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GRADUATE SCHOOL OF SCIENCE AND ENGINEERING

SYNTHESIS OF NEW COUMARIN DERIVATIVES AND THEIR POTANTIAL APPLICATIONS

Selen GÜNER

MASTER OF SCIENCE THESIS

Department of Chemistry

Chemistry (English) Program

Supervisor

Prof. Dr. Feray AYDOĞAN

June, 2023

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A thesis submitted by Selen GÜNER in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE is approved by the committee on 05.07.2023 in Department of Chemistry, Chemistry (English) Program.

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Selen GÜNER

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June 2023,

Selen GÜNER

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LIST OF ABBREVIATIONS

CAs	Carbonic anhydrases
CuAAC	Azide-Alkyne Cycloaddition
CVA16	Coxsackievirus A16
DMAPP	Dimethylallyl pyrophosphate
EAA	Ethyl acetoacetate
EV71	Enterovirus 71
FTIR	Fouirer Transform Infrared Spectrophotometer
HCV	Hepatitis C virus
HSV	Herpes Simplex Virus
LC-MS	Liquid chromatography–mass spectrometry
MOF	Metal-Organic Framework
NMR	Nuclear Magnetic Resonance Spectroscopy
SARs	Structural Activity Relationship Studies
SSA	Starch Sulfuric Acid
TLC	Thin layer chromatography

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ABSTRACT

Synthesis of New Coumarin Derivatives and Their Potential Applications

Selen GÜNER

Department of Chemistry

Chemistry (English) Program

Master of Science Thesis

Supervisor: Prof. Dr. Feray AYDOĞAN

In these days, the usage of coumarins as bactericides, fungicides, anti-inflammatory, anticoagulant, and antitumor medicines makes them a significant category of chemical substances. Pharmacological characteristics of these coumarins inspired interest of chemists in creating a variety of novel compounds with various heterocyclic rings fused to the coumarin moiety in an effort to produce more potent coumarins that are pharmacologically active. Due to their varied biological actions, triazoles, which include 1,2,3-triazole and 1,2,4-triazole as well as coumarins, play a significant role in medicinal chemistry. Some of these compounds have even been utilized in clinical settings. Because of its dependability, selectivity, and biocompatibility, the copper(I)-catalyzed 1,2,3-triazole-forming reaction between azides and terminal alkynes has emerged as the gold standard of "click chemistry." The triazole compounds are more than basically inert linkers; through hydrogen bonds and interactions between dipole-dipole, they easily bind to biological targets. In this work, triazole-coumarin hybrid compounds with the ability to display a variety of biological activities were synthesized based on three different coumarin motifs, and their structures were identified by their spectral data.

Keywords: Coumarin, triazole, click chemistry, biological activity

YILDIZ TECHNICAL UNIVERSITY

GRADUATE SCHOOL OF SCIENCE AND ENGINEERING

ÖZET

Yeni Kumarin Türevlerinin Sentezi ve Potansiyel Uygulamaları

Selen GÜNER

Kimya Bölümü

Kimya (İngilizce) Anabilim Dalı

Yüksek Lisans Tezi

Danışman: Prof. Dr. Feray AYDOĞAN

Kumarinler, günümüzde bakterisit, fungisit, anti-inflamatuar, antikoagülan ve antitümör ajanlar olarak kullanılan önemli bir organik bileşik grubudur. Kumarinlerin farmakolojik özellikleri, sentetik kimyagerlerin kumarin iskeletine farklı heterosiklik halkaların birleştirildiği yeni bileşiklerin sentezlenmesine olan ilgisini uyandırmış ve daha etkili farmakolojik olarak aktif bileşikler elde etmek amacıyla araştırmalar yapılmıştır. 1,2,3-triazol ve 1,2,4-triazol gibi triazoller ile kumarinler, çeşitli biyolojik aktivitelere sahip olmaları nedeniyle tıbbi kimyada önemli bir konuma sahiptir ve bazıları klinik uygulamalarda kullanılmıştır. Azitler ve terminal alkinler arasındaki bakır(I)-katalizli 1,2,3-triazol oluşumu reaksiyonu, güvenirliği, özgüllüğü ve biyolojik uyumluluğu nedeniyle "klik kimyası"nın altın standartı haline gelmiştir. Triazol ürünleri yalnızca pasif bağlayıcılar değildir; hidrojen bağı ve dipol-dipol etkileşimleri yoluyla biyolojik hedeflerle kolayca etkileşime girerler. Bu çalışmada, üç farklı kumarin motifine dayanarak çeşitli biyolojik aktiviteler sergileyebilecek triazol-kumarin hibrit bileşiklerin sentezi gerçekleştirilmiş ve yapıları spektral verileri kullanılarak aydınlatılmıştır.

Anahtar Kelimeler: Kumarin, triazol, klik kimyası, biyolojik aktivite

YILDIZ TEKNİK ÜNİVERSİTESİ

FEN BİLİMLERİ ENSTİTÜSÜ

1
INTRODUCTION

In recent years, clinical and pharmaceutical investigation has become much more interested in the synthesis of organic molecules and the study of their varied biological functions. A family of substances known as coumarin derivatives has a variety of biological activities, including antioxidant, anticancer, antibacterial, antifungal and antiviral characteristics. Triazole compounds are also a large class of heterocyclic chemicals with essential uses in biology and medicine (Figure 1.1).

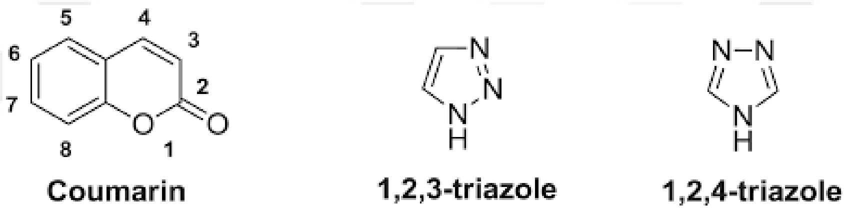


Figure 1.1 General Structure of Comarin and Triazole

The second-generation metabolites known as coumarins are extensively distributed in nature and might be found in the roots, flowers, leaves, peels, seeds, and fruits of several plant species [1]. Angelica dahurica, Calophyllum inophyllum, and Ferula flabelliloba can be accepted as only a few examples of these plants having numerous isolated coumarins. Since the majority of recovered coumarins exhibit biological activity, coumarin derivatives are increasingly being synthesized because it is time-consuming and uneconomical to extract them from plants [2].

The 1,2,3-triazole is one of two chemical compounds known as triazoles that have the molecular formula $C_2H_3N_3$. As seen in the Figure 1.1, triazoles consist of five-membered structures containing two carbon atoms and three nitrogen atoms. Various methods can be employed for the synthesis of triazole rings. Like coumarins, triazoles are also accepted as biologically active compounds.

New molecules with combined features can be synthesized by combining coumarin and triazole compounds. Heterocyclic ring structures of the coumarins has the ability to increase the biological activity of the chemical. Triazoles also have a variety of biological activities, including antibacterial, anticancer, and antiviral characteristics. Therefore, the synthesis of novel coumarin-triazole hybrid derivatives is crucial for the identification of physiologically active molecules that can be utilized to the development of new drugs.

During this study, it was aimed to synthesis and characterization of new coumarin and triazole hybrid compounds (Figure 1.2). FTIR, NMR, LC-MS were utilized for the characterization of the compounds. It is expected that these newly synthesized compounds will possess pharmacologically active properties.

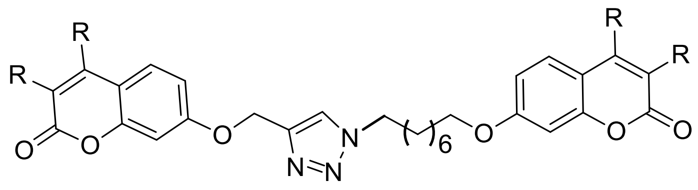


Figure 1.2 General structure of synthesized coumarin-triazole hybrids derivatives

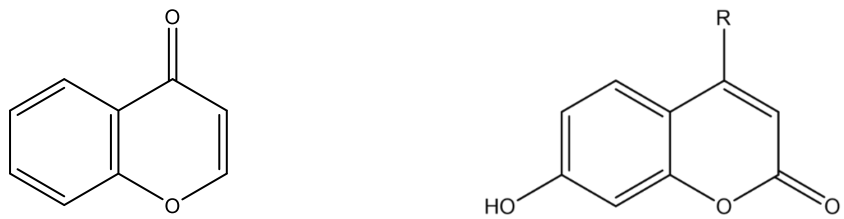
The main purpose of this master thesis is to create new coumarin-triazole hybridization compounds that combine the qualities of coumarin and triazole molecules through their synthesis and characterization. The findings of this study may have an impact on medication development and the search for physiologically active chemicals. Additionally, it is anticipated that this thesis will be a useful resource for scientists and researchers interested in organic synthesis and medication development.

2
COUMARINS

Coumarins are the largest group of 1-benzopyran derivatives found in plants. The initial member of this group of compounds, coumarin (2*H*-1-benzopyran-2-one), a fragrant colorless compound, was first isolated from the Tonka bean [3].

2.1 Structure of Coumarin and Its Derivatives

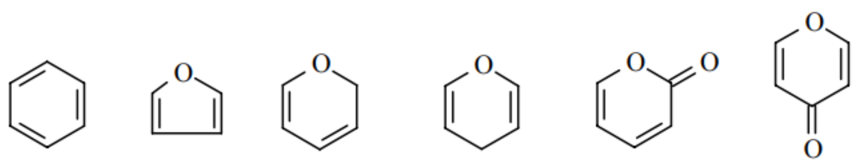
The ring structure that contains an oxygen atom is called a pyran ring, and heterocyclic compounds obtained by the condensation of the pyran ring with the benzene ring are referred to as benzopyrans. These compounds are classified into two groups: *2H*-1-benzopyran-2-one and *4H*-1-benzopyran-4-one. (Figure 2.1) The reason for their classification into two different categories is related to the position of the carbonyl group. If the carbonyl group is located at the beta position of the compound, attached to the second carbon atom of the pyran ring, it is called a chromone. On the other hand, if the carbonyl group is present at the alpha position of the pyran ring, attached to the first carbon atom, it is referred to as a coumarin.



4*H*-1-benzopyran-4-one (Chromone)

2*H*-1-benzopyran-2-one (Coumarin)

Figure 2.1 Structures of chromone and coumarin



Benzene Furan 2H-pyran 4H-pyran α-pyrone ɣ-pyrone

Figure 2.2 Basic structural units of coumarin and chromone compounds

2.2 Historical Development and Usage of Coumarins

Coumarins are derived from a French term known as coumaru and they were firstly isolated from Tonka bean by Vogel in 1820. Since coumarin was first discovered, numerous coumarin derivatives have been identified from various natural sources, particularly higher plants. In recent days, the most common application for coumarin is as a fragrance ingredient, where it serves as a scent, a stabilizer, and a fragrance enhancer. In lotions, hand soaps, detergents, and perfumes, the chemical coumarin is present in amounts ranging from 0.01% to 2.4%. It is used to cover up offensive odors or give household products pleasant aromas. Also, high protein lymphedema is treated with coumarin pharmaceutically, which also improves venous circulation and has been tested in antineoplastic clinical studies. Additionally, green tea, carrots, celery, strawberries, cinnamon, peppermint, and other edible plants as well as partially fermented tea, red wine, beer, and other foods all contain coumarin. Although coumarin is utilized as a tobacco taste, its direct usage as a food additive is currently prohibited, despite the fact that it can be used in meals via natural ingredients like cinnamon. Additionally, the electroplating sector uses coumarin [4].

Although coumarin is a colorless compound, the substituents attached to the coumarin ring make coumarins colored and give them very strong fluorescence properties. Studies on the fluorescence properties of newly synthesized coumarins and their crown ether derivatives have attracted considerable interest. In addition to the fluorescence properties, studies on the luminescence properties of coumarins are also carried out [5].

The anticoagulant properties of coumarins on blood coagulation may be its most well-known usage. Commercially, some coumarin compounds are offered as oral anticoagulants. Coumarins are used in numerous biological and medicinal experiments due to their antibacterial [6] and anticancer [7] properties, in addition to their anticoagulant actions [8,9]. Due to their substantial bioactivity, new types of coumarin compounds with useful pharmacological value have been created recently [10,11].

2.3 General Characteristics of Coumarin Derivatives

The numerous desirable properties of coumarins including their low molecular weight, simple structure, high bioavailability, high solubility in the majority of organic solvents, and low toxicity along with their diverse range of biological activities ensure that they play a significant role as lead compounds in drug development.

The pharmacological actions of coumarins include antiproliferative, antibacterial, anti-inflammatory, neuroprotective, antidiabetic, and anticoagulant. Their significance is also evident in the food business, where their antifungal and antioxidant properties are researched and used. Additionally, a few natural benzocoumarins have anti-algal properties [12]. The industry has focused a lot of attention on luminous qualities of coumarin, despite the fact that they are known for their biological activity. Some derivatives' luminescence is caused by the inherent charge transfer capabilities of conjugated, electron-rich systems.

In liver microsomes, coumarin is metabolized by the cytochrome P450-linked mono-oxygenase enzyme (CYP2A6) system, which results in hydroxylation. The hydroxylated metabolite then proceeds to phase II conjugation processes. Although hydroxylation of coumarin at any of its six probable sites (i.e., carbon atoms 3, 4, 5, 6, 7 and 8) is theoretically feasible [13].

2.4 Classification of Coumarins

Coumarins are often categorized based on structural distinctions, and these classes may have various characteristics and biological functions. However, this categorization provides a general understanding and some coumarins may belong to more than one class because their structures may mix several features.

It is possible to classified coumarins into four group in terms of their structures [14].

a.) Simple Coumarins

b.) Pyranocoumarins,

c.) Furanocoumarines,

d.) Pyrone-substituted coumarins

2.4.1 Simple Coumarins

Simple coumarins carry a benzo α-pyrone skeleton and have –OH, alcohol and other substituents attached to this skeleton (Figure 2.3). They can be free as well as in the form of heterosides.

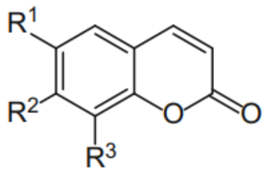


Figure 2.3 General structure of Simple Coumarins

Umbelliferone is an example of simple coumarin and it was first isolated from the family Umbelliferae (syn. Apiaceae). Umbelliferone, also known as 7-hydroxycoumarin, is considered biosynthetically as the parent compound for other highly oxygenated, prenylated, geranylated, farnesylated, and more complex forms of coumarin derivatives [15] (Figure 2.4).

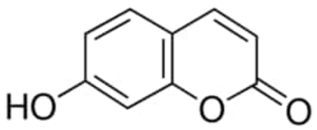
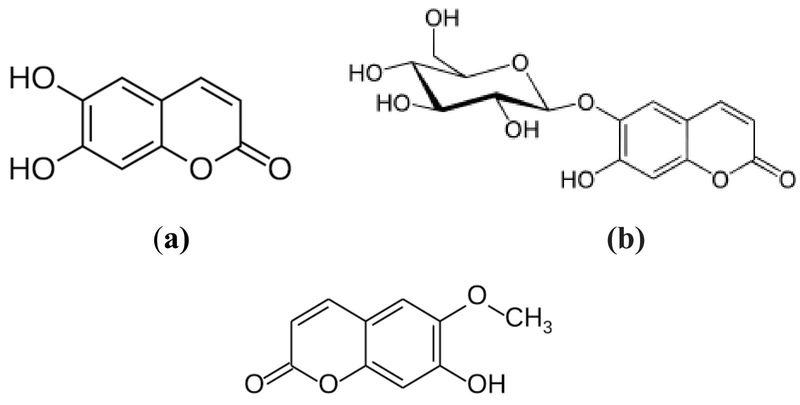


Figure 2.4 Structure of Umbelliferone

Aesculetin, aesculin, chicoriin, scopoletin, and umbelliferone were isolated from an aqueous ethanolic extract of the leaves of *Calendula officinalis* [16] (Figure 2.5).



(a) **(b)**

(c)

Figure 2.5 Structure of a.) Aesculetin b.) Aesculin c.) Scopoletin

2.4.2 Pyranocoumarins

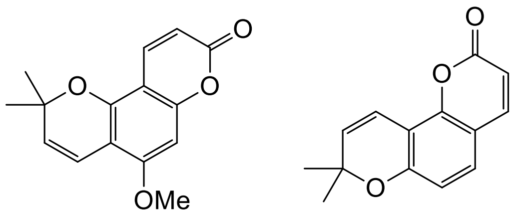
In pyranocoumarins, such as xanthyletin, the pyran (or dihydropyran) ring is typically fused with the aromatic ring of the coumarin skeleton. Different angular xanthyletin pyranocoumarins are produced by fusing these two rings in diverse ways.

The biosynthesis process for pyranocoumarins begins with the coupling of dimethylallyl pyrophosphate (DMAPP) with umbelliferone. This mechanism is similar to that for furanocoumarins. As a difference, the pyrans ring is formed from the prenyl group instead of forming furan ring.

Also, pyranocoumarins are classified into two different groups: Angular and linear pyranocoumarins.

2.4.2.1 Angular Pyranocoumarins

The formation of angular pyranocoumarins often involves either the coumarin nucleus' C-5 and C-6, which results in the alloxanthoxyletin-type angular pyranocoumarins, or the coumarin nucleus' C-7 and C-8, which results in the seselin-type.



(a) (b)

Figure 2.6 Structure of a) alloxanthoxyletin b) seselin

Seselin and alloxanthoxyletin, naturally occurring pyranocoumarins, were recently isolated from a number of plant sources, such as family of Rutaceae. It was previously reported that their natural and synthetic derivatives show cytotoxic and antitumor activity [17] (Figure 2.6).

2.4.2.2 Linear Pyranocoumarins

A well-known linear pyranocoumarin, xanthoxyletin (Figure 2.7) and its isomer, luvangetin, were produced by the roots and stems of Zanthoxylum avicennae (Rutaceae), with the latter also being isolated from the stem bark of Zanthoxylum ailanthoides using centrifugal partition chromatography.

Hibiscus vitifolius (Malvaceae) was found to contain xanthoxyletin and xanthyletin.

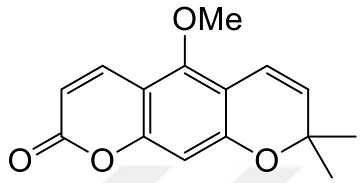


Figure 2.7 Structure of xanthoxyletin

2.4.3 Furanonocoumarins

The first furanocoumarin, 5-methoxypsoralen (Figure 2.8), was isolated in 1838 by Kalbrunner from bergamot oil [18]. Furanocoumarins have a furan (or dihydrofuran) ring fused to the coumarin skeleton. The so-called psoralens, allopsoralens, angelicins, and are the most well-known and prevalent instances in nature of how the furan ring can be fused to produce various isomers [19].

Like pyranocoumarins, furanocumarins are also typically produced through a coupling of dimethylallyl pyrophosphate (DMAPP) with umbelliferone. Additionally, furanocoumarins are categorized into two different groups as angular and linear furanocoumarins [20].

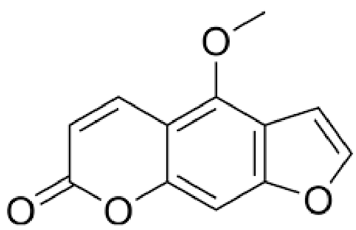


Figure 2.8 Structure of 5-methoxypsoralen

2.4.3.1 Angular Furanocoumarins

Plants contain just a small number of angular furanocoumarins (Figure 2.9) and even more recent research has only uncovered known members of this class. Isopsoralen, also known as angelicin (Figure 2.10), the most basic angular furanocoumarin, was discovered in the seeds of Psoralea corylifolia and was found to have potential for treating diabetes.

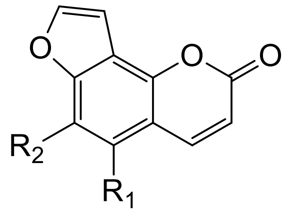


Figure 2.9 Structure of angular furanocoumarin

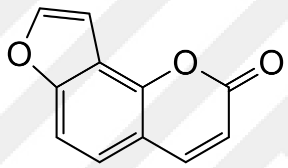


Figure 2.10 Structure of angelicin

2.4.3.2 Linear Furanocoumarins

There haven't been any newly discovered simple linear furanocoumarins recently; all reported coumarins in this group are known natural compounds (Figure 2.11).

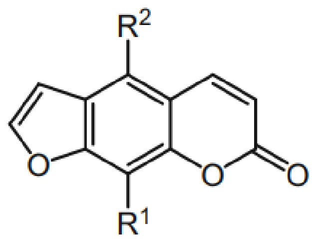


Figure 2.11 General structure of linear furanocoumarin

Several geranylated linear furanocoumarins were recently discovered in a variety of plants, primarily belonging to the families Apiaceae and Rutaceae. Some of these are brand-new natural compounds. Psoralens can be given as an example of linear furanocoumarins (Figure 2.12).

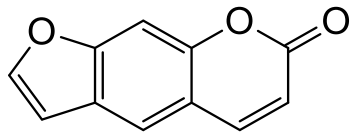


Figure 2.12 Structure of psoralens

2.4.4 Pyron-substituted coumarins

Coumarins with modifications and substitutions on the pyrone ring are known as pyrone-substituted coumarins [21].

These are divided into three categories: 3,4-Benzocoumarin (Aeternaryiol), 3-Phenylcoumarin (Flavanoid) and 4-Hydroxycoumarin (Novobiocin and Dicumarol). Plants do not contain 4-hydroxycoumarins in their free form. The synthetic substance warfarin is a member of this class [22] (Figure 2.13).

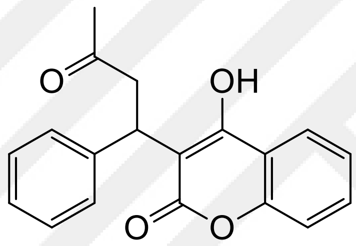


Figure 2.13 Structure of warfarin

2.5 Synthesizing Methods Of Coumarins

Coumarins have been frequently used in scientific studies due to their pharmacological wide spectrum ranges and their biologically active properties. Many synthesis methods have been developed for the synthesis of coumarin derivatives and coumarin triazole hybrid molecules, which are also the subject of this thesis.

2.5.1 Pechmann Condensation

The Pechmann reaction, which includes the condensation of phenols with β-keto esters in the presence of a range of acidic condensing agents and produces good yields of 4-substituted coumarins, is the most extensively used technique for creating coumarins [23].

This method was used while synthesizing the three coumarin motifs, which constitute the basic stage of this thesis. While resorcinol, which is highly active, forms the phenol structure, ethyl acetoacetate as a β-ketonic ester is combined with resorcinol under acidic conditions and high yield coumarin derivatives were synthesized at room temperatures (Figure 2.14).

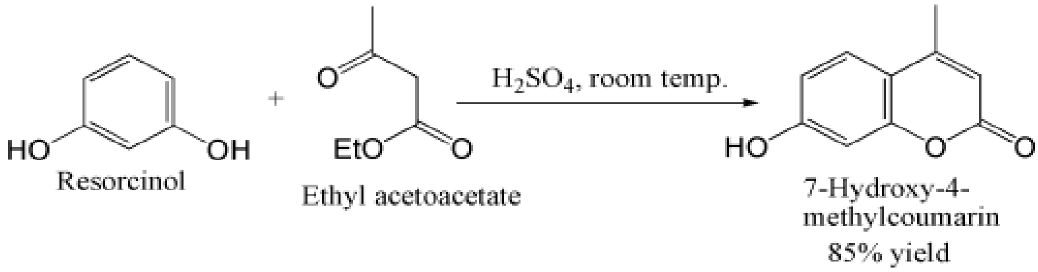


Figure 2.14 Example of Pechmann Condensation

Advantages of Pechmann condensation are given below:

-It generally offers versatility in using different phenol derivatives and acylation agents and is an easy and cost-affected approach.

-Excellent synthetic efficiency that frequently results in the production of the desired coumarin derivatives.

-Extensively used in a variety of commercial and industrial applications.

This method has several key benefits, including a quick reaction time, high yields, easy workup, the use of a cheap and readily available catalyst, nonchromatographic product purification through straightforward recrystallization from EtOH, and the use of solvent-free conditions in place of organic solvents in accordance with green chemistry standards [24].

Although this method has a variety of advantages, it has some limitations and possibly difficult situations as:

-In some circumstances, undesirable side effects (such ester hydrolysis) may occur, lowering overall effectiveness.

-It might be necessary to improve the synthetic processes and modify the reaction conditions.

-Under some circumstances, certain phenol derivatives or acylation agents may not be reactive or demonstrate low reactivity.

-The instability or disintegration of some components can be brought on by high temperatures and an acidic environment. This drawback has been overcome by our new methodology by using trifluoroacetic acid as solvent and catalyst under ultrasonic effect.

2.5.2 Effects of the Catalyst in Pechmann Condensation

In recent years, Pechmann reactions have been catalyzed by Lewis acids such $InCl_3$, $AlCl_3$-nBPC, $Yb(OTf)_3$, $ZrCl_4$, GaI_3, Zr-SG, and $Sm(NO3)_3$. Additionally, there is room for further advancement toward softer reaction conditions and the development of effective and innovative catalytic systems for various chemical transformations [25].

It has been proposed that resorcinol and ethyl acetoacetate (EAA) undergo a Pechmann condensation to produce 7-hydroxy-4-methyl coumarin which is also synthesized in this thesis, in three steps: transesterification, intramolecular hydroxylation, and dehydration [26] (Figure 2.15). The acid sites of catalyst engage with the keto group of EAA to transfer protons to it. After that, an intermediate and ethanol are formed as a result of a nucleophilic attack of resorcinol's hydroxyl group to the intermediate. Through an intramolecular condensation, the intermediate quickly cycles to produce 7-hydroxy-4-methyl coumarin [27].

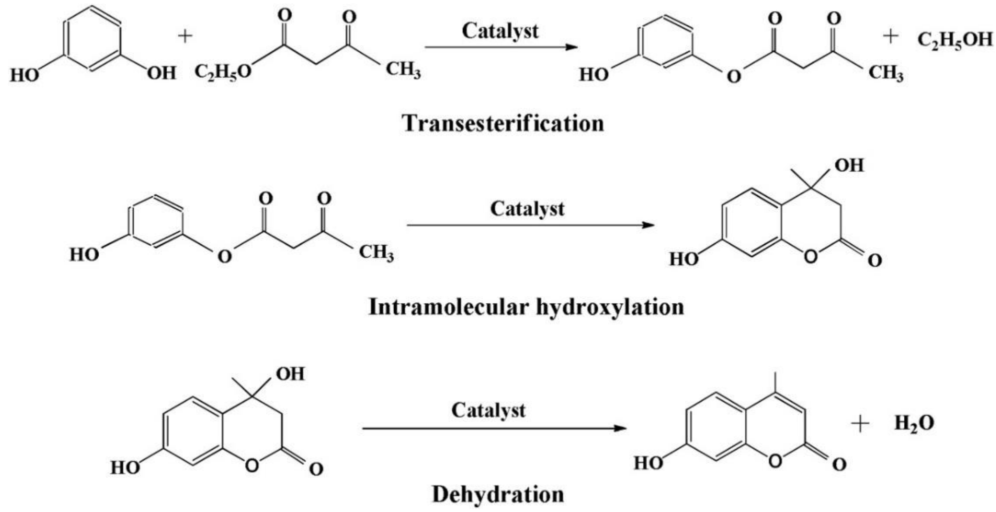


Figure 2.15 Three synthesis steps of 7-hydroxy-4-methyl

Some researches demonstrate that barium dichloride might be also an option for synthesizing new coumarin derivatives. In the study, for the optimization process, they worked with different catalyst amount and temperature. Then, it was observed that with the increasing $BaCl_2$ and temperature, the yield of the reaction increased. Therefore, the paper shows that coumarins can be easily synthesized using the Pechmann reactions and barium dichloride [28].

In another study, it was discovered that ultrasound helped to synergistically speed up the condensation of phenol with ketoesters in the presence of $BiCl_3$. The reaction was shown to be delayed under the same circumstances without ultrasonography. Thus, the reaction can be carried out at room temperature with ultrasound present, with a significantly shorter reaction time. Also, the yield and purity of the coumarins are high [29].

Another study employed perchloric acid supported by silica as a catalyst ($HClO_4 \cdot SiO_2$). In an environment devoid of solvents, this catalyst is reusable and heterogeneous. The benefit of the reaction is that it is quick, simple, and inexpensive [30].

Also, in some researches starch sulfuric acid (SSA) is used as a catalyst to synthesize coumarin derivatives. Results demonstrate that when the amount of SSA is increased, the yield of the reaction also increase. Like the other methods, by using starch sulfuric acid it is possible to benefit from some advantages such as simple, quick, cheap and eco-friendly synthesizing method [31].

2.5.3 Perkin Condensation

This method takes its name from William Henry Perkin, an English chemist who developed this method to synthesize cinnamic acid. This reaction method is used to produce β-keto acid esters through the reaction of aliphatic acids and aromatic aldehydes in an acidic environment.

A base catalyst or an acidic catalyst is required for this reaction to occur in an aliphatic acid and aromatic aldehyde reaction. Catalysts with bases like sodium or potassium hydroxide or with acids like sulfuric acid are frequently used. A β-keto ester having an ester group is created by the process.

The successful technique of Perkin condensation is frequently used to create C-C bonds. This reaction provides a simple, affordable synthetic approach. Additionally, different aliphatic acids and aromatic aldehydes can be used to create distinct β-keto esters, demonstrating the versatile potential of the reaction.

Perkin condensation followed by intramolecular esterification, which is where the intermediate molecule was intended to be identified, is part of the reaction's claimed mechanism of the reaction to give coumarin compounds [32] (Figure 2.16).

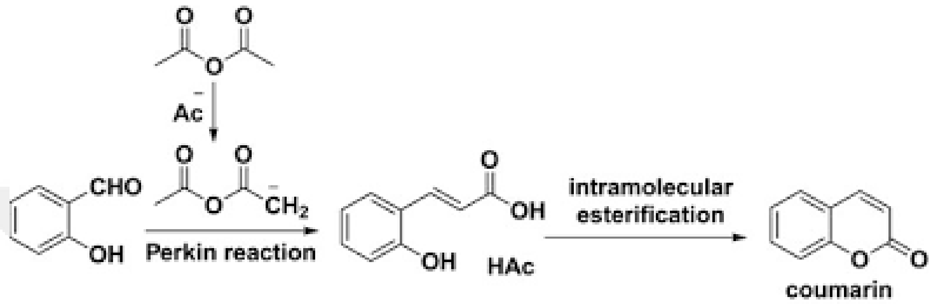


Figure 2.16 Perkin Condensation reaction for coumarin synthesis

2.5.4 Knoevenagel Condensation

Aldehydes or ketones react with active methylene compounds in a process known as Knoevenagel condensation, which results in the production of an, α,β-unsaturated carbonyl compounds. Wilhelm Knoevenagel discovered this reaction, which bears his name.

In the past, the Knoevenagel condensation reaction has been carried out successfully using catalysts like primary, secondary, and tertiary amines, ammonium salts, ionic liquids, amino acids, Lewis acids like $ZnCl_2$, $TiCl_4$, Al_2O_3, and $LaCl_3$, as well as organometallic catalysts in homogeneous conditions but the homogeneous system has a number of drawbacks, such as catalyst recovery, high reaction temperatures, product separation, and use of too much solvent, which results in the production of a lot of waste and environmental damage [33].

Knoevenagel condensation often occurs in the presence of base catalysts. A carbonyl compound (often an aldehyde or ketone) and an active methylene compound, also known as an aldehyde or ketone, engage in a reaction. As a result, an α,β-unsaturated double bond is created in an alkene or ketone (Figure 2.17).

By exploiting the electrophilic and nucleophilic properties of the carbonyl molecule and the active methylene compound, this reaction helps in the creation of the double bond. Knoevenagel condensation is an efficient technique frequently employed in the production of different chemicals as coumarin derivatives.

Figure 2.17 An example of Knoevenagel Condensation reaction

Even though Knoevenagel condensation offers flexibility and mild reaction conditions, it's vital to take into account the risks of side effects, sensitivity to reaction conditions, and restrictions with substrates that are sterically inhibited. These limitations can be removed and the synthetic utility of Knoevenagel condensation increased with careful optimization and experimental considerations.

2.5.5 Hauben-Hoesch Condensation

This reaction method takes its name from Franz Houben and Alfred Hoesch. It is an organic chemical reaction that involves the condensation of an aromatic amine and an α,β-unsaturated nitrile compound to form a new carbon-carbon bond (Figure 2.18).

When a potent base like potassium tert-butoxide or sodium ethoxide is used, the Houben-Hoesch condensation often takes place under simple conditions. A new carbon-carbon double bond is formed as a result of the nucleophilic addition of the aromatic amine to the, α,β-unsaturated carbonyl compound and the subsequent elimination of a water molecule. A modification of Hauben-Hoesch condensation is used to synthesize coumarin derivatives.

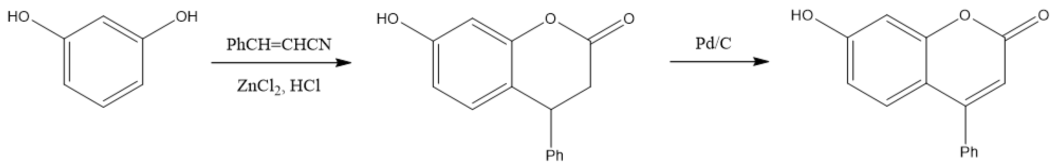


Figure 2.18 An example of Hauben-Hoesch Condensation reaction

The capacity to produce highly conjugated systems, which can be useful in the synthesis of aromatic compounds and pharmaceutical intermediates, is one of the main benefits of the Houben-Hoesch condensation. The reaction offers a simple and effective method for creating carbon-carbon double bonds, enabling the synthesis of a wide range of molecules.

2.5.6 Reformatsky Reaction

Aldehydes or ketones react with α-halocarboxylic esters in the reformatsky reaction to create β-hydroxycarboxylic ester molecules. By passing through dehydration or intramolecular interactions to control the development of the coumarin ring, these β-hydroxycarboxylic esters in turn act as intermediate products in the synthesis of coumarin. [34] (Figure 2.19)**.**

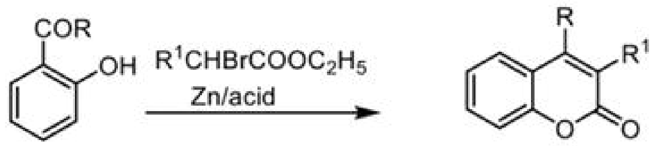


Figure 2.19 An example of Reformatsky reaction

Contrary to the aldol reaction, which often requires a base to produce the enolate or an acid to activate the electrophile, the Reformatsky reaction operates in neutral circumstances. However, Reformatsky reactions do have a few drawbacks, though, as has been known in the past. The unselective dehydration of the aldols first generated is a difficulty that arises in many reactions, but this issue has been solved by either significantly decreasing the reaction temperature or by employing silylated starting materials [35].

2.5.7 Wittig Reaction

By reacting aldehydes or ketones with phosphonium salts, the Wittig reaction involves the selective production of an alkene. The Wittig reaction, which transforms aldehydes or ketones into alkenes to control the development of the coumarin ring, is essential in the context of coumarin synthesis. It is well acknowledged that this reaction is a successful coumarin synthesis technique (Figure 2.20).

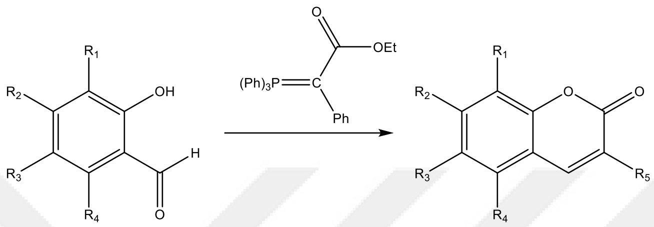


Figure 2.20 An example of Witting reaction

In this reaction, an aldehyde or ketone interacts with a phosphonium salt, commonly referred to as triaryl phosphonium salts (Wittig reagent), in the presence of a base to produce a highly selective alkene. When placed under the suitable circumstances, this alkene goes through further changes that help the coumarin ring form.

2.6 Properties of Coumarins

2.6.1 Photophysical and Photochemical Properties of Coumarins

The solvent environment and the substituent groups present in the structures affect the photophysical characteristics of coumarin derivatives. Due to their unique properties, coumarin derivatives present a wide range of research opportunities. These characteristics can be categorized as crucial laser dyes, nonlinear optical chromophores, and having good response as probes in research on solvation dynamics in homogenous solutions [36].

Because of their conjugated double bond structure, coumarins often absorb light in the ultraviolet (UV) or visible (VIS) spectrum. The different peaks in the absorption spectra enable their categorization and study. Coumarins go through fluorescence when light is absorbed, emitting light with longer wavelengths. The emission spectra have distinctive peaks that can be used for identification and detection.

Coumarins can be identified by their lasing behavior. The C-7 position of the coumarin nucleus is where the hydroxyl or amino group is found in the coumarin class of laser dyes. There have been reports on how substituents affect these compounds' lasing capabilities. Numerous new laser dyes have been created, and it has also been reported on how substituents affect their fluorescence maxima and fluorescence quantum yields [37].

The distance between the absorption and emission wavelengths is known as the Stokes shift, and coumarins are renowned for having a significant Stokes shift.

They are excellent for fluorescence-based assays and sensing applications thanks to this characteristic, which facilitates efficient energy transfer and reduces self-quenching effects. According to some studies, the effects of substituents in different positions on the coumarin ring have been evaluated. It has been observed that if the substituent is located at the third position of the ring, a larger Stokes shift and lower quantum yield are observed. Based on this, a comparison was made between 5,6-benzocoumarin derivatives and 8,9-benzocoumarin derivatives. As a result, it was found that 5,6-benzocoumarin derivatives exhibit high emission characteristics [38].

2.6.2 Biological Activity Properties of Coumarin Derivatives

Coumarin derivatives are known to exhibit diverse biological activities, making them important compounds in medicinal chemistry and drug discovery. There is a relation between the biological activity and binding properties to the various metal ions of coumarins.

They can also be produced synthetically, and numerous coumarin derivatives have demonstrated promising anticancer, antitumor, and anti-proliferative properties [39].

Numerous of these coumarin derivatives have demonstrated efficacy against cancer, bacteria, fungi, blood clotting and inflammation [40].

2.6.2.1Anticoagulant and Antiplatelet Activity

Warfarin and acenocoumarol are two common anticoagulant drugs. Coumarin derivatives also have antiplatelet activity. They stop the production of coagulants by inhibiting the activity of vitamin K epoxide reductase, an enzyme involved in the manufacture of clotting components. Furthermore, several coumarin derivatives have antiplatelet action, which prevents platelet aggregation and lowers the risk of thrombosis.

In one study, antiplatelet effects on people with coronary artery disease were investigated using phenprocoumon, a coumarin sample. During this study, 1223 patients were treated and phenprocounmon was used in the treatment of some of them and not used in others. As a result, it was observed that platelet aggregation was significantly higher than the patients who did not receive phenprocoumon treatment [41].

Some studies highlight the fact that oral anticoagulants containing derivatives of 4-hydroxycoumarin, such as warfarin and phenprocoumon, were utilized widely for a long period, especially over the past 20 years. In a research, a universal biological examination was developed to check for protein accumulation carried on by under- or over-carboxylated prothrombin or vitamin K antagonists (PIVKA-II). After then, it was discovered that the newly created 4-hydroxycoumarin derivatives pyridine, pyrimidine, and pyrazole might be used as possible anticoagulant drugs [35].

Additionally, according to research conducted on Angelica shikokiana, a plant used for therapeutic purposes in cardiovascular diseases, the isolated coumarins from the Angelica plant exhibit anticoagulant and antiplatelet properties as evidenced by prolonged prothrombin time [42].

2.6.2.2 Antibacterial and Antifungal Activity

Significant antibacterial and antifungal action has been demonstrated by coumarin derivatives against a variety of diseases. Both Gram-positive and Gram-negative kinds of bacteria, as well as fungi, can be prevented from growing and multiplying by them. The potential for developing novel antibacterial agents using these substances can be investigated [43].

Researches are showed that multiple coumarin derivatives have been isolated from the plant Ferulago campestris, such as Aegelinol and Agasyllin (Figure 2.21), it has been observed that these coumarin derivatives exhibit antibacterial activity against both gram-negative and gram-positive bacteria. Furthermore, they have shown significant activity against Salmonella typhi, which is responsible for severe infections and often resistant to traditional antibiotics [44].

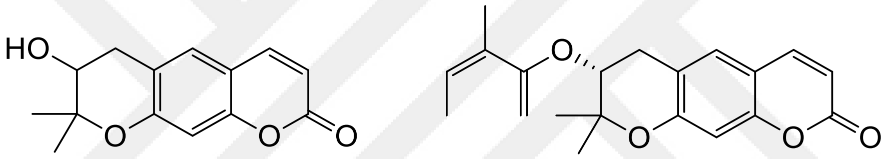


Figure 2.21 Aegelinol and Agasyllin

In another study, the antifungal activity properties of different coumarin derivatives were compared against three fungal species, namely Candida albicans, Aspergillus fumigatus, and Fusarium solani. The researchers conducted the study using the broth microdilution method and evaluated the fungal susceptibility to coumarins by determining the minimum inhibitory concentration. The results indicated that pyranocoumarins exhibited the highest antifungal activity, particularly against Candida albicans [45].

In Brazil, there is a need for treatment against Sporotrichosis, a disease that poses a threat to human and pet health. To address this, studies have been conducted, and it has been demonstrated that coumarin derivatives obtained through Knoevenagel condensation reaction exhibit effective antifungal activity against Sporothrix schenckii and Sporothrix brasiliensis, the fungi responsible for Sporotrichosis [46].

The antibacterial activity properties of coumarin derivatives were investigated against Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus bacteria using the microdilution method. According to the results, coumarin derivatives that possess a prenyl chain at the C8 position of the benzene ring and a hydroxyl group at the C7 position exhibit high antibacterial activity. Additionally, Osthenol, a coumarin derivative, has been shown to possess the most effective antibacterial activity against gram-positive bacteria [47] (Figure 2.22).

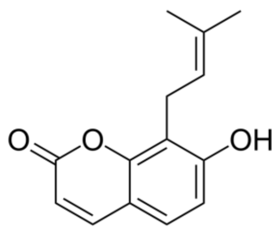


Figure 2.22 Structure of Osthenol

2.6.2.3 Anticancer Activity

Some coumarin compounds have shown anticancer activity by preventing the growth of tumor cells, causing apoptosis (programmed cell death), and obstructing a number of signaling pathways implicated in the spread of cancer. These compounds have been researched for their potential to be added to current cancer treatments or as chemotherapeutic agents.

Coumarin derivatives are not only effective anticancer agents but also exhibit minimal side effects. Based on various substitution patterns, they have demonstrated tremendous potential in regulating their anticancer activities [48].

Coumarin derivatives are ubiquitously found in nature and can readily interact with various enzymes and receptors in cancer cells through weak binding interactions. Therefore, coumarin serves as a privileged pharmacophore for the development of novel anticancer agents. A new type of coumarin, Neopeucedalactone, has been isolated from the roots of Peucedanum praeruptorum Dunn. Studies have shown that this coumarin derivative exhibits moderate in vitro cell growth inhibitory activities [49].

Numerous routes by which coumarins function as anticancer agents were uncovered by biological studies on coumarins. Inhibiting kinases, cell cycle arrest, angiogenesis, heat shock protein (HSP90), telomerase, antimitotic activity, carbonic anhydrase, monocarboxylate transporters, aromatase, and sulfatase are just a few of the cancer-related pathways that coumarins aim to block. Additionally, these researches contributed to the development of structural activity relationship studies (SARs), which helped to widen the activity continuum by revealing several coumarin nucleus substitutions [50].

2.6.2.4 Antiviral Activity

Some coumarin derivatives have been shown to be effective against a variety of viruses, including the hepatitis C virus (HCV), herpes simplex virus (HSV), influenza, and HIV. They present prospective therapeutic alternatives for viral illnesses because they can obstruct viral reproduction, entrance, or adhesion to host cells.

Coumarin, is a promising therapeutic candidate because of its stability, solubility, and low toxicity. Numerous studies have demonstrated its inhibitory effect on the spread of many viruses, including HIV, influenza, EV71, and CVA16. The mechanisms either involve the inhibition of proteins required for viral entry, replication, and infection or the regulation of cellular pathways and the anti-oxidative pathway. The study covers the current state of knowledge with an emphasis on the antiviral properties of coumarins and their potential molecular pathways against influenza, HIV, hepatitis, dengue, and chikungunya viruses [51].

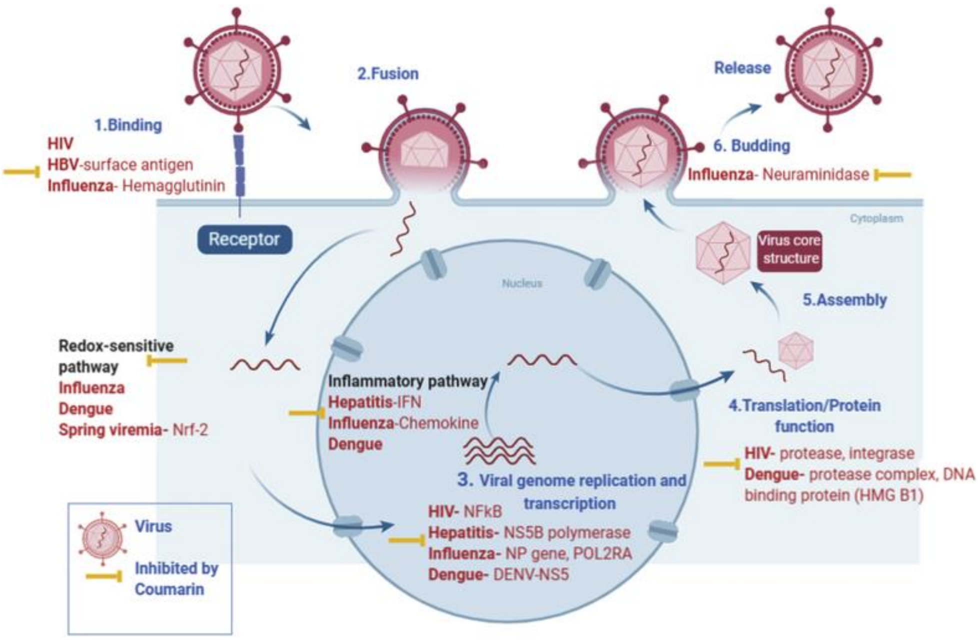


Figure 2.23 Antiviral mechanism of the Coumarin

Viral infection occurs over a number of steps, starting with virion attachment to a cell surface receptor, then fusion and entry, viral genome replication and transcription, translation and virion assembly, budding and release. These essential viral life cycle stages are the focus of chemotherapy. Similarly, coumarin blocks a large number of the proteins involved in the transcription and translation machinery essential to the life cycle of viruses. Furthermore, coumarin alters NF-B, inflammatory redox-sensitive pathways, and host cell signaling pathways, all of which prevent viral replication. As shown, coumarin's anti-viral action on various viruses has been shown to take several different forms [51] (Figure 2.23).

3
TRIAZOLES

Triazoles are a type of organic compounds that are a part of the significant azole chemical family. They are made up of distinct functional groups connected at various points along a triazole ring, which has five members. Triazoles are used extensively in a variety of biological and medicinal sectors, as well as in materials science, agriculture, and chemical synthesis.

Three nitrogen atoms comprise the ring which forms triazoles. The characteristics and uses of triazoles are defined by the functional groups fixed to various locations of this ring. 1,2,3-triazoles and 1,2,4-triazoles are two different kinds of triazoles having having nitrogen atoms in different positions on the five membered ring (Figure 3.1). Substituents can be positioned differently among the three nitrogen atoms in triazoles [52].

Figure 3.1 Structures of 1,2,3- and 1,2,4- triazole

In this thesis, 1,2,3-triazole compounds were studied, so this type of triazole will be discussed detaily.

3.1 Synthesizing Methods of 1,2,3-Triazoles

1,2,3-Triazoles have attracted a lot of interest because of their wide range of chemical properties with potential uses in domains like medical chemistry, materials science, and chemical biology. There are numerous synthetic techniques available to prepare 1,2,3-triazoles.

3.1.1 Huisgen 1,3-Dipolar Cycloaddition

The Huisgen 1,3-dipolar cycloaddition, which comprises the reaction of an alkyne and an azide to produce 1,4- and 1,5-disubstituted-triazole regioisomers, was developed in the 1960s by Huisgen, who was the first to examine the synthesis of 1,2,3-triazoles in depth [53].

For the synthesis of 1,2,3-triazoles, the Huisgen 1,3-dipolar cycloaddition is a well-known technique. An organic azide and a dipolarophile, usually an alkyne or an alkene, react in this process. This process can be carried out under heat effect or with the help of transition metal catalysts. However, due to its greater efficiency and regioselectivity, the copper(I)-catalyzed variant (CuAAC) has acquired increasing popularity.

As a reaction mechanism, Huisgen cycloaddition happens in a single step without the creation of any intermediates (Figure 3.2). The product's regiochemistry depends on where the substituents are positioned on the 1,3-dipole and the dipolarophile.

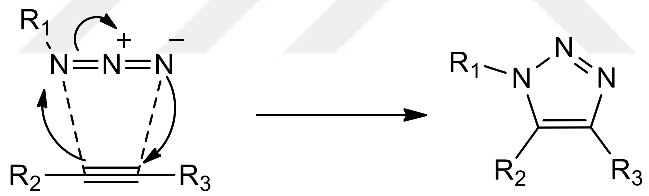


Figure 3.2 Mechanism of Huisgen cycloaddition reaction

1,3-Dipoles are species with a dipolar nature because they have both a positively and a negatively charged end. The most typical 1,3-dipoles employed in the Huisgen cycloaddition are azides. Azides (RN_3) have a linear configuration of three nitrogen atoms, two of which are negatively charged by the azide group (-N_3) and one of which is positively charged. The 1,3-dipole in the cycloaddition is represented by the nitrogen atoms with the azide group. Dipolarophiles are substances that engage in cycloaddition reactions with 1,3-dipoles. The dipolarophile in the Huisgen cycloaddition is commonly an alkyne or an alkene. The alkyne or alkene engages in a 1,3-dipolar cycloaddition with the 1,3-dipole to produce a 1,2,3-triazole (Figure 3.2).

Barbosa at al reported [54] that Huisgen invented the catalyst-free azide-alkyne cycloaddition in 1963, but it required high temperatures and pressures due to the low reactivity of azides and alkynes toward one another and other functional groups found in the biological environment at atmospheric pressure and room temperature. Due to the mild aqueous conditions, Huisgen cycloaddition reaction is known to be extremely slow and inactive in vivo. Additionally, this cycloaddition exhibits limited regioselectivity since it produces the 1,4- and 1,5- substituted triazole, two exceedingly challenging for the seperation of regioisomers (Figure 3.3). Several transition metal-based techniques were developed to modulate the regioselectivity.

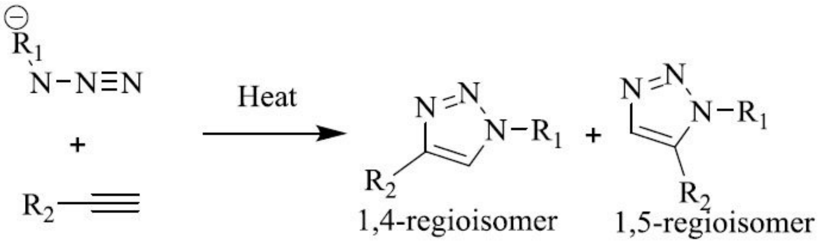


Figure 3.3 Triazol formation produced by Huisgen 1,3-dipolar cycloaddition

3.1.2 Azide-Alkyne Cycloaddition (CuAAC) Catalyzed by Copper(I)

As a variant of Huisgen cycloaddition reactions, the CuAAC reaction is a frequently used technique for producing 1,2,3-triazoles. The regioselectivity and efficiency problems in Huisgen cycloaddition reaction were eventually resolved by Torne and Meldal, who made alkyne-azide coupling processes faster and more selective by introducing Cu(I) catalysis. The presence of copper as a catalyst favored the creation of only the 1,4-regioisomer. (Figure 3.4 b) High efficiency, regioselectivity, and compatibility with a variety of functional groups are characteristics of CuAAC.

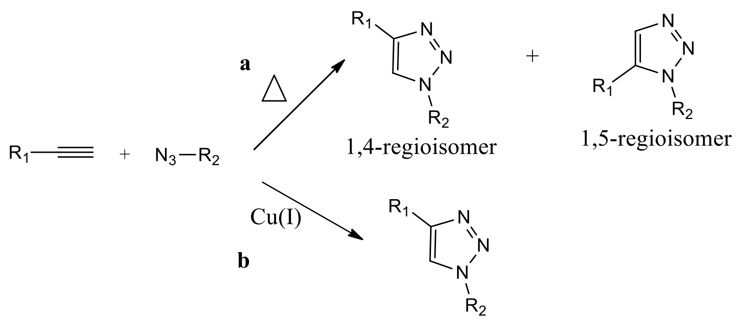


Figure 3.4 (a) a mixture of the 1,4- and 1,5-triazole regioisomers is produced via an inactive azide-alkyne cycloaddition (b) CuAAC leads the 1,4-triazole isomer to form regioselectively.

The CuAAC reaction entails the cyclic addition of an azide to an alkyne at the terminal while the reaction is catalysed by a copper(I) catalyst like CuBr or $CuSO_4$ which is reduced by sodium ascorbate. A copper acetylide intermediate is created during the reaction, and it interacts with the azide to produce the 1,2,3-triazole end product (Figure 3.5) [55].

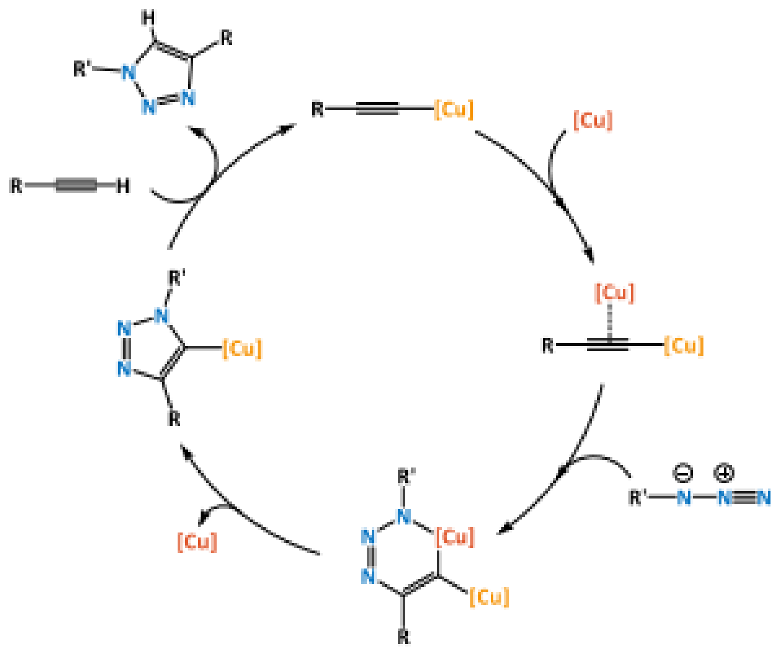


Figure 3.5 Mechanism of CuAAC reaction [55]

Özçubukcu and coworkers [56] demonstrated that $CuSO_4$ and sodium ascorbate are typically utilized as a precatalyst system in CuAAC reactions to produce the Cu(I) product in the reaction medium. Later, it was found that polydentate nitrogen ligands not only speed up the catalytic reaction but also stabilize Cu(I) intermediates, allowing direct use of Cu(I) crystals as catalysts in CuAAC processes.

As a summary, The CuAAC can be accepted as a variation of Huisgen's reaction. It is a particular Huisgen cycloaddition technique that makes use of a copper catalyst to produce 1,2,3-triazoles with increased efficiency and regioselectivity. In the most general way, the Huisgen cycloaddition covers a variety of 1,3-dipolar cycloaddition reactions that may or may not include copper catalysts.

The use of microwave irradiation to speed up chemical reactions has been identified as microwave-assisted synthesis. Compared to conventional thermal procedures, it is a technique that is used to increase the rate of reaction, improve yields, and shorten reaction periods. The polar molecules in the system rotate quickly when the reaction mixture is exposed to microwave energy, which improves molecular collisions and heat transfer and accelerates up reaction kinetics. A broad strategy that can be used for many other kinds of reactions, including cycloadditions, is microwave-assisted synthesis.

Triazole synthesis using microwaves has been extensively researched. Internal heat transmission is made effective by microwave irradiation, which boosts reaction rate and yield while shortening reaction time [57]. Studies which are performed to indicate that it is possible to synthesize novel triazoles based on a microwave-assisted reaction and synthesize new derivatives as a anticanger agent.

Souza at al [58] demonstrated that it is possible to form imine by using one pot reaction of α-thioaldehyde, propargylamine and an azide (Figure 3.6). Acetic acid was used as a catalyst, sodium sulfate as a drying agent, and dichloromethane as a solvent to carry out the reaction. Also during the study, they compared the method by utilizing enery sources like microwave and ultrasound with traditional methods. Results showed that when the microwave was used, the reaction time would be short and reaction yield was still the same. In addition to that, efficiency was very high.

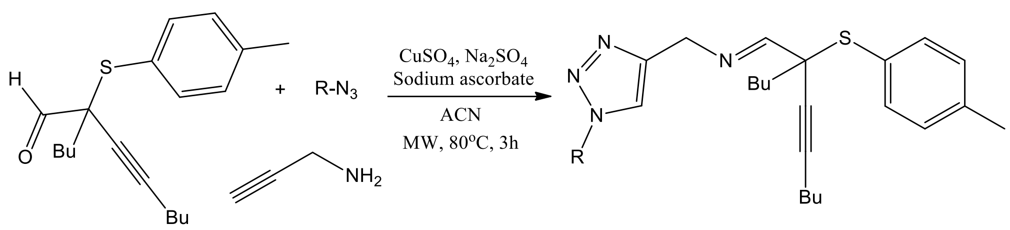


Figure 3.6 Microwave assisted synthesis of imine substituted 1,2,3-triazole

Costa and cowerkers [59] proved that by using microwave-assisted reaction it was possible to obtain racemic 1’-homo-3’-isoazanucleosides from 3,5-disubstituted proline derivative with various alkynes (Figure 3.7).

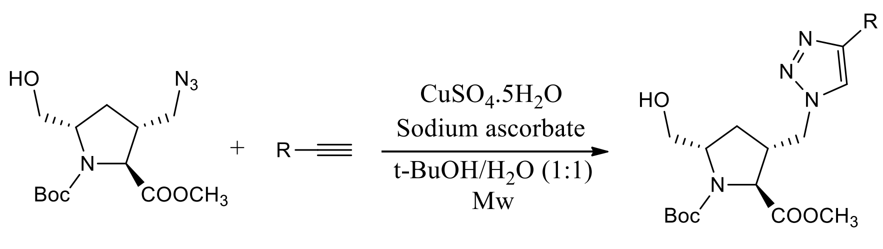


Figure 3.7 Microwave assited reaction of proline azide with alkynes

3.2 Applications of 1,2,3-Triazoles

Due to their unique chemical characteristics, triazoles, especially the 1,2,3-triazole rings, have a wide range of uses in a variety of industries. Firstly, triazoles have become significant structural motifs in the research and development of pharmaceuticals. Numerous triazole-containing substances have a range of biological activities, including antibacterial, antiviral, antifungal, anticancer, and antitubercular effects. There are various 1,2,3- and 1,2,4-triazole based drugs in market with several activities. TSAO, Cefatrizine, Tazobactum and CAI are some examples of 1,2,3-trizole drugs with anti-HIV, antibiotic, antibacterial and anticancer activity (Figure 3.8) [52]. Letrozole, Itraconazole and Ribafirin are 1,2,4-triazole based drugs which have anticancer, antifungal and antiviral activities (Figure 3.9).

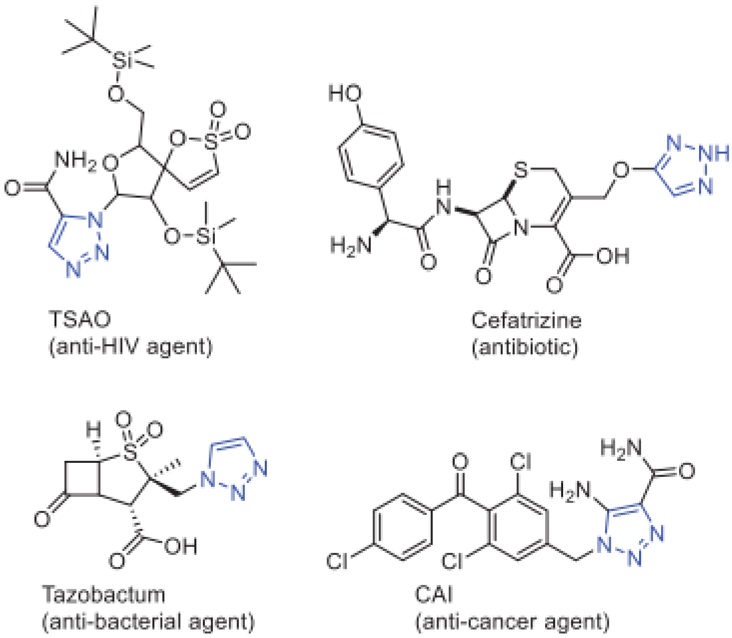


Figure 3.8 Some 1,2,3-triazol based drug molecules

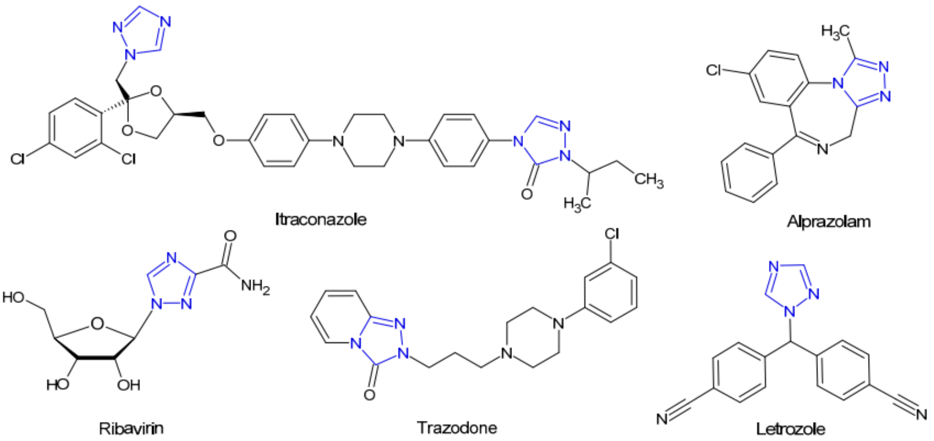


Figure 3.9 Example of biologicaly active 1,2,4-triazoles

Triazoles have also a variety of features that make them useful in materials research. In the creation of catalysts, metal-organic frameworks (MOFs), as well as coordination polymers, functionalized triazoles can act as ligands for metal coordination. Triazole-containing polymers and copolymers have been used in the manufacture of electronic devices, sensors, and medicine delivery systems. Li at all [60] described the successful creation of a very porous MOF with accessible nitrogen-rich triazole units that have a high affinity for CO_2 and unsaturated Cu sites. This MOF exhibits an excellent performance on catalytic carbon dioxide cycloaddition with smaller epoxides at 1 atm and room temperature.

Triazoles are used in the creation of agricultural products including fungicides and herbicides. The broad-spectrum activity of triazole-based fungicides against fungal diseases inhibits the development of fungi used for agriculture and preserves crops. Tebuconazole, propiconazole, and epoxiconazole can be given examples of this triazole types. Toda at al [61] indicated that Aggressive mold infections are most commonly carried on by the fungus Aspergillus fumigatus (A. fumigatus), which can lead to serious illness and even death in those with impaired immune systems. However, according to results, the patient survival rate has increased recently due to the use of triazole antifungal medicines.

3.3 Biological Importance of 1,2,3- Triazoles

Due to their broad biological significance, 1,2,3-triazoles have attracted a lot of research in the fields of biology and pharmaceutical chemistry. 1,2,3-triazoles are able to establish hydrogen bonds and are resistant to metabolic degradation, which might increase their solubility and make them more attractive for binding to biomolecular targets. 1,2,3- triazoles are desirable building blocks for drugs due to their special characteristics [62].

3.3.1 Antibacterial Agents

Gram-positive and Gram-negative bacteria have both been tested for the antibacterial effects of triazoles. In the fight against antibiotic resistance, certain triazole-based substances have proven to have strong antibacterial activity against drug-resistant microorganisms.

Bangalore and coworkers [63] demonstrates the biological activity of novel 1,2,3-triazoles conjugated to usnic acid enaminone. Both antibacterial and antitubercular properties were demonstrated. Gram-positive bacteria *Bacillus subtilis, Staphylococcus aureus*, and *Staph epidermidis* as well as Gram-negative species *Escherichia coli, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* were used to test in vitro antibacterial activities of synthesized compounds. More fluorine atoms are beneficial for inhibiting bacterial growth, however only one fluorine atom reduced the antibacterial effect.

Hryhoriv and coworkers [64] studied on a synthetic process for ciprofloxacin and norfloxacin derivatives with 1,2,3-triazole substitutions. One of the compounds shown a relatively broad spectrum of antibacterial activity against all tested test microorganisms in vitro studies against *Staphylococcus aureus*, *Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa*, and *Candida albicans* (Figure 3.10).

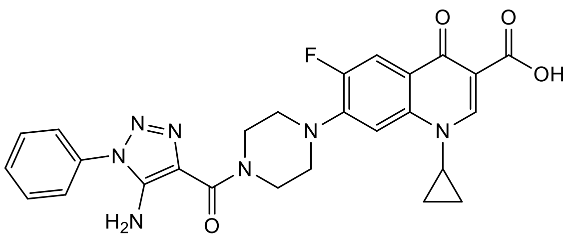


Figure 3.10 An effective antibacterial compound synthesized by Hryhoriv et al**.**

3.3.2 Antifungal Agents

1,2,3-triazole cores in particular have been discovered to have the greatest antifungal properties. New 1,2,3-triazole quinolinone, benzyl, and coumarin derivatives were created and evaluated for antifungal activity by Marzi et al. Eight separate fungal strains, four of which belonged to the *Candida species* and the other four to the *Aspergillus species*, were used to determine the antifungal activity of all the azole derivatives. Almost each of the compounds showed great antifungal efficacy [65].

Aher and coworkers [66] developed 1,2,3-triazole-based new mimics as antifungal drugs, based on fluconazole. The minimum inhibitory concentrations (MICs) were measured to determine their antifungal activity in vitro. According to the results, the long alkyl chained 1,4-disubstituted 1,2,3-triazole compounds and have high antifungal efficacy against *Candida* species (Figure 3.11).

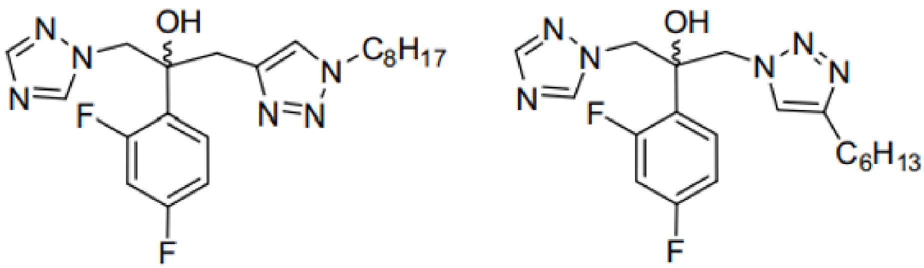


Figure 3.11 The active compounds synthesized by Aher et al. as antifungal agents

3.3.3 Anticancer Agents

Through various pathways, a number of triazole compounds have demonstrated anticancer effects by concentrating on cancer cells. They have the ability to cause apoptosis (programmed cell death), limit tumor angiogenesis, and inhibit critical enzymes involved in the development of cancer cells. Breast, lung, prostate, and colon cancer are only a few of the cancer types against which triazoles have demonstrated potential as cytotoxic agents.

Different mechanisms of action for 1,2,3-triazoles have been found to have anticancer effects. They work to prevent the development of this deadly illness by inhibiting the carbonic anhydrases (CAs), thymidylate synthase, aromatase, tryptophan, vascular endothelial growth factor receptor, and edipermal growth factor receptor [67] (Figure 3.12).

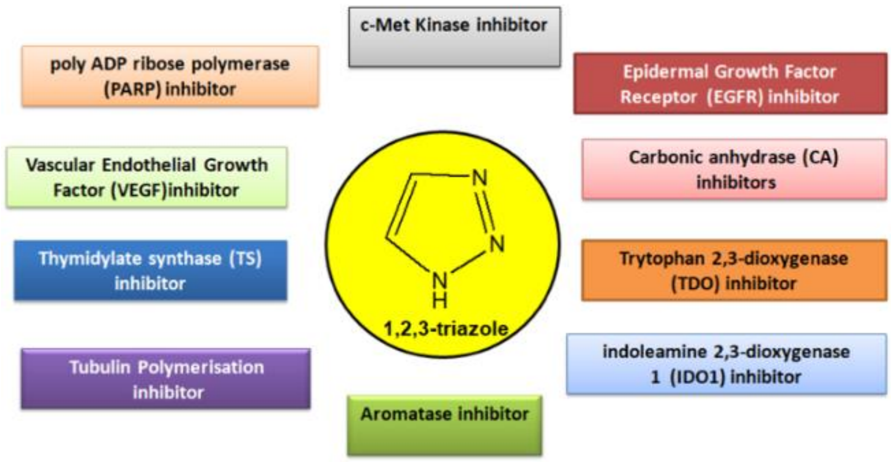


Figure 3.12 Action mechanism of 1,2,3-triazoles as anticancer agents

Bebenek and coworkers [68] report that The cytotoxic activity of a series of 1,2,3-triazoles of betulinic acid substituted with C-3 aryls was investigated against a variety of human cancer lines, including amelanotic melanoma C-32, ductal carcinoma T47D and glioblastoma SNB-19. In contrast to betulinic acid, some of the compounds showed promising IC50 values against cancer cell line.

Sophora flavescens Ait, a traditional Chinese herb used for hundreds of years to cure cancers, cardiovascular illness, liver disease, and asthma, contains the active ingredient matrine in significant amounts in the root. While chalcones are abundantly distributed in most natural fruits and vegetables as biological precursors of flavonoids as well as cancers, they also have a range of biological actions. Zhao and coworkers demonstrated that by combining matrine, 1*H*-1,2,3-triazole, and chalcones, it is possible to produce novel anticancer compounds that exhibited synergistic effects (Figure 3.13). The double bond of the α,β-unsaturated moiety was thought to be the main factor in these compounds [69].

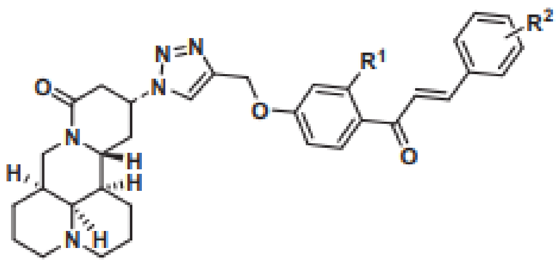


Figure 3.13 Conjugation of matrine-1*H*-1,2,3-triazole and chalcones as potantial anticancer agent

3.3.4 Anti-inflammatuar Agents

It has been discovered that substances containing triazoles have inhibitory effects on a variety of inflammatory mediators. Pro-inflammatory cytokines including tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 play crucial roles in the start and spread of inflammatory reactions, and they have the ability to modify their synthesis and release.

Haider at al. [70] demonstrated that it is possible to synthesize a benzoxazolinone based 1,2,3-triazoles. Then they were tried to observed anti-inflammatory activity level of these new products with the help of in vivo and in vitro experiments. While 3 hours later, the activity was almost 81.5%, 5 hours later it was 80.6% inhibition. The same experiment was performed with indomethacin. As a result, triazole based product synthesized TNF-α inhibatory activity with 50% ratio which leads to decrease the inflammatory effect. This effect was comparable with standart drug Indomethacin (Figure 3.14).

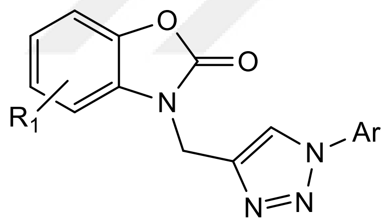


Figure 3.14 Benzoxazolinone based 1,2,3-triazoles with promising COX-2 and TNF-a inhibitory activity

Singh, synthesized some 1,2,3-triazol derivatives by the reaction of 2-azido-N-phenylacetamide with cinnamic acid in the presence of ethanol (Figure 3.15). All substances had considerable anti-inflammatory efficacy. According to the results, there was noticeable anti-inflammatory activity that was comparable to Ibuprofen [71].

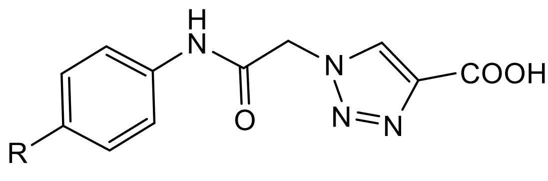


Figure 3.15 1,2,3-Triazoles having considerable anti-inflammatory efficacy

3.4 Biological Importance of 1,2,3-Triazole-Coumarin Hybrid Compounds

A group of chemical compounds known as coumarin-1,2,3-triazole hybrids combines the structural elements of coumarin and 1,2,3-triazole. These substances have exhibited a variety of biological activities. The biological activity of coumarin-1,2,3-triazole hybrid compounds might differ based on their particular chemical structure and modifications.

A library of coumarin derivatives conjugated with 1,2,3-triazole was recently developed, and it was shown that these compounds had strong anticancer and antibacterial properties. Accordingly, novobiocin analogue with 1,2,3-triazole at the C-3 position of coumarin (Figure 3.16) demonstrated strong cytotoxic action against breast cancer cell lines [72].

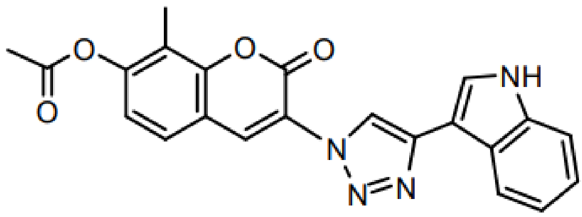


Figure 3.16 Structure of Novoiocin analogue with 1,2,3- triazole

Kaushik and coworkers [73] demonstrated that click chemistry has been used to synthesize 1,4-disubstituted 1,2,3-triazole hybrids with coumarin attached. Antimalarial and antioxidant properties were tested on all produced compounds in vitro. Some of the coumarin-triazole hybrids shown positive antioxidant and antimalarial activities. In contrast to electron withdrawing groups, electron donating groups on the benzyl ring of produced triazoles have a higher antioxidant potential. Interestingly, methyl group substitutions at any location for benzylic hydrogen demonstrated more activity than nitro group substitutions. When compared to 4-chromen-2-one derivatives, triazoles with a 7-chromen-2-one ring performed better in terms of antioxidant activity. Methyl substituted 1,2,3-triazoles are more effective in scavenging free radicals than nitro substituted triazoles.

4
CLICK CHEMISTRY

A collection of very dependable, selective, and effective reactions known as "click chemistry" may be used to link or "click" together molecular building blocks. K. Barry Sharpless came up with the term in 2001 to emphasize the efficiency and simplicity of these reactions.

Click reactions frequently have high conversion rates, which leads to a high yield of the product you want. This guarantees that the reaction can be carried out effectively, which is crucial for practical applications. Since click reactions only happen between the chosen functional groups and do not affect any other functional groups in the system, they are very selective. This selectivity reduces the possibility of undesirable side effects and simplifies the reaction conditions. They may be carried out either simultaneously or consecutively without interacting with one another because the reactions in click chemistry are orthogonal. By combining several click reactions, this permits the modular creation of complex molecular structures. In addition to these, water may be used as a reaction media in a wide variety of click chemical processes. Since the majority of biological systems function in an aqueous environment, this is useful for biological applications.

Researchers may covalently bind artificial chemical groups, such as inorganic catalysts or photosensitizers, to any location of a target protein with strong site-selectivity using genetically encoded click chemistry reaction reagents. Another unnatural amino acid that the click chemistry reagent can change into is glycosylated amino acids, which can be too challenging to integrate. Unnatural amino acids were functionalized by click chemistry using reagents from bioorthogonal reactions. Ring strain assisted cycloaddition of azide and alkyne and photoassisted cycloaddition of tetrazole and alkyne are more appropriate for biological systems due to the toxicity of Cu(I) [74] (Figure 4.1).

The "click" in "click chemistry" was intended to represent the simplicity and satisfaction that comes from joining items with a baggage strap connection. Whatever the components, as long as the buckle's two ends can touch, the connection will be created. An wide variety of activities in various domains, including materials science, surface science, analytical chemistry, chemical biology, and drug discovery, have been driven or encouraged by this potent concept that excellent chemistry may enable anybody to produce significant chemical entities. Also, the related disciplines of click and bioorthogonal chemistry have worked together to create novel, complex chemical reactions with the highest level of mechanical comprehension since it is difficult to find ways for the selective and dependable creation of bonds [75].

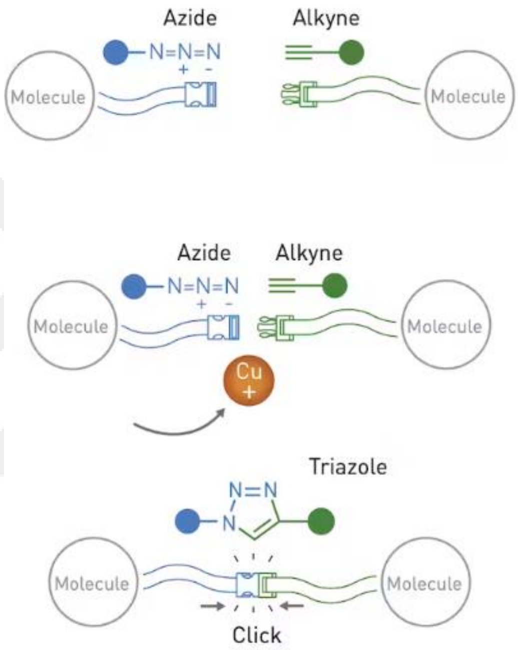


Figure 4.1 Click chemistry

The most recent development in click chemistry is that it is the subject of the Nobel Prize in chemistry in 2022. For simplifying complicated processes, Prof. Carolyn R. Bertozzi, professor K. Barry Sharpless and professor Morten Meldal were awarded the Nobel Prize in Chemistry [76]. These researchers have put forth a theory that explains how click chemistry and bioorthogonal chemistry may be used to swiftly and effectively assemble molecular building blocks even under physiological conditions.

It is possible to now artificially create nearly anything that can be thought of because to click chemistry and bioorthogonal reactions, which have thrust chemistry into a new era of simplicity and usefulness. By combining substances with other materials that already have those particular characteristics, it is now possible to enrich substances with any kind of desired property, such as antibacterial properties, electrical conductivity, light absorption capabilities, or protection against ultraviolet radiation.

5
EXPERIMENTAL PART

5.1 Chemicals Used

Table 5.1 Chemicals used in experimental parts

Compound Name	Company Name	Catalog Number
Resorsinol	Sigma-Aldrich	398047
Ethyl acetoacetate	Sigma-Aldrich	537349
Trifluoroacetic acid	Sigma-Aldrich	T6508
Dichloromethane	Merck	06050
Methanol	Merck	105012
Ethyl benzoylacetate	Sigma-Aldrich	W242306
Ethyl 2-oxocyclohexane carboxylate	Sigma-Aldrich	E20004
Acetone	Sigma-Aldrich	179124
Potassium carbonate	Sigma-Aldrich	590681
1,8-dibromooctane	Sigma-Aldrich	4549320
Ethyl acetate	Merck	100864
Dimethylformamide	Merck	100397
Sodyum azid	Merck	06688
n-Hexane	Merck	104368
Cupper iodide	Merck	18311

Table 5.1 Chemicals used in experimental parts (Continued)

Tetrahydrofuran (THF)	107025	107025
Chloroform-d ($CDCl_3$)	Merck	03296
Chloroform	Merck	107024
Silica TLC plate 60 F254	Merck	5554
Dichloromethane	Merck	06050

5.2 Devices Used

Merck 5554 silica gel plates and "Merck Silica Gel 60" (70-230 mesh) with fluorescent indicator were utilized for column chromatography. A "Camag" UV lamp with wavelengths of 254 nm and 366 nm was used to observe the separation.

A "Heidolph Laborota 4000" rotary evaporator was utilized to remove solvents throughout the chemical synthesis and separation processes.

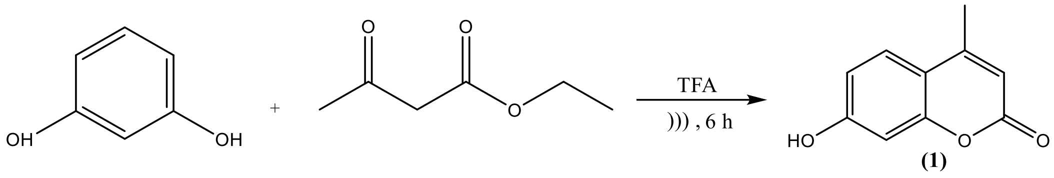
Reactions using ultrasonic vibrations were carried out in an ultrasonic bath of the "Intersonik" brand.

The "Bruker AVANCE 3 500 MHz NMR" instrument at the Nuclear Magnetic Resonance Laboratory of Yildiz Technical University and the "Bruker BioSpin Avance NEO 500 MHz NMR" instrument at the Drug Application and Research Laboratory of Bezm-i Alem University were both used to obtain the nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR). The measurements were made in $CDCl_3$ (chloroform-d).

The "Bruker ALPHA" instrument with 102113 serial number and ATR connection was used to collect the infrared spectra (FTIR) at the Eczacibasi Monrol Nuclear Products R&D Laboratory.

The Agilent 6200 series TOF/6500 series Q-TOF B.09.00 equipment was used to conduct LC-MS (Q-TOF) measurements at Central Laboratory of Yildiz Technical University.

5.3 Synthesis of 7-Hydroxy-4-methyl-2*H*-chromen-2-one (Compound 1, $C_{10}H_8O_3$)



Resorcinol (1.0 mmol) and ethyl acetoacetate (1.0 mmol) were interacted with ultrasonic waves in an ultrasonic bath in trifluoroacetic acid (5 mL, TFA) which was used as a solvent and catalyst. The reaction was completed after 6 hours. The progress of the reaction was followed by thin layer chromatography with a dichloromethane:methanol (10:1) system. Then, TFA was removed with the help of a rotary evaporator. Then, solid product was crystallized from methanol.

White solid, 85%, m.p. 185-187 ºC, (m.p 180-182 ºC [77])

Spectral Data of Compound 1:

FTIR (ATR): ν = 3130 (OH stretching), 3065 (aromatic, CH stretching), 2818 (aliphatic, CH stretching), 1683 (C=O stretching), 1608 and 1570 (aromatic C=C stretchings), 1392 and 1322 (aliphatic in-plane C-H bending), 1271 (C-O stretching) cm^{-1}.

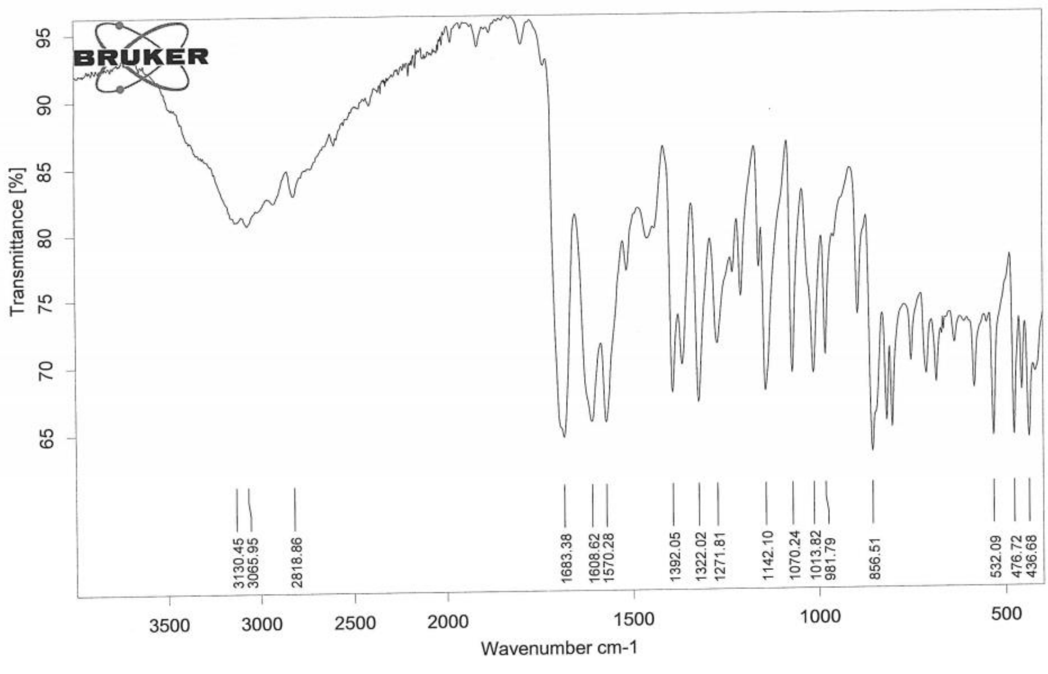
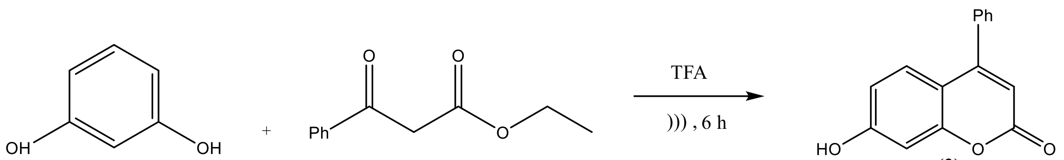


Figure 5.1 FTIR Spectrum of Compound 1

5.4 Synthesis of 7-Hydroxy-4-phenyl-2*H*-chromen-2-one (Compound 2, $C_{15}H_{10}O_3$)



(2)

Resorcinol (1.0 mmol) and ethyl benzoylacetate (1.0 mmol) were reacted according to method described for compound 1.

White solid, 90%, m.p. 250-252ºC, (m.p 250-253 ºC [78])

Spectral Data of Compound 2:

FTIR (ATR): ν = 3095 (aromatic, CH stretching), 1682 (C=O stretchings), 1590 (aromatic C=C stretching), 1237 (C-O stretching), 861 (C-H bending) cm^{-1}.

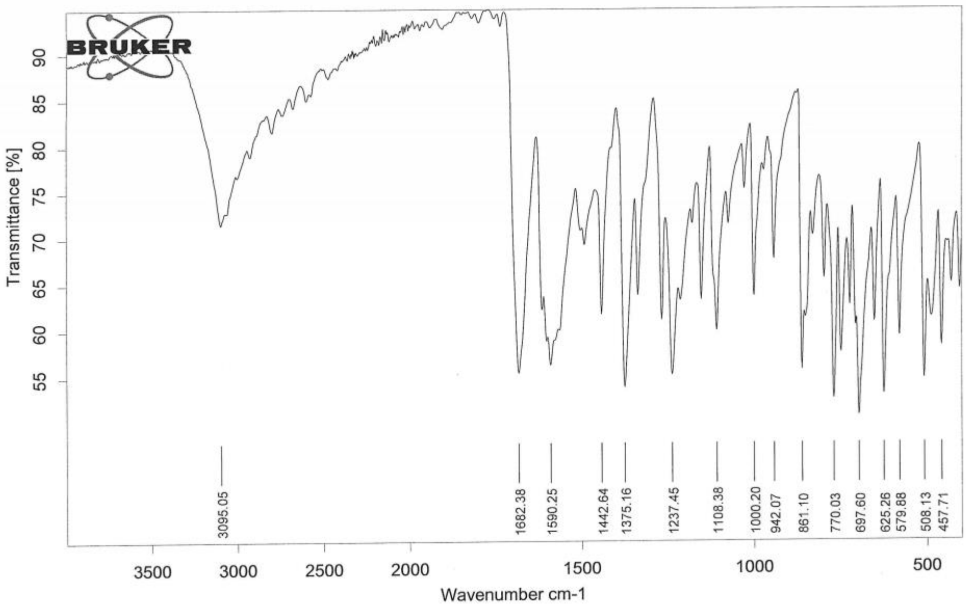
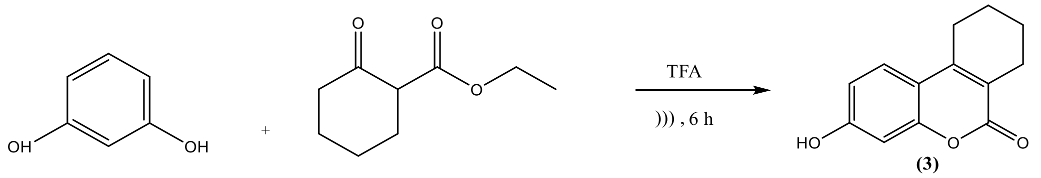


Figure 5.2 FTIR Spectrum of Compound 2

5.5 Synthesis of 3-Hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (Compound 3, $C_{13}H_{12}O_3$)



Resorcinol (1.0 mmol) and ethyl 2-oxocyclohexane carboxylate (1.0 mmol) were reacted using the method given for Compound 1.

White solid, 85%, m.p. 224-227 ºC (m.p 223.7-226.9 ºC [79])

Spectral Data of Compound 3:

FTIR (ATR): ν = 3205 (OH stretching), 2941 (aliphatic, CH stretchings), 1678 (C=O stretching), 1613, 1562 (aromatic C=C stretching), 1510, 1387 (aliphatic, in plane C-H stretching), 1148 (C-O stretching) cm^{-1}.

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=217.0859 for $C_{13}H_{12}O_3$, Found=217.0857.

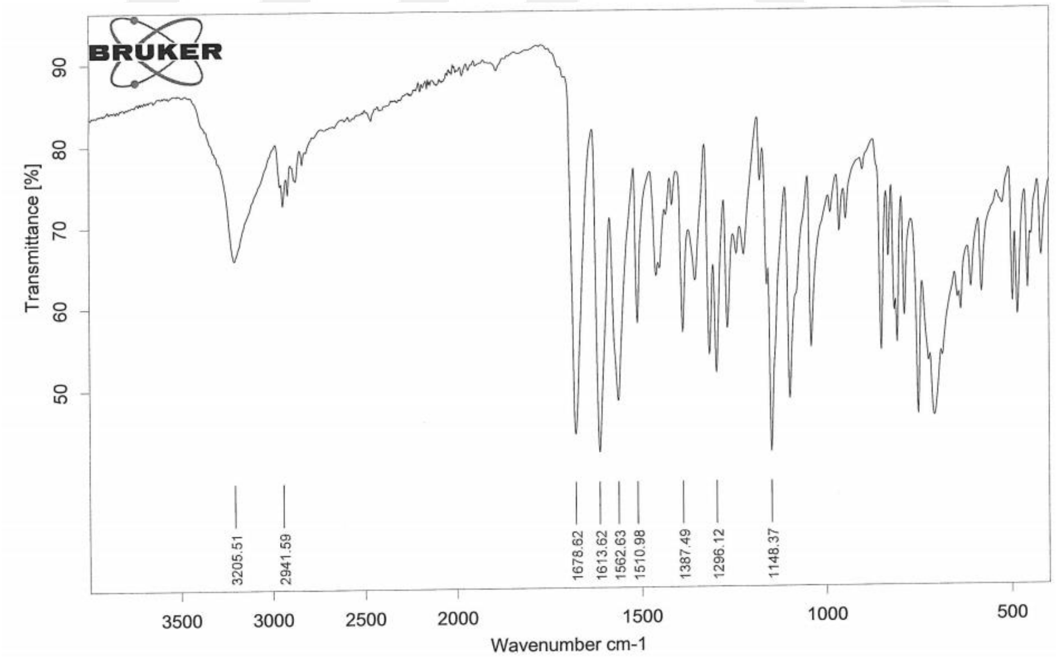


Figure 5.3 FTIR Spectrum of Compound 3

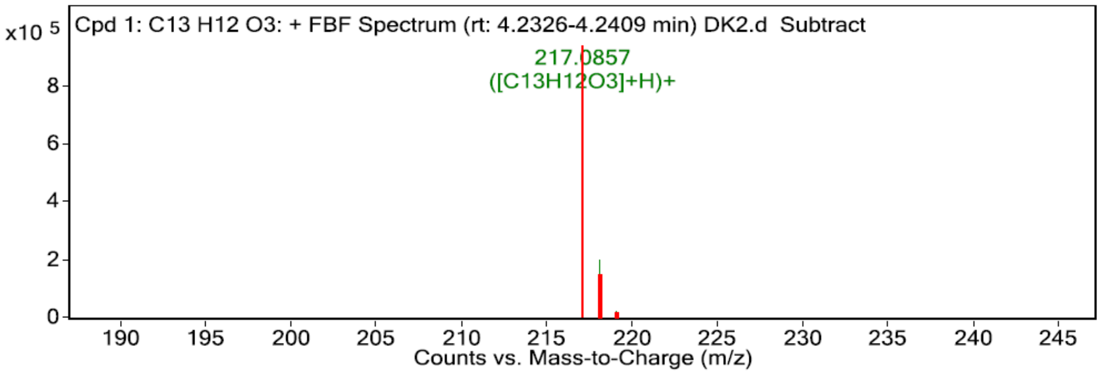
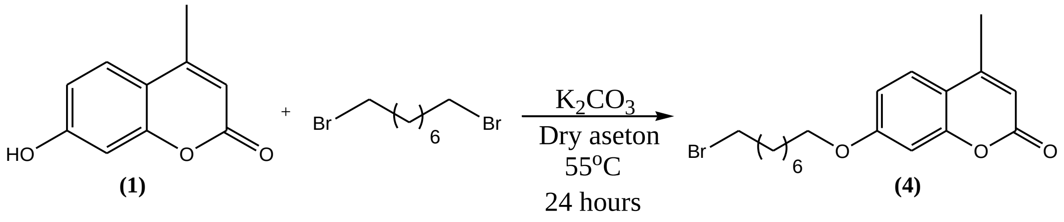


Figure 5.4 LC-MS Spectrum of Compound 3

5.6 Synthesis of 7-((8-Bromooctyl)oxy)-4-methyl-2*H*-chromen-2-one (Compound 4, $C_{18}H_{23}BrO_3$)



Compound 1 (1.0 mmol) was dissolved in 15 mL of dry acetone. Overheated K_2CO_3 (3.0 mmol) was added into the reaction flask. The reaction was carried out under nitrogen atmosphere. After an hour, 1,8-dibromooctane (2.0 mmol) was added to the reaction flask. The progress of the reaction was followed by thin layer chromatography with the ethyl acetate:hexane (1:2) system. It was observed that the reaction was completed in 24 hours. Solvent was evaporated in a rotary evaporator. The crude product was purified using column chromatography (ethyl acetate:hexane 1:2).

White crystal, 77%, m.p. 48-49 ºC (m.p 49-50 ºC [80])

Spectral Data of Compound 4:

FTIR (ATR): ν = 3066 (aromatic, CH streching), 2917, 2857, 2850 (aliphatic, CH stretching), 1727 (C=O stretching), 1607 (aromatic C=C stretching), 1467 and 1388 (aliphatic, in plane C-H stretching) cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ= 1.33-1.40 (m, 8H, CH_2) 1.85-1.89 (m, 4H, CH_2) 2.41 (s, 3H, CH_3), 3.43 (t, 2H, *J*= 6.5 Hz, CH_2Br), 4.02 (t, 2H, *J*= 6.5 Hz, O-CH_2), 6.14 (s, 1H, =CH) 6.81 (bd, 1H, *J*= 2.5 Hz, ArH), 6.87 (dd, 1H, *J*= 11.0 Hz, 2,5 Hz, ArH) 7.50 (d, 1H, *J*= 8.5 Hz, ArH) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ= 18.68 (CH_3), 25.87 (CH_2), 28.04 (CH_2), 28.57 (CH_2), 28.94 (CH_2), 29.14 (CH_2), 32.74 (CH_2CH_2Br), 33.9 (CH_2Br), 68.53 (O-CH_2), 101.33 (C_{aro}H), 111.83 (C_{aro}H), 112.68 (C_{aro}), 113.43 (=CH), 125.48 (C_{aro}H), 152.59 (C_{aro}), 155.91 (C_{aro}), 161.38 (C_{aro}, C-O), 162.20 (C=O) ppm.

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=368.09 for $C_{18}H_{23}BrO_3$, Found=369.0878

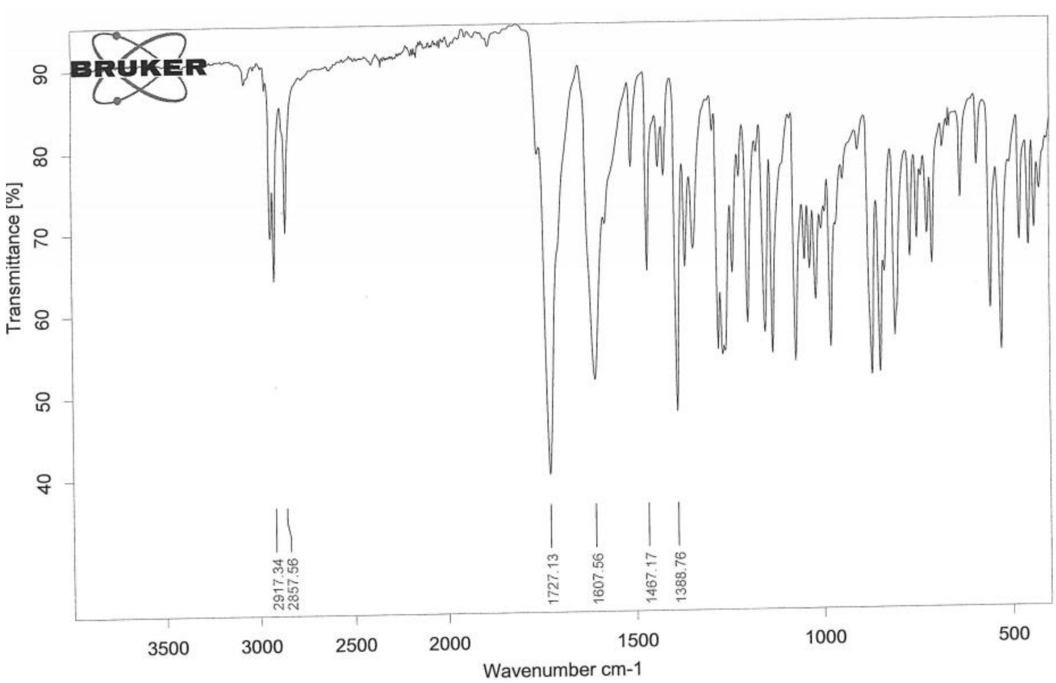


Figure 5.5 FTIR Spectrum of Compound 4

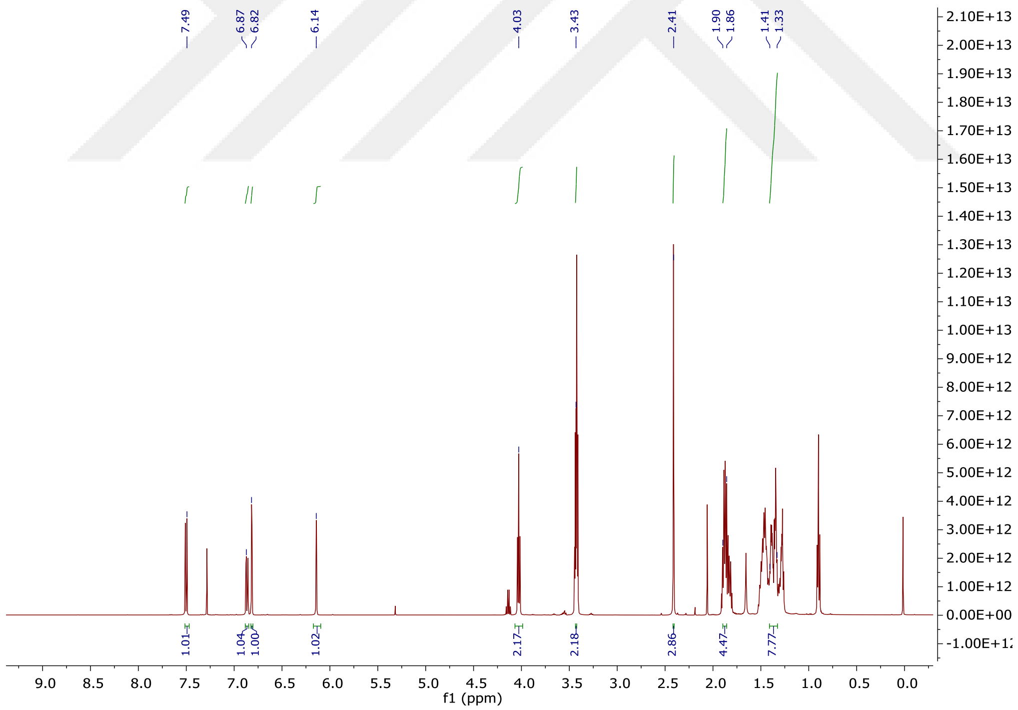


Figure 5.6 ^{1}H NMR Spectrum of Compound 4

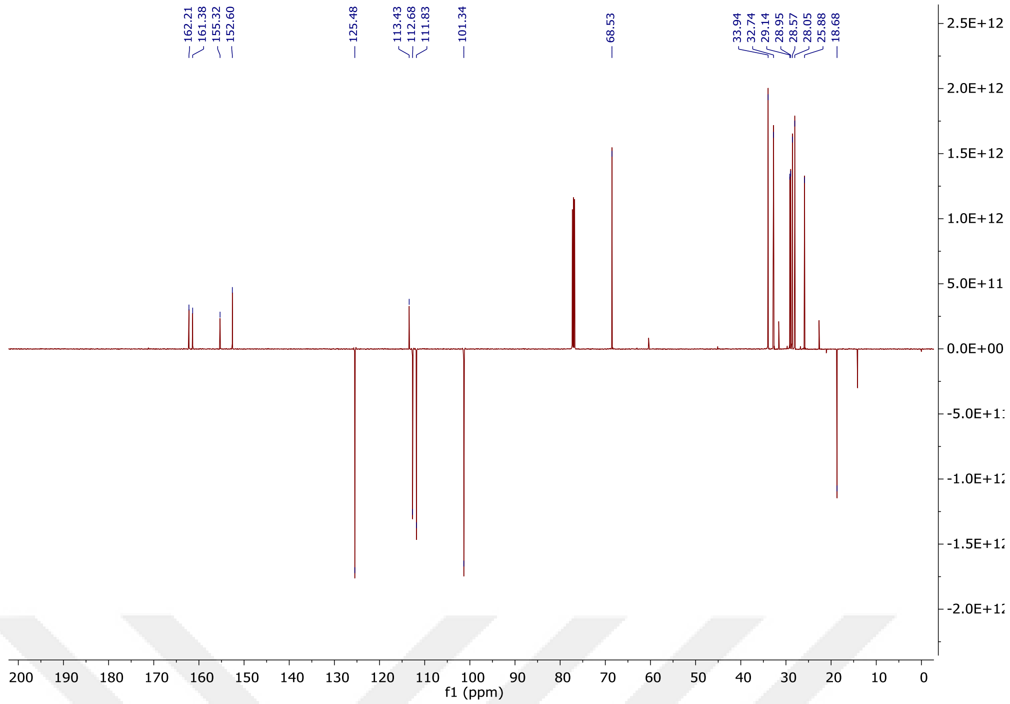


Figure 5.7 ^{13}C NMR Spectrum of Compound 4

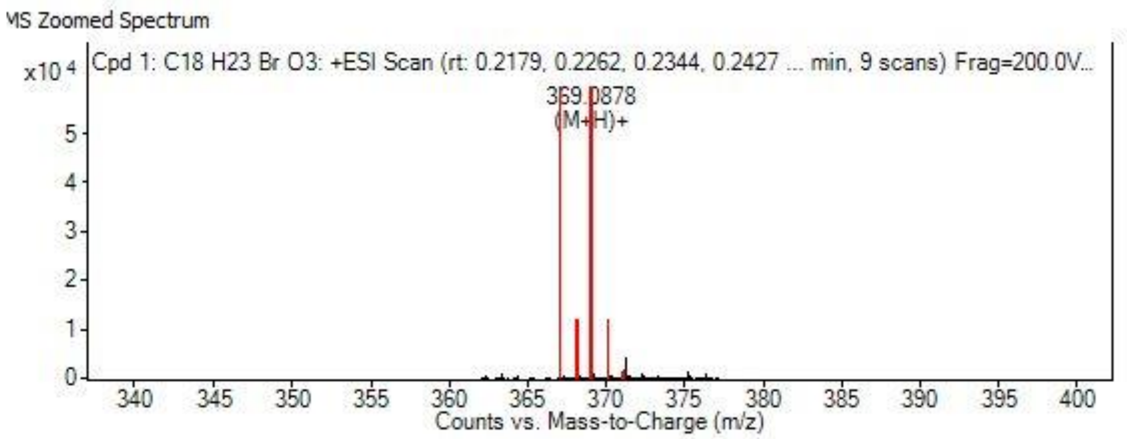
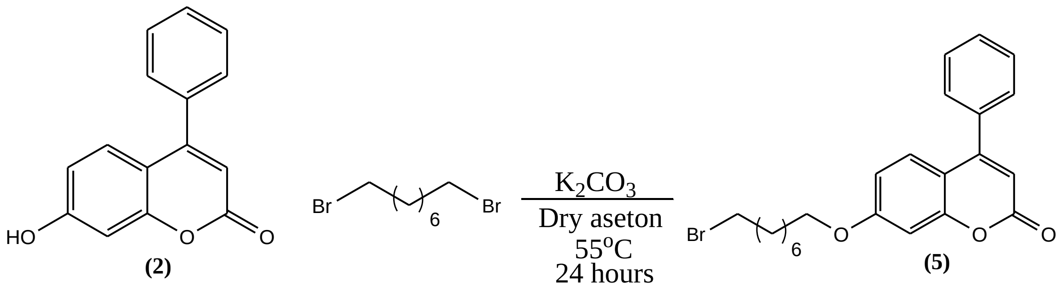


Figure 5.8 LC-MS Spectrum of Compound 4

5.7 Synthesis of 7-((8-Bromooctyl)oxy)-4-methyl-2*H*-chromen-2-one (Compound 5, $C_{23}H_{25}BrO_3$)



Compound 2 (1.0 mmol) was interacted with 1,8-dibromooctane (2.0 mmol) as Compound 1 in previous experiment. The crude product was purified using column chromatography (ethyl acetate:hexane 1:4).

White crystal, %72, m.p. 88-90 °C

Spectral Data of Compound 5:

FTIR (ATR): ν = 3060 (aromatic, CH stretching), 2937, 2851 (aliphatic, CH stretching), 1718 (C=O stretching), 1602 (aromatic C=C stretching), 1444 and 1373 (aliphatic, in plane C-H stretching), 1261 (C-O stretching) cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ= 1.34-1.41 (m, 4H, CH_2), 1.42-1.51 (m, 4H, CH_2), 1.79-1.89 (m, 4H, CH_2), 3.41 (t, 2H, *J*= 6.5 Hz, CH_2Br), 4.03 (t, 2H, *J*= 6.5 Hz, O-CH_2), 6.21 (s, 1H, =CH), 6.78 (dd, 1H, *J*= 9.0 Hz, 2.5 Hz, ArH), 6.88 (d, 1H, *J*= 2.5 Hz, ArH), 7.37 (dd, 1H, *J*= 9.0 Hz, ArH), 7.42-7.44 (m, 2H, ArH), 7.50-7.52 (m, 3H, ArH) ppm.

^{13}C (125 MHz, $CDCl_3$): δ= 25.87 (CH_2), 28.07 (CH_2), 28.64 (CH_2), 28.92 (CH_2), 29.14 (CH_2), 32.75 (CH_2), 33.94 (CH_2Br), 68.60 (O-CH_2), 101.59 (C_{aro}H), 111.79 (C_{aro}H), 112.35 (C_{aro}), 112.74 (=CH), 127.91 (C_{aro}H), 128.38 (C_{aro}H), 128.82 (C_{aro}H), 129.56 (C_{aro}H), 135.64 (C_{aro}), 155.86 (C_{aro}), 156.03 (C_{aro}), 161.32 (C_{aro}), 162.36 (C=O) ppm.

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=430.10 for $C_{23}H_{25}BrO_3$, Found=431.1046.

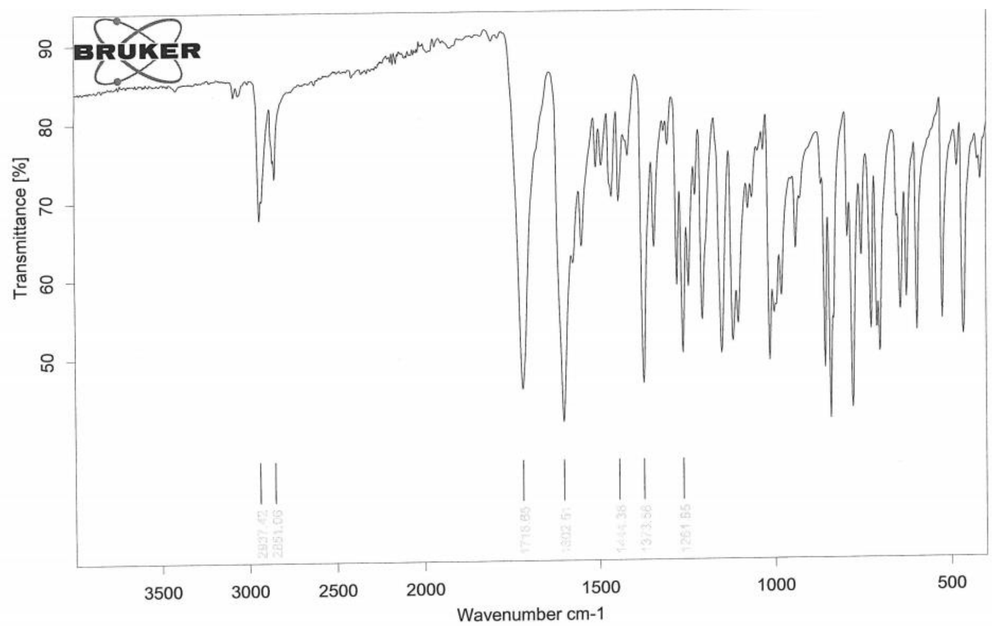


Figure 5.9 FTIR Spectrum of Compound 5

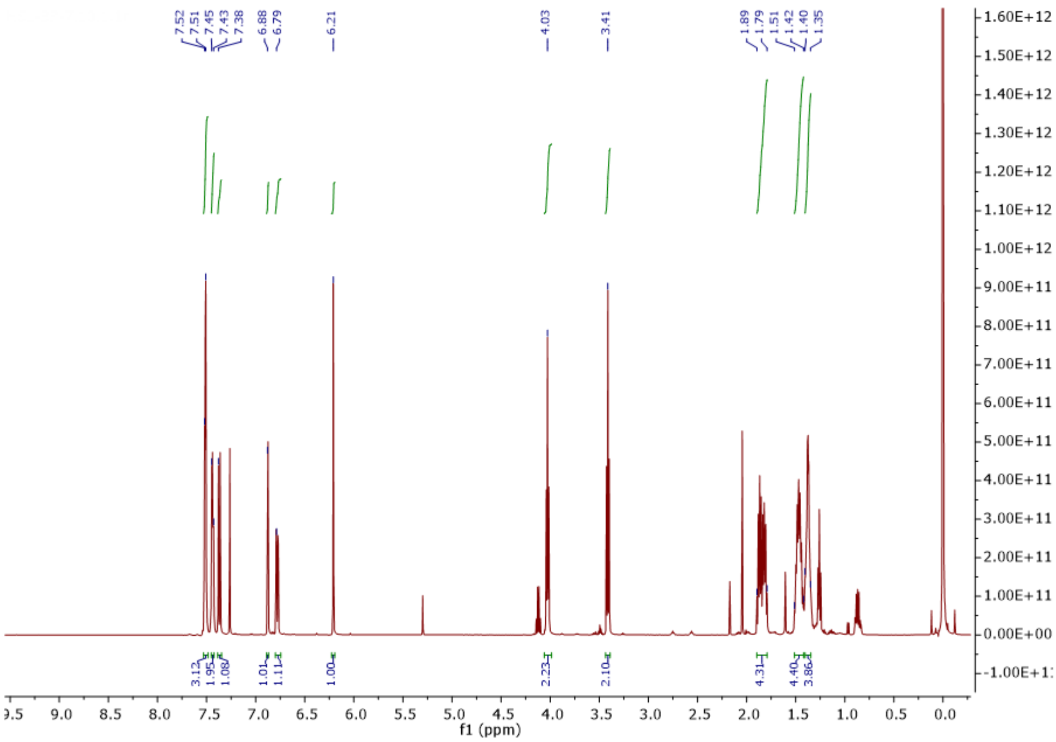


Figure 5.10 ^{1}H NMR Spectrum of Compound 5

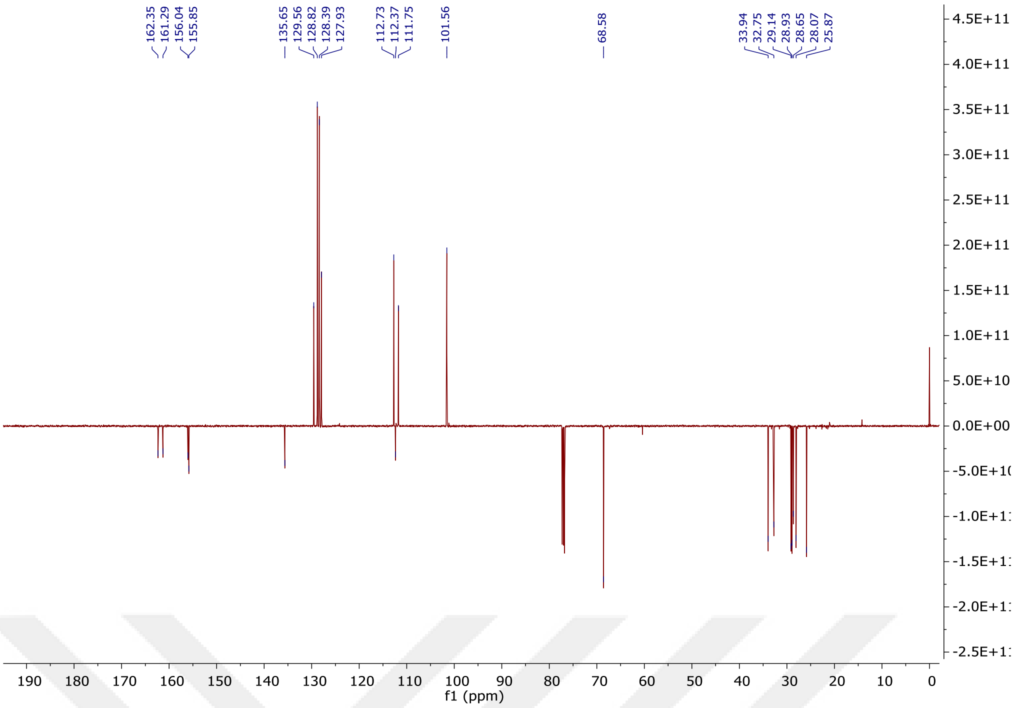


Figure 5.11 [13]C NMR Spectrum of Compound 5

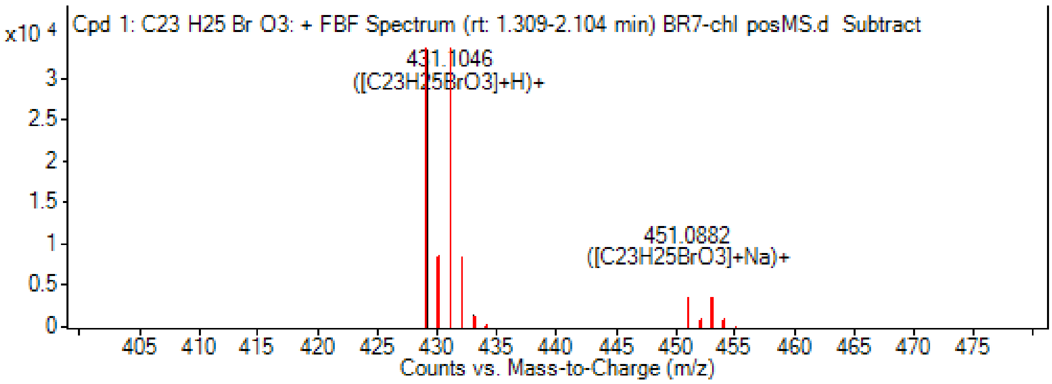
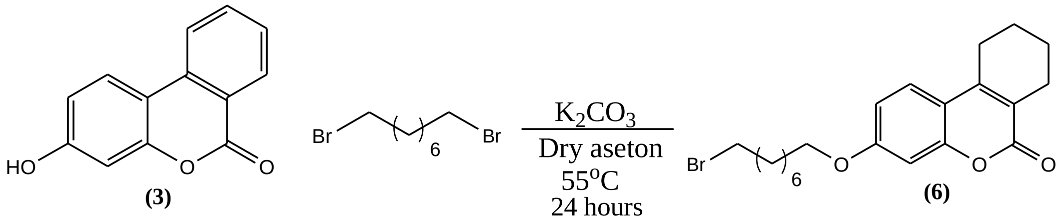


Figure 5.12 LC-MS Spectrum of Compound 5

5.8 Synthesis of 3-((8-Bromooctyl)oxy)-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (Compound 6, $C_{21}H_{27}BrO_3$)



Compound 3 (1.0 mmol) was reacted with 1,8-dibromooctane (2.0 mmol) according to the procedure used for Compound 4. The crude product was purified using column chromatography (ethyl acetate:hexane 1:3).

White crystal, 69.3%, m.p. 80-82 ºC.

Spectral Data of Compound 6:

FTIR (ATR): ν = 3070 (aromatic, CH stretching), 2931, 2851 (aliphatic, CH stretching), 1713 (C=O stretching), 1610 and 1505 (aromatic C=C stretching), 1468, 1431 ve 1391 (aliphatic, in plane C-H stretching), 1259 (C-O stretching) cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ= 1.34-1.40 (m, 4H, CH_2), 1.42-1.51 (m, 4H, CH_2), 1.78-1.89 (m, 8H, CH_2), 2.56 (ddt, 2H, CH_2), 2.75 (ddt, 2H, CH_2), 3,42 (t, 2H, *J*= 6.5 Hz, CH_2Br), 4.00 (t, 2H, *J*= 6.5 Hz, O-CH_2), 6.78-6.84 (m, 2H, ArH), 7.45 (d, 1H, *J*= 9.0 Hz, ArH) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ= 21.40 (CH_2), 21.71 (CH_2), 23.83 (CH_2), 25.22 (CH_2), 25.90 (CH_2), 28.07 (CH_2), 28.66 (CH_2), 28.99 (CH_2), 29.15 (CH_2), 32.75 (CH_2), 33.97 (CH_2Br), 68.39 (O-CH_2), 101.09 (C_{aro}), 112.34 (C_{aro}), 113.60 ($C_{aro}H$), 120.38 ($C_{aro}H$), 124.04 ($C_{aro}H$), 147.31 (C_{aro}), 153.51 (C_{aro}), 160.93 (C_{aro}), 162.22 (C=O) ppm.

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=407.1217 for $C_{21}H_{27}BrO_3$, Found=407.1216

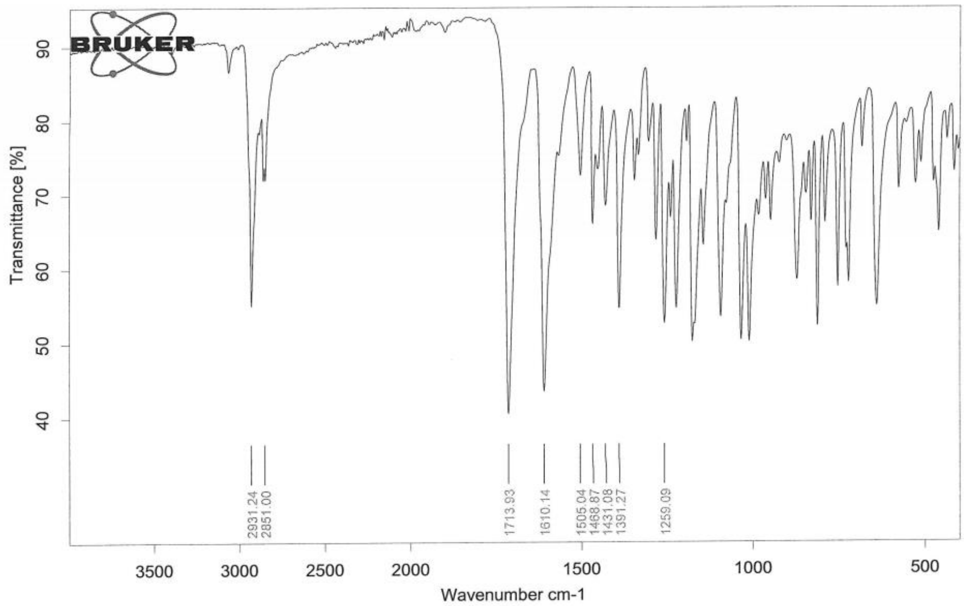


Figure 5.13 FTIR Spectrum of Compound 6

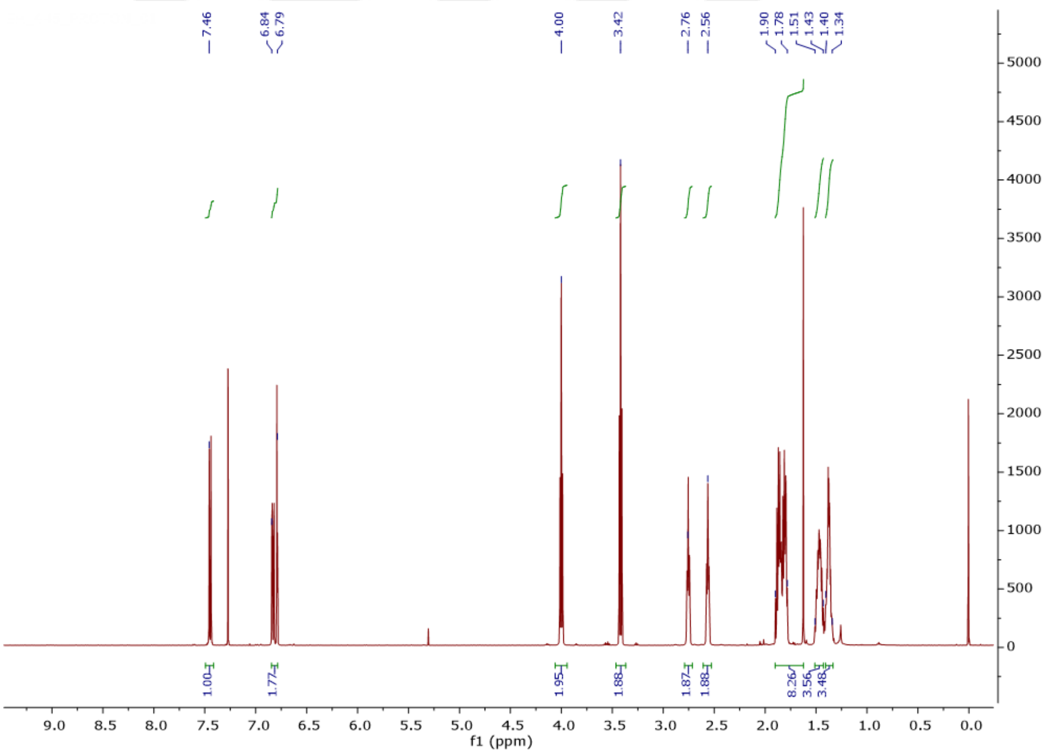


Figure 5.14 ^{1}H NMR Spectrum of Compound 6

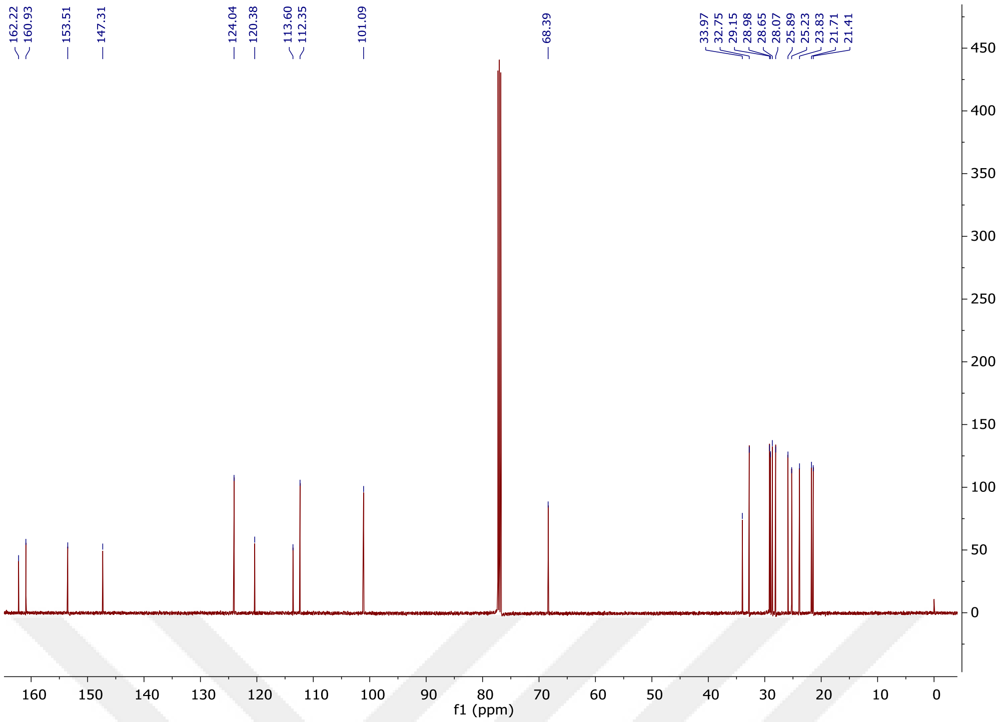


Figure 5.15 ^{13}C NMR Spectrum of Compound 6

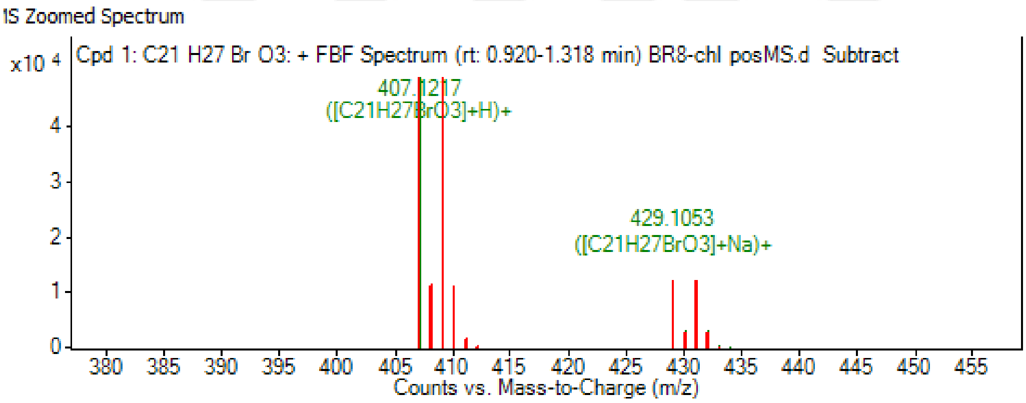
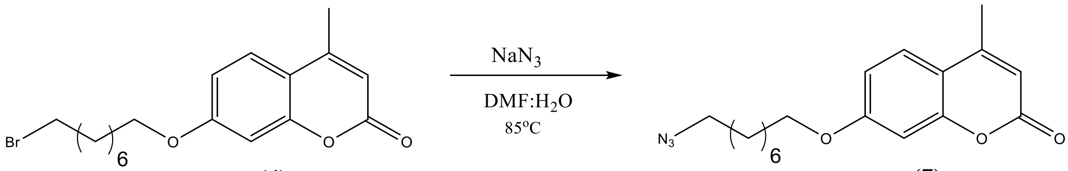


Figure 5.16 LC-MS Spectrum of Compound 6

5.9 Synthesis of 7-((8-Azidooctyl)oxy)-4-methyl-2*H*-chromen-2-one (Compound 7, $C_{18}H_{23}N_3O_3$)



(4) **(7)**

Compound 4 (3.21 mmol) was dissolved in 8 mL of DMF and transferred to the reaction flask. NaN_3 (9.64 mmol) was dissolved in 2 mL of distilled water and added to the reaction flask. The reaction was stirred at 85°C for 24 hours. According to TLC (1:4 ethyl acetate/n-hexane) result, it was observed that the reaction completed after 24 hours. After cooling, the mixture was poured into ice water and extracted with ether-brine. The organic phase was dried with $MgSO_4$, filtered and the solvent was evaporated under vacuum. A cream-colored crystalline substance was obtained. The compound was pure enough, so used without any purification.

Cream colored crystal, 84%, m.p. 48-49 ºC.

Spectral Data of Compound 7:

FTIR (ATR): ν = 3085 (aromatic, CH stretching), 2929, 2854 (aliphatic, CH stretching), 2089 (N=N stretching) 1712 (C=O stretching), 1615 and 1555 (aromatic C=C stretching), 1474, 1442 ve 1380 (aliphatic, in plane C-H stretching), 1263 (C-O stretching) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.33-1.43 (m, 6H, CH_2), 1.45-1.51 (m, 2H, CH_2), 1.58-1.62 (m, 2H, CH_2),1.78-1.84 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 3.27 (t, J=6.5Hz, 2H, N_3CH_2), 4.01 (t, J=6.5Hz, 2H, OCH_2), 6.13 (s, 1H, =CH), 6.80 (d, J=2.5H, 1H, ArH), 6.85 (dd, J=2.5, 8.8Hz, 1H, ArH), 7.48 (d, J=9.0 Hz, 1H, ArH)

^{13}C NMR ($CDCl_3$): δ 18.67 (CH_3), 25.87 (CH_2), 26.63 (CH_2), 28.81 (CH_2), 28.94 (CH_2), 29.04 (CH_2), 29.17 (CH_2), 51.45 (N_3CH_2), 68.52 (OCH_2), 101.32 (C_{aro}H), 111.83 (C_{aro}H), 112.68 (C_{aro}H), 113.43 (C_{aro}), 125.47 (C_{aro}H), 152.59 (C_{aro}), 155.31 (C_{aro}), 161.38 (C_{aro}), 161.20 (C=O).

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=329.40 $C_{18}H_{23}N_3O_3$, Found=330.1805

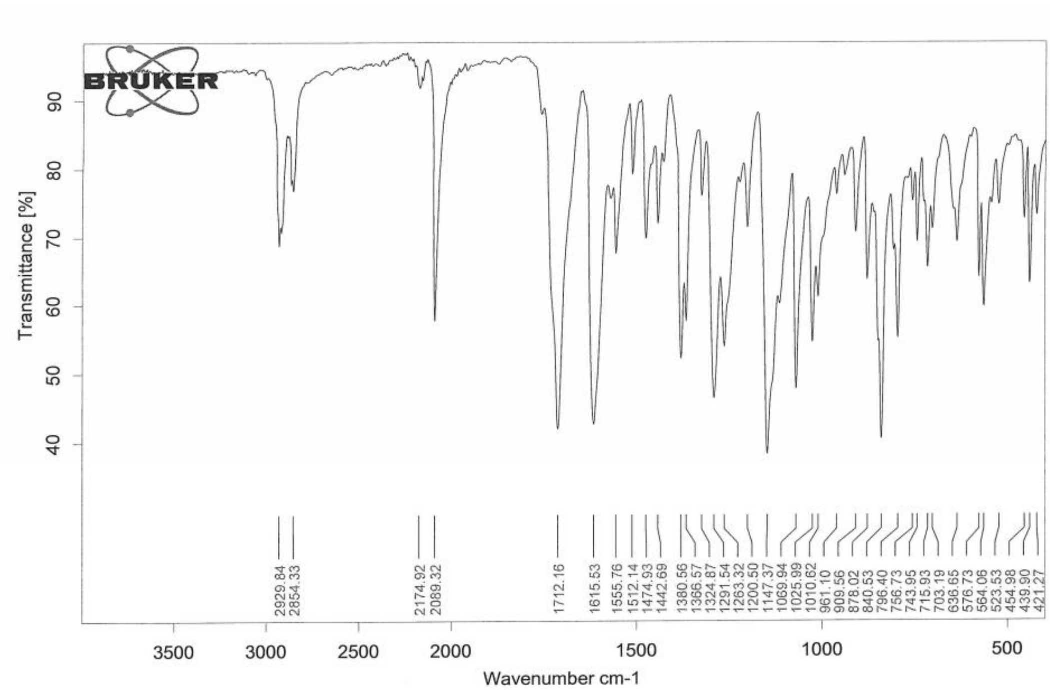


Figure 5.17 FTIR Spectrum of Compound 7

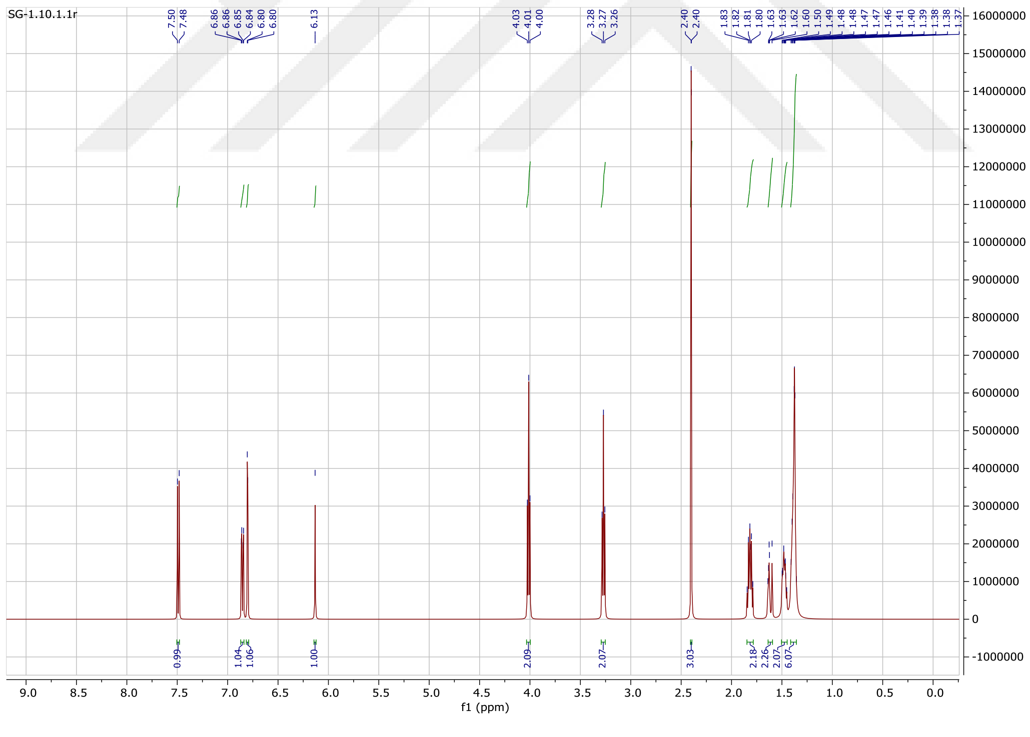


Figure 5.18 ^{1}H NMR Spectrum of Compound 7

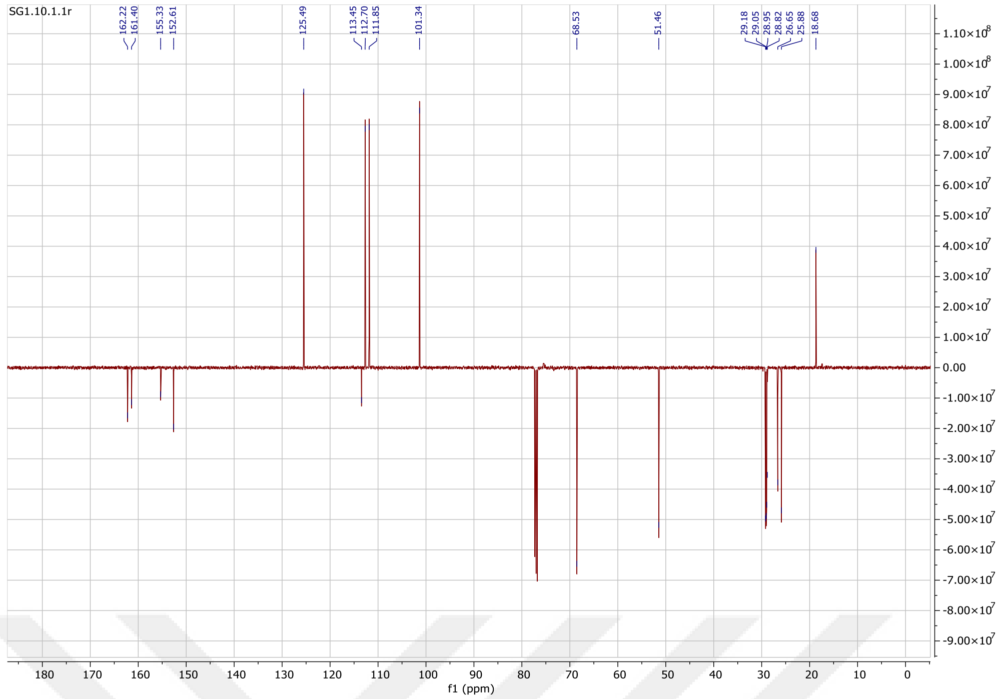


Figure 5.19 ^{13}C NMR Spectrum of Compound 7

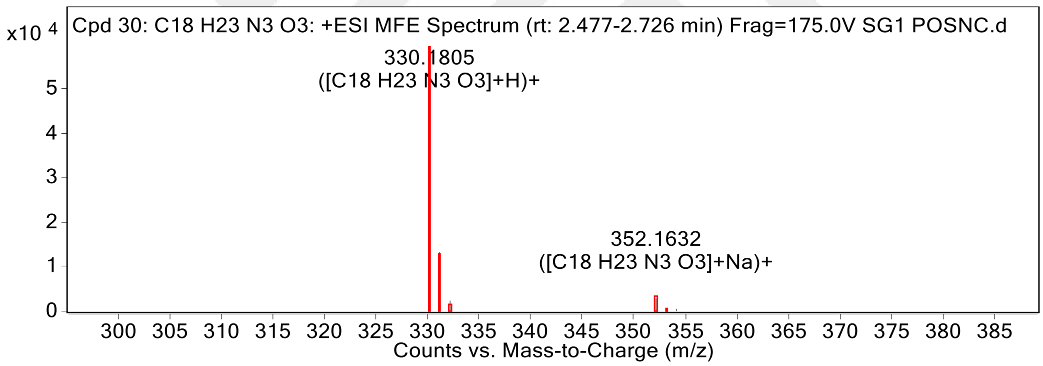
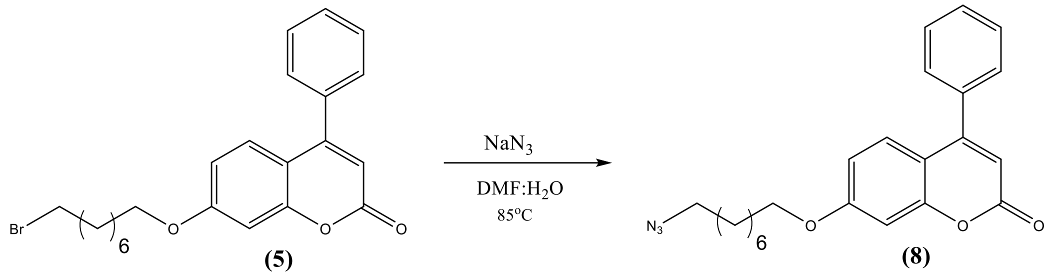


Figure 5.20 LC-MS Spectrum of Compound 7

5.10 Synthesis of 7-((9-Azidooctyl)oxy)-4-phenyl-2*H*-chromen-2-one (Compound 8, $C_{23}H_{25}N_3O_3$)



(5) (8)

Compound 5 was reacted with NaN_3 according to procedure used for Compound 7. Pure compound 8 was obtained after evaporation.

White crystal, 63% , m.p. 50-51 ºC.

Spectral Data of Compound 8:

FTIR (ATR): ν =3060 (aromatic CH stretching), 2933, 2854 (aliphatic, CH stretching), 2093 (N=N stretching) 1722 (C=O stretching), 1605 and 1546 (aromatic C=C stretching), 1474, 1444 and 1371 (aliphatic, in plane C-H stretching), 1259 (C-O stretching) cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.33-1.42 (m, 6H, CH_2), 1.45-1.49 (m, 2H, CH_2), 1.58-1.62 (m, 2H, CH_2), 1.79-1.85 (m, 2H, CH_2), 3.27 (t, J=7.0 Hz, 2H, N_3CH_2), 4.027 (t, J=6.5Hz, 2H, OCH_2), 6.21 (s, 1H, =CH), 6.78 (dd, J=2.5, 6.0Hz, 1H, ArH), 6.88 (d, J=2.0Hz, 1H, ArH) 7.37 (d, J=8.5Hz, 1H, ArH), 7.43-7.45 (m, 2H, ArH), 7.50-7.52 (m, 3H, ArH).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 25.87 (CH_2), 26.64 (CH_2), 28.81 (CH_2), 28.93 (CH_2) 29.05 (CH_2), 29.17 (CH_2) 51.45 (N_3CH_2), 68.58 (OCH_2), 101.55 (C_{aro}H), 111.74 (C_{aro}H), 112.36 (C_{aro}), 112.74 (C_{aro}H), 127.93 (C_{aro}H), 128.39(C_{aro}H), 128.82 (C_{aro}H) 129.57 (C_{aro}H), 135.64 (C_{aro}), 155.87 (C_{aro}), 156.03 (C_{aro}), 161.32 (C_{aro}), 162.35 (C=O)

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=391.47 for $C_{23}H_{25}N_3O_3$, Found=392.1969

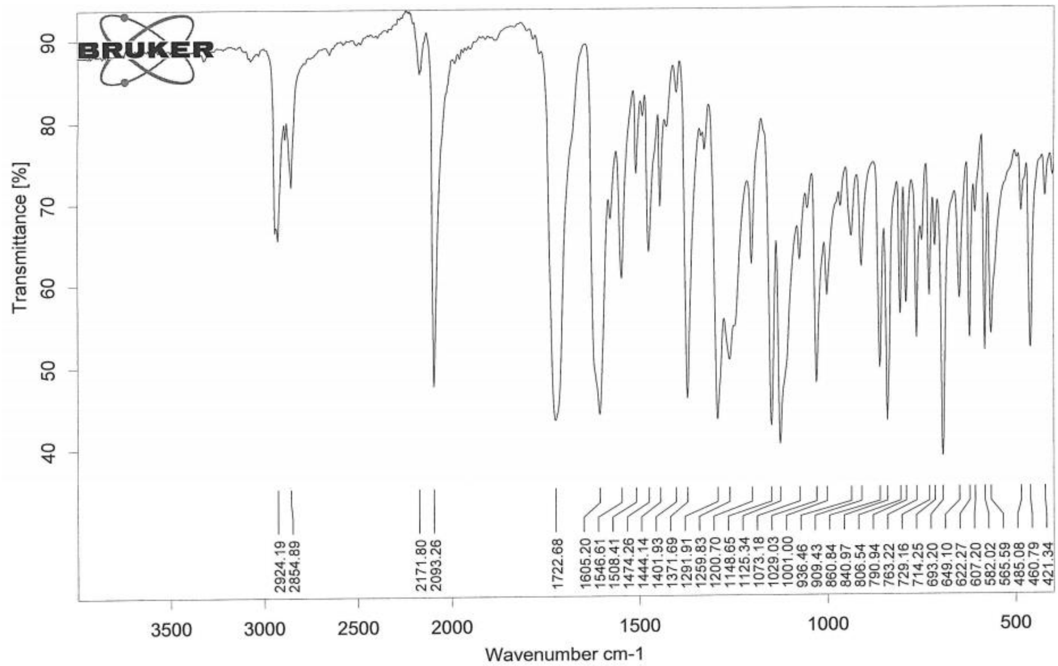


Figure 5.21 FTIR Spectrum of Compound 8

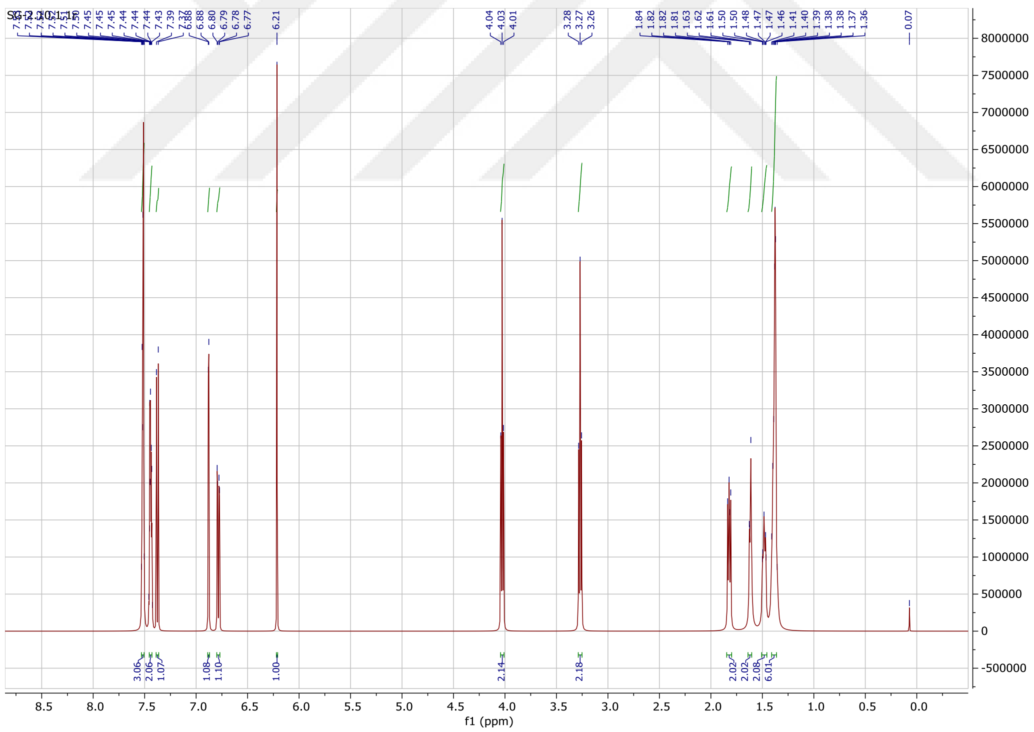


Figure 5.22 ^{1}H NMR Spectrum of Compound 8

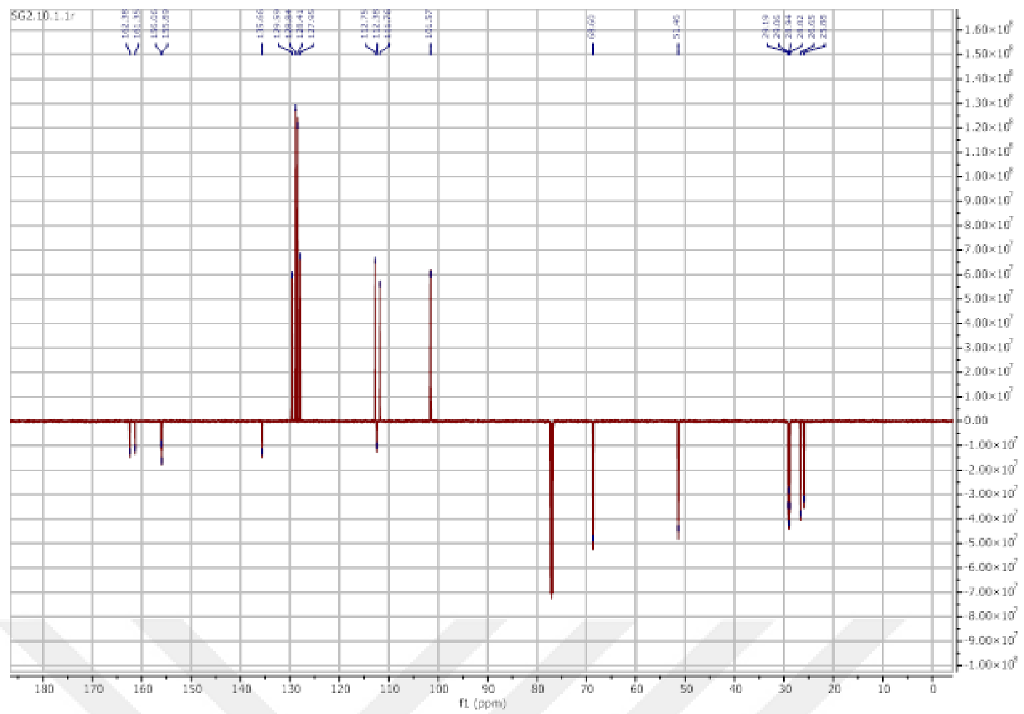


Figure 5.23 ^{13}C NMR Spectrum of Compound 8

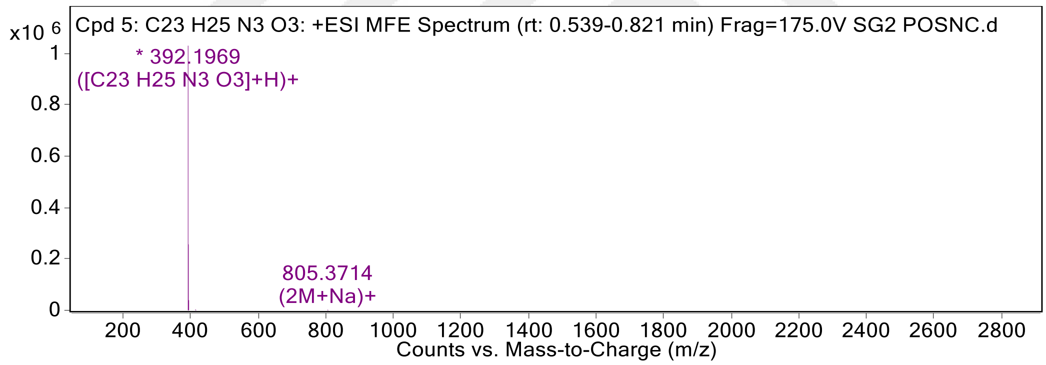
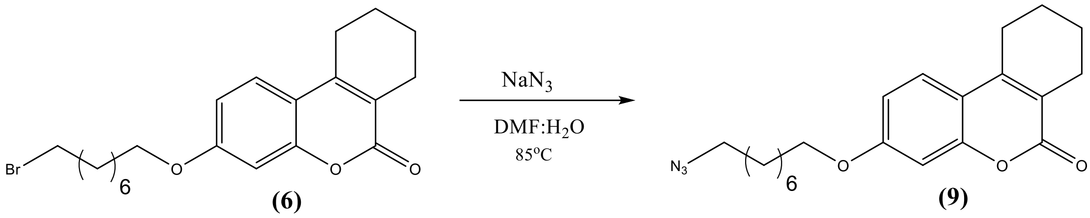


Figure 5.24 LC-MS Spectrum of Compound 8

5.11 Synthesis of 3-((8-Azidooctyl)oxy)-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (Compound 9, $C_{21}H_{27}N_3O_3$)



Compound 6 (3.21 mmol) was reacted with NaN_3 using the method given for Compound 7. Pure product was obtained after evaporation process.

White crystal, 67%, m.p. 54-55°C.

Spectral Data of Compound 9:

FTIR (ATR): ν = 3070 (aromatic C-H stretching), 2933, 2865 (aliphatic, CH stretching), 2085 (N=N stretching) 1707 (C=O stretching), 1611 and 1562 (aromatic C=C stretching), 1474, 1435 and 1382 (aliphatic, in plane C-H stretching), 1152 (C-O stretching) cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.34-1.40 (m, 6H, CH_2), 1.44-1.49 (m, 2H, CH_2), 1.57-1.64 (m, 2H, CH_2), 1.78-1.87 (m, 6H, CH_2), 2.55-2.57 (m,2H, CH_2), 2.74-2.76 (m, 2H, CH_2), 3.26 (t, J=7,0 Hz, 2H, $N_3CH_{2,}$), 3.99 (t, J=6.5 Hz, 2H, $OCH_{2,}$), 6.78 (d, J=2.5 Hz, 1H, ArH), 6.83 (dd, J=2.5, 8.5 Hz, 1H, ArH), 7.44 (d, J=9.0 Hz, 1H, ArH)

^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.41 (CH_2), 21.71 (CH_2), 23.84 (CH_2), 25.23 (CH_2), 25.89 (CH_2), 26.64 (CH_2), 28.81 (CH_2), 28.98 (CH_2), 29.05 (CH_2), 29.19 (CH_2), 51.45 (N_3CH_2), 68.39 (OCH_2), 101.09 (C_{aro}H), 112.30 (C_{aro}H), 113.62 (C_{aro}), 120.39 (C_{aro}), 124.06 (C_{aro}H), 147.34 (C_{aro}), 153.53 (C_{aro}), 160.95 (C_{aro}), 162.25 (C=O)

LC-MS (ESI-QTOF): *m/z* [M+H], Calculated= 369.473 for $C_{21}H_{27}N_3O_3$, Found=370.2127

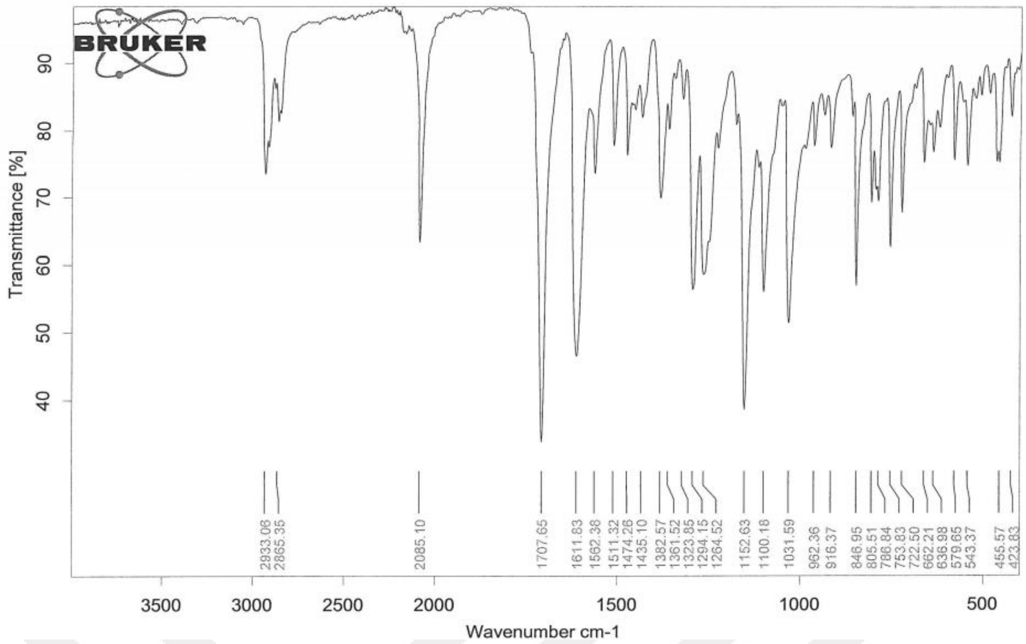


Figure 5.25 FTIR Spectrum of Compound 9

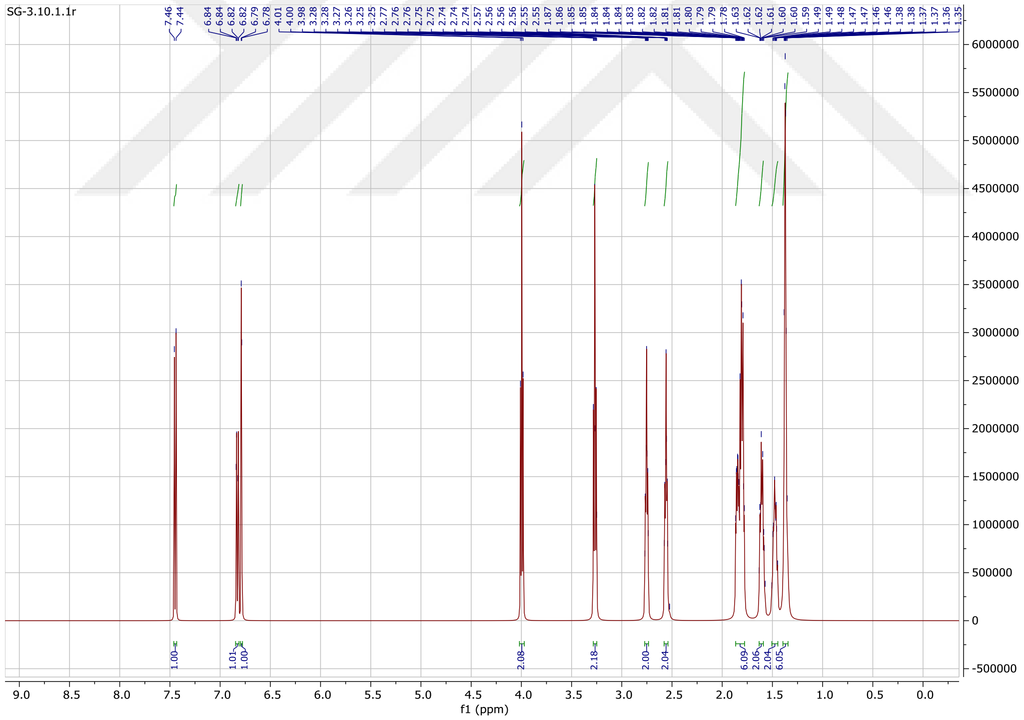


Figure 5.26 ^{1}H NMR Spectrum of Compound 9

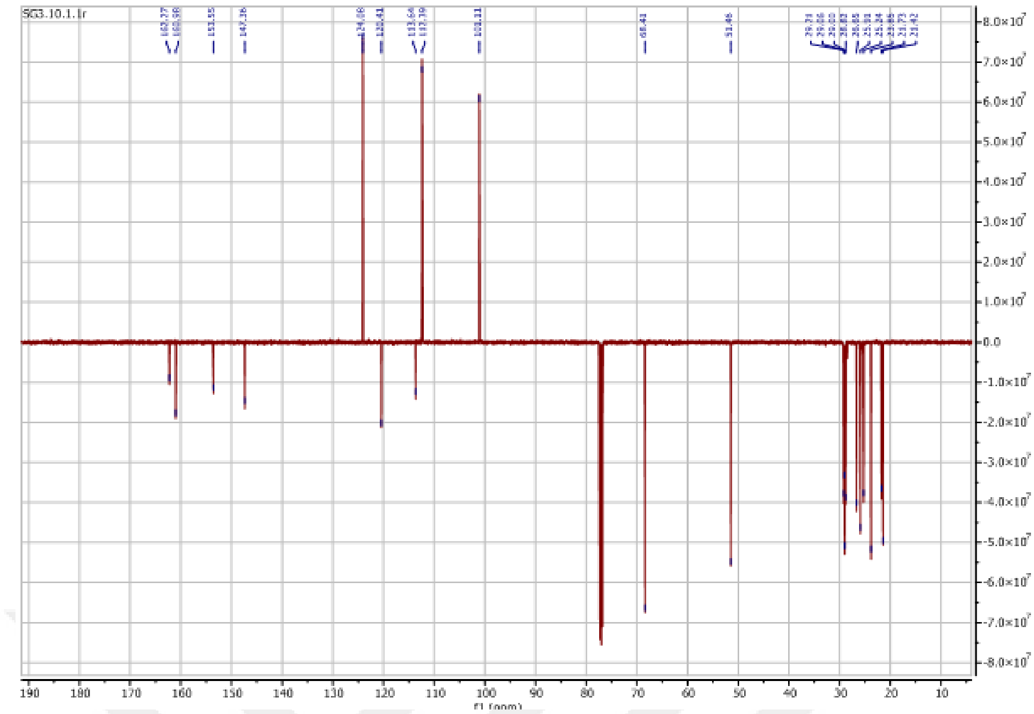


Figure 5.27 ^{13}C NMR Spectrum of Compound 9

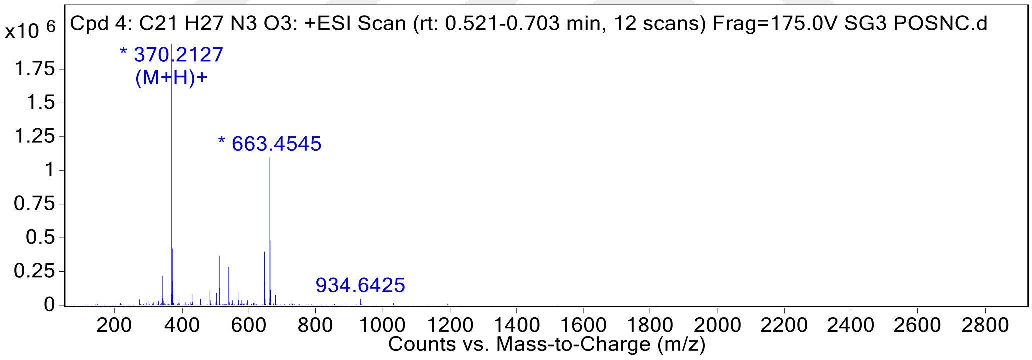
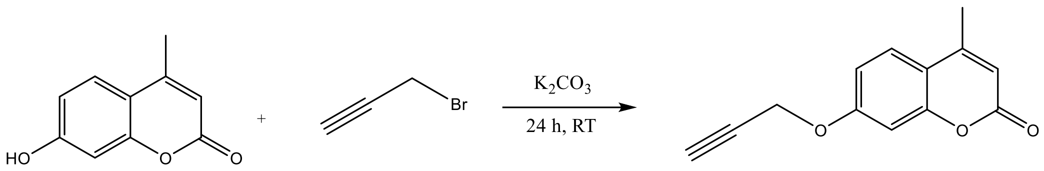


Figure 5.28 LC-MS Spectrum of Compound 9

5.12 Synthesis of 4-methyl-7-(prop-2-yn-1-yloxy)-2*H*-chromen-2-one (Compound 10, $C_{13}H_{10}O_3$)



(1) **(10)**

Compound 1 (2.8 mmol) was reacted with propargyl bromide (5.3 mmol) according to method given for Compound 4. The progress of the reaction was followed by thin layer chromatography (TLC) with the ethyl acetate:hexane (1:1) system. The pure product was obtained after synthesis process. Therefore, it was used without any purification.

White solid, %99 m.p. 142-144 ºC (Lit m.p. 136-138 ºC [81])

Spectral Data of Compound 10:

FTIR (ATR): ν = 3301 (acetylenic –CH strecthing), 3068 (aromatic CH streching), 2025, 2871 (aliphatic, CH stretching), 1712 (C=O strectching), 1605, 1509 (aromatic C=C stretchings), 1425, 1380 (aliphatic in-plane C-H bendings), 1138 (C-O stretching) cm^{-1}.

LC-MS (ESI-QTOF): *m/z* [M+H], Calculated=215.0702 for $C_{13}H_{10}O_3$,

Found= 215.0699

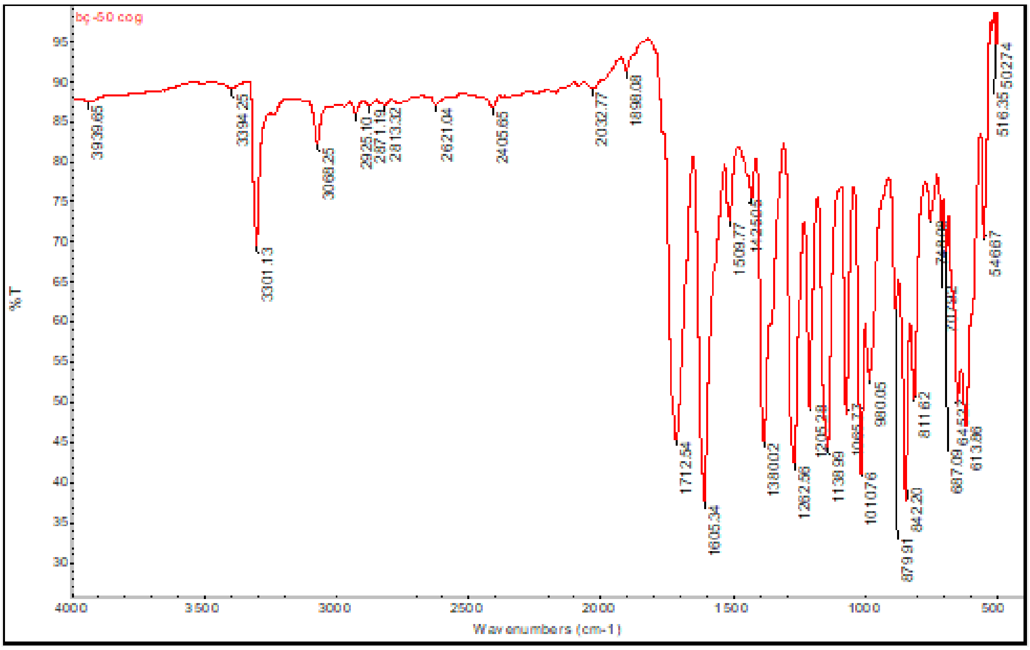


Figure 5.29 FTIR Spectrum of Compound 10

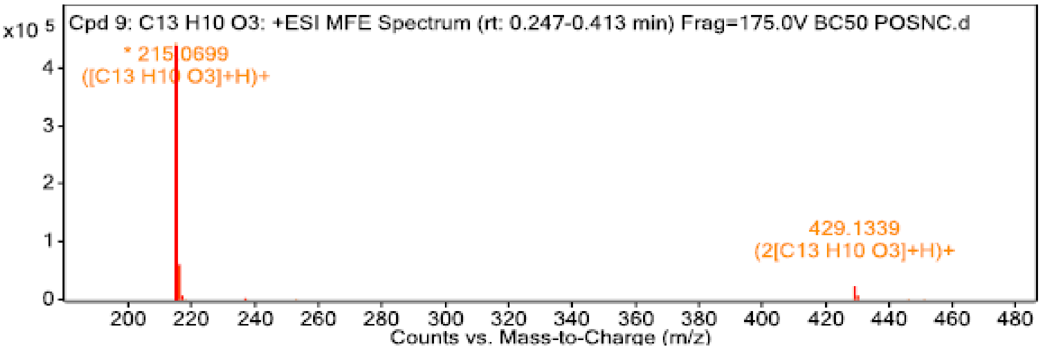
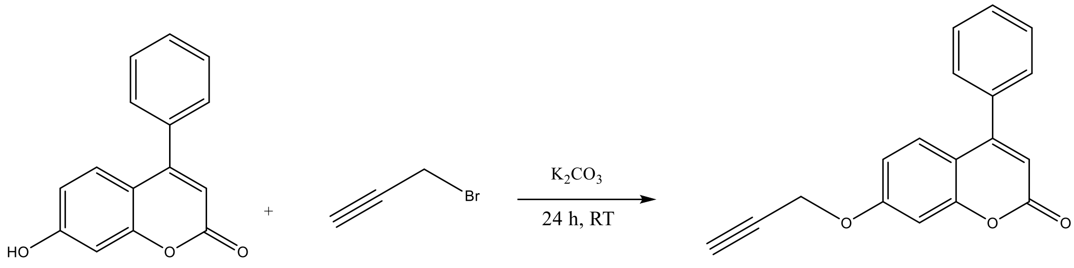


Figure 5.30 LC-MS Spectrum of Compound 10

5.13 Synthesis of 4-Phenyl-7-(prop-2-yn-1-yloxy)-2H-chromen-2-one (Compound 11, $C_{18}H_{12}O_3$)



(2) **(11)**

Compound 2 (1 mmol) was reacted with propargyl bromide (2 mmol) by synthetic procedure given for Compound 4. The crude product was purified using column chromatography (ethyl acetate:hexane 1:3).

Bright brown crystal, 75%, m.p. 106-107 ºC (Lit.m.p. 108-110ºC [81])

Spectral Data of Compound 11:

FTIR (ATR): ν =3294 (acetylenic –CH stretching), 3072 (aromatic –CH stretching), 2818 (aliphatic, CH stretching), 1712 (C=O stretching), 1605 (aromatic C=C stretchings), 1376 (aliphatic in-plane C-H bending), 1244 (C-O stretching) cm^{-1}.

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=277.0859 for $C_{18}H_{12}O_3$, Found=277.0851.

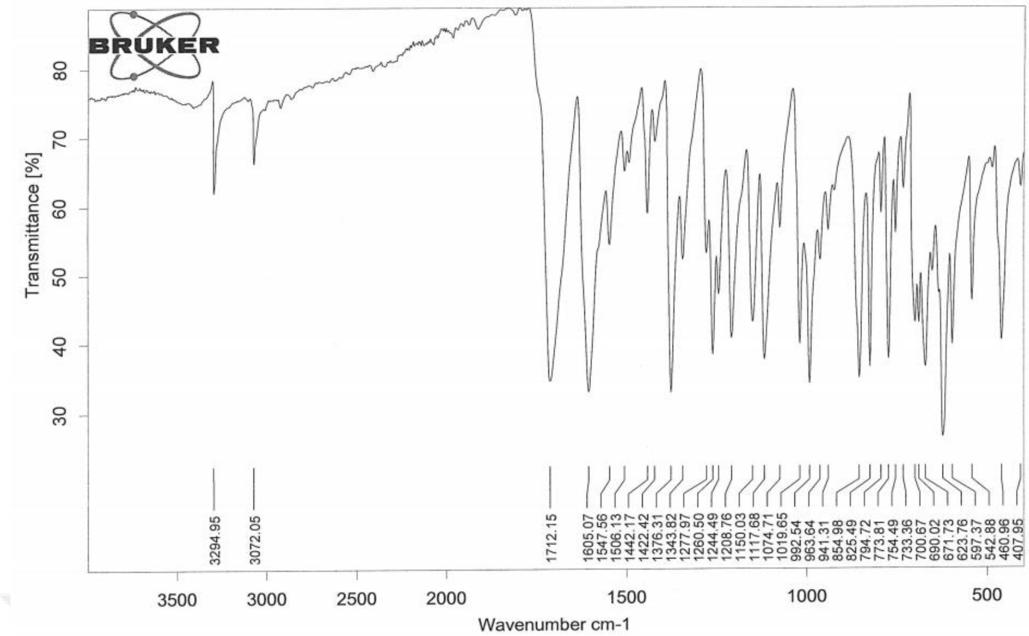


Figure 5.31 FTIR Spectrum of Compound 11

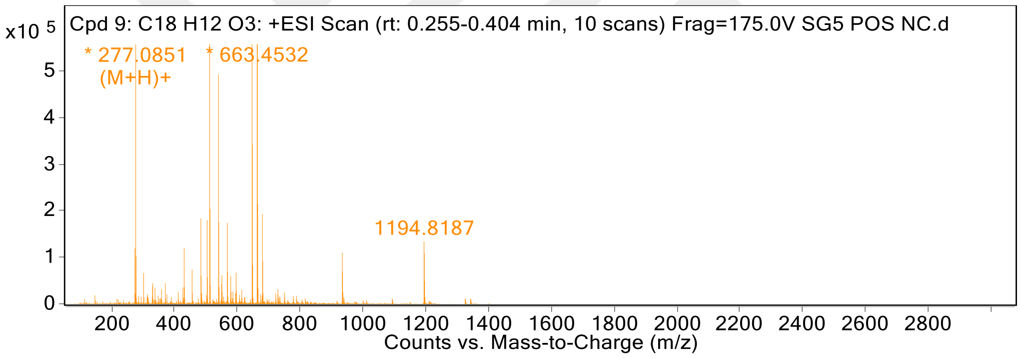
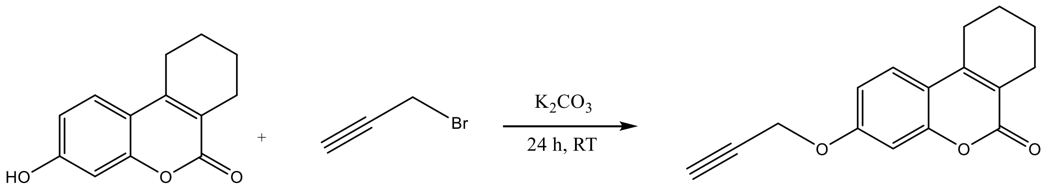


Figure 5.32 LC-MS Spectrum of Compound 11

5.14 Synthesis of 3-(Prop-2-yn-1-yloxy)-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (Compound 12, $C_{16}H_{14}O_3$)



(3) **(12)**

Compound 3 (1 mmol) was reacted with propargyl bromide (2 mmol) by using the method used for Compound 4. The crude product was purified using column chromatography (ethyl acetate:hexane 1:3).

Cream colored crystal, 78%, m.p. 116.5-117.0 ºC

Spectral Data of Compound 12 [82]:

FTIR (ATR): ν = 3191 (acetylenic -CH stretchinging), 3096 (aromatic, CH stretching), 2938, 2862 (aliphatic, CH stretchinging), 1701 (C=O stretching), 1607 (aromatic C=C stretching), 1379 (aliphatic in-plane C-H bending), 1257 (C-O stretching) cm^{-1}.

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=255.1015 for $C_{16}H_{14}O_3$, Found=255.1013.

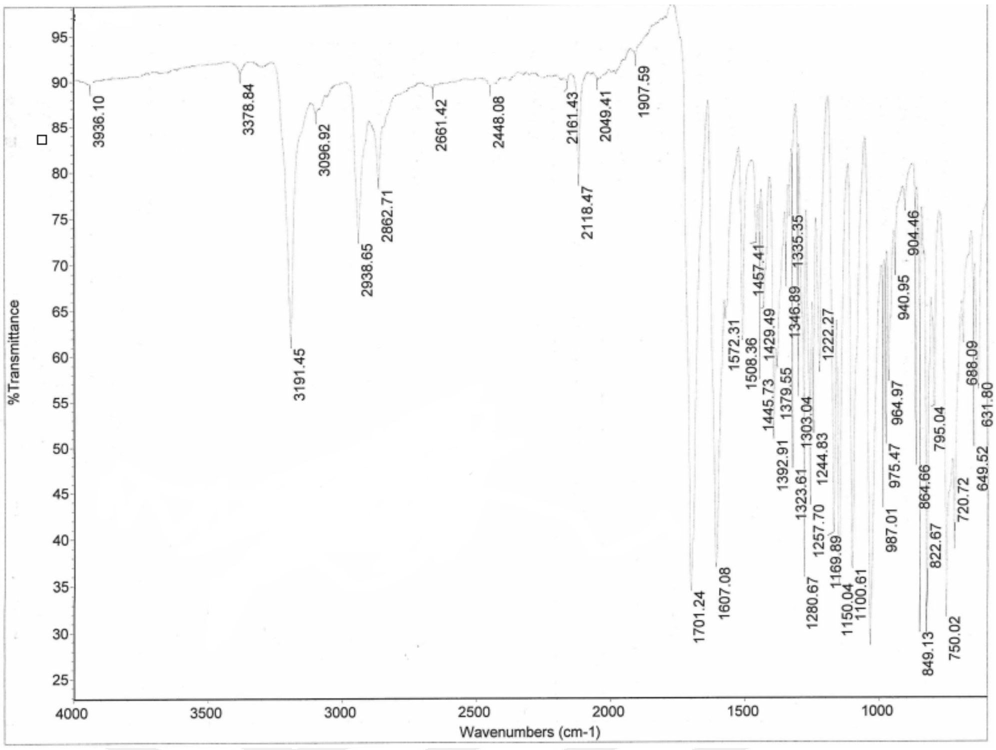


Figure 5.33 FTIR Spectrum of Compound 12

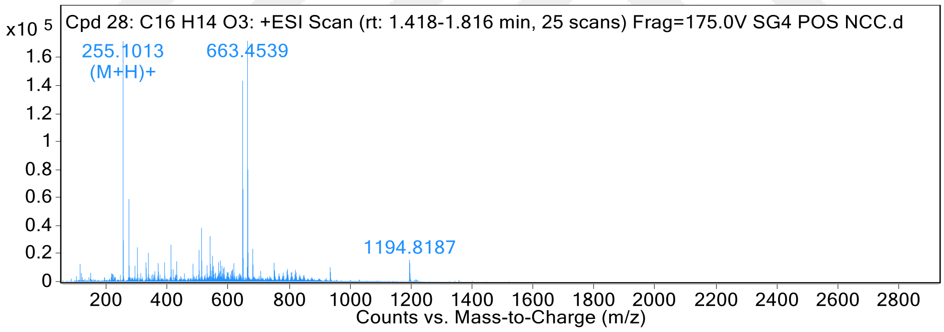
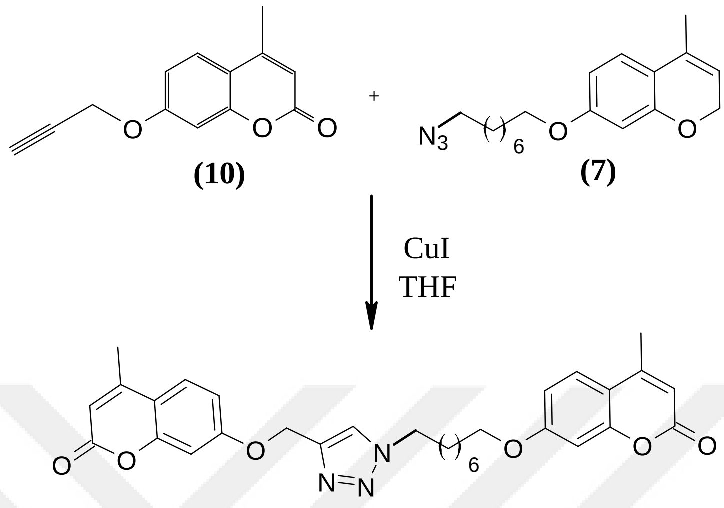


Figure 5.34 LC-MS Spectrum of Compound 12

5.15 Synthesis of 4-Methyl-7-((8-(4-(((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)octyl)oxy)-2*H*-chromen-2-one (Compound 13, $C_{31}H_{33}N_3O_6$)



(13)

Compound 10 (0.74 mmol) and Compound 7 (0.64 mmol) were taken in a reaction flask. Then, 5 ml THF and CuI (1.89 mmol) were added into this flask, the mixture was stirredat room temperature. The reaction was completed almost 48 hours. The progress of the reaction was followed by thin layer chromatography. Solvent was evaporated in a rotary evaporator. The crude product was purified using column chromatography (ethyl acetate:hexane 3:1).

White solid, 79%, m.p. 138.5-139.0 ºC.

Spectral Data of Compound 13:

FTIR (ATR): ν =3072 (aromatic, CH stretching), 2929, 2855 (aliphatic, CH stretching), 1706 (C=O stretching), 1609, 1552 (aromatic C=C stretching), 1466, 1443 ve 1381 (aliphatic in-plane C-H), 1277 (C-N bending), 1147 (C-O stretching) cm^{-1}.

^{1}H NMR: δ 1.34-1.40 (m, 6H, CH_2), 1.43-1.48 (m, 2H, CH_2), 1.77-1.82 (m, 2H, CH_2), 1.92-1.96 (m, 2H, CH_2), 2.39 (ap.t, 6H, CH_3), 4.00 (t, J= 6.0 Hz, 2H, NCH_2), 4.38 (t, J= 7.0 Hz, 2H, OCH_2), 5.26 (s, 2H, OCH_2), 6.12 (ap.d, 1H, =CH), 6.15 (ap.d, 1H, =CH), 6.78 (d, J= 2.5 Hz, 1H, ArH), 6.84 (dd, J= 2.5 Hz, 8.5 Hz, 1H, ArH), 6.92 (d, J= 2.5 Hz, 1H, ArH), 6.95 (dd, J= 2.5 Hz, 9.0 Hz 1H, ArH), 7.48 (d, J= 8.5 Hz, 1H, ArH), 7.51 (d, J= 8.5 Hz, 1H, ArH), 7.65 (s, 1H, ArH) ppm.

^{13}C NMR: δ 18.68 (2xCH_2), 25.82 (CH_2), 26.38 (CH_2), 28.85 (CH_2), 28.89 (CH_2), 29.05 (CH_2), 30.23 (CH_2), 50.49 (NCH_2), 62.36 (OCH_2), 68.46 (OCH_2), 101.32 (C_{aro}H), 102.13 (CaroH), 111.84 (C_{aro}H), 112.29 (C_{aro}H), 112.49 (C_{aro}H), 112.66 (C_{aro}H), 113.45 (C_{aro}), 114.06 (C_{aro}), 122.74 (C_{aro}H), 125.50 (C_{aro}H), 125.72 (C_{aro}H), 142.98 (C_{aro}), 152.47 (C_{aro}), 152.62 (C_{aro}), 155.13 (C_{aro}), 155.29 (C_{aro}), 161.16 (C_{aro}), 161.17 (C_{aro}), 161.38 (C=O), 162.16 (C=O) ppm.

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=544.2436 for $C_{31}H_{33}N_3O_6$, Found=544.2438

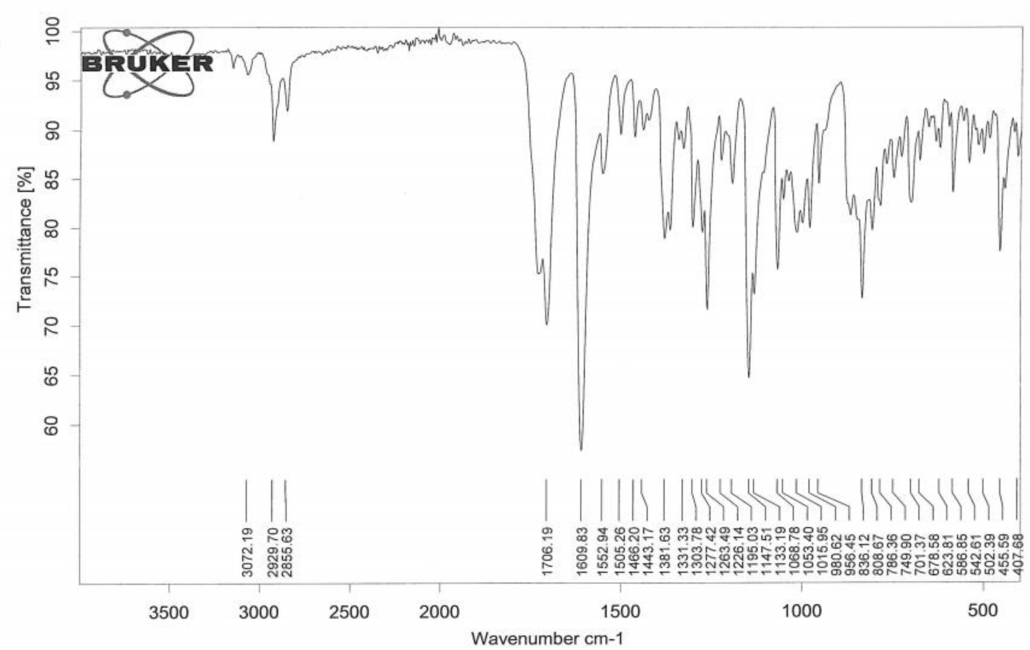


Figure 5.35 FTIR Spectrum of Compound 13

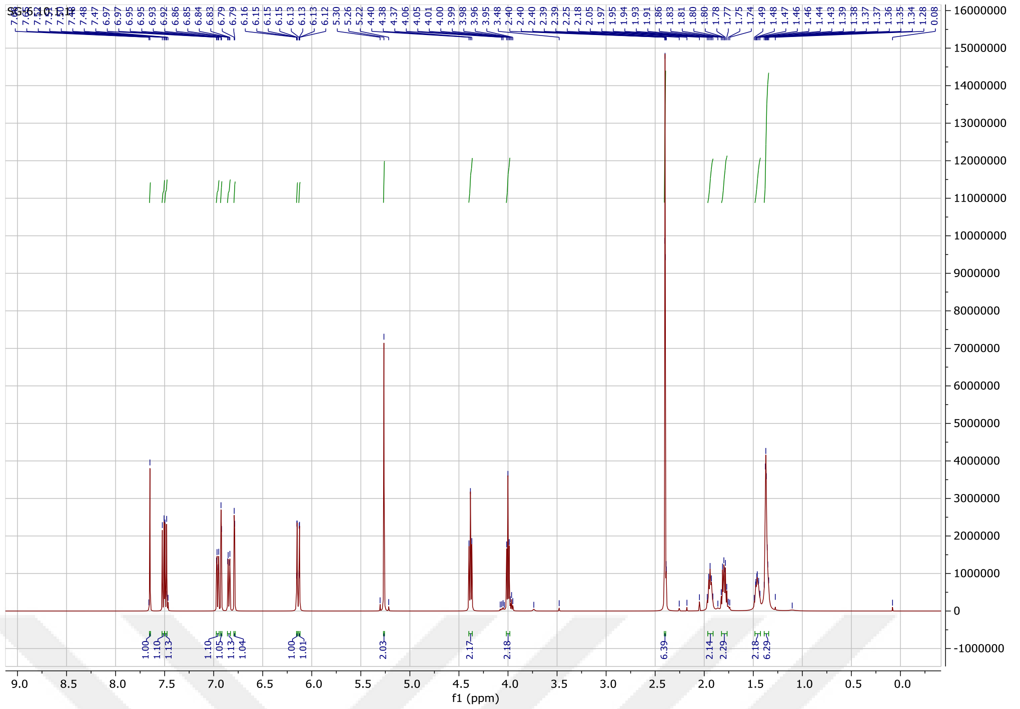


Figure 5.36 ^{1}H NMR Spectrum of Compound 13

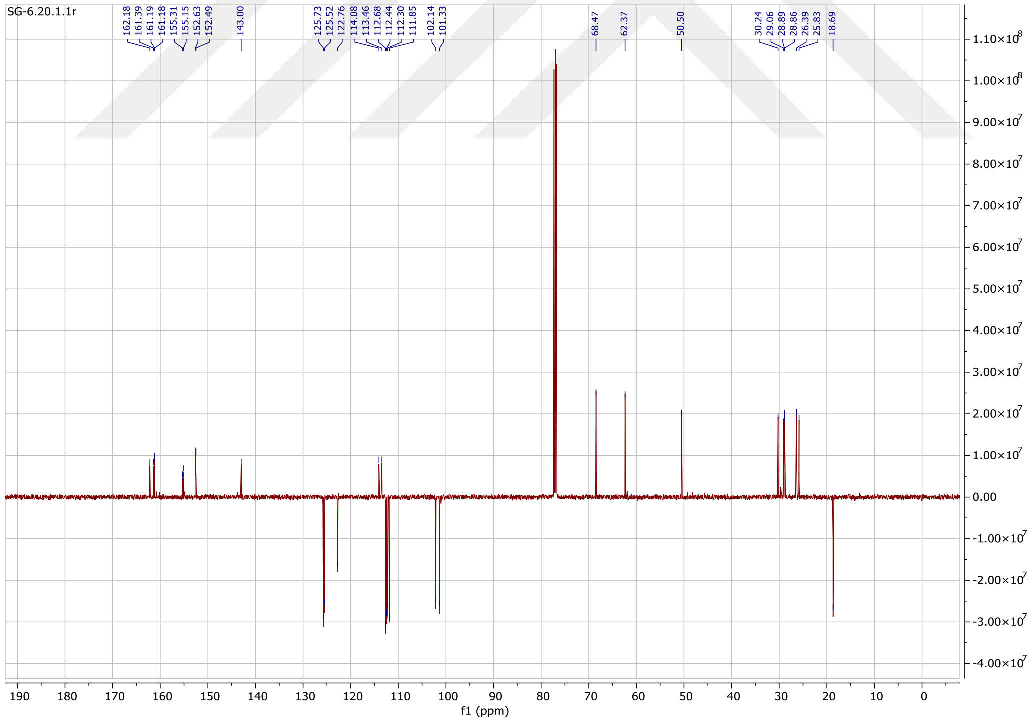


Figure 5.37 ^{13}C NMR Spectrum of Compound 13

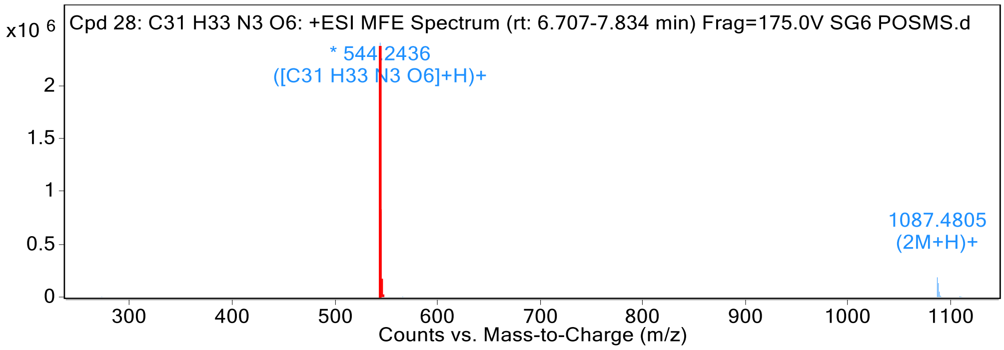
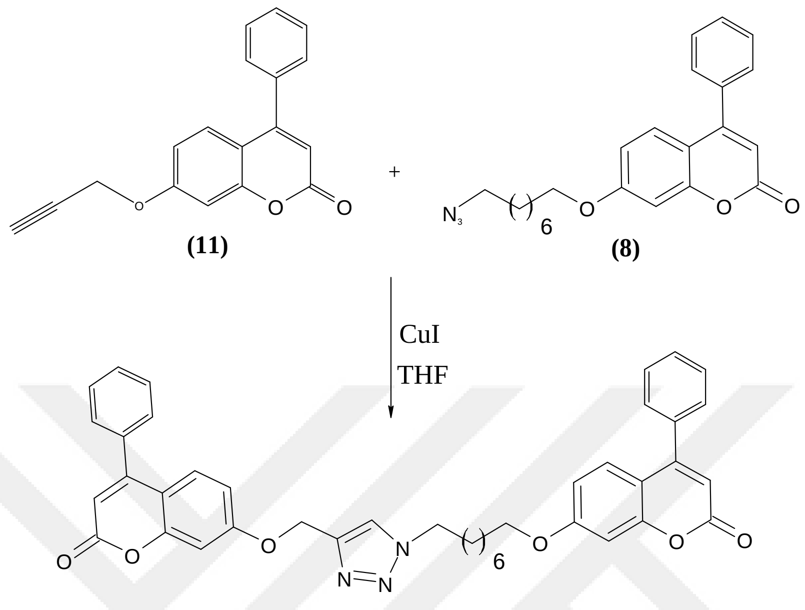


Figure 5.38 LC-MS Spectrum of Compound 13

5.16. Synthesis of 7-((8-(4-(((2-Oxo-4-phenyl-2*H*-chromen-5-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)octyl)oxy)-4-phenyl-2*H*-chromen-2-one (Compound 14, $C_{41}H_{37}N_3O_6$)



(14)

Compound 11 (0.62 mmol) and Compound 8 (0.54 mmol) were reacted with CuI (1.59 mmol) according to method given for Compound 13. The crude product was purified using column chromatography (ethyl acetate:hexane 3:1).

Cream colored crystal, m.p. 92.5-93.0 ºC, 88%.

Spectral Data of Compound 14:

FTIR (ATR): ν = 3062 (aromatic, CH stretching), 2927, 2861 (aliphatic, CH stretching), 1708(C=O stretching), 1608, 1546 (aromatic C=C stretching), 1467, 1444 and 1376 (aliphatic in-plane C-H), 1266 (C-N bending), 1154 (C-O stretching) cm^{-1}.

^{1}H NMR: δ 1.35-1.38 (m, 6H, CH_2), 1.44-1.49 (m, 2H, CH_2), 1.77-1.83 (m, 2H, CH_2), 1.92-1.97 (m, 2H, CH_2), 4.015 (t, J= 6.5 Hz, 2H, NCH_2), 4.38 (t, J= 7.5 Hz, 2H, OCH_2), 5.27 (s, 2H, OCH_2), 6.20 (s, 1H, =CH), 6.23 (s, 1H, =CH), 6.77 (dd, J= 2.5 Hz, 8.7 Hz, 1H, ArH), 6.86 (d, J= 2.5 Hz, 1H, ArH), 6.89 (dd, J= 2.5 Hz, 9.0 Hz, 1H, ArH), 7.00 (d, J= 2.5 Hz, 1H, ArH), 7.37 (d, J= 9.0 Hz, 1H, ArH), 7.40 (d, J= 9.0 Hz, 1H, ArH), 7.42-7.44 (m, 4H, ArH), 7.50-7.52 (m, 6H, ArH), 7.65 (s, 1H, ArH) ppm.

^{13}C NMR: δ 25.84 (CH_2), 26.40 (CH_2), 28.87 (2xCH_2), 29.06 (CH_2), 30.24 (CH_2), 50.49 (NCH_2), 62.39 (OCH_2), 68.51 (OCH_2), 101.55 ($C_{aro}H$), 102.34 ($C_{aro}H$), 111.74 ($C_{aro}H$), 112.19 ($C_{aro}H$), 112.37 (C_{aro}), 112.48 ($C_{aro}H$), 112.71 ($C_{aro}H$), 113.04 (C_{aro}), 122.76 ($C_{aro}H$), 127.96 ($C_{aro}H$), 128.18 ($C_{aro}H$), 128.38 (2x$C_{aro}H$), 128.83 ($C_{aro}H$), 128.86 ($C_{aro}H$), 129.59 ($C_{aro}H$), 129.66 ($C_{aro}H$), 135.46(C_{aro}), 135.61 (C_{aro}), 142.92 (C_{aro}), 155.74 (C_{aro}), 155.84 (C_{aro}), 155.87 (C_{aro}), 156.02 (C_{aro}), 161.12 (C_{aro}), 161.31 (2xC_{aro}), 162.31 (C=O) ppm.

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=668.2757 for $C_{41}H_{37}N_3O_6$, Found=668.2755

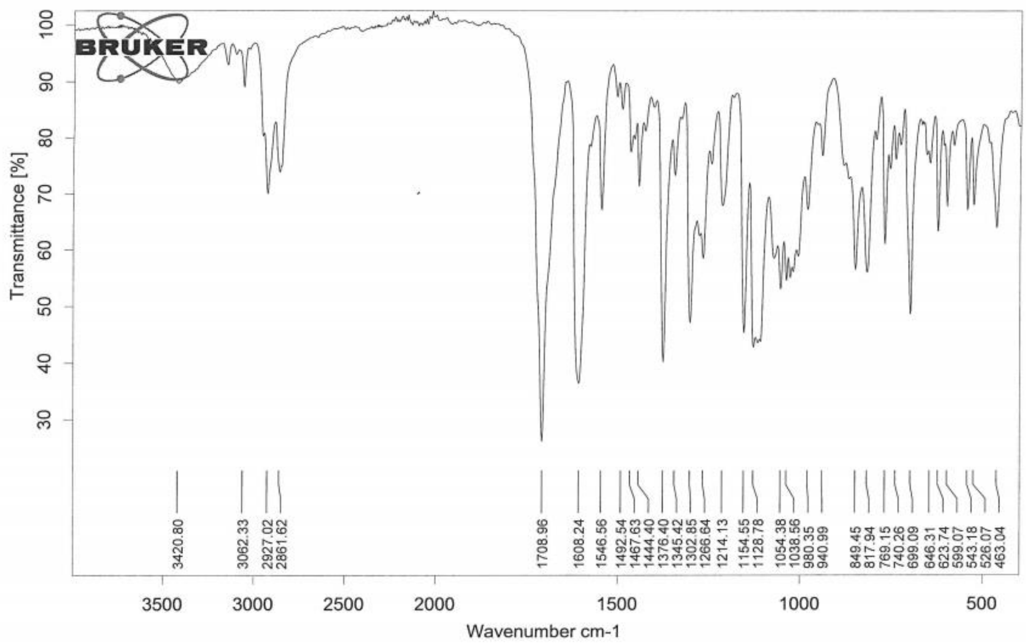


Figure 5.39 FTIR Spectrum of Compound 14

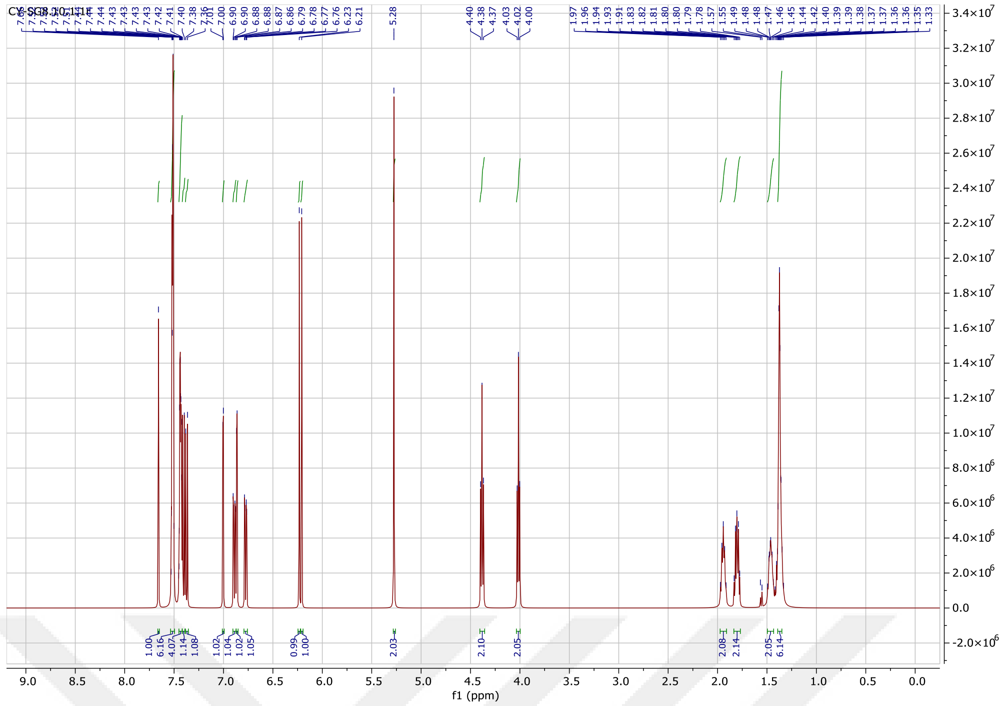


Figure 5.40 ^{1}H NMR Spectrum of Compound 14

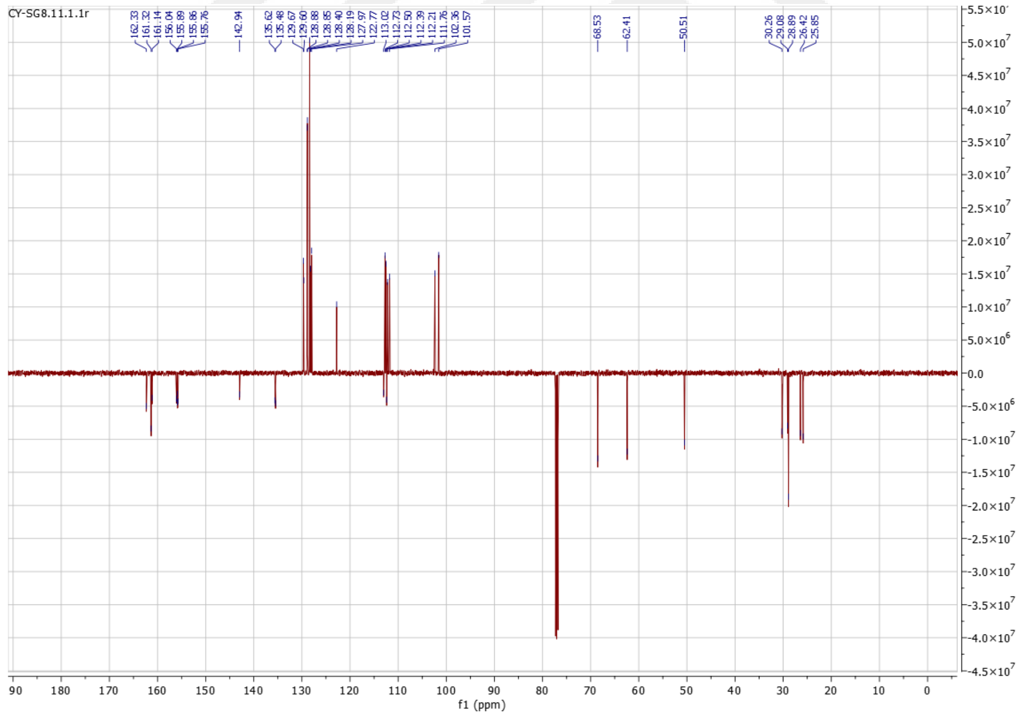


Figure 5.41 ^{13}C NMR Spectrum of Compound 14

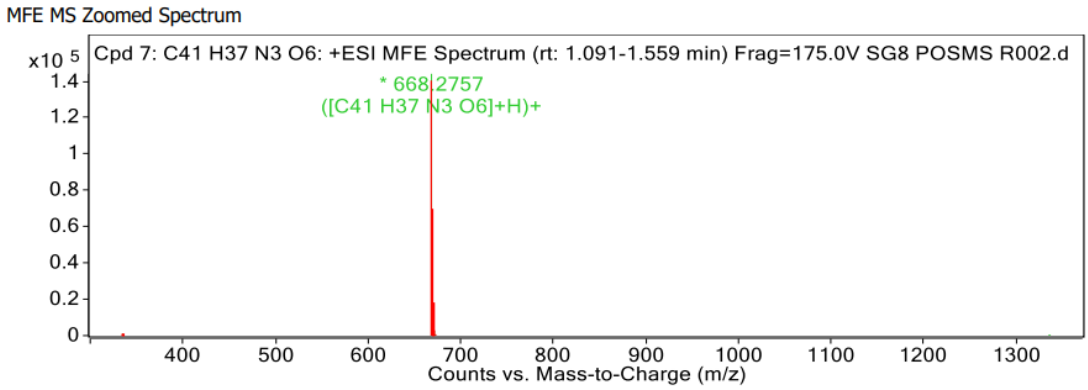
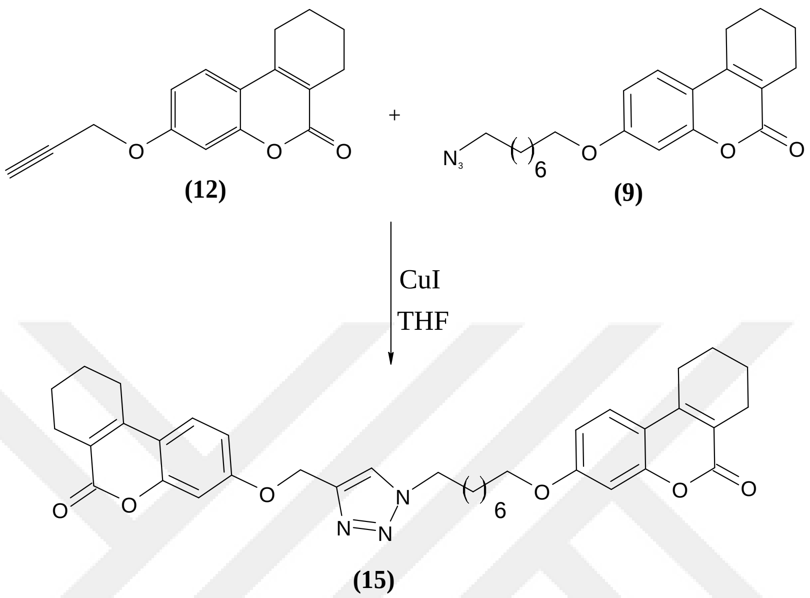


Figure 5.42 LC-MS Spectrum of Compound 14

5.17 Synthesis of 3-((8-(4-(((6-Oxo-7,8,9,10-tetrahydro-6H benzo[c]chromen-3-yl)oxy)methyl)-1H-1,2,3-triazol-1yl)octyl)oxy)-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one (Compound 15, $C_{37}H_{41}N_3O_6$)



Compound 12 (0.66 mmol) and Compound 9 (0.57 mmol) were interacted with CuI (1.69 mmol) according to method given for Compound 13. The crude product was purified using column chromatography (ethyl acetate:hexane 3:1).

White solid, 71%, m.p. 114.5-115.0 ºC.

Spectral Data of Compound 15:

FTIR (ATR): ν = 3076 (aromatic CH stretching), 2925, 2856 (aliphatic, CH stretching), 1708 (C=O stretching), 1608, 1561 (aromatic C=C stretching), 1466, 1428 and 1378 (aliphatic in-plane C-H), 1261 (C-N bending), 1148 (C-O stretching) cm^{-1}.

^{1}H NMR: δ 1.34-1.36 (m, 6H, CH_2), 1.42-1.48 (m, 2H, CH_2), 1.77-1.81 (m, 6H, CH_2), 1.83-1.87 (m, 4H, CH_2), 1.92-1.96 (m, 2H, CH_2), 2.54-2.57 (m, 4H, CH_2), 2.73-2.76 (m, 4H, CH_2), 3.98 (t, J= 6.5 Hz, 2H, NCH_2), 4.37 (t, J= 7.0 Hz, 2H, OCH_2), 5.27 (s, 2H, OCH_2), 6.77 (d, J= 2.5 Hz, 1H, ArH), 6.82 (dd, J= 2.5 Hz, 9.0 Hz, 1H, ArH), 6.90 (d, J= 2.5 Hz, 1H, ArH), 6.92 (dd, J= 2.5 Hz, 8.7 Hz, 1H, ArH), 7.44 (d, J= 9.0 Hz, 1H, ArH), 7.47 (d, J= 8.5 Hz, 1H, ArH), 7.64 (s, 1H, ArH) ppm.

^{13}C NMR: δ 21.38 (CH_2), 21.40 (CH_2), 21.68 (CH_2), 21.71 (CH_2), 23.84 (CH_2), 23.86 (CH_2), 25.23 (2xCH_2), 25.84 (CH_2), 26.38 (CH_2), 28.85 (CH_2), 28.93 (CH_2), 29.06 (CH_2), 30.23 (CH_2), 50.48 (NCH_2), 62.32 (OCH_2), 68.34 (OCH_2), 101.09 ($C_{aro}H$), 101.88 ($C_{aro}H$), 112.13 ($C_{aro}H$), 112.35 ($C_{aro}H$), 113.64 (C_{aro}), 114.27 (C_{aro}), 120.41 (C_{aro}), 120.92 (C_{aro}), 122.69 ($C_{aro}H$), 124.09 ($C_{aro}H$), 124.29 ($C_{aro}H$), 143.18 (C_{aro}), 147.20 (C_{aro}), 147.35 (C_{aro}), 153.38 (C_{aro}), 153.52 (C_{aro}), 159.95 (C_{aro}), 160.92 (C_{aro}), 162.07 (C=O), 162.24 (C=O) ppm.

LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, Calculated=624.3068 for $C_{37}H_{41}N_3O_6$, Found=624.3072

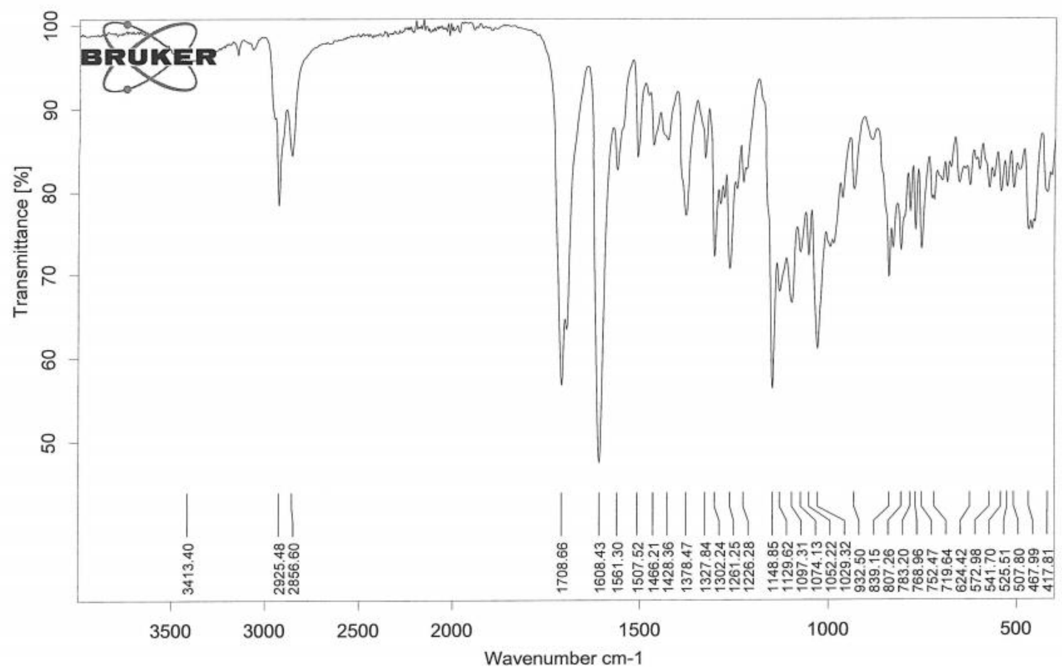


Figure 5.43 FTIR Spectrum of Compound 15

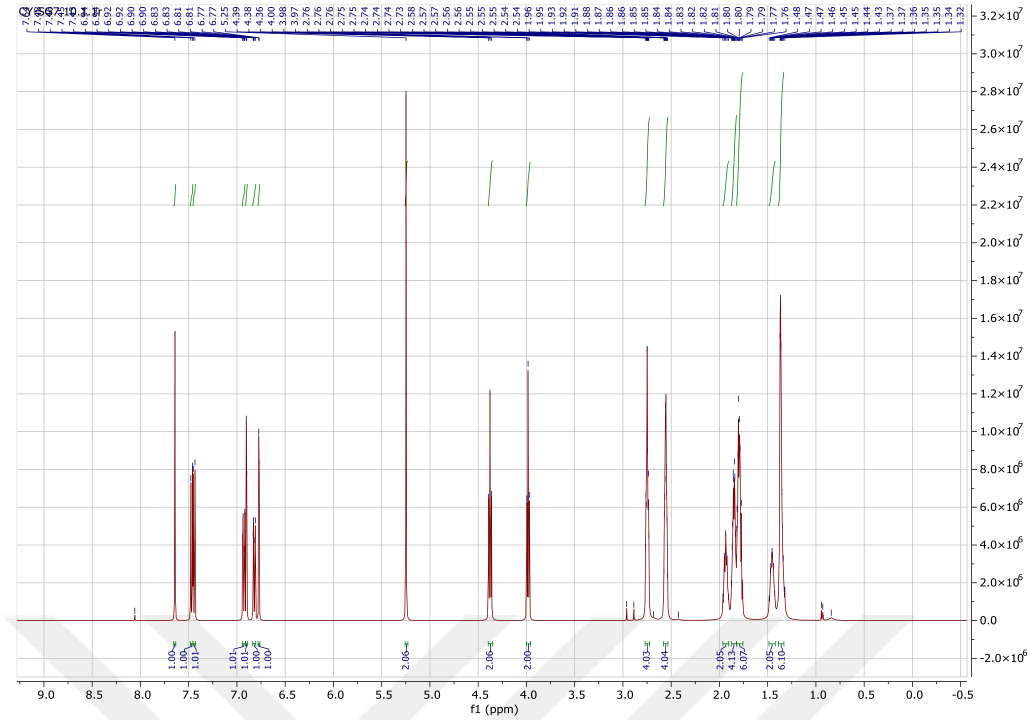


Figure 5.44 ^{1}H NMR Spectrum of Compound 15

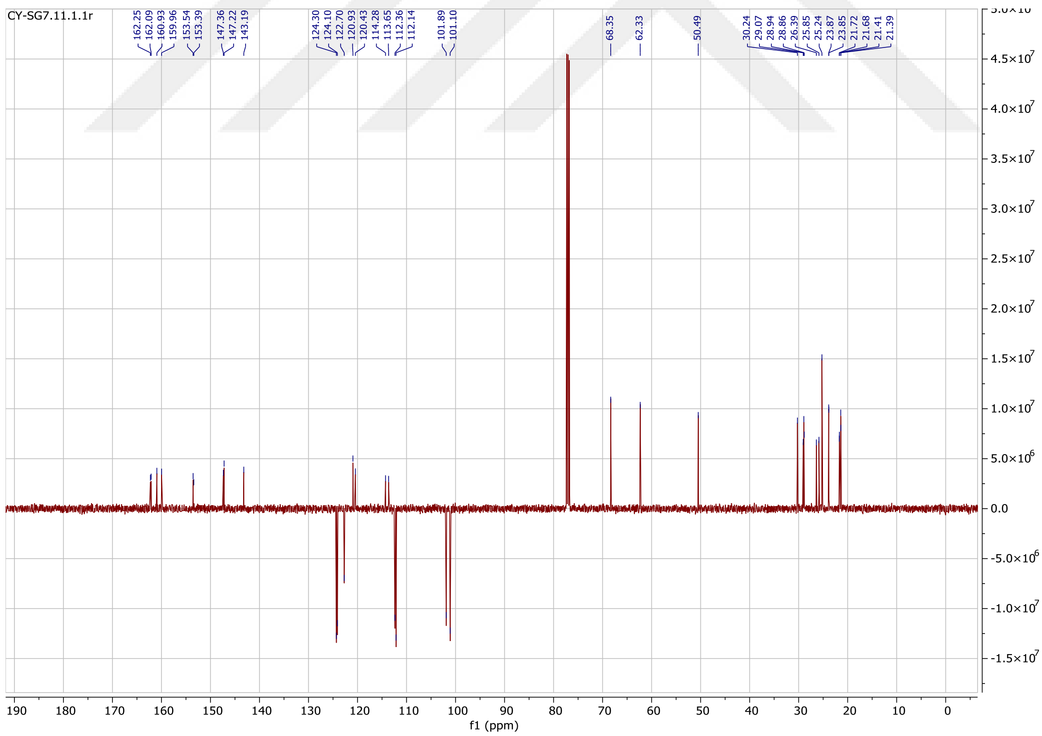


Figure 5.45 ^{13}C NMR Spectrum of Compound 15

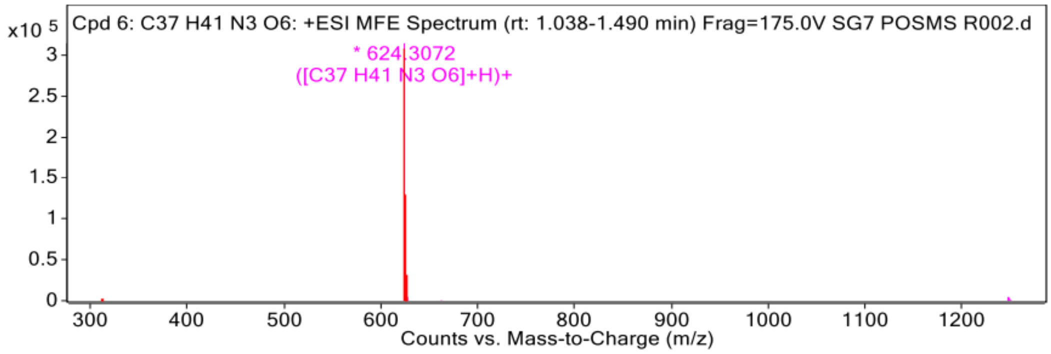
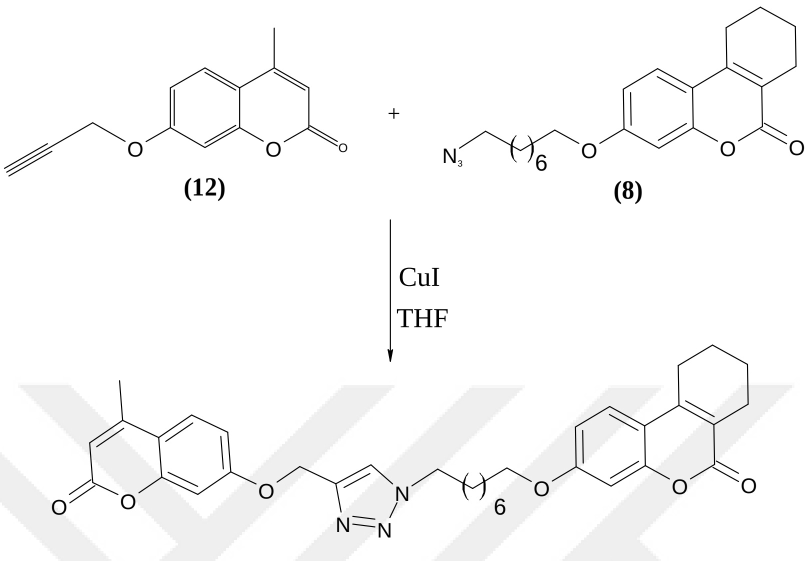


Figure 5.46 LC-MS Spectrum of Compound 15

5.18. Synthesis of 3-((8-(4-(((4-Methyl-2-oxo-2H-chromen-5 yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)octyl)oxy)-7,8,9,10tetrahydro-6H-benzo[c]chromen-6-one (Compound 16, $C_{34}H_{37}N_3O_6$)



Compound 12 (0.57 mmol) and Compound 8 (0.66 mmol) were interacted with CuI (1.69 mmol) by following the method given for Compound 13. The crude product was purified using column chromatography (ethyl acetate:hexane 3:1).

White crystal, 74%, m.p. 145.5-146.0 ºC.

Spectral Data of Compound 16:

FTIR (ATR): ν = 3071 (aromatic, CH stretching), 2921, 2853 (aliphatic, CH stretching), 1696 (C=O stretching), 1606, 1509 (aromatic C=C stretching), 1457, 1428 (aliphatic in-plane C-H), 1261 (C-N bending), 1262 (C-O stretching) cm^{-1}.

^{1}H NMR: δ 1.370 (brs, 6H CH_2), 1.44-1.48 (m, 2H, CH_2), 1.77-1.81 (m, 4H, CH_2), 1.84-1.87 (m, 2H, CH_2), 1.92-1.96 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.54-2.56 (apt, 2H, CH_2), 2.73-2.75 (apt, 2H, NCH_2), 3.98 (t, J= 6.5 Hz, 2H, NCH_2), 4.38 (t, J= 7.0 Hz, 2H, OCH_2), 5.26 (s, 2H, OCH_2), 6.14 (s, 1H, =CH), 6.76 (d, J= 2.5 Hz, 1H, ArH), 6.82 (dd, J= 8.5 Hz, 1H, ArH), 6.92 (d, J= 2.5 Hz, 1H, ArH), 6.95 (dd, J= 2.5 Hz, 8.5 Hz, 1H, ArH), 7.44 (d, J= 8.5 Hz, 1H, ArH), 7.51 (d, J= 8.5 Hz, 1H, ArH), 7.65 (s, 1H, ArH) ppm.

^{13}C NMR: δ 18.68 (CH_3), 21.40 (CH_2), 21.71 (CH_2), 23.84 (CH_2), 25.24 (CH_2), 25.85 (CH_2), 26.38 (CH_2), 28.86 (CH_2), 28.93 (CH_2), 29.06 (CH_2), 30.24 (CH_2), 50.50 (NCH_2), 62.36 (OCH_2), 68.33 (OCH_2), 101.09 ($C_{aro}H$), 102.11 ($C_{aro}H$), 112.28 ($C_{aro}H$), 112.34 ($C_{aro}H$), 112.44 ($C_{aro}H$), 113.64 (C_{aro}), 114.05 (Caro), 120.41(C_{aro}), 122.77 ($C_{aro}H$), 124.10 ($C_{aro}H$), 125.72 ($C_{aro}H$), 142.97 (C_{aro}), 147.36 (C_{aro}), 152.48 (C_{aro}), 153.51 (C_{aro}), 155.12 (C_{aro}), 160.91 (C_{aro}), 161.16 (Caro), 161.17 (C=O), 161.24 (C=O) ppm.

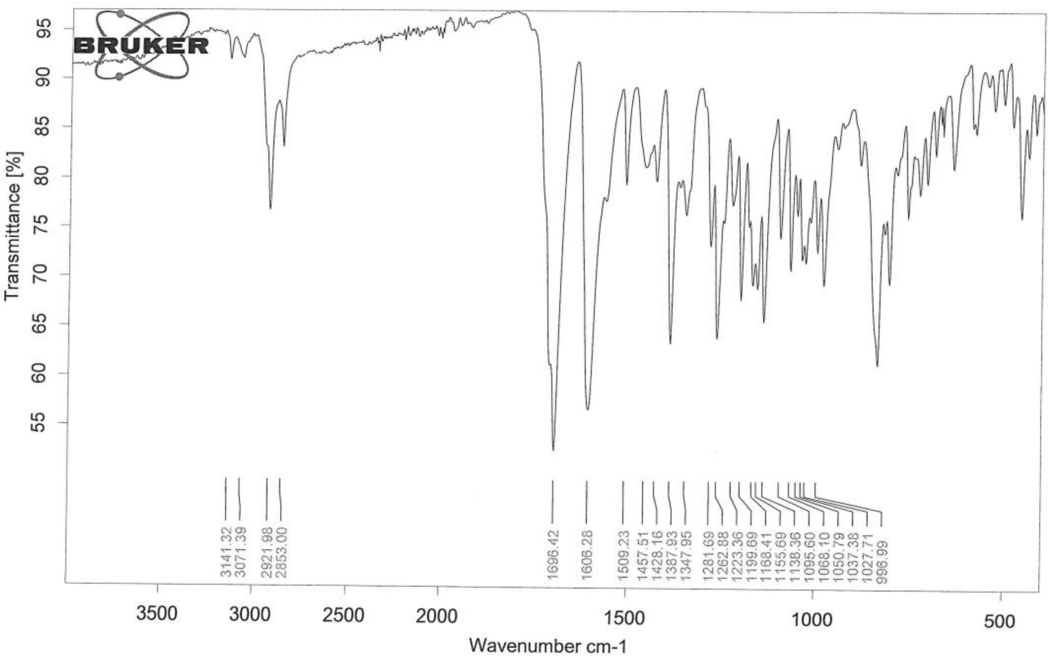


Figure 5.47 FTIR Spectrum of Compound 16

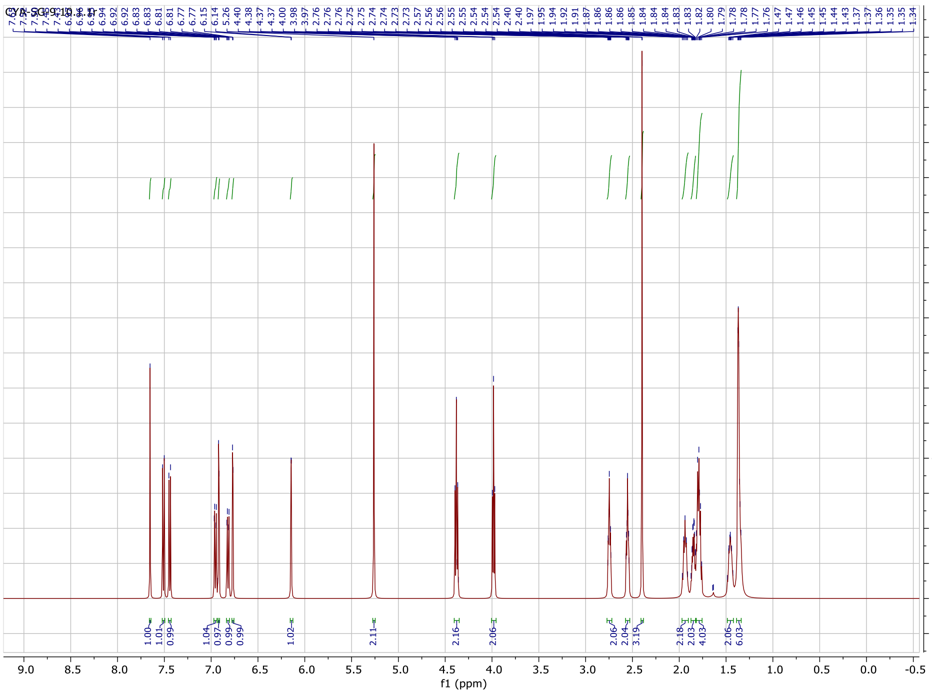


Figure 5.48 ^{1}H NMR Spectrum of Compound 16

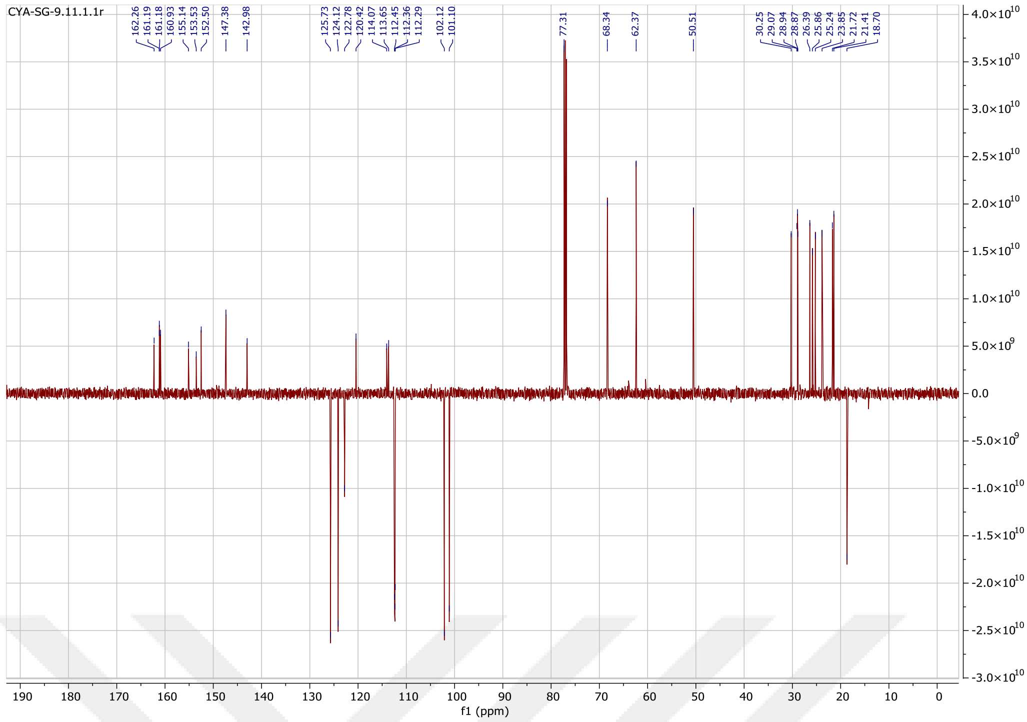
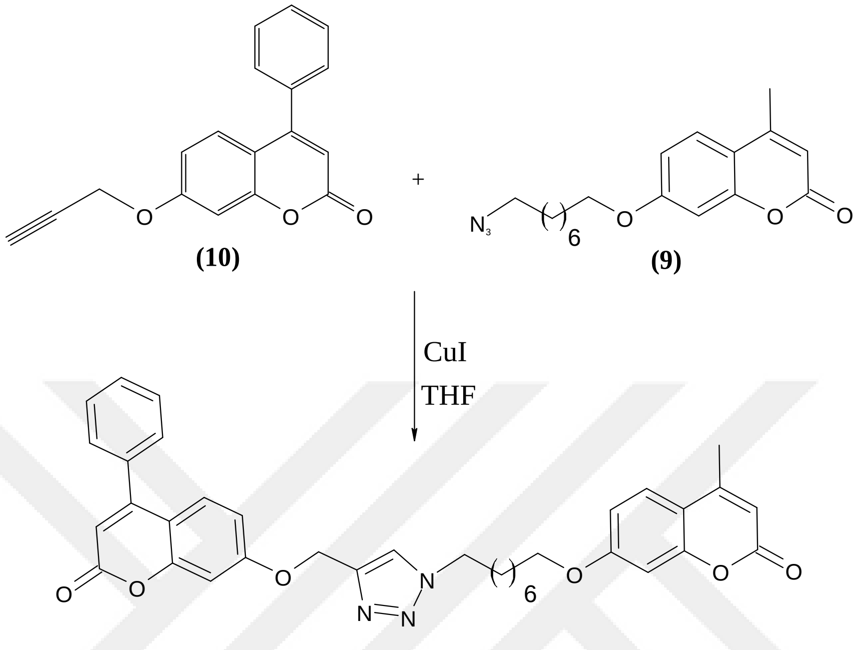


Figure 5.49 ^{13}C NMR Spectrum of Compound 16

5.19 Synthesis of 4-Methyl-7-((8-(4-(((2-oxo-4-phenyl-2H-chromen-5-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)octyl)oxy)-2H-chromen-2one (Compound 17, $C_{36}H_{35}N_3O_6$)



Compound 10 (0.62 mmol) and Compound 9 (0.54 mmol) were reacted with CuI (1.59mmol) by utilizing the method used in Compound 13. The crude product was purified using column chromatography (ethyl acetate:hexane 3:1).

White crystal, 56 %, m.p. 107.5-108.0 ºC.

Spectral Data of Compound 17:

FTIR (ATR): ν = 3078 (aromatic, CH stretching), 2929, 2855 (aliphatic, CH stretching), 1711 and 1697 (C=O stretchings), 1605 and 1552 (aromatic C=C stretching), 1465, 1442 (aliphatic in-plane C-H), 1261 (C-N bending), 1142 (C-O stretching) cm^{-1}.

^{1}H NMR: δ 1.37 (brs, 6H CH_2), 1.44-1.47 (m, 2H, CH_2), 1.77-1.82 (m, 2H, CH_2), 1.91-1.97 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 4.00 (t, J= 6.5 Hz, 2H, NCH_2), 4.38 (t,J=7.5 Hz, 2H, OCH_2), 5.27 (s, 2H, OCH_2), 6.12 (s, 1H, =CH), 6.23 (s, 1H, =CH), 6.78 (d, J= 2.5 Hz, 1H, ArH), 6.84 (dd, J= 2.5 Hz, 8.5 Hz, 1H, ArH), 6.89 (dd, J= 2.5 Hz, 9.0 Hz,1H, ArH), 7.00 (d, J= 2.5 Hz, 1H, ArH), 7.40 (d, J= 9.0 Hz, 1H, ArH), 7.42-7.44 (m, 2H, ArH), 7.48 (d,J=8.5Hz,1H, ArH), 7.51-7.52 (m, 3H, ArH), 7.65 (s,1H,ArH) ppm.

^{13}C NMR: δ 18.70 (CH_3), 25.84 (CH_2), 26.40 (CH_2), 28.88 (CH_2), 28.89 (CH_2), 29.07 (CH_2), 30.25 (CH_2), 50.51 (NCH_2), 62.40 (OCH_2), 68.46 (OCH_2), 101.32 ($C_{aro}H$), 102.34 ($C_{aro}H$), 111.85 ($C_{aro}H$), 112.19 ($C_{aro}H$), 112.49 (C_{aro}), 112.67 ($C_{aro}H$), 113.00 (C_{aro}), 113.45 (C_{aro}), 122.76 ($C_{aro}H$), 125.51 ($C_{aro}H$), 128.18 ($C_{aro}H$), 128.38 ($C_{aro}H$), 128.86 ($C_{aro}H$), 129.66 ($C_{aro}H$), 135.46 (C_{aro}), 142.92 (C_{aro}), 152.62 (C_{aro}), 155.75 (C_{aro}), 155.84 (C_{aro}), 161.14 (C_{aro}), 161.31 (C_{aro}), 161.39 (C=O), 162.16 (C=O) ppm.

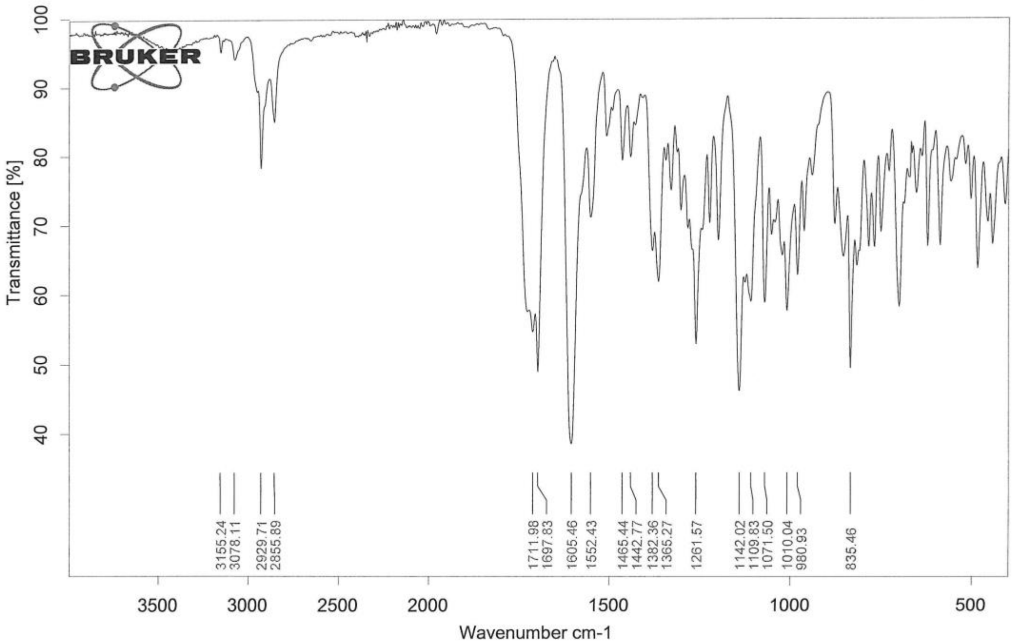


Figure 5.50 FTIR Spectrum of Compound 17

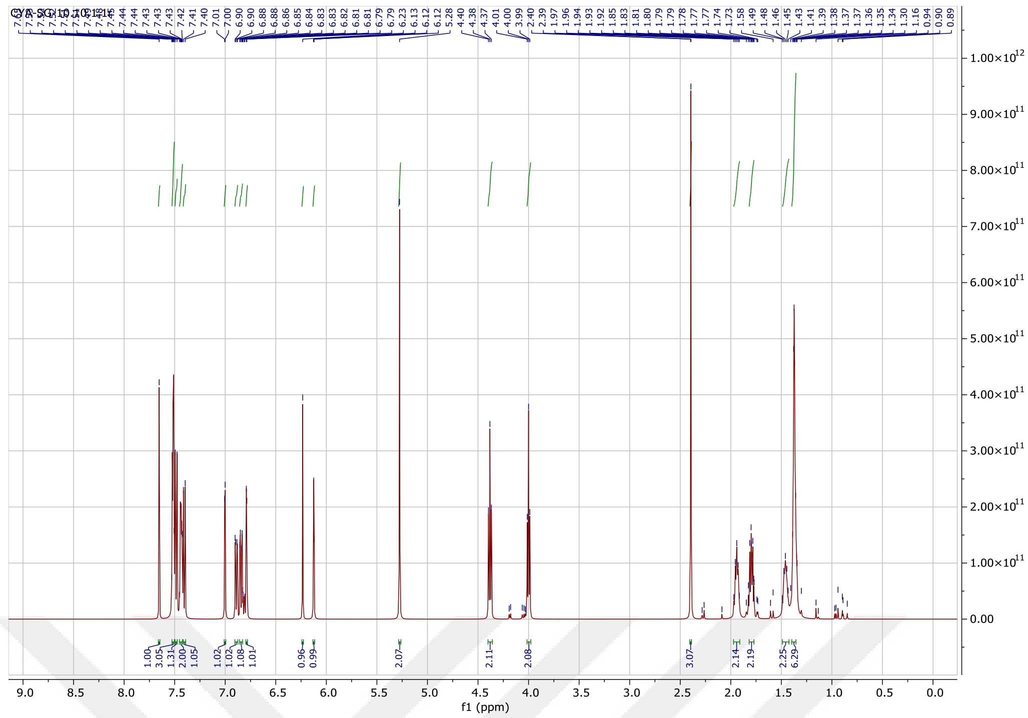


Figure 5.51 ^{1}H NMR Spectrum of Compound 17

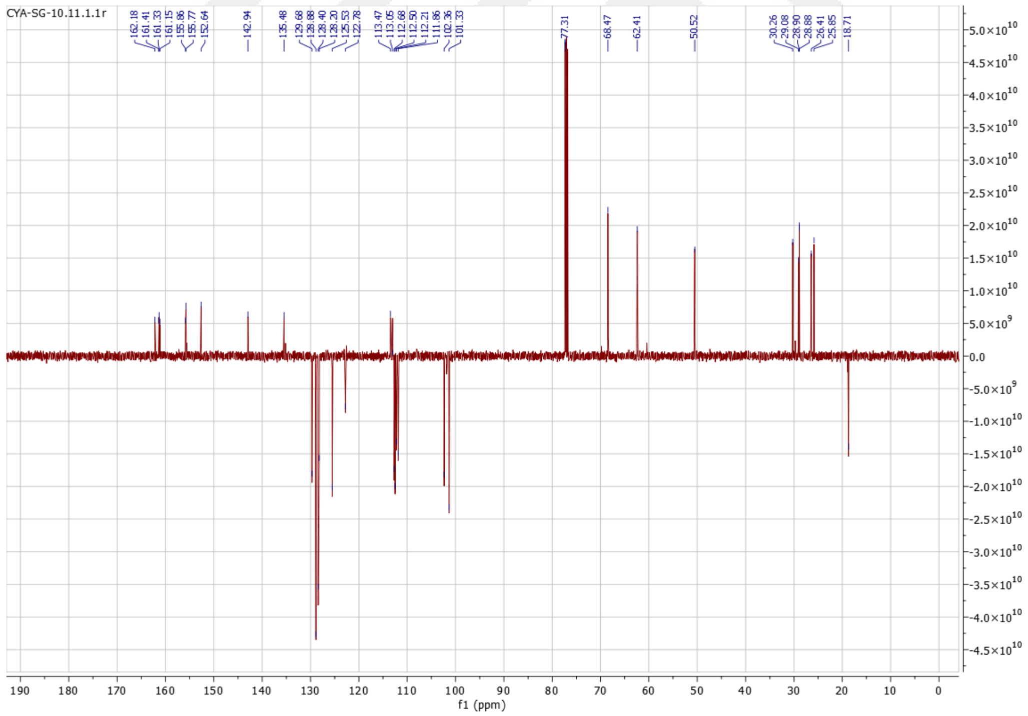
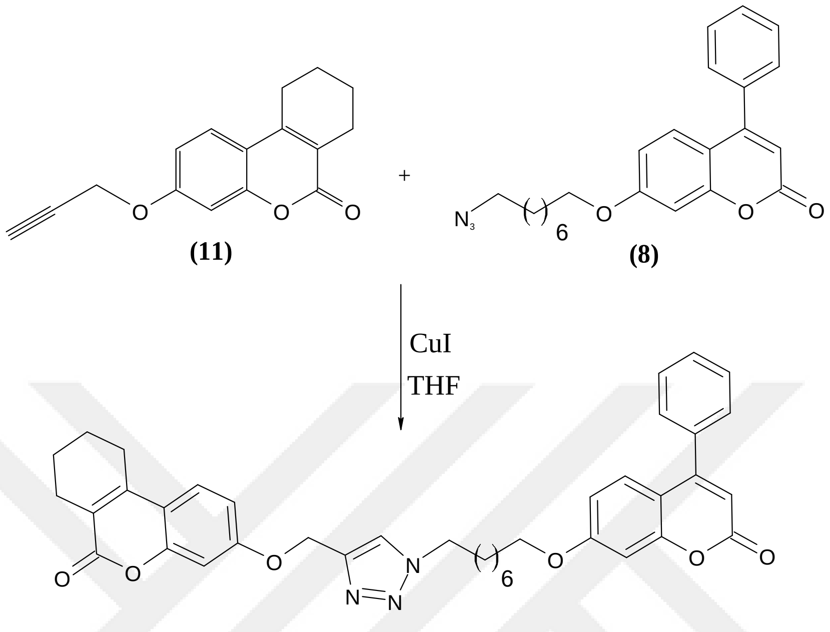


Figure 5.52 ^{13}C NMR Spectrum of Compound 17

5.20 Syhnthesis of 41-((1-(8-((2-Oxo-4-phenyl-2*H*-chromen-7-yl)oxy)octyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one (Compound 18, $C_{39}H_{39}N_3O_6$)



Compound 11 (0.62 mmol) and Compound 8 (0.54 mmol) were reacted with CuI (1.69 mmol) by following the method given for Compound 13. The crude product was purified using column chromatography (ethyl acetate:hexane 3:1).

White crystal, 65%, m.p. 122.5-123.0 ºC

Spectral Data of Compound 18:

FTIR (ATR): ν =3059 (aromatic, CH stretching), 2932, 2852 (aliphatic, CH stretching), 1704 (C=O stretching), 1618, 1606 (aromatic C=C stretching), 1379 (aliphatic in-plane C-H), 1298 (C-N bending), 1159 (C-O stretching) cm^{-1}.

^{1}H NMR: δ 1.37 (brs, 6H CH_2), 1.44-1.48 (m, 2H, CH_2), 1.77-1.81 (m, 4H, CH_2), 1.83-1.87 (m, 2H, CH_2), 1.92-1.96 (m, 2H, CH_2), 2.55 (apt, 3H, CH_3), 2.74(apt, 2H, CH_2), 4.01 (t, J= 6.5 Hz, 2H, NCH_2), 4.37 (t, J= 7.0 Hz, 2H, OCH_2), 5.24 (s, 2H, OCH_2), 6.20 (s, 1H, =CH), 6.77 (dd, J= 2.5 Hz, 8.Hz, 1H, ArH), 6.86 (d, J= 2.0 Hz, 1H, ArH), 6.90 (d, J= 2.5 Hz, 1H, ArH), 6.93 (dd, J= 2.5 Hz, 9 Hz, 1H, ArH), 7.37 (d, J= 9.0 Hz, 1H, ArH), 7.42-7.44 (m, 2H, ArH), 7.47 (d, J=9.0 Hz, 1H, ArH), 7.51-7.52 (m, 3H, ArH), 7.63 (s, 1H, ArH) ppm.

^{13}C NMR: δ 21.38 (CH_2), 21.68 (CH_2), 23.87 (CH_2), 25.24 (CH_2), 25.84 (CH_2), 26.40 (CH_2), 28.89 (2 x CH_2), 29.07 (CH_2), 30.25 (CH_2), 50.48 (NCH_2), 62.32 (OCH_2), 68.53 (OCH_2), 101.55 $C_{aro}H$), 101.89 ($C_{aro}H$), 111.74 ($C_{aro}H$), 112.13 ($C_{aro}H$), 112.38 (C_{aro}), 112.72 ($C_{aro}H$), 114.28 (C_{aro}), 120.93 (C_{aro}), 122.69 ($C_{aro}H$), 124.30 ($C_{aro}H$), 127.96 ($C_{aro}H$), 128.39 ($C_{aro}H$), 128.84 ($C_{aro}H$), 129.59 ($C_{aro}H$), 135.61 (C_{aro}),1 43.19 (C_{aro}), 147.21 (C_{aro}), 153.38 (C_{aro}), 155.88 (C_{aro}), 156.02 (C_{aro}), 159.94 (C_{aro}), 161.32 (C_{aro}),162.08 (C=O), 162.32 (C=O)

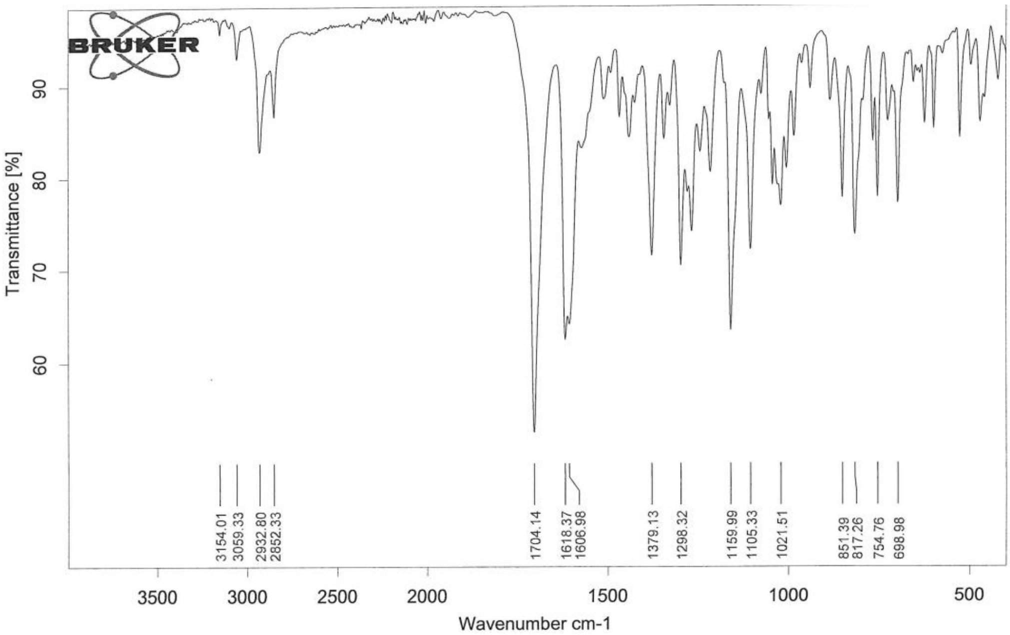


Figure 5.53 FTIR Spectrum of Compound 18

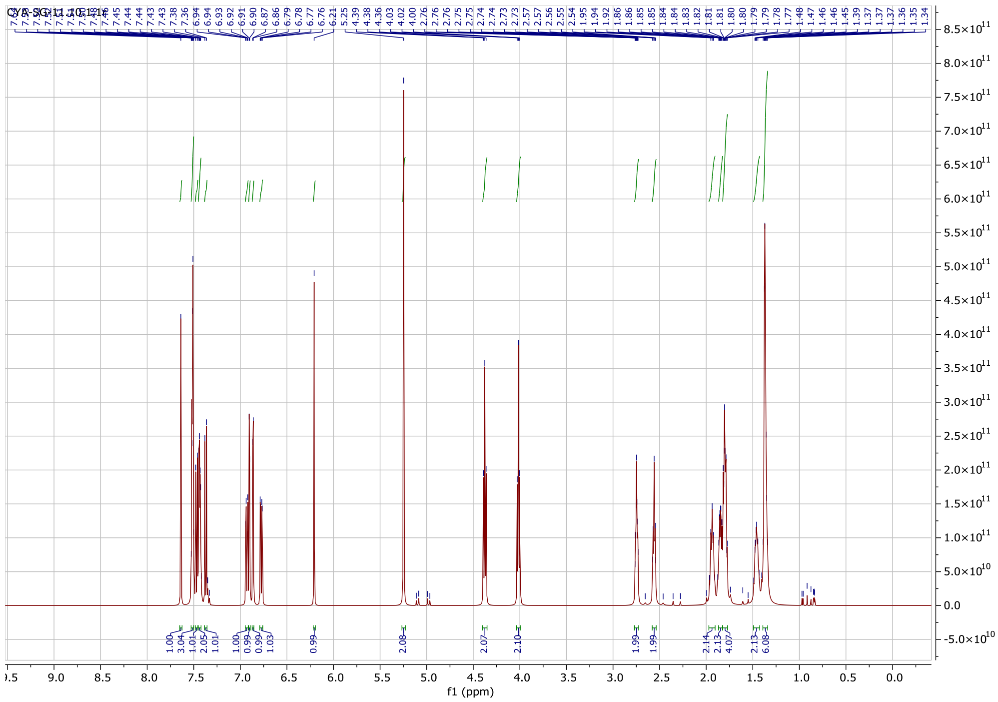


Figure 5.54 ^{1}H NMR Spectrum of Compound 18

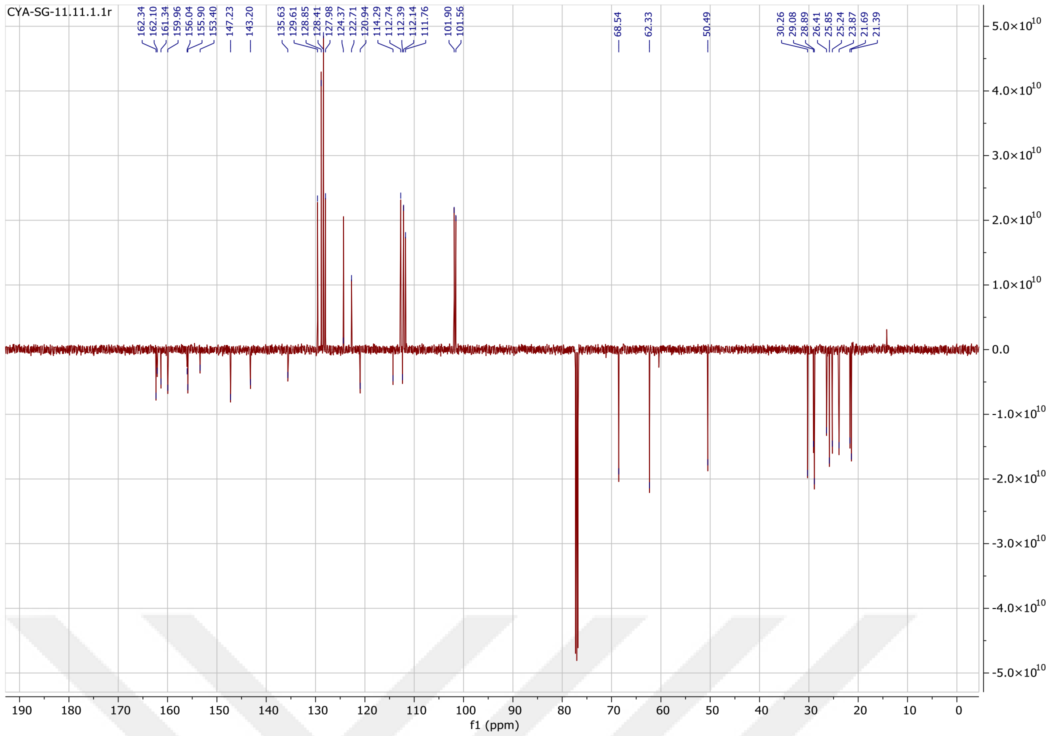
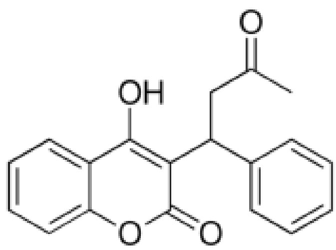
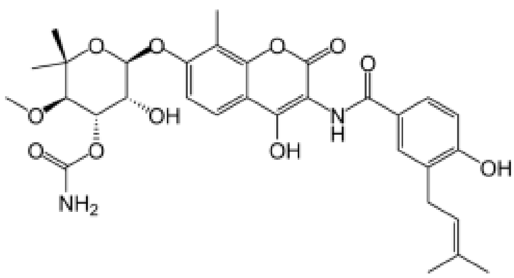


Figure 5.55 ^{13}C NMR Spectrum of Compound 18

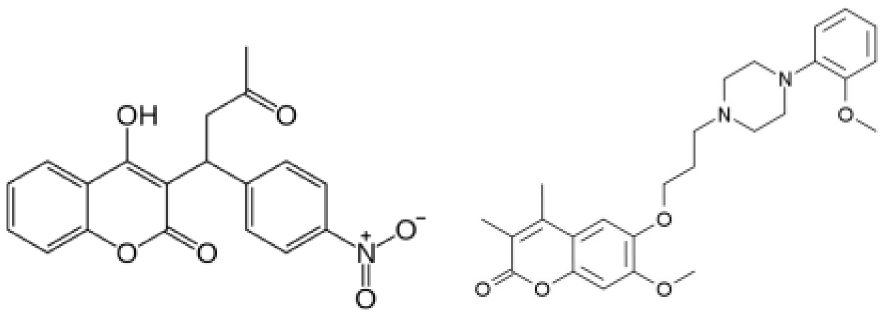
6
CONCLUSION

Natural substances known as coumarins which have heterocyclic structure are frequently discovered in plants, either on their own or in combination with various groups, and have recently become more significant due to their range of biological functions. Various coumarin derivative such as Warfarin (anticoagulant), Novobiocin (antibiotic), Acenocumarol (anticoagulant), Hymecromone (for bile disorters), Ensaculin (treatment of dementhia), Trioxalen (antivitiligo), Calanolide-A (Anti-HIV) are in market as drug, in Figure 6.1 some drug molecules containing coumarine ring are given [83-85]. Cumarin skeleton can be functionalized from six different position, thus to obtain various new cumarin compounds with different biological activity became possible [84-88]. The effect of the substituents attached to different positions on cumarin ring on activity is investigated by structure-activity studies [89, 90]. As a consequence, coumarins are now a well-liked studied subject with a wide range of uses. Studies concentrating on the synthesis of various derivatives of these substance class have become more prevalent. The researches on the synthesis and potential applications of cumarin derivatives keep their actuality due to their synthetic efficiency and variation in application area [91-95]. As a result of these important properties, our research attention have been focused on the synthesis of new coumarin compounds and various coumarin derivatives having biological activity have been synthesized and characterized in our reseach group [97-99].





Warfarin (anticoagulant) Novobiocin (antibiotic)

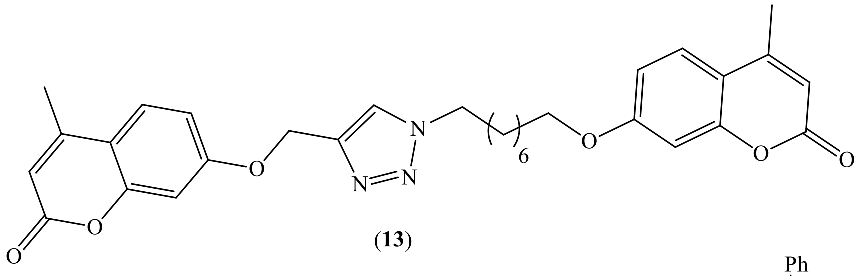


Acenocumarol (anticoagulant) Ensaculin (treatment of dementhia)

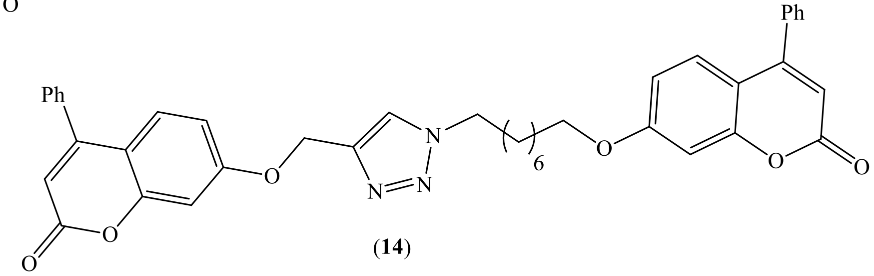
Figure 6.1 Some marketed coumarin drugs

The combination of two or more drug to provide more terapeutical effect is a well accepted dissease treatment way. By this treatment approach in hand, medicinal chemists tried to combine two or more active drug functionalities in same molecule to have more synergistic effect [100]. In recent studies, it has been shown that hybride molecules which contain two or more active units in one molecule show good, improved or novel biological activities compared with parent molecules. After these promising results, new heterocyclic hybride molecule design and synthesis become an interesting area for researchers. Nowadays, coumarin ring also combined with different heterocyclic rings such as triazole, morpholine, piperidine to improve their biological activity. One of the important heterocyclic unit is triazole which is a useful linker and also an important biologically active structure. Triazole derivatives show important biological activities such as antibacterial, antiviral, antifungal and anticancer. Some trizol derivatives are also marketed drugs (Figure 3.8). Coumarin-trizole hybride compounds attract the researcher's attention because of their improved activities, and various new molecules have been synthesized and investigated for their activities [101-104].

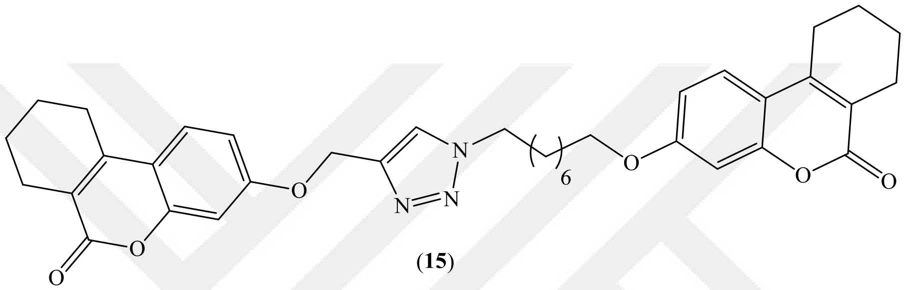
These investigations have piqued our interest in these substances as well, prompting us to create coumarin-triazole hybrid compounds in an effort to add novel substances to the literature. So, the aim of this thesis was to synthesize new coumarin-triazole hybrides which possibly have impotant biological activities. By this aim six novel compounds which contain two coumarin and one trizole ring have been synthesized by CuAAC reaction. The structures of all compounds (**13-18**) are shown in Figure 6.2.



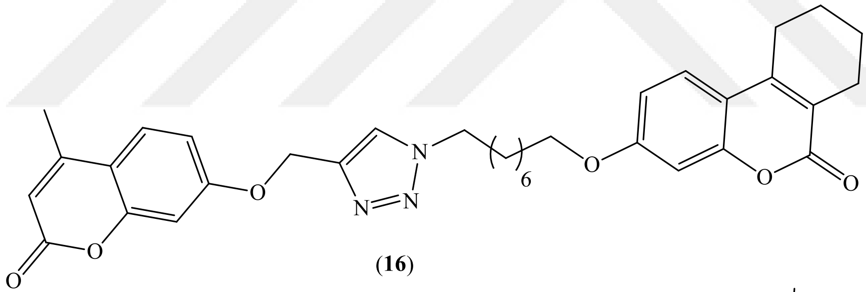
(**13**)



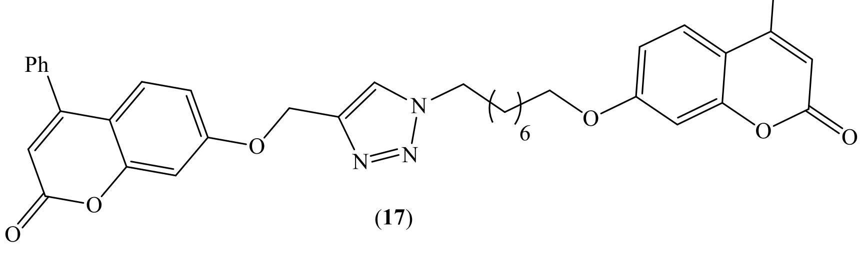
(**14**)



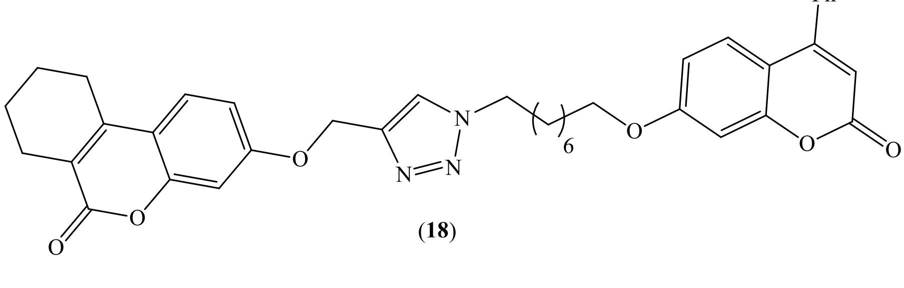
(**15**)



(**16**)



(**17**)



(**18**)

Figure 6.2 The structures of synthesized coumarin-trizole hybrides

In this part of the thesis, the results of the synthesis of new coumarin-triazole hybrid compounds are presented, along with a thorough analysis of the results. The experimental approach includes using several synthetic pathways and reaction conditions to synthesize a number of molecules possibly having important biological activity. After that, the produced compounds were rigorously characterized utilizing a variety of spectroscopic methods.

Utilizing methods including ^{1}H NMR, ^{13}C NMR, FT-IR and LC-MS the purity and identification of the produced compounds were verified. The outcomes of the experiments indicated that the desired coumarin-triazole hybrid compounds were successfully formed. Additionally, the physical characteristics of the compounds comprising melting point and appearance were assessed.

First of all, by using Pechmann condensation, three different coumarin motifs (**1-3**) were synthesized. Resolcinol were reacted with ethyl acetoacetate, ethyl benzoylacetate and ethyl 2-oxocyclohexane carboxylate (Figure 6.3). Since the rest of the study was built on these three synthesized coumarin variants, they can be called coumarin nuclei.

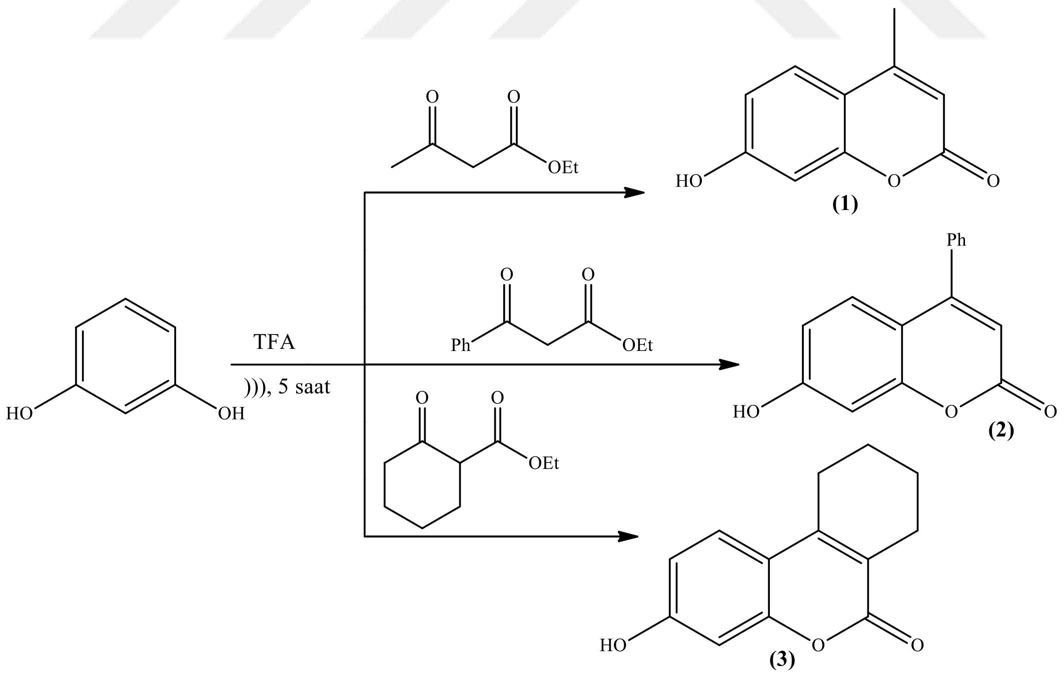


Figure 6.3 The structures of coumarin nuclei

Then, coumarin nuclei were combined with 1,8-dibromoctane with the alkylation of 7-OH group to give 7-bromoalkyloxy-substituted coumarin derivatives (**4-6**). After the alkylation, these three coumarin products were azidated by using NaN_3 in the presence of DMF to obtain 1,3-dipolarophile components of the Click reaction (**7-9**) (Figure 6.4).

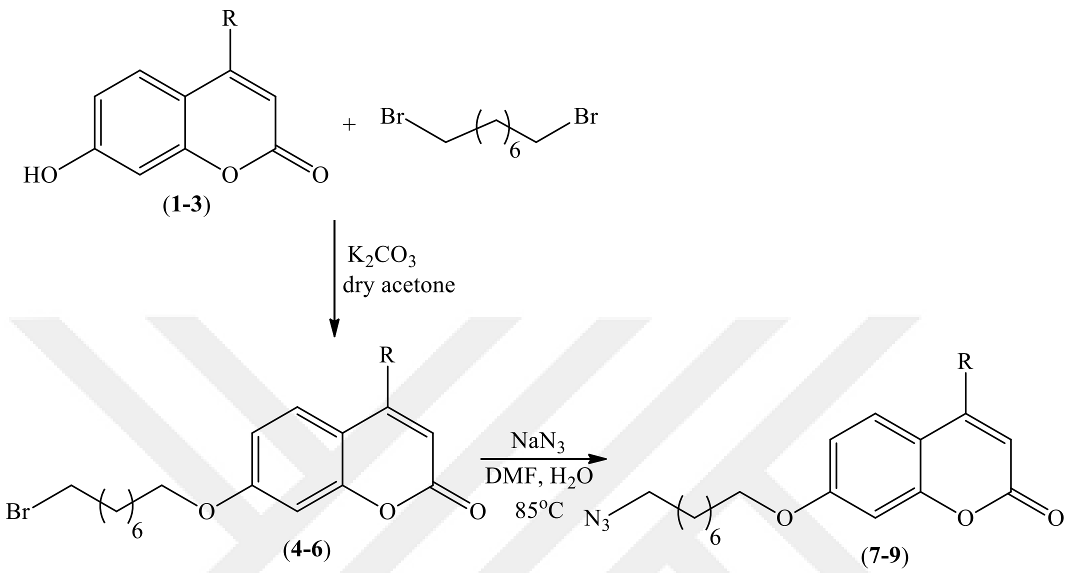


Figure 6.4 Synthesis of 7-bromoalkyloxy-substuted coumarine derivatives (4-6) and 1,3-dipolarophiles (7-9)

On the other hand, three dipolarophile (**10-12**) were synthesized by utilizing propargyl bromide (Figure 6.5). These three recently synthesized products [81, 84] had created the alkynes that were required for the CuAAC cycloaddition process.

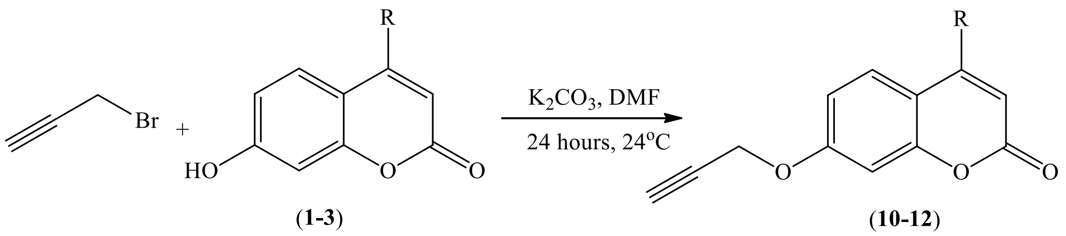


Figure 6.5 Synthesis of dipolarophiles

As the final part of the study, the alkynes and the azides were clicked to each other by a click reaction in the presence of Cu(I) catalyst to obtain coumarin-triazole hybrids (**13-18**) (Figure 6.6).

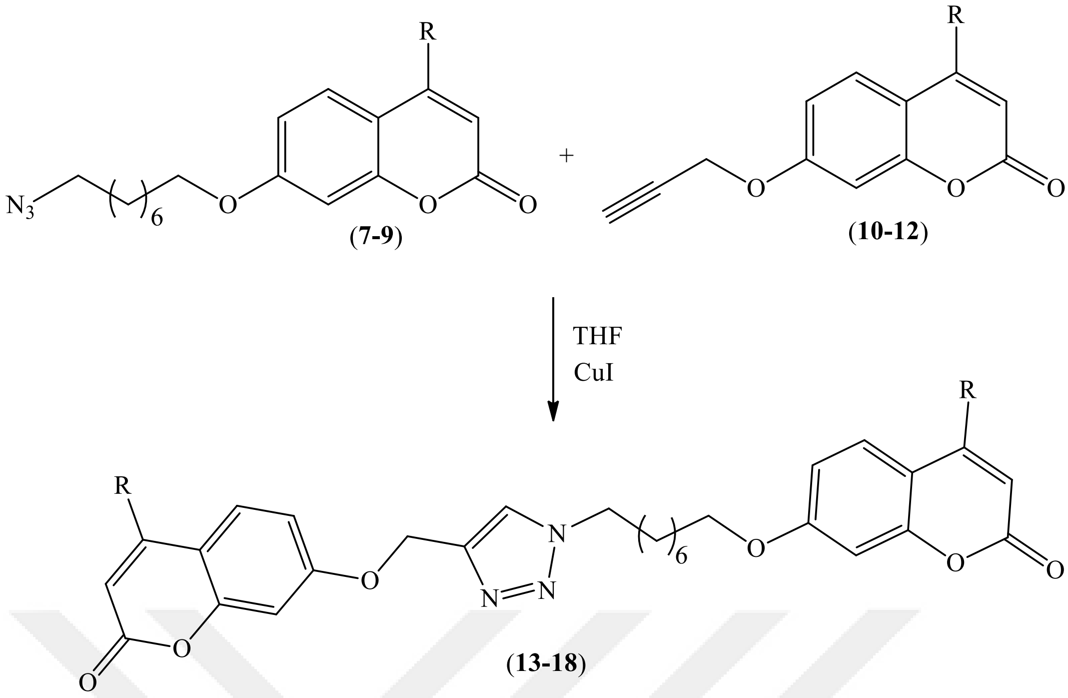


Figure 6.6 The Click reaction for the synthesis of coumarin-triazole hybrides

The structures of all compounds were characterized by their spectral data. The FT-IR spectra of compounds provided key bands to show the formation of intermediate compounds in each step. For instance, in the the FT-IR spectrum of Compound 4, it can be seen that the OH bonds in 3130 cm^{-1} were disappeared after alkylation of the coumarin nuclei (Compound 1) with 1,8-dibromooctane. At the same time, the bands related to alkyl groups of the compound was increased at 2197, 2857 and 2850 cm^{-1}. Also, after the azide group was substituted with bromine atom to give Compound 7, the N_3 peaks appeared at 2174 cm^{-1}. On the other hand, while combining the alkyl and the azides to form triazole ring in Compound 13, this N_3 band disappeared (Figure 6.7).

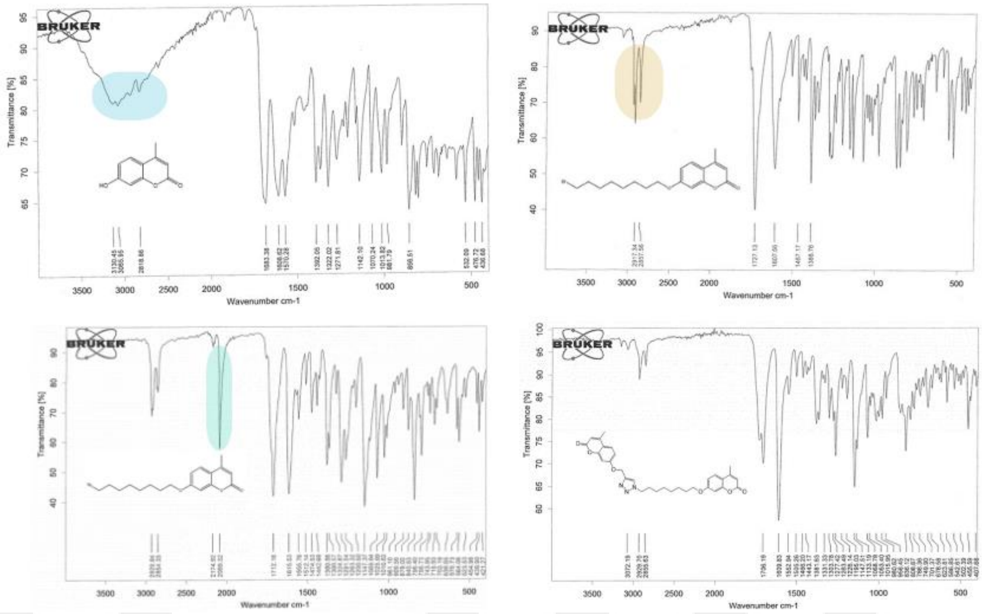


Figure 6.7 FT-IR Spectra of the Compounds 1,4,7 and 13

The structures of the produced coumarin triazole hybrid compounds were verified by ^{1}H NMR and ^{13}C NMR analysis as well as FT-IR spectra. In the ^{1}H NMR spectra, triazole ring -CH proton signals were seen at 7.63-7.65 ppm, the protons of $-OCH_2$ groups came from Compounds 10-12 were placed at 5.24-5.27 ppm and =CH protons in coumarin pyranone rings were observed at 6.12-6.23 ppm as common signals. The other proton signals as well as carbon signals in ^{13}C NMR spectra resonanced as expected. Final results showed that the molecular structures matched up with the the desired goals and in accordance with literature data.

As conclusion, six new bis-coumarin-triazole hybrid molecules were designed and synthesized to contribute to the biologically active hybride compounds in literature in this study. By combining two coumarin unit with a triazole ring, it is expected that the biological activity would be improved with these class of compounds. The desired compounds were synthesized successfuly by a serie of reaction as substitution and Click reactions and their structures confirmed by their spectral data. This study guides future research on the possible uses and biological activities of hybrid molecules. Additional research might focus on discovering various applications and evaluating their biological activity.

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