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Synthesis of some new 2,4-dihydroxyquinoline derivatives by cyclization reaction of *N*-phenylmalonamic acid and study the biological activity for some of them

Naji M. Ali, College of Pharmacy, Department of Pharmaceutical Chemistry, University of Kufa
Ahmed H. Mageed

Abstract

In this paper a synthesis of some new 2,4-dihydroxyquinoline and 4-hydroxycoumarin derivatives have been described. The route of preparation involved the uses of Meldrum's acid as starting material and treated with different substitution hydroxy and amino aromatic compounds and the product have been cyclized by using polyphosphoric acid . The spectral were used (FT-I.R, ^{1}H-NMR) and CHN analysis to support the structures of the products. The prepared compounds have been tested against *Staphylococcus arueus* bacteria.

الخلاصة

تم في هذا البحث تحضير عدد من مشتقات 4,2- ثنائي هيدروكسي كوينولين و 4- هيدروكسي كيومارين من خلال مفاعلة حامض الميلدرم مع عدد من مركبات الهيدروكسي والامينو الاروماتية المعوضة . ومن ثم تم حولقة الناتج باستخدام حامض البولي فوسفوريك . لقد استخدمت الطرائق الطيفية (^{1}H-NMR, FT-I.R) وتحليل العناصر الدقيق.C.H.N للتحقق من تراكيب النواتج. وتم ايضا في هذا البحث دراسة الفعالية البايولوجية لهذه المركبات المحضرة تجاه بكتريا ستافيلوكوكوس ايريس .

Introduction

Coumarin derivatives possessing diverse biological activities play important roles as versatile building blocks for the synthesis of natural products and biologically active compounds.(1) In particular, 4-hydroxycoumarin derivatives, such as 4-hydroxycoumarin(2) and 4-hydroxythiocoumarin,(3) have been used as useful intermediates for the synthesis of anticoagulants, herbicides, and anticancer agents. Recent reports show 4-hydroxy-2-quinolone derivatives are selective glycine site antagonists related to several central nervous system disorders including stroke, epilepsy, schizophrenia, Parkinson's disease, and Alzheimer's disease.(4) Furthermore, coumarin derivatives, possessing a hetrocyclic skeleton with a ring oxygen on a carbonyl group, are well-known fluorescence dyes for their high photoluminescence quantum efficiencies. A number of coumarins have been synthesized and explored the possibility of their application to electrooptic materials, such as laser dyes, organic scintillators, and photoelectonic sensitizers.(5)

One of the method used in the literature for synthesize of coumarin derivatives is reported by Pechman reaction which involves the condensation of phenols with β-ketoesters in the presence of a variety of Lewis acid catalysts and gives good yields of 4-substituted coumarins.(6)

Experimental

Instruments

The following measurements were used to characterize the prepared organic compounds.

1- Melting point measurement:
Electro thermal 1A melting point apparatus was used to measure the melting point of prepared compounds, Kufa University (Iraq) .
2- Infrared spectra:
Infrared spectra were recorded as KBr discs using Fourier Transform Infrared Spectrophotometer FTIR-8400s SHIMADZU, Kufa University (Iraq).
3- Nuclear Magnetic Resonance (^{1}H-NMR) spectra:
^{1}H-NMR spectra were recorded by Brukur ,Ultra Shield 300 MHz, Switzerland with TMS as internal standard in DMSO-d^{6}, Al-albayt University(Jordan) .
4- C.H.N. Analysis:
Elemental Analysis, E. A. G. E. R. -100, Carlo Erba strumentazione, Italy, Babylon University (Iraq)
5- The biological test have been done in College of Science , Department of Biology , Kufa University (Iraq)

Preparation of compound (A1)

2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid)

Malonic acid (52g , 0.5 mol) , acetone (40 mL , 0.55 mol) and sulfuric acid (1.5 mL , 0.03 mol) were placed in a reactor at 0 ^{o}C with stirring under nitrogen purge . Within one half hour , addition of acetic anhydride (60 mL , 0.6 mol) was begun dropwise at a rate of approximately 2mL/min . The mixture began as a white slurry and gradually turned pale yellow by the end of the addition of acetic anhydride ; the mixture was left out for 18 hrs at 0 ^{o}C ; after which the mixture becomes a yellow slurry .Filtered the crystals of Meldrum's acid by suction, and washed three times with enough ice water to covered the cake. The air-dried product is afterwards purified by recrystallization.(7) Recrystallization of Meldrum's acid from acetone gave a colorless crystal with a M.P.of 95-96 ^{o}C. for a total of 40g (76.92 percent yield) of Meldrum's acid .

Preparation of compounds (A2 and A3)

N-phenylmalonamic acid

A mixture of aniline derivative (0.002 mol) and Meldrum's acid (0.288g 0.002 mol) was stirred at 85 ^{o}C for 9 hrs . After cooling to room temperature , the reaction mixture was partitioned with ethyl acetate (3×20 mL) and saturated $NaHCO_3$ solution . The aqueous layer was acidified to pH = 1-2 with conc. HCl and extracted with methylene chloride (3× 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated to give 86% of product .(8)

Preparation of compound (A4)
3,3'-(1,4-phenylene bis(azanediyl))bis(3-oxopropanoic acid)

A mixture of *p*-phenylene diamine (0.21g , 0.002 mol) and Meldrum's acid (0.57g,0.004 mol) was stirred at 85 ^{o}C for 9 hrs . After cooling to room temperature , the reaction mixture was partitioned with ethyl acetate (3×20 mL) and saturated $NaHCO_3$ solution . The aqueous layer was acidified to pH = 1-2 with conc. HCl and extracted with methylene chloride (3× 20 mL). The combined extracts were dried over $MgSO_4$ [8]. The violet colored compound was recrystallized from ethanol to give the product(A4) M.P. 169 – 171 ^{o}C. ,(62.5% yield).

Preparation of compound (A5)

3,3'- (3,3'-dimethylbiphenyl-4,4'-diyl)bis(azanediyl)bis(3-oxopropanoic acid)

A mixture of *o*-Tolidine (0.42g , 0.002 mol) and Meldrum's acid (0.57g 0.004 mol) was stirred at 85 ^{o}C for 9 hrs . After cooling to room temperature , the reaction mixture was partitioned with ethyl acetate (3×20 mL) and saturated $NaHCO_3$ solution . The aqueous layer was acidified to pH = 1-2 with conc. HCl and extracted with methylene chloride (3× 20 mL). The combined extracts were dried over $MgSO_4$ [8]. The green colored compound was recrystallized from ethanol to give the product(A5) M.P. 167 - 169 ^{o}C. , (60% yield) .

Preparation of compound (A6)

3,3'-(1,3-phenylene bis(oxy))bis (3-oxopropanoic acid)

A mixture of Resorcinol (0.22g , 0.002 mol) and Meldrum's acid (0.57g, 0.004 mol) was stirred at 90 ^{o}C for 4 hrs . After cooling to room temperature , the reaction mixture was partitioned with ethyl acetate (3×20 mL) and saturated $NaHCO_3$ solution . The aqueous layer was acidified to pH = 1-2 with conc. HCl and extracted with methylene chloride (3× 20 mL). The combined extracts were dried over $MgSO_4$ [9]. The pink colored compound was recrystallized from benzene to give the product (A6) M.P. 87 - 89 ^{o}C. , (90% yield).

Preparation of compound (A7)
2,4-dihydroxy-6- methoxy quinoline

P_2O_5 (5g) was added to 2.5 mL of 85% H_3PO_4 ,then the mixture was stirred at 100 ^{o}C for two hrs to obtain polyphosphoric acid (PPA) (molar ratio of P_2O_5 / H_3PO_4 : 1.0).

The prepared polyphosphoric acid 4 mLwas added to (0.41 g , 0.002 mol) of compound (A2), and the mixture was heated with stirring at 140 ^{o}C for 4 hrs.

After completion of the reaction, the mixture was poured into distilled water . The precipitate was filtered by suction , washed with distilled water and dried in the air to give a solid [10]which was recrystallized from acetic acid to afford 0.1 g (25%) of compound (A7), as a violet powder, M.P. 299 - 301 ^{o}C .

preparation of compound (A8)

2,4-dihydroxy-7,8-dimethyl quinoline

P_2O_5 (5g) was added to 2.5 mL of 85% H_3PO_4 ,then the mixture was stirred at 100 ^oC for 2 hrs to obtain polyphosphoric acid (molar ratio of P_2O_5 / H_3PO_4 : 1.0).

The prepared polyphosphoric acid 4 mL was added to compound (A3) (0.41 g , 0.002 mol) then the mixture was heated with stirring at 140 ^oC for 4 hrs.

After completion of the reaction, the mixture was poured into distilled water . The precipitate was filtered by suction , washed with distilled water and dried in the air to give a solid[10] which was recrystallized from acetic acid to afford 0.15 g (36.5%) of compound (A8), as a yellow powder, M.P. 306 - 308 ^oC .

Preparation of compound (A9)

2,4,7,9-tetrahydroxy pyrido(2,3-g)quinoline

P_2O_5 (10 g) was added to 5 mL of 85% H_3PO_4 then the mixture was stirred at 100 ^oC for 2 hrs to obtain polyphosphoric acid (molar ratio of P_2O_5 / H_3PO_4 : 1.0).

The prepared polyphosphoric acid (11 mL) was added to compound (A4) (0.56 g , 0.002 mol) then the mixture was heated with stirring at 140 ^oC for 6 hrs.

After completion of the reaction, the mixture was poured into distilled water . The precipitate was filtered by suction , washed with distilled water and dried in the air to give a solid[10] which was recrystallized from acetic acid to afford 0.2 g (35.7%) of compound (A9), as a pink powder, M.P. 319 - 321 ^oC .

Preparation of compound (A10)

8,8'-dimethyl-2,2',4,4'-tetrahydroxy-6,6'-biquinoline

P_2O_5 (15 g) was added to 7.5 mL of 85% H_3PO_4 then the mixture was stirred at 100 ^oC for 2 hrs to obtain polyphosphoric acid (molar ratio of P_2O_5 / H_3PO_4 : 1.0).

The prepared polyphosphoric acid (4mL) was added to compound (A5) (0.76 g , 0.002 mol) then the mixture was heated with stirring at 140 ^oC for 6 hrs.

After completion of the reaction, the mixture was poured into distilled water . The precipitate was filtered by suction , washed with distilled water and dried in the air to give a solid[10] which was recrystallized from acetic acid to afford 0.25 g (32.8 %) of compound (A10), as a yellow powder, M.P. 289 - 291 ^oC .

Preparation of compound (A11)

4,6-dihydroxypyrano(3,2-g)chromene-2,8-dione

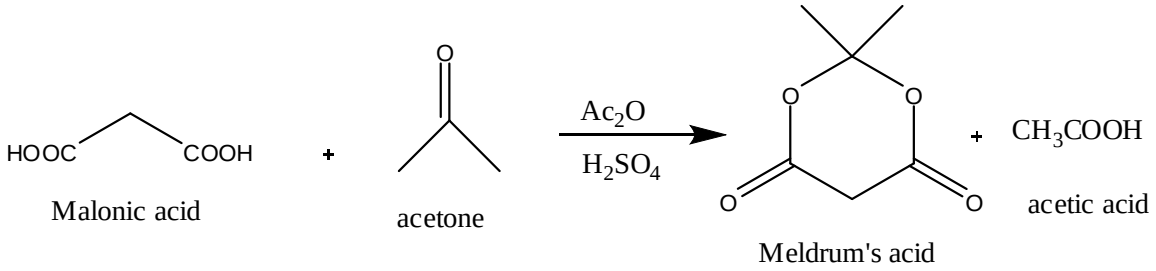
P_2O_5 (10 g) was added to 5 mL of 85% H_3PO_4 then the mixture was stirred at 100 ^oC for 2 hrs to obtain polyphosphoric acid (molar ratio of P_2O_5 / H_3PO_4 : 1.0).

The prepared polyphosphoric acid(11 mL) was added to compound(A6) (0.56 g , 0.002 mol) then the mixture was heated with stirring at 120 ^oC for 16 hrs.

After completion of the reaction, the mixture was poured into distilled water . The precipitate was filtered by suction , washed with distilled water and dried in the air to give a solid[(11)] which was recrystallized from ethanol to afford 0.3 g (53.5 %) of compound (A11), as a yellow powder, M.P. 199 - 201 ^oC .

Results and Discussion

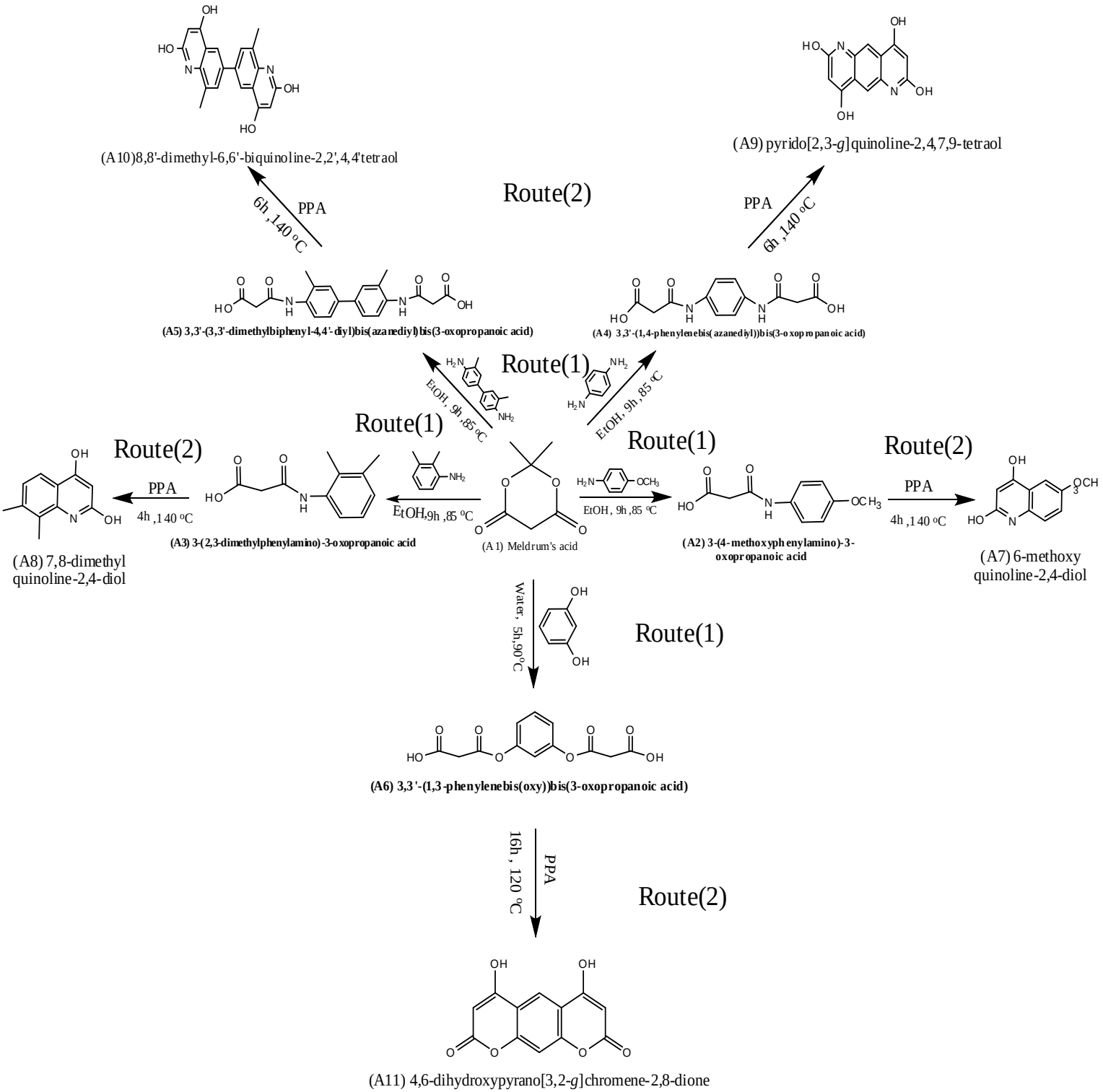
In our work for cyclization of *N*-phenylmalonamic acid to 2,4-dihydroxyquinoline and preparation of 4-hydroxycoumarin derivatives involves the following steps: the first step involves the preparation of Meldrum's acid(A1) according to scheme(1)



Malonic acid + acetone → Meldrum's acid + acetic acid

Scheme(1)

The prepared Meldrum's acid(A1) was reacted with a number of aromatic compounds containing an amino group or hydroxy group which gave the Meldrum's acid derivatives as in (scheme 2,route1) and the results of this step were shown in table (I).

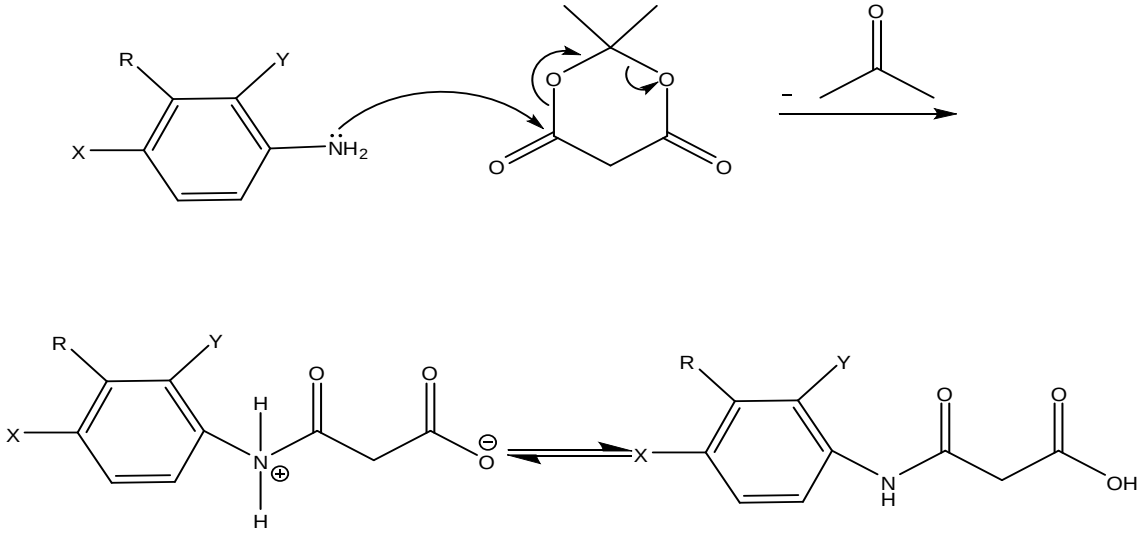

(A10)8,8'-dimethyl-6,6'-biquinoline-2,2',4,4'tetraol
(A9) pyrido[2,3-g]quinoline-2,4,7,9-tetraol
Route(2)
6h ,140 °C
PPA
PPA
6h ,140 °C
(A5) 3,3'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(azanediyl)bis(3-oxopropanoic acid)
(A4) 3,3'-(1,4-phenylenebis(azanediyl))bis(3-oxopropanoic acid)
Route(1)
EtOH, 9h ,85 °C
EtOH, 9h ,85 °C
Route(1)
Route(1)
Route(2)
Route(2)
PPA
4h ,140 °C
EtOH,9h ,85 °C
EtOH, 9h ,85 °C
PPA
4h ,140 °C
(A8) 7,8-dimethyl quinoline-2,4-diol
(A3) 3-(2,3-dimethylphenylamino)-3-oxopropanoic acid
(A1) Meldrum's acid
(A2) 3-(4-methoxyphenylamino)-3-oxopropanoic acid
(A7) 6-methoxy quinoline-2,4-diol
Water, 5h,90°C
Route(1)
(A6) 3,3'-(1,3-phenylenebis(oxy))bis(3-oxopropanoic acid)
16h , 120 °C
PPA
Route(2)
(A11) 4,6-dihydroxypyrano[3,2-g]chromene-2,8-dione

Scheme (2)

Table(I): FTIR,^{1}H-NMR data and CHN analysis of the prepared compounds(A1-A6)

Product	IR(KBr) cm^{-1}	^{1}H-NMR (DMSO) (ppm)	CHN analysis	
			Calculated	Found
A1	ν CH 3002 (s) ν C=O 1791 – 1770(s)	δ 1.4 (s,6H) ; δ 2.7 (s,2H)	C, 50.00% H, 5.59%	C, 50,45% H, 5,78%
A2	ν NH 3292 (s) ν C=O amide 1650(s) ν C=O carboxylic acid 1728 (s) ν OH 3200-2600 br ν C=C 1600 (m)			
A3	ν NH 3263 (s) ν C=O amide 1660(s) ν C=O carboxylic acid 1730 (s) ν OH 3134-2500 br ν C=C 1600 (m)			
A4	ν NH 3340 (s) ν C=O amide 1640(s) ν C=O carboxylic acid 1680 (s) ν OH 3110-2416 br ν C=C 1600 (m)	δ 2.6(s,4H); δ 9.3(s,2H); δ12.3(s, 2H); δ 7.2(m, 4H)		
A5	ν NH 3282 (s) ν C=O amide 1650(s) ν C=O carboxylic acid 1690 (s) ν OH 3145-2500 br ν C=C 1600 (m)	δ 2.3 (s,6H); δ 2.9 (s,4H); δ 9.9 (s,2H); δ12.4 (s, 2H); δ 6.3 (m,2H) δ 7.2 (m, 2H); δ 7.8 (m,2H)		
A6	ν OH 3350-2600 br ν C=O carboxylic acid 1750 (s) ν C=O ester 1720 (s) ν C=C 1608 (m)	δ 2.6 (s,4H); δ12.5(s, 2H); δ 7.8 (m,1H); δ 7.5(m, 1H); δ 7.2(m, 1H); δ 7.1(m, 1H)		

The mechanism of this step is as followed:



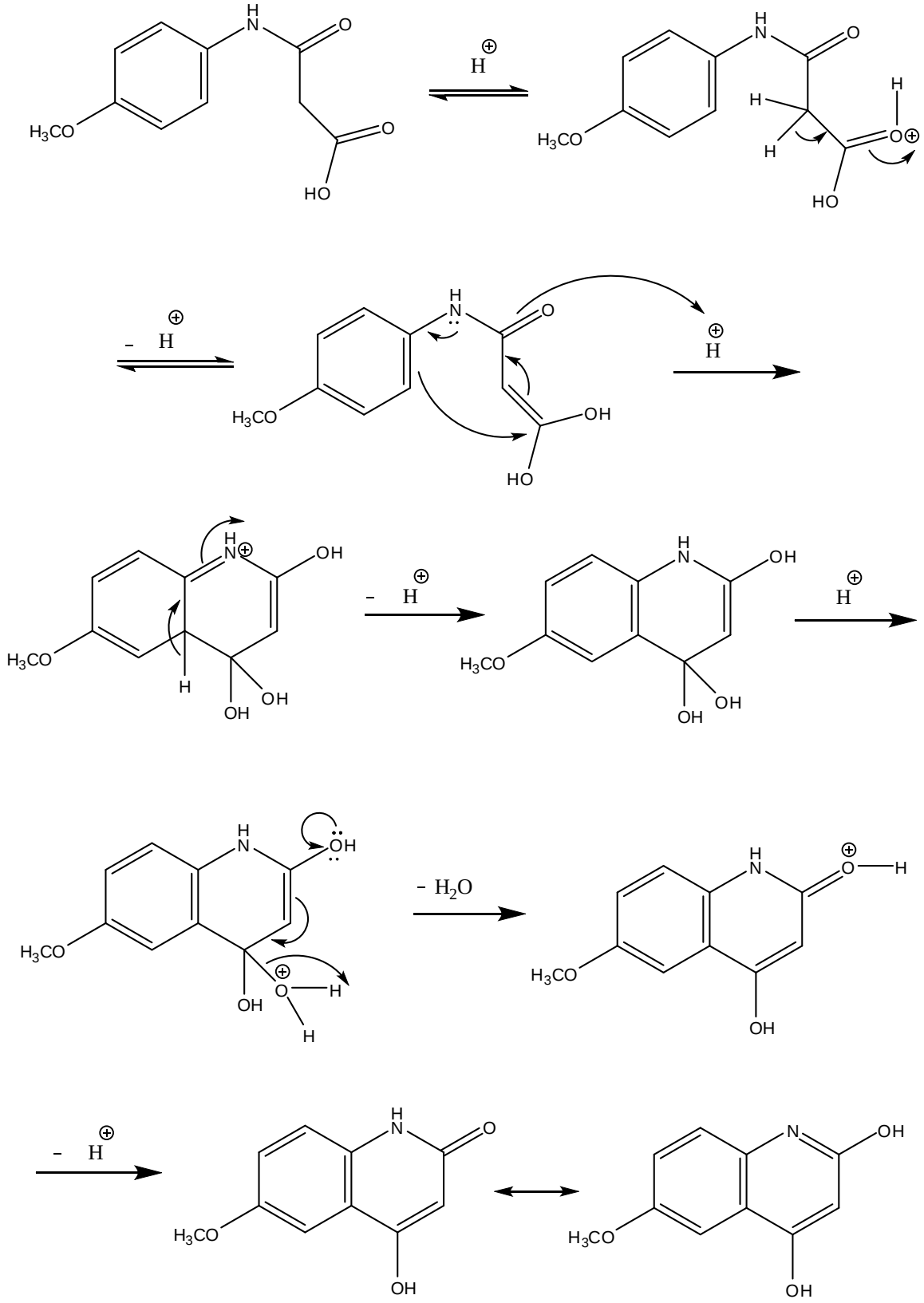
Scheme (3)

Then the above derivatives were cyclized using polyphosphoric acid (PPA) to give derivatives (A7-A11) , as shown in(scheme2,route2),and the results of this step are shown in table (II).

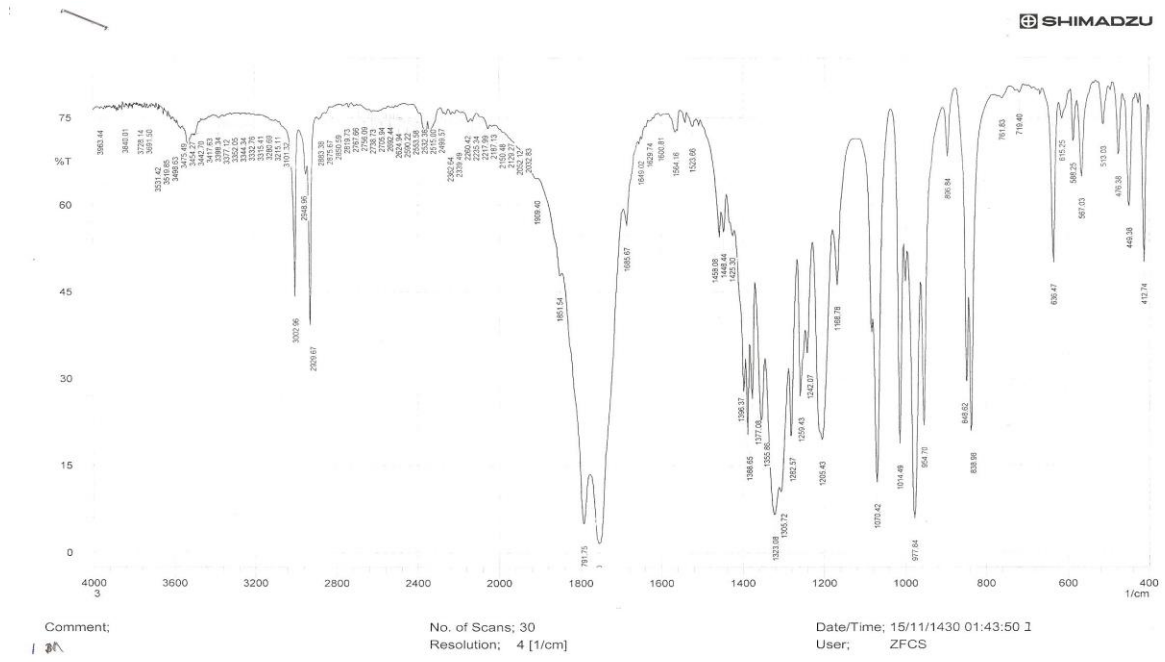
Table(II):FTIR data and CHN analysis of the prepared compounds (A7-A11)

Product	IR(KBr) cm^{-1}	CHN analysis	
		Calculated	Found
A7	ν OH 3350 br ν C=N 1650(s) ν C=C 1600(m)	C, 62.82% H, 4.74 % N, 7.33%	C, 62.11 % H, 4.58% N, 7.71 %
A8	ν OH 3400 br ν methyl group 2918(m) ν C=N 1650(s) ν C=C 1620(m)		
A9	ν OH 3400 br ν C=N 1650(s) ν C=C 1600(m)	C, 59.02 % H, 3.30% N, 11.47%	C, 59.68% H, 3.2% N, 11.48 %
A10	ν OH 3390 br ν methyl group 2900(m) ν C=N 1650(s) ν C=C 1627(m)	C, 68.96% H, 4.63% N, 8.04%	C, 69.05% H, 4.37% N, 8.22 %.
A11	ν OH 3420 br ν C=O 1650(s) ν C=C 1600(m)	C, 58.55% H, 2.46%	C, 58.25% H, 2.61 %.

The mechanism of cyclization step was suggested to be as follows:



Scheme (4)



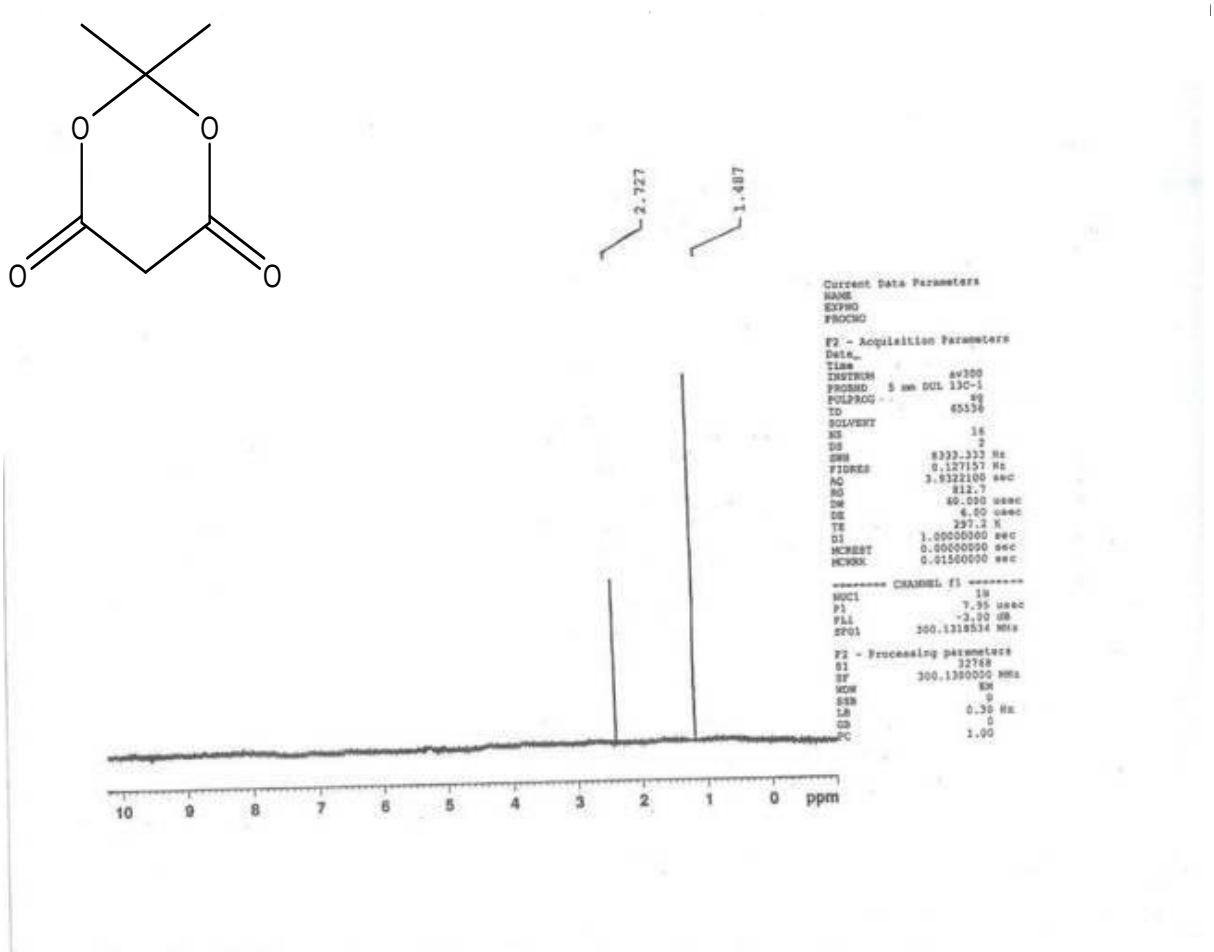
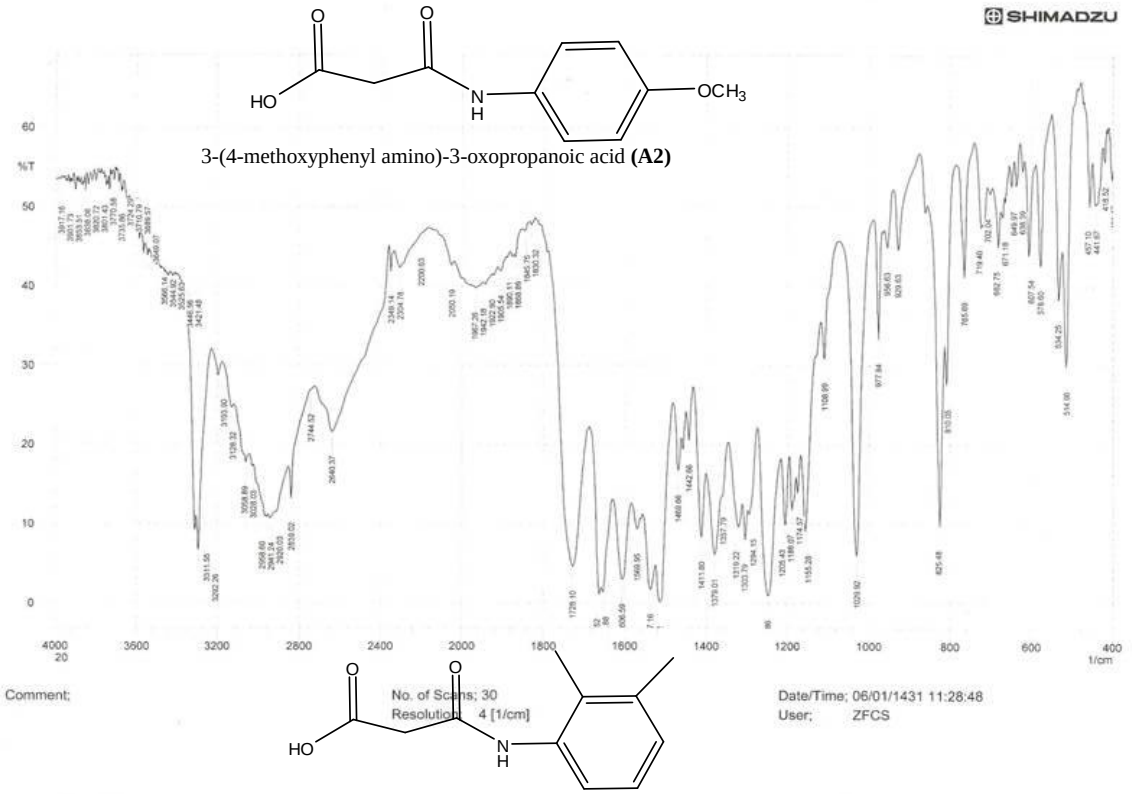


Fig. (1) : FTIR and ^{1}H-NMR Spectra of Meldrum's Acid



3-(4-methoxyphenyl amino)-3-oxopropanoic acid **(A2)**

3-(2,3-dimethylphenyl amino)-3-oxopropanoic acid **(A3)**

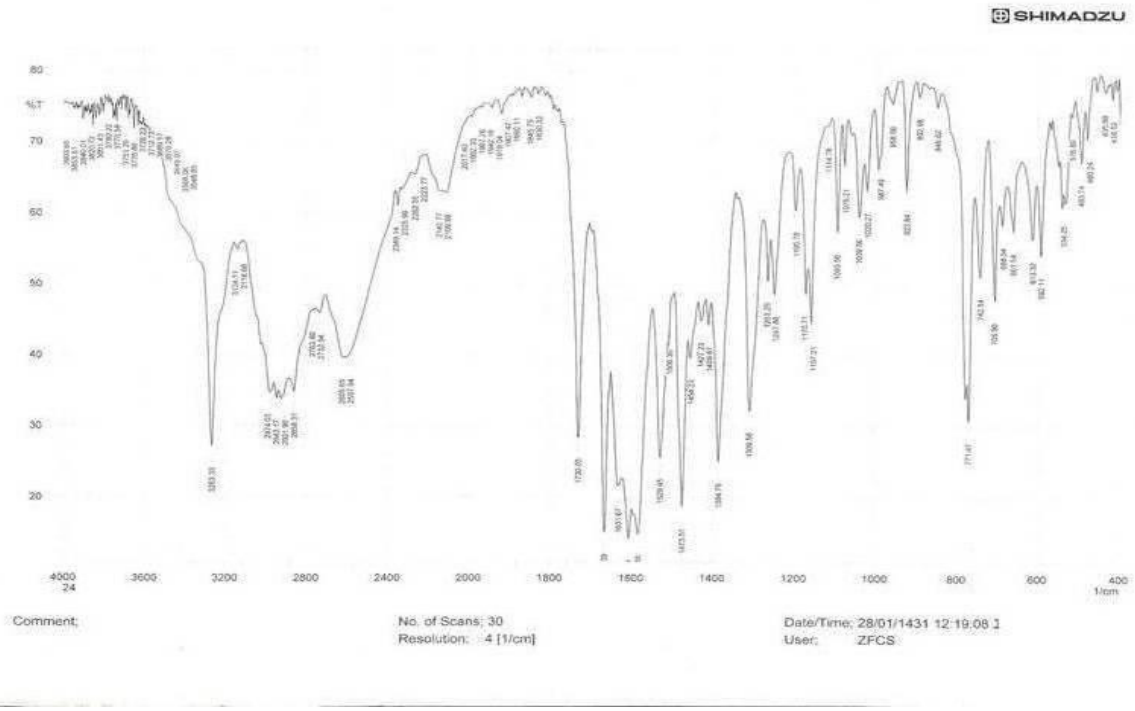
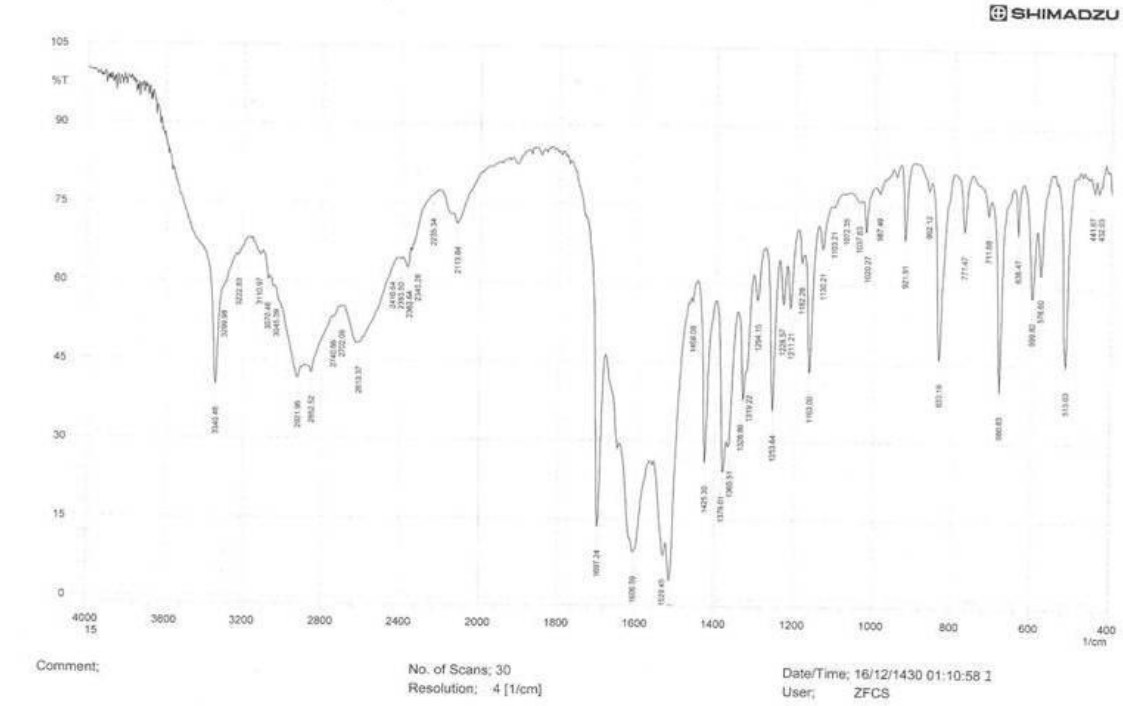


Fig. (2): FTIR Spectra of Compounds (A2 and A3)



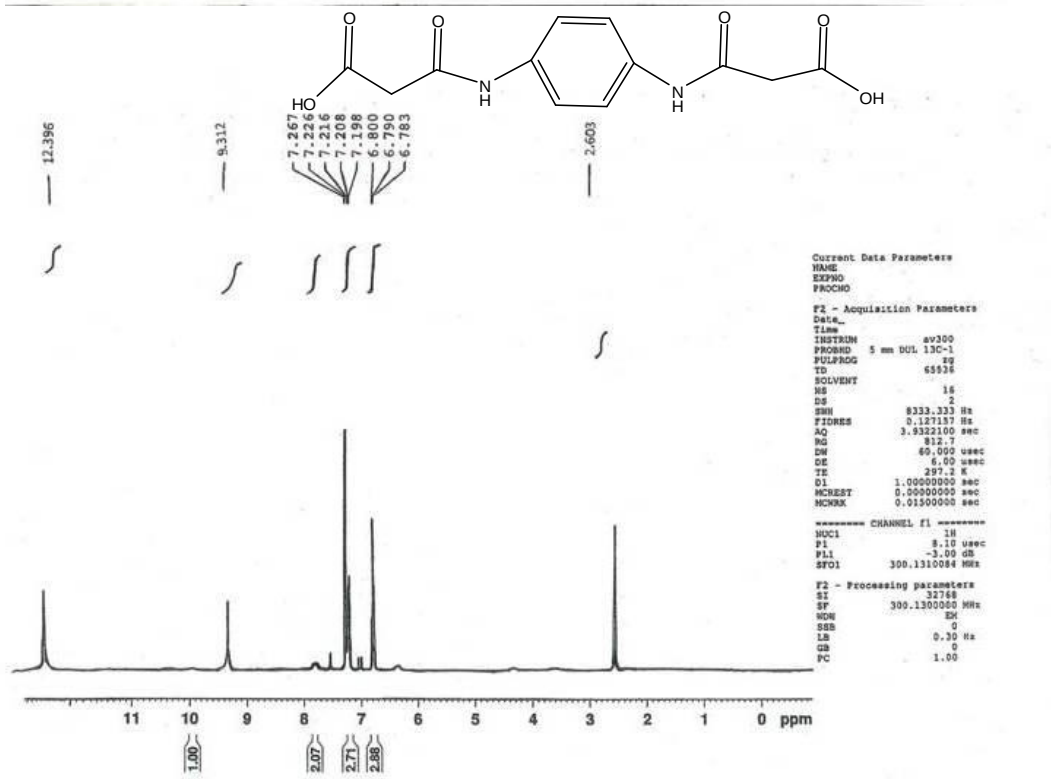


Fig. (3) : FTIR and ^{1}H-NMR Spectra of Compound(A4)

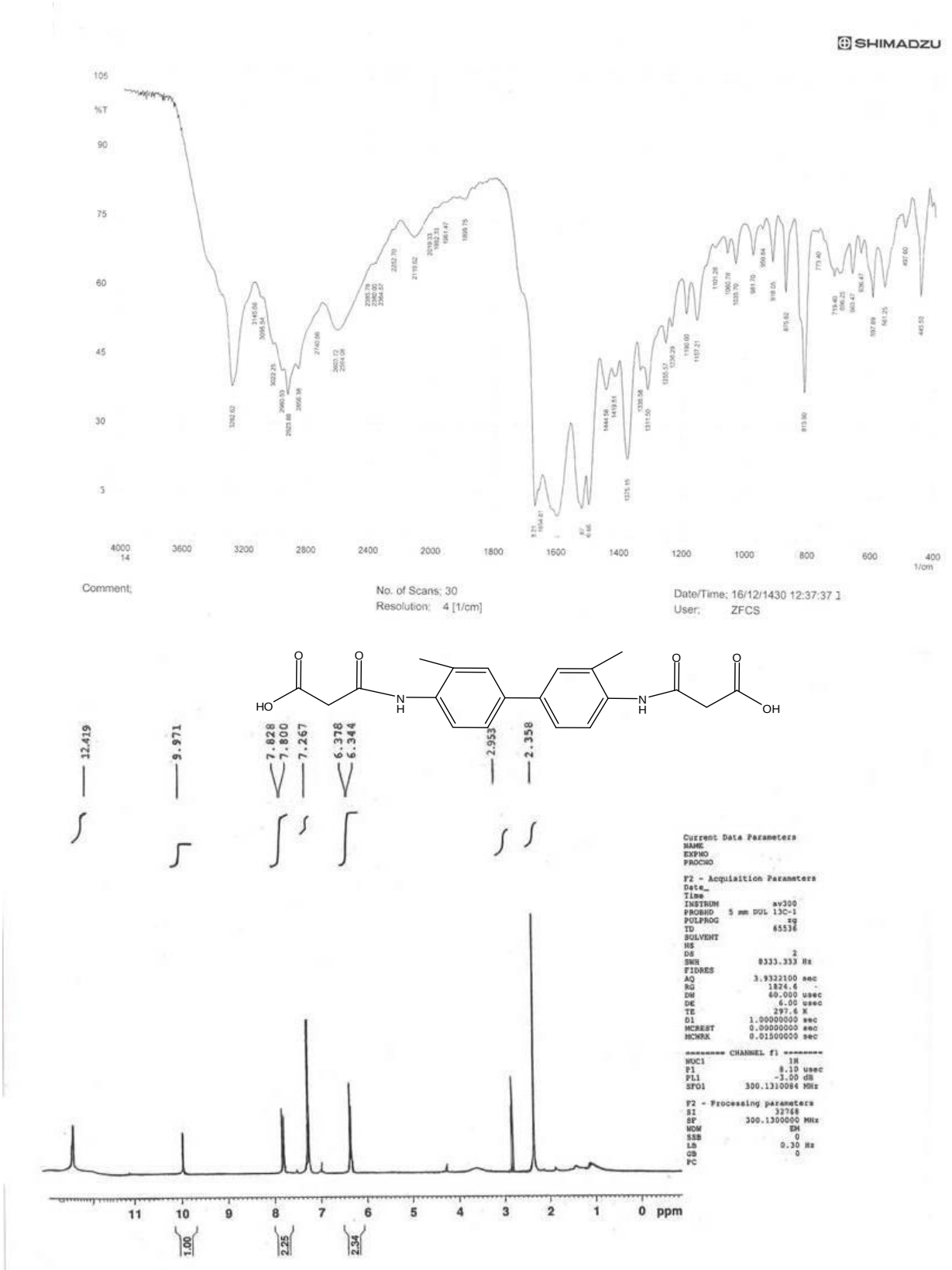


Fig. (4) : FTIR and ^{1}H-NMR Spectra of Compound(A5)

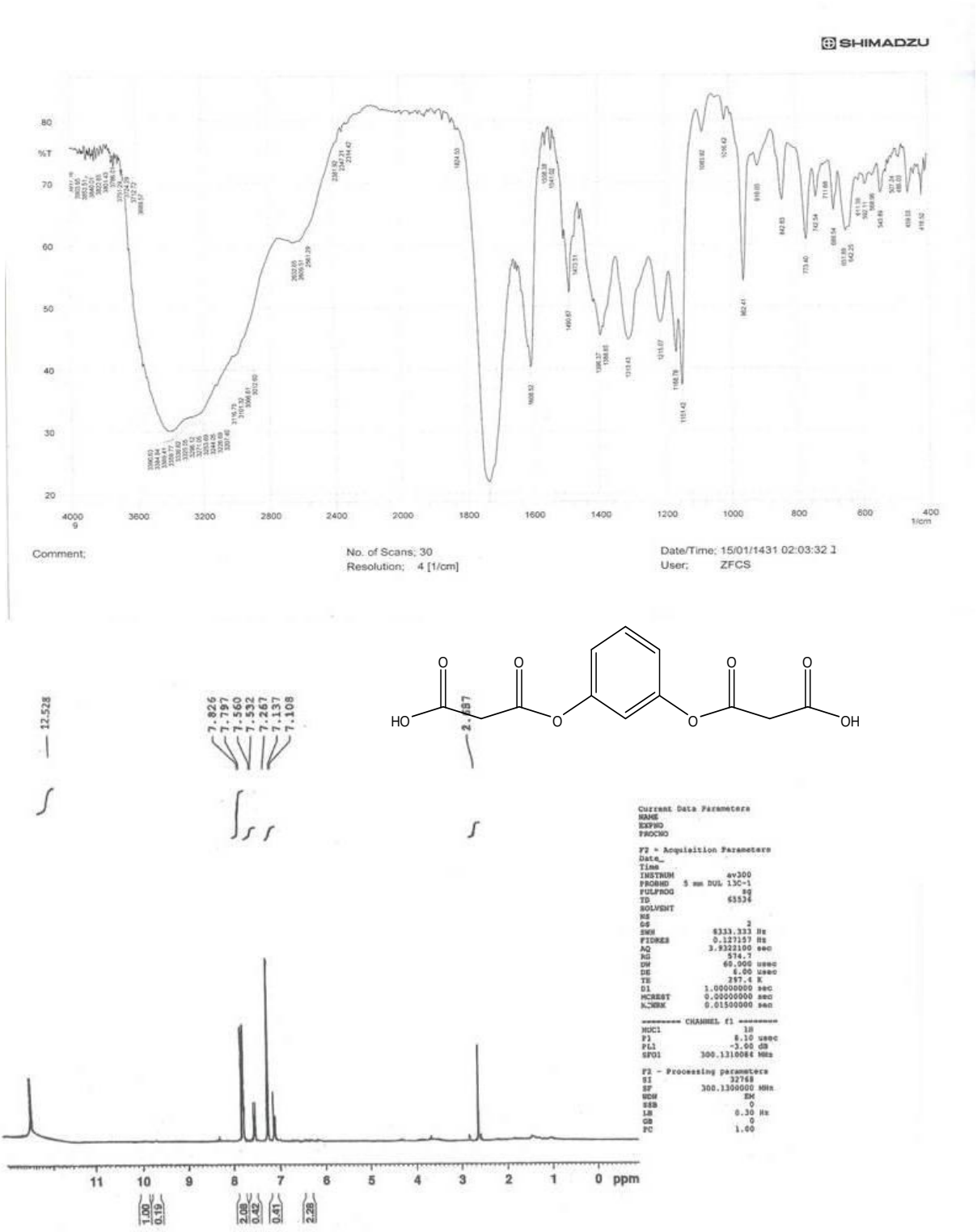


Fig. (5) : FTIR and ^{1}H-NMR Spectra of Compound(A6)

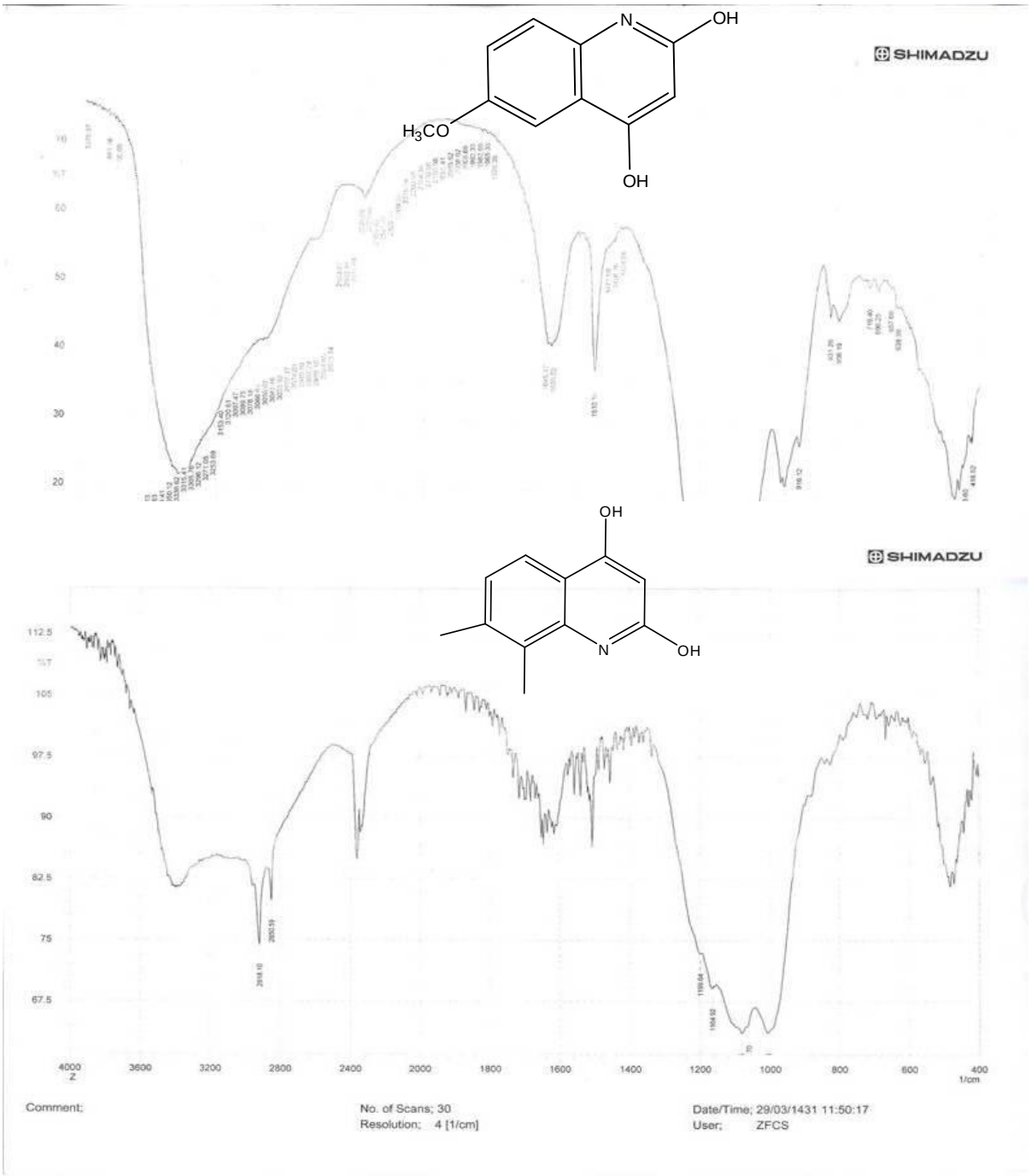


Fig. (6): FTIR Spectra of Compounds (A7 and A8)

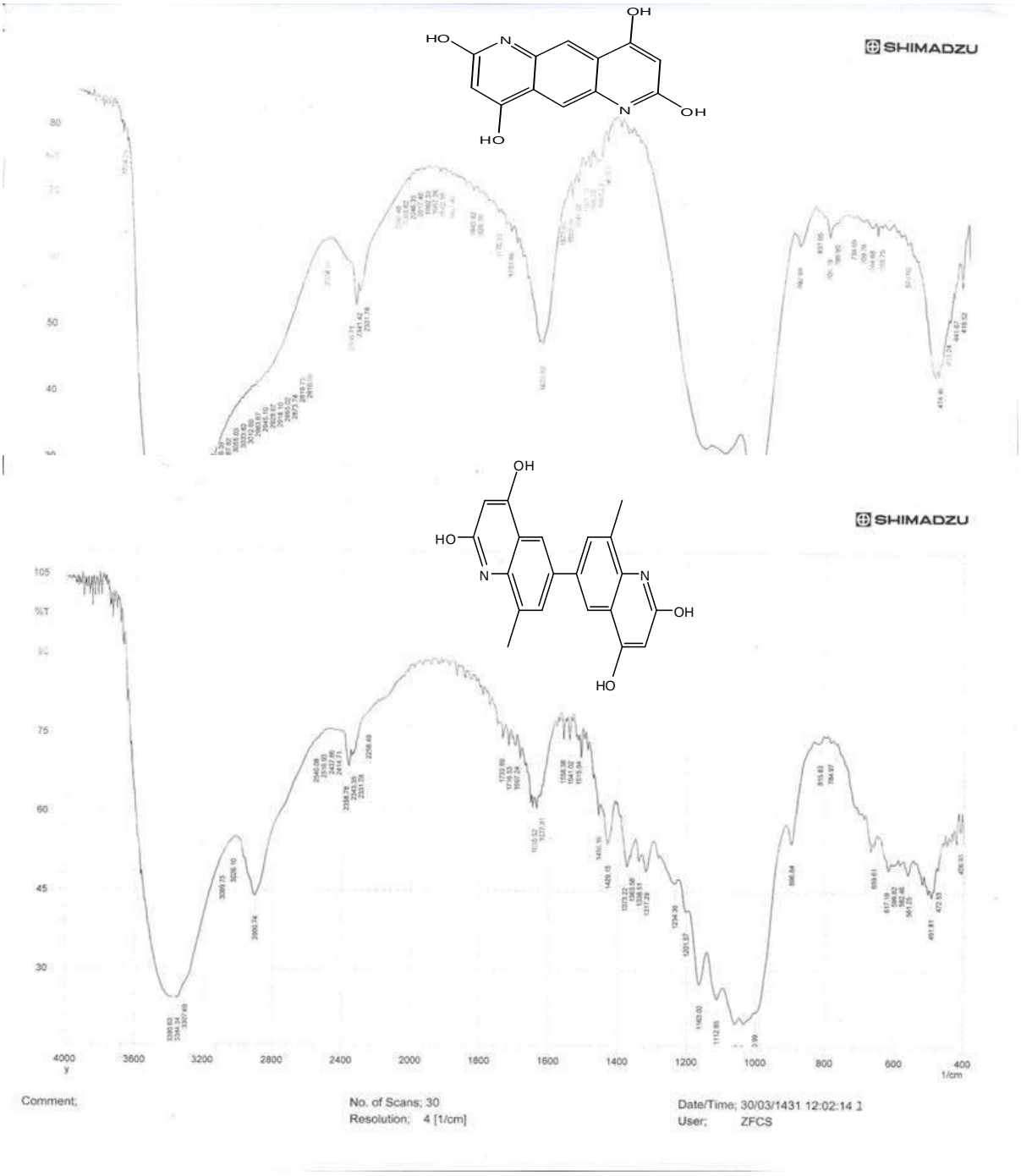


Fig. (7): FTIR Spectra of Compounds (A9 and A10)

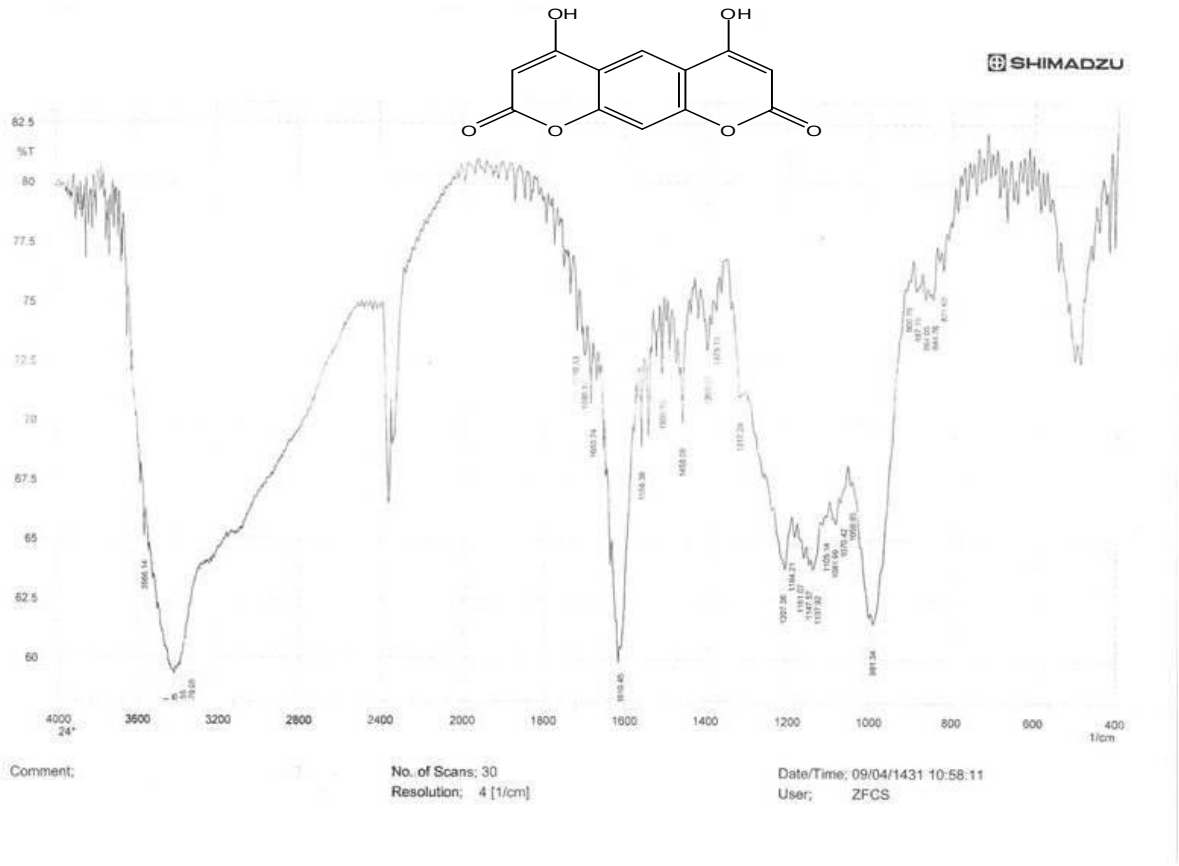


Fig. (8): FTIR Spectrum of Compound (A11)

The biological activity of the effect of some prepared compounds in this research (A2,A7,A10 and A11) on growth of one type of bacteria was studied and the results were shown on table(III).

Meantime, the observable inhibition zone was determined during prepare concentration by dilution with DMSO (5, 10, 20, 30and 40) mg/ml of each compound, and the diagrams (1,2,3 and 4) show these observation .

The results gave an indication for inhibition of bacteria under investigation during testing with the prepared compounds. In case of increasing the concentration of the prepared compounds and repeat the above testing, we found that the inhibition will be increased.

Table (III): Inhibition zone of some compounds using Toda method[12]

Conc. / Comp. No.	5 mg/ml	10mg/ml	20mg/ml	30mg/ml	40mg/ml	Control (DMSO)
A2	R	15	18	20	21	R
A7	12	16	19	23	26	R
A10	RM	14	16	18	20	R
A11	16	19	22	25	27	R

Table (IV) shows that in comparison to effect of tetracycline , streptomycin , neomycin and ciprofloxacin effect against standard , sensitive strains of *Staphylococcus arueus*.

Table (IV): Inhibition zone of some well known antibiotics using Bauer method[13]

Antibiotic	Disc potency	Zone diameter of inhibition(mm)
Tetracycline (TE)	30µg	15
Streptomycin(S)	10 µg	17
Neomycin (N)	30 µg	15
Ciprofloxacin (CIP)	5 µg	35

Staphylococcus arueus was found in vitro were sensitive to these compounds(A2,A7,A10 and A11) combinations of previous compounds reduced such activity or there is no activity at all. Thus antagonistic effect may be expectant and suggested.[14]

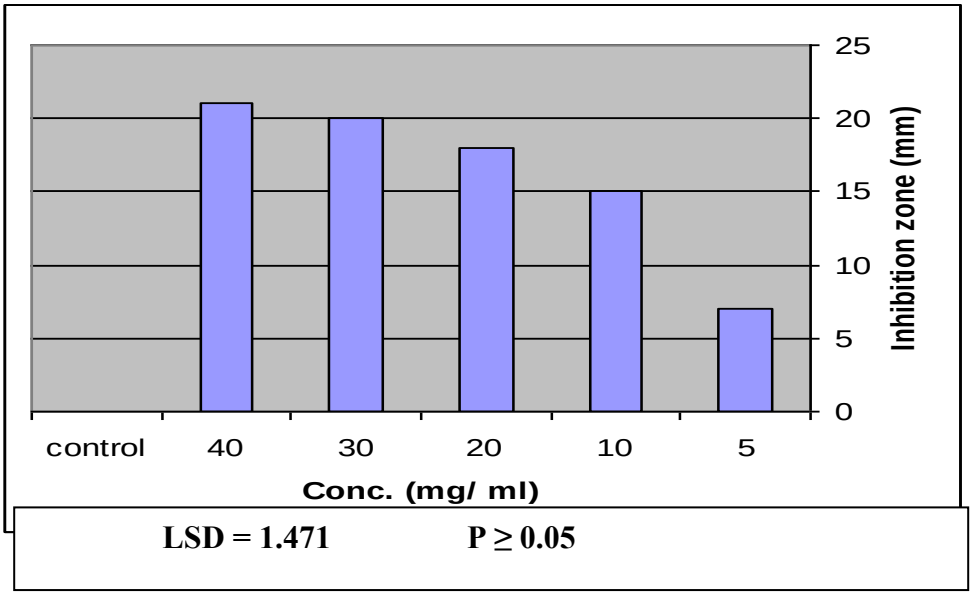


Diagram (1) : Shows the relationship of concentration with inhibition zone for compound(A2)

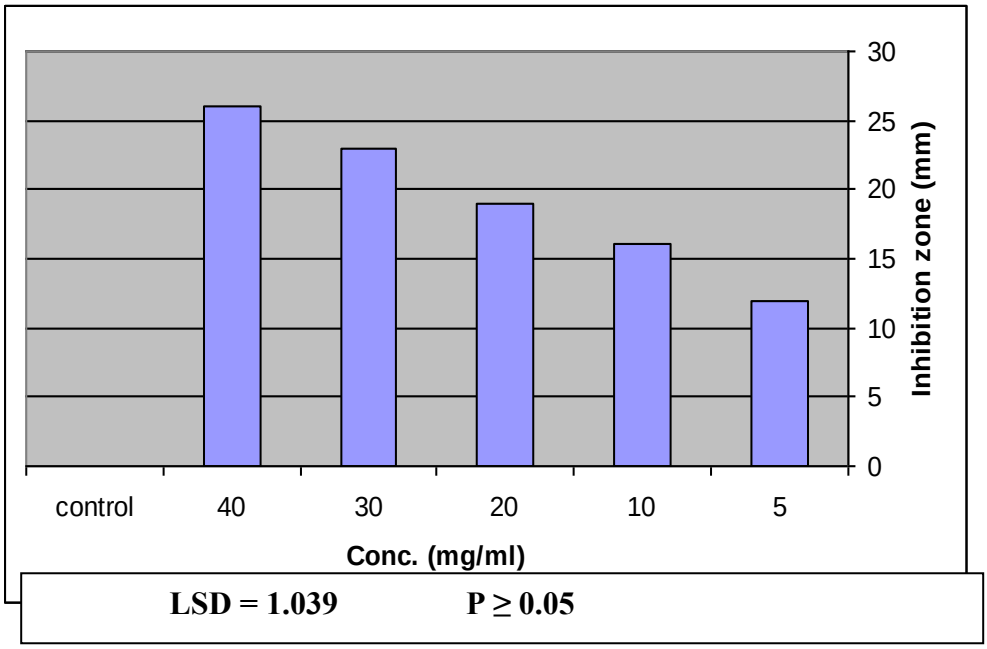


Diagram (2) : Shows the relationship of concentration with inhibition zone for compound(A7)

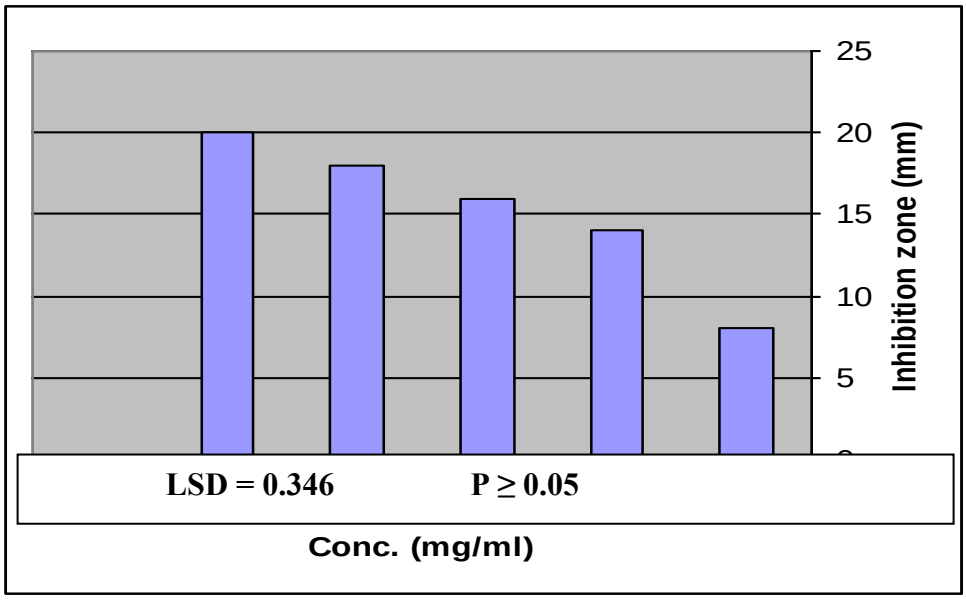


Diagram (3) : Shows the relationship of concentration with inhibition zone for compound(A10)

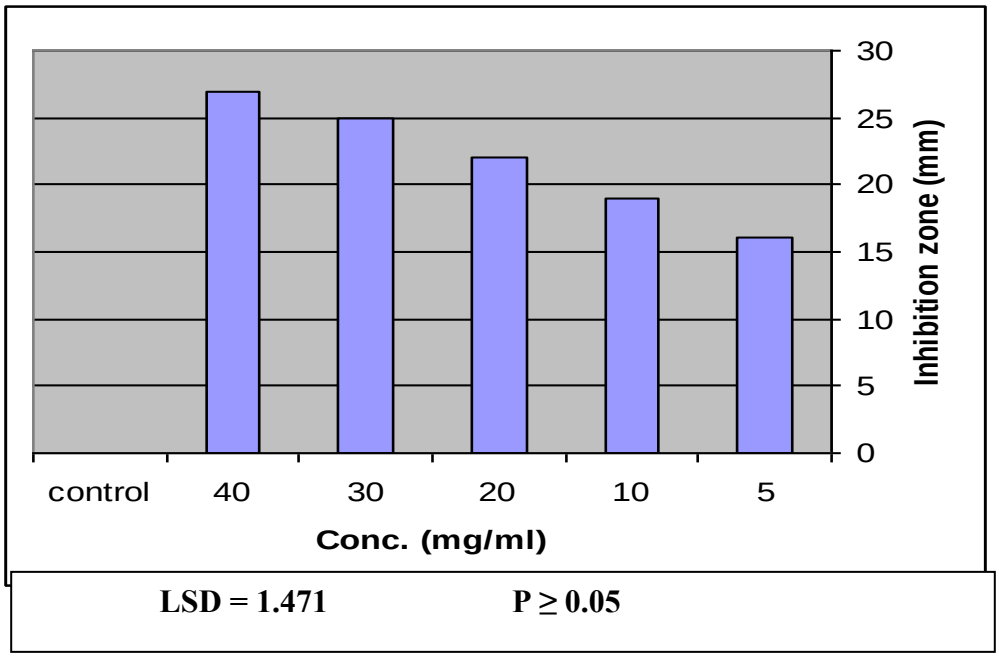


Diagram (4) : Shows the relationship of concentration with inhibition zone for compound(A11)

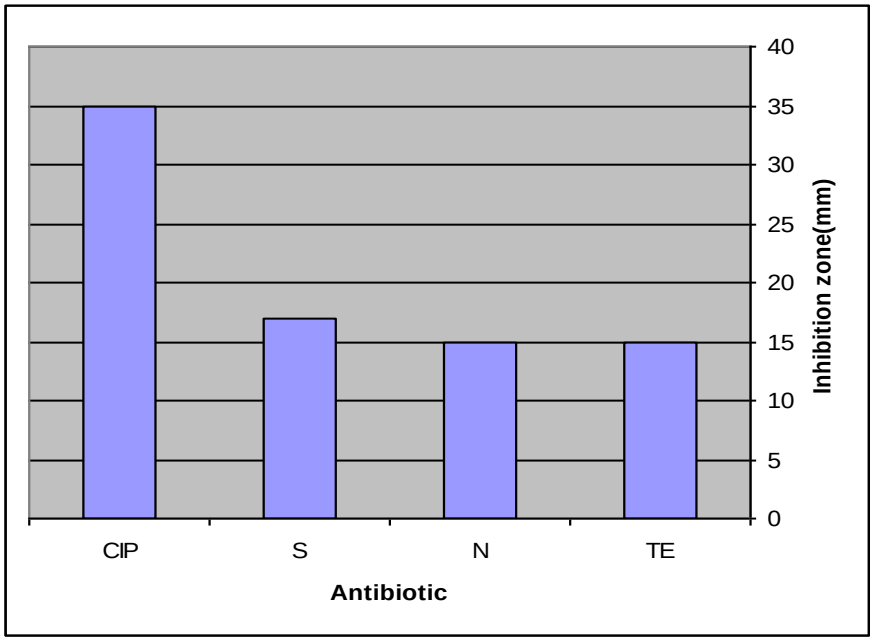


Diagram (5): Shows relationship of antibiotics with inhibition zone

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