STUDIES ON NEW SYNTHETIC METHODOLOGIES FOR SYNTHESIS OF PHTHALAZINONE DERIVATIVES VIA CYCLIZATION OF 2-ETHYNYLBENZOHYDRAZIDES

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STUDIES ON NEW SYNTHETIC METHODOLOGIES FOR SYNTHESIS OF PHTHALAZINONE DERIVATIVES VIA CYCLIZATION OF 2-ETHYNYLBENZOHYDRAZIDES

submitted by **TOLGA YAMAN** in partial fulfillment of the requirements for the degree of **Master of Science in Department of Chemistry, Middle East Technical University** by,

Prof. Dr. Gülbin Dural Ünver _____

Dean, **Graduate School of Natural and Applied Sciences**

Prof. Dr. Cihangir Tanyeli _____

Head of Deparment**, Chemistry**

Prof. Dr. Özdemir Doğan _____

Supervisor, **Dept. of Chemistry, METU**

Examining Committee Members:

Prof. Dr. Özdemir Doğan _____

Dept. of Chemistry, METU

Prof. Dr. Metin Balcı _____

Dept. of Chemistry, METU

Prof. Dr. Metin Zora _____

Dept. of Chemistry, METU

Prof. Dr. Adnan Bulut _____

Dept. of Chemistry, Kırıkkale University

Assoc. Prof. Dr. Akın Akdağ _____

Dept. of Chemistry, METU

Date: 08.09.2017

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name: Tolga Yaman

Signature :

ABSTRACT

STUDIES ON NEW SYNTHETIC METHODOLOGIES FOR SYNTHESIS OF PHTHALAZINONE DERIVATIVES VIA CYCLIZATION OF 2-ETHYNYLBENZOHYDRAZIDES

Yaman, Tolga

M.S., Department of Chemistry

Supervisor: Prof. Dr. Özdemir Doğan

Co-Supervisor: Prof. Dr. Metin Balcı

September 2017, 62 pages

Nitrogen-containing heterocyclic compounds display a wide range of biological activities, which account for the increasing interest for their synthesis. In particular, the pyridazinone and phthalazinone derivatives represent a privileged structural motif in biologically active natural products and pharmaceutical compounds. For example, 4-aminophthalizinones have shown potential as anticancer agents. We have developed a methodology for the synthesis of various substituted phthalazinone derivatives. The starting material, ethyl 2-iodobenzoate was first converted to ethyl 2-ethynylbenzoate and its derivatives substituted at the alkyne carbon atom. Ester functionality was converted into the corresponding hydrazide derivatives. Gold catalyzed cyclization of 2-ethynylbenzohydrazide resulted in the formation of some target compounds. Also, heating of hydrazide derivatives at the reflux temperature of propanol gave the target compounds.

Keywords: Heterocyclic, phthalazinone, alkyne, alkyne cyclization, gold catalyst

ÖZ

FİTALAZİNON TÜREVLERİNİN 2-ETİNİLBENZOHİDRAZİT ÜZERİNDEN HALKALAŞMA REAKSİYONLARI İÇİN YENİ SENTETİK METODOLOJİLER GELİŞTİRİLMESİ ÜZERİNE ÇALIŞMALAR

Yaman, Tolga

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Özdemir Doğan

Eş Tez Yöneticisi: Prof. Dr. Metin Balcı

Eylül 2017, 62 sayfa

Azot içeren heterosiklik bileşiklerin geniş çapta biyolojik aktivite göstermeleri, sentezleri için gösterilen ilginin artmasına sebep olmuştur. Bunların içinde, piridazinon ve fıtalazinon türevleri, biyolojik olarak aktif doğal bileşikler ve farmasötik bileşiklerde bulunan özel bir yapısal motife sahiptir. Örnek olarak, 4-aminofıtalizinon türevleri anti-kanser aktivite gösterme potansiyeline sahiptir. Bu çalışmada, çeşitli sübstitüe fitalazinon türevleri sentezlemek adına yeni bir stratejik metodoloji geliştirildi. İlk olarak, başlangıç maddesi etil 2-iyodobenzoat, etil 2-etinilbenzoat ve onun alkin karbonundan sübstitüe edilmiş türevlerine dönüştürüldü. Ester fonksiyonel grubu, belirtilen hidrazit türevlerine dönüştürüldü. 2-etinilbenzohidrazitin altın katalizörlüğünde kapanması sonucu belirlenen bazı hedef ürünlere ulaşıldı. Bununla birlikte, hidrazitleri propanolün kaynama noktasında ısıtarak da hedef ürünlere ulaşıldı.

Anahtar Kelimeler: heterosiklik, fıtalazinon, alkin, altın katalizörü

To my beloved family...

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I would like to express my deepest gratitude to my co-supervisor Prof. Dr. Metin Balcı. His exceptional knowledge, leadership, and guidance was the most prominent factor in shaping me of what I am as a candidate chemist. His helpful and encouraging attitude always made me attach more to my research. Working with him was the best of the privileges I have ever had.

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I would like to thank all of the members of the Department of Chemistry.

Finally, I would like to state my greatest appreciation for my family. Their support throughout the process was an extremely exceptional one, which have always been the most important factor for me to keep pushing myself every time I face difficulties.

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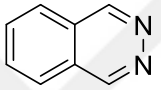
CHAPTER 1

INTRODUCTION

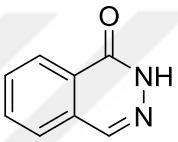
1.1 Phthalazines and Phthalazinones

Phthalazine (**1)** and phthalazinone (**2)**, besides known as benzopyridazines and benzopyridazinones, are heterocyclic molecules that consist of pyridazine and pyridazinone skeletons fused to a benzene ring.



Phthalazine

1

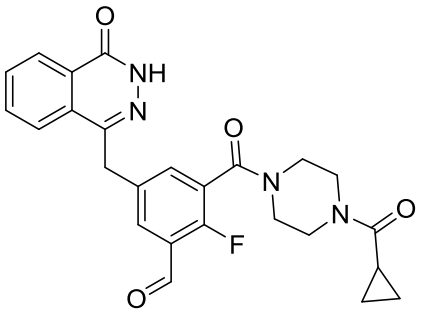


Phthalazinone

2

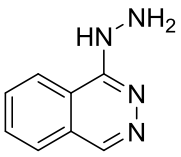
Among them, phthalazinone derivatives are especially known to contain an array of biological activity. They were proved to show potent anti-cancer,[1] anti-convulsant[2] and anti-inflammatory[3] activities.

The biological activity of phthalazinones have made them a potential skeleton for many of the commercial drugs. To illustrate, Olaparib (**3)** is a very commonly used chemical in the drugs that treat advanced ovarian cancer in women. [4] Similarly, hydralazine (**4)**, the molecule that includes a phthalazinone skeleton, used for treatment of hypertension in pregnant women.[5]



Olaparib

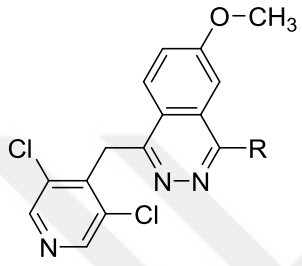
3



Hydralazine

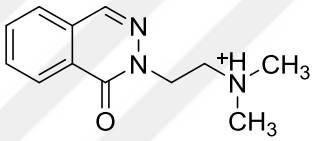
4

Phthalazinone based molecules can also be found as biological inhibitors. For example, phthalazinone derivative **5** is known to be a phosphodiesterase 4 (PDE4) inhibitor.[3] Inhibition of PDE4 is very important in a range of activities that can be labeled as anti-inflammatory to treatment of central nervous system disorders.[6] In addition to these, novel computational studies show that HIV-1 protease, an enzyme that is responsible for the replication of HIV-1 virus, can be successfully inhibited by 1-2*H*-phthalazinone derivative **6** due to their ability to form stable complexes as calculated by simulations.[7]



PDE4 inhibitor

5



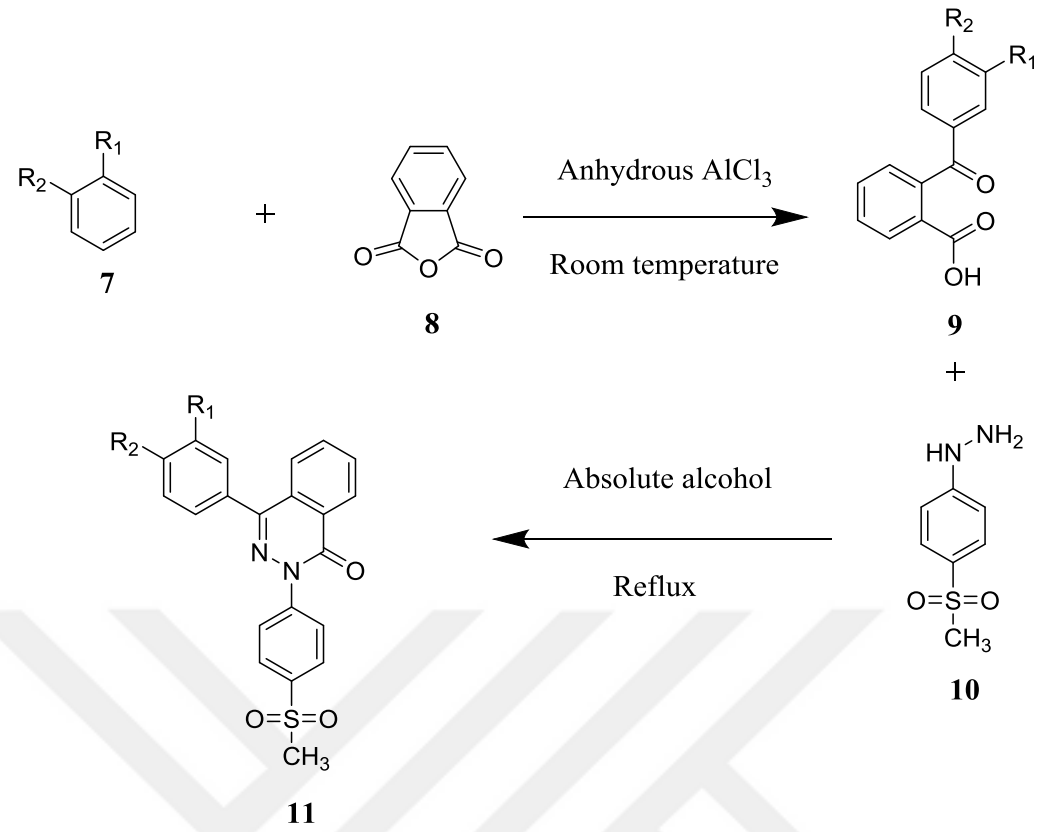
HIV-1 Protease inhibitor

6

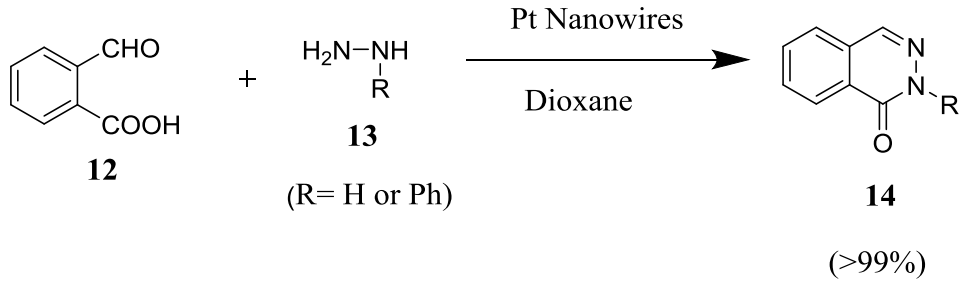
1.1.1 Synthesis of Phthalazines and Phthalazinones

Hameed *et al.*[3] have synthesized phthalazinone **11**, one of the potential anti-inflammatory molecules,[3] as shown in Scheme 1. Aromatic hydrocarbon **7** formed a complex with aluminum chloride which reacted with phthalic anhydride **8** in situ. Resultant dicarbonyl derivative **9** was cyclized with 4-(metyhlsulfonyl)phenylhydrazine (**10)** in absolute alcohol at the reflux temperature to yield the phthalazinone derivative **11**.

Shi *et al.*[8] used platinum nanocatalysts to synthesize phthalazinone derivatives. Reacting 2-carboxybenzaldehyde (**12)** and amine derivatives **13** under 1 bar of hydrogen gas and catalyzed by ultrathin platinum nanowires gave phthalazinone derivatives **14** as shown in Scheme 2**.**



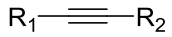
Scheme 1. Synthesis of phthalazinone derivatives **11**



Scheme 2. Pt-Nanowire catalyzed synthesis of phthalazinones **14**

1.2 Alkyne Cyclizations

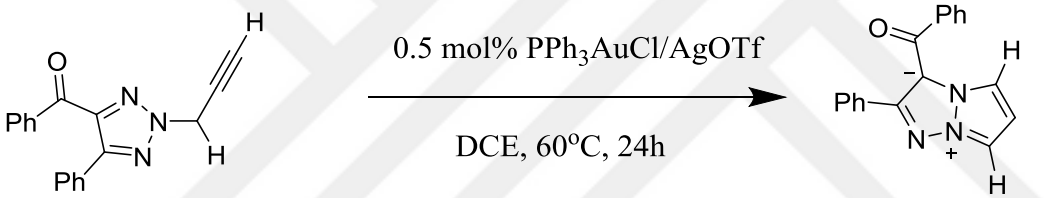
Cyclization reactions with an alkyne functionality **15** are abundant in literature.[9] They are widely used especially for the synthesis of cyclic systems that contain a double bond, which is a part of many heterocyclic skeletons.



15

(R_1, R_2 = H or alkyl)

Cai *et al*.[10] synthesized zwitterionic triazapentalene **17** by the intramolecular alkyne cyclization of **16** in a gold-catalyzed environment as shown in Scheme 3.

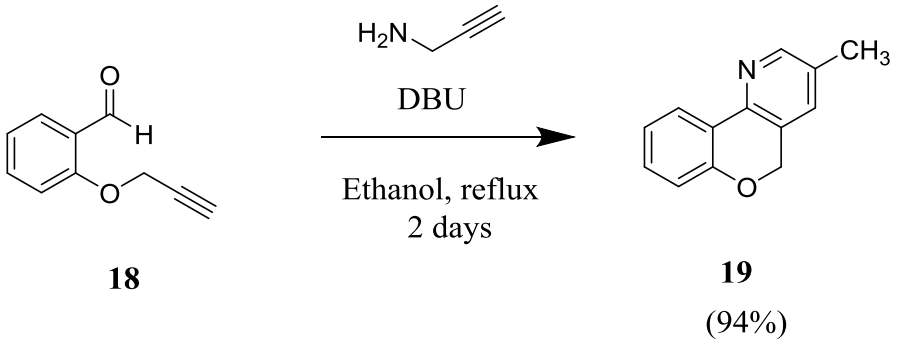


16 **17**

(37%)

Scheme 3. Gold-catalyzed intramolecular cyclization of **16** to **17**

Balcı *et al*.[11] successfully applied alkyne cyclizations to the synthesis of chromenopyridine derivative **19** starting from **18.** The interesting feature of this reaction is the alkyne cyclization step that did not require any metals to promote the process (Scheme 4).



18 **19** (94%)

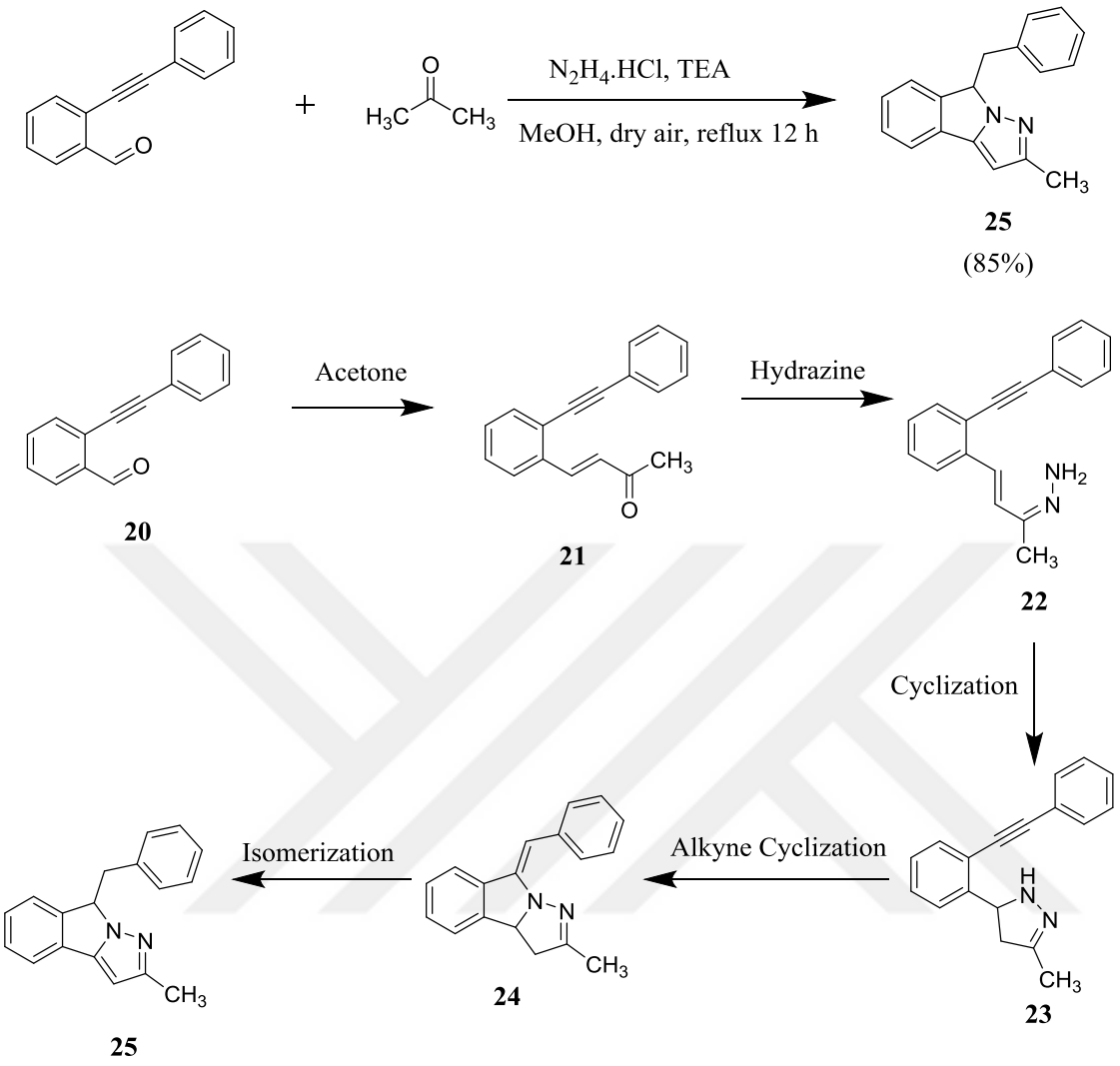
Scheme 4. Successful synthesis of chromenopyridine **19**

1.3 Cyclization Reactions Using Hydrazine

Hydrazine is an extremely noxious inorganic compound, which is a very common and efficient reagent. It is so toxic that it must be stored within a solvent. Hydrazine has a variety of uses as a reagent. It can be used in amidification reactions, hydrazone formation or a reduction reactions. Specifically in the current literature, hydrazine has been widely used for the formation of heterocyclic skeletons.[12]

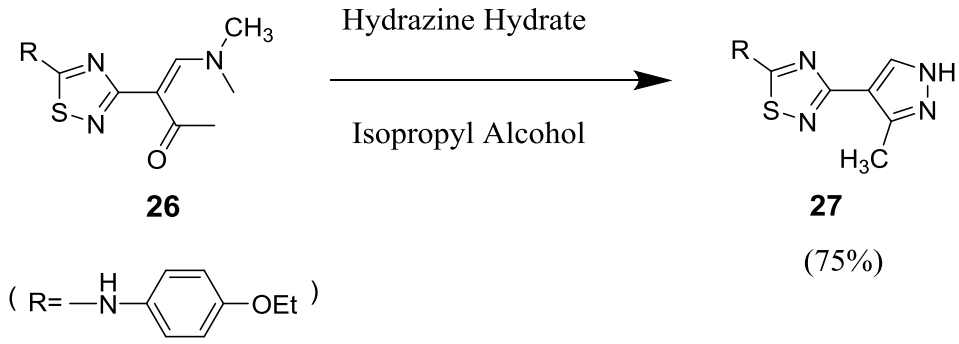
Qiao *et al.*[13] successfully synthesized pyrazoloisoindoline **25** through the steps including hydrazine as the vital point of the cyclization process. Compound **20** was first reacted with acetone to yield compound **21**. Then, hydrazine was added to the medium and after the compound **22** formed, it in situ cyclized to form pyrazoline derivative **23**. The lone pair of the secondary amine then was added to the triple bond via an intramolecular cyclization and yielded **24**, which isomerizes to the target product. The reaction and its proposed steps for its synthesis can be found in Scheme 5.

Steps of synthesis:



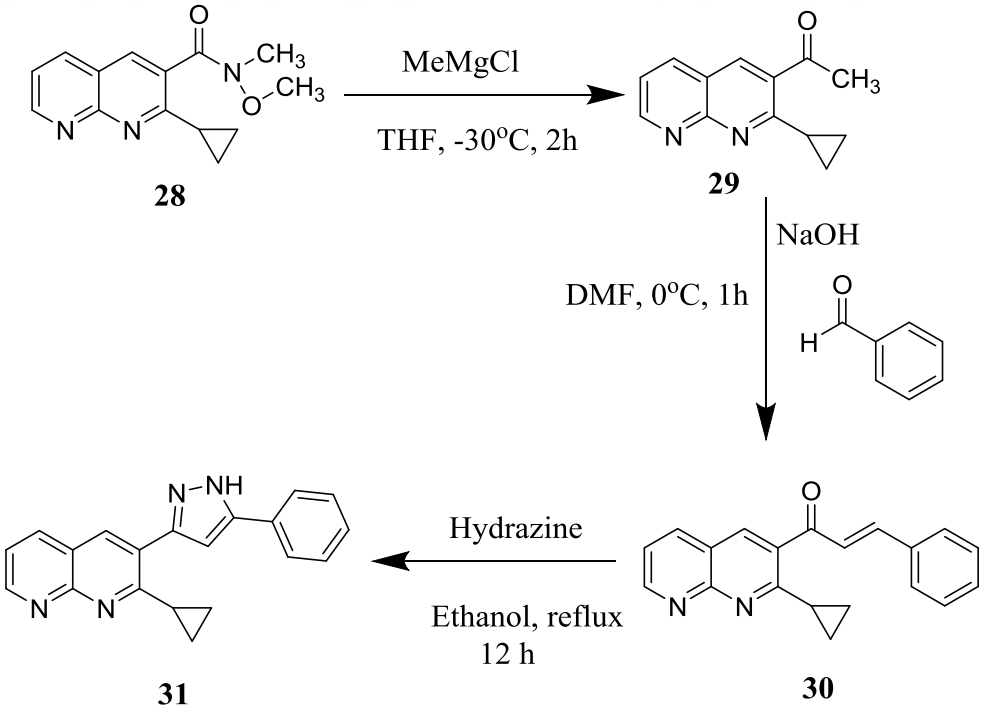
Scheme 5. Synthesis of pyrazoloisoindoline **25** with hydrazine

Shikhaliev *et al.*[14] synthesized pyrazole derivative **27** by the reaction of starting material **26** with hydrazine hydrate in isopropyl alcohol. The reaction of hydrazine with compound **26** generated an imine, which intramolecularly cyclized to **27 (**Scheme 6**)**.



Scheme 6. Cyclization of **27** with hydrazine hydrate

Bucha *et al.*[15] synthesized 1,8-naphtyridine derivatives **31** as shown in Scheme 7**.** The starting amide **28** was first converted into ketone **29** by Grignard reagent. Then, compound **29** was reacted with arylaldehydes to yield compound **30**. Addition of hydrazine hydrate turned the carbonyl functionality in **30** to an imine and intramolecular attack yielded the aimed compound **31**.

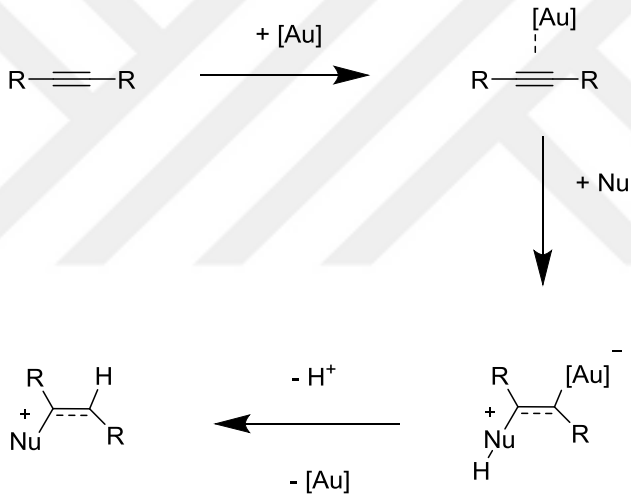


Scheme 7. Synthesis of Naphtyridine Derivative **31**

1.4 Gold Catalyzed Cyclizations

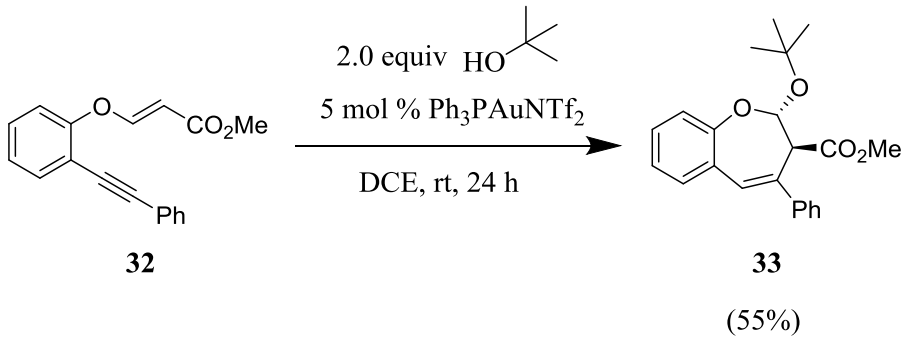
Gold is one of the most well-known elements in the world. As Hashmi[16] states: "It is probably the only chemical element that literally every adult has heard about." Its uses in chemistry is becoming as famous as its fame for every people on earth. Gold catalysis can be described as one of the hottest topics in synthetic organic chemistry. Its variety of uses in synthesis has undescribably accelerated the amount and success of the syntheses made.

Usage of gold catalysis for nucleophilic addition and cyclization reactions on multiple carbon-carbon bonds are probably their most mainstream usage in the field of synthetic organic chemistry. As seen in Scheme 8**,** Hashmi[16] describes their effect on the multiple carbon-carbon bond that makes the bond susceptible to nucleophilic attack.



Scheme 8. Mechanism of gold catalysts

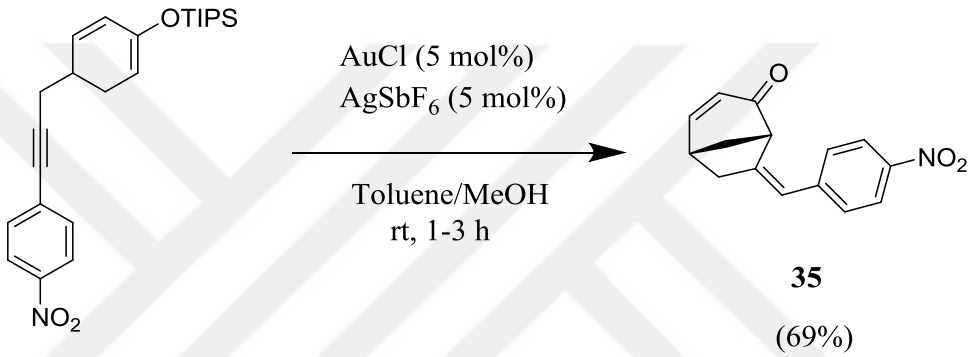
To this date, it is also common to see studies that focus on gold-catalyzed cyclizations. Liu *et al.*[17] synthesized benzo[*b*]oxepine derivatives **33** with gold catalysts.
Carrer *et al.*[18] has optimized a synthetic route for bicyclo[3.2.1]octanone derivatives starting from alkynyl silyl enol ethers. Product **35** was synthesized from the reaction of **34** with gold (AuCl) and silver ($AgSbF_6$) catalysts by an intramolecular Diels-Alder reaction. **(**Scheme 10**).**



32 **33**

(55%)

Scheme 9. Synthesis of benzo[b]oxazepine derivative **33**



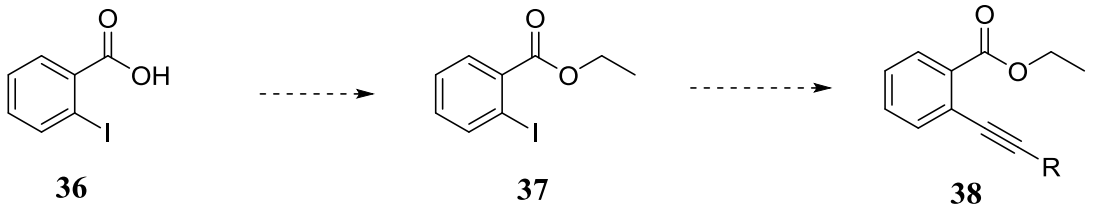
34 **35**

(69%)

Scheme 10. Synthesis of bicyclo[3.2.1]octanone derivative **35**

1.5 Aim of the Study

The aim of the study can be stated as the development of novel synthetic methodologies for synthesis of phthalazinone derivatives starting from substituted benzoic acid esters. To start, ester derivatives **38** will be synthesized from commercially avaiable *o*-iodobenzoic acid (**36)**. The suitable starting materials **38** for cyclization will be synthesized by Sonogashira cross-coupling reaction.

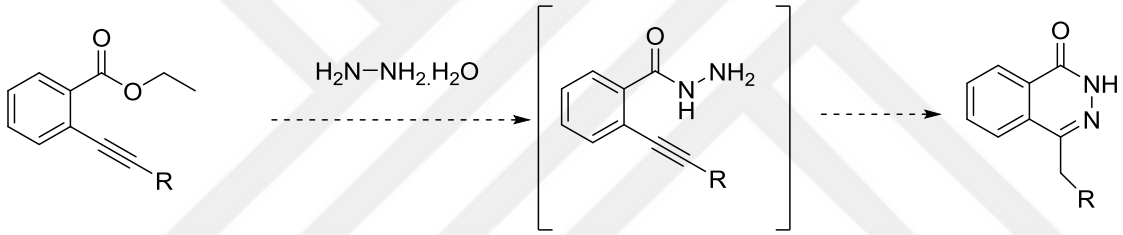


36 **37** **38**

(R= H, aryl derivatives)

Scheme 11. Aim of the study

Then, the corresponding ethynyl derivatives **38** will be reacted in a medium containing hydrazine hydrate for the synthesis of amide **39**, where in situ cyclization of amides to the phthalazinone derivatives **40** is expected.



38 **39** **40**

Scheme 12. Route of synthesis for the target compounds

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of Phthalazinone Derivatives

For the synthesis of phthalazinone derivatives, 2-iodobenzoic acid (**36**) was selected as the starting material. It is a commercially available chemical. The key compound is ethyl-2-iodobenzoate (**37**). The goal was to synthesize ethynyl benzoate derivatives for the ultimate synthesis of phthalazinone derivatives.

2.1.1 Synthesis of the Starting Compound: Ethyl-2-iodobenzoate

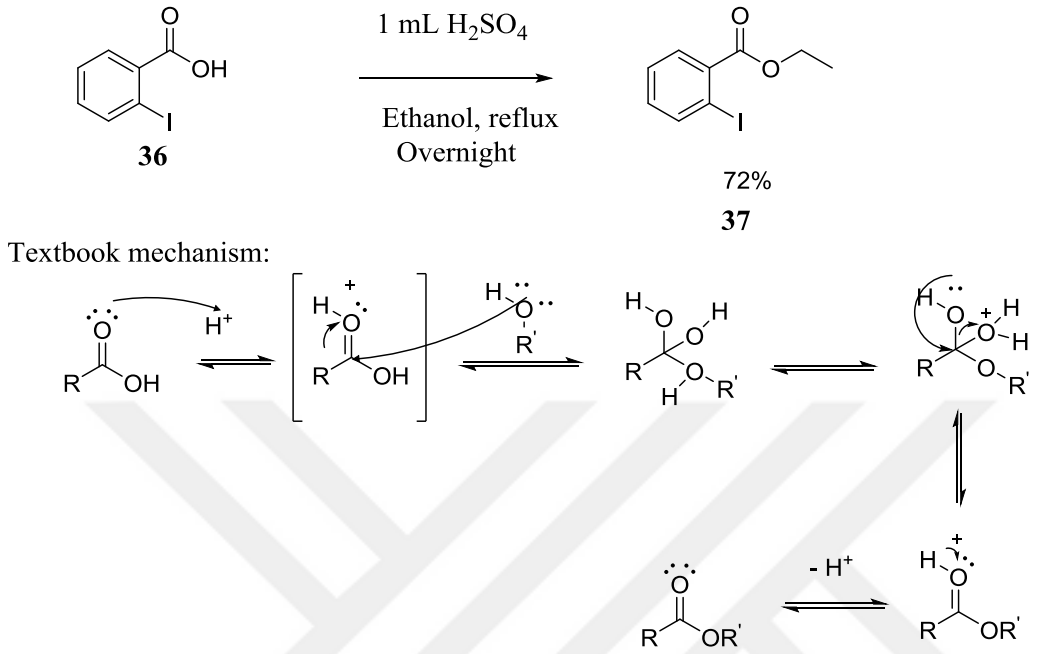
For the synthesis of ester **37**, we tried Fischer esterification reaction as the initial trial for the method (Scheme 13). In Fischer esterification, carboxylic acid, that is initally protonated by a proton source, is attacked by an alcohol, generally via solvolysis. A tetrahedral intermediate is reached after the attack, where one of the two hydroxyl groups present on the intermediate leaves the molecule after being protonated to become H_2O and leave as it is. The remaining product becomes the ester desired to be reached.

In our study, ethanol was used as the solvent and reagent, where the proton source was chosen as H_2SO_4, which was readily available and a strong acid. At the reflux temperature of ethanol, stirring overnight successfully formed **37** in 72% yield.

2.1.2 Sonogashira Cross-Coupling Reaction

For many years, creating new carbon-carbon bonds have been a challenging issue.[19] Studying on the issue for so many years, chemists came up with novel and effective reactions such as but not limited to Heck, Suzuki, Negishi and Sonogashira couplings.[20] Sonogashira coupling reaction, which lead the way for the coupling

reactions between aryl or vinyl halides and terminal alkynes, has been widely used by synthetic organic chemists.

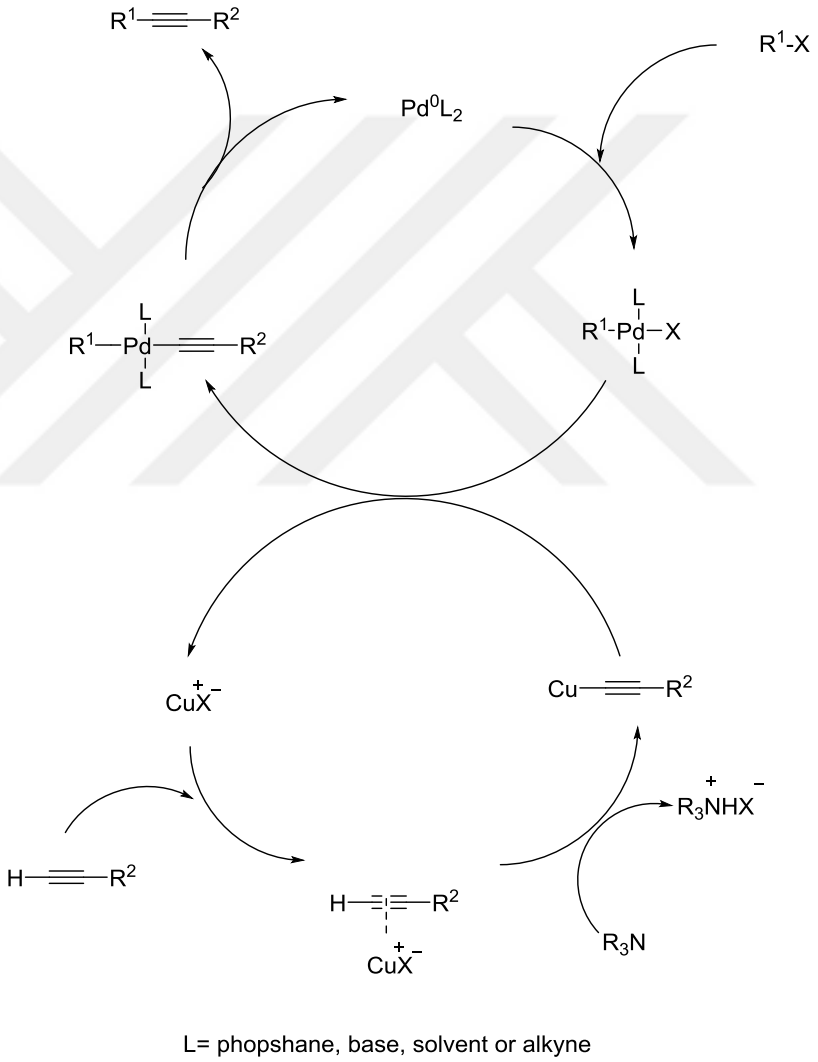


Scheme 13. Synthesis of **37** and mechanism of Fischer esterification

Having a look at its mechanism,[19] it includes 2 catalysts to run the reaction, of which are a palladium source and a copper source. Importance of them can be clearly seen in the proposed reaction mechanism (which is still may be subject to change).[19] The mechanism is proposed to have two independent cycles, the palladium one and the copper one. Scheme 12 illustrates the mechanism.

For the initiation of palladium cycle, a $[Pd(0)L_2]$ complex must be formed from the reagents, complexes can be the ones such as $PdCl_2(PPh_3)_2$ or from Pd(0) complexes like $Pd(PPh_3)_4$.[19] The resultant complex undergoes an oxidative addition process by the attack of aryl or vinyl halide. This then undergoes a "transmetalation" reaction from the copper acetylide that is formed at the copper cycle. After a final reductive elimination, the desired cross-coupling product is formed while regenerating the $[Pd(0)L_2]$ complex.

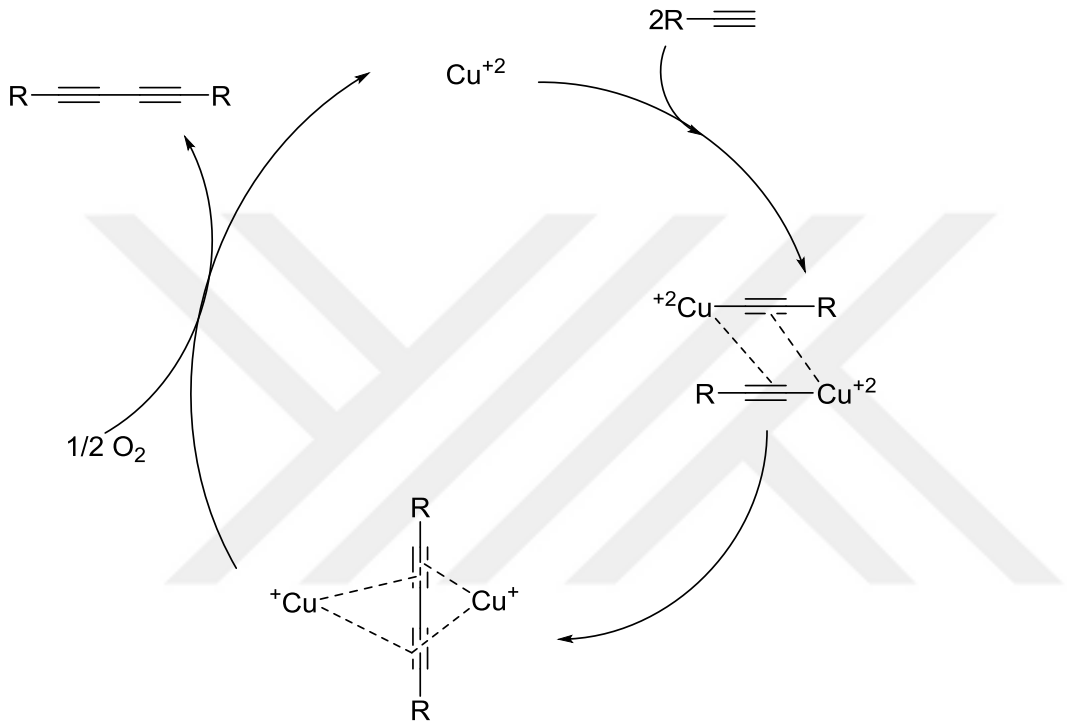
The copper cycle is relatively less known than the palladium one. It is assumed that terminal alkyne adds to CuX forming a complex. Proton abstraction is believed to be the promoter of the copper acetylide formation.[21] The involvement of the copper cycle generally produces an undesired reaction product, the Glaser coupling, better known as homocoupling.[22] It is formed when two terminal alkynes are bonded to each other. In some cases, homocoupling product can be the desired product. Burri *et al.*[23] showed that usage of a specific copper(II) complexes very effectively yield the homocoupling product, with their proposed mechanism as shown in Scheme 13**.**



Scheme 14. Mechanism of Sonogashira Cross-Coupling Reaction

2.1.3 Synthesis of Cross-Coupling Products

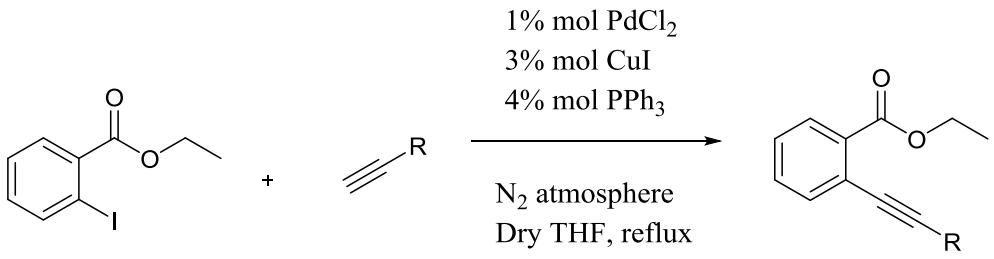
For the synthesis of the cross-coupling products, two different pathways were used. For the products **38a-d**, one Sonogashira cross-coupling was used and the products were formed. However; for the products **38e-g**, the process involved two Sonogashira cross-coupling reactions followed by a desilylation reactions.



Scheme 15. Mechanism of homocoupling product[23]

2.1.3.1 Synthesis of Cross-Coupling Products 38a-d

As seen in Scheme 14, after dissolving compound **37** in dry THF, $PdCl_2$, CuI, PPh_3 and triethylamine were added to the reaction medium. After the addition of catalysts and reagents, appropriate terminal alkyne was added to the medium. After the addition of those catalysts and appropriate terminal alkyne was added to the medium. All reactions were carried out under reflux conditions and under N_2 atmosphere, which was used for the prevention of the undesired formation of homocoupling products. TLC control was done throughout the reaction for the optimization. Depending on the terminal alkyne including groups, reaction time was varied.



37 **38a-d**

38a R= - phenyl (60%)
38b R= - n-butyl
38c R= - H
38d R= - TMS

Scheme 16. Synthesis of ester derivatives **38a-d** by Sonogashira cross coupling

Among the products, **38a** was successfully isolated and characterized. Figures 1 and 2 illustrate the ^{1}H and ^{13}C NMR spectra. The triplet signal at 1.40 arises from the methyl protons of the ethyl moiety bonded to ester oxygen. Likewise, the quartet at 4.42 belongs to the neighbouring metrhylene protons and, shifted to low field because of the neighbouring ester carbonyl functionality. In the ^{13}C NMR spectrum, the peaks at 88.3 and 94.2 are the clear indications of the triple bond carbon atoms, and the peak at 61.2 arises from the carbon neighboring the ester oxygen. Values of both spectra are competent with the literature values.[24]

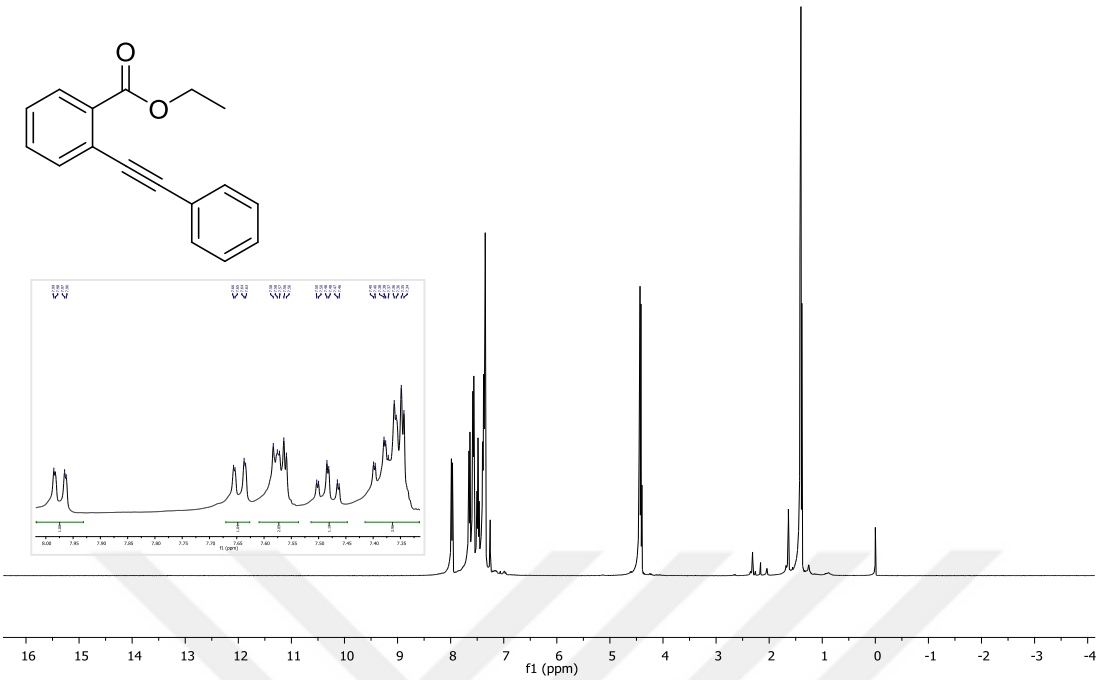


Figure 1: ^{1}H NMR spectrum of compound **38a**

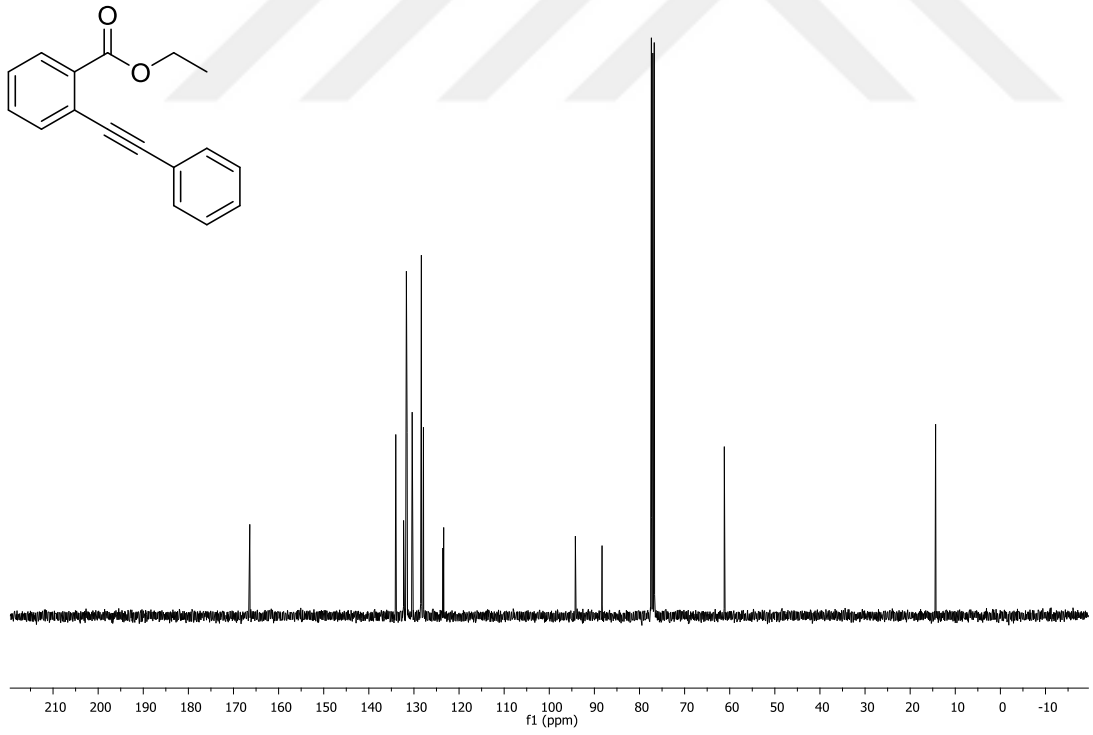
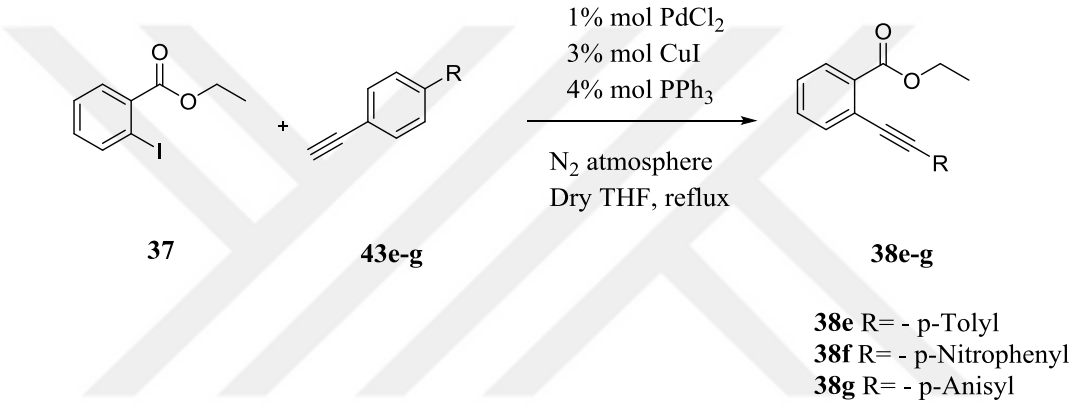


Figure 2: ^{13}C NMR spectrum of compound **38a**

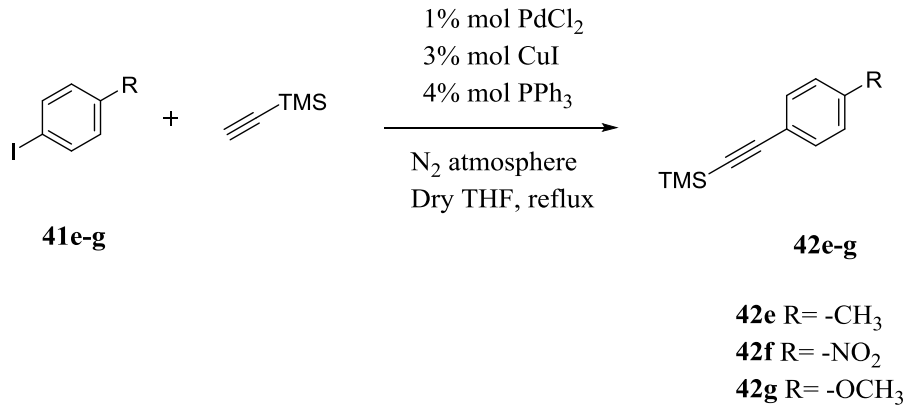
2.1.3.2 Synthesis of Cross-Coupling Products 38e-g

As for the first step of the synthesis of the products **38e-g**, aryl derivatives **43e-g** (Scheme 15) were needed. The products **43e-g** were synthesized starting from silylated compounds **42e-g** which were reacted under the same reaction conditions: 1 equivalent of TBAF and dry THF as the solvent in 0° C. (Scheme 16)

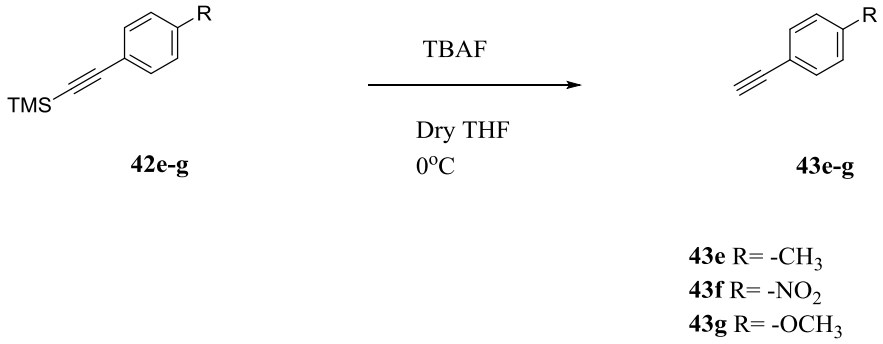
To synthesize compounds **42e-g**, commercially available compounds **41e-g** were coupled with TMS-acetylene under Sonogashira cross-coupling conditions that were used to synthesize compounds **38a-d**. (Scheme 17)



Scheme 17. Synthesis of ester derivatives **38e-g** by Sonogashira cross coupling



Scheme 18. Synthesis of silylated compounds **42e-g**



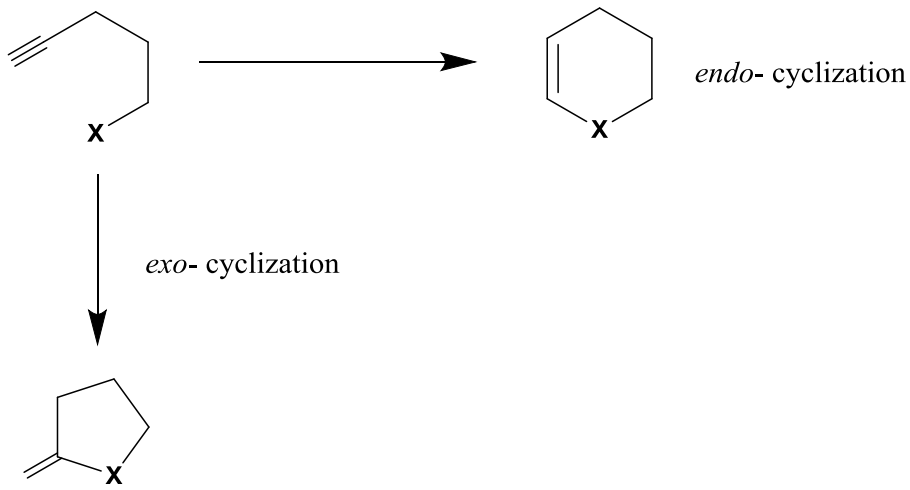
Scheme 19. Desilylation reactions of compounds **42e-g**

2.1.4 Baldwin's Rules and Their Uses in Alkyne Cyclizations

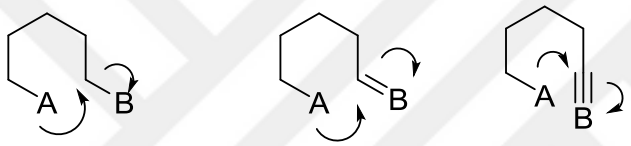
Cyclization reactions always had the lion's share among the methods that are used to synthesize heterocyclic molecules. A great number of the current methodologies are based alkyne cyclizations; especially for those heterocyclic molecules having an *endo*-double bond.

Before specific discussion of cyclizations with alkynes, Baldwin's rules should be revisited.[25]

Baldwin described the cyclizations by two categories:[25] the first layer describing the position of the breaking bond, saying: "I will describe a ring-forming process with the prefix *exo,* when the breaking bond is exocyclic to the *smallest* so *formed ring* and *endo* correspondingly" (Scheme 18). Also, he coined the terms "tet, trig and dig" to describe the geometry of the carbon atom that undergoes the cyclization (Scheme 19).



Scheme 20. *Endo*- and *exo*- cyclizations



tet **trig** **dig**

Scheme 21. Hybridization of the carbon at the ring closure point

Tet is used the describe the tetrahedral geometry, likewise trig is to describe trigonal and dig is to describe diagonal geometry.

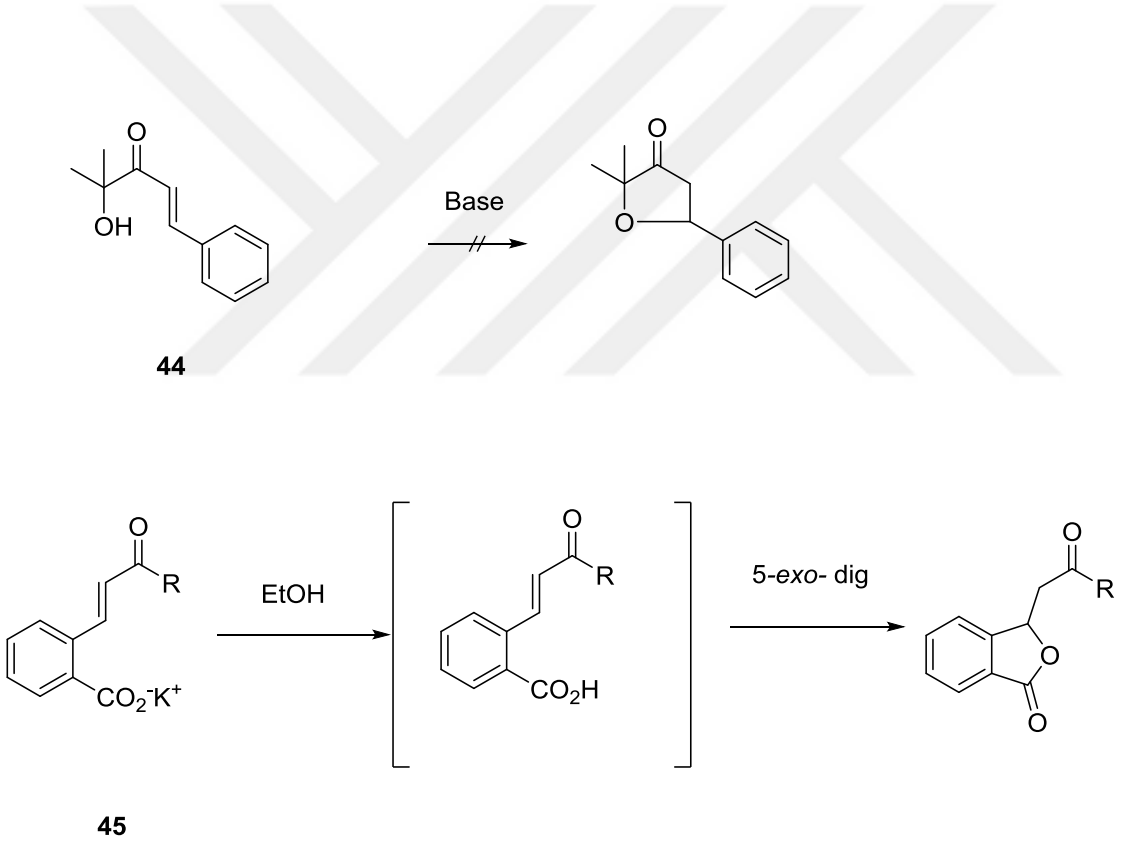
General rules that are applicable in the reactions can be summarized in Table 1.

	Favored	Disfavored
Tet	3-exo 5-exo 7-exo 4-exo 6-exo	5-endo 6-endo
Trig	3-exo 5-exo 7-exo 7-endo 4-exo 6-exo 6-endo	3-endo 5-endo
Dig	5-exo 6-exo 7-exo 3-endo 4-endo 5-endo 6-endo 7-endo	3-exo 4-exo

Table 1: Favored and disfavored cyclizations

It is also stated[25] that in these rules, the atom designated here as A must be a first row element; since large atomic radii may have an overcoming effect on the strains that yield a cyclization as disfavored.

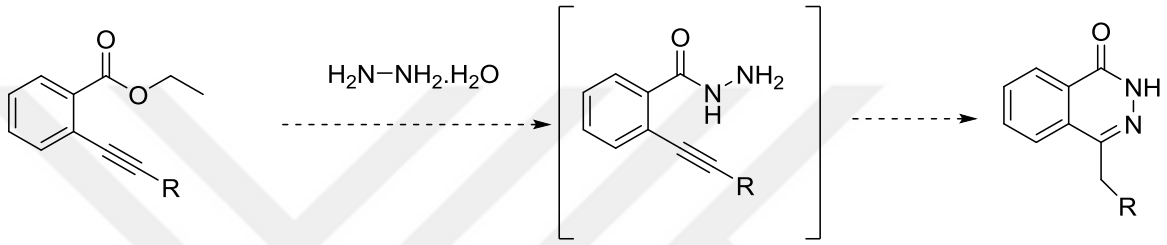
Baldwin *et al.*[26] managed to support these observations by experiments of their own. Their study was mainly focused on the comparison of *5-endo-* trig cyclizations to *5-exo-* trig cyclizations. As shown in Scheme 20, cyclization of compound **44** where the projected nucleophilic *endo-* attack failed, whereas *exo-* cyclization on compound **45** was successful.



Scheme 22. Unsuccessful 5-*endo-* trig cyclization and successful 5-*exo-* trig cyclization

2.1.5 Synthesis of Phthalazinone Derivatives

The abundance of phthalazinone skeleton especially in bioorganic media captured the interest of our group, and their derivatives were synthesized in the past by the group.[27] In the literature, there is no record of a phthalazinone synthesis that is based on alkyne cyclization where the nucleophilic attack is conducted by an intramolecular nitrogen attack of a hydrazide (Scheme 21). Therefore, we were interested in the synthesis of phthalazinone derivatives without a catalyst and with a gold catalyst.



38 **39** **40**

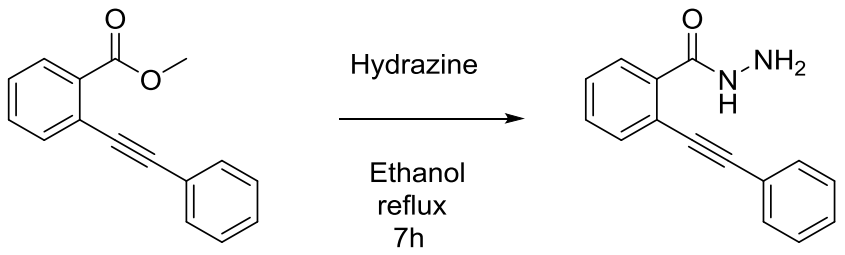
Scheme 23. Route of synthesis for the target compounds without a catalyst

2.1.5.1 Synthesis of Phthalazinone Derivatives Without a Catalyst

Reasoning from the point that the literature has an abundant amount of examples of reactions where the increase in heat drastically changes the outcome of the reaction. Therefore, we first reacted ester **38** at different temperatures with hydrazine and finally found out that 1-propanol was the suitable solvent under reflux conditions for the formation of desired cyclization products.

2.1.5.1.1 Synthesis of Phthalazinone Derivative 40a

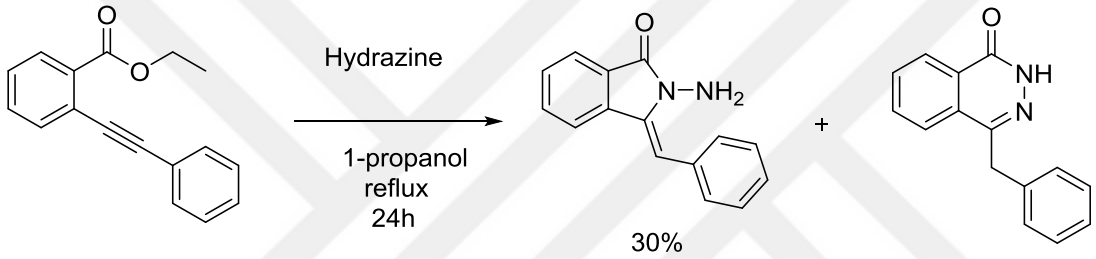
The method that was used in this part was relatively simple. The unsuccessful trials done by Shvartsberg *et al.*[28] were the starting point. Their work included the reaction of ester **46a** with hydrazine at the reflux temperature of ethanol. As shown in the Scheme 22, they reported to yield only the hydrazide **39a**, without any production of a possible phthalazinone **40a**.



46a **39a**

Scheme 24. Reaction of **46a** by Shvartsberg.

However; running this reaction at a different solvent, propanol (Scheme 23), proved to be successful for phthalazinone **40a** formation in the reflux temperature. Trials by propanol are shown in Table 2.



38a **47** **40a**

Scheme 25. Synthesis of **47** and desired phthalazinone **40a**

Reactant	Solvent	Temperature (° C)	Resultant product(s)
38a	Propanol	50	**39a**
38a	Propanol	78	**39a**
38a	Propanol	98	**40a** and **47**

Table 2: Trials to synthesize **40a** that were made by propanol

Compound **40a** was characterized by using ^{1}H and ^{13}C NMR. As shown in Figure 3, the singlet at 4.24 belongs to the methylene protons that bridge phthalazinone and phenyl skeletons. The broad singlet at 11.50 is the signal of the hydrogen atom bonded to the nitrogen atom. Also, the integration value of the broad singlet is the half of the two methylene protons at 4.24, which also shows that the spectra is compatible. As shown in Figure 4, peak at 161.1 arises from the carbonyl carbon, whereas peak at 39.9 is a definite show of a tetrahedral carbon as the bridge. All signals are in agreement with the proposed structure.[29]

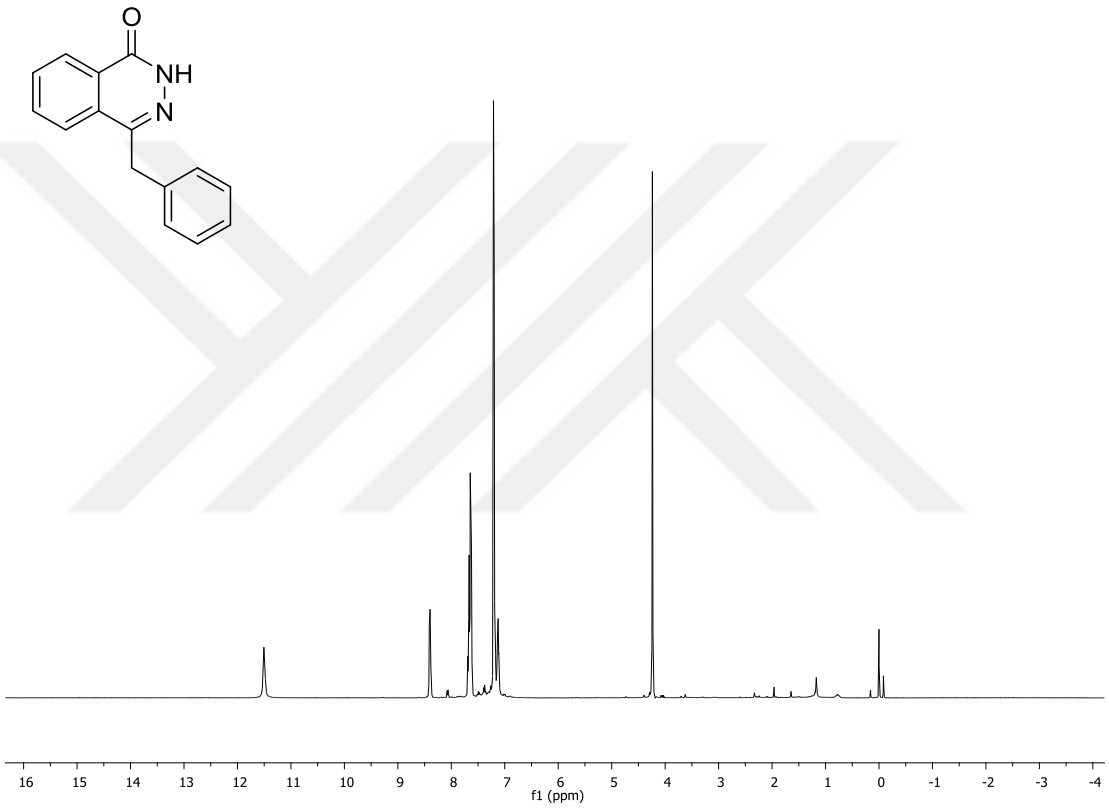


Figure 3: ^{1}H NMR spectra of compound **40a**

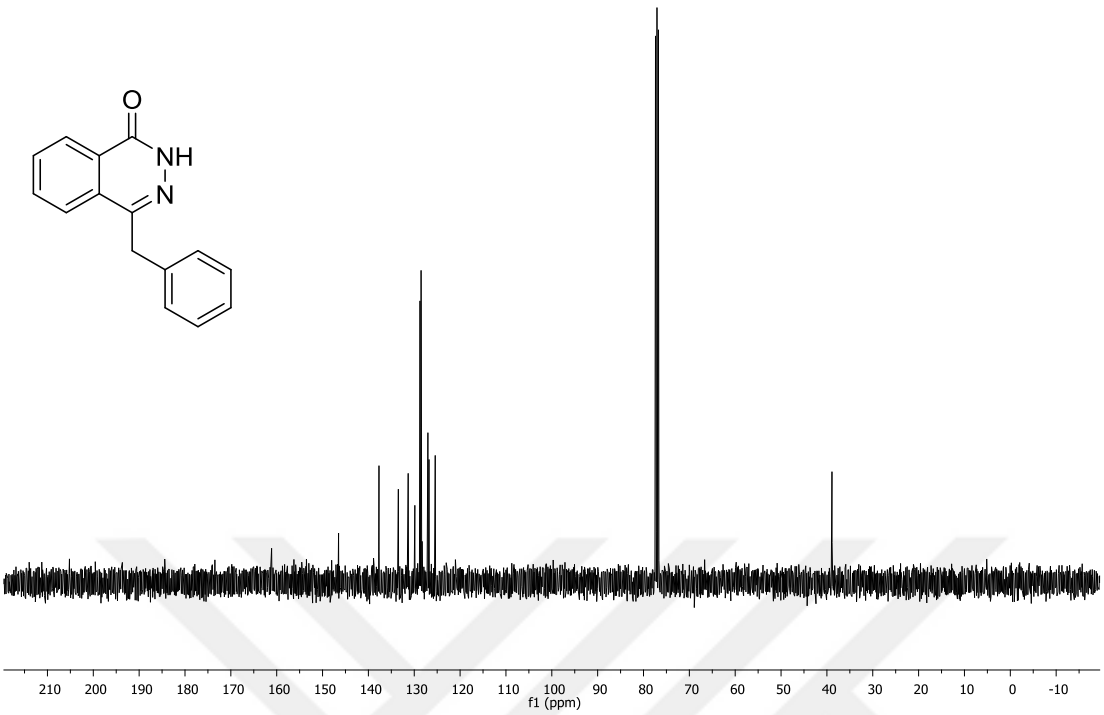
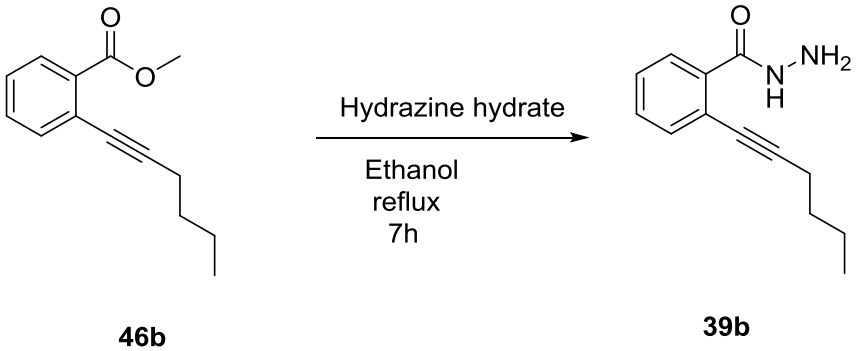


Figure 4: ^{13}C NMR spectra of compound **40a**

2.1.5.1.2 Attempted Synthesis of Phthalazinone Derivative 40b

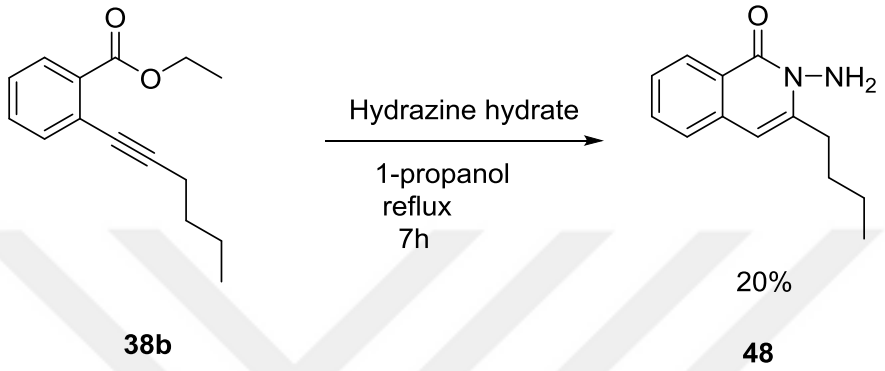
After succeeding in synthesis of phthalazinone derivative **40a,** we moved on with another starting compound, which is **38b**. Vasilevsky *et al.*[30] stated in their work that the reaction of **46b** with hydrazine hydrate in ethanol under reflux conditions yielded only the hydrazide **39b** of the compound **46b**. (Scheme 24)



46b **39b**

Scheme 26. Reaction of **46b** by Vasilevsky.

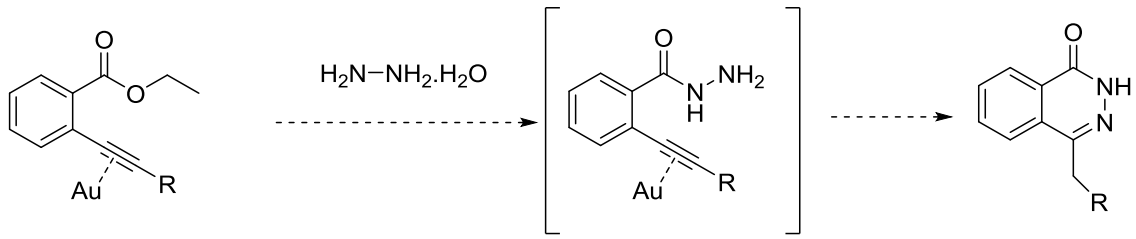
Encouraged by the success of synthesis of **40a**, again we used the same method by having 1-propanol as the solvent and under reflux conditions. Here, the reaction was completed in 12 hours. Unfortunately, isoquinolinone derivative **48** was the only compound that was formed and isolated (Scheme 25). Heating the mixture to higher temperatures again changed the intercourse of the reaction; however, desired phthalazinone derivative **40b** was not formed.



Scheme 27. Attempt to synthesize **40b**

2.1.5.2 Synthesis of Phthalazinone Derivatives with Gold Catalyst

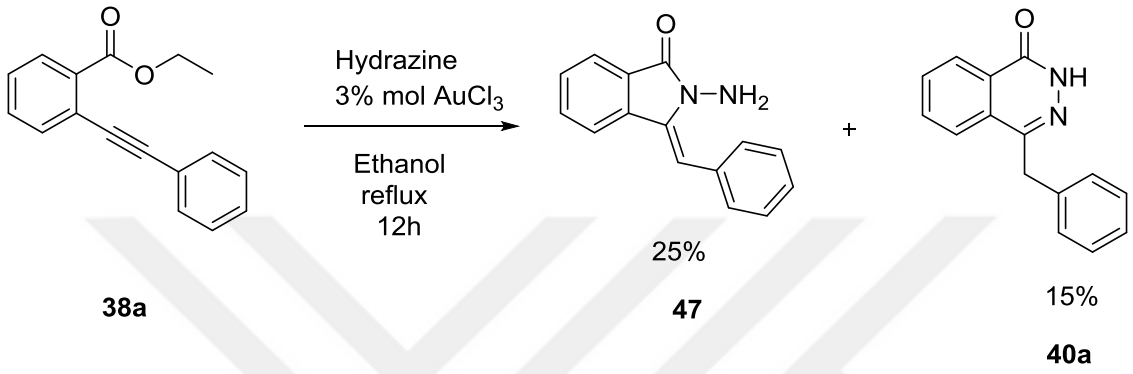
Since the aim of this study was to find novel methods to synthesize phthalazinone derivatives. Novel method trials were the ones that include a gold catalyst ($AuCl_3$) and the reactions included an alkyne cyclization step (Scheme 26).



Scheme 28. Schematic representation of our study in the presence of gold catalyst

2.1.5.2.1 Synthesis of Phthalazinone Derivative 40a

Encouraged by the success of synthesis of **40a**, we also conducted the same reaction by having ethanol as solvent and in reflux conditions with 3% mol of $AuCl_3$, recalling past reactions done in ethanol produced only hydrazides. Reaction was successful and had produced **40a** and **47** again in 12 hours (Scheme 27).



Scheme 29. Synthesis of **40a** and **47** by a gold catalyst

2.1.5.2.2 Attempted Synthesis of Phthalazinone Derivatives 40c-d

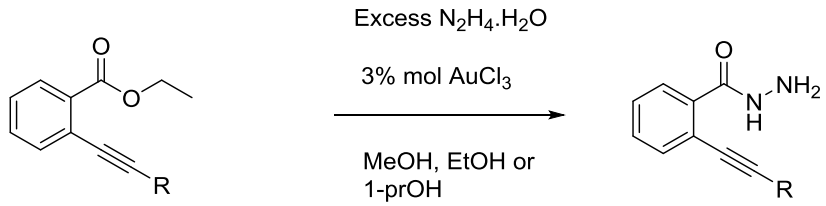
Trials were started where the starting compounds were **38c** and **38d** (Scheme 27). Trials were done with three different solvents, methanol, ethanol and 1-propanol at different temperatures. All the reactions were carried out with 3% $AuCl_3$ as the catalyst (Table 3). Unfortunately, none of the reactions yielded phthalazinone derivatives **40c** and **40d**, as the reactions stopped at the hydrazides **39c** and **39d** (Scheme 28).

At this point, it was discussed that why the phenyl derivative gave phthalazinone products but the others did not. Knowing that phenyl has a stabilizing effect to its substituents, and the phthalazinone production is based on 6-*exo* dig cyclization, the explanation in Scheme 29 holds. At the intermediate of the cyclization reaction, 6-*exo* dig attack of nitrogen electrons pushed one pair of π electrons to the adjacent carbon. Then, the carbon becomes a carbanion. Since carbanions are reactive intermediates, a stabilization effect on them may be helpful towards the progress of the reaction. Here,

in the example of **38a**, phenyl group provided that stabilization. On the other hand, none of the substituents of **38b-d** could provide such an effect.

Reactant	Solvent	Temperature (° C)	Result without catalyst	Result with catalyst
38c-d	Methanol	25	**39c-d**	**39c-d**
38c-d	Methanol	65	**39c-d**	**39c-d**
38c-d	Ethanol	25	**39c-d**	**39c-d**
38c-d	Ethanol	50	**39c-d**	**39c-d**
38c-d	Ethanol	78	**39c-d**	**39c-d**
38c-d	1-propanol	50	**39c-d**	**39c-d**
38c-d	1-propanol	78	**39c-d**	**39c-d**
38c-d	1-propanol	98	**39c-d**	**39c-d**

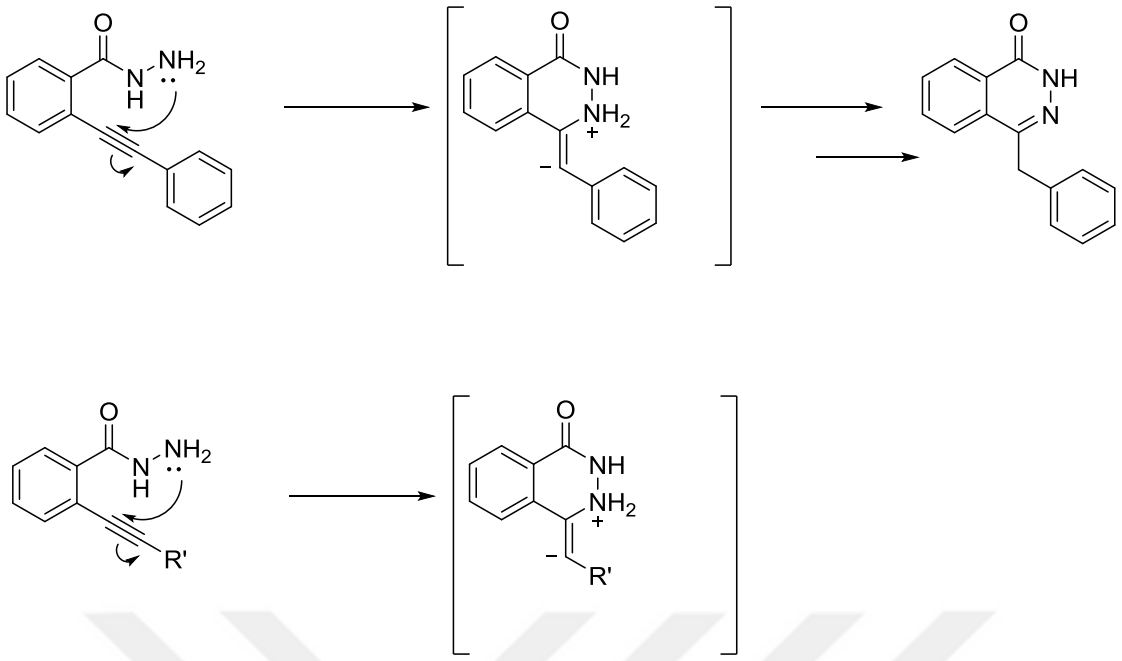
Table 3: Reaction conditions and resultant products



38c R= -H
38d R= -TMS

39c R= -H
39d R= -TMS

Scheme 30 Attempted synthesis of phthalazinones **40c-d**

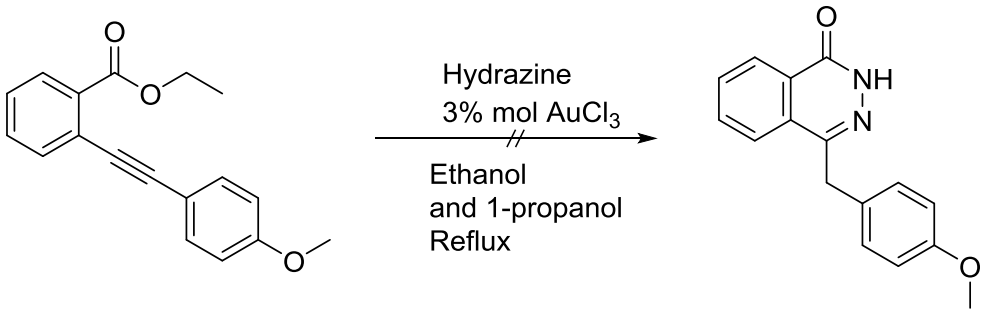


(R'= -H, -TMS, -n-Bu)

Scheme 31. Stabilization effect of phenyl group on nearby anion

2.1.5.2.3 Synthesis of Phthalazinone Derivatives 40e-g

The successful synthesis of phthalazinone **40a** encouraged us to run reactions on its derivatives where the phenyl group attached to the ring could now be substituted at para position, yielding compounds **38e-g**. These compounds were also reacted with 3% $AuCl_3$ with hydrazine, directly in 1-propanol and ethanol at the reflux temperatures. Trials of derivative **38g** unfortunately resulted in an unknown complex mixture rather than the desired phthalazinone **40g**. (Scheme 30)



38g **40g**

Scheme 32. Attempted synthesis of **40g**

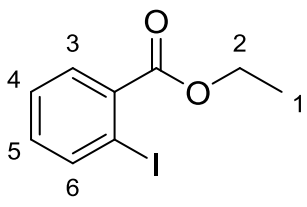
CHAPTER 3

EXPERIMENTAL SECTION

3.1 General

All reagents were commercially available and used without further purification. 400 MHz and 101 MHz NMR instruments, respectively, were used to record ^{1}H-NMR and ^{13}C-NMR spectra while using $CDCl_3$ as its solvent and TMS as an internal standard. Coupling constants, *J*, were reported in Hertz (Hz) and chemical shifts, δ, were reported in parts per million (ppm). The peak patterns of ^{1}H NMR are designated as follows: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; dt; doublet of triplet and m, multiplet. IR spectra were recorded via ATR Diamond. Reaction products were purified by column chromatography using silica gel (60-mesh). TLC activites was carried out on Merck 0.2 mm silica gel 60 F254 analytical aluminum plates. Melting point apparatus was used in measuring melting points and they were uncorrected. A rotary vacuum evaporator is used in evaporation of solvents at reduced pressure.

3.2 Synthesis of Ethyl 2-iodobenzoate (37)[31]: Starting compound 2-iodobenzoic acid **(36)** (5.0 g, 0.018 mol) was dissolved in ethanol (50 mL) and followed by addition of sulfuric acid (1 mL) as catalyst. reaction mixture was heated at the reflux temperature overnight while stirring. After the completion of the reaction, solvent was removed under reduced pressure and sat. $NaHCO_3$ was added until the pH of the medium equals to 7. Then the resulting mixture was extracted with ethyl acetate (3 x 50 mL). Organic phases were combined and dried over $MgSO_4$. Finally, the solvent was evaporated under reduced pressure to give ethyl-2-iodobenzoate (3.94 g, 72%) as pale yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.0 Hz, 1H, H-3), 7.79 (dd, *J* = 7.8, 1.7 Hz, 1H, H-6), 7.39 (dt, *J* = 7.6, 1.1 Hz, 1H, H-4), 7.14 (dt, *J* = 7.8 Hz, 1H, H-5), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H)

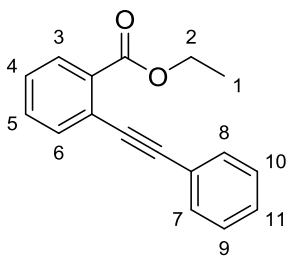
^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2, 61.7, 94.0, 128.0, 130.8, 132.5, 135.6, 141.2, 166.6

IR (ATR, cm^{-1}) 2979, 1721, 1286, 1247, 1014, 738

3.3 General Procedure for Coupling Products 38 a-g

Coupling catalysts $PdCl_2$ (0.036 mmol, 6 mg), CuI (0.108 mmol, 10 mg) and PPh_3 (0.144 mmol, 36 mg) were added to a flask that was being flushed with nitrogen gas at room temperature. Following that, NEt_3 (1 mL) was added to the flask. Then, ethyl 2-iodobenzoate (1 g, 3.6 mmol) was dissolved in THF (15 mL). Finally, alkyne derivatives (1.2 eq) were added to reaction flask and stirred at reflux temperature. Reactions were monitored on TLC. The completion of the reaction was followed by an extraction with EtOAc (3 x 100 mL) and the organic phase was dried over $MgSO_4$. After removal of the solvent, the crude products were purified by column chromatography (silica gel). Depending to the acetylene derivatives; column solvent ratios, yields, and structures were different.

3.3.1 Synthesis of Ethyl 2-(phenylethynyl)benzoate (38a)[32]: (Yellow oil, 60%, 5:1 hexane/ethyl acetate)

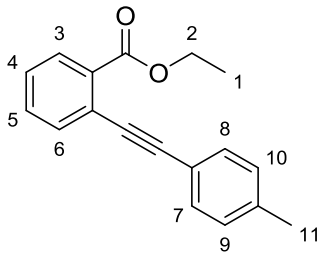


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.9, 1.2 Hz, 1H, H-3), 7.64 (dd, *J* = 7.8, 1.1 Hz, 1H, H-6), 7.57 (m, 2H), 7.48 (dt, *J* = 7.6, 1.3 Hz, 1H, H-11), 7.37 (m, 4H), 4.42 (q, *J* = 7.11 Hz, 2H), 1.40 (t, *J* = 7.13 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 61.2, 88.3, 94.2, 123.4, 123.6, 127.9, 128.4, 128.5, 130.4, 131.5, 131.7, 132.3, 134.0, 166.4

IR (ATR, cm^{-1}) 1724, 1289, 1248, 1127, 1074, 753, 689

3.3.5 Synthesis of Ethyl 2-(*p*-tolylethynyl)benzoate (38e)[32]: (Yellow oil, 57%, 5:1 hexane/ethyl acetate)



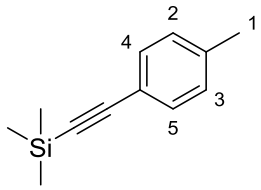
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.8, 1.1 Hz, 1H, H-3) 7.63 (dd, *J* = 7.8, 1.0 Hz, 1H, H-6), 7.46 (m, 3H), 7.35(m, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 4.42 (q, *J* = 7.16 Hz, 2H), 2.36 (s, 3H), 1.40 (t, J = 7.14 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 21.6, 61.2, 87.7, 94.5, 120.3, 123.8, 127.7, 129.1, 130.4, 131.5, 131.6, 132.2, 134.0, 138.7, 166.5

3.4 General Procedure for Coupling Products 42 e-g

To an empty flask flushed by nitrogen gas was added the coupling catalysts $PdCl_2$ (1.4 mg, 0.01 eq), CuI (2,6 mg, 0.03 eq) and PPh_3 (4,8 mg, 0.04 eq) at room temperature followed by addition of NEt_3 (1 mL). Then, compounds **43 e-g** (1 eq, 100 g for the case of **43e)** were dissolved in THF (15 mL) and added to the flask. Finally, TMS-acetylene (1.2 eq) was added to the mixture and stirred at reflux temperature for 1-3 hours. Reactions were monitored on TLC. After the completion of the reaction the mixture was extracted with EtOAc (3 x 100 mL) and the organic phase being dried over $MgSO_4$. After removal of solvent under reduced pressure, the crude products were purified by column chromatography (silica gel). Depending on the acetylene derivatives; column solvent ratios, yields, and structures were different.

3.4.1 Synthesis of Trimethyl(p-tolylethynyl)silane (42e)[33] (Dark yellow oil, 80%, 4:1 hexane/ethyl acetate)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.1 Hz, 2H, H-4,5) 6.88 (d, *J* = 7.9 Hz, 2H, H-2,3), 2.12 (s, 3H), 0.04 (s, 9H)

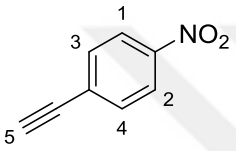
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 131.8, 128.9, 120.1, 105.3, 93.18, 21.4, 0.0

IR (ATR, cm^{-1}) 2958, 2156, 1507, 1250, 862, 839, 758

3.5 General Procedure for Desilylation Products 43 e-g

Silylated products **42 e-g** were dissolved in THF (15 mL) and were reacted with dry tetra n-butyl ammonium flouride, TBAF, (1 eq). The reaction was run in an ice bath. Reactions were monitored on TLC and all reactions were completed in 15 min. The solution was diluted with 100 mL of ethyl acetate and was washed with brine (4 x 50 mL). Then, the organic phase was dried over $MgSO_4$. Solvent was removed under reduced pressure. The products were used without further purification.

3.5.2 Synthesis of 1-ethynyl-4-nitrobenzene (43f)[34] (Yellow solid, 90%)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.8 Hz, 2H, H-1,2), 7.57 (d, *J* = 8.8 Hz, 2H, H-3,4), 3.29 (s, 1H, H-5)

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 133.0, 129.0, 123.6, 82.3, 81.6

IR (ATR, cm^{-1}) 3249, 1593, 1508, 1340, 1105, 851, 676

Melting point: 148-149 ºC (lit. m. p. 150-151ºC)

3.6 Synthesis of 47 and 40a

Without a catalyst: Ethyl 2-(phenylethynyl)benzoate (**38a**, 1,6 mmol, 400 mg) was dissolved in 1-propanol (5 mL). Hydrazine monohydrate (8 mmol, 408 mg) was added to the solution and then the temperature rose to the reflux temperature. Reaction was monitored by TLC. After 24 hours, the reaction was completed. Firstly, the solvent was removed under reduced pressure. Then, the crude product was extracted with EtOAc (3 x 25 mL) and the resulting organic phase was dried over $MgSO_4$. The product was then purified by column chromatography (silica gel) using 5:1 hexane/ethyl acetate as the eluent (Table 4).

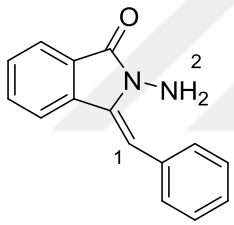
With catalyst: : Ethyl 2-(phenylethynyl)benzoate (**38a**, 1,6 mmol, 400 mg) was dissolved in 5 mL of ethanol. Hydrazine monohydrate (8 mmol, 408 mg) was added to the solution and then the temperature rose to the reflux temperature. Reaction was monitored by TLC. After 12 hours, the reaction was completed. Firstly, the solvent

was removed under reduced pressure. Then, the crude product was extracted with EtOAc (3 x 25 mL) and the resulting organic phase was dried over $MgSO_4$. The product was then purified by column chromatography (silica gel) using 5:1 hexane/ethyl acetate as the eluent (Table 4).

	Without catalyst in 1-propanol	Gold catalyst in ethanol
47	30% (112 mg)	25% (94 mg)
40a	20% (75 mg)	15% (56 mg)

Table 4: Yields of **47** and **40a**

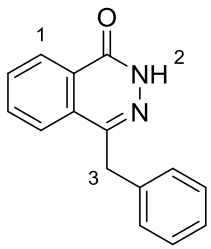
3.6.1 Synthesis of 2-amino-3-benzylideneisoindolin-1-one (47)[28] Yellow solid (112 mg, %30)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 1H), 7.37 (t, *J* = 6.8 Hz ,4H), 7.32 (m, 3H), 7.25 (dd, *J* = 7.7, 1.1 Hz , 1H), 6.98 (s, 1H, H-1), 4.33 (bs, 2H, H-2)

Melting point: 101-102 °C (lit. m. p. 102-103°C)

3.6.2 Synthesis of Benzylphthalazin-1(2H)-one (40a)[29] White powder (75 mg, %20).



^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (bs, 1H, H-2), 8.40 (dd, *J* = 6.1, 3.0 Hz, 1H, H-1), 7.65 (m, 3H), 7.16 (m, 5H), 4.24 (s, 2H)

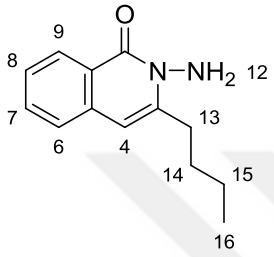
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 146.5, 137.7, 133.5, 131.3, 130.0, 128.8, 128.5, 128.3, 127.0, 126.8, 125.4, 39.9

IR (ATR, cm^{-1}) 3009, 2902, 1655, 1609, 1338, 903, 873, 768, 739, 702

Melting point: 198 °C (lit m.p. 200-201°C)

3.7 Synthesis of 2-amino-3-butylisoquinolin-1(2H)-one (48)[30]

Ethyl 2-(hex-1-yn-1-yl)benzoate (0.86 mmol, 200 mg) **(38b)** was dissolved in 1-propanol (5 mL). Hydrazine monohydrate (0.43 mmol, 220 mg) was added to the solution and heated at the reflux temperature. Reaction was monitored by TLC. After 7 hours, the reaction was completed. Firstly, the solvent was removed under reduced pressure. Then, the crude product was extracted with EtOAc (3 x 25 mL) and the resulting organic phase was dried over $MgSO_4$. The product was then purified by column chromatography (silica gel) using 5:1 hexane/ethyl acetate as the eluent to give **48** as yellow solid (38 mg, %20).



^{1}H NMR (400 MHz, $CDCl_3$) 8.36 (d, *J* = 7.6 Hz, 1H), 7.59 (m, 1H), 7.43 (m 2H), 6.34 (s, 1H, H-4), 4.98 (bs, 2H, H-12), 2.83 (m, 2H), 1.67 (m, 2H), 1.46 (m, 2H), 0.98 (t, *J* = 7.33 Hz, 3H)

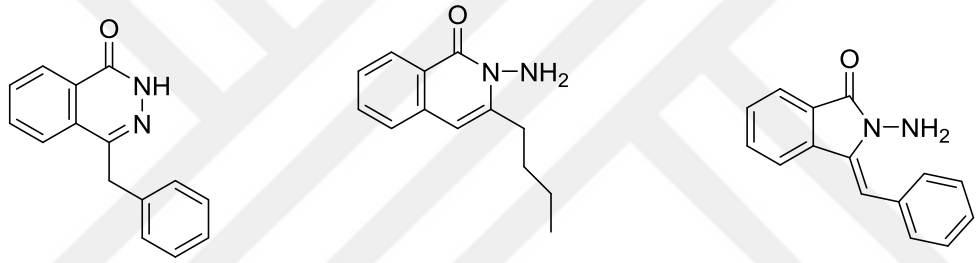
IR (ATR, cm^{-1}) 3197, 2955, 2929, 2870, 1593, 1467, 1339, 998, 688

Melting point: 73 °C (lit. m.p. 75-76°C)

CHAPTER 4

CONCLUSION

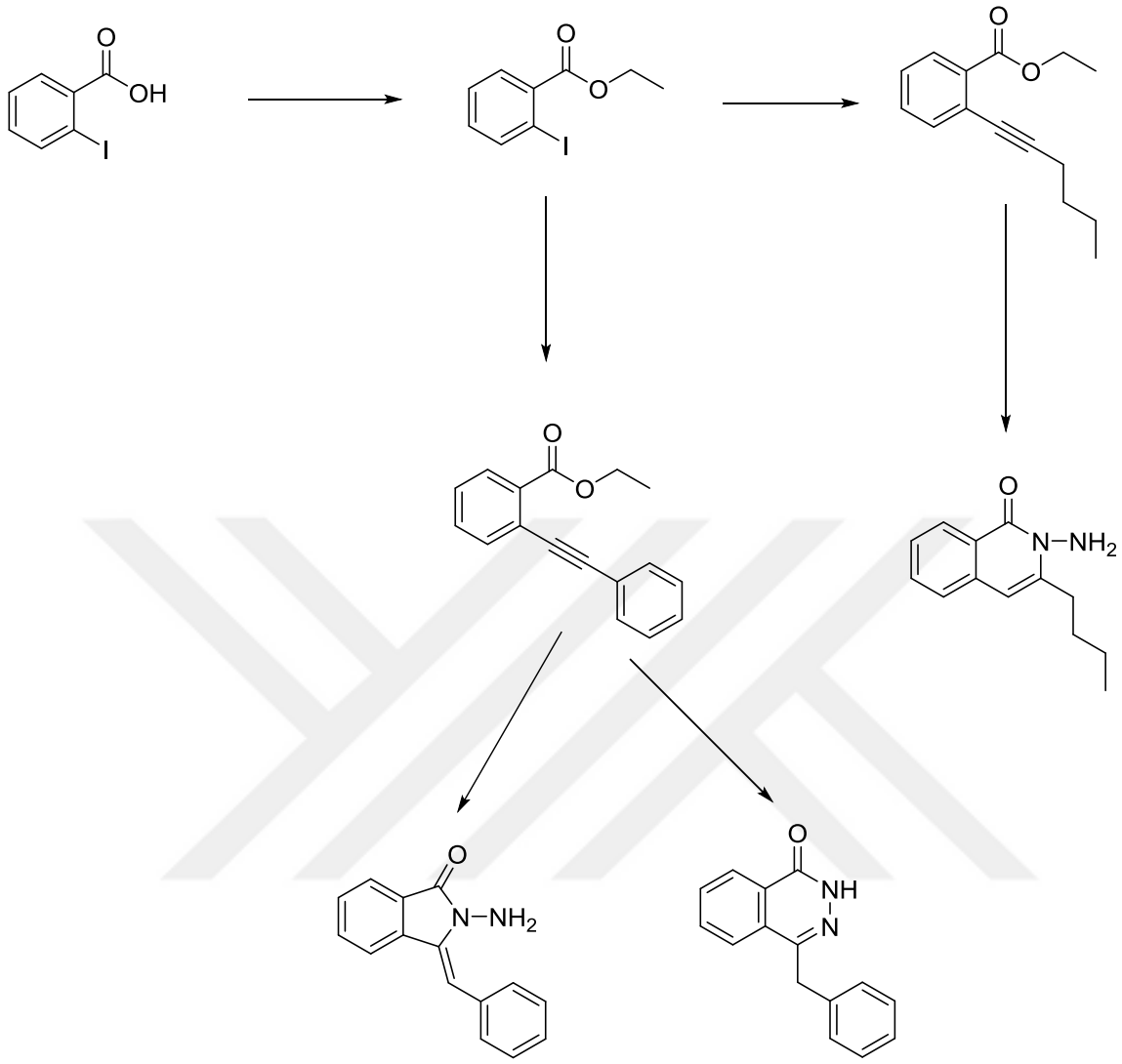
In this study, we developed novel synthetic methodologies for the synthesis of phthalazinone derivative **40a** and isoquinoline derivative **48** (Scheme 31). Especially phthalazinone skeletons and derivatives having potential for showing potent activity for cancer treatment.



40a **48** **47**

Scheme 33. Products synthesized in novel fashion

In the first part of our study, iodobenzoate **37** was synthesized by Fischer esterification reaction. Then, ester **37** was converted into ethynyl derivatives **38a** and **38d** by Sonogashira cross coupling reactions. Lastly, to obtain products **40a** and **48,** ethynyl derivatives were reacted with hydrazine monohydrate in 1-propanol without a catalyst. Isoindolinone derivative **47** was also produced in the reaction of **38a** with hydrazine. Then, we successfully reacted **38a** with hydrazine in the presence of gold catalyst in ethanol and reaction concluded giving the same products that were not formed in the reactions carried out in ethanol without the catalyst. (Scheme 32).



Scheme 34. Overall reaction scheme

REFERENCES

1) Xue, D.Q.; Zhang, X.Y.; Wang, C.J.; Ma, L.Y.; Zhu, N.; He, P.; Shao, K.P.; Chen, P.J.; Gu, Y.F.; Zhang, X.S.; Wang, C.F.; Ji, C.H.; Zhang, Q.R.; Liu, H.M. *Eur. J. Med. Chem.* **2014**, *85*, 235-244.

2) El-Helby, A.G.A.; Ayyad, R.R.; Sakr, H.M.; Abdelrahim, A.S.; El-Adl, K.; Sherbiny, F.S.; Eissa, I.H.; Khalifa, M.M. *J. Mol. Struct.* **2017**, *1130*, 333-351.

3) Hameed, A.D; Ovais, S.; Yaseen, R.; Rathore, P.; Samim, M.; Singh, S., Sharma, K.; Akhtar, M.; Javed, K. *Arch. Pharm.* **2016**, *349*,150-159.

4) Fong, P.C.; Boss, D.S.; Yap, T.A.; Tutt, A.; Wu, P.J.; Mergui-Rovelnik, M.; Mortimer, P.; Swaisland, H.; Lau, A.; O'Connor, M.J.; Ashworth, A.; Carmichael, J.; Kaye, S.B.; Schellens, J.H.M.; de Bono, J.S. *N. Engl. J. Med*. **2009**, *361*, 123–134.

5) Vigil-De Gracia, P.; Lasso, M.; Ruiz, E.; Vega-Malek, J. C.; de Mena, F. T.; Lopez, J. C. Eur. *J. Obstet. Gynecol. Reprod. Biol*. **2006**, *128*, 157–162.

6) Maxwell, C.R.; Kanes, S.J.; Abel, T.; Siegel, S.J. *Neuroscience* **2014**, *129*, 101–107.

7) Sroczynki, D.; Malinowski, Z.; Szczesniak, A.K.; Pakulsksa, W. *Mol. Simulat.* **2017**, *42*, 628-641.

8) Shi, L.Y.; Hu, L.; Wang, J.Q.; Cao, X.Q.; Gu, H.W. *Org. Lett.* **2012**, *14*, 1876-1879.

9) Godoi, B.; Schumacher, R.F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937-2980.

10) Cai, R.; Wang, D.W.; Chen, Y.F.; Yan, W.M.; Geise, N.R.; Sharma, S.; Li, H.Y.; Petersen, J.L.; Li, M.Y.; Shi, X.D. *Chem. Commun.* **2014**, *50*, 7303-7305.

11) Keskin, S.; Balci, M. *Org. Lett.* **2015**, *17*, 964–967.

12) Fustero, S.; Simon-Fuentes, A.; Sanz-Cervera, J.F. *Org. Prep. Proced. Int.* **2009**, *41*, 253-290.

13) Qiao, J.X.; Liu, B.; Liao, Z.Q.; Li, Y.; Ma, L.; Dong, C.N.; Zhou, H.B. *Tetrahedron* **2014**, *70*, 3782-3787.

14) Shikhaliev, K.S.; Romanov, P.S.; Shestakov, A.S.; Stopovskaya, N.V.; Krysin, M.Y.; Potapov, A.Y.; Proshin, A.N. *Russ. Chem. B.* **2016**, *65*, 1008-1012.

15) Bucha, M; Eppakayala, L.; Maringanti, T.C.; Tharikoppula, G.; Kethireddy, S. *Org. Med. Chem. Lett.* **2014**, *4.*

16) Hashmi, A.S.K. *Chem. Rev.* **2007**, *107*, 3180-3211.

17) Liu, J.; Liu, Y. *Org. Lett.* **2012**, *14*, 4742–4745.

18) Carrer, A.; Pean, C.; Perron-Sierra, F.; Mirguet, O.; Michelet, V. *Adv. Synth. Catal.* **2016**, *358*, 1540-1545.

19) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874-922.

20) Johansson, S.C.C.C.; Kitching, M.O.; Colacot, T.J.; Snieckus, V. *Angew. Chem. Int. Ed*. **2012**, *51*, 5062 – 5085

21) Bertus, P.; Fecourt, F.; Bauder, C.; Pale, P. *New J. Chem.* **2004**, *28*, 12-14.

22) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2633-2657.

23) Narani, A.; Marella, R. K.; Ramudu, P.; Rao, K. S .R.; Burri, D. R. *RSC Adv*. **2014**, *4*, 3774-3781.

24) Kim, H.; Lee, P.H. *Adv. Synth. Catal.* **2009**, *17*, 2827-2832.

25) Baldwin, J. E. *J. C. S. Chem. Comm*. **1976**, *18*, 734-736.

26) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846-3852.

27) Koza, G.; Keskin, S.; Özer, M. S.; Cengiz, B.; Şahin, E.; Balci, M. *Tetrahedron*. **2013**, *69*, 395-409.

28) Vasilevskii, S.F.; Pozyndakov, A.V.; Shvartsberg, M.S. *B. Acad. Sci. USSR. Ch.* **1985**, *33*, 2383-2385.

29) Munin, J.; Santana, L.; Uriarte, E.; Borges, F.; Quezada, E. *Tetrahedron*, **2015**, *56*, 828-830.

30) Vasilevsky, S.F.; Mikhailovskaya, T.F.; Mamatyuk, V I.; Salnikov, G.E.; Bogdanchikov, G. A.; Manoharan, M.; Alabugin, I. V. *J. Org. Chem*. **2009**, *74*, 8106-8117.

31) Zhdankin, V.V.; Koposov, A.Y.; Litvinov, D.N.; Ferguson, M.J.; McDonald, R.; Luu, T.; Tykwinski, R.R. *J. Org. Chem.* **2005**, *70*, 6484-6491.

32) Tovar, J.D.; Swager, T. *J. Org. Chem*. **1999**, *64*, 6499-6504.

33) Lei, Y.; Hu, T.; Wu, X.; Wu, Y.; Xiang, H.; Sun, H.; You, Q.; Zhang, X. *Tetrahedron Lett.* **2016**, *57*, 1100-1103.

34) Quesada, E.; Raw, S.A.; Reid, M.; Roman, E.; Taylor, J.K. *Tetrahedron.* **2006**, *62*, 6673-6680

APPENDIX

SPECTRAL DATA

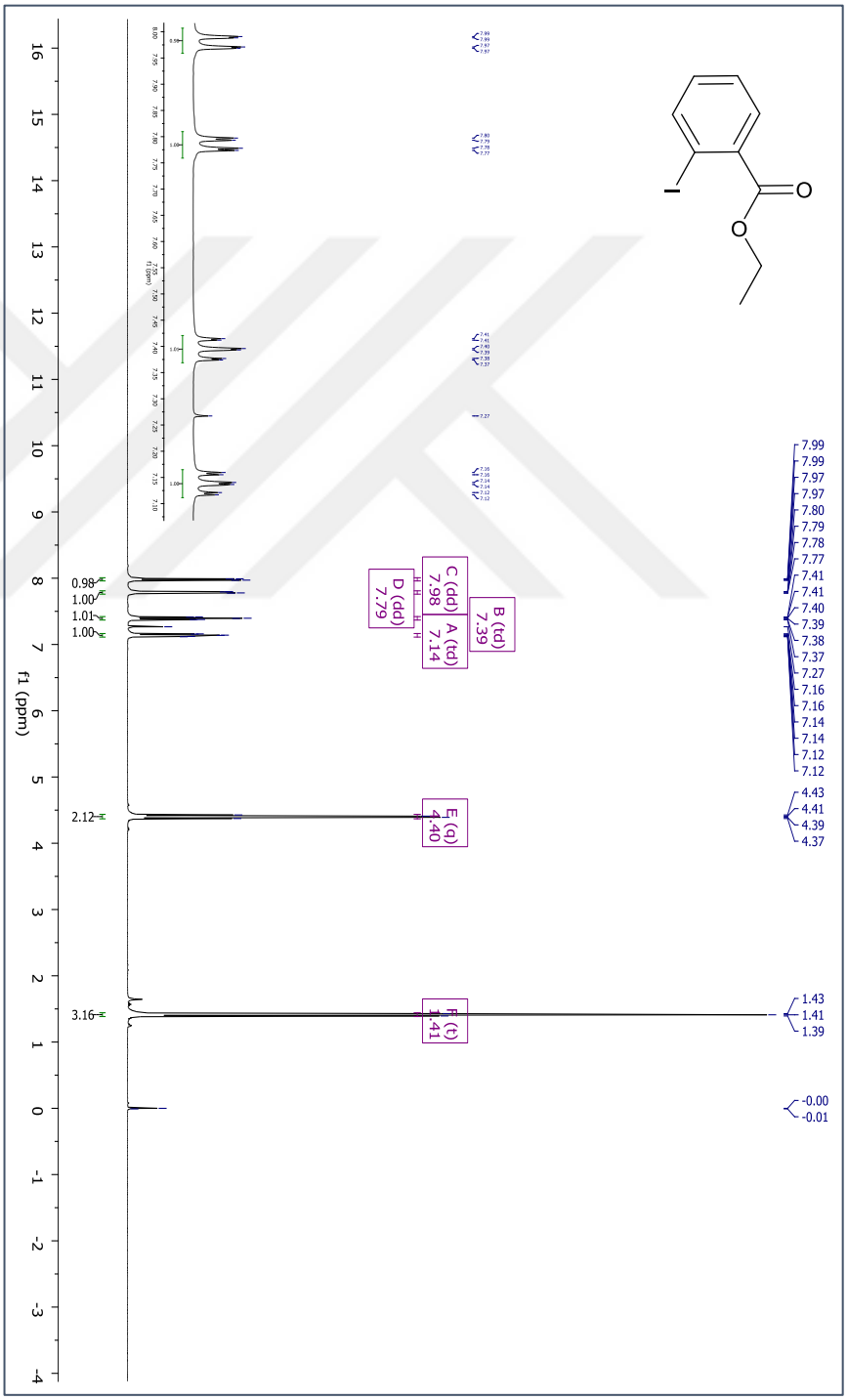


Figure 5: ^{1}H NMR spectrum of compound **37**

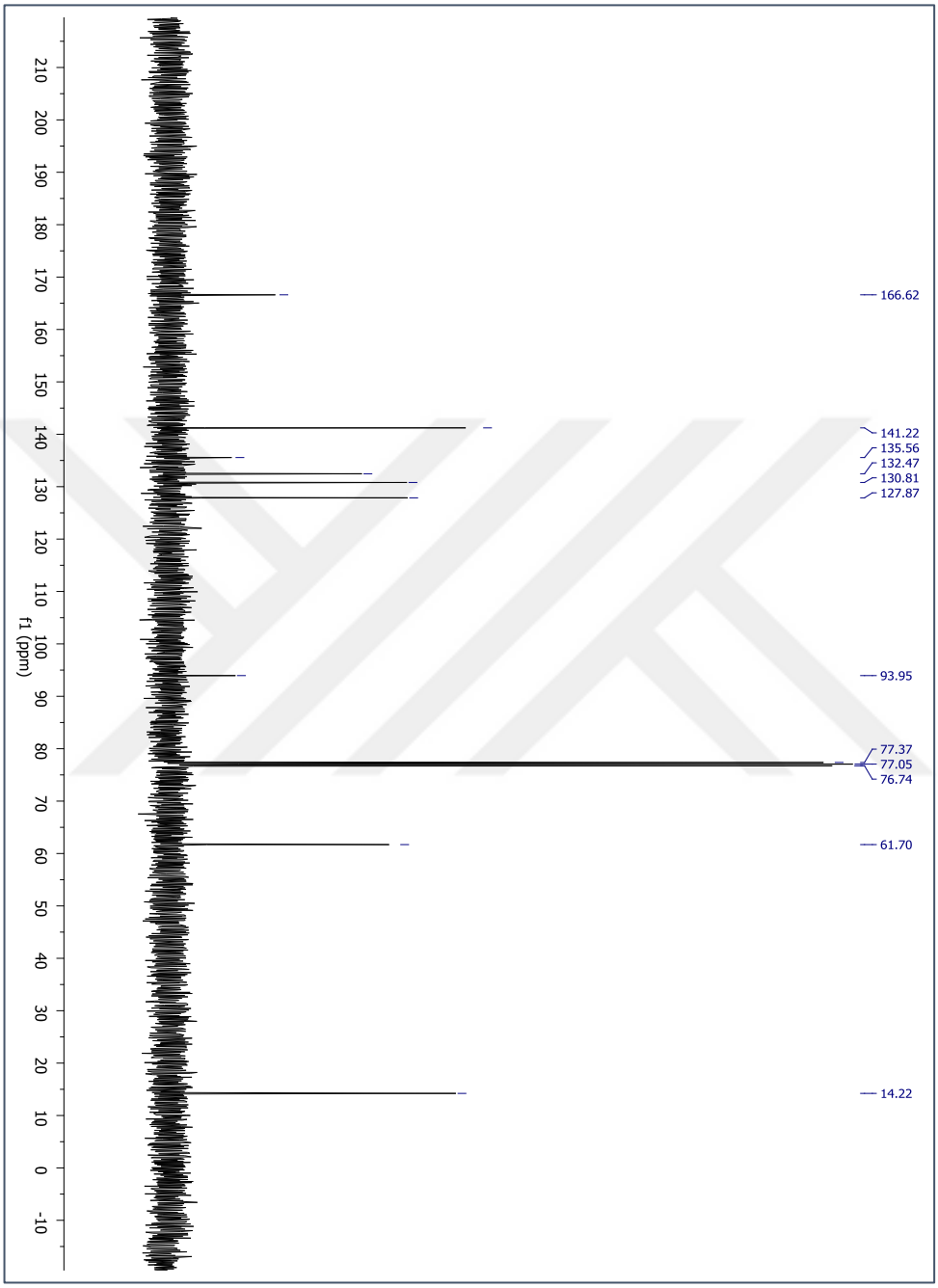


Figure 6: ^{13}C NMR spectrum of compound **37**

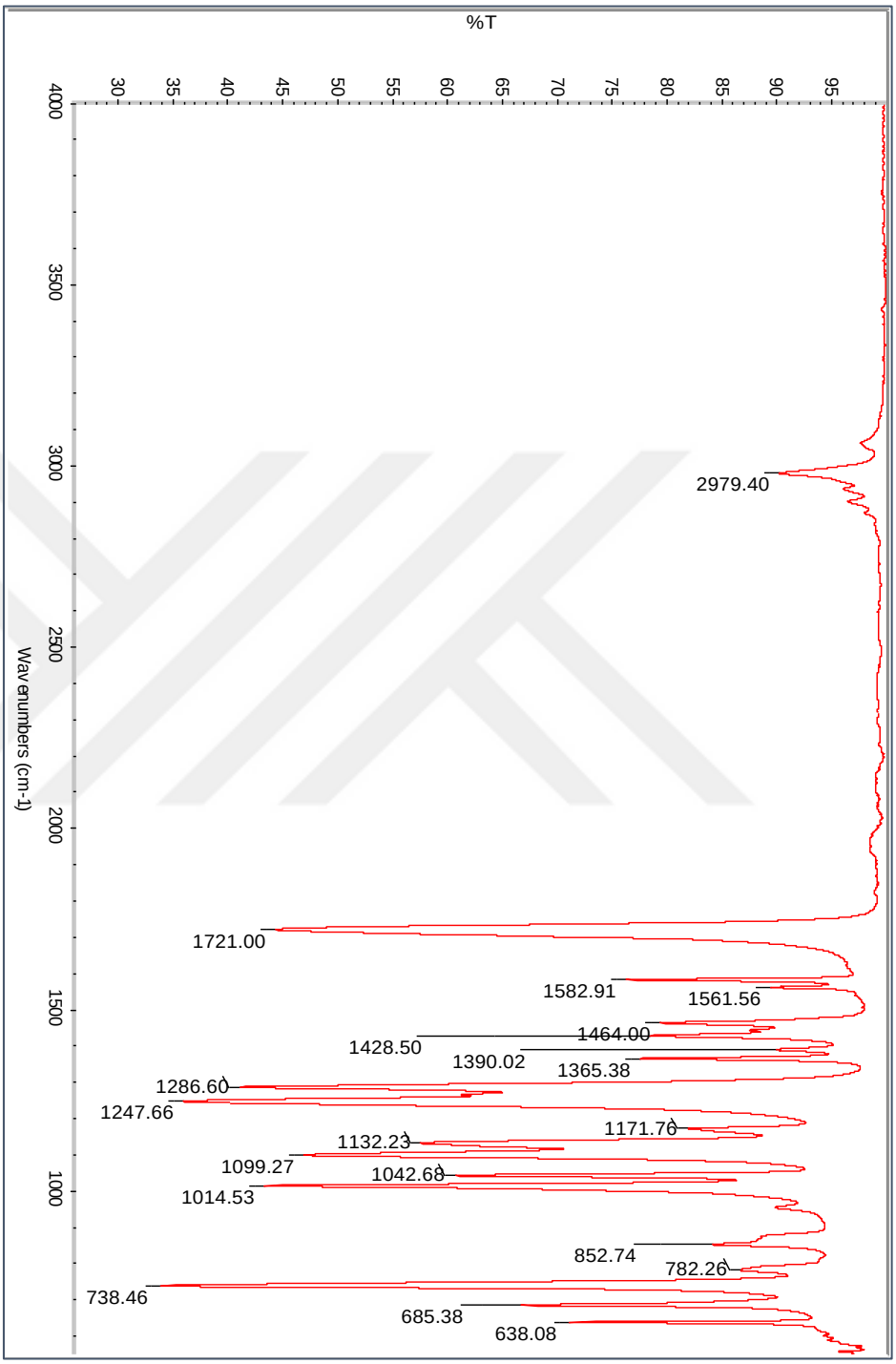


Figure 7: IR spectrum of compound **37**

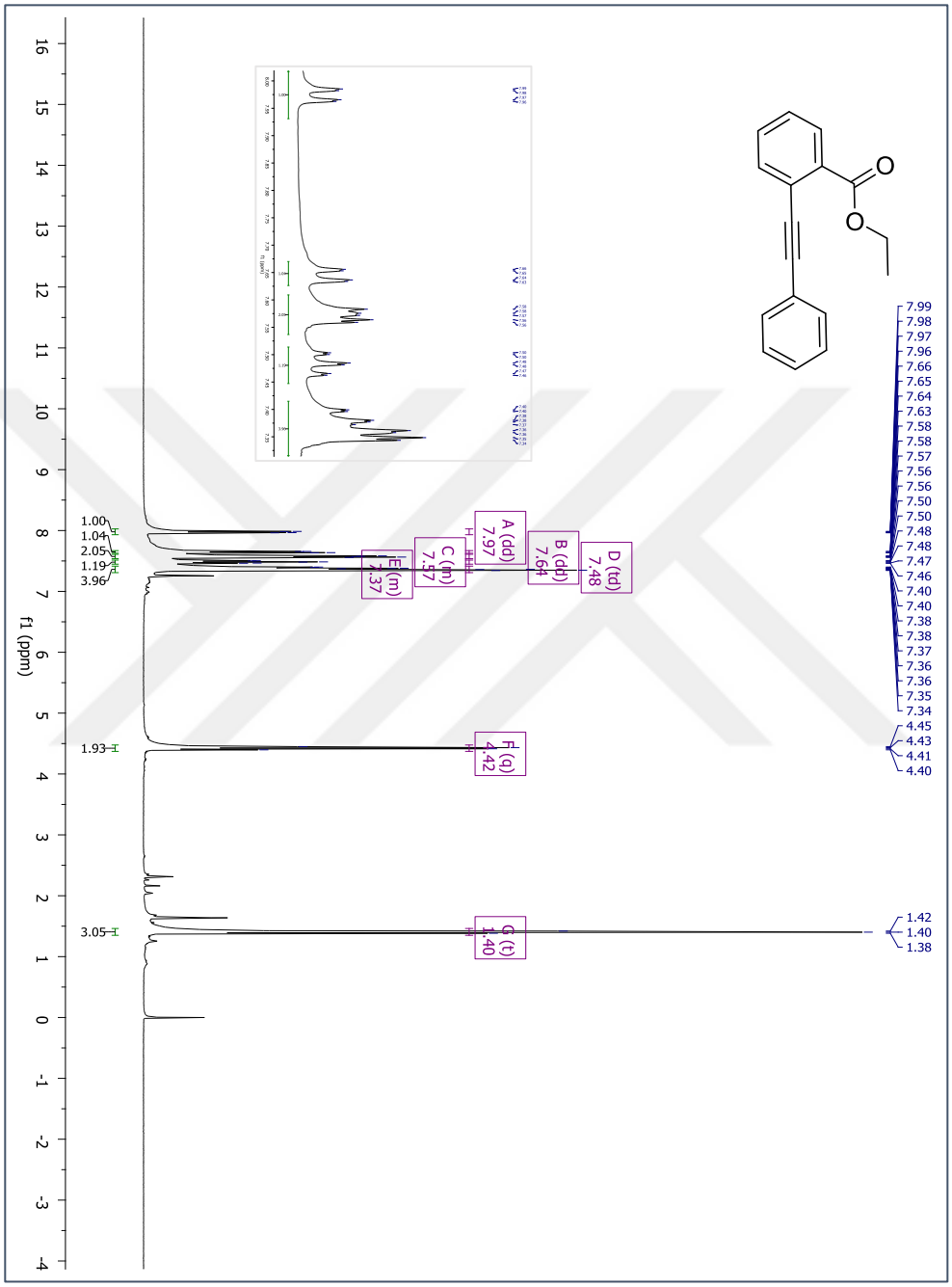


Figure 8: ^{1}H NMR spectrum of compound **38a**

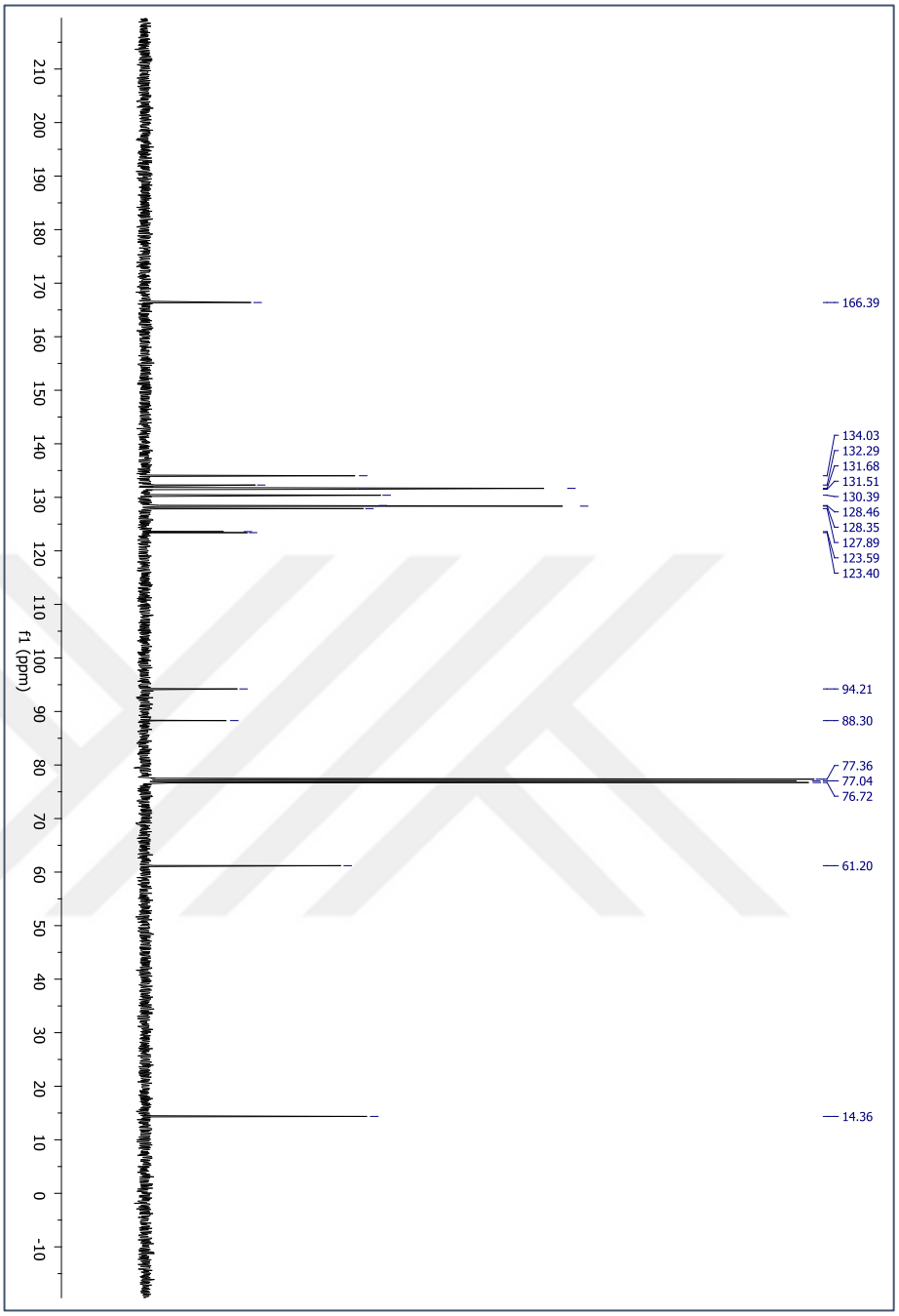


Figure 9: ^{13}C NMR spectrum of compound **38a**

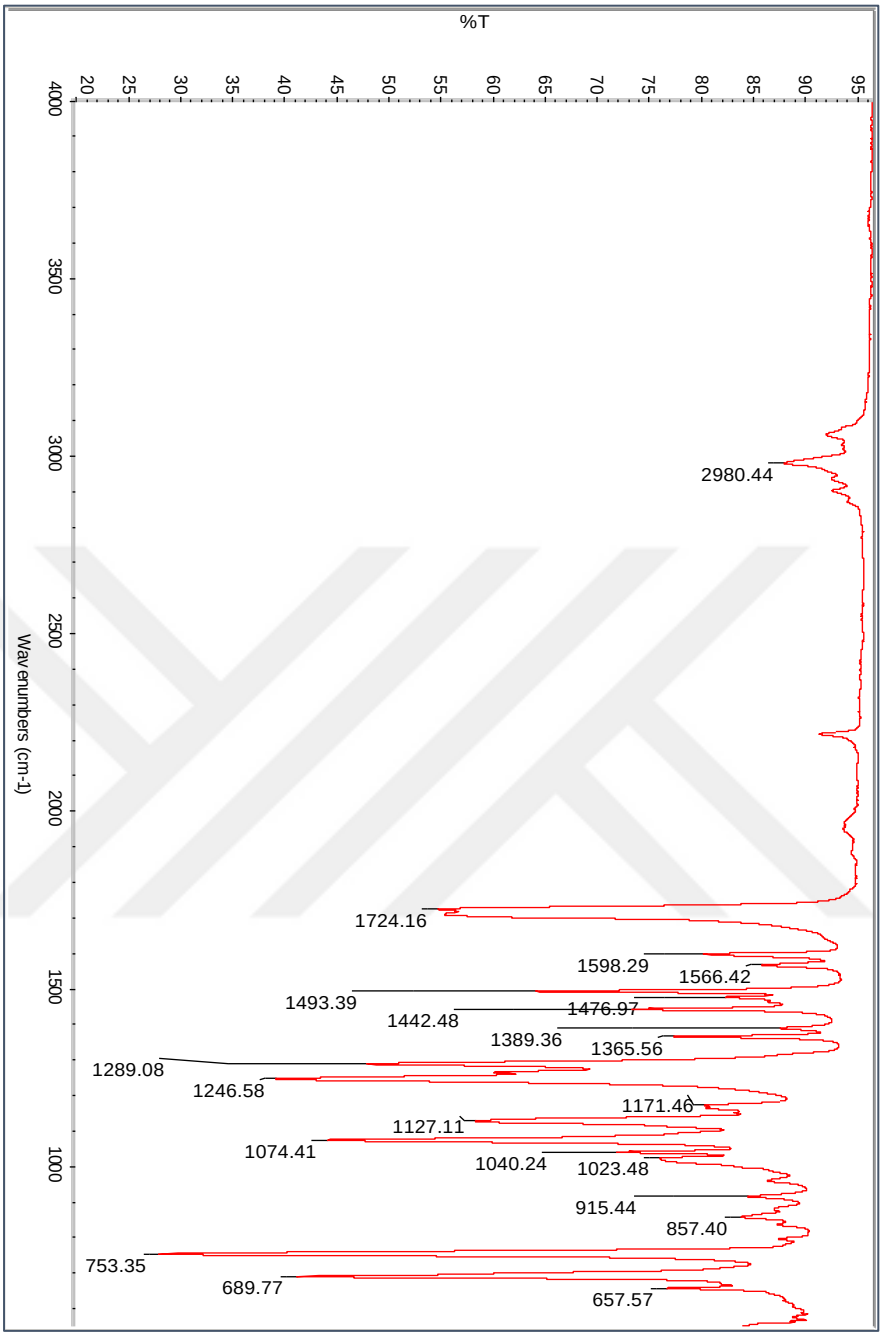


Figure 10: IR spectrum of compound **38a**

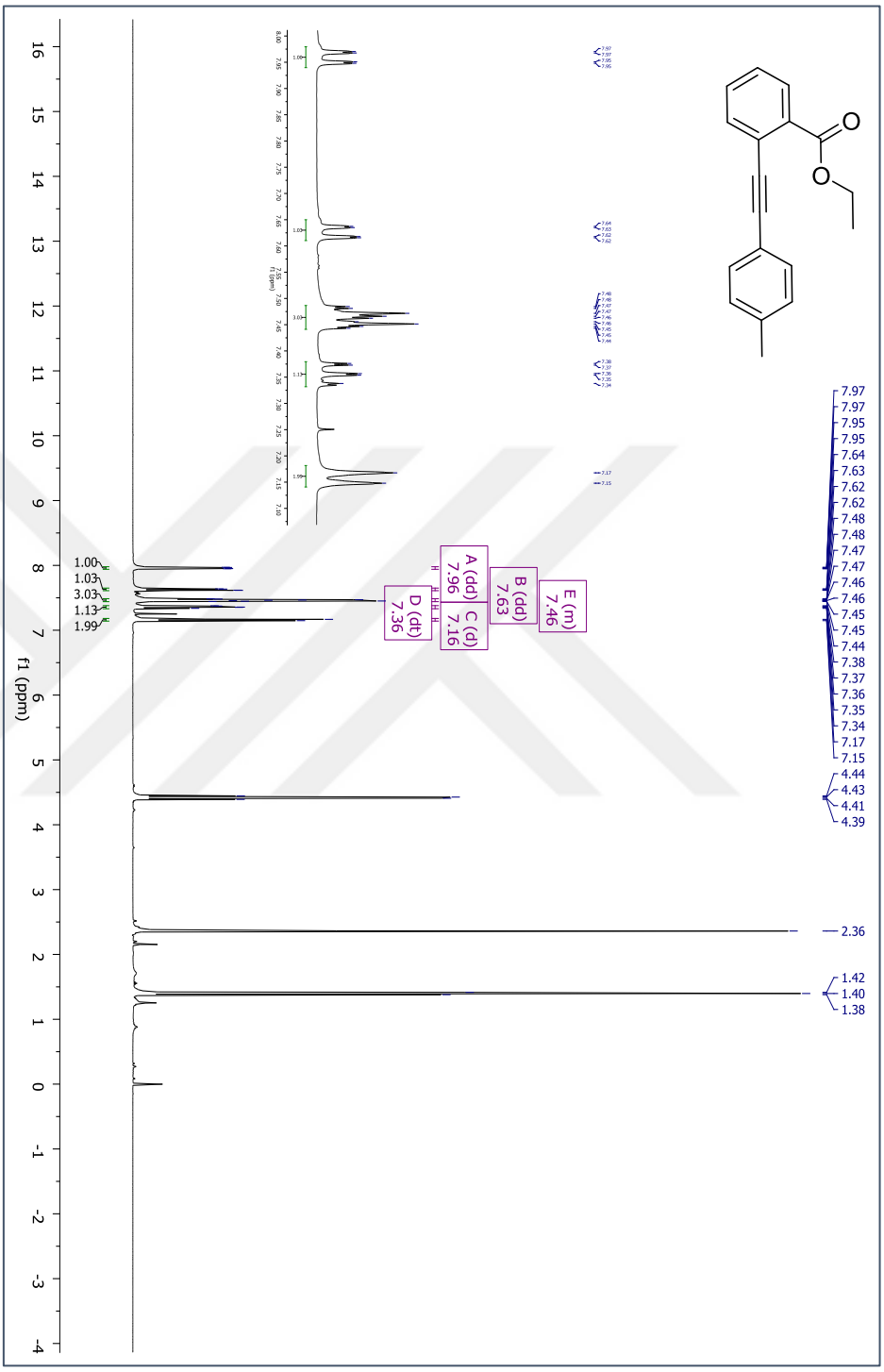


Figure 11: ^{1}H NMR spectrum of compound **38e**

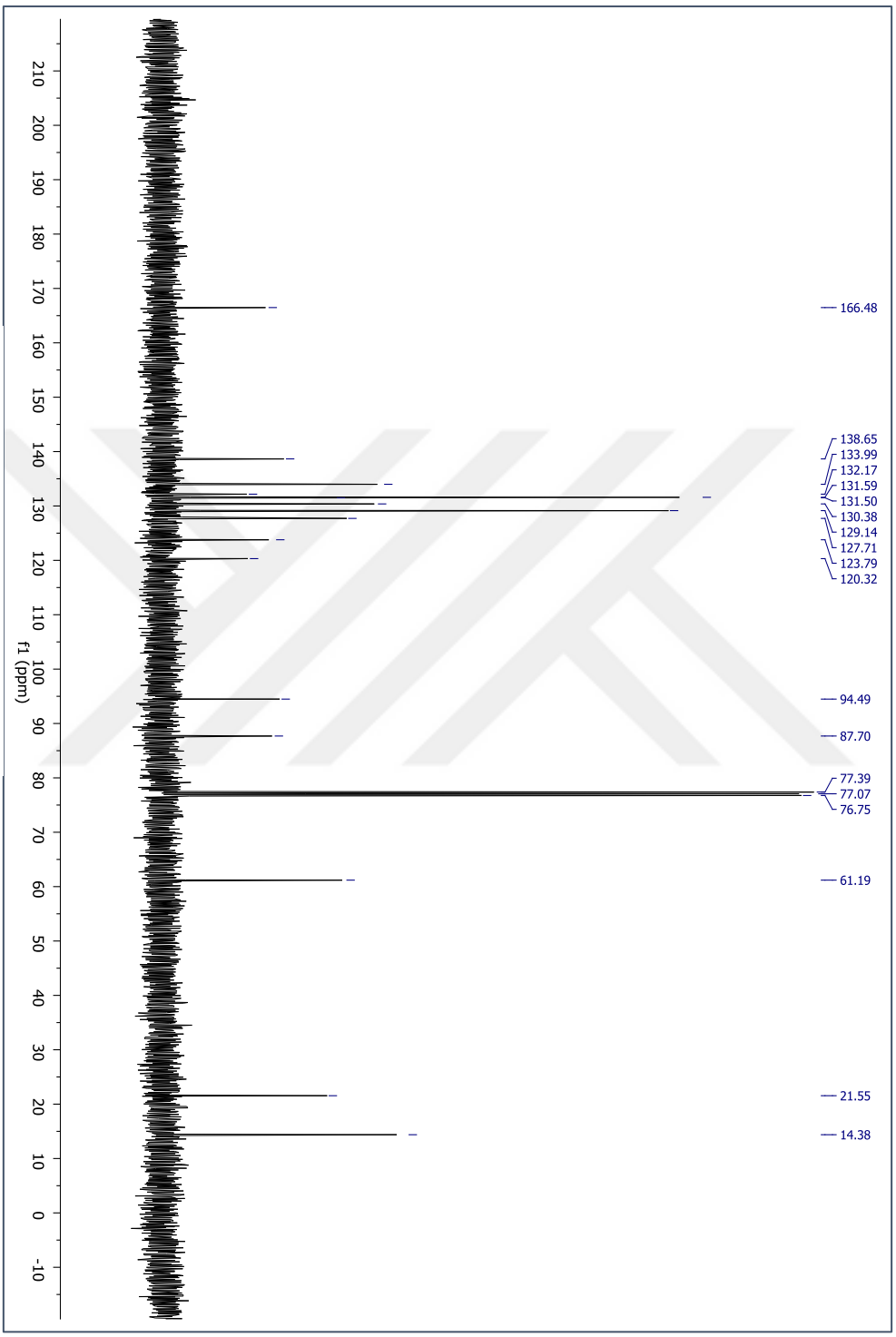


Figure 12: ^{13}C NMR spectrum of compound **38e**

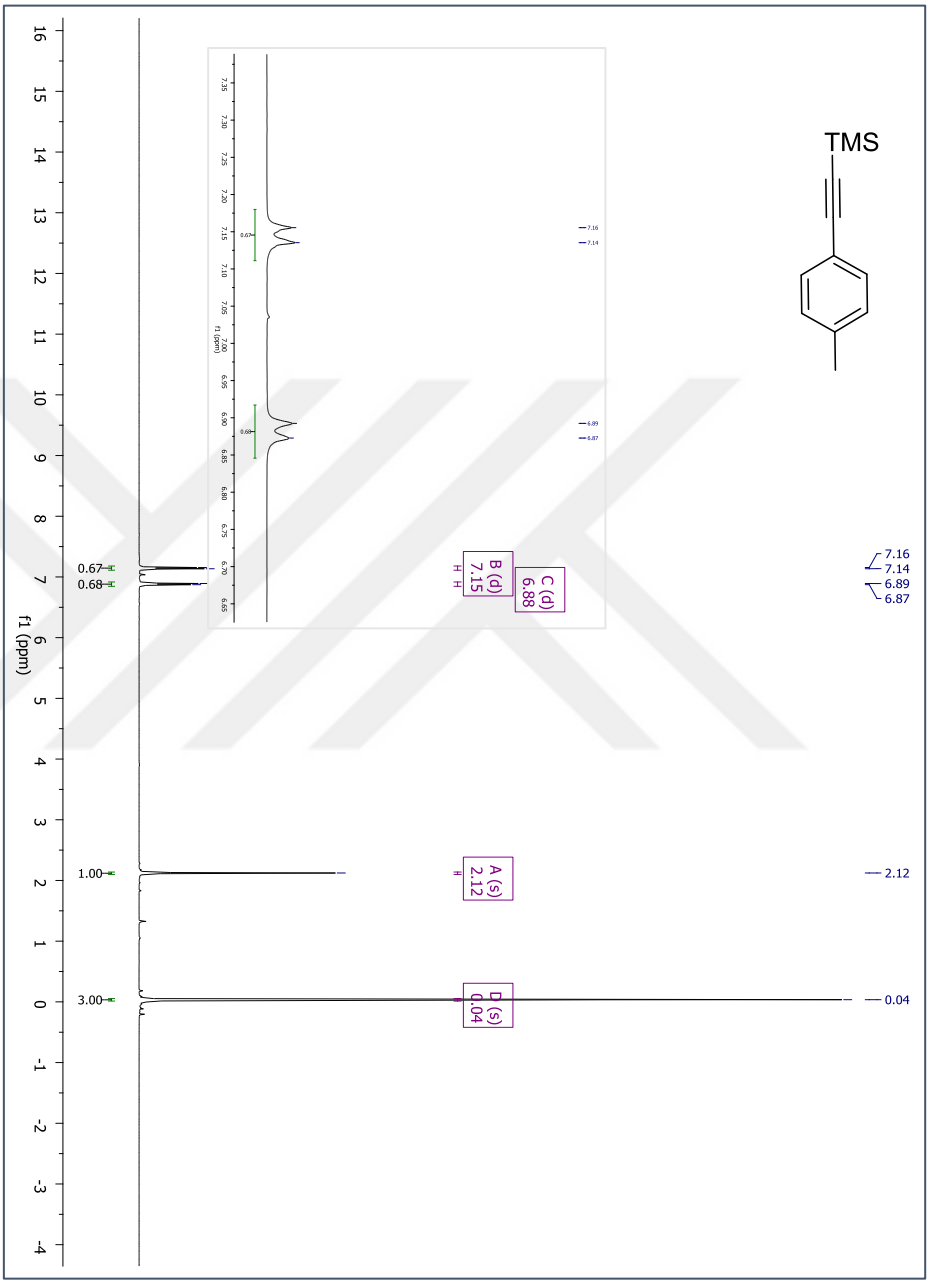


Figure 13: ^{1}H NMR spectrum of compound **42e**

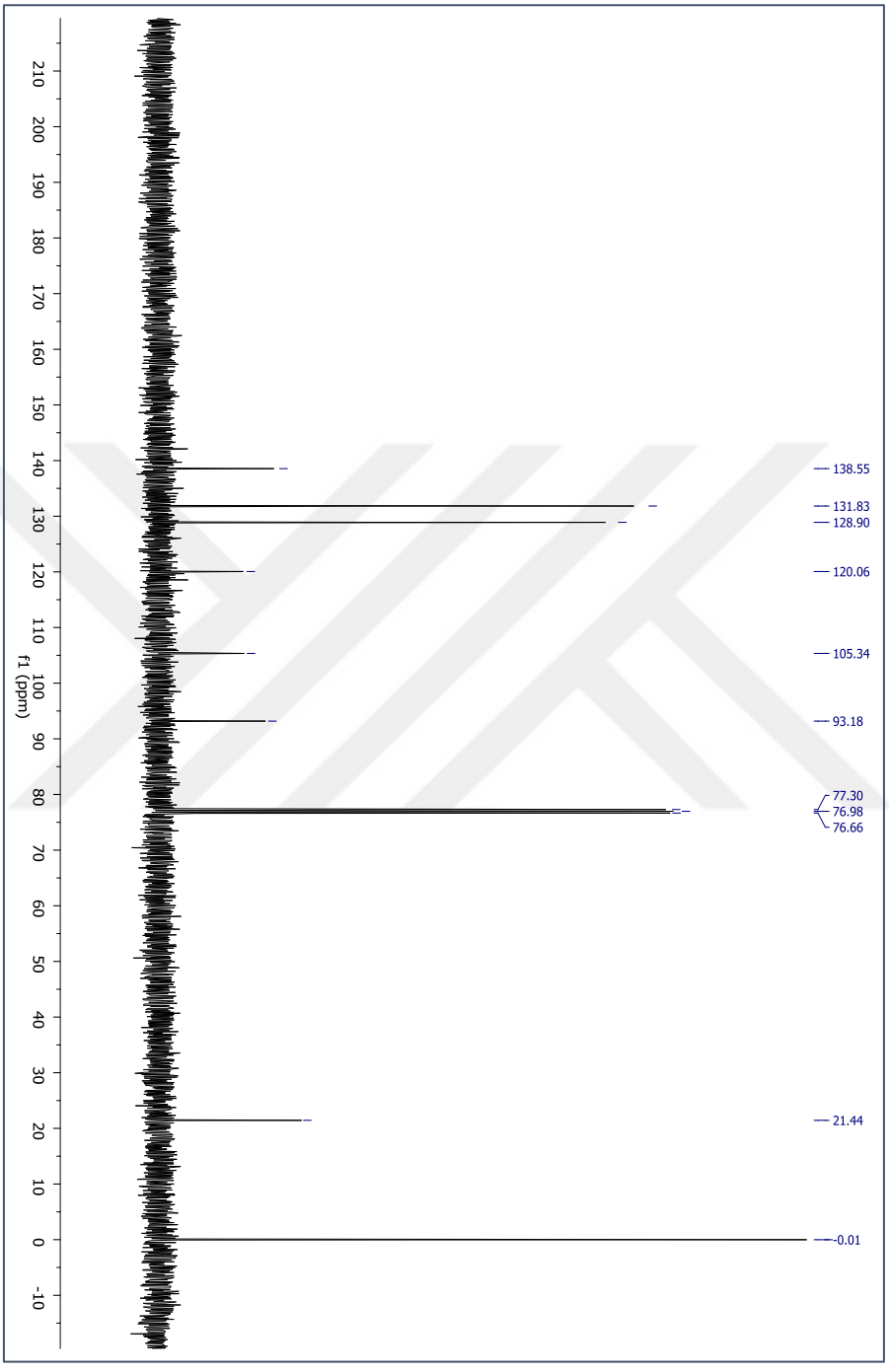


Figure 14: ^{13}C NMR spectrum of compound **42e**

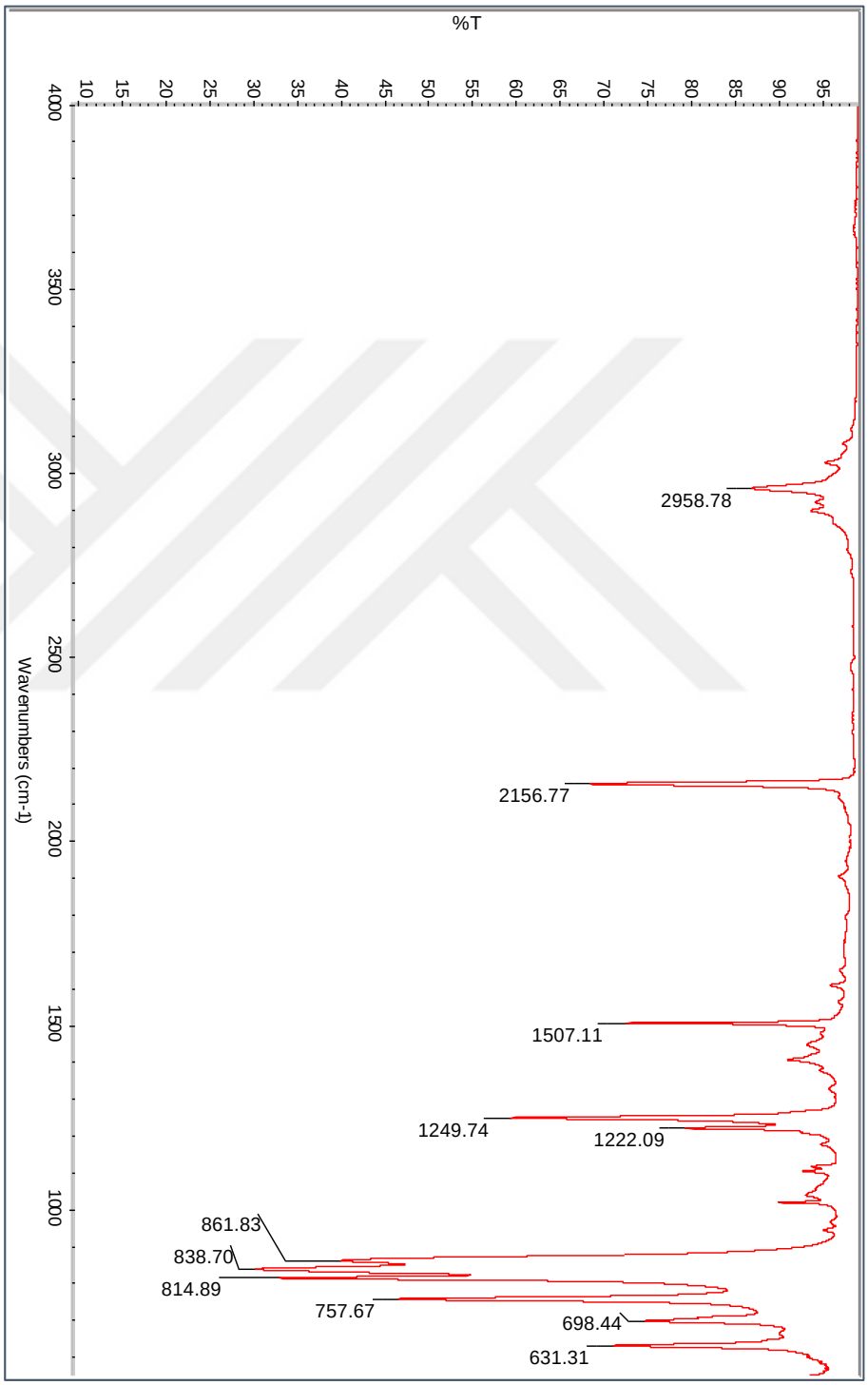


Figure 15: IR spectrum of compound **42e**

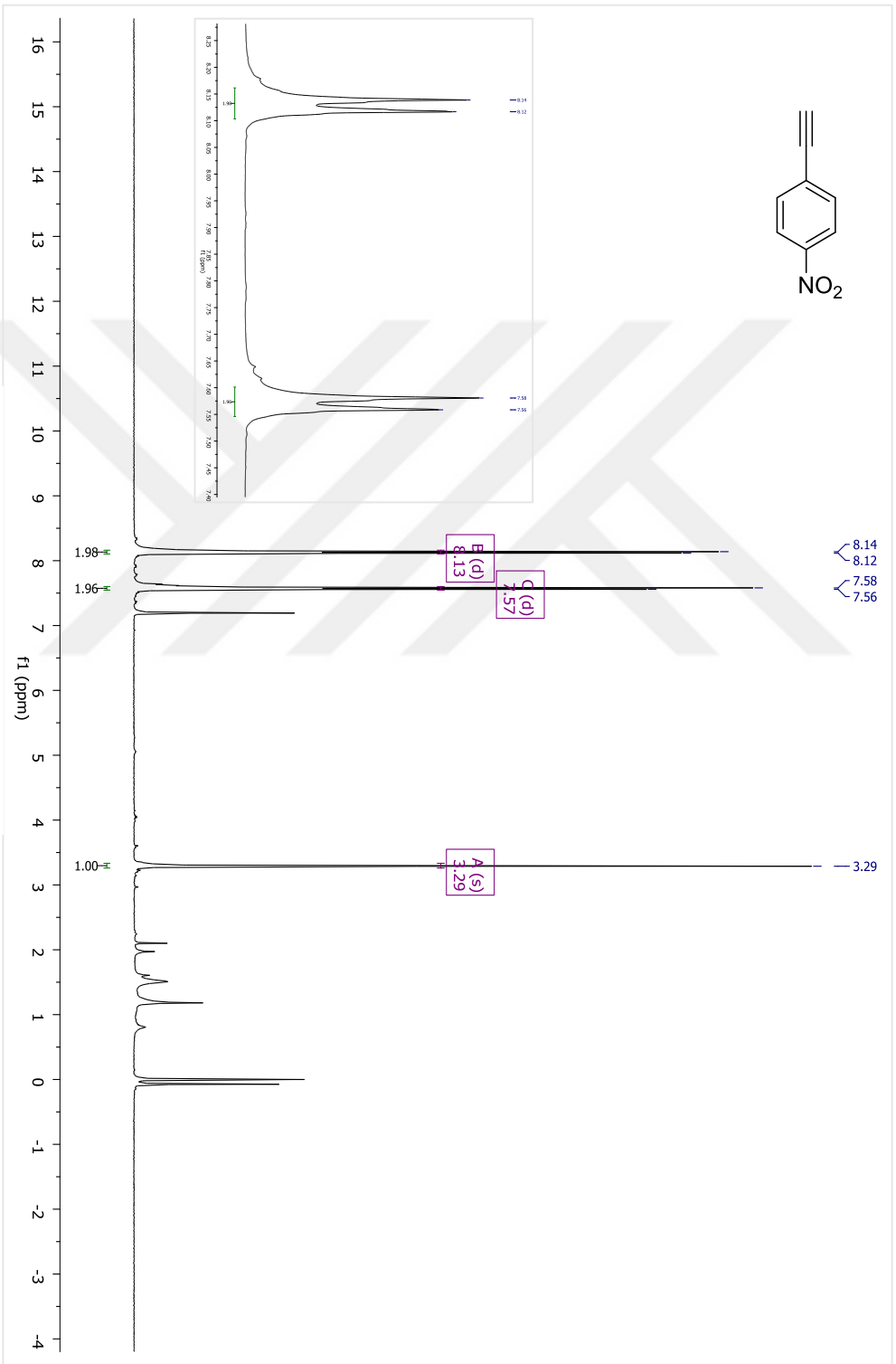


Figure 16: ^{1}H NMR spectrum of compound **43f**

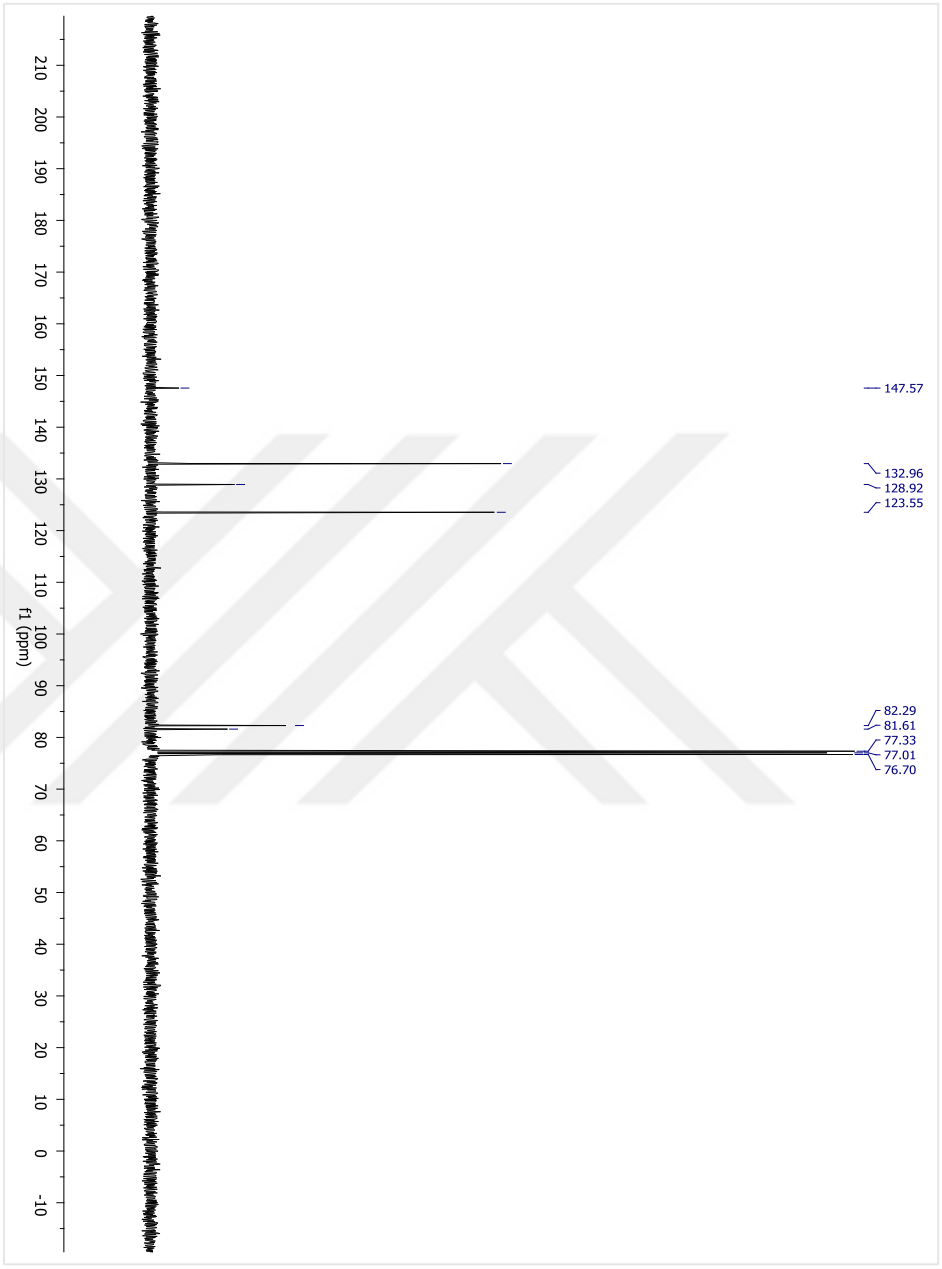


Figure 17: ^{13}C NMR spectrum of compound **43f**

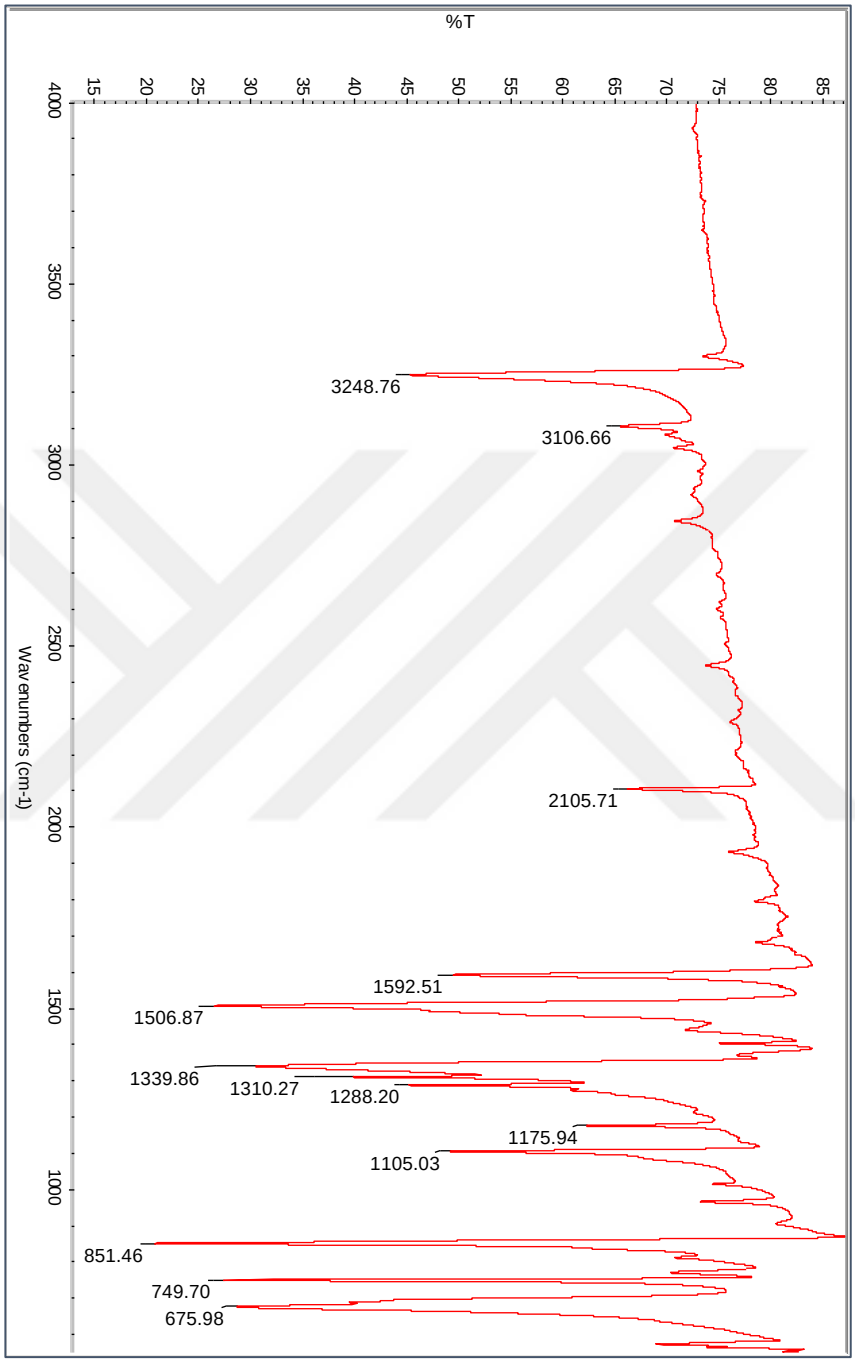


Figure 18: IR spectrum of compound **43f**

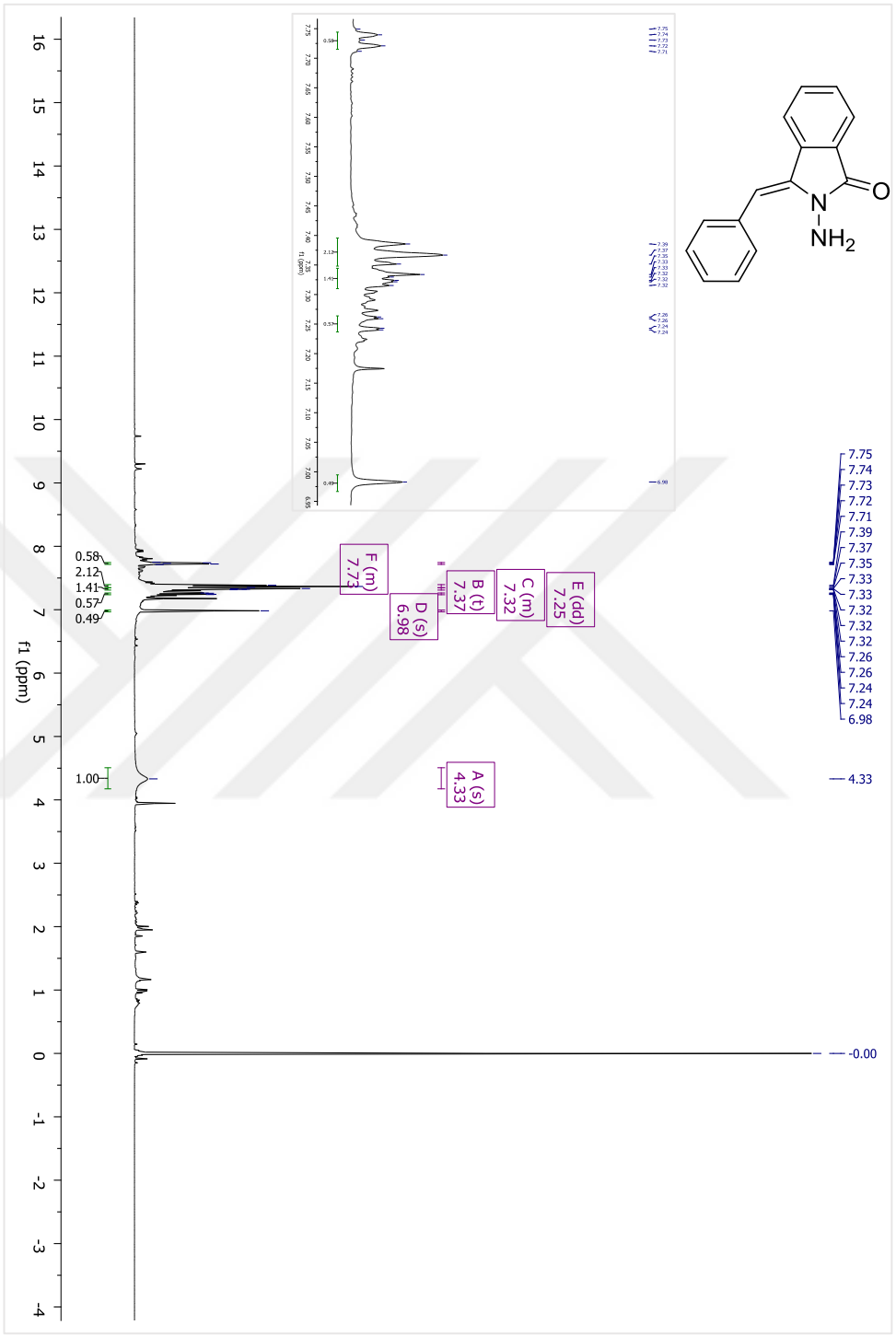


Figure 19: ^{1}H NMR spectrum of compound **47**

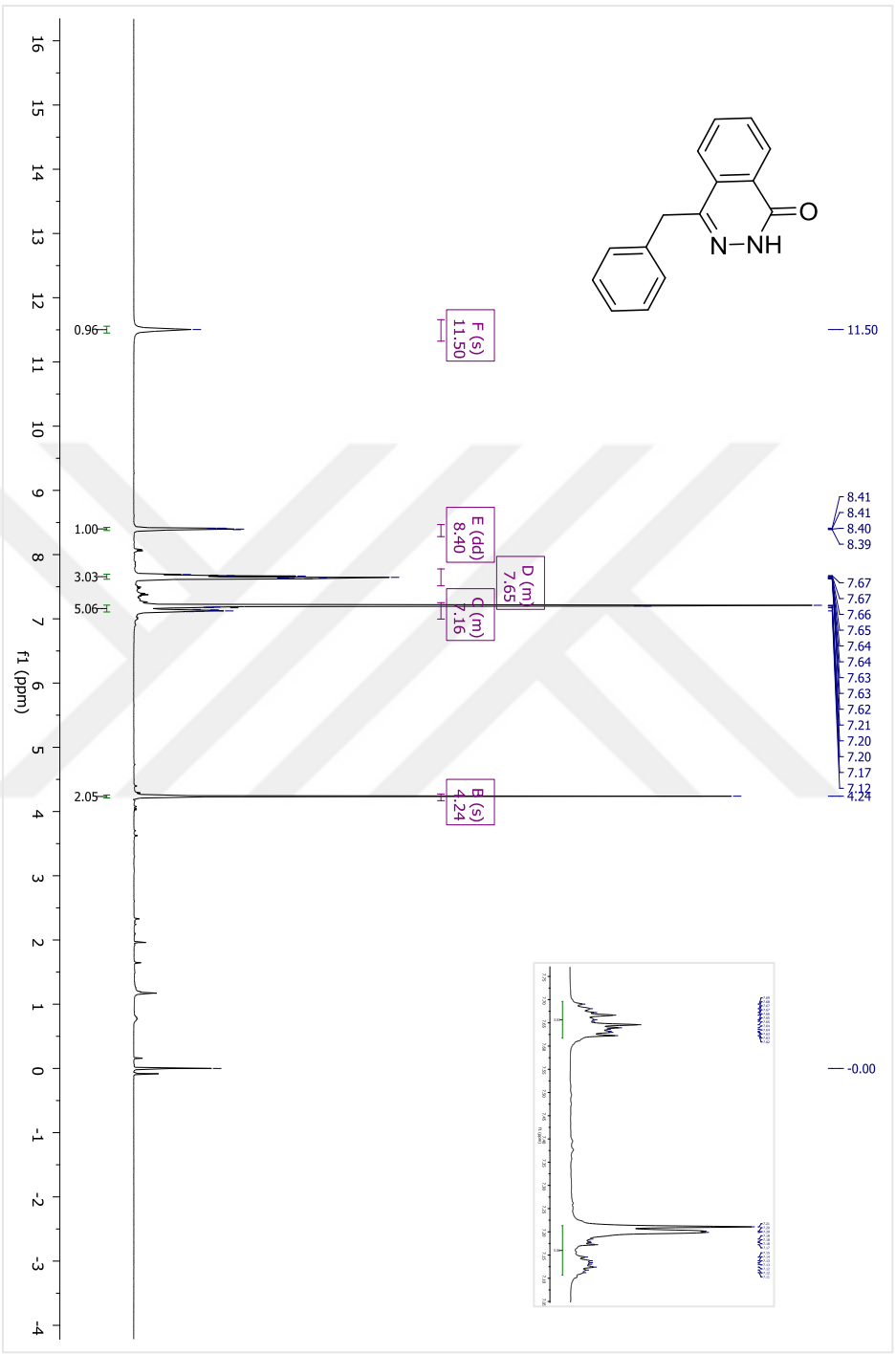


Figure 20: ^{1}H NMR spectrum of compound **40a**

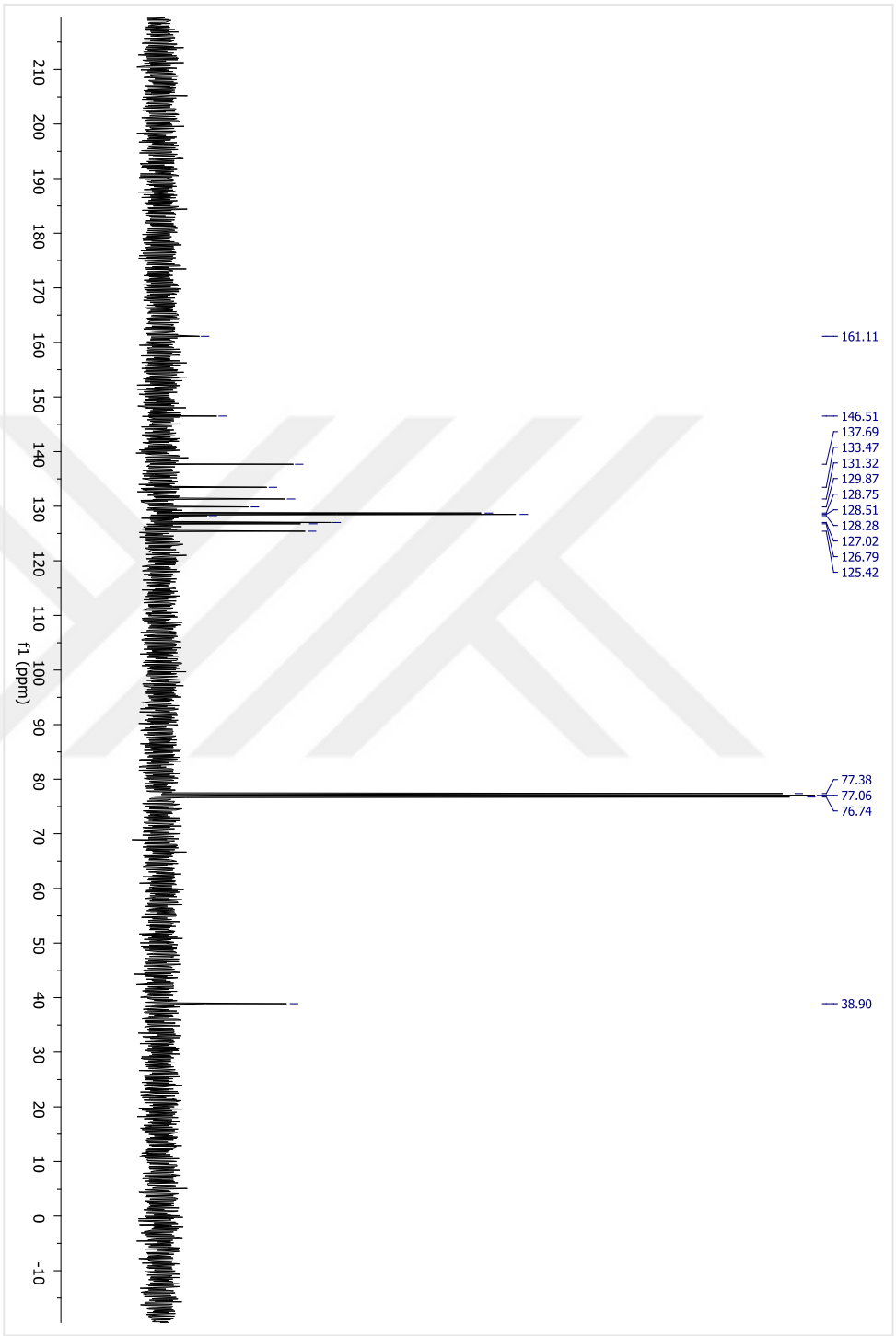


Figure 21: ^{13}C NMR spectrum of compound **40a**

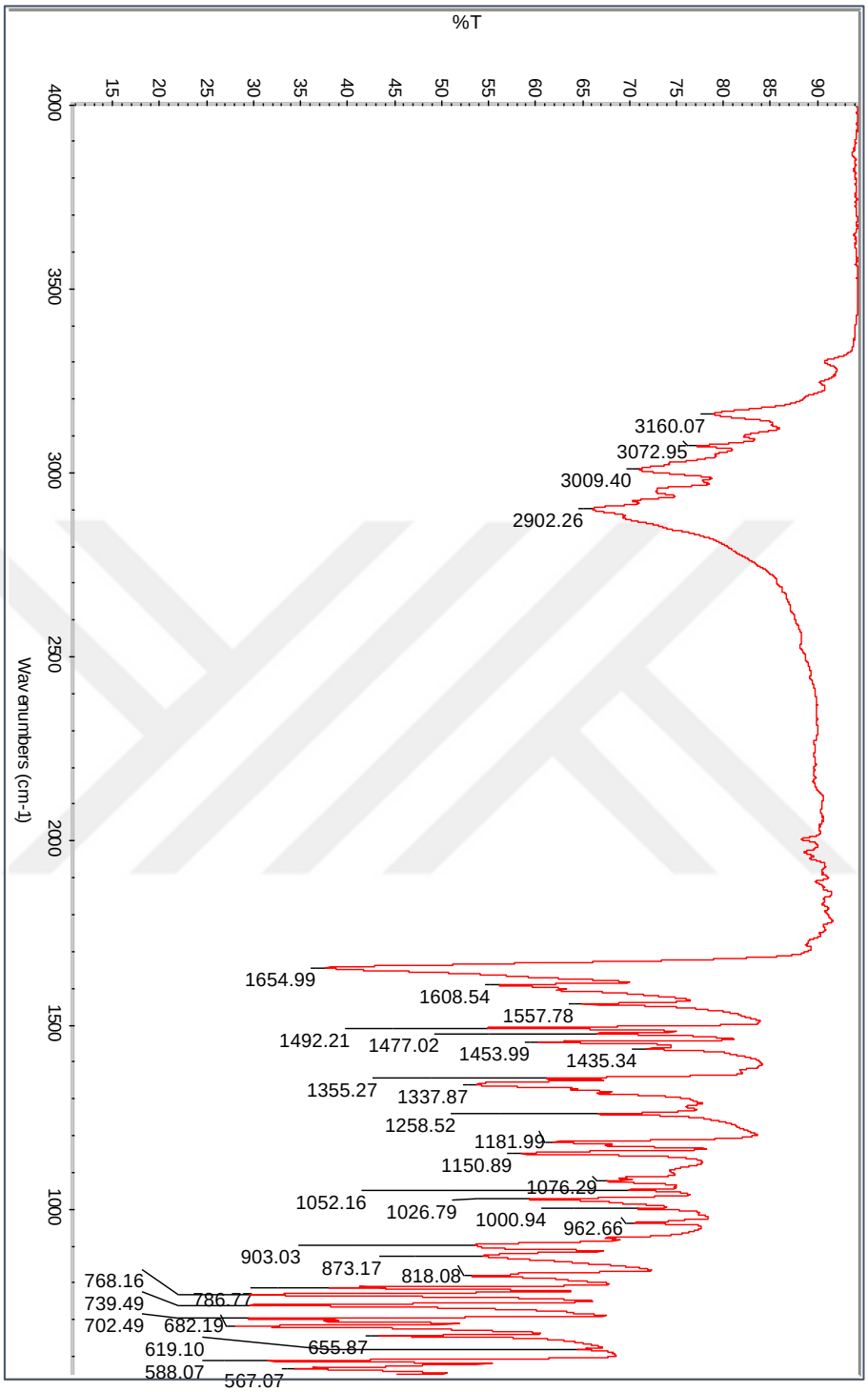


Figure 22: IR spectrum of compound **40a**

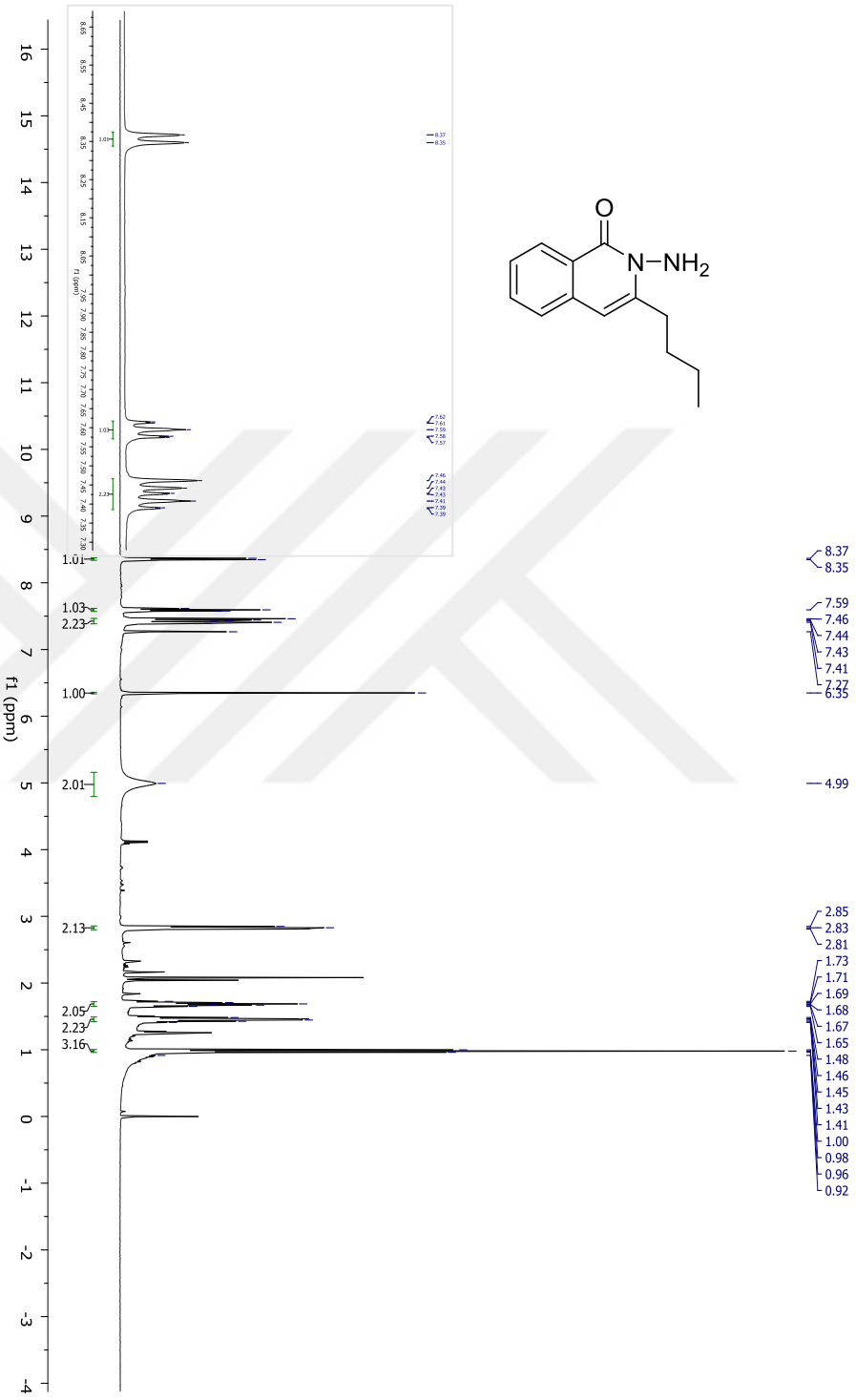


Figure 23: ^{1}H NMR spectrum of compound **48**

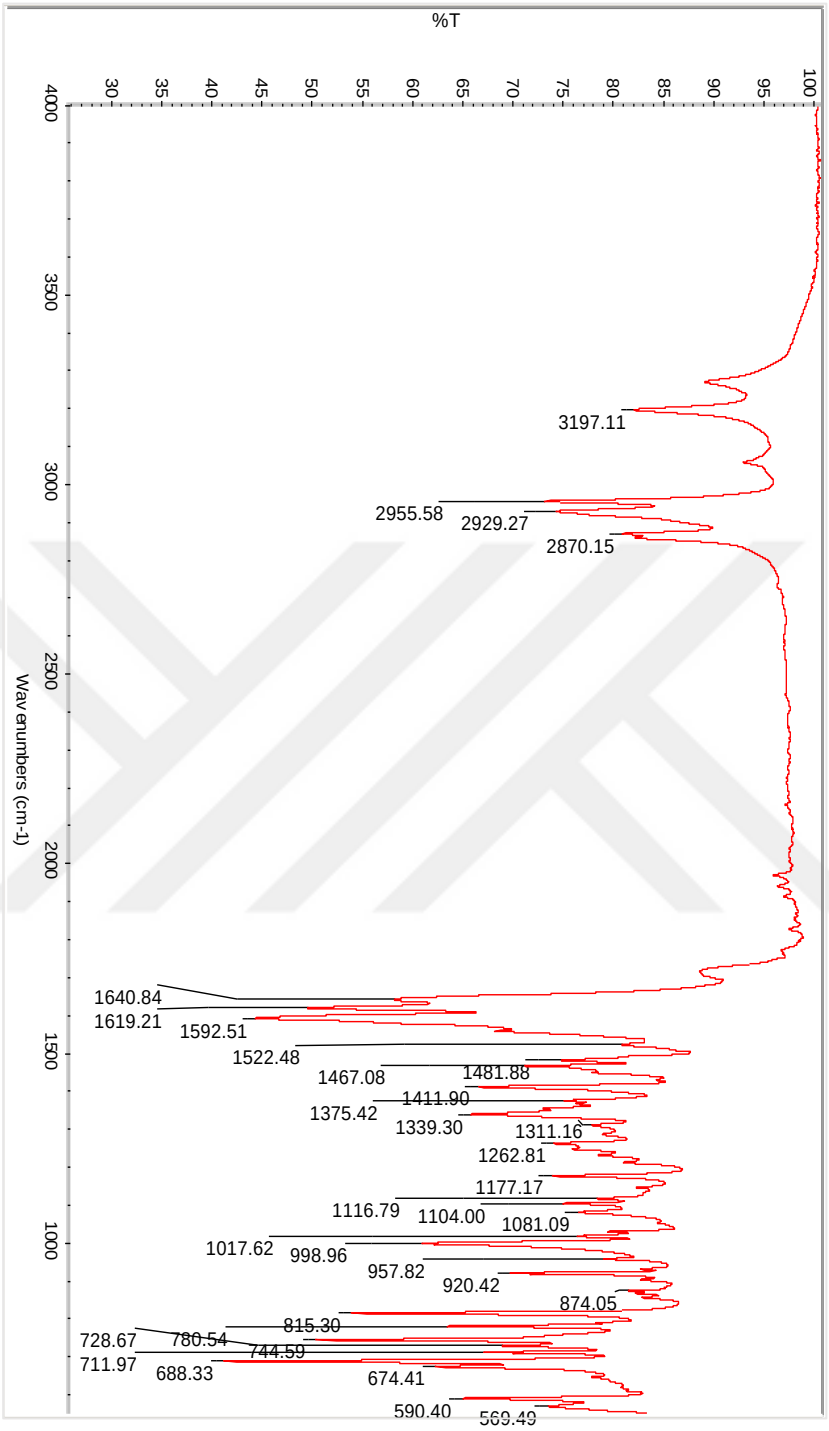


Figure 24: IR spectrum of compound **48**