

**ABANT İZZET BAYSAL UNIVERSITY**  
**THE GRADUATE SCHOOL OF NATURAL AND APPLIED**  
**SCIENCES**



**SYNTHESIS OF NEW PYRROLIZINE DERIVATIVES VIA**  
**BASE-CATALYZED CARBOCYCLIZATIONS**

**MASTER OF SCIENCE**

**GARBA SULEIMAN**

**BOLU, DECEMBER 2015**

**ABANT İZZET BAYSAL UNIVERSITY**  
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**DEPARTMENT OF CHEMISTRY**



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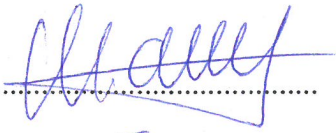
## APPROVAL OF THE THESIS

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in partial fulfillment of the requirements for the degree of Master of Science in  
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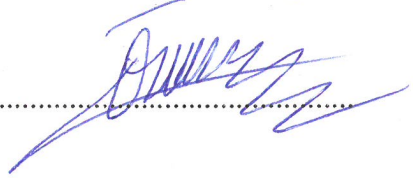
### Examining Committee Members

### Signature

Supervisor  
Assoc.Prof. Dr. Muhammet YILDIRIM  
Abant İzzet Baysal University



Member  
Assist.Prof.Dr.Öznur DEMİR ORDU  
Abant İzzet Baysal University



Member  
Assist.Prof.Dr.Fatma YILMAZ  
Abant İzzet Baysal University

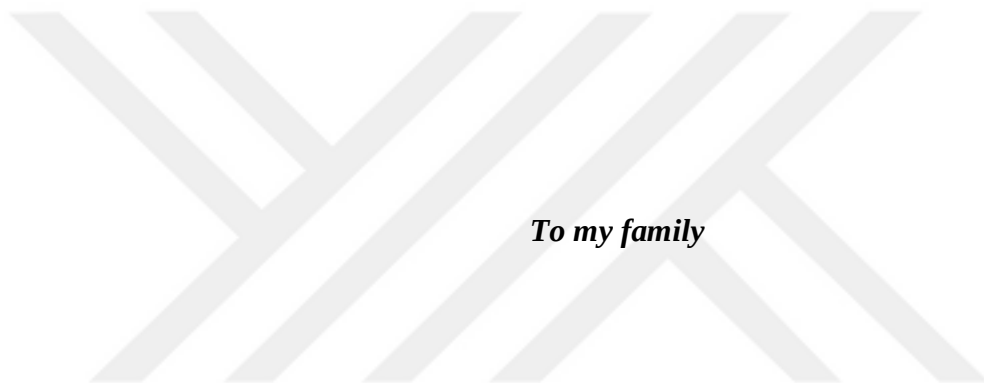


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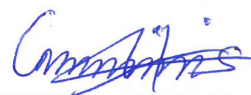


*To my family*

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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.

**Garba SULEIMAN**



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## ABSTRACT

### SYNTHESIS OF NEW PYRROLIZINE DERIVATIVES VIA BASE-CATALYZED CARBOCYCLIZATIONS

MSC THESIS

GARBA SULEIMAN

ABANT IZZET BAYSAL UNIVERSITY GRADUATE SCHOOL OF  
NATURAL AND APPLIED SCIENCES

DEPARTMENT OF CHEMISTRY

(SUPERVISOR: ASSOC. PROF. DR. MUHAMMET YILDIRIM)

BOLU, DECEMBER 2015

Pyrrolizines have been considered of great importance due to their various biological activities like anticancer, antitumor, antimalarial, anti-inflammatory, etc. They have been extensively studied in the application and synthesis of many bio-active compounds since they exhibit substantial pharmaceutical activities.

Recent researches have revealed that integration of aryl or alkyl unit with structural features of pyrrolizine can be effective in the formation of new products with enriched or/and surprising biochemical effect since a number of pyrrolizines have already been proven to be active against several disorders.

Within the scope of the present work, the nucleophilic cyclizations of *N*-alkynyl substituted proline moieties have been investigated to afford the new aryl or alkyl substituted pyrrolizine derivatives. First, the requisite *N*-alkynyl proline derivatives were synthesized by either the reactions of proline esters with propargyl bromide followed by the Sonogashira coupling for derivatization or via one pot  $A^3$  coupling of pyrrolidine-2-carboxylates, formaldehyde, together with a series of acetylenes yielding the precursors for cyclization products in good to moderate yield. In the following step, the nucleophilic cyclizations or more specifically the nucleophilic carbocyclizations of the *N*-alkynyl substituted prolines were investigated by treating them with lithium bis(trimethylsilyl)amide as a non-nucleophilic steric strong base. By employing these carbocyclization reactions, a novel series of 7-phenyl-2,3,5,7a-tetrahydro-1*H*-pyrrolizine carboxylates and 7-butyl-2,3,5,7a-tetrahydro-1*H*-pyrrolizine carboxylates have been synthesized in good to excellent yields.

Summarily, a small and new library of pyrrolizines has been obtained by a simple and efficient three-steps methodology including different coupling reactions and besides, it's understood that this smooth conversion of *N*-alkynyl compounds into pyrrolizines have been controlled by an *endo*-dig cyclisation mechanism in the final step.

#### KEYWORDS:

Proline Esters, *N*-propargyl systems, 5-*endo*-dig, Cyclizations, Baldwin's rule

## ÖZET

### YENİ PİROLİZİN TÜREVLERİNİN BAZ-KATALİZLİ KARBOHALKALAŞMA YOLUYLA SENTEZİ

YÜKSEK LİSANS TEZİ

GARBA SULEİMAN

ABANT İZZET BAYSAL ÜNİVERSİTESİ FEN BİLİMLERİ  
ENSTİTÜSÜ

KİMYA ANABİLİM DALI

(TEZ DANIŞMANI: DOÇ. DR. MUHAMMET YILDIRIM)

BOLU, ARALIK 2015

Pirolizinler, antikanser, antitümör, antimalaryal, antiinflamatuvar gibi çeşitli biyolojik aktiviteleri nedeniyle çok büyük öneme sahiptirler. Bu bileşikler, çok sayıda farmasötik aktivite göstermeleri sebebiyle birçok biyoaktif bileşiğin sentezinde ve uygulamasında yoğunlukla kullanılmaktadır.

Çok sayıda pirolizinin çeşitli rahatsızlıklara karşı aktivitelerinin daha önceden kanıtlanmış olmasından dolayı, güncel araştırmalar pirolizinin yapısal özellikleriyle aril veya alkil gruplarının entegrasyonunun şaşırtıcı ve/veya zenginleşmiş biyokimyasal etkiler gösteren yeni ürünlerin oluşumunda etkili olabildiğini ortaya koymaktadır.

Bu çalışma kapsamında, yeni aril veya alkil substitute pirolizin türevleri verebilen *N*-alkinil substitute olan pirolin yapılarının nükleofilik halkalaşmaları araştırılmıştır. Öncelikle, gerekli olan *N*-alkinil prolin türevleri, prolin esterlerin proparjil bromürle reaksiyonunu takiben Sonogashira kenetlenmesiyle türevlendirme yoluyla veya pirolidin-2-karboksilatlar, formaldehit ve bir seri asetilenle birlikte tek-kap A<sup>3</sup>-kenetlenmesiyle halkalaşma başlatıcılarının iyi ve orta verimlerde vermesiyle sentezlenmiştir. Takip eden basamakta, *N*-alkinil substitute prolinlerin nükleofilik halkalaşmaları veya daha özel olarak nükleofilik karbohalkalaşmaları, bu bileşikleri nükleofilik olmayan sterik ve kuvvetli bir baz olan lityum bis(trimetilsilil)amit ile muamele ederek yapılmıştır. Bu karbohalkalaşma reaksiyonlarının uygulanmasıyla, 7-fenil-2,3,5,7a-tetrahidro-1*H*-pirolizin karboksilatlar ve 7-butil-2,3,5,7a-tetrahidro-1*H*-pirolizin karboksilatların yeni bir serisi iyi ve mükemmel verimlerle hazırlanmıştır.

Özetle, pirolizinlerin küçük ve yeni bir kütüphanesi, basit ve etkili üç basamaklı farklı kenetlenme reaksiyonlarını içeren bir yöntemle elde edilmiş ve bunun yanında *N*-alkinil bileşiklerinin pirolizinelere bu kolay dönüşümünün, son basamakta *endo*-dig halkalaşma mekanizmasıyla kontrol edildiği anlaşılmıştır.

#### ANAHTAR KELİMELER:

Prolin esterleri, *N*-proparjil sistemler, 5-*endo*-dig, halkalaşmalar, Baldwin kuralı

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## LIST OF ABBREVIATIONS AND SYMBOLS

|                         |                                                                                                |
|-------------------------|------------------------------------------------------------------------------------------------|
| <b>AcOH</b>             | : Acetic acid                                                                                  |
| <b>Ar</b>               | : Aryl                                                                                         |
| <b>ATR</b>              | : Attenuated Total Reflectance                                                                 |
| <b>b.p.</b>             | : Boiling point                                                                                |
| <b>Bn</b>               | : Benzyl                                                                                       |
| <b>Boc</b>              | : <i>tert</i> -Butoxycarbonyl                                                                  |
| <b>Bu</b>               | : Butyl                                                                                        |
| <b>cat.</b>             | : Catalyst                                                                                     |
| <b>CDCl<sub>3</sub></b> | : Deuterated chloroform                                                                        |
| <b>DCM</b>              | : Dichloromethane                                                                              |
| <b>DCE</b>              | : Dichloroethane                                                                               |
| <b>de</b>               | : Diastereomeric excess                                                                        |
| <b>DIPEA</b>            | : Diisopropylethylamine                                                                        |
| <b>DMF</b>              | : <i>N,N</i> -Dimethylformamide                                                                |
| <b>DMSO</b>             | : Dimethylsulfoxide                                                                            |
| <b>EDG</b>              | : Electron-donating group                                                                      |
| <b>ee</b>               | : Enantiomeric excess                                                                          |
| <b>eq.</b>              | : Molar equivalents                                                                            |
| <b>ESI<sup>-</sup></b>  | : Electrospray ionisation (negative)                                                           |
| <b>ESI<sup>+</sup></b>  | : Electrospray ionisation (positive)                                                           |
| <b>Et</b>               | : Ethyl                                                                                        |
| <b>Et<sub>3</sub>N</b>  | : Triethylamine                                                                                |
| <b>Et<sub>2</sub>O</b>  | : Diethyl ether                                                                                |
| <b>EtOAc</b>            | : Ethyl acetate                                                                                |
| <b>EtOH</b>             | : Ethanol                                                                                      |
| <b>h</b>                | : Hour                                                                                         |
| <b>HATU</b>             | : <i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium Hexafluorophosphate |
| <b>HBTU</b>             | : 2-(1H-benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium Hexafluorophosphate                     |
| <b>HMPA</b>             | : Hexamethylphosphoramide                                                                      |
| <b>HRMS</b>             | : High resolution mass spectrometry                                                            |
| <b>Hz</b>               | : Hertz                                                                                        |

|                         |                                  |
|-------------------------|----------------------------------|
| <b>i-Bu</b>             | : Iso-butyl                      |
| <b>i-Pr</b>             | : Iso-propyl                     |
| <b>IR</b>               | : Infrared spectroscopy          |
| <b><i>J</i></b>         | : Coupling constant (NMR)        |
| <b>KHMDS</b>            | : Potassium hexamethyldisilazide |
| <b>LiHMDS</b>           | : Lithium hexamethyldisilazide   |
| <b>m.p.</b>             | : Melting point                  |
| <b>MCR</b>              | : Multicomponent reactions       |
| <b>Me</b>               | : Methyl                         |
| <b>MeCN</b>             | : Acetonitrile                   |
| <b>MeOH</b>             | : Methanol                       |
| <b>min</b>              | : Minutes                        |
| <b>MS</b>               | : Mass spectrometry              |
| <b>NaBH<sub>4</sub></b> | : Sodium borohydride             |
| <b>NMR</b>              | : Nuclear magnetic resonance     |
| <b>OMe</b>              | : Methoxy                        |
| <b>OTf</b>              | : Trifluoromethanesulfonate      |
| <b>Ph</b>               | : Phenyl                         |
| <b>ppm</b>              | : Parts per million (NMR)        |
| <b>Pr</b>               | : Propyl                         |
| <b>R<sub>f</sub></b>    | : Retardation Factor             |
| <b>rt</b>               | : Room temperature               |
| <b>SFC</b>              | : Solvent free condition         |
| <b>t-BuOK</b>           | : Potassium tert-butoxide        |
| <b>Tf</b>               | : Trifluoromethanesulfonyl       |
| <b>TFA</b>              | : Trifluoroacetic acid           |
| <b>THF</b>              | : Tetrahydrofuran                |
| <b>TIPSCI</b>           | : Chlorotriisopropylsilane       |
| <b>TLC</b>              | : Thin layer chromatography      |
| <b>TMS</b>              | : Tetramethylsilane              |
| <b>TOF</b>              | : Time of flight                 |
| <b>Ts</b>               | : Tosyl                          |
| <b>δ</b>                | : Chemical shift (NMR)           |

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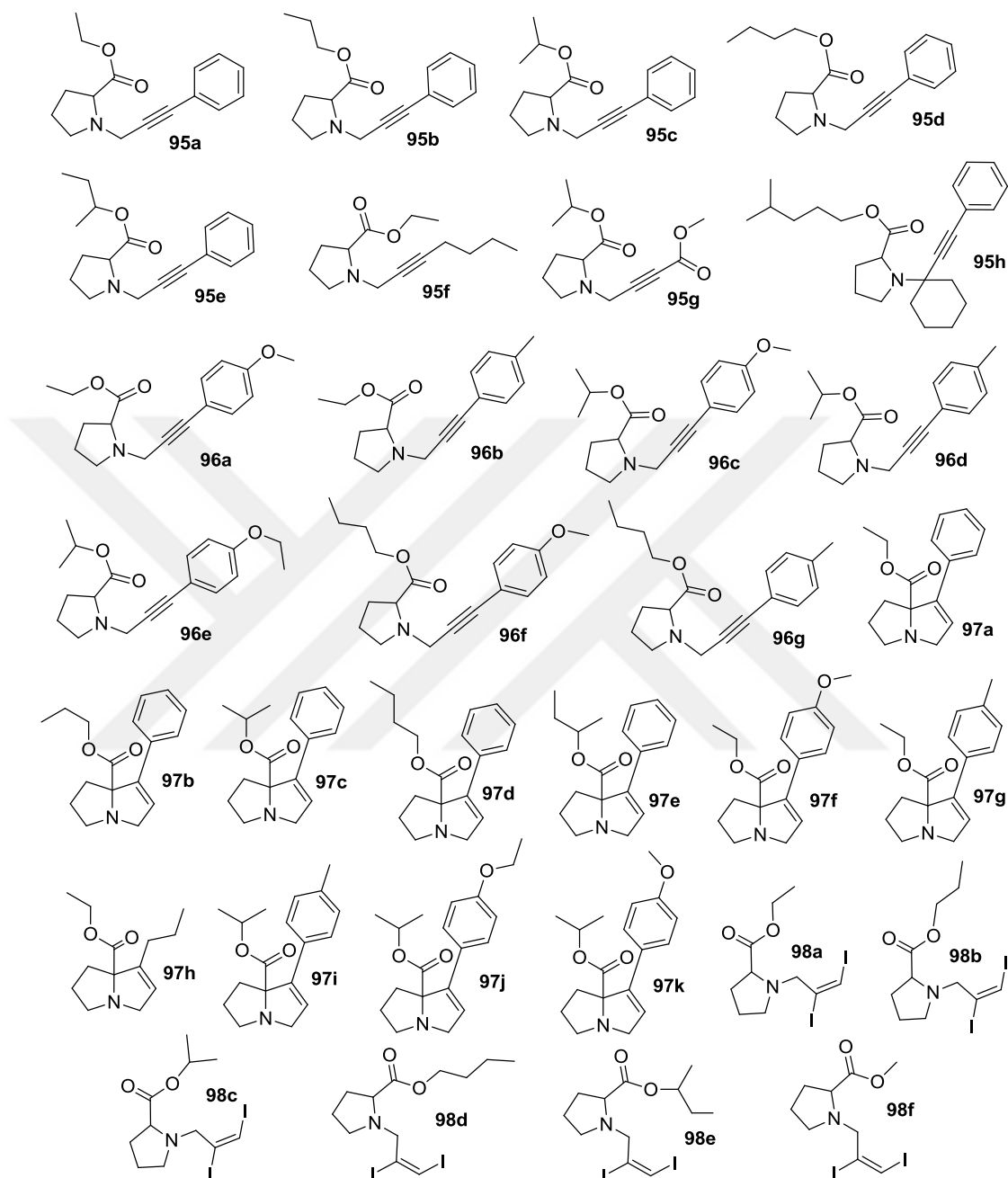
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# FORMULAE



## 1. INTRODUCTION

Vast majority of the molecules isolated from nature generally contain either a carbocyclic or heterocyclic moiety in their structure. Generally, the regioselectivity and stereoselectivity in the formation of these kind of cyclic structures from suitable precursors is the main problem for the synthesis of complex structures.

### 1.1 CHAPTER 1

#### 1.1.1 Baldwin's rule and intramolecular cyclisation of alkyne systems

The mechanisms that controls the formation of heterocycles (or carbocycles) in different sizes (4-, 5-, 6-, 7- membered or larger) are explained by the Baldwin's rules. These rules describe and classify ring closure steps by geometric and orbital overlapping manner to predict the favorable products (Baldwin, 1976). According to the rule, cyclisation mechanism is characterized by three factors; number of atoms ( $\geq 3$ ) in the forming ring, position of bond that has to be broken (*endo*- or *exo*-) and hybridization (*-tet*: tetrahedral; *-trig*: trigonal; *-dig*: diagonal) at ring closure point (site of attack) (Figure 1.1).

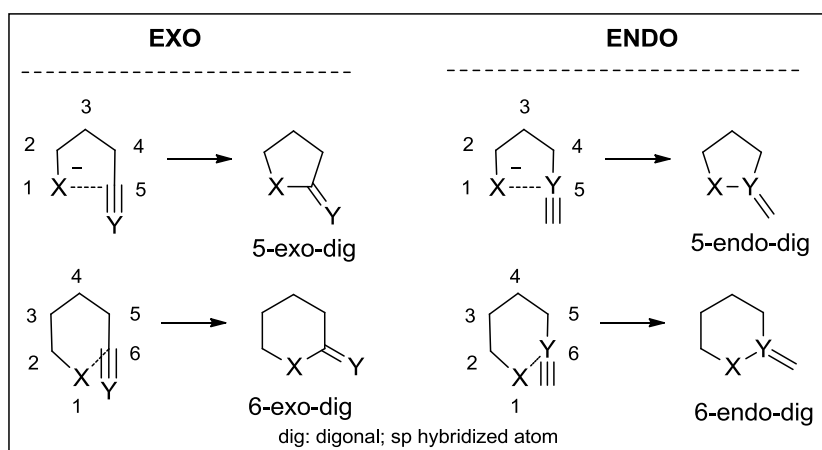


**Figure 1.1.** Cyclisation of alkynes over *exo*- or *endo*- mechanism for the formation of 5- or 6-membered rings

According to Baldwin terminology, two orbitals need to be aligned during cyclisation such as the cyclisations of alkyne systems to give 5- or 6-membered rings (Figure 1.1). Generally, the cyclisations of alkynes is often governed by basic stereoelectronic factors other than steric or electronic factors of substituents and also, these cyclisations are all favorable over 5-(or 6-)endo-dig and 5-(or 6-)exo-dig mechanisms by Baldwin's rules.

X atom on the isolated reactive center should be one of the first row elements such as C, N, O and attack trajectory of X atom to alkyne systems should prefer an angle of  $120^\circ$  (obtuse angle) between three interacting atoms in digonal system. The attack to any  $\pi$ -system (alkene, alkyne etc.) containing molecule would be over nucleophilic, electrophilic or radicalic mechanisms (Figure 1.2) (Alabugin et.al, 2011).

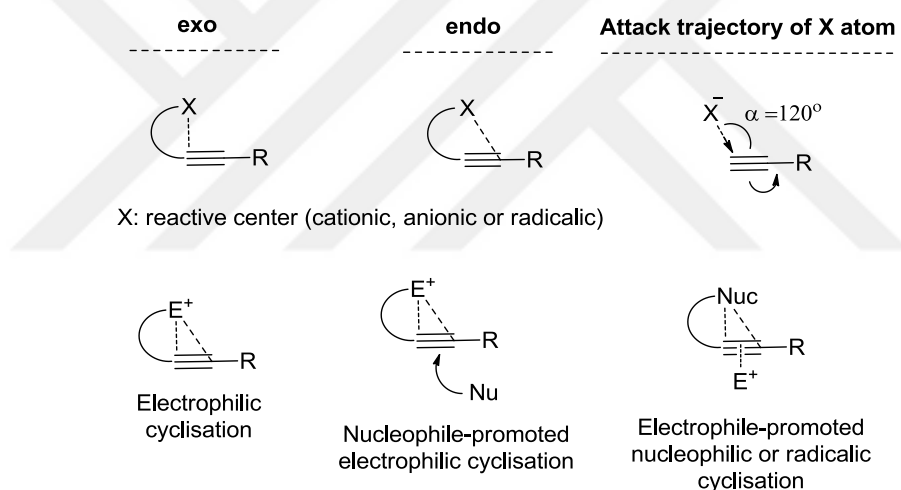


**Figure 1.2.** Attack trajectories, types of reactive centers and cyclisations

#### 1.1.1.1 Nucleophilic Cyclisations of Alkyne Systems

In nucleophilic cyclisations of alkynes, incoming reactive center can attack in-plane  $\pi$ -bond, thus avoiding the additional distortion in 5-*endo*-trig process (in alkenes) and providing the product formation over 5-*endo*-dig mechanism (Figure 1.3). So, in cycylisation of alkynes *endo*-dig mechanism is favorable process.

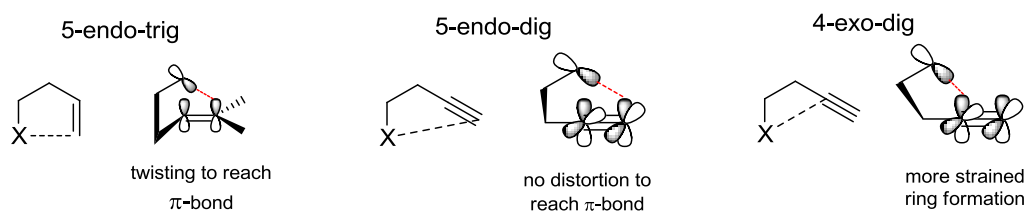
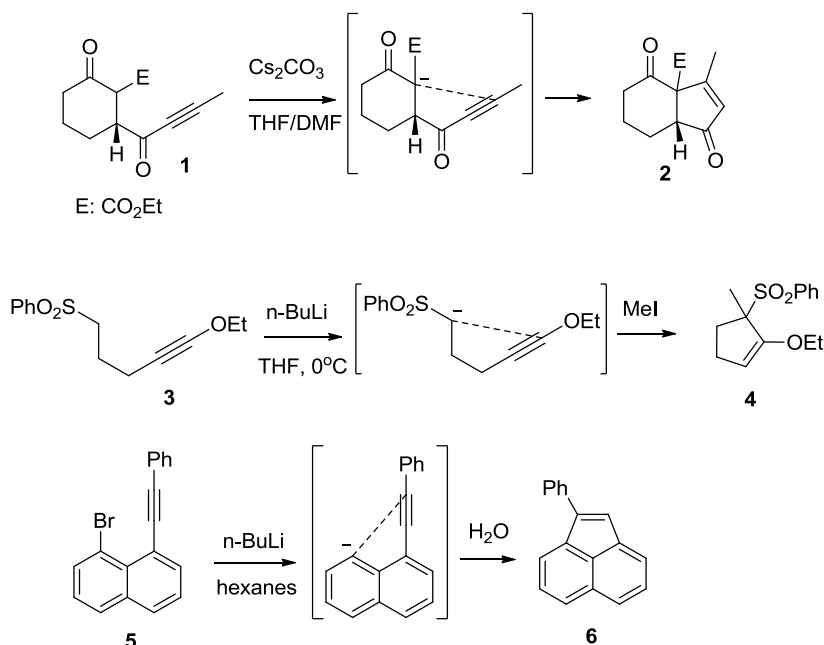


**Figure 1.3.** Intramolecular nucleophilic cyclisation processes on  $\pi$ -systems

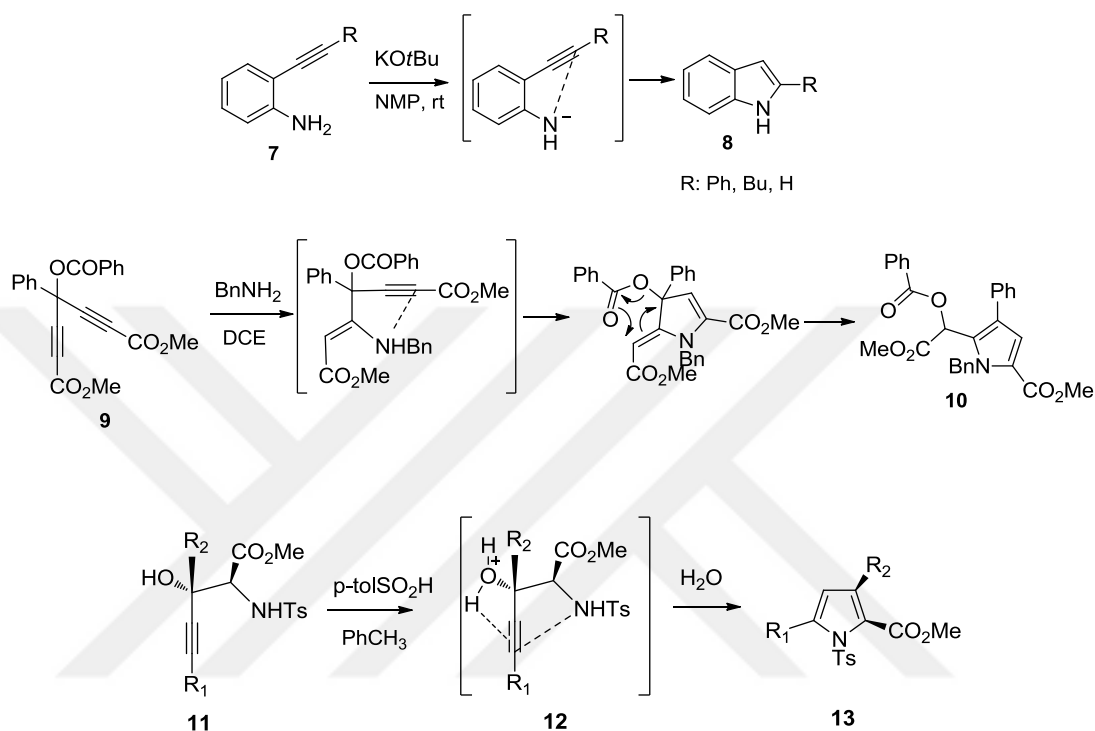
The regioselectivity in attacking point of 4-*exo*/5-*endo* reactions compete when regarding the digonal cyclisations. Two regioselective products are possible in these processes but one reaction is relatively favored in comparison with the alternative one (unfavored). Herein, in the nucleophilic cyclisations, 4-*exo*-product is more strained than 5-*endo* one and endo cyclisation is much more exothermic, which is more favored, than *exo*-cyclisation due unfavorable secondary orbital interactions in *exo* mechanism (Wilson, 1969).

Generally, the carbon nucleophiles can be formed by abstraction of  $\alpha$ -H adjacent to a heteroatom or  $\beta$ -H to an electrophilic group in the molecules by a strong base, thus the reactions give fused (2,6) or monocyclic (4) carbocycles in 5-*endo*-dig fashion (Scheme 1.1) (Lavalley et.al, 1986; Funk et.al, 1993). Also, some nitrogen nucleophiles formed by treatment with strong bases gave indole and pyrrole-based heterocycles (8,10) (Scheme 1.2) (Tejedor et.al, 2009).



**Scheme 1.1.** Cyclisation by different carbon nucleophiles

However, Knight et al. (2003) obtained 5-*endo* pyrrole products in good yields in the reaction of  $\gamma$ -alkynyl- $\delta$ -hydroxy-*R*-amino esters **11** with *p*-toluene sulfinic (or sulfonic) acid. Here, the intramolecular coordination of alkyne with the protonated propargylic alcohol **12** assists this cyclizations which favors the 5-*endo*-dig mechanism (Scheme 1.2).

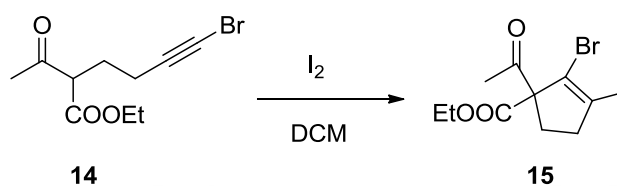


**Scheme 1.2.** Cyclisation by different nitrogen nucleophiles

#### 1.1.1.2 Carbocyclizations of Alkyne Systems

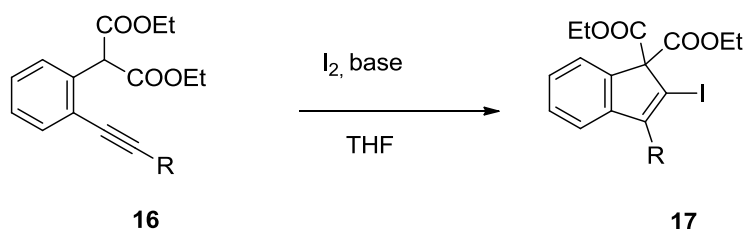
One of the most general methods in synthesizing carbocyclic (or heterocyclic) compounds is the carbocyclization reactions. This reaction has to do with the ring formation of a system, either in intramolecular or intermolecular pattern, forming carbon-carbon or carbon-heteroatom bonds (Kitagawa et al., 1998; Barluenga et al., 2007). The ensuing discussion will cover the chemistry of alkyne/alkene undergoing carbocyclization reactions with the aid of Lewis acids such as  $I_2$ ,  $ICl$ , transition metal complexes (Kitagawa et al., 1998), alkali bases such as NaHMDS, LiHMDS (Kourra et al., 2011), and in some cases combination of protic and Lewis acid (Corkey and Toste, 2005).

The iodine-catalyzed carbocyclization of alkyne moieties has been an effective method in synthesizing different types of carbocyclic and heterocyclic compounds (Mehta and Larock, 2010; Janreddy et al., 2014). Iodocyclopentenones **15** were synthesized from the reaction of alkynyl-ketoesters **14** at room temperature upon treatment with iodine in DCM (Barluenga et al., 2007). These products were the first examples of the iodonium-promoted 5-*endo*-dig carbocyclization reported in the literature (Scheme 1.3).



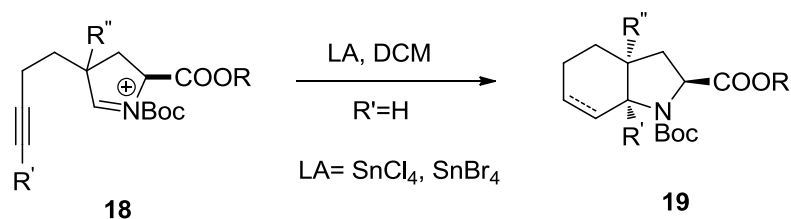
**Scheme 1.3.** Iodine-catalyzed carbocyclization of alkynyl-ketoesters.

Zulfiqar and Thomas (2009) reported the synthesis of 3-Iodo-1*H*-indene derivatives **17** via the same iodonium-promoted 5-*endo*-dig carbocyclizations. However, the products were prepared from various *o*-substituted ethynylmalonates **16** instead of using ketoesters (Scheme 1.4).



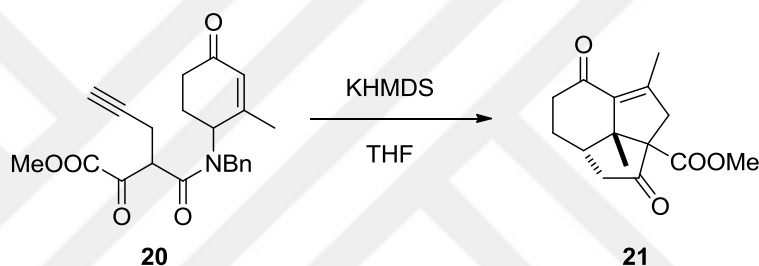
**Scheme 1.4.** Synthesis of 3-Iodo-1*H*-indene derivatives.

*N*-protected iminium ions **18** from 4-substituted pyroglutamic alkynyl esters undergo rapid Lewis acid-mediated carbocyclizations yielding stereo-defined azacyclic products **19** stereoselectively (Scheme 1.5) (Hanessian et al., 2005).



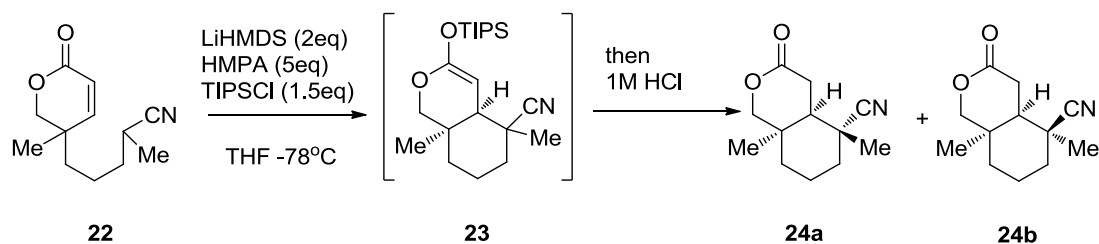
**Scheme 1.5.** Carbocyclization of *N*-Acyloxyiminium ions.

Kourra et al. (2011) demonstrated the facile access to a tricyclic compound **21** from unactivated alkyne **20** using a strong non-nucleophilic base (Scheme 1.6). The reaction proceeded over the formation of Michael addition product followed by an intramolecular alkyne carbocyclization furnishing **21** as a single diastereoisomer having three neighbouring stereocentres with high selectivity and good yield.



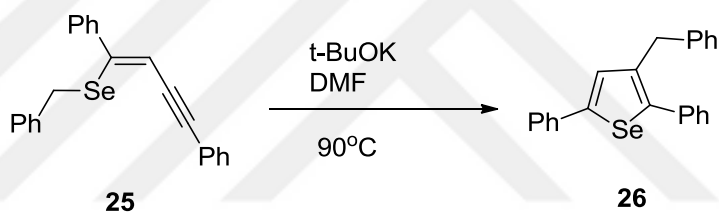
**Scheme 1.6.** A base-catalyzed carbocyclization reaction of  $\alpha$ -propargylic- $\beta$ -amido esters.

Yoshimura et al. (2012) have recently reported the synthesis of carbocycles having all carbon quaternary atoms via intramolecular addition reaction by employing different base combination. Interestingly, they found that using LiHMDS/TIPSCl yielded unsatisfactory results compared to combination of TMSOTf and  $\text{Et}_3\text{N}$ . However, when unsaturated lactone **22** was treated with LiHMDS/TIPSCl in the presence of HMPA at  $-78^\circ\text{C}$ , the intramolecular reaction progressed efficiently affording cyclic ketene silyl acetal **23**. Spontaneous treatment of the intermediate **23** with 1 M HCl afforded diastereomeric mixture of bicyclic lactones **24a** and **24b** in more than 90% yield, respectively (Scheme 1.7).



**Scheme 1.7.** Base-mediated intramolecular carbocyclization reaction.

(*Z*)-benzylselenoenynes **25** undergo selective base-mediated synthesis of selenophene derivatives **26** via carbocyclization reaction. The reaction was believed to proceed under mild conditions using *t*-BuOK as the sole base with no additives or transition metal added yielding the final product in moderate to good yield (Scheme 1.8) (Barancelli et al., 2011).



**Scheme 1.8.** Synthesis of selenophenes via carbocyclization of (*Z*)-benzylselenoenynes promoted by *t*-BuOK.

## 1.2 CHAPTER 2

### 1.2.1 Proline

Amino acids, being the building blocks of protein that play a significant role in discharging most of the biological processes in living organisms, are in principle described as any organic compound containing amine and carboxylic acid functional groups. *L*-Proline **27** is one of the twenty natural proteinogenic (protein building) amino acids, which is considered unique as its amine gives a tertiary amide when reacted with other compounds such as acyl halides, esters, anhydrides among other carbonyl containing functional groups, or integrated into biopolymers, thereby counteracting hydrogen bond formation (Mothes et al.,2013).

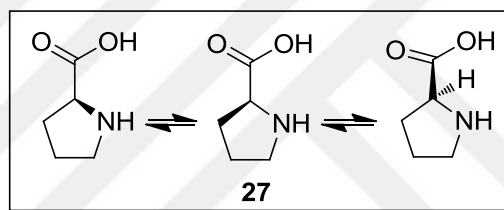


**Figure 1.4.** Schematic representation of *L*-Proline

It has been used as a potential intermediate in the synthesis of a variety of significant natural products such as; [4.4] spiro lactams (Kelleher and Kelly, 2006), spiro-pyrrolidines/pyrrolizines derivatives (Almansour et al.,2014; Belal and El-Genddy, 2014). Using proline itself alone, its derivatives, or in combination with other compounds enhance cyclization reaction by acting as a catalyst. Several publications have reported its usage as catalyst for Mannich reaction, enantioselective, heterogeneous, homogeneous, and transition metal catalysis (List, 2004).

#### 1.2.1.1 General Properties of *L*-proline

*L*-proline is one of the amino acids in all the twenty natural proteinogenic units. It exists as a transparent crystals. It contains five membered ring as its side

chain. In addition, it is termed as a secondary amine (called imino group) because of the cyclic attachment of the three-carbon chains to the nitrogen atom. The distinct cyclic nature of proline's side chain provides it with a special conformational rigidity compared to other amino acids. Moreover, it's optically active and forms right handed isomer (*L*- or levorotatory) like any other amino acid with the exception of glycine (Karppanen and Koskinen, 2010).

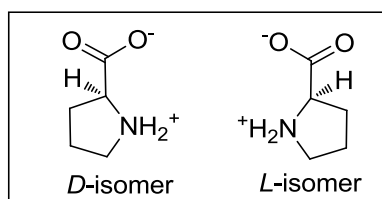


**Figure 1.5.** Isomeric structures of proline enantiomers.

The other essential features of proline are their *cis*/*trans* configurations which play an important part in the folding of proteins. Generally, most of the peptide bonds choose the *trans*-isomer because of the small amount of steric effect between amide hydrogen compared to *cis*-isomer (Figure 1.6). However, as it is shown by many authors, proline is mainly found in the *cis* form compare to other amino acids (Wedemeyer et al., 2002)

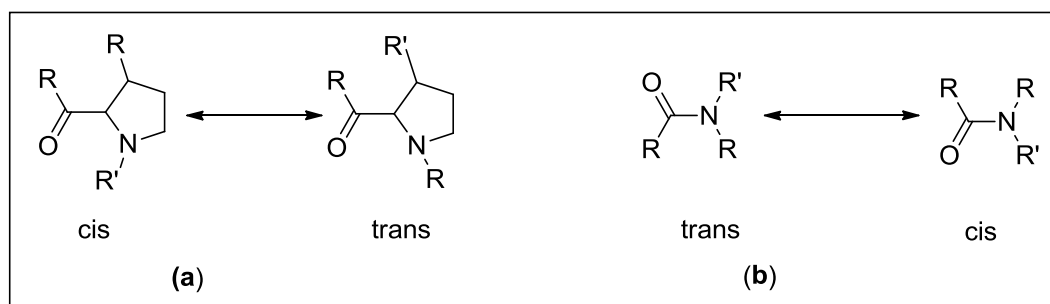
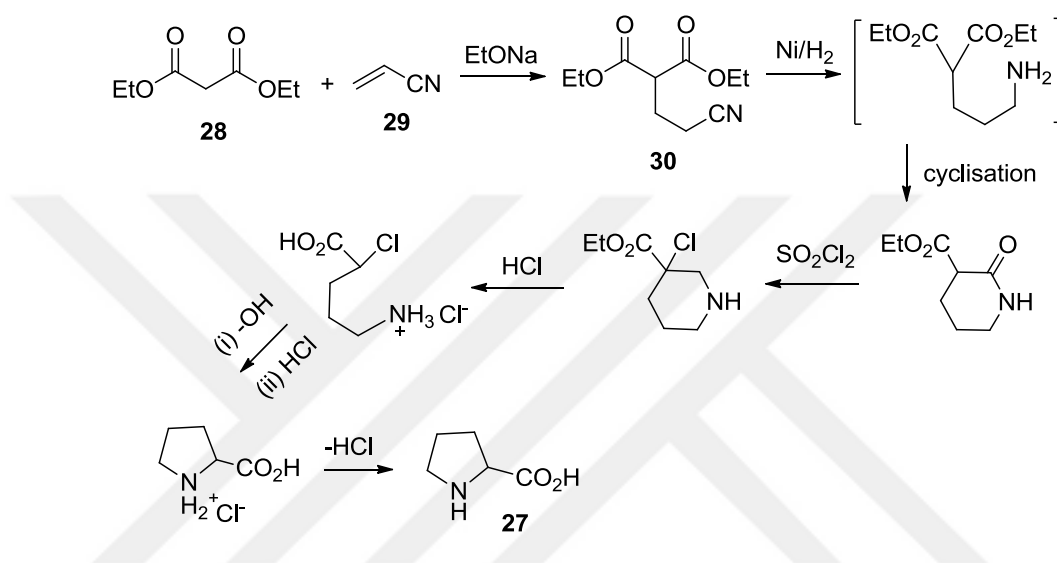


**Figure 1.6.** *Cis-Trans* a) proline and b) non-proline structures.

#### 1.2.1.2 Synthesis of Proline

Proline can be obtained synthetically in the laboratories or derived naturally from plant sources. Many studies have shown synthetic paths of obtaining proline containing core structures (Natelson and Kahn, 1942). Due to the fact that proline is

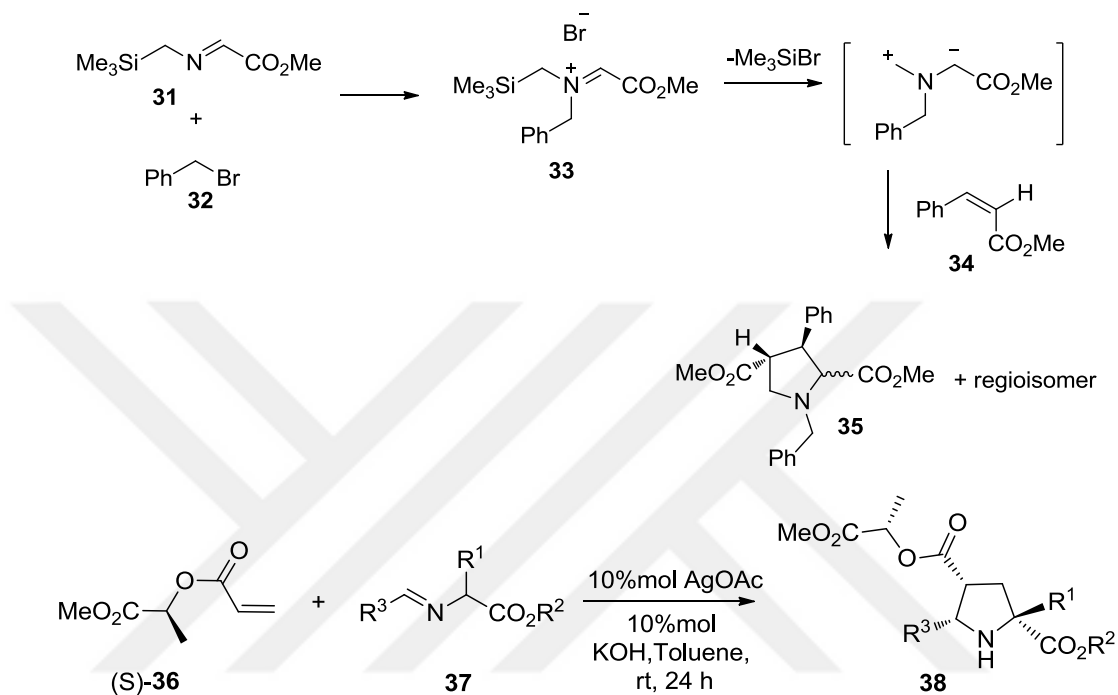
a non-essential amino acid, it can be synthesized by body biosynthetically through the breakdown of *L*-glutamate among other processes. A multistep synthetic way for preparation of proline starts with the reaction of diethyl malonate **28** with acrylonitrile **29**. It is believed that the reaction proceed via the formation of Michael adduct **30**, catalytic reduction and intramolecular cyclisation of this adduct and with few steps following the cyclisation. This process generally yields a racemic mixture of proline **27** at final step (Scheme 1.9).



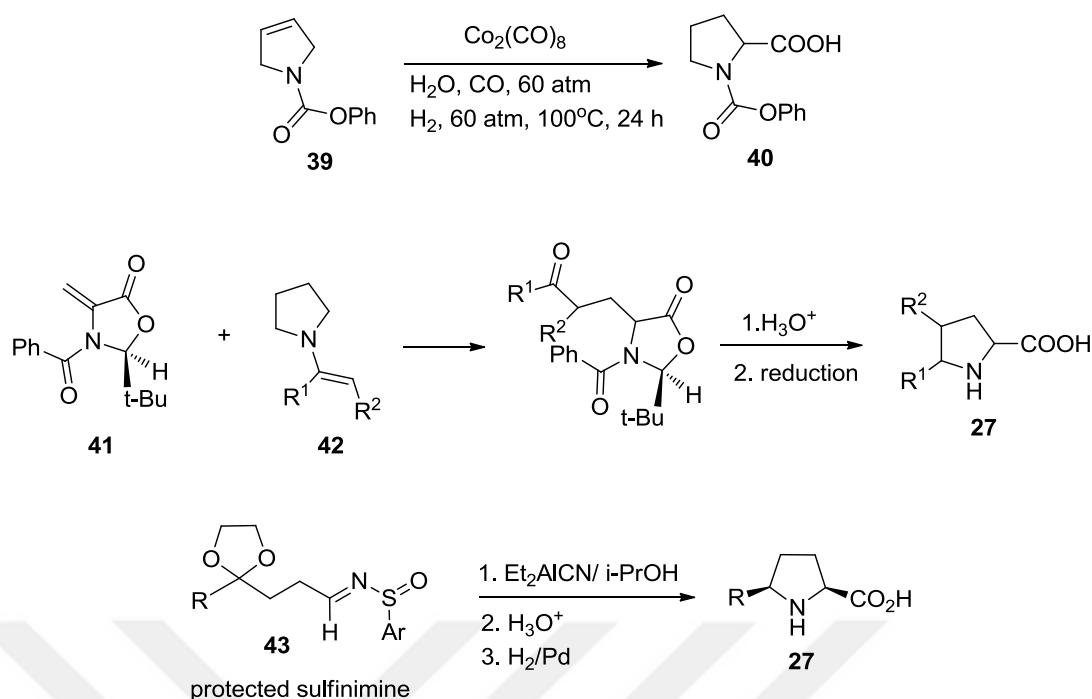
**Scheme 1.9.** Synthesis of proline from the reaction of diethyl malonate and acrylonitrile.

Another one-pot method of proline synthesis is 1,3-dipolar cycloaddition chemistry. Imai and co-workers (1987) have prepared the derivatives of proline by 1,3-dipolar cycloaddition reaction of azomethine ylides generated from methyl *N*-(trimethylsilylmethyl)iminoacetate and benzyl bromide or a catalytic amount of TFA. More recently, by the 1,3-dipolar cycloaddition of azomethine ylides generated from iminoesters **37** with lactate-driven acrylate **36** dipolarophiles, several chiral proline derivatives **38** have been obtained in high diastereoselectivities (Najera and Sansano, 2011) (Scheme 1.10). In previous works, *N*-acyl proline derivatives **40** have been obtained from *N*-acyl unsaturated cyclic amines **39** through cobalt-catalysed isomerisation-carboxylation in the hydroformylation conditions (Amino et.al, 1991). Also, Pyne and co-workers (1995) developed a protocol involving the conjugate addition of an enamine **42** to the oxazolidinone **41** to give a ketone and subsequently, acid hydrolysis of oxazolidinone ring and reduction steps afforded

substituted prolines **27**. Davis et.al (2001) developed a new method for preparation of proline derivatives using the proteinogenic amino acids by treating  $\text{Et}_2\text{AlCN}/i\text{-PrOH}$  with masked sulfinimines **43** to give  $\alpha$ -aminonitriles that affords  $\alpha$ -aminoacids by hydrolysis. Then the cyclisation and reduction of these  $\alpha$ -aminoacids provided cis-prolines **27** (Scheme 1.11).



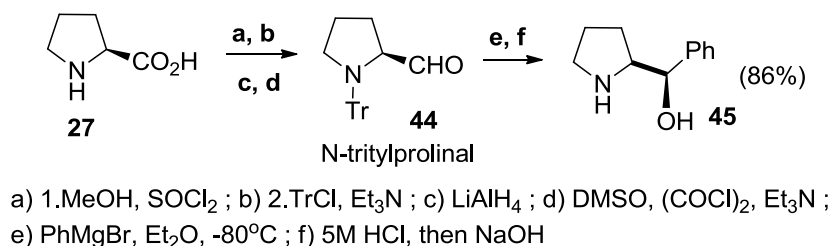
**Scheme 1.10.** Preparation of proline derivatives via 1,3-dipolar cycloaddition reactions



**Scheme 1.11.** Preparation of proline derivatives with various synthetic ways

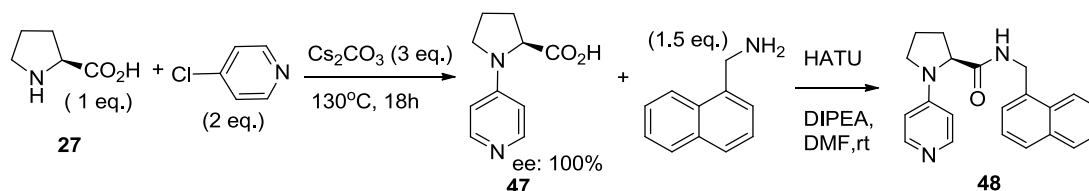
### 1.2.1.3 Reactions of Proline

Since proline-based molecules have pharmaceutical importance and being the building block of many natural products, its synthetic potential has been investigated by many research groups using different synthetic ways. In order to explain the synthetic importance of proline, here, some recent examples involving its reactions will be given. Bejjani and coworkers (2003) have converted *L*-proline into some syn-amino alcohols **45** over the formation of *N*-tritylprolinal **44** in totally 5 steps and high overall yields (Scheme 1.12).



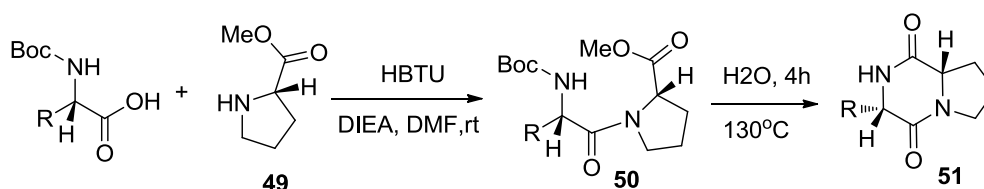
**Scheme 1.12.** Synthesis of syn-amino alcohols from *L*-proline

4-pyridinyl proline derivatives as potential stereoselective catalyst **48** can be prepared by starting from *L*-proline in two-step synthetic route very efficiently (Priem et al., 2002).

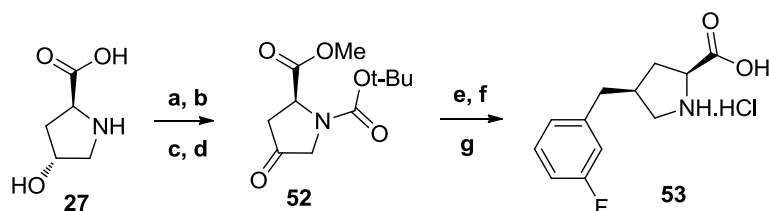


**Scheme 1.13.** Preparation of chiral catalyst from *L*-proline

Lately, *L*-Proline-based cyclic dipeptides **51** were synthesized from *N*-Boc-protected dipeptide methyl esters **50** under catalyst-free condition using water as a solvent in good yields (Thajudeen et al., 2010). Besides, a potent series of substituted (2*S*,4*S*)-benzylproline  $\alpha 2\delta$  ligands **53** have been prepared from the readily available starting material (2*S*,4*R*)-hydroxy-*L*-proline **27** over a multistep synthetic route (Rawson et al., 2011). These ligands are useful in the treatment of neuropathic pains when orally used (Scheme 1.15).



**Scheme 1.14.** Preparation cyclic dipeptides over *L*-proline precursors



a. AcCl, MeOH; b. BOC<sub>2</sub>O, DCM, Et<sub>3</sub>N; c. TEMPO, trichloroisocyanuric acid, DCM; d. 3-florobenzyltriphenylphosphonium bromide, KOt-Bu, DCM; e. H<sub>2</sub>/PtO<sub>2</sub>, DCM; f. 6M HCl; g. recrystallization from MeCN/H<sub>2</sub>O ;

**Scheme 1.15.** Synthetic design of neuropathic agent starting from a *L*-proline precursor

### 1.3 CHAPTER 3

#### 1.3.1 Pyrrolizine/pyrrolizidine

Pyrrolizines are one of the important members of heterocyclic compounds comprising of two fused five membered rings with one nitrogen atom situated at the ring junction. The parental structure of this class is 3*H*-pyrrolizine **54** (Figure 1.7) (Joule and Mills, 2010).

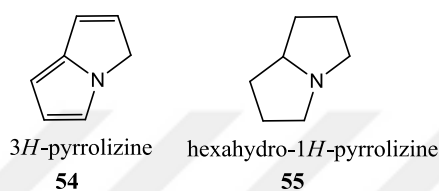


**Figure 1.7.** Simple pyrrolizine structures.

Pyrrolizine derivatives constitute an important group of natural products with a wide range of biological activities such as anticancer, antimalarial, antimicrobial, antiproliferative, antiviral, antitumor, antileukemic, anti-inflammatory and also display carcinogenic glycosidase inhibitory, aromatase, analgesic, and antagonism activities (Becker et al., 2006; Sengupta et al., 2013; Belal and El-Ghandi, 2014). Because of their bioactivity and vast application in pharmaceutical and drug industry, they have gained significant interest in the field of synthetic chemistry (Sengupta et al., 2013; Lim et al., 2013; Gouda et al., 2014). For example, hexahydropyrrolizine scaffold **55** is an essential building block of about 400 biologically active natural products (Figure 1.7) (Sengupta et al., 2013).

Pyrrolizines form the main frame of around 600 alkaloids found in over 600 plants across the globe. Hosch et al. (1996) demonstrated a quantitative method for analyzing pyrrolizidine alkaloids from plant sample. The chromatographic method was applied to the analysis of senecionine (**56**), seneciphylline (**57**) and spartioidine (**58**) isolated from *Senecio leucophyllus* (Figure 1.8)

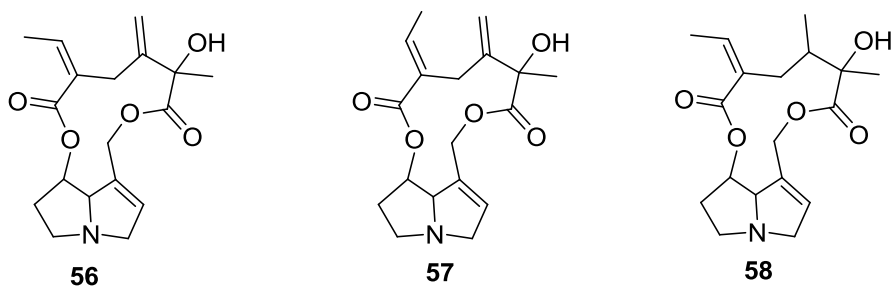


**Figure 1.8.** Structures of pyrrolizines isolated from plant sources.

Although pyrrolizidine alkaloids do not occur naturally, many of their offshoots have been isolated from plants and animals sources (Hosch et al., 1996; Xiong et al., 2009). Supinidine **59**, Retronecine **60**, Heliotridine **61**, and Crotanecine **62** belong to the example of this class. These compounds are known for their significant hepatotoxicity (Smith and Culvenor, 1981). They are synthesized by plants biosynthetically as secondary metabolites playing a fundamental role in protecting them against herbivores (Figure 1.9) (Schoental, 1968).

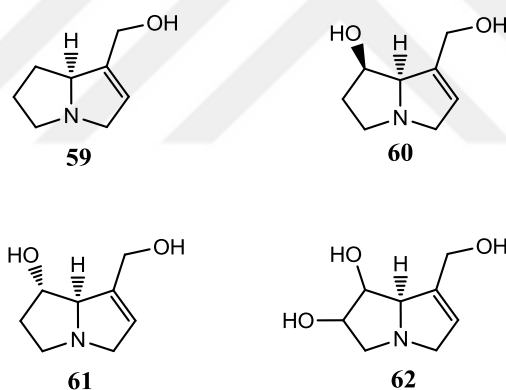


**Figure 1.9.** Examples of pyrrolizine alkaloids exhibiting hepatotoxicity.

### 1.3.1.1 Biologically Important Pyrrolizine Derivatives

Pyrrolizine derivatives are important organic compounds in medicinal chemistry due to their presence in many biologically active structures. Pyrrolizine containing scaffolds constitute essential part for a wide range of pharmacological and technological applications like medicine, agrochemistry, etc. In medicine they are found in the structures of many anticancer, antitumor, anti-inflammatory, antiproliferative agents, etc. (Hanna et al., 2012; Abbas et al., 2010; Gouda et al.,

2014). In agriculture, they are potentially used as insecticides (Quiroga et al., 2014). Therefore, the research and reviews on pyrrolizines have been attractive over the last few decades and unremittingly new derivatives are reported in the literature.

Mitomycin C (**63**), one of the early uncovered antitumor drugs obtained from *Streptomyces caespitosus*, was successfully used in treating colon and breast cancers, upper esophageal carcinoma, and superficial bladder tumors. It functions as a DNA alkylating agent through crosslinking the DNA with high effectiveness and specificity. Other examples of this antibiotic class includes clazamycin A (**64**), and clazamycin B (**65**) (Figure 1.10)(Hanna et al., 2012; Gouda et al., 2014).

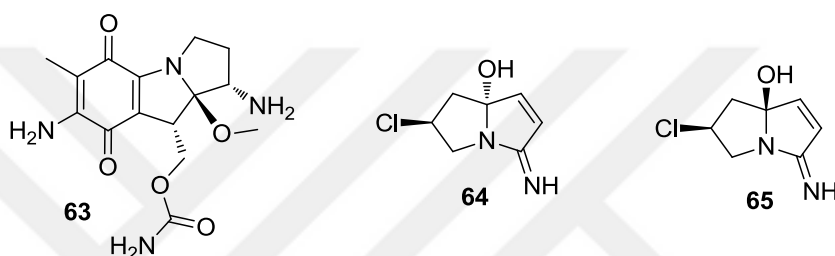


**Figure 1.10.** Antibiotics with antitumor properties

In addition to the antitumor and anticancer activity shown by pyrrolizines in the aforementioned compounds, many other structures with different substituents have been reported to exhibit variety of biological functions. Antibiotics presently used for diminishing inflammation are steroids, particularly glucocorticoids. These anti-inflammatory drugs are generally consumed for the cure of pain and swelling related with inflammation. They reduce pain by offsetting the cyclooxygenase enzyme and subsequently binding to cortisol receptors. To illustrate, Licofelone (ML3000), (**66**) is an anti-inflammatory remedy with effective activity experimentally proven on numerous brands of animals for both chronic and acute inflammation. Another important pyrrolizine moiety is Ketorolac **67**. It is proven to selectively inhibit the COX-enzymes that play a vital role in treating severe neuropathic pain (Cossy and Belotti, 1997). Other effective anti-inflammatory drugs **68** and **69** with other groups attached are also reported (Figure 1.11) (Abbas et al., 2010; Barsoum, 2011).

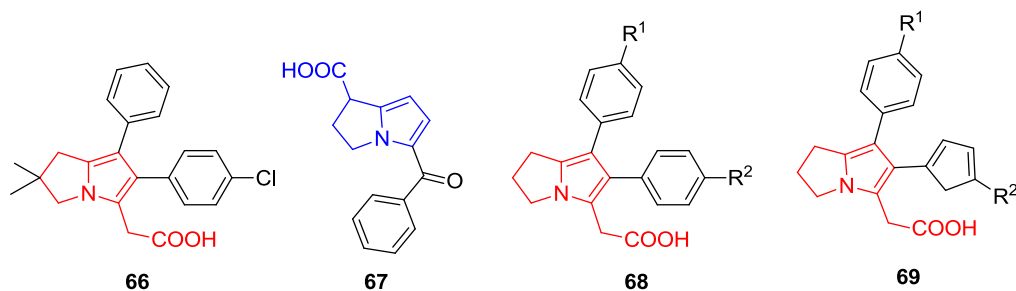


**Figure 1.11.** Examples of pyrrolizine scaffolds with anti-inflammatory effects.

Other drug-like pyrrolizine molecules with biological activities have been constructed and reported by many authors. To illustrate, alexine **70** and australine **71** exhibit glucosidase inhibitory features as well as viral and retroviral repression properties (Figure 1.12) (Denmark, E.S and Herbert.B, 1998).

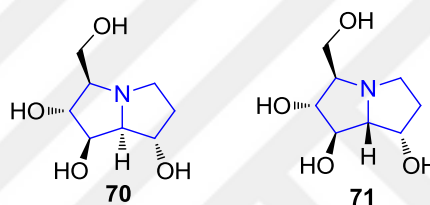


**Figure 1.12.** Antibiotics with viral and retroviral repression properties.

In agriculture, toxicological action of some pyrrolizine alkaloids was the subject of discussion. For instance, the heterocyclic portion of necine bases; heliotridine **72** and crotanecine **73** (Figure 1.13) have a strong toxicity against insects and thus termed as a new potential insecticides (Brandi et al., 2009).

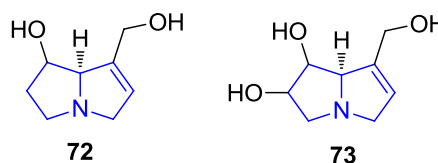
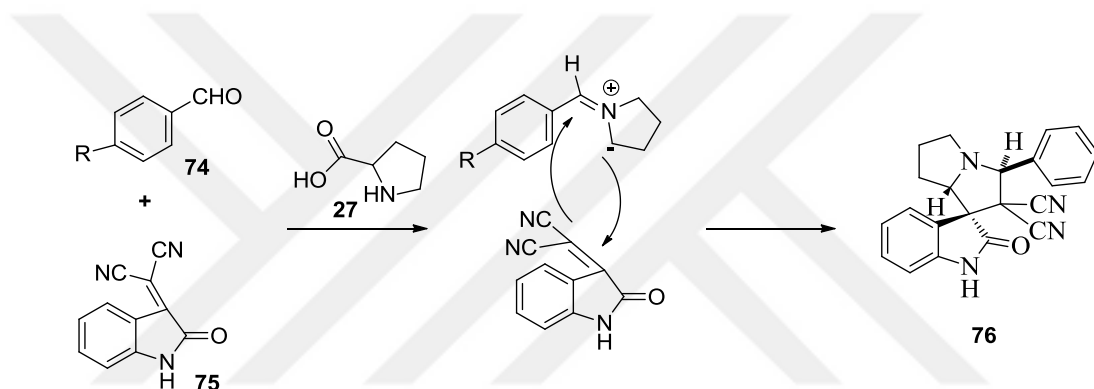


**Figure 1.13.** Necine bases with potential insecticidal effects.

### 1.3.1.2 Synthesis of Pyrrolizidine/Pyrrolizine Derivatives

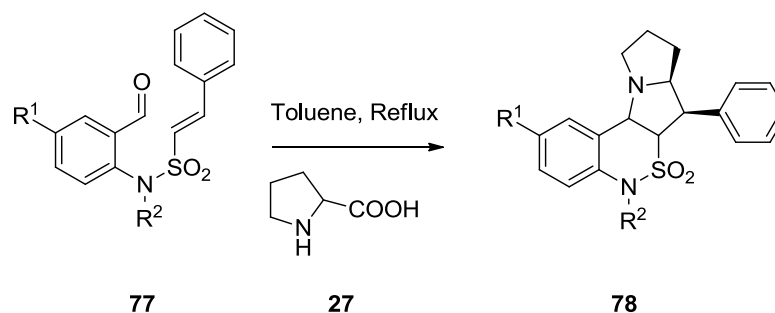
Synthesis of pyrrolizine derivatives are described by countless number of procedures in the literature (Hanna et al., 2012; Sengupta et al., 2013; Gouda et al.,

2014; Lemaire et al., 2004; Snider and Duvall, 2005). The type of substituents affects how the methodology of reactions or transformations of synthetic techniques proceed. Although there are several methods to construct pyrrolizine rings, the construction through 1,3-dipolar cycloaddition of azomethine ylides with dipolarophiles is the most common one (Ghandi et al.,2014). For instance, 1,3-dipolar cycloaddition of azomethine ylides (generated in situ from proline **27** and aromatic aldehyde **74**) with 2-oxo-(3*H*)-indole-3-ylidene-malononitrile **75** (generated through condensation of malononitrile and isatin) has been utilized for the formation of pyrrolizines **76** (Scheme1.16) (Ghandi et al.,2009). These compounds are of great importance for the construction of diverse biochemical libraries with lots of biological activities.



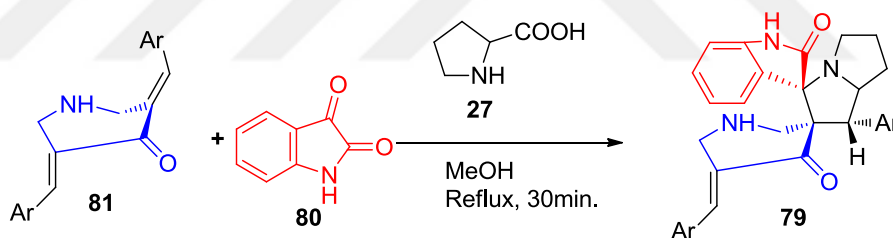
**Scheme 1.16.** Synthesis of pyrrolizine scaffolds via 1,3-dipolar cycloaddition of azomethine ylides.

Ghandi and coworkers recently reported a diastereoselective synthesis of pyrrolizine-fused benzosultams via 1,3-dipolar cycloaddition. The intramolecular [3+2] cycloaddition of (*E*)-*N*-(2-formylphenyl)-*N*-methyl-2-phenylethene sulfonamides **77** with azomethine ylides (generated in situ from the reaction of proline **27** with the aldehydic portion of the sulfonamides) afforded the corresponding pyrrolizine derivatives **78** (Scheme 1.17). The reaction was accomplished by refluxing the two reagents in toluene for 12 h furnished the desired product in good yield (Ghandi et al., 2014).



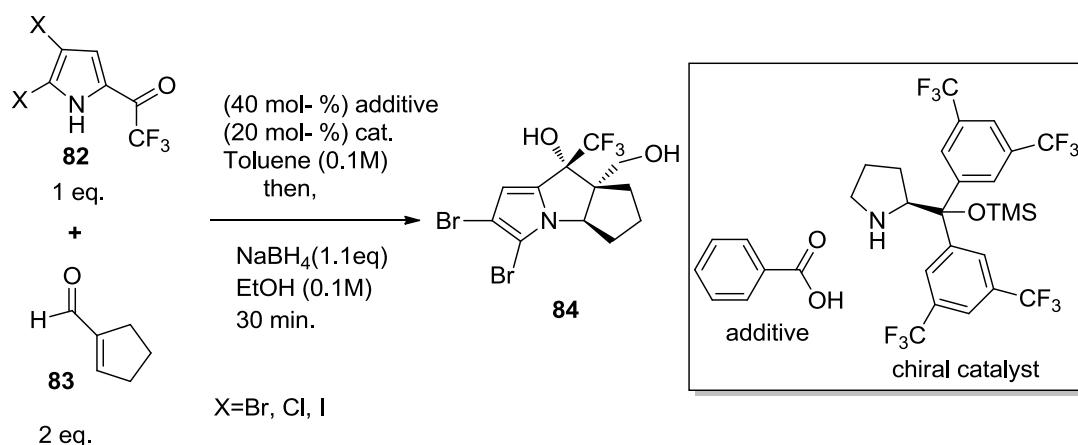
**Scheme 1.17.** Synthesis of pyrrolizine-fused benzo-sultams via [3+2] cycloaddition.

Almansour and his group synthesized spiro-pyrrolizine derivatives **79** from azomethine ylides (produced in situ by the reaction of 1*H*-indole-2,3-dione **80** and proline **27**) with 3,5-bis[*E*]-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **81**. The [3+2] cycloaddition of azomethine ylides with **81** afforded the targeted spiro-pyrrolizines **79** in moderate to good yield regioselectively (Scheme 1.18). The synthesized cycloadducts were evaluated and found to demonstrate a potential antiproliferative activity against human breast carcinoma, ovarian carcinoma, and leukemia lymphoblastic cells (Almansour et al., 2014).



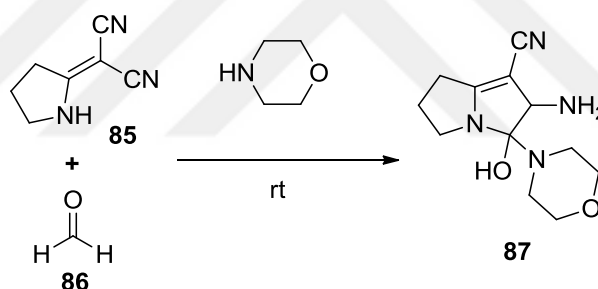
**Scheme 1.18.** Pyrrolizines via azomethine ylide cycloadditions.

An alternative strategy for the synthesis of pyrrolizines is the asymmetric cascade aza-Michael–Aldol reaction using organocatalysts as shown by Li and Cho, (2014). They demonstrated the synthesis of new chiral pyrrolizine-based triheterocycles via organocatalytic cascade reaction of distinct 1-(4,5-dibromo-1*H*-pyrrol-2-yl)-2,2,2-trifluoroethanone **82** and cyclopent-1-enecarbaldehyde **83** in the presence of (40 mol%) acid additive, and (20 mol%) chiral organocatalyst. The reaction was performed in toluene at 0°C furnishing the cascade product **84** as a single diastereomer in moderate yield (Scheme 1.19).



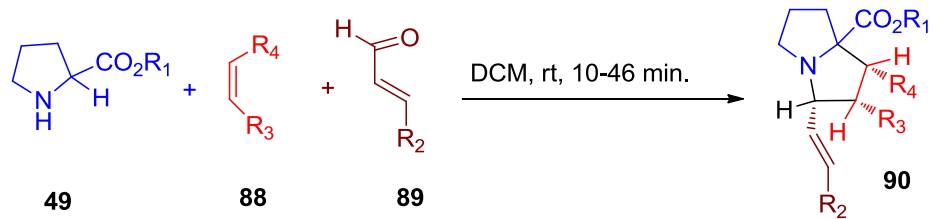
**Scheme 1.19.** Catalytic synthesis of pyrrolizines via asymmetric cascade aza-Michael–Aldol reaction.

Belal and El-Gendy (2013) reported synthesis of pyrrolizine motif by mixing 2-(pyrrolidin-2-ylidene)malononitrile **85**, formaldehyde **86** and morpholine at ambient temperature overnight furnishing the substituted pyrrolizine **87** with higher antitumor activity than the drug doxorubicin (Scheme1.20).



**Scheme 1.20.** Pyrrolizine synthesis via one pot multicomponent reaction.

Sengupta et al (2013) demonstrated a catalyst-free regio- and stereoselective cascade annulation strategy of assembling new hexahydropyrrolizines **90** via multicomponent systems. It should be mentioned that this procedure permits a one-pot synthesis of pyrrolizines from secondary amines. Interestingly, the reaction was reported to have high yield when  $\alpha,\beta$ -unsaturated aldehydes (generally aromatic) **89**, reacted with deactivated olefins **88**, and proline ester **49** without any catalysts in DCM at room temperature within short period of time (Scheme1.21) (Sengupta et al., 2013).



**Scheme 1.21.** Catalyst-free synthesis of hexahydropyrrolizines.

## 2. AIM AND SCOPE OF THE STUDY

Throughout their existence in chemistry, both heterocyclic and carbocyclic compounds have been a subject of exploration for most of the researchers due to their interesting biochemical and biological applications. The bioactivities and the challenge related with the formation of heterocyclic and carbocyclic compounds make these synthetic targets very attractive.

The main objective of this study is to develop a new synthetic methodology to synthesize one of the bioactive carbocycle, tetrahydro-1*H*-pyrrolizine derivatives **97** from different *N*-alkynyl proline esters **95a-h** and **96a-e** via base mediated carbocyclization. Although pyrrolizines have been researched extensively, there are very few findings about pyrrolizines esters.

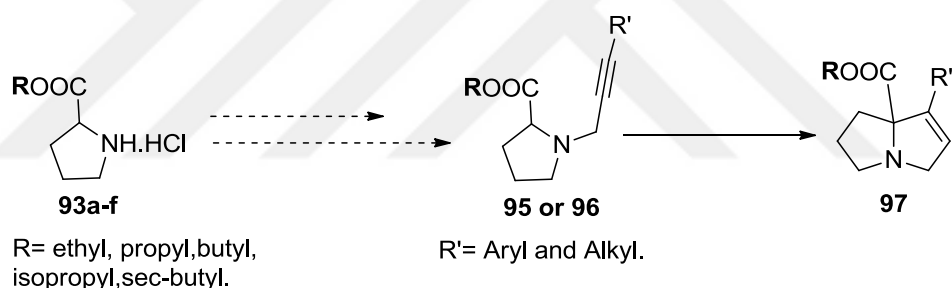


**Figure 2. 1.** Synthetic route to pyrrolizine esters.

In the course of this work, we focused on developing a concise method for the construction of pyrrolizines **97** from *N*-alkynyl substituted proline derivatives **95a-h** and **96a-e** in two different ways (Figure 2.1);

- ❖ The first route involved the synthesis of *N*-propargylated proline esters **94a-f** in good yield followed by the Sonogashira coupling for derivatization yielding the precursor molecules **96a-e** ready for the cyclization. And,
- ❖ One pot synthesis of *N*-alkynyl substituted proline derivatives **95a-h** via A<sup>3</sup> coupling of proline esters, formaldehyde and acetylenes in solvent free conditions.

### 3. MATERIALS AND METHODS

All reagents and solvents were commercially available with analytical grade (Merck, Sigma-Aldrich, TCI) and used as received.

$^1\text{H}$ - and  $^{13}\text{C}$ - NMR spectra were recorded on VARIAN NMR spectrometers (400 MHz for proton and 100 MHz for carbon) and a JEOL-ECS400 Delta2 NMR spectrometer (400 MHz for proton and 100 MHz for carbon) spectrometer at ambient temperature. All chemical shifts ( $\delta$ ) are reported in parts per million (ppm) downfield from TMS;  $J$  values are given in Hz. The abbreviations used for NMR signals are: s =singlet, d =doublet, t =triplet, q =quartet, quint =quintet, sep =septet, hep=heptet, m =multiplet, dd= doublet of doublets, ddd=doublet of doublet of doublets, dddd= doublet of doublet of doublet of doublets, dq= doublet of quartet, dt=doubet of triplets, dtd= doublet of triplet of doublets, td= triplet of doublets, tq= triplet of quartets, tt=triplet of triplets and tdt=triplet of doublet of triplets.

IR spectra were recorded on a SHIMADZU FTIR-8400S instrument (KBr pellet or NaCl discs) and a Shimadzu FT-IR Spectormeter with ATR system.

High resolution mass spectra were run on a Waters Lct Premier XE oa-TOF Mass Spectrometer, on an orthogonal acceleration-TOF mass spectrometer and a FTMS (4.7T) mass spectrometer.

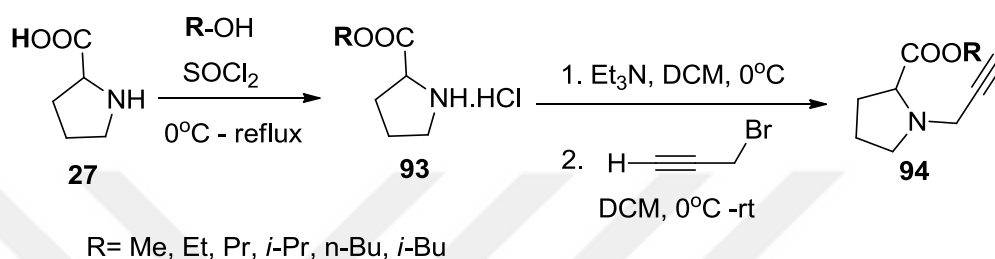
Melting points were determined on a MELTEMP apparatus and are uncorrected. TLC was carried out using precoated plates with fluorescent indicator (60,F<sub>254</sub>,Merck 5735 and 5554) for monitoring the reactions. Column chromatographic separations were performed on silica gel 60 (Merck-109385, 0.040–0.063mm) and the eluent was a mixture of ethyl acetate (EA) and hexanes (H) or only ethyl acetate. Staining solutions of permanganate, phosphomolybdic acid (PMA) and iodine were used for visualization of the TLC spots.

### 3.1 EXPERIMENTAL

#### PREPARATION OF STARTING MATERIALS

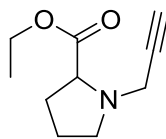
##### General Procedure for the Preparation of *N*-propargyl proline esters (94a-c)

**Method A– Step 1**(Moore et al., 2005).



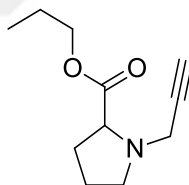
To a stirred suspension of *L*-proline **27** (587mg, 5.1mmol) in alcohol (20 mL) at 0°C was added thionyl chloride (654 mg, 5.5mmol) dropwise over 20 min, the resulting mixture was refluxed for 8 h. After completion of the reaction, the solvent was removed in vacuo to afford **93** (5.6mmol) as a hydrochloric salt which was then dissolved in 10mL of DCM under inert atmosphere before triethylamine (1.03g, 10.2mmol) and propargyl bromide (991mg, 8.4mmol) were added at 0°C. The reaction mixture was stirred at same temperature for 1h, then at room temperature overnight. After the disappearance of the starting materials as indicated by TLC, the reaction was quenched with water (10ml), extracted with DCM (2×20mL), washed with H<sub>2</sub>O, sat. NaHCO<sub>3</sub> solution and brine. The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give *N*-propargyl esters **94** as oily products. The product was used in the next step without further purification. (71-100 %).

**Ethyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (94a):**



Following general procedure (**Step 1**), treating ethyl pyrrolidine-2-carboxylate hydrochloride (780mg, 4.3mmol) with triethylamine (878mg, 8.68mmol) and propargyl bromide (773 mg, 6.5 mmol) for 16 h afforded **94a** (562mg), yield: 71%. Light yellow oil.  $R_f$ : 0.45 (33% EtOAc/hexane). IR (neat):  $\nu_{\max}/\text{cm}^{-1}$  = 3290 (C $\equiv$ C-H), 2978-2823(aliph. CH), 2102 (C $\equiv$ C), 1739 (ester C=O), 1639 (C-N), 1184 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.21-4.13 (m, 2H), 3.60 (t, 2H,  $J$  = 2.4 Hz), 3.42-3.38 (dd, 1H,  $J$  = 9.2;6.4 Hz), 3.07-3.02 (m, 1H), 2.74-2.68 (m, 1H), 2.19 (t, 1H,  $J$  = 2.2 Hz), 2.02-1.74 (m, 2H), 1.25 (t, 3H,  $J$ =7.2 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.5 (ester C=O), 78.3(C $\equiv$ C), 73.3( $\equiv$ C-H), 62.5(CH), 60.9(CH $_2$ -O), 52.3(CH $_2$ -N), 41.2(N-CH $_2$ -C $\equiv$ ), 29.6(CH $_2$ -), 23.2(CH $_2$ -), 14.3(CH $_3$ -).

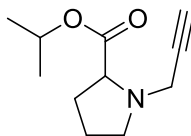
**Propyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (94b):**



Following general procedure (**Step 1**), treating propyl pyrrolidine-2-carboxylate hydrochloride (917mg, 4.75mmol) with triethylamine (959mg, 9.5mmol) and propargyl bromide (832mg, 7.0mmol) overnight afforded **94b** (800mg), yield: 86%. Light yellow oil.  $R_f$ : 0.41 (33% ethyl acetate/hexane). IR (neat):  $\nu_{\max}/\text{cm}^{-1}$  = 3290 (C $\equiv$ C-H), 2970-2823(aliph. CH), 2102 (C $\equiv$ C), 1739 (ester C=O), 1635 (C-N), 1180 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.14-4.03 (m, 2H), 3.62-3.61 (t, 2H,  $J$  = 2.8 Hz), 3.45-3.41 (dd, 1H,  $J$  = 8.4;6.0 Hz), 3.08-3.03 (m, 1H), 2.76-2.70 (q, 1H,  $J$ =8.8 Hz), 2.21 (t, 1H,  $J$ =2.2 Hz), 2.19-2.13 (m, 1H), 2.03-1.78 (m, 3H), 1.72-1.63 (sep, 2H,  $J$ =7.2 Hz), 0.94 (t, 3H,  $J$ =7.2 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.6 (ester C=O), 78.4(C $\equiv$ C), 73.1( $\equiv$ C-H), 66.3(CH), 62.4(CH $_2$ -O), 52.1(CH $_2$ -N), 41.1(N-CH $_2$ -C $\equiv$ ), 29.5(CH $_2$ -), 23.2(CH $_2$ -), 22.0(CH $_2$ -), 10.3(CH $_3$ -).

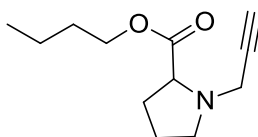
).m/z (TOF-MS ES<sup>+</sup>) 196 (100, MH<sup>+</sup>), 194 (5); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 196.1329. C<sub>11</sub>H<sub>18</sub>NO<sub>2</sub> requires 196.1338.

**Isopropyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (94c):**



Following general procedure (**Step 1**), treating isopropyl pyrrolidine-2-carboxylate hydrochloride (871mg, 4.5mmol) with triethylamine (909mg, 9.0mmol) and propargyl bromide (832mg, 7.0mmol) for 17 h afforded **94c** (742mg), yield: 84%. pale yellow oil. R<sub>f</sub> : 0.40 (33% ethyl acetate/hexane). IR (neat):  $\nu_{\max}/\text{cm}^{-1}$  = 3290 (C≡C-H), 2978-2823(alip. CH), 2102 (C≡C), 1739 (ester C=O), 1635 (C-N), 1180 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.11-5.02 (hep, 1H, J = 2.0 Hz), 3.64-3.62 (dd, 2H, J = 3.6, 2.0), 3.42-3.38 (dd, 1H, J = 8.8; 6.4 Hz), 3.10-3.05 (m, 1H), 2.78-2.71 (q, 1H, J = 8.8 Hz), 2.22 (t, 1H, J = 2.4 Hz), 2.21-2.09 (m, 1H), 2.01-1.77 (m, 2H), 1.26 (t, 6H, J = 6.0 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.9 (ester C=O), 78.3 (C≡C), 73.5 (=C-H), 68.5 (CH), 67.8, 62.5 (CH<sub>2</sub>-O), 52.2 (CH<sub>2</sub>-N), 41.1 (N-CH<sub>2</sub>-C≡), 29.4 (CH<sub>2</sub>-), 23.0 (CH<sub>3</sub>-), 21.8 (CH<sub>3</sub>-).m/z (TOF-MS ES<sup>+</sup>) 196 (100, MH<sup>+</sup>), 154 (5); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 196.1337. C<sub>11</sub>H<sub>18</sub>NO<sub>2</sub> requires 196.1338.

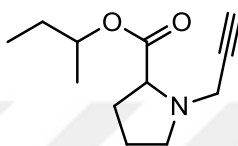
**Butyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (94d):**



Following general procedure (**Step 1**), treating butyl pyrrolidine-2-carboxylate hydrochloride (780mg, 4.34mmol) with triethylamine (946mg, 9.37mmol) and propargyl bromide (836mg, 7.03mmol) for 17 h afforded **94d** (1004mg), yield: quantitative. Pale yellow oil. R<sub>f</sub>: 0.53 (33% ethyl acetate/hexane). IR (neat):  $\nu_{\max}/\text{cm}^{-1}$  = 3298 (C≡C-H), 2962-2823 (alip. CH), 2102 (C≡C), 1739 (ester C=O), 1635 (C-N), 1180-1130 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.11-3.98 (m, 2H), 3.53-3.51 (dd, 2H, J = 3.9, 2.4 Hz), 3.36-3.32 (dd, 1H, J = 9.0, 6.7

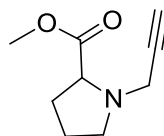
Hz), 3.02-2.93 (m, 1H), 2.68-2.61 (dd, 1H, J=16.6, 8.9 Hz), 2.14 (t, 1H, J = 2.4 Hz), 2.11-2.02 (dtd, 1H, J= 11.8, 8.9,6.9 Hz), 1.93-1.69 (m, 3H), 1.60-1.49 (m, 2H), 1.33-1.24 (dq, 2H, J=14.7, 7.4 Hz), 0.84 (3H, t, J=7.4 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.5 (ester C=O), 78.3( $\text{C}\equiv\text{C}$ ), 73.2( $\equiv\text{C-H}$ ), 72.9, 64.6(CH), 62.3( $\text{CH}_2\text{-O}$ ), 52.5( $\text{CH}_2\text{-N}$ ), 41.0( $\text{N-CH}_2\text{-C}\equiv$ ), 30.6( $\text{CH}_2\text{-}$ ), 23.1( $\text{CH}_3\text{-}$ ), 19.1, 13.7( $\text{CH}_3\text{-}$ ).  $m/z$  (TOF-MS  $\text{ES}^+$ ) 210 (100,  $\text{MH}^+$ ), 208 (30), 189 (1); HRMS (TOF-MS  $\text{ES}^+$ ):  $\text{MH}^+$ , found 210.1494.  $\text{C}_{12}\text{H}_{20}\text{NO}_2$  requires 210.1494.

**Sec-butyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (94e):**



Following general procedure (**Step 1**), treating sec-butyl pyrrolidine-2-carboxylate hydrochloride (780mg, 4.34mmol) with triethylamine (576mg, 5.7mmol) and propargyl bromide (636mg, 4.28mmol) for 17 h afforded **94e** (501mg), yield: 84% after work-up. Pale yellow oil.  $R_f$ : 0.54 (33% hexane/ethyl acetate).

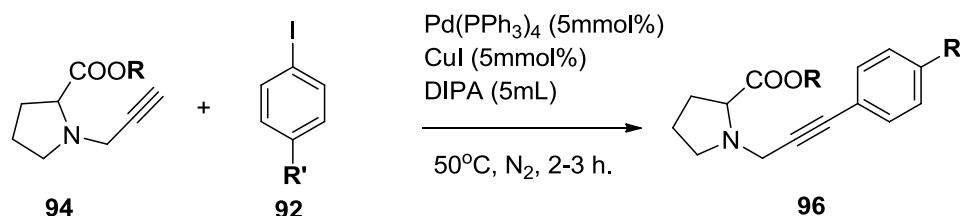
**Methyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (94f):**



Following general procedure (**Step 1**), treating methyl pyrrolidine-2-carboxylate hydrochloride (3760mg, 22.8mmol) with triethylamine (4610mg, 45.6mmol) and propargyl bromide (3200mg, 26.9mmol) for 17 h afforded **94f** (3250mg), yield: 85% after work-up. Yellow oil.  $R_f$ : 0.36 (33% ethyl acetate/hexane). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3294 ( $\text{C}\equiv\text{C-H}$ ), 2953-2821 (alip. CH), 2102 ( $\text{C}\equiv\text{C}$ ), 1735 (ester C=O), 1437, 1174-1132(C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.66 (s, 3H), 3.53-3.51 (t, 2H, J=2.5 Hz), 3.38-3.34 (dd, 1H, J = 9.1, 6.7 Hz), 3.01-2.92 (m, 1H), 2.68-2.61 (td, 1H, J=9.0, 7.6 Hz), 2.15 (t, 1H, J = 2.4 Hz), 2.13-2.02 (m, 1H), 1.96-1.69 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.4 (ester C=O), 78.2 ( $\text{C}\equiv\text{C}$ ), 73.3 ( $\equiv\text{C-H}$ ), 62.4( $\text{CH}_2\text{-O}$ ), 52.1( $\text{CH}_2\text{-N}$ ), 51.9, 41.3 ( $\text{N-CH}_2\text{-}$

C≡), 29.5(CH<sub>2</sub>-), 23.2(CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 168 (100, MH<sup>+</sup>); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 168.1020. C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub> requires 168.1025.

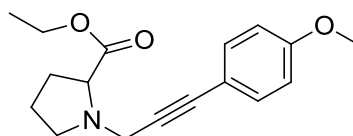
**General Procedure for Synthesis of *N*-alkynyl substituted proline esters (96a-e) via Sonogashira coupling (Alami et. al, 1993; Bera et. al, 2011)**



**Method A –Step 2** (Alami et al,1993)

To a stirred suspension of proline ester **94** (5.0 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (5mmol%) in DIPA (5 ml), under an inert atmosphere, was added CuI (5mmol%) and 4-iodophenyl derivative **92** (5.0 mmol) successively. After stirring at 50°C for 3 h, the mixture was hydrolyzed with a saturated aqueous solution of ammonium chloride, extracted with diethyl ether and dried over Na<sub>2</sub>SO<sub>4</sub>. The compound was purified using silica gel column chromatography to afford the *N*-alkynyl substituted proline ester **96** in good to moderate yield.

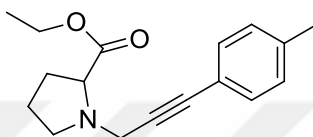
**Ethyl 1-(3-(4-methoxyphenyl)prop-2-yn-1-yl)pyrrolidine-2-carboxylate (96a):**



Following general procedure (**Step 2**), compound **96a** was synthesized from the reaction of *N*-propargyl proline ethylester **94a** (400mg, 2.2mmol), 4-iodoanisole **92b** (514mg, 2.2mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (5mmol %), and CuI (5mmol %) at 50°C for 3 h. The product was obtained as yellow oil (403mg), yield: 64%. R<sub>f</sub>: 0.38 (33% ethyl acetate/hexane). IR (neat): ν<sub>max</sub>/cm<sup>-1</sup> = 3043 (arom.CH), 2978-2839 (alip. CH), 2222 (C≡C), 2048-1890 (arom overt.), 1739 (ester C=O), 1639 (C-N), 1604 (arom C=C), 1508, 1446, 1176 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.38-7.34 (d, arom. 2H, J= 8.8), 6.84-6.80 (d, arom. 2H, J=8.8 Hz), 4.25-4.13 (m, 2H), 3.80 (s, CH<sub>3</sub>O, 3H),

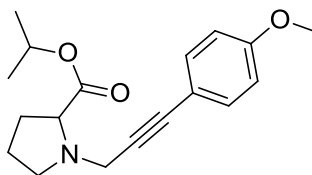
3.78 (s, CH<sub>2</sub>O-, 2H), 3.49-3.45 (dd, 1H, J = 8.8;6.4 Hz), 3.15-3.11 (m, 1H), 2.81-2.75 (q, 1H, J= 8.8 Hz), 2.20-2.13(m, 1H), 2.03-1.81 (m, 3H), 1.27 (t, 3H, J=7.2 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.7 (ester C=O), 159.4 (ipso C), 133.1 (arom. CH), 115.2 (ipso C), 113.8 (arom. CH), 85.1 (C≡C), 82.7 (C≡C), 62.9 (CH), 60.7 (CH<sub>2</sub>-O), 55.2 (CH<sub>3</sub>-O), 52.5 (CH<sub>2</sub>-N), 42.2 (N-CH<sub>2</sub>-C≡), 29.6 (CH<sub>2</sub>-), 23.3 (CH<sub>2</sub>-), 14.2 (CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 288 (100, MH<sup>+</sup>), 246 (1), 156 (5); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 288.1602. C<sub>17</sub>H<sub>22</sub>NO<sub>3</sub> requires 288.1600.

**Ethyl 1-(3-(p-tolyl)prop-2-yn-1-yl)pyrrolidine-2-carboxylate (96b):**



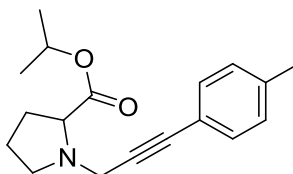
Following general procedure (**Step 2**), treating *N*-propargyl proline ethylester **94a** (400mg, 2.2mmol), 4-iodotoluene **92a** (480mg, 2.2mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mmol%), CuI (5mmol%) in DIPA (5mL) at 50°C for 3 h to afford **96b** (360mg) as dark-red oil, yield: 59%. R<sub>f</sub>: 0.49 (33% ethyl acetate/hexane). IR (neat): ν<sub>max</sub>/cm<sup>-1</sup> = 3074 (arom.CH), 2978-2816 (alip. CH), 2229 (C≡C), 1905 (arom overt.), 1743 (ester C=O), 1639 (C-N), 1508, 1446, 1180 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.33-7.31 (d, arom. 2H, J= 8.4), 7.11-7.08 (d, arom. 2H, J=8.0 Hz), 4.26-4.14 (m, 2H), 3.80 (s, CH<sub>2</sub>O, 2H), 3.51-3.47 (dd, 1H, J = 8.8;6.4 Hz), 3.16-3.11 (m, 1H), 2.82-2.76 (q, 1H, J= 7.6 Hz), 2.34 (s, CH<sub>3</sub>-, 3H), 2.20-2.15 (m, 1H), 2.02-1.81 (m, 3H), 1.28 (t, 3H, J=7.2 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.7 (ester C=O), 138.1 (ipso C), 131.6 (arom. CH), 129.0 (arom. CH), 119.9 (ipso C), 85.4 (C≡C), 83.4 (C≡C), 62.9 (CH), 60.7 (CH<sub>2</sub>-O), 52.5 (CH<sub>2</sub>-N), 42.2 (N-CH<sub>2</sub>-C≡), 29.6 (CH<sub>2</sub>-), 23.3 (CH<sub>2</sub>-), 21.4 (CH<sub>3</sub>-), 14.2 (CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 272 (100, MH<sup>+</sup>), 246 (1); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 272.1660. C<sub>17</sub>H<sub>22</sub>NO<sub>2</sub> requires 272.1651.

**Isopropyl 1-(3-(4-methoxyphenyl)prop-2-yn-1-yl)pyrrolidine-2-carboxylate (96c):**



Following general procedure (**Step 2**), treating *N*-propargyl proline isopropylester **94c** (487mg, 2.5mmol), 4-iodoanisole **92b** (585mg, 2.5mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mmol%), CuI (5mmol%) in DIPA (5mL) at 50°C for 2 h afforded **96c** (450mg) as a brown oil, yield 60%. R<sub>f</sub>: 0.47 (33% ethyl acetate/hexane). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3039 (arom. C-H), 2978-2835 (alip. CH), 2225 (C≡C), 1735 (ester C=O), 1643 (C-N), 1604(arom C=C), 1508, 1462, 1176 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.37-7.34 (d, arom. 2H, J= 8.8), 6.84-6.80 (d, arom. 2H, J=8.8 Hz), 5.11-5.03 (sep, 1H, J= 6.0 Hz), 3.80-3.78 (d, CH<sub>3</sub>O, 3H, J= 5.6 Hz), 3.46-3.42 (dd, 1H, J = 8.8;6.0 Hz), 3.15-3.11 (m, 1H), 2.81-2.75 (q, 1H, J= 8.4 Hz), 2.20-2.10 (m, 1H), 1.99-1.79 (m, 3H), 1.26-1.24 (dd, 6H, J=10.0, 2.0 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.2 (ester C=O), 159.4 (ipso C), 133.1(arom. CH), 115.2 (ipso C), 113.8 (arom. CH), 84.9(C≡C), 82.7(C≡C), 67.9 (CH), 62.9(CH), 55.2(CH<sub>3</sub>-O), 52.4 (CH<sub>2</sub>-N), 42.0 (N-CH<sub>2</sub>-C≡), 29.5 (CH<sub>2</sub>-), 23.2 (CH<sub>3</sub>-), 21.8 (CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 302 (100, MH<sup>+</sup>), 300 (1), 295 (1); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 302.1767. C<sub>18</sub>H<sub>24</sub>NO<sub>3</sub> requires 302.1756.

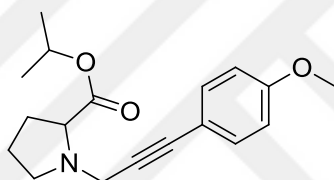
**Isopropyl 1-(3-(p-tolyl)prop-2-yn-1-yl)pyrrolidine-2-carboxylate (96d) :**



Following general procedure (**Step 2**), treating *N*-propargyl proline isopropylester **94c** (487mg, 2.5mmol), 4-iodotoluene **92a** (545mg, 2.5 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mmol%), CuI (5mmol%) in DIPA (5mL) at 50°C for 2 h affording **96d** (585 mg) as yellow oil, yield 82%. R<sub>f</sub>: 0.58 (33% ethyl acetate/hexane). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3051(arom. C-H), 2978-2820 (alip. CH), 2227 (C≡C), 1735 (ester C=O),

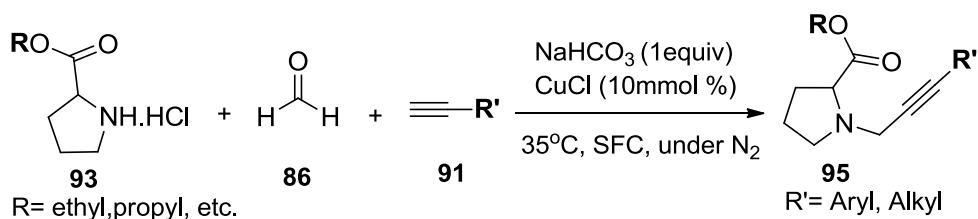
1643 (C-N), 1508, 1454, 1180 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-7.32 (d, arom. 2H,  $J$  = 8.0), 7.12-7.10 (d, arom. 2H,  $J$  = 8.0 Hz), 5.13-5.03 (quint, 1H,  $J$  = 6.4 Hz), 3.81 (s,  $\text{CH}_2$ , 2H), 3.48-3.44 (dd, 1H,  $J$  = 9.2;6.0 Hz), 3.16-3.12 (m, 1H), 2.83-2.77 (q, 1H,  $J$  = 8.8 Hz), 2.35 (s,  $\text{CH}_3$ -, 3H), 2.22-2.11 (m, 1H), 2.02-1.79 (m, 3H), 1.27-1.23 (dd, 6H,  $J$  = 6.4, 4.0 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.2 (ester C=O), 138.1 (ipso C), 131.6 (arom. CH), 129.0 (arom CH), 120.0 (ipso C), 85.3( $\text{C}\equiv\text{C}$ ), 83.5( $\text{C}\equiv\text{C}$ ), 67.9 ( $\text{CH-O}$ ), 62.9(CH), 52.5( $\text{CH}_2\text{-N}$ ), 42.1( $\text{N-CH}_2\text{-C}\equiv$ ), 29.6( $\text{CH}_2$ -), 23.2( $\text{CH}_3$ -), 21.4( $\text{CH}_3$ -).  $m/z$  (TOF-MS  $\text{ES}^+$ ) 286 (100,  $\text{MH}^+$ ), 284 (10), 279 (1); HRMS (TOF-MS  $\text{ES}^+$ ):  $\text{MH}^+$ , found 286.1812.  $\text{C}_{18}\text{H}_{24}\text{NO}_2$  requires 286.1807.

**Isopropyl 1-(3-(4-ethoxyphenyl)prop-2-yn-1-yl)pyrrolidine-2-carboxylate (96e):**



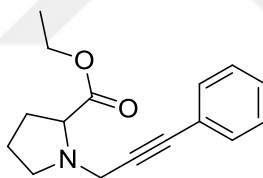
Following general procedure (**Step 2**), compound **96e** was prepared from the reaction of *N*-propargyl proline isopropylester **94c** (487 mg, 2.5mmol), 1-iodo-4-methoxybenzene **92c** (620 mg, 2.5 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (5 mmol %), and  $\text{CuI}$  (5 mmol %) at  $50^\circ\text{C}$  for 3 h. The product was isolated as dark red oil (578mg), yield: 73%.  $R_f$ : 0.53 (33% ethyl acetate/hexane). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3043 (arom.C-H), 2982-2820 (alip. CH), 2229 ( $\text{C}\equiv\text{C}$ ), 1735 (ester C=O), 1604 (arom.C=C), 1508, 1477, 1176 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33-7.31 (d, arom. 2H,  $J$  = 9.2), 6.80-6.77 (d, arom. 2H,  $J$  = 9.2 Hz), 5.09-4.99 (quint, 1H,  $J$  = 6.4 Hz), 4.01-3.96 (q, 2H,  $J$  = 7.2 Hz), 3.76 (s,  $\text{CH}_2\text{O}$ , 2H), 3.44-3.39 (dd, 1H,  $J$  = 9.2;6.4 Hz), 3.12-3.08 (m, 1H), 2.78-2.70 (q, 1H,  $J$  = 8.8. Hz), 2.18-2.08 (m, 1H), 1.95-1.74 (m, 3H), 1.38 (t, 3H,  $J$  = 7.6 Hz), 1.23-1.21 (dd, 6H,  $J$  = 6.4, 2.4 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.3 (ester C=O), 158.9 (ipso C), 133.2(arom. CH), 115.2 (ipso C), 114.5 (arom. CH), 85.3( $\text{C}\equiv\text{C}$ ), 82.7( $\text{C}\equiv\text{C}$ ), 68.1( $\text{CH}_2\text{-O}$ ), 63.6(CH), 63.0(CH), 52.6( $\text{CH}_2\text{-N}$ ), 42.2( $\text{N-CH}_2\text{-C}\equiv$ ), 29.7( $\text{CH}_2$ -), 23.4( $\text{CH}_3$ -), 21.9( $\text{CH}_3$ -), 14.8( $\text{CH}_3$ -).  $m/z$  (TOF-MS  $\text{ES}^+$ ) 316 (100,  $\text{MH}^+$ ), 309 (1), 298 (1); HRMS (TOF-MS  $\text{ES}^+$ ):  $\text{MH}^+$ , found 316.1913.  $\text{C}_{19}\text{H}_{26}\text{NO}_3$  requires 316.1915.

**General Procedure for the Synthesis of *N*-alkynyl substituted proline ester via A<sup>3</sup> coupling (Method B) (Shi et al., 2004; Uhlig and Li , 2012)**



Formaldehyde **86** (0.25 mmol, 1.25 equiv.), acetylene **91** (0.25 mmol, 1.25 equiv.), sodium bicarbonate (0.2 mmol, 1 equiv.), and CuCl (0.02 mmol) were stirred for 18h with proline ester hydrochloride (0.2 mmol) at 35°C under N<sub>2</sub>. Reaction mixture was diluted with ethyl acetate, eluted through a short plug of silica and Celite, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The compound was purified using silica gel column chromatography to afford the *N*-alkynyl substituted proline ester **95** in good to moderate yield.

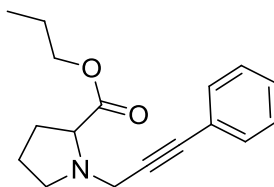
**Ethyl 1-(3-phenylprop-2-yn-1-yl)pyrrolidine-2-carboxylate (**95a**):**



Following the above synthetic route (**Method B**), formaldehyde **86** (3.75 mmol, 1.25 equiv.), phenyl acetylene **91a** (3.75 mmol, 1.25 equiv.), sodium bicarbonate (3 mmol, 1 equiv.), CuCl (0.3 mmol), and proline ethyl ester hydrochloride **93a** (3 mmol) were stirred at 35°C under N<sub>2</sub> for 18h to afford **95a** as a yellow oil (540 mg), yield: 70%. *R<sub>f</sub>*: 0.49 (33% ethyl acetate/hexane). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3055 (arom. C-H), 2978-2816 (alip. CH), 2229 (C≡C), 1739 (ester C=O), 1597 (arom C=C), 1489, 1442, 1180 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.42-7.38 (m, arom. 2H), 7.29-7.24 (m, arom. 3H), 4.25-4.12 (m, 2H), 3.79 (s, CH<sub>2</sub>O, 2H), 3.48-3.44 (dd, 1H, *J* = 9.2;6.4 Hz), 3.14-3.10 (m, 1H), 2.80-2.74 (q, 1H, *J* = 8.8. Hz), 2.21-2.10 (m, 1H), 2.02-1.76 (m, 3H), 1.25 (t, 3H, *J*=7.2 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.3 (ester C=O), 131.5 (arom. CH), 127.8 (arom CH), 122.7 (ipso C), 113.8 (arom. CH), 85.4 (C≡C), 84.3 (C≡C), 63.0 (CH),

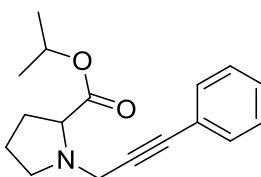
60.8(CH<sub>2</sub>-O), 52.6(CH<sub>2</sub>-N), 42.3(N-CH<sub>2</sub>-C≡), 29.7(CH<sub>2</sub>-), 23.4(CH<sub>2</sub>-), 14.5(CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 258 (100, MH<sup>+</sup>), 256 (1), 246 (1); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 258.1496. C<sub>16</sub>H<sub>20</sub>NO<sub>2</sub> requires 258.1494.

**Propyl 1-(3-phenylprop-2-yn-1-yl)pyrrolidine-2-carboxylate (95b):**



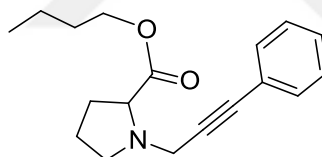
Following the general synthetic route (**Method B**), formaldehyde **86** (2.5 mmol, 1.25 equiv.), phenyl acetylene **91a** (2.5 mmol, 1.25 equiv.), sodium bicarbonate (2 mmol, 1 equiv.), CuCl (0.2 mmol), and proline propyl ester hydrochloride **93b** (2 mmol) were stirred at 35°C under N<sub>2</sub> for 20h to afford **95b** as pale yellow oil (461 mg), yield: 85%. R<sub>f</sub>: 0.64 (33% ethyl acetate/hexane). IR (neat): ν<sub>max</sub>/cm<sup>-1</sup> = 3055 (arom.C-H), 2966-2816 (alip. CH), 2229 (C≡C), 1743 (ester C=O), 1597 (C-N), 1489, 1180-1130 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.44 – 7.39 (m, arom. 2H), 7.30-7.25 (m, arom. 3H), 4.15 - 4.02 (m, 2H), 3.80 (s, 2H, *J* = 1.7 Hz), 3.49 (dd, 1H, *J* = 9.1;6.6 Hz), 3.12 (dd, 1H, *J* = 5.3, 3.3 Hz), 2.78 (dd, 1H, *J* = 16.5, 8.9 Hz), 2.23 – 2.10 (m, 1H), 2.06 – 1.88 (m, 2H), 1.86 – 1.78 (m, 1H), 1.72 – 1.61 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.77 (ester C=O), 131.70 (arom. CH), 128.21 (arom. CH), 128.05 (ipso C), 123.06 (arom. CH), 85.26 (C≡C), 84.23 (C≡C), 66.27 (CH), 62.88 (CH<sub>2</sub>-O), 52.46 (CH<sub>2</sub>-N), 42.11 (N-CH<sub>2</sub>-C≡), 29.64 (CH<sub>2</sub>-), 23.28 (CH<sub>2</sub>-), 21.98 (CH<sub>2</sub>-), 10.32 (CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 272 (100, MH<sup>+</sup>); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 272.1645. C<sub>17</sub>H<sub>21</sub>NO<sub>2</sub> requires 272.1651.

**Isopropyl 1-(3-phenylprop-2-yn-1-yl)pyrrolidine-2-carboxylate (95c):**



Following the general synthetic route (**Method B**), formaldehyde **86** (7.5 mmol, 1.25 equiv.), phenyl acetylene **91a** (7.5 mmol, 1.25 equiv.), sodium bicarbonate (6 mmol, 1 equiv.), CuCl (0.6 mmol), and proline isopropyl ester hydrochloride **93c** (6 mmol) were stirred at 35°C under N<sub>2</sub> for 20h to afford **95c** as pale yellow oil (1310 mg), yield: 81%. R<sub>f</sub>: 0.60 (33% ethyl acetate/hexane). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3055 (arom. C-H), 2978-2816 (alip. CH), 2229 (C≡C), 1739 (ester C=O), 1597 (C=C), 1489, 1442, 1180 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.42-7.39 (m, arom. 2H), 7.29-7.25 (m, arom. 3H), 5.10-5.00 (quint, 1H, J=6.0 Hz), 3.79 (s, CH<sub>2</sub>O-, 2H), 3.44-3.40 (dd, 1H, J = 8.8;6.4 Hz), 3.14-3.09 (m, 1H), 2.80-2.73 (q, 1H, J= 8.8. Hz), 2.19-2.09 (m, 1H), 2.02-1.75 (m, 3H), 1.24-1.22 (dd, 6H, J=6.4, 2.0 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.0 (ester C=O), 131.8(arom. CH), 128.3, 128.1(arom. CH), 123.2 (ipso C), 113.8 (arom. CH), 85.3(C≡C), 84.4(C≡C), 68.1(CH-O), 63.1(CH), 52.6(CH<sub>2</sub>-N), 42.2(N-CH<sub>2</sub>-C≡), 29.7(CH<sub>2</sub>-), 23.4(CH<sub>3</sub>-), 21.9(CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 272 (100, MH<sup>+</sup>), 246 (1); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 272.1649. C<sub>17</sub>H<sub>22</sub>NO<sub>2</sub> requires 272.1651.

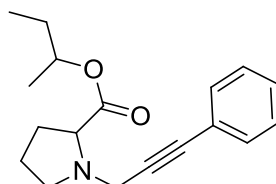
**Butyl 1-(3-phenylprop-2-yn-1-yl)pyrrolidine-2-carboxylate (95d):**



Following the general synthetic route (**Method B**), formaldehyde **86** (6.25 mmol, 1.25 equiv.), phenyl acetylene **91a** (6.25 mmol, 1.25 equiv.), sodium bicarbonate (5 mmol, 1 equiv.), CuCl (0.5 mmol), and proline isopropyl ester hydrochloride **93d** (5 mmol) were stirred at 35°C under N<sub>2</sub> for 30h to afford **95d** as pale yellow oil (1200 mg), yield: 84%. R<sub>f</sub>: 0.66 (33% ethyl acetate/hexane). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3055 (arom.C-H), 2958-2820 (alip. CH), 2229 (C≡C), 1739 (ester C=O), 1597 (C-N), 1489, 1180-1130 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.44 – 7.39 (m, arom. 2H), 7.31 – 7.26 (m, arom 3H), 4.19 – 4.07 (m, 2H), 3.80 (s, 2H J = 1.8 Hz), 3.48 (dd, 1H, J = 9.1, 6.6 Hz), 3.16 – 3.08 (m, 1H), 2.78 (dd, 1H, J = 16.5, 8.9 Hz), 2.16 (dd, 1H J = 7.0, 5.2 Hz), 2.05 – 1.88 (m, 2H), 1.87 – 1.79 (m, 1H), 1.66 – 1.57 (m, 2H), 1.42 – 1.31 (m, 2H), 0.91 (t, 3H, J = 7.4 Hz,) ; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.78 (ester C=O), 131.70 (arom. CH), 128.21 (arom. CH), 128.04

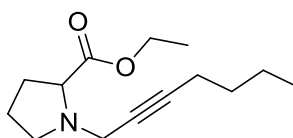
(ipso C), 123.07 (arom. CH), 85.26 (C≡C), 84.24 (C≡C), 64.60 (CH), 62.89 (CH<sub>2</sub>-O), 52.47 (CH<sub>2</sub>-N), 42.11 (N-CH<sub>2</sub>-C≡), 30.66 (CH<sub>2</sub>-), 29.63 (CH<sub>2</sub>-), 23.28 (CH<sub>2</sub>-), 19.09 (CH<sub>2</sub>-), 13.68 (CH<sub>3</sub>-). <sup>-</sup>. m/z (TOF-MS ES<sup>+</sup>) 286 (100, MH<sup>+</sup>); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 286.1797. C<sub>18</sub>H<sub>23</sub>NO<sub>2</sub> requires 286.1807.

#### Sec-butyl 1-(3-phenylprop-2-yn-1-yl)pyrrolidine-2-carboxylate (**95e**)



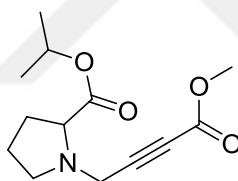
Following the general synthetic route (**Method B**), formaldehyde **86** (6.25 mmol, 1.25 equiv.), phenyl acetylene **91a** (6.25 mmol, 1.25 equiv.), sodium bicarbonate (5 mmol, 1 equiv.), CuCl (0.5 mmol), and proline isopropyl ester hydrochloride **93e** (5 mmol) were stirred at 35°C under N<sub>2</sub> for 30h to afford **95e** as pale yellow oil (1230 mg), yield: 86%. R<sub>f</sub>: 0.69 (33% EtOAc/ hexane). IR (neat): ν<sub>max</sub>/cm<sup>-1</sup> = 3055 (arom.C-H), 2970-2820 (alip. CH), 2229 (C≡C), 1735 (ester C=O), 1597 (C-N), 1489, 1180-1124 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.44 – 7.38 (m, arom. 2H), 7.30 – 7.25 (m, arom. 3H), 4.95 – 4.85 (m, 1H), 3.80 (s, 2H *J* = 3.8 Hz), 3.45 (dd, 1H *J* = 9.0, 6.6 Hz), 3.15 – 3.08 (m, 1H), 2.78 (dd, 1H *J* = 16.5, 8.7 Hz), 2.22 – 2.10 (m, 1H), 2.03 – 1.87 (m, 2H), 1.85 – 1.75 (m, 1H), 1.68 – 1.49 (m, 2H), 1.20 (dd, 3H *J* = 6.3, 2.7 Hz), 0.88 (t, *J* = 7.5 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.32 (ester C=O), 173.29 (ester C=O), 131.70 (arom. CH), 128.19 (arom. CH), 128.01 (ipso C), 123.11 (arom. CH), 85.19 (C≡C), 84.31 (C≡C), 84.27 (CH), 72.48 (CH-O), 72.44 (CH<sub>2</sub>-N), 62.97 (N-CH<sub>2</sub>-C≡), 52.40 (CH<sub>2</sub>-), 42.01 (CH<sub>2</sub>-), 41.95 (CH<sub>2</sub>-), 29.65 (CH<sub>2</sub>-), 29.58 (CH<sub>2</sub>-), 28.76 (CH<sub>2</sub>-), 23.15 (CH<sub>2</sub>-), 23.14 (CH<sub>2</sub>-), 19.51 (CH<sub>3</sub>-), 19.43 (CH<sub>3</sub>-), 9.69 (CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 286 (100, MH<sup>+</sup>); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 286.1800. C<sub>18</sub>H<sub>23</sub>NO<sub>2</sub> requires 286.1807.

#### Ethyl 1-(hept-2-yn-1-yl)pyrrolidine-2-carboxylate (**95f**)



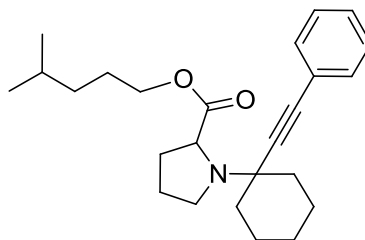
Following the general synthetic route (**Method B**), formaldehyde **86** (3.75 mmol, 1.25 equiv.), 1-hexyne **91b** (3.75 mmol, 1.25 equiv.), sodium bicarbonate (3 mmol, 1 equiv.), CuCl (0.3 mmol), and proline ethyl ester hydrochloride **93a** (3 mmol) were stirred at 35°C under N<sub>2</sub> for 17h to afford **95f** as colorless oil (619 mg), yield: 87%. R<sub>f</sub>: 0.49 (33% EtOAc/hexane). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 2958-2820 (alip. CH), 2256 (C≡C), 1743 (ester C=O), 1458, 1442, 1180 (C-O)  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.20-4.13 (m, 2H), 3.52-3.51 (m, 2H), 3.38-3.34 (dd, 1H, J = 9.2;6.8 Hz), 3.04-3.00 (m, 1H), 2.69-2.62 (q, 1H, J = 9.2 Hz), 2.18-2.05 (m, 3H), 1.98-1.71 (m, 3H), 1.48-1.33 (m, 4H), 1.25 (t, 3H, J = 7.6 Hz), 0.87 (t, 3H, J = 7.6 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.9 (ester C=O), 85.6 (C≡C), 74.3 (C≡C), 62.8 (CH), 60.7 (CH<sub>2</sub>-O), 52.4 (CH<sub>2</sub>-N), 41.7 (N-CH<sub>2</sub>-C≡), 31.1 (CH<sub>2</sub>-), 29.7 (CH<sub>2</sub>-), 23.3 (CH<sub>2</sub>-), 22.0, 18.4, 14.2 (CH<sub>3</sub>-), 13.7 (CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 238 (100, MH<sup>+</sup>), 224 (1); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 288.1811. C<sub>14</sub>H<sub>24</sub>NO<sub>2</sub> requires 238.1807.

**Isopropyl-1-(4-methoxy-4-oxobut-2-yn-1-yl)pyrrolidine-2-carboxylate (95g):**



Following the general synthetic route (**Method B**), formaldehyde **86** (2.5 mmol, 1.25 equiv.), methyl propiolate **91c** (2.5 mmol, 1.25 equiv.), sodium bicarbonate (2 mmol, 1 equiv.), CuCl (0.2 mmol), and proline isopropyl ester hydrochloride **93b** (2 mmol) were stirred at 35°C under N<sub>2</sub> for 20h to afford **95g** as yellow oil (280 mg), yield: 55%. R<sub>f</sub>: 0.42 (33% EtOAc/hexane). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 2982-2820 (alip. CH), 2229 (C≡C), 1739 (ester C=O), 1720 (ester C=O), 1639 (C-N), 1253 (C-O)  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.07-5.00 (m, 1H), 3.77-3.74 (m, MeO-, 3H), 3.36-3.32 (m, 1H), 3.07-3.03 (m, 1H), 2.74-2.67 (q, 1H, J = 8.0 Hz), 2.19-2.08 (m, 1H), 1.98-1.77 (m, 3H), 1.27 (td, 6H, J = 6.4, 2.8 Hz).

**4-methylpentyl-1-(1-(phenylethynyl)cyclohexyl)pyrrolidine-2-carboxylate (95h):**



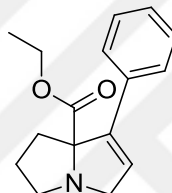
Following the general synthetic route (**Method B**), cyclohexanone (2.5 mmol, 1.25 equiv.), phenyl acetylene **91a** (2.5 mmol, 1.25 equiv.), sodium bicarbonate (2 mmol, 1 equiv.), CuCl (0.2 mmol), and proline isoamyl ester hydrochloride **93b** (2 mmol) were stirred at 35°C under N<sub>2</sub> for 20h to afford **95h** as colorless oil (200 mg), yield: 27%. R<sub>f</sub>: 0.88 (33% EtOAc/hexane). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3055 (arom.CH), 2931-2820 (alip. CH), 2214 (C≡C), 1743 (ester C=O), 1597 (C-N), 1489, 1446, 1176-1118 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.43-7.41 (dd, 2H, J=7.0, 2.8 Hz), 7.29-7.25 (dd, 3H, J=5.1, 2.1 Hz), 4.97-4.88 (m, 1H), 3.79-3.75 (ddd, CH-O-, 1H, J= 9.9, 6.0, 2.8 Hz), 3.25-3.17 (m, 1H), 3.07-3.03 (m, 1H), 2.88-2.78 (m, 1H), 2.10-1.74 (m, 6H), 1.72-1.27 (m, 12H), 1.19-1.17 (d, 4H, J=6.3 Hz), 0.91-0.87 (td, 3H, J=7.2, 1.7 Hz).

### 3.1.2 SYNTHESIS OF TARGET COMPOUNDS

#### General Procedure for the Preparation of products (97a-k)

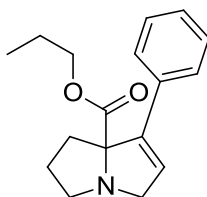
A solution of LiHMDS (1.5 eq) in hexane was added in a dropwise manner to a solution of *N*-propargyl proline ester (1.0 eq) in dry THF (5 mL) at 0°C under inert atmosphere. The resulting solution was stirred vigorously for 30min at the same temperature, then at room temperature until the starting material was completely consumed. The solvent was rotaevaporated under reduced pressure and the residue was purified through silica column using EtOAc/hexane mixture as an eluent.

#### Ethyl 7-phenyl-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-7a-carboxylate (**97a**):



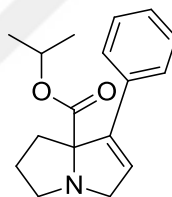
Following the general synthetic route as indicated above, target product was synthesized by treating **95a** (0.5 mmol) with LiHMDS (0.75 mmol) solution in hexane at 0°C – rt for 2h to afford compound **97a** as yellow-green oil (151mg), yield: 69%.  $R_f$ : 0.39 (15 % hexane/ethyl acetate). IR (neat):  $\nu_{\max}/\text{cm}^{-1}$  = 3055 (arom. CH), 2974-2816 (alip. CH), 1724 (ester C=O), 1600 (arom. C=C), 1496 (olefinic C=C), 1446, 1269-1234 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43-7.24 (m, arom H, 5H), 6.25 (t, -C=CH, 1H,  $J=2.0$  Hz), 4.24-4.06 (m, 3H), 3.57-3.52 (dd, 1H,  $J = 16.6, 2.4$  Hz), 3.56-3.11 (m, 1H), 2.94-2.88 (ddd, 1H,  $J=16.6, 6.9, 2.6$  Hz), 2.56-2.50 (ddd, 1H,  $J=10.2, 9.1, 5.4$  Hz), 2.02-1.91 (m, 1H), 1.87-1.80 (m, 2H), 1.75-1.68 (m, 1H), 1.47 (t, 3H,  $J=7.2$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.0 (ester C=O), 142.1 (olef. C=C), 132.9 (ipso C, arom), 128.1, 127.2, 125.9, 123.8 (C=CH, olefinic), 121.2, 82.7 (ipso C), 60.9 ( $\text{CH}_2\text{-O}$ ), 57.1 ( $\text{CH}_2\text{-N}$ ), 32.7 ( $\text{N-CH}_2\text{-C=}$ ), 26.0 ( $\text{CH}_2\text{-}$ ), 13.6 ( $\text{CH}_3\text{-}$ ).  $m/z$  (TOF-MS  $\text{ES}^+$ ) 258 (100,  $\text{MH}^+$ ), 256 (1), 246 (1); HRMS (TOF-MS  $\text{ES}^+$ ):  $\text{MH}^+$ , found 258.1483.  $\text{C}_{16}\text{H}_{20}\text{NO}_2$  requires 258.1494.

**Propyl 7-phenyl-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate**  
**(97b):**



Following the general synthetic route as indicated above, target product was synthesized by treating **95b** (1.70 mmol) with LiHMDS (2.56 mmol) solution in hexane at 0°C – rt for 2h to afford compound **97b** as pale yellow oil (320 mg), yield: 69%.  $R_f$ : 0.43 (15% hexane/ethyl acetate). IR (neat):  $\nu_{\max}/\text{cm}^{-1}$  = 3059 (arom. CH), 2966-2850 (alip. CH), 1728 (ester C=O), 1600 (arom. C=C), 1496 (olefinic C=C), 1446, 1269-1230 (C-O)  $\text{cm}^{-1}$ ;

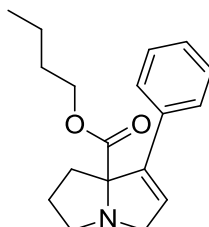
**Isopropyl 7-phenyl-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate**  
**(97c):**



Following the general synthetic route as indicated above, target product was synthesized by treating **95c** (0.50mmol) with LiHMDS (0.75 mmol) solution in hexane at 0°C – rt for 2h to afford compound **97c** as yellow-green oil (141 mg), yield: quantitative.  $R_f$ : 0.41 (15% hexane/ethyl acetate). IR (neat):  $\nu_{\max}/\text{cm}^{-1}$  = 3059 (arom. CH), 2978-2820 (alip. CH), 1724 (ester C=O), 1600 (arom. C=C), 1496 (olefinic C=C), 1450, 1273-1238 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37-7.21 (m, arom H, 5H), 6.21 (t, -C=CH, 1H,  $J=2.0$  Hz), 5.01-4.90 (quint, 1H,  $J=6.4$  Hz), 4.13-4.08 (dd, 1H,  $J=12.8, 2.4$  Hz), 3.53-3.49 (dd, 1H,  $J=12.4, 6.0$  Hz), 3.32-3.28 (m, 3H), 2.89-2.83 (ddd, 1H,  $J=9.2, 7.2, 2.4$  Hz), 2.54-2.48 (m, 1H), 2.02-1.90 (m, 1H), 1.83-1.81 (m, 1H), 1.73-1.66 (m, 1H), 1.19-1.18 (d, 3H,  $J=6.4$  Hz), 1.08-1.06 (d, 3H,  $J=6.4$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.7 (ester C=O), 142.6 (olef. C=C), 133.4 (ipso C, arom), 128.4, 127.4, 126.3, 124.1 (C=CH, olefinic),

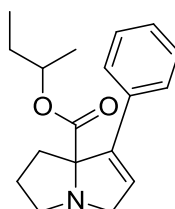
121.1, 83.1 (ipso C), 68.5 (CH-O), 61.2 (CH<sub>2</sub>-), 57.5 (CH<sub>2</sub>-N), 33.0(N-CH<sub>2</sub>-C=), 21.6(CH<sub>3</sub>-), 21.4(CH<sub>3</sub>). m/z (TOF-MS ES<sup>+</sup>) 272 (100, MH<sup>+</sup>), 270 (5), 254 (1) ; HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 272.1658. C<sub>17</sub>H<sub>22</sub>NO<sub>2</sub> requires 272.1651.

**Butyl 7-phenyl-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate (97d):**



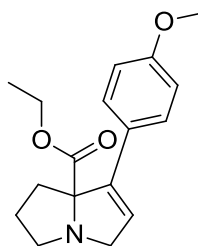
Following the general synthetic route as indicated above, target product was synthesized by treating **95d** (0.50mmol) with LiHMDS (0.75 mmol) solution in hexane at 0°C – rt for 2h to afford compound **97d** as yellow-green oil (798 mg), yield: 74%. R<sub>f</sub>: 0.51 (15% hexane/ethyl acetate). IR (neat): ν<sub>max</sub>/cm<sup>-1</sup> = 3059 (arom. CH), 2958-2850 (alip. CH), 1724 (ester C=O), 1600 (arom. C=C), 1496 (olefinic C=C), 1450, 1269-1234 (C-O) cm<sup>-1</sup>;

**Sec-butyl 7-phenyl-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate (97e):**



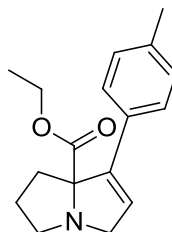
Following the general synthetic route as indicated above, target product was synthesized by treating **95e** (1.0mmol) with LiHMDS (1.5 mmol) solution in hexane at 0°C – rt for 2h to afford compound **97e** as yellow oil (272 mg), yield: 95%.R<sub>f</sub>: 0.50 (15% hexane/ethyl acetate). IR (neat): ν<sub>max</sub>/cm<sup>-1</sup> = 3059 (arom. CH), 2970-2847 (alip. CH), 1724 (ester C=O), 1600 (arom. C=C), 1496 (olefinic C=C), 1450, 1269-1234 (C-O) cm<sup>-1</sup>.

**Ethyl 7-(4-methoxyphenyl)-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate (97f):**



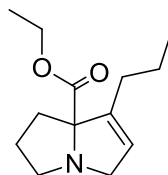
Following the general synthetic route as indicated above, target product was synthesized by treating **96a** (0.5 mmol) with LiHMDS (0.75 mmol) solution in hexane at 0°C – rt for 2h to afford compound **97f** as yellow oil (110 mg), yield: 76%.  $R_f$ : 0.32 (15% hexane/ethyl acetate). IR (neat):  $\nu_{\max}/\text{cm}^{-1}$  = 3059 (arom. CH), 2966-2839 (alip. CH), 1724 (ester C=O), 1608 (arom. C=C), 1512, 1462 (olefinic C=C), 1446, 1261-1238 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32-7.30 (d, arom H, 2H,  $J=8.9$  Hz), 6.85-6.82 (d, arom H, 2H,  $J=8.9$  Hz), 6.08 (t, -C=CH, 1H,  $J=2.0$  Hz), 4.22-4.05 (m, 3H), 3.79 (s,  $\text{OCH}_3$ , 3H), 3.52-3.48 (dd, 1H,  $J = 16.3, 2.4$  Hz), 3.32-3.27 (ddd, 1H,  $J=8.7, 6.0, 2.6$  Hz), 2.90-2.85 (ddd, 1H,  $J=12.3, 6.9, 2.6$  Hz), 2.55-2.48 (ddd, 1H,  $J=10.3, 9.0, 5.4$  Hz), 2.01-1.89 (dddd, 2H,  $J= 12.9, 10.5, 6.9, 5.1$  Hz), 1.86-1.81 (m, 2H), 1.74-1.66 (ddd, 1H,  $J= 12.4, 10.8, 7.1$  Hz), 1.14 (t, 3H,  $J=7.1$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.4 (ester C=O), 159.0 (ipso C), 141.8 (olef. C=C), 128.6 (ipso C, arom), 127.5, 125.9, 121.8 (C=CH, olefinic), 114.3, 113.8, 83.1 (ipso C), 61.2 ( $\text{CH}_2\text{-O}$ ), 57.4( $\text{CH}_2\text{-N}$ ), 55.2 ( $\text{CH}_2\text{-O}$ ), 33.1( $\text{N-CH}_2\text{-C=}$ ), 26.5( $\text{CH}_2\text{-}$ ), 13.9( $\text{CH}_3\text{-}$ ).  $m/z$  (TOF-MS  $\text{ES}^+$ ) 288 (100,  $\text{MH}^+$ ), 286 (5), 275 (1); HRMS (TOF-MS  $\text{ES}^+$ ):  $\text{MH}^+$ , found 288.1596.  $\text{C}_{17}\text{H}_{22}\text{NO}_3$  requires 288.1600.

**Ethyl 7-(p-tolyl)-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate (97g):**



Following the general synthetic route as indicated above, target product was synthesized by treating **96b** (1 mmol) with LiHMDS (1.5 mmol) solution in hexane at 0°C – rt for 2h to afford compound **97g** as red oil (110 mg), yield: 81%. R<sub>f</sub>: 0.35 (15% hexane/ethyl acetate). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3059 (arom. CH), 2974-2847(alip. CH), 1728 (ester C=O), 1600 (arom. C=C), 1512, 1450 (olefinic C=C), 1446, 1269-1234(C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27-7.25(d, 2H,  $J$  = 8.2 Hz), 7.12-7.10 (d, 2H,  $J$  = 8.0 Hz), 6.17-6.16 (t, 1H,  $J$  = 2.1 Hz), 4.22 – 4.04 (m, 3H), 3.53-3.49 (dd, 1H,  $J$  = 16.4, 2.4 Hz), 3.32-3.28 (ddd, 1H,  $J$  = 8.8, 6.1, 2.5 Hz), 2.91-2.85 (ddd, 1H,  $J$  = 12.3, 6.9, 2.6 Hz), 2.55-2.49 (ddd, 1H,  $J$  = 10.1, 9.1, 5.4 Hz), 2.32 (s, 3H), 2.02 – 1.89 (m, 1H), 1.87 – 1.78 (m, 1H), 1.73-1.66 (ddd, 1H,  $J$  = 12.4, 10.8, 7.1 Hz), 1.14 (t, 3H,  $J$  = 7.1 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.4 (ester C=O), 142.7 (olef. C=C), 137.3 (ipso C, arom), 130.3, 129.6, 129.1(arom.CH), 126.9, 126.1 (arom CH), 123.0 (C=CH, olefinic), 120.2, 83.0 (ipso C), 61.2 ( $\text{CH}_2\text{-O}$ ), 57.4( $\text{CH}_2\text{-N}$ ), 33.0( $\text{N-CH}_2\text{-C=}$ ), 26.3( $\text{CH}_2\text{-}$ ), 21.2 ( $\text{CH}_3\text{-}$ ), 13.9( $\text{CH}_3\text{-}$ ).m/z (TOF-MS  $\text{ES}^+$ ) 272 (100,  $\text{MH}^+$ ), 270 (1), 258 (1); HRMS (TOF-MS  $\text{ES}^+$ ):  $\text{MH}^+$ , found 272.1657.  $\text{C}_{17}\text{H}_{22}\text{NO}_2$  requires 272.1651.

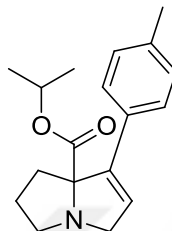
**Ethyl 7-propyl-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate (97h):**



Following the general synthetic route as indicated above, target product was synthesized by treating **95f** (1.0 mmol) with LiHMDS (1.5 mmol) solution in hexane at 0°C – rt for 2h to afford compound **97h** as pale yellow oil (170 mg), yield: 72%. R<sub>f</sub>: 0.41 (15% hexane/ethyl acetate). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3059 (olef. CH), 2958-2870 (alip. CH), 1728 (ester C=O), 1458 (olefinic C=C), 1265-1230 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.40-5.38 (m,  $\text{-C=CH}$ , 1H), 4.24-4.15 (m, 1H), 4.13-4.05 (dq, 1H,  $J$ =10.8, 7.1 Hz), 3.96-3.91 (ddd, 1H,  $J$  = 15.3, 4.3, 2.5 Hz), 3.33-3.28 (dq, 1H,  $J$ =15.3, 2.2 Hz), 3.26-3.22 (ddd, 1H,  $J$ =9.4, 5.9, 3.7 Hz), 2.50-2.42 (m, 2H), 2.01-1.95 (dtd, 1H,  $J$ =12.9, 4.4, 1.9 Hz), 1.86-1.68 (m, 2H), 1.66-1.58 (ddd, 1H,  $J$ =12.3, 9.9, 6.9 Hz), 1.52-1.42 (m, 2H), 1.38-1.28 (m, 2H), 1.23 (t, 3H,  $J$ =7.1 Hz), 0.89 (t, 3H,  $J$ =7.3 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.6 (ester C=O), 143.3

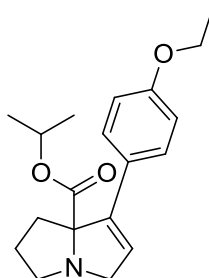
(olef. C=C), 128.4, 126.5, 121.0 (C=CH, olefinic), 84.9 (ipso C), 60.9 (CH<sub>2</sub>-O), 57.4 (CH<sub>2</sub>-N), 32.8 (N-CH<sub>2</sub>-C=), 29.8 (CH<sub>2</sub>-), 26.7 (CH<sub>2</sub>-), 25.6(CH<sub>3</sub>-), 13.9 (CH<sub>3</sub>-).m/z (TOF-MS ES<sup>+</sup>) 238 (100, MH<sup>+</sup>), 236 (1), 224 (1) ; HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 238.1810 C<sub>14</sub>H<sub>24</sub>NO<sub>2</sub> requires 238.1807.

**Isopropyl 7-(p-tolyl)-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate (97i):**



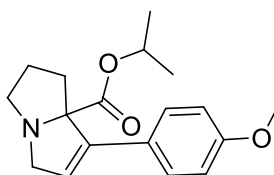
Following the general synthetic route as indicated above, target product was synthesized by treating **96c** (0.5 mmol) with LiHMDS (0.75 mmol) solution in hexane at 0°C – rt for 2h to afford compound **97i** as pale yellow oil (129 mg), yield: 90%. R<sub>f</sub>: 0.45 (15% hexane/ethyl acetate). IR (neat): ν<sub>max</sub>/cm<sup>-1</sup> = 3059 (arom. CH), 2978-2847 (alip. CH), 1724 (ester C=O), 1516 (arom C=C), 1454 (olefinic CH), 1273-1234 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.24-7.26 (d, arom H, 2H, J=8.0 Hz), 7.10(d, 2H, J=8.0 Hz), 6.15 (t, -C=CH, 1H, J=2.1 Hz), 5.01-4.91 (m, 1H), 4.11-4.07 (dd, 3H, J=16.4, 1.7 Hz), 3.51-3.47 (dd, 1H, J = 16.4, 2.4 Hz), 3.31-3.27 (ddd, 1H, J=8.6,6.1,2.5 Hz), 2.88-2.82 (ddd, 1H, J=12.4, 6.9, 2.5 Hz), 2.53-2.47 (ddd, 1H, J=10.3, 9.0, 5.3 Hz), 2.32 (s, 3H), 2.02-1.85 (m, 1H), 1.85-1.76 (m, 1H), 1.72-1.64 (ddd,1H, J=12.4, 10.8, 7.1 Hz), 1.20-1.19 (d, 3H, J=6.3 Hz), 1.09-1.07 (d,3H, J=6.2 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ173.8 (ester C=O), 142.4 (olef. C=C), 137.1 (ipso C, arom), 130.5, 129.0, 126.1, 123.0 (C=CH, olefinic), 121.2, 83.1 (ipso C), 68.4 (CH-O), 61.2, 57.4(CH<sub>2</sub>-N), 32.9(N-CH<sub>2</sub>-C=), 26.3(CH<sub>2</sub>-), 21.6(CH<sub>3</sub>-), 21.4, 21.1(CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 286 (100, MH<sup>+</sup>), 284 (20), 276 (1) ; HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 286.1810. C<sub>18</sub>H<sub>24</sub>NO<sub>2</sub> requires 286.1807.

**Isopropyl 7-(4-ethoxyphenyl)-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate (97j):**



Following the general synthetic route as indicated above, target product was synthesized by treating **96d** (0.5 mmol) with LiHMDS (0.75 mmol) solution in hexane at 0°C – rt for 1.5h to afford compound **97j** as pale yellow oil (170 mg), yield: quantitative.  $R_f$ : 0.43 (15% hexane/ethyl acetate). IR (neat):  $\nu_{\max}/\text{cm}^{-1}$  = 3059(arom. CH), 2978-2847(alip. CH), 1724(ester C=O), 1608(arom. C=C), 1512(olefinic C=C), 1477, 1257(C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.27 (d, arom H, 2H,  $J=9.9$  Hz), 6.82-6.80 (d, 2H,  $J=8.9$  Hz), 6.05 (t, -C=CH, 1H,  $J=2.1$  Hz), 5.00-4.89 (m, 1H), 4.10-4.05 (dd, 1H,  $J = 16.1, 2.0$  Hz), 4.04-3.98 (q, 1H,  $J=7.0$  Hz), 3.50-3.45 (dd, 1H,  $J=16.3, 2.4$  Hz), 3.31-3.26 (ddd, 1H,  $J=8.5, 5.9, 2.4$  Hz), 2.87-2.82 (ddd, 1H,  $J=12.3, 6.9, 2.5$  Hz), 2.52-2.46 (ddd, 1H,  $J= 10.4, 9.0, 5.3$  Hz), 2.00-1.87 (m, 1H), 1.85-1.76 (m, 1H), 1.72-1.65 (ddd, 1H,  $J=12.3, 10.8, 7.1$  Hz), 1.39 (t, 3H,  $J=7.0$  Hz), 1.20-1.18 (d, 3H,  $J=6.3$  Hz), 1.08-1.06 (d, 3H,  $J=6.2$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.9 (ester C=O), 158.3 (ipso C), 142.0 (olef. C=C), 127.5, 125.9(ipso C, arom), 121.7, 114.6 (C=CH, olefinic), 83.6 (ipso C), 68.4 ( $\text{CH}_2\text{-O}$ ), 63.3, 61.2, 57.4 ( $\text{CH}_2\text{-N}$ ), 33.0 (N- $\text{CH}_2\text{-C=}$ ), 26.3( $\text{CH}_2\text{-}$ ), 21.6( $\text{CH}_3\text{-}$ ), 21.4( $\text{CH}_3\text{-}$ ), 14.8 ( $\text{CH}_3\text{-}$ ).  $m/z$  (TOF-MS  $\text{ES}^+$ ) 316 (100,  $\text{MH}^+$ ), 314 (5), 307 (1) ; HRMS (TOF-MS  $\text{ES}^+$ ):  $\text{MH}^+$ , found 316.1910.  $\text{C}_{19}\text{H}_{26}\text{NO}_3$  requires 316.1913.

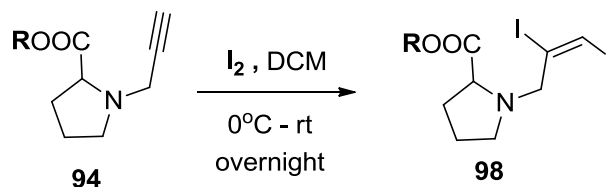
**Isopropyl 7-(4-methoxyphenyl)-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate (97k):**



Following the general synthetic route as indicated above, target product was synthesized by treating **96e** (0.5 mmol) with LiHMDS (0.75 mmol) solution in hexane at 0°C – rt for 2h to afford compound **97k** as yellow oil (160 mg), yield: quantitative. R<sub>f</sub>: 0.43 (15% hexane/ethyl acetate). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3059 (arom. CH), 2978-2839 (alip. CH), 1720 (ester C=O), 1608 (arom C=C), 1512, 1462 (olefinic CH), 1257 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31-7.29 (d, arom H, 2H, J=8.8 Hz), 6.84-6.82 (d, arom.H,2H, J=8.8 Hz), 6.06 (t, -C=CH, 1H, J=2.1Hz), 5.00-4.91 (hept, 1H, J=6.3 Hz), 4.11-4.06 (dd, 1H, J=16.3, 1.7 Hz), 3.79 (s, 3H), 3.51-3.46 (dd, 1H, J = 16.3, 2.4 Hz), 3.32-3.27 (ddd, 1H, J=8.7, 6.1, 2.5 Hz), 2.88-2.82 (ddd, 1H, J=12.3, 6.9, 2.4 Hz), 2.54-2.46 (m, 1H), 2.03-1.88 (m, 2H), 1.84-1.80 (tdt, 1H, J=9.9, 5.2, 2.5 Hz), 1.74-1.64 (m,1H), 1.21-1.19 (d, 3H, J=6.3 Hz),1.09-1.07 (d, 3H, J=6.3 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 173.9 (ester C=O), 158.9 (ipso C), 142.0 (olef. C=C), 127.5 (ipso C, arom), 126.1, 121.8 (C=CH, olefinic), 113.7, 83.2 (ipso C), 68.4 (CH-O), 61.2, 57.4(CH<sub>2</sub>-N), 55.2 (CH<sub>3</sub>O), 32.9(N-CH<sub>2</sub>-C=), 26.0(CH<sub>2</sub>-), 21.6(CH<sub>3</sub>-), 21.4(CH<sub>3</sub>-). m/z (TOF-MS ES<sup>+</sup>) 302 (100, MH<sup>+</sup>), 300 (5); HRMS (TOF-MS ES<sup>+</sup>): MH<sup>+</sup>, found 302.1757. C<sub>18</sub>H<sub>23</sub>NO<sub>3</sub> requires 302.1756.

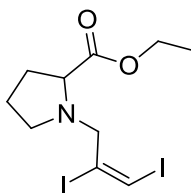
#### General method for the preparation of diiodo addition products (98a-f)

A solution of compound **94** (1.0 mmol) in DCM (10 mL) at 0°C was stirred for 15 min and iodine (3.0 equiv.) was added into the solution under inert atmosphere. The resulting solution was left to warm up to room temperature for 2 hours and reaction progress was controlled by TLC until the starting material was completely consumed. The reaction mixture was treated with a saturated solution Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with DCM (3x15 mL). Combined organic phases were washed with brine (15 mL). After drying over Na<sub>2</sub>SO<sub>4</sub>, the solvent was rotaevaporated and the residue was purified through a silica column using EtOAc/hexane (1:7) as an eluent to afford compound **98**.



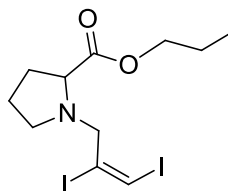
R= Me, Et, Pr, *i*-Pr, n-Bu, *i*-Bu

**(E)-ethyl 1-(2,3-diiodoallyl)pyrrolidine-2-carboxylate (98a):**



Following the general procedure as indicated above, addition product was obtained by treating **94a**, ethyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (181 mg, 1.0 mmol) with iodine (761mg, 3.0mmol) in DCM at 0°C – rt for 22h to afford compound **98a** as viscous dark green oil (148 mg), yield: 34%.  $R_f$ : 0.67 (15% hexane/ethyl acetate). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 3066 (olef. CH), 2974-2804 (alip. CH), 1728 (ester C=O), 1589, 1442 (olefinic C=C), 1180-1145 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.00 (s, olefinic CH, 1H), 4.20-4.14 (qd, 2H,  $J=7.1, 2.0$  Hz), 3.65-3.49 (d, 1H,  $J = 14.0$  Hz), 3.54-3.46 (m, 2H), 3.12-3.10 (td, 1H,  $J=8.1, 3.9$  Hz), 2.67-2.63 (dd, 1H,  $J=16.3, 7.7$  Hz), 2.16-2.13 (ddd, 1H,  $J=16.0, 12.4, 8.9$  Hz), 2.09-1.79 (m, 3H), 1.27 (t, 3H,  $J=7.1$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.5 (ester C=O), 101.9 (I-C=, olefinic), 81.2 (=CHI), 80.5 (CH), 64.5 ( $\text{CH}_2\text{-O}$ ), 60.8 ( $\text{CH}_2\text{-}$ ), 52.1( $\text{CH}_2\text{-N}$ ), 29.3( $\text{CH}_2\text{-}$ ), 23.4( $\text{CH}_2\text{-}$ ), 14.5( $\text{CH}_3\text{-}$ ).

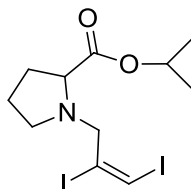
**(E)-propyl 1-(2,3-diiodoallyl)pyrrolidine-2-carboxylate (98b):**



Following the general procedure as indicated above, addition product was obtained by treating **94b**, propyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (193mg, 1mmol) with iodine (761mg, 3.0mmol) in DCM at 0°C – rt for 20 h to

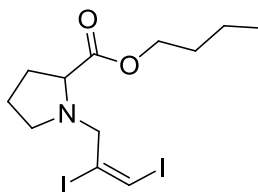
afford compound **98b** as viscous dark green oil (115 mg), yield: 26%.  $R_f$ : 0.68 (15% hexane/ethyl acetate).  $m/z$  (TOF-MS  $ES^+$ ) 449 (100,  $MH^+$ ); HRMS (TOF-MS  $ES^+$ ):  $MH^+$ , found 449.9429.  $C_{11}H_{17}I_2NO_2$  requires 449.9427-449.9416.

**(E)-isopropyl 1-(2,3-diiodoallyl)pyrrolidine-2-carboxylate (98c):**



Following the general procedure as indicated above, addition product was obtained by treating **94c**, isopropyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (390mg, 1mmol) with iodine (1522mg, 6.0mmol) in DCM at 0°C – rt for 21 h to afford compound **98c** as dark brown oil (279 mg), yield: 31%.  $R_f$ : 0.66 (15% hexane/ethyl acetate). IR (neat):  $\nu_{max}/cm^{-1}$  = 3066 (olef. CH), 2978-2804 (alip. CH), 1724 (ester C=O), 1612, 1462 (olefinic C=C), 1196-1139 (C-O)  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  6.97 (s, olefinic CH, 1H), 5.07-4.97 (hept, 1H,  $J=6.3$  Hz), 3.61-3.58 (dd, 1H,  $J = 13.9, 1.1$  Hz), 3.51-3.40 (m, 2H), 3.12-3.01 (m, 1H), 2.66-2.55 (m, 1H), 2.17-2.03 (m, 1H), 2.00-1.73 (m, 3H), 1.24 (dd, 6H,  $J=6.3, 4.0$  Hz);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  173.2 (ester C=O), 102.6 (I-C=, olefinic), 80.8 (=CHI), 79.9 (CH), 67.7 ( $CH_2-O$ ), 64.6 ( $CH_2-$ ), 52.4( $CH_2-N$ ), 29.3( $CH_2-$ ), 23.4( $CH_2-$ ), 22.1( $CH_3-$ ), 22.0( $CH_3-$ ).  $m/z$  (TOF-MS  $ES^+$ ) 449 (100,  $MH^+$ ); HRMS (TOF-MS  $ES^+$ ):  $MH^+$ , found 449.9405.  $C_{11}H_{17}I_2NO_2$  requires 449.9416-449.9427.

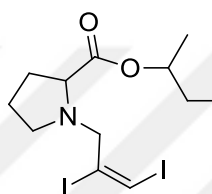
**(E)-butyl 1-(2,3-diiodoallyl)pyrrolidine-2-carboxylate (98d):**



Following the general procedure as indicated above, addition product was obtained by treating **94d**, butyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (209mg, 1mmol) with iodine (761mg, 3.0mmol) in DCM at 0°C – rt for 21 h to afford compound **98d** as viscous dark green oil (108 mg), yield: 23%.  $R_f$ : 0.72 (15%

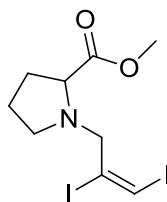
hexane/ethyl acetate). IR (neat):  $\nu_{\max}/\text{cm}^{-1} = 3066$  (olef. CH), 2958-2804 (alip. CH), 1728 (ester C=O), 1608, 1462 (olefinic C=C), 1176-1145 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.04 (s, olefinic CH, 1H), 4.19-4.08 (m, 2H), 3.70-3.67 (d, 1H,  $J = 14.0$  Hz), 3.62-3.52 (m, 2H), 3.17-3.15 (td, 1H,  $J=8.1, 4.1\text{Hz}$ ), 2.73-2.69 (dd, 1H,  $J=15.8, 7.6$  Hz), 2.26-2.13 (m, 1H), 2.08-1.83 (m, 3H), 1.70-1.57 (m, 2H), 1.46-1.33 (m, 2H), 0.92 (t, 3H,  $J=7.4$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.4 (ester C=O), 101.2 (I-C=, olefinic), 81.8 (=CHI), 81.2 (CH), 64.8( $\text{CH}_2\text{-O}$ ), 63.7 ( $\text{CH}_2\text{-}$ ), 52.5( $\text{CH}_2\text{-N}$ ), 30.7( $\text{CH}_2\text{-}$ ), 29.3( $\text{CH}_2\text{-}$ ), 23.3( $\text{CH}_2\text{-}$ ), 19.3 ( $\text{CH}_2\text{-}$ ), 13.8( $\text{CH}_3\text{-}$ ).

**(*E*)-sec-butyl 1-(2,3-diiodoallyl)pyrrolidine-2-carboxylate (**98e**):**



Following the general procedure as indicated above, addition product was obtained by treating **94e**, sec-butyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (209mg, 1mmol) with iodine (761mg, 3.0mmol) in DCM at  $0^\circ\text{C}$  – rt for 21 h to afford compound **98e** as viscous dark green oil (255 mg), yield: 55%.  $R_f$ : 0.70 (15% hexane/ethyl acetate). IR (neat):  $\nu_{\max}/\text{cm}^{-1} = 3051$  (olef. CH), 2974-2850 (alip. CH), 1732 (ester C=O), 1458 (olefinic C=C), 1265-1203 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.01 (s, olefinic CH, 1H), 4.94-4.84 (m, 1H), 3.68-3.63 (ddd, 1H,  $J = 14.0, 4.7, 0.9$  Hz), 3.56-3.48 (m, 2H), 3.14-3.09 (td, 1H,  $J=7.6, 3.8$  Hz), 2.69-2.63 (qd, 1H,  $J=7.6, 3.5$  Hz), 2.24-2.13 (tt, 1H,  $J=11.9, 7.4\text{Hz}$ ), 2.05-1.80 (m, 3H), 1.72-1.49 (m, 2H), 1.25-1.23 (dd, 3H,  $J=6.3, 3.2$  Hz), 0.93-0.89 (td, 3H,  $J=7.5, 2.9$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.2 (ester C=O), 102.2 (I-C=, olefinic), 80.5 (=CHI), 72.7(CH), 64.6 ( $\text{CH}_2\text{-O}$ ), 63.5 ( $\text{CH}_2\text{-}$ ), 52.3( $\text{CH}_2\text{-N}$ ), 29.4( $\text{CH}_2\text{-}$ ), 28.8( $\text{CH}_2\text{-}$ ), 23.3( $\text{CH}_2\text{-}$ ), 19.6( $\text{CH}_3\text{-}$ ), 9.8( $\text{CH}_3\text{-}$ ).  $m/z$  (TOF-MS  $\text{ES}^+$ ) 463 (100,  $\text{MH}^+$ ); HRMS (TOF-MS  $\text{ES}^+$ ):  $\text{MH}^+$ , found 463.9572.  $\text{C}_{12}\text{H}_{19}\text{I}_2\text{NO}_2$  requires 463.9572-463.9584.

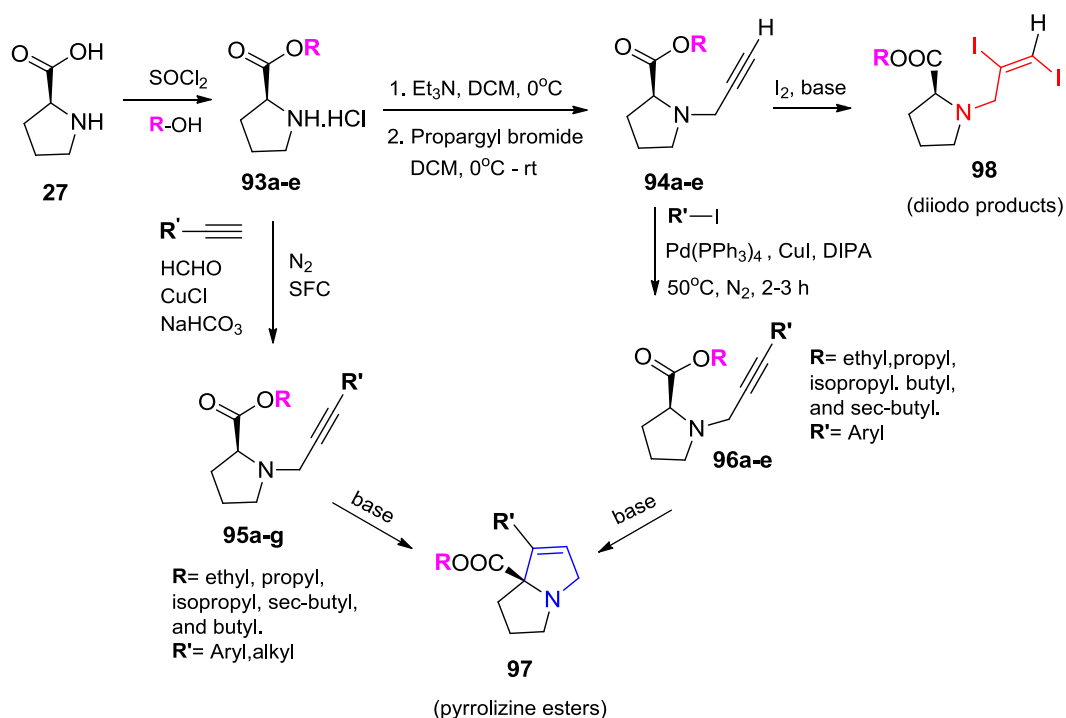
**(E)-methyl 1-(2,3-diiodoallyl)pyrrolidine-2-carboxylate (98f):**



Following the general procedure as indicated above, addition product was obtained by treating **94f**, methyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (167mg, 1mmol) with iodine (761mg, 3.0mmol) in DCM at 0°C – rt for 21 h to afford compound **98f** as viscous dark green oil (240 mg), yield: 57%.  $R_f$ : 0.65 (15%hexane/ethyl acetate). IR (neat):  $\nu_{\max}/\text{cm}^{-1}$  = 3066 (olef. CH), 2947-2804 (alip. CH), 1732 (ester C=O), 1608, 1435 (olefinic C=C), 1199-1172 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.99 (s, olefinic CH, 1H), 3.72 (s, 3H), 3.63-3.59 (d, 1H,  $J$  = 14.1 Hz), 3.54-3.45 (m, 2H), 3.14-3.09 (td, 1H,  $J$ =8.1, 3.9 Hz), 2.67-2.61 (dd, 1H,  $J$ =16.1, 7.9 Hz), 2.12-2.09 (m, 1H), 2.05-1.78 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.3 (ester C=O), 102.3 (I-C=, olefinic), 80.4 (=CHI), 64.3 ( $\text{CH}_2\text{-O}$ ), 63.8 ( $\text{CH}_2\text{-}$ ), 52.5( $\text{CH}_2\text{-N}$ ), 51.9, 29.4( $\text{CH}_2\text{-}$ ), 23.5( $\text{CH}_2\text{-}$ ).  $m/z$  (TOF-MS  $\text{ES}^+$ ) 421 (100,  $\text{MH}^+$ ); HRMS (TOF-MS  $\text{ES}^+$ ):  $\text{MH}^+$ , found 421.9102.  $\text{C}_9\text{H}_{13}\text{I}_2\text{NO}_2$  requires 421.9114.

## 4. RESULTS AND DISCUSSIONS

In the present work, a new synthetic strategy was tried to establish for the efficient preparation of new pyrrolizine scaffolds **97** through few steps including esterification, *N*-substitution, Sonogashira and  $A^3$ -couplings and the base-catalysed intramolecular cyclization reaction of *N*-alkynyl substituted proline esters in the last step. To achieve this goal, first of all, the starting materials, *N*-propargyl esters (**94a-f**) and *N*-alkynyl substituted esters (**95a-h** and **96a-e**), were prepared using slightly modified literature procedures. By the efficient preparation of the starting materials, several alkynyl-substituted prolines (**95a-h** and **96a-e**) was subjected to the intramolecular electrophile- or base- catalysed cyclisations, however, the final products **97**, have been only synthesized over base-catalysed cyclisations. Besides, electrophile-driven reactions of *N*-propargyl-substituted proline esters **94a-f** have furnished some diiodo-addition products **98**. A general scheme is presented below (Scheme 4.1), but the details of each step in the synthetic pathway will be discussed under different chapters separately.



**Scheme 4.1.** Synthetic route leading to the target compounds (**97**, **98**).

## 4.1 SYNTHESIS OF STARTING MATERIALS

### 4.1.1 Synthesis of N-Propargyl Proline Esters

In the first part of the work, the synthesis of starting materials, 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate derivatives (**94**) from *L*-proline (**27**) were carried out as exemplified in Table 4.1 with a two-step synthetic route including slightly modified methods in the literature.

**Table 4.1.** *N*-propargylation of proline esters.

| Entry | R    | Product ( <b>94</b> ) | Yield (%) <sup>a</sup> |
|-------|------|-----------------------|------------------------|
| 1     | Et   | a                     | 71                     |
| 2     | Pr   | b                     | 86                     |
| 3     | i-Pr | c                     | 84                     |
| 4     | Bu   | d                     | 100                    |
| 5     | i-Bu | e                     | 84 <sup>a</sup>        |
| 6     | Me   | f                     | 85 <sup>a</sup>        |

<sup>a</sup> Yields after work-up.

The first precursors, **93** was easily and efficiently obtained in 100% yield via Fischer esterification reaction by heating pyrrolidine-2-carboxylic acid **27** and thionyl chloride (SOCl<sub>2</sub>) together in suitable alcohol at reflux conditions (Huy et al., 2011). The proline ester hydrochloride (**93**) was then reacted with propargyl bromide in the presence of triethylamine at 0°C-rt overnight (Moore et al., 2005). In the last step, an efficient S<sub>N</sub>2 substitution reaction have been performed to afford 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylates **94** in good yields (Table 4.1). Their structures were characterized by IR, proton, carbon NMR and HRMS analyses. The structure of **94a** was determined by -C≡C-H (acetylenic proton) and -CO<sub>2</sub>R (ester) stretching vibrations at about 3290 and 1739 cm<sup>-1</sup> in infrared spectrum, respectively. Also,

acetylenic ( $\text{-C}\equiv\text{C-H}$ ) proton resonates at about 2.19 ppm as triplets in proton NMR spectrum (fig. 4.1).

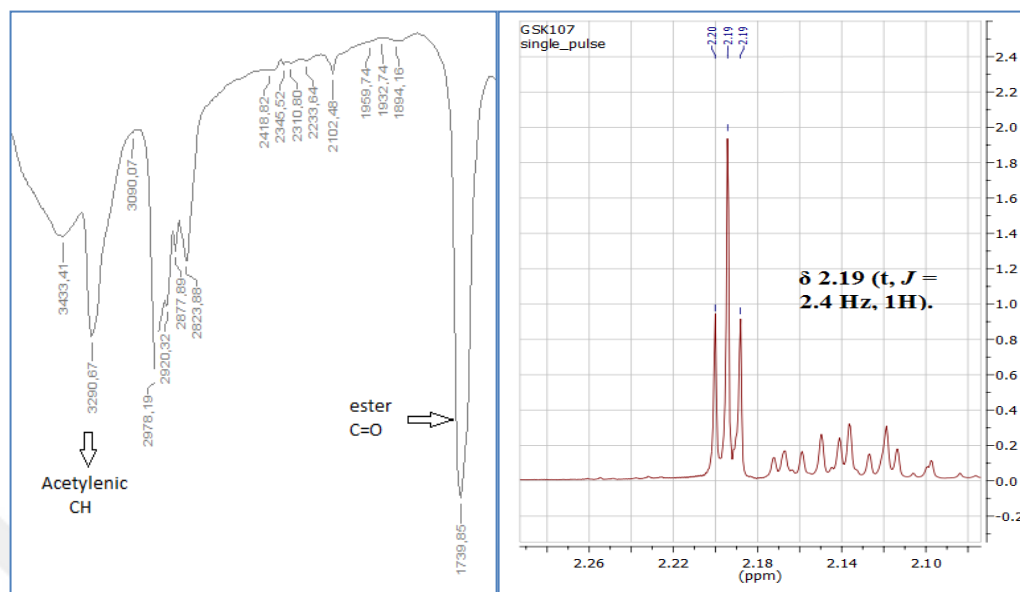


**Figure 4. 1.**  $\equiv\text{CH}$  and  $\text{C=O}$  absorption peaks in IR and the triplet of  $\equiv\text{CH}$  signal in proton NMR

In the carbon NMR spectrum of **94a**,  $\text{C}\equiv\text{C}$  (acetylenic carbons) and  $\text{-CO}_2\text{R}$  (ester) peaks resonated around 73.3 and 173.5 ppm, respectively. Similarly, the structures of other starting compounds **94b-f** were determined by regarding absorption peaks of acetylenic H and ester functionalities in IR and NMR spectra (see Table 4.2). It's observed that the methinic carbons resonated around 62.0-68.0 ppm in the derivatives of **94**.

**Table 4. 2.** IR and NMR data for the compounds **94a-f**

| Comp.     | IR ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) |              |                          | $^1\text{H-NMR}$ ( $\delta$ ,ppm) |              | $^{13}\text{C-NMR}$ ( $\delta$ ,ppm) |                           |              |
|-----------|------------------------------------------|--------------|--------------------------|-----------------------------------|--------------|--------------------------------------|---------------------------|--------------|
| <b>94</b> | $\equiv\text{CH}$                        | $\text{C=O}$ | $\text{C}\equiv\text{C}$ | $\equiv\text{CH}$                 | $\text{-CH}$ | $\text{C=O}$                         | $\text{C}\equiv\text{CH}$ | $\text{C-H}$ |
| <b>a</b>  | 3290                                     | 1739         | 2102                     | 2.19,t                            | 3.07-3.02,m  | 173.5                                | 73.3                      | 62.5         |
| <b>b</b>  | 3290                                     | 1739         | 2102                     | 2.21,t                            | 3.08-3.03,m  | 173.6                                | 73.1                      | 66.3         |
| <b>c</b>  | 3290                                     | 1739         | 2102                     | 2.22,t                            | 3.10-3.05,m  | 172.9                                | 73.1                      | 68.5         |
| <b>d</b>  | 3298                                     | 1739         | 2102                     | 2.14,t                            | 3.02-2.93,m  | 173.5                                | 73.5                      | 64.6         |
| <b>e</b>  | 3300                                     | 1739         | 2102                     | -                                 | -            | -                                    | -                         | -            |
| <b>f</b>  | 3294                                     | 1735         | 2102                     | 2.15,t                            | 3.01-2.92,m  | 174.4                                | 73.3                      | 64.0         |

The HRMS results of product **94b-f** (see appendices) have supported the data in IR and NMR spectra and thus, the structures of *N*-propargyl proline esters **94a-f** have been fully characterized with suitable physical data (table 4.2).

#### 4.1.2 *N*-aryl substituted proline esters via Sonogashira Coupling

Sonogashira coupling is one of the useful methods for constructing new C-C bonds (Bera et al., 2011). Various examples of Sonogashira cross-coupling reactions have been described in the literature, especially the copper co-catalyzed coupling (Alami et al., 1993). This coupling utilizes Pd and CuI as catalyst and co-catalyst with generally an organic base, in which aryl or vinyl iodides and terminal alkynes get coupled and additives such as tetrabutylammonium bromide and potassium iodide accelerates this reaction. Copper-catalyzed Sonogashira coupling mechanism is governed by two cycles; Cu-cycle and Pd-cycle. First, in the presence of a base a  $\pi$ -alkyne complex forms and this leads to formation of copper acetylide which then transmetalates the  $\text{Pd}^{\text{II}}$  intermediate (complex B) and complex C forms. In the final step, formation of alkyne and regeneration Pd catalyst are provided via trans-cis isomerization and reductive elimination reactions, respectively (Figure 4.2).

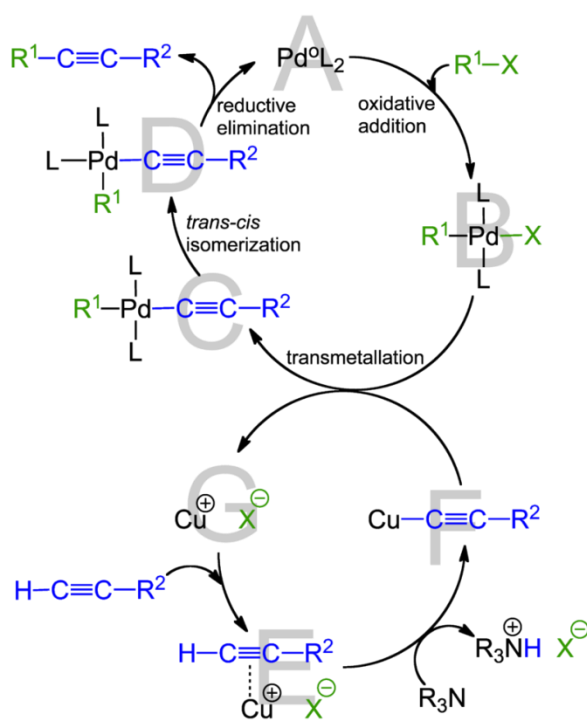


**Figure 4. 2.** Copper and Palladium cycles in Sonogashira mechanism

In the second part of the work, Sonogashira coupling was applied to our terminal alkynes **94**, produced in previous step, with aryl iodides; 1-iodo-4-toluene **92a**, 1-iodo-4-anisole **92b**, and 1-ethoxy-4-iodobenzene **92c** to generate aryl substituted *N*-alkynyl proline esters (**96a-i**) in the presence of DIPA. Sonogashira couplings giving **96** derivatives took place smoothly in mild conditions with moderate to good yields as it's expected (Table 4.3).

**Table 4.3.** Synthesis of *N*-alkynyl aryl proline esters.

| Entry | R         | R'                               | Product | Yield (%)* |
|-------|-----------|----------------------------------|---------|------------|
| 1     | ethyl     | OCH <sub>3</sub>                 | 96a     | 64         |
| 2     | ethyl     | CH <sub>3</sub>                  | 96b     | 59         |
| 3     | isopropyl | CH <sub>3</sub>                  | 96c     | 60         |
| 4     | isopropyl | OCH <sub>2</sub> CH <sub>3</sub> | 96d     | 82         |
| 5     | isopropyl | OCH <sub>3</sub>                 | 96e     | 73         |

\* Isolated yields after column chromatography.

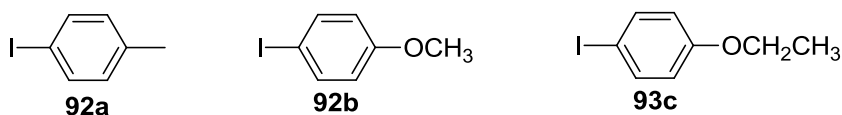


**Figure 4. 3.** Iodobenzene derivatives used in Sonogashira coupling.

These coupling products were synthesized solely to examine the activity of different substituents on aryl ring during cyclization reaction. It's expected that the electron donating effect of alkoxy groups, and methyl group on the aryl ring will play a significant role while cyclization is being done. The structures of the coupling products were characterized by IR, proton and carbon NMR spectra, and HRMS, respectively. To illustrate, the structure of **96a** was determined by the disappearance of  $\text{-C}\equiv\text{C-H}$  (proton) stretching around  $3290\text{ cm}^{-1}$  in IR and triplet around  $2.19\text{ ppm}$  in proton NMR (table 4.2 and fig.4.4). Also, the formation of some aromatic stretching vibrations around  $3043, 1600\text{ cm}^{-1}$ , their overtones between  $1800\text{-}2050$

$\text{cm}^{-1}$  and corresponding aromatic H signal resonating between 7.38-6.80 ppm in proton NMR, internal  $\text{C}\equiv\text{C}$  stretchings at  $2222\text{ cm}^{-1}$  in the corresponding IR spectra and  $\text{C}\equiv\text{C}$  signals around 85.1, 82.7 ppm in carbon NMR spectrum give extra supportive information on the structure of expected coupling product **96a** (fig.4.4).

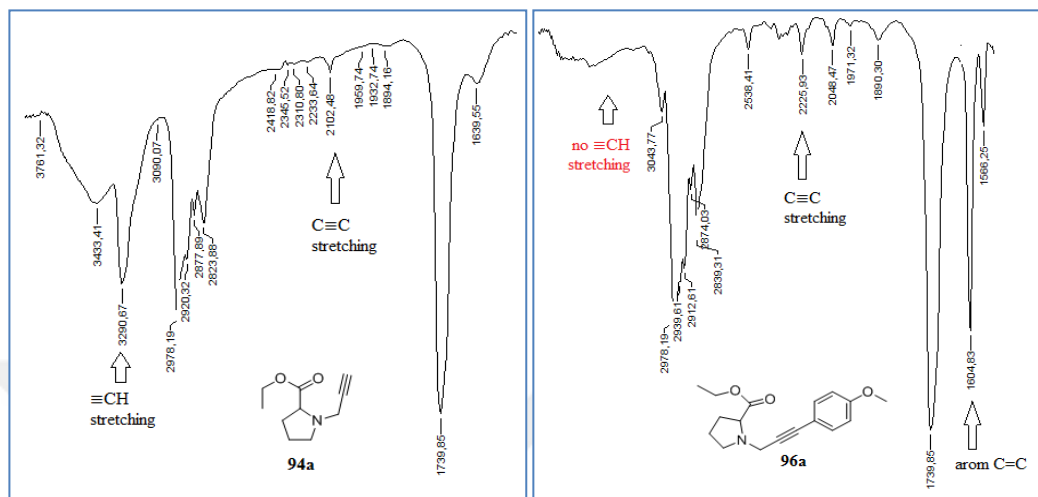


**Figure 4. 4.** Dissappearance of  $\equiv\text{CH}$  absorption by the formation of new C-C bond in IR via Sonogashira coupling

In the carbon NMR spectrum of **96a**,  $\text{C}=\text{CH}-$  (aromatic carbons) and  $-\text{CO}_2\text{R}$  (ester) peaks resonated around 115-135 ppm and 173.5 ppm, respectively. Analogously, compounds **96b-e** were characterized in the same manner by using their IR and NMR spectra (table 4.4).

**Table 4. 4.** IR and NMR data for the compounds **96a-g**

| Comp.     | IR ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) |      |                          | $^1\text{H-NMR}$ ( $\delta$ ,ppm) |             | $^{13}\text{C-NMR}$ ( $\delta$ ,ppm) |                          |      |
|-----------|------------------------------------------|------|--------------------------|-----------------------------------|-------------|--------------------------------------|--------------------------|------|
| <b>96</b> | ArCH                                     | C=O  | $\text{C}\equiv\text{C}$ | Ar CH                             | -CH         | C=O                                  | $\text{C}\equiv\text{C}$ | C-H  |
| <b>a</b>  | 3043                                     | 1739 | 2222                     | 7.38-6.80                         | 3.15-3.11,m | 173.7                                | 85.1,82.7                | 62.9 |
| <b>b</b>  | 3074                                     | 1743 | 2229                     | 7.33-7.08                         | 3.16-3.11,m | 173.7                                | 85.4,83.4                | 62.9 |
| <b>c</b>  | 3039                                     | 1735 | 2225                     | 7.37-6.84                         | 3.15-3.11,m | 173.2                                | 84.9,82.7                | 62.9 |
| <b>d</b>  | 3051                                     | 1735 | 2227                     | 7.34-7.12                         | 3.16-3.12,m | 173.2                                | 85.3,83.5                | 62.9 |
| <b>e</b>  | 3043                                     | 1735 | 2229                     | 7.33-6.80                         | 3.12-3.08,m | 173.3                                | 85.3,82.7                | 63.0 |
| <b>f</b>  | 3039                                     | 1739 | 2225                     | nd                                | nd          | nd                                   | nd                       | nd   |
| <b>g</b>  | 3028                                     | 1743 | 2229                     | nd                                | nd          | nd                                   | nd                       | nd   |

nd = no available data for now

HRMS data available for **96a-e** give the promising results supporting IR and NMR data of products. In short, the structures of newly obtained *N*-alkynyl aryl proline esters **96a-e** were determined and fully characterized by using IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and HRMS measurements (Table 4.3 and 4.4).

#### 4.1.3 *N*-alkynyl Substituted proline esters via A<sup>3</sup>-Coupling.

“A<sup>3</sup>-coupling is a powerful tool that allows the direct coupling of alkynes with imines (produced in situ from amine and aldehyde) in a one pot catalytic multicomponent and atom economical way” (Sharma et al.,2014). Many complexes or salts of the transition metals have been employed as catalyst such as; Ni, Zn, Cu, Co, Cr, Ag, etc. However, the most widely reviewed reagent has been copper, specifically when dealing with secondary amines.

For the one-pot synthesis of *N*-alkynyl phenyl/alkyl substituted esters **95a-g**, the salts of pyrrolidine 2-carboxylates **93** were first prepared from *L*-proline **27** using a well-known method from the literature (Huy et al., 2011). After the isolation of *L*-proline carboxylate salts **93**, the alkylation with formaldehyde **86** and terminal aryl/alkyl substituted acetylenes (**91**) proceeded efficiently via A<sup>3</sup>-coupling reaction giving the desired internal alkynes (**95**) in moderate to good yields (Shi et al., 2004; Uhlig and Li, 2012) . Only the substitution of formaldehyde **86** with cyclohexanone afforded coupling product **95h** in quite low yields (entry 8, Table 4.5).

**Table 4.5.** Synthesis of *N*-alkynyl substituted proline esters via A<sup>3</sup> coupling

| Entry | R'                 | R              | Product | Yield (%) |
|-------|--------------------|----------------|---------|-----------|
| 1     | Phenyl             | Ethyl          | 95a     | 70        |
| 2     | Phenyl             | Propyl         | 95b     | 85        |
| 3     | Phenyl             | Isopropyl      | 95c     | 81        |
| 4     | Phenyl             | Butyl          | 95d     | 84        |
| 5     | Phenyl             | 2-butyl        | 95e     | 86        |
| 6     | n-butyl            | Ethyl          | 95f     | 87        |
| 7     | Methyl carboxylate | Isopropyl      | 95g     | 55        |
| 8     | Phenyl             | 4-methylpentyl | 95h     | 27        |

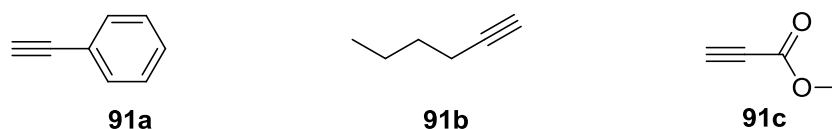


**Figure 4. 5.** Structures of acetylene derivatives **91a-c** used in  $A^3$ -coupling.

As a usual analysis practice, the structures of the one-pot Michael addition  $A^3$  coupled products (**95**) were characterized by IR, proton and carbon NMR spectra. In addition, HRMS analysis also supported the structures completely. To cite an example here, the structure of compound **95a** was elucidated by using IR spectrum by the appearance of weak  $-C\equiv C-$  stretching vibration peak at  $2229\text{ cm}^{-1}$ , some aromatic stretching vibrations around  $1597\text{ cm}^{-1}$  and overtones between  $1800\text{-}1950\text{ cm}^{-1}$ , respectively. In the proton NMR spectrum, appearance of the protons around  $7.24\text{-}7.42\text{ ppm}$  showed the presence of the aromatic ring on the newly coupled products (table 4.6). Moreover, carbon NMR spectrum showed the  $C=CH-$  (aromatic carbons),  $-C\equiv C-$  (acetylenic carbons) and  $-\text{CO}_2\text{R}$  (ester carbon) signals resonated around  $128\text{-}133\text{ ppm}$ ,  $74\text{-}85\text{ ppm}$  and  $173\text{-}174\text{ ppm}$ , respectively.

**Table 4. 6.** IR and NMR data for the compounds **95a-h**

| Comp.       | IR ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) |      |              | $^1\text{H-NMR}$ ( $\delta, \text{ppm}$ ) |             | $^{13}\text{C-NMR}$ ( $\delta, \text{ppm}$ ) |              |      |
|-------------|------------------------------------------|------|--------------|-------------------------------------------|-------------|----------------------------------------------|--------------|------|
|             | ArCH                                     | C=O  | C $\equiv$ C | Ar CH                                     | -CH         | C=O                                          | C $\equiv$ C | C-H  |
| <b>95 a</b> | 3055                                     | 1739 | 2229         | 7.42-7.24                                 | 3.14-3.10,m | 173.3                                        | 85.4,84.3    | 63.0 |
| <b>b</b>    | 3055                                     | 1743 | 2229         | 7.44-7.25                                 | 3.12-3.08,m | 173.77                                       | 85.3,84.2    | 62.8 |
| <b>c</b>    | 3055                                     | 1739 | 2229         | 7.42-7.25                                 | 3.14-3.09,m | 173.0                                        | 85.3,84.4    | 63.1 |
| <b>d</b>    | 3055                                     | 1739 | 2229         | 7.44-7.26                                 | 3.16 – 3.08 | 173.78                                       | 85.3,84.2    | 62.9 |
| <b>e</b>    | 3055                                     | 1735 | 2229         | 7.44-7.25                                 | 3.15 – 3.08 | 173.3                                        | 85.2,84.3    | nd   |
| <b>f</b>    | -                                        | 1743 | 2256         | -                                         | 3.04-3.00,m | 173.9                                        | 85.6,74.3    | 62.8 |
| <b>g</b>    | -                                        | 1739 | 2229         | -                                         | 3.07,3.03,m | nd                                           | nd           | nd   |
| <b>h</b>    | 3055                                     | 1743 | 2214         | 7.43-7.25                                 | 3.07-3.03,m | nd                                           | nd           | nd   |

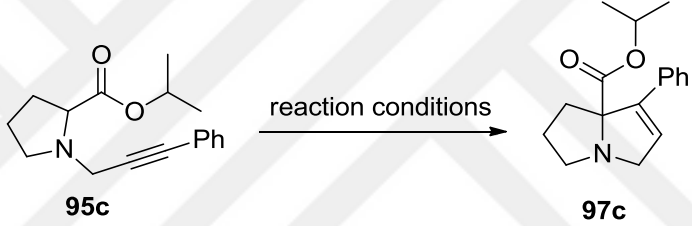
nd = no available data for now

In the HRMS, calculated value of  $\text{MH}^+$  ion for compound **95a** was 258.1494 whereas 258.1496 was found reaffirming and proving the expected product exclusively (see appendices). To sum up, the other products **95b-g** were also proven based on the above mentioned spectroscopic analyses and the summary of their results was tabulated above.

## 4.2 SYNTHESIS OF THE TARGET PRODUCTS VIA BASE-CATALYSED CARBOCYCLIZATIONS

As the aim and objective of our successful study, in this part, the synthesis of new pyrrolizine derivatives was explored via base-mediated cyclization of *N*-alkynyl substituted proline derivatives (**95**, **96**). Accordingly, in order to obtain the ideal conditions, we tried a comprehensive set of reaction conditions using different set of combinations to attain optimum yield. Table 4.7 displayed how the factors like temperature, base, reaction time and solvent altered the results of reaction yields and its efficiency. In each case, the reaction completion was determined by TLC analysis.

**Table 4.7.** Optimization of reaction conditions for the synthesis of compound **97**

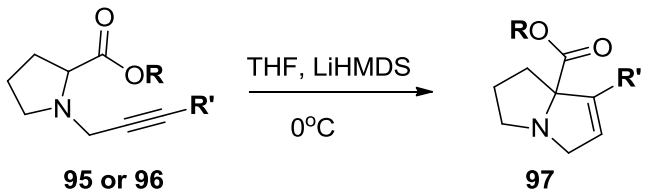
|  |         |               |          |         |              |
|-------------------------------------------------------------------------------------|---------|---------------|----------|---------|--------------|
| Reaction conditions                                                                 |         |               |          |         |              |
| Entry                                                                               | Solvent | Base (equiv.) | Temp.    | Time(h) | Yield (%)    |
| 1                                                                                   | MeCN    | NaH(1.0)      | rt       | 3       | Decomposed   |
| 2                                                                                   | DMF     | NaH(1.0)      | 0°C-rt   | 2       | Unidentified |
| 3                                                                                   | THF     | KOtBu(1.0)    | rt-60°C  | 9       | NR           |
| 4                                                                                   | DMF     | LiHMDS(0.5)   | rt       | 1       | trace        |
| 5                                                                                   | THF     | LiHMDS(0.75)  | rt       | 1.5     | 50           |
| 6                                                                                   | THF     | LiHMDS(0.75)  | 0°C-rt   | 1.5     | 60           |
| 7                                                                                   | THF     | LiHMDS(0.75)  | 0°C-40°C | 1.5     | 52           |
| 8                                                                                   | THF     | LiHMDS(1.5)   | rt       | 2       | 85           |
| 9                                                                                   | THF     | LiHMDS(1.5)   | 0°C-rt   | 2       | Quantitative |

First of all, in model cyclisation reaction, **95c** was subjected to cyclisations with different bases under several conditions in order to obtain product **97c**. With this purpose, the reaction was first performed in a polar aprotic solvent (MeCN) with one equivalent of a base (NaH) at room temperature for 3 hours (Table 4.7, Entry 1). This trial furnished no product with only decomposition of the starting compound.

Whereas the use of NaH and KO<sup>t</sup>-Bu bases showed no activity to induce the cyclisation (entries 1-3, table 4.7), the non-nucleophilic strong base, LiHMDS was moderately active and enabled the formation of target product in trace amounts with another polar aprotic solvent, DMF (entry 4, table 4.7). First cyclisation trial in a nonpolar aprotic solvent, THF (dry) with 0.75 equiv. of LiHMDS afforded the expected product **97c** in moderate yields at rt within 1.5 hour (entry 5, table 4.7). The success in cyclisation reactions with LiHMDS directed us to alter the equiv. of LiHMDS, reaction temperature and time only. After several trials (entries 6-9, table 4.7), especially by lowering the reaction temperature, the best conditions for the formation of product **97c** have been found when the reaction was started at 0°C and allowed rising up to rt within 2 hour in quantitative yields (entry 9, table 4.7).

After finding the optimized conditions for the model reaction, we subjected the variety of our *N*-alkynyl substituted proline derivatives **95** and **96** via base-mediated carbocyclizations. The title compounds **97a-k** were obtained in good to excellent yields using LiHMDS at 0°C for 30 minutes then rt for 1.5 h (table 4.8).

**Table 4.8.** Formation of pyrrolizine derivatives **97a-k** and reaction yields

|  |        |      |         |                        |
|--------------------------------------------------------------------------------------|--------|------|---------|------------------------|
| Entry                                                                                | R'     | R    | Product | Yield (%) <sup>a</sup> |
| 95a                                                                                  | Phenyl | Et   | 97a     | 69                     |
| 95b                                                                                  | Phenyl | Pr   | 97b     | 69                     |
| 95c                                                                                  | Phenyl | i-Pr | 97c     | quantitative           |
| 95d                                                                                  | Phenyl | Bu   | 97d     | 74                     |
| 95e                                                                                  | Phenyl | 2-Bu | 97e     | 95                     |
| 95f                                                                                  | MeO-Ph | Et   | 97f     | 76                     |
| 96a                                                                                  | Me-Ph  | Et   | 97g     | 81                     |
| 96b                                                                                  | n-Bu   | Et   | 97h     | 72                     |
| 96c                                                                                  | Me-Ph  | i-Pr | 97i     | 90                     |
| 96d                                                                                  | EtO-Ph | i-Pr | 97j     | quantitative           |
| 96e                                                                                  | MeO-Ph | i-Pr | 97k     | quantitative           |

The cyclisation products (**97a-k**) have been fully characterized by using IR, proton and carbon NMR and HRMS analyses. As an example, if we consider the physical data of product **97a** obtained by these techniques, the principle absorption peaks in IR spectrum are the stretching vibrations of aromatic C-H, ester C=O and olefinic C=C groups at around 3055, 1724 and 1496  $\text{cm}^{-1}$ , respectively. In proton NMR of **97a**, the characteristic signals supporting the expected structure are the aromatic CH and olefinic CH signals resonating at around 7.43-7.24 ppm as multiplets and 6.25 ppm as triplets, respectively. As for carbon NMR, the basic signals depicting the cyclisation product are of the ester C=O, olefinic quaternary C=C and olefinic =CH resonating at around 174.0, 142.1 and 123.8 ppm, respectively (fig.4.6). In HRMS spectrum of **97a**, molecular ion has been found as  $\text{MH}^+$ , 258.1483 accurately by TOF-MS electrospray ionization (positive pole), which is in accordance with calculated accurate mass, 258.1494 (see experimental and appendices).

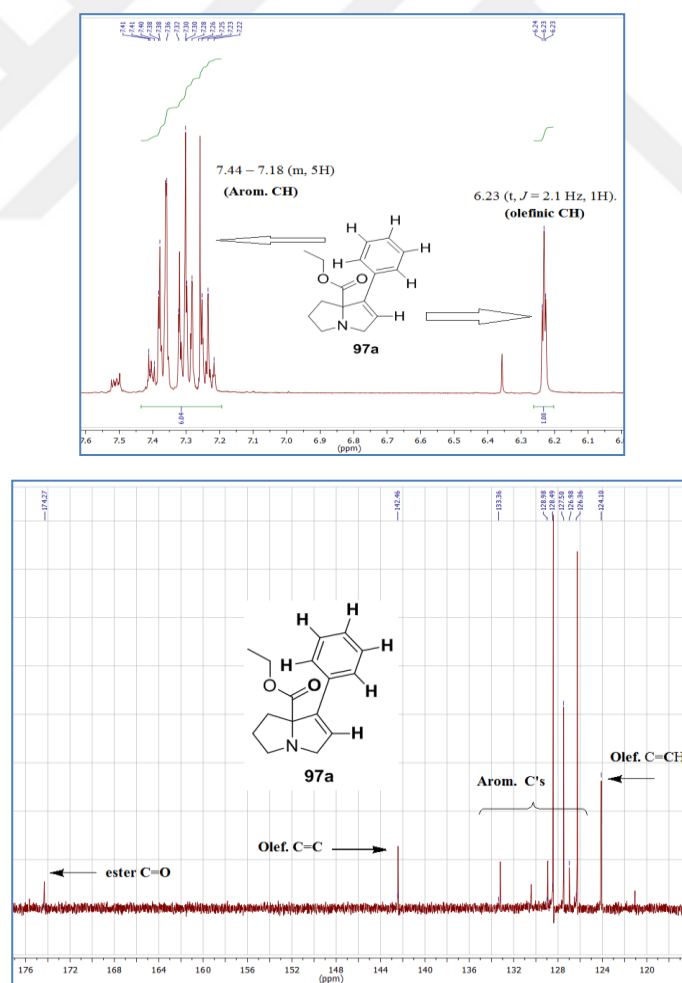


**Figure 4. 6.** Principle proton and carbon NMR signals of **97a**

The derivatives of products **97b-k** were fully characterized with IR, proton and carbon NMR and HRMS analyses by using the data in similar fashion. The obtained data from the analyses are in accordance with each other and with those of expected structures from the cyclisation reactions (table 4.9).

**Table 4. 9.** IR and NMR data for the compounds **97a-k**

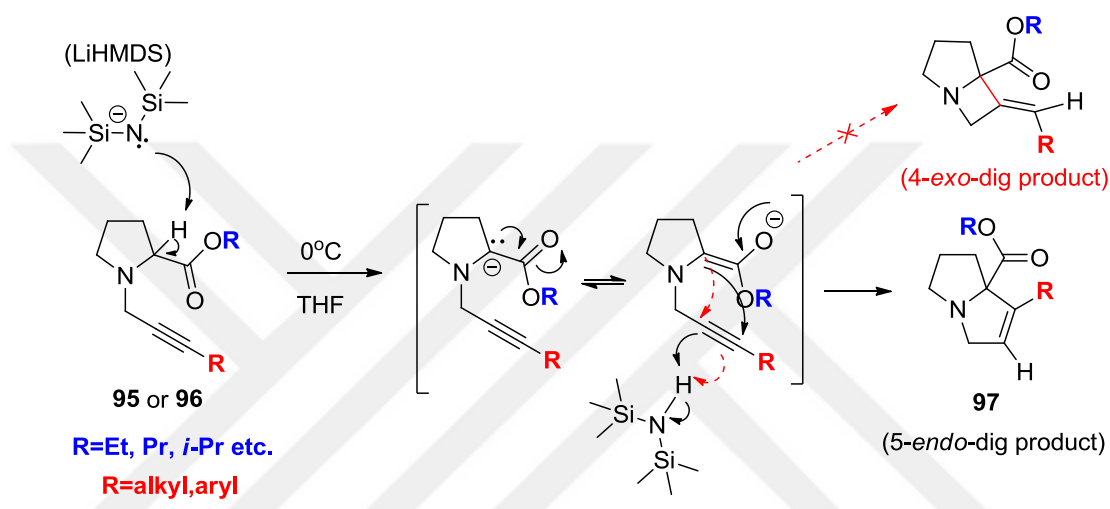
| Comp.     | IR ( $\nu_{\max}/\text{cm}^{-1}$ ) |      |      | $^1\text{H-NMR}$ ( $\delta$ ,ppm) |        | $^{13}\text{C-NMR}$ ( $\delta$ ,ppm) |       |       |
|-----------|------------------------------------|------|------|-----------------------------------|--------|--------------------------------------|-------|-------|
|           | ArCH                               | C=O  | C=C  | Ar CH                             | =CH    | C=O                                  | C=C   | =C-H  |
| <b>97</b> |                                    |      |      |                                   |        |                                      |       |       |
| <b>a</b>  | 3055                               | 1724 | 1496 | 7.43-7.24                         | 6.25,t | 174.0                                | 142.1 | 123.8 |
| <b>b</b>  | 3059                               | 1728 | 1496 | nd                                | nd     | nd                                   | nd    | nd    |
| <b>c</b>  | 3059                               | 1724 | 1496 | 7.37-7.21                         | 6.21,t | 173.7                                | 142.6 | 124.1 |
| <b>d</b>  | 3059                               | 1724 | 1496 | nd                                | nd     | nd                                   | nd    | nd    |
| <b>e</b>  | 3059                               | 1724 | 1496 | nd                                | nd     | nd                                   | nd    | nd    |
| <b>f</b>  | 3059                               | 1724 | 1462 | 7.32-6.82                         | 6.08,t | 174.4                                | 141.8 | 121.8 |
| <b>g</b>  | 3059                               | 1728 | 1450 | 7.27-7.10                         | 6.16,t | 174.4                                | 142.7 | 123.0 |
| <b>h</b>  | -                                  | 1728 | 1458 | -                                 | 5.39,m | 174.6                                | 143.3 | 121.0 |
| <b>i</b>  | 3059                               | 1724 | 1454 | 7.24-7.10                         | 6.15,t | 173.8                                | 142.4 | 123.0 |
| <b>j</b>  | 3059                               | 1724 | 1512 | 7.29-6.80                         | 6.05,t | 173.9                                | 142.0 | 121.7 |
| <b>k</b>  | 3059                               | 1720 | 1462 | 7.31-6.82                         | 6.06,t | 173.9                                | 142.0 | 121.8 |

nd = no available data for now

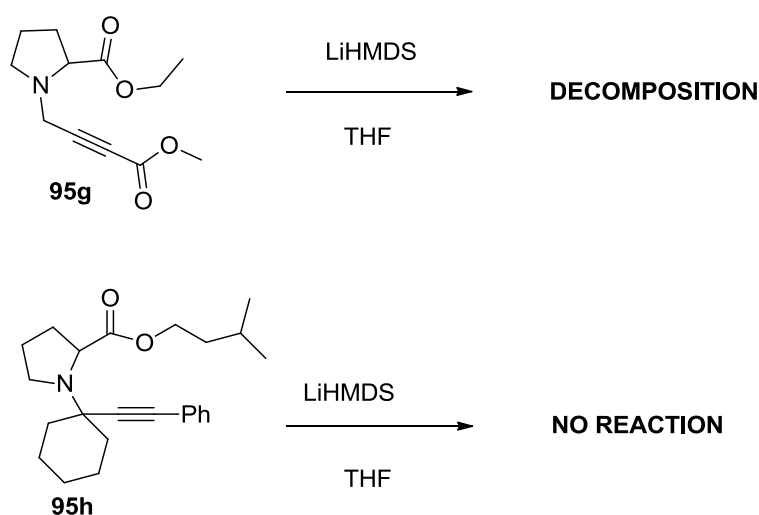
The mechanism of the cyclisation reaction was believed to proceed via 5-*endo* dig fashion far from following the 4-*exo* fashion to give *exo*-products when we consider the data obtained from IR and NMR spectra (Scheme 4.2). No data was obtained either from the spectra supporting any *exo*-product or any second product from TLC controls while reaction progress, only one product containing 5-membered fused ring has been obtained after the reaction or isolation studies.

When *N*-alkynyl substituted proline esters **95g** and **95h** were subjected to cyclisation reactions under optimized conditions, no cyclisation product was able to be obtained by the reactions. Surprisingly, the decomposition of starting compound **95g** took place less than 5 minutes, possibly, by the electron-withdrawing effect of C=O group, the  $\beta$ -C will be more positive and perhaps due to electron deficient centre, any possible cyclisation should prefer *exo*-mode affording the 4-membered *exo*-product, so no way for formation of 5-*endo* product is possible. Since the 4-

membered ring is more strained and needed a larger activation energy to form, also, the possible exo-product did not form and thus, no product was obtained in the reaction. Similarly, when **95h** was treated with optimized amount of the LiHMDS, neither a change showing formation of any product in the TLC nor a change in the IR spectrum has been observed (Scheme 4.3). Due to the presence of cyclohexane moiety  $\alpha$  to N or C $\equiv$ C bond in **95h**, that steric hindrance will block the formation of any cyclic product which would be very unstable after formation due to ring strain in the system (energy of the system will be large).



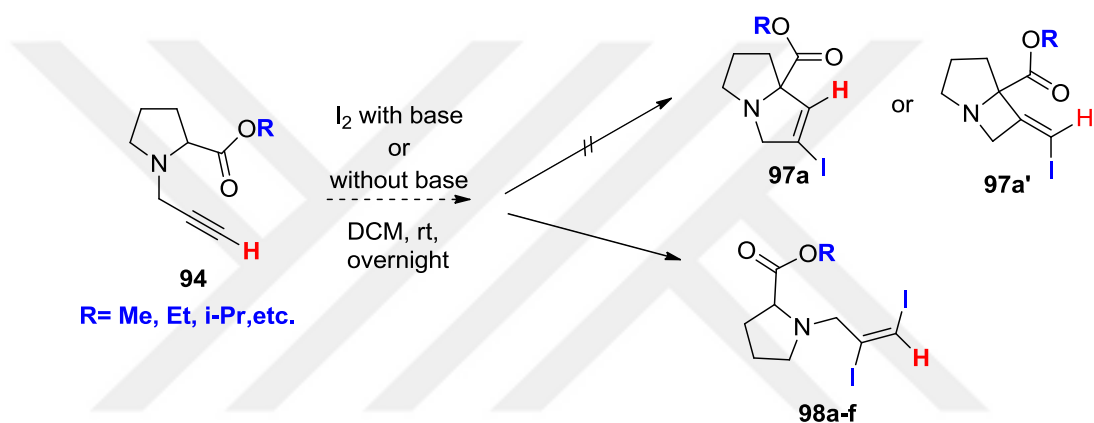
**Scheme 4.2.** Proposed mechanism for the formation of pyrrolizines.



**Scheme 4.3.** Unsuccessful cyclisation results of **95h** and **95g**.

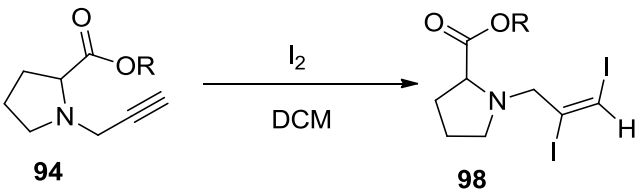
### 4.3 SYNTHESIS OF DI-iodoADDITION PRODUCTS VIA ELECTROPHILIC REACTIONS

*N*-propargyl proline esters **94** were treated with different set of reagents such as bases or acids (H<sub>2</sub>SO<sub>4</sub>, TFA, p-TSA..etc), and Lewis acids (I<sub>2</sub>, ICl...etc.) to afford some cyclisation products (**97a** or **97a'**). Unfortunately, use of different solvents, reaction conditions or reagents in several trials could not induce any cyclisation product. Instead of cyclisation products, only some diiodo addition products **98a-f** have been obtained by the reaction of compounds **94** with I<sub>2</sub> alone in DCM at room temperature overnight in low to moderate yields (Scheme 4.4).



**Scheme 4.4.** Unexpected formation of diiodo products (**98a-f**).

**Table 4.10.** Formation of diiodo products (**98a-f**)

|  |           |         |                        |
|--------------------------------------------------------------------------------------|-----------|---------|------------------------|
| Entry                                                                                | R         | Product | Yield (%) <sup>a</sup> |
| 1                                                                                    | Ethyl     | 98a     | 34                     |
| 2                                                                                    | Propyl    | 98b     | 26                     |
| 3                                                                                    | Isopropyl | 98c     | 31                     |
| 4                                                                                    | Butyl     | 98d     | 23                     |
| 5                                                                                    | 2-Butyl   | 98e     | 55                     |
| 6                                                                                    | Methyl    | 98f     | 57                     |

<sup>a</sup> The yields after purification by column chromatography

Any attempt to optimize the reaction conditions was unsuccessful and the reaction yields were obtained low in some of the reactions affording the products **98a**, **98b-d** (entries 1, 2-4, table 4.10), and in some of the reactions affording products **98e-f** (entries 5, 6, table 4.10). After purification and isolation of products by column chromatography, all the products have been characterized by using IR, proton and carbon NMR and MS analyses. When the product **98a** was considered for the structure determination of the *trans*-diiodo addition products, olefinic C=CH, ester C=O and C=C absorption peaks will be observed at around 3066, 1728, 1442  $\text{cm}^{-1}$ , respectively. In proton NMR of **98a**, a singlet peak resonating at 7.00 ppm shows the presence of olefinic CH absorption and a multiplet between 3.12-3.10 ppm will be evidence of methinic proton between C=O and N atom. The most characteristic data was found in carbon NMR of **98a**, the signals belonging to C=O, I-C= and =CHI carbons resonate at 173.5, 101.9 and 81.2 ppm, respectively. Especially, the last two carbon chemical shifts are the evidence of uncyclisation reaction products. The rest of the diiodo addition products have characterized by the same techniques and similar data (table 4.11).

**Table 4. 11.** IR and NMR data for the compounds **98a-f**

| Comp.    | IR ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) |      |      | $^1\text{H-NMR}$ ( $\delta$ ,ppm) |              | $^{13}\text{C-NMR}$ ( $\delta$ ,ppm) |       |      |
|----------|------------------------------------------|------|------|-----------------------------------|--------------|--------------------------------------|-------|------|
|          | =CH                                      | C=O  | C=C  | =CH                               | -CH          | C=O                                  | IC=   | =CHI |
| <b>a</b> | 3066                                     | 1728 | 1442 | 7.00,s                            | 3.12-3.1,m   | 173.5                                | 101.9 | 81.2 |
| <b>b</b> | nd                                       | nd   | nd   | nd                                | nd           | nd                                   | nd    | nd   |
| <b>c</b> | 3066                                     | 1724 | 1462 | 6.97,s                            | 3.12-3.01,m  | 173.2                                | 102.6 | 80.8 |
| <b>d</b> | 3066                                     | 1728 | 1462 | 7.04,s                            | 3.17-3.15,td | 173.4                                | 101.2 | 81.8 |
| <b>e</b> | 3051                                     | 1732 | 1458 | 7.01,s                            | 3.14-3.09,td | 173.2                                | 102.1 | 80.5 |
| <b>f</b> | 3066                                     | 1732 | 1435 | 6.99,s                            | 3.14-3.09,td | 174.3                                | 102.3 | 80.4 |

nd = no available data for now

The mechanism for the formation of diiodo addition products (**98**) has been thought to follow a general anti- addition reaction to triple bonds in alkynes affording the *trans*- diiodo vinylic systems attached to proline ester moiety.

## 5. CONCLUSIONS

In summary, the synthesis of tetrahydro-1*H*-pyrrolizine derivatives by base-catalyzed carbocyclization reaction has been investigated in this work. The fact that both pyrrolizine and pyrrolizidine containing structures contribute to numerous fields of science such as chemistry, medicine, biochemistry, agriculture, etc. is one of the reasons why scientists have been studying the synthetic and application of coexisting structures. The introduction of different esters on to the pyrrolizine core structure might have significant applications with better activities.

In the first part of the study, starting materials, pyrrolidine-2-carboxylates **93** and *N*-propargyl pyrrolidine-2-carboxylates **94** were synthesized according to literature methods. Later on, those starting compounds were used to obtain *N*-alkynyl substituted proline derivatives through one-pot  $A^3$  coupling affording compounds **95**, or Sonogashira coupling affording compounds **96**, respectively.

In the second part of the work, the synthesis of the target compounds, pyrrolizines **97** was achieved successfully via base-mediated carbocyclization of *N*-alkynyl substituted proline derivatives (**95** and **96**) with LiHMDS base in moderate to quantitative yields. This way, we are pleased to report the synthesis of newly synthesized pyrrolizines **97a-o** that has been unprecedented in the literature. The aforementioned structures obtained were fully analyzed and characterized by means of IR, NMR and HRMS spectroscopic measurements.

The tests of biological activity of these bioactive compounds will be performed by cooperation of researchers in pharmacological laboratories since various biologically active molecules having pyrrolizine cores are of great concern in a pharmaceutical perception.

Finally, diiodo compounds (**98a-f**) have been obtained from starting compounds **94** via *trans*- addition of  $I_2$  to the terminal alkyne moiety in very mild conditions and they have been fully characterized by means of IR, NMR (proton, carbon) and HRMS analyses.

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# APPENDICES

## 7. APPENDICES

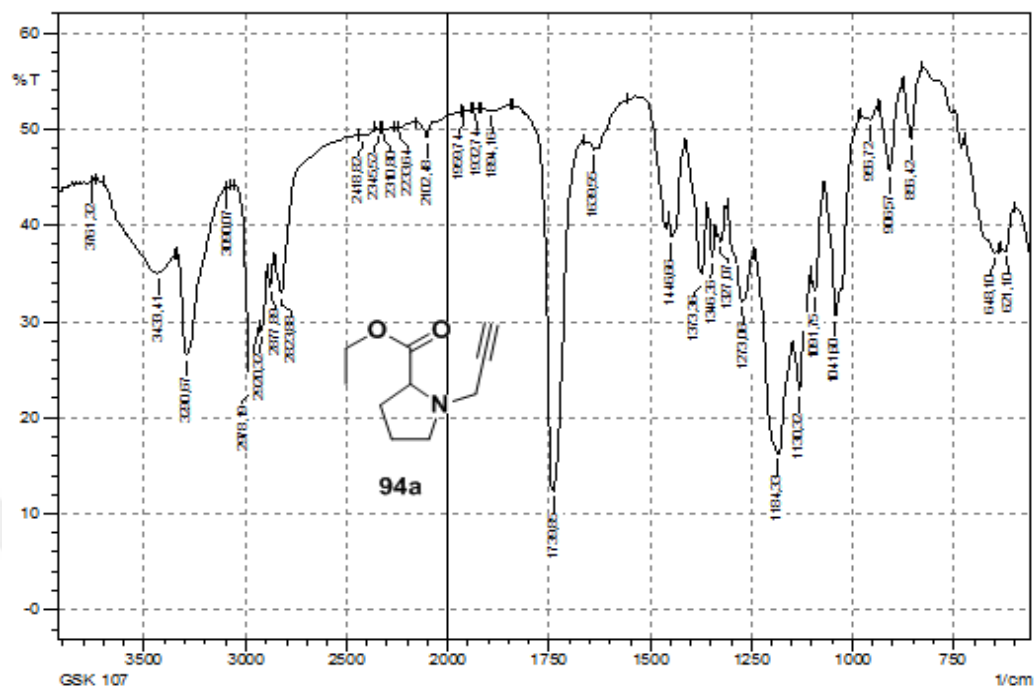


Figure 7. 1. IR spectrum of compound **94a**

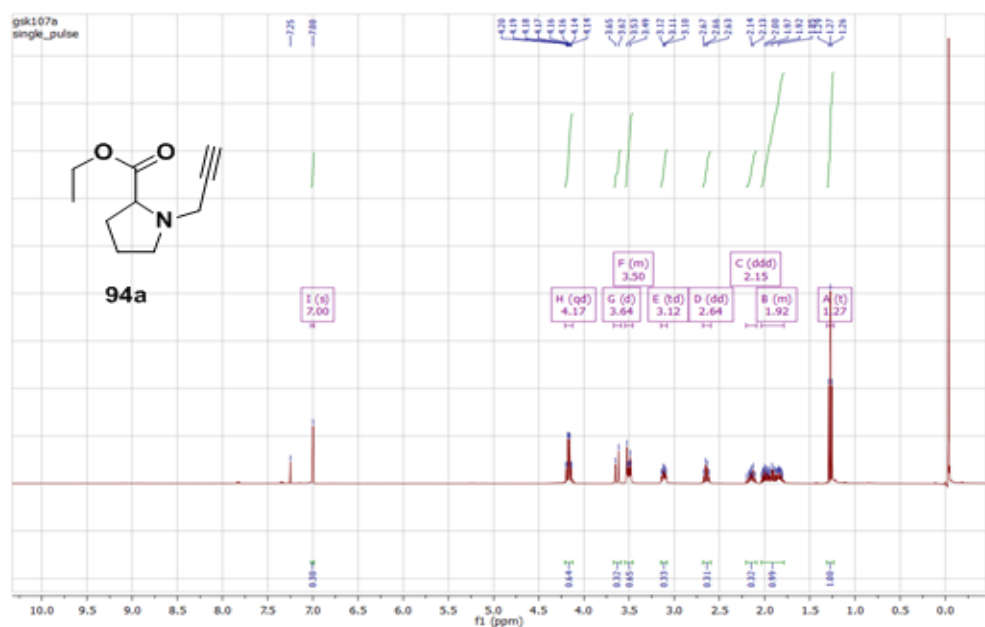


Figure 7. 2.  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound **94a**





### Single Mass Analysis

Tolerance = 12.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

16 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa  | PPM  | DBE | Formula      | i-FIT | i-FIT (Norm) | C  | H  | N | O | I |
|----------|------------|------|------|-----|--------------|-------|--------------|----|----|---|---|---|
| 196.1329 | 196.1338   | -0.9 | -4.6 | 3.5 | C11 H18 N O2 | 322.3 | 0.0          | 11 | 18 | 1 | 2 |   |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

GSK111\_03 61 (1.875) Cm (61-38.44)

1: TOF MS ES+

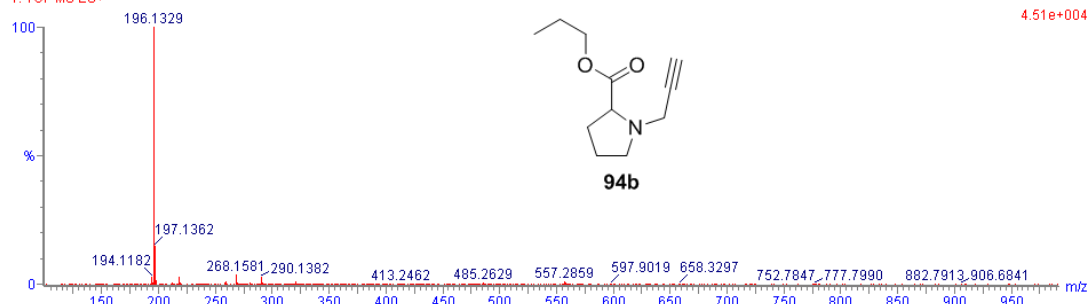


Figure 7. 7. HRMS spectrum of compound 94b

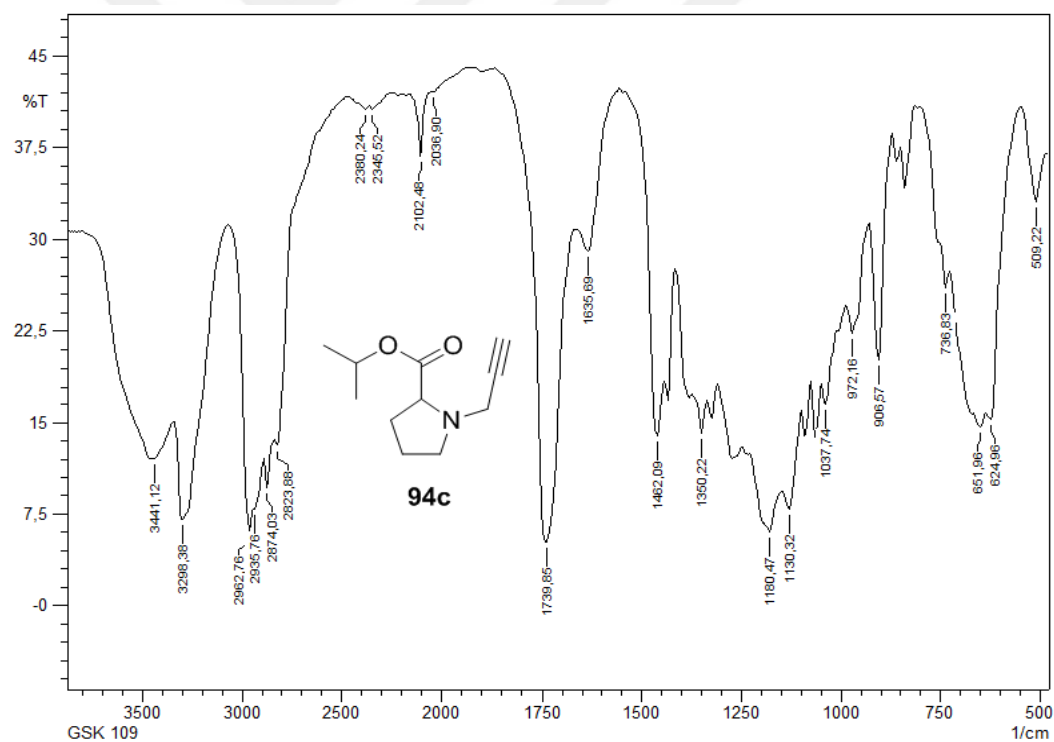
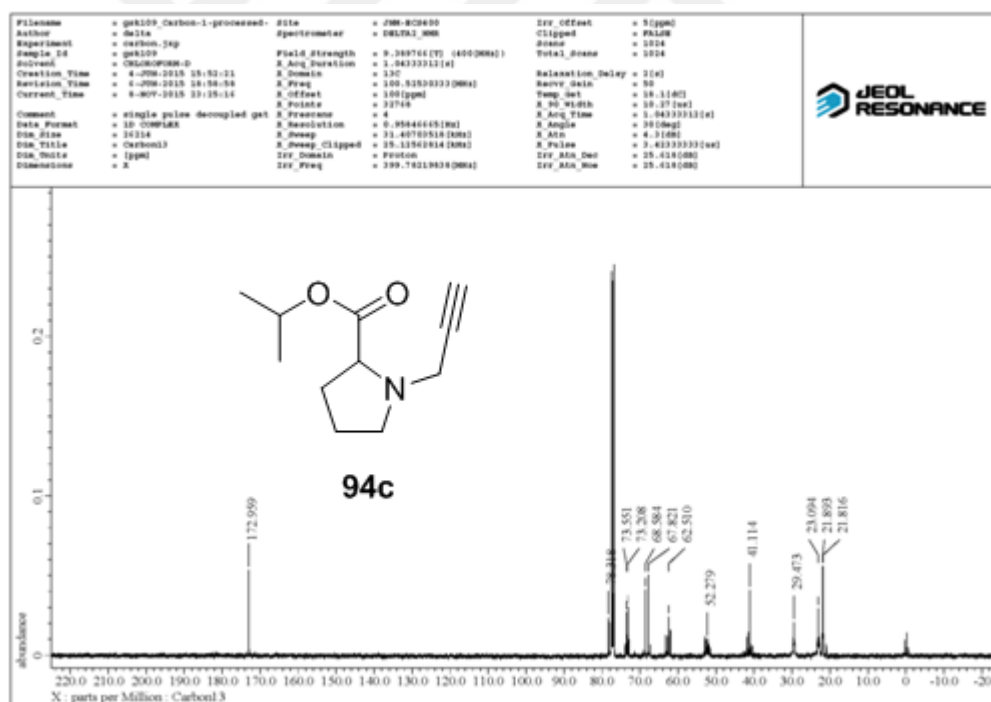
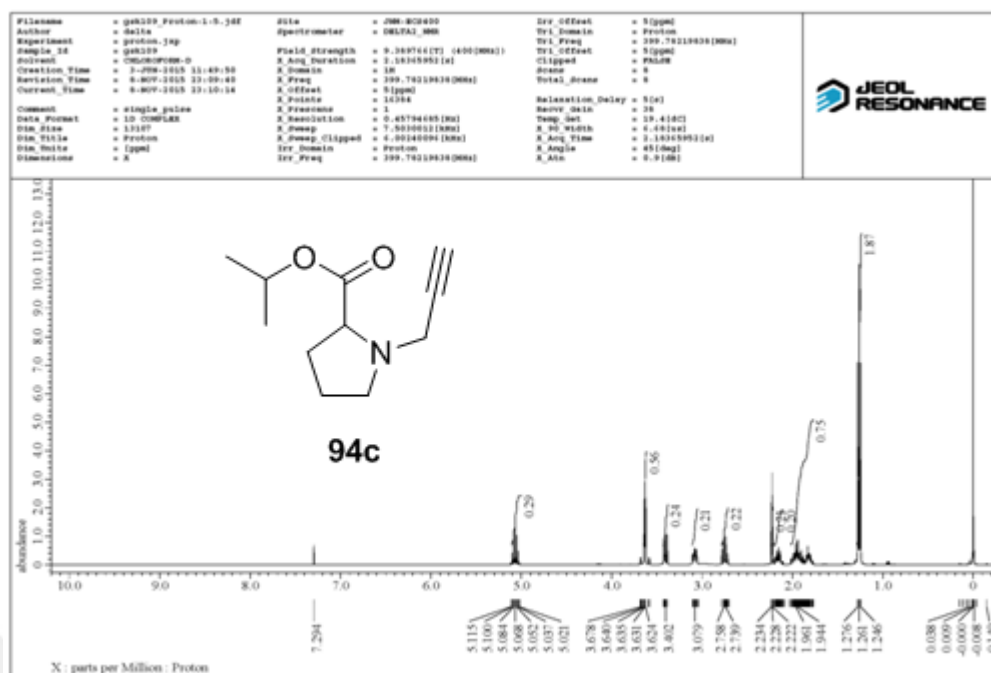


Figure 7. 8. IR spectrum of compound 94c



### Single Mass Analysis

Tolerance = 12.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

16 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa  | PPM  | DBE | Formula                                                       | i-FIT | i-FIT (Norm) | C  | H  | N | O | I |
|----------|------------|------|------|-----|---------------------------------------------------------------|-------|--------------|----|----|---|---|---|
| 196.1337 | 196.1338   | -0.1 | -0.5 | 3.5 | C <sub>11</sub> H <sub>18</sub> N <sub>1</sub> O <sub>2</sub> | 296.9 | 0.0          | 11 | 18 | 1 | 2 |   |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

GSK109\_03 42 (1.633) Cm (42-29:35)

1: TOF MS ES+

2.87e+004

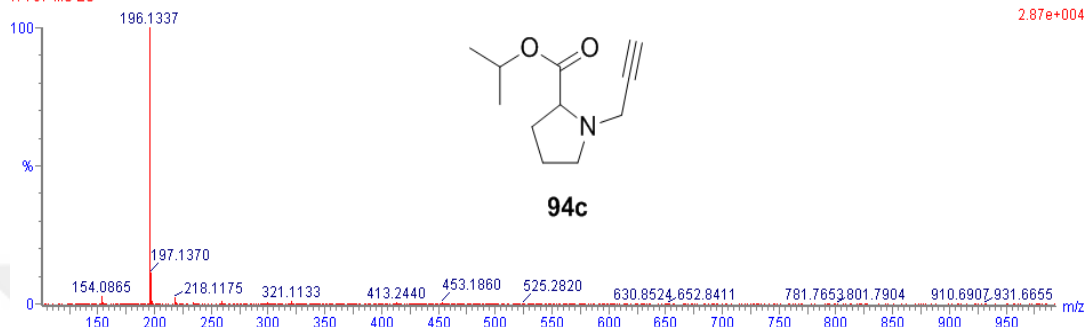


Figure 7. 11. HRMS spectrum of compound 94c

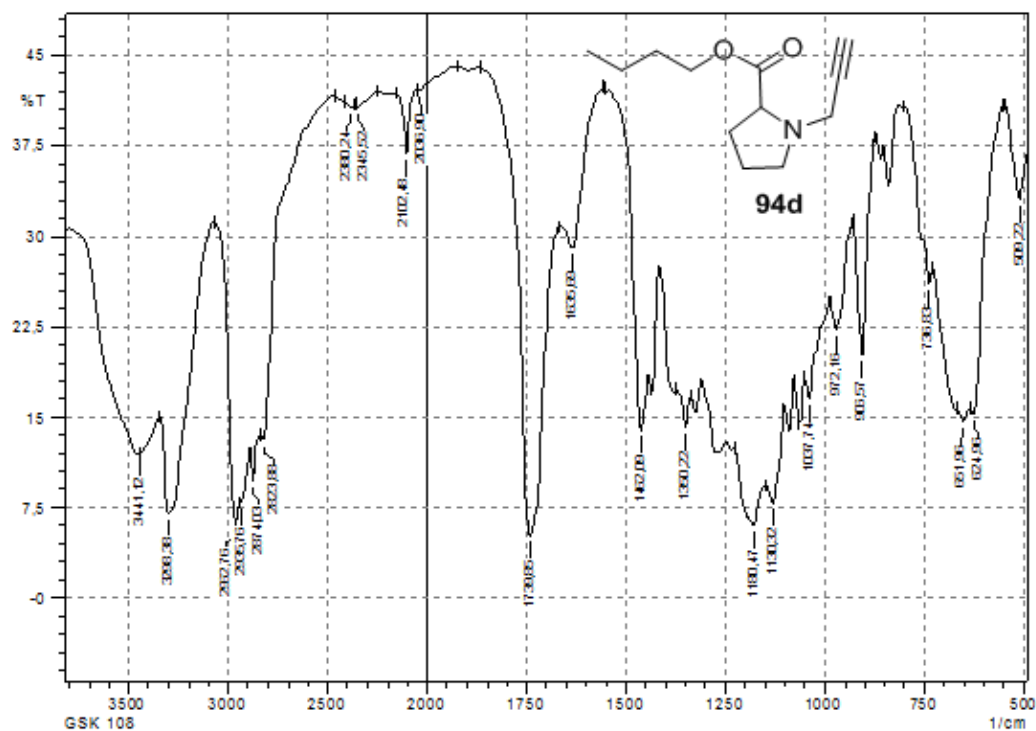


Figure 7. 12. IR spectrum of compound 94d

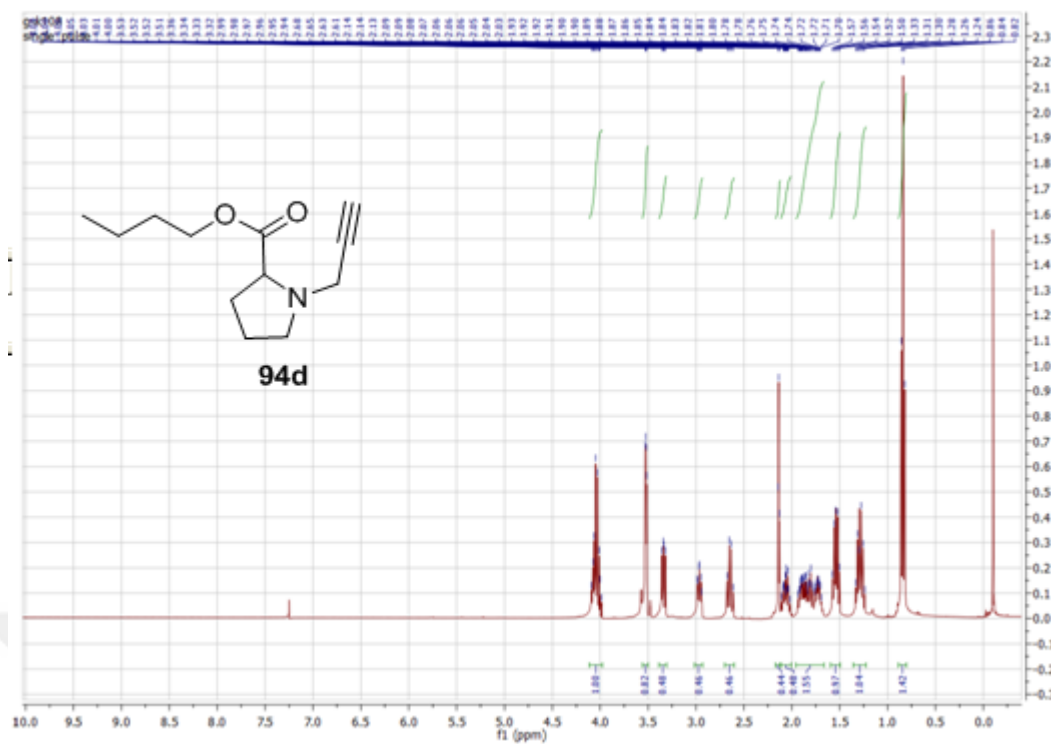


Figure 7. 13. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **94d**

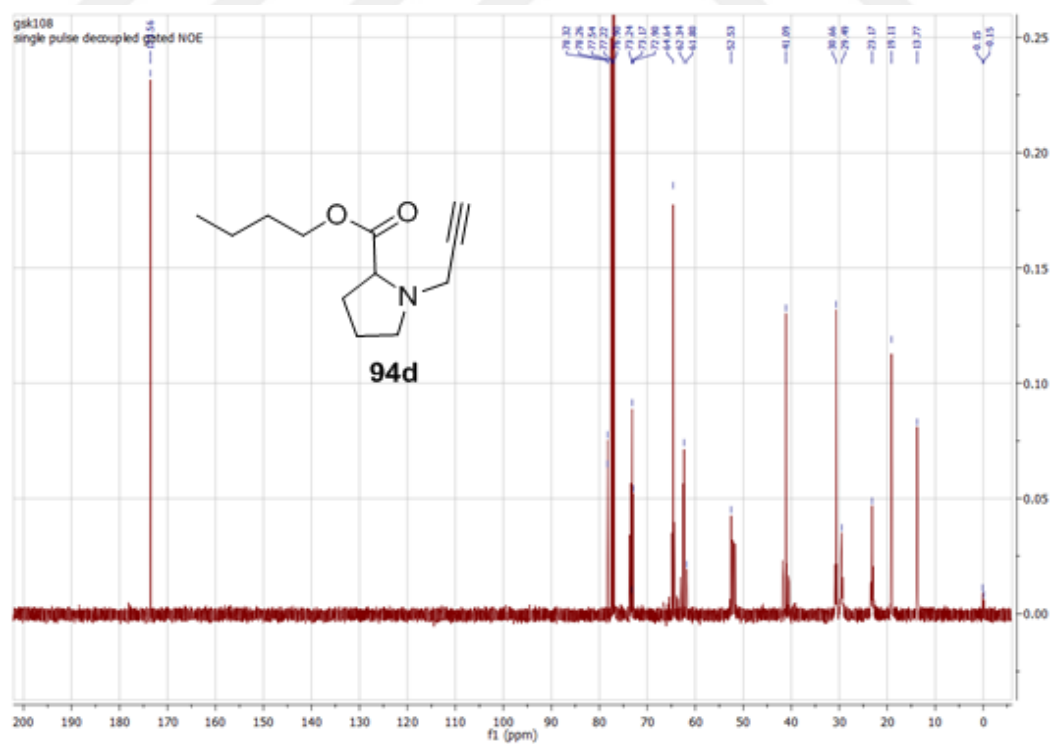


Figure 7. 14. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) spectrum of compound **94d**

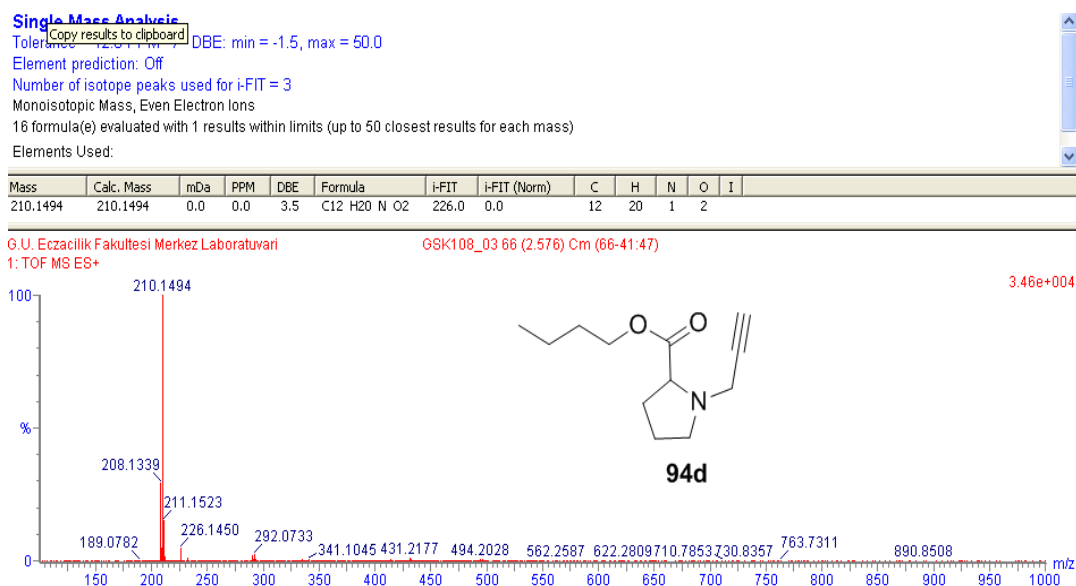


**Figure 7. 15. HRMS spectrum of compound 94d**

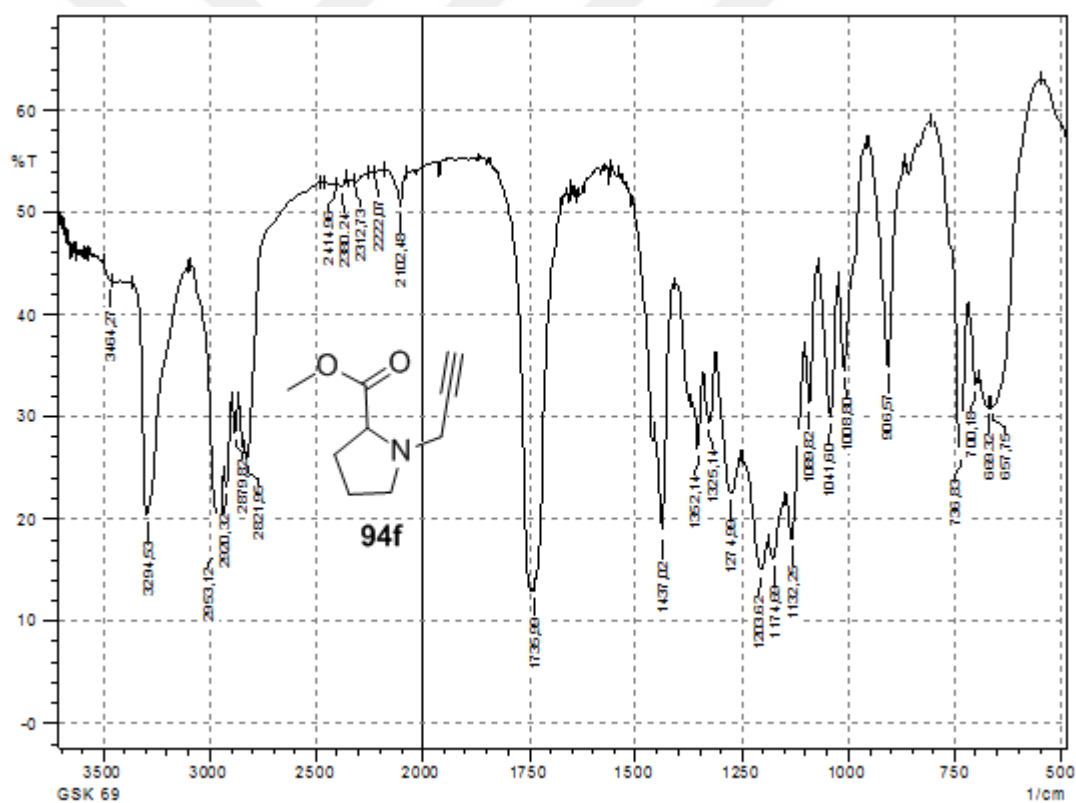


**Figure 7. 16. IR spectrum of compound 94f**

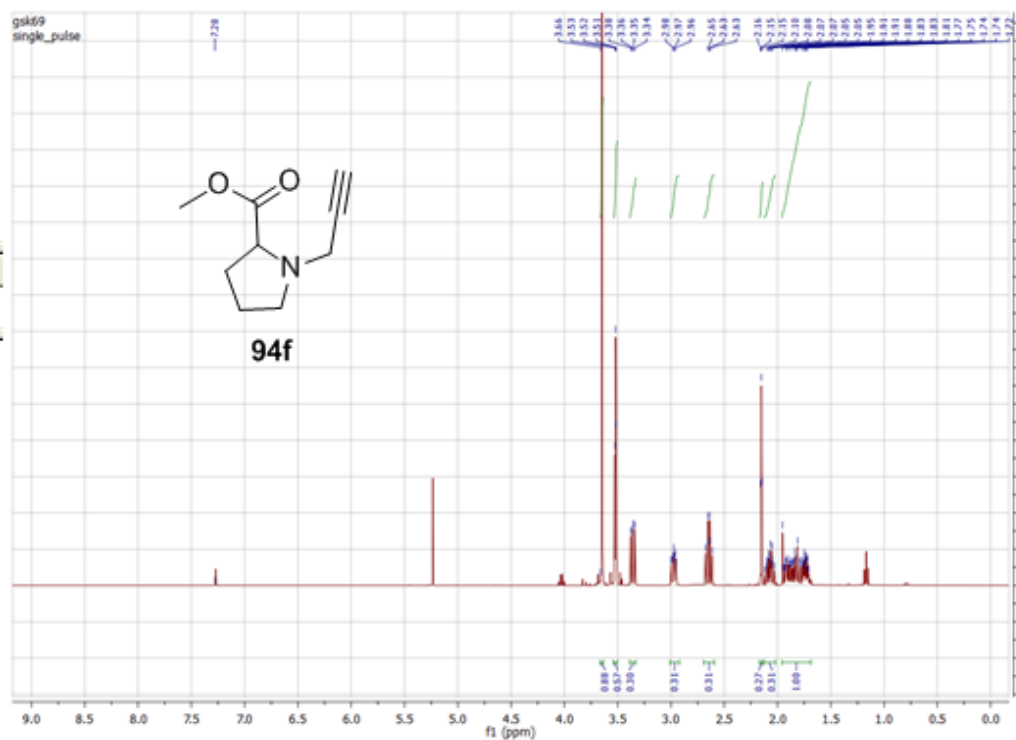


**Figure 7. 17.**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound **94f**

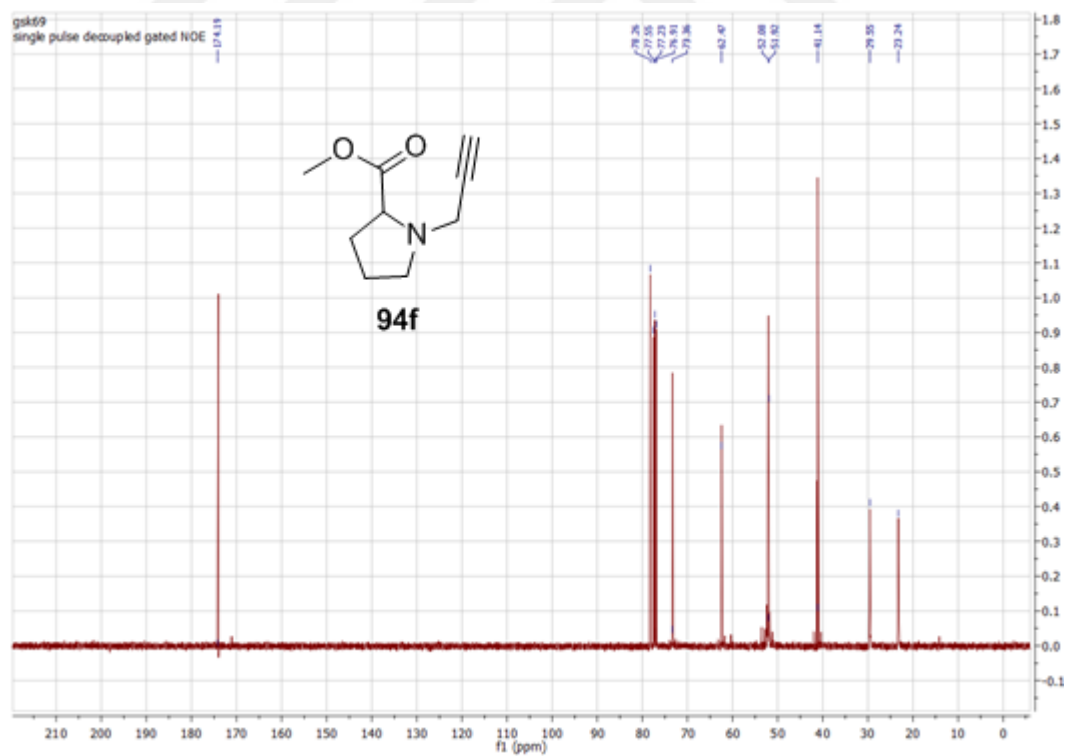


**Figure 7. 18.**  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **94f**

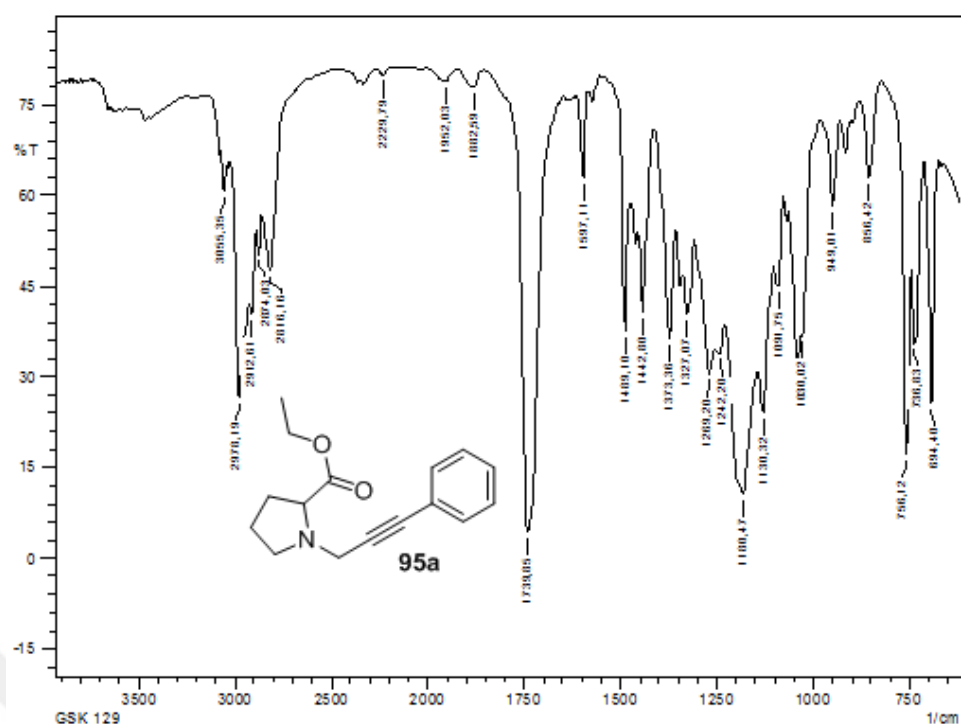


Figure 7. 19. IR spectrum of compound 95a

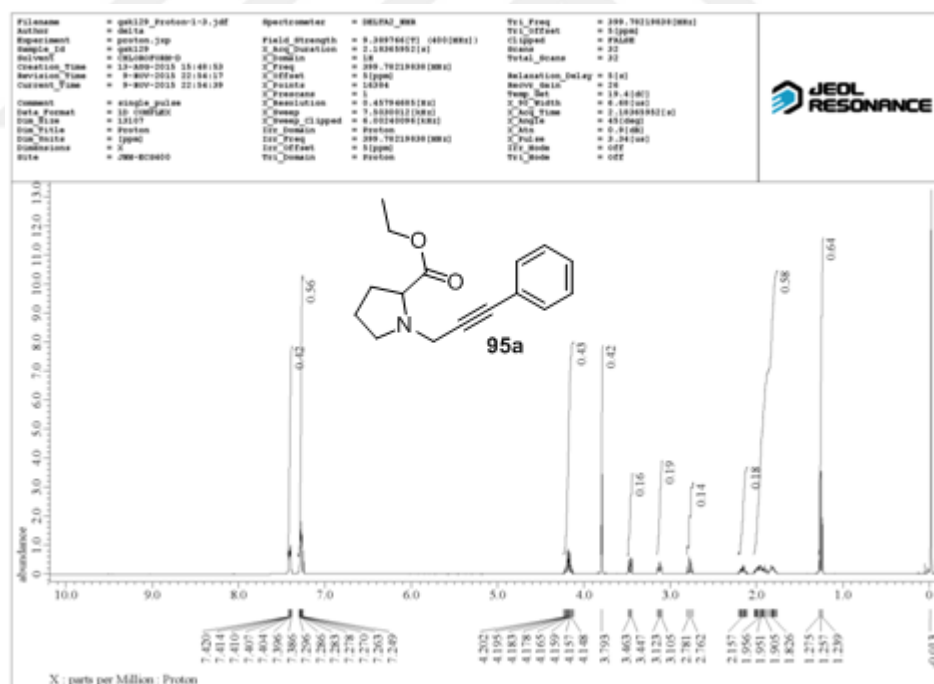


Figure 7. 20. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound 95a

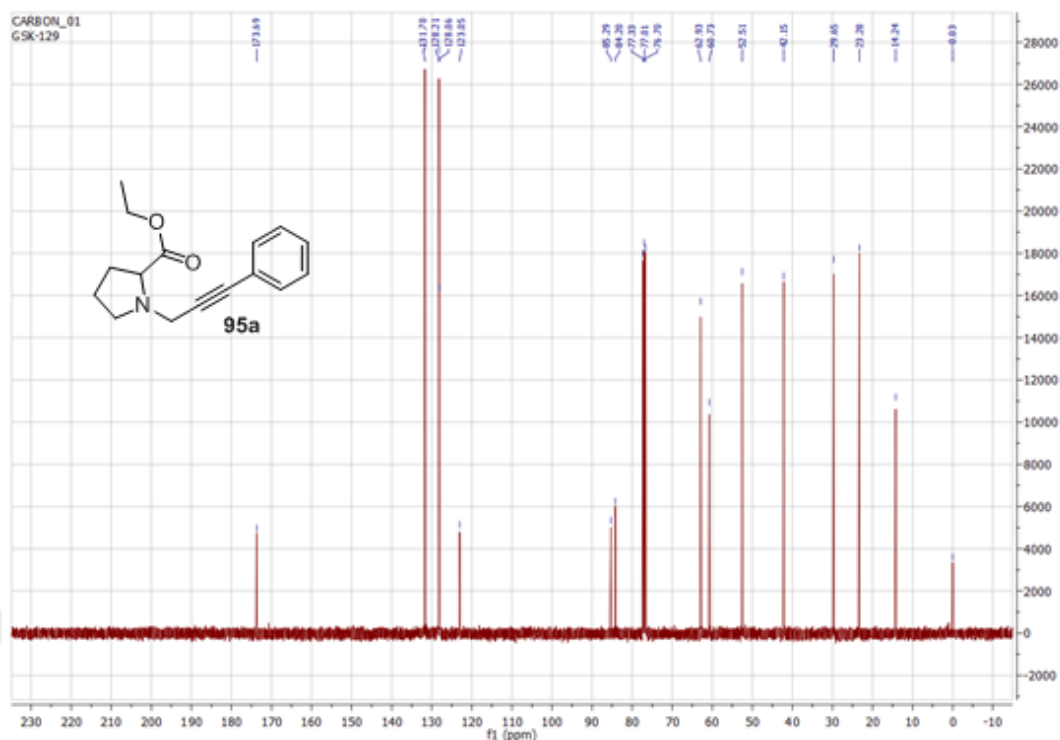


**Figure 7. 21.**  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **95a**

#### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

93 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula                                        | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|------------------------------------------------|-------|--------------|----|----|---|---|
| 258.1496 | 258.1494   | 0.2 | 0.8 | 7.5 | $\text{C}_{16}\text{H}_{20}\text{N}\text{O}_2$ | 172.0 | 0.0          | 16 | 20 | 1 | 2 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

GSK-129\_01 300 (3.038)

1: TOF MS ES+

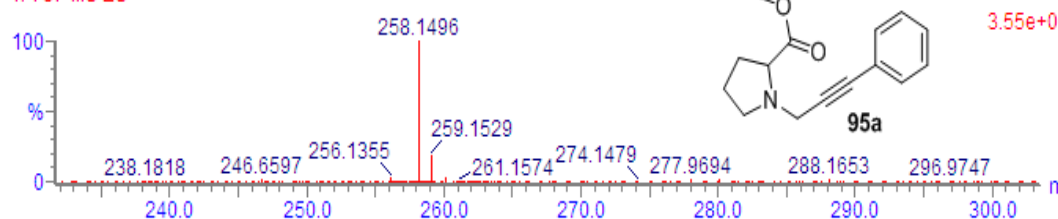


**Figure 7. 22.** HRMS spectrum of compound **95a**

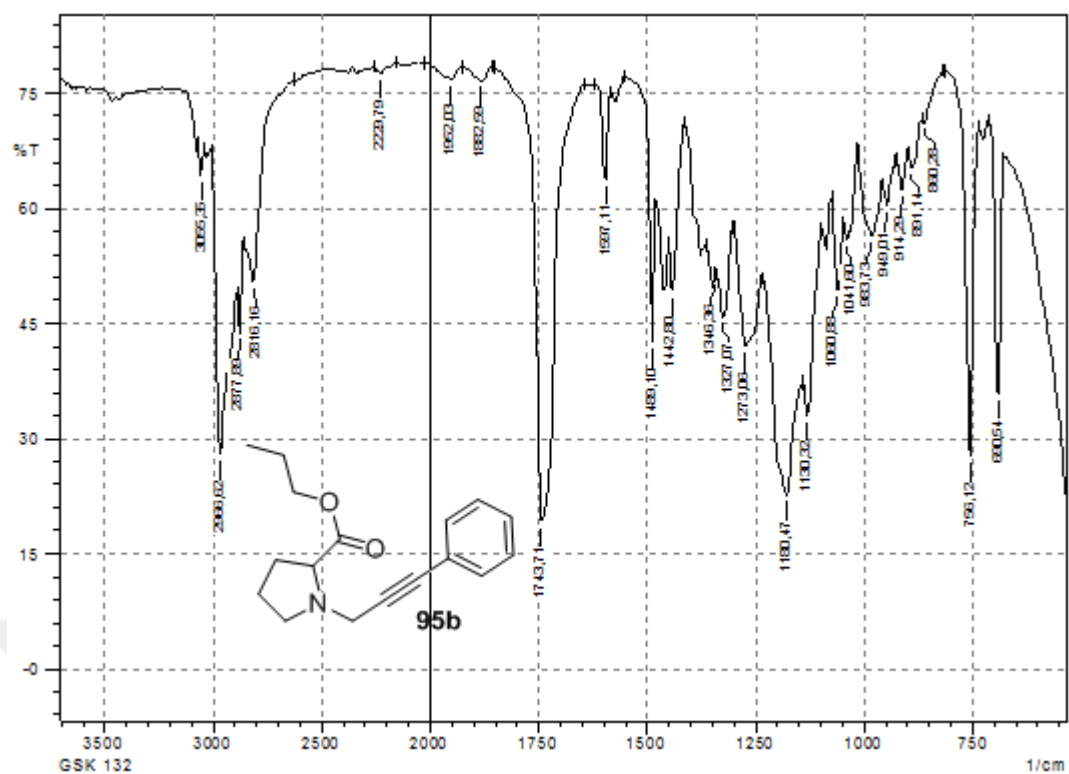


Figure 7. 23. IR spectrum of compound **95b**

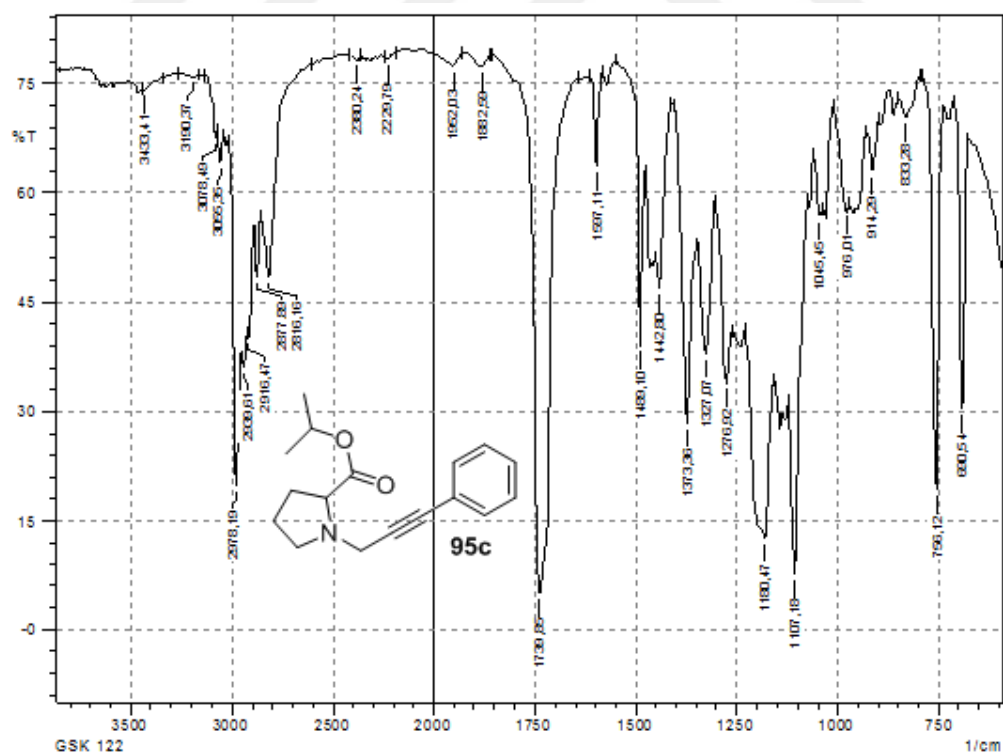


Figure 7. 24. IR spectrum of compound **95c**

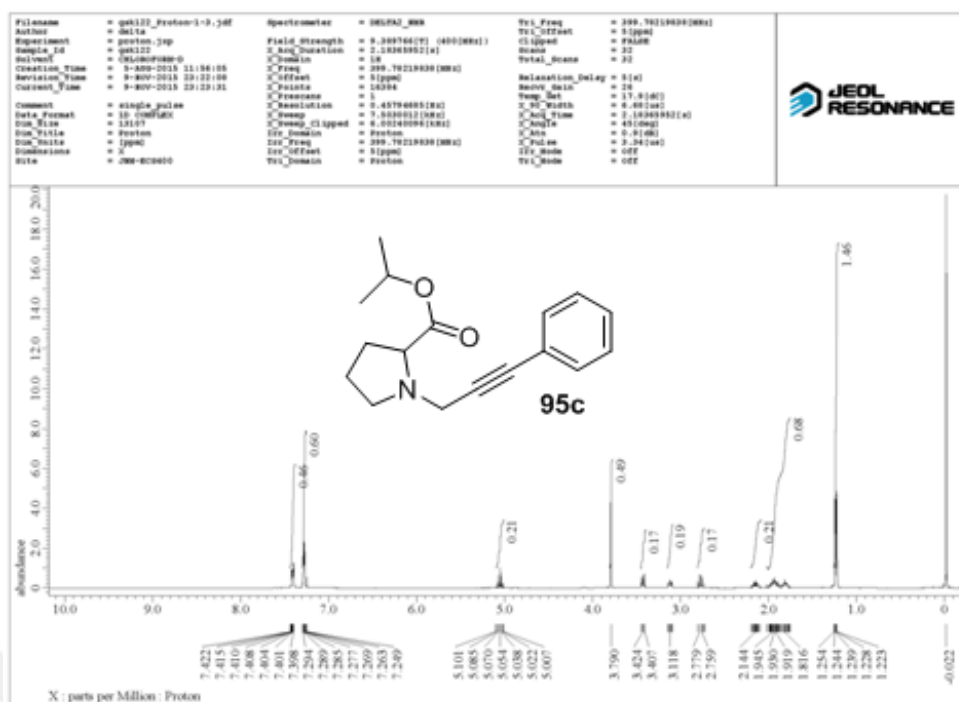


Figure 7. 25. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound 95c

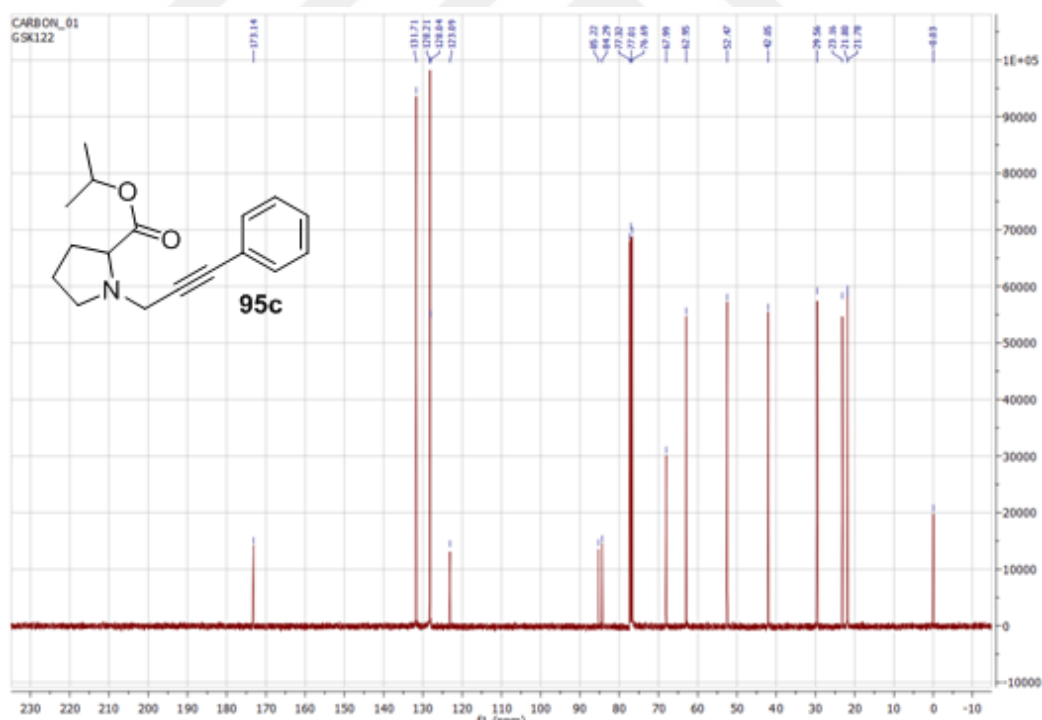


Figure 7. 26. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) spectrum of compound 95c

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

97 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa  | PPM  | DBE | Formula                                                       | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|------|------|-----|---------------------------------------------------------------|-------|--------------|----|----|---|---|
| 272.1649 | 272.1651   | -0.2 | -0.7 | 7.5 | C <sub>17</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> | 582.9 | 0.0          | 17 | 22 | 1 | 2 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+

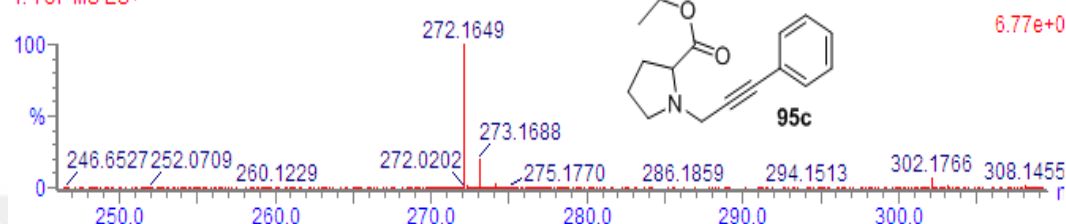


Figure 7. 27. HRMS spectrum of compound 95c

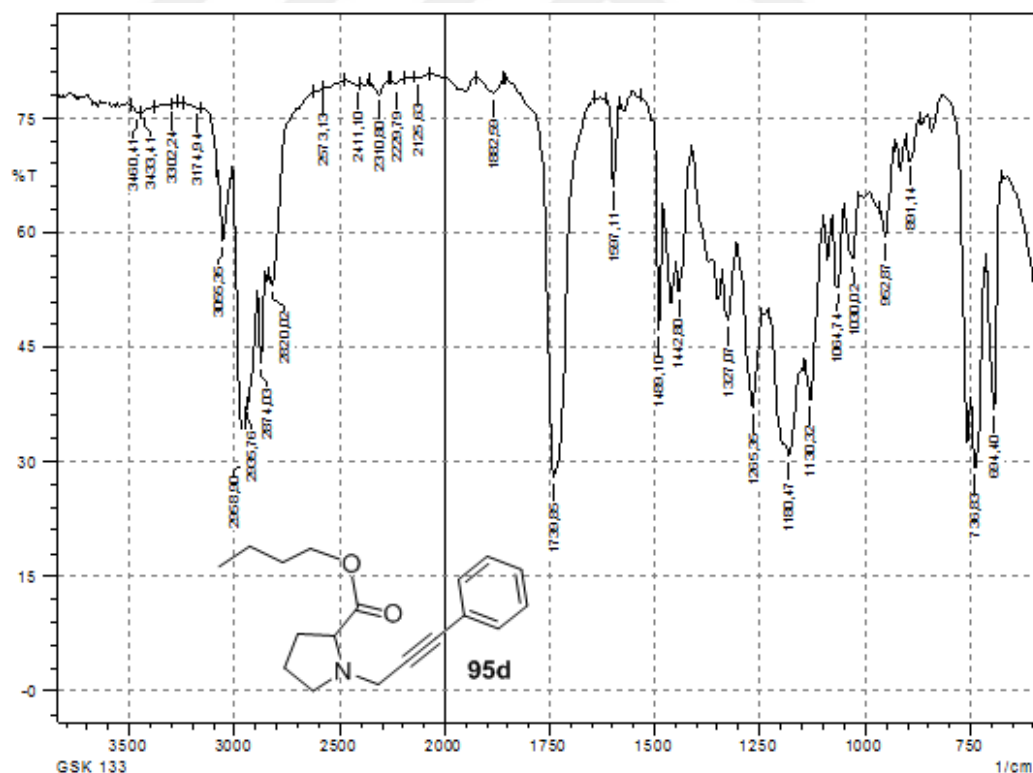


Figure 7. 28. IR spectrum of compound 95d

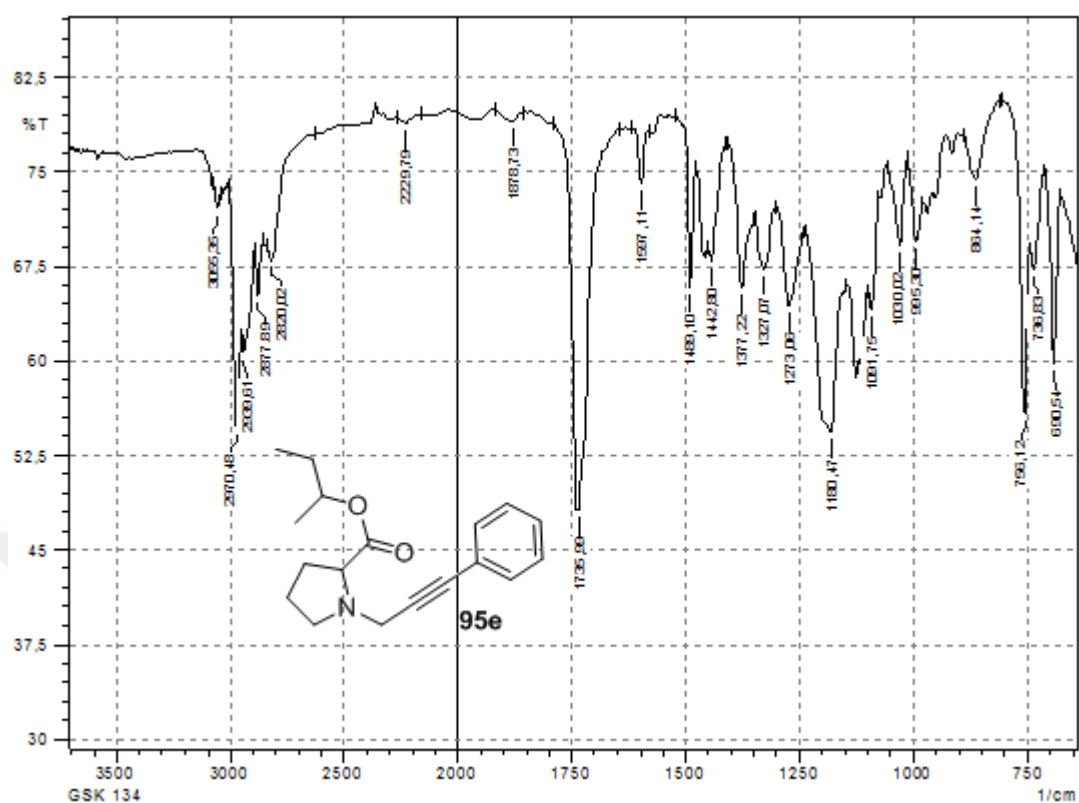


Figure 7. 29. IR spectrum of compound 95e

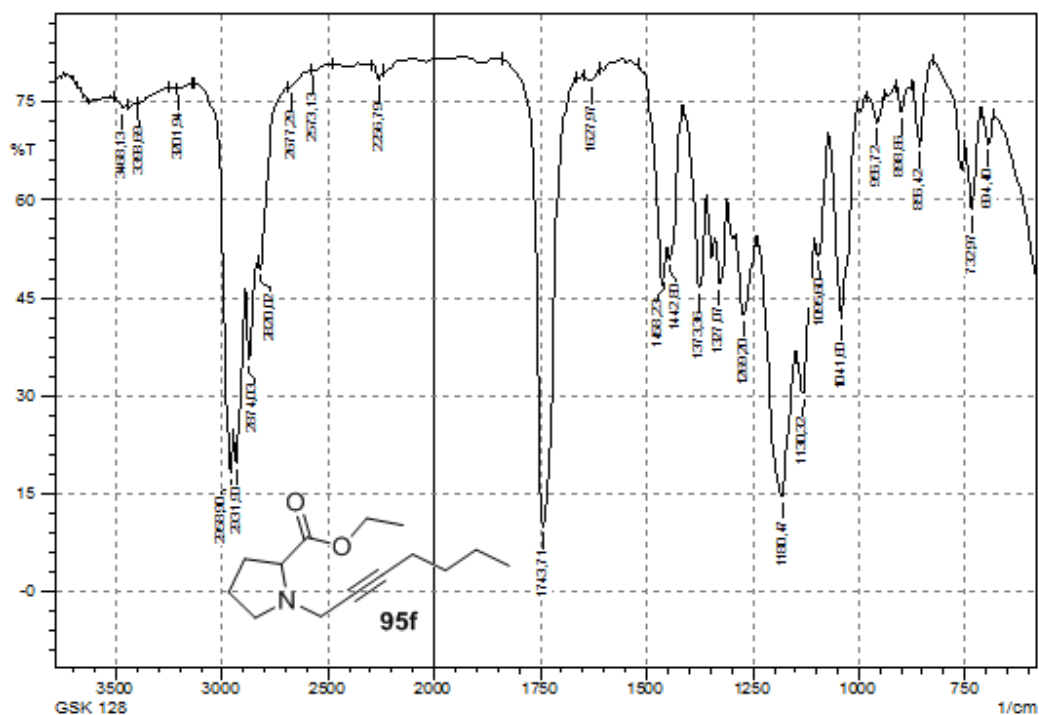
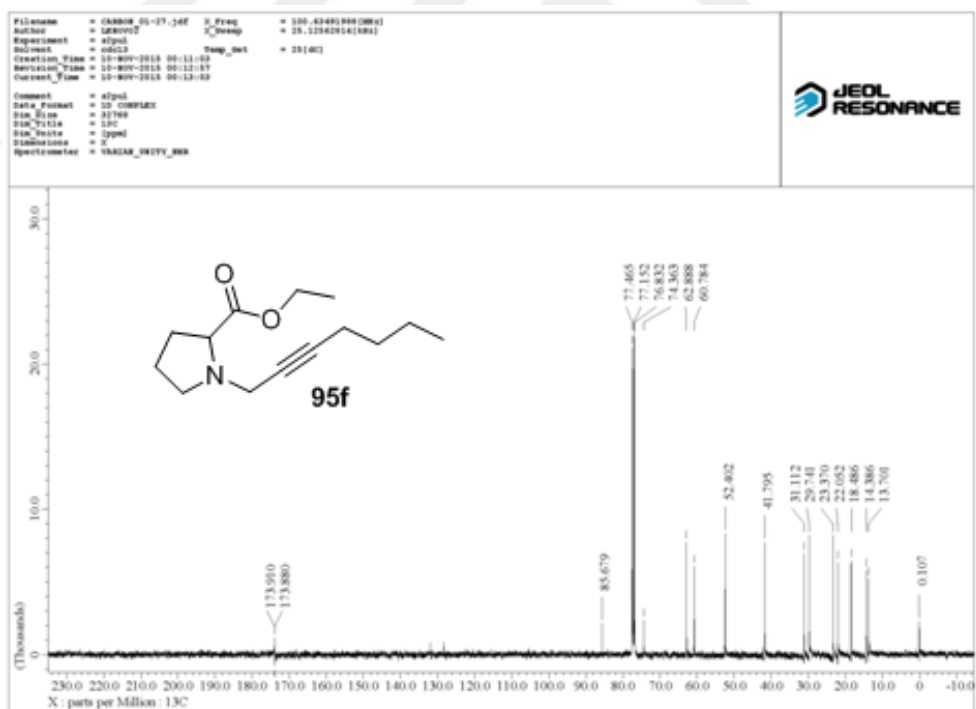
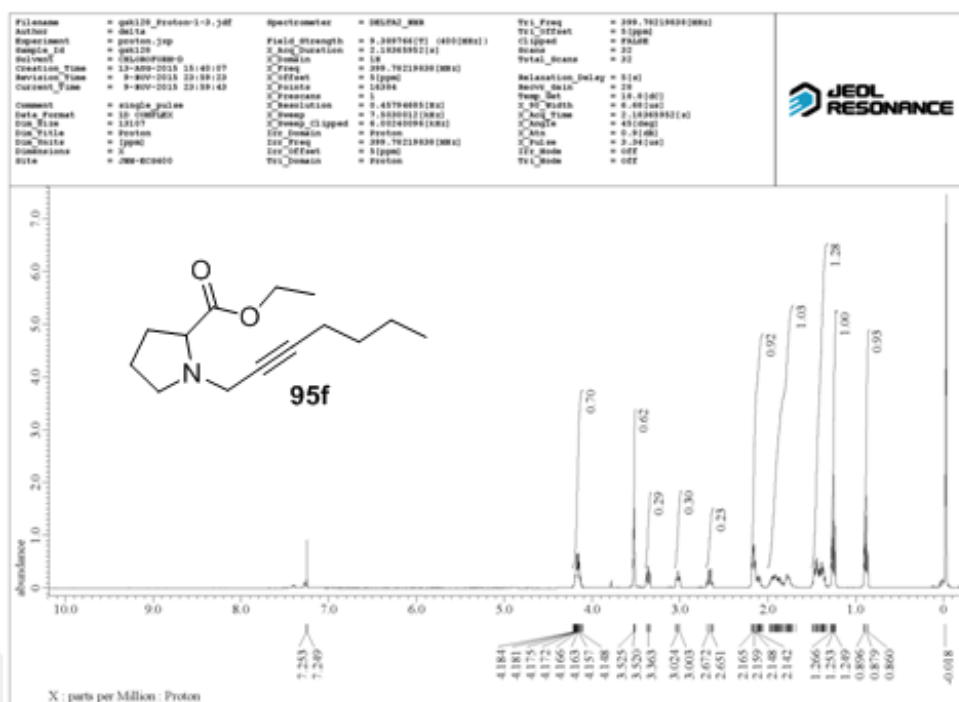


Figure 7. 30. IR spectrum of compound 95f



### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

89 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula                                          | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|--------------------------------------------------|-------|--------------|----|----|---|---|
| 238.1811 | 238.1807   | 0.4 | 1.7 | 3.5 | C <sub>14</sub> H <sub>24</sub> N O <sub>2</sub> | 338.0 | 0.0          | 14 | 24 | 1 | 2 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+

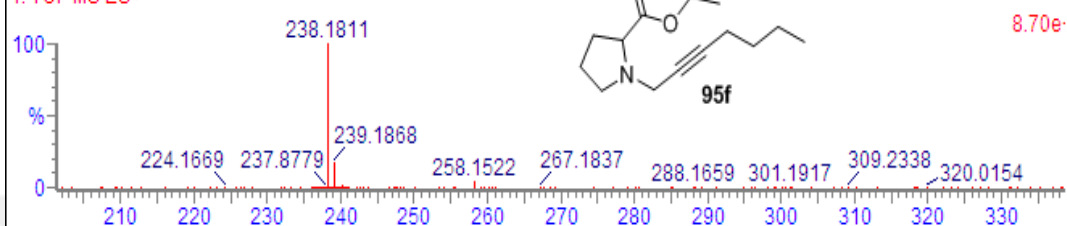


Figure 7. 33. HRMS spectrum of compound 95f

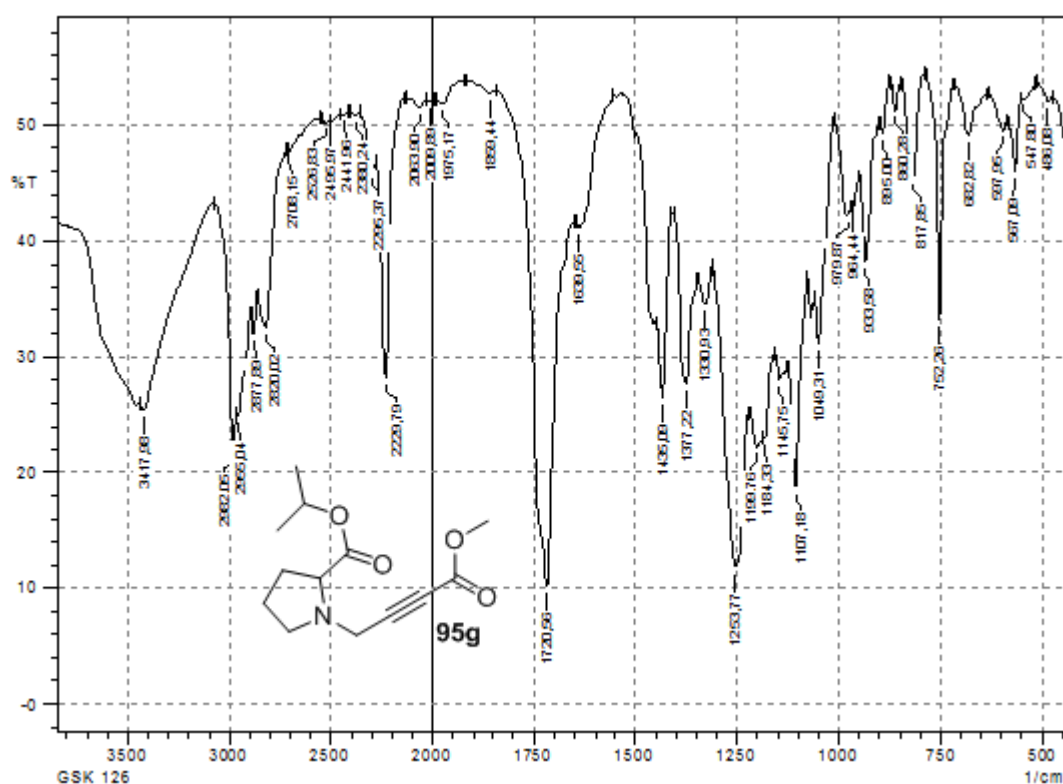


Figure 7. 34. IR spectrum of compound 95g

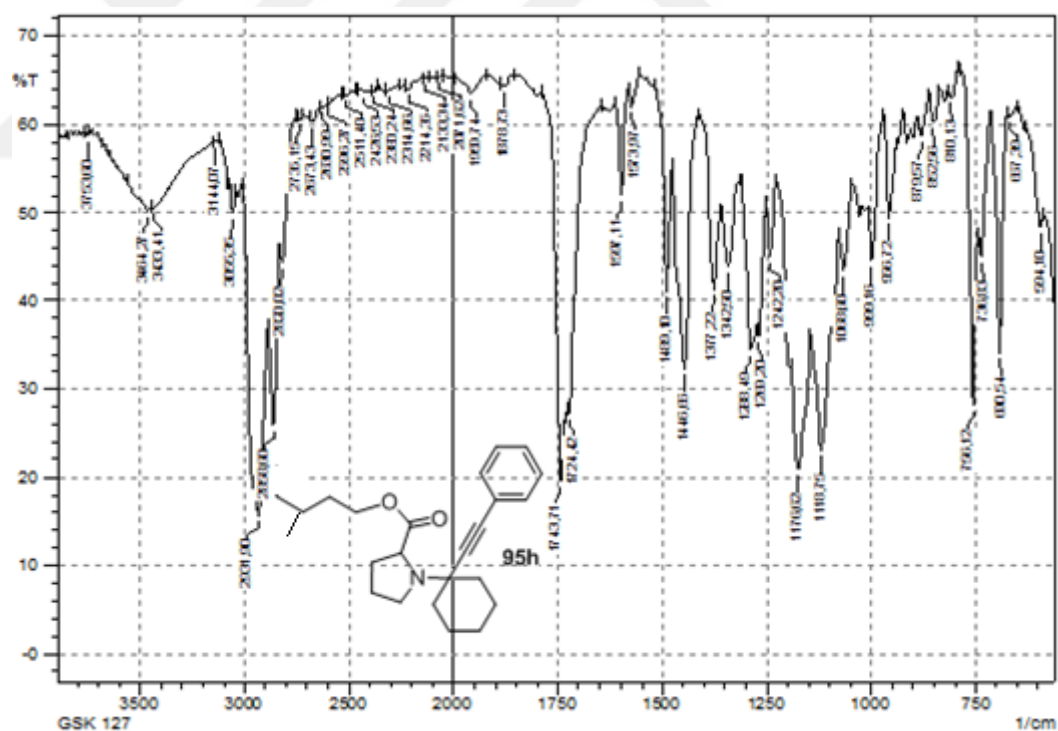
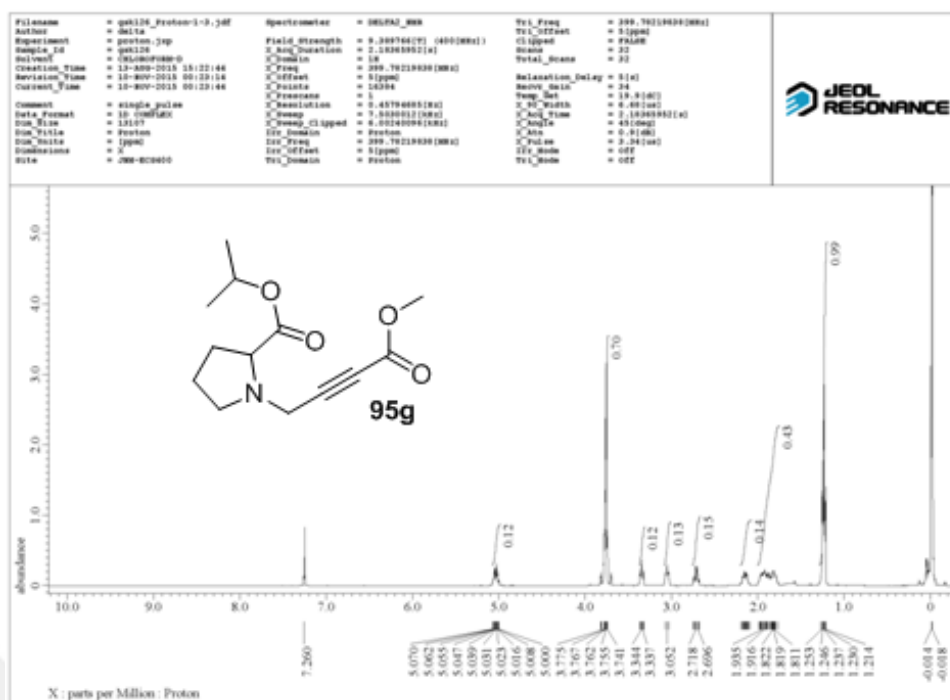


**Figure 7. 36.** IR spectrum of compound **95h**

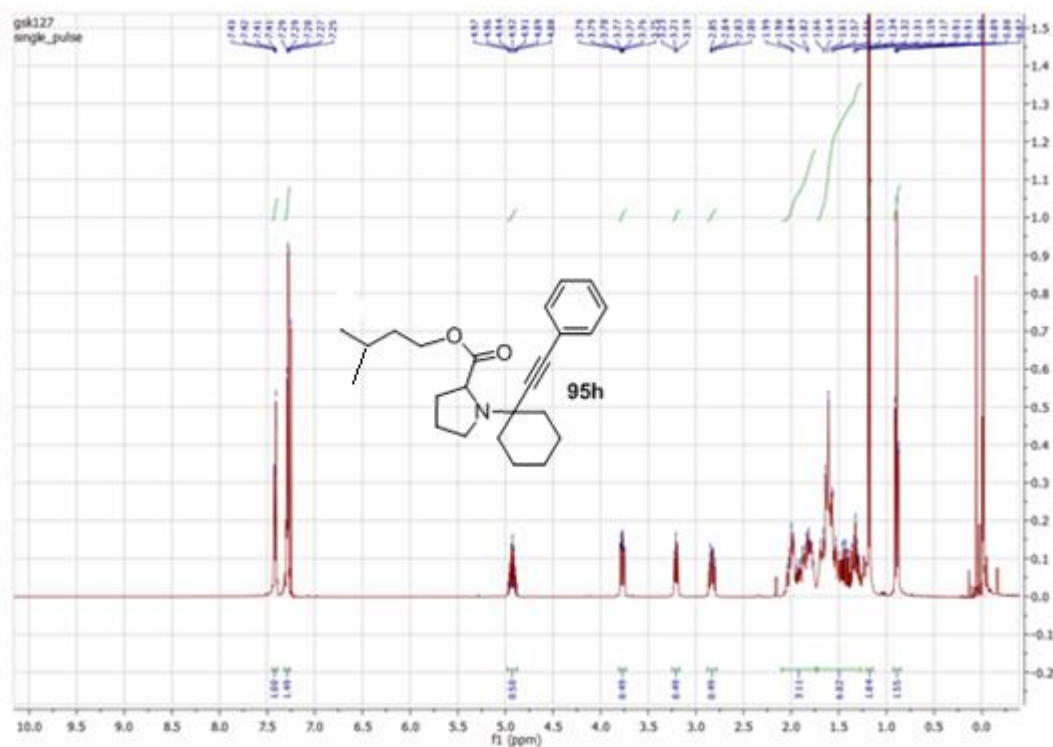


Figure 7. 37. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound 95h

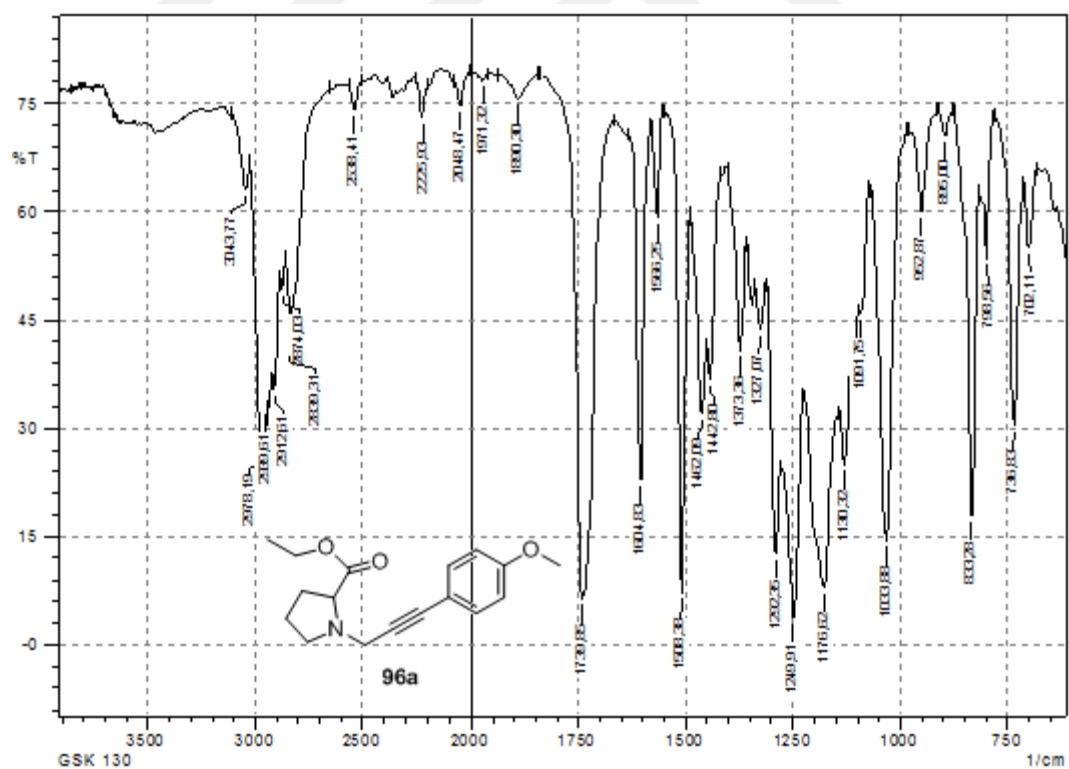


Figure 7. 38. IR spectrum of compound 96a

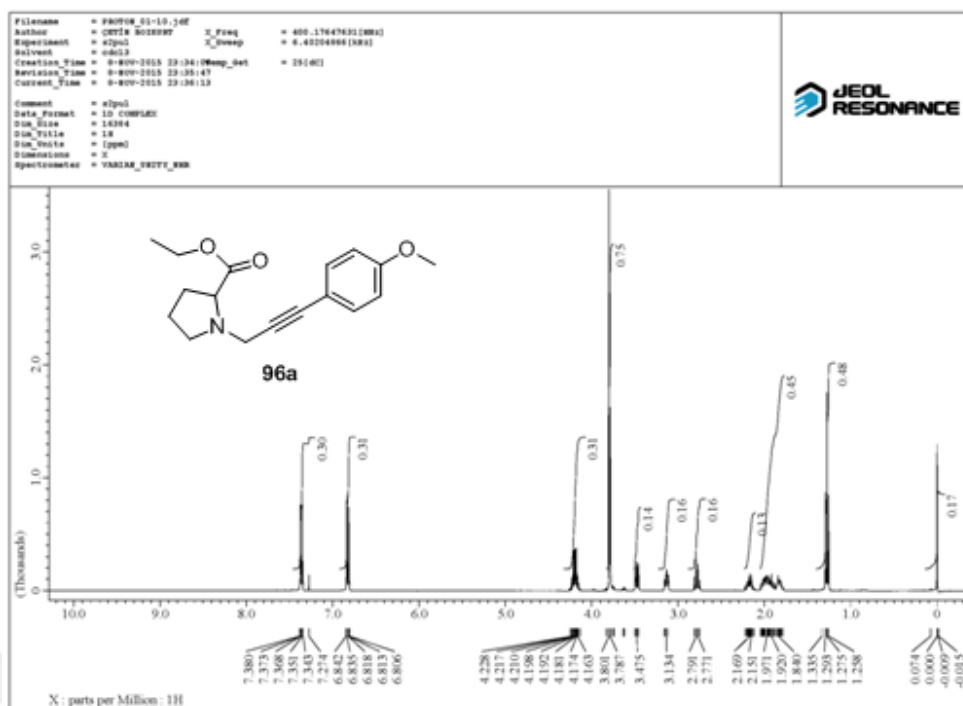


**Figure 7. 39.**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound **96a**

#### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

100 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula                                          | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|--------------------------------------------------|-------|--------------|----|----|---|---|
| 288.1602 | 288.1600   | 0.2 | 0.7 | 7.5 | C <sub>17</sub> H <sub>22</sub> N O <sub>3</sub> | 366.7 | 0.0          | 17 | 22 | 1 | 3 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+

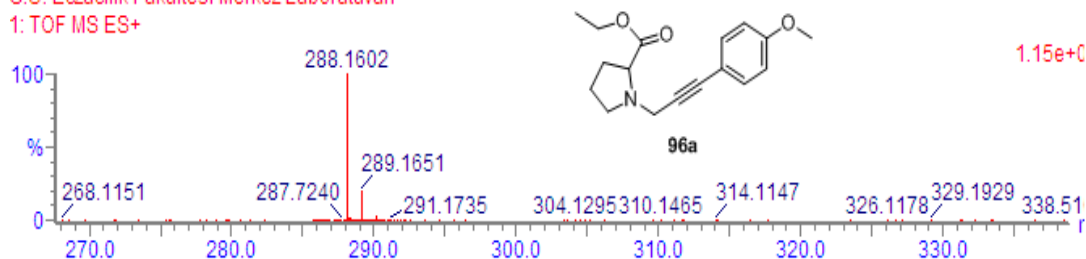


**Figure 7. 40.** HRMS spectrum of compound **96a**

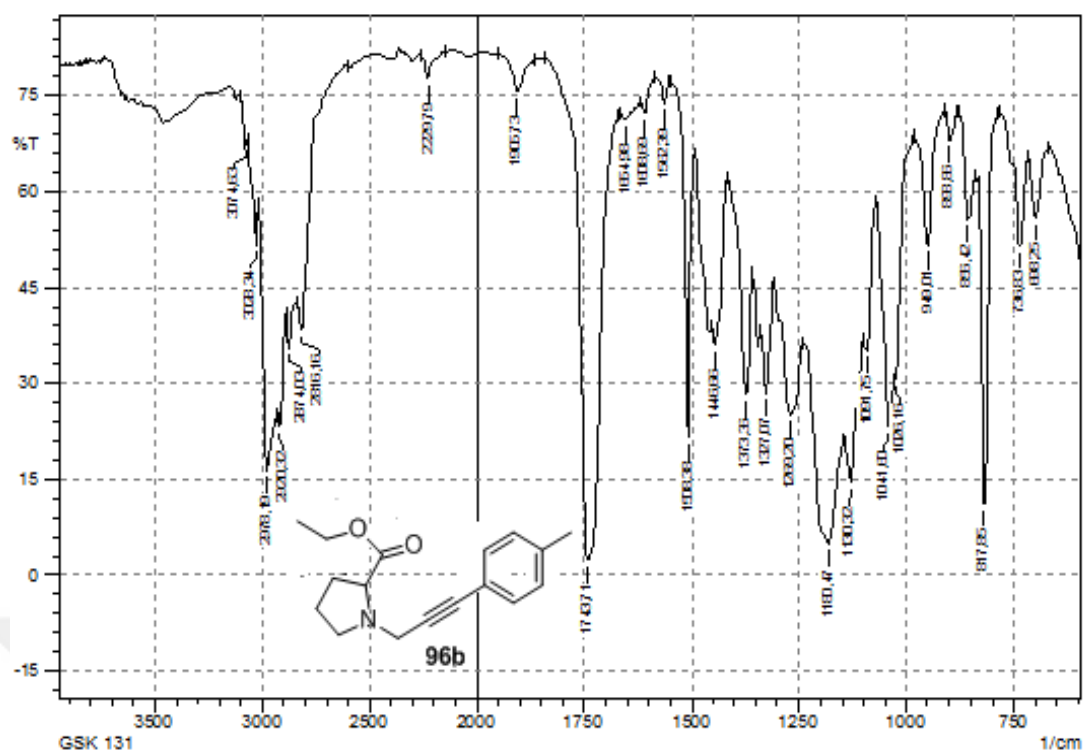


Figure 7. 41. IR spectrum of compound **96b**

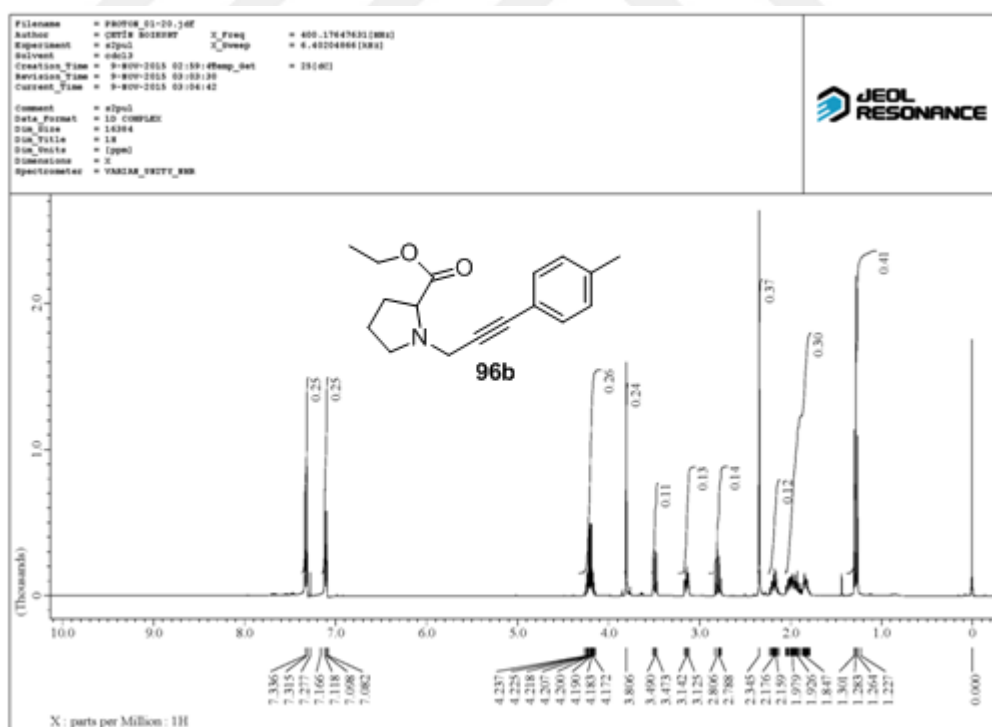


Figure 7. 42. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **96b**

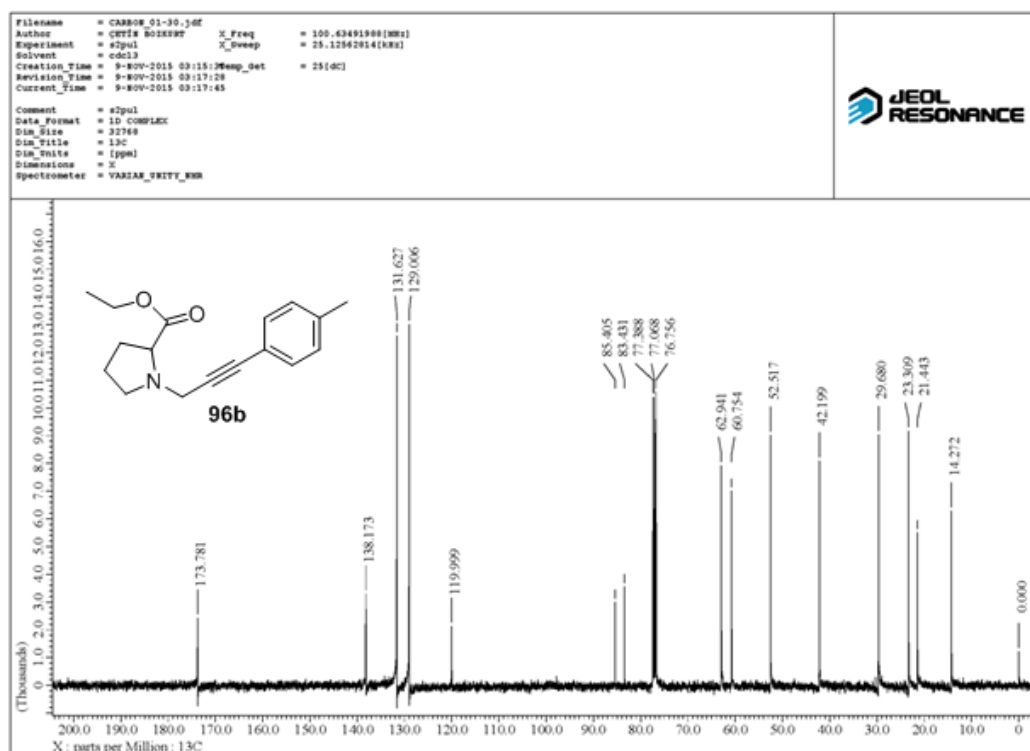


Figure 7. 43.  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound 96b

#### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

97 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula                                                       | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|---------------------------------------------------------------|-------|--------------|----|----|---|---|
| 272.1660 | 272.1651   | 0.9 | 3.3 | 7.5 | C <sub>17</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> | 310.8 | 0.0          | 17 | 22 | 1 | 2 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+

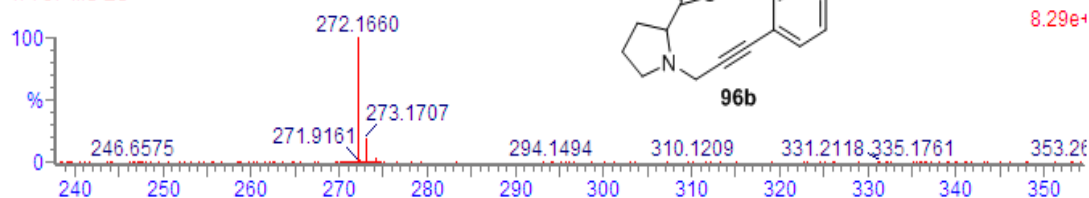


Figure 7. 44. HRMS spectrum of compound 96b

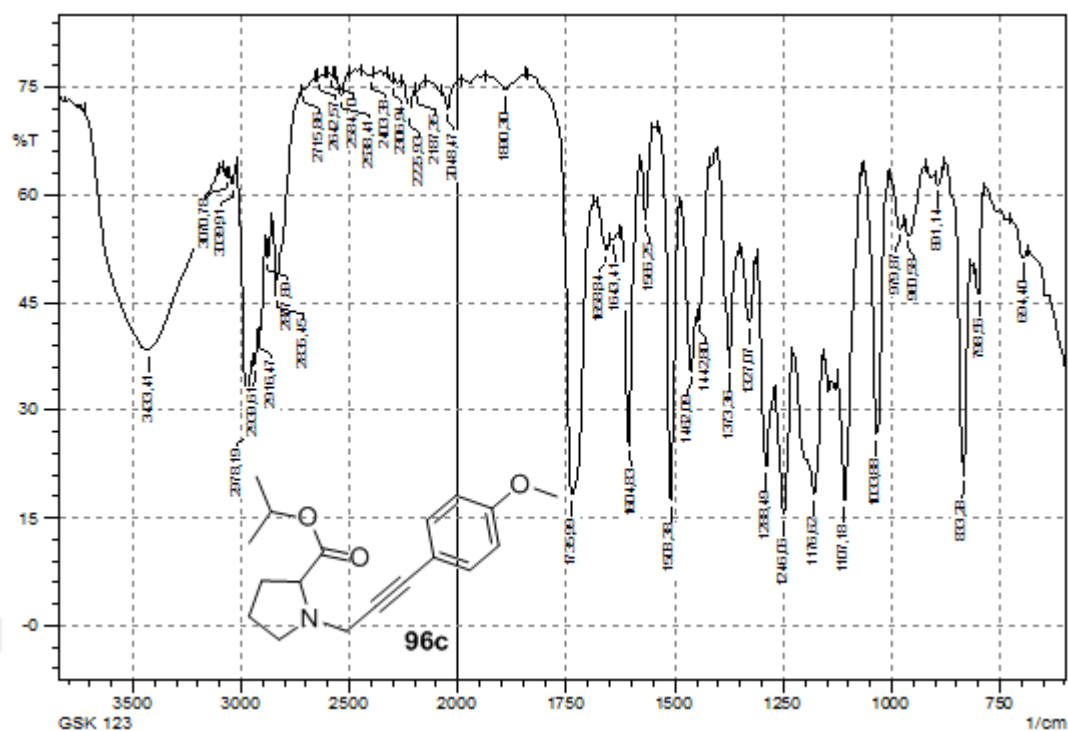


Figure 7. 45. IR spectrum of compound 96c

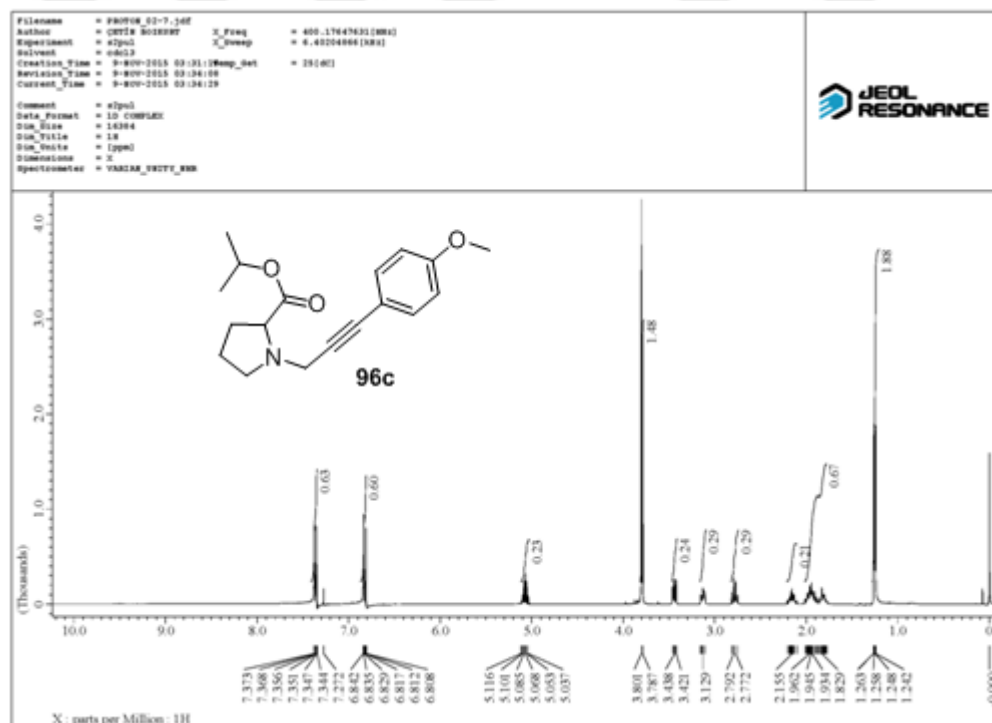


Figure 7. 46. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound 96c

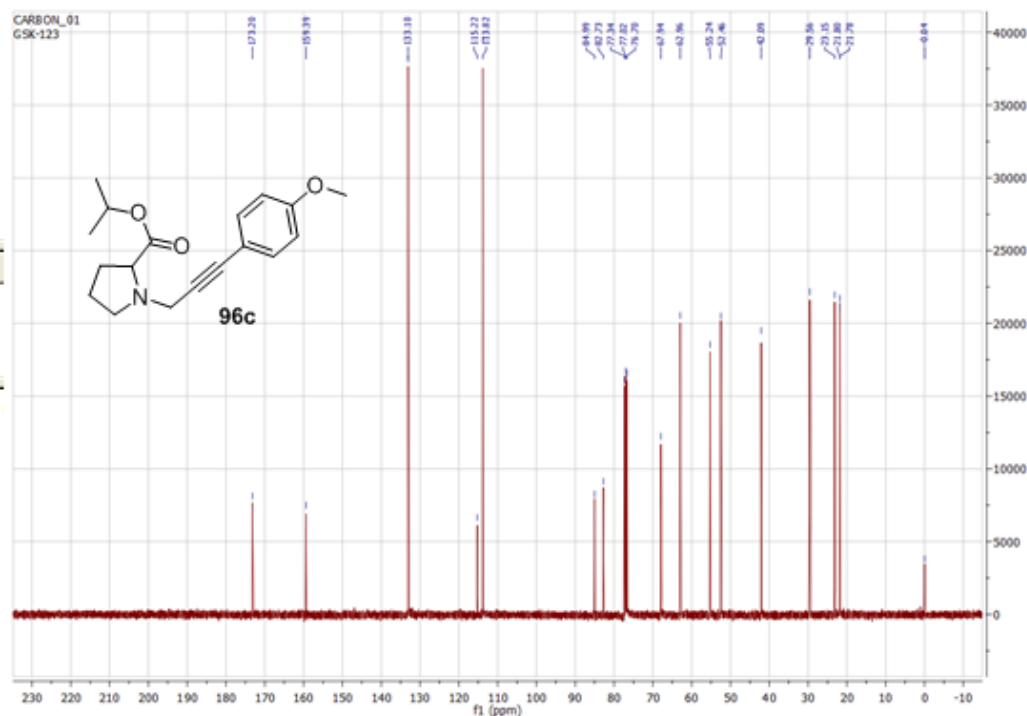


Figure 7. 47.  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **96c**

#### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

99 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula                                        | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|------------------------------------------------|-------|--------------|----|----|---|---|
| 302.1767 | 302.1756   | 1.1 | 3.6 | 7.5 | $\text{C}_{18}\text{H}_{24}\text{N}\text{O}_3$ | 225.2 | 0.0          | 18 | 24 | 1 | 3 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı  
1: TOF MS ES+

GSK-123\_01 325 (3.301)



Figure 7. 48. HRMS spectrum of compound **96c**

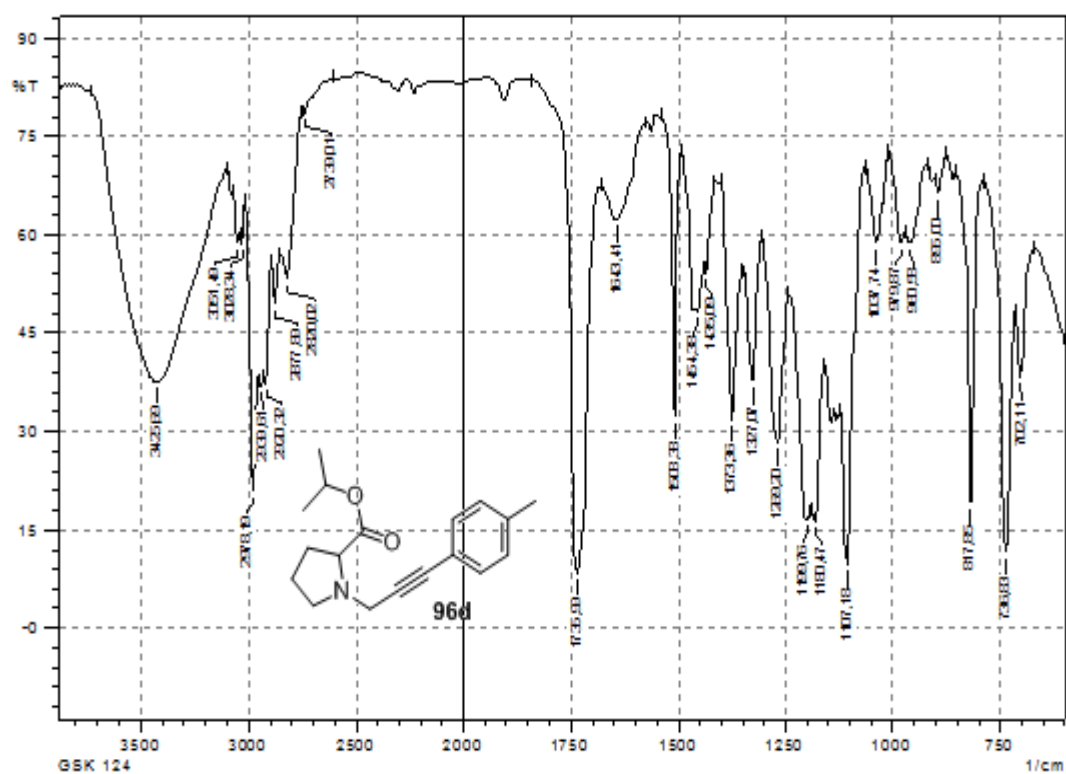


Figure 7. 49. IR spectrum of compound **96d**

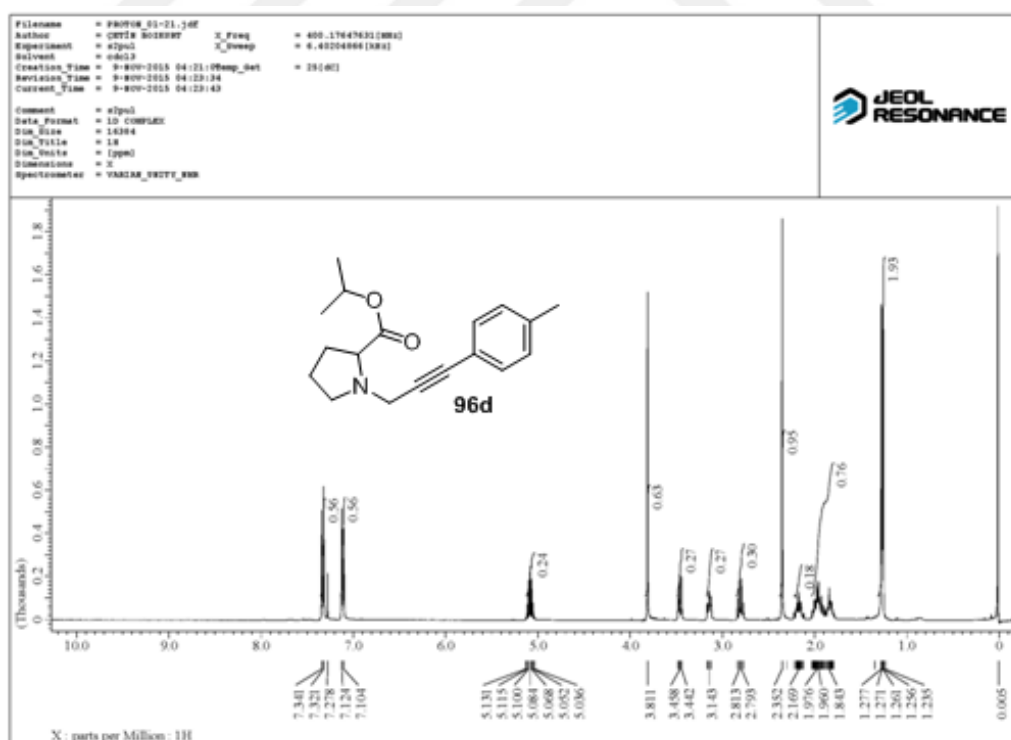


Figure 7. 50.  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound **96d**

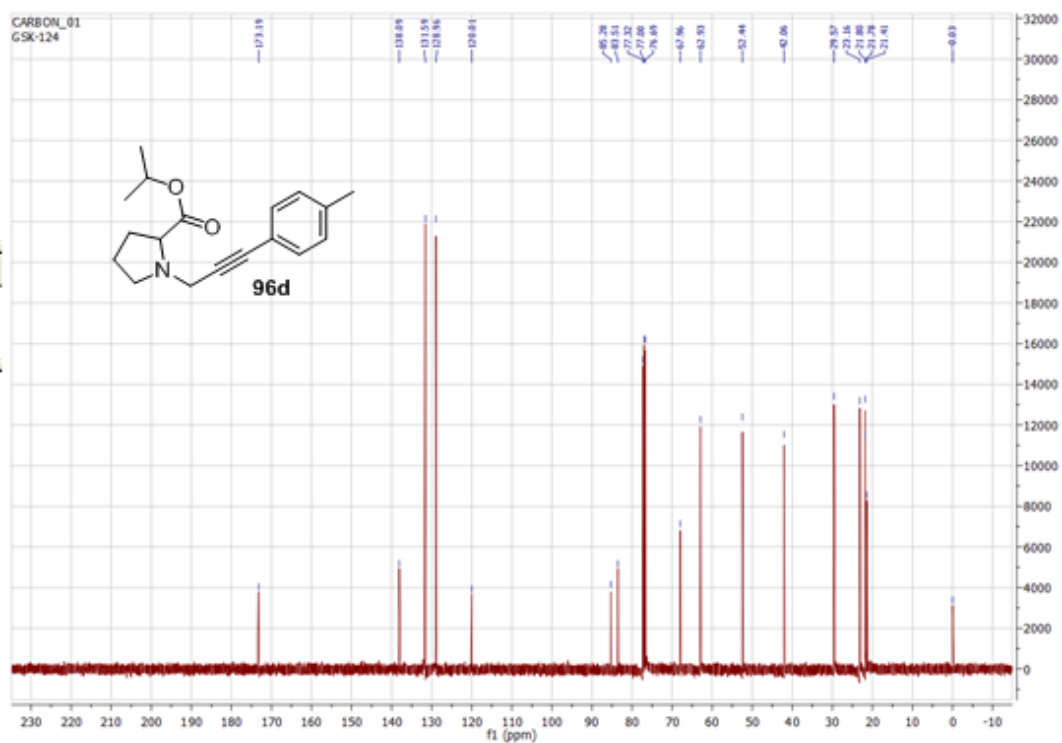


**Figure 7. 51.**  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **96d**

#### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

96 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula                                        | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|------------------------------------------------|-------|--------------|----|----|---|---|
| 286.1812 | 286.1807   | 0.5 | 1.7 | 7.5 | $\text{C}_{18}\text{H}_{24}\text{N}\text{O}_2$ | 327.1 | 0.0          | 18 | 24 | 1 | 2 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+

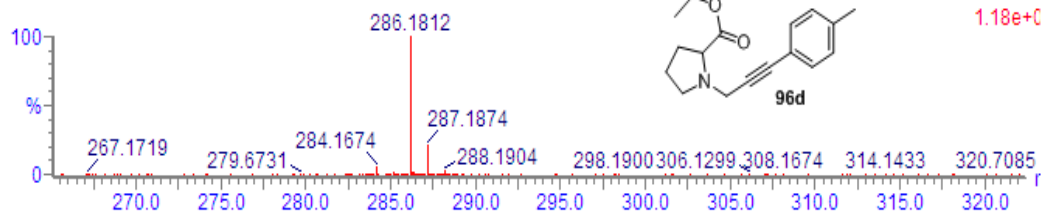


**Figure 7. 52.** HRMS spectrum of compound **96d**

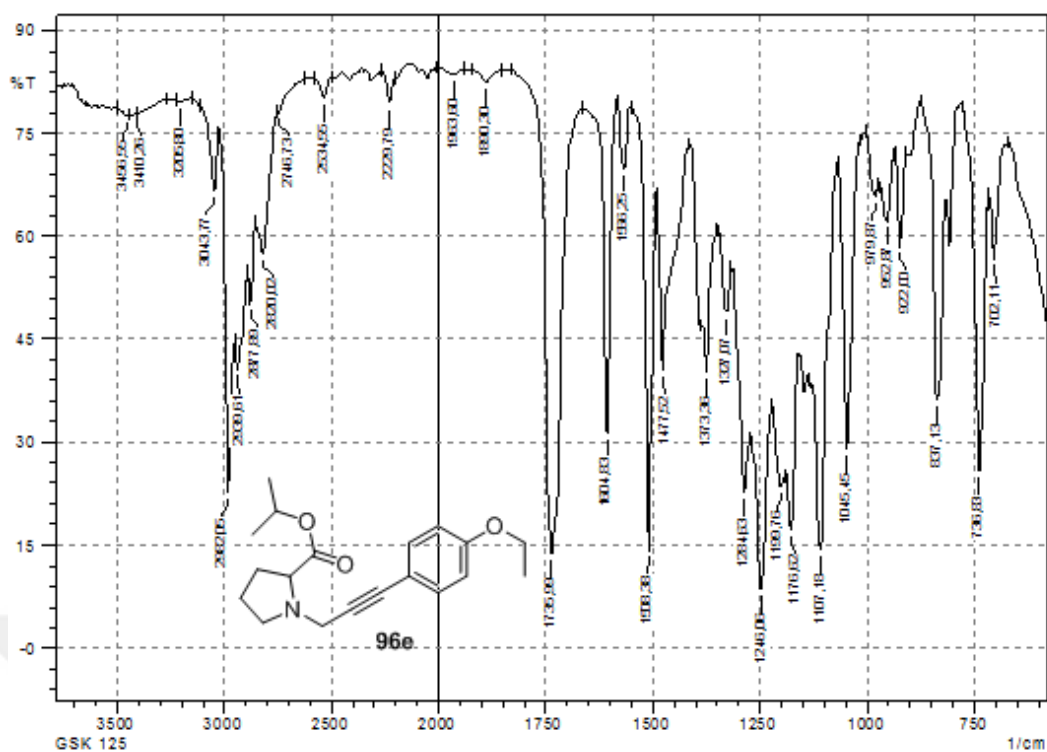


Figure 7. 53. IR spectrum of compound **96e**

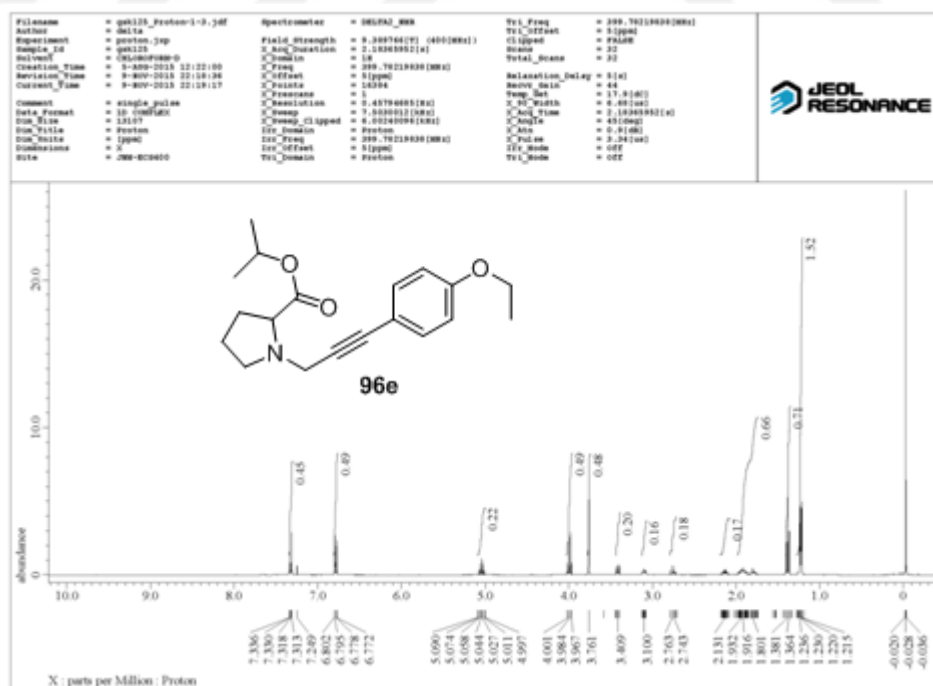


Figure 7. 54. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **96e**



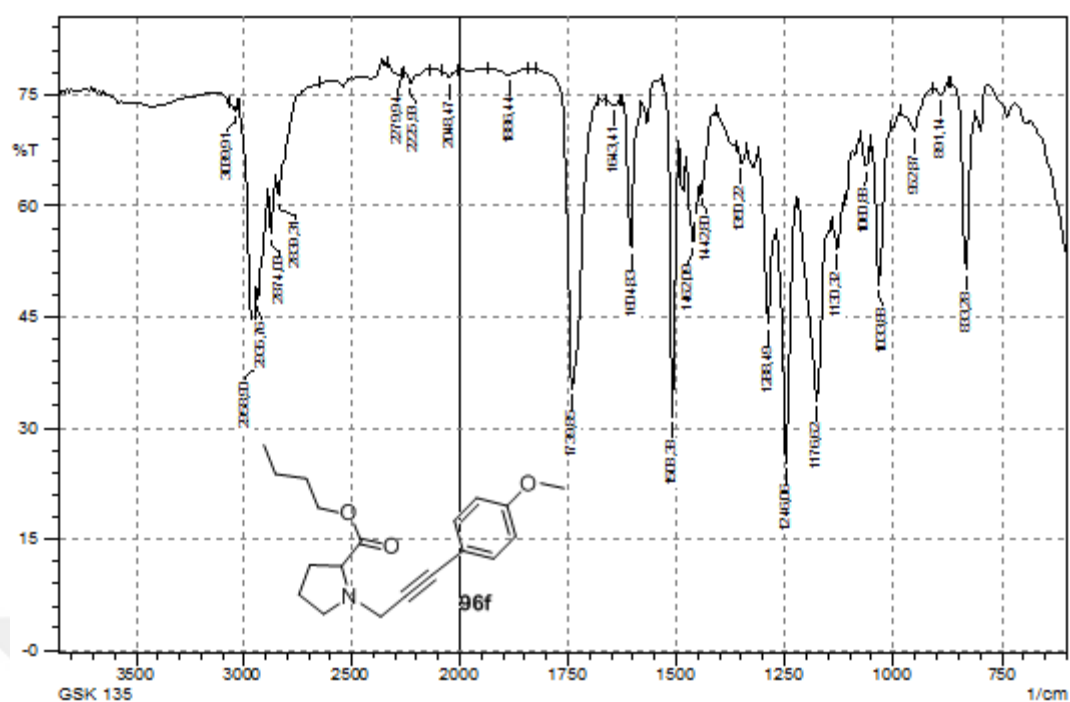


Figure 7. 57. IR spectrum of compound 96f

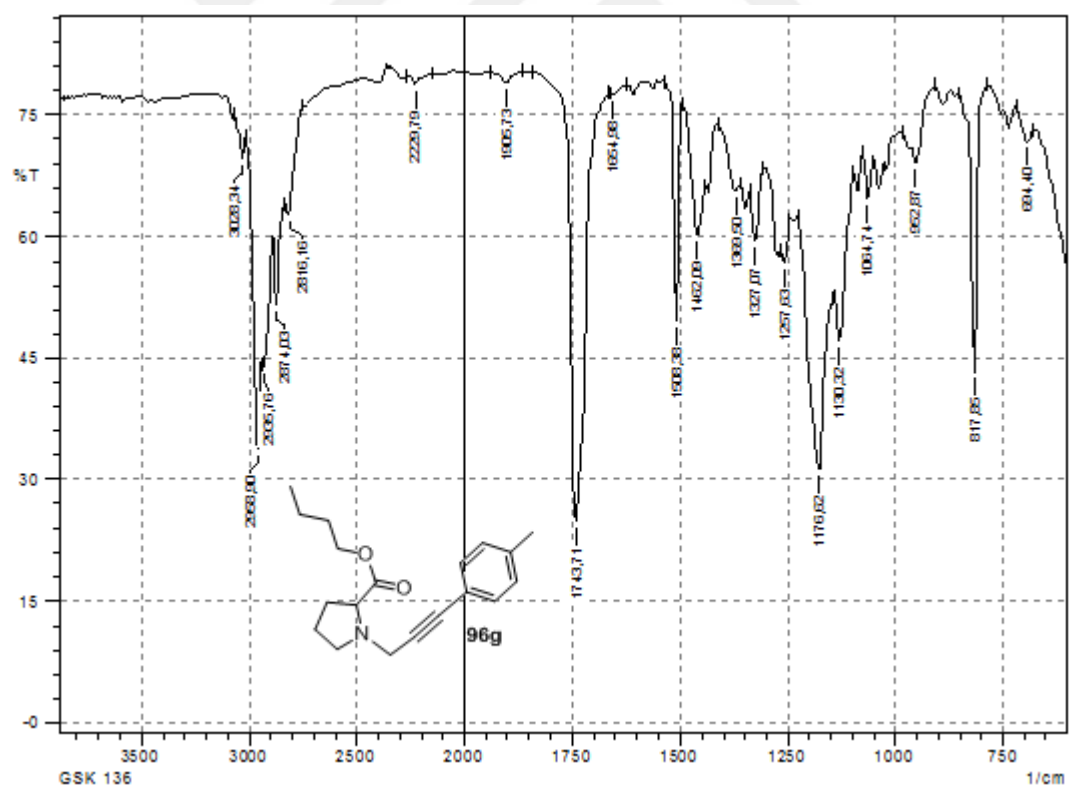


Figure 7. 58. IR spectrum of compound 96g

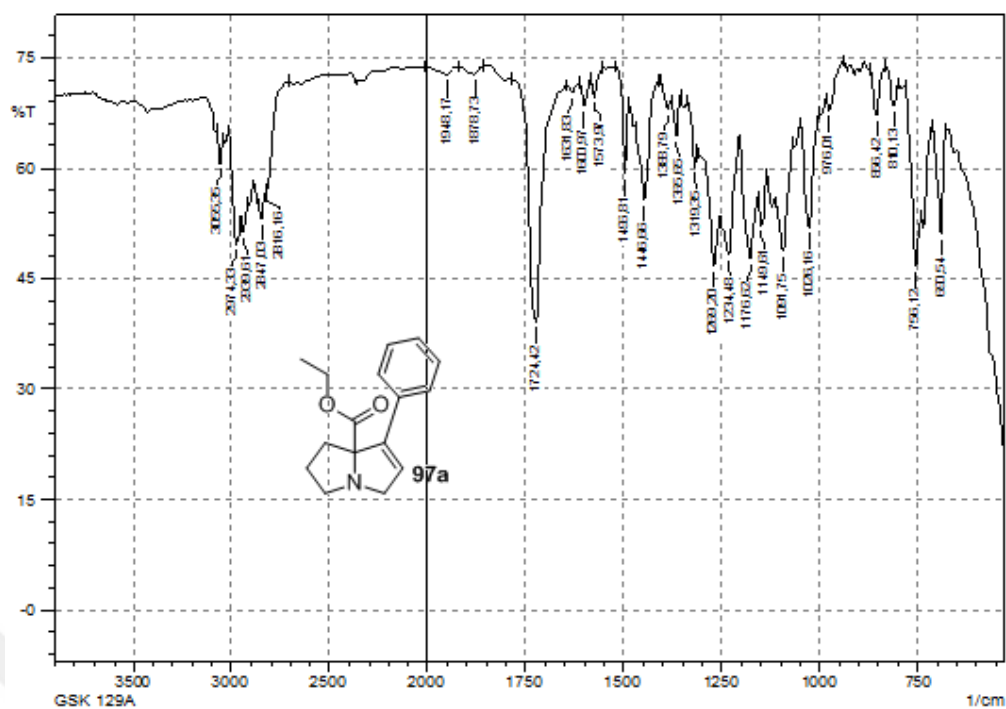


Figure 7. 59. IR spectrum of compound 97a

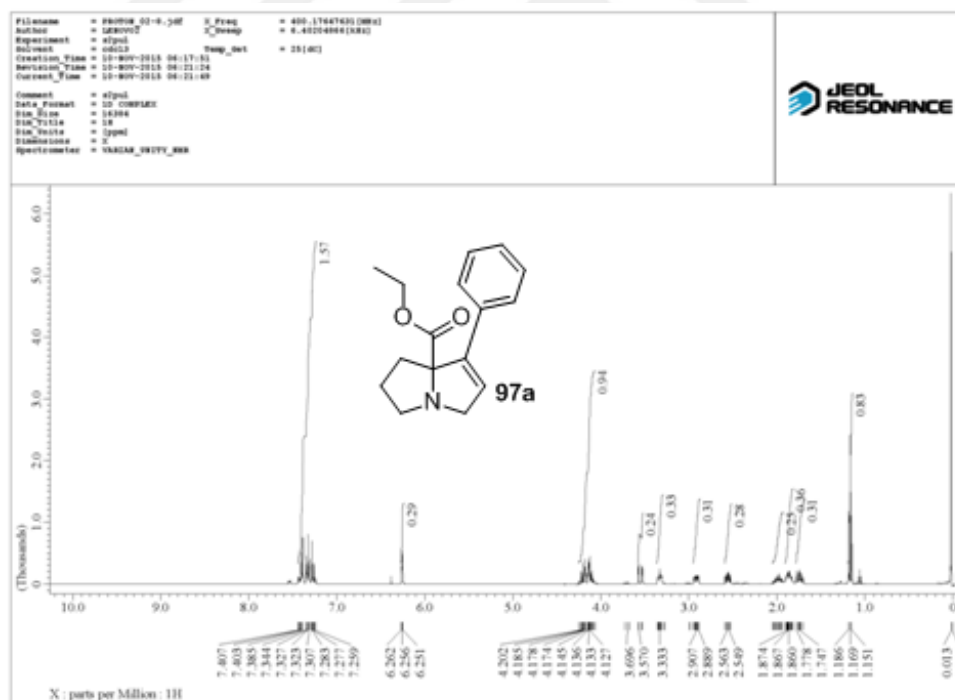


Figure 7. 60. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound 97a

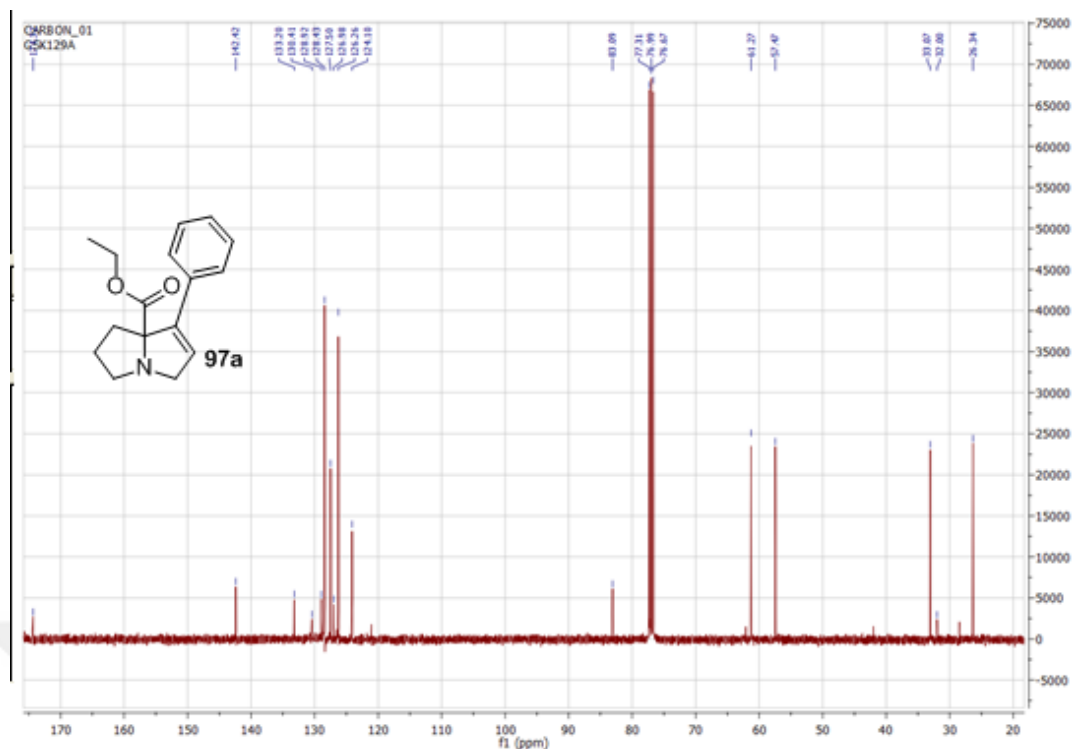


**Figure 7. 61.** <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) spectrum of compound **97a**

#### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

93 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa  | PPM  | DBE | Formula                                          | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|------|------|-----|--------------------------------------------------|-------|--------------|----|----|---|---|
| 258.1483 | 258.1494   | -1.1 | -4.3 | 7.5 | C <sub>16</sub> H <sub>20</sub> N O <sub>2</sub> | 278.7 | 0.0          | 16 | 20 | 1 | 2 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+

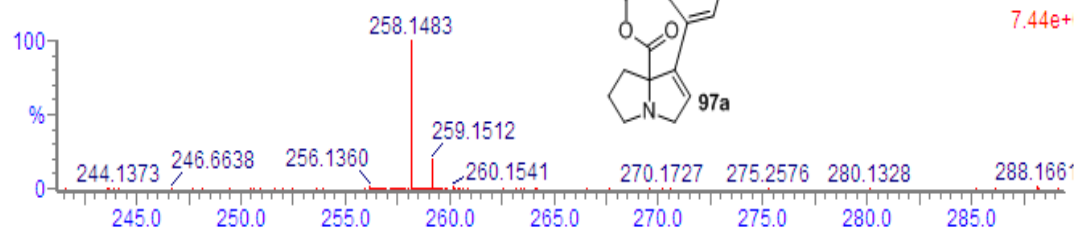


**Figure 7. 62.** HRMS spectrum of compound **97a**

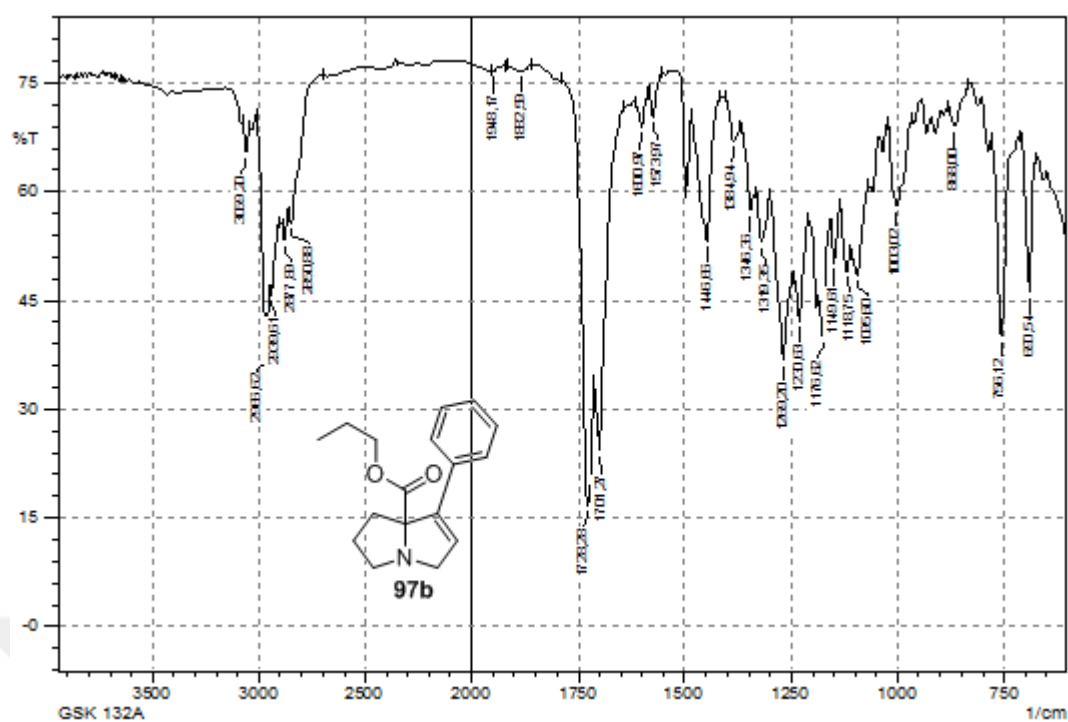


Figure 7. 63. IR spectrum of compound 97b

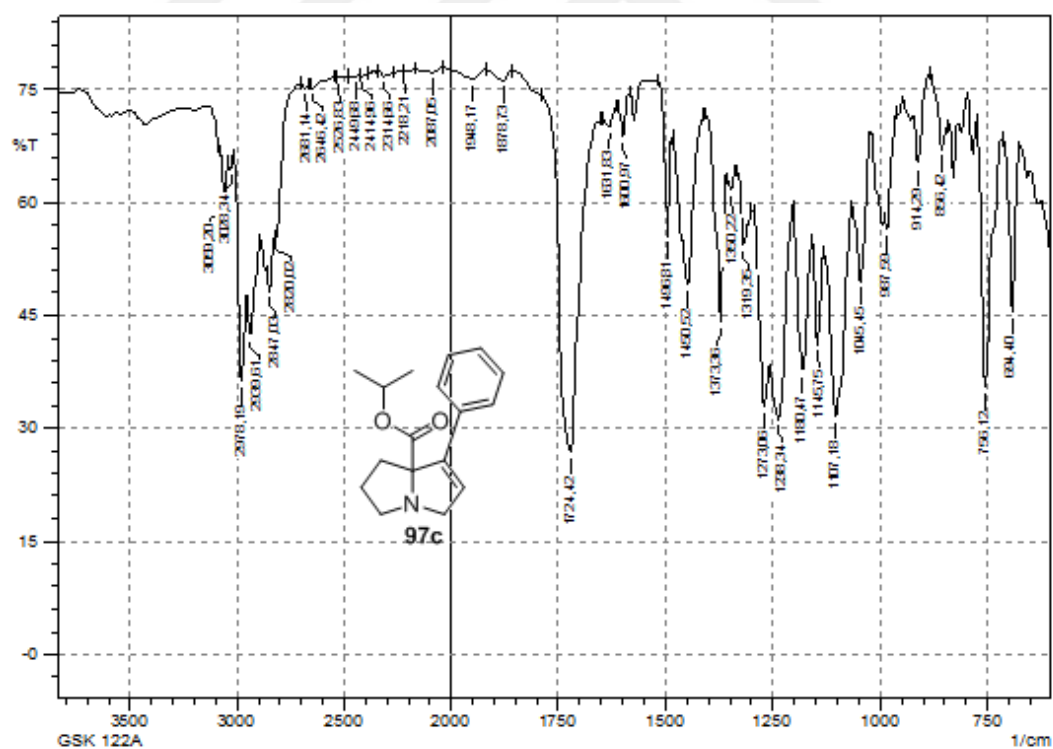


Figure 7. 64. IR spectrum of compound 97c

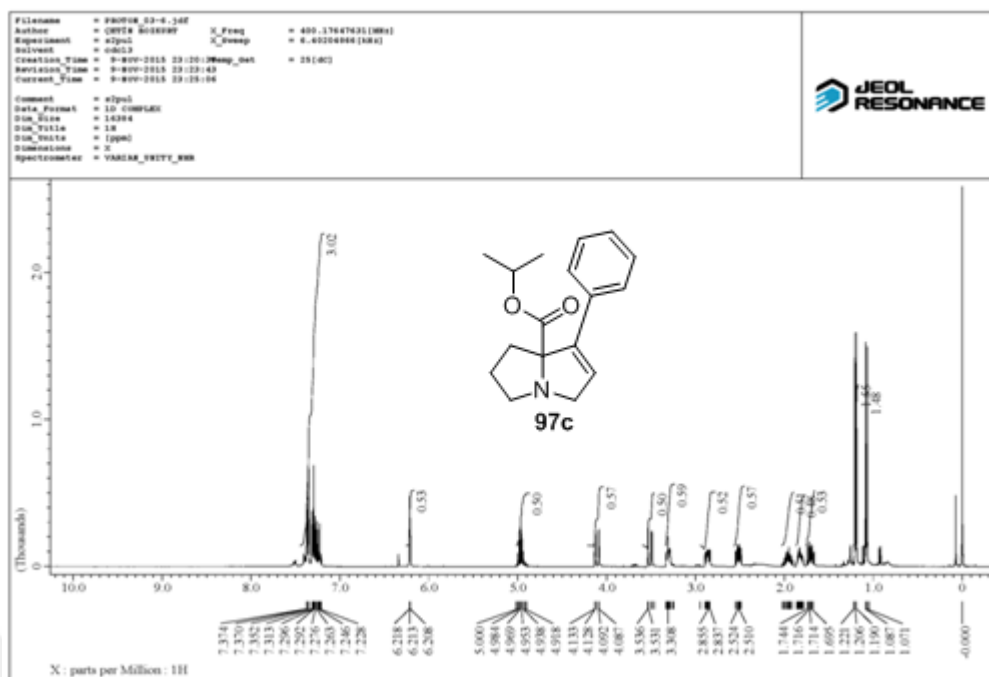


Figure 7. 65.  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound 97c

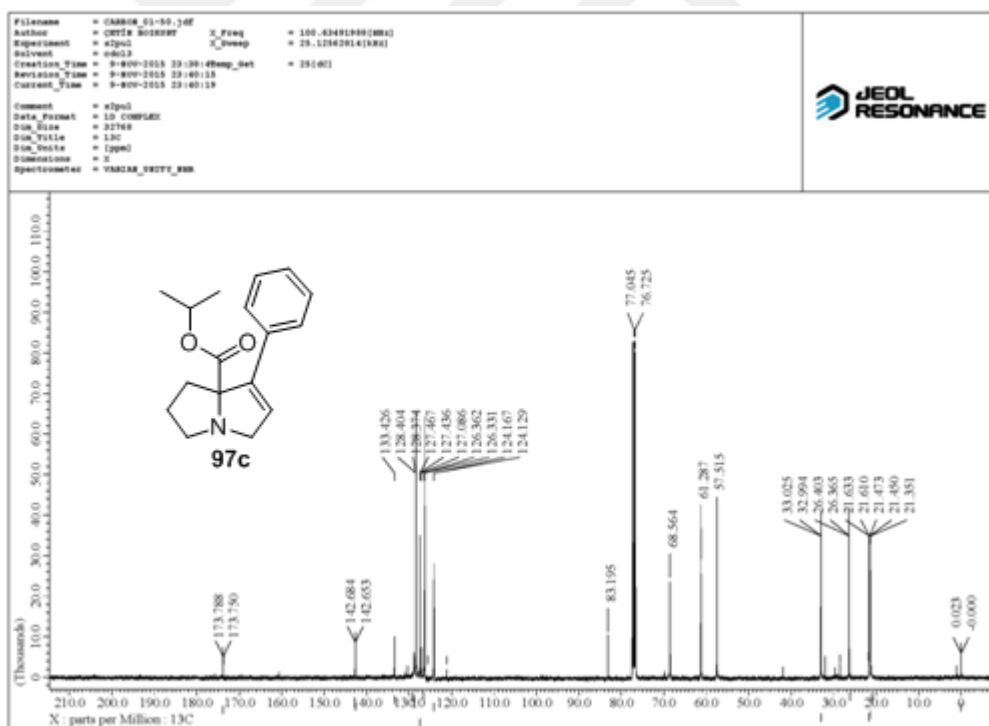


Figure 7. 66.  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound 97c

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

97 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula                                                       | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|---------------------------------------------------------------|-------|--------------|----|----|---|---|
| 272.1658 | 272.1651   | 0.7 | 2.6 | 7.5 | C <sub>17</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> | 237.4 | 0.0          | 17 | 22 | 1 | 2 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+

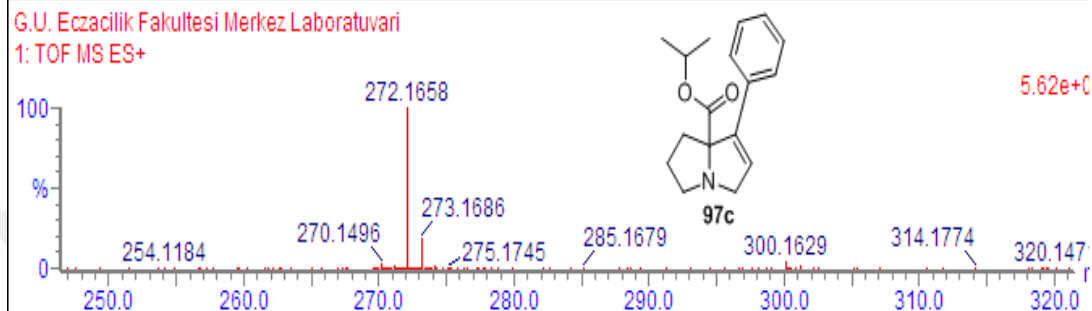


Figure 7. 67. HRMS spectrum of compound 97c

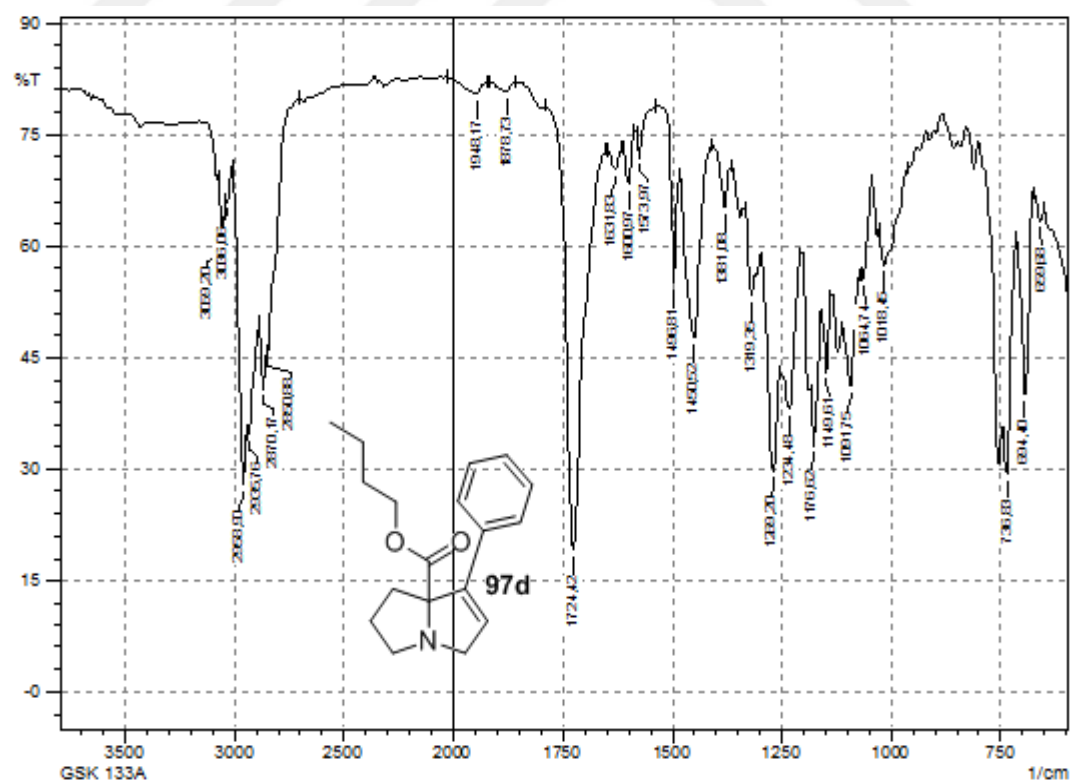


Figure 7. 68. IR spectrum of compound 97d

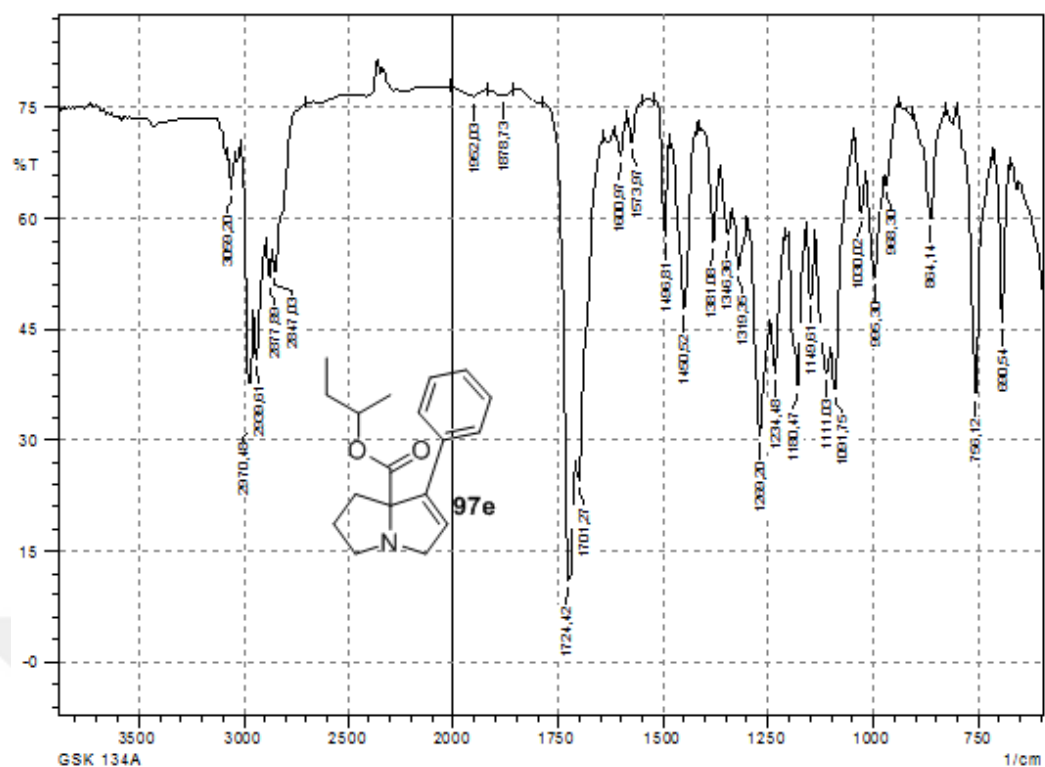


Figure 7. 69. IR spectrum of compound 97e

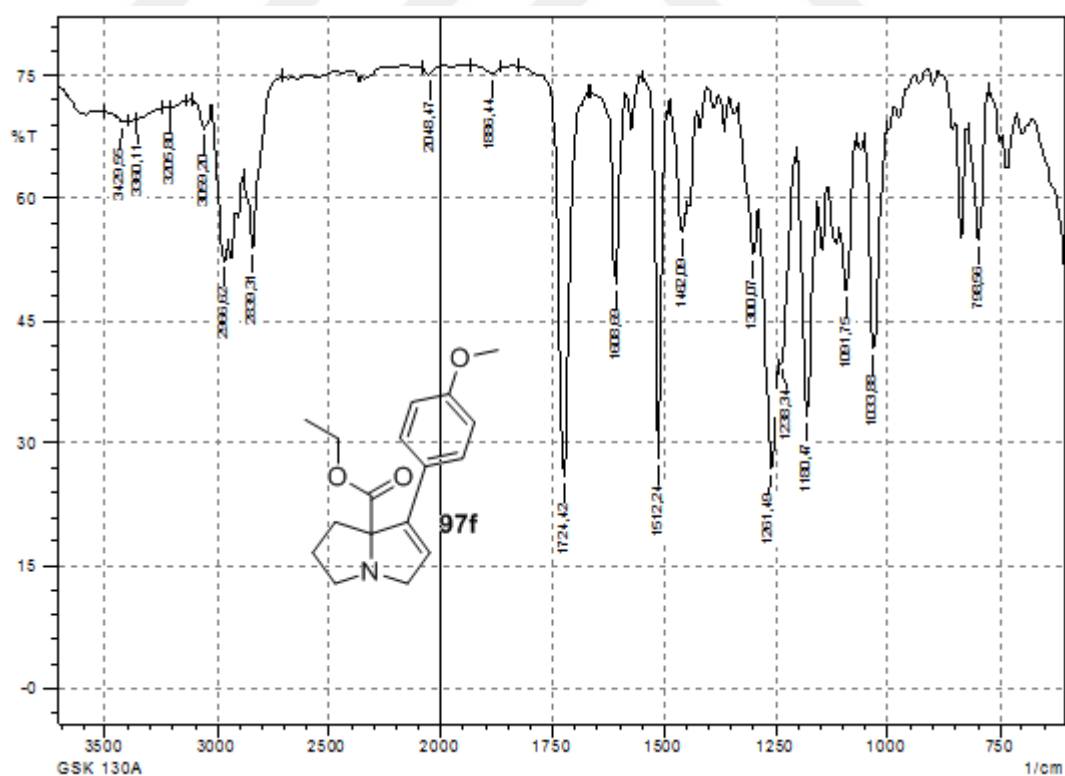


Figure 7. 70. IR spectrum of compound 97f

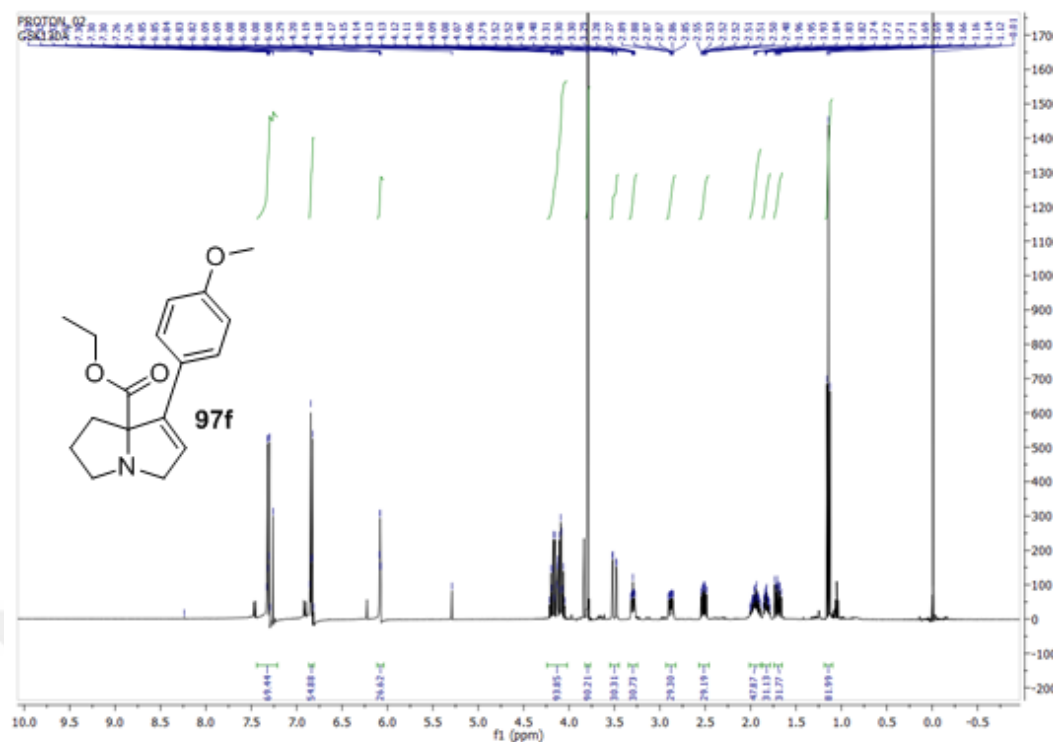


**Figure 7. 71.**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound **97f**

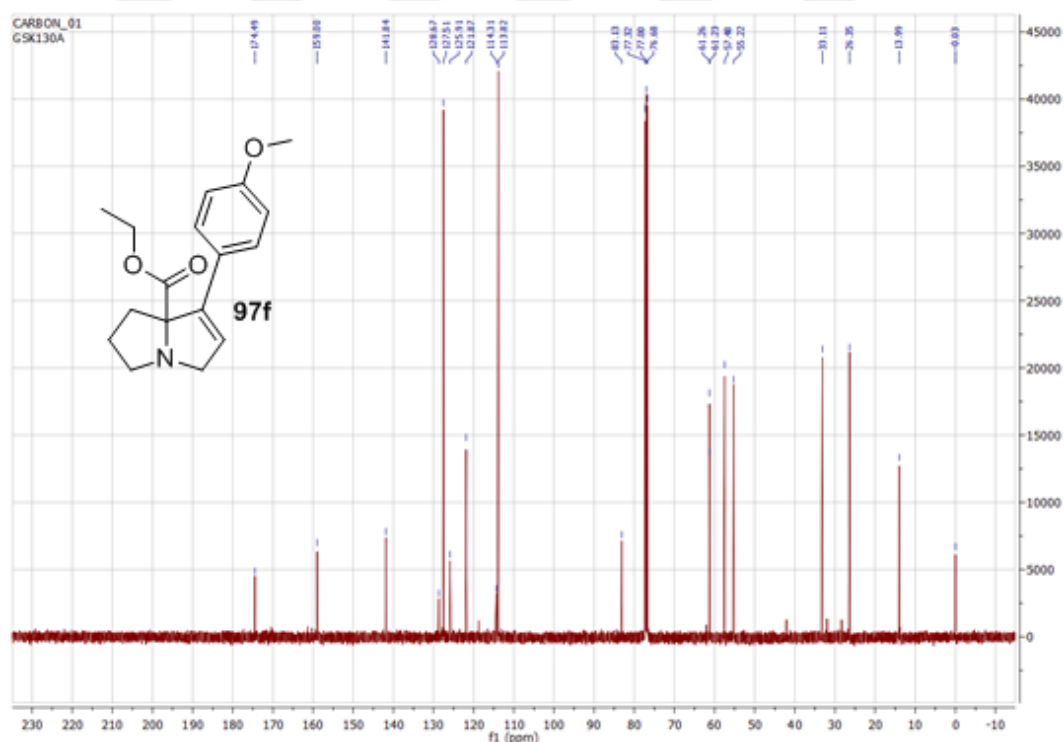


**Figure 7. 72.**  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **97f**

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

100 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa  | PPM  | DBE | Formula                                          | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|------|------|-----|--------------------------------------------------|-------|--------------|----|----|---|---|
| 288.1596 | 288.1600   | -0.4 | -1.4 | 7.5 | C <sub>17</sub> H <sub>22</sub> N O <sub>3</sub> | 318.5 | 0.0          | 17 | 22 | 1 | 3 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+

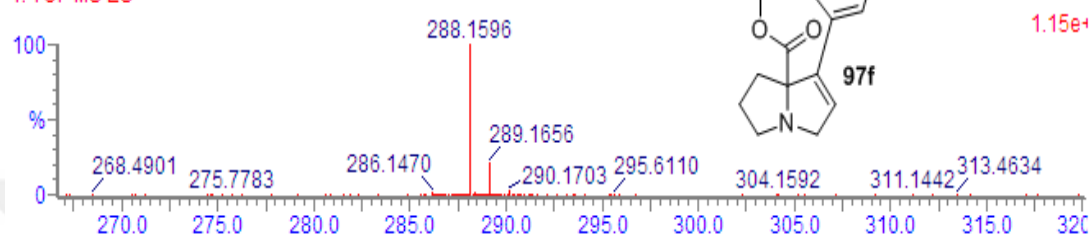


Figure 7. 73. HRMS spectrum of compound 97f

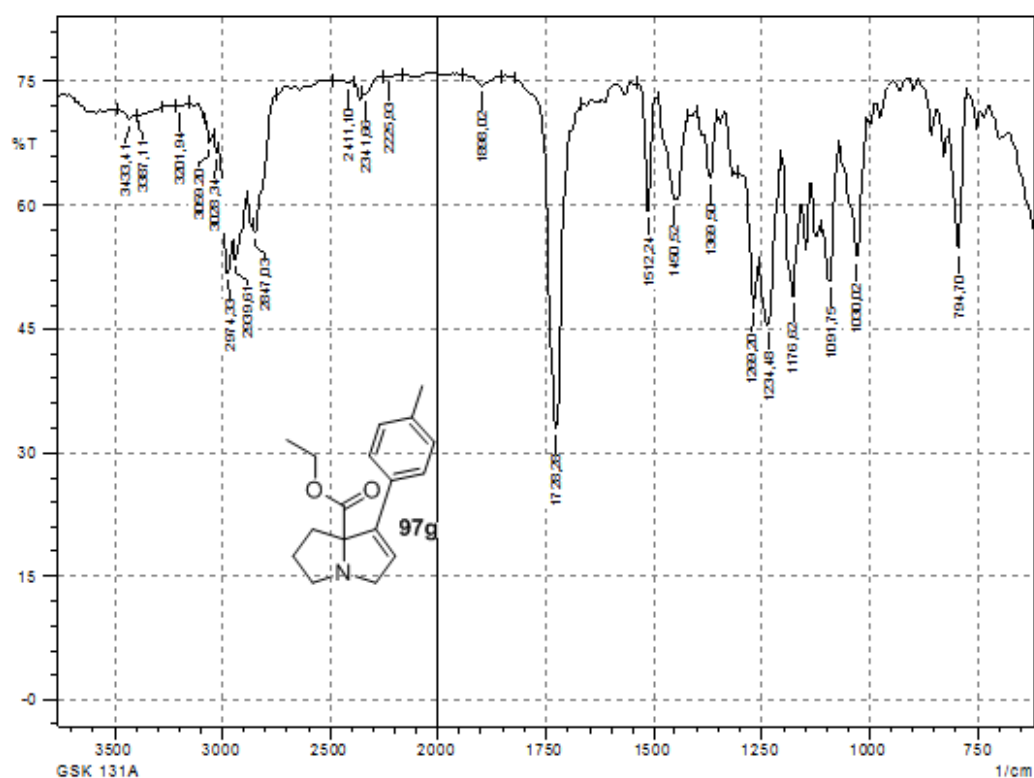


Figure 7. 74. IR spectrum of compound 97g

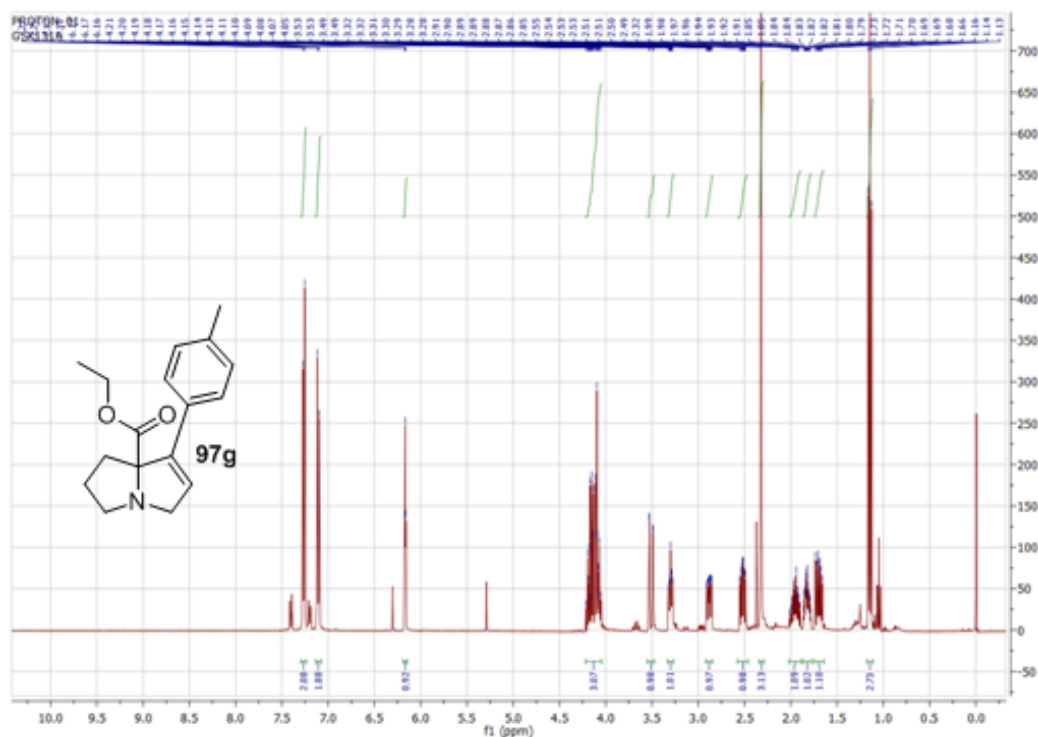


Figure 7. 75.  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound 97g

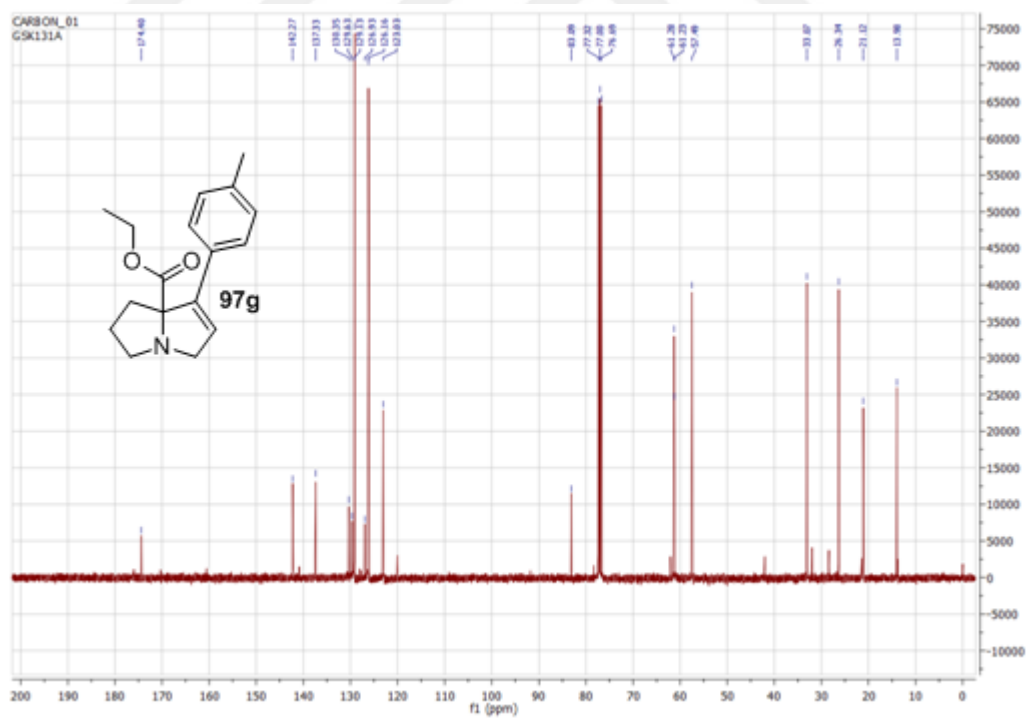


Figure 7. 76.  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound 97g

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

97 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula                                          | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|--------------------------------------------------|-------|--------------|----|----|---|---|
| 272.1657 | 272.1651   | 0.6 | 2.2 | 7.5 | C <sub>17</sub> H <sub>22</sub> N O <sub>2</sub> | 222.7 | 0.0          | 17 | 22 | 1 | 2 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

GSK-131A\_02 290 (2.941)

1: TOF MS ES+

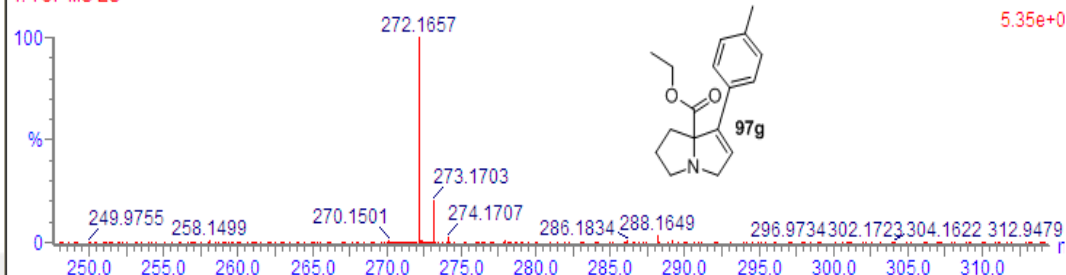


Figure 7. 77. HRMS spectrum of compound 97g

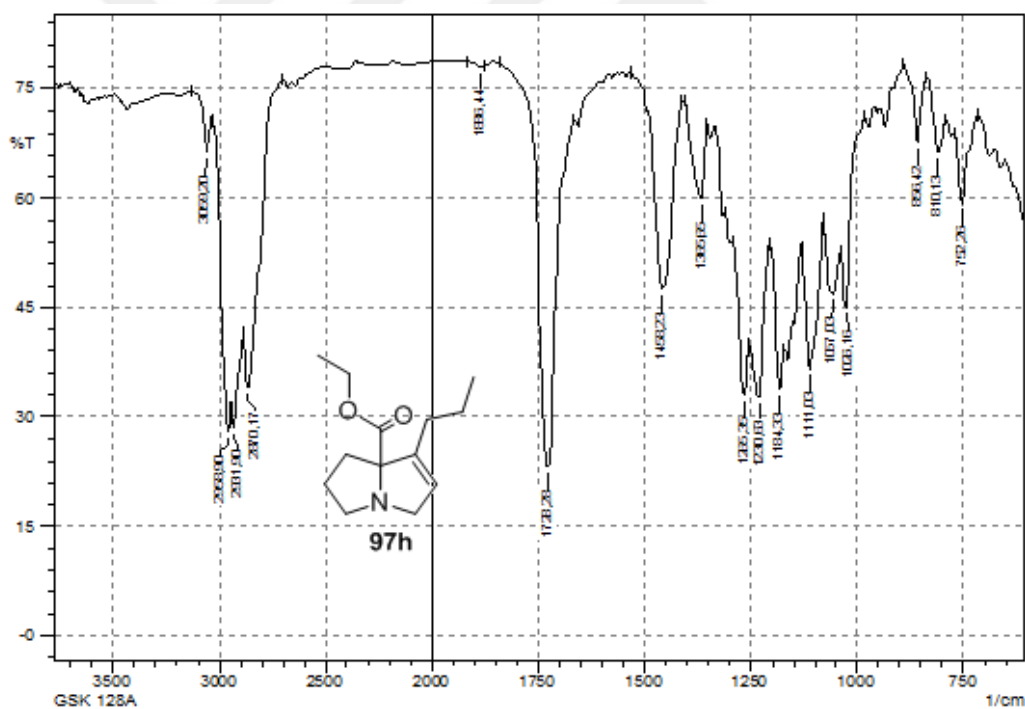


Figure 7. 78. IR spectrum of compound 97h



### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

89 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula      | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|--------------|-------|--------------|----|----|---|---|
| 238.1810 | 238.1807   | 0.3 | 1.3 | 3.5 | C14 H24 N O2 | 382.3 | 0.0          | 14 | 24 | 1 | 2 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+

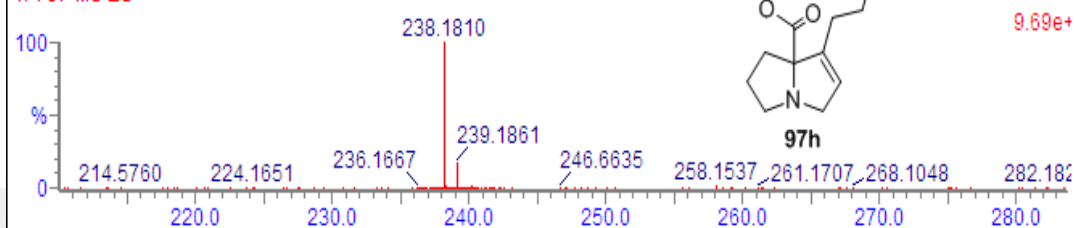


Figure 7. 81. HRMS spectrum of compound 97h

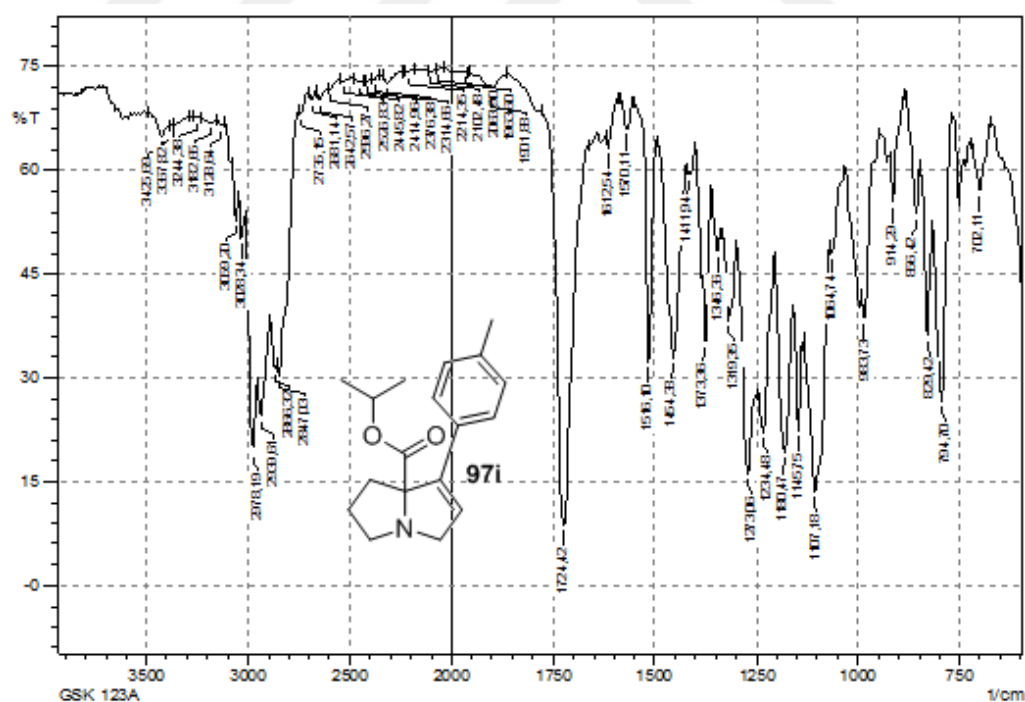


Figure 7. 82. IR spectrum of compound 97i

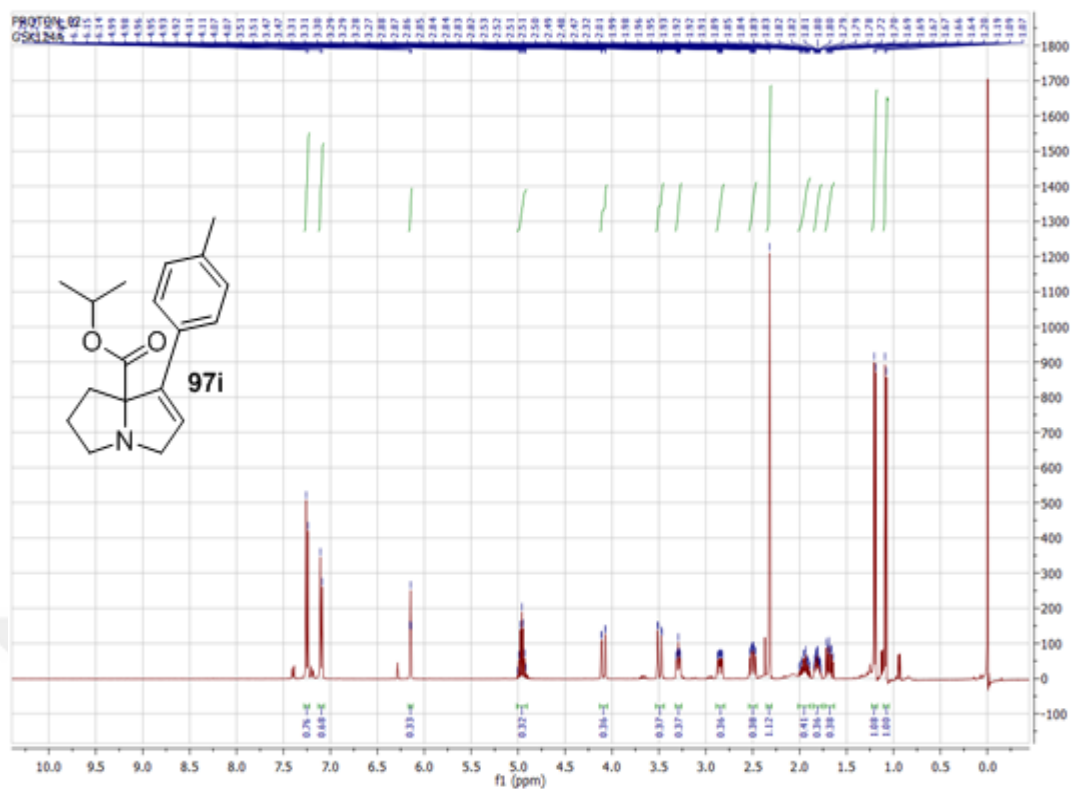


**Figure 7. 83.**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound **97i**

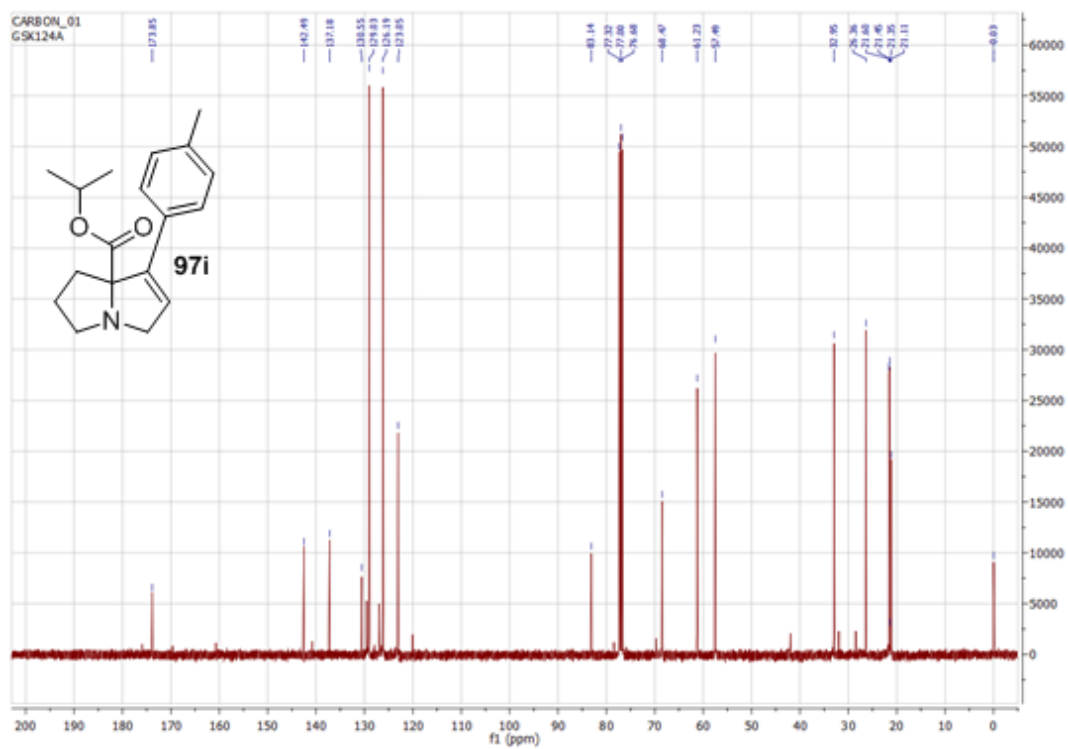


**Figure 7. 84.**  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **97i**

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

96 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula                                          | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|--------------------------------------------------|-------|--------------|----|----|---|---|
| 286.1810 | 286.1807   | 0.3 | 1.0 | 7.5 | C <sub>18</sub> H <sub>24</sub> N O <sub>2</sub> | 293.0 | 0.0          | 18 | 24 | 1 | 2 |

G.U. Eczacılık Fakultesi Merkez Laboratuvarı

1: TOF MS ES+



Figure 7. 85. HRMS spectrum of compound 97i

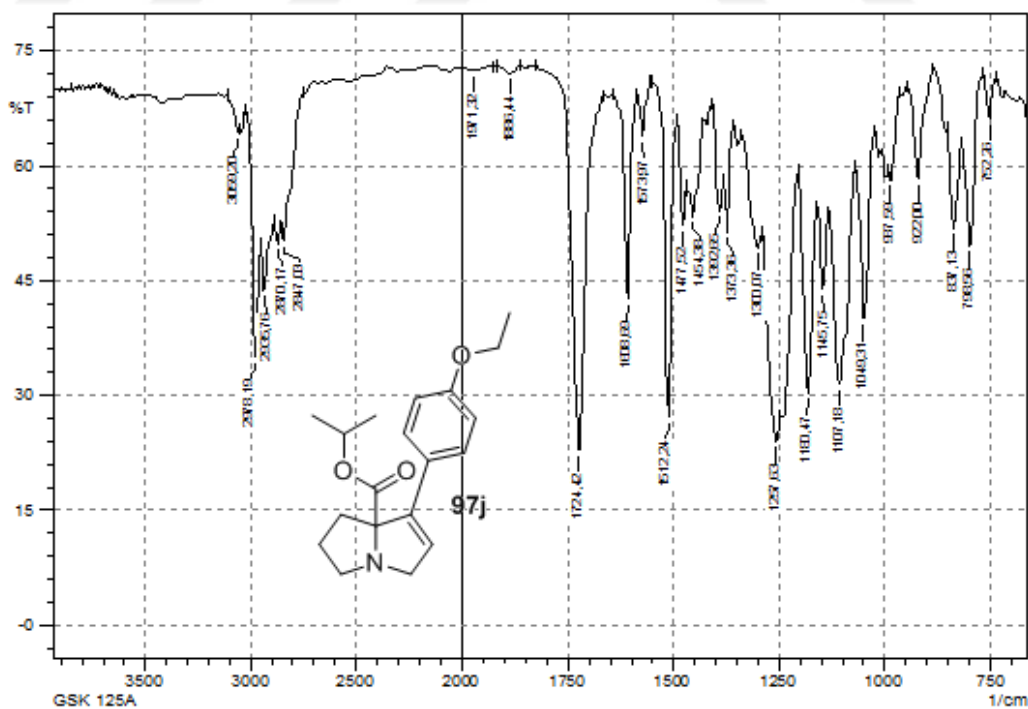


Figure 7. 86. IR spectrum of compound 97j

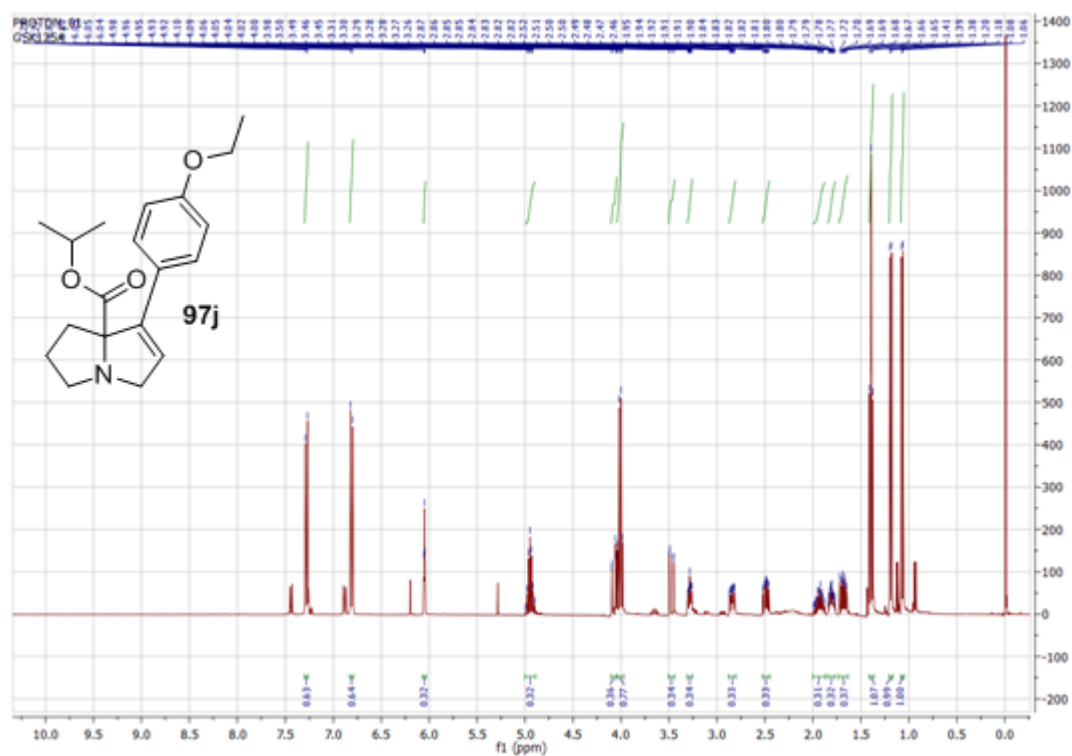


**Figure 7. 87.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **97j**

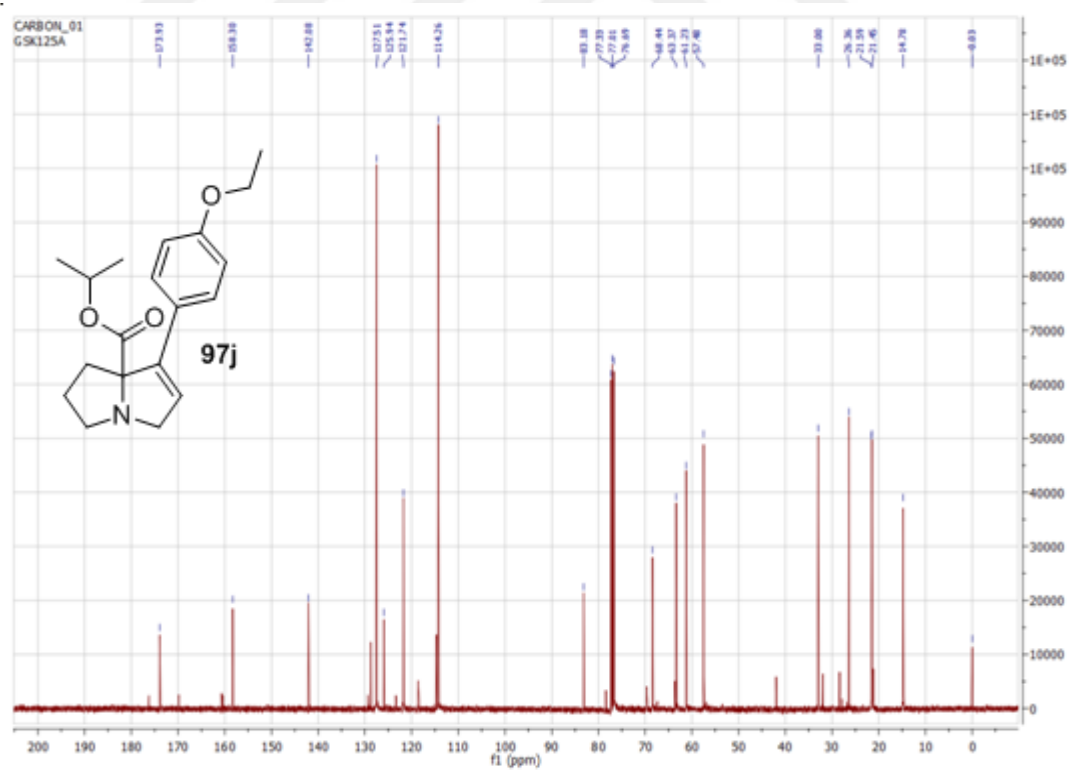


**Figure 7. 88.** <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) spectrum of compound **97j**

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

102 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa  | PPM  | DBE | Formula                                          | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|------|------|-----|--------------------------------------------------|-------|--------------|----|----|---|---|
| 316.1910 | 316.1913   | -0.3 | -0.9 | 7.5 | C <sub>19</sub> H <sub>26</sub> N O <sub>3</sub> | 301.6 | 0.0          | 19 | 26 | 1 | 3 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+



Figure 7. 89. HRMS spectrum of compound 97j

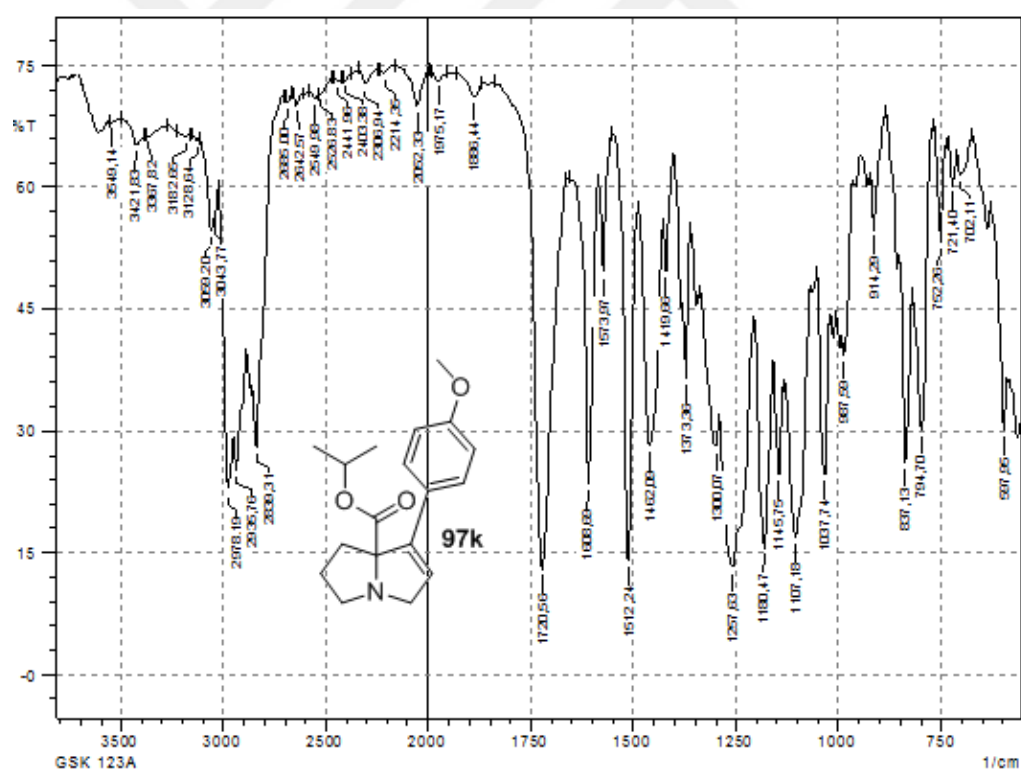
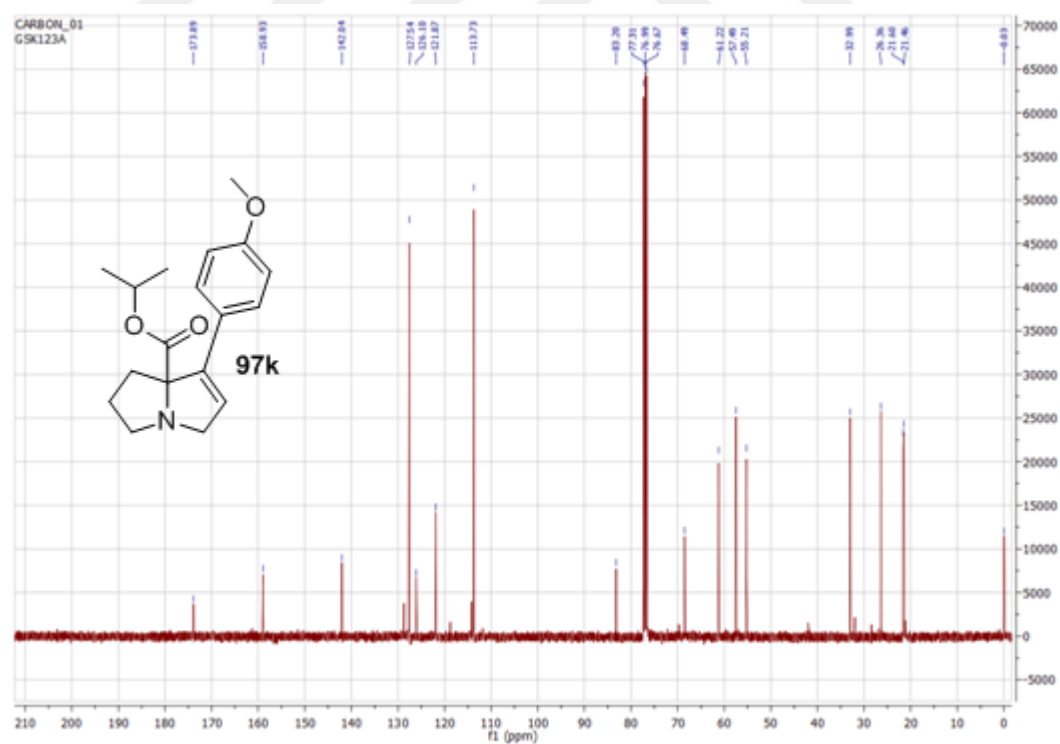
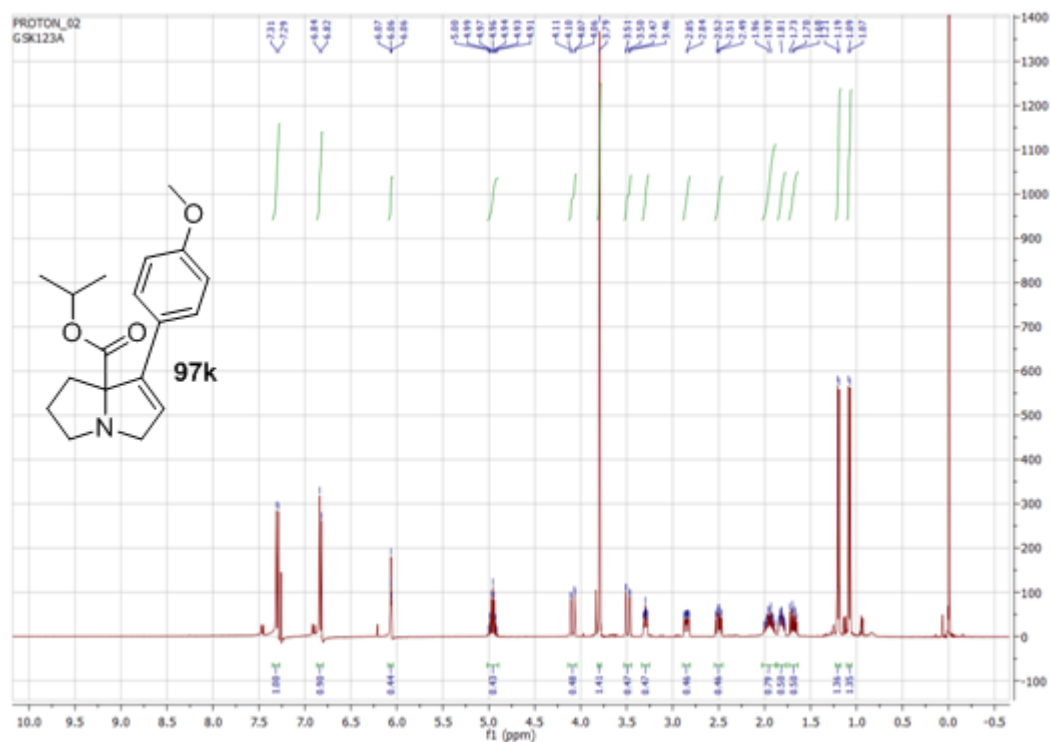


Figure 7. 90. IR spectrum of compound 97k



### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

99 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

| Mass     | Calc. Mass | mDa | PPM | DBE | Formula                                          | i-FIT | i-FIT (Norm) | C  | H  | N | O |
|----------|------------|-----|-----|-----|--------------------------------------------------|-------|--------------|----|----|---|---|
| 302.1757 | 302.1756   | 0.1 | 0.3 | 7.5 | C <sub>18</sub> H <sub>24</sub> N O <sub>3</sub> | 303.2 | 0.0          | 18 | 24 | 1 | 3 |

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

1: TOF MS ES+

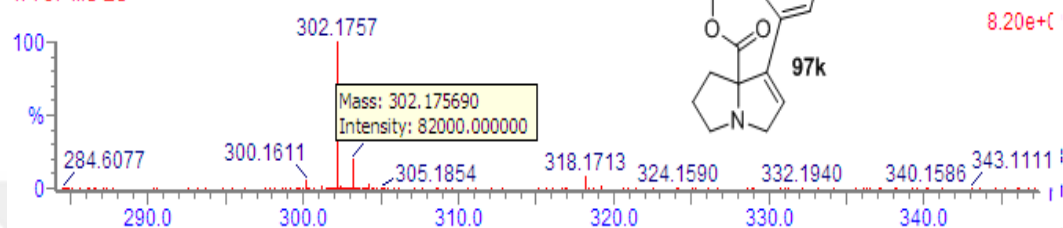


Figure 7. 93. HRMS spectrum of compound 97k

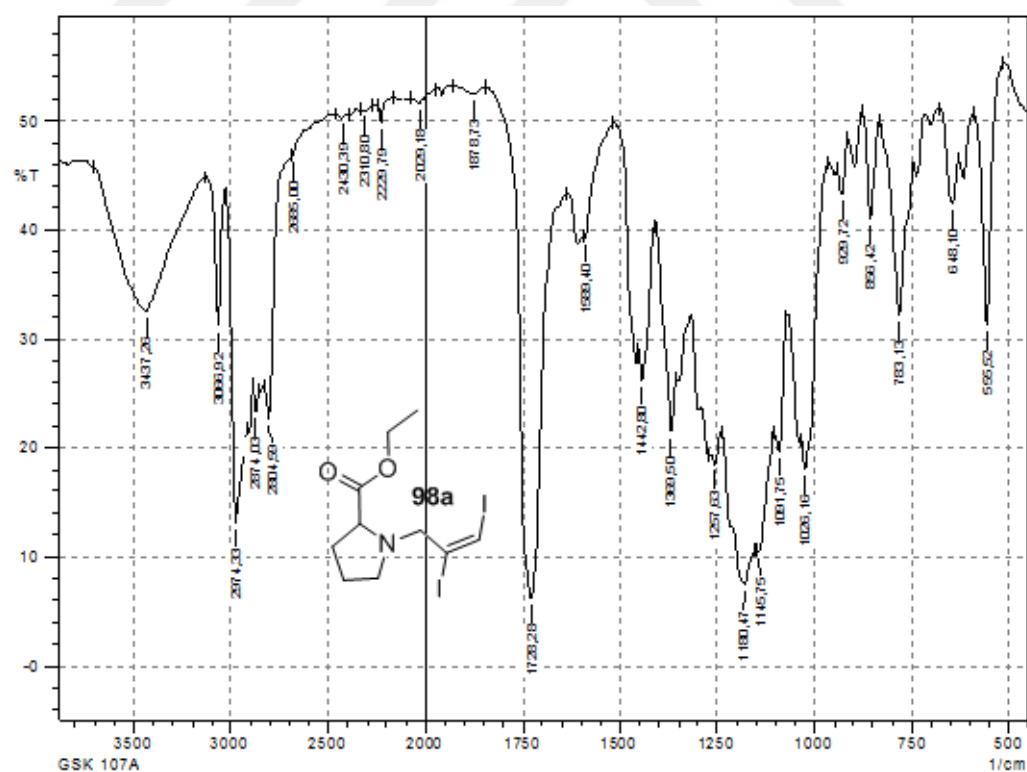


Figure 7. 94. IR spectrum of compound 98a

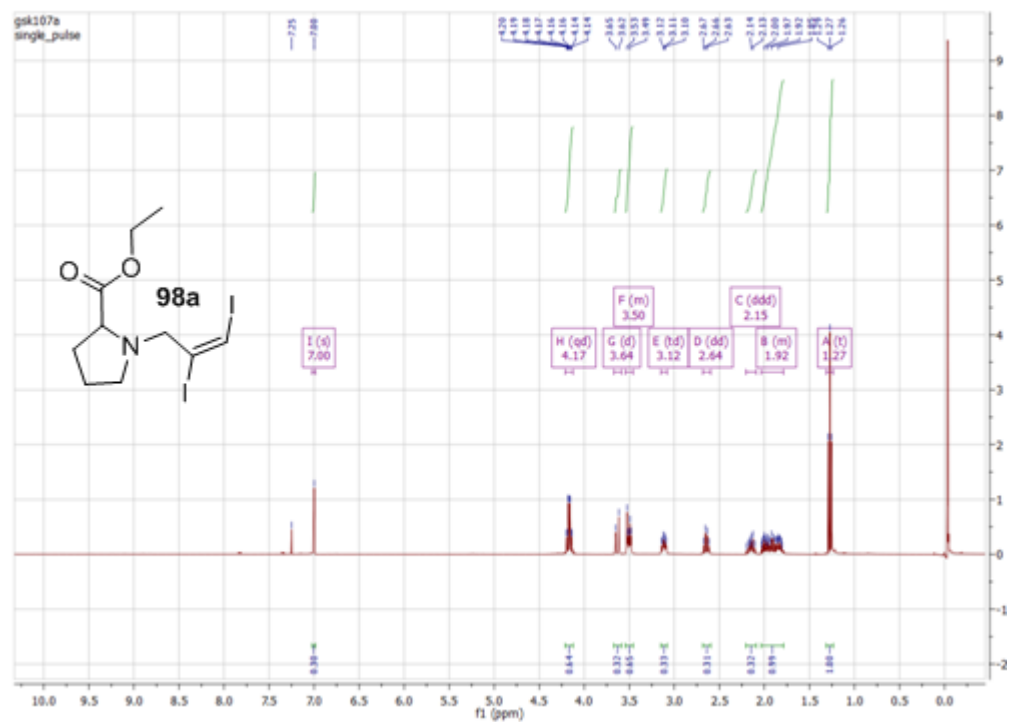


Figure 7. 95. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound 98a

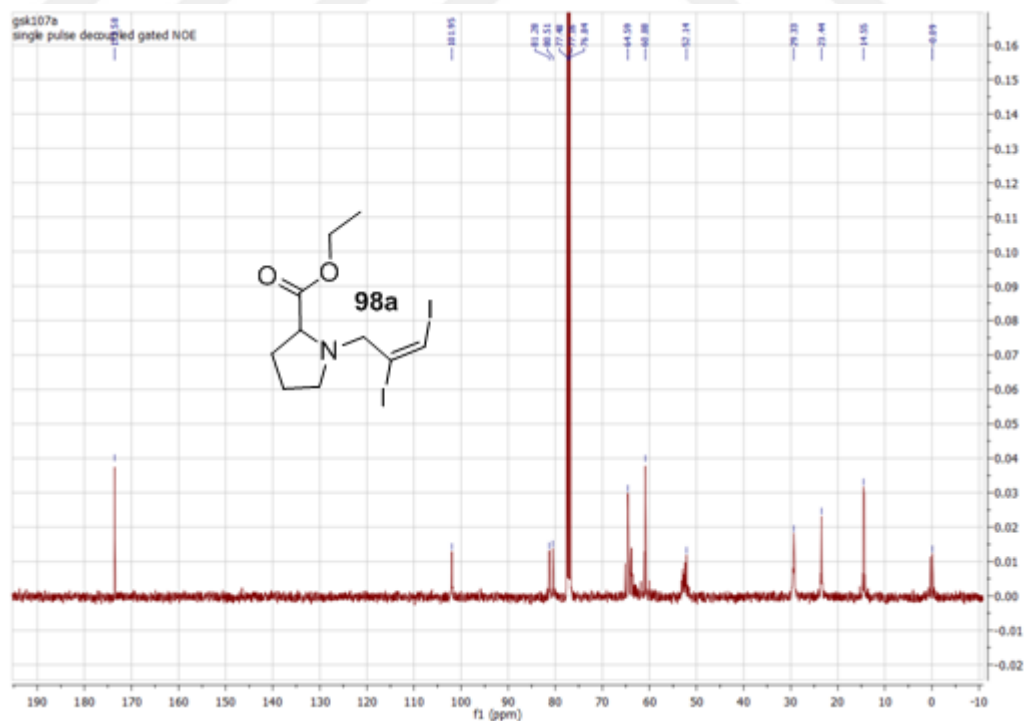


Figure 7. 96. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) spectrum of compound 98a

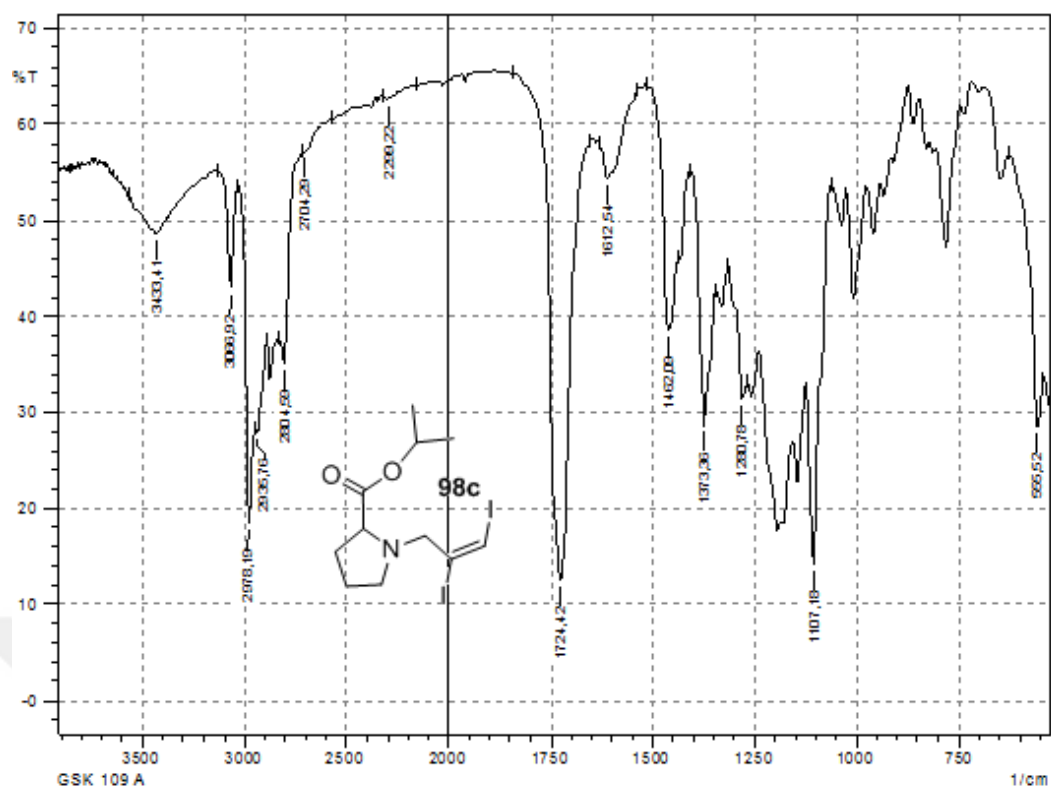


Figure 7. 97. IR spectrum of compound **98c**

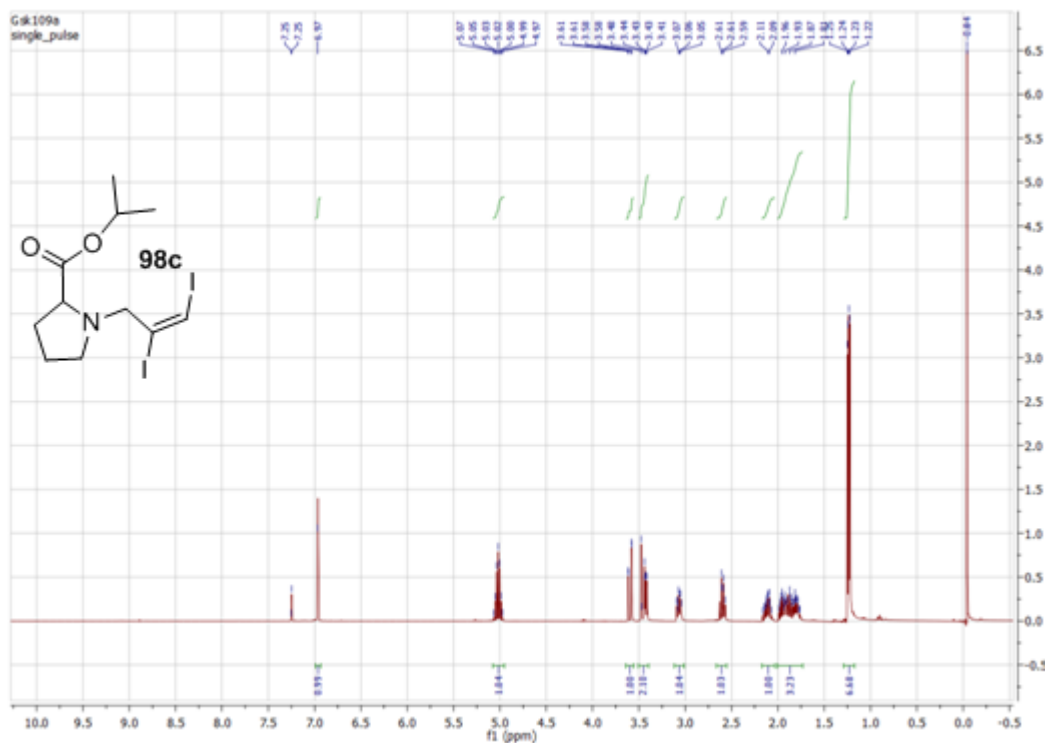


Figure 7. 98. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **98c**

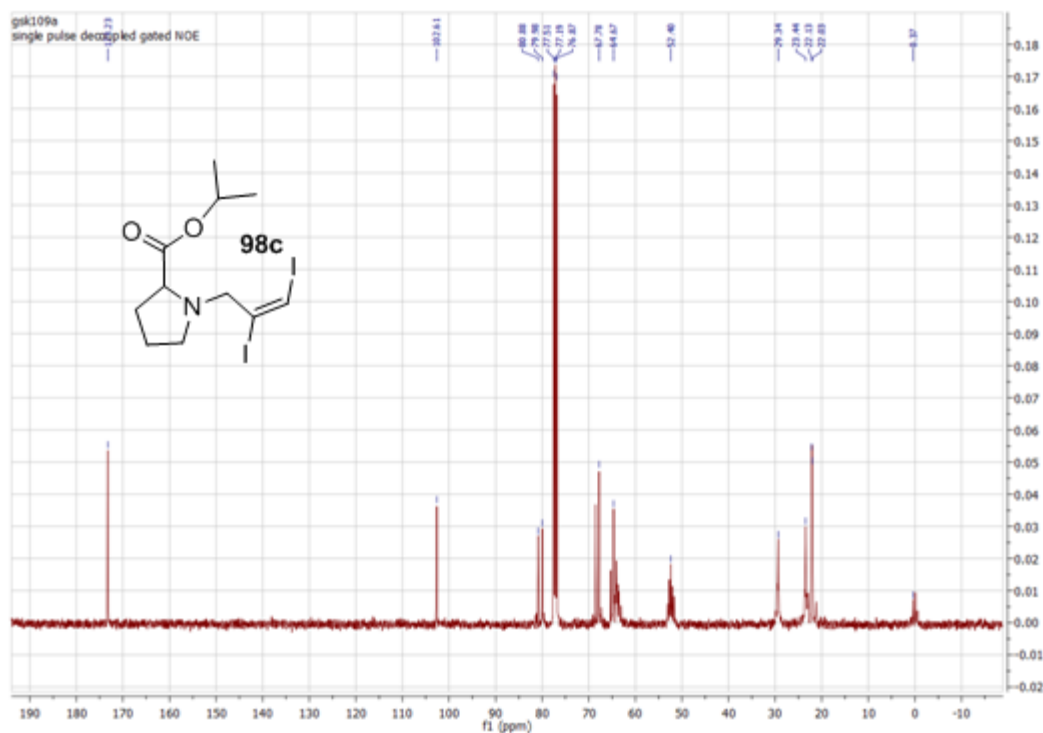


Figure 7. 99.  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **98c**

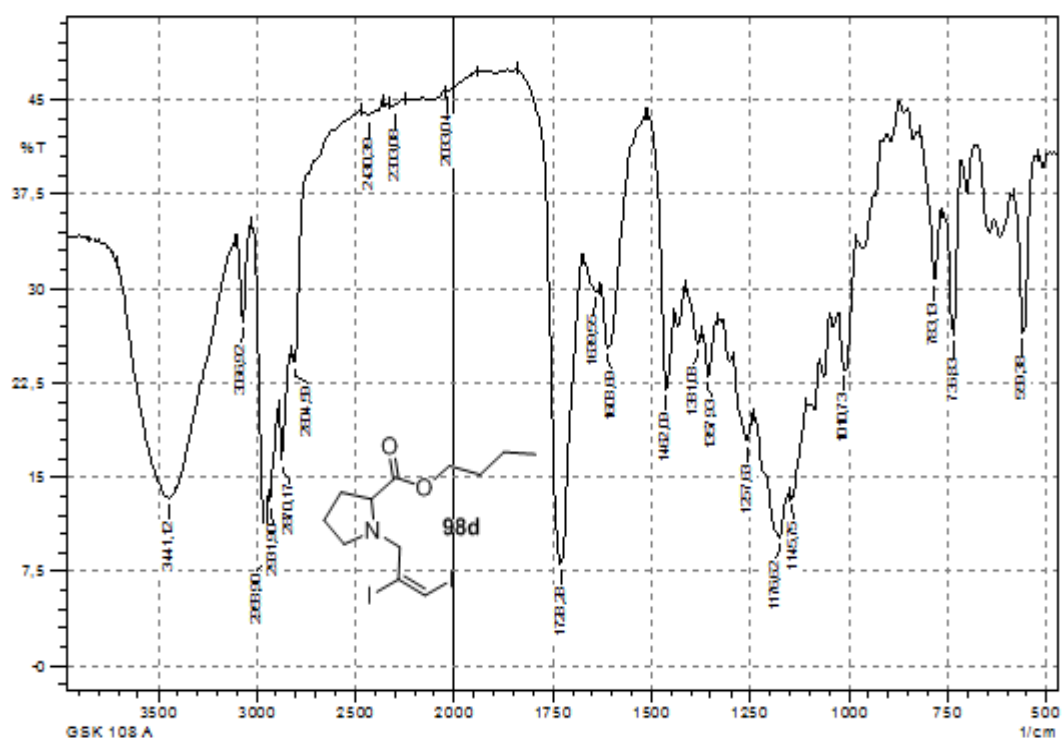


Figure 7. 100. IR spectrum of compound **98d**



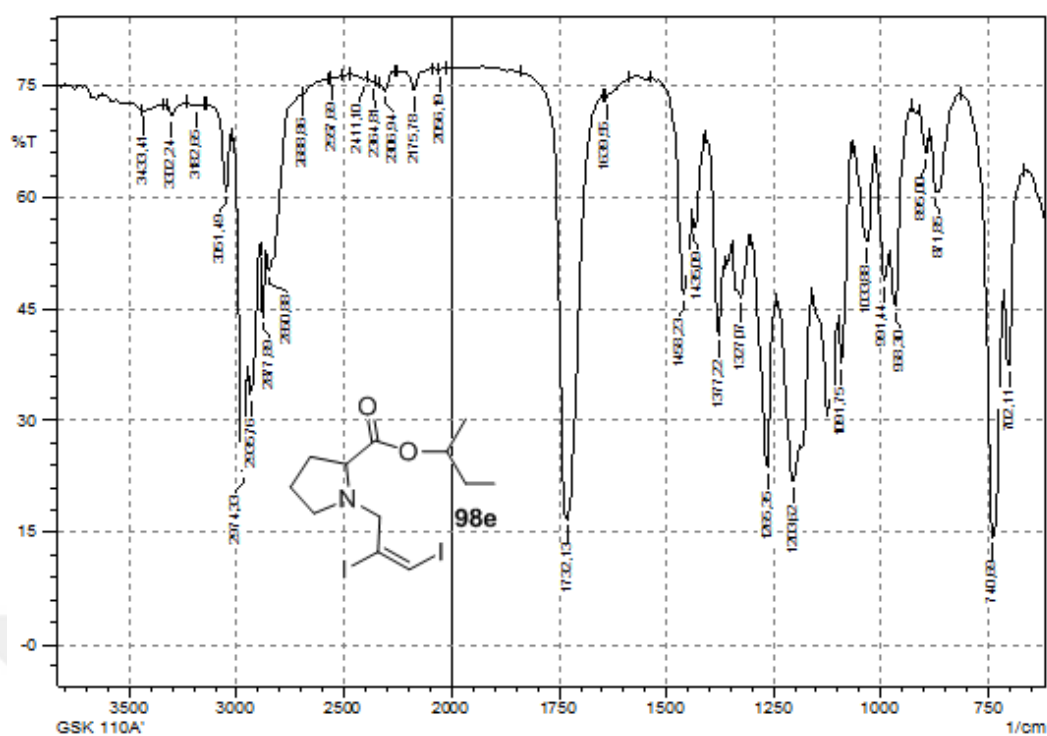


**Figure 7. 103.** IR spectrum of compound **98e**

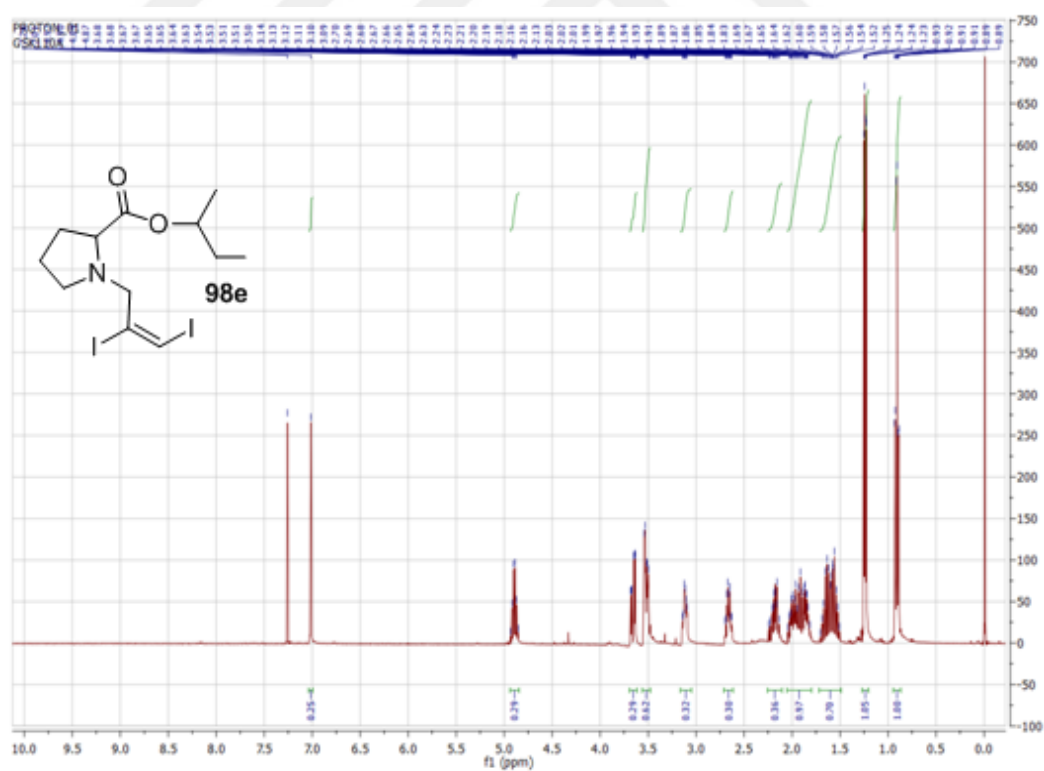


**Figure 7. 104.**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of compound **98e**

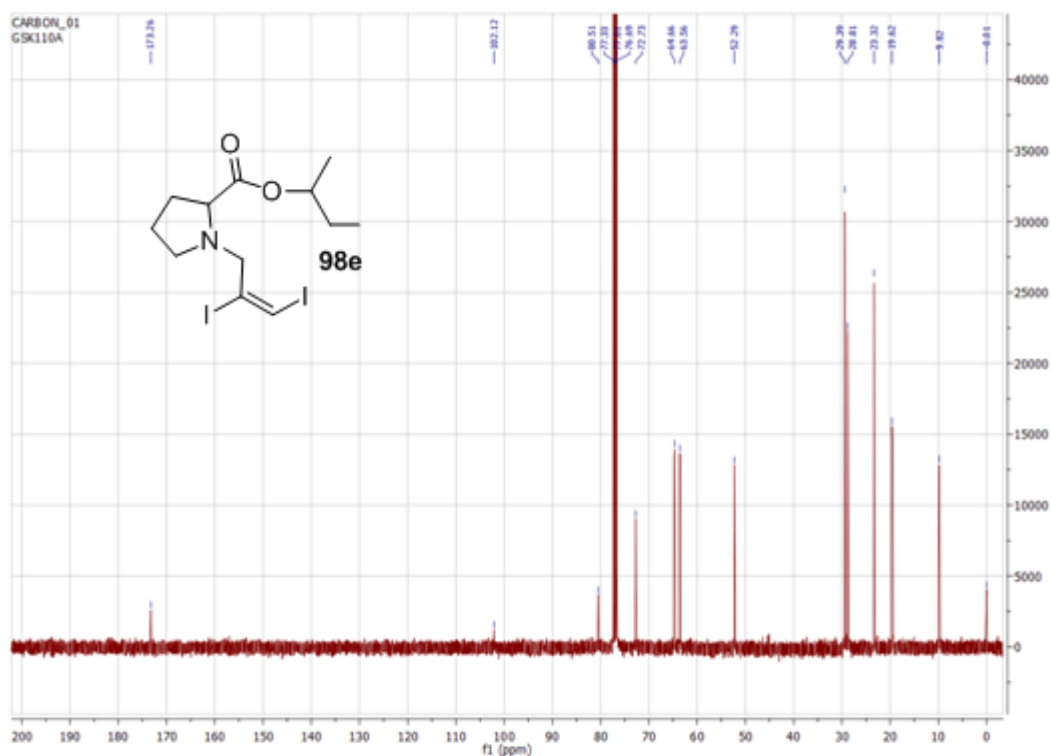


Figure 7. 105.  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ ) spectrum of compound **98e**

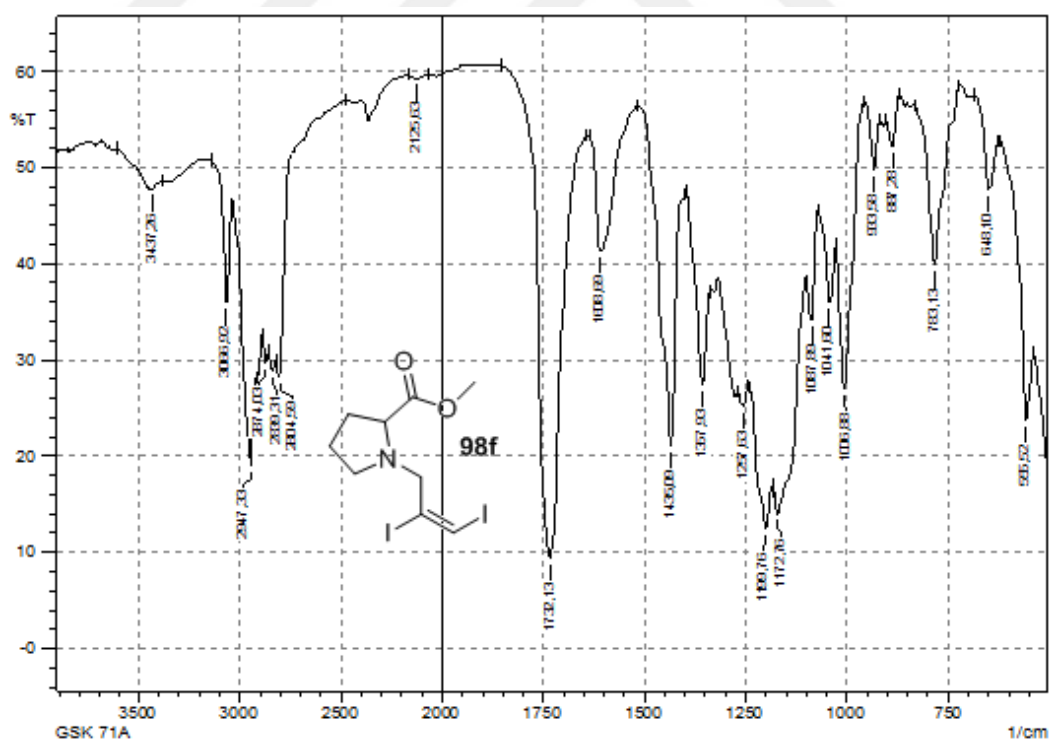


Figure 7. 106. IR spectrum of compound **98f**

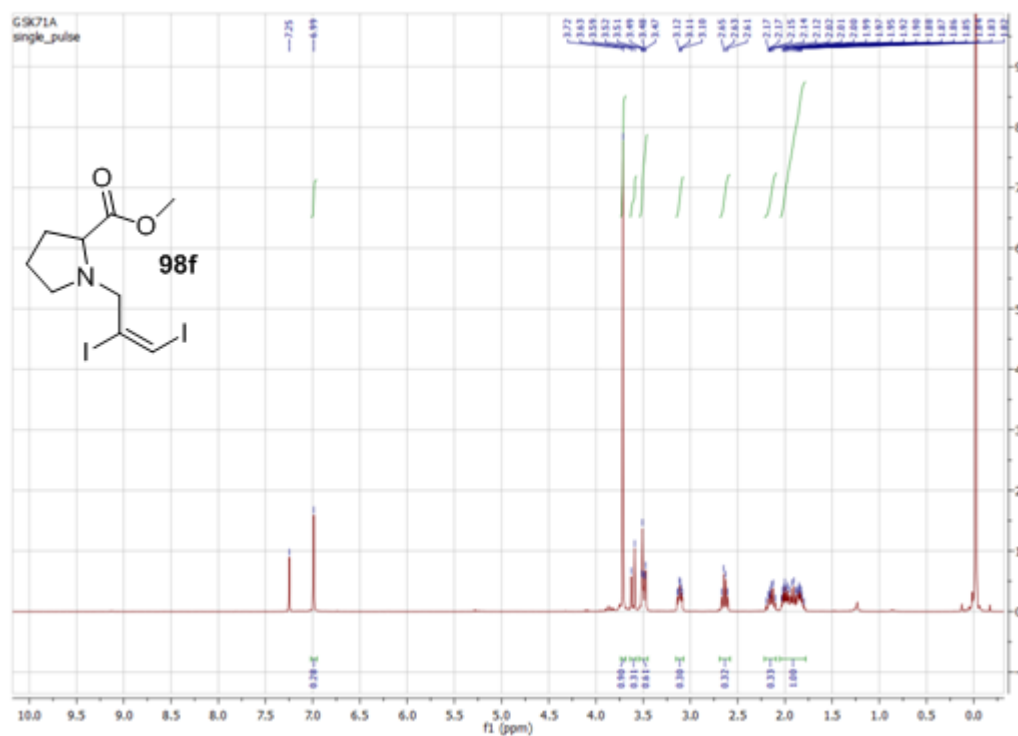


**Figure 7. 107.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of compound **98f**

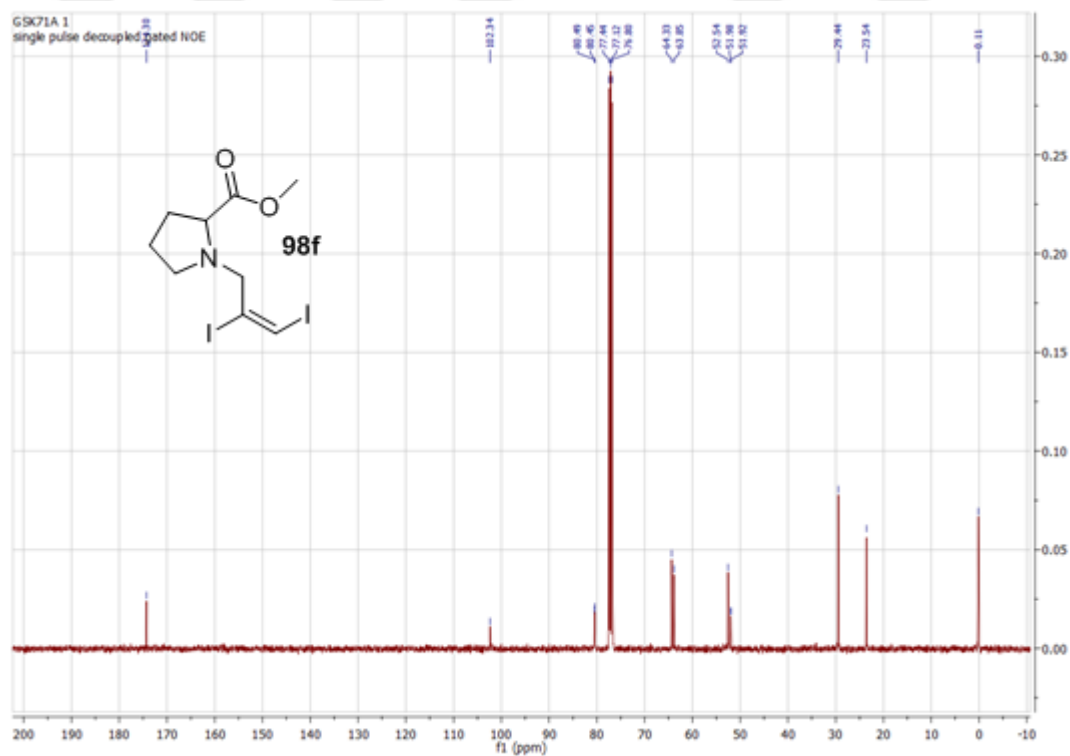


**Figure 7. 108.** <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) spectrum of compound **98f**

## **8. CURRICULUM VITAE**

**Name SURNAME : Garba SULEIMAN**

**Place and Date of Birth : DAMATURU**

**Universities**

**- Bachelor's Degree : AIBU-BOLU, TURKEY**

**e-mail : sulei2006@gmail.com**

**Address : ALI MARAMI ESTATE DTR,F-182, NIG.**

**List of Publications :-----**

**Awards : UNDERGRADUATE STUDIES SCHOLARSHIP  
BY YOBE STATE GOVERNMENT, NIGERIA.**