SAKARYA UNIVERSITY
INSTITUTE OF SCIENCE AND TECHNOLOGY

SYNTHESIS AND CARBONIC ANHYDRASE I-II ACTIVITY STUDIES OF 1,2,3-TRIAZOLYL-1,3-DIOXOISOINDOLINE SULFONAMIDES

M.Sc. THESIS

Chnar Taher Mahmood KAKA KHAN

Department	**:**	**CHEMISTRY**
Field of Science	**:**	**ORGANIC CHEMISTRY**
Supervisor	**:**	**Prof. Dr. Mustafa ARSLAN**

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This thesis has been accepted unanimously / by the examination committee on 07.12.2021.

Head of Jury **Jury Member** **Jury Member**

DECLERATION

I declare that all the data in this thesis was obtained by myself in academic rules, all visual and written information and results were presented in accordance with academic and ethical rules, there is no distortion in the presented data, in case of utilizing other people's works they were refereed properly to scientific norms, the data presented in this thesis has not been used in any other thesis in this university or in any other university.

Chnar KAKAKHAN

. . 2021

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LIST OF SYMBOLS AND ABBREVIATIONS

A.A	: Acetic acid
Sodium A.A	: Sodium Ascorbic Acid
^{o}C	: Degree Celsius
$CuSO_4.5H_2O$	: Copper(II) sulfate pentahydrate
DMF	: N,N-dimethylformamide
DMSO	: Dimethyl sulfoxide
g	: Gram
HCl	: Hydrochloric acid
IR	: Infrared Spectroscopy
K_2CO_3	: Potassium carbonate
mL	: Milliliter
mmol	: Millimole
mp	: Melting point
NaN_3	: Sodium azide
$NaNO_2$	: Sodium nitrite
NMR	: Nuclear Magnetic Resonance
TBAB	: Tetrabutylammonium bromide

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SUMMARY

Keywords: Sulfonamide, triazole, isoindoline, drug discovery.

Sulfonamides are a group of synthetic antibacterial agents that are structurally related to p-amino benzoic acid (PABA). Sulfonamides have a broad range of biological applications. Sulfonamide derivatives; differ mainly in substitution at the sulfonamide side chain. Discovering the first sulfonamide drug, prontosil, opened a new era in medicine. Prontosil was the first drug to successfully treat bacterial infections and the first of many sulfa drugs, which are major antibiotics. Sulfonamide derivatives show extensive pharmacological properties. Examples of derivatives that are used clinically:- are acetazolamide (AAZ), ethoxzolamid (EZA), and indisulfam (IND). Heterocyclic compounds have a wide range of applications and are a major class of organic compounds, possessing physiological and pharmacological properties. These compounds are mostly used as medicinal drugs, agrochemicals, and veterinary products. The best known simple heterocyclic compounds are pyridine, pyrrole, furan, and thiophene.

A new series of twelve sulfonamide derivative **7a-l** compounds was synthesized. New heterocyclic compounds **7a-l** containing a 1,2,3-triazole ring and bearing a benzene sulfonamide moiety were characterized via ^{1}HNMR, ^{13}CNMR, and IR spectroscopy. Acetazolamide was used as the standard inhibitor in the enzyme inhibition assay. The Ki values of these inhibitors were determined to be 20.92 ± 2.60 nm for **7d** against human carbonic anhydrase hCA I and 9.72 ± 1.91 nm for **7e** against hCA II.

1,2,3-TRİAZOLİL-1,3-DİOKSOİZOİNDOLİN SÜLFONAMİDLERİN SENTEZ VE KARBONİK ANHİDRAZ I-II AKTİVİTE ÇALIŞMALARI

ÖZET

Anahtar Kelimeler: Sülfonamit, triazol, izoindolin, ilaç keşfi.

Sülfonamidler, yapısal olarak p-amino benzoik asit (PABA) ile ilişkili bir grup sentetik antibakteriyel ajandır. Sülfonamidlerin çok çeşitli biyolojik uygulamaları vardır. Sülfonamid türevleri; esas olarak sülfonamid yan zincirindeki ikame bakımından farklılık gösterir. İlk sülfonamid ilacı olan prontosil'i keşfetmek, tıpta yeni bir dönem açtı. Prontosil, bakteriyel enfeksiyonları başarılı bir şekilde tedavi eden ilk ilaçtı ve birçok sülfa ilacının ilkiydi. başlıca antibiyotiklerdir. Sülfonamid türevleri kapsamlı farmakolojik özellikler gösterir. Klinik olarak kullanılan türev örnekleri:- asetazolamid (AAZ), etokszolamid (EZA) ve indisülfamdır (IND). Heterosiklik bileşikler geniş bir uygulama alanına sahiptir ve ana organik bileşikler sınıfıdır. fizyolojik ve farmakolojik özelliklere sahiptir. Bu bileşikler çoğunlukla tıbbi ilaçlar, zirai kimyasallar, ve veteriner ürünleri. En iyi bilinen basit heterosiklik bileşikler piridin, pirol, furan ve tiyofendir.

Yeni bir dizi on iki sülfonamid türevi **7a-1** bileşiği sentezlendi. 1,2,3-triazol halkası içeren ve bir benzensülfonamid parçası taşıyan yeni heterosiklik bileşikler **7a-1**, şu şekilde karakterize edildi. ^{1}HNMR, ^{13}CNMR ve IR spektroskopisi. Enzim inhibisyon deneyinde standart inhibitör olarak asetazolamid kullanıldı. Bu inhibitörlerin Ki değerleri olarak belirlendi İnsan karbonik anhidraz hCA I'e karşı **7d** için 20.92 ± 2.60 nm ve hCA II'ye karşı **7e** için 9.72 ± 1.91 nm.

CHAPTER 1. INTRODUCTION

Heterocyclic chemicals consisting of nitrogen are important components of many medicinal drugs, and biological molecules, including:- vitamins, DNA, RNA, antigens, agrochemicals, and many others. These compounds are also an important and characteristic category among applied organic chemistry and have a wide variety of physiological and pharmacological characteristics. A study that was recently conducted by the (World Health Organization (WHO) evaluated the structures, chemical reactions, and biological activities of cyclic nitrogen systems [1]. Triazole has occupied a unique position in heterocyclic chemistry, due to its numerous biological activities. Triazole exhibits isomers such as 1,2,4-triazole and 1,2,3-triazole and is used as an essential part of the design and synthesis of medical compounds. Triazole is included in a wide range of interesting therapeutic candidate drugs, such as analgesic, antiseptic, antimicrobial, antioxidants, anti-urea, anti-inflammatory, diuretic, anticancer, anticonvulsant, antidiabetic, and anti-granulocyte drugs [2]. In medical chemistry, 1,2,3-triazole is considered a hetrocyclic 1,4-unsubstituted 1,2,3-triazole derivative, and can be synthesized via 1,3-dipolar reactions. 1,3-Dipolar cycloaddition reactions are regarded as a powerful synthetic tool in constructing heterocyclic cycles, with uses in various fields. A well-recognized example:- is Huisgen cycloaddition regularized between an azide (dipolar) and alkyne (dipolarphile), which produces a triazole ring. In 1906, the first sulfanilamide drug (sulfa drug) was developed, and sulfa drugs are a group of synthetic drugs containing the chemical group sulfonamide. Discovering the first sulfonamide drug, -prontosil (Figure 1.1.), began a new era in medicine. Since than, nitrogen containing heterocycles and sulfonamides have attracted the attention of several researchers.

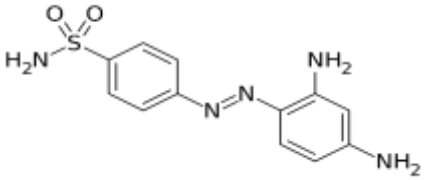


Figure 1.1. First sulfonamide drug- Prontosil.

Sulfonamides are also used to describe any compound with a portion of SO_2NH_2. The general formula consists of (A-SO_2NHR), to which the functional group is directly attached (aromatic, heterocyclic, aliphatic scaffold, (type A), connected like a scaffold by a heterocyclic atom, mostly oxygen or nitrogen). Sulfonamides have a broad range of biological applications and can potentially be used as medicinal molecules in drug development and discovery. Sulfonamides constitute an essential group of pharmacological agents, including many types of drugs that have anticarbonic, antibacterial, antiobesity, hypoglycaemic, diuretic, antithyroid, antitumour, antineuralgic, and antibacterial properties. Acetazolamide is a CA inhibitor and a diuretic [4,5]. The aim of this study was to find a biologically active triazole-bearing sulfonamide compound by synthesizing many derivatives through a click reaction of a phthalimide moiety and azide derivatives bearing a sulfonamide moiety. Isoindolines are also of interest due to their bioactivity. They contain an imide functional group (-CO-N(R) -CO-) N-substituted derivatives. Synthetic methodologies have been utilized to prepare more derivatives of triazole-based sulfonamides that possess drug-like properties. It has important biological properties in the field of medicinal and synthetic organic chemistry [3,6]. We report herein a new series of **7a-l** 1,2,3-triazole sulfonamide derivatives, synthesized using copper(II) catalysed click chemistry. First, 1,3-dioxoisoindole-5-carboxylic acid derivatives were synthesized using different amines, followed by propargylation of the compounds using propargyl bromide using K_2CO_3, and TBAB in DMSO at room temperature. Later, the targeted compounds were prepared via a click reaction with azide derivatives bearing sulfonamide moieties using $CuSO_4$ and sodium ascorbate in DMF. The structures were determined using ^{1}H-NMR, ^{13}C-NMR and Fourier transform infrared (FT-IR)spectroscopy and elemental analysis. The inhibitory effects of sulfonamide derivatives **7a-l** on human carbonic anhydrase (hCA) I and hCA II were evaluated, and the Ki values of these inhibitors were Ki = 20.92 ± 2.60 nm for **7d** against hCA I and Ki = 9.72 ± 1.91 nm for **7e** against hCAII.

CHAPTER 2. HETEROCYCLIC CHEMISTRY

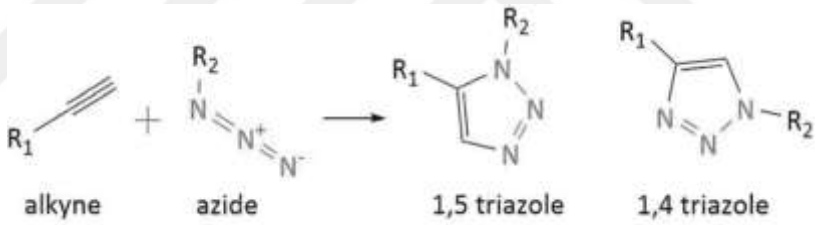
Heterocyclic chemistry is one of the largest classes of organic chemistry. Heterocyclic compounds contain one or more heteroatoms in their structure. The most common elements in these compounds are N, O, and S. Heterocyclic compounds are classified into two classes: i) aliphatic heterocyclic compounds, and ii) aromatic heterocyclic compounds. Cyclic amines, cyclic amides, cyclic eithers or cyclic thioethers are aliphatic heterocycles that contain double bonds. Heterocyclic compounds are similar to benzene in terms of aromaticity. According to Huckel's rule, an aromatic compound must be cyclic in nature with a planar geometry due to cyclic double bonds and contain $(4n+2)\pi$ electrons. Heterocyclic compounds have numerous applications in veterinary products, in fields as diverse as photography, biopesticide synthesis and polymer science. Heterocycles are the most important structural scaffolds, and this group is present in molecules that are biologically active and substances of general interest in their molecular structure, such as, DNA, RNA, drugs, proteins, hormones, carbohydrates, and natural products.

2.1. 1,3-Dipolar Cycloaddition

1,3-Dipolar cycloaddition reactions of azide alkynes have been broadly used in recent years to prepare functional materials for various purposes. In this regard, a number of new compounds with different biological activities have been designed in pharmaceutical and medicinal chemistry. In 2002, the use of copper in processing 1,3-dipolar cycloadditions was reported by Morten Meldal and Karl Barry Sharpless. 1H-1,2,3-triazole derivatives are considered one of the most prominent numerical groups for heterocyclic compounds. Studies consisting of 1H-1,2,3-triazole have shown many important biological activities such as anti-inflammatory, trypanosome, antimicrobial, and antibacterial activities, and today, these derivatives are used as synthetic

intermediates in the manufacture of photostabilizers and agrochemicals. Some studies have worked develop more effective molecules with specific and improved biological properties [7,8,9].

Ram et al. revealed a benzene sulfonamide carrying a 1,2,4-triazole scaffold [10]. In the 1960s, Rolf Husigen introduced the concept of 1,3-dipolar cycloaddition. Rolf Huisgen was a German chemist, and one of his major achievements was the development of the 1,3-dipolar cycloaddition reaction, also known as Huisgen cycloaddition. 1,3-Dipolar cycloaddition is an important route to the regioselectivity synthesis of five-membered heterocycle derivatives [11,12,13]. The general method of 1,2,3-triazole synthesis, Huisgen cycloaddition, includes a dipolar cycloaddition between azides and alkynes. The azide–alkyne Huisgen cycloaddition plays a key role in click chemistry and a powerful tool in pharmaceutical and medicinal chemistry (Scheme 2.1.) [14,15].



Scheme 2.1. 1,4 and 1,5 reaction (Huisgen 1,2,3-dipolar cycloaddition).

1,3-Dipole cycloaddition of terminal azides and alkenes, to construct triazoles represents an essential class and has a broad category application in bioactive drugs [3]. Balci et al. revealed the synthesis and evaluation of a series of N-heteroaryl derivatives that substituted triazole sulfonamide (Figure 2.1.) [16].

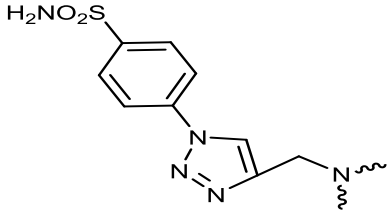


Figure 2.1. N-hetroaryl triazole sulfonamide derivatives.

Mechanism of the Huisgen 1,3-dipolar cycloaddition is shown in (Figure 2.2.) [17].

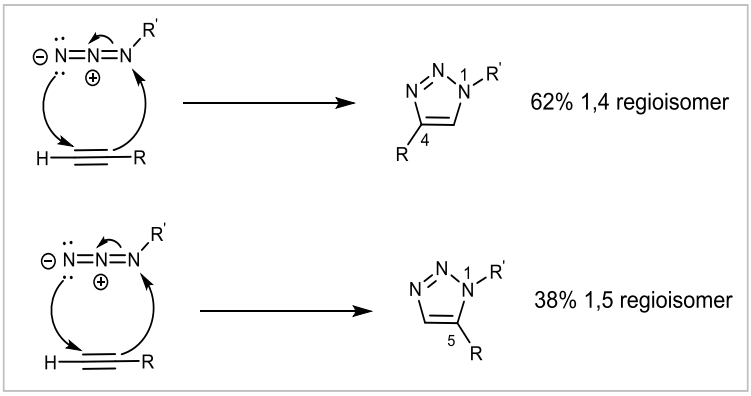


Figure 2.2. Mechanism of the 1,3-Dipolar Cycloaddition.

The cycloaddition consists of several types of reactions, including:- 2+2, 4+2, and 1+3 reactions. The 4+2 reaction is similar to that of Diels Alder, and this reaction consists of a diene and dienophile to produce a cycle. Two electron dipolarphiles and 4 electron dipolars participate in a coordinated circular transformation [17]. A similar mechanism of the Diels-Alder reaction and the 1,3-dipolar cycloaddition is shown in (Figure 2.3.). Diels-Alder is a reaction between diene and the dienophile system, that forms a more stable product and is an important reaction to make six-membered rings. Sharma et al. revealed a reproducible reaction of cycloaddition using sulfamic acid as an additive towards the synthesis of 4-aryl-NH-1,2,3-triazole. This method is accepted as the classical Huisgen cycloaddition reaction [18,19].

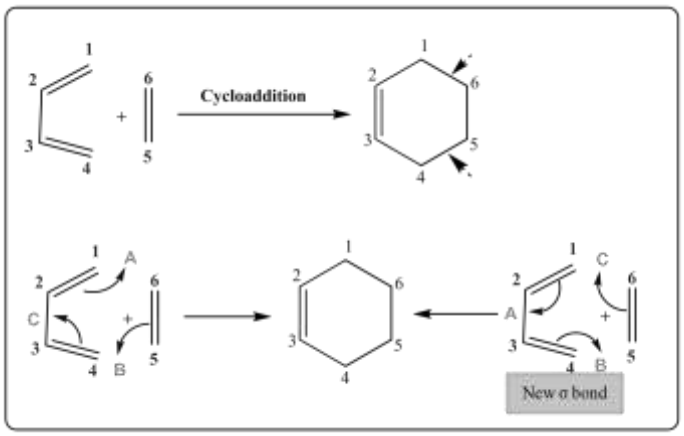


Figure 2.3. Diels-Alder Reaction.

2.2. Click Chemistry

Click chemistry is a term that was introduced by K. B. Sharpless in 2001 to describe reactions that are high yielding and wide in scope. Karl Barry Sharpless is a chemist and Nobel Laureate and is known for his work on stereoselective reactions and click chemistry. In the last five years, many studies have focused on the reaction of Huisgen heterocyclic chemistry approaches based on click chemistry, and this concept has led to an increase in diverse applications in the development of medicinal chemistry [20,21]. The first and most studied example of click reactions was a 1,3-dipole copper(I) azide-alkyne (CuAAC) catalyzed known as Huisgen cycloaddition [7], and click chemistry has been increasingly used in drug discovery. 1,2,3-Triazoles that are formed via the Huisgen reaction are the most common click reaction products. The click reaction and pharmacological applications present a distinct method for the synthesis of molecules containing 1,2,3-triazole, as shown in (Figure 2.4.), which is one of the most potent click reactions (azides and alkynes yielding 1,2,3-triazole). Clearly, the concept of click chemistry is a reliable, highly efficient, and rapidly generating reaction mechanism, that has proven to be powerful in the pharmaceutical field, and has applications in biology and materials science. Additionally, it is possible to form a very stable 1,2,3-triazole moiety via this mechanism under physiological conditions [22,23,24].

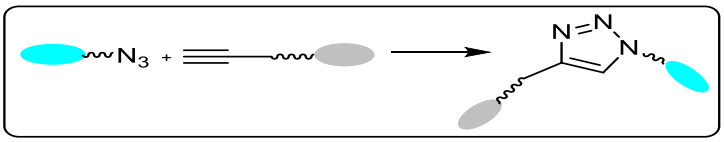
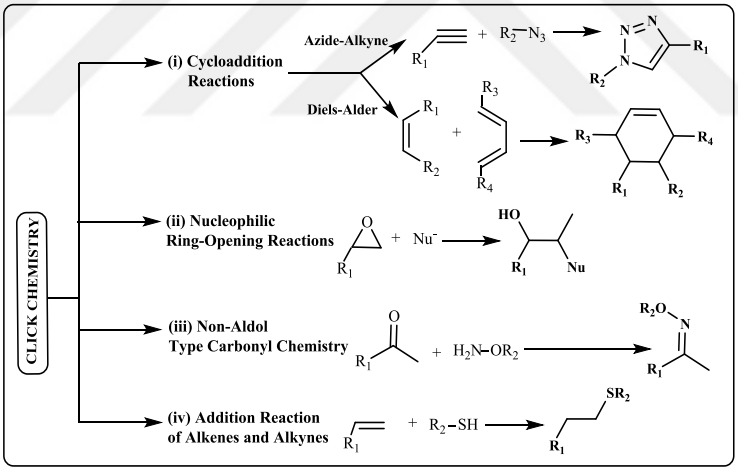


Figure 2.4. The reaction of formation of 1,2,3-triazole compounds.

Click chemistry is a class of biologically compatible interactions used to bind desired substrates to specific biomolecules. Natural products are synthesized by joining small standard units by biosynthesis along with photosynthesis. The role of the click reaction in organic synthesis is as follows: a) The click reaction involves a group of strong bonding chemical reactions that are easy to perform, produce high product yield, and do not require purification. b) The click reaction is flexible in combining different structures without the need for pre-protection steps. c) Molecular diversity, modularity

and efficiency play crucial roles in synthetic organic chemistry. d) These functions are expected to participate in the preparation of various complexes and multipurpose syntheses. e) The click reaction provides a pathway for the synthesis of multiple heterocyclic scaffolds, proteins and the triazole-fused heterocyclic ring. Usually, click interactions have been defined by four main classifications:

- Cycloaddition reactions, such as:- azide-alkyne, and Diels-Alder reactions.
- Nucleophilic ring opening reactions, such as:- aziridines, aziridinium ions, cyclic sulfates episulfonium ions, and epoxides.
- Non-aldol nucleophilic addition reaction involving carbonyl groups such as:- thioureas, oxime ethers, aromatic heterocycles, and amides.
- Additional reactions of alkenes and alkynes, including aziridination, dihydroxylation, epoxidation, sulfenyl halide addition, nitrosylide addition, and certain Michael additions (Scheme 2.2.) [25,26].



Scheme 2.2. Different types of click reactions.

2.3. 1,2,3-Triazole Compounds

1,2,3-Triazole compounds have found applications in many major technological areas, especially in drug discovery, and have various chemical, biological and technical properties. Heterocyclic organic chemistry is the most important branch of biochemistry, and the 1,2,3-triazole ring is a heterocyclic nitrogen-containing pharmacokinetic system. The general synthetic path of bioactive 1,2,3-triazoles using

the click reaction is shown in (Figure 2.5.). In addition, 1,2,3- triazole has different biological and chemical properties of medicinal chemistry, such as treatment in different fields, such as cancer diseases, and hepatitis virus, and has special importance as a synthetic compound [27,28,29]. The triazole moiety is a typical bond, i) is similar to amide bonds, ii) provides major solubility in water, iii) is comparatively resistant to hydrolysis reactions, and iv) is stable under typical biological conditions. Furthermore, the triazole ring is very solid; therefore, there is no interaction between the two bonded substances. These properties make the triazole moiety an inactive linker, even though under specific conditions they can potentially work as a biological reactant on their own [3].

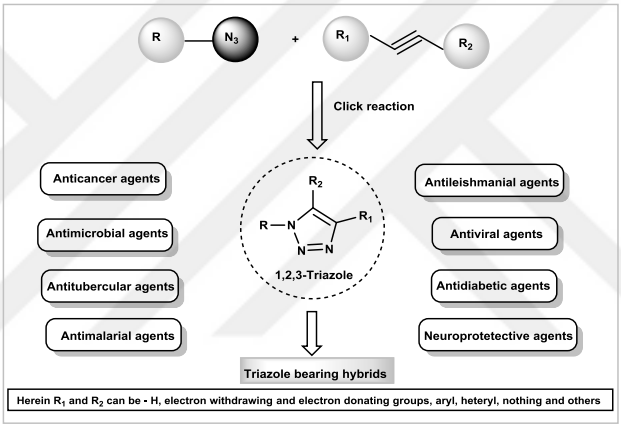
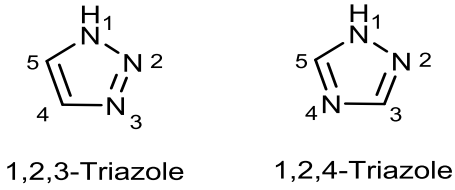


Figure 2.5. The general synthetic path of bioactive.

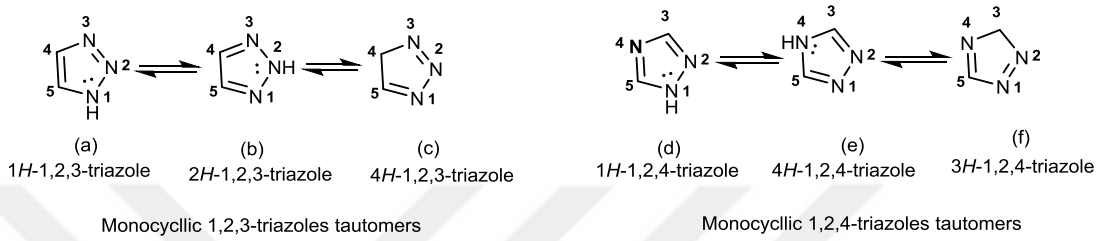
Triazole is an important heterocyclic fraction that has occupied a unique position in heterocyclic chemistry, due to its biological activities. According to the position of the nitrogen atoms, triazole has two isomeric chemical compounds 1,2,3- triazole, and 1,2,4-triazole (Scheme 2.3.), with a molecular formula of $C_2N_3H_3$, a faint scent, melting point of 120 ^oC, and a crystalline white to pale yellow colour. Yatin et al. revealed a series of Schiff bases containing 1,2,4-triazole ring systems [30,31].



Scheme 2.3. Isomeri chemical compounds, 1,2,3-triazole and 1,2,4-triazole.

2.4. Tautomerism in Triazoles

As shown in (Scheme 2.4.), equilibrium of the two forms of NH-tautomers for each of the isomeric classes 1,2,3-triazole and 1,2,4-triazole and [(a), (b) 1,2,3-triazole and (d), (e) 1,2,4-triazole] is reached, and forms (c) and (f) do not have aromatic properties or stabilizing properties in this equilibrium [7].



Scheme 2.4. Tautomerism in triazoles.

Kılıcaslan et al. revealed the inhibitory effects of a series of thiazole-bearing sulfonamide derivatives [32]. In the 1960's, Huisgen was the first to comprehensively study the synthesis of 1,2,3-triazoles. Synthesis routes to 1,2,3-triazole are illustrated in (Figure 2.6.). Through this reaction, 1,4- or 1,5-1,2,3-triazole at high temperature is prepared. Copper(I) and ruthenium(II) (known as the reactions of CuAAC and RuAAC) were used in the Huisgen 1,3-dipole cycloaddition reaction between azides and alkenes [9,33].

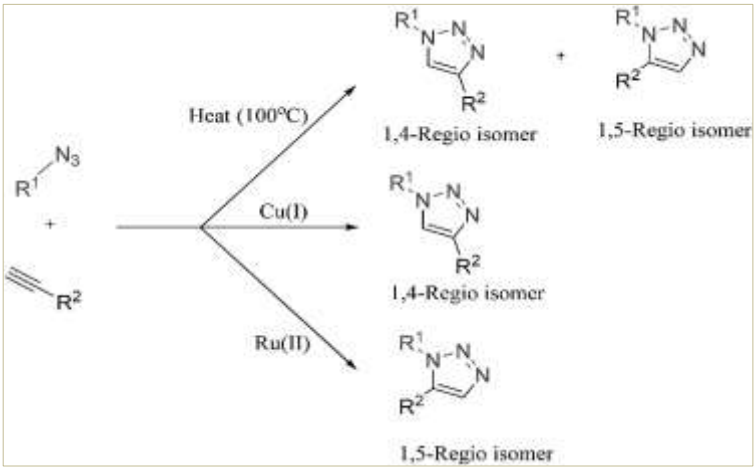


Figure 2.6. Synthetic of 1,4- and 1,5- 1,2,3-triazoles.

Several studies have been conducted on triazole and its derivatives, through which it was found and proven that triazole plays a significant role in many medical factors, has importance in terms of pharmaceutical preparations and is the most common compound of the many that are used in the production of natural and medicinal products [34]. Janam revealed a new series of combinations of 4,5-dihydro-1H-1,2,3-triazoles derived from 2-azido-N-phenyl acetamide, which were synthesized and characterized by spectroscopic and elemental analysis [35]. 1,2,3-Triazole participates in dipole-dipole reactions and hydrogen bond formation and has a high dipole-dipole moment. Structurally, the triazole substitution moiety shows similarity to the amide bond, and this shows that 1,4-triazole substitution is similar to the trans-amide (Z-amide) structure (Figure 2.7.). The main characteristics of the triazole and amide moieties are shown in (Figure 2.8.) trans-amide mimicked by 1,4-disubstituted 1,2,3-triazole and cis-amide mimicked by 1,5-disubstituted 1,2,3- triazole; the polarized C-H at position 5 is a H-bond donor, similar to the NH amide bond. Although the R^1-R^2 distance in the Z-amides is approximately 1 ^oA shorter than that in the 1,4-disubstituted triazoles, the total dipole moment of the 1,4-disubstituted triazoles (approximately 5.0 D) is slightly greater than that of the secondary amides (approximately 3.5-4.0 D). Therefore, the properties of the hydrogen bond donor and acceptor are more pronounced than those of the amide. The electrophilic carbonyl carbon is replaced by a negatively polarized nitrogen atom, which indicates the main difference in the polarization of the atom [3].

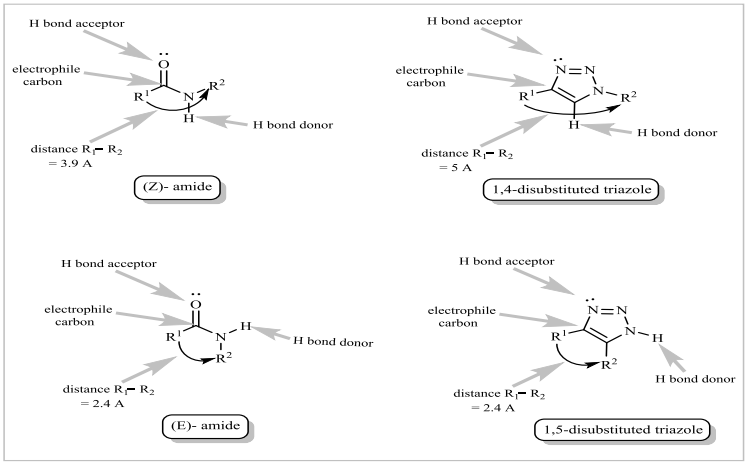


Figure 2.7. Amide moieties and 1,4- and 1,5- substituted triazole.

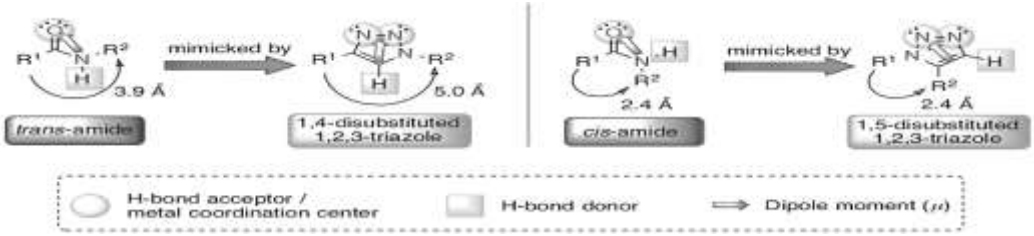


Figure 2.8. The main characteristics of triazole and amide moieties.

2.5. Sulfonamides

Sulfonamides, known as sulfa drugs, were first developed in 1906. These drugs are basic compounds containing a sulfonamide moiety and have broad biological activities in the medical field. Sulfonamides inhibit carbonic anhydrase (CA) and have been clinically used as a treatment for diseases such as heart failure and cancer as well as to lower blood pressure. Clinical sulfonamides such as ethoxolamide, acetazolamide, dichlorphenamide, and methazolamide have been used as systemic CA inhibitors since the 1950s. Primary sulfonamides (RSO_2NH_2: R is an aliphatic, aromatic, or heterocyclic moiety) constitute an important class of drugs comprising several pharmacological agents with anti-CA activities [36,37,38]. The general structure of sulfonamide is shown below in (Figure 2.9.). Sulfonamide derivatives are bacteriostatic factors and find use in both human therapy and animal husbandry. After the discovery of sulfanilamide, thousands of different studies were conducted, and the optimal therapeutic results were obtained from compounds in which a hydrogen atom of the SO_2NH_2 group was replaced by a heterocycle. The use of sulfonamides as protective agents in various diseases on a large scale and some of their derivatives are of commercial importance and are used as carbonic anhydrase inhibitors. In 1940, there were discoveries and scientific applications of CA inhibitors with sulfonilamide by Mann and Killeen. Many procedures have been performed on the preparation of aromatic sulfonamides for their inhibitory effect on CA [39,40,41].

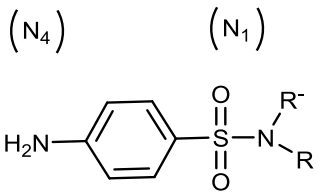


Figure 2.9. The general structure of sulfonamides

The class of chemical sulfonamides shares a common sulfonamide moiety with an aromatic amine group at position C_4 and differs in the sulfonamide substitution group at position C_1. The tetrahedral sulfur atom and multiple substitution vectors for nitrogen atoms lead to structural and compositional diversity, as shown in (Figure 2.10.) [37].

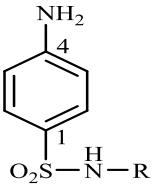


Figure 2.10. The backbone of the sulfonamides

Sulfanilamide is a stable substance under normal temperature and pressure conditions. The solubility of sulfanilamide in acetone (~200 mg/cm^3) and ethanol (~27 mg/cm^3) is greater than that in water. This compound is sensitive to light, and sulfanilamide ionization is shown in (Figure 2.11.) [42].

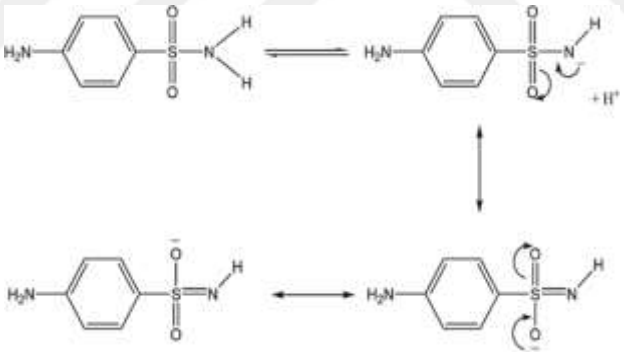


Figure 2.11. Schematic exemplification of sulfanilamide ionization.

Sulfonamide-bearing groups have long been known to be potent inhibitors of CAs and have shown significant inhibitory activity against several CA groups. Acetazolamid (AAZ), ethoxzolamid (EZA) and indisulfam (IND) shown in (Figure 2.12.) are examples of some of the first clinically applied derivatives [43,44,45].

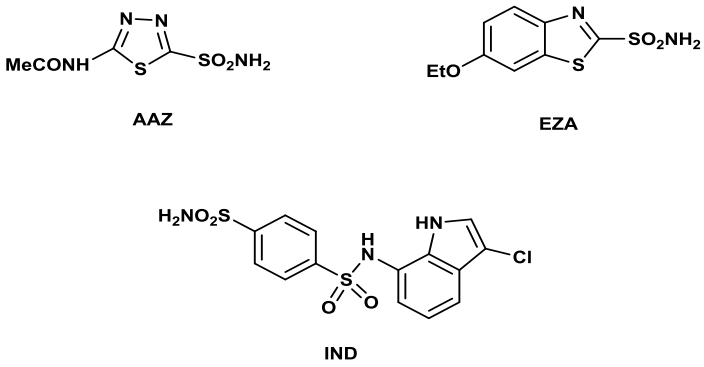


Figure 2.12. Some examples clinically used derivatives, AAZ, EZA and IND

Aromatic/heterocyclic sulfonamides act as potent inhibitors of zinc CA (EC 4.2.1.1). Furthermore, sulfonamide derivatives are potent CA inhibitors. Through the interaction between sulfonamide and catalytic Zn^{2+}, which inhibits the enzymatic activity of CA, these compounds bind to the active site of the enzyme. CA inhibitors are mainly used as antiglaucoma agents, some antithyroid drugs, hypoglycaemic sulfonamides, and eventually some new types of anticancer agents [46,47,48].

2.6. N-Substituted Phthalimides

Phthalimide is an organic aromatic compound containing a nitrogen heteroatom and is an imide derivative of phthalic anhydride. This compound is widely used in the pharmaceutical industry to produce different chemical compounds containing nitrogen and in the synthesis of medicines. As shown in a recent review by Sharma and colleagues, N-substituted phthalimides are well known to display a wide range of biological profiles. Phthalimide (isoindoline-1,3-dione) derivatives (Figure 2.13.) are among the most important properties of biological activity and have been reported to have anticancer, antimicrobial, antioxidant and anti-inflammatory properties. In 1950, a drug based on the phthalimide scaffold (Talidomide) was marketed as a sedative, although it was withdrawn from the market (11 years later) due to teratogenic effects. This drug has recently returned to use in the treatment of leprosy and other related diseases. As a biological application, the utility of phthalimide-containing compounds has also been reported in the fields of liquid crystal, functional material, polymer and supramolecular chemistry. The most widely used method for the synthesis of N-

substituted phthalimide is thermocyclic hardening between phthalic anhydride and secondary amines [49,50,51].

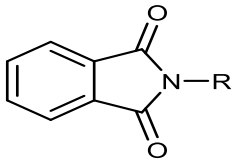


Figure 2.13. N-Substituted Phthalimide.

Türkeş et al. revealed new N-substituted phthalazine sulfonamides that have been tested as inhibitors of hCA I and hCA II, including AchE. Imides have solubility in polar media because the N-H bond is highly polar. The N-H of imides can participate in hydrogen bonding; hence, they are more acidic than amides for the following reasons: electron-withdrawing inductance and more negative charge delocalization by resonance. (Figure 2.14.) shows the stable resonance structures of phthalimide [34,52].

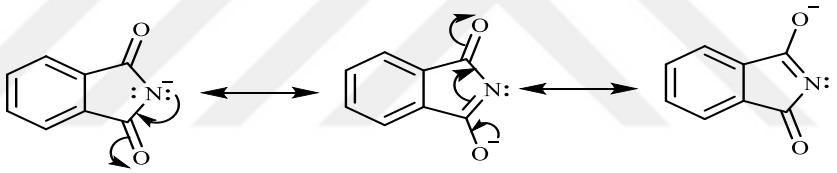


Figure 2.14. Resonance stabilized.

Berber et al. revealed new thiazole-substituted sulfonamide derivatives for the inhibition of two pharmacologically and physiologically relevant isoforms, hCA I and II [5]. Aliphatic or aromatic cyclic imides and their derivatives are obtained by the reaction of dicarboxylic acids or their corresponding anhydride with reagents bearing a reactive amino functional group (–NH2) by nucleating an amino group attack on the anhydride moiety, which is shown in (Figure 2.15.) [52,53].

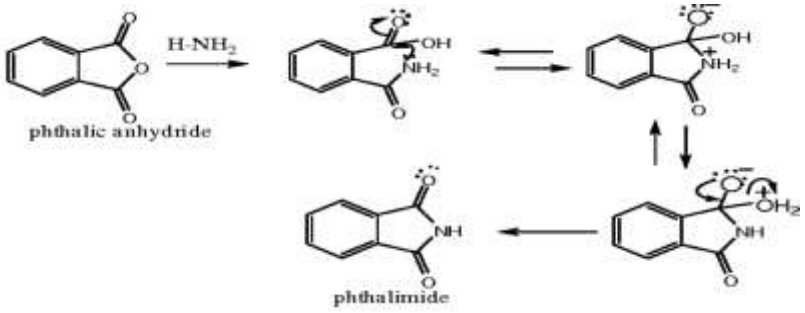


Figure 2.15. Mechanism of imide formation.

2.7. Carbonic Anhydrase

CAs are classified as metalloenzymes that assist in rapidly converting carbon dioxide and water into carbonic acid in living organisms, and their active site contains zinc ions (Zn^{2+}). As shown below [54].

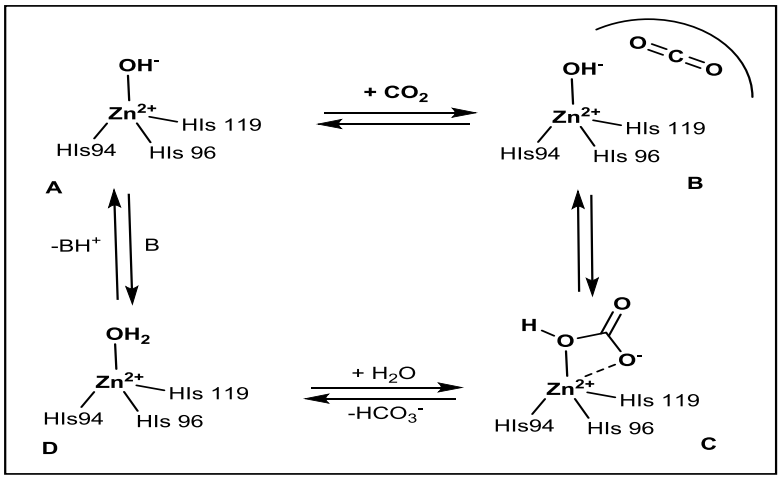
$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

CA is a readily available class of metalloenzymes, and CA acts as a catalyst in the reversible hydration and dehydration process of carbonic acid (H_2CO_3) and carbon dioxide (CO_2). In the drying process H_2CO_3 is converted to CO_2 while hydrogen ions (H^+) and bicarbonate (HCO^{3-}) are produced in the hydration process from CO_2. This interaction is simple but crucial because it produces products involved in basic physiological processes such as respiration, carbon dioxide/bicarbonate transport between tissues and the lungs, pH and carbon dioxide balance, gluconeogenesis, and many additional physiological and pathological processes [55-62]. There are five main classes of CA enzymes namely, α-, β-, γ-, δ- and ζ-CAs, among the 16 different forms of class A CAs found thus far hCA I and hCA II are found widely within the human body and are cellularly balanced enzymes [62,63,64]. Furthermore, the two-dimensional membrane glycoproteins hCA IX and XII are isoforms associated with humans and have extracellular active sites that are markers of a wide variety of hypoxic tumour types. When these isoforms are overexpressed, they lead to increased acidification of the extracellular hypoxic environment (pH =6.8), while in normal tissues (pH =7.4) they lead to enhanced survival of tumour cells in acidic environments by decreasing uptake of weak essential antibody drugs [65-68]. Sulfonamide

compounds are potent CA inhibitors, that have been used as blood pressure lowering agents in the treatment of diseases such as cancer, glaucoma, heart failure and epilepsy for over 50 years [69-71]. In 1940, Mann and Keillin's discoveries of inhibition of sulfonamide CA marked the beginning of many scientific applications. Therefore, many studies have been conducted to prepare aromatic sulfonamides; among these studies, benzene sulfonamides showed the best inhibitory effect of CA. CA inhibitors are categorized into two main groups of metal complex anions and unsubstituted sulfonamides. CA isoforms are involved in many important biological processes [48]. CAs (EC 4.2.1.1) include six genetically distinct families described thus far in different organisms, and there are 16 known CA isoforms in humans. hCA I and hCA II are ubiquitous cellular isoforms, and CAs are enzymes that target drugs. Acetazolamide (AZA) is one of the most popular CA inhibitors and is also used as a standard in CA inhibitor assays. Sulfonamides (known as strong CA inhibitors) in the transported form bind to critical Zn(II) ions at an enzyme's active site, which also contributes to extensive hydrogen bonding and van der Waals interactions with amino acid residues in an enzyme's active site [34,72].

2.7.1. General Mechanism of Action of CAs

The Zn(II) ion of CAs is essential for catalysis, and the active form of the enzyme is the primary form with hydroxide bound to Zn(II) [A]. This strong nucleophile (CO_2) attacks a suitable nucleophilic site and the bicarbonate ion is then displaced by a water molecule and liberated into [D] solution yielding the acidic form of the enzyme with water coordinated with Zn(II), which is catalytically inactive. To regenerate the primary form a proton transfer reaction occurs from the active site to the environment, which can be assisted by active site residues or buffers in the medium. The rate-limiting step of the reaction is the second step in which the hydroxide is regenerated by proton transfer. The interaction is shown as follows (Scheme 2.5.) [48].



Scheme 2.5. General mechanism of action of CA.

CAs are zinc enzymes found in mammals. There are at least 14 different forms of CA found in mammals, some of which are cytosolic (CA I, CA II, CA III, CA VII), while others are membrane-bound (CA IV, CA IX, CA XII and CA XIV); CA V is found in mitochondria, and CA VI is secreted in saliva [64,65]. Between the zinc enzymes that have been studied extensively in the past, CAs are unique for the following reasons: 1) These enzymes are ubiquitous in all kingdoms of life from archaea, Eubacteria, algae and all green plants, to superior animals, including vertebrates. 2) The physiological function of these enzymes is essential for the survival of these organisms. 3) Inhibition can be used in treatment. CA isoenzymes serve important physiological and pathophysiological functions. These enzymes catalyse the interconversion between carbon dioxide and bicarbonate ions which is a simple but critical physiological process associated with respiration and transport of carbon dioxide (bicarbonate) between tissues and lungs, pH and CO_2 homeostasis, electrolyte excretion in many tissues and organs, biosynthesis reactions, resorption bone, calcification, tumours, and many other physiological or pathological processes. Moreover, CA catalyses several other reactions, such as: cyanate hydration of the carbamic acid reaction (1) (Figure 2.16.) [73-76].

$O=C=O + H_2O \rightleftharpoons HCO_3^- + H^+$	1
$O=C=NH + H_2O \rightleftharpoons H_2NCOOH$	2
$HN=C=NH + H_2O \rightleftharpoons H_2NCOONH_2$	3
$RCHO + H_2O \rightleftharpoons RCH(OH)_2$	4
$RCOO\text{-}Ar + H_2O \rightleftharpoons RCOOH + Ar\text{-}OH$	5
$RSO_3Ar + H_2O \rightleftharpoons RSO_3H + Ar\text{-}OH$	6
$ArF + H_2O \rightleftharpoons HF + ArOH$ (Ar = 2,4-dinitrophenyl)	7
$PhCH_2OCOCl + H_2O \rightleftharpoons PhCH_2OH + CO_2 + HCl$	8
$RSO_2Cl + H_2O \rightleftharpoons RSO_3H + HCl$ (R = Me; Ph)	9

Figure 2.16. Reactions catalyzed.

2.7.2. CA mechanism of action

The carbon dioxide released from cells diffuses into the blood through the membranes of red blood cells. The gaseous form of carbon dioxide is poorly dissolved in blood plasma, and CA inside red blood cells converts carbon dioxide into the water-soluble bicarbonate anion (HCO^{3-}). CA contains the zinc ion at its active site; hence, CA are classified as metalloenzymes: i) CA have a common reaction mechanism, ii) undergo nucleophilic attack on CO by a Zn^{2+}-linked hydroxide, iii) displace the produced bicarbonate with water, iv) and dehydrate to regenerate the hydroxide. The synthetic zinc group in the enzyme is coordinated in three positions by histidine side chains. The fourth coordination position is taken by water, which leads to the polarization of the hydrogen-oxygen bond. Hence, the oxygen is slightly more negative and thus weakens the bond. The fourth histidine is located close to the aqueous substrate and accepts a proton, in the example of a general acid - a general basic catalyst leaving a zinc-bound hydroxide. The active site also has a special pocket for carbon dioxide and is close to the hydroxide group, which allows for the electron-rich hydroxide to attack carbon dioxide, forming bicarbonate. The reaction catalysed by CA is as follows: [77,78,79].

$$H_2CO_3 \xleftrightarrow{\text{Carbonic anhydrase}} CO_2 + H_2O \text{ (in tissues)}$$

$$HCO_3^- + H^+ \longrightarrow H_2CO_3 \longrightarrow CO_2 + H_2O \text{ (in lungs and kidneys)}$$

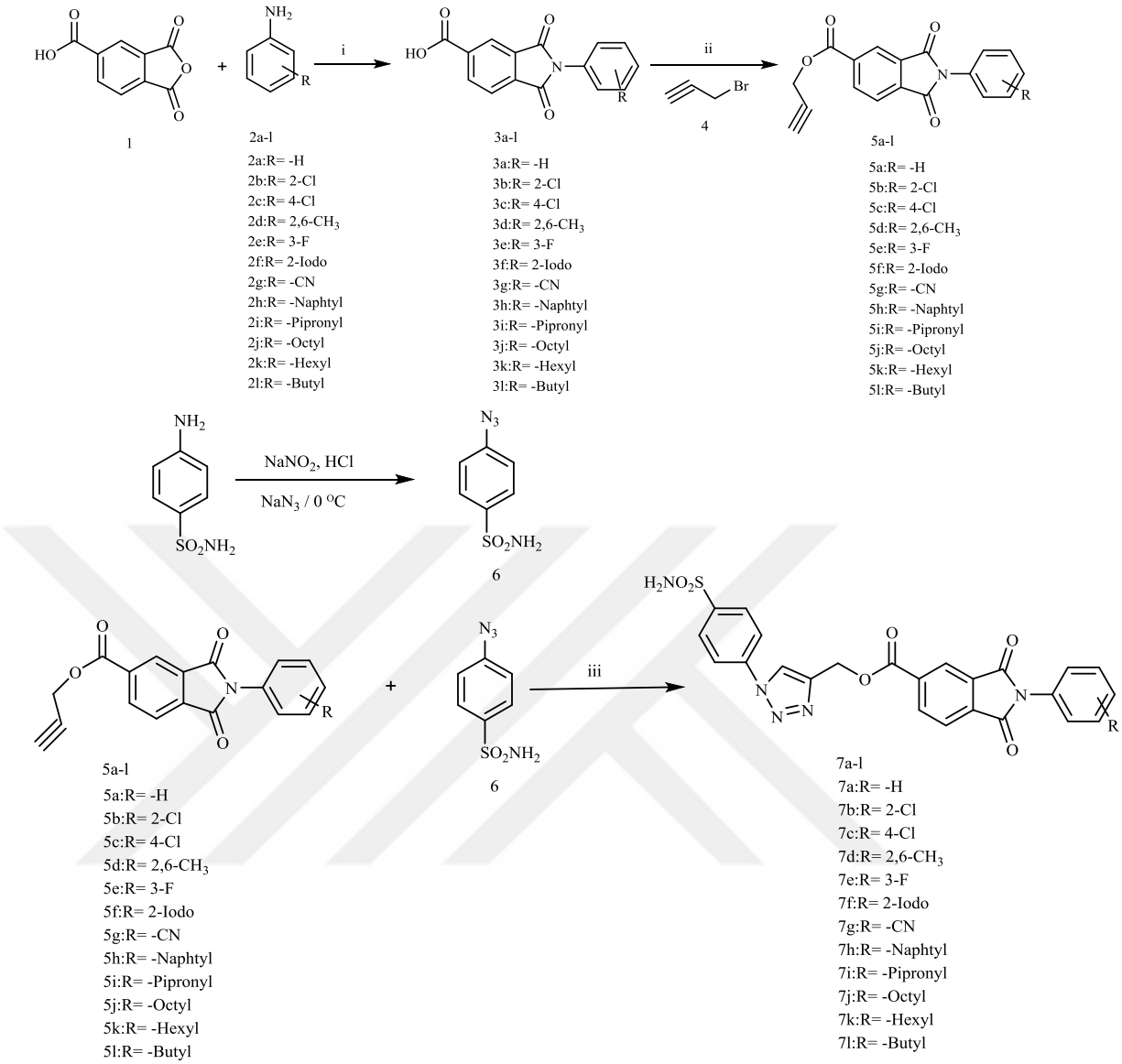
CHAPTER 3. EXPERIMENTAL

3.1. Equipments and Chemicals

Melting points (m.p) were determined by a Yanagimoto micro-melting point apparatus (Surrey, UK).NMR spectra were obtained in VARIAN at 300 and 75 Hz. The Fouirer transform Infraret Spectrums (FTIR) were obtained on a SHIMADZU (koyoto, Japan).

3.2. Synthetic methods of the compounds

Twelve new 1,2,3-triazole sulfonamide drevatives substituted 1,2,3-dioxoisoindolin-5-carboxylate compounds were synthesized starting with 1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxylic acid. First, 1,3-dioxoisoindole-5-caroxylic acid derivatives were synthesised using different amines, then propargylation of the compounds using propargyl bromide using K_2CO_3, TBAB in DMSO at room temperature and later the targeted compounds were prepared via click reaction with azide derivatives bearing sulphonamide moiety using $CuSO_4$, Sodium ascorbate in DMF. The reaction schematically shown as below (Scheme 3.1.). The structures were determined using techniques including ^{1}H-NMR, ^{13}C-NMR, FT-IR and elemental analysis.



Reagents and Conditions: (i) A.A, 100 ^{o}C/6h; (ii) DMSO, K_2CO_3, TBAB, RT/6h; (iii) DMF, $CuSO_4.5H_2O$, Sodium Ascorbate, 90 ^{o}C/2h.

Scheme 3.1. Procedures for target compounds.

3.2.1. General products for preparation of compounds 3a-l.

A mixture of (1,3-dioxo-1,3-dihydoibenzofuran-5-carboxylic acid) compound **1** (2mmol) and compound **2** (2mmol) in acetic acid (10ml) was reflux at 100 ^{o}C for 6 hours. After the reaction was completed, the reaction mixture is cooled to room temperature and ice water was added to it with stirring for 30 minutes (if the reaction not precipitation K_2CO_3 was added solution slowly) and the separated solid was filtered, and then dried.

3.2.2. General produce for the preparation of compounds 5a-l.

Compound **3** (1mmol) was dissolved in DMSO (5ml) with addition of K_2CO_3 (2mmol), a catalytic amount of TBAB and compound **4** 1mmol propargyl bromide at room temperature for 6 hours. After the reaction was completed, ice water was added to it and stirred for 30 minutes, the separated solid was filtered, then dried.

3.2.3. Synthesis method of the preparation of 4-azidobenzenesulfonamide.

4-Aminobenzenesulfonamide (5g) was dissolved in HCl 6M stirred at 0 ^oC in ice bath until complete solubility. Sodium nitrite (2.5g) was dissolved in cold water and added to the reaction. After complete addition, we waited 1h and then sodium azide (2.8g) was add slowly to the reaction. The reaction was stirred at room temperature for overnight. After the reaction was completed, the separated solid was filtered, and then dried.

3.2.4. General produce for the preparation of compounds 7a-l.

Compound **5 (**1mmol) was dissolved in DMF (5ml) with addition of compound **6** 1mmol (4-azidobenzenesulfonamide) and (0.02g $CuSO_4.5H_2O$ with 0.02g sodium ascorbate dissolved in little bit of water) was reflux at 90 ^oC for 2 hours. After completion, the reaction was cooled to room temperature, ice-water was added to it and the mixture was neutralized with concentrated HCl, which led to the precipitation of a solid with stirring for 30 minutes, solid was filtered, washed with water, and then dried.

3.3. Experimental findings and conclusions

(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 1,3-dioxo-2 phenylisoinodoline -5- carboxylate (7a):

Pink solid, Yield 91%, m.p.204 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.11(s,1H, H-Ar), 8.45(d,1H, H-Ar), 8.34(d,1H, H-Ar), 8.14(s,1H, H-triazole), 8.11(d,2H, H-Ar), 8.04(d,2H, H-Ar), 7.60-7.25(m,3H, H-Ar), 7.53(s,2H, -NH_2), 7.46(d,2H, H-Ar), 5.60(s,2H, -CH_2).^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 166.82, 164.75, 144.66, 143.72, 139.17, 136.31, 136.11, 135.50, 132.82, 132.35, 129.60, 128.98, 128.20, 127.99, 124.67, 124.24, 124.11, 121.19, 59.20. IR (ν,cm^{-1}): 3371(NH_2), 3153(=C-H), 1775(C=O), 1714(C=O), 1595(C=C), 1505(C=C), 1098(C-O), 1161(SO_2). Anal Calculated For $C_{24}H_{21}N_5O_6S$: C, 56.80; H, 4.17; N, 13.80; O, 18.91; S, 6.32. Found:- C, 56.86; O, 18.94; N, 13.84; S, 6.36; H, 4.2.

(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2 (2-chlorophenyl)-1,3-dioxoisoinodline-5-carboxylate (7b):

White solid, Yield 49%, m.p.195 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.10(s,1H, H-Ar), 8.51(d,1H, H-Ar), 8.43(d,1H, H-Ar), 8.17(s,1H, H-triazole), 8.14 (d,2H, H-Ar), 8.04(d,2H, H-Ar), 7.74(t,1H, H-Ar), 7.71(t,1H, H-Ar), 7.68(d,1H, H-Ar), 7.54(d,1H, H-Ar), 7.57(s,2H, -NH_2), 5.63(s,2H, -CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 166.11, 164.63, 144.66, 143.74, 139.17, 136.71, 135.79, 132.77, 132.57, 132.06, 131.98, 130.65, 129.98, 128.96, 125.12, 124.55, 124.21, 121.19, 59.37. IR (ν,cm^{-1}): 3225(NH_2), 3011(=C-H), 1779(C=O), 1720(C=O), 1595(C=C), 1488(C=C), 1095(C-O), 1163(SO_2). Anal. Calculated For $C_{24}H_{16}ClN_5O_6S$: C, 53.59; H, 3.00; Cl, 6.59; N, 13.02; O, 17.85; S, 5.96. Found:- C, 53.63; N, 13.06; S, 6.00; H, 3.03.

(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(4-chlorophenyl)-1,3-dioxoisodoline-5-carboxylate (7c):

Brown solid, Yield 28%, m.p.229 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.13(s.1H. H-Ar), 8.45(d,1H, H-Ar), 8.35(d,1H, H-Ar), 8.18(s,1H, H- triazole), 8.14 (d,2H, H-Ar), 8.04(d,2H, H-Ar), 7.60-7.30(m,6H, H-Ar, -NH_2), 5.60(s,2H, -CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 166.60, 164.72, 144.63, 143.70, 136.38, 136.08, 135.39, 133.43, 131.24, 129.68, 128.20, 124.75, 124.25, 12.14, 121.18, 59.30. IR (ν, cm^{-1}): 3071(=C-H), 3261 (NH_2), 1785(C=O), 1719(C=O), 1595(C=C), 1494(C=C), 1092(C-O), 1152(SO_2), Anal. Calculated For $C_{24}H_{16}ClN_5O_6$: C, 53.59; H, 3.00; Cl, 6.59; N, 13.02; O, 17.85; S, 5.96. Found:- C, 53.63; N, 13.06; S, 6.00 H, 3.03.

(1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(2,6-dimethylphenyl)-1,3-dioxoisoindoline-5-carboxylate (7d):

Pink solid, Yield 50%, m.p.173 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.12(s,1H, H-Ar), 8.51(d,1H, H-Ar), 8.40(d,1H, H-Ar), 8.15(s,1H, H-triazole), 8.14 (d,2H, H-Ar), 8.03(d,2H, H-Ar), 7.54(d,2H, H-Ar), 7.32(t,1H, H-Ar), 7.24(s,2H, -NH_2), 5.61(s,2H, -CH_2), 2.22(s,6H, -CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 166.52, 164.68, 144.66, 143.77,139.17, 137.31, 136.63, 135,74, 135.67, 132.50, 130.29, 130.12, 129.03, 128.20, 125.14, 124.61, 124.17, 121.19, 59.35, 18.22. IR (ν, cm^{-1}): 3266(NH_2), 3071(=C-H), 1779(C=O), 1716(C=O), 1597(C=C), 1505(C=C), 1100(C-O), 1163(SO_2). Anal. Calculated for $C_{26}H_{21}N_5O_6S$: C, 58.75; H, 3.98; N, 13.18; O, 18.06; S, 6.03. Found:- C, 58.78; O, 18.10; N, 13.21; S, 6.06; H, 4.02.

(1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(3-fluorophenyl)-1,3-dioxoisoindoline-5-carboxylate (7e):

Beige solid, Yield 68%, m.p.207 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.16(s,1H, H-Ar), 8.51(d,1H, H-Ar), 8.37(d,1H, H-Ar), 8.17(s,1H, H- triazole), 8.12 (d,2H, H-Ar), 8.07(d,2H, H-Ar), 8.02(s,1H, H-Ar), 7.62-7.30(m,7H, H-Ar, -NH_2) 5.63(s,2H, -CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 166.52, 164.70, 144.63,

143.69, 139.15, 136.42, 135.94, 135.45, 132.67, 131.30, 131.18, 128.22, 124.79, 124.25, 124.21, 124.12, 121.17, 115.26, 114.94, 59.29. IR (ν, cm^{-1}): 3235(NH_2), 3061(=C-H), 1776(C=O), 1715(C=O), 1596(C=C), 1495(C=C), 1097(C-O), 1159(SO_2). Anal. Calculated for $C_{24}H_{16}FN_5O_6S$: C, 55.28; H, 3.09; F, 3.64; N, 13.43; O, 18.41; S, 6.15. Found:- C, 55.32; N, 13.47; S, 6.19; H, 3.12.

(1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(2-iodophenyl)-1,3-dioxoisoindoline-5-carboxylate (7f):

White solid, Yield 31%, m.p.191^oC; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.12(s,1H, H-Ar), 8.50(d,1H, H-Ar), 8.42(d,1H, H-Ar), 8.19(s,1H, H-triazole), 8.14(d,2H, H-Ar), 8.03(d,2H, H-Ar), 7.99(d,1H, H-Ar), 7.56-7.40(m,4H, H-Ar, -NH_2), 7.25(m,1H, H-Ar), 5.61(s,2H, -CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 166.17, 164.63, 144.62, 139.80, 139.18, 136.76, 135.86, 135.79, 135.55, 132.60, 132.17, 131.30, 130.14, 128.22, 125.10, 124.55, 124.17, 121.20, 100.86, 59.38. IR (ν, cm^{-1}): 3264(NH_2), 3077(=C-H), 1781(C=O), 1720(C=O), 1598(C=C), 1506(C=C), 1098(C-O), 1161 (SO_2). Anal. Calculated for $C_{24}H_{16}IN_5O_6S$: C, 45.80; H, 2.56; I, 20.16; N, 11.13; O, 15.25; S, 5.09. Found:- C, 45.83; N, 11.16; S, 5.13; H, 2.60.

(1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(4-cyanophenyl)-1,3-dioxoisoindoline-5-carboxylate (7g):

Brown solid, Yield 60%, m.p.179 ^oC; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.11(s,1H. H-Ar), 8.47(d,1H, H-Ar), 8.35(d,1H, H-Ar), 8.16(s,1H, H- triazole), 8.13 (d,2H, H-Ar), 8.04(d,2H, H-Ar), 7.71(d, 2H, H-Ar), 7.68(d,2H, H-Ar), 7.55(s,2H, -NH_2), 5.59(s,2H, -CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 166.27, 164.65, 144.64, 143.71, 139.17, 136.56, 136.49, 135.91, 135.56, 133.72, 132.67, 128.31, 128.21, 124.87, 124.31, 121.17, 119,08, 11.24, 59.34. IR (ν, cm^{-1}): 3315(NH_2), 3077(=C-H), 1779(C=O), 1717(C=O), 1598(C=C), 1507(C=C), 1091(C-O), 1151(SO_2). Anal. Calculated For $C_{25}H_{16}N_6O_6S$: C, 56.82; H, 3.05; N, 15.90; O, 18.16; S, 6.07. Found:- C, 56.85; N, 19.94; O, 18.19; S, 6.11; H, 3.09.

(1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(naphthalen-1-yl)-1,3-dioxoisoindoline-5-carboxylate (7h):

Pink solid, Yield 35%, m.p.185 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.16(s,1H, H-Ar), 8.55(d,1H, H-Ar), 8.43(s,1H, H-Ar), 8.20(s,1H, H-triazole), 8.17(d,1H, H-Ar), 8.10(d,1H, H-Ar), 8.06(d,1H, H-Ar), 7.91(d,1H, H-Ar), 7.85(d,2H, H-Ar), 7,82-7.56(m,7H, H-Ar, -NH_2), 5.65(s,2H, -CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 167.50, 164.82, 144.65, 143.75, 139.18, 136.46, 136.32, 1355.38, 134.41, 133.18, 130.73, 130.33, 128.97, 128.21, 128.08, 127.84, 127.35, 126.32, 124.86, 124.31, 124.24, 123.63, 121.21, 59.32. IR (ν,cm^{-1}): 3563(NH_2), 3045(=C-H), 1779(C=O), 1719(C=O), 1597(C=C), 1509(C=C), 1099(C-O), 1162(SO_2). Anal. Calculated for $C_{28}H_{19}N_5O_6S$: C, 60.75; H, 3.46; N, 12.65; O, 17.34; S, 5.79. Found:- C, 60.78; O, 17.37; N, 12.69; S, 5.82; H, 3.49.

(1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(benzo[d][1,3]dioxol-5-ylmethyl)-1,3-dioxoisoindoline-5-carboxylate (7i):

Beige solid, Yield 87%, m.p.210 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.09(s,1H, H-Ar), 8.39(d,1H, H-Ar), 8.25-8.00(m,7H, H-Ar, H-triazole), 7.55(s,2H, -NH_2), 6.85(d,1H, H-Ar), 6.80(s,1H, H-Ar), 5.94(s,2H, -CH_2), 5.58(s,2H, -CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 167.50, 164.71, 148.03, 147.27, 144.63, 143.72, 139.16, 136.16, 136.06, 135.18, 132.78, 130.74, 128.0, 124.40, 124.18, 123.93, 121.76, 121.15, 108.80, 101.71, 59.23. IR (ν,cm^{-1}): 3265(NH_2), 3074(=C-H), 1777(C=O), 1708(C=O), 1597(C=C triazole), 1505(C=C), 1094(C-O), 1160(SO_2). Anal. Calculated For $C_{26}H_{19}N_5O_8S$: C, 55.61; H, 3.41; N, 12.47; O, 22.79; S, 5.71. Found:- C, 55.65; O, 22.81; N, 12.5; S, 5.75; H, 3.44.

(1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-octyl-1,3-dioxoisoindoline-5-carboxylate (7j):

White solid, Yield 47%, m.p.181^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.11(s,1H, H-Ar), 8.38(d,1H, H-Ar), 8.24(d,1H, H-Ar), 8.17(s,1H, H-triazole), 8.14

(d.2H, H-Ar), 8.03(d,2H, H-Ar), 7.55(s,2H, -NH_2), 5.58(s,2H, -CH_2), 3.55(t,2H, -CH_2), 1.56(quin,2H, -CH_2), 1.20(m,10H, -CH_2),), 0.83(t,3H, -CH_3), ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 167.69, 164.69, 144.62, 143.70,139.15, 136.06, 135.05, 132.77, 128.19, 128.18, 123.67, 121.09, 59.20, 40.96, 31.87, 29.23, 29.19, 28.47, 26.91, 22.74, 14.58. IR (ν,cm^{-1}): 3340(NH_2), 3156(=C-H), 2923(-CH), 1771 (C=O), 1706(C=O), 1627(C=C), 1598(C=C), 1089(C-O), 1162(SO_2). Anal. Calculated For $C_{26}H_{29}N_5O_6S$: C, 57.87; H, 5.42; N, 12.98; O, 17.79; S, 5.94. Found:- C, 57.9; O, 17.82; N, 13.00; S, 5.98; H, 5.46.

(1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-hexyl-1,3-dioxoisoindoline-5-carboxylate (7k):

Orange solid, Yield 40%, m.p.194 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.08(s,1H, H-Ar), 8.37(d,1H, H-Ar), 8.20(d,1H, H-Ar), 8.12(s,1H, H-triazole), 8.03(d,2H, H-Ar), 7.94(d,2H, H-Ar), 7.54(s,2H, -NH_2), 5.56(s,2H, -CH_2), 3.53(t,2H, -CH_2), 1.54(quin,2H, -CH_2), 1.21(m,6H, -CH_2), 0.79(t,3H, -CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 167.69, 164.70, 144.64, 143.71, 139.15, 136.05, 135.07, 132.76, 128.20, 124.17, 124.13, 123.68, 121.11, 59.21, 40.97, 31.42, 28.43, 26.56, 22.61, 14.51. IR (ν,cm^{-1}): 3366(NH_2), 3265(=C-H), 2927(-CH), 1770(C=O), 1707(C=O), 1595(C=C), 1503(C=C), 1102(C-O), 1152(SO_2). Anal. Calculated For $C_{24}H_{25}N_5O_6S$: C, 56.35; H, 4.93; N, 13.69; O, 18.77; S, 6.27. Found:- C, 56.38; O, 18.80; N, 13.72; S, 6.30; H, 4.95.

(1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-butyl-1,3-dioxoisoindoline-5-carboxylate (7l):

Beige solid, Yield 74%, m.p.213 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.09(s,1H, H-Ar), 8.36(d,1H, H-Ar), 8.13(s,1H, H-triazole), 8.03(d,2H, H-Ar), 8.01(d,2H, H-Ar), 7.90(t,1H, H-Ar), 7.55(s,2H, -NH_2), 5.57(s,2H,-CH_2), 3.55(t,2H, -CH_2), 1.53(quin,2H, -CH_2), 1.27(sextet,2H, -CH_2), 0.86(t,3H, -CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 167.75, 164.73, 144.63, 143.72, 139.10, 136.10, 136, 135, 132.81, 128.20, 124.20, 123.68, 121.15, 59.22, 39.29, 30.57, 20.16, 14.16. IR (ν,cm^{-}

[1]): 3334(NH_2), 3256(=C-H), 2963(-CH), 1773(C=O), 1701 (C=O), 1598(C=C), 1503(C=C), 1094(C-O), 1160(SO_2). Anal. Calculated For $C_{22}H_{21}N_5O_6S$: C, 54.65; H, 4.38; N, 14.49; O, 19.85; S, 6.63. Found:- C, 54.67; O, 19.88; N, 14.52; S, 6.67; H, 4.41.

3.4. Biological Activity

Biological activity and docking studies of the synthsises compounds were done by Assoc. Prof. Dr. Cüneyt TÜRKEŞ and his group from Erzincan Binali Yıldırım Üninersity, Faculty of Pharmacy. The results are shown in the table below.

Table 3.1. Inhibition data of (hCA I, hCA II) with compounds (7a–l), AZA.

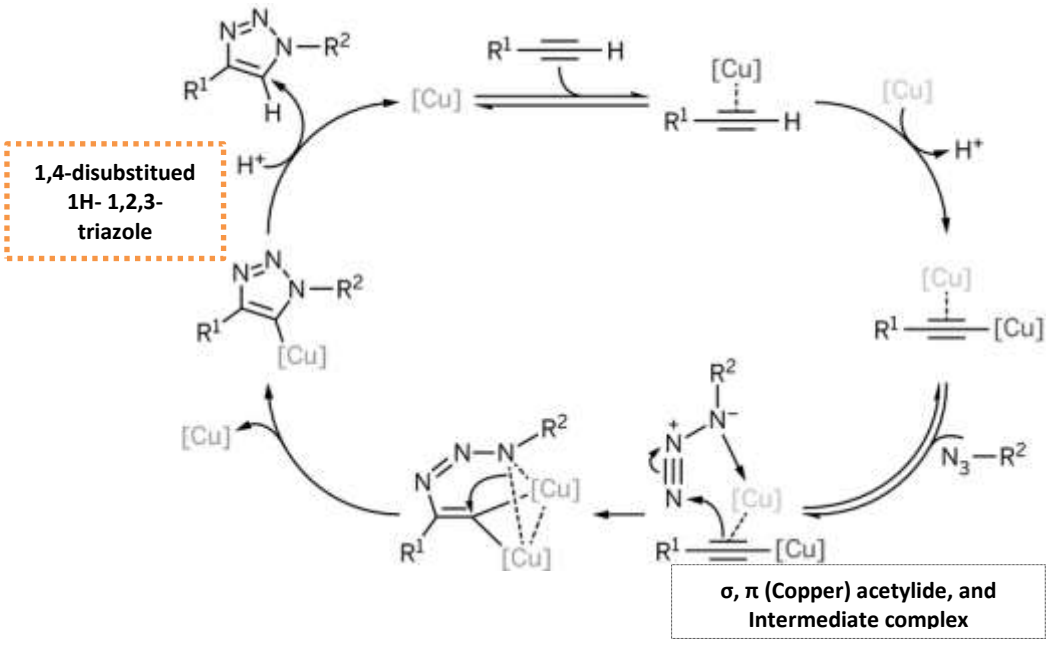
Compound ID	hCA I			hCA II		
	K_I (nM)	R^2	Inhibition type	K_I (nM)	R^2	Inhibition type
7a	38.22 ± 7.27	0.9425	Competitive	50.13 ± 6.29	0.9815	Competitive
7b	38.41 ± 7.54	0.9466	Competitive	37.75 ± 7.32	0.9448	Competitive
7c	48.97 ± 6.39	0.9793	Competitive	75.94 ± 12.00	0.9729	Competitive
7d	20.92 ± 2.60	0.9770	Competitive	50.60 ± 10.83	0.9359	Competitive
7e	48.12 ± 8.68	0.9564	Competitive	9.72 ± 1.91	0.9516	Competitive
7f	105.00 ± 10.63	0.9495	Noncompetitive	23.37 ± 3.38	0.9715	Competitive
7g	25.17 ± 2.80	0.9821	Competitive	16.87 ± 2.42	0.9713	Competitive
7h	32.11 ± 4.36	0.9771	Competitive	30.79 ± 5.65	0.9618	Competitive
7i	27.25 ± 4.41	0.9621	Competitive	38.25 ± 5.57	0.9722	Competitive
7j	42.78 ± 7.58	0.9519	Competitive	67.27 ± 13.16	0.9643	Competitive
7k	37.81 ± 7.40	0.9446	Competitive	32.84 ± 4.96	0.9658	Competitive
7l	34.99 ± 4.01	0.9805	Competitive	35.79 ± 5.29	0.9733	Competitive
Acetazolamide	451.80 ± 59.13	0.9398	Noncompetitive	327.30 ± 32.75	0.9712	Noncompetitive

CHAPTER 4. RESULT AND DISCUSSIONS

The compounds 3a-l shown in (Scheme 3.1.) were prepared from a mixture of 1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxylate and various amines in acetic acid by refloux at 100 °C for 6 hours. . The synthesized compounds 3a-l, were purified and characterized by ^{1}H NMR spectrum, and ^{13}C NMR spectrum. 5a-l compounds were prepared from dissolving compound 3 in DMSO with K_2CO_3, TBAB, and compound (propargyl bromide) at room temperature for 6 hours. The synthesis of triazole compounds with sulfonamide-bearing azide derivatives was prepared using $CuSO_4.5H_2O$, sodium ascorbate in DMF at 90 °C for 2 h. All NMR spectra were indicated to tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. The structures of compounds 7a-l were confirmed by the data ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. All benzene sulfonamide-substituted derivatives 1,2,3-triazole are shown to be the carbonic anhydrase isoform hCA 1 and hCA II inhibitors, and compounds 7d, 7e are the most effective inhibitors among them. The ^{1}H NMR spectrum for 7d showed a singlet (1H) at 8.15 ppm for the triazole proton, a singlet (2H) at 7.24 ppm for NH_2, and a -CH_2 attached to the triazole at 5.61 ppm (2H). 7e showed a singlet (1H) at 8.17 ppm for the triazole proton, a singlet (2H) at 7.34 ppm for NH_2, and -CH_2 attached to the triazole at 5.63 ppm (2H). In addition to the ^{1}H NMR analysis, the ^{13}C NMR resonance assignments were also studied. Carbonyl carbonate peaks are observed at about 190 and 163 ppm. Infrared (IR) spectra were measured with wave numbers (ν, cm^{-1}). The IR spectrum of the compound 7d showed characteristic absorption bands at 3266 cm^{-1} for NH_2, 3071cm^{-1} for =C-H, and 1505 cm^{-1} for C=C- triazole. 7e showed at 3235 cm^{-1} for NH_2, 3061cm^{-1} for =C-H, and 1495 cm^{-1} for C=C- triazole.

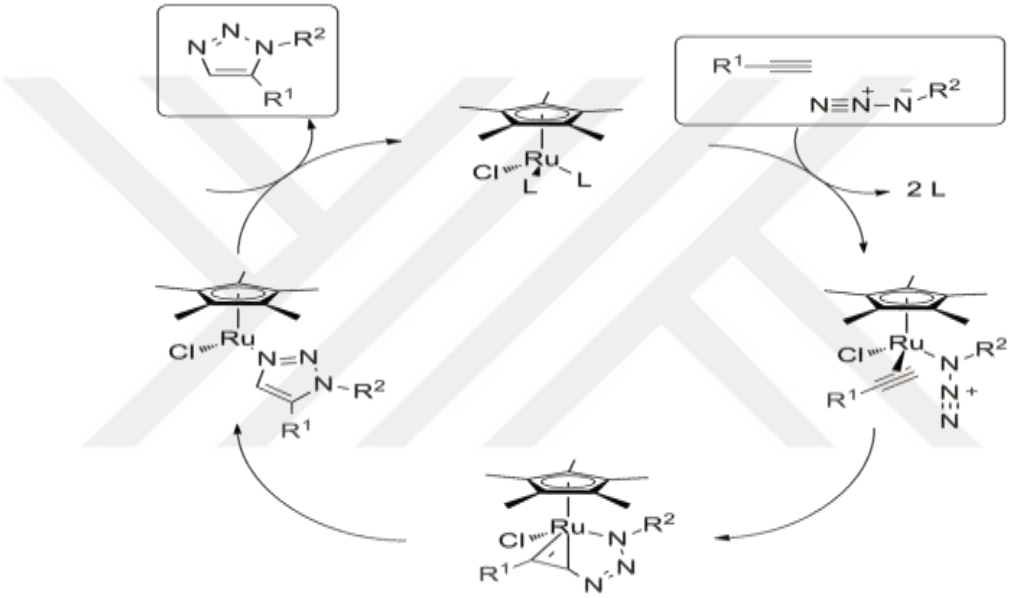
One of the major challenges encountered during this project was in the preparation of triazole in which the compound triazole sulfonamide was not readily produced. In an

attempt to overcome this issue, we increased the azide in mmol at a rate of 1 starting at 1.8 mmol at room temperature. The samples were left overnight but triazole sulfonamide was not produced. Eventually, we decided to increase the temperature to 90 ^{o}C for 2 h, which is when the compound triazole sulfonamide was produced. In this study, copper(I) ($CuSO_4$) was used as a catalyst so that the reaction pathway yields 1,4-regioselectivity. In click reactions where ruthenium is used as a catalyst, the reaction pathway directs azide-alkene cycloaddition towards 1,5-retrospective selections. Therefore, we used the Cu(II) ($CuSO_4$). Cycloaddition loading mechanism:- starts from the catalyst copper (Cu^{+}), which can be generated from copper (Cu^{2+}) salts using sodium ascorbate as the reducing reagent. i) copper plus (Cu^{+}) attacks the alkyne forming bond; ii) another copper attacks the carbon that releases hydrogen; and iii) the copper-bound acetylide coordinates that carry the copper-bound azide. Then, an additional copper complex is formed. The second copper atom acts as a stabilizer for the donor ligand. The copper is released after hydrogen (H^{+}) is introduced. Ring contraction of the triazole and copper derivative is tracked by proton decomposition that delivers the triazole product and stops the catalytic cycle (Scheme 4.1.).



Scheme 4.1. The mechanistic cycloaddition of 1,4- disubstituted.

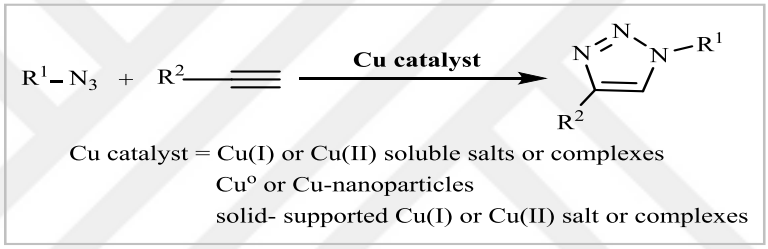
The mechanistic cycloaddition of 1,5-disubstituted compounds is only retroselective for a specific isomer, and therefore, a different path must be taken for the reaction mechanism. Studies indicate that oxidative coupling occurs between azide and alkyne in the initial step of the reaction; when the six-membered ring is formed next to the more electronegative carbon of the alkyne, ruthenium is placed. This allows for carbon and nitrogen to transfer a nitrogen bond to form the selective product of triazole, followed by reductive elimination. (Scheme 4.2.) shows the mechanistic pathway for the synthesis of unsubstituted 1,5-triazole [80,81].



Scheme 4.2. The mechanistic cycloaddition of 1,5-disubstituted.

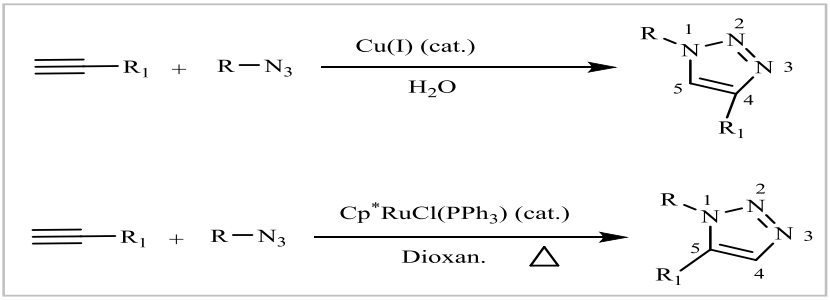
Copper is a versatile transition metal and is the first transition metal element used to catalyse the formation of C-C and C-X bonds. Copper is also an essential element that is responsible for important biological processes. The Ullman and Goldberg C-C and C-N cross coupling interactions were discovered more than a century ago, and their development has already flourished over the past 20 years. In the 1970s, the cross-coupling reaction entered a new era with the introduction of palladium (Pd) as one of the strongest noble metals in the cross-coupling reactions [52,82]. Copper is usually the metal of choice in organic synthesis reactions. The following are the properties of copper: (1) it is an abundant transition metal in the Earth's crust and is therefore cheaper than other grade 2 or grade 3 precious metals (for example, Pd, Pt, Rh, Ir, or Au); (2) copper presents a variety of oxidation states (Cu(0), Cu(I), Cu(II) or even

Cu(III)) with different coordination environments (e.g., linear, planar square or tetrahedral); (3) each copper form accommodates both hard or soft donor bonds in its coordination domain and forms reactions with unsaturated organic substrates (e.g., alkenes or alkynes); (4) copper is an important mineral in biology (found in enzymes and proteins), and it is also the least toxic of the class I metals (along with iron); and (5) it is active under homogeneous or heterogeneous conditions [53]. The CuAAC reaction, discovered in 2002, has since been developed into an excellent tool in organic synthesis. Recent results since 2010 have been reviewed and categorized according to the nature of the catalytic starting material: copper(I) or copper(II) salts or compounds, metallic copper or nanoparticles and various solid copper systems (Scheme 4.3.) [81,83].



Scheme 4.3. The nature of the catalyst.

To further clarify when copper sulfate or copper pentahydrate ($CuSO_4.5H_2O$) is used, the reaction is directed towards the pathway that results in 1,4-selectivity. Moreover, click reactions catalysed by ruthenium direct azide-alkene loading to 1,5-regio-selectivity. (Scheme 4.4.) shows how a cyclic bipolar load becomes selective and effective depending on the condition used. In addition to the catalyst, click reactions can be carried out in a medium of water as well as an organic solvent in various proportions. In addition to reaction conditions, if Cu^{2+} is used as a catalyst, a reducing agent must be used to allow copper to catalyse the reaction [80].



Scheme 4.4. The azide-alkyne cycloaddition.

According to docking and in vitro studies, all the synthesized 1,2,3-triazole substituted benzene sulfonamide derivatives were shown to be hCA I, hCA II inhibitors, and the substituents compounds 7d and 7e were the two strongest inhibitors. Two amino acids possessing an uncharged polar side chain, an amino acid with electrically charged side chains and an amino acid with a hydrophobic side chain were included in this work to prepare novel alternative benzene derivatives 1,2,3-triazole as potential inhibitors. Intermolecular interactions of compound 7d with Gln bound to hCA I are shown in (Figure 4.1.). Threonine 199 creates an H-bond with the sulfonamide functional group, glutamine 92 and lysine 57 bind to the carboxyl group, and lysine 57 creates a heterocyclic interaction with the benzene ring. The shape of the 7e molecule with Gln in hCA II differs slightly from that in hCA I (Figure 4.2.). Threonine 199 forms an H-bond with the sulfonamide group, glutamine 92 bonds to nitrogen in the triazole cycle, forming an H-bond, and the triazine cycle forms a π-π interaction with phenylalanine 131. The results showed that compounds 7d and 7e were able to inhibit hCA I and hCA II enzyme activity. The inhibition values of compounds against CAs are presented in (Table 3.1.) the Ki values of these inhibitors were determined to be 20.92 ± 2.60 nm for 7d against human carbonic anhydrase hCA I and 9.72 ± 1.91 nm for 7e against hCA II.

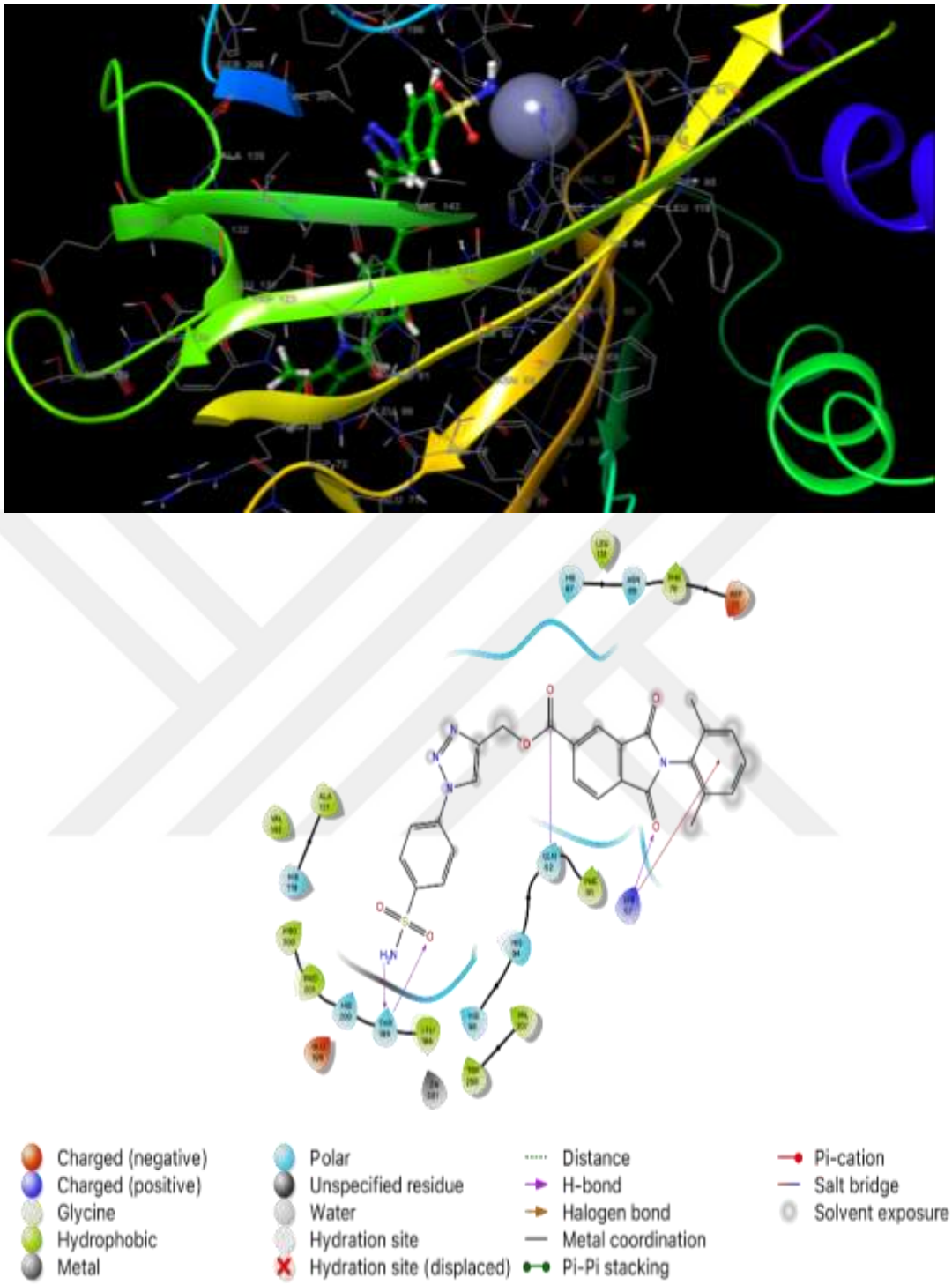


Figure 4.1. The 3D ligand interaction diagram of hCA I (PDB code 4WUQ) with compound 7d (top) and 2D docking pose of compound 7d with the key amino acids within the binding pocket of the 4WUQ (bottom).

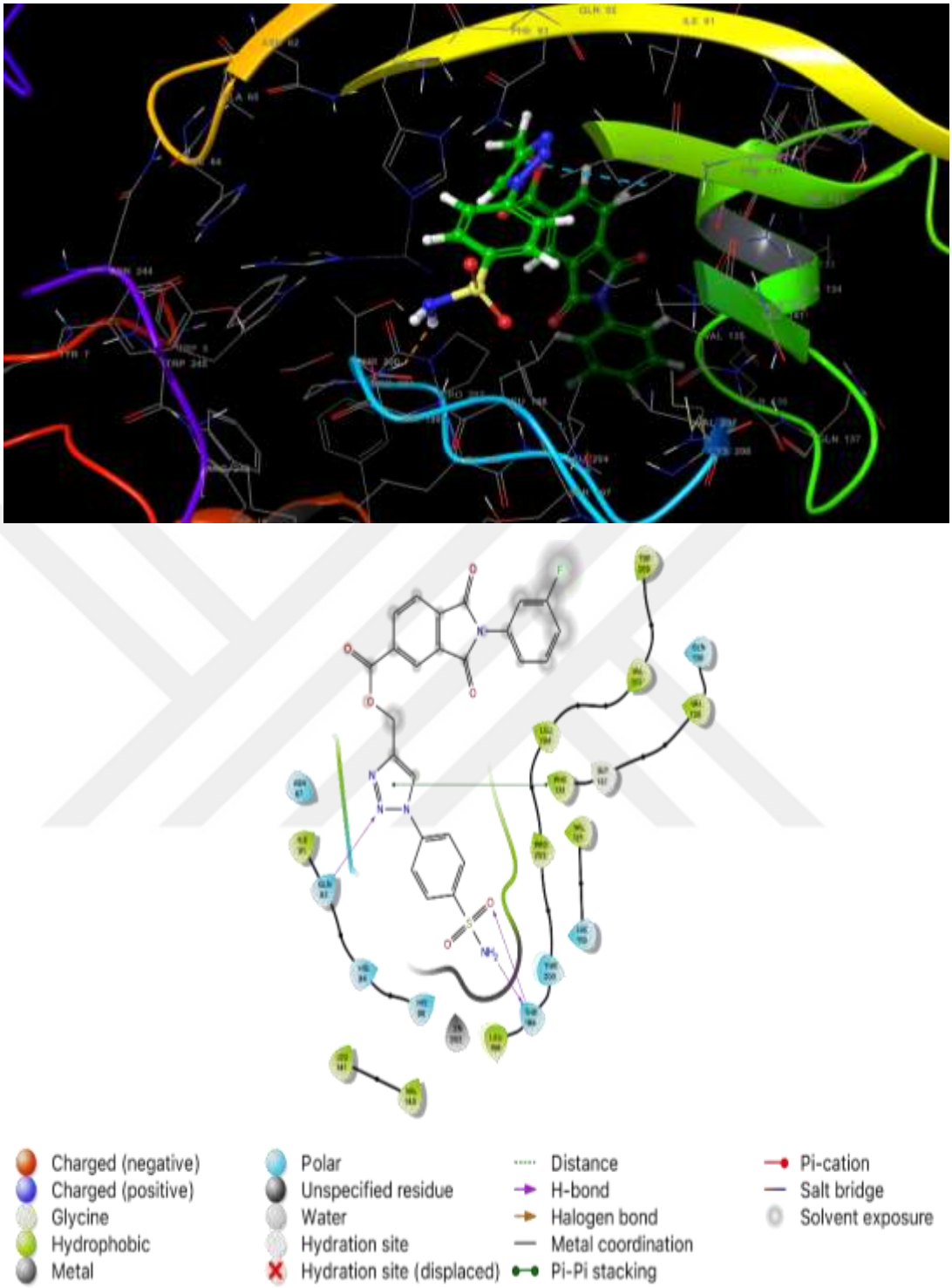


Figure 4.2. The 3D ligand interaction diagram of hCA II (PDB code 4FU5) with compound 7e (top) and 2D docking pose of compound 7e with the key amino acids within the binding pocket of the 4FU5 (bottom).

CHAPTER 5. SUGGESTIONS

A new series of 1,2,3-triazole bearing sulfonamide 7a-l derivatives have been synthesized utilizing click reaction and screened for their antibacterail activitis. The prepared compounds showed significant potent inhibitory activity against two CAs isoforms including hCA I and hCA II. Among the synthesized compounds, compound 7d showed potency inhbation against hCA I with Ki value of 20.92 ± 2.60 nm while 7e showed potent activity against hCA II with Ki value of 9.72 ± 1.91 nm. Our significant results can be used as a start point for further discovery of triazole bearing compounds that have potent antibacterial activity in which can be enhancing the drug discovery and medicinal chemistry researchs.

REFERENCES

[1] Alanzy, A., Bakhotm, D., Abdel-Rahman, R., Design, Synthesis, Chemistry and Biological Evaluation of Some Polyfunctional Heterocyclic Nitrogen System. International Journal of Organic Chemistry, Vol. 10, 39-62, 2020.

[2] Kumari, M., Tahlan, S., Narasimhan, B., Ramasamy, K., Meng, S., Lim, Adnan, S., Ali Shah, Mani, V., Kakkar, S., Synthesis and biological evaluation of heterocyclic 1,2,4-Triazole scaffolds as promising pharmacological agents, BMC Chemistry, Vol. 15, 2021.

[3] Lauria, A., Delisi, R., Mingoia, F., Terenzi, A., Martorana, A., Barone, G., Maria, A., Almerico, 1,2,3-Triazole in heterocyclic compounds, endowed with biological activity, through 1,3-dipolar cycloadditions, European Journal of Organic Chemistry, Vol. 2014, 3289–3306.

[4] Monda, S., Malakar, S., Synthesis of Sulfonamide and their synthetic and therapeutic applications: recent advances. Tetrahedron, Vol. 76, 131662, 2020.

[5] Berber, N., Arslan, M., Vural, F., Ergun, A., Gençer, N., Arslan, O., Synthesis of new series of thiazol-(2(3H) -ylideneamino) benzenesulfonamide derivatives as carbonic anhydrase inhibitors. Journal of Biochemical and Molecular Toxicology, Vol. 34, 22596, 2020.

[6] Tan, A., Kizilkaya, S.,Gunduz, B., and Kara, Y., Synthesis and optical properties of some isoindole-1,3-dione compounds: Optical band gap, refractive index and absorbance band edge, Organic Communications, Vol. 11, 173-180, 2018.

[7] Silva, C., Santos, Romário, J., de Oliveira, Ronaldo N., de Oliveira, and Juliano, C., Rufino Freitas, 1,2,3- Triazoles: general and key synthetic strategies, Journal of Organic Chemistry, 2020.

[8] Abdelkader, N., Amer, D., Mouhamad, O., Ridha, Mokhtar, L., Boualem, Najet, L., Dienisa, R., H.A., HÃ©lio, A., Ricardo, M., F., Paz, A., Filipe, A., H., Multicomponent and 1,3-dipolar cycloaddition synthesis of triazole and isoxazole acridinedione/xanthenedione heterocyclic hybrids: cytotoxic effects on human cancer cells, Journal of Molecular Structure, Vol. 1217, 128325, 2020.

[9] Pokhodyloa,N., T., Tupychaka, A., M., Shyykaa, O., Ya., and Obushaka, M., D., Some Aspects of the Azide–Alkyne 1,3-Dipolar Cycloaddition Reaction, Journal of Organic Chemistry, Vol. 55, 1310-1321, 2019.

[10] Ram, S., Celik, G., Khloya, P., Vullo, D., Supuran, C., T., Sharma, P., Benzenesulfonamide bearing 1,2,4-triazole scaffolds as potent inhibitors of tumor associated carbonic anhydrase isoforms hCA IX and hCA XII, Bioorganic & Medicinal Chemistry, Vol. 22, 1873-1882, 2014.

[11] Berugest, M., Reissig, H., The Huisgen Reaction: Milestones of the 1,3-Dipolar Cycloaddition, German Chemical Society, Vol. 59, 12293-12307, 2020.

[12] Berg, R., Straub, B., Advancements in the mechanistic understanding of the copper-catalyzed azide–alkyne cycloaddition, Journal of Organic Chemistry, Vol. 9, 2715-2750, 2013.

[13] Gulevskava, A., Nemtseva, J., 1,3-Dipolar cycloaddition reactions of azomethine ylides and alkynes, Chemistry of Heterocyclic Compounds, Vol. 54, 1084-1107, 2018.

[14] Lebeau, A., Abrioux, C., Bénimèlis, D., Benfodd, Z., and Meffre, P., Synthesis of 1,4-disubstituted 1,2,3-triazole derivatives using click chemistry and their Src kinase activities, Journal of Medicinal Chemistry, Vol. 13, 40-48, 2017.

[15] Danese, M., Bon, M., Mari, G., Piccini, and Passerone, D., The reaction mechanism of the azide–alkyne Huisgen cycloaddition, The Journal of Physical Chemistry, Vol. 21, 19281, 2019.

[16] Balci, A., Arslan, M., Rifati, A., Nixh, Bilen, C., Ergun, A., Gençer, N., Synthesis and evaluation of N-heteroaryl substituted triazolo sulfonamides as carbonic anhydrase inhibitors, Journal of Enzyme Inhibition Medicinal Chemistry, Vol. 30, 377-382, 2015.

[17] Das, R., Majumdar, N., and Lahir, A., A review on 1,3-Dipolar cycloaddition reactions in bioconjugation and its importance in pharmaceutical chemistry, International Journal of Research in Pharmacy and Chemistry, Vol. 4, 467- 472, 2014.

[18] Mandal, D., Pericyclic reactions: Introduction, classification, and the Woodward–Hoffmann rules, Pericyclic Chemistry Orbital Mechanisms and Stereochemistry, 63-106, 2018.

[19] Sharma, P., Niggula, P., Kumar, Kishna, R., Senwar, Forero-Doria, O., F., Fabiane, M., Nachtigall, Leonardo, S., Santos, and Shankaraiah, N., Effect of Sulfamic Acid on 1,3-Dipolar Cycloaddition Reaction: Mechanistic Studies and Synthesis of 4-Aryl-NH-1,2,3-triazoles from Nitroolefins, Journal of Brazilian Chemistry Society, Vol. 28, No. 4, 589-597, 2017.

[20] Ostrovskis, P., Chandra, M., R., Volla, Turks, M., Markovic D., Application of metal free click chemistry in biological studies, Current Organic Chemistry, Vol. 17, 610-640, 2013.

[21] Totobenazara, J., Burke, A., J., New click-chemistry methods for 1,2,3-triazoles synthesis: recent advances and applications, Tetrahedron Letters, Vol. 56, 2853-2859, 2015.

[22] Hou, J., Liu, X., Shen, J., Zhao, G., George P., Wang, The impact of click chemistry in medicinal chemistry, Expert Opinion on Drug Discovery, Vol. 7, 489-501, 2012.

[23] Sandip, G., Agalave, Suleman, R., Maujan, Vandana, S., Pore, Click Chemistry: 1,2,3-Triazoles as Pharmacophores, Chemistry: An Asian Journal, Vol. 6, 2696-2796, 2011.

[24] Rani, A., Singh, G., Singh, A., Maqbool, U., Kaur, G., and Singh, J., CuAAC ensembled 1,2,3-triazole-linked isosteres as pharmacophores in drug discovery: review, Royal Society Chemistry Advance, Vol. 10, 5610, 2020.

[25] Sethiy, A., Sahib, N., and Agarwal, S., Role of Click Chemistry in Organic Synthesis, 2021.

[26] Atilla, M., Tasdelen, Kiskan, B., Yagci, Y., Externally stimulated click reactions for macromolecular syntheses, Progress in Polymer Science, Vol. 52, 19-78, 2016.

[27] Shafran, E.,A., Bakulev, V.,A., Rozin, Yu., A., and Shafran, Yu., M., Condensed 1,2,3-Triazoles, Chemistry of Heterocyclic Compounds, Vol. 44, 104-1069, 2008.

[28] Totobenazara, J., Burke, A., J., New click-chemistry methods for 1,2,3-triazoles synthesis: recent advances and applications, Tetrahedron Letters, Vol. 56, 2853-2859, 2015.

[29] Bozorova, K., Zhao, J., Ais, H., A., 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry, Bioorganic & Medicinal Chemistry, Vol. 27, 3511-3531, 2019.

[30] Kharb, R., Chander, P., Sharma & Shahar, M., Yar, Pharmacological significance of triazole scaffold, Journal of Enzyme Inhibition and Medicinal Chemistry, Vol. 26, 1-21, 2011.

[31] Yatin, J., Mange, Arun, M., Isloor, Shridhar, M., Shrikrishna, I., Hoong-Kun, F., Synthesis and antimicrobial activities of some novel 1,2,4-triazole derivatives. Arabian Journal of Chemistry, Vol. 6, 177-181, 2013.

[32] Kılıcaslan, S., Arslan, M., Ruya, Z., C., Bilen, Ç., Ergün A., E., Gençer, N., and Arslan, O., A., Synthesis and evaluation of sulfonamide-bearing thiazole as carbonic anhydrase isoforms hCA I and hCA II, Journal of Enzyme Inhibition and Medicinal Chemistry, Vol. 31, 1300-1305, 2016.

[33] Rajabi-Moghaddam, H., Naimi-Jamal, R., & Tajbakhsh, M., Fabrication of copper (II)-coated magnetic core-shell nanoparticles. Fe_3O_4@ SiO_2-2-aminobenzohydrazide and investigation of its catalytic application in the synthesis of 1,2,3-triazole compounds, Nature Research, Vol. 11, 2073, 2021.

[34] Türkeş, C., Arslan, M., Demir, Y., Çoçaj, L., Rifat, A., Nixha, Beydemir, Ş., Synthesis, biological evaluation and in silico studies of novel N-substituted phthalazine sulfonamide compounds as potent carbonic anhydrase and acetylcholinesterase inhibitors, Bioorganic Chemistry, Vol. 89, 103004, 2019.

[35] Janam, R., Singh, 1,2,3- Triazole derivatives as possible anti-inflammatory agents, Rasayan Journal of Chemistry, Vol. 2, 706-708, 2009.

[36] Maria, O., Parasca, Gheata, F., Panzariu, A., Geangalau, I., Profire, L., Importance of sulfonamide moiety in current and future therapy, Journal of the Medical- Surgical, Vol. 117, 558-564, 2013.

[37] Abdul Qadir, M., Ahmed, M., Iqbal, M., Synthesis, Characterization, and antibacterial activities of novel sulfonamides derived through condensation of amino group containing drugs, amino acids, and their analogs, BioMed Research International, page 7, 2015.

[38] Pushpa, K., Kumar, Vedavathi, P., Venkata, K., Subbaiah, Venkata, D., Ramana, and Naga, C., Raju, Design, synthesis, spectral characterization, and bioactivity evaluation of new sulfonamide and carbamate derivatives of 5- Nitro-1H-indazole, Organic Communications, Vol. 10, 239-249, 2017.

[39] Kolaczek, A., Fusiarz, I., Lawecka, J., Branowska, D., Biological activity, and synthesis of sulfonamide derivatives: a brief review, Chemik, Vol. 68, 620-628, 2014.

[40] Hulya, G., Akıncıoglu, A., leyman, S., Goksu, Gulcin, I., Carbonic anhydrase inhibitory properties of phenolic sulfonamides derived from dopamine related compounds, Arabian Journal of Chemistry, Vol. 29, 2014.

[41] Supuran, C., T., Maresca, A., Gregaň, F., and Remko, M., Three new aromatic sulfonamide inhibitors of carbonic anhydrases I, II, and XII, Jounal of Enzyme Inhibition and Medicinal Chemistry, Vol. 28, 289-293, 2013.

[42] Gokcen, T., Gulcin, I., Ozturk, T., and Goren, A., C., A class of sulfonamides as carbonic anhydrase I and II inhibitors, Journal of Enzyme Inhibition and Medicinal Chemistry, Vol. 31, 180-188, 2016.

[43] Gokcen, T., Melike, T., A., Topal,A., M., Gulcin, I., Ozturk, T., and Goren. A., C., Synthesis of some natural sulphonamide derivatives as carbonic anhydrase inhibitors, Organic Communications, Vol. 10, 15-23, 2017.

[44] Supuran, C., T., and Scozzafava, A., Carbonic anhydrase inhibitors: Aromatic sulfonamides and disulfonamides act as efficient tumor growth inhibitions, Journal of Enzyme Inhibition, Vol. 15, 597-610, 2000.

[45] Nurpelin, B., Sağlık, Osmaniye, D., Arcar, U., Çevik, Levent, S., Kaya, B., Çavuşoğlu, Büyükemir, O., Nezir, D., Burak, A., Karaduman, Özkay, Yusuf, Savaş, A., Koparal, Beydemir, Ş., Asım, Z., Kaplancıklı, Synthesis, characterization, and carbonic anhydrase I and II inhibitory evaluation of new sulfonamide derivatives bearing dithiocarbamate. European Journal of Medicinal Chemistry, Vol. 198, 112392, 2020.

[46] Cakir, U., Ibrahim, H., Uğraş, Ozensoy, O., Sinan, S., Arslan, O., In Vitro Inhibition Effects of some New Sulfonamide Inhibitors on Human Carbonic Anhydrase I and II, Journal of Enzyme Inhibition and Medicinal Chemistry, Vol. 19, 257-261, 2004.

[47] Gokcen, T., Gulcin, I., Ozturk, T., Goren, A., C., A class of sulfonamides as carbonic anhydrase I and II inhibitors, Journal of Enzyme Inhibition and Medicinal Chemistry, Vol. 31, 180-188, 2016.

[48] Barua, H., Bhagat, N., Toraskar, M., P., Study of binding interactions of human carbonic anhydrase XII, Intrenational Journal of Current Pharmaceutical Research, Vol. 9, 118-125, 2017.

[49] Ricardo, A., W., Filho, N., Mieder, A., T., Forster, P., & Ronaldo, N., de Oliveir, Imidazole-promoted synthesis of N-substituted phthalimide from N,N-disubstituted ureas in solvent less conditions, Synthetic Communications, Vol. 43, 1571-1576, 2013.

[50] Lamie, Ph. F., Philoppes, J., N., El-Gendy, A., O., Rarova, L., and Gruz, J., Design, synthesis, and evaluation of novel phthalimide derivatives as in vitro anti-microbial, antioxidant and anti-inflammatory agents, Molecules, Vol. 20, 16620-16642, 2015.

[51] Kushwahaa, N., Kaushik, D., Recent Advances and Future Prospects of Phthalimide Derivatives, Journal of Applied Pharmaceutical Science Vol. 6, 159-171, 2016.

[52] Chemler, Sh., R., Copper catalysis in organic synthesis, Journal of Organic Chemistry, Vol., 11, 2252-2253, 2015.

[53] Baqi,Y., Recent Advances in Microwave-Assisted Copper-Catalyzed Cross-Coupling Reactions, Catalysts, Vol. 11, 46, 2021.

[54] Göcer, H., Akıncıoğlu, A., Göksu, S., G., Gülçin, I., Carbonic anhydrase inhibitory properties of phenolic sulfonamides derived from dopamine related compounds, Arabian Journal of Chemistry, Vol. 10, 398-402, 2017.

[55] Claudiu, T. S. Carbonic anhydrase inhibitors and activators for novel therapeutic applications, Future Medicinal Chemistry, Vol. 3, 2011.

[56] James,M. McKiernan, Ralph,B, Neil, H. Bander, Michael, D. Stifelman, Aaron, E. Katz, M. Chen, Carl, A. Olsson and Ihor, S. Sawczuk, Expression of the tumor-associated gene MN: a potential biomarker for human renal cell carcinoma, American Association for Cancer Research, Vol. 57, 2362–2365, 1997.

[57] Supuran, C., T., Scozzafava, A., Carbonic anhydrase inhibitors and their therapeutic potential, Expert Opinion on Therapeutic Patents, Vol. 10, 575-600, 2000.

[58] Innocenti, A., Gülçin, I., Scozzafava, A., Supuran, C., T., Carbonic anhydrase inhibitors. Antioxidant polyphenols effectively inhibit mammalian isoforms I-XV, Bioorganic & Medicinal Chemistry Letters, Vol. 20, 5050-5053, 2010.

[59] Supuran, C., T., Carbonic anhydrases: novel therapeutic applications for inhibitors and activators, Nature Reviews Drug Discovery, Vol. 7, 167-181, 2008.

[60] Maren, T. H., Carbonic anhydrase: chemistry, physiology, and inhibition, The American Physiological Society, Vol. 47, 595-781, 1967.

[61] Esbaugh, A., J., Tufts, B., L., The structure and function of carbonic anhydrase isozymes in the respiratory system of vertebrates, Respiratory Physiology & Neurobiology, Vol. 154, 185-198, 2006.

[62] Nishimori, I., Minakuchi,T., Onishi, S., Vullo, D., Cecchi, A., Scozzafzva, A., Supuran, C., T., Carbonic anhydrase inhibitors: Cloning, characterization, and inhibition studies of the cytosolic isozyme III with sulfonamides, Bioorganic & Medicinal Chemistry, Vol. 15, 7229-7236, 2007.

[63] Nishimori, I., Vullo, D., Innocenti, A., Scozzafava, A., Mastrolorenzo, A., Supuran, C., T., Carbonic anhydrase inhibitors. The mitochondrial isozyme VB as a new target for sulfonamide and sulfamate inhibitors, Medicinal Chemistry, Vol. 48, 7860-7866, 2005.

[64] Neri, D., Supuran, C., T., Interfering with pH regulation in tumours as a therapeutic strategy, Nature Review Drug Discovery, Vol. 10, 767-777, 2011.

[65] Svastova, E., Hulíková, A., Rafajová, M., Zat'ovicová, M., Gibadulinová, A., Casini, A., Cecchi,A., Scozzafava, A., Supuran, C., T., Pastorek, J., Pastorekova, S., Hypoxia activates the capacity of tumor-associated carbonic anhydrase IX to acidify extravehicular pH, FEBS Letters, Vol. 577, 439, 2004.

[66] Singer, M., Lopez, M., Laurent, F., Bornaghi, Innocenti, A., Vullo, D., Supuran, C., T., and Poulsen, S., Inhibition of carbonic anhydrase isozymes with benzene sulfonamides incorporating thio, sulfinyl and sulfonyl glycoside moieties, Cancer Research, Vol. 60, 7075, 2000.

[67] Ozensoy, O., G., Simone, G., De, Supuran, C., T., Drug design studies of the novel antitumor target's carbonic anhydrase IX and XII, Current Medicinal Chemistry, Vol. 17, 1516, 2010.

[68] Willkinson, B., Bornaghi, L., Houston, T., Innocenti, A., Vullo, D., Supuran, C., T., and Poulsen, S., Carbonic anhydrase inhibitors: Inhibition of isozymes I and II, and IX with Triazole- Linked O-Glycosides of benzene sulfonamides, Journal of Medicinal Chemistry, Vol. 50, 1651-1657, 2007.

[69] Yıldırım, A., Atmaca, U., Keskin, A., Topal, M., Çelik, M., Gülçin, l., Supuran, C., T., N-Acylsulfonamides strongly inhibit human carbonic anhydrase isoenzymes I and II, Bioorganic and Medicinal Chemistry, Vol. 15;23, 25982605, (2015).

[70] Gulçin, I., Taslimi, P., Sulfonamide inhibitors: a patent review 2013-present, Expert Opinion on Therapeutic Patents, Vol. 28, 541–549, 2018.

[71] Daniela, V., Franchi, M., Gallori, E., Pastorek, J., Scozzafava, A., Pastorekova, S., Supuran, C., T., Carbonic anhydrase inhibitors: inhibition of the tumor-associated isozyme IX with aromatic and heterocyclic sulfonamides, Bioorganic Medicinal Chemistry, Vol. 13, 1005-1009, 2003.

[72] Güleç, Ö., Arslan, M., Gencer, N., Ergun, A., Bilen, C., & Arslan, O., Synthesis and carbonic anhydrase inhibitory properties of new spiroindoline-substituted sulphonamide compounds. Archives of Physiology and Biochemistry, Vol. 123, 1381-3455, 2017.

[73] Supuran, C., T., & Scozzafava, A., Application of carbonic anhydrase inhibitors and activators in therapy, Expert Opinion on Therapeutic Patents, Vol. 12, 217, 2002.

[74] Supuran, C., T., & Scozzafava, A., Carbonic anhydrase inhibitors and their therapeutic potential, Expert Opinion on Therapeutic Patents, Vol. 10, 575-600, 2000.

[75] Jonna, L., Shen, B., Vihinen, M., Casini, A., Scozzafava, A., Supuran, C.T., Parkkila, A., K., Saarnio, J., Kivelä, A., Waheed, A., Sly, W., S., Parkkila, S., Characterization of CA XIII, a novel member of the carbonic anhydrase isozyme family, Journal of Biological Chemistry, Vol. 279, 2719-2727, 2004.

[76] Guerri,A., Briganti,F., Scozzafava, A., Supuran, C., T., Mangani, S., Mechanism of cyanamide hydration catalyzed by carbonic anhydrase II suggested by cryogenic X-ray diffraction, Biochemistry, Vol. 39,12391-12397, 2000.

[77] Coleman, J., E., Mechanism of action of carbonic anhydrase. Substrate, sulfonamide, and anion binding, Journal of Biological Chemistry, Vol. 242, 5212-5219, 1967.

[78] Tripp, B., C., Smith K., and Ferry, J., G., Carbonic anhydrase: new insights for an ancient enzyme, Journal of Biological Chemistry, Vol. 276, 48615-48618, 2001.

[79] Supuran, C.T, "Carbonic anhydrases: novel therapeutic applications for and activators. Natuer Reviews Drug Discovery, Vol. 7, 168-181, 2008.

[80] Alotaibi, F., Design, synthesis, and biological evaluation of novel estradiol triazole analogs targeting epidermal growth factor receptors in colorectal cancer, Public Research Access Institutional Repository and Information Exchange, 1189, 2017.

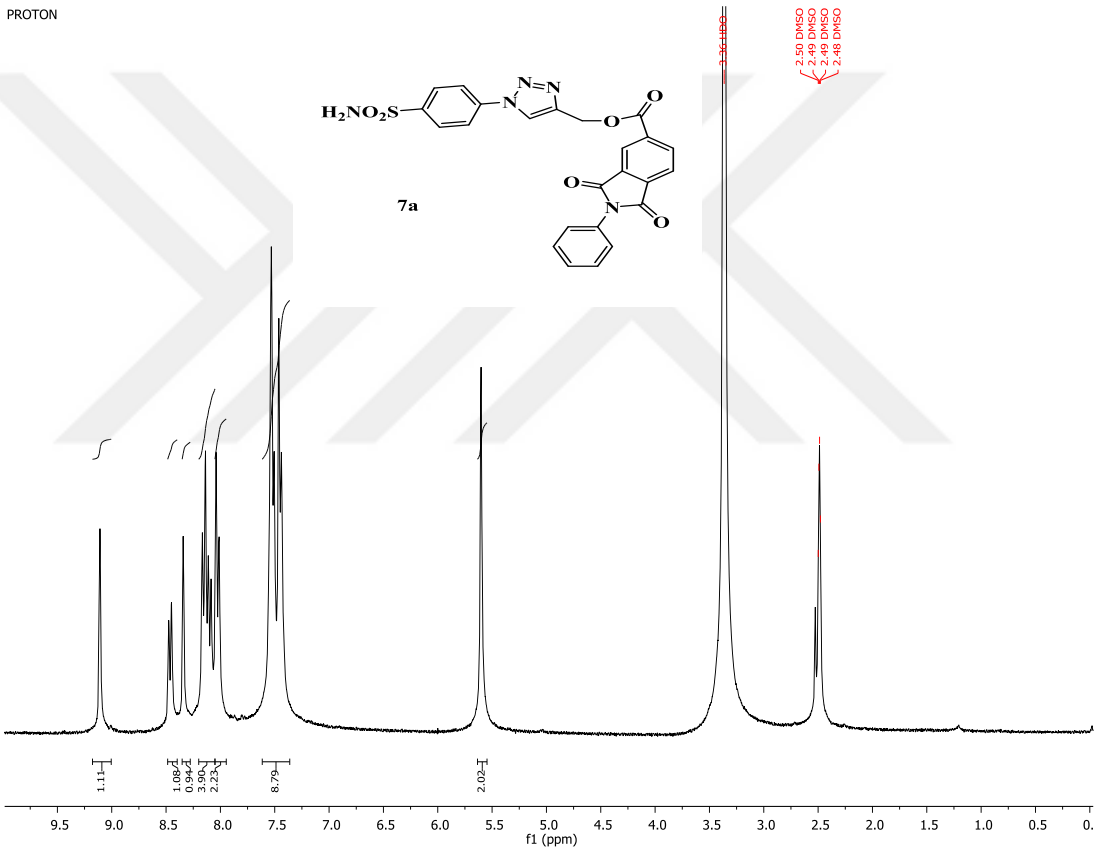
[81] Nebra, N., and Garcia-Aivarez, J., Recent progress of Cu- catalyzed azide-alkyne cycloaddition reactions (CuAAC) in sustainable solvents: glycerol, deep eutectic solvents, and aqueous media, Molecules, Vol., 26, 2020.

[82] Kushwaha, N., Kaushik, D., Recent advances, and future prospects of phthalimide derivatives, Journal of Applied Pharmaceutical Science, Vol. 6, 159-171, 2016.

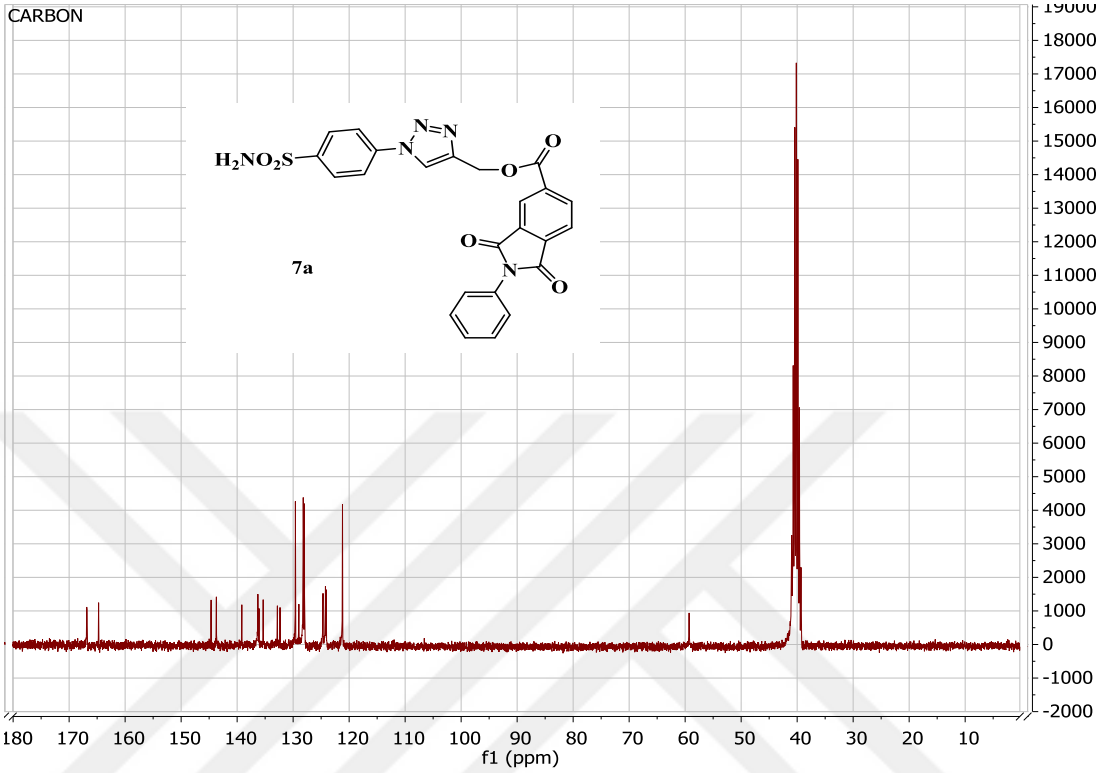
[83] Haldón, E., Carmen, M., Nicasio, Pérez, P., J., Copper- catalysed azide–alkyne cycloadditions (CuAAC), Organic Biomolecular Chemistry, Vol. 13, 9528-9550, 2015.

ANNEX

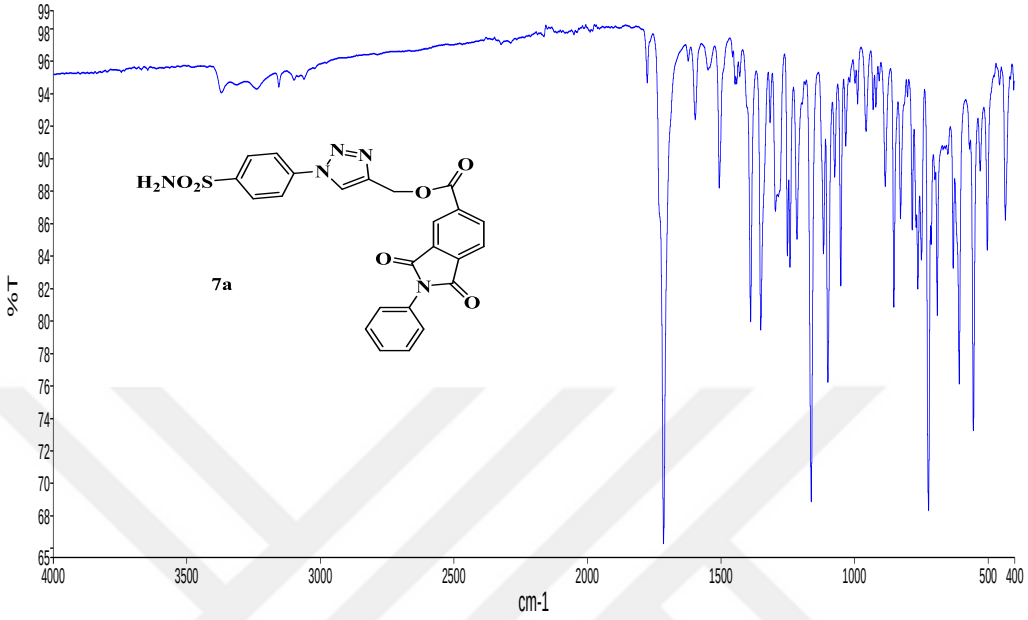
App 1: (1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 1,3-dioxo-2-phenylisoinodoline-5- carboxylate (7a).



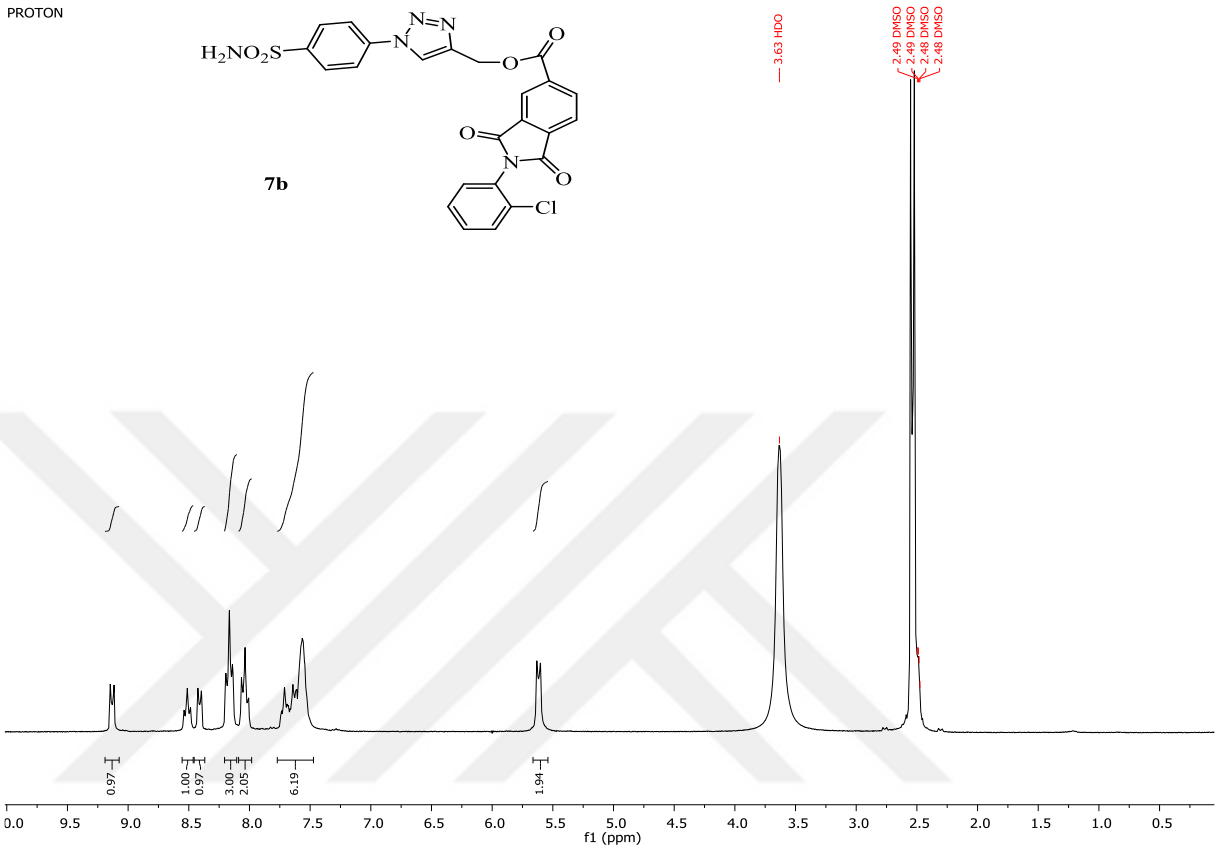
App 2: (1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 1,3-dioxo-2-phenylisoinodoline-5- carboxylate (7a).



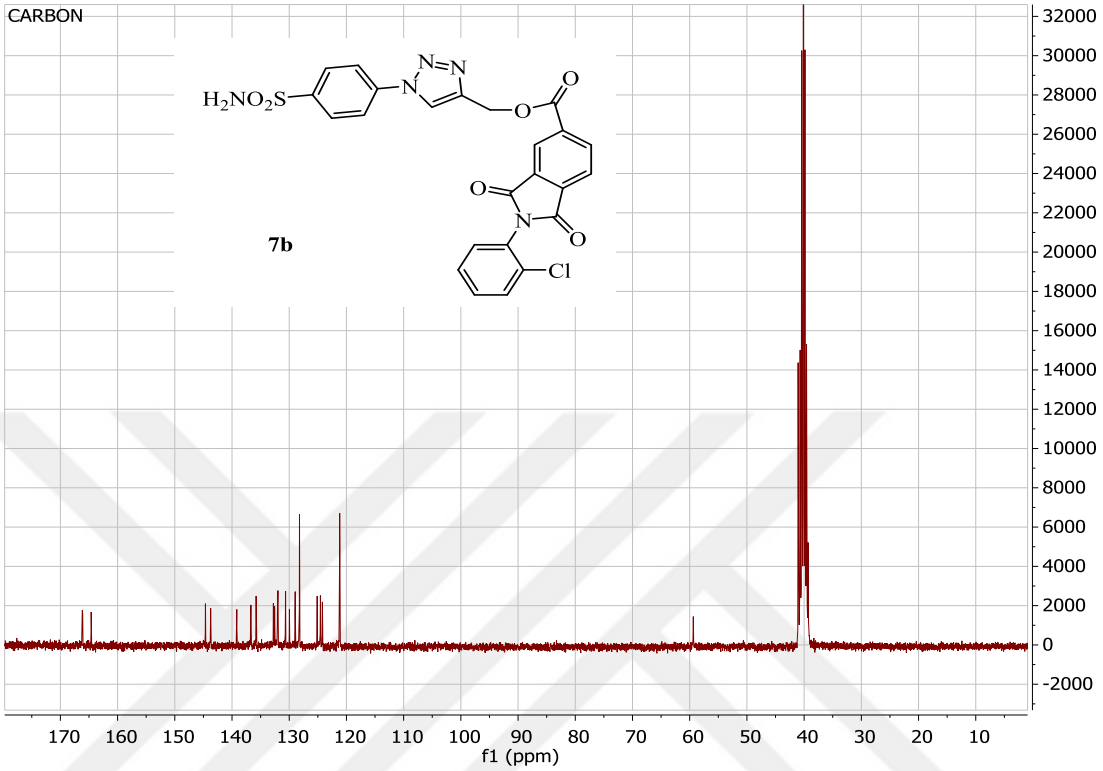
App 3: (1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 1,3-dioxo-2-phenylisoinodoline-5- carboxylate (7a).



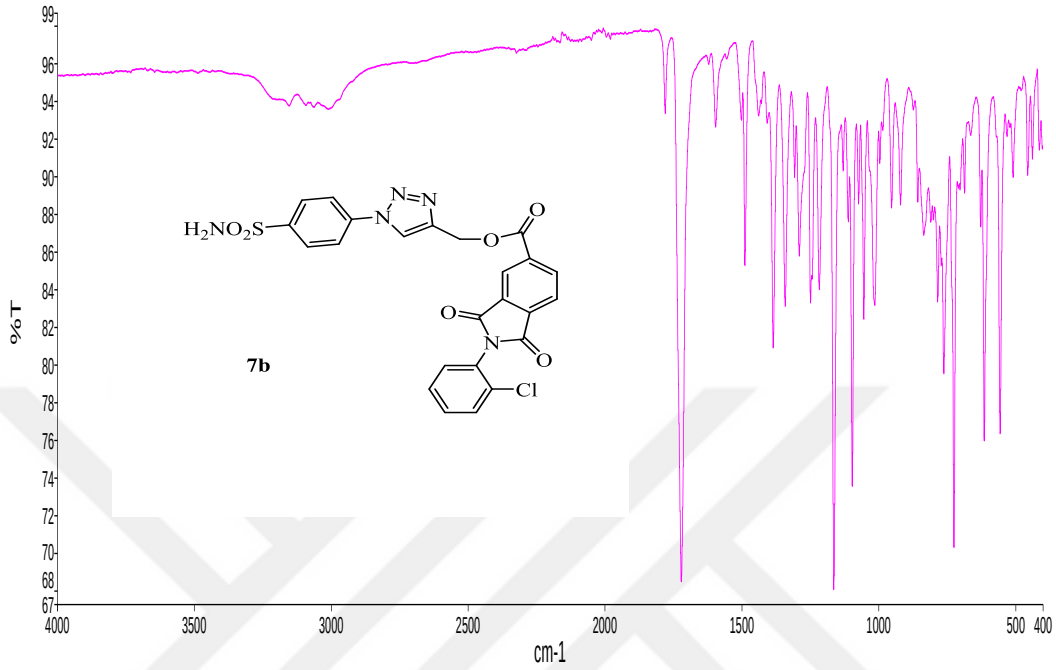
App 4: (1-(4-sulfamoylphenyl)-1H-1,2,3=triazol-4-yl) methyl 2-(2-chlorophenyl)-1,3-dioxoisoinodline-5-carboxylate (7b).



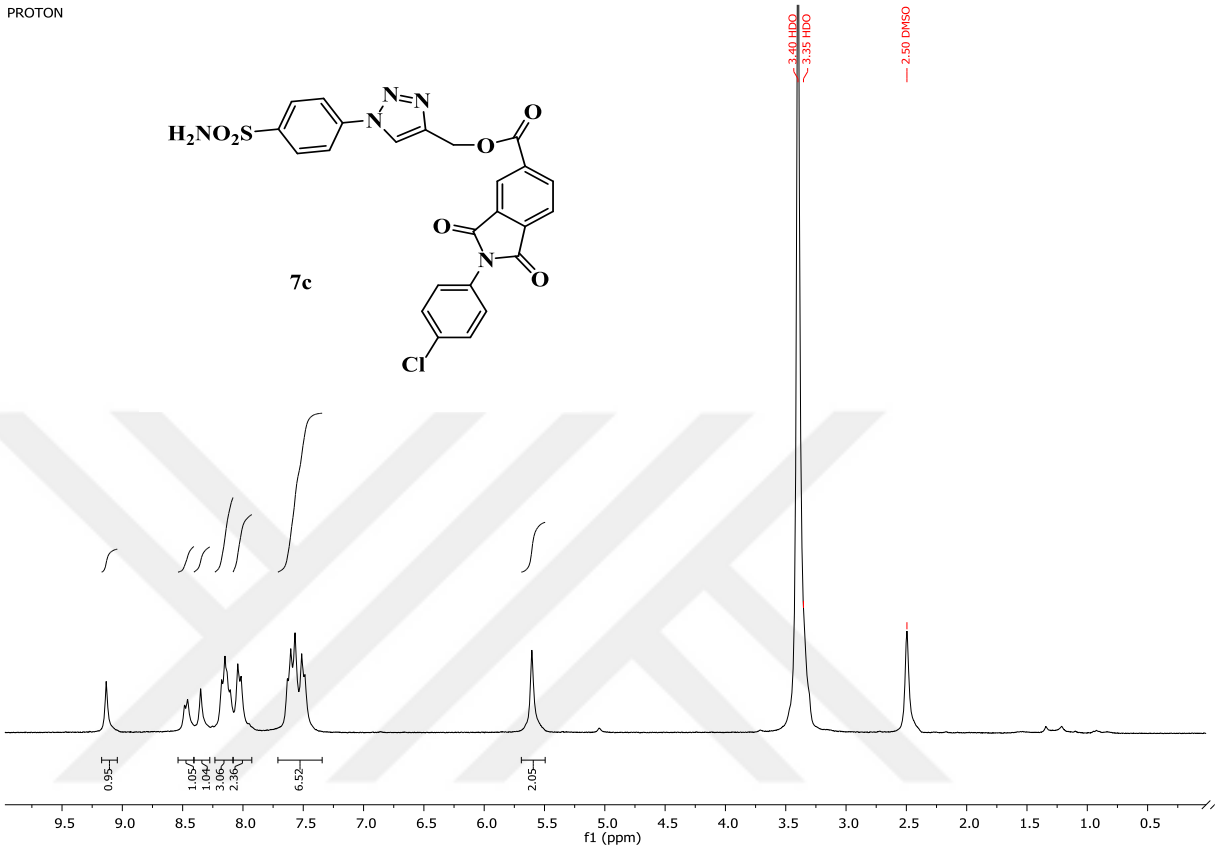
App 5: (1-(4-sulfamoylphenyl)-1H-1,2,3=triazol-4-yl) methyl 2-(2-chlorophenyl)-1,3-dioxoisoinodline-5-carboxylate (7b).



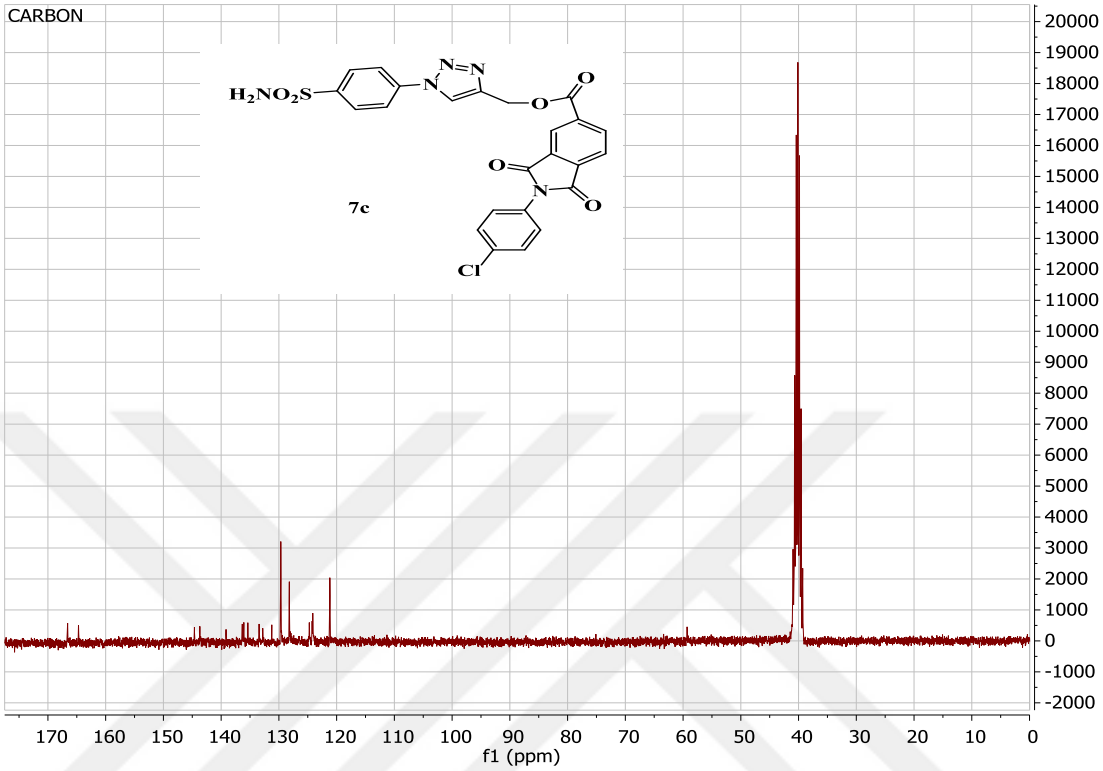
App 6: (1-(4-sulfamoylphenyl)-1H-1,2,3=triazol-4-yl) methyl 2-(2-chlorophenyl)-1,3-dioxoisoinodline-5-carboxylate (7b).



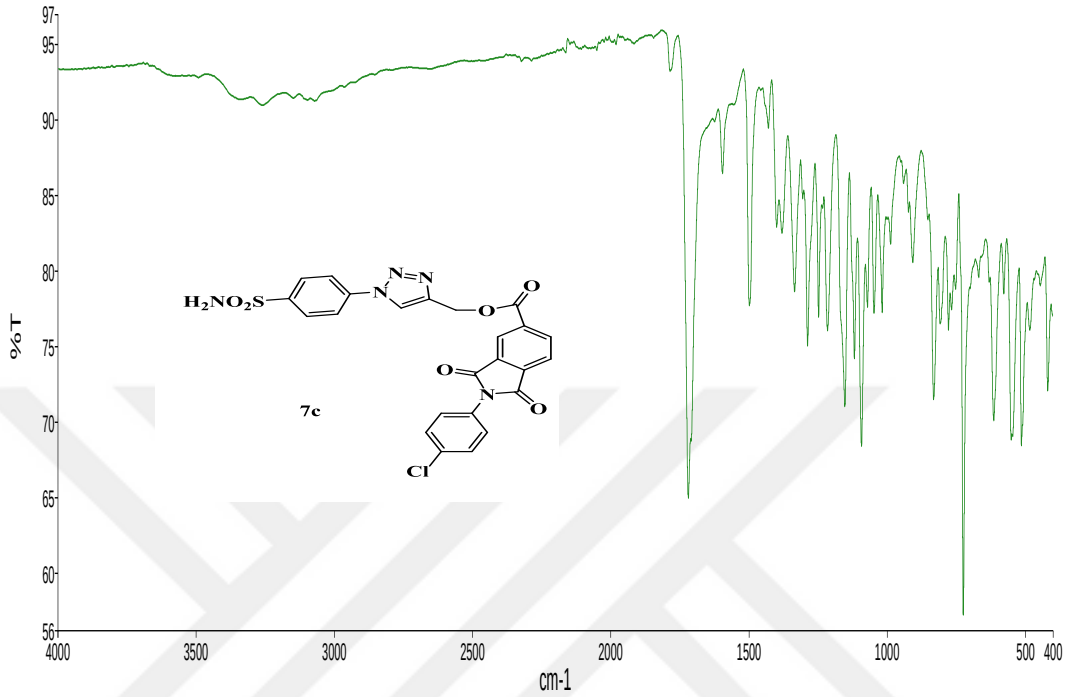
App 7: (1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(4-chlorophenyl)-1,3-dioxoisodoline-5-carboxylate (7c).



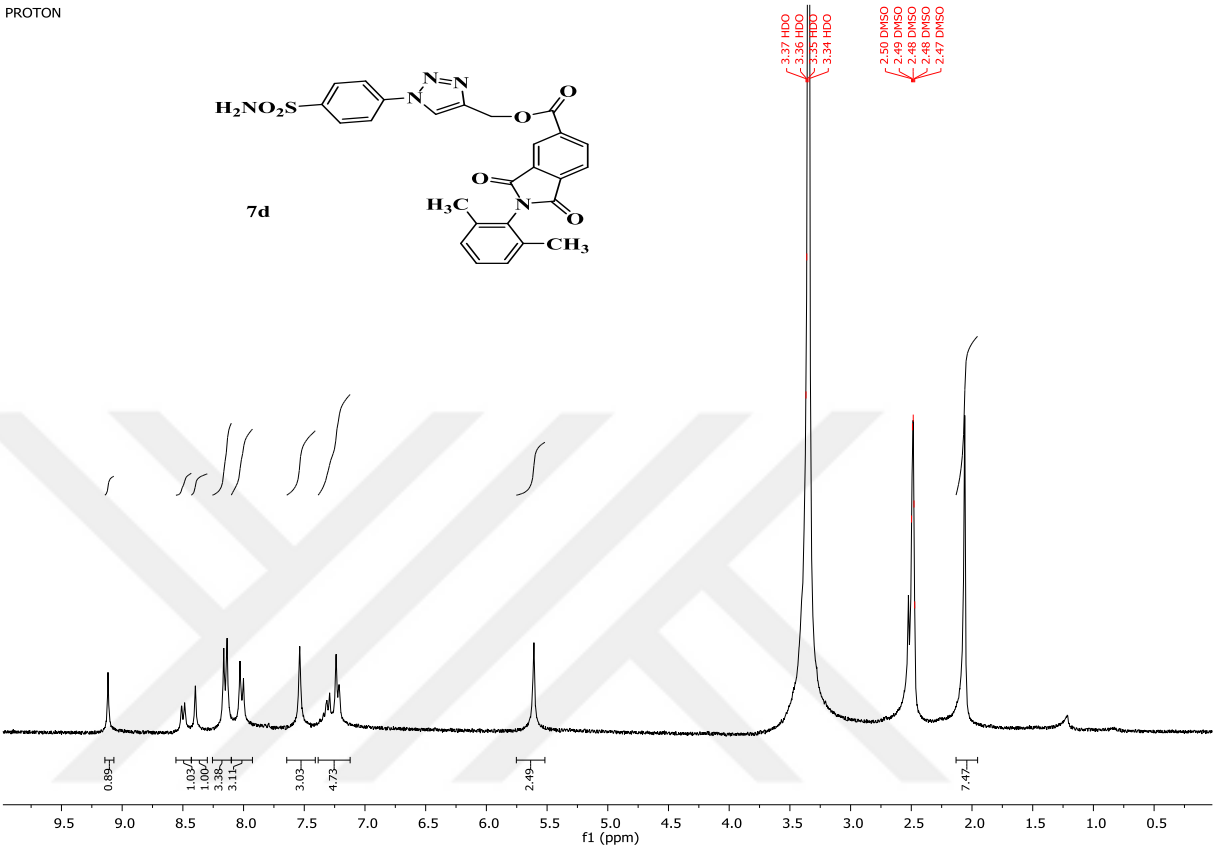
App 8: (1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(4-chlorophenyl)-1,3-dioxoisodoline-5-carboxylate (7c).



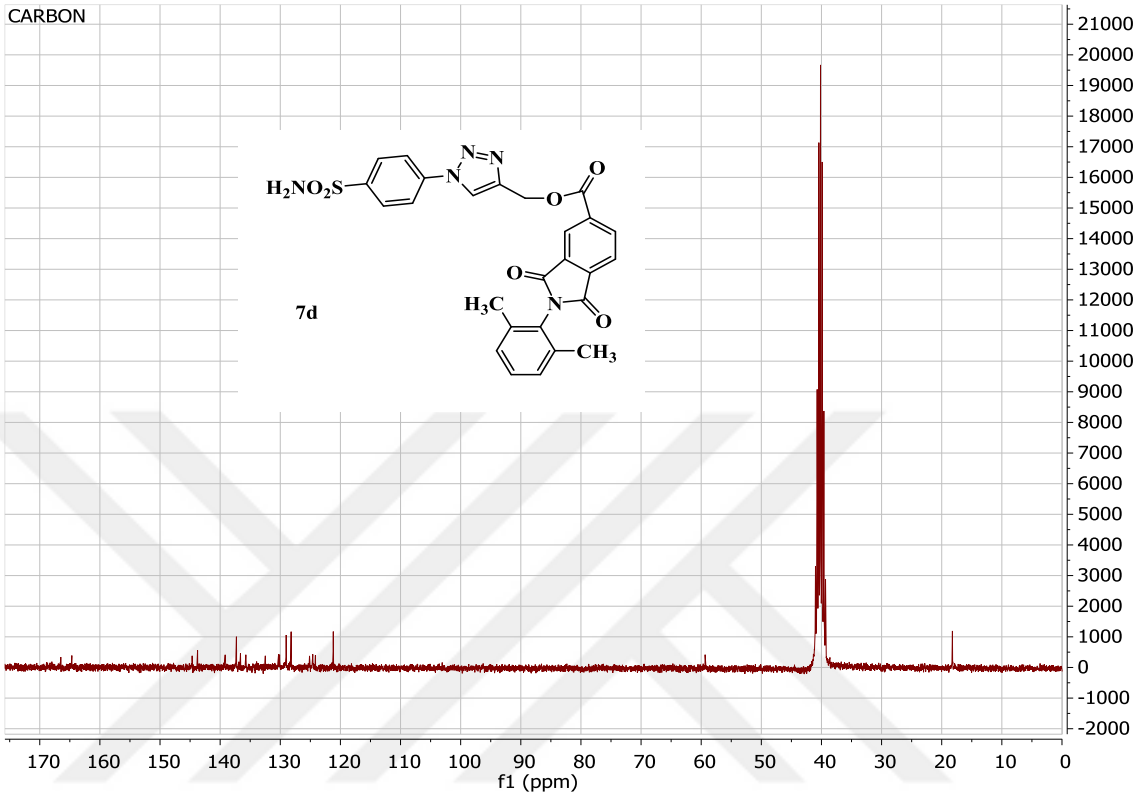
App 9: (1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(4-chlorophenyl)-1,3-dioxoisodoline-5-carboxylate (7c).



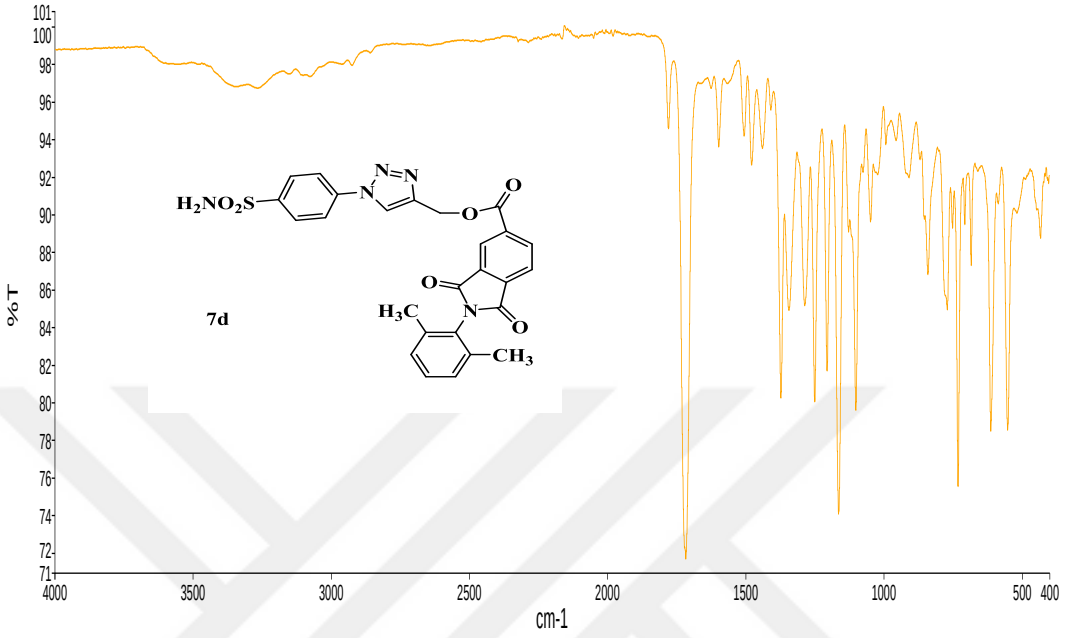
App 10: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(2,6-dimethylphenyl)-1,3-dioxoisoindoline-5-carboxylate (7d).



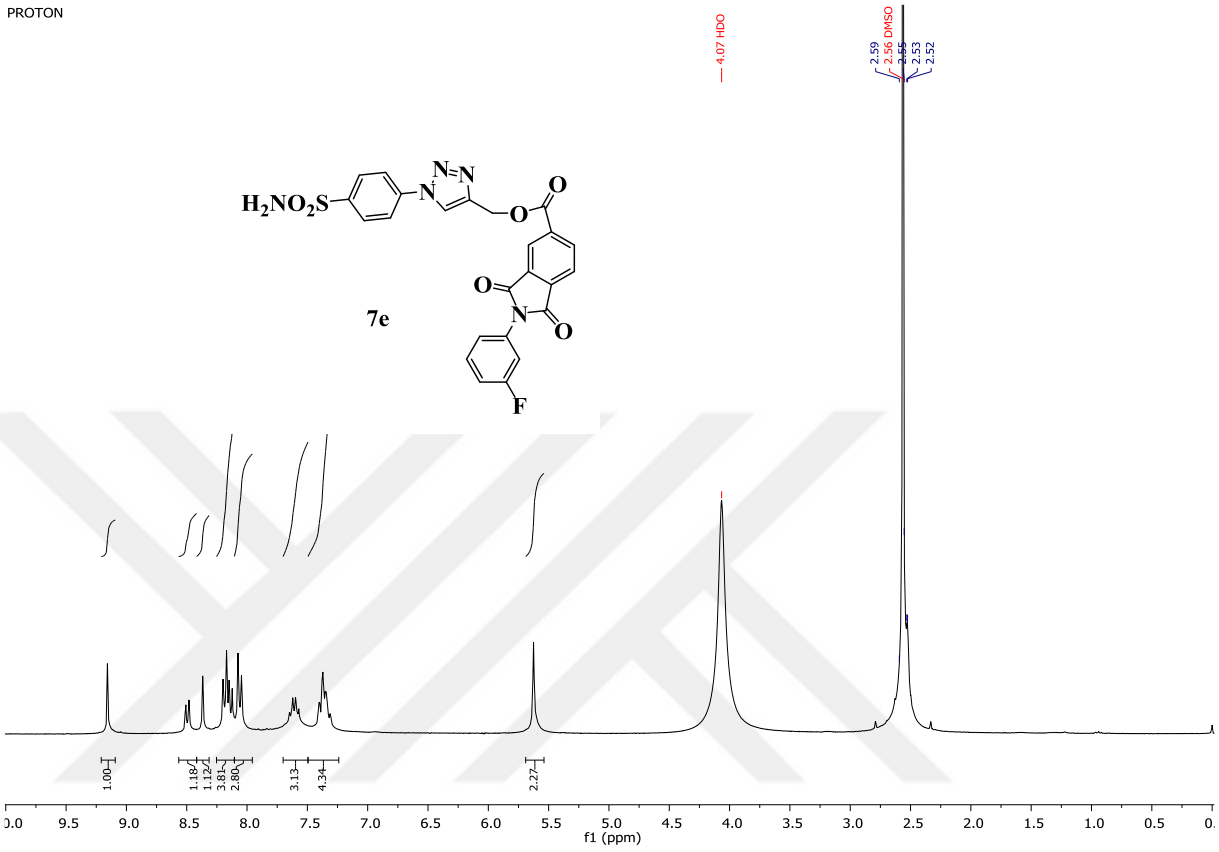
App 11: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(2,6-dimethylphenyl)-1,3-dioxoisoindoline-5-carboxylate (7d).



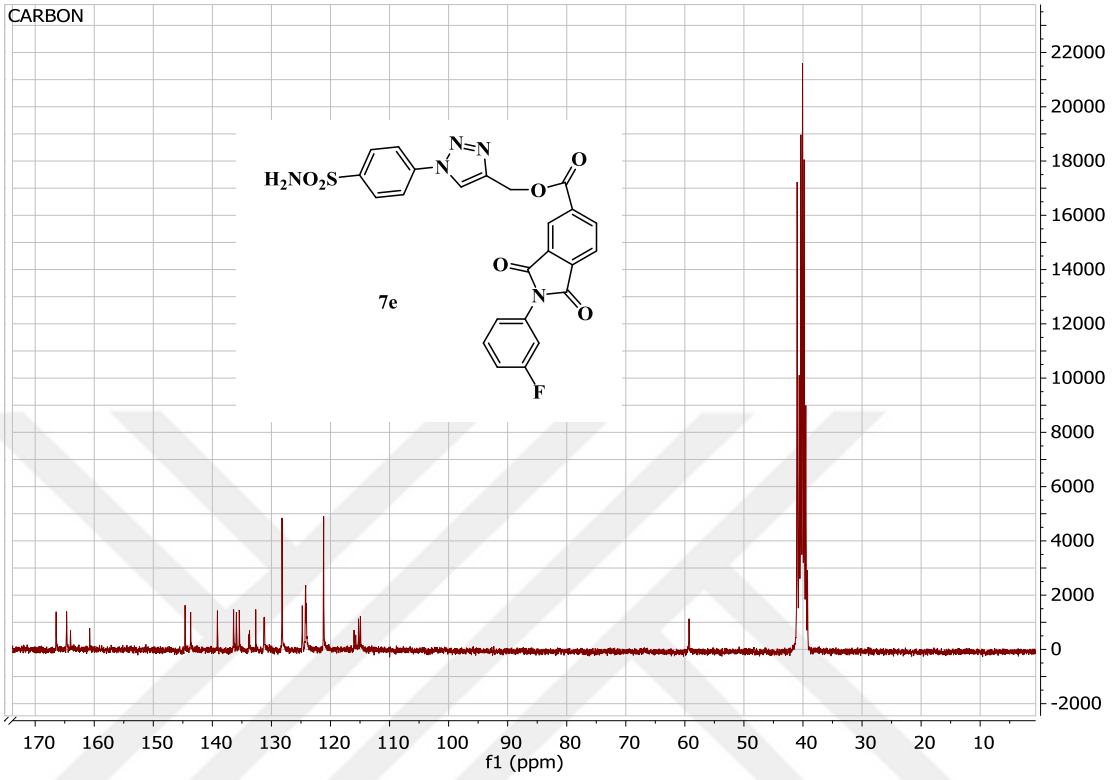
App 12: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(2,6-dimethylphenyl)-1,3-dioxoisoindoline-5-carboxylate (7d).



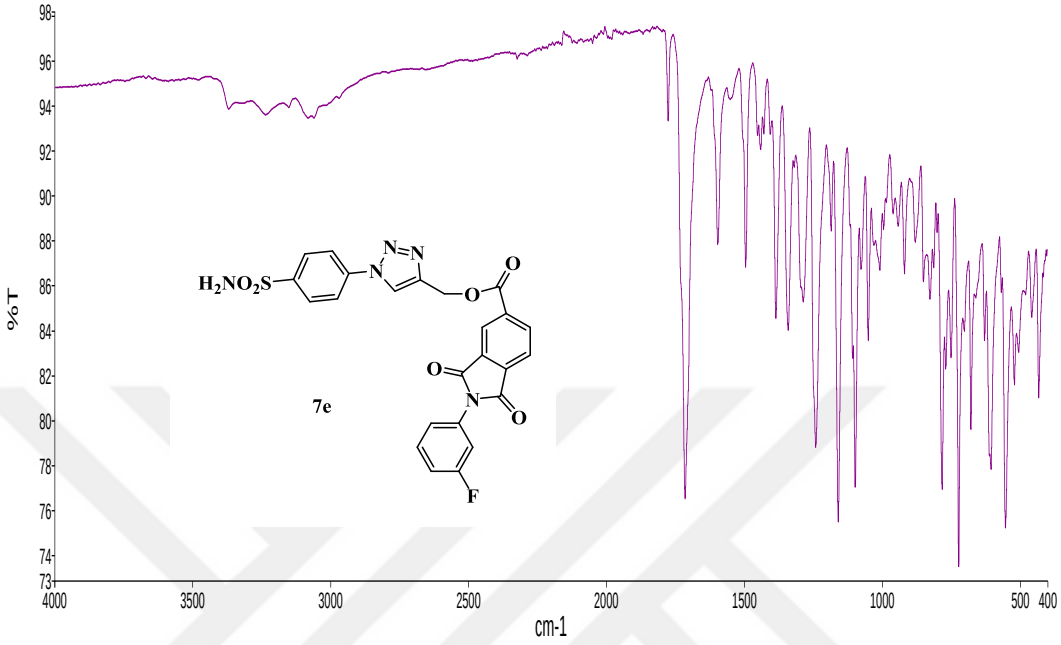
App 13: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(3-fluorophenyl)-1,3-dioxoisoindoline-5-carboxylate (7e).



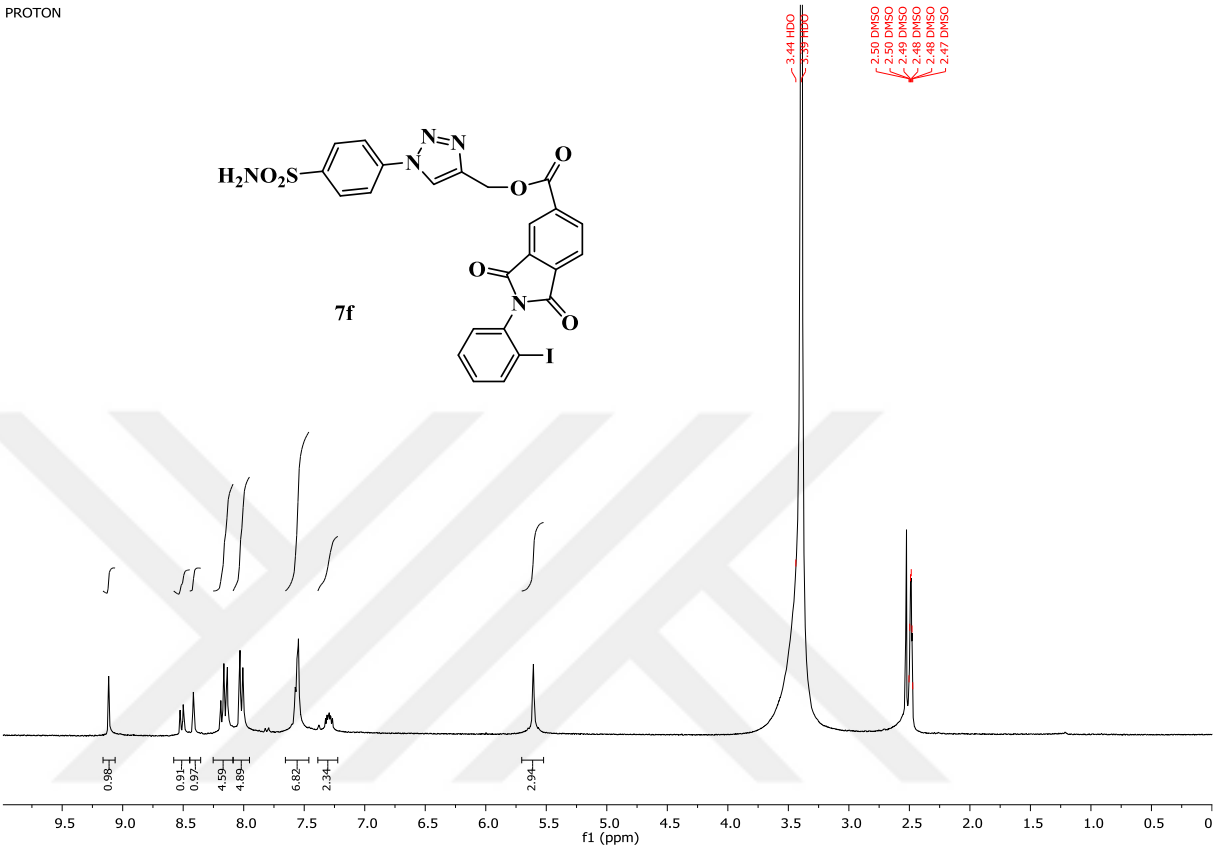
App 14: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(3-fluorophenyl)-1,3-dioxoisoindoline-5-carboxylate (7e).



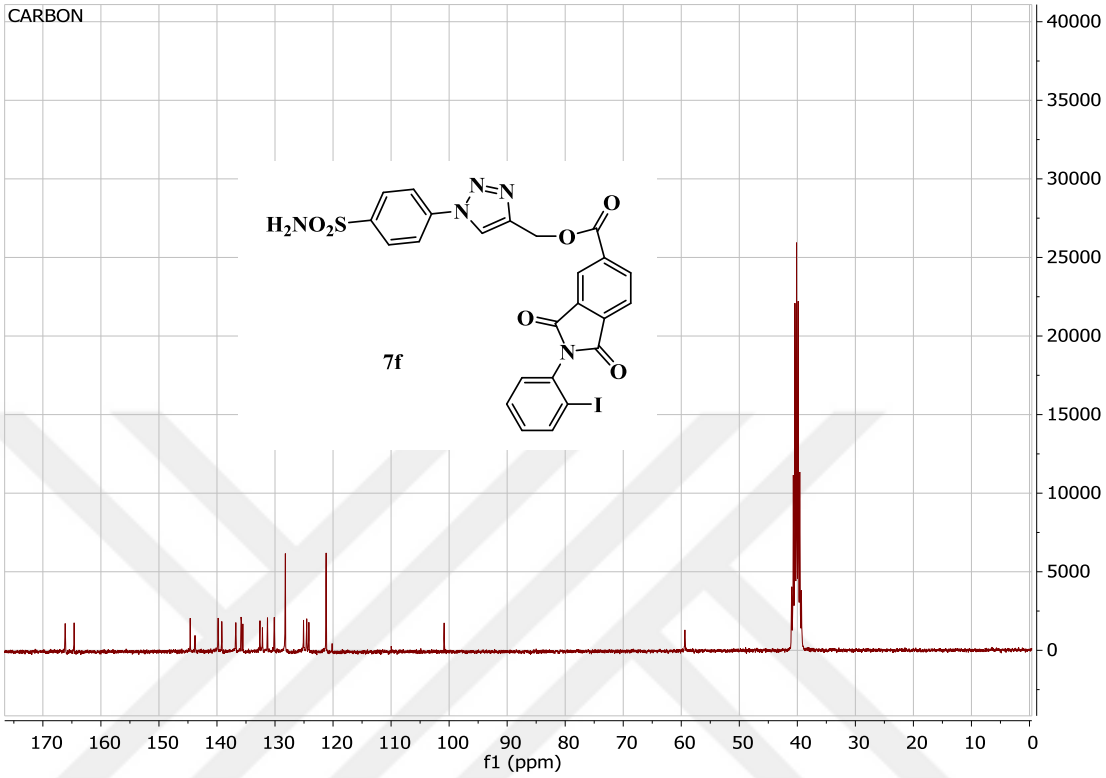
App 15: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(3-fluorophenyl)-1,3-dioxoisoindoline-5-carboxylate (7e).



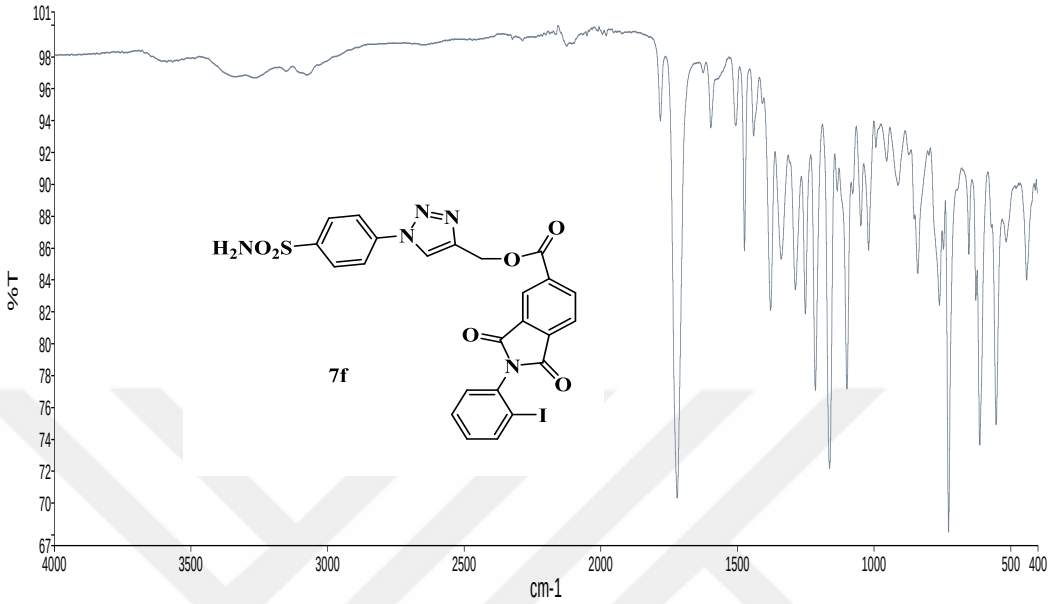
App 16: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(2-iodophenyl)-1,3-dioxoisoindoline-5-carboxylate (7f).



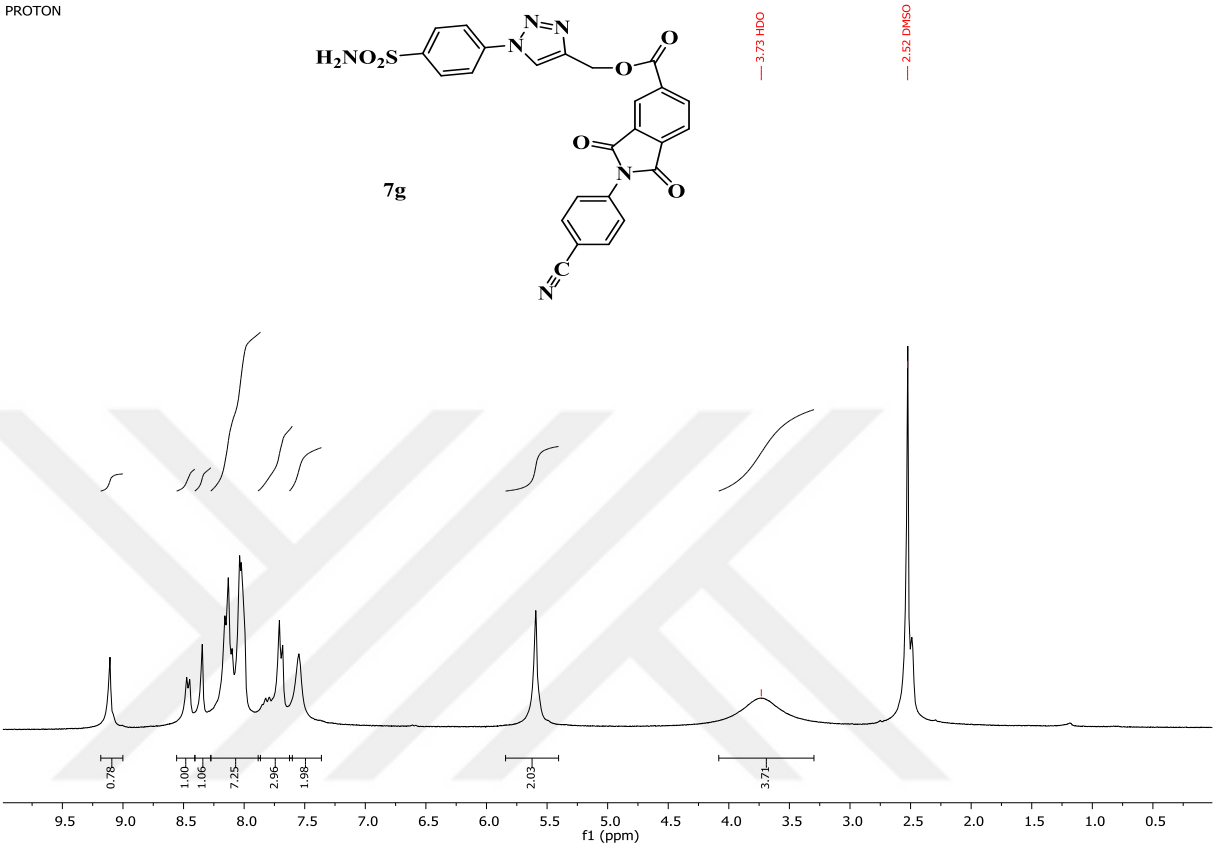
App 17: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(2-iodophenyl)-1,3-dioxoisoindoline-5-carboxylate (7f).



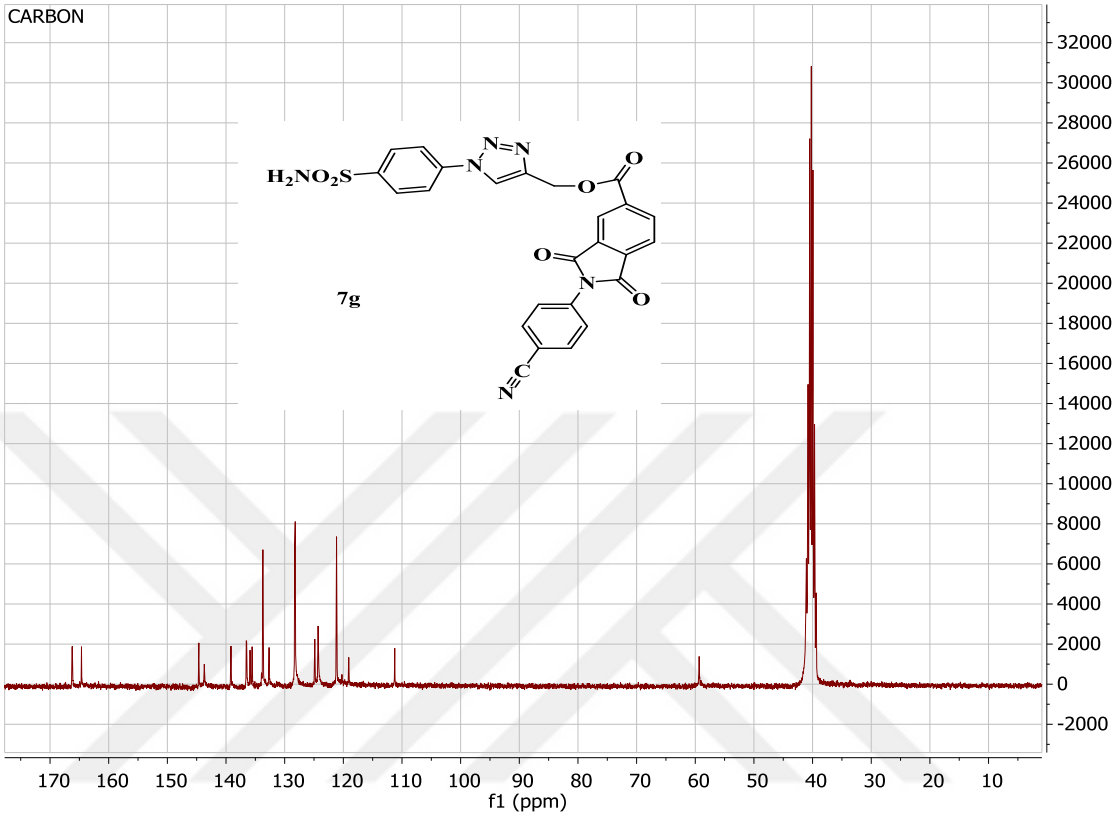
App 18: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(2-iodophenyl)-1,3-dioxoisoindoline-5-carboxylate (7f).



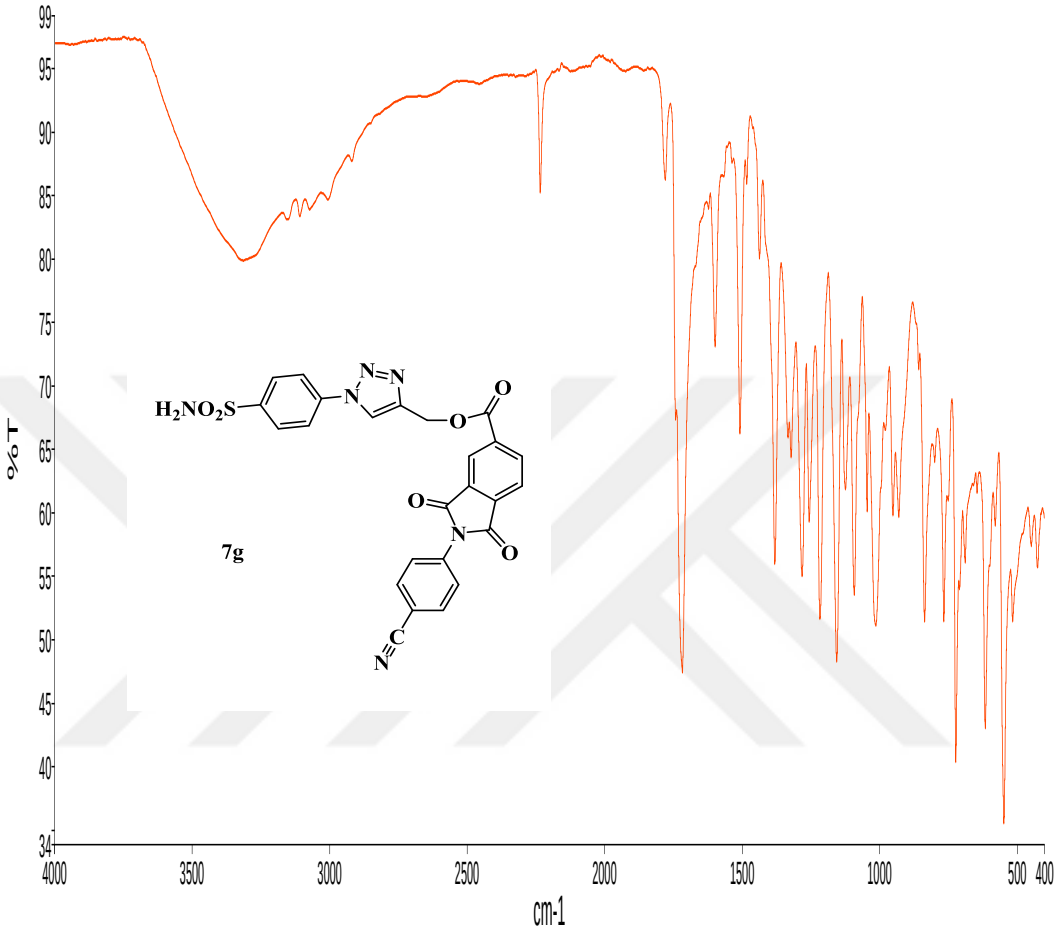
App 19: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(4-cyanophenyl)-1,3-dioxoisoindoline-5-carboxylate (7g).



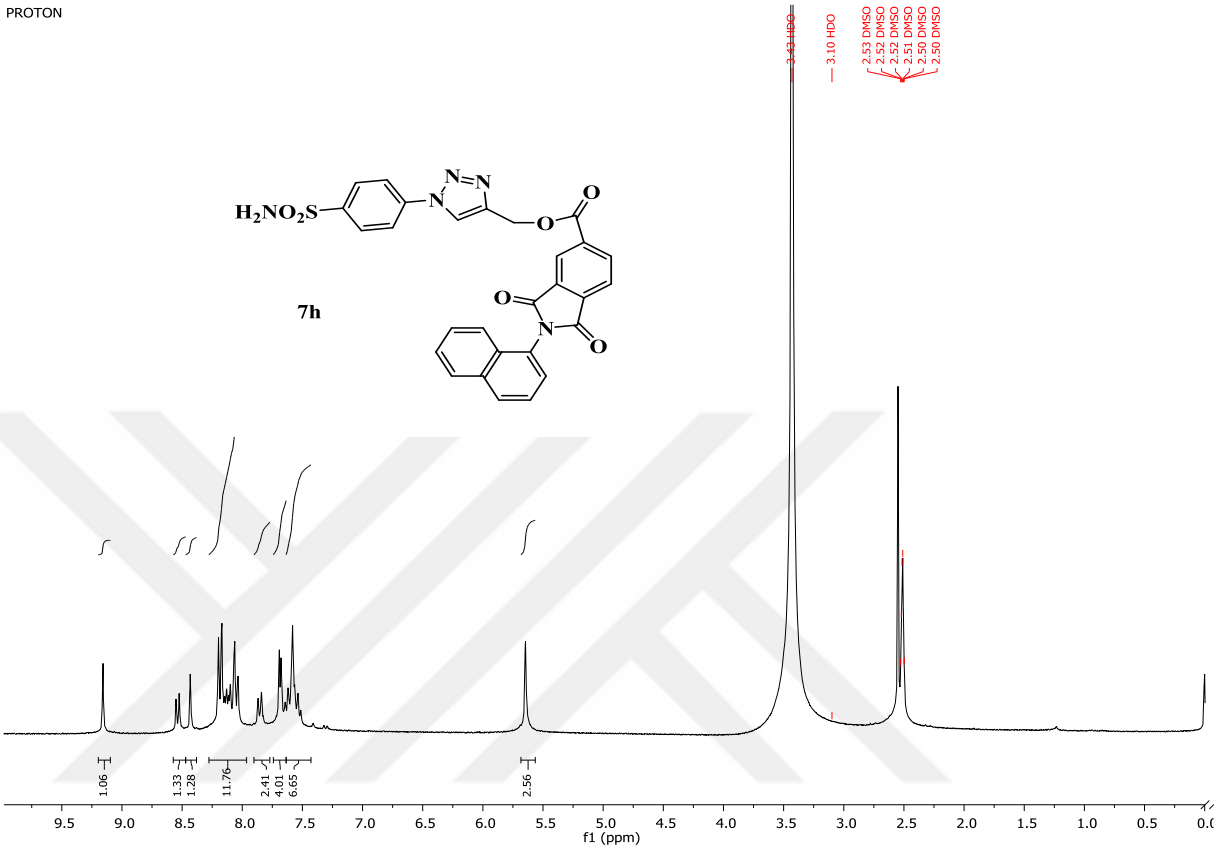
App 20: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(4-cyanophenyl)-1,3-dioxoisoindoline-5-carboxylate (7g).



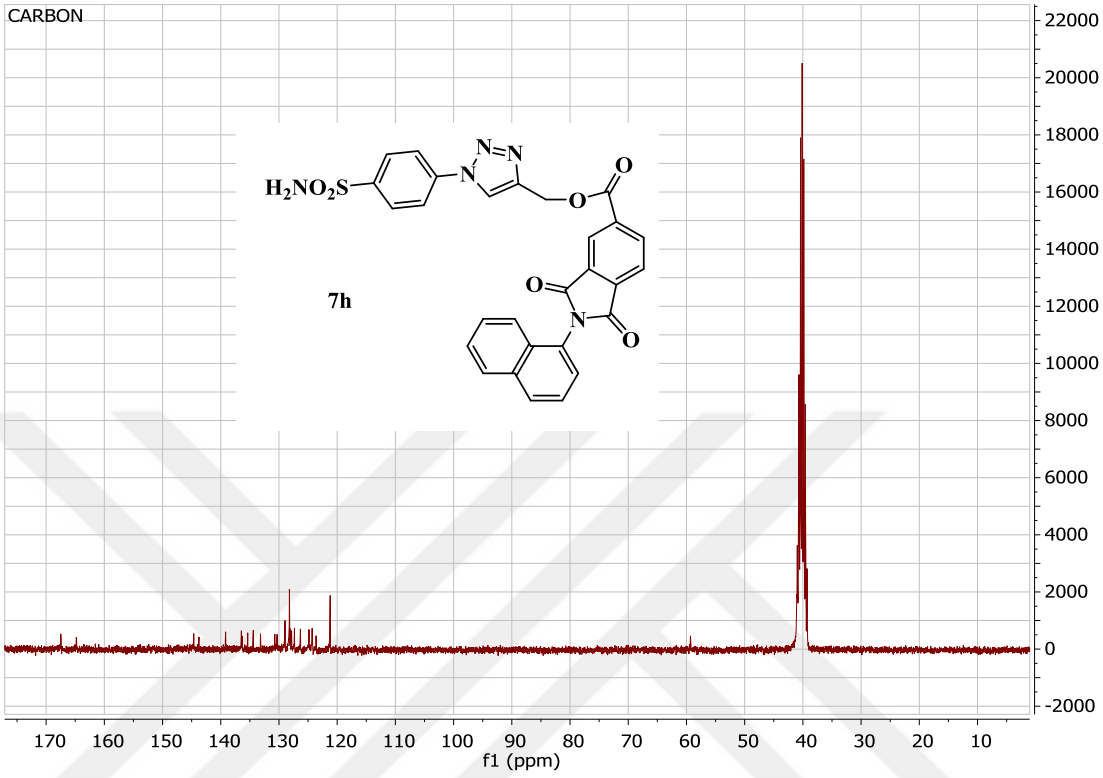
App 21: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(4-cyanophenyl)-1,3-dioxoisoindoline-5-carboxylate (7g).



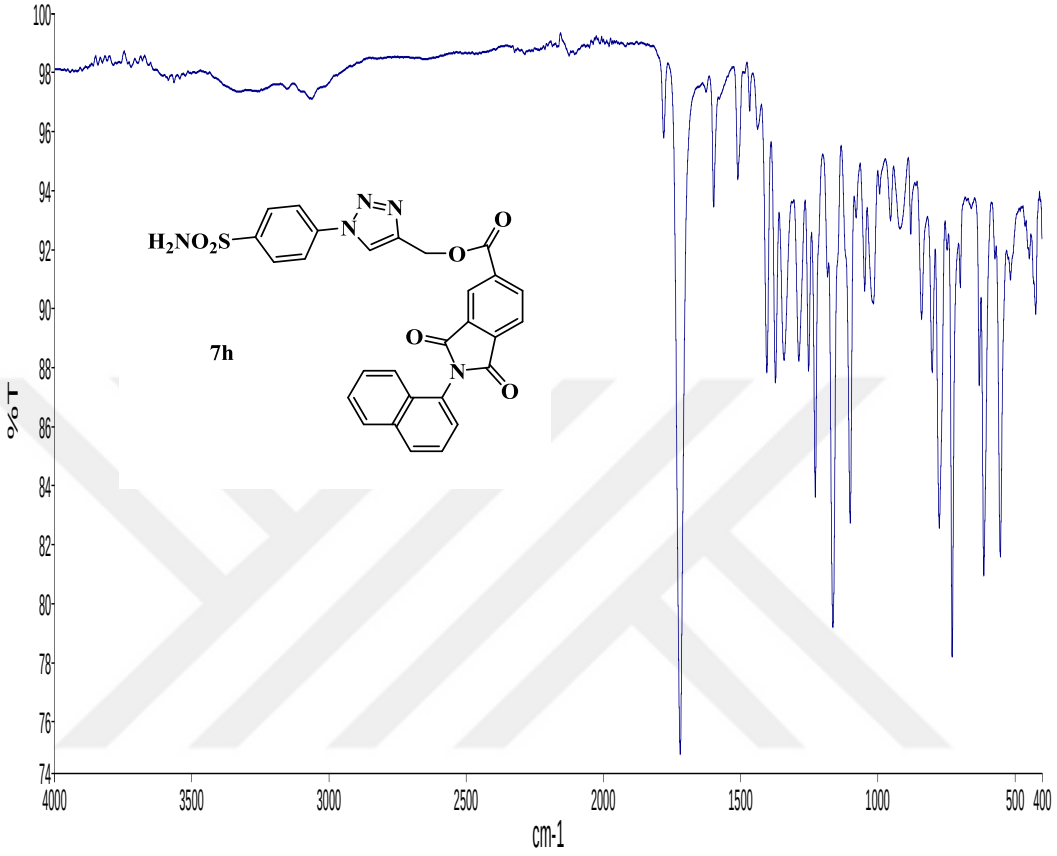
App 22: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(naphthalen-1-yl)-1,3-dioxoisoindoline-5-carboxylate (7h).



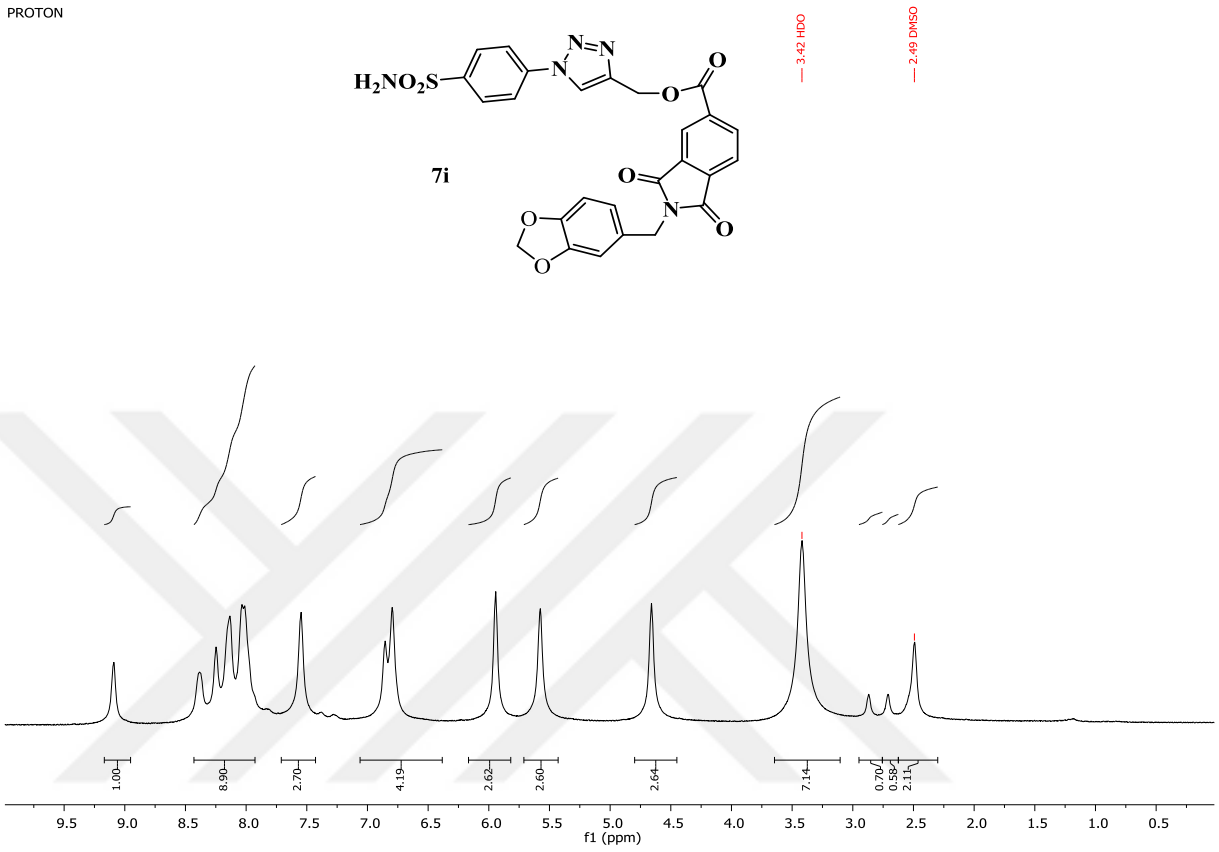
App 23: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(naphthalen-1-yl)-1,3-dioxoisoindoline-5-carboxylate (7h).



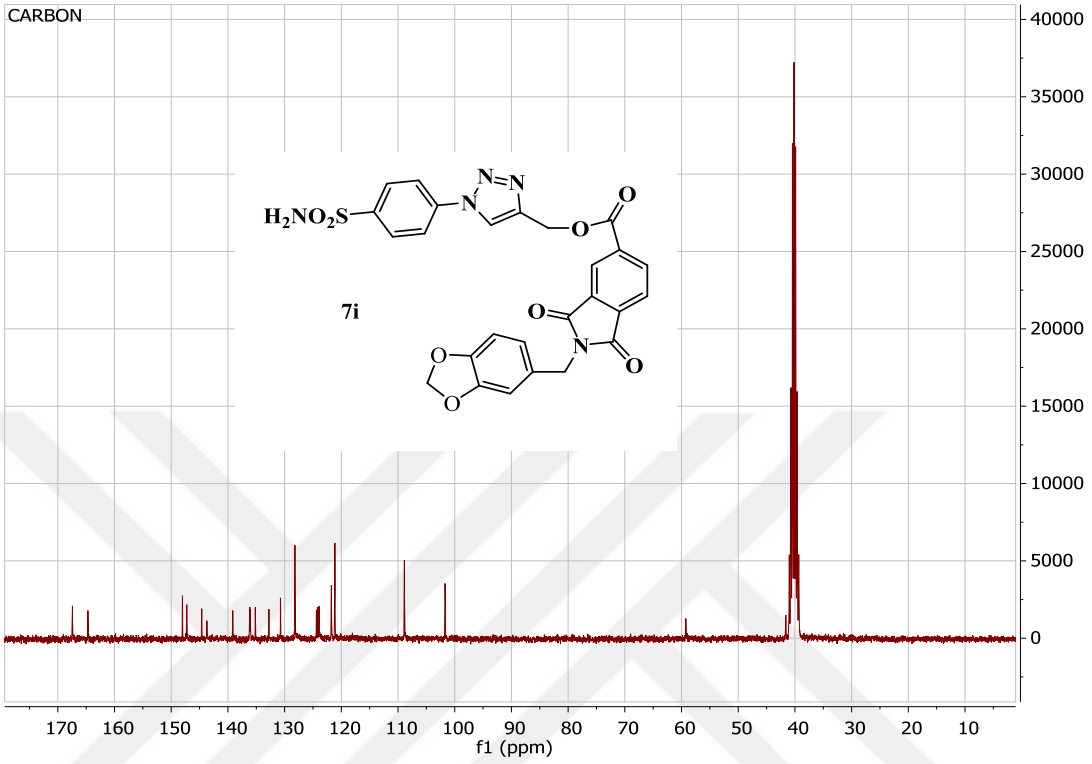
App 24: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(naphthalen-1-yl)-1,3-dioxoisoindoline-5-carboxylate (7h).



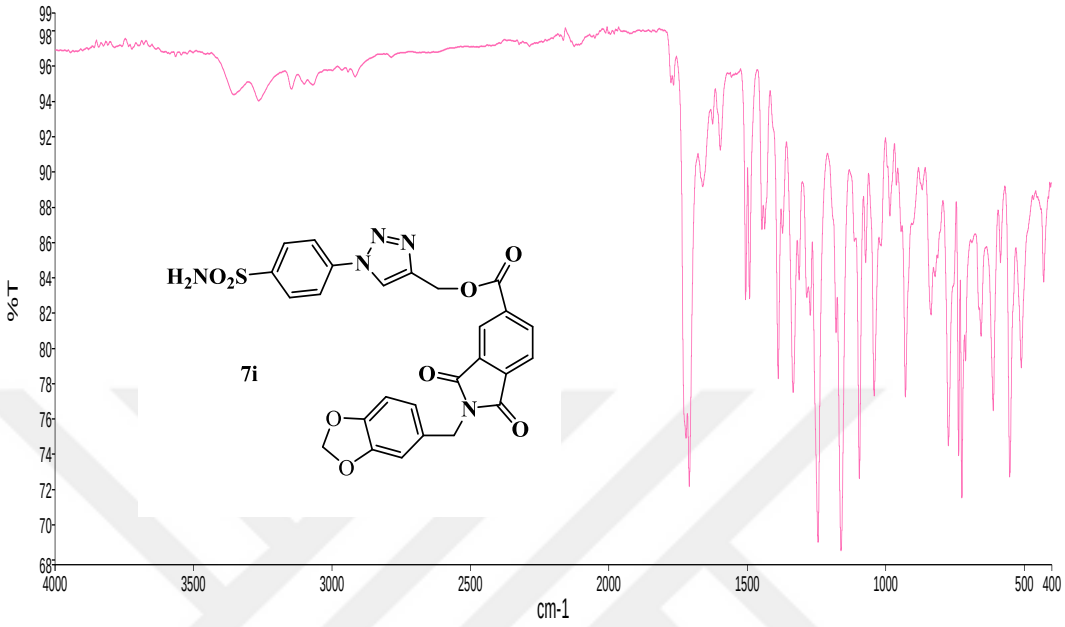
App 25: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(benzo[d][1,3] dioxol-5-ylmethyl)-1,3-dioxoisoindoline-5-carboxylate (7i).



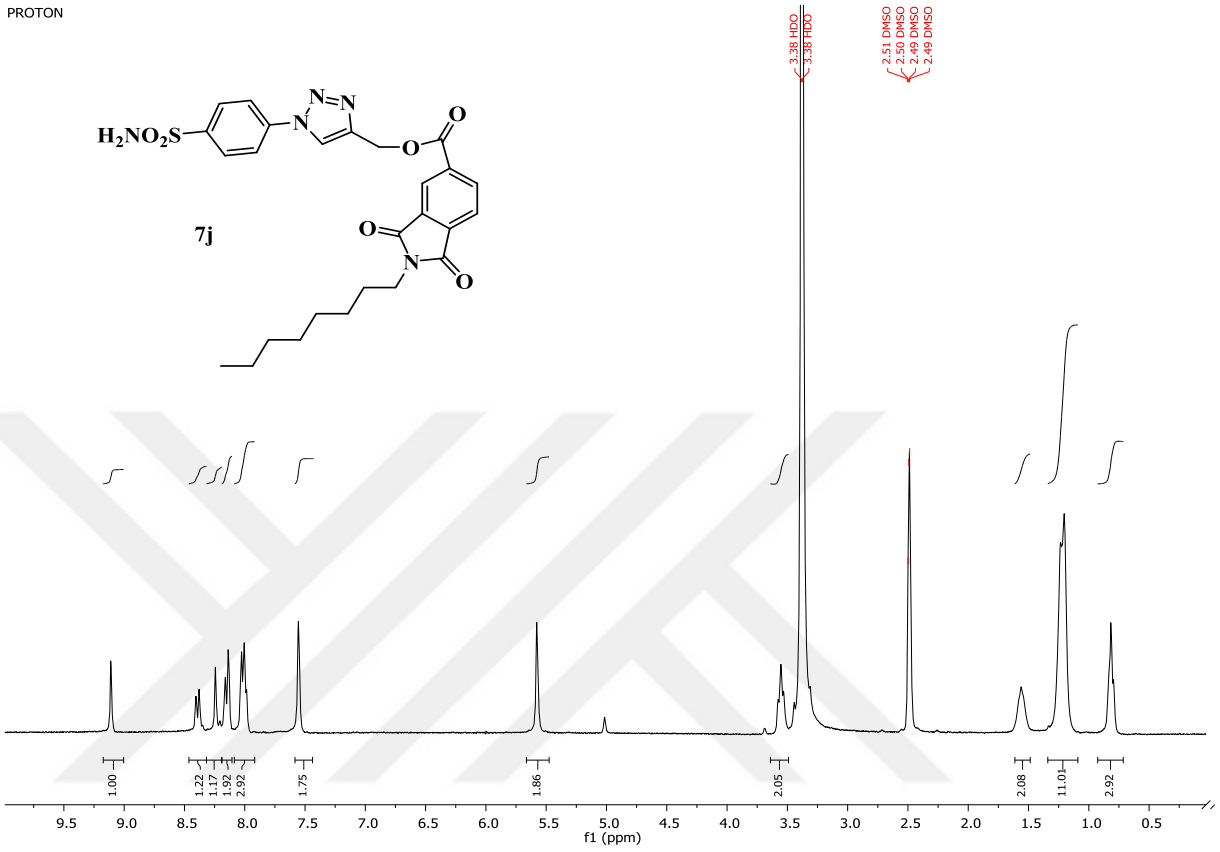
App 26: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(benzo[d][1,3] dioxol-5-ylmethyl)-1,3-dioxoisoindoline-5-carboxylate (7i).



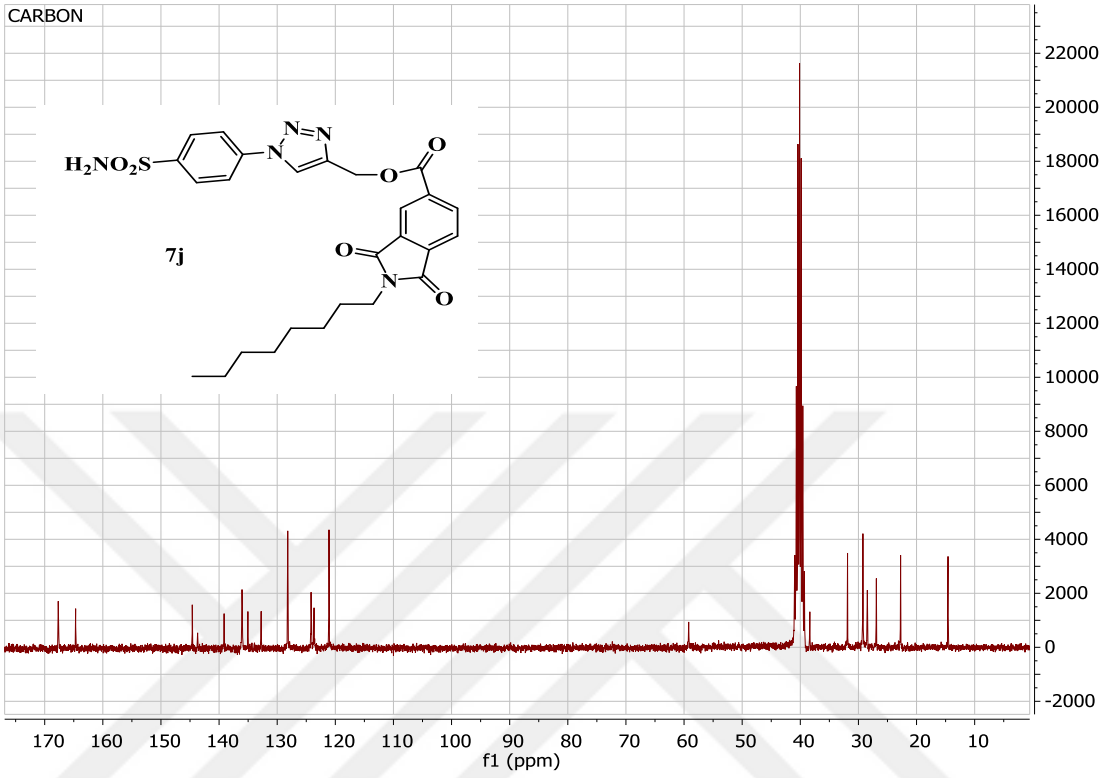
App 27: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-(benzo[d][1,3] dioxol-5-ylmethyl)-1,3-dioxoisoindoline-5-carboxylate (7i).



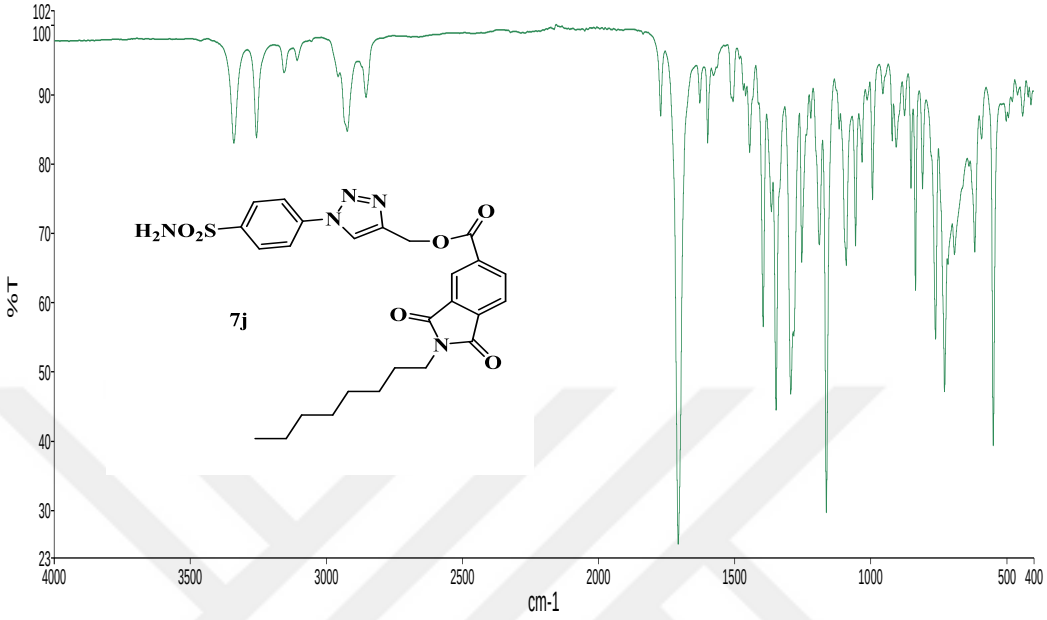
App 28: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-octyl-1,3-dioxoisoindoline-5-carboxylate (7j).



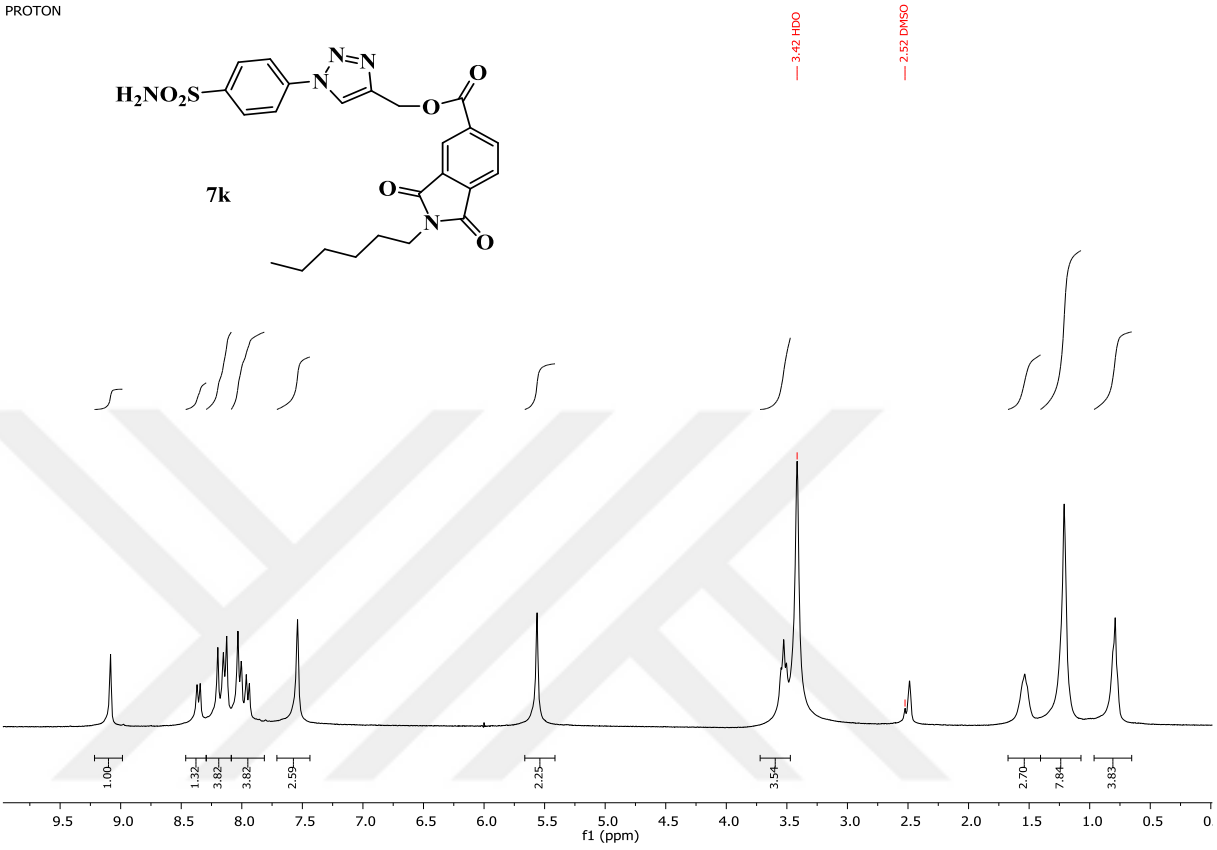
App 29: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-octyl-1,3-dioxoisoindoline-5-carboxylate (7j).



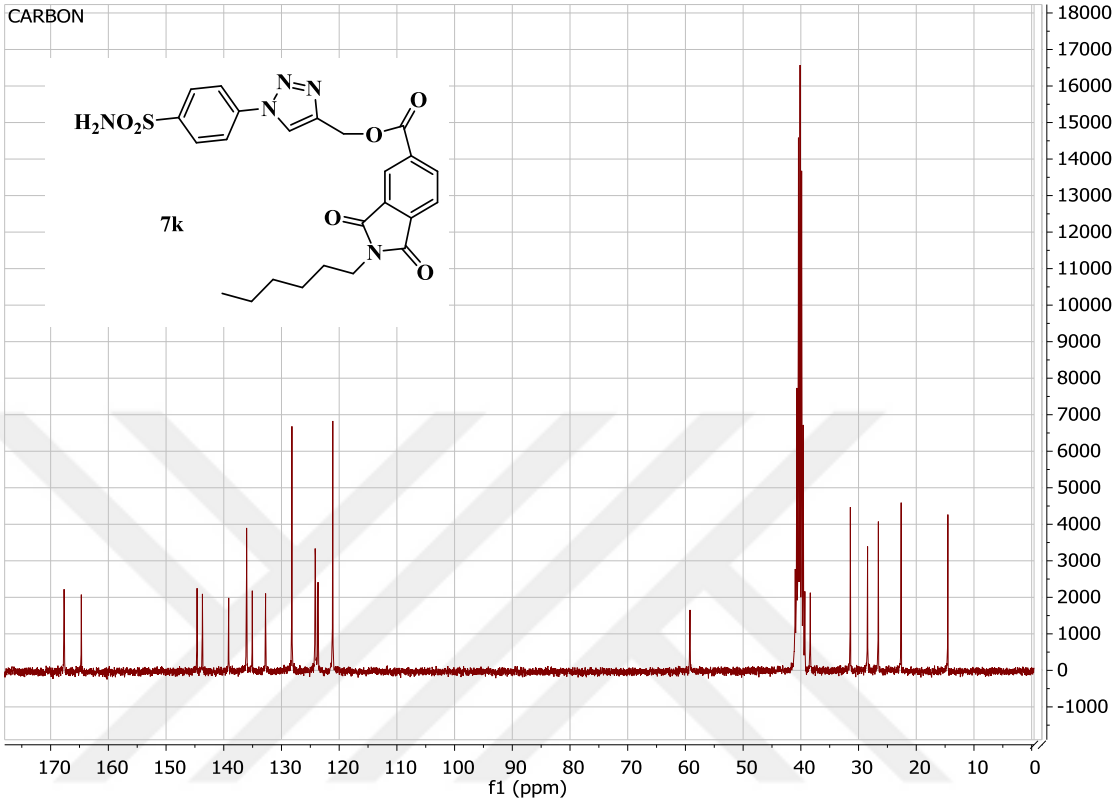
App 30: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-octyl-1,3-dioxoisoindoline-5-carboxylate (7j).



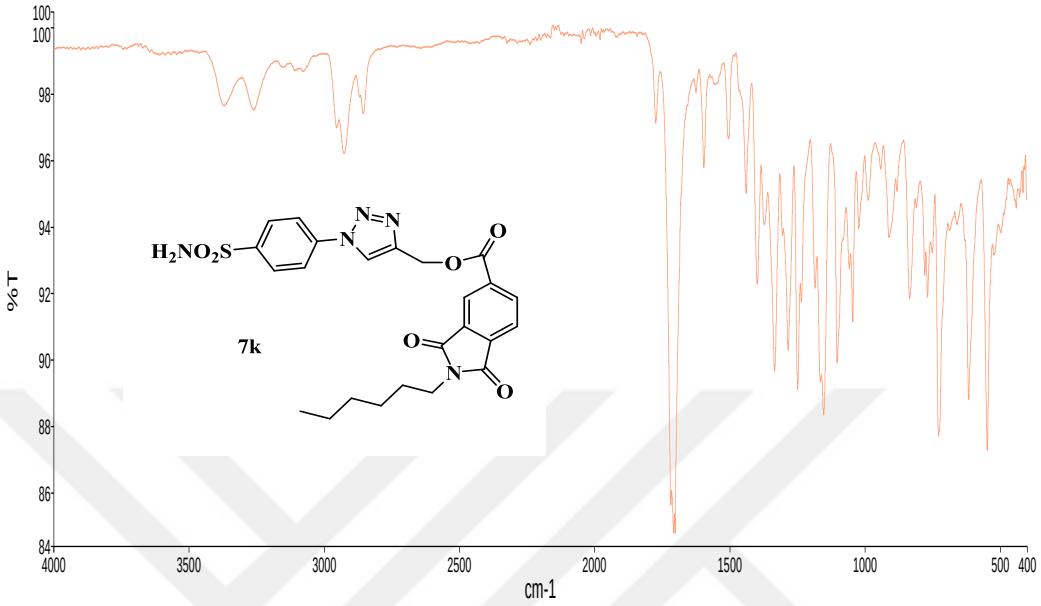
App 31: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-hexyl-1,3-dioxoisoindoline-5-carboxylate (7k).



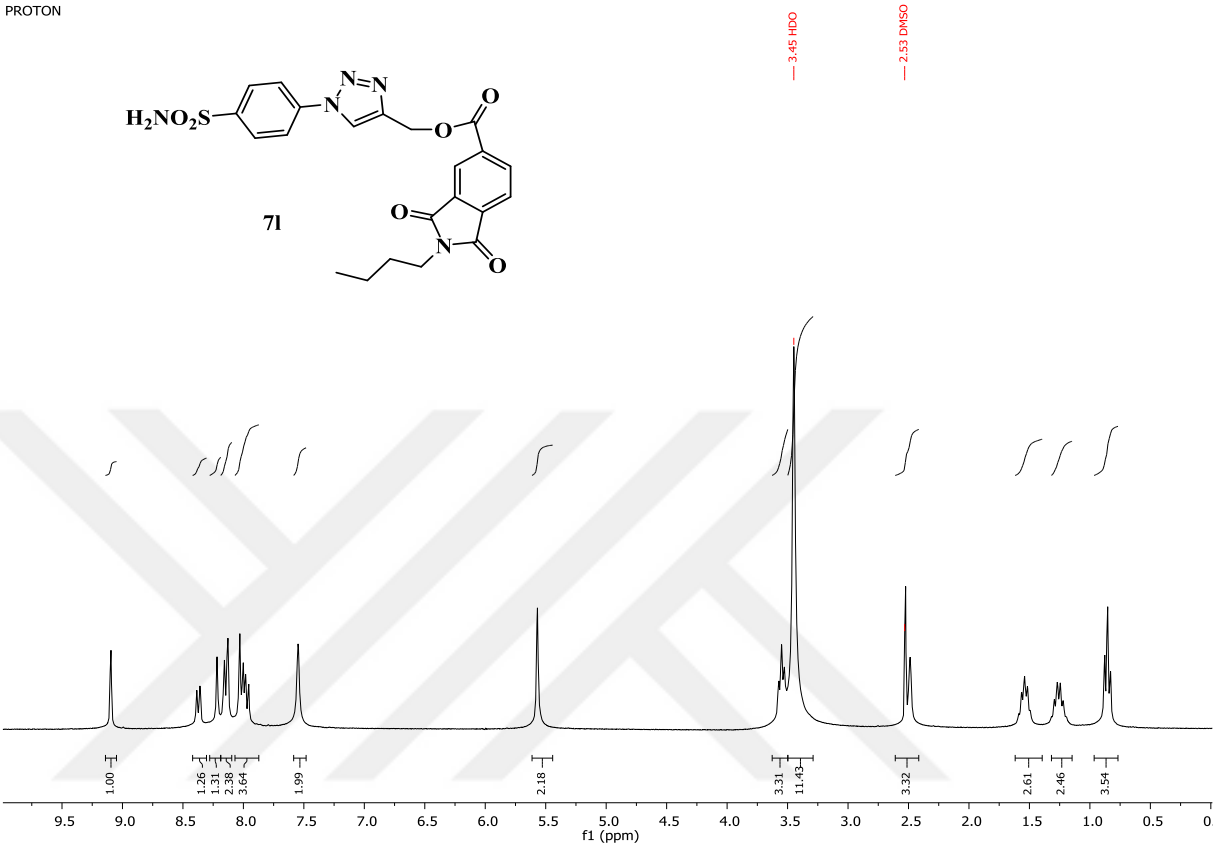
App 32: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-hexyl-1,3-dioxoisoindoline-5-carboxylate (7k).



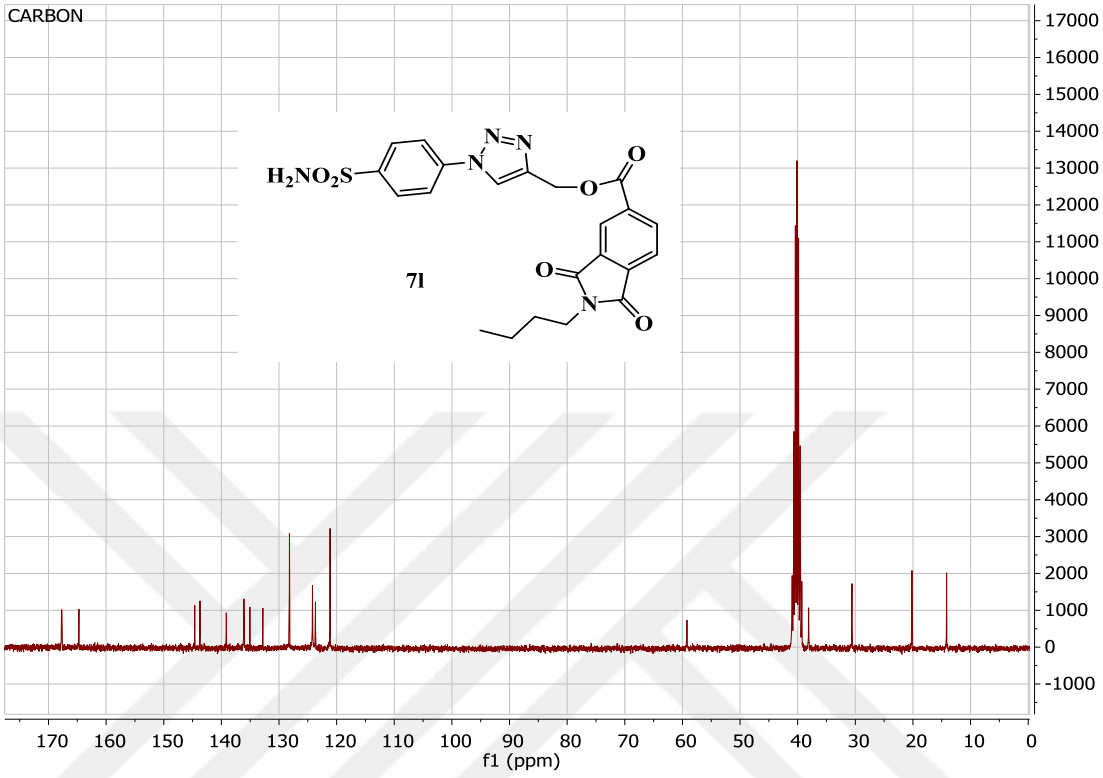
App 33: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-hexyl-1,3-dioxoisoindoline-5-carboxylate (7k).



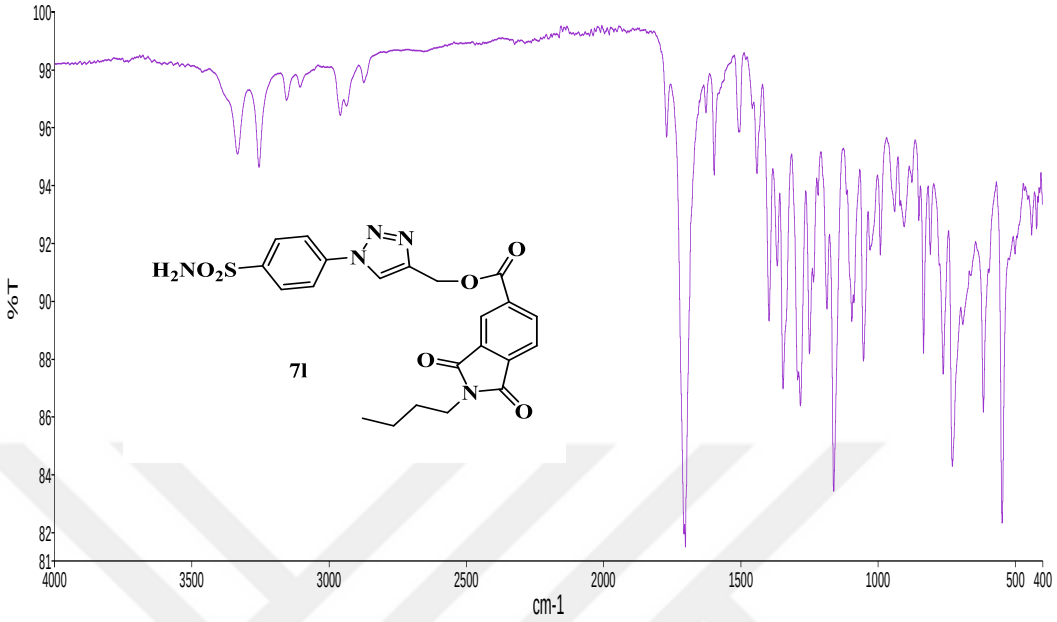
App 34: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-butyl-1,3-dioxoisoindoline-5-carboxylate (7l).



App 35: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-butyl-1,3-dioxoisoindoline-5-carboxylate (7l).



App 36: (1-(4-sufamoylphenyl)-1H-1,2,3-triazol-4-yl) methyl 2-butyl-1,3-dioxoisoindoline-5-carboxylate (7l).



RESUME

Name Surname **:** Chnar KAKAKHAN

EDUCATION

Degree	**School**	**Graduation Year**
Master	Sakarya University / Institute of Science and Technology / Organic Chemistry.	Continue
Bachelor's	University of Mosul/ College of Education For Pure Sciences, Iraq /Department of Chemistry	1990

JOB EXPERIENCE

Year	**Place**	**Position**
2015-Still	Hawler Medical University/ College of Health Sciences/ Department of Chemistry	- Chemistry laboratory/ Health and Safety Officer
1996	Salahaddin University/ College of Dentistry/ Department of Chemistry	- Chemistry Labrotory/ Directore of Planning & Follow-up Unit
1993	High School/ Ministry of Education	- Teacher

FOREIGN LANGUAGE

English

HOBBIES

Reading , Traviting , Sport.