

T.R.
BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
Department of Chemistry



**SYNTHESIS OF SOME NOVEL HETEROCYCLIC
FRAGRANT COMPOUNDS AND DETERMINATION OF
THEIR OLFACTIVE PROPERTIES**

DOCTOR OF PHILOSOPHY

MUHAMMET BÜYÜKBAYRAM

ACADEMIC SUPERVISOR
Prof. Dr. Cevher ALTUĞ

BOLU, OCAK - 2024

APPROVAL OF THE THESIS

SYNTHESIS OF SOME NOVEL HETEROCYCLIC FRAGRANT COMPOUNDS AND DETERMINATION OF THEIR OLFACTIVE PROPERTIES submitted by **Muhammet BÜYÜKBAYRAM** and defended before the Examining Committee Members listed below in partial fulfillment of the requirements for the degree of **Doctor of Philosophy** in **Department of Chemistry, Institute of Graduate Studies of Bolu Abant Izzet Baysal University** in **5.01.2024** by

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ABSTRACT

SYNTHESIS OF SOME NOVEL HETEROCYCLIC FRAGRANT COMPOUNDS AND DETERMINATION OF THEIR OLFACTIVE PROPERTIES

PHD THESIS

**MUHAMMET BÜYÜKBAYRAM
BOLU ABANT IZZET BAYSAL UNIVERSITY
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DEPARTMENT OF CHEMISTRY
(SUPERVISOR: PROF. DR. CEVHER ALTUĞ)**

**BOLU, JANUARY 2024
(XXVIII+190)**

In this thesis study, the pursuit of fragrant molecule design for potential applications in the fragrance industry, a diverse array of aldoxime and aldonitrone derivatives with aromatic and aliphatic substituents was synthesized. The synthesis yielded these aldoximes with gram scale yields, demonstrating a lack of diastereoselectivity as confirmed by GC-MS measurements. Employing these aldoximes and aldonitrone in 1,3-dipolar cycloaddition reactions, high regioselectivity was observed within a 5 position in the production of isoxazoline and isoxazolidine carboxylate derivatives when treated dipolarophilic reagents methyl methacrylate (MMA), glycidyl methacrylate (GMA) with nitrile oxide and MMA and ethyl methacrylate (EMA) with nitrones. Various characterization techniques, including NMR, FT-IR, GC-MS, and TOF-LCMS analysis, were employed to characterize the obtained compounds. The microbial properties of the synthesized molecules were determined by investigating whether the molecules were capable of allowing bacterial and fungal growth in the final product. Through this multifaceted investigation, the research not only advances fragrant molecule design but also provides a promising avenue for future olfactory innovations.

KEYWORDS: Isoxazoline carboxylate, Isoxazolidine carboxylate, Fragrance, 1,3-dipolar cycloaddition

ÖZET

BAZI YENİ HETEROHALKALI KOKULU BİLEŞİKLERİN SENTEZİ VE OLFAKTİF ÖZELLİKLERİNİN BELİRLENMESİ

DOKTORA TEZİ

MUHAMMET BUYUKBAYRAM

BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ

LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ

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(TEZ DANIŞMANI: PROF. DR. CEVHER ALTUĞ)

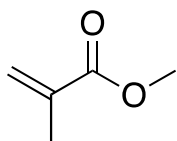
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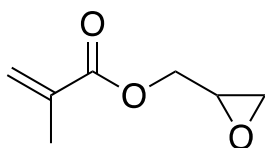
Bu tez çalışmasında, potansiyel olarak parfüm endüstrisinde kullanılabilir kokulu molekül tasarımının araştırılması amacıyla aromatik ve alifatik substitüentlere sahip çeşitli aldoksim ve aldonitron türevleri sentezlenmiştir. Sentezlenen bu aldoksimlerin eldesinin gram ölçeklerde gerçekleşmesine ek olarak diastereoseçicilikleri de GC-MS analizleri ile belirlenmiştir. 1,3-dipolar siklokatılma reaksiyonlarında dipolarofilik reaktifler olan metil metakrilat (MMA) ve glisidil metakrilat (GMA) nitril oksitler ile; MMA ve etil metakrilat (EMA) ise nitronlar ile reaksiyona sokularak izoksazolin ve izoksazolidin karboksilat türevleri sentezlenmiş ve bu sentezlerde 5 pozisyonunda yüksek yer seçimi gözlemlenmiştir. Elde edilen bileşiklerin karakterizasyonu için NMR, FT-IR, GC-MS ve TOF-LCMS analizi de dahil olmak üzere çeşitli karakterizasyon teknikleri kullanılmıştır. Sentezlenen moleküllerin mikrobiyal özellikleri, moleküllerin son üründe bakteri ve fungal büyümeye izin verip vermediğini belirleyerek değerlendirilmiştir. Bu çok yönlü araştırma, sadece kokulu molekül tasarımını ilerletmekle kalmayıp aynı zamanda gelecekteki koku yenilikleri için umut verici bir yol sunmaktadır.

ANAHTAR KELİMELE: İzoksazolin karboksilat, İzoksazolidin karboksilat, Koku, 1,3-dipolar halka katılma

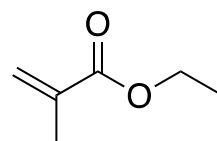
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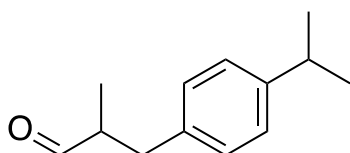
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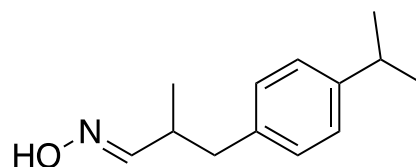
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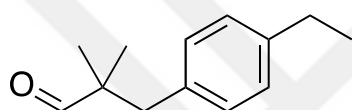
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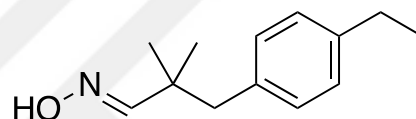
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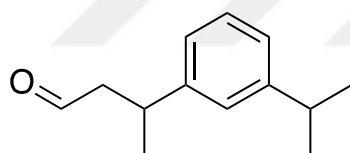
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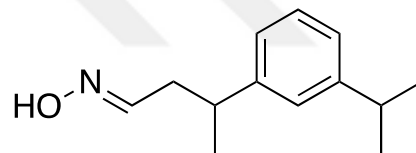
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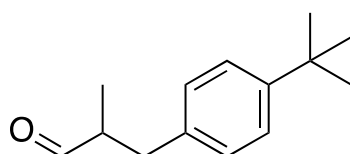
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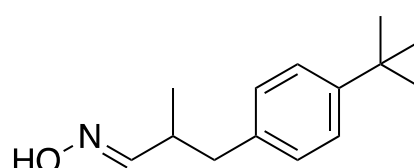
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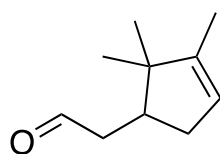
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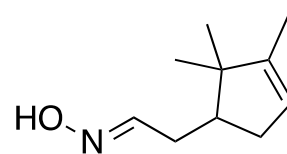
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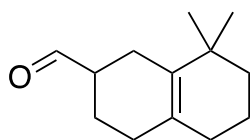
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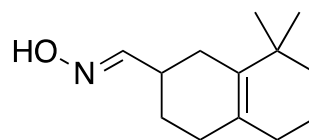
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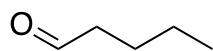
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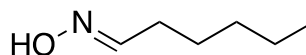
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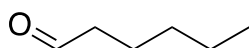
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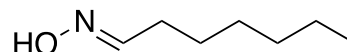
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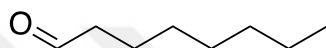
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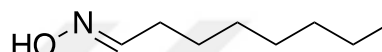
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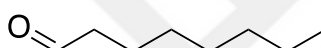
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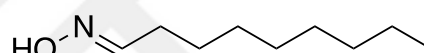
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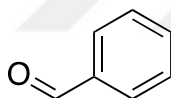
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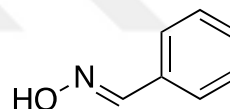
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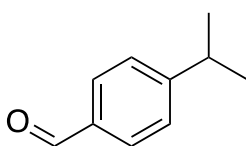
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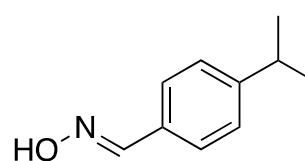
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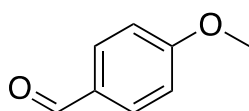
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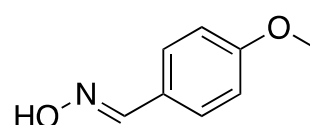
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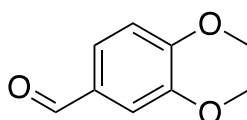
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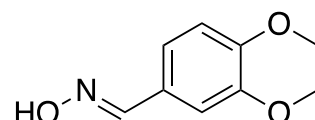
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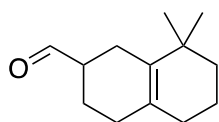
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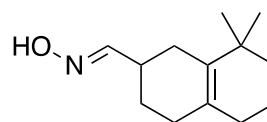
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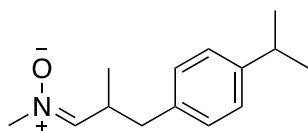
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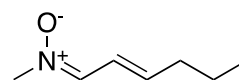
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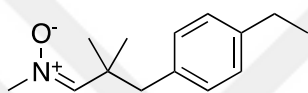
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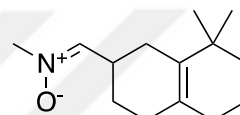
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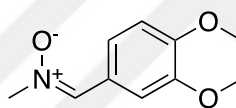
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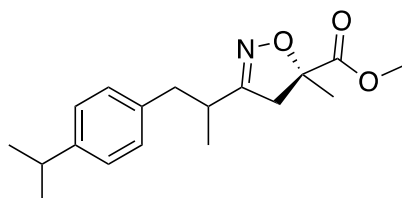
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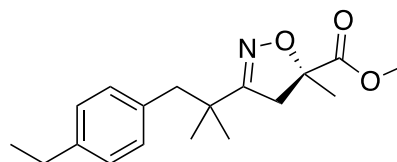
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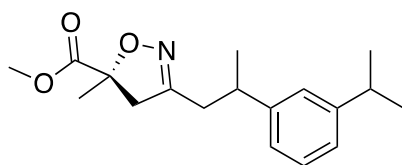
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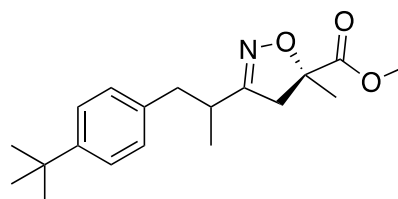
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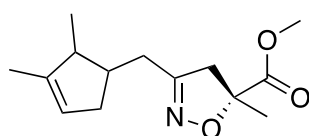
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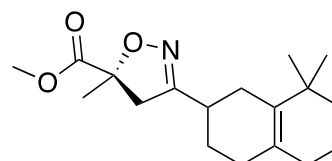
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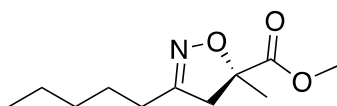
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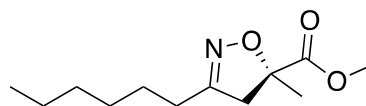
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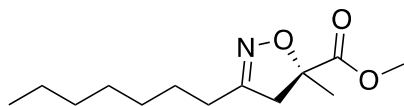
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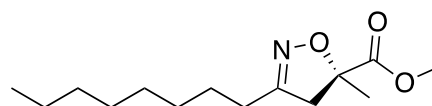
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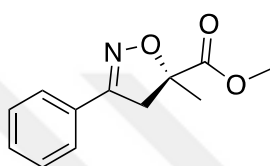
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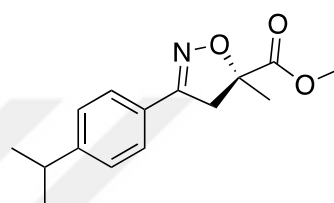
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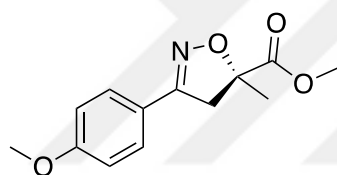
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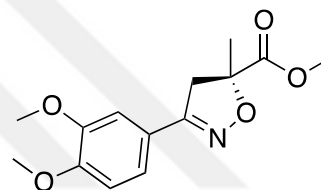
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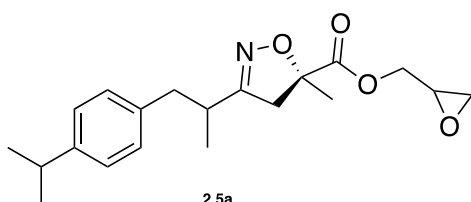
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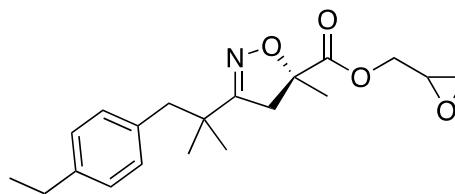
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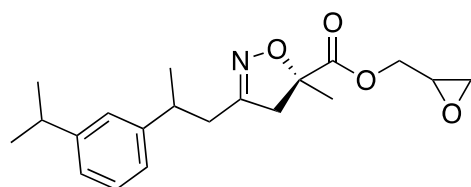
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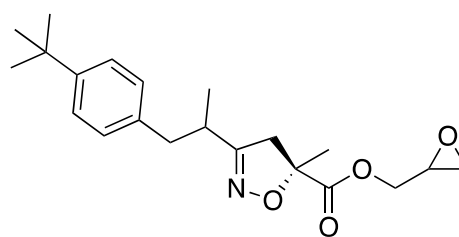
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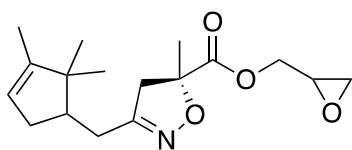
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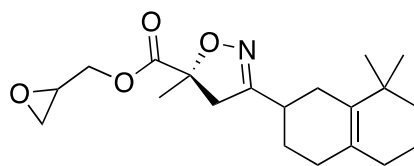
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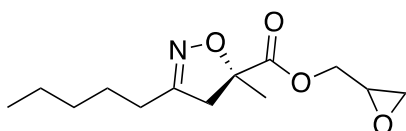
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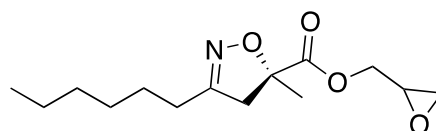
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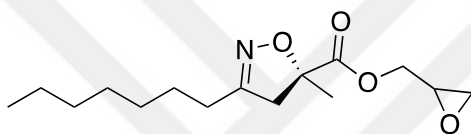
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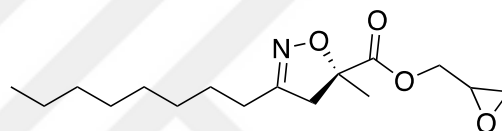
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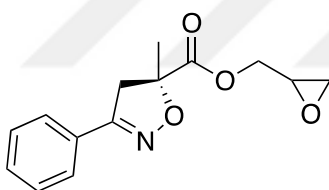
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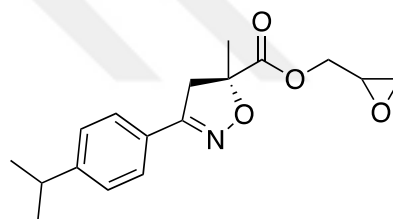
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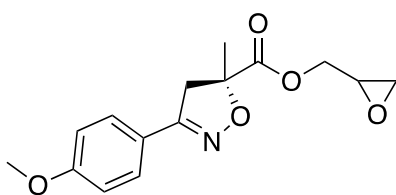
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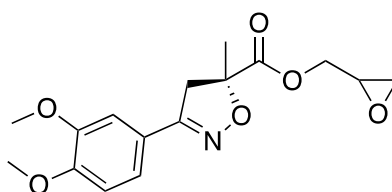
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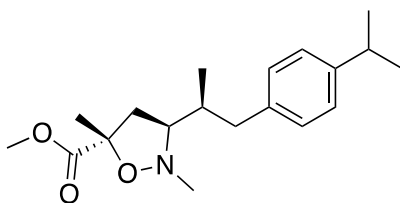
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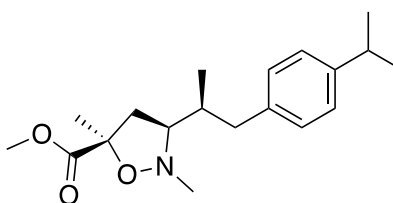
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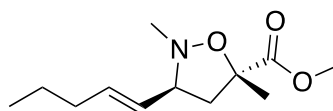
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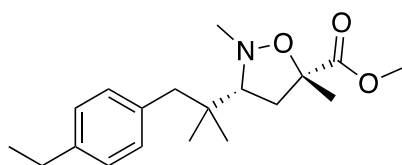
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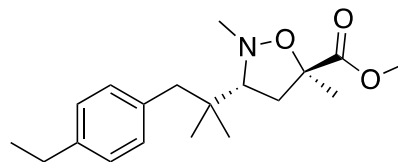
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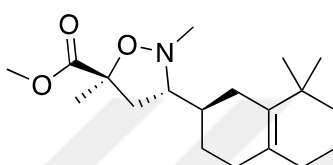
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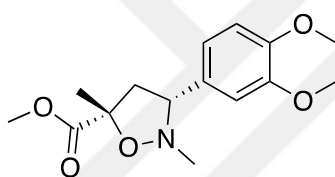
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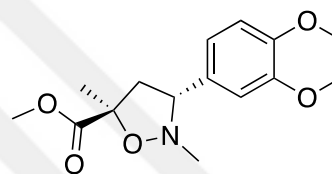
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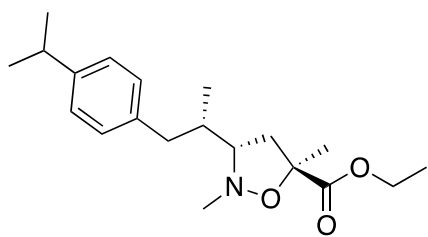
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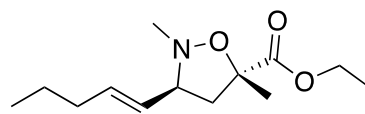
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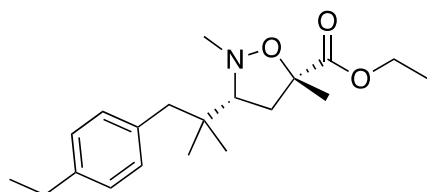
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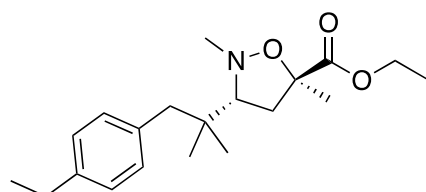
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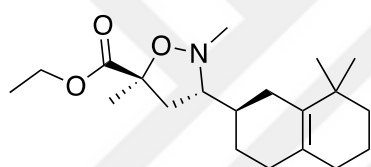
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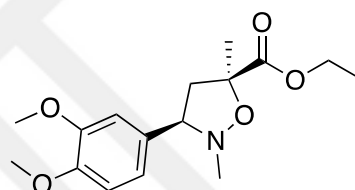
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2.7c'



2.7d



2.7e

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LIST OF ABBREVIATIONS AND SYMBOLS

1,3-DC	: 1,3-dipolar cycloaddition
Δ	: Heat
\$	: Dollar
π	: Pi
°C	: Santigrad degrees
¹H-NMR	: Proton nuclear magnetic resonance
¹³C-NMR	: Carbon nuclear magnetic resonance
ASTM	: American Society for Testing and Materials International
Co.	: Corporation
d	: Doublet
DCM	: Dichlorometane
dd	: Doublet of doublet
DPG	: Dipropylene glycol
dt	: Doublet of triplet
EMA	: Ethyl methacrylate
EtOH	: Ethanol
E/Z	: Isomeric structures
Et	: Ethyl
FT-IR	: Fourier transform infrared spectrometry
FT-MS	: Fourier transform mass spectrometry
GC-MS	: Gas chromatography mass spectormetry
GMA	: Glycidyl methacrylate
h	: Hour
HR-MS	: High resolution mass spectrometry
Hz	: Hertz
IR	: Infrared spectrometry
IFRA	: International Fragrance Association
J	: Coupling constant
Kg	: Kilogram
LC-MS	: Liquid chromatography mass spectrometry
M	: Molarity
m	: Multiplet

Me	: Methyl
min	: Minute
mL	: Mililiter
mmol	: Milimole
MHz	: Megahertz
MMA	: Methyl methacrylate
NEt₃	: Triethylamine
Ppm	: Parts per million
rt	: Room temperature
s	: Singlet
SAR	: Structure-Activity relationship
t	: Triplet
Temp.	: Temperature
TLC	: Thin Layer Chromatography
TOF	: Time of Flight
W	: Watt

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1. INTRODUCTION

1.1 Chemistry in the Fragrance Industry

Fragrances, known for their allure, have perpetually been hailed as potent triggers of subconscious emotions, unveiling concealed desires. The pursuit of new scents has spurred the evolution of diverse methods for obtaining fragrances. Among these, distillation, refined by Persians and introduced to Europe in the 9th century, stands as a preferred technique. Extraction is another method allowing the isolation of a blend of fragrance compounds, capturing the essence of natural materials.¹

The coexistence of these refined techniques laid the groundwork for the eventual industrialization of essential oils, a process realized a millennium later. While successful, the limited chemical stability of key components restricted the range of collectible oils, constraining options for perfumers. Despite some oils like lavender and eucalyptus being economically accessible due to ease of cultivation and extraction (priced at 69 to 82 \$/Kg),^{2,3} others like Jasmine oils remain notably expensive (around \$3,700/Kg),^{4,5} limiting their use to niche applications.⁶

To mitigate the economic challenges associated with aromatic chemicals and diversify the perfumer's palette, Synthetic Chemistry emerged as a valuable tool. This approach aimed not only to alleviate the cost burden but also to unveil novel molecules, adding richness and variety to the world of perfumery.

The 19th century marked a revolution in fragrance chemistry with the introduction of naturally occurring materials like coumarin **1.1** (1866),⁷ vanillin **1.2** (1876),⁸ and β -ionone **1.3** (1893),⁹ alongside the emergence of novel synthetic odorants such as musk xylol **1.4** (1891),¹⁰ methyl ionone **1.6** (1893),¹¹ and ethyl vanillin **1.5** (1894).¹² This period witnessed a transformative impact on various sectors, from the burgeoning perfumery industry to the rapidly evolving household cleaning market.¹³

Between 1759 and 1998, around 2,500 active fragrance ingredients became available for use by perfumers. Notably, during the early stages of this evolving chemistry, the discovery of synthetic ingredients often happened by chance (as observed in cases like musk xylene and cyclamen aldehyde)¹¹⁻¹⁴ or through the logical exploration of analogues based on known fragrances.^{15,16} In the last two decades, the inventory of fragrance ingredients has increased significantly to nearly 4,000, according to the International Fragrance Association (IFRA).^{17,18} This surge is credited to advancements in scientific and technological domains, especially in theory and computational chemistry, as well as in the understanding of odorant chemoreception.¹⁹⁻²¹ These breakthroughs have facilitated the creation of more efficient methods for identifying potent and novel odorants, employing techniques such as ligand-olfactory receptor design, conformational analysis, and structure-activity relationship (SAR).²²⁻²⁴

In tandem with these innovative strategies, early-stage implementation of toxicological and bio-accumulative tests has become standard practice. This proactive approach aids in the design of safer and more environmentally friendly synthetic odorants, reflecting a commitment to both olfactory innovation and sustainability.²⁵⁻²⁷

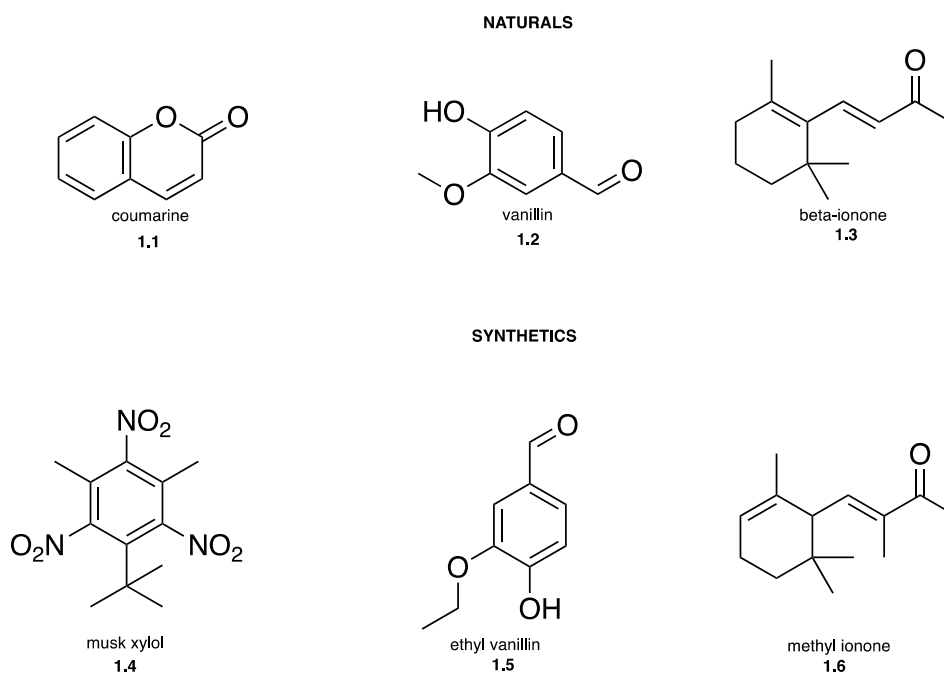


Figure 1-1. Natural and synthetic fragrant molecules

As the variety of odorants expanded, there arose a need for a more comprehensive classification system to bring order and facilitate comparisons among different fragrance materials. In 1983, Michael Edwards introduced a groundbreaking system known as the "fragrance wheel," which has since become the standard for categorizing fragrances. This wheel systematically classifies scents into four primary families: Floral, Oriental, Fresh, and Woody. Despite being based on the insights of a single perfumer, the system has proven highly consistent when compared to other classification approaches. The principal notes within each family are further subdivided into related sub-classes, providing a more detailed description.²⁸

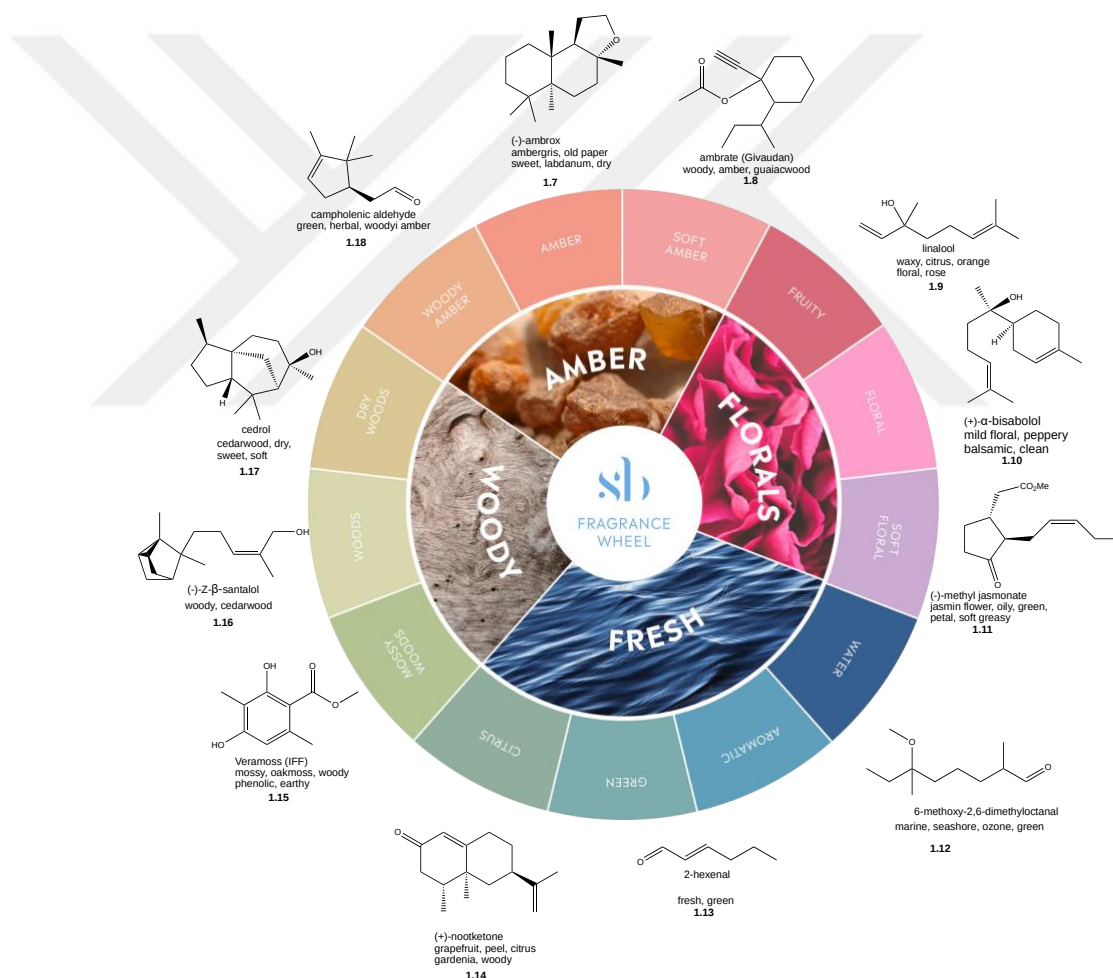
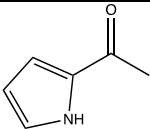
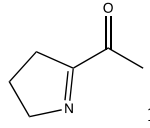
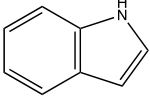
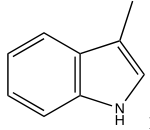


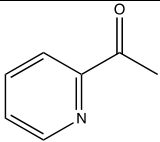
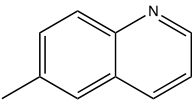
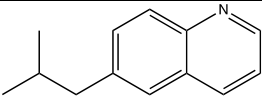
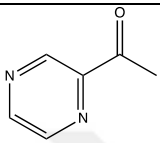
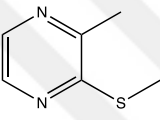
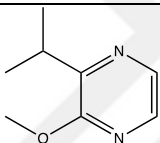
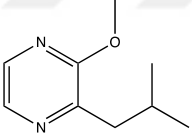
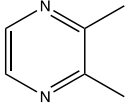
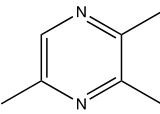
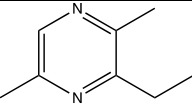
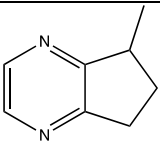
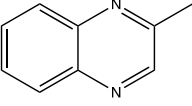
Figure 1-2- Fragrance Wheel

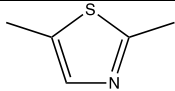
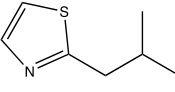
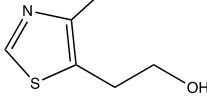
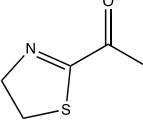
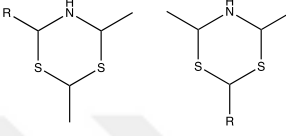
1.2 Nitrogen Containing Heterocyclic Fragrance and Flavour Compounds

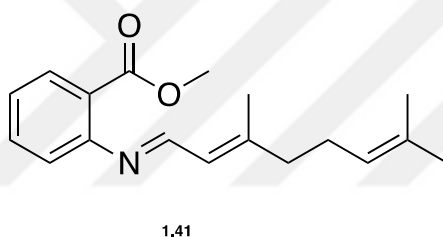
Numerous nitrogen- and sulfur-containing heterocycles have been detected in the aromatic components of various foods.^{48-51, 52, 53} In the case of roasted products such as coffee and heat-treated foods like baked bread or fried meat, these heterocycles originate from the interaction between reducing sugars and simple or sulfur-containing amino acids through Maillard reactions.^{52, 53} Despite being produced in smaller quantities compared to previously mentioned products, their impact on aroma quality is substantial, given their remarkably low odor threshold values.^{54, 55} Consequently, even trace amounts can significantly contribute to the overall aroma profile of many items. Nitrogen-containing heterocycles like pyrroles, indoles, pyridines, quinolines, and pyrazines serve as examples of fragrance and flavor compounds generated through these processes. On the other hand, thiazoles and dithiazines exemplify nitrogen- and sulfur-containing heterocycles. These compounds find predominant use in aroma compositions, with the noteworthy exceptions of indoles and quinolines, which play essential roles as fragrance substances.⁵⁶

Table 1-1 Some commercially available nitrogen and sulfur containing fragrance and flavor molecules

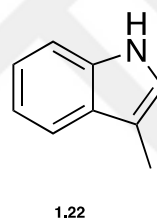
 1.19	2-acetylpyrrole	Roast odor
 1.20	2-acetyl-3,4-dihydro-5H-pyrrole	Characteristic odor of white bread crust
 1.21	Indole	Fecal odor, floral in high dilution
 1.22	3-methylindole, skatole	Indole-like odor, fecal

 1.23	2-acetylpyridine	Roast odor
 1.24	6-methylquinoline	Blossom odor, sweet animalic upon dilution
 1.25	6-isobutylquinoline	Mossy-earthly odor
 1.26	2-acetylpyrazine	Popcorn-like odor
 1.27	2-methylthio-3-methylpyrazine	Nutty, sweet, meaty, slightly green flavor
 1.28	2-methoxy-3-isopropylpyrazine	Green pea odor
 1.29	2-methoxy-3-isobutylpyrazine	Green pepper odor
 1.30	2,3-dimethylpyrazine	Roast odor, reminiscent of nuts
 1.31	Trimethylpyrazine	Roast odor, reminiscent of coffee and cocoa
 1.32	3-ethyl-2,5-dimethylpyrazine	Roast odor, reminiscent of nuts
 1.33	5-methyl-6,7-dihydro[5H]cyclopentapyrazine	Nutty, roast odor
 1.34	2-methylquinoxaline	Musty, roasted flavor

 1.35	2,5-dimethylthiazole	Meat-like odor
 1.36	2-isobutylthiazole	Tomato odor
 1.37	4-methyl-5-thiazolethanol	Meaty, roast odor
 1.38	2-acetyl-2-thiazoline	Cooked beef odor
 1.39 1.40	Alkyldimethyl-1,3,5-dithiazines	Roast odor



Citral methylanthranilate
schiff's base
fresh sweet lemon orangeflower fruity



Skatole
High conc. fecet odor
Low conc. floral odor

Figure 1-3 Nitrogen containing compounds as fragrance raw materials

Heterocyclic compounds play a crucial role in synthetic organic chemistry, given their significance in numerous naturally occurring molecules and their pivotal applications in pharmaceuticals and the cosmetic industries.⁵⁷⁻⁵⁸ These compounds, commonly featuring oxygen, sulfur, and nitrogen atoms in their structures, contribute to the flavors and fragrances of food, exhibiting valuable organoleptic characteristics.⁶⁰ Among these heterocycles, isoxazoline emerges as an intriguing option, as there are limited reported studies regarding its fragrant characteristics.⁶¹ Consequently, the synthesis of novel heterocycles with potential fragrant properties becomes highly desirable and presents a challenging endeavor.

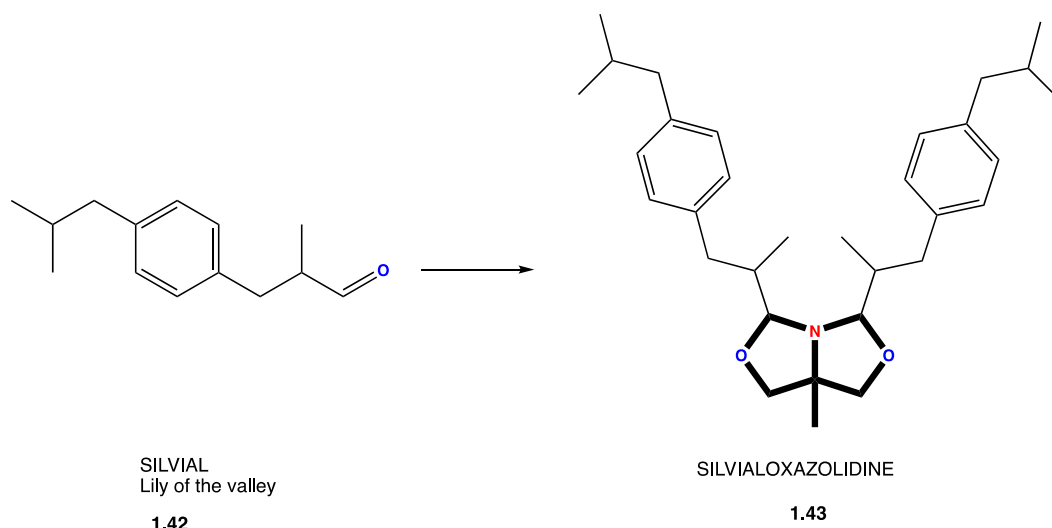


Figure 1-4- A commercial isoxazolidine odorant compound by Henkel Co.

1.3 1,3- Dipolar Cycloaddition Reactions

Cycloaddition reactions play a pivotal role in the practical synthesis of heterocycles, offering advantages such as complete atom economy and excellent compatibility with various functional groups.²⁹⁻³⁰ The 1,3-dipolar cycloaddition reaction involves the combination of two or more unsaturated molecules, or components within the same molecule, resulting in the formation of a cyclic adduct. Importantly, this process leads to a net reduction in the multiplicity of bonds.

1,3-Dipoles consist of elements primarily from main groups IV, V, and VI. The fundamental 1,3-dipoles predominantly involve second-row elements, with the central atom limited to either N or O, carrying both positive and negative charges distributed over three atoms and possessing 4π electrons. Consequently, only a restricted number of structures can be generated through permutations of N, C, and O. By excluding higher row elements, we can derive twelve allyl anion type and six allenyl anion type 1,3-dipoles. Given the diverse range of dipoles, Figure 1.5 illustrates a small selection, although various other dipole types also exist. Dipoles can be categorized into two groups: the allyl anion type, characterized by a bent structure, and the propargyl/allenyl anion type, exhibiting a linear structure as depicted below.

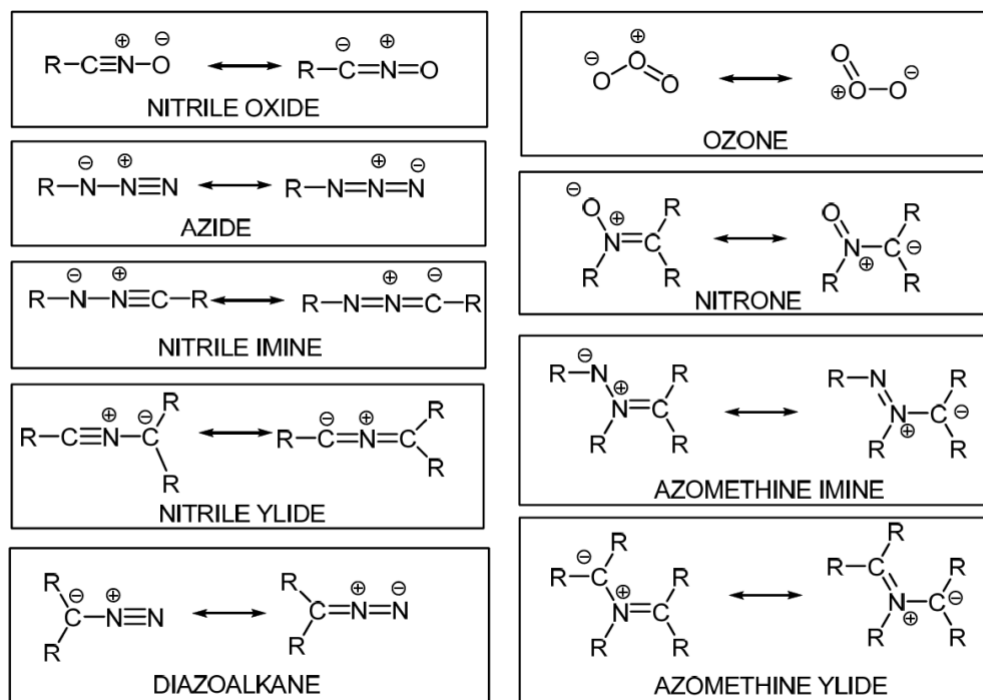


Figure 1-5 Right column is propargyl/allenyl anion type dipoles and left column is allyl anion type dipoles

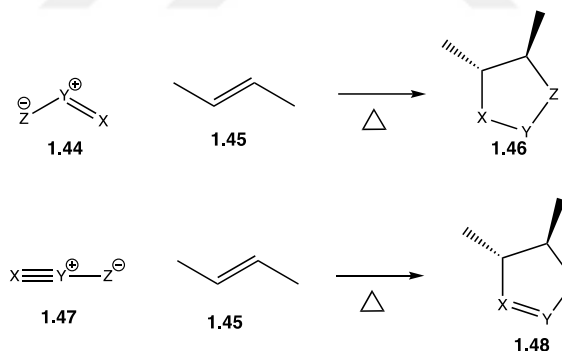


Figure 1-6- 1,3-Dipolar cycloaddition

One of the most efficient procedure for generating heterocyclic molecules in a single synthetic step is through conventional 1,3-dipolar cycloaddition reactions. The resulting regio- and/or stereochemistry of the products can be controlled depending on the substituents of the starting materials.³¹⁻³² Nitrile oxides stand out as one of the most commonly utilized 1,3-dipoles in these cycloaddition reactions, particularly for obtaining nitrogen-containing 5-membered heterocycles. Hence, considerable attention is directed towards the cycloaddition reaction of

nitrile oxides. This is attributed to the easy handling and high reactivity of nitrile oxides in their reactions with olefins and alkynes, leading to the formation of isoxazolines and isoxazoles.³³⁻³⁴

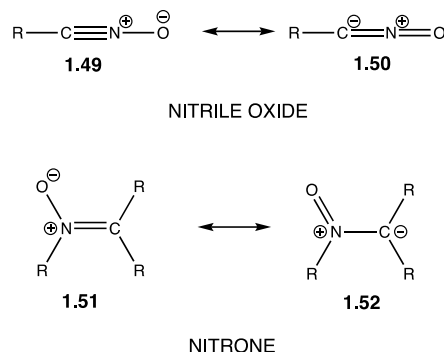


Figure 1-7- Nitrile oxide and nitron dipoles

In recent years, various theoretical models have been proposed to elucidate the observed regio- and stereoselectivity in 1,3-dipolar cycloadditions. Understanding how substituents influence reaction rates can be rationalized using Frontier Molecular Orbital (FMO) theory. This theory, initially developed by Woodward and Hoffmann and independently by Fukui, explores the role of orbital symmetry in pericyclic reactions. Houk further contributed by providing HOMO-LUMO values for dipolar compounds and their orbital coefficients at the terminal atoms. The orbital energy separation of interactions [HOMO(1,3-dipole)/LUMO(dipolarophile) and LUMO(1,3-dipole)/HOMO(dipolarophile)] is compared based on the nature of the dipole and the dipolarophile. When these energy differences exhibit distinct values, the FMO interaction associated with the lower value is presumed to dominate.

In 1,3-dipolar cycloaddition reactions, particularly those involving allyl anion type 1,3-dipoles and alkenes, the formation of diastereomers can occur through either an endo or exo mode. The endo approach is electronically favored, while the exo approach is sterically favored.

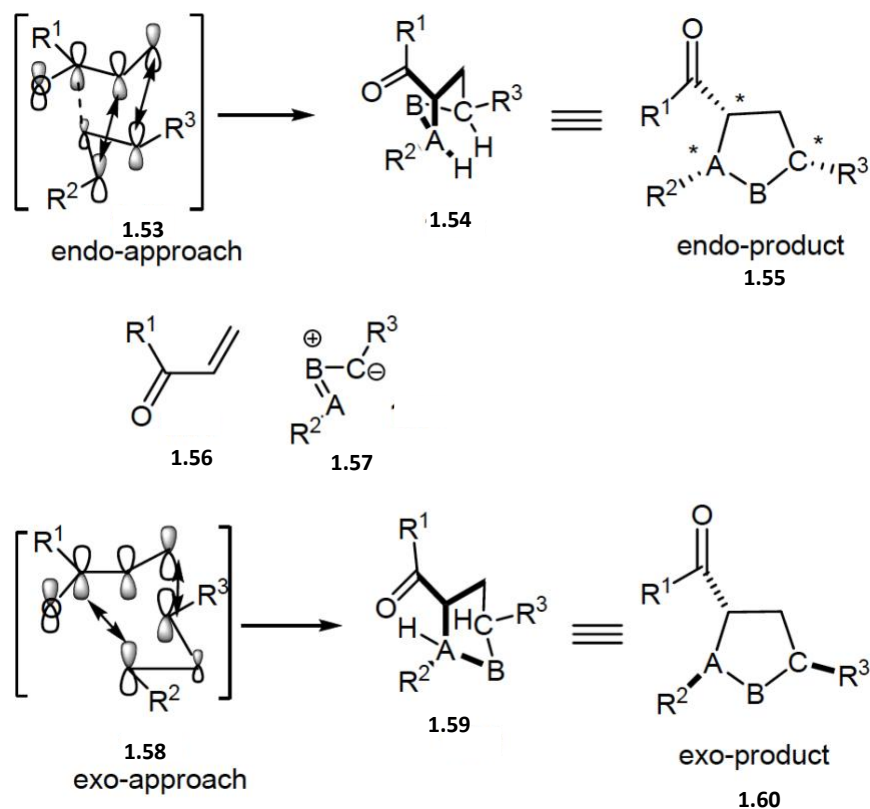


Figure 1-8 The endo/exo interactions in 1,3-dipolar cycloaddition

1,3-Dipolar cycloaddition reactions proceed by concerted mechanism and its transition state is controlled by the frontier molecular orbitals (FMO) of substrates. According to the relative dispositions of the HOMOs and LUMOs of the 1,3-dipole and the dipolarophile, they are classified as Type I, II and III reactions. According to Sustmann classification, nitron and nitrile oxide dipoles are examples of **Type II** reactions.

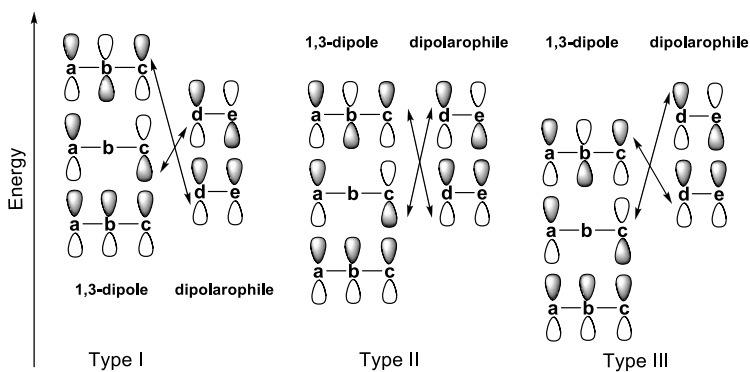


Figure 1-9 Sustmann classification of 1,3-dipole-dipolarophile HOMO-LUMO interactions

1.4 Introduction to Isoxazoli(di)nes

Depending on the choice of oxidants, the synthesis of nitrile oxide can be achieved either by the dehydrohalogenation of hydroxyimoyl chlorides or through the direct oxidation of aldoximes.³⁵ The resulting isoxazolines derived from nitrile oxides have undergone extensive scrutiny, primarily due to their wide-ranging applications within the pharmaceutical industry. These heterocyclic systems have already transcended the laboratory, finding a place as active pharmaceutical ingredients on pharmacy shelves. Isoxazolines, known for their versatility, exhibit diverse medicinal activities, encompassing antibacterial, anticonvulsant, antibiotic, antituberculosis, and antifungal properties.³⁶

Over the previous decades, there has been an increasing focus on synthesizing heterocyclic compounds containing isoxazolidine.³⁷ While various approaches, such as the cyclization of unsaturated hydroxylamines³⁸ and isoxazolines or isoxazolidinones asymmetric reduction,³⁹ have been employed to achieve isoxazolidines, the 1,3-dipolar cycloaddition is a recognized pathway that allows for the synthesis of a diverse array of compounds.⁴⁰⁻⁴¹

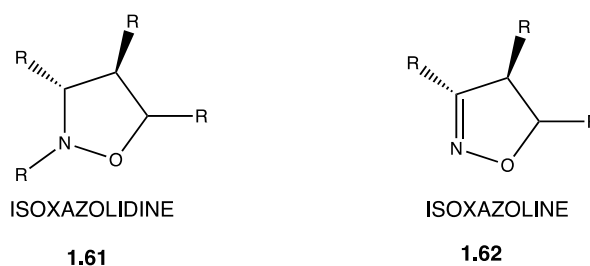


Figure 1-10- Isoxazolidine and isoxazoline core moieties

In a 1,3-dipolar cycloaddition, the dipolarophile refers to a reactive alkene moiety containing 2π electrons. Dipolarophiles can be broadly categorized into three classes: electron-rich, electron-deficient, and conjugated dipolarophiles. Depending on the specific dipole present, α , β -unsaturated aldehydes, ketones, esters, allylic alcohols, allylic halides, vinylic ethers, and alkynes are examples of dipolarophiles that exhibit ready reactivity. It's worth noting that besides these, other 2π -moieties, such as carbonyls and imines, also have the capacity to undergo cycloaddition with dipoles⁴².

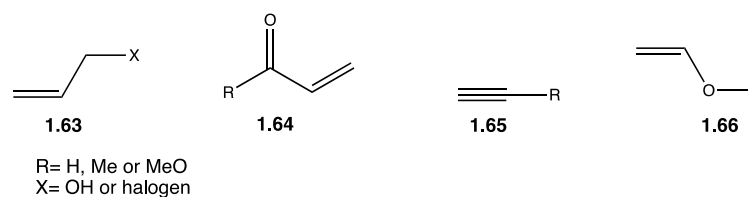


Figure 1-11- Some examples for dipolarophiles

Isoxazolidines, recognized as privileged cores found in various biogenic products and drug candidate molecules, exhibit significant bioactivities including antifungal⁴³, antiviral⁴⁴, anti-inflammatory⁴⁵, antimicrobial⁴⁶, and cytotoxic activities⁴⁷. The N-O bond reactivity in the isoxazolidine ring makes them valuable intermediates, capable of leading to a diverse array of functional groups, complex molecules, or open-chain products.

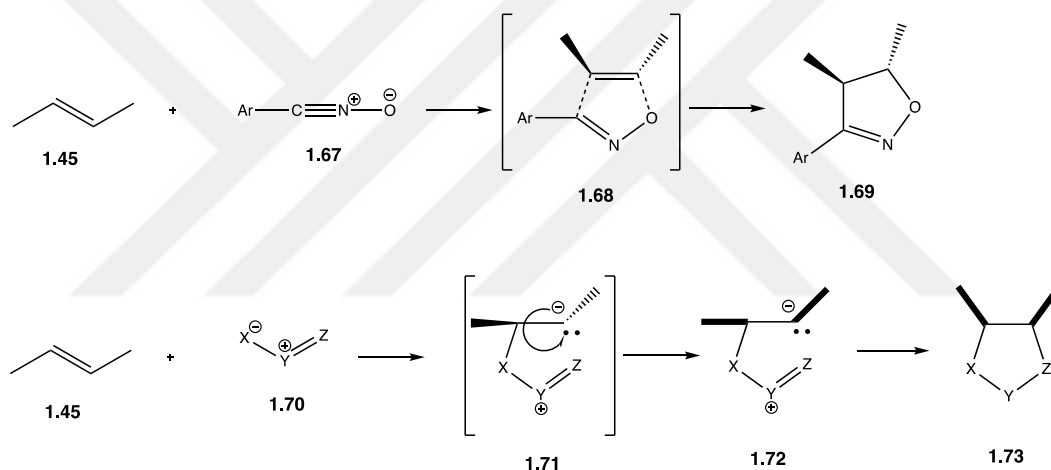


Figure 1-12- 1,3-dipolar cycloaddition and isomerization of dipolarophiles

Methyl methacrylate (MMA) and glycidyl methacrylate (GMA) stand as pivotal monomers in the realm of polymer chemistry.⁶²⁻⁶³ MMA, known for its versatility, undergoes polymerization through various techniques—free radical polymerization, emulsion polymerization, and suspension polymerization—resulting in polymers with diverse properties. These polymers find widespread applications in industries such as automotive, construction, and medical, owing to their exceptional traits, including high transparency, weather resistance, and biocompatibility.

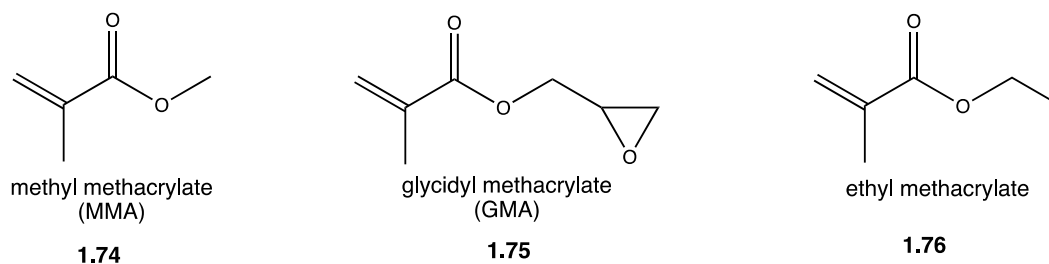


Figure 1-13- Methyl methacrylate, glycidyl methacrylate and ethyl methacrylate

Conversely, GMA, a bifunctional monomer, encompasses both a methacrylate group and an epoxy group. This dual functionality makes GMA a crucial component in the synthesis of advanced materials like adhesives, coatings, and composites. The inclusion of GMA significantly enhances adhesion, toughness, and durability in the final materials. The significance of both MMA and GMA lies in their adaptability, offering the potential to contribute to the creation of novel materials with unique and desirable properties.

As a result, the selection of MMA and GMA as dipolarophilic reagents in this thesis study is deliberate, given their broad applicability and widespread availability on a commercial scale.⁶⁴ This choice aligns with the goal of exploring their versatile nature to contribute to the development of innovative materials.

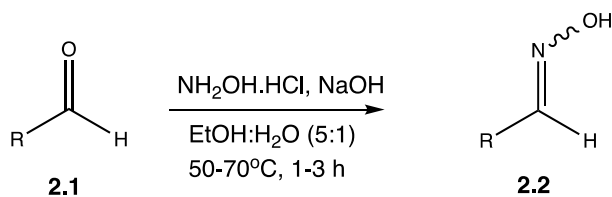
2. EXPERIMENTAL

2.1 Materials and Apparatus

All commercially available chemicals were utilized without additional purification. Infrared (IR) spectra were captured using a SHIMADZU FTIR-8400S instrument with NaCl discs. Proton (^1H) and carbon-13 (^{13}C) nuclear magnetic resonance (NMR) spectra (at 400 MHz for proton and 100 MHz for carbon, respectively) were recorded on an Agilent 400 MHz instrument in CDCl_3 . Multiplicities were denoted as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets). Liquid chromatography-mass spectrometry (LC-MS) spectra were acquired using a Waters 2695 Alliance Micromass ZQ instrument. HRMS of compounds were obtained using an orthogonal acceleration TOF mass spectrometer and a Fourier-transform mass spectrometer (4.7 T). All chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS). Coupling constants (J) were expressed in Hertz. Standard thin-layer chromatography (TLC) analyses were conducted on pre-coated silica gel plates with a fluorescent indicator. Flash column chromatography was executed on silica gel (230-400 Mesh ASTM). Staining solutions of potassium permanganate and phosphomolybdic acid were employed for visualizing TLC spots. As all aldoximes are documented in the literature, only NMR data are presented.

2.2 General Procedure for Aldoxime Synthesis

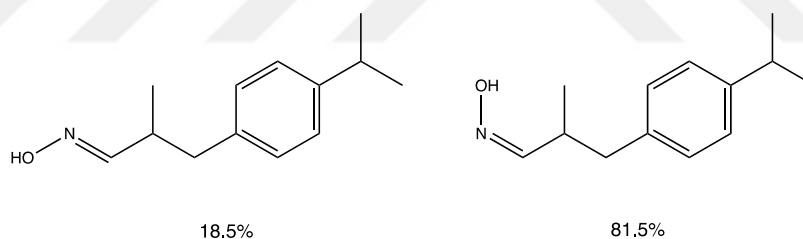
In this thesis study, isoxazoles and isoxazolidines were synthesized in order to evaluate their organoleptic features. For isoxazoles synthesis, aldoximes were prepared according to the known methods from the literature,⁶⁸ and for isoxazolidine synthesis aldonitriles were prepared according to the known methods from the literature.⁶⁹



Scheme 2-1- Aldoxime synthesis procedure

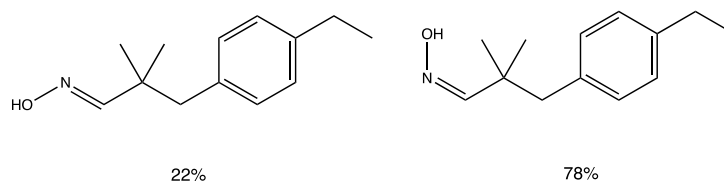
The hydroxylamine hydrochloride (1.2 mol) was dissolved in 400 ml 95% EtOH and 50 ml H₂O. Then, NaOH (1.2 mol) was added to this mixture portion wisely. To this resulting mixture, aldehyde (1mol) was added and left for stirring at room temperature. The reaction was monitored by TLC. After completion of reaction, ethanol was evaporated under vacuum. The crude product was extracted with (200 ml x 2) ethyl acetate. After drying of ethyl acetate over Na₂SO₄, it was evaporated under vacuum to give desired aldoxime.

2.2.1 3-(4-Isopropylphenyl)-2-methylpropanal oxime (2.2a)



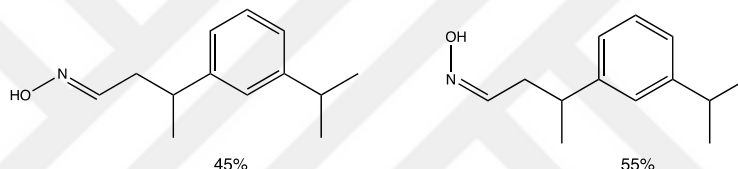
Pale yellow crystal, 174.2 g (0.85 mol) of **2.2a**, yield 85%, with a GC E/Z isomer ratio of 18,5/81,5. For the major isomer: ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 6.2 Hz, 1H, N=CH), 7.18 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 2.92 (dq, J = 13.9, 6.9 Hz, 1H), 2.84 (dt, J = 13.2, 6.5 Hz, 1H), 2.71 (dt, J = 13.0, 6.5 Hz, 1H), 2.61 (dd, J = 13.1, 7.9 Hz, 1H), 1.27 (d, J = 6.9 Hz, 6H), 1.11 (d, J = 6.7 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 155.8 (C=N), 146.8, 136.4, 129.1, 126.4, 40.5, 36.2, 33.7, 24.1, 17.3.

2.2.2 3-(4-Ethylphenyl)-2,2-dimethylpropanal oxime (2.2b)



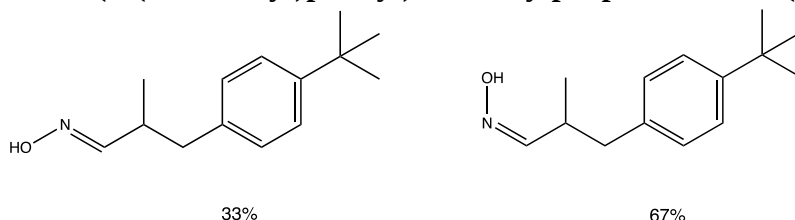
Pale yellow liquid 168.1g (0.82 mol) of **2.2b**, yield 82%, with a GC E/Z isomer ratio of 22/78. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.49 (s, 1H, N=CH), 7.19 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 2.75 (s, 2H), 2.70 (dd, J = 15.8, 8.1 Hz, 2H), 1.31 (t, J = 7.7 Hz, 3H), 1.17 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 158.7(C=N), 142.3, 134.5, 130.5, 127.5, 47.0, 37.7, 28.5, 25.1, 15.7.

2.2.3 3-(3-Isopropylphenyl) butanal oxime (2.2c)



Yellow to amber liquid 164 g (0.8 mol) of **2.2c**, yield 80%, with a GC E/Z isomer ratio of 45/55. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.46 (dd, J = 7.0, 5.9 Hz, 1H, N=CH), 7.34 (t, J = 7.8 Hz, 2H), 7.21 – 7.12 (m, 2H), 3.12 – 2.95 (m, 1H), 2.91 – 2.83 (m, 1H), 2.74 (ddd, J = 16.1, 8.0, 5.0 Hz, 1H), 2.66 – 2.52 (m, 1H), 1.42 (t, J = 6.7 Hz, 3H), 1.36 (d, J = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 151.4 (C=N), 149.2, 145.8, 128.6, 125.3, 124.5, 124.3, 38.1, 37.3, 34.3, 24.2, 22.4.

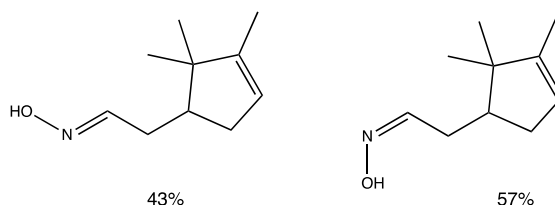
2.2.4 3-(4-(Tert-butyl)phenyl)-2-methylpropanal oxime (2.2d)



Yellow liquid 186.1g (0.85 mol) of **2.2d**, yield 85%, with a GC cis/trans isomer ratio of 33/67. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, J = 6.2 Hz, 1H, N=CH), 7.35 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 2.84 (d, J = 6.2 Hz, 1H), 2.79 – 2.68 (m, 1H), 2.64 (d, J = 7.9 Hz, 1H), 1.35 (s, 9H), 1.12 (d,

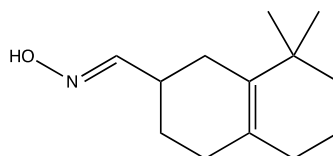
$J = 6.7 \text{ Hz, 3H}$). ^{13}C NMR (100 MHz, CDCl_3) δ 151.4 (C=N), 149.2, 145.8, 128.6, 125.3, 124.5, 124.2, 38.1, 37.3, 34.3, 24.2, 22.4.

2.2.5 2-(2,2,3-Trimethylcyclopent-3-en-1-yl)acetaldehyde oxime (2.2e)



While 80 g of sodium acetate and 61 g of hydroxylamine hydrochloride are mixed in 1000 mL of water in a 5000 mL flask, 152 g of campholenal in 1000 mL of acetonitrile is slowly added at room temperature. The mixture is continued under these conditions for 3 hours. The reaction mixture, which comes to room temperature, is extracted with DCM. Then the DCM is removed with the help of the evaporator. According to GC-MS data, oxime was obtained as diastereomer mixture with 81.5% purity. Yellow to orange liquid 141.9g (0.85 mol) of **2.2e**, yield 85%, with a GC cis/trans isomer ratio of 43/57. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.45 (t, $J = 6.4 \text{ Hz}$, 1H, C=NH), 6.79 (t, $J = 5.4 \text{ Hz}$, 1H, C=CH), 5.23 (s, 1H, OH), 2.44 – 2.29 (m, 2H), 2.17 (ddd, $J = 14.2, 10.2, 6.6 \text{ Hz}$, 1H), 2.03 – 1.86 (m, 2H), 1.62 (s, 3H), 1.01 (d, $J = 6.3 \text{ Hz}$, 3H), 0.82 (d, $J = 7.3 \text{ Hz}$, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 152.3(C=N), 148.3, 121.5, 47.8, 35.4, 30.3, 25.8, 19.8, 12.7.

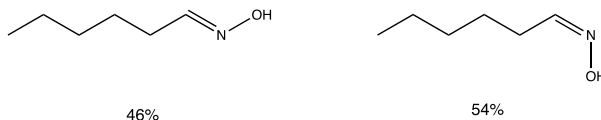
2.2.6 8,8-Dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalene-2-carbaldehyde oxime (2.2f)



Amber liquid 149 g (0.72 mol) of **2.2f**, yield 72%. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.39 (d, $J = 6.5 \text{ Hz}$, 1H, N=CH), 2.45 – 2.38 (m, 1H), 1.98 – 1.86 (m, 4H), 1.57 (dt, $J = 12.5, 6.4 \text{ Hz}$, 4H), 1.47 – 1.38 (m, 4H), 0.94 (s,

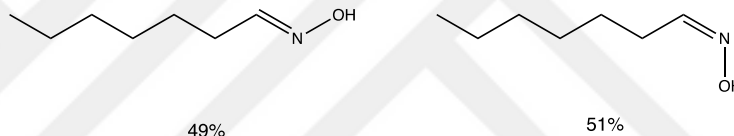
6H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.7 (C=N), 133.1, 127.1, 39.5, 35.5, 33.7, 31.1, 29.8, 28.2, 27.1, 26.6, 19.2.

2.2.7 Hexanal oxime (2.2g)



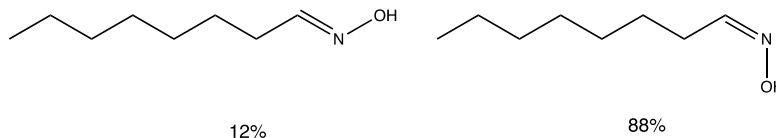
White crystal 88.5 g (0.77mol) of **2.2g**, yield 77%, with a GC E/Z isomer ratio of 46/54. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.42 (t, J = 6.2 Hz, 1H, N=CH), 2.37 (td, J = 7.6, 5.5 Hz, 2H), 2.19 (dd, J = 13.8, 7.4 Hz, 2H), 1.52 – 1.42 (m, 2H), 1.34 – 1.26 (m, 2H), 0.92 – 0.86 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 152.8 (C=N), 31.2, 29.4, 26.3, 22.3, 13.9.

2.2.8 Heptanal oxime (2.2h)



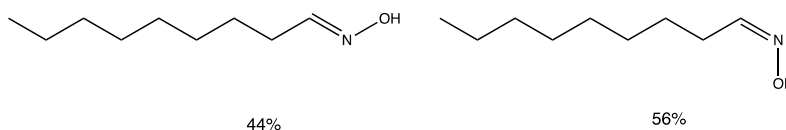
White crystal 103.2g (0.80 mol) of **2.2h**, yield 80%, with a GC cis/trans isomer ratio of 49/51. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.40 (t, J = 6.2 Hz, 1H, N=CH), 2.36 (td, J = 7.5, 5.5 Hz, 2H), 2.18 (dd, J = 14.1, 7.0 Hz, 2H), 1.51 – 1.42 (m, 2H), 1.35 – 1.21 (m, 4H), 0.90 – 0.85 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 152.7 (C=N), 31.5, 28.7, 26.6, 25.0, 22.5, 14.0.

2.2.9 Octanal oxime (2.2i)



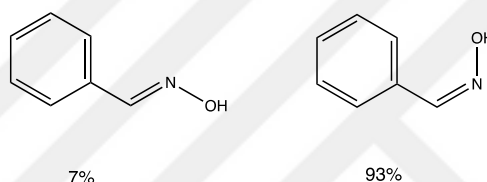
White crystal 131.6 g (0.92 mol) of **2.2i**, yield 92%, with a GC E/Z isomer ratio of 12/88. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.40 (t, J = 6.2 Hz, 1H, N=CH), 2.36 (td, J = 7.5, 5.5 Hz, 2H), 2.17 (dd, J = 13.8, 7.4 Hz, 2H), 1.50 – 1.42 (m, 2H), 1.33 – 1.20 (m, 6H), 0.85 (dt, J = 6.9, 3.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 152.8 (C=N), 31.7, 29.3, 29.0, 26.6, 25.0, 22.6, 14.0.

2.2.10 Nonanal oxime (2.2j)



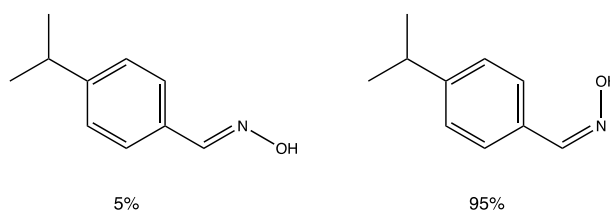
White crystal 141.3 g (0.90 mol) of **2.2j**, yield 90%, with a GC E/Z isomer ratio of 44/56. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.40 (t, J = 6.2 Hz, 1H, $\text{N}=\text{CH}$), 2.36 (td, J = 7.5, 5.5 Hz, 2H), 2.17 (dd, J = 13.8, 7.4 Hz, 2H), 1.51 – 1.41 (m, 4H), 1.34 – 1.20 (m, 6H), 0.85 (dt, J = 6.9, 3.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 152.9 ($\text{C}=\text{N}$), 31.8, 29.5, 29.3, 26.5, 26.0, 25.0, 22.6, 14.1.

2.2.11 Benzaldehyde oxime (2.2k)



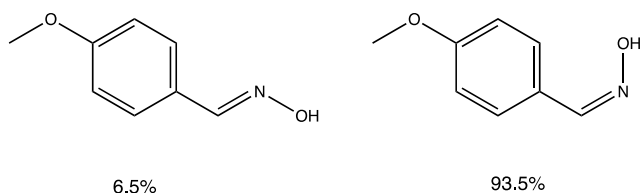
Amber liquid 115 g (0.95 mol) of **2.2k**, yield 95%, with a GC E/Z isomer ratio of 7/93. ^1H NMR (400 MHz, CDCl_3) δ 8.27 (s, 1H, $\text{N}=\text{CH}$), 7.66 – 7.63 (m, 2H), 7.43 – 7.40 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 150.7 ($\text{C}=\text{N}$), 131.9, 130.2, 128.9, 127.2.

2.2.12 4-Isopropylbenzaldehyde oxime (2.2l)



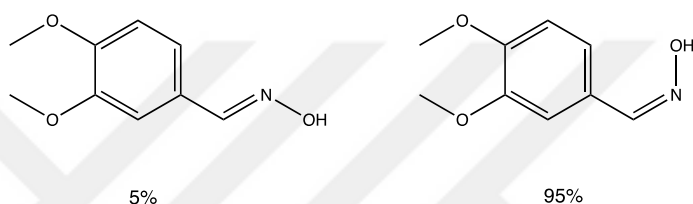
Pale yellow crystal 146.7g (0.90 mol) of **2.2l**, yield 90%, with a GC E/Z isomer ratio of 5/95. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 8.19 (s, 1H, $\text{N}=\text{CH}$), 7.54 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 2.98 – 2.89 (m, 1H), 1.27 (d, J = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 151.3 ($\text{C}=\text{N}$), 150.3, 129.4, 127.2, 126.9, 34.1, 23.8.

2.2.13 4-Methoxybenzaldehyde oxime (2.2m)



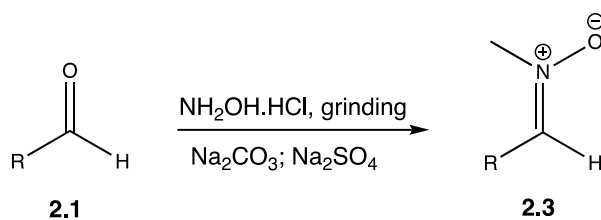
Milky brown solid 132.9 g (0.88 mol) of **2.2m**, yield 88%, with a GC E/Z isomer ratio of 6.5/93.5. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H, N=CH), 7.53 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 161.1 (C=N), 149.9, 128.6, 124.5, 114.3, 55.3.

2.2.14 3,4-Dimethoxybenzaldehyde oxime (**2.2n**)



Pale brown 153.9g (0.85 mol) of **2.2n**, yield 85%, with a GC E/Z isomer ratio of 5/95. For the major isomer: ^1H NMR (400 MHz, CDCl_3) δ 8.08 (s, 1H, N=CH), 7.21 (d, J = 1.8 Hz, 1H), 7.02 (dd, J = 8.3, 1.9 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 3.89 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 150.8 (C=N), 150.2, 149.3, 124.8, 121.7, 110.7, 108.0, 55.9.

2.3 General Procedure for Aldonitrone Synthesis

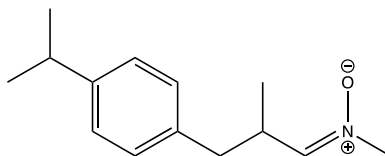


Scheme 2-2- Aldonitrone synthesis procedure

A mixture of aromatic aldehyde (10 mmol), hydroxylamine hydrochloride (1.65 g, 20 mmol), sodium carbonate (2.33 g, 22 mmol) and sodium sulphate (0.71 g, 5 mmol) were added in a mortar and ground rapidly with a pestle at room temperature. The reaction was monitored by TLC. Ethyl acetate (50 mL) was added to the crude product mixture and filtered. The filtrate was extracted three times with

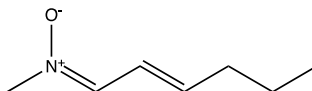
water. After drying of ethyl acetate over Na₂SO₄, it was evaporated under vacuum to give aldonitrone in pure state.

2.3.1 (Z)-N-(3-(4-Isopropylphenyl)-2 methylpropylidene) methanamine oxide (2.3a)



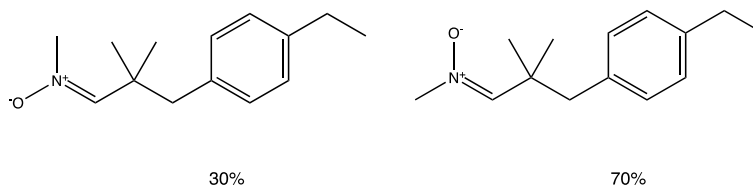
Colorless oil, yield (65%, 1423 mg), only Z isomer. IR (KBr, cm⁻¹): 2958, 2927(C-H aliphatic), 1600(C=N), 1512, 1458, 1407, 1139, 963, 808, 570. ¹H NMR (300 MHz, CDCl₃) δ 7.06 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.46 (dd, J = 7.2, 0.7 Hz, 1H, C=NH), 3.53 (s, 3H, NCH₃), 3.28 (dt, J = 14.0, 7.0 Hz, 1H), 2.81 – 2.71 (m, 2H), 2.57 (dd, J = 13.7, 7.6 Hz, 1H), 1.15 (d, J = 6.9 Hz, 6H), 1.00 (d, J = 6.9 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 146.9, 144.3 (C=N), 136.4, 129.1, 126.5, 52.7 (NCH₃), 38.8, 33.8, 32.8, 24.2, 16.1. HRMS *m/z* (+APCI-TOF) calcd for C₁₄H₂₁NO [M+H]⁺ : 220.0701, found 220.0700.

2.3.2 (Z)-N-((E)-Hex-2-en-1-ylidene)methanamine oxide (2.3b)



Light yellow oil, yield (44%, 559 mg), only Z isomer. IR (KBr, cm⁻¹): 2958, 2928, 2870 (C-H aliphatic), 1575(C=N), 1457, 1397, 1257, 1144, 976, 930, 802. HRMS *m/z* (+APCI-TOF) calcd for C₇H₁₃NO [M+H]⁺ : 128.1075, found 128.1067.

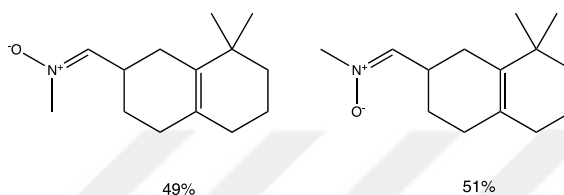
2.3.3 (Z)-N-(3-(4-Ethylphenyl)-2,2-dimethylpropylidene)methanamine oxide (2.3c)



Colorless oil, yield (62%, 1360 mg), isomer ratio, E/Z : (30:70). IR (KBr, cm⁻¹): 2960, 2927, 2870 (C-H aliphatic), 1593 (C=N), 1512, 1412, 1226, 1154, 931,

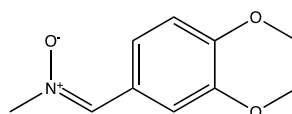
850, 753, 603. For the major isomer; ^1H NMR (400 MHz, CDCl_3) δ 7.05 (d, $J = 8.3$ Hz, 2H), 7.00 (d, $J = 8.1$ Hz, 2H), 6.33 (d, $J = 0.7$ Hz, 1H, C=NH), 3.63 (d, $J = 0.6$ Hz, 2H), 2.56 (q, $J = 7.6$ Hz, 2H), 1.99 (s, 3H), 1.21 (s, 6H), 1.18 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 147.7, 142.1 (C=N), 135.6, 129.8, 127.6, 53.6 (NCH₃), 42.6, 37.7, 28.4, 24.7, 21.1, 15.5. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{14}\text{H}_{21}\text{NO}$ $[\text{M}+\text{H}]^+$: 220.0701, found 220.1713.

2.3.4 (Z)-N-((8,8-Dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)methylene)methanamine oxide (2.3d)



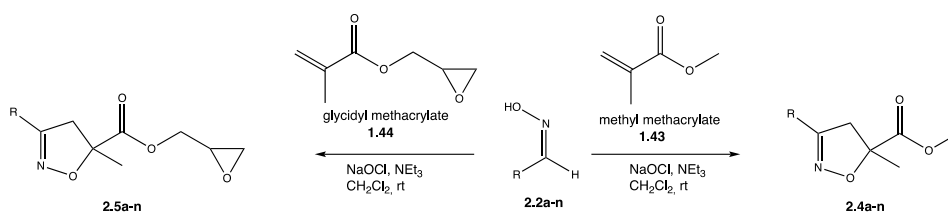
Colorless oil, yield (70%, 1360 mg), isomer ratio, E/Z : (49:51). IR (KBr, cm^{-1}): 2924, 2865, 2830 (C-H aliphatic), 1600 (C=N), 1408, 1169, 1153, 936, 731, 533. For the major isomer; ^1H NMR (400 MHz, CDCl_3) δ 6.53 (s, 1H, C=NH), 3.65 (s, 3H, NCH₃), 3.25 – 2.94 (m, 1H, CH), 2.04 – 1.99 (m, 1H), 1.85 – 1.77 (m, 6H), 1.60 – 1.52 (m, 3H), 1.43 – 1.37 (m, 2H), 0.93 (s, 6H, CH₃). ^{13}C NMR (100 MHz, CDCl_3) δ 144.3 (C=N), 134.9, 125.2, 52.7 (NCH₃), 39.5 (ipso C), 33.6, 32.1, 31.2, 29.3, 27.3, 25.5, 24.7, 23.0, 19.2. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{14}\text{H}_{23}\text{NO}$ $[\text{M}+\text{H}]^+$: 222.1858, found 222.1859.

2.3.5 (Z)-N-(3,4-Dimethoxybenzylidene)methanamine oxide (2.3e)



White solid, yield (68 %, 1326 mg), only Z isomer. IR (KBr, cm^{-1}): 1592 (C=N), 1508, 1456, 1415, 1268, 1236, 1167, 1139, 1015, 808, 750, 631, 536. ^1H NMR (400 MHz, CDCl_3) δ 8.29 (d, $J = 1.8$ Hz, 1H, C=NH), 7.48 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.38 (s, 1H), 6.90 (d, $J = 8.5$ Hz, 1H), 3.93 (s, 6H, OCH₃), 3.89 (s, 3H, NCH₃). ^{13}C NMR (75 MHz, CDCl_3) δ 150.9, 148.7, 135.4 (C=N), 124.0, 123.1, 111.0, 110.8, 56.1 (OCH₃), 54.2. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 196.0974, found 196.0978.

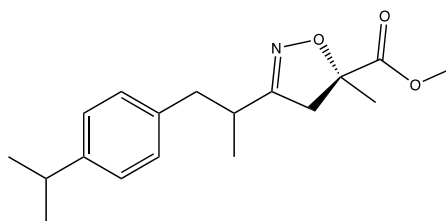
2.4 General Procedure for Isoxazoline Carboxylate Synthesis



Scheme 2-3- General synthetic route for isoxazoline derivatives

To a mixture of methyl methacrylate or glycidyl methacrylate (10 mmol) and NEt_3 (10 mmol) in 25 mL of dichloromethane was added 55 mL of 5 % NaOCl solution at 0-5 °C. To this mixture, aldoxime (12 mmol) was added drop wisely under vigorous stirring over a period of 15 min. The mixture was slowly allowed to warm to 25 °C with vigorous stirring for 120 min. After completion of reaction based on TLC (Thin Layer Chromatography) the organic layer was extracted with 2x50 mL water. The combined organic layers were dried over Na_2SO_4 . After evaporation of solvent under vacuum, By column chromatography major diastereomer was separated and purified to give desired isooxazoline carboxylated product.

2.4.1 Methyl 3-(1-(4-isopropylphenyl)propan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.4a)

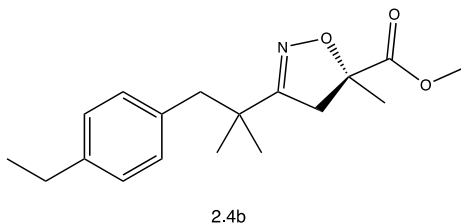


2.4a

After evaporation of solvent under vacuum, the major diastereomer was purified by column chromatography to give 2.61 g (8.6 mmol) of **2.4a** 86%, Only one isomer: IR (KBr): $\nu = 2960, 2933$ (alif. C-H), 1737 (C=O), 1672 (C=N), 1514, 1456, 1294, 1199, 1170, 1112, 866, 734 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.22 (d, $J = 1.4$ Hz, 2H), 7.04 (d, $J = 2.7$ Hz, 2H), 3.66 (s, 3H), 3.32 (d, $J = 8.2$ Hz, 1H), 2.85 – 2.81 (m, 1H), 2.80 (d, $J = 6.5$ Hz, 1H), 2.65 (d, $J = 1.6$ Hz, 1H), 2.63 – 2.57 (m, 2H), 1.50 (s, 3H), 1.23 (s, 6H), 1.07 (d, $J = 3.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 172.8 (C=O), 162.5 (C=N), 149.1, 135.9, 128.6, 125.2, 84.7, 52.8, 45.1,

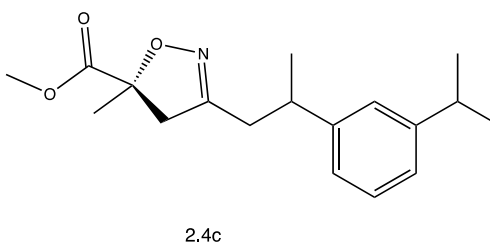
40.2, 34.6, 34.3, 31.3, 23.2, 17.7. HRMS m/z (+APCI-TOF) calcd for $C_{18}H_{25}NO_3$ $[M+H]^+$: 304.1913, found 304.1900.

2.4.2 Methyl 3-(1-(4-ethylphenyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.4b)



By column chromatography major diastereomer was separated and purified to give 2.61 g (8.6 mmol) of **2.4b**, 80%, with a GC diastereomer ratio of 26/74. For the major isomer: IR (KBr): ν = 2964, 2931 (alif. C-H), 1737 (C=O), 1620 (C=N), 1514, 1456, 1296, 1197, 1174, 1111, 879, 759 cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 3.79 (s, 3H, OCH_3), 3.45 (d, J = 17.3 Hz, 1H), 2.78 (d, J = 4.4 Hz, 2H), 2.71 (d, J = 14.2 Hz, 1H), 2.62 (q, J = 7.6 Hz, 2H), 1.59 (s, 3H), 1.23 (t, J = 6.5 Hz, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.17 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (C=O), 165.2(C=N), 142.4, 134.4, 130.4, 127.5, 85.1, 46.5, 45.0, 37.3, 28.4, 25.9, 25.6, 23.5, 15.6. HRMS m/z (+APCI-TOF) calcd for $C_{18}H_{25}NO_3$ $[M+H]^+$: 304.1913, found 304.1896.

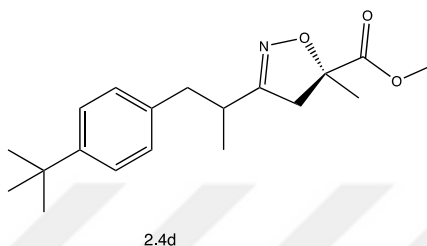
2.4.3 Methyl 3-(2-(3-isopropylphenyl)propyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.4c)



By column chromatography major diastereomer was separated and purified to give 2.42 g (8 mmol) of **2.4c**, 85%, Only one isomer: IR (KBr): ν = 2958, 2929 (alip. C-H), 1737 (C=O), 1655 (C=N), 1604, 1458, 1298, 1199, 1168, 1112, 893, 707 cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J = 7.6 Hz, 1H), 7.10 – 7.04 (m, 2H), 7.02 (d, J = 7.8 Hz, 1H), 3.69 (s, 3H), 3.22 (t, J = 17.5 Hz, 1H), 2.87 (dt, J =

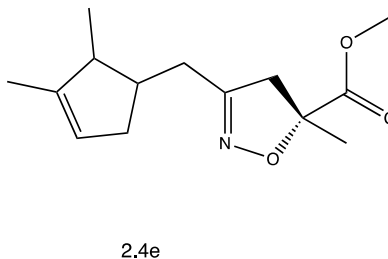
13.8, 6.9 Hz, 1H), 2.72 – 2.52 (m, 4H), 1.47 (s, 3H), 1.30 (d, J = 5.8 Hz, 3H), 1.24 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 172.7 (C=O), 157.8 (C=N), 149.2, 145.3, 128.6, 125.2, 124.6, 124.1, 84.8, 52.8, 47.2, 38.3, 35.9, 34.1, 24.0, 23.4, 22.1. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 304.1913, found 304.1894.

2.4.4 Methyl 3-(1-(4-(tert-butyl)phenyl)propan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.4d)



By column chromatography major diastereomer was separated and purified to give 2.5 g (7.9 mmol) of **2.4d**, 76%, Only one isomer: IR (KBr): ν = 2960 (alif. C-H), 1737 (C=O), 1650 (C=N), 1508, 1456, 1294, 1199, 1170, 1109, 866, 765 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.29 (d, J = 8.1 Hz, 2H), 7.09 (dd, J = 8.3, 2.8 Hz, 2H), 3.73 (s, 3H, OCH_3), 3.38 (d, J = 8.2 Hz, 1H), 2.97 – 2.88 (m, 2H), 2.86 (d, J = 6.5 Hz, 1H), 2.66 (d, J = 4.8 Hz, 1H), 1.56 (s, 3H), 1.29 (s, 9H, CH_3), 1.13 (dd, J = 6.7, 3.5 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 172.9 (C=O), 162.6 (C=N), 149.2, 136.0, 128.6, 125.3, 84.7, 52.8, 45.2, 40.3, 34.7, 34.4, 31.4, 23.3, 17.8. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 318.2069, found 318.2062.

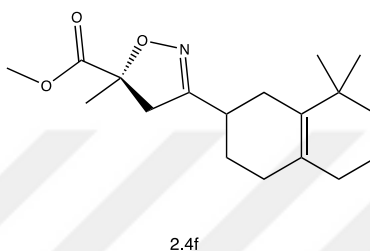
2.4.5 Methyl 5-methyl-3-((2,2,3-trimethylcyclopent-3-en-1-yl)methyl)-4,5-dihydroisoxazole-5-carboxylate (2.4e)



By column chromatography major diastereomer was separated and purified to give 2.33 g (8.8 mmol) of **2.4e**, 68%, Only one isomer: ^1H NMR (400 MHz,

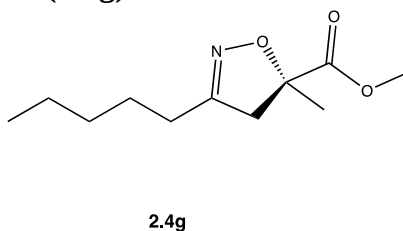
CDCl₃) δ 5.24 (s, 1H), 3.80 (s, 3H, OCH₃), 3.49 (dd, J = 17.2, 11.2 Hz, 1H), 2.83 (dd, J = 17.2, 9.6 Hz, 1H), 2.45 – 2.35 (m, 2H), 2.32 – 2.22 (m, 1H), 2.09 – 1.87 (m, 2H), 1.65 (s, 3H, CH₃), 1.62 (s, 3H), 1.02 (d, J = 3.1 Hz, 3H, CH₃), 0.83 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 173.0 (C=O), 159.1 (C=N), 148.2, 121.5, 85.0, 53.0, 47.4, 47.1, 35.5, 28.3, 25.7, 23.7, 23.5, 19.8, 12.7. HRMS m/z (+APCI-TOF) calcd for C₁₅H₂₃NO₃ [M+H]⁺ : 266.1756, found 266.1742.

2.4.6 Methyl 3-(8,8-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.4f)



By column chromatography major diastereomer was separated and purified to give 2.71g (8.9 mmol) of **2.4f**, 65%, with a GC diastereomer ratio of 66/34. For the major isomer: IR (KBr): ν = 2927, 2906 (alip. C-H), 1737 (C=O), 1620 (C=N), 1514, 1456, 1286, 1199, 1170, 1109, 891, 734 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 3.76 (s, 3H, OCH₃), 3.48 (d, J = 17.6 Hz, 1H), 2.83 (d, J = 17.8 Hz, 1H), 2.65 – 2.48 (m, 2H), 2.25 – 2.08 (m, 1H), 2.06 – 1.74 (m, 6H), 1.59 (s, 3H), 1.51 – 1.32 (m, 4H), 0.93 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 172.9 (C=O), 162.7 (C=N), 133.2, 127.0, 84.7, 52.9, 45.3, 39.5, 34.4, 33.7, 31.0, 30.3, 28.1, 27.0, 26.6, 23.4, 19.2. HRMS m/z (+APCI-TOF) calcd for C₁₈H₂₇NO₃ [M+H]⁺ : 306.2069, found 306.2049.

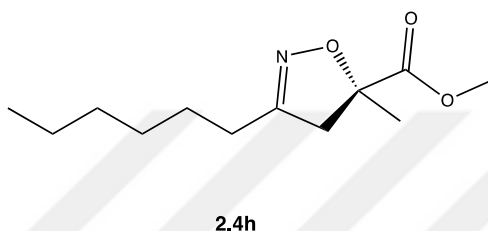
2.4.7 Methyl 5-methyl-3-pentyl-4,5-dihydroisoxazole-5-carboxylate (2.4g)



By column chromatography major diastereomer was separated and purified to give 1.70 g (8 mmol) of **2.4g**, 85%, Only one isomer: IR (KBr): ν = 2954, 2931

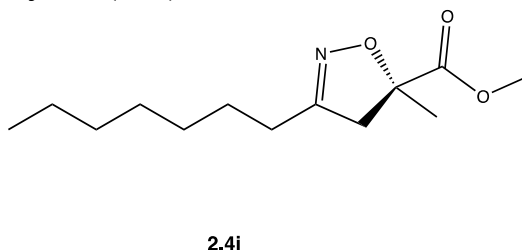
(alip. C-H), 1737 (C=O), 1625 (C=N), 1456, 1290, 1174, 1110, 877, 752 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 3.69 (s, 3H, OCH_3), 3.36 (dd, $J = 17.0, 8.2$ Hz, 1H), 2.73 (d, $J = 17.3$ Hz, 1H), 2.24 (t, $J = 7.7$ Hz, 2H), 1.51 (s, 3H), 1.52 – 1.42 (m, 2H), 1.28 – 1.20 (m, 4H), 0.80 (t, $J = 6.9$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 172.7 (C=O), 159.0 (C=N), 84.7, 52.7, 46.7, 31.2, 27.4, 25.8, 23.3, 22.2, 13.8. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 214.1443, found 214.1433.

2.4.8 Methyl 3-hexyl-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.4h)



By column chromatography major diastereomer was separated and purified to give 1.91 g (8.4 mmol) of **2.4h**, 82%, Only one isomer: IR (KBr): $\nu = 2954, 2929$ (alip. C-H), 1737 (C=O), 1620 (C=N), 1456, 1294, 1201, 1170, 869, 763 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 3.73 (s, 3H, OCH_3), 3.39 (d, $J = 17.2$ Hz, 1H), 2.74 (d, $J = 17.2$ Hz, 1H), 2.28 (t, $J = 7.6$ Hz, 2H), 1.55 (s, 3H), 1.49 (dt, $J = 15.1, 7.6$ Hz, 2H), 1.31 – 1.17 (m, 6H), 0.82 (t, $J = 6.8$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 172.9 (C=O), 159.1 (C=N), 84.7, 52.8, 46.7, 31.4, 28.8, 27.5, 26.2, 23.4, 22.4, 14.0. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 228.1600, found 228.1590.

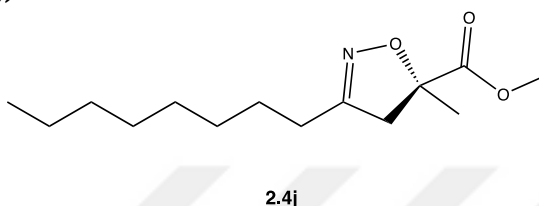
2.4.9 Methyl 3-heptyl-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.4i)



By column chromatography major diastereomer was separated and purified to give 1.86 g (7.7 mmol) of **2.4i**, 80%, Only one isomer: IR (KBr): $\nu = 2953, 2926$ (alip. C-H), 1737 (C=O), 1625 (C=N), 1456, 1294, 1199, 1170, 1120, 875, 765 cm^{-1} .

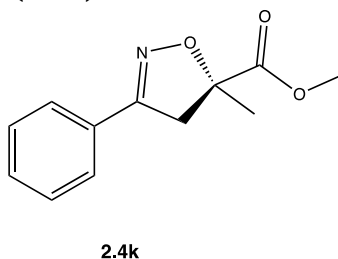
¹. ¹H NMR (400 MHz, CDCl₃) δ 3.75 (s, 3H, OCH₃), 3.41 (d, J = 17.2 Hz, 1H), 2.77 (d, J = 17.2 Hz, 1H), 2.30 (t, J = 7.7 Hz, 2H), 1.58 (s, 3H), 1.56 – 1.47 (m, 2H), 1.34 – 1.17 (m, 8H), 0.84 (t, J = 6.9 Hz, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 172.9 (C=O), 159.1 (C=N), 84.8, 52.8, 46.8, 31.6, 29.1, 28.9, 27.5, 26.2, 23.4, 22.6, 14.0. HRMS *m/z* (+APCI-TOF) calcd for C₁₃H₂₃NO₃ [M+H]⁺ : 242.1707, found 242.1742.

2.4.10 Methyl 5-methyl-3-octyl-4,5-dihydroisoxazole-5-carboxylate (2.4j)



By column chromatography major diastereomer was separated and purified to give 2.17g (8.5 mmol) of **2.4j**, 76%, Only one isomer: IR (KBr): ν = 2953, 2928 (alip. C-H), 1737 (C=O), 1650 (C=N), 1458, 1294, 1201, 1170, 1120, 881, 765 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 3.73 (s, 3H, OCH₃), 3.39 (d, J = 17.2 Hz, 1H), 2.75 (d, J = 17.2 Hz, 1H), 2.28 (t, J = 7.6 Hz, 2H), 1.56 (s, 3H), 1.49 (dt, J = 14.9, 7.5 Hz, 2H), 1.31 – 1.14 (m, 10H), 0.82 (t, J = 6.8 Hz, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 172.9 (C=O), 159.1 (C=N), 84.7, 52.8, 46.7, 31.7, 29.1, 29.1, 27.5, 26.2, 23.4, 22.6, 14.1. HRMS *m/z* (+APCI-TOF) calcd for C₁₄H₂₅NO₃ [M+H]⁺ : 256.1913, found 256.1906.

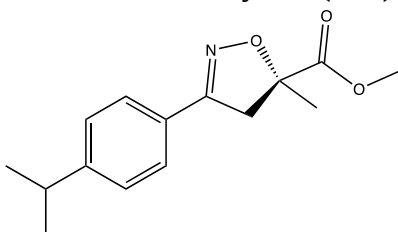
2.4.11 Methyl 5-methyl-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (2.4k)



By column chromatography major diastereomer was separated and purified to give 1.93 g (8.8 mmol) of **2.4k**, 88%, Only one isomer: IR (KBr): ν = 2954 (alip. C-H), 1745 (C=O), 1595 (C=N), 1450, 1435, 1280, 1195, 1174, 1095, 883, 759 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.68 (dd, J = 7.1, 2.2 Hz, 2H), 7.46 – 7.39 (m, 3H),

3.91 (d, $J = 16.9$ Hz, 1H), 3.83 (s, 3H, OCH₃), 3.25 (d, $J = 16.9$ Hz, 1H), 1.74 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 172.7 (C=O), 156.4 (C=N), 130.4, 128.8, 126.8, 86.2, 53.1, 44.8, 23.7. HRMS m/z (+APCI-TOF) calcd for C₁₂H₁₃NO₃ [M+H]⁺: 220.0974, found 220.0963.

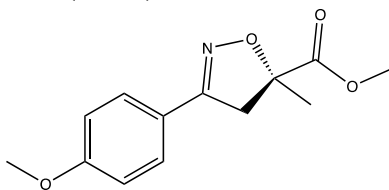
2.4.12 Methyl 3-(4-isopropylphenyl)-5-methyl-4,5-dihydroisoxazole-5 carboxylate (2.4l)



2.4l

By column chromatography major diastereomer was separated and purified to give 2.19 g (8.4 mmol) of **2.4l**, 85%, Only one isomer: IR (KBr): $\nu = 2958, 2933$ (alip. C-H), 1737 (C=O), 1610 (C=N), 1456, 1300, 1197, 1174, 1107, 833, 734 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, $J = 8.2$ Hz, 2H), 7.26 (d, $J = 8.2$ Hz, 2H), 3.87 (d, $J = 16.9$ Hz, 1H), 3.79 (s, 3H, OCH₃), 3.21 (d, $J = 16.9$ Hz, 1H), 2.92 (dt, $J = 13.8, 6.9$ Hz, 1H), 1.70 (s, 3H), 1.25 (d, $J = 7.0$ Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 172.8 (C=O), 156.3 (C=N), 151.6, 130.3, 126.8, 126.5, 86.0, 53.1, 45.0, 34.1, 23.8, 23.6. HRMS m/z (+APCI-TOF) calcd for C₁₅H₁₉NO₃ [M+H]⁺ : 262.1443, found 262.1440.

2.4.13 Methyl 3-(4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.4m)

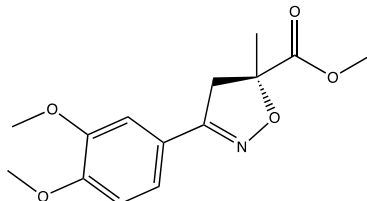


2.4m

By column chromatography major diastereomer was separated and purified to give 2.12 g (8.5 mmol) of **2.4m**, 88%, Only one isomer: IR (KBr): $\nu = 2958$ (alif. C-H), 1724 (C=O), 1610 (C=N), 1608, 1541, 1294, 1199, 1170, 1093, 817, 769 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, $J = 8.9$ Hz, 2H), 6.90 (d, $J = 8.9$ Hz, 2H), 3.84 (d, $J = 18.2$ Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.18 (d, $J = 16.8$ Hz, 1H), 1.69 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 172.8 (C=O), 161.2 (C=N), 155.9,

128.3, 121.5, 114.1, 85.8, 55.4, 53.0, 45.0, 23.6. HRMS m/z (+APCI-TOF) calcd for $C_{13}H_{15}NO_4$ $[M+H]^+$: 250.1079, found 250.1070.

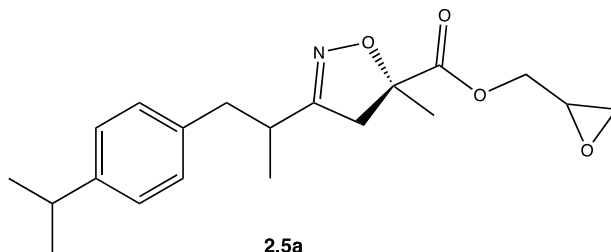
2.4.14 Methyl 3-(3,4-dimethoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.4n)



2.4n

By column chromatography major diastereomer was separated and purified to give 2.50 g (7.8 mmol) of **2.4n**, 84%, Only one isomer: IR (KBr): ν = 2935 (alip. C-H), 1734 (C=O), 1602 (C=N), 1516, 1172, 1143, 808, 763 cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 1.9 Hz, 1H), 6.96 (dd, J = 8.3, 1.9 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 4.43 (d, J = 3.0 Hz, 1H), 4.04 (d, J = 7.1 Hz, 1H), 3.83 (s, 6H), 3.78 (d, J = 2.8 Hz, 1H), 3.18 – 3.16 (m, 1H), 3.17 (d, J = 16.9 Hz, 1H), 2.77 (dd, J = 9.0, 4.2 Hz, 1H), 2.59 (dd, J = 4.9, 2.6 Hz, 1H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C=O), 156.1 (C=N), 151.0, 149.1, 121.6, 120.4, 110.5, 108.7, 85.9, 65.7, 55.9, 49.0, 44.5, 23.5, 21.0, 14.1. HRMS m/z (+APCI-TOF) calcd for $C_{16}H_{19}NO_6$ $[M+H]^+$: 322.1291, found 322.1275.

2.4.15 Oxiran-2-ylmethyl 3-(1-(4-isopropylphenyl)propan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.5a)

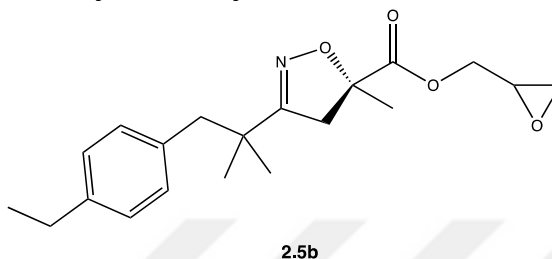


2.5a

After evaporation of solvent under vacuum, By column chromatography major diastereomer was separated and purified to give 2.67 g (8.8 mmol) of **2.5a**, 80%, Only one isomer: IR (KBr): ν = 2960, 2932 (alif. C-H), 1737 (C=O), 1620 (C=N), 1514, 1456, 1290, 1178, 1111, 857, 734 cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 7.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 4.41 (dd, J = 4.7, 3.1 Hz, 1H), 4.04 (dd, J = 5.9, 3.0 Hz, 1H), 3.39 (dd, J = 3.7, 2.1 Hz, 1H), 3.24 – 3.16 (m, 2H),

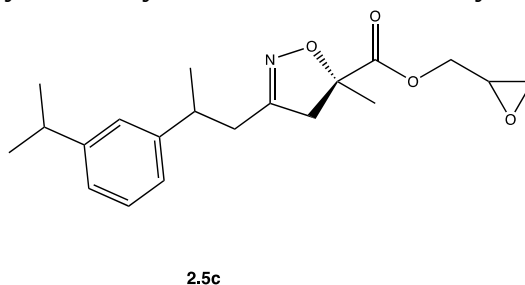
2.99 – 2.91 (m, 1H), 2.89 (d, $J = 8.8$ Hz, 2H), 2.83 – 2.80 (m, 1H), 2.72 (d, $J = 4.7$ Hz, 1H), 2.66 (dd, $J = 4.9, 2.7$ Hz, 1H), 1.57 (d, $J = 3.9$ Hz, 3H), 1.29 (s, 6H), 1.14 (d, $J = 2.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 172.0(C=O), 162.5(C=N), 149.2, 128.6, 125.3, 84.7, 65.6, 49.0, 45.3, 44.8, 44.5, 40.2, 34.4, 23.2, 17.7. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 346.2018, found 346.2002.

2.4.16 Oxiran-2-ylmethyl 3-(1-(4-ethylphenyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.5b)



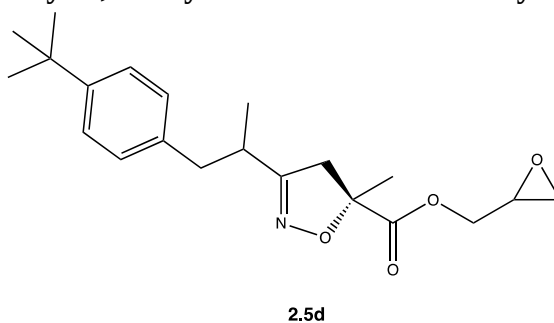
By column chromatography major diastereomer was separated and purified to give 2.55 g (8.4 mmol) of **2.5b**, 78%, with a GC diastereomer ratio of 24/76. For the major isomer: IR (KBr): $\nu = 2966, 2931$ (alip. C-H), 1737 (C=O), 1650 (C=N), 1514, 1458, 1292, 1180, 1111, 877, 759 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.09 (d, $J = 7.9$ Hz, 2H), 7.02 (d, $J = 8.0$ Hz, 2H), 4.47 (dd, $J = 12.2, 3.0$ Hz, 1H), 4.10 – 4.01 (m, 1H), 3.45 (dd, $J = 17.2, 2.5$ Hz, 1H), 3.22 (ddt, $J = 9.5, 6.4, 3.1$ Hz, 1H), 2.83 (t, $J = 4.5$ Hz, 1H), 2.77 (d, $J = 4.4$ Hz, 2H), 2.69 – 2.63 (m, 2H), 2.60 (q, $J = 7.6$ Hz, 2H), 1.59 (d, $J = 3.6$ Hz, 3H), 1.20 (t, $J = 7.6$ Hz, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.14 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 172.1 (C=O), 165.3 (C=N), 142.4, 134.4, 130.4, 127.5, 85.0, 65.8, 49.1, 46.4, 45.0, 44.6, 37.2, 28.4, 25.9, 25.6, 23.4, 15.6. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 346.2018, found 346.2001.

2.4.17 Oxiran-2-ylmethyl 3-(2-(3-isopropylphenyl) propyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.5c)



By column chromatography major diastereomer was separated and purified to give 2.36 g (7.8 mmol) of **2.5c**, 80%, with a GC diastereomer ratio of 95.5/2.8. For the major isomer: IR (KBr): ν = 2960, 2927 (alip. C-H), 1737 (C=O), 1650 (C=N), 1604, 1458, 1292, 1174, 1109, 904, 715 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.26 (t, J = 8.4 Hz, 1H), 7.13 – 7.02 (m, 3H), 4.51 – 4.38 (m, 1H), 4.10 – 3.99 (m, 1H), 3.35 – 3.17 (m, 2H), 3.02 (dt, J = 14.3, 7.1 Hz, 1H), 2.95 – 2.82 (m, 2H), 2.69 – 2.63 (m, 2H), 1.52 (d, J = 5.0 Hz, 1H), 1.47 (d, J = 4.2 Hz, 3H), 1.32 (d, J = 6.2 Hz, 3H), 1.26 (d, J = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.9 (C=O), 157.8 (C=N), 149.3, 145.3, 128.6, 125.1, 124.7, 124.2, 84.9, 65.9, 49.1, 46.8, 44.6, 37.8, 36.0, 35.7, 34.2, 24.1, 23.2, 22.1. HRMS m/z (+APCI- TOF) calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 346.2018, found 346.2004.

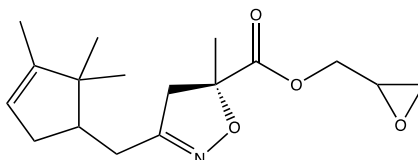
2.4.18 Oxiran-2-ylmethyl 3-(1-(4-(tert-butyl)phenyl)propan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (**2.5d**)



By column chromatography major diastereomer was separated and purified to give 2.94 g (8.2 mmol) of **2.5d**, 72%, with a GC diastereomer ratio of 95.3/3.1. For the major isomer: IR (KBr): ν = 2960, 2927 (alip. C-H), 1737 (C=O), 1650 (C=N), 1604, 1458, 1292, 1174, 1109, 904, 715 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.26 (t, J = 8.4 Hz, 1H), 7.13 – 7.02 (m, 3H), 4.51 – 4.38 (m, 1H), 4.10 – 3.99 (m, 1H), 3.35 – 3.17 (m, 2H), 3.02 (dt, J = 14.3, 7.1 Hz, 1H), 2.95 – 2.82 (m, 2H), 2.69 – 2.63 (m, 2H), 1.52 (d, J = 5.0 Hz, 1H), 1.47 (d, J = 4.2 Hz, 3H), 1.32 (d, J = 6.2 Hz, 3H), 1.26 (d, J = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.9 (C=O), 157.8 (C=N), 149.3, 145.3, 128.6, 125.1, 124.7, 124.2, 84.9, 65.9, 49.1, 46.8, 44.6,

37.8, 36.0, 35.7, 34.2, 24.1, 23.2, 22.1. HRMS m/z (+APCI-TOF) calcd for $C_{20}H_{27}NO_4$ $[M+H]^+$: 346.2018, found 346.2004.

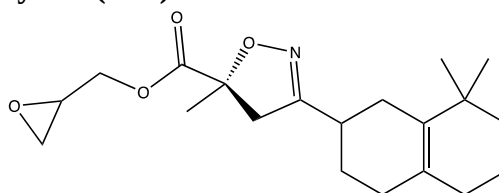
2.4.19 Oxiran-2-ylmethyl 5-methyl-3-((2,2,3-trimethylcyclopent-3-en-1-yl)methyl)-4,5-dihydroisoxazole-5-carboxylate (2.5e)



2.5e

By column chromatography major diastereomer was separated and purified to give 2.67g (8.7 mmol) of **2.5e**, 62%, with a GC diastereomer ratio of 15.7:54.6:29.8. For the major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 1H), 4.49 (ddd, J = 12.1, 7.0, 3.4 Hz, 1H), 4.12 – 4.04 (m, 1H), 3.54 – 3.44 (m, 1H), 3.28 – 3.22 (m, 1H), 2.89 – 2.80 (m, 2H), 2.72 – 2.66 (m, 1H), 2.48 – 2.23 (m, 2H), 2.09 – 1.86 (m, 2H), 1.67 – 1.64 (m, 1H), 1.63 (s, 3H), 1.62 (s, 3H, CH_3), 1.02 (d, J = 2.1 Hz, 3H, CH_3), 0.83 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (C=O), 159.2 (C=N), 148.3, 121.6, 85.0, 65.9, 49.3, 47.5, 47.2, 44.8, 35.6, 28.4, 25.9, 23.7, 23.5, 19.9, 12.9. HRMS m/z (+APCI-TOF) calcd for $C_{17}H_{25}NO_4$ $[M+H]^+$: 308.1862, found 308.1849.

2.4.20 Oxiran-2-ylmethyl 3-(8,8-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.5f)

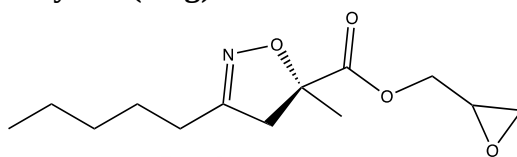


2.5f

By column chromatography major diastereomer was separated and purified to give 2.95 g (8.5 mmol) of **2.5f**, 60%, with a GC diastereomer ratio of 28.4:39.1:14.3:17.9. For the major isomer: IR (KBr): ν = 2926, 2906 (alip. C-H), 1737 (C=O), 1620 (C=N), 1510, 1456, 1286, 1176, 1109, 850, 734 cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (ddd, J = 12.2, 5.5, 2.7 Hz, 1H), 4.05 – 3.97 (m, 1H),

3.43 (d, $J = 3.0$ Hz, 1H), 3.22 – 3.13 (m, 1H), 2.79 (d, $J = 5.0$ Hz, 1H), 2.66 – 2.59 (m, 1H), 2.59 – 2.47 (m, 1H), 2.13 (d, $J = 17.0$ Hz, 1H), 2.06 – 1.74 (m, 8H), 1.57 (s, 3H), 1.49 – 1.30 (m, 4H), 0.92 (s, 6H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 171.9 (C=O), 162.6 (C=N), 133.1, 127.0, 84.6, 65.6, 49.0, 45.3, 44.5, 39.5, 34.3, 33.9, 33.7, 31.0, 30.2, 28.1, 27.0, 26.6, 24.0, 23.2, 19.1. HRMS m/z (+APCI-TOF) calcd for C₂₀H₂₉NO₄ [M+H]⁺ : 348.2175, found 348.2155.

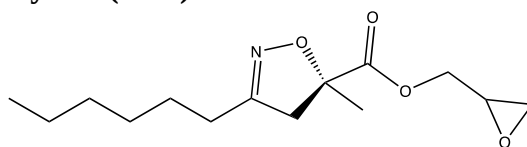
2.4.21 Oxiran-2-ylmethyl 5-methyl-3-pentyl-4,5-dihydroisoxazole-5-carboxylate (2.5g)



2.5g

By column chromatography major diastereomer was separated and purified to give 2.07 g (8.1 mmol) of **2.5g**, 75%, with a GC diastereomer ratio of 61:39. For the major isomer: IR (KBr): $\nu = 2954, 2931$ (alip. C-H), 1737 (C=O), 1625 (C=N), 1456, 1290, 1174, 1110, 877, 752 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 4.44 (dd, $J = 12.3, 2.9$ Hz, 1H), 4.01 (dt, $J = 12.2, 6.1$ Hz, 1H), 3.40 (dd, $J = 17.3, 2.9$ Hz, 1H), 3.22 – 3.15 (m, 1H), 2.79 (d, $J = 4.1$ Hz, 1H), 2.78 (d, $J = 23.0$ Hz, 2H), 2.63 (ddd, $J = 7.8, 4.9, 2.6$ Hz, 1H), 2.28 (t, $J = 7.7$ Hz, 2H), 1.58 (d, $J = 4.3$ Hz, 3H), 1.51 (dt, $J = 14.9, 7.4$ Hz, 2H), 1.32 – 1.22 (m, 4H), 0.84 (t, $J = 6.9$ Hz, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 171.9 (C=O), 159.0 (C=N), 84.7, 65.6, 49.0, 46.8, 44.5, 31.2, 27.4, 25.9, 23.3, 22.2, 13.9. HRMS m/z (+APCI-TOF) calcd for C₁₃H₂₁NO₄ [M+H]⁺ : 256.1549, found 256.1533.

2.4.22 Oxiran-2-ylmethyl 3-hexyl-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.5h)

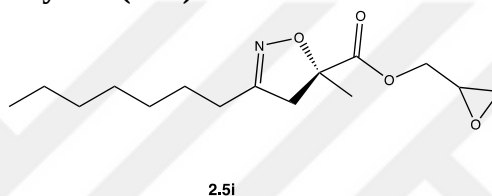


2.5h

By column chromatography major diastereomer was separated and purified to give 2.13 g (7.9 mmol) of **2.5h**, 74%, with a GC diastereomer ratio of 52.5:47.5.

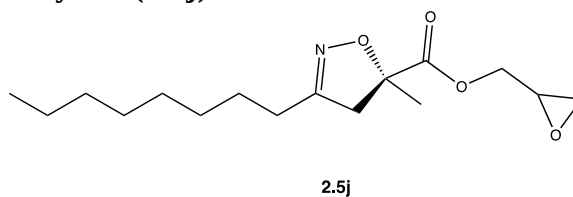
For the major isomer: IR (KBr): ν = 2954, 2927 (alif. C-H), 1739 (C=O), 1625 (C=N), 1456, 1290, 1174, 1118, 866, 759 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 4.48 (dt, J = 12.2, 2.5 Hz, 1H), 4.06 (dt, J = 12.4, 6.4 Hz, 1H), 3.45 (d, J = 17.2 Hz, 1H), 3.27 – 3.20 (m, 1H), 2.86 – 2.83 (m, 1H), 2.81 (d, J = 17.5 Hz, 1H), 2.70 – 2.64 (m, 1H), 2.33 (t, J = 7.6 Hz, 2H), 1.62 (d, J = 4.8 Hz, 3H), 1.55 (dt, J = 14.7, 5.3 Hz, 2H), 1.36 – 1.22 (m, 6H), 0.87 (t, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 172.0 (C=O), 159.1 (C=N), 84.7, 65.9, 49.1, 46.8, 44.6, 31.4, 28.8, 27.5, 26.2, 23.3, 22.5, 14.0. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 270.1715, found 270.1694.

2.4.23 Oxiran-2-ylmethyl 3-heptyl-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.5i)



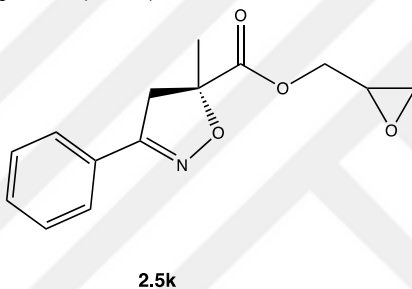
By column chromatography major diastereomer was separated and purified to give 2.32 g (8.2 mmol) of **2.5i**, 74%, with a GC diastereomer ratio of 45.5:54.5. For the major isomer: IR (KBr): ν = 2953, 2926 (alif. C-H), 1739 (C=O), 1630 (C=N), 1456, 1290, 1176, 1120, 873, 754 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 4.46 (dd, J = 12.3, 2.7 Hz, 1H), 4.03 (dt, J = 12.3, 6.2 Hz, 1H), 3.42 (dd, J = 17.3, 2.8 Hz, 1H), 3.25 – 3.17 (m, 1H), 2.81 (d, J = 4.0 Hz, 1H), 2.80 (d, J = 24.5 Hz, 2H), 2.68 – 2.62 (m, 1H), 2.30 (t, J = 7.6 Hz, 2H), 1.60 (d, J = 4.4 Hz, 3H), 1.57 – 1.47 (m, 2H), 1.36 – 1.20 (m, 7H), 0.84 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 172.0 (C=O), 159.1 (C=N), 84.7, 65.6, 49.0, 46.8, 44.5, 31.6, 29.1, 28.9, 27.5, 26.3, 23.3, 22.6, 14.1. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 284.1862, found 284.1846.

2.4.24 Oxiran-2-ylmethyl 5-methyl-3-octyl-4,5-dihydroisoxazole-5-carboxylate (2.5j)



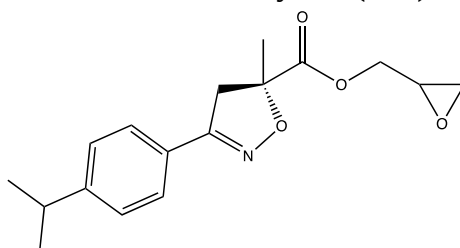
By column chromatography major diastereomer was separated and purified to give 2.61 g (8.8 mmol) of **2.5j**, 70%, Only one isomer: IR (KBr): $\nu = 2954, 2928$ (alip. C-H), 1739 (C=O), 1635 (C=N), 1456, 1290, 1176, 1120, 879, 750 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 4.29 (d, $J = 4.9$ Hz, 1H), 4.15 – 4.08 (m, 1H), 3.71 (dd, $J = 14.0, 7.0$ Hz, 1H), 3.64 – 3.59 (m, 2H), 3.45 (d, $J = 17.3$ Hz, 1H), 2.81 (d, $J = 17.3$ Hz, 1H), 2.32 (t, $J = 7.6$ Hz, 2H), 1.62 (s, 3H), 1.53 (dt, $J = 14.8, 7.5$ Hz, 2H), 1.33 – 1.20 (m, 10H), 0.87 (t, $J = 6.7$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 172.3 (C=O), 159.6 (C=N), 84.9, 69.2, 66.3, 46.8, 45.5, 31.8, 29.2, 29.1, 27.6, 26.3, 23.3, 22.6, 14.1. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{16}\text{H}_{27}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 298.2018, found 298.2000.

2.4.25 Oxiran-2-ylmethyl 5-methyl-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (**2.5k**)



By column chromatography major diastereomer was separated and purified to give 2.24 g (8.6 mmol) of **2.5k**, 86%, with a GC diastereomer ratio of 43.8:54.4. For the major isomer: IR (KBr): $\nu = 2935$ (alip. CH), 1737 (C=O), 1650 (C=N), 1446, 1290, 1180, 1107, 906, 758 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.65 (dd, $J = 7.3, 1.7$ Hz, 2H), 7.43 – 7.36 (m, 3H), 4.50 (d, $J = 12.3$ Hz, 1H), 4.10 – 4.01 (m, 1H), 3.89 (dd, $J = 17.0, 2.2$ Hz, 1H), 3.24 (d, $J = 16.9$ Hz, 1H), 2.82 (q, $J = 4.4$ Hz, 1H), 2.66 (ddd, $J = 15.2, 4.7, 2.5$ Hz, 1H), 1.72 (d, $J = 4.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.7 (C=O), 156.3 (C=N), 130.4, 128.9, 128.8, 126.8, 86.1, 66.0, 65.8, 49.1, 44.6, 23.6. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 262.1079, found 262.1063.

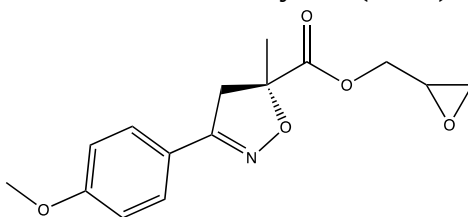
2.4.26 Oxiran-2-ylmethyl 3-(4-isopropylphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.5l)



2.5l

By column chromatography major diastereomer was separated and purified to give 2.61g (8.6 mmol) of **2.5l**, 80%, with a GC diastereomer ratio of 45.4:54.6. For the major isomer: IR (KBr): ν = 2960, 2933 (alip. C-H), 1737 (C=O), 1610 (C=N), 1456, 1296, 1180, 1107, 833, 738 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.59 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 4.50 (ddd, J = 12.2, 2.9, 1.1 Hz, 1H), 4.08 (ddd, J = 12.3, 8.1, 5.9 Hz, 1H), 3.89 (dd, J = 16.9, 2.5 Hz, 1H), 3.27 – 3.22 (m, 1H), 3.23 (d, J = 16.8 Hz, 1H), 2.93 (dt, J = 13.8, 6.9 Hz, 1H), 2.83 (dd, J = 8.4, 4.2 Hz, 1H), 2.67 (ddd, J = 15.4, 4.8, 2.6 Hz, 1H), 1.72 (d, J = 4.1 Hz, 3H), 1.25 (d, J = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.8 (C=O), 156.2 (C=N), 151.6, 126.9, 126.5, 85.9, 66.0, 65.8, 49.1, 45.0, 44.6, 34.1, 23.8, 23.6. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 304.1549, found 304.1548.

2.4.27 Oxiran-2-ylmethyl 3-(4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.5m)

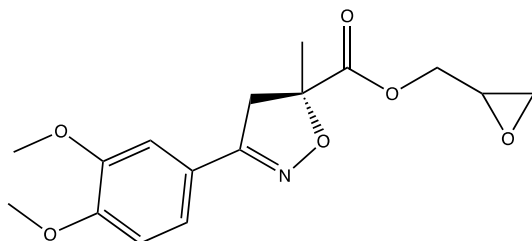


2.5m

By column chromatography major diastereomer was separated and purified to give 2.39 g (8.2 mmol) of **2.5m**, 82%, with a GC diastereomer ratio of 47:53. For the major isomer: IR (KBr): ν = 2939 (alip. C-H), 1726 (C=O), 1606 (C=N), 1514, 1294, 1176, 1099, 837, 765 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.58 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 4.47 (dd, J = 3.1, 0.9 Hz, 1H), 3.86 (dd, J = 16.8, 2.7 Hz, 2H), 3.83 (s, 3H), 3.82 (d, J = 5.1 Hz, 1H), 3.20 (d, J = 16.8 Hz, 1H), 2.83 (dd, J = 9.0, 4.7 Hz, 1H), 2.65 (dd, J = 4.8, 2.6 Hz, 1H), 1.72 (s, 3H). ^{13}C NMR (100

MHz, CDCl₃) δ 171.9 (C=O), 161.2 (C=N), 155.9, 128.3, 121.4, 114.2, 85.8, 65.9, 55.4, 49.0, 45.1, 44.6, 23.5. HRMS m/z (+APCI-TOF) calcd for C₁₅H₁₇NO₅ [M+H]⁺ : 292.1185, found 292.1175.

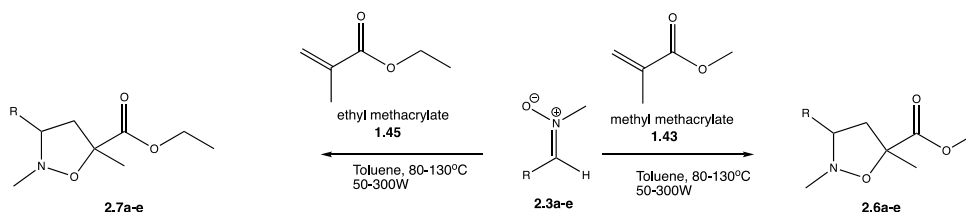
2.4.28 Oxiran-2-ylmethyl 3-(3,4-dimethoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2.5n)



2.5n

By column chromatography major diastereomer was separated and purified to give 2.44 g (7.6 mmol) of **2.5n**, 80%, with a GC diastereomer ratio of 40:60. For the major isomer: IR (KBr): ν = 2935 (alip. C-H), 1734 (C=O), 1602 (C=N), 1516, 1172, 1143, 808, 763 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, J = 1.9 Hz, 1H), 6.96 (dd, J = 8.3, 1.9 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 4.43 (d, J = 3.0 Hz, 1H), 4.04 (d, J = 7.1 Hz, 1H), 3.83 (s, 6H), 3.78 (d, J = 2.8 Hz, 1H), 3.18 – 3.16 (m, 1H), 3.17 (d, J = 16.9 Hz, 1H), 2.77 (dd, J = 9.0, 4.2 Hz, 1H), 2.59 (dd, J = 4.9, 2.6 Hz, 1H), 1.65 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 171.8 (C=O), 156.1 (C=N), 151.0, 149.1, 121.6, 120.5, 110.5, 108.7, 85.9, 65.7, 55.9, 49.0, 44.5, 23.5, 21.0, 14.1. HRMS m/z (+APCI- TOF) calcd for C₁₆H₁₉NO₆ [M+H]⁺ : 322.1291, found 322.1275.

2.5 General Procedure for Isoxazolidine Carboxylate Synthesis

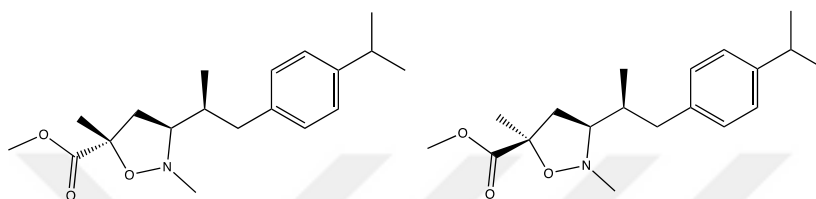


Scheme 2-4- General synthetic route for isoxazolidine derivatives

A mixture of aldonitrone **2.3 a-e** (5mmoles) and methacrylate esters **1.45** and **1.43** (5.5 mmoles) in 2 mL of toluene or without solvent was irradiated by microwave (Cem Discover Explorer SP) at temperatures ranging from 80 to 130°C.

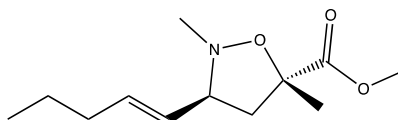
The reaction was controlled by TLC (n-hexane: EtOAc). After completion of reaction, the solvent was removed under reduced pressure. The major diastereomer was purified by column chromatography and the target isoxazolidine (**2.6**, **2.7**) was obtained as only one diastereomer or diastereomer mixture (endo-exo).

2.5.1 (3S,5S)-methyl 3-((S)-1-(4-isopropylphenyl)propan-2-yl)-2,5-dimethylisoxazolidine-5-carboxylate (2.6a), (3S,5R)-methyl 3-((S)-1-(4-isopropylphenyl)propan-2-yl)-2,5-dimethylisoxazolidine-5-carboxylate (2.6a')



Colorless oil, yield (52%, 829 mg), IR (KBr, cm^{-1}): 2957, 2871 (C-H aliphatic), 1732 (C=O), 1514, 1458, 1299, 1202, 1173, 1134, 941, 818. For the major (endo) isomer; ^1H NMR (300 MHz, CDCl_3) δ 7.05 (d, $J = 7.9$ Hz, 2H), 6.97 (d, $J = 8.1$ Hz, 2H), 3.67 (s, 3H, OCH_3), 2.80 (dd, $J = 13.7, 7.0$, 1H), 2.75 – 2.72 (m, 1H), 2.65 (dd, $J = 5.9, 3.3$ Hz, 2H), 2.54 (s, 3H, NCH_3), 2.30 (dd, $J = 13.4, 8.4$ Hz, 1H), 2.16 – 2.03 (m, 1H), 1.91 (dd, $J = 12.5, 8.4$ Hz, 1H), 1.39 (s, 3H, CH_3 isoxazolidine ring), 1.17 (d, $J = 4.3$ Hz, 6H), 0.74 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.9 (C=O), 146.8, 137.7, 129.0, 126.6, 81.8, 72.3, 52.7 (OCH_3), 41.6 (NCH_3), 39.9, 36.4, 35.2, 33.9, 29.9, 24.3, 14.3. HRMS m/z (+APCI-TOF) calcd for $\text{C}_{19}\text{H}_{29}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 320.2226, Found 320.2237.

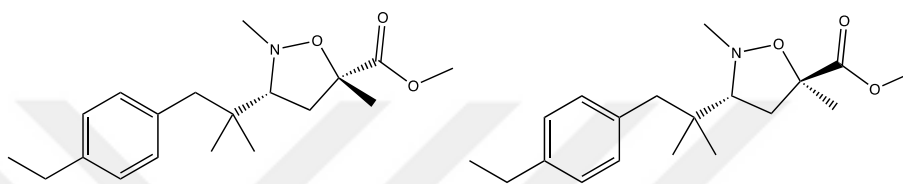
2.5.2 (3S,5S)-methyl 2,5-dimethyl-3-((E)-pent-1-en-1-yl)isoxazolidine-5-carboxylate (2.6b)



Light yellow oil, yield (60%, 681 mg), IR (KBr, cm^{-1}): 2957, 2932, 2872 (C-H aliphatic), 1733 (C=O), 1456, 1297, 1203, 1155, 1137, 1083, 987, 943, 826. For the major (endo) isomer; ^1H NMR (400 MHz, CDCl_3) δ 5.65 (dd, $J = 14.8, 7.2$ Hz, 1H), 5.29 (dd, $J = 15.6, 8.3$ Hz, 1H), 3.78 (s, 3H, OCH_3), 2.97 (dd, $J = 16.4, 8.7$ Hz, 1H), 2.68 (dd, $J = 12.9, 9.3$ Hz, 1H), 2.63 (s, 3H, NCH_3), 2.25 (dd, $J = 12.8, 7.8$

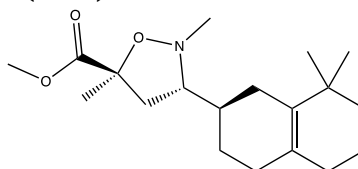
Hz, 1H), 2.00 (dd, $J = 14.4, 7.5$ Hz, 2H), 1.49 (s, 3H, CH₃ isoxazolidine ring), 1.44 – 1.33 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 175.5 (C=O), 136.2, 127.2, 80.8, 72.1, 52.6 (OCH₃), 46.3, 42.8 (NCH₃), 34.3, 24.2, 22.1, 13.6. HRMS m/z (+APCI-TOF) calcd for C₁₂H₂₁NO₃ [M+H]⁺: 228.1600, found 228.1607.

2.5.3 (3R,5S)-methyl 3-(1-(4-ethylphenyl)-2-methylpropan-2-yl)-2,5-dimethylisoxazolidine-5-carboxylate (2.6c), (3R,5R)-methyl 3-(1-(4-ethylphenyl)-2-methylpropan-2-yl)-2,5-dimethylisoxazolidine-5-carboxylate (2.6c')



Colorless oil, yield (68%, 1085 mg). IR (KBr, cm⁻¹): 2964, 2872 (C-H aliphatic), 1731 (C=O), 1513, 1454, 1297, 1196, 1169, 1026, 831, 764. For the major (endo) isomer; ¹H NMR (400 MHz, CDCl₃) δ 7.09 (d, $J = 8.1$ Hz, 2H), 7.02 (d, $J = 8.1$ Hz, 2H), 3.76 (s, 3H, OCH₃), 2.94 (dd, $J = 13.1, 6.6$ Hz, 1H), 2.83 (s, 3H, NCH₃), 2.62 (d, $J = 7.6$ Hz, 2H), 2.60 (dd, $J = 9.7, 7.5$ Hz, 1H), 2.49 (d, $J = 3.9$ Hz, 2H), 2.27 (dd, $J = 13.1, 9.8$ Hz, 1H), 1.53 (s, 3H), 1.22 (t, $J = 7.6$ Hz, 3H), 0.83 (d, $J = 2.5$ Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 175.4 (C=O), 141.9, 135.2, 130.7, 127.2, 81.1, 77.6, 52.7, 48.4, 44.9, 42.7 (NCH₃), 36.8, 28.4, 24.7, 24.4, 23.6, 15.5. HRMS m/z (+APCI-TOF) calcd for C₁₉H₂₉NO₃ [M+H]⁺: 320.2226, found 320.2216.

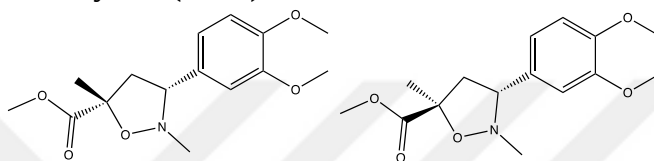
2.5.4 (3S,5S)-methyl 3-((R)-8,8-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)-2,5-dimethylisoxazolidine-5-carboxylate (2.6d)



Colorless oil, yield (72%, 1155 mg). IR (KBr, cm⁻¹): 2953, 2924, 2858 (C-H aliphatic), 1736 (C=O), 1456, 1370, 1297, 1201, 1170, 1134, 1087, 946, 828, 763. For the major (endo) isomer; ¹H NMR (400 MHz, CDCl₃) δ 3.77 (s, 3H,

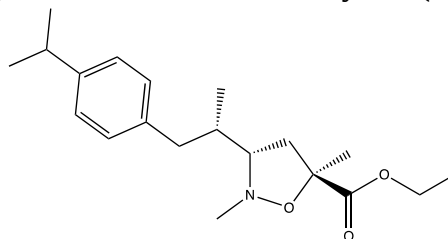
OCH₃), 2.73 (s, 3H, NCH₃), 2.16 – 2.00 (m, 2H), 1.98 – 1.86 (m, 3H), 1.86 – 1.77 (m, 3H), 1.76 – 1.63 (m, 4H), 1.62 – 1.53 (m, 4H), 1.50 (s, 3H, CH₃ isoxazolidine ring), 0.96 (d, J = 5.1 Hz, 3H), 0.94 (d, J = 3.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 175.8 (C=O), 134.1, 126.3, 81.0, 73.1, 52.8, 44.8, 41.5 (NCH₃), 39.8, 36.2, 35.5, 33.9, 31.3, 31.1, 29.6, 28.5, 27.3, 24.6, 19.5. HRMS *m/z* (+APCI-TOF) calcd for C₁₉H₃₁NO₃ [M+H]⁺ : 322.2382, found 322.2385.

2.5.5 (3R,5S)-methyl 3-(3,4-dimethoxyphenyl)-2,5-dimethylisoxazolidine-5-carboxylate (2.6e), (3R,5R)-methyl 3-(3,4-dimethoxyphenyl)-2,5-dimethylisoxazolidine-5-carboxylate (2.6e')



Colorless oil, yield (62%, 915 mg). IR (KBr, cm⁻¹): 2995, 2955, 2839 (C-H aliphatic), 1732 (C=O), 1517, 1462, 1252, 1235, 1136, 1027, 762. For the major (endo) isomer; ¹H NMR (400 MHz, CDCl₃) δ 6.86 (d, J = 1.9 Hz, 1H), 6.80 (d, J = 1.9 Hz, 1H), 6.77 (s, 1H), 3.84 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.44 (t, J = 7.6 Hz, 1H, CH₃ isoxazolidine ring), 2.95 (dd, J = 12.9, 9.1 Hz, 1H), 2.53 (s, 3H, NCH₃), 2.41 (dd, J = 12.9, 8.2 Hz, 1H), 1.51 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 175.5 (C=O), 149.1, 148.8, 130.4, 120.5, 110.8, 110.4, 81.2, 73.5, 55.8, 52.6, 48.4, 42.9 (NCH₃), 23.9. HRMS *m/z* (+APCI-TOF) calcd for C₁₅H₂₁NO₅ [M+H]⁺ : 296.1498, found 296.1514.

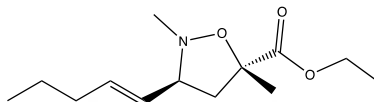
2.5.6 (3S,5S)-ethyl 3-((S)-1-(4-isopropylphenyl)propan-2-yl)-2,5-dimethylisoxazolidine-5-carboxylate (2.7a)



Colorless oil, yield (64%, 1066 mg), IR (KBr, cm⁻¹): 2959, 2930, 2871 (C-H aliphatic), 1727 (C=O), 1513, 1460, 1295, 1190, 1170, 1131, 1020, 848, 808, 550. For the major (endo) isomer; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 4.30 – 4.16 (m, 2H), 2.89 (dd, J = 13.8, 6.9 Hz,

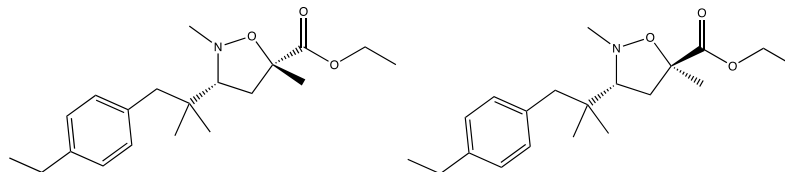
1H), 2.85 – 2.79 (m, 1H), 2.63 (s, 3H, NCH₃), 2.55 (dd, J = 6.0, 3.5 Hz, 2H), 2.39 (dd, J = 13.5, 8.5 Hz, 1H), 1.99 (dd, J = 12.6, 8.5 Hz, 1H), 1.95 – 1.87 (m, 1H), 1.48 (s, 3H, CH₃ isoxazolidine ring), 1.29 (t, J = 7.1 Hz, 3H), 1.24 (d, J = 6.9 Hz, 6H), 0.83 (d, J = 6.7 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 175.0 (C=O), 146.6, 137.5, 128.7, 126.4, 80.7, 71.8, 61.2, 43.4, 41.1 (NCH₃), 39.6, 35.0, 33.7, 24.1, 24.0, 14.1, 13.2. HRMS *m/z* (+APCI-TOF) calcd for C₂₀H₃₁NO₃ [M+H]⁺ : 334.2382, Found 334.2400.

2.5.7 (3S,5S)-ethyl 2,5-dimethyl-3-((E)-pent-1-en-1-yl)isoxazolidine-5-carboxylate (2.7b)



Light yellow oil, yield (46%, 554 mg), IR (KBr, cm⁻¹): 2959, 2931, 2871 (C-H aliphatic), 1730 (C=O), 1456, 1371, 1292, 1194, 1152, 1026, 971, 858. For the major (endo) isomer; ¹H NMR (300 MHz, CDCl₃) δ 5.58 (dt, J = 14.9, 6.8 Hz, 1H), 5.22 (dd, J = 15.3, 8.4 Hz, 1H), 4.24 – 4.09 (m, 2H), 2.91 (t, J = 7.8 Hz, 1H), 2.61 (dd, J = 13.3, 9.8 Hz, 1H), 2.56 (s, 3H, NCH₃), 2.16 (dd, J = 12.7, 7.8 Hz, 1H), 1.93 (dd, J = 14.2, 6.9 Hz, 2H), 1.41 (s, 3H, CH₃ isoxazolidine ring), 1.31 (dd, J = 14.7, 7.4 Hz, 2H), 1.21 (dd, J = 12.7, 5.5 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 173.9 (C=O), 134.8, 126.5, 71.0, 60.3, 45.2, 41.7 (NCH₃), 33.3, 28.7, 23.0, 21.1, 13.2, 12.6. HRMS *m/z* (+APCI-TOF) calcd for C₁₃H₂₃NO₃ [M+H]⁺ : 242.1756, found 242.1736.

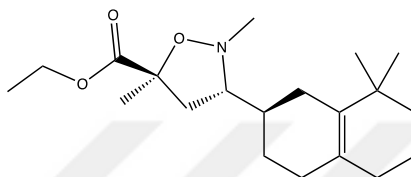
2.5.8 (3R,5S)-ethyl 3-(1-(4-ethylphenyl)-2-methylpropan-2-yl)-2,5-dimethylisoxazolidine-5-carboxylate (2.7c), (3R,5R)-ethyl 3-(1-(4-ethylphenyl)-2-methylpropan-2-yl)-2,5-dimethylisoxazolidine-5-carboxylate (2.7c')



Colorless oil, yield (60%, 999 mg). IR (KBr, cm⁻¹): 2955, 2938, 2872 (C-H aliphatic), 1726 (C=O), 1513, 1454, 1367, 1295, 1170, 1135, 1092, 1022, 845, 763. For the major (endo) isomer; ¹H NMR (400 MHz, CDCl₃) δ 7.09 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 8.1 Hz, 2H), 4.27 – 4.16 (m, 2H), 2.94 (dd, J = 13.1, 6.6 Hz, 1H),

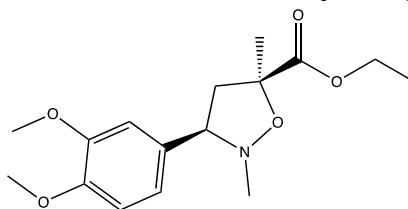
2.83 (s, 3H, NCH₃), 2.62 (d, J = 7.7 Hz, 2H), 2.60 (dd, J = 9.7, 7.6 Hz, 1H), 2.50 (d, J = 3.5 Hz, 2H), 2.27 (dd, J = 13.1, 9.7 Hz, 1H), 1.52 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.6 Hz, 3H), 0.83 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 174.7 (C=O), 141.8, 135.3, 130.7, 127.2, 81.0, 77.6, 61.3, 48.5, 44.8, 42.5 (NCH₃), 37.9, 36.8, 28.4, 24.8, 24.5, 23.7, 15.5, 14.2. HRMS *m/z* (+APCI-TOF) calcd for C₂₀H₃₁NO₃ [M+H]⁺ : 334.2382, found 334.2386.

2.5.9 (3S,5S)-ethyl 3-((R)-8,8-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)-2,5-dimethylisoxazolidine-5-carboxylate (2.7d)



Colorless oil, yield (70%, 1172 mg). IR (KBr, cm⁻¹): 2924, 2866 (C-H aliphatic), 1728 (C=O), 1456, 1370, 1173, 1133, 1024, 949, 851, 763. For the major (endo) isomer; ¹H NMR (400 MHz, CDCl₃) δ 4.28 – 4.15 (m, 2H), 2.69 (s, 3H, NCH₃), 2.12 – 1.99 (m, 2H), 1.98 – 1.85 (m, 3H), 1.85 – 1.77 (m, 3H), 1.76 – 1.62 (m, 3H), 1.61 – 1.52 (m, 3H), 1.48 (d, J = 3.0 Hz, 3H, CH₃ isoxazolidine ring), 1.43 – 1.34 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 1.9 Hz, 3H), 0.94 (d, J = 1.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 174.7 (C=O), 133.8, 126.0, 80.9, 73.0, 61.3, 44.5, 41.0 (NCH₃), 39.5, 35.7, 34.6, 33.6, 31.3, 31.0, 29.4, 28.3, 27.1, 24.2, 19.2, 14.1. HRMS *m/z* (+APCI-TOF) calcd for C₂₀H₃₃NO₃ [M+H]⁺ : 336.2539, found 336.2543.

2.5.10 (3R,5S)-ethyl 3-(3,4-dimethoxyphenyl)-2,5-dimethylisoxazolidine-5-carboxylate (2.7e)



Colorless oil, yield (60%, 927 mg). IR (KBr, cm⁻¹): 2957, 2846 (C-H aliphatic), 1726 (C=O), 1592, 1517, 1462, 1420, 1370, 1261, 1195, 1165, 1135, 1027, 809, 762. For the major (endo) isomer; ¹H NMR (400 MHz, CDCl₃) δ 6.88 (d, J = 1.6 Hz, 1H), 6.82 (dd, J = 8.2, 1.8 Hz, 1H), 6.77 (s, 1H), 4.32 – 4.19 (m, 2H),

3.84 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.44 (t, J = 7.3 Hz, 1H, CH₃ isoxazolidine ring), 2.96 (dd, J = 12.9, 9.0 Hz, 1H), 2.54 (s, 3H, NCH₃), 2.41 (dd, J = 12.9, 8.3 Hz, 1H), 1.51 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 174.9 (C=O), 149.1, 148.8, 130.7, 120.5, 110.8, 110.4, 97.9, 81.1, 73.4, 61.4, 55.9, 55.8, 48.4, 43.0 (NCH₃), 23.8, 14.2. HRMS *m/z* (+APCI-TOF) calcd for C₁₆H₂₃NO₅ [M+H]⁺ : 310.1654, found 310.1669.

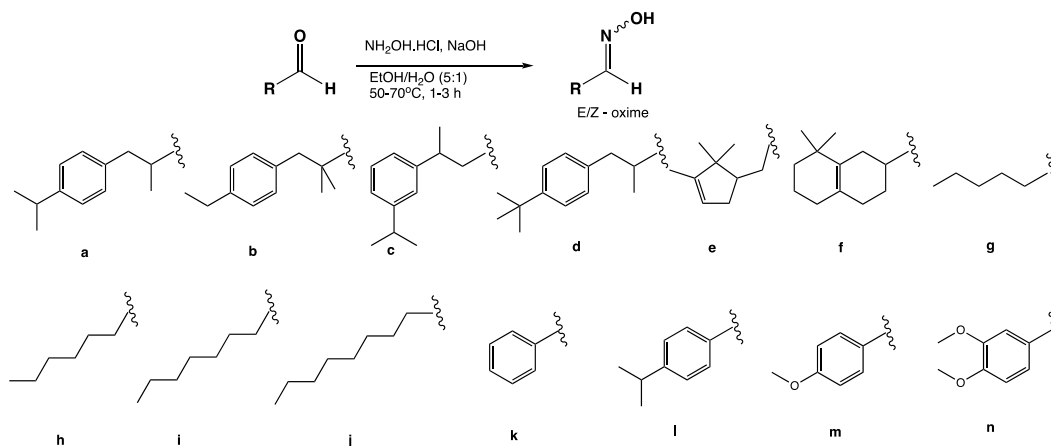


3. RESULT AND DISCUSSION

3.1 Synthesis, Characterization and Olfactory Evaluation of Isoxazoline-5-carboxylates and Isoxazolidine-5-carboxylates

3.1.1 Synthesis, Characterization and Olfactory Evaluation of Isoxazoline-5-carboxylates

The aim of this thesis is to synthesize a wide and diverse range of aldoxime derivatives with aromatic and aliphatic substituents, to be used as precursors of nitrile oxide in the cycloaddition reaction. Aldoximes are considered good candidates for kilogram-scale synthesis due to their high stability and ease of preparation. Traditionally, aldoxime was obtained by the condensation reaction of an aldehyde with hydroxylamine hydrochloride in the presence of bases, either in solvent or solvent-free conditions. Commonly used bases for this purpose include K_2CO_3 , $NaOH$, $NaHCO_3$, and NEt_3 .⁶⁵⁻⁶⁶ Considering the availability of the aforementioned bases for industrial usage, 1 equivalent of 14 fragrant aldehydes (aliphatic or aromatic) were reacted with 1.2 equivalents of hydroxylamine in the presence of 1.2 equivalents of sodium hydroxide (2M) at temperatures between 50-70°C to form aldoximes as starting materials with good to high yields (70-95%). As expected, all aldoximes were obtained with a lack of diastereoselectivity. The optimized reaction conditions for the formation of aldoxime **2a-n** and the corresponding diastereomeric ratios, confirmed by GC-MS measurements, are provided in **Table 3.1-1**.



Scheme 3-1- 14 aldoxime derivatives

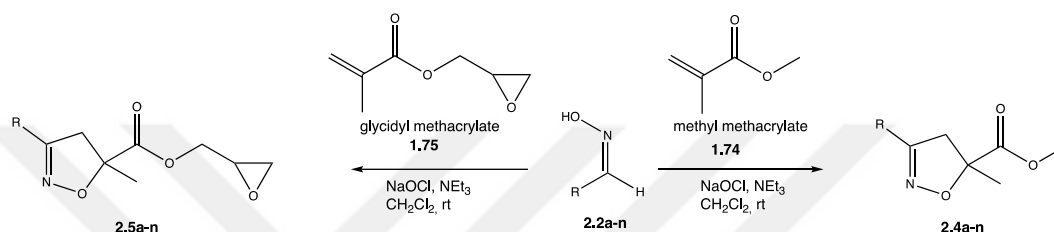
Table 3-1- Synthesis of aldoxime efficacy data

Product	Temp.(°C)	Time (min.)	E/Z ratio ^a	Yield%	Product	Temp.(°C)	Time (min.)	E/Z ratio ^a	Yield%
2.2a	50	45	18.5:81.5	85	2.2h	50	30	49:51	72
2.2b	50	50	22:78	82	2.2i	50	30	12:88	70
2.2c	50	45	45:55	80	2.2j	60	45	44:56	75
2.2d	50	30	33:67	85	2.2k	50	30	07:93	95
2.2e	60	40	43:57	82	2.2l	50	60	05:95	90
2.2f	70	75	Mix of diastreo.	72	2.2m	50	45	6.5:93.5	88
2.2g	50	25	46:54	77	2.2n	50	45	05:95	85

^a Determined by GCMS analysis

After obtaining aldoximes **2.2 a-n**, the synthesis of new isoxazoline-5 carboxylates through the 1,3-dipolar cycloaddition reaction of **2.2 a-n** with methyl or glycidyl methacrylate (**1.43** or **1.44**) in a one-pot manner. When considering the industrial application of this reaction, the direct oxidation of aldoxime to generate in situ nitrile oxide as a 1,3-dipole appears to be more practical. Among the various oxidants commonly used for aldoxime-nitrile oxide conversion, such as sodium hypochlorite (NaOCl), dimethyldioxirane, ceric ammonium nitrate, and hypervalent iodine compounds, NaOCl stands out as the most suitable candidate due to its affordability and widespread availability. The reaction of aldoxime with % 5 NaOCl solution in the presence of NEt₃ results in the in situ generation of nitrile oxide, which reacts with **1.74** or **1.75** in a 1,3-dipolar fashion to yield the isoxazoline-5 carboxylates **2.4 a-n** and **2.5 a-n** in good to high yields (62-88%) as a single regioisomer (Scheme 3.2). Previous studies have reported that the 1,3-dipolar cycloaddition reaction of methyl methacrylate with certain aryl aldoximes produces diastereomeric mixtures of isoxazolines, with the 5-substituted isomer being the predominant product. These results were consistent with this thesis nitrile oxide-methacrylate ester cycloadditions in terms of stereoselectivity, providing the 5-substituted isomer as well.

Nevertheless, considering that the utilization of fourteen distinct aldoximes may lead to varying outcomes in the cycloaddition reactions, the reaction conditions will be tailored and optimized for each aldoxime derivative individually. It is well understood that methyl methacrylate **1.74**, when reacted with corresponding aldoximes, provides better reaction yields and comparatively shorter reaction times when compared to glycidyl conjugates **1.75**. This behavior of **1.75** in terms of reactivity could be explained by the bulkiness of the glycidyl group in the 1,3-dipolar cycloaddition reaction, which possibly reduces the 1,3-dipole-dipolarophile interaction.



Scheme 3-2- Isoxazoline carboxylate synthesis route

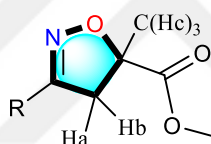


Table 3-2- Isoxazolines ¹H NMR chemical shift table

	Comp.	Ha-Hb δ(ppm)J(Hz)	Hc (CH ₃) δ(ppm)J(Hz)	Diastereomer Ratio ^a		Comp.	Ha-Hb δ(ppm)J(Hz)	Hc (CH ₃) δ(ppm)J(Hz)	Diastereomer Ratio ^a
1	2.4a	3.32,d,8.2 - 2.80,d,6.5	1.50, s	100:0	15	2.4h	3.39,d,17.2- 2.74,d, 17.2	1.55,s	100:0
2	2.5a	3.39,dd, 3.7, 2.1- 2.89,d,8.8	1.57,d, 3.9	100:0	16	2.5h	3.45,d,17.2- 2.81,d,17.5	1.62,d,4.8	52.5:47.5
3	2.4b	3.45,d, 17.3- 2.71,d,14.2	1.59,s	26:74	17	2.4i	3.41,d,17.2- 2.77,d, 17.2	1.58,s	100:0
4	2.5b	3.45,dd,17.2, 2.5-3.22,ddt, 9.5, 6.4, 3.1	1.59,d, 3.6	24:76	18	2.5i	3.42,dd,17.3, 2.8-2.81,d, 4.0	1.60,d, 4.4	45.5:54.5
5	2.4c	3.22,t,17.5- 2.87,dt,13.8, 6.9	1.47,s	100:0	19	2.4j	3.39,d,17.2- 2.75,d,17.2	1.56,s	100:0
6	2.5c	3.02,dt,14.3, 7.1- .52,d, 5.0	1.47,d, 4.2	95.5:2.8	20	2.5j	3.45,d,17.3- 2.81,d,17.3	1.62,s	100:0
7	2.4d	3.38,d, 8.2 - 2.86,d,6.5	1.56,s	100:0	21	2.4k	3.91,d,16.9- 3.25,d,16.9	1.74,s	100:0
8	2.5d	3.27 - 3.16,m - 2.74,d,4.6	1.59,d, 4.2	95.3:3.1	22	2.5k	3.89,dd,17.0, 2.2-3.24,d, 16.9	1.72,d,4.1	43.8:54.4
9	2.4e	3.49,dd, 17.2, 11.2-2.83,dd, 17.2, 9.6	1.62,s	100:0	23	2.4l	3.87,d, 16.9- 3.21,d, 16.9	1.70,s	100:0
10	2.5e	23.54-3.44,m - 3.28-3.22,m	1.63,s	15.7:54.6:29 .8	24	2.5l	3.89,dd,16.9, 2.5-2.83,dd,8.4, 4.2	1.72,d,4.1	45.4:54.6
11	2.4f	3.48,d,17.6- 2.83,d,17.8	1.59,s	66:34	25	2.4m	3.84,d,18.2- 3.18,d,16.8	1.69,s	100:0

12	2.5f	3.43,d,3.0-2.79,d, 5.0	1.57s	28.4:39.1:14.3:17.9	26	2.5m	3.82,d, 5.1-3.20,d, 16.8	1.72,s	47:53
13	2.4g	3.36,dd,17.0, 8.2-2.73,d, 17.3	1.51,s	100:0	27	2.4n	3.80d,16.8-3.16,d,16.8	1.65,s	100:0
14	2.5g	3.40,dd,17.3, 2.9-2.79,d,4.1	1.58,d,4.3	61:39	28	2.5n	3.78,d,2.8-3.17,d,16.9	1.65,s	40:60

^a Determined value obtained from the GC-MS analysis.

The structure characterization of target isoxazoline derivatives was performed using NMR (¹H, ¹³C), FT-IR, GC-MS and TOF-LCMS analysis. According to the ¹H-NMR results, the indicator peaks showing the formation of the isoxazoline heterocycle are the CH₃ group attached to the quaternary carbon and the CH₂ protons adjacent to the C=N carbon, respectively. Since the chemical environment of each isoxazoline compound differs, shifts are observed in these indicator peaks. While the CH₃ protons resonated singlet at about 1.50 ppm, the diastereotopic CH₂ protons resonated separately doublet or doublet of doublet peaks at around 3.80-3.30 and 3.20-2.70 ppm, as expected. The coupling values indicate that the protons are strongly coupled to each other. In ¹³C-NMR analysis, on the other hand, the peaks at around 170 ppm, 160 ppm and 85 ppm correspond to ester carbonyl, imine carbon and quaternary carbon respectively. In addition, the GC-MS analysis showed the mass of each isoxazoline and indicated that 8 derivatives (**2.4b**, **2.5b**, **2.4f**, **2.5f**, **2.5h**, **2.5i**, **2.5j**, **2.5n**) were obtained as diastereomeric mixtures (**Table 3.1-2**).

After the structural characterization of isoxazoline carboxylates, the olfactory properties of the target compounds were identified by a panel of three experts (Parkim Corp.). For the test, 10% dipropylene glycol (DPG) solutions of each compound (**2.4** or **2.5**) were prepared and applied to perfume test strips. Olfactory properties of the corresponding compounds were determined by making odor identifications in both fresh and 24-hour periods. The main odor notes and durability for each molecule were presented in **Table 3.1-3**. The olfactory evaluation of these isoxazoline carboxylates showed that there is no connection between isoxazolines and their precursors (aldehydes) in terms of odor notes. They completely lost their odor profile when transformed into their corresponding isoxazolines. It is well understood that the odor notes and durability of isoxazoline carboxylates strongly depend on the substituent attached to the 3-position of the isoxazoline ring. Specifically, floralozone and its analogues (florhydral, cyclamen aldehyde, lilial) and aliphatic aldehydes provided isoxazolines with remarkable fragrant properties compared to other precursors. Interestingly, while isoxazoline

2.4a, the methyl ester substituted one, exhibited no interesting odor character, the glycidyl ester analogue **5a** provided a very intense and extremely durable odor with slightly vanillic, slightly floral, and medicinal undertones. Considering durability and odor quality, **2.4b**, **2.4d**, **2.5d**, **2.4i**, **2.4j** can be regarded as promising fragrant compounds.

Table 3-3-Odour durability and Olfactory description of **2.4 a-n** and **2.5 a-n**

Compound	Olfactory Description	Top	DD	Compound	Olfactory Description	Top	DD
4a	Very weak	++		4h	Slightly spicy, woody, ambery	+	
5a	Slightly vanillic, medicinal, slightly floral	++++++	+	5h	Very weak	+	
4b	Vanillic, anisic	+++++	+	4i	Citrus, aldehydic, waxy, metallic	++++++ +++	++
5b	Slightly vanillic	++		5i	Very weak	+	
4c	Watery, floral, muguet	++++		4j	Orange, sweet, citrus, aldehydic	++++++ ++	+
5c	Very weak	+		5j	Very weak	+	
4d	Citrus, aldehydic, waxy, metallic	++++	+	4k	Very weak	+	
5d	Floral, muguet, aldehydic, watery	++++++	+	5k	Very weak	+	
4e	Sandalwood, aldehydic	+		4l	Fresh, citrus, metallic, waxy	+	
5e	Watery, sandalwood, acrylic	+		5l	Very weak		
4f	Very weak	+		4m	Slightly vanillic	++	
5f	Very weak	+		5m	Very weak		
4g	Anisic, slightly vanillic	+++		4n	Fresh, citrus, metallic, waxy	++	
5g	Anisic, slightly spicy	+++		5n	Fresh, citrus, metallic, waxy	+	

The Top notes correspond to the evaluations at 0-15 min, while the Dry-down (DD) notes correspond to the evaluations after 24 hours.

3.1.2 Synthesis, Characterization and Olfactory Evaluation of Isoxazolidine-5-carboxylates

The initial phase of this study involved synthesizing five nitrones from randomly chosen aldehydes, each possessing distinct odor characteristics. Floralozone **2.1b** was selected as a pilot precursor compound for optimizing the nitrone reaction. The reaction conducted with NEt₃ in DCM at both room temperature and reflux yielded compound **2.3c** in 45% and 52% yields, respectively

(refer to Table 3.1-4, Entry 1 and 2). In an alternative attempt using NaOH instead of NEt₃ in an aqueous medium, the yield for **2.3c** decreased, even with prolonged heating at 80°C (refer to **Table 3.1-4, Entry 3 and 4**). Ultimately, a yield of 62% for **2.3c** was achieved by grinding **2.1b**, NH₂OH.HCl, Na₂SO₄, and Na₂CO₃ in a mortar and pestle. This grinding method proved to be comparatively rapid and efficient for the preparation of **2.3c** in comparison to other methods (refer to **Table 3.1-4, Entry 5**). Consequently, the solvent-free grinding method was employed for synthesizing derivatives **2.3a-e**, resulting in moderate to good yields of the desired aldonitrones.

Table 3-4-Reaction optimizations and conditions for **2.3a-e**

Entry	Compound	Reaction Conditions ¹	Yield (%) ²
1	2c	DCM, NEt ₃ 25°C, 24 h	45
2	2c	DCM, NEt ₃ 40°C, 10 h	52
3	2c	H ₂ O, NaOH, 25°C, 24 h	30
4	2c	H ₂ O, NaOH, 80°C, 12 h	38
5	2c	Na ₂ CO ₃ , Na ₂ SO ₄ , grinding, 10 min	62
6	2a	Na ₂ CO ₃ , Na ₂ SO ₄ , grinding, 10 min	65
7	2b	Na ₂ CO ₃ , Na ₂ SO ₄ , grinding, 5 min	44
8	2d	Na ₂ CO ₃ , Na ₂ SO ₄ , grinding, 15 min	70
9	2e	Na ₂ CO ₃ , Na ₂ SO ₄ , grinding, 10 min	68

¹Time determined by TLC control ; ²isolated yield

The structural elucidation of aldonitrones **2.3a-e** was meticulously executed employing a multi-faceted approach encompassing infrared spectroscopy (IR), nuclear magnetic resonance (NMR), and mass spectrometry measurements. The discernment of the diastereomeric ratio (E or Z) for the aldonitrones, as meticulously outlined in **Table 3.1-5**, entailed a judicious comparison of integral values derived from indicative proton signals within the ¹H-NMR dataset. Although **Table 3.1-5** comprehensively details the indicative proton and carbon signals associated with the iminic and NMe groups across **2.3a-e**, it is imperative to note the conspicuous absence of pertinent NMR data for the enigmatic compound **2.3b**. This conspicuous lacuna is ascribed to the ostensibly intricate nature of intermolecular rearrangements potentially impacting **2.3b**. Regrettably,

notwithstanding diligent efforts, the attainment of conclusive NMR data for compound **2.3b** remained elusive. This lacuna, while intriguing, is tempered by the absence of structural evidence substantiating the postulated intermolecular rearrangement, as elucidated in **Scheme 3-3**.



Scheme 3-3-Plausible intramolecular cyclization product of **2.3b**

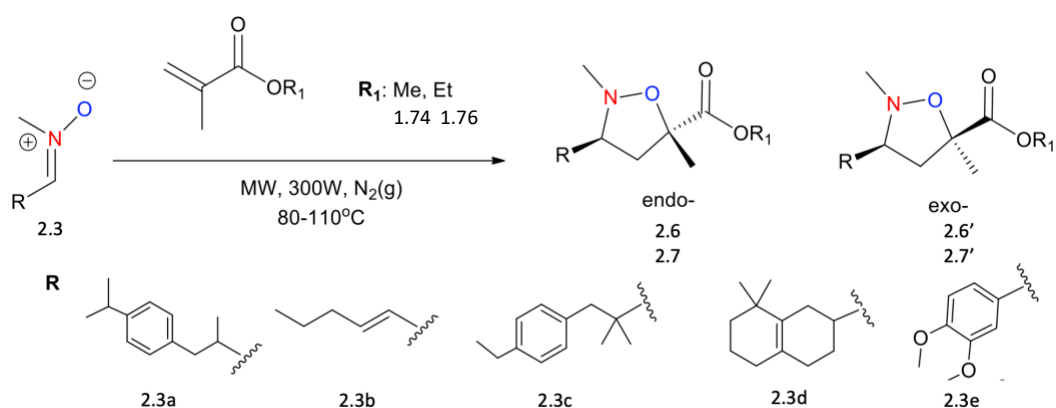
Table 3-5-Indicative structural data for aldonitrone derivatives **2.3a-e**

Entry	Compound	IR	¹ H-NMR		¹³ C-NMR		Z/E isomer ratio
		(C=N) cm ⁻¹	δ (ppm) NCH ₃	J(Hz) C=NH	δ (ppm) NCH ₃	C=NH	
1	2.3a	1600	3.53 (Z)	6.46, dd, 7.2, 0.7 (Z)	52.72 (Z)	144.30 (Z)	100:0
2	2.3b	1575	-	-	-	-	-
3	2.3c	1593	3.63 (Z)	6.33, d, 0.7 (Z)		142.05 (Z)	70:30
			3.66 (E)	6.39, d, 0.7 (E)	53.55 (Z) 53.39 (E)	143.25 (E)	
			3.64 (Z)	6.53, d, 0.4 (Z)		144.30 (Z)	
			3.65 (E)	6.55, d, 0.4 (E)	52.72 (Z) 52.53 (E)	144.44 (E)	
4	2.3d	1600	3.84 (Z)	6.89, d, 8.5 (Z)	54.23 (Z)	135.37 (Z)	100:0

Following the successful synthesis of novel aldonitrone derivatives **2.3 a-e**, our focus shifted towards the creation of the initial series of isoxazolidine-5-carboxylates. This was achieved through the treatment of **2.3 a-e** with methacrylate derivatives **1.74**, **1.76**, employing a one-pot approach and microwave heating. According to Badoiu and Kündig, when electron-donating groups were present on the nitrone's α-aryl substituent, a mixture of products resulted with the *exo* product prevailing as the major diastereoisomer and conversely, in cases where electron-withdrawing groups were introduced to the nitrone's α-aryl substituent, the *endo* product became the predominant diastereoisomer⁶⁷. Prior research indicated that the 1,3-dipolar

cycloaddition (1,3-DC) reaction involving methyl methacrylate and certain aryl aldonitrones resulted in isoxazolidines, predominantly yielding the *endo* isomer. Our nitrone-methacrylate cycloadditions aligned with these findings, favoring the *endo* isomer. However, considering the variability introduced by five different nitrones, optimization of reaction conditions was undertaken for each aldonitrone derivative.

Initially, the irradiation of **2.3a** and **1.74** at 110°C for 5 hours yielded product **2.6a-2.6a'** with a 45% yield (refer to **Table 3.1-6, Entry 1**). The incorporation of an inert atmosphere (N₂ gas) marginally increased the reaction yield to 52% (**Table 3.1-6, Entry 2**). Subsequent aldonitrone-methacrylate reactions were conducted either in toluene or under neat conditions, both with microwave irradiation and under inert atmospheres (**Table 3.1-6, Entry 2-15**). The treatment of **2.3b** and **1.74** at 110°C in toluene yielded **2.6b** with a 45% yield (**Table 3.1-6, Entry 4**). Interestingly, the absence of product formation in toluene at lower temperatures led to a surprising increase in the reaction yield to 60% when **2.3b** and **1.74** were heated under solvent-free conditions at 60°C for 2 hours (**Table 3.1-6, Entry 5**). Notably, despite numerous attempts, no substantial increase in reaction yield was observed under neat conditions for compounds **2.6a-e**, **2.6a'-e'**, **2.7a-e**, and **2.7a'-e'**. Ultimately, the optimal protocol for the preparation of these compounds involved heating aldonitrones with methacrylate esters in toluene under reflux conditions for the specified time outlined in **Table 3.1-6**.



Scheme 3-4- Isoxazolidine carboxylate synthetic route

Table 3-6- Microwave assisted synthetic route data

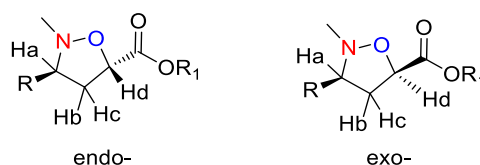
Entry	Methacrylate		Compound	Reaction	Total Yield (%) ¹
	Aldonitrone	Ester		Condition	
1	2.3a	1.74	2.6a-2.6a'	110°C, 5h, Toluene, 300W	45
2	2.3a	1.74	2.6a-2.6a'	110°C, 5h, Toluene, 300W, N ₂ (g)	52
3	2.3a	1.76	2.7a	110°C, 2h, Toluene, 300W, N ₂ (g)	64
4	2.3b	1.76	2.6b	110°C, 2h, Toluene, 300W, N ₂ (g)	48
5	2.3b	1.74	2.6b	60°C, 2h, Neat, 50W, N ₂ (g)	60
6	2.3b	1.76	2.7b	80°C, 2h, Neat, 50W, N ₂ (g)	46
7	2.3c	1.74	2.6c-2.6c'	110°C, 2h, Neat, 300W, N ₂ (g)	55
8	2.3c	1.74	2.6c-2.6c'	110°C, 2h, Toluene, 300W, N ₂ (g)	68
9	2.3c	1.76	2.7c-2.7c'	110°C, 8h, Toluene, 300W, N ₂ (g)	60
10	2.3d	1.74	2.6d	110°C, 3h, Neat, 300W, N ₂ (g)	55
11	2.3d	1.74	2.6d	110°C, 3h, Toluene, 300W, N ₂ (g)	72
12	2.3d	1.76	2.7d	110°C, 3h, Toluene, 300W, N ₂ (g)	70
13	2.3e	1.74	2.6e-2.6e'	110°C, 5h, Neat, 300W, N ₂ (g)	48
14	2.3e	1.74	2.6e	110°C, 5h, Toluene, 300W, N ₂ (g)	62
15	2.3e	1.76	2.7e	110°C, 8h, Toluene, 300W, N ₂ (g)	60

¹ The quantity of major diastereomers after purified by column chromatography

The identification of the structures of the targeted isoxazolidines was accomplished through a comprehensive analysis involving infrared spectroscopy (IR), nuclear magnetic resonance (NMR), and mass spectrometry measurements. Within the IR spectra, a prominent vibration band around 1726-1736 cm⁻¹ was indicative of the ester carbonyl stretching in the target isoxazolidines. The ¹H NMR measurements revealed key proton signals affirming the formation of the isoxazolidine ring, particularly focusing on the diastereotopic methylene hydrogens, the hydrogen adjacent to the nitrogen of the ring, and the methyl proton attached to the quaternary carbon of the ring.

Examination of the chemical displacements and coupling values associated with these protons, particularly focusing on the aliphatic protons within the heterocyclic moiety, elucidated that only **2.7a**, **2.6b**, **2.7b**, **2.6d**, **2.7d**, and **2.7e** were acquired as endo isomers. In contrast, the remaining heterocycloadducts were obtained in the

form of indivisible diastereomeric mixtures (endo/exo), and their ratios were established through the comparison of integral values pertaining to methylene protons (refer to **Table 3.1-7**). As an illustrative example, the expanded ^1H -NMR spectrum of **2.7e**, featuring three assignable aliphatic and methyl protons, is depicted in **Scheme 3-5** notably, among the aliphatic protons, Ha emerged as experiencing the greatest deshielding owing to its proximity to nitrogen, resonating at 3.44 ppm as a triplet. Isoxazolidine ring methylene protons (Hc and Hd) exhibited a characteristic ABX pattern spin, with Hc and Hd manifesting as a doublet of doublet with coupling constants of 12.0 and 9.0 Hz, respectively. These observations align with prior reports on N-methyl nitron cycloaddition and methyl methacrylate, where the endo isomer predominated as the main product. Additionally, the ^{13}C -NMR spectra of the cycloadducts highlighted major signals corresponding to the methacrylate ester carbonyl carbon in the range of 173-175 ppm, along with the quaternary carbon of the isoxazolidine ring in the range of 79-81 ppm. Furthermore, time-of-flight mass spectrometry (TOF-MS) measurements supplied the anticipated molecular ions.



Scheme 3-5- Endo-, exo- demonstration of isoxazolidine core

Table 3-7- Indicative ^1H and ^{13}C NMR data of isoxazolidin-5-carboxylate derivatives (**2.6**, **2.6'**, **2.7**, **2.7'**)

Entry	Comp.	N(CH ₃) $\delta(\text{ppm})J(\text{Hz})$	Ha $\delta(\text{ppm})J(\text{Hz})$	Hb-Hc $\delta(\text{ppm})J(\text{Hz})$	Hd(CH ₃) $\delta(\text{ppm})J(\text{Hz})$	Ca $\delta(\text{ppm})$	Cd $\delta(\text{ppm})$	C=O(ester) $\delta(\text{ppm})$	Endo/Exo Ratio
1	2.6a-2.6a'	2.54, s, (n)	2.80, dd,	2.30, dd, 13.4, 8.4,	1.39, s, (n)	72.30, (n)	81.77, (n)	175.85, (n)	65:35
		2.61, s, (x)	13.7, 7.0, (n)	(n) - 1.91, dd, 12.5, 8.4, (n)	1.45, s, (x)	73.32, (x)	81.00, (x)	175.00, (x)	

2	2.7a	2.63, s, (n)	2.89, dd, 13.8, 6.9, (n)	2.39, dd, 13.5, 8.5, (n) - 1.99, dd, 12.6, 8.5, (n)	1.48, s, (n)	71.81, (n)	80.70, (n)	174.97, (n)	100:0
3	2.6b	2.63, s, (n)	2.97, dd, 16.4, 8.7, (n)	2.68, dd, 12.9, 9.3, (n) - 2.25, dd, 12.8, 7.8, (n)	1.49, s, (n)	72.10, (n)	80.76, (n)	175.33, (n)	100:0
4	2.7b	2.56, s, (n)	2.91, t, 7.8, (n)	2.61, dd, 13.3, 9.8, (n) - 2.16, dd, 12.7, 7.8, (n)	1.41, s, (n)	71.04, (n)	79.58, (n)	173.91, (n)	100:0
5	2.6c-2.6c'	2.83, s, (n) 2.88, s, (x)	2.94, dd, 13.1, 6.6, (n)	2.60 (dd, J = 9.7, 7.5, (n) - 2.27, dd, 13.1, 9.8, (n)	1.53, s, (n) 1.54, s, (x)	77.57, (n)	81.07, (n)	175.36, (n)	100:0
6	2.7c-2.7c'	2.83, s, (n) 2.87, s, (x)	2.94, dd, 13.1, 6.6, (n)	7.6, (n) - 2.27, dd, 13.1, 9.7, (n)	1.52, s, (n) 1.53, s, (x)	77.56, (n) 77.60, (x)	81.03, (n) 81.19, (x)	174.69, (n) 174.78, (x)	73:27
7	2.6d	2.73, s, (n)	-	-	1.50, s, (n)	73.06, (n)	80.96, (n)	175.78, (n)	100:0
8	2.7d	2.69, s, (n)	-	-	1.48, s, (n)	73.02, (n)	80.87, (n)	174.74, (n)	100:0
9	2.6e-2.6e'	2.53, s, (n) 2.62, s, (x)	3.44, t, 7.3, (n)	2.95, dd, 12.9, 9.1, (n) - 2.41, dd, 12.9, 8.2, (n)	1.51, s, (n) 1.61, s, (x)	72.38, (n) 73.46, (x)	81.17, (n) 81.85, (x)	175.45, (n) 173.91, (x)	88:22
10	2.7e	2.54, s, (n)	3.44, t, 7.6, (n)	2.96, dd, 12.9, 9.0, (n) - 2.41, dd, 12.9, 8.2, (n)	1.51, s, (n)	73.42, (n)	81.10, (n)	174.87, (n)	100:0

(n)=endo, (x)=exo

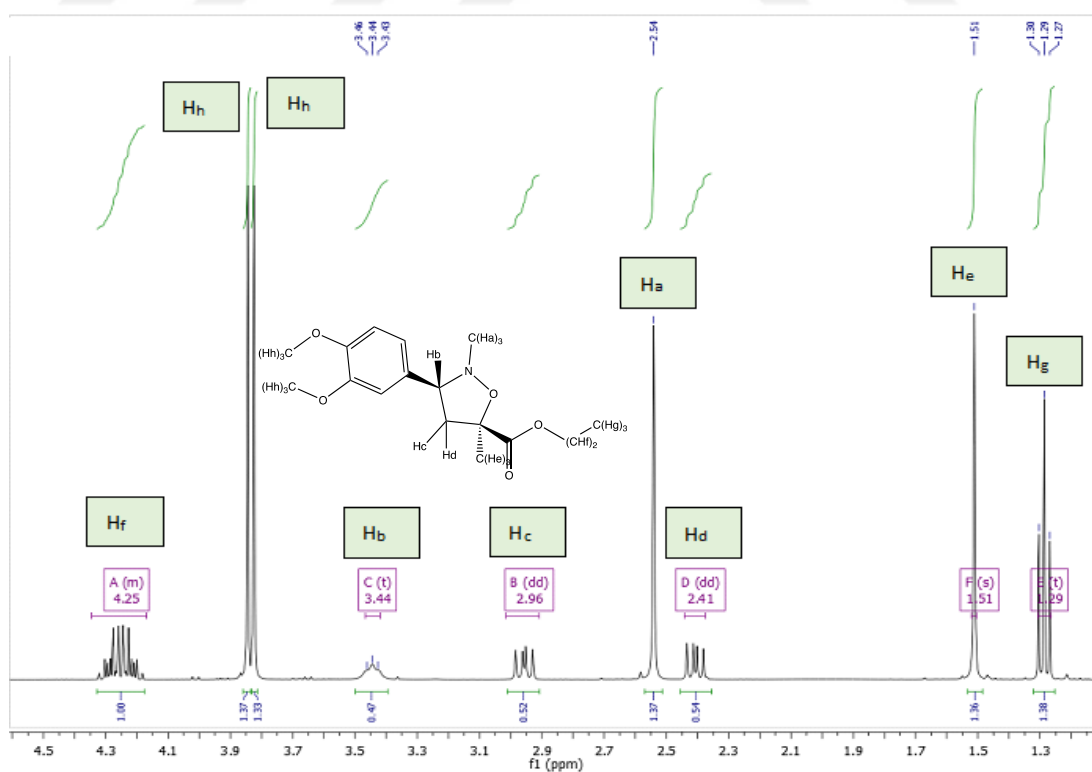


Figure 3-1-Expanded aliphatic region in ^1H -NMR spectrum of **2.7e**

Following the synthesis of aldonitrones **2.3a-e** and the subsequent creation of target isoxazolidines **2.6a-e**, **2.6a'-e'**, **2.7a-e**, and **2.7a'-e'**, our subsequent objective involved assessing the olfactory characteristics of these meticulously purified products through expert evaluation by Parkim Corp. The evaluation process involved preparing 10% dipropylene glycol (DPG) solutions for each compound (**2.3**, **2.6**, or **2.7**) and applying them to perfume test strips. The olfactory properties of these compounds were discerned by an expert nose at different time intervals (fresh, 4-hour, and 24-hour periods), with the primary odor notes summarized in **Table 3.1-8**.

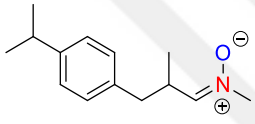
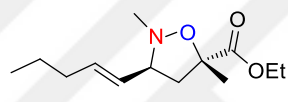
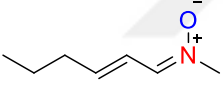
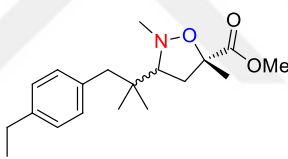
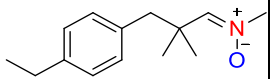
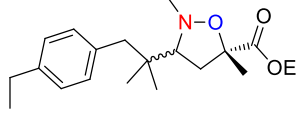
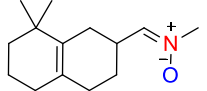
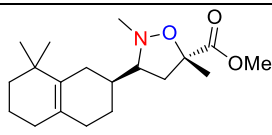
The outcomes of the olfactory evaluation revealed a profound transformation in the odor notes of the aldehydes employed in the study upon their conversion into aldonitrones (refer to **Table 3.1-8**). For instance, muguet carboxyaldehyde **2.1f**, known for its floral, clean, muguet, ozone, marine, sandy, and balsamic notes, underwent a significant shift. Compound **2.3d**, derived from **2.1f**, exhibited strong aquatic, muguet, lily, and dusty notes initially, maintaining a persistent aquatic note even after 24 hours at the tested concentrations.

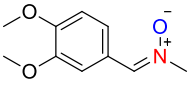
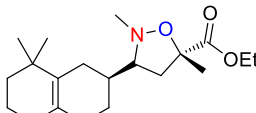
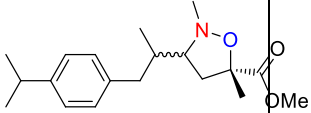
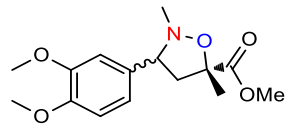
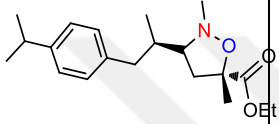
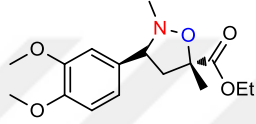
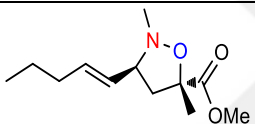
Surprisingly, there was no discernible olfactory correlation between aldonitrones **2.3a-e** and their corresponding isoxazolidines. Their odor profiles were markedly distinct, with aldonitrones **2.3b** displaying ozonic, medical, and fatty characteristics, while isoxazolidines **2.6a-2.6a'**, **2.7a** derived from **2.3a** exhibited primarily animalic, thinneric, and waxy notes. Similar observations were made across other aldonitrones and their corresponding isoxazolidines in terms of odor characteristics.

Conversely, despite the varied groups originating from aldonitrones and methacrylate esters in target isoxazolidine-5-carboxylates, common olfactory notes

such as animalic, medical, waxy, and ozonic were observed. Intriguingly, altering the ester group (Me or Et) on the same molecule resulted in entirely different olfactory tonalities for certain derivatives (refer to **Table 3.1-8**). For instance, compounds **2.6b** and **2.7b**, representing the methyl and ethyl esters of pentenyl-substituted isoxazolidine, respectively, exhibited distinct top notes—paint and weak fatty for **2.6b**, and unmistakable garlic, along with more cut grass and heavy green undertones for **2.7b**.

Table 3-8- Organoleptic data

Compound	Olfactory description	Compound	Olfactory description
 2.3a	Top: <i>Ozonic and Medical</i> DD: <i>Fatty</i>	 2.7b	Top: <i>Garlic and Cut grass</i> DD: <i>Weak</i>
 2.3b	Top: <i>Strong naphthyl and floral</i> DD: <i>Weak</i>	 2.6c-2.6c'	Top: <i>Strong thinneric, animalic</i> DD: <i>Strong animalic</i>
 2.3c	Top: <i>Naphthyl and Floral</i> DD: <i>Weak fatty and ozonic</i>	 2.7c-2.7c'	Top: <i>Animalic and barnyard</i> DD: <i>Animalic</i>
 2.3d	Top: <i>Muguet, Aquatic, Lily and Dusty</i> DD: <i>Strong Aquatic</i>	 2.6d	Top: <i>Strong Medical</i> DD: <i>Medical</i>

 2.3e	Top: <i>Ozonic</i> DD: <i>Ozonic and Aquatic</i>	 2.7d	Top: <i>Thinneric, paint, cresolic and animalic</i> DD: <i>Weak animalic</i>
 2.6a-2.6a'	Top: <i>Thinneric, Animalic and Napthyl</i> DD: <i>Animalic</i>	 2.6e-2.6e'	Top: <i>Ozonic, aquatic and fatty</i> DD: <i>Weak fatty and waxy</i>
 2.7a	Top: <i>Thinneric</i> DD: <i>Waxy and Fatty</i>	 2.7e	Top: <i>Ozonic and napthyl</i> DD: <i>Weak ozonic</i>
 2.6b	Top: <i>Paint</i> DD: <i>Weak</i>		

The top notes corresponds to the evaluations 0-10 min, while the dry down (DD) notes corresponds to the evaluations after 24 h.

3.1.3 Microbial Proliferation Control

Microbial growth in raw materials plays a vital role in the use of cosmetics and similar products. For this reason, microbial growth should not occur in the raw materials that will be used or can be used in cosmetic production. Antimicrobial agents are used in raw materials where microbial growth occurs, but this not only brings extra costs but also causes an increase in the chemical load in the cosmetic product. For this reason, it is advantageous that the raw materials intended to be used in the production of cosmetic products do not contain any chemical preservatives.

All microbiological proliferation analysis were carried out by ILAC MRA and TURKAK accredited Scopbio Laboratories.

As a result of this thesis study, it was investigated whether the odorant raw materials synthesized could cause microbial growth through microbial production tests. No growth was detected in any of the raw materials obtained, and no increase in microbial loads was observed. Result reports of all microbial tests performed are given in the appendix.



4. CONCLUSION

In summary, the synthesis of aldoxime derivatives from 14 fragrant raw material aldehydes, encompassing both aliphatic and aromatic groups, was successfully accomplished. Subsequently, these aldoximes served as precursors for the synthesis of 28 isoxazoline carboxylates, incorporating both MMA and GMA substitutions, yielding raw materials of olfactory significance. These isoxazolines demonstrated attributes conducive to industrial-scale production, featuring high yields, purity, and productivity attainable through conventional industrial reactors and systems. Additionally, another facet of this thesis involved the preparation of aldonitrones from five commercially available fragrant aldehydes, employing a solvent-free approach. These aldonitrones were then subjected to microwave irradiation in combination with methacrylate esters, resulting in the generation of new isoxazolidine carboxylates characterized by high regio- and diastereoselectivity. Moreover, the olfactory evaluation conducted on both aldonitrones and the target isoxazolidines brought to light a substantial fragrance diversity between these chemical entities. This comprehensive exploration and successful synthesis of diverse fragrance compounds underscore the potential applications and versatility of the developed methodologies in the fragrance industry.

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3. Vinevida. Bulk Lavender Essential Oil Gallon (8 Pounds) in Aluminum Bottle - 100% Pure & Undiluted Essential Oil for DIY Soaps, Candles and Blends 231 https://www.etsy.com/uk/listing/904104402/bulk-lavender-essential-oil-gallon-8?ref=shop_home_recs_73.
4. Vinevida. Bulk Jasmine Absolute Oil Gallon (8 Lbs) in Aluminium Bottle - 100% Pure & Undiluted Essential Oil for DIY Soaps, Candles and Blends https://www.etsy.com/uk/listing/918545857/bulk-jasmine-absolute-oil-gallon-8-lbs?ref=sim_items_sameshopitems-1.
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6. APPENDICES

^1H , ^{13}C NMR and GCMS Spectra of 2.2 a-e

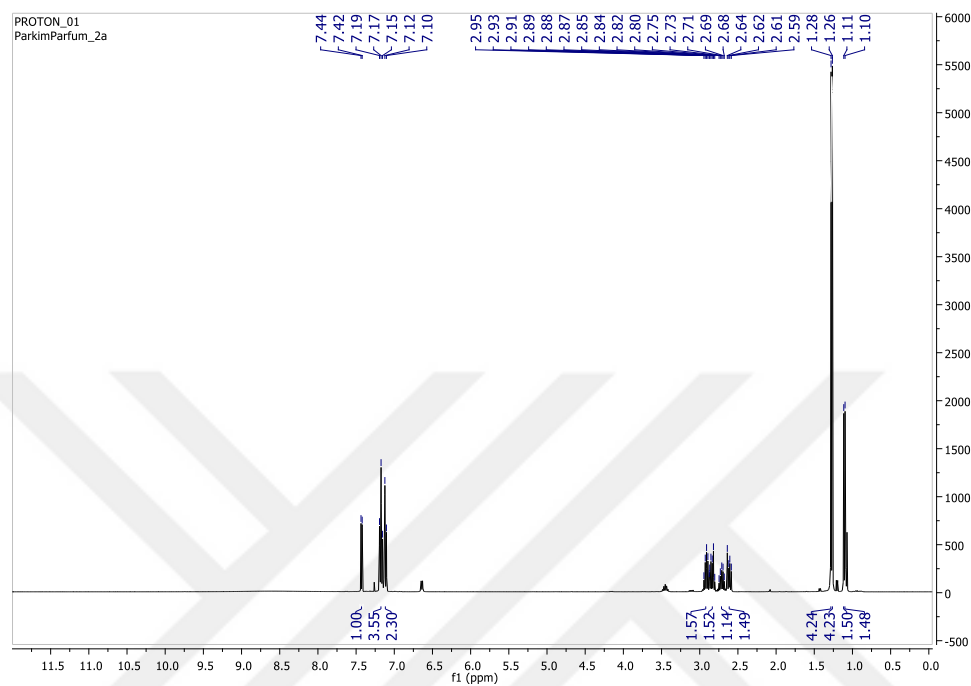


Figure 6-1- ^1H -NMR spectrum of 2.2a

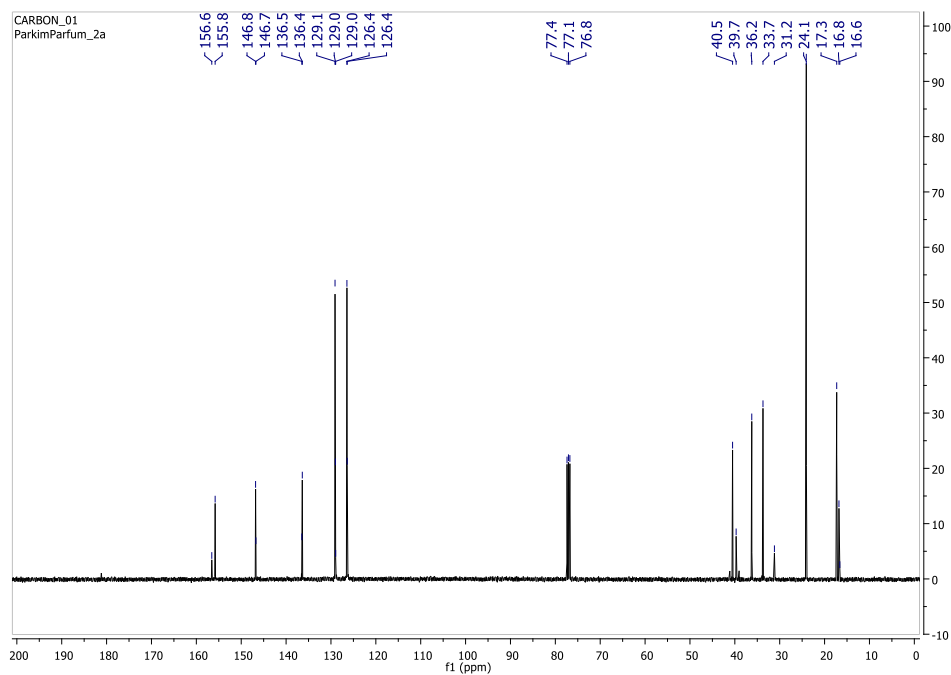


Figure 6-2- ^{13}C -NMR spectrum of 2.2a



Figure 6-3-GC-MS spectrum of 2.2a

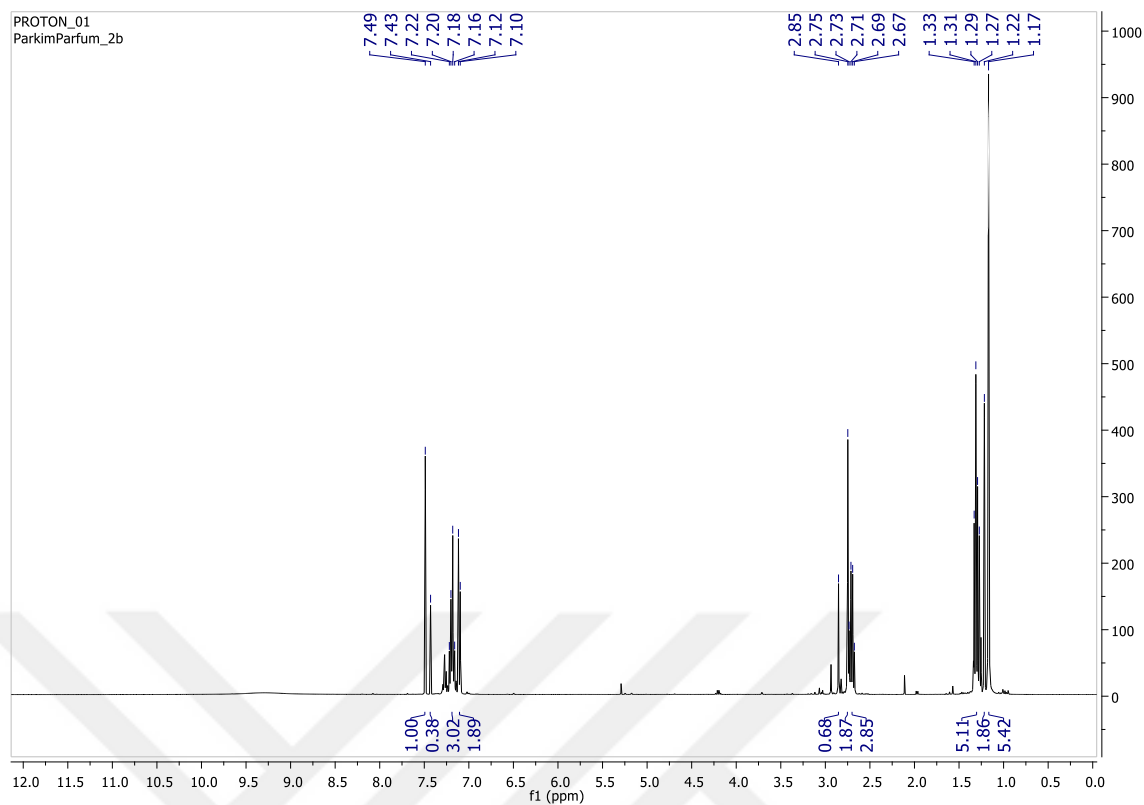


Figure 6-4- ^1H -NMR spectrum of 2.2b

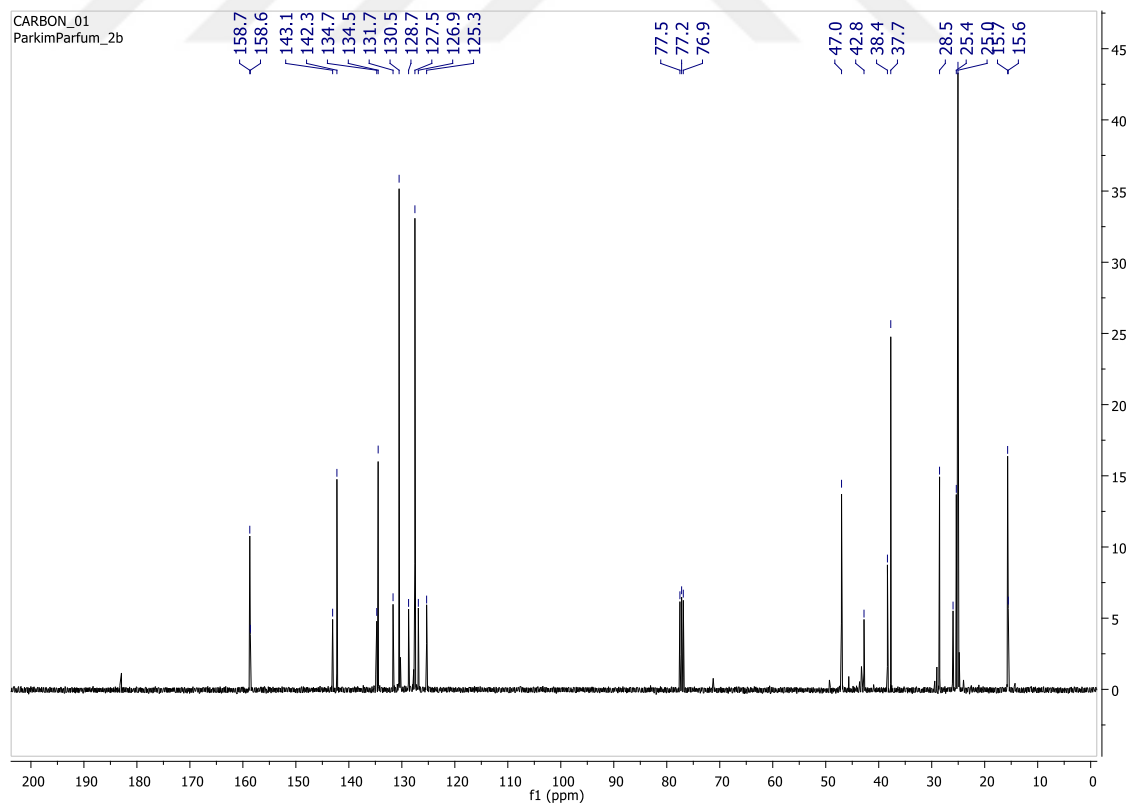
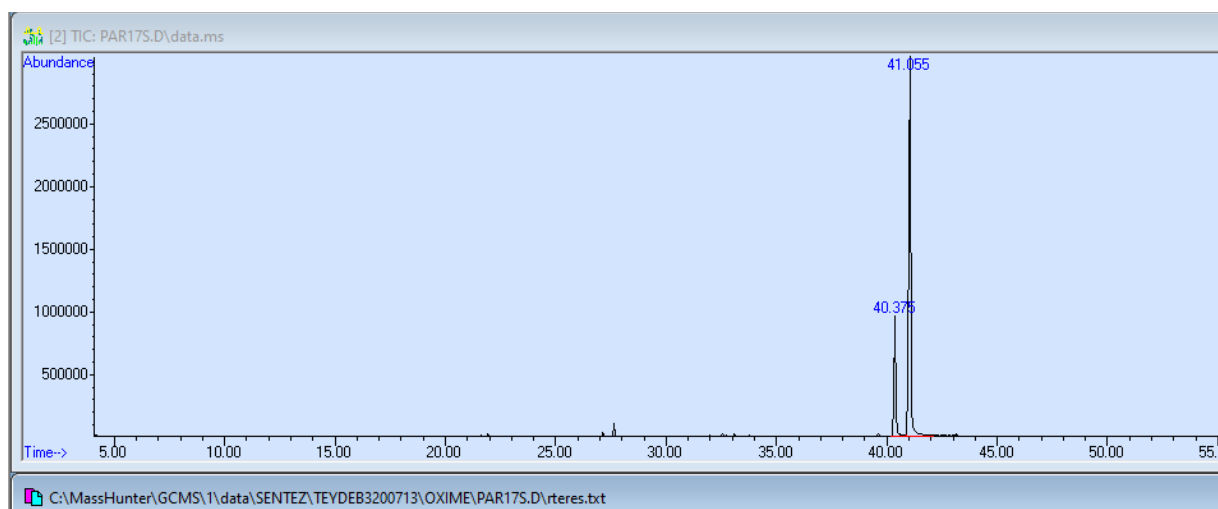


Figure 6-5- ^{13}C -NMR spectrum of 2.2b



Integration Parameters: autoint1.e
Integrator: ChemStation

Method : C:\MassHunter\GCMS\1\methods\deneme5.M
Title :

Signal : TIC: PAR17S.D\data.ms

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	40.375	8438	8475	8586	M2	958493	54293625	28.32%	22.069%
2	41.055	8588	8634	8879	M2	3038032	191727406	100.00%	77.931%

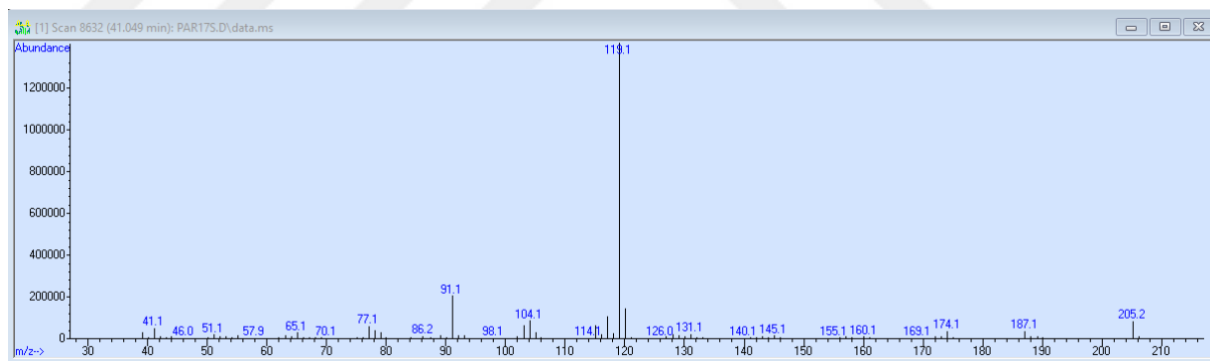


Figure 6-6-GC-MS spectrum of 2.2b

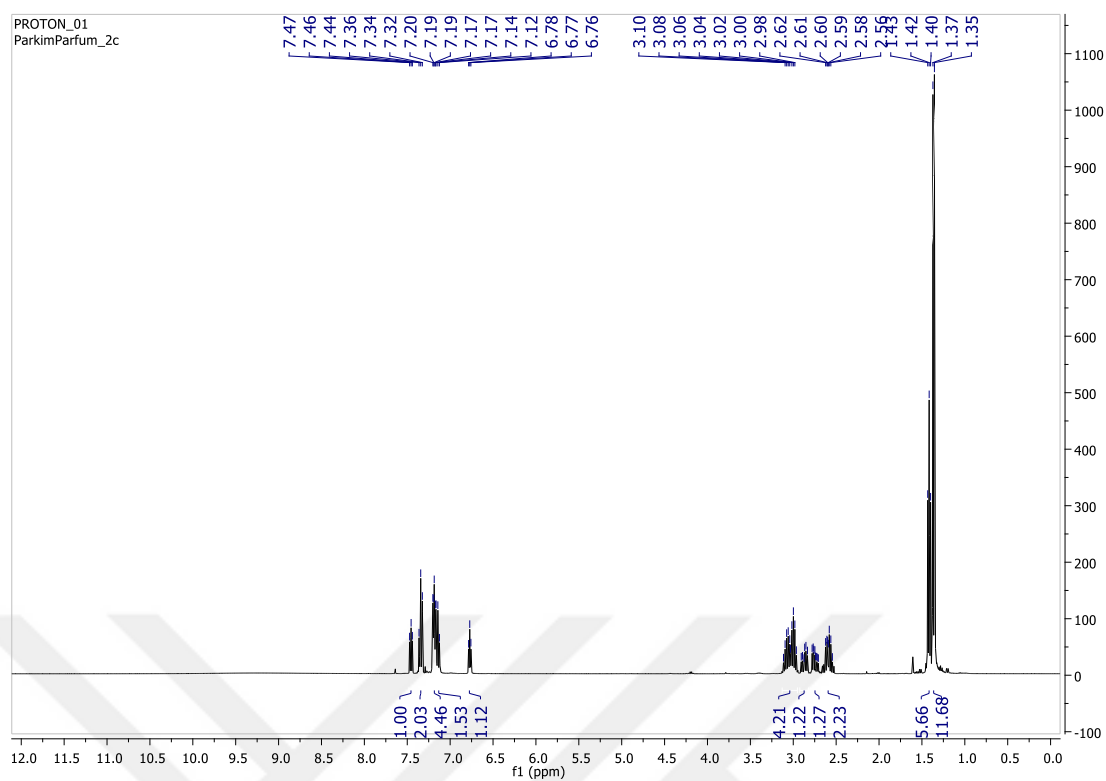


Figure 6-7- ^1H -NMR spectrum of 2.2c

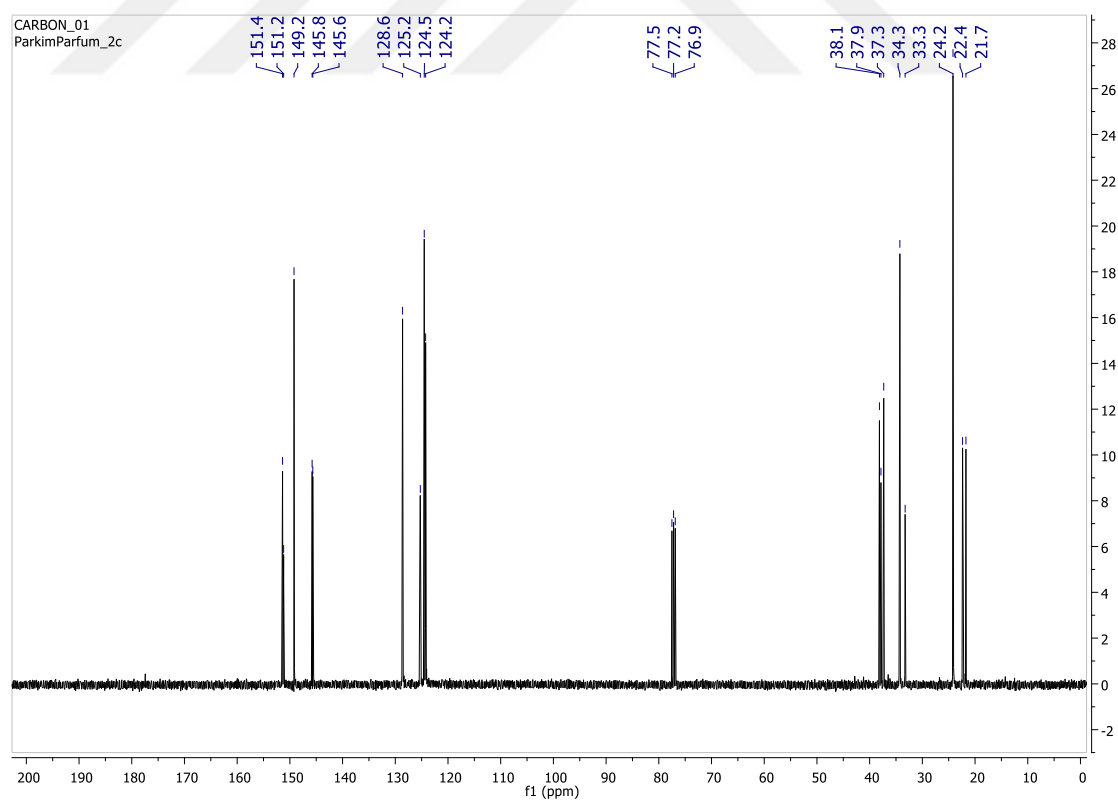


Figure 6-8- ^{13}C -NMR spectrum of 2.2c

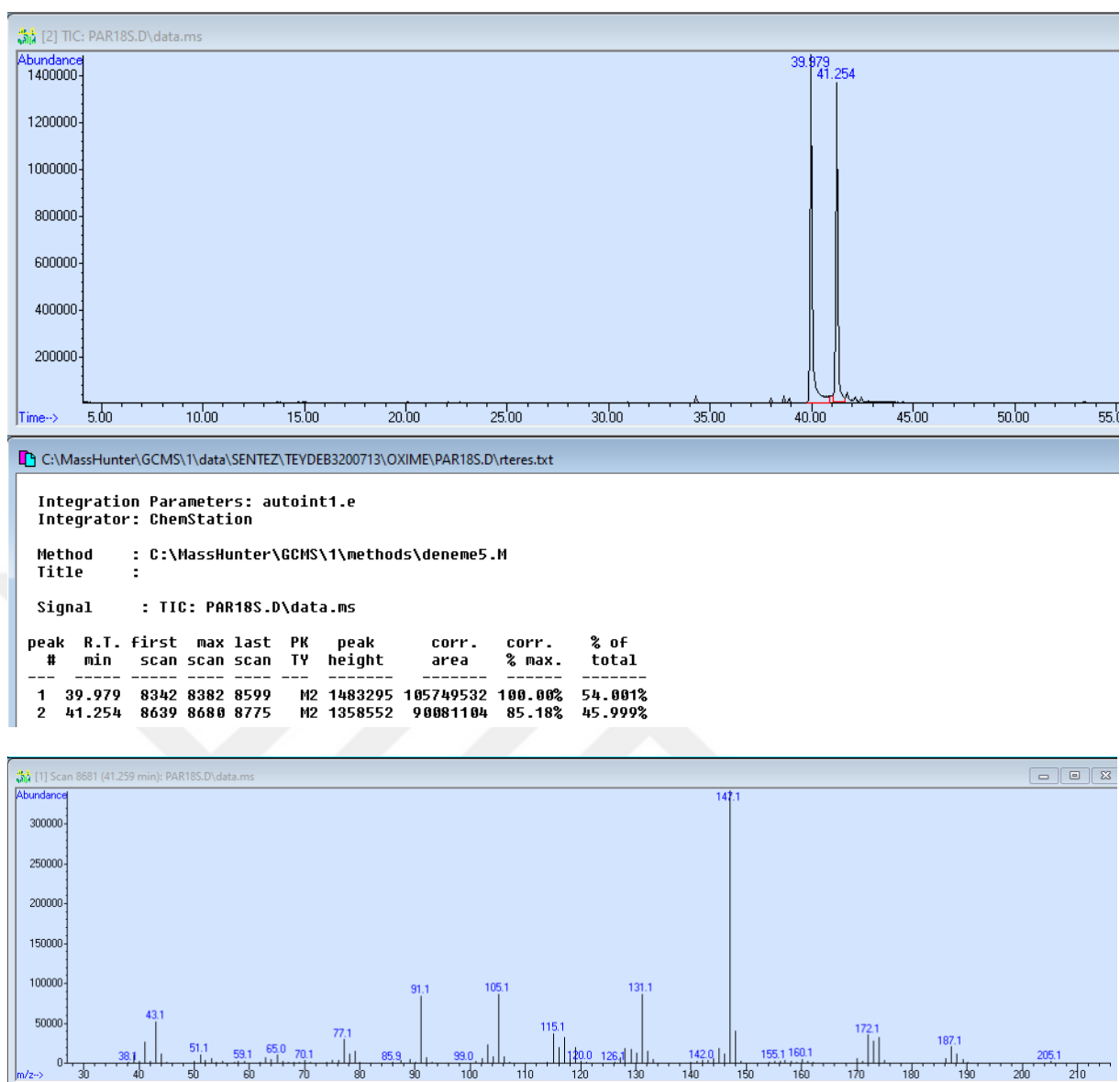


Figure 6-9-GC-MS spectrum of 2.2c

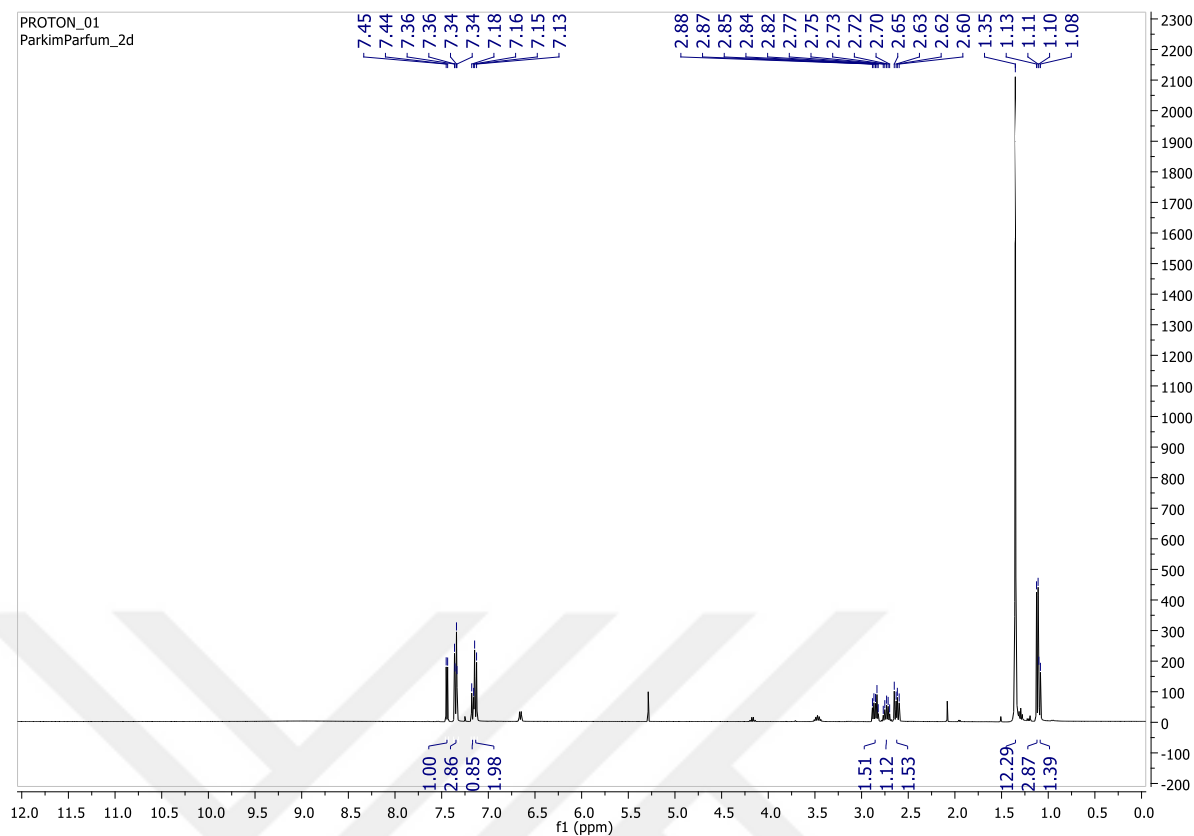


Figure 6-10- ^1H -NMR spectrum of 2.2d

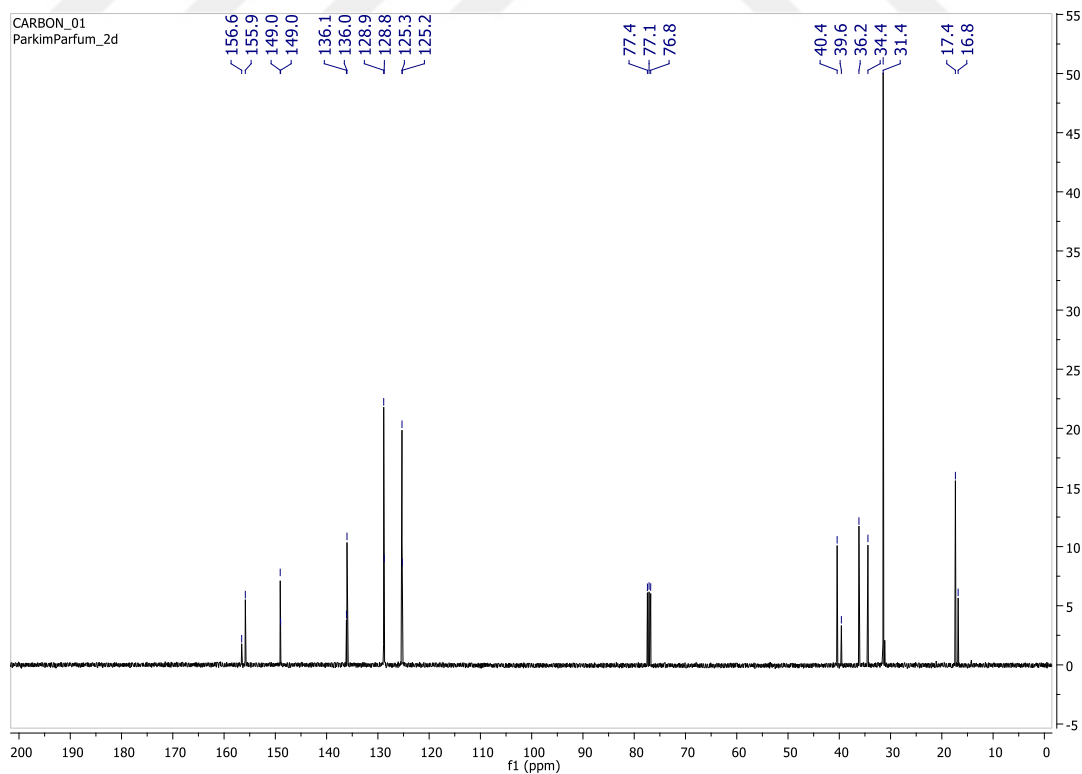


Figure 6-11- ^{13}C -NMR spectrum of 2.2d

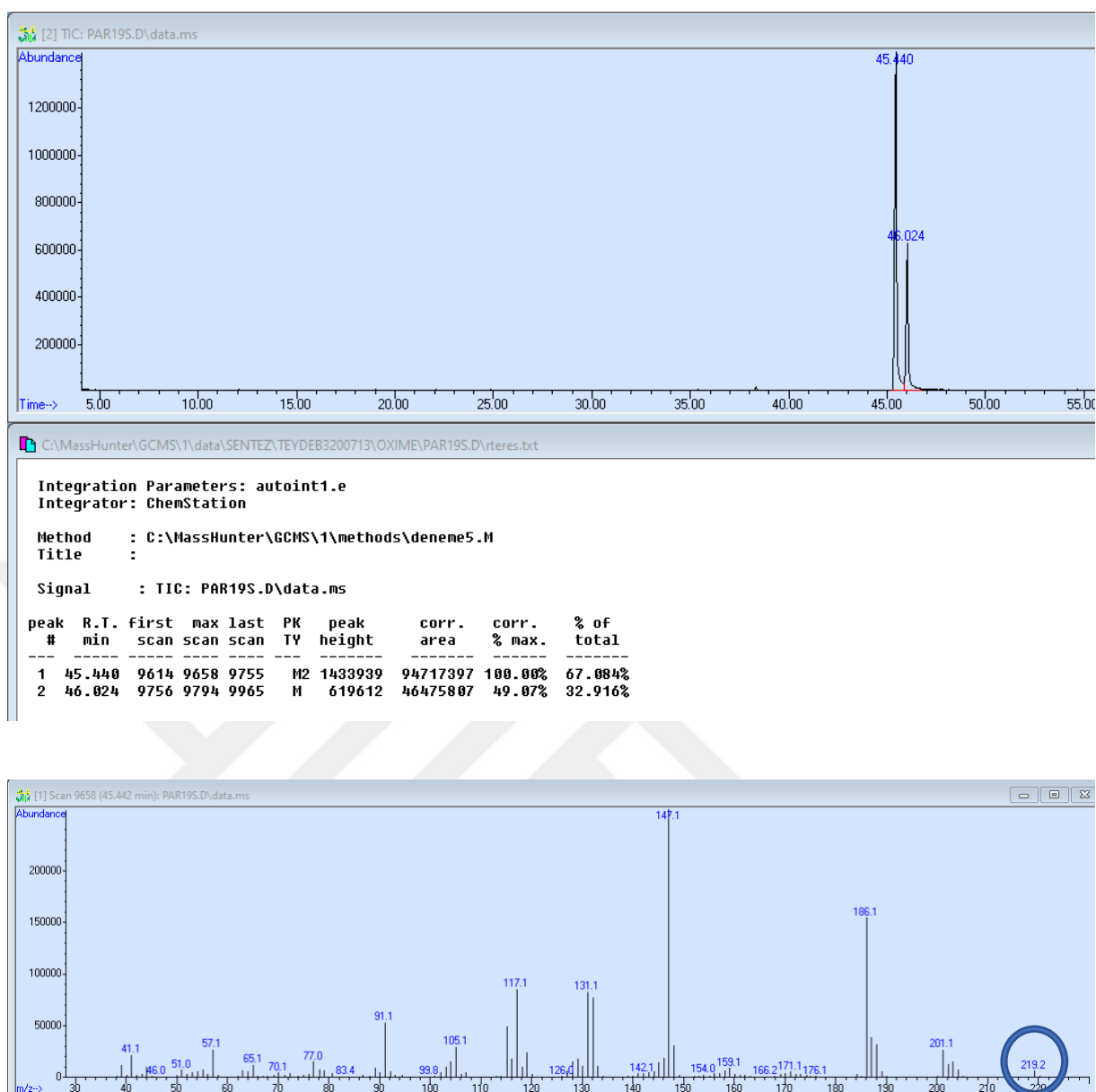


Figure 6-12-GC-MS spectrum of 2.2d

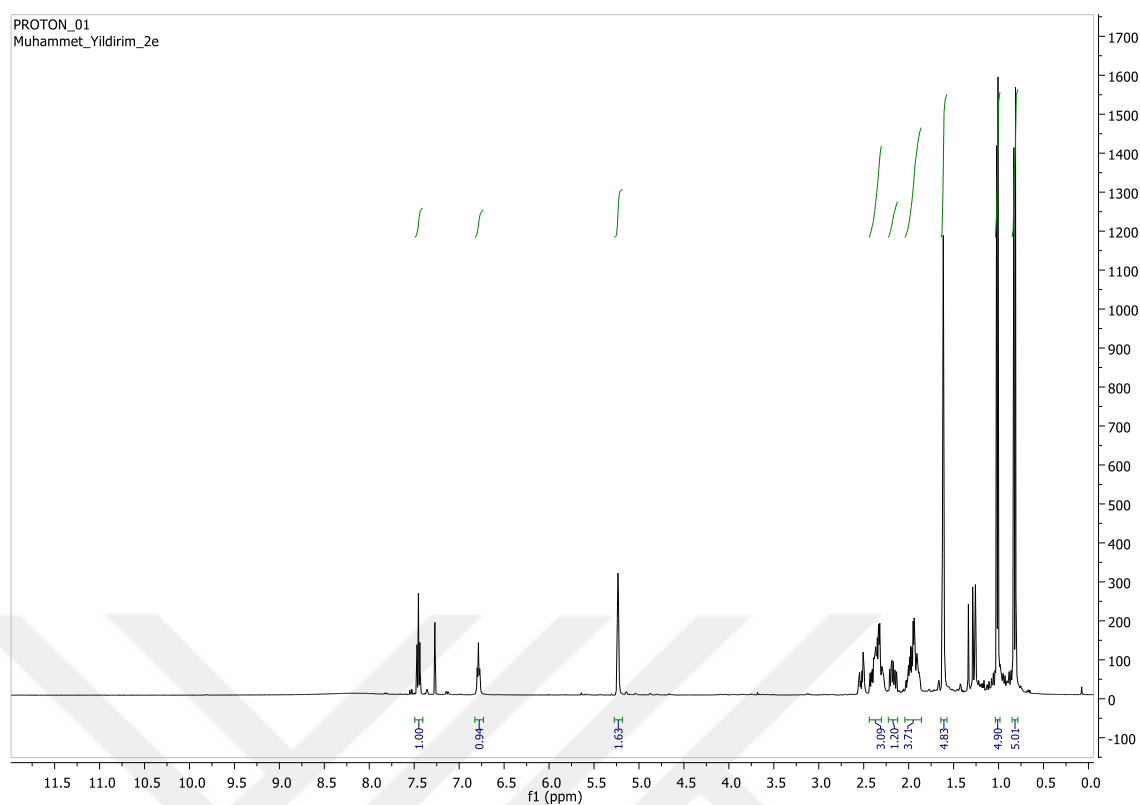


Figure 6-13- ^1H -NMR spectrum of 2.2e

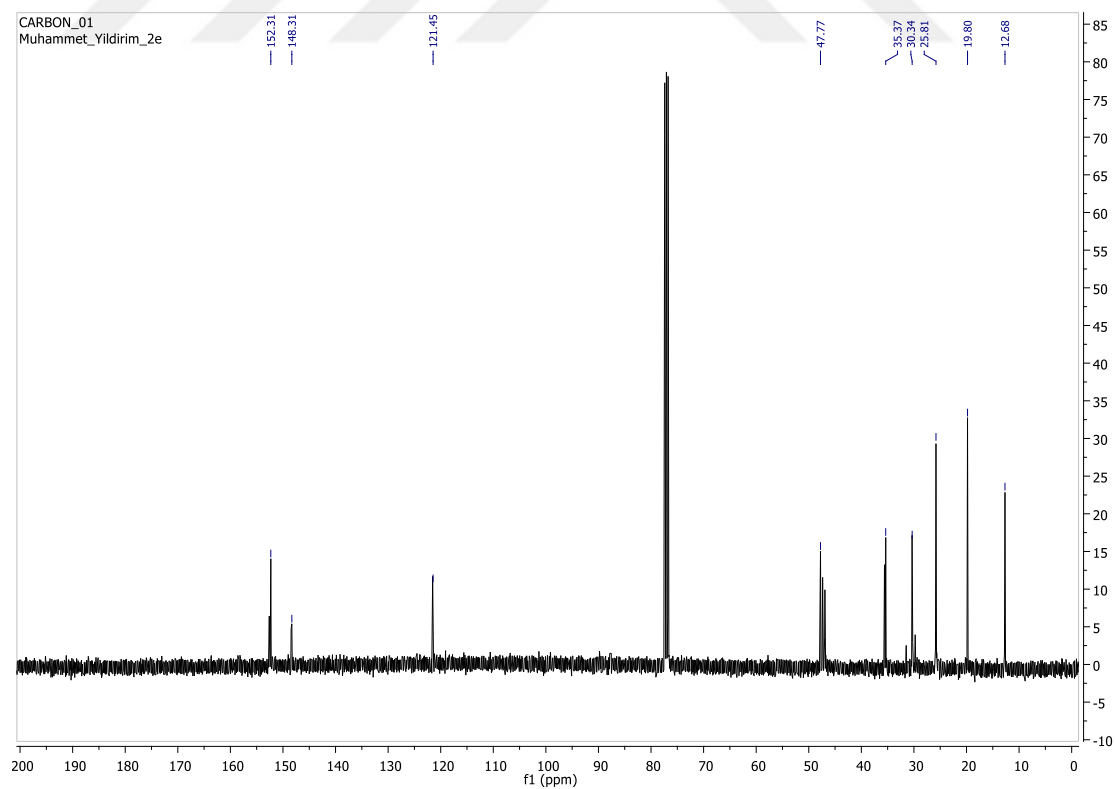


Figure 6-14- ^{13}C -NMR spectrum of 2.2e

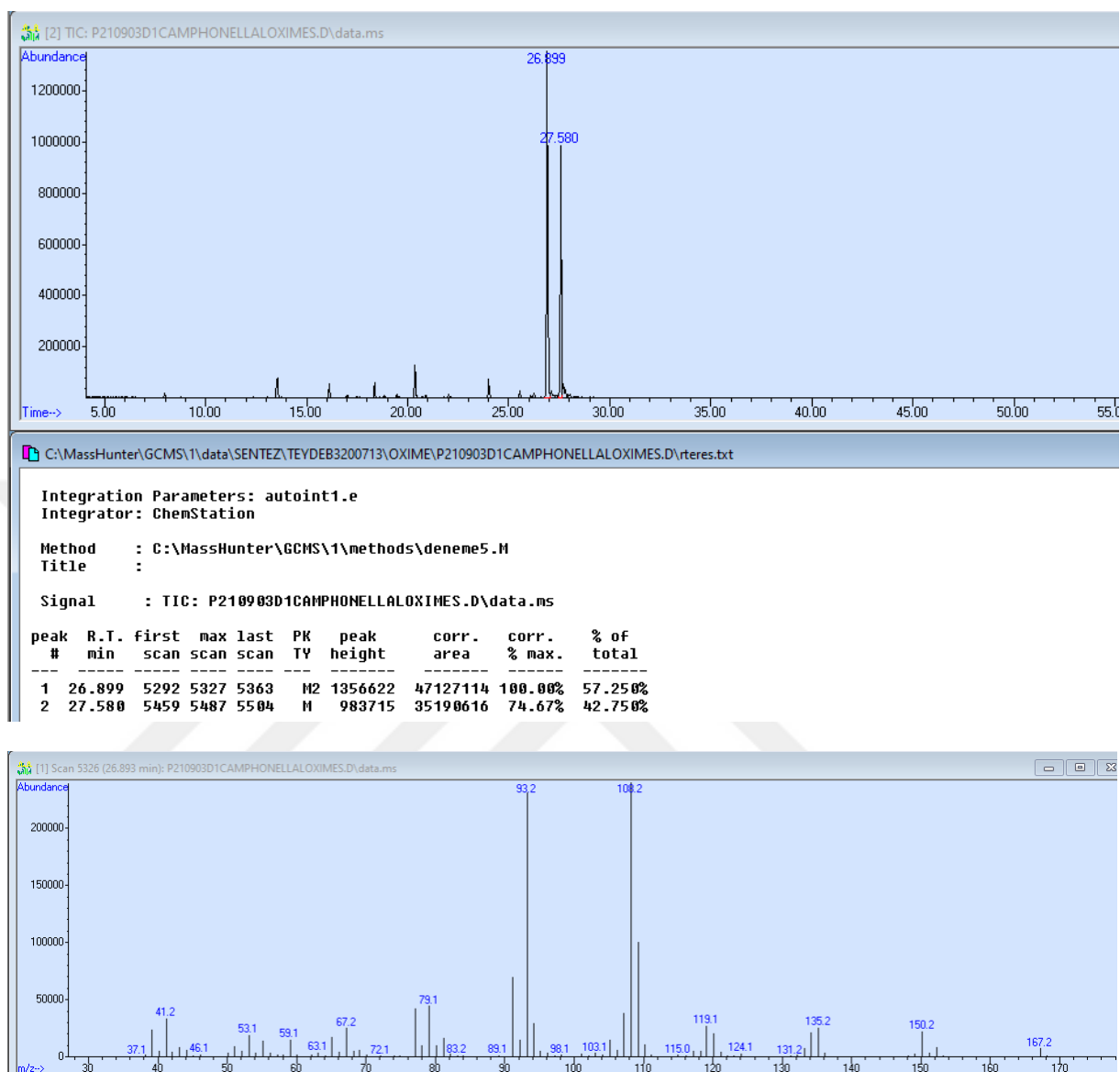


Figure 6-15- GC-MS spectrum of 2.2e

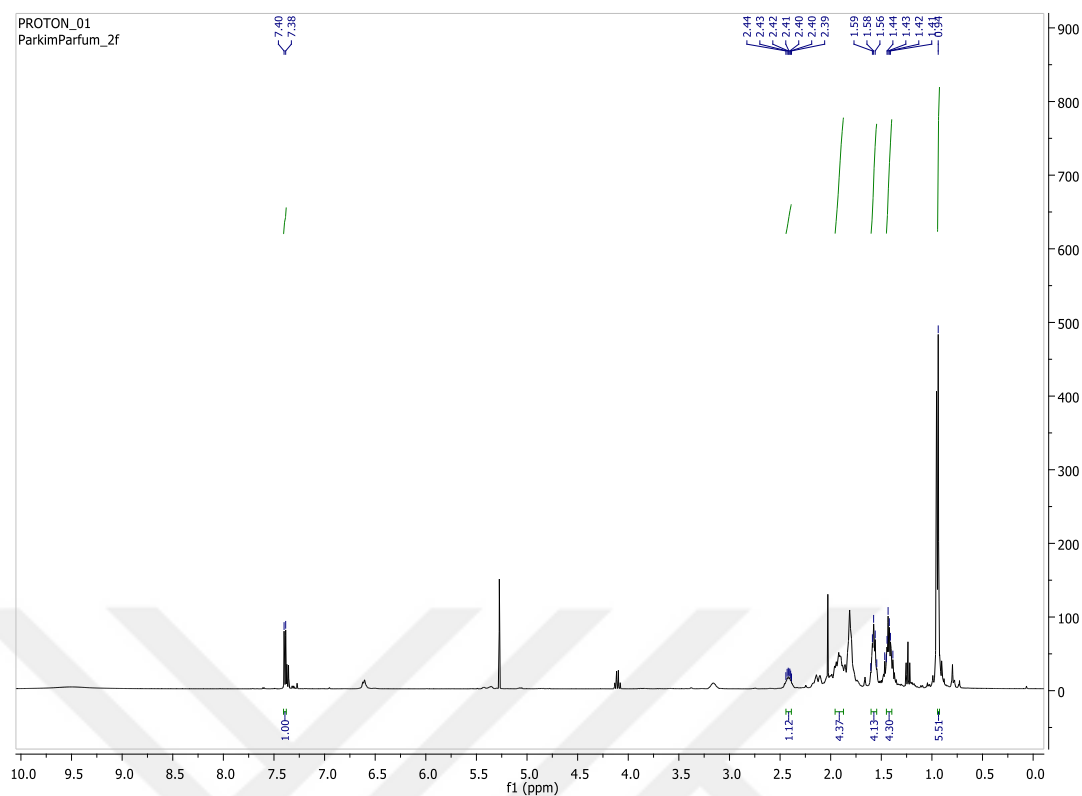


Figure 6-16- ^1H -NMR spectrum of 2.2f

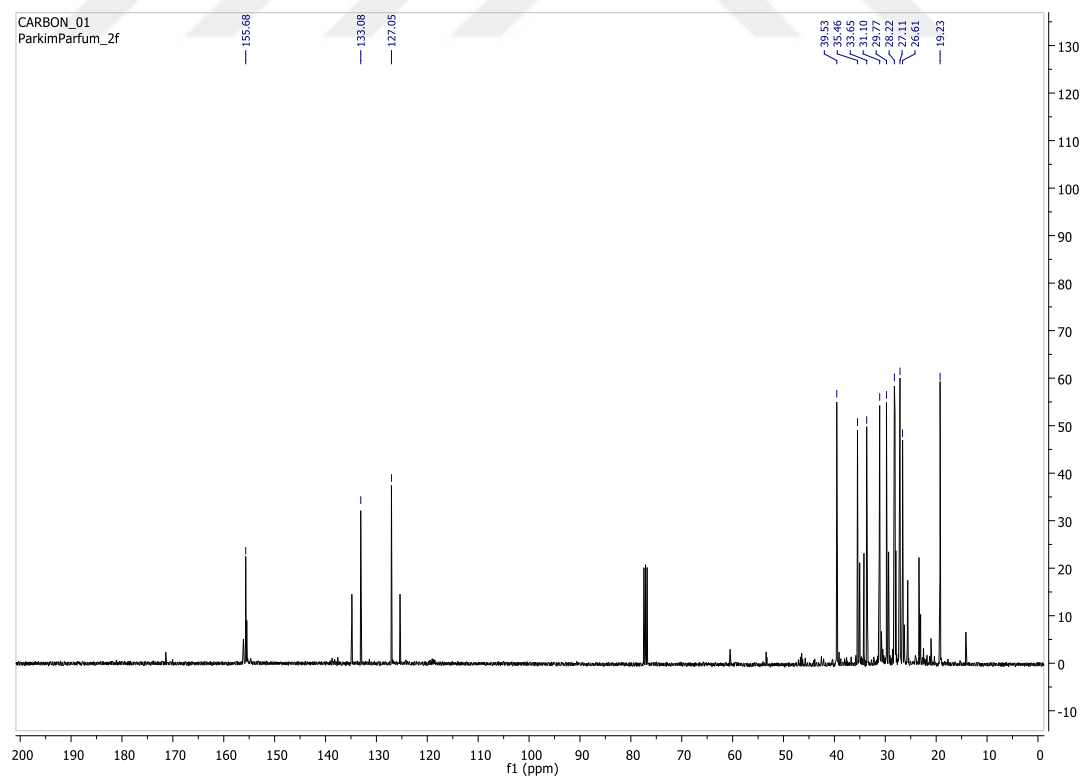


Figure 6-17- ^{13}C -NMR spectrum of 2.2f

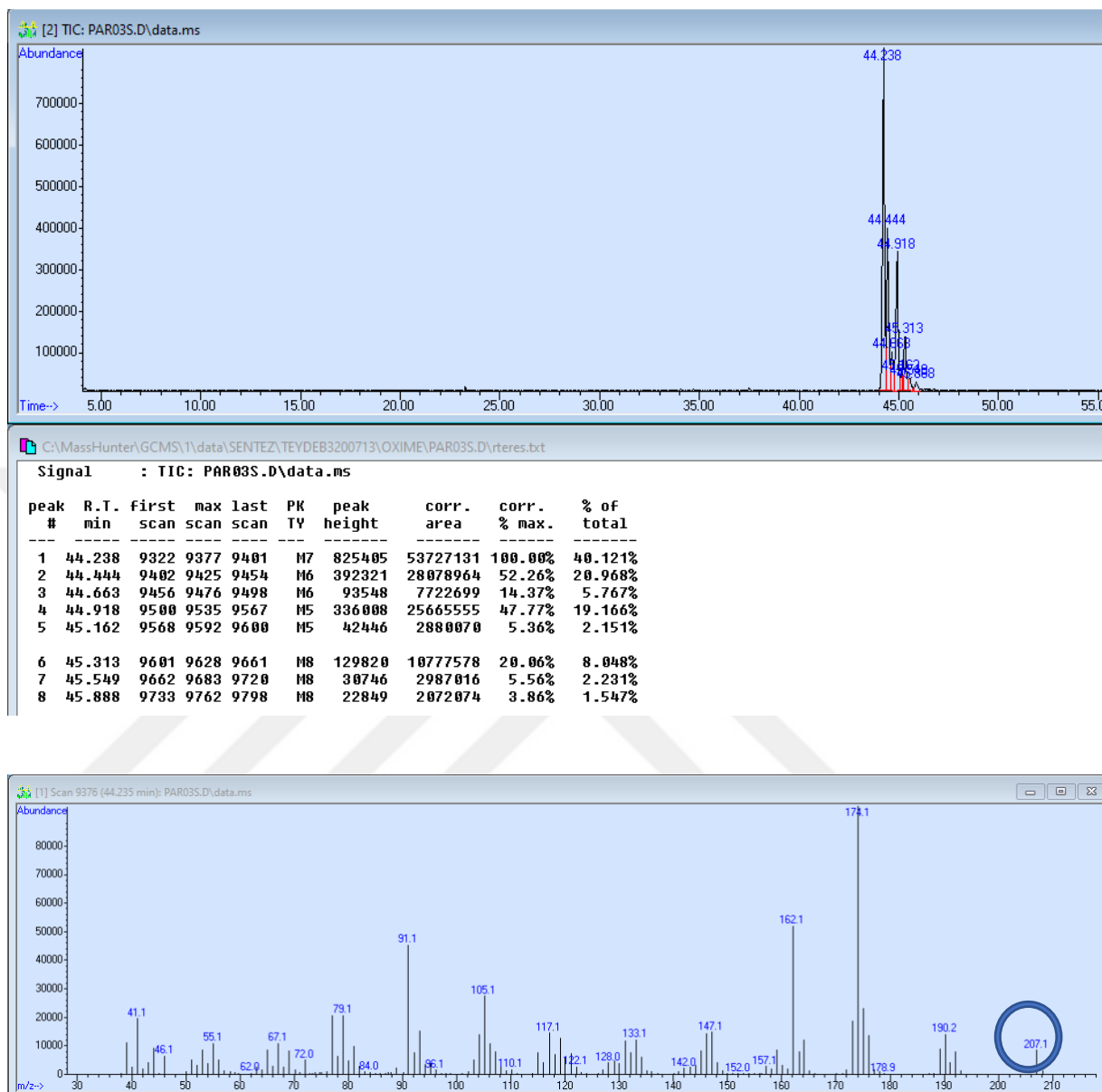


Figure 6-18-GC-MS spectrum of 2.2f

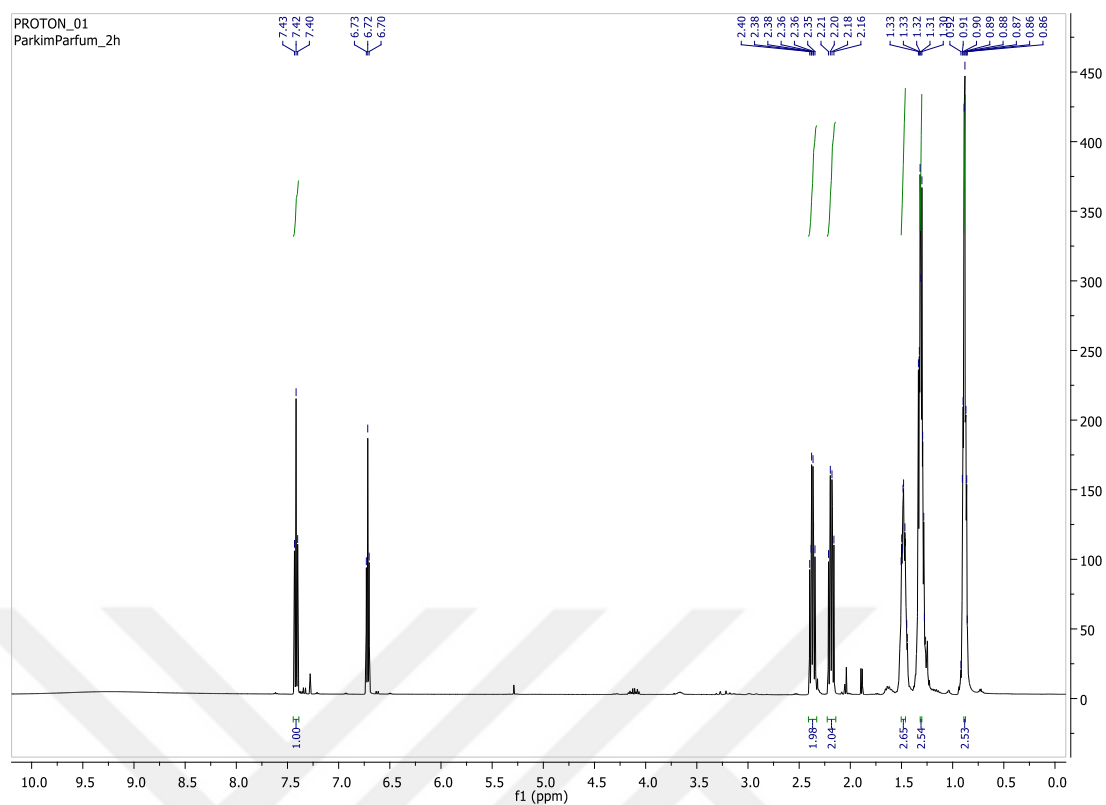


Figure 6-19- ^1H -NMR spectrum of 2.2g

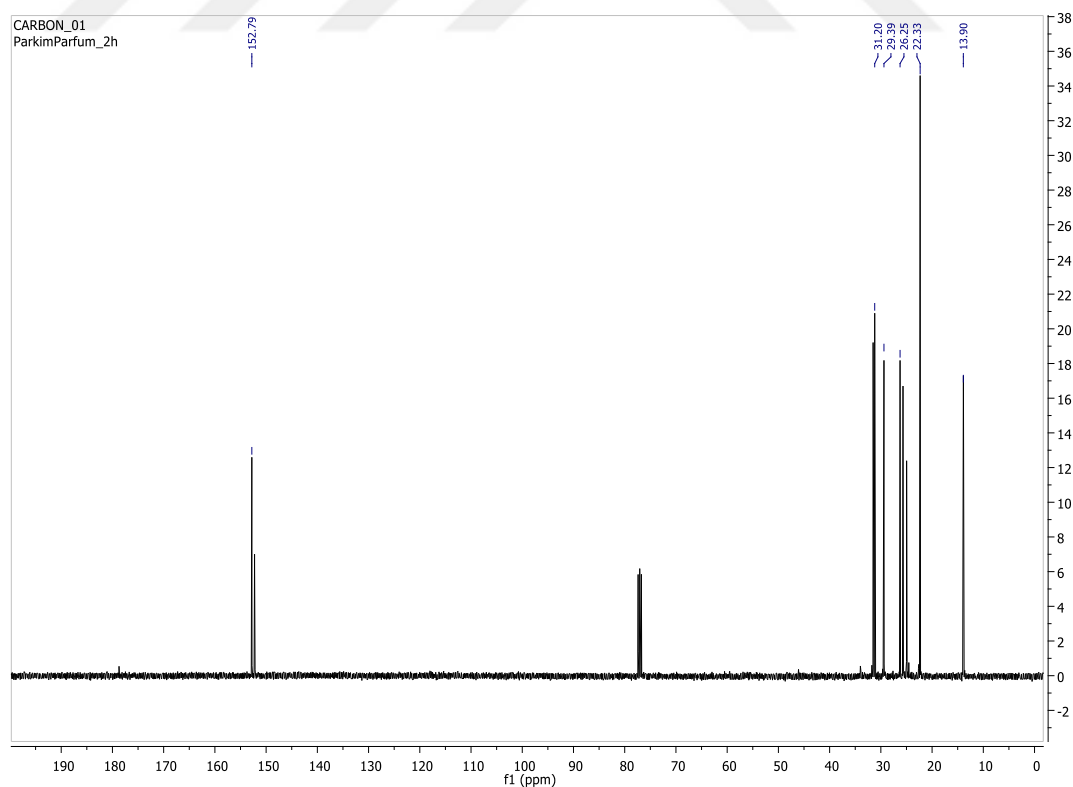


Figure 6-20- ^{13}C -NMR spectrum of 2.2g

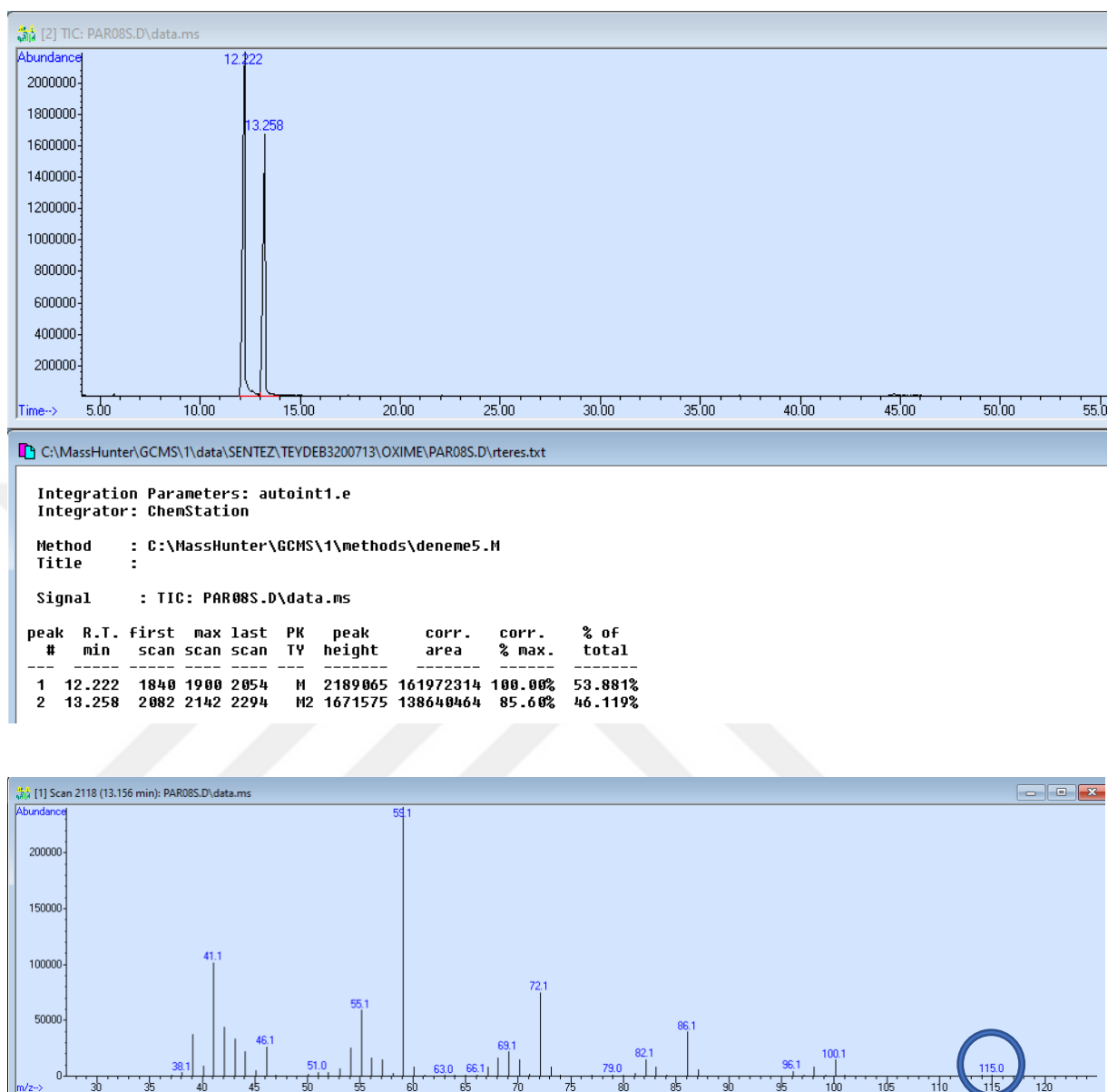


Figure 6-21-GC-MS spectrum of 2.2g

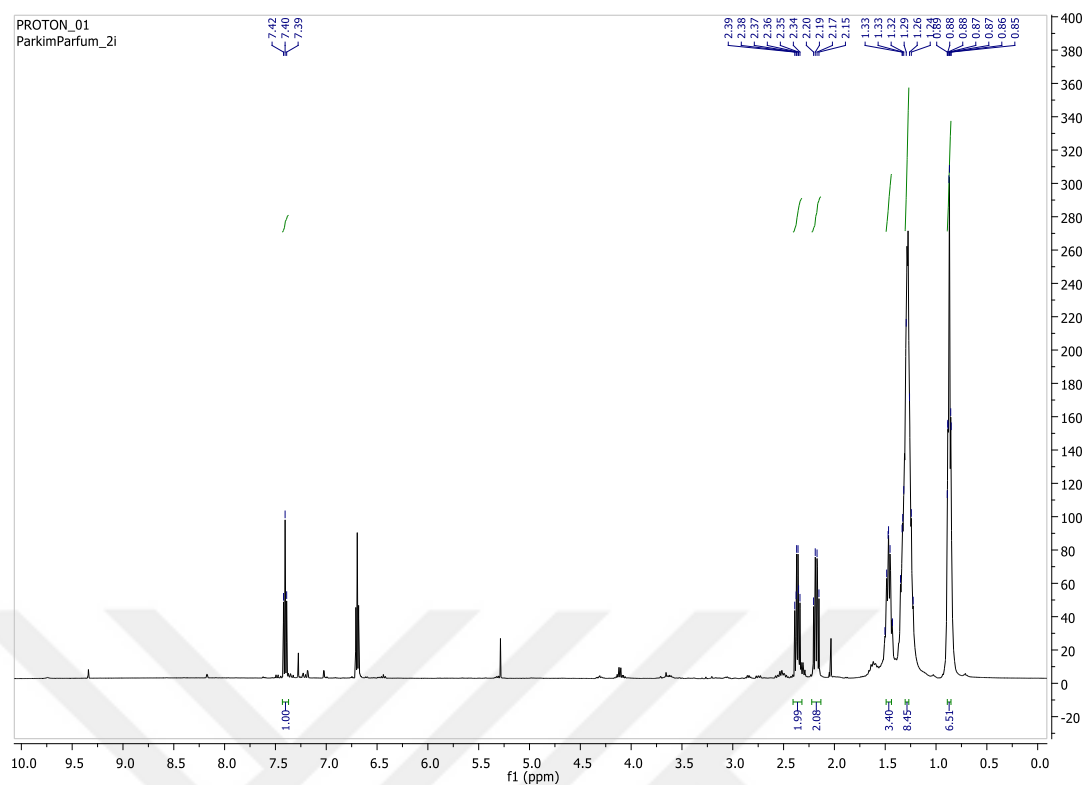


Figure 6-22- ^1H -NMR spectrum of 2.2h

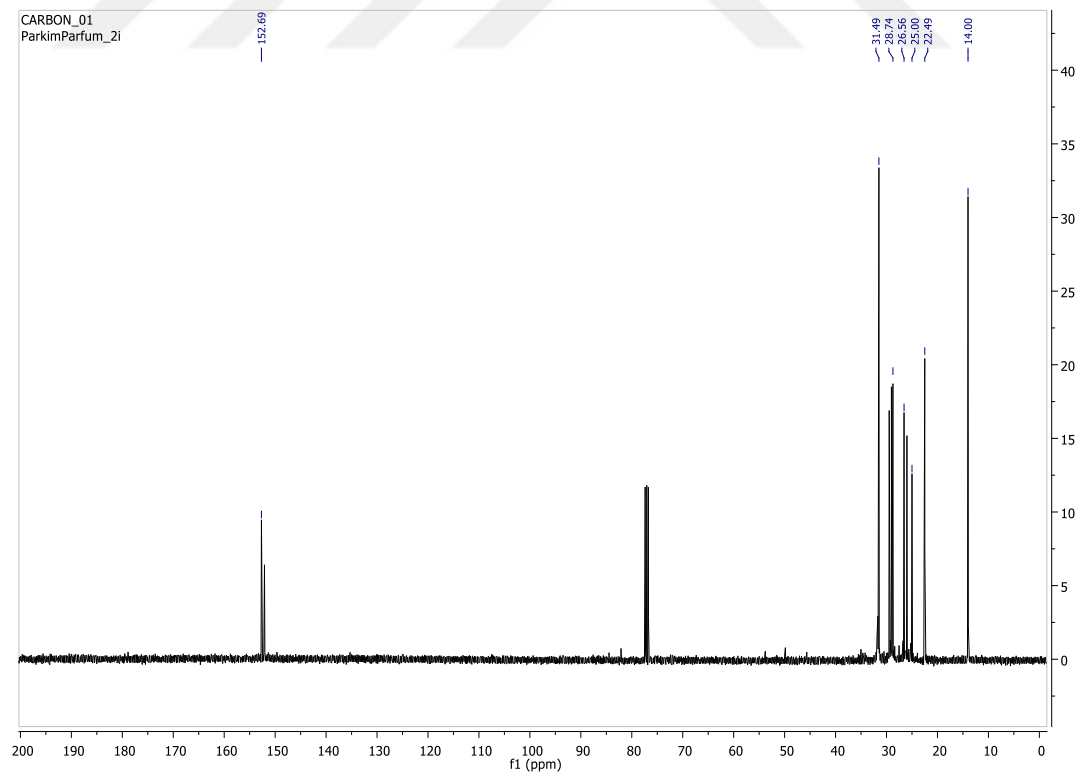


Figure 6-23- ^{13}C -NMR spectrum of 2.2h



Figure 6-24-GC-MS spectrum of 2.2h

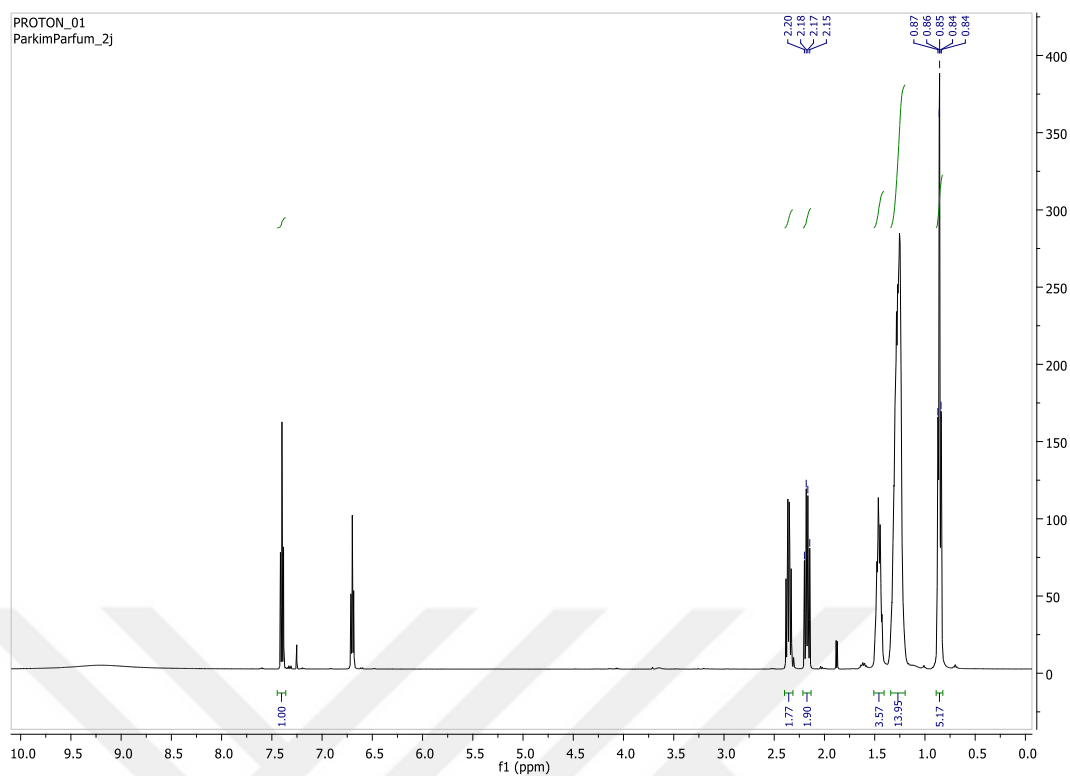


Figure 6-25- ^1H -NMR spectrum of 2.2i

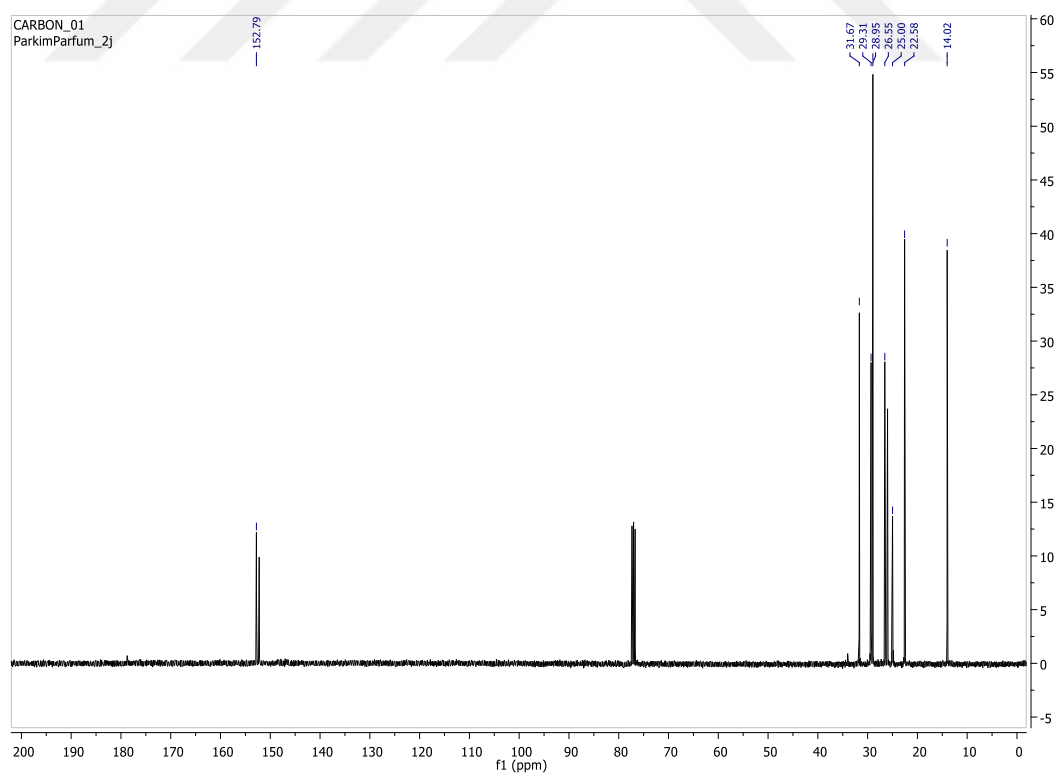


Figure 6-26- ^{13}C -NMR spectrum of 2.2i

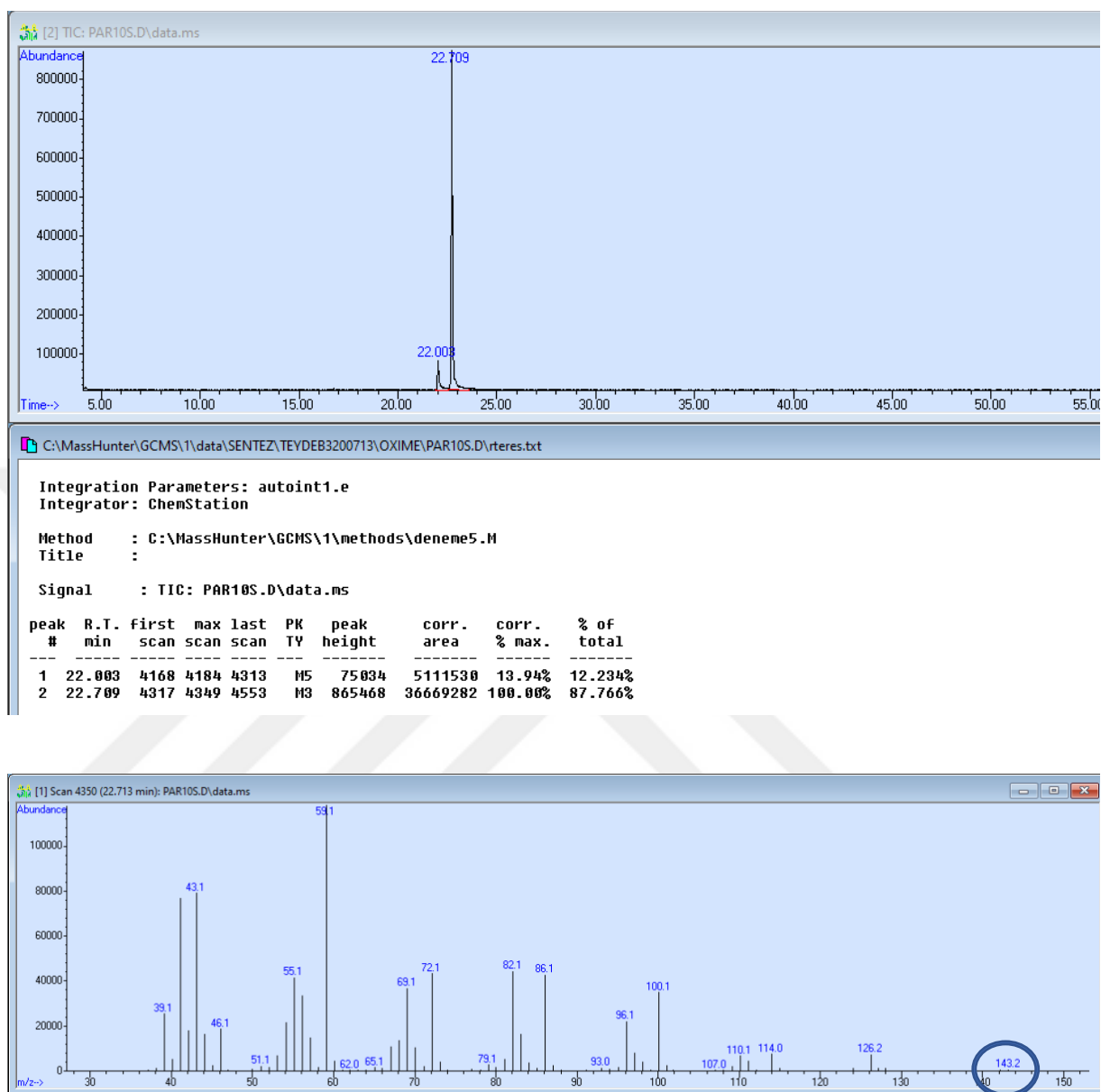


Figure 6-27-GC-MS spectrum of 2.2i

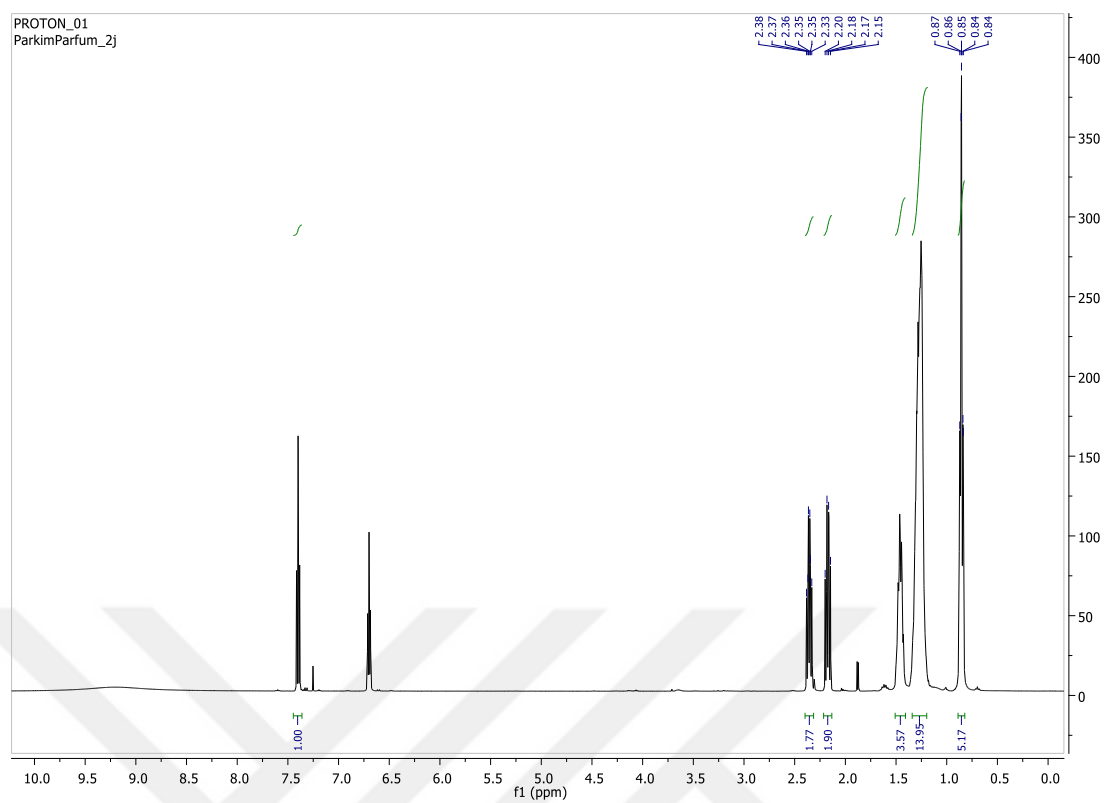


Figure 6-28- ^1H -NMR spectrum of 2.2j

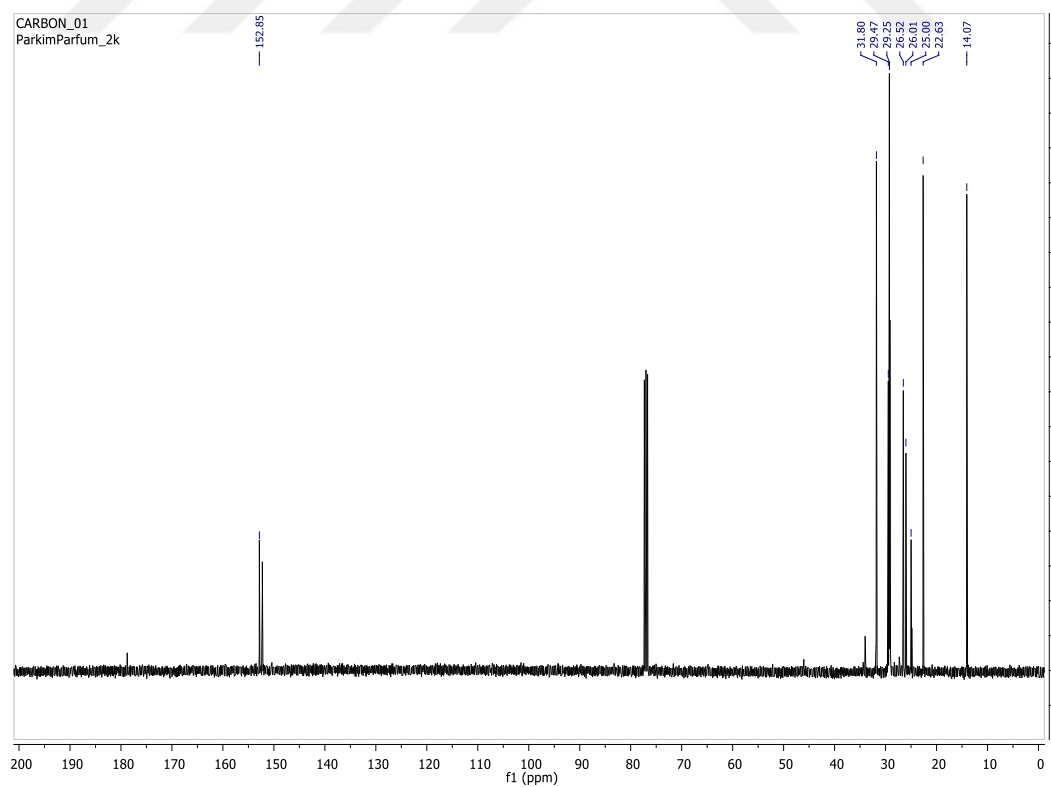


Figure 6-29- ^{13}C -NMR spectrum of 2.2j

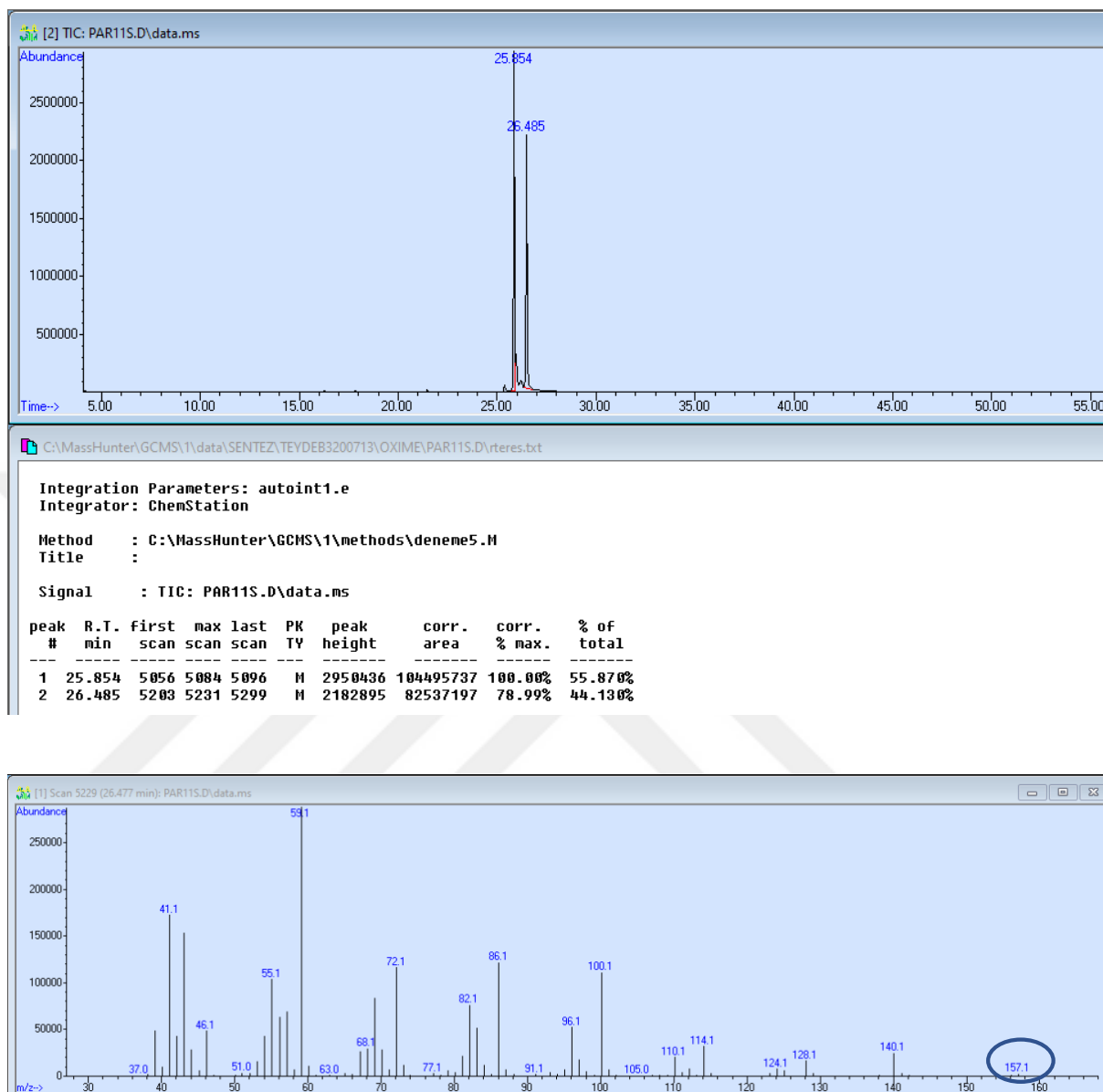


Figure 6-30-GC-MS spectrum of 2.2j

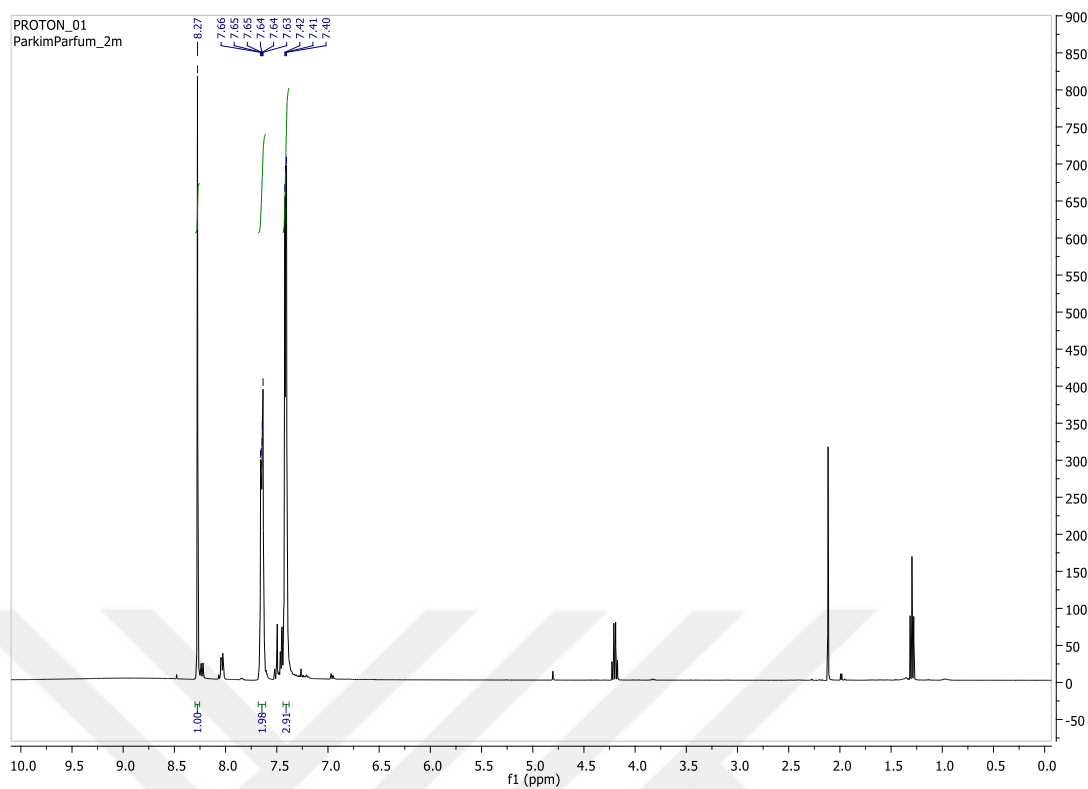


Figure 6-31- ^1H -NMR spectrum of 2.2k

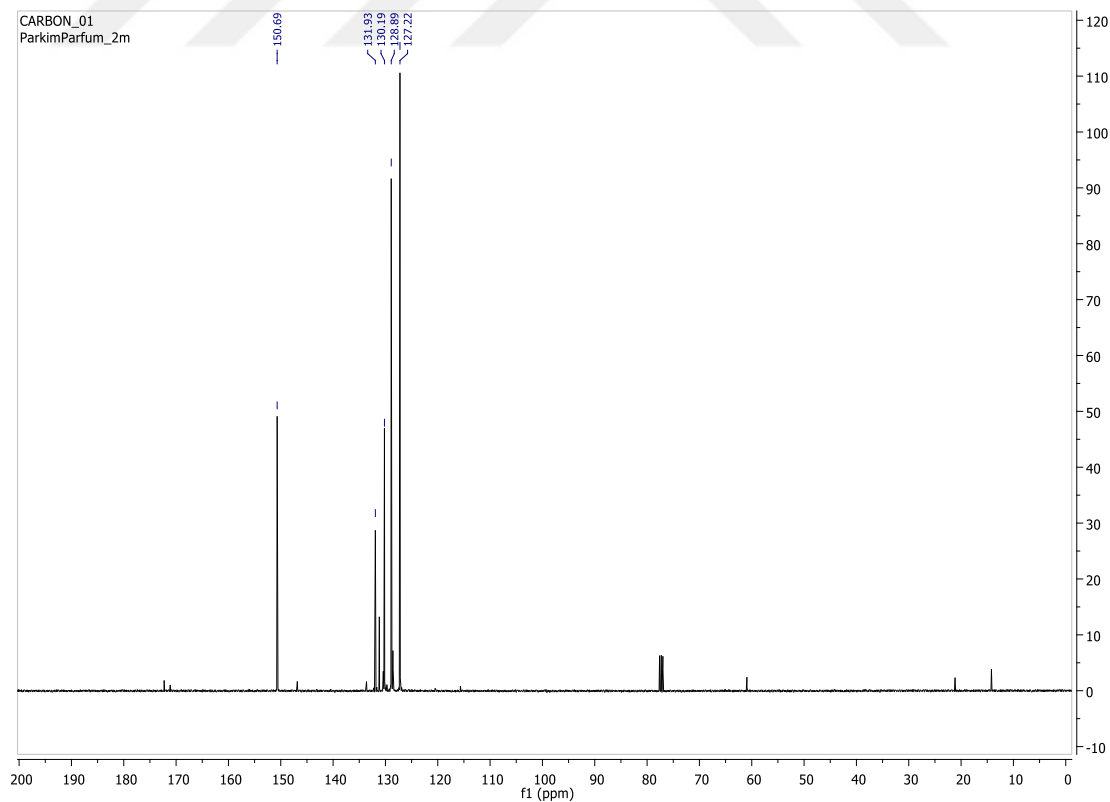


Figure 6-32- ^{13}C -NMR spectrum of 2.2k

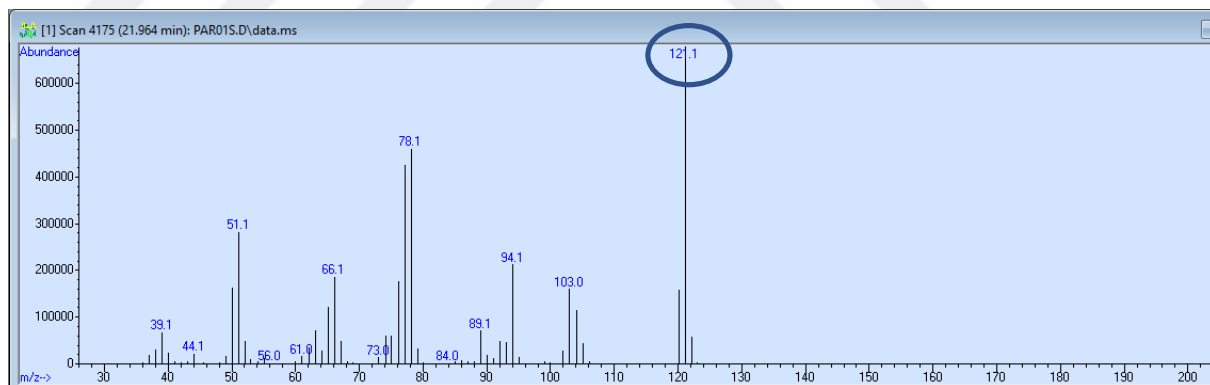
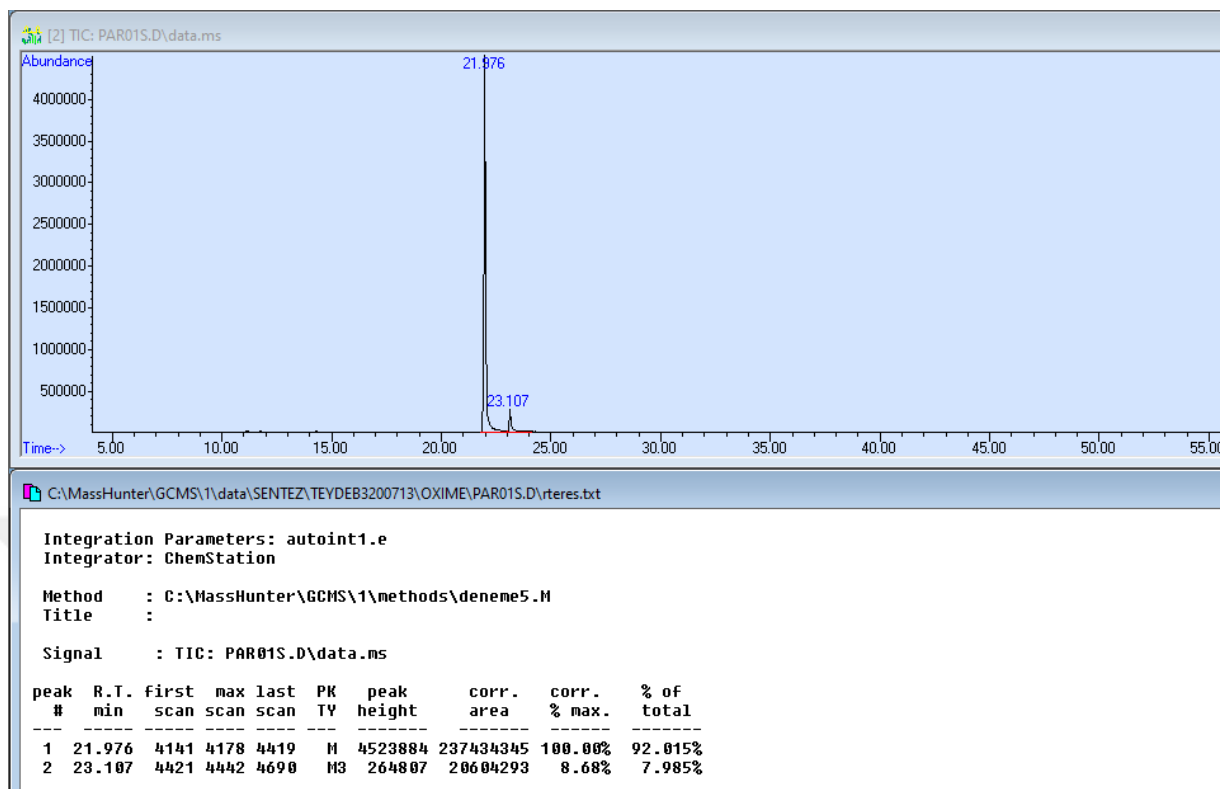


Figure 6-33-GC-MS spectrum of 2.2k

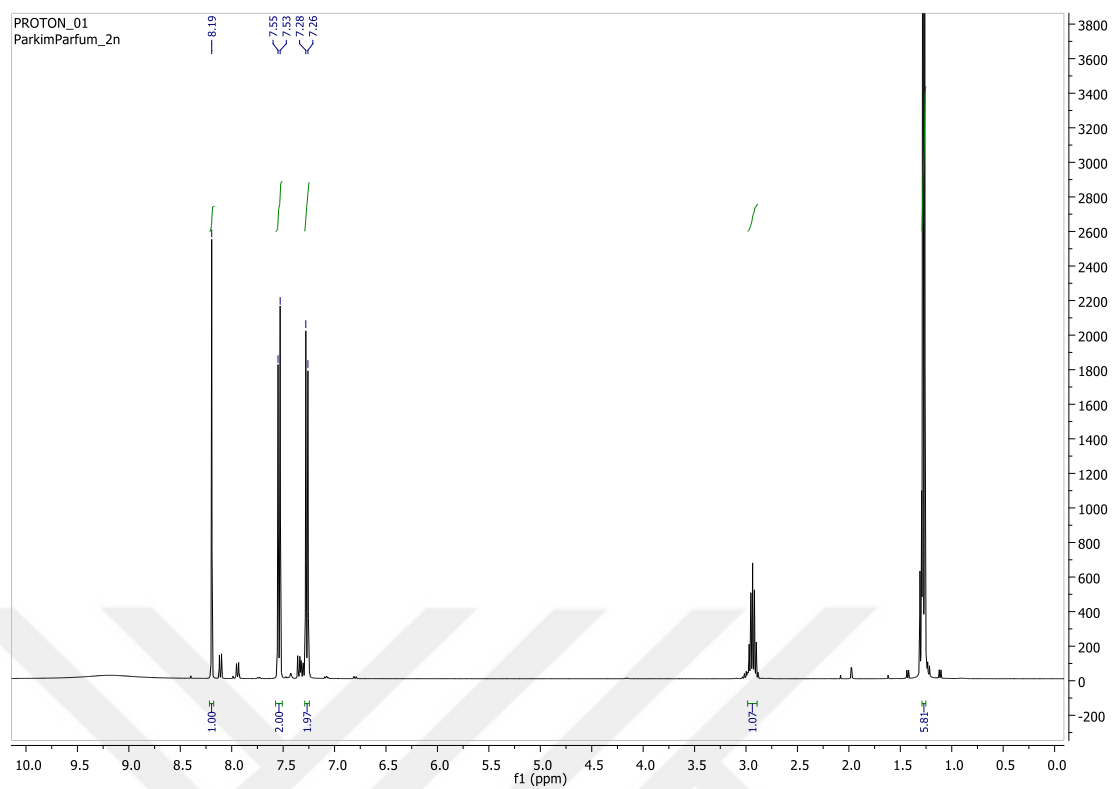


Figure 6-34- ^1H -NMR spectrum of 2.21

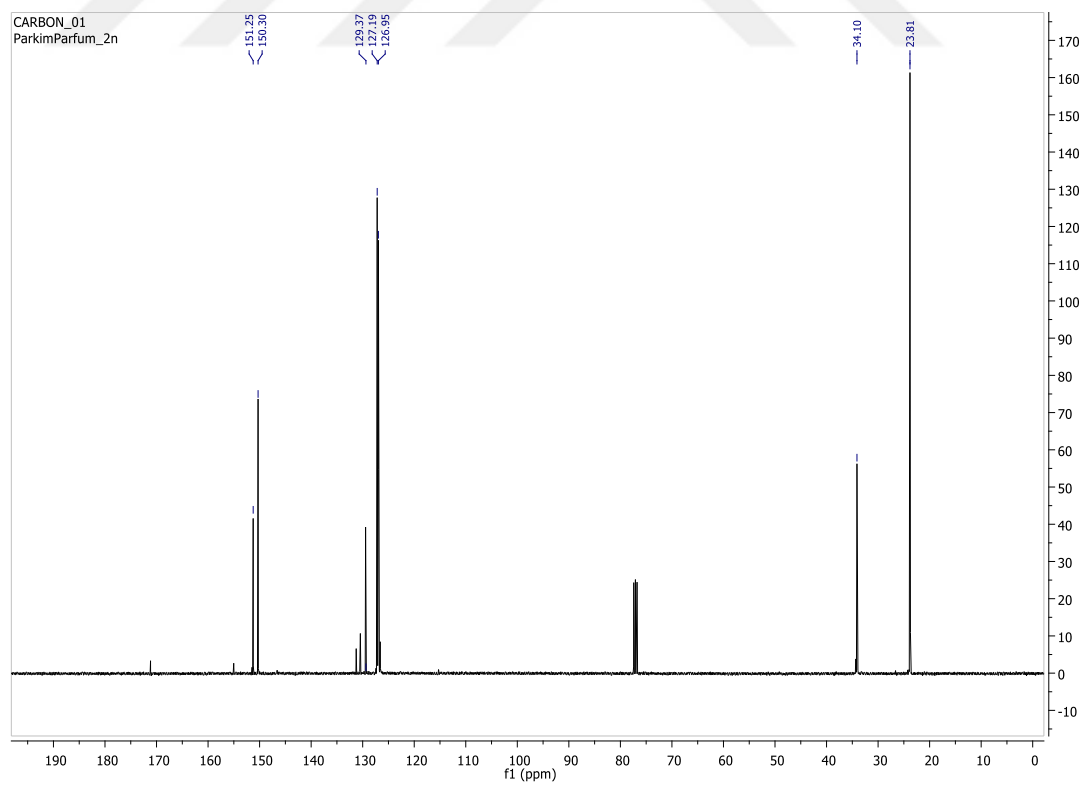


Figure 6-35- ^{13}C -NMR spectrum of 2.21



Figure 6-36-GC-MS spectrum of 2.21

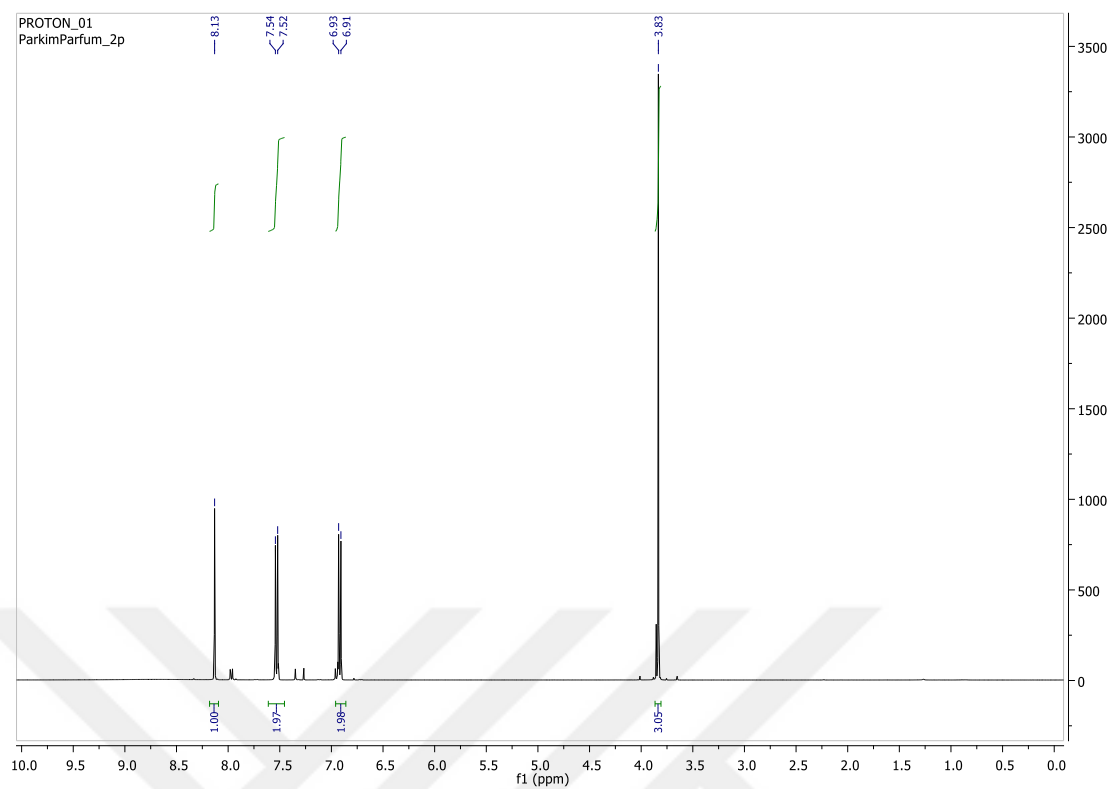


Figure 6-37- ^1H -NMR spectrum of 2.2m

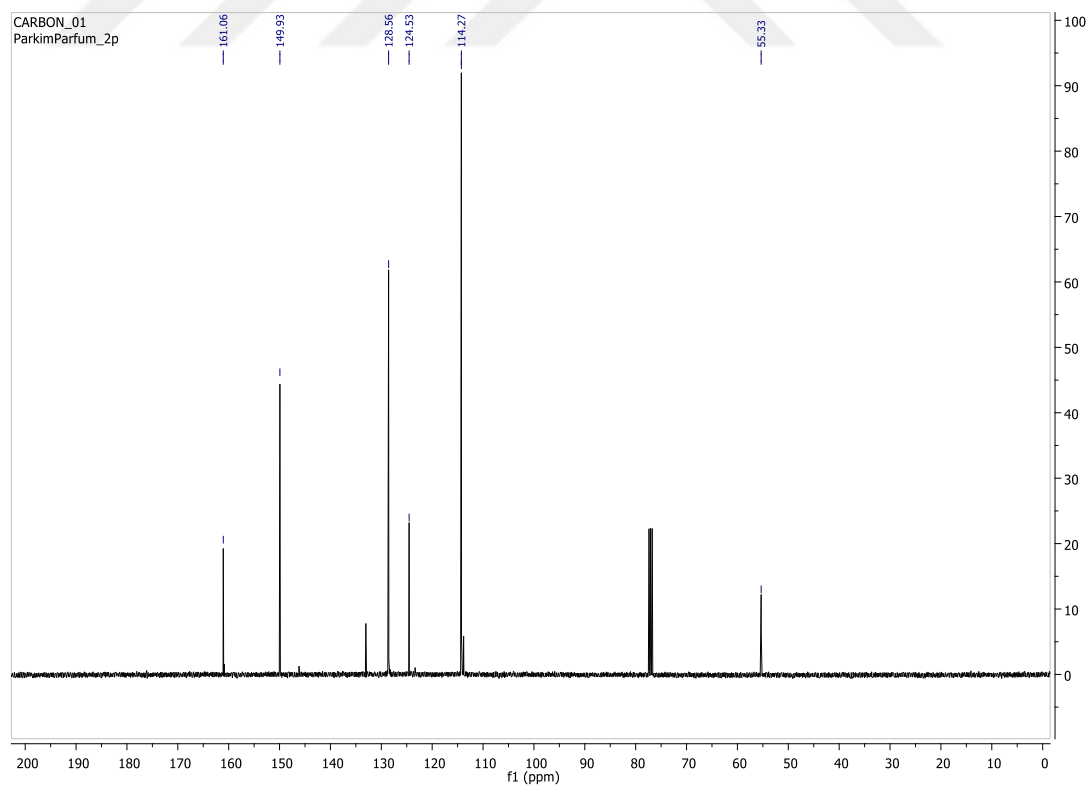


Figure 6-38- ^{13}C -NMR spectrum of 2.2m

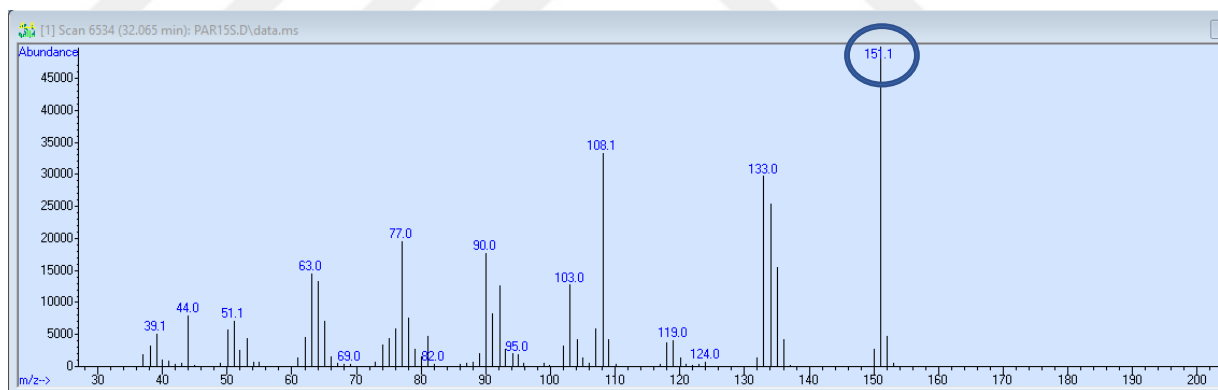
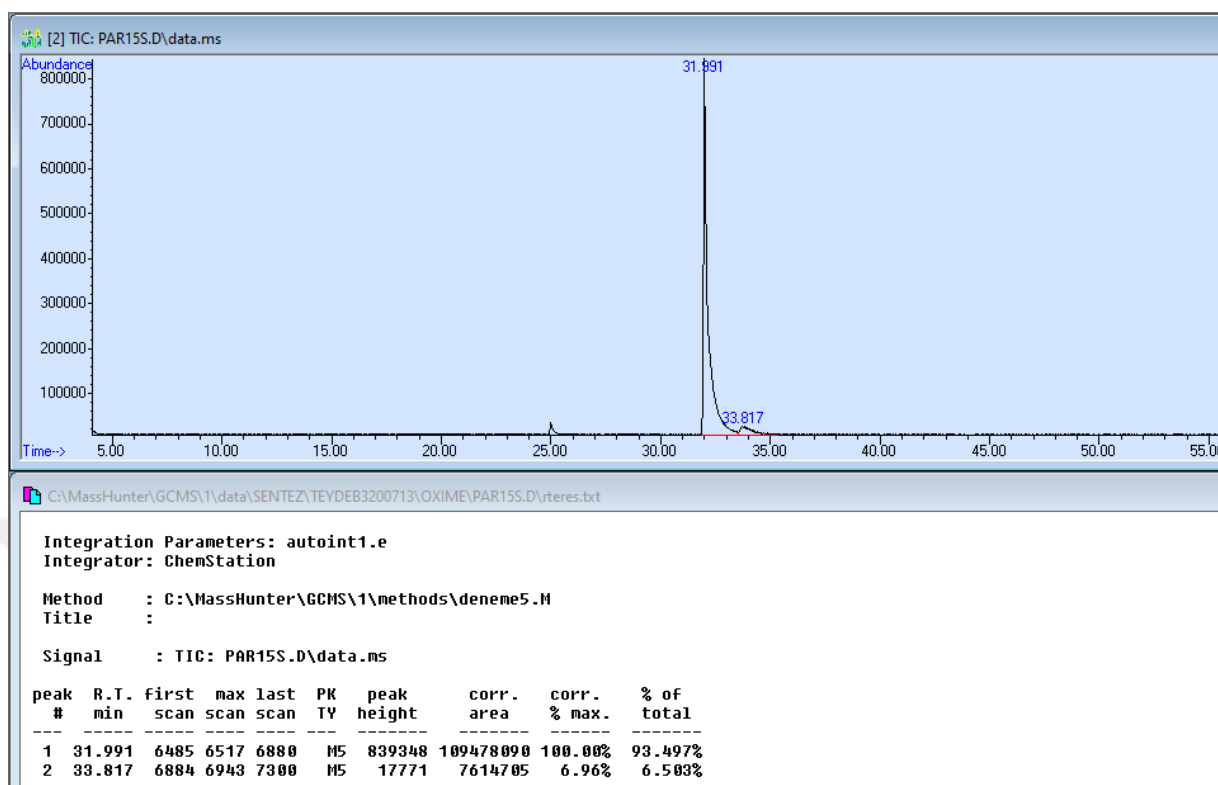


Figure 6-39-GC-MS spectrum of 2.2m

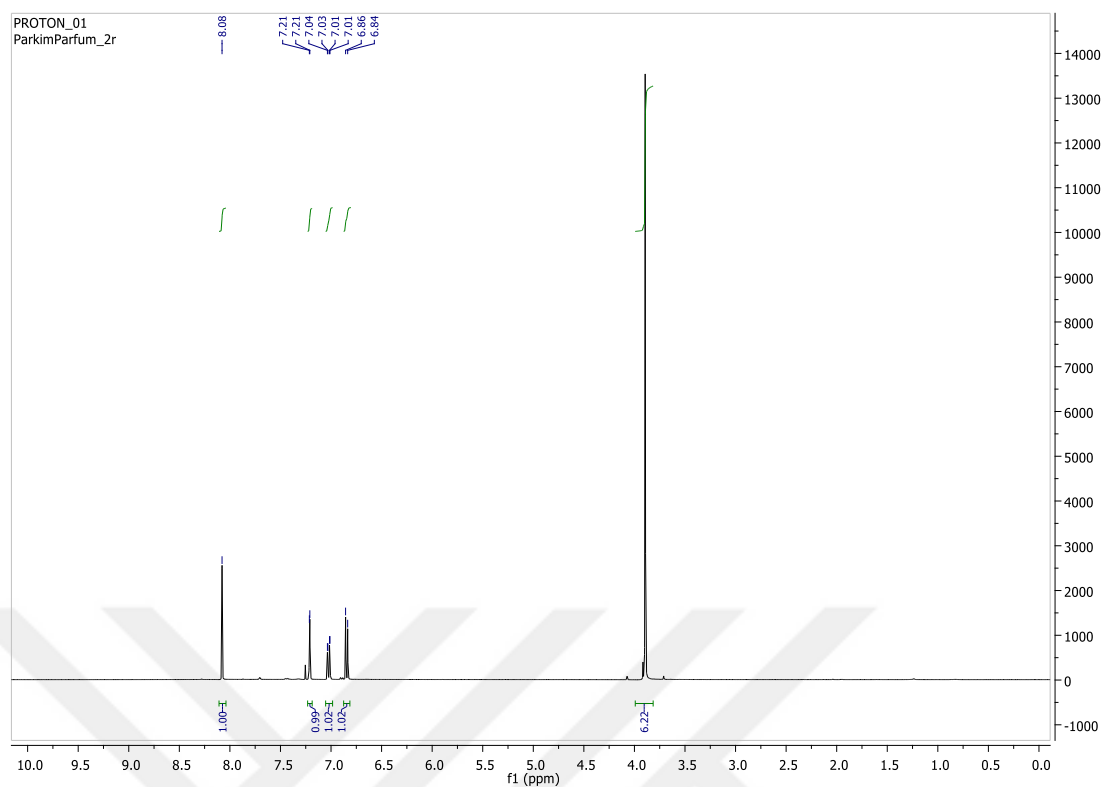


Figure 6-40- ^1H -NMR spectrum of 2.2n

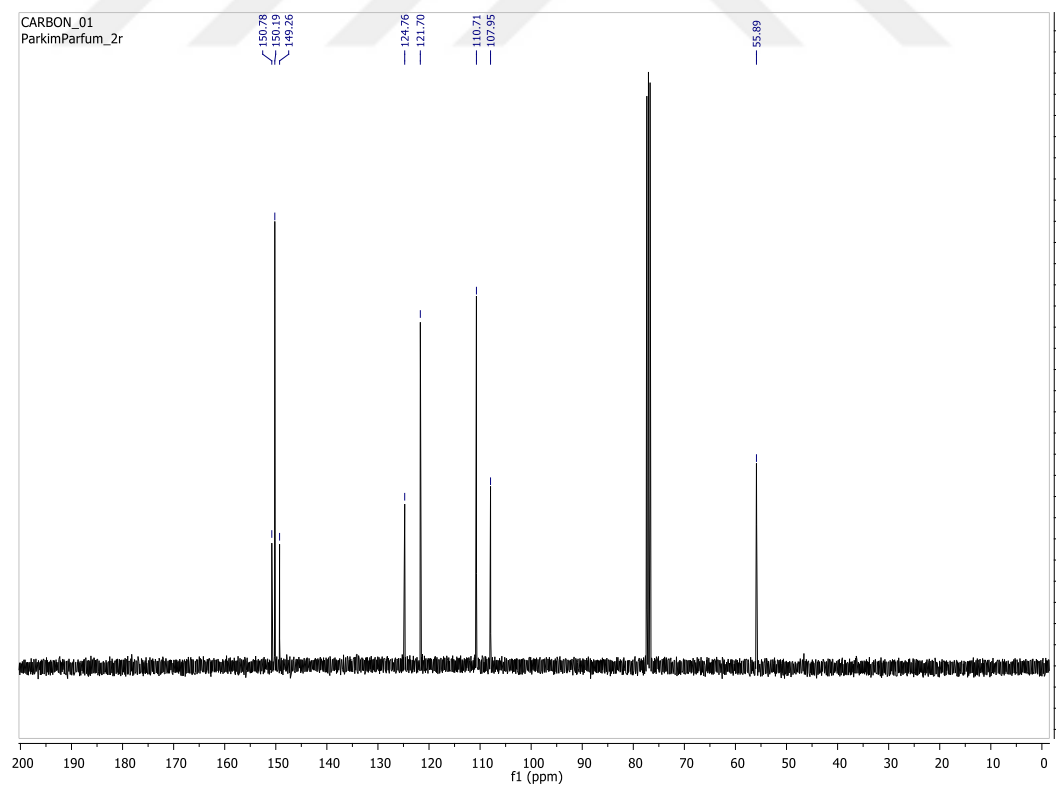


Figure 6-41- ^{13}C -NMR spectrum of 2.2n

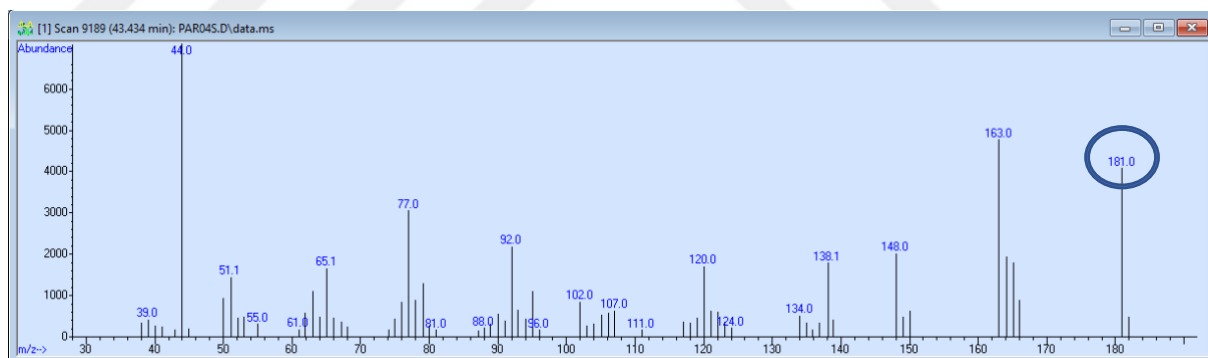
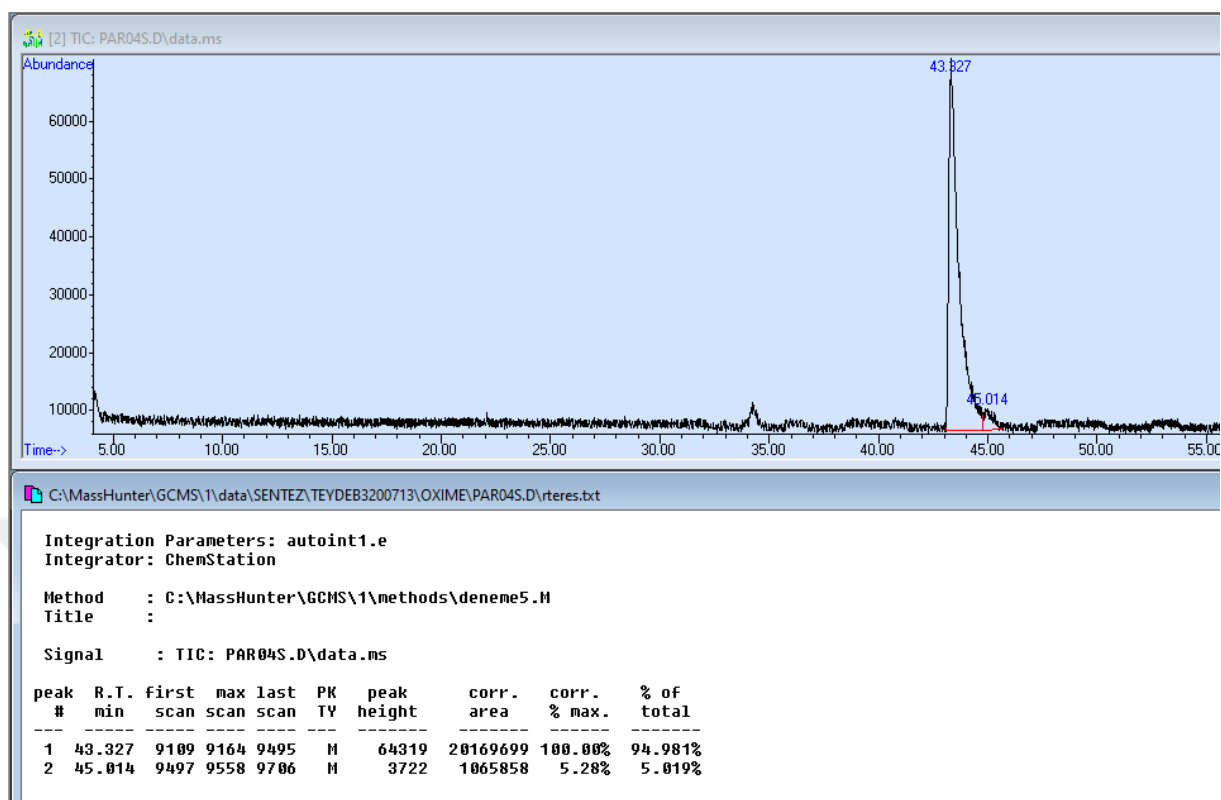


Figure 6-42-GC-MS spectrum of 2.2n

IR, ^1H , ^{13}C NMR, GCMS and TOF-LCMS Spectra of isoxazoline-5-carboxylates (2.4a-n,
2.5a-n)

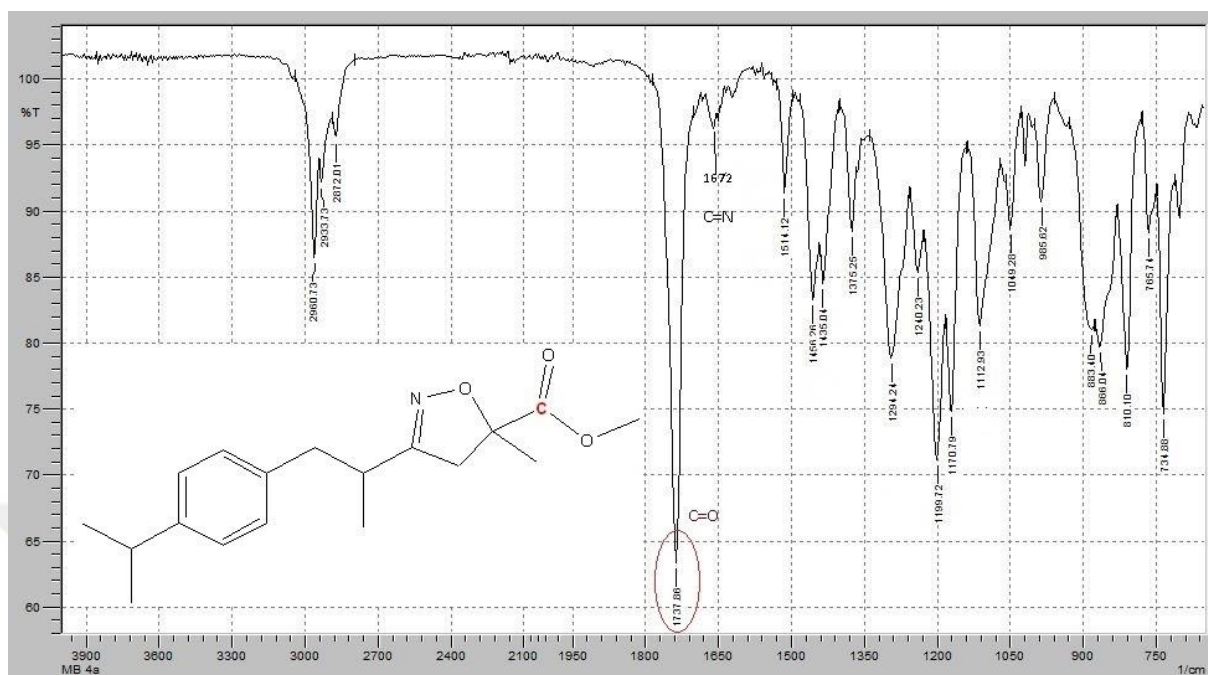


Figure 6-43-IR spectrum of 2.4a

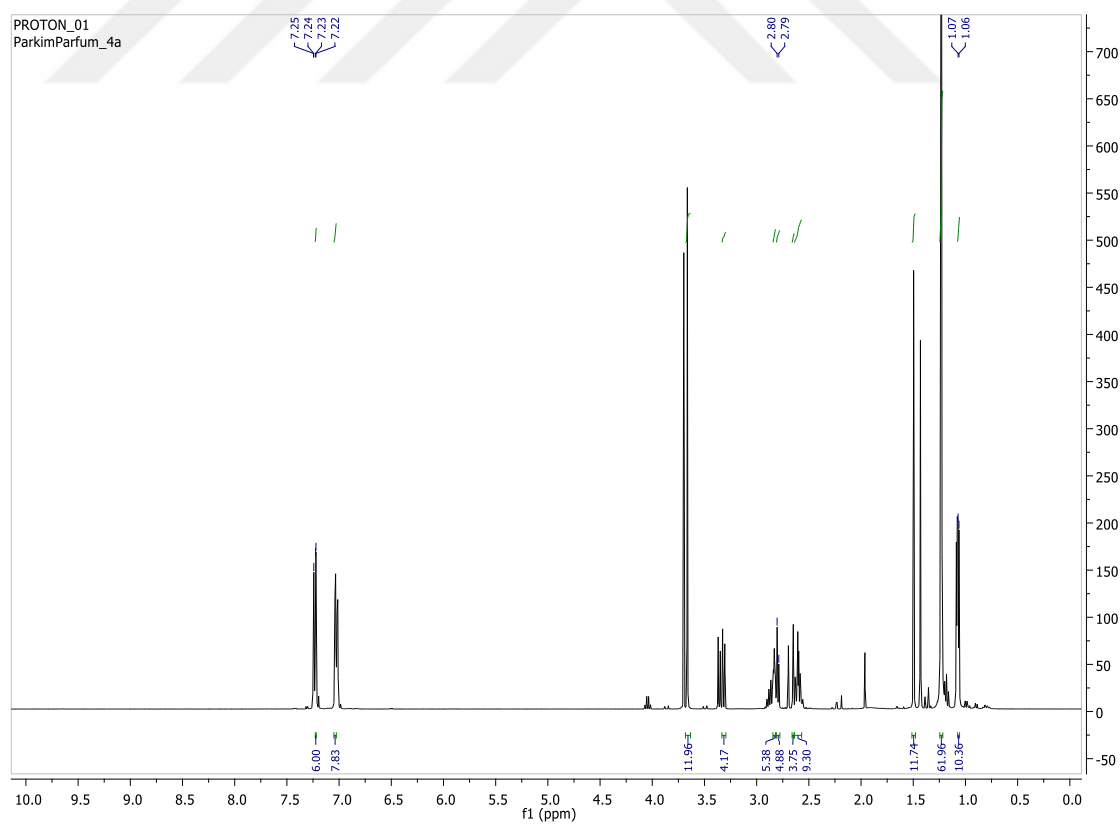


Figure 6-44- ^1H -NMR spectrum of 2.4a

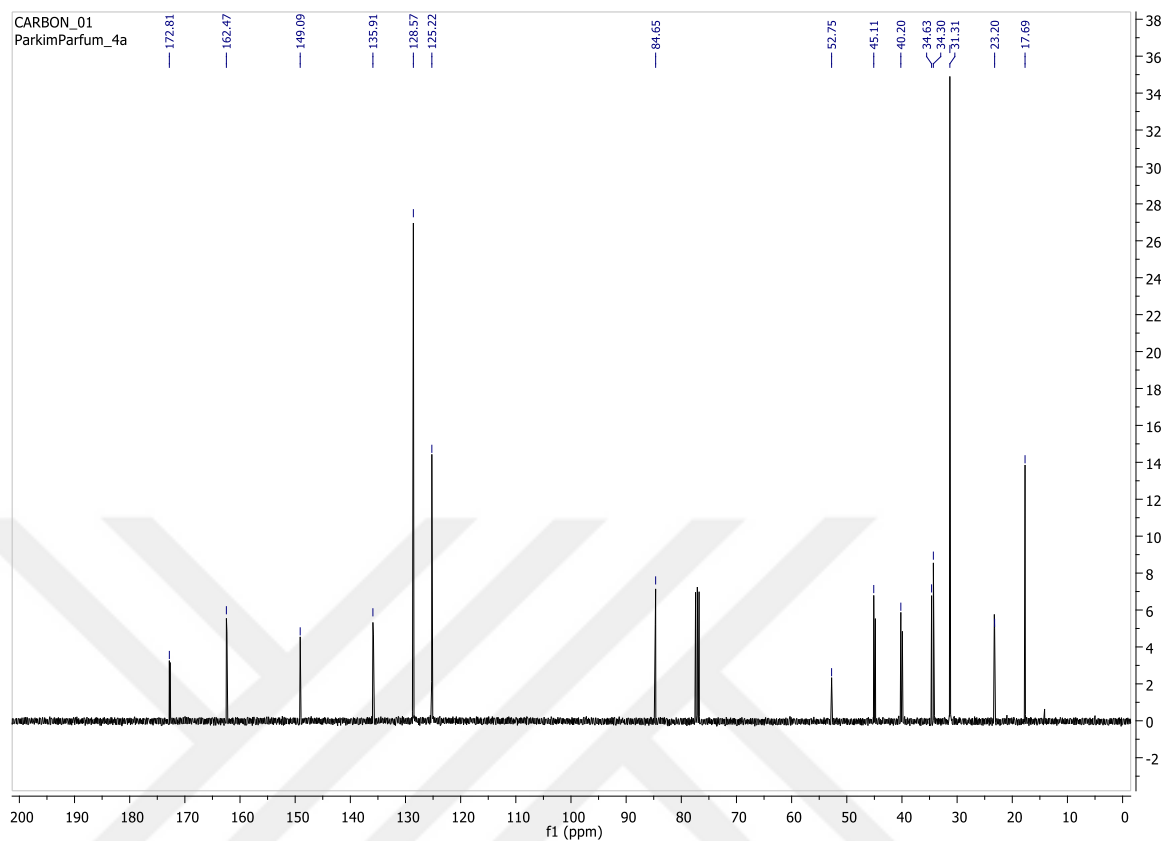
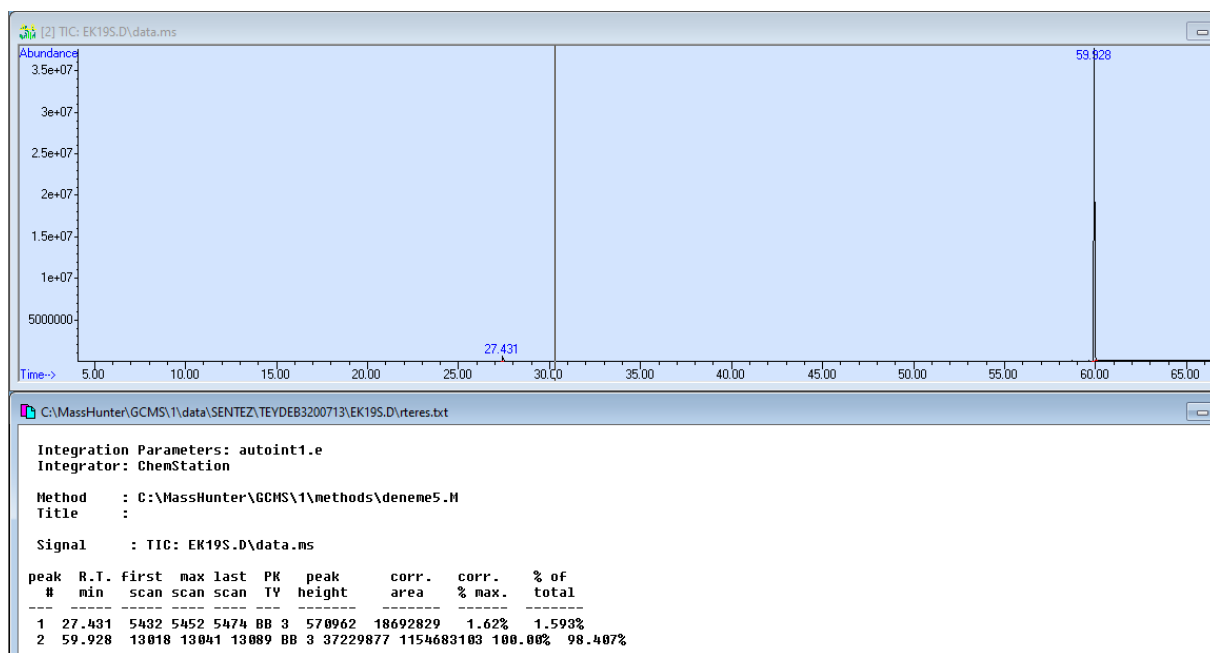


Figure 6-45- ^{13}C -NMR spectrum of 2.4a



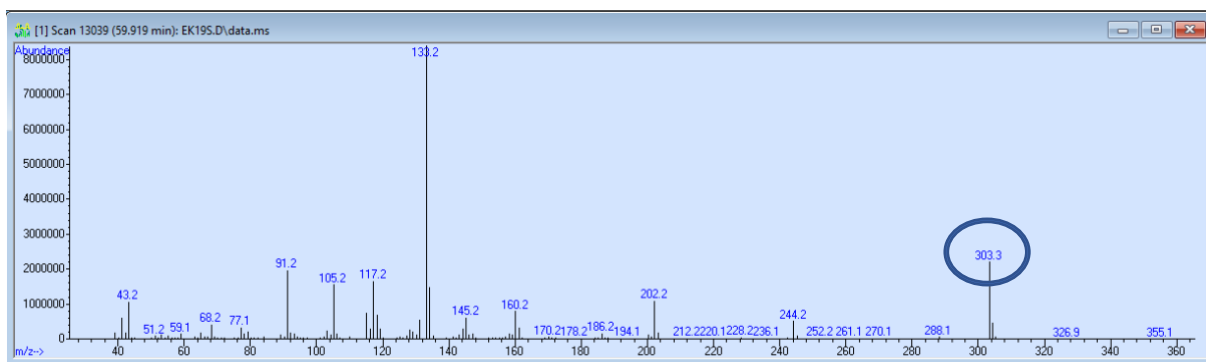


Figure 6-46-GC-MS spectrum of 2.4a

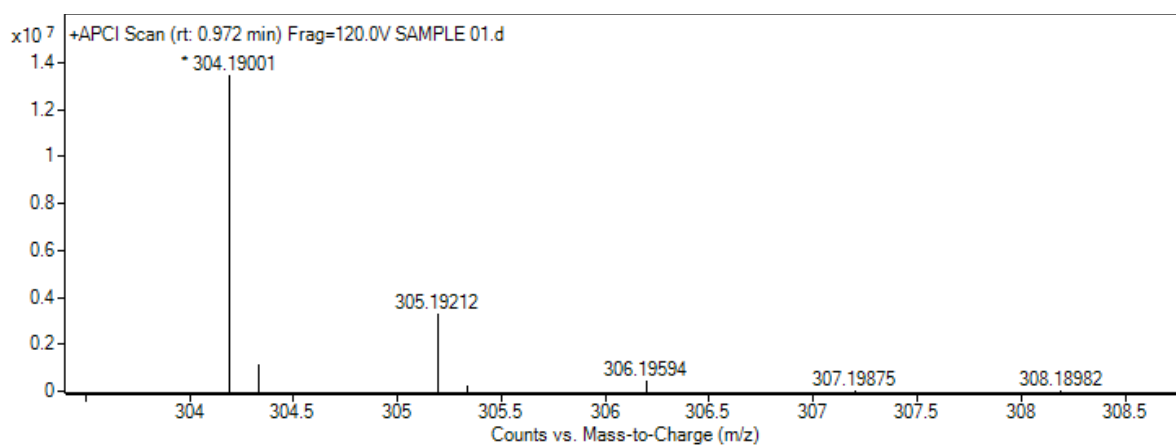


Figure 6-47-(TOF) LC-MS spectrum of 2.4a

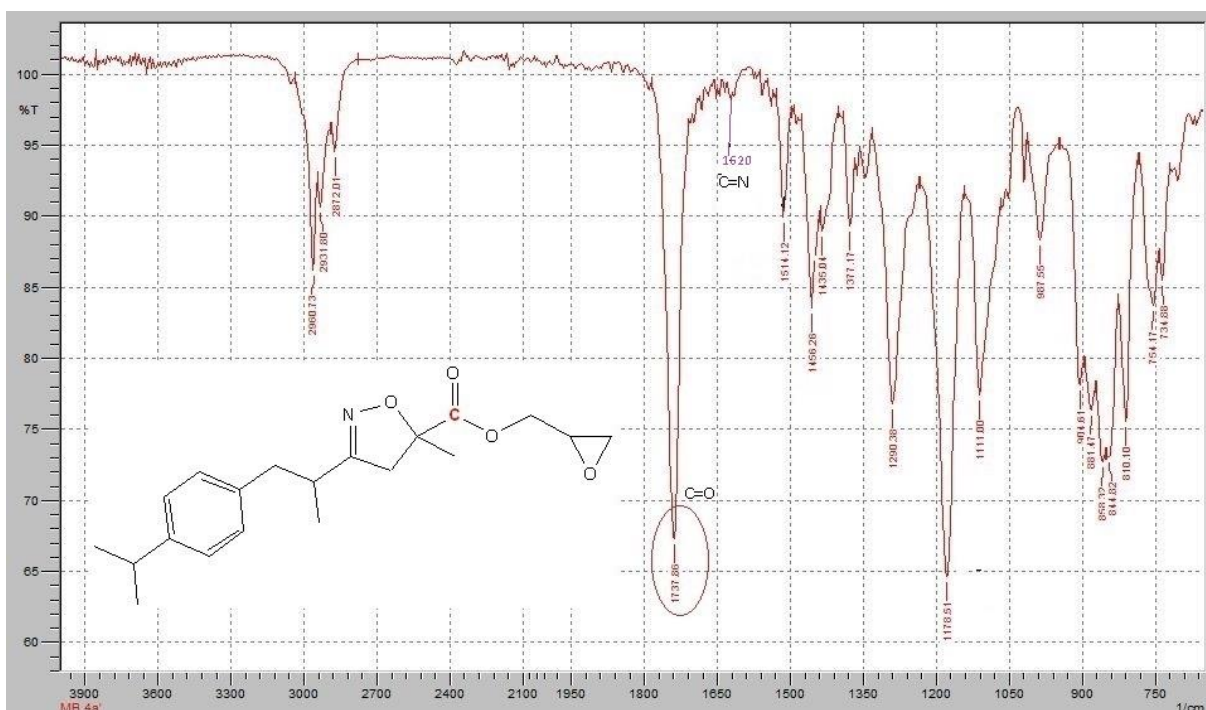


Figure 6-48-IR spectrum of 2.5a

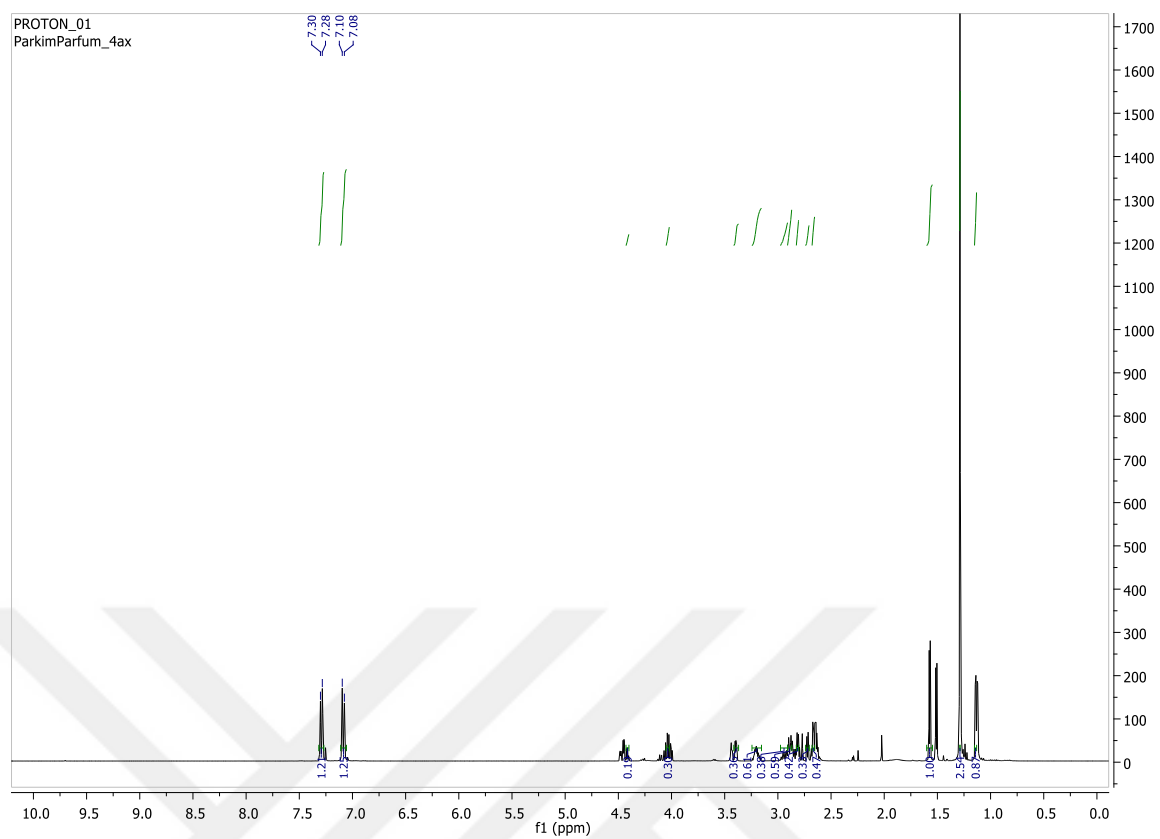


Figure 6-49- ^1H -NMR spectrum of 2.5a

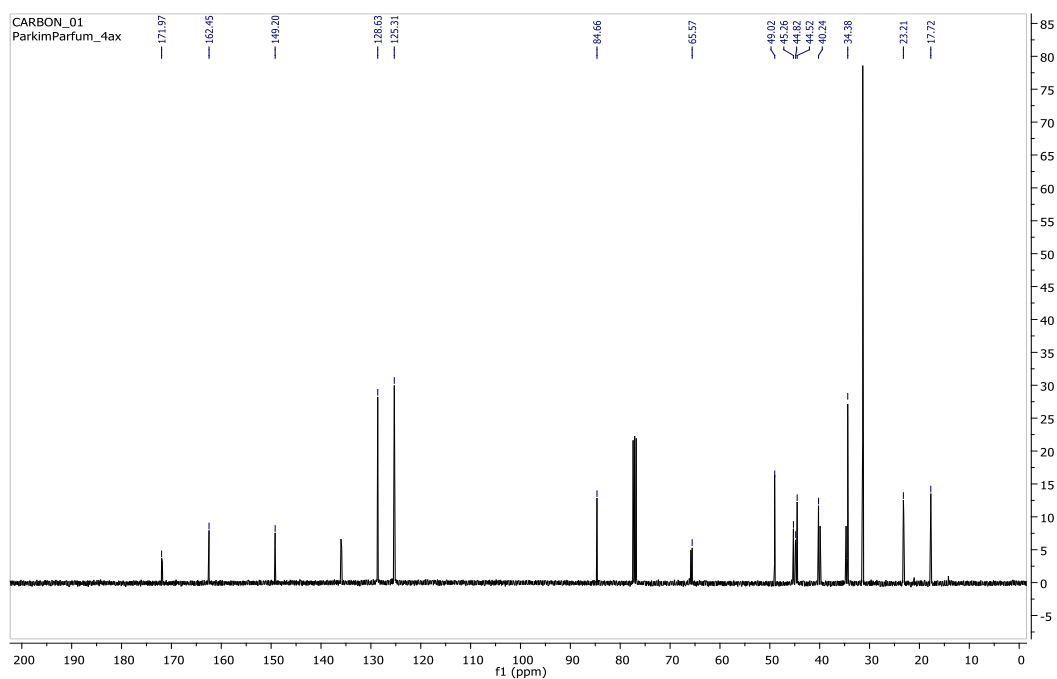


Figure 6-50- ^{13}C -NMR spectrum of 2.5a

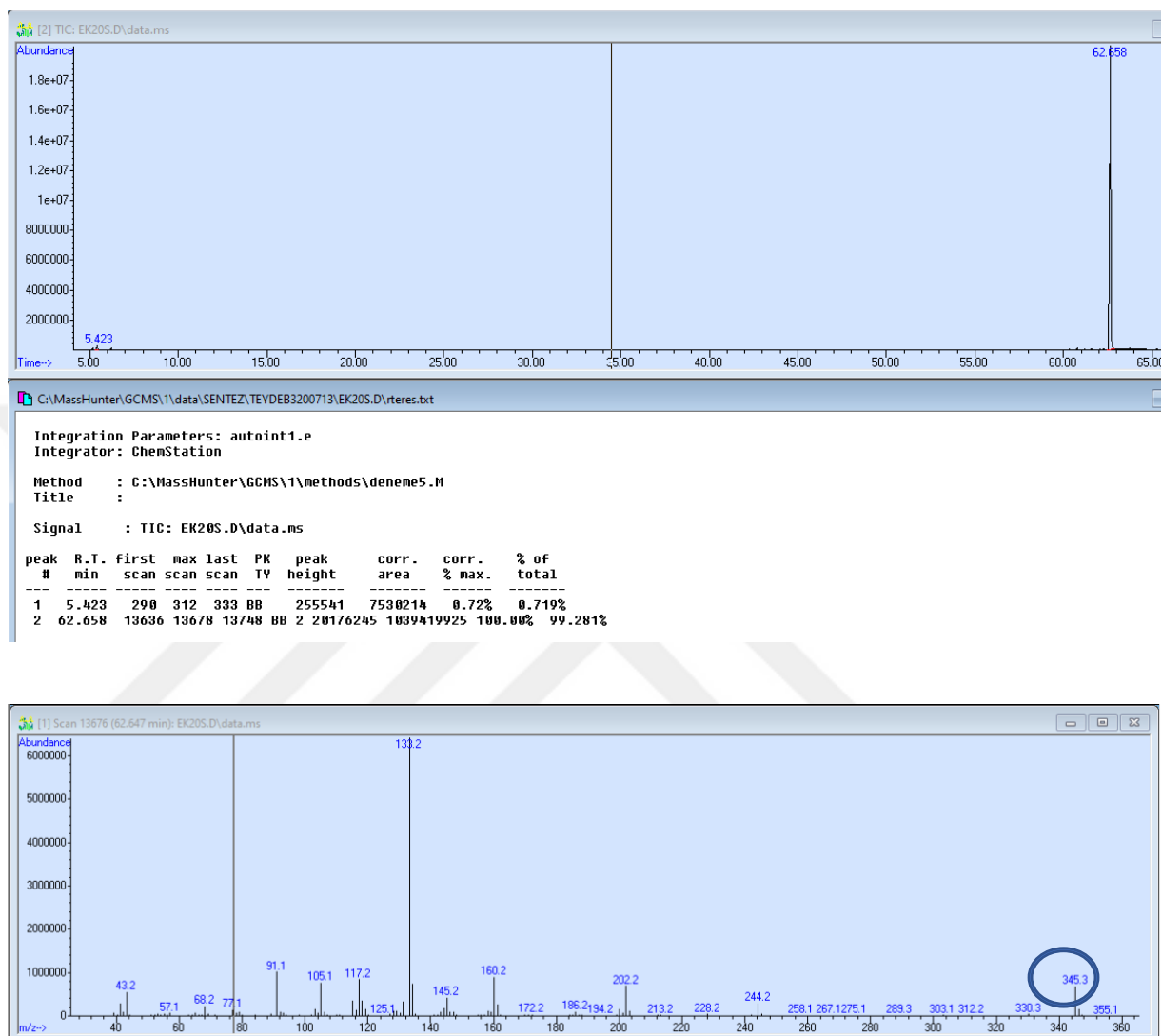


Figure 6-51-GC-MS spectrum of 2.5a

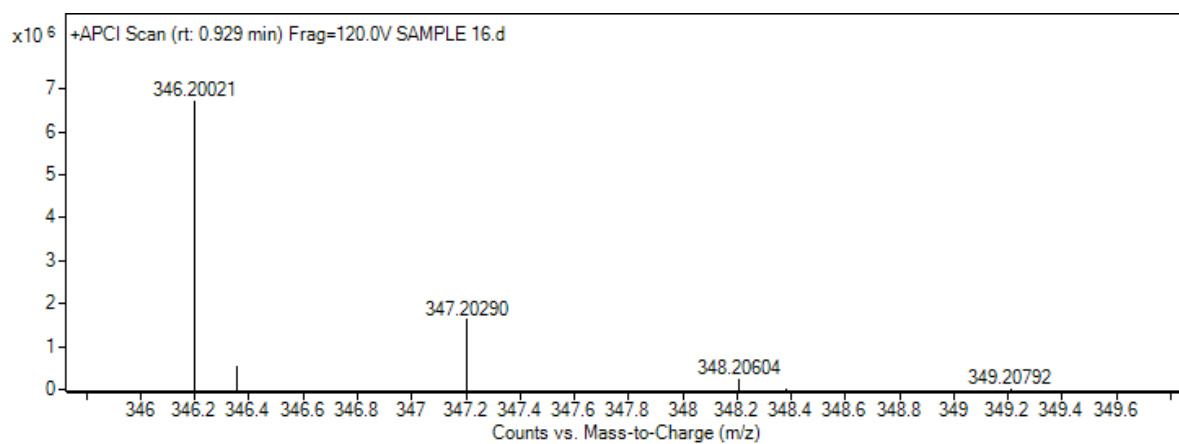


Figure 6-52-(TOF) LC-MS spectrum of 2.5a

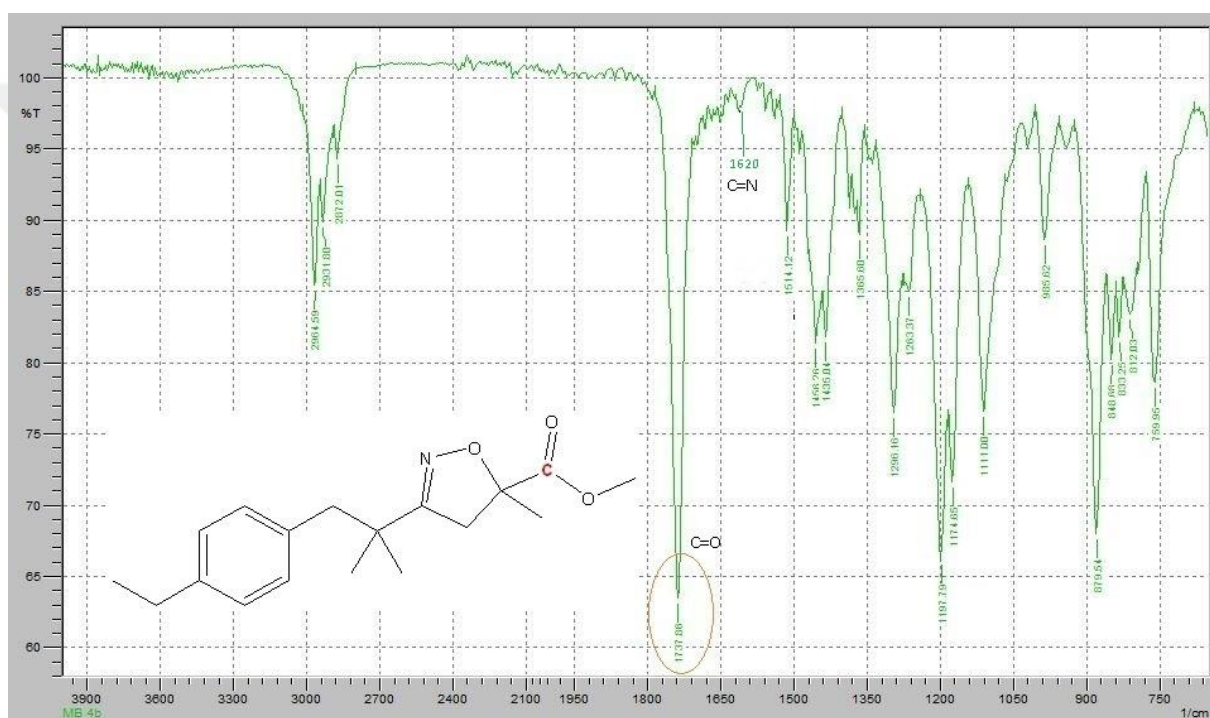


Figure 6-53-IR spectrum of 2.4b

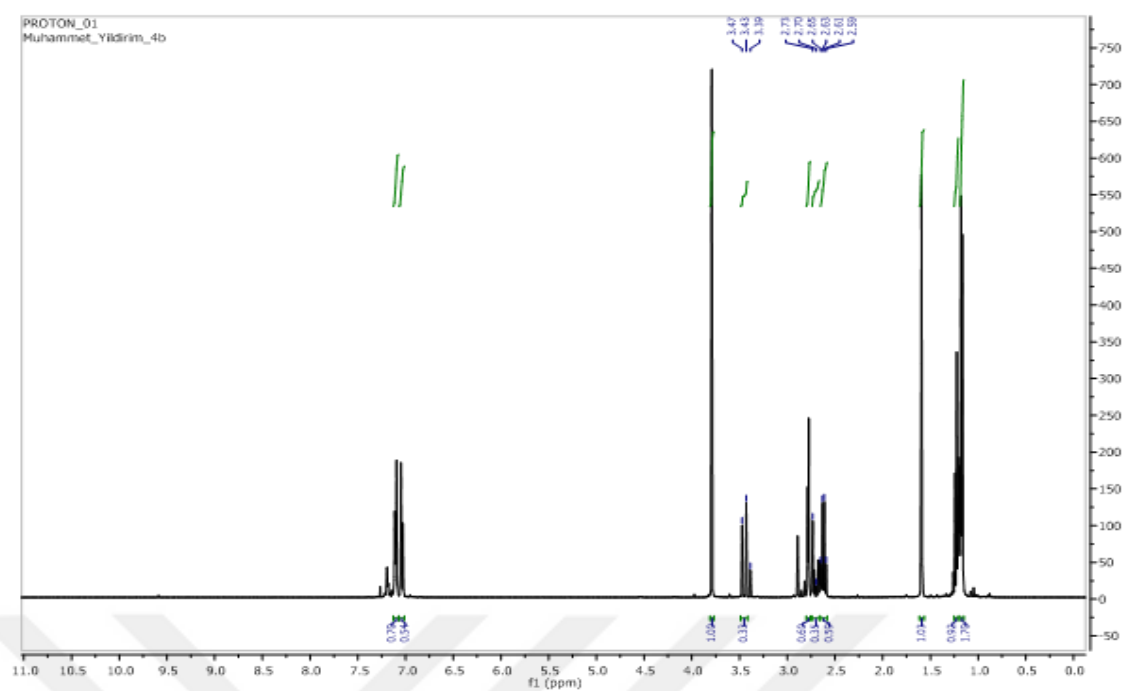


Figure 6-54- ^1H -NMR spectrum of 2.4b

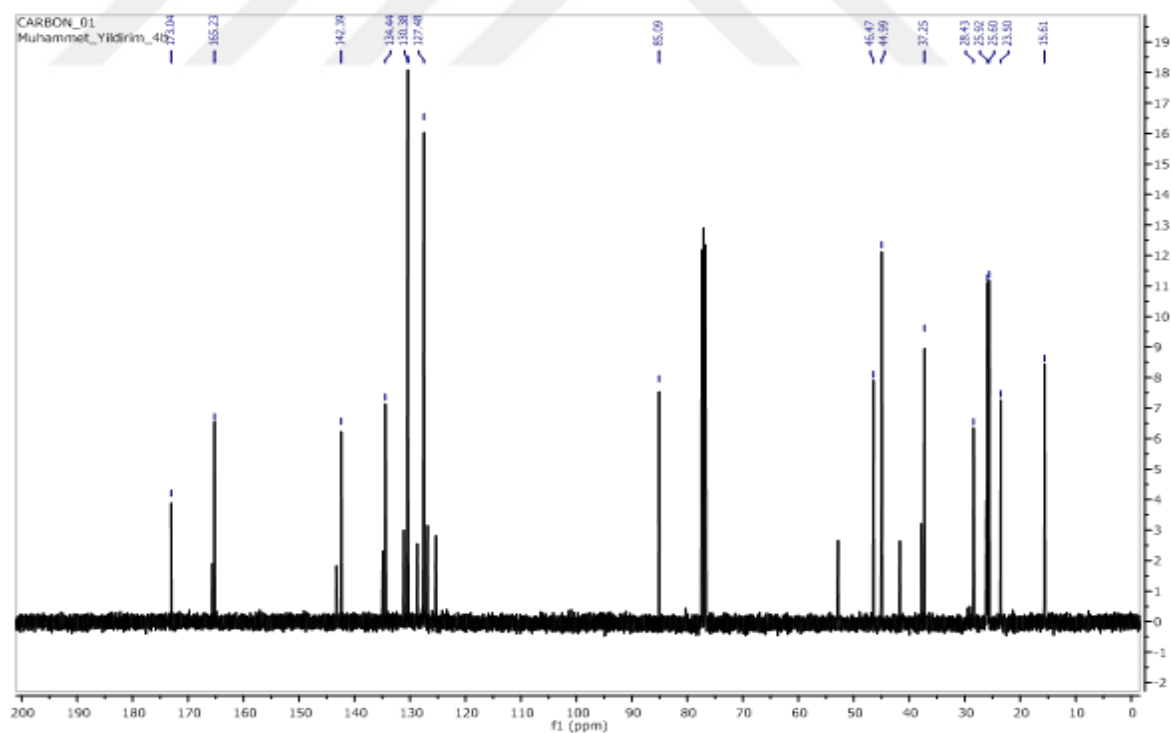


Figure 6-55- ^{13}C -NMR spectrum of 2.4b

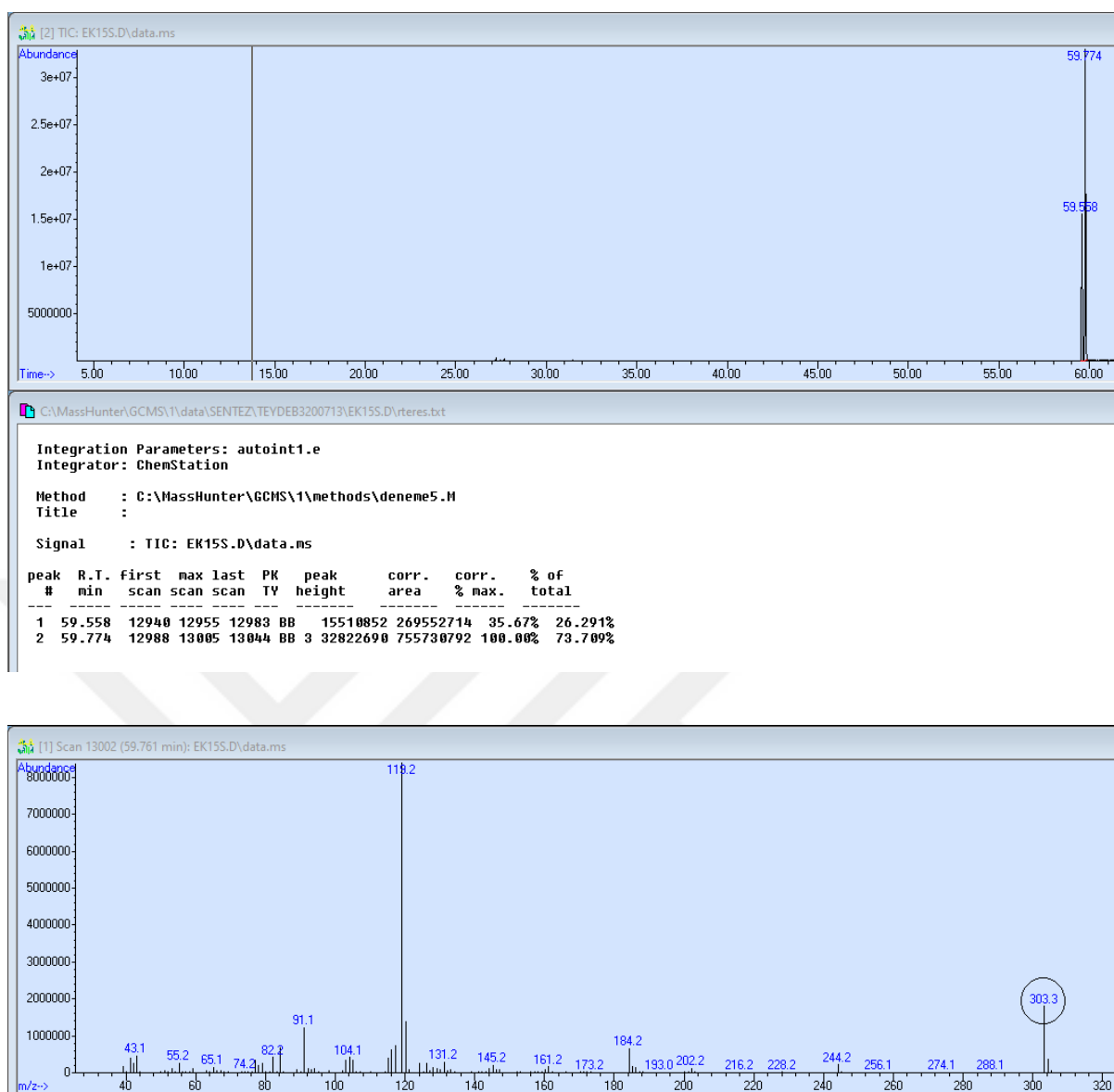


Figure 6-56-GC-MS spectrum of 2.4b

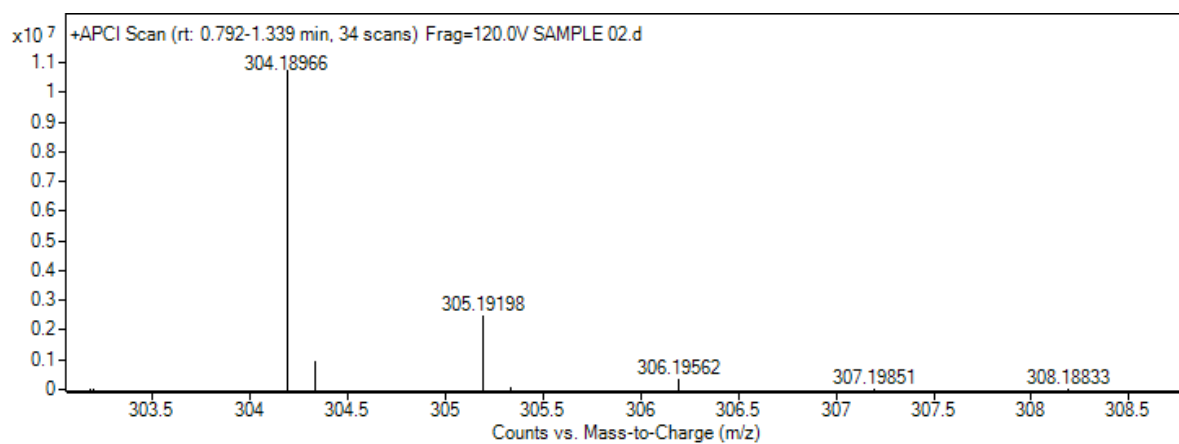


Figure 6-57-(TOF) LC-MS spectrum of 2.4b

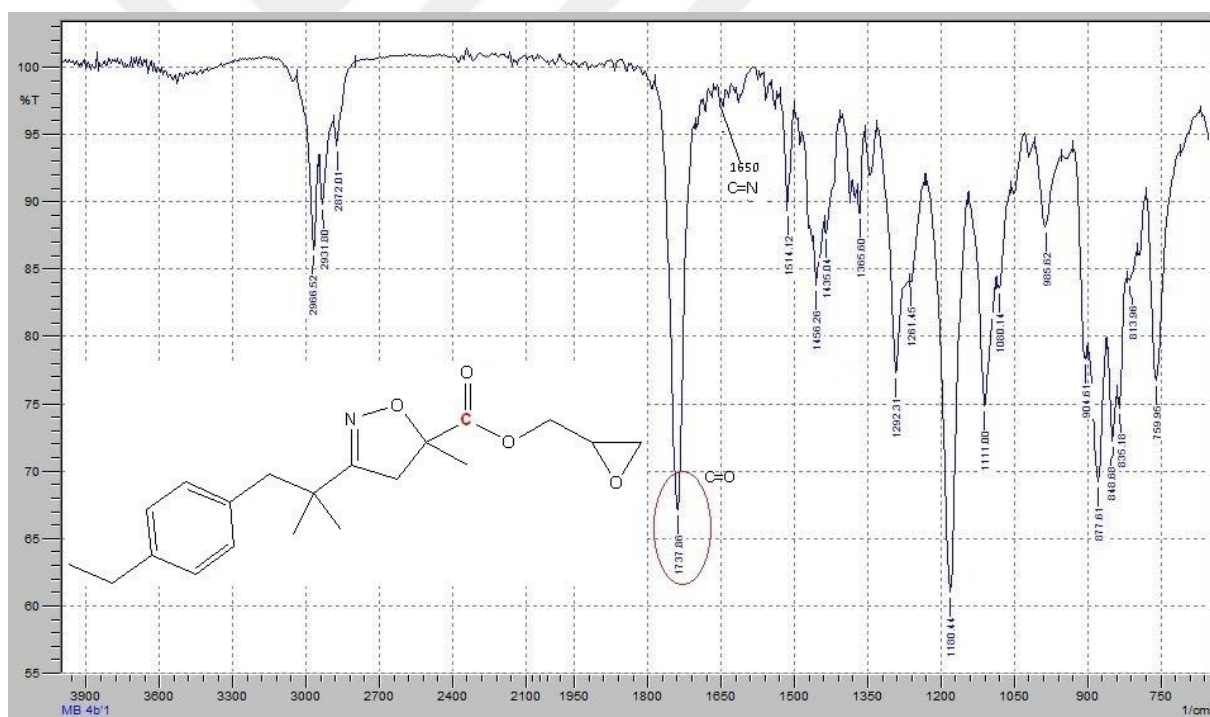


Figure 6-58-IR spectrum of 2.5b

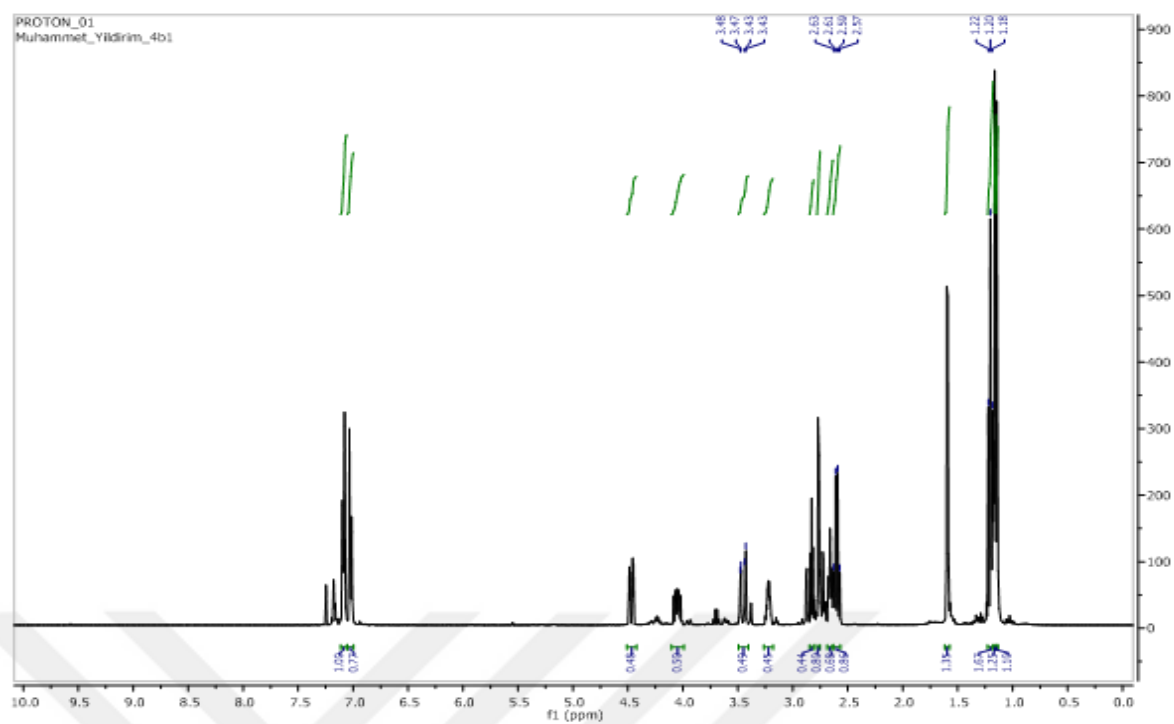


Figure 6-59- ^1H -NMR spectrum of 2.5b

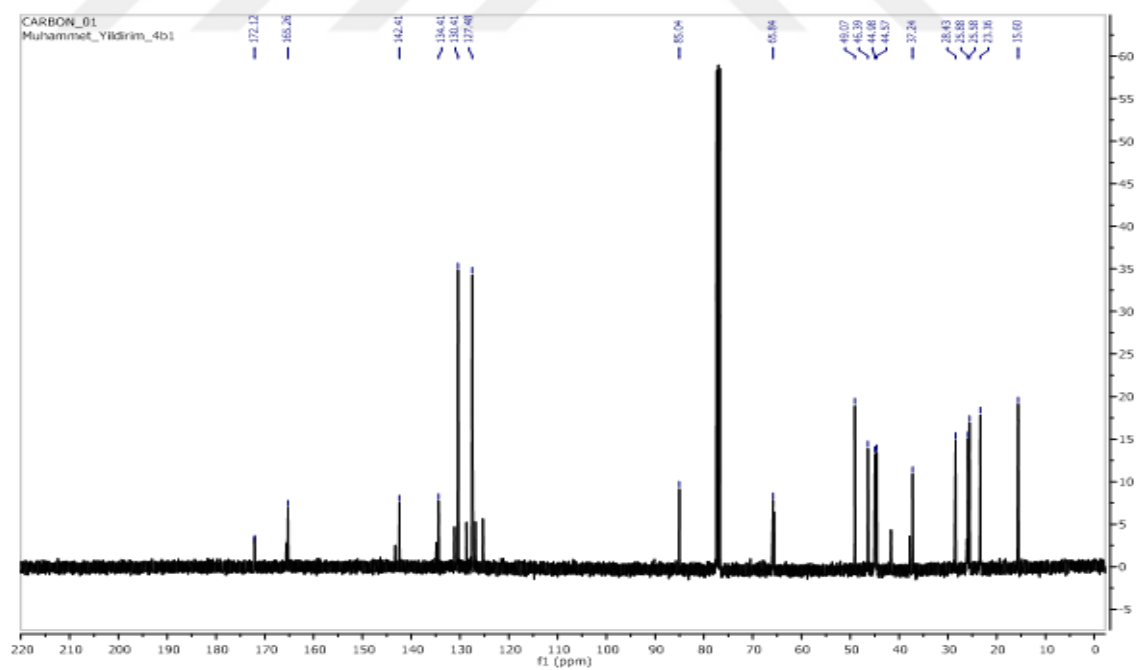


Figure 6-60- ^{13}C -NMR spectrum of 2.5b

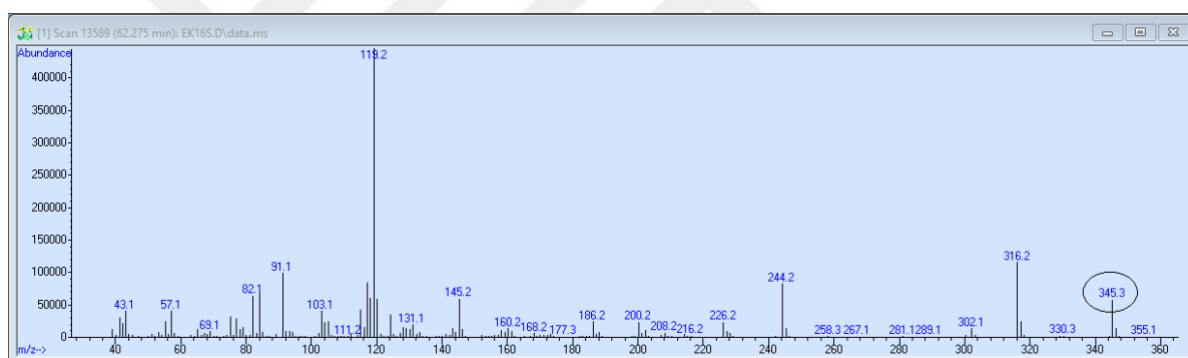
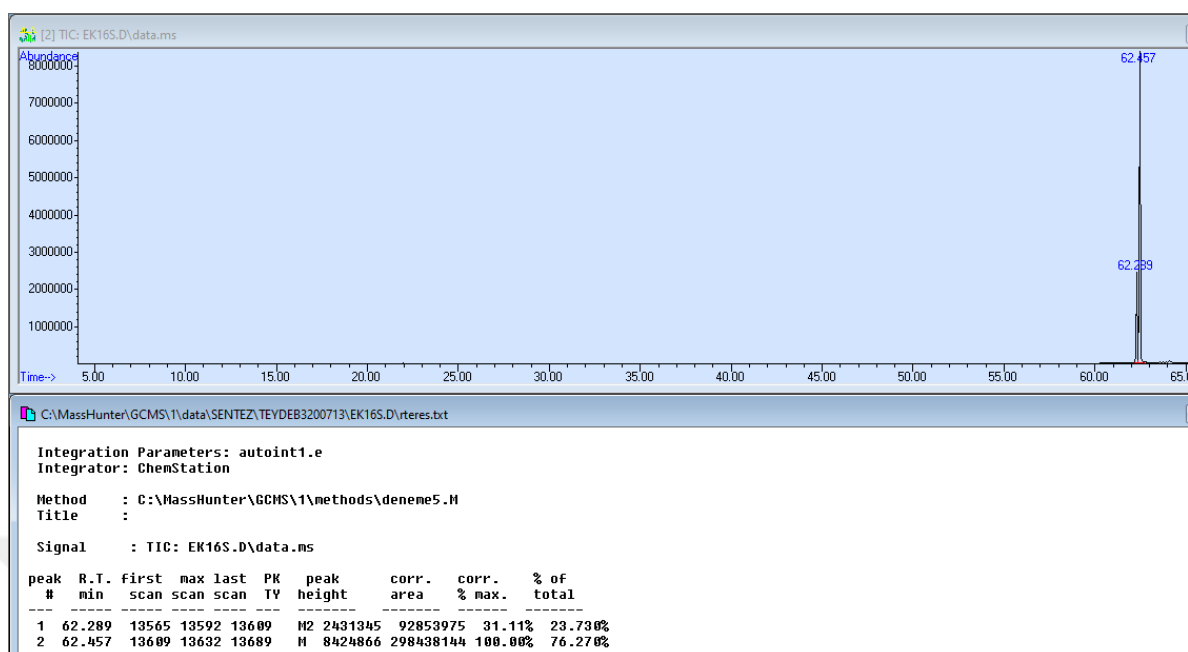


Figure 6-61-GC-MS spectrum of 2.5b

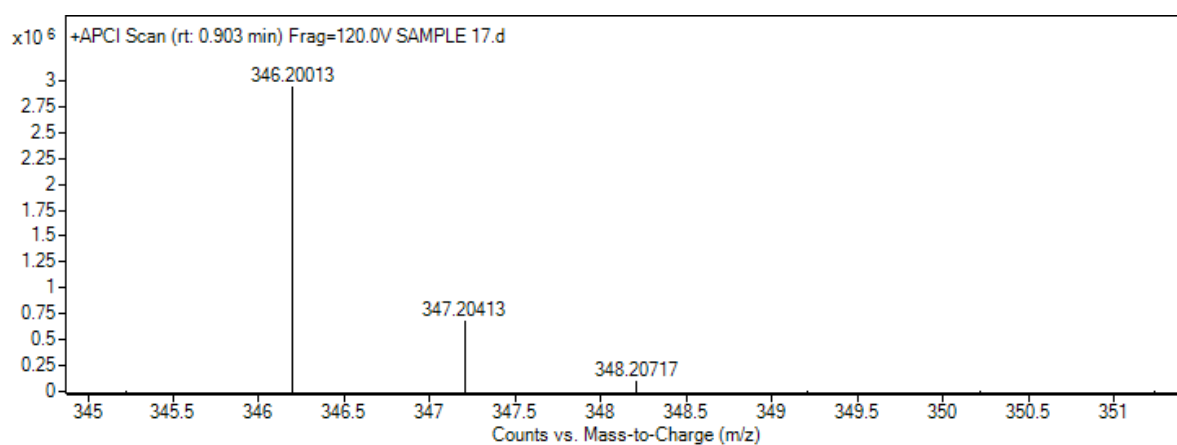


Figure 6-62-(TOF) LC-MS spectrum of 2.5b

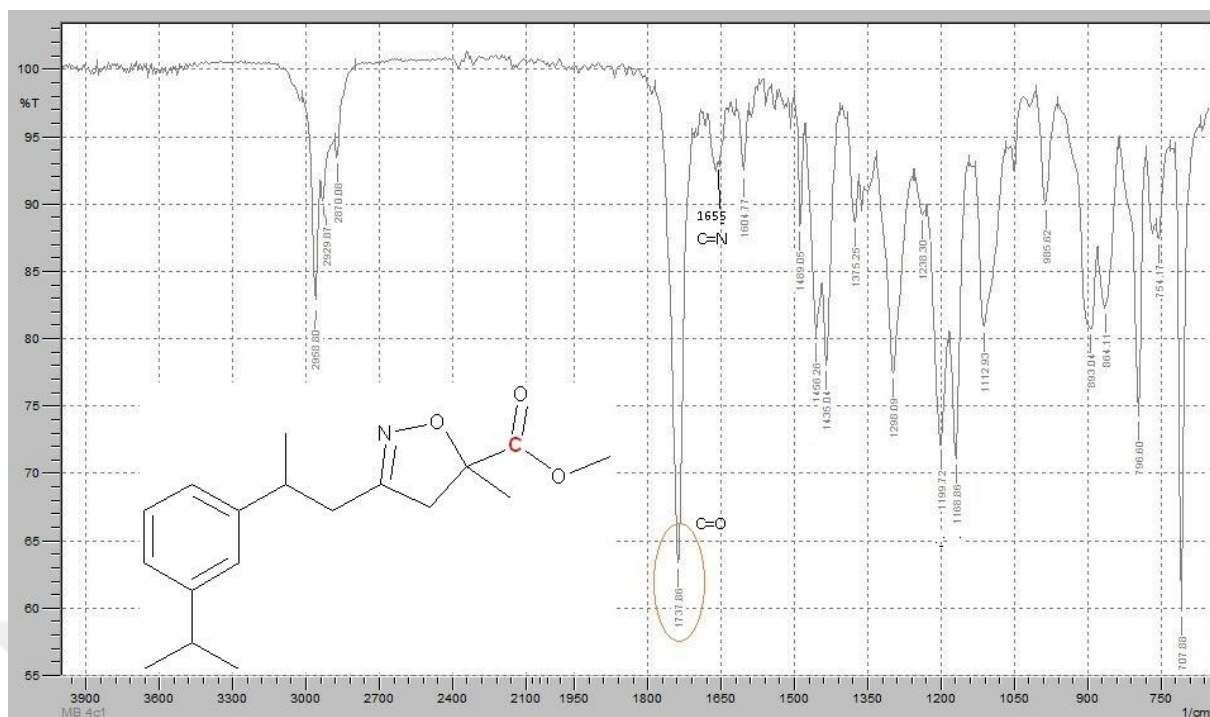


Figure 6-63-IR spectrum of 2.4c

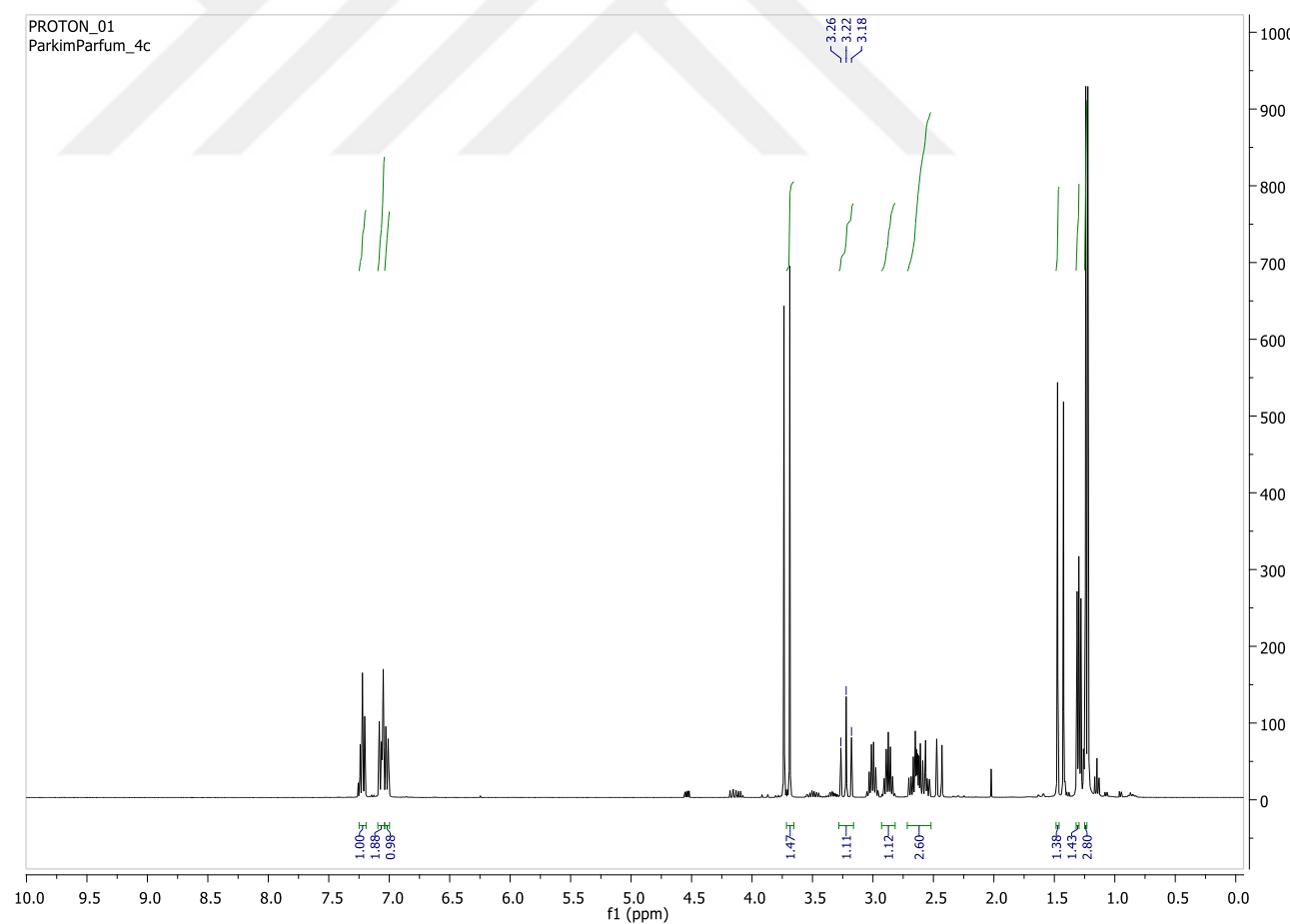


Figure 6-64-¹H-NMR spectrum of 2.4c

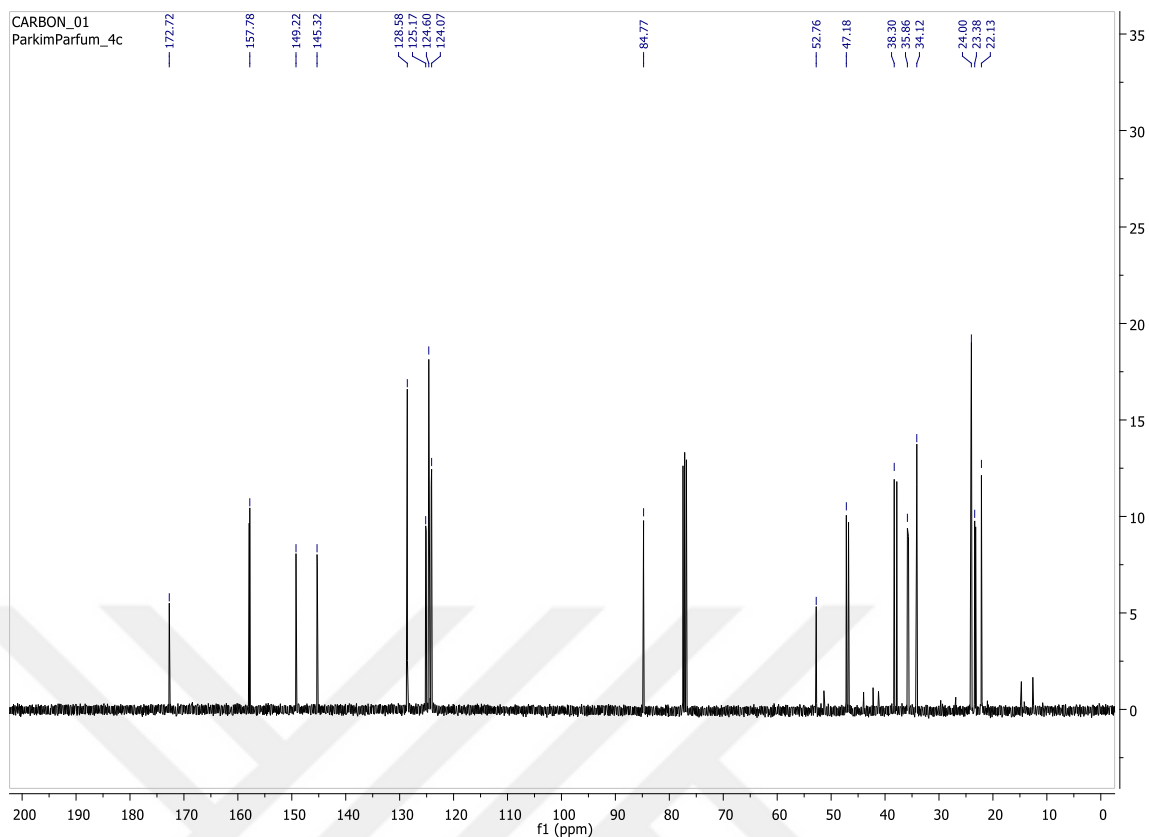
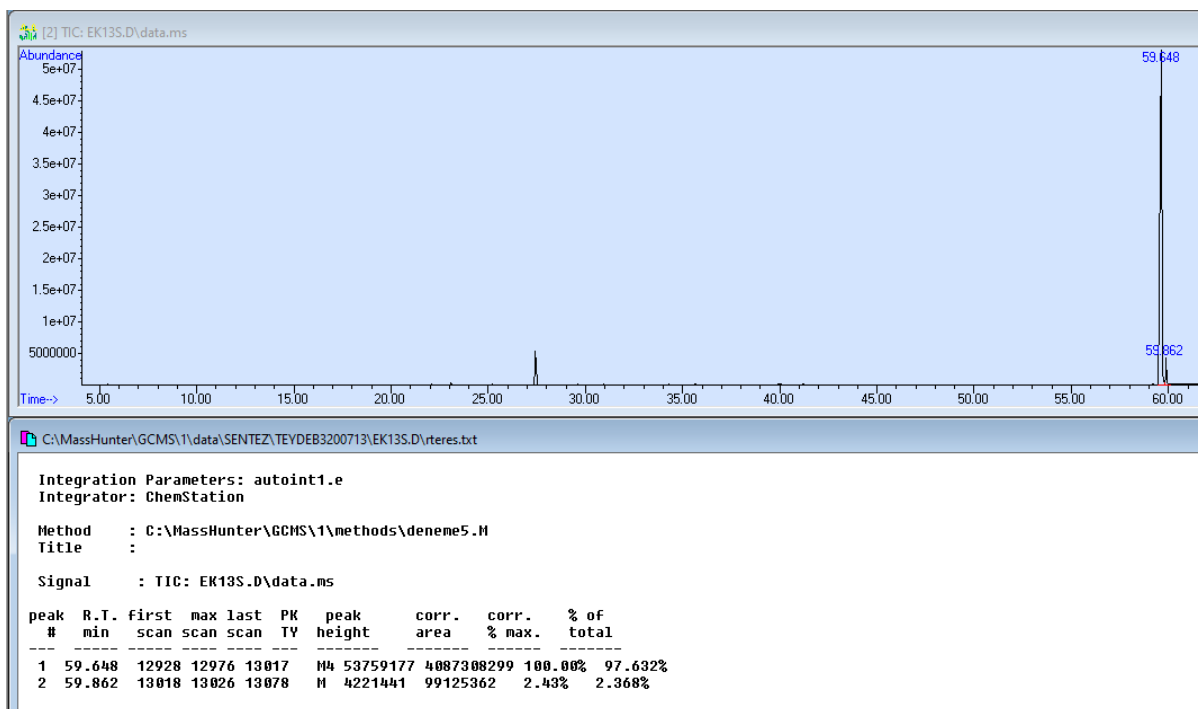


Figure 6-65- ^{13}C -NMR spectrum of 2.4c



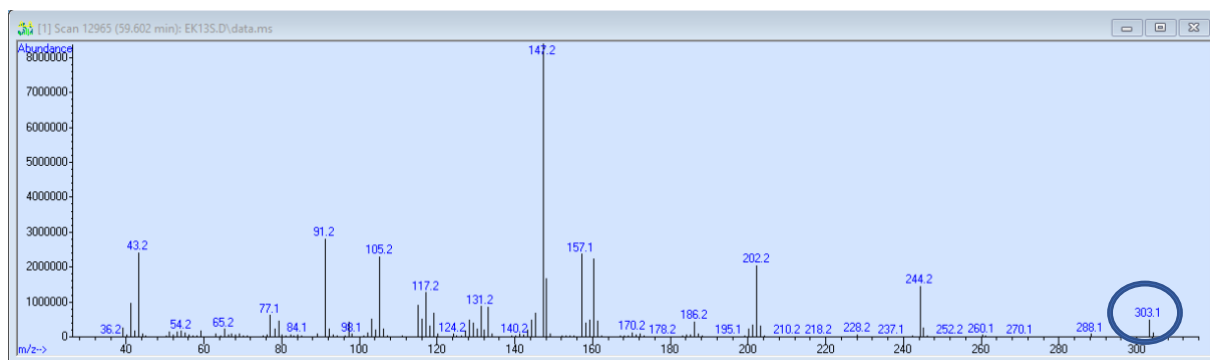


Figure 6-66-GC-MS spectrum of 2.4c

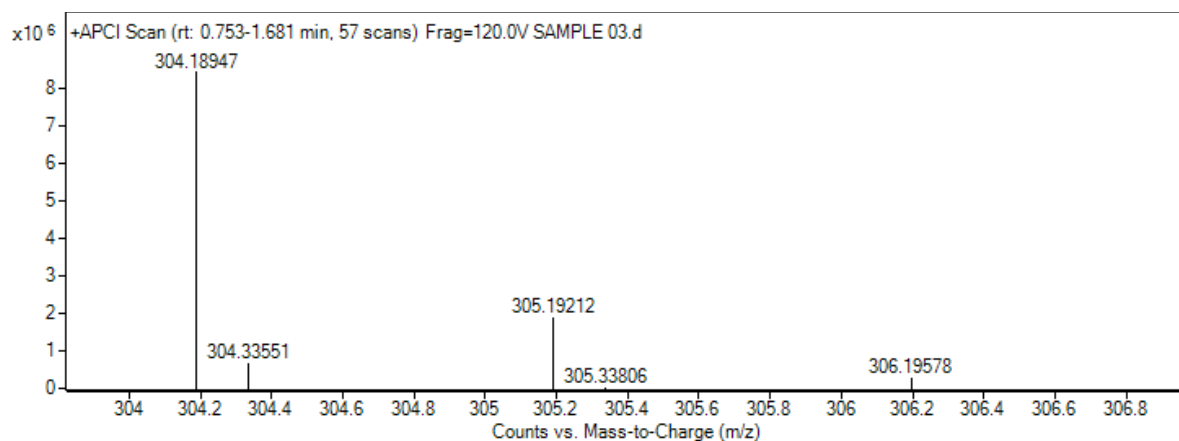


Figure 6-67-(TOF) LC-MS spectrum of 2.4c

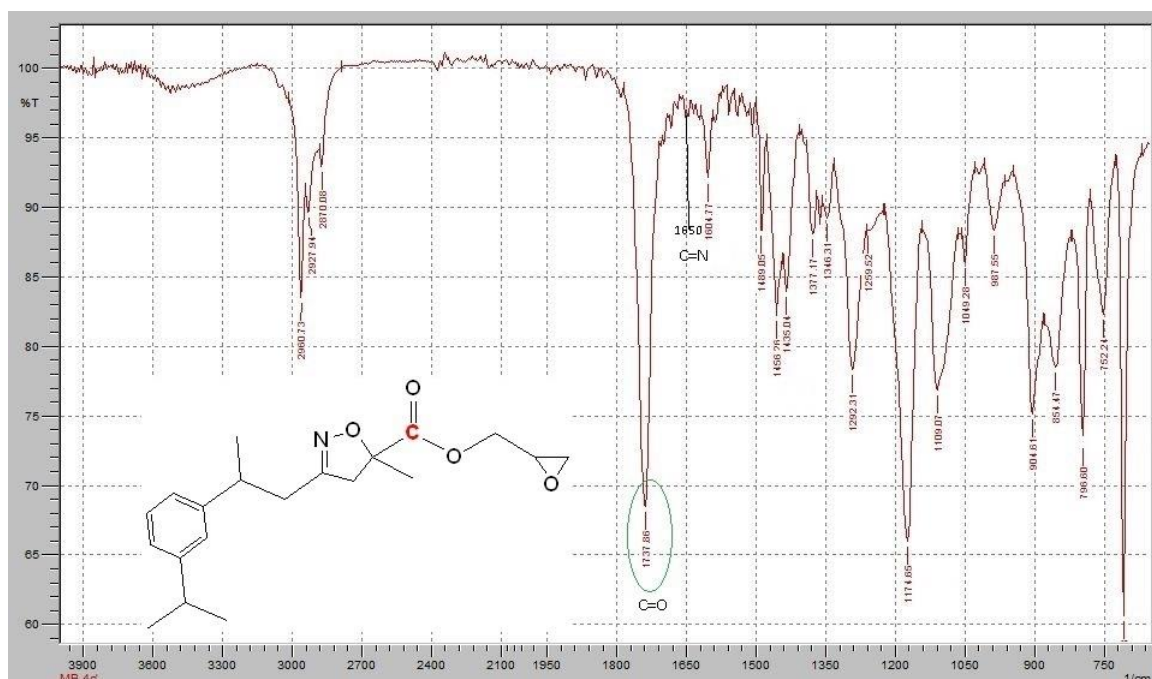


Figure 6-68-IR spectrum of 2.5c

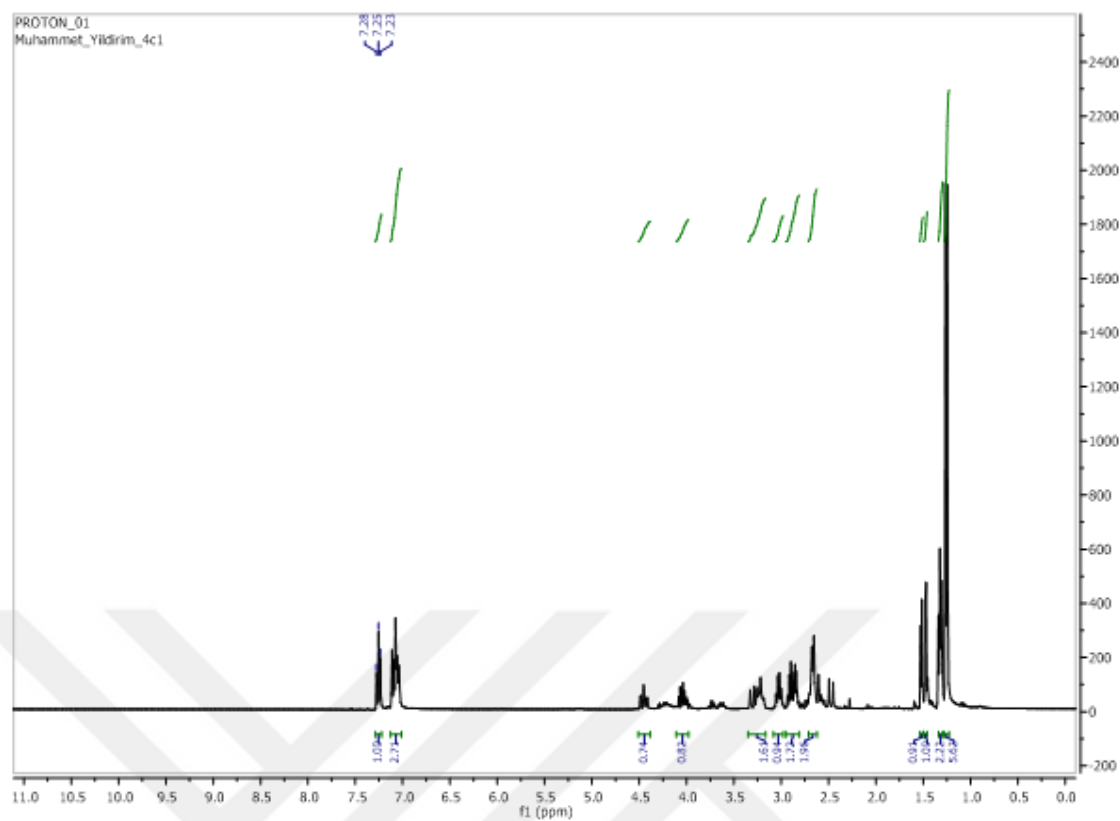


Figure 6-69- ^1H -NMR spectrum of 2.5c

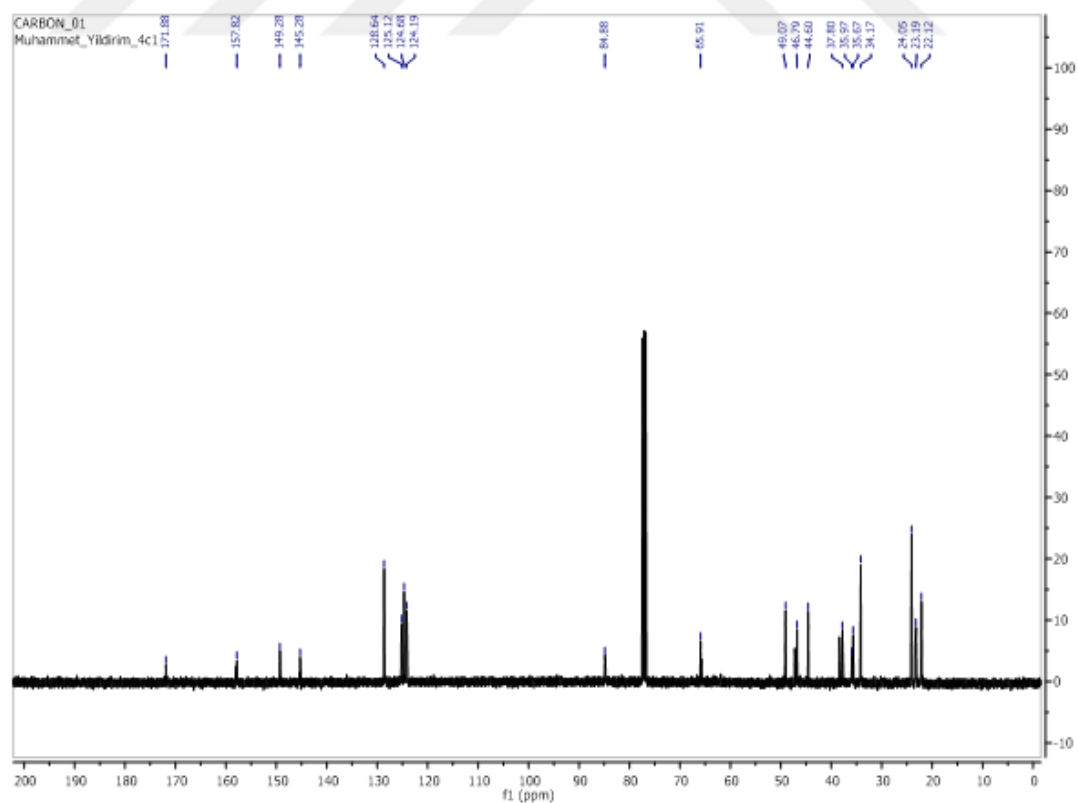


Figure 6-70- ^{13}C -NMR spectrum of 2.5c

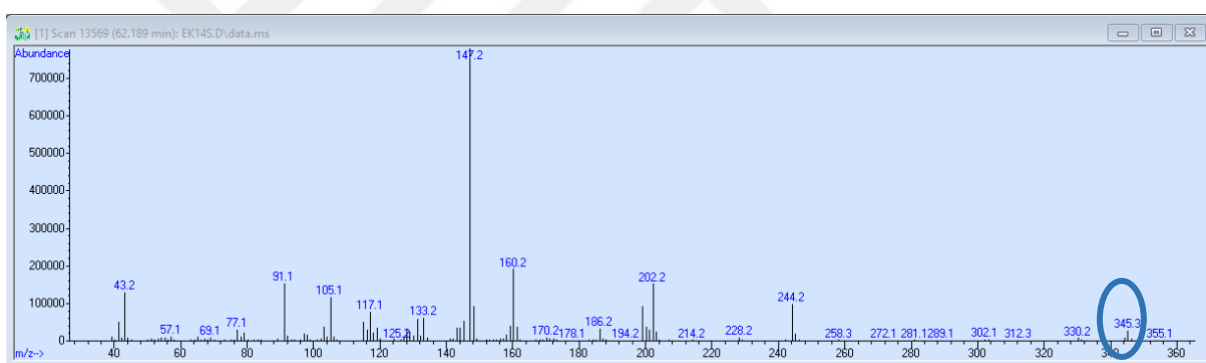
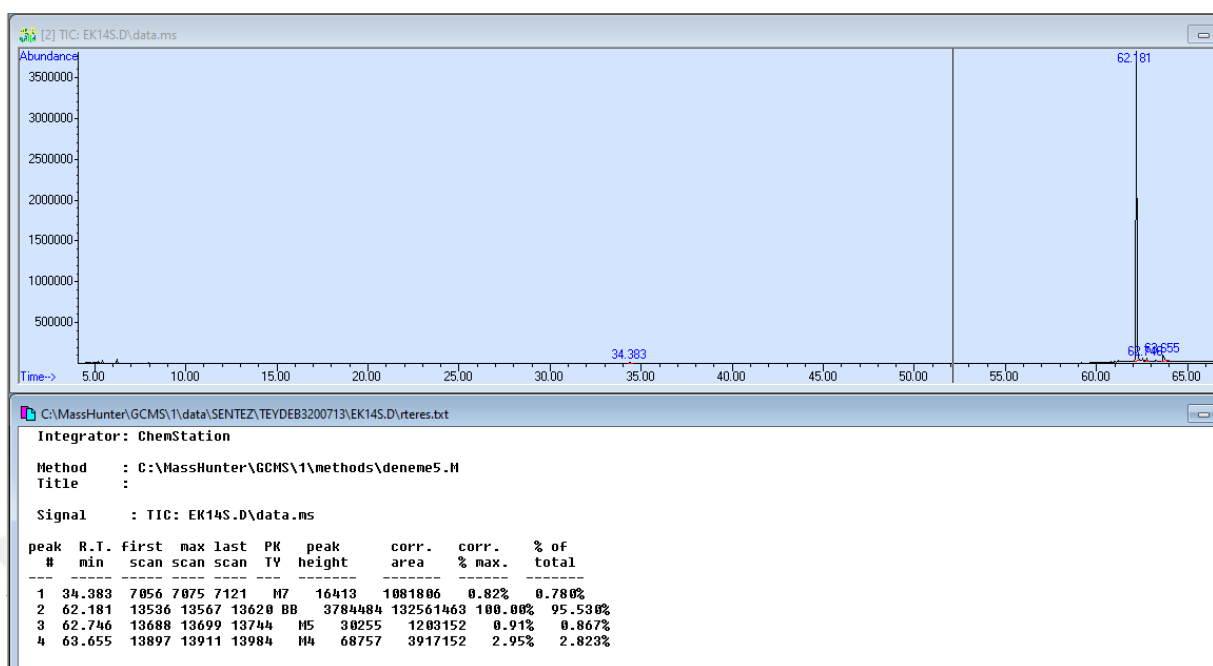


Figure 6-71-GC-MS spectrum of 2.5c

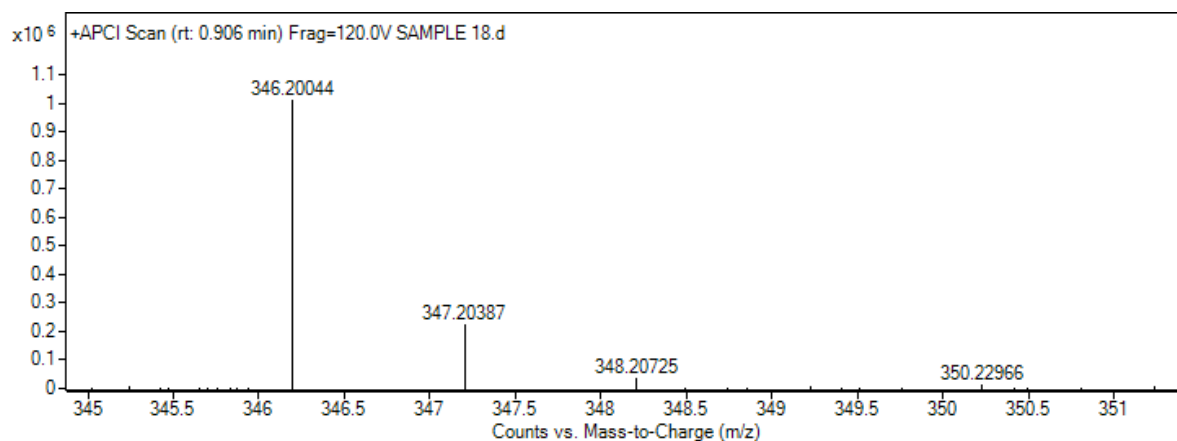


Figure 6-72-(TOF) LC-MS spectrum of 2.5c

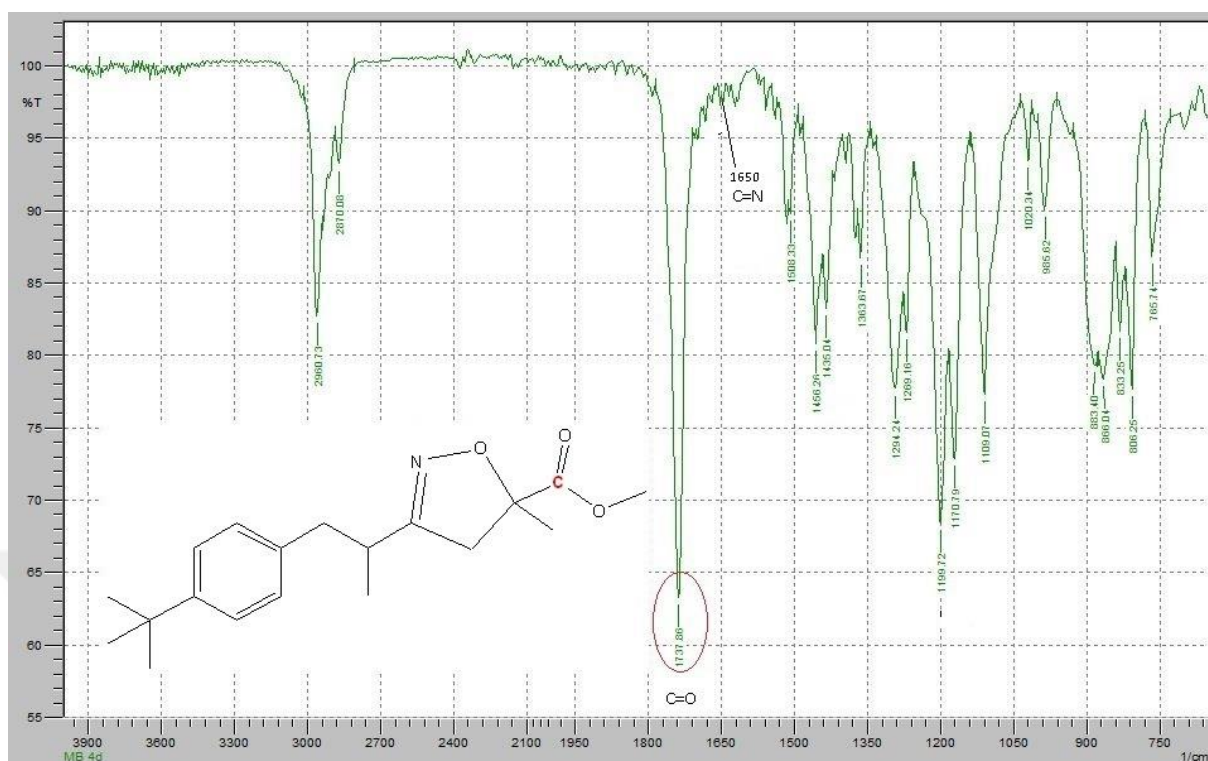


Figure 6-73-IR spectrum of 2.4d

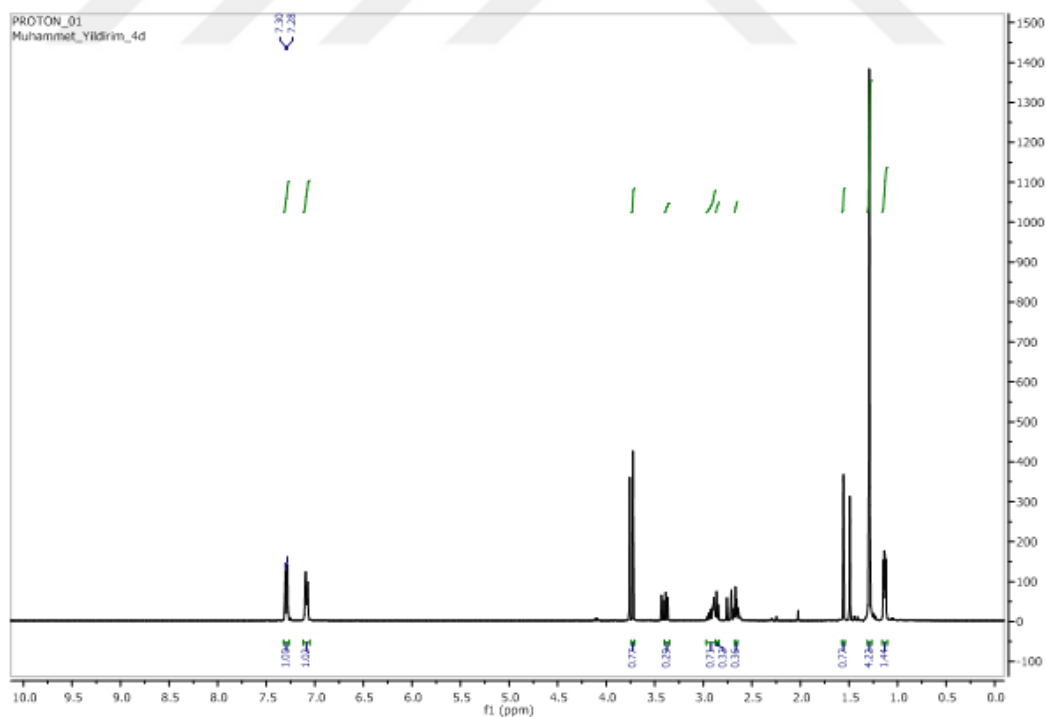


Figure 6-74-¹H-NMR spectrum of 2.4d

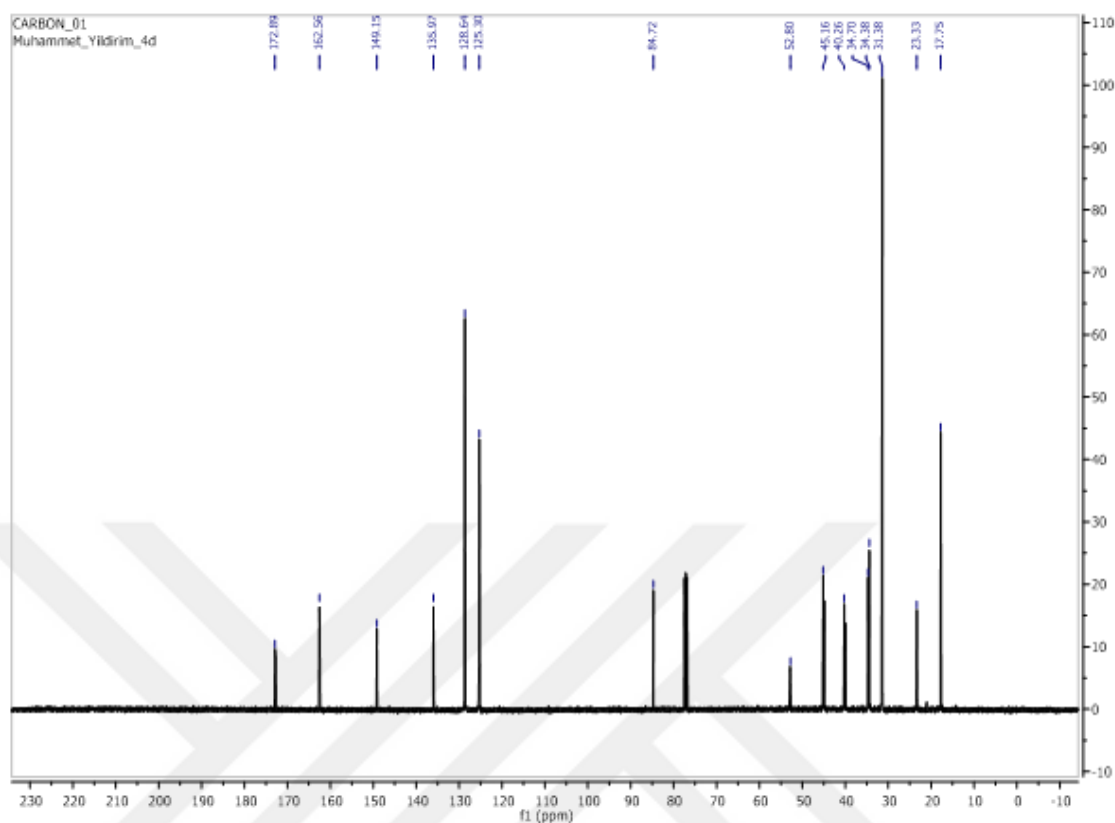
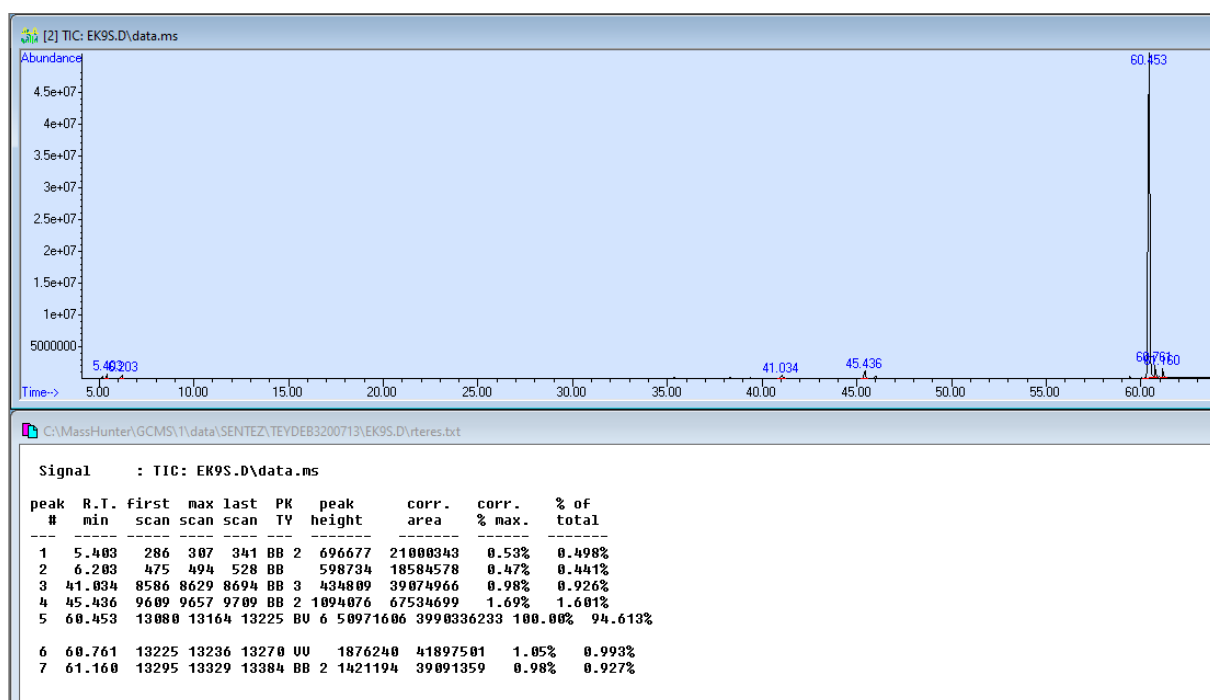


Figure 6-75- ^{13}C -NMR spectrum of 2.4d



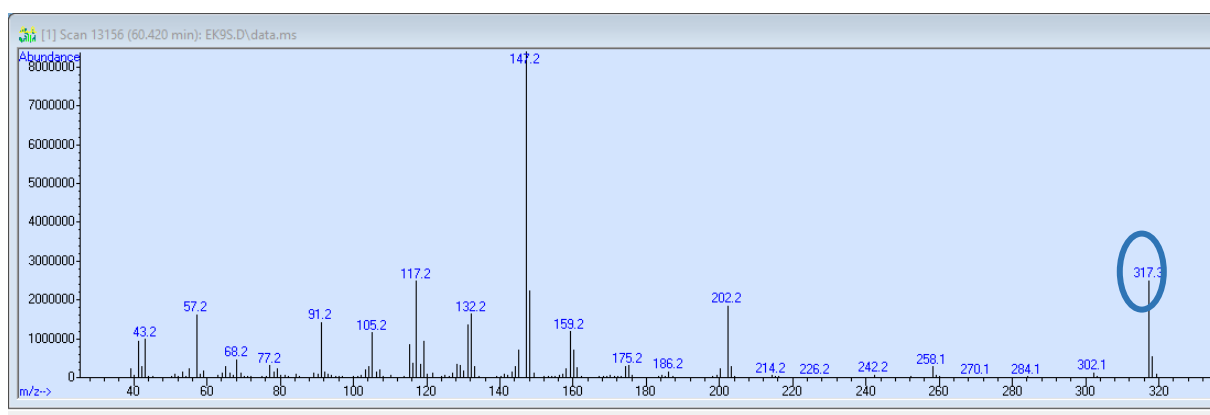


Figure 6-76-GC-MS spectrum of 2.4d

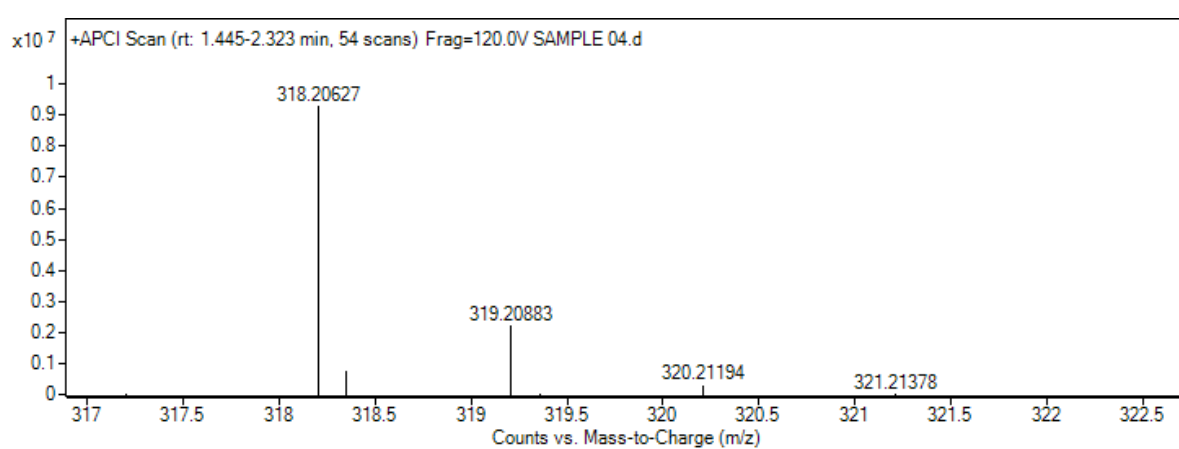


Figure 6-77-(TOF) LC-MS spectrum of 2.4d

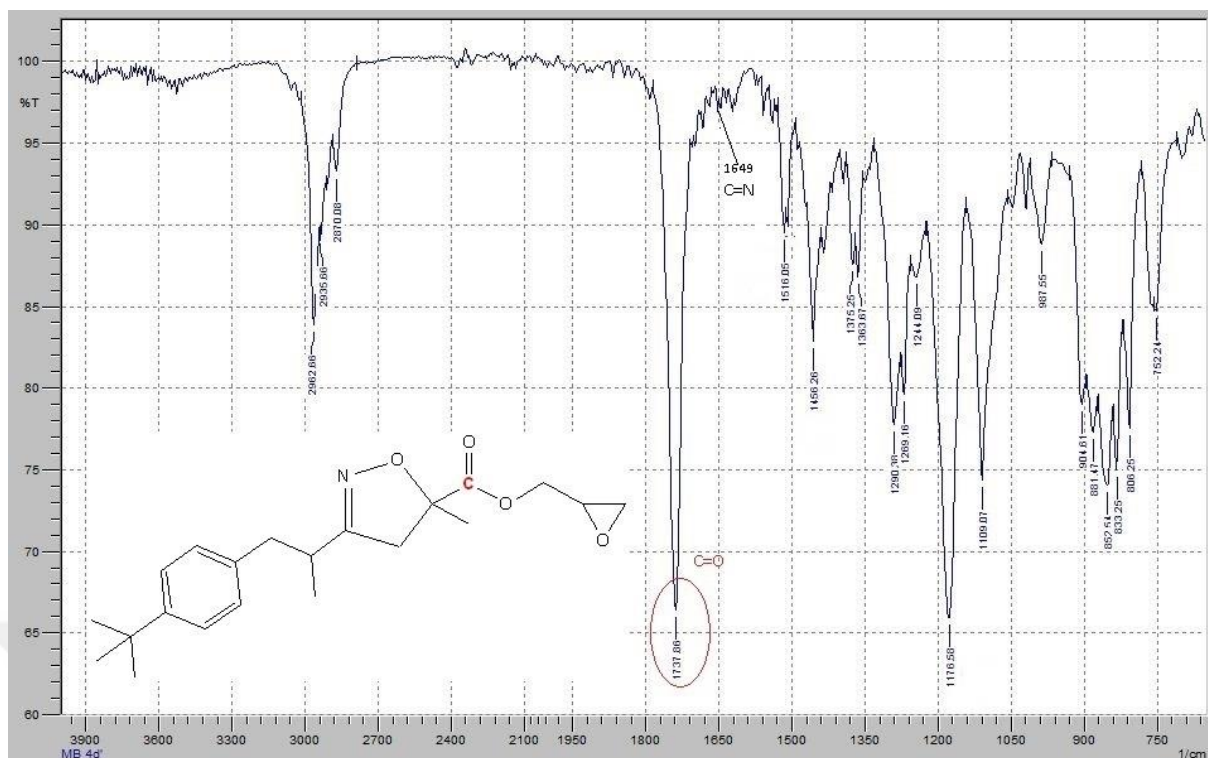


Figure 6-78-IR spectrum of 2.5d

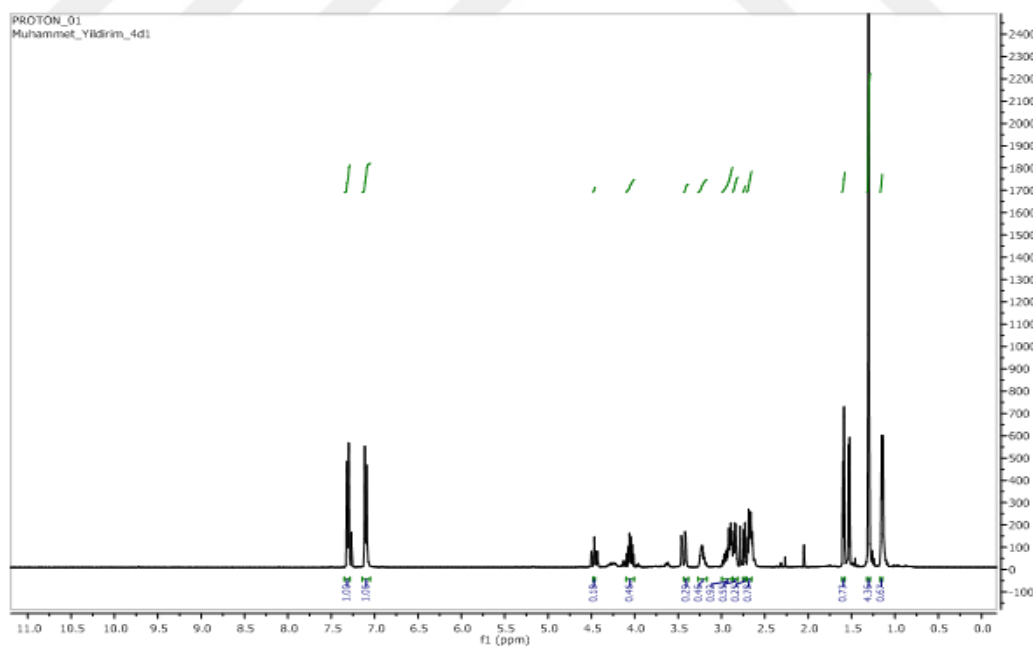


Figure 6-79-¹H-NMR spectrum of 2.5d

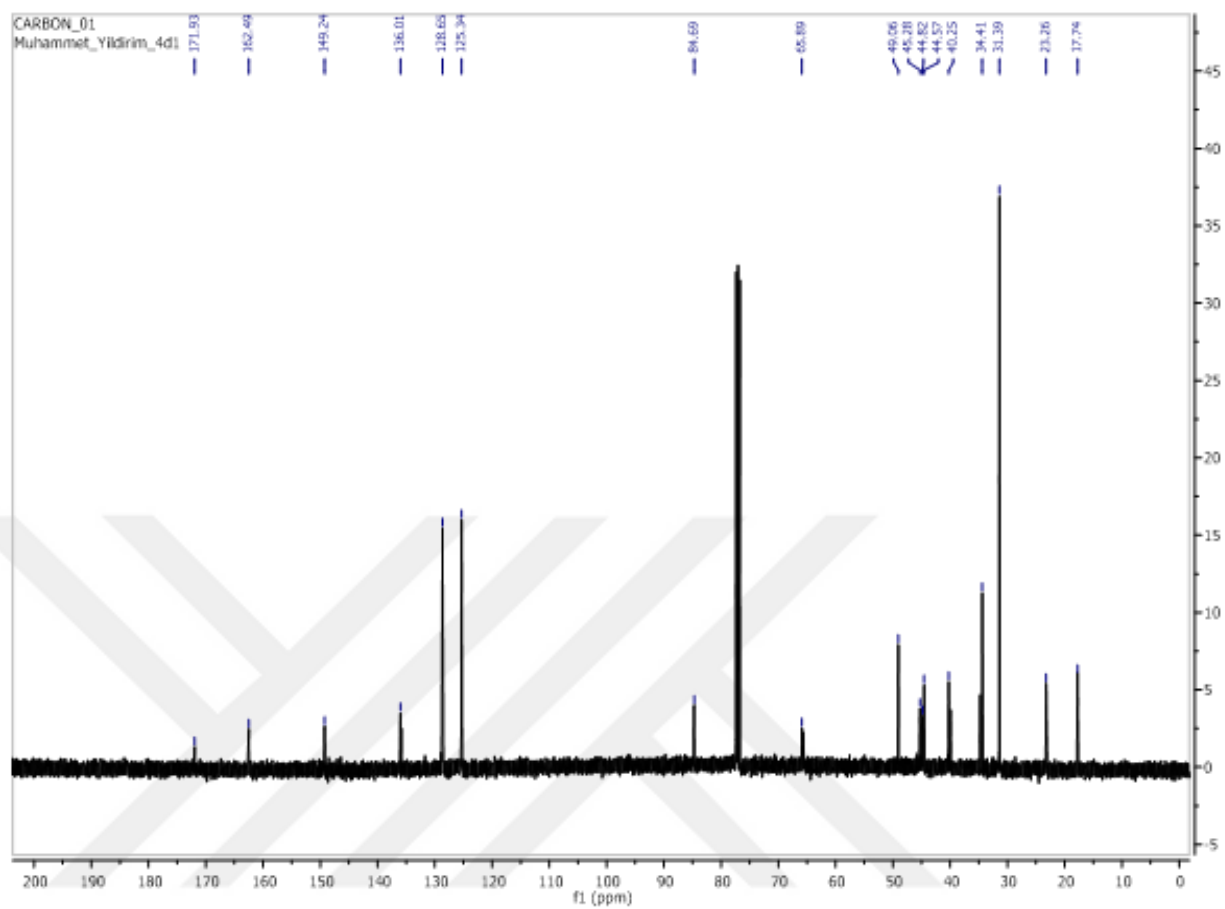


Figure 6-80- ^{13}C -NMR spectrum of 2.5d

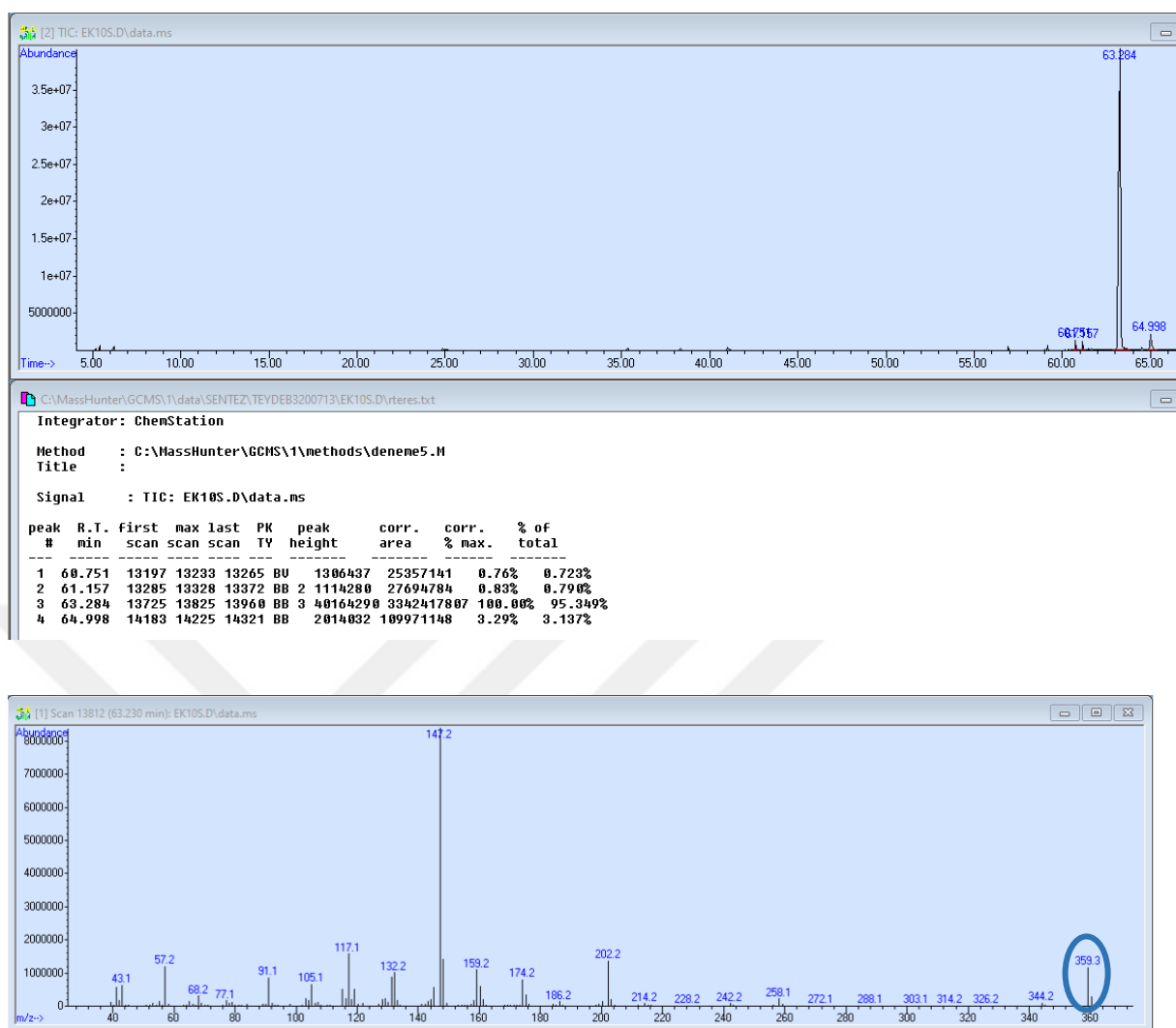


Figure 6-81- GC-MS spectrum of 2.5d

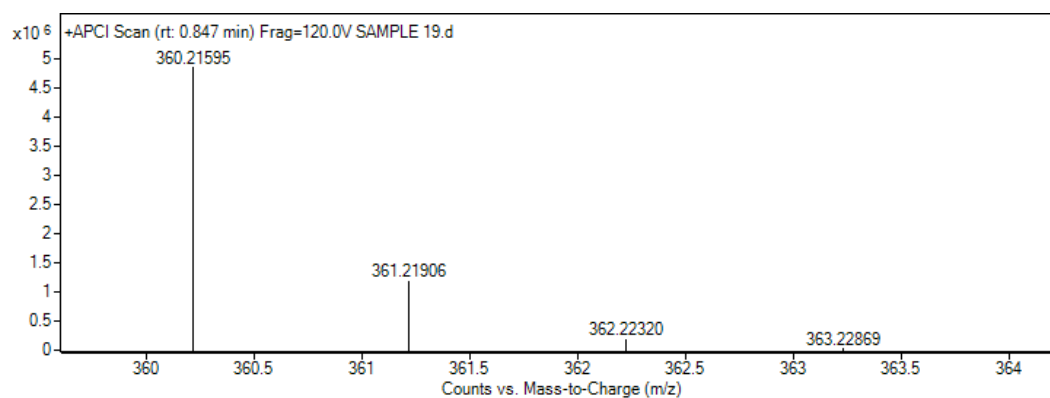


Figure 6-82--(TOF) LC-MS spectrum of 2.5d

Fig. S82 (TOF) LC-MS spectrum of 5d

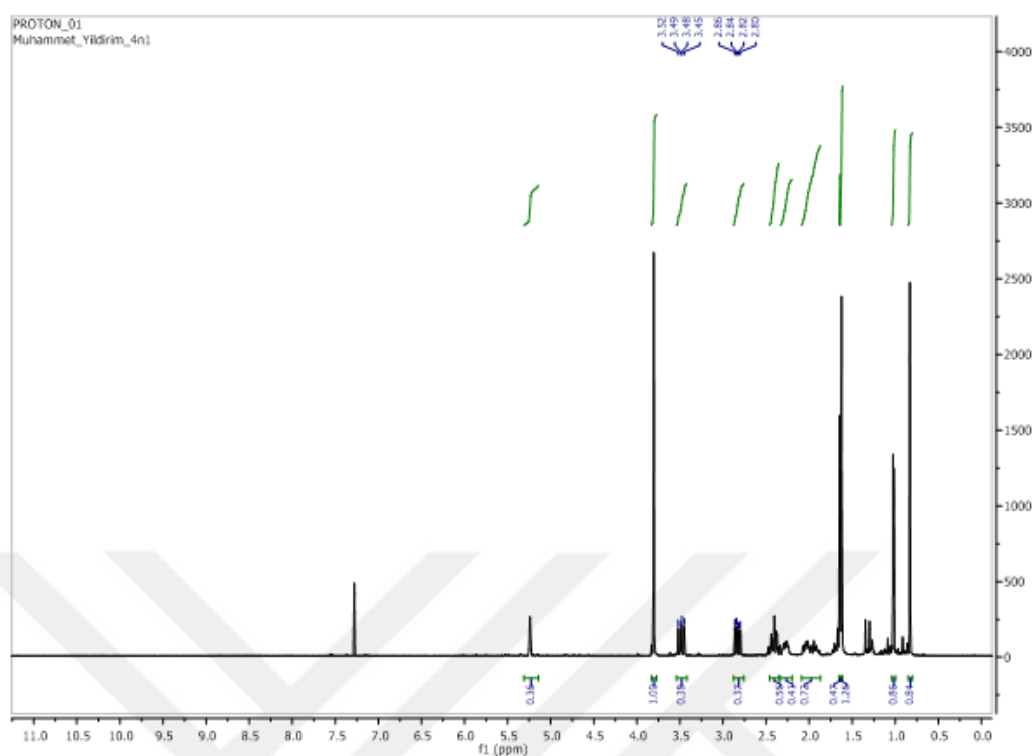


Figure 6-83- ^1H -NMR spectrum of 2.4e

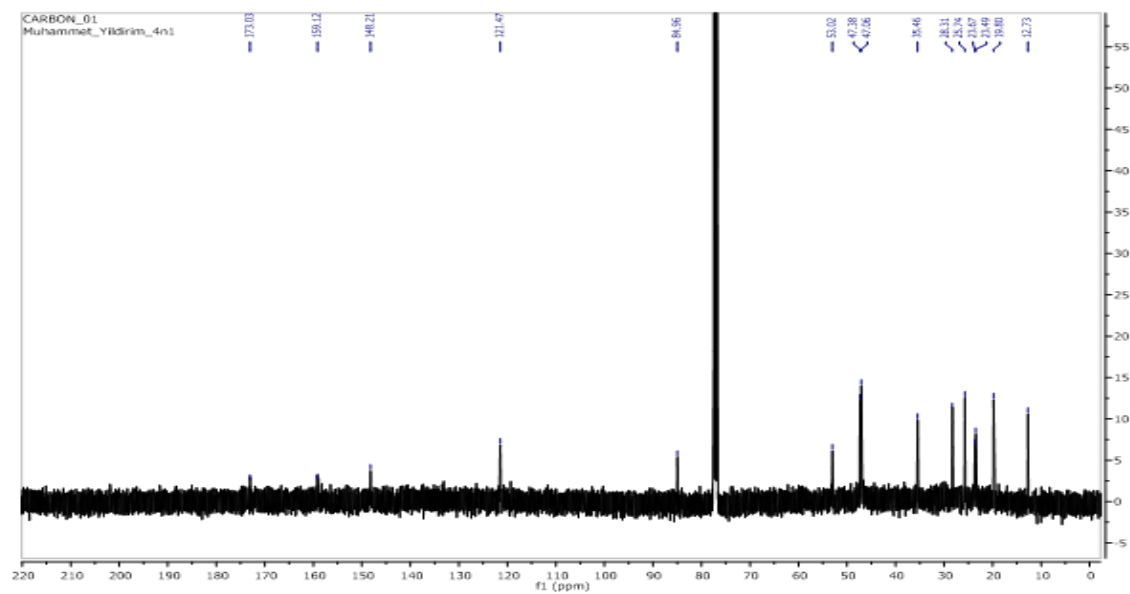


Figure 6-84- ^{13}C -NMR spectrum of 2.4e

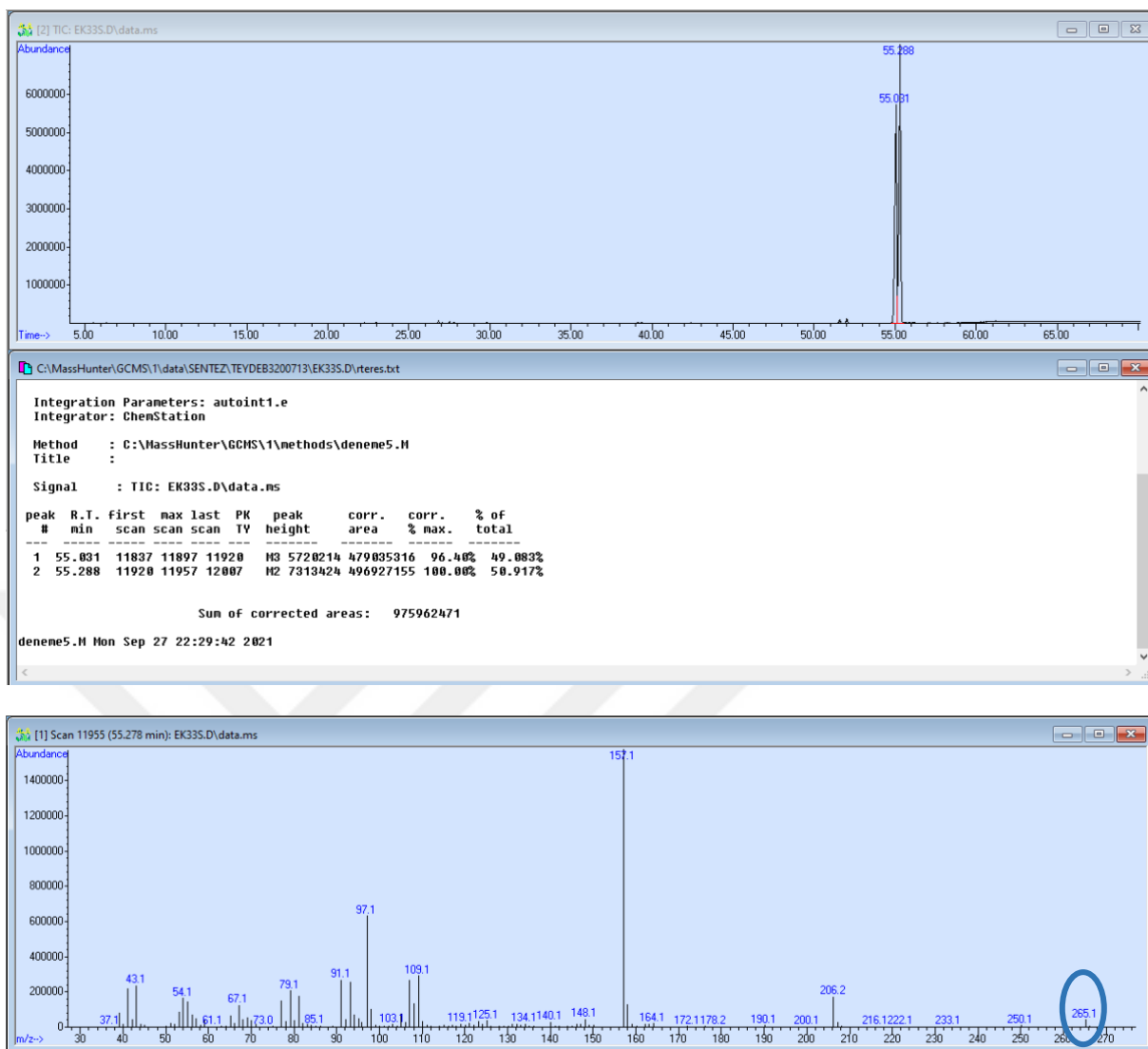


Figure 6-85-GC-MS spectrum of 2.4e

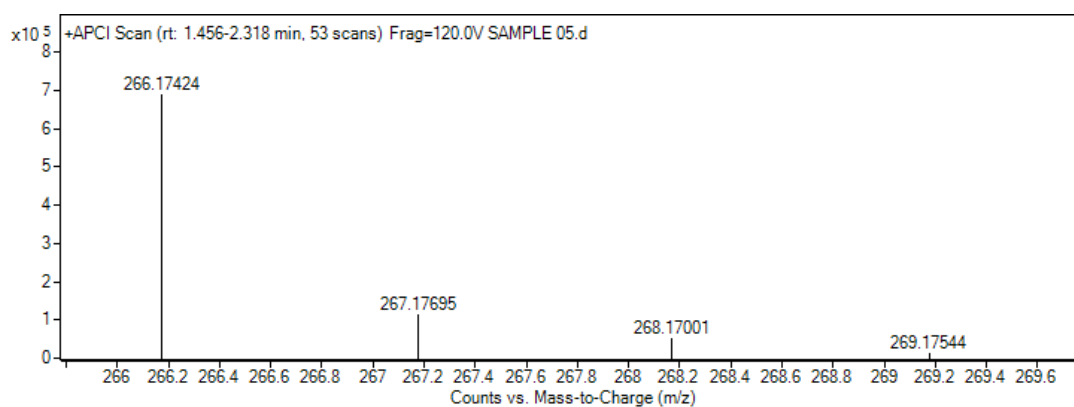


Figure 6-86-(TOF) LC-MS spectrum of 2.4e

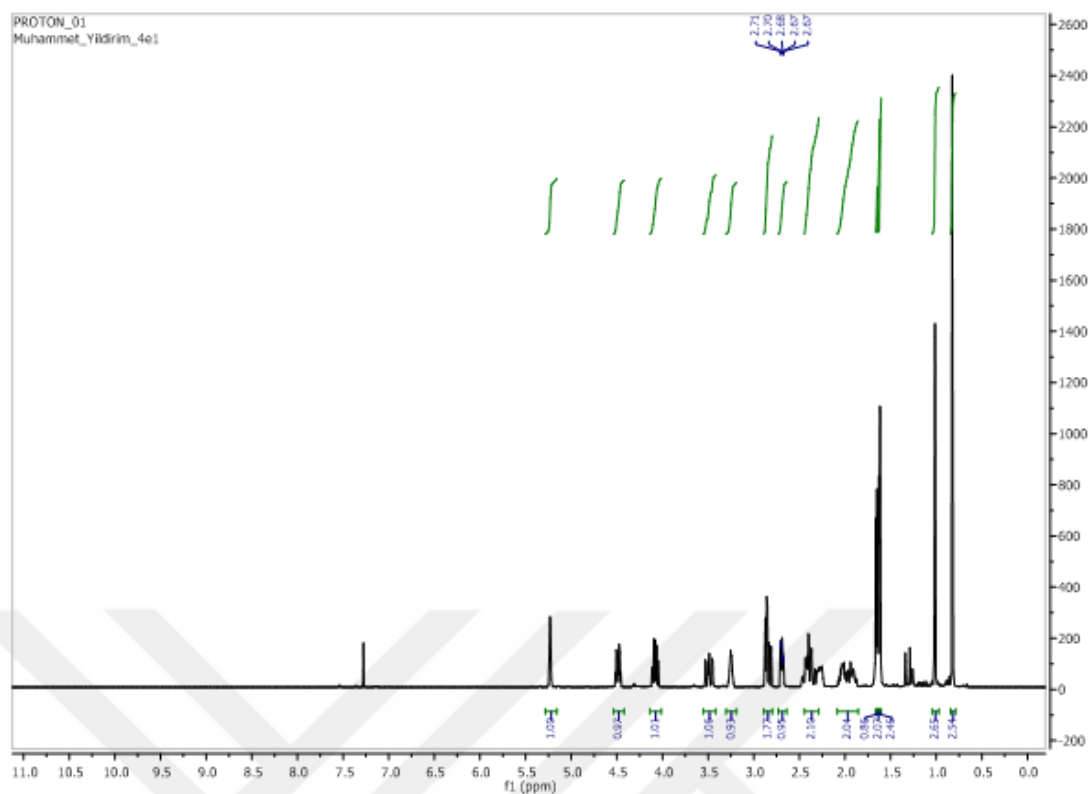


Figure 6-87- ^1H -NMR spectrum of 2.5e

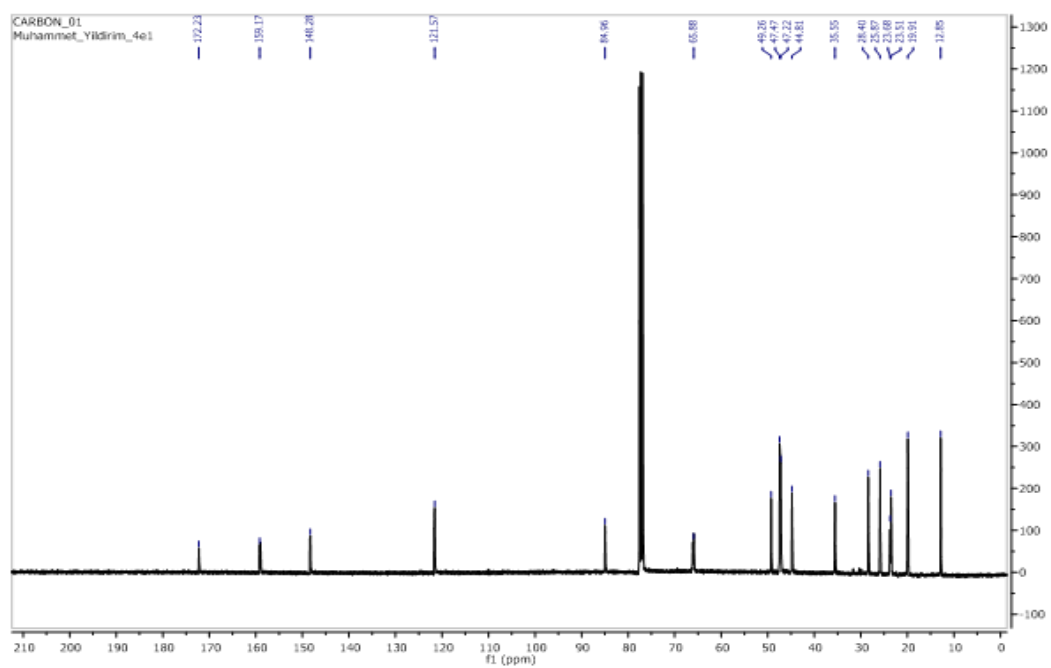


Figure 6-88- ^{13}C -NMR spectrum of 2.5e

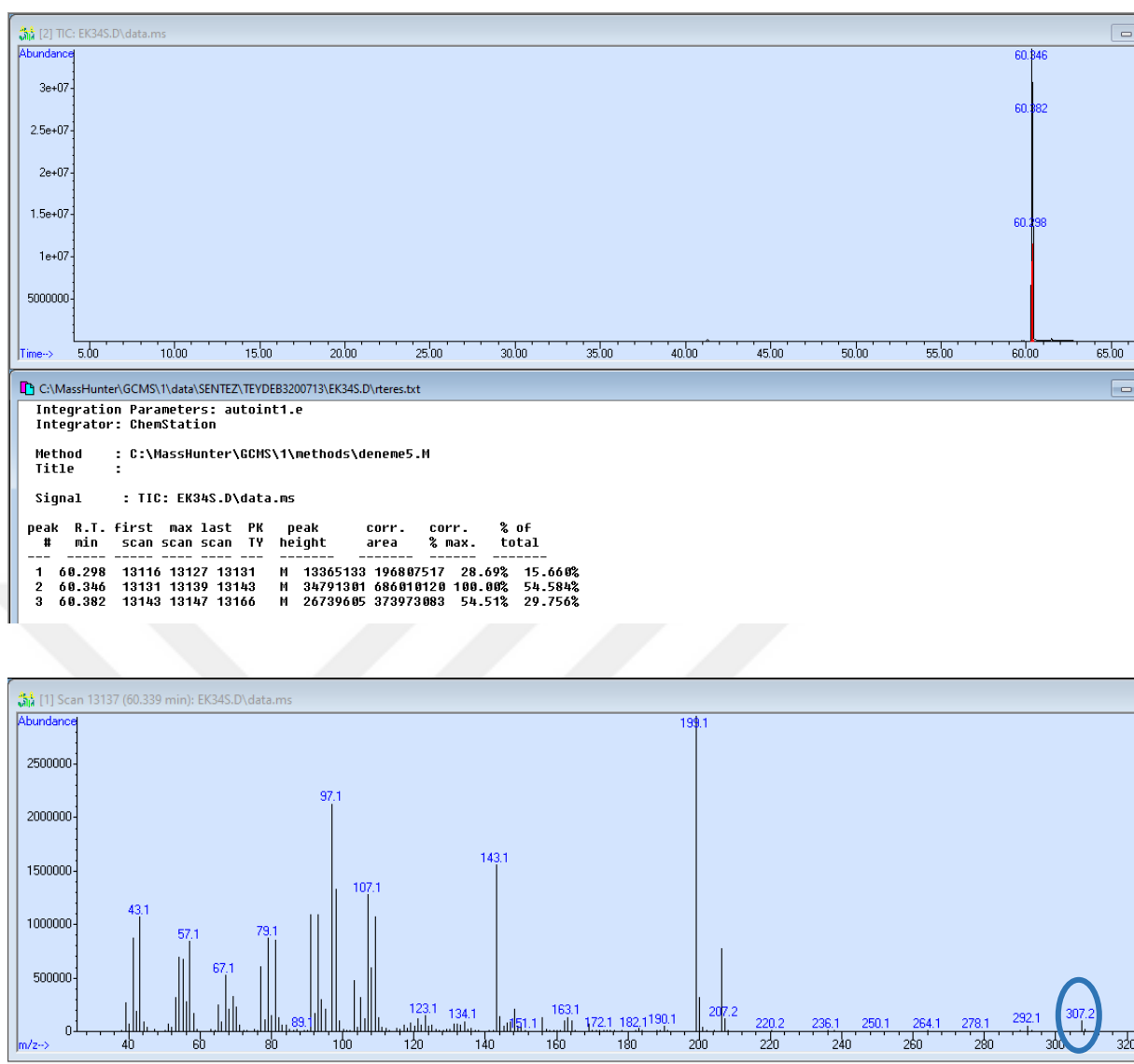


Figure 6-89-GC-MS spectrum of 2.5e

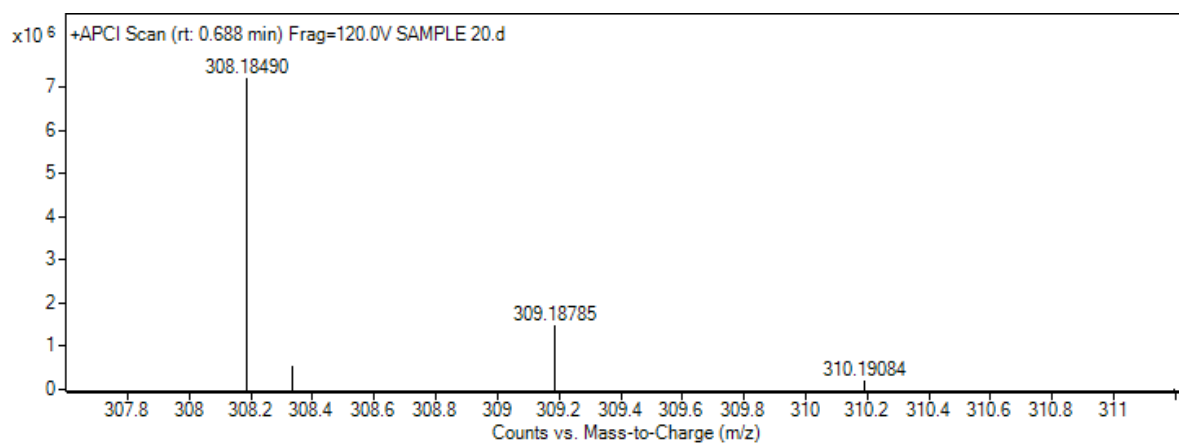


Figure 6-90-(TOF) LC-MS spectrum of 2.5e

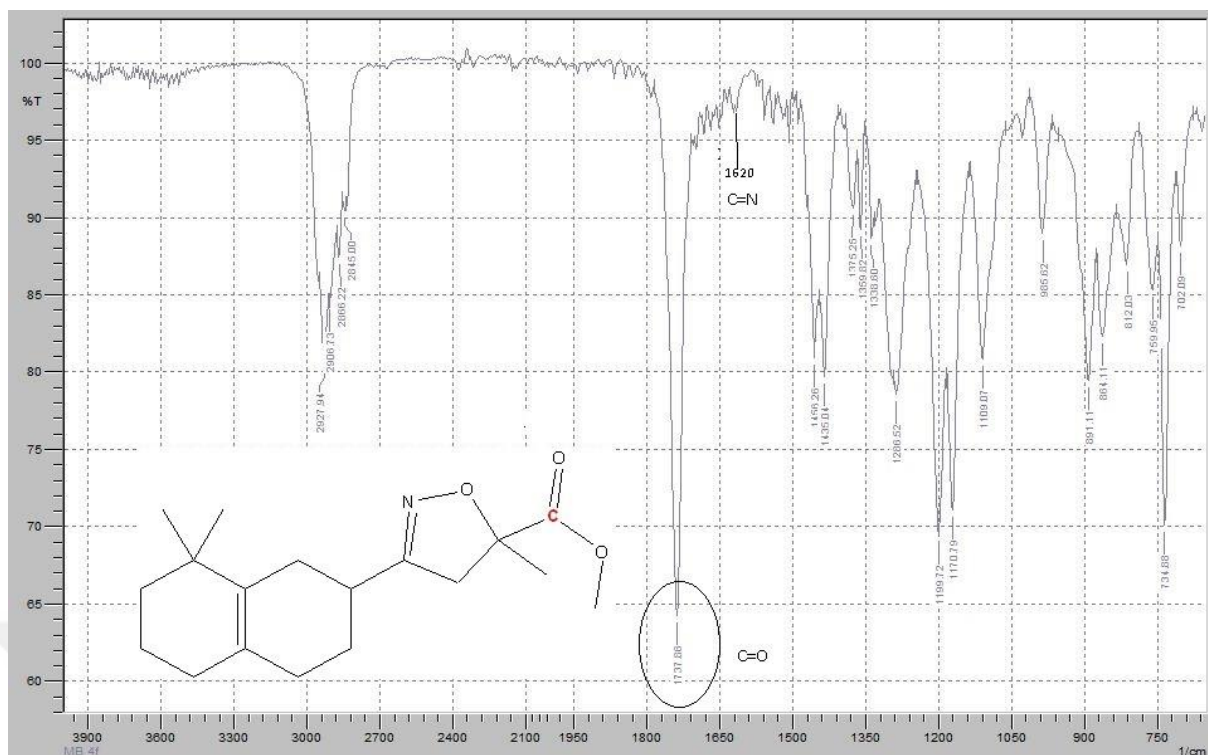


Figure 6-91- IR spectrum of 2.4f

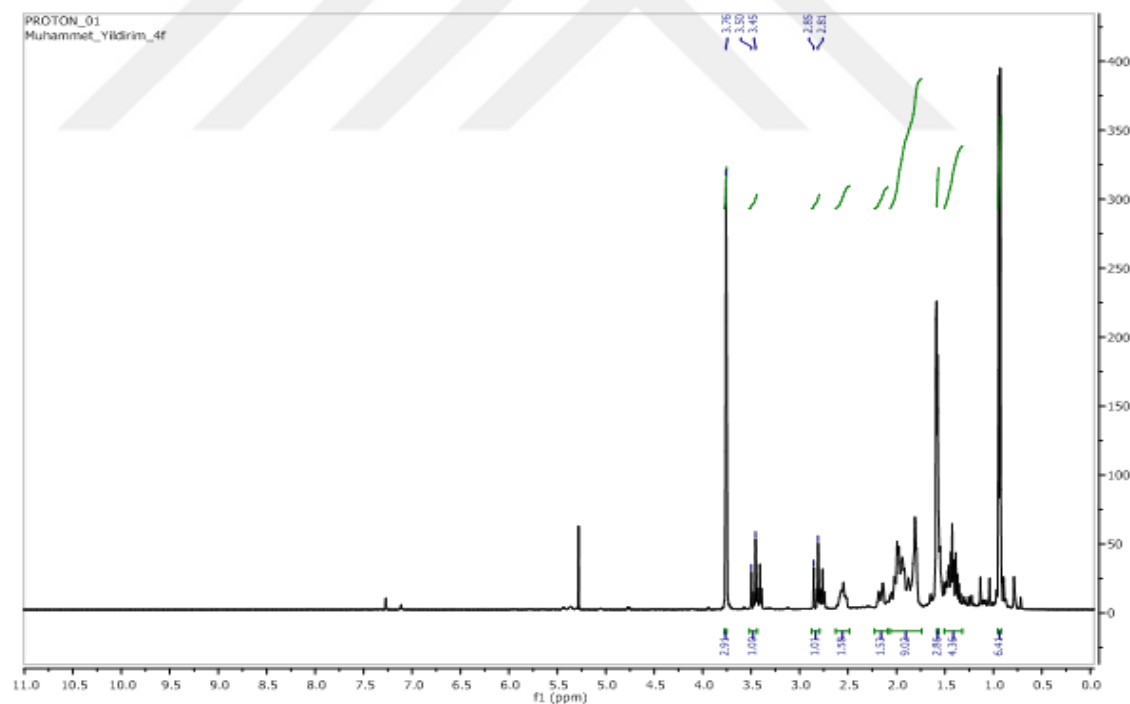


Figure 6-92-¹H-NMR spectrum of 2.4f

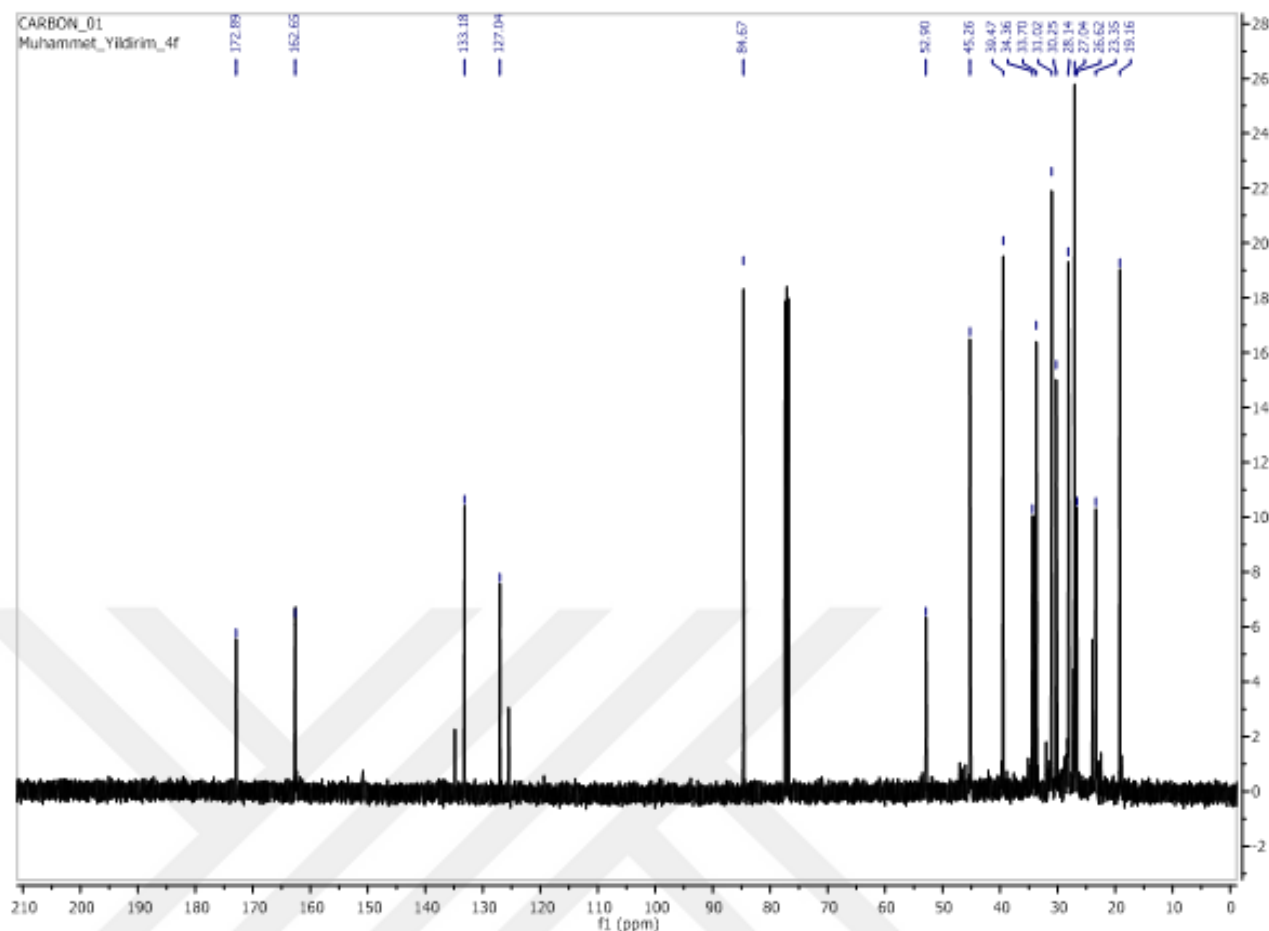
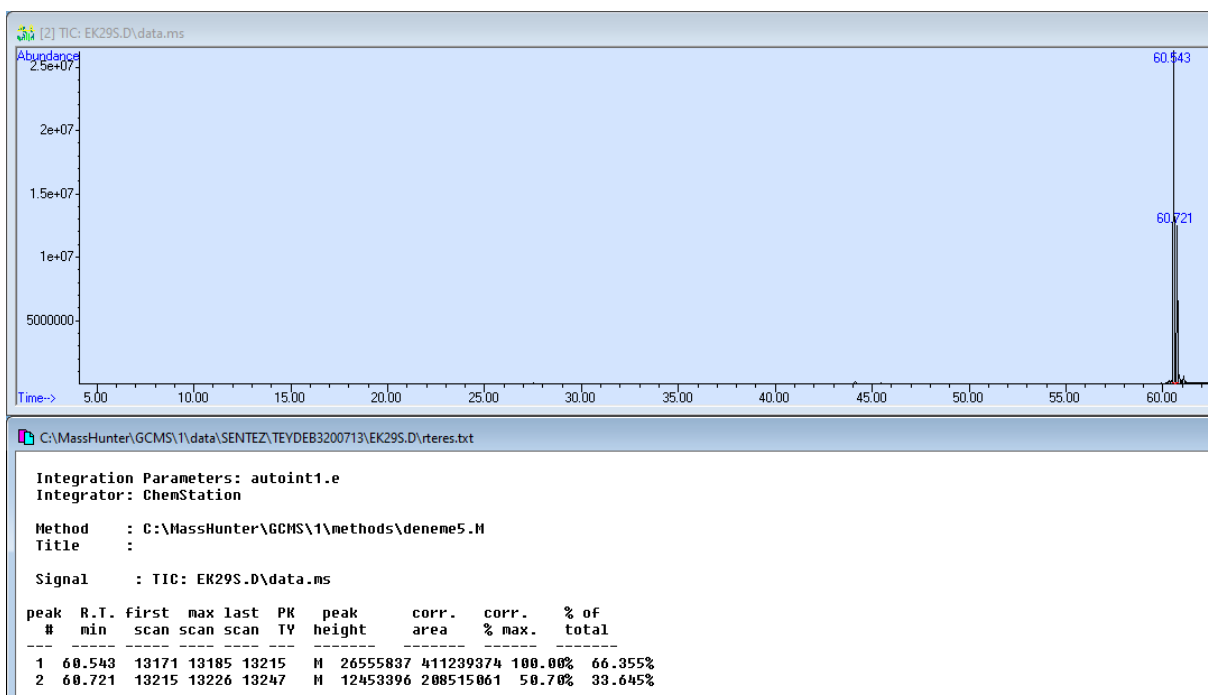


Figure 6-93- ^{13}C -NMR spectrum of 2.4f



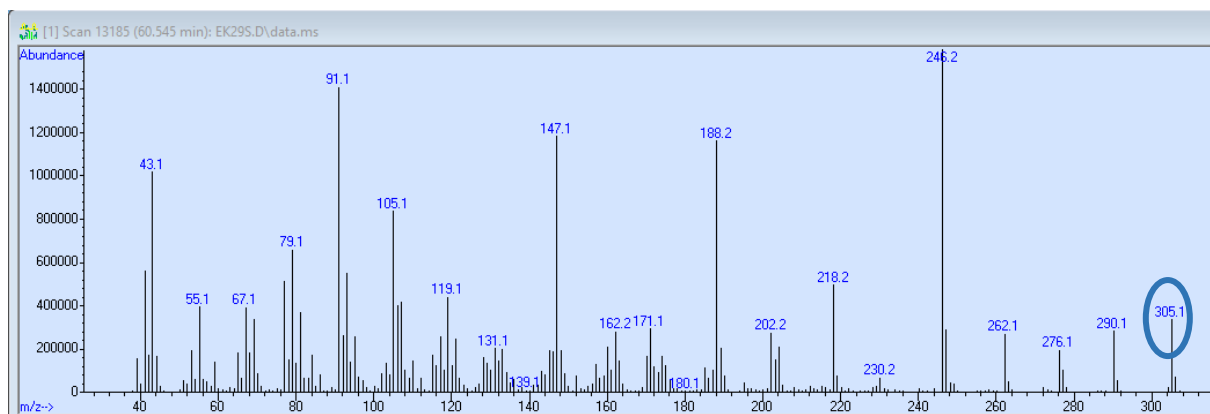


Figure 6-94-GC-MS spectrum of 2.4f

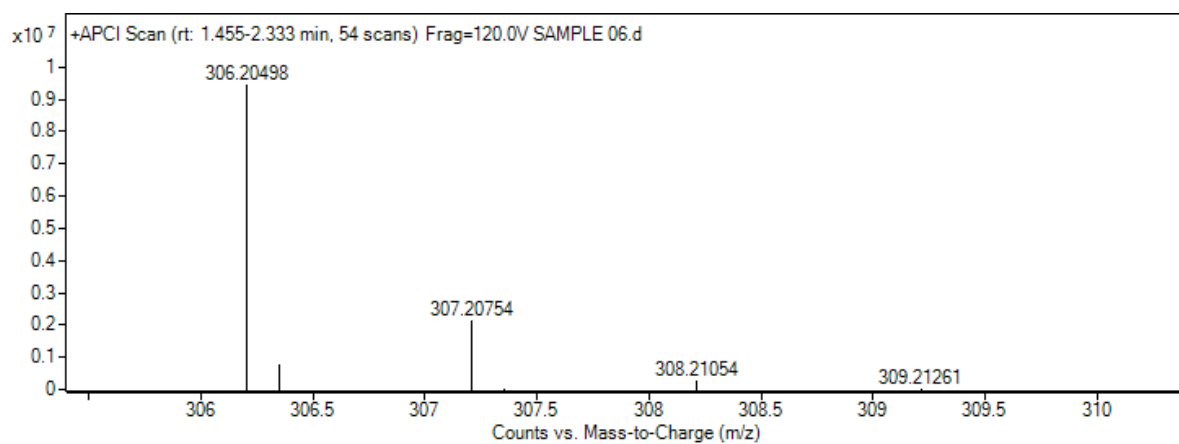


Figure 6-95-(TOF) LC-MS spectrum of 2.4f

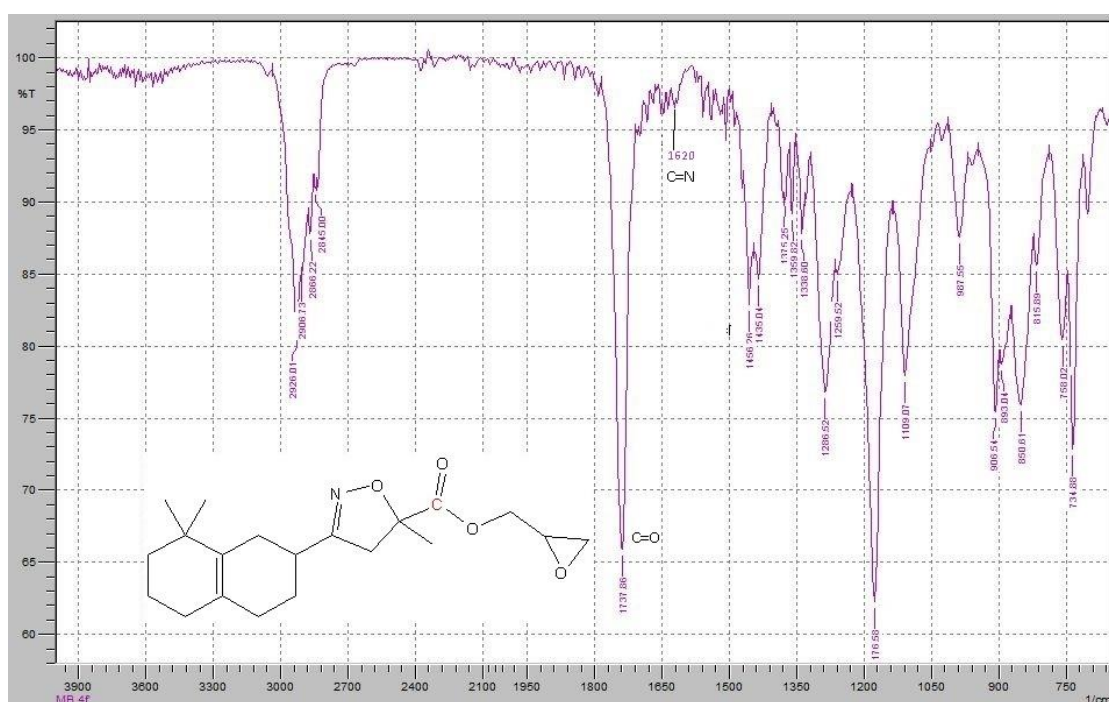


Figure 6-96-IR spectrum of 2.5f

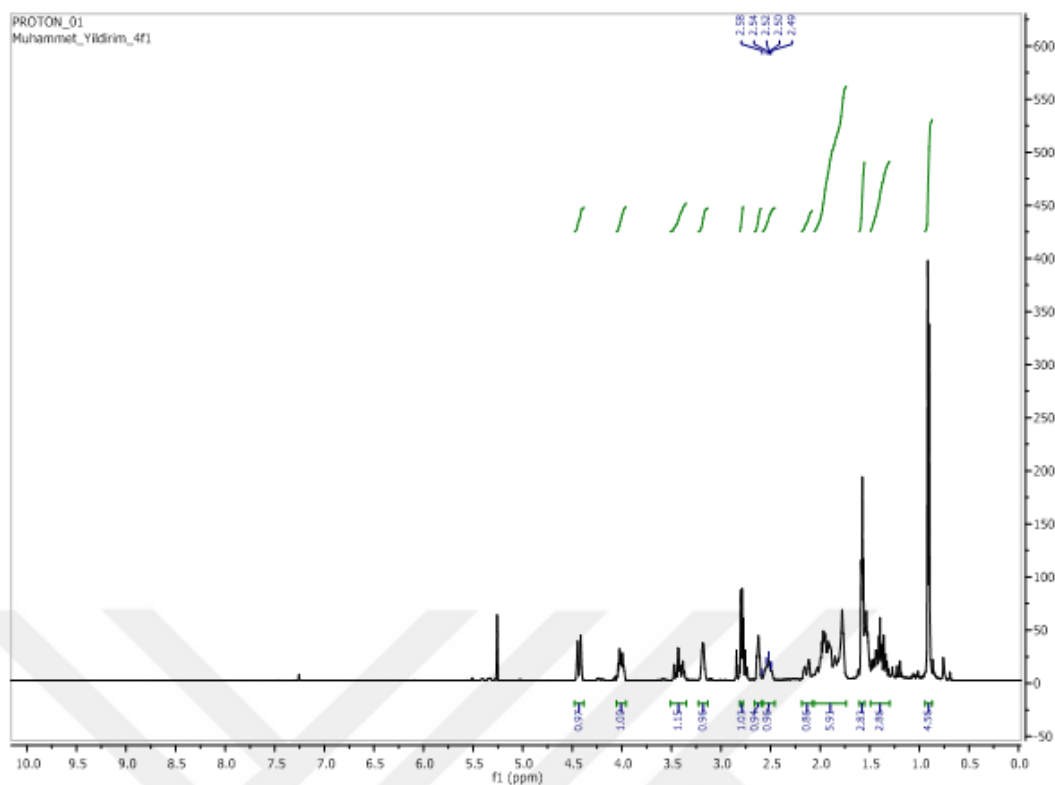


Figure 6-97- ^1H -NMR spectrum of 2.5f

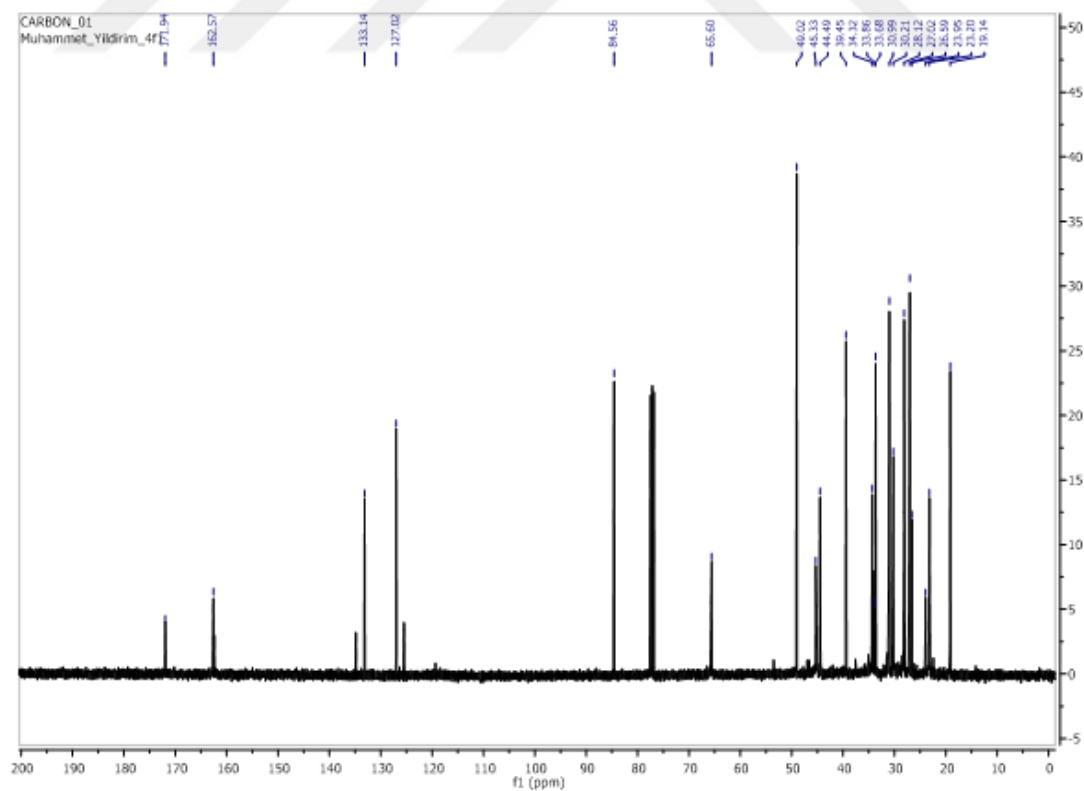


Figure 6-98- ^{13}C -NMR spectrum of 2.5f

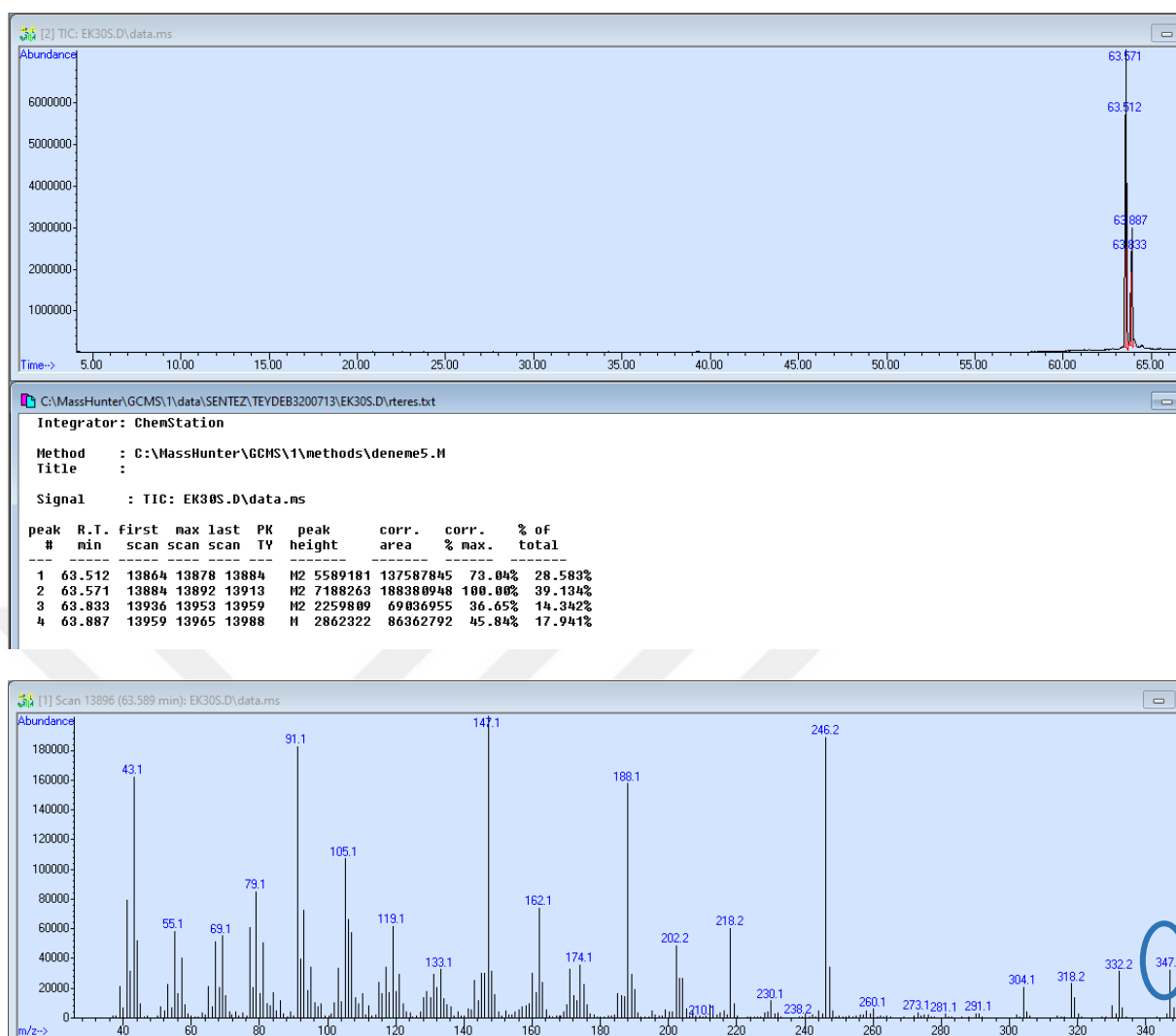


Figure 6-99-GC-MS spectrum of 2.5f

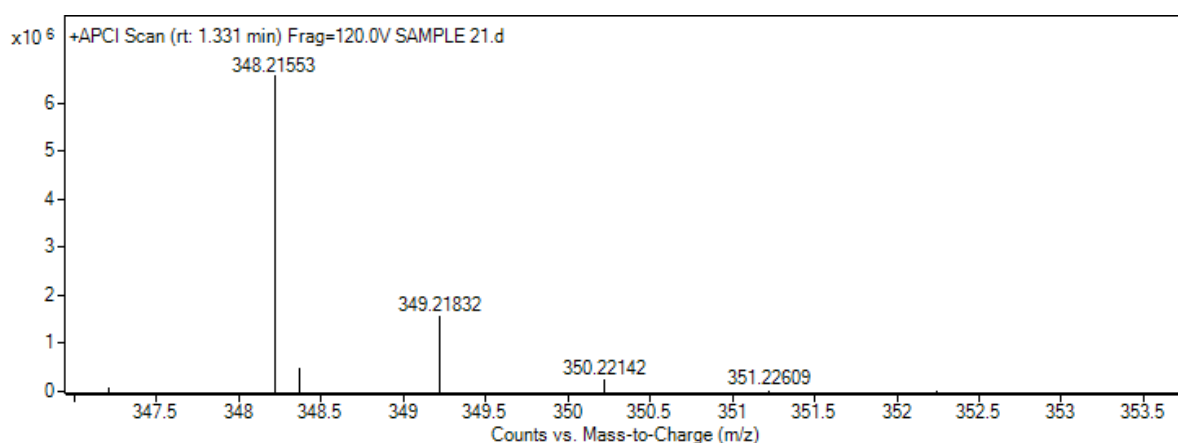


Figure 6-100-(TOF) LC-MS spectrum of 2.5f

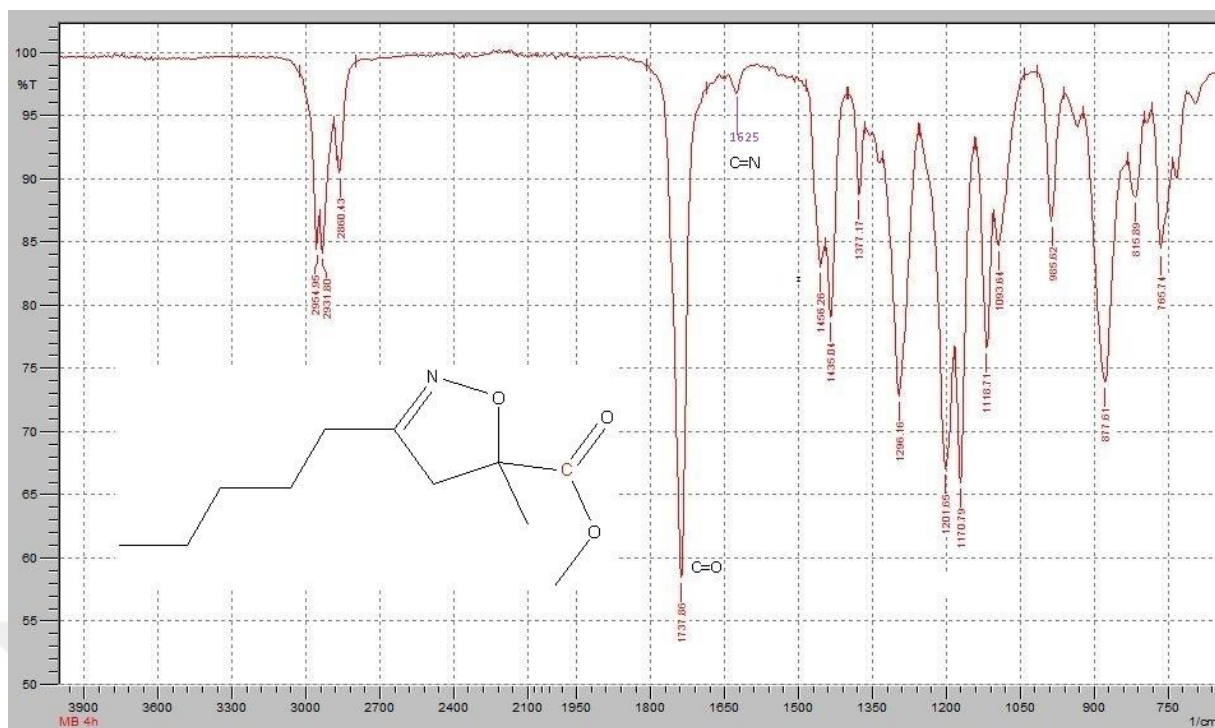


Figure 6-101-IR spectrum of 2.4g

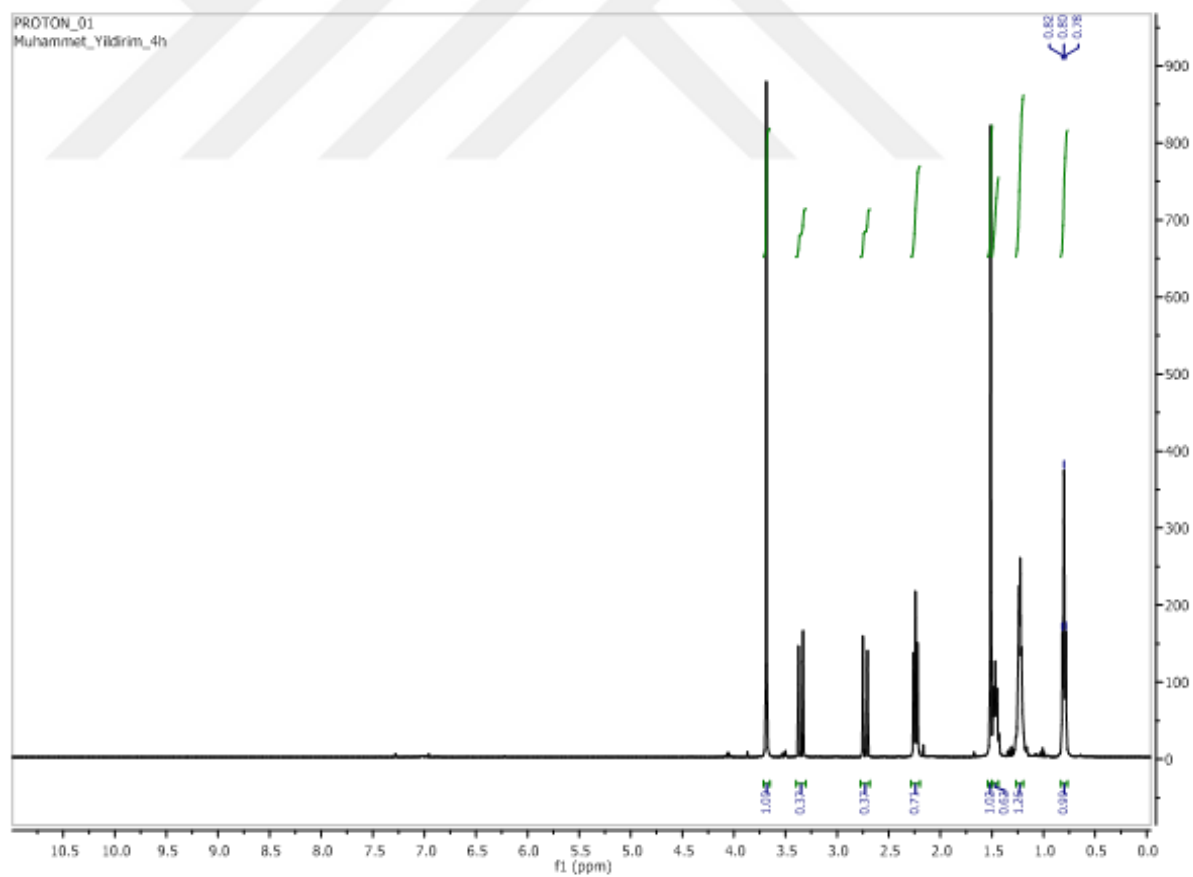


Figure 6-102-¹H-NMR spectrum of 2.4g

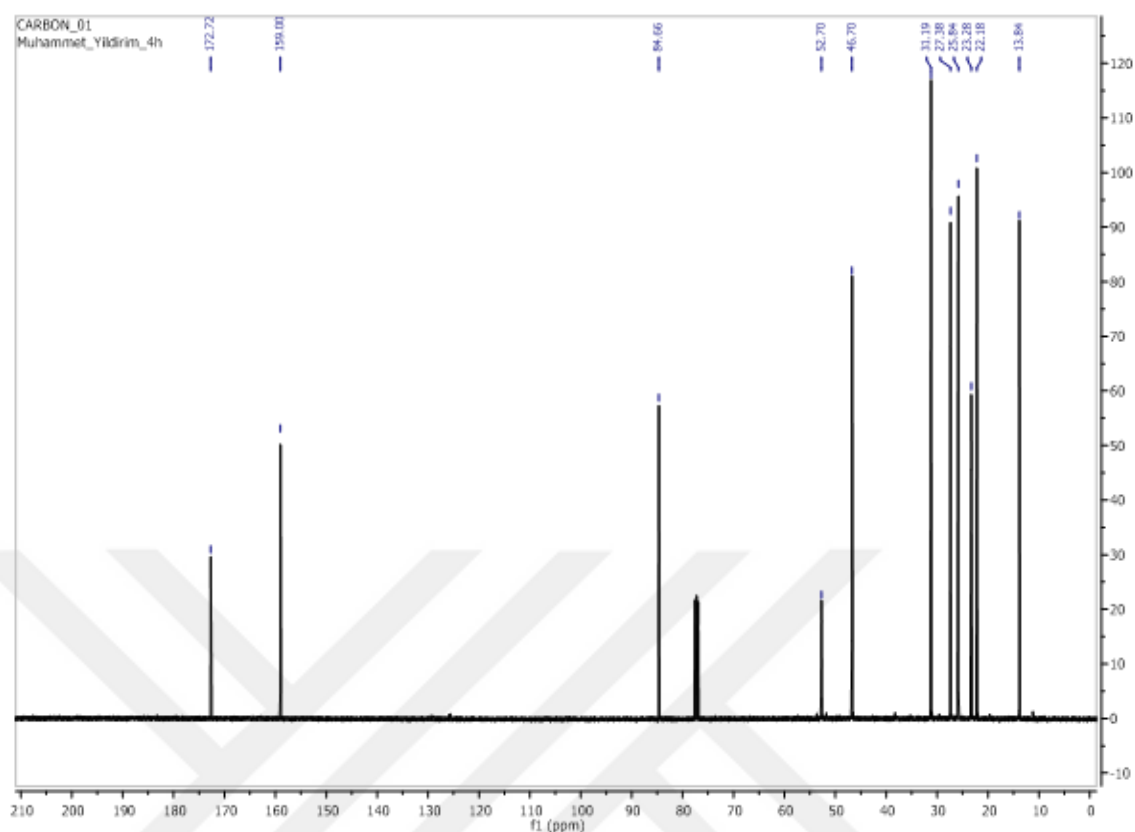
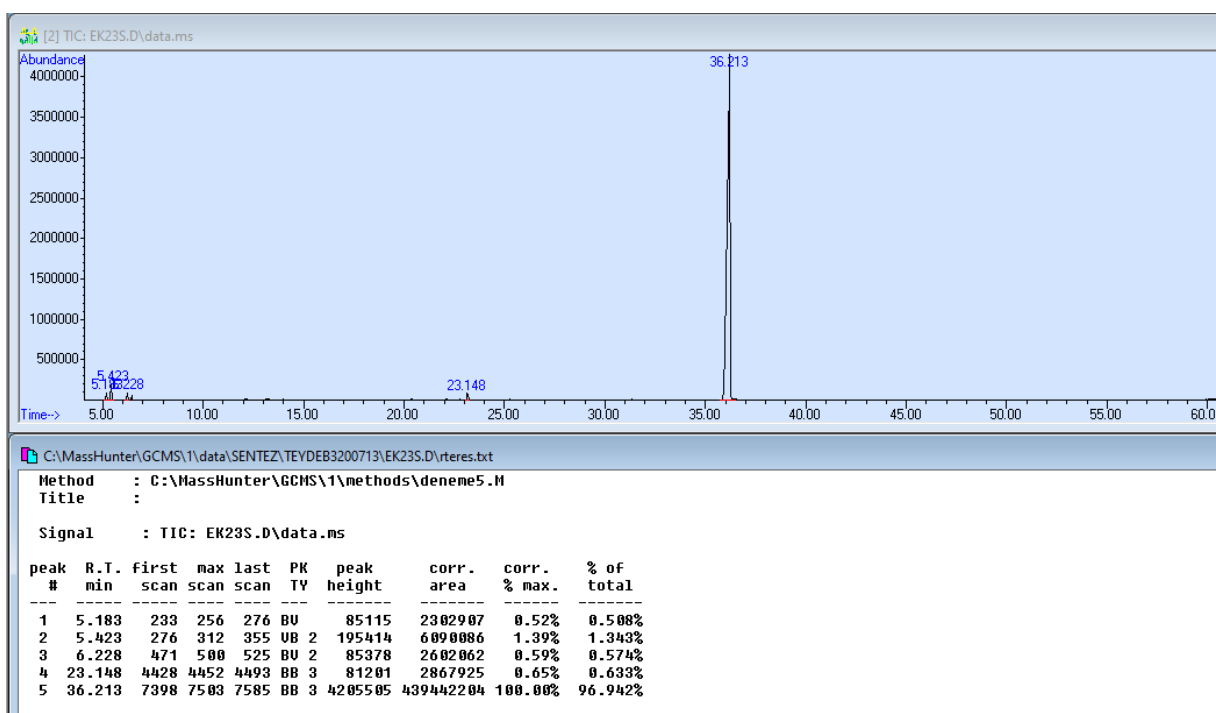


Figure 6-103- ^{13}C -NMR spectrum of 2.4g



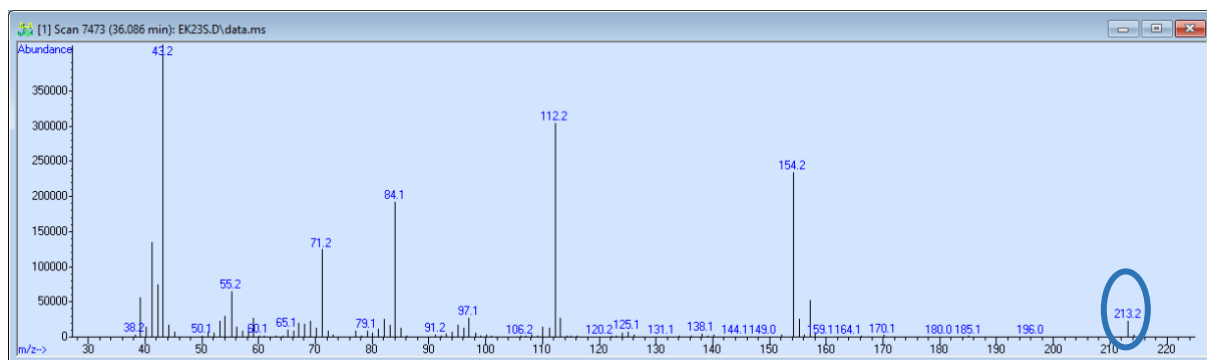


Figure 6-104-GC-MS spectrum of 2.4g

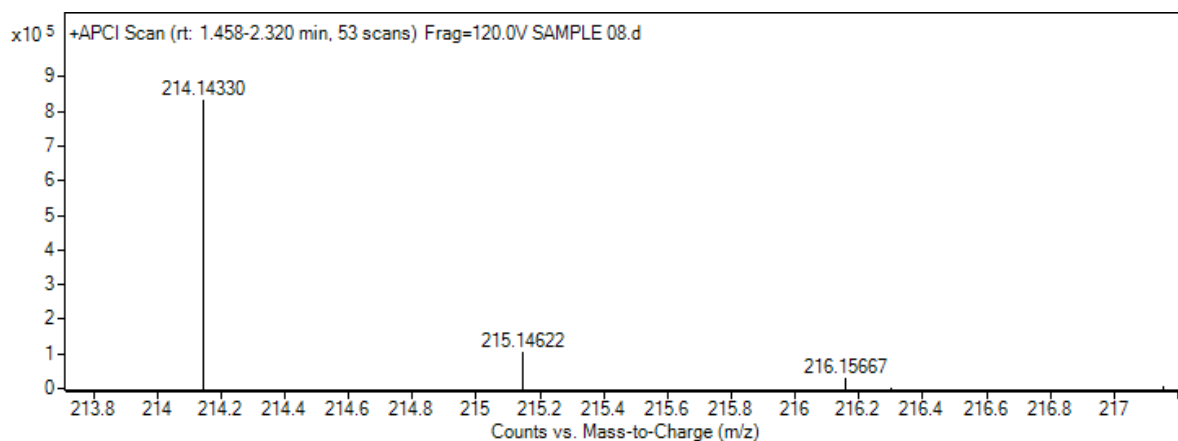


Figure 6-105-HR-MS spectrum of 2.4g

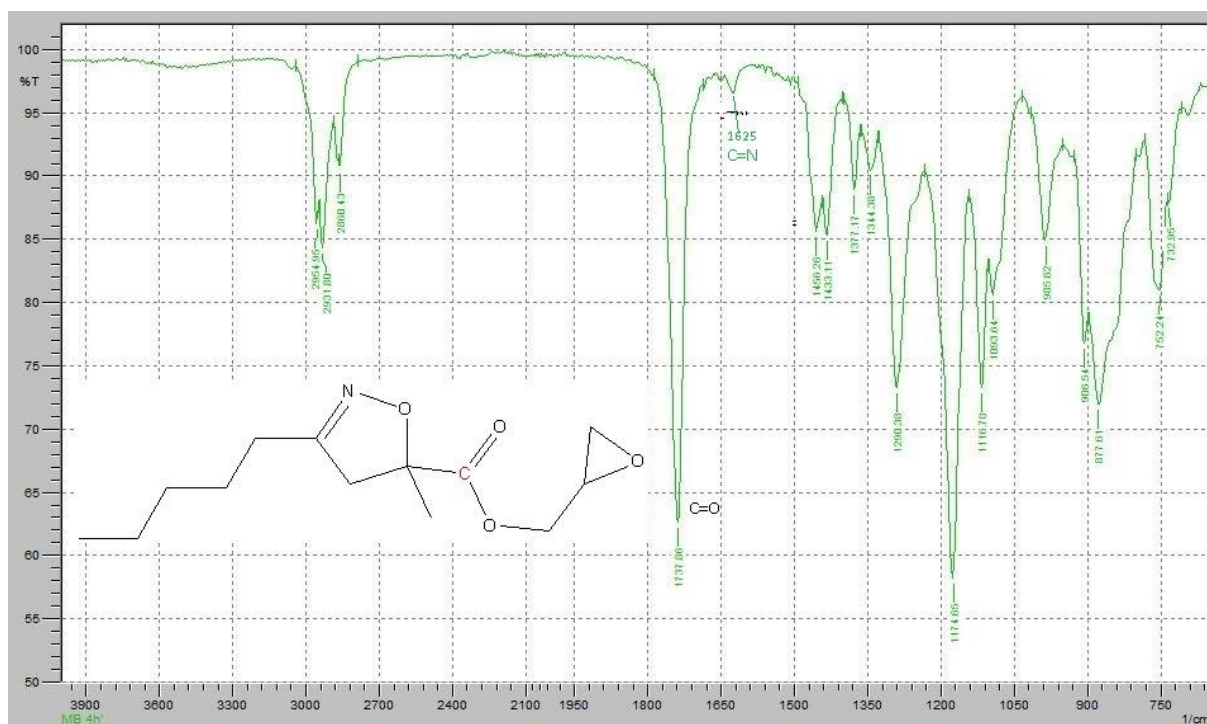


Figure 6-106-IR spectrum of 2.5g

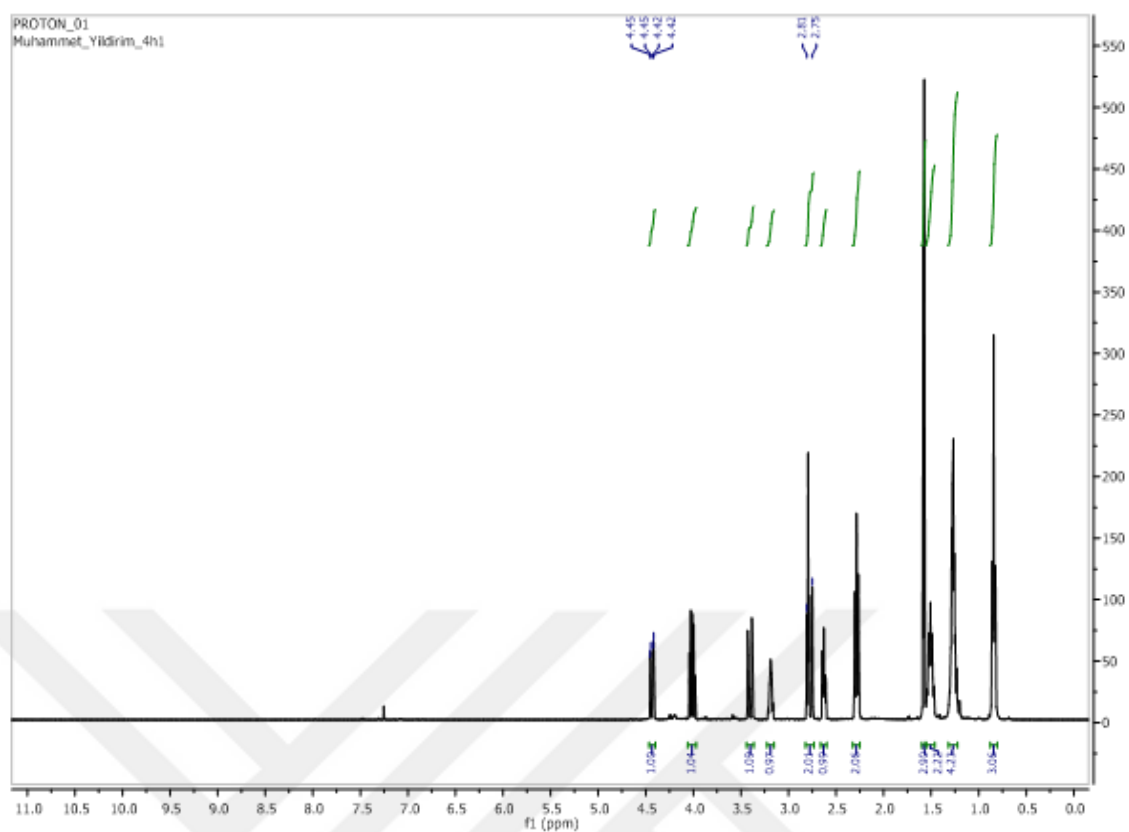


Figure 6-107- ^1H -NMR spectrum of 2.5g

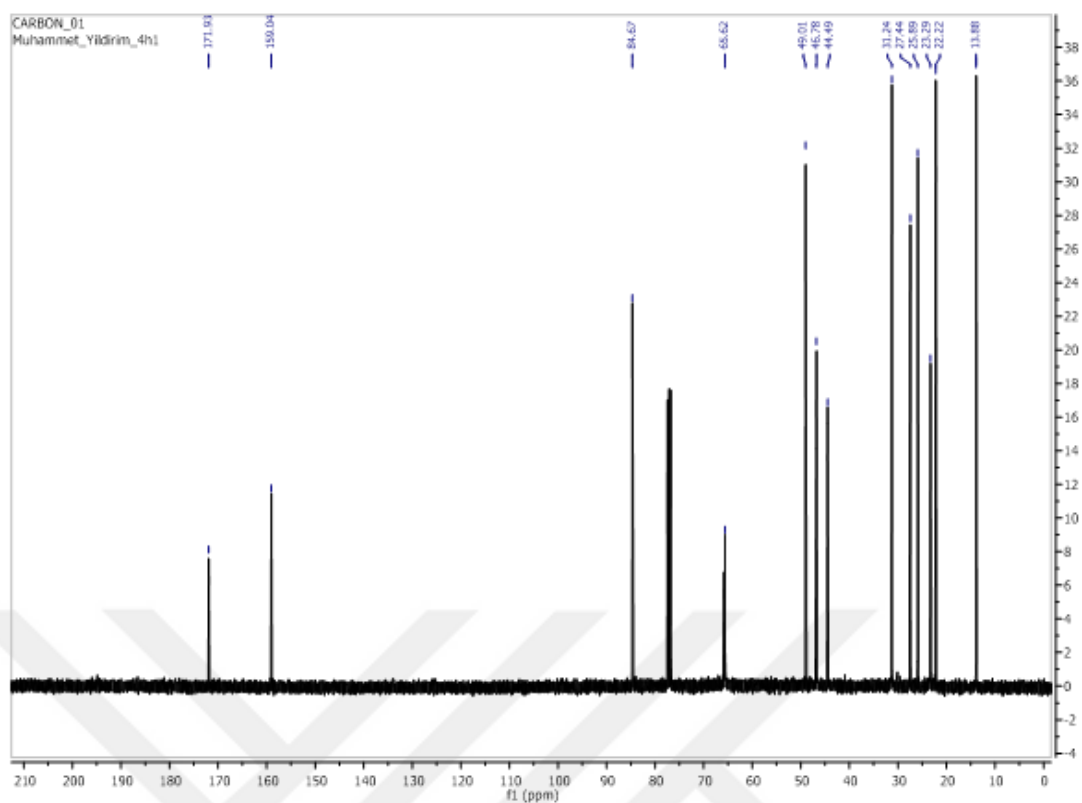
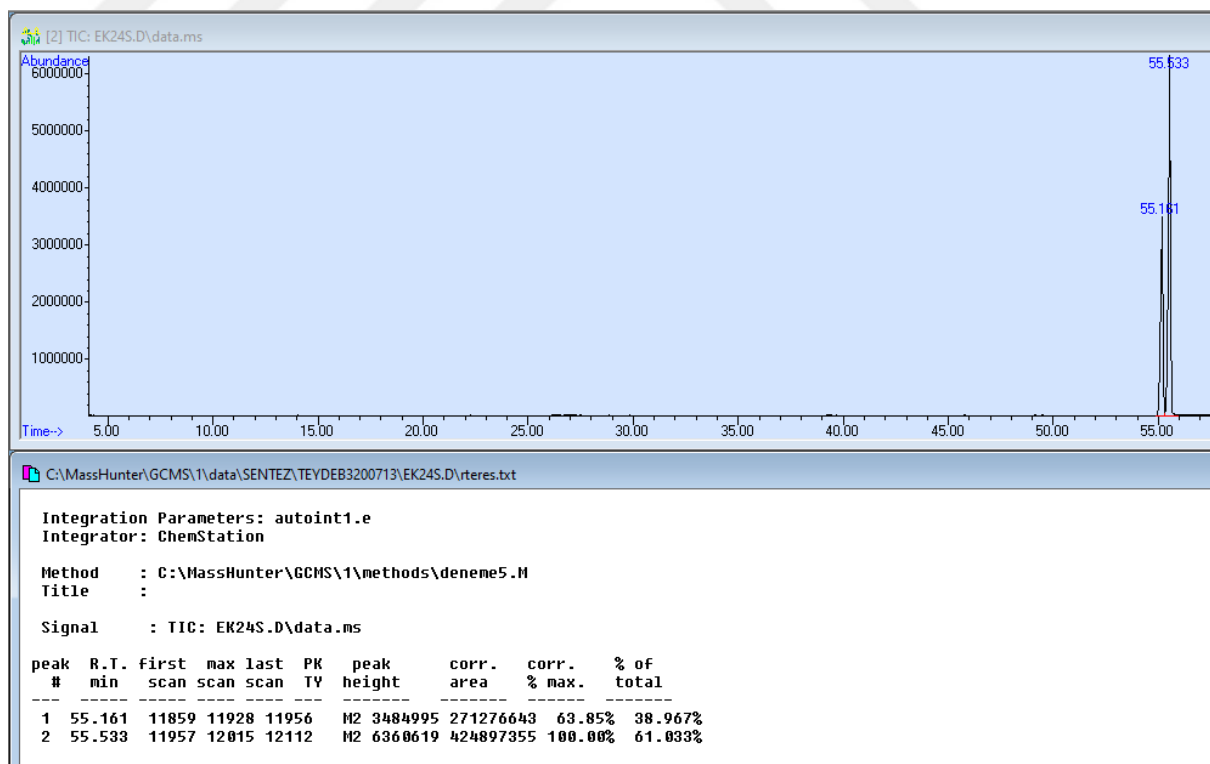


Figure 6-108- ^{13}C -NMR spectrum of 2.5g



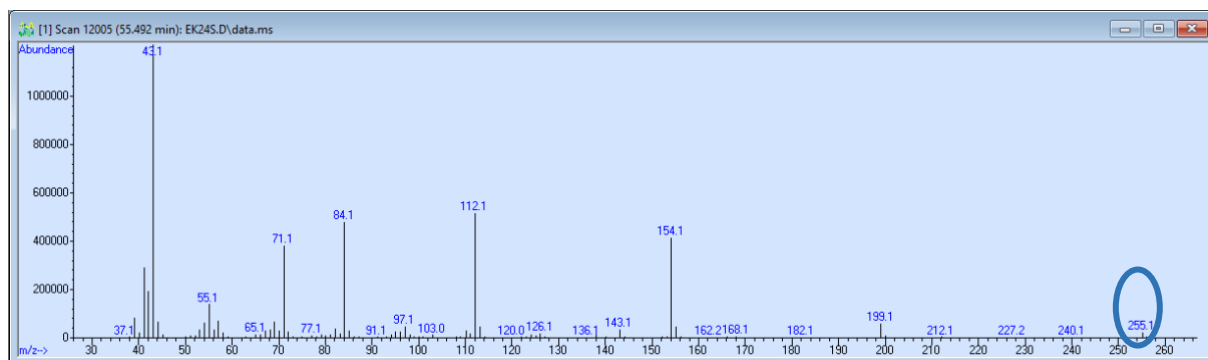


Figure 6-109-GC-MS spectrum of 2.5g

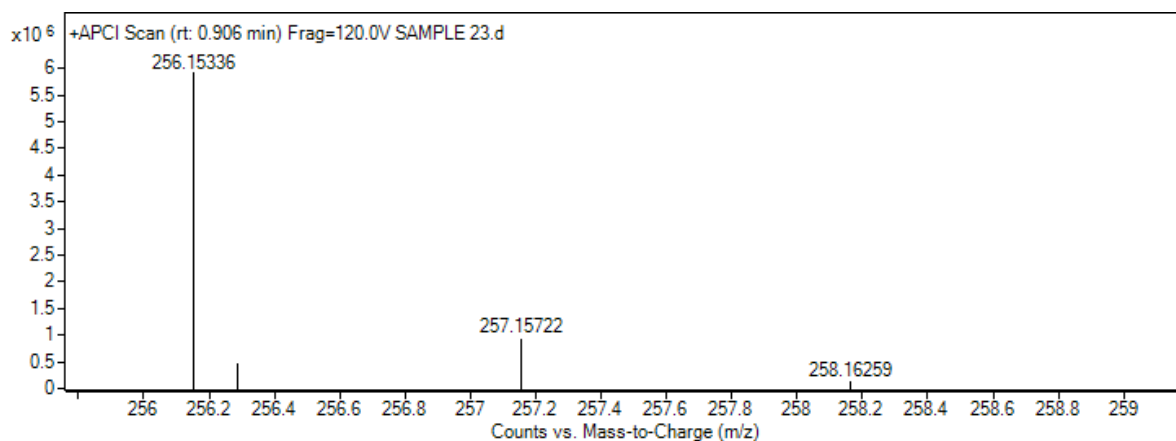


Figure 6-110-(TOF) LC-MS spectrum of 2.5g

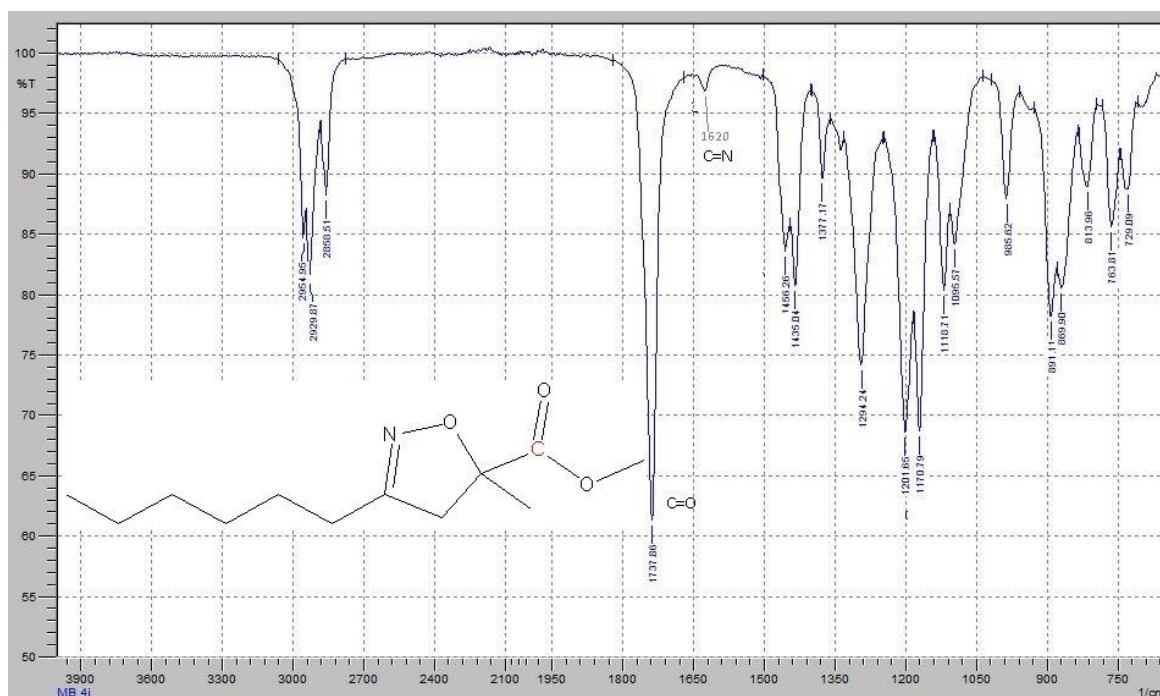


Figure 6-111-IR spectrum of 2.4h

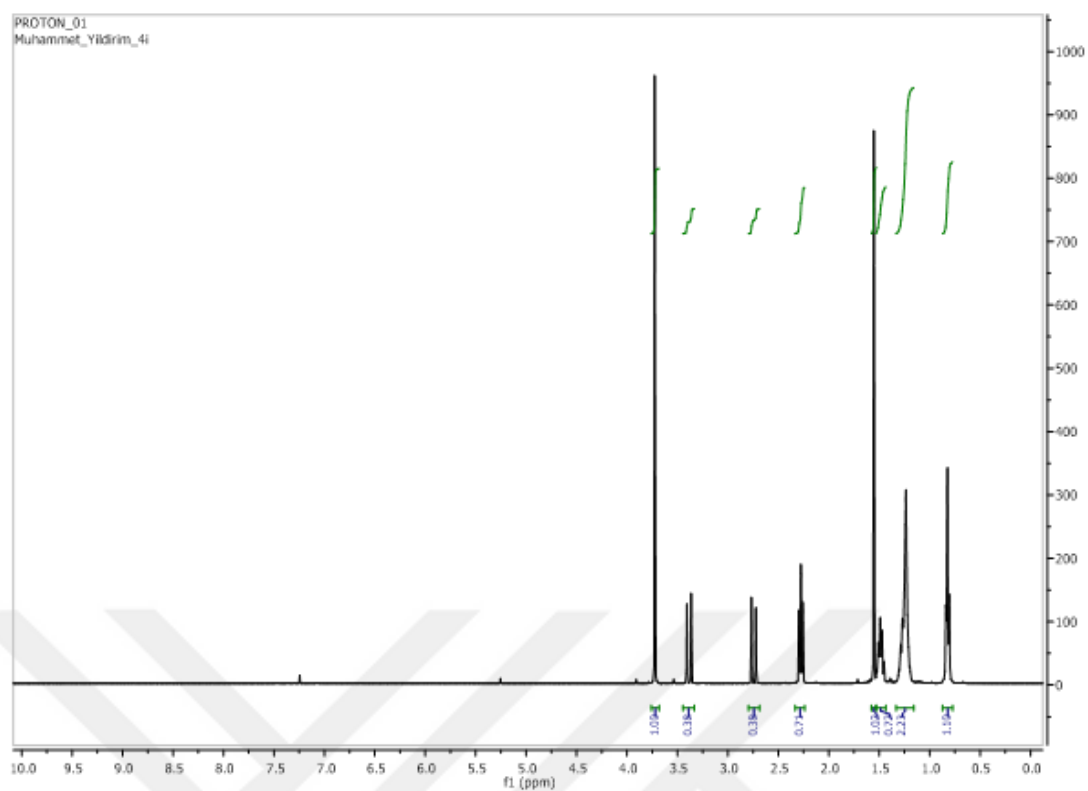


Figure 6-112- ^1H -NMR spectrum of 2.4h

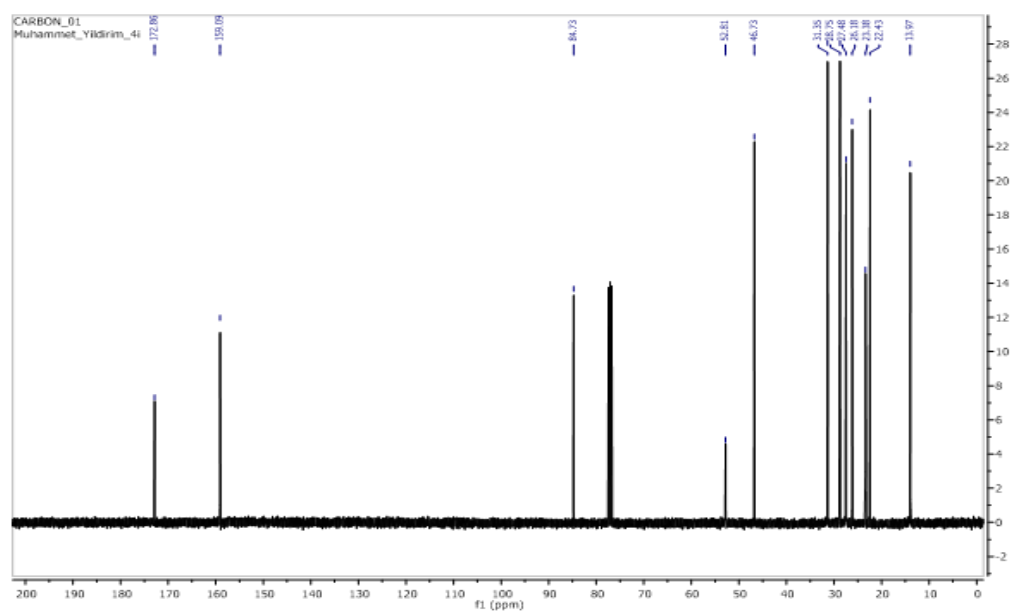


Figure 6-113- ^{13}C -NMR spectrum of 2.4h

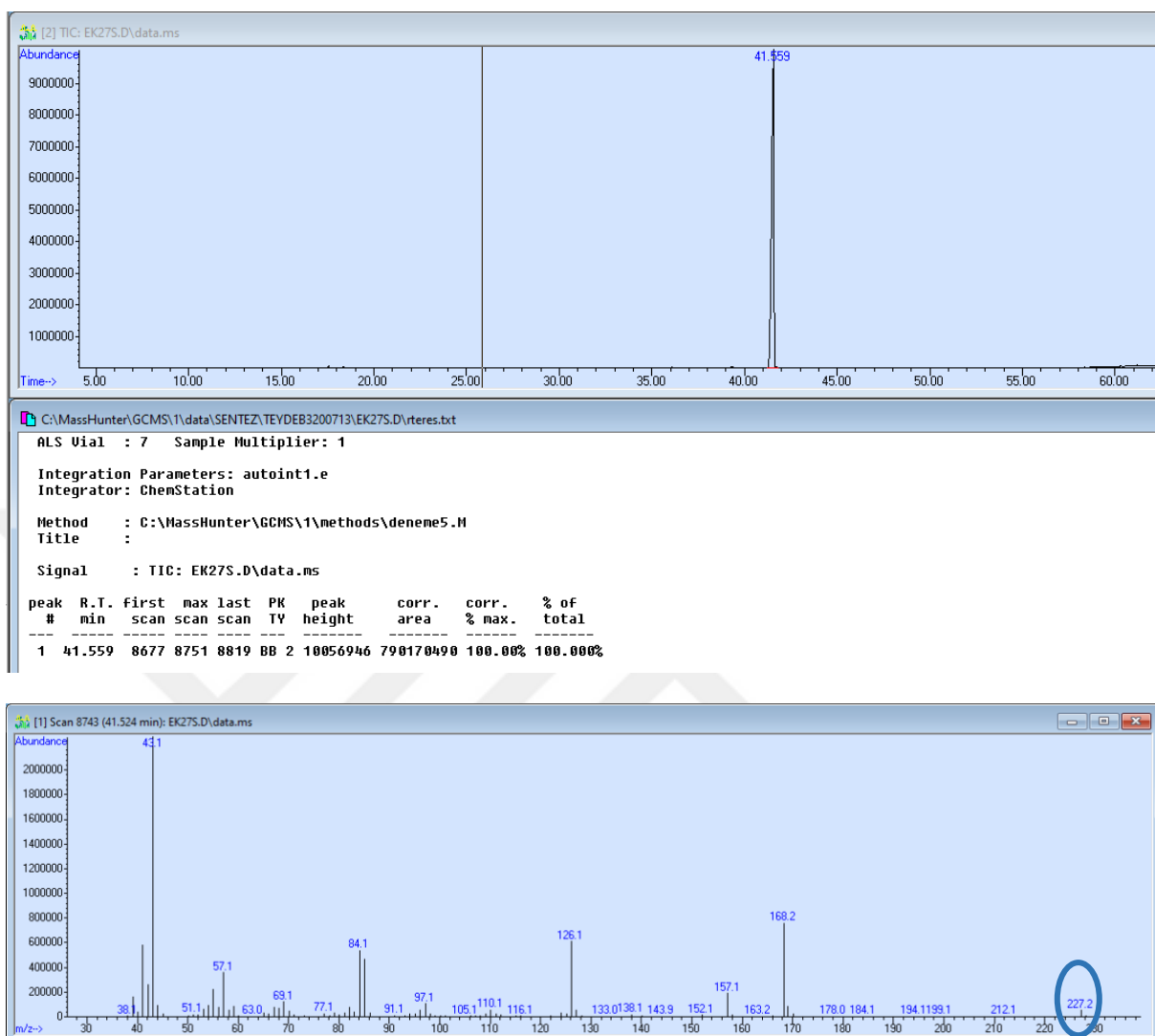


Figure 6-114-GC-MS spectrum of 2.4h

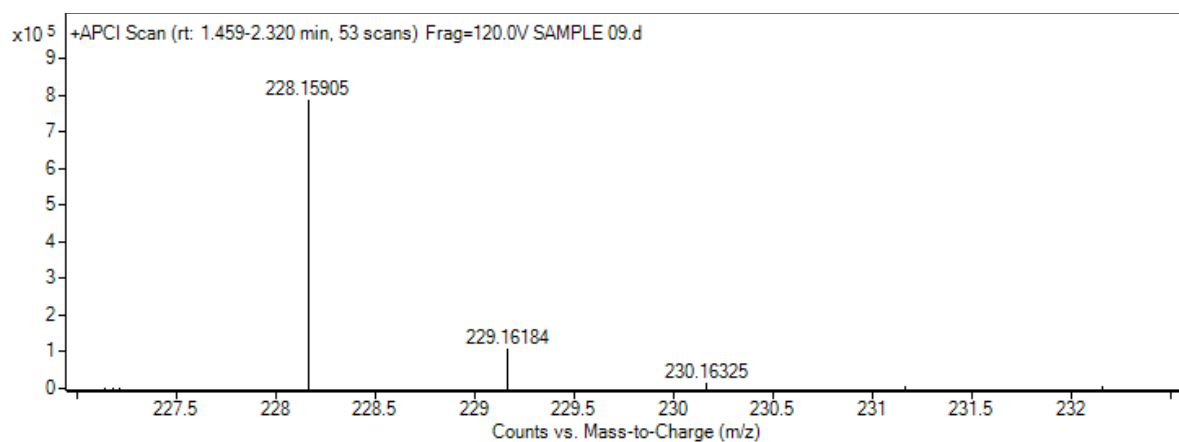


Figure 6-115-(TOF) LC-MS spectrum of 2.4h

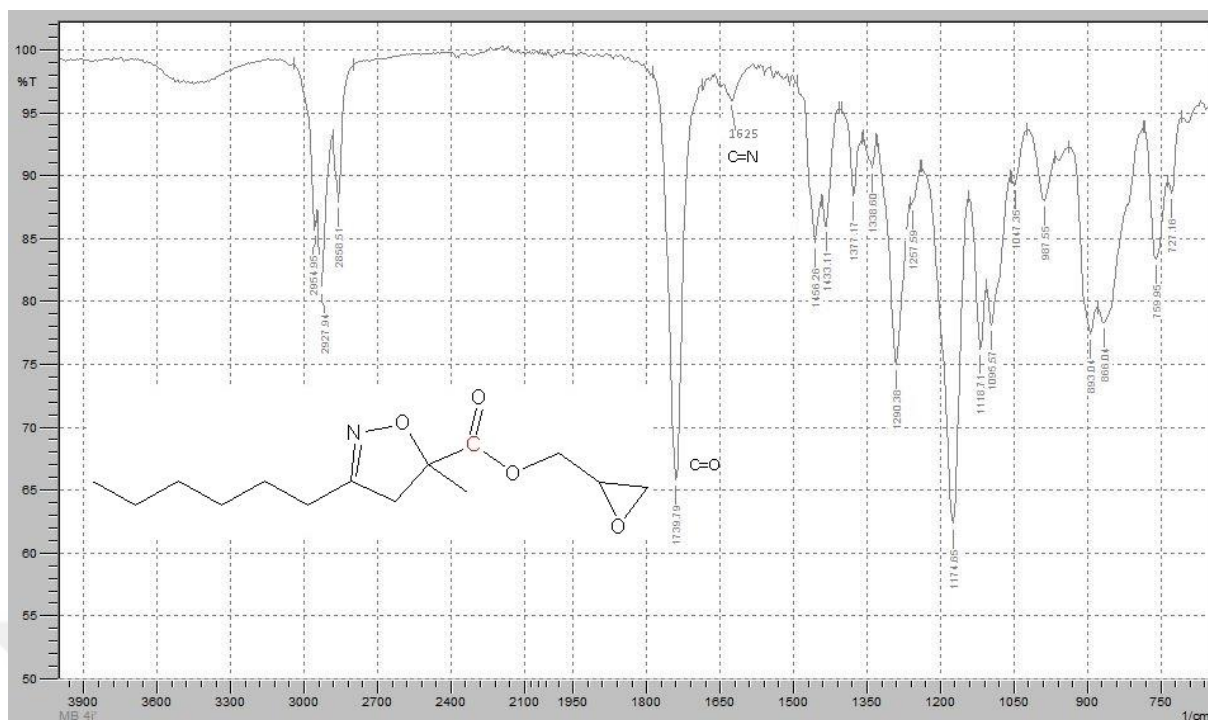


Figure 6-116-IR spectrum of 2.5h

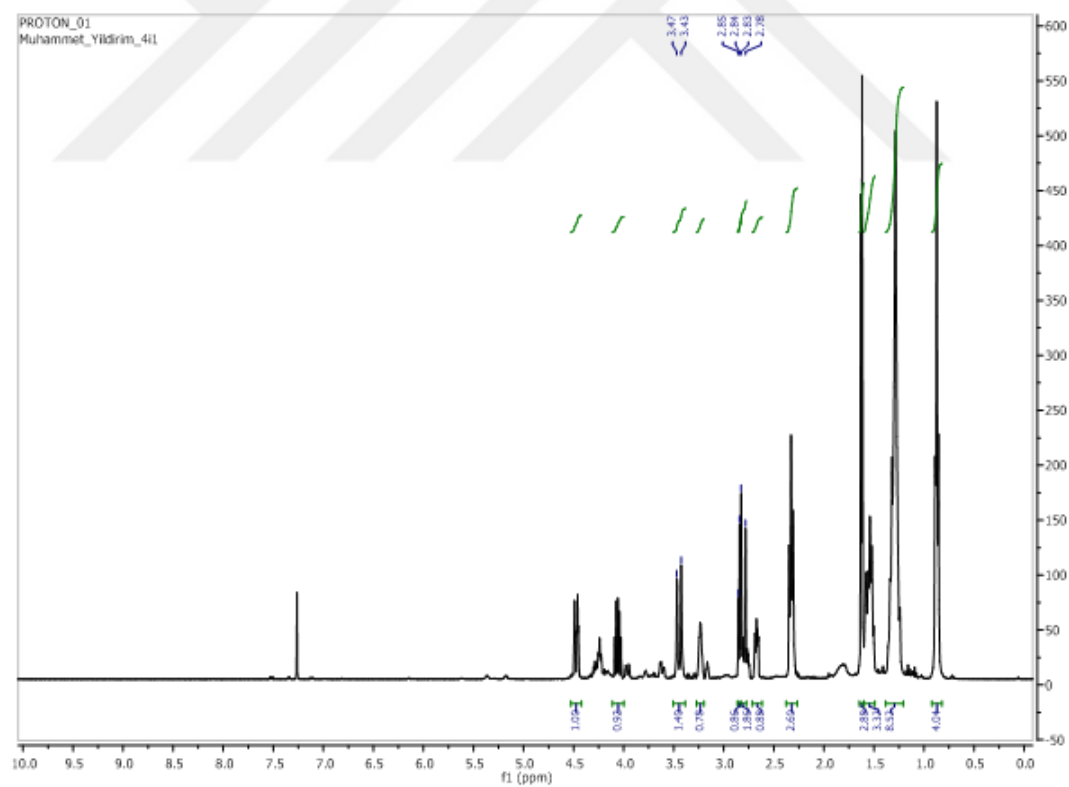


Figure 6-117-¹H-NMR spectrum of 2.5h

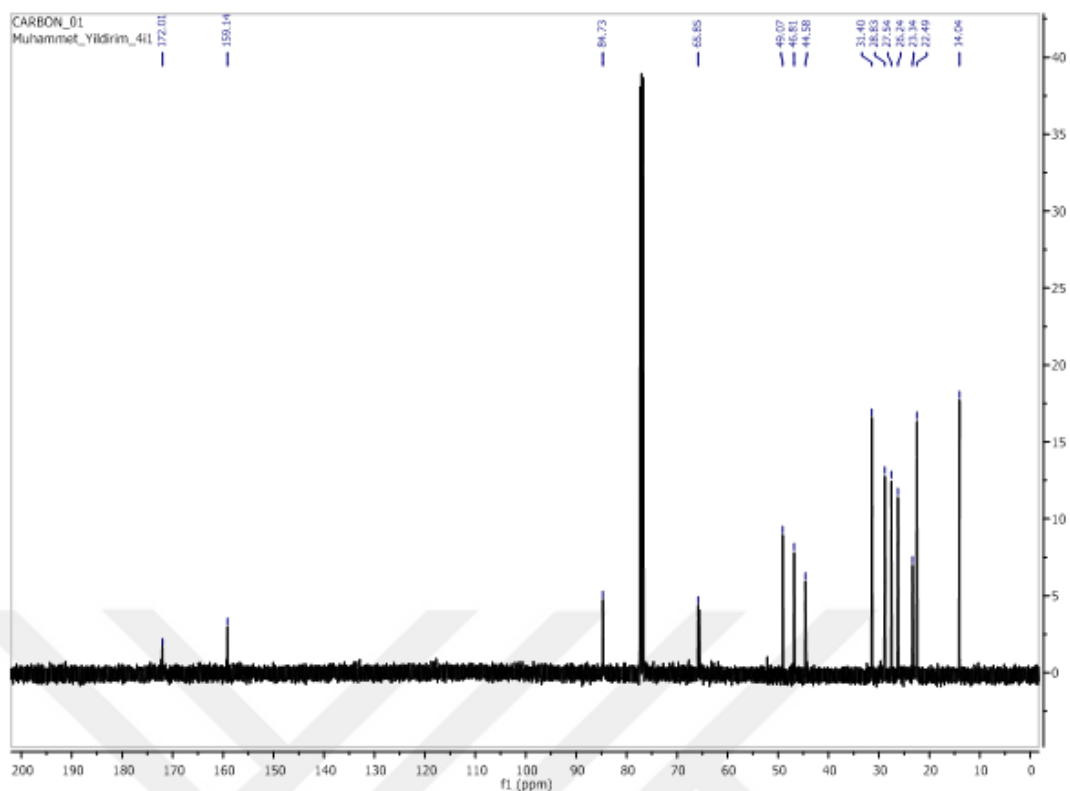
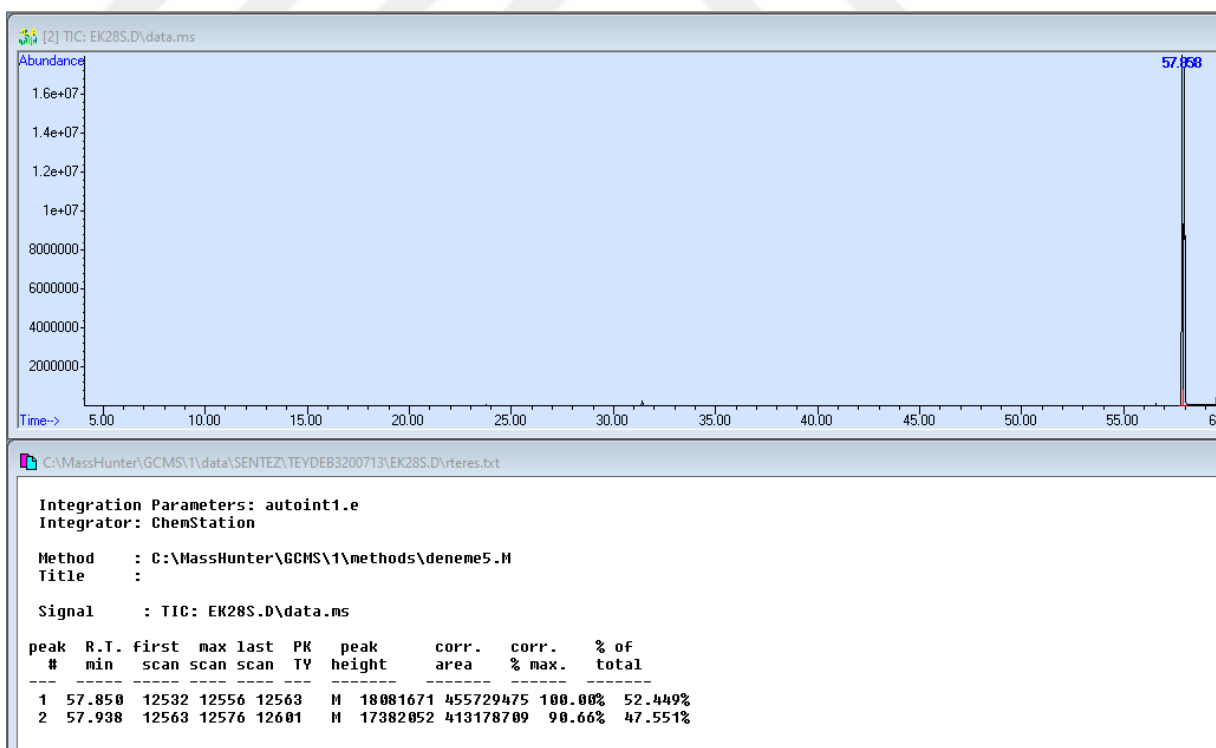


Figure 6-118- ^{13}C -NMR spectrum of 2.5h



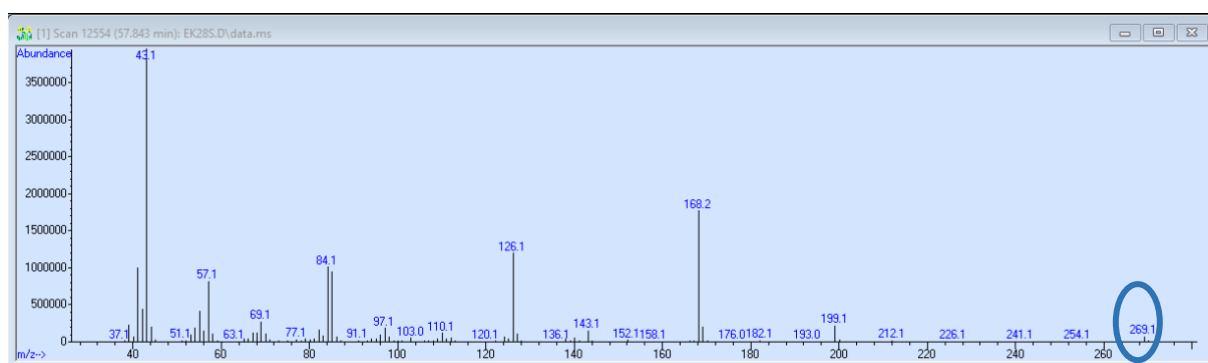


Figure 6-119-GC-MS spectrum of 2.5h

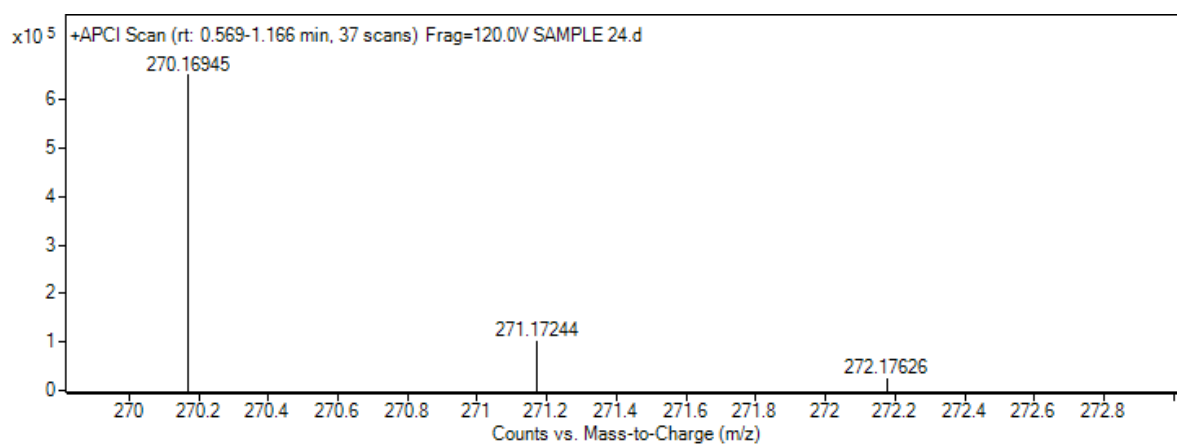


Figure 6-120-(TOF) LC-MS spectrum of 2.5h

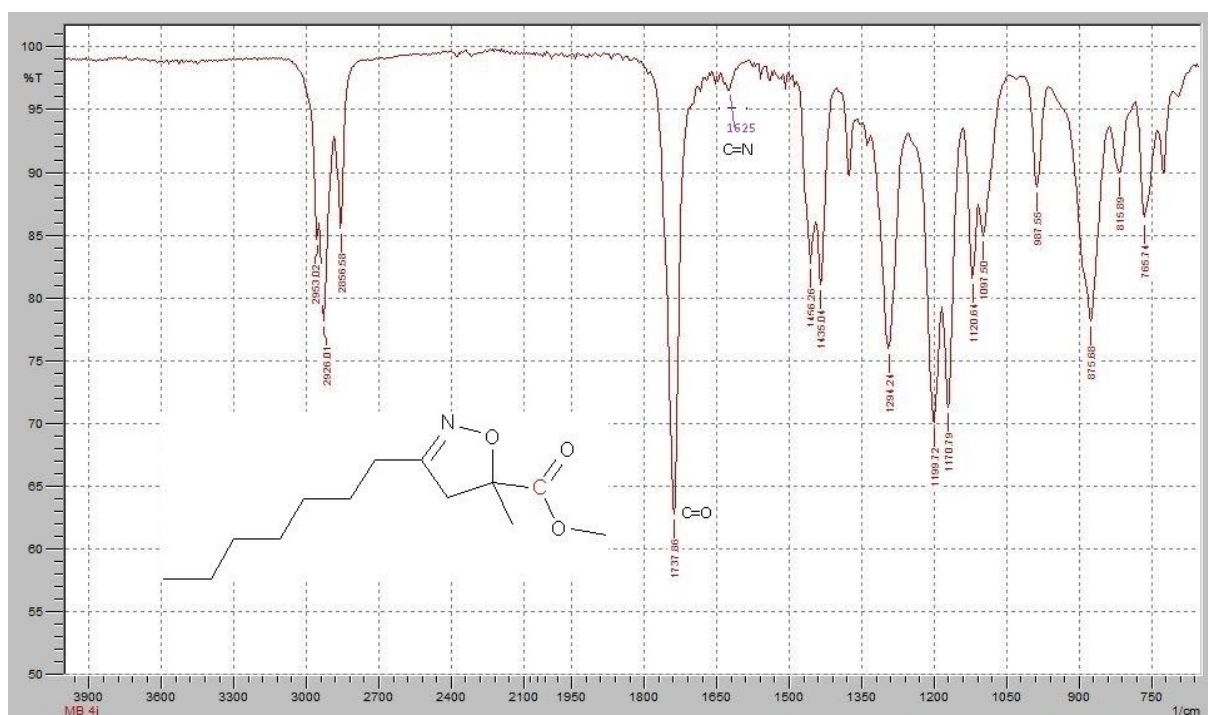


Figure 6-121-IR spectrum of 2.4i

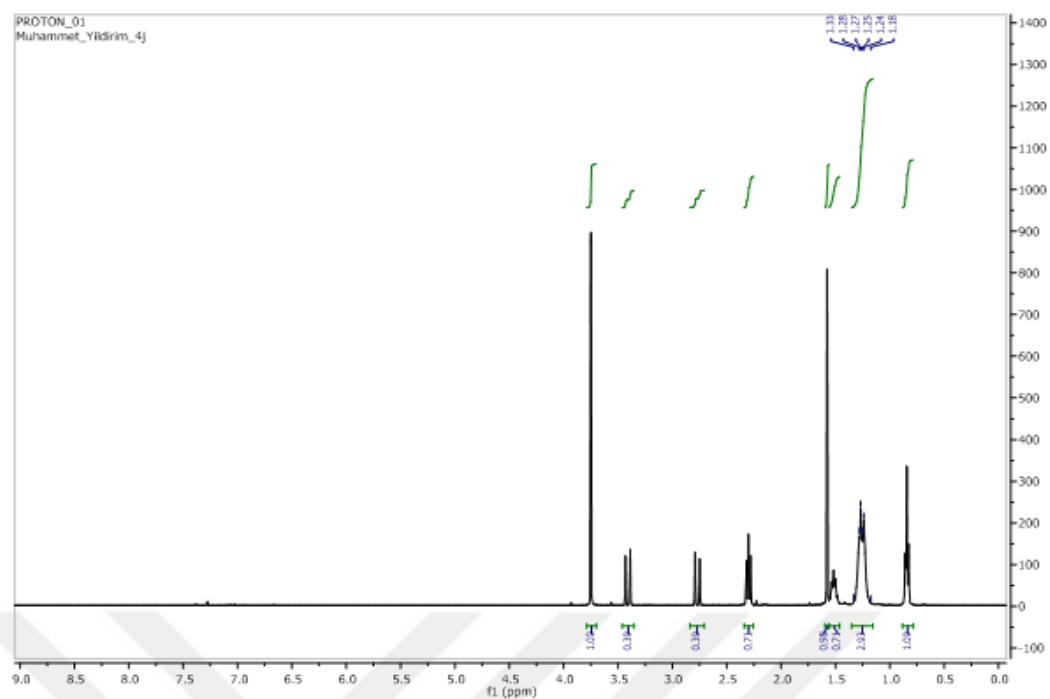


Figure 6-122- ^1H -NMR spectrum of 2.4i

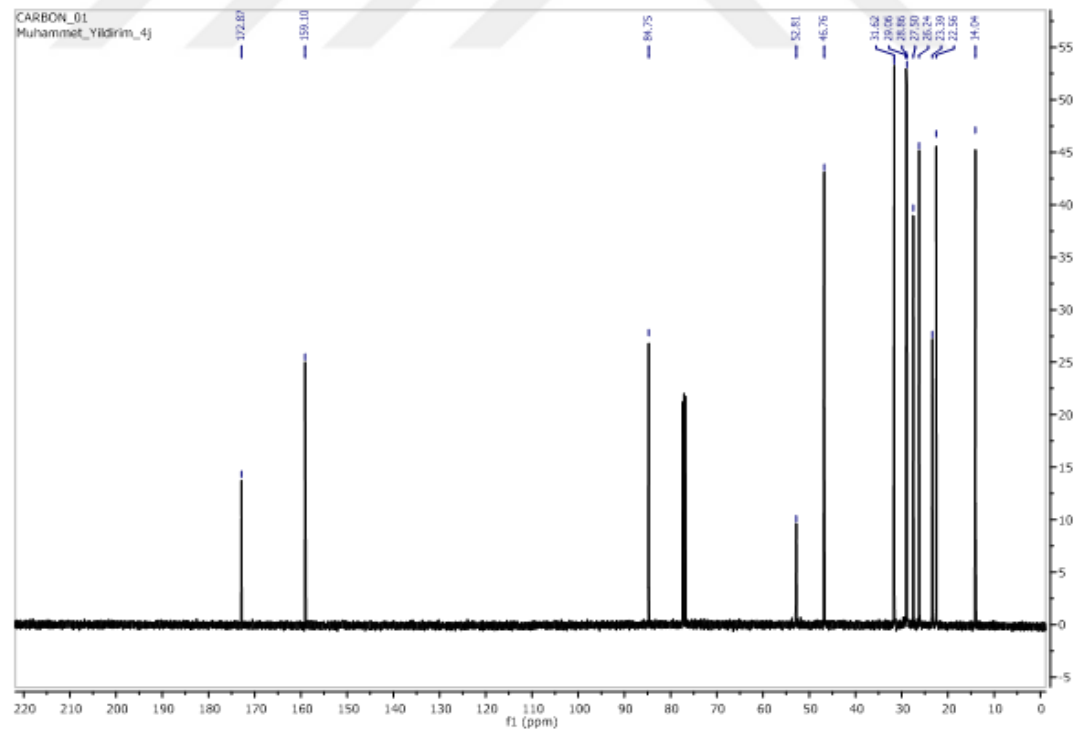


Figure 6-123- ^{13}C -NMR spectrum of 2.4i

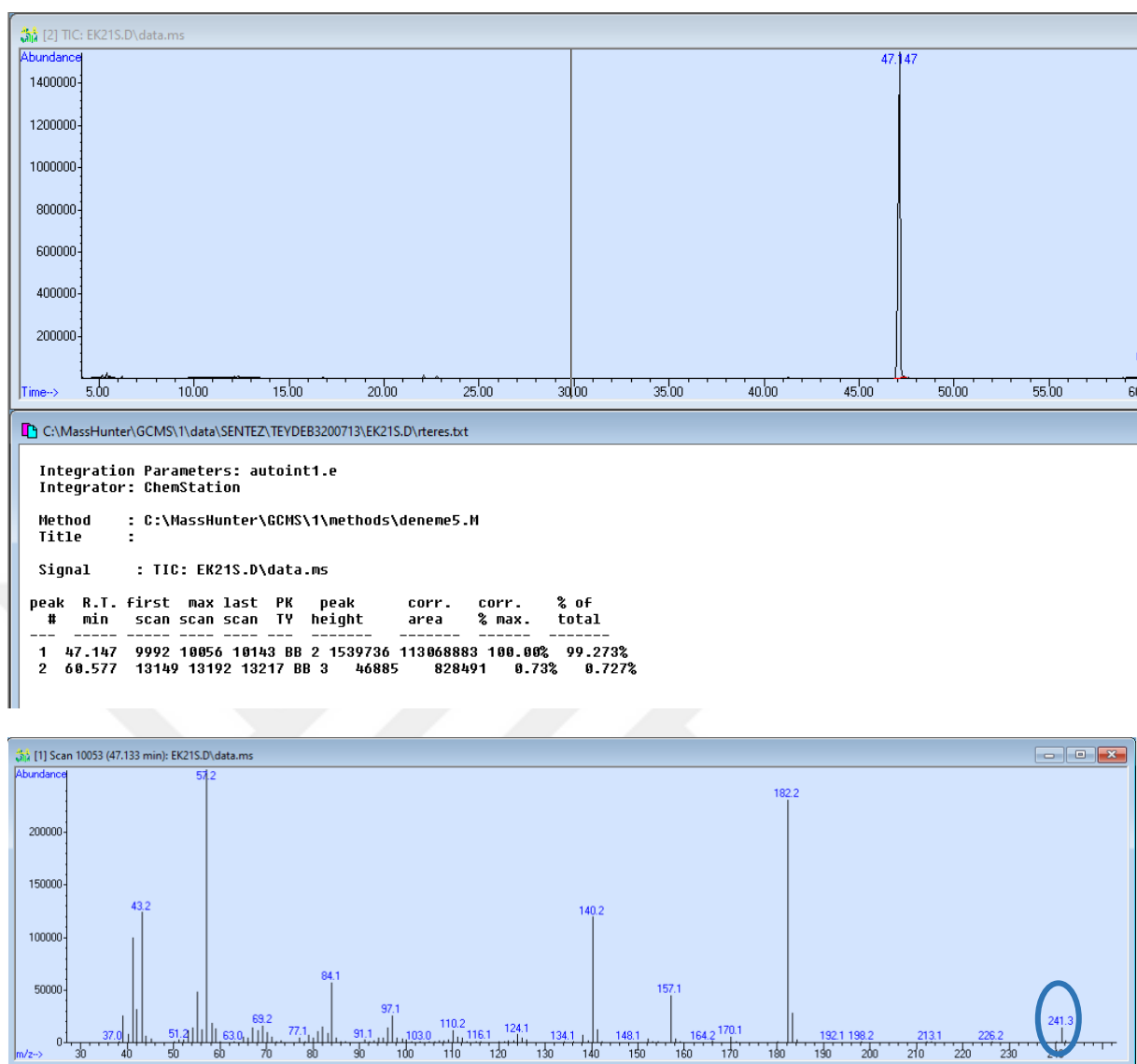


Figure 6-124-GC-MS spectrum of 2.4i

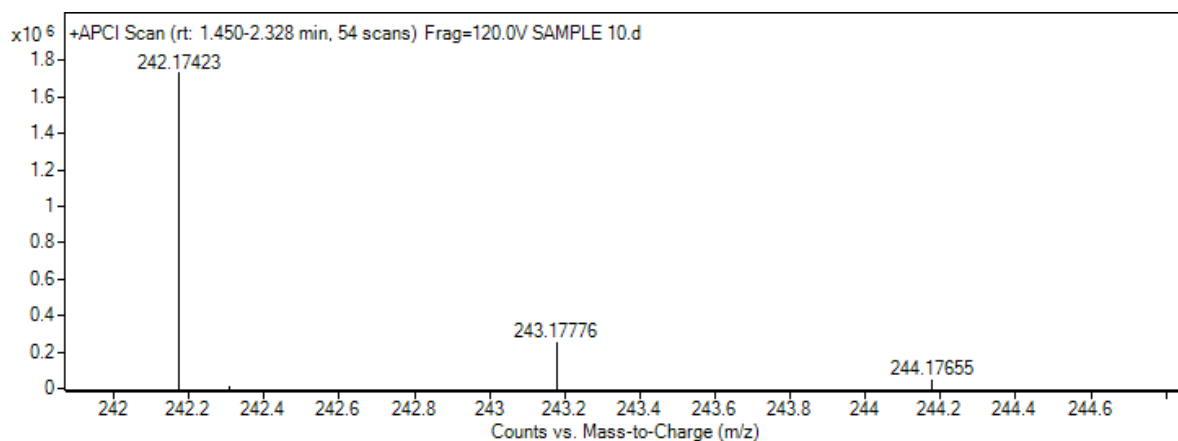


Figure 6-125-(TOF) LC-MS spectrum of 2.4i

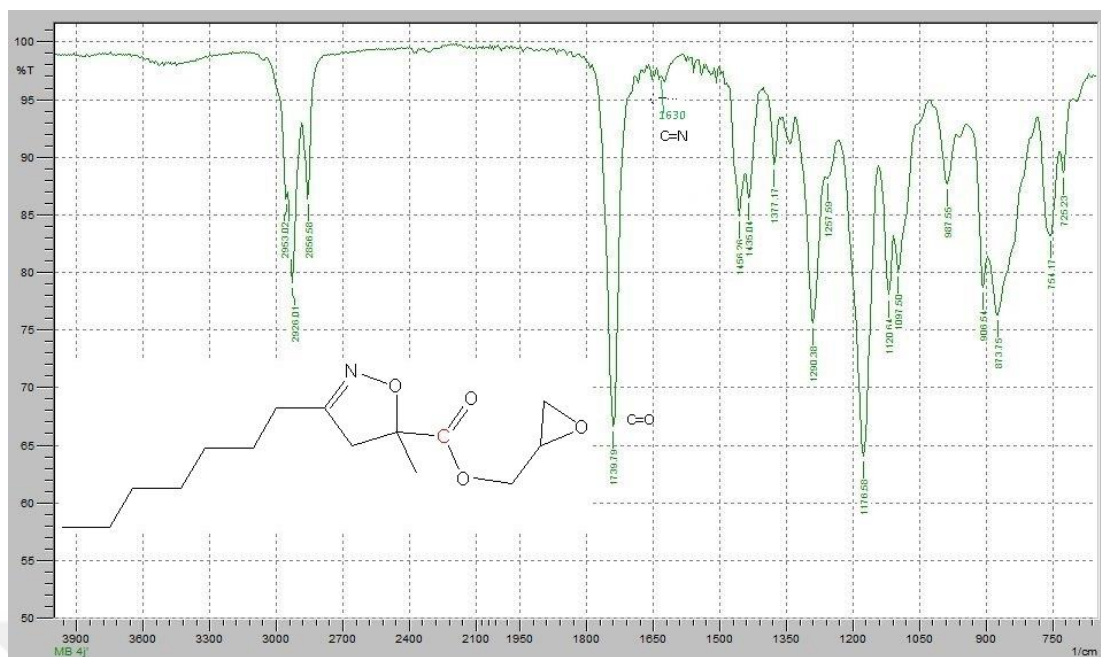


Figure 6-126-IR spectrum of 2.5i

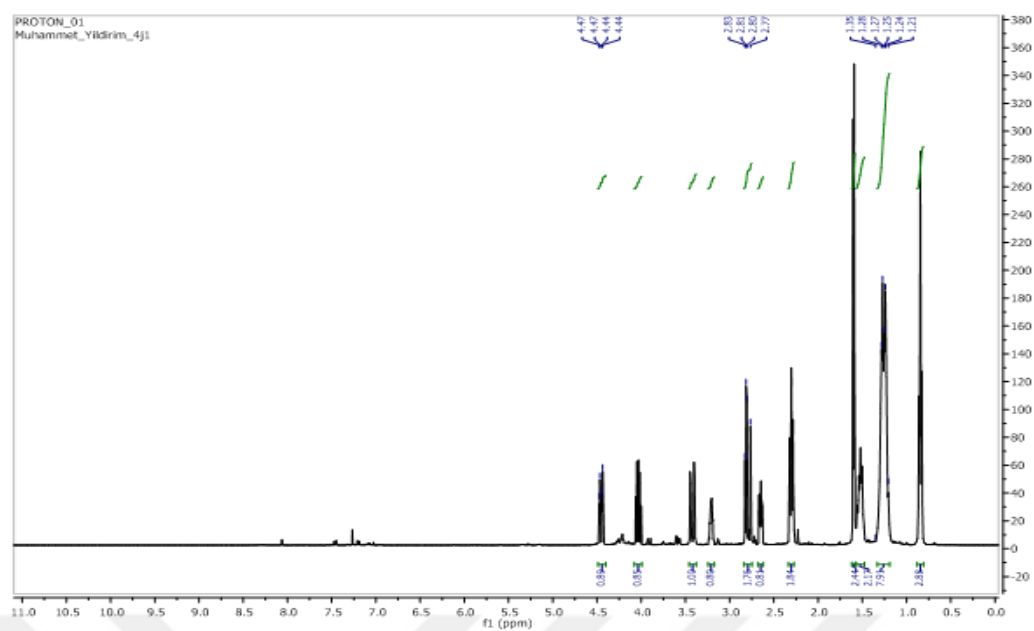


Figure 6-127- ^1H -NMR spectrum of 2.5i

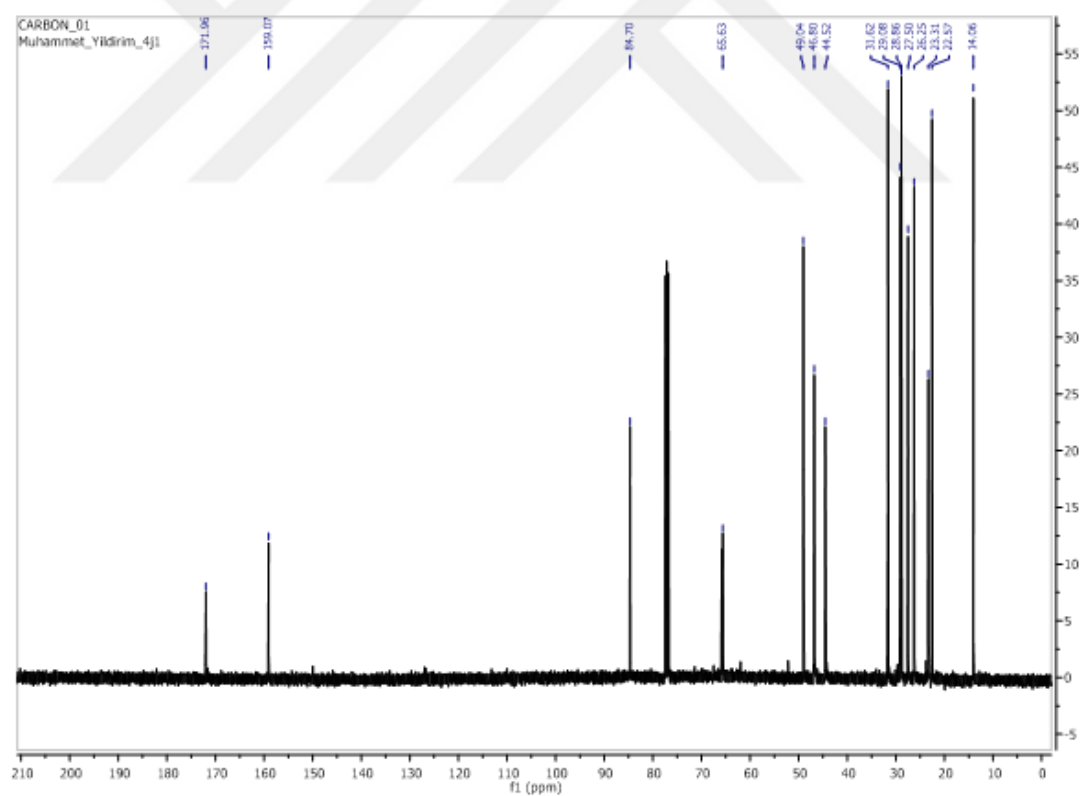


Figure 6-128- ^{13}C -NMR spectrum of 2.5i

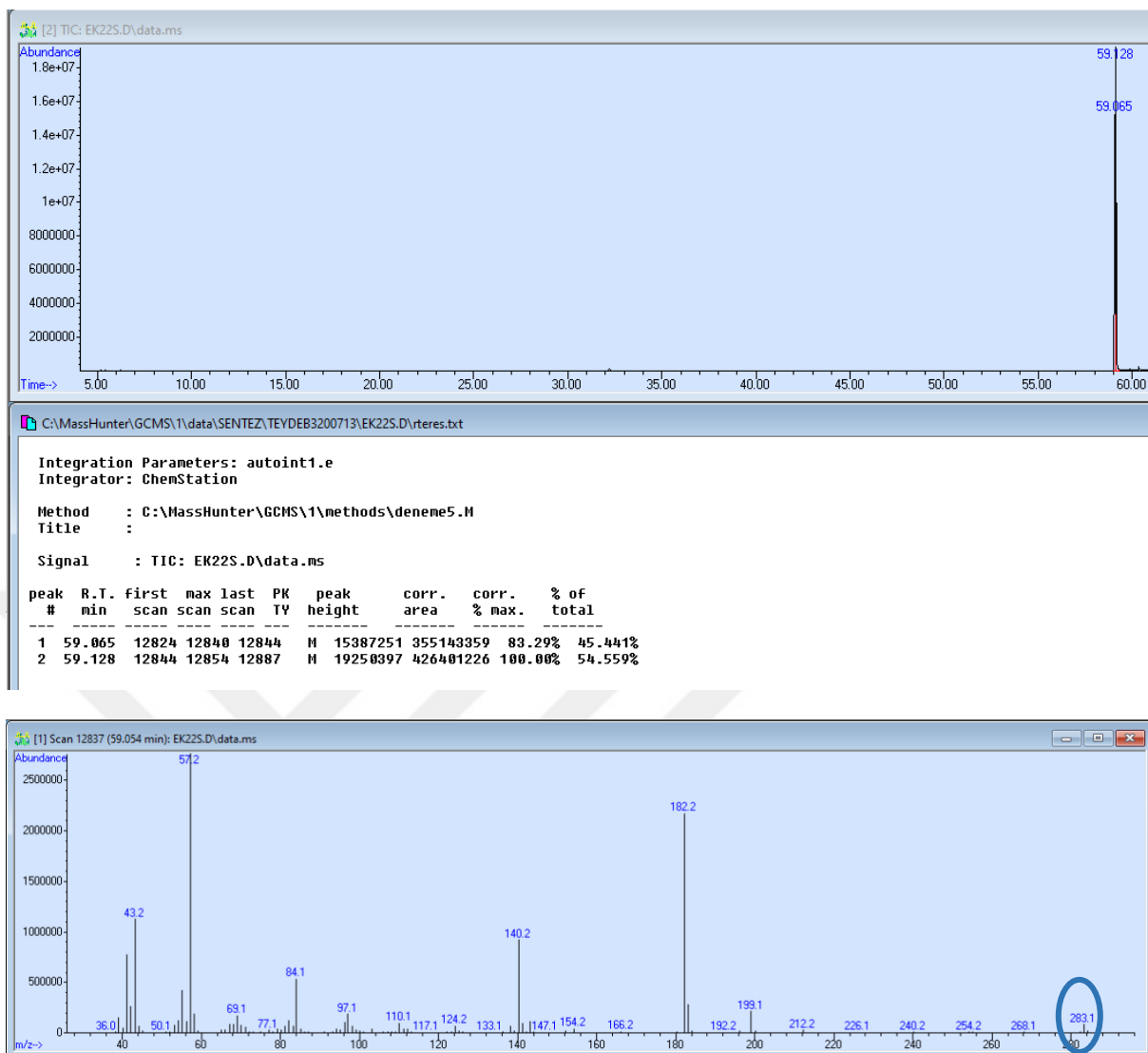


Figure 6-129-GC-MS spectrum of 2.5i

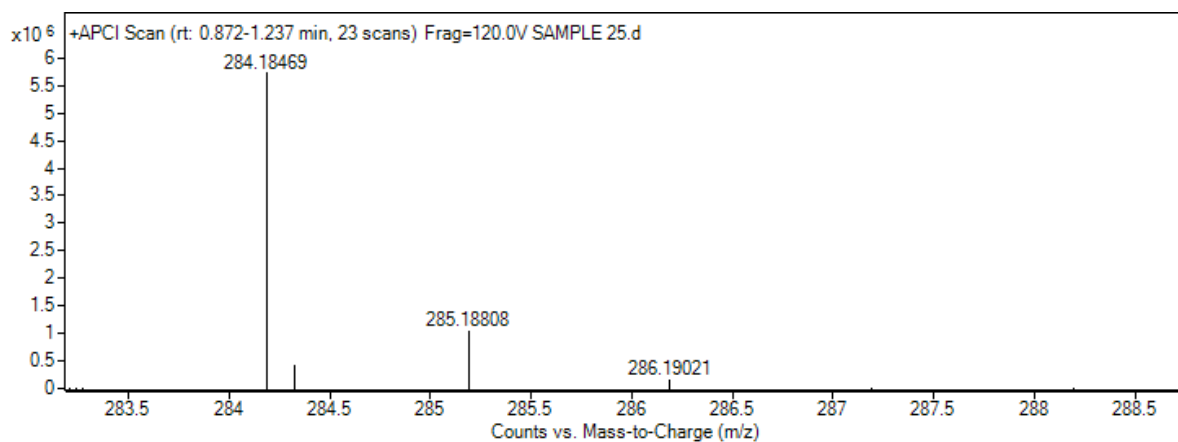


Figure 6-130-(TOF) LC-MS spectrum of 2.5i

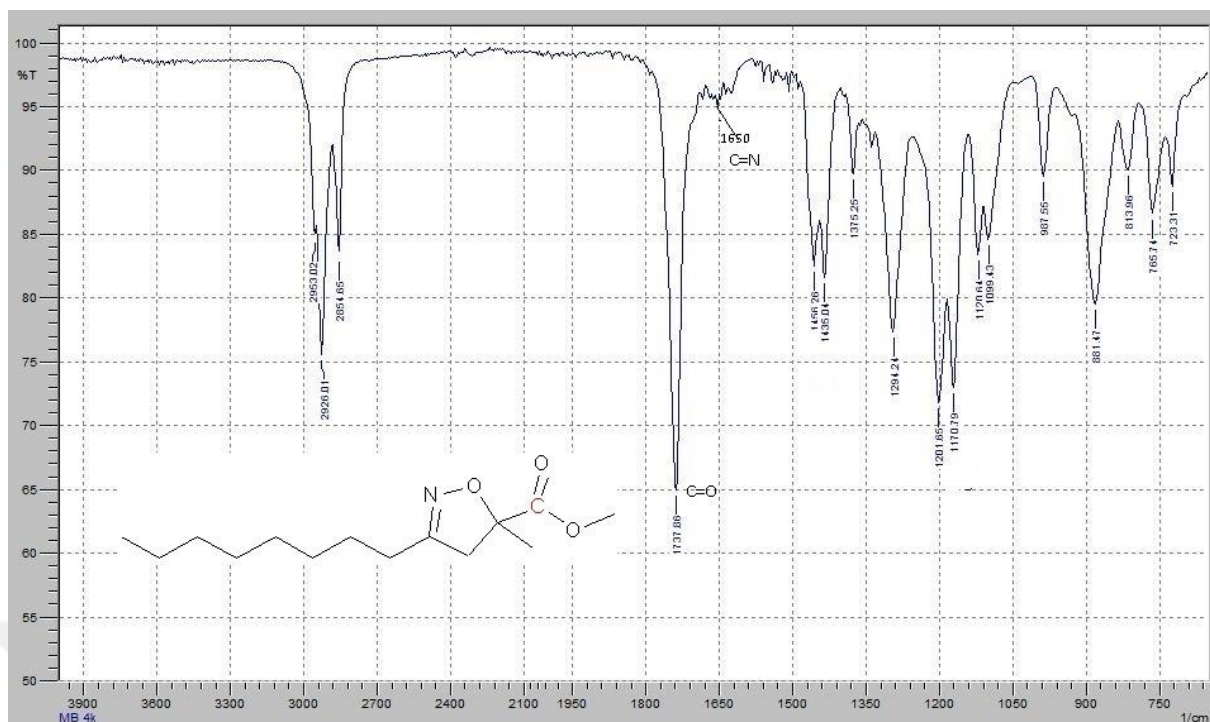


Figure 6-131-IR spectrum of 2.4j

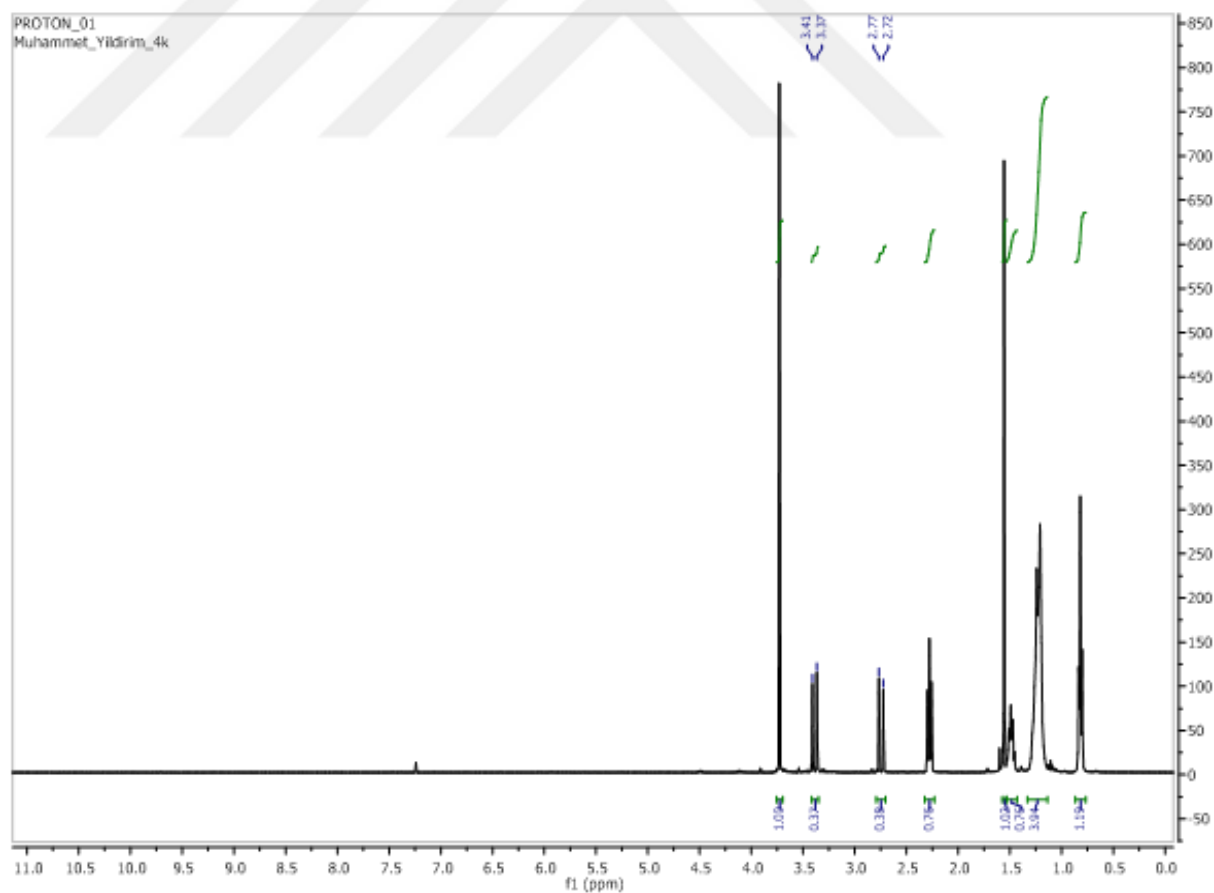


Figure 6-132-¹H-NMR spectrum of 2.4j

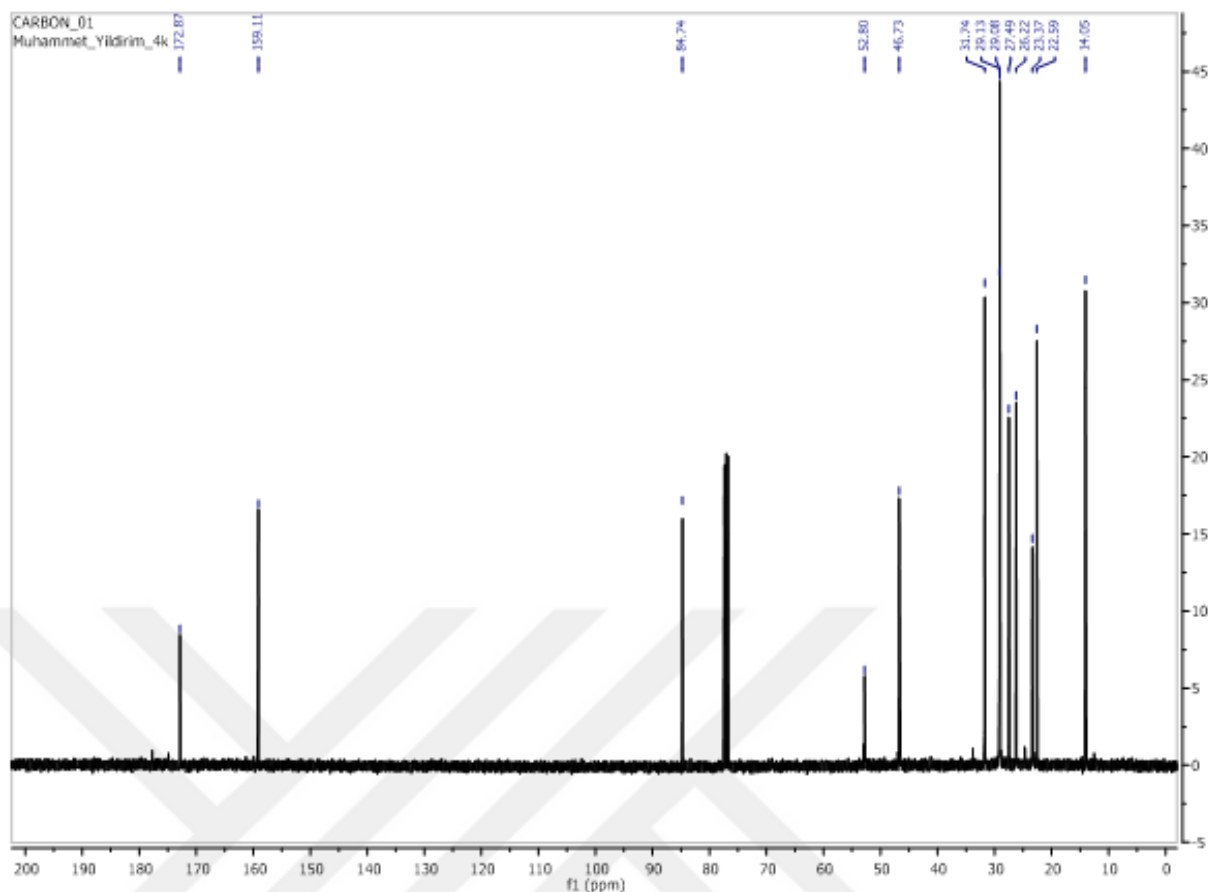
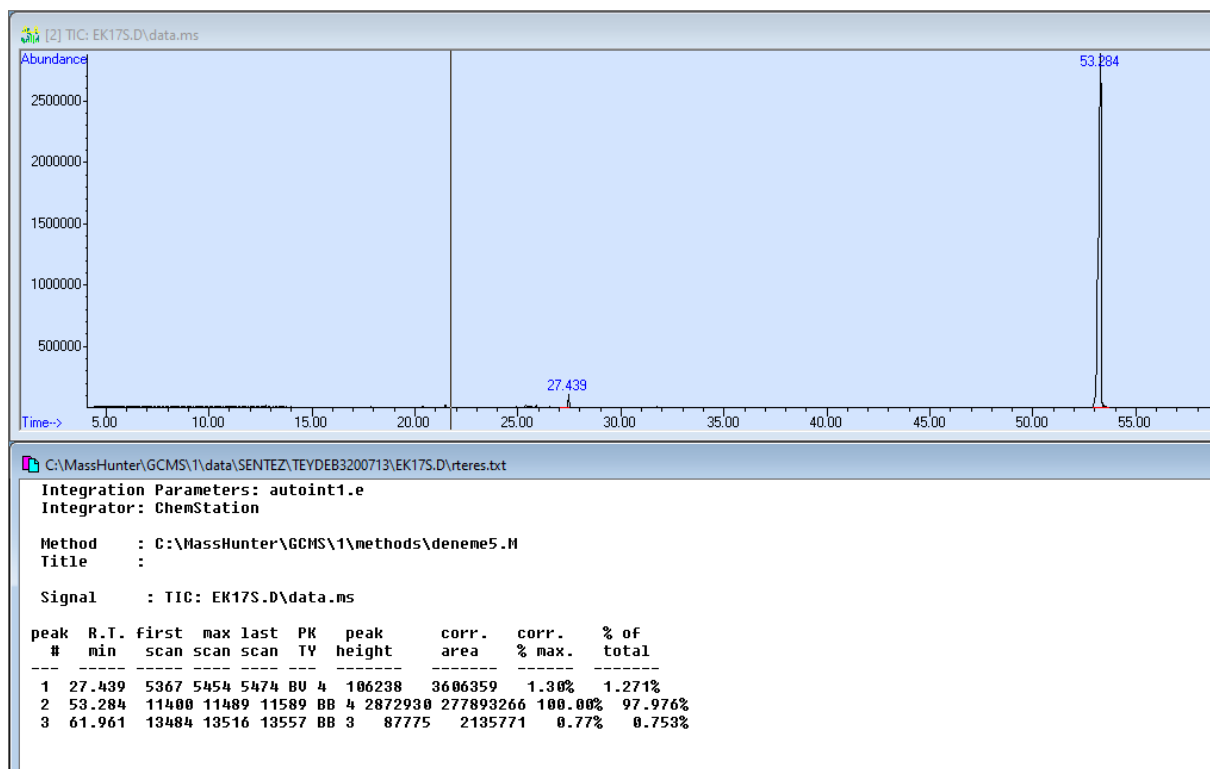


Figure 6-133- ^{13}C -NMR spectrum of 2.4j



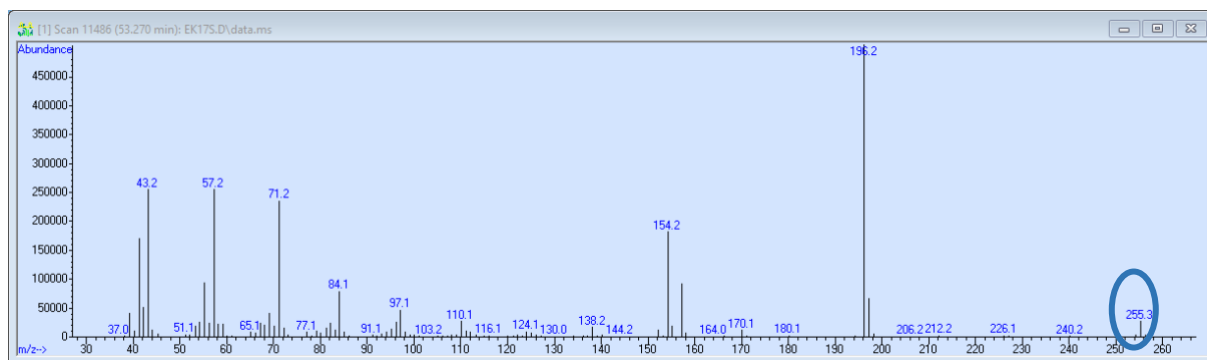


Figure 6-134-GC-MS spectrum of 2.4j

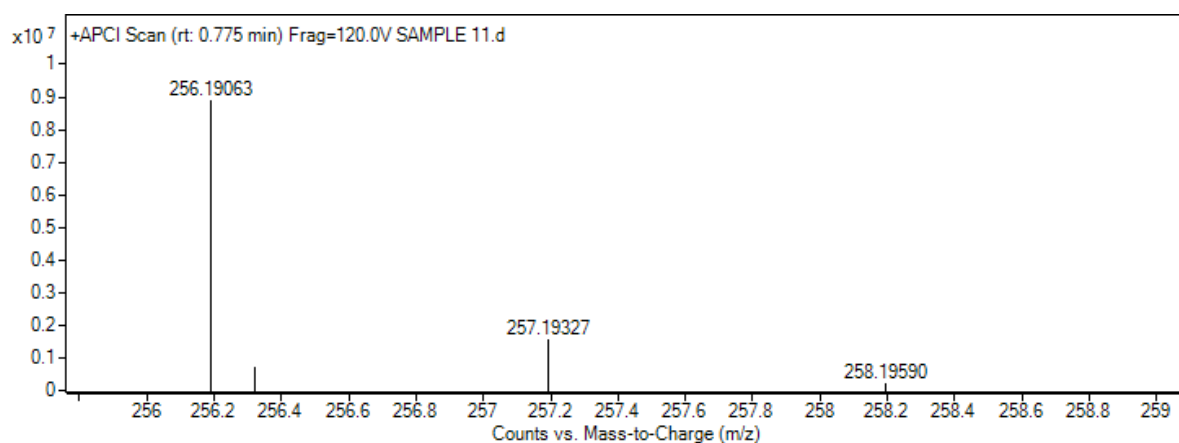


Figure 6-135-(TOF) LC-MS spectrum of 2.4j

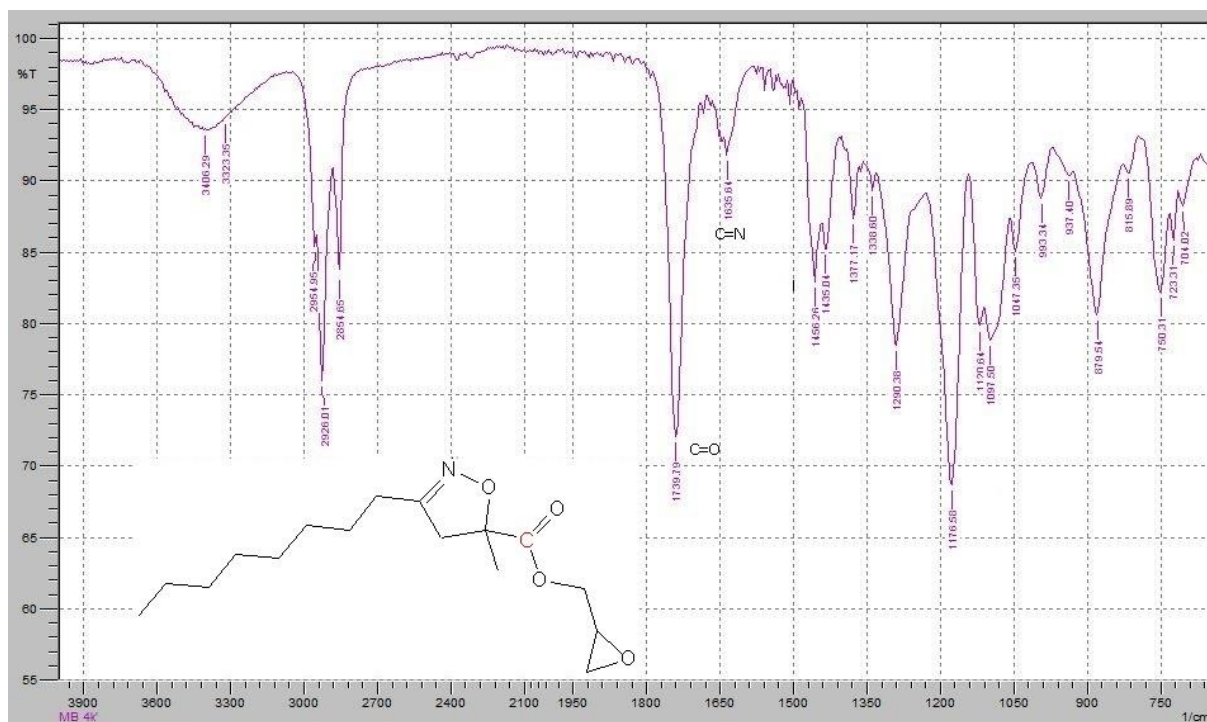


Figure 6-136-IR spectrum of 2.5j

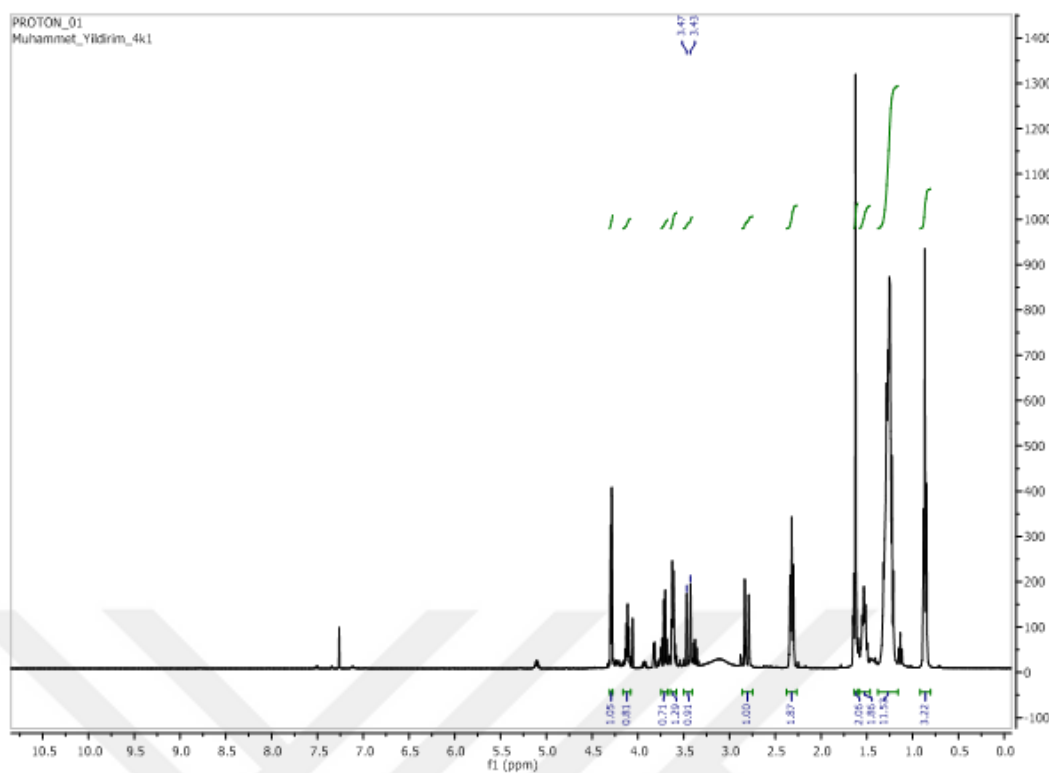


Figure 6-137- ^1H -NMR spectrum of 2.5j

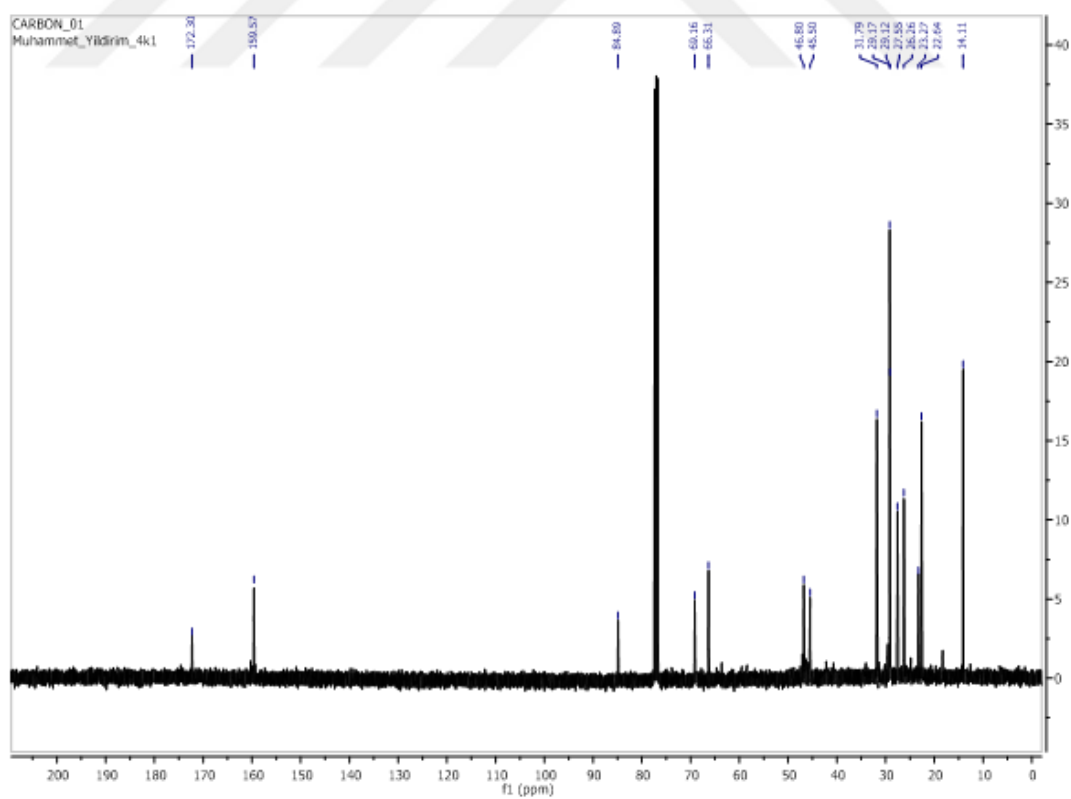


Figure 6-138- ^{13}C -NMR spectrum of 2.5j

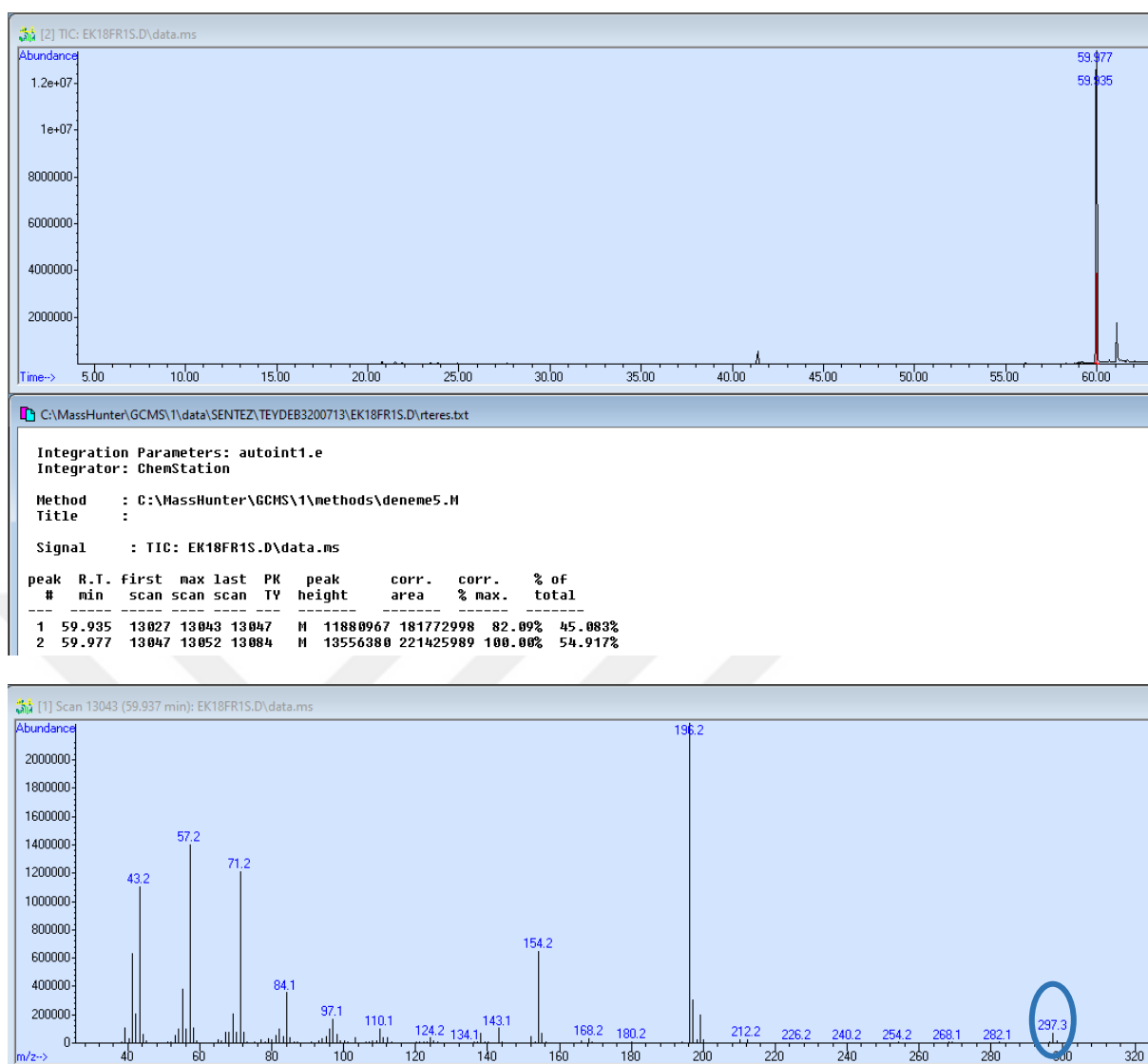


Figure 6-139-GC-MS spectrum of 2.5j

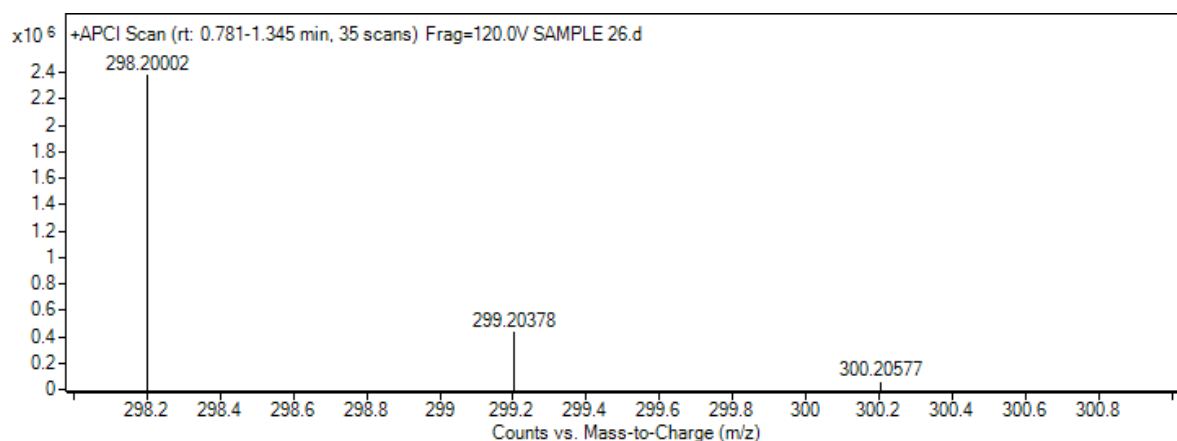


Figure 6-140-(TOF) LC-MS spectrum of 2.5j

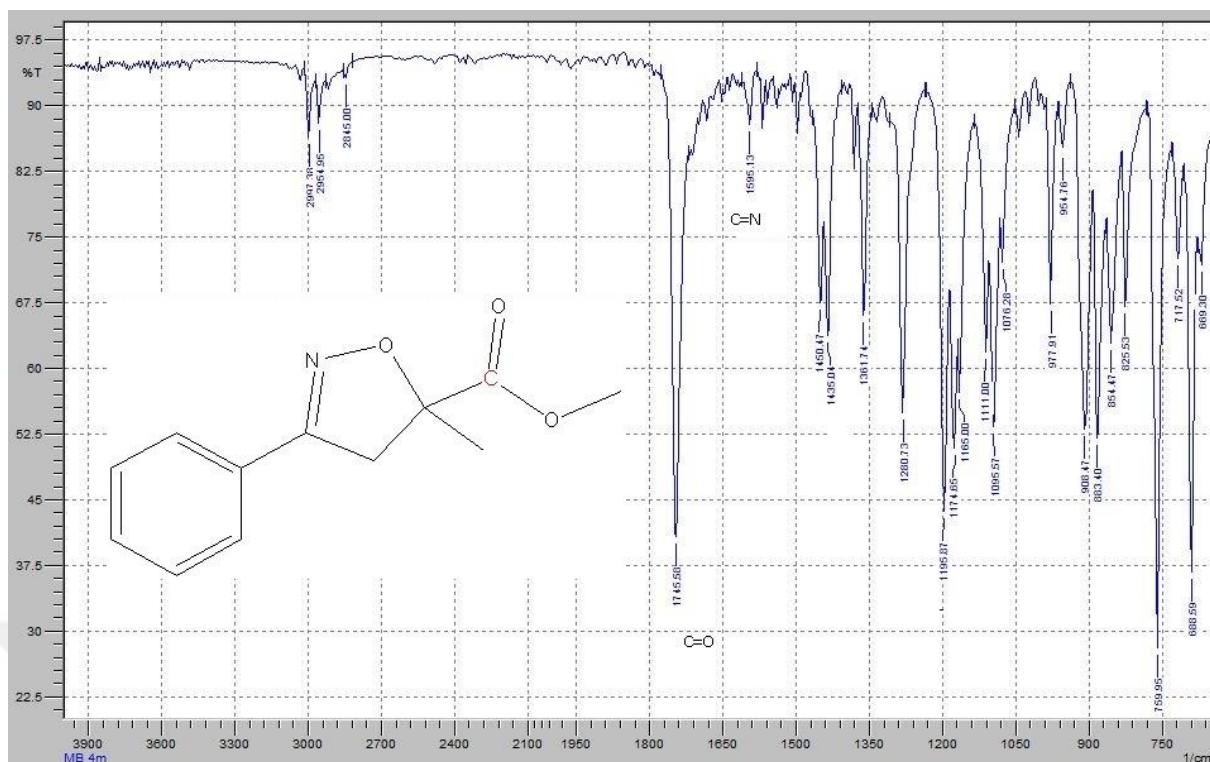


Figure 6-141-IR spectrum of 2.4k

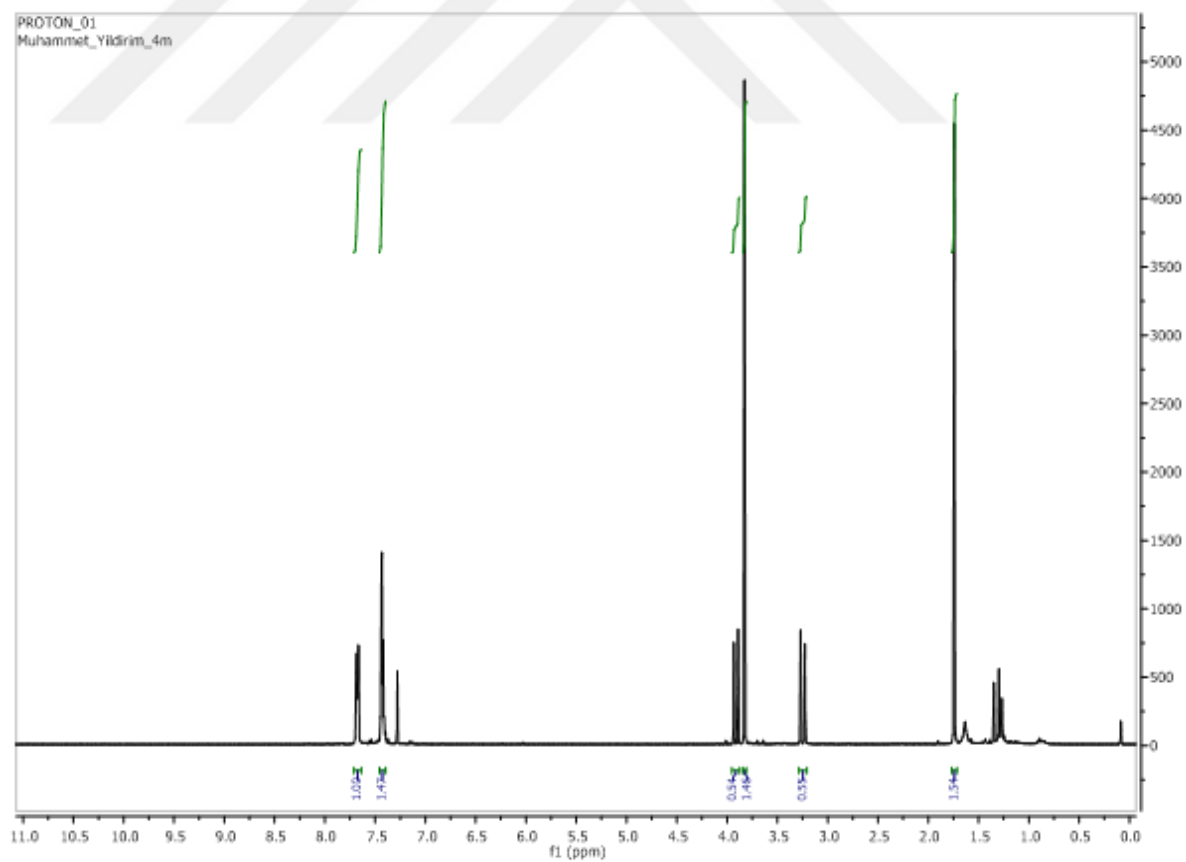


Figure 6-142-¹H-NMR spectrum of 2.4k

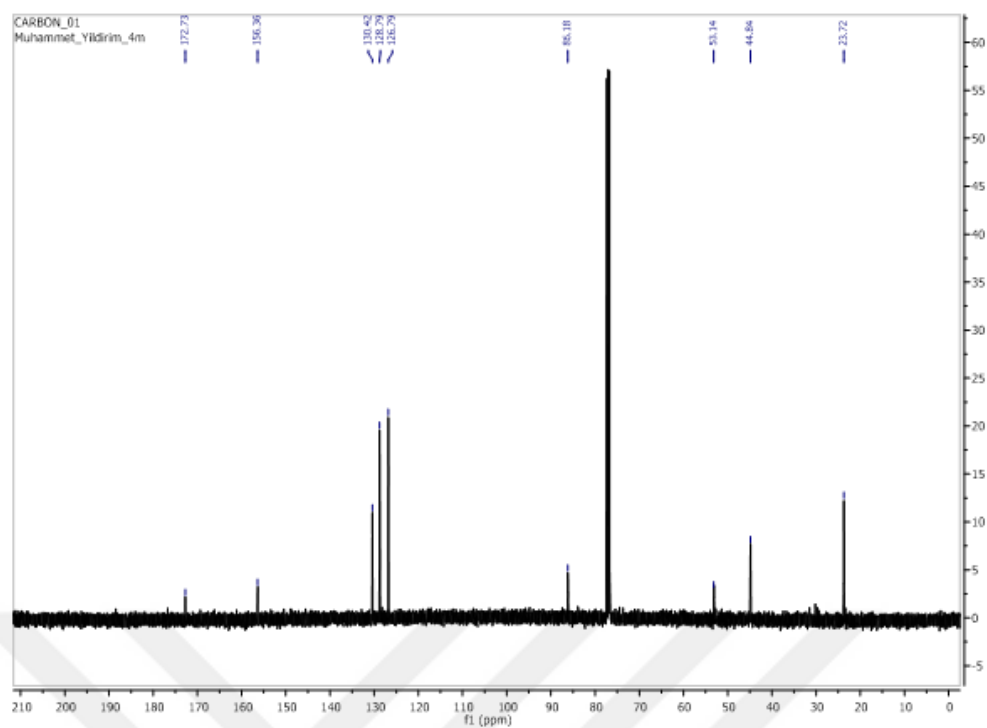


Figure 6-143- ^{13}C -NMR spectrum of 2.4k

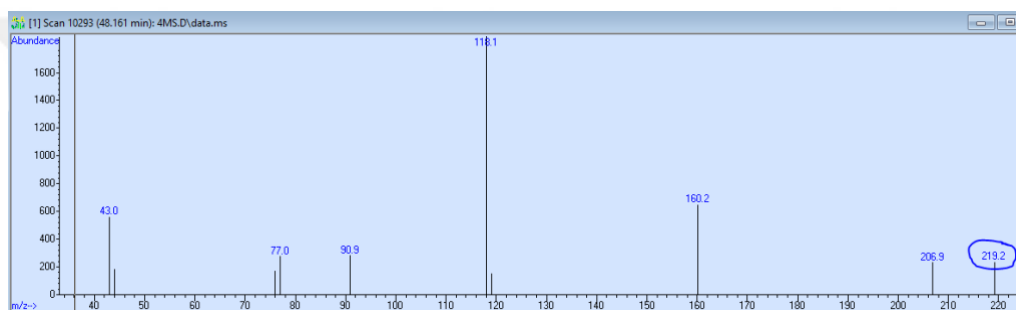
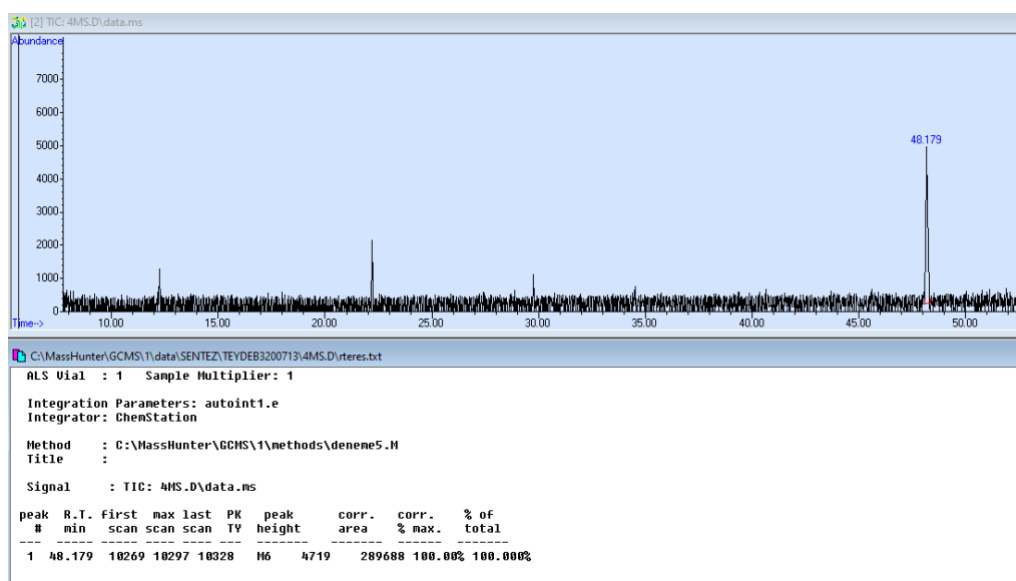


Figure 6-144-GC-MS spectrum of 2.4k

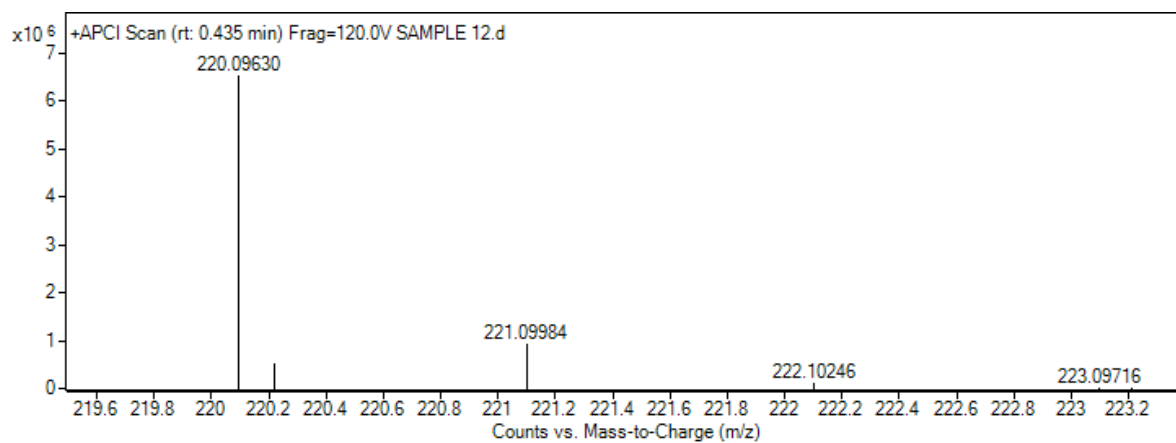


Figure 6-145-(TOF) LC-MS spectrum of 2.4k

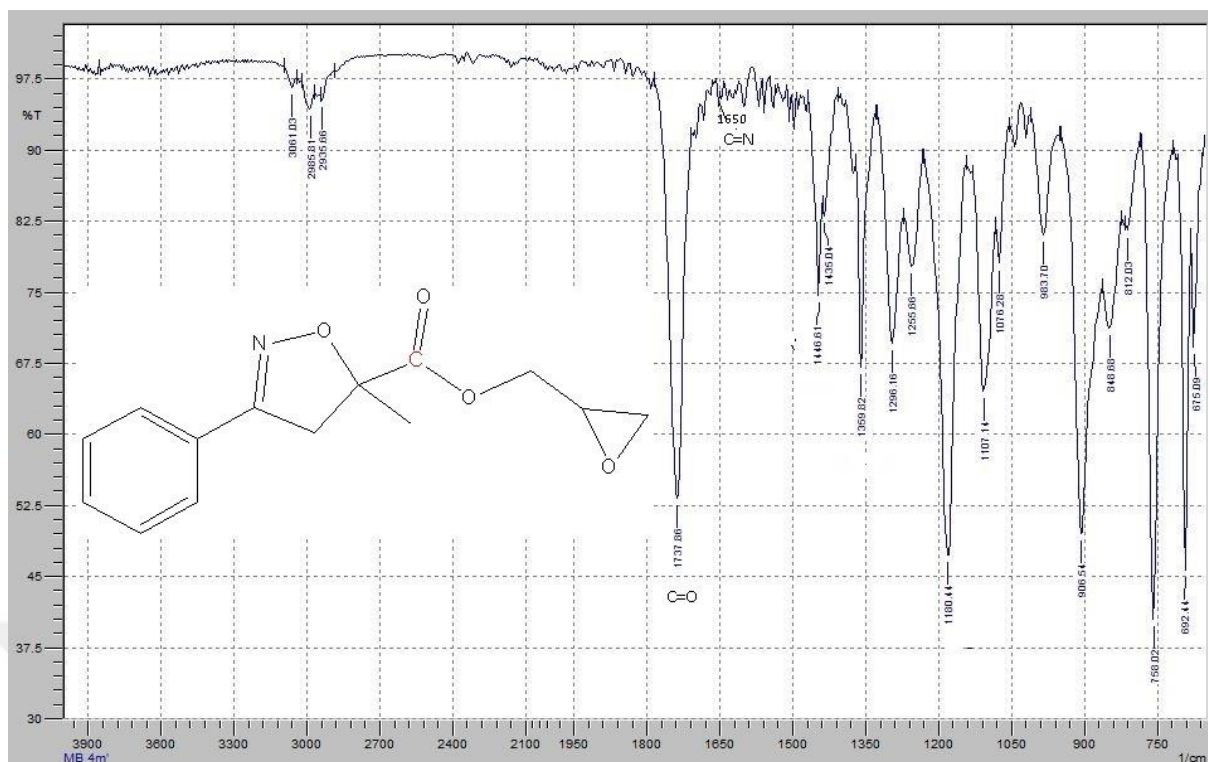


Figure 6-146-IR spectrum of 2.5k

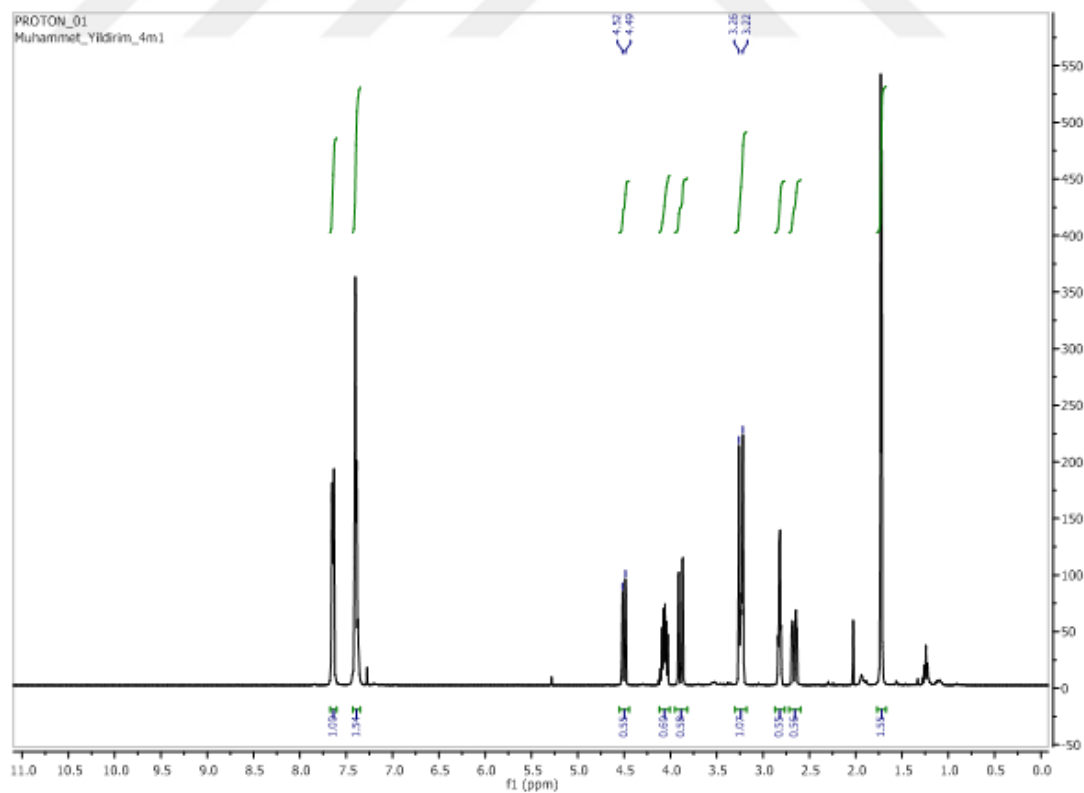


Figure 6-147-¹H-NMR spectrum of 2.5k

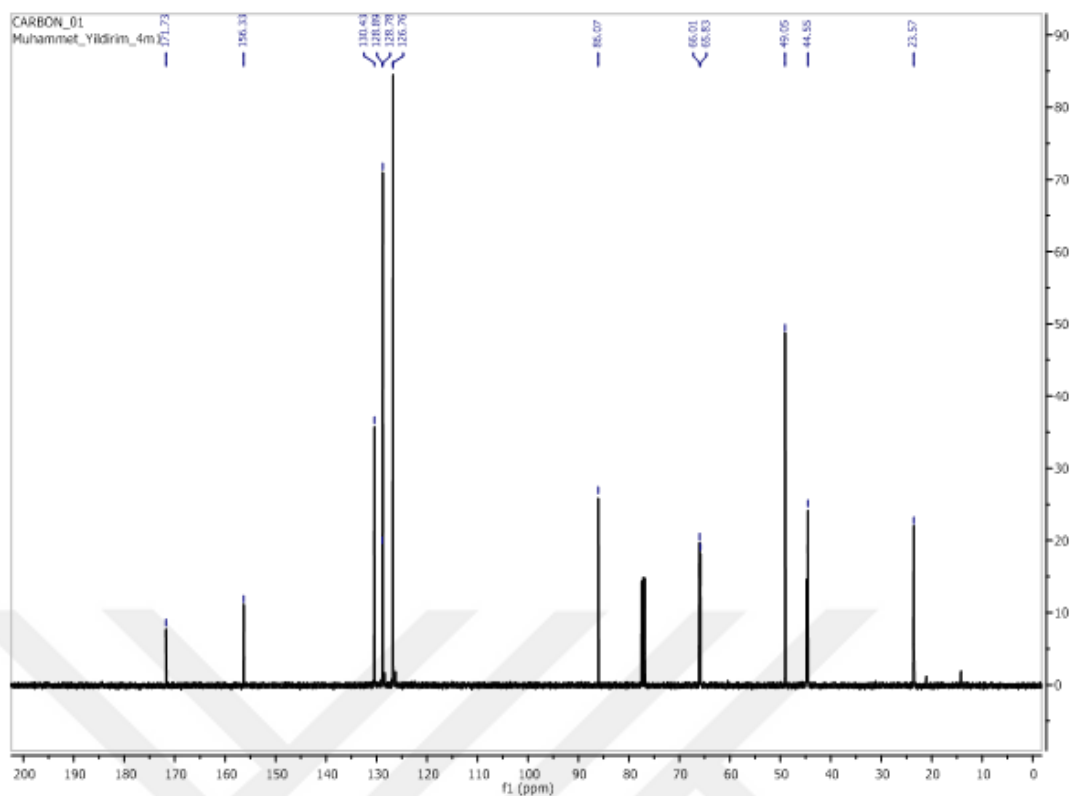
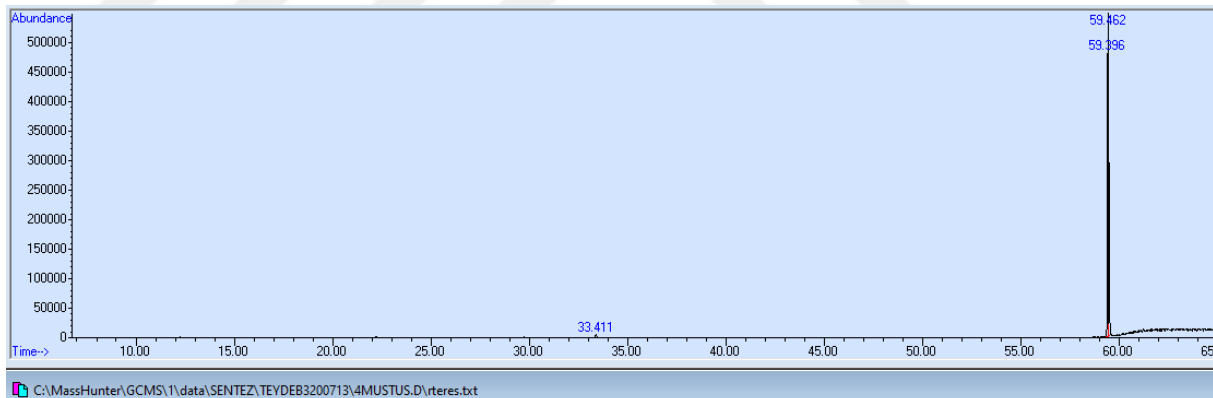


Figure 6-148- ^{13}C -NMR spectrum of 2.5k



Integration Parameters: autoint1.e
Integrator: ChenStation

Method : C:\MassHunter\GCMS\1\methods\deneme5.M
Title :

Signal : TIC: 4MUSTUS.D\data.ms

peak #	R.T. min	First scan	max scan	last scan	PK TV	peak height	corr. area	corr. % max.	% of total
1	33.411	6828	6848	6874	M3	5345	277023	3.16%	1.719%
2	59.396	12908	12917	12925	H	483196	7067745	80.57%	43.853%
3	59.462	12925	12932	12960	H	555149	8772273	100.00%	54.429%

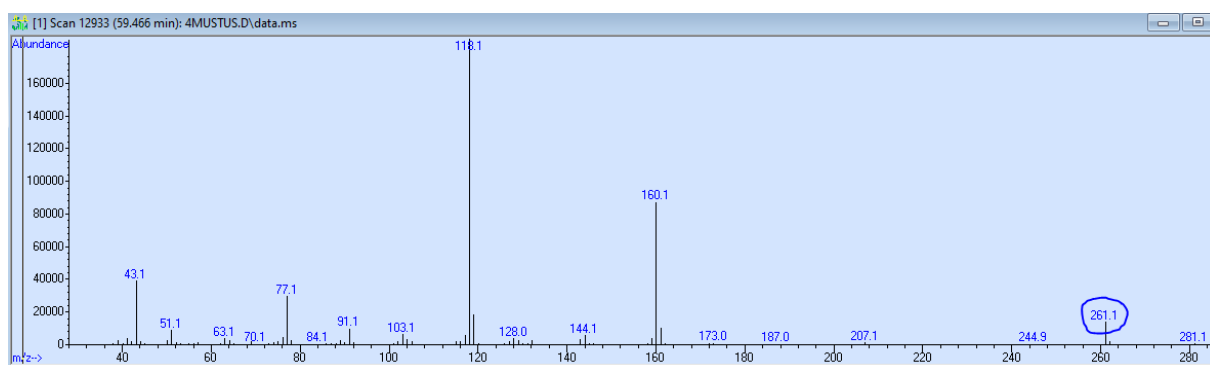


Figure 6-149-GC-MS spectrum of 2.5k

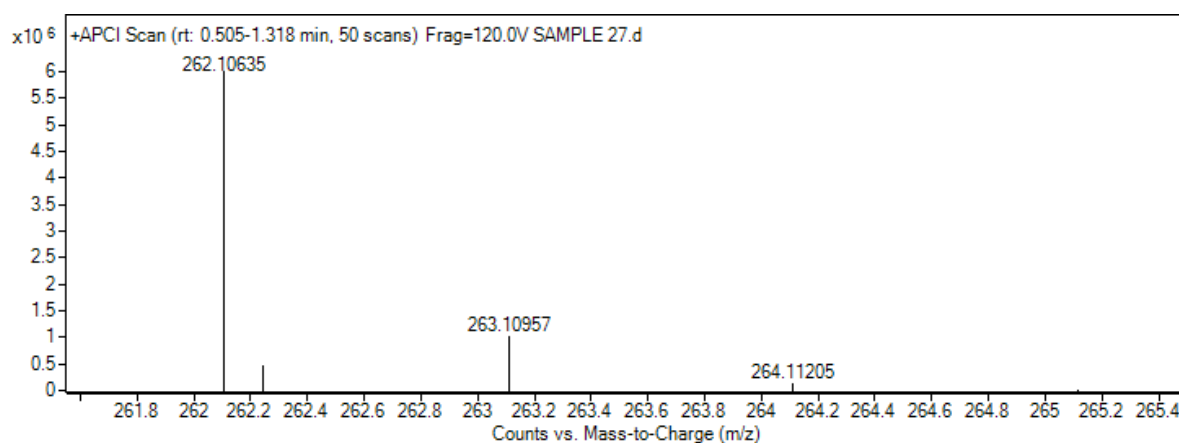


Figure 6-150-(TOF) LC-MS spectrum of 2.5k

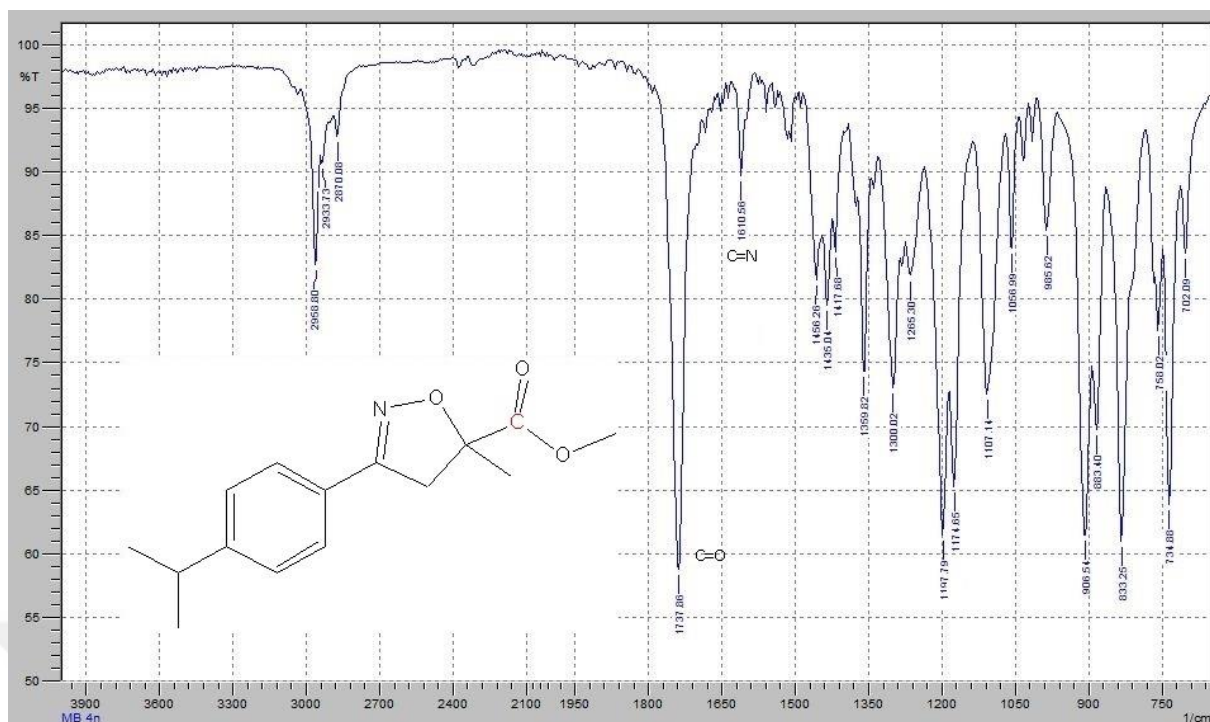


Figure 6-151-IR spectrum of 2.4l

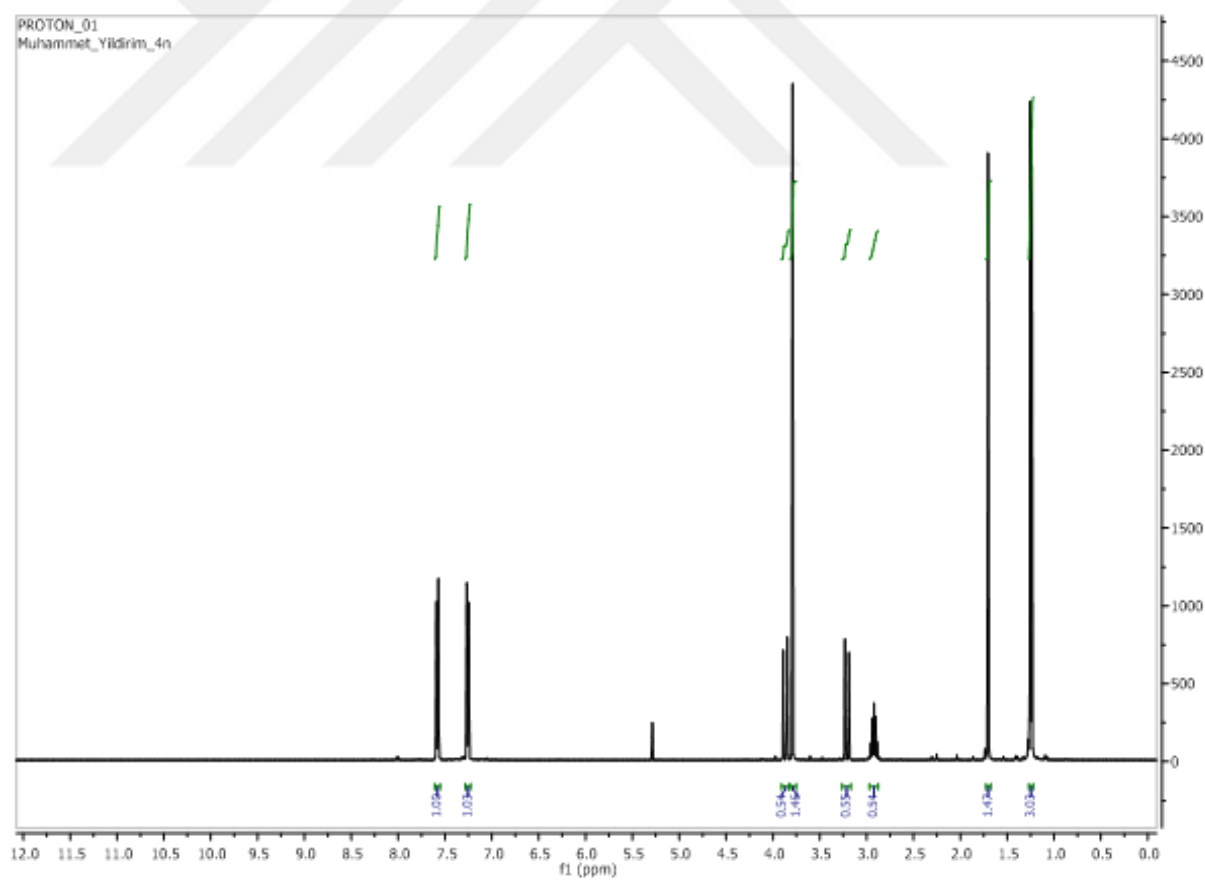


Figure 6-152-¹H-NMR spectrum of 2.4l

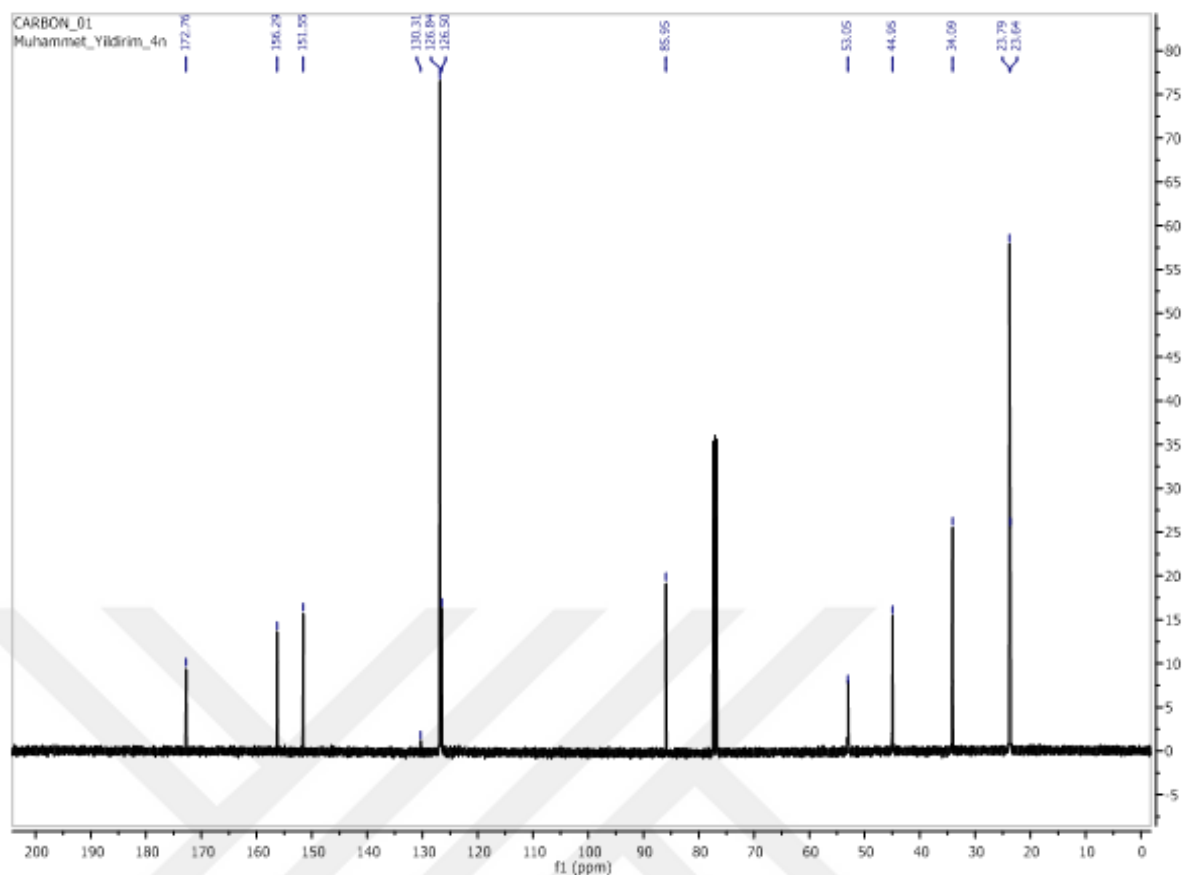
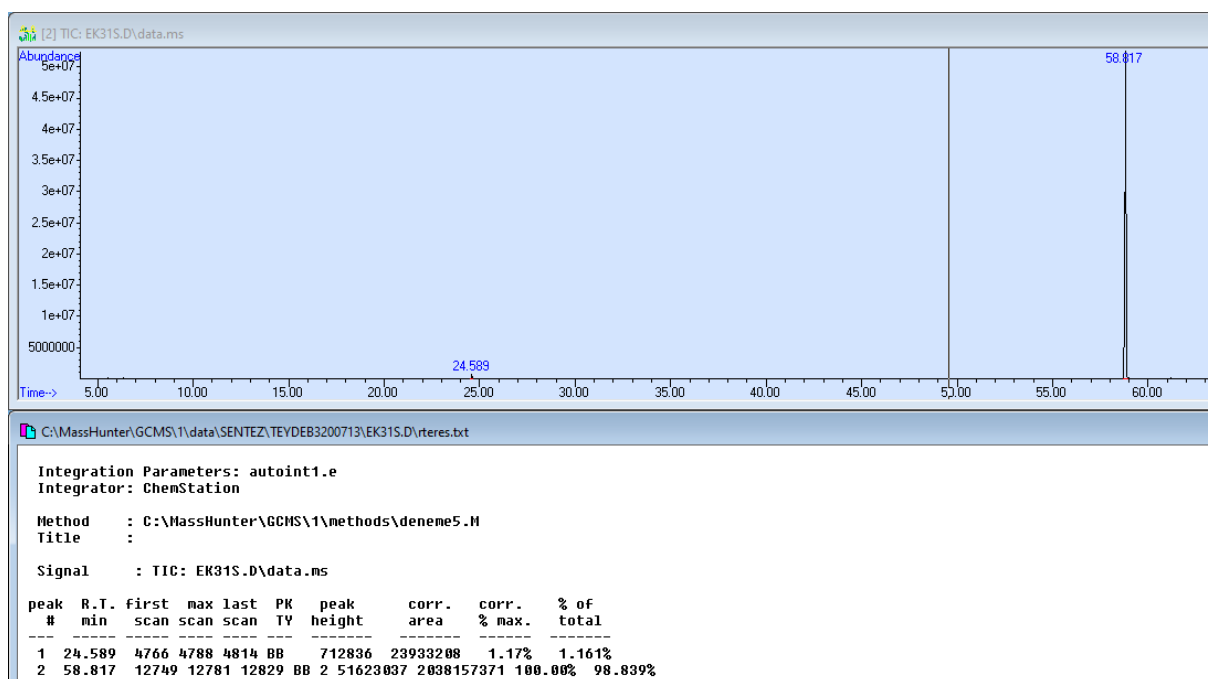


Figure 6-153- ^{13}C -NMR spectrum of 2.4l



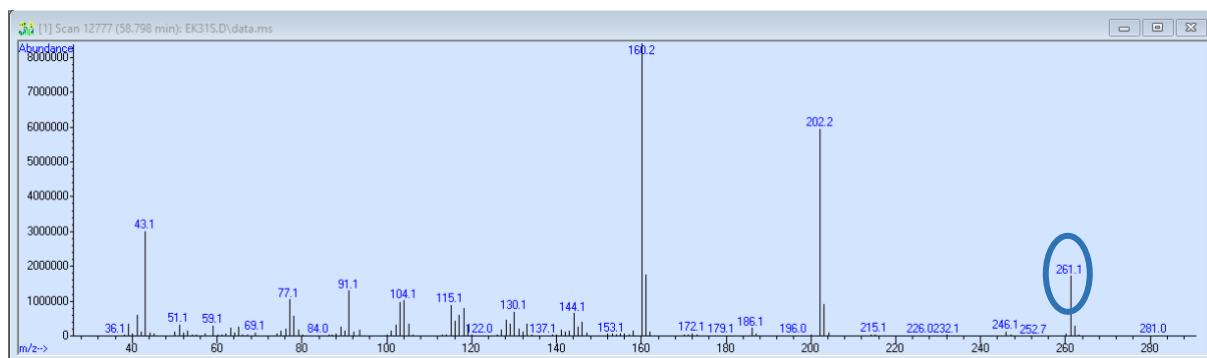


Figure 6-154-GC-MS spectrum of 2.4l

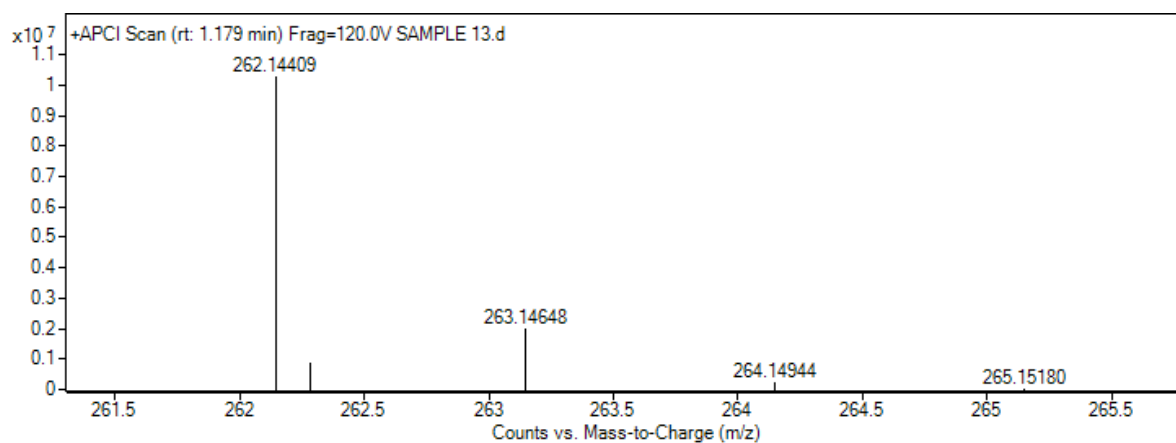


Figure 6-155-HR-MS spectrum of 2.4l

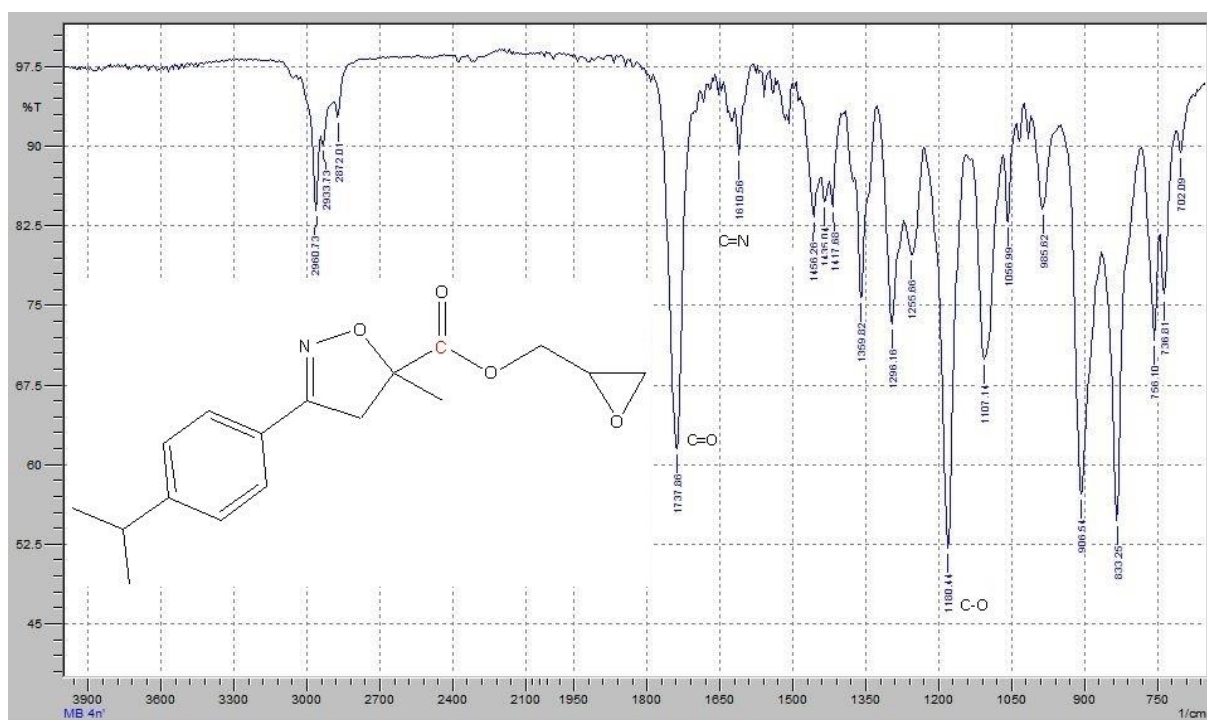


Figure 6-156-IR spectrum of 2.5l

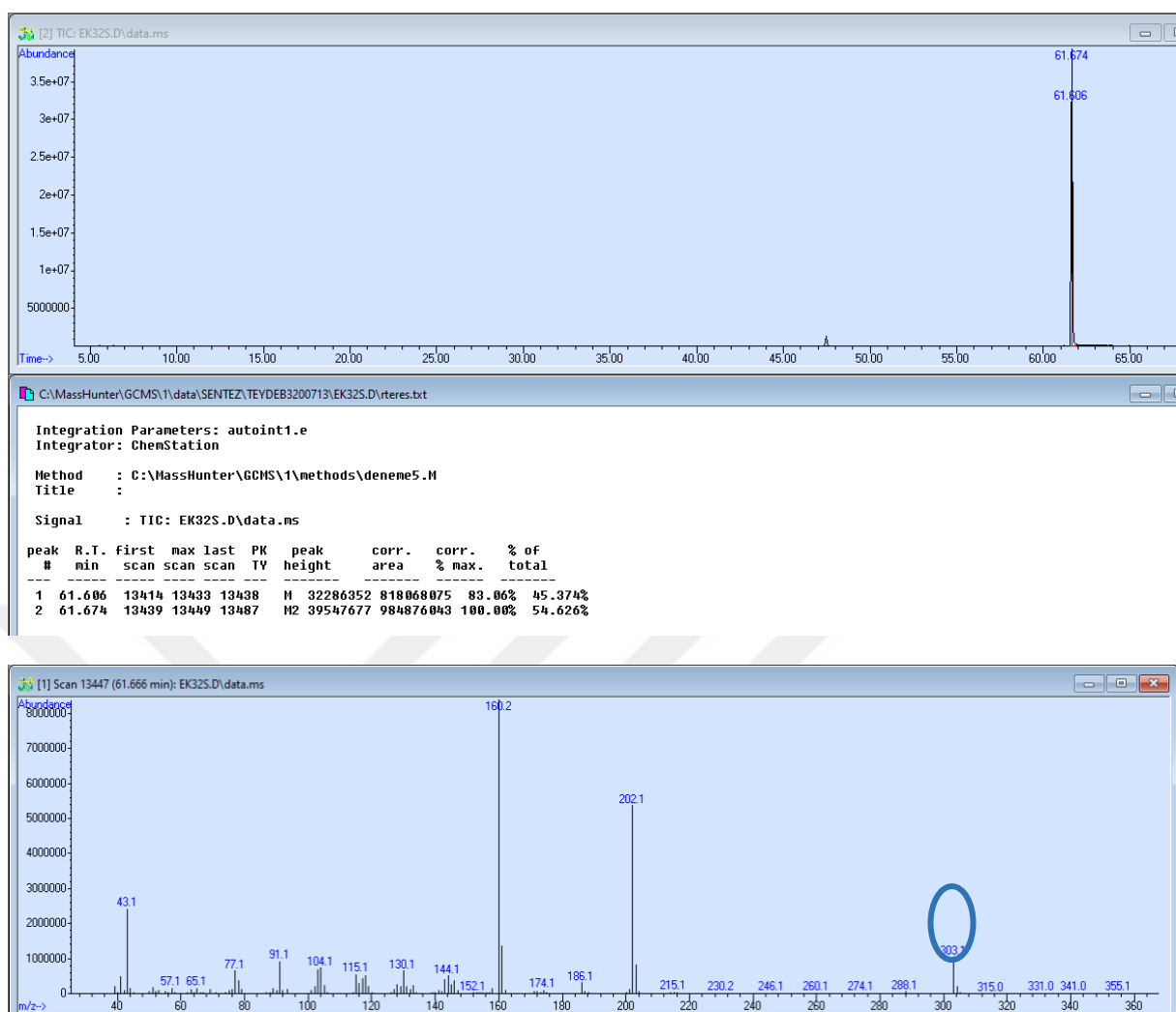


Figure 6-159-GC-MS spectrum of 2.5l

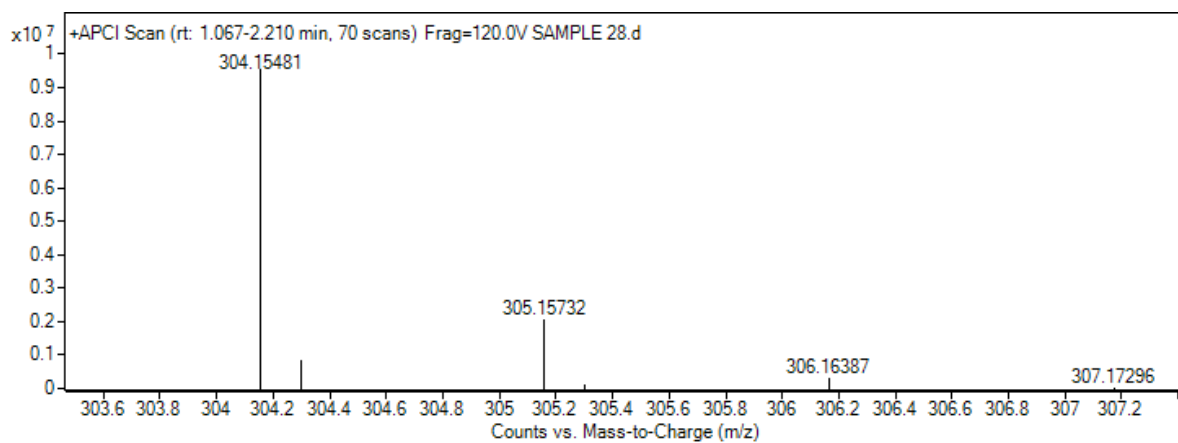


Figure 6-160-(TOF) LC-MS spectrum of 2.5l

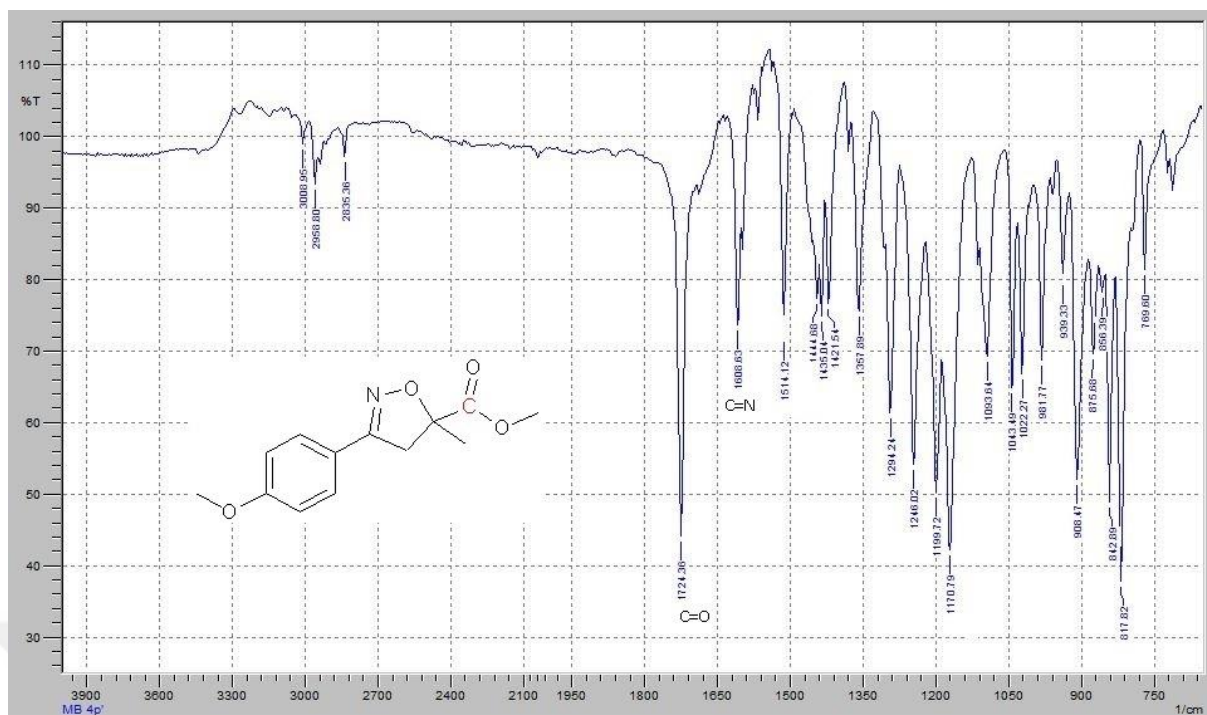


Figure 6-161-IR spectrum of 2.4m

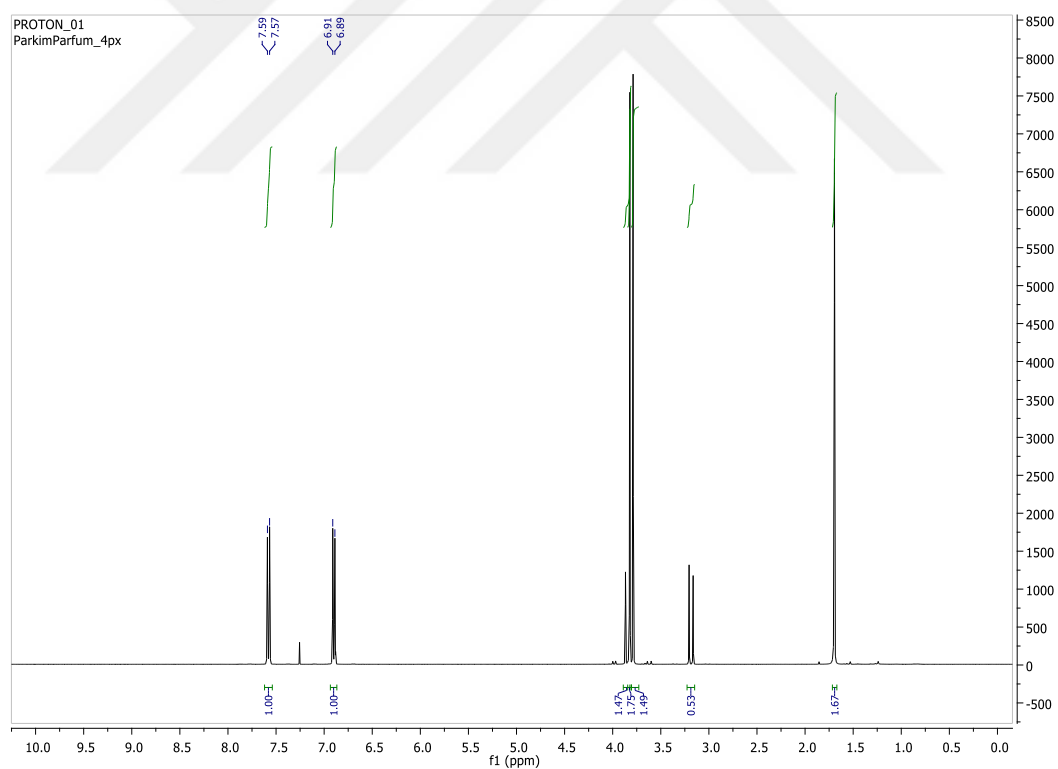


Figure 6-162- $^1\text{H-NMR}$ spectrum of 2.4m

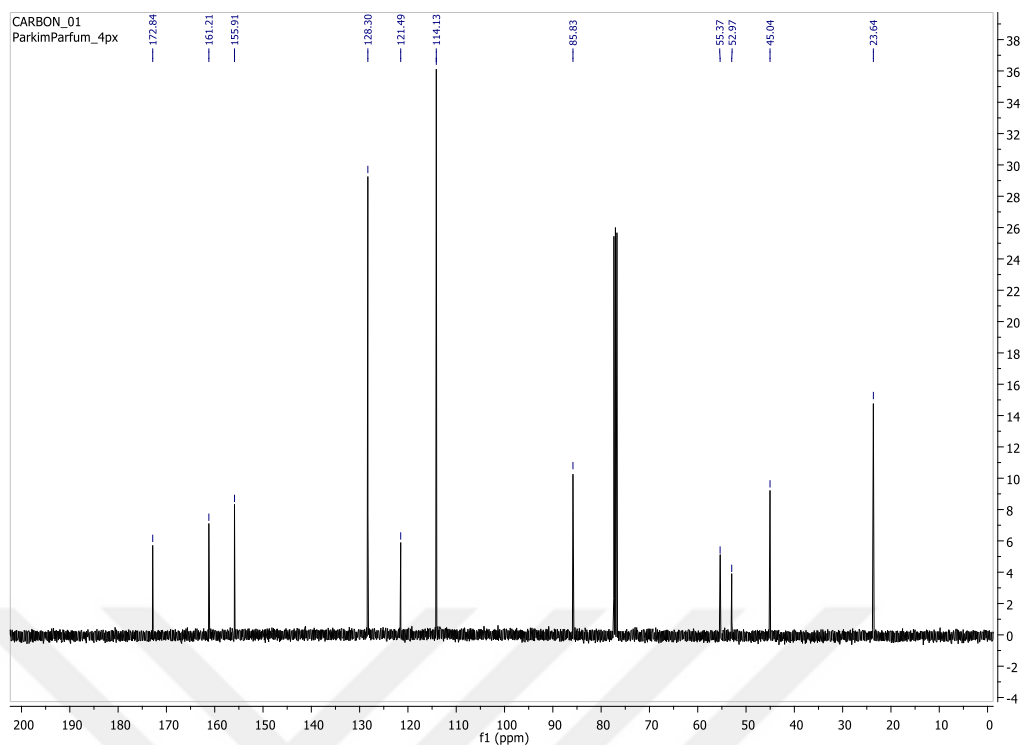


Figure 6-163- ^{13}C -NMR spectrum of 2.4m

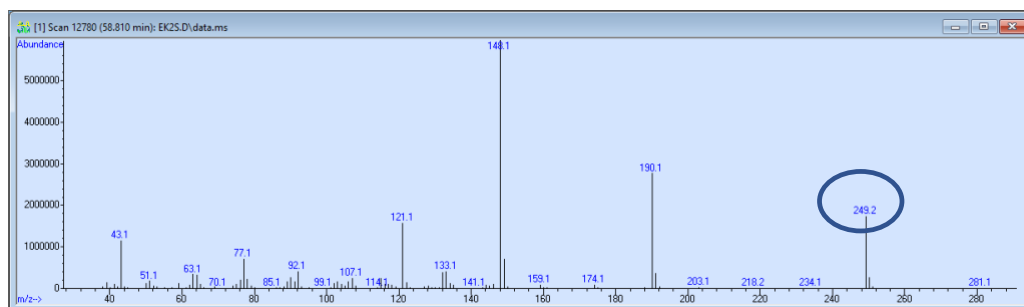
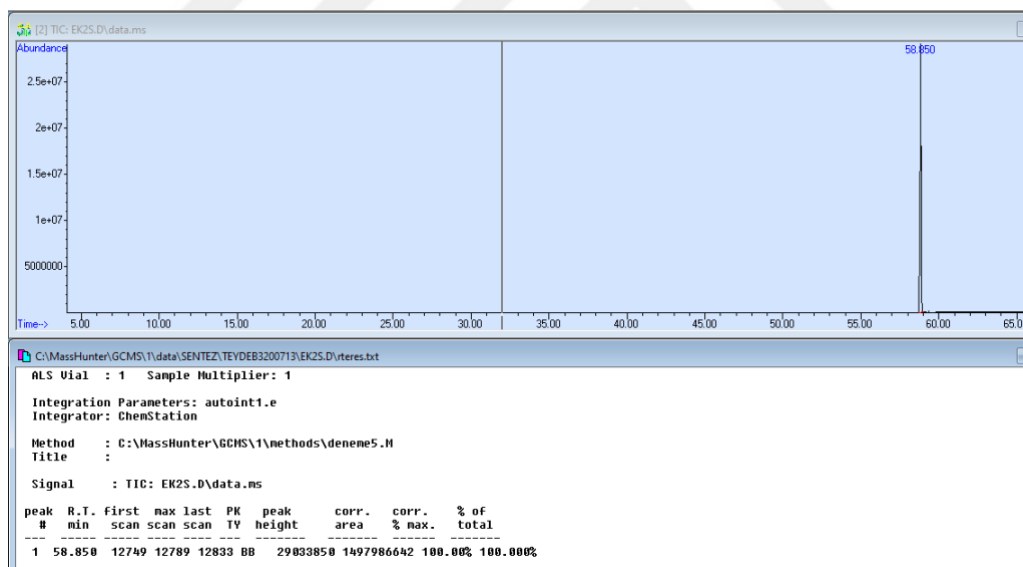


Figure 6-164-GC-MS spectrum of 2.4m

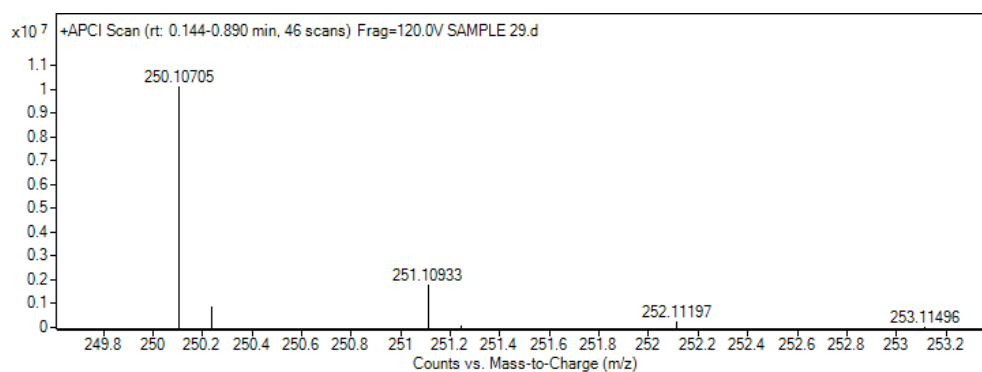


Figure 6-165-(TOF) LC-MS spectrum of 2.4m

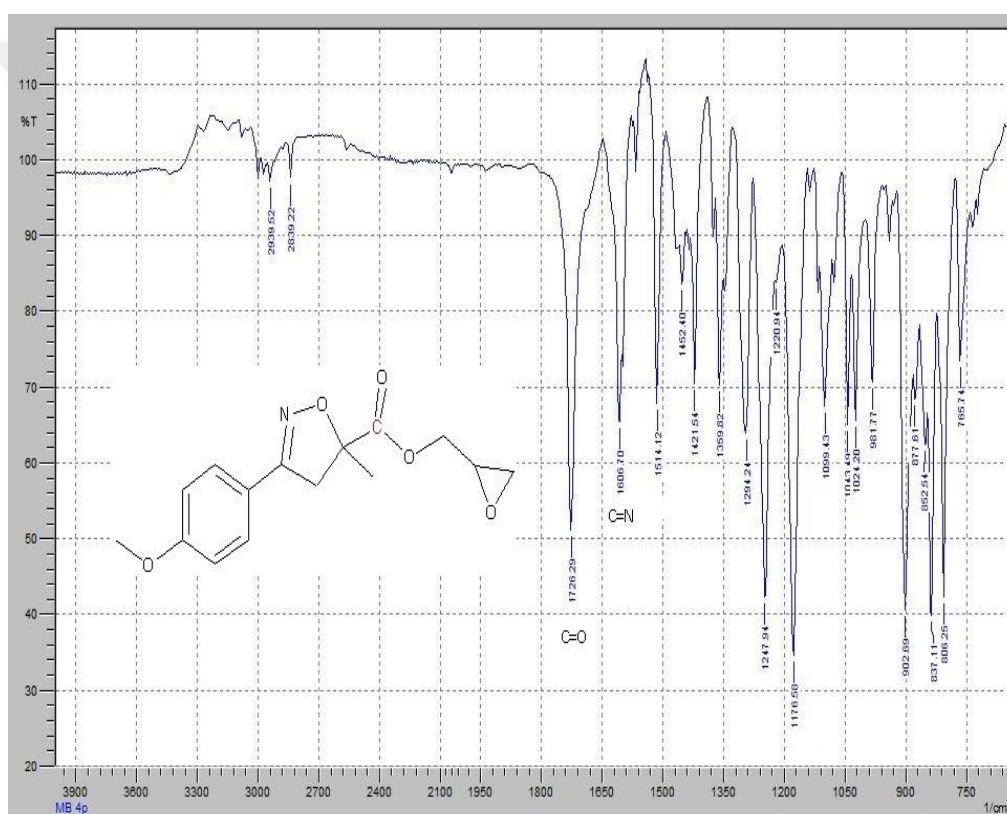


Figure 6-166-IR spectrum of 2.5m

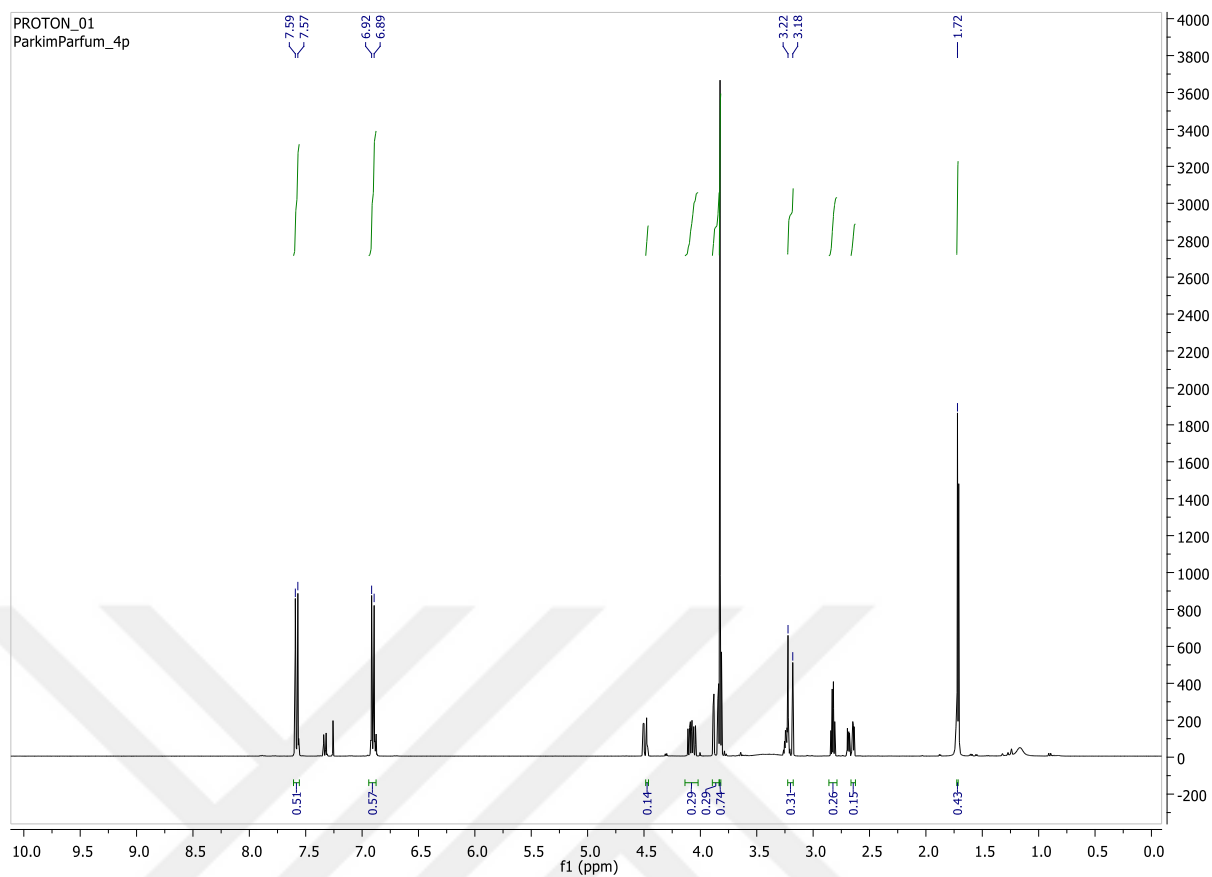


Figure 6-167- ^1H -NMR spectrum of 2.5m

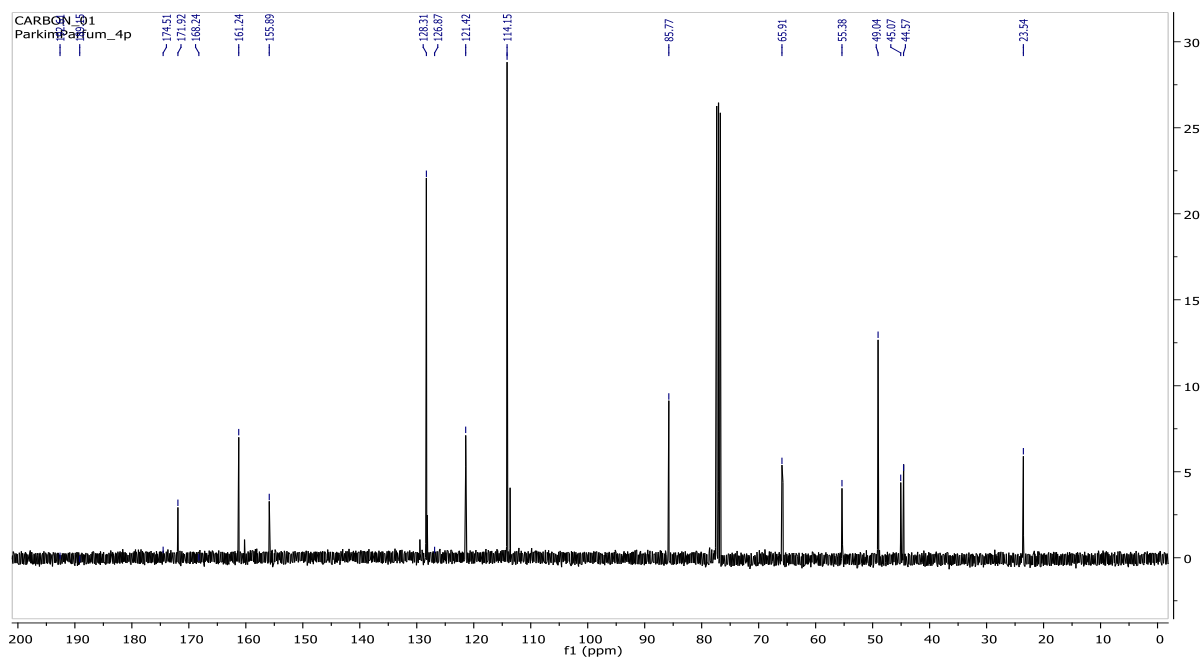


Figure 6-168- ^{13}C -NMR spectrum of 2.5m

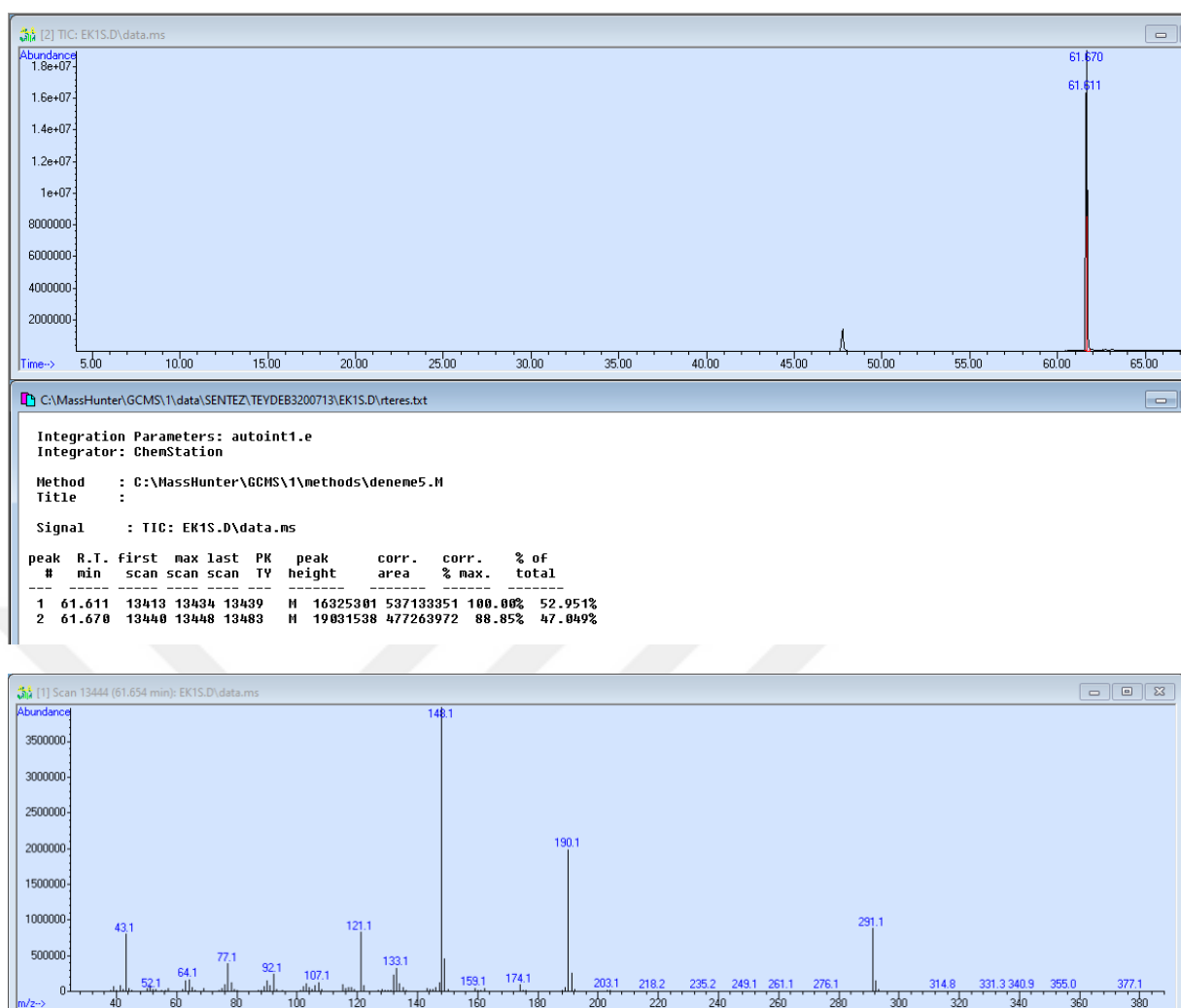


Figure 6-169-GC-MS spectrum of 2.5m

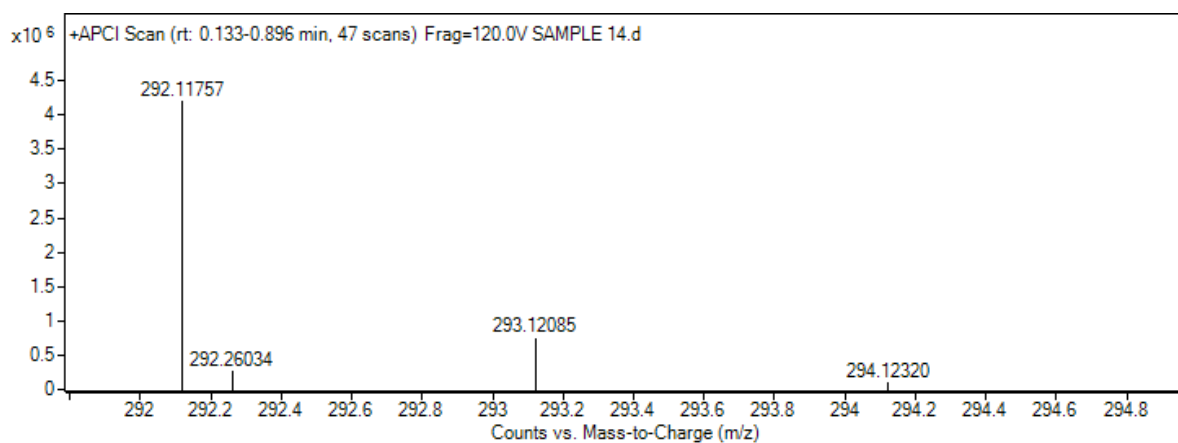


Figure 6-170-(TOF) LC-MS spectrum of 2.5m

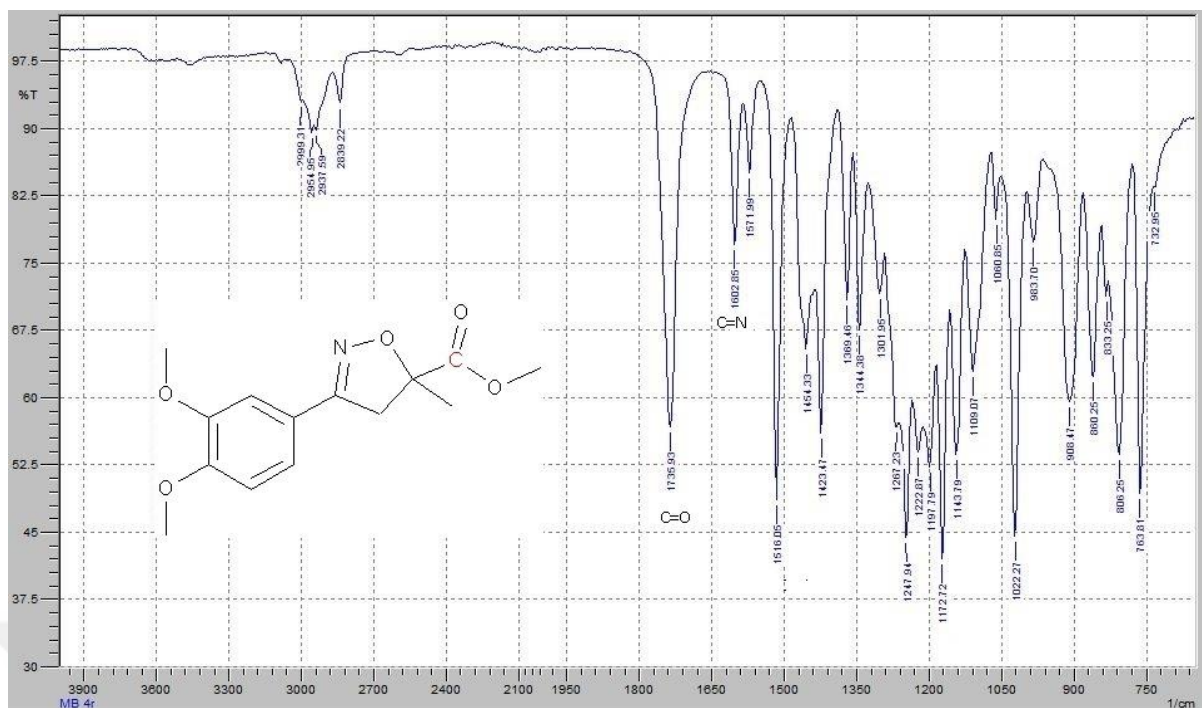


Figure 6-171-IR spectrum of 2.4n

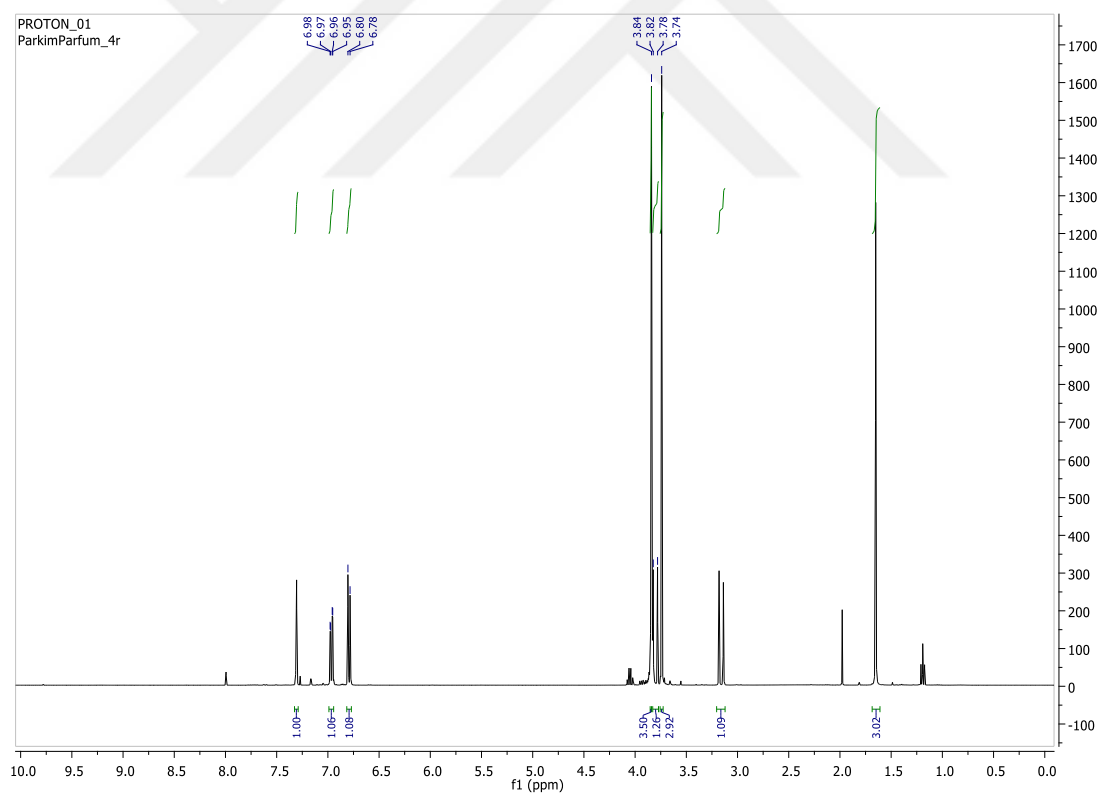


Figure 6-172-¹H-NMR spectrum of 2.4n

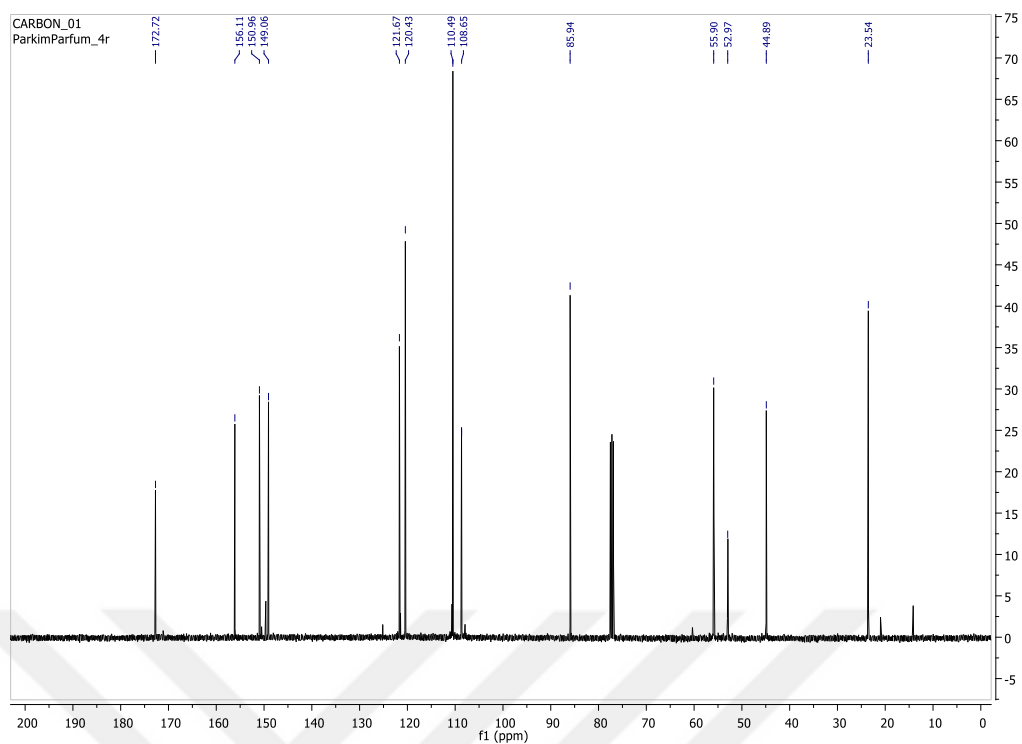


Figure 6-173- ^{13}C -NMR spectrum of 2.4n

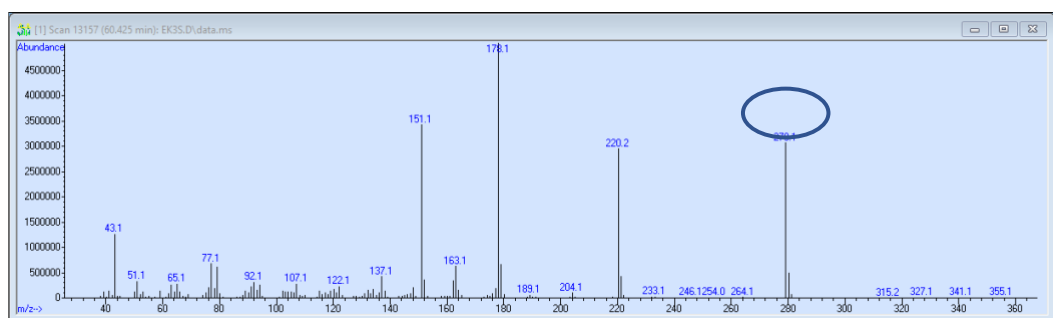
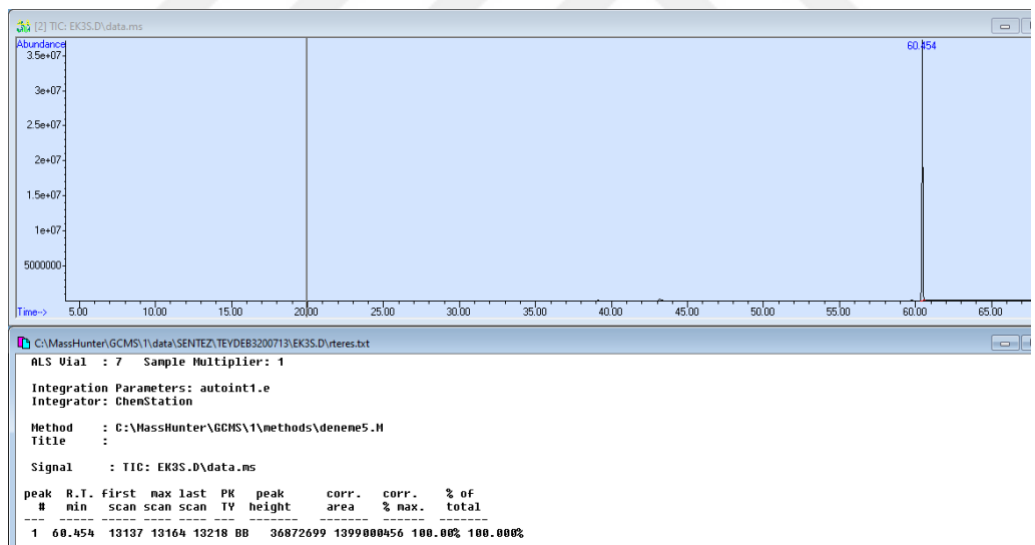


Figure 6-174-GC-MS spectrum of 2.4n

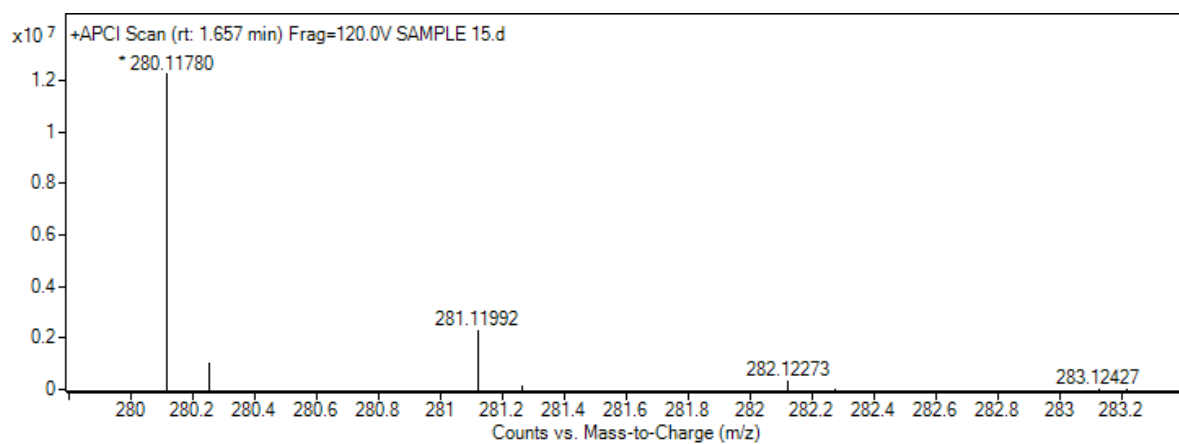


Figure 6-175-(TOF) LC-MS spectrum of 2.4n

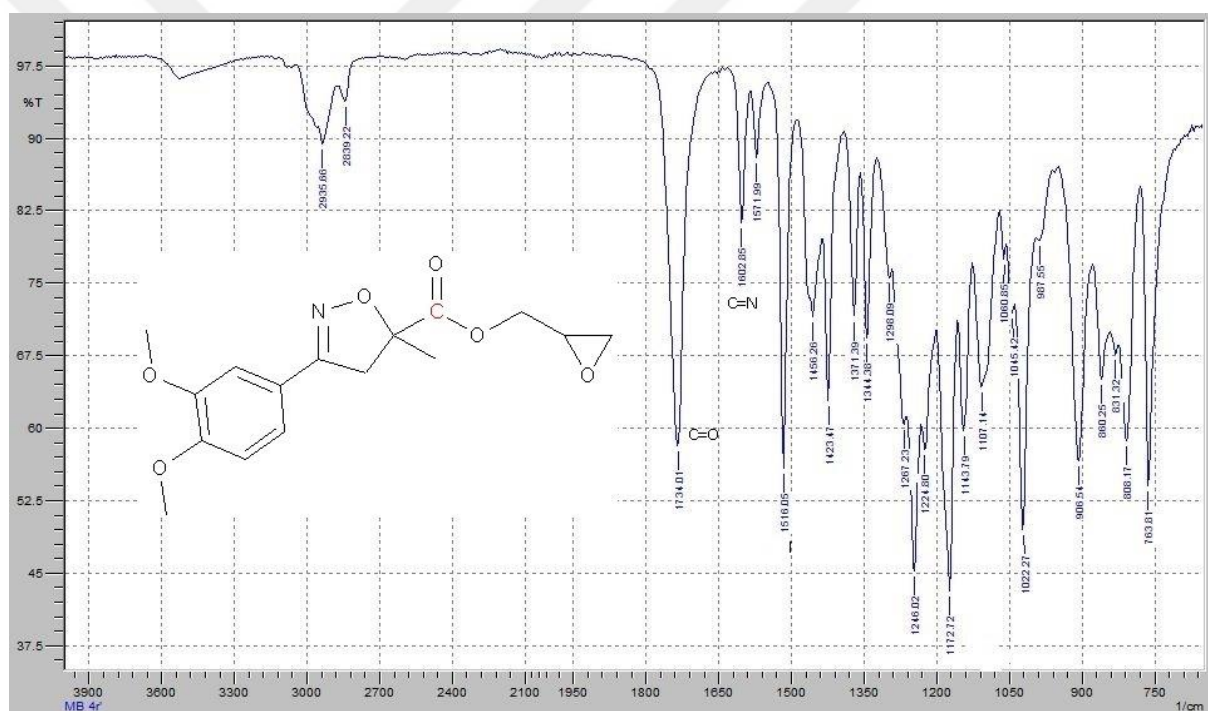


Figure 6-176-IR spectrum of 2.5n

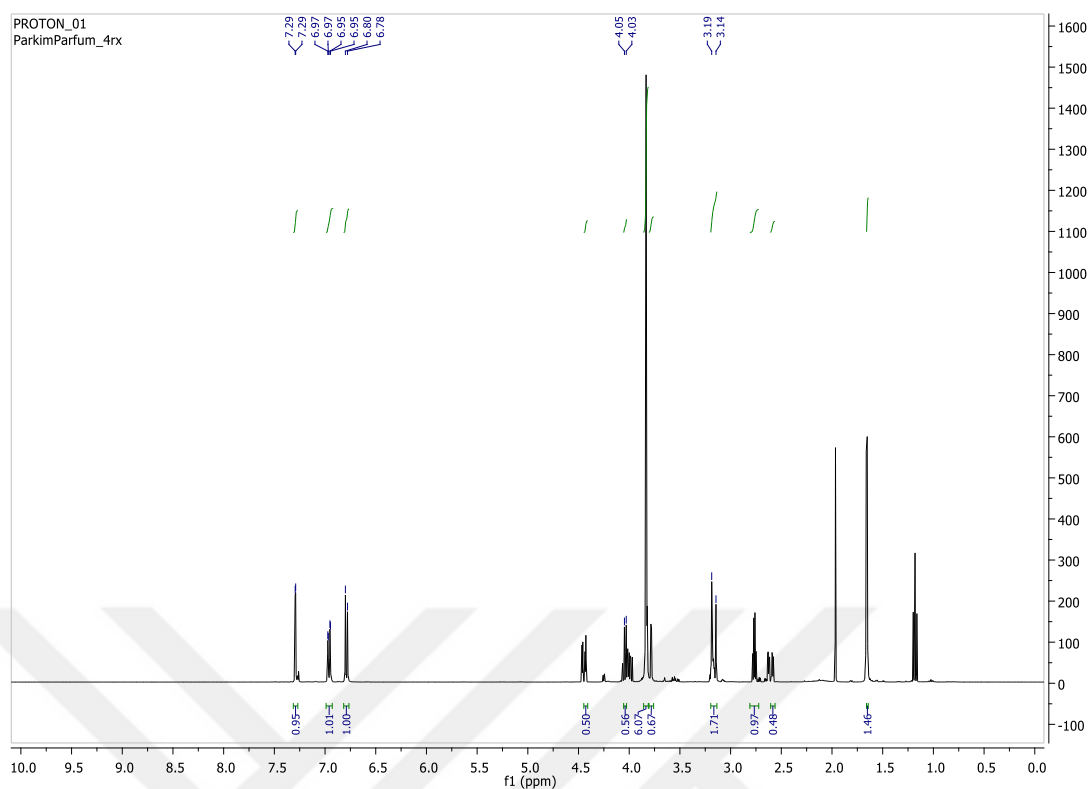


Figure 6-177- ^1H -NMR spectrum of 2.5n

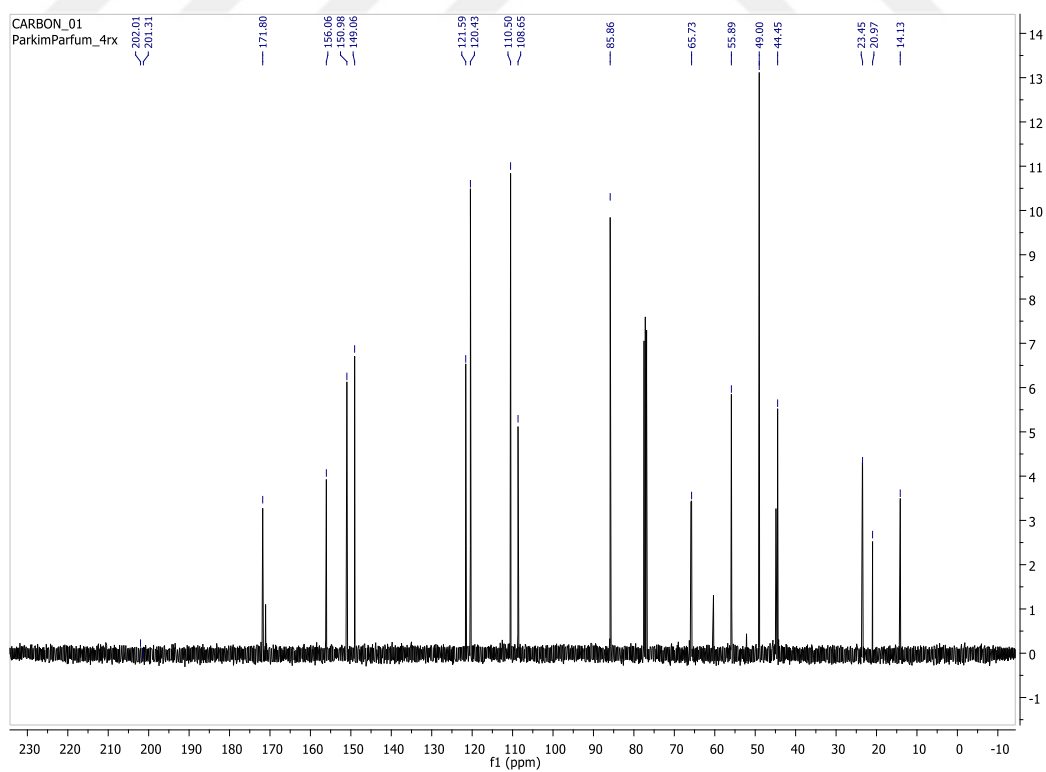


Figure 6-178- ^{13}C -NMR spectrum of 2.5n

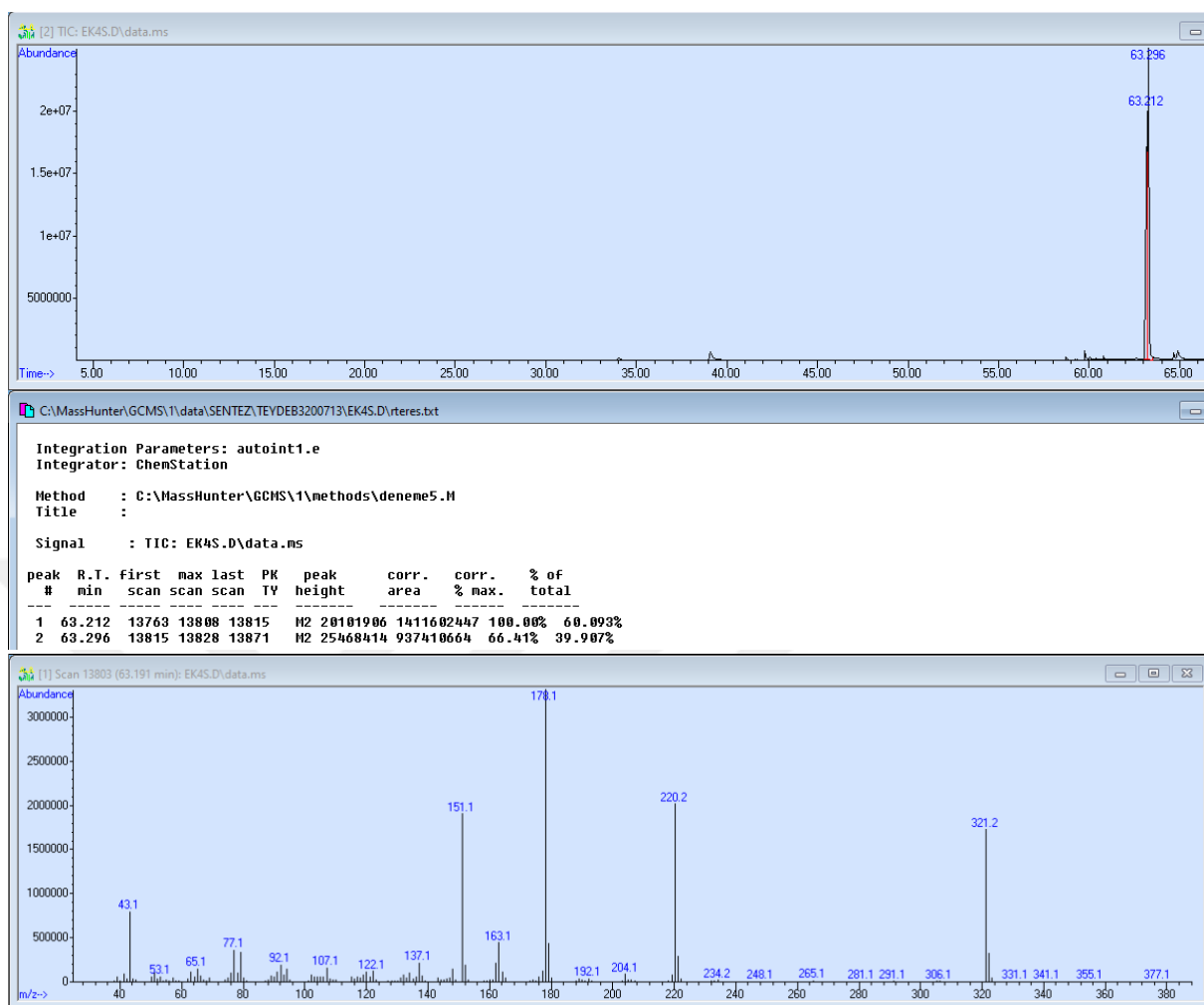


Figure 6-179-GC-MS spectrum of 2.5n

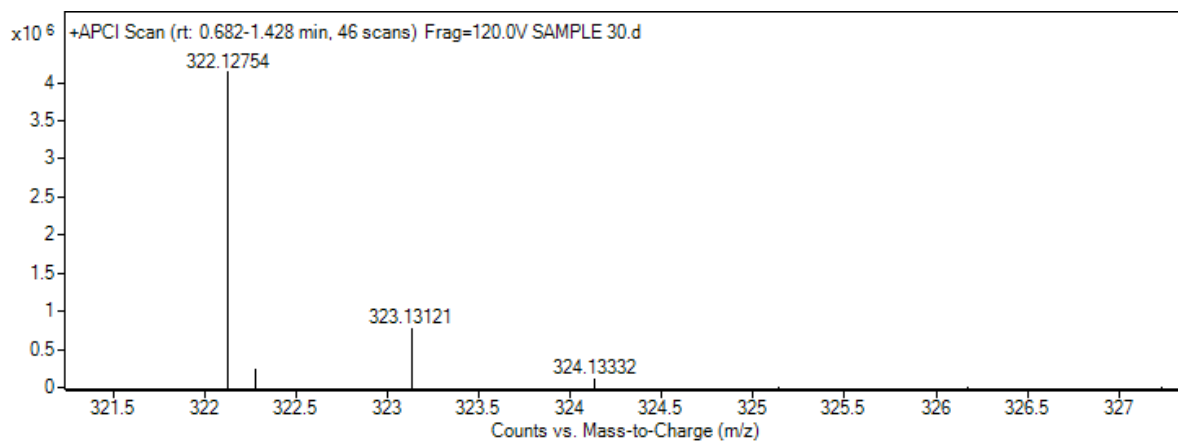


Figure 6-180-(TOF) LC-MS spectrum of 2.5n

^1H and ^{13}C NMR Spectra of 2.3a-e

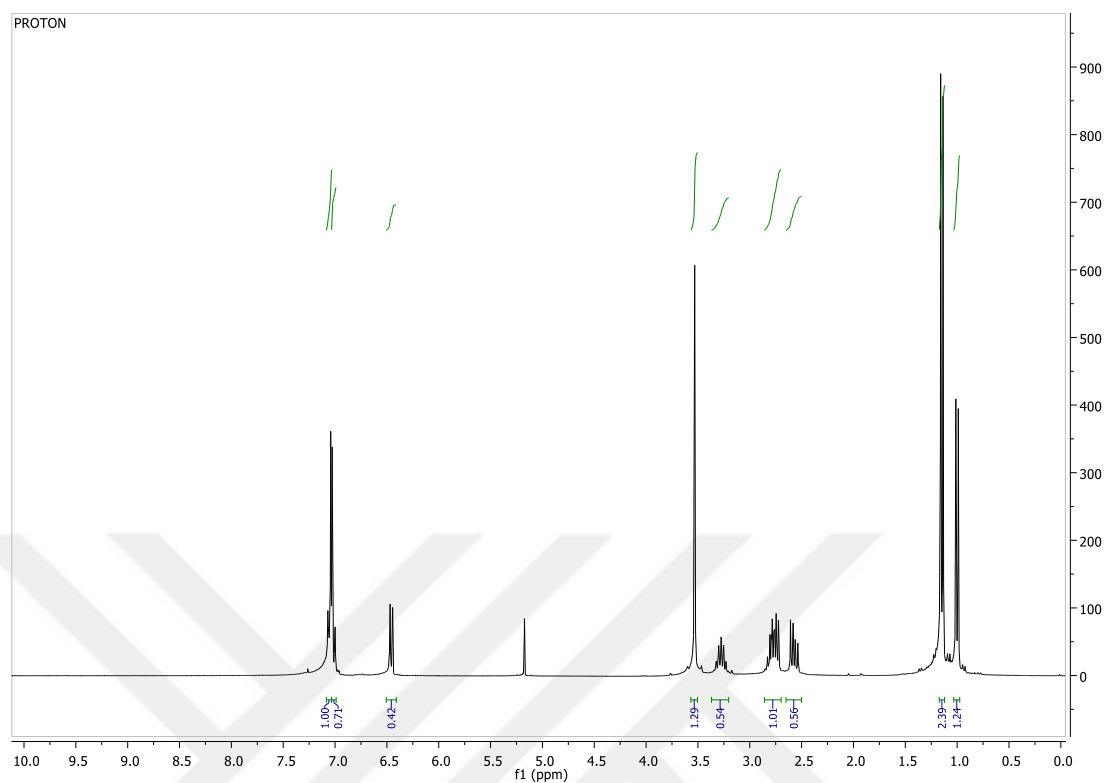


Figure 6-181- ^1H -NMR spectrum of 2.3a

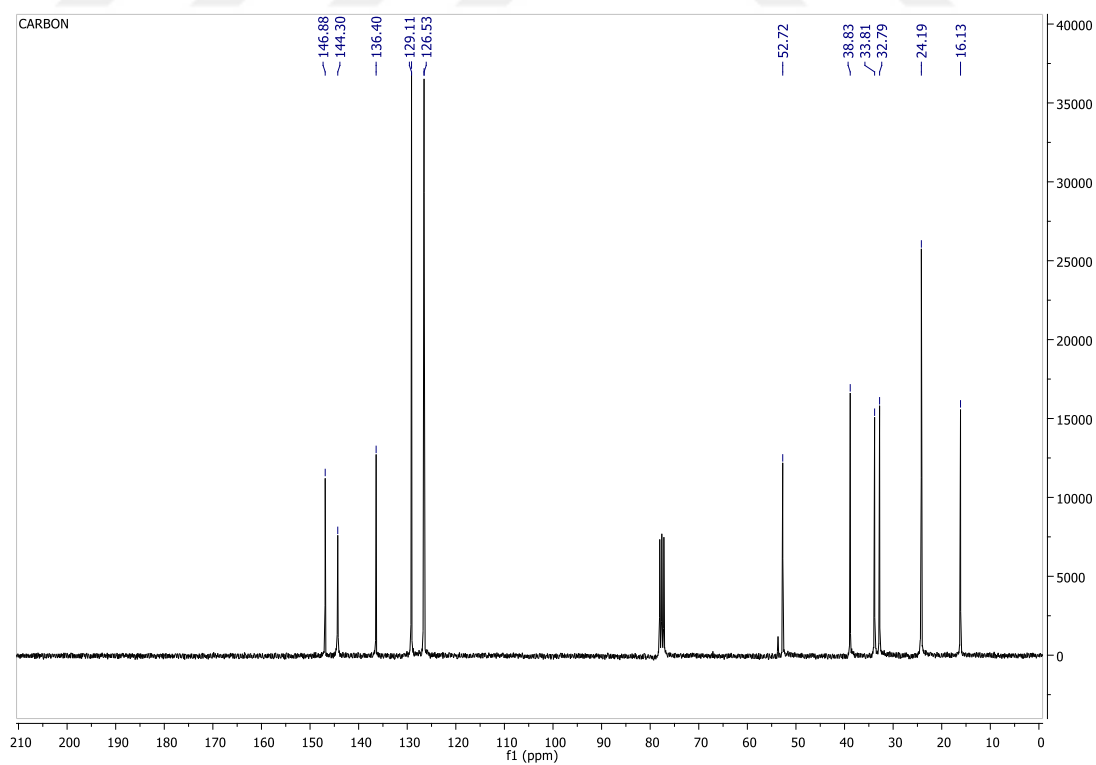


Figure 6-182- ^{13}C -NMR spectrum of 2.3a

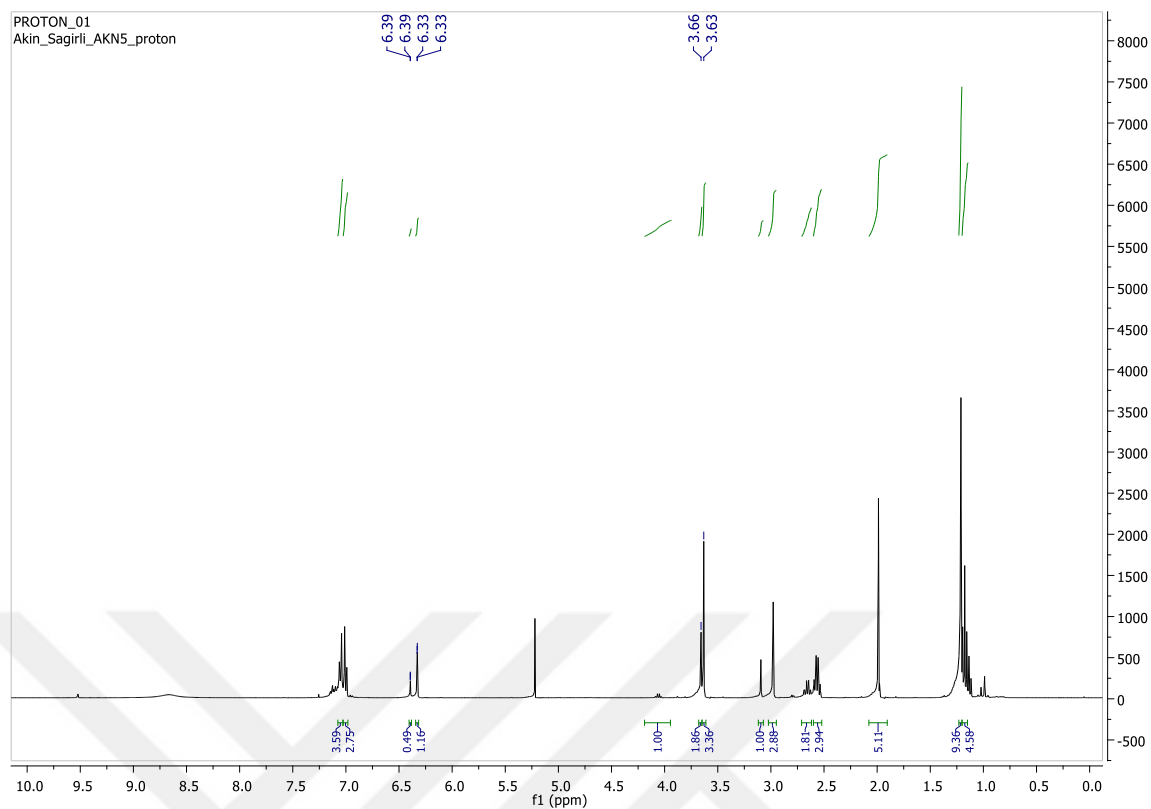


Figure 6-183- ^1H -NMR spectrum of 2.3c

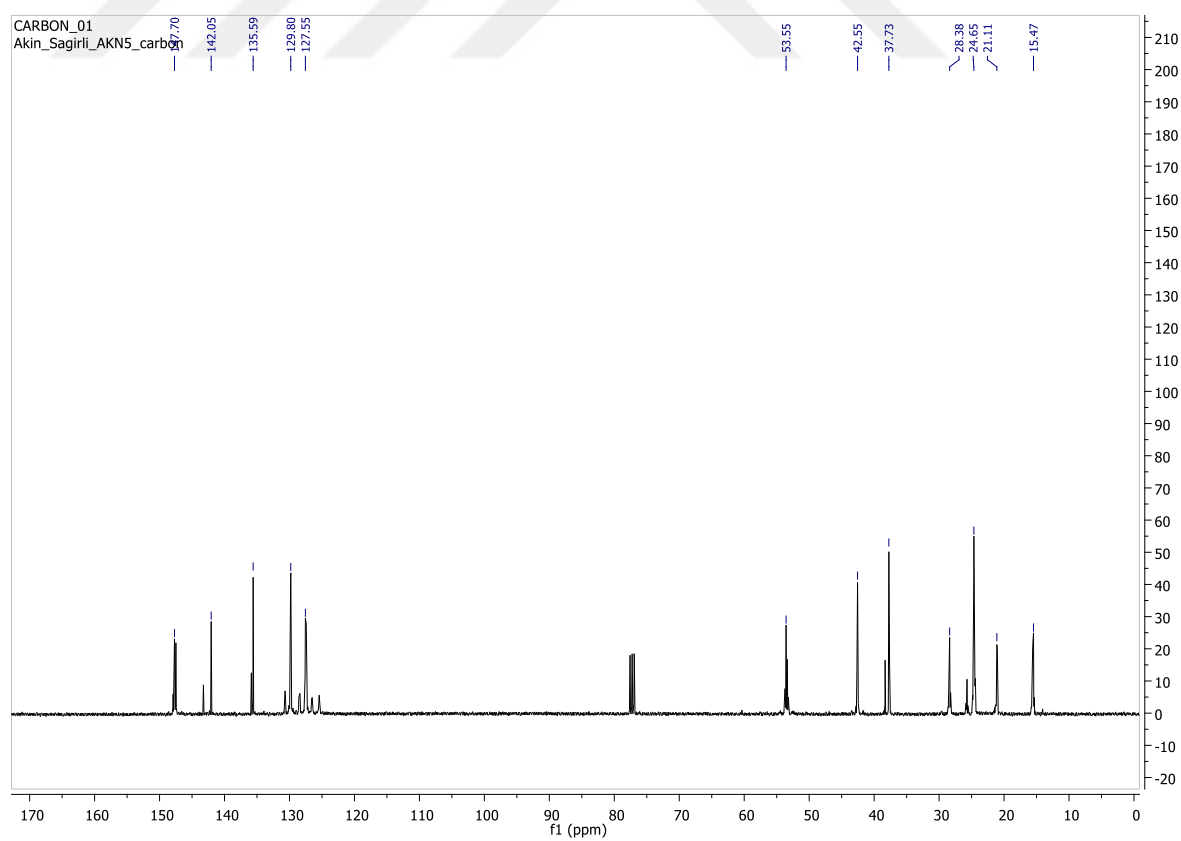


Figure 6-184- ^{13}C -NMR spectrum of 2.3c

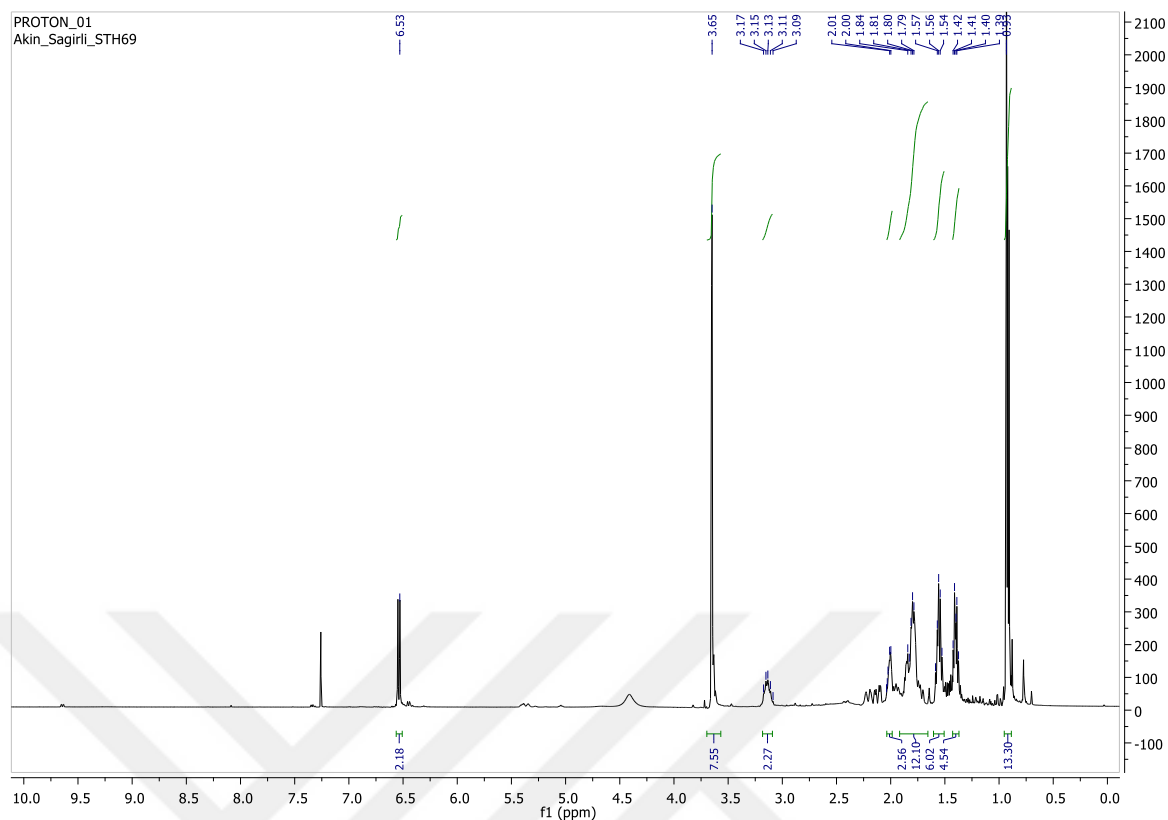


Figure 6-185- ^1H -NMR spectrum of 2.3d

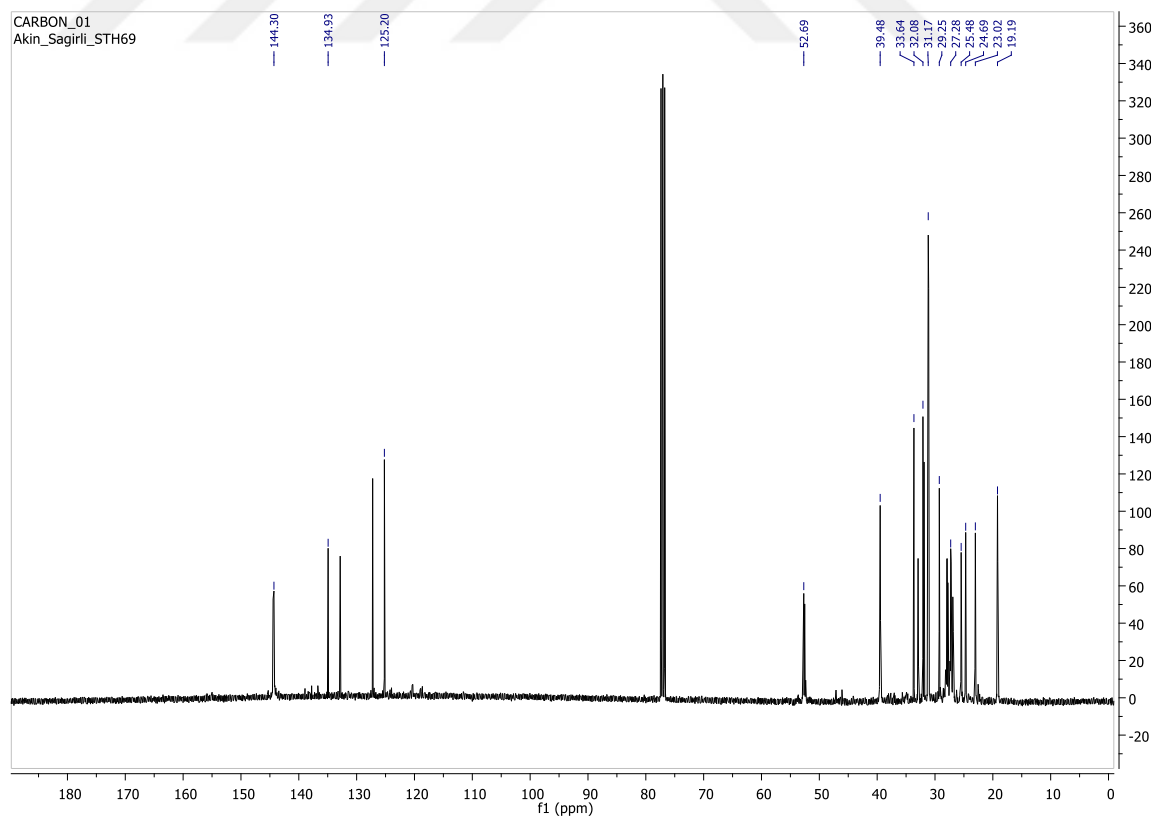


Figure 6-186- ^{13}C -NMR spectrum of 2.3d

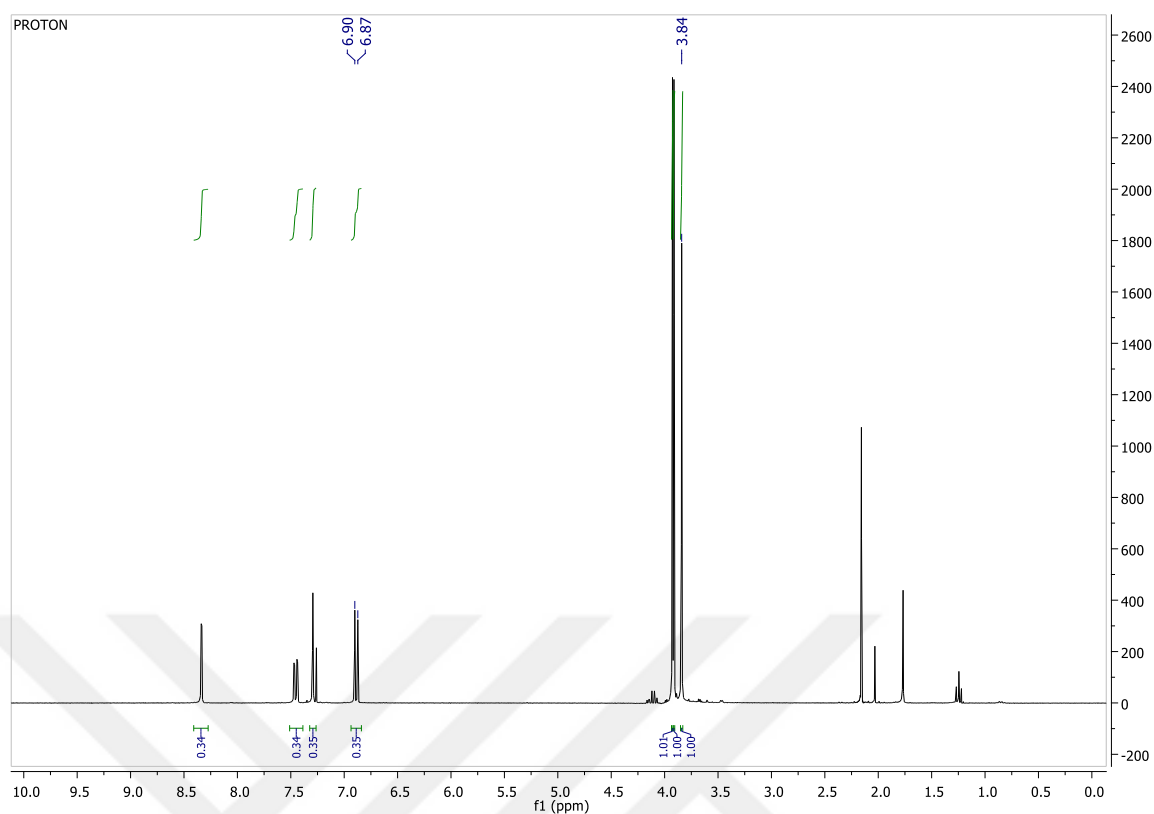


Figure 6-187- ^1H -NMR spectrum of 2.3e

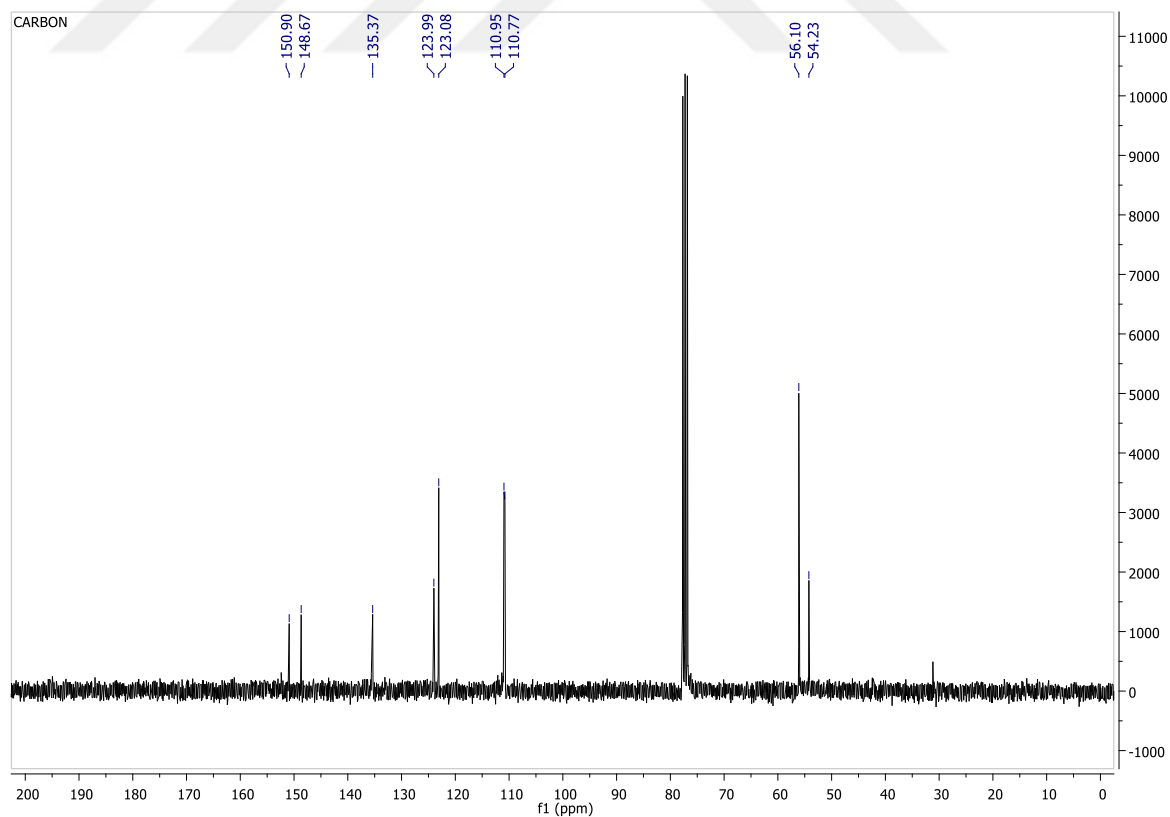


Figure 6-188- ^{13}C -NMR spectrum of 2.3e

^1H and ^{13}C NMR Spectra of isoxazolidine-5-carboxylates 2.6, 2.6', 2.7, 2.7'

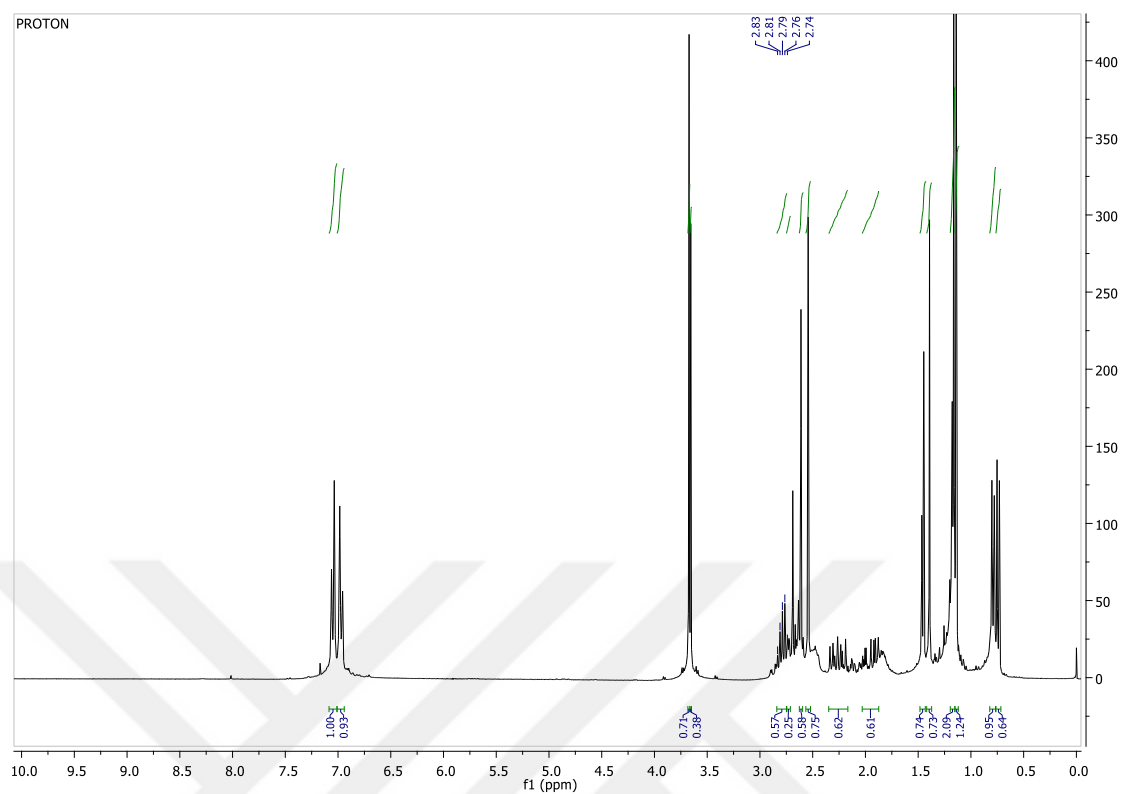


Figure 6-189- ^1H -NMR spectrum of 2.6a-2.6a'

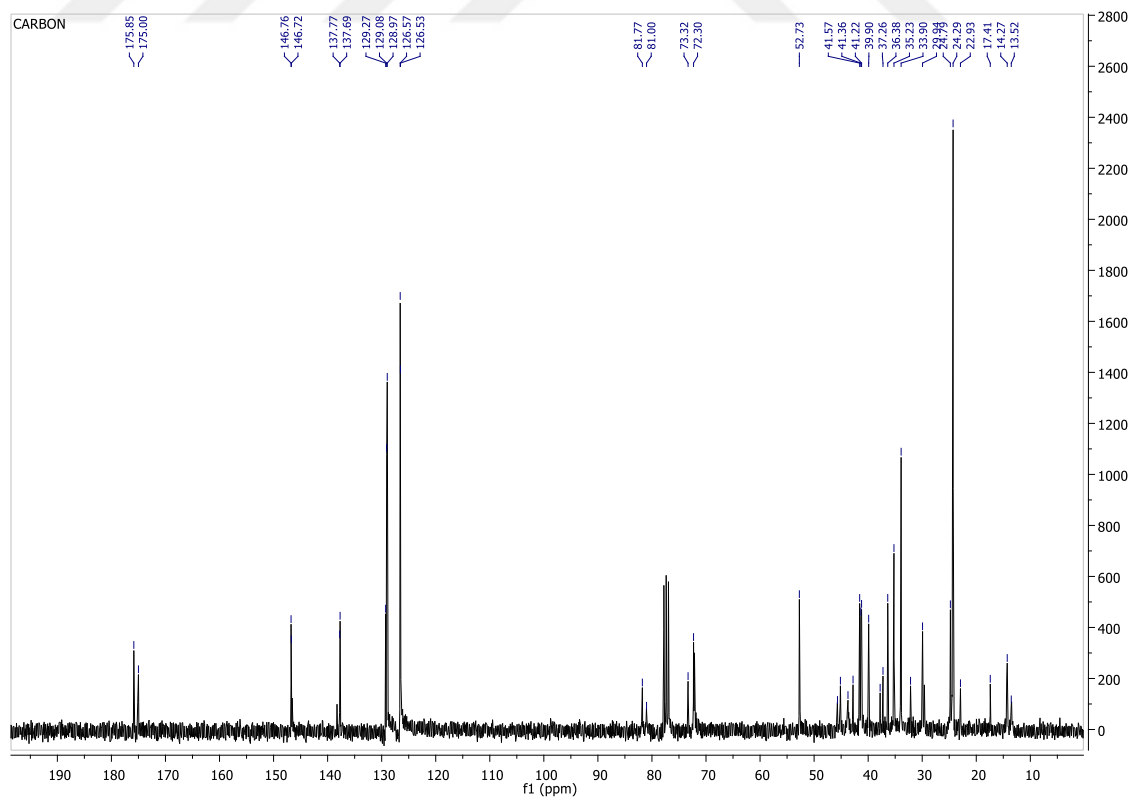


Figure 6-190- ^{13}C -NMR spectrum of 2.6a-2.6a'

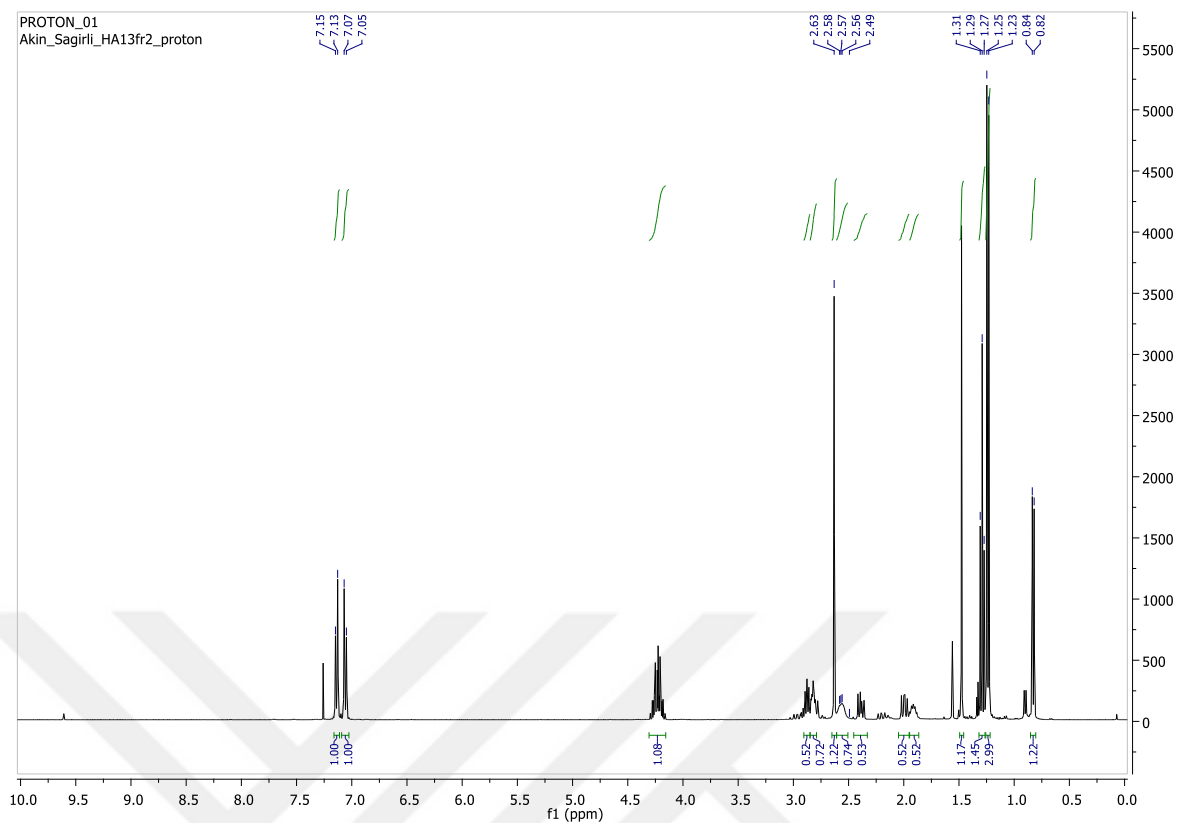


Figure 6-191- ^1H -NMR spectrum of 2.7a

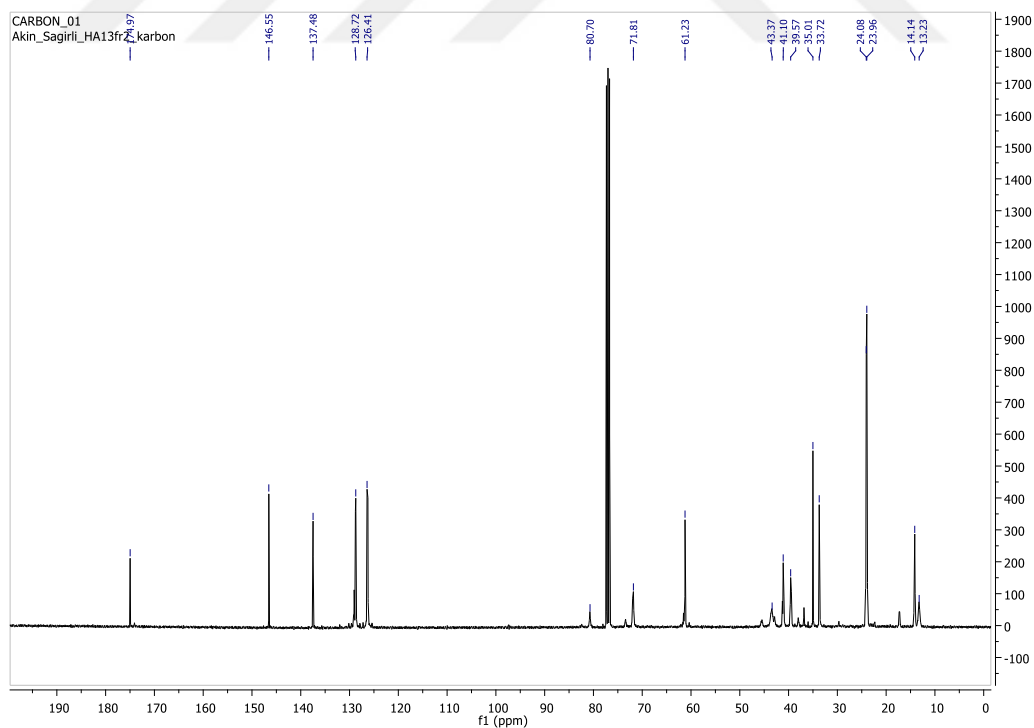


Figure 6-192- ^{13}C -NMR spectrum of 2.7a

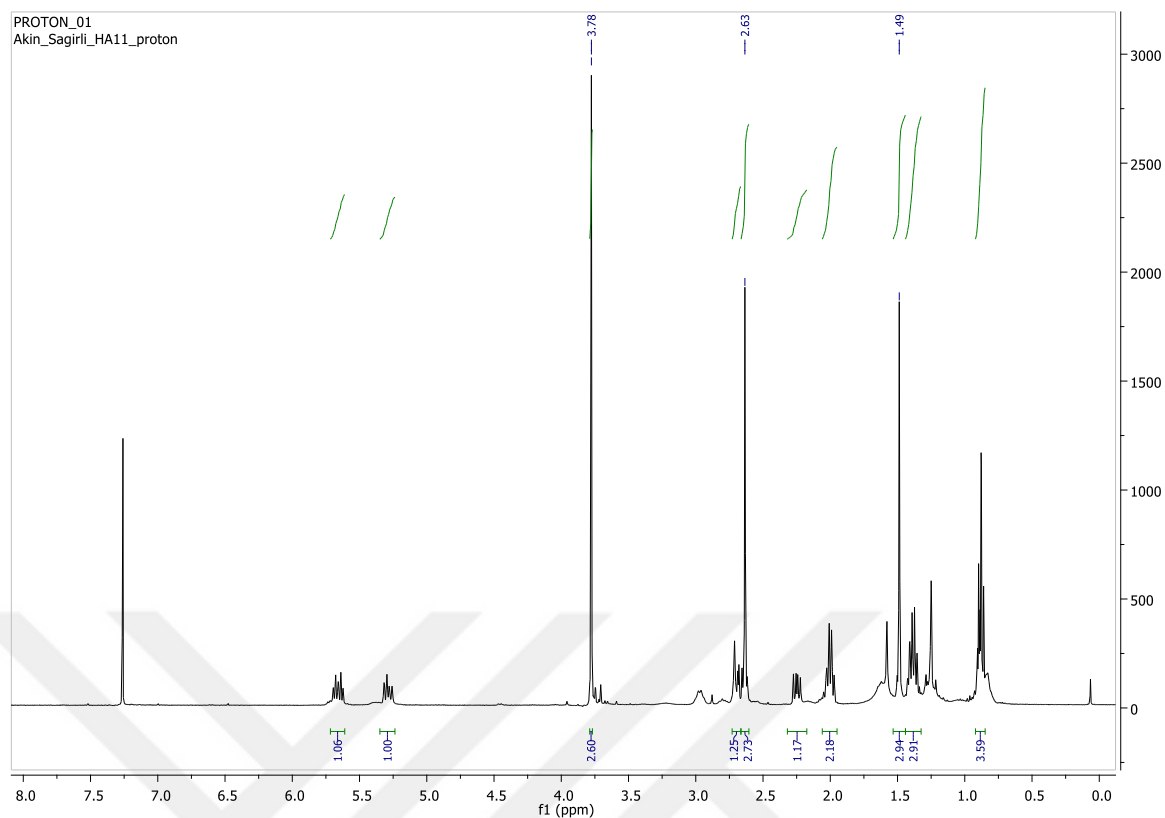


Figure 6-193- ^1H -NMR spectrum of 2.6b

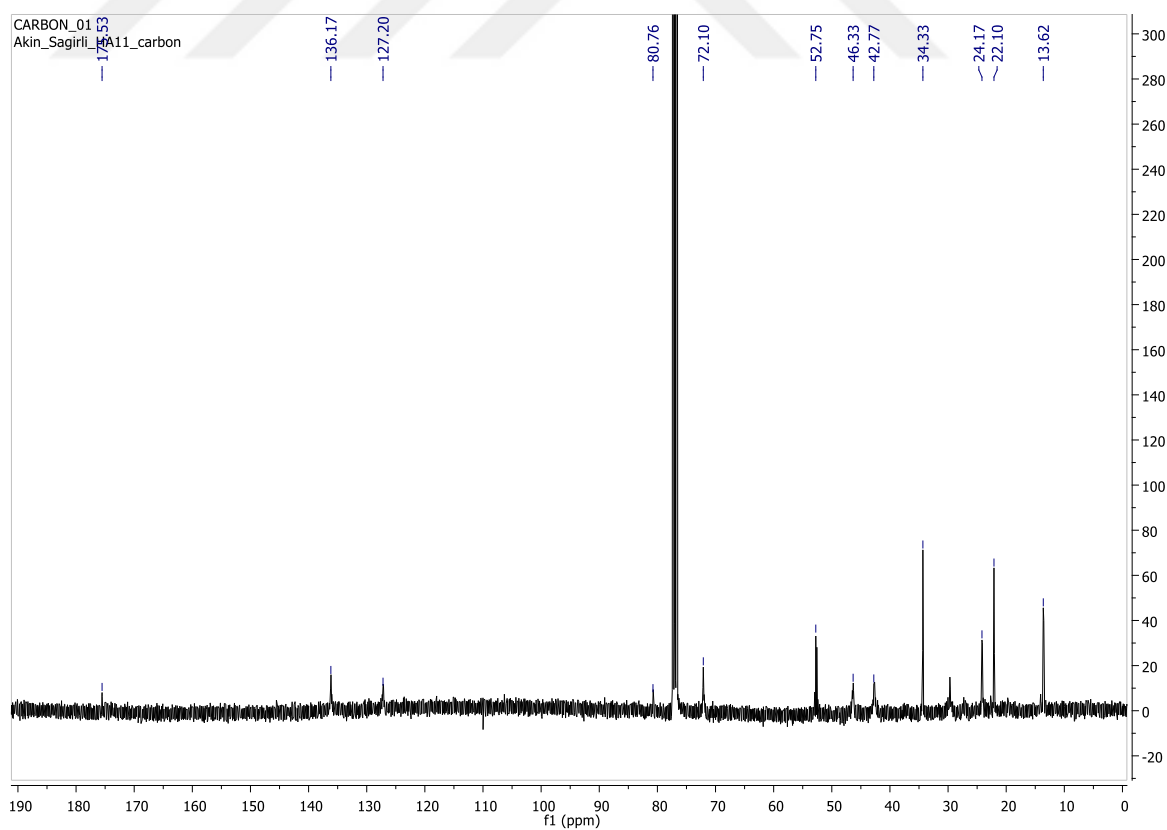


Figure 6-194- ^{13}C -NMR spectrum of 2.6b

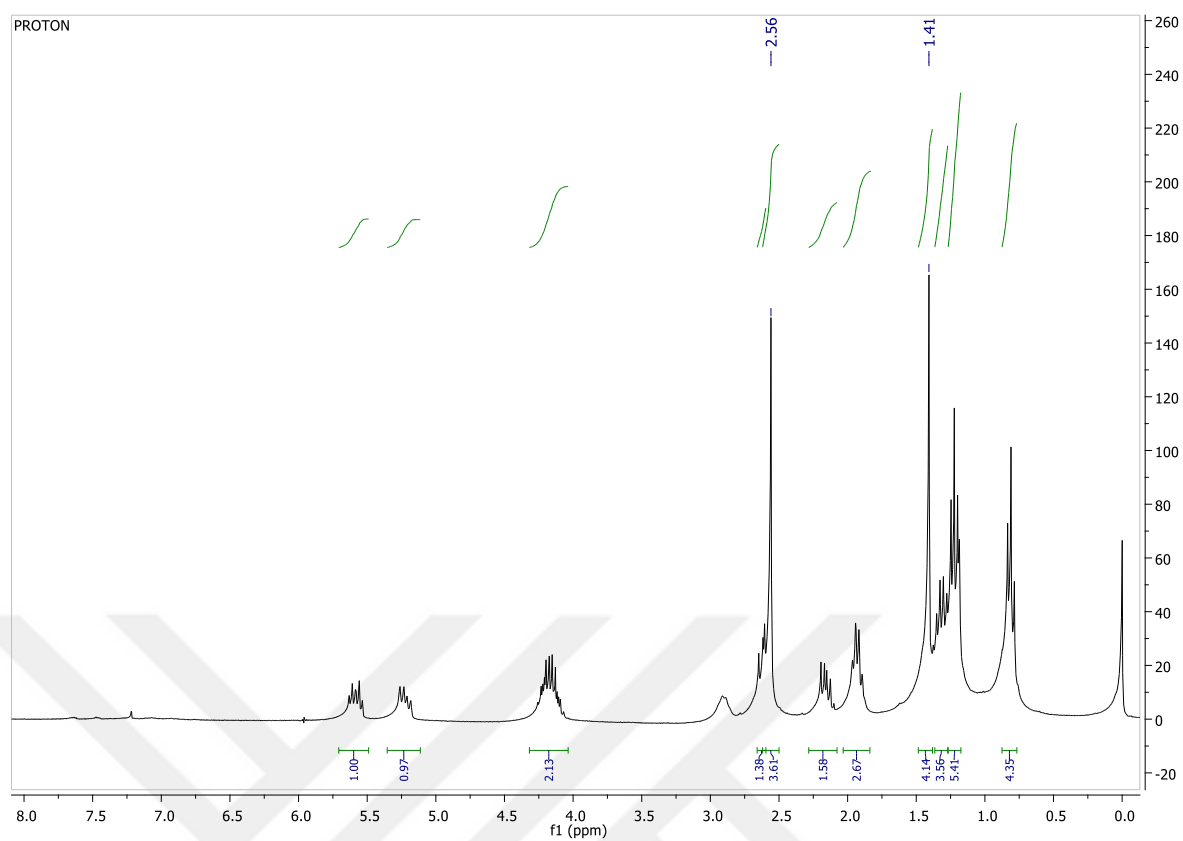


Figure 6-195- ^1H -NMR spectrum of 2.7b

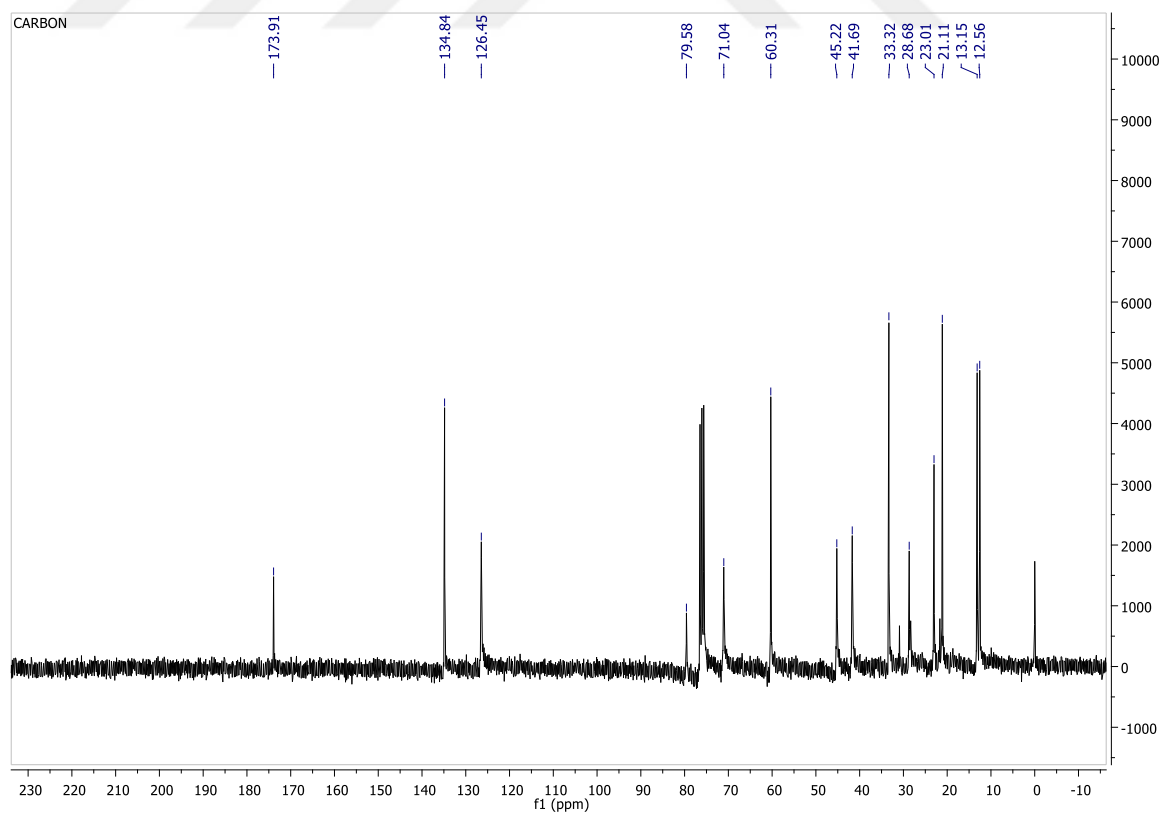


Figure 6-196- ^{13}C -NMR spectrum of 2.7b

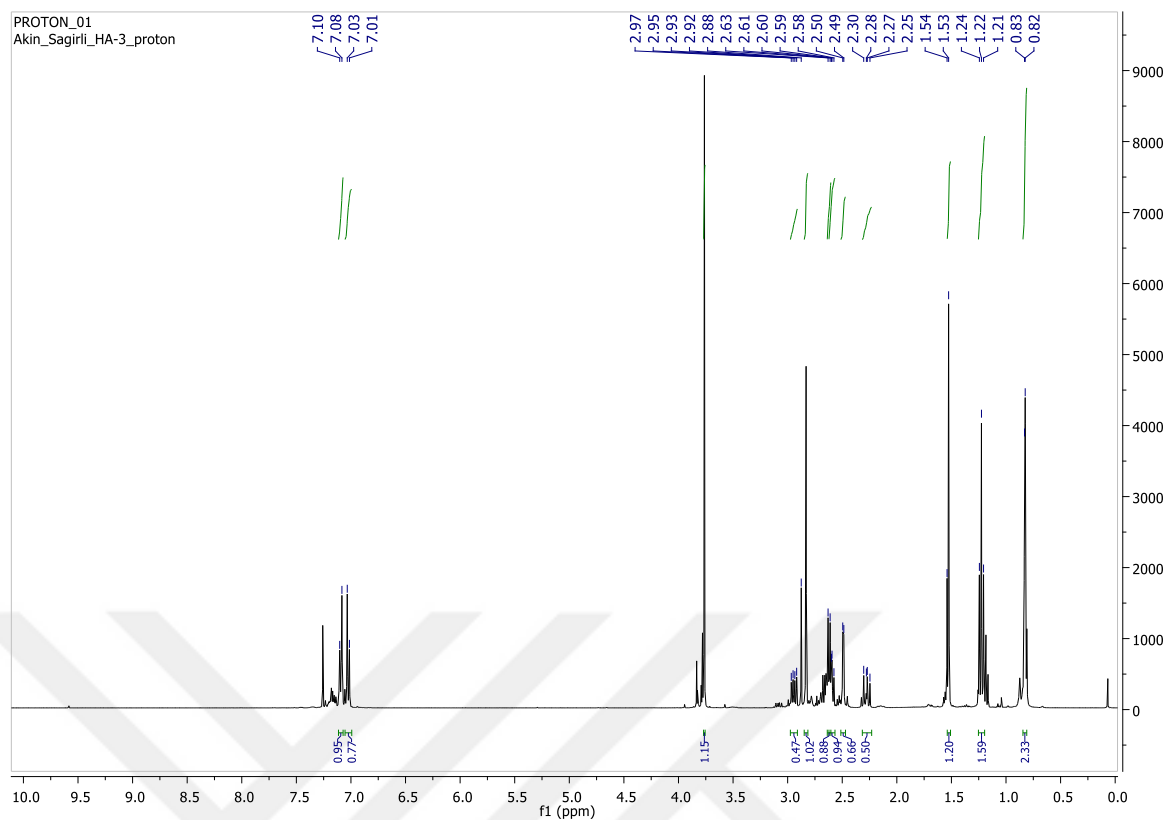


Figure 6-197- ^1H -NMR spectrum of 2.6c-2.6c'

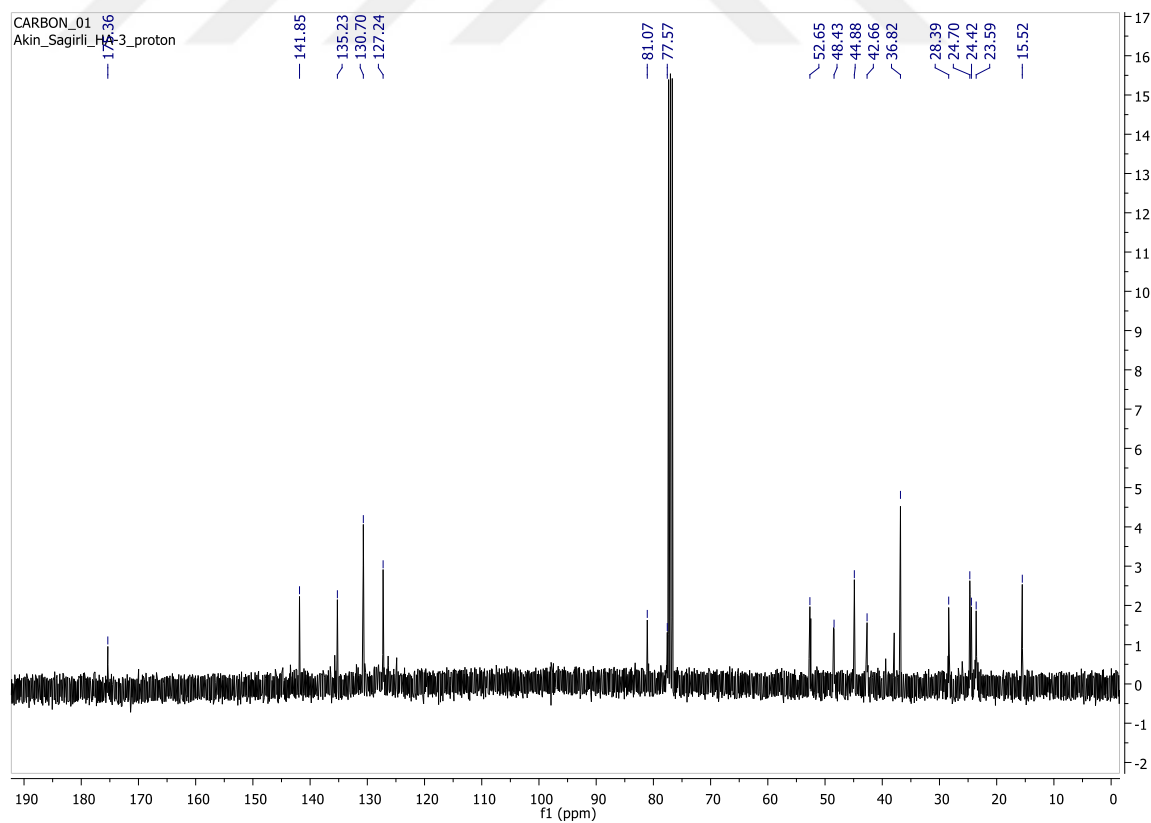


Figure 6-198- ^{13}C -NMR spectrum of 2.6c-2.6c'

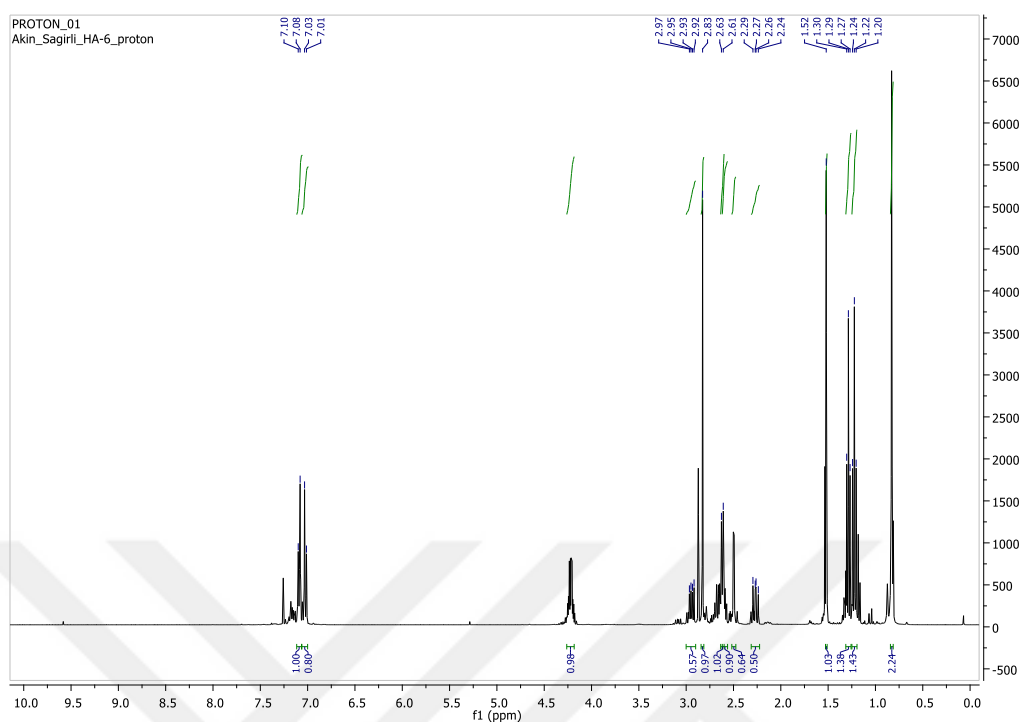


Figure 6-199- ^1H -NMR spectrum of 2.7c-2.7c'

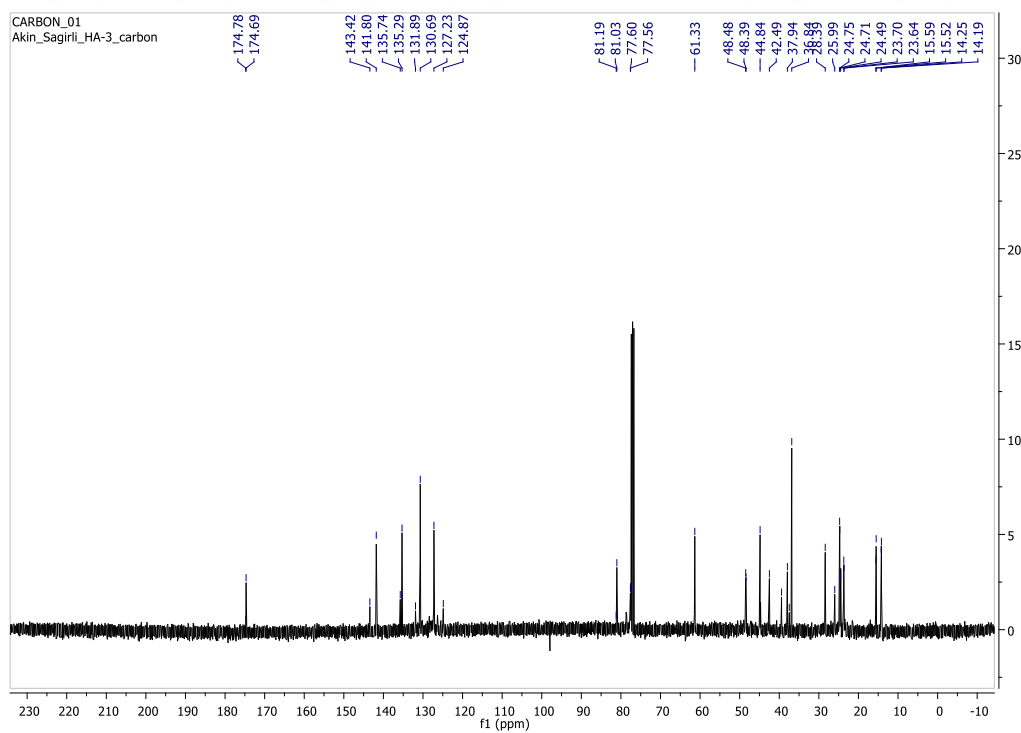


Figure 6-200- ^{13}C -NMR spectrum of 2.7c-2.7c'

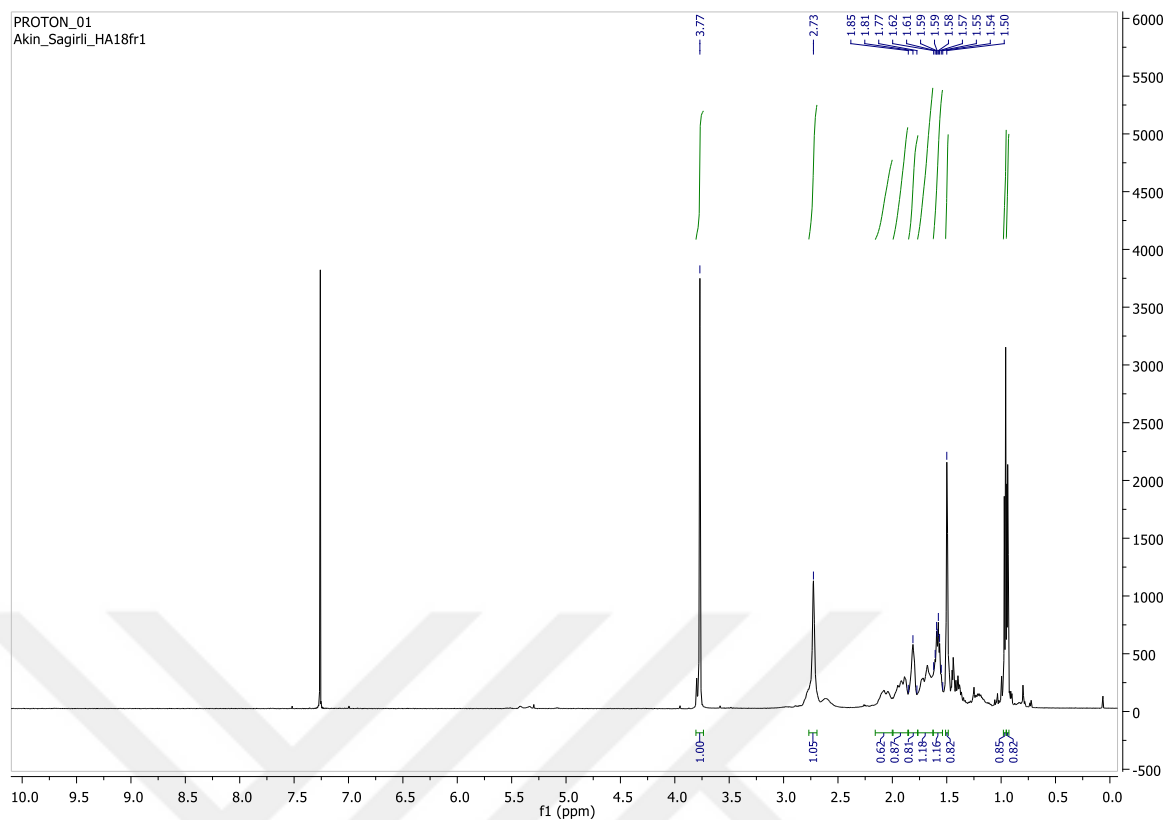


Figure 6-201- ^1H -NMR spectrum of 2.6d

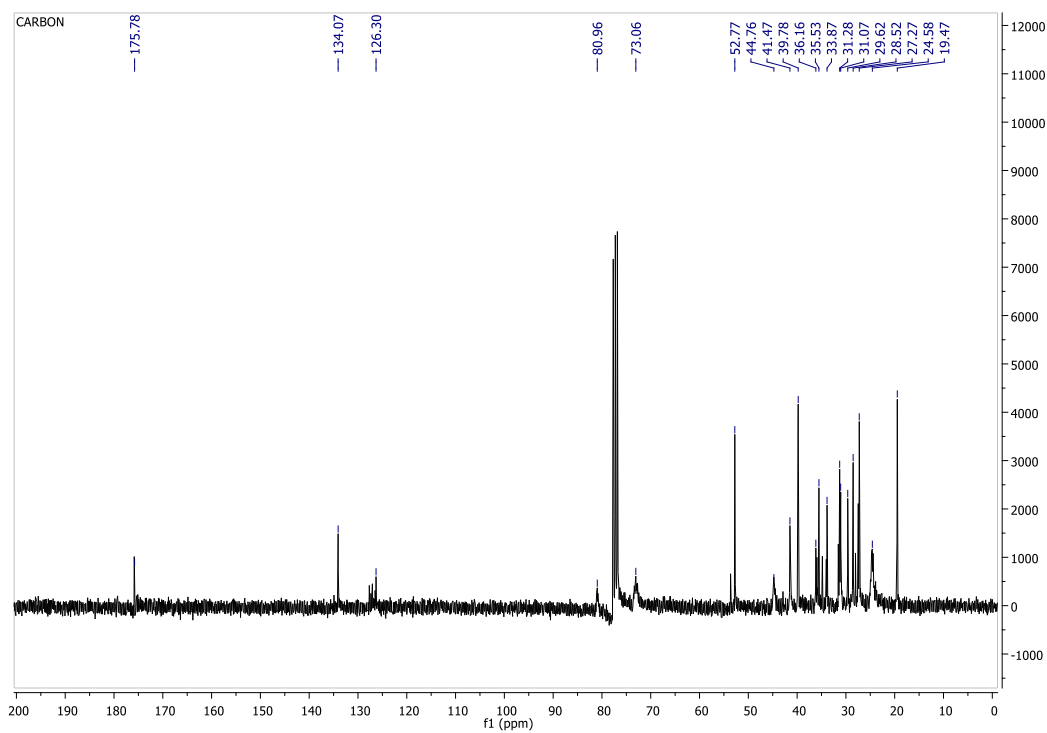


Figure 6-202- ^{13}C -NMR spectrum of 2.6d

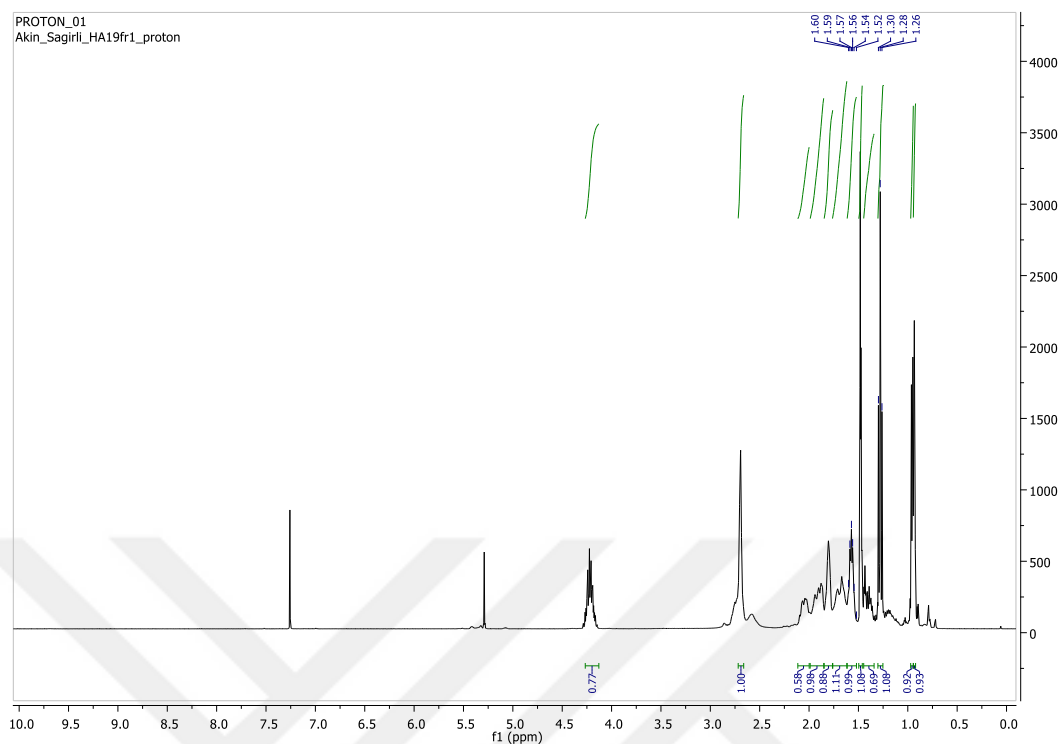


Figure 6-203- ^1H -NMR spectrum of 2.7d

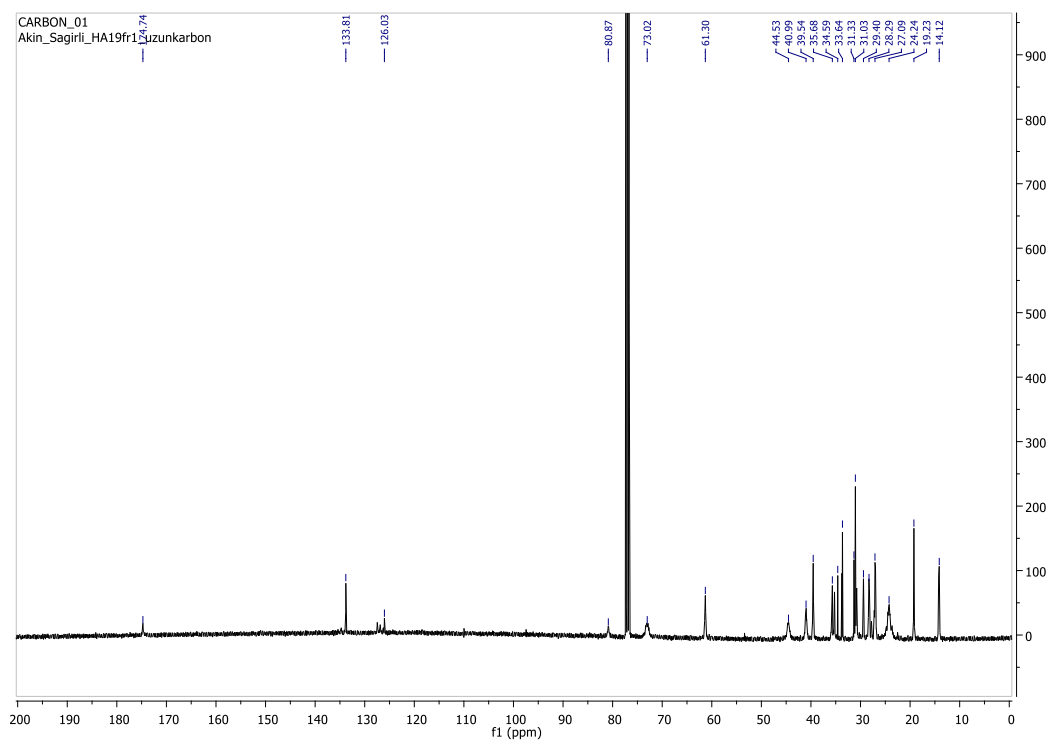


Figure 6-204- ^{13}C -NMR spectrum of 2.7d

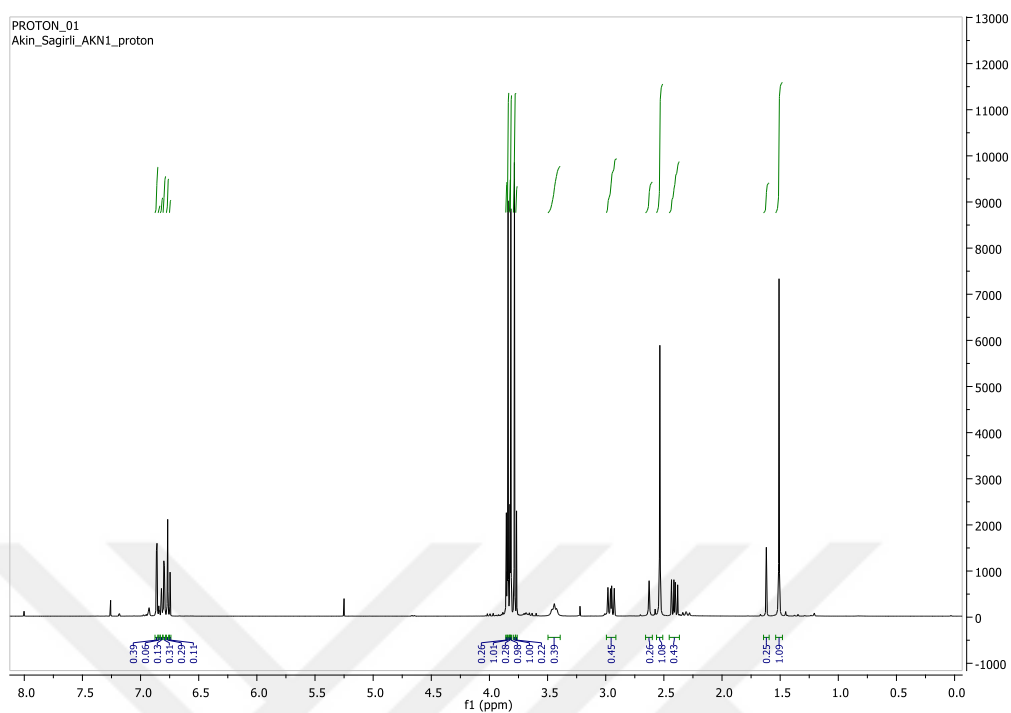


Figure 6-205- ^1H -NMR spectrum of 2.6e-2.6e'

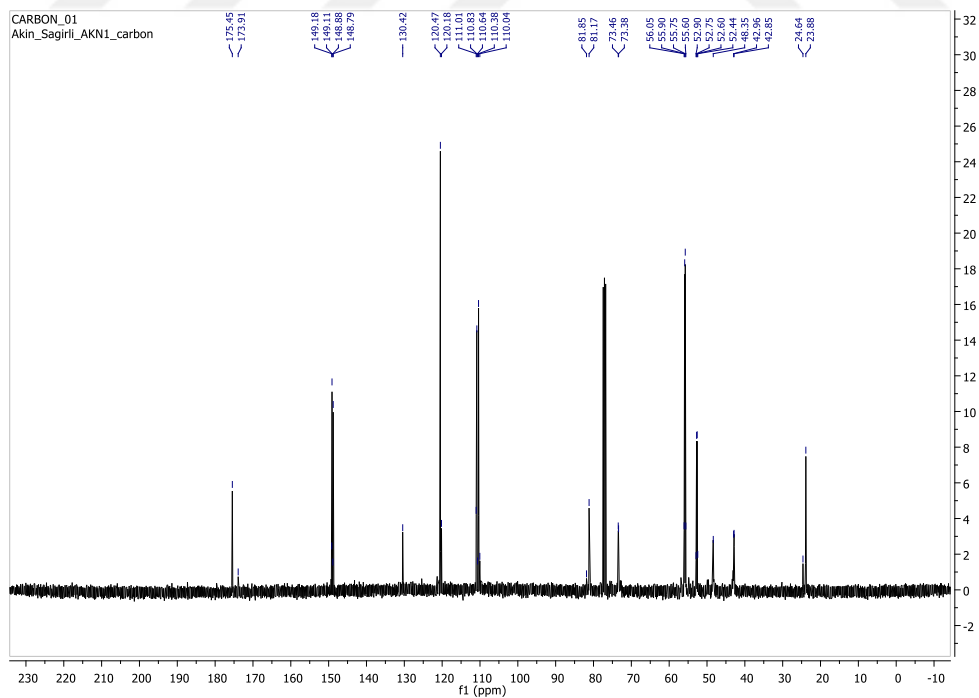


Figure 6-206- ^{13}C -NMR spectrum of 2.6e-2.6e'

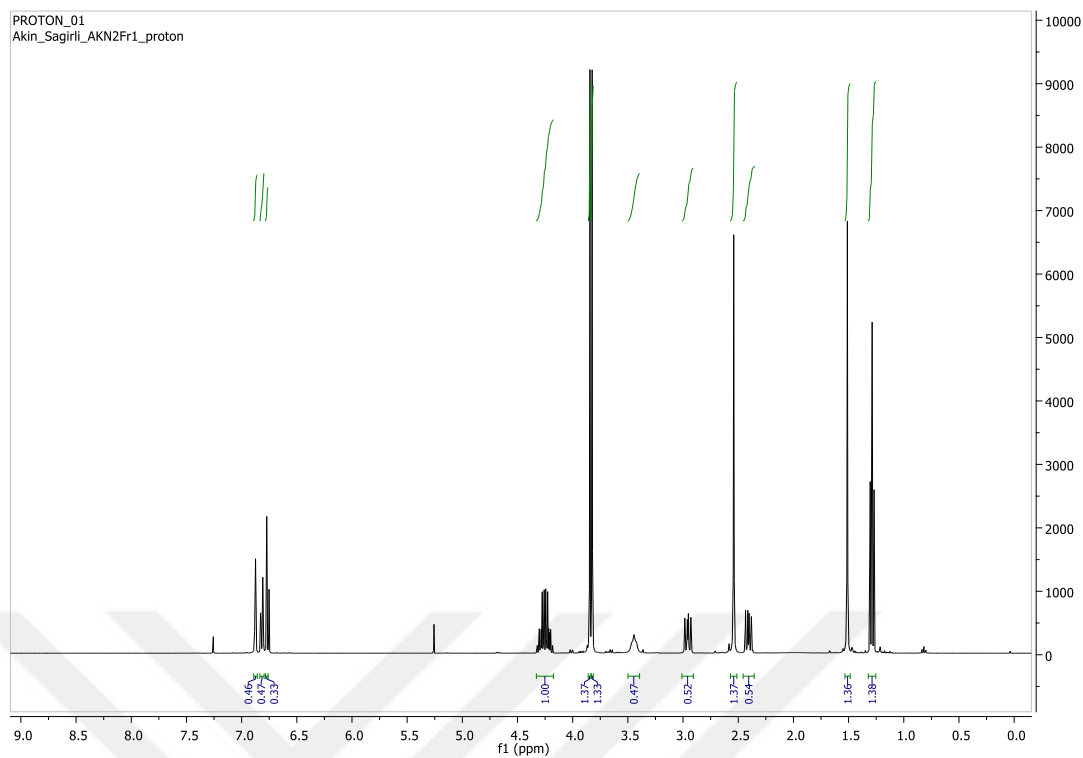


Figure 6-207- ^1H -NMR spectrum of 2.7e

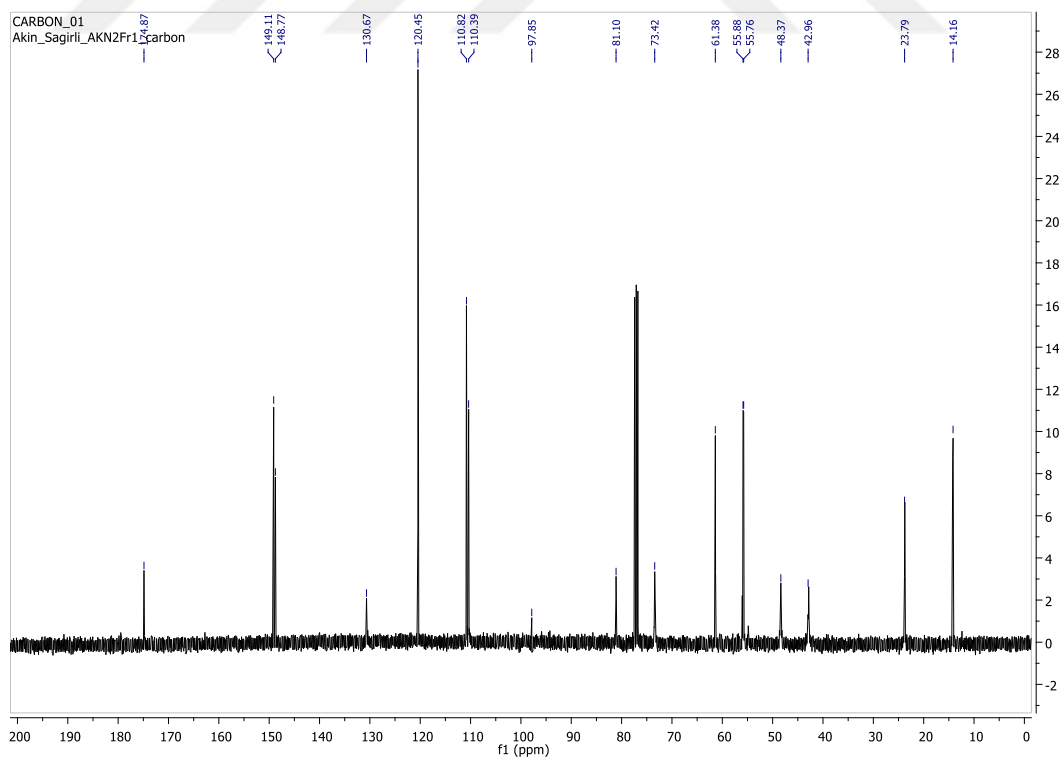


Figure 6-208- ^{13}C -NMR spectrum of 2.7e

Microbial Assessment of 2.4 and 2.5

ANALYSIS REPORT

EXPLANATION: -

Microbiological quality control of the product		Neutralizing Validation
Bacteria (cfu/g.)	1/10	DE Broth
Neutralizing Validation (cfu/g.)	1/10	DE Broth

Used Media and Incubation Times-Temperatures

Analysis	Total Microorganism Count	Total Yeast and Mould Count	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Candida albicans</i>
Selective Media	TSA	SDCA	Cetrimide Agar	Baird Parker Agar	MacConkey Agar	SDCA
Incubation Times-Temperatures	32,5 ± 2,5°C 72±6 hour	25 ± 2,5°C 3-5 day	32,5 °C ± 2,5°C min. 24 hour	32,5 °C ± 2,5 °C min. 24 hour	32,5°C ± 2,5°C min. 24 hour	32,5°C ± 2,5°C min. 24 hour
Validation Media			<i>Pseudomonas</i> Agar P Agar	Catalase or coagulase test kit	EMB Agar	Corn Meal Agar
Validation Incubation Times-Temperatures			32,5 °C ± 2,5°C 24,48, and 72 hour		32,5 °C ± 2,5°C min. 24 hour	32,5 °C ± 2,5°C 3 day

Figure 6-209 Microbial assessment criteria

Product Full Name/Definition: Methyl 3-(1-(4-isopropylphenyl)propan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-210 2.4a microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 3-(1-(4-isopropylphenyl)propan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-211 2.5a microbial growth results

Product Full Name/Definition: Methyl 3-(1-(4-ethylphenyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-212 2.4b microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 3-(1-(4-ethylphenyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-213 2.5b microbial growth results

Product Full Name/Definition: Methyl 3-(2-(3-isopropylphenyl)propyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-214 2.4c microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 3-(2-(3-isopropylphenyl)propyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-215 2.5c microbial growth results

Product Full Name/Definition: Methyl 3-(1-(4-(tert-butyl)phenyl)propan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-216 2.4d microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 3-(1-(4-(tert-butyl)phenyl)propan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-217 2.5d microbial growth results

Product Full Name/Definition: Methyl 5-methyl-3-((2,2,3-trimethylcyclopent-3-en-1-yl)methyl)-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-218 2.4e microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 5-methyl-3-((2,2,3-trimethylcyclopent-3-en-1-yl)methyl)-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-219 2.5e microbial growth results

Product Full Name/Definition: Methyl 3-(8,8-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-220 2.4f microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 3-(8,8-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-221 2.5f microbial growth results

Product Full Name/Definition: Methyl 5-methyl-3-pentyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-222 2.4g mcicrobial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 5-methyl-3-pentyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-223 2.5g microbial growth results

Product Full Name/Definition: Methyl 3-hexyl-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-224 2.4h microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 3-hexyl-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-225 2.5h microbial growth results

Product Full Name/Definition: Methyl 3-heptyl-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-226 2.4i microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 3-heptyl-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-227 2.5i microbial growth results

Product Full Name/Definition: Methyl 5-methyl-3-octyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-228 2.4j microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 5-methyl-3-octyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-229 2.5j microbial growth results

Product Full Name/Definition: Methyl 5-methyl-3-phenyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-230 2.4k microbial growth results

Product Full Name/Definition: Oxiran-2-Ylmethyl 5-Methyl-3-Phenyl-4,5-Dihydroisoxazole-5-Carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

EXPLANATION: -

Figure 6-231 2.5k microbial growth results

Product Full Name/Definition: Methyl 3-(4-İsopropylphenyl)-5-Methyl-4,5-Dihydroisoxazole-5-Carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

EXPLANATION: -

Figure 6-232 2.4l microbial growth results

Product Full Name/Definition: Oxiran-2-Ylmethyl 3-(4-Isopropylphenyl)-5-Methyl-4,5-Dihydroisoxazole-5-Carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-233 2.5l microbial growth results

Product Full Name/Definition: Methyl 3-(4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-234 2.4m microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 3-(4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-235 2.5m microbial growth results

Product Full Name/Definition: Methyl 3-(3,4-dimethoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-236 2.4n microbial growth results

Product Full Name/Definition: Oxiran-2-ylmethyl 3-(3,4-dimethoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate - Plastic Package – 1 Piece (100 ml.)

ANALYSIS	METHODS	RESULT	VALUE	LIMITS
Total Microorganism Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ²
Total Yeast and Moulds Count	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	<10	kob/ml	10 ¹
<i>Pseudomonas aeruginosa</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Staphylococcus aureus</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Escherichia coli</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence
<i>Candida albicans</i>	European Pharmacopoeia Chapter 2.6.12 ve 2.6.13	Absence	g/ml	Absence

Figure 6-237 2.5n microbial growth results