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BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY

SYNTHESIS AND FRAGRANCE PROPERTIES OF SOME NEW MONOTERPENE-BASED CARBAMATES

MASTER OF SCIENCE

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ACADEMIC SUPERVISOR
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BOLU, OCAK - 2023

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KAWTHAR EL BOUYOUSFI

ABSTRACT

SYNTHESIS AND FRAGRANCE PROPERTIES OF SOME NEW MONOTERPENE-BASED CARBAMATES
MSC THESIS
KAWTHAR EL BOUYOUSFI
BOLU ABANT IZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: PROF.DR. MUHAMMET YILDIRIM)
BOLU, JANUARY 2023
(xvii + 75)

Fragrances mostly come from molecules known as terpenes, which are fragrant oil that give all botanicals their unique aromatic signature. Terpenes are the most numerous and structurally diverse and abundant plant natural products and they are simple hydrocarbons containing one or more double bond. Also, they all consist of isoprene units $(C5)_n$ and more often in cyclic form. In nature, terpenes exist mainly as in the form of hydrocarbons, alcohols and their glycosides, ethers, aldehydes, ketones, carboxylic acids and esters. Because of this chemical diversity, terpenes have great industrial uses especially in fragrances and flavors.

Based on the important and widespread odor properties of terpenes, synthetic preparation of terpene-based novel O-geranyl carbamate derivatives (**86a-j**) were aimed starting from a well-known terpene alcohol, geraniol. For this purpose, O-geranylamine **85** was first prepared over a two-step method including allylic bromination and Gabriel amine synthesis reactions. Subsequently, novel O-geranyl carbamate derivatives (**86a-j**) were synthesized successfully via a base-catalysed condensation reaction of isolated O-geranylamine **85** with various chloroformates. Structures of all the precursors and carbamate products were identified with IR, ^{1}H-NMR and ^{13}C-NMR analyses. Finally, O-geranylamine **85** and O-geranyl carbamates (**86**) were tested for their odor characteristics by expert perfumers and it was understood that they exhibited a variety of fragrance notes like floral, citrus, fresh, mineral, woody-earthy, animalic.

KEYWORDS: Terpenes, Geraniol, Chloroformates, Olfactory property, Carbamate.

ÖZET

BAZI MONTERPEN TABANLI KARBAMATLARIN SENTEZİ VE KOKU ÖZELLİKLERİ
YÜKSEK LISANS TEZI
KAWTHAR EL BOUYOUSFİ
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
KİMYA ANABİLİM DALI
(TEZ DANIŞMANI: PROF.DR. MUHAMMET YILDIRIM)
BOLU, OCAK - 2023
(xvii + 75)

Çoğunlukla terpen olarak bilinen moleküllerden geldiği bilinen kokular, tüm bitkilere eşsiz aromatik imzasını veren koku verici yağlardır. Terpenler, en yüksek sayıda ve yapısal olarak çok çeşitli bitkisel doğal ürünlerdir ve bir veya daha fazla ikili bağ içeren basit hidrokarbonlardır. Ayrıca, hepsi izopren birimlerinden $(C5)_n$ oluşur ve çok sıklıkla halkalı yapıdadır. Doğada, terpenler ağırlıklı olarak hidrokarbonlar, alkoller ve glikozitleri, eterler, aldehitler, ketonlar, karboksilli asitler ve esterlerler olarak oluşmaktadır. Bu kimyasal çeşitlilikten dolayı, terpenler özellikle koku ve aroma bileşikleri olarak yüksek miktarda endüstriyel kullanıma sahiptir.

Terpenlerin önemli ve yaygın koku özelliklerini baz alarak, terpen tabanlı yeni O-geranil karbamat türevlerinin (**86a-j**), iyi bilinen bir terpen alkol olan geraniyolden başlanarak sentetik olarak hazırlanması amaçlanmıştır. Bu amaçla, öncelikle O-geranilamin **85** alilik bromlama ve Gabriel amin sentez reaksiyonlarını içeren 2 basamaklı bir yöntemle hazırlandı. Devamında, yeni O-geranil karbamat türevleri (**86a-j**), izole edilen O-geranilamin **85** ile çeşitli kloroformatların bir baz-katalizli kondenzasyon reaksiyonu yoluyla başarılı şekilde sentezlendi. Tüm başlangıç bileşikleri ve karbamat ürünlerinin yapıları, IR, ^{1}H-NMR ve ^{13}C-NMR analizleriyle belirlenmiştir. Son olarak, O-geranilamin **85** ve O-geranil karbamatlar (**86**) koku özellikleri için uzman parfümörler tarafından test edildi ve bileşiklerine çiçeksi, limonumsu, taze, mineral, odunsu ve hayvansı gibi çeşitli koku notalarını gösterdikleri tespit edildi.

ANAHTAR KELİMELER: Terpen, Geraniyol, Kloroformat, Olfaktif etki, Karbamat.

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LIST OF ABBREVIATIONS AND SYMBOLS

Ac_2O	: Acetic ahydride
bs	: Broad singlet
BTC	: Bis(trichloromethyl) carbonate
$CDCl_3$	: Deuterated Chloroform
CH_3CN	: Acetonitrile
d	: Doublets
DBU	: 1,8-Diazabicyclo[5.4.0]undec-7-ene
DBU	: 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine
DCM	: Dichloromethane
dd	: Doublet of doublets
DMSO	: Dimethyl sulfoxide
DMSO-d6	: Deuterated Dimethylsulfoxide
dq	: Doublet of quartets
ED	: Electon-donating
EDG	: Electon-donating group
ee	: enantiometric excess
er	: enantiomeric ratio
EWG	: Electron-withdrawing group
FT-IR	: Fourier Transform infrared
H_2SO_4	: Sulfuric acid
HCl	: Hydrogen Chloride
Hz	: Hertz
IBQ	: Isobutylquinoline
J	: Coupling constant
K_2CO_3	: Potassium Carbonate

L-(+)-DET : L-(+)-diethyltartrate

$LiAlH_4$: Lithium Aluminium Hydride

m : Multiplets

MeI : Methyl Iodide

$MeNHNH_2$: Methyl Hydrazine

MeOH : Methanol

$N(CH_2CH_3)_3$: Triethylamine

Na_2SO_4 : Sodium Sulfate

NaHg : Sodium Amalgam

NBS : N-Bromosuccinimide

NMR : Nuclear Magnetic Resonance

PPh_3 : Triphenylphosphine

ppm : Parts per million

q : Quartets

s : Singlet

t : Triplets

TBHP : *tert*-butylhydroperoxide

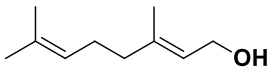
TEA : Triethylamine

$Ti(OiPr)_4$: Titanium (IV) tetraisopropoxide

TLC : Thin-layer chromatography

TMS : Tetramethylsilane

FORMULAE



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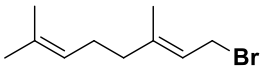

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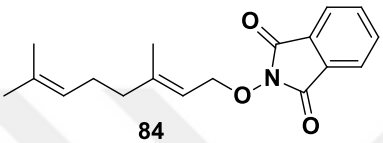

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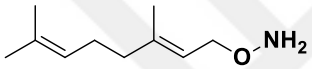

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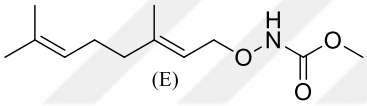

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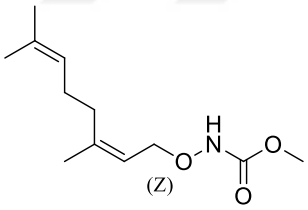

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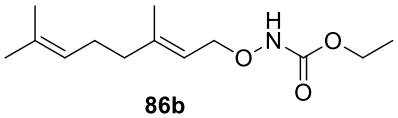

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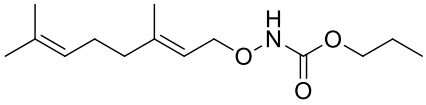

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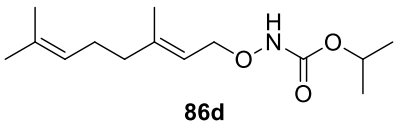

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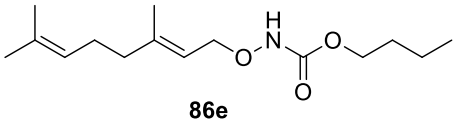

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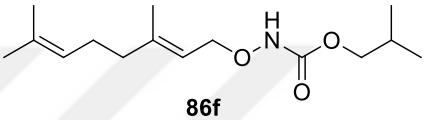

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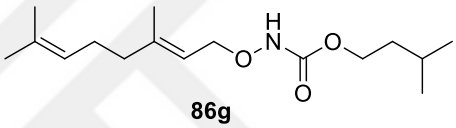

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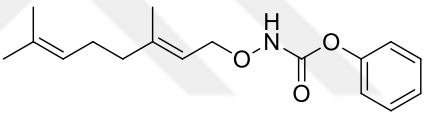

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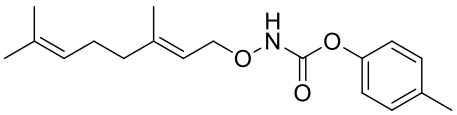

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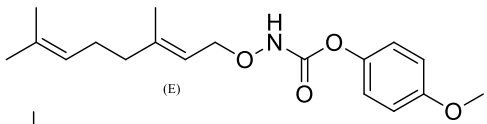

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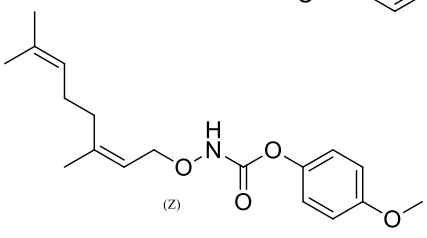

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I also thank all those who contributed directly or indirectly to the realization of this project.

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DEDICATION

It is with great honor that I dedicate this modest work to the dearest person to me in the world; my dear parents and my dear brother Rayan who allowed me to continue my studies in the best conditions and who taught me never to give up.

1. INTRODUCTION

1.1. Scents Compounds

Smell is a chemical sense, and it is only stimulated by gaseous molecules. These can be derived directly from the air we breathe or from volatile substances. The molecules that we concider as odors are called odorants. [1]

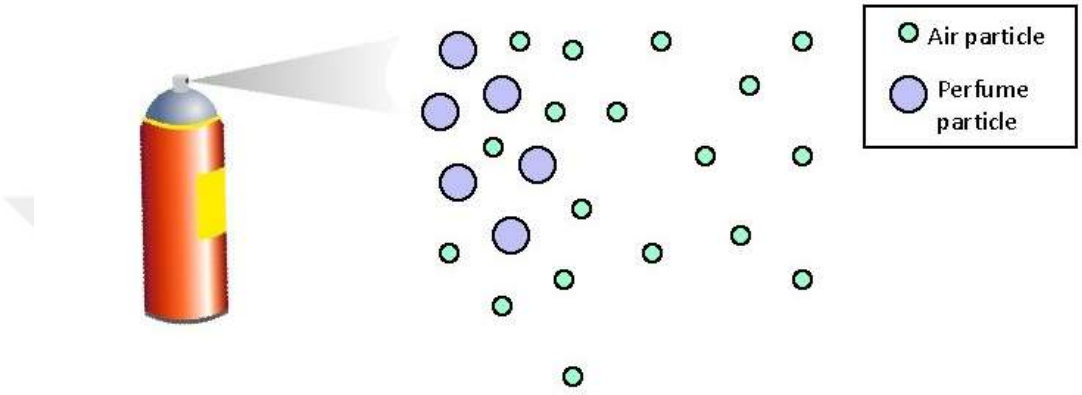


Figure 1.1. Fragrant compound diffusing in air

Besides, plants or flowers present different smells and the fragrance value of the plants is due to their secondary metabolites.

There are conventionally four main categories of secondary metabolites in plants; phenolic compounds, saponins, alkaloids and terpene compounds.
Secondary metabolites can be subdivided into two categories;

- Non-volatile substances: Alkaloids, Anthocyanins, Flavonoids, Tannins or Sapogenins, known for their pharmacological activity or their pigmentary properties.
- Volatile substances: terpenes and aromatic compounds, which constitute the essential oils used in perfumery, aromatherapy, traditional pharmacopoeia, pharmacy or as food flavors. [3]

Among the secondary metabolites, Terpenes are the most various and chemically diverse plant natural products. For instance, smell comes from terpenes, which are fragrant oils that give all botanicals their unique aromatic signature.

In particular, terpenes (essential oils, scents…) are the major group of plant secondary metabolites (55%). Phenolic compounds (mainly flavonoids, phenolic acids and tannins) constitute a wealth widely exploited by the agro-food, cosmetic and pharmaceutical industries.

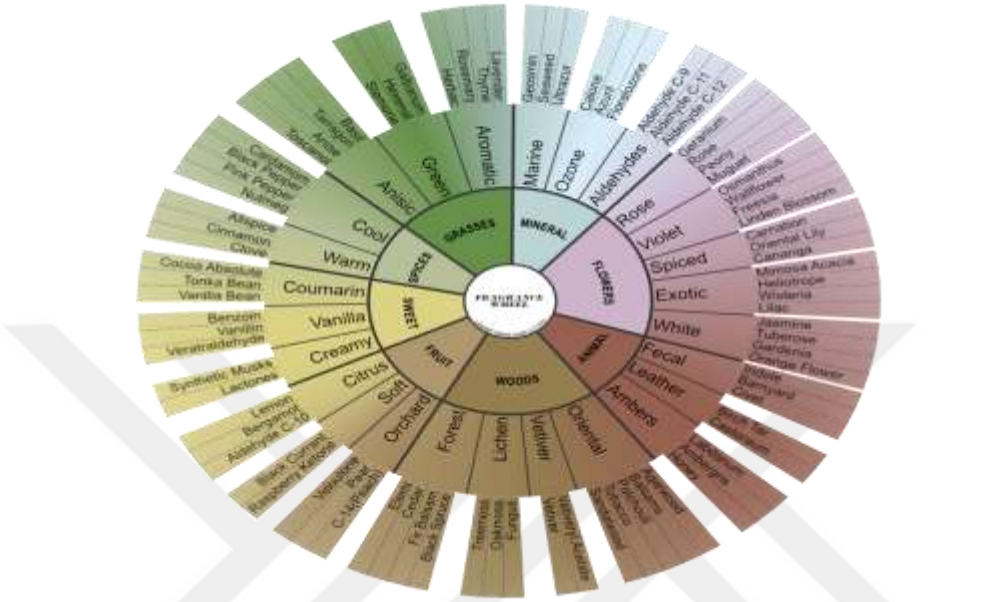


Figure 1.2. Fragrance wheel showing the main fragrance classes

Fragrances can be classified in 8 major groups ;

- Floral : Jasmine, Lavender…
- Citrus : Lemon, Orange…
- Fruity : Strawberry, Apple…
- Woody : Cedarwood, Sandalwood…
- Herbal : Peppermint, Citronella…
- Spicy : Cinnamon, Clove…
- Musky|Animalic : Musk, Civet…
- Aldehydic : C -10, C-11…

Chemists can now separate an essential oil into its constituents and identify the odorous chemicals using modern analytical techniques. Gas-liquid chromatography (GC) and high performance liquid chromatography (HPLC) are chromatographic methods that are utilized in the process of separating components. Mass spectroscopy (MS), infra-red spectroscopy (IR), and nuclear magnetic

resonance (NMR) spectroscopy are the spectroscopic techniques that provide information about the structure of molecules.

1.2. Terpenes

1.2.1. Definition Of Terpenes

Terpenes are a family of hydrocarbons whose structures contain multiple condensations of isoprene units. Simple terpenes are highly volatile and are assumed to be the essential oils that give plants their distinct odors, causing the fragrance, taste, and pigment of plants. Their odors have an ability to attract or repel other organisms like insects or flies [20]

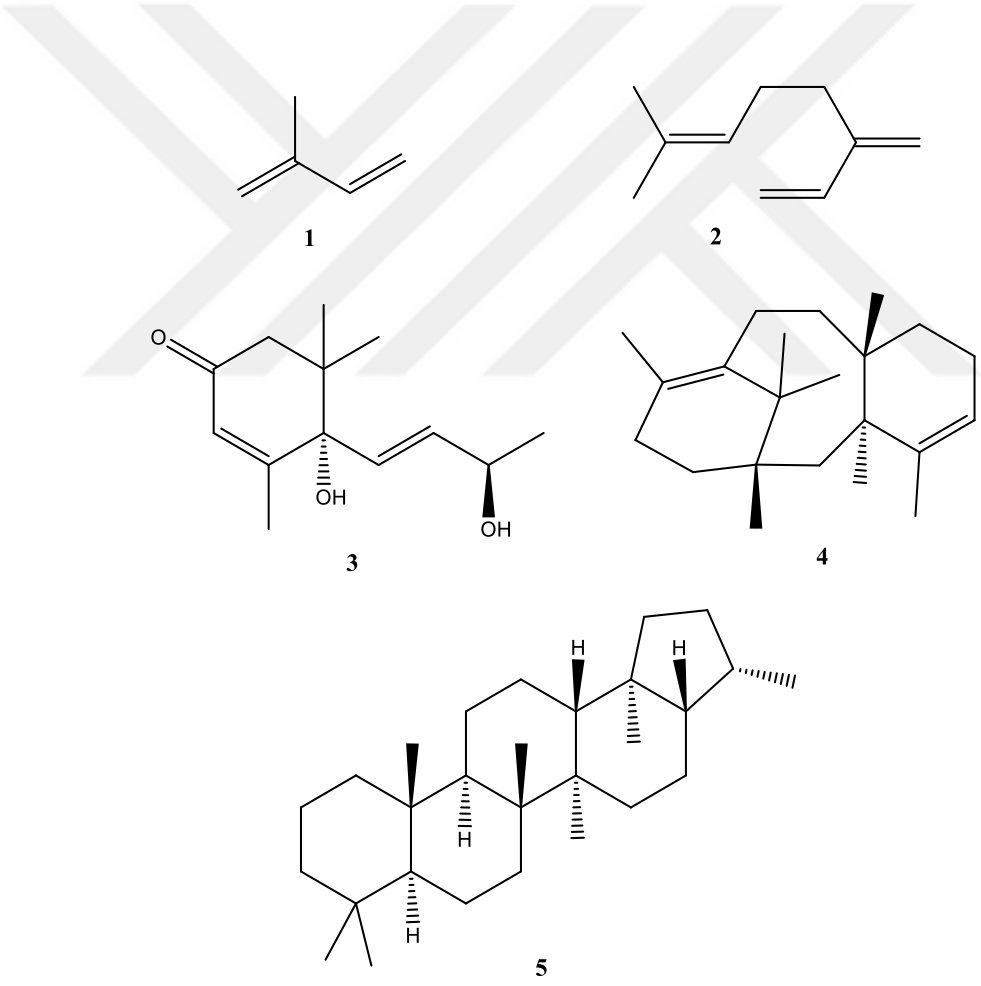


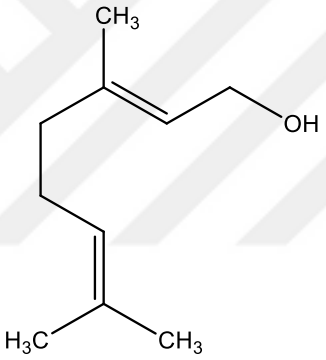
Figure 1.3. Isoprene (1), Monoterpene (2), Sesquiterpene (3), Diterpene (4) and Triterpene (5) structures

Terpenes are classified as hemiterpenes with a maximum of five carbon atoms, monoterpenes with a maximum of ten carbon atoms, sesquiterpenes with a maximum of fifteen carbon atoms, and diterpenes with a maximum of twenty carbon atoms; triterpenes up to 30 carbon atoms and polyterpenes more than 30 carbon atoms.

1.2.1.1. Terpene Alcohols

Terpene alcohols are terpenes containing a hydroxyl groups such as terpene monoalcohols or a terpene dialcohols. We can divide terpene alcohols into three subgroups:

- Aliphatic are the ones which can be divided into saturated and unsaturated (Geraniol, linalool) components.



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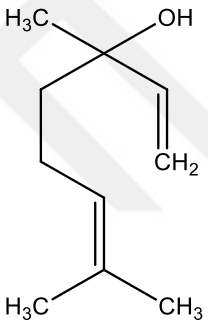

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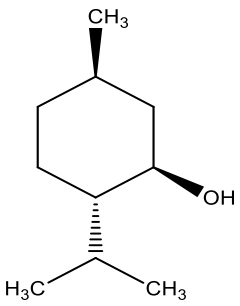
Figure 1.4. Geraniols' (6) and Linalools' (7) structure

- Alicyclic are the ones which can be divided into monocyclic (Menthol), Bicyclic (Borneol) and Sesquiterpene (Santalol)



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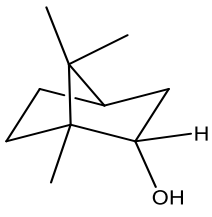

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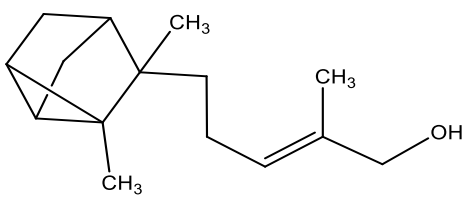

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Figure 1.5. Menthols' (8), Borneols' (9) and Santalols' (10) structures

- Aromatics are like the benzyl alcohols (11)

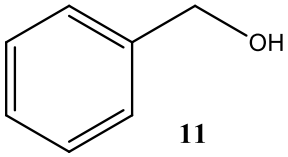

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Figure 1.6. Benzyl alcohol structure

1.2.1.2. Fragrance Properties Of Terpene Molecules

Terpenes are aromatic compounds that add flavor and smell. Some examples of terpene molecules exhibiting various fragrance properties are given below: [19]

- **Alpha-pinene (12):** which have woody and pine like smell
- **Limonene (13):** which is a citrus smelling terpene that is found in lemons, oranges and most citrus fruits
- **Beta-caryophyllene (14):** which have peppery, woody, spicy scents. Find in cloves, clove oil, black pepper, roemary, hops and cotton.
- **Myrcene (15):** which its aromas are flowery, musky, earthy, herbal, slight citrus and fruity notes. Myrcene is mostly used to make fragrances. Produced semi-synthetically from the myrtle family of plants which contains guava, clove, allspice, eucalyptus. The essantial oils are woody and flowery, is commomly found in wild thyme, cannabis…
- **Linalool (16):** which is found in many flowers and spices, the smell is described simply as floral with a touch of spice. It is often extracted from lavender.

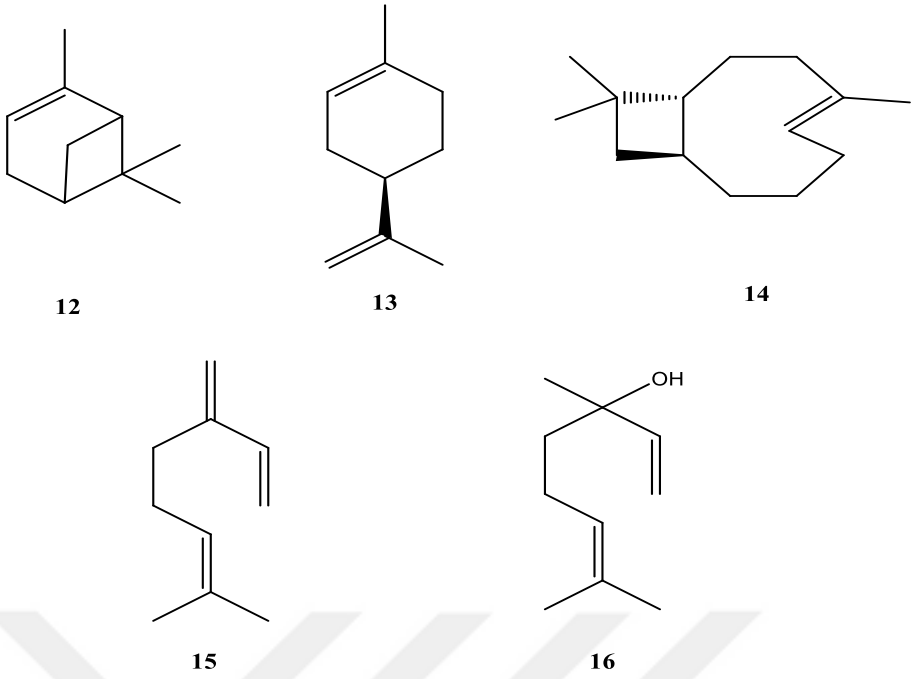
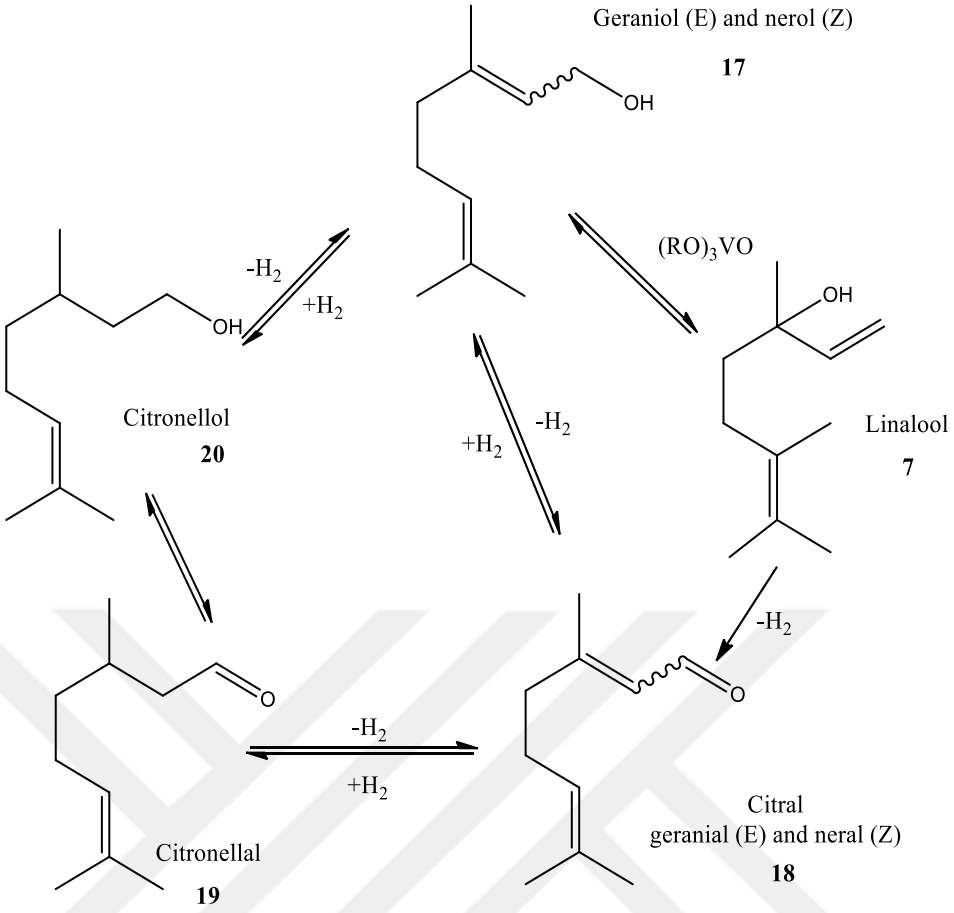


Figure 1.7. Some examples of terpene molecules

Five of the most important terpenoids in the perfume industry are geraniol Nerol, linalool, citronellol, citronellal, and citral. They are all used in perfumes, with the exception of citral. Each of them are necessary building blocks for other terpenoids. As shown in the figure, those terpenoids are easily interconverted.



Scheme 1.1. The structure of 5 common terpenes and their interconversion

1.2.1.3. Sources Of Terpenes

Terpenes are the principal sources of essential oils and are found only in plants. Cannabis is one of the most common sources of medicinal terpenes. Some of the most different and more complicated terpenes (such as squalene and lanosterol) are found in both animals and insects. [18]

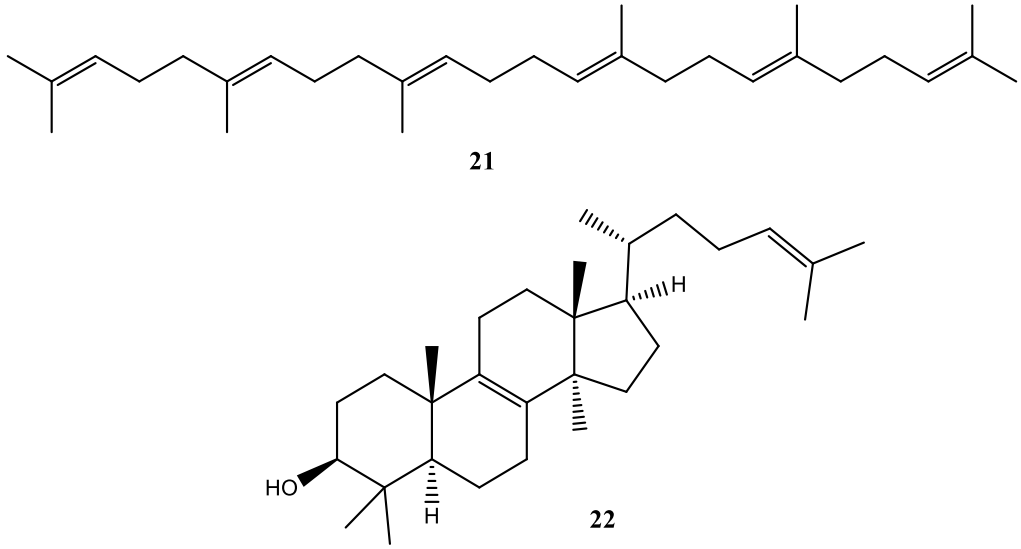


Figure 1.8. Squalene (21) and Lanosterol (22) structures

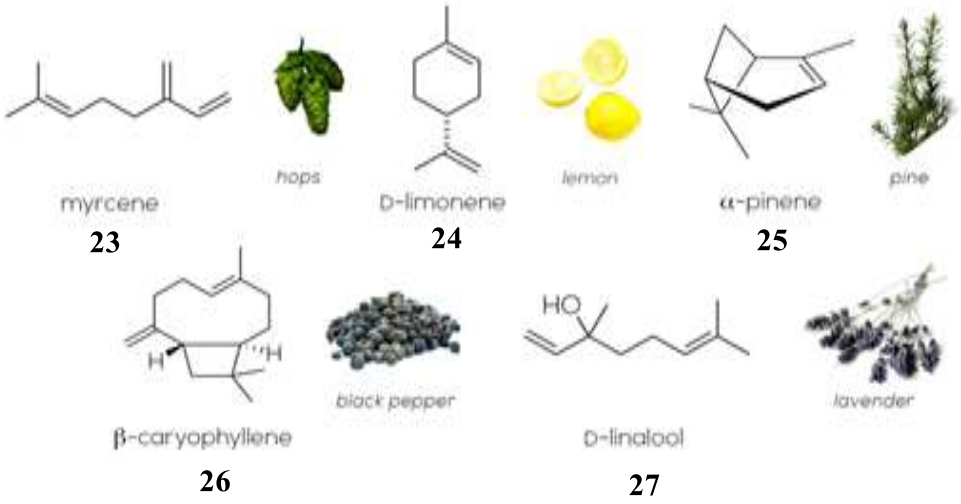


Figure 1.9. Terpenes structure from different plants

1.3. Geraniol

1.3.1. Definition, Sources And Uses

Geraniol which has a systematic name of 3,7-dimethylocta-trans-2,6-dien-1-ol is a monoterpene alcohol, its chemical formula is $C_{10}H_{18}O$. Geraniol is a mixture of two isomers, geraniol and nerol. Geraniol is manly a colorles oil, but the color of its commercial samples may appear yellow. It is miscible with many organic solvents but it is immiscible with water and presents a characteristic rose-like odor.

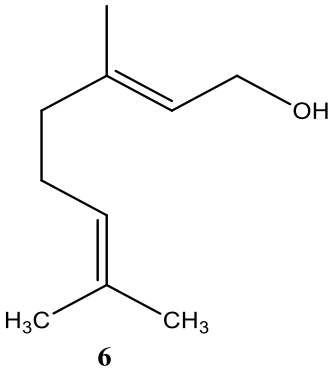


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Figure 1.10. Structure of Geraniol

Geraniol is extracted from the flowers of many species and many plants have it in their leaf tissues and is usually in the geranial and neral (aldehyde form). Also it is isolated from Palmarosa oil and is a major component of several essential oils and occurs in Monarda fistulosa (95%), ninde oil (66.0%), rose oil (44.4%), palmarosa oil (53.5%) and citronella oil (24.8%). [5]

Figure 1.11. Some sources of Geraniol

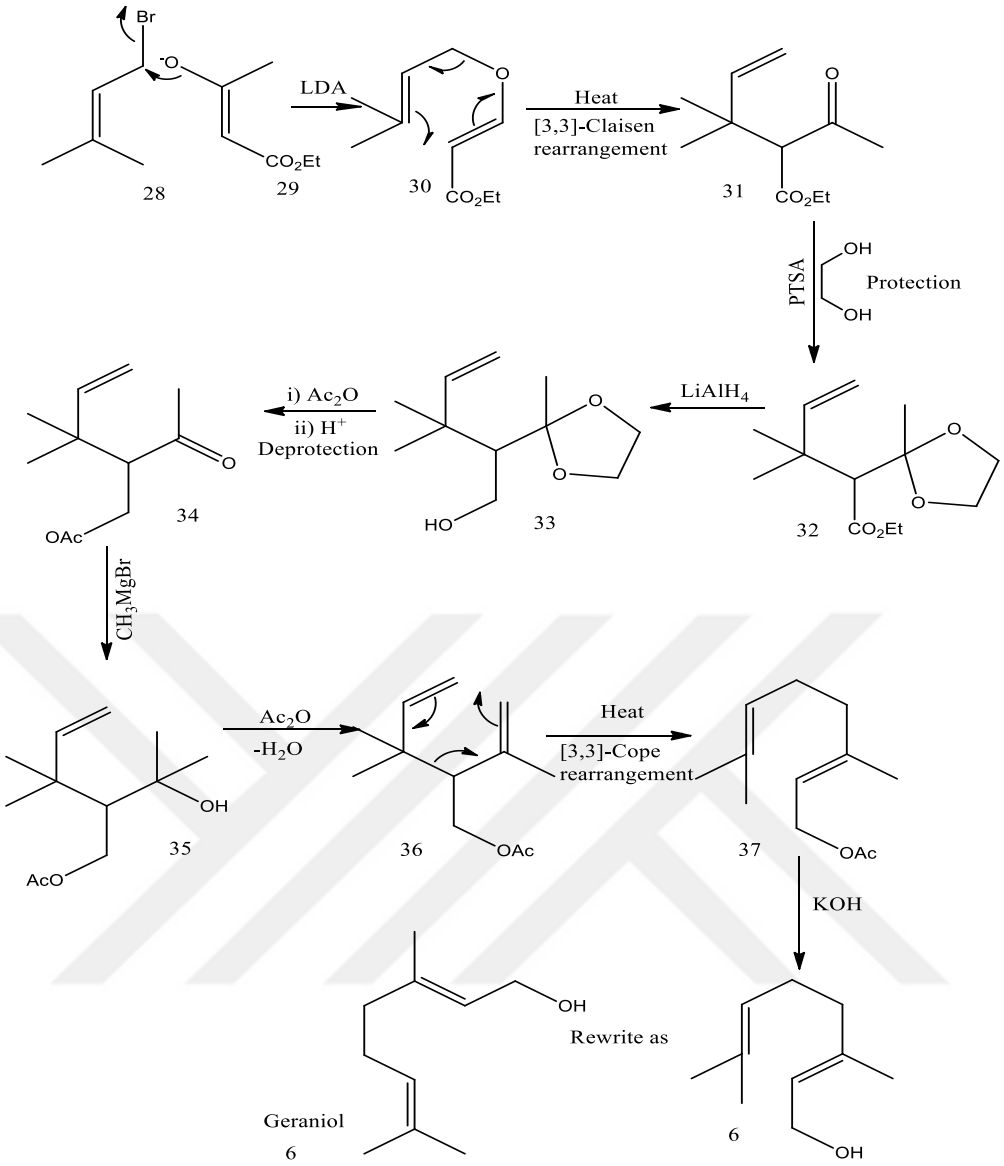
Perfumes frequently contain geraniol monoterpene alcohol. According to a consumer survey, it is found in 76% of investigated deodorants on European markets. It's also in 41% of domestic and household products, and 33% of natural-ingredient cosmetic formulations. Besides perfumes and flavors, geraniol can be used in therapy as an analgesis or anti-inflammatory. It is also commonly used in pesticide as a mosquito repellent or against mites. [6]

1.3.2. Synthesis Of Geraniol

Geraniol have been prepared from many sources. The first synthesis was done over reduction of *trans*-methyl geranate (Burrell et al. 1966) and It is also produced using geranyl pyrophosphate via a hydrolysis reaction (Sell 2009). α-pinene is an important precursor to synthesize the geraniol used by the manufacturers (Sell 2000).

1.3.2.1. Geraniol Over Allylbromide

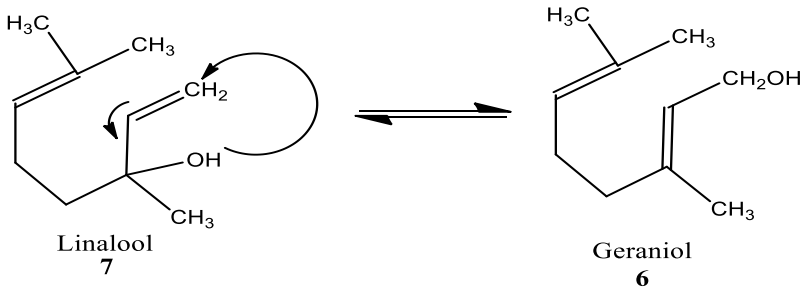
The synthesis of geraniol requires the reaction of allyl bromide with ethyl acetoacetate. After a group of reaction including the [3,3]-Claisen rearrangement, protection, reduction and acetylation, the product reacts with ethyl magnesium bromide to give a tertiary alcohol. Then, it undergoes a [3,3]-Cope rearrangement and a deprotection by basic hydrolysis, will then afford the the geraniol.



Scheme 1.2. Synthesis of geraniol starting from allylbromide

1.3.2.2. By Isomerization Of Linalool

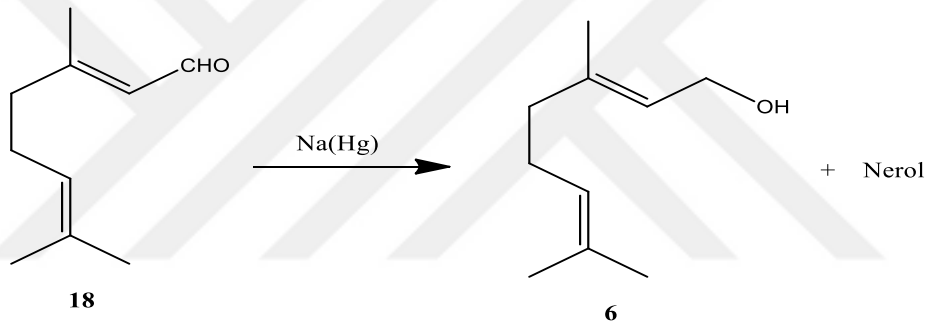
Commercial production of geraniol generally is based on the catalytic liquid-phase isomerization of linalool (3,7-dimethyl-1,6-octadiene-3-ol). Both isomers – geraniol and nerol are obtained from linalool due to 1,3-migration of the OH group and appropriate shift (allylic rearrangement) of the double bond.[7]



Scheme 1.3. Isomerization of linalool to geraniol

1.3.2.3. By Reduction Of Citral

Both isomers geraniol and nerol are obtained by the simple reduction of citral using sodium-mercury amalgam. [8]



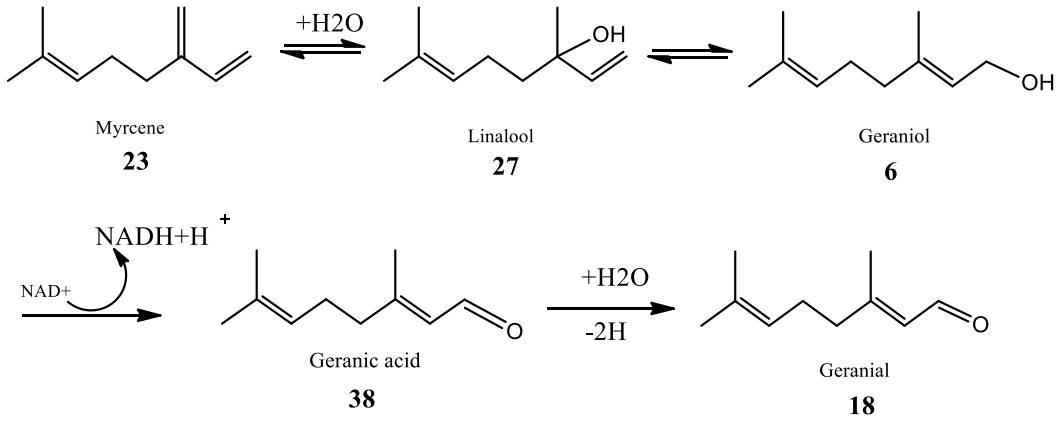
Scheme 1.4. Reduction of citral to geraniol

1.3.3. Reactions Of Geraniol

Geraniol undergoes lots of reactions such as oxidation, hydrogenation, epoxidation etc.

1.3.3.1. The Oxidation Of Geraniol To Geranic Acid 'Allylic Oxidation'

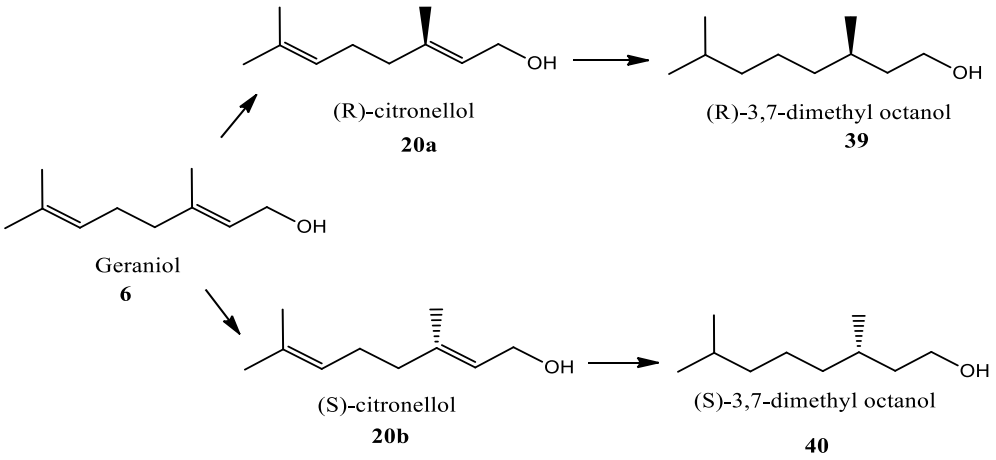
The selective oxidation of alcohols to aldehydes is a significant transformation. Using appropriate reagents for primary alcohol oxidation, the geranial and neral products of geraniol are known as citral. Citral is a key ingredient in the manufacture of perfumes, fragrances, and medical products. The oxidation of citral to geranic acid takes place in two phases. To produce a hydrate, water is added in the presence of an acidic catalyst in the first step. The hydrate is then oxidized to carboxylic acid using a suitable oxidizing agent, formally removing water. [9]



Scheme 1.5. Oxidation of geraniol to geranic acid

1.3.3.2. The Hydrogenation Of Geraniol To Citronellol

Geraniol is good starting material for the preparation of enantiomerically pure (R)-(+)-citronellol by a reduction by microorganisms. Also, it is possible to reduce it into (S)-citronellol. At 60 °C, ruthenium BINAP catalysts were used to perform asymmetric hydrogenation of geraniol (3,7-dimethylocta-2,6-dien-1-ol) to citronellol. Solvent (methanol, ethanol, 1-propanol, and 2-propanol), R-Ru(OAc)2(T-BINAP) catalyst, and hydrogen pressure (5–40 bar).

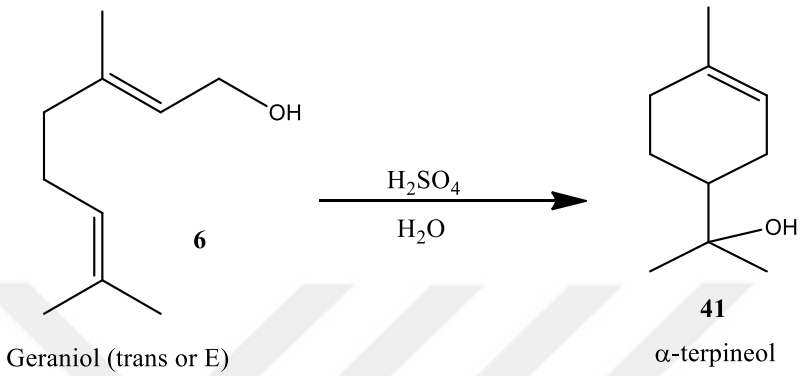


Scheme 1.6. Hydrogenation of geraniol

1.3.3.3. The Oxidation Of Geraniol To α-Terpineol

Cyclisation of geraniol to α-terpineol took place by treatment of aqueous H_2SO_4. Geraniol is protonated, a good leaving group forms and a carbocation is

obtained. The cyclisation is very slow due to the distance between the carbon which is involved in the ring formation and the alcoholic group, tertiary carbocation is obtained and is trapped by water molecule, after a deprotection the α-terpineol is obtained.



Scheme 1.7. Oxidation of geraniol to α-terpineol

1.3.3.4. The Sharpless Asymmetric Epoxidation Of Geraniol

Sharpless Asymmetric Epoxidation is described as a strong asymmetric synthetic method. Asymmetry in the allylic alcohol is provided by the use of a catalyst, Ti(O*i*Pr)$_4$, TBHP, and L-(+)-DET.

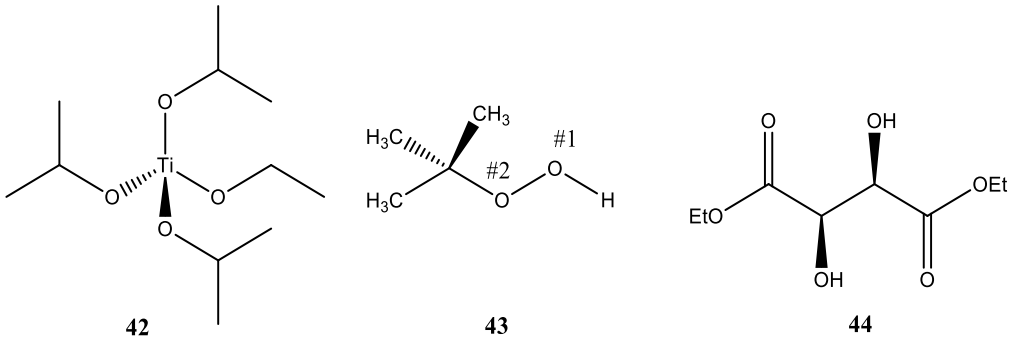
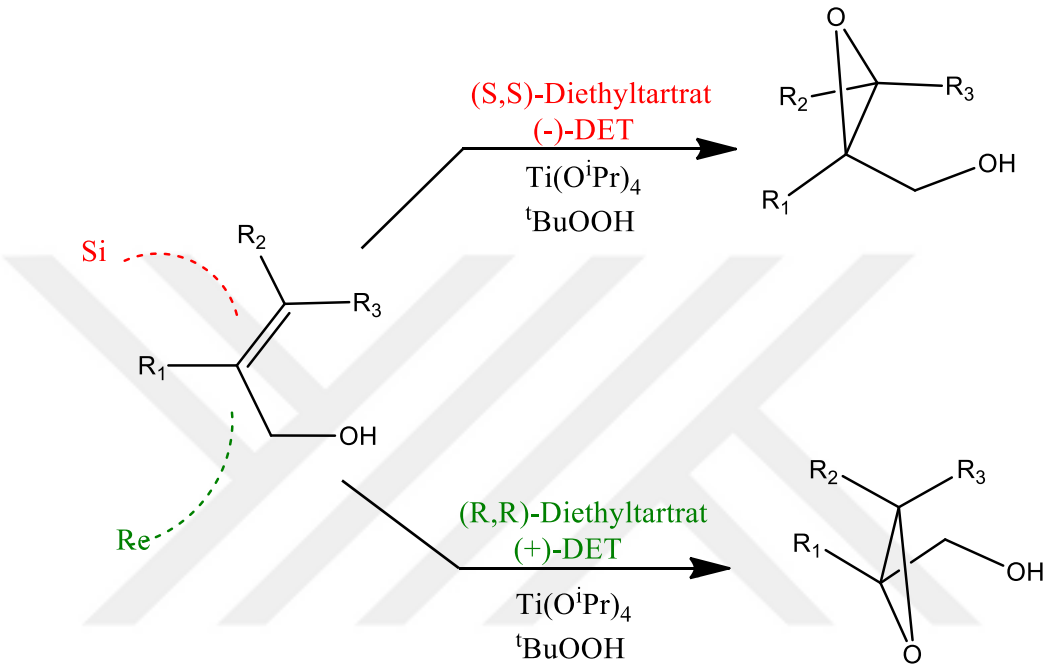


Figure 1.12. Structures of titanium (IV) tetraisopropoxide, *tert*-butylhydroperoxide, and L-(+)-diethyltartrate

A catalytic cycle is used in the Sharpless Asymmetric Epoxidation mechanism. First, titanium (IV) tetraisopropoxide forms a complex with

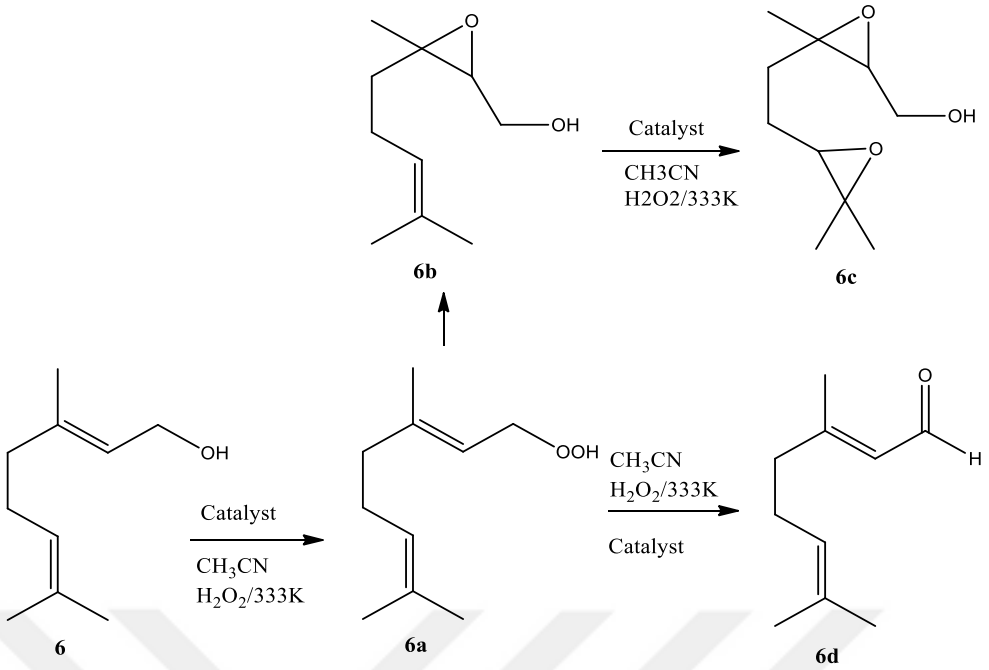
diethyl tartrate and allylic alcohol. Moreover, the coordination of the Ti(O*i*Pr)$_4$ and DET provides a chiral reaction environment. O#1 of TBHP does a nucleophilic attacks the Ti(O*i*Pr)$_4$, then it undergoes an intramolecular attack by O#2 of the TBHP. In the meantime, O#1 interacts with the πe^{-}'s of the alkene to give epoxide. Then, O#1 departs from the titanium to afford the epoxy alcohol and the catalytic cycle continue. [10]



Scheme 1.8. The sharpless epoxidation of geraniol

1.3.3.5. The Oxidation Of Geraniol With Hydrogen Peroxide

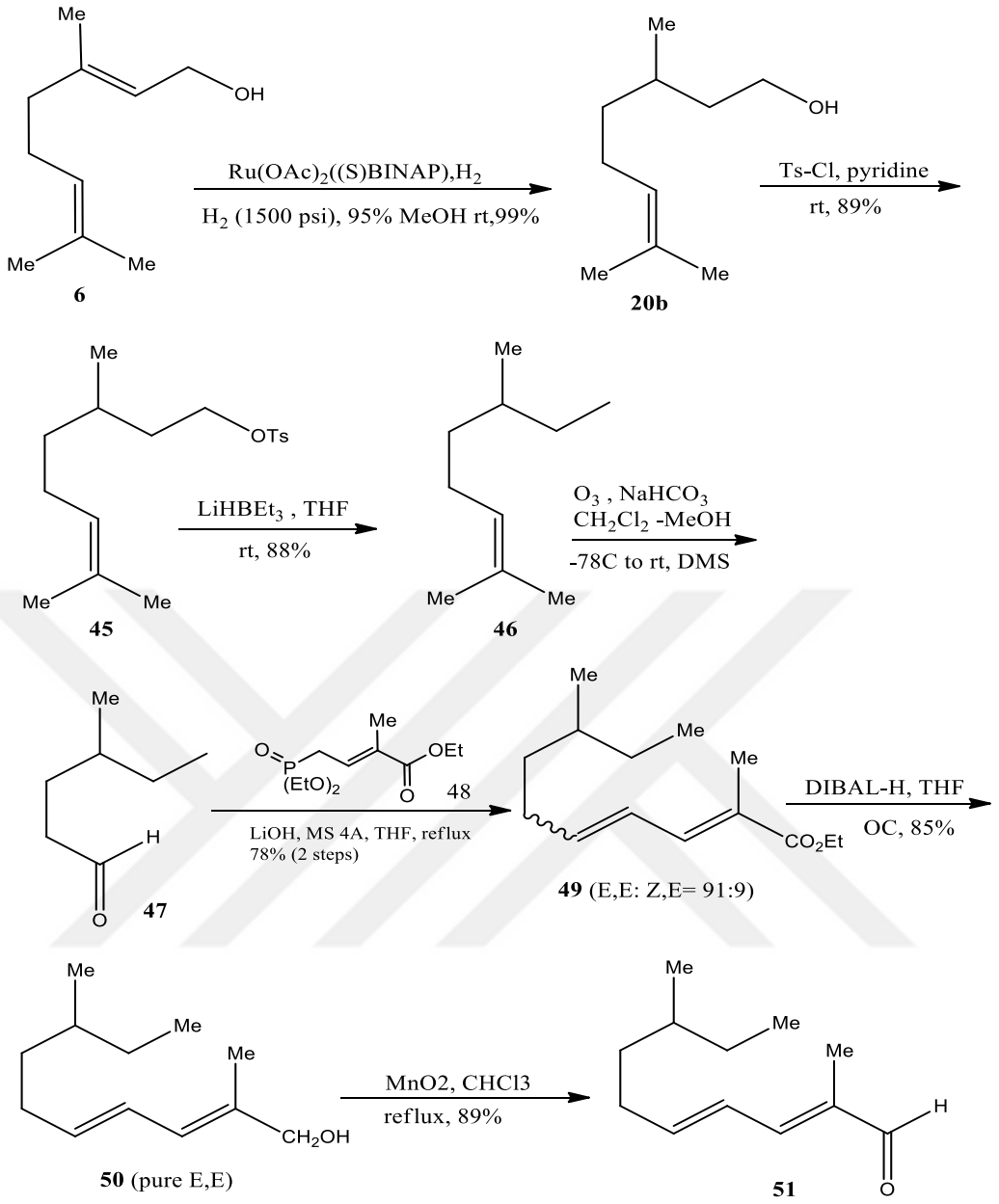
Geraniol epoxide (**6b**) is the main product and the latter are geraniol diepoxide (**6c**) and aldehyde (*i.e.*, citral, **6d**). The most possible intermediate in these reaction series is geraniol peroxide 6a. [21]



Scheme 1.9. The oxidation of geraniol with H_2O_2

1.3.3.6. The Preparation Of Dienyladehyde From Geraniol

Asymmetric hydrogenation of geraniol is provided with $Ru(OAc)_2$[(***S***)-BINAP] to give (***S***)-citronellol (**20b**) in excellent yield with 99% ee and 97:3 er. Alcohol is tosylated and followed by deoxygenation using $LiHBEt_3$ to afford hydrocarbon **46** (88%) yield over two steps. Formed alkene **46** was oxidized by ozonolysis and olefinated via vinylogous Horner–Wadsworth–Emmons reaction using phosphonate **48** to give unsaturated ester **49**. Subsequently, ester is reduced with DIBAL-H to afford geometrical isomers of the allylic alcohol and oxidation of it afforded aldehyde **51** in high yields. [23]



Scheme 1.10. Preparation of dienylaldehyde from geraniol

1.4. Chloroformates

Chloroformates are sophisticated intermediates and quite reactive. Derivatives of chloroformates are usually obtained with alcohols and amines and wide variety of carbamates have been described for their industrial uses. Chloroformates are useful intermediates for the production of pesticides, perfumes, drugs, foodstuffs, dyes and so on.

1.4.1. Definition, Examples And Uses

Organic compounds with the formula ROC(O)Cl are known as chloroformates. They are actually chloroformic acid esters. The majority of them are colorless, volatile liquids that deteriorate when exposed to moisture. In organic chemistry, chloroformates are utilized as reagents. In general, chloroformates have low melting points and higher boiling points than 100°C. Their solubility is good in organic solvents, but poor in water. They are easily hydrolyzed in water. [11]

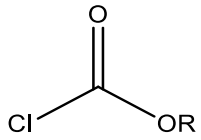


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Figure 1.13. General structure of chloroformates

Chloroformates are useful synthetic intermediates and reactive chemical entities. Chloroformates are commonly derivatized with alcohols and amines, and the resulting carbamates and carbonates have a variety of industrial applications.

Table 1.1. Common commercially available chloroformates and their formulas.

Chloroformates	Formulas	Uses
Ethyl	$ClCOOC_2H_5$	To introduce the ethyl carbamate protecting group and to produce carboxylic anhydrides.
Methyl	$ClCOOCH_3$	To introduce the methoxycarbonyl functionality to a suitable nucleophile.
Butyl	$ClCOO(CH_2)_3CH_3$	In the synthesis of dextran alkyl carbonates and of *S-tert*-alkyl-*N*,*N*-alkoxycarbonylmethyl-dithiocarbamate, radical polymerization with reversible addition-fragmentation chain transfer agent.
Isobutyl	$ClCOOCH_2CH(CH_3)_2$	Utilized to make phenethyl-carbamic acid isobutyl ester.
4-nitrophenyl	$ClCOO(4\text{-}NO_2C_6H_5)$	A reagent for the activation of amines, alcohols and thiols and in the synthesis of 4-substituted phenyl derivatives of 1,2,4-triazolidindiones.
Isopropyl	$ClCOOCH(CH_3)_2$	In the preparation of isopropyl cyclohexane via alkylation of cyclohexene.

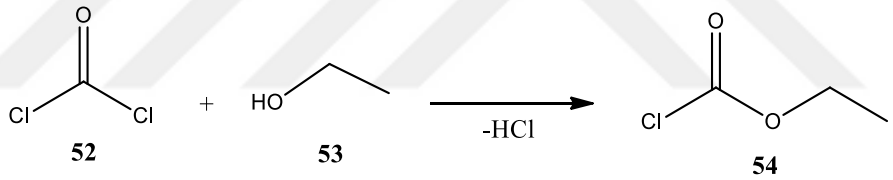
Benzyl	$ClCOOCH_2C_6H_5$	To introduce the benzyloxycarbonyl (Cbz) protecting group and also in a 3-step synthesis of 1,2,4-oxadiazoles.
Phenyl	$ClCOOC_6H_5$	Poly(2-(phenoxycarbonyloxy) ethylmethacrylate) and phenyl-(4-vinylphenyl)carbonate synthesis.

1.4.2. Synthesis Of Chloroformates

A variety of chloroformates can be prepared over a few efficient methods found in the literature.

1.4.2.1 Chloroformates Using Phosgene

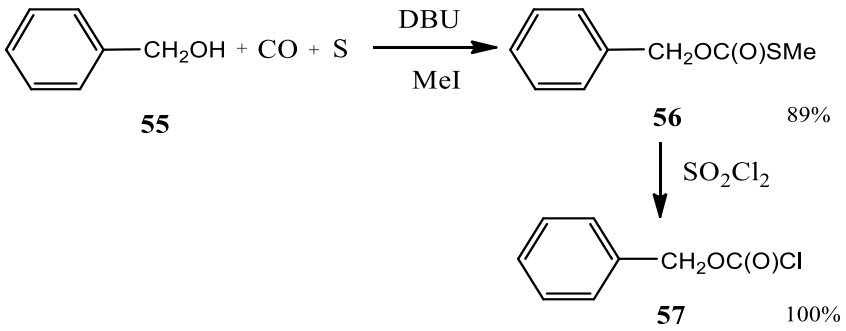
The majority of chloroformates are synthesized by reacting phosgene with alcohols (or phenols). [12] Methyl or ethyl chloroformate can be synthesized using ethanol and phosgene. During this reaction, the temperature must be kept down below 10° C.



Scheme 1.11. Synthesis of ethyl chloroformate

1.4.2.2 Benzyl Chloroformates From Benzyl Alcohol

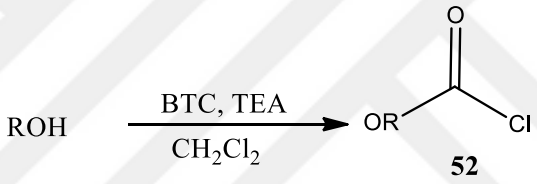
Benzyl chloroformate was produced by carbonylation of benzyl alcohol with carbon monoxide and sulfur (or carbonyl sulfide) in the presence of DBU, followed by chlorination with sulfuryl chloride (CbzCl). [13]



Scheme 1.12. Synthesis of benzyl chloroformate

1.4.2.3 Chloroformates Using Bis(Trichloromethyl) Carbonate

Triphosgene, also known as BTC, has been noted to be a safer option to phosgene and trichloromethyl chloroformate. BTC is a solid that is crystalline and stable. Acylation of alcohols with BTC produces some chloroformates. [14]

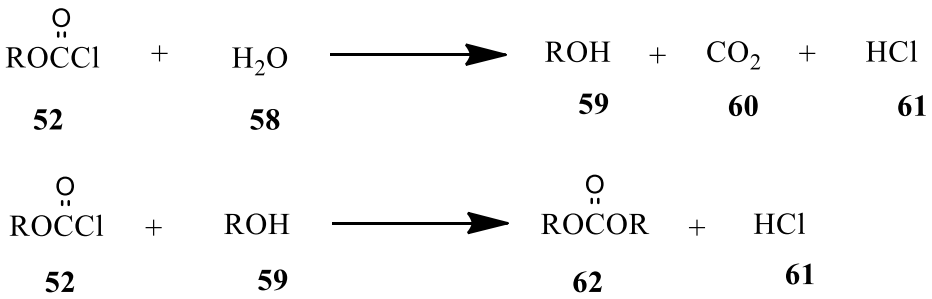


Scheme 1.13. Acylation of alcohol to chloroformate

1.4.3. Reactions Of Chloroformates

1.4.3.1 Reactions With Hydroxy Compounds

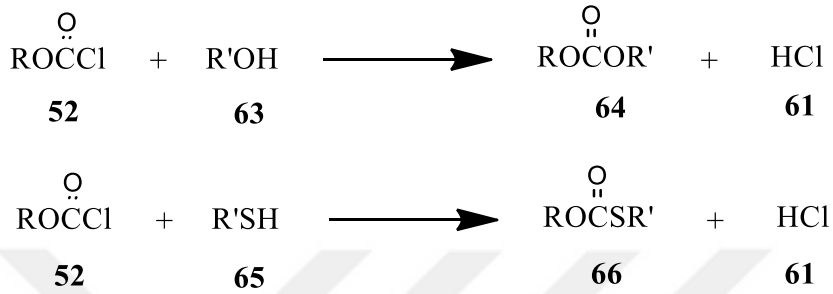
When chloroformates react with water, they produce corresponding hydroxy compounds, besides, an alcohol reacts with chloroformate to give the symmetrical carbonate compound. [14]



Scheme 1.14. Reaction of chloroformate with Oxygen moieties

1.4.3.2 Reactions With Aliphatic Alcohols And Thiols

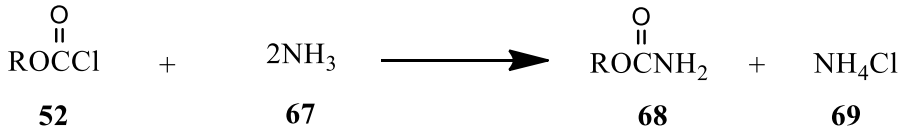
At room temperature, the reaction of aliphatic alcohols with chloroformates produces carbonates without the use of a catalyst. However, in the involvement of alkali metals or their hydroxides, or tertiary amines, reaction yields and rates will be higher. When chloroformates react with thiols, monothiolocarbonates are formed quickly. [14]



Scheme 1.15. Reaction of chloroformate with Aliphatic alcohols and thiols

1.4.3.3 Reactions With Nitrogen Compounds

A well-known technique for producing primary carbamates is the ammonia reaction. Abundance ammonia acts as an acid acceptor during the reaction, removing formed HCl.

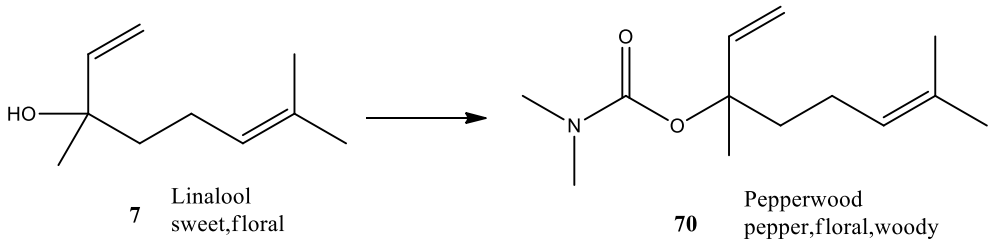


Scheme 1.16. Reaction of chloroformate with Nitrogen compounds

1.5. Carbamates

Flachsmann and Bachmann's report of a different kinds of carbamates as fragrance ingredients in 2004 started a new episode in fragrance chemistry, but they were neglected in this domain. This underutilized functionality, for example, transforms the scent of aromatic alcohols into peppery woody tones.

Pepperwood, a linalool dimethyl carbamate derivative, has a dazzling spicy-peppery character that brings coolness and elevation to several scent designs., as seen in 'Hermann Mes Côtés Me Paraissaît Une Ombre' (Etat Libre d'Orange, 2015). [15]



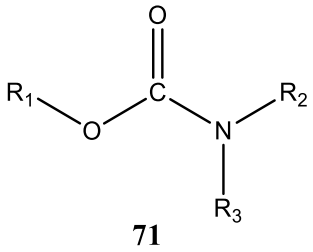
7 Linalool
sweet,floral

70 Pepperwood
pepper,floral,woody

Scheme 1.17. Synthesis of pepperwood

1.5.1. Definition, Examples And Uses

A carbamate is a type of organic compound that is formally derived from carbamic acid (NH2COOH). Organic molecules (for example, the ester ethyl carbamate) that are formally procured by substituting one or more hydrogen atoms with other organic functional groups, and also salts containing the carbamate anion H2NCOO, are included in the term (e.g. ammonium carbamate).



71

R_1, R_2 and/or R_3= alkyl or aryl

Figure 1.14. General structure of a carbamate

Several carbamates are used in human drug therapy, including the acetylcholinesterase inhibitors neostigmine (72) and rivastigmine (73), both of which have a molecular structure based on the naturally occurring alkaloid physostigmine 74. Other anxiolytic and muscle relaxant drugs that were popularly used in the 1960s and are still used in some cases today include meprobamate 75 and its derived products, such as carisoprodol 76, felbamate 77, and mebutamate 78. Carbachol 79 is most commonly found in ophthalmic applications. **[16]**

Methocarbamol 80 was first used to treat muscle spasms and pain in the 1950s. In addition to rest, physical therapy, and other measures, methocarbamol tablets and intramuscular transfusions are prescribed drugs used in the United States to relieve pain associated with acute, painful musculoskeletal conditions. [22]

Fenbendazole 81 is a benzimidazole with wide ranging anthelmintic activity. It is used to treat gastrointestinal parasites such as giardia, roundworms, hookworms, whipworms, the Taenia tapeworm genus, pinworms, aelurostrongylus, paragonimiasis, strongyles, and Strongyloides. Fenbendazole is approved for use in sheep, cattle, horses, fish, dogs, cats, rabbits, and seals under veterinary supervision. [24]

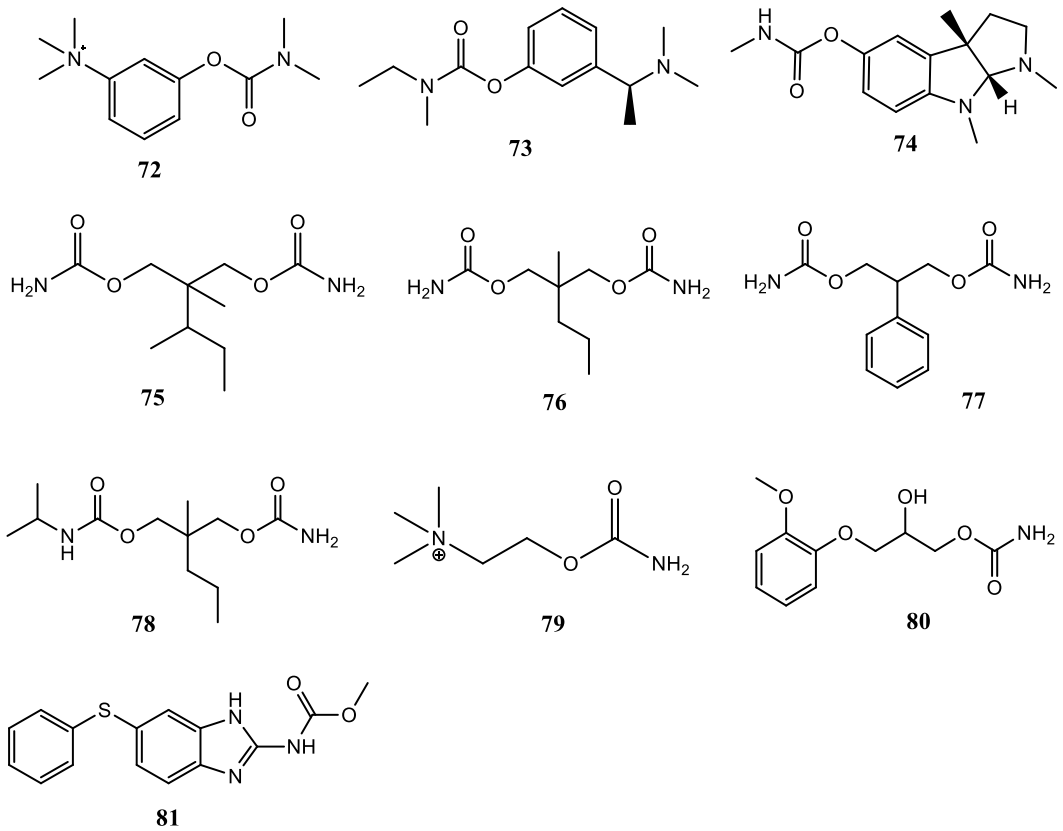


Figure 1.15. Biologically active carbamate derivatives

In addition, carbamate is also often used in fragrances due to its characteristic odors. Tertiary non-vinylic carbamates have spicy, herbal or floral-rosy range odors with excellent affinity for use as fragrance ingredients.

1.5.2. Synthesis Of Carbamates

Over the years, various carbamates have been prepared over several synthetic methods detailed below. [17]

1.5.2.1. By Hoffmann Rearrangement Of Amides

Hoffman rearrangement (method I, scheme 1) is widely known as a beneficial way for the conversion of primary amides to amines or carbamates which is described by the reduction of carbon in the structure.

1.5.2.2. By Curtius Rearrangement Of Acyl Azides

In Curtius rearrangement (method II, Scheme 1), acyl azides are thermally decomposed to isocyanate intermediates. This method is commonly used to convert carboxylic acids to carbamates and urea.

1.5.2.3. By Reductive Carbonylation Of Nitroaromatics

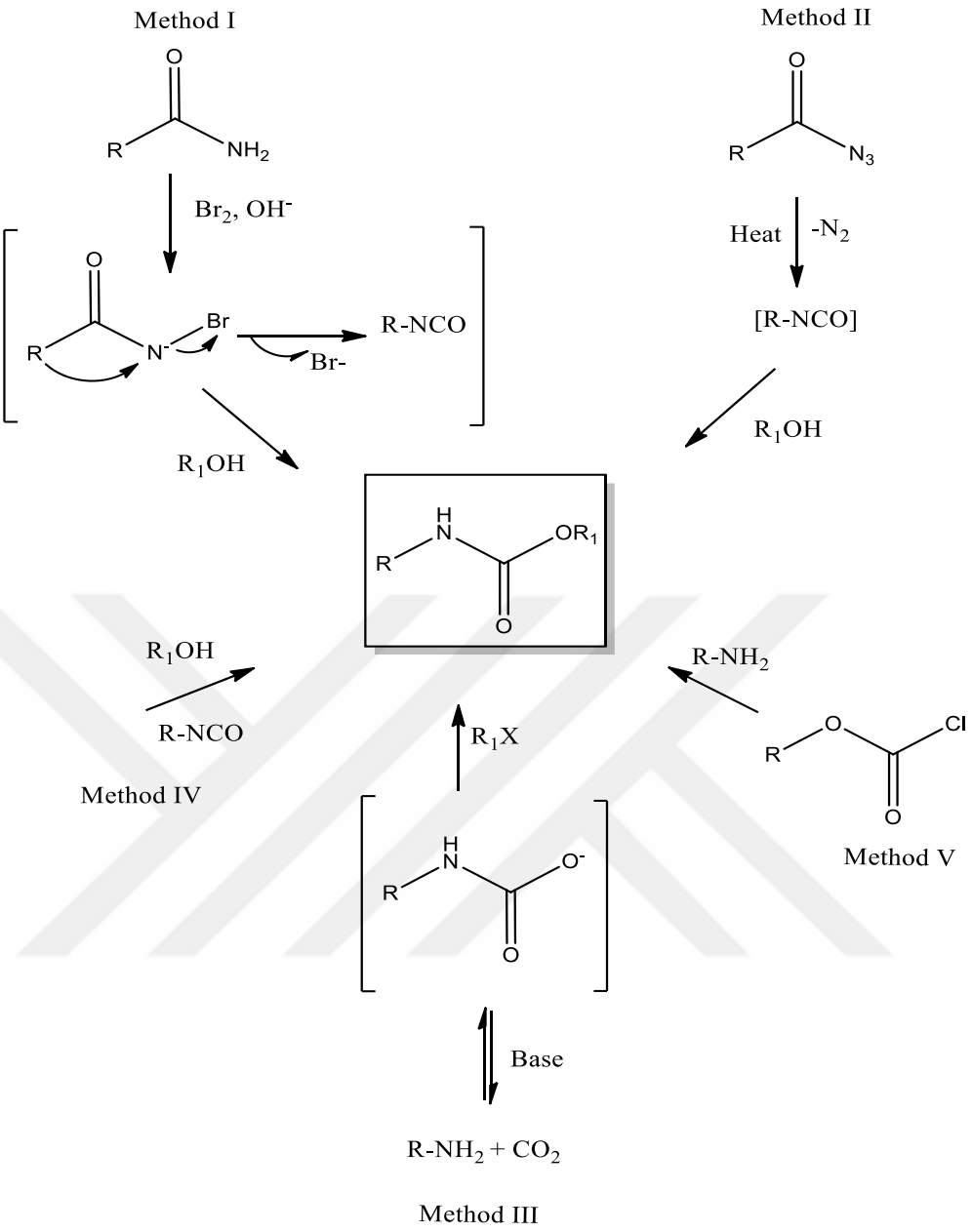
A very good alternative to phosgene is the use of carbon dioxide, as it is a kind of renewable resource (Method III, Scheme 1). Carbon dioxide reacts rapidly with amines to give carbamic acid ammonium salts. Most methods in this regard are based on the formation of carbamate anions through the reaction of carbon dioxide and amines and subsequent reaction with electrophiles.

1.5.2.4. By The Reaction Of Alcohols With Isocyanates

Production of carbamates from isocyanates (Method IV, Scheme 1) is the basis of the polyurethane industry. However, due to synthetic limitations and toxicity of phosgene, this method is the most common route to get isocyanates.

1.5.2.5. By The Reaction Of Amines With Chloroformates

Many commercially available alkyl chloroformates are the most commonly used precursors for the syntheses of carbamates (Method V, Scheme 1)



Scheme 1.18. General synthetic ways for the synthesis carbamates

2. AIM AND SCOPE OF THE STUDY

Terpenes are found in the plant essential oils and give their original odors to the plants. The importance of terpenes covers their use in perfume formulations. Naturally occurring substances such as menthol, citrus, and spices are commonly used terpenes in perfume ingredients. Other terpenes found in cosmetics include turpentine oil, chamomile and arnica oils, and shark sourced oils. Limonene and pinene terpenes are commonly used as air fresheners and improve a person's mood. [20] Among the terpenes, geraniol is an important example that is a monoterpenoid alcohol and main part of rose, palmarosa and citronella oils. It is used as a component in various aromatic and essential oils for cosmetic products, most commonly found in perfume formulations. In cosmetics it functions as a fragrance, masking and tonic ingredients. Moreover, carbamates constitute a valuable component for the fragrance industry. The vast majority of personal-care products (cosmetics, perfumes etc.) includes fragrances in their ingredients. Many carbamates are available commercially but some perfumers prefer to formulate their fragrances using different formates.

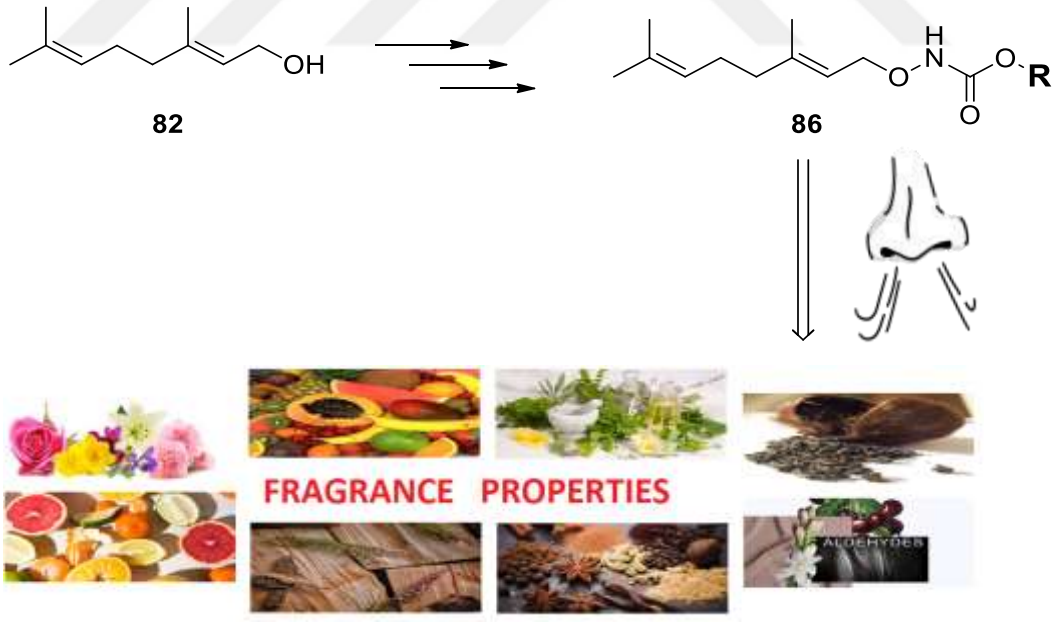


Figure 2.1. Synthetic route to O-geranyl carbamates and olfactive study

For this purpose, it was aimed first the preparation of a new series of O-geranyl carbamates (**86**) following simple and effective two-step synthetic protocol and secondly, the determination of their olfactory properties.

In the synthetic part of the current study, the preparation of O-geranyl amine **85** was achieved starting from geraniol by a stepwise method including allylic bromination and Gabriel amine synthesis reactions. Subsequently, a new series of target O-geranyl carbamates **(86**) was prepared by a base-catalyzed nucleophilic addition-eliminaton reaction of O-geranyl amine and different aryl or alkyl chloroformates (**52**).

In the second part of the study, produced carbamates (**86**) and precursor amine **85** was analysed by specialist perfumers for their olfactory properties to determine their odor characteristics, basic and subnotes, intensities and the changes of odors in time. Ultimately if there is cosmetic value of a produced carbamate in the current study, it will be further evaluated by our partner perfume company for its commercial value and capacity.

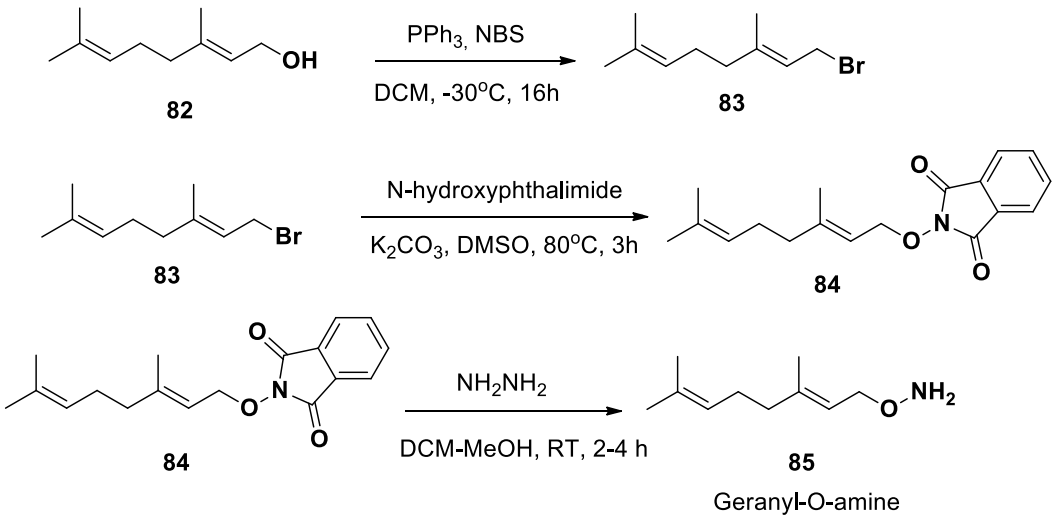
3. MATERIALS AND METHODS

Commercial providers supplied the reagents and solvents. in analytical and reagents grades (Merck, Acros, Sigma-Aldrich, TCI, Isolab). All reactions were stirred either at room temperature or refluxing using hot plates with magnetic stirrer. Heidolph Laborota 4000 efficient was used for solvents evaporations. TLC analysis were carried out for monitoring the reaction progress on TLC Silica gel 60 F_{254} sheets and stained with $KMnO_4$ for the visualization of the TLC spots using UVGL-58 Handheld UV Lamp. Column chromatographic separations of precursors and products were performed on silica gel (CDH, 230-400 mesh for TLC) and the eluents were mixtures of ethyl acetate and hexane. IR spectra were obtained on the Thermo Scientific Nicolet iS20 FT-IR Spectrometer instrument. Proton and carbon-13 NMR spectra have been measured on Bruker DPX 400 spectrometers (400 MHz for proton and 100 MHz for carbon) at room temperature. Chemical shifts (δ) are reported in ppm relative to TMS standard, $CDCl_3$ or DMSO-d_6 were used as deuterated solvent, and J values was given in Hz. Splitting patterns were classified as singlet (s), broad singlet (bs), doublets (d), doublet of doublets (dd), doublet of quartets (dq), triplets (t), quartets (q), and multiplets (m).

3.1. Experimental

3.1.1. Preparation Of Precursor

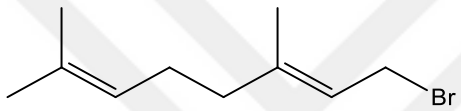
3.1.1.1. Synthesis Of O-Geranylamine



General Method- Preparation of geranylbromide (Step 1)

Geraniol (19.45 mmol, 1 equiv.) is added in a round-bottomed flask and dissolved by the addition of dry DCM (60 mL), it is coold in -20°C using NaCl-ice mixture (1:3). Then, PPh_3 (21.39 mmol, 1.1 equiv.) is added to the mixture. After dissolving of PPh_3, NBS (21.39 mmol, 1.1 equiv.) is added over 20 min portionwise every 30 seconds. The resulting mixture is stirred in ice-bath for 16 hours and the reaction progress is followed by TLC. After completion of the reaction, solvent is evaporated and the crude product is extracted with 100 mL of petroleum benzene/water (1 :1) mixture. Organic part is dried over Na_2SO_4 and filtered, rotaevaporated till dryness to afford a pale-yellow liquid product in pure state.

Geranyl bromide (83)



Pale yellow oil, 2.49 g (%88.5). Rf: 0.9 (20% EA: Hexanes).

IR (ATR) (cm^{-1}): 2961-2864 (alif.CH), 1454 (C=C), 750 (C-Br).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 – 5.50 (m, 1H), 5.14 – 5.04 (m, 1H), 4.05 (d, *J*= 8.5 Hz, 2H), 2.09 (q, *J* = 6.5 Hz, 4H), 1.75 (s, 3H), 1.71 (s, 3H), 1.62 (s, 3H).

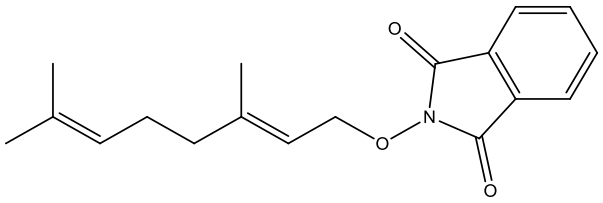
^{13}C-NMR ($CDCl_3$,100 MHz): δ 142.3, 141.1, 128.9, 123.4, 41.1, 39.8, 36.3, 36.2, 35.4, 18.9, 18.7.

General Method- Preparation of N-geranyloxyphthalimide (Step 2)

N-hydroxyphthalimide (6.58 mmol, 0.7 equiv.) is added in a round-bottomed flask and dissolved by the addition of DMSO (25 mL), then potassium carbonate (15.98 mmol, 1.7 equiv.) is added to the mixture. After 5 min of stirring at room temperature, a solution of geranylbromide from the previous step (9.4 mmol, 1 equiv.) in DMSO is added. The resulting mixture is refluxed for 3 hours and the reaction progress is followed by TLC. After completion of the reaction, the resulting mixture is poured into ice-water and the product is extracted with 100 mL of diethylether/water (1:1) mixture. Organic part is dried over Na_2SO_4 and filtered, rotaevaporated till dryness. Impurities were purified by column chromatography

using mixture of ethyl acetate: hexanes (1:20) to obtain a pale yellow solid product in pure state.

(E)-2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)isoindoline-1,3-dione (84)



Pale yellow creamy solid, 2.09 g (%70). Rf: 0.8 (50% EA: Hexanes).

IR (ν, cm^{-1}): 2970-2830 (alif.CH), 1783 (C=O), 1715 (C=O), 1462 (C=C).

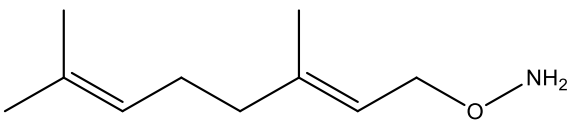
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J* = 5.1 Hz, 2H), 7.78 – 7.68 (m, 2H), 5.53 (t, *J* = 7.5 Hz, 1H), 5.04 (s, 1H), 4.74 (d, *J* = 7.6 Hz, 2H), 2.03 (s, 4H), 1.71 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 163.9, 147.1, 134.4, 132.0, 128.9, 123.8, 123.4, 116.7, 74.1, 39.7, 26.3, 25.7, 17.6, 16.5.

General Method- Synthesis of O-geranyl amine (Step 3)

A solution of *N*-geranyloxyphthalimide (6.49 mmol, 1 equiv.) from the previous step is put in a round-bottomed flask and dissolved by the addition of DCM (25 mL) and MeOH (20 mL). Hydrazine monohydrate (12.98 mmol, 2 equiv.) is added dropwise into reaction mixture. The resulting mixture is stirred at room temperature for 2 hours and the reaction progress is followed by TLC. After completion of the reaction, the resulting precipitate is filtered and washed using 5N aqueous NH_3, then extracted with 30 mL of DCM twice. Organic layers are collected, dried over Na_2SO_4, filtered and solvent is removed under rotary evaporator to afford the O-geranylamine as yellow liquid in pure state.

(E)-O-(3,7-dimethylocta-2,6-dienyl)hydroxylamine (85)



Pale yellow oil, 1.89 g (%76). Rf: 0.65 (25% EA: Hexanes).

IR (ν, cm^{-1}): 3313 (NH_2 str.), 2968, 2912, 2852, 1667 (N-H bending), 1587, 1442, 1376, 1179, 1065, 982, 828 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.58 (s, 3 H), 1.66 (s, 3 H), 1.69 (s, 3 H), 2.09-2.02 (m, 4 H), 4.25 (d, J=6.7 Hz, 2 H), 5.06 (m, 1 H), 5.32 (m, 1 H), 5.37 (bs, 2 H, NH_2).

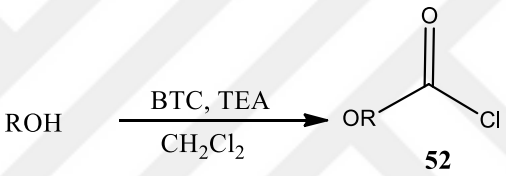
^{13}C-NMR ($CDCl_3$, 125 MHz): δ 143.2, 132.1, 128.6, 123.1, 118.6, 72.3, 39.6, 26.3, 25.7, 17.7, 16.6.

EI: m/z 169, 152 (m-NH_3), 137 (m-ONH_2).

3.1.2. Synthesis Of Geranyl Carbamates

3.1.2.1. Synthesis Of Chloroformates

General Method [14]

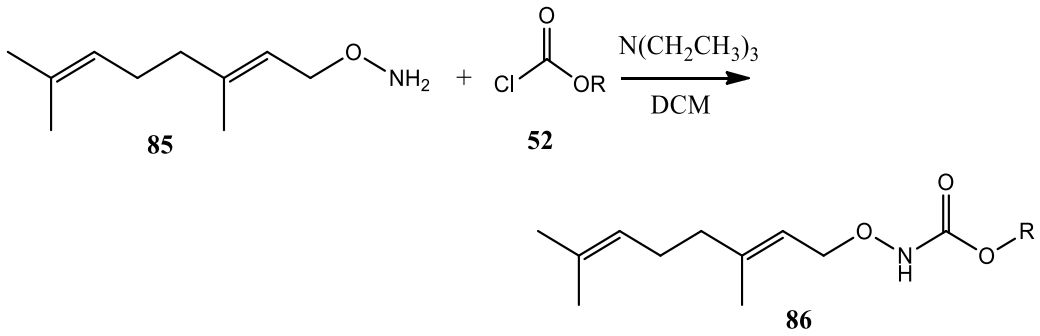


52

Corresponding alcohol (0.2mol) is added dropwise into a stirred solution of BTC (0.067mol) in DCM (50ml) and cooled to 0°C and then a solution of pyridine (0.2mol) in DCM (10ml) was added within half an hour. After the addition is completed, the temperature of reaction mixture is allowed to rise to room temperature and resulting mixture is stirred for 2-3h and monitored with TLC. The resulting mixture is extracted with cold water (3x50 mL), dried over sodium sulfate and filtered and then the residue is concentrated under vacuum to give corresponding chloroformate (**52**) which is then used without further purification.

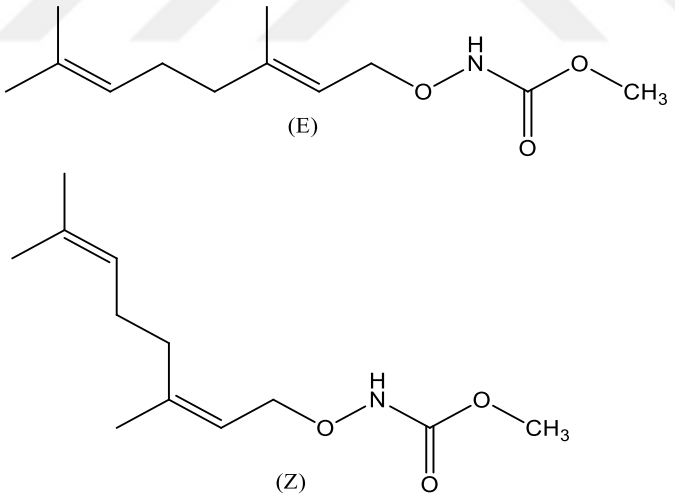
3.1.2.2. Synthesis Of O-Geranyl Carbamates

General Method



O-geranylamine **85** (2.96 mmol, 1 equiv.) is put in a round-bottomed flask and dissolved by the addition of DCM (10 mL) at 0°C, triethylamine (3.26 mmol, 1.1 equiv.) is added dropwise, after 5 minutes of stirring suitable chloroformate **52** (3.26 mmol, 1.1 equiv.) is added to reaction mixture. The resulting mixture is stirred at room temperature for 1-2 hours and the reaction progress is followed by TLC. After completion of the reaction, solvent is rotaevaporated under reduced pressure and crude products were purified by column chromatography using mixture of ethyl acetate:hexane (1:20) to afford the expected carbamates (**86**) in pure state.

(E/Z)-methyl (3,7-dimethylocta-2,6-dien-1-yl)oxycarbamate (86a)



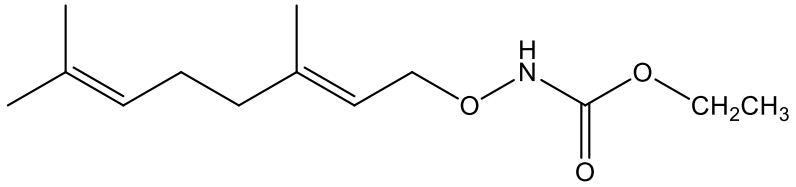
(Mixture of E/Z isomers) Yellow Liquid. (0.41g, 61.2%), R_f (25% EtOAc/Hex): 0.31.

IR (ν, cm^{-1}) : 3317 (NH str.), 2921 (C-H str.), 1794, 1757 (N-C=O str), 1436 (C=C str.), 1271 (sym. C-O str.), 1106 (unsym. C-O str.).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.34 (1H, s, NH), 5.41 (1H, t, *J*= 7.5 Hz), *5.38 (1H,t, J= 7.4 Hz)*, 5.05 (1H, m), 4.47 (2H, d, *J*= 7.4 Hz), *4.36 (2H, d, J= 7.6 Hz)*, 3.88(3H, s), *3.75 (3H, s)*, 2.06 (4H, m), 1.73 (3H, s), *1.69 (3H,s)*, 1.66 (3H,s), 1.58 (3H, s).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 157.*9*, 152.0, 146.7, *144.6*, 131.9, 123.8, 123.6, *123.5*, 117.7, *117.60*, 116.2, *116.1*, *72.6*, 72.5, *54.2*, 54.1, 52.8, *52.7*, 39.6, 29.6, 26.2, 25.7, *25.6*, 17.7, *17.6*, 16.5, *16.4*.

(E)-ethyl (3,7-dimethylocta-2,6-dien-1-yl)oxycarbamate (86b)



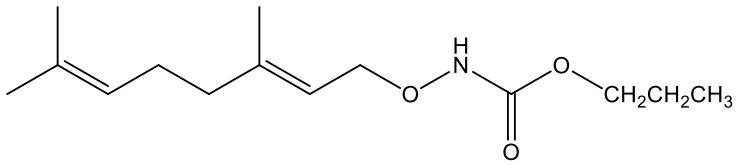
Yellow Liquid. (0.26 g, 56%), R_f (25% EtOAc/Hex): 0.4.

IR (ν, cm^{-1}): 3287 (NH str.), 2977-2916 (C-H str.), 1722 (N-C=O str), 1444 (C=C str.), 1243 (sym. C-O str.), 1108 (unsym. C-O str.).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.31 (1H, s, NH), 5.38 (1H, t, *J*=7.3 Hz), 5.08 (1H, t, *J*=6.7 Hz), 4.38 (3H, d, *J*=7.4 Hz), 4.21 (2H, q, *J*=7.2 Hz), 2.12-2.07 (4H, m), 1.71 (3H, s), 1.68 (3H, s), 1.29 (3H, t, *J*=7.1 Hz).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 157.3, 144.6, 131.9, 123.9, 117.6, 73.5, 61.6, 39.7, 26.4, 25.7, 17.7, 16.3, 14.5.

(E)-propyl (3,7-dimethylocta-2,6-dien-1-yl)oxycarbamate (86c)



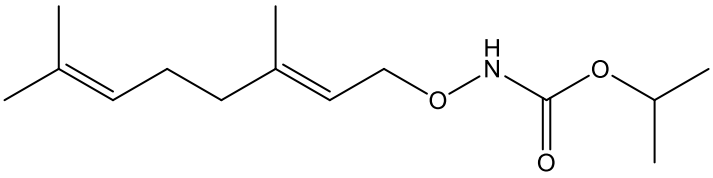
Beige liquid. (0.30g, 37.5%), R_f (25% EtOAc/Hex): 0.64.

IR (ν, cm^{-1}): 3280 (NH str.), 2965-2878 (C-H str.), 1720 (N-C=O str), 1453 (C=C str.), 1243 (sym. C-O str.), 1110 (unsym. C-O str.).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.41 (s, 1H, NH), 5.35 (t, *J* = 7.3 Hz, 1H), 5.05 (t, *J* = 6.2 Hz, 1H), 4.35 (d, *J* = 7.4 Hz, 2H), 4.08 (t, *J* = 6.7 Hz, 2H), 2.07-2.01 (m,4H), 1.68 (s, 3H), 1.65 (s, 3H), 1.64 – 1.59 (m, 2H), 1.57 (s, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 157.6, 144.4, 131.8, 123.8, 123.6, 117.7, 117.6, 72.5, 67.3, 39.6, 26.2, 25.6, 25.6, 22.1, 17.6, 16.4, 16.3, 10.2.

(E)-isopropyl (3,7-dimethylocta-2,6-dien-1-yl)oxycarbamate (86d)

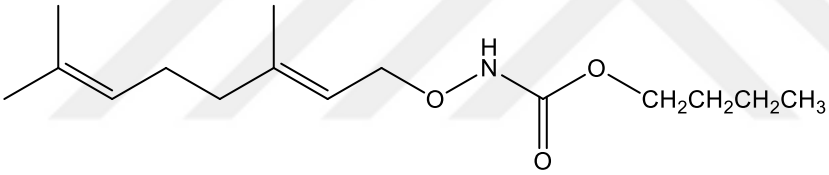


Yellow Liquid. (0.41 g, 61%), R_f (25% EtOAc/Hex): 0.31.
IR (ν, cm^{-1}): 3288 (NH str.), 2978-2925 (C-H str.), 1717 (N-C=O str), 1452 (C=C str.), 1245 (sym. C-O str.), 1109 (unsym. C-O str.).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.26 (s, 1H, NH), 5.35 (t, *J* = 7.3 Hz, 1H), 5.05 (dd, *J* = 12.6, 5.9 Hz, 1H), 4.97 (dq, *J* = 12.5, 6.3 Hz, 1H), 4.35 (d, *J* = 7.4 Hz, 2H), 2.18 – 1.99 (m, 4H), 1.69 (s, 3H), 1.66 (s, 2H), 1.58 (s, 3H), 1.25 (d, *J* = 6.3 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 157.1, 144.5, 131.9, 123.8, 117.8, 72.4, 69.6, 69.4, 39.6, 29.7, 26.2, 25.7, 22.0, 17.7,16.4.

(E)-butyl (3,7-dimethylocta-2,6-dien-1-yl)oxycarbamate (86e)

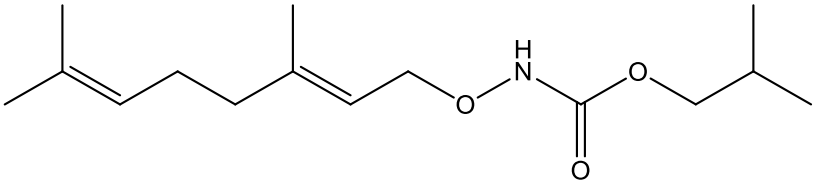


Yellow Liquid. (0.34 g, 42%), R_f (25% EtOAc/Hex) : 0.57.
IR (ν, cm^{-1}): 3430 (NH str.), 2960-2873 (C-H str.), 1789, 1754 (N-C=O str), 1458 (C=C str.), 1257 (sym. C-O str.), 1102 (unsym. C-O str.).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 5.40 (t, *J* = 7.6 Hz, 1H), 5.06 (t, *J* = 5.9 Hz, 1H), 4.45 (d, *J* = 7.6 Hz, 2H), 4.24 (t, *J* = 6.6 Hz, 2H), 2.13 – 1.99 (m, 4H), 1.72 (s, 3H), 1.71 – 1.66 (m, 2H), 1.66 (d, *J* = 4.4 Hz, 3H), 1.57 (s, 3H), 1.46 – 1.34 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 151.7, 146.2, 131.8, 123.7, 123.5, 116.4, 72.4, 67.2, 39.6, 30.5, 26.2, 25.6, 19.0, 17.6, 16.4, 13.6.

(E)-isobutyl (3,7-dimethylocta-2,6-dien-1-yl)oxycarbamate (86f)

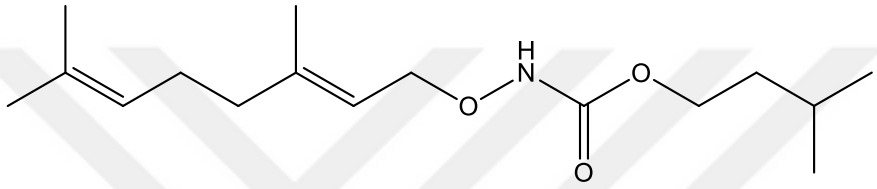


Yellow Liquid. (0.29 g, 34%), R_f (25% EtOAc/Hex) : 0.62.
IR (ν, cm^{-1}): 3422 (NH str.), 2961-2875 (C-H str.), 1790, 1754 (N-C=O str), 1469 (C=C str.), 1259 (sym. C-O str.), 1105 (unsym. C-O str.).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 5.43 (t, *J* = 7.6 Hz, 1H), 5.08 (t, *J* = 5.9 Hz, 1H), 4.50 (d, *J* = 7.6 Hz, 2H), 4.05 (d, *J* = 6.7 Hz, 2H), 2.06 (dq, *J* = 20.2, 6.6 Hz, 5H), 1.75 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 151.7, 145.9, 131.8, 123.7, 123.5, 116.5, 73.3, 72.5, 39.6, 27.7, 26.2, 25.6, 18.9, 16.4.

(E)-isoamyl (3,7-dimethylocta-2,6-dien-1-yl)oxycarbamate (86g)

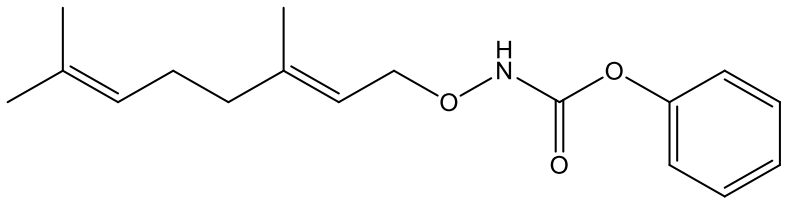


Yellow Liquid. (0.32 g, 31%), R_f (25% EtOAc/Hex): 0.28.
IR (ν, cm^{-1}): 3281 (NH str.), 2957-2870 (C-H str.), 1721 (N-C=O str), 1464 (C=C str.), 1244 (sym. C-O str.), 1108 (unsym. C-O str.).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.50 (s, 1H, NH), 5.35 (t, *J* = 7.3 Hz, 1H), 5.06 (t, *J* = 6.2 Hz, 1H), 4.35 (d, *J* = 7.4 Hz, 2H), 4.16 (t, *J* = 6.9 Hz, 2H), 2.06 (tt, *J* = 9.6, 4.9 Hz, 4H), 1.69 (s, 3H), 1.65 (d, *J* = 8.0 Hz, 3H), 1.58 (s, 3H), 1.52 (q, *J* = 6.9 Hz, 2H), 0.90 (d, *J* = 6.7 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 157.7, 144.4, 131.8, 123.8, 123.6, 117.7, 72.5, 64.4, 39.6, 37.5, 26.2, 25.6, 24.9, 22.4, 17.6, 16.4.

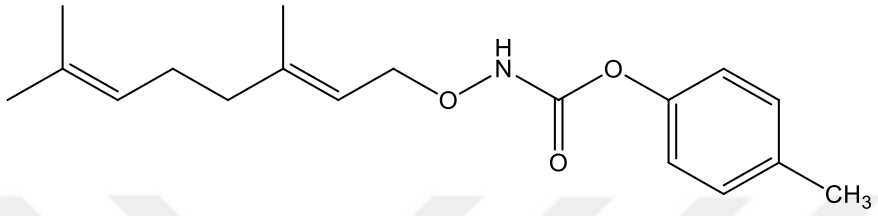
(E)-phenyl (3,7-dimethylocta-2,6-dien-1-yl)oxycarbamate (86h)



Yellow liquid. (0.48 g, 57%), R_f (25% EtOAc/Hex): 0.42.
IR (ν, cm^{-1}): 3289 (NH str.), 2924-2853 (C-H str.), 1732 (N-C=O str), 1666, 1592 (arom C=C), 1455 (C=C str.), 1200 (sym. C-O str.), 1079 (unsym. C-O str.).

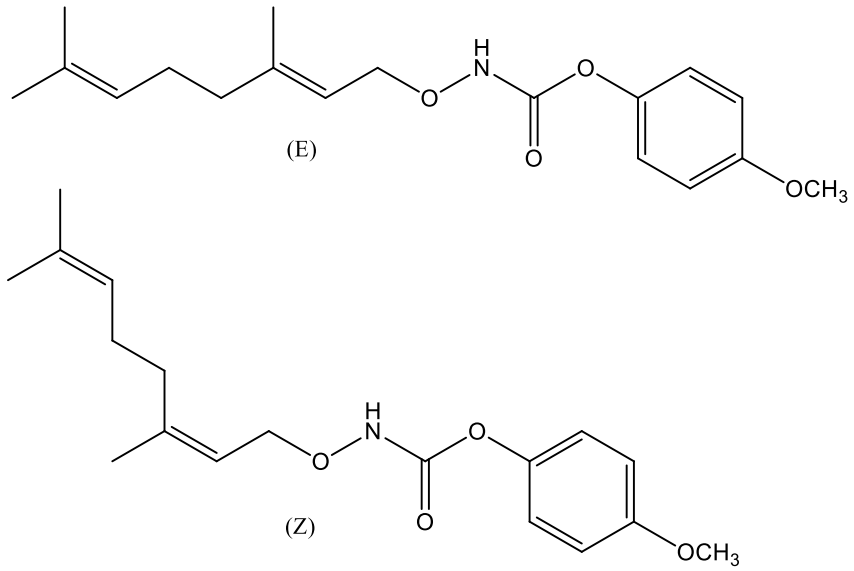
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.72 (1H, s, NH), 7.41-7.34 (2H, m), 7.22-7.19 (1H, m), 7.15-7.13 (2H, d, *J* = 8.1 Hz), 5.42 (1H, t, *J* = 7.3 Hz), 5.07 (1H, t, *J* = 7.1 Hz), 4.47, d, *J* = 7.4 Hz), 2.14-2.06 (4H, m), 1.74 (3H, s), 1.68 (3H, s), 1.60 (3H, s).
^{13}C-NMR ($CDCl_3$, 100 MHz): δ 155.3, 150.4, 145.3, 132.1, 129.4, 125.8, 123.7, 121.3, 117.5, 72.7, 39.6, 26.2, 25.7, 17.7, 16.5.

(E)-p-tolyl (3,7-dimethylocta-2,6-dien-1-yl)oxycarbamate (86i)



Yellow Liquid. (0.32 g, 38%), R_f (25% EtOAc/Hex): 0.62.
IR (ν, cm^{-1}): 3318 (NH str.), 3032 (arom CH), 2922-2854 (C-H str.), 1731 (N-C=O str), 1614, 1596 (arom C=C), 1452 (C=C str.), 1200 (sym. C-O str.), 1102 (unsym. C-O str.).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.74 (s, 1H, NH), 7.03 (d, *J* = 8.2 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 5.44 (t, *J* = 7.4 Hz, 1H), 5.12 (t, *J* = 5.9 Hz, 1H), 4.50 (d, *J* = 7.4 Hz, 2H), 2.29 (s, 3H), 2.20 – 2.05 (m, 2H), 1.77 (s, 3H), 1.72 (s, 3H), 1.63 (s, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): δ 153.4, 148.0, 145.4, 135.6, 132.1, 130.0, 129.9, 129.6, 123.8, 123.6, 121.1, 118.3, 117.4, 115.1, 72.8, 39.6, 29.7, 26.2, 20.5, 20.4, 16.5.

(E/Z)-4-methoxyphenyl (3,7-dimethylocta-2,6-dien-1-yl)oxycarbamate (86j)



(Mixture of E/*Z* isomers) Yellow Liquid. (0.30 g, 32%), R_f (25% EtOAc/Hex): 0.28. IR (ν, cm^{-1}): 3295 (NH str.), 2929-2836 (C-H str.), 1736 (N-C=O str), 1666, 1597 (arom C=C), 1440 (C=C str.), 1196 (sym. C-O str.), 1099 (unsym. C-O str.).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.69 (s, 1H, NH), 7.14 *(d, J = 9.0 Hz, 2H)*, 7.06 (d, *J* = 9.0 Hz, 2H), *6.91 (d, J = 9.2 Hz, 2H)*, 6.88 (d, *J* = 9.0 Hz, 2H), *5.54 (t, J = 7.7 Hz, 1H)*, 5.42 (t, *J* = 7.4 Hz, 1H), *5.31 (s, 1H)*, 5.08 (d, *J* = 6.4 Hz, 1H), *4.73 (d, J = 7.7 Hz, 2H)*, 4.47 (d, *J* = 7.4 Hz, 2H), 3.79 (s, 3H), *3.73 (s, 3H)*, 2.18 – 2.01 (m, 4H), *1.80 (s, 3H)*, 1.74 (s, *J* = 9.2 Hz, 3H), 1.69 (s, 3H), *1.67 (s, 3H)*, 1.61 (s, 3H), *1.58 (s, 3H)*.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ *157.6*, 157.2, 153.5, 150.4, *149.7*, 145.3, *143.8*, 143.7, 132.0, *123.8*, 123.6, *122.3*, 122.2, *117.5*, 117.4, *116.1*, 116.0, 114.7, *114.4*, 72.7, 55.6, *55.5*, *39.7*, 39.6, 26.2, *25.7*, 17.7, *17.6*, *16.6*, 16.5.

3.1.3. Olfactory Studıes

After completing the synthesis-characterization studies of precursors (**83-85**) and carbamate products (**86a-j**), first level test has been applied to determine the olfactory properties of the products.

General Method

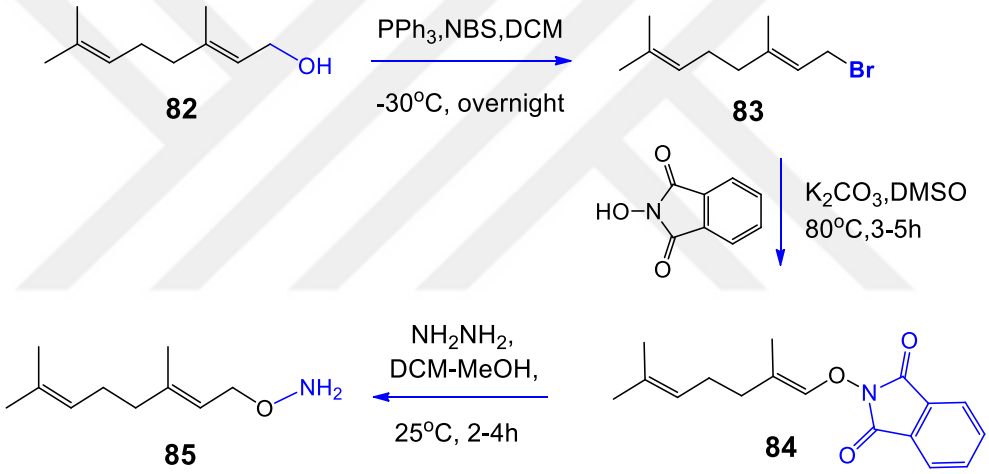
In the first level test, 10% dipropylene glycol solution of each sample is prepared applied on parfum test sticks. The odor description of each sample is performed as fresh and for 4-hour, 24-hour period of time and fragrance classes of samples have been identified by expert perfumers. In the meantime, perfumers

identify the molecules of which is the highest in fragrance density and they also make determinations about whether they can be new essential compounds or not. Olfactory studies of the compounds produced in the current thesis study is performed by the expert perfumers working in Parkim Perfume Plastic and Chemical Industry LC and the results were reported us in detail.

4. RESULTS AND DISCUSSION

4.1. Preparation Of Precursor Compounds

First of all, geranyl bromide **83** was prepared by radicalic bromination of geraniol **82**, then it was followed by the synthesis of geranyl phthalimide **84** from the reaction of geranyl bromide **83** and N-hydroxy phthalimide. In final step, geranyl phthalimide **84** was reduced to geranyl-O-amine **85** using hydrazine in DCM-MeOH mixture at r.t. Overally, the precursor compounds were isolated in good yields (70-88.5%) over a 3-step transformation under mild conditions (scheme 4.1 and table 4.1)



Scheme 4.1. Synthetic route affording geranyl-O-amine (**85**)

Table 4.1. The physical data and reaction yields for the precursor compounds

Precursor	Physical state	Rf	Time (h)	Yield (%)
83	Pale yellow oil	0.9[a]	16	88.5
84	Pale yellow creamy solid	0.8[b]	3	70
85	Pale yellow oil	0.6[a]	2	76

[a] Eluent: 25% EA: Hexanes; [b] Eluent: 50% EA: Hexanes

IR and NMR analyses were used to determine the structures of precursor compounds (83-85). First of all, the structure of geranyl bromide **83** was primarily

confirmed using aliphatic CH (2961-2884 cm^{-1}), C=C (1454 cm^{-1}) and C-Br (750 cm^{-1}) IR stretching vibrations. Besides, olefinic CH (5.60-5.04 ppm), CH_2 (4.05 ppm) proton signals in ^{1}H-NMR and olefinic, methylenic C signals at 129, 41 ppm in C-13 NMR were in accordance with the expected structure of **83** (figures 4.1-4.3). Structure of second precursor **84** was also confirmed by C=O stretchings (1783, 1715 cm^{-1}) in IR spectrum. In proton and C-13 NMR spectra of **84**, aromatic CH proton (7.82-7.68 ppm), olefinic and aromatic carbon signals (147-116 ppm) supported the formation of product (figures 4.4-4.6). In the final step, formation of O-geranylamine **85** was clarified primarily with IR stretching and bending vibrations of NH_2 (3312 cm^{-1}), N-H (1667 cm^{-1}) groups in its IR spectrum (figure 4.7). Also, NH_2 proton (5.37 ppm as broad singlet) and olefinic CH proton (5.06, 5.32 ppm) signals in ^{1}H-NMR spectrum of **85** supported the expected structure. Moreover, C signals at 123.8, 118.6 ppm (=CH) and 72.3 ppm (OCH_2) in the C-13 spectrum of **85** suited well with expected structure (figures 4.8-4.9).

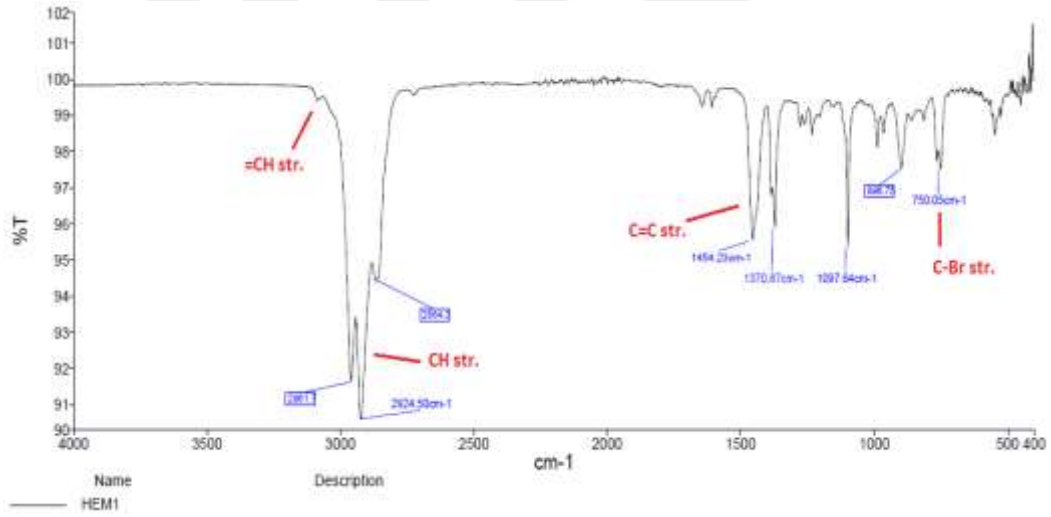


Figure 4.1. IR spectrum of geranyl bromide **83**

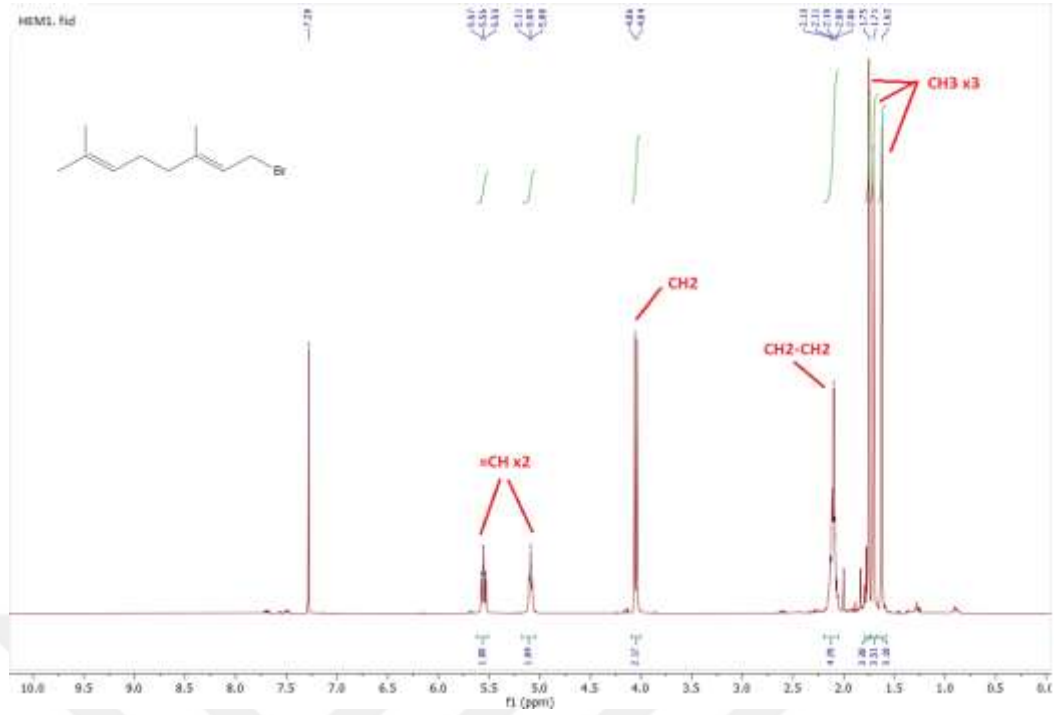


Figure 4.2. [1]H-NMR spectrum of geranyl bromide **83**

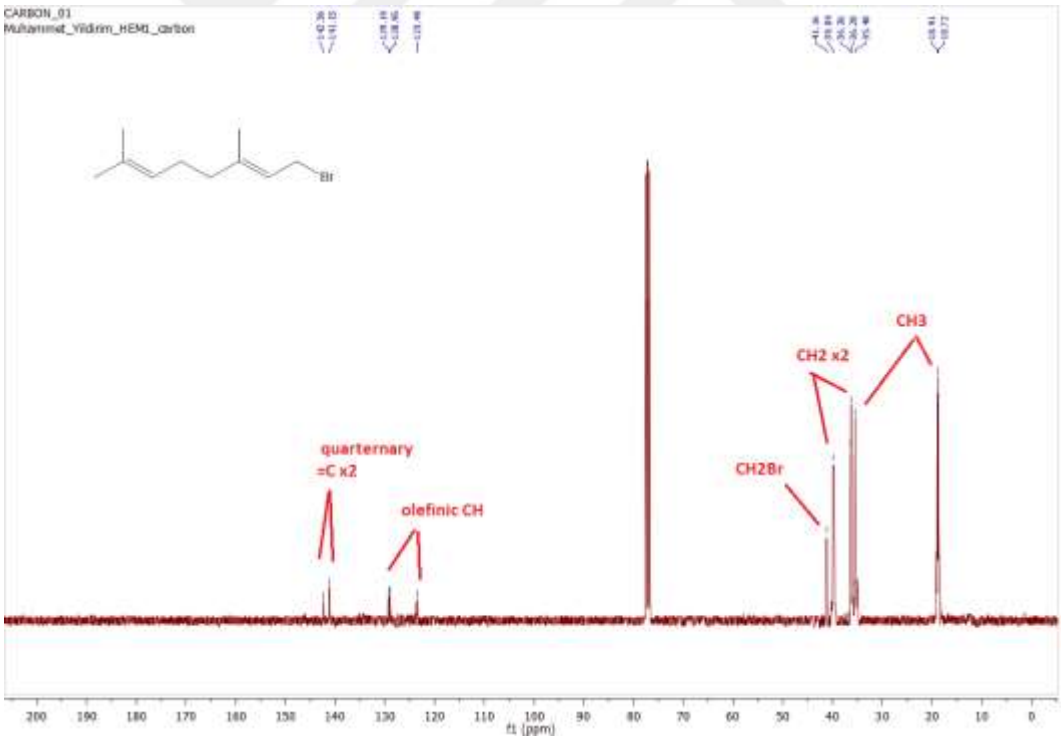


Figure 4.3. [13]C-NMR spectrum of geranyl bromide **83**

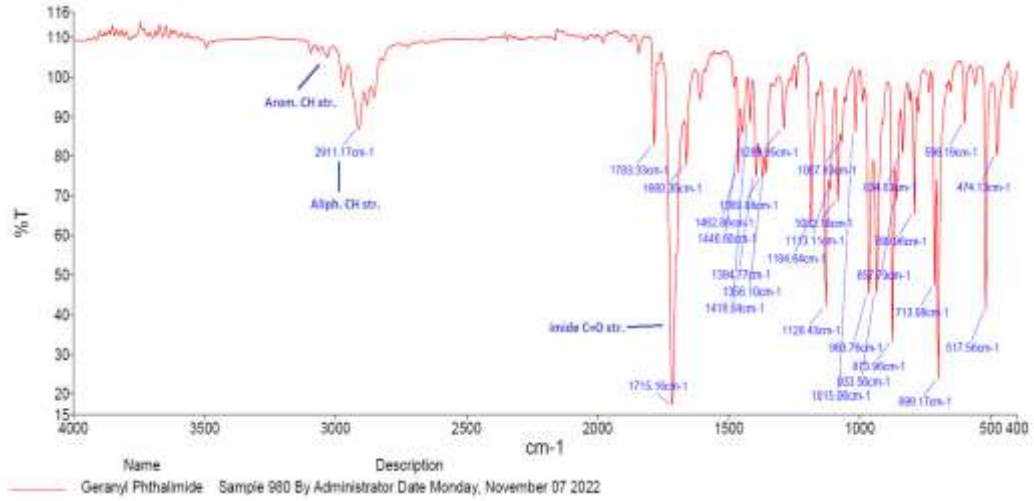


Figure 4.4. IR spectrum of geranyl phthalimide **84**

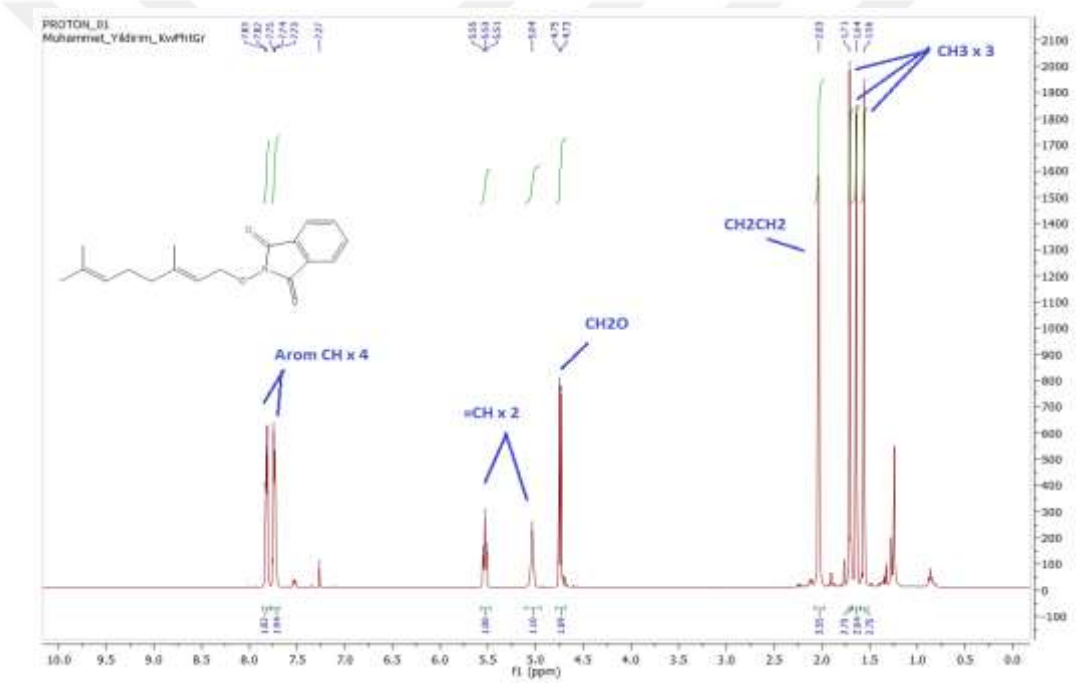


Figure 4.5. ^{1}H-NMR spectrum of geranyl phthalimide **84**

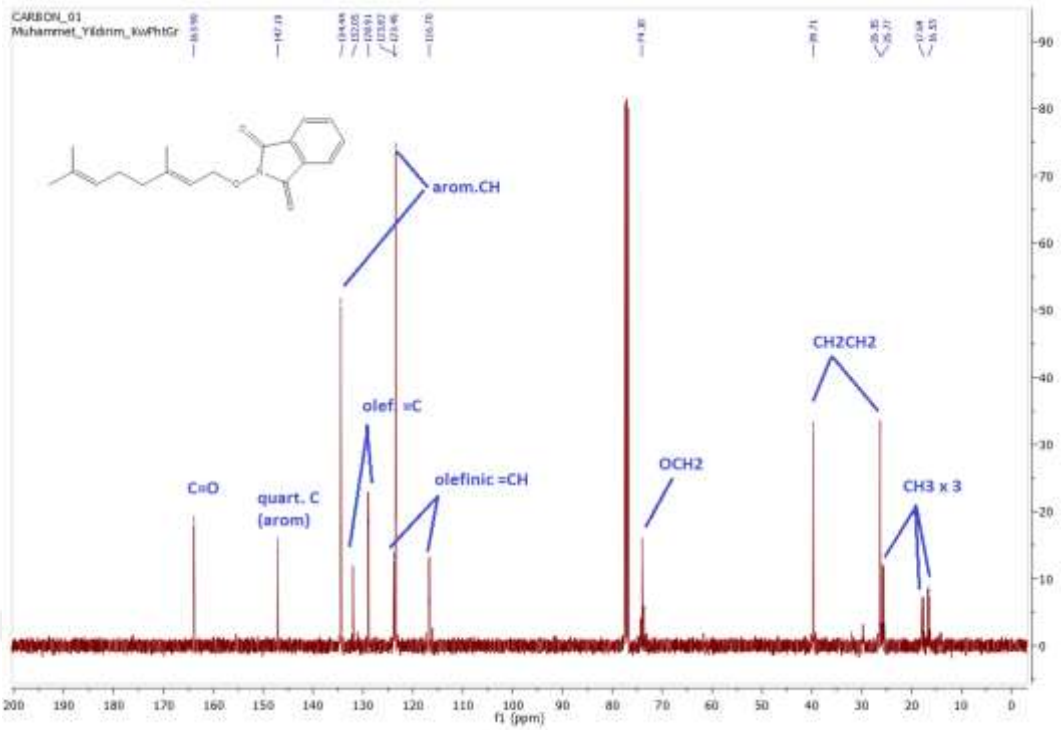


Figure 4.6. ^{13}C-NMR spectrum of geranyl phthalimide **84**

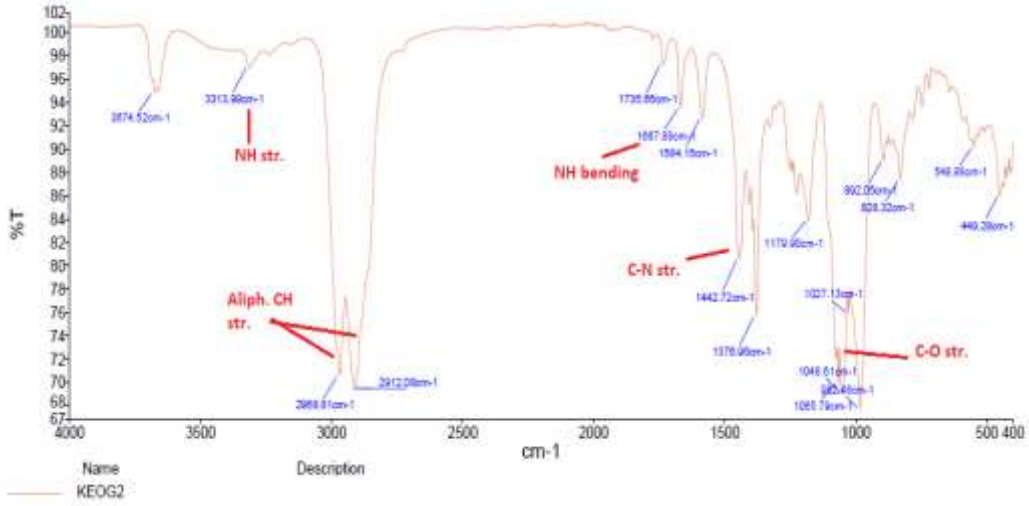


Figure 4.7. IR spectrum of geranyl O-amine **85**

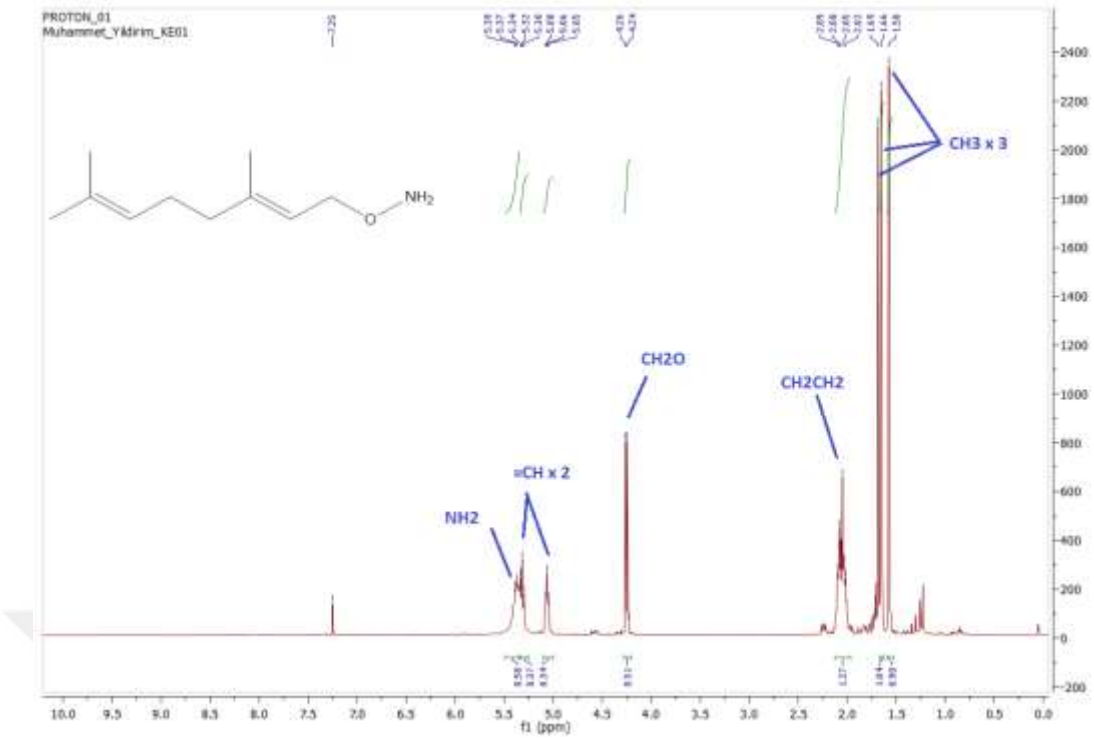


Figure 4.8. ^{1}H-NMR spectrum of geranyl O-amine **85**

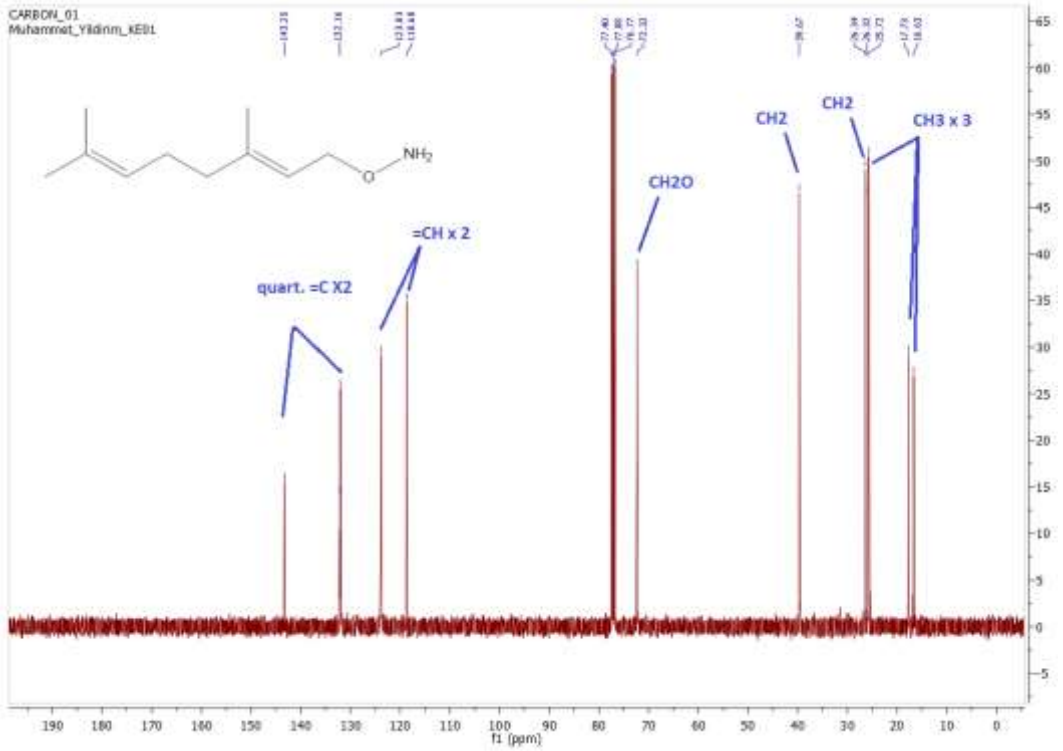
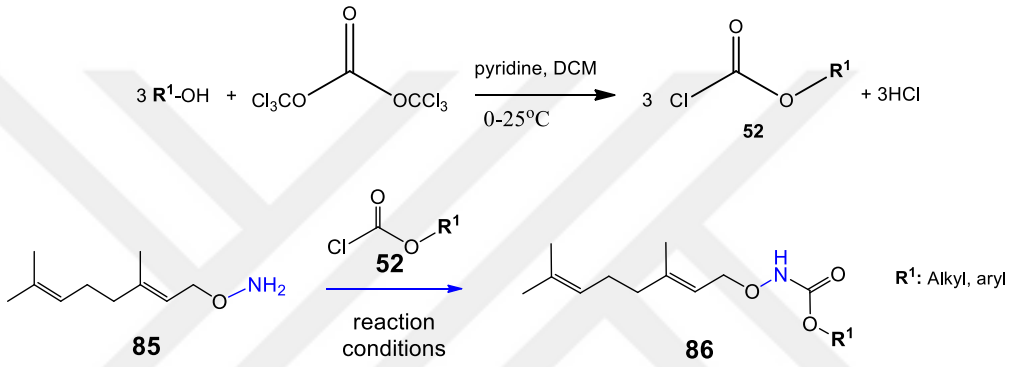


Figure 4.9. ^{13}C-NMR spectrum of geranyl O-amine **85**

4.2. Synthesis Of O-Geranyl Carbamates

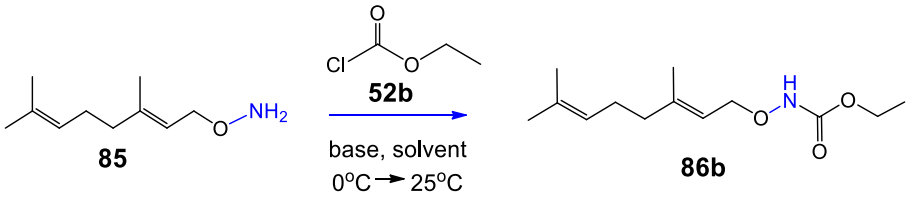
In the second part of synthetic studies, new O-geranyl carbamate derivatives (**86**) have been prepared over geranyl-O-amine (**85**) precursor which was produced in previous steps. The synthesis of O-geranyl carbamate derivatives (**86**) was planned to perform by a base-mediated reaction of geranyl-O-amine **85** and a variety of alkyl or aryl chloroformates (**52**). The chloroformate derivatives were purchased commercially or made by following a published method that included a very mild reaction of different alcohols with bis(trichloromethyl)carbonate. [14] (scheme 4.2).



Scheme 4.2. Synthesis of chloroformates **(52**) and O-geranyl carbamates (**86**)

Firstly, some optimization studies have been performed to specify the ideal conditions for the synthesis of O-geranyl carbamate derivatives (**86**). In this regard, a base-catalyzed condensation between geranyl-O-amine **85** and ethyl chloroformate **52b** was used as a model reaction. In first two trials, the precursors **85** and **52b** in 1/1.1 equivalent ratio was stirred in acetonitrile with or without a base, however O-geranyl ethyl carbamate **86b** was isolated in 15 to 40% yields, respectively (table 4.2, entries 1-2). When the same composition of precursors (1/1.1) was reacted in ethanol (polar protic solvent) and DCM (less polar non-protic), a sequential increase in reaction yields (42 to 56%) was observed under basic conditions (table 4.2, entries 3-4). In last two trials, use of another base or addition of higher amounts of bases in reaction mixture did not cause a remarkable increase in reaction yields (45-50%) (table 4.2, entries 5-6). After optimization studies with model reaction, the best conditions for the synthesis of O-geranyl carbamates (**86**) was found as in the reaction between 1 equiv. of **85** and 1.1 equiv. of **52b** in the presence of triethylamine in DCM within 2 hours (table 4.2, entry 4).

Table 4.2. Optimizations for synthesis of O-geranyl carbamates (**86**)

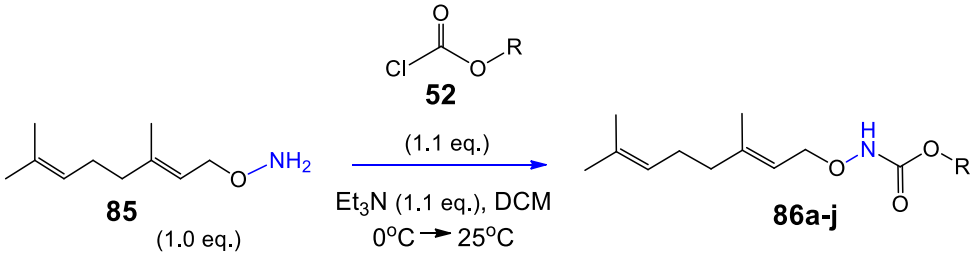


Entry[a]	**85** (equiv.)	**52b** (equiv.)	Base (equiv.) solvent	Time (h)	Yield (%)[b]
1	1	1.1	No base, CH_3CN	6	15
2	1	1.1	Et_3N (1.1), CH_3CN	2	40
3	1	1.1	Et_3N (1.1), EtOH	3	42
4	1	1.1	Et_3N (1.1), DCM	2	**56**
5	1	1.1	Et_3N (1.5), DCM	2.5	50
6	1	1.1	K_2CO_3 (1.5), DCM	5	45

[a] In each trial, ethyl chloroformate was added at 0°C, then continued at r.t.
[b] Yields after chromatographic purification

Under optimized conditions, a series of novel alkyl and aryl substituted O-geranyl carbamates (**86a-j**) were synthesized and purified by column chromatography using non-polar mixtures of hexanes:EtOAc (Table 4.3). Among the carbamate products, benzyl O-geranylcarbamate **86k** was relatively sensitive to silica during chromatographic separation, thus complete decomposition took place without isolation of any product (Table 4.3). The results of carbamate synthesis reactions and other details were presented below in Table 4.3.

Table 4.3. Synthesis and reaction yields of O-geranyl carbamates (**86a-j**)



86	R	Physical form	Rf [a]	Time (h)	Yield (%)[b]
a	Methyl	Yellow liquid	0.31	1	61
b	Ethyl	Yellow liquid	0.40	0.75	56
c	propyl	Beige liquid	0.64	1	38
d	i-propyl	Yellow liquid	0.31	1.5	61
e	butyl	Yellow liquid	0.57	2	42
f	i-butyl	Yellow liquid	0.62	1	34
g	isoamyl	Yellow liquid	0.28	1	31
h	phenyl	Yellow liquid	0.42	1	57
i	p-tolyl	Yellow liquid	0.62	1.5	38
j	p-OCH_3Ph	Yellow liquid	0.28	1	32
k	benzyl	-	0.70	1	- [c]
l	p-NO_2Ph	Beige solid	0.25	1	25[d]

[a] Rf value (25% Hexane:EtOAc). [b] Yields after chromatographic purification.
[c] Decomposition during column chromatorgraphy. [d] not expected product.

When the reaction yields of alkyl and aryl O-geranyl carbamates (**86a-l**) were examined in general, all aryl O-geranyl carbamates were obtained low to moderate yields (32-57%) except **86l** (*p*-nitrophenyl). Besides, a similar trend have been observed in the reaction yields of alkyl carbamates (31-61%) (Table 4.3). Additionally, a sequential decrease in reaction yields of alkyl O-geranylcarbamates (**86a-g**) is seen with increasing C chain length of carbamates. However, the best yields (56-61%) among all products were obtained for the carbamates **86a** (Me)**, 86d** (i-Pr)**, 86h** (Ph)**, 86b**(Et), respectively. On the contrary, the lowest yields (31-32%) were found for the products **86g** (isoamyl) and **86j** (*p*-MeOPh) and such decreases in product yields were possibly due to either steric effect of isoamyl group or ED effect of methoxy group which lowered the reactivity of their chloroformates. However, reaction yield for *p*-nitrophenyl carbamate (**86l**) was quite low due formation of complex product mixture during the reaction (Table 4.3). Most of the carbamate formation reactions have been completed within a hour but even if the

reaction times were prolonged in some carbamates (**86d, 86e, 86i**) to 1.5-2 h, no significant increase was observed in their reaction yields (Table 4.3).

FT-IR, ^{1}H- and ^{13}C-NMR analyses and also physical data were used in the structural characterization of carbamate products **86a-j**. The main and indicative data used for the structural characterization of ethyl O-geranylcarbamate, **86b**, can be given as an example. For instance, indicative IR stretching vibrations of **86b** at 3287 cm^{-1} (NH), 2916 cm^{-1} (aliph.CH), 1722 cm^{-1} (C=O), 1243 cm^{-1} (C-O-C); proton NMR signals at 7.31 (NH), 5.38-5.08 (=CH), 4.38 (OCH_2) ppm; ^{13}C-NMR signals at 157 (C=O), 73.5 (CH_2O), 61.6 (OCH_2) and 144.6-117.6 (=CH) ppm have confirmed the formation of expected product (Figures 4.10-4.12).

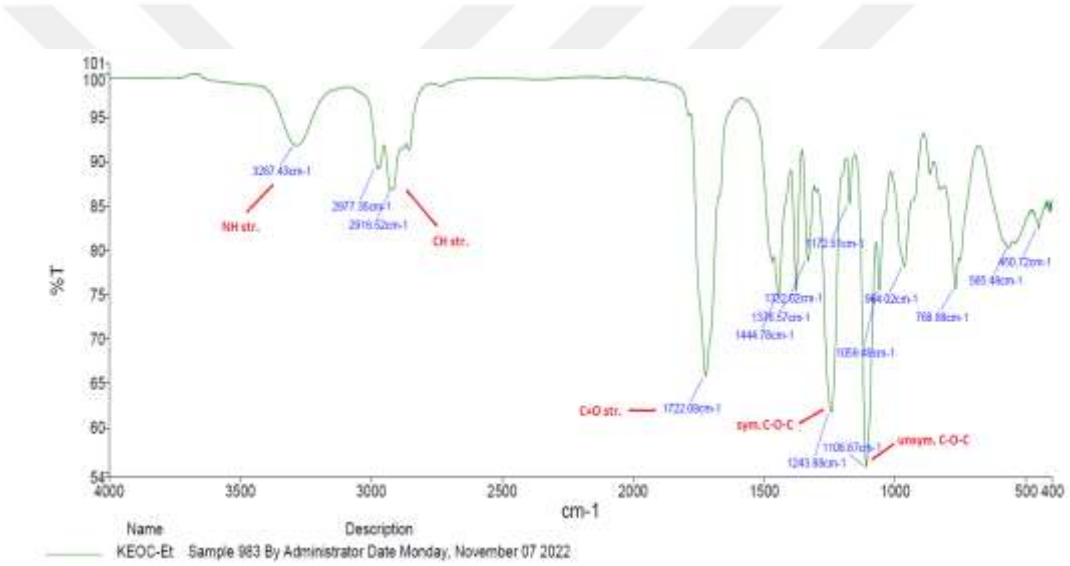


Figure 4.10. IR spectrum of ethyl O-geranyl carbamate (**86b**)

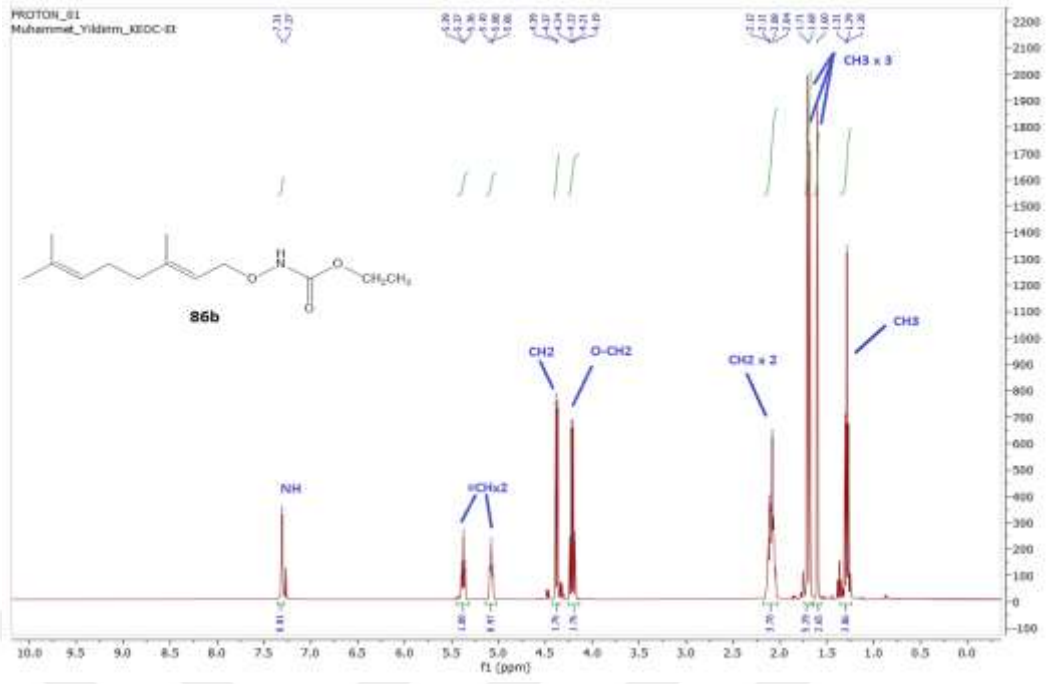


Figure 4.11. ^{1}H-NMR spectrum of ethyl O-geranyl carbamate (**86b**)

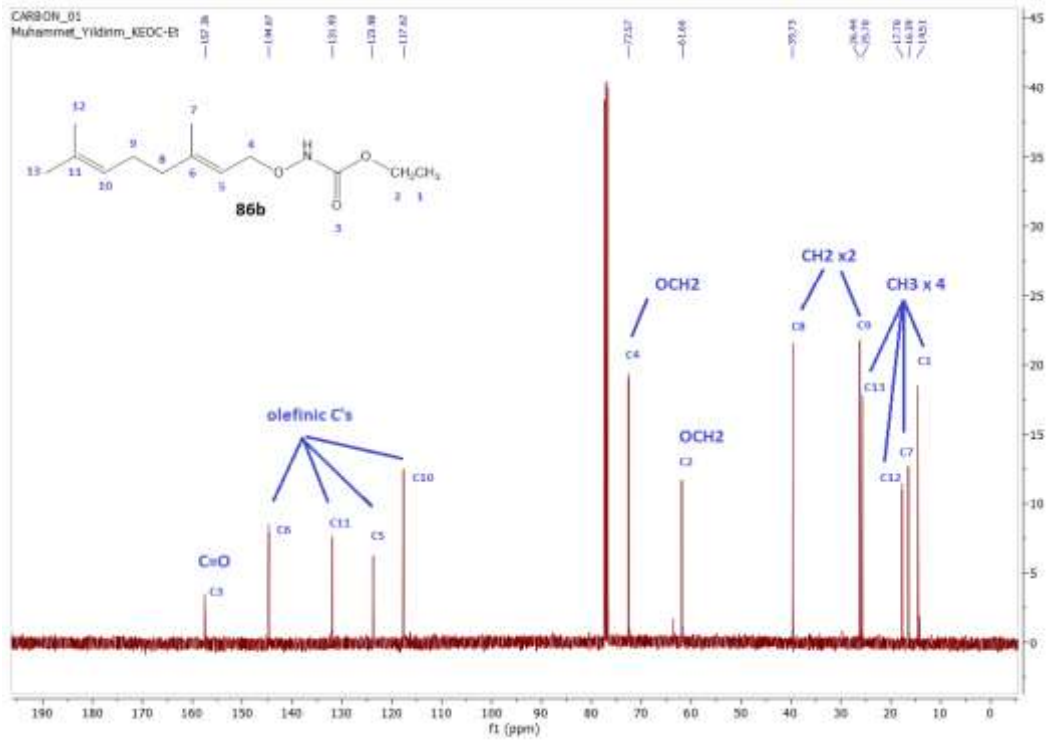
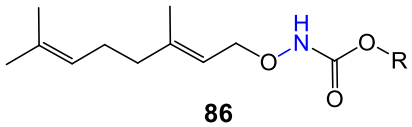


Figure 4.12. ^{13}C-NMR spectrum of ethyl O-geranyl carbamate (**86b**)

Table 4.4. Indicative characterization data for alkyl and aryl O-geranyl carbamates (**86a-j**)



86

		IR (cm^{-1})		^{1}H-NMR (δ,ppm)			^{13}C-NMR (δ,ppm)		
86	**R**	**NH str.**	**C=O str.**	**=CH x2**	**NH**	**CH_2O**	**C=O**	**=CH**	**CH_2O**
a	Me	3317	1757	5.41, 5.05	7.34	4.47	157.9	146.7-117.7	72.5
b	Et	3287	1722	5.38, 5.08	7.31	4.38	157.3	144.6-117.6	73.5
c	Pr	3280	1720	5.35, 5.05	7.41	4.35	157.6	144.4-117.7	72.5
d	i-Pr	3288	1717	5.35, 5.05	7.26	4.35	157.1	144.5-117.8	72.4
e	Bu	3430	1754	5.40, 5.06	-	4.45	151.7	146.2-116.4	72.4
f	i-Bu	3422	1754	5.43, 5.08	-	4.50	151.7	145.9-116.5	72.5
g	i-amyl	3281	1721	5.35, 5.06	7.50	4.35	157.7	144.4-117.7	72.5
h	Ph	3289	1732	5.42, 5.07	7.72	4.47	155.3	145.3-117.5	72.7
i	*p*-tolyl	3318	1731	5.44, 5.12	7.74	4.50	153.4	145.4-117.4	72.8
j	*p*-MeOPh	3295	1736	5.42, 5.08	7.69	4.47	153.5	145.3-117.4	72.7

All the new O-geranyl carbamates **86a-j** were characterized over their indicative IR, ^{1}H-NMR, and ^{13}C-NMR data as explained above. In general, characteristic IR absorption peaks of product **86a – j** appeared at around 3280-3430 cm^{-1} for NH and 1717-1757 cm^{-1} for C=O bond stretchings (table 4.4). In the ^{1}H NMR spectra of carbamates **86a–j**, proton signals resonated at around 7.26-7.74 (NH), 5.05-5.44 (olefinic CH) and 4.35-4.50 (CH_2O) ppm confirmed the expected structures (table 4.4). Besides, the ^{13}C-NMR spectra of **86a-j** derivatives indicated the specific carbon signals of C=O, =CH and CH_2O groups at around 152-158, 116-146, and 72.4-73.5 ppm, respectively which also supported the structure of the expected products (table 4.4). After characterization of *p*-nitrophenyl substituted

product **86l** with NMR analysis it was found as a different and simpler molecule rather than the expected carbamate.

All characterization data of products (**86a-j**) are presented in table 4.4 and the experimental section, also all the spectra of target products **86a-j** are given in the appendices section as supporting information. Lastly, in order to support the structural characterization, the high-resolution mass analyses of all the products (**86a-j**) are still underway in collaboration with a mass analysis laboratory.

4.3. Olfactory Properties Of Precursors And Carbamates

In the last part of the current dissertation study, O-geranlamine **85** and all the carbamate products (**86a-j**) which were already synthesized, purified and characterized were subjected to the olfactory analysis by the expert noses working in our industrial partner (Parkim LLC) and the odor descriptions have been reported for each tested compound as below in table 4.5. When the olfactory tests results of products were analyzed using fragrance wheel, the fragrance range was found quite wide from floral, citrus, fresh fragrance families to mineral, woody-earthy, animalic families (figure 4.13).

Table 4.5. Olfactory test results for precusor O-amine **85** and carbamates (**86a-j**)

Test sample	Odor description*
85 (O-amine)	Isoamyl → fruity → FLORAL
86a (Me)	-[a]
86b (Et)	-[a]
86c (Pr)	-[a]
86d (i-Pr)	Bergamot-→Fresh → CITRUS linally acetate → Sweet → FRESH
86e (Bu)	Bergamot-→Fresh → CITRUS
86f (i-Bu)	pine, clean → Rich → WOODY Ozonic → MINERAL
86g (i-amyl)	-[a]
86h (Ph)	Leather → ANIMALIC
86i (p-tolyl)	Creosolic, phenyl acetate→ ANIMALIC IBQ → WOODY-EARTHY
86j (p-MeOPh)	-[a]

* Olfactory test results within first 1 hour. [a] Test result is not available yet.

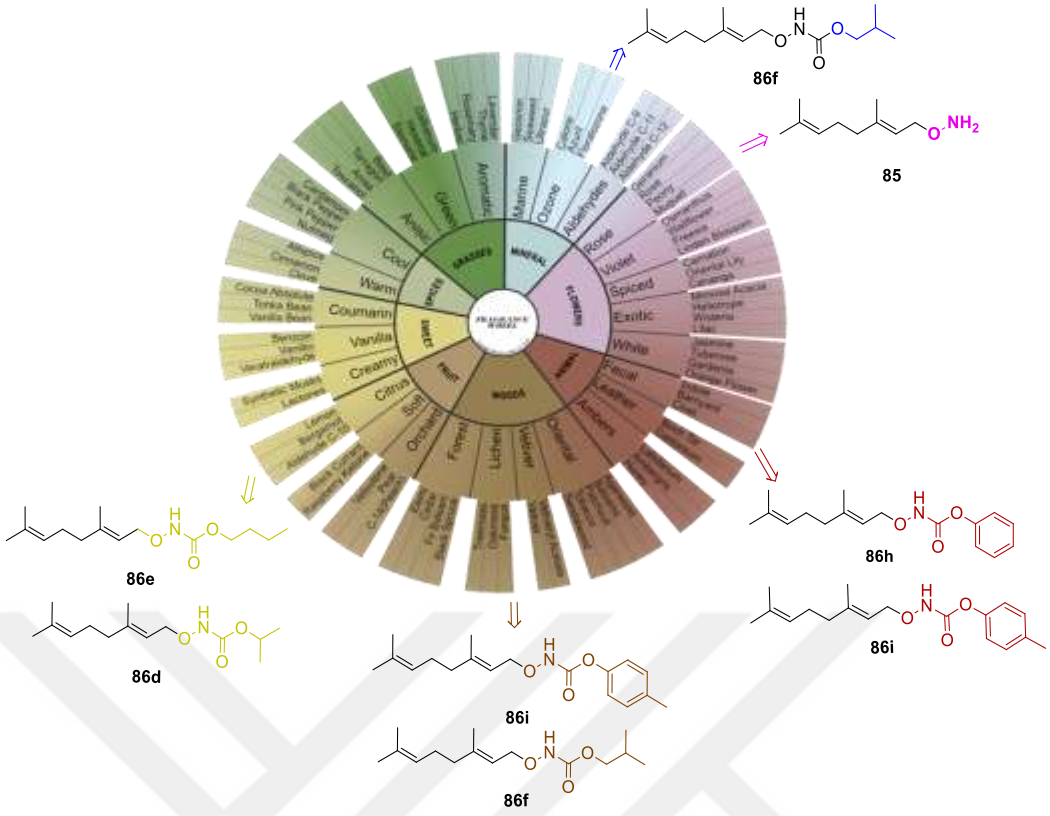


Figure 4.13. Odors of O-amine **85** and carbamates (**86a-j**) on fragrance wheel

5. CONCLUSIONS

Some conclusions can be drawn from the results of current dissertation study as follows:

In the first part of the study, starting from geraniol, three precursor compounds, homogeranyl bromide **83**, geranyl phthalimide **84** and geranyl-O-amine **85** have been prepared in good yields over allylic bromination and Gabriel amine reation series under mild conditions. And their structures were characterized using IR and NMR techniques and also supported by physical analyses (color, physical state, Rf).

Subsequently, in the second part of the study, 12 novel geranyl-O-carbamates **86a-j** were attempted to synthesize and 11 products (**86a-j**, **86l**) were isolated successfully after chromatographic separation in low to moderate yields via the base-catalyzed condensation reactions of geranyl-O-amine **85** and chloroformates. Only benzyl O-carbamate **86k** was unable to be purified by chromatography due to decomposition. The structures of 10 target compounds **86a-j** were elucidated by means of physical data (color, physical state, Rf) and spectroscopic analyses (IR, ^{1}H-NMR, ^{13}C-NMR). As the result of spectroscopic analysis, the structure of *p*-nitrophenyl O-carbamate **86l** was understood that it was different from the expected product.

In the last part of the current study, the geranyl-O-amine **85** and five of geranyl-O-carbamates (**86d,e,f,h,i**) were subjected to olfactory tests by expert noses to identify their odor characteristic and fragrance potential. As the result of olfactory tests, it was seen that geranyl-O-amine **85** and carbamates (**86a-j**) had some top notes like floral, citrus, fresh, and heart notes like mineral, woody-earthy, animalic.

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7. APPENDICES

IR, NMR, HRMS Spectra for the precursors and products

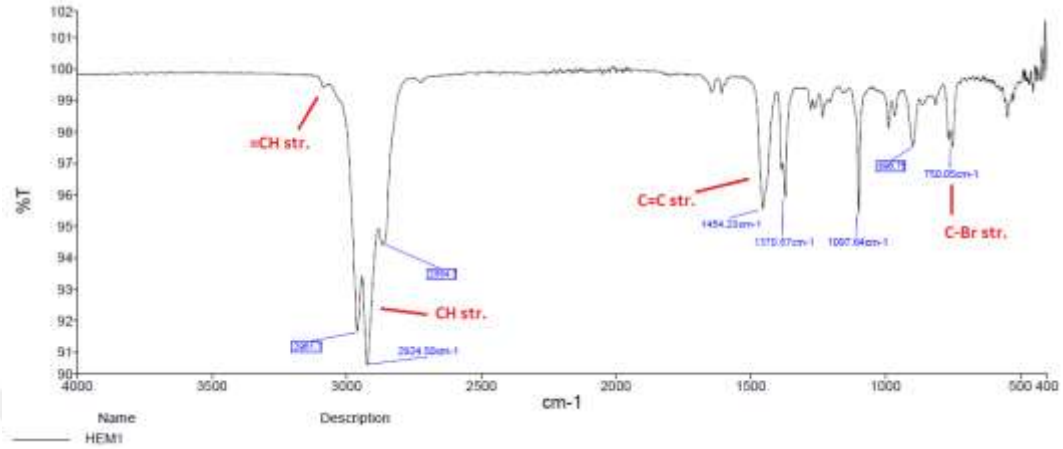

Figure 7.1. IR spectrum for compound **83**

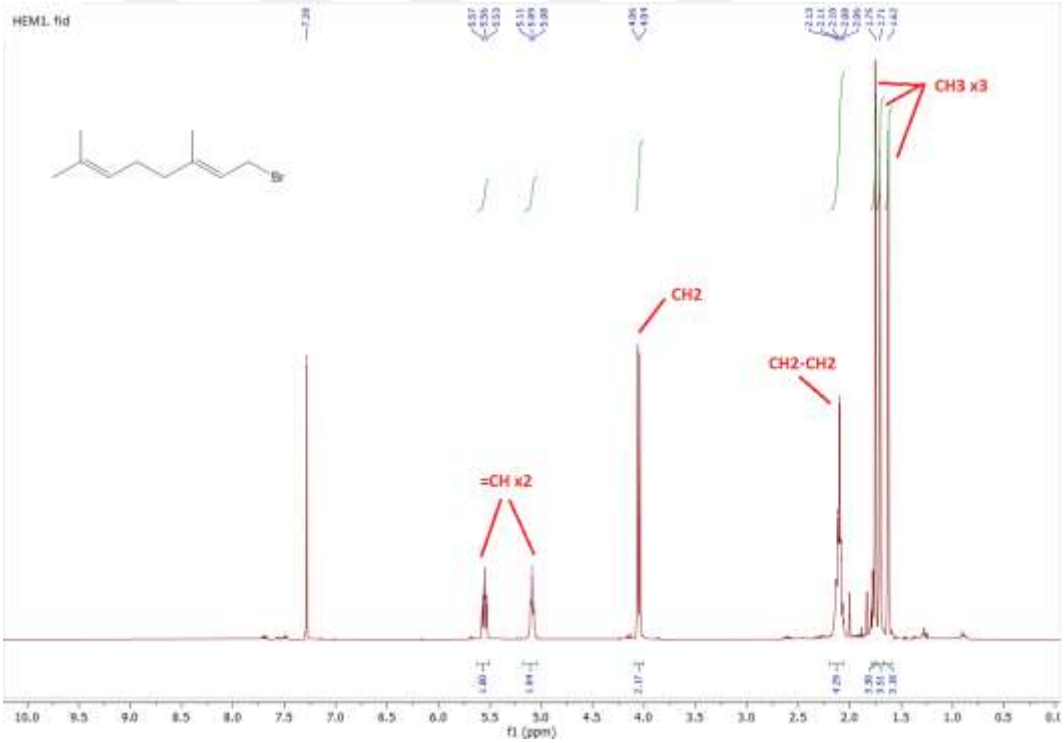

Figure 7.2. ^{1}HNMR spectrum for compound **83**

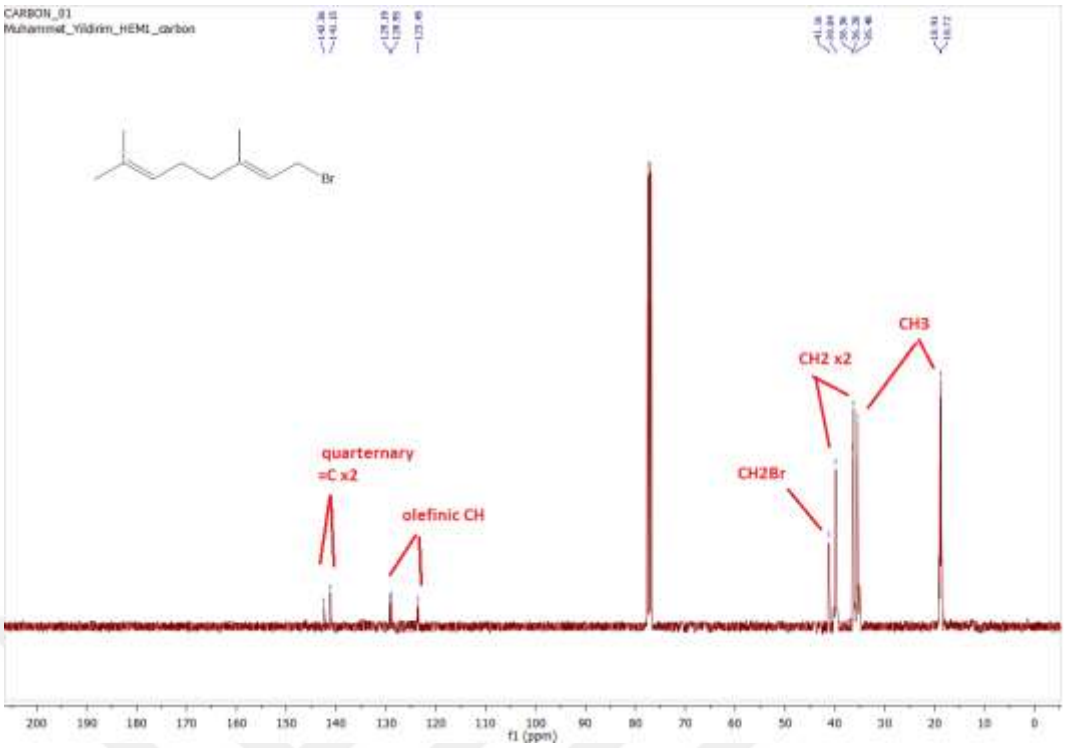

Figure 7.3. ^{13}CNMR spectrum for compound **83**

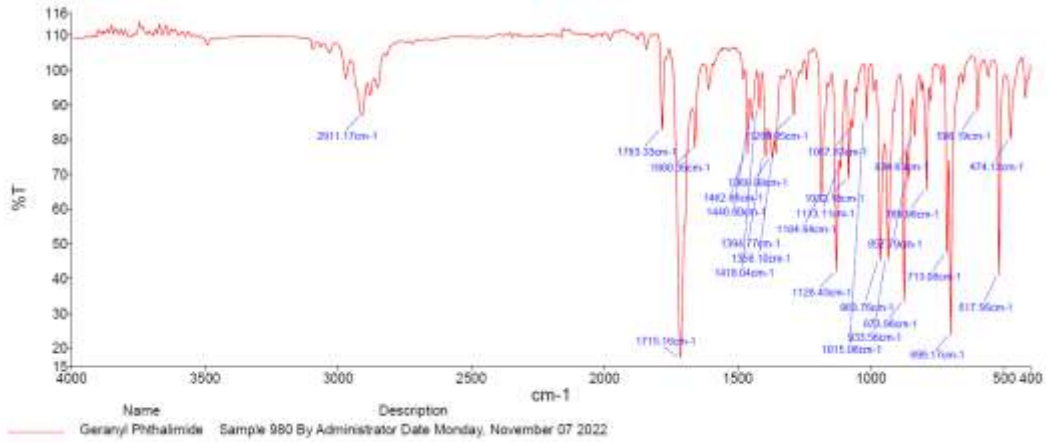

Figure 7.4. IR spectrum for compound **84**

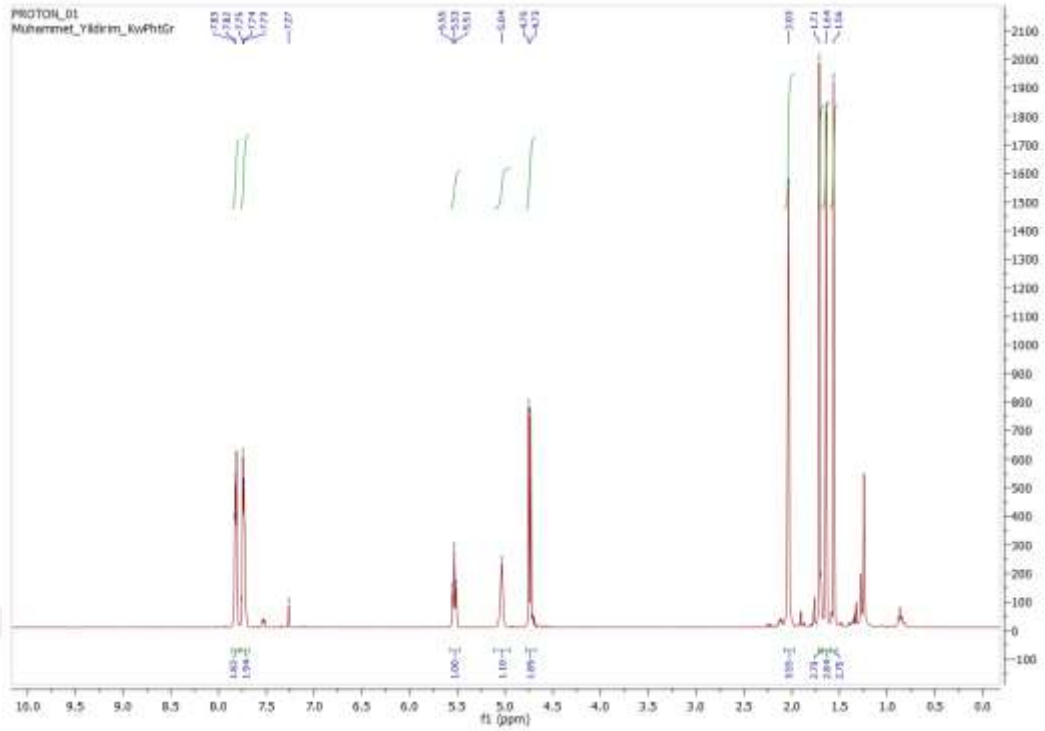

Figure 7.5. ^{1}HNMR spectrum for compound **84**

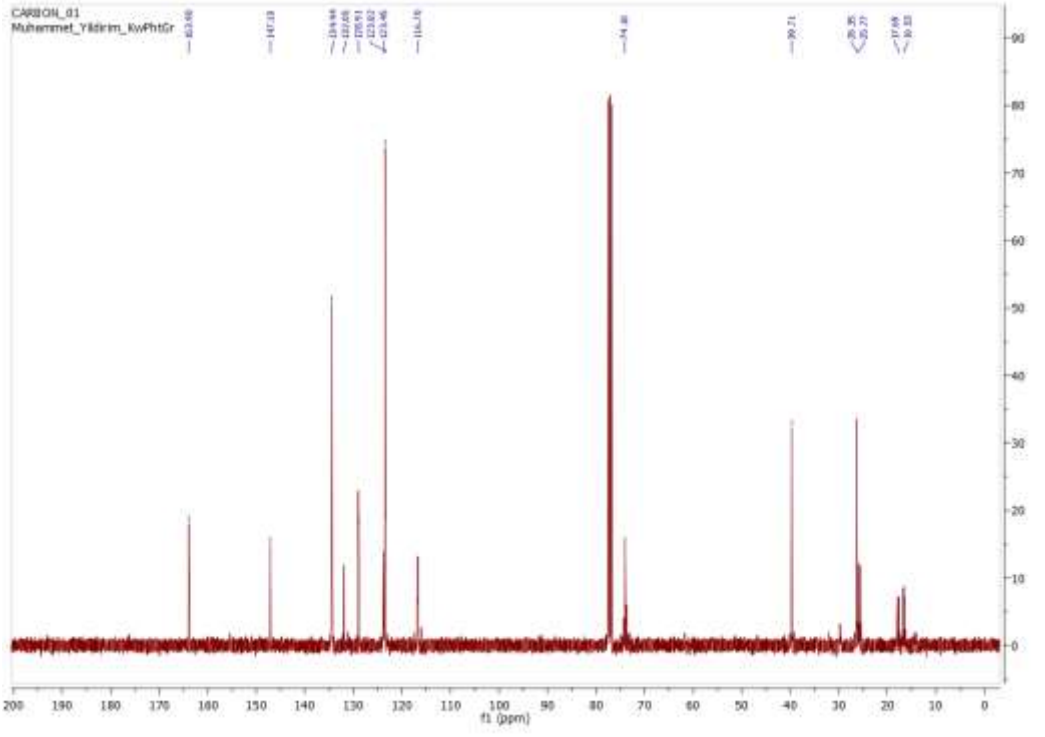

Figure 7.6. ^{13}CNMR spectrum for compound **84**

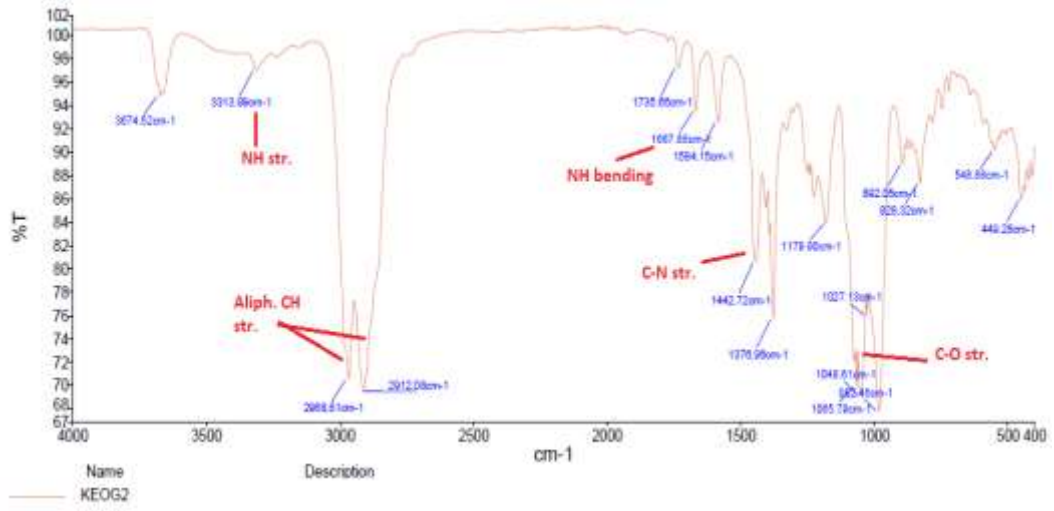

Figure 7.7. IR spectrum for compound **85**

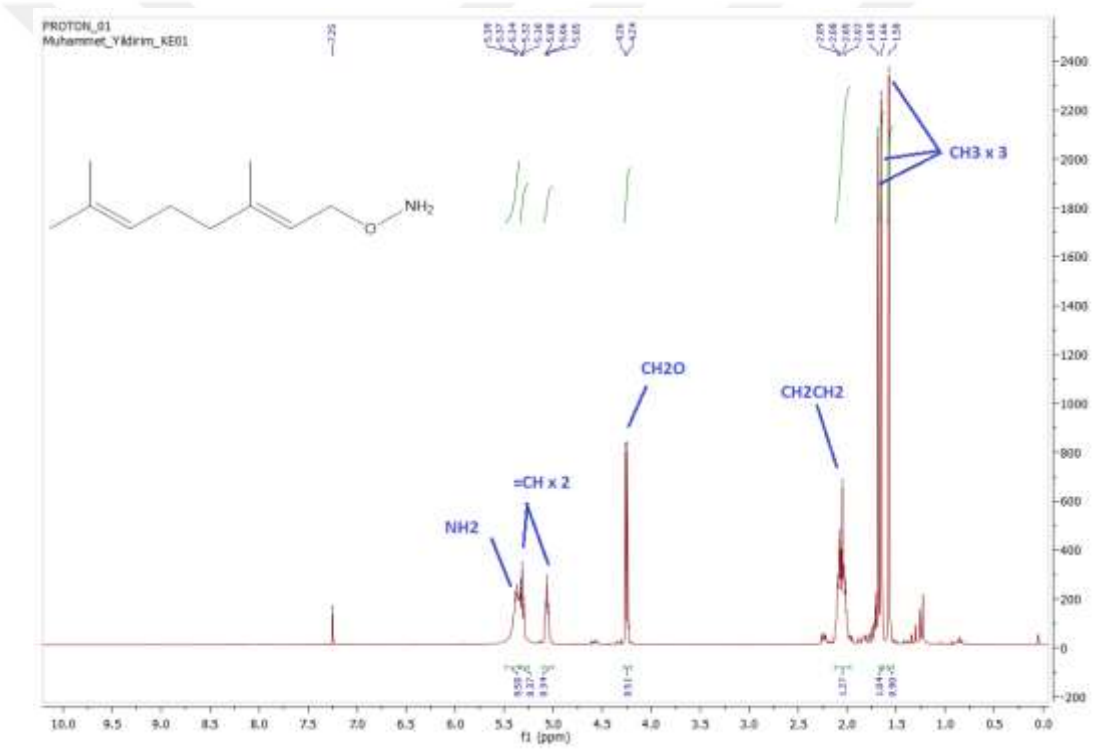

Figure 7.8. ^{1}HNMR spectrum for compound **85**

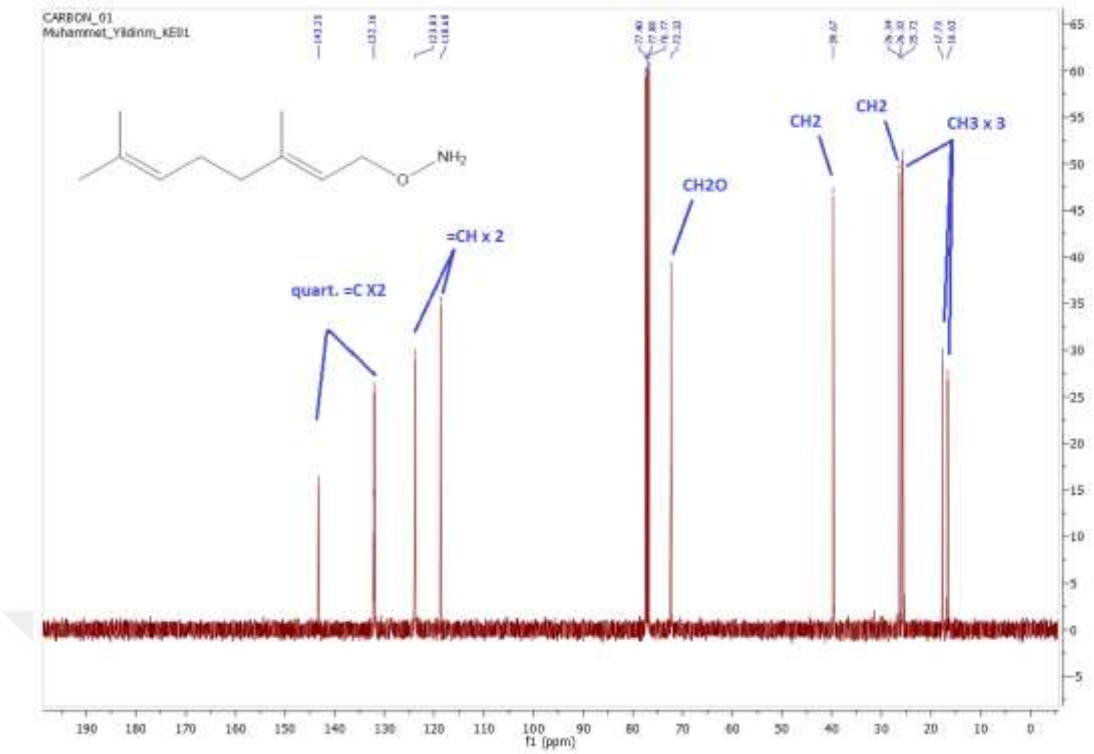

Figure 7.9. ^{13}CNMR spectrum for compound **85**

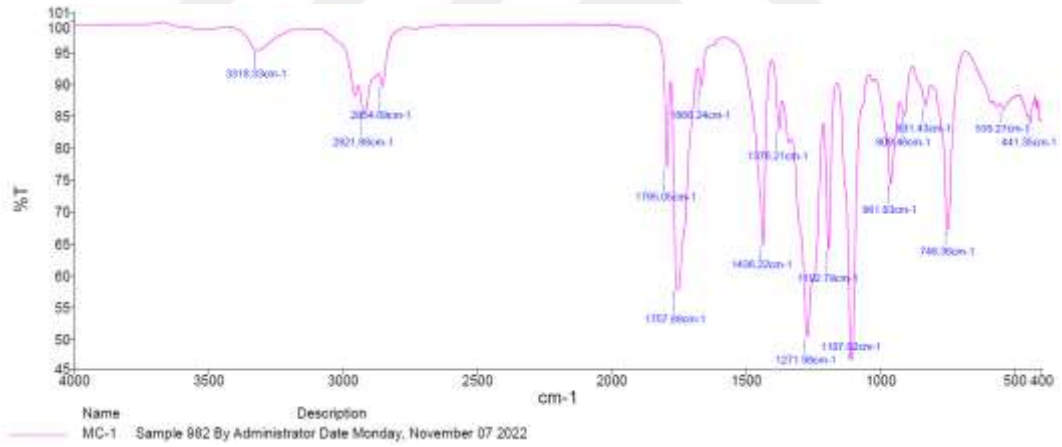

Figure 7.10. IR spectrum for compound **86a**

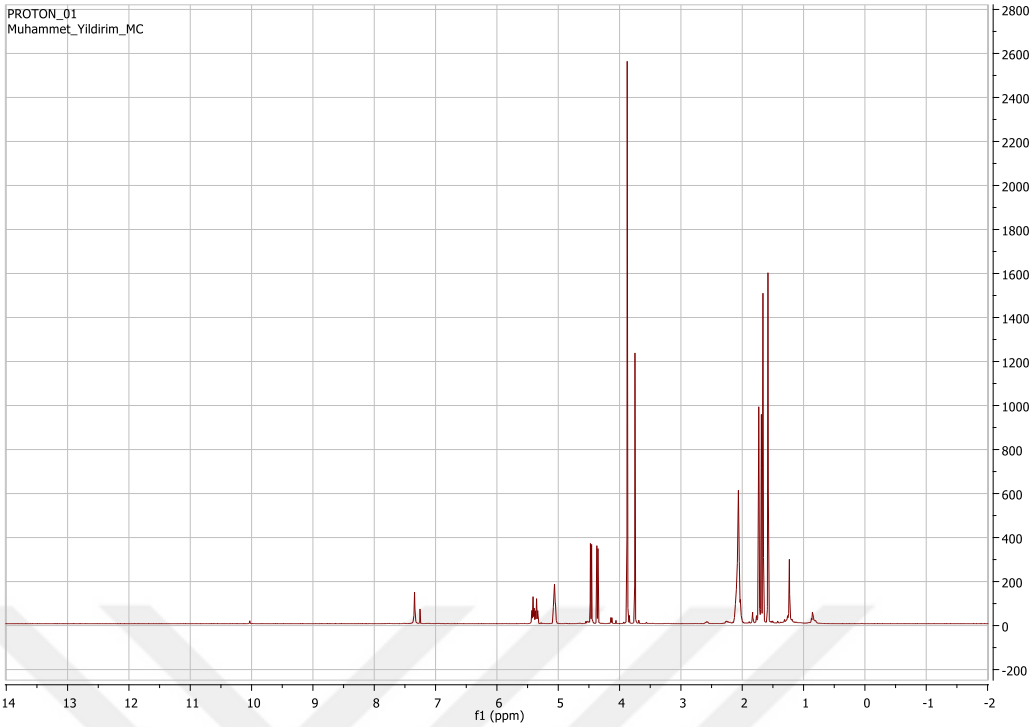

Figure 7.11. ^{1}HNMR spectrum for compound **86a**

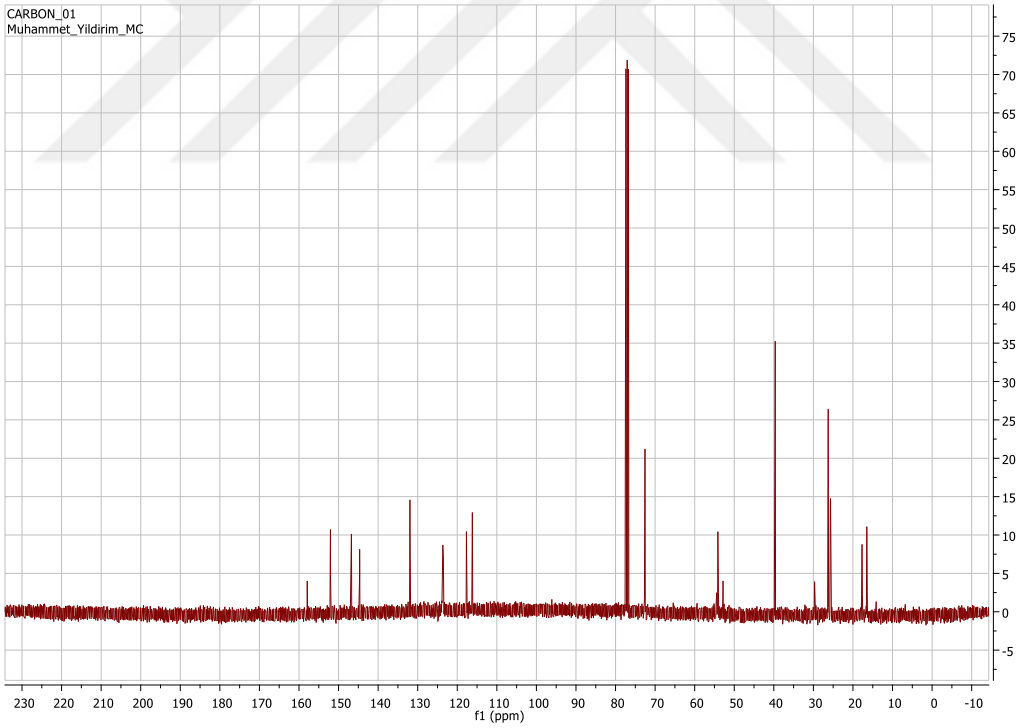

Figure 7.12. ^{13}CNMR spectrum for compound **86a**

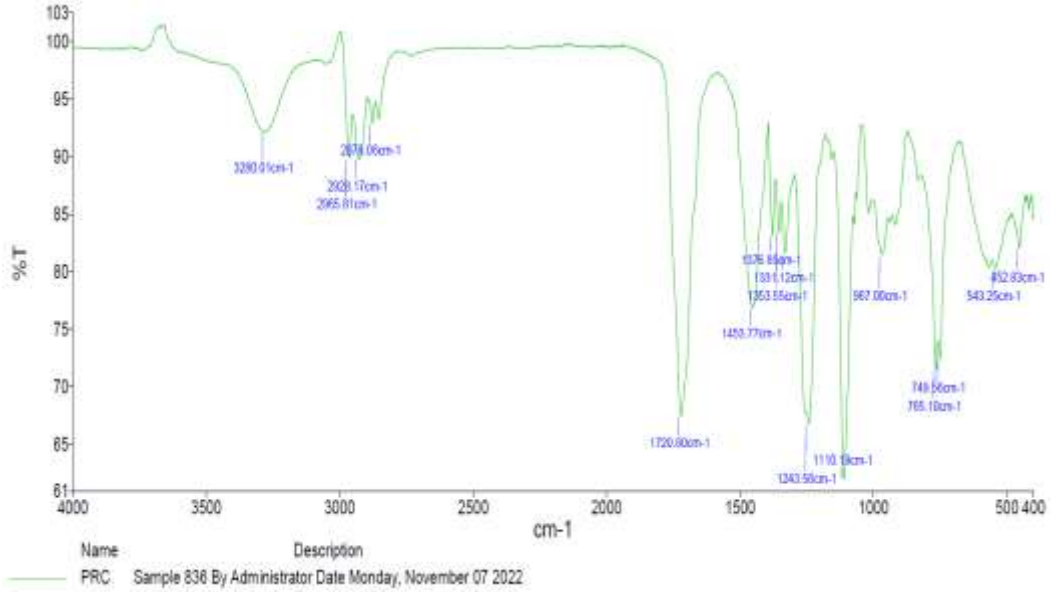

Figure 7.13. IR spectrum for compound **86c**

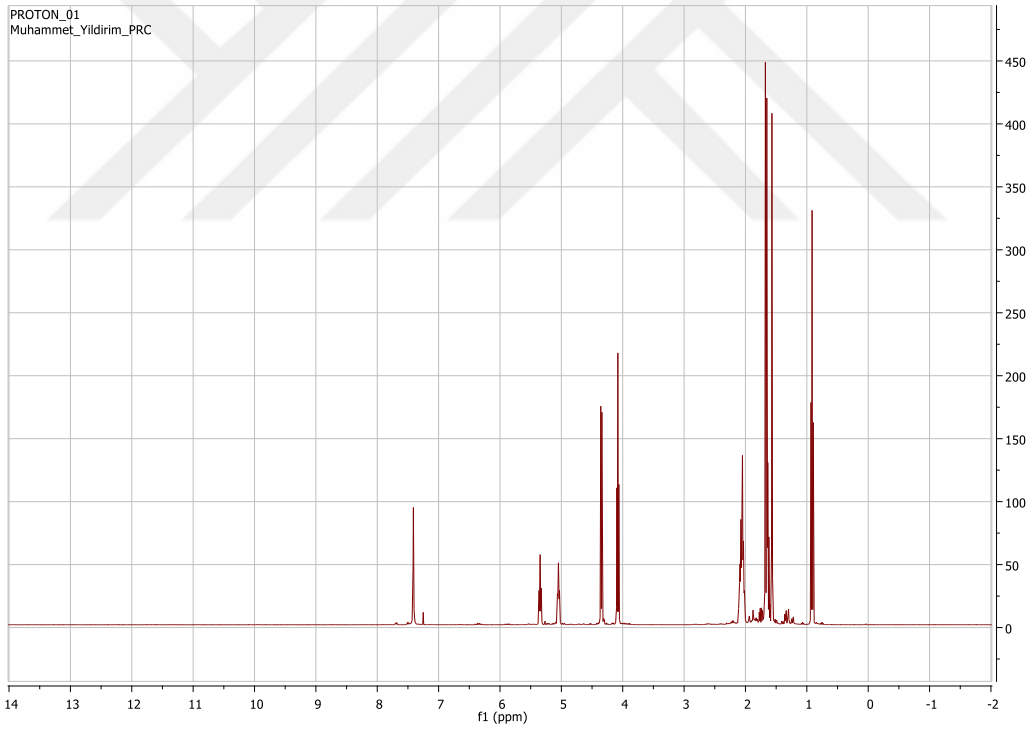

Figure 7.14. [1]HNMR spectrum for compound **86c**

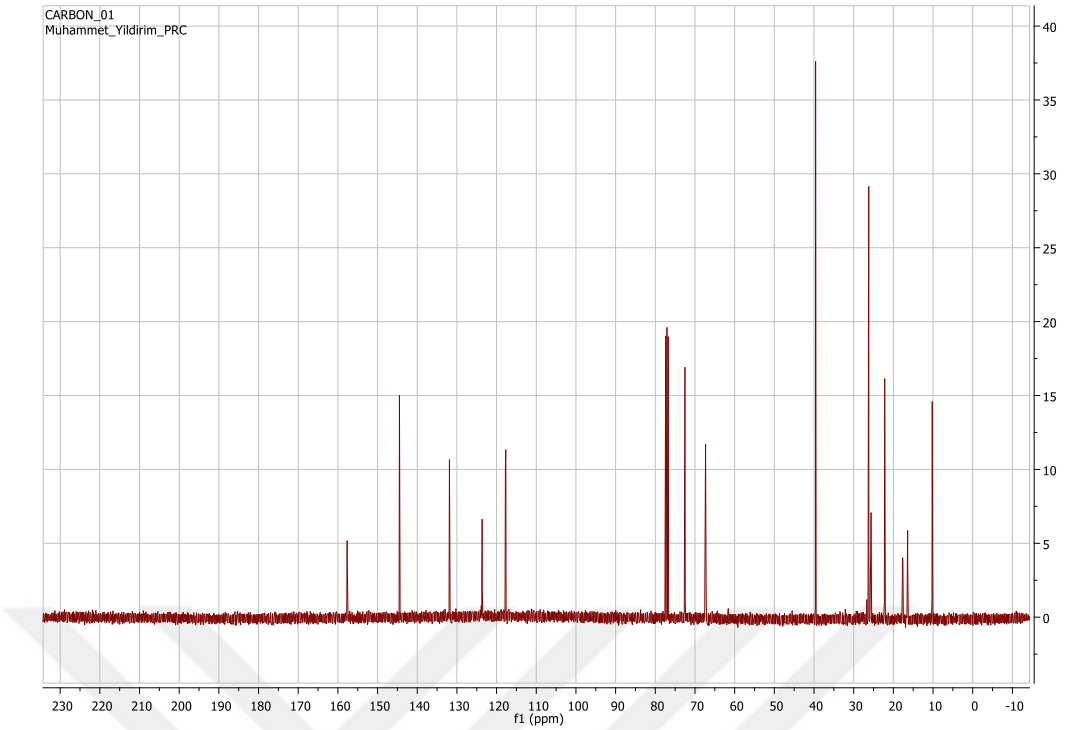

Figure 7.15. ^{13}CNMR spectrum for compound **86c**

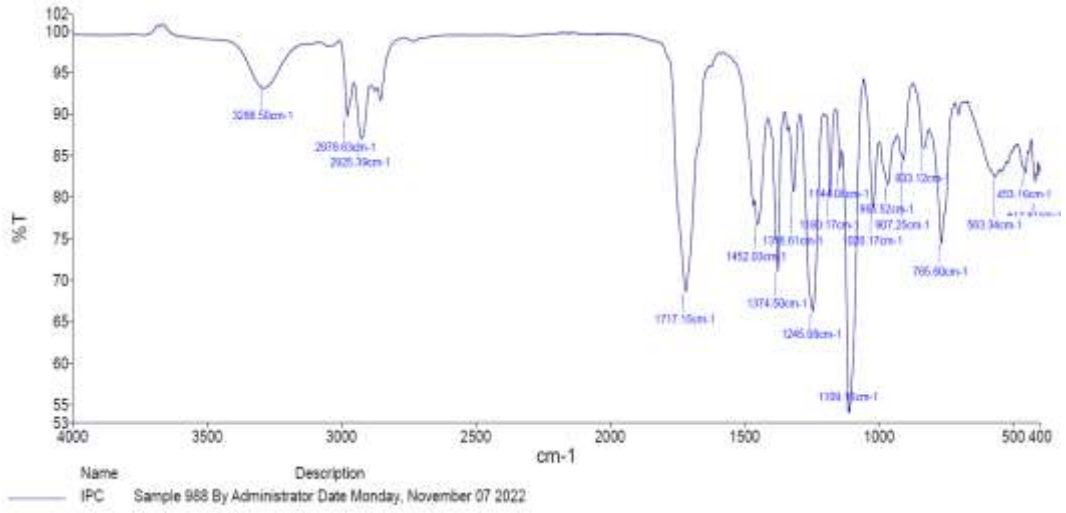

Figure 7.16. IR spectrum for compound **86d**

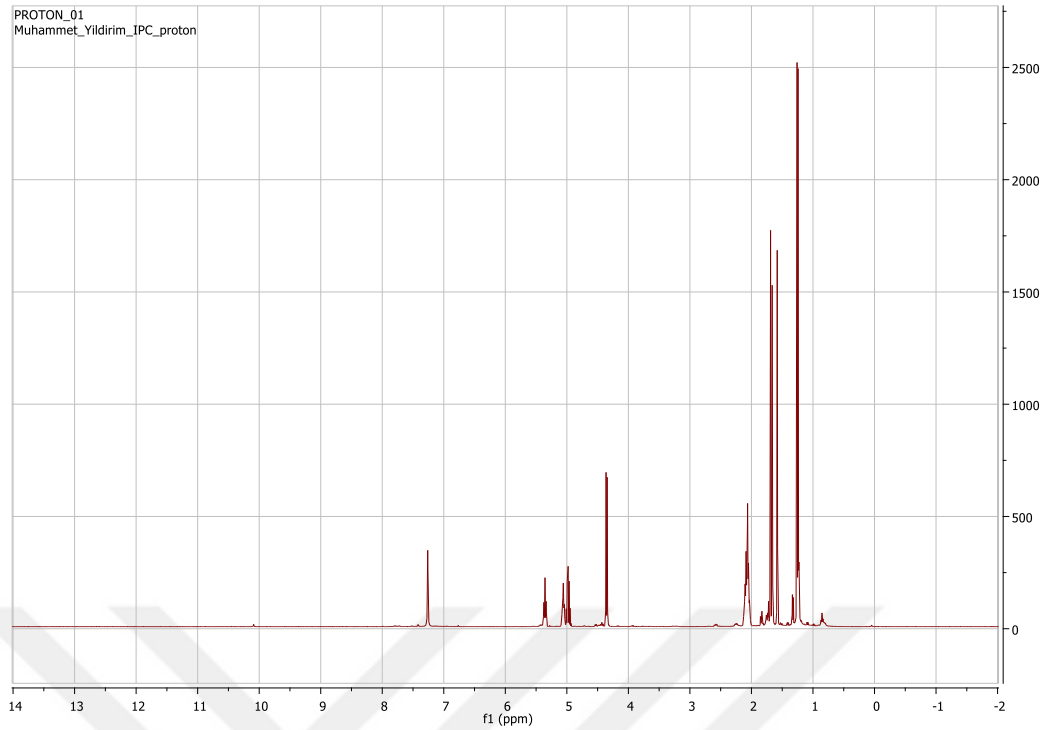

Figure 7.17. [1]HNMR spectrum for compound **86d**

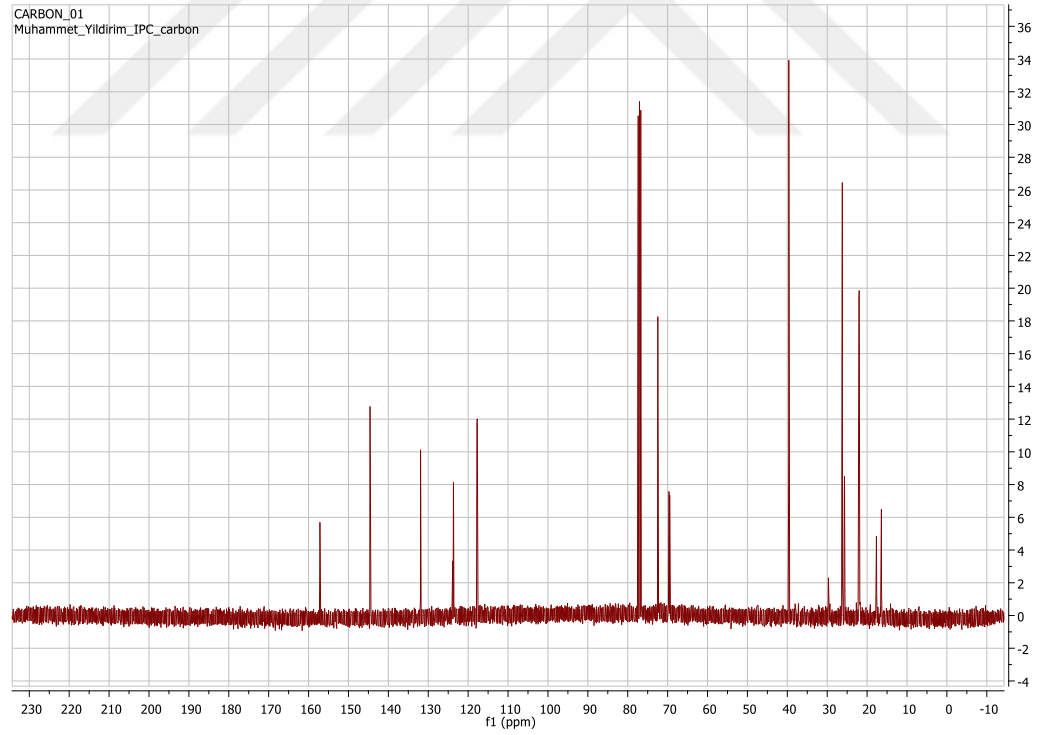

Figure 7.18. [13]CNMR spectrum for compound **86d**

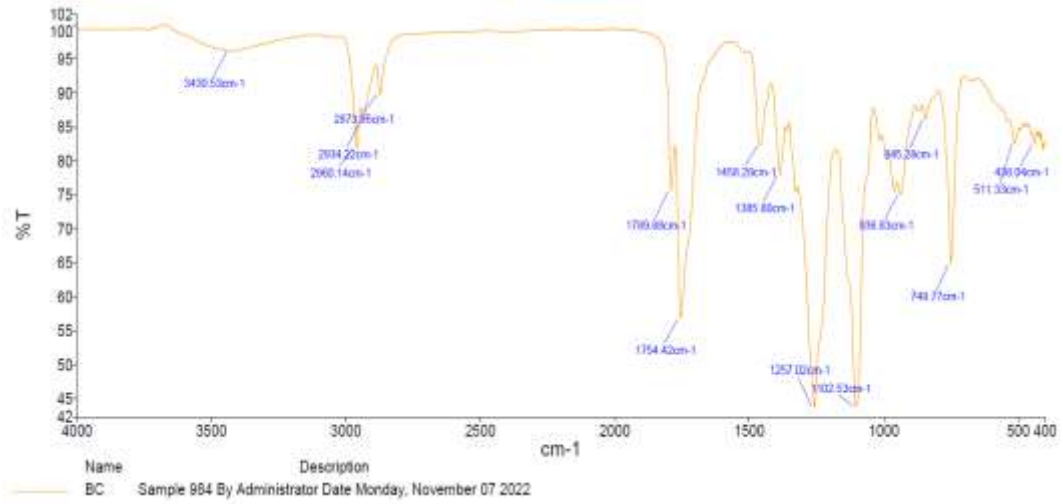

Figure 7.19. IR spectrum for compound **86e**

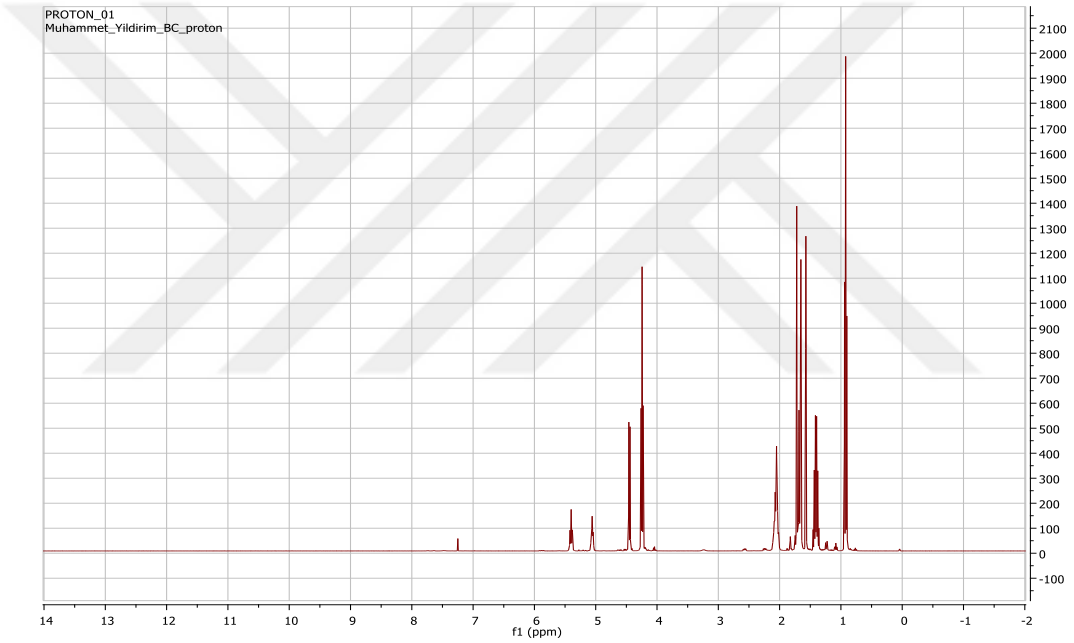

Figure 7.20. ^{1}HNMR spectrum for compound **86e**

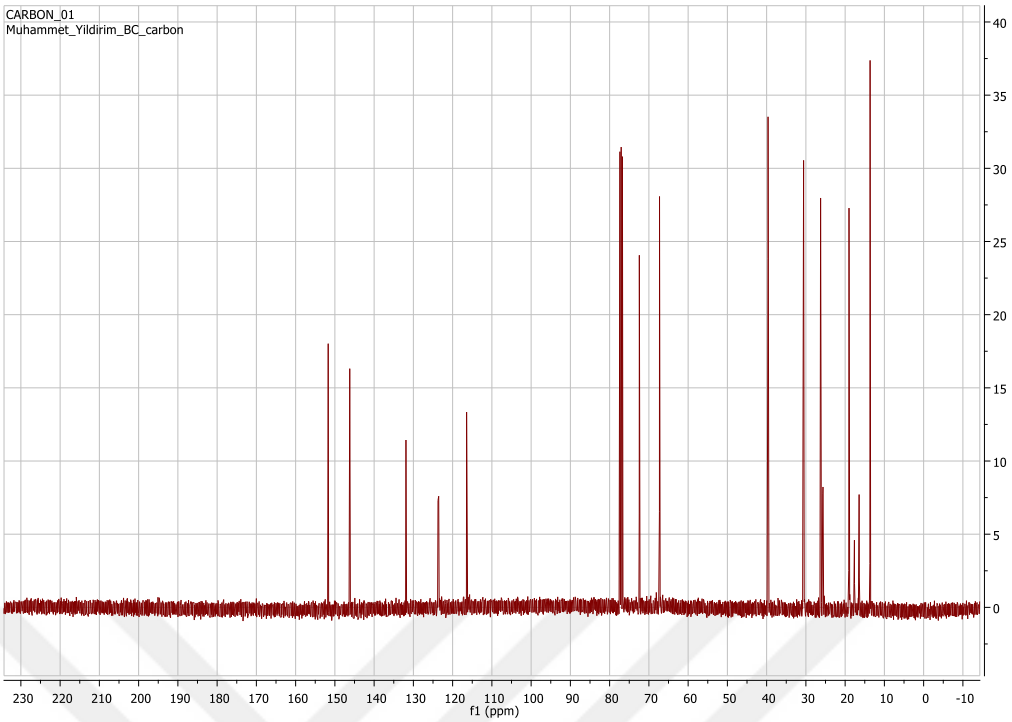

Figure 7.21. ^{13}CNMR spectrum for compound **86e**

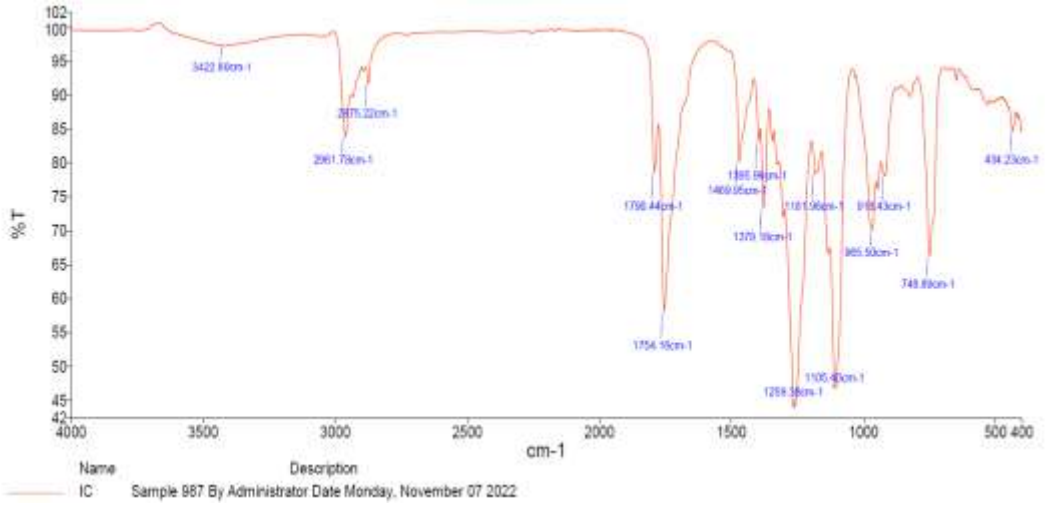

Figure 7.22. IR spectrum for compound **86f**

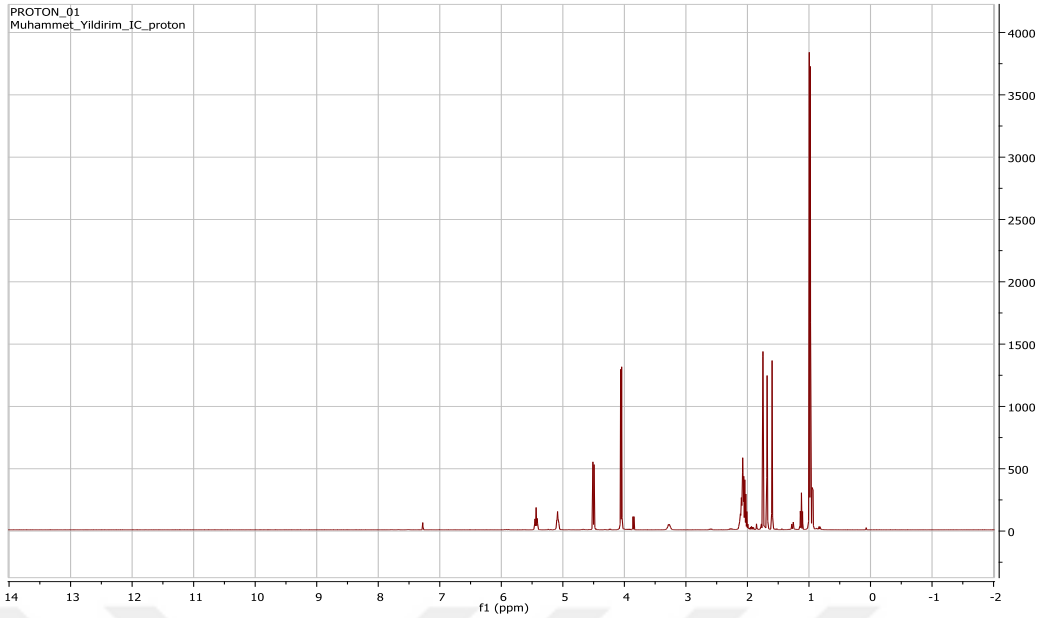

Figure 7.23. ^{1}HNMR spectrum for compound **86f**

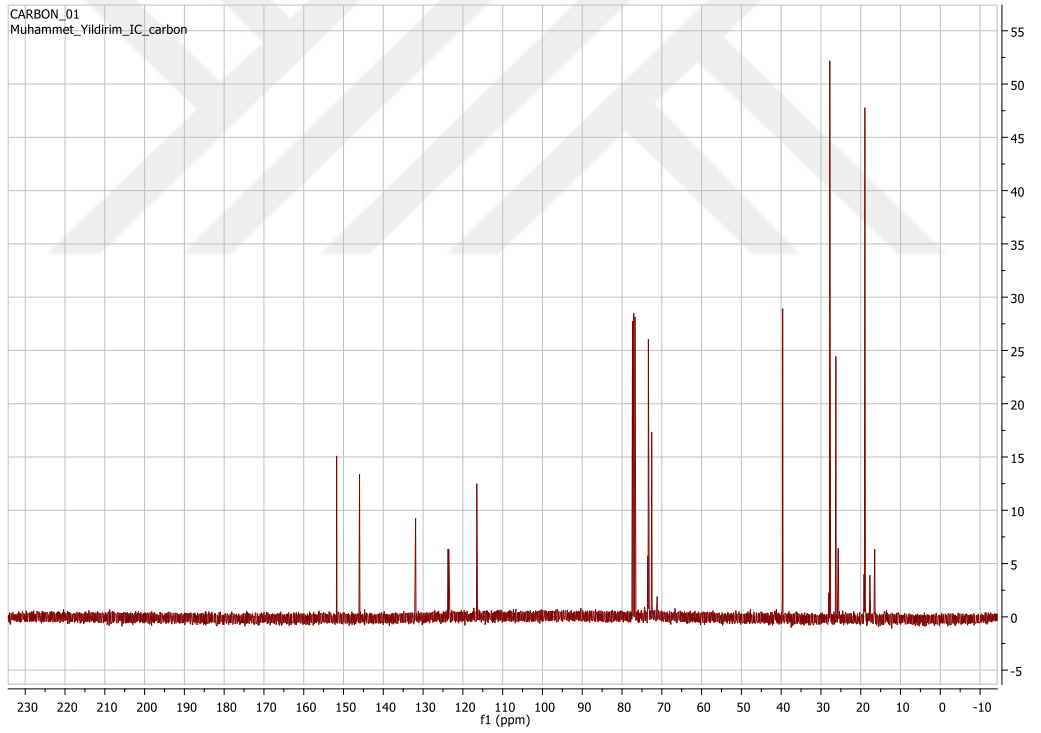

Figure 7.24. ^{13}CNMR spectrum for compound **86f**

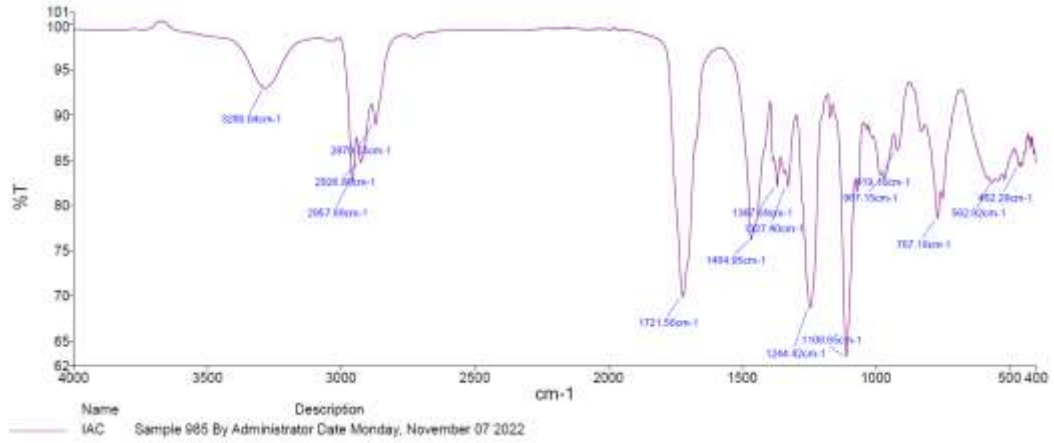

Figure 7.25. IR spectrum for compound **86g**

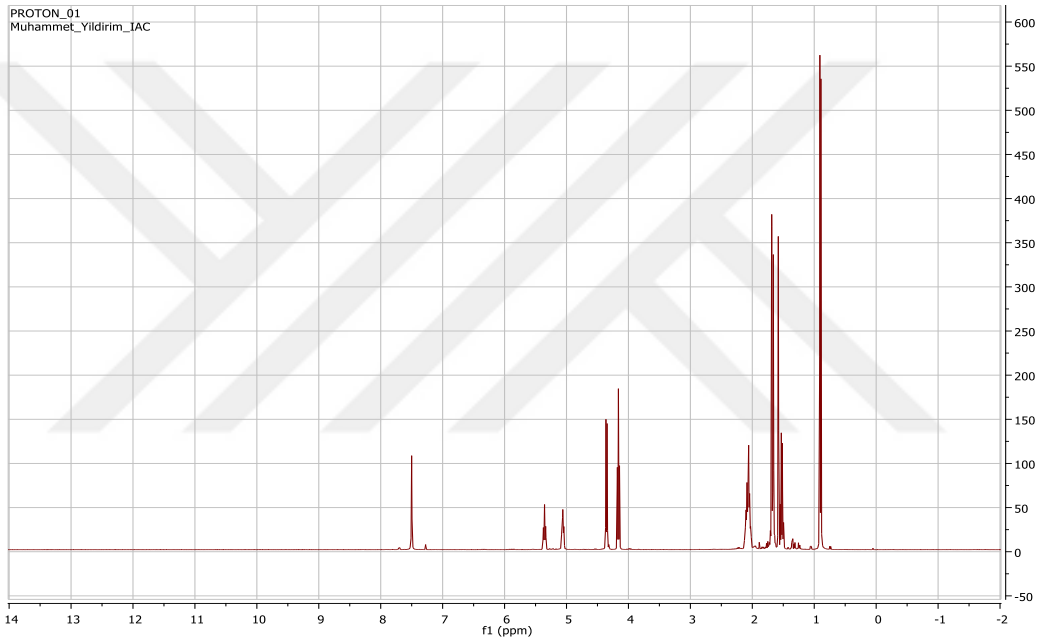

Figure 7.26. ^{1}HNMR spectrum for compound **86g**

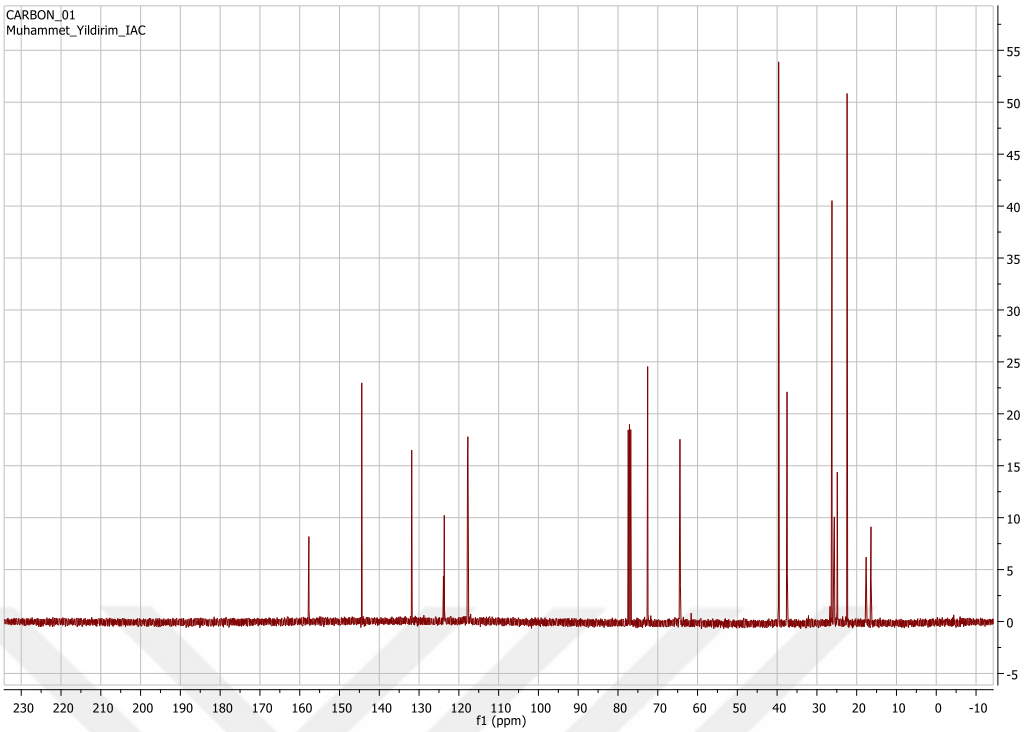

Figure 7.27. ^{13}CNMR spectrum for compound **86g**

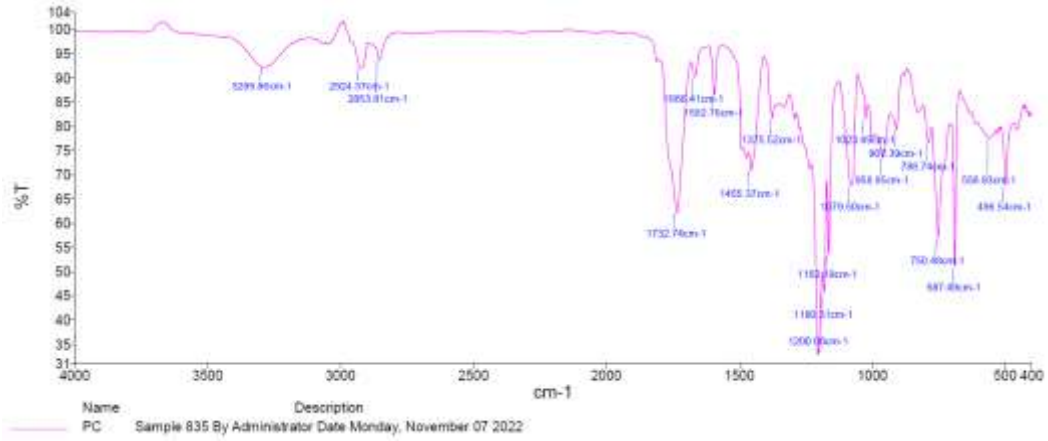

Figure 7.28. IR spectrum for compound **86h**

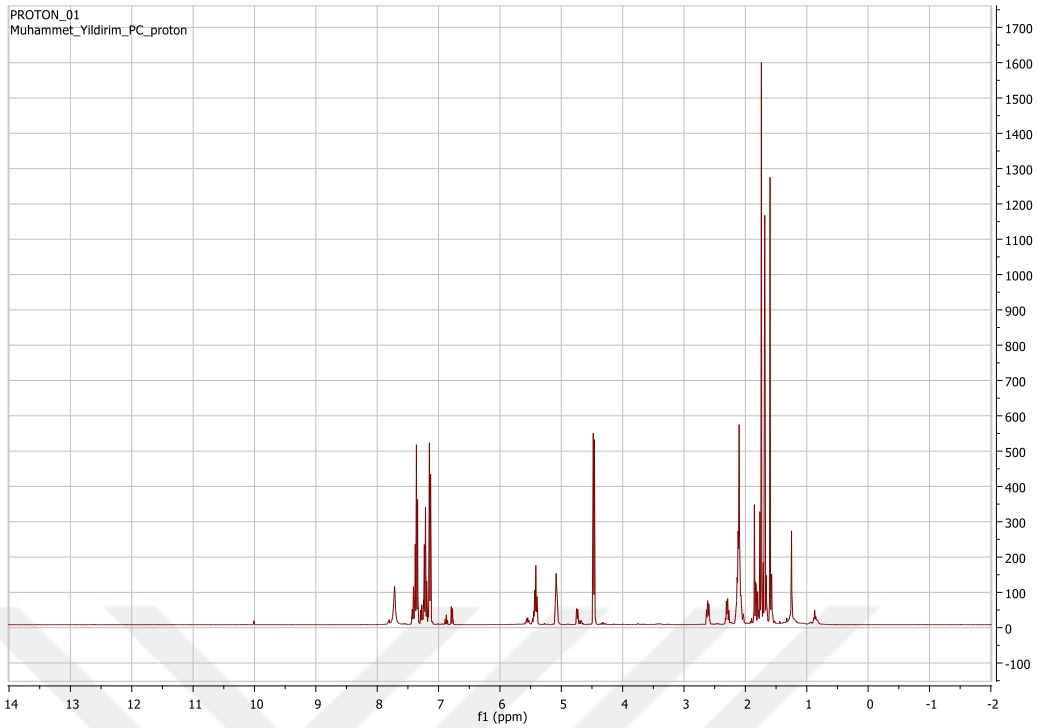

Figure 7.29. ^{1}HNMR spectrum for compound **86h**

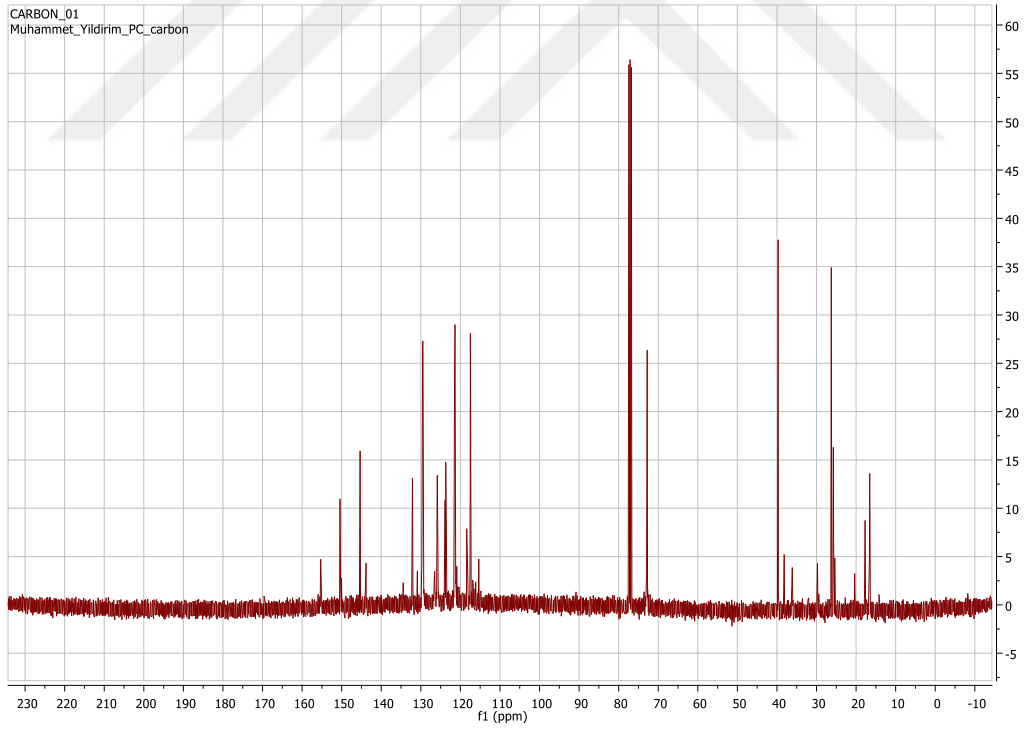

Figure 7.30. ^{13}CNMR spectrum for compound **86h**

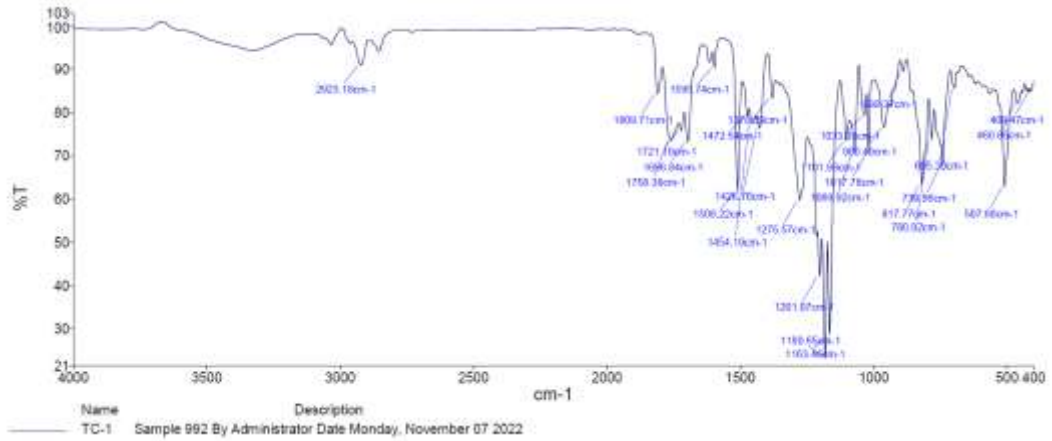

Figure 7.31. IR spectrum for compound **86i**

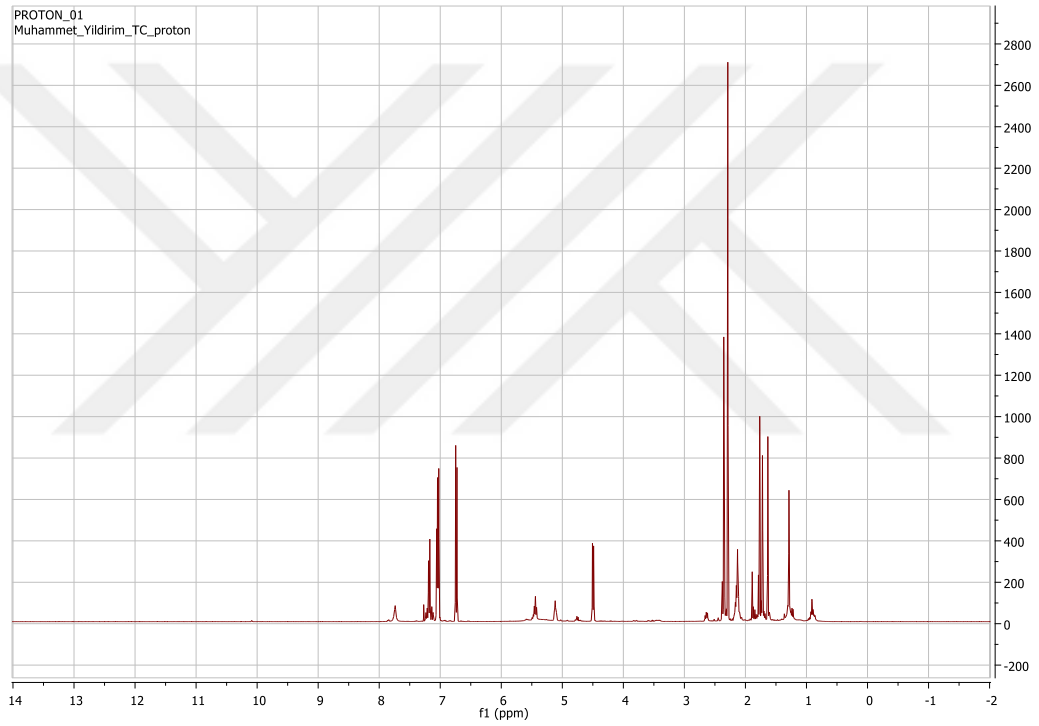

Figure 7.32. ^{1}HNMR spectrum for compound **86i**

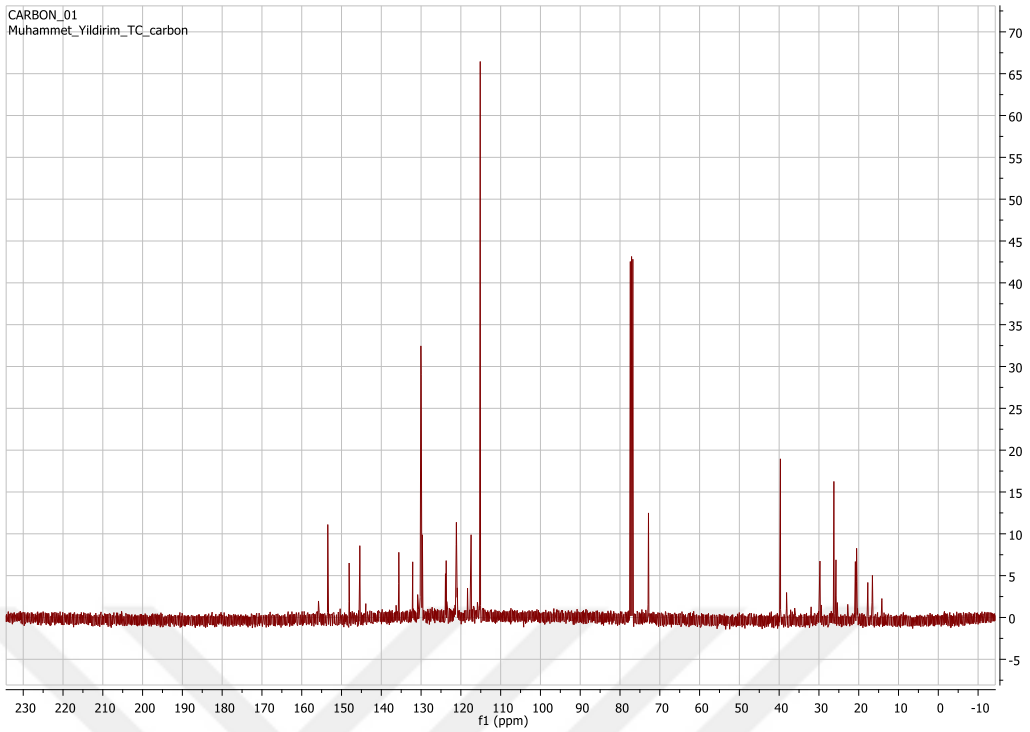

Figure 7.33. ^{13}CNMR spectrum for compound **86i**

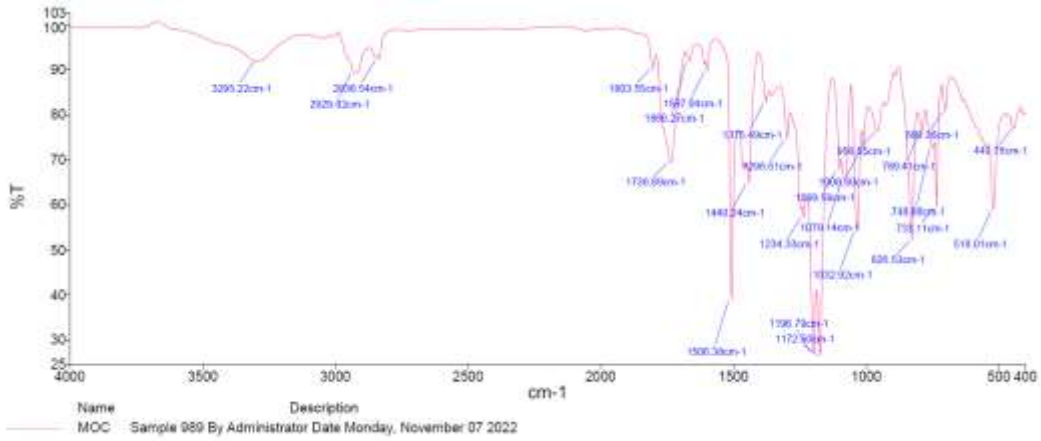

Figure 7.34. IR spectrum for compound **86j**

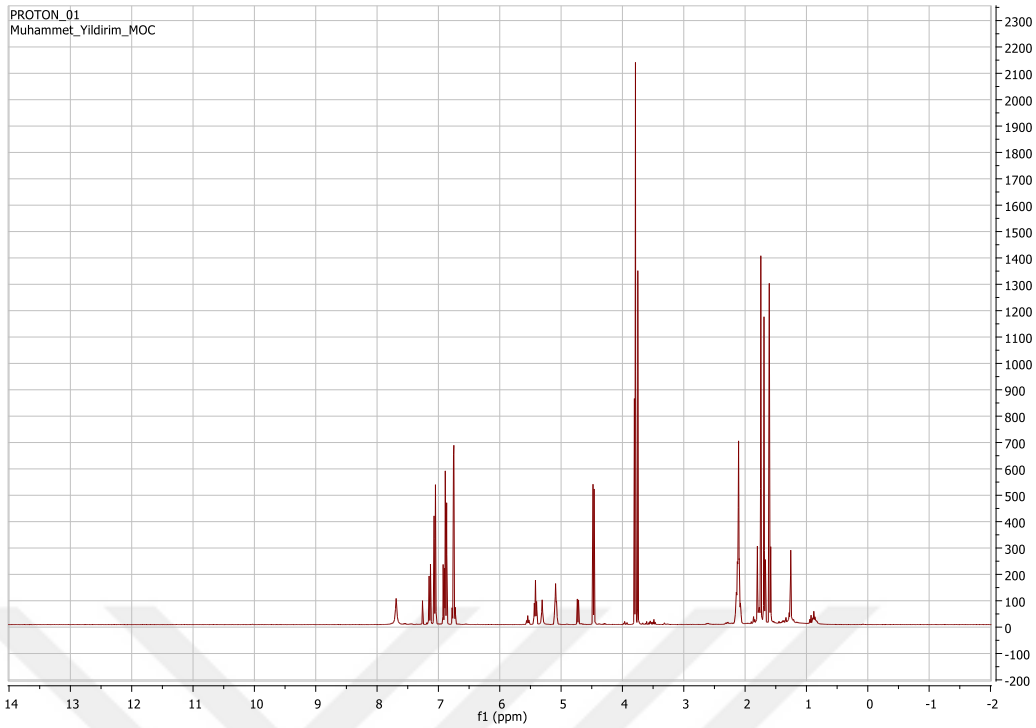

Figure 7.35. ^{1}HNMR spectrum for compound **86j**

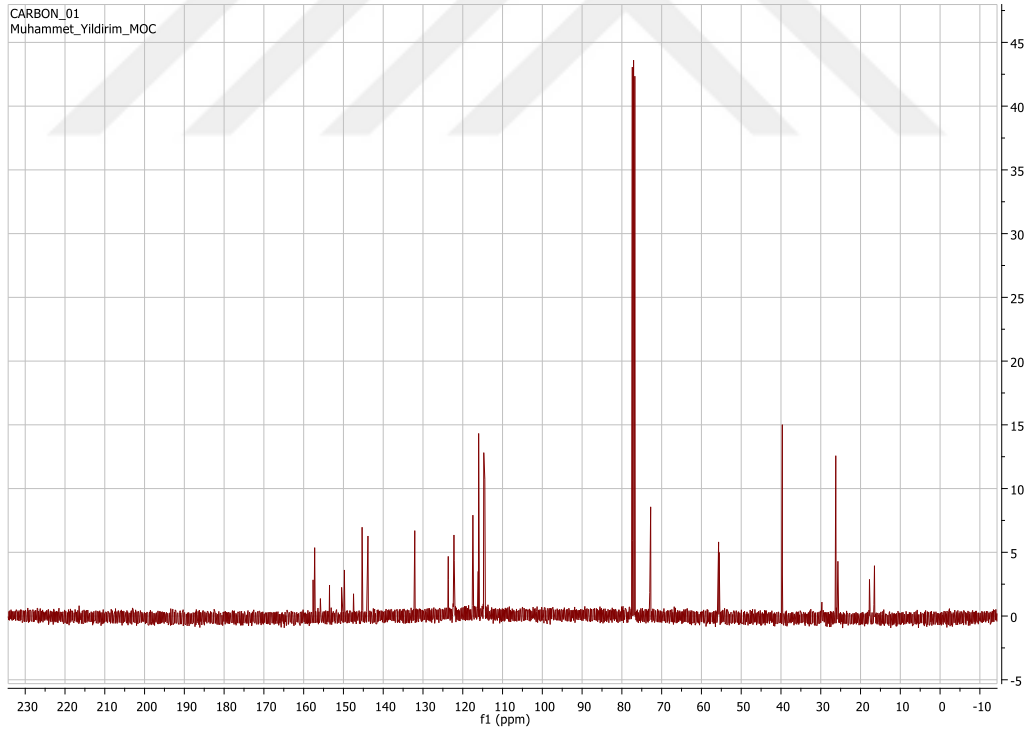

Figure 7.36. ^{13}CNMR spectrum for compound **86j**

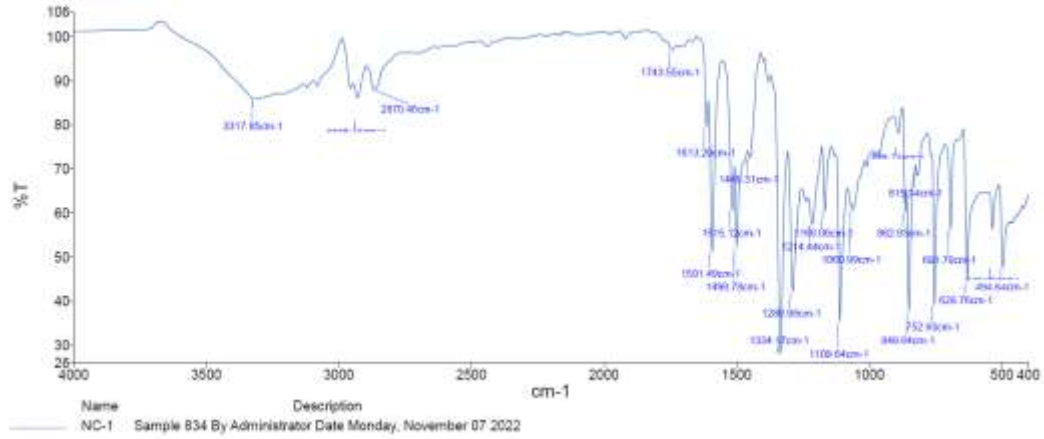

Figure 7.37. IR spectrum for compound **86l**

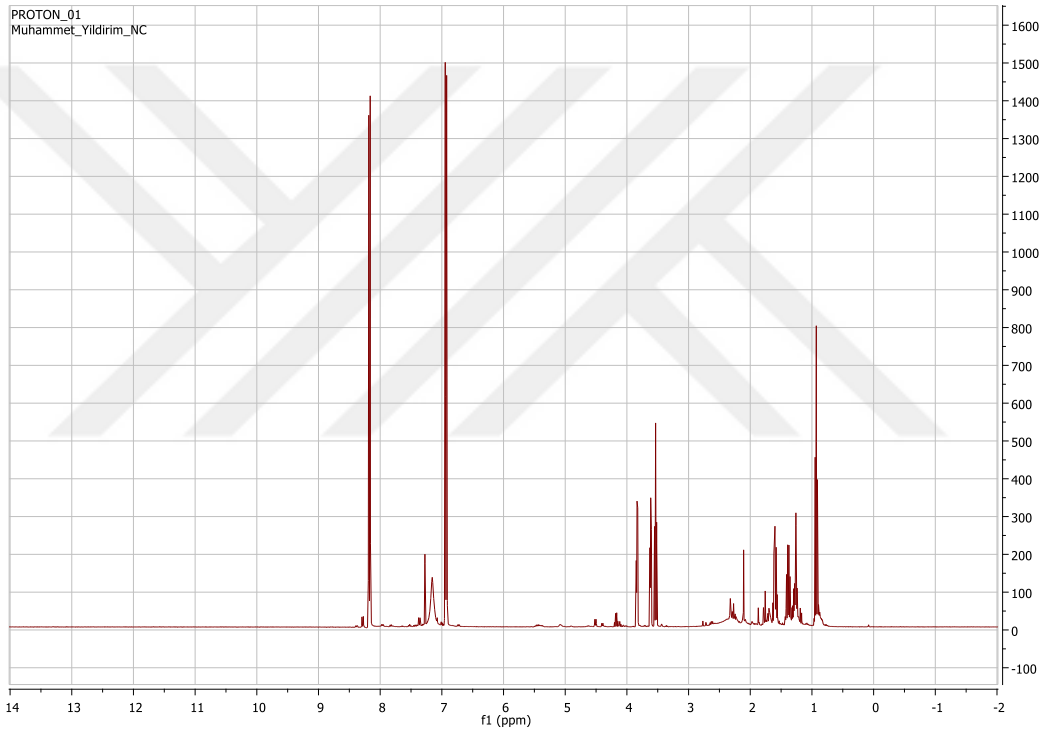

Figure 7.38. ^{1}HNMR spectrum for compound **86l**

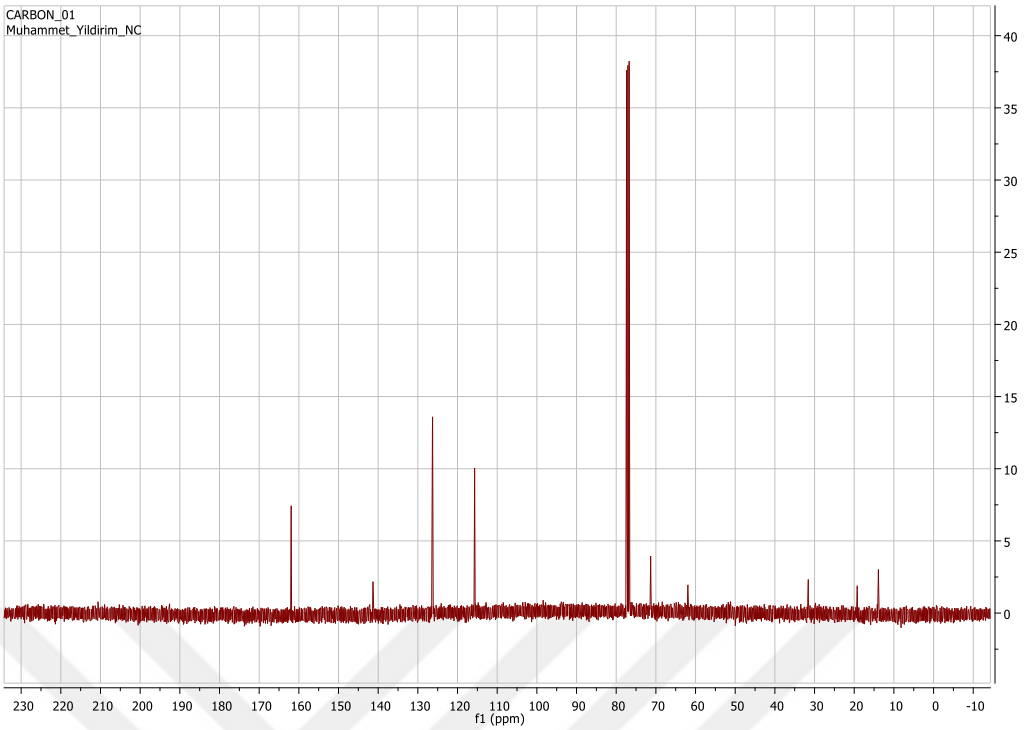

Figure 7.39. ^{13}CNMR spectrum for compound **86l**