric acid (0.4ml,d1.4) was added at(0-5)C^{O} and reaction was stirred for 3 hours at $5C^{O}$ .then the mixture was poured into ice /cold water ,the solid product was filtered and dried ,then the crude mixture was separated in ethanol by using schexualite apparatus ,the precipitate that did not dissolve in hot ethanol is 4,7 dimethy-6-nitro coumarin (II)m.p 259-260C^{O} ,yield 80%recrystallized from ethyl acetate . concentrated the filtrate ,cooled ,the ppt. was 4,7-dimethyl -8-nitrocoumarin(III) soon crystallized out .recrystallized from ethanol m.p242-243C^{O} yield 20%

Synthesis of 1- amino-4, 7-dimethyl -6-nitro-1H-quinoline-2-one: (IV)[14]

Compound (II) (0.05mole) was dissolved in anhydrous pyridine (20ml), $N_2H_4.H_2O$(80%) 0.15mole was added to above solution . the reaction mixture was refluxed for 6hr.with stirred at $117C^{O}$. The solvent was consterated by rotary then added additional amount from ethanol(10ml) and the excess solvent was removed by rotary again. The crude product was recrystallized m.p 269-271C^{O} pale yellow color. 95%

Synthesis of 2- hydroxyl -5-(phenyldiazenyl) benzaldehyde (V-VII)[15]

Azo dye was synthesized according to the published procedure [15] with some modification. Primary aromatic amines (0.1mole) was dissolved in conc. HCl (5ml) by heating to $70C^{O}$ for about (10mint.) until complete dissolution and formed salt .then this solution was cooled to (0-4C^{o}) and was diazotized below $4C^{0}$ with aqueous sodium nitrite (0.1mole,100ml) with vigorous stirring and the temperature was kept to (0-4C^{O}) for 30mint to give diazonium salt . then poured this solution was carefully added with stirring to mixture of salicyladehyde in water (100ml, 0.1mole)at (1-4C^{O}).the pH of reaction mixture must be at (8.5-9) by simultaneous addition of 5%NaOH aqueous solution .the mixture was kept overnight in refrigerator .the mixture was saturated with NaCl then extracted by ethyl acetate with separatory funnel the organic layer was separated then evaporated it to give the azo compounds

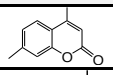
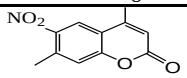
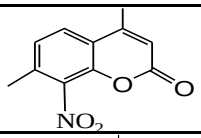
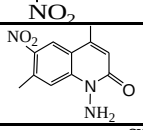
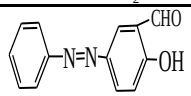
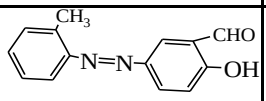
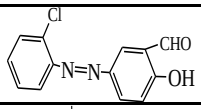
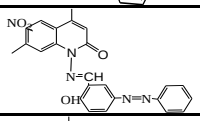
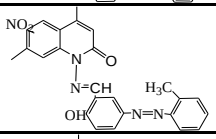
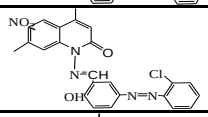
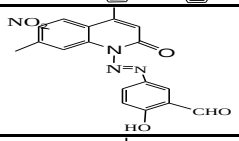
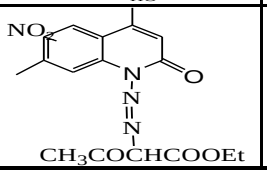
Synthesis of 4,7dimethyl -6-nitro-1-{[(2-hydroxy-5-((aryl)diazenyl) phenyl) methylidene]amino}(2H) quinoline-2-one (VIII-X)[16]

A mixture of 2-hydroxy-5-((aryl)diazenyl)benzaldehyde (V-VII)(0.015mole) and 1-amino-4,7-dimethyl-6-nitro-1H-quinoline-2-one(IV) (0.015mole) in ethanol absolute and in presence of 4 drops of glicail acetic acid was refluxed for (8-10hrs.) the progress of the reaction was monitored by T.L.C hexane : ethylacetate (7:3) after complete the period of time ,the mixture was cooled and poured into few ice/cold water .the precipitated compounds were filtered .They were recrystallized in mixture of (EtOH:H_2O); (1:1) ratio)

Compound (XI) and (XII) [17]

A suspension of compound (IV) (10 mmol) in hydrochloric acid (9 mL) and water (4 mL) was heated to 70 °C until complete dissolve. The clear solution was poured into ice water and was diazotized below 5 °C with aqueous sodium nitrite (0.7g, 10 mmol) dissolved in water (2.5 mL). The cold diazonium solution was added over the course of 30 min at 0 °C to a solution of either salicylaldehyde or ethyl acetoacetate (, 40 mmol)in water (18.75 mL) containing sodium hydroxide (0.4 g) and sodium carbonate (3.7 g). During the addition process, the solution was vigorously stirred. The product was collected by vacuum filtration and wash with NaCl solution (25ml, 10%). Coupling of the diazonium reagent to the salicylaldehyde occurred at the position para to the hydroxyl group. Physical properties of all these new compounds showed in table-1.

Table 1-physical properties of compound (1-12)

Comp .No.	Structures	M.P.^{0}C	color	Spectral data UV, ƛmax in DMF	Purification solvent	Yield%	R.F in hexane: etheyl acetate 7:3
I		131-133	white	371 281	Ethanol:H20	75	0.6
II		259-260	Pale yellow	317 265 231	Ethyl acetate	80	0.5
III		242-243	yellow	310 260 230	Ethyl acetate	20	0.4
IV		269-271	yellow	349 257	Ethanol or Toluene	90	0.16
V		290 decomp.	red	451 370 247	Ethanol	75	0.66
VI		171-172	brown	451 247	Ethanol:H_2O	73	0.71
VII		133-135	Orange	463 256	Ethanol	80	0.72
VIII		212dec..	Reddish yellow	502 245	Ethyl acetate	72	0.77
IX		277-279	Brown	352 240	Ethanol	62	0.86
X		140-145	Reddish yellow	511 250	Ethanol	80	0.81
XI		190-193	Pale yellow	425 226	Ethanol	40	0.74
XII		220-225	orange	420 220	Ethanol	30	0.7

Results and discussion

Coumarin is used for preparation of heterocyclic compounds starting from *m*-cresol to produce 4,7dimethyl coumarin (I).the FTIR spectrum of it showed the appearance of characteristic absorption very strong band near 1716 cm^{-1} belonging to (C=O) band of lactone ring. The ^{1}H-NMR spectrum of compound(I) showed the proton signals due to two groups of CH_3 were recorded at 2.4 ppm and 2.6 ppm also showed three signals appeared at 7.2-7.7ppm for three aromatic protons and singlet signal at 6.3ppm for one proton of lactone ring while the ^{13}C-NMR spectrum for the same compound showed 17.9 ppm and 20ppm for two groups of CH_3, the signal at 116,117,125,125,142,152,and153 ppm belong to aromatic carbons and 159 ppm for carbonyl carbon. The nitration compound (I) using concentrated nitric acid sulphric acid at 0C^O gives mixture from 80% 4,7-dimethyl- 6-nitro coumarin

(II) m.p259-260 ^{0}C,and 20%4,7-dimethyl- 8-nitro coumarin(III) m.p 242-243. FTIR spectrum of compound (II) showed appearance of absorption band for C=O of ring lactone at 1734cm^{-1} and appearance of new absorption band at 1354 cm^{-1} and 1527 cm^{-1} belonging to symmetric and asymmetric to the NO_2 group[18]. The ^{1}H-NMR spectrum of the 4,7-dimethyl- 6-nitro coumarin (II) showed signals at 2.4ppm (3H,s,4-CH_3); 2.6 ppm (3H,s,7-CH_3); 8.375ppm (s,1H,CH-C-NO_2) ; 6.525ppm (s,IH,CH-C=O),and 7.56ppm (s,1Haromatic, (CH-C-O)).^{13}C-NMRspecrum showed signals at (17.82 and 19.708ppm) for 2CH_3,154(C-O),152ppm(C-NO_2), (122-115)ppm for three aromatic ring carbons and 158 ppm for carbonyl carbon of lactone ring (O-C=O).

Another isomer of nitro coumarin derivatives was 4,7- dimethyl -8-nitro coumarin Compound (III) showed difference solubility in hot ethanol , melting point and RF of TLC from compound (II) 4,7-dimethyl -6-nitro coumarin. FTIR of compound (III) showed strong band at 1737 cm^{-1} for carbonyl compound and two strong bands at 1518and 1348cm^{-1} for asymmetric and symmetric for NO_2 group

The treatment of compound (II) with the hydrazine hydrate 80% produced N-amino quinoline -2-one derivatives (IV) the reaction was proceeded by nucleophilic substitution of hydrazine to the cyclic ester (lactone) carbonyl group giving the corresponding amino compound (IV).the FTIR spectrum of compound(IV) showed the appearance of characteristic absorption band at 3229 and 3196 cm^{-1} which belong to the NH_2 and 1672cm^{-1} due to amid carbonyl cyclic lactam group υ C=O.The^1 H-NMR spectrum of compound (IV) showed signal at 2.4ppm and 2.6ppm for (s, 6H,2CH_3)for two methyl groups(2CH_3) and at 5.85 ppm for (s, 2H,NH_2) ,and signals at 6.717,7.917,and8.412ppm for three aromatic protons.^{13}C-NMR spectrum for compound(IV) showed signals at 18.5 And 20.5ppm for (2CH_3) and showed signals at 117.86,117.99,134.73,135.4,and141.76ppm for aromatic carbons, 142ppm for carbon of amino group C-NH_2 , 145ppm for (C-NO_2) and 159 ppm for carbonyl group.

The compound (IV) treated with different azo compounds that contain aldehydic group by Schiff base reaction to produce the compounds (VIII-X). The intermediate compounds 2-hydroxy-5 ((aryl)diazenyl) benzaldehyde (V-VII) were synthesized by the reaction of salicyladehyde with different aromatic amines in conc.HCl and $NaNO_2$ mixture .The IR spectra for these compounds are the following :-

Compound (V)

2-hydroxy-5-(phenyl daizenyl) benzaldehyde1604 υ (C=C), 1477 υ (N=N),1660(aldehydic υ C=O)

Compound (VI)

2-hydroxy-5-(o-tolyl diazenyl) benzaldehyde 1598 υ (C=C), 1479 υ (N=N),1689(aldehydic υ (C=O))

Compound (VII)

2-hydroxy-5-((o-chlorophenyl) diazenyl) benzaldehyde 1607 υ (C=C),1476 υ (N=N),1649 (aldehydic υ C=O) All these data are listed in Table-2. And the spectra FTIR of some these compounds are showed in figures -1-3.

Table 2-FTIR for compounds (I- VI)

Comp. No	υ OH	υ NH	υ CH aromatic	υ CH aliphatic	υ C=O	υ C=N	υ C=C aromatic	υ NO_2	Other bands
I	-	-	3078	2960as 2869sy	Ester 1716	-	1620		-
II	-	-	3124	2960	1734	-	1622	1354 1527	-
III	-	-	3086	2950	1737	-	-	1348 1518	-
IV		3293 3196	3086	2983as 2929sy	1672	-	1616	1344 1519	-
V	3460 broad	-	3059	-	1660	-	1604	-	1477=N, 2853, 2744for C-H alde
VI	3415 broad	-	3040	2954asy 2923sy	1689	-	1598	-	1479 N=N, 2853 2745 for C-H alde
VII	3477 broad		3062	2948 2867	1649	-	1607	-	2867 2742 for C-H alde 619C-Cl

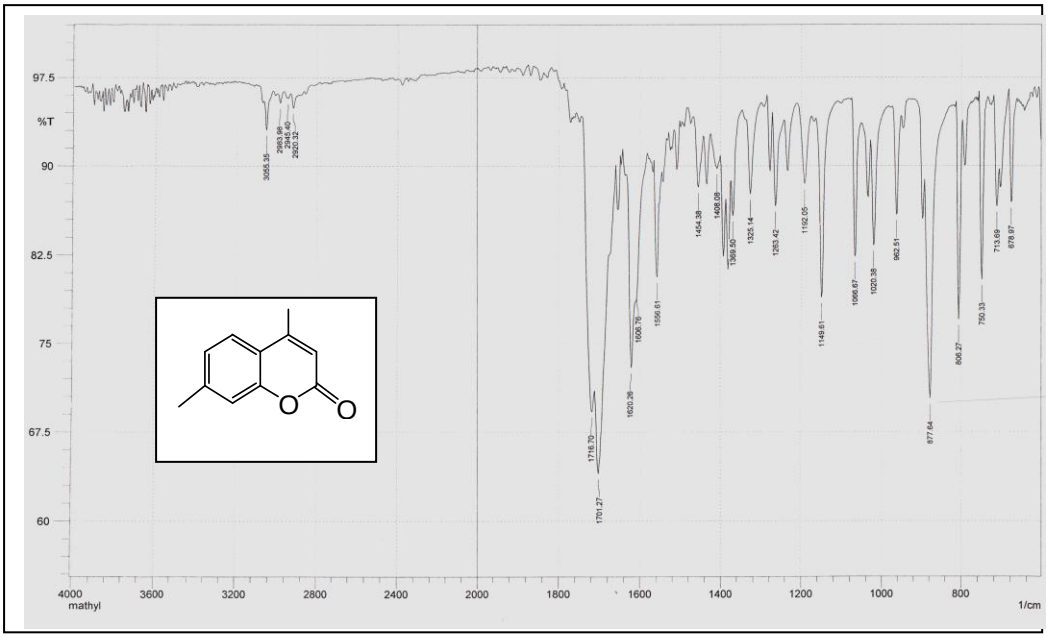


Figure 1- FTIR spectrum for compound (I)

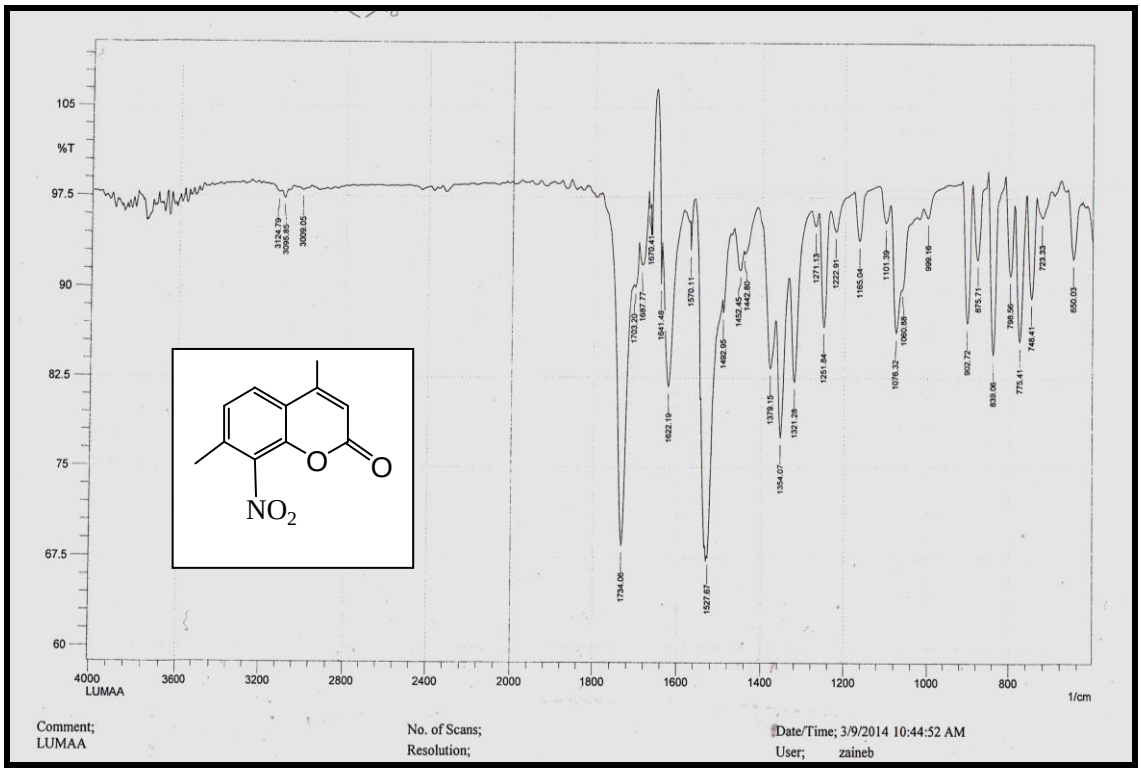


Figure 2- FTIR spectrum for compound (III)

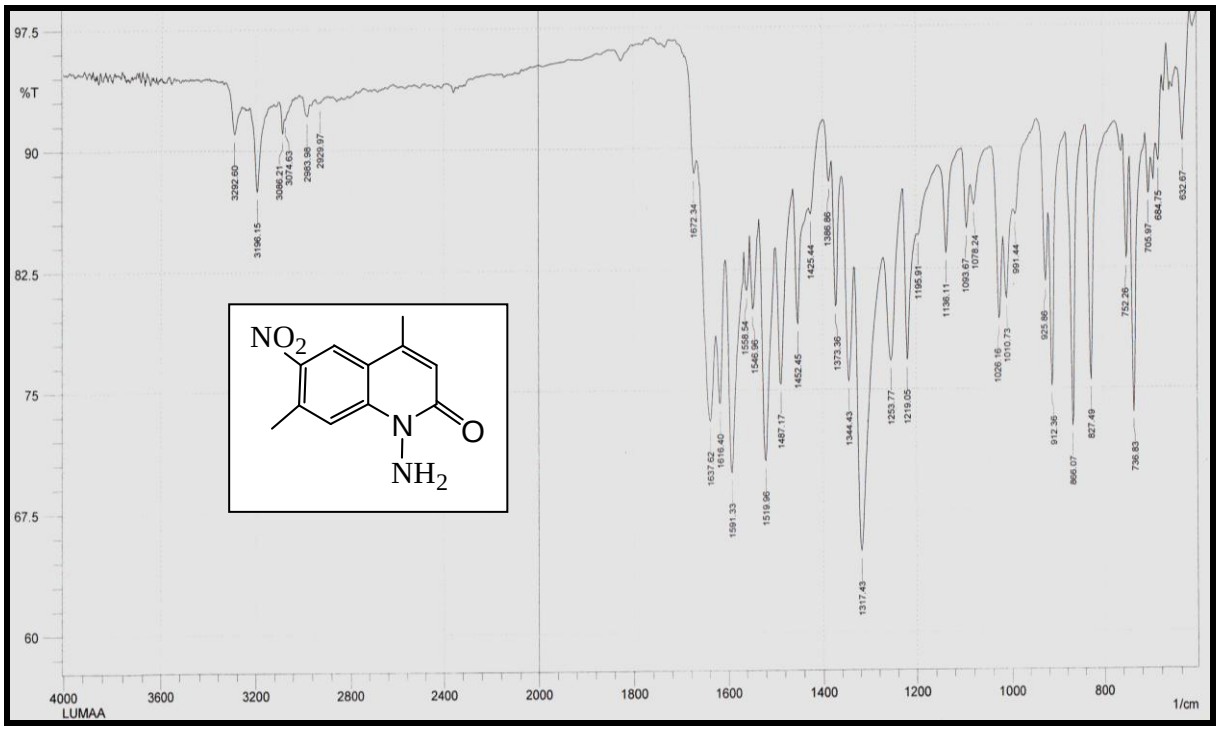


Figure 3- FTIR spectrum for compound (V)

The spectra data of ^{1}H-NMR and ^{1}C-NMR of these compounds (I, II, IV,) are showed in table-3 and table-4.

Table 3- ^{1}H-NMR spectra of some synthesized compounds

Comp.No.	^{1}H-NMR
I	2.4(s,3H,CH_3),2.6(s,3H,CH_3),6.3 (s,1H,C-H lactam ring), 7.2-7.7 (m,3H,C-H aromatic)
II	2.4(s,3H,CH_3),2.6(s,3H,CH_3), 6.5(s,1H,C-H lactam ring), 7.5 (s,1Haromatic),8.3(s,1H aromatic),
IV	2.4(s,3H,CH_3),2.6(s,3H,CH_3),5.8(s,2H,NH_2),6.7(s,1H,H lactam ring), 7.9(s,H,1 H aromatic),8.4(s,1H,Haromatic)

Table 4- ^{13}C-NMR of some preparing compounds (I -IV)

Comp.No.	^{13}C-NMR
I	17.9,20,113,116,117,125,125,142,152,153, 159
II	17.8,19.7,115,118,110,122,137,144,152,154,158
IV	18,21, 117,121, 123,134, 135, 141, 142, 145,159

And the spectra of ^{1}H-NMR and ^{1}C-NMR of some these compounds are showed in figures-4-9.

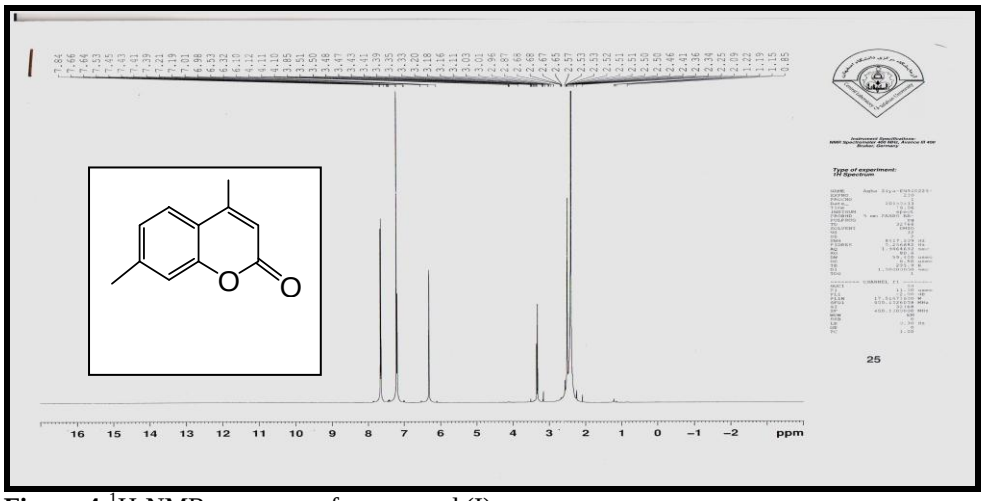


Figure 4-^{1}H-NMR spectrum of compound (I)

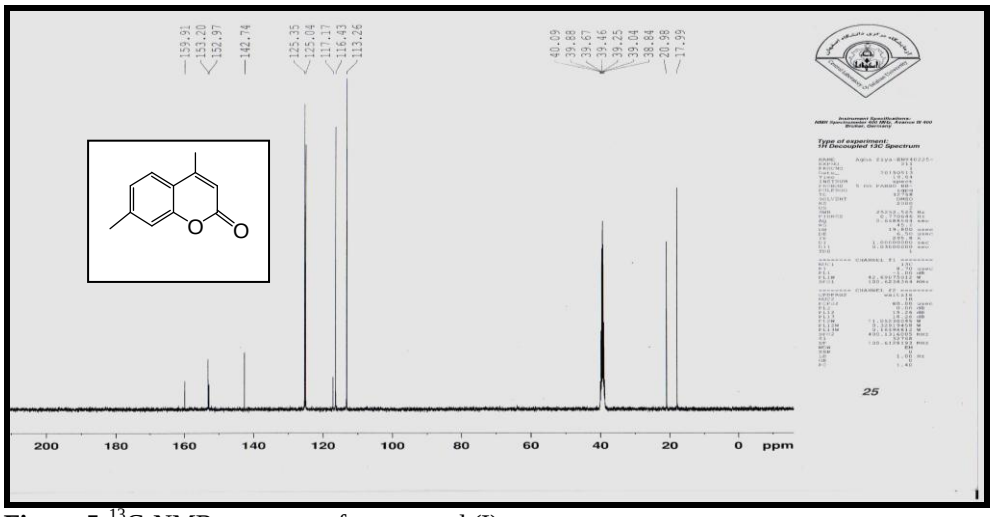


Figure 5-^{13}C-NMR spectrum of compound (I)

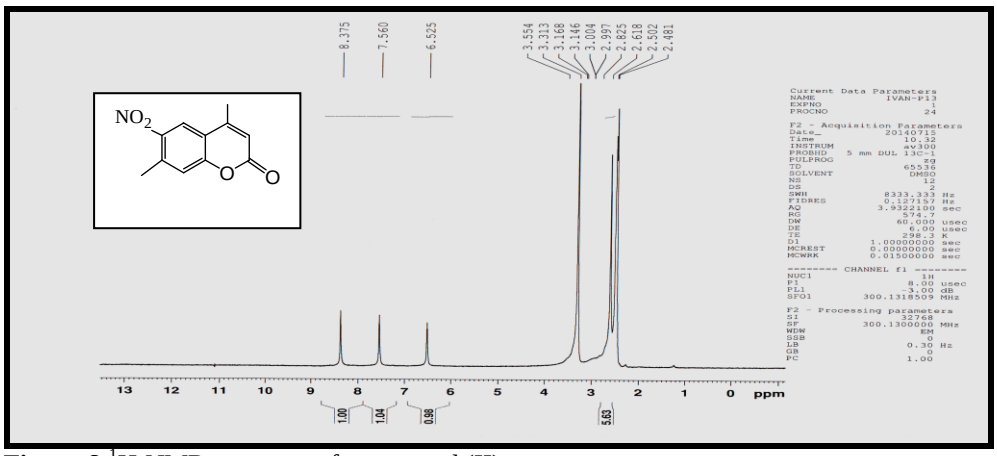


Figure 6-^{1}H-NMR spectrum of compound (II)

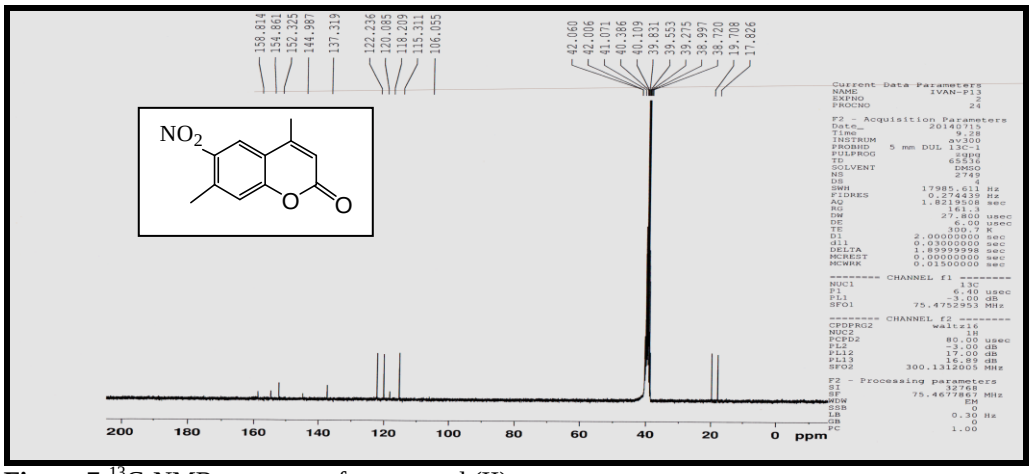


Figure 7-^{13}C-NMR spectrum of compound (II)

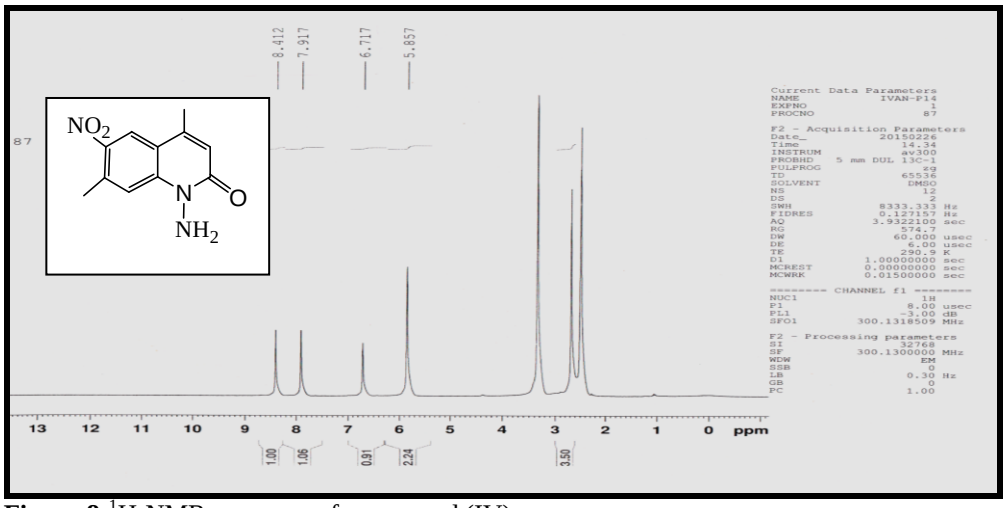


Figure 8-^{1}H-NMR spectrum of compound (IV)

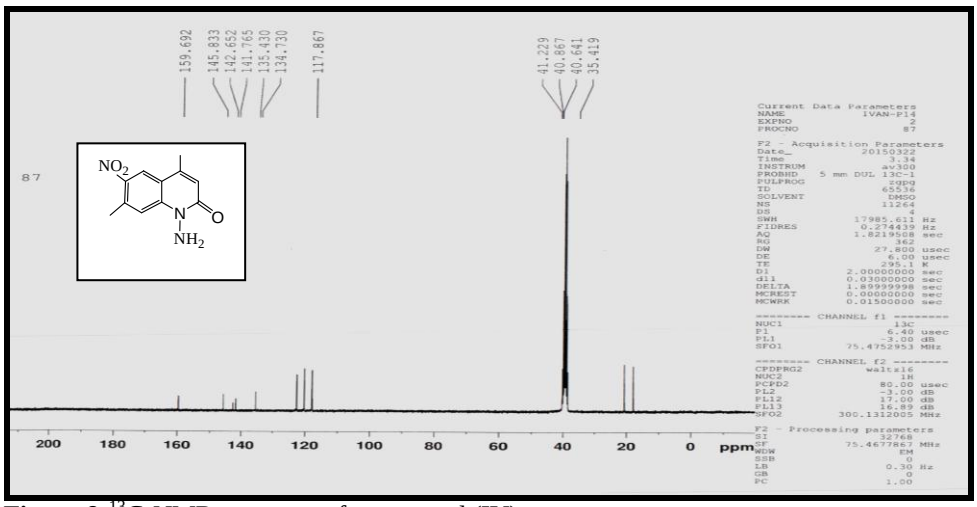


Figure 9-^{13}C-NMR spectrum of compound (IV)

The condensation reaction between N-amino-4,7-dimethyl-6-nitrocoumarin-2-one (IV) and different aromatic azo aldehyde compounds (V-VII) involved nucleophilic addition of aromatic amine (IV) to carbonyl group of prepared azo compounds to produce the desirable Schiff base (VIII-X) FTIR spectra of compounds (VIII-X) showed bands at (1660-1624)cm^{-1} due to υ(C=N) and disappearance absorption bands at(3293,3196) cm^{-1} due to υ(NH_2) asymmetric and symmetric bands. ^{1}H-NMR spectrum data of compound IX showed singlet signal at1.9 ppm due to CH_3 protons of phenyl group,

two singlet signals at 2.3 and 2.6 ppm for two CH_3 groups (4-$CH_3$and 7-CH_3) , singlet signals at 9.14ppm for imine proton (N=C-H) ,multi signals at (6.9-8.39)ppm due to aromatic protons and signal at10.3 ppm for (Ar-OH) proton. Table-3 ^{1}H-NMR spectrum data of compound X showed 2.3 ppm due to CH_3 of lactam ring , multi signals (7-8.3ppm) due to aromatic protons, singlet signal at 9.11ppm for proton of imine (N=CH). Table-3. The FTIR spectra of compound (XI) showed band at 1773 $cm^{-1}$for aldehyde carbonyl group ,1660 cm^{-1} for carbonyl amide of lactam ring, broad band at 3300 cm^{-1}due to hydroxyl group of phenol and two band 2800and 2740 $cm^{-1}$for υ (C-H) aldehydic group All spectral data of prepared compounds (VIII -XII)are listed in table-5 and table-6.

The FTIR spectra of compound (XII) showed band at 1755cm^{-1} due to ester carbonyl group, 1714 cm^{-1} due to ketone carbonyl group, 1672 cm^{-1} due to amide carbonyl of lactam ring and the spectral of some these compounds are showed in figure-10-13.

Table 5- IR spectral data of compounds (VIII -XII)

Comp. No	υ OH	υ NH	υ CH aromatic	υ CH aliphatic	υ C=O	υ C=N	υ C=C aromatic	υ NO_2	Other bands
VIII	3450 broad		3050	2900 2850	1639		1569	1325 1489	
IX	3481 broad		3022	2923	1624	1624	1571	1309 1485	
X	3357 broad	3600-3220	3064	2927 2879	1625	1625	1577	1315 1485	C-Cl
XI	3300 broad	-	3063	2962 2926 2858	1660 amid 1773 alde	1626	1600	1525 1323	C-H aldehydic 2800 2740
XII	3379 tou		3153	2982 2918 2854	1755 ester 1714 ketone 1672 amide	1660	1612	1527 1321	

Table 6-^{1}H-NMR spectra of some synthesized compounds(IX and X)

Comp.No.	^{1}H-NMR
IX	1.9(s,3H,CH_3,CH_3ph),2.3(s,3H,CH_3),2.6(s,3H,CH_3),6.9-8.39(m,10H for aromatic protons), 9.14(s,1H,N=CH imine proton), 10.3(s,1H,OHAr)
X	2.3(s,3H,CH_3 lactam ring) 2.5(s,3H,CH_3 for fused ring),7-8.3(m,10H aromatic protons),9.11(s,1H,N=CH,imine proton),11.2(s,1H,OHAr)

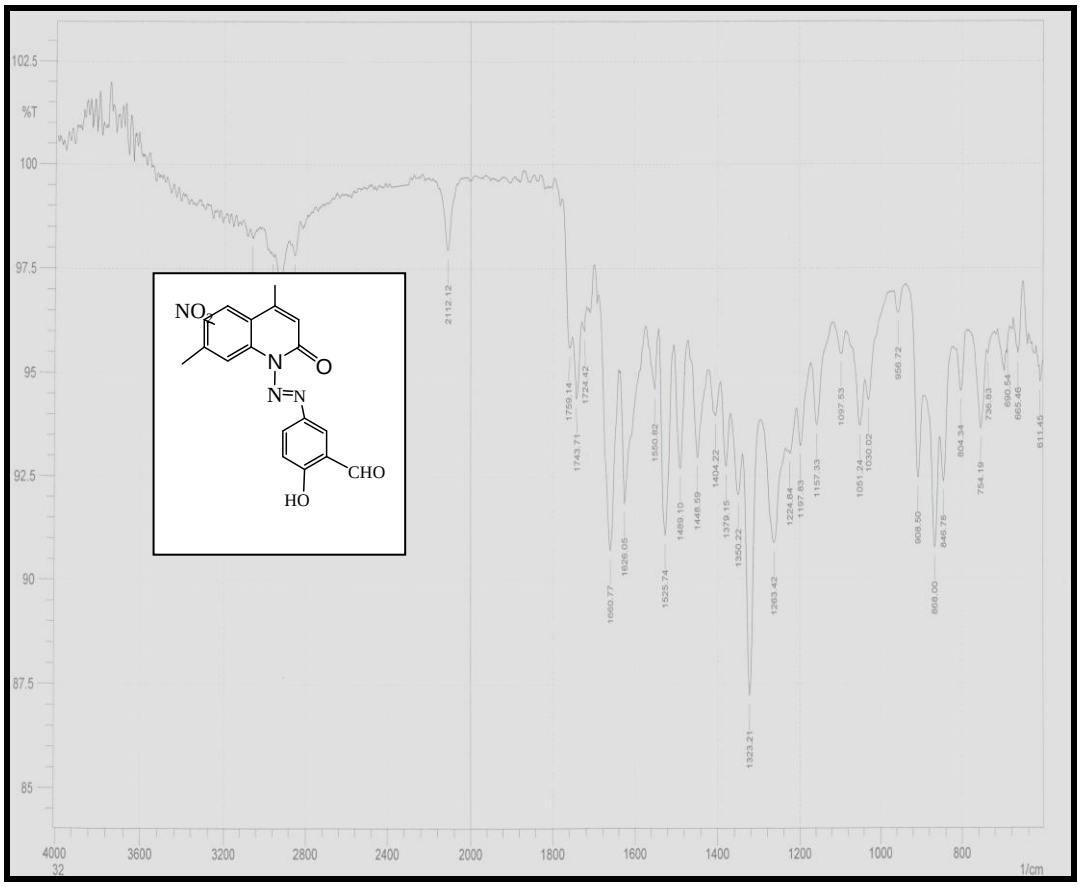


Figure 1- FTIR spectrum for compound (XI)

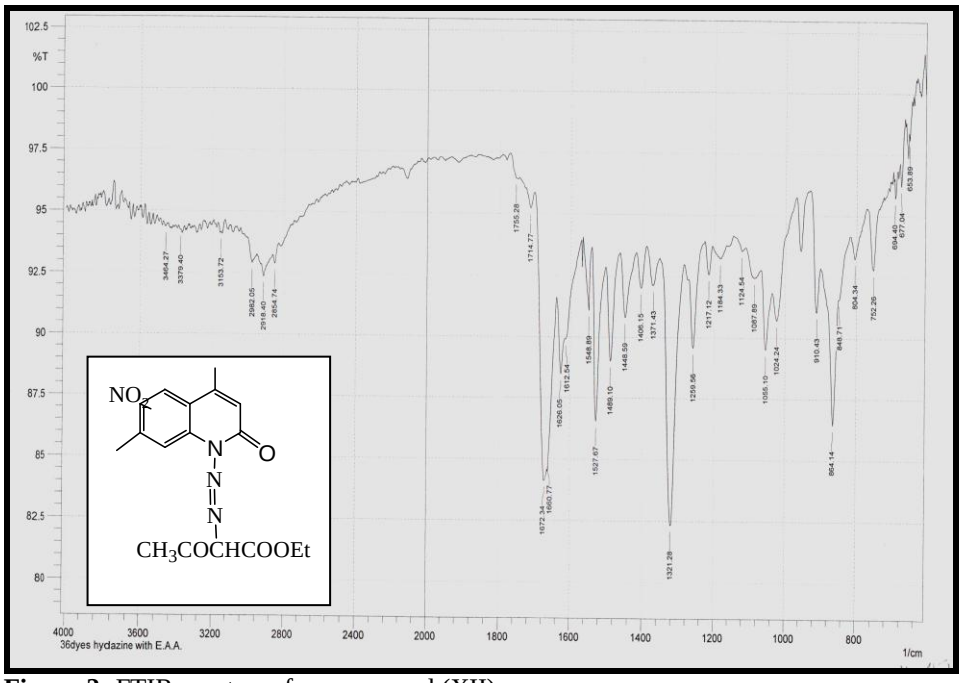


Figure 2- FTIR spectrum for compound (XII)

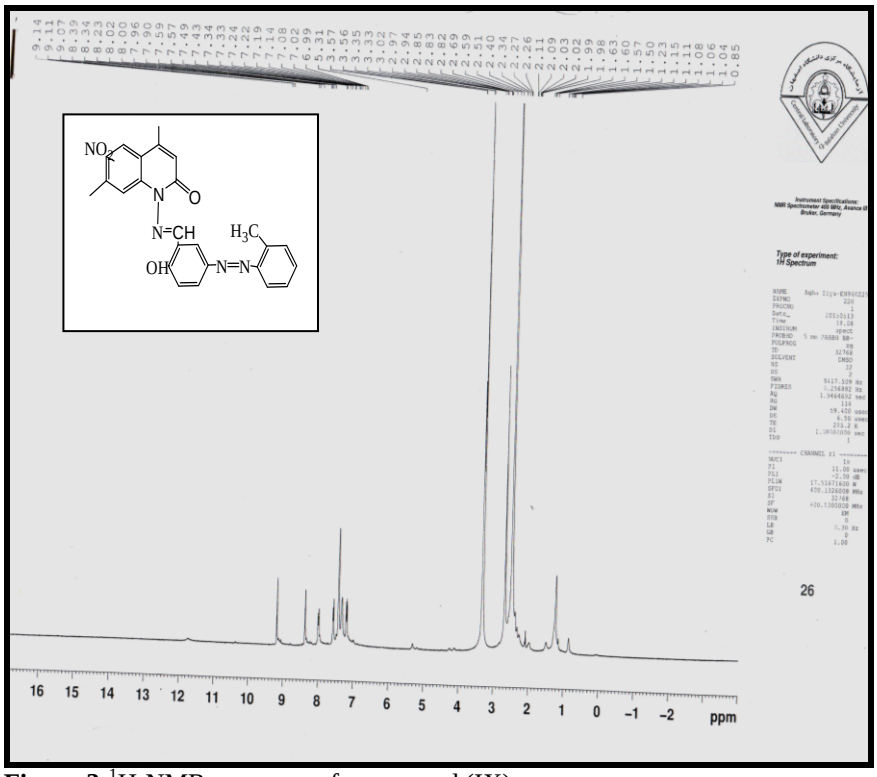


Figure 3-[1]H-NMR spectrum of compound (IX)

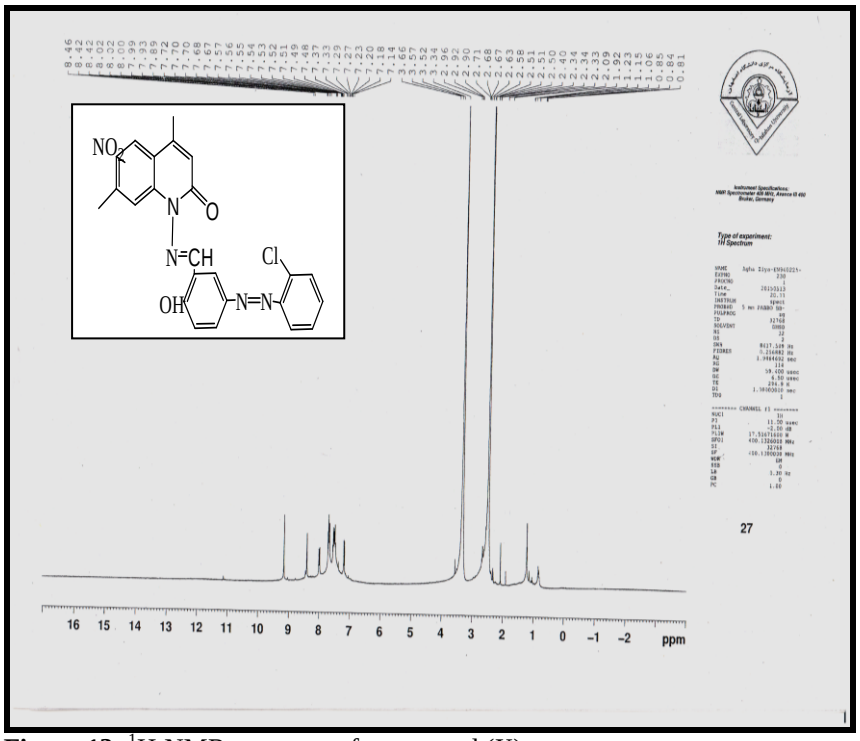


Figure 13- [1]H-NMR spectrum of compound (X)

Conclusions

In conclusion, new compounds of synthesis of new quinoline -2-one derivatives were synthesized in good yield and they were characterized by different spectral studies. UV-Visble, FTIR, [1]H-NMR and [12] C-NMR spectra**.**

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