Ministry Of High Education and Scientific Research
University Of Babylon
College Of Science
Chemistry Department

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

A Thesis

Submitted to the council of College of Science, University of Babylon in Partial Fulfillment of the Requirements for the Degree of Master in Chemistry Science

By

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B.Sc. in chemistry/university of Babylon (2019)

Supervisor

Asst. Prof. Dr. Hala Shkyair Lihumis

2022 A.D **1444 A.H**

وزارة التعليـــم العـــالي و البـــحث العـــلمي

جـــامـــعة بـــابـــل

كليـــة العـــلوم

قســـم الكـــيميـــاء

تحضير و تشخيص مركبات عضوية جديدة من حامض الكروموجليكسيك و دراسة بعض تطبيقاته

رسالة

مقدمة الى مجلس كلية العلوم – جامعة بابل كجزء من متطلبات نيل درجة الماجستير

في العلوم / الكيمياء

من قبل

عبيـــر حـــــسن مـــظلـــوم كـــاظـــم

بكالوريوس علوم كيمياء / جامعة بابل (٢٠١٩)

بإشـــراف

أ.م.د. حـــــلا شـــخـــير لـــــهميـــص

١٤٤٤ هـ ٢٠٢٢ م

بسم الله الرحمن الرحيم

يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ

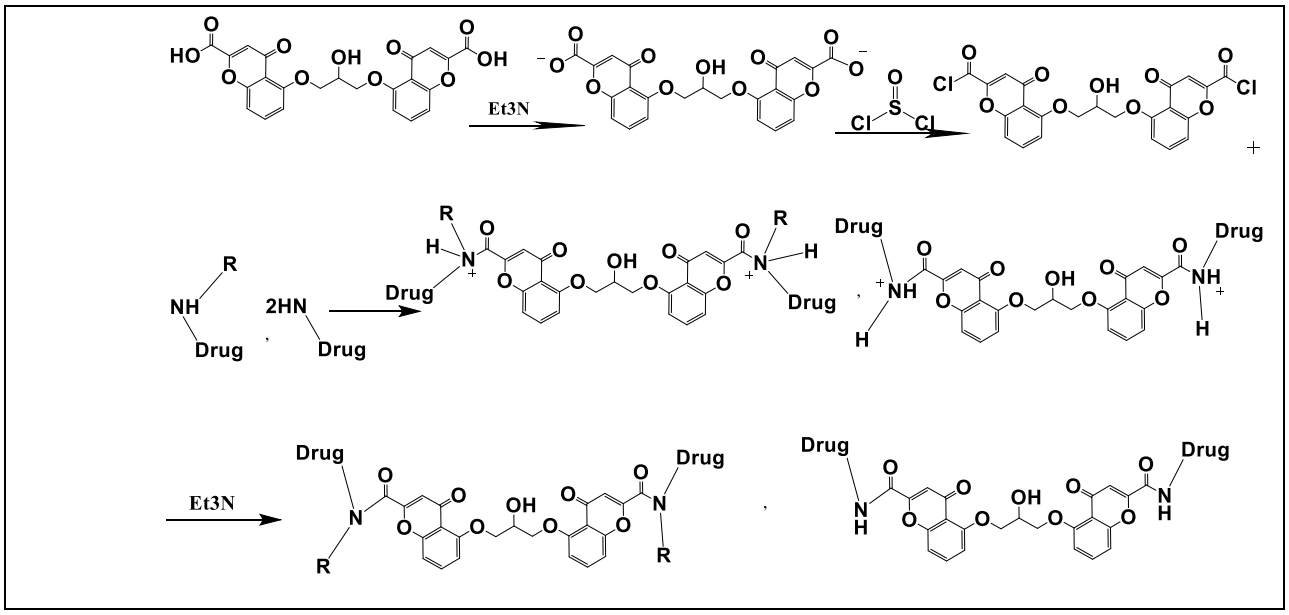
صدق الله العلي العظيم

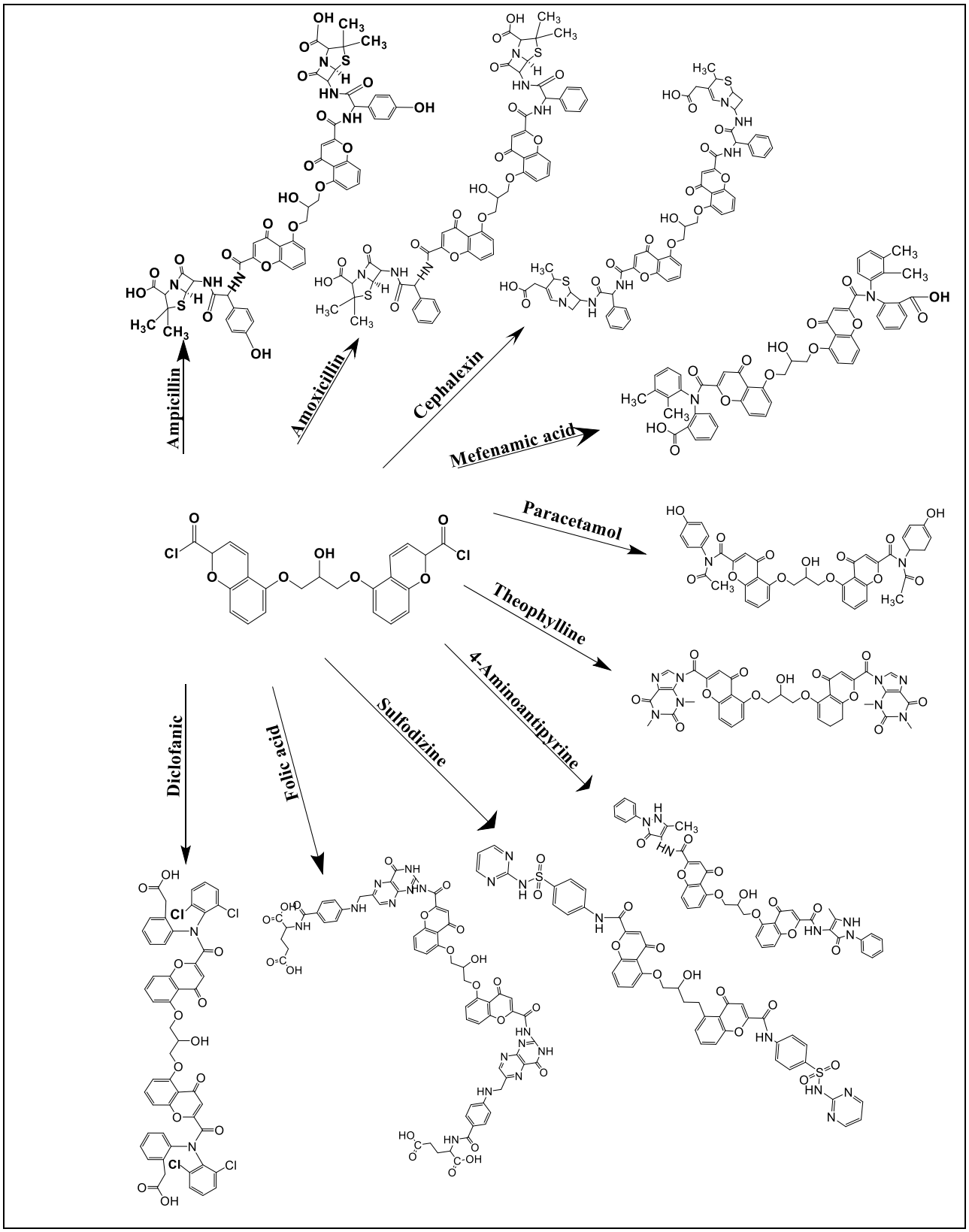
الخلاصة:-

في هذا العمل ، تم إنشاء مشتقات جديدة من حمض الكروموجليكسيك والتي لها خصائص جديدة. يشكل حمض Cromoglicic نوعًا رئيسيًا من المركبات العضوية الصيدلانية. يمكن استخدام مشتقاته في تصنيع أنواع جديدة من الأدوية ويمكن أن تمتلك نطاقًا واسعًا من النشاط البيولوجي وتقليل الآثار الجانبية. تضمن العمل عدة مسارات. كالآتي:-

المسار الاول: -

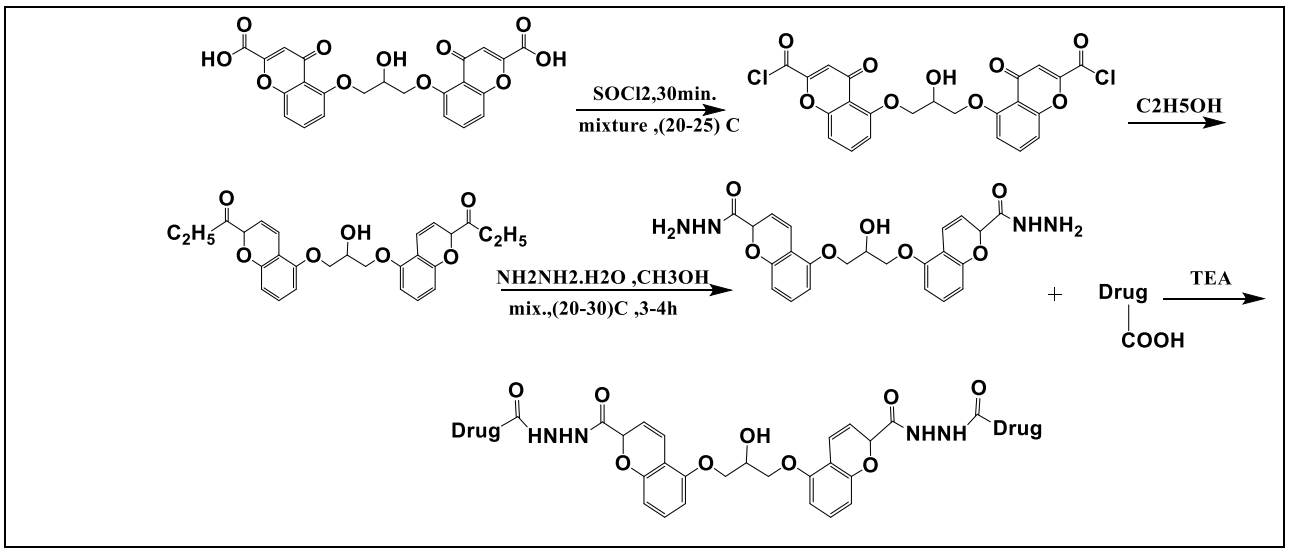
تفاعل مباشر لعشرة عقاقير أمينية (أمبيسلين ، حمض الفوليك ، حمض الميفيناميك ، سلفودايزين ، ديكلوفيناك ، باراسيتامول ، ثايوفينيل ، سيفاليكسين ، ٤-أمينو أنتيبيرين) بعد تحويل الحامض المستخدم إلى كلوريد الحامض بأستخدام $SOCl_2$ و DCM ، بعد ذلك يضاف ثلاثي مثيل امين إلى المركبات الناتجة (حمض كلوريد).

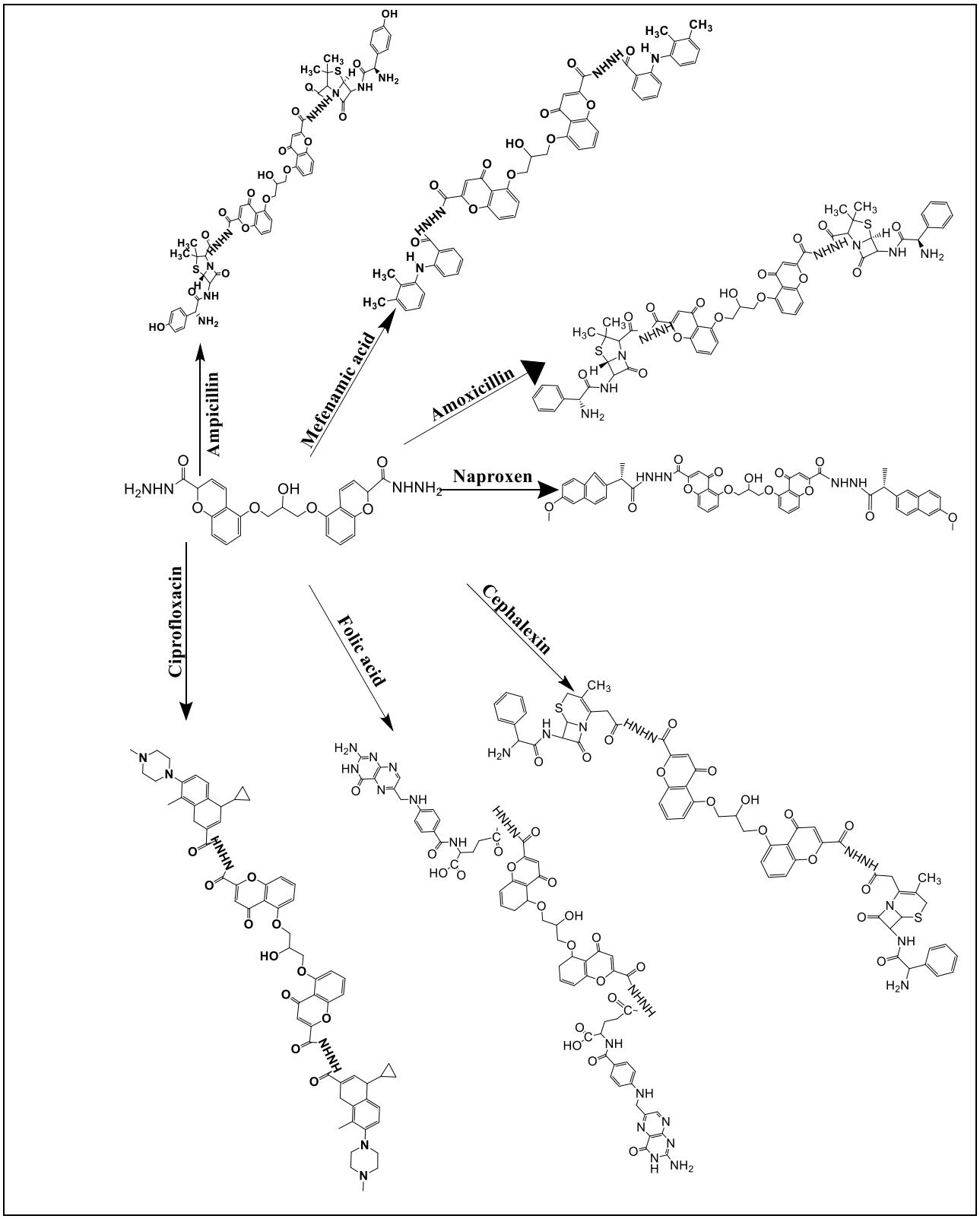



Ampicillin
Amoxicillin
Cephalexin
Mefenamic acid
Paracetamol
Theophylline
4-Aminoantipyrine
Sulfodizine
Folic acid
Diclofanic

المسار الثاني: -

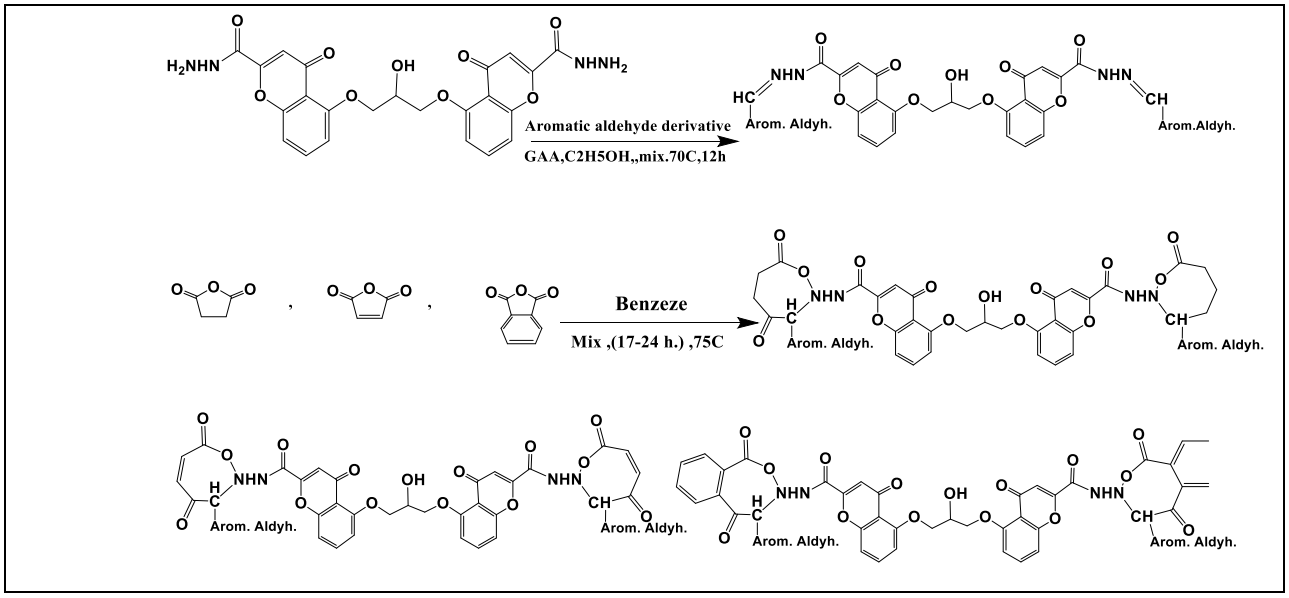
يتضمن تحويل حمض الكروموجليكسيك إلى مشتق هيدرازيد للحمض عن طريق تحويل مجموعة الكاربوكسيل للمركب إلى كلوريد الحمض بواسطة كلوريد الثايونيل ، تم تحويل كلوريد الحمض المتشكل إلى مشتق ميثيل إستر عن طريق إضافة ميثيل الكحول قطرة في الغرفة درجة الحرارة ، ثم يضاف محلول من الهايدرازين المائي (٨٠٪) في إيثانول قطرة عند درجة حرارة الغرفة إلى الإستر المتشكل وبعد الانتهاء من الإضافة ، تمت إعادة تدفق الخليط لمدة ٤ ساعات. تم تسخين الهايدرازيد المتكون بواسطة سبعة عقاقير كربوكسيلية (اموكسيلين ، امبسيلين، حمض الفولك، حمض الميفيناميك، سيفالكسين، سبروفلاكسين، نابروكسين) بعد أن تم تحويل مجموعة الكاربوكسيل الموجودة فيه إلى كلوريد حمض بواسطة كلوريد الثايونيل.

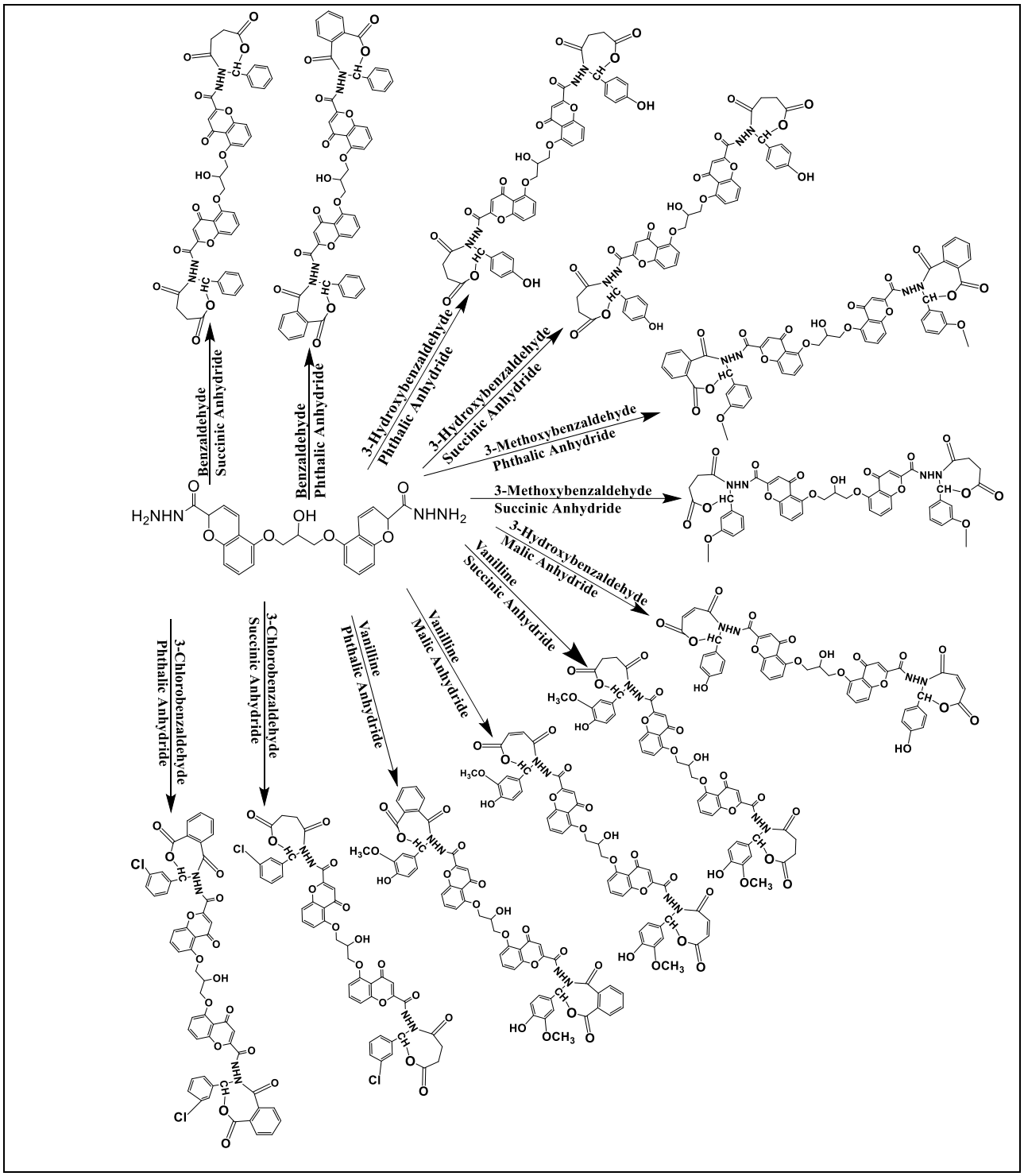



Ampicillin
Mefenamic acid
Amoxicillin
Naproxen
Ciprofloxacin
Folic acid
Cephalexin

المسار الثالث:-

لتخليق بعض مشتق الأوكزايبين الجديد باستخدام مشتق الألديهايد العطري وثلاثة أنواع من أنهيدريد تم إذابة الألديهايد العطري في الإيثانول المطلق وقطرتين من حمض الخليك الجليدي ثم تم اضافة الهايدرازيد الى خليط التفاعل مع التحريك على حمام مائي عند ٧٠ درجة مئوية لمدة (١٢-١٨ ساعة) ، بعد ذلك يضاف فثالك ومماليك وساسنيك أنهيدريد مع البنزين الجاف لمدة (١٧-٢٤ ساعة) مع التحريك في حمام مائي عند ٧٥ درجة مئوية.





تم تشخيص المركبات المحضرة باستخدام القياس الطيفي بالأشعة تحت الحمراء ، NMR، CHNS و TLC.

Acknowledgments

Praise be to Allah, Lord of the Worlds, and prayers and peace be upon the Seal of the Prophets and Messengers, who was sent as a mercy to the worlds, and upon his good and pure family.

Thanks be to Allah first and foremost for all of his blessings, and thanks to him for his constant kindness and success. My thanks go to the Messenger of Allah and his pure family, especially the remnants of Allah the Awaited Justice and Resurrection (may God's blessings be upon them all).

Great thanks and great gratitude to Dr. Hala Shkyair Lihumis for his continuous and his accurate observations during the study period.

I would like to thank the Deanship of the College of Science for their continuous support to postgraduate students. All thanks and gratitude to the Head of the Department of Chemistry for providing this opportunity and thanks to all the professors of the department for their efforts and providing a helping hand throughout the study period.

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My thanks, appreciation and gratitude to all my colleagues in the Department of Chemistry. and I'd like to thank all postgraduate students for their continuous moral support especially my friends Teeba saleh and Tuqa sattar and sabreen saleh

My father, my mother, my brothers and wives , I thank you inexpressible thanks for your unlimited financial and moral support and for bearing all the burdens on me during the study period.

The completion of this thesis could not have been possible without assistance and participation of many people whose names may not all be enumerated Their contribution are sincerely appreciated and gratefully acknowledged .

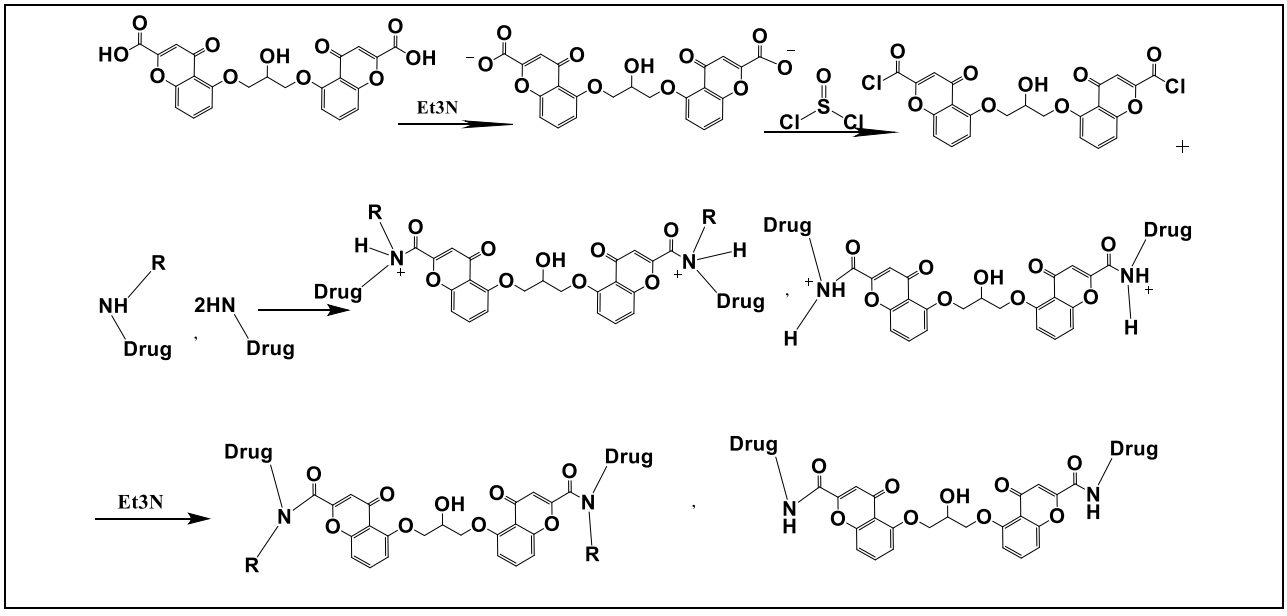
Summary

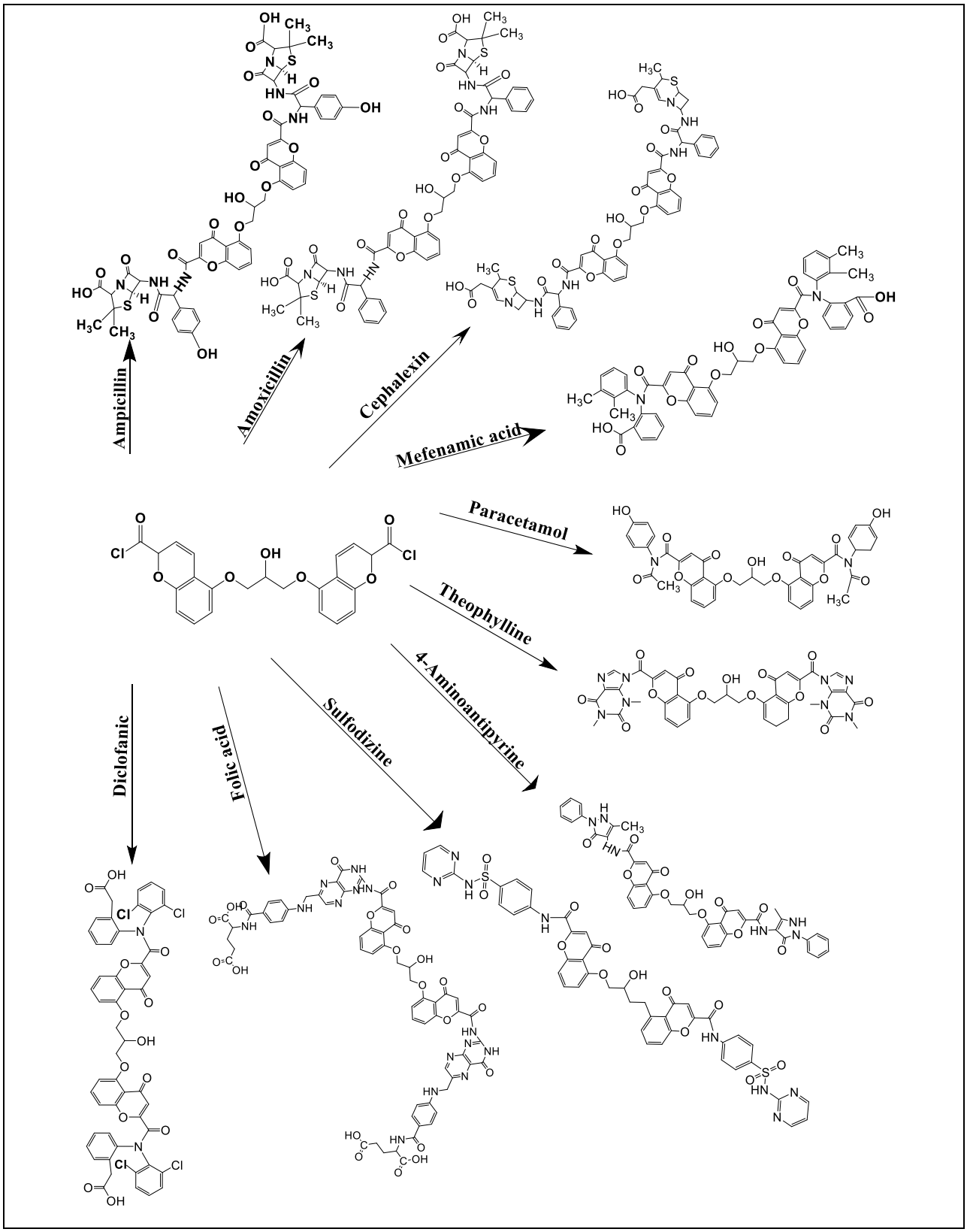
In this work, new derivatives of cromoglicic acid have been created that have new properties. Cromoglicic acid constitutes a major type of pharmaceutical organic compound. Its derivatives can be used in the manufacture of new types of drugs and can possess a wide range of biological activity and reduce side effects. The work included several paths. as follows: -

The first line:-

Direct interaction of ten amino drugs (Ampicillin, Folic Acid, Mefenamic Acid, Sulfodisine, Diclofenac, Paracetamol, Theophenyl, Cephalexin, 4-Aminoantipyrine) after converting the acid to the use of $SOCl_2$ and DCM to form acid chloride ,after that add Trimethylamine to the resulting compounds (acid chloride).

Scheme (1): Description for the synthesis of derivatives (A1-A10)

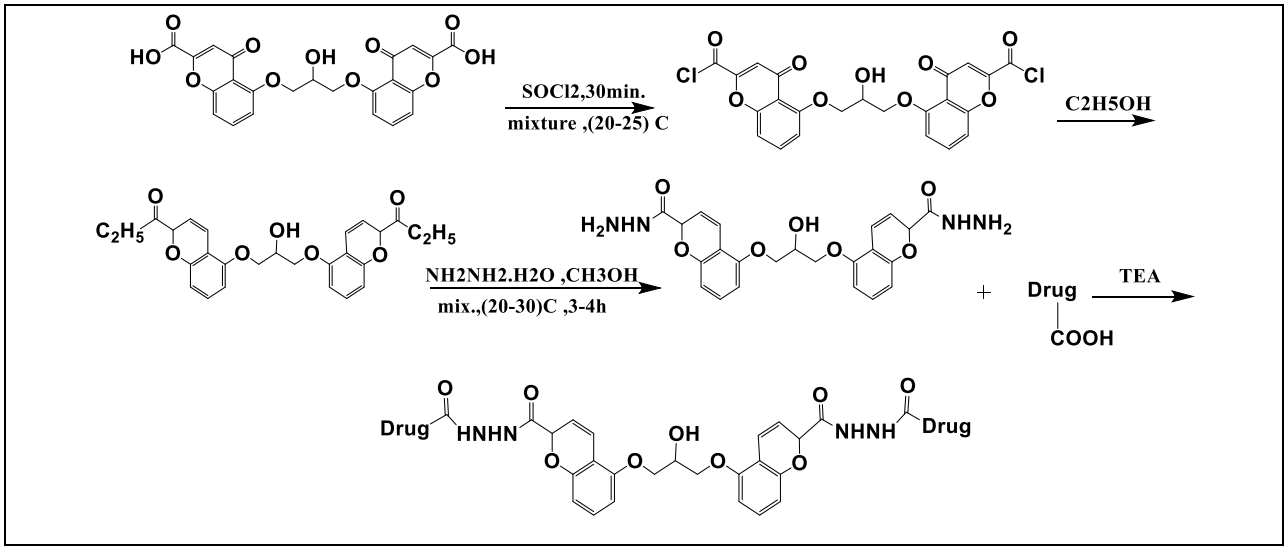


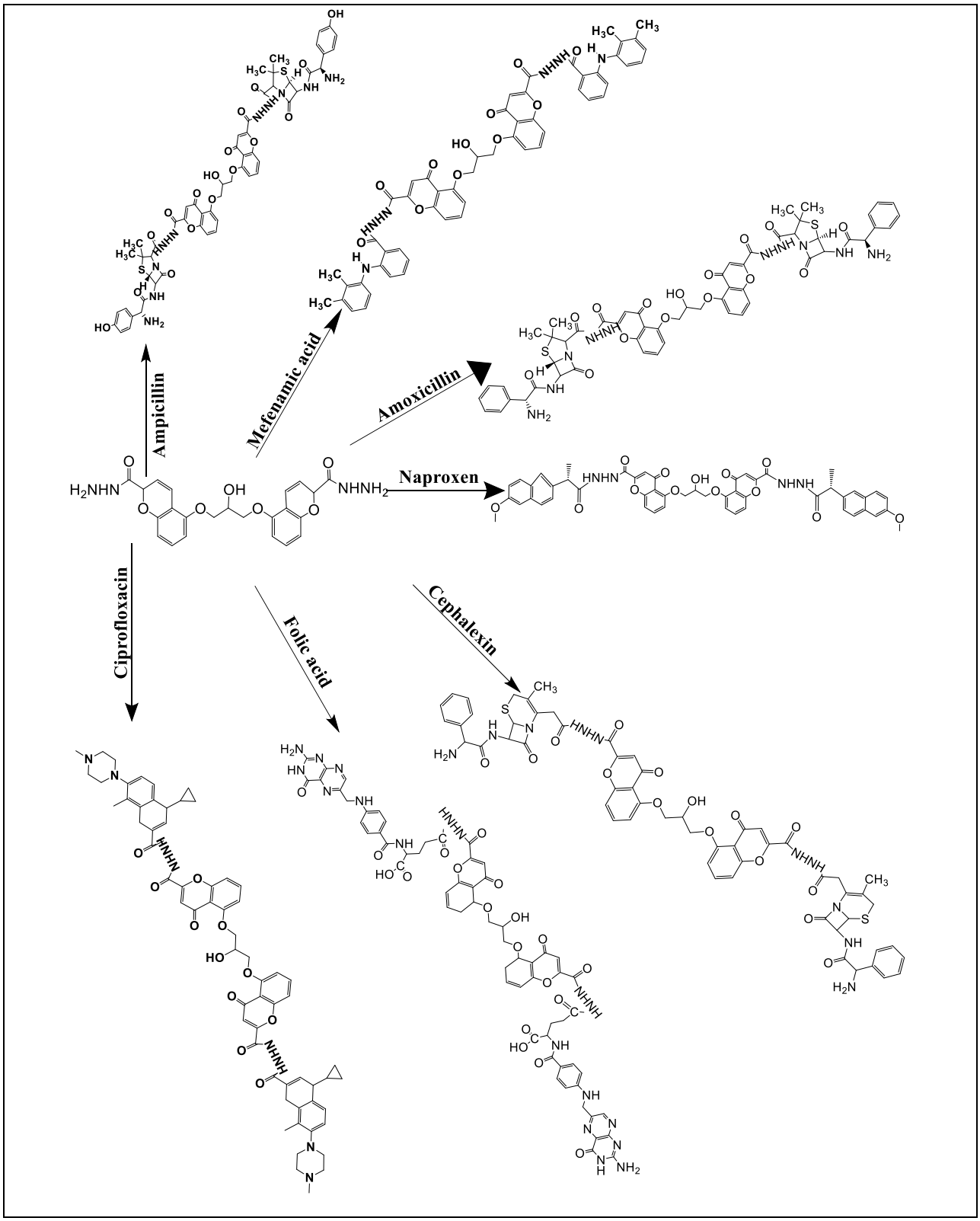

Ampicillin
Amoxicillin
Cephalexin
Mefenamic acid
Paracetamol
Theophylline
4-Aminoantipyrine
Sulfodizine
Folic acid
Diclofanic

The second line:

It involves 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.

Scheme (2): Description for the synthesis of derivatives (A11-A17)

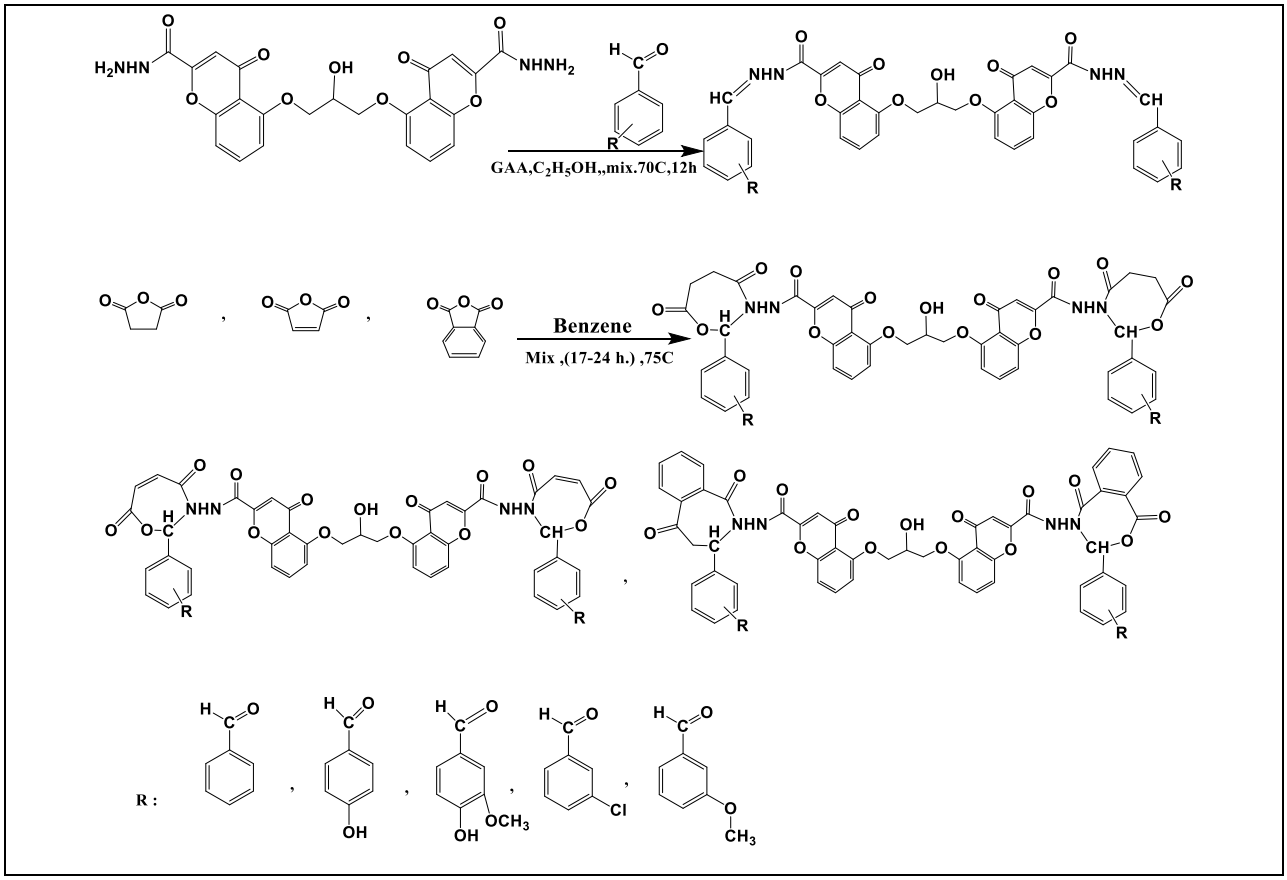


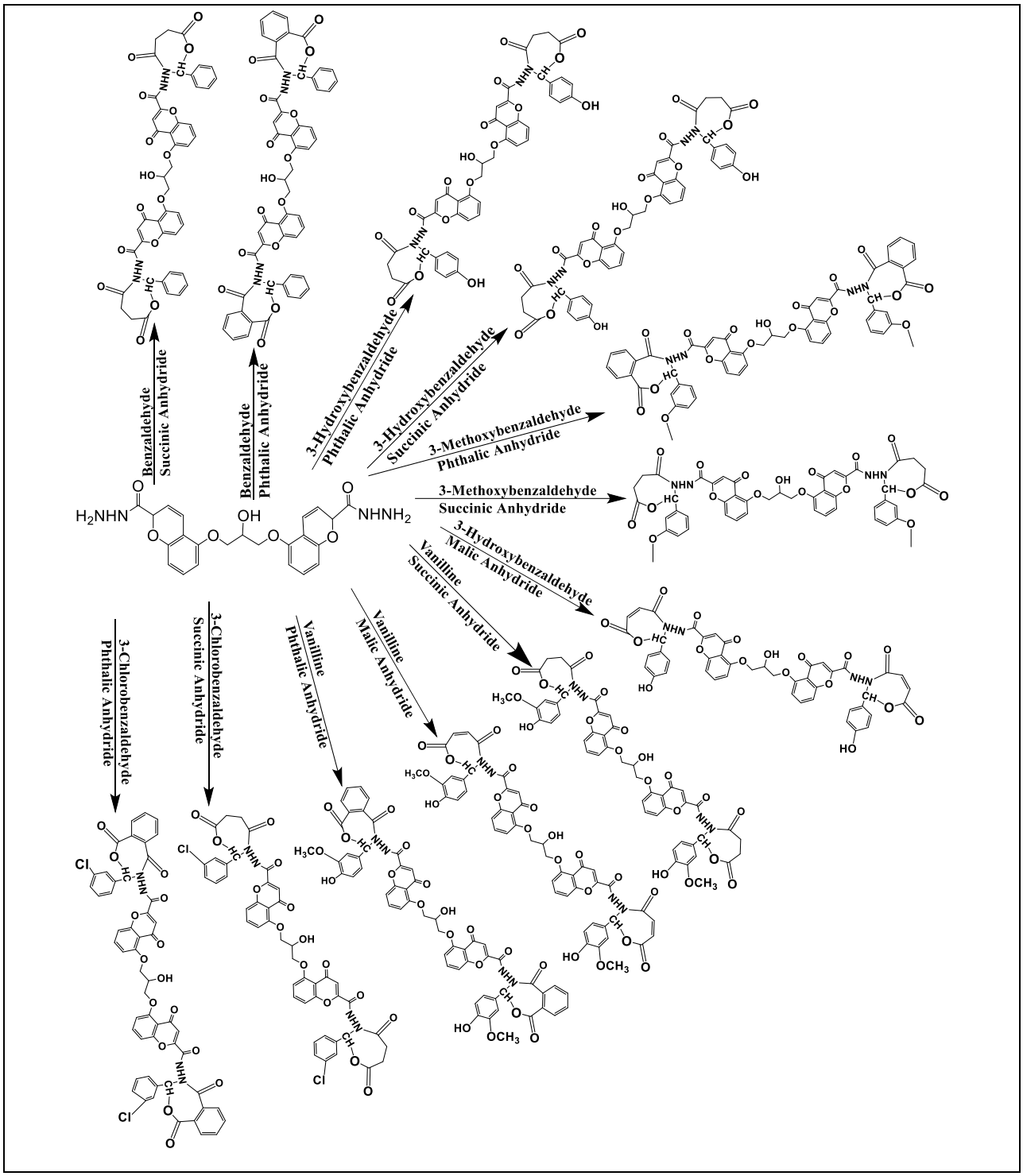

Ampicillin
Mefenamic acid
Amoxicillin
Naproxen
Ciprofloxacin
Folic acid
Cephalexin

The Third line

To Synthesis some of New Oxazepine derivative by used aromatic aldehyde derivative and three type from anhydrides, aromatic aldehyde was dissolved in absolute ethanol and two drops of glacial acetic acid, then hydrazide were added. The reaction mixture with stirring on a water bath at 70C for (12-18 h.), After that add phthalic, malic and succinic anhydride with dry benzene and mixture for (17-24 h.) with stirring on a water bath at 75C.

Scheme (3): Description for the synthesis of derivatives (A18-A29)





The prepared compounds were diagnosed using infrared spectrophotometry, NMR, CHNS and TLC.

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List of Abbreviations

Symbol	Description
FT-IR	Fourier Transform Infra-Red
TLC	Thin-layer chromatography
^{1}H-NMR	Proton Nuclear magnetic resonance
^{13}C-NMR	Carbon Nuclear magnetic resonance
δ	chemical shifts
ppm	Part per million
CHNS	elemental Analysis
g	gram
mmol	mill mole
Hr.	hour
mL	Milliliter
DMSO	Dimethyl sulfoxide
TEA	Triethylamine
R.T.	Room temperature
Comp. symbol.	Compounds symbol
M. formula	Molecular formula
M.Wt.	Molecular weight
m.p.	Melting point
º C	Celsius degree
Rf	Retardation factor
DCM	dichloromethane
GAA	Glacial Acetic Acid
Str.	Stretch
Ar.	Aromatic
Carb.	Carboxylic
Min.	Minute
Refl.	Reflux
Add.	Addition

1-1. Cromones

New natural compounds with potential pharmacological uses are always being sought after(1) . In addition to spending a lot of time looking for these compounds in nature, researchers also put a lot of effort into synthesizing them in order to create derivatives with improved biological activities and prepare them in quantities that will enable in-depth pharmacological research and, eventually, clinical applications. Chromones (4H-chomen-4-ones) Figure 1. The synthesis of Cromones have employed a variety of techniques over the years. Heywang and Kostanecki created one of the first processes in which 2'-hydroxyacetophenones combine with an anhydride to create the Cromones core (2). Since then, a number of additional techniques have been created, offering greater yields and more tolerable reaction conditions (3). Cromones scaffold-containing molecules currently exhibit a wide range of biological properties, including anti-inflammatory, antifungal, antimicrobial, antiallergenic, antiviral, anti-hypertensive, and anti-tumor activities . They also have the ability to inhibit a number of enzymes involved in a variety of disease states (4,5). Cromone derivatives as favored drug discovery structures(6) are one of the kinds of naturally occurring substances that are most prevalent in nature, particularly in plants (7, 8) They are benzoannelated -pyrone-ringed heterocyclic compounds that include oxygen, and their parent molecule is Cromons (4H-chromen-4-one or 4H-l-benzopyran-4-one). Cromones-containing molecules (such as flavonoids, isoflavonoids, and Cromons) exhibit a wide range of biological activities, such as tyrosine and protein kinase C inhibitory effects, antitumoral and anticancer agents, as well as being active at benzoazepine receptors, lipoxygenase, and cycloxygena(9-11) . Cromone derivatives are widely prevalent in the diet due to their abundance in plants and

minimal toxicity to mammals. Some are also becoming available as medications on the market (5-3).

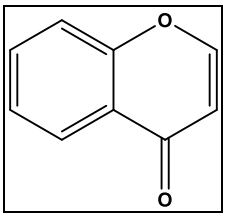


Figure (1): Structural of Cromons

1-2. Cromoglicic acid

Cromoglicic acid (CGA) is non-corticosteroid treatment of choice in the treatment of asthma, Cromoglicic acid is A white, crystalline powder ,odorless, sweet taste and water soluble. A di-carboxylic acid that is the bis-cromone derivative of glycerol. It is effective as a mast cell stabilizer and It has several widely used. 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 show that in equation(1 -1 (12). 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 (13) Therefore, there was a need to develop and find solutions to this issue . cromoglicic acid is a preventive medication used to treat asthma, allergic reactions of the eyes and nose, as well as other mast cell reactions (6) A very recent research elaborates on the pharmacological rationale of repositioning the cromoglicic acid derivatives as an adjunct therapy for SARS-CoV-2 infection, and proposes their practical clinical trial as an early, safe, and

affordable anti-inflammatory treatment of COVID-19(14). Cromoglicic acid: The available data on Cromoglicic acid in animals did not report increased rates of congenital malformations. In a study reporting 151 pregnant women diagnosed with asthma and treated with intranasal, inhaled, and ophthalmic Cromoglicic acid in the first trimester(15) although limited, these human data are reassuring.

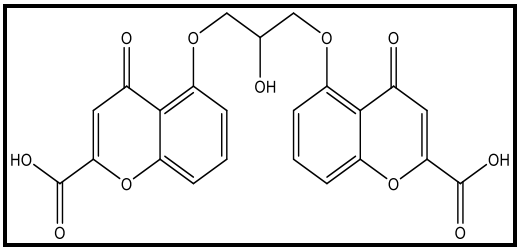
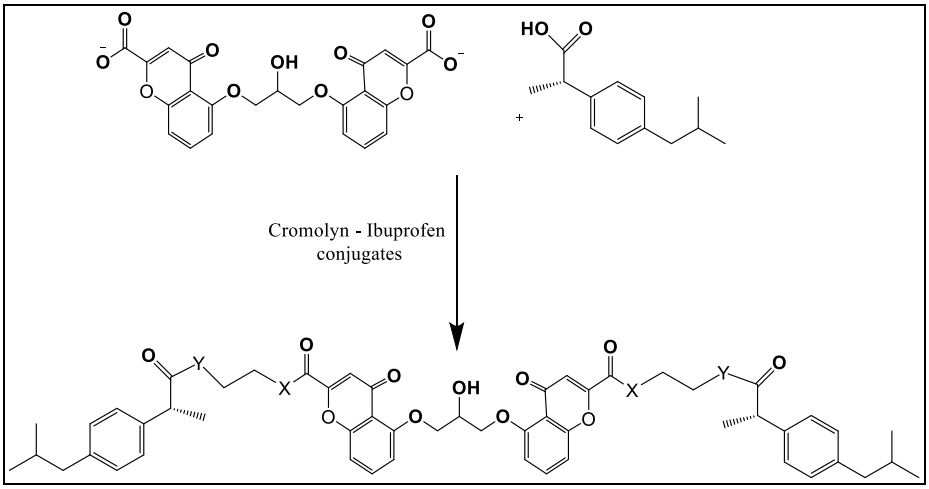


Figure (1-2): Structural of Cromoglicic Acid



Equation (1-1): Cromolyn - Ibuprofen conjugates

1-3. Sodium cromoglycate

Sodium cromoglycate (CG), originally derived from the khella (Ammi visnaga) plant, has been utilized for several years to regulate allergic episodes.(16). It works in mast cells by two different mechanisms: a) phosphorylating a 78-kDa protein that is found on the outside of the mast cell granules. b) Ca^{2+} release-

activated Ca^{2+} channel blockade (17,18). Sodium cromoglycate is a mast cell stabilizer that prevents type I allergic reactions, and therefore, it might alleviate the ocular signs and symptoms of hay fever, acute and chronic, and vernal keratoconjunctivitis. Moreover, it is suggested to decrease the need for supplementary oral antihistamines , Cromolyn Sodium (CS) and nedocromil, generically referred to as chromones, were synthesized in the 1960 s and have since been extensively used in the treatment of allergic diseases, based on their "mast cell (MC) stabilizing" properties, inhibiting MC degranulation with a decrease in histamine release *in vitro* from human (19- 22) . Cromolyn sodium is an FDA-approved medication used for prophylaxis of mild to moderate bronchial asthma and adjunctive treatment of allergic rhinitis and systemic mast cell disease (mastocytosis) in pediatric patients and adults It is not immediate-acting, has no direct bronchodilator effects, and thus does not treat acute asthma attacks. (23)(24) . Cromolynsodium5-[3-(2-carboxylato-4-oxochromen-5-yl)oxy-2-hydroxypropoxy]-4-oxochromene-2- carboxylate (CS), is a mast cell stabilizer that has been used for the management of allergic and exercise-induced asthma, systemic mastocytosis, and has also been reported to effectively prevent allergic reactions associated with atopic dermatitis it functions to inhibit histamine and leukotriene release that act as inflammatory mediators in an allergic response caused by antigen stimulation, as well as other nonspecific triggers like exercise CS also presents as a more attractive alternative to steroids, lacking the complications associated with them, such as gastric issues and decreased immunity (25-28). In a recent investigation, Discovered that pretreatment with a single dosage of CG prolonged the time it took for lithium-pilocarpine-induced SE to begin and decreased neuronal damage in the hippocampus as measured 24 hours after status epilepticus (post-SE). The goal of

the current investigation was to demonstrate that CG taken after SE can change both its immediate and long-term effects. We looked at the cortex and hippocampus, two brain regions that have sustained considerable long-term damage from SE (29,30). The use of sodium cromoglycate is to stop allergic responses. It works by stabilizing the membranes of hypersensitive mast cells, blocking the release of inflammatory mediators from those cells. It has no inherent antihistaminic effects, and it is usually thought to have no bronchodilator effects. Asthmatic reactivity to a number of allergic and non-allergic stimuli can be reduced by sodium cromoglycate.(31). The relevance of sodium cromoglycate (SCG) in the management of asthma is widely acknowledged. A common medication for the preventative treatment of bronchial asthma is sodium cromoglycate (SCG). Despite the fact that this medication's purported method of action is mast cell stabilization (32) , it can reduce bronchoconstrictor reactions brought on by methacholine and histamine in some people, even when mast cell destruction is not clearly a factor. (33) . Since the medication does not relax bronchial smooth muscle and is neither atropine-like nor an antihistamine (32) Its manner of operation in these situations is unclear. One hypothesis is that it interferes with the reflex element of these bronchoconstrictor reactions by affecting sensory nerves that can modify airway diameter.

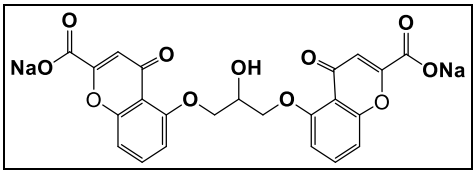


Figure (1-3): Structural of Sodium cromoglycate

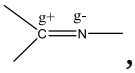
1-4. Schiff bases

Schiff bases function as ligands in various metal complexes and are also known as imines or azomethines. They develop from primary amines and aldehydes or ketones as condensation products. However, due to steric and electronic factors, aldehydes react more quickly in condensation processes than ketones.(34) . German chemist Hugo Schiff was the first to create Schiff bases by combining primary amines with carbonyl compounds (in 1864) (35) . A particular example of Schiff bases are hydrazides in their iminol tautomeric form. Hydrazides are a group of unique monosubstituted hydrazine derivatives that not only retain their specific -NH-NH- nitrogen bridge but also contain a carbonyl or sulfonyl group linked directly to one of the nitrogen atoms. Later, he created metal-salicylaldehyde complexes containing primary amines (36) . Salicylaldehyde and a primary amine were condensed to create a Schiff base, which showed a 2:1 stoichiometry upon complexation with the metal (37) . Similarly, a thorough and organized study was conducted to create a number of complexes formed from salicylaldehyde Schiff bases and their substituents (38,39) .Later, a number of multinuclear and binuclear Schiff base-transition metal complexes with widespread applications were created (e.g., material science, catalysis, magneto chemistry, bioinorganic chemistry, bioinorganic modeling studies, multi electron redox chemistry, and super conductivity)(40,41) .A particular example of Schiff bases are hydrazides in their iminol tautomeric form. Hydrazides are a group of unique monosubstituted hydrazine derivatives that not only retain their specific -NH-NH- nitrogen bridge but also contain a carbonyl or sulfonyl group linked directly to one of the nitrogen atoms the distinctive terminally occurring hydrazide moiety is as follows: R-NH-NH_2 it should be noted that the illustrated hydrazide moiety may be partly analogous to the characteristic amide (peptide) moiety: (O=)C-NH-, the presence of which makes one think of hydrazides as potential peptidomimetics. An additional consequence of such a close proximity to oxygen and nitrogen atoms

endowed with lone electron pairs, forming a torsion angle with the carbonyl atom and the hydrogen atom connected to the nitrogen atom, respectively, is the possibility of the migration of the double bond between the carbon and nitrogen atoms, with the formation of the hydroxyl group by the carbonyl oxygen atom (42-43-44) . The majority of Schiff bases exhibit biological properties, particularly those that are anti-inflammatory, anti-plasmodial, antioxidant, antibacterial(45), anti-fungal(46), anti-cancer, and antidepressant(47) .

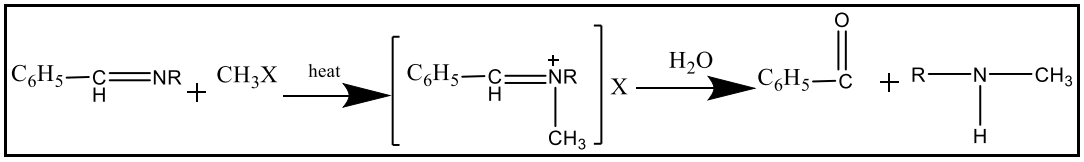
1-4-1. Reactions of Schiff bases

1-4-1-1. Addition reactions

As reagents are added to the polarized double bond of the azomethine group in addition reactions,  , nucleophilic reagents attack the carbon atom of the azomethine linkage.

1-4-1-2. Addition of alkyl halides

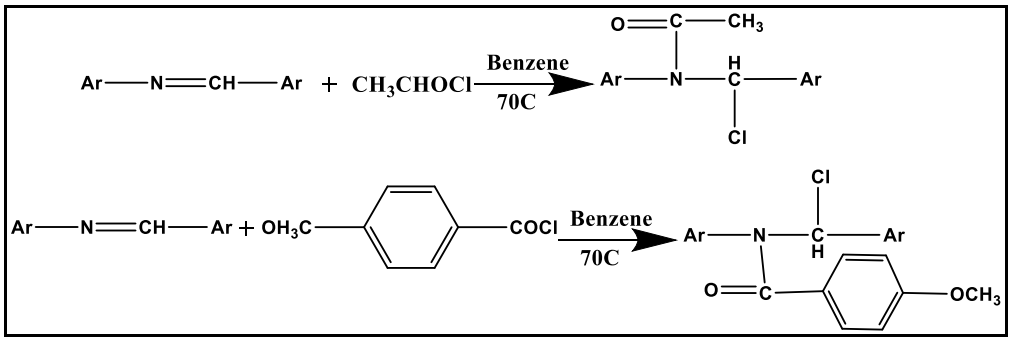
Alkylation of Schiff bases with alkyl halides produces quaternary iminium salts, which following hydrolysis are changed into secondary amines (48) . Secondary amines are created by the process of alkylation.



Equation (1-1): Addition of alkyl halides

1-4-1-3. Addition of carboxylic acid chlorides

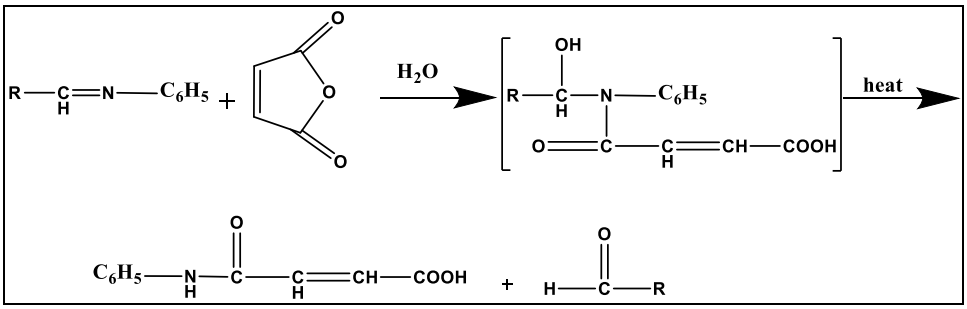
It has been discovered that adding acid chlorides to Schiff bases results in the formation of addition products and, respectively, acetyl chloride and p-anisoyl chloride (49,50) .



Equation (1-2): Addition of carboxylic acid chlorides

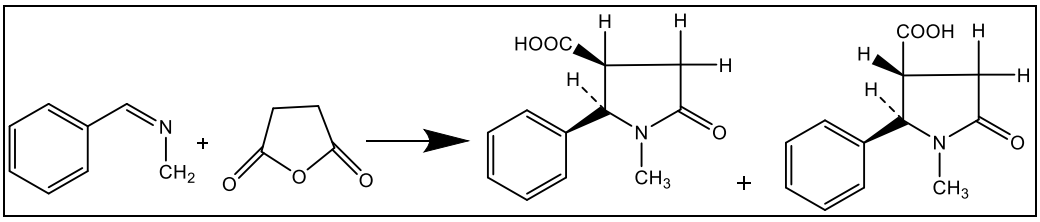
1-4-1-4. Addition of maleic and succinic anhydrides

In the presence of water, anils react with maleic anhydride to produce maleanilic acid and aldehydes (51) . Maleanilic acid is also produced when an anil is burned with maleic anhydride in toluene. However, it has been observed that when the combination is heated without the solvent, a condensation product forms. Maleic anhydride in xylene reacts with crotonaldehydeanil, cinnamaldehydeanil, and other compounds to produce further products (52).



Equation (1-3): Addition of maleic anhydrides

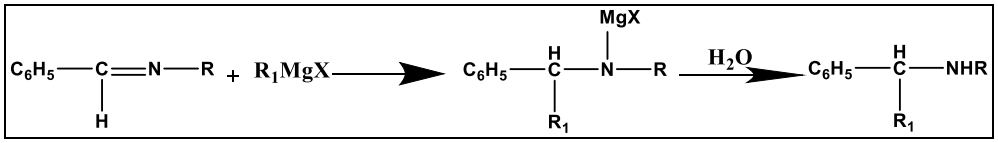
Trans-cis-1-methyl-4-carboxy-5-phenyl-2-pyrrolidinone and respectively are producedwhen benzylidenemethylamine and succinic anhydride are combined(53).



Equation (1-4): Addition of succinic anhydrides

1-4-1-5. Addition of Grignard reagents

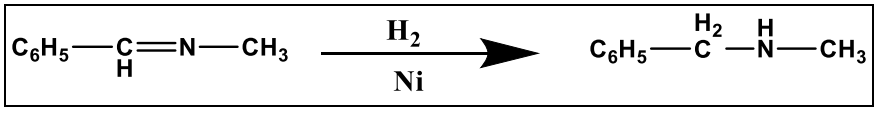
Aziomethine compounds and Grignard reagents combine to create addition products, which, when hydrolyzed, yield secondary amines. Typically, the process is used to create Schiff bases from aryl aldehydes.(54) .



Equation (1-5): Addition of Grignard reagents

1-4-1-5. Addition of hydrogen

Schiff bases can be hydrogenated in the presence of catalyst to give the corresponding secondary amines(55) .



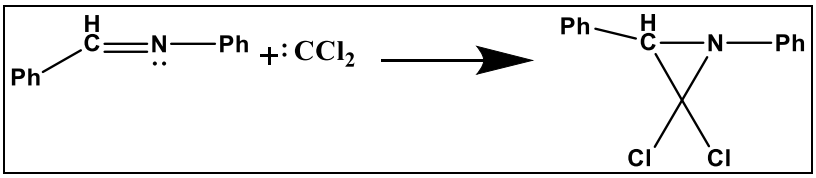
Equation (1-6): Addition of hydrogen

1-4-1-6. Cycloaddition reactions

For a while, the only commonly applicable example of the so-called cycloaddition reactions was the Diels-Alder reaction(56) . New research directions have been made possible by Huisgen and his school's extensive generalization of Schmidt's 1,3-dipolar cycloadditions notion. have reviewed cycloaddition reactions of alkenes, and here we will deal with the various cycloaddition of the azomethine bond. Dimerazation of olefins, as well as the addition of carbenes and nitrenes to unsaturated centers, have extended the series to include three, four, five, and six-membered ring systems(57).

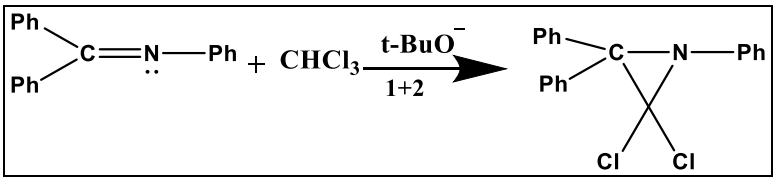
1-4-1-6-1. Formation of three-membered rings

N-benzylideneaniline is combined with dichlorocarbene to produce the equivalent dichloroaziridine. (58) .



Equation (1-7): Formation of three-membered rings

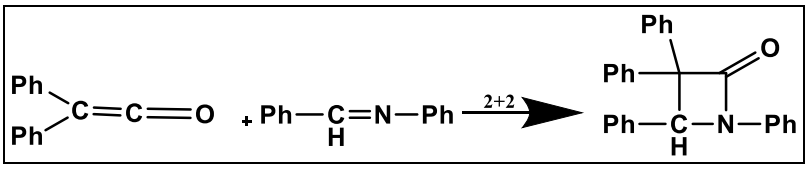
Diphenylmethyleneaniline reacts with chloroform and potassium t-butoxide to produce 3,3- dichloro-1,2,2-triphenylaziridine, as demonstrated by Deyrup and Grunewald (59) .



Equation (1-8): Formation of three-membered rings

1-4-1-6-2. Formation of four- membered rings

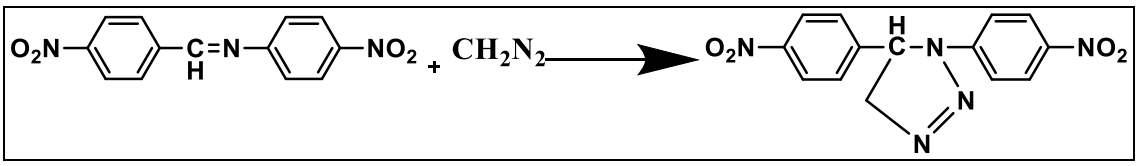
Staudinger(60). reported the [2+2] cycloaddition of diphenylketene with N-benzylideneaniline to produce 1,3,3,4-tetraphenyl-2- azetidinone.



Equation (1-9): Formation of Four-membered rings

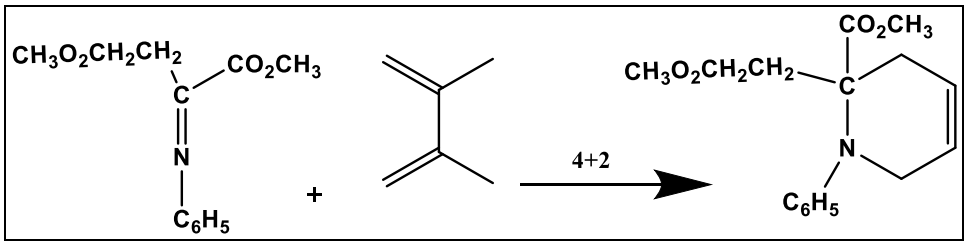
1-4-1-6-3. Formation of five-membered rings

Buckley(61). reported the reaction of diazomethane with p-nitro-N-(pnitrobenzylidene) aniline and via 1,3-dipolar cycloaddition assigned the 1,2,3-triazoline structure.



Equation (1-10): Formation of five-membered rings

Tetrahydropyridine is produced when the imino form of dimethyl anilinomaleate reacts with cis dienes, according to Alder(62) . The important element in carrying out the reaction is the effect of an electron-withdrawing group connected to an imine bond.



Equation (1-11): Formation of six-membered rings

1-4-2. Schiff bases uses

Schiff bases serve as the foundation for the synthesis of several heterocyclic compounds(63) . and their entanglement(64) . They are also employed in the production of super-conductive polymers(65) . According to reports, Schiff bases exhibit a range of intriguing biological effects, including antibacterial and antifungal properties(66) ,antivirus(MHV)(67) , It is also known that the presence of an azo moiety in many types of Schiff bases might cause them to exhibit pesticidal activity in addition to their anticonvulsant, anticancer, and herbicidal properties. (68) . In the medical and pharmaceutical industries, azo compounds and Schiff bases are both significant structural types. (67) . Furthermore, it has been hypothesized that the biological actions of Schiff bases may be caused by the azomethine connection. (69) . Considering the intriguing range of biological functions displayed by molecules with an azo and azomethine bond. There have been so many different ways to synthesize Schiff bases documented. Schiff bases are substances with an azomethine group (-C=N-). In addition to their biological activity, which includes antibacterial, antifungal, and anticancer properties, they have essential applications in polymer chemistry.(70-72)

1-5. Heterocyclic compounds

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.(73) . Although the number of heteroatoms inside the ring has grown over time, carbon is still the atom that most frequently makes up the heterocyclic skeleton of these compounds (74,75) . 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.(76) 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(77). Consequently, the goal of this effort was to create these heterocyclic compounds and examine their antibacterial efficacy ,due to their wide range of uses, particularly in the fields of chemotherapeutic, anti-microbial, pesticidal, agricultural, and fungicidal, five, six, and seven membered heterocyclic compounds have attracted a lot of interest(78) .Based on the structural and electronic arrangement the heterocyclic compounds may be classified into two categories. i. Aliphatic heterocyclic compounds ii. Aromatic heterocyclic compounds . Aliphatic heterocycles those do not contain double bonds are called saturated heterocycles. aromatic heterocyclic compounds are analogous of benzene. The aromatic heterocyclic compounds also follow the Huckel’s rule. According to Huckel’s rule an aromatic compounds must be cyclic in nature with planar geometry due to conjugate double bonds and must have $(4n+2)\pi$ electrons .Organic molecules known as heterocyclic compounds have a ring structure and one or more heteroatoms (79-81) .

1-6. Oxazepine

Oxazepine The compound oxazepine belongs to the non-homologous class and has a seven-membered structure with two non-homologous atoms (oxygen and

nitrogen) (82) . Oxazepines have a variety of biological and pharmacological effects, including antifungal, antibacterial, hypnotic muscle relaxant, and antagonistic(83-85) characteristics .

The utilization of heterocyclic compounds in various applications makes them a crucial class of organic molecules. (86,87) One oxygen, one nitrogen, and five carbon atoms make up the heterocyclic molecule oxyazepine. Heterogeneous organic molecules with nitrogen in their composition have a very wide range of medicinal uses.(88), and oxazepine derivatives are one of them. Oxazepine molecules come in three isomers: (1, 2), (1, 3), and (1, 4). The oxygen and nitrogen atoms' positions within the seven-membered ring determine how many there are. When compared to the benzene ring, the ring is uneven due to the increase in size. In order to alleviate the tension on the ring and make it more stable, the distribution of vacuum atoms causes it to take the shape of a boat. The 2-azetidinone molecules, which are frequently categorized as b-lactams, have served as the building blocks for the production of crucial biological substances (89-90).

Importance of Oxazepine

The biological pharmacological effects of oxyazepine and its derivatives include the inhibition of certain enzymes, analgesic, antidepressant, and psychedelic effects. Amoxapine belongs to the class of medications known as tricyclic antidepressants(91) . It is employed to treat agitation, anxiety, and depressive symptoms.

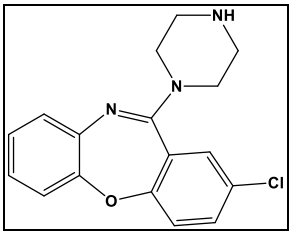


Figure (1-4): Structural of Amoxapine

Chemical weapons employ 1,4-oxazepine(92) as tear gas. A chemical with low concentrations that hurts the eyes, causes tears to flow, and makes it difficult to keep the eyes open is known as "tear gas." It is mostly utilized for military training exercises and riot control.

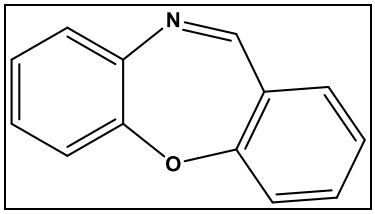


Figure (1-5): Structural 1,4-oxazepine

novel 1,3- oxazepine- 4,7- dione compounds were prepared(93). The 1,3-oxazepines are a seven-membered ring complex with two heteroatoms at positions 1 and 3 , respectively. Oxazepine derivatives demonstrated a variety of biological actions, including antibacterial (94) and enzyme activity inhibitors (95). Oxazepine derivatives are also used in numerous applied sectors, and they have been the subject of much chemical and biological research (96). Derivatives of the 2-azetidinone molecule play a significant role in medicinal chemistry since they exhibit a diversity of microbiological action.Due to their extensive spectrum of biological functions, 7-membered heterocyclic ring structures have recently attracted a lot of attention in chemistry(85). For the same reason, researchers became interested in natural products with seven rings, with a particular focus on heterocyclic rings with N, O, and S heteroatoms and fused rings systems with benzo derivatives(97). In chemical studies, the chemistry of the bonds between carbon and nitrogen was crucial. This is a result of the Schiff bases, which are named after Schiff, who synthesized the isomethane group's lon pair for the first

time (>C=N).(98,99). At this time, oxyazepine-derived medications were introduced for use in reducing anxiety and stress-related mental discomfort(100). Oxazepine is an unsaturated, seven-membered compound with five carbon atoms, heteroatoms, oxygen in position 1, and nitrogen in position 3. By pericyclic cycloaddition of Schiff bases with anhydrides, it can be made(101). Oxazepine and its derivatives are used in medicine and pharmaceuticals and have biological and medical significance(102). Oxazepine (benzodiazepine) compounds were first used in 1965 to treat psychoneurosis, a condition marked by anxiety and tension. Oxazepine is a seven-membered ring with nitrogen and oxygen atoms in its structure (103) .Oxazepine molecules are used in medicine and biology, as well as in pharmaceutical products. A hetero polymer with activity and effectiveness against cancer(104), is one of the many chemical derivatives. They are also efficient against fungus and bacteria. It was discovered that several oxazepine derivatives are regarded as a medicine to treat the condition(105) . Oxazepine and its derivatives exhibit a number of significant biological pharmacological activities10, including those of analgesics, antidepressants, and psychotropic and enzyme inhibitors (106-108) . Amoxapine belongs to a class of medicines known as tricyclic antidepressants. It is employed to treat agitation, anxiety, and depressive symptoms(109) . There are numerous therapeutic uses for benzodiazepines and its derivatives. Numerous members of the diazepine family are frequently used as analgesics, anticonvulsants, antianxiolytics, antidepressants, and hypnotics.(110-113) . For acrylic fibers, benzodiazepine derivatives are utilized as dyes (114) .The biological and pharmacological effects of oxyazepines are known to include antifungal , anti-inflammatory(115), antagonistic(85), antiepileptic(116), hypnotic muscle relaxant, and antibacterial (117)properties. Schiff bases react with phthalic, maleic, succinic, and nitrophthalic anhydrides to create these compounds(118) .

The seven-membered ring heterocyclic molecule known as oxazepine. He is a nonaromatic molecule because of the nitrogen and oxygen atoms in his structure. Following their biological activity in life, oxazepines have been extensively studied for a variety of purposes, including: antihistamines, anticancer, antiviral, analgesic, antifungal, anticonvulsant, antithrombotic, antidepressant(119) , nonnarcotic antimicrobial(120) , sedatives, and hypnotics(121).

1-7. Drugs

1-7-1. Amoxicillin

Amoxicillin is a p-hydroxy derivative of ampicillin, and its chemical name is D-[-]-a-amino-p hydroxybenzyl penicillin trihydrate. It is a member of the amino penicillin class of antibiotics. One of the most common ß-lactam antibiotics, it has the chemical formula (C16H19O5S), is highly bactericidal, and is effective against both Gram-negative and Gram-positive bacteria. The penicillin class is distinct from the OH group case. A number of bacterial infections, including pneumonia, skin infections, and middle ear infections, are treated with amoxicillin as a therapeutic agent (122,123).Amoxicillin prevents bacteria from synthesizing their cell walls. The lining of the duodenum and the lining of the stomach can both be infected by Gram-negative bacteria like Helicobacter pylori. Many antimicrobial drugs (therapeutics), including amoxicillin, break down quickly in an acidic environment.(124) .

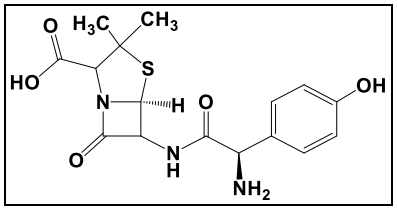


Figure (1-6): Structural of Amoxicillin

1-7-2. Cephalexin

Cephalexine (CFX) is an antibiotic that has a vast range of bactericidal activity, thus high inhibitory activities against a wide spectrum of gram-negative and gram-positive organisms. Cephalexin represented the first generation of cephalosporin antibiotics , it possesses better controlling over acute infections, with maximum utilization of drugs by enabling a reduction in the total dose amount of the administered and leads patient submission Cephalexin (CFX) (125,126).injection into the muscle. There are numerous adverse effects of cephalexin, including skin irritation, stomach discomfort, and diarrhea. An overdose of cephalexin is hazardous and necessitates medical treatment (127,128) .

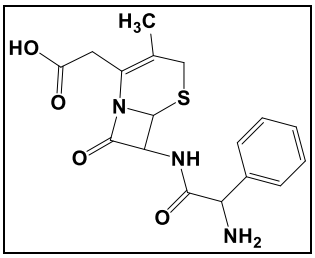


Figure (1-7): Structural of Cephalexin

1-7-3.4-Aminoantipyrine

The antipyrine derivative amino antipyrine (4-AAP), also known as [4-amino-1,5-dimethyl-2-phenylpy razole-3-one] ,has shown outstanding pharmacological capabilities, including antiviral, anti-inflammatory, analgesic (pain reliever), antirheumatic, antipyretic, and antibacterial actions. Additionally, it serves as a precursor in the manufacture of bioactive substances such ß-lactams. In addition, several antipyrine derivatives as well as 4-aminoantipyrine being studied for their anti-inflammatory, anticancer, and analgesic actions in the prevention of different disorders, including cancer(129,130) Additionally bioactive, the 4-

Aminoantipyrine variant has anti-inflammatory, analgesic, anti-cancer, and antibacterial properties(131). Due to their numerous chemotherapeutic agents, pharmacological, clinical, biological, physical, and analytical applications, aminoantipyrine derivatives have been well studied.(132,133)

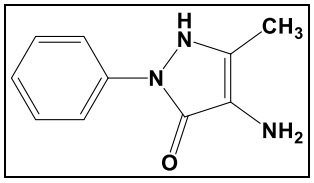


Figure (1-8): Structural of 4-Aminoantipyrine

1-7-4. Ciprofloxacin

A fluoroquinolone antibiotic, ciprofloxacin (CIP) is effective for both human and veterinary use. (CIP) has remarkable anti-respiratory infection properties. Fluoroquinolones are acknowledged by (WHO) as a very essential therapeutic agent (antibiotic) for human medicine and can be transferred to exert an immune modifying effect on numerous "cell types." Recurrent bacterial suppurative otitis media (middle ear illness) is treated topically with fluoroquinolones.(134,135) .Due of its apoptotic and antiproliferative effects on a number of cancer cell lines, the widely used broad-spectrum antibiotic ciprofloxacin has also garnered considerable interest from scientists. Strong experimental evidence has been presented by numerous research demonstrating the therapeutic and/or preventive effectiveness of CIP in the treatment of bladder transitional cell carcinoma (136,137).

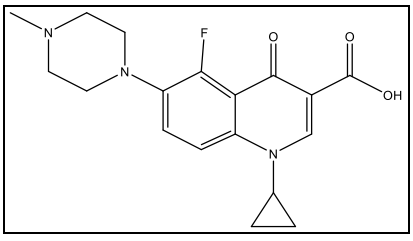


Figure (1-9): Structural of ciproflaxine

1-7-5. Ampicillin

Many bacterial infections are routinely treated with ampicillin. infections of the skin, lungs, ears, skin, and urinary tract, as well as bronchitis, pneumonia, and others (UTI). Studies on the pharmacodynamics and pharmacokinetics of ampicillin have been undertaken due to its significance as a broad-spectrum antibiotic; ampicillin is frequently recommended due to its broad spectrum of low toxicity and antibacterial capabilities (138,139).Gram-negative (-Ve) bacteria, which include several different kinds, can be penetrated by ampicillin and prevented from growing.

Middle ear infections, cystitis, and sinus infections are all frequently treated with ampicillin. Numerous characteristics of ampicillin include its high solubility, broad spectrum of activity, stability in acidic environments, and faster absorption rate.(140).

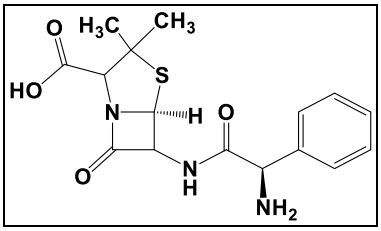


Figure (1-10): Structural of Ampicillin

1-7-6. Paracetamol

The most common uses of paracetamol (N-acetyl-para-aminophenol), often known as acetaminophen (PAPA), are as a pain reliever and antipyretic, as well as to treat adults' and children's high fevers and mild to moderate pain. Along with immunization, it is also used to cure fever and relieve newborn pain, even in pregnant mothers.(141-144) .PAPA is still available today, has better tolerance

than non-steroidal anti-inflammatory drugs (NSAIDs), and may be slightly less effective than other medications. Despite the possibility of some COX-1 and COX-2 enzyme activation, this action is different from that demonstrated with (NSAIDs)(145-148).

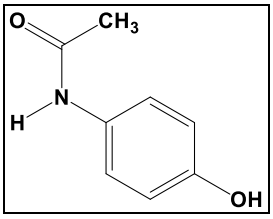


Figure (1-11): Structural of Paracetamol

1-7-7. Theophylline

Theophylline is a derivative of the methylxanthine,1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione. Asthma and adult COPD are both treated with it. Tea and cocoa beans both naturally contain small levels of theophylline. Although it only has a moderately strong non-selective inhibitory effect on phosphodiesterase enzymes, rather high doses are necessary to induce the greatest relaxation. Although the 2015 Global Asthma Initiative report "GINA" continues to mention the use of theophylline derivatives as a supplemental treatment agent to therapy(149-152) .

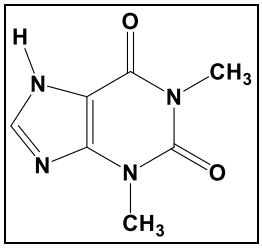


Figure (1-12): Structural of Theophylline

1-7-8. Mefenamic acid

Since the early 1960s, mefenamic acid has been a prescription-only medication in the United Kingdom and Europe. It is a fenamate non-steroidal anti-inflammatory drug (NSAID)(153), The anti-inflammatory properties of MA are regarded as being subpar. However, MA is frequently utilized to treat muscular-skeletal disorders such rheumatoid arthritis (RA), osteoarthritis (OA), and others. Additionally, MA has been demonstrated to possess or improve anticancer properties, similar to other NSAIDs(154).Metal complex formation is an important process in biological systems, and mefenamic acid can form complexes with a variety of metal ions. Metal-binding compounds are a class of chemicals that have given rise to a number of useful medications and other drugs with selective toxicity, many of which function by chelation. They are used in a wide variety of veterinary and human medical procedures.

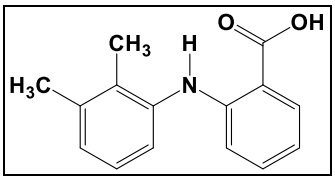


Figure (1-13): Structural of Mefenamic acid

Aim of this study:

Synthesis of new organic compounds from a cromoglicic acid as a starting material. These compounds may have biological activity due to the cromoglicic acid as a precursor and characterization of the synthesized compound by FT-IR , NMR and CHNS .

The main goals of this work include:

1- Synthesis of cromoglicic acid derivative from direct linkage with amino drugs.
2- Synthesis of cromoglicic acid derivative from direct linkage with carboxylic drugs.
3- Synthesis of new organic compounds with Schiff Base.
4- Synthesis of new seven member organic compound
5- These compounds have biological activity as antibacterial and antioxidant .

2.1 Chemicals

The highest purity chemical ingredients are being used. Table included the chemicals, source, and purity (2-1).

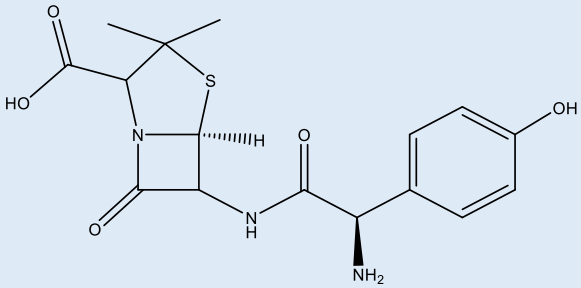
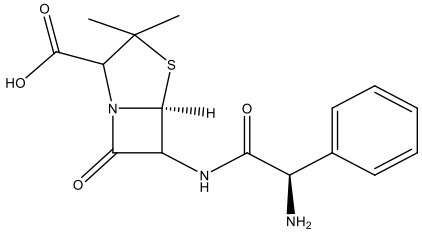
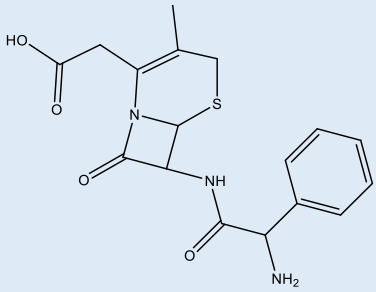
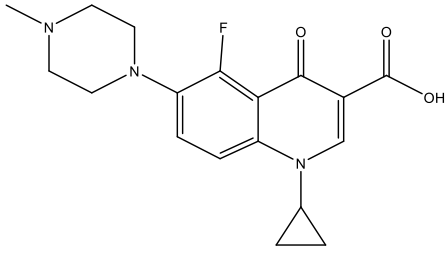
Table (2-1): supplier and purity for used chemicals

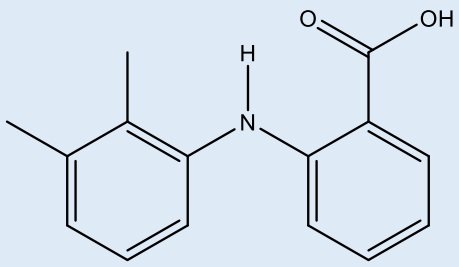
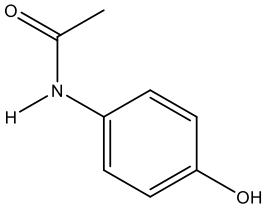
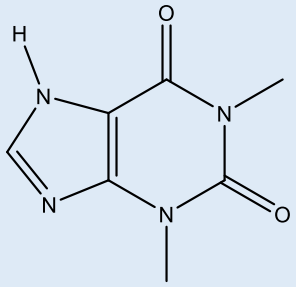
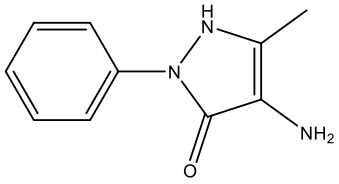
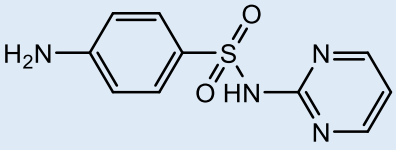
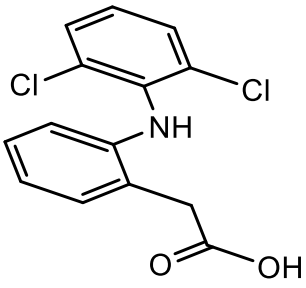
Chemicals	Supplier	Purity%
Cromoglicic acid	Baoji Guokang Bio-Technology co., Limited	**99.9**
Acetone	Fluka	**99.9**
Chloroform	Fluka	**99.9**
Dichloromethane	Fluka	**99.7**
Diethyl ether	Fluka	**99.9**
Dimethylsulfoxide	Fluka	**99.5**
n-Hexane	Fluka	**99.7**
Methanol	Fluka	**99.9**
Petroleum ether	Fluka	**99.9**
Sodium bicarbonate	Fluka	**99.9**
Thionyl chloride	Fluka	**99.9**
Triethylamine	Fluka	**99.9**
NaOH	Fluka	**99.9**
HCl	Fluka	**99.9**

Dimethylfurmate	Fluka	**99.9**
1,4-Dioxine	Fluka	**99.9**
Benzene	Fluka	**99.9**
Ethanol absolute	CDH	**99.9**
Ethyl acetate	CDH	**99.9**
Folic acid	Samarra comp.	**99.9**
Mefenamic acid	Samarra comp.	**99.9**
Naproxen	Samarra comp.	**99.9**
Amoxilline	Samarra comp.	**99.9**
Ampcilline	Samarra comp.	**99.9**
Cephalexine	Samarra comp.	**99.9**
Ciproflaxine	Samarra comp.	**99.9**
Paracetamol	Samarra comp.	**99.9**
Theophylline	Samarra comp.	**99.9**
4-aminoantipyrine	Samarra comp.	**99.9**
Diclofenac	Samarra comp.	**99.9**
Succinic anhydride	Sigma-Aldrich	**99.9**
Malic anhydride	Sigma-Aldrich	**99.9**

Phthalic anhydride	Sigma-Aldrich	**99.9**

Table (2-2): Name and chemical makeup of medications used in co-drug manufacturing

Comp. Sym.	Structural formula	M.Wt	m.p°C
Amoxilline		365.4	194-196
Ampicilline		349.4	199-201
Cephalexine		347.39	326-328
Ciprofloxacine		331.34	290-292

Mefenamic acid		241.8	230-232
Paracetamole		151.17	169-171
Theophylline		180-164	164-166
4-aminoantipyrine		203.24	209-211
Sulfadiazine		250.28	252-254
Diclofenac		296.15	283-285

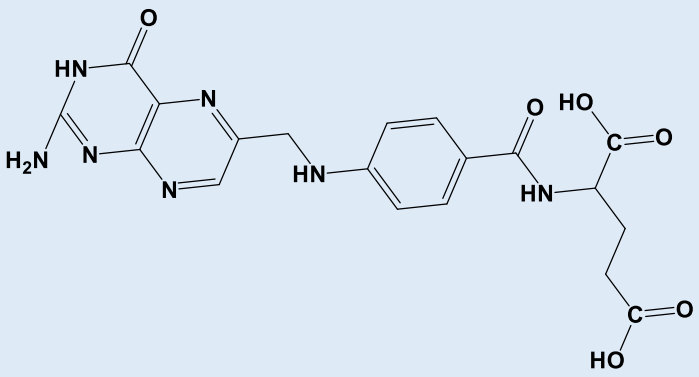
Folic Acid		441.404	250-252

Table (2-3): Other devices used

Devices	The Company's name
Magnetic stirrer with heating	Heidolph
Digit sensitive balance	Denver Instrument

2-2 Instruments analysis and equipment:

2-2-1. The Fourier Transform ultraviolet spectrophotometer FT-IR:

In the Chemistry Department of the College of Science ,Babylon University, Iraq , FT-IR spectra for produced compounds were recorder on a Bruker.

2-2-2. Melting point equipment

Chemistry Department, College of Science, Babylon University , Iraq ; melting points for produced derivatives obtained using SMP30-Melting Point Apparatus; uncorrected melting points.

2-2-3. Nuclear magnetic resonance spectrophotometer:

spectrophotometer for nuclear magnetic resonance

On an Innova model Innova 5-oxford 500 Magnet NMR spectrophotometer, which operates at (500MHz for 1HNMR and (125MHz for 13CNMR), measurements of ^{1}HNMR and ^{13}C-NMR were made. In the Central lab of the

University of Tehran, chemical-shifts (δ) were quantified in ppm using TMS as a reference (δ =0.0 ppm).

2-2-4. Micro elemental Analysis (CHN):

Euro EA3000Elemental Analyzes In the central laboratory of the University of Tehran, analyses of the microelements carbon, hydrogen,nitrogen, and sulfur were performed.

2-2-5. Thin layer chromatography (TLC)

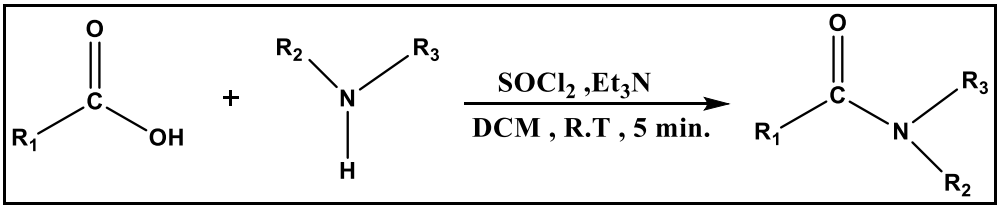
Aluminum plates covered in a 0.25mm layer of si lica-gel underwent TLC (Fluka)

2-3. Preparations:

In the tables (2-1), (2-3), and (2-4), the structural and physical information for created derivatives were documented.

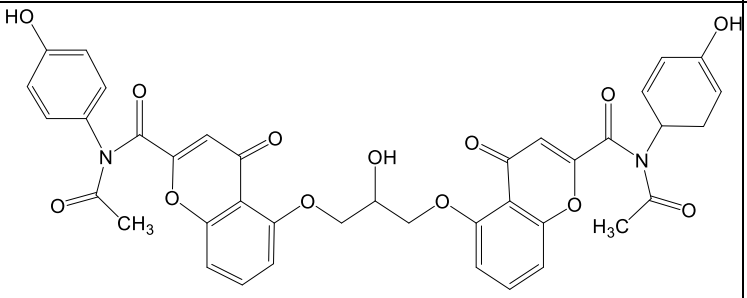
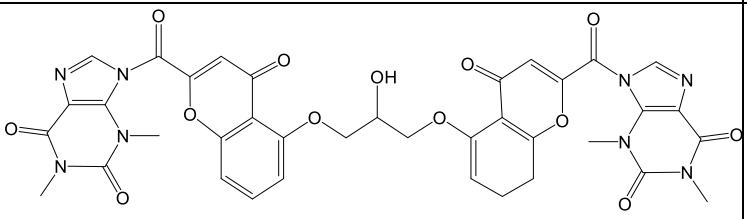
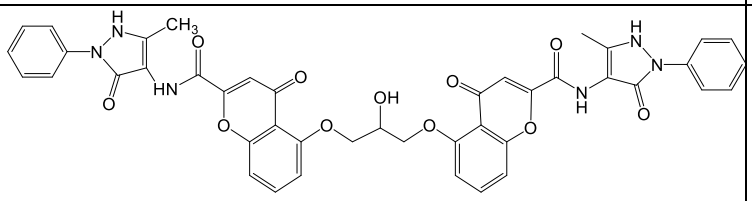
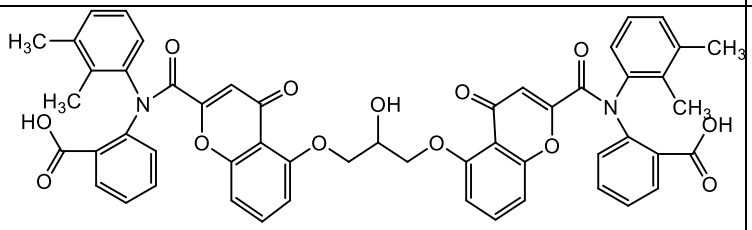
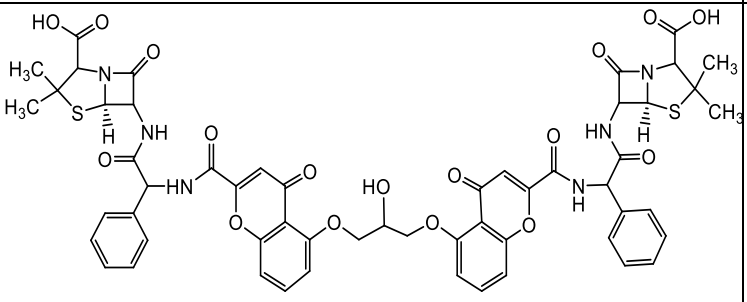
2-3-1. One pot Synthesis of compound (A1_A10).

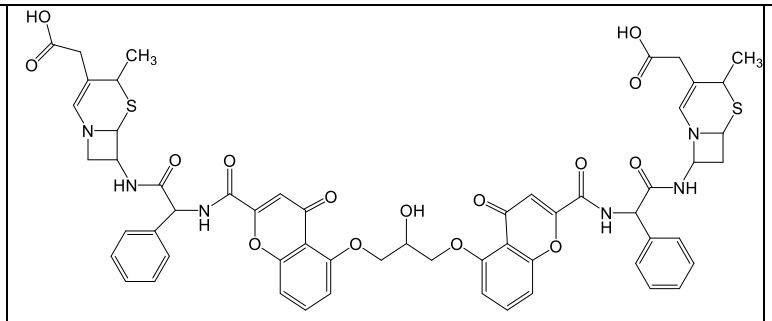
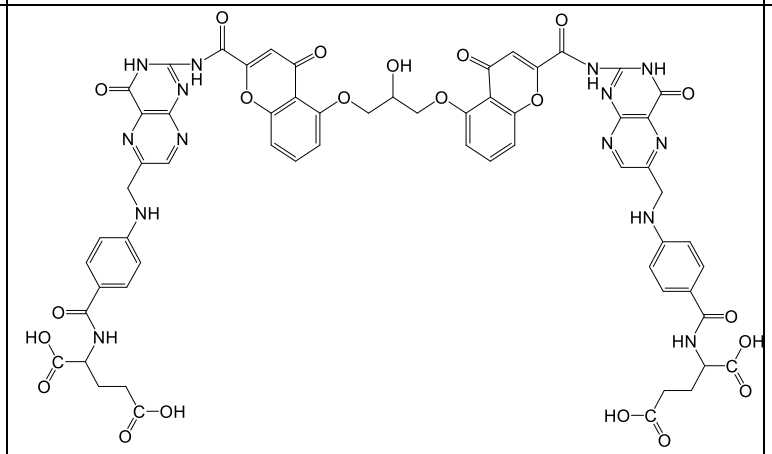
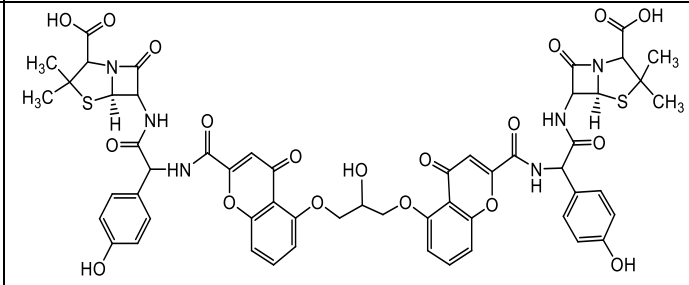
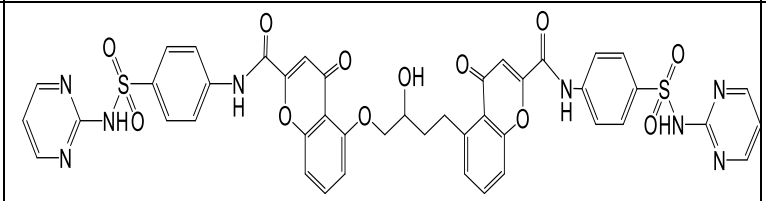
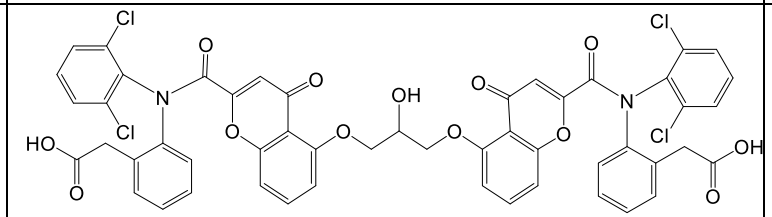
(2 mmol) of amino drug, (6mmol) of triethylamine (TEA), and (2 mmol) of $SOCl_2$ are added to the mixture after one mole of cromoglicic acid is added. At room temperature, the mixture is stirred for (5 -20 min.). The solvent is evaporated in order to restore the product. TLC is used to assess the development of the response after the resulting residue is absorbed in dichloromethane and washed with 1N HCl, and finally with 1N NaOH(163).



Equation (2-1): General equation for synthesis A1-A10

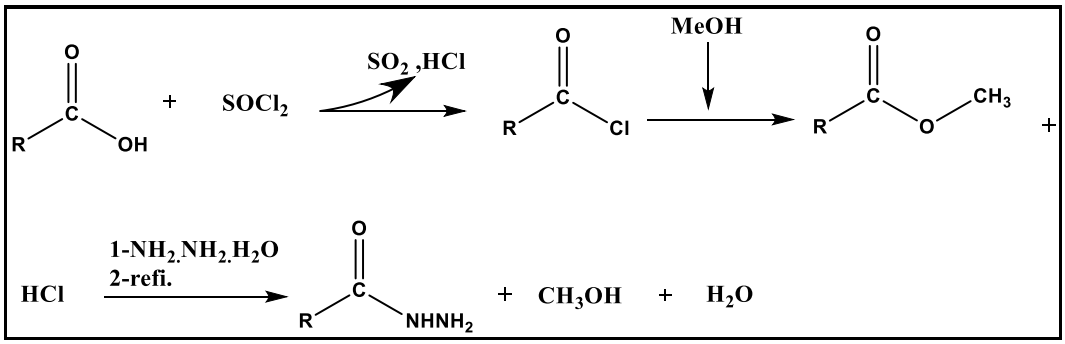
Table 2.4: Some of physical properties of compound (A1_A10)

Comp. Sym.	Structural formula	color	M. formula	M.Wt	m.p°C	Yield %	Rf
A1		**Orange**	**$C_{39}H_{30}N_2O_{13}$**	**734.67**	**146-148**	**70%**	**0.74**
A2		**Off White**	**$C_{37}H_{28}N_8O_{13}$**	**792.663**	**208-210**	**89%**	**0.96**
A3		**Orange**	**$C_{43}H_{34}N_6O_{11}$**	**810.78**	**118-120**	**80%**	**0.81**
A4		**Light brawn**	**$C_{53}H_{42}N_2O_{13}$**	**914.92**	**146-149**	**71%**	**0.76**
A5		**Reddish Brawn**	**$C_{55}H_{50}N_6O_{17}S_2$**	**1131.15**	**109-111**	**90%**	**0.60**

A6		**Brawn**	$C_{56}H_{57}N_6O_{15}S_2$	**1123.18**	**104-106**	**79%**	**0.68**
A7		**Dark Yellow**	$C_{61}H_{50}N_{14}O_{21}$	**1315.15**	**123-125**	**84%**	**0.40**
A8		**Dark Red**	$C_{55}H_{50}N_6O_{19}S_2$	**1163.15**	**103-105**	**88%**	**0.45**
A9		**Yellow**	$C_{43}H_{32}N_8O_{13}S_2$	**932.89**	**184-186**	**90%**	**0.53**
A10		**Red**	$C_{51}H_{34}N_2Cl_4O_{13}$	**1024.63**	**201-203**	**68%**	**0.71**

2-3-2. Synthesis of hydrazide by one put method:

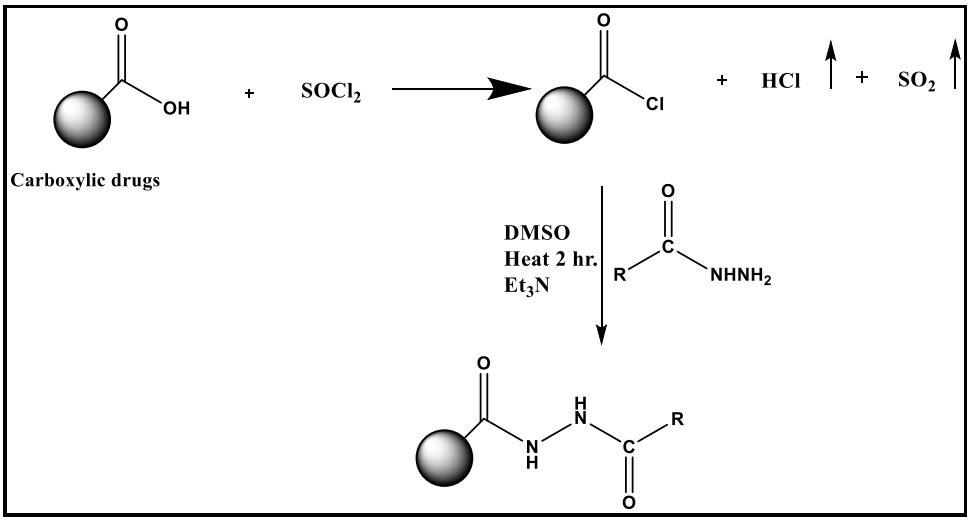
Cromoglicic acid (1mmol) and thionyl chloride (2mmol) were combined, and the mixture was then stirred at 20–25 °C for 30 min. Drop by drop, at room temperature, and while stirring, (7.5 mmol) of methanol was added to this mixture. Then, at room temperature (20–30°C), 10 mL of an 80% $NH_2NH_2.H_2O$ (7.5 mmol) solution in ethanol was gradually added while stirring to the aforementioned mixture. The reaction's mixture was refluxed for (3-4 hrs.), The development of the reaction was checked by TLC (165).



Equation (2-2): General equation for synthesis acid hydrazide

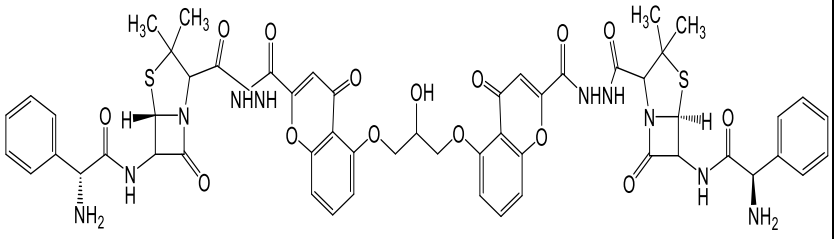
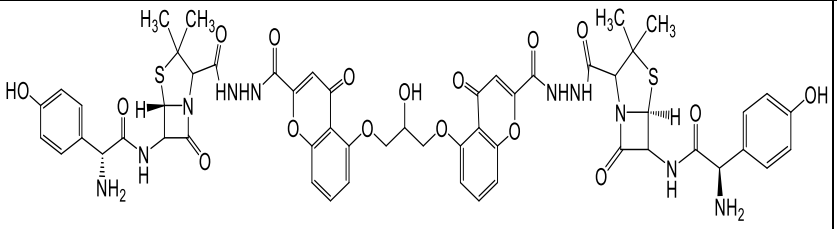
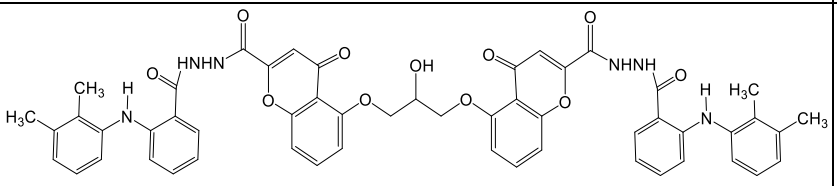
2-3-3. Synthesis for derivatives A11_A17:

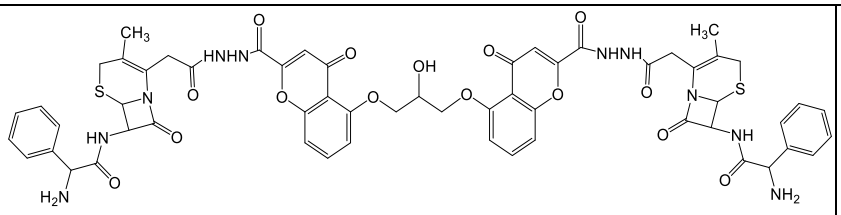
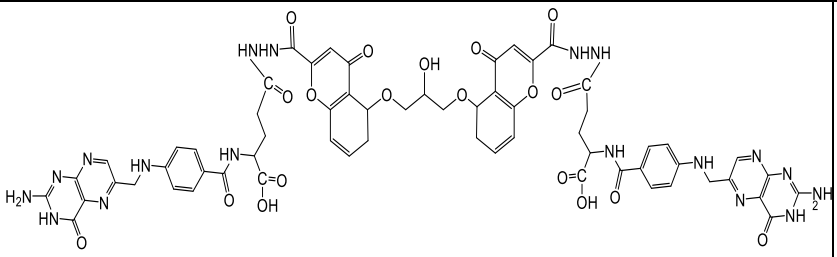
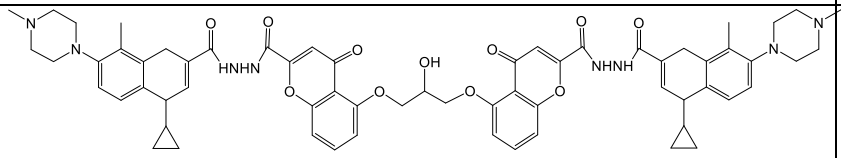
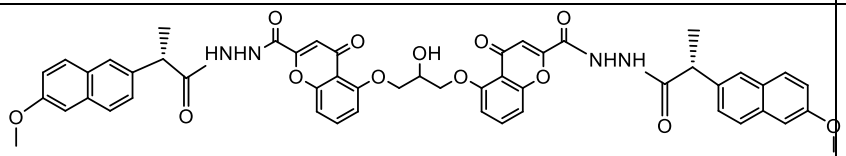
(1mmol) Seven different carboxylic drugs was added to (2 mmol) of thionyl chloride before being stirred at room temperature for 30 min. The aforementioned mixes received one mmol of hydrazide in DMSO, which was heated for 1.5 hours at 60 to 70 °C. The liquids were heated once more for after the addition of triethylamine (TEA) (30 min.). 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.(165).



Equation (2-3): General equation for synthesis A11-A17

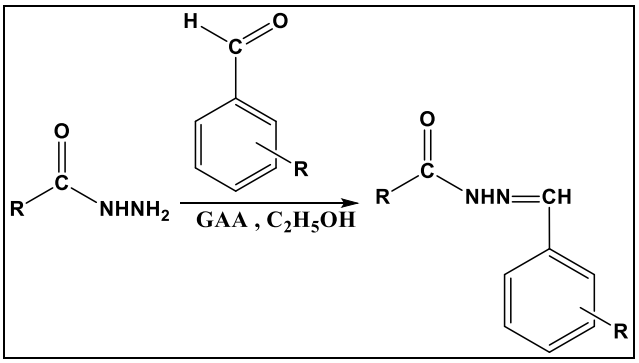
Table 2-5: Some of physical properties of compound (A11_A17)

Comp. Sym.	Structural formula	color	M. formula	M.Wt	m.p°C	Yield%	R*f*
A11		**Brawn**	**$C_{55}H_{54}N_{10}O_{17}S_2$**	**1190.21**	**233-236**	**64%**	**0.35**
A12		**Light brawn**	**$C_{55}H_{54}N_{10}O_{15}S_2$**	**1158.32**	**240-242**	**67%**	**0.48**
A13		**Yellow**	**$C_{53}H_{46}N_6O_{11}$**	**942.98**	**171-174**	**75%**	**0.44**

A14		**Dark Brawn**	**$C_{57}H_{54}N_{10}S_2$**	**1183.23**	**213-215**	**81%**	**0.72**
A15		**Brawn**	**$C_{61}H_{54}N_{18}O_{19}$**	**1343.21**	**92-95**	**85%**	**0.90**
A16		**Yellow**	**$C_{63}H_{68}N_8O_{11}$**	**1113.28**	**145-148**	**90%**	**0.69**
A17		**Red**	**$C_{53}H_{48}N_4O_{11}$**	**916.98**	**216-218**	**73%**	**0.55**

2.3-4 General procedure for Synthesis of derivatives [A18-A29]

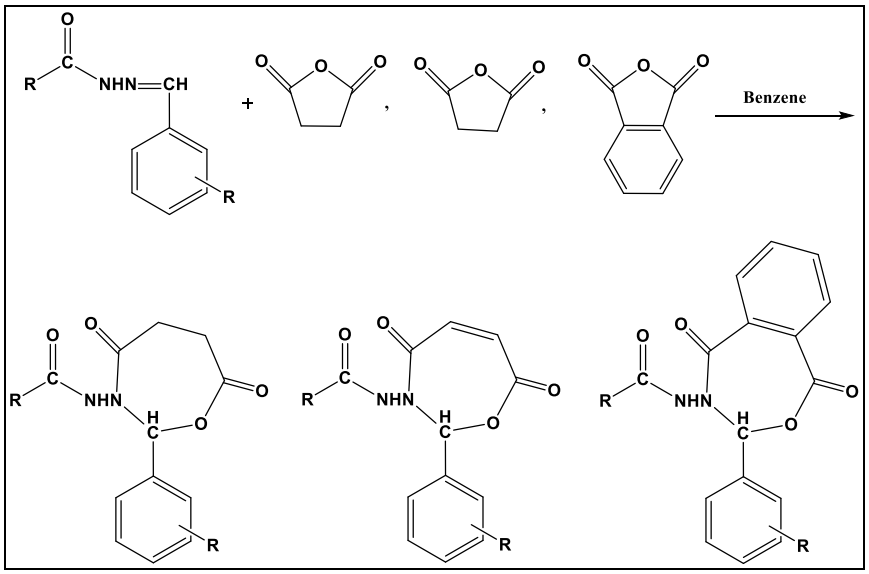
In absolute ethanol (20 mL) with two drops of glacial acetic acid, an aromatic aldehyde derivative (2 mmol) was dissolved. Hydrazide (1 mmol) was then added. The reaction mixture was refluxed at 70°C for 12 to 18 hours while being stirred on a water bath. The reaction was finished, as evidenced by the TLC (166).



Equation (2-4): General equation for synthesis A18-A29

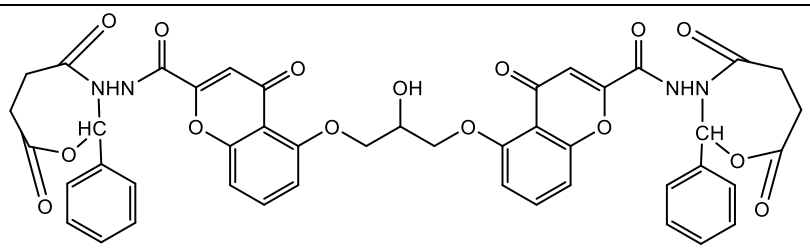
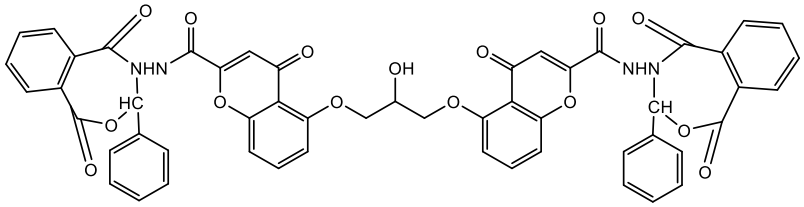
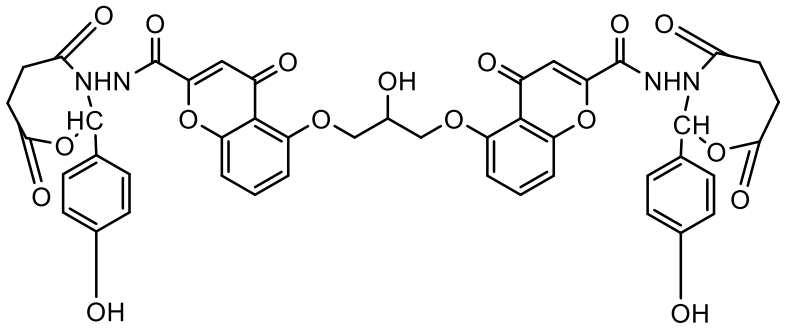
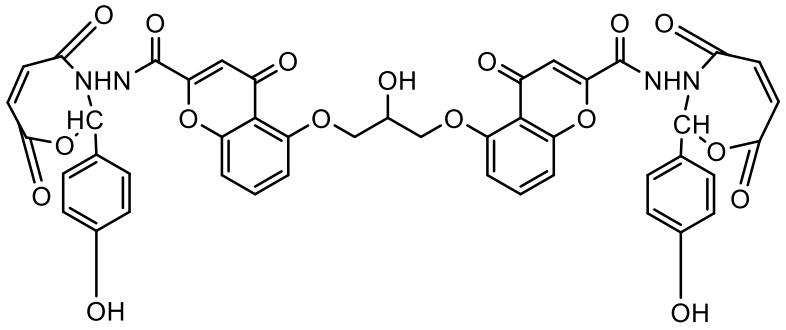
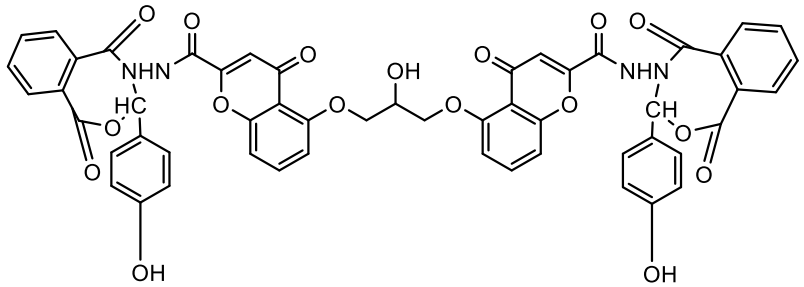
2.3-5 General procedure for synthesis of derivatives [A18-A29]

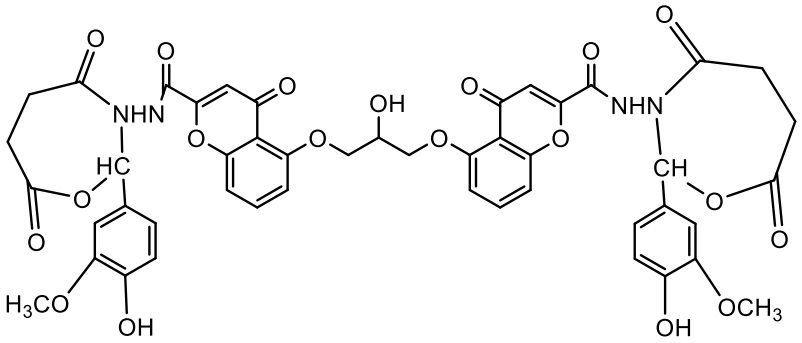
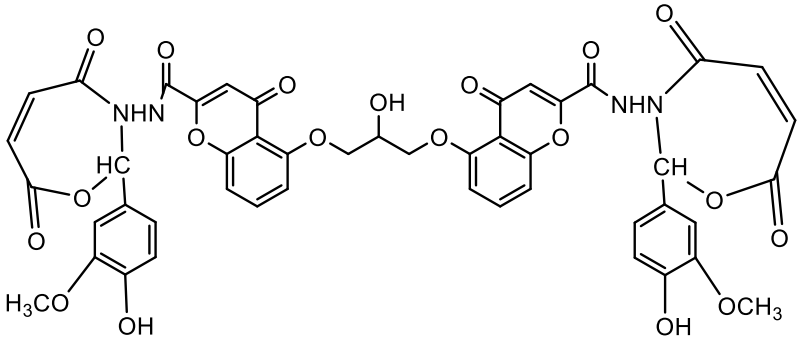
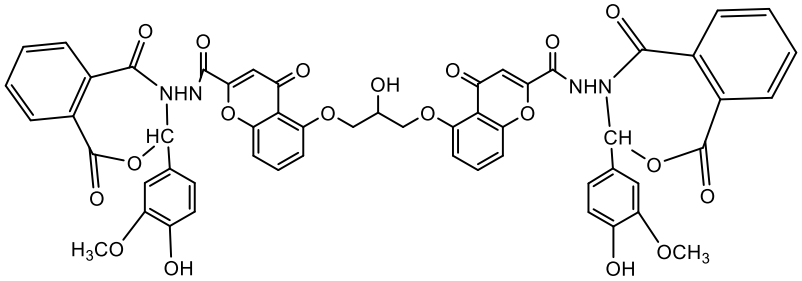
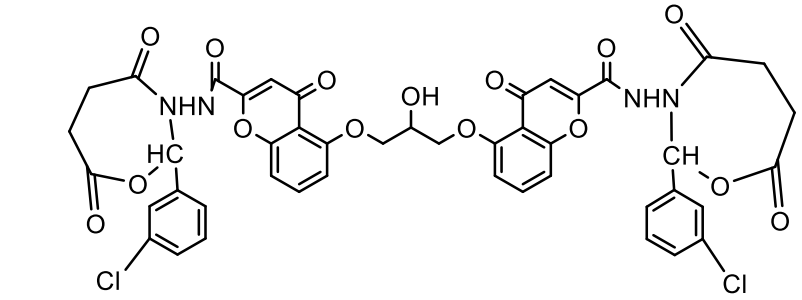
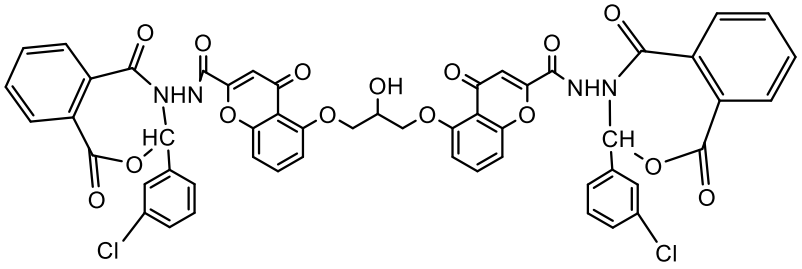
Mixtures of (1 mmol) from the result of the previous step and (2 mmol) succinic, phthalic, and malic anhydrides were refluxed in dry benzene at a temperature of 20 °C for 17 to 24 hours while stirring At 75°C The progress of reactions was monitored by TLC (166).

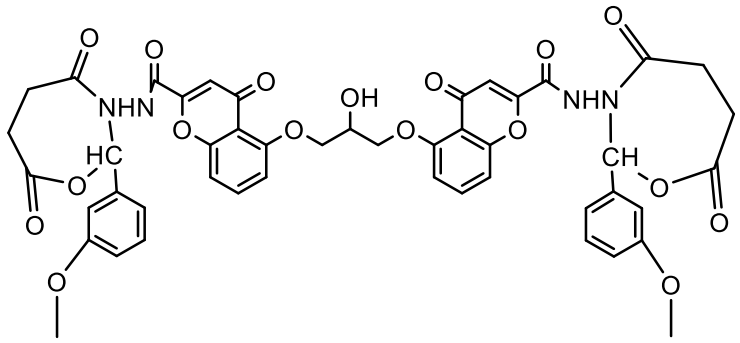
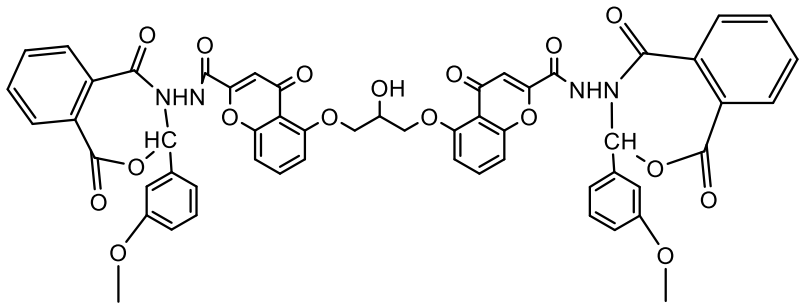


Equation (2-5): General equation for synthesis A18-A29

Table (2-6): The physical properties of compounds [A18-A29]

Comp. Sym.	Structural formula	color	M. formula	M.Wt	m.p°C	Yield %	Rf
A18		**Pale orange**	$C_{45}H_{36}N_4O_{15}$	**872.80**	**101-103**	**72%**	**0.85**
A19		**orange**	$C_{53}H_{36}N_4O_{15}$	**968.88**	**184-187**	**60%**	**0.63**
A20		**dark orange**	$C_{45}H_{36}N_4O_{17}$	**904.79**	**177-179**	**89%**	**0,46**
A21		**brown**	$C_{45}H_{32}N_4O_{17}$	**900.79**	**257-259**	**67%**	**0.59**
A22		**dark brown**	$C_{53}H_{36}N_4O_{17}$	**1000.88**	**150-153**	**78%**	**0.39**

A23		**dark red**	**$C_{47}H_{40}N_4O_{19}$**	**964.85**	**170-173**	**82%**	**0,57**
A24		**Dark Yellow**	**$C_{47}H_{36}N_4O_{19}$**	**960.81**	**178-180**	**79%**	**0.62**
A25		**yellow**	**$C_{47}H_{36}N_4O_{19}$**	**960.81**	**235-237**	**91%**	**0.77**
A26		**Pale brown**	**$C_{45}H_{34}N_4O_{15}cl_2$**	**941.68**	**188-190**	**52%**	**0.41**
A27		**Pale yellow**	**$C_{45}H_{30}N_4O_{15}cl_2$**	**937.11**	**142-144**	**63%**	**0.83**

A28		orange	$C_{47}H_{40}N_4O_{17}$	932.85	152-155	81%	0.54
A29		yellow	$C_{55}H_{40}N_4O_{17}$	1028.94	179-181	68%	0.61

2.4-Biological Activity:

2.4.1-Antibacterial activity:

A few synthetic substances have had their antimicrobial susceptibility tested using the "nicely diffusion approach." Staphylococcus aureus, a gram-fine bacteria, and Gram-terrible bacteria were used to test the synthetic chemicals (Klebsiella pneumonia). For a period of 24 hours, samples were cultivated on Muller Hinton agar medium at a temperature of 37 °C, and the results were accurate for a few chemicals, as shown in table. (167).

2.4.2- Antioxidants activity:

100 mL of methanol were used to dissolve 4 mg of DPPH. Some of the substances that were created were utilized to create many concentrations of (25, 50 and 100) ppm. It was created by first combining 1 milligram of the chemical with 10 mL of methanol to create 100 ppm, then diluting that mixture to create 50 and 25 ppm. The concentrations had been created internally in a same manner. 1 mL of the diluted or regular solution (25, 50 and 100 ppm) was mixed with at least one

mL of the DPPH solution in a test tube. After 30 min. of incubation at 37 °C, each response's absorbance was measured using a 517 nm spectrophotometer. The following equation was used to calculate the ability to neutralize DPPH radicals. (168).

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

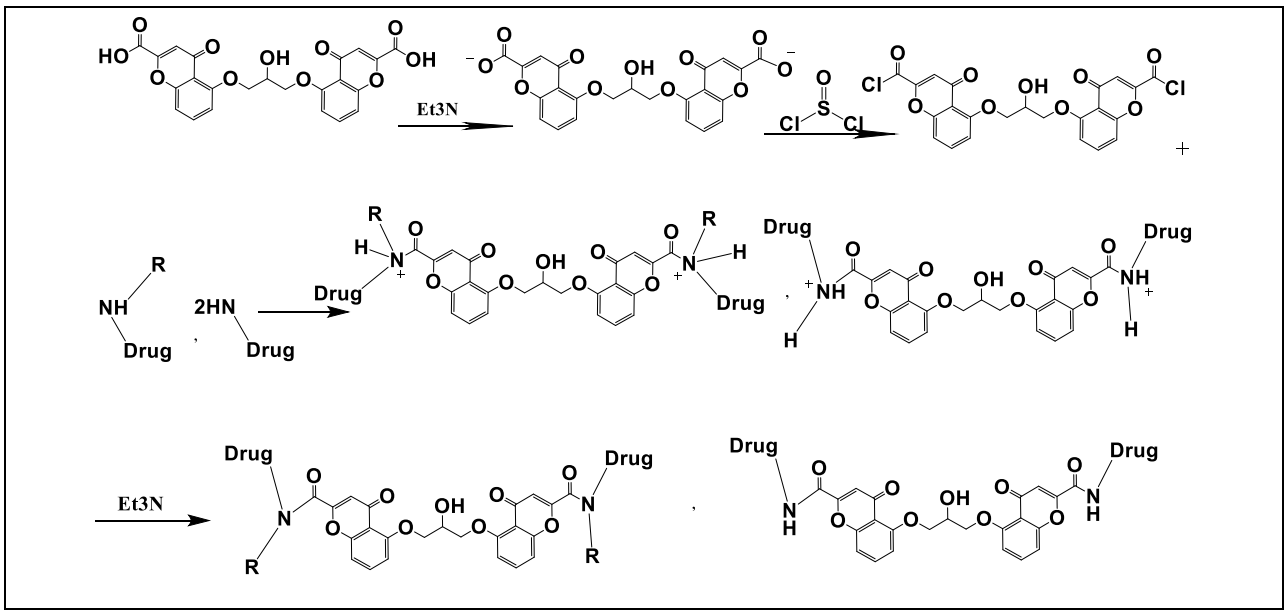
Absorption blank=0.003

2.5 The solubility:

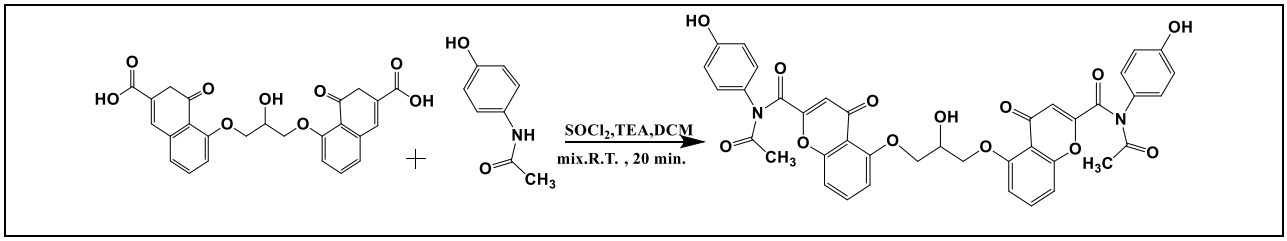
All generated compounds are moderately soluble in water due to their relatively high molecular weight, while they are entirely soluble in DMSO and ethanol. The solubility of synthesized compounds was examined using various polarity solvents. Because the polarity of created compounds is higher than the polarity of these solvents, all synthesized compounds are insoluble in diethyl ether, petroleum ether, and ethyl acetate.

3-1. First line:

New amino-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 used to react with ten amino medicines to create the compounds (A1-A10).



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



Equation (3-1): synthesis of A1

FT-IR (Vmax.,cm^{-1})spectrum of compound(A)showed the following values: 3416(NH,amide),3298(OH,Alcohol),2943(CH,stretch),1720(C=O, Ketone),1651 (C=O,amid),1604(C=C,Aromatic),1247,1398.44(CN,Aryl).^{1}HNMR(500MH,δppm):A;3.6,B;4.6(CH_2,ethylene),D;6.8,U;E;7.5,F;7.0,Q;6.2,R;6.9(Benzene),M;7.2(H,

Ethylene),V;2.6(CH_3,ethane),Z;9.4,X;5.7(Alcohol),2.5(DMSO).^{13}CNMR(125MH, δppm):A;68.7,B;71.4(CH_2,aliphatic),D;109.7,E;138.3,F;107.6,C;S;158.2,K;115.3,J ;156.4,P;126.5,Q;129.5,R;116.8,(Benzene),L;182.8(Carbonyl),O;175.4,a;170.5 (Amide),M;118.8,N;163.3(Ethylene),V;26.1(CH_3,aliphatic),40(DMSO).

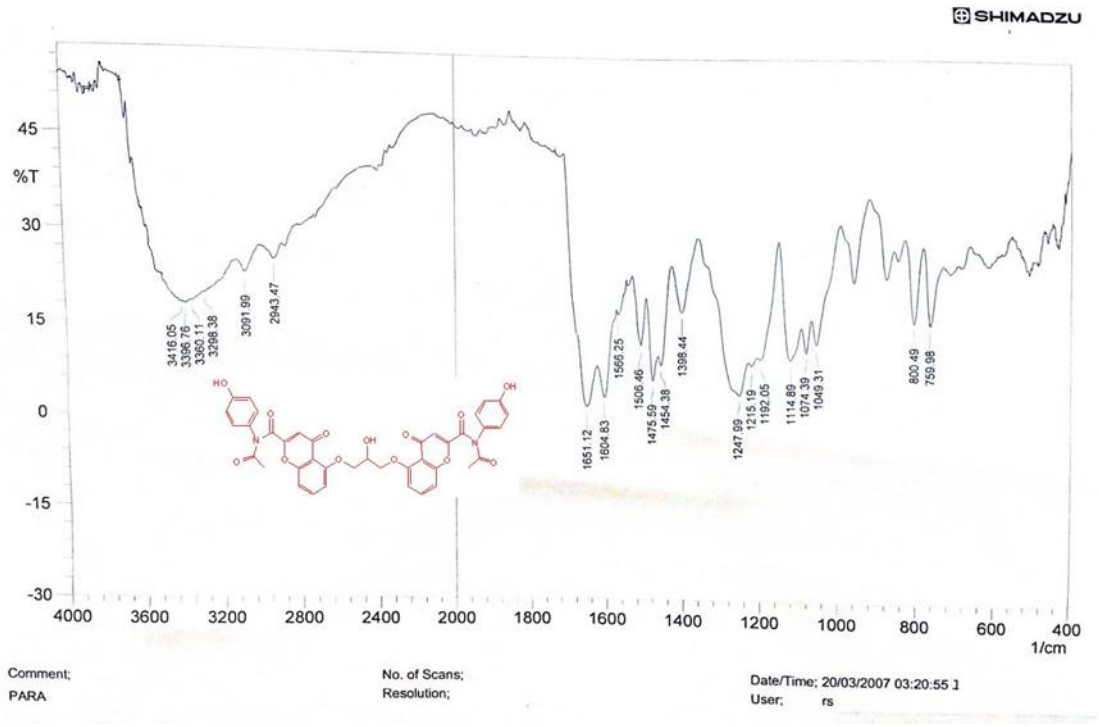


Figure (3-1): FT-IR spectrum for A1

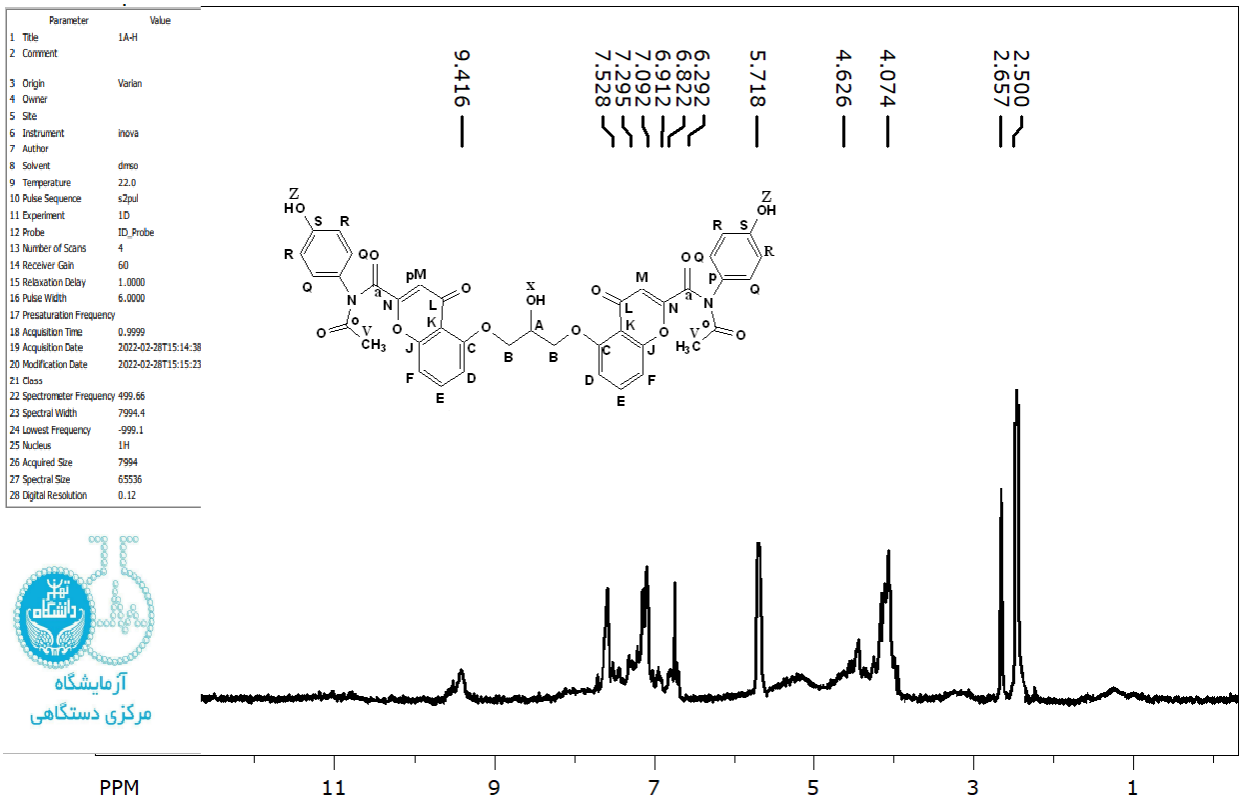


Figure (3-2): ^{1}H-NMR spectrum for A1

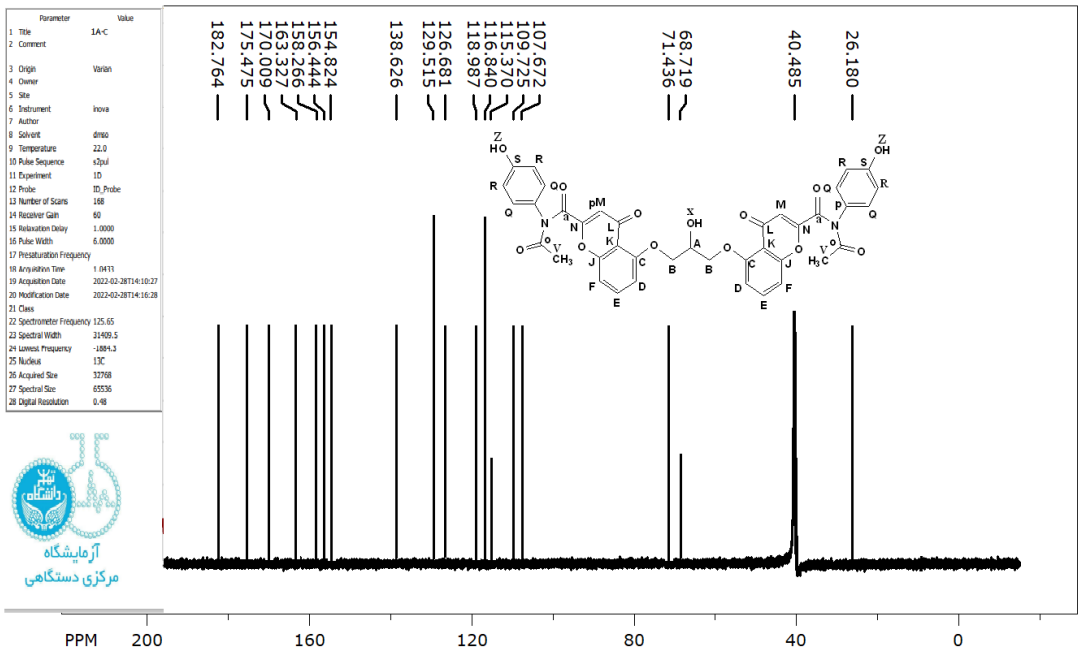
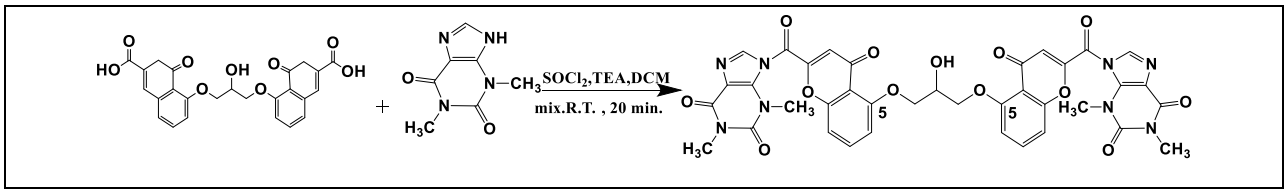


Figure (3-3): ^{13}C-NMR spectrum for A1



Equation (3-2): synthesis of A2

FT-IR(Vmax.,cm^{-1})spectrum of compound(A2)showed the following values: 3414(OH,Alcohol)3190(NH,amide),2945(CH,str.),1732(C=O,Ketone),1651(C=O,amid),1602(C=C,Ar.),1265-1334(CN,Aryl).^{1}HNMR(500MH,δppm):A;3.9 ,B;4.4(CH_2,ethylene),C;5.8,D;7.2,F;6.8,(Benzene),J;7.8(H,Ethylene),X;3.3,W;3.2 (CH_3, ethane),T;8.7(Imidazole),M;4.7(Alcohol),2.5(DMSO).^{13}CNMR(125MH,δppm):A; 69.0,B;70.1(CH_2,aliphatic),C;109.0,D;138.8,F;107.1,G;157.1,H;115.2 ,E;157.9 (Benzene),I;182.1,V;164.2(Carbonyl),Q;150.1(Amide),J;127.2,K;173.0(Ethylene), W;31.7,X;29.0(CH_3,aliphatic),N;138.0,R;114.6,T;136.7(Imidazole),P;151.9(Urea), 40(DMSO).

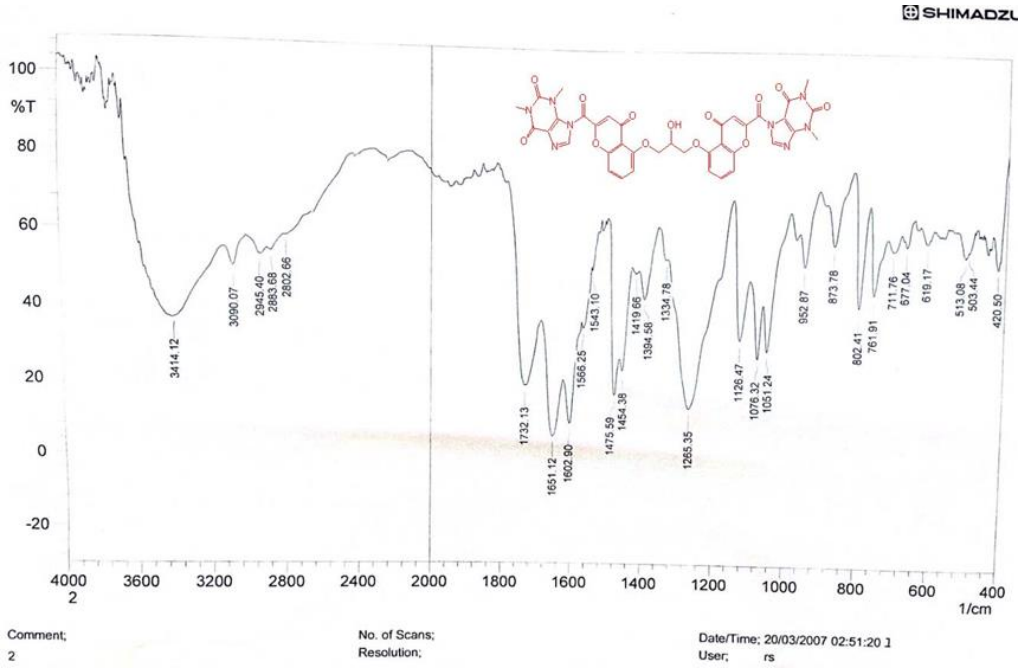


Figure (3-4): FT-IR spectrum for A2

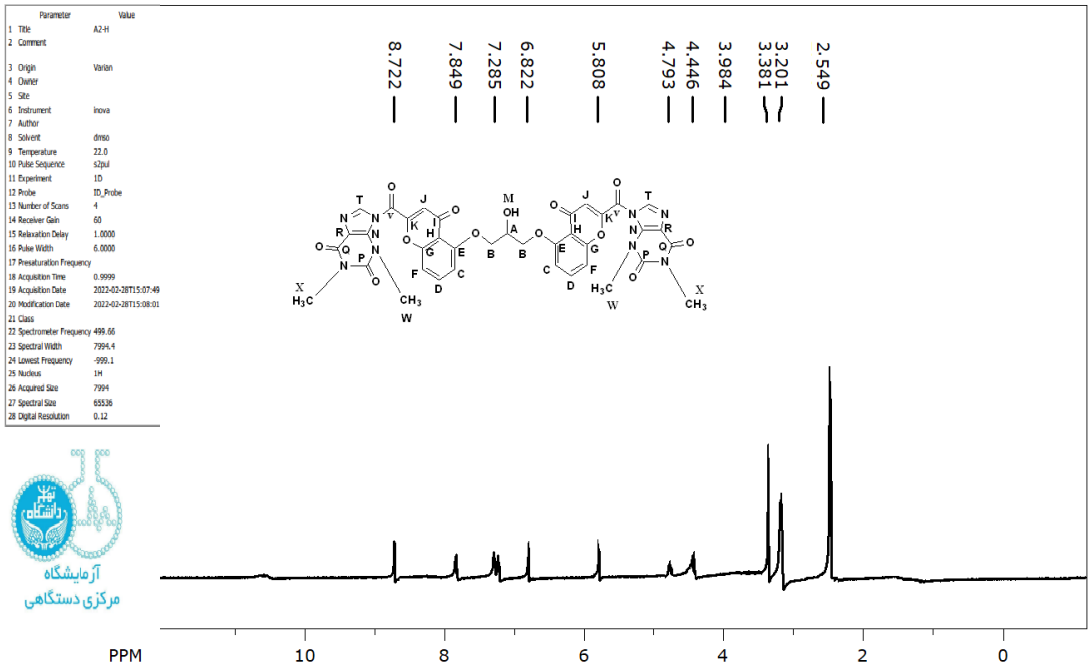


Figure (3-5): ^{1}H-NMR spectrum for A2

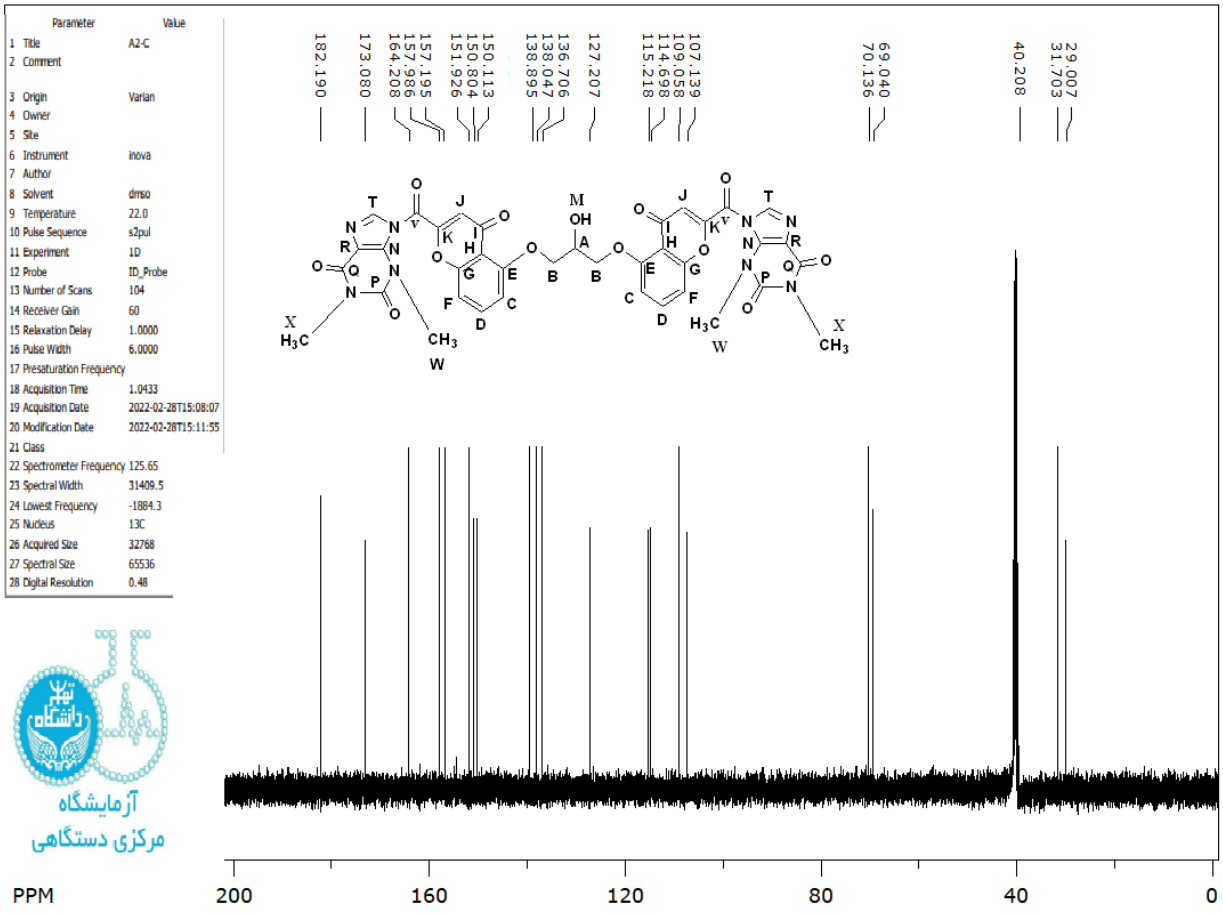
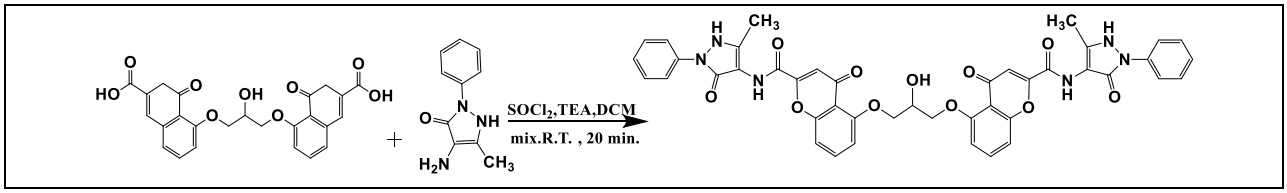


Figure (3-6): ^{13}C-NMR spectrum for A2



Equation (3-3): synthesis of A3

FT-IR(Vmax.,cm^{-1})spectrum of compound(A3)showed the following values: 3264(NH,amide),3394(OH,Phenol),3082(C=CH),2974(CH,str.),1716(C=O, Ketone),1612(N-C=O,amid),1602(C=C,Arom.),1230-1309(C-N,Aryl). ^{1}H-NMR (500MH,δppm):A;4.6,B;3.9(CH_2,ethylene),C;6.8,D;7.5,E;7.2,P;5.9,Q;7.6, (Benzene),J;7.3(H,Ethylene),2.2(CH_3,ethane),4.9(Alcohol),O;10.0(NH),2.5(DMSO).^{13}CNMR(125MH,δppm):A;69.0,B;70.1(CH_2,aliphatic),C;109.5,D;138.8, E;107.1 ,H;115.3,G;158.7,P;137.7,Q;122.8,S;129.9,F;156.4(Benzene),I;182.3(Carbonyl),M ;164.8,162.2(Amide),K;163.7,J;118.1,L;103.2,N;133.6(Ethylene),15.1(CH_3,aliphat ic) ,40(DMSO).

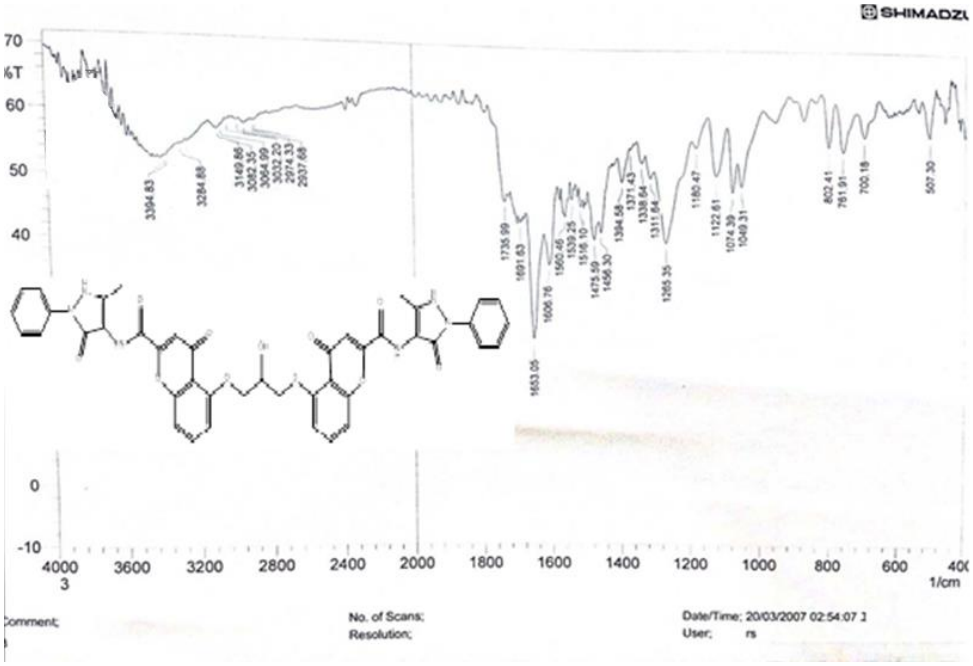


Figure (3-7): FT-IR spectrum for A3

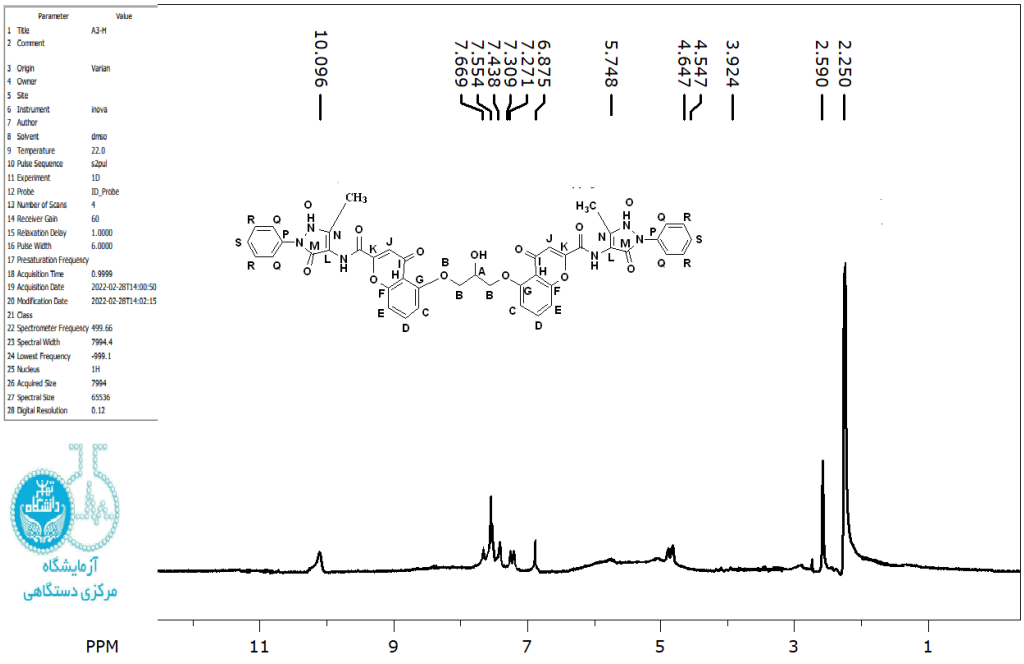


Figure (3-8): ^{1}H-NMR spectrum for A3

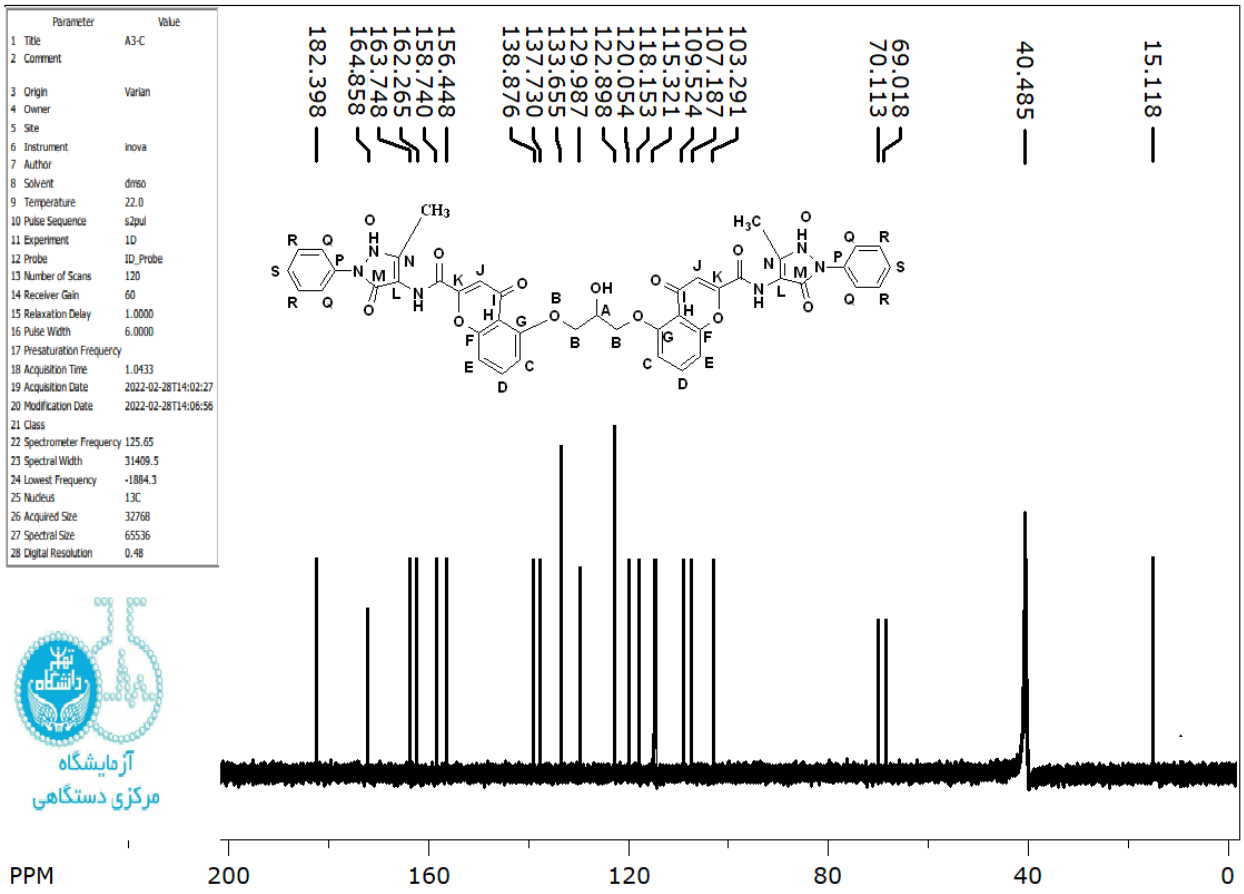
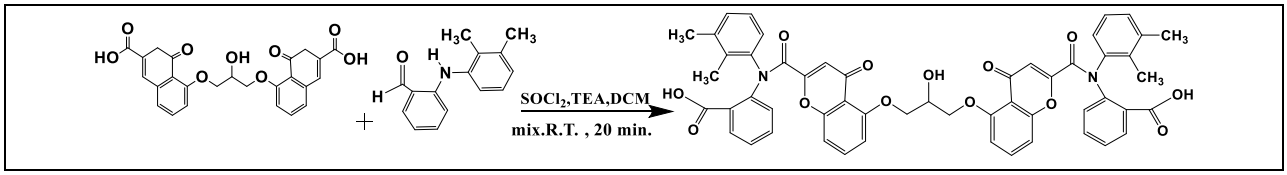


Figure (3-9): ^{13}C-NMR spectrum for A3



Equation (3-4): synthesis of A4

FT-IR(Vmax.,cm^{-1})spectrum of compound(A4)showed the following values: 2492-3416(NH amide,OH carboxylic Acid,OH Alcohol Overlap),2995(CHstr.), 1716(C=O,Ketone),1661(C=O,amide),1601(C=C,Ar),1209-1307(CN,Aryl). ^{1}HNMR(500MH,δppm):A;4.6,B;4.0(CH_2,ethylene),D;6.8,;F;7.5,G;7.0,S;P;8.1,Q; R;8.3, X;U;Z;7.3(Benzene),J;7.3(H,Ethylene),a;2.1,e;1.6(CH_3,ethane),O;13.1(Carboxyl),2.4(DMSO).^{13}CNMR(125MH,δppm):A;69.0,B;70.1(CH_2,aliphatic),D;109.6,E;136.7,F;138.7,G;107.7,H;158.1,I;115.6,J;118.9,L;156.9,P;127.3,Q;R;118.5,S;131.8,T;113.0,U;127.5,V;137.4,W;126.1,Y;141.1(Benzene),K;182.0(Carbonyl),N;163.7(Amide),M;159.3(Ethylene),b;169.9(Carboxyl),a;18.4,e;13.3(CH_3,aliphatic),40(DMSO).

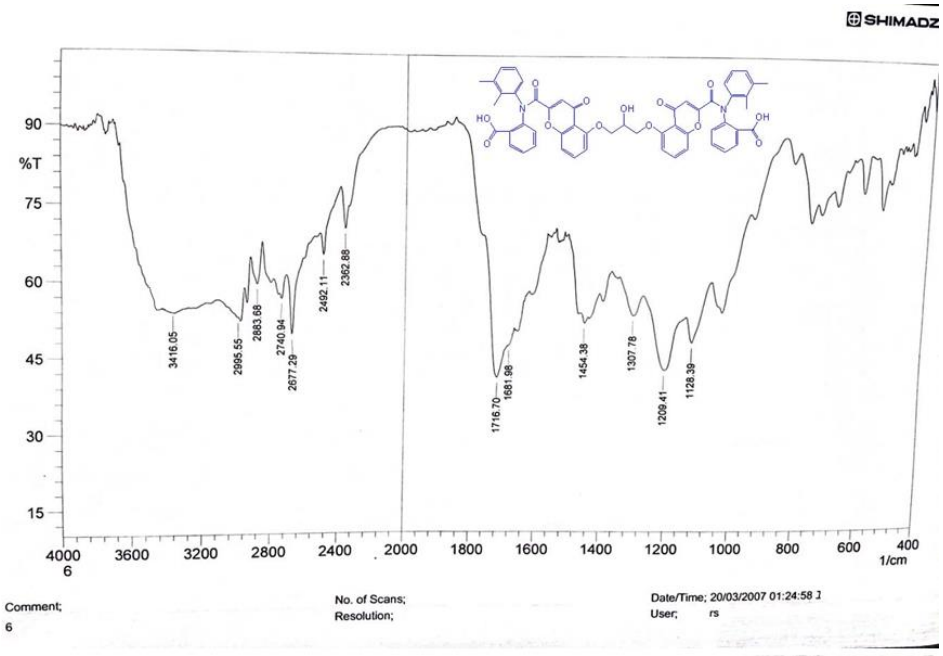


Figure (3-10): FT-IR spectrum for A4

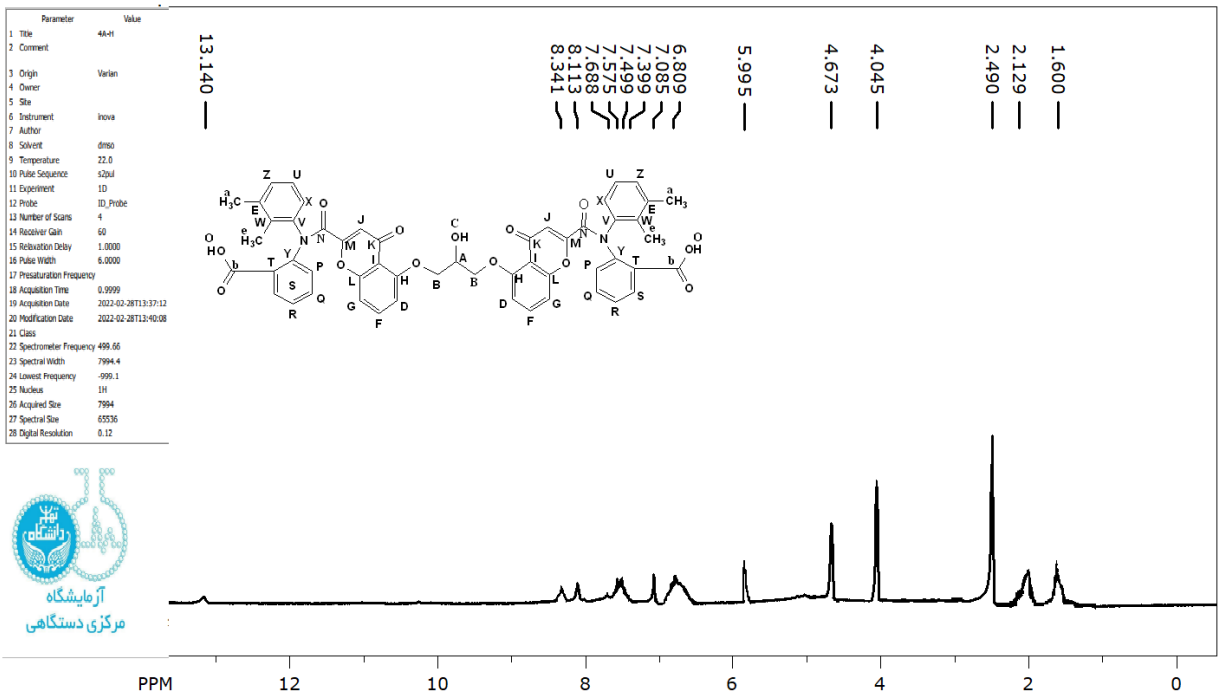


Figure (3-11): ^{1}H-NMR spectrum for A4

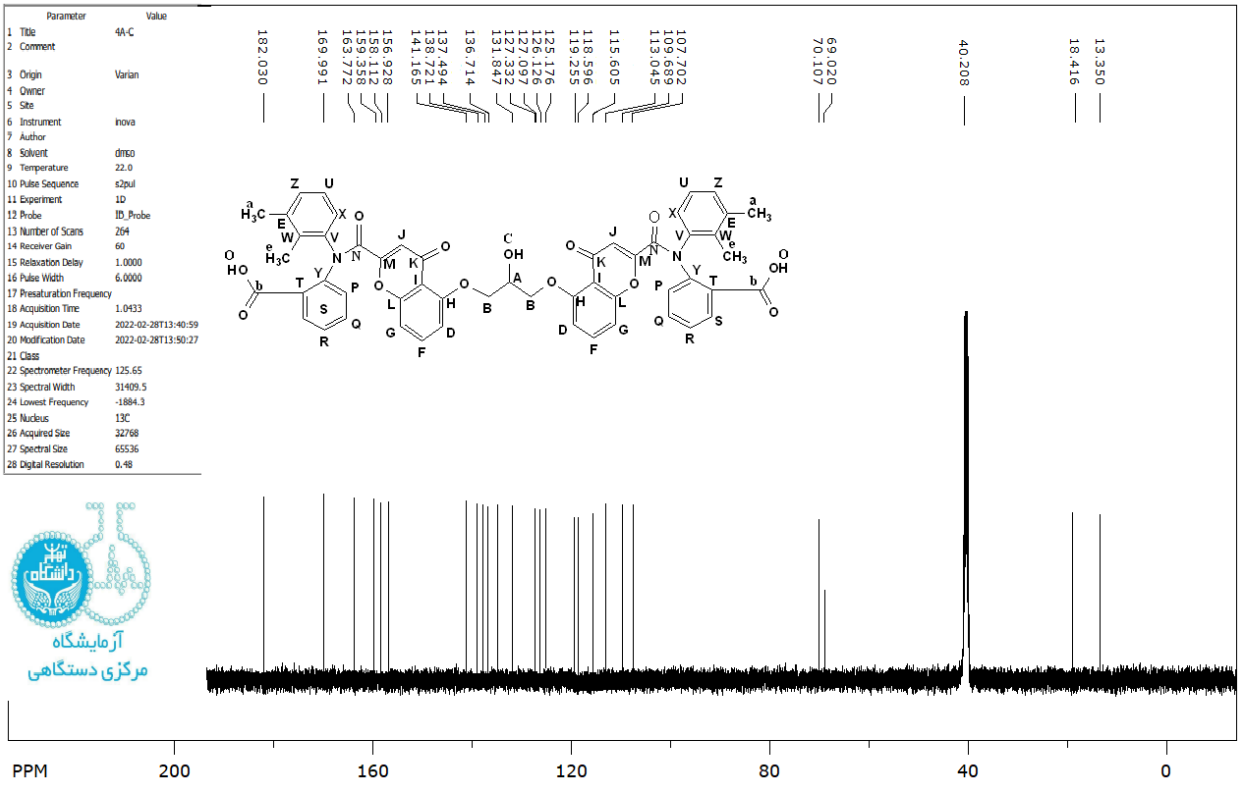
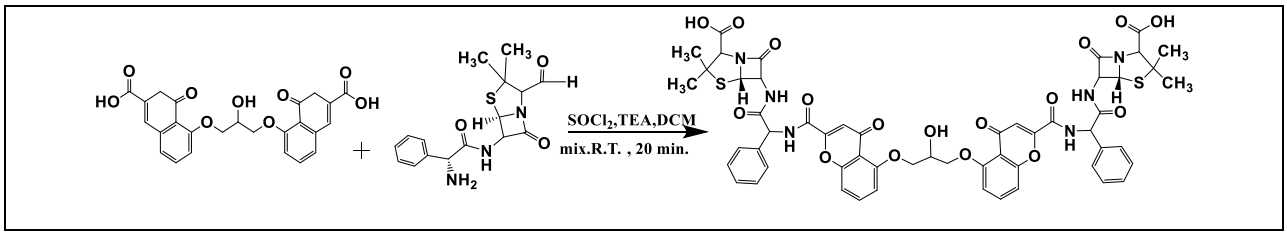


Figure (3-12): ^{13}C-NMR spectrum for A4



Equation (3-5): synthesis of A5

FT-IR(Vmax.,cm^{-1})spectrum of compound(A5)showed the following values: 2362-3390(NH amide,OH Carb. acid,OH Alcohol Overlap),2945(CH,str.),1716(C=O,Ketone),1654(C=Oamid),1606(C=C,Ar.),1217(CN,Aryl).^{1}HNMR(500MH ,δppm):A;J;4.0,B;4.3(CH_2,ethylene),D;6.8,E;7.5,F;7.0,S;T;7.4(Benzene),R;K;7.1(H,Ethylene),P;5.5,U;4.5(CH,methane),N;9.4,e;8.7(Amide),g;5.5,(Alcohol),b;12.3 (Carboxyl),Y;4.6(CH),Z;1.5(CH_3),2.5(DMSO).^{13}CNMR(125MH,δppm):A;69.8, B;70.9(CH_2,aliphatic),D;110.1,E;P;138.3,Q;F;108.6,H;115.8,C;158.5,G;156.6,K; ,R;118.0,S;129.9,T;128.7(Benzene),I;182.9(Carbonyl),O;169.2,M;163.9,V;174.2 (Amide),L;163.3(Ethylene),U;79.9,W;72.7,X;60.0,X;64.3(CH,aliphatic),Z;29.8(C H_3,aliphatic),a;166.8(Carboxyl),40(DMSO).

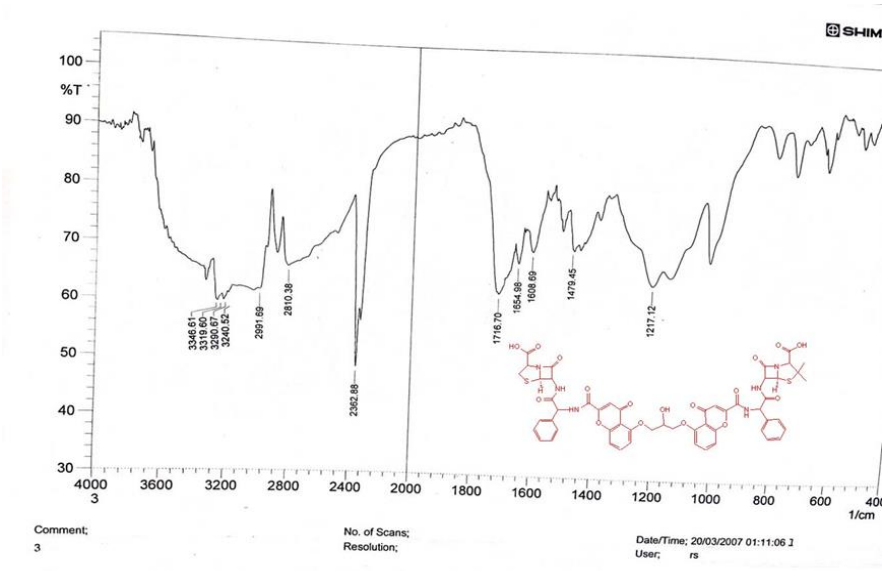


Figure (3-13): FT-IR spectrum for A5

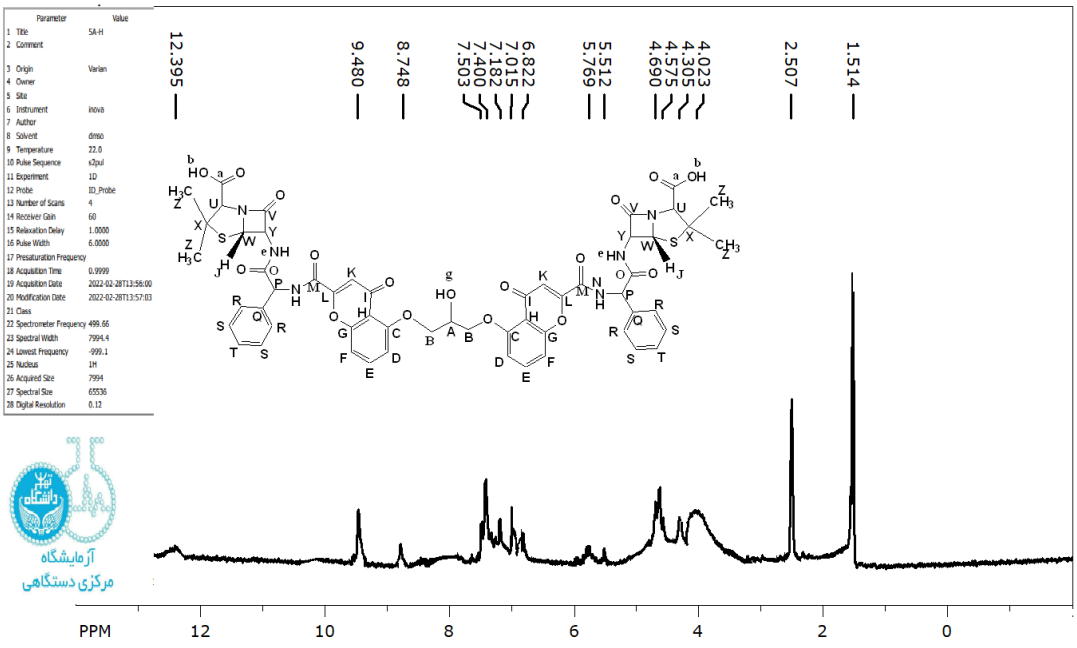


Figure (3-14): ^{1}H-NMR spectrum for A5

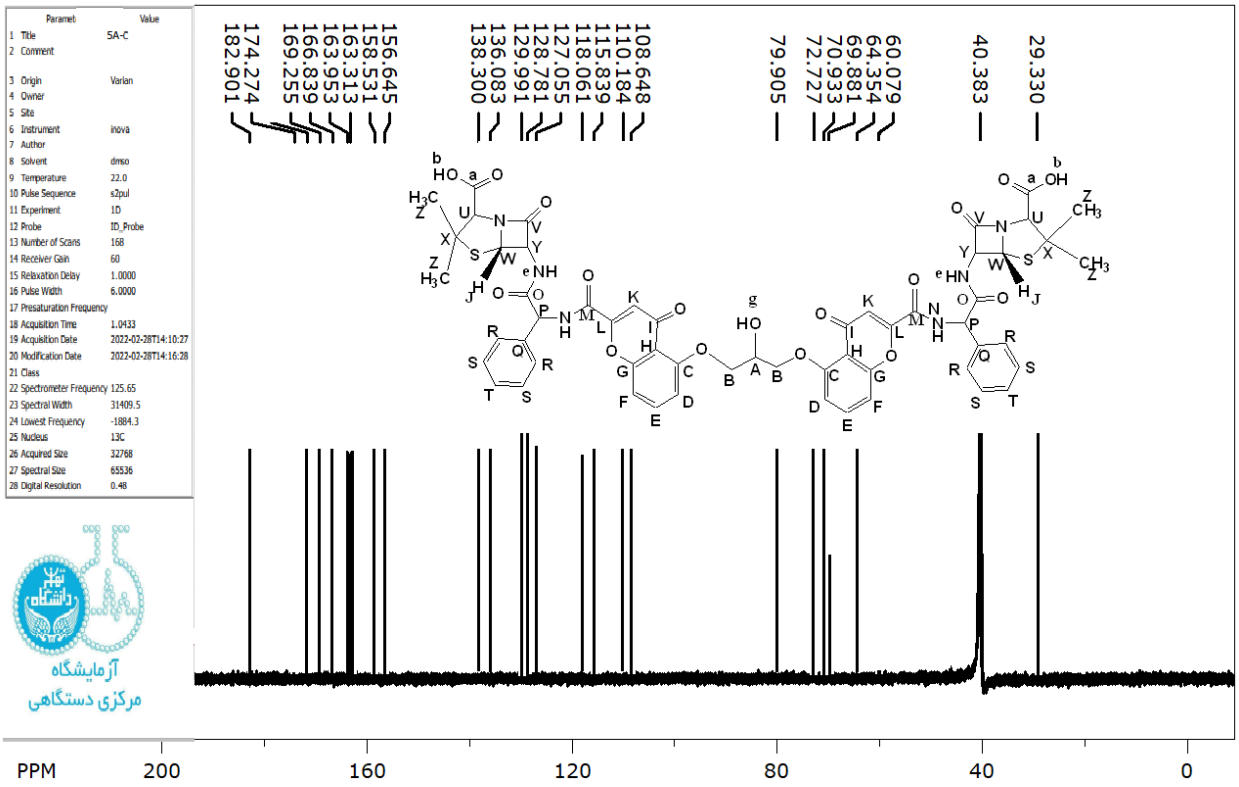
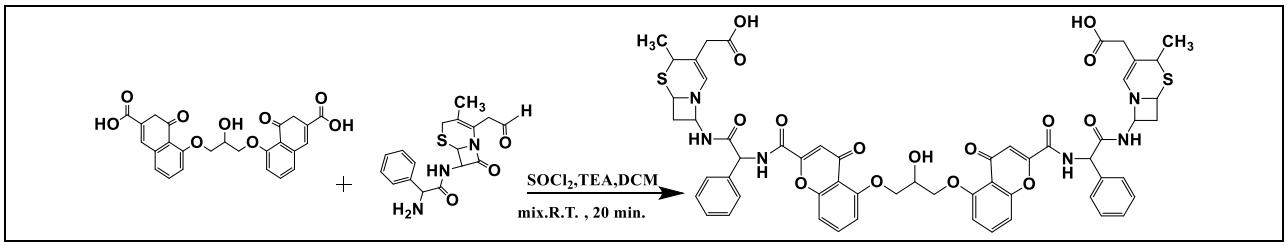


Figure (3-15): ^{13}C-NMR spectrum for A5



Equation (3-6): synthesis of A6

FT-IR(Vmax.,cm^{-1})spectrumofcompound(A6)showed the following values: 2400-3390(NH amide ,OH Carb. OH Alcohol overlap),),2989(CH,str.),1716(C=O, Ketone),1612(C=O,amid),1602(C=C,Ar.),1230-1309(C-N,Aryl).^{1}H-NMR(500 MH,δppm):b;1.2,(CH_3),Z;3.6,X;3.2,B;4.7(CH_2),A;3.8,T;2.9,U;4.0,S;5.8,V;Q;5.8(C H),a;5.7(Alcohol),E;6.8,F;7.9,G;7.4,N;7.0,P;7.6,O;7.7(Benzene),K;7.5(H,Ethylene),f;8.1,e;8.7(amide),g;12.2(Carb.acid),2.5(DMSO).^{13}CNMR(125MH,δppm):J;181. 8(Carbonyl),Y;177.2(Carboxyl),R;169.2,d;166.8(amide),G;107.5,E;109.4.P;127.8, O;129.2,N;129.9,M;136.9,H;156.5,C;158.0,I;115.7,F;138.7(benzene),S;74.9,U;64. 2(CH,Azetidine),T;33.0(CH_2,Azetidine),V;136.0,W;114.5,L;163.7,K;118.8(ethyle ne),A;69.0,Y;Z;34.4,Q;64.2(CH,aliphatic),B;70.1,X;48.8(CH_2,aliphatic),b;25.9(CH $_3$,aliphatic),40(DMSO).

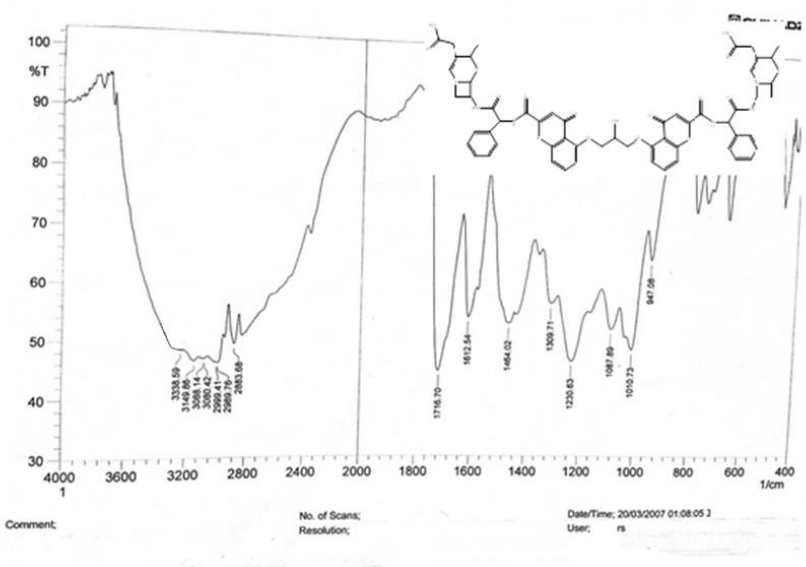


Figure (3-16): FT-IR spectrum for A6

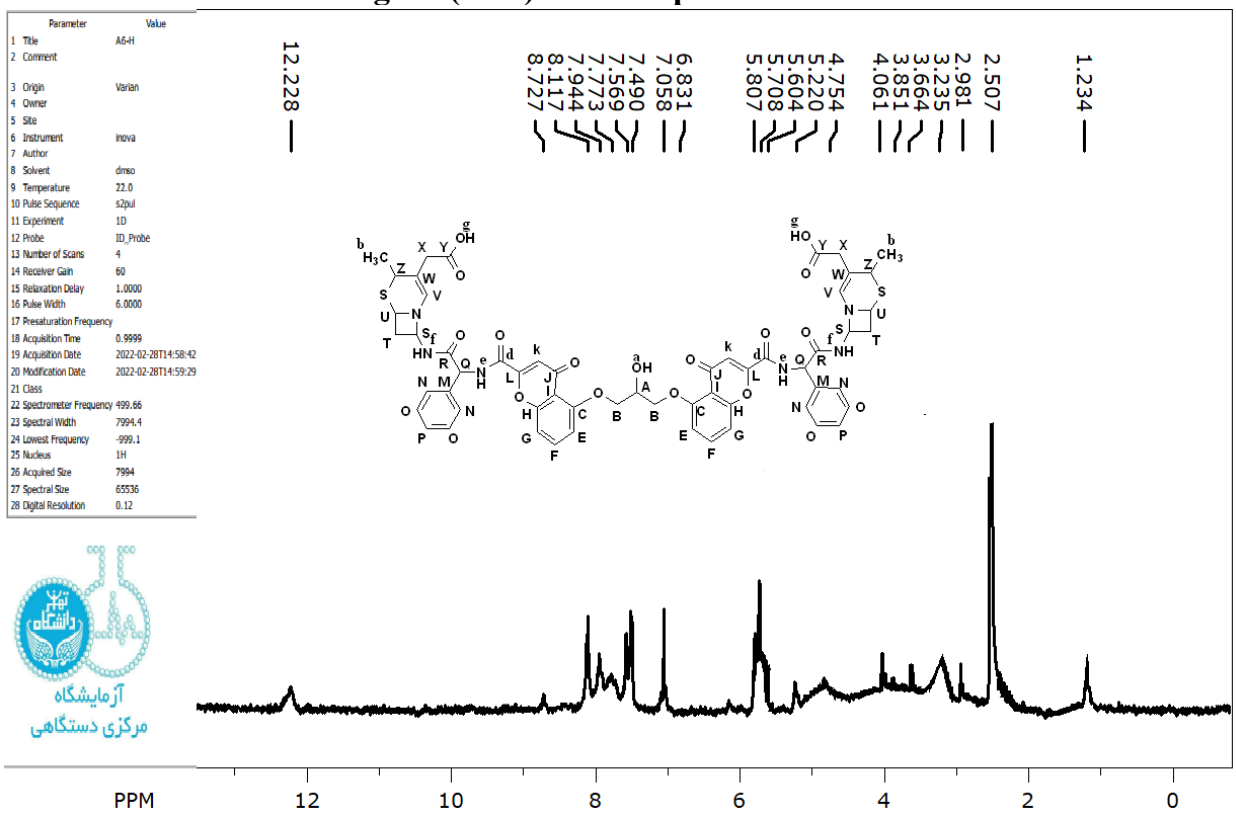


Figure (3-17): ^{1}H-NMR spectrum for A6

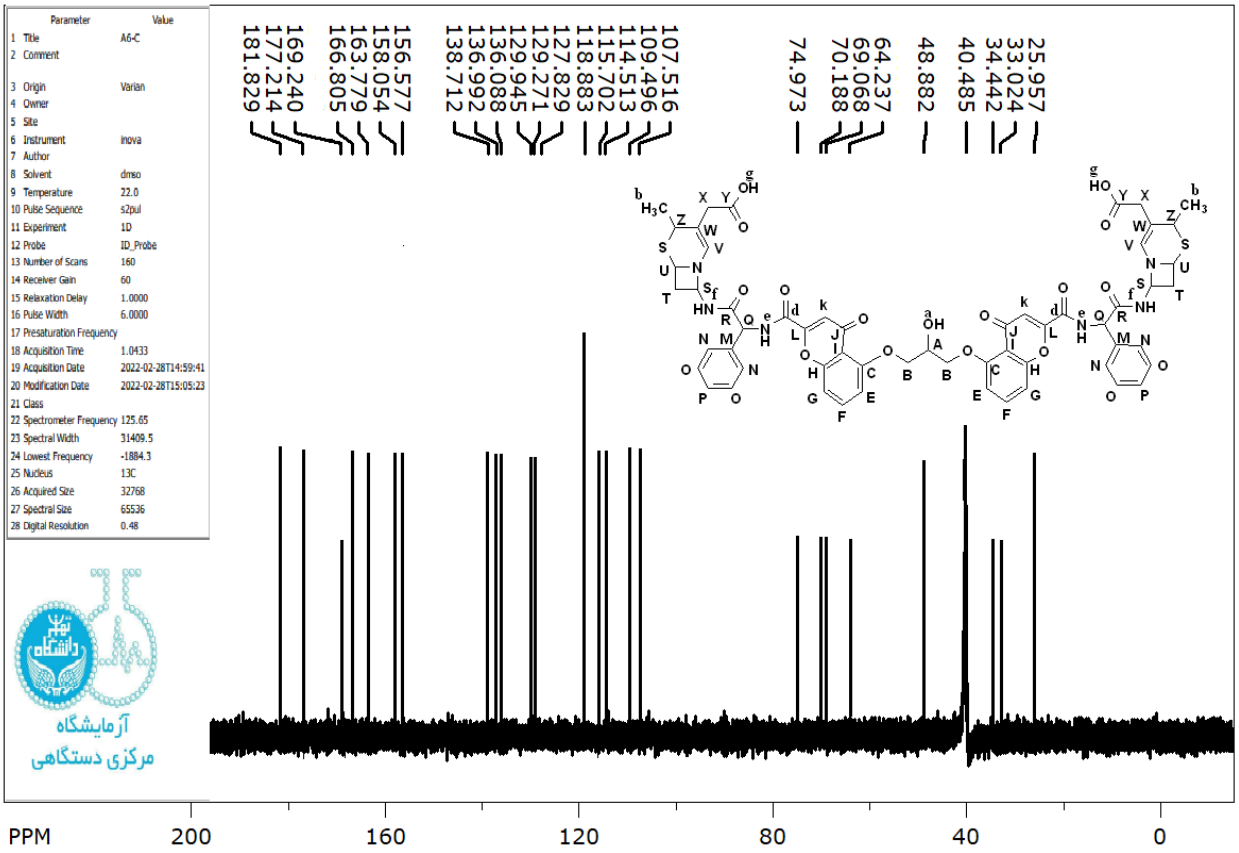
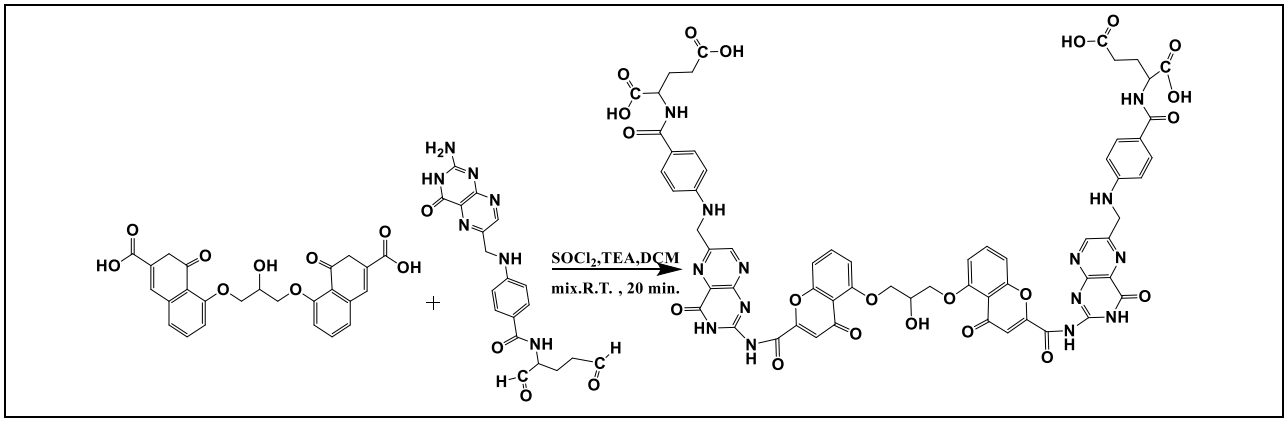


Figure (3-18): ^{13}C-NMR spectrum for A6



Equation (3-7): synthesis of A7

FT-IR(Vmax.,cm^{-1})spectrum of compound(A7)showed the following values :3408(amine),2362-3319(NH amide,OHCarb.acid,OH Alcohol Overlap), 2995(CH str.),1720(C=O,Ketone),1658(C=O,amide),1606(C=C,Ar.),1213-1307(C-N,Aryl).

^{1}H-NMR(500MH,δppm):A;3.0,B;4.6(CH_2,ethylene),C;6.7,D;7.4,E;7.3,Y;6.8,Z;7.5 (Benzene),I;7.37(H,Ethylene),h;2.0,r;4.59(CH,methane),V;4.54,f;2.2(CH_2,ethylene),W;6.2,d;L;8.7(Amide),i;5.7(Alcohol),m;n;12.01(Carboxyl),N;10.5(NH),T;U;9.2(CH,Pyrazine),2.5(DMSO).^{13}CNMR(125MH,δppm):A;69.0,B;70.1,V;47.2,f;30.8,h; 26.1(CH_2,aliphatic),C;109.3,D;138.7,E;107.2,G;115.6,a;158.9,F;156.5,X;152.7,Y; 112.1,Z;130.0,b;122.3(Benzene),H;182.1(Carbonyl),c=o,K;167.5,O;157.7(Amide), J;163.7,I;118.0(Ethylene),M;147.9(Imine),r;56.1(CH,aliphatic),P;147.0,Q;129.1,U, T;150.8(Pyrazine),e;174.6,g;178.2 (Carboxyl),40(DMSO) .

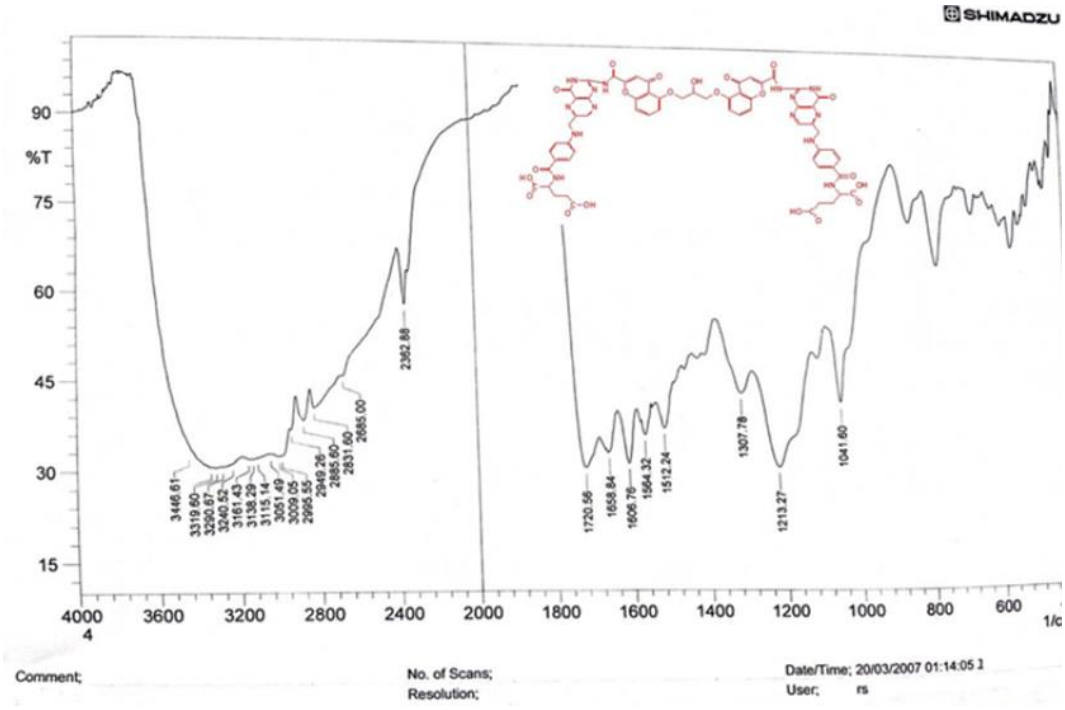


Figure (3-19): FT-IR spectrum for A7

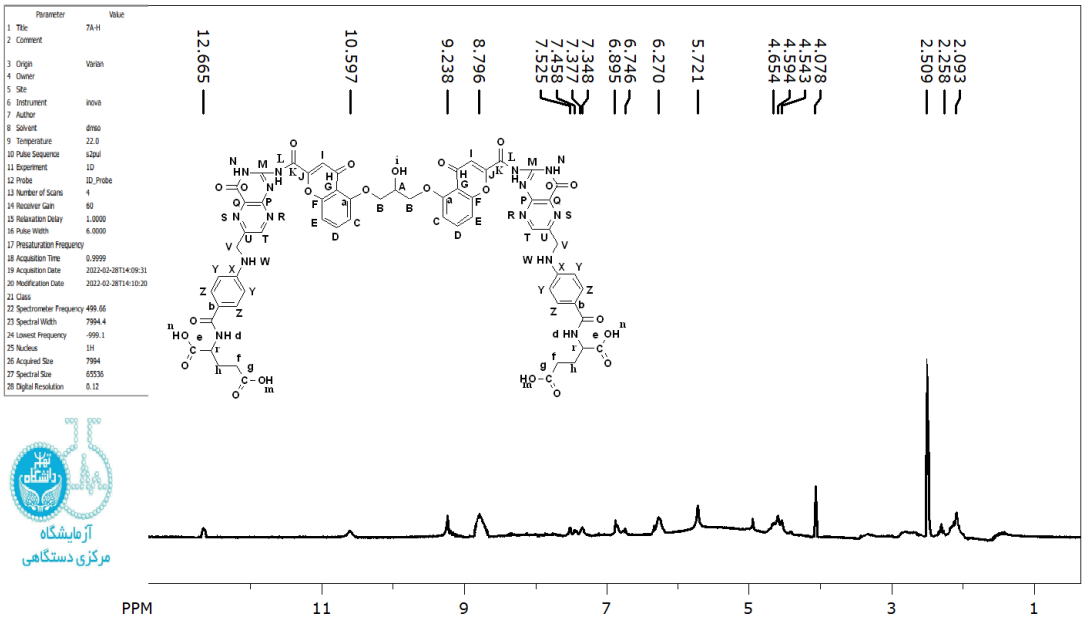


Figure (3-20): ^{1}H-NMR spectrum for A7

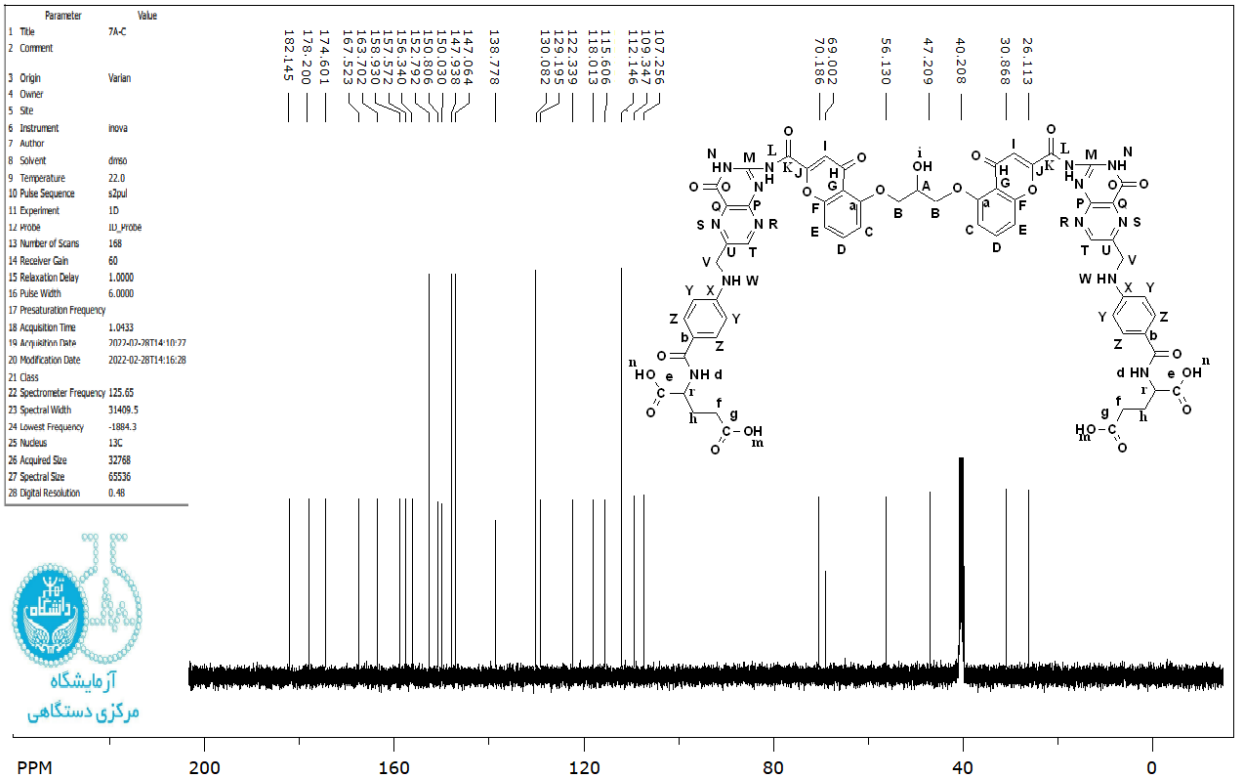
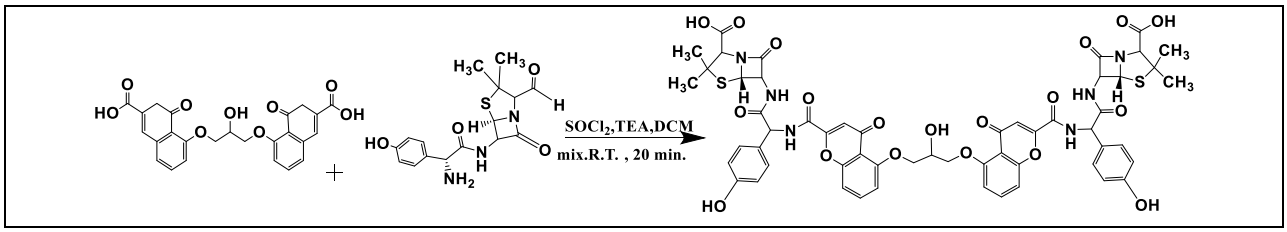


Figure (3-21): ^{13}C-NMR spectrum for A7



Equation (3-8): synthesis of A8

FT-IR(Vmax.,cm^{-1})spectrum of compound (A8)showed the following values :2495-3345(NH amide,OH Carb.acid,OH Alcohol Overlap),2906(CH,str.),1720 (C=O,Ketone),1640(C=Oamid),1612(C=C,Ar.),1220,1301(CN,Aryl).^{1}HNMR(500 MH,δppm):A;4.0,B;4.3(CH_2,ethylene),D;6.8,E;7.5,F;K;7.2,S;6.7,R;6.9(Benzene), P;5.7,J;U;4.4(CH,methane),N;9.4,e;8.6(Amide),g;4.6,r;9.0(Alcohol),b;11.5(Carbox yl),Y;5.5(H),Z;1.5(CH_3),2.5(DMSO).^{13}CNMR(125MH,δppm):A;60.7,B;70.1(CH_2, aliphatic),D;109.5,E;Q;138.8,F;107.3,S;H;115.5,T;C;158.3,G;156.3,P;129.9,R;128 .3(Benzene),I;182.4(Carbonyl),M;166.5,V;O;171.5(Amide),L;163.7,K;118.6(Ethyl ene),U;79.3,W;72.6,X;69.5,Y;64.7(CH,aliphatic),Z;29.9(CH_3,aliphati),a;169.5(Car boxyl),40(DMSO).

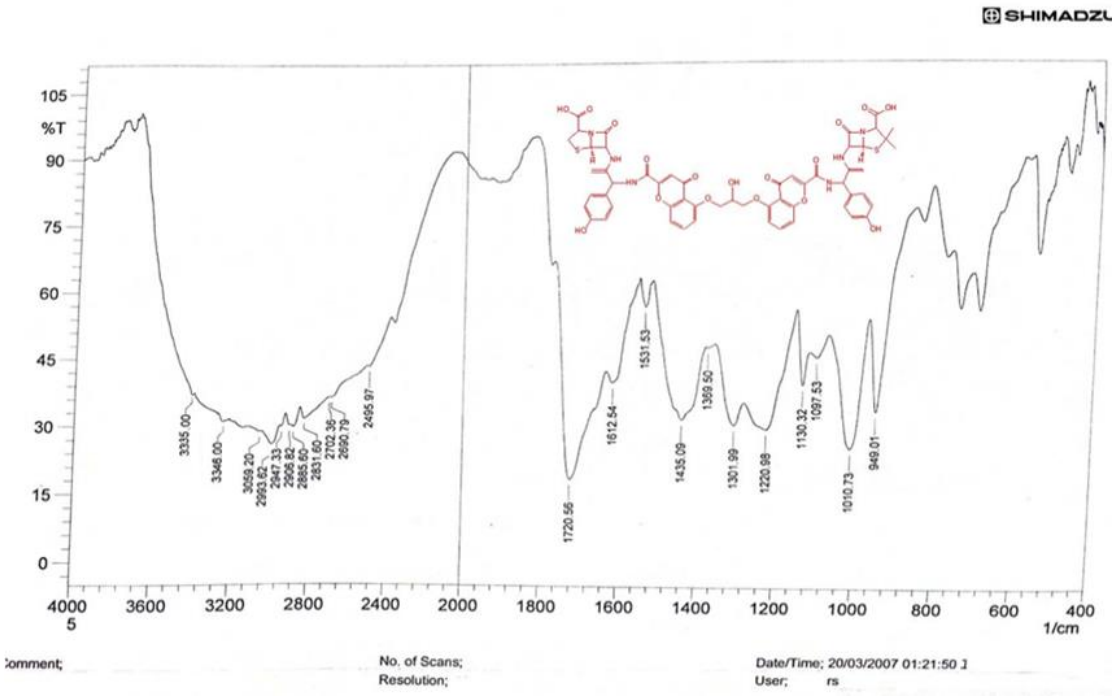


Figure (3-22): FT-IR spectrum for A8

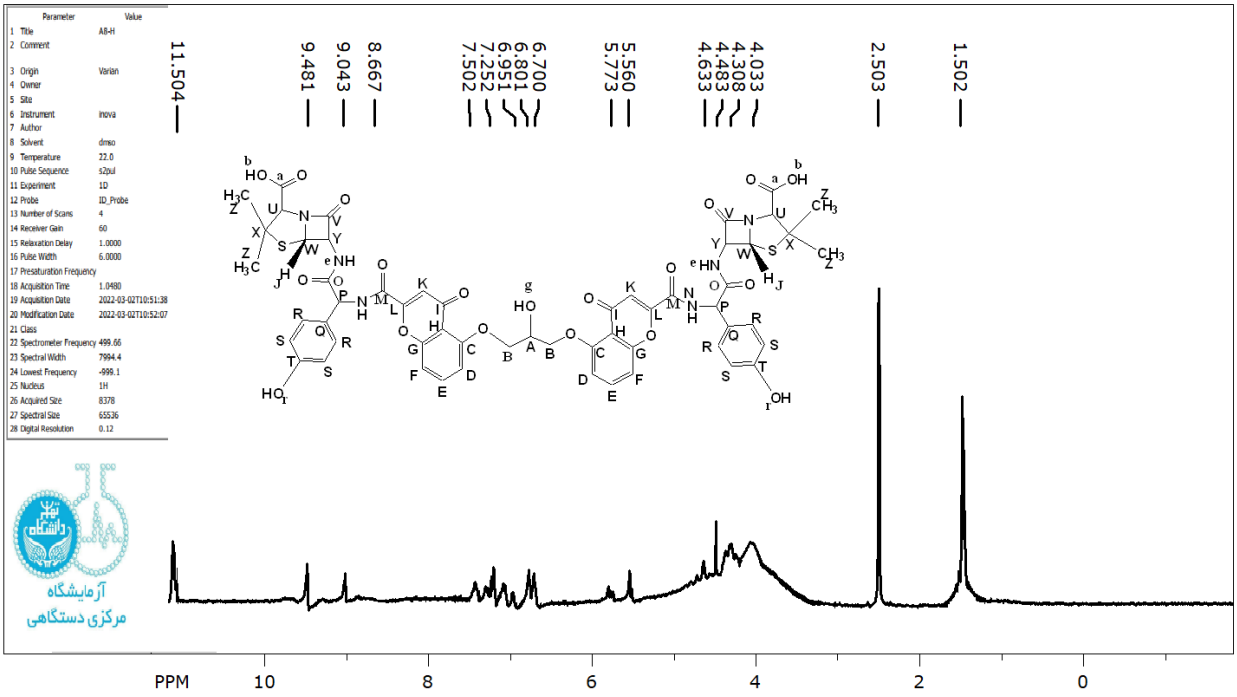


Figure (3-23): ^{1}H-NMR spectrum for A8

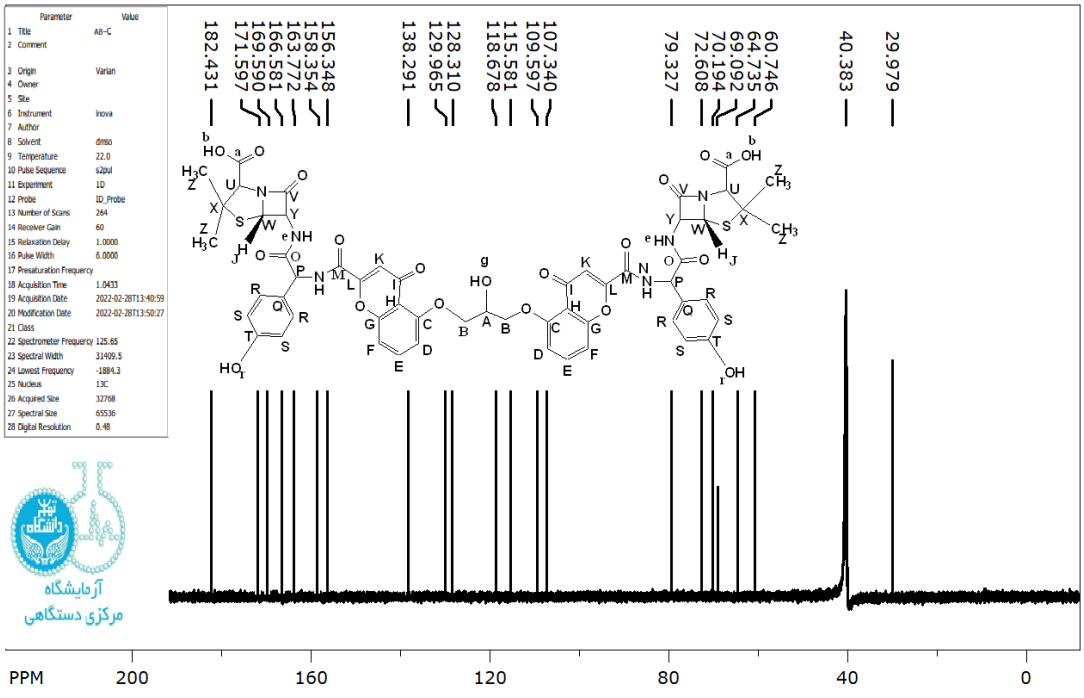
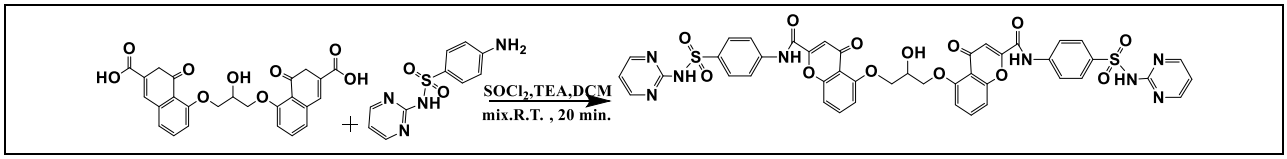


Figure (3-24): ^{13}C-NMR spectrum for A8



Equation (3-9): synthesis of A9

FT-IR(V max.,cm^{-1})spectrum of compound (A9) showed the following values :2621-3420(NH amide ,OH Carb. Acid ,OH Alcohol Overlap),2883(CH,str.), 1720(C=O,Ketone),1647(C=Oamid),1585(C=C,Ar.),1225(CN,Aryl).^{1}HNMR(500 MH,δppm):B;4.3,A;3.6(CH_2,ethylene),D;6.8,F;7.4,G;V;7.0,P;7.6,Q;7.7(Benzene), K;7.2(H,Ethylene),W;10.6,M;11.1(Amide),X;4.8(Alcohol),U;8.6,V;7.0(CH,Pyrazine),2.5(DMSO).^{13}CNMR(125MH,δppm):A;69.6,B;72.7(CH_2,aliphatic),D;111.6,F; 137.6,G;109.1,I;V;117.3,C;158.1,O;142.1,P;118.8,Q;125.4,R;131.3,S;N;170.6,H;156.8(Benzene),J;184.1(Carbonyl),L;165.1,K;120.4(Ethylene),U;160.3(Pyrazine),39-40(DMSO).

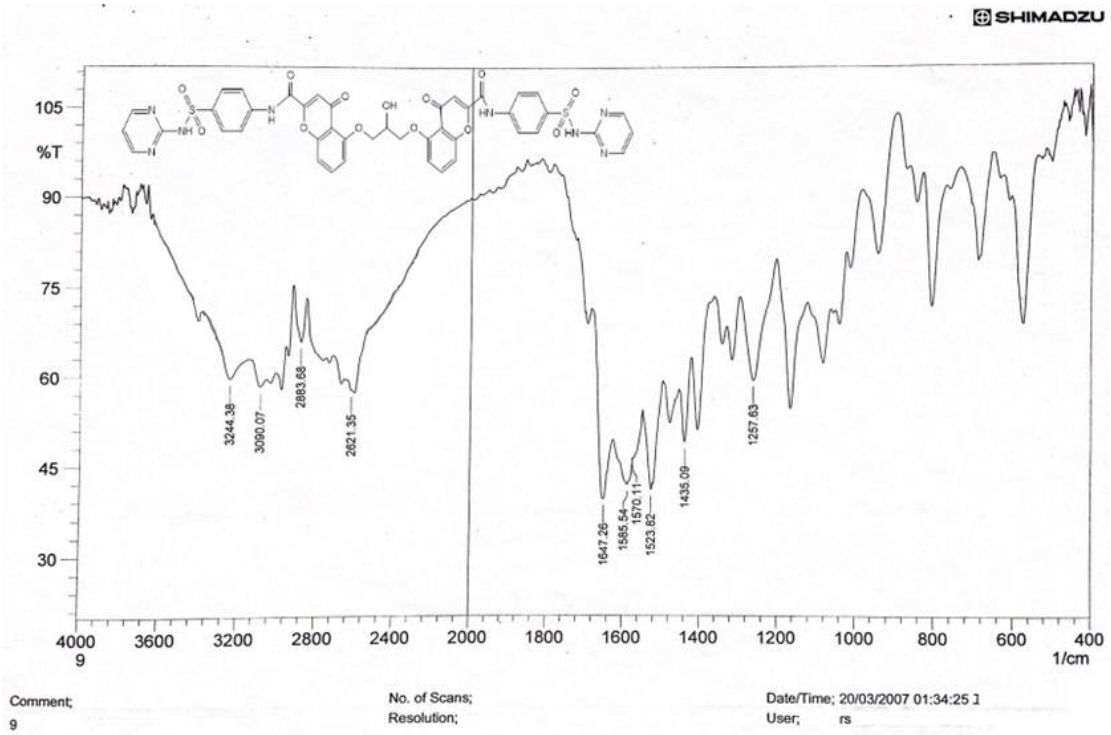


Figure (3-25): FT-IR spectrum for A9

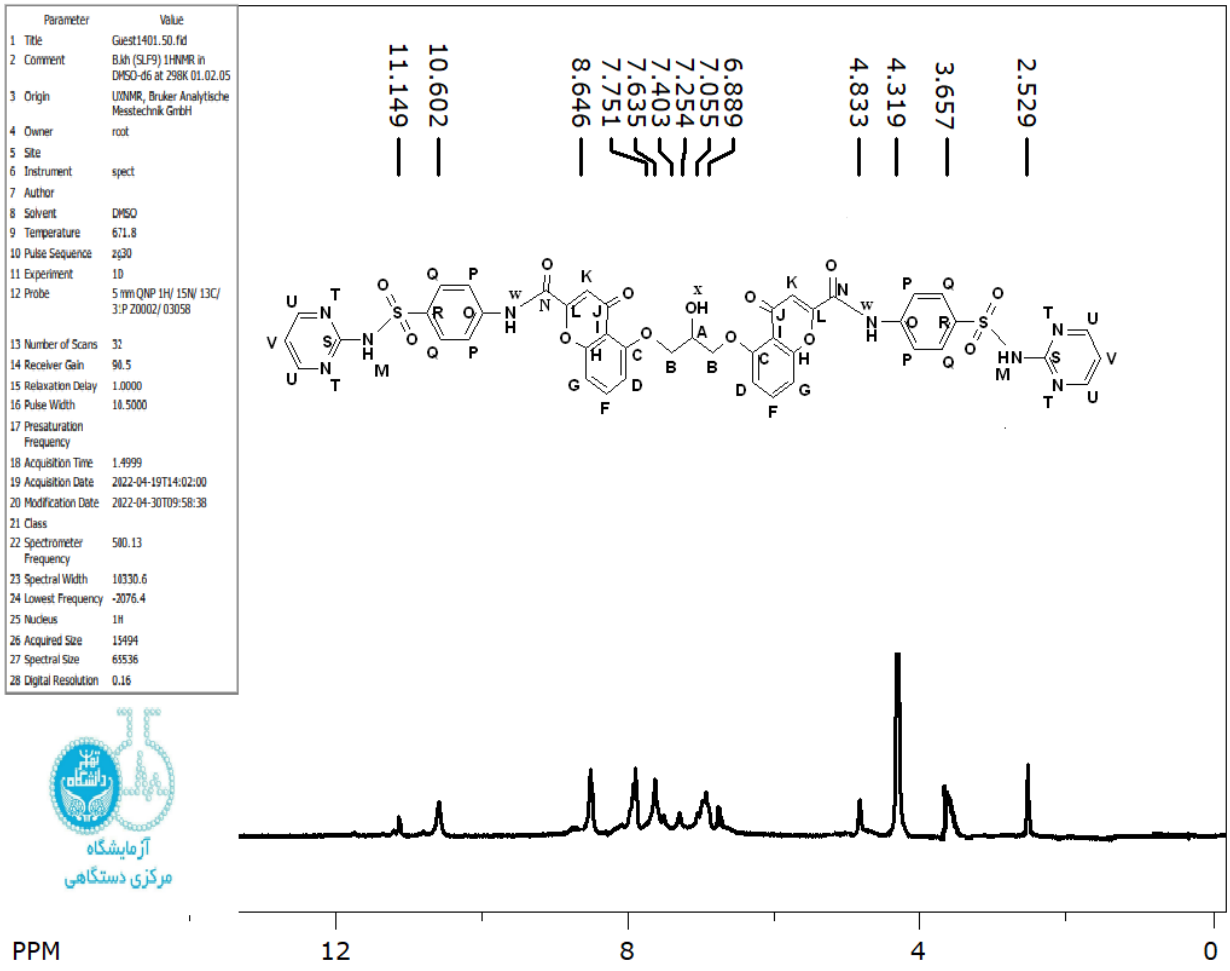


Figure (3-26): ^{1}H-NMR spectrum for A9

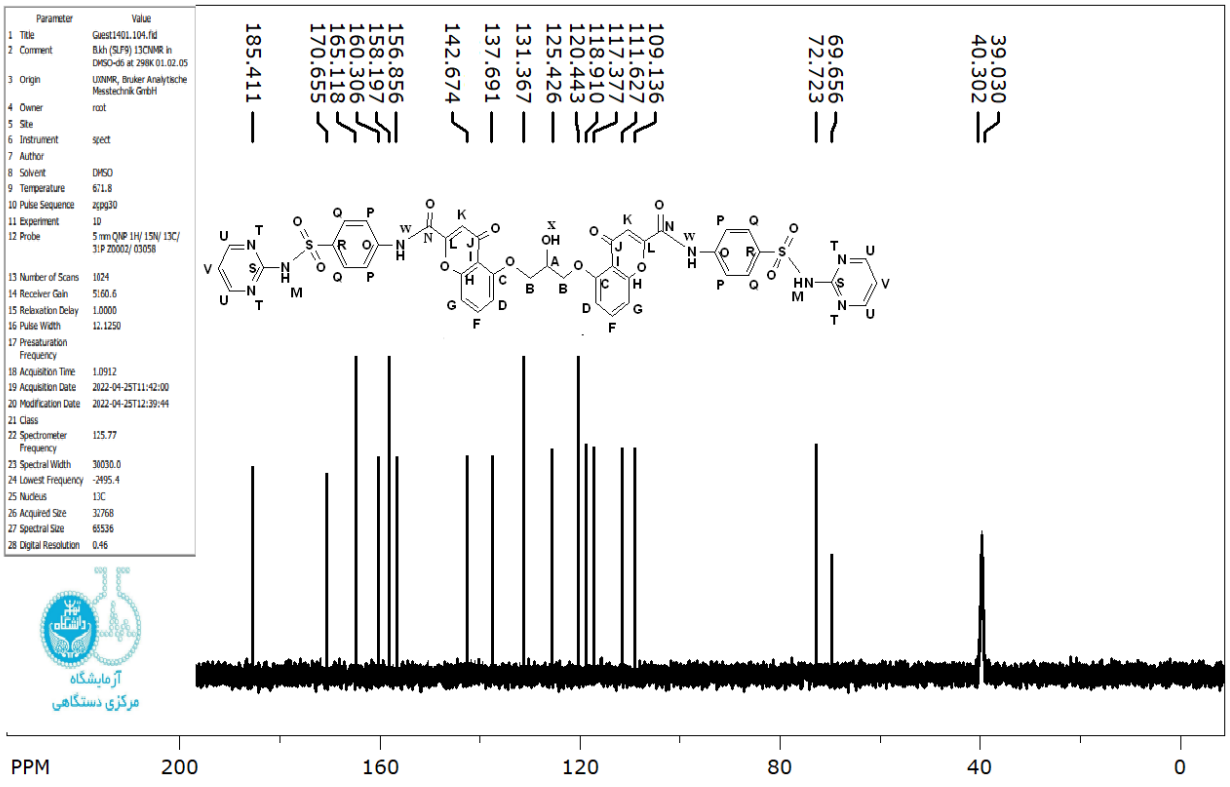
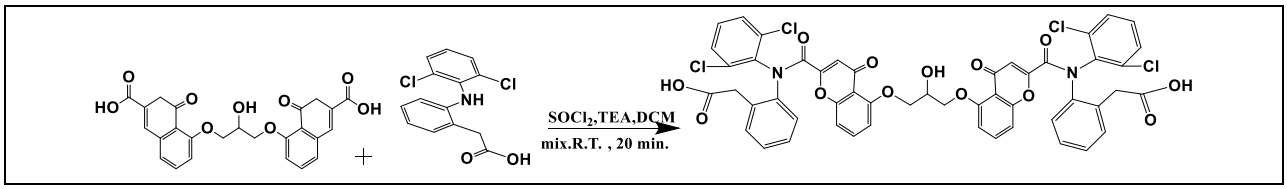


Figure (3-27): ^{13}C-NMR spectrum for A9



Equation (3-10): synthesis of A10

FT-IR(Vmax.,cm^{-1})spectrum of compound(A10)showed the following values:2492-3456(NH amide ,OH Carb.acid ,OH Alcohol Overlap),2941(CH,str.), 1735(C=O,Ketone),1651(C=Oamid),1604(C=C,Ar.),1210(CN,Aryl).^{1}HNMR(500 MH,δppm):A;4.2,B;4.6(CH_2,ethylene),D;6.9,E;7.32,F;7.70,N;7.75,O;7;6,P;7.0,Q;7 .1,W;7.8,X;7.4(Benzene),J;7.37(H,Ethylene),S;3.8(CH_2,methylene),a;5.9(Alcohol), b;12.4(Carboxyl),2.5(DMSO).^{13}CNMR(125MH,δppm):A;70.8,B;72.5,S;38.0(CH_2, aliphatic),F;138.8,G;156.2,D;E;110.1,C;158.4,M;138.8,H;P;116.2,O;127.8,N;118. 7,Q;126.6,R;124.2,V;Z;130.9,U;146.0,W;129.8,X;123,9(Benzene),I;183.8(Carbon

yl),J;120.0 K;160.8(Ethylene),T;178.5(Carboxyl),e;165.4(amide),39-40(DMSO).

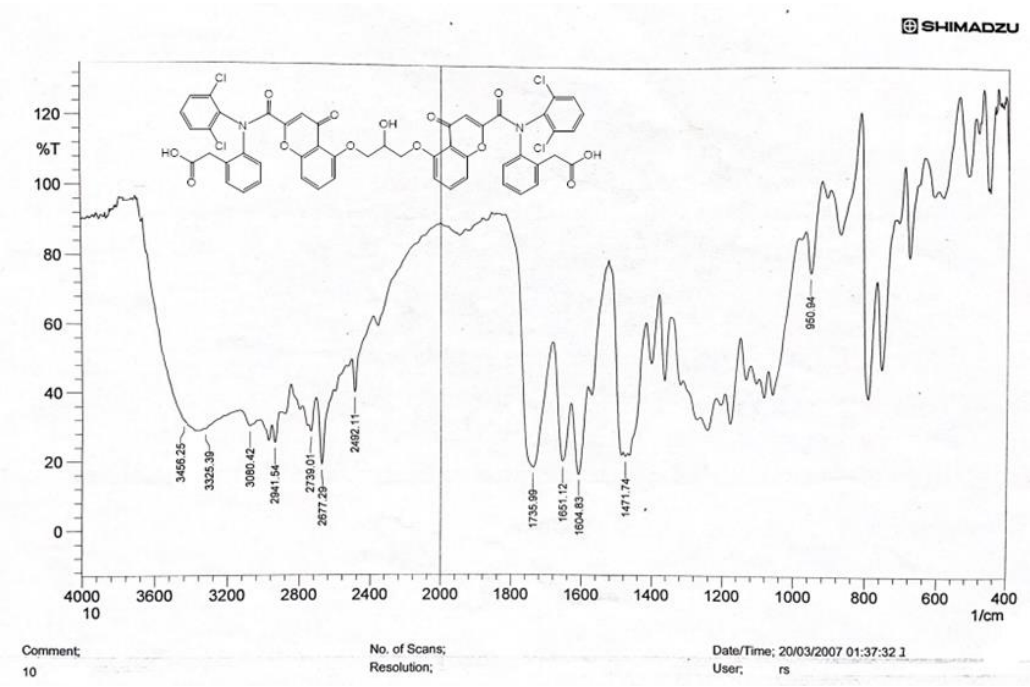


Figure (3-28): FT-IR spectrum for A10

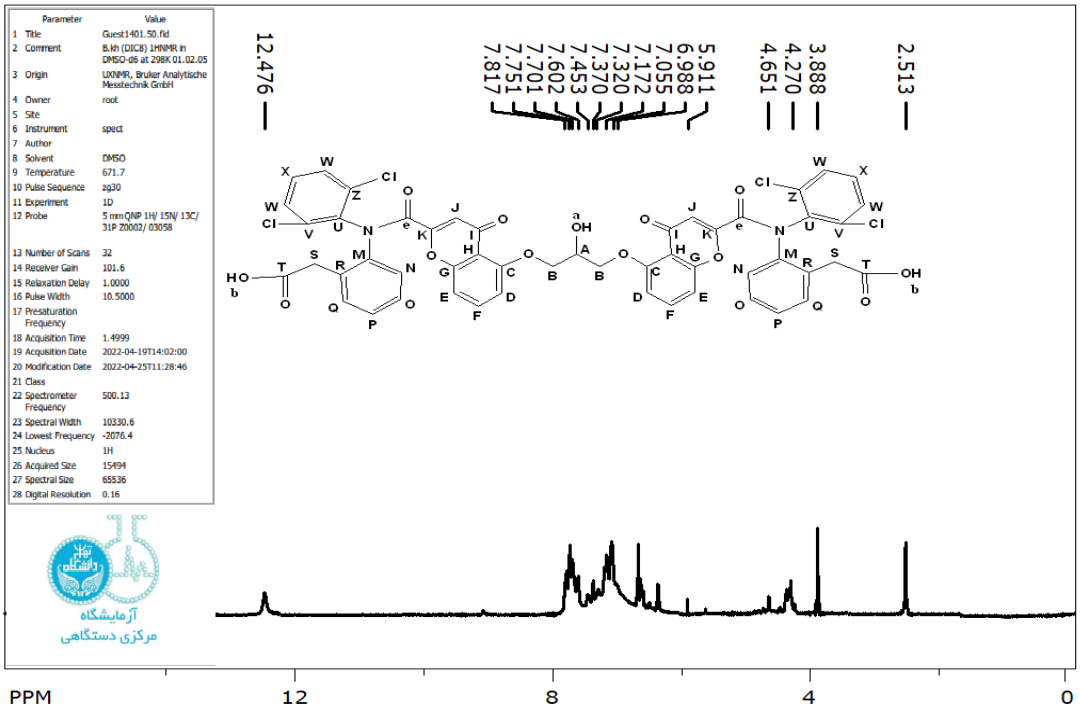


Figure (3-29): ^{1}H-NMR spectrum for A10

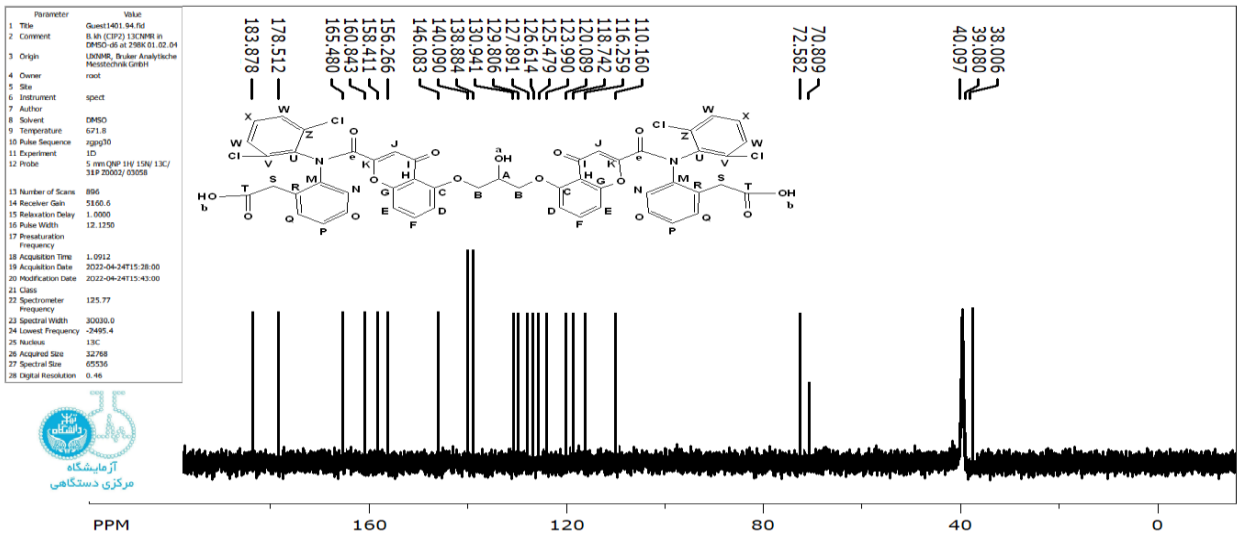
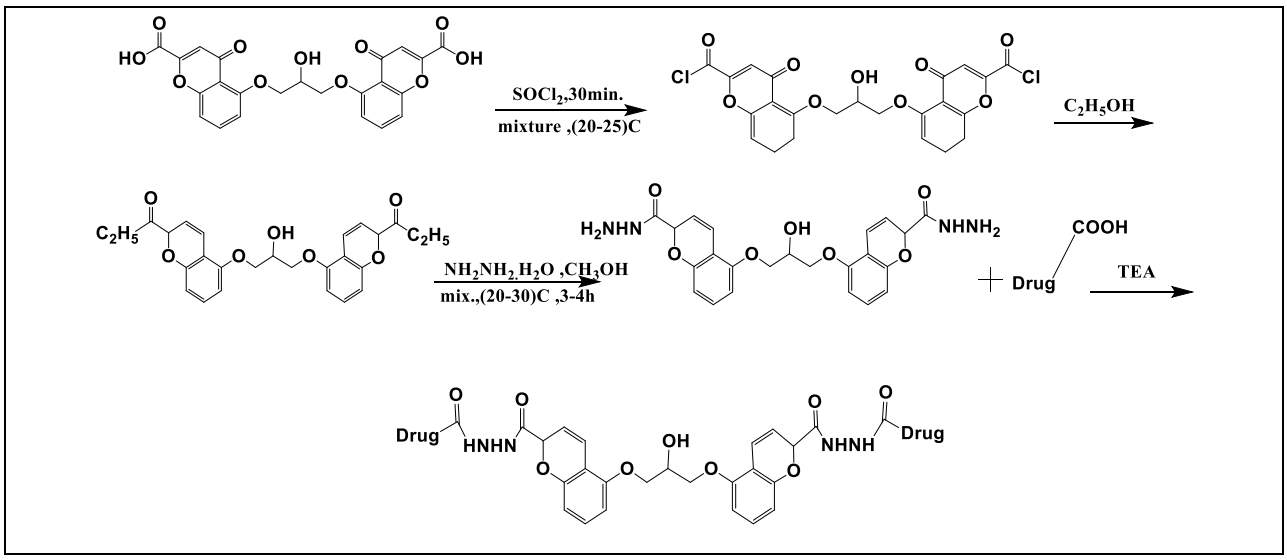


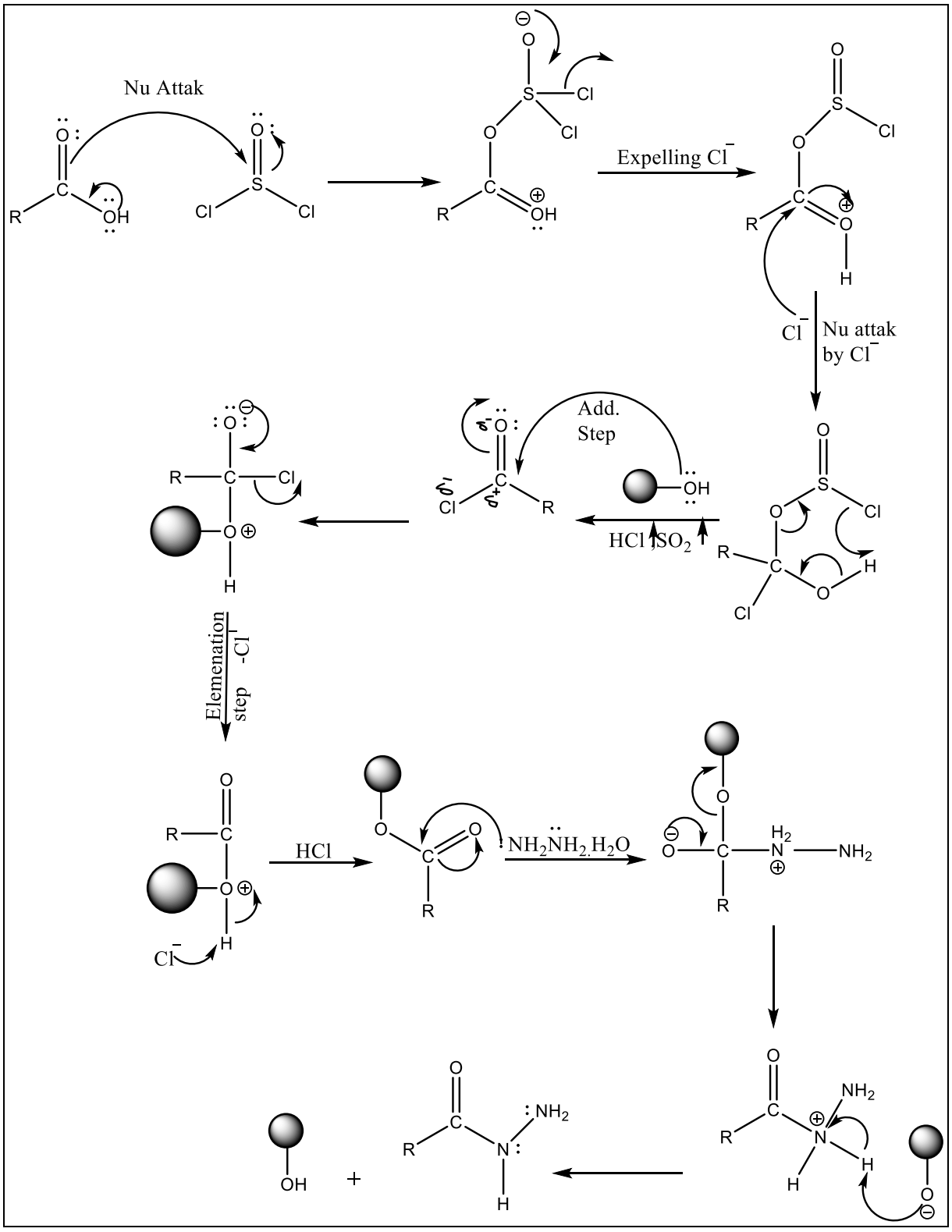
Figure (3-30):^{13}C-NMR spectrum for A10

3-2. Second Line

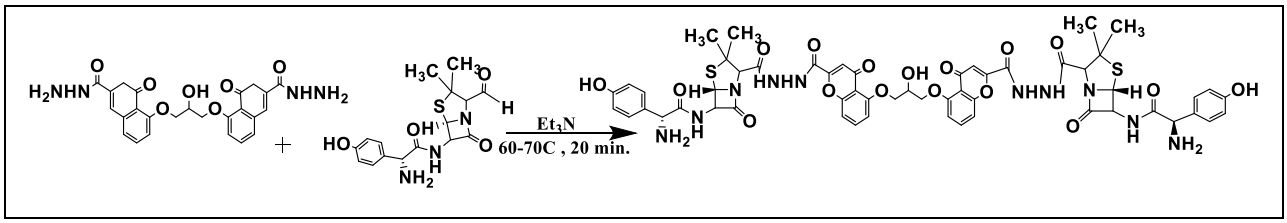
New Carboxylic-containing medications were created via the creation of amide bonds to improve the characteristics of Cromoglicic acid (CGA) and lessen its negative effects. A Cromoglicic acid was reacted with to create the compounds (A11-A17).



Scheme (3-2): A general equation for line two



Scheme (3-4): The mechanism for preparation hydrazide



Equation (3-11): synthesis of A11

FT-IR (V max., cm^{-1}) spectrum of compound (A11) showed the following values:3413(Phenol),3287(NH),2987(CH str.),1696(C=O,Ketone),1651(N-C=O, amid),1597-1518(C=C,Arom.),1267-1201(CN,Aryl).[1] HNMR(500MH,δppm):A; 4.6,B;4.0(CH_2,ethylene),e;d:1.9(CH_3,Methyl),S;H;5.0,(CH,Methyl),X;8.9(NH2,amine),D;6.9,E;7.7,F;7.5,U;7.9,V;6.0(Benzene),J;7.4(H,Ethylene),M;4.8(CH,methane),L;12.5,Y;8.4(Amide),b; 5.2,10.9(Alcohol),2.5(DMSO).[13]CNMR(125MH,δppm): A;67.9,B;72.5,Q;74.9(CH_2,aliphatic),D;110.6,E;140.3,F;108.9,H;117.1,G;160.3,C ;162.6,T;131.9,U;V;120.0,W;158.1(Benzene),I;183.3(Carbonyl),Z;167.7,P;R;178.5 (Amide),K;165.8,J; 129.9(Ethylene),M;90.7,N;62.7,O;70.8,S;59.6(CH,aliphatic) ,e;d 32.0(CH_3,aliphatic),39-40(DMSO) .

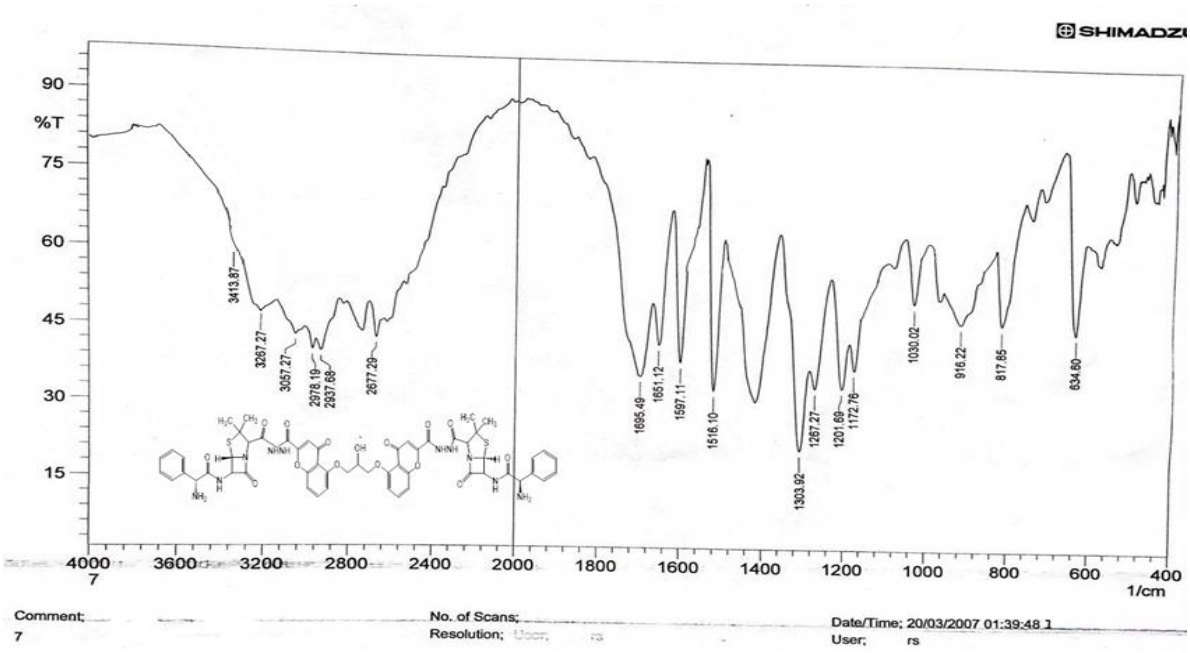


Figure (3-31): FT-IR spectrum for A11

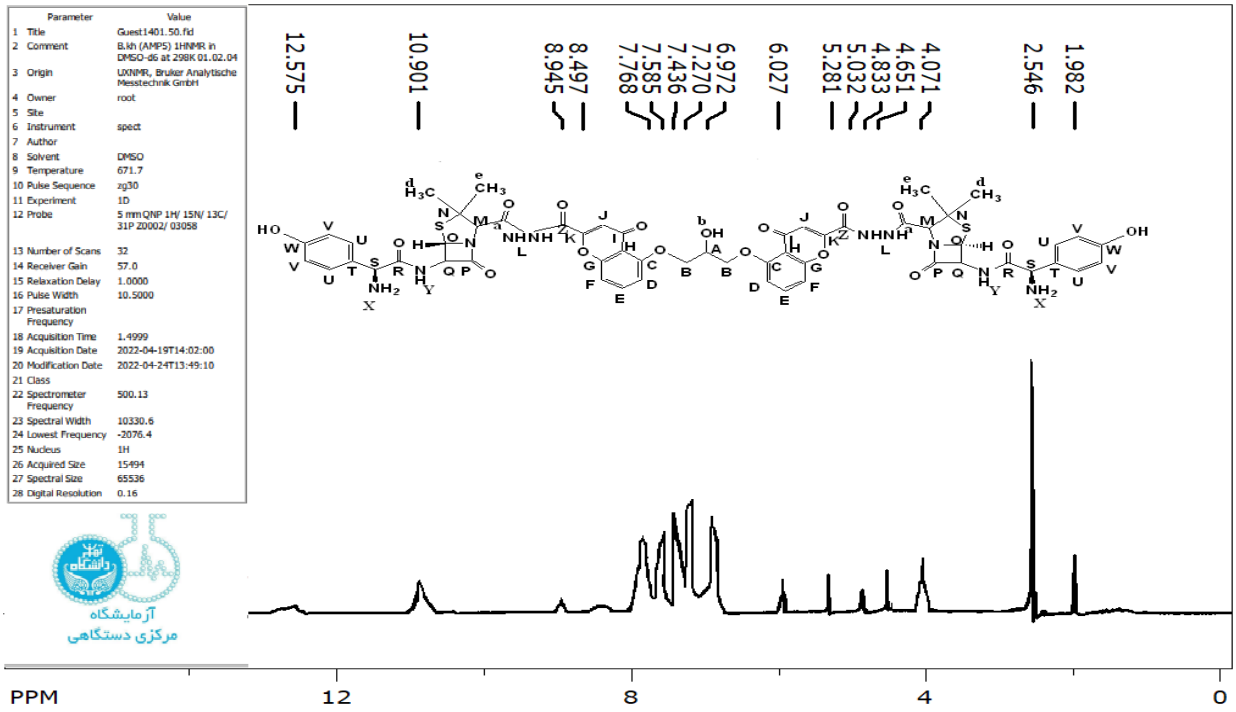


Figure (3-32): ^{1}H-NMR spectrum for A11

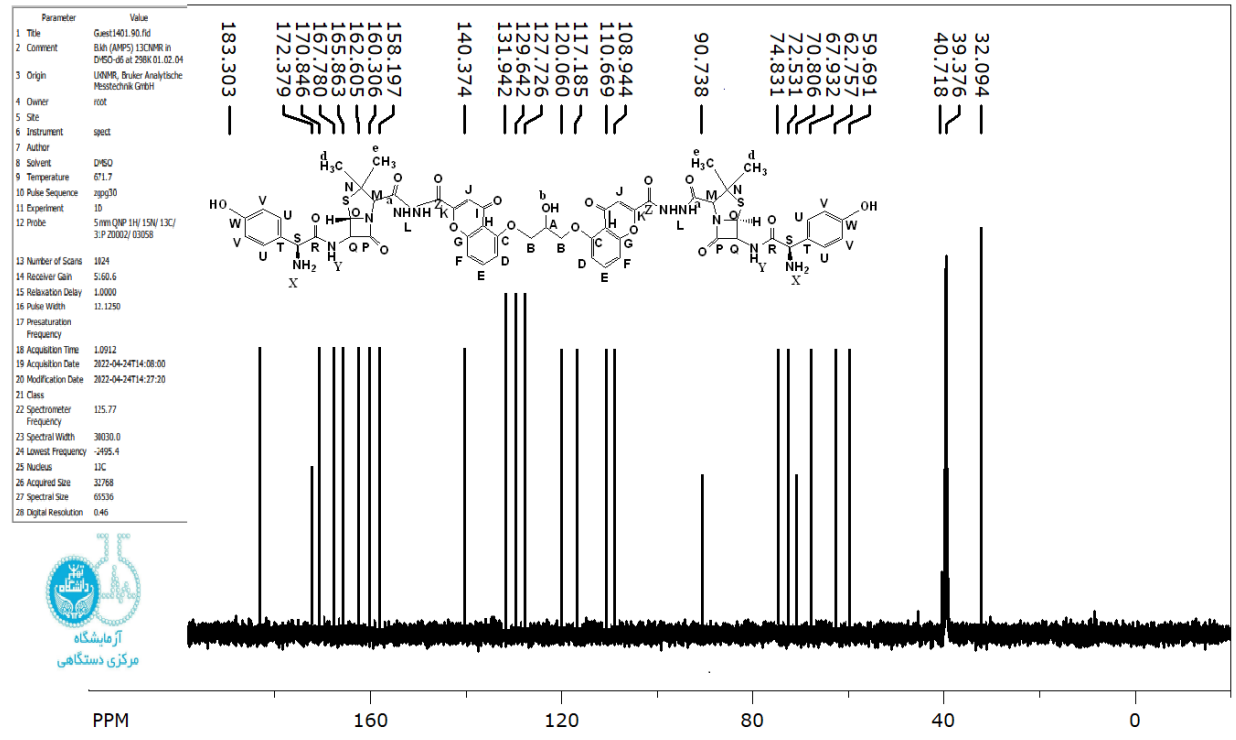
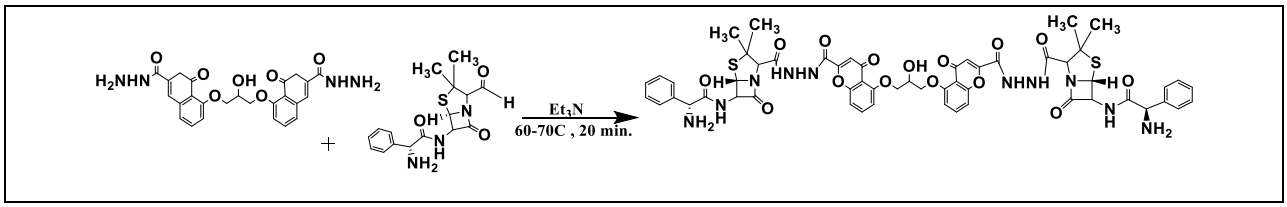


Figure (3-33): ^{13}C-NMR spectrum for A11



Equation (3-12): synthesis of A12

FT-IR(Vmax.,cm^{-1})spectrum of compound(A12)showed the following values:3490(Phenol),3244(NH,amide),2903(CH,str.),1734(C=O,Ketone),1653(N-C=O,amid),1602(C=C,Ar.),1247-1311(C-N,Aryl).^{1}H-NMR(500MH,δppm):A;4.7, B;5.0(CH_2,ethylene),e;d;1.7(CH_3,Methyl),S+H,atom;5.4(CH,Methyl),X;8.2(NH2,amine),D;6.7,E;7.1,F;6.8,U;6.9,W;7.4(Benzene),J;V;7.7(H,Ethylene),M;4.8(CH,methane)L;12.2,Y;8.4(Amide),b;5.7(Alcohol),2.5(DMSO).^{13}CNMR(125MH,δppm):A;62.9,B;71.0,Q;72.1(CH_2,aliphatic),D;110.0,E;140.9,F;108.3,H;116.7,C;159.3,G;156.8,T;130.0,U;V;128.1,W;118.1(Benzene),I;183.8(Carbonyl),Z;165.6,P;R;170.8(Amide),K;164.1,J;118.3(Ethylene),M;88.6,N;72.1,O;74.4,S;59.6,Q;72.9(CH,aliphatic),e;d;32.7(CH_3,aliphatic),39-40 (DMSO).

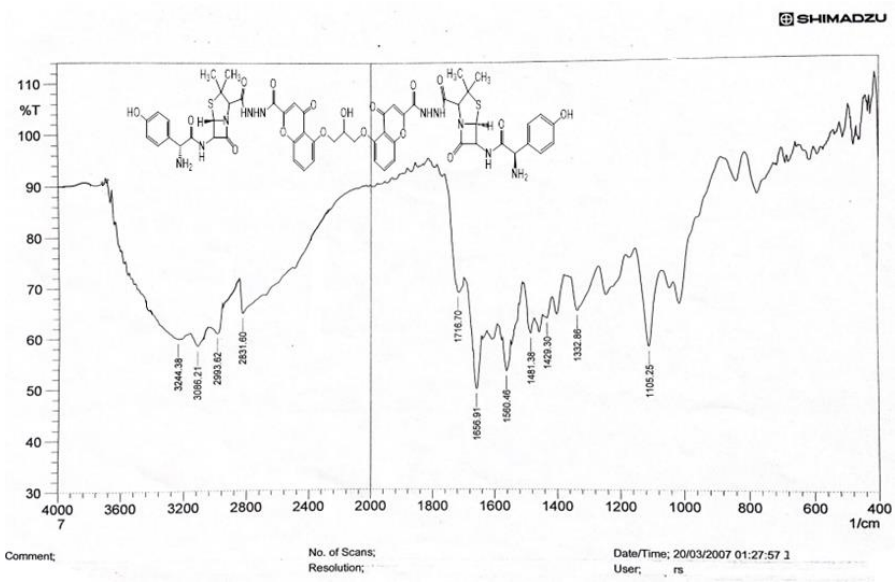


Figure (3-34): FT-IR spectrum for A12

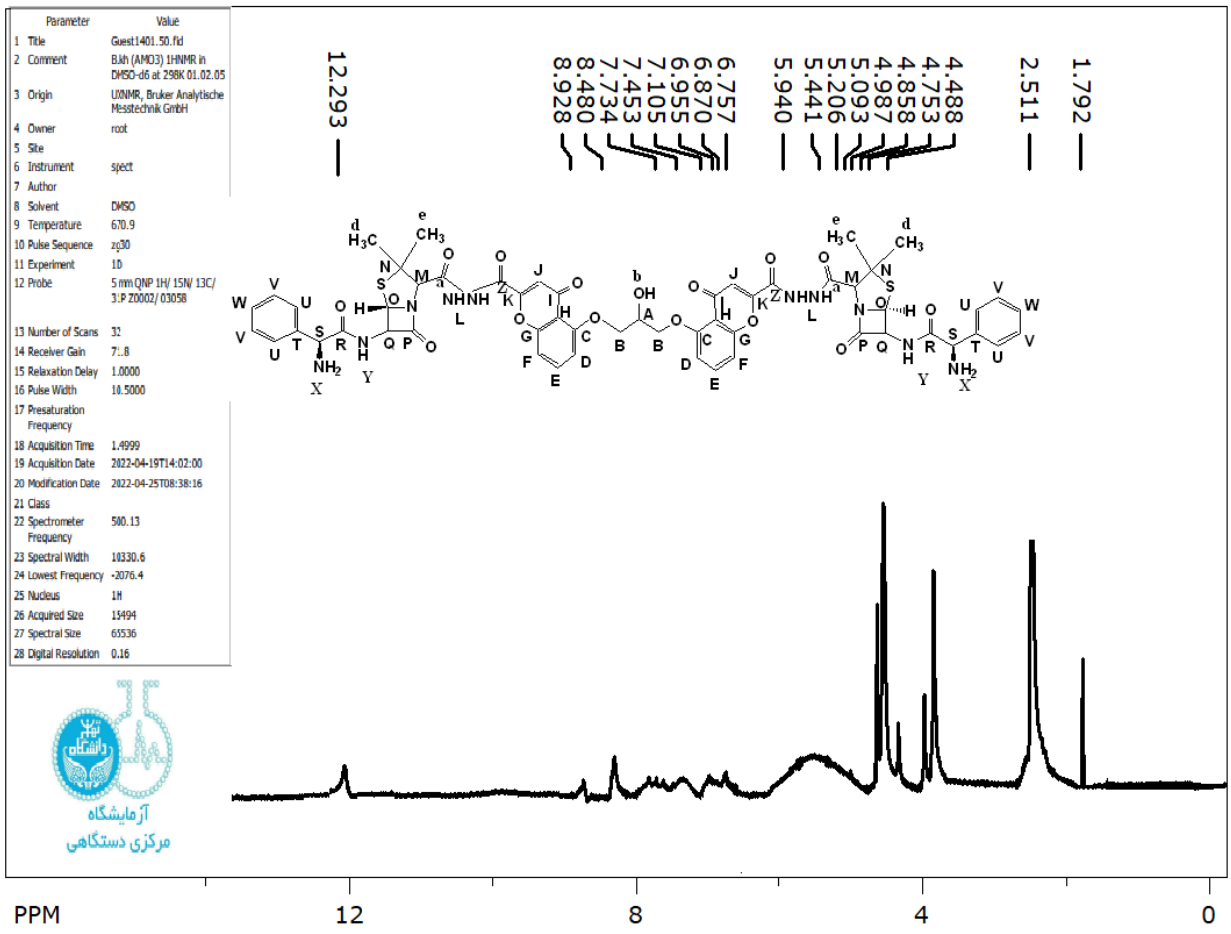


Figure (3-35): ^{1}H-NMR spectrum for A12

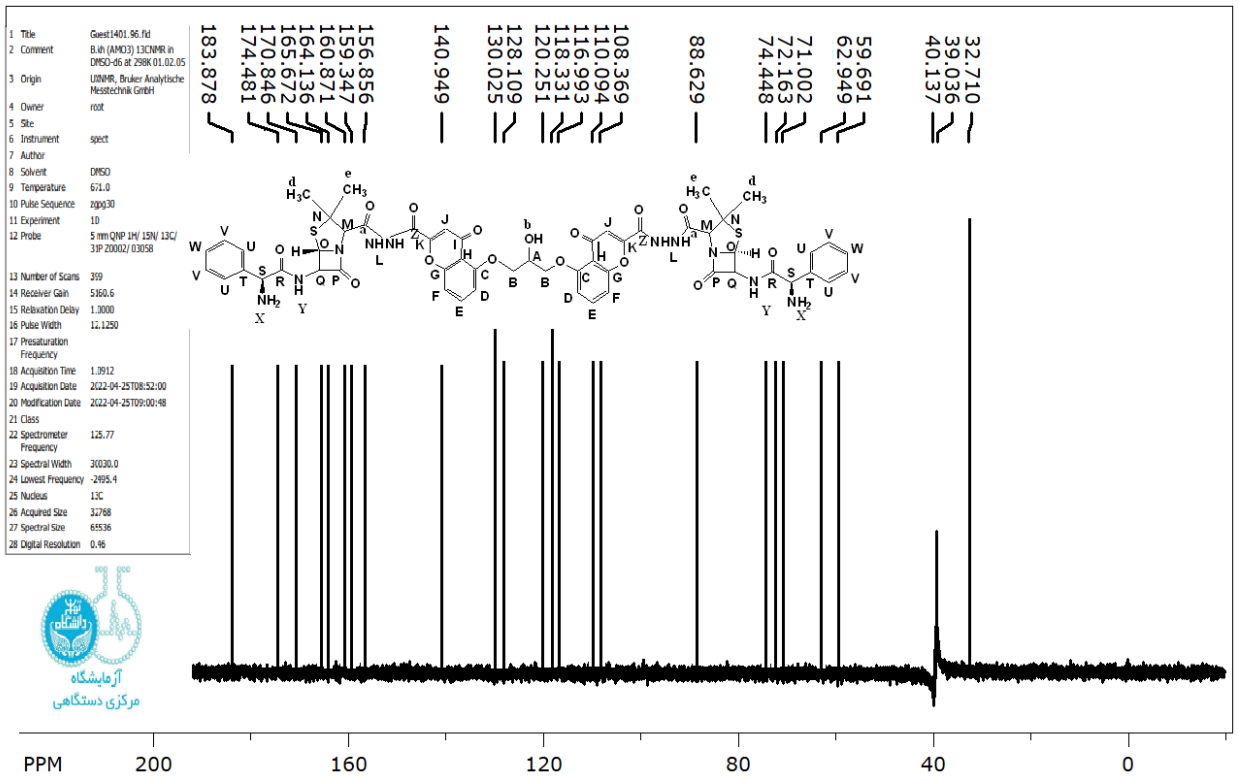
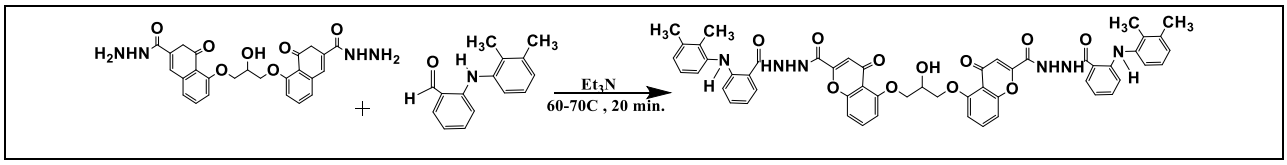


Figure (3-36): ^{13}C-NMR spectrum for A12



Equation (3-13): synthesis of A13

FT-IR (Vmax.,cm^{-1}) spectrum of compound (A13) showed the following values:3425(phenol),3285(NH),2937(CH str.),1734(C=O Ketone),1653(C=O,amid),1602(C=C,Ar),1247-1311(C-N,Aryl).^{1} HNMR (500MH,δppm): A;4.5,B;5.0(CH_2, ethylene),a;b;2.3(CH_3, Methyl),D;6.1,E;7.7,F;7.5,P;M;7.9;N;6.9,O;7.8,S;T;7.3,U;6 .8 (Benzene),J;7.6(H,Ethylene),Y;10.8,NH;8.0(Amide),e;5.9(Alcohol),2.5(DMSO) .^{13} CNMR(125MH,δppm):A;70.2,B;72.4(CH_2,aliphatic),D;110.0,E;137.3,F;108.6 ,H;115.8,C;160.3,G;158.7,L;127.1,M;128.4,O;133.2,P;U;119.8,R;139.7,Q;140.9,S;

127.1,T;122.7,V;130.6,W;135.5(Benzene),I;185.2(Carbonyl),X;Z;165.6(Amide),K ;163.7,J;N;120.4(Ethylene),a;21.0,b;19.0(CH_3,aliphatic),39-40(DMSO).

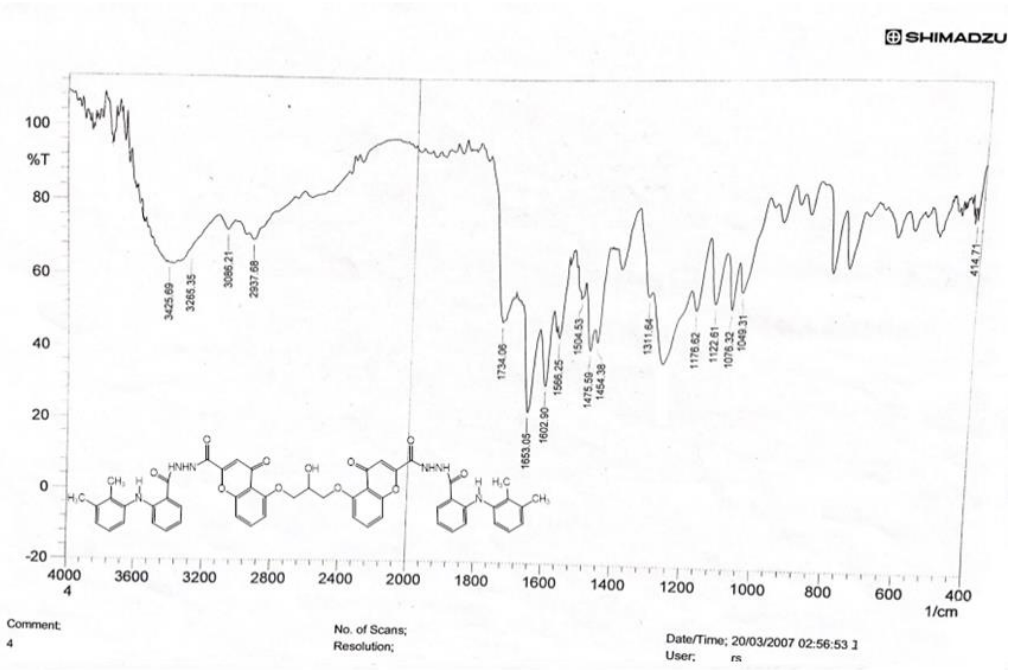


Figure (3-37): FT-IR spectrum for A13

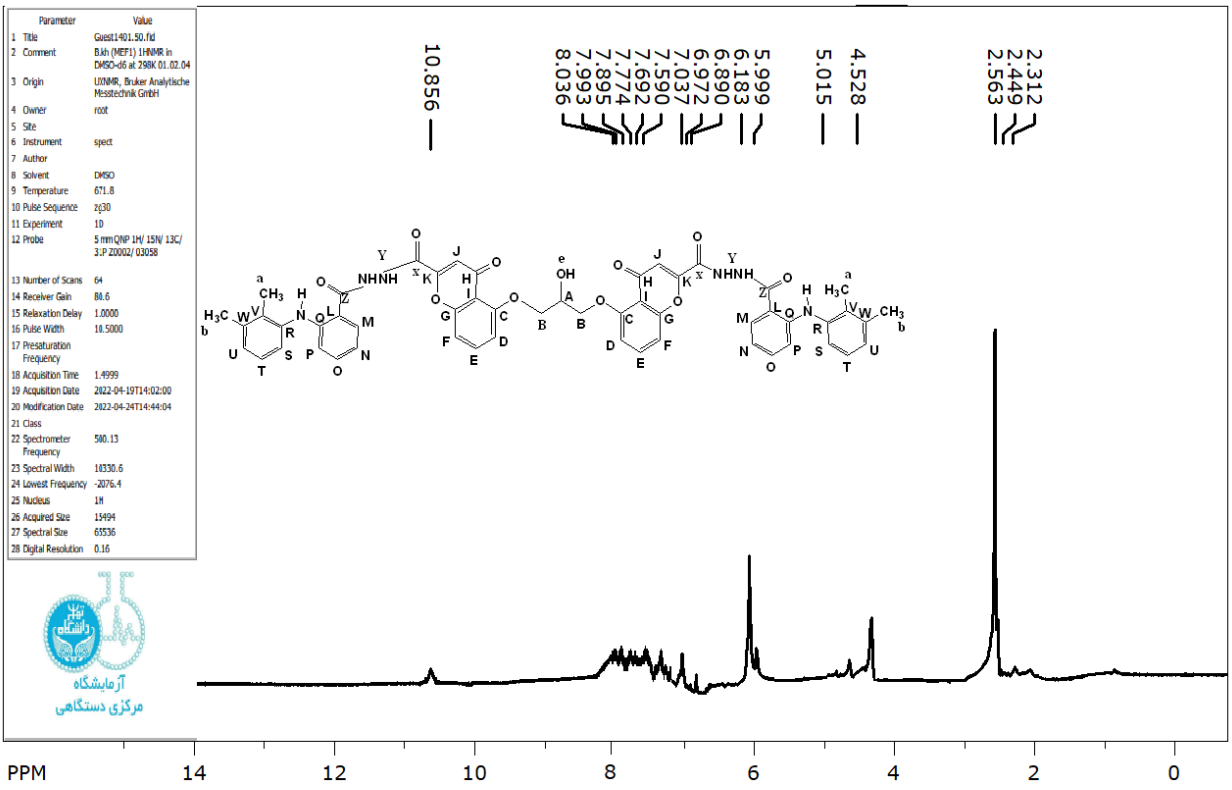


Figure (3-38): ^{1}H-NMR spectrum for A13

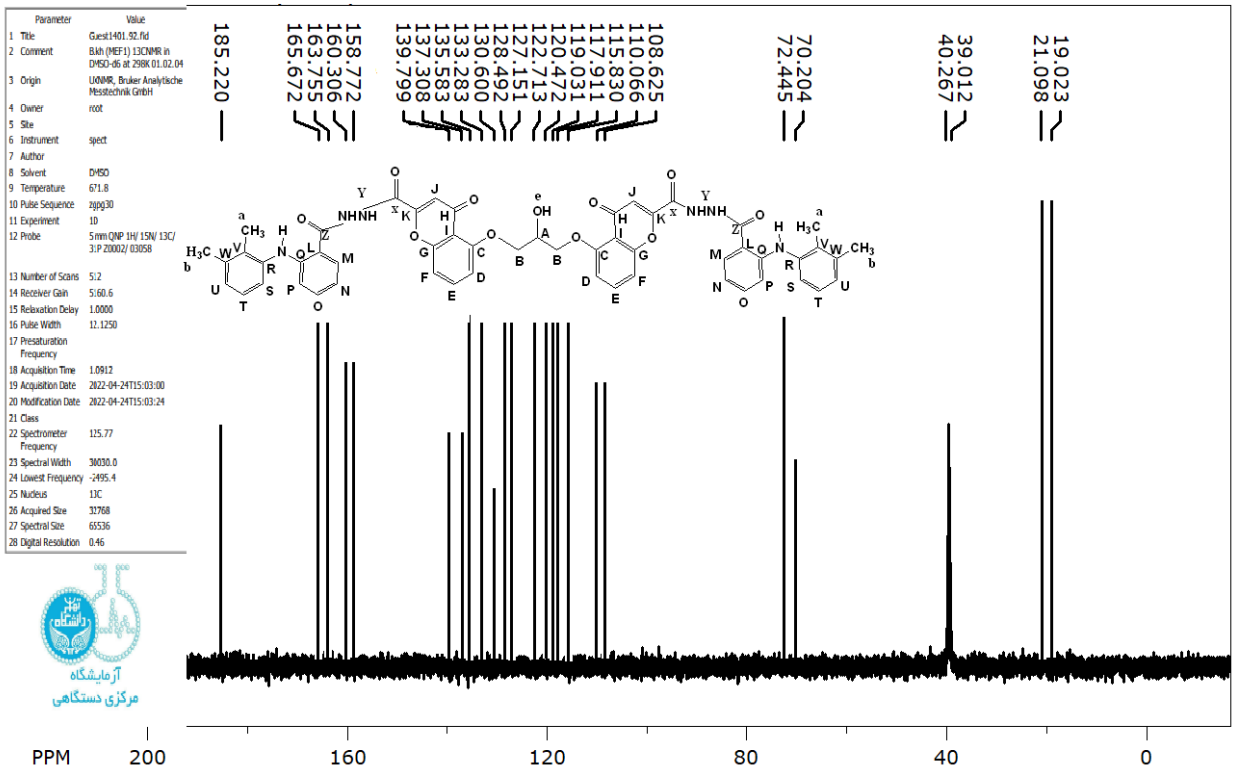
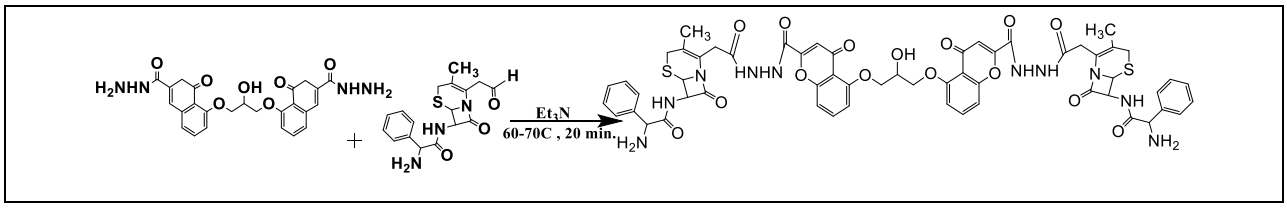


Figure (3-39): ^{13}C-NMR spectrum for A13



Equation (3-14): synthesis of A14

FT-IR(Vmax.,cm^{-1})spectrum of compound(A14)showed the following values:3342(Phenol),3272(NH_2),3200(NH),2943(CH,str.),1739(C=O,Ketone),1653 (N-C=O,amid),1590(C=C,Arom.),1236(C-N,Aryl).^{1}HNMR(500MH,δppm):A;4.1, B;4.8,O;3.5,L;3.1(CH_2,methylene),D;6.0,E;7.9,F;7.0,W;7.7,X;7.5(Benzene),J;f;7.3 (H,Ethylene),b;9.9(Amide),f;2.1(CH_3)Y;5.6(Alcohol),P;5.0,R;5.6(CH,Propilactam) ,T;5.3(CH,methane),Z;8.7,a;8.0(NH_2,amine),2.5(DMSO).^{13}CNMR(125MH,δppm): B;72.0,A;70.1,L;39.0,O;31.9(CH_2,aliphatic),D;110.9,E;139.2,F;105.1,H;116.5,C;1 57.8,G;155.8,d;166.4,U;135.3,V;130.2,W;128.3,X;129.0,M;127.1(Benzene),I;184. 4(Carbonyl),Q;162.9,e;S;170.0174.8(Amide),K;160.1,J;119.9,N;107.9(Ethylene), f;19.5(CH_3,aliphatic),R;62.6,T;59.4P;65.6(CH,aliphatic),39-40(DMSO).

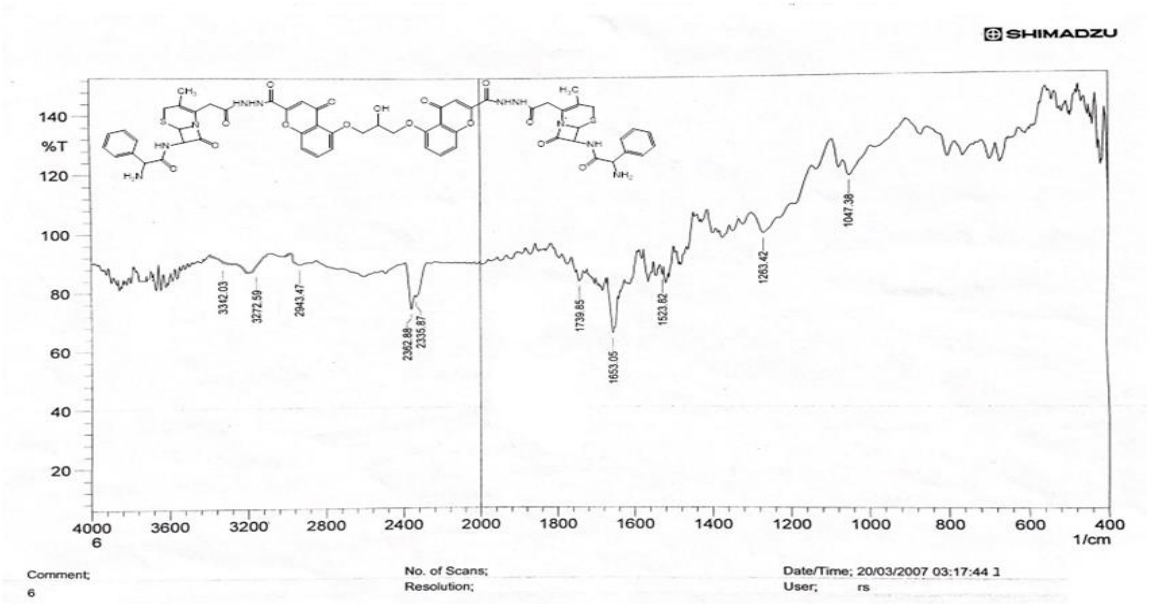


Figure (3-40): FT-IR spectrum for A14

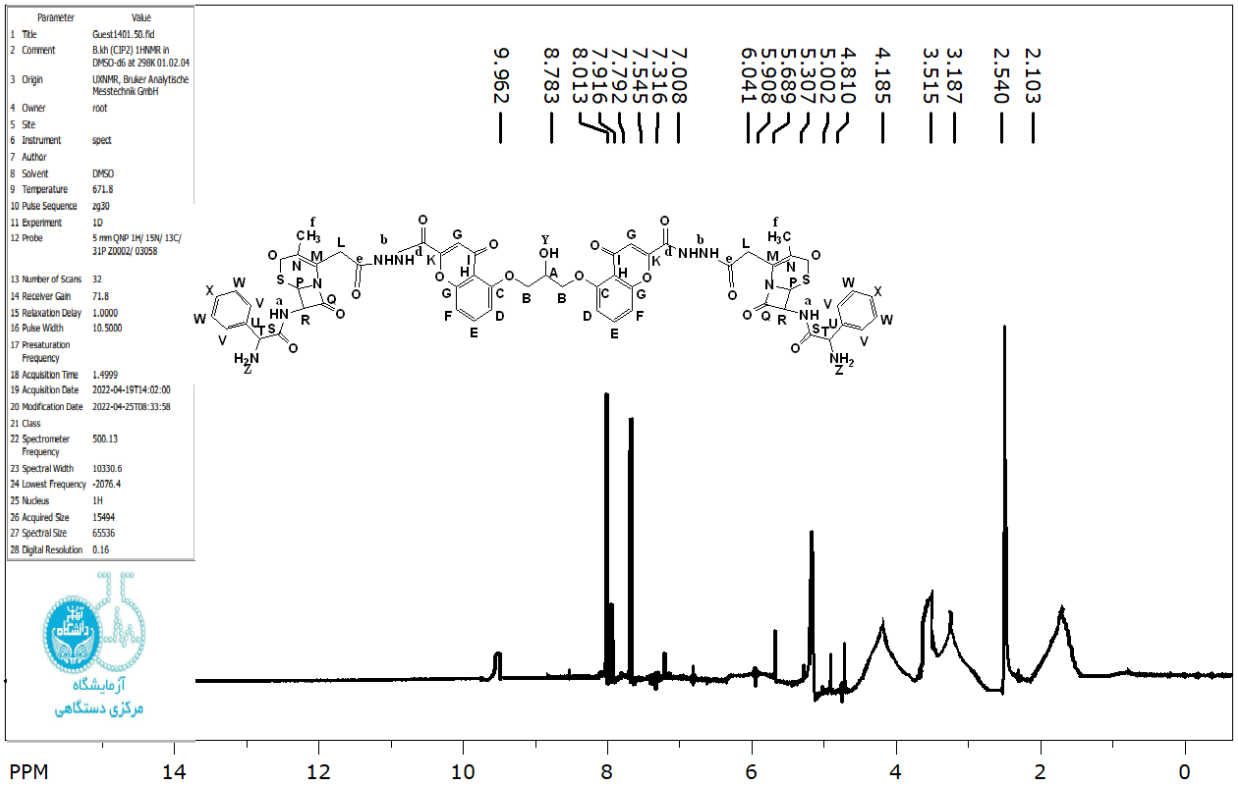


Figure (3-41): ^{1}H-NMR spectrum for A14

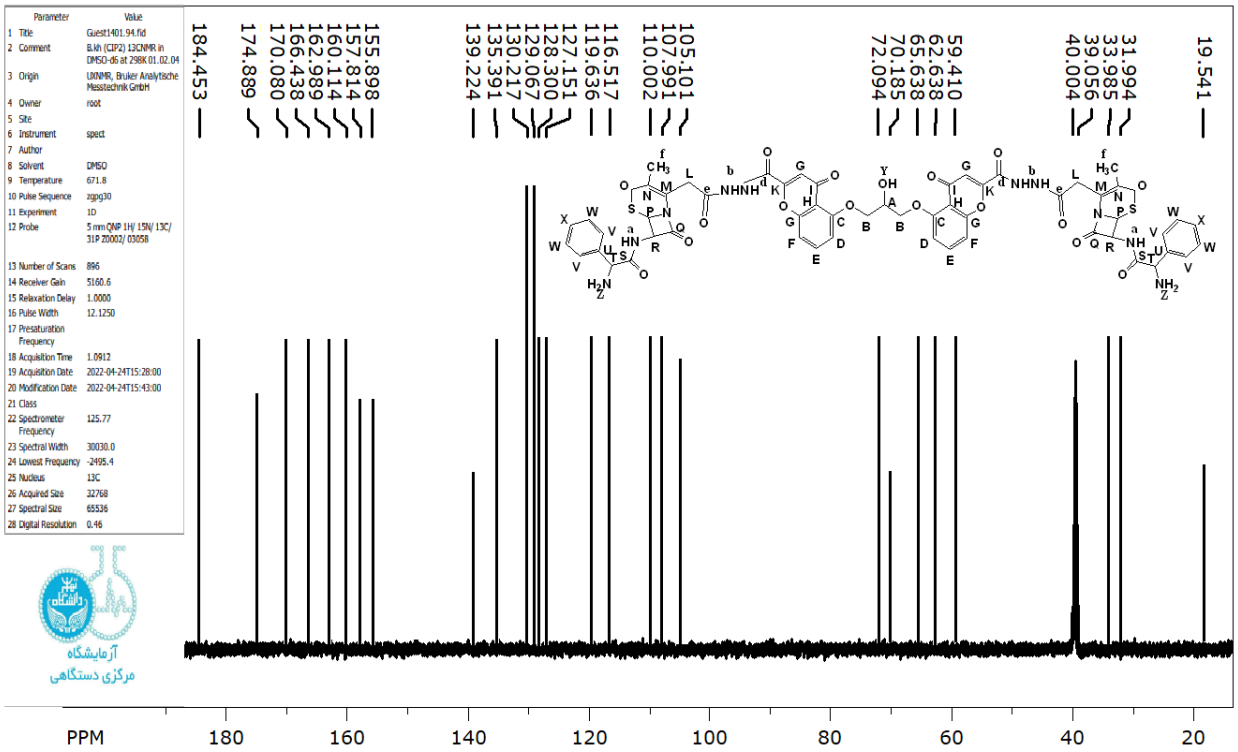
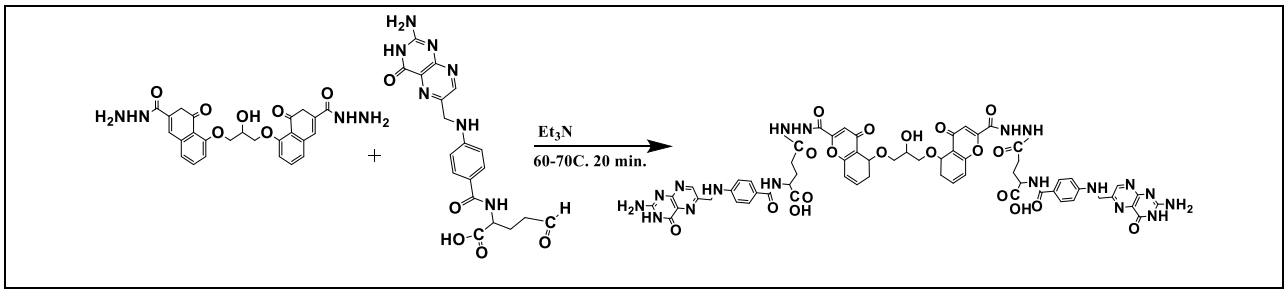


Figure (3-42): ^{13}C-NMR spectrum for A14



Equation (3-15): synthesis of A15

FT-IR(Vmax.,cm^{-1})spectrum of compound(A15)showed the following values:2362-3462(NH,NH_2amine,OHCarb.acid,Phenol Overlap),2985(CH,str.), 1739(C=O,Ketone),1689(NC=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;6.5,E;7.6,F;7.0,R;7.9, S;6.8(Benzene),J;7.3(H,Ethylene),b;11.0,f;g;9.5,h;6.1(Amide),m;5.2(Alcohol),O;4. 6,V;4.5(CH_2,methylene),12.9(Carboxyl),b;11.0,r;6.3(NH,Quinidine),2.5(DMSO).^{13} CNMR(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;151.1,Q;124.0,R;133.8,S;114.1(Be nzene),I;187.9(Carbonyl),P;173.7(Carboxyl),L;175.4,e;165,2,a;155.8,i;170.2(Amid e),K;163.9,J;120.0(Ethylene),O;59.8(CH,aliphatic),d;153.5(Imine),X;W;150.1,Y;1 48.4,Z;130.0(CH,Pyrazine),39-40(DMSO).

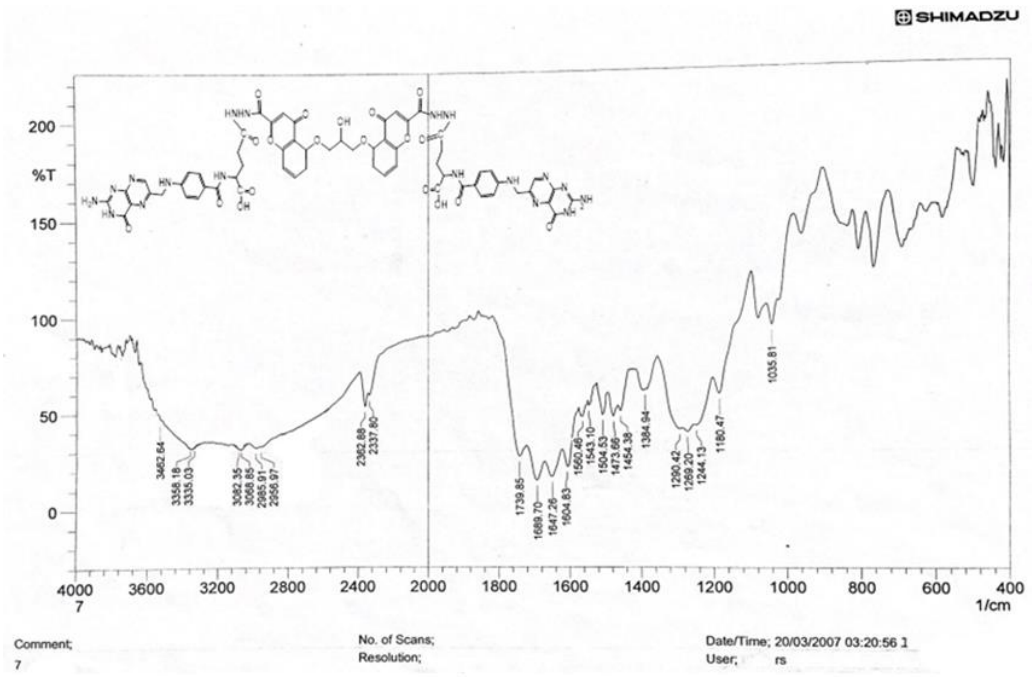


Figure (3-43): FT-IR spectrum for A15

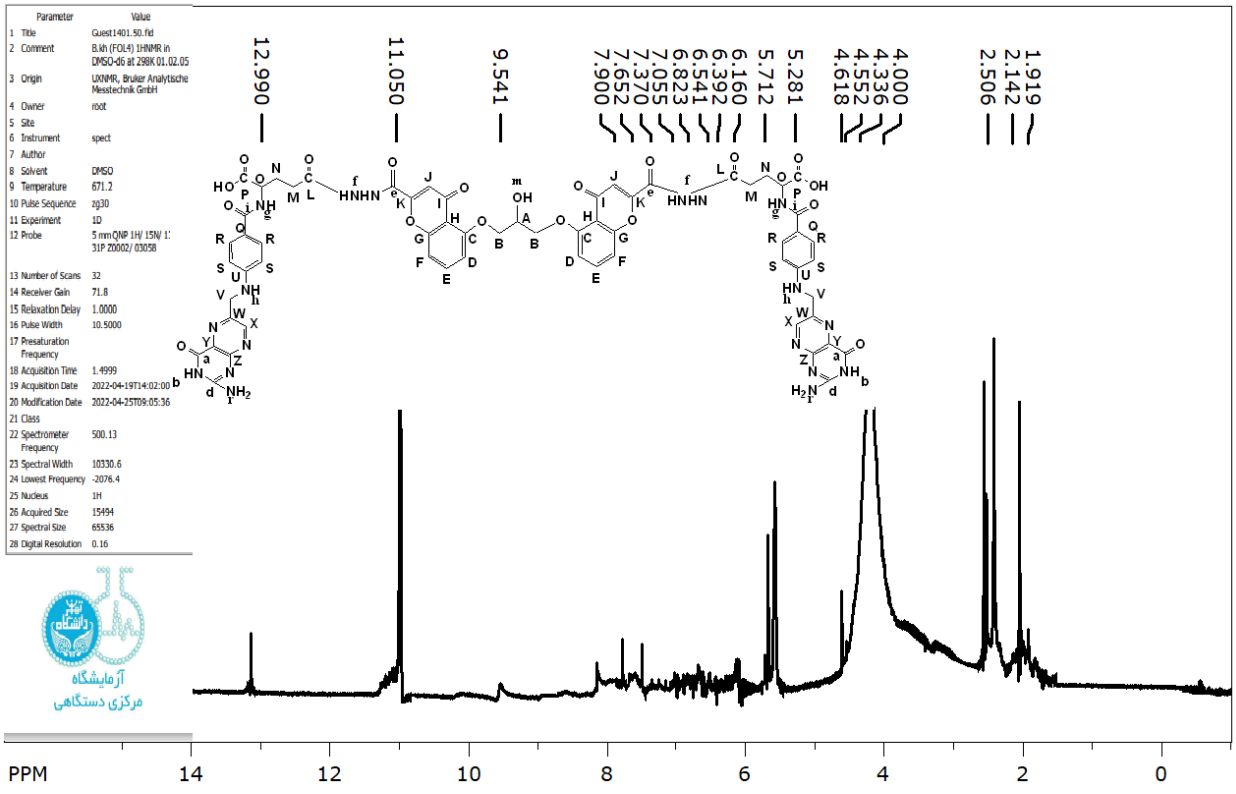


Figure (3-44): ^{1}H-NMR spectrum for A15

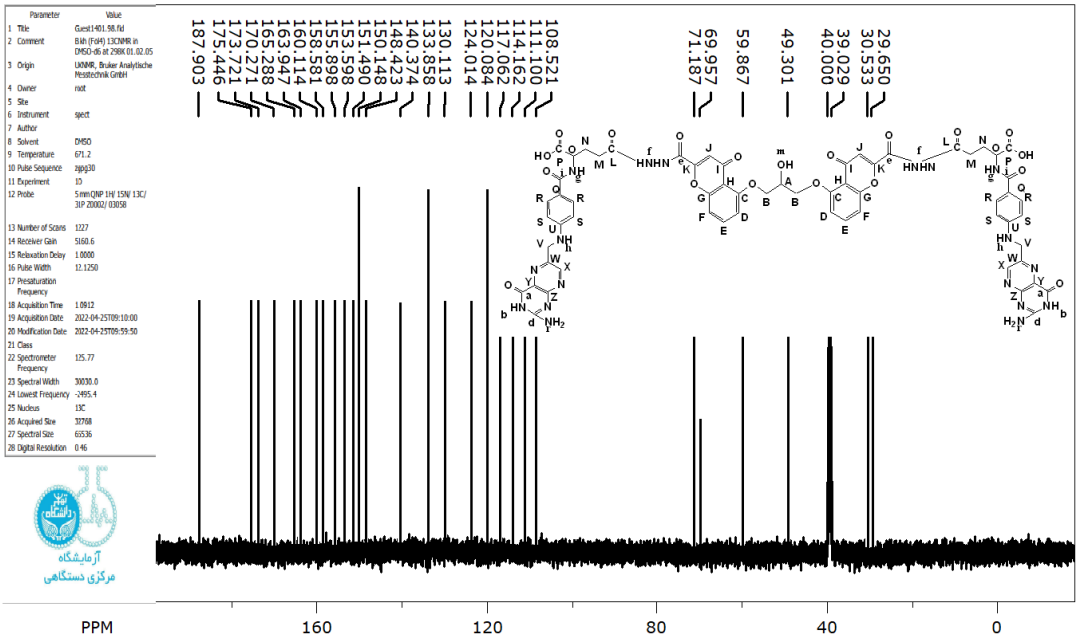
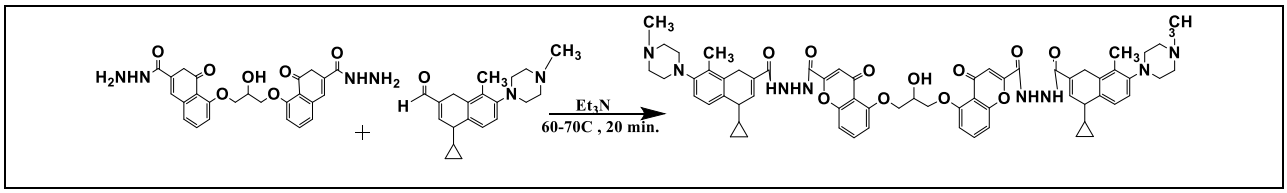


Figure (3-45): ^{13}C-NMR spectrum for A15



Equation (3-16): synthesis of A16

FT-IR(Vmax.,cm^{-1})spectrum of compound(A16)showed the following values:3400(Phenol),3271(NH),2980(CH,str.),1718(C=O,Ketone),1629(NC=O,amid),1477(C=CArom.),1396(CN,Aryl).^{1}HNMR(500MH,δppm):h;2.2,f;2.1(CH_3),R;1.2,S;T;0.4(CH,cycloprop.),a;e;3.6,A;4.6,B;4.3,O;3.4,b;g,3.2(CH_2),m;4.9(OH),L;12.2,11.4(amid),C;6.8,Q;D;7.5,W;7.1,E;7.23(CH,Benzene),2.5(DMSO),J;7.27,X;6.9(ethylene).^{13}CNMR(125MH,δppm):O;31.1,Q;e;a;52.3,b;g;57.3(CH,Aliphatic),A;69.0,B;70.1(CH_2,Aliphatic),I;182.1(C=O,Carbonyl),M;r;165.2(C=O,amide),K;163.8,J;118.8,P;144.3(Ethylene),F;156.6,G;158.7,Y;144.4,H;115.6,U;131.3,V;127.6,C;109.1,Z;120.5X;117.2,W;120.0,F;107.7,D;137.3(benzene),h;46.6,f;14.0(CH_3,Aliphatic),R;16.3(CH,cyclopropane),S;T;3.8(CH2,cyclopropane),39-40(DMSO).

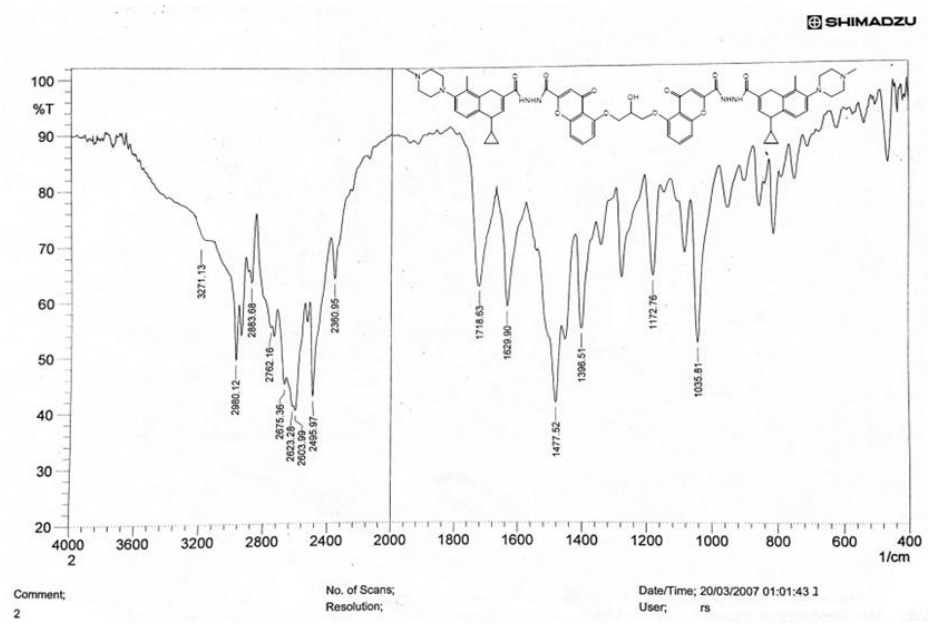


Figure (3-46): FT-IR spectrum for A16

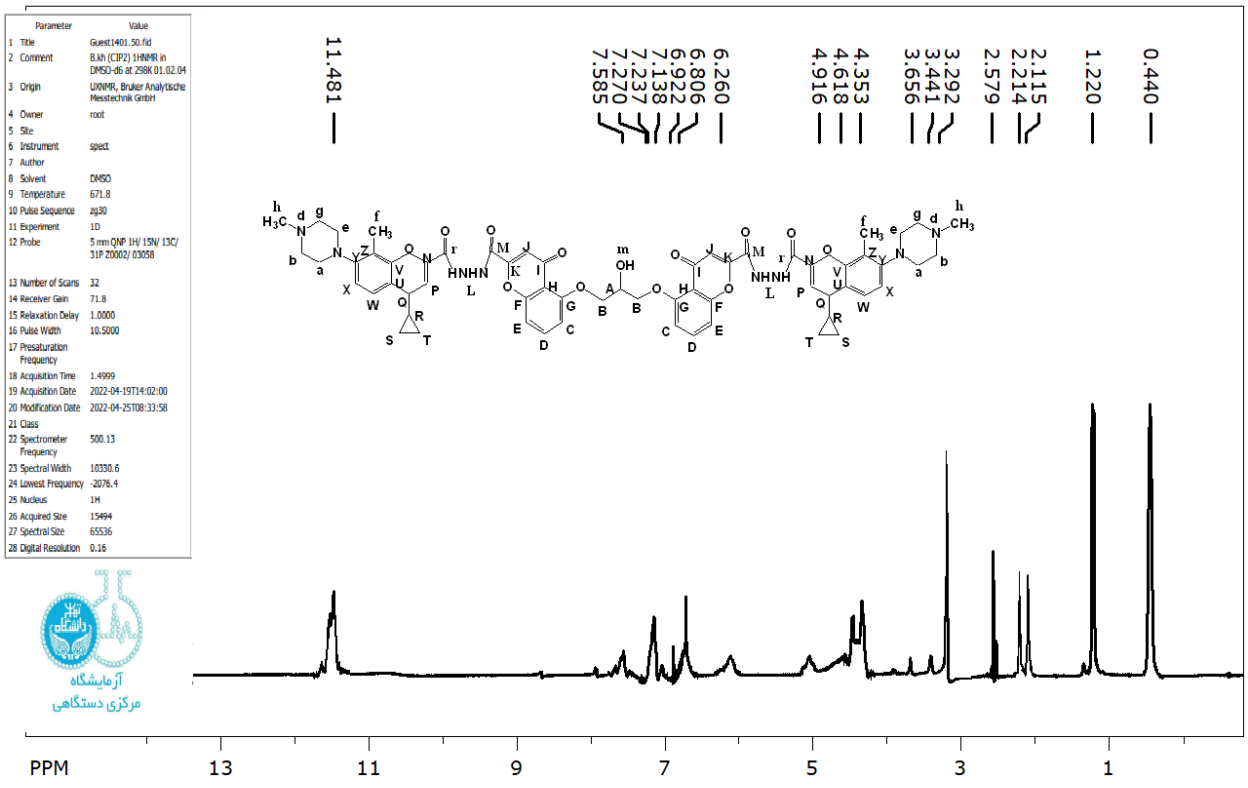


Figure (3-47): ^{1}H-NMR spectrum for A16

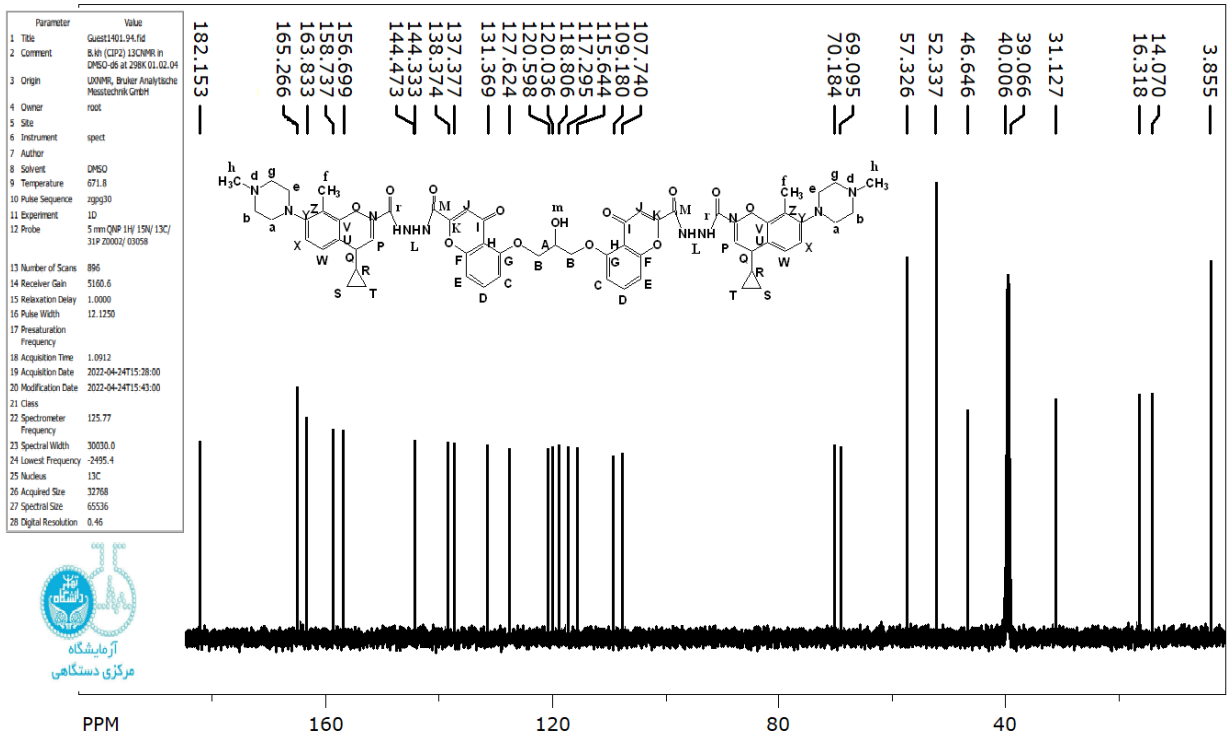
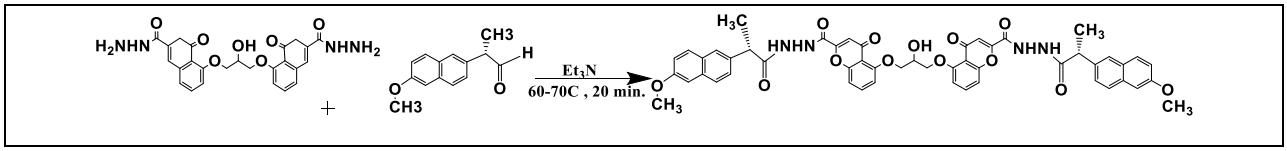


Figure (3-48): ^{13}C-NMR spectrum for A16



Equation (3-17): synthesis of A17

FT-IR(Vmax.,cm^{-1})spectrum of compound(A17)showed the following values:3410(Phenol),3244(NH),2993(CH,str.),1716(C=O,Ketone),1656(C=O,amid),1560(C=CAr.),1332(CN,Aryl).^{1}HNMR(500MH,δppm):A;4.8,B;5.6(CH_2,methylene),D;6.4,F;7.4,E;7.66,W;6.9(Benzene),J;7.3(H,Ethylene),b;10.9(Amide),e;5.9(Alcohol),b;1.5,N;4.0(CH_3,methyl),Z;4.5(CH,methane),Q;7.6,R;7.9,S;7.5,V;7.8,X;6.5(CH,Naphthalene),2.5(DMSO).^{13}CNMR(125MH,δppm):A;69.8,B;72.3(CH_2,aliphatic),D;109.5,E;138.2,F;107.7,X;H;114.8,C;157.4,G;155.1,P;135.9,Q;127.9,R;121.7,S;125.8,U;h;132.9,V;129.8,Y;150.3(Benzene),I;175.6(Carbonyl),M;169.6,a;159.3(

Amide),K;159.3,J;120.0(Ethylene),b;16.1(CH_3,aliphatic),N;46.6(CH,aliphatic),39-40(DMSO).

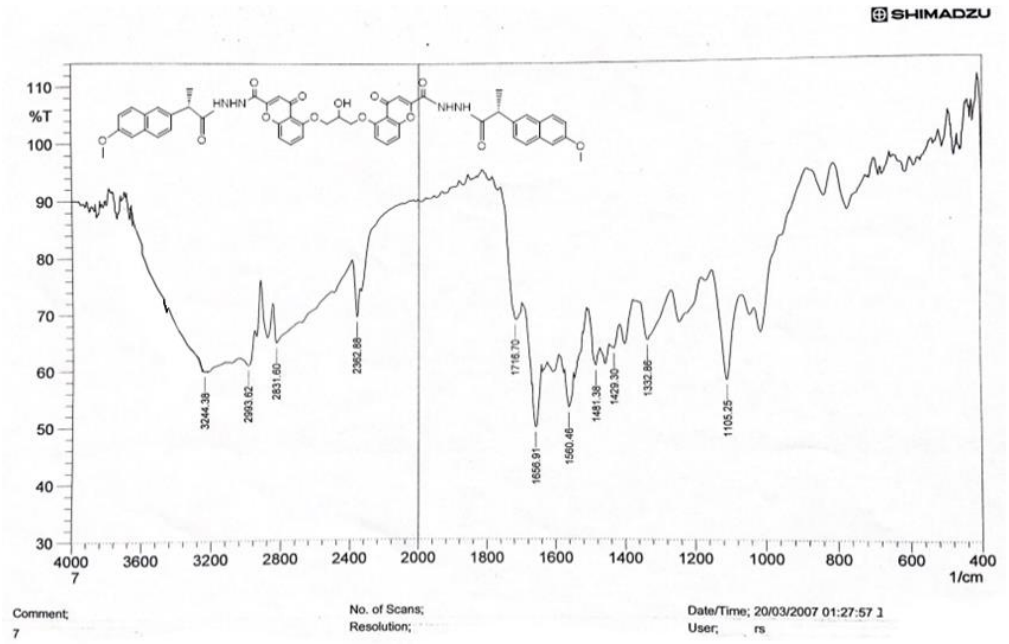


Figure (3-49): FT-IR spectrum for A17

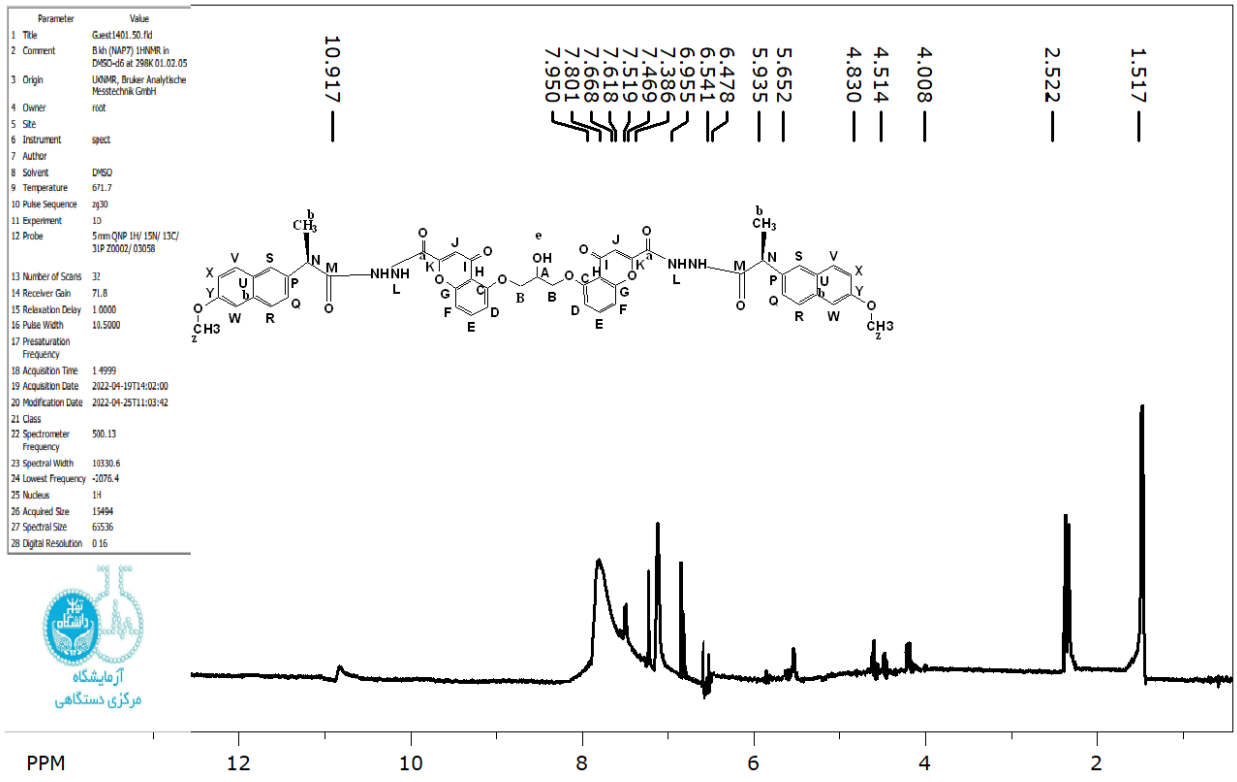


Figure (3-50): ^{1}H-NMR spectrum for A17

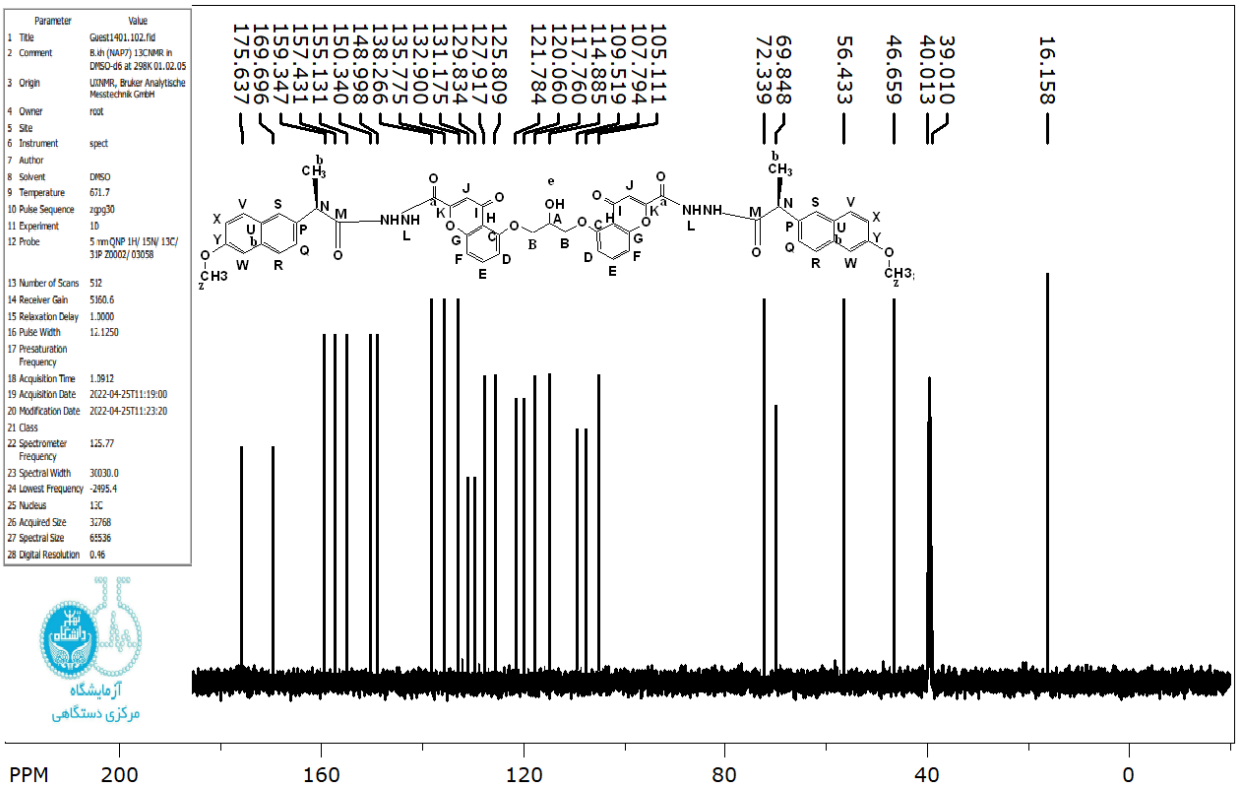
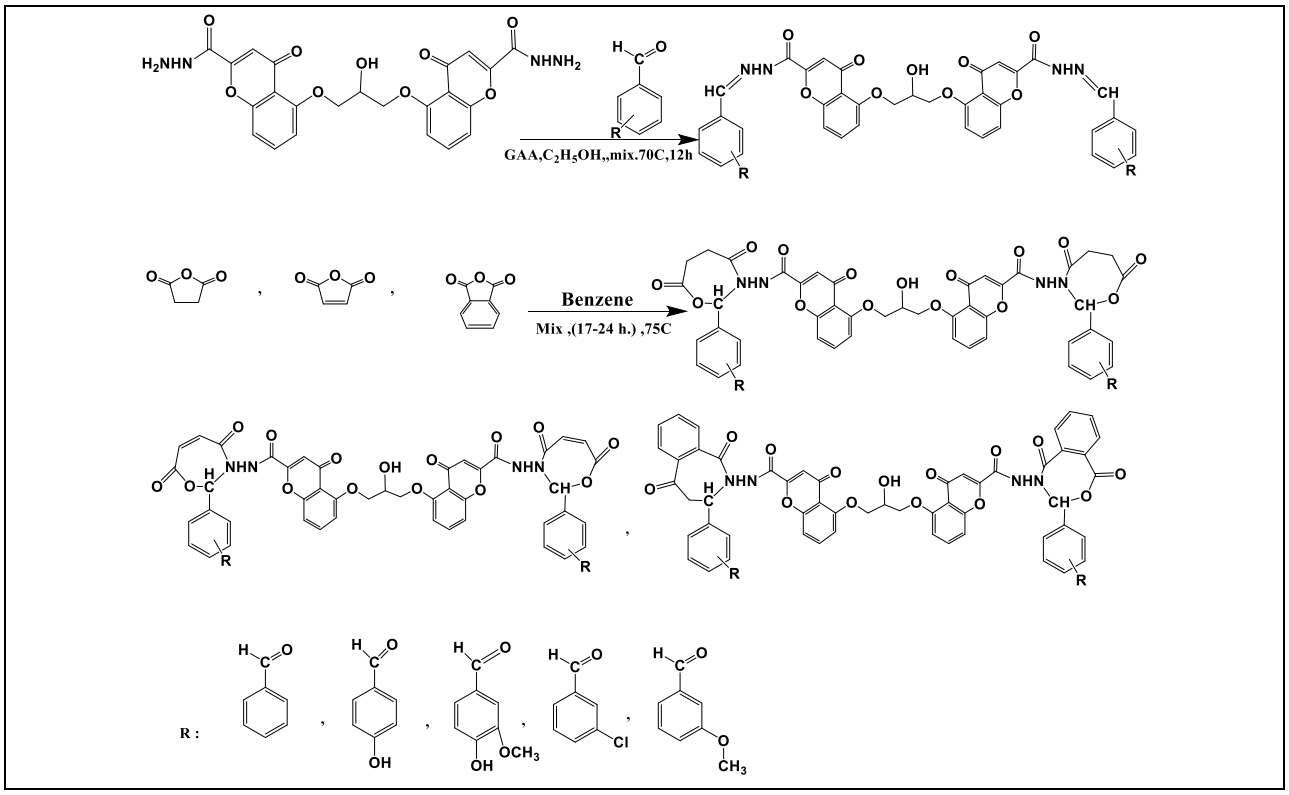


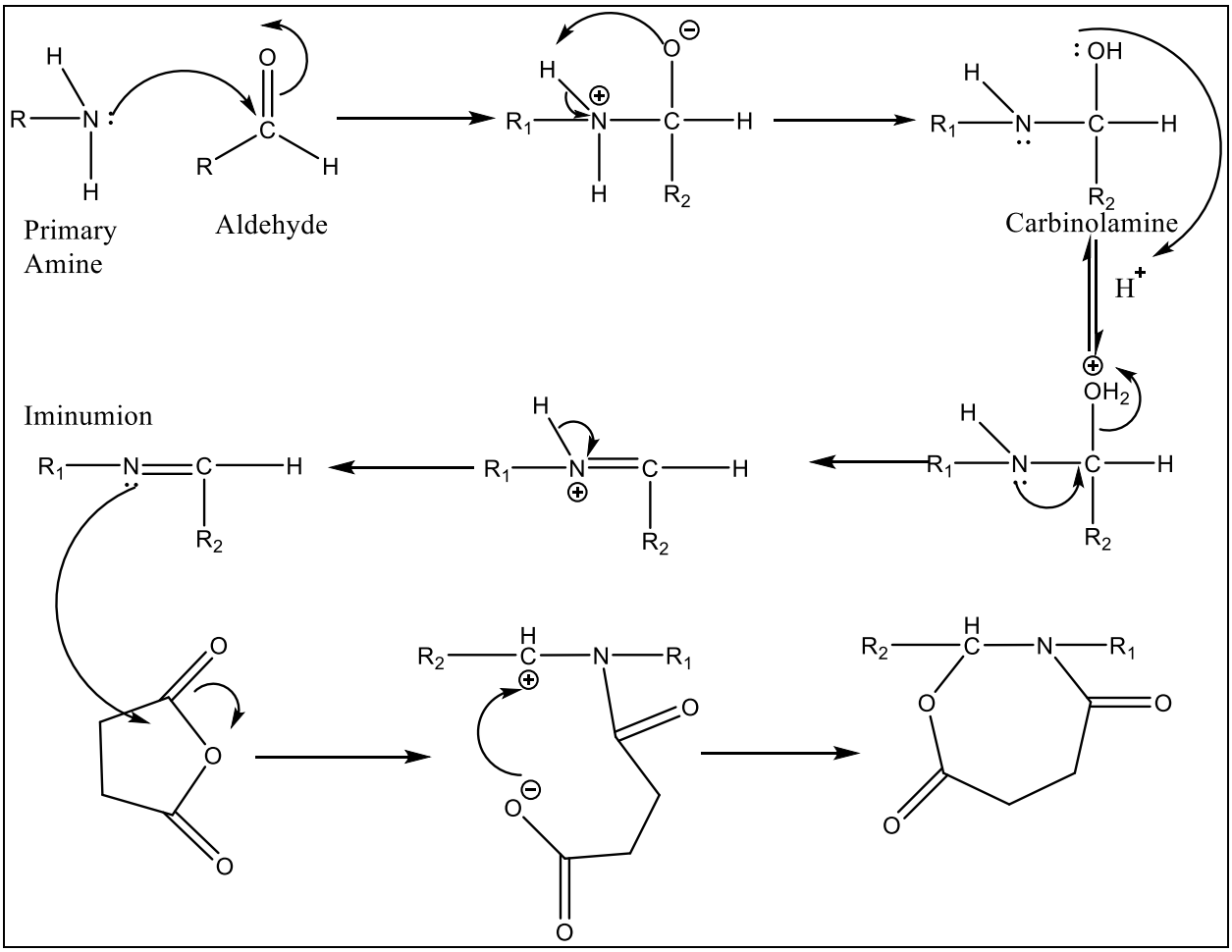
Figure (3-51): ^{13}C-NMR spectrum for A17

3-3. Third line

New ozaxipen were created through the creation of amide bonds to improve the characteristics of cromoglicic acid (CGA) and lessen its adverse effects. A Cromoglicic acid was reacted with to create the compounds (A18-A29).

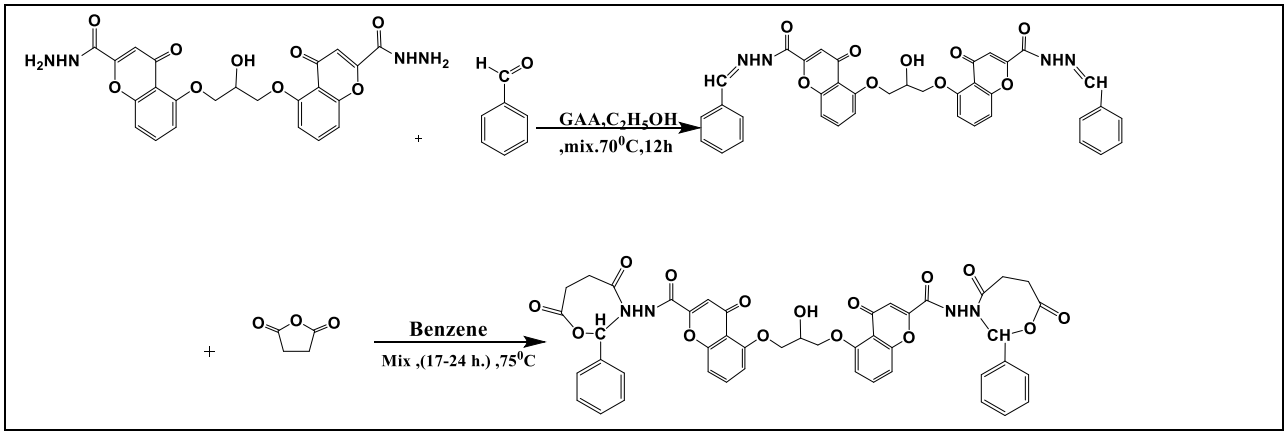


Scheme (3-1): A general equation for line three



Scheme (3-4): The mechanism for preparation Schiff base

The same mechanism apply to maleic and phthalic anhydride



Equation (3-18): synthesis of A18

FT-IR (V max., cm^{-1}) spectrum of compound (A19) showed the following values:3362(OH, alcohol),3131(NH ,amide) ,2974(CH str.),1718(C=O,Ketone), 1707(O=C-O,Oxazepine),164 (C=O,amid),1629(O=C-N,Oxazepine),1469(C=C , Ar.),1201(C-N aryl). ^{1}H-NMR(500 MH, δppm):W;2.0,V;2.2,B;4.1 (CH_2,ethylene), D;6.9,E;7.5,Q;7. 3,F;7.5,R;7.6,P;7.8(Benzene), J;7.3(H,Ethylene),A;4.7,N;7.8(CH ,methane),M;10.0(Amide),Z;5.9(Alcohol),2.5(DMSO). ^{1}H-NMR (500 MH,δppm) :B;4.4 (CH_2,ethylene), D;6.8,E;7.8,Q;7.7,F;7. 3,R;7.6, P;7.5(Benzene),J;7.4,V; 2.2 ,W;2.0(H,Ethylene), A;4.9,N;8.01(CH, methane),M;12.2 (Amide),Z;4.9(Alcohol), 2.5(DMSO).^{13}CNMR(125MH,δppm):B;70.2,W;29.9,V;27.5(CH_2,aliphatic), D;F;109 .3,E;139.0, H;116.8 ,C;159.1,G;157.3,P;127.4,Q;129.6,R;125.6,O;141.7 (Benzene),I;182.6,U;177.6,X;175.6(Carbonyl),L;166.1(Amide),K;164.3,J;119.2(Et hylene), N;107.5(CH,aliphatic),39-40(DMSO).

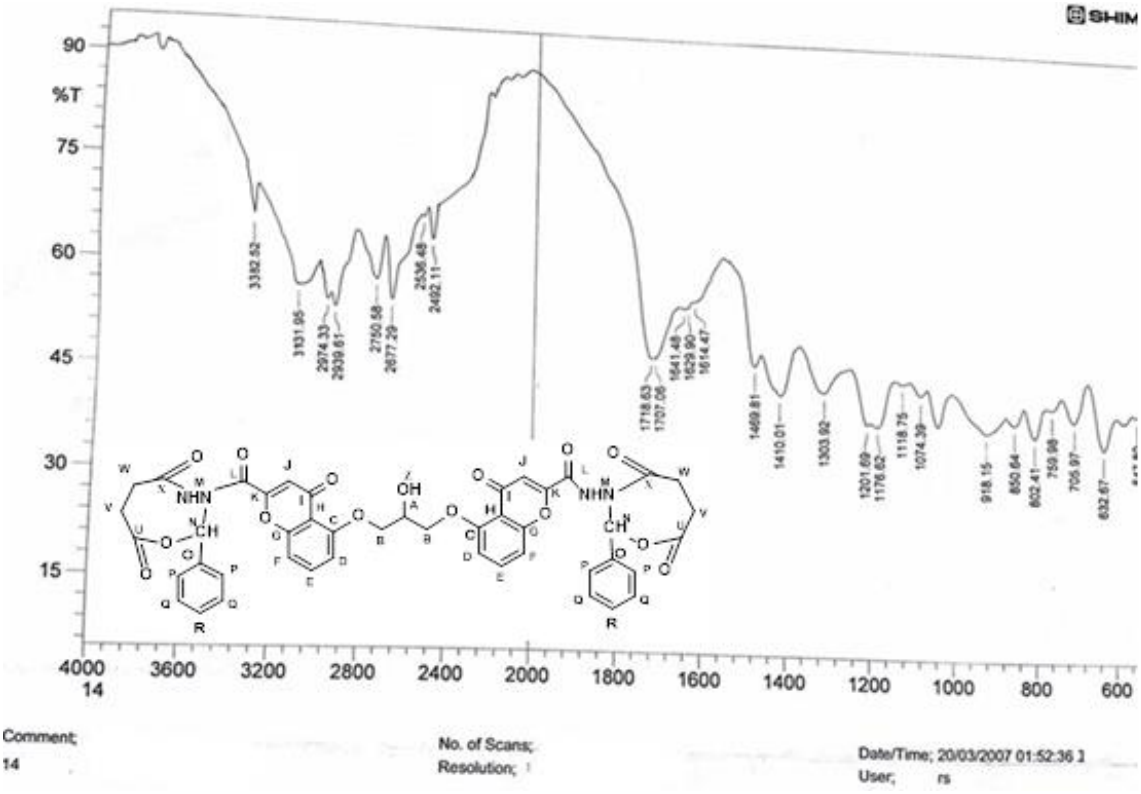


Figure (3-52): FT-IR spectrum for A18

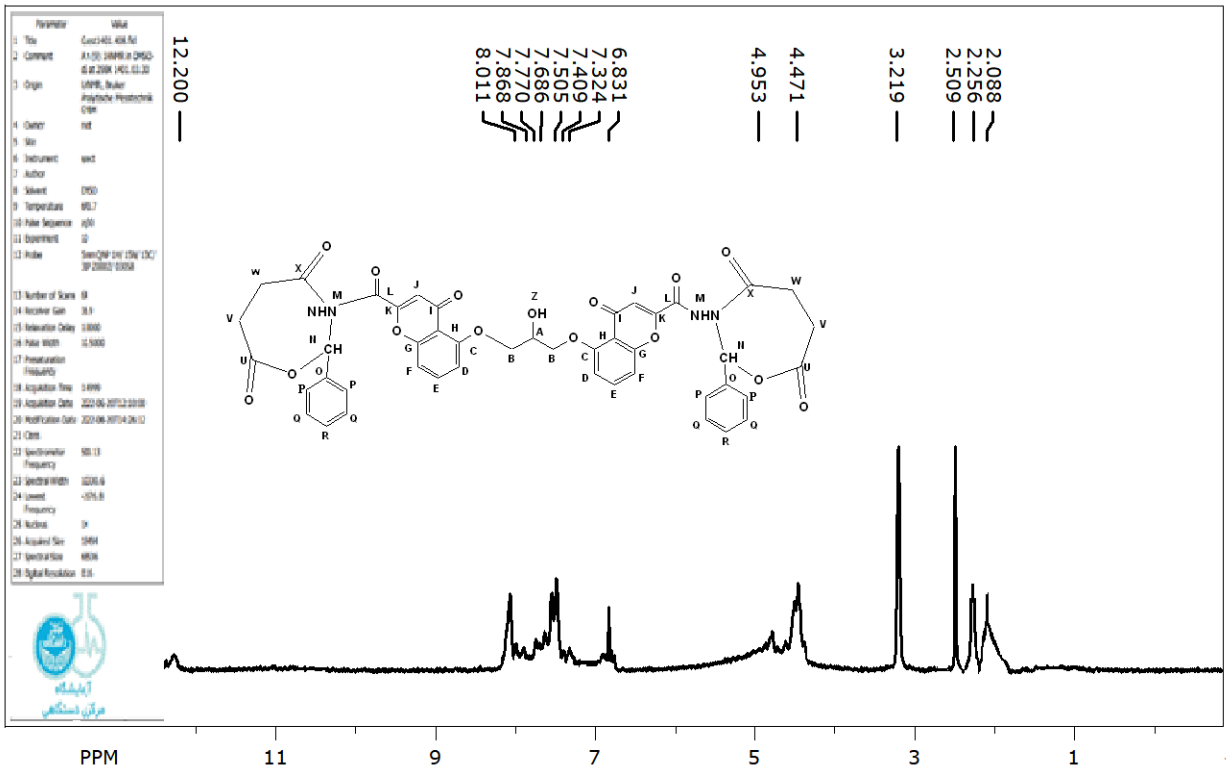


Figure (3-53): ^{1}H-NMR spectrum for A18

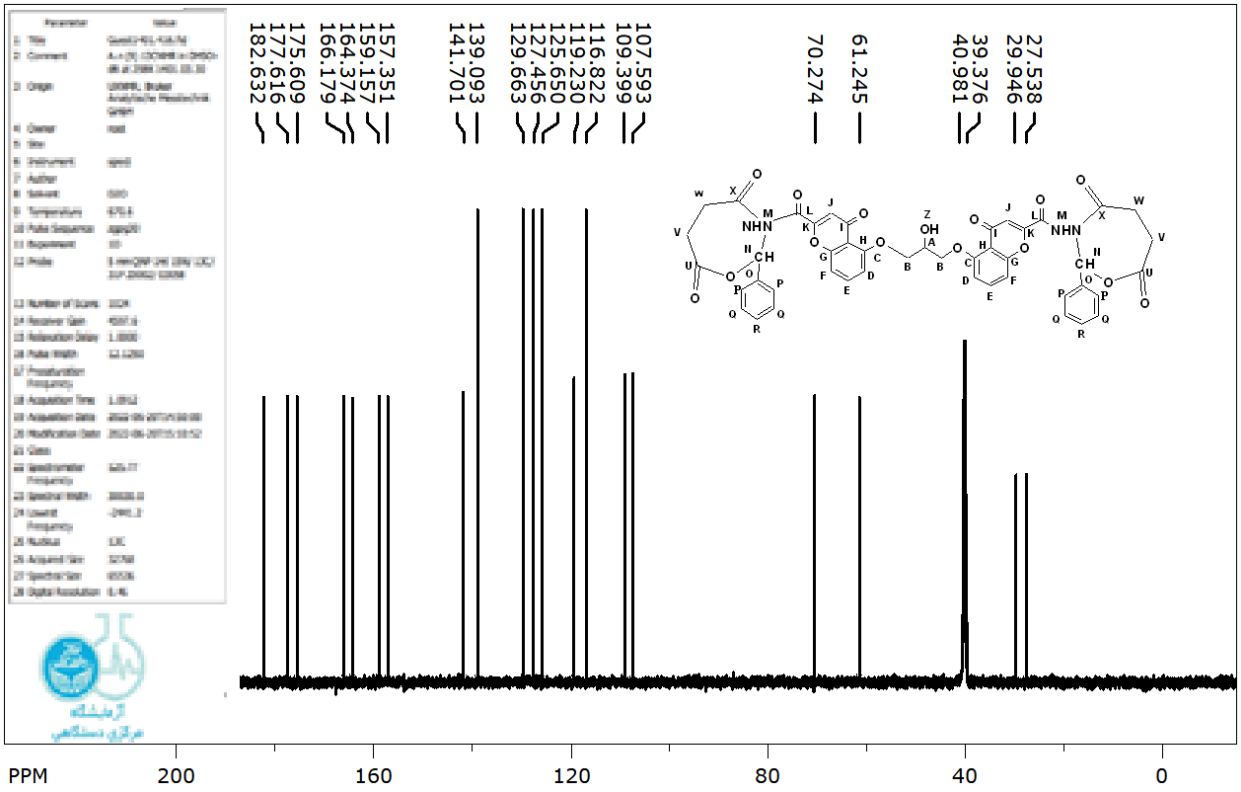
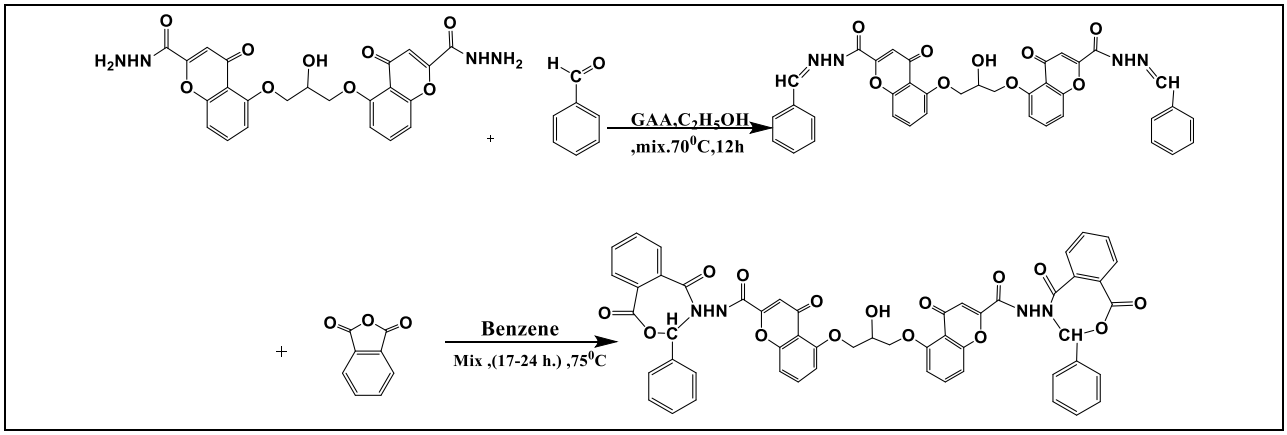


Figure (3-54): ^{13}C-NMR spectrum for A18



Equation (3-19): synthesis of A19

FT-IR (V max., cm^{-1}) spectrum of compound (A19) showed the following values: 3432(OH alcohol),3199(NH amide), 2943(CH str.),1687(O=C-O , Oxazepine), 1655(C=O amid),1585 (O=C-N , Oxazepine) , 1466 (C=C ,Ar.) ,1276 (C-N aryl). ^{1}H-NMR (500 MH, δ ppm):B;4.5 (CH_2,ethylene), D;6.8,E;7.8, Q;7.4,F;7.3,R;7.37,P;7.28,a;7.9,b;9.0, (Benzene),J;7.31(H,Ethylene), A;3.9,N;8.09 (CH,methane),M;12.4(Amide),Z;5.0(Alcohol),2.5(DMSO).^{13}CNMR(125MH, δppm):B;69.8 (CH_2,aliphatic), D;109.8,E;139.8, F;108.5,H;116.6,C;159.1,G;156. 3,P;127.2,b;128.2,Q;129.4,R;125.2,O;142.1,W;131.4,V;133.4,a;125.8,d;e;133.8 (Benzene),I;182.4,U;172.6,X;170.9(Carbonyl),L;167.5(Amide), K;165.7,J;118.6 (Ethylene),A;61.2,N;101.7(CH, aliphatic),39-40(DMSO).

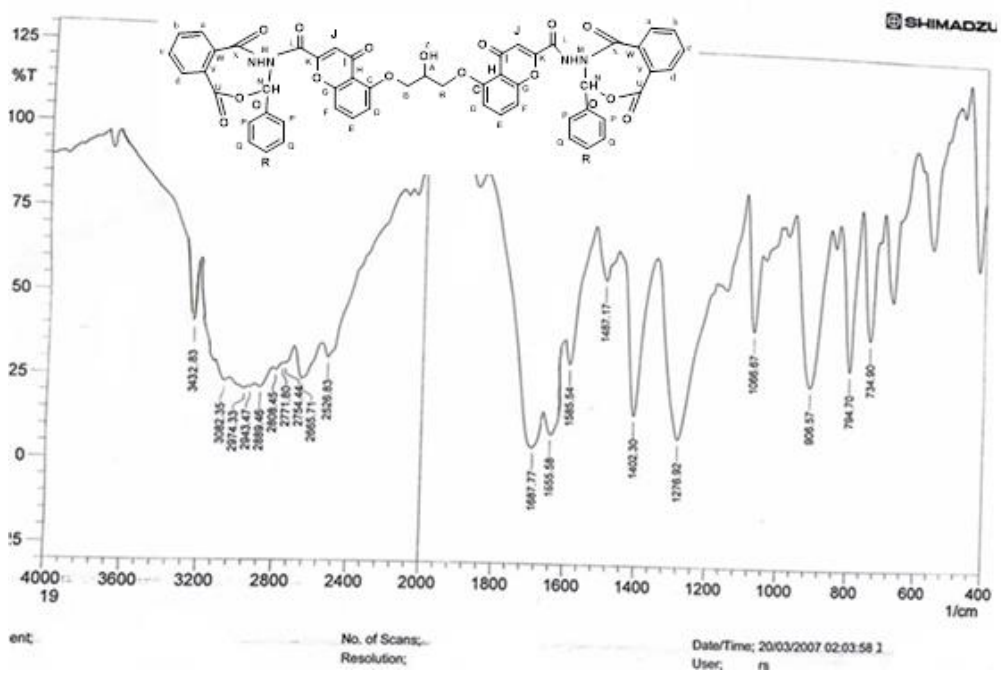


Figure (3-55): FT-IR spectrum for A19

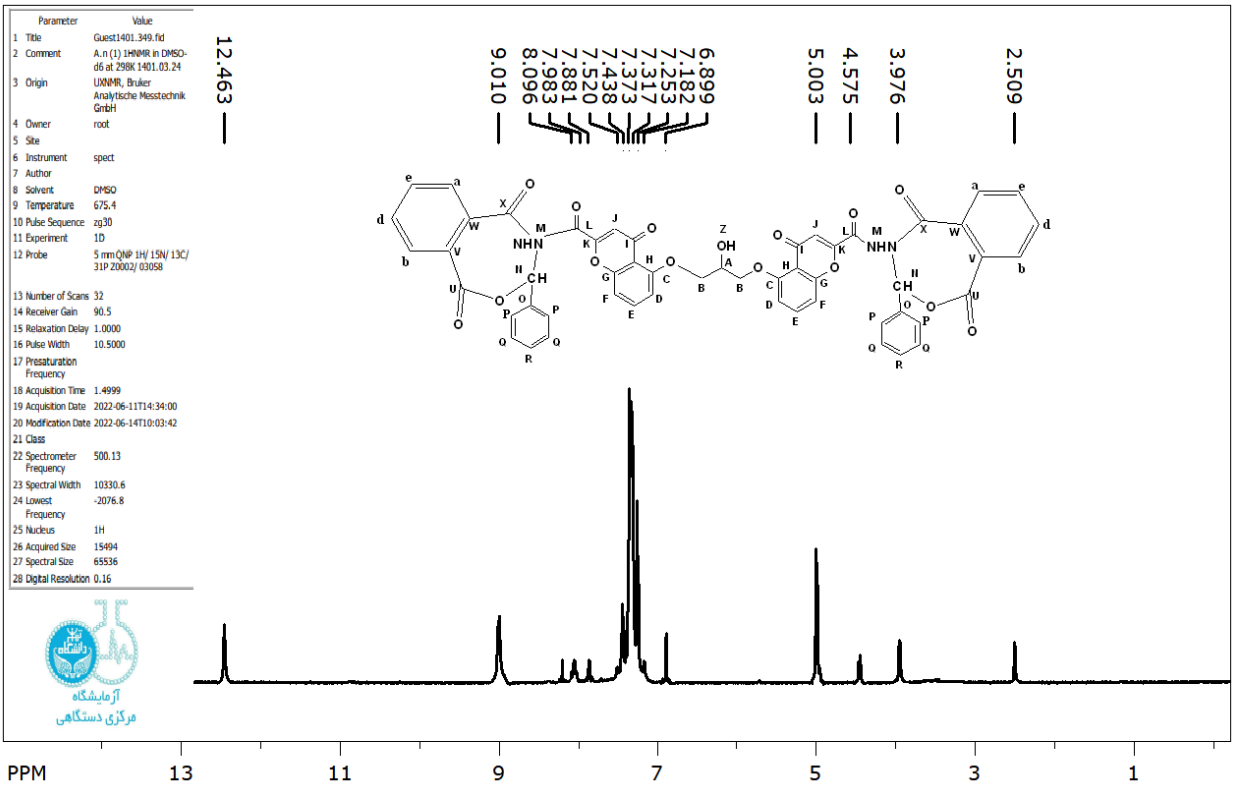


Figure (3-56): ^{1}H-NMR spectrum for A19

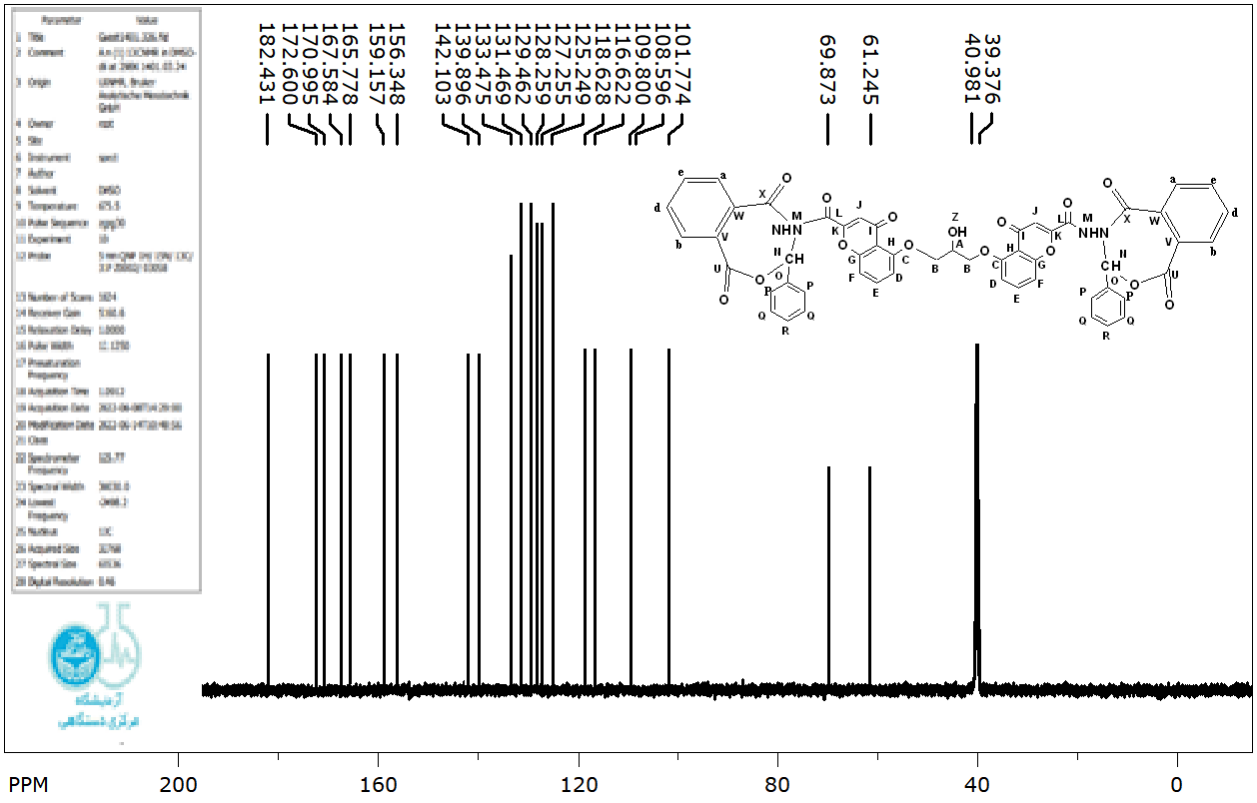
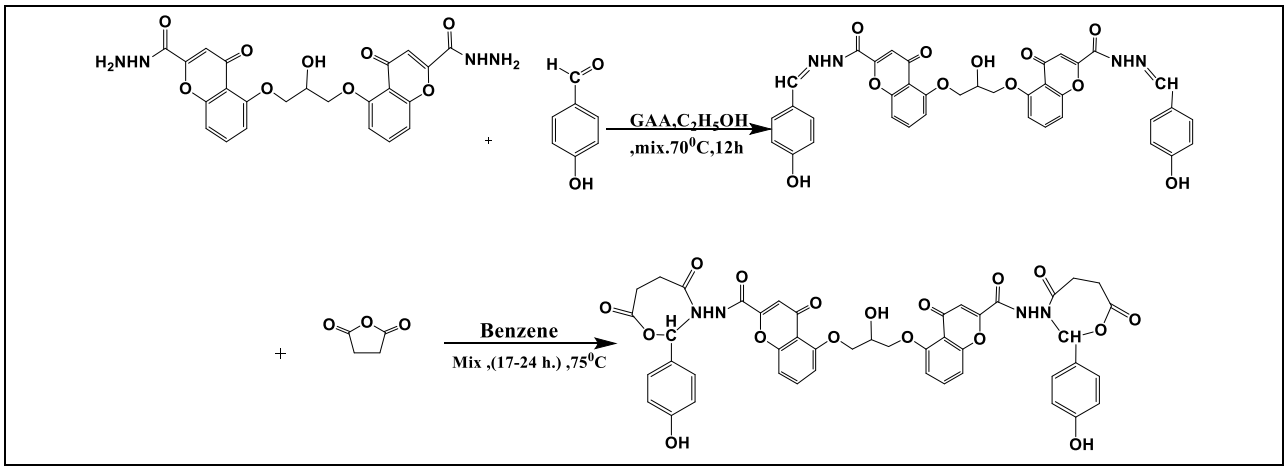


Figure (3-57): ^{13}C-NMR spectrum for A19



Equation (3-20): synthesis of A20

FT-IR (V max., cm^{-1}) spectrum of compound (A20) showed the following values:3470(OH),3180(NH),2935(CH,str.),1740(Ketone),1693(O=C-O, Oxazepine),1653(C=O,amid),1602(O=C-N,Oxazepine),1473(C=C,Ar),1201(C-N,aryl).^{1}H-NMR(500MH,δppm):W;2.2,V;2.4,B;4.6(CH_2,ethylene),D;6.9,E;7.7,Q;6.8,F;7.3

,P;7.5(Benzene),J;7.4(H,Ethylene),A;3.8,N;8.08(CH,methane),M;12.5(Amide) ,Z; 4.9(Alcohol),2.5(DMSO).^{13}CNMR(125MH,δppm):B;69.8,W;27.9,V;29.9(CH_2,aliphatic),D;109.5,E;138.8,F;107.9,H;115.6,C;158.8,G;156.9,Q;117.6,P;129.4,O;138.8,R;155.3(Benzene),I;182.9,U;174.7,X;172.6(Carbonyl),L;166.1(Amide),K;164.7,J; 119.1(Ethylene),N;99.9,A;61.0(CH,aliphatic),39-40(DMSO).

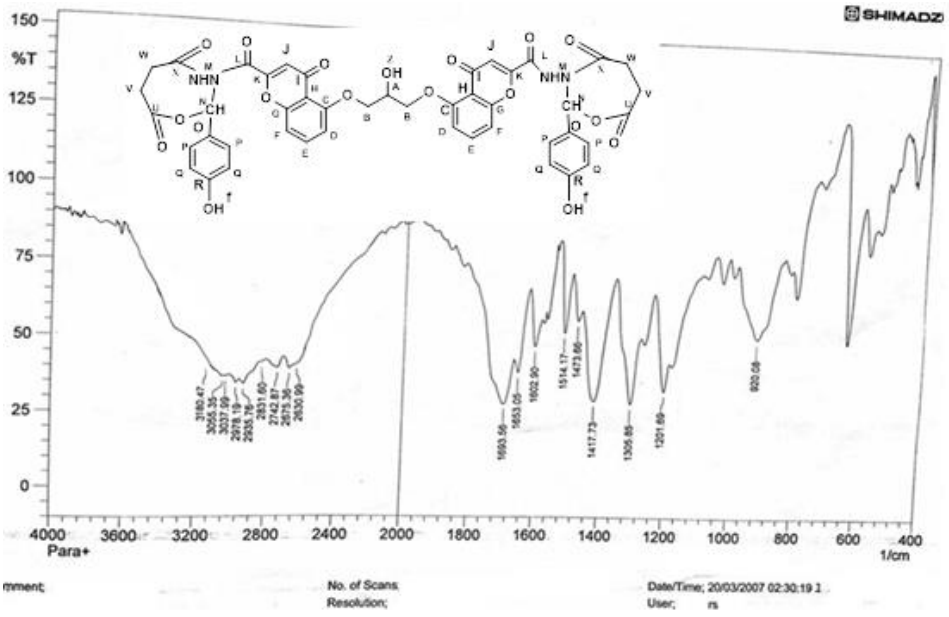


Figure (3-58): FT-IR spectrum for A20

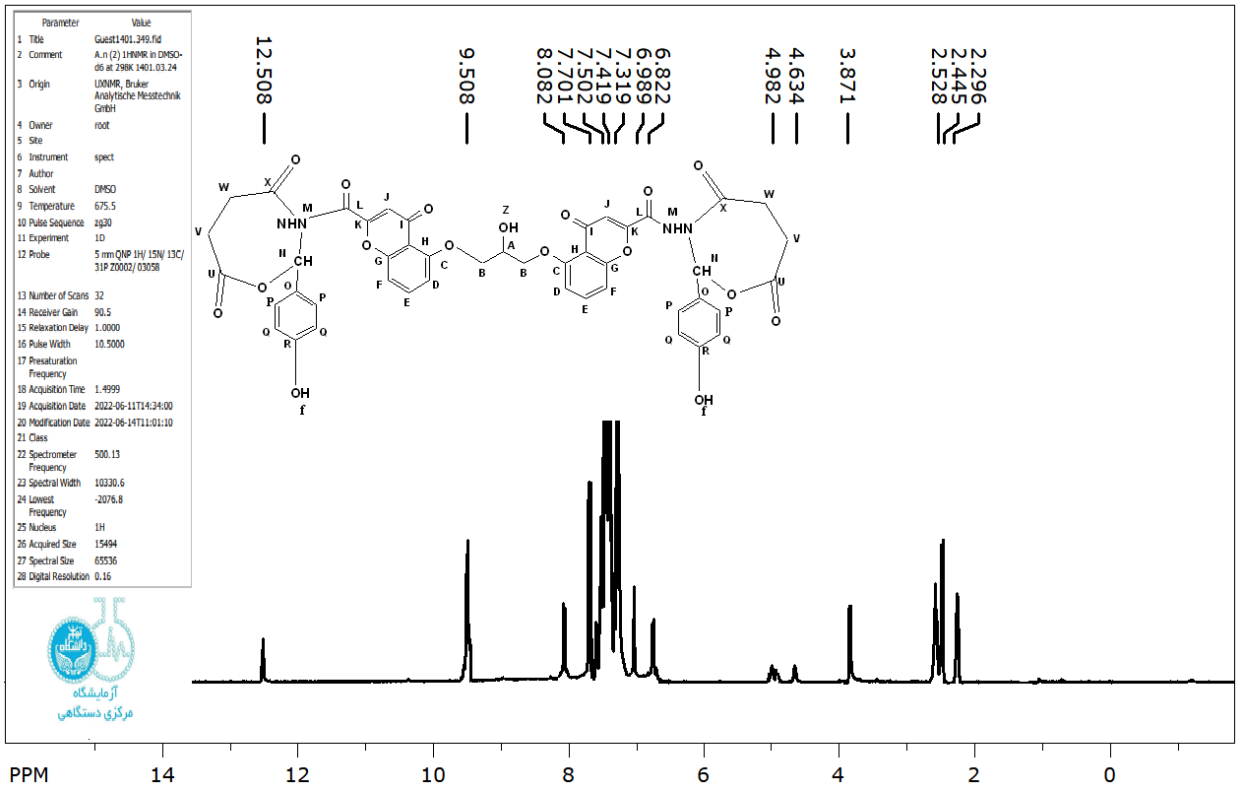


Figure (3-59): ^{1}H-NMR spectrum for A20

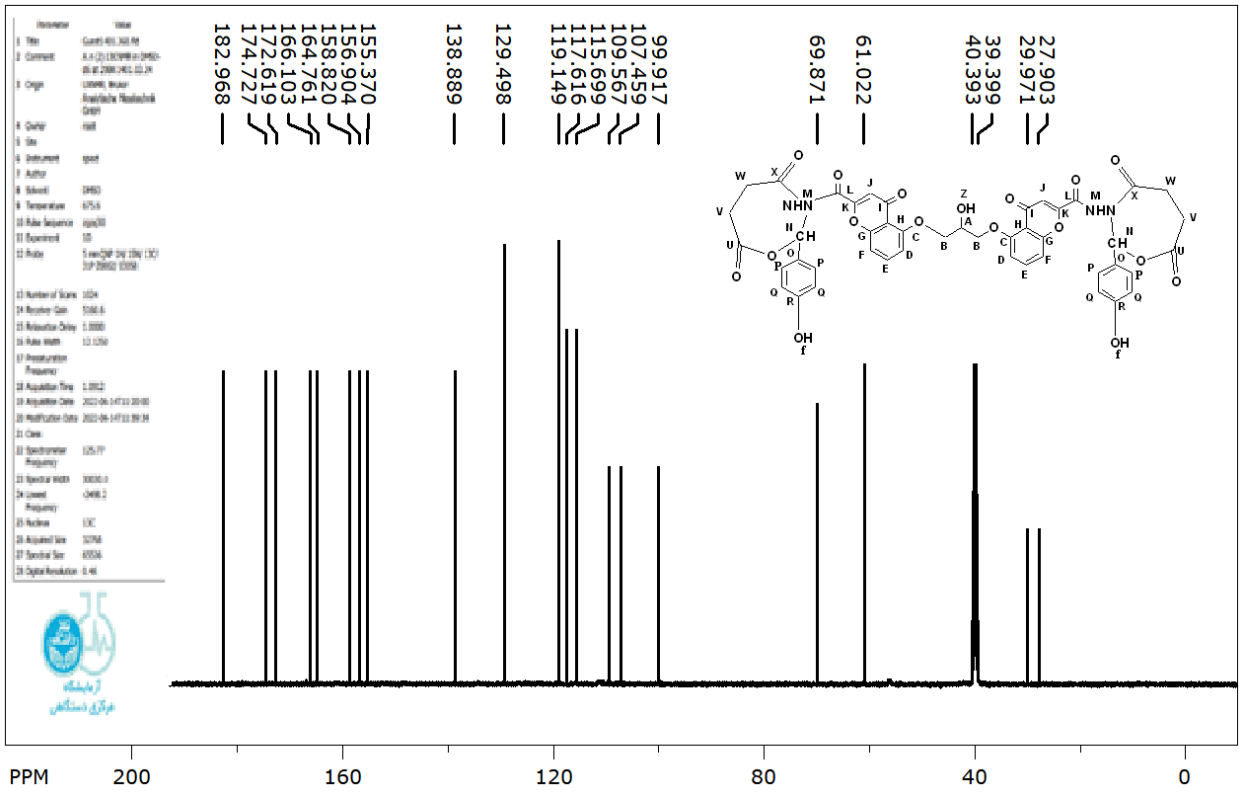
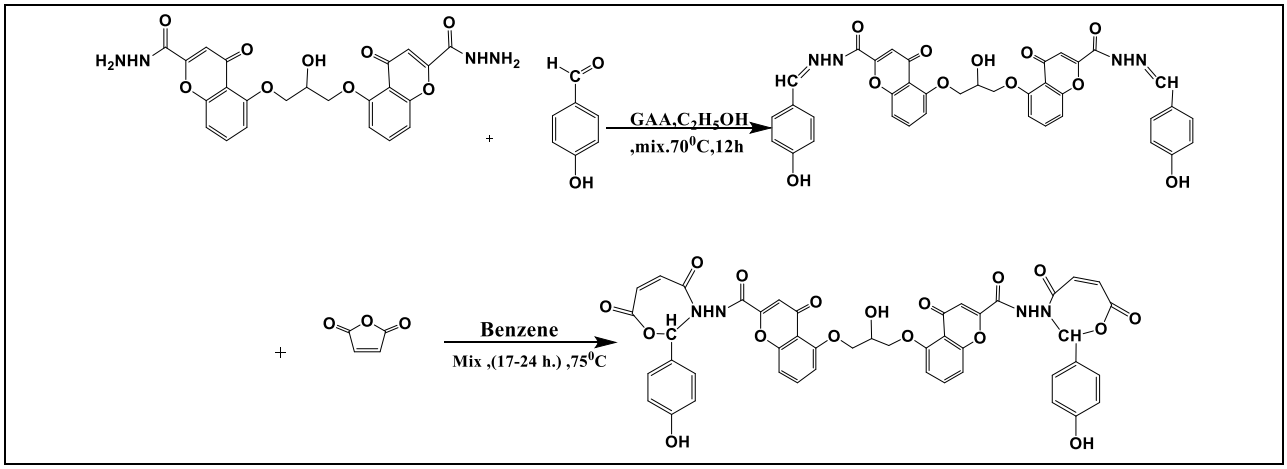


Figure (3-60): ^{13}C-NMR spectrum for A20



Equation (3-21): synthesis of A21

FT-IR (V max., cm^{-1}) spectrum of compound (A21) showed the following values:3400(OH,alcohol),3174(NH,amide),2935(CH,str.),1725(Ketone),1699(O=C-O,Oxazepine),1653(C=O,amid),1609(O=C-N,Oxazepine),1429(C=C, Ar.), 1229 (C-N,aryl).^{1}HNMR(500MH,δppm):B;4.7(CH_2,ethylene),D;6.8,E;7.8,Q;6.7,F;7.2, P;7.6(Benzene),J;7.4,V;6.9,W;6.5(H,Ethylene),A;3.9,N;8.06(CH,methane),M;9.9(Amide),Z;4.9,f;9.2(Alcohol),2.5(DMSO).^{13}CNMR(125MH,δppm):B;69.4(CH_2,aliphatic),D;108.8,E;138.8,F;106.7,H;115.0,C;158.9,G;156.3,P;128.3,Q;116.7,R;155.5,O;138.8(Benzene),I;182.5,U;168.7,X;164.7(Carbonyl),L;167.5(Amide),K;166.2,J;118.6,W;121.2,V;135.6(Ethylene),N;101.1,A;61.3(CH,aliphatic),39-40(DMSO).

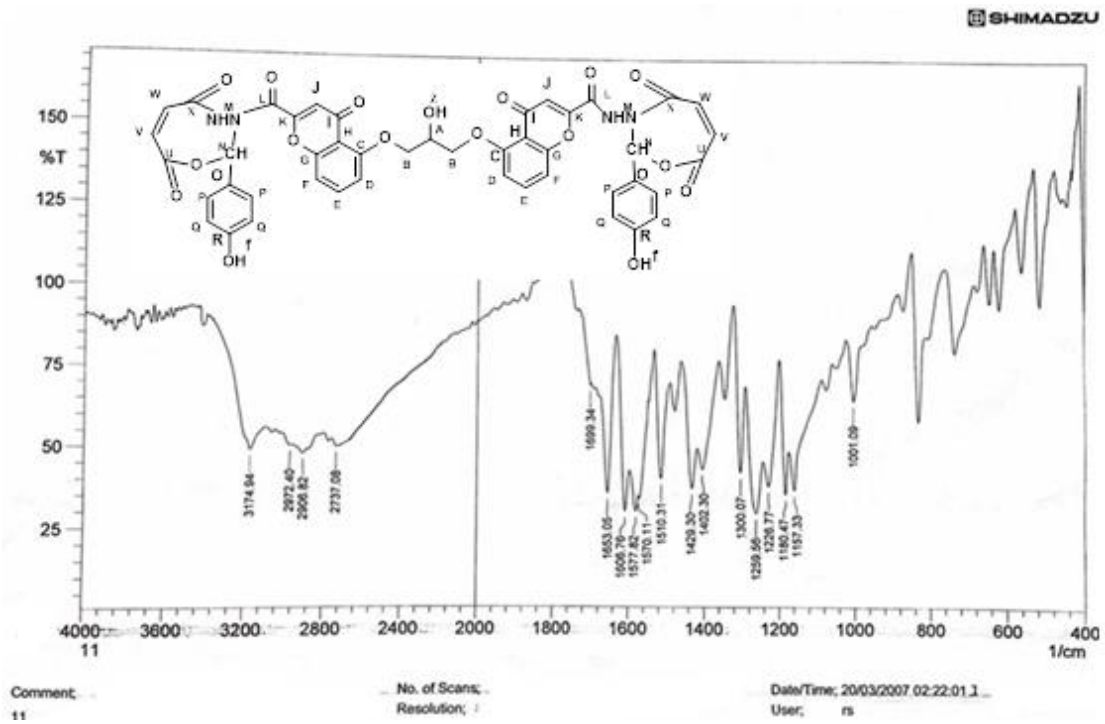


Figure (3-61): FT-IR spectrum for A21

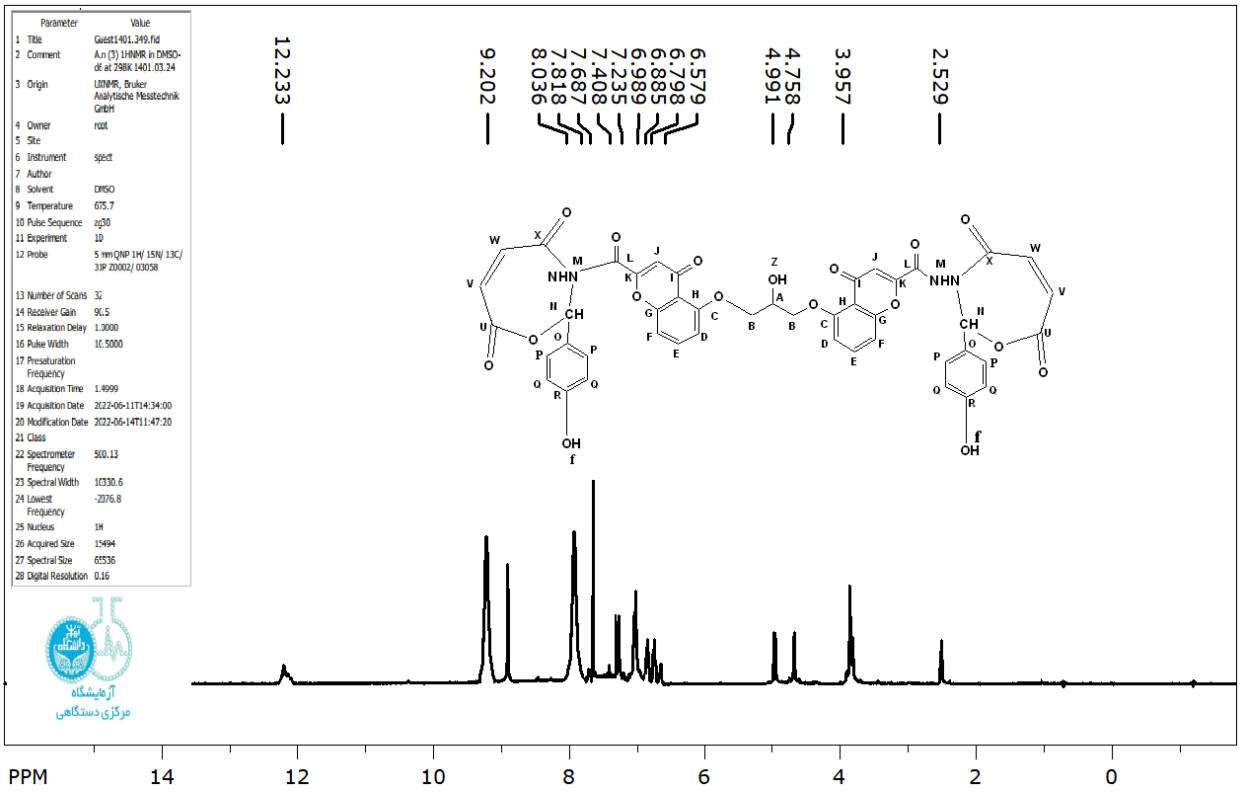


Figure (3-62): ^{1}H-NMR spectrum for A21

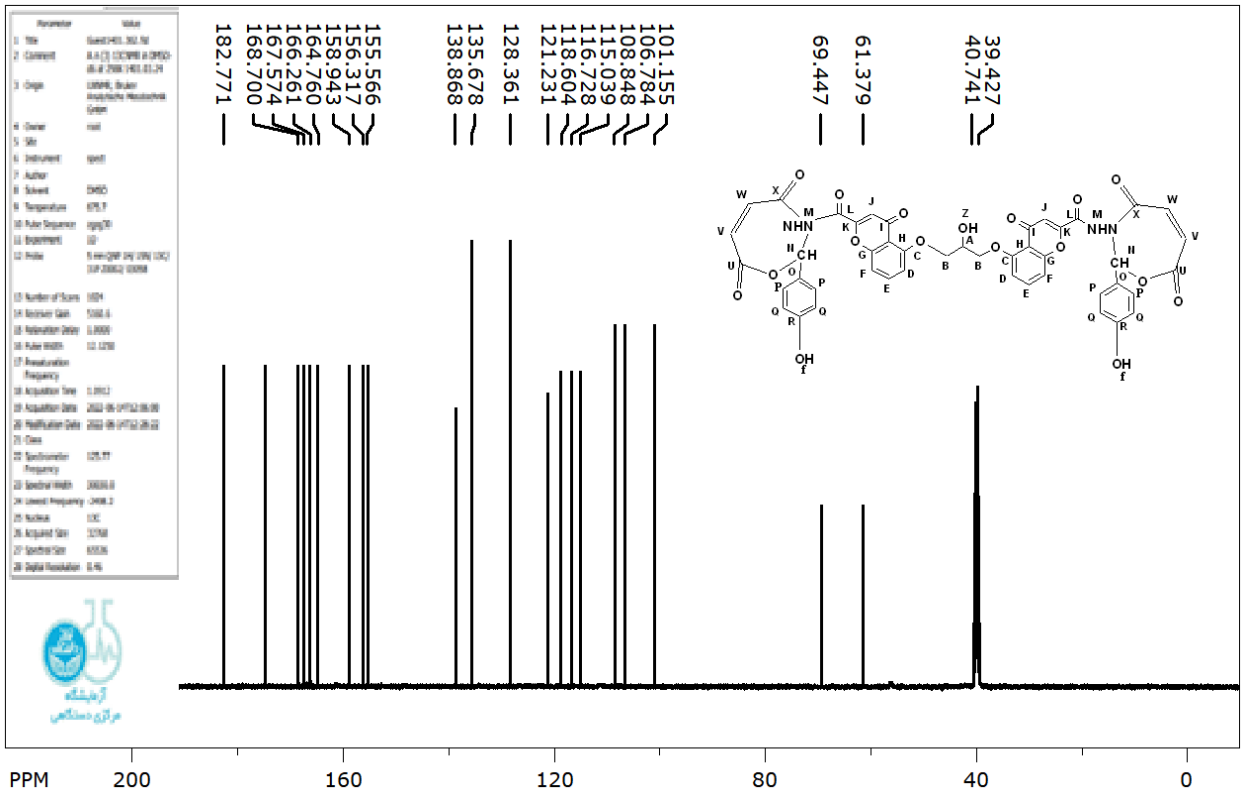
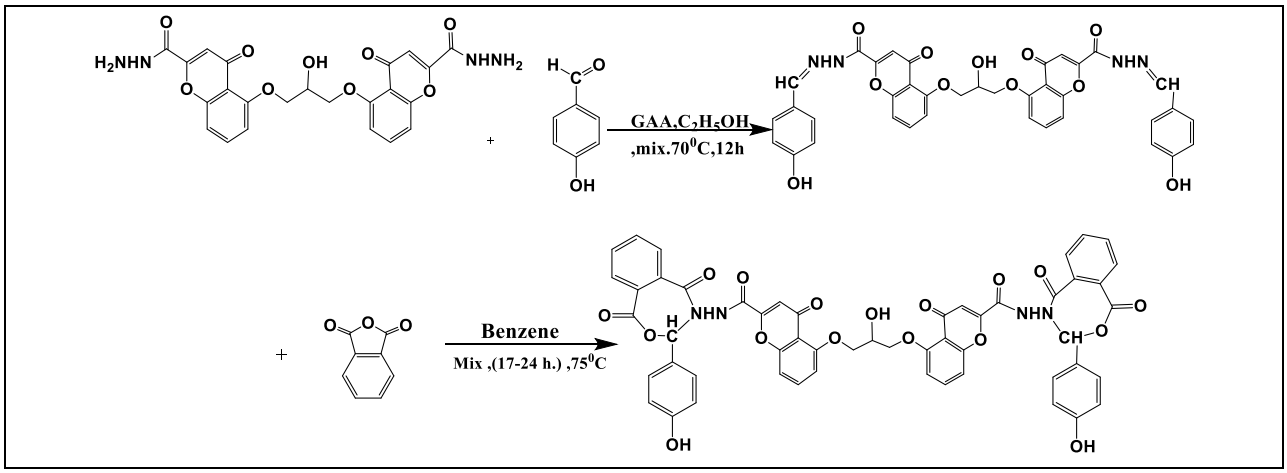


Figure (3-63): ^{13}C-NMR spectrum for A21



Equation (3-22): synthesis of A22

FT-IR (V max., cm^{-1}) spectrum of compound (A22) showed the following values:3400(OH,Alcohol),3276(NH,amide),2976(CH,str.),1693(O=CO,Oxazepine),1650(C=O,amide),1604(O=C-N,Oxazepine),1427(C=C,Ar.),1276(C-N aryl). ^{1}H-NMR(500MH,δppm):B;4.7(CH_2,ethylene),D;6.8,E;7.7,Q;6.6,F;7.2,P;7.5,a;7.8,b;

7.9(Benzene),J;7.3(H,Ethylene),A;3.8,N;8.0(CH,methane),M;12.1(Amide),Z;4.9, f;9.3(Alcohol),2.5(DMSO). ^{13}CNMR(125MH,δppm):B;69.8(CH_2,aliphatic),D;110. 9,E;138.3,F;106.5,H;115.4,C;158.7,G;156.6,P;128.9,b;128.1,W;131.5,Q;116.9,a; 124.9,V;133.8,R;156.6(Benzene),I;182.9,U;173.5,X;171.1(Carbonyl),L;166.8 (Amide) ,K;168.7 ,J;118.9(Ethylene),A;62.8,N;102(CH,aliphatic),39-40(DMSO).

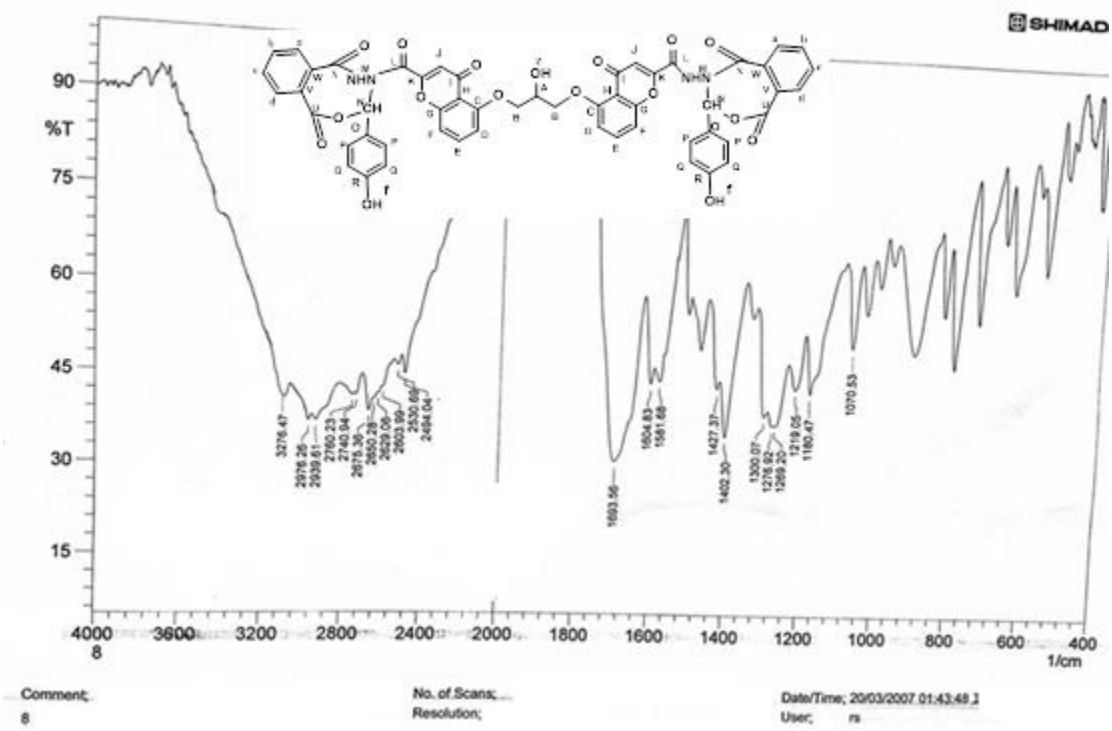


Figure (3-64): FT-IR spectrum for A22

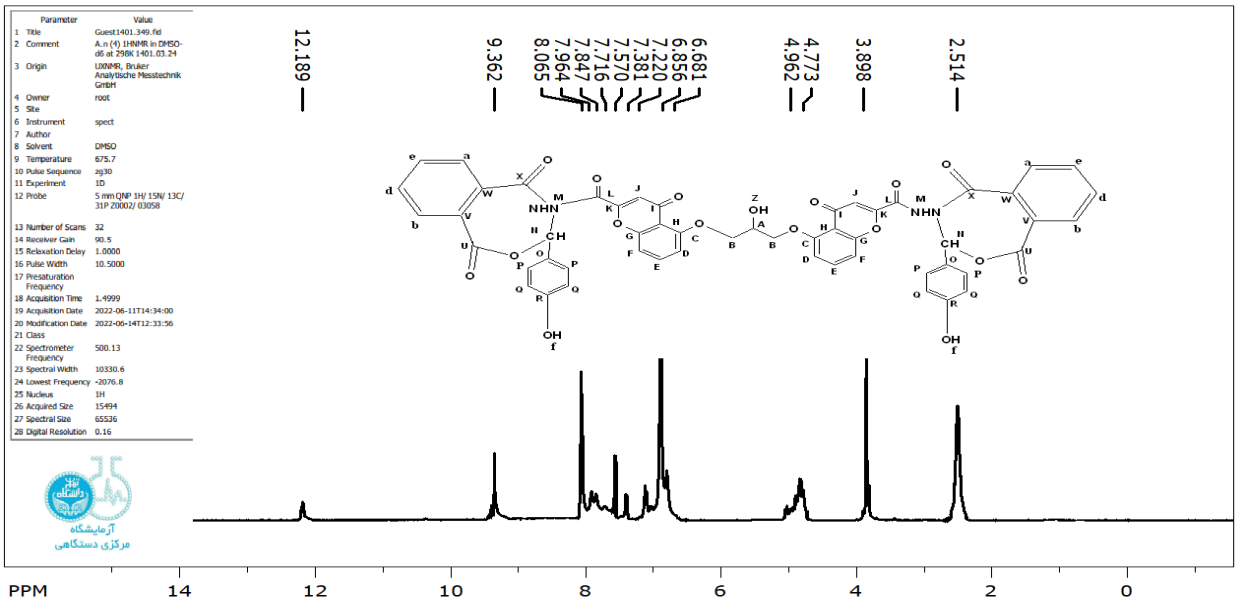


Figure (3-65): ^{1}H-NMR spectrum for A22

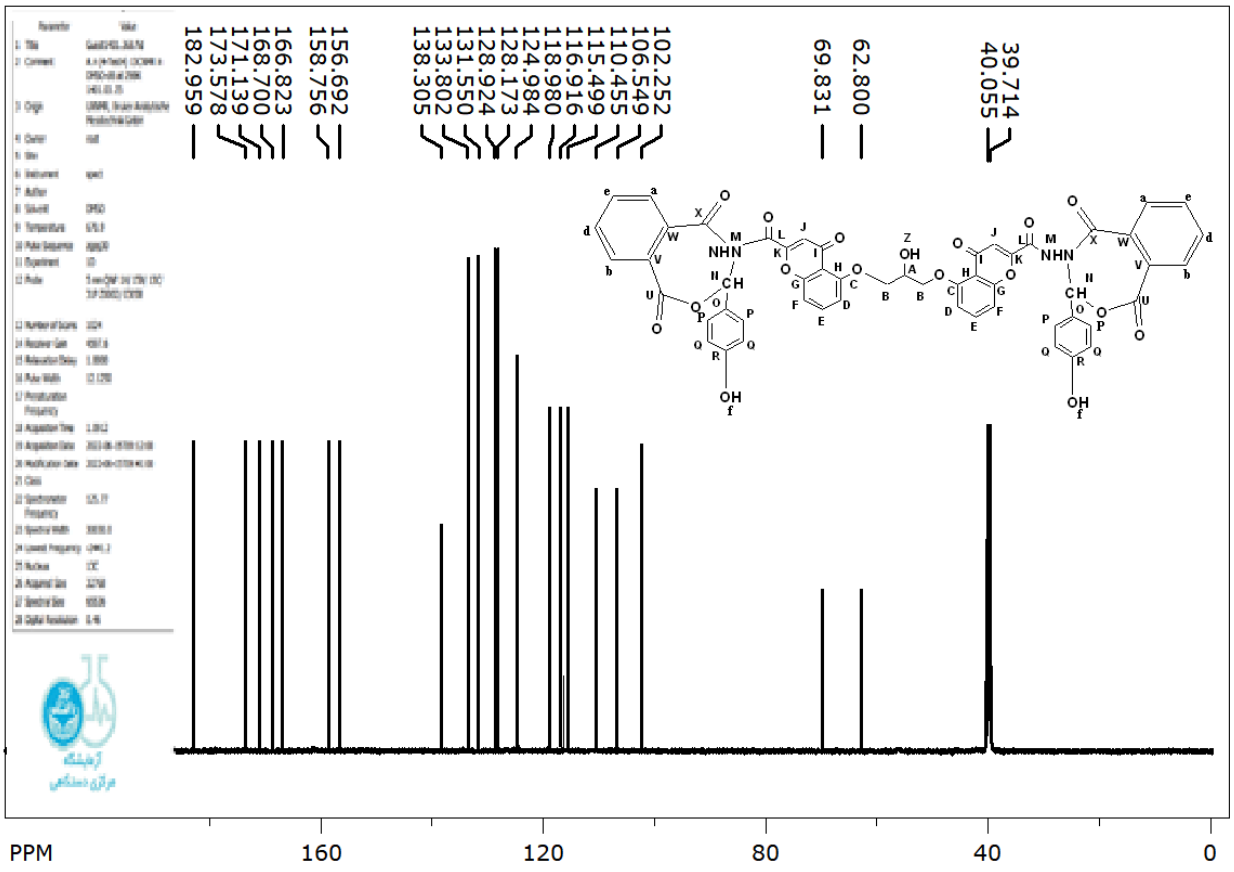
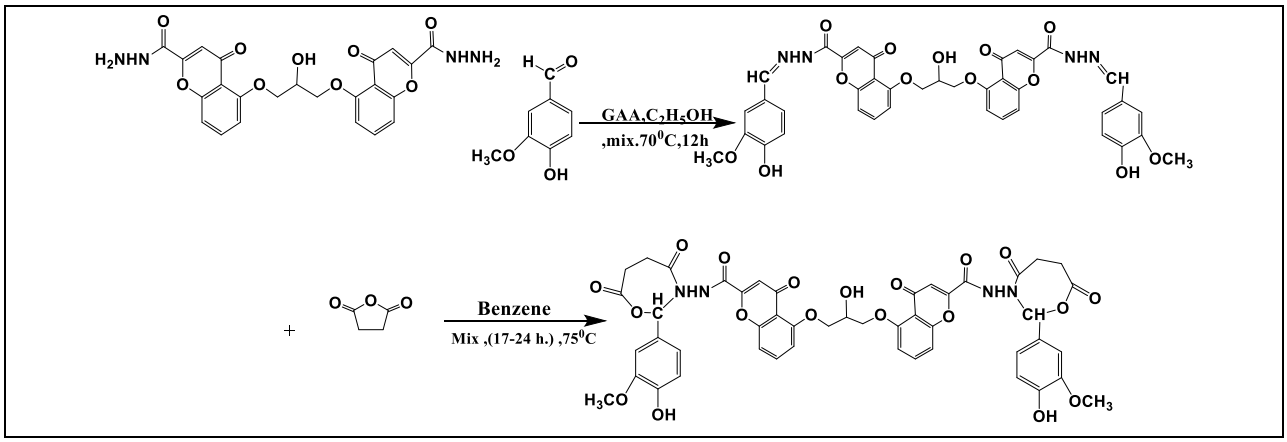


Figure (3-66): ^{13}C-NMR spectrum for A22



Equation (3-23): synthesis of A23

FT-IR (V max., cm^{-1}) spectrum of compound (A23) showed the following values:3340(OH,alcohol),3290(NH,amide),2978(CH,str.),1720(Ketone), 1693(O=CO,Oxazepine),1651(C=O,amid),1597(O=C-N,Oxazepine),1413(C=C,Ar.), 1267(C-N,aryl).^{1}H-NMR(500MH,δppm):W;2.2,V;2.3,B;4.6(CH_2,ethylene),D;6.9,E;7.7,F;7.2,P;6.8,m;7.0,h;6.8(Benzene),J;7.6(H,Ethylene),A;3.7,N;8.08(CH,methane),M;12.0(Amide),Z;4.9,f;9.9(Alcohol),g;3.8(CH_3,methyl),2.5(DMSO).^{13}CNMR(125MH,δppm):B;69.9,W;28.1,V;29.8(CH_2,aliphatic),g;56.1(CH_3,aliphatic),D;109.9,F;107.6,H;115.8,m;122.3,G;156.2,P;113.1,Q;148.2,R;146.8,O;133.8,C;158.8,E;138.8(Benzene),I;183.0,U;175.0,X;173.6(Carbonyl),L;166.0(Amide),K;164.1,J;118.9(Ethylene),A;60.2,N;106.5(CH,aliphatic)g;56.4(CH_3,ethylene),39-40(DMSO).

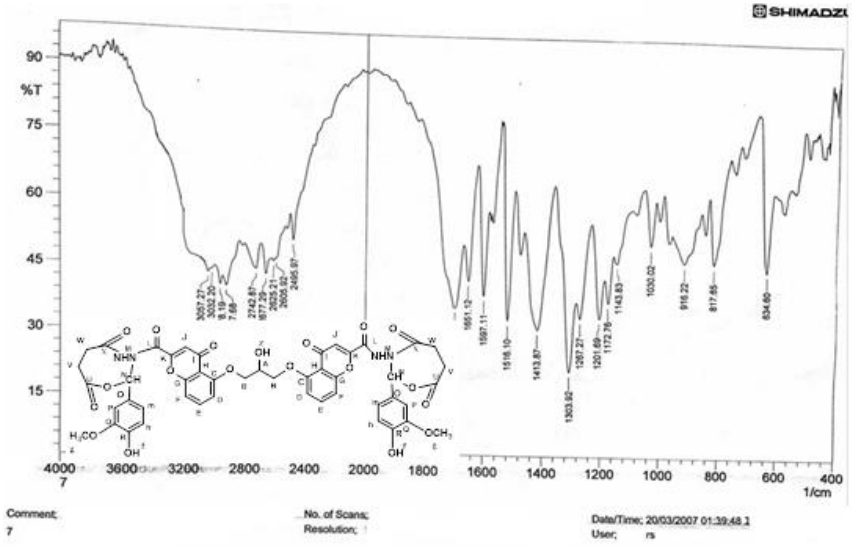


Figure (3-67): FT-IR spectrum for A23

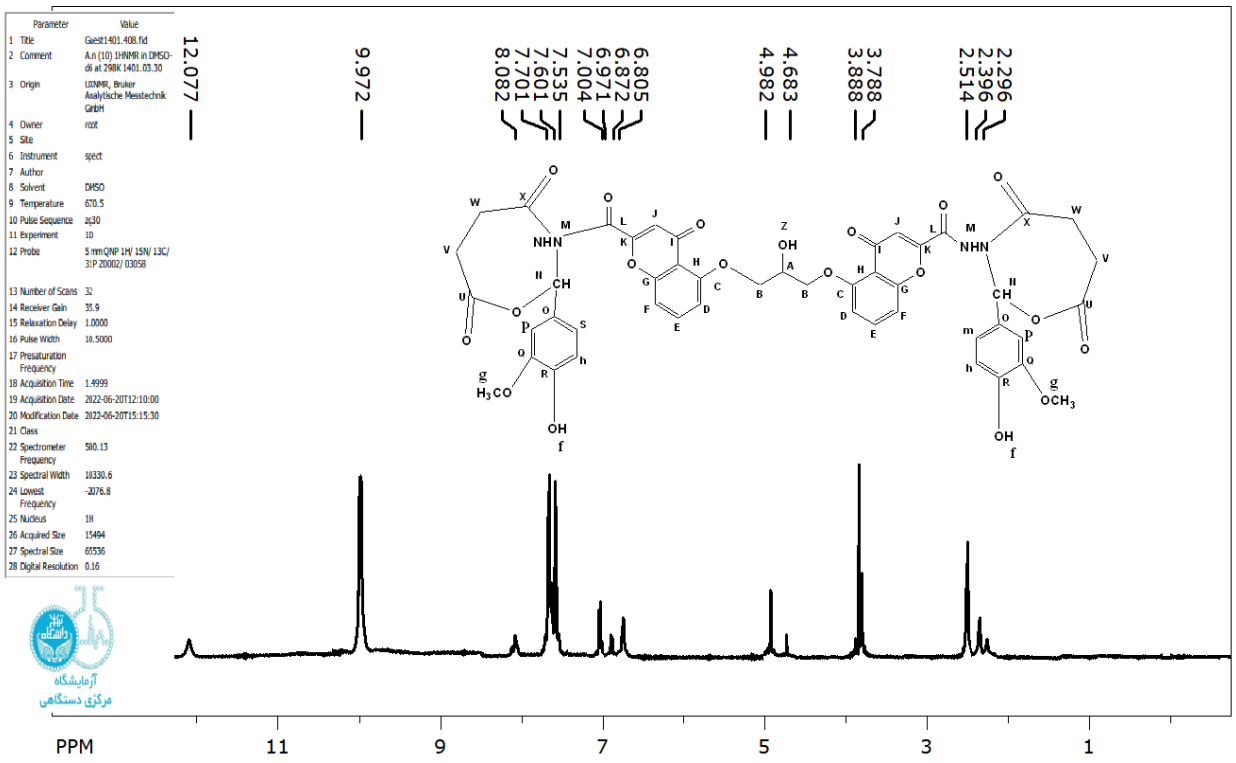


Figure (3-68): ^{1}H-NMR spectrum for A23

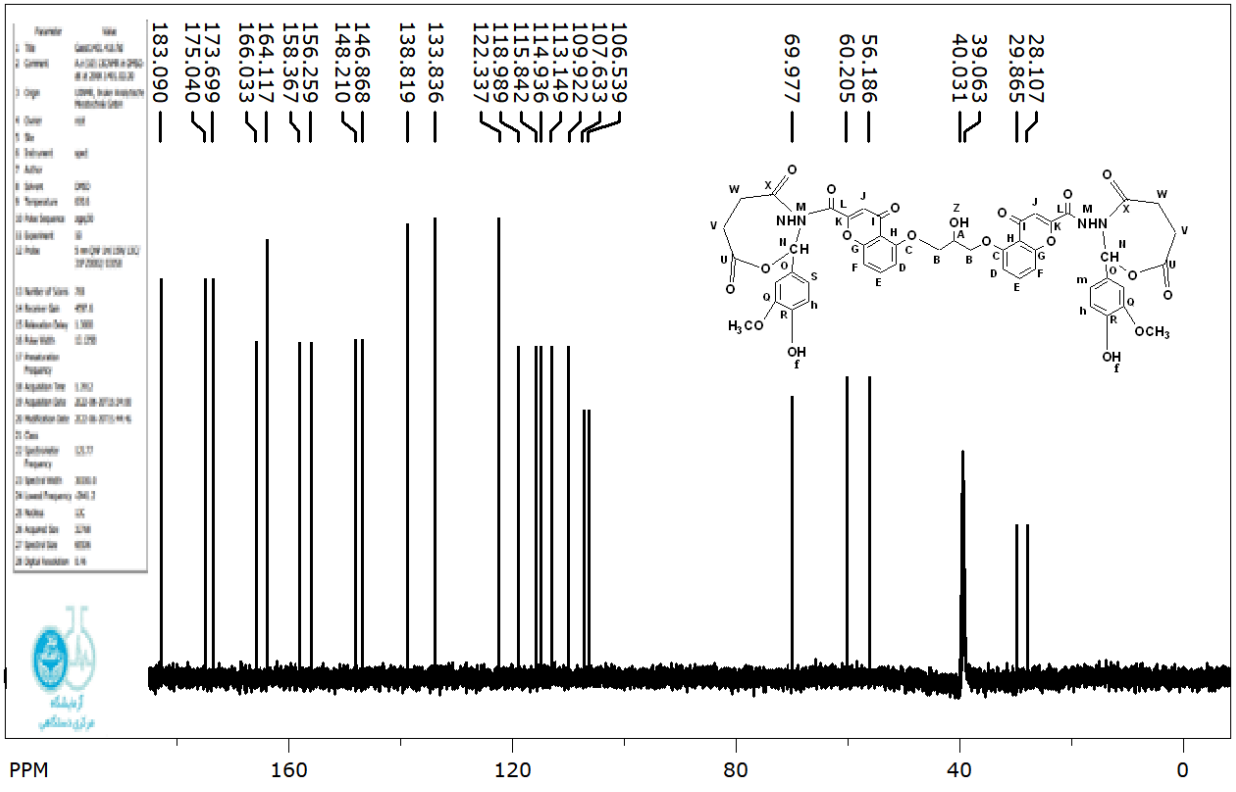
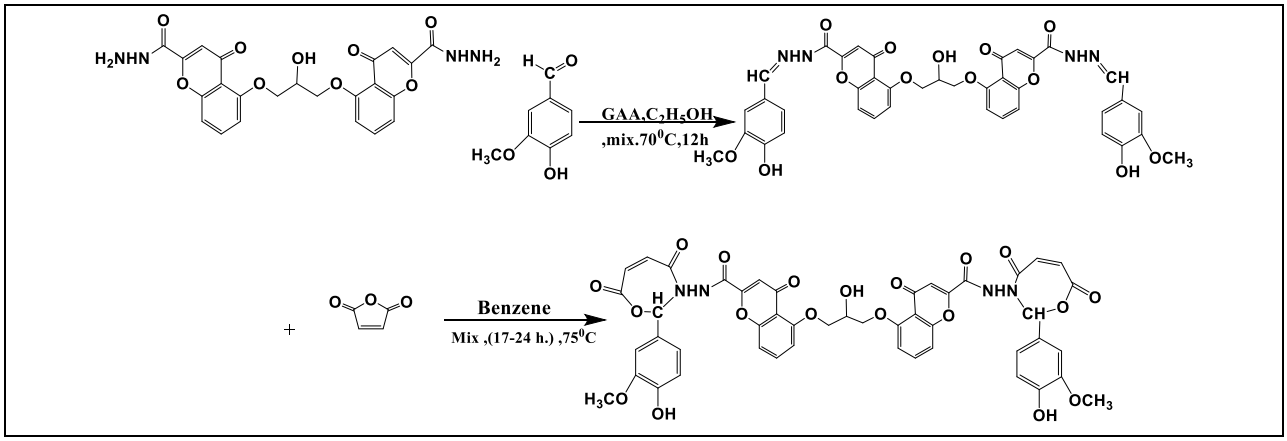


Figure (3-69): ^{13}C-NMR spectrum for A23



Equation (3-24): synthesis of A24

FT-IR (V max., cm^{-1}) spectrum of compound (A24) showed the following values:3400(OH,alcohol),3204(NH,amide),2978(CH,str.),1730(Ketone), 1689(O=CO,Oxazepine),1649(C=O,amid),1597(O=C-N,Oxazepine),1410(C=C ,Ar.),1265(C-N,aryl).^{1}HNMR(500MH,δppm):B;4.4(CH_2,ethylene),g;3.8(CH_3, ethylene),F;7.4,E;7.6,D;6.8,P;6.7,m;6.9,h;6.8(Benzene),J;7.5,V;6.9,W;6.6(H,Ethyl ene),A;3.9 ,N;8.01(CH,methane),M;12.1(Amide),Z;4.9,f;9.9(Alcohol),2.5(DMSO). ^{13}CNMR (125MH,δppm):B;69.6(CH_2,alip.),g;57.7(CH_3,ethylene)D;109.9,E;139.3 ,F;107.7 ,H;117.9,C;158.8,G;156.7,P;115.6,Q;149.1,R;147.2,O;134.9,W;121.4,V ;135.8,m;123.3(Benzene),I;182.9,U;167.9,X;164.6(Carbonyl),L;168.8 (Amide),K;165.8,J;118.9

(Ethylene),A;61.2,N;106.9(CH,alip.),39-40(DMSO).

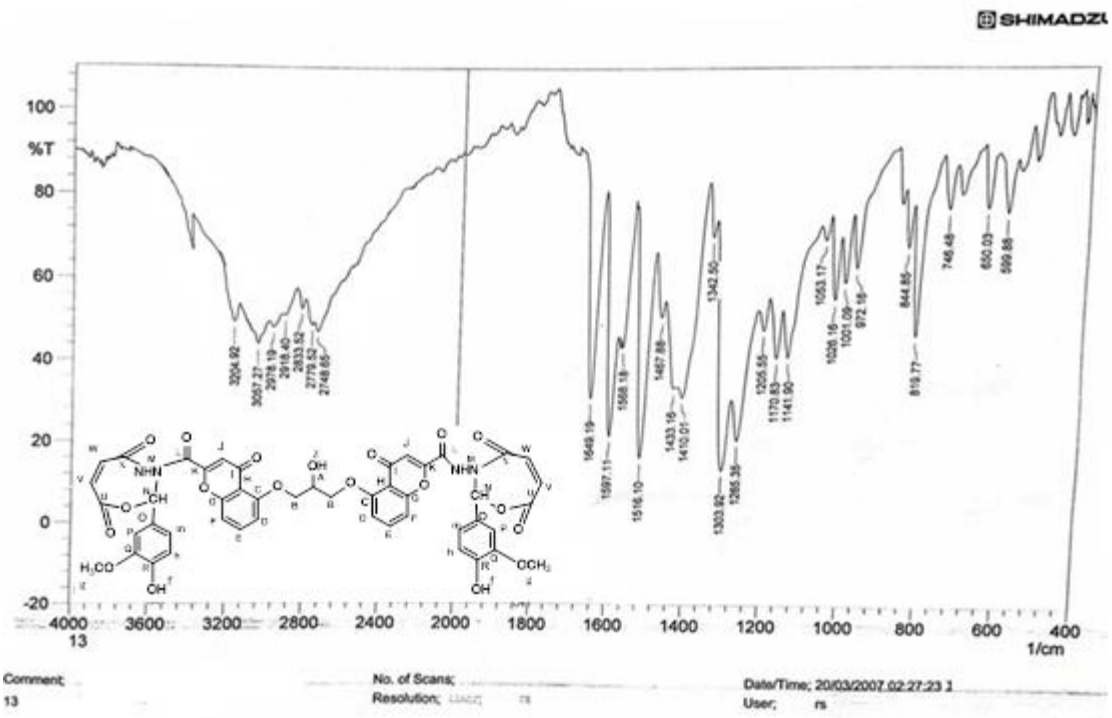


Figure (3-70): FT-IR spectrum for A24

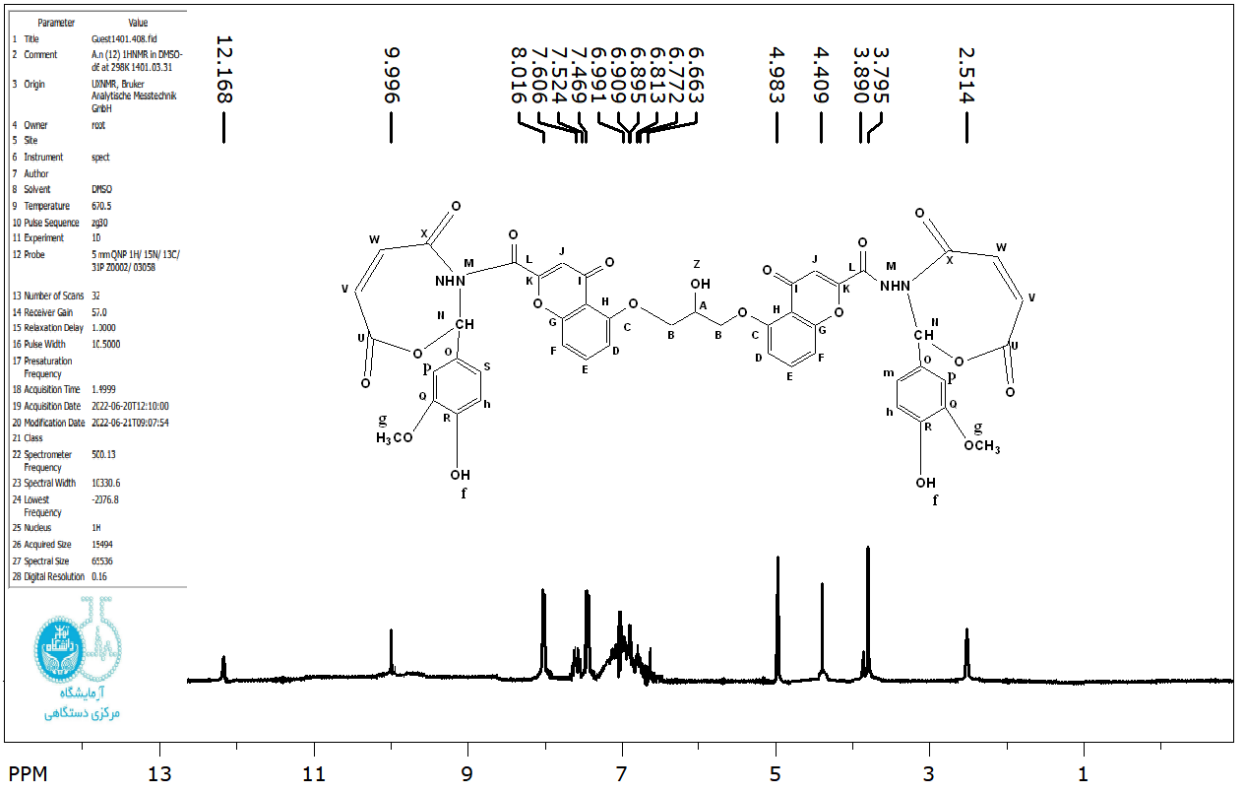


Figure (3-71): ^{1}H-NMR spectrum for A24

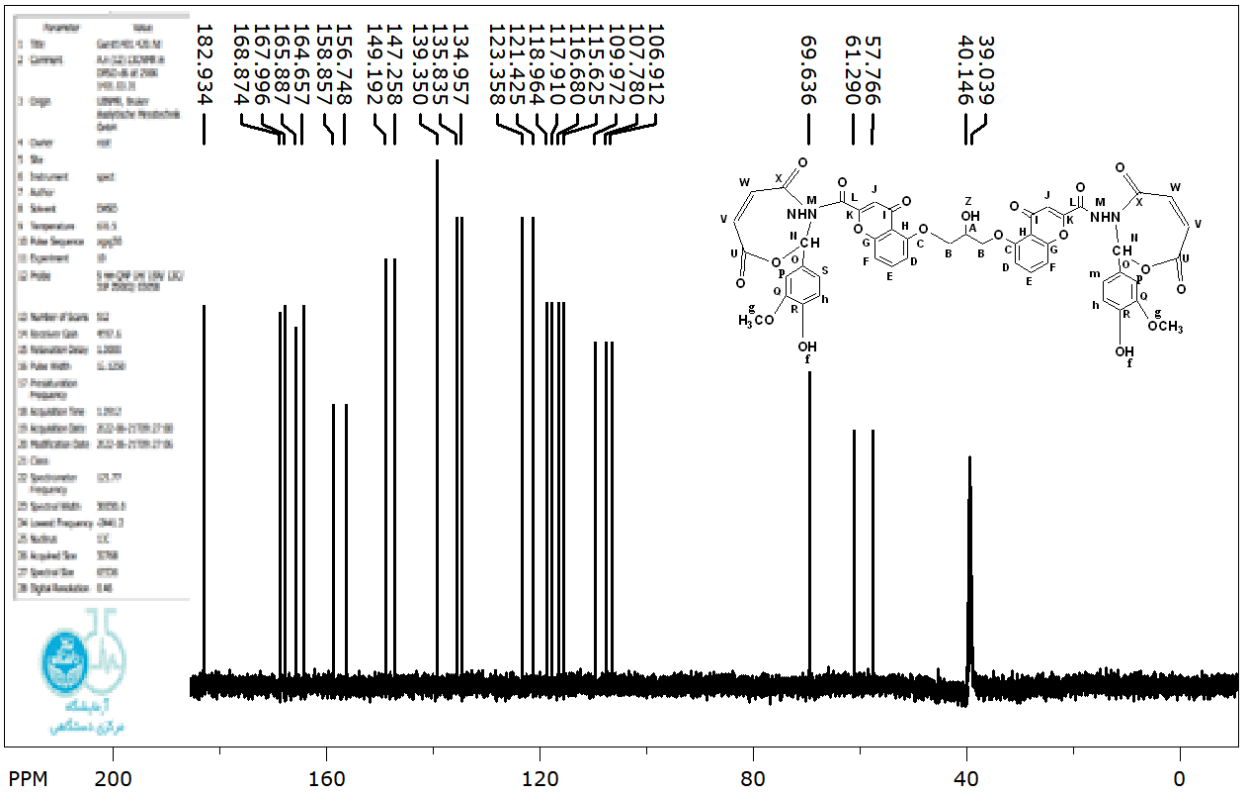
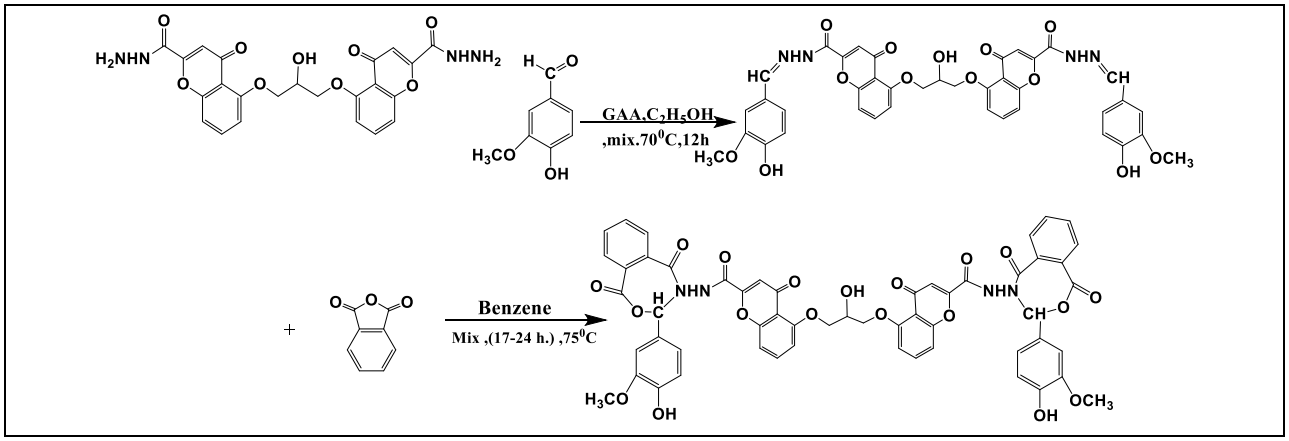


Figure (3-72): ^{13}C-NMR spectrum for A24



Equation (3-25): synthesis of A25

FT-IR (V max., cm^{-1}) spectrum of compound (A25) showed the following values:3390(OH,alcohol),3210(NH,amide),2974(CH,str.),1730(Ketone), 1689(O=C-O,Oxazepine),1661(C=O,amid),1593(O=C-N,Oxazepine),1402(C=C,Ar.), 1271 (C-N,aryl).^{1}HNMR(500MH,δppm):B;4.3(CH_2,ethylene),g;3.8(CH_3,ethylene),F;7.6, E;7.8,a;7.9,D;6.9,P;6.7,b;8.2,m;7.0,h;6.8(Benzene),J;7.7(H,Ethylene),A;3.8,N;8.1

(CH,methane),M;12.1(Amide),Z;4.9,f;9.8(Alcohol),2.5(DMSO).^{13}CNMR(125MH, δppm):B;70.1(CH_2,alip.),g;58.3(CH_3,ethylene)D;109.8,E;140.0,F;107.8,H ;117.6 ,C;158.9,G;156.7,P;115.2,Q;150.0,R;148.7,O;135.0,W;131.5,V;133.7,a;124.0,h; 116.0,m;121.2,b;129.8,(Benzene),I;181.7,U;174.1,X;167.6(Carbonyl),L;168.9 (Amide),K;166.7,J;118.9(Ethylene),A;61.8,N;104.5(CH,alip.),39-40(DMSO).

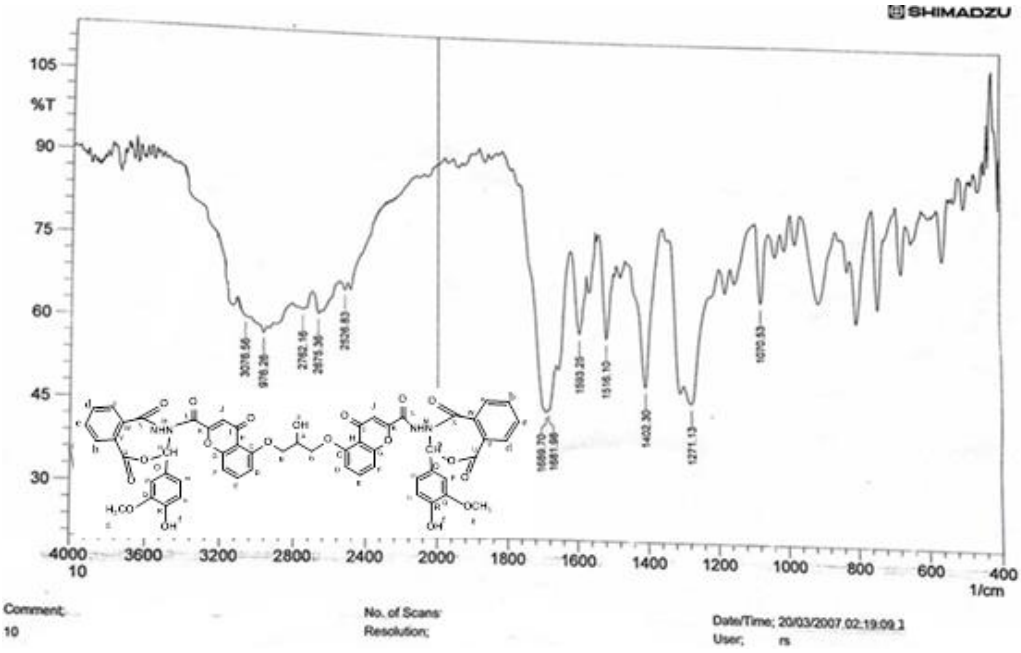


Figure (3-73): FT-IR spectrum for A25

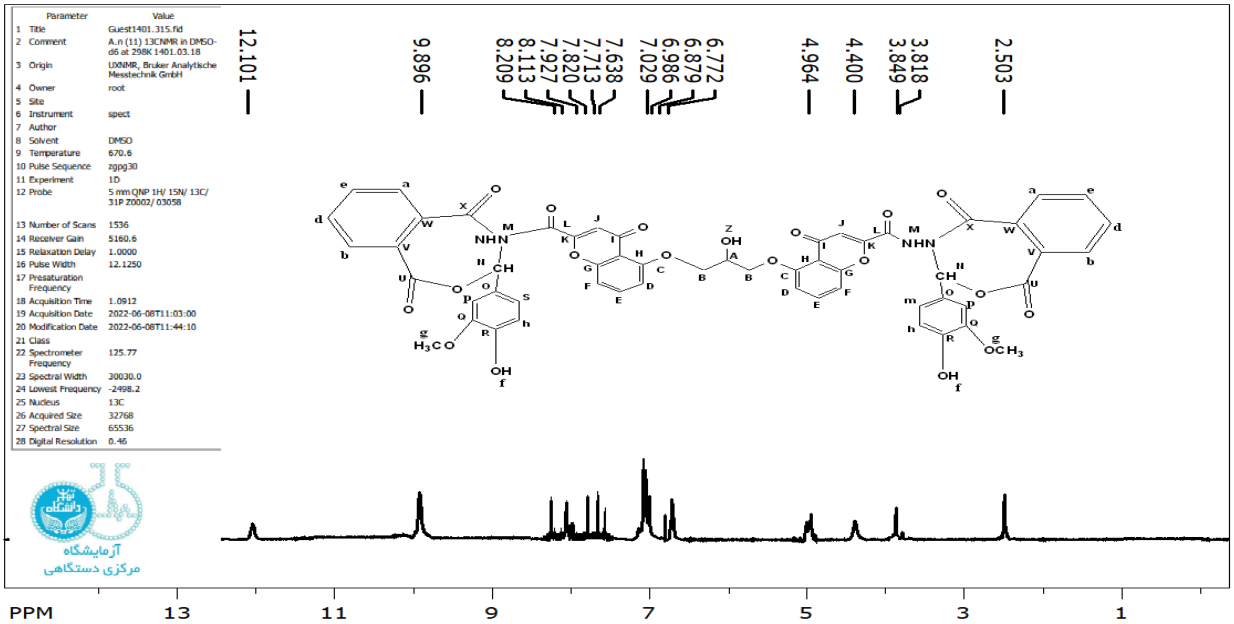


Figure (3-74): ^{1}H-NMR spectrum for A25

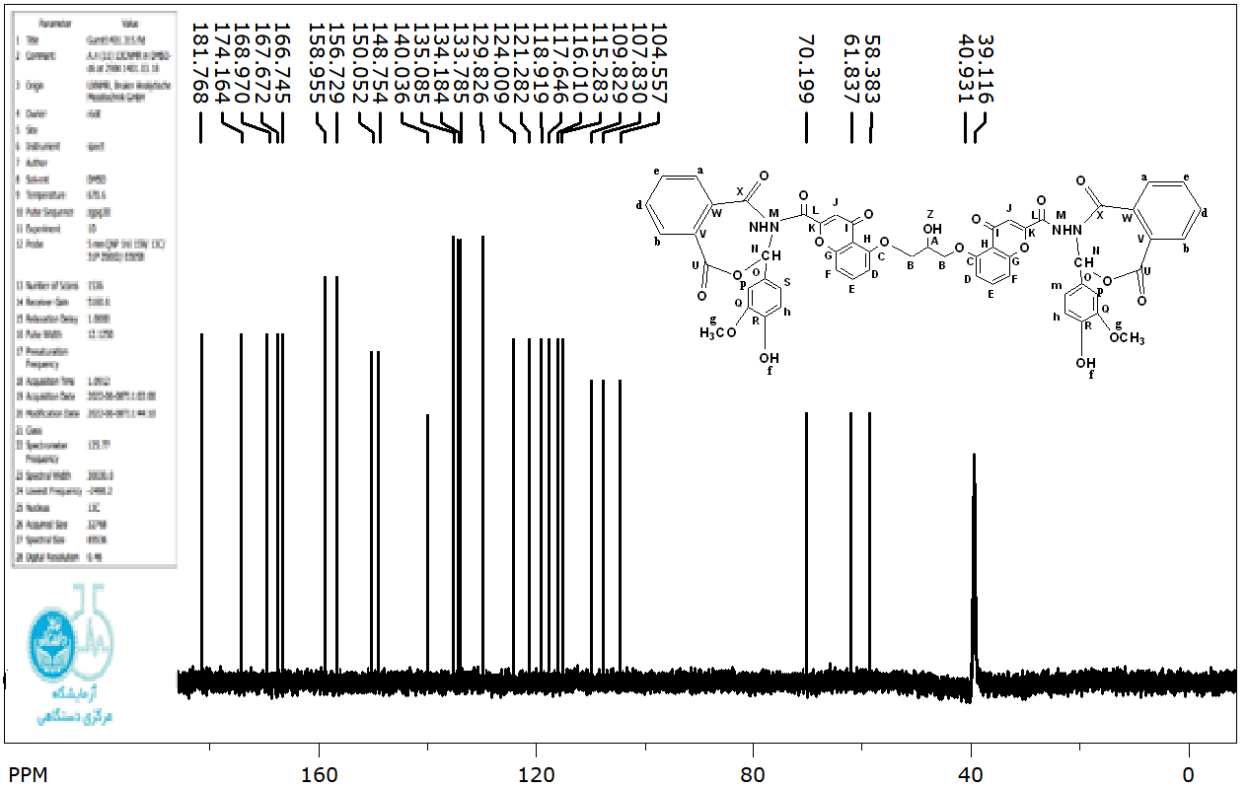
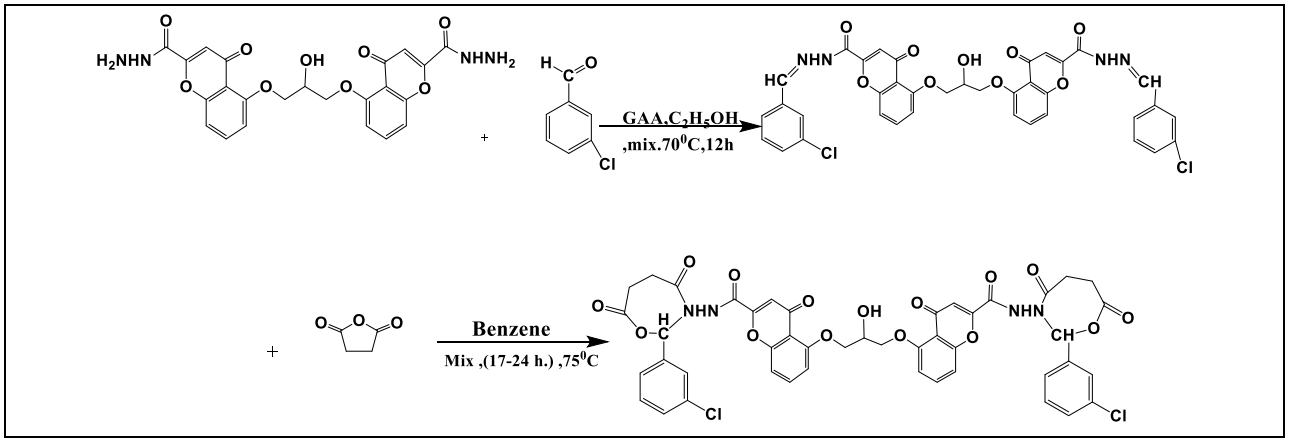


Figure (3-75): ^{13}C-NMR spectrum for A25



Equation (3-26): synthesis of A26

FT-IR (V max., cm^{-1}) spectrum of compound (A26) showed the following values:3400(OH,alcohol),3210(NH,amide),2976(CH,str.),1715(Ketone), 1693(O=C-O,Oxazepine),1639(C=O,amide),1590(O=C-N,Oxazepine),1419(C=C,Ar.),

1201(C-N,aryl).[1]HNMR(500MH,δppm):W;2.3,V;2.4,B;4.3(CH_2,ethylene), D;6.7,E;7.5,F;7.1,S;7.0,R;h;7.3,P;7.4(Benzene),J;7.0(H,Ethylene),A;3.6,N;8.1 (CH ,methane),M;12.1(Amide),Z;4.9(Alcohol),2.5(DMSO).[13]CNMR(125MH,δppm): B;69.2,W;27.0,V;29.9(CH_2,alip.),D;109.7,E;138.5,O;142.1,F;107.1,H;115.0,G;155 .9,C;158.8,P;126.8,Q;133.4,R;128.5,h;130.2,S;125.2(Benzene),I;182.5,U;174.9,X; 173.7(Carbonyl),L;165.3(Amide),K;163.6,J;118.2(Ethylene),A;60.5,N;105.2(CH,a lip.),39-40(DMSO).

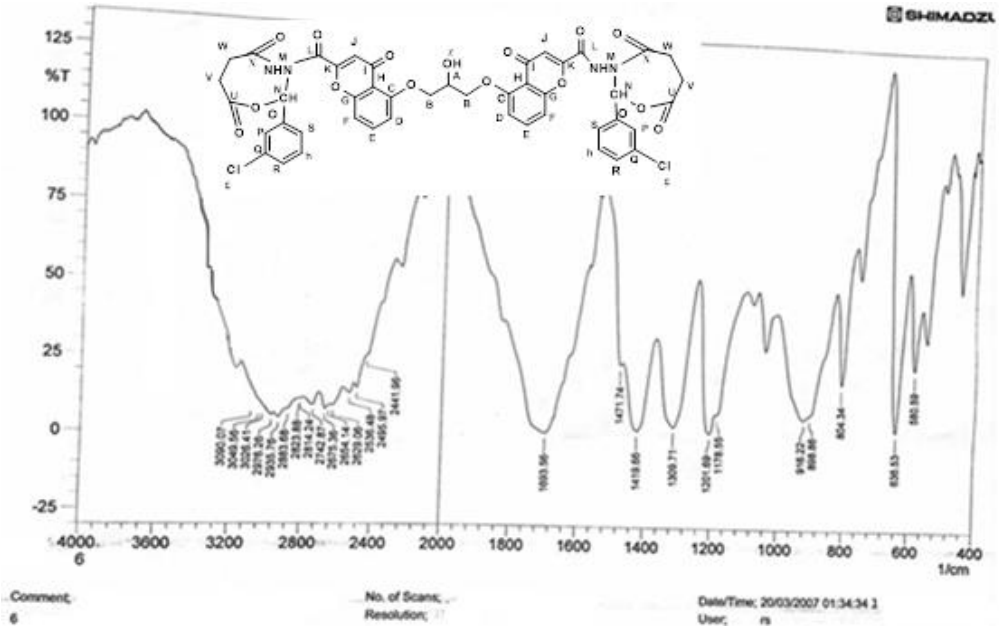


Figure (3-76): FT-IR spectrum for A26

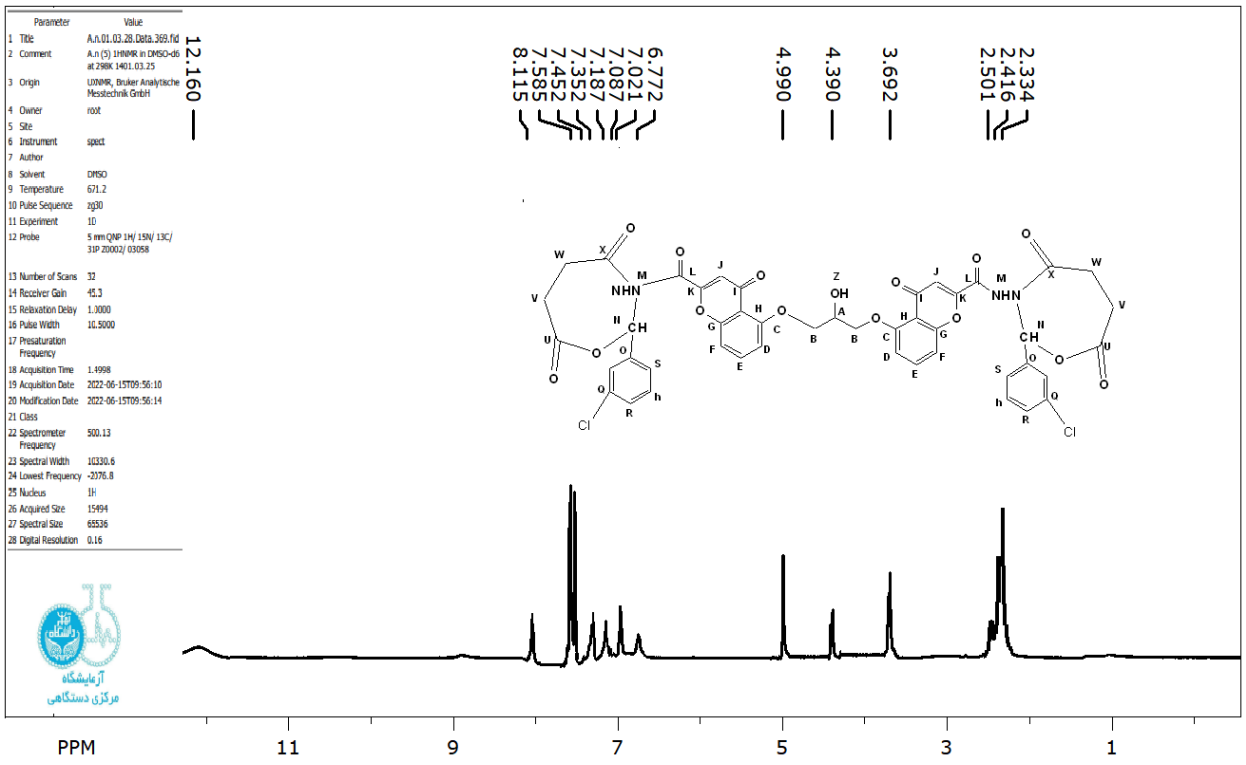


Figure (3-77): ^{1}H-NMR spectrum for A26

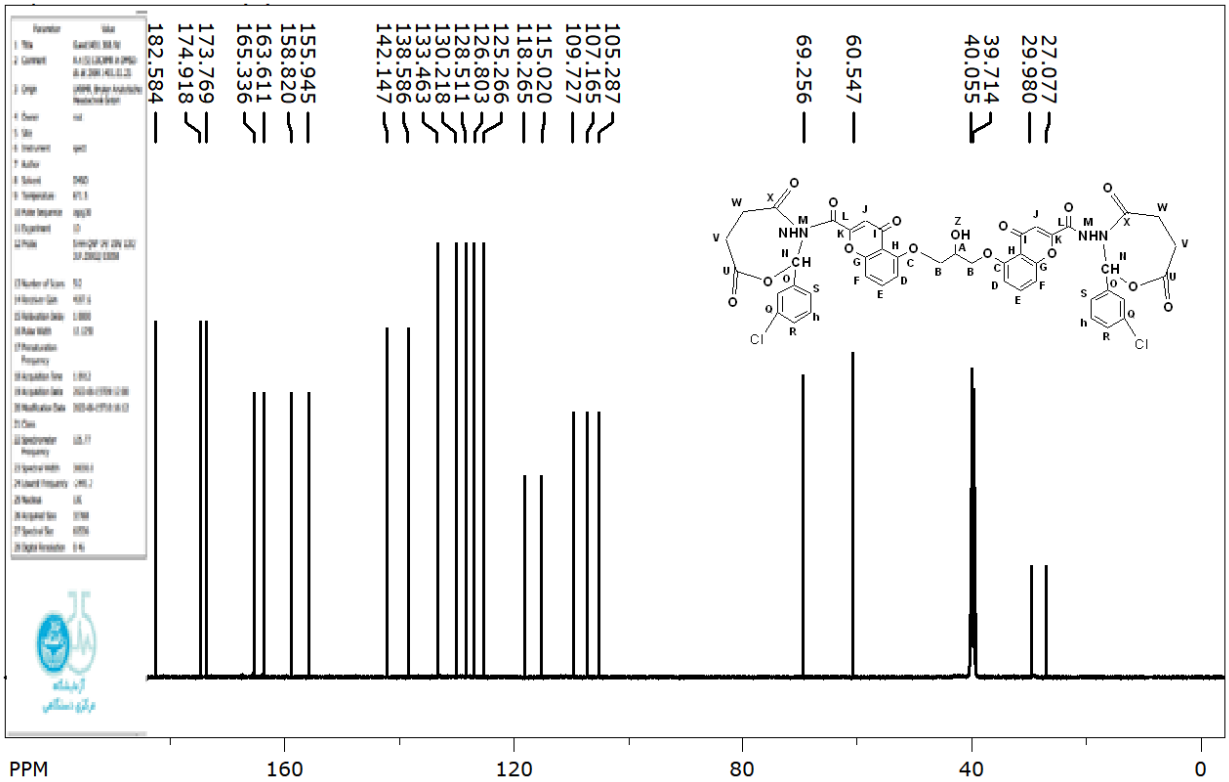
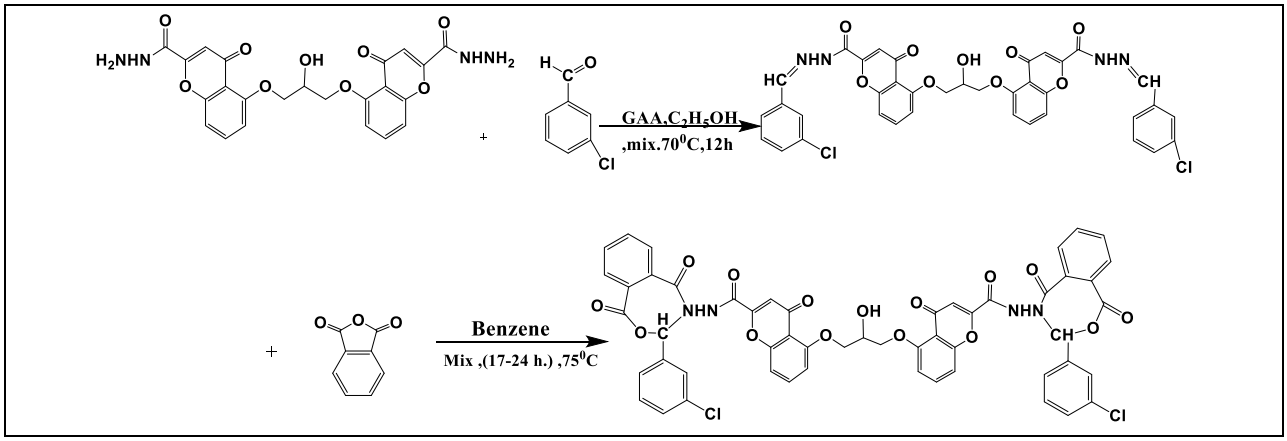


Figure (3-78): ^{13}C-NMR Spectrum for A26



Equation (3-27): synthesis of A27

FT-IR (V max., cm^{-1}) spectrum of compound (A27) showed the following values: 3490(OH alcohol) , 3320(NH amide) , 2997(CH str.) , 1707(Ketone) , 1651 (O=C-O, Oxazepine), 1631 (C=O amide),1600 (O=C-N , Oxazepine) , 1454 (C=C,Ar.),1257(C-N aryl).^{1}H-NMR(500MH,δppm):B;4.3(CH_2,ethylene), D;6.7,E ; 7.5,F;7.19,S;7.12,R;h;7.3,P;7.4,a;6.3,b;6.9(Benzene),J;7.2(H,Ethylene) ,A;3.6,N; 8.1(CH, methane),M;12.1(Amide),Z;4.9(Alcohol),2.5(DMSO).^{13}CNMR(125MH, δppm):B;69.5(CH_2,aliphatic),D;109.9,E;138.5,F;107.9,H;115.6,C;159.0,G;156.5, P;R;128.0,Q;134.7,O;144.6,W;122.3,V;135.6,a;126.2,b;129.6,h;131.6 (Benzene) ,I;182.7,U;168.2,X;166.0(Carbonyl),L;167.3(Amide),K;165.1,J;118.1(Ethylene),A; 61.5,N;105.9(CH,aliphatic),39-40(DMSO).

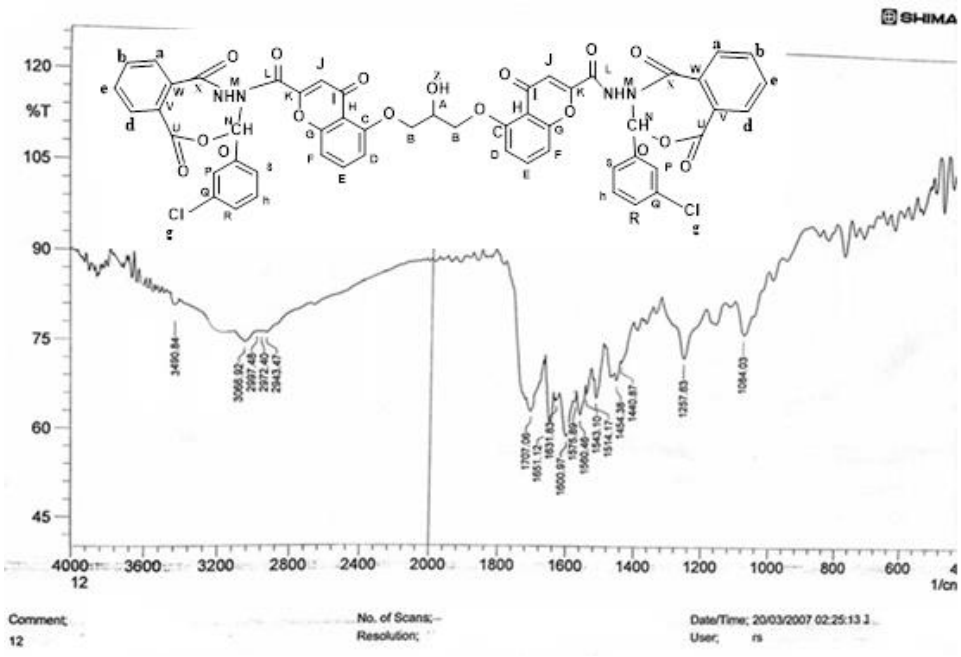


Figure (3-79): FT-IR spectrum for A27

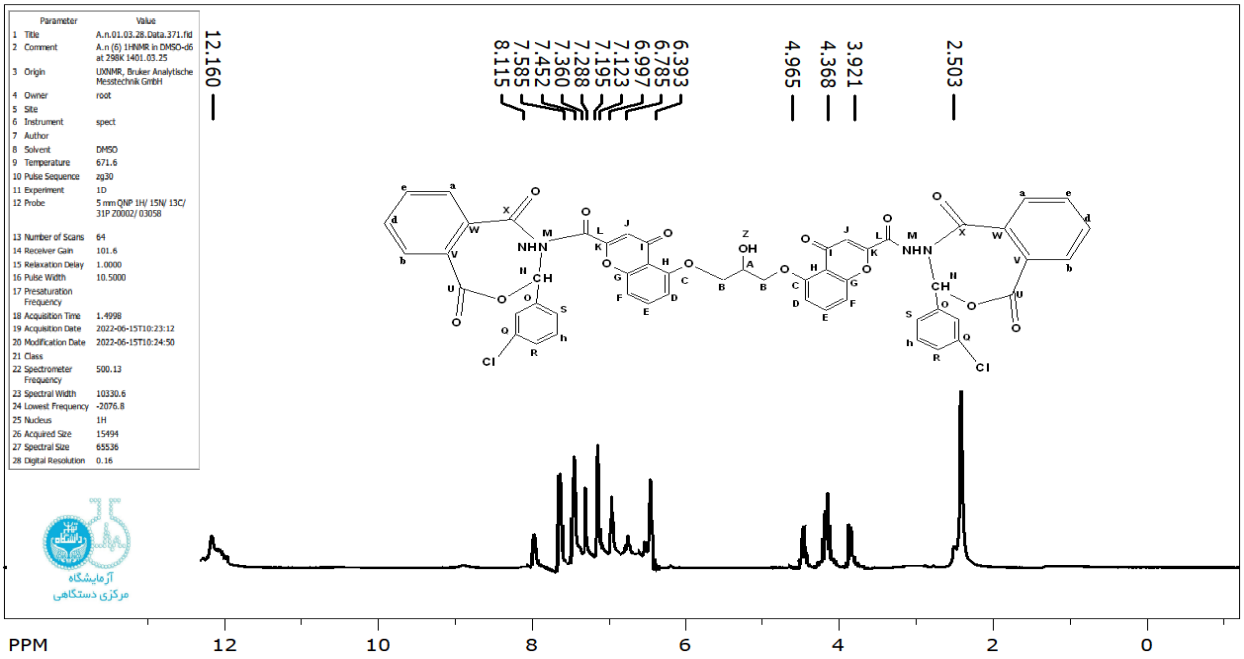


Figure (3-80): ^{1}H-NMR spectrum for A27

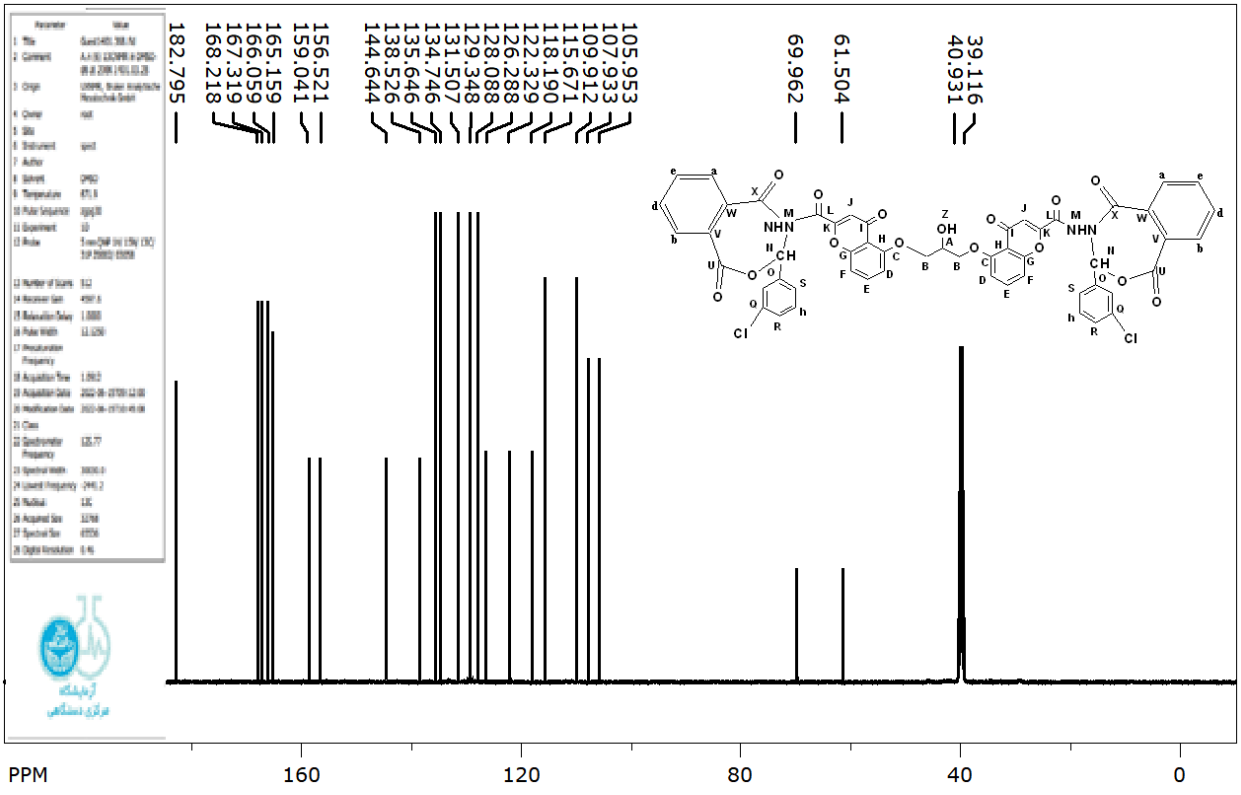
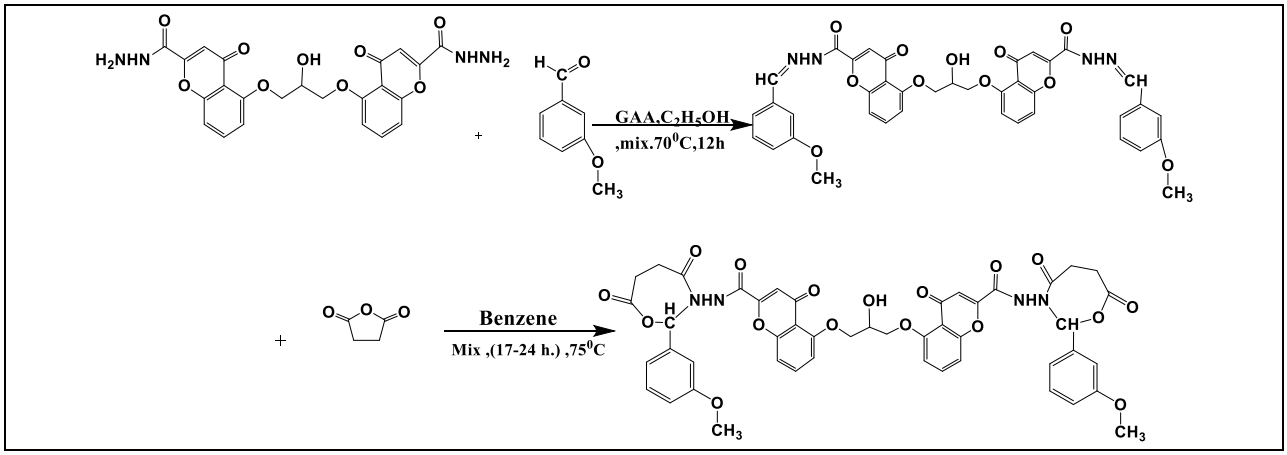


Figure (3-81): ^{13}C-NMR spectrum for A27



Equation (3-28): synthesis of A28

FT-IR (V max., cm^{-1}) spectrum of compound (A28) showed the following values: 3490(OH alcohol) , 3250(NH amide) , 2987(CH str.) ,1715(Ketone) , 1701(O=C-O, Oxazepine),1680(C=O amid),1640(O=C-N,Oxazepine),1427 (C=C, Ar.),1257(C-N,aryl).^{1}HNMR(500MH,δppm):W;2.2,V;2.3,B;4.4(CH_2,ethylene)

,g;3.8(CH_3,ethylene),D;6.6,E;7.5,F;7.2,S;6.8,R;6.7,P;6.9,h;7.1(Benzene),J;7.3(H,Ethylene),A;3.7,N;8.1(CH,methane),M;12.0(Amide),Z;4.9(Alcohol),2.5(DMSO).^{13}C NMR(125MH,δppm):B;69.5,W;28.1,V;29.6(CH_2,aliphatic),g;56.8(CH_3),D;108.7,E;138.4,F;106.3,H;118.8,G;156.1,C;158.5,P;113.6,R;116.4,S;119.8,h;128.2,O;143.7,Q;160.3(Benzene),I;183.2,U;175.4,X;172.3(Carbonyl),L;165.9(Amide),K;163.9,J;118.8 (Ethylene),A;61.2,N;103.1(CH,aliphatic),39-40(DMSO).

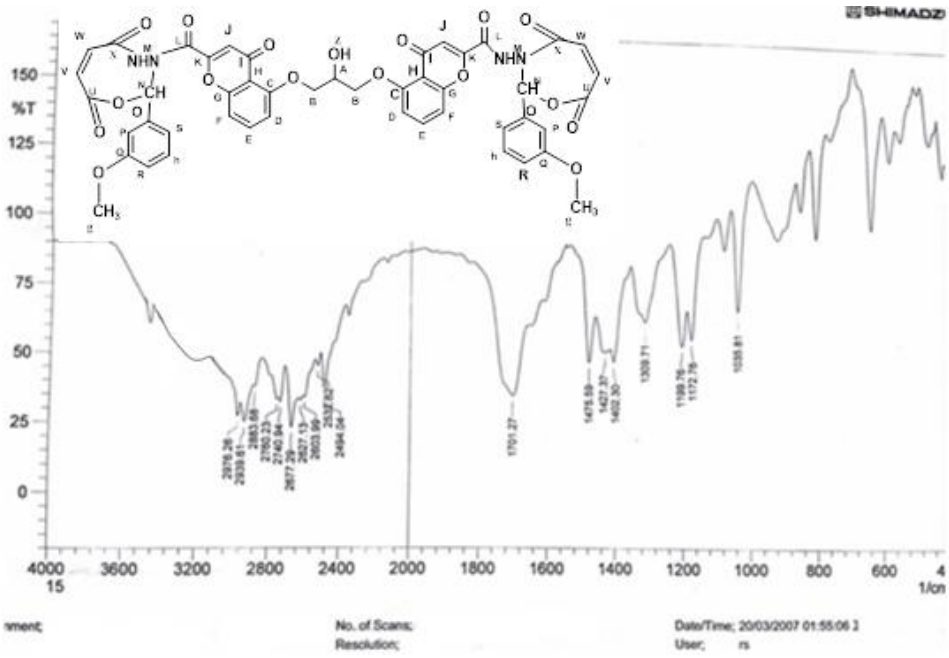


Figure (3-82): FT-IR spectrum for A28

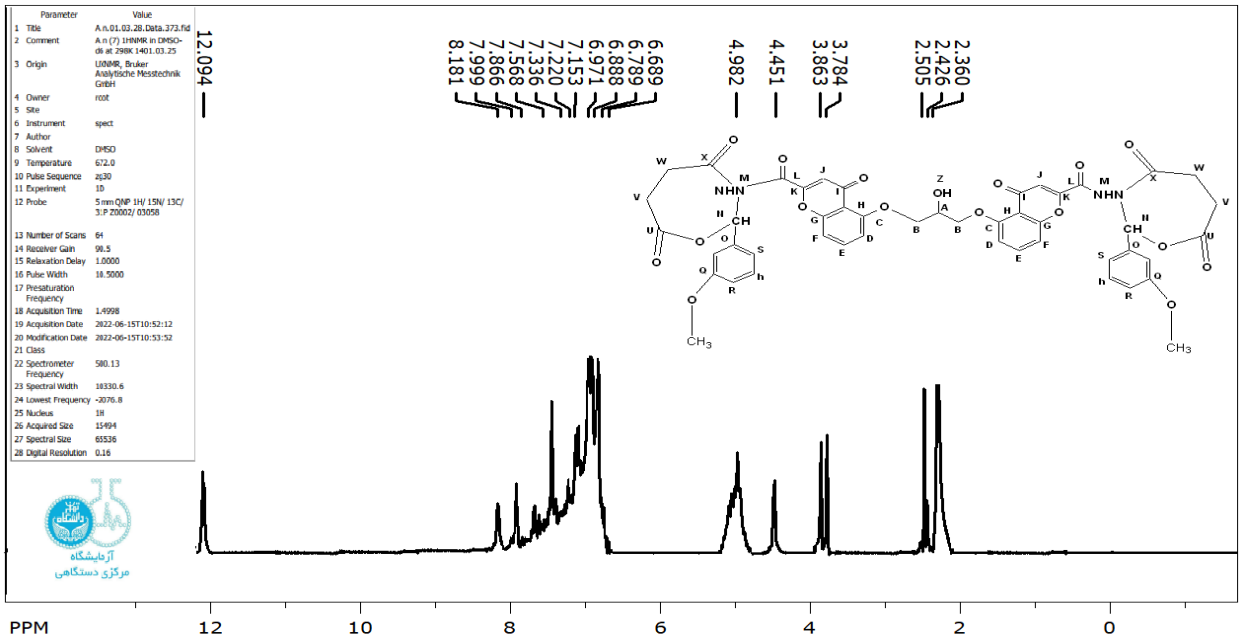


Figure (3-83): ^{1}H-NMR spectrum for A28

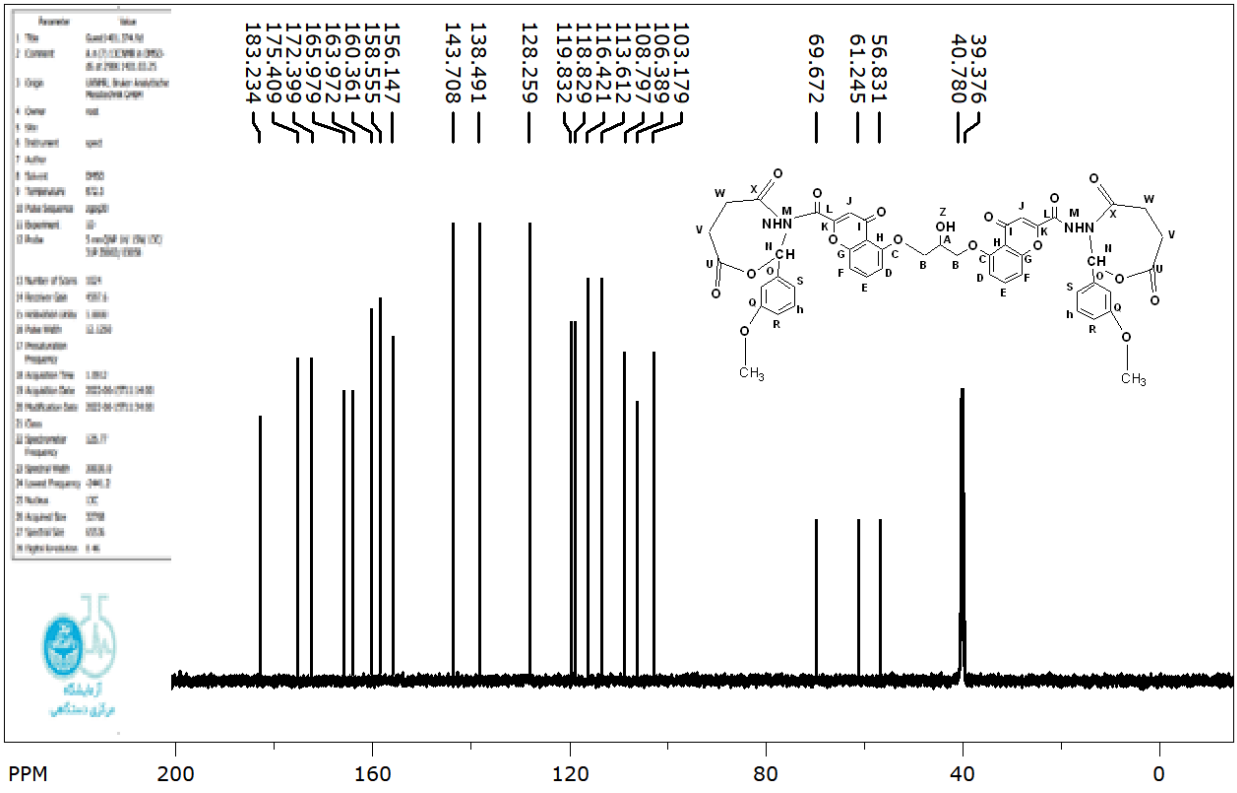
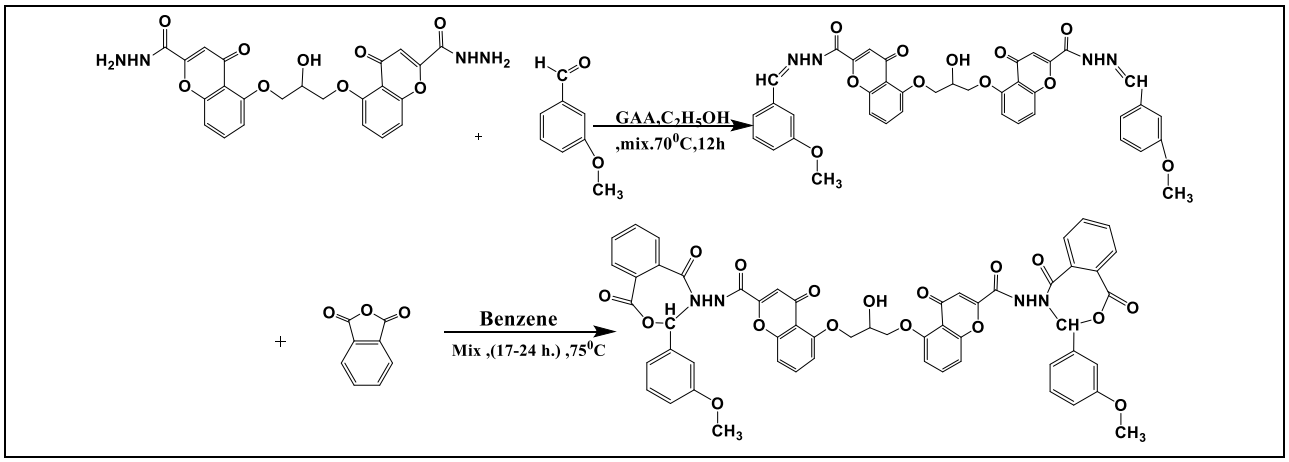


Figure (3-84): ^{13}C-NMR spectrum for A28



Equation (3-29): synthesis of A29

FT-IR (V max., cm^{-1}) spectrum of compound (A29) showed the following values: 3434(OH alcohol) , 3269(NH amide) , 2972(CH str.) , 1740 (Ketone)1687(O=C-O,Oxazepine) ,1720(C=Oamid) , 1587(O=C-N,Oxazepine), 1471 (C=C,benzenering),1309(CN).^{1}HNMR(500MH,δppm):B;4.3(CH_2,ethylene),g;3.9(CH_2,ethylene),D;6.8,E;Q;7.3,S;6.9,F;7.15,R;6.92,P;6.97,a;7.8,b;7.9,h;7.12 (Benzene),J;7.2(H,Ethylene),A;3.7,N;8.1(CH,methane),M;12.1(Amide),Z;4.9 (Alcohol),2.5(DMSO).^{13}CNMR(125MH,δppm):B;69.5(CH_2,aliphatic),g;55.9(CH_3, aliphatic),D;109.9,E;138.5,F;107.4,H;J;118.1,C;158.2,G;156.1,P;112.8,Q;161.3,R; 116.3,O;142.3,W;131.6,V;132.8,a;124.5,b;128.1,h;129.3,S;119.5(Benzene),I;182.2 ,U;167.0,X;173.7(Carbonyl),L;166.1(Amide),K;164.1,J;118.9(Ethylene),A;60.6,N; 105.3(CH,aliphatic),39-40(DMSO).

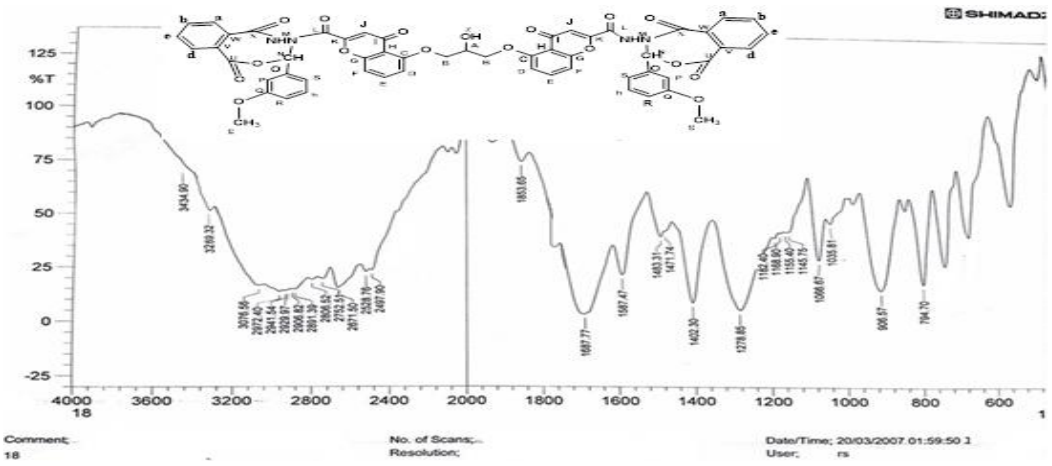


Figure (3-85): FT-IR spectrum for A29

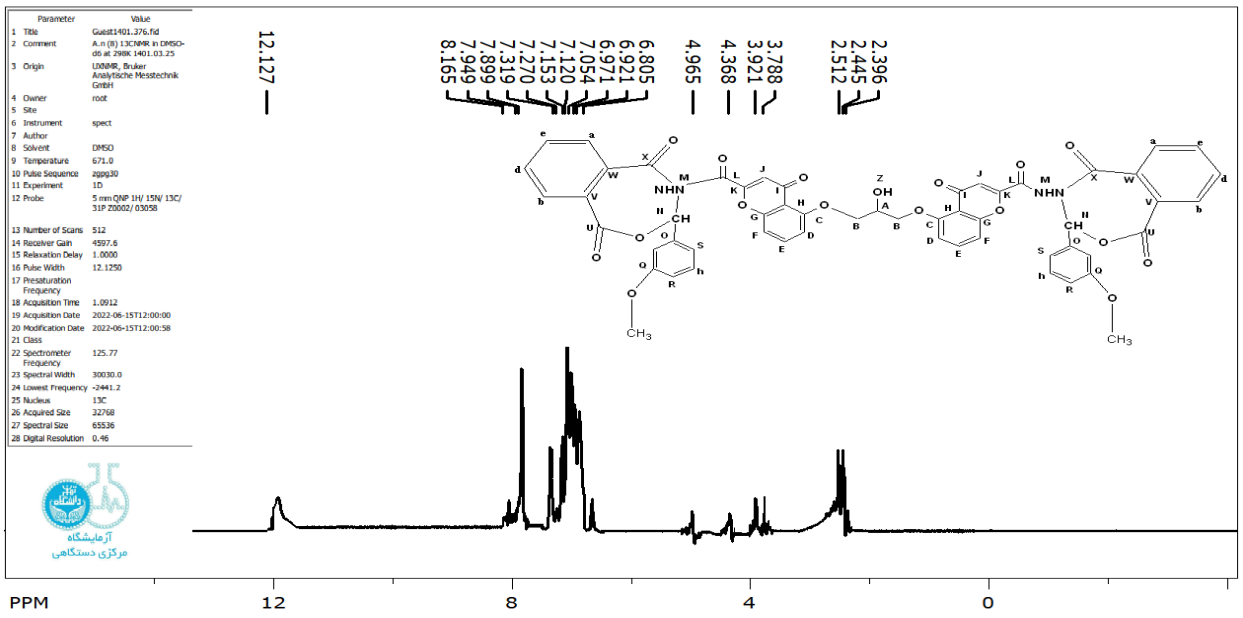


Figure (3-86): ^{1}H-NMR spectrum for A29

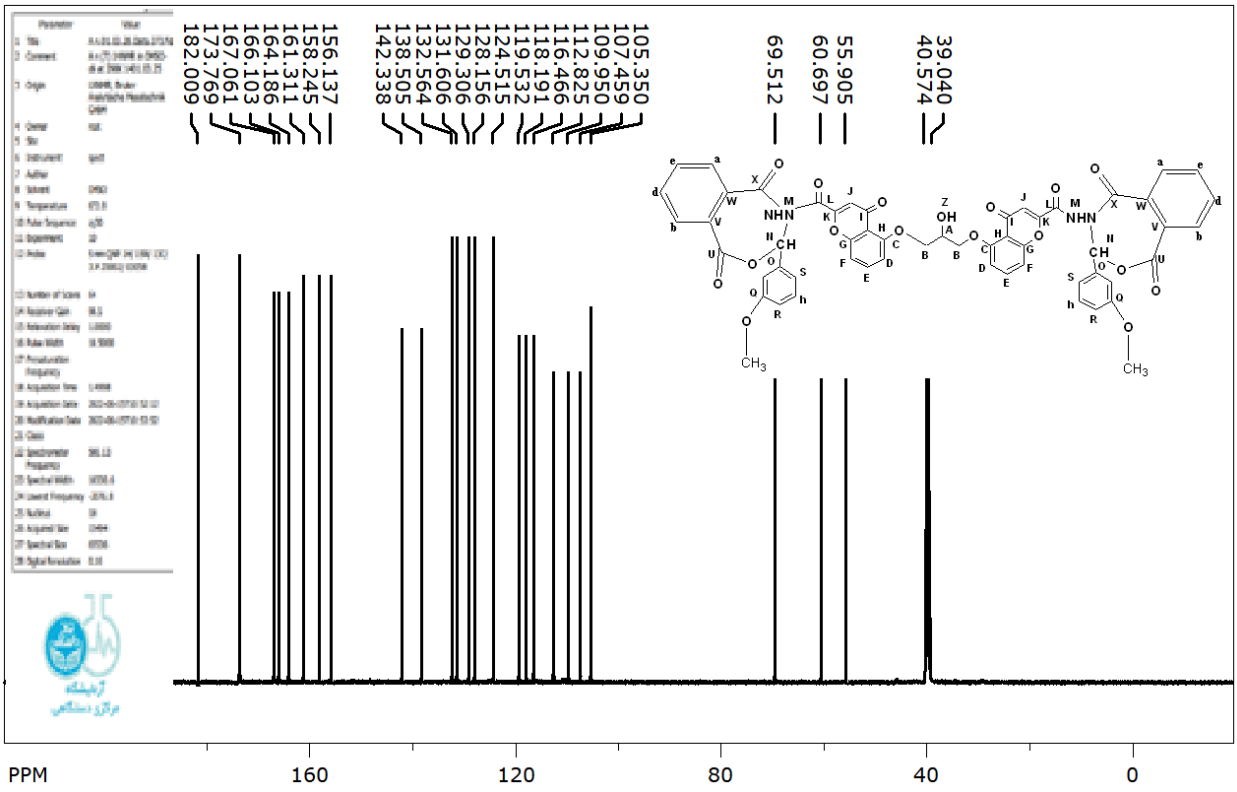


Figure (3-87): ^{13}C-NMR spectrum for A29

3-4. Micro elemental Analysis (CHN):

Table (3-1): C.H.N Elementary analysis for prepared derivative

Comp. Sym.	Calculated %				Found values %			
	C	S	H	N	C	S	H	N
A3	63.76	-	4.23	10.37	63.65	-	4.19	**10.32**
A5	58.4	5.67	4.46	7.43	58.0	5.61	4.40	**7.40**
A15	54.55	-	4.05	18.77	54.49	-	4.00	**18.74**
A16	67.97	-	6.16	10.07	67.90	-	6.12	**10.03**
A19	62.21	-	3.71	6.45	62.11	-	3.65	**6.41**

A20	65.70	-	3.75	5.78	65.64	-	3.70	**5.74**
A24	58.51	-	4.18	5.81	58.43	-	4.13	**5.74**
A27	57.40	7.53	3.64	5.95	57.34	7.47	3.60	**5.89**
A28	57.64	7.56	3.23	5.98	57.60	7.51	3.18	**5.92**

3-5. The solubility:

All generated compounds are moderately soluble in water due to their relatively high molecular weight, while they are entirely soluble in DMSO and ethanol. The solubility of synthesized compounds was examined using various polarity solvents. Because the polarity of created compounds is higher than the polarity of these solvents, all synthesized compounds are insoluble in diethyl ether, petroleum ether, and ethyl acetate.

Table (3- 2): the solubility of prepared derivatives in different solvents.

Solv. / Comp.	DMSO	water	Etha.	Ace.	Meth.	Haxe.	1,4-dioxan	DCM	DMF	Diet. ether	P. ether	Ethyl ace.
A1	+	-	+	+	partial	-	+	partial	+	-	-	-
A2	+	-	-	+	partial	-	-	-	+	-	-	-
A3	+	-	partial	+	partial	partial	partial	-	+	partial	-	**partial**
A4	+	-	+	+	+	-	+	+	+	-	-	+
A5	+	partial	+	+	+	-	partial	partial	+	-	-	**partial**
A6	+	+	-	-	+	-	partial	-	+	-	-	-
A7	+	partial	-	partial	-	-	-	-	-	partial	-	-
A8	+	partial	+	+	+	partial	+	partial	+	partial	-	**partial**
A9	+	partial	+	+	+	-	+	partial	-	partial	-	-
A10	+	partial	+	+	partial	-	-	+	-	-	-	-
A11	+	partial	+	+	+	partial	partial	-	-	-	-	**partial**
A12	+	partial	+	+	partial	-	partial	-	-	-	-	-
A13	+	partial	+	+	partial	-	-	-	-	partial	-	-
A14	+	-	-	Partial	-	-	partial	+	+	-	-	-
A15	+	-	Partial	-	-	Partial	-	-	+	-	-	-
A16	+	partial	+	+	+	-	partial	-	-	partial	-	-
A17	+	-	-	partial	-	Partial	Partial	-	+	-	-	**Partial**
A18	+	partial	+	+	partial	-	-	partial	-	-	-	-
A19	+	partial	+	+	-	-	-	+	-	partial	-	**partial**

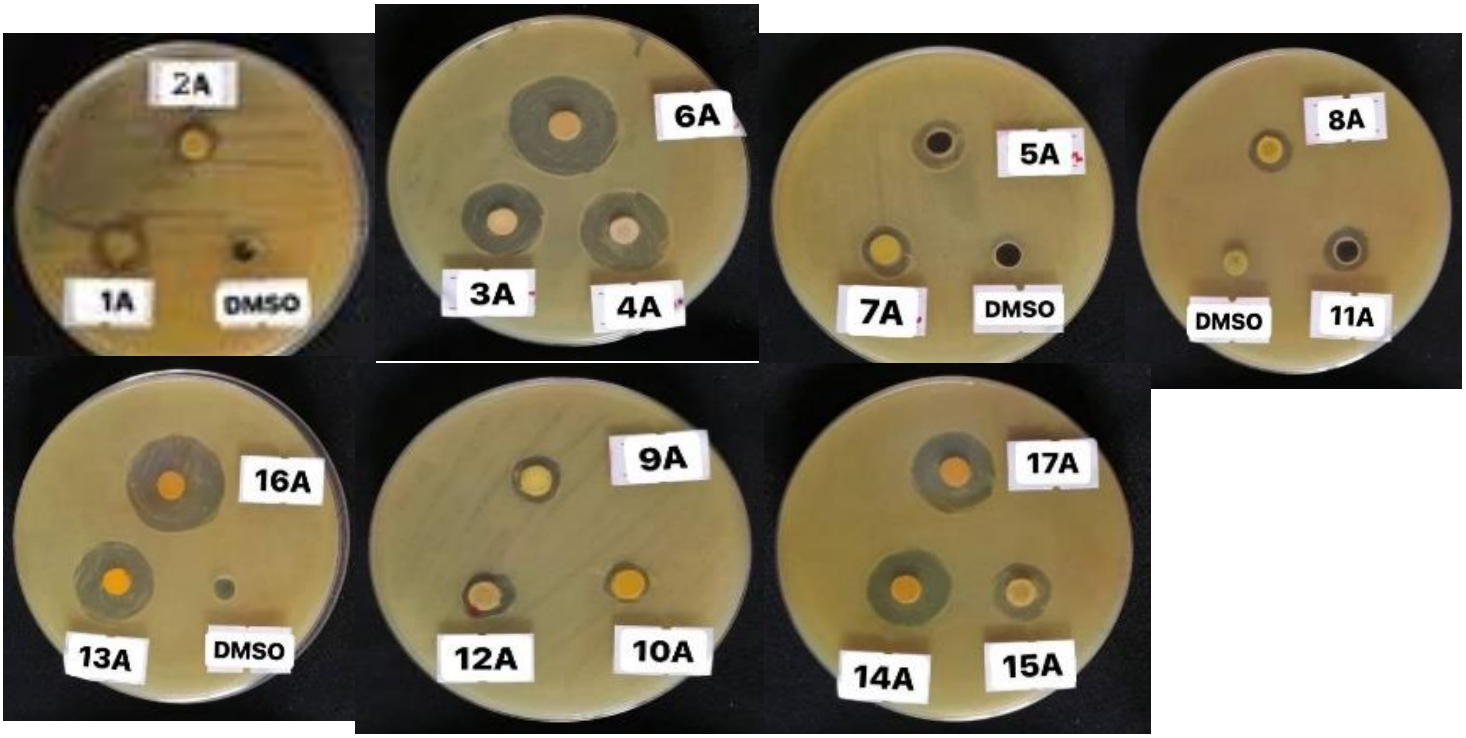
A20	+	partial	+	+	-	-	-	-	-	partial	-	-
A21	+	partial	+	+	partial	-		-	-	partial	-	-
A22	+	partial	+	+	-	partial	partial	-	-	-	-	-
A23	+	partial	+	+	-	-	-	-	-	-	-	-
A24	+	partial	+	+	partial	partial	-	-	-	-	-	-
A25	+	partial	+	+	-	partial	-	-	-	-	-	-
A26	+	partial	+	+	-	partial	partial	-	-	-	-	**partial**
A27	+	partial	+	+	-	-	-	partial	partial	-	partial	**partial**
A28	+	partial	+	+	-	-	-	partial	partial	-	partial	**partial**
A29	+	partial	+	+	-	partial	-	-	-	-	-	**partial**

3-6. Biological Activity:

3-6-1. Antibacterial activity

The results showed that most of the investigated chemicals have good antibacterial activity. These bacteria were selected due to their vast clinical value and the fact that they are resistant to a wide range of antibiotics and chemical drugs in addition to causing a number of ailments. According to Table 2, the synthesized chemicals can suppress the bacteria by changing their concentrations, proving that they have biological action against them.

figure (3-88,3-89). illustrates the variation in toxicity caused by changes to functional groups or structures .



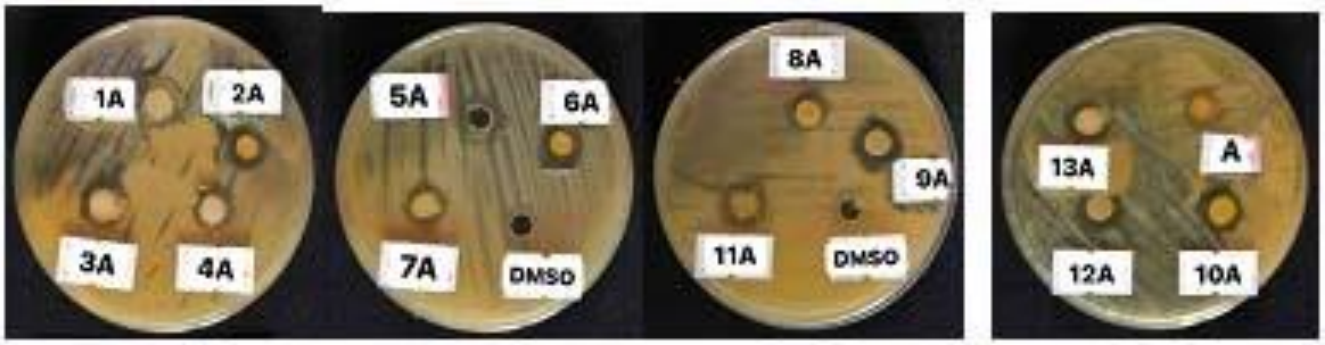


Figure (3-88) *Klebsiella pneumonia* activity test

No. of	Antibacterial activity test

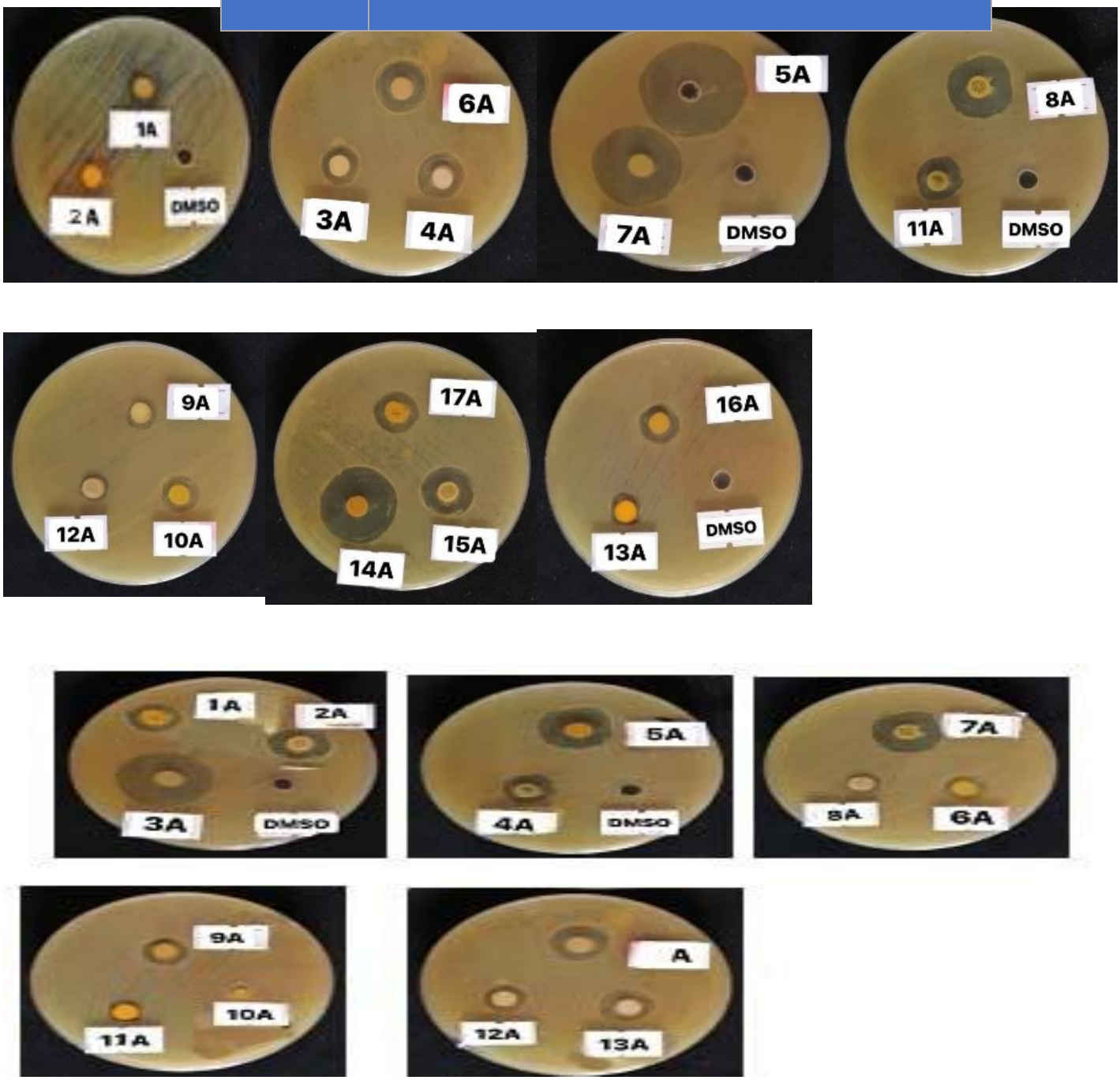


Figure (3-89). *Staphylococcus aureus* activity test

Table (3-3): applications of Antibacterial activity for compounds (A1-A29)

Comp.	*klebsiella pneumonia* (Gram-negative bacteria)	*Staphylococcus aureus* bacteria (Gram-positive
Control	16	14
1A	11	15
2A	14	11
3A	20	15
4A	22	17
5A	15	30
6A	26	19
7A	14	28
8A	13	22
9A	13	12
10A	12	14
11A	14	16
12A	13	11
13A	21	11
14A	20	27
15A	16	19

16A	26	15
17A	21	16
18A	16	20
19A	16	22
20A	15	15
21A	17	26
22A	15	14
23A	14	13
24A	14	13
25A	17	12
26A	16	14
27A	15	13
28A	11	21
29A	20	20

3-6-2. Antioxidants activity

The conventional DPPH method was used to perform the compounds' antiradical action.Table (4) Fig: (3-90) The majority of the substances had moderate to high antioxidant activity when compared to normal (ascorbic acid) activity (IC50=28.72 mg/mL). In compounds (A1-A8) with considerable activity, the OH group was responsible for the greatest activity. Generic ascorbic acid has an IC50 value of 28.72 M. When compared to the reference, the test compounds' antioxidant forces are in the following order: A22>A23>A26>A17>A19>A12>A25>A5>A20>A13>A2>A14>A1>A6>A16+20 >A9>A4>A8>A3>A10>A18>A29>A15>A7> A11>A27>A24>A28.

Table (3-4): applications of Antioxidants activity: for compounds (A1-A29)

Comp. No.	Inhibition %			IC50 mg/mL
	25 mg/mL	50 mg/mL	100mg/mL	
A1	54.76	55.83	60.77	27.92
A2	49.05	55.12	58.6	24.45
A3	46.13	52.11	60.02	43.5
A4	48.04	53.05	57.12	36.36
A5	48.06	58.56	90.91	21.33
A6	49.46	53.02	59.16	30.08
A7	44.22	51.44	60.03	50.38
A8	49.01	50.01	55.21	42.23
A9	48.22	55.44	56.55	33.87

A10	46.28	52.36	57.21	47.3
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
A18	45.28	51.36	59.21	48.05
A19	50.05	55.12	58.6	16.9
A20	56.32	62.14	65.01	22.53
A21	55.2	59.11	63.23	31.4
A22	51.41	58.09	62.22	5.07
A23	50.46	56.02	59.16	11.1
A24	41.24	47.52	56.17	71
A25	49.33	58.05	65.16	21.15
A26	52.43	55.67	65.17	13.6
A27	57.32	63.08	65.01	68.27
A28	39.24	46.52	53.7	79.7
A29	45.22	50.44	63.03	48.1
Ascorbic acid(STD)	46.12	60.14	65.01	28.72

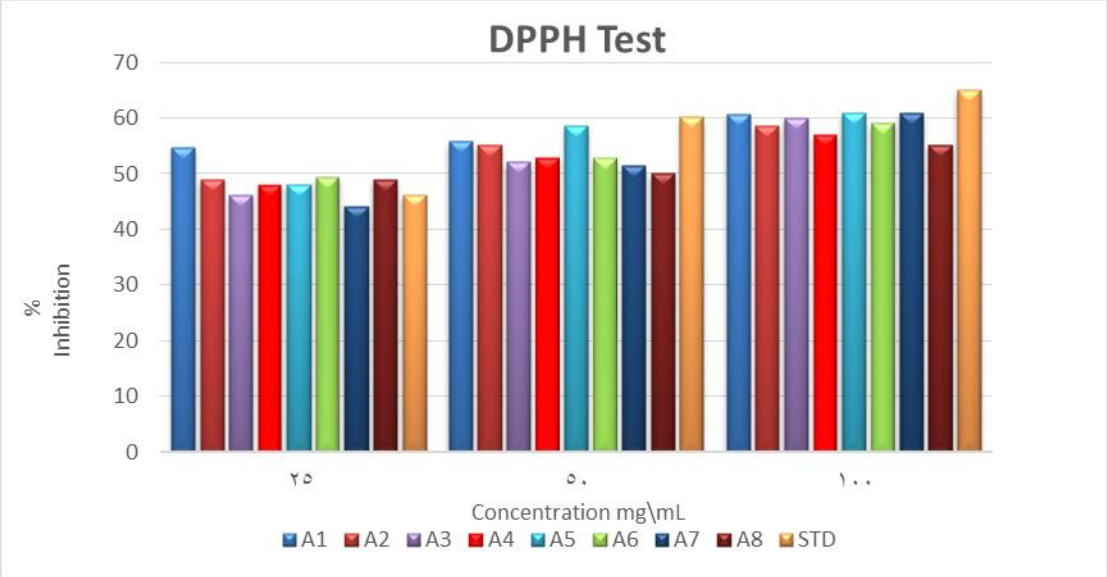


Figure (3-90): standard DPPH method for compound (A1-A8)

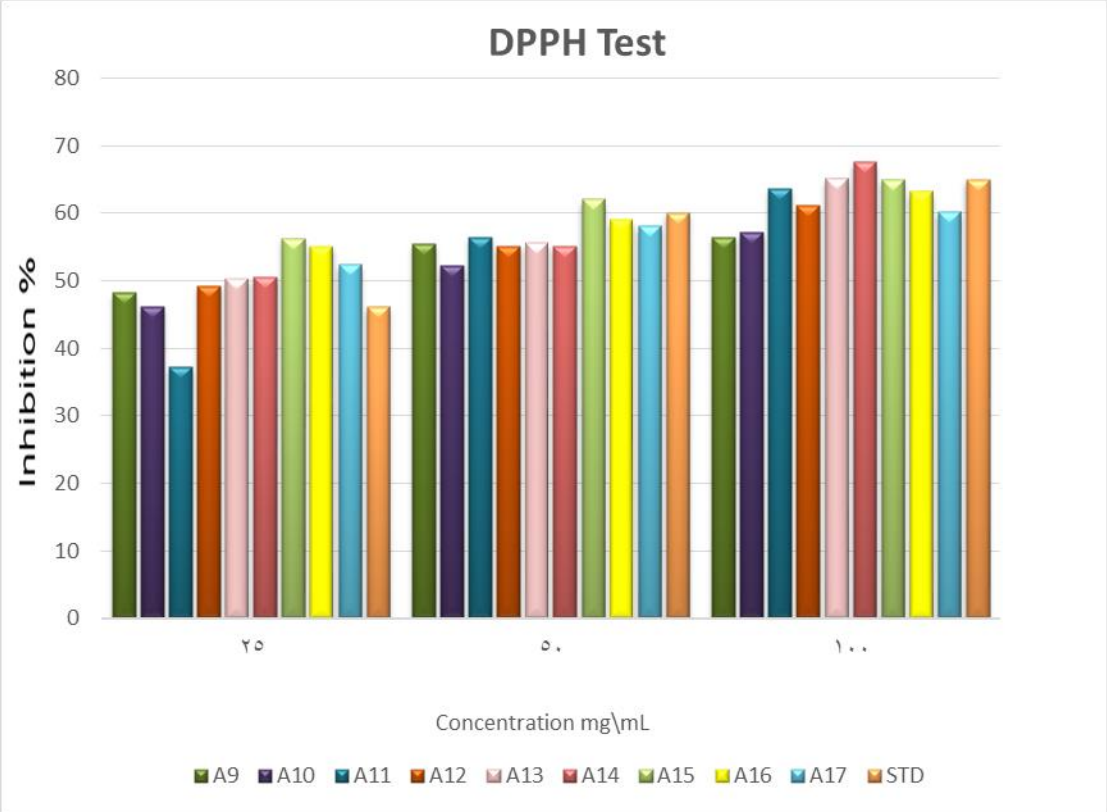


Figure (3-91): standard DPPH method for compound (A9-A17)

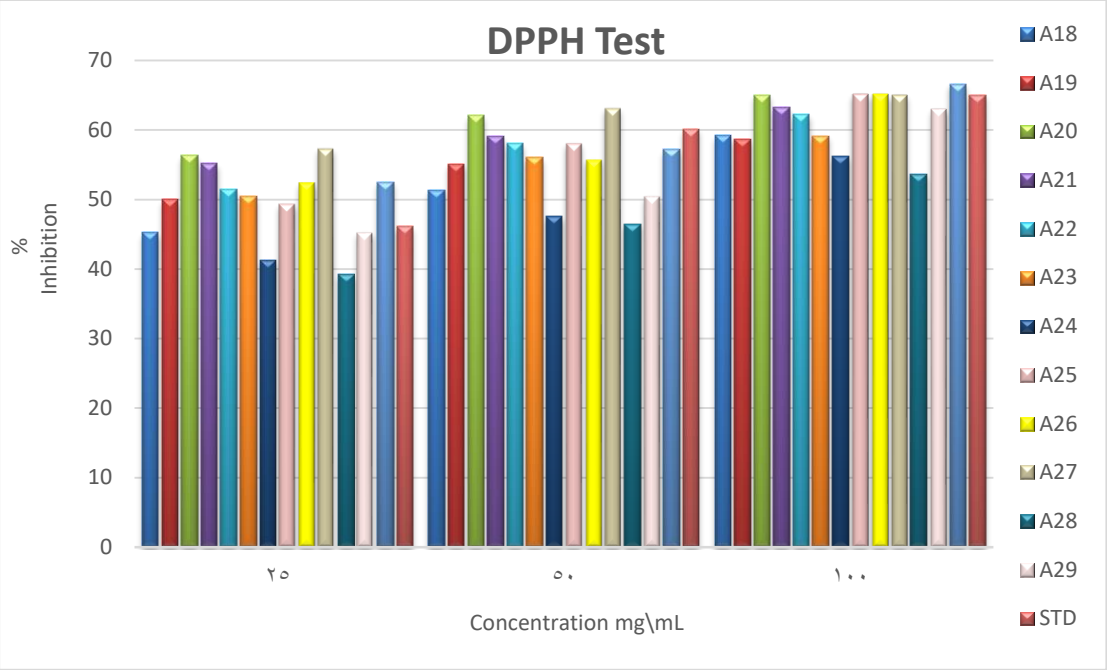


Figure (3-92): standard DPPH method for compound (A18-A29)

Supervision Certificate

I certify that this thesis (Synthesis and Characterization of new organic compounds from Cromoglicic acid and Study Some of Their Applications) was prepared by Abeer Hassan Madloum, under my supervision in the Department of Chemistry, College of Science / University of Babylon, partially fulfilling the requirements for a master's degree in Chemistry / Organic chemistry.

Signature

Supervisor: **Hala Shkyair Lihumis**

College of Science, University of Babylon

Address Department of Chemistry - University of Babylon - College of Science

Date: / / 2022

Recommendation of the head of the chemistry department

I certify that this thesis was carried out in the department of chemistry, I nominate it to be presented to discussion.

Signature

Name: Prof. Dr. Abbas Jasim Atiyah Lafta

Address: Head of Chemistry Department - University of Babylon - College of Science

Date: / / 2022

Conclusions:

- ✓ A1-A29 compound were successfully synthesized dependent drugs containing amino and carboxyl groups.
- ✓ TLC and m.p are confirmed that the synthesized derivatives are of high purity.
- ✓ Confirmed all new derivatives structures via characterization with different techniques including FT-IR, 1HNMR, 13CNMR, and CHNS.
- ✓ Most of the synthesized derivatives give good antibacterial activity and they showed an activity more than the cromoglicic acid and the used drugs.
- ✓ Most of the synthesized derivatives give good antioxidant activity and they showed an activity more than the cromoglicic acid and the used drugs.
- ✓ The physical properties compounds are studied like the solubility.

The future work and the recommendation:

Due to the importance of cromoglicic acid derivatives in different fields such as medicinal, pharmaceutical, industrial, etc. we recommended:

- Studying the medicinal uses of the prepared compounds.
- Studying the mechanism of bacterial inhibition of the prepared compounds.
- Studying the anticancer activity against different types of human cancer cells, such as Lung cancer cancer, etc.
- Preparation of new pharmaceutical derivatives using the prepared compounds as starting materials

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