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Synthesis and Characterization of new organic compounds from Cromoglicic acid and Study Some of Their Applications

Hala shkyair lihumis

Abeer Hassan madloum
Department of Chemistry, College of science , University of Babylon,Iraq
abeer.kadim.scihigh128@student.uobabylon.edu.iq

Abstract:

In this work new cromoglicic acid compounds with novel characteristics have been produced. One important class of medicinal chemical substance is cromoglicic acid. Its derivatives can be utilized to create new classes of medications, and they can have a variety of biological activities and lessen adverse effects, and the work included the conversion of cromoglicic acid to the hydrazide derivative of the acid by converting the carboxyl group of the compound to the acid chloride by thionyl chloride, The formed acid chloride was converted into a methyl ester derivative by adding methyl alcohol drop by drop at room temperature, then a solution of hydrazine hydrate (80%) in ethanol was added drop by drop at room temperature to the formed ester and after the addition was finished, the mixture was refluxed for 4 hours. The formed hydrazide was heated with some seven carboxylic drugs (Amoxiline , Ampicillin, Folic Acid, Mefenamic Acid , Cephalexin, Ciprofloxin, Naproxen) after the carboxyl group in it was converted to acid chloride by thionyl chloride. The DPPH method was used to test the synthesized compounds' antioxidant activity, and the findings showed that all of them had good antioxidant activity that was significantly higher than that of the ascorbic acid medication. TLC was used to control the chemical reaction and to characterize the new derivatives using FT-IR, C13-NMR, and H1-NMR techniques.

الملخص:

في هذا العمل تم إنتاج مركبات حمض كروموجليكسيك جديدة بخصائص جديدة. فئة واحدة مهمة من المواد الكيميائية الطبية هو حمض كروموجليكسيك. يمكن استخدام مشتقاته لإنشاء فئات جديدة من الأدوية ، ويمكن أن يكون لها مجموعة متنوعة من الأنشطة البيولوجية وتقليل الآثار الضارة ، وشمل العمل تحويل حمض كروموجليكيك إلى مشتق هيدرازيد من الحمض عن طريق تحويل مجموعة الكربوكسيل للمركب إلى كلوريد الحمض بواسطة كلوريد الثيونيل ، تم تحويل كلوريد الحمض المتشكل إلى مشتق ميثيل إستر عن طريق إضافة كحول الميثيل قطرة قطرة عند درجة حرارة الغرفة ، ثم يضاف محلول هيدرات الهيدرازين (80٪) في الإيثانول قطرة بقطرة عند درجة حرارة الغرفة إلى الإستر المتشكل وبعد الانتهاء من الإضافة ، تمت إعادة تدفق الخليط لمدة 4 ساعات. تم تسخين الهيدرازيد المتكون بواسطة سبعة عقاقير كربوكسيلية (Amoxiline، Ampicillin، Folic Acid، Mefenamic Acid، Cephalexin، Ciprofloxin، Naproxen) بعد أن تم تحويل مجموعة الكربوكسيل الموجودة فيه إلى كلوريد حمض بواسطة كلوريد الثيونيل. تم استخدام طريقة DPPH لاختبار النشاط المضاد للأكسدة

للمركبات المركبة ، وأظهرت النتائج أن جميعها لديها نشاط جيد كمضاد للأكسدة أعلى بكثير من نشاط دواء حمض الأسكوربيك. تم استخدام TLC للتحكم في التفاعل الكيميائي وتوصيف المشتقات الجديدة باستخدام تقنيات FT-IR و C13-NMR و H1-NMR

Key wards: cromoglicic acid ,drug, biological activity, antioxidant activity.

Introduction:-

Heterocyclic substances are cyclic substances with at least one carbon atom and at least one additional element. The opposite of a monocyclic compound is a heterocycle, which is a ring containing only heteroatoms. Heterocyclic compounds result from replacing a carbon atom in an organic ring structure with an atom of oxygen, nitrogen, sulphur, or another similar element.[1] . Infections caused by bacteria and fungi have become much more common in recent years. Resistance to drug therapy against bacterial and fungal infections was caused by the extensive use of antifungal and antibacterial medications, which resulted in major health risks.[2] Imidazole, Pyrazole, and New Oxadiazole Incorporated. It is commonly acknowledged that heterocyclic compounds with an azole nucleus play an essential role as pharmacophores in a variety of pharmaceutical agents, biochemical processes, and pharmacological activities. These heterocyclic substances are abundantly present in nature, make up a significant portion of organic chemistry, and are essential to living cells' metabolism. Because of their wide variety of practical uses in areas including medicine, agriculture, photochemistry, biocidal formulation, and polymer science in addition to their significant clinical use[3] .cromoglicic acid is being examined for its effectiveness in treating Alzheimer's disease in clinical trials. A neuroprotective state is promoted by cromoglicic acid in combination with ibuprofen by activating microglia and causing the phagocytosis of amyloid-beta proteins. Amyloid-beta protein is a pathology biomarker for Alzheimer's disease.[4]. A mast cell stabilizer called cromoglycate is frequently given by inhalation or intranasal route to treat respiratory problems caused by allergies. Due to cromoglycate's high solubility but low permeability across gastrointestinal epithelial membranes, oral dosage of the substance remains difficult. It is obvious that better formulation solutions are required[5]. Asthma, allergic rhinitis, and other mast cell reactions are all treated with the prophylactic drug cromoglicic acid. [6] In a fairly recent study, the pharmacological basis for the repositioning of cromoglicic acid derivatives as an adjuvant therapy for SARS-CoV-2 infection was discussed in detail. Their practical clinical trial is suggested as an early, safe, and economical anti-inflammatory treatment for COVID-19[7].

2. Experimental

2.1-Chemicals: Sigma , Fluka, BDH and CDH developed all of the chemicals used: EtOH Absolute, MeOH, HCl, NaOH , $SOCI_2$, DCM, TEA and Chromoglicic acid .

2.2-Instruments

The melting factors of the compounds organized have been decided the usage of the SMP30 melting factor instrument, even though the ranges of melting had been now no longer corrected. The "Testseon Shimadzu (FT- IR 8400Series Japan)" the use of the KBr disk method (T L C) changed into as soon as done for TLC on silk gel G and spots had been visualized through I2 vapors. The H1-NMR spectra have been received the use of DMSO as solvent and TMS as an inner general with "Bruker, Ultra Shield four hundred MHZ Switzerland

2.3-2 Synthesis of hydrazide by one put method:

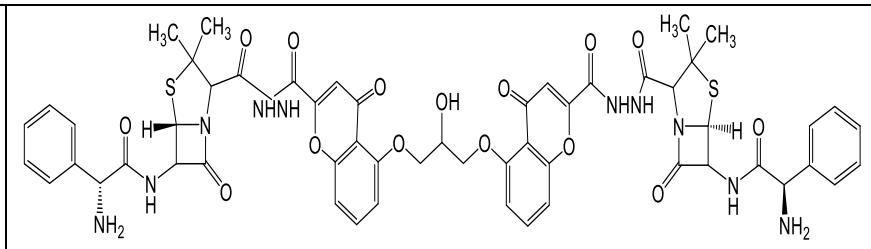
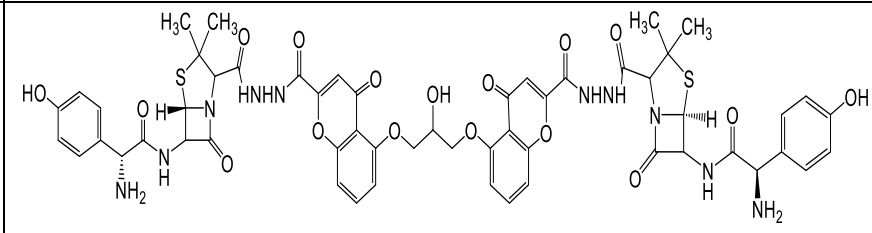
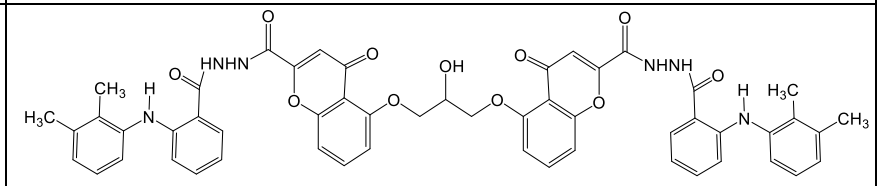
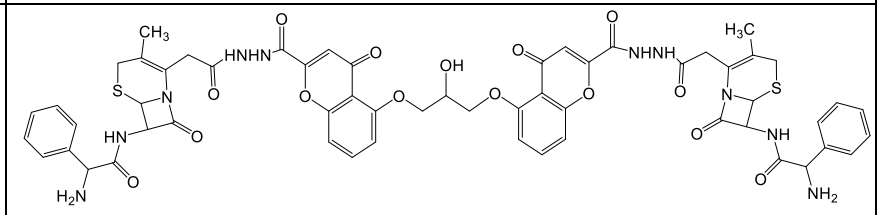
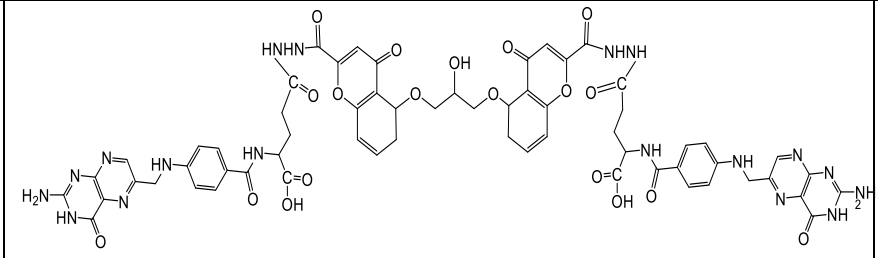
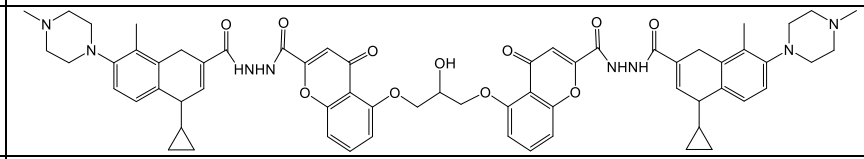
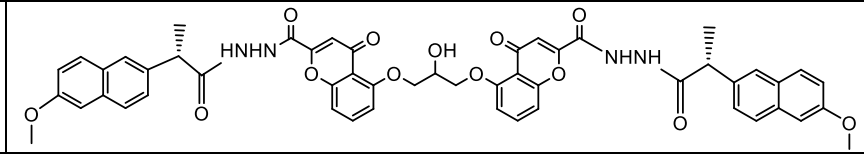
Cromoglicic acid (0.001mmol) and thionyl chloride (0.002mml) were combined, and the mixture was then stirred at 20–25 °C for 30 min. Drop by drop, at room temperature, and while stirring, (7.5 mL) of methanol (0.002mml) was added to this mixture. Then, at room temperature (20–30°C), 10 mL of an 80% $NH_2NH_2.H_2O$ (0.002mml) solution in ethanol was gradually added while stirring to the aforementioned mixture. The reaction's mixture was refluxed for (3-4 hrs.)[8].

2.3-3 Synthesis for derivatives A11_A17:

Seven different carboxylic drugs each received 2 mmol of thionyl chloride before being stirred at room temperature for 30 minutes. The aforementioned mixes received one mmol of hydrazide in DMSO, which was heated for 1.5 hours at 60 to 70 degrees Celsius. The liquids were heated once more for after the addition of triethylamine (TEA) (30 mins). TLC kept track of how the reactions were developing. Ice water was added to the round flask's contents after cooling. The precipitates were filtered under vacuum pressure, the solid products were repeatedly washed with DCM, and then the mixture of DCM and ethanol was used to recrystallize the precipitates.[8].

Table2.5: Some of physical properties of compound (AH1_AH10)

Comp. Sym.	Structural formula	Rf	Yield %	m.p	M.Wt	M. formula	color

A11		0.35	64%	233-236	1190.21	$C_{55}H_{54}N_{10}O_{17}S_2$	Brawn
A12		0.48	67%	240-242	1158.32	$C_{55}H_{54}N_{10}O_{15}S_2$	Light brawn
A13		0.44	75%	171-174	942.98	$C_{53}H_{46}N_6O_{11}$	Yellow
A14		0.72	81%	213-215	1183.23	$C_{57}H_{54}N_{10}S_2$	Dark Brawn
A15		0.90	85%	92-95	1343.21	$C_{61}H_{54}N_{18}O_{19}$	Brawn
A16		0.69	90%	145-148	1113.28	$C_{63}H_{68}N_8O_{11}$	Yellow
A17		0.55	73%	216-218	916.98	$C_{53}H_{48}N_4O_{11}$	Red

2.4-Biological Activity:

2.4.1- Antibacterial activity :

Some synthetic compounds had their antimicrobial susceptibility tested using the "well diffusion technique." Staphylococcus aureus, a gram-great bacteria,

and a gram-horrible bacteria were used as test subjects for the evaluation of synthetic substances (Klebsiella pneumonia). Samples were cultivated at a facility using Muller-Hinton agar medium.

For several substances, the results were singular at a temperature of 37 °C for a period of 24 hours[9].

2.4.2- Antioxidants activity :

The solution modified into protected from moderate thru protecting the test tubes with aluminum foil. DPPH (4 mg) was dissolved in 100 mL of methanol. Some of the produced compounds were used to make severa concentrations of (25, 50, a hundred) ppm. It was created by first making 100 additives per million by dissolving 1 milligram of the chemical in 10 mL of methanol, then diluting it to 50 and 25 additives per million. The concentrations were created in a similar way. One mL of the ordinary or diluted solution (25, 50, or 100 ppm) was added to at least one mL of the DPPH solution in a test tube.After 30 min. of incubation at 37 °C, the absorbance of each solution turn out to be measured using a spectrophotometer at 517 nm. The following equation was used to determine the potential to scavenge DPPH radicals

I % = (Absorption control – Absorption sample) /Absorption clean x 100

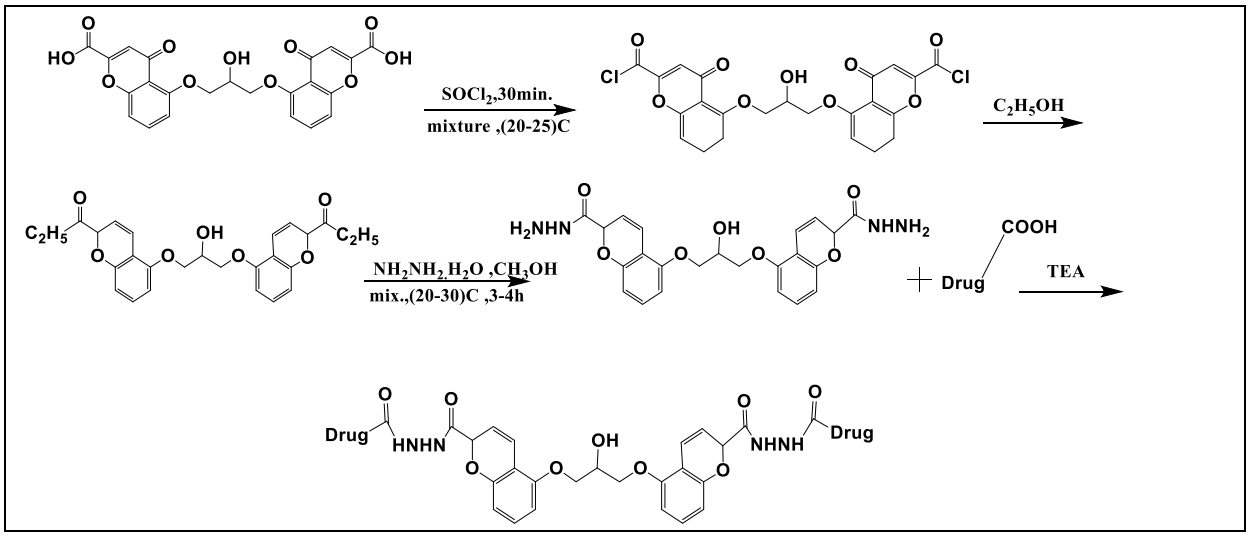
Absorption clean=0.003 [10].

2.5_The solubility

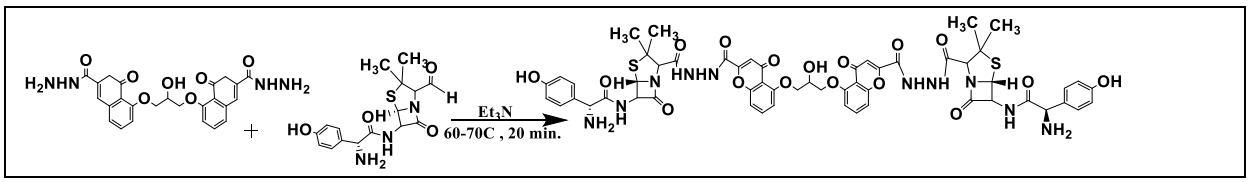
Due to their relatively large molecular weight, all structured compounds are soluble in DMSO and ethanol entirely, but only partially in water. according to research on the solubility of synthetic compounds utilizing specific polarity solvents. Because organized compounds have better polarity than those of diethyl ether, petroleum ether, and ethyl acetate, all synthetic compounds are insoluble in each and every one of these solvents. **Table (1- 2):** the solubility of organized derivatives in exceptional solvents

3- The results and discussion:-

New Carboxylic-containing medications were created via the creation of amide bonds to improve the characteristics of Cromoglicic acid (CGA) and lessen its negative effects. A Cromoglicic acid was reacted with to create the compounds (A11-A17).



Scheme (3-1): A general equation for line two



Equation (3-1): synthesis of A11

For A11 The following values were visible in the FT-IR spectra (V maximum, cm-1):3600(NH),3287(Phenol),3057(C=CH),2987(CHstr.),1696(C=O,Ketone),1651(N-C=O amid),1597-1518(C=C,Arom.),1267-1201(C-N,Aryl).^{1}H-NMR (500 MH, δ ppm):A;4.0,B;4.6(CH_2,ethylene),e;1.9(CH_3,Methyl),S;5.2(CH,Methyl),X;8.4(NH2,amine),D;6.9,E;7.5,F;7.2,U;7.9,V;7.7(Benzene),J;7.4(H,Ethylene),M;4.8(CH,methane),L;12.5,10.9,Y;8.4(Amide),b;5.0,W;10.9(Alcohol),2.5(DMSO).^{13}CNMR(125MH,δppm):A;67.9,B;70.8,Q;62.7(CH_2,aliphatic),D;110.6,E;135.9,F;108.4,H;117.1,C;160.3,G;158.3,T;129.6,U;131.9,V;127.7,W;162.6(Benzene),I;183.3(Carbonyl),Z;172.3,P;175.2,R;178.5(Amide),K;165.8,J;120.0(Ethylene),M;90.7,

N;74.8,O;88.8,S;72.5(CH, aliphatic),e;32.0(CH_3,aliphatic),39-40(DMSO) .

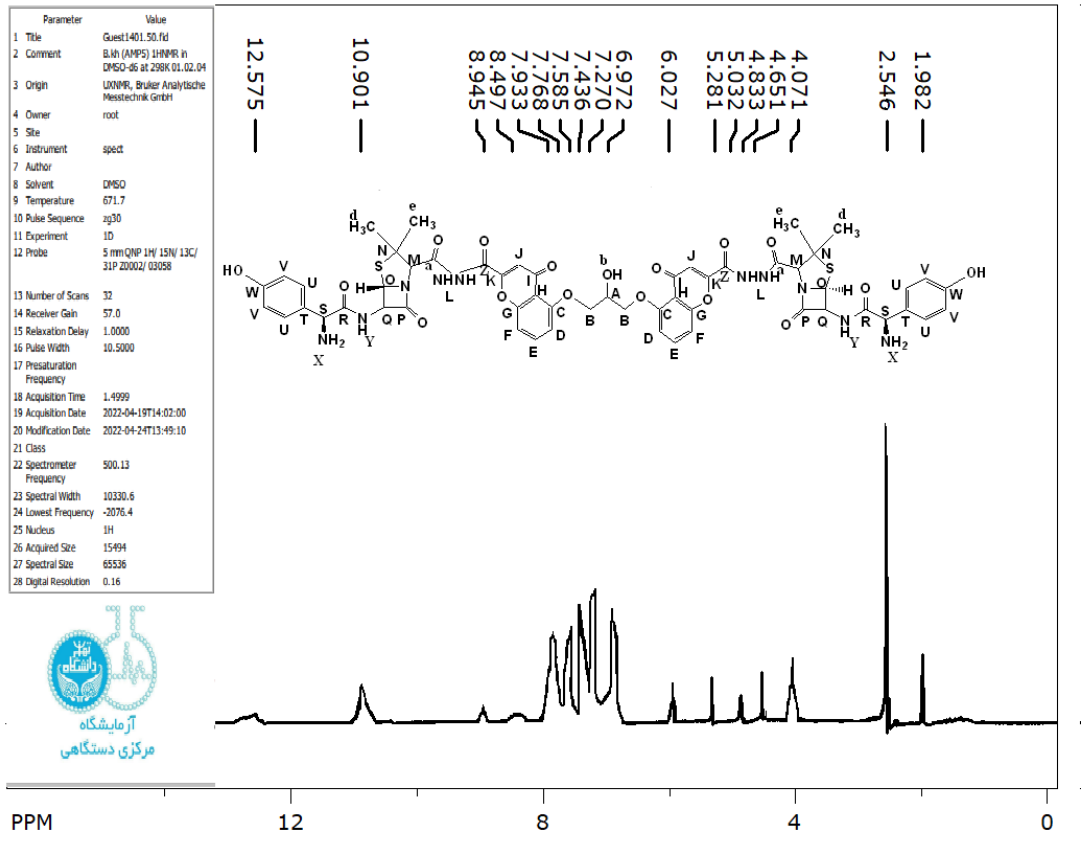


Figure (3-1): ^{1}H-NMR spectrum for A11

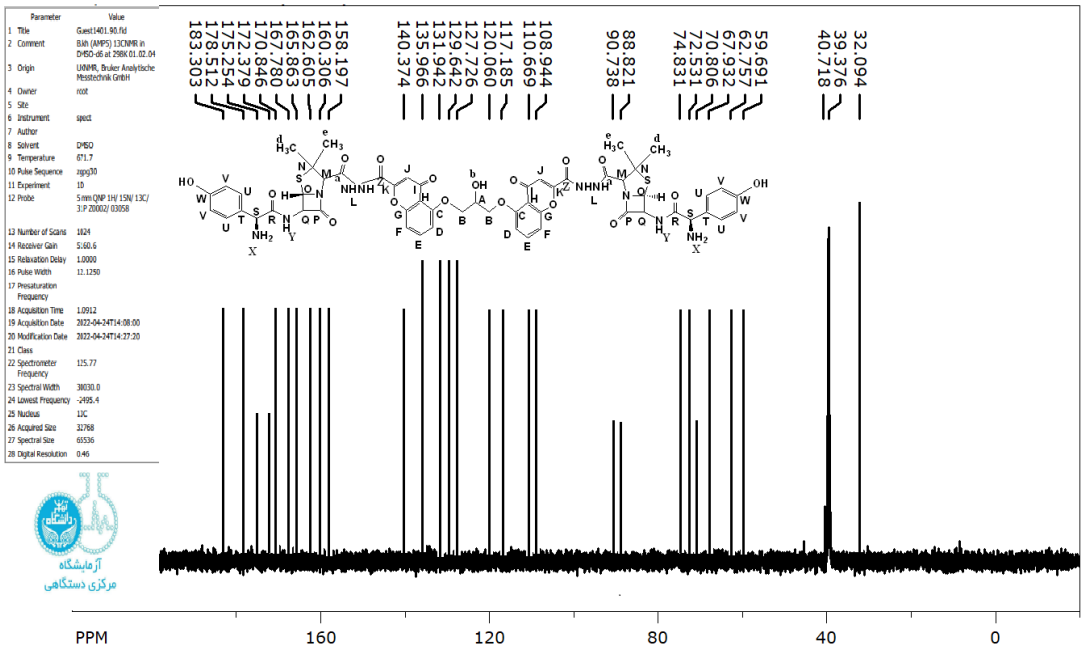


Figure (3-2): ^{13}C-NMR spectrum for A11

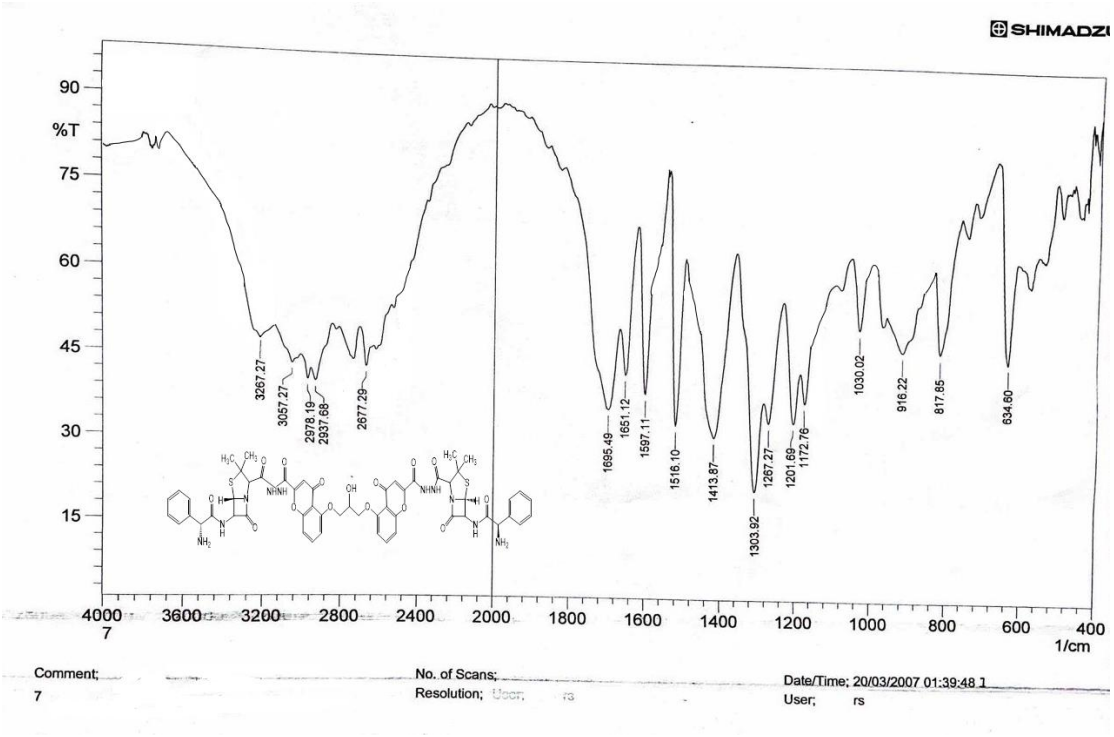
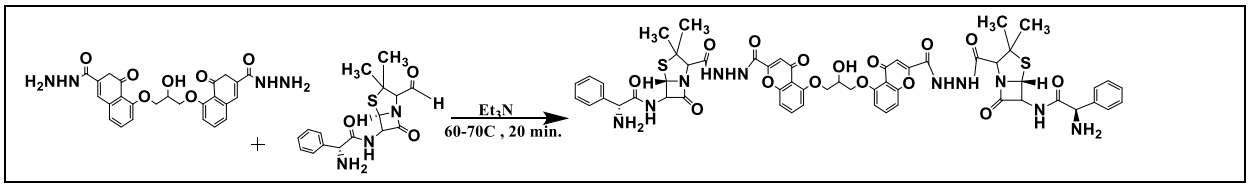


Figure (3-3): FT-IR spectrum for A11



Equation (3-2): synthesis of A12

For A12 The following values (V maximum, cm-1) were displayed in the FT-IR spectrum:3700 (NH) ,3244 (H-OH Phenol), 3085 (C=CH) ,2903 (CH str.), 1734 (C = O Ketone), 1653 (N-C=O amid), 1602 (C=C Ar),1247-1265-1311(C-N ,Aryl) .^{1}H-NMR (500 MH, δ ppm):A;4.4,B;4.7(CH_2 , ethylene) , e;1.7(CH_3,Methyl),S;4.9(CH,Methyl),X;8.9(NH2,amine),D;5.9,E;6.7,F;6.8,U;6.9,V;7.7,W;7.1 (Benzene) ,J;7.4(H, Ethylene) ,M;4.8(CH, methane)L;9.2,Y;8.4(Amide),b;5.4(Alcohol),2.5(DMSO).^{13}CNMR(125MH,δppm):A;62.9,B;71.0,Q;72.1(CH_2,aliphatic),D;110.0,E;130.0,F;108.3,H;116.7,C;159.3,G;156.8,T;164.1,U;160.8,V;128.1,W;118.1(Benzene),I;183.8(Carbonyl),Z;170.8,P;174.4,R;176.7(Amide) ,K;165.6,J;120.0(Ethylene) ,M;88.6,N;62.9,O;74.4,S;59.6(CH, aliphatic) , e;32.7(CH_3, aliphatic) , 39-40 (DMSO).

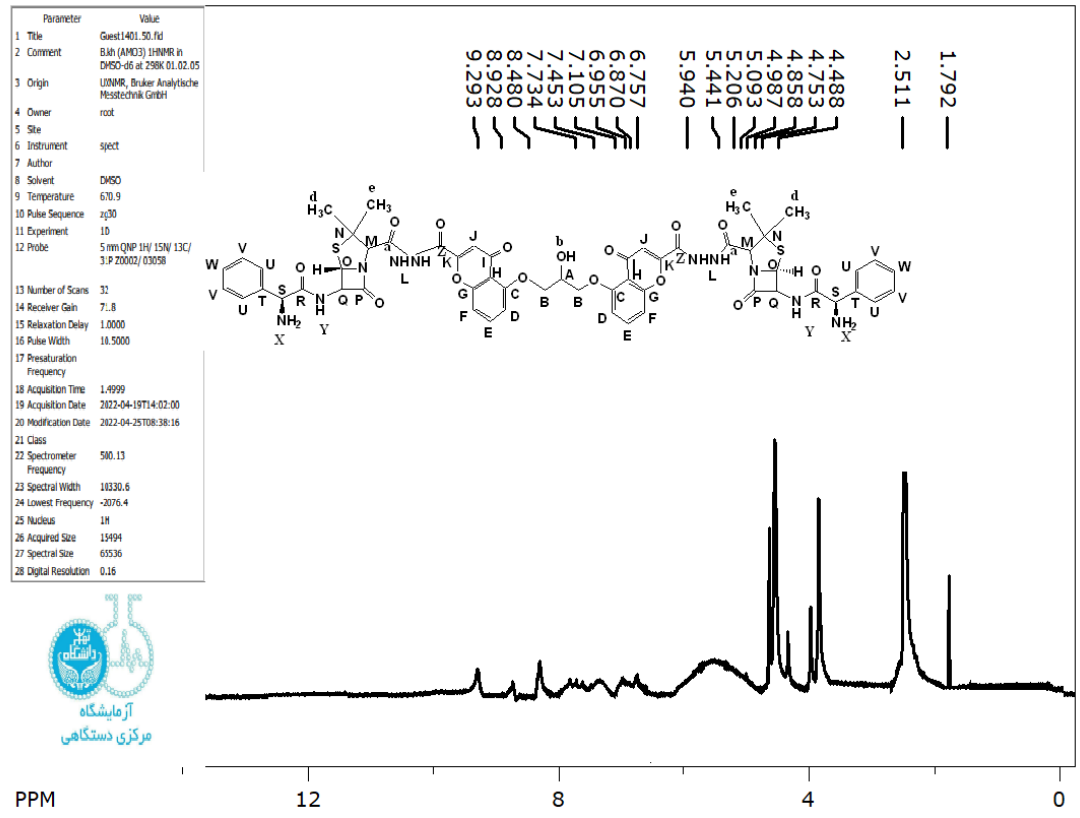


Figure (3-4): ^{1}H-NMR spectrum for A12

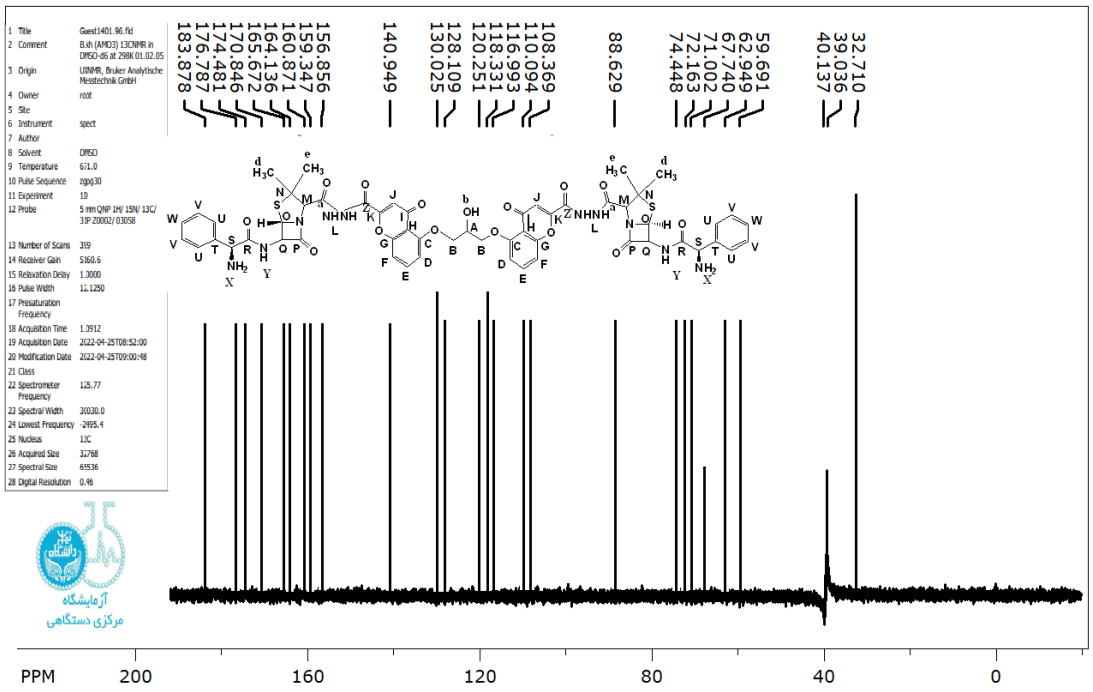


Figure (3-5): ^{13}C-NMR spectrum for A12

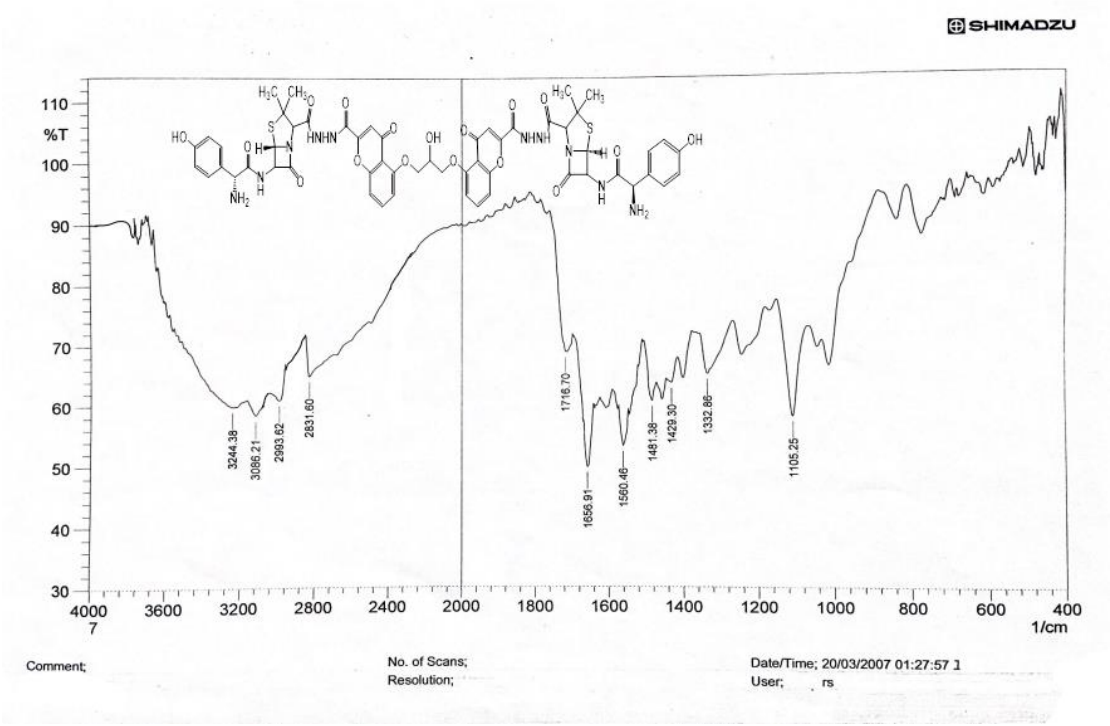
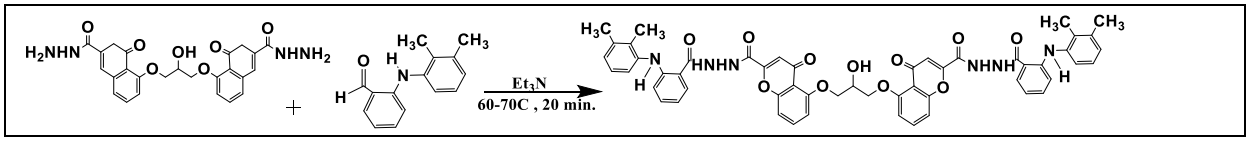


Figure (3-6): FT-IR spectrum for A12



Equation (3-3): synthesis of A13

ForA13 These values (V maximum, cm-1) were visible in the FT-IR spectrum:3751 (NH) ,3425 (H-OH Phenol), 3066 (C=CH) ,2937 (CH str.), 1734 (C = O Ketone), 1653 (N-C=O amid), 1602 (C=C Ar),1247-1265-1311(C-N ,Aryl) . ^{1}H-NMR (500 MH, δ ppm):A;4.5,B;5.0 (CH_2 , ethylene) , a;2.3,b;2.4(CH_3,Methyl) ,D;6.8,E;7.8,F;7.0,M;7.7;N;6.9,O;7.6 (Benzene) , J;7.5(H ,Ethylene) ,L;9.8,h;8.0 (Amide) ,e;5.9 (Alcohol) , 2.5 (DMSO). ^{13}CNMR(125MH,δppm):A;Q;70.2,B;72.4(CH_2,aliphatic),D;110.0,E;133.2,F;108.6,H;115.8,C;160.3,G;158.7,L;127.1,M;T;130.6,N;117.9,O;133.2,P;119.0,R;139.7,Q;140.9,S;128.4, U;122.7,V;135.5,W;137.3(Benzene) , I;185.2(Carbonyl) ,X;178.3, Z;165.6(Amide),K;163.7,J;120.4(Ethylene) ,a;21.0,b;19.0 (CH_3, aliphatic) , 39-40 (DMSO).

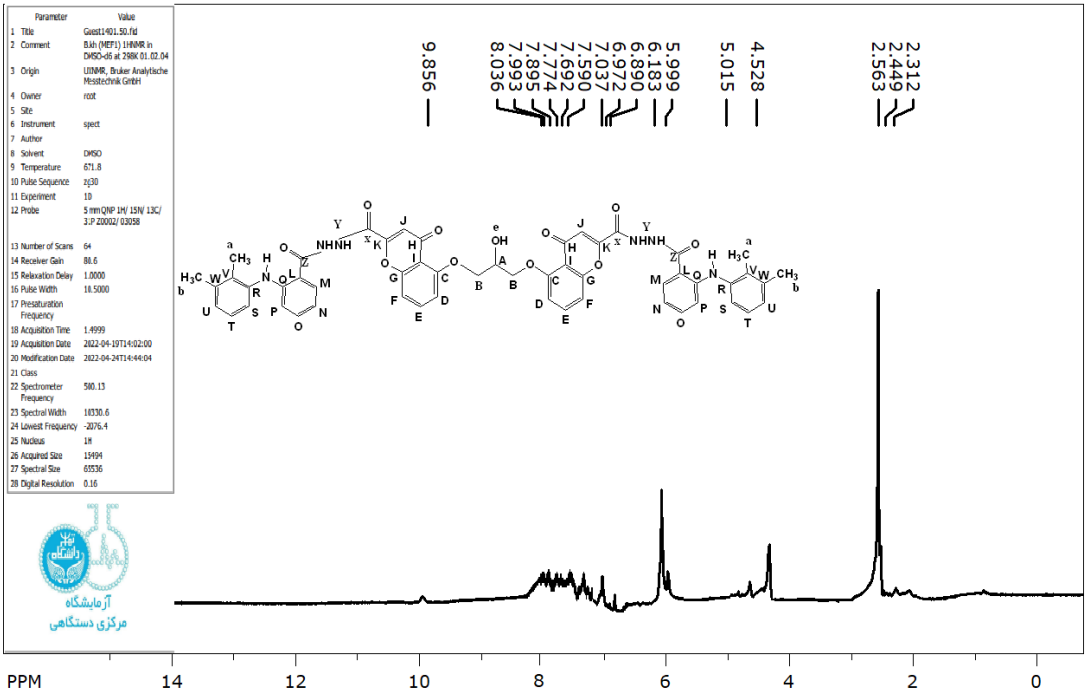


Figure (3-7): ^{1}H-NMR spectrum for A13

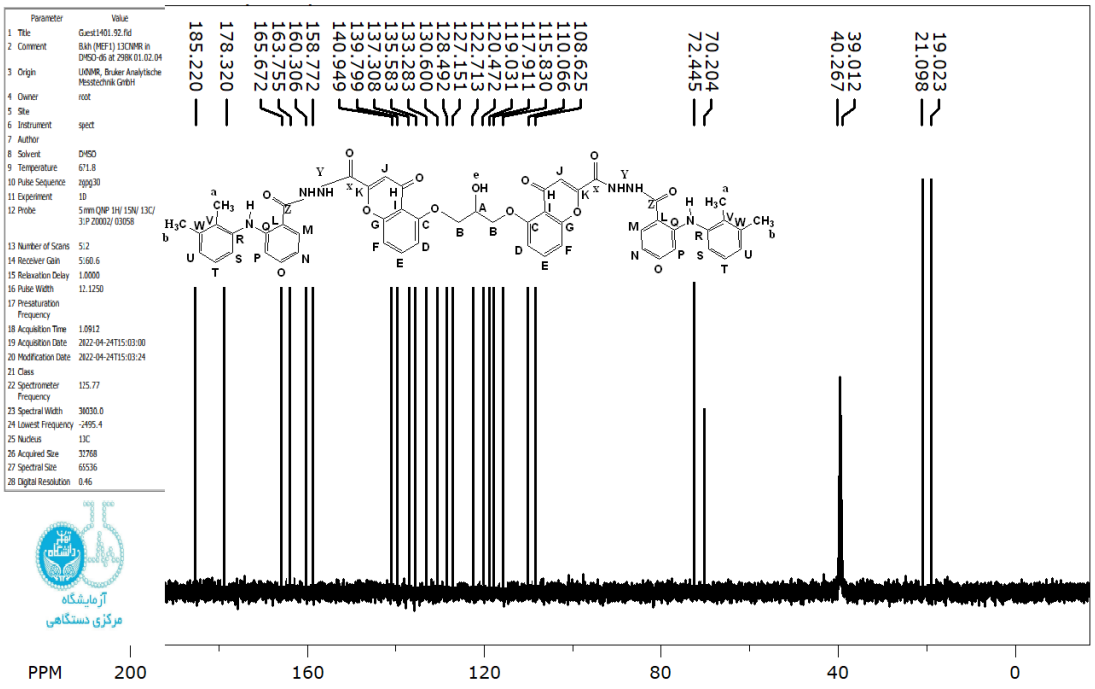


Figure (3-8): ^{13}C-NMR spectrum for A13

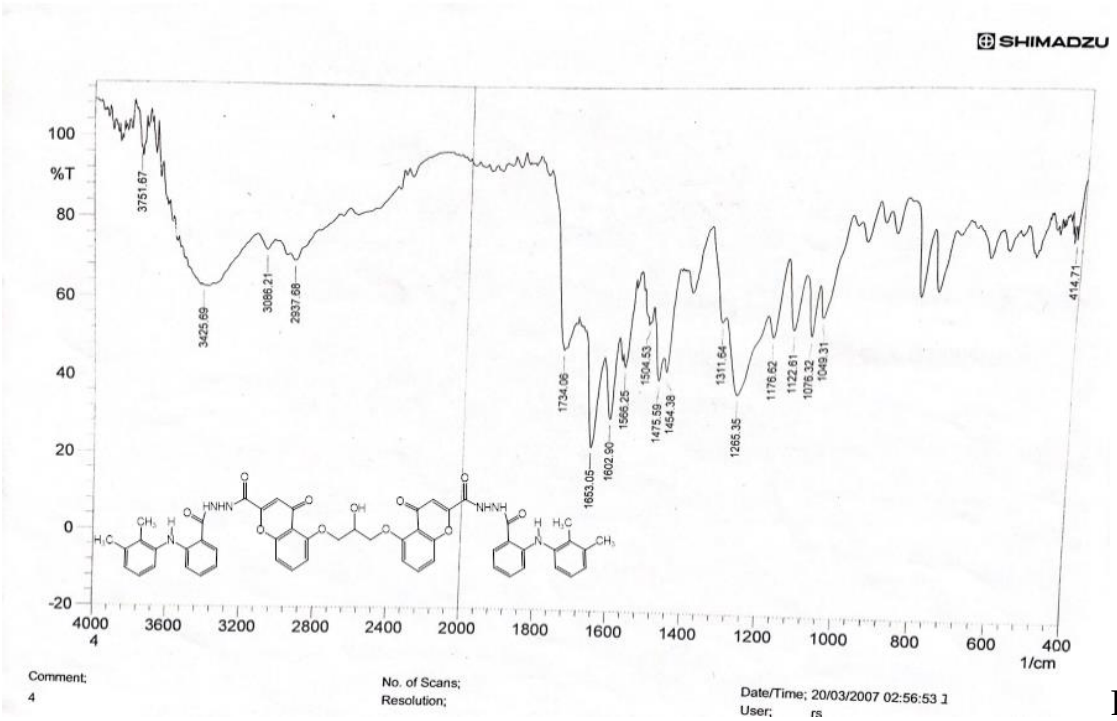
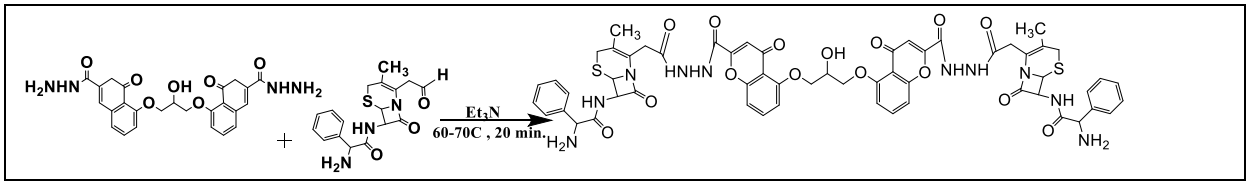


Figure (3-9): FT-IR spectrum for A13



Equation (3-4): synthesis of A14

For A14 The FT-IR spectra revealed the following values (V maximum, cm-1): 3742(NH) , 3672(NH2) ,3200(H-OH Phenol), 2943 (CH str.), 1739 (C = O Ketone), 1653 (N-C=O amid), 1590(C=C Ar),1236 (C-N,Aryl).[1]HNMR(500MH,δppm)

:A;3.5,B;4.1,O;3.1,3.1,L;2.1(CH_2,methylene),D;6.0,E;7.5,F;7.0,W;8.0,X;7.9,V;7.7(Benzene),J;7.3(H,Ethylene),b;9.0(Amide),f;2.1(CH_3Y;5.9(Alcohol),P;5.6,R;5.9(CH,Propilactam),T;5.3(CH,methane),Z;8.7(NH_2,amine),2.5(DMSO).[13]CNMR (125MH,δppm):A;62.6,B;70.1,L;33.9,O;31.9 (CH_2,aliphatic),D;110.0,E;139.2,F;107.9,H;116.5,C;160.1,G;157.8,d;155.8,U;135.3,V;130.2,W;129.0,X;M;128.3(Benzene),I;184.4(Carbonyl),Q;166.4,Z;169.2,e;170.0(Amide),K;162.9,J;119.6,N;127.1(Ethylene) ,f;31.9 (CH_3, aliphatic) ,R;72.0,T;59.4(CH , aliphatic) , 39-40 (DMSO) .

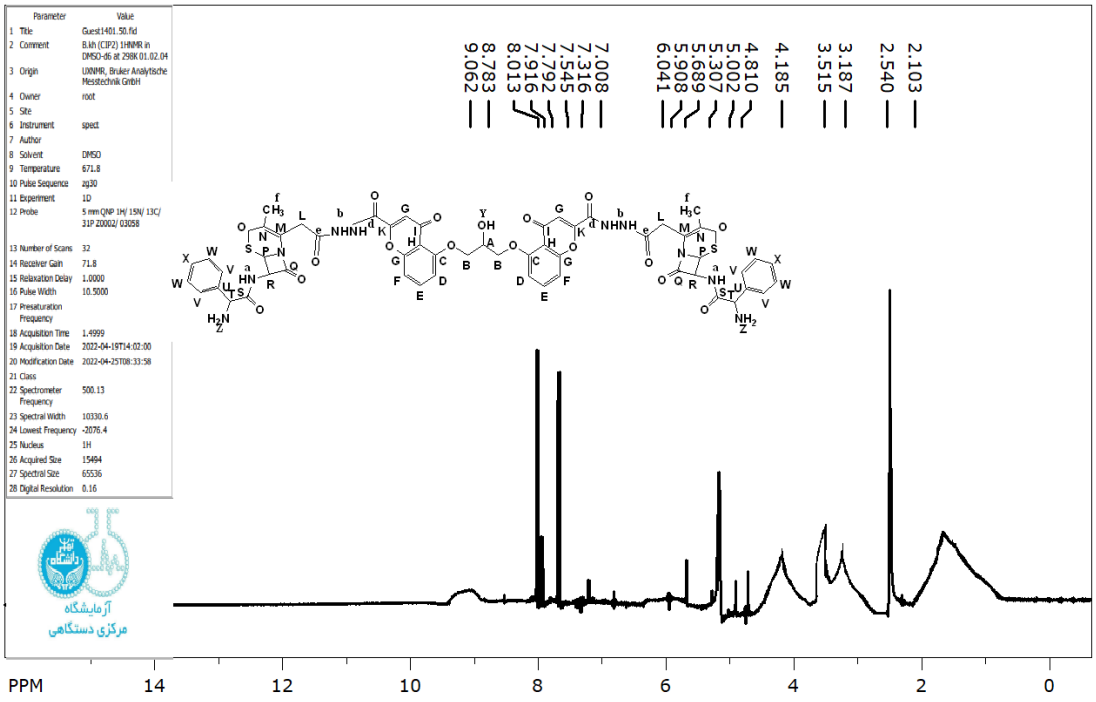


Figure (3-10): ^{1}H-NMR spectrum for A14

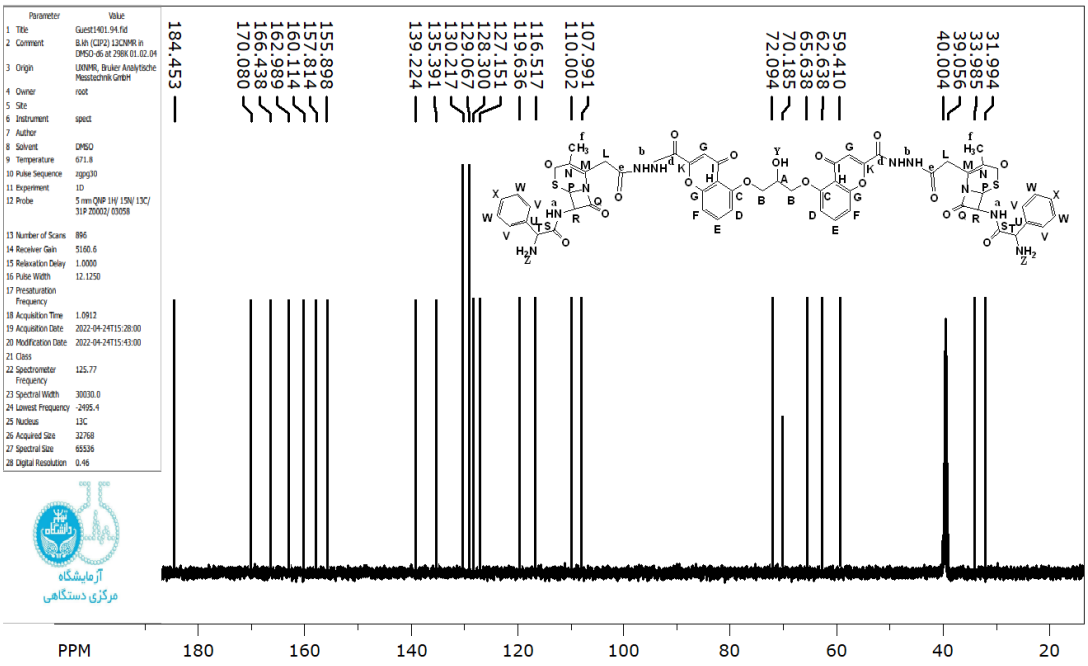


Figure (3-11): ^{13}C-NMR spectrum for A14

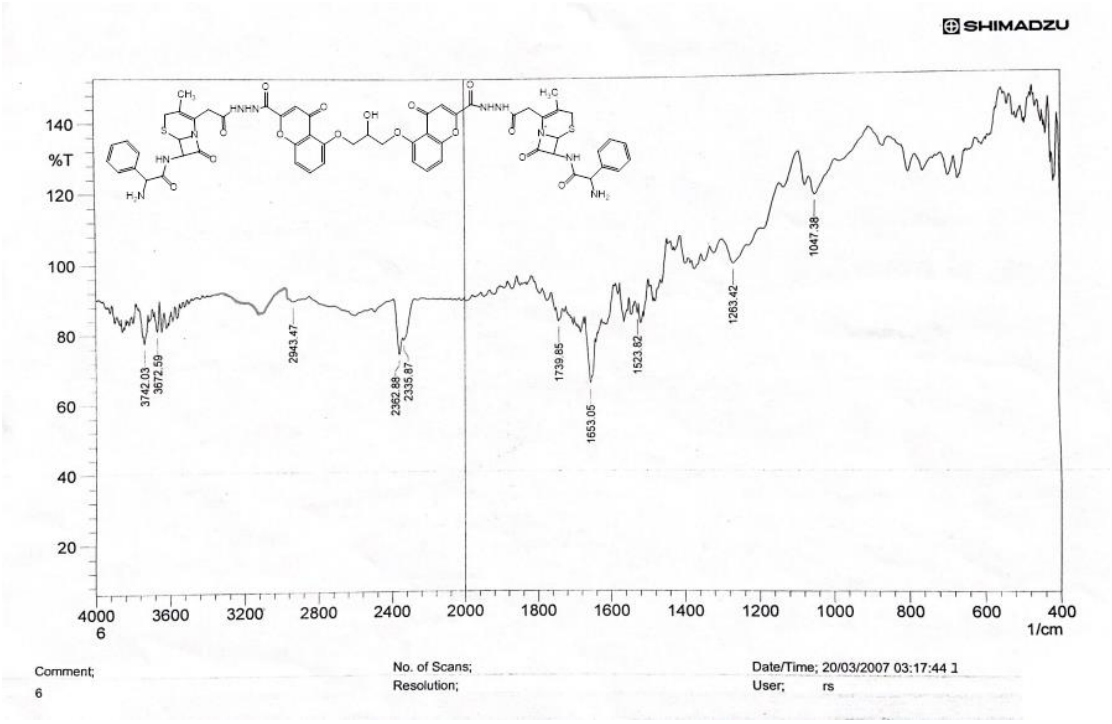
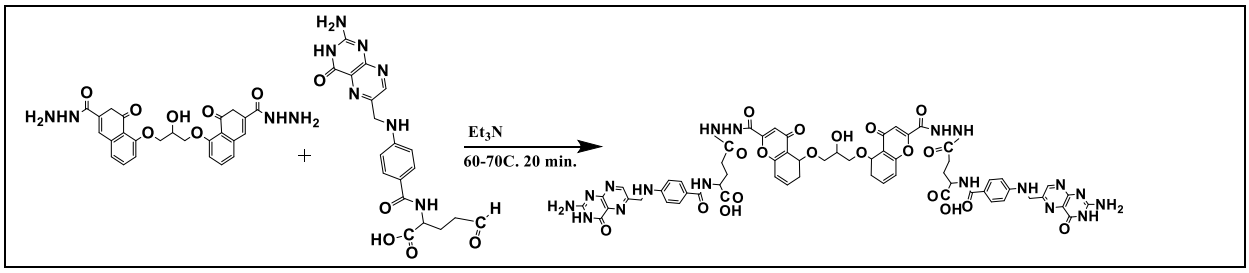


Figure (3-12): FT-IR spectrum for A14



Equation (3-5): synthesis of A15

For A15 the FT-IR spectrum showed the following values (V max., cm^{-1}):3751(NH2),3600(NH),2362-3562(OH, Carboxylic acid ,Phenol Overlape),3082(C=C-H),2985(CH str.),1739(C = O Keto.),1689(N-C=O amid), 1604 (C=CAr),12441290(CN,Aryl).^{1}HNMR(500MH,δppm):A;4.0,B;4.3,M;1.9,N;2.1(CH_2,methylene),D;6.8,E;7.5,F;7.3,R;7.6,S;6.5(Benzene),J;7.3(H,Ethylene),b;12. 9,11.0,g;8.8,h;6.3(Amide),m;5.7(Alcohol),O;4.6,V;4.5(CH_2,methylene),o;12.9(Carboxyl),X;7.9(CH,Pyrazine),b;11.0,r;9.5(NH,Quinidine),2.5(DMSO).^{13}CNM R(125MH,δppm):A;69.9,B;71.1,M;30.5,N;29.6,V;49.3(CH_2,aliphatic),D;111.1, E;140.3,F;108.5,H;117.0,C;160.1,G;158.5,U;155.8,Q;124.0,R;130.1,S;114.1(Be nzene),I;187.9(Carbonyl),P;173.7(Carboxyl),L;175.4,e;165,2,a;157.1,I;170.2(A mide),K;163.9,J;120.0(Ethylene),O;59.8(CH_2aliphatic),d;153.5(Imine),X;148.4, W;151.4,Y;133.8,Z;150.4(CH,Pyrazine),39-40 (DMSO).

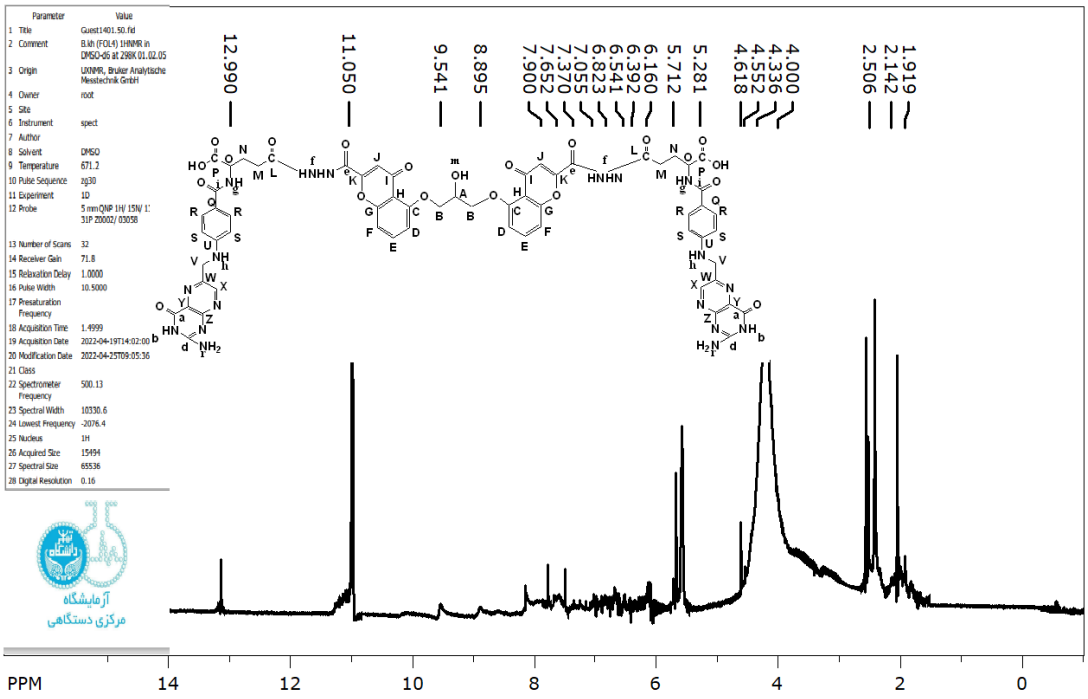


Figure (3-13): ^{1}H-NMR spectrum for A15

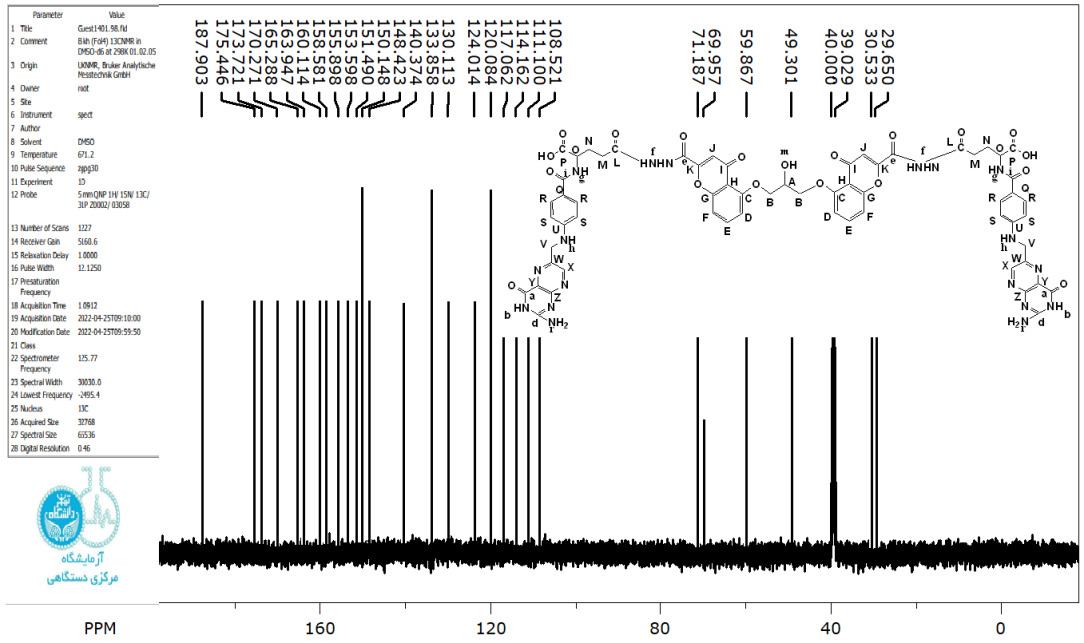


Figure (3-14): ^{13}C-NMR spectrum for A15

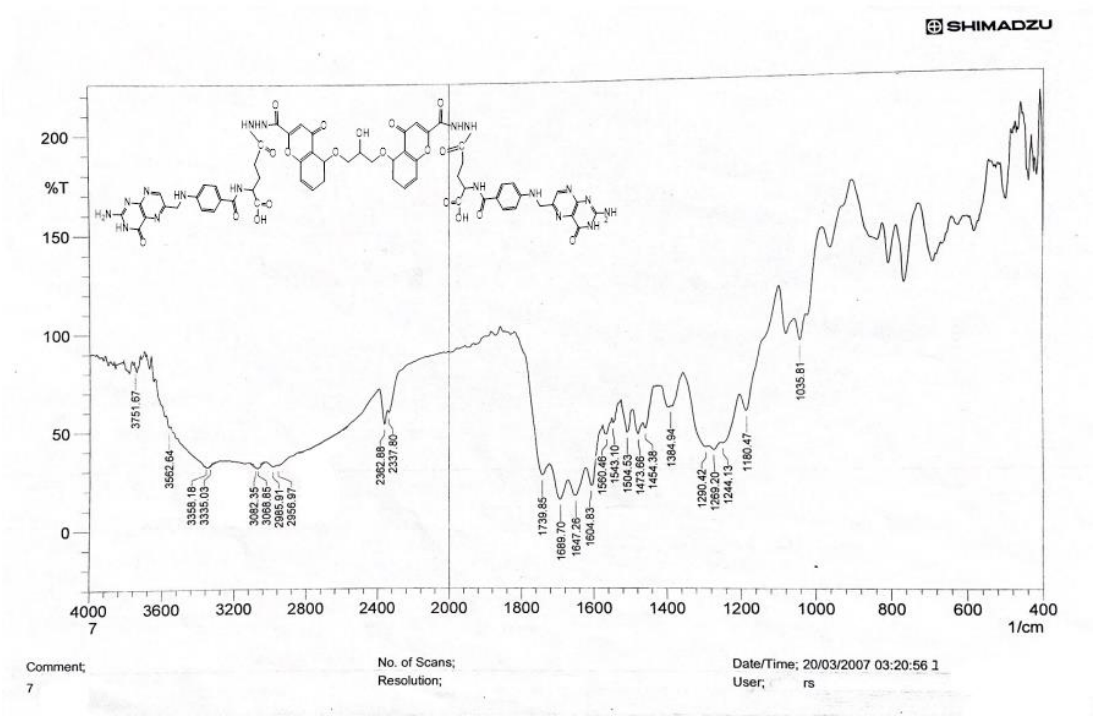
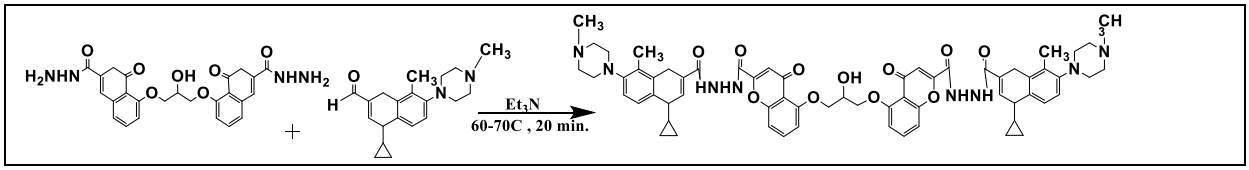


Figure (3-15): FT-IR spectrum for A15



Equation (3-6): synthesis of A16

For A16 the FT-IR spectrum showed the following values (V max., cm-1): 3600(NH), 3000 (H-OH Phenol), 2980(CH str.), 1718 (C = O Ketone), 1629 (N-C=O amid), 1477 (C=C Aromatic),1271-1396(C-N, Aryl).^{1}HNMR (500MH,δppm):h;f;2.2,(CH_3),O;4.6,Q;3.2(CH),R;1.2,S;0.4,0.1(CH,cycloprop.), A;b;3.6,B;4.3,a;Q;3.4(CH_2),m;4.9(OH),L;12.2,11.4(amid),C;6.8,D;7.5,W;7.1,E; 7.23(CH,Benzene),2.5(DMSO),J;7.27,X;6.9(ethylene).^{13}C-NMR (125MH,δppm):Q;31.1,O;52.3(CH,Aliphatic),A;69.0,B;70.1(CH_2,Aliphatic),I;1 82.1(C=O,Carbonyl),M;165.9,r;165.2(C=Oamide),K;163.8,N;131.3,J;118.8,P;1 44.3(Ethylene),F;156.6,G;158.7,Y;144.4,H;115.6,U;137.3,V;127.6,Z;120.5,C;10 9.1,X;117.2,W;120.0,F;107.7,E;138.3(benzene),h;46.6,f;14.0(CH_3,Aliphatic),R; 16.3(CH,cyclopropane),S;3.8(CH2,cyclopropane),39-40(DMSO).

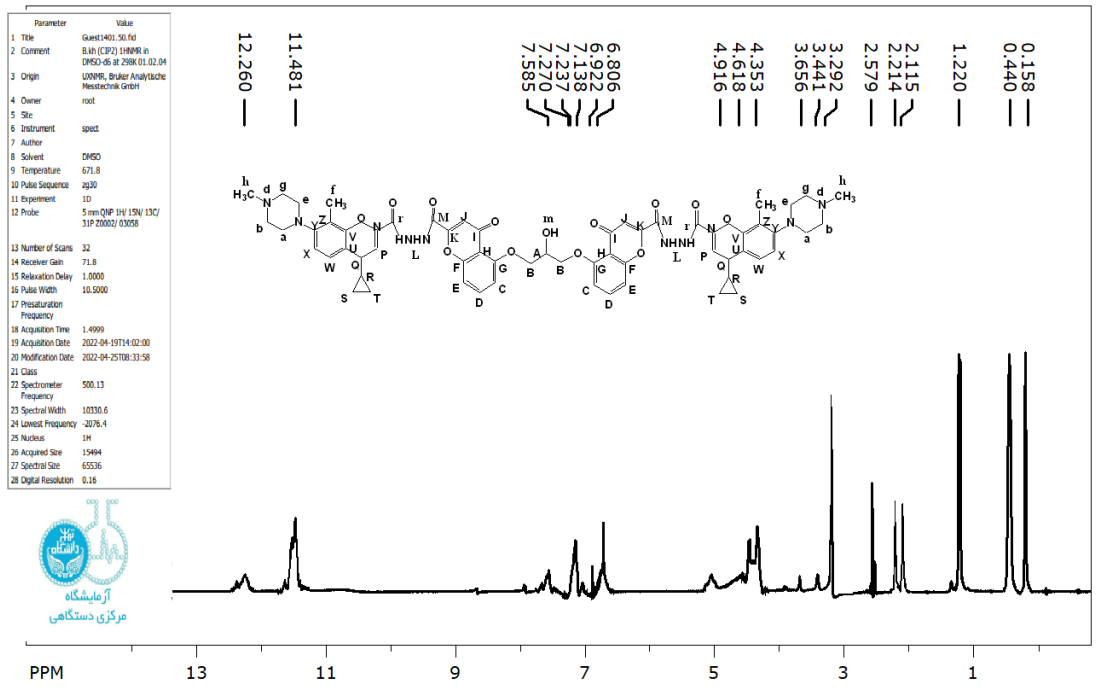


Figure (3-16): ^{1}H-NMR spectrum for A16

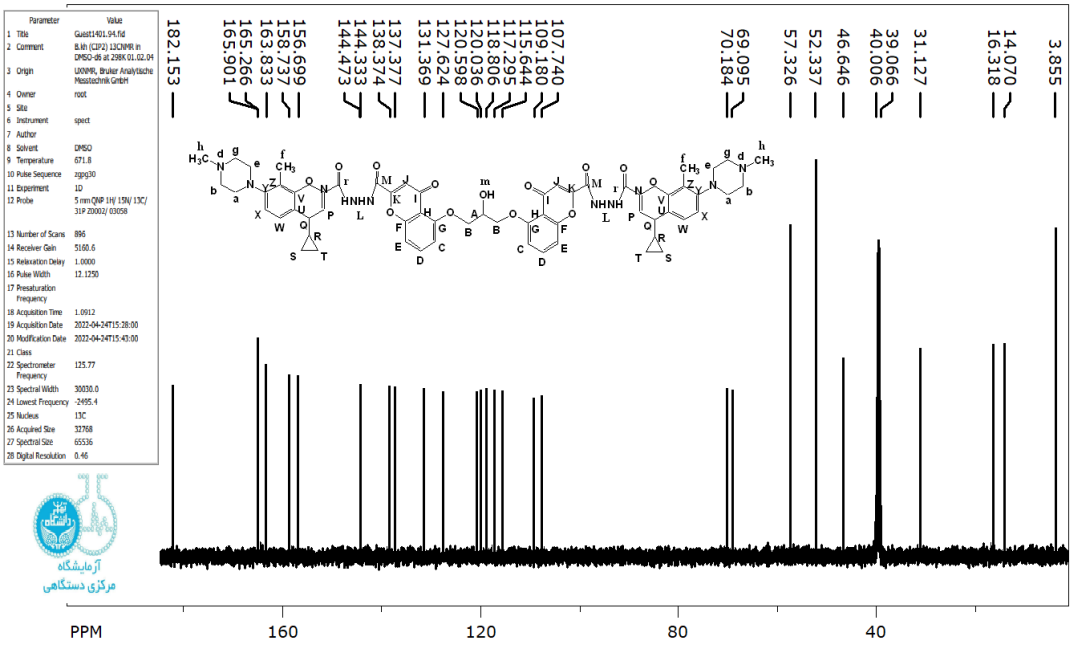


Figure (3-17): ^{13}C-NMR spectrum for A16

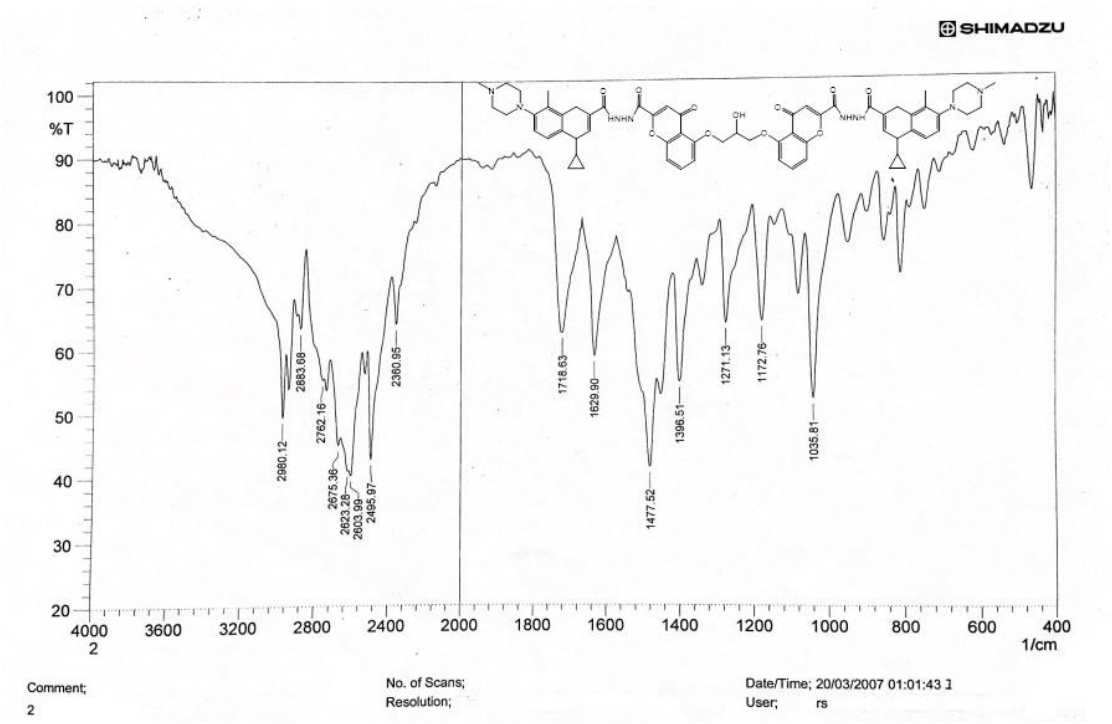
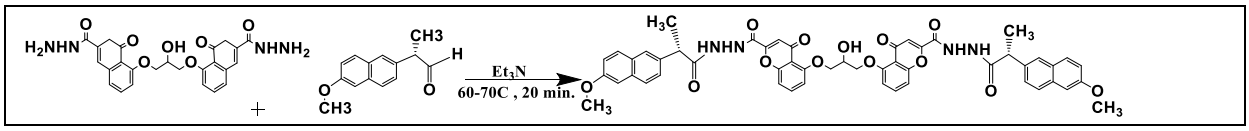


Figure (3-18): FT-IR spectrum for A16



Equation (3-7): synthesis of A17

For A17 the FT-IR spectrum showed the following values (V max., cm-1):3610(NH), 3244(H-OH Phenol), 2993(CH str.),1716 (C = O Ketone), 1656(N-C=O amid),1560(C=C Arom),1332(C-N ,Aryl). ^{1}H-NMR (500MH ,δ ppm):A;4.5,B;4.8(CH_2,methylene),D;6.9,E;7.5,F;7.6,W;7.3(Benzene),J;7.3 (H,Ethylene),b;12.0,10.9(Amide),C;5.90(Alcohol),b;1.5,Z;4.0(CH_3,methyl),N;5.3(CH,methane),Q;6.5,R;7.9,S;7.6,V;7.8,X;6.4(CH,Naphthalene),2.5(DMSO).[13] CNMR(125MH,δppm):A;69.8,B;72.3(CH_2,aliphatic),D;107.7,E;138.2,F;105.1, H;109.5,C;150.3,G;155.1,P;132.9,Q;127.9,R;123.8,S;125.8,U;131.1,b;135.7,V;129.8,X;117.7,Y;148.91(Benzene),I;175.6(Carbonyl),M;169.6,a;159.3(Amide),K;157.4,J;120.0(Ethylene),b;16.1(CH_3,aliphatic),N;46.6(CH,aliphatic),39-40(DMSO).

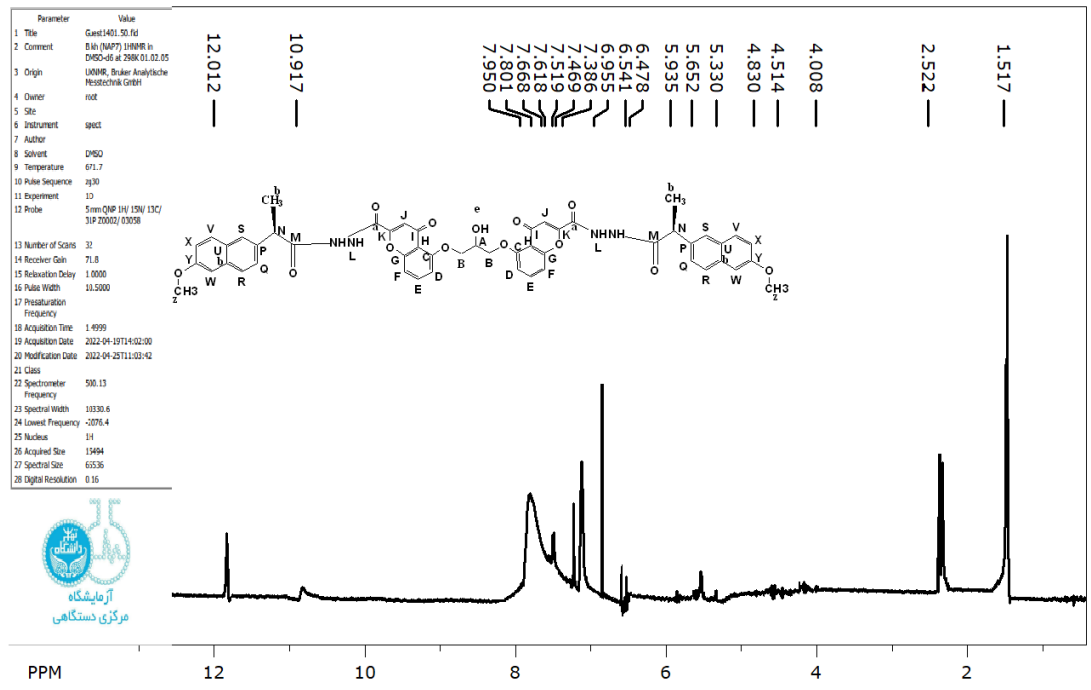


Figure (3-49): ^{1}H-NMR spectrum for A17

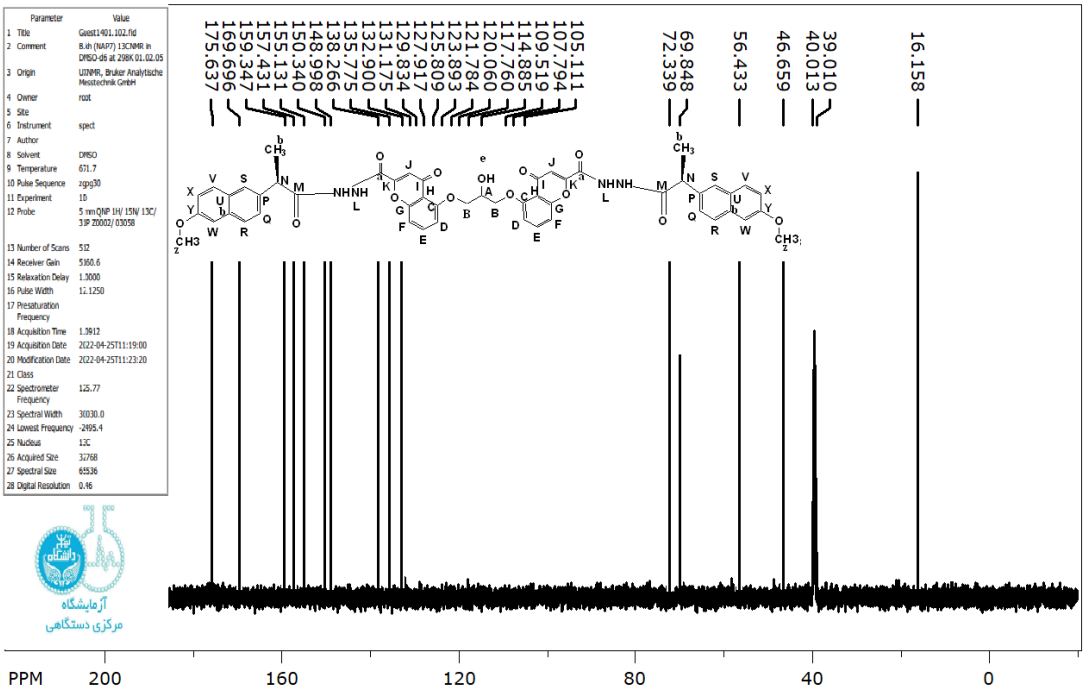


Figure (3-50): ^{13}C-NMR spectrum for A17

No. of Comp.	Antibacterial activity test

Figure (3-51): FT-IR spectrum for A17

Biological Activity:

Activity against bacteria

a healthy pastime The research revealed that practically all of the chemicals looked at have specific antibacterial interests.. These micro organism had been selected due to their huge significance with inside the scientific field, as they motive loads of sicknesses further to their numerous antibiotic and chemical drug resistance. Table (2) well-known shows that the produced compounds have organic pastime towards the micro organism due to the fact they'll suppress the micro organism with the aid of using various the quantities of the compounds. This distinction in toxicity because of extrade in useful organization or structures, as proven in figure (25,26).

figure (3-88)klebsiella pneumonia activity test

figure (3-89).*Staphylococcus aureus* activity test

	klebsiella pneumonia (Gram-negative bacteria)	*Staphylococcus aureus (Gram-positive bacteria)*
Control	16	14
13A	21	11
14A	20	27
15A	16	19
16A	26	15
17A	21	16

Table (3): applications of Antibacterial activity for compounds (A11-A17)

Antioxidants activity :

Compounds antiradical operation turned into finished the use of the usual DPPH method. Fig: (1-27).Table (4) In as compared to normal (ascorbic acid) pastime (IC50=28.seventy two mg / mL), the bulk of compounds confirmed mild to excessive antioxidant hobby.The most interest become due to the OH institution in compounds (A11-A17)with huge interest. Ascorbic acid, a accepted medication, with an IC50 of 28.72 M.

Comp. No.	Inhibition %			IC50 mg/mL
	25 mg/mL	50mg/mL	100mg/mL	
A11	37.24	56.52	63.7	51.09
A12	49.33	55.05	61.16	18.2
A13	50.43	55.67	65.17	22.73
A14	50.51	55.22	67.61	24.73
A15	56.32	62.14	65.01	48.8
A16	55.2	59.11	63.23	31.4
A17	52.41	58.09	60.22	14.1
Ascorbic acid(STD)	46.12	60.14	65.01	28.72

Table (4): applications of Antioxidants activity :for compounds (AH11-AH17)

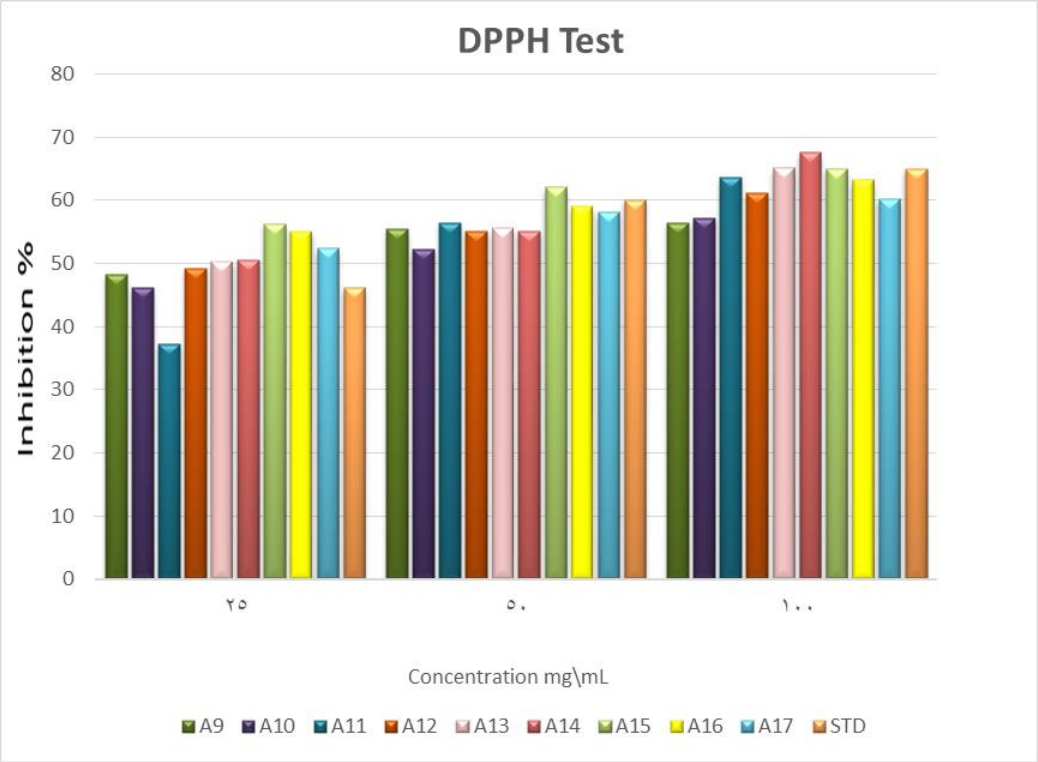


Figure (27): standard DPPH method.

Solubility:-

Solv. / Comp.	DMSO	water	Etha.	Ace.	Meth.	Haxe.	1,4-dioxan	DCM	DMF	Diet. ether	P. ether	Ethyl ace.
A11	+	partial	+	+	+	partial	partial	-	-	-	-	partial
A12	+	partial	+	+	partial	-	partial	-	-	-	-	-
A13	+	partial	+	+	partial	-	-	-	-	partial	-	-
A14	+	-	-	Partial	-	-	partial	+	+	-	-	-
A15	+	-	Partial	-	-	Partial	-	-	+	-	-	-
A16	+	parti	+	+	+	-	parti	-	-	part	-	-

		al					al			ial		
A17	+	-	-	part ial	-	Parti al	Parti al	-	+	-	-	Part ial

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