

T.R.
BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY



**LEWIS-ACID CATALYZED CYCLISATIONS OF
HOMOGGERANYL CARBAMATES**

MASTER OF SCIENCE

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ABSTRACT

LEWIS-ACID CATALYZED CYCLISATIONS OF HOMOGERANYL CARBAMATES

MSC THESIS

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(xxiv + 177)

Geraniol, a member of the terpenoid family known for its various pleasant aromas, has widespread applications in the cosmetic and perfume industry. Many terpenoid derivatives derived from geraniol are known in the literature. In our study, various alkyl and aryl homogeranyl carbamates derived from geraniol and their sequential cyclizations through iodine-mediated reactions were presented. To synthesize homogeranyl carbamates, first, homogeranyllamine was obtained through a series of reactions, including radical bromination, nucleophilic displacement, and reduction. Subsequently, obtained homogeranyllamine was transformed into homogeranyl carbamates through a nucleophilic addition-elimination. Then, on these homogeranyl carbamate derivatives, iodine-catalyzed electrophilic sequential cyclizations, also known as green chemistry, were performed as described in the literature. Out of the resulting iodotrimethyl octahydroindole carbamates, five compounds were selected and converted into trimethyl octahydroindole carbamates through palladium or tributyltin hydride-catalyzed reduction reactions. The structures of all target compounds were confirmed using various spectroscopic methods such as IR, proton and carbon-13 NMR, and HRMS. The olfactory properties of 33 products were determined by expert evaluators (perfumers), and their *in vitro* cytotoxicity tests were performed and completed.

KEYWORDS: Iodocyclizations, Cascade, Indole, Terpenes, Fragrance.

ÖZET

**HOMOGERANİL KARBAMATLARIN LEWIS ASİT
KATALİZÖRLÜ HALKALAŞMALARI
YÜKSEK LİSANS TEZİ
HAKAN EMRE ÖZÇAL
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Çeşitli hoş kokulara sahip terpenoid ailesinin bir üyesi olan geraniol, kozmetik ve parfüm sektöründe yaygın bir kullanım alanına sahiptir. Geraniolden elde edilen birçok terpenoid türevi literatürde bilinmektedir. Çalışmamızda geraniolden elde ettiğimiz terpenoid tabanlı çeşitli alkil ve aril homogeranil karbamatlar ve onların iyot aracılığıyla sıralı halkalaşmaları sunuldu. Homogeranil karbamatları sentezlemek için öncelikle homogeranilamin sentezine çeşitli reaksiyonlarla ulaşıldı. Bu reaksiyonlar sırası ile radikalik bromlama, nükleofilik yer değiştirme ve indirgemedir. Sonrasında elde edilen homogeranilamin bileşiği nükleofilik katılma-eliminasyon ile homogeranil karbamat bileşiklerine dönüştürüldü. Daha sonrasında elde edilen bu homogeranil karbamat bileşikleri üzerinde, literatürde yeşil kimya olarak da bilinen sıralı reaksiyon yöntemi ile iyot katalizli elektrofilik sıralı halkalaşmalar gerçekleştirildi. Bu halkalaşmalarda elde edilen iyot-trimetiloktahidroindol karbamat bileşiklerinden 5 bileşik seçildi ve Pd- veya tribütiltin hidrür katalizli indirgeme reaksiyonlarıyla trimetiloktahidroindol karbamatlara dönüştürüldü. Elde edilen tüm hedef ürünlerin yapıları çeşitli spektroskopik yöntemler (IR, proton ve carbon-13 NMR, HRMS) aracılığı ile doğrulandı. 33 bileşiğin olfaktif özellikleri uzman değerlendiriciler (parfümör) tarafınca saptandı ve bileşiklerin *in vitro* stotoksisite testleri yapılarak tamamlandı.

ANAHTAR KELİMELE: İyot halkalaşmaları, Sıralı, İndol, Terpenler, Koku.

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LIST OF ABBREVIATIONS AND SYMBOLS

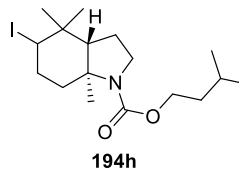
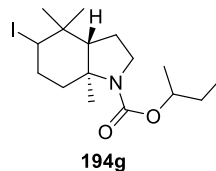
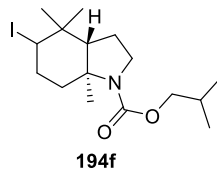
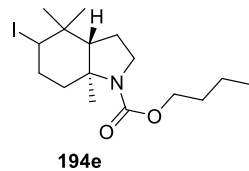
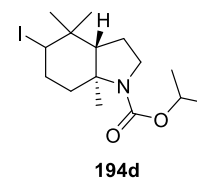
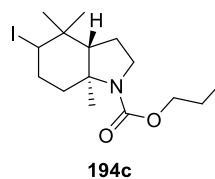
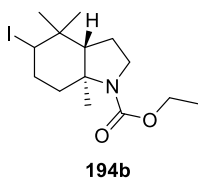
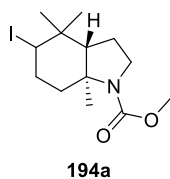
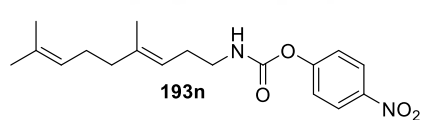
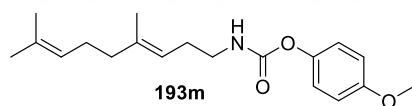
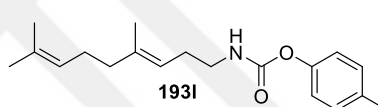
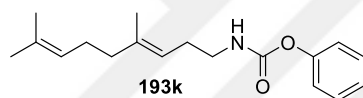
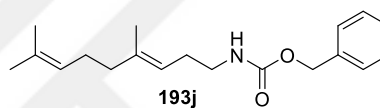
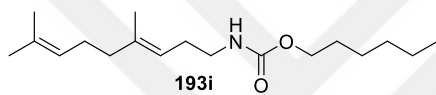
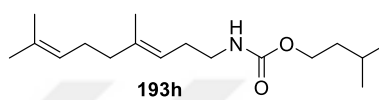
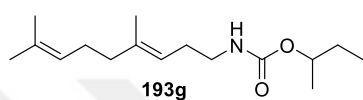
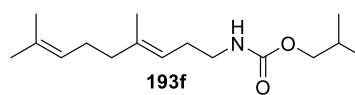
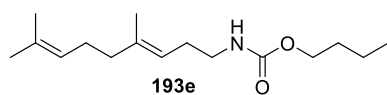
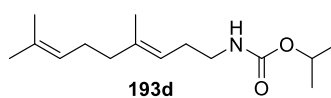
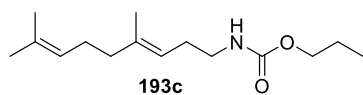
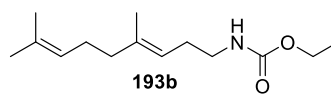
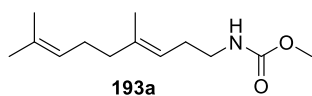
[Ru(phd)₃]²⁺	: Ruthenium 1,10-phenanthroline-5,6-dione
[RuCl₂(p-cymene)]₂	: Dichloro(p-cymene)ruthenium(II) Dimer
1,2-DCE	: 1,2-Dichloroethane
¹³C NMR	: Carbon-13 Nuclear Magnetic Resonance
¹H NMR	: Proton Nuclear Magnetic Resonance
Å	: Angstrom
4-NsCl	: 4-Nitrobenzenesulfonyl Chloride
AChE	: Acetylcholinesterase
Aliph.	: Aliphatic
Anhyd.	: Anhydrous
Ar	: Aryl
atm	: Atmosphere
ATR	: Attenuated Total Reflectance
B(OH)₂	: Boronic Acid
BF₃.OEt₂	: Boron Trifluoride Diethyl Etherate
BiCl₃	: Bismuth Trichloride
bs	: Broad Singlet
Bu	: Butyl
Bu₃SnH	: Tributyltin Hydride
Bz	: Benzyl
CC	: Column Chromatography
CDCl₃	: Deuterated Chloroform
CF₃	: Trifluoromethyl
CF₃S	: Trifluoromethanethio
CH₂-Ph	: Benzyl
CH₃CN	: Acetonitrile
ClSO₃H	: Chlorosulfonic Acid
CM	: Carbamate
CN	: Cyanide
Cu(OAc)₂	: Copper (II) Acetate
d	: Doublet
DBN	: 1,5-Diazabicyclo(4.3.0)non-5-ene

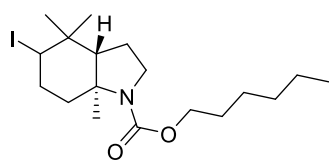
DBU	: 1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	: Dichloromethane
dd	: Doublet of Doublets
ddt	: Doublet of Doublet of Triplets
DMA	: Dimethylacetamide
DMF	: N,N-Dimethylformamide
DMSO	: Dimethyl sulfoxide
DMSO-d₆	: Hexadeuterodimethyl sulfoxide
dp	: Doublet of Pentets
DPPA	: Diphenylphosphoryl Azide
dq	: Doublet of Quartets
dt	: Doublet of Triplets
dtd	: Doublet of Triplet of Doublets
EA	: Ethyl Acetate
eq.	: Equivalent
Et	: Ethyl
Et₂O	: Diethyl Ether
EtOAc	: Ethyl Acetate
FPP	: Farnesyl Diphosphate
FT-IR	: Fourier Transform Infrared Spectroscopy
GC	: Gas Chromatography
GC-MS	: Gas Chromatography – Mass Spectrometry
H₂CN	: Protonated Hydrogen Cyanide
Hex	: Hexane
HFIP	: 1,1,1,3,3,3-Hexafluoro-2-propanol
HRMS	: High Resolution Mass Spectrometry
IDSi	: Iodosulfonium Antimonate
IMFIS	: Intramolecular Fischer Indole Synthesis
IR	: Infrared Spectrometry
<i>i</i>-Amyl	: Isopentyl
<i>i</i>-Bu	: Isobutyl
<i>i</i>-Pr	: Isopropyl
<i>i</i>-Pr₂EtN	: N,N-Diisopropylethylamine
<i>i</i>-PrNO₂	: Isopropyl Nitrite

<i>J</i>	: Coupling Constant
K₂CO₃	: Potassium Carbonate
K₃PO₄	: Potassium Phosphate
L.A.	: Lewis Acid
LC-MS	: Liquid Chromatography - Mass Spectrometry
m	: Multiplet
m/z	: Mass to Charge Ratio
Me	: Methyl
MeCN	: Methyl Cyanide
MeOH	: Methanol
MgSO₄	: Magnesium Sulfate
mmol	: Milimole
MOM	: Methoxymethyl Ether
MS	: Mass Spectrometry
MSA	: Methanesulfonic Acid
MW	: Molecular Weight
Na₂SO₄	: Sodium Sulfate
NaOEt	: Sodium Ethoxide
NBS	: N-Bromosuccinimide
NEt₃	: Triethylamine
NIS	: N-Iodosuccinimide
NMR	: Nuclear Magnetic Resonance
NXS	: N-Halosuccinimide
OMe	: Methoxy
OP	: Organophosphate
Pd(PhCN)₂Cl₂	: Bis(benzonitrile)palladium Dichloride
Pd/C	: Palladium on Carbon
PdCl₂(PPh₃)₂	: Bis(triphenylphosphine)palladium(II) Dichloride
Ph	: Phenyl
PhCl	: Chlorobenzene
PMA	: Phosphomolybdic Acid
p-MeO	: para-Methoxyphenyl
p-Me	: para-Methyl
PPh₃	: Triphenylphosphine

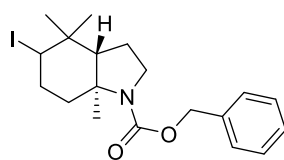
ppm	: Parts Per Million
p-TolSO₂Na	: Sodium p-toluenesulfinate
q	: Quartet
qd	: Quartet of Doublets
R	: Rest of Molecule
r.t.	: Room temperature
Rf	: Retardation Factor
Ru(PPh₃)₃Cl	: Tris(triphenylphosphine)rhodium(I) Chloride
s	: Singlet
sec-Bu	: Secondary Butyl
S_NAr	: Nucleophilic Aromatic Substitution
str.	: Stretching
t	: Triplet
TBAI	: Tetrabutylammonium Iodide
<i>t</i>-BuOH	: tertiary Butanol
<i>t</i>-BuONO	: tertiary Butyl Nitrite
<i>t</i>-Butyl	: tertiary Buyl
td	: Triplet of Doublets
Tet	: Tetrahedral
TFAA	: Trifluoroacetic Anhydride
TFMS	: Trifluoromethanesulfonic Acid
THF	: Tetrahydrofuran
TLC	: Thin Layer Chromatography
TMS	: Trimethylsilane
TMSN₃	: Trimethylsilyl Azide
tq	: Triplet of Quartets
Ts	: Tosyl
TsNBr₂	: N,N-Dibromo-p-Toluenesulfonamide
TsOH	: p-Toluenesulfonic Acid
UV	: Ultraviolet
[O]	: Oxidation
[R]	: Reduction

FORMULAS

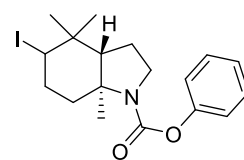




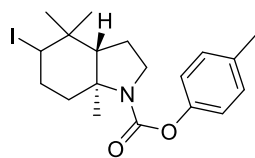
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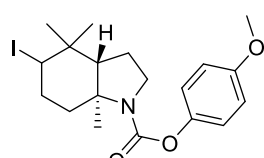
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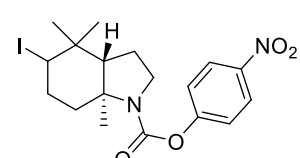
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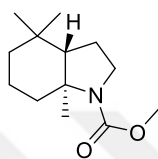
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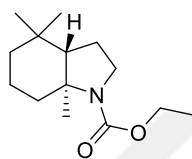
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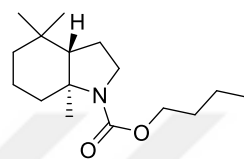
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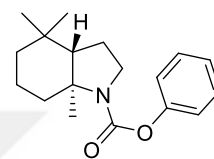
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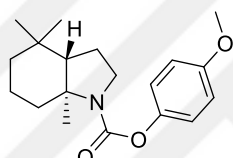
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1. INTRODUCTION

1.1 TERPENES

1.1.1 General Description and Classifications

Terpene name is originated from the turpentine that resin of pine trees. Terpenes are constructed by isoprene **1** (2-methyl-1,3-butadiene) subunits and over 30,000 species are known in literature (1). Terpenes are the largest secondary metabolite compounds that are generated by mainly plants, animals or microorganisms. Terpenes are defined as simple hydrocarbons that contain only isoprene **1** units, while terpenoids **27** are more complex structures involve different functional groups (2). Terpenes are divided into five classes monoterpenes, sesquiterpenes, diterpenes, triterpenes and tetraterpenes (3).

Monoterpenes consist of two isoprene **1** subunits (C_{10}). They are prevalent in plants such as rutales, lamiales, asterales, cornales and many others (4). They are divided into acyclic, monocyclic, bicyclic and cannabinoids (5).

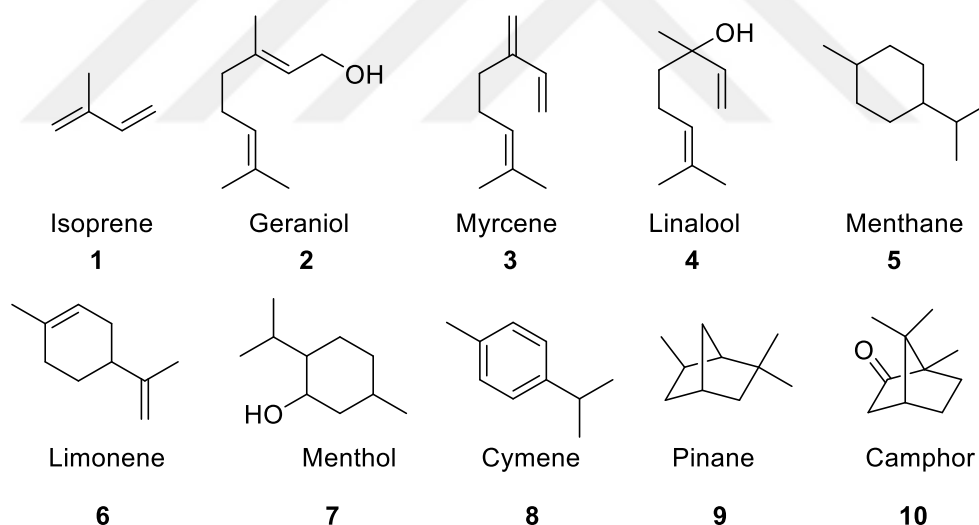


Figure 1.1. Some monoterpenoids.

Sesquiterpenes are constructed from three isoprene **1** subunits (C_{15}). They are found mainly in higher plants and microorganisms such as marine organisms and fungi (6).

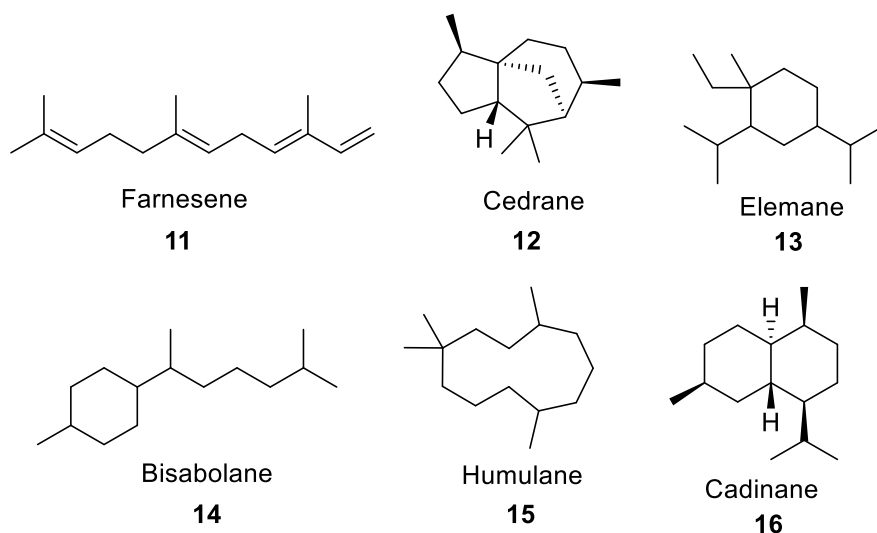


Figure 1.2. Some sesquiterpenes.

Diterpenes are made of four isoprene 1 units (C_{20}). They are less volatile according to monoterpenes, so they are utilized as solvent rather than odorant (7).

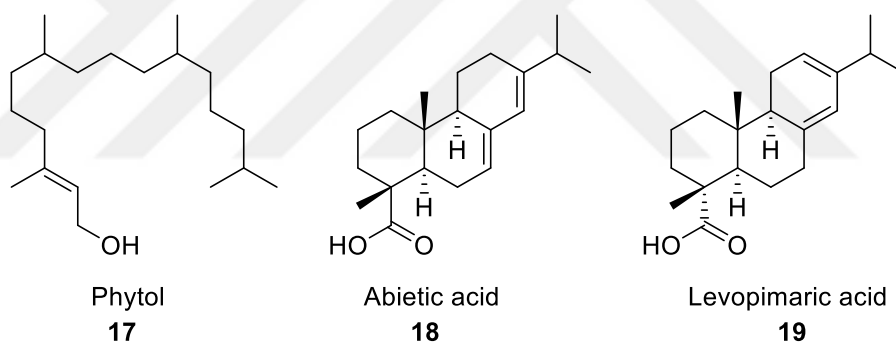


Figure 1.3. Some diterpene structures (8).

Triterpenes (C_{30}) are isoprenoids that derived from two sesquiterpene precursors, farnesyl diphosphate (FPP) (9). Triterpenoids have the capacity to form fused cyclic structures because of their long chain structures. Therefore, they are used in the field of medicine, they are also found in the structure of saponins and hormones such as steroids (10).

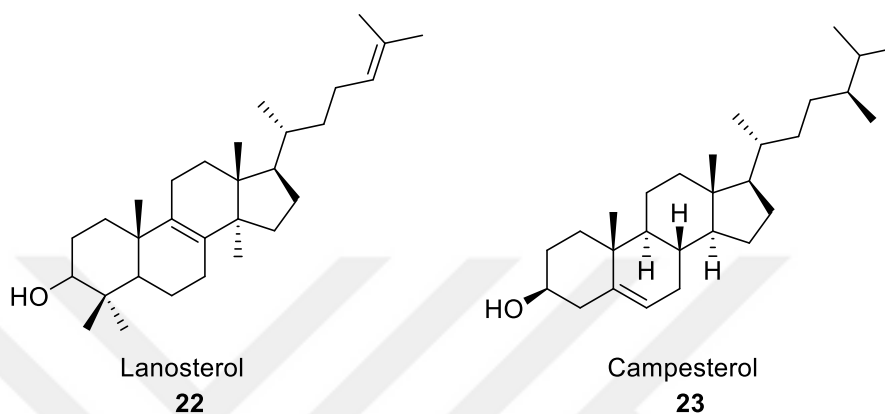
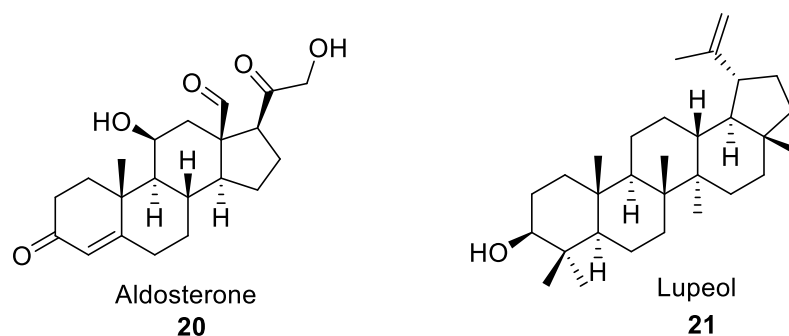


Figure 1.4. Medicinal and hormonal triterpenoids.

Tetraterpenes are made of eight isoprene 1 subunits (C_{40}) (3). The most known class of tetraterpenes are carotenoids (11).

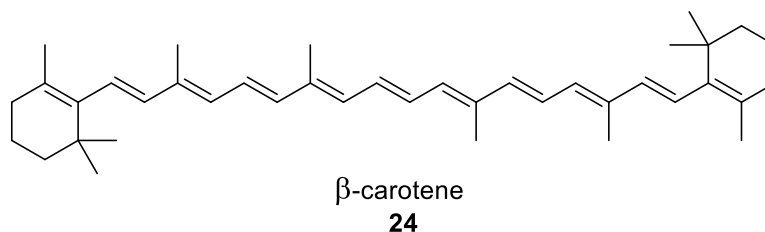
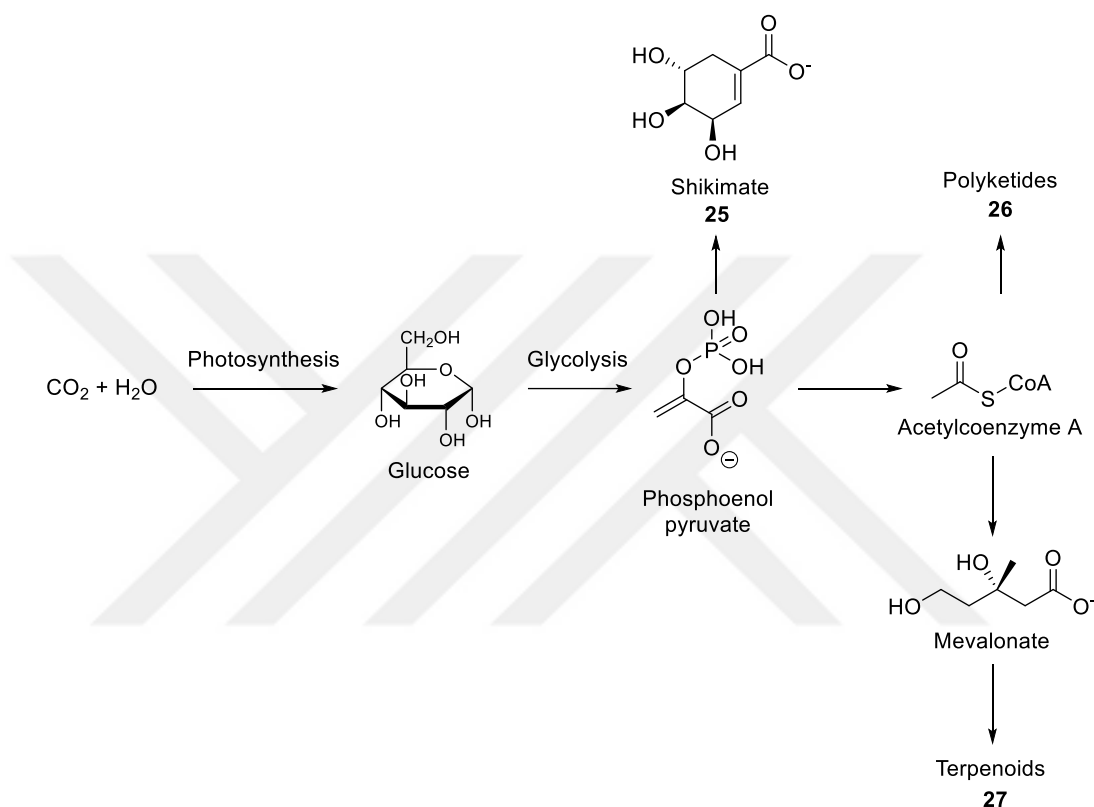


Figure 1.5. The most common carotenoid and the precursor of vitamin A.

Terpenes are widely used in the perfume industry due to their pleasant odor and volatility. In addition, they are used as cosmetics (12), drugs (13), flavouring agents (14), biofuels (15), polymers (16), food preservatives (17), insect repellants (18), plant communications (19) and pheromones (20).

1.1.2 Fragrance Properties of Terpenes

Perfume ingredients are generally secondary metabolites that are produced by biosynthetic pathways of plants, animals and microorganisms. These are shikimic acids **25**, polyketides **26**, terpenoids **27** and alkaloids (Scheme 1.1). Most abundant ingredients are terpenoids **27**, alkaloids usually used as treatments (7).



Scheme 1.1. Biosynthetic pathway of secondary metabolites.

For instance, cannabis contains more than 483 natural compounds. Major groups of these compounds are terpenes, cannabionids, flavonoids, hydrocarbons, sugars and miscellaneous compounds (21). The simplest monoterpene, myrcene **3** is the most abundant terpene in cannabis species. β -caryophyllene is the most important sesquiterpene in cannabis plant. Linalool, limonene, α - or β -pinene and several more terpene/terpenoid **27** compounds in hemp and cannabis varieties were remarked (Figure 1.6) (22).

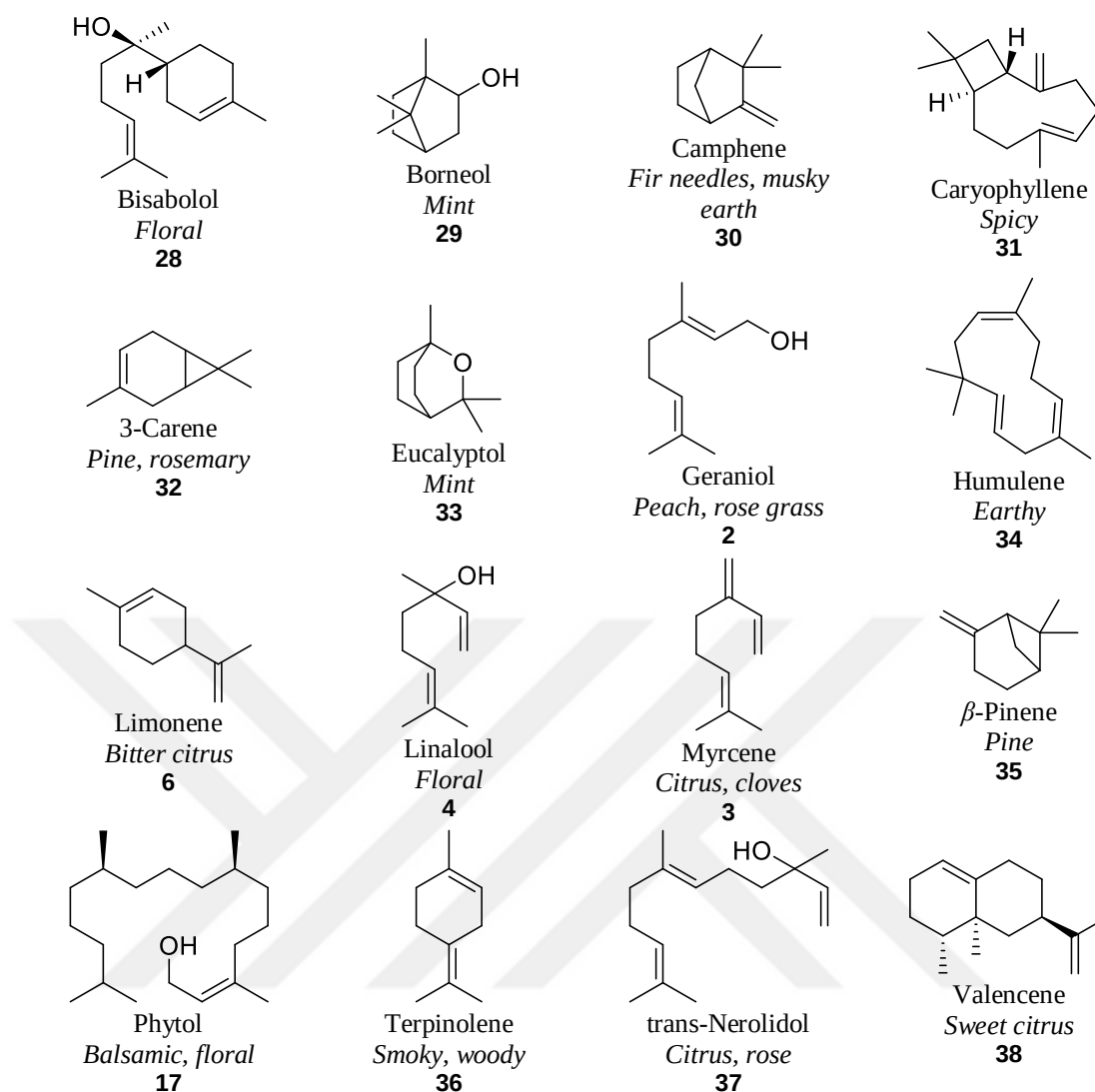


Figure 1.6. Plenty found terpene/terpenoids **27** in cannabis with their characteristic odors (23).

Essential oils contain phytochemicals predominantly consisting mixture of terpenoids. Some examples of plant essentials and their contents are given in Table 1.1. (24).

Table 1.1. Some essential oils with terpene/terpenoid abundant compounds.

Name of the oil	INCI name	Main components
Eucalyptus	Eucalyptus Globulus Leaf Oil	1,8-Cineole: minimum 70% Limonene: $\geq 12\%$ α -Pinene: $\geq 9\%$ α -Phellandrene: $\leq 1.5\%$ β -Pinene: $\leq 1.5\%$ Sabinene: $\leq 0.3\%$ Camphor: $\leq 0.1\%$
Lavender	Lavandula Angustifolia Herb Oil	Linalyl acetate: 25–46% Linalool: 20–45% 1,8-Cineole: $\leq 2.5\%$ Camphor: $\leq 1.2\%$ 3-Octanone: 0.1–2.5% Terpinen-4-ol: 0.1–6% α -Terpineol: $\leq 2\%$ Limonene: $\leq 1\%$ Lavandulyl acetate: $\leq 0.2\%$ Lavandulol: $\leq 0.1\%$
Lemon	Citrus Limon Leaf Oil	Limonene: 56–78% β -Pinene: 7–17% γ -Terpinene: 6–12% Sabinene: 1–3% Geranial: 0.5–2.3% Neral: 0.3–1.5% Neryl acetate: 0.2–0.9% Geranyl acetate: 0.1–0.8% α -Terpineol: $\leq 0.6\%$ β -Caryophyllene: $\leq 0.5\%$
Pine	Pinus Mugo Twig Oil	α -Pinene: 10–30% δ -3-Carene: 10–20% β -Phellandrene: 10–19% Limonene: 8–14% β -Pinene: 3–14% β -Myrcene: 3–12% Terpinolene: $\leq 8\%$ Bornyl acetate: 0.5–5% β -Caryophyllene: 0.5–5% <i>p</i> -Cymene: $\leq 2.5\%$ Camphene: $\leq 2\%$
Rosemary	Rosmarinus Officinalis Flower Oil	1,8-Cineole: 38–55% α -Pinene: 9–14% Camphor: 5–15% β -Pinene: 4–9% Camphene: 2.5–6% Borneol: 1.5–5% Limonene: 1.5–4% β -Myrcene: 1–2% α -Terpineol: 1–2.6% <i>p</i> -Cymene: 0–2.5% Bornyl acetate: 0.1–1.5% Verbenone: $\leq 0.4\%$

1.2 CARBAMATES

1.2.1 General Structure and Spectroscopic Properties

Carbamates are carbamic acid esters that contains an ester and an amine group. Salts of carbamates are not stable and can decompose relatively. In aqueous solutions, they are hydrolyzed to corresponding metal carbonates and amines. Unsubstituted and *N*-aryl carbamates are generally crystalline, while mono- and di- *N*-alkyl substituted carbamates are liquids in mild temperature (25).

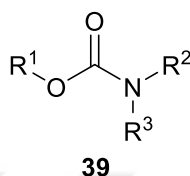


Figure 1.7. General structure of carbamates.

IR absorption bands of carbonyl group of carbamates according to their structure as primary 40, secondary 41 or tertiary 42 (26).

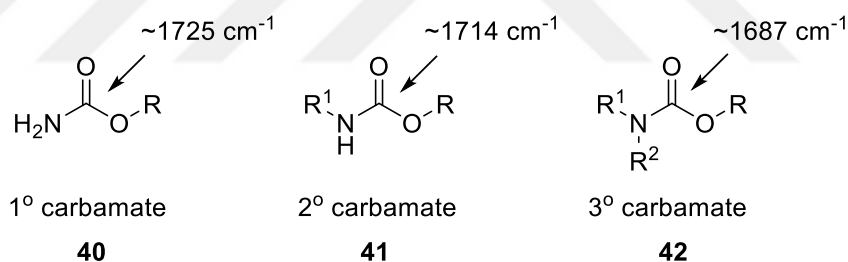


Figure 1.8. Carbonyl stretches of carbamates.

In ^1H NMR of carbamates, *N*-methyl 43 and *N*-aryl 44 substituted derivatives have quite different chemical shifts. For instance, *N*-methyl protons resonates at 2.4-3.0 ppm as multiplet and *N*-aryl protons give chemical shifts at 7.18-7.29 ppm as doublets (27).

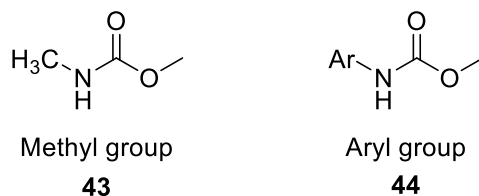


Figure 1.9. Example carbamate scaffolds to ^1H NMR spectroscopy.

^{13}C NMR spectrum of primary **45** and secondary **46** carbamates given carbon chemical shifts are a, a' ($\sim 164.0\text{--}165.0$ ppm), b (~ 38.0 ppm) and b' (~ 47.0 ppm), c (~ 50.0 ppm), and c' (~ 38.7 ppm), d (~ 33.0 ppm) and d' (~ 34.6 ppm) (28).

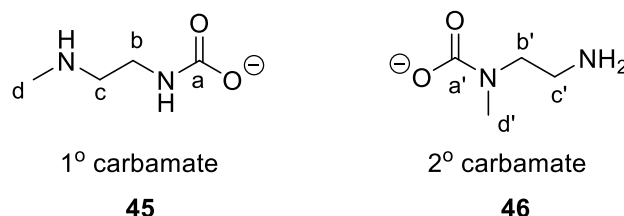
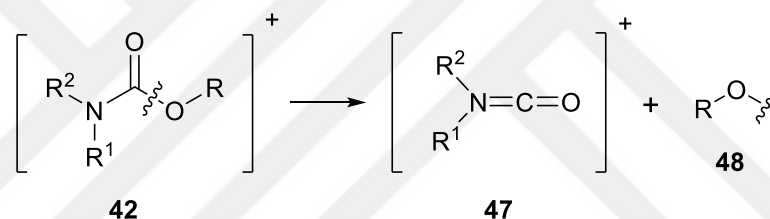


Figure 1.10. Example carbamate scaffolds to ^{13}C NMR spectroscopy.

Fragmentations of carbamates in mass analysis, yield favorable fragments as isocyanates **47** and alkoxy group **48** because of stability (29,30).



Scheme 1.2. Favorable MS fragmentation of carbamates.

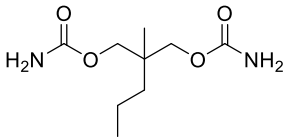
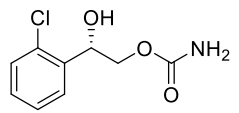
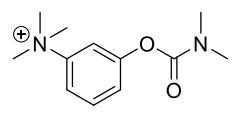
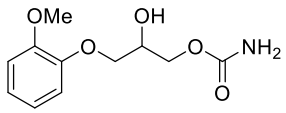
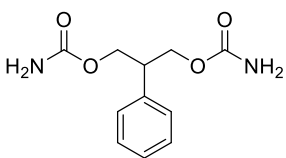
1.2.2 Biological Properties of Carbamates

Carbamates are widely utilized in medicinal chemistry and drug design due to their amide-ester hybrid properties (Table 1.2). Organic carbamates have therapeutic effects. In addition to many biological effects of carbamates, they are used as peptide bond surrogate in that their chemical stability and ability to penetrate the cell membrane (31). Among the areas, most well-known of its are agrochemicals, polymer industry and peptide synthesis (32–34).

Carbamates are also used in pesticides to protect fruits, vegetables and crops. The first pesticide introduced in this area was carbaryl in 1956. Carbamate (CM) pesticide poisoning causes serious health problems. Like organophosphates (OP), carbamates inhibit the enzyme acetylcholinesterase. They bind to the AChE enzyme from the esteric side. Compared to organophosphates, the binding of carbamates is a reversible process, hence the poisoning times are shorter (35).

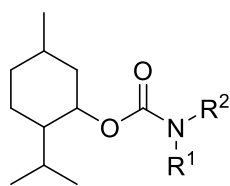
Since this enzyme is neurologically important, when inhibited, serious neurological diseases such as Parkinson's and Alzheimer's are eventuated (36–38). Aldicarb, bendiocarb, carbaryl, carbofuran, propoxur and more CM pesticides cause nervous and skin damages, furthermore weakness, blurred vision, headache, nausea, tremor, sweating, diarrhea etc. (39).

Table 1.2. Some examples of carbamate drug according to their classes and metabolisms (40).

DRUGS	CLASS	METABOLISM
 Meprobamate	Anxiolytic	Hydroxylation to 2-hydroxypropyl metabolite
 Carisbamate	Antiepileptic	Glucuronidation
 Neostigmine	Cholinergic, miotic, antidote for neuromuscular blocking agent	Hydrolysis of carbamate
 Methocarbamol	Muscle relaxant	O-demethylation, aromatic hydroxylation
 Felbamate	Anticonvulsant	Aromatic 4-hydroxylation, hydrolysis of carbamoyl, then oxidation to aldehyde, then elimination to α,β -unsaturated aldehyde

1.2.3 Carbamates in Cosmetics

Some studies related with carbamates have also been carried out in the field of cosmetics. Meyer's group published a patent about anti-cellulite ingredients of menthyl carbamate **49** compounds. Later, Vielhaber et al. patented these compounds as hair and skin lightening. The relevance of these compounds with cosmetics, dermatology and medicine are also emphasized (41,42).



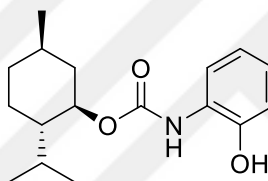
49

$R^1 = \text{H or Org. Rad. 1 to 14 C}$

$R^2 = \text{Org. Rad. 1 to 14 C}$

Figure 1.11. Structure of menthyl carbamate.

Hillers and co-workers invented an antiperspirant, L-Menthyl-*N*-(2-hydroxyphenyl) carbamate **50**. It inhibits perspiration odors that are released by bacteria live on armpit or foot such as *staphylococcus epidermidis*, *brevibacterium epidermidis* and *corynebacterium xerosis* (43).



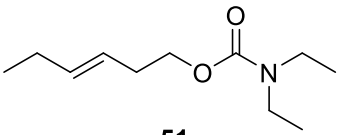
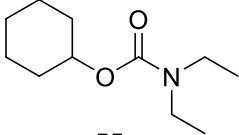
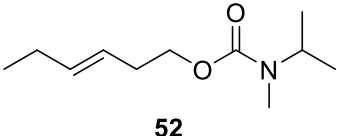
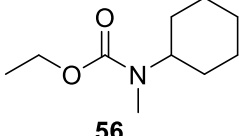
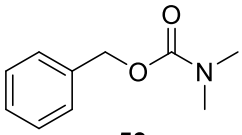
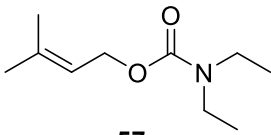
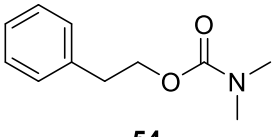
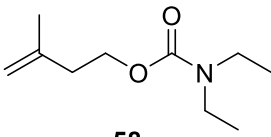
50

Figure 1.12. Antiperspirant carbamate patented by Hillers' group.

In addition, carbamates have been used as insect repellent (44), emulsifier (45), adjuvant for odor durability (46), fragrance ingredient (47) and flavouring agent (48).

Carbamates as fragrance compounds were submitted firstly by Flachsmann and his co-worker Bachmann in 2004. They synthesized tertiary non-vinyl carbamates that MW less than 350, including floral, fruity, spicy and woody odors (Table 1.3) (49).

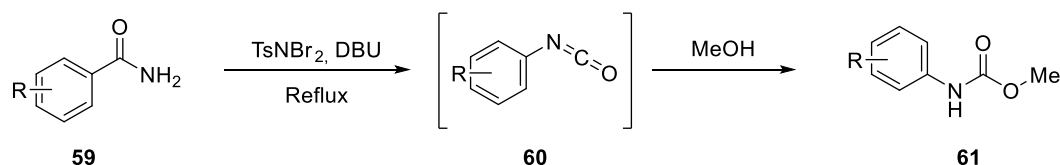
Table 1.3. Some fragrance carbamate derivatives synthesized by Flachsmann and Bachmann, associated with olfactory descriptions.

Structure	Olfactory description	Structure	Olfactory description
 51	Green, Peppery, Liquorice	 55	Floral, Minty, Terpenyl acetate
 52	Peach, Veloutone, Nectaryl	 56	Mushroom, Minty, Herbal
 53	Fruity, Rosy	 57	Celery, Spicy, Animalic
 54	Balsamic, Spicy, Rosy	 58	Salicylate, Quinoline, Green, Earthy

1.2.4 Synthesis of Carbamates

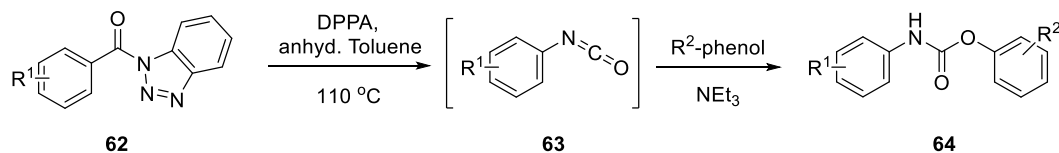
For the synthesis of carbamates, the well-known method is the reaction of isocyanates with alcohols. The most common methods used in the synthesis of isocyanate precursors are Hofmann, Curtius and Lossen rearrangements (50).

Hofmann rearrangement reaction was described first in 1881 (51). Intermediate isocyanate **60** is occurred via carboxylic amide **59** in the presence of a base (52).



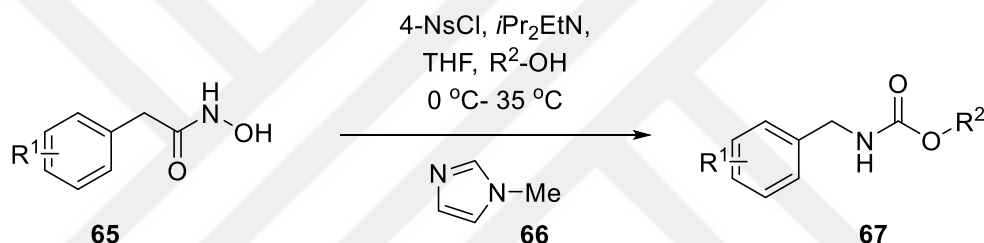
Scheme 1.3. Hofmann type example of carbamate synthesis (53).

Curtius rearrangement reactions was described first in 1890 (54). Isocyanate intermediate **63** is formed by thermal decomposition of acyl azides **62** that are generally produced from acyl chlorides and azide salts (55).



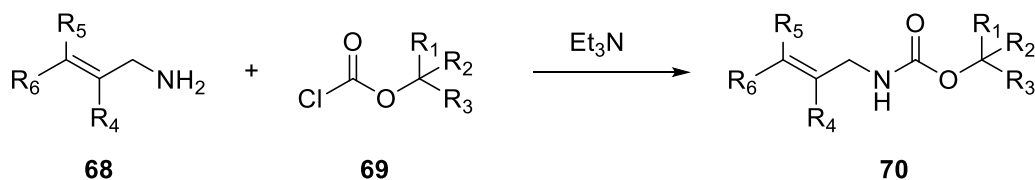
Scheme 1.4. Curtius type example of carbamate synthesis (56).

Lossen rearrangement reaction was described first in 1872 (57). In the reaction, hydroxamic acid **65** is turned into isocyanate in the presence of base **66** or heat via O-acyl, sulfonyl, phosphoryl intermediate (58).



Scheme 1.5. Lossen type example of carbamate synthesis (59).

In 2011, Pei's group patented some unsaturated carbamates **70**. These compounds had some taste properties such as salt, umami or sweet and able to flavor quality enhancement. Reaction takes place with unsaturated amine **68** and chloro formate **69** in the presence of a strong bulky base (60).



Scheme 1.6. Synthesis of unsaturated cyclic or acyclic carbamates.

In addition to this, carbamates can be synthesized via CO₂ that create new C-N bond in the presence of various catalysts (61), formamides in the presence of transition-metal-catalyst (62) or cyclic carbonates in the presence of organocatalyst as high stereoselective products (63).

1.3 INDOLES

1.3.1 General Structure, Classification and Types of Indoles

Indole or benzopyrrole **71**, is a heterocyclic compound that fused in C-2 and C-3 position carbons of pyrrole to benzene ring. It is one of the most abundant heterocyclic structures in natural and biologically active products (64).

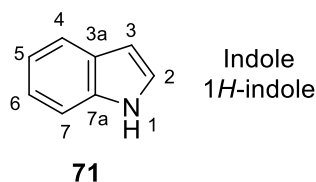
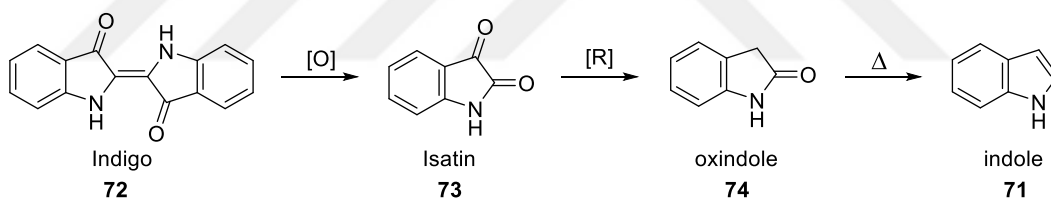


Figure 1.13. Structure of indole.

In 1841, indigo **72** was oxidized to isatin **73** (65). In 1866 Baeyer and Knop reduced isatin **73** to dioxindole and oxindole **74** (66). After that, in 1866 Baeyer synthesized indole **75** via zinc-dust pyrolysis of oxindole **74**. In 1869, Baeyer and Emmerling identified the structure of indole **71** (67).



Scheme 1.7. First indole synthesis route by Baeyer et al.

There are tautomers and isomers of indole **71**. In tautomeric structures, hydrogen and double bond in five membered rings are on different positions. Two types of isomers exist which are isoindole **78** and indolizine **79**. Isoindole **78** is 3, 4 and indolizine **79** is 1, 2 position fused structures of pyrrole (Figure 1.14) (64).

Indoles are subdivided into 2 types as alkaloid and non-alkaloid indoles. Alkaloid term is that a compound contains nitrogen atom which has molecular complexity and is produced by plants, at the same time has biological activities. Terpene indole alkaloids are generally produced from Apocynaceae and Rubiaceae and have more than 2500 members (68).

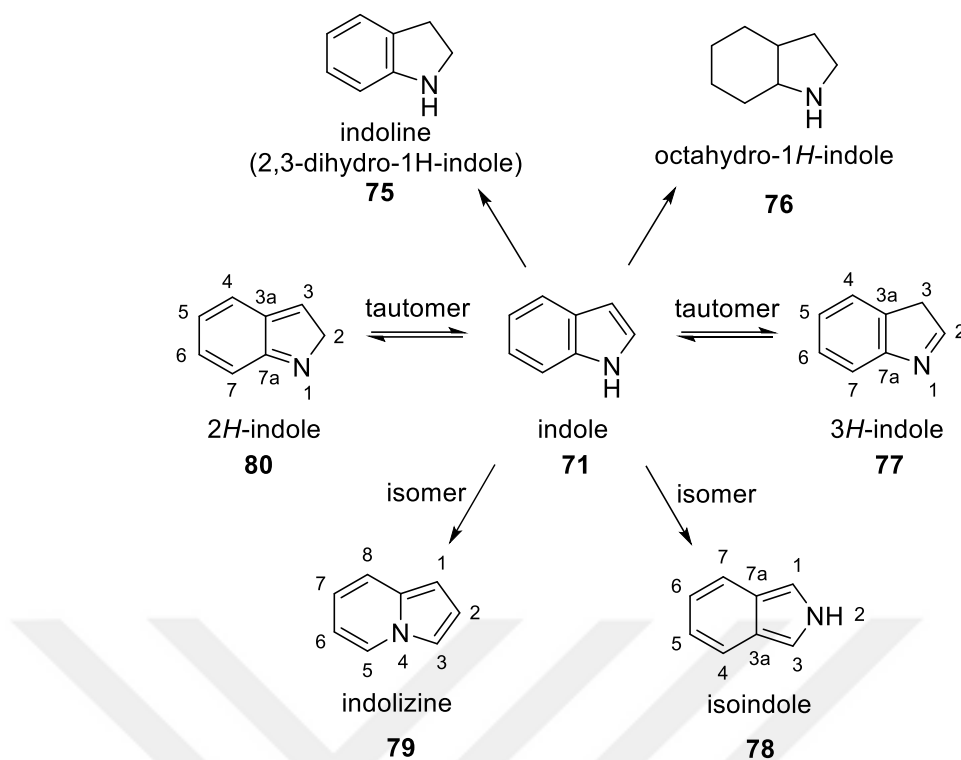


Figure 1.14. Tautomeric and isomeric structures of indole.

1.3.2 Physical and Spectroscopic Properties

Indole **71** is crystalline solid and melts down about 52-54 °C. It is flat and partial polar (2.38 δ). But indoline **75** is not planar and molecules are packed closely lower than indole **71**, so it is liquid in room temperature.

Small groups in indole skeleton that do not increase polarity or provide intermolecular hydrogen bonding dramatically, do not affect to melting point too much. For example, 2-methylindole, 5-methoxyindole or 5-chloroindole. On the contrary, substituents which afford high intermolecular hydrogen bonding increase melting point in huge amounts such as, indole 3-carboxaldehyde, indole-3-carboxylic acid or 3-acetylindole (69).

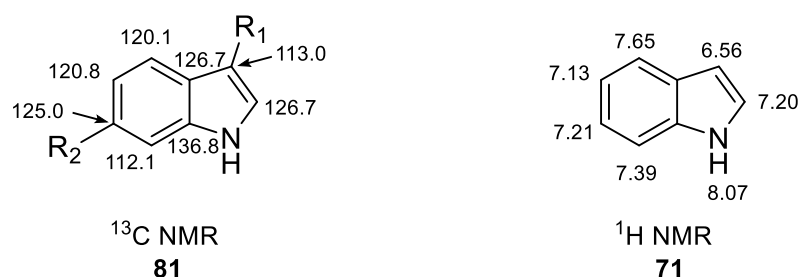
Table 1.4. Melting point of some indole derivatives.

Compounds	Melting Points (°C)
Indole	52-54
2-Methylindole	58-60
5-Methoxyindole	56-58
5-Chloroindole	69-71
Isatin	201-203
3-Acetylindole	188-192
Indole-3-Carboxaldehyde	198-199
Indole-3-Carboxylic Acid	235-236
2-Phenylindole	186-188

Indole **71** has solubility in organic solvents such as chloroform, petroleum ether, benzene, alcohol and in hot water. Oxindole **74** is also soluble in most organic solvents but the more polar isatin **73** is better soluble in polar solvents such as alcohols or acetic acid, lower in hydrocarbons or ether (69).

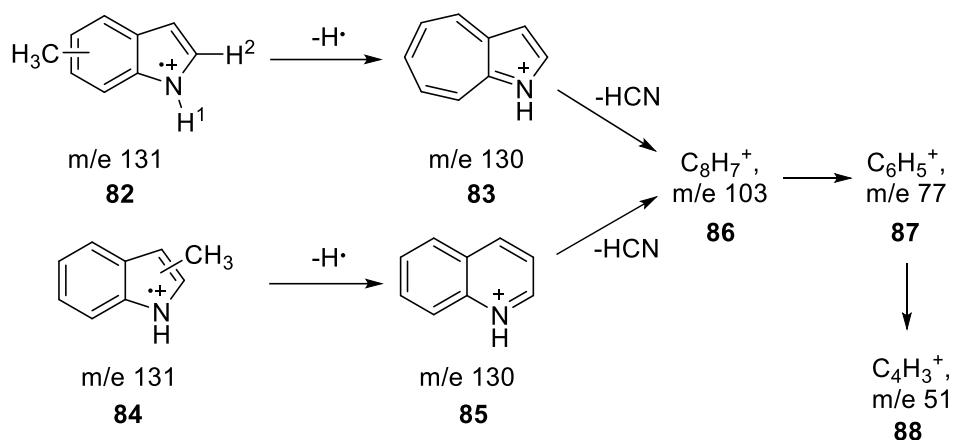
In IR spectra of indoles, N-H absorption peak is sharp and more intense than aniline or saturated amines ($\sim 3500\text{ cm}^{-1}$). Substituted indoles on 2- or 3- has lower absorption band ($\sim 3425\text{--}3144\text{ cm}^{-1}$). According to the nature of substituents band shift changes. Electron acceptors cause lower absorption frequencies than electron donors (69).

^{13}C NMR shifts of C-3 and C-6 substituted indoles relative to TMS and CDCl_3 solutions (70) and ^1H NMR (71) are given in Figure 1.15.

**Figure 1.15.** ^{13}C and ^1H chemical shifts (ppm) of indole **71** and its derivatives.

The main fragment of indole **71** in mass spectrometry are HCN or H_2CN lose from H^1/H^2 or both. Base peak is m/z 117. HCN and H_2CN loss give strong peaks m/z 90 and m/z 89 respectively. Further fragmentation is C_5H_3^+ (m/z 63).

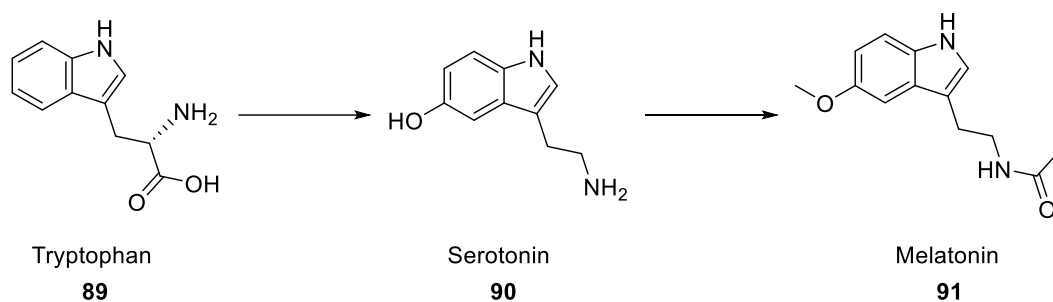
However, methyl substituted on benzene or pyrrole ring indoles gives different strong peak. Loss of hydrogen atom from methyl group yield ring expansion (72).



Scheme 1.8. Mass spectroscopy fragmentation of methyl substituted indoles.

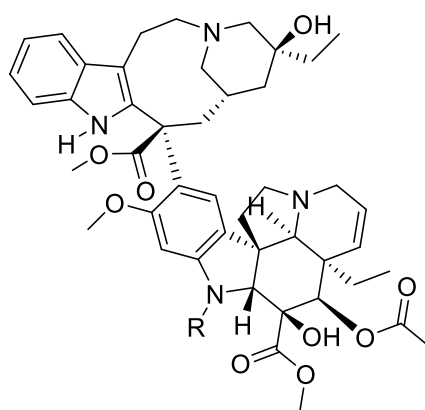
1.3.3 Biological Properties of Indoles

Indoles have biological activity, therefore more than ten thousand derivatives in nature, and more than two hundred are used in pharmaceutical chemistry (73). Tryptophan **89** is an amino acid that involve indole **71** structure and it is also biosynthetic precursor of serotonin **90** hormone, later serotonin is biologically converted to melatonin hormone **91** (74).



Scheme 1.9. Biosynthetic pathway of melatonin hormone.

One of the indole alkaloids, vinca alkaloids were isolated first time from Madagascar periwinkle plant in 1950s, vinblastine **92** and vincristine **93** that are used as antitumor agents (75).



R = Me (Vinblastine) **92**

R = CHO (Vincristine) **93**

Figure 1.16. Structure of vinblastine **92** and vincristine **93**.

Indoles are frequently utilized as anticancer, tubulin inhibition, anti-HIV, anti-inflammatory, antihypertensive, toxin, antipsychotic, antiviral, antibacterial, antihypertensive, almost every therapy of disease (76).

Some example drugs are given (figure 3), mitraphylline **94** as anticancer, Delavirdine **95** as anti-HIV, Indometacin **96** as anti-inflammatory, Pindolol **97** as antihypertensive and Oxypertine **98** as antipsychotic and antidepressant therapy (77).

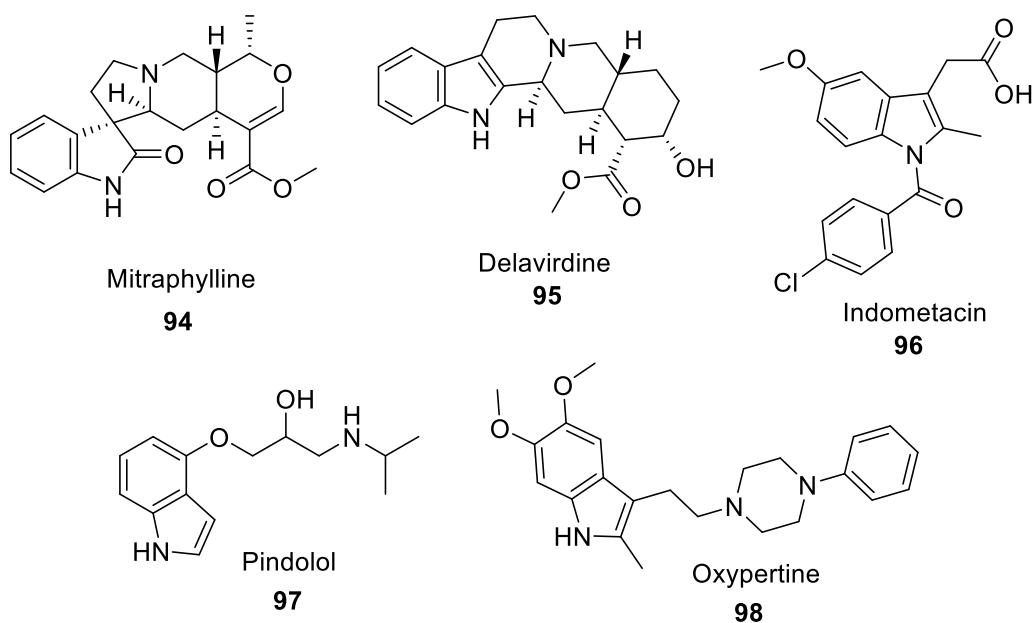


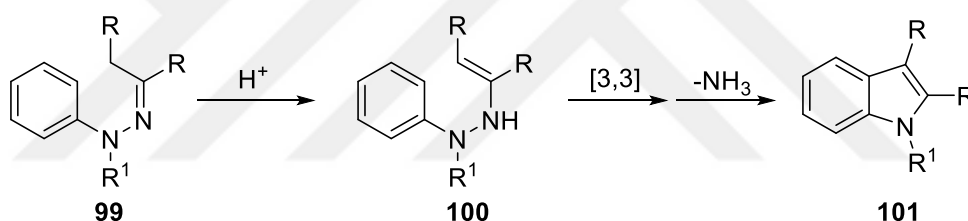
Figure 1.17. Examples to indole scaffold containing drugs.

1.3.4 Synthesis of Indoles

There are comprehensive synthesis methods for indoles, more than seventy-five and more than half of which are specific methods. According to the nature of these synthesis methods, they can be classified as sigmatropic rearrangements, nucleophilic cyclizations, electrophilic cyclizations, reductive cyclizations, oxidative cyclizations, radical cyclizations, cycloaddition and electrocyclizations, indoles from pyrroles, indoles from indolines, transition-metal-catalyzed, miscellaneous (78).

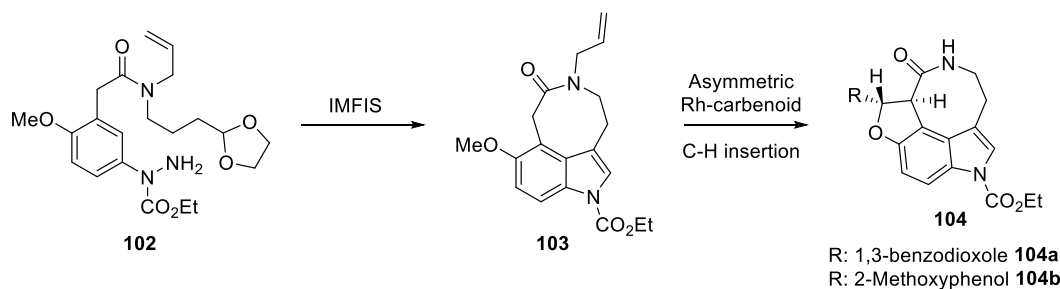
1.3.4.1 Fischer Indole Synthesis

Emil Fischer published indole **101** synthesis via aryl hydrazone **99** and pyruvic acid in the presence of alcoholic hydrogen chloride (79). Many studies have been developed according to Fischer method (80). Reaction involves new C-C bond formation via [3,3] sigmatropic rearrangement and loss of ammonia.



Scheme 1.10. General reaction process of Fischer indole synthesis.

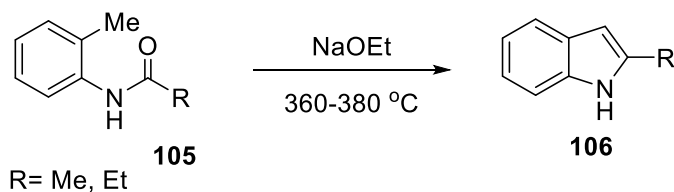
Kim and co-workers synthesized indole alkaloids (+)-Decursivine **104a** and (+)-Serotobenine **104b** via intramolecular Fischer-indole synthesis and intramolecular Rh-carbenoid C-H insertion (81).



Scheme 1.11. Intramolecular Fischer indole synthesis of (+)-Decursivine **104a** and (+)-Serotobenine **104b**.

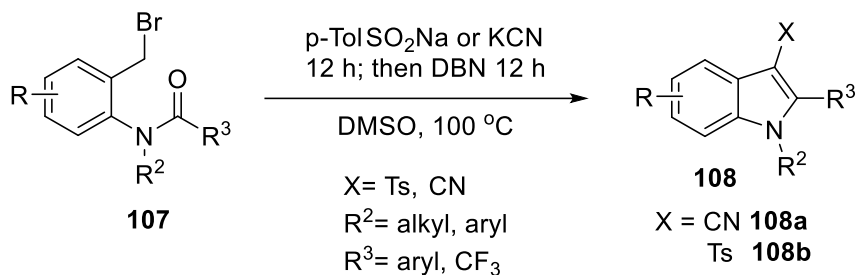
1.3.4.2 Madelung Indole Synthesis

Madelung indole synthesis is an example of nucleophilic cyclization reaction that *N*-(*o*-alkyl)amides **105** with alkoxy bases at elevated temperatures (82). Until now, many conditions such as substituent, base, temperature, solvent alteration have been applied on the madelung indole synthesis, and better efficient results have been obtained (83).



Scheme 1.12. General synthesis method of 2-substituted indole **106** via madelung indole synthesis.

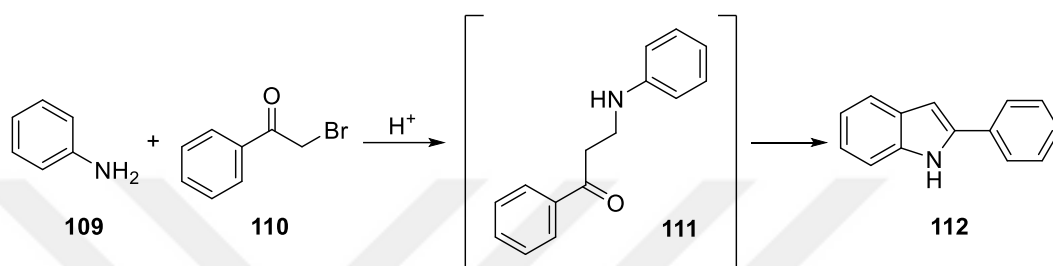
Sterligov and co-workers synthesized one-pot 1,2-disubstituted-3-cyano **108a** and -3-tosylindoles **108b** in the presence of DBN. These indole derivatives are important precursors in medicinal chemistry. Results were remarked in good yields up to 89.0% (84).



Scheme 1.13. Synthesis of 3-tosyl **108b**, 3-cyano **108a** substituted indoles via nucleophilic indole cyclization.

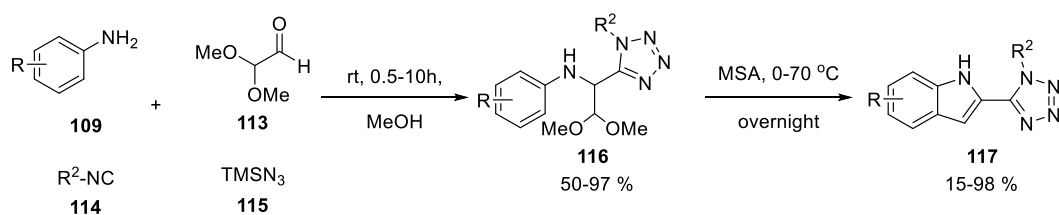
1.3.4.3 Bischler-Möhlau Indole Synthesis

2-Arylindole synthesis via electrophilic cyclization process was discovered by Bischler and Möhlau several years ago (85,86). Process involved excess aniline **109** and 2-bromoacetophenone **110** reaction in the presence HCl acid at high temperatures to yield 2-Phenylindole **112**. After years, they submitted α , β -diphenylindole synthesis (87), but reactions suffered from yields. Until now, numerous developments were applied (88).



Scheme 1.14. Bischler-Möhlau indole synthesis of 2-phenylindole **112** via electrophilic indole cyclization.

Lei and co-workers reported that one-pot 2-tetrazole indole **117** synthesis with multi-components. The first step involves Ugi-tetrazole **116** synthesis via aniline **109**, aq. 2,2-dimethoxy acetaldehyde **113**, isocyanide **114** and TMSN₃ **115** at room temperature. Next step is ring closure via methanesulfonic acid. Reaction gives excellent yields up to 98 % (89).

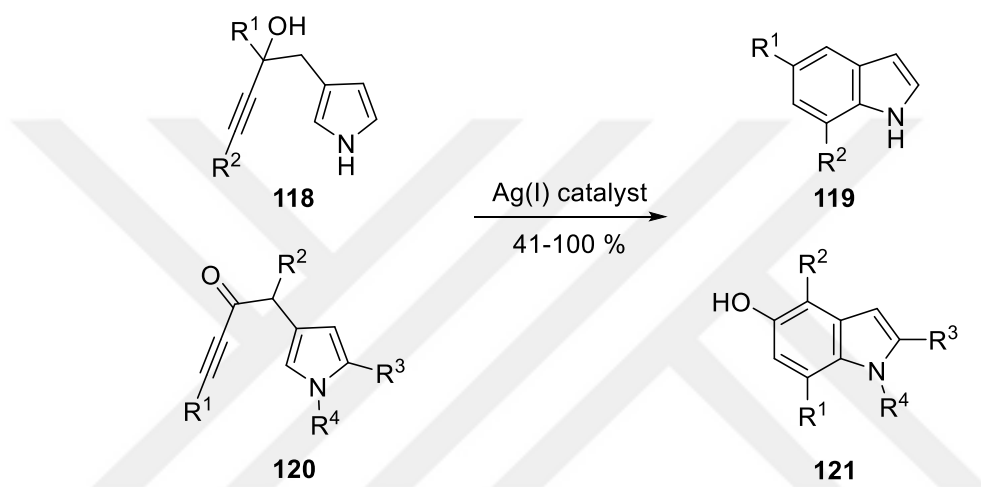


Scheme 1.15. One-pot multicomponent 2-tetrazole substituted Bischler-Möhlau indole **117** synthesis.

1.3.4.4 Indoles from Pyrroles

Indoles can be synthesized by pyrroles in many methods (90). Some of these methods are electrophilic (91–93), transition-metal-catalyzed (94,95) and electro-cyclizations (96,97) of pyrroles, cycloaddition (98) and dehydrogenation (99) of pyrroles, miscellaneous indole synthesis (100).

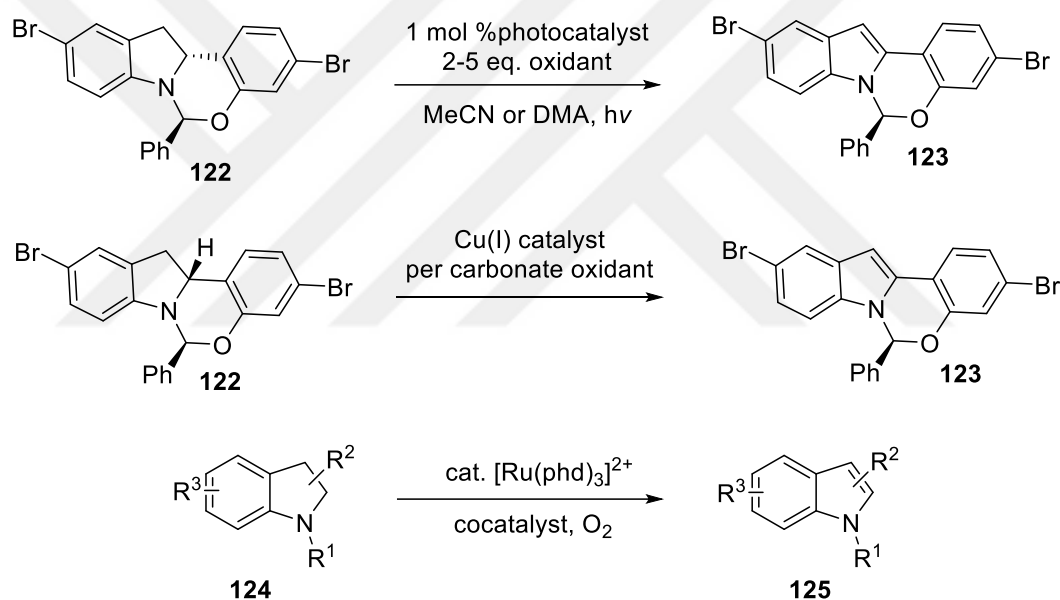
Clarke et al. published ‘‘back-to-front’’ type substituted indole synthesis with silver(I) catalyst. Ynols **118** into indoles **119** and ynones **120** into 5-hydroxy-indoles **121** were converted (101).



Scheme 1.16. Ynol **118** and ynone **120** substituted pyrroles cyclizations via silver (I) catalyst.

1.3.4.5 Indoles from Indolines

Oxidation (dehydrogenation) of indolines at C-2 and C-3 positions gives indoles. Yayla et al. reported photoredox oxidation of indoline derivative **122** to its indole form **123** which is used as Elbasvir drug precursor up to 99.9% yield. As photocatalyst they utilized iridium photosensitizer and several different oxidant materials (102). Another example to Elbasvir drug precursor synthesis was reported by Peng and co-workers that copper(I) catalyst and per carbonate oxidant were utilized. Results were in good yields up to 99.9% (103). Li's group submitted aerobic dehydrogenation of tertiary indolines **124** to their indoles **125** via low potential *o*-quinone catalyst up to 94.0% yield. They also applied process on Enzastaurin and LY290154 drug precursors (Scheme 1.17) (104).



Scheme 1.17. Indoline oxidation reactions.

1.4 CASCADE REACTIONS

1.4.1 What is a Cascade?

Benefit and sustainability in scientific studies are increasing day by day. Many methods meet these requirements in different ways. One of these methods, cascade reactions, with other names "domino" (105) or "tandem" (106) reactions, has an important place in atom (107), time, workload, resource and waste management as well as many benefits. Synthesize of complex compounds due to structural and stereochemical conditions can be difficult. The procedure steps that applied to synthesize these compounds are very long and cause an increase in time, work and resource consumption. Yield loss occurs due to the work-up and purification methods applied in each reaction step. Cascade reactions can be applied to avoid this consumption. Under favor of cascade reactions, instead of applying a multi-step procedure, a product can be obtained in a single step with a few chemicals. Consequently, cascade reactions can be considered as "green chemistry". Therefore, cascade reactions are frequently used in the total synthesis of natural products. Due to the chiral center and structural complexity in natural products, it can be quite difficult to synthesize them. By means of cascade reaction, the synthesis steps of these substances can be reduced, and this difficulty can be overcome.

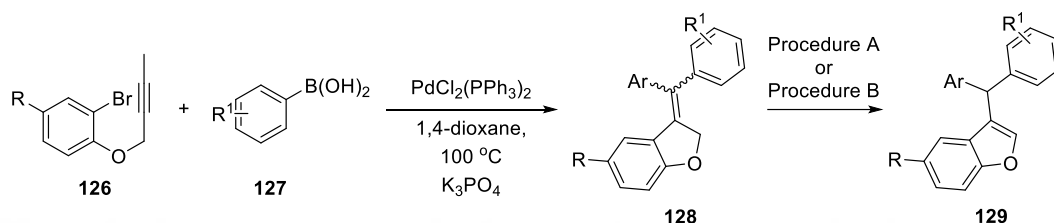
1.4.2 Types of Cascade Reactions

For clarity, these reactions can be grouped under five main headings: transition-metal-catalyzed, radical, pericyclic, nucleophilic, and electrophilic (108).

Considering cascade reactions, transition metals act as catalysts and ensure that the reaction is completed as a "one-pot", moreover it is important in terms of atom economy (109). Another benefit of transition metal catalysts is that by forming bonds that are difficult or impossible to form naturally, the molecular complexity is readily acquired (108).

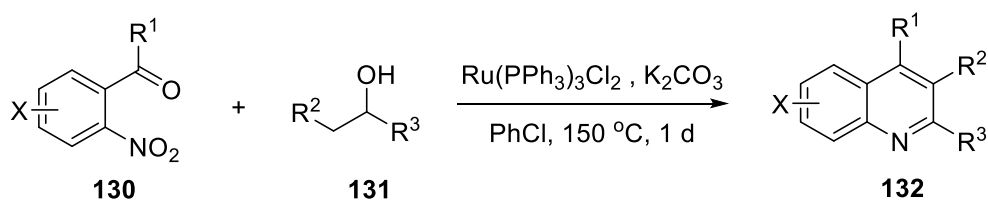
Palladium catalyst has a wide range of applications in step reactions due to its high specificity, especially chemo and stereoselectivity (110). The reaction variety for palladium catalysts used in the construction of new C-C bonds is very broad. The well-known for cascade reactions via palladium-catalyst are Heck (111,112), Stille (113), Suzuki (114), and Sonogashira (115) reactions.

For instance, Arcadi and co-workers, achieved cascade reactions of propargylic aryl ethers **126** and organoboron **127** compounds by cyclocarbopalladation reaction followed by Suzuki-Miyaura coupling method. They synthesized benzofuran **129** derivatives functionalized on the C-3 via 1-(3-arylprop-2-ynoxy)-2-bromo benzene **126** derivatives and organoboron compounds **2**.



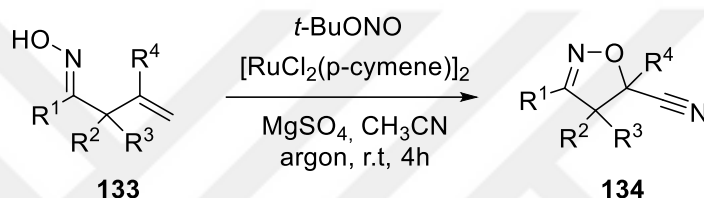
Scheme 1.18. Cyclocarbopalladation and Suzuki-Miyaura coupling cascade reaction.

Two or more fundamentally different transformations (116). These transformations can be brought about by other transition elements such as rhodium (117), ruthenium (118) or copper (119). Ruthenium compounds have properties such as high electron transfer, high Lewis acidity, low redox potential and stabilization of other metal types (110). As a good example, Li and co-workers synthesized quinolines **132** from non-reactive alcohol **131** and 2-nitrobenzaldehyde **130** derivatives by hydrogen transfer and Friedländer ring using a ruthenium catalyst (120).



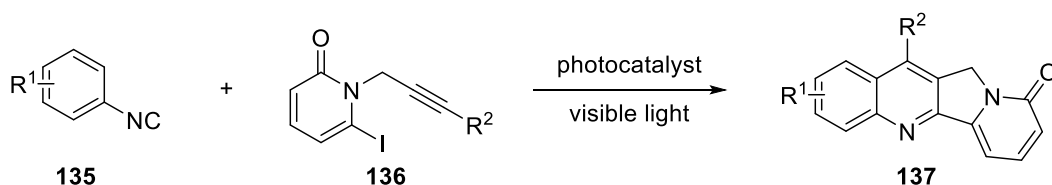
Scheme 1.19. Ruthenium catalyzed synthesis of quinolines via Friedländer annulation.

Radical reactions ordinarily occur in moderate conditions, not many requirements are needed, and they are highly stereoselective reactions (121–123). Radical cascade reactions have various types and their function in polycyclic and heterocyclic chemistry is extensive due to their ability and atom-economy (124–126). For example, Wang and collaborators synthesized 5-cyanide isoxazoline derivatives **134** in high potency and yield by a non-toxic radical initiator and cyanide source in a moderate and neutral circumstance. Tert-butyl nitrite, which was used as a radical initiator, was also used as oxidant and nitrogen source. Another important feature is the formation of both C-O bond and C≡N bond from unstable alkyl radical in one-pot.



Scheme 1.20. Radicalic cascade transformation of β,γ -unsaturated ketoximes **133** to 5-cyanated isoxazolines **134**.

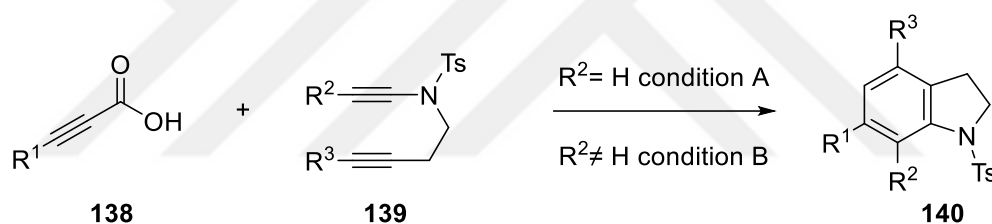
Yuan and colleagues developed a new synthetic pathway to generate ring skeleton of camptothecins by introducing isocyanoarenes **135** and N-(alkyl-2-yn-1-yl)-pyridin-2-(1H)-ones **136** into radical cascade reactions under visible light and photocatalysts.



Scheme 1.21. Radicalic cascade synthesis of quinolin derivative **137** with photocatalyst and visible light.

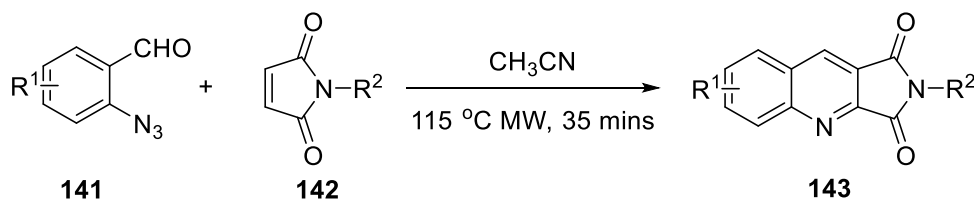
Pericyclic reaction is described first by Woodward and Hoffmann (127). Cyclic structure is formed because of the continuously rearrangement of π electrons in a reaction and the orbitals overlap, these reactions are pericyclic reactions (128,129). The reasons for the usage of pericyclic reactions in cascade reactions include high stereospecificity and spontaneous bond formation. These formations mostly occur in a single step.

Pericyclic cascade reactions are used in the synthesis of complex natural products. A large number of cyclic scaffolds and stereocenters contained in natural products are produced (130–132). As an example, Shen and colleagues developed the synthesis of amino α -pyrones via coupling reaction, then converted these pyrones to indolines **140** and anilines by Diels-Alder cascade reaction. In this process, simple compounds used in synthetic chemistry and bioactive molecules are transformed into desired complex structures and made practicable in pharmaceutical chemistry and total synthesis (133).



Scheme 1.22. Synthesis of indoline derivatives.

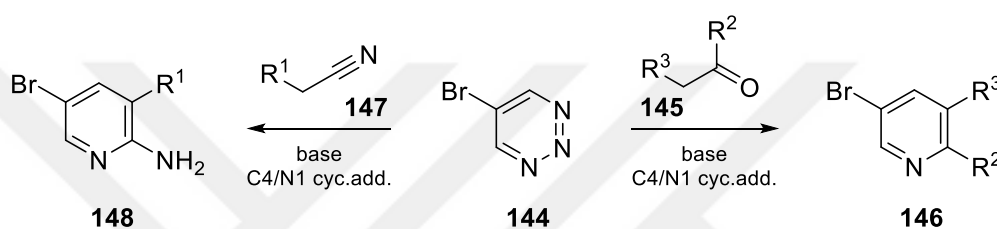
Also, Zhang and his group developed the synthesis of catalyst-free pyrroloquinolinediones **143** and quinolinedicarboxylates. The procedure takes place in one step and involves the formation of the aza-Diels-Alder precursor, $[4+2]$ cycloaddition. As a result of the reaction, it can be considered as green chemistry as it only forms N_2 and H_2O side products (134).



Scheme 1.23. Greener synthesis method of quinoline derivatives.

In nucleophilic cascade reactions, a nucleophilic attack can occur in the beginning or within a cascade reaction. However, other transformations such as rearrangements (135,136), additions (137), cyclizations (138) may occur in the reaction.

Zhang and co-workers developed new synthetic methods of substituted pyridine derivatives via cascade nucleophilic addition of 1,2,3-triazines **144** and activated ketones **145** or acetonitriles **146**. They also achieved bi- and terpyridine derivatives which have pharmaceuticals and bioactive compounds. Furthermore, these compounds may be used as medicinal precursors (139).

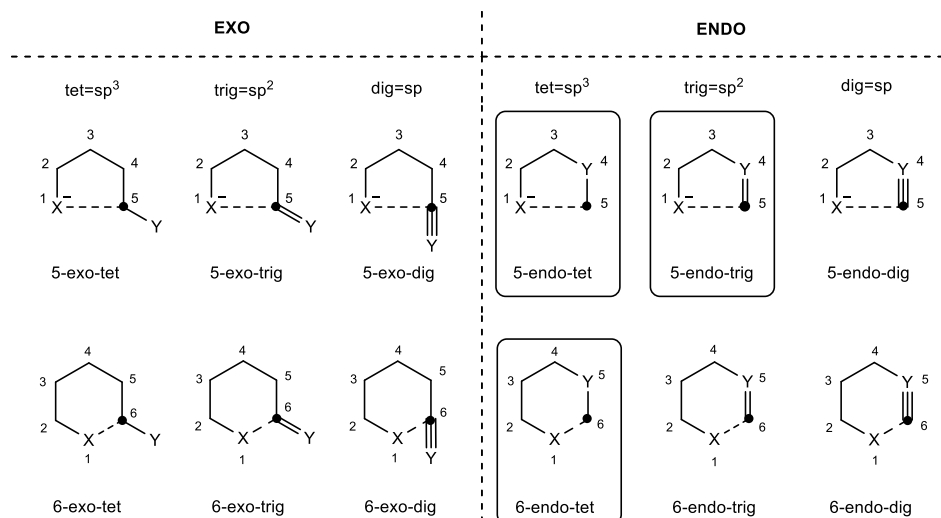


Scheme 1.24. Cascade nucleophilic addition reactions.

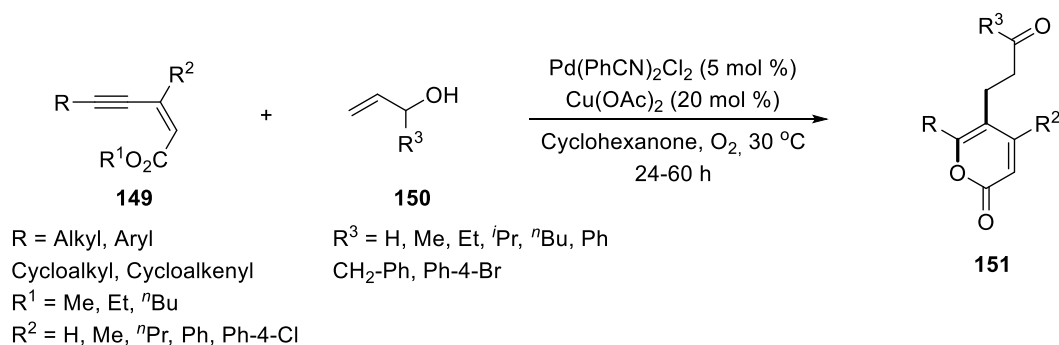
1.4.3 Baldwin's Rule

In 1976 Sir J. E. Baldwin published the "Rules of Ring Closure". By means of these rules, appropriate cyclization can be predicted utilizing the basic geometry and orbital overlap. Baldwin remarked classification of cyclizations in three prefixes basic depends on his rules. First prefix indicates number of atoms in cyclization (≥ 3), seconds prefix indicates bond breaking types outside (-exo) or inside (-endo) and the last one indicates breaking bond hybridizations. These hybridizations are shown as geometrical names, tetrahedral (-tet) for sp^3 , trigonal (-trig) for sp^2 and diagonal (-dig) for sp (140). Despite of these rules, some conditions such as bond length, temperature, reaction types may deviate from these rules (141,142).

Table 1.5. Ring closure of 5- and 6-endo/-exo cyclics. Boxed patterns are unfavourable, however may be formed as intermediate (142).

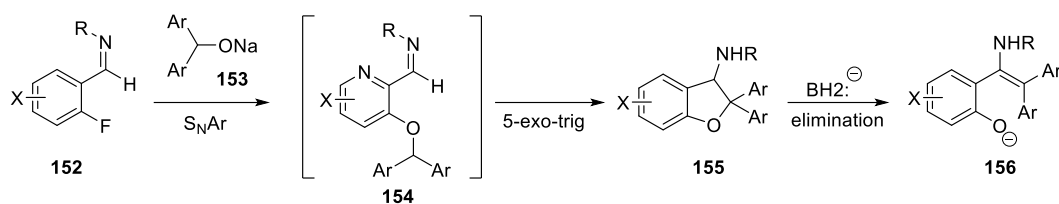


Ahmad et al. submitted Pd(II)-catalyzed cascade cyclization/alkylation reactions of allylic alcohols **150** with enynones **149**. By the help of Pd(II) catalyst, highly regioselective 6-endo-dig cyclization was observed. Further steps, 2-alkanones **151** were produced via β -hydrogen elimination of allylic alcohols (143).



Scheme 1.25. 6-endo-dig cyclization synthesis of α -pyrone

Koy and his team reported synthesis of 3-amino-2,3-dihydro-2,2-diarylbenzofurans **155** from *N*-Alkyl and -arylimines **152** and diarylmethoxide **153** via cascade S_NAr/5-exo-trig cyclization. Diarylmethoxide served as nucleophile in the S_NAr step and catalytic base. In the presence of excess base and time, base-mediated elimination side product **156** was observed (144).

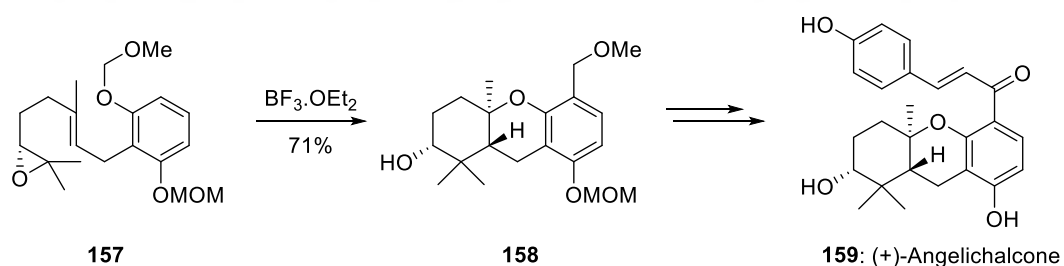


Scheme 1.26. 5-exo-trig cyclization reaction.

1.4.4 Electrophile-Catalyzed Cascade Reactions

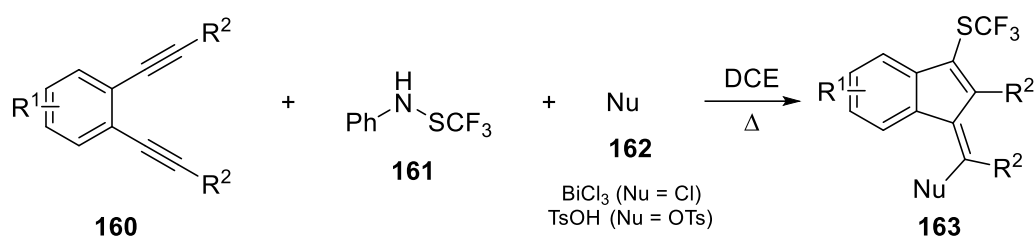
Electrophilic cascade reactions predominate in C-C bond formation in the biosynthesis of terpenoid compounds (145) and has also been used in total synthesis in pharmaceutical chemistry (146). Although many materials are used for the electrophilic cascade reaction, Lewis-acid-catalysts are frequently used as electrophilic precursors (147–150).

For instance, Topczewski et al. synthesized the (+)-Angelichalcone precursor **158** via cyclization-electrophilic aromatic substitution cascade reaction in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. In order to achieve xanthene scaffold, they utilized MOM-protector on resorcinol and further steps to synthesize (+)-Angelichalcone **159** (151).



Scheme 1.27. Electrophilic cascade synthesis of (+)-Angelichalcone.

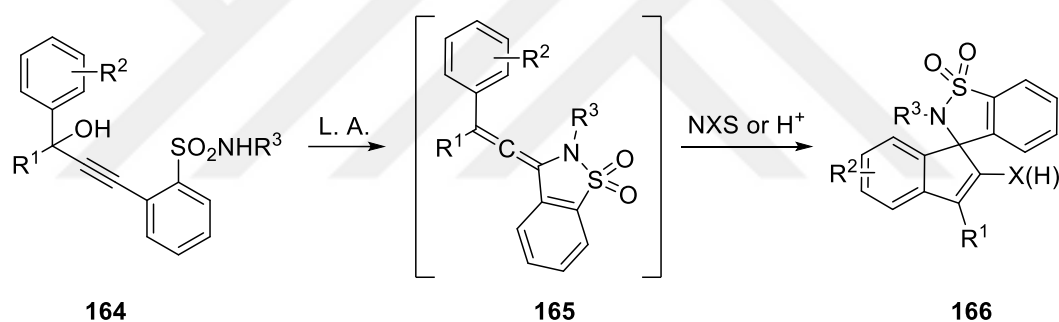
In another example, Xiao and co-workers introduced electrophilic cascade cyclization synthesis of trifluoromethanesulfanylbzofulvenes **163**. The synthesis was started via Lewis-acid BiCl_3 or TsOH . The purpose of these acids provided the activation of trifluoromethanesulfanylamide **161** and then formation of electrophile (CF_3S^+) and nucleophile **162**. They remarked that some organic compounds contain SCF_3 moiety were bioactive (152).



Scheme 1.28. Electrophilic cascade synthesis of TFMS-benzofulvenes.

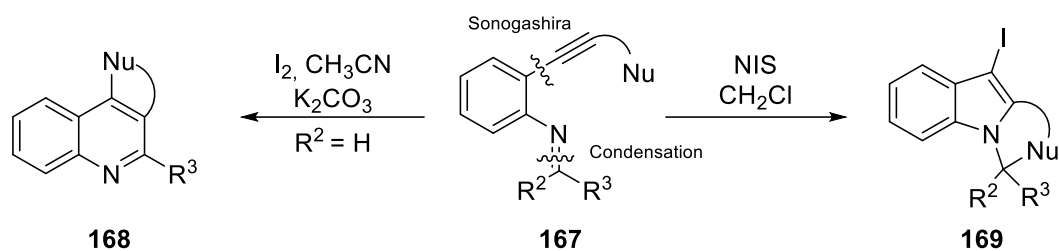
1.4.4.1 Iodine-Catalyzed Electrophilic Cascade Cyclization

Iodine or iodine-based reagents as a Lewis acid, also has an extensive place in electrophilic cascades. For instance, Sun and collaborators developed Lewis-acid-catalyzed cascade spiro [indene-sultam] scaffolds **166** from propargylic alcohols **164**. The process included allene carbocation trapping with sulfonamide **165**, electrophilic spirocyclization by the help of NIS or NBS and intramolecular Friedel-Crafts alkylation (153).



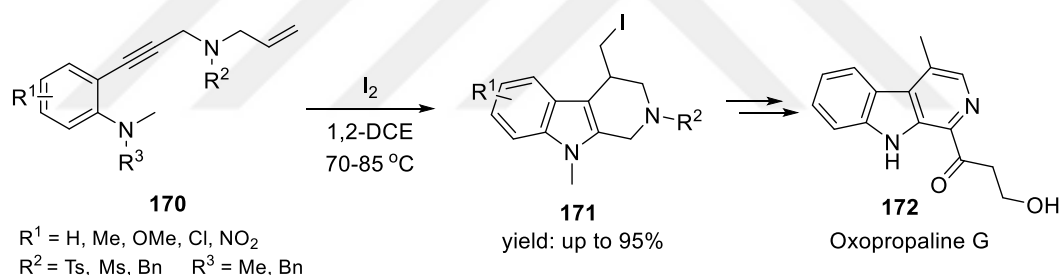
Scheme 1.29. Electrophilic spiro cascade cyclization via iodine cation.

Besides, Halim et al. submitted iodonium-mediated electrophilic cascade reaction generated ring fused quinoline **168** and indole **169** based polycycles. *N*-(*o*-alkynylphenyl)imines **167** intermediate was produced by condensation and Sonogashira coupling. Further two different processes yield quinoline **168** and indole **169** derivatives via electrophilic iodonium addition and intramolecular nucleophilic attack (154).



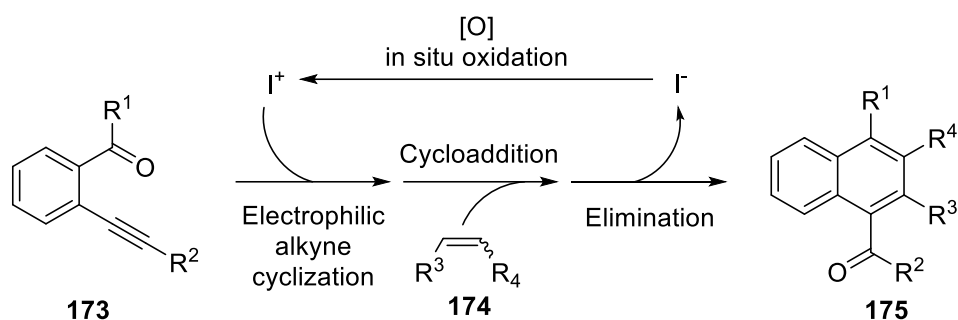
Scheme 1.30. Iodine mediated cascade cyclization for quinolines and indoles.

In the study of Song and co-workers introduced synthesis of 4-iodomethyl substituted tetrahydro- β -carboline **171**. Further steps performed for oxopropaline G **172** that has β -carboline skeleton. These scaffolds have been used in natural products and pharmaceuticals (155–157). Iodine acts as Lewis-acid and coordinates triple bond. In the following intramolecular nucleophilic cyclization occurs via nitrogen atom and forms five-membered cyclic ring. Subsequently, excess iodine coordinate double bond and second cyclization is generated to form 6-membered cyclic ring (158).



Scheme 1.31. Lewis-acid catalyzed tetrahydro- β -carboline synthesis.

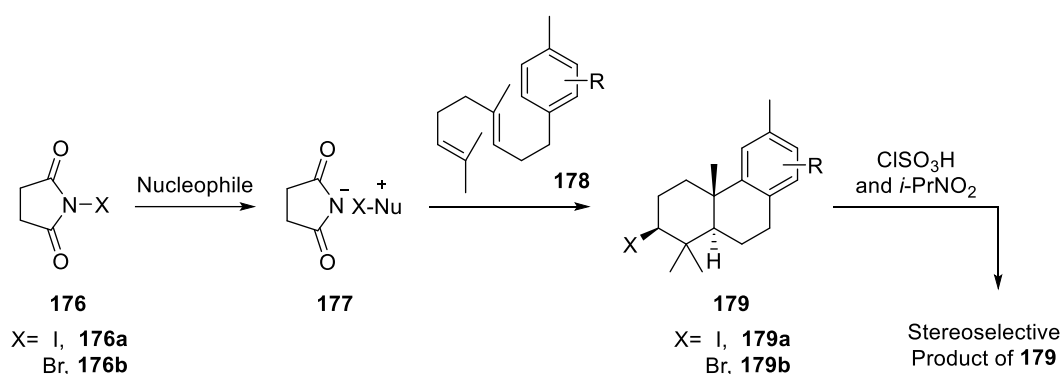
Synthesis of highly substituted 1-naphthalenones **175** via iodocyclization of o-alkynylphenyl carboxaldehydes **173** was reported by Kloeckner and his co-workers. In the reaction, tetrabutylammonium iodide (TBAI) as iodide source, oxone as co-oxidation which help oxidation of iodide ion (I^-) to iodonium ion (I^+), HFIP as fluorinated protic solvent were utilized. The reaction process included halocyclization/cycloaddition/elimination cascades (159).



Scheme 1.32. Electrophilic cascade cyclization involves three steps in one.

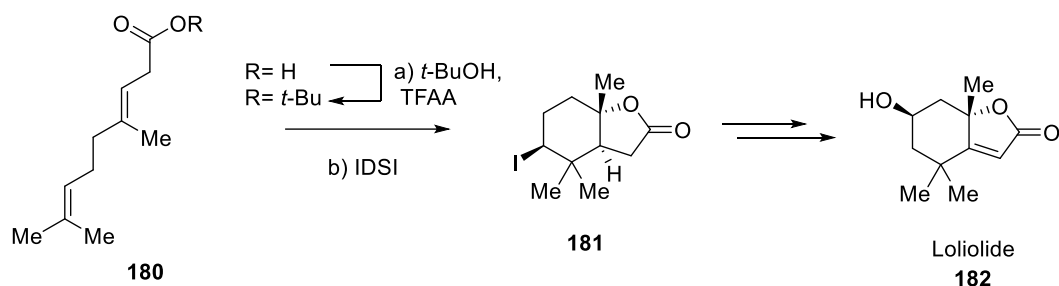
Polyenes are widely used in the synthesis of natural products due to their multiple cyclic structure content. Cascade polyene cyclizations are an effective method to use in the synthesis of natural products, in the construction of multiple bonds, in other words, in achievement molecular complexity (160).

In 2007, Sakakura and co-workers introduced enantioselective electrophilic halocyclization of 4-(homogeranyl)toluene **178** via phosphoramidites that chiral nucleophilic promoters and *N*-halosuccinimides **176**. They pointed that nucleophilic promoters were higher enantioselective than Lewis-acid (161,162) promoters. Chiral phosphoramidates promoted *N*-iodosuccinimide **176a** to yield iodinated cyclic products **179a** up to 99% enantiometric and diastereomeric excess (163). ClSO_3H and *i*-PrNO₂ were utilized to give stereoselective products.



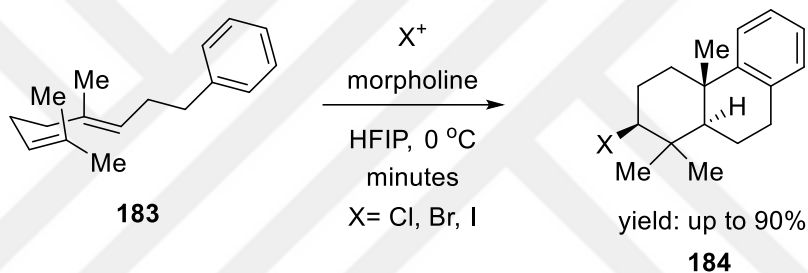
Scheme 1.33. Electrophilic cascade halocyclization of monoterpene.

Besides, Synder et al. published halonium-induced polyene cyclizations. They developed electrophilic I^+ source that iodosulfonium antimonate (IDSI). Application of IDSI to some terpenoids **180** produced precursors for loliolide **182**, K-76 and stemodin in good yields (164).



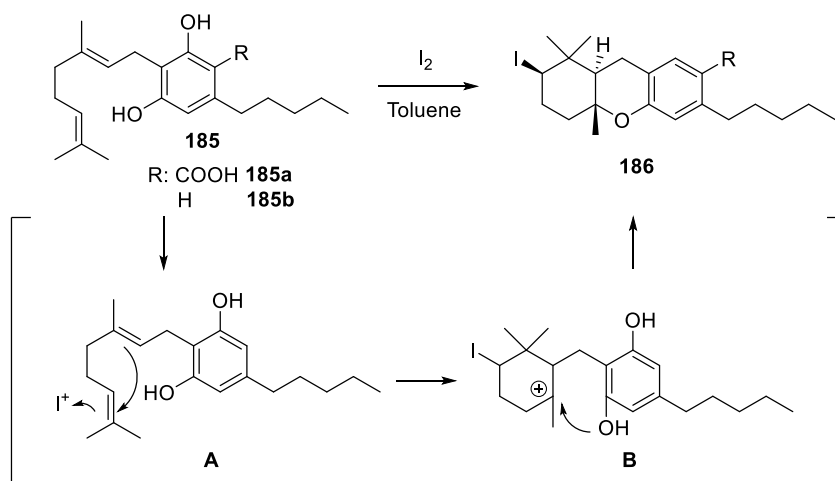
Scheme 1.34. Halonium polyene cascade cyclization of monoterpene.

In 2018, Arnold et al. published different halojen polyene cyclizations in high stereoselectivities and yields. According to previous works, they developed new synthetic method includes Lewis-base morpholine and Lewis-acid HFIP. X^+ reagents are suitable for the biomimetic cation- π cyclization (165).



Scheme 1.35. Lewis-acid/base catalyzed cascade cyclization.

Lopatriello and co-workers submitted iodine-mediated cascade cyclization of cannabigerolic acid **185a** and cannabigerol **185b**. Electrophilic attack on double bond provided intramolecular isoprenoid cyclization (166).



Scheme 1.36. Electrophilic cyclization of cannabigerols.

2. AIM AND SCOPE OF THE STUDY

Terpenes are ingredients that found predominantly in plants, in addition animals, bacteria and fungi. However, herbal terpenes are the most interesting because of their pleasant odors. Geraniol **2**, menthane **5**, limonene **6**, 3-carene **32**, α - and β -pinene **35** etc. are well-known terpenes procured from nature. Terpenes are obtained as essential oils from plants, but they are mixture of lots of terpenes (24). Separation from each other takes many processes, so they are obtained faster and more by the synthetic method.

Geraniol **2** is important terpenoid **27** in perfume industry, it has characteristic rose-like odor, and it is key material to synthesize other terpenoids (7). In current study, we aimed the synthesis of terpenoid-based homogeranyl carbamates **193** starting from geraniol **2** over a radical bromination-substitution-reduction-acylation sequence. After that, homogeranyl carbamates **193** were transformed into trans-iodooctahydroindole carbamates **194** using iodine via electrophilic cascade cyclizations. Also, some of trans-iodooctahydroindole carbamates **194** were reduced into trans-octahydroindole carbamates **195** via catalytic hydrogenation reactions. Furthermore, the olfactory and cytotoxic properties of all the carbamate products were determined.

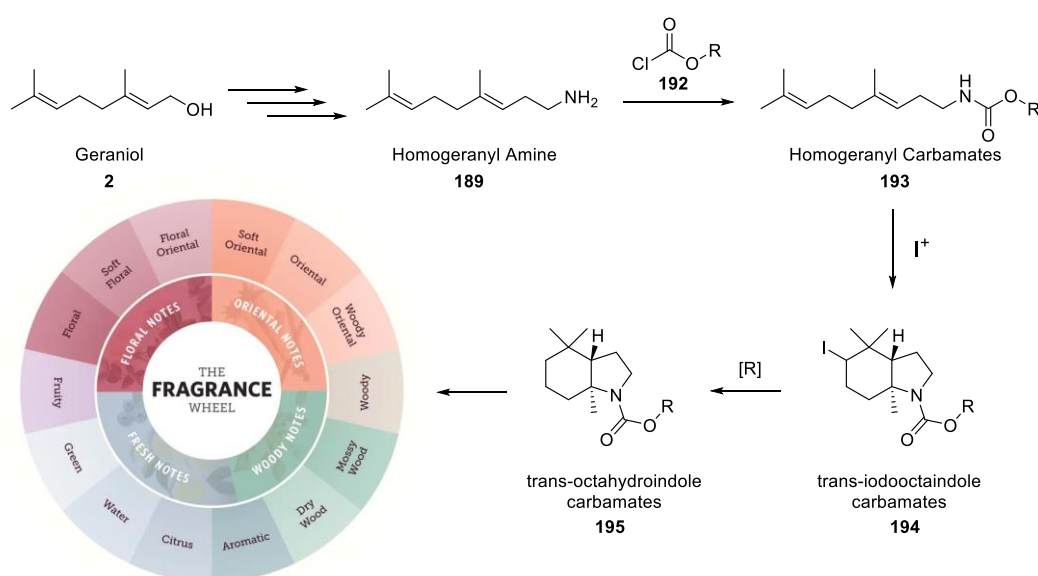


Figure 2.1. Synthetic route of thesis.

3. MATERIALS AND METHODS

Chemicals and starting materials were purchased from commercial suppliers in analytical and reactive grade (Merck, Acros, Sigma-Aldrich, TCI, Isolab, BLDPharm), while solvents were obtained from commercial suppliers in both reactive and technical grades (95%). Also, the technical grade solvents were purified by distillation before use, to ensure their purity and suitability for synthesis, extraction, and chromatographic purification processes. All reactions were carried out at room temperature or at the boiling point of the solvents using Heidolph brand magnetic stirring hotplates. Pd-catalyzed hydrogenation reactions were performed by filling a double-neck flask with hydrogen gas and adding it to the reaction flask equipped with a septum, and additional additions were made if the hydrogen gas level decreased during the reaction. Solvents were evaporated under reduced pressure using a Heidolph Laborota 4000 efficient rotary evaporator. Melting point determinations for solid compounds were conducted using an "Electrothermal IA9200" melting point apparatus, but were not verified. The progress of reactions was monitored using aluminum thin-layer chromatography (TLC) plates (TLC sheets Silica gel 60 F254). The formation of reaction products on TLC plates was visualized by staining with KMnO_4 or PMA and examining under a UV lamp (UVGL-58 Handheld) and cabinet in the range of 254-366 nm wavelengths. All synthesized compounds were purified by column chromatography using a glass column packed with silica gel (CDH, 230-400 mesh for CC). Ethyl acetate-hexane (1:20-1:30) mixtures were used as the mobile phase. FT-IR spectra were recorded using a "Thermo Scientific Nicolet iS20" FT-IR Spectrometer with the ATR method. Proton and carbon-13 NMR spectra were measured at room temperature using a Bruker DPX 400 NMR spectrometer (400 MHz for proton and 100 MHz for carbon) at Balıkesir University BÜBTAM. Chemical shifts (δ) were reported in parts per million (ppm) relative to the TMS internal standard. CDCl_3 or DMSO-d_6 were used as deuterated solvents. Coupling constants (J values) were reported in hertz (Hz). Splitting patterns in proton spectra were classified as singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of quartets (dq), triplet (t), quartet (q), and multiplet (m). High-resolution mass spectra (HR-MS) were acquired in (ESI-) and (ESI+) modes using a liquid chromatography-mass spectrometry system (Agilent 6530 QTOF

LC/MS) at Dumlupınar University ILTEM. GC-MS spectra were obtained using a gas chromatography-mass spectrometry system (Agilent 5975 C GC/MS) at various oven temperatures.

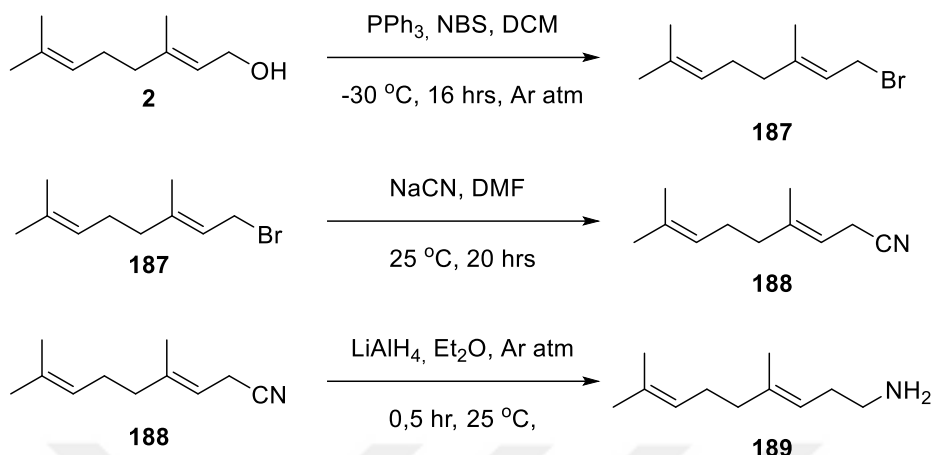
For cytotoxicity tests, the following commercially available materials were utilized in the study: Fetal bovine serum (FBS) (Gibco/BRL, USA), Dulbecco's Modified Eagle Medium (DMEM) (Gibco/BRL) (Supplemented with 1% penicillin and 1% L-glutamine) (Sigma-Aldrich), and Cell Proliferation Kit (XTT based- Biological Industries).

L929 mouse fibroblast cell lines (NCTC clone 929, ATCC CCL1, Rockville Md.) were obtained commercially from ATCC.

During the cytotoxicity studies, the following equipment was employed: Thermo Scientific Multiskan FC (used for ELISA analyses), -80°C freezer (used for storage of cell lines, tissues, and blood samples), Olympus CX41 Fluorescence Microscope (used for cell production control), MMM Medcenter Einrichtungen GmbH Ecocell Etuv (used for heating liquid products), Thermo Scientific Heracell 150 L CO₂ incubator (used for cell production), and Biosafety Cabinet Class II safety cabinet (used for cell production).

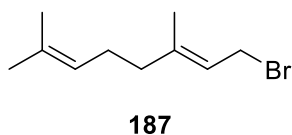
3.1 Experimental

3.1.1 Synthesis of Homogeranyllamine (189)



3.1.1.1 Synthesis of Geranyl Bromide (187)

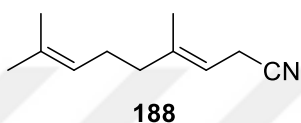
Under argon atmosphere, geraniol **2** (2.0 g, 12.97 mmol, 1.0 eq.) was dissolved in dry DCM (35 mL) at $-30\text{ }^\circ\text{C}$, PPh_3 (3.74 g, 14.26 mmol, 1.1 eq.) was added in mixture. After 5 mins, NBS (2.54 g, 14.26 mmol 1.1 eq.) was added part by part over 20 mins. Reaction turned up for 16 hours (overnight). In the continuation, DCM was evaporated by rotary evaporator and petroleum ether (100 mL) was added to crude mixture and cooled it to $0\text{ }^\circ\text{C}$ under ice bath. Solid phase was removed by filtration and organic phase was extracted with water (3x100 mL), dried with MgSO_4 and evaporated by rotary evaporator. If there is precipitate left, repeat extraction until there is no precipitate. Dry geranyl bromide **187** under high vacuum for 1 hr. and hide at $-20\text{ }^\circ\text{C}$ until usage.



Pale yellow oil, 2.49 g (88.5%). Rf: 0.9 (20% EA: Hex). IR (ATR) (cm^{-1}): 2961-2864 (aliph. CH), 1454 (C=C), 750 (C-Br). ^1H NMR (400 MHz, CDCl_3) δ 5.60 – 5.50 (m, 1H), 5.14 – 5.04 (m, 1H), 4.05 (d, $J = 8.5\text{ Hz}$, 2H), 2.09 (q, $J = 6.5\text{ Hz}$, 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.

3.1.1.2 Synthesis of Geranyl Nitrile (**188**)

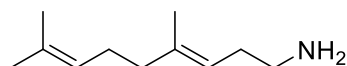
Geranyl bromide **187** (4.0 g, 18.4 mmol, 1.0 eq.) was added drop by drop to the suspension of NaCN (1.8 g, 36.8 mmol, 2.0 eq.) in DMF (10 mL) at 0 °C. After 20 hours, reaction mixture was poured into ice-water (50 mL) and extracted with diethyl ether (3x50 mL). Ether phases were combined and washed with cold water (2x50 mL) and brine solution (1x50 mL) again, dried over Na₂SO₄ and organic solvent was evaporated by rotary evaporator. Obtained geranyl nitrile **188** was purified by column chromatography with EtOAc: Hexane (1:20) mobil phase. After that it was dried under high vacuum to yield pure geranyl nitrile **188**.



Colorless oil, 2.5g (83.0%). Rf: 0.65 (20% EA: Hex). IR (ATR) (cm⁻¹): 2922 (aliph.CH), 2249 (C≡N). ¹H NMR (400 MHz, CDCl₃) δ 5.15 – 5.06 (m, 1H), 5.03 – 4.95 (m, 1H), 2.98 (d, *J* = 6.9 Hz, 2H), 2.07 – 1.93 (m, 4H), 1.62 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 142.7, 132.6, 123.8, 119.1 (C≡N), 112.0, 39.6, 26.6, 26.1, 18.1, 16.8, 16.6.

3.1.1.3 Synthesis of Homogeranylamine (**189**)

Geranyl nitrile **188** (2.5 g, 15.3 mmol, 1.0 eq.), dissolved in dry diethyl ether (15 mL), was added to a separate container containing dry diethyl ether (10 mL) and solution of 1M LiAlH₄ (0.64 g, 16.8 mmol, 1.1 eq.). After stirring of mixture for 15-30 mins at room temperature, 15% NaOH (25 mL) was added slowly drop by drop. Then, mixture was extracted with ethyl acetate (3x20 mL) and organic phase dried over Na₂SO₄ and evaporated by rotary evaporator. Crude homogeranylamine **189** was dried under high vacuum for 1h.

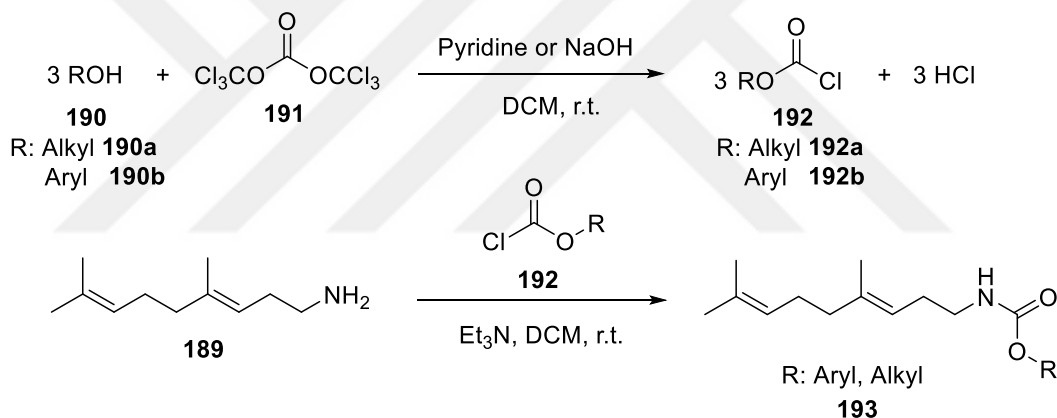


189

Orange oil, 2.0 g (78.0%). IR (ATR) (cm^{-1}): 3290 (NH_2 str.), 2965-2854 (aliph. CH), 1651 (NH bend). ^1H NMR (400 MHz, CDCl_3) δ 5.17 – 5.05 (m, 2H), 2.76 – 2.71 (m, 2H), 2.18 (d, $J = 6.9$ Hz, 2H), 2.14 – 1.98 (m, 4H), 1.70 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H).

3.1.2 Synthesis of Homogeranyl Carbamates (193)

In order to synthesize homogeranyl carbamates, various chloroformates **192** were utilized. Some of them were purchased commercial sources, while some others were prepared using bis(trichloromethyl)carbonate **191** and the related alcohols **190** described in the literature (167).



3.1.2.1 Synthesis of Chloroformates (192)

3.1.2.1.1 Synthesis of Alkyl Chloroformates (192a)

Alkyl alcohol **190a** (9 mmol, 3.0 eq.) was added dropwise to a solution of BTC **191** (3 mmol, 1.0 eq.) in dry DCM (7.5 mL) at 0 °C. After 5 mins, pyridine (9 mmol, 3.0 eq.) in dry DCM (2.5 mL) was added dropwise to reaction mixture over 10 mins, during the addition reaction temperature was kept between 0-5 °C. Reaction was stirred for 1 h in room temperature. Prepared alkyl chloroformate **192a** was used freshly for further reaction without any purification method.

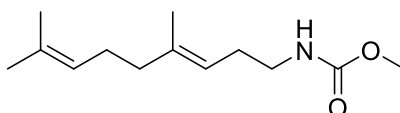
3.1.2.1.2 Synthesis of Aryl Chloroformates (192b)

Aryl alcohol **190b** (9 mmol, 3.0 eq.) in dry DCM (2.5 mL) was added dropwise to a solution of BTC **191** (3 mmol, 1.0 eq.) in dry DCM (7.5 mL) at 0 °C. During the addition reaction temperature was kept between 0-5 °C. After that, sodium hydroxide (9 mmol, 3.0 eq.) in 4 mL water was added and reaction was stirred for 1 h at room temperature. Freshly prepared aryl chloroformate **192b** was transferred to separatory funnel and water layer was separated, organic layer dried over Na₂SO₄ and filtered into further reaction flask.

3.1.2.2 General Method for Synthesis of Homogeranyl Carbamates (193)

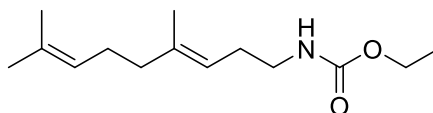
Homogeranyl amine **189** (6 mmol, 1.0 eq.) was dissolved in dry DCM (20 mL) at 0 °C and triethyl amine (6.6 mmol, 1.1 eq.) was added drop wise. After 5 mins, chloroformate **192** (6.6 mmol, 1.1 eq.) in DCM (10 mL) was added. Reaction was stirred for 1 h and temperature raised slowly to room temperature. After an hour, reaction was controlled with TLC and when its solvent was evaporated with rotary evaporator. Obtained crude product was purified by column chromatography, EtOAc: Hexane (1:20) mobile phase and homogeranyl carbamate **193** was achieved.

(E)-methyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193a)



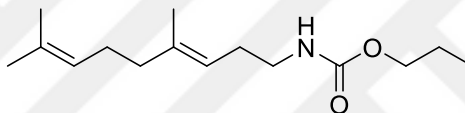
Light yellow oil, 0.1041 g (77%). R_f: 0.55 (20% EA: Hexane). IR (ATR) (cm⁻¹): 3338 (NH str.), 2917 (aliph. CH), 1699 (NHC=O str.), 1251 (C-O-C str.). ¹H NMR (400 MHz, CDCl₃) δ 5.06 (s, 2H), 4.77 – 4.69 (m, 1H), 3.64 (s, 3H), 3.17 (dd, *J* = 12.8, 6.5 Hz, 2H), 2.19 (q, *J* = 6.9 Hz, 2H), 2.11 – 1.96 (m, 4H), 1.67 (s, 3H), 1.60 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 157.0 (C=O), 138.2, 131.6, 124.0, 120.5, 51.9, 40.8, 39.6, 28.3, 26.4, 25.6, 17.6, 16.0. HRMS (TOF-MS APCI⁻): [M]⁺, found 225.17281. C₁₃H₂₃NO₂ requires 225.17288.

(E)-ethyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193b)



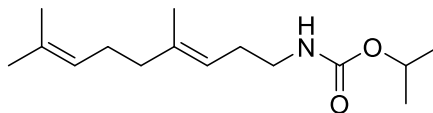
Light yellow oil, 0.122 g (85%). Rf: 0.75 (20% EA: Hexane). IR (ATR) (cm^{-1}): 3338 (NH str.), 2966-2854 (aliph. CH), 1696 (NHC=O str.), 1245 (C-O-C str.). ^1H NMR (400 MHz, CDCl_3) δ 5.07 (t, J = 7.3 Hz, 2H), 4.65 (d, J = 11.0 Hz, NH), 4.17 – 4.05 (m, 2H), 3.23 – 3.13 (m, 2H), 2.19 (q, J = 6.7 Hz, 2H), 2.15 – 1.95 (m, 4H), 1.68 (s, 3H), 1.60 (s, 6H), 1.23 (d, J = 15.6 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.6 (C=O), 138.2, 131.6, 124.2, 124.0, 120.7, 120.5, 60.7, 40.6, 39.6, 28.4, 26.4, 25.6, 17.6, 16.0, 14.6. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 239.18897. $\text{C}_{14}\text{H}_{25}\text{NO}_2$ requires 239.18853.

(E)-propyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193c)



Light yellow oil, 0.760 g (%50). Rf: 0.65 (20% EA: Hexane). IR (ATR) (cm^{-1}): 3341 (NH str.), 2923 (aliph. CH), 1700 (NHC=O str.), 1243 (C-O-C str.). ^1H NMR (400 MHz, CDCl_3) δ 5.04 (dd, J = 12.6, 6.3 Hz, 2H), 4.74 (s, 1H), 3.96 (t, J = 6.7 Hz, 2H), 3.13 (dd, J = 12.8, 6.4 Hz, 2H), 2.16 (q, J = 7.0 Hz, 2H), 2.07 – 1.94 (m, 5H), 1.64 (s, 3H), 1.57 (s, 7H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.7, 138.0, 131.5, 124.0, 120.6, 66.2, 40.7, 39.6, 28.4, 26.4, 25.6, 22.3, 17.6, 16.0, 10.3. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 253.20352. $\text{C}_{15}\text{H}_{27}\text{NO}_2$ requires 253.20418.

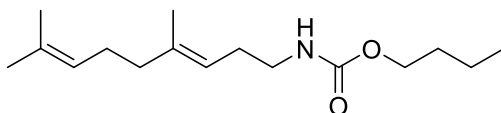
(E)-isopropyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193d)



Light yellow oil, 0.912 g (60%). Rf: 0.70 (20% EA: Hexane). IR (ATR) (cm^{-1}): 3342 (NH str.), 2976 (aliph. CH), 1693 (NHC=O str.), 1250 (C-O-C str.). ^1H NMR (400 MHz, CDCl_3) δ 5.10 – 5.00 (m, 2H), 4.89 (dt, J = 12.4, 6.2 Hz, 1H), 4.66 (s, 1H), 3.15 (dd, J = 12.4, 6.2 Hz, 2H), 2.17 (q, J = 6.9 Hz, 2H), 2.11 – 1.88 (m, 4H), 1.67 (s, 3H), 1.59 (s, 6H), 1.21 (dd, J = 13.3, 5.6 Hz, 6H). ^{13}C NMR

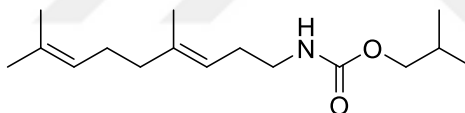
(101 MHz, CDCl₃) δ 156.2, 138.0, 131.5, 124.1, 120.7, 67.7, 40.6, 39.6, 28.4, 26.4, 25.6, 22.1, 17.6, 16.0. HRMS (TOF-MS APCI): [M]⁺, found 253.20217. C₁₅H₂₇NO₂ requires 253.20418.

(*E*)-butyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193e)



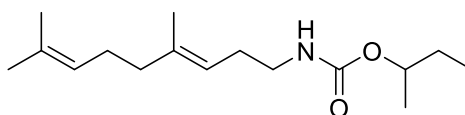
Light yellow oil, 0.1524 g (95%). Rf: 0.85 (20% EA: Hexane). IR (ATR) (cm⁻¹): 3339 (NH str.), 2960 (aliph. CH), 1697 (NHC=O str.), 1247 (C-O-C str.). ¹H NMR (400 MHz, CDCl₃) δ 5.03 (s, 2H), 4.76 (s, 1H), 4.02 – 3.96 (m, 2H), 3.14 – 3.10 (m, 2H), 2.18 – 2.10 (m, 2H), 2.05 – 1.93 (m, 4H), 1.63 (d, *J* = 4.7 Hz, 3H), 1.56 (s, 8H), 1.33 (dd, *J* = 16.1, 10.3 Hz, 2H), 0.88 (dd, *J* = 12.3, 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 156.7, 138.0, 131.5, 124.1, 120.6, 64.5, 40.7, 39.6, 31.10, 28.4, 26.4, 25.6, 25.6, 19.0, 17.6, 15.9, 13.7. HRMS (TOF-MS APCI): [M]⁺, found 267.22039. C₁₆H₂₉NO₂ requires 267.21983.

(*E*)-isobutyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193f)



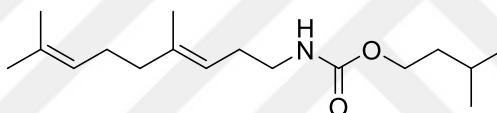
Light yellow oil, 0.1123 g (70%). Rf: 0.65 (20% EA: Hexane). IR (ATR) (cm⁻¹): 3339 (NH str.), 2962 (aliph. CH), 1696 (NHC=O str.), 1246 (C-O-C str.). ¹H NMR (400 MHz, CDCl₃) δ 5.06 – 5.00 (m, 2H), 4.76 (s, 1H), 3.79 (d, *J* = 6.5 Hz, 2H), 3.12 (s, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 2.01 (dq, *J* = 19.4, 7.6 Hz, 5H), 1.93 – 1.79 (m, 1H), 1.64 (d, *J* = 0.5 Hz, 3H), 1.56 (d, *J* = 3.5 Hz, 6H), 0.87 (d, *J* = 6.7 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 156.8, 138.0, 131.5, 124.1, 120.6, 70.8, 40.7, 39.6, 28.4, 27.99, 26.4, 25.6, 19.0, 17.6, 16.0. HRMS (TOF-MS APCI): [M]⁺, found 267.21975. C₁₆H₂₉NO₂ requires 267.21983.

(E)-sec-butyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193g)



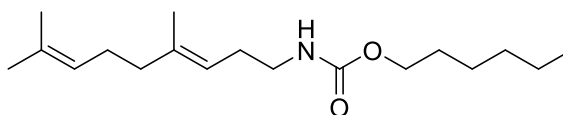
Light yellow oil, 0.1283 g (%80). Rf: 0.70 (20% EA : Hekzan). IR (ATR) (cm⁻¹): 3341 (NH str.), 2968 (aliph. CH), 1693 (NHC=O str.), 1250 (C-O-C str.). ¹H NMR (400 MHz, CDCl₃) δ 5.01 (dd, *J* = 14.1, 7.1 Hz, 2H), 4.78 (s, 1H), 4.66 (dt, *J* = 12.5, 6.1 Hz, 2H), 3.10 (dd, *J* = 12.8, 6.4 Hz, 2H), 2.13 (dd, *J* = 14.0, 7.0 Hz, 2H), 1.98 (dq, *J* = 19.7, 7.4 Hz, 5H), 1.61 (s, 3H), 1.53 (s, 6H), 1.45 (ddd, *J* = 20.5, 14.0, 6.9 Hz, 2H), 1.12 (d, *J* = 6.2 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 156.4, 137.8, 131.4, 124.1, 124.0, 120.8, 120.7, 72.2, 40.6, 39.6, 29.1, 28.4, 26.4, 25.6, 19.7, 17.5, 15.9, 9.6. HRMS (TOF-MS APCI): [M]⁺, found 267.22019. C₁₆H₂₉NO₂ requires 267.21983.

(E)-isopentyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193h)



Light yellow oil, 0.1098 g (68%). Rf: 0.75 (20% EA: Hexane). IR (ATR) (cm⁻¹): 3339 (NH str.), 2923 (aliph. CH), 1701 (NHC=O str.), 1248 (C-O-C str.). ¹H NMR (400 MHz, CDCl₃) δ 5.06 (d, *J* = 6.8 Hz, 2H), 4.63 (s, 1H), 4.07 (t, *J* = 6.7 Hz, 2H), 3.17 (d, *J* = 6.2 Hz, 2H), 2.18 (q, *J* = 6.9 Hz, 2H), 2.11 – 1.97 (m, 4H), 1.68 (s, 3H), 1.60 (s, 6H), 1.50 (dt, *J* = 13.5, 7.2 Hz, 2H), 0.90 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 156.8, 138.1, 131.6, 124.1, 120.7, 63.4, 40.7, 39.7, 37.8, 28.4, 26.5, 25.7, 24.9, 22.5, 17.7, 16.1. HRMS (TOF-MS APCI): [M]⁺, found 281.23519. C₁₇H₃₁NO₂ requires 281.23548.

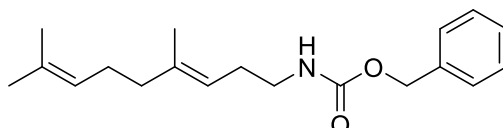
(E)-hexyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193i)



Light yellow oil, 0.1206 g (50%). Rf: 0.80 (20% EA: Hexane). IR (ATR) (cm⁻¹): 3339 (NH str.), 2925 (aliph. CH), 1697 (NHC=O str.), 1249 (C-O-C str.). ¹H NMR (400 MHz, CDCl₃) δ 5.03 (dd, *J* = 12.8, 6.3 Hz, 2H), 4.77 (s, 1H), 3.99 (t, *J* = 6.7 Hz, 2H), 3.13 (dd, *J* = 12.8, 6.4 Hz, 2H), 2.15 (dd, *J* = 14.0, 7.0 Hz,

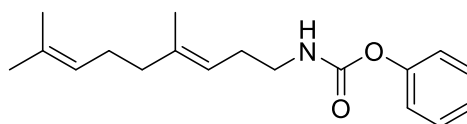
2H), 2.01 (dq, $J = 18.9, 7.4$ Hz, 5H), 1.64 (s, 3H), 1.56 (s, 7H), 1.26 (t, $J = 15.0$ Hz, 7H), 0.84 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.7, 137.9, 131.5, 124.1, 120.6, 64.8, 40.7, 39.6, 31.5, 29.0, 28.4, 26.4, 25.6, 25.5, 22.5, 17.6, 15.9, 13.9. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 295.25137. $\text{C}_{18}\text{H}_{33}\text{NO}_2$ requires 295.25113.

(*E*)-benzyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193j)



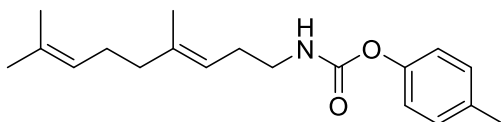
Light yellow oil, 0.905 g (50%). Rf: 0.80 (20% EA: Hekzan). IR (ATR) (cm^{-1}): 3339 (NH str.), 2923 (aliph. CH), 1701 (NHC=O str.), 1248 (C-O-C str.). ^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.28 (m, 5H), 5.07 (dd, $J = 8.1, 6.9$ Hz, 4H), 4.83 (s, 1H), 3.20 (dd, $J = 12.8, 6.5$ Hz, 2H), 2.20 (dd, $J = 13.8, 6.8$ Hz, 2H), 2.11 – 1.95 (m, 4H), 1.67 (s, 3H), 1.59 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.4, 138.2, 136.6, 131.6, 128.5, 128.1, 128.1, 124.1, 120.5, 66.5, 40.8, 39.7, 28.4, 26.5, 25.7, 17.7, 16.1. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 301.20198. $\text{C}_{19}\text{H}_{27}\text{NO}_2$ requires 301.20418.

(*E*)-phenyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193k)



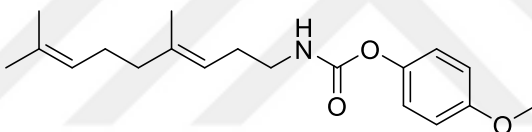
White solid, 0.948 g (55%). m.p. 48-52°C. Rf: 0.70 (20% EA: Hexane). IR (ATR) (cm^{-1}): 3335 (NH str.), 2922 (aliph. CH), 1715 (NHC=O str.), 1200 (C-O-C str.). ^1H NMR (400 MHz, CDCl_3) δ 7.38 (t, $J = 7.9$ Hz, 2H), 7.21 (t, $J = 7.4$ Hz, 1H), 7.15 (d, $J = 7.8$ Hz, 2H), 5.18 – 5.09 (m, 2H), 4.87 (s, 1H), 3.29 (dd, $J = 12.9, 6.6$ Hz, 2H), 2.30 (q, $J = 6.9$ Hz, 2H), 2.17 – 2.05 (m, 4H), 1.73 (s, 3H), 1.68 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 154.6 (C=O), 151.0, 138.5, 131.7, 129.3, 125.2, 124.1, 121.6, 120.4, 41.0, 39.7, 28.2, 26.5, 25.7, 17.7, 16.1. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 287.18747. $\text{C}_{18}\text{H}_{25}\text{NO}_2$ requires 287.18853.

(E)-p-tolyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193l)



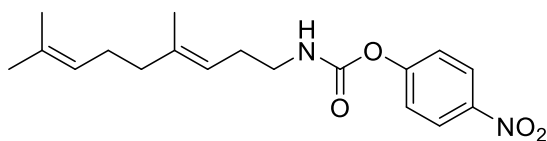
White solid, 0.1719 g (95%). m.p. 67°C. Rf: 0.75 (20% EA: Hexane). IR (ATR) (cm⁻¹): 3344 (NH str.), 2919 (aliph. CH), 1702 (NHC=O str.), 1256 (C-O-C str.). ¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 5.16 – 5.07 (m, 2H), 5.03 (s, 1H), 3.27 (q, *J* = 6.5 Hz, 2H), 2.34 (s, 3H), 2.28 (dd, *J* = 13.8, 6.9 Hz, 2H), 2.14 – 2.03 (m, 5H), 1.71 (s, 3H), 1.66 (s, 3H), 1.62 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 154.8, 148.8, 138.5, 134.8, 131.7, 129.8, 124.1, 121.4, 120.4, 77.4, 77.0, 76.73, 40.9, 39.7, 28.2, 26.5, 25.74, 20.9, 17.7, 16.1. HRMS (TOF-MS APCI): [M]⁺, found 301.19616. C₁₉H₂₇NO₂ requires 301.20418.

(E)-4-methoxyphenyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193m)



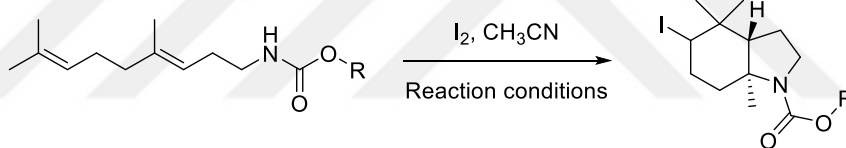
White solid, 0.1867 g (98%). m.p. 49-51°C. Rf: 0.50 (20% EA: Hexane). IR (ATR) (cm⁻¹): 3338 (NH str.), 2922 (aliph. CH), 1715 (NHC=O str.), 1196 (C-O-C str.). ¹H NMR (400 MHz, CDCl₃) δ 7.04 – 6.99 (m, 2H), 6.88 – 6.83 (m, 2H), 5.15 – 5.07 (m, 2H), 5.06 (dd, *J* = 6.5, 5.1 Hz, 1H), 3.78 (s, 3H), 3.25 (dd, *J* = 12.9, 6.6 Hz, 2H), 2.26 (q, *J* = 6.9 Hz, 2H), 2.16 – 1.98 (m, 4H), 1.69 (s, 3H), 1.64 (s, 3H), 1.61 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 156.8, 155.0, 144.5, 138.5, 131.7, 124.1, 122.5, 120.4, 114.3, 77.4, 77.05, 76.73, 55.6, 40.97, 39.7, 28.2, 26.5, 25.7, 17.7, 16.1. HRMS (TOF-MS APCI): [M]⁺, found 317.19770. C₁₉H₂₇NO₃ requires 317.19909.

(E)-4-nitrophenyl (4,8-dimethylnona-3,7-dien-1-yl)carbamate (193n)



Light yellow solid, 0.704 g (35%). m.p. 54-56°C. Rf: 0.75 (20% EA: Hexane). IR (ATR) (cm^{-1}): 3338 (NH str.), 2965 (aliph. CH), 1695 (NHC=O str.), 1246 (C-O-C str.). ^1H NMR (400 MHz, CDCl_3) δ 8.22 (d, J = 9.1 Hz, 2H), 7.29 (d, J = 9.1 Hz, 2H), 5.21 (s, 1H), 5.09 (dt, J = 12.7, 6.8 Hz, 2H), 3.28 (q, J = 6.5 Hz, 2H), 2.28 (dd, J = 13.9, 6.9 Hz, 2H), 2.12 – 2.00 (m, 4H), 1.68 – 1.56 (m, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 155.9, 153.1, 144.6, 138.9, 131.7, 125.1, 124.0, 120.0, 41.1, 39.7, 28.1, 26.4, 25.7, 17.7, 16.1. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 332.17153. $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_4$ requires 332.17361.

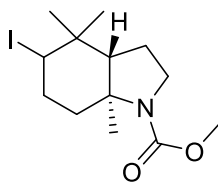
3.1.3 Synthesis of trans-5-iodo-trimethyloctahydroindole carbamates (194)



A. (Without base) Homogeranyl carbamate **193** (1 mmol) was dissolved in dry acetonitrile (10 mL) at 0 °C and stirred for 2-3 minutes, after that iodine (3 mmol) was added part by part. Reaction temperature was increased from 0 °C to 25 °C slowly. Reaction controlled with TLC at every 15 minutes until all homogeranyl carbamate **193** consumed. Reaction was finished about 1 h. Saturated sodium thiosulfate solution (1-2 mL) was added to reaction mixture until pale yellow color occurred. Following, extraction was applied with DCM (3x10 mL) and organic phase was dried over Na_2SO_4 , filtered and organic solvent evaporated by rotary evaporator. Obtained crude product was purified with column chromatography, (EA: Hex, 1:25- 1:20) mobile phase and silica gel and pure trans-5-iodotrimethyloctahydroindole carbamate **194** product was obtained.

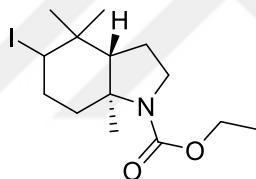
B. (With base) Same procedure with A method, however K_2CO_3 (3 mmol) was added with homogeranyl carbamate **193** at the beginning of reaction.

Methyl 5-iodo-trimethyloctahydroindole carbamate (194a)



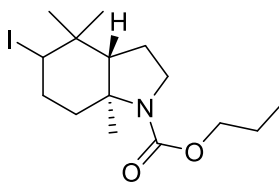
White solid, 0.245 g (70%). M.p. 115-117 °C. Rf: 0.55 (20% EA: Hexane) IR (ATR) (cm⁻¹): 2957-2864 (aliph. CH), 1681 (C=O str.), 1446 (CH₂ bend.), 1133 (C-O-C str.), 556 (C-I). ¹H NMR (400 MHz, CDCl₃) δ 4.08 (dt, *J* = 12.6, 3.7 Hz, 1H, I-CH), 3.64 (d, *J* = 18.0 Hz, 3H, OCH₃), 3.48 – 3.26 (m, 2H, CH₂N), 2.53 – 2.20 (m, 3H), 1.92 – 1.45 (m, 4H), 1.20 (s, 3H, CH₃), 1.00 (d, *J* = 9.5 Hz, 6H, 2xCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 155.43, 154.29 (C=O), 61.31 (CH₃-C-N), 61.06, 55.54, 55.10 (C-H), 51.95, 51.68, 49.20, 48.96, 45.61, 45.00, 41.38, 40.90 (C-I), 38.61, 35.23, 32.50, 29.71, 23.38, 22.84, 20.46, 18.88, 17.89. HRMS (TOF-MS APCI⁻): [M]⁺, found 351.06376. C₁₅H₂₆INO₂ requires 351.06952.

Ethyl 5-iodo-trimethyloctahydroindole carbamate (194b)



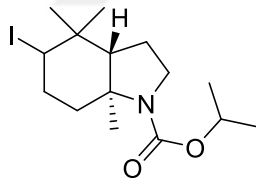
White solid, 0.292 g (80%). M.p. 98-100 °C. Rf: 0.50 (20% EA: Hexane). IR (ATR) (cm⁻¹): 2953-2867 (aliph. CH), 1692 (C=O str.), 1458 (CH bend.), 1126 (C-O-C str.), 579 (C-I str.). ¹H NMR (400 MHz, CDCl₃) δ 4.10 (dp, *J* = 19.8, 7.1 Hz, 3H, O-CH₂ and I-CH), 3.38 (tq, *J* = 19.8, 10.7 Hz, 2H, CH₂N), 2.54 – 2.22 (m, 3H), 1.94 – 1.48 (m, 4H), 1.25 (m, 3H, OCH₂-CH₃), 1.21 (s, 3H), 1.02 (d, *J* = 9.4 Hz, 6H, 2xCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 155.07, 154.02 (C=O), 61.24 (CH₃-C-N), 61.11, 60.70, 60.22, 55.62 (C-H), 55.15, 49.28, 49.11, 45.50, 45.00, 41.55, 40.98 (C-I), 38.65, 35.28, 32.54, 32.51, 29.73, 23.35, 22.85, 20.46, 18.81, 17.88, 14.78. HRMS (TOF-MS APCI⁻): [M]⁺, found 365.08360. C₁₄H₂₄INO₂ requires 365.08517.

Propyl 5-iodo-trimethyloctahydroindole carbamate (194c)



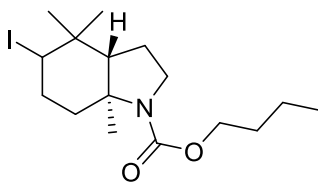
White solid, 0.281 g (74%). M.p. 60 °C. Rf: 0.60 (20% EA: Hexane). IR (ATR) (cm⁻¹): 2963-2887 (aliph. CH), 1692 (C=O str.), 1455 (CH bend.), 1130 (C-O-C str.), 557 (C-I str.). ¹H NMR (400 MHz, CDCl₃) δ 4.07 (dd, *J* = 12.9, 4.4 Hz, 1H, I-CH), 3.98 (dt, *J* = 28.5, 6.6 Hz, 2H, O-CH₂), 3.44 – 3.28 (m, 2H, CH₂N), 2.52 – 2.21 (m, 3H), 1.90 – 1.49 (m, 6H), 1.17 (d, *J* = 14.0 Hz, 3H, OCH₂-CH₃), 0.99 (d, *J* = 9.5 Hz, 6H, 2xCH₃), 0.92 (td, *J* = 7.4, 4.4 Hz, 3H, OC₂H₅-CH₃). ¹³C NMR (101 MHz, CDCl₃) δ 155.15, 154.06 (C=O), 66.53, 65.86, 61.19 (CH₃-C-N), 61.10, 55.59 (C-H), 55.11, 49.32, 49.00, 45.52, 44.95, 41.55, 40.95 (C-I), 38.63, 35.27, 32.51, 23.33, 22.85, 22.47, 22.38, 20.45, 18.84, 17.86, 10.80, 10.49. HRMS (TOF-MS APCI⁻): [M]⁺, found 379.09700. C₁₅H₂₆INO₂ requires 379.10082.

***i*-Propyl 5-iodo-trimethyloctahydroindole carbamate (194d)**



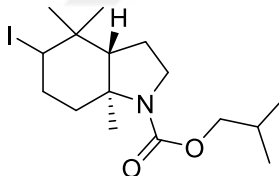
White solid, 0.266 g (70%). M.p. 75-77 °C. Rf: 0.56 (20% EA: Hexane). IR (ATR) (cm⁻¹): 2970-2887 (aliph. C-H), 1686 (C=O str.), 1454 (C-H bend.), 1112 (C-O-C str.), 556 (C-I). ¹H NMR (400 MHz, CDCl₃) δ 4.88 (d, *J* = 14.2 Hz, 2H, O-CH₂), 4.08 (dd, *J* = 12.8, 4.6 Hz, 1H, I-CH), 3.35 (t, *J* = 9.4 Hz, 2H, CH₂-N), 2.53 – 2.17 (m, 3H), 1.90 – 1.48 (m, 4H), 1.22 – 1.12 (m, 8H), 0.99 (d, *J* = 9.2 Hz, 6H, 2xCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 154.59, 154.02 (C=O), 67.90, 67.27, 61.08 (CH₃-C-N), 55.58 (C-H), 55.12, 49.38, 49.13, 45.36, 44.97, 41.66, 41.02 (C-I), 38.63, 35.29, 32.51, 31.94, 31.52, 31.46, 30.18, 30.13, 29.67, 29.38, 23.26, 22.85, 22.71, 22.35, 20.44, 18.73, 17.86. HRMS (TOF-MS APCI⁻): [M]⁺, found 379.10511. C₁₅H₂₆INO₂ requires 379,10082.

Butyl 5-iodo-trimethyloctahydroindole carbamate (194e)



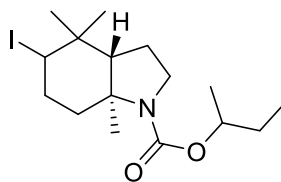
White solid, 0.279 g (71%). M.p. 48-50 °C. Rf: 0.57 (20% EA: Hexane). IR (ATR) (cm⁻¹): 2956-2864 (aliph. C-H), 1687 (C=O str.), 1467 (C-H bend.), 1139 (C-O-C str.), 554 (C-I str.). ¹H NMR (400 MHz, CDCl₃) δ 4.08 – 3.91 (m, 3H, O-CH₂ and I-CH), 3.33 (tq, *J* = 19.7, 10.6 Hz, 2H, CH₂-N), 2.54 – 2.12 (m, 3H), 1.88 – 1.44 (m, 7H), 1.32 (dq, *J* = 13.1, 6.5 Hz, 2H), 1.13 (d, *J* = 16.2 Hz, 2H), 0.96 (d, *J* = 9.4 Hz, 6H, 2x CH₃), 0.87 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 155.12, 154.04 (C=O), 64.66, 64.13, 61.16, 61.05 (CH₃-C-N), 55.54 (C-H), 55.08, 49.34, 49.21, 49.02, 48.88, 45.49, 44.92, 41.50, 40.92 (C-I), 38.58, 35.23, 32.46, 31.16, 31.15, 23.28, 22.80, 20.40, 19.34, 19.19, 18.78, 17.85, 17.80, 13.79, 13.75. HRMS (TOF-MS APCI-): [M]⁺, found 393.11079. C₁₆H₂₈INO₂ requires 393.11647.

***i*-Butyl 5-iodo-trimethyloctahydroindole carbamate (194f)**



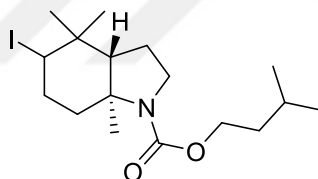
White solid, 0.271 g (69%). M.p. 44-46 °C. Rf: 0.56 (20% EA: Hexane). IR (ATR) (cm⁻¹): 2957-2872 (aliph. C-H str.), 1696 (C=O str.), 1455 (C-H bend.), 1130 (C-O-C str.), 558 (C-I str.). ¹H NMR (400 MHz, CDCl₃) δ 4.07 (m, 1H, I-CH), 3.89 – 3.72 (m, 2H, O-CH₂), 3.42 – 3.32 (m, 2H, CH₂-N), 2.52 – 2.21 (m, 3H), 1.98 – 1.47 (m, 8H), 0.99 (d, *J* = 9.4 Hz, 6H, 2xCH₃), 0.91 (t, *J* = 6.1 Hz, 6H, 2xCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 155.19, 154.04 (C=O), 71.29, 70.42, 61.18, 61.11 (CH₃-C-N), 55.59 (C-H), 55.10, 49.37, 49.24, 48.98, 48.85, 45.58, 44.92, 41.60, 40.94 (C-I), 38.64, 38.61, 35.26, 32.51, 32.48, 28.07, 28.00, 23.32, 22.84, 20.45, 20.42, 19.42, 19.37, 19.15, 17.88, 17.82. HRMS (TOF-MS APCI-): [M]⁺, found 393.11503. C₁₆H₂₈INO₂ requires 393.11647.

sec-Butyl 5-iodo-trimethyloctahydroindole carbamate (194g)



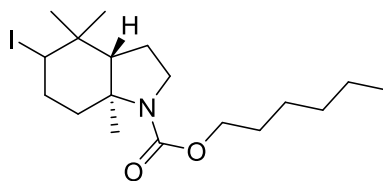
Light yellow oil, 0.236 g (60%). Rf: 0.55 (20% EA: Hexane). IR (ATR) (cm^{-1}): 2966-2886 (aliph. CH str.), 1686 ($\text{C}=\text{O}$ str.), 1454 (CH bend.), 1125 (C-O-C str.), 556 (C-I str.). ^1H NMR (400 MHz, CDCl_3) δ 4.72 (ddt, $J = 25.4, 12.6, 6.3$ Hz, 1H, O-CH), 4.10 (dd, $J = 13.1, 4.4$ Hz, 1H, CH-I), 3.39 (m, 2H, $\text{CH}_2\text{-N}$), 2.56 – 2.20 (m, 3H), 1.92 – 1.50 (m, 7H), 1.23 – 1.08 (m, 5H), 1.02 (dd, $J = 9.3, 2.2$ Hz, 6H, $2\times\text{CH}_3$), 0.90 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 154.91, 154.05 ($\text{C}=\text{O}$), 72.73, 71.99, 61.28 ($\text{CH}_3\text{-C-N}$), 55.77 (C-H), 55.27, 49.59, 49.27, 45.59, 45.09, 41.86, 41.21 (C-I), 38.84, 35.48, 32.72, 32.68, 29.35, 29.31, 23.44, 23.01, 20.64, 20.60, 20.18, 20.14, 20.04, 20.00, 18.92, 17.97, 9.96. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 393.11673. $\text{C}_{16}\text{H}_{28}\text{INO}_2$ requires 393.11647.

i-Amyl 5-iodo-trimethyloctahydroindole carbamate (194h)



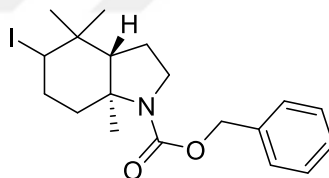
Light yellow oil, 0.293 g (72%). Rf: 0.60 (20% EA: Hexane). IR (ATR) (cm^{-1}): 2956-2869 (aliph. C-H str.), 1693 ($\text{C}=\text{O}$ str.), 1455 (C-H bend.), 1130 (C-O-C str.), 557 (C-I str.). ^1H NMR (400 MHz, CDCl_3) δ 4.10 – 3.93 (m, 3H, O- CH_2 and I-CH), 3.38 – 3.26 (m, 2H, $\text{CH}_2\text{-N}$), 2.52 – 2.14 (m, 3H), 1.88 – 1.40 (m, 8H), 1.13 (d, $J = 17.2$ Hz, 2H, O- $\text{CH}_2\text{-CH}_2$), 0.96 (d, $J = 9.5$ Hz, 6H, $2\times\text{CH}_3$), 0.87 (d, $J = 6.7$ Hz, 6H, $2\times\text{CH}_3$). ^{13}C NMR (101 MHz, CDCl_3) δ 155.08, 154.01 ($\text{C}=\text{O}$), 63.41, 62.94, 61.16, 61.04 ($\text{CH}_3\text{-C-N}$), 55.54 (C-H), 55.06, 49.27, 48.94, 45.49, 44.93, 41.49, 40.92 (C-I), 38.59, 38.58, 37.79, 37.75, 35.24, 32.47, 25.16, 25.06, 23.29, 22.80, 22.55, 22.53, 22.44, 20.41, 18.82, 17.83. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 407.13105. $\text{C}_{17}\text{H}_{30}\text{INO}_2$ requires 407.13212.

Hexyl 5-iodo-trimethyloctahydroindole carbamate (194i)



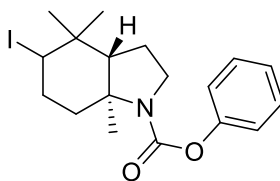
Light yellow oil, 0.295 g (70 %). Rf: 0.60 (20% EA: Hexane). IR (ATR) (cm^{-1}): 2954-2867 (aliph. C-H str.), 1692 (C=O str.), 1454 (C-H bend.), 1131 (C-O-C str.), 557 (C-I str.). ^1H NMR (400 MHz, CDCl_3) δ 4.10 – 3.92 (m, 3H, O-CH₂ and I-CH), 3.34 (ddt, J = 27.7, 18.8, 10.7 Hz, 2H, CH₂-N), 2.51 – 2.17 (m, 3H), 1.90 – 1.47 (m, 7H), 1.36 – 1.20 (m, 6H, hexyl CH₂), 1.15 (d, J = 15.4 Hz, 2H), 0.97 (d, J = 9.4 Hz, 6H, 2xCH₃), 0.84 (t, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 155.12, 154.05 (C=O), 64.95, 64.43, 61.17, 61.06 (CH₃-C-N), 55.56 (C-H), 55.09, 49.29, 48.98, 45.49, 44.93, 41.53, 40.93 (C-I), 38.60, 35.24, 32.48, 31.46, 31.37, 29.05, 28.94, 25.73, 25.64, 23.31, 22.82, 22.55, 22.52, 20.42, 18.81, 17.84, 14.03. HRMS (TOF-MS APCI⁺): $[\text{M}]^+$, found 421.14816. $\text{C}_{18}\text{H}_{32}\text{INO}_2$ requires 421.14777.

Benzyl 5-iodo-trimethyloctahydroindole carbamate (194j)



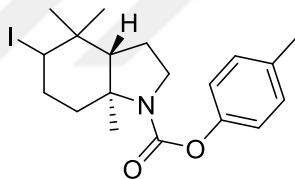
White solid, 0.261 g (61%). M.p. 74-76 °C. Rf: 0.50 (20% EA: Hexane). IR (ATR) (cm^{-1}): 2960-2887 (aliph. C-H str.), 1694 (C=O str.), 1454 (C-H bend.), 557 (C-I str.). ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, J = 5.7 Hz, 5H, C=C-H), 5.12 (d, J = 21.3 Hz, 2H, O-CH₂), 4.09 (td, J = 11.8, 4.4 Hz, 1H, CH-I), 3.42 (qd, J = 11.5, 8.7 Hz, 2H, CH₂-N), 2.57 – 2.22 (m, 3H), 1.95 – 1.53 (m, 4H), 1.33 – 1.16 (m, 3H), 1.08 – 0.81 (m, 6H, 2xCH₃). ^{13}C NMR (101 MHz, CDCl_3) δ 153.63 (C=O), 138.92, 137.13, 128.47, 128.02, 127.83, 127.69, 124.39, 123.51, 66.77, 65.99, 61.46 (CH₃-C-N), 55.62, 55.13 (C-H), 49.15, 48.85, 45.72, 45.13, 41.54, 40.92 (CHI), 38.65, 35.25, 35.00, 32.76, 32.52, 31.97, 31.55, 31.48, 30.21, 30.16, 30.08, 29.75, 29.70, 29.41, 23.36, 22.86, 22.74, 20.46. HRMS (TOF-MS APCI⁺): $[\text{M}]^+$, found 427.10556. $\text{C}_{19}\text{H}_{26}\text{INO}_2$ requires 427.10082.

Phenyl 5-iodo-trimethyloctahydroindole carbamate (194k)



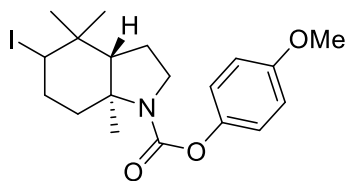
White solid, 0.310 g (75%). M.p. 69-70 °C. Rf: 0.45 (20% EA: Hexane). IR (ATR) (cm⁻¹): 2927-2866 (aliph. C-H str.), 1716 (C=O str.), 1493 (C-H bend.), 490 (C-I str.). ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.08 (m, 5H, C=C-H), 4.12 (m, 1H, CH-I), 3.66 – 3.54 (m, 2H, CH₂-N), 2.56 – 2.22 (m, 3H), 2.02 – 1.58 (m, 4H), 1.32 (d, *J* = 17.9 Hz, 3H), 1.06 (dd, *J* = 10.0, 1.9 Hz, 6H, 2xCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 154.32 (C=O), 151.51, 151.07, 129.42, 129.31, 129.22, 125.24, 125.10, 121.90, 121.80, 121.64, 115.31, 61.89 (CH₃-C-N), 55.63 (C-H), 55.12, 48.87, 48.49, 45.91, 45.63, 41.50, 40.71 (C-I), 38.73, 38.70, 35.20, 32.53, 29.74, 23.48, 22.90, 20.50, 19.34, 17.99, 14.28, 13.45. HRMS (TOF-MS APCI): [M]⁺, found 413.08164. C₁₈H₂₄INO₂ requires 413.08517.

p-Tolyl 5-iodo-trimethyloctahydroindole carbamate (194l)



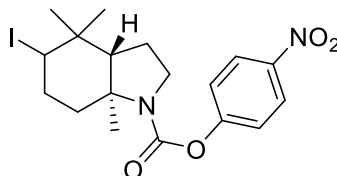
White solid, 0.352 g (76%). M.p. 115-117 °C. Rf: 0.65 (20% EA: Hexane). IR (ATR) (cm⁻¹): 2956-2853 (aliph. C-H str.), 1721 (C=O str.), 1455 (C-H bend.), 1204 (C-O-C str.), 516 (C-I str.). ¹H NMR (400 MHz, CDCl₃) δ 7.15 (dd, *J* = 8.6, 3.1 Hz, 2H, O=C=CH), 6.98 (d, *J* = 8.2 Hz, 2H, C=CH), 4.12 (dd, *J* = 12.9, 4.5 Hz, 1H, I-CH), 3.64 – 3.47 (m, 2H, CH₂-N), 2.55 – 2.39 (m, 3H), 2.00 – 1.79 (m, 4H), 1.68 (dtd, *J* = 41.0, 11.4, 4.6 Hz, 3H), 1.30 (m, 3H), 1.06 (d, *J* = 9.8 Hz, 6H, 2xCH₃). ¹³C NMR (101 MHz, CDCl₃) δ 153.14, 152.13 (C=O), 148.81, 134.76, 134.59, 129.80, 129.68, 121.59, 121.33, 61.81 (CH₃-C-N), 55.64, 55.12 (C-H), 48.97, 48.60, 45.87, 45.59, 41.51, 40.73 (C-I), 38.70, 35.23, 32.54, 30.21, 30.16, 29.74, 29.70, 23.48, 22.91, 20.87, 20.50, 19.31, 17.97. HRMS (TOF-MS APCI): [M]⁺, found 427.09713. C₁₈H₂₄INO₂ requires 427.10082.

p-Methoxyphenyl 5-iodo-trimethyloctahydroindole carbamate (194m)



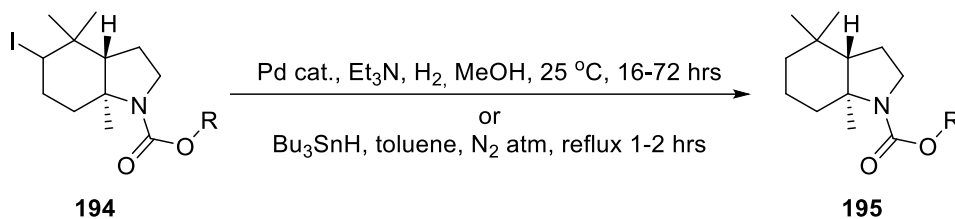
White solid, 0.386 g (87%). M.p. 78-80 °C. Rf: 0.55 (20% EA: Hexane). IR (ATR) (cm^{-1}): 2957-2856 (aliph. C-H str.), 1708 (C=O str.), 1506 (C-H bend.), 1206 (C-O-C str.), 611 (C-I str.). ^1H NMR (400 MHz, CDCl_3) δ 7.02 (m, 2H, O-C=CH), 6.87 (m, 2H, $\text{CH}_3\text{O-C=CH}$), 4.13 (dt, $J = 12.8, 3.7$ Hz, 1H, I-CH), 3.80 (d, $J = 2.9$ Hz, 3H, O- CH_3), 3.69 – 3.40 (m, 2H, $\text{CH}_2\text{-N}$), 2.55 – 2.24 (m, 3H), 2.02 – 1.56 (m, 4H), 1.29 (m, 3H), 1.06 (dd, $J = 10.1, 2.0$ Hz, 6H, $2\times\text{CH}_3$). ^{13}C NMR (101 MHz, CDCl_3) δ 156.75, 153.33 (C=O), 152.31, 144.62, 144.58, 122.71, 122.47, 114.34, 114.24, 61.83, 61.77 ($\text{CH}_3\text{-C-N}$), 55.65 (C-H), 55.12, 48.94, 48.57, 45.88, 45.57, 41.52, 40.73 (C-I), 38.73, 38.70, 35.22, 35.00, 32.53, 31.96, 31.54, 31.47, 30.20, 30.15, 29.74, 29.41, 23.49, 22.90, 22.74, 20.52, 20.49, 19.31, 17.97. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 443.09536. $\text{C}_{19}\text{H}_{26}\text{INO}_2$ requires 443.09524.

p-Nitrophenyl 5-iodo-trimethyloctahydroindole carbamate (194n)



White solid, 0.321 g (70%). M.p. 135-137 °C. Rf: 0.40 (20% EA: Hexane). IR (ATR) (cm^{-1}): 2965-2895 (aliph. C-H str.), 1721 (C=O str.), 1513 (NO_2 asym. str.), 1372 (NO_2 sym. str.) 1120 (C-O-C str.), 510 (C-I str.). ^1H NMR (400 MHz, CDCl_3) δ 8.25 – 8.16 (m, 2H, $\text{NO}_2\text{-C=CH}$), 7.32 – 7.22 (m, 2H, O-C=CH), 4.07 (m, 1H, I-CH), 3.63 – 3.51 (m, 2H, $\text{CH}_2\text{-N}$), 2.49 – 2.20 (m, 3H), 2.04 – 1.54 (m, 4H), 1.29 (d, $J = 15.1$ Hz, 3H), 1.03 (dd, $J = 11.5, 2.3$ Hz, 6H, $2\times\text{CH}_3$). ^{13}C NMR (101 MHz, CDCl_3) δ 156.10 (C=O), 155.96, 151.27, 150.23, 144.65 (C- NO_2), 144.46, 125.11, 124.97, 122.18, 122.00, 62.32 ($\text{CH}_3\text{-C-N}$), 62.21, 55.53 (C-H), 55.04, 48.27, 47.70, 46.12, 45.80, 41.39, 40.48 (CHI), 38.67, 35.05, 32.46, 23.43, 22.85, 20.47, 19.54, 18.00. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 458.07082. $\text{C}_{18}\text{H}_{23}\text{IN}_2\text{O}_4$ requires 458.07025.

3.1.4 Synthesis of trans-trimethyloctahydroindole carbamates



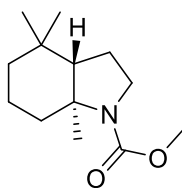
3.1.4.1 General method for synthesis trans-trimethyloctahydroindole carbamates **195** via Pd catalyst

5-iodotrimethyloctahydroindole carbamate **194** (0.4 mmol) was dissolved in dry methanol (10 mL), and then 5% Pd/C (3-5 mg) and triethylamine (0.45 mmol) were added. After passing nitrogen through the resulting mixture for 5 minutes, it was connected to a reaction flask equipped with a septum, which was filled with H₂ gas using a balloon or gas inlet. The reaction progress was monitored by TLC until completion (16-72 hours). Once completed, the reaction mixture was filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified by column chromatography (1:15 EA: Hexane).

3.1.4.2 General method for synthesis of trans-trimethyloctahydroindole carbamates **195** via tributyltin hydride (Alternative method)

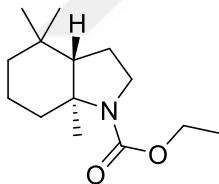
trans-5-iodotrimethyloctahydroindole carbamate **194** (1 mmol) was placed in dry toluene (50 mL) under a nitrogen atmosphere and brought to reflux temperature. Tributyltin hydride (10 mmol) was added to the mixture. The reaction mixture was stirred for 1-2 hours, or until the starting compound is consumed, as confirmed by TLC analysis. After completion of the reaction, the mixture was cooled and toluene was removed. The resulting crude product was dissolved in acetonitrile (10 mL) and extracted with hexane (3 × 10 mL) to remove organotin residues. The acetonitrile was evaporated, and the obtained trans-product was purified by column chromatography (1:15 EA: Hexane).

Methyl trans-trimethyloctahydroindole carbamate (195a)



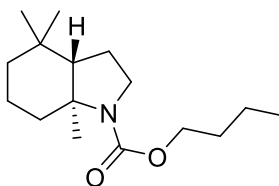
Colorless oil, 0.086 g (95%). Rf: 0.52 (20% EA: Hex). IR (ATR) (cm^{-1}): 2952-2866 (aliph. C-H str.), 1696 (C=O str.), 1443 (CH_2 bend.), 1127 (C-O-C str.). ^1H NMR (400 MHz, CDCl_3) δ 3.62 (d, J = 17.7 Hz, 3H, O- CH_3), 3.33 (ddt, J = 51.8, 28.9, 10.4 Hz, 2H, CH_2N), 2.70 – 2.42 (m, 1H), 1.77 (d, J = 11.3 Hz, 2H), 1.68 – 1.47 (m, 4H), 1.47 – 1.38 (m, 2H), 1.23 (s, 3H, N-C- CH_3), 0.90 (s, 3H, CH_3), 0.84 (s, 3H, CH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 155.78, 154.48 (C=O), 61.99, 61.67 (CH_3 -C-N), 57.67, 57.49, 57.29 (C-H), 51.94, 51.64 (O- CH_3), 51.34, 51.06, 45.53, 44.86, 40.88, 40.68, 38.68, 38.50, 38.30, 38.10, 37.92, 29.73, 21.34, 21.10, 18.97, 14.24, 14.03. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 225.17290. $\text{C}_{13}\text{H}_{23}\text{NO}_2$ requires 225.17288.

Ethyl trans-trimethyloctahydroindole carbamate (195b)



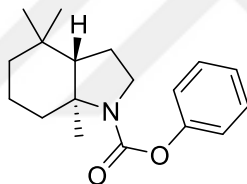
Colorless oil, 0.079 g (83%). Rf: 0.65 (20% EA: Hex). IR (ATR) (cm^{-1}): 2953-2853 (aliph. C-H str.), 1697 (C=O str.), 1461 (CH_2 bend.). ^1H NMR (400 MHz, CDCl_3) δ 4.10 (dq, J = 20.6, 6.8 Hz, 2H, O- CH_2), 3.38 (dd, J = 40.6, 30.1 Hz, 2H, CH_2N), 2.69 – 2.59 (m, 1H), 1.77 (ddt, J = 22.1, 16.2, 8.4 Hz, 2H), 1.69 – 1.45 (m, 4H), 1.48 – 1.22 (m, 4H), 1.22 (s, J = 7.0 Hz, 3H, N-C- CH_3), 1.12 (dt, J = 10.2, 5.7 Hz, 2H), 0.91 (s, 3H, CH_3), 0.85 (s, 3H, CH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 155.42 (C=O), 154.33 (C=O), 61.80 (CH_3 -C-N), 60.27 (O- CH_2), 57.48 (C-H), 45.11, 40.94, 38.53, 33.03, 32.98, 32.96, 32.20, 32.11, 21.93, 21.86, 21.77, 21.19, 20.83, 20.76, 18.15, 14.90. HRMS (TOF-MS APCI): $[\text{M}-2\text{H}]^+$ found 237.17105. $\text{C}_{14}\text{H}_{25}\text{NO}_2$ requires 237.17288.

Butyl trans-trimethyloctahydroindole carbamate (195e)



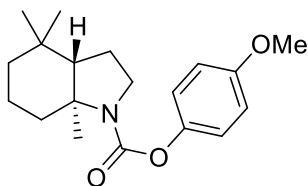
Colorless oil, 0.086 g (75%). Rf: 0.60 (20% EA: Hex). IR (ATR) (cm^{-1}): 2955-2867 (aliph. C-H str.), 1693 (C=O str.), 1456 (CH_2 bend.), 1126 (C-O-C str.). ^1H NMR (400 MHz, CDCl_3) δ 4.13 – 3.97 (m, 2H, O- CH_2), 3.44 – 3.27 (m, 2H, CH_2 -N), 2.54 (dd, $J = 92.4, 14.7$ Hz, 1H), 1.81 – 1.73 (m, 2H), 1.61 (q, $J = 14.4$ Hz, 6H), 1.48 – 1.31 (m, 2H), 1.25 (s, 3H, N-C- CH_3), 1.13 (d, $J = 17.9$ Hz, 2H), 1.00 – 0.81 (m, 9H, 3x CH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 155.66, 154.46 (C=O), 64.69, 64.16, 61.99 (CH_3 -C-N), 57.80, 57.40 (C-H), 45.57, 45.04, 41.00, 39.00, 38.42, 33.02, 31.42, 29.93, 21.49, 20.91, 19.50, 18.06, 14.07. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 267.21961. $\text{C}_{16}\text{H}_{29}\text{NO}_2$ requires 267.21983.

Phenyl trans-trimethyloctahydroindole carbamate (195k)



Colorless oil, 0.069 g (60%). Rf: 0.59 (20% EA: Hex). IR (ATR) (cm^{-1}): 2953-2853 (aliph. C-H str.), 1723 (C=O), 1457 (CH_2 bend.), 1206 (C-O-C str.). ^1H NMR (400 MHz, CDCl_3) δ 7.36 (td, $J = 7.8, 3.5$ Hz, 2H), 7.19 (dt, $J = 13.4, 6.7$ Hz, 1H), 7.13 (d, $J = 7.7$ Hz, 2H), 3.59 – 3.39 (m, 2H, CH_2 -N), 2.64 (dd, $J = 29.7, 11.8$ Hz, 1H), 1.87 (dq, $J = 17.9, 8.6$ Hz, 2H), 1.77 – 1.61 (m, 4H), 1.61 – 1.45 (m, 2H), 1.34 – 1.24 (m, 3H, N-C- CH_3), 0.98 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 153.34 (C=O), 152.19, 151.46, 129.37, 129.05, 125.12, 124.97, 122.24, 122.08, 121.95, 121.79, 62.76 (CH_3 -C-N), 57.87, 57.42 (C-H), 54.90, 54.38, 46.04, 45.90, 45.69, 45.52, 41.07, 40.79, 38.96, 38.15, 33.16, 33.11, 32.98, 32.15, 21.92, 21.63, 20.99, 20.87, 20.83, 19.59, 19.50, 18.23, 18.14. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 287.18736. $\text{C}_{18}\text{H}_{25}\text{NO}_2$ requires 287.18853.

p-Methoxyphenyl trans-trimethyloctahydroindole carbamate (195m)

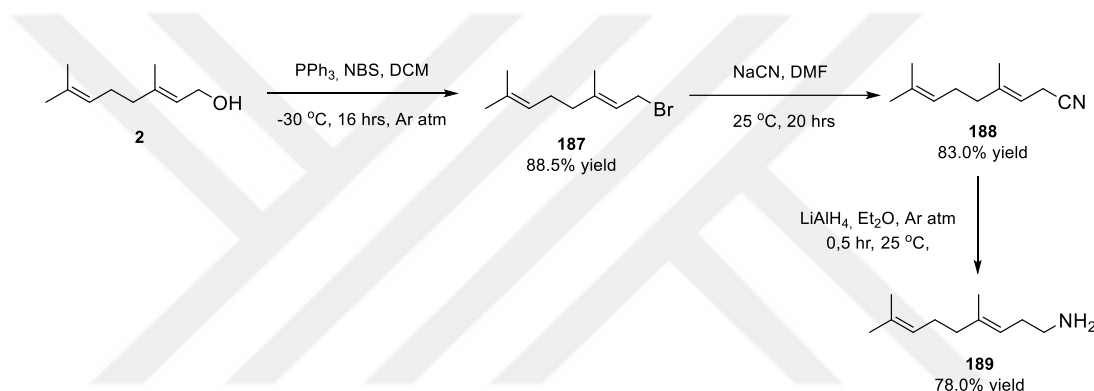


White solid, 0.114 g (90%). M.p. 90-92 °C. Rf: 0.52 (20% EA: Hex). IR (ATR) (cm^{-1}): 2953-2856 (aliph. C-H str.), 1720 (C=O str.), 1507 (CH_2 bend.), 1197 (C-O-C str.). ^1H NMR (400 MHz, CDCl_3) δ 7.01 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H, O- CH_3), 3.40 – 3.26 (m, 2H, CH_2 -N), 2.31 (d, J = 12.3 Hz, 1H, C-H), 1.85 – 1.74 (m, 2H), 1.65 (d, J = 10.3 Hz, 2H), 1.59 – 1.29 (m, 4H), 1.24 (s, 3H, N-C- CH_3), 1.10 (s, 3H, CH_3), 0.93 (s, 3H, CH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 156.81 (C=O), 152.60, 145.08, 123.29, 122.74, 114.72, 114.12, 62.96 (CH_3 -C-N), 56.45 (C-H), 56.14, 55.75, 46.54, 35.12, 32.91, 32.38, 31.47, 29.69, 26.04, 24.73, 19.50. HRMS (TOF-MS APCI): $[\text{M}]^+$, found 317.19856. $\text{C}_{19}\text{H}_{27}\text{NO}_3$ requires 317.19909.

4. RESULTS AND DISCUSSIONS

4.1 Synthesis of Starting Compounds

In our study, the synthesis of main precursors, homogeranyyl carbamates **193** were primarily carried out from homogeranylamine **189**. To achieve this, a three-step route was followed, beginning with the conversion of geraniol **2** into geranyl bromide **187** through radical bromination. Subsequently, geranyl bromide underwent a nucleophilic displacement reaction with NaCN to give geranyl nitrile **188**. In the final step, the reduction of geranyl nitrile with lithium aluminum hydride resulted in the formation of the main starting compound, homogeranylamine **189**.



Scheme 4.1 Synthesis route of homogeranylamine **189**.

In the first step, a slight increase by 15-20% in reaction yield was observed when the synthesis of geranyl bromide **187** was conducted under an inert atmosphere. The addition of *N*-bromosuccinimide (NBS) was carried out over a 20-minute period. Rapid addition of NBS results in a color change of the reaction mixture from yellow to pink and leads to a decrease in yield by approx. 30%. The crude product obtained from the reaction is dried under high vacuum and used without purification in the next step, the product was stored at $-20\text{ }^\circ\text{C}$ until use (3.1.1.1.).

Characterised by IR, proton NMR and carbon-13 NMR after isolation. Spectrums proved structure **187** we expected (Figure 4.1-4.3).

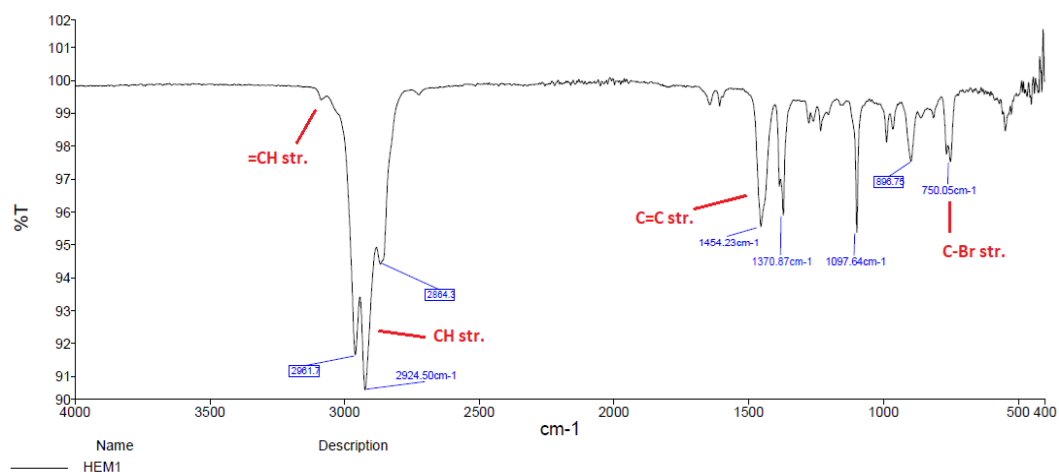


Figure 4.1. IR spectrum of homogeranyl bromide **187**.

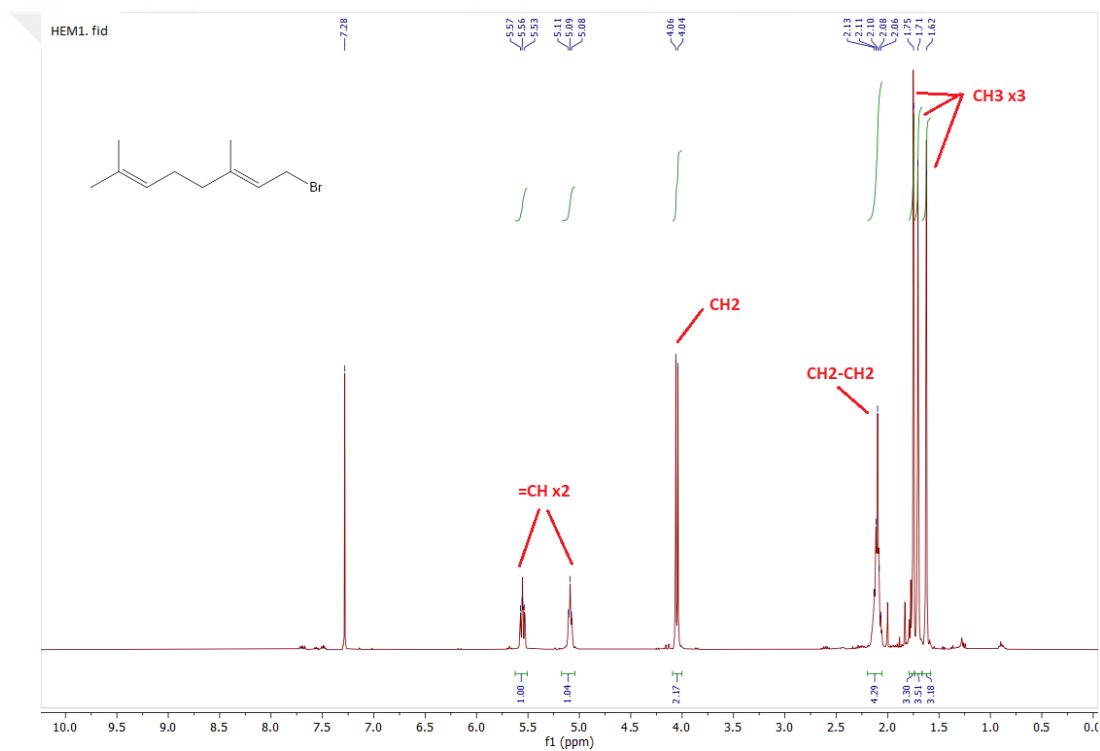


Figure 4.2. ^1H NMR spectrum of homogeranyl bromide **187**.

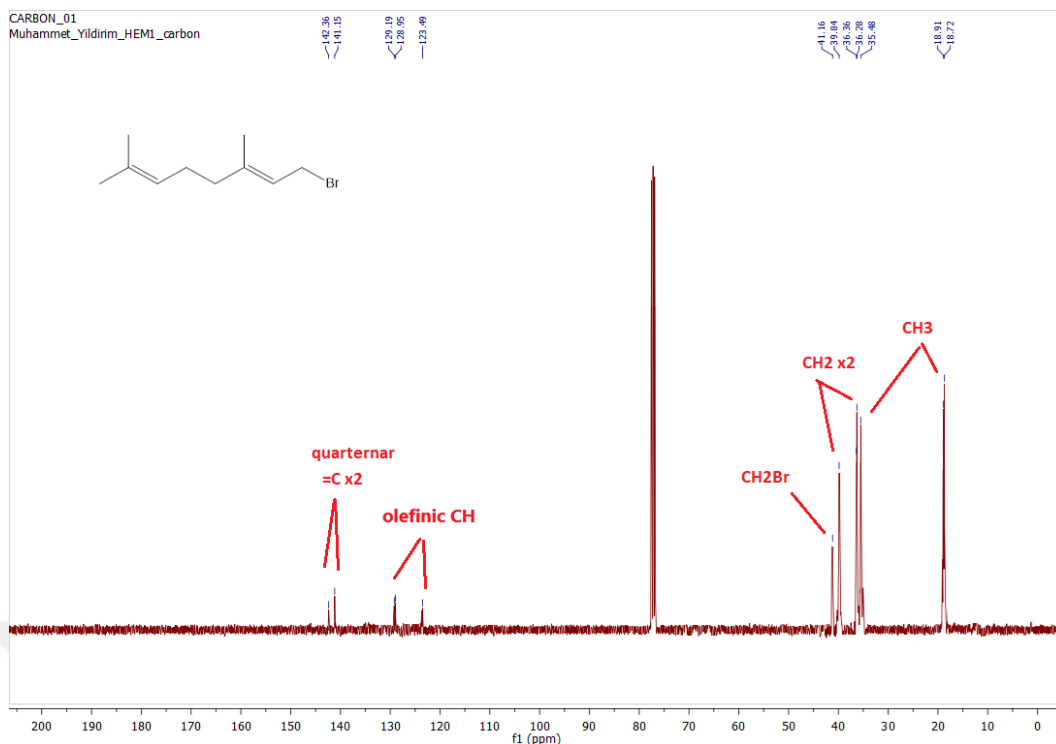


Figure 4.3. ^{13}C NMR spectrum of homogeranyl bromide **187**.

In the second step, prior to the addition of geranyl bromide **187**, the NaCN was allowed to stir in dimethylformamide (DMF) for about 30 minutes. The reaction mixture in DMF was poured into ice-cold water to extract geranyl nitrile **188** in a cold environment. Given that DMF is high boiling solvent to remove, the DMF-water phase is initially extracted three times with diethyl ether (alternatively, ethyl acetate). Subsequently, the diethyl ether phases are combined, washed twice with water and removed under vacuum. The crude geranyl nitrile **188** is then purified by CC and dried under high vacuum and the product was stored at -20°C until use (3.1.1.2.).

Characterised by IR, proton NMR and carbon-13 NMR after purification. Spectrums proved structure **188** we expected (Figure 4.4-4.6).

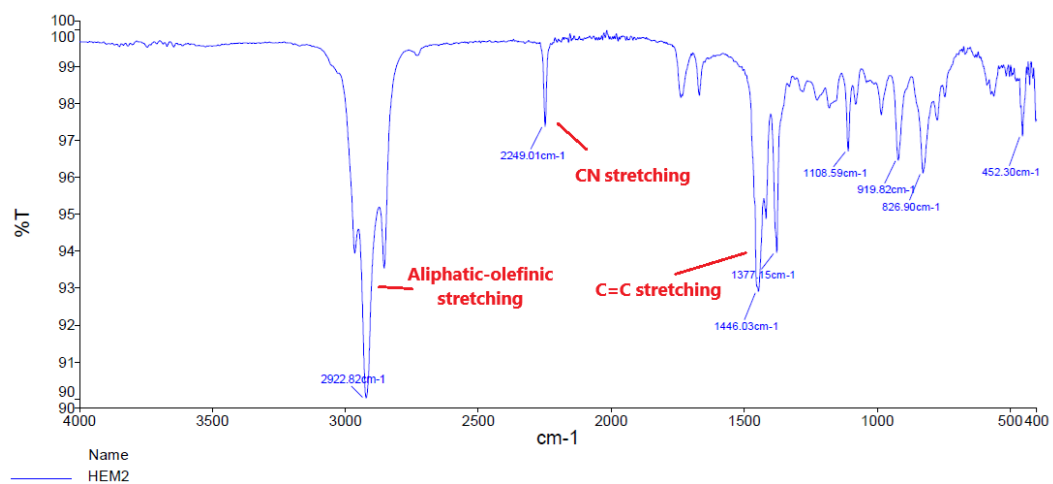


Figure 4.4. IR spectrum of homogeranyl nitrile **188**.

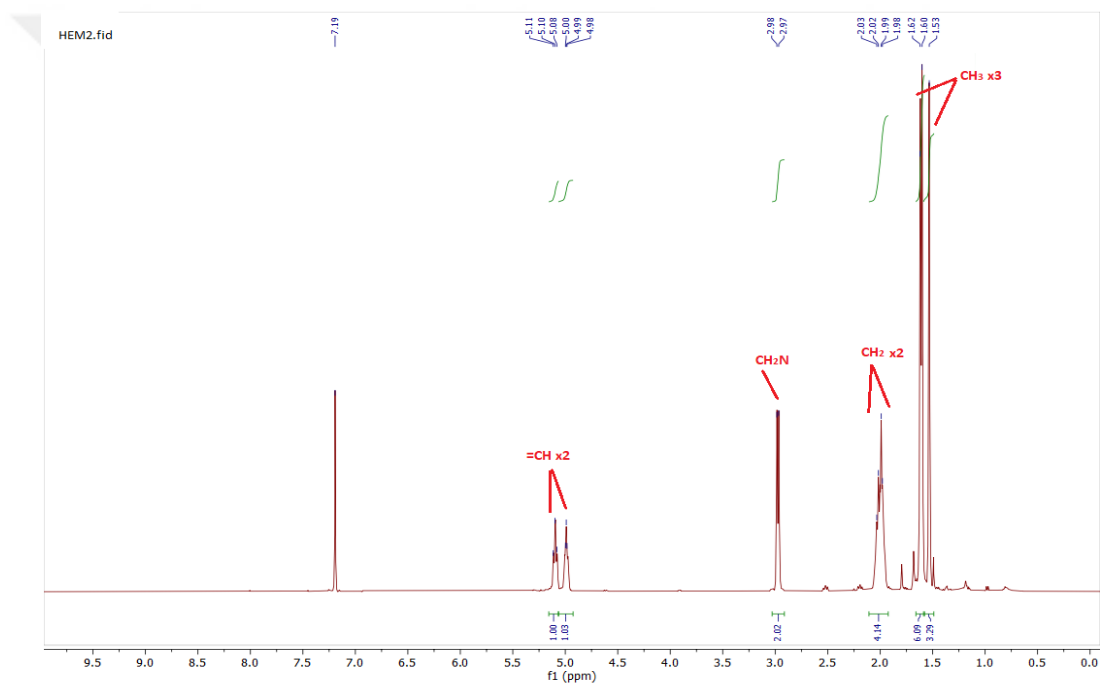


Figure 4.5. ^1H NMR spectrum of homogeranyl nitrile **188**.

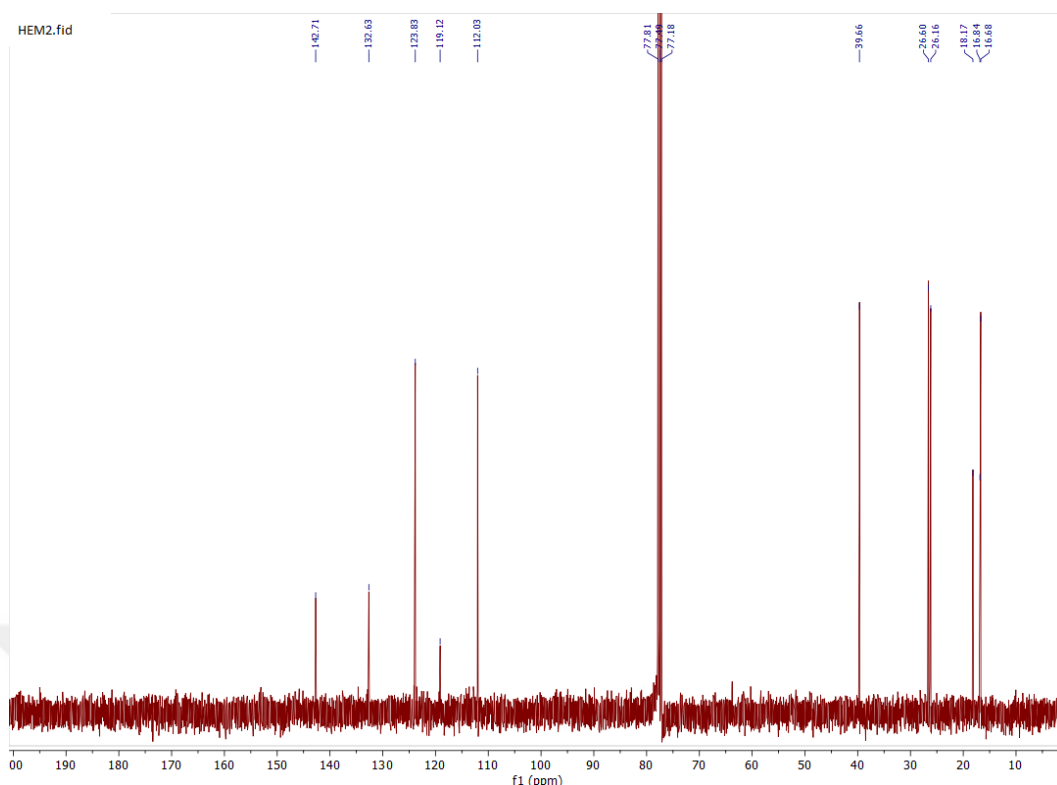


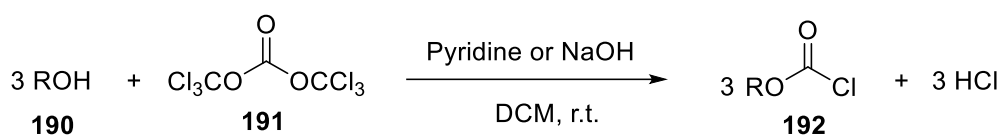
Figure 4.6. ^{13}C NMR spectrum of homogeranyl nitrile **188**.

In the third step, LiAlH_4 was suspended and stirred in dry diethyl ether as a 1M solution. It is crucial for the ether to be dry because LiAlH_4 reacts vigorously and ignites in the presence of water. Geranyl nitrile **188** preferably in ether was added dropwise to the LiAlH_4 solution since rapid addition causes solvent boiling and overflow from the reaction flask due to the heat released. The same caution was taken after completion of the reaction to neutralize the mixture using NaOH solution. Subsequently, the mixture is extracted with a water: EtOAc mixture and the solvent is rotaevaporated. The resulting crude homogeranylamine **189** is used without purification in the next step. Also, the product was kept at -20°C until use (3.1.1.3.).

Characterised by IR and proton NMR. It was understood through the indicative signals in both the IR spectrum (NH_2 and aliphatic C-H stretches) and the proton NMR spectrum (olefinic C-H at 5.05-5.17 ppm; CH_2 at 2.7 ppm) that the expected product **189** was obtained (Figure 4.7-4.8).

4.2 Synthesis of Homogeranyl Carbamates

Main starting compounds, homogeranyl carbamates **193** were synthesized via a base-catalyzed acylation reaction of various alkyl or aryl chloroformates **192** with homogeranyllamine **189**. While most of the chloroformates **192** were supplied commercially, some of them were prepared using a literature method involving the use of bis(trichloromethyl) carbonate **191** under basic conditions from the suitable alcohols **190**.

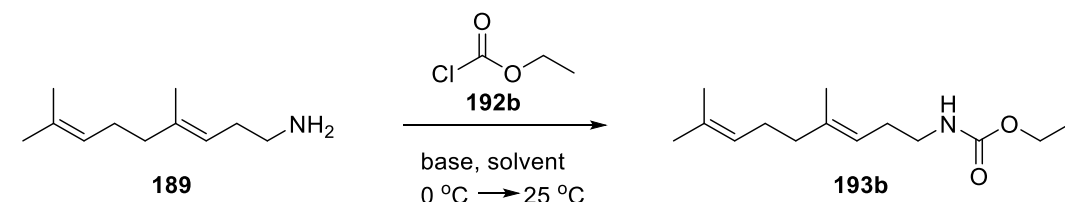


Scheme 4.2. synthesis method of chloroformates **192**.

For the synthesis of chloroformates **192**, an initial attempt was made using synthesis with phosgene. However, phosgene is highly toxic gaseous compound and difficult to handle. In the synthesis of chloroformates **192** with phosgene, the presence of toluene significantly reduced the yield since it cannot be removed after the reaction. Therefore, a more convenient, safer, and higher-yielding method was adopted. In this method, BTC **191** is used as the phosgene source. One mole of BTC **191** produces three moles of phosgene. BTC **191** is a solid at room temperature and does not release toxic gas unless left unused for an extended period. Two different methods were employed for the synthesis of alkyl and aryl chloroformates. Pyridine was used for alkyl chloroformates, while a NaOH solution was utilized for aryl chloroformates. In the literature, a small amount of water extraction was preferred at the end of the reaction, however, in our synthesis, we observed that the presence of even a small amount of water caused the conversion of chloroformates **192** into their carboxylic acids. Hence, we skipped the water extraction. In the synthesis of alkyl chloroformates, after the completion of the reaction, the mixture was directly added to the homogeranyllamine **189**. For aryl chloroformates, we separated the water which originated from NaOH solution and dried solution, after filtration, it was directly added into the reaction mixture containing homogeranyllamine **189**. Since both reactions were carried out in DCM. When commercially obtained pure chloroformates were used, the reaction yield was slightly better.

In order to determine the optimum reaction conditions for the synthesis of homogeranyl carbamates **193**, several optimizations were performed. For this purpose, a base-catalyzed reaction between homogeranylamine **189** and ethyl chloroformate **192b** was selected as a model reaction in optimization reactions.

Table 4.1. Optimization conditions of homogeranyl carbamates.

					
Entry ^a	189 (e.q.)	192b (e.q.)	Base (e.q.), solvent	Time	193b Yield (%) ^b
1	1	1.1	K ₂ CO ₃ (1.5), CH ₃ CN	3	40
2	1	1.1	K ₂ CO ₃ (1.5), DCM	2	48
3	1	1.1	Et₃N (1.1), DCM	1	85
4	1.1	1.1	Et ₃ N (2.0), DCM	1	70
5	2	1	Et ₃ N (1.1), DCM	1	65
6	2	1	Et ₃ N (2.0), DCM	2	63

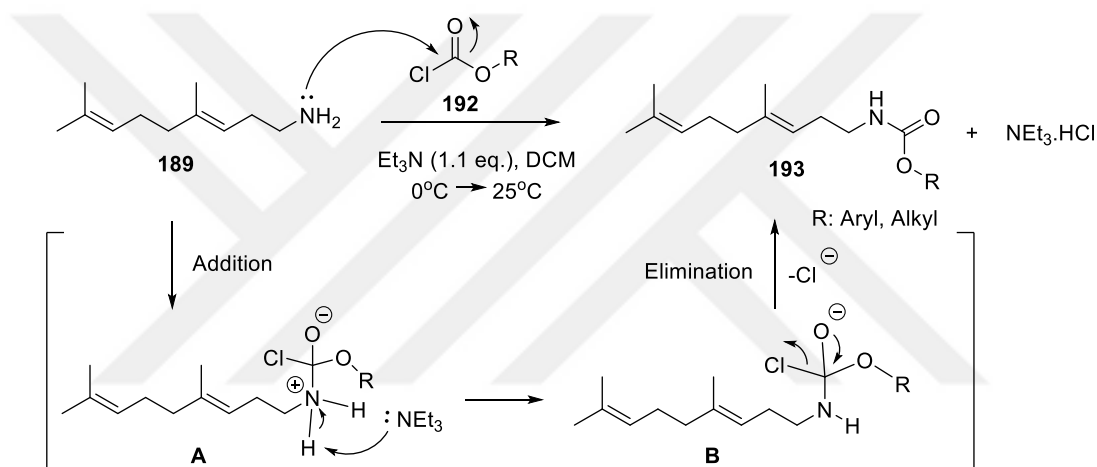
^a Addition of ethyl chloroformate was done at 0 °C, later reaction was continued at room temperature.

^b Yields after column chromatography.

In the first trial, compounds **189** and **192b** were reacted in a 1-1.1 e.q. ratio in acetonitrile with K₂CO₃, resulting in the synthesis of homogeranyl carbamate **193b** with moderate to low yield (40%) (Table 4.1, Entry 1). When the reaction was repeated using the same amounts of compounds in DCM, an increase in yield (48%) was observed (Table 4.1, Entry 2). By keeping the ratio of compounds **189** and **192b** constant and conducting the reaction in DCM with Et₃N, a higher yield of 85% was achieved in the synthesis of **193b** (Table 4.1, Entry 3). However, when precursors **189** and **192b** were used in a 1.1 e.q. ratio and the reaction was performed in DCM with Et₃N at two e.q. ratio, a slight decrease in yield was observed (Table 4.1, Entry 4). In the last two trial reactions, where compound **189** was used in twice the amount compared to compound **192b**, and different ratios of Et₃N (1.1, 2.0) were tested, no increase in reaction yields was observed (Table 4.1, Entry 5-6).

Based on the optimization studies conducted using the model reaction, best conditions for the synthesis of homogeranyl carbamates was determined that it involved using **189** and **192b** in a 1-1.1 eq. ratio and conducting the reaction in DCM with Et₃N. Further details are provided in the method section (3.1.2.2).

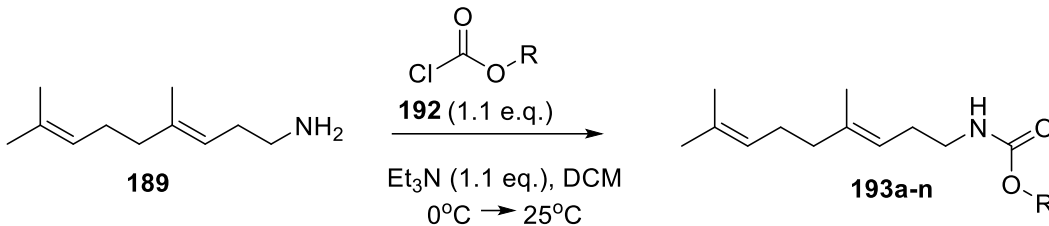
In the synthesis of homogeranyl carbamates **193**, the addition of the base is carried out dropwise at 0°C to prevent the formation of excessive by-products. To protect chloroformates **192** from decomposition by atmospheric moisture, they are added all at once in a small amount of DCM. After the addition, the reaction flask is left open for a while to allow the release of HCl gas, and then it is sealed and left to stir at room temperature.



Scheme 4.3. Proposed mechanism for synthesis of homogeranyl carbamates **193**.

A series of new alkyl and aryl homogeranyl carbamates (**193a-n**) were successfully prepared under optimized reaction conditions, characterized, and purified. The results and data related to the synthesis reactions are provided below in order.

Table 4.2. Synthesis and yields of homogeranyl carbamates (**193a-n**).

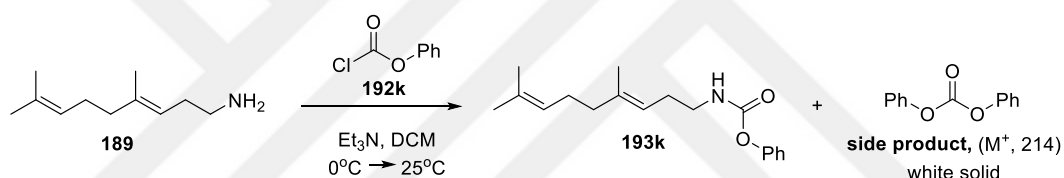
						
193	R	Physical Property	Rf ^a	Time (h)	Column Polarity	Yield (%) ^b
a	Me	Light Yellow Oil	0.55	1	EA-Hex (1:8)	77
b	Et	Light Yellow Oil	0.75	1	EA-Hex (1:20)	85
c	Pr	Light Yellow Oil	0.65	1	EA-Hex (1:20)	50
d	<i>i</i> -Pr	Light Yellow Oil	0.70	1	EA-Hex (1:20)	60
e	Bu	Light Yellow Oil	0.85	1	EA-Hex (1:25)	95
f	<i>i</i> -Bu	Light Yellow Oil	0.65	1	EA-Hex (1:20)	70
g	sec-Butyl	Light Yellow Oil	0.70	1	EA-Hex (1:25)	80
h	<i>i</i> -Amyl	Light Yellow Oil	0.60	1	EA-Hex (1:25)	65
i	Hexyl	Light Yellow Oil	0.75	1	EA-Hex (1:25)	68
j	Benzyl	Light Yellow Oil	0.80	1	EA-Hex (1:20)	50
k	Ph	White solid	0.70	1	EA-Hex (1:20)	55
l	<i>p</i> -Me-Ph	White Solid	0.75	1	EA-Hex (1:8)	95
m	<i>p</i> -MeO-Ph	White Solid	0.50	1	EA-Hex (1:10)	98
n	<i>p</i> -NO ₂	Light Yellow Solid	0.75	1	EA-Hex (1:25)	35
o	<i>t</i> -Butyl	-	0.70	1	EA-Hex (1:30)	- ^c

^a Rf value EtOAc: Hex (1:5). ^b Yield obtained after column chromatography purification.

^c Product decomposed in column.

It is observed that the reaction yields of aryl homogeranyl carbamate compounds, except for compound **193n** (*p*-nitro), are moderate to high (55-98%) (Table 4.2). The lower reaction yield in compound **193n** can be attributed to the electron-withdrawing effect of the nitro group through resonance, which may lead to faster decomposition of the chloroformate and a decrease in the reaction yield. Additionally, the purification of *p*-nitrophenyl homogeranyl carbamate through column chromatography took significantly longer compared to the others (approx. 5 times longer). Furthermore, in the synthesis of alkyl homogeranyl carbamates, the yields ranged from 50% to 95%. It was observed that the yields of homogeranyl carbamates with alkyl groups up to four carbons were higher, but for those with five to six carbons, the yields slightly decreased. The low yield in *i*-propyl homogeranyl carbamate **193d** can be attributed to the unstable of the carbamate in the presence of the toluene solvent. Additionally, the low yield of propyl homogeranyl carbamate **193c** is due to the impurity in the chloroformate

we synthesized because we did not purify the chloroformate. In the synthesis of *t*-butyl carbamate **193o** using *t*-butyl chloroformate, the product was obtained in low amounts due to the instability of the chloroformate, and during the purification by column chromatography, it was observed that the product decomposed. In most of homogreranyl carbamate synthesis, extending the reaction time to 2-2.5 hours did not result in a change in the product yields. Particularly, in the formation of phenyl homogreranyl carbamate **193k**, a significant amount of byproduct formation led to a decrease in the yield, and GC-MS analysis of the byproduct revealed the conversion of a portion of phenyl chloroformate to diphenyl carbonate (Scheme 4.4, Figure 4.9). Similarly, the formation of diaryl carbonate was observed in low amounts in the synthesis of *p*-tolyl and *p*-methoxyphenyl homogreranyl carbamates **193l-m**, resulting in higher reaction yields (Table 4.2).



Scheme 4.4. Side product (diphenyl carbonate) occurred in the sytnthesis of phenyl homogreranyl carbamate **193k**.

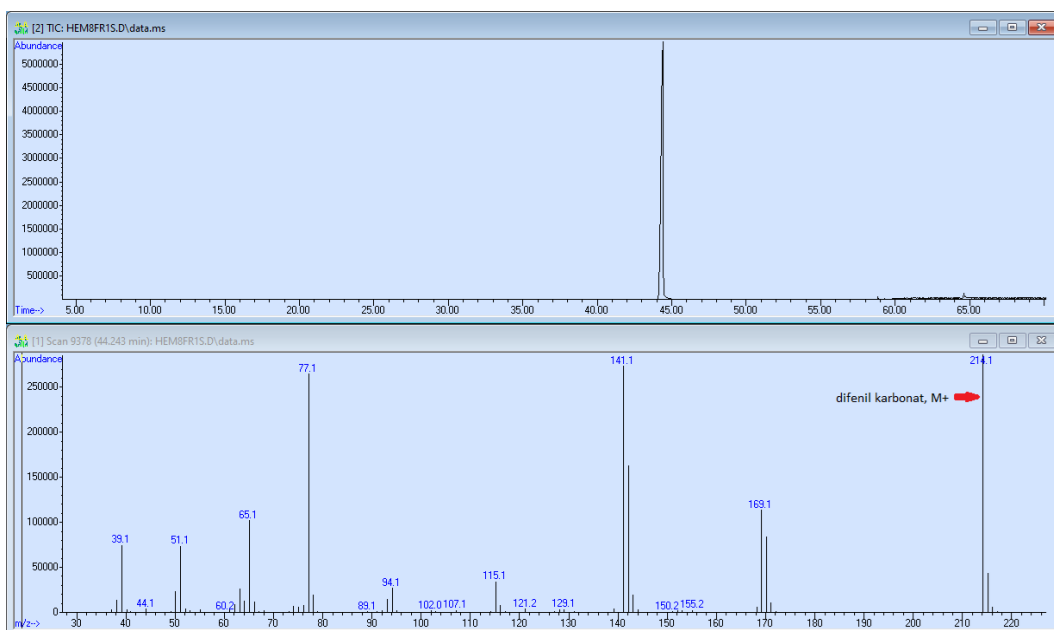


Figure 4.9. GC-MS chromatogram and mass spectrum for side product.

Homogeranyl carbamates (**193a-n**) obtained were subjected to IR, proton, and carbon-13 NMR analyses. The IR spectra of the homogeranyl carbamates (**193a-n**) exhibited characteristic NH stretching vibrations at around 3340 cm⁻¹ and C=O stretching vibrations in the range of 1693-1715 cm⁻¹. Furthermore, the proton NMR spectra of compounds (**193a-n**) showed the expected signals for olefinic CH, -NH, and -CH₂N- protons at chemical shifts of 5.0-5.13, 4.63-5.20, and 3.09-3.29 ppm, respectively. Additionally, the signals for C=O, =CH, and -CH₂N carbons in the ¹³C NMR spectra of the compounds were observed within the expected ranges of 156-157, 138-120, and 40-41 ppm, respectively (Table 4.3). All spectroscopic data provided conclusive evidence for the successful synthesis of homogeranyl carbamates (**193a-n**).

For example, methyl homogeranyl carbamate **193a**, were confirmed with spectroscopic data below. According to IR spectrum 3338 cm⁻¹ (N-H str.), 1699 cm⁻¹ (C=O str.) absorption peaks (Figure 4.10), proton NMR 5.06 ppm (olefinic H's), 4.73 ppm (N-H) demonstrate expected structure (Figure 4.11). Also, carbon-13 NMR 157.0 ppm (C=O), 138-120 ppm (olefinic C's) and 52 ppm (O-CH₃) peaks prove structure accuracy (Figure 4.12).

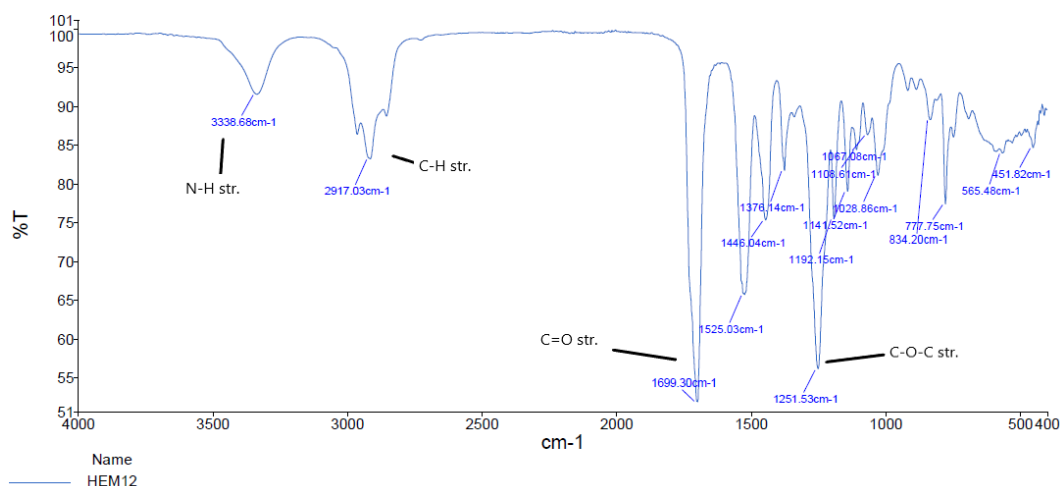


Figure 4.10. IR spectrum of methyl homogeranyl carbamate **193a**.

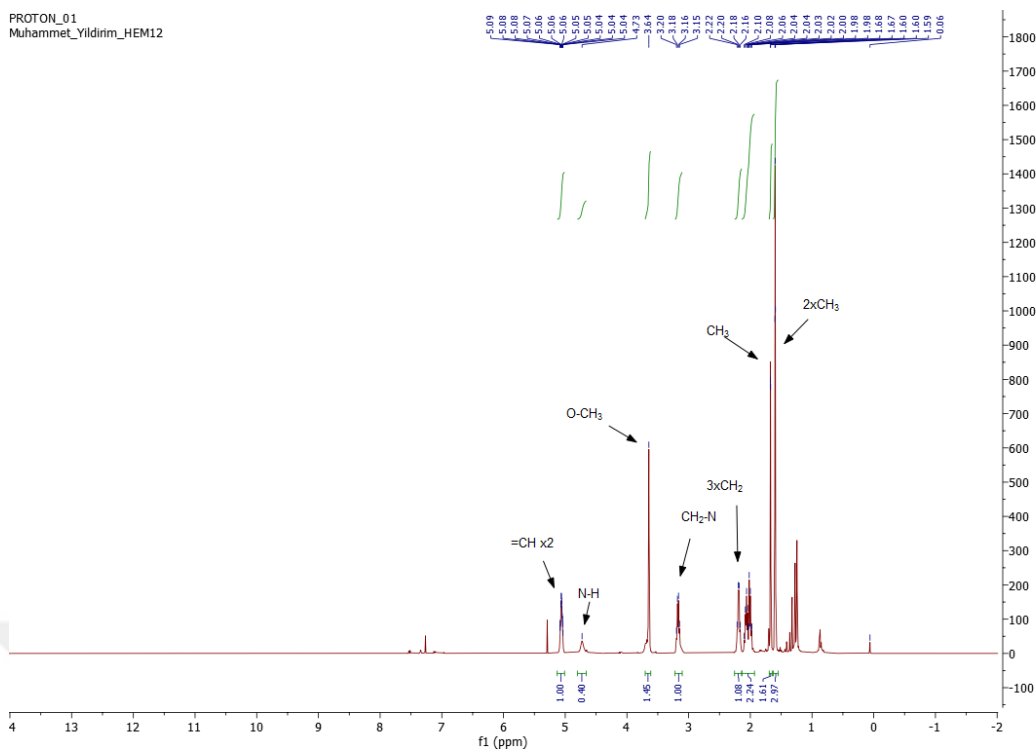


Figure 4.11. ^1H NMR spectrum of methyl homogeranyl carbamate **193a**.

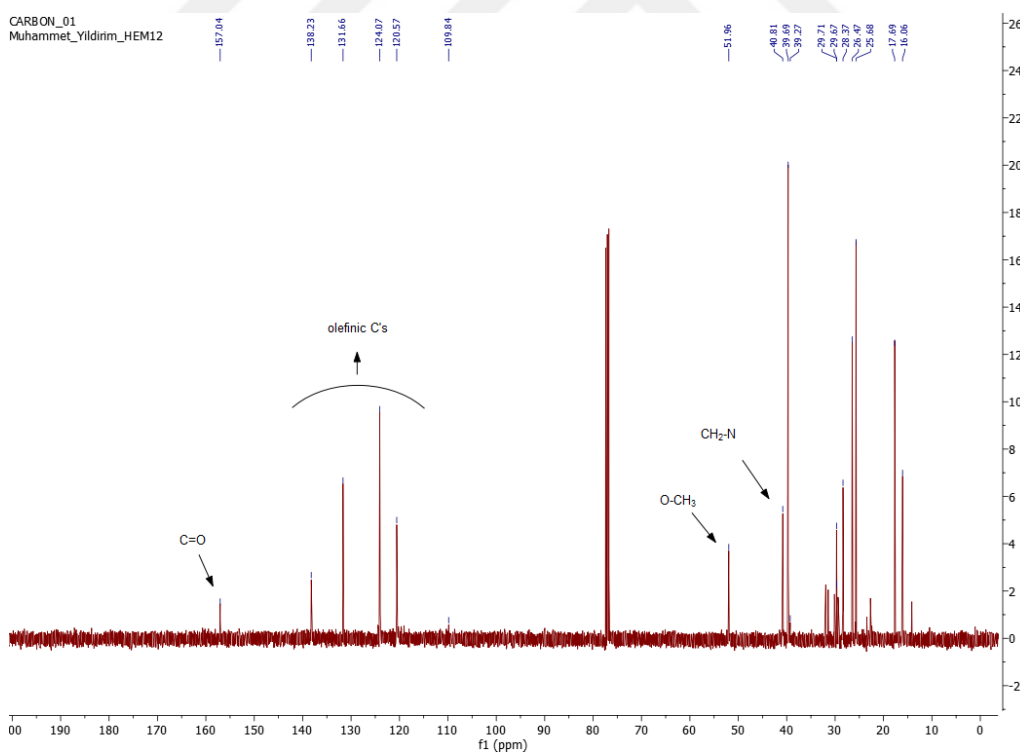
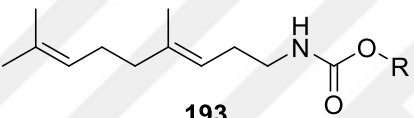


Figure 4.12. ^{13}C NMR spectrum of methyl homogeranyl carbamate **193a**.

Finally, in order to confirm the masses of the compounds, some GC-MS analyses were conducted. However, based on the analysis results, only the mass of compound **193c** (M^+ , 253.2) could be accurately determined (Figure 4.13). When examining the GC-MS results of the other carbamates, it was found that either the expected molecular mass was not observed, or certain groups underwent fragmentation resulting in different ions. For instance, from compound **193k**, the elimination of PhOH (-94) resulted in the detection of a stable ion at m/z 193.2 (Figure 4.14). Similarly, from compound **193h**, the elimination of isopropyl (-43) led to the observation of a stable ion at m/z 238.2.

Table 4.3. Characterization datas of alkyl and aryl homogeranyl carbamates

(193a-n).  193									
		IR (cm ⁻¹)		¹ H-NMR (δ, ppm)			¹³ C-NMR (δ, ppm)		
193	R	N-H str.	C=O str.	=CH	NH	CH ₂ N	C=O	=CH	CH ₂ N
a	Me	3338	1699	5.06, m	4.73, br s	3.17, q	157.0	138-120.5	40.8
b	Et	3338	1696	5.07, t	4.65, br s	3.18, m	156.6	138.2-120.5	40.6
c	Pr	3341	1700	5.04, q	4.74, br s	3.13, q	156.7	138-120.6	41.4
d	<i>i</i> -Pr	3342	1693	5.06, m	4.66, br s	3.15, q	156.2	138-120.0	40.6
e	Bu	3339	1697	5.03, m	4.75, br s	3.12, q	156.7	138-120.6	40.7
f	<i>i</i> -Bu	3339	1696	5.04, q	4.76, br s	3.13, m	156.7	138-120.6	40.7
g	sec-Bu	3341	1693	5.00, q	4.78, br s	3.09, m	156.4	137.8-120.7	40.6
h	<i>i</i> -Amyl	3342	1697	5.06, m	4.63, br s	3.16, m	156.7	138.1-120.6	40.7
i	Hexyl	3339	1697	5.03, m	4.76, br s	3.13, m	156.7	137.9-120.6	40.7
j	Bz	3339	1701	5.06, m	4.83, br s	3.19, q	156.4	138.2-120.5	40.8
k	Ph	3335	1715	5.13, m	5.10, br s	3.29, q	154.6	138.5-120.4	41.0
l	<i>p</i> -Tolyl	3344	1702	5.11, m	5.03, br s	3.27, q	154.6	138.5-120.4	40.9
m	<i>p</i> -MeO	3338	1715	5.08, m	5.04, br s	3.25, q	156.8	138.5-120.4	40.9
n	<i>p</i> -NO ₂	3338	1695	5.08, m	5.20, br s	3.28, q	155.9	138.8-121.9	41.1

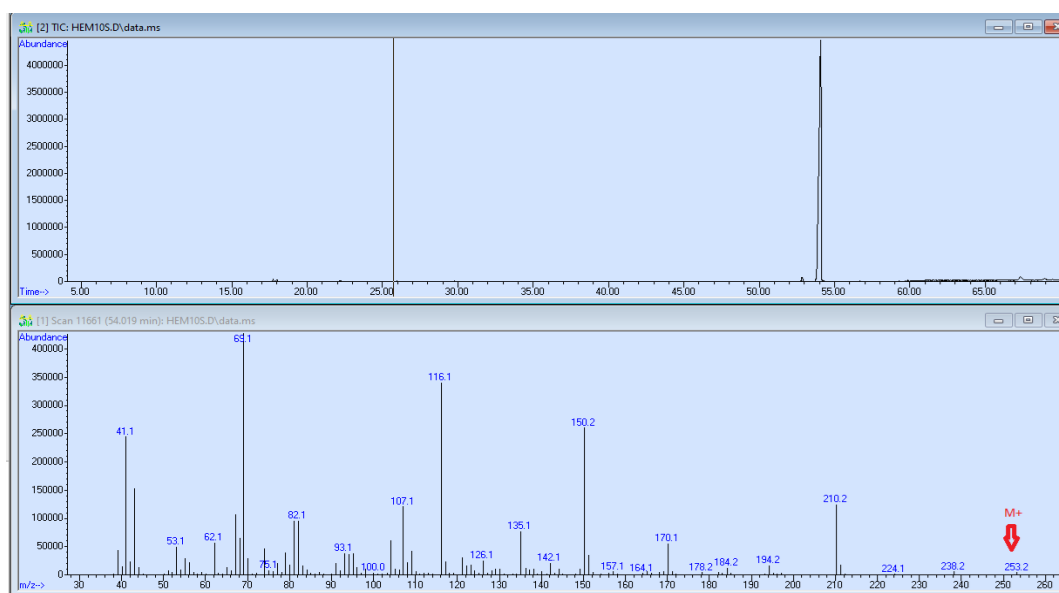


Figure 4.13. GC chromatogram and mass spectrum belonging to propyl homogeranyl carbamate **193c**.

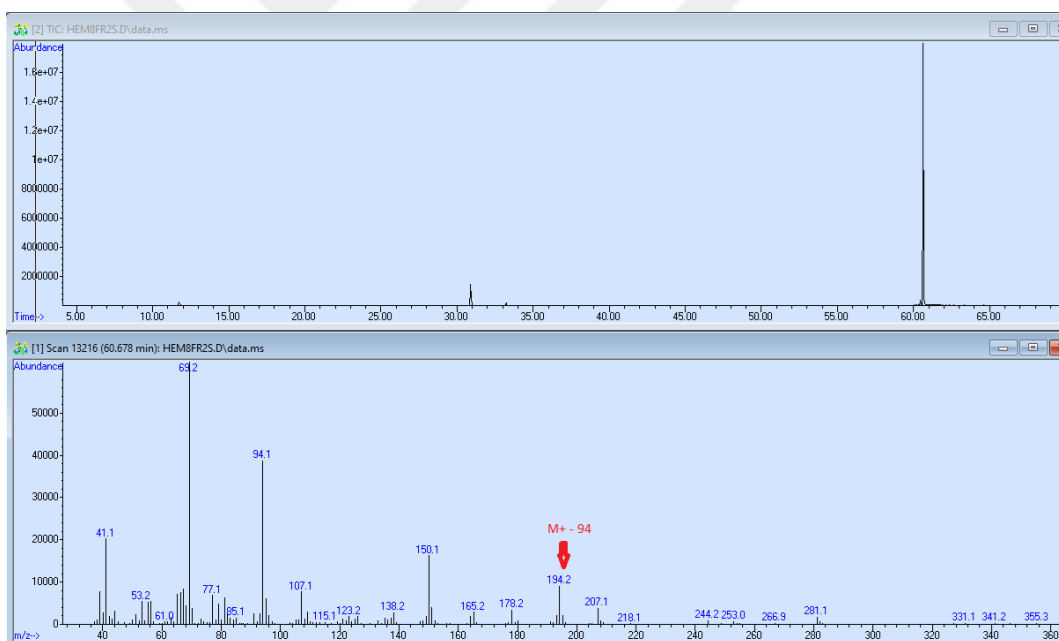


Figure 4.14. GC chromatogram and mass spectrum belonging to phenyl homogeranyl carbamate **193k**.

In GC-MS analyses, it has been observed that especially carbamates with 4 carbons and above do not provide the expected masses after decomposition. Therefore, the determination of the exact masses (HR-MS) of the obtained homogeranyl carbamates (**193a-n**) was performed using a softer technique, namely LC-MS analysis method in ESI (+) mode (Kütahya Dumlupınar

University, ILTEM MS lab). To illustrate with an example, for the carbamate compound **193a** (methyl substituted), the expected (theoretical) exact mass of m/z 225.17288 [M^+] was detected with high precision as m/z 225.17281 in LC-MS analysis.

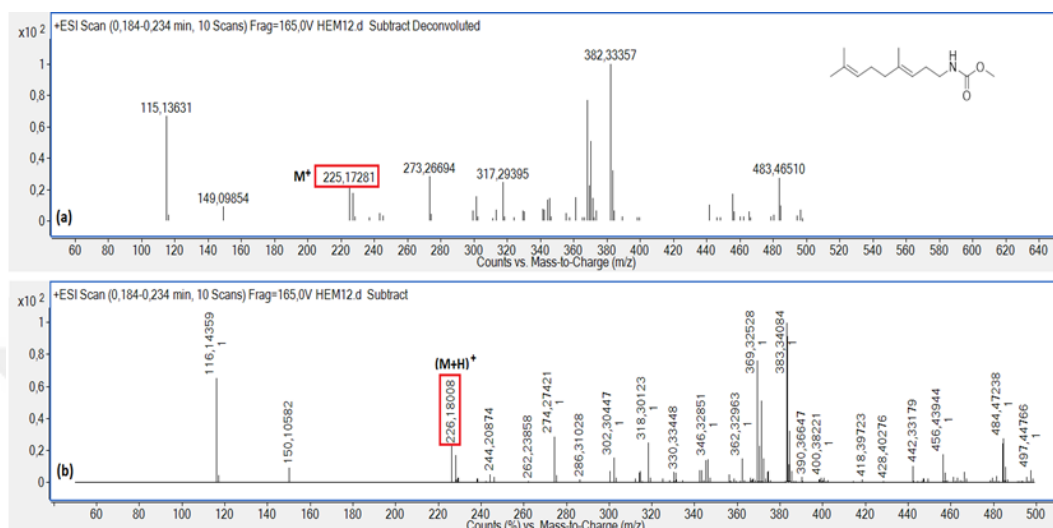


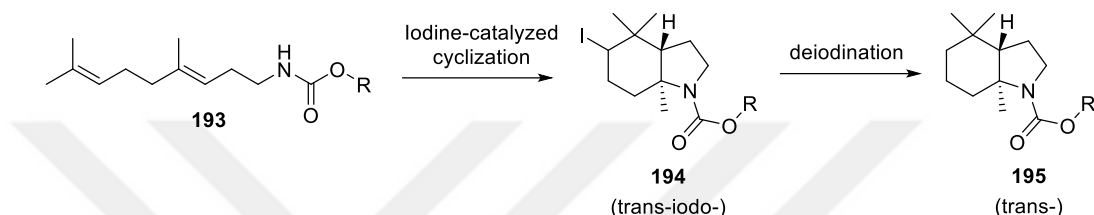
Figure 4.15. The full mass (HRMS) spectrum of the **193a** (methyl) in M^+ and $(M+H)^+$.

Table 4.4. Exact Mass (HRMS) of Homogeranyl Carbamates **193**.

Carbamate	Ion	Theoretical (expected) Exact Mass, m/z	Experimental (found) Exact Mass, m/z
193a (Me-)	M ⁺	225.17288	225.17281
	M+H ⁺	226.18070	226.18008
193b (Et-)	M ⁺	239.18853	239.18897
	M+H ⁺	240.19635	240.19625
193c (Pr-)	M ⁺	253.20418	253.20352
	M+H ⁺	254.21200	254.21080
193d (i-Pr-)	M ⁺	253.20418	253.20217
	M+H ⁺	254.21200	254.20944
193e (Bu-)	M ⁺	267.21983	267.22039
	M+H ⁺	268.22765	268.22767
193f (i-Bu-)	M ⁺	267.21983	267.21975
	M+H ⁺	268.22765	268.22703
193g (sec-Bu-)	M ⁺	267.21983	267.22019
	M+H ⁺	268.22765	268.22746
193h (i-Amyl-)	M ⁺	281.23548	281.23519
	M+H ⁺	282.24330	282.24247
193i (hexyl-)	M ⁺	295.25113	295.25137
	M+H ⁺	296.25895	296.25865
193j (Bz-)	M ⁺	301.20418	301.20198
	M+H ⁺	302.21200	302.20925
193k (Ph-)	M ⁺	287.18853	287.18747
	M+H ⁺	288.19635	288.19475
193l (p-Tolyl-)	M ⁺	301.20418	301.19616
	M+H ⁺	302.21200	302.20343
193m (p-MeO-)	M ⁺	317.19909	317.19770
	M+H ⁺	318.20692	318.20497
193n (p-NO ₂ -)	M ⁺	332.17361	332.17153
	M+H ⁺	333.18143	333.17880

4.3 Iodine-mediated synthesis of *trans*-trimethyloctahydroindole carbamates

In our study, we also aimed synthesis of *trans*-trimethyloctahydroindole carbamates. The synthesis of *trans*-5-iodo-trimethyloctahydroindole carbamates **194** was carried out using homogeranyl carbamates (**193a-n**) through iodine-catalyzed cyclization reactions. Subsequently, the synthesis of some *trans*-trimethyloctahydroindole carbamates **195** was achieved through the deiodination reaction of **194** derivatives.



Scheme 4.5. Synthesis of *trans*-5-iodo- **194** and **195** trimethyloctahydroindole carbamates.

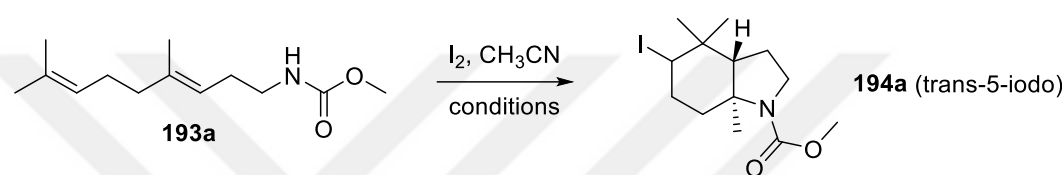
4.3.1 Synthesis and characterization of *trans*-5-iodotrimethyloctahydroindole carbamates (**194**)

In order to determine the optimum reaction conditions for the synthesis of *trans*-5-iodotrimethyloctahydroindole carbamates **194**, several optimization studies were conducted. Therefore, the iodine-catalyzed cyclization reaction of homogeranyl methyl carbamate **193a** was used as a model, and the formation of product **194a** was investigated under different conditions including base-free or base-mediated reactions and varying reaction times. In the first experiment, I₂ was added to a solution of **193a** in CH₃CN at 0°C, followed by raising the reaction temperature to room temperature and stirring. The product **194a** was isolated with moderate to good yield (Table 4.5, Entry 1). Under the same conditions, it was determined that the reaction was completed in 1 hour and the product yield increased up to 70% when only K₂CO₃ (3 mmol) was added (Table 4.5, Entry 2). When the reaction mixture was stirred at room temperature for extended reaction times of 3 or 16 hours, the product yields decreased to 45% and 36%, respectively (Table 4.5, Entry 3-4). In the optimizations of the iodine-catalyzed cyclization reactions, there was no significant yield difference between the first and second

entry, both conditions were accepted as the optimum conditions and the details of the general method are given in 3.1.3.

Removal of acetonitrile before the extraction step as described yielded better results due to good miscibility of acetonitrile with water, and so this avoided the loss of products in the extraction. *Trans*-5-iodotrimethyloctahydroindole carbamates **194** are slightly more polar than homogeranyl carbamates **193** and they appear as spots just below the homogeranyl carbamate **193** spots on TLC.

Table 4.5. Synthesis optimization of *trans*-5-iodotrimethyloctahydroindole carbamates **194**.

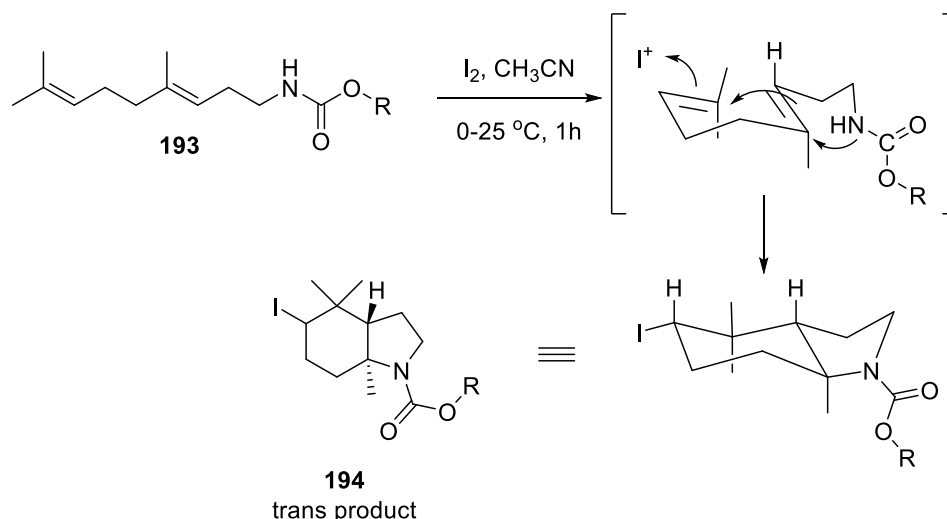


Entry ^a	193a (mmol)	I ₂ (mmol)	Conditions	Time (h)	194a Yield (%) ^b
1	1	3	0-25 °C	1	66
2	1	3	K ₂ CO ₃ (3 mmol), 0-25 °C	1	70
3	1	3	K ₂ CO ₃ (3 mmol), 0-25 °C	3	45
4	1	3	K ₂ CO ₃ (3 mmol), 0-25 °C	16	36

^aIodine was added in each reaction at 0°C in one go, and then the reaction was slowly brought to room temperature and stirred.

^bYields obtained after column chromatography.

A suitable mechanism for the formation of *trans*-iodo-isomers in iodine-catalyzed cyclization reactions of homogeranyl carbamate compounds **193** was proposed as follows (Figure 4.19)

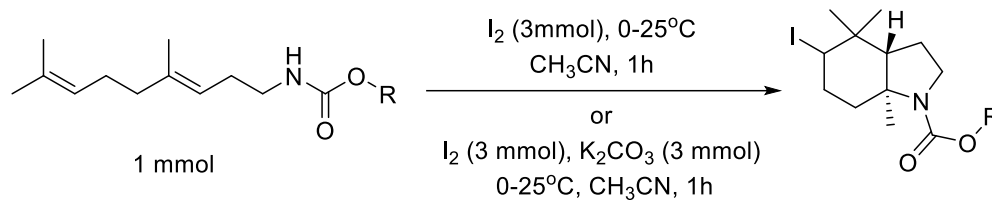


Scheme 4.6. Mechanism of *trans*-5-iodotrimethyloctahydroindole carbamate **194** formation.

New alkyl and aryl 5-iodotrimethyloctahydroindole carbamates (**194a-n**) were synthesized through iodine-catalyzed cyclizations of homogeranyl carbamate compounds (**193a-n**) under optimized reaction conditions. The products were purified through column chromatography and the results and reaction details for the synthesis of products are provided below (Table 4.6).

Trans-5-iodotrimethyloctahydroindole carbamates (**194a-n**) were synthesized through two pathways (base-mediated and base-free) via iodine-catalyzed cyclization, and the reaction yields ranged from moderate to good levels (50-87%) (Table 4.6). Except for the syntheses of compounds **194b**, **194d**, and **194h**, the yields of the products obtained with the addition of K_2CO_3 were found to be partially higher compared to base-free iodine cyclizations. Among the base-free iodine cyclizations, the highest yield (80%) was observed for compound **194b** (ethyl), while the lowest yield was observed for compound **194j** (benzyl). Regarding the iodine cyclizations with K_2CO_3 , the highest yield (87%) was obtained for compound **194m** (p-MeO-Ph), while the lowest yield was obtained for compound **194g** (sec-butyl). The expected products in the synthesis of trans-5-iodotrimethyloctahydroindole carbamates **194** were formed within 1 hour, and the reactions were not extended further to prevent yield loss.

Table 4.6. Syntheses and yields of alkyl and aryl *trans*-5-iodotrimethyloctahydroindole carbamates (**194a-n**).



194	R	Physical Property	R _f ^a	Time	Column Mobil Phase	Yield (%) ^b (I_2)	Yield (%) ^b (I_2 , K_2CO_3)
a	Me	White Solid	0.55	1	EA: Hex (1:30)	66	70
b	Et	White Solid	0.50	1	EA: Hex (1:20)	80	72
c	Pr	White Solid	0.60	1	EA: Hex (1:30)	65	74
d	<i>i</i> -Pr	White Solid	0.56	1	EA: Hex (1:25)	70	65
e	Bu	White Solid	0.57	1	EA: Hex (1:25)	67	71
f	<i>i</i> -Bu	White Solid	0.56	1	EA: Hex (1:25)	60	69
g	sec-Bu	Light Yellow Oil	0.55	1	EA: Hex (1:25)	55	60
h	<i>i</i> -Amyl	Light Yellow Oil	0.60	1	EA: Hex (1:25)	72	61
i	hexyl	Light Yellow Oil	0.60	1	EA: Hex (1:25)	53	70
j	Bz	White Solid	0.50	1	EA: Hex (1:25)	50	61
k	Ph	White Solid	0.45	1	EA: Hex (1:30)	55	75
l	<i>p</i> -Me-Ph	White Solid	0.65	1	EA: Hex (1:25)	59	76
m	<i>p</i> -MeO	White Solid	0.55	1	EA: Hex (1:20)	68	87
n	<i>p</i> -NO ₂	White Solid	0.40	1	EA: Hex (1:25)	56	70

^aR_f value (1:5-EA: Hex), ^b Yields after purification by column chromatography.

The structure characterization of all the *trans*-5-iodotrimethyloctahydroindole carbamate (**194a-n**) was performed using IR, proton, and carbon-13 NMR analyses. For the determination of the structures of the new derivatives, the signals and peaks confirmed. The detailed characterization data was provided below (Table 4.7).

For example, the structure of the compound methyl trans-5-iodo-trimethyloctahydroindole carbamate **194a** was determined by IR, ^1H -NMR, and ^{13}C -NMR analyses after CC purification. The FT-IR spectrum of the compound exhibited absorption peaks at 2957-2864 cm^{-1} (aliph. CH str.), 1681 cm^{-1} (C=O str.) (Figure 4.16). In the proton NMR spectrum, signals at 4.08 ppm (I-CH), 3.64 ppm (OCH_3), and 3.48-3.26 ppm (CH_2N) indicated the formation of the expected cyclization product, along with a signal at 2.53 ppm (bridge CH) (Figure 4.17). The carbon-13 NMR spectrum confirmed the structure of the expected cyclization product with signals at 154.3 ppm (C=O), 61.3 ppm (N-C- CH_3), 55.1 ppm (C-H), and 40.9 ppm (I-CH) (Figure 4.18).

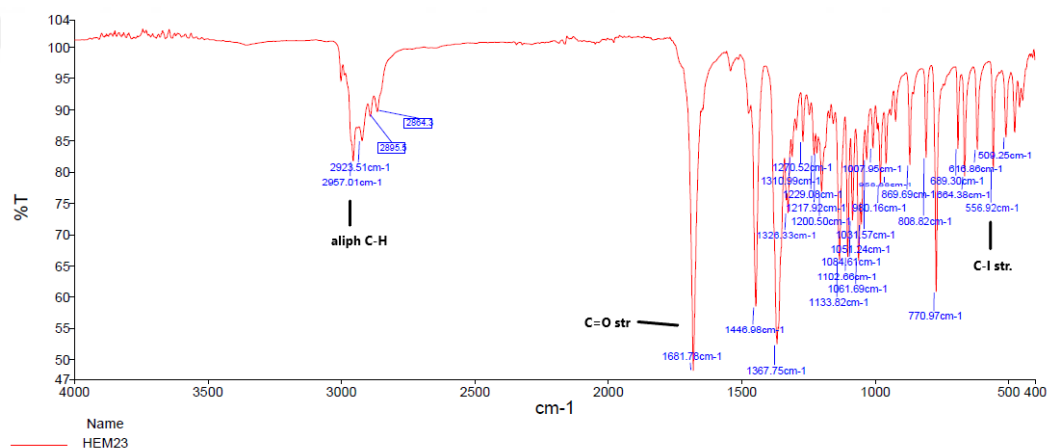


Figure 4.16. IR spectrum for methyl 5-iodo-trimethyloctahydroindole carbamate **194a**.

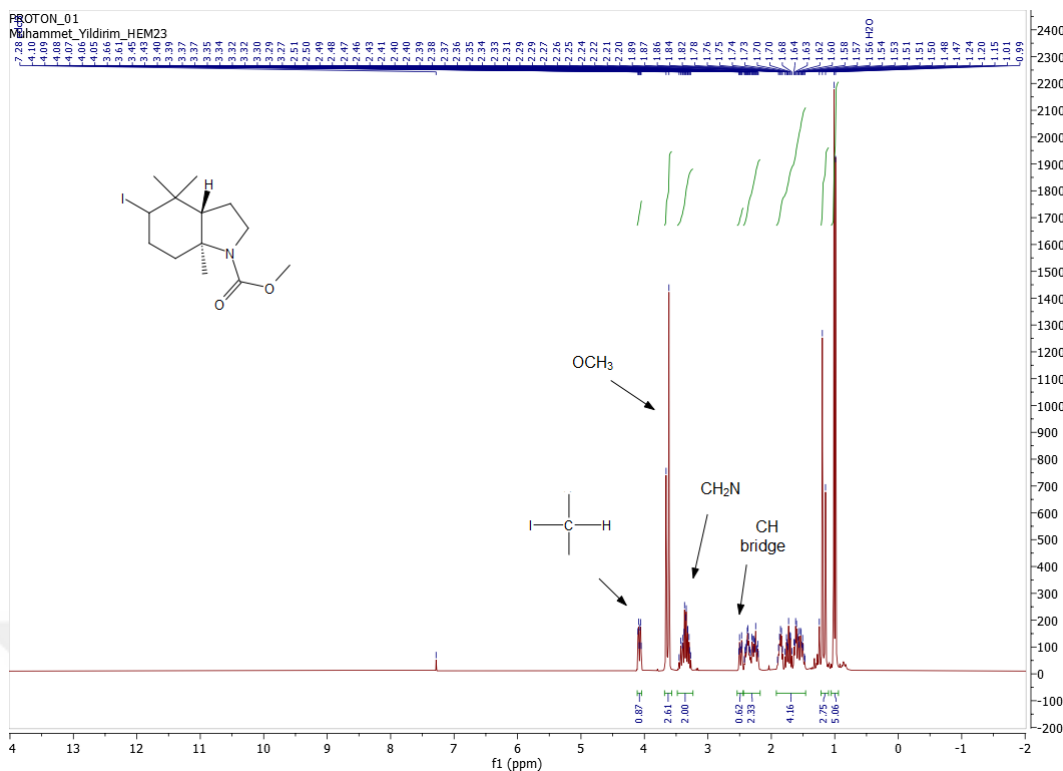


Figure 4.17. ^1H NMR spectrum for methyl 5-iodo-trimethyl-octahydroindole carbamate **194a**.

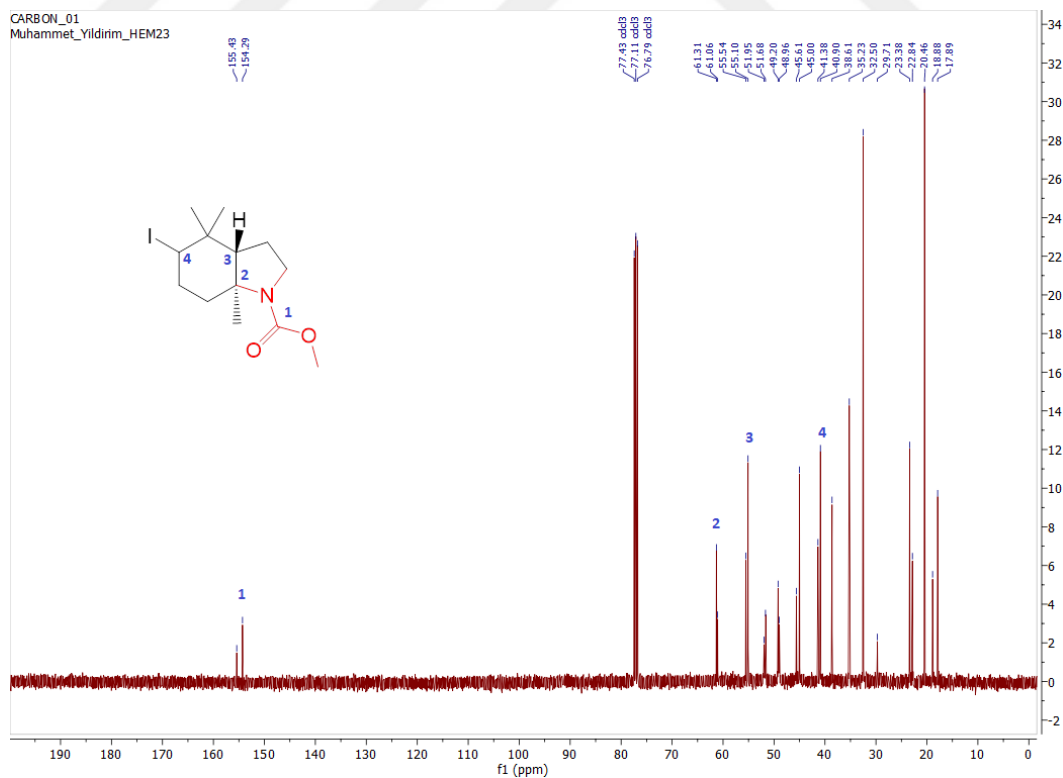
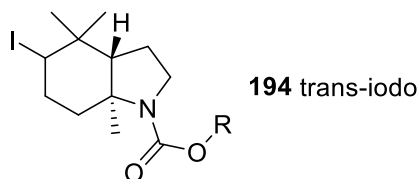


Figure 4.18. ^{13}C NMR spectrum for methyl 5-iodo-trimethyl-octahydroindole carbamate **194a**.

Table 4.7. Characterization and spectroscopic datas of trans-5-iodotrimethyloctahydroindole carbamates (**194a-n**).



R	IR (cm ⁻¹)		¹ H-NMR (δ, ppm)			¹³ C-NMR (δ, ppm)		
	Aliph C-H	C=O	I-CH	Bridge CH	CH ₂ N	C=O	N-C-CH ₃	Bridge C-H
Me	2957-2864	1681	4.08, m	2.48, d	3.48-3.26	154.3	61.3	55.1
Et	2953-2867	1692	4.10, m	2.51, d	3.48-3.28	154.0	61.2	55.6
Pr	2963-2887	1692	4.05, m	2.49, d	3.44-3.28	154.0	61.2	55.6
<i>i</i> -Pr	2970-2887	1686	4.08, m	2.48, d	3.40-3.30	154.0	61.0	55.6
Bu	2956-2864	1697	4.05, m	2.45, d	3.40-3.26	154.0	61.1	55.5
<i>i</i> -Bu	2957-2872	1696	4.07, m	2.47, d	3.42-3.32	154.0	61.1	55.6
sec-Bu	2966-2886	1686	4.08, m	2.41, d	3.43-3.35	154.0	61.3	55.8
<i>i</i> -Amyl	2956-2869	1693	4.06, m	2.44, d	3.38-3.26	154.0	61.0	55.5
Hexyl	2954-2867	1692	4.05, m	2.45, d	3.40-3.28	154.1	61.1	55.6
Bz	2960-2887	1694	4.09, m	2.51, d	3.47-3.37	153.6	61.5	55.1
Ph	2927-2866	1716	4.12, m	2.50, d	3.66-3.54	154.3	61.9	55.6
p-Tolyl	2956-2853	1721	4.12, m	2.50, d	3.64-3.47	152.1	61.8	55.1
p-MeO	2957-2856	1708	4.13, m	2.50, d	3.69-3.40	153.3	61.8	55.7
p-NO ₂	2965-2895	1721	4.07, m	2.44, m	3.63-3.51	156.1	62.3	55.5

Upon detailed examination of all spectral data of trans-5-iodotrimethyloctahydroindole carbamates (**194a-n**), the FT-IR spectra revealed aliphatic CH stretching vibrations in the range of 2927-2853 cm⁻¹ and C=O stretching vibrations in the range of 1683-1724 cm⁻¹ (Table 4.7). Furthermore, the H and C skeleton of compounds (**194a-n**) were elucidated through NMR analyses. Proton NMR spectra exhibited I-CH, bridge CH, and -CH₂N- proton signals supporting the expected structures, in the ranges of 4.05-4.13, 2.41-2.51, and 3.26-3.80 ppm, respectively. The ¹³C-NMR spectra of the products (**194a-n**) revealed signals of C=O, bridge CH, and bridge quaternary carbon (N-C-CH₃) in

the expected ranges of 152.1-154.3, 55.1-55.7, and 61.1-61.8 ppm, respectively, consistent with the expected structures (Table 4.7). The spectroscopic data confirmed the successful synthesis of trimethyl -octahydroindole carbamate derivatives (**194a-n**).

Lastly, to verify the masses of iodocyclization products **194**, the compound **194e** underwent GC-MS analysis. The fragment having m/z 378.9 ($M^+ - CH_3$) molecular ion mass due to the loss of CH_3 indicates fragmentation in the GC-MS analysis (Figure 4.19). Consequently, accurate mass results and isomer ratios in the products cannot be determined due to the fragmentation observed in the GC-MS analysis.

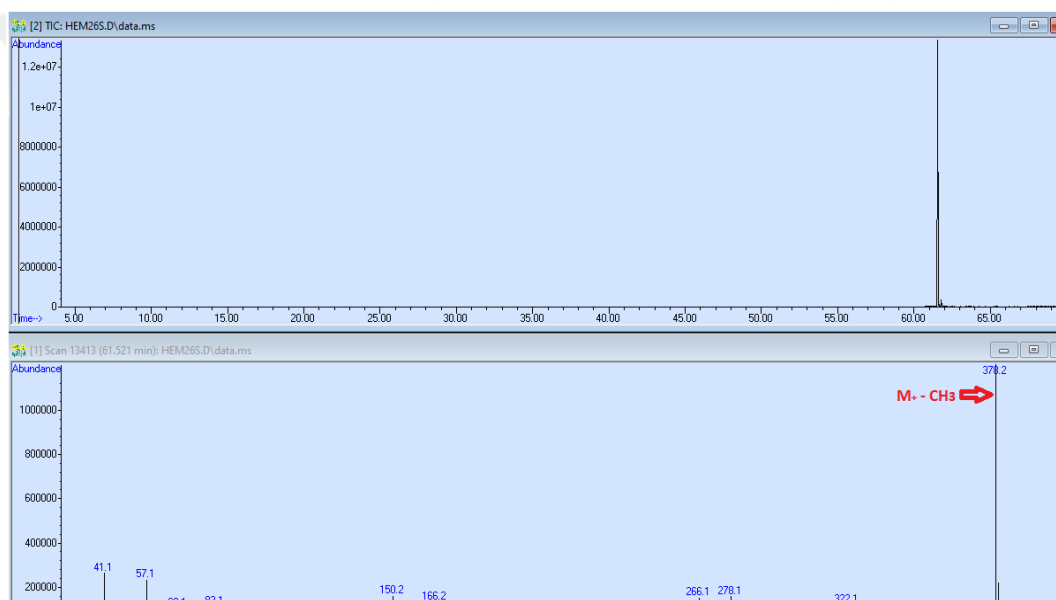


Figure 4.19. GC analysis of butyl 5-iodotrimethyloctahydroindole carbamate **194e**.

Upon examining the carbon-13 NMR spectra of the compounds (**194a-n**), isomeric peaks were observed in almost all the products. However, due to the overlapping of indicative proton (bridge CH) signals with methylene proton (CH_2) signals in the proton NMR spectra of the compounds, isomer ratios could not be determined.

In the final stage, the determination of the exact masses (HRMS) of the products (**194a-n**) was carried out using LC-MS analysis, and the expected masses of all products were accurately found. For instance, compound **194b**,

trans-5-iodotrimethyloctahydroindole ethyl carbamate, exhibited an expected mass of m/z 365.08517 [M^+], while the LC-MS analysis yielded a highly accurate result of m/z 365.08560 [M^+] (Table 4.8, Figure 4.20a). Additionally, the exact mass of compound **194b** as ($M+H$) $^+$ ion was confirmed with high precision (Table 4.8, Figure 4.20b). Furthermore, the exact masses of all other trans-5-iodotrimethyl-octahydroindoles (**194a-n**) were determined with high sensitivity as M^+ , $M+H^+$ ions using LC-MS analysis, and the results are presented in Table 4.8.

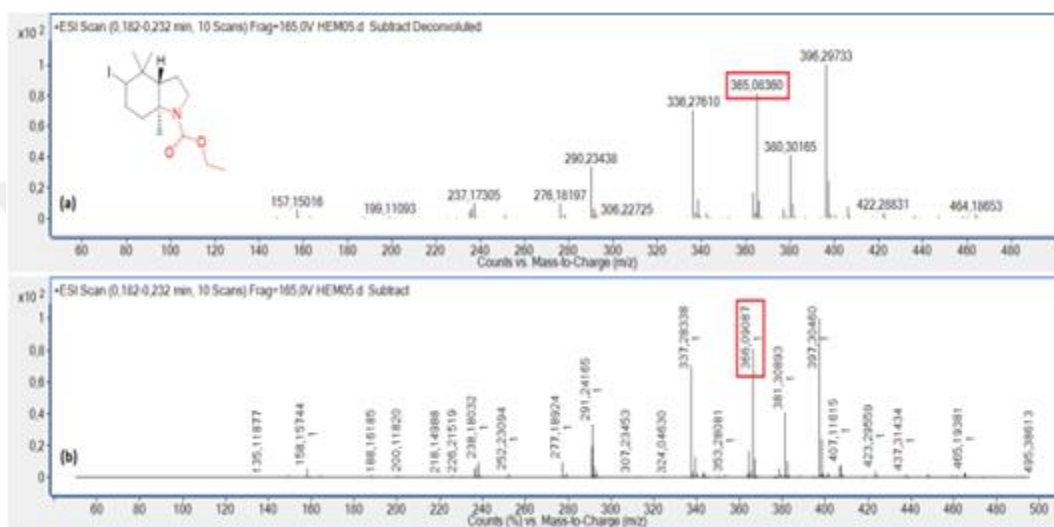


Figure 4.20. M^+ and ($M+H$) $^+$ exact mass (HRMS) spectrum for ethyl trans-5-iodotrimethyloctahydroindole carbamate **194b**.

Table 4.8. Exact mass (HRMS) results of trans-5-iodotrimethyloctahydro carbamates.

Carbamates	Ion	Theoric (Expected) Exact Mass, m/z	Experimental (Founded) Exact Mass, m/z
194a (Me)	M ⁺	351.06952	351.06376
	M+H ⁺	352.07735	352.07104
194b (Et)	M ⁺	365.08517	365.08360
	M+H ⁺	366.09300	366.09087
194c (Pr)	M ⁺	379.10082	379.09700
	M+H ⁺	380.10865	380.10427
194d (<i>i</i> -Pr)	M ⁺	379.10082	379.10511
	M+H ⁺	380.10865	380.11239
194e (Bu)	M ⁺	393.11647	393.11079
	M+H ⁺	394.12430	394.11807
194f (<i>i</i> -Bu)	M ⁺	393.11647	393.11503
	M+H ⁺	394.12430	394.12230
194g (sec-Bu)	M ⁺	393.11647	393.11673
	M+H ⁺	394.12430	394.12401
194h (<i>i</i> -amyl)	M ⁺	407.13212	407.13105
	M+H ⁺	408.13995	408.13833
194i (hexyl)	M ⁺	421.14777	421.14816
	M+H ⁺	422.15560	422.15543
194j (Bz)	M ⁺	427.10082	427.10556
	M+H ⁺	428.10865	428.11283
194k (Ph)	M ⁺	413.08517	413.08164
	M+H ⁺	414.09300	414.08892
194l (<i>p</i> -Tolyl)	M ⁺	427.10082	427.09713
	M+H ⁺	428.10865	428.10441
194m (<i>p</i> -MeOPh)	M ⁺	443.09524	443.09536
	M+H ⁺	444.10307	444.10264
194n (<i>p</i> -NO ₂ Ph)	M ⁺	458.07025	458.07082
	M+H ⁺	459.07808	459.07810

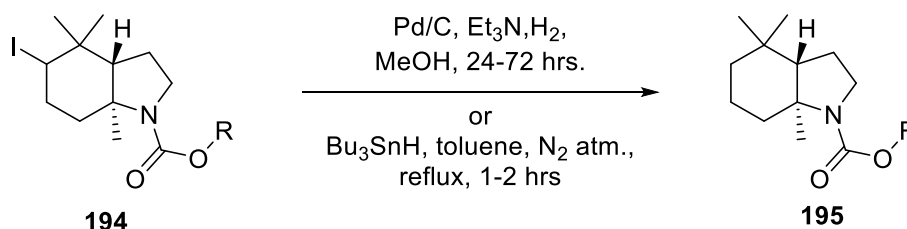
4.3.2 Synthesis and Characterization of trans-trimethyloctahydroindole carbamates (195)

For the synthesis of trans-trimethyloctahydroindole carbamates **195**, Pd-catalyzed hydrogenation reactions of trans-5-iodotrimethyloctahydroindole carbamates **194** were initially applied. In this reaction, catalytic amounts of 5-8% Pd/C was used, and base-catalyzed hydrogenation was carried out at room temperature. Additionally, an alternative reduction method was pursued using tributyltin hydride (Bu₃SnH). No optimization study was conducted, and only reaction times were determined based on product formation. The details of the the syntheses were provided in the method section (3.1.4).

In the Pd-catalyzed method, dry methanol as the solvent is crucial for the success of the reaction. The reaction time increases depending on the moisture content in the solvent, and if the moisture content is too high, the reaction does not proceed. The activity of the Pd catalyst decreases due to moisture, making the adsorption of H₂ gas more challenging. So, the methanol was dried under inert atmosphere by distillation and distilled MeOH was stored in a tightly sealed container with 3Å molecular sieves. Continuous passage of H₂ gas through the reaction mixture is not necessary. We observed that even when the reaction mixture was tightly sealed with a septum and covered with parafilm, the reaction still occurred enough.

In the second method involving tributyltin hydride, bubbles were observed in the reaction mixture when Bu₃SnH was initially added at room temperature, followed by reflux at 80 °C. However, no product formation was observed based on TLC analysis. Subsequently, when reaction temperature was increased to 110 °C (reflux) and the same quantity of Bu₃SnH was used at this temperature, the reaction was completed within one hour. The bubbles formed when Bu₃SnH was added at room temperature indicated a possible decomposition of the compound, which is believed to be caused by moisture in the solvent. In contrast, when Bu₃SnH was added at 110°C, no impact of moisture on the reaction was observed.

Although the *trans*-trimethyloctahydroindole carbamates **195** obtained from both reaction methods appeared to be highly pure, they were further purified by passing through a short column. The product spots on TLC appeared just above the iodo-octahydroindole carbamates **194**, approximately aligned with the homogeranyl carbamates **193**.



Scheme 4.7. Synthesis method for compounds **195**.

Five *trans*-trimethyloctahydroindole carbamates **195a-e** were synthesized using Pd/C catalyst, and their yields were observed in moderate to high (65-90%). The reactions took place within a range of 24-72 hours. However, in reactions for (**195e-m**) involving Bu₃SnH, the yields were also good to high (60-90%), and the reactions were generally completed within 1 hour (Table 4.9).

Table 4.9. Synthesis conditions and yields of alkyl and aryl *trans*-trimethyloctahydroindole carbamates.

195	R	Physical Property^a	Rf^b	Catalyst	Time (h)	Column M.P. (EA: Hex)	Yield (%)^c
a	Me	CO	0.52	Pd/C	48	1:25	95
b	Et	CO	0.65	Pd/C	24	1:15	83
e	Bu	CO	0.60	Pd/C	72	1:15	75
e	Bu	CO	0.60	Bu ₃ SnH	1	1:25	60
k	Ph	WS	0.68	Pd/C	24	1:15	60
k	Ph	CO	0.59	Bu ₃ SnH	1	1:25	75
m	p-MeO-Ph	WS	0.52	Pd/C	48	1:25	90
m	p-MeO-Ph	WS	0.52	Bu ₃ SnH	1	1:25	90

^aCO for colorless oil, WS for white solid, ^b Rf values (1: 5- EA: Hex)

^c Yields after purification by column

When the spectral data of *trans*-trimethyloctahydroindole carbamates (**195a-m**) were examined, it was observed that in the IR spectra, aliphatic CH stretching bands were generally observed in the range of 2955-2853 cm⁻¹, and C=O stretching bands were detected in the range of 1693-1723 cm⁻¹ (Table 4.10). Furthermore, in the proton NMR spectra of the compounds **195**, signals corresponding to the expected structure, including bridge CH₃, bridge CH, and -CH₂N- protons, were observed in the ranges of 1.22-1.52, 2.31-2.67, and 3.20-3.59 ppm, respectively. In the ¹³C-NMR spectra of the products **195**, signals corresponding to C=O, bridge CH, and bridge quaternary carbon (N-C-CH₃) were detected in the expected ranges of 153.3-156.8, 56.4-57.4, and 61.6-62.9 ppm, respectively (Table 4.10). The spectroscopic data indicated the successful synthesis of *trans*-trimethyloctahydroindole carbamates **195**.

As an example, the spectroscopic data used for the structural characterization of compound **195a** are provided. In the IR spectrum of compound **195a**, absorption peaks were observed at 2952-2866 cm^{-1} (aliph. CH str.) and 1696 cm^{-1} (C=O str.), indicating the formation of the expected cyclization product (Figure 4.21). In the proton NMR spectrum, signals at 3.62 ppm (O-CH₃), 3.33 ppm (CH₂N), 2.56 ppm (bridge CH), and 1.23 ppm (bridge CH₃) further confirmed the formation of the expected cyclization product (Figure 4.22). Additionally, the carbon-13 NMR spectrum of the product showed signals at 154.5 ppm (C=O), 61.7 ppm (N-C-CH₃), and 57.3 ppm (C-H), supporting the formation of the expected cyclization product (4.23).

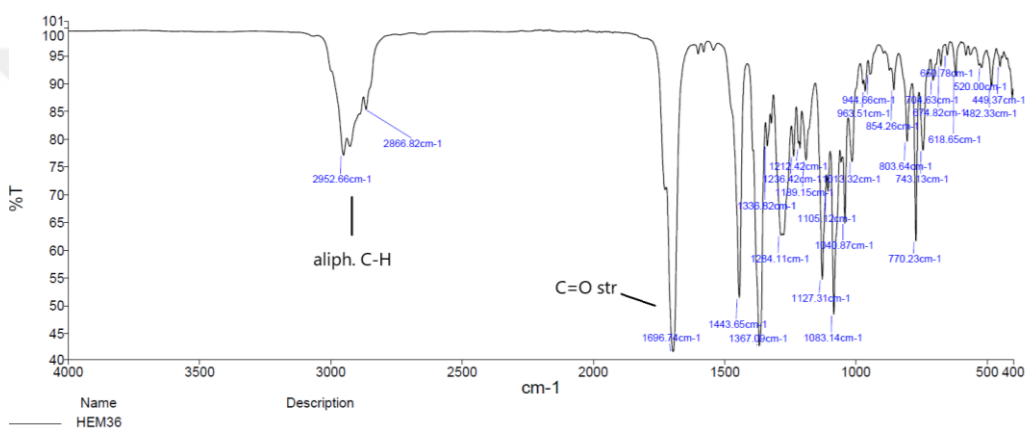


Figure 4.21. IR spectrum of methyl trimethyloctahydroindole carbamate **195a**.

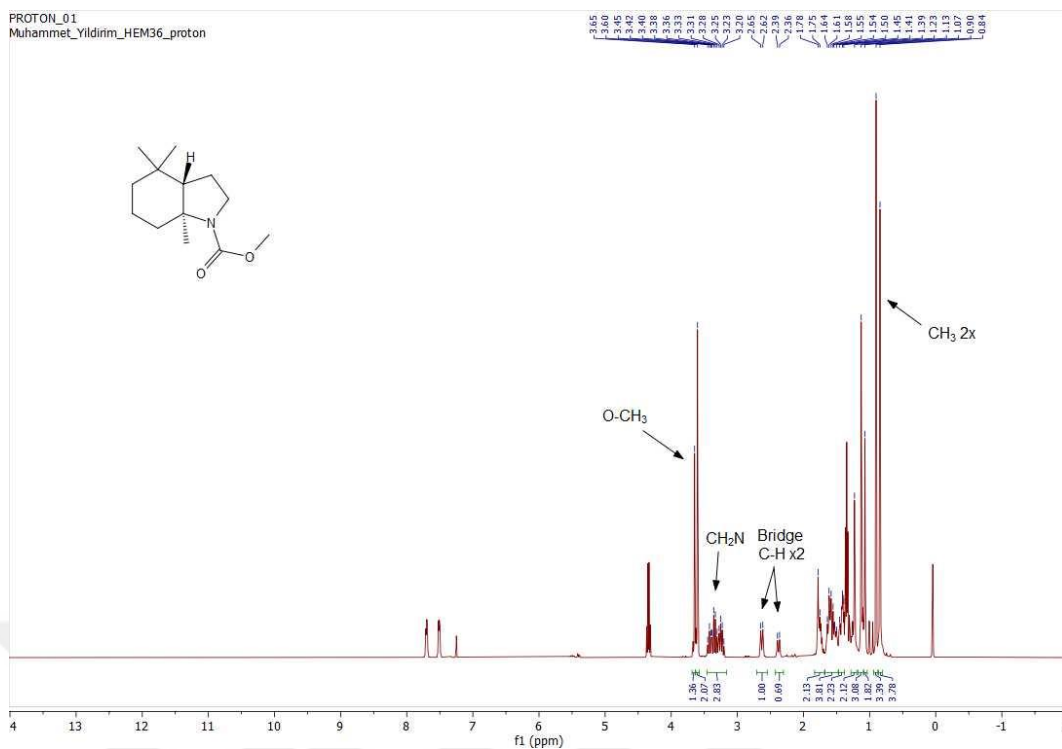


Figure 4.22. ^1H NMR spectrum of methyl *trans*-trimethyloctahydroindole carbamate **195a**.

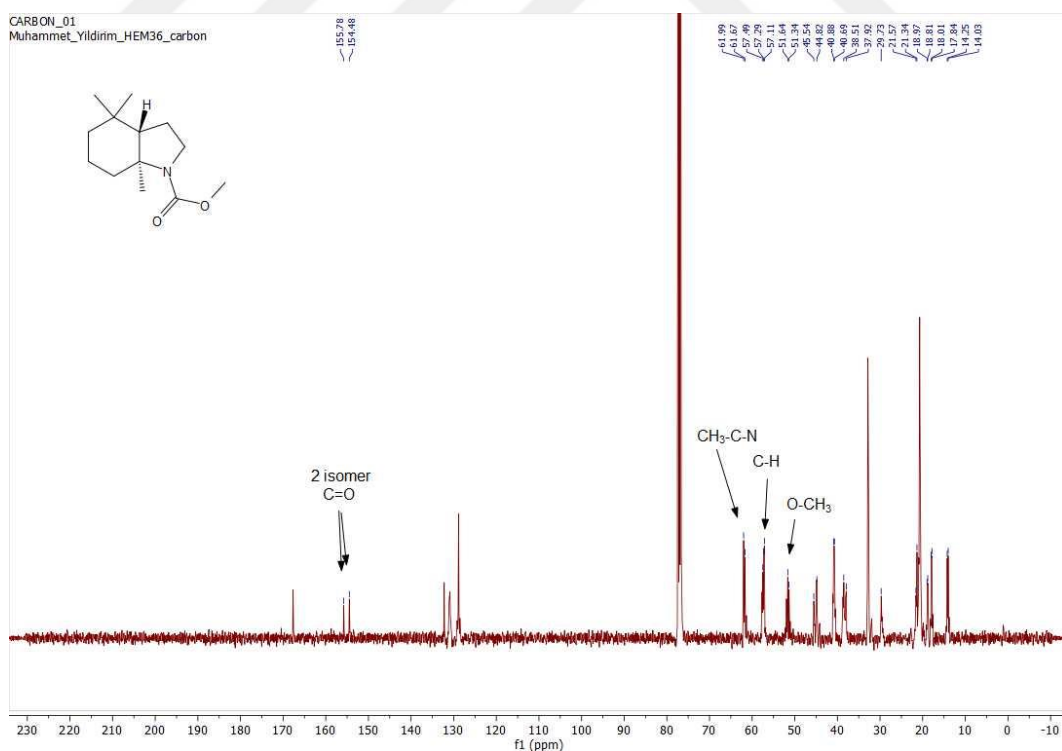
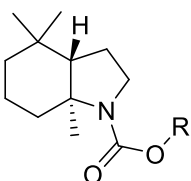


Figure 4.23. ^{13}C NMR spectrum of methyl *trans*-trimethyloctahydroindole carbamate **195a**.

Table 4.10. Spectroscopic data for characterization of trans-trimethyloctahydroindole carbamates **195**.

 195 (trans-)									
		IR (cm ⁻¹)		¹ H-NMR (δ, ppm)			¹³ C-NMR (δ, ppm)		
195	R	Aliph CH str.	C=O str.	Bridge CH	Bridge CH₃	CH₂N	C=O	N-C-CH₃	Bridge CH
a	Me	2952-2866	1696	2.56, d	1.23, s	3.45-3.20	154.5	61.7	57.3
b	Et	2953-2853	1697	2.64, d	1.22, s	3.47-3.28	154.3	61.8	57.5
c	Bu	2955-2867	1693	2.65, d	1.25, s	3.44-3.27	154.5	62.0	57.4
d	Ph	2953-2853	1723	2.67, m	1.29, m	3.59-3.39	153.3	62.8	57.4
e	p-MeO	2953-2856	1720	2.31, d	1.24, s	3.40-3.26	156.8	63.0	56.5

When the proton NMR spectra of the reduction products (**195a-e**) were examined, it was evident that many of compounds **195** was obtained as a mixture of diastereomers, particularly in the signals of the bridge CH protons. By comparing the integrated areas of bridge CH peaks for both isomers as indicative signals, the diastereomer ratios were determined (Table 4.11). For example, in the proton NMR spectrum of compound **195a**, the diastereomeric ratio was determined as 1/0.7 (Figure 4.24). On the other hand, upon analyzing the proton NMR spectrum of compound **195m** (p-MeO), it was found that no isomer formation occurred, indicating the presence of a single product (Figure 4.25).

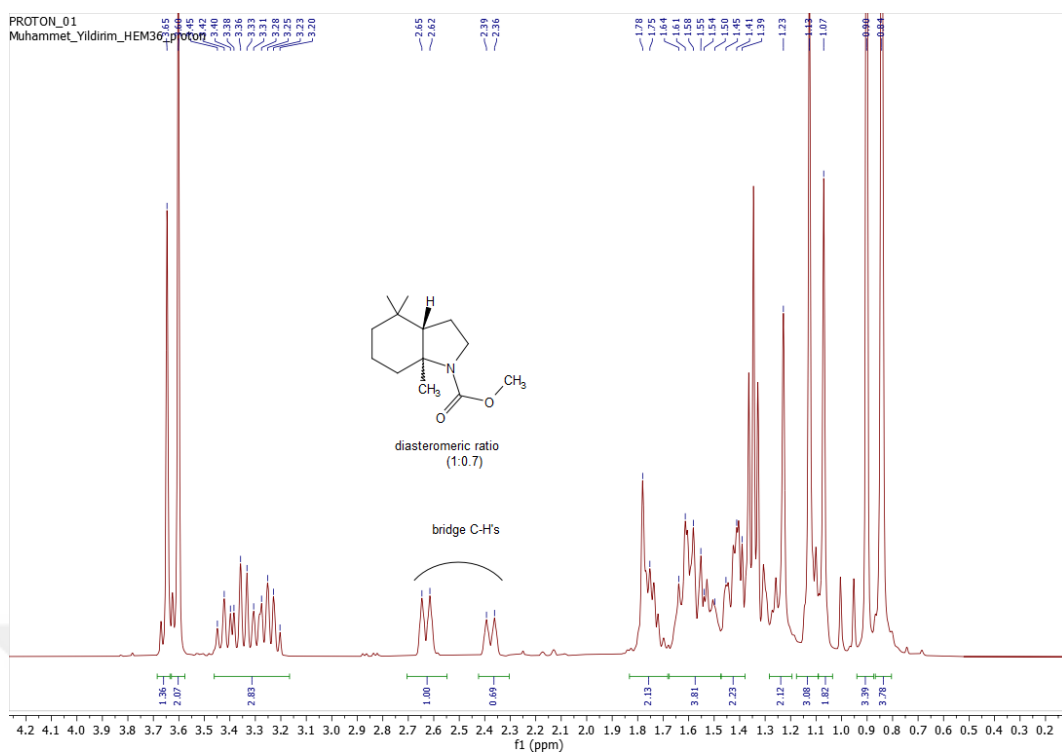


Figure 4.24. The bridge CH signals in the proton NMR of compound **195a** indicating the diastereomeric ratio.

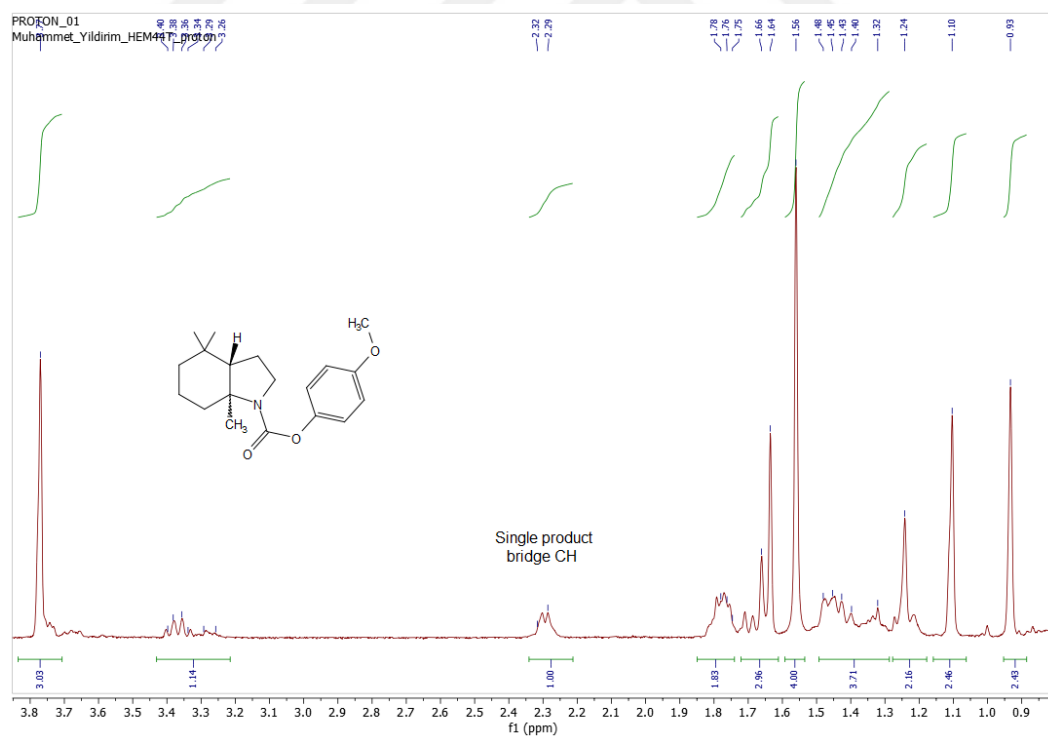


Figure 4.25. The bridge CH signal in the proton NMR of compound **195m** indicates the presence of a single product.

Table 4.11. Diastereomeric ratios of compounds **195**.

195	R	Diastereomeric ratio
a	Me	1/0.7
b	Et	1/0.66
e	Bu	1/1.07
k	Ph	1/0.68
e	p-MeO-Ph*	1

* Single product

The determination of the exact masses (HRMS) of compounds (**195a-e**) was performed using LC-MS analysis. For instance, in the case of **195b**, the expected HRMS result for *trans*-trimethyloctahydroindole ethyl carbamate should be m/z 237.17288 $[M-2H]^+$, while the LC-MS analysis resulted in m/z 237.17105 $[M-2H]^+$, indicating a high level of precision (Table 4.12, Figure 4.26a). Furthermore, the exact mass result of **195b** as $(M-H)^+$ ion was also confirmed with high sensitivity (Table 4.12, Figure 4.26b). Additionally, the exact masses of all other *trans*-trimethyloctahydroindole compounds **195a-e** were determined with high sensitivity using LC-MS analysis, and the results are presented in Table 4.12.

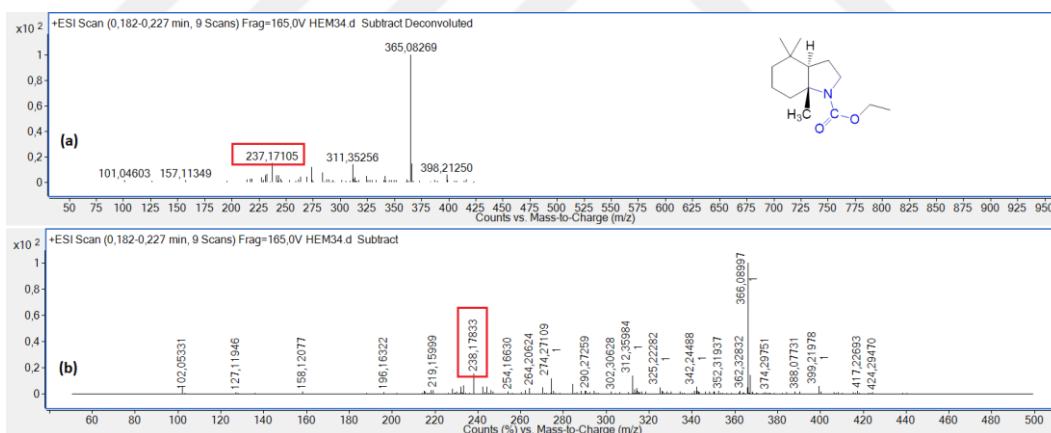


Figure 4.26. Exact mass (HRMS) spectrum as $(M-2H)^+$ and $(M-H)^+$ for ethyl *trans*-trimethyloctahydroindole carbamate.

Table 4.12. Exact mass (HRMS) datas of trans-trimethyloctahydroindole carbamates.

Carbamates	Ion	Theoric (Expected) Exact Mass, m/z	Experimental (Founded) Exact Mass, m/z
195a (Et)	M-2H ⁺	237.17288	237.17105
	M-H ⁺	238.18070	238.17833
195b (Me)	M ⁺	225.17288	225.17290
195c (Bu)	M ⁺	267.21983	267.21961
	M+H ⁺	268.22765	268.22688
195d (Ph)	M ⁺	287.18853	287.18736
	M+H ⁺	288.19635	288.19464
195e (p-MeO)	M ⁺	317.19909	317.19856
	M+H ⁺	318.20692	318.20584

4.4 Olfactive and In Vitro Cytotoxicity Tests

4.4.1 Olfactive Results

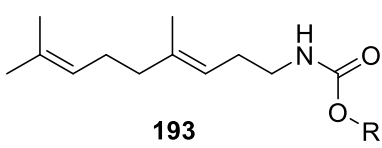
A first-level test was conducted to determine the olfactory properties of the synthesized and characterized homogeranyl carbamate compounds (**193a-n**) and trimethyloctahydroindole carbamate esters **194-195**. Samples of each compound were prepared in quantities of 0.1-0.2 g for the test. An organoleptic test, administered by expert individuals, was used to determine the nature, intensity, strength, and longevity of the odor. Solutions of each compound in 10% dipropylene glycol were prepared for use in the test and applied to perfume test strips. Expert perfumers (a group of 3 people) conducted scent identification tests at room temperature (20-25°C) at fresh, 4-hours, and 24-hours intervals, with 3-4 scent identifications performed consecutively in 1-2 minutes intervals. Upper and lower notes were determined for each compound. By identifying the compounds with high scent intensity, the perfumers were able to make determinations regarding their potential as fragrance components.

The olfactory test results and details for the first series homogeranyl carbamate compounds (**193a-n**) are presented below.

According to the olfactory test studies, compounds **193a**, **193b**, **193h**, **193j**, **193k** were found to have a "solvent-like" odor, except for compound **193k**, the other carbamates **193a**, **193b**, **193h**, **193j** were evaluated to be volatile after 4 hours. In addition, compounds **193f**, **193g**, and **193i** were reported to have no odor characteristics. Compounds **193c** and **193d** were found to have woody-earthy-camphor and woody-earthy persistent upper and lower fragrance notes respectively (up to 24 hours), compound **193e** was determined to have herbal-green upper and lower fragrance notes (up to 4 hours). Finally, it was determined that aryl-substituted derivatives such as **193l**, **193m**, and **193n** generally had medicinal upper and lower fragrance notes. Compound **193n** was found to be persistent for up to 24 hours, while compounds **193l** and **193m** were persistent for up to 4 hours before exhibiting volatile properties (Table 4.13).

In general, considering these results, it can be understood that among the homogeranyl carbamate compounds, derivatives **193a**, **193b**, **193c**, **193d**, **193e**, **193h**, **193j**, **193k**, **193l**, **193m** and **193n** (a total of 11) exhibit olfactory properties, with particularly 6 of them **193c**, **193d**, **193e**, **193l**, **193m**, **193n** showing a greater potential to be fragrance components.

Table 4.13. Olfactive test results of homogeranyl carbamates (**193a-n**).

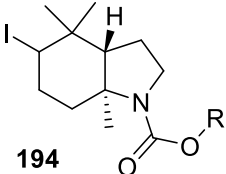
 193				
Compound	R	Fresh	4 hours	24 hours
a	Me	Solvent-Like	Solvent-Like	-
b	Et	Solvent-Like	Solvent-Like	-
c	Pr	Woody-Earthy-Camphor	Woody-Earthy-Camphor	Woody-Earthy-Camphor
d	<i>i</i> -Pr	Woody-Earthy	Woody-Earthy	Woody-Earthy
e	Bu	Herbal-Green	Herbal-Green	-
f	<i>i</i> -Bu	No odor	No odor	No odor
g	sec-Bu	No odor	No odor	No odor
h	<i>i</i> -Amyl	Solvent-Like	Solvent-Like	-
i	Hexyl	No odor	No odor	No odor
j	Bz	Solvent-Like	Solvent-Like	Solvent-Like
k	Ph	Solvent-Like	Solvent-Like	-
l	<i>p</i> -Tolyl	Medicinal	Medicinal	-
m	<i>p</i> -MeO	Medicinal	Medicinal	-
n	<i>p</i> -NO ₂	Medicinal	Medicinal	Medicinal

The details of the olfactory test results for the second series trans-5-iodotrimethyloctahydroindole carbamate compounds (**194a-n**) are provided below.

Based on the olfactory test studies, it was determined that compounds **194a**, **194b**, **194j**, and **194k** had a "solvent-like" odor and exhibited volatile properties after 4 hours. In addition, it was reported that compounds **194c**, **194d**, **194e**, **194f**, **194g**, **194i**, **194m** and **194n** had no olfactory value. Compound **194h** (*i*-amyl) and **194l** (*p*-tolyl), on the other hand, were found to have animalic-cedarwood-atlas-like upper and lower fragrance notes and exhibited persistence for up to 24 hours (Table 4.14).

In general, among the trans-5-iodotrimethyloctahydroindole carbamate compounds **194**, it was observed that 6 of them **194a**, **194b**, **194h**, **194j**, **194k**, **194l** exhibited olfactory properties, and only derivatives **194h** and **194l** (2 in total) had a high potential to be fragrance components.

Table 4.14. Olfactive results of trans-5-iodotrimethyloctahydroindole carbamate (194a-n).

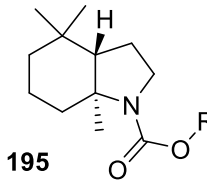
 194				
Compound	R	Fresh	4 hours	24 hours
a	Me	Solvent-Like	Solvent-Like	No odor
b	Et	Solvent-Like	Solvent-Like	No odor
c	Pr	No olfactive value	No odor	No odor
d	<i>i</i> -Pr	No olfactive value	No odor	No odor
e	Bu	No olfactive value	Solvent-Like	No odor
f	<i>i</i> -Bu	No olfactive value	No odor	No odor
g	sec-Bu	No olfactive value	No odor	No odor
h	<i>i</i> -Amyl	Animalic-Cedarwood-Atlas	Animalic-Cedarwood-Atlas	Animalic-Cedarwood-Atlas
i	Hexyl	No olfactive value	No odor	No odor
j	Bz	Solvent-Like	No odor	No odor
k	Ph	Solvent-Like	No odor	No odor
l	<i>p</i> -Tolyl	Animalic-Cedarwood-Atlas	Animalic-Cedarwood-Atlas	Animalic-Cedarwood-Atlas
m	<i>p</i> -MeO	No olfactive value	No odor	No odor
n	<i>p</i> -NO ₂	No olfactive value	No odor	No odor

The olfactory test results and details for trans-trimethyloctahydroindole carbamate compounds (**195a-e**), which are reduction products as the fourth series, are explained below.

According to the conducted olfactory test studies, it has been reported to us that compounds **195e** and **195m** do not have "olfactory value." Additionally, compounds **195b** and **195k** were found to have earthy top and base scent notes, exhibiting persistence for up to 4 hours (moderately persistent). Furthermore, compound **195a** in this series was determined to have fresh-bergamot top and base scent notes and exhibited persistence for up to 24 hours (Table 4.15).

In general, it can be concluded that among the compounds **195**, derivatives **195a**, **195b** and **195k** (a total of 3 compounds) possess olfactory value, displaying various fragrance nuances. Moreover, it is understood that these 3 derivatives have a significant potential to be used as fragrance compounds.

Table 4.15. Olfactory test results of trans-trimethyloctahydroindole carbamates (195a-e).

 195				
Compound	R	Fresh	4 hours	24 hours
a	Me	Fresh-Bergamot	Fresh-Bergamot	Fresh-Bergamot
b	Et	Earthy	Earthy	No odor
e	Bu	No olfactive value	No odor	No odor
k	Ph	Earthy	Earthy	No odor
m	p-MeO	No olfactive value	No olfactive value	No olfactive value

4.4.2 In Vitro Cytotoxicity Results

Cytotoxicity studies consist of two stages: preparation of cell lines and subsequent cell viability measurements with samples. The details regarding these stages are provided below in order.

For cell culture studies, cells (L929, fibroblast) are propagated in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 1% penicillin-streptomycin, 1% L-glutamine, and 10% Fetal Bovine Serum (FBS) at 37°C with 5% CO₂. The cells are examined daily under an inverted microscope, and when they reach approximately 75-80% confluence, they are passaged.

The XTT method, which is widely used today, was employed to evaluate cell viability. For this purpose, cells were seeded in 96-well plates with each well containing 1x10⁴ cells in DMEM medium. After 24 hours, the culture medium within the plates was removed. Homogenaryl carbamate **193** or trimethyl octahydroindole carbamate **194,195** compounds were applied to the wells in three different concentrations, namely 10⁻⁵, 10⁻⁶, and 10⁻⁷ M, in phenol red-free DMEM, and incubated for 24 hours. Following incubation, the active compounds were removed by washing the cells twice with phenol red-free DMEM. XTT (Cell Proliferation Kit II) solution was added to the cells and incubated for 4 hours. At the end of the incubation period, the absorbance values at 450 nm wavelength were measured using a microplate reader (Thermo Scientific Multiskan FC).

One of the necessary preliminary tests in our study is the cytotoxicity testing, which aims to determine the potential of compounds with olfactory characteristics to act as fragrance compounds. For this purpose, cytotoxicity studies were conducted for all the carbamate products (**193**, **194**, **195**) in the Department of Pharmacology at BAIBU Medical Faculty, and the results were reported below.

The solutions of the first series in the study, which are homogeranyl carbamate compounds (**193a-n**), were prepared at three different concentrations (10^{-5} , 10^{-6} , 10^{-7} M), and in vitro cytotoxicity studies were conducted against fibroblast cell lines (L929). Based on the test results, the cytotoxicity of the **193** compounds was evaluated considering the cell viability results observed at the highest concentration, which was 10^{-5} M. In this concentration, a cytotoxic effect criterion of 90% cell viability or lower was accepted. According to this criterion, it was determined that none of the 14 compounds in series **193** exhibited a significant cytotoxic effect (Table 4.16).

Table 4.16. Cytotoxicity results of homogeranyl carbamates (**193a-n**).

	Molarity (M)	Cell Viability* (%)		Molarity (M)	Cell Viability* (%)
Control		100	Control		100
193a	10^{-7}	97.4 ± 0.2	193h	10^{-7}	98.4 ± 0.2
	10^{-6}	96.5 ± 0.2		10^{-6}	97.5 ± 0.4
	10^{-5}	96.5 ± 0.4		10^{-5}	98.0 ± 0.2
193b	10^{-7}	95.6 ± 1.0	193i	10^{-7}	98.1 ± 0.7
	10^{-6}	97.3 ± 1.0		10^{-6}	98.0 ± 0.4
	10^{-5}	97.1 ± 0.9		10^{-5}	98.0 ± 0.3
193c	10^{-7}	97.2 ± 1.2	193j	10^{-7}	98.1 ± 0.3
	10^{-6}	98.0 ± 1.1		10^{-6}	99.0 ± 0.3
	10^{-5}	96.9 ± 1.4		10^{-5}	97.2 ± 0.2
193d	10^{-7}	97.6 ± 0.2	193k	10^{-7}	96.7 ± 1.1
	10^{-6}	97.2 ± 0.3		10^{-6}	96.8 ± 1.2
	10^{-5}	97.9 ± 0.5		10^{-5}	99.5 ± 0.7
193e	10^{-7}	97.3 ± 0.4	193l	10^{-7}	97.5 ± 0.6
	10^{-6}	96.8 ± 0.3		10^{-6}	97.2 ± 1.6
	10^{-5}	93.5 ± 1.6		10^{-5}	97.8 ± 0.2
193f	10^{-7}	98.7 ± 0.1	193m	10^{-7}	99.3 ± 0.3
	10^{-6}	97.3 ± 0.3		10^{-6}	98.7 ± 0.2
	10^{-5}	97.2 ± 0.2		10^{-5}	98.0 ± 0.6
193g	10^{-7}	96.9 ± 0.9	193n	10^{-7}	97.4 ± 0.4
	10^{-6}	96.7 ± 0.8		10^{-6}	97.3 ± 0.3
	10^{-5}	99.1 ± 0.4		10^{-5}	96.3 ± 0.2

The compounds of the second series, trans-5-iodotrimethyloctahydroindole carbamate (**194a-n**), were also prepared at three different concentrations (10^{-5} , 10^{-6} , 10^{-7} M) and tested in vitro against fibroblast cells (L929). Once again, the cell viability results at the highest concentration, 10^{-5} M, were considered, with values of 90% or lower considered cytotoxic. The cytotoxicity of the **194** compounds was examined accordingly. Based on the cell viability results obtained at this concentration, compounds **194b**, **194c**, **194d**, **194e**, and **194g** showed a high degree of cytotoxicity (31.6-45.5% cell viability), while compounds **194a**, **194f**, **194h**, **194i**, **194j**, and **194m** exhibited moderate to good cytotoxicity (52.8-89.7% cell viability). However, compounds **194k**, **194l**, and **194n** did not show significant cytotoxicity. In conclusion, out of the **194** compounds, 5 showed significant cytotoxicity, 6 exhibited moderate to good cytotoxicity, and 3 were non-cytotoxic. (Table 4.17).

Table 4.17. Cytotoxicity results of trans-5-iodotrimethyloctahydroindole carbamates (**194a-n**).

Molarity (M)			Molarity (M)		
Cell Viability* (%)			Cell Viability* (%)		
Control			Control		
100			100		
194a	10^{-7}	95.9 ± 0.4	194h	10^{-7}	97.2 ± 0.3
	10^{-6}	96.8 ± 0.5		10^{-6}	97.1 ± 1.2
	10^{-5}	77.9 ± 0.5		10^{-5}	89.7 ± 0.4
194b	10^{-7}	97.4 ± 0.3	194i	10^{-7}	97.5 ± 0.6
	10^{-6}	95.2 ± 0.1		10^{-6}	96.8 ± 0.3
	10^{-5}	45.0 ± 0.9		10^{-5}	75.7 ± 1.8
194c	10^{-7}	96.5 ± 0.4	194j	10^{-7}	97.8 ± 0.3
	10^{-6}	96.8 ± 0.3		10^{-6}	96.7 ± 0.4
	10^{-5}	39.3 ± 3.7		10^{-5}	85.1 ± 0.8
194d	10^{-7}	96.5 ± 0.3	194k	10^{-7}	95.4 ± 0.4
	10^{-6}	96.5 ± 0.3		10^{-6}	96.2 ± 0.5
	10^{-5}	45.5 ± 4.3		10^{-5}	95.3 ± 0.5
194e	10^{-7}	96.9 ± 0.4	194l	10^{-7}	96.7 ± 0.3
	10^{-6}	92.4 ± 0.8		10^{-6}	97.2 ± 0.2
	10^{-5}	36.6 ± 0.7		10^{-5}	92.5 ± 0.3
194f	10^{-7}	95.6 ± 0.6	194m	10^{-7}	96.5 ± 0.4
	10^{-6}	92.8 ± 1.3		10^{-6}	95.6 ± 1.3
	10^{-5}	52.8 ± 0.7		10^{-5}	80.5 ± 0.8
194g	10^{-7}	97.2 ± 0.6	194n	10^{-7}	98.6 ± 1.5
	10^{-6}	97.6 ± 0.4		10^{-6}	96.3 ± 0.5
	10^{-5}	31.6 ± 1.3		10^{-5}	101.3 ± 0.4

The last series, trans-trimethyl octahydroindole carbamate compounds (**195a-e**), were also tested against fibroblast cells (L929) at three different concentrations (10^{-5} , 10^{-6} , 10^{-7} M) by preparing solutions. Once again, results with cell viability below 90% at the highest concentration, 10^{-5} M, were considered cytotoxic, and the cytotoxicity of the **195** compounds was evaluated. Based on the cell viability results obtained at the 10^{-5} M concentration, compounds **195e**, **195k** and **195m** showed moderate to good cytotoxicity (53.3-83.5% cell viability). However, compounds **195a** and **195b** were found to have no significant cytotoxicity. (Table 4.18). As a result, it was determined that 3 of the **195** compounds showed moderate to good cytotoxicity, and the remaining 2 were non-cytotoxic.

Table 4.18. Cytotoxicity results of trans-trimethyloctahydroindole carbamates (**195a-e**).

	Molarity (M)	Cell Viability* (%)
Control		100
195a	10^{-7}	99.2 ± 0.7
	10^{-6}	100.1 ± 1.4
	10^{-5}	98.6 ± 2.3
195b	10^{-7}	96.3 ± 0.4
	10^{-6}	96.6 ± 0.4
	10^{-5}	96.7 ± 0.3
195e	10^{-7}	94.7 ± 1.4
	10^{-6}	98.2 ± 2.0
	10^{-5}	83.5 ± 0.9
195k	10^{-7}	97.8 ± 1.2
	10^{-6}	89.4 ± 8.3
	10^{-5}	65.5 ± 3.1
195m	10^{-7}	96.7 ± 0.9
	10^{-6}	96.7 ± 1.3
	10^{-5}	55.3 ± 2.3

5. CONCLUSIONS

The current dissertation study yielded several conclusions based on the results obtained;

In initial part of the study, namely, homogeranyl bromide **187**, homogeranyl nitrile **188** and homogeranylamine **189** were successfully synthesized from geraniol. These compounds were obtained in good yields through allylic bromination, nitrile and amine synthesis reactions, conducted under mild conditions. Their structures were elucidated using IR and NMR techniques and their characterization was further supported by physical analyses such as color, physical state, and R_f values.

In second part of our research, 15 novel homogeranyl carbamates (**193a-o**) were attempted to synthesize however, except **193o** 14 homogeranyl carbamates (**193a-n**) were successfully isolated in moderate to good yields after chromatographic separation through a base-catalyzed condensation reaction between homogeranylamine **189** and several chloroformates (**192a-n**). The structures of target compounds (**193a-n**) were characterized using physical data (color, physical state) and spectroscopic analyses (IR, ¹H-NMR, ¹³C-NMR and HRMS).

In the third part of the study, new 14 trans-5-iodo-trimethyloctahydroindole carbamates (**194a-n**) were obtained in moderate to good yields by base-mediated or base-free iodocyclizations of corresponding homogeranyl carbamates (**193a-n**) under very mild conditions. Subsequently, the synthesis of some trans-trimethyloctahydroindole carbamates **195** was achieved through the deiodination reaction of **194** derivatives. Following that, deiodination reaction of **194** derivatives led to the successful synthesis of trans-trimethyloctahydroindoles **195** in good to high yields. The structures of iodocyclization **194** and hydrogenation products **195** were fully characterized with physical data and spectroscopic analyses including IR, ¹H-NMR, ¹³C-NMR and HRMS.

In the fourth part of the study, olfactory tests were conducted by some expert noses to evaluate the odor characteristics and fragrance potential of homogeranylamine **189**, homogeranyl **193**, 5-iodo-trans-octahydroindole **194** and trans-octahydroindole **195** carbamates. The results of olfactory tests revealed that

the homogeranyl carbamates **193** exhibited certain top and heart notes, such as solvent-like, woody-earthly-camphor, woody-earthly, green-herbal, medicine-like. Besides, the trans-octahydroindole carbamate products **194**, **195** presented some solvent-like, animalic-earthly, animalic-cedarwood-atlas, earthy, fresh-bergamot fragrance notes.

In the final part of study, cytotoxic effect studies were conducted for all the carbamate products (**193**, **194**, **195**), a notable cytotoxic effect was not observed for any homogeranyl carbamate **193** products. However, for trimethyloctahydroindole carbamate **194**, **195** compounds, generally, five of them exhibited significant toxicity, nine of the products exhibited moderate-good toxicities. But five of them exhibited no toxicity.

6. REFERENCES

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7. APPENDICES

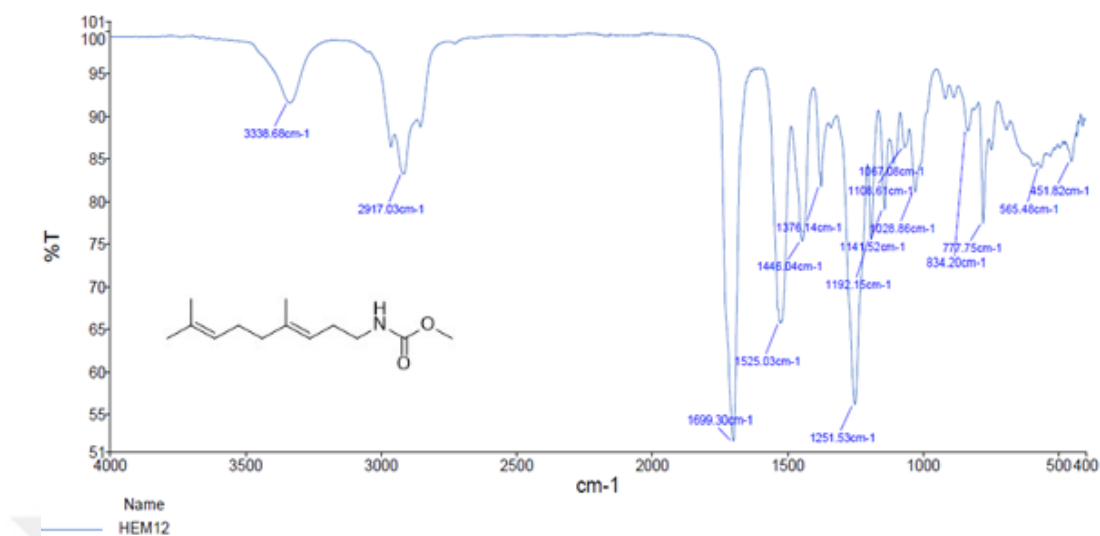


Figure 7.1. IR spectrum of methyl homogeranyl carbamate **193a**.

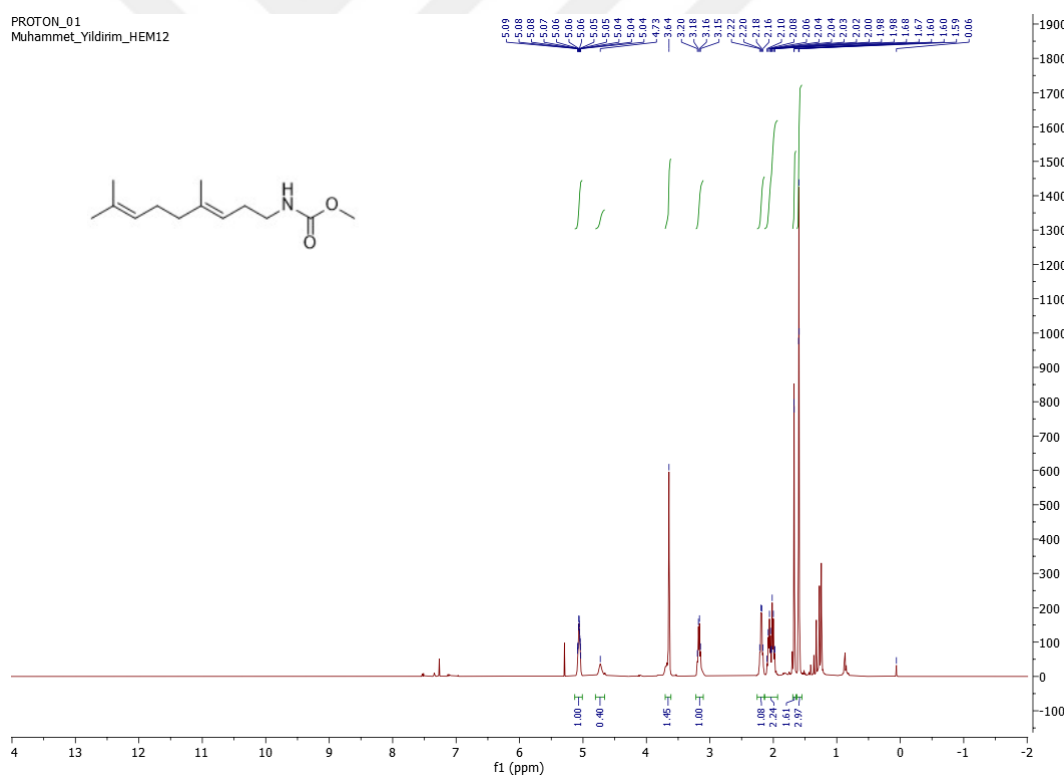


Figure 7.2. ^1H NMR spectrum of methyl homogeranyl carbamate **193a**.

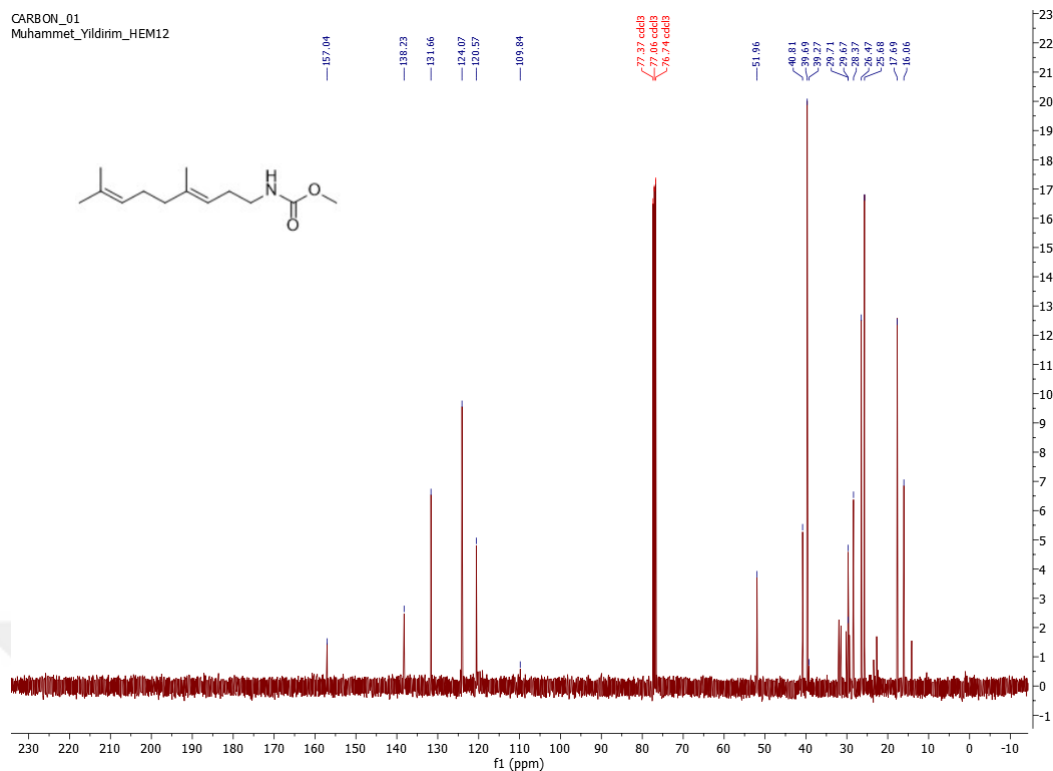


Figure 7.3. ¹³C NMR spectrum of methyl homogeranyl carbamate 193a.

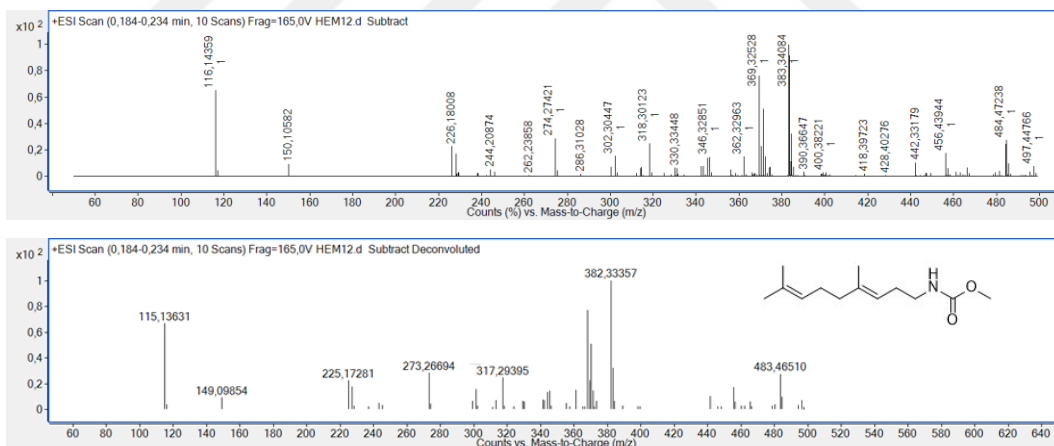


Figure 7.4. Exact mass (HRMS) spectrum of methyl homogeranyl carbamate 193a.

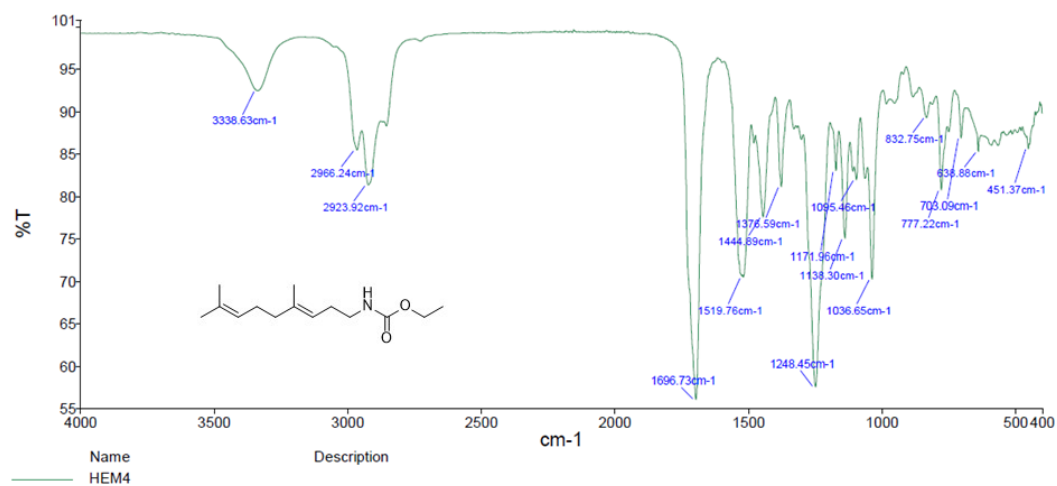


Figure 7.5. IR spectrum of ethyl homogeranyl carbamate **193b**.

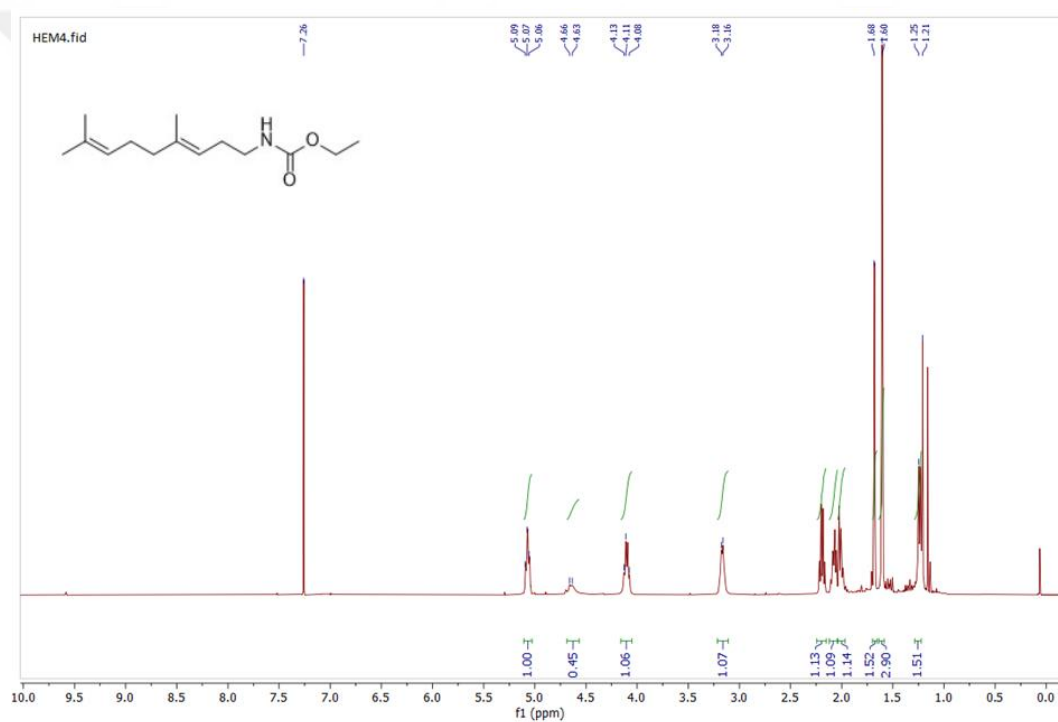


Figure 7.6. ^1H NMR spectrum of ethyl homogeranyl carbamate **193b**.

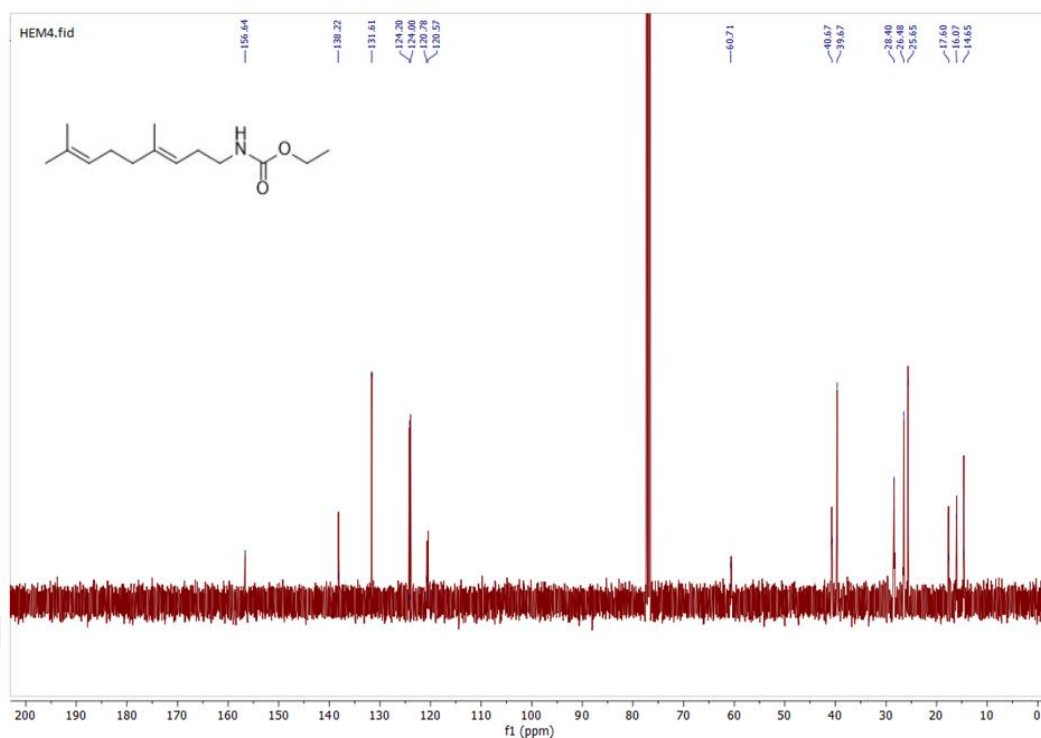


Figure 7.7. ¹³C NMR spectrum of ethyl homogreranyl carbamate **193b**.

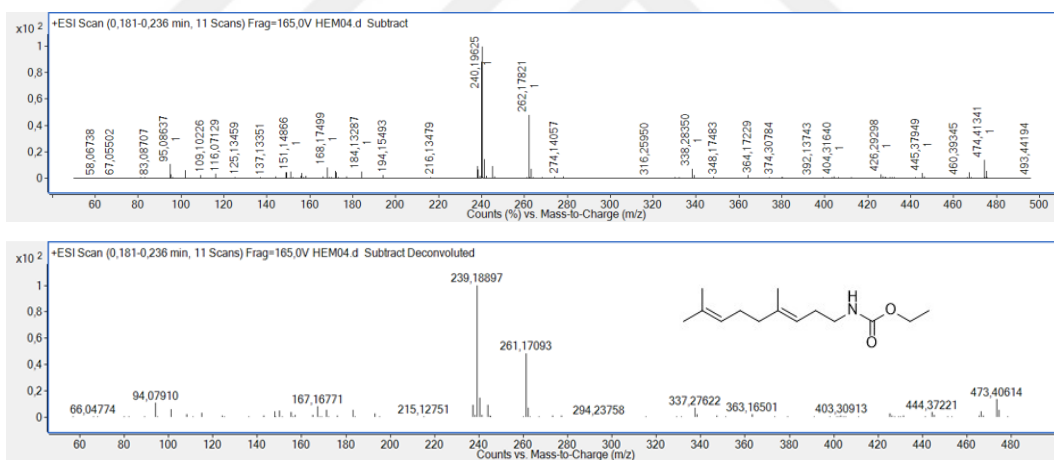


Figure 7.8. Exact mass (HRMS) spectrum of ethyl homogreranyl carbamate **193b**.

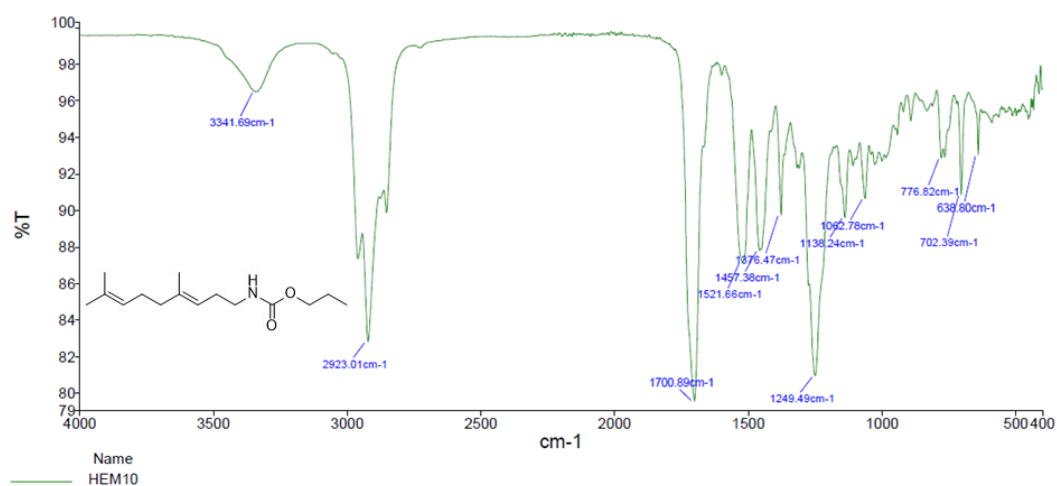


Figure 7.9. IR spectrum of propyl homogeranyl carbamate **193c**.

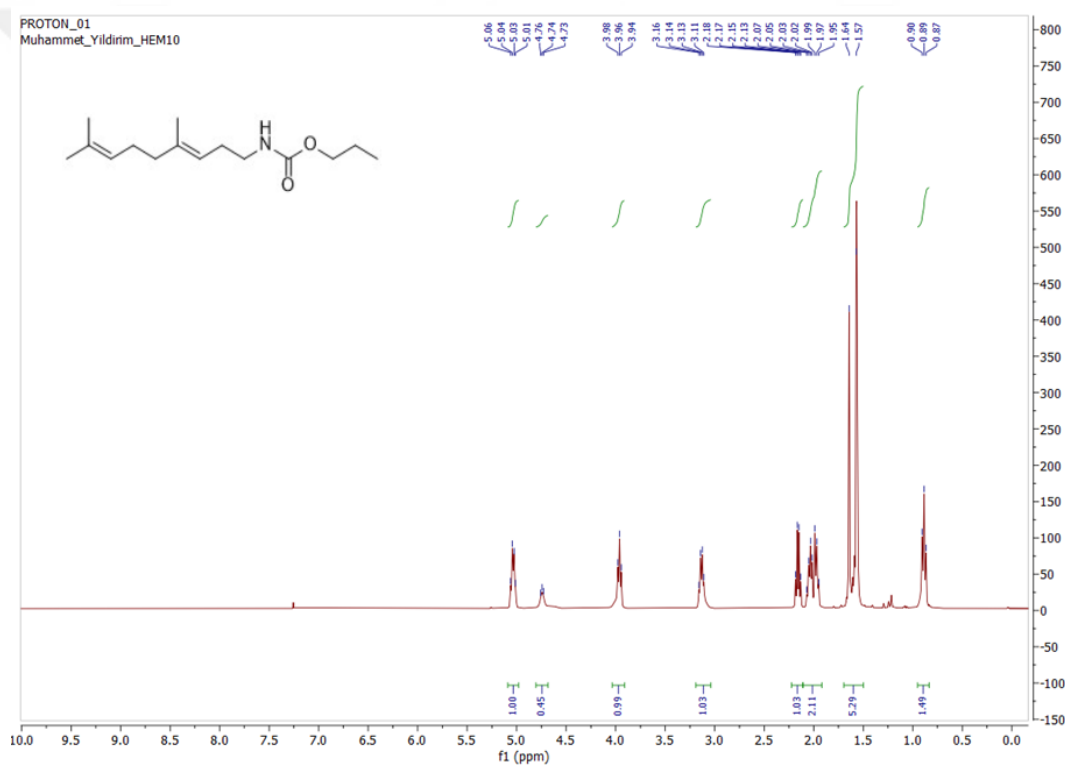


Figure 7.10. ¹H NMR spectrum of propyl homogeranyl carbamate **193c**.

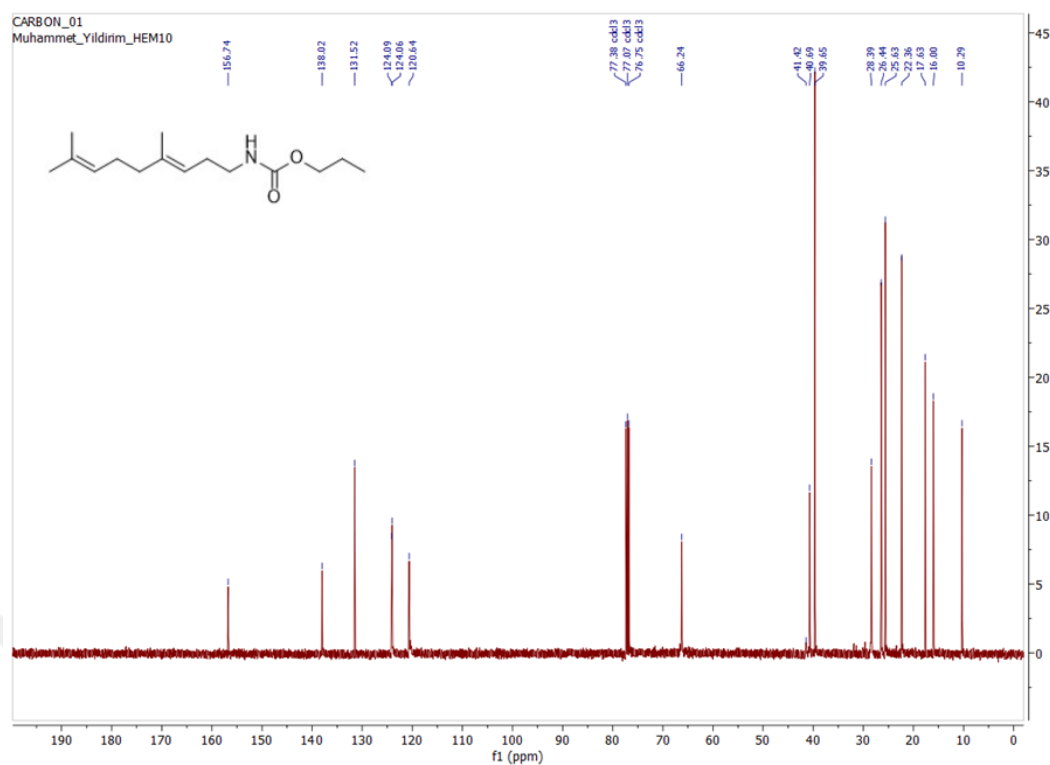


Figure 7.11. ^{13}C NMR spectrum of propyl homogeranyl carbamate **193c**.

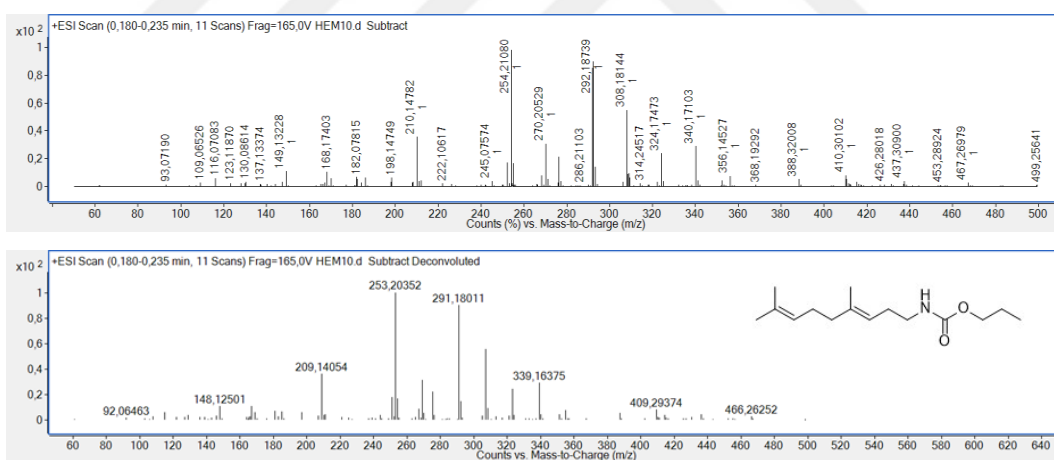


Figure 7.12. Exact mass (HRMS) spectrum of propyl homogeranyl carbamate **193c**.

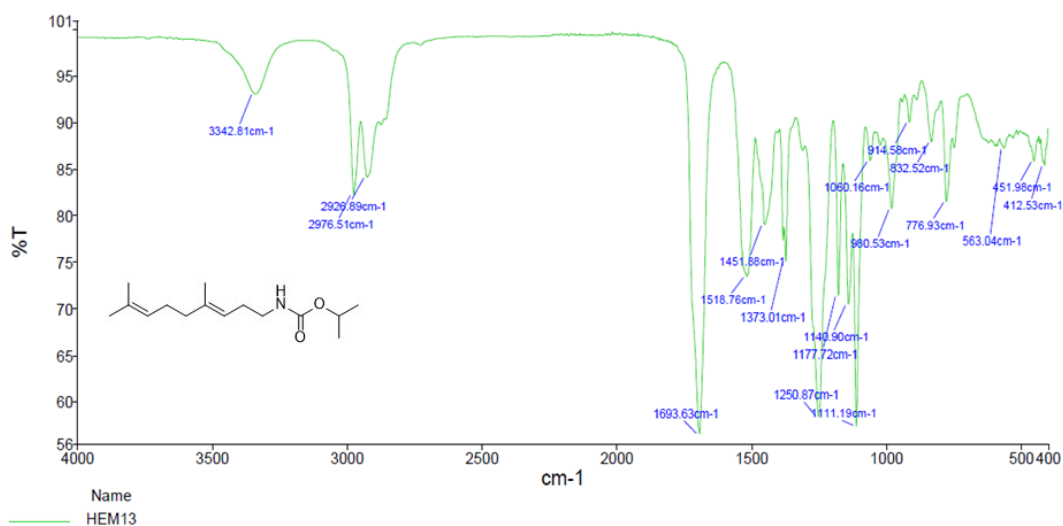


Figure 7.13. IR spectrum of *i*-propyl homogeranyl carbamate **193d**.

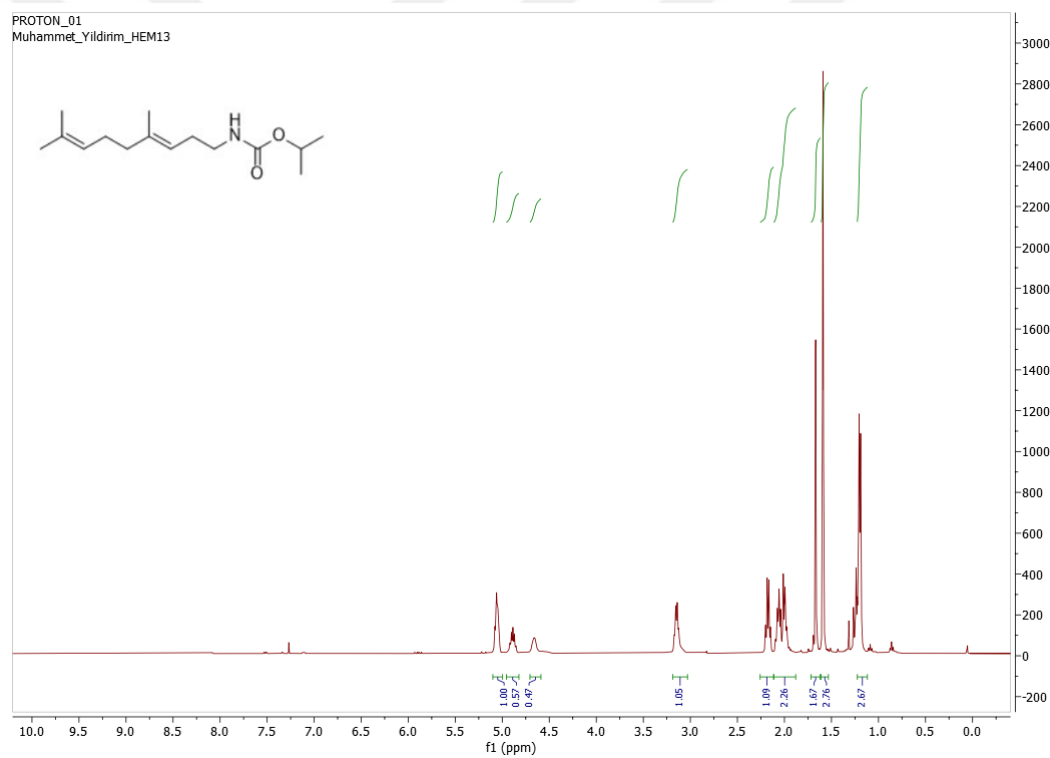


Figure 7.14. ¹H NMR spectrum of *i*-propyl homogeranyl carbamate **193d**.

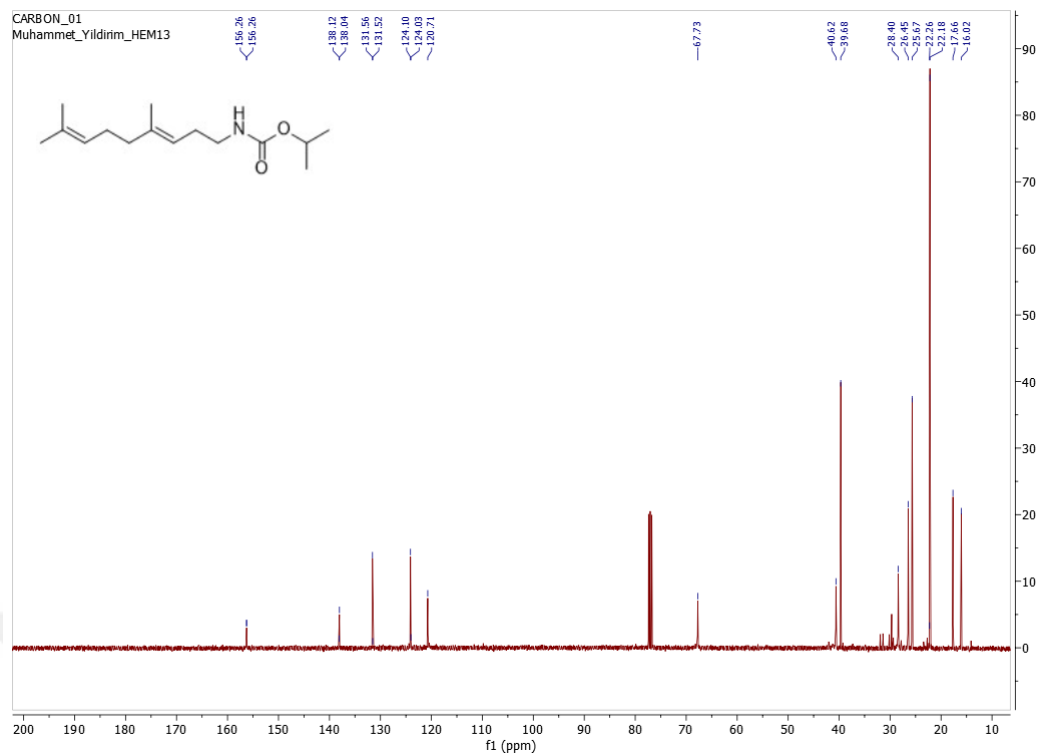


Figure 7.15. ^{13}C NMR spectrum of *i*-propyl homogreranyl carbamate **193d**.

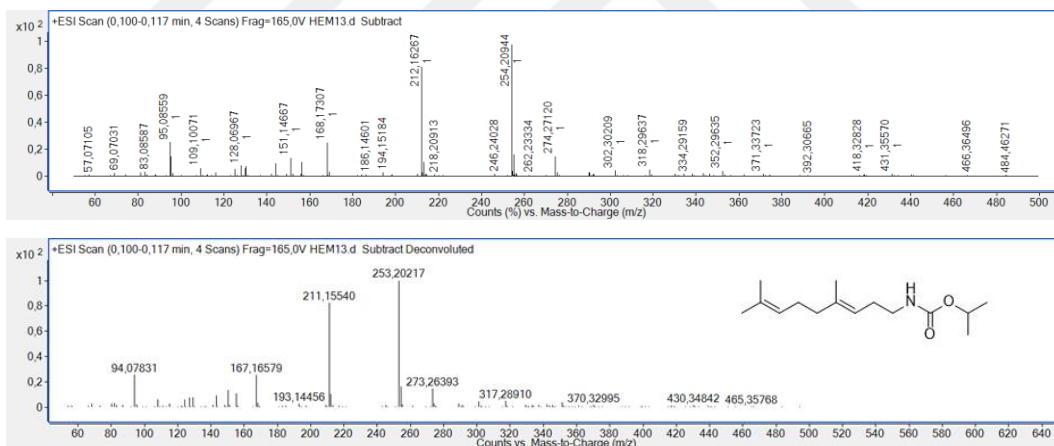


Figure 7.16. Exact mass (HRMS) spectrum of *i*-propyl homogreranyl carbamate **193d**.

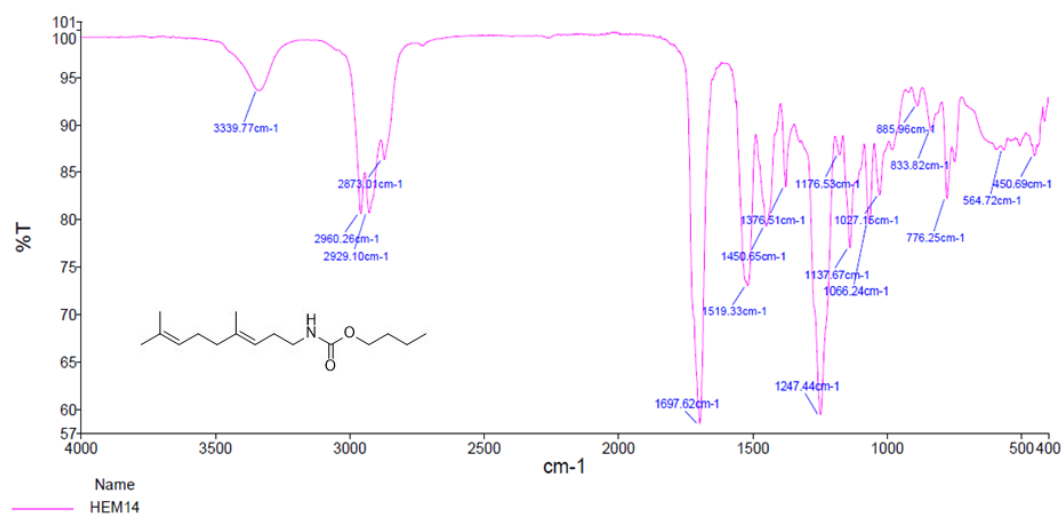


Figure 7.17. IR spectrum of butyl homogeranyl carbamate **193e**.

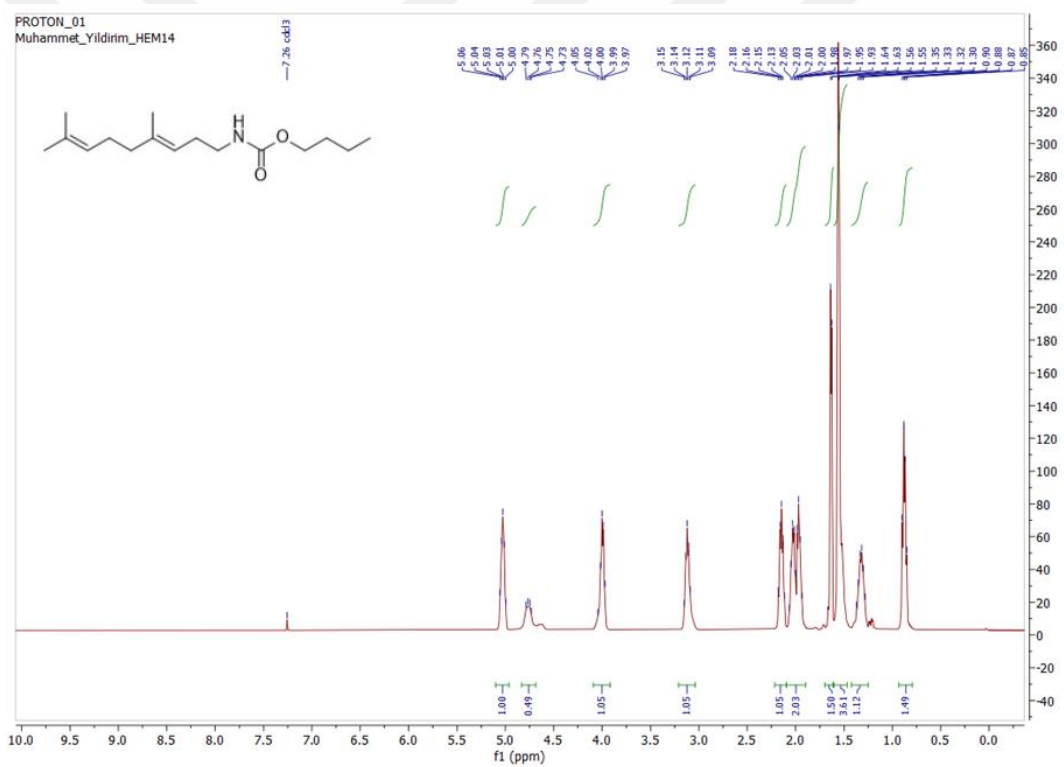


Figure 7.18. ^1H NMR spectrum of butyl homogeranyl carbamate **193e**.

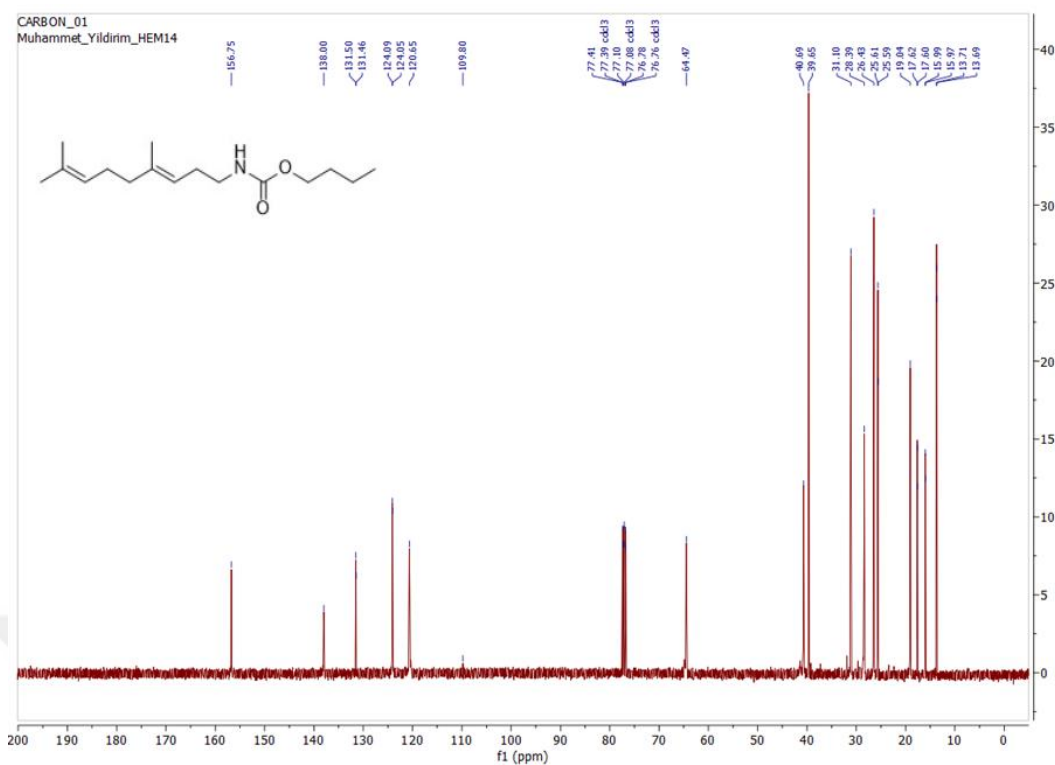


Figure 7.19. ^{13}C NMR spectrum of butyl homogeranyl carbamate **193e**.

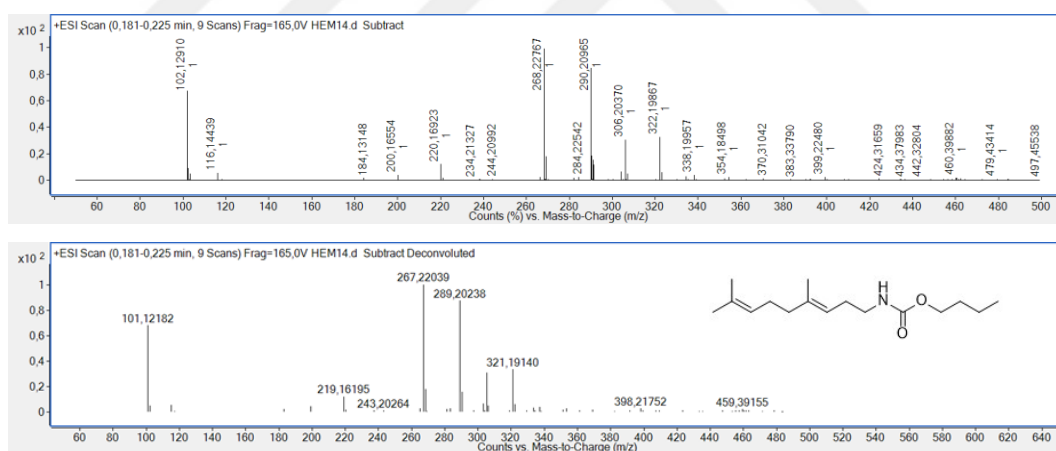


Figure 7.20. Exact mass (HRMS) spectrum of butyl homogeranyl carbamate **193e**.

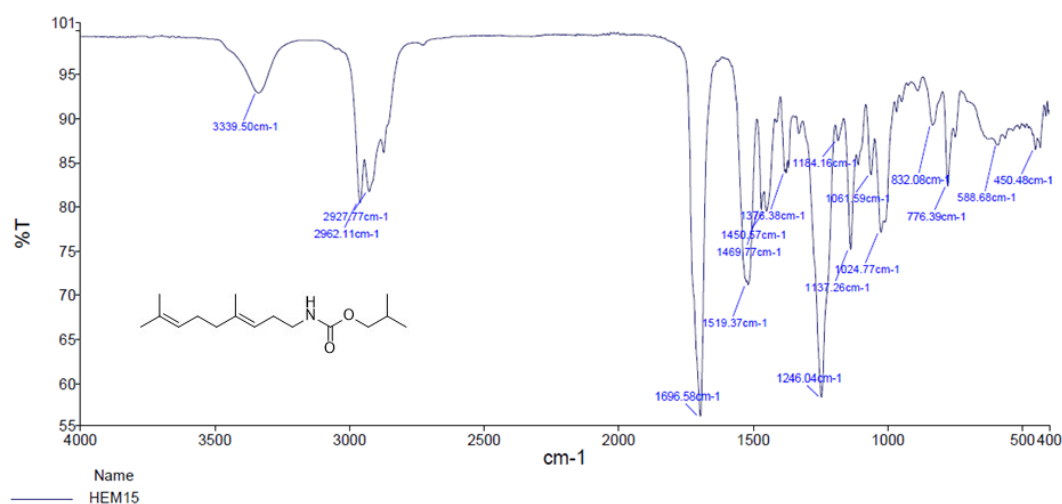


Figure 7.21. IR spectrum of *i*-butyl homogeranyl carbamate **193f**.

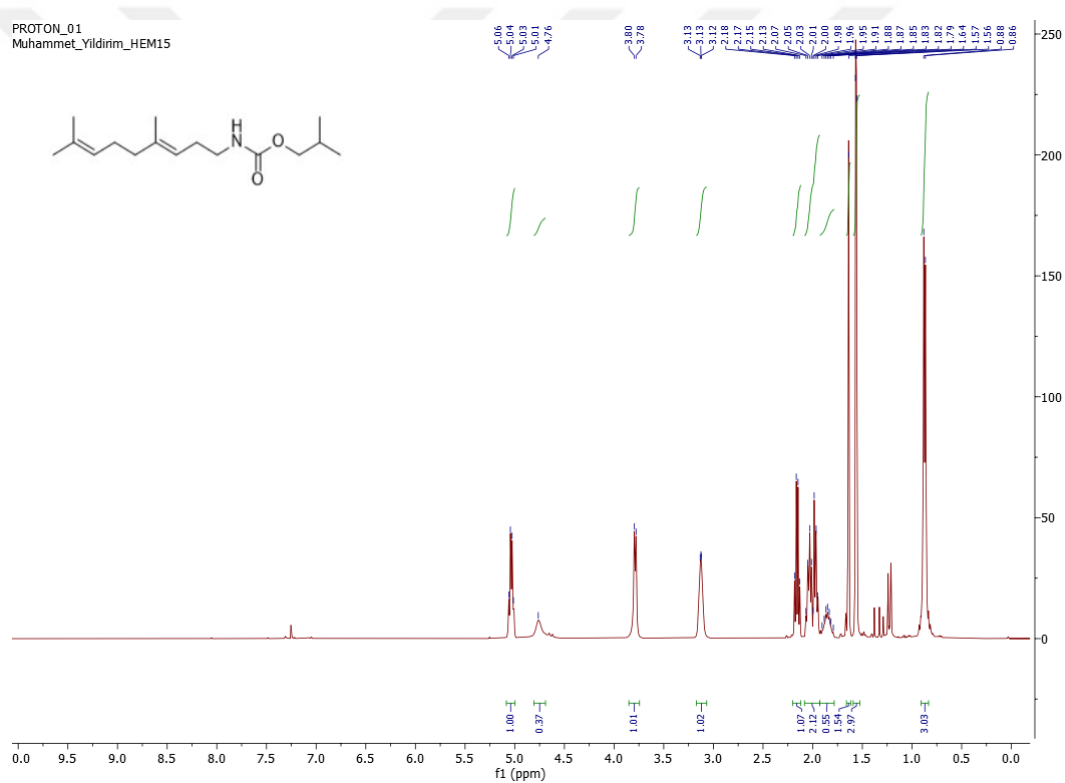


Figure 7.22. ¹H NMR spectrum of *i*-butyl homogeranyl carbamate **193f**.

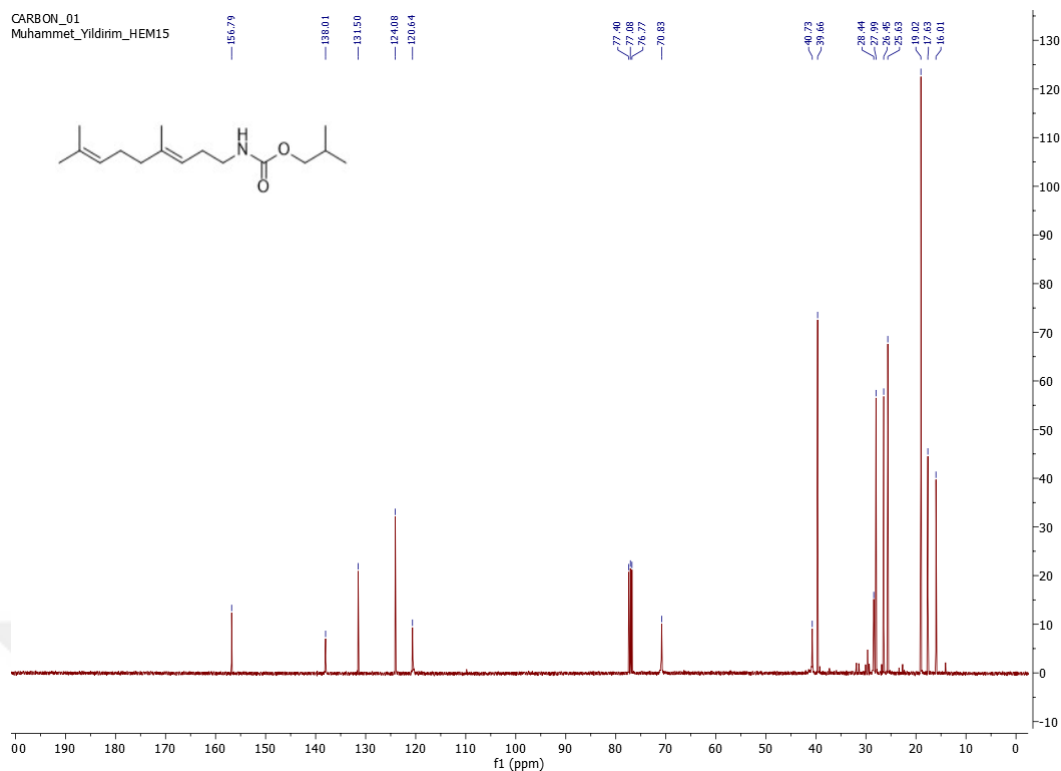


Figure 7.23. ^{13}C NMR spectrum of *i*-butyl homogeranyl carbamate **193f**.

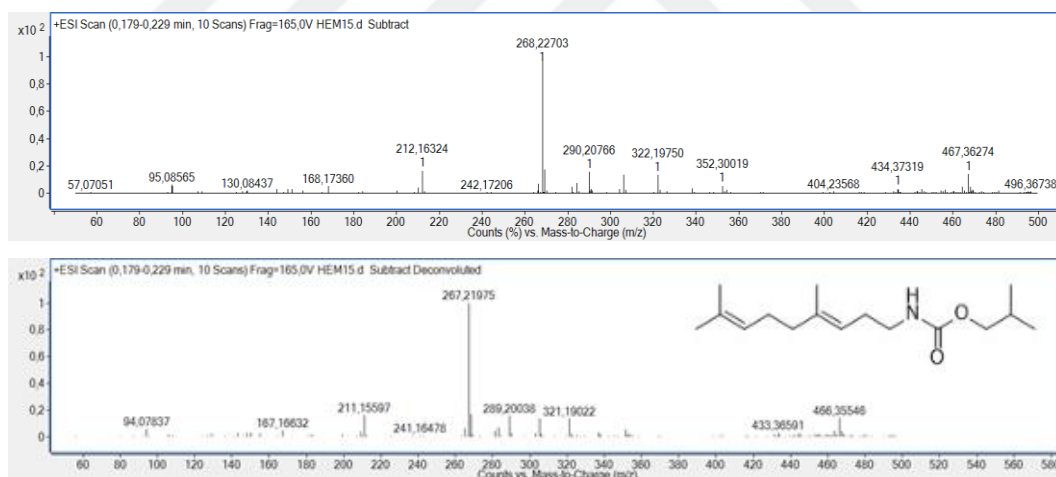


Figure 7.24. Exact mass (HRMS) spectrum of *i*-butyl homogeranyl carbamate **193f**.

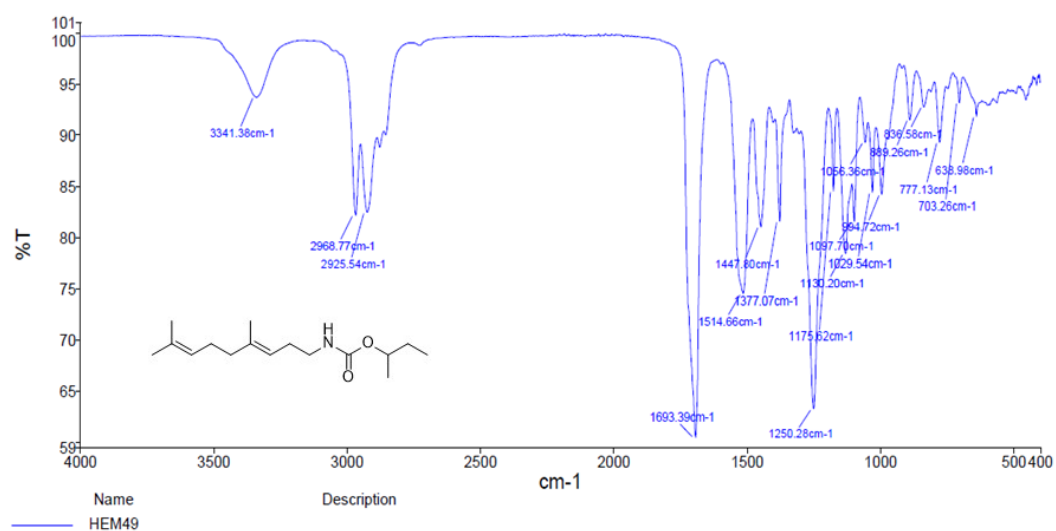


Figure 7.25. IR spectrum of sec-butyl homogeryl carbamate **193g**.

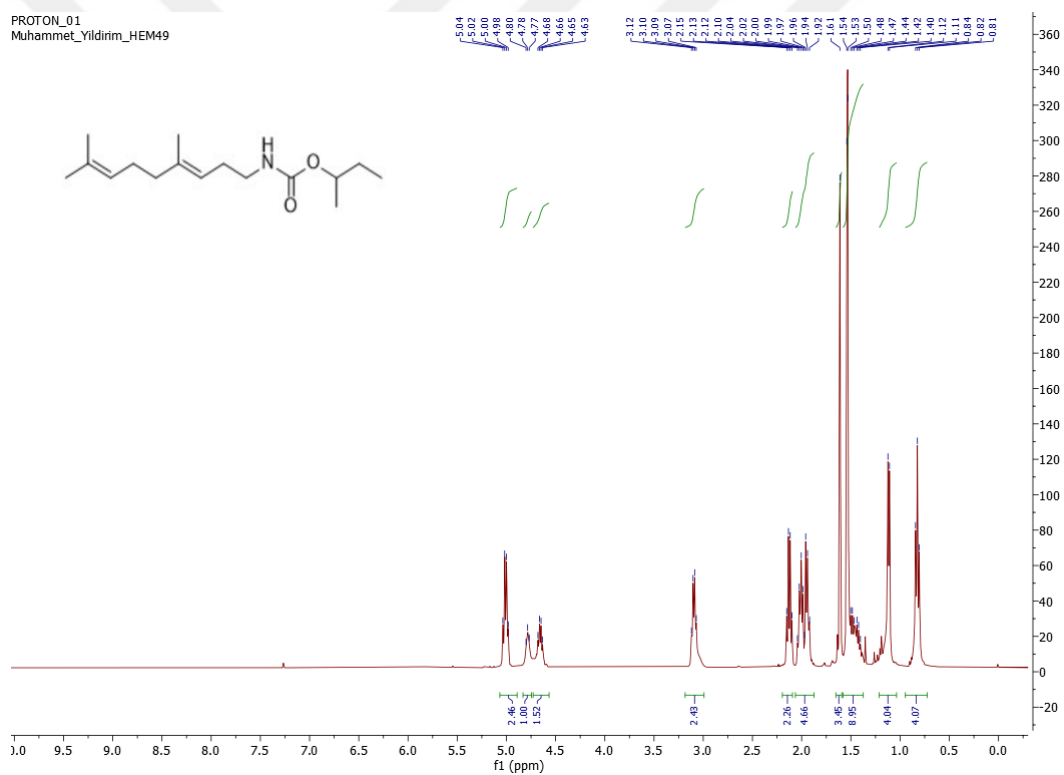


Figure 7.26. ¹H NMR spectrum of sec-butyl homogeryl carbamate **193g**.

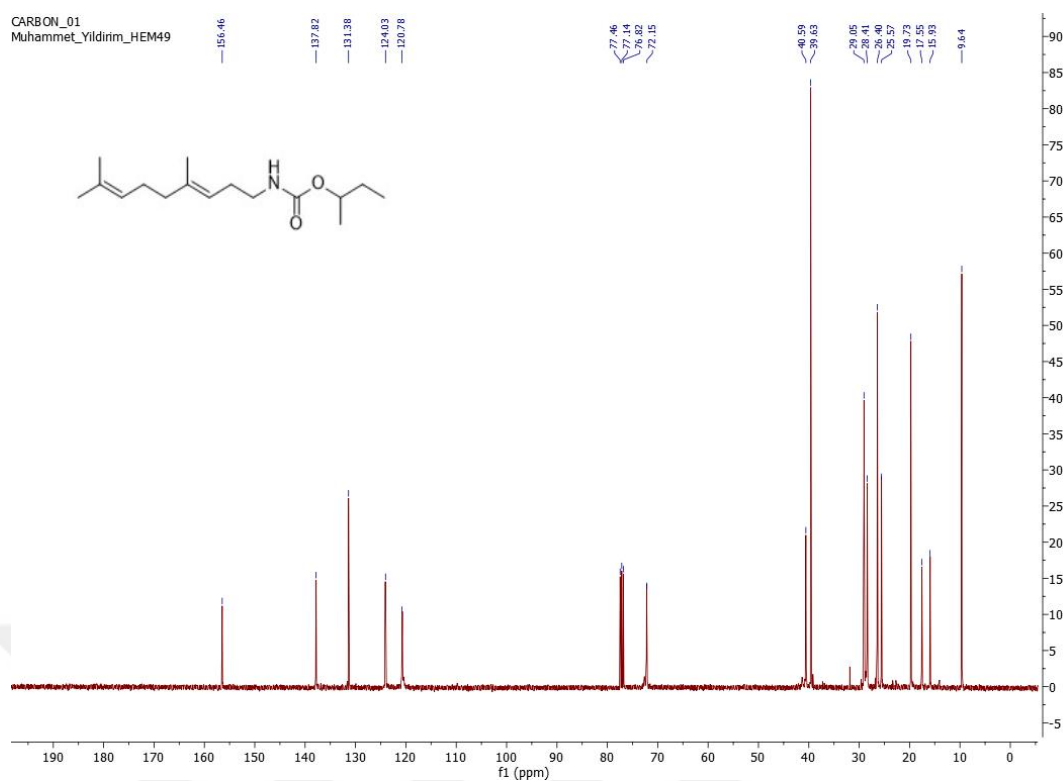


Figure 7.27. ^{13}C NMR spectrum of sec-butyl homogeranyl carbamate **193g**.

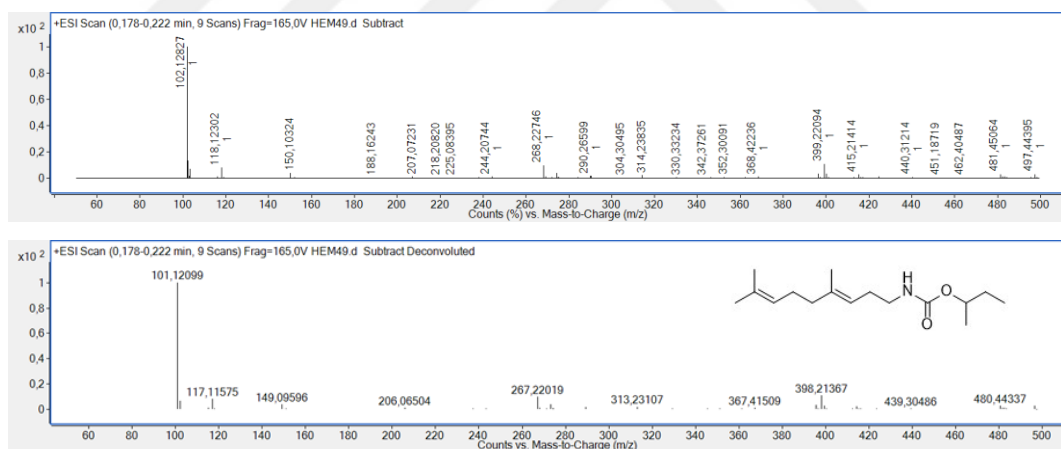


Figure 7.28. Exact mass (HRMS) spectrum of sec-butyl homogeranyl carbamate **193g**.

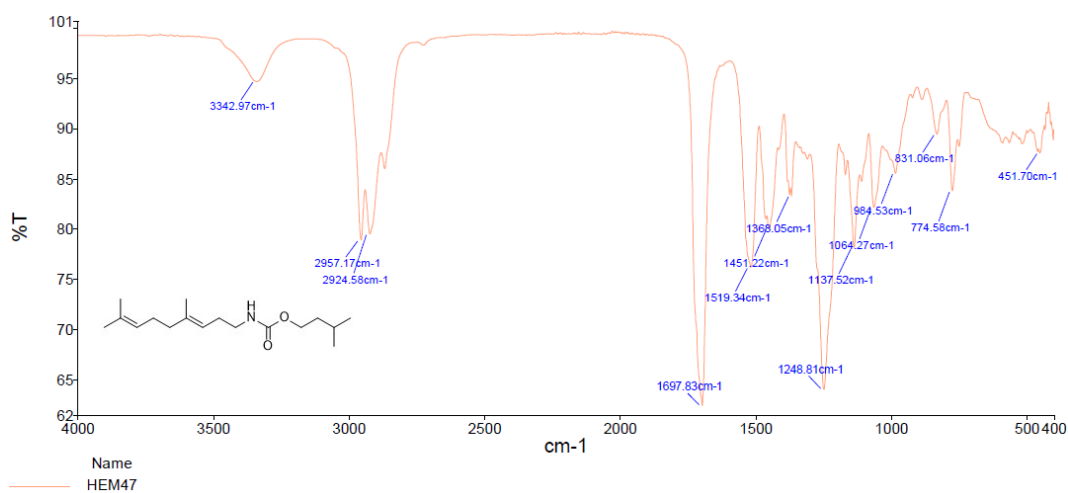


Figure 7.29. IR spectrum of *i*-amyl homogeranyl carbamate **193h**.

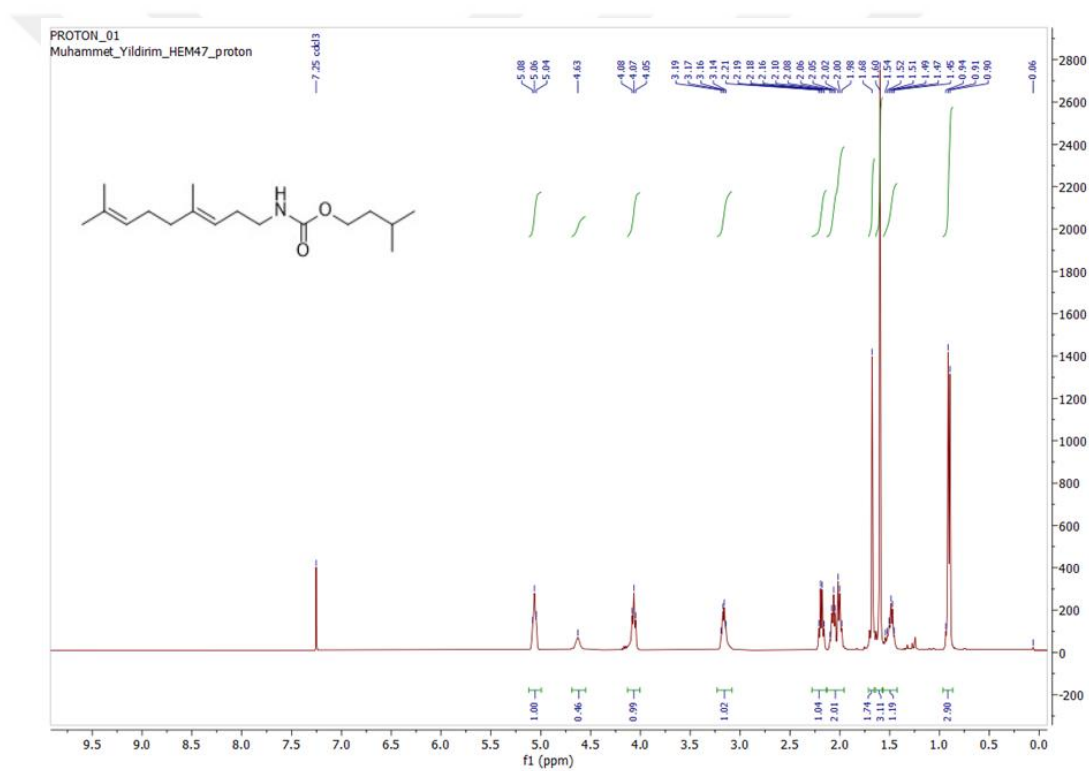


Figure 7.30. ¹H NMR spectrum of *i*-amyl homogeranyl carbamate **193h**.

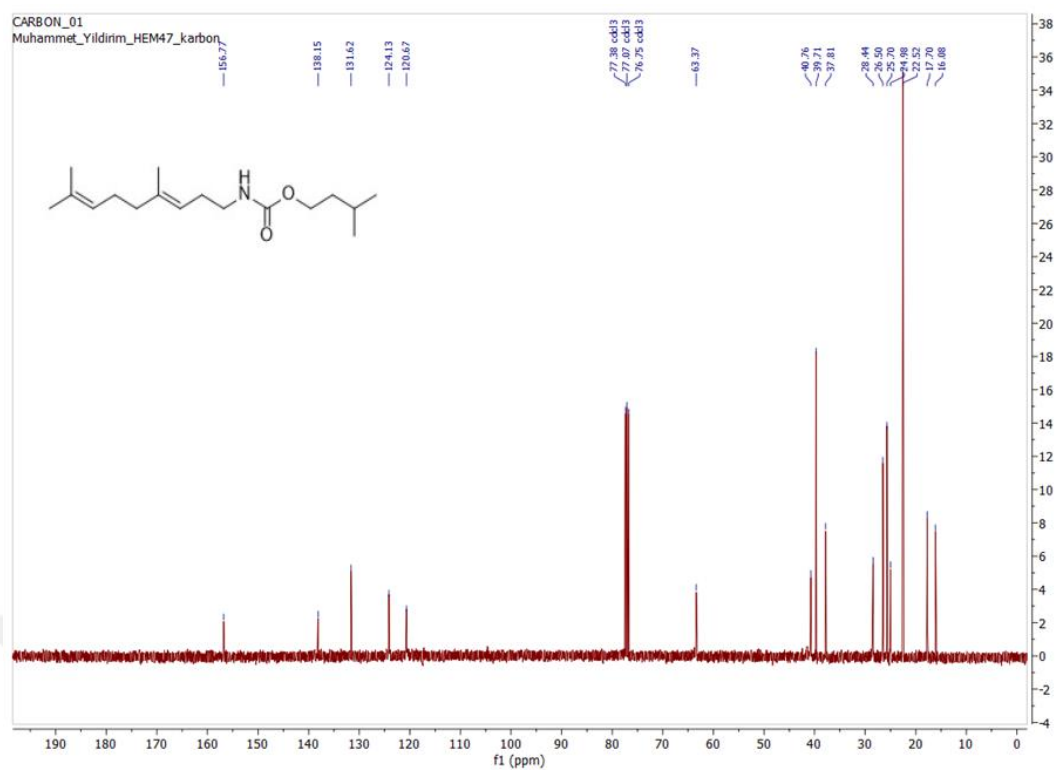


Figure 7.31. ^{13}C NMR spectrum of *i*-amyl homogeranyl carbamate **193h**.

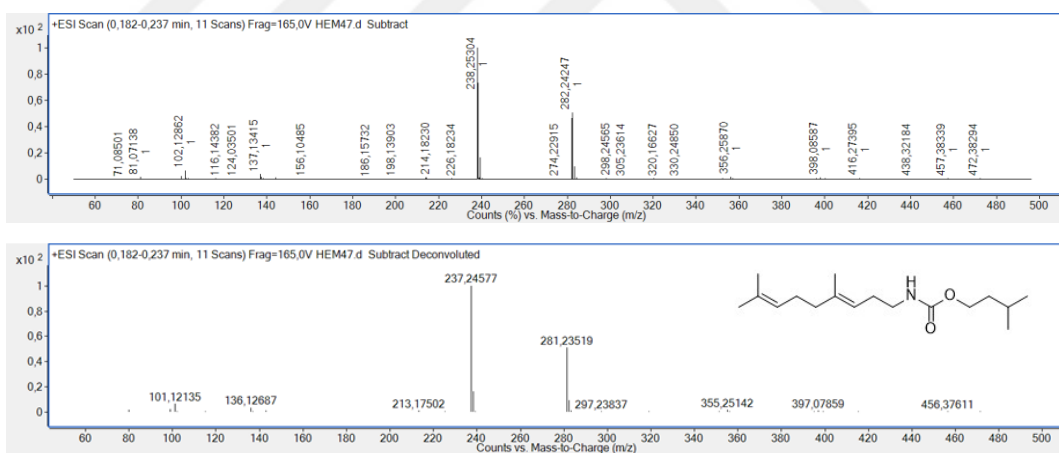


Figure 7.32. Exact mass (HRMS) spectrum of *i*-amyl homogeranyl carbamate **193h**.

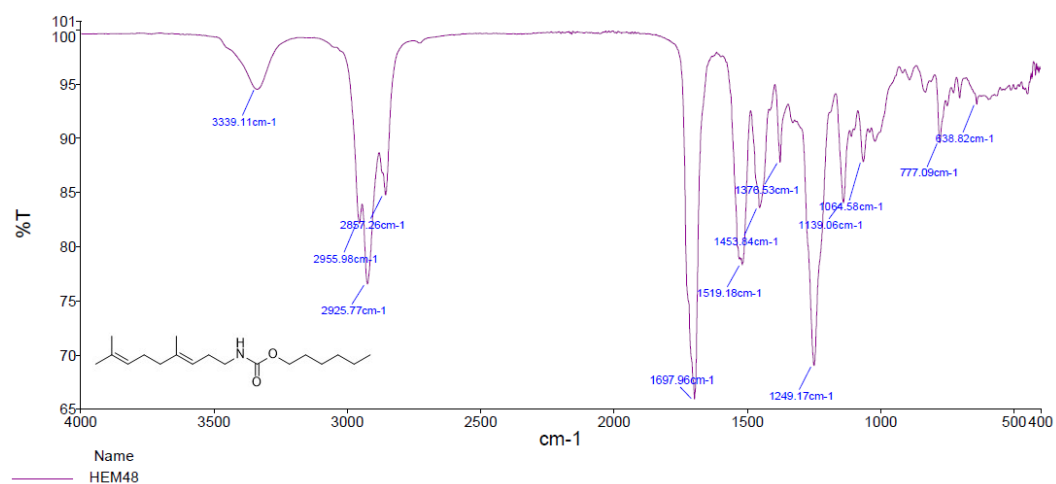


Figure 7.33. IR spectrum of hexyl homogeranyl carbamate **193i**.

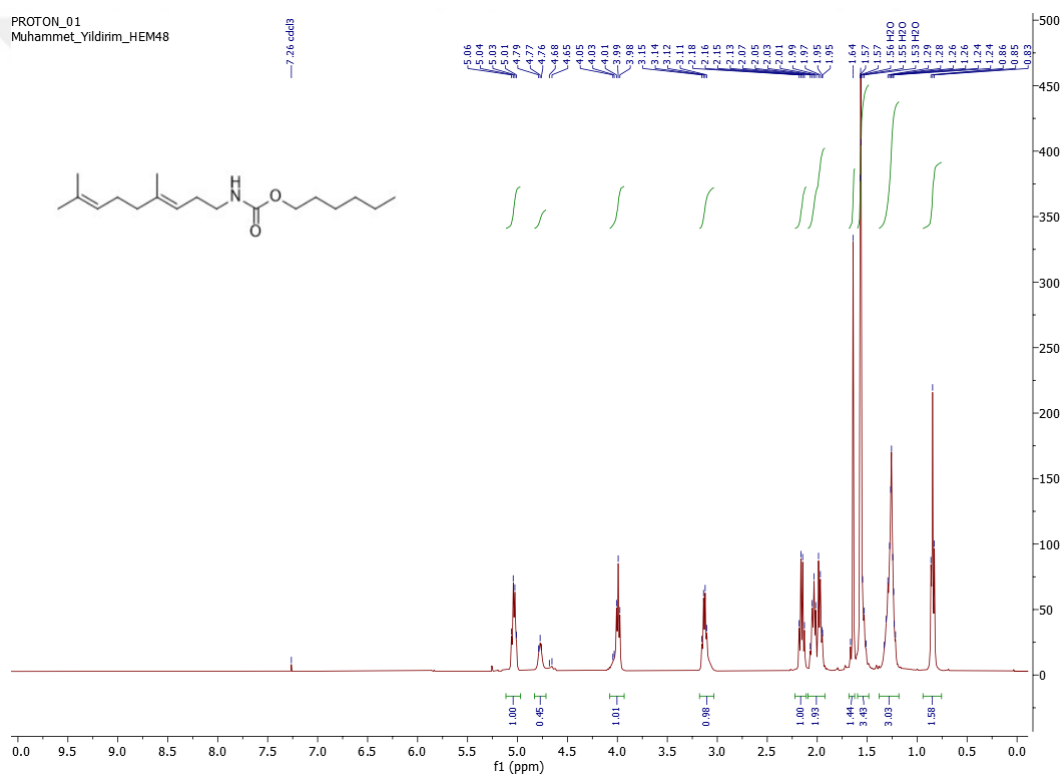


Figure 7.34. ¹H NMR spectrum of hexyl homogeranyl carbamate **193i**.

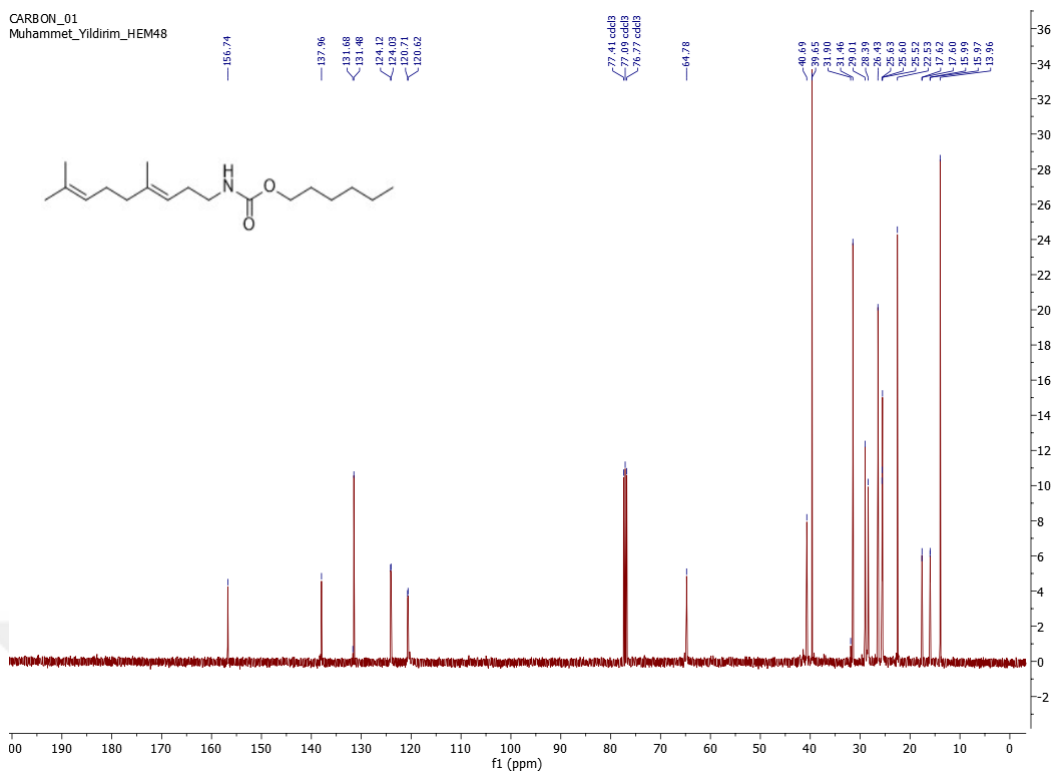


Figure 7.35. ^{13}C NMR spectrum of hexyl homogeranyl carbamate **193i**.

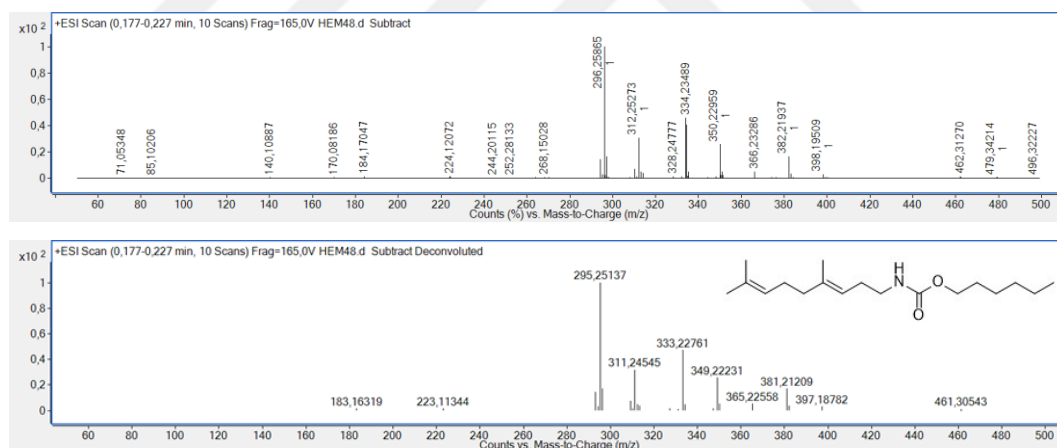


Figure 7.36. Exact mass (HRMS) spectrum of hexyl homogeranyl carbamate **193i**.

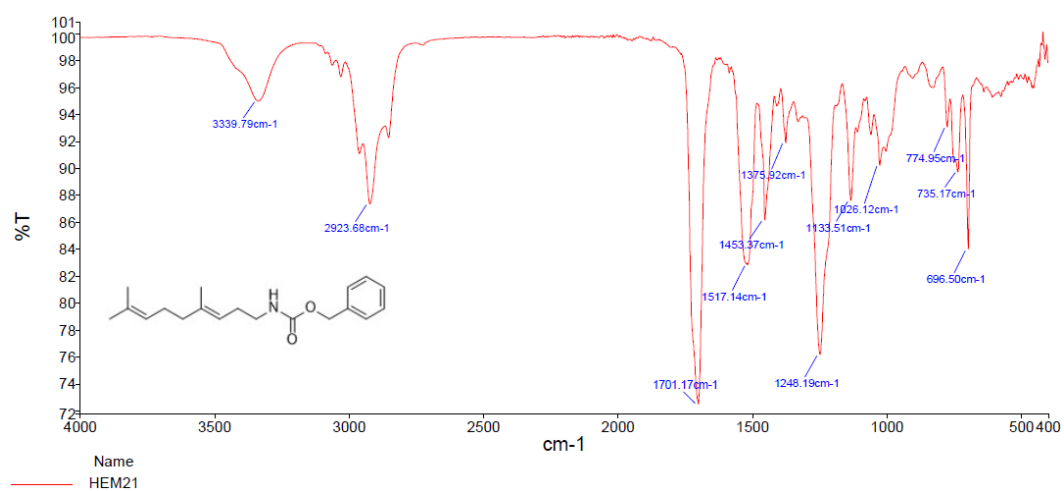


Figure 7.37. IR spectrum of benzyl homogeranyl carbamate **193j**.

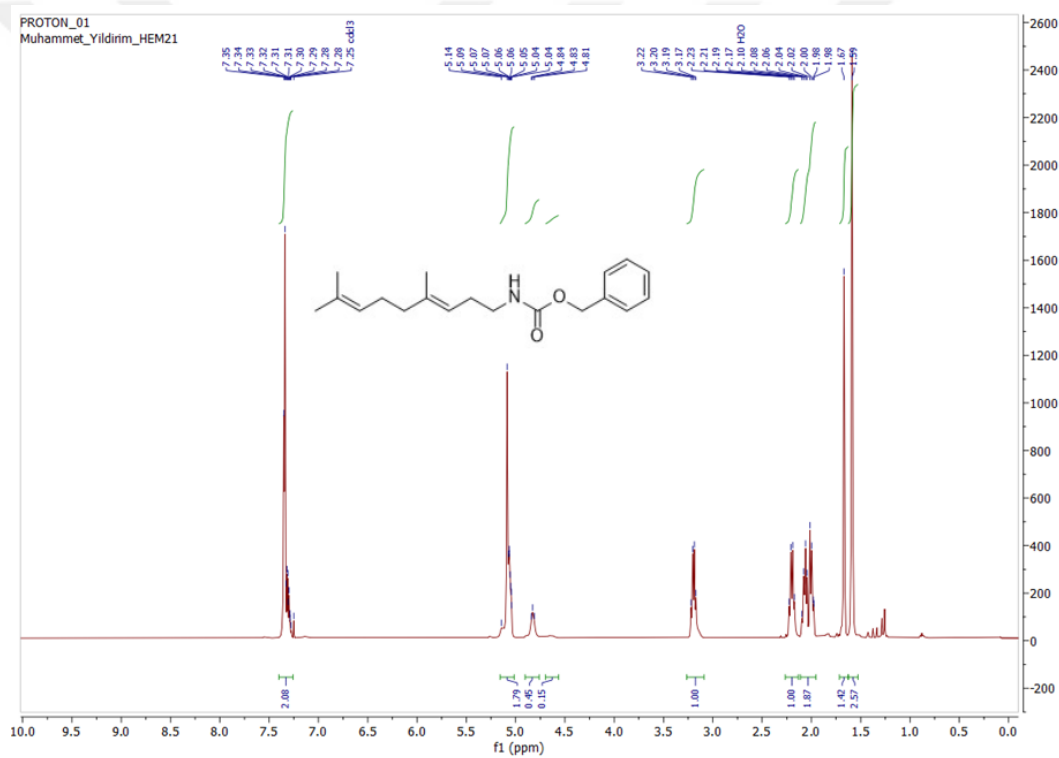


Figure 7.38. ¹H NMR spectrum of benzyl homogeranyl carbamate **193j**.

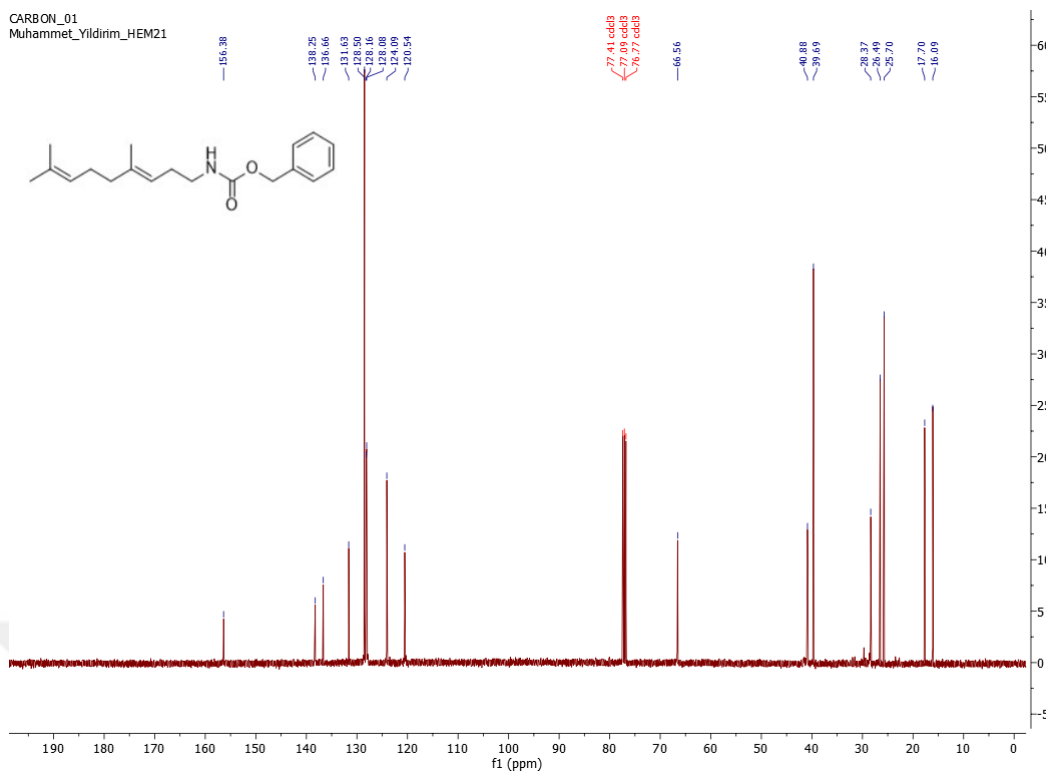


Figure 7.39. ¹³C NMR spectrum of benzyl homogeranyl carbamate **193j**.

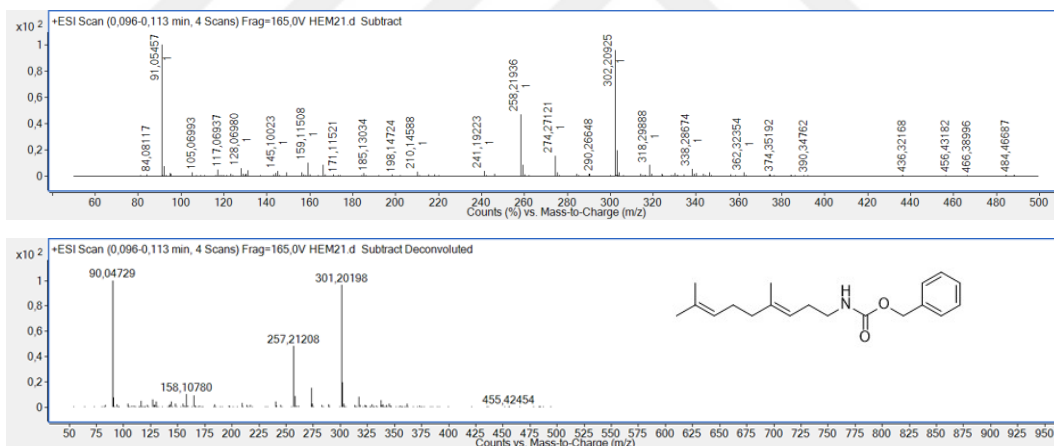


Figure 7.40. Exact mass (HRMS) spectrum of benzyl homogeranyl carbamate **193j**.

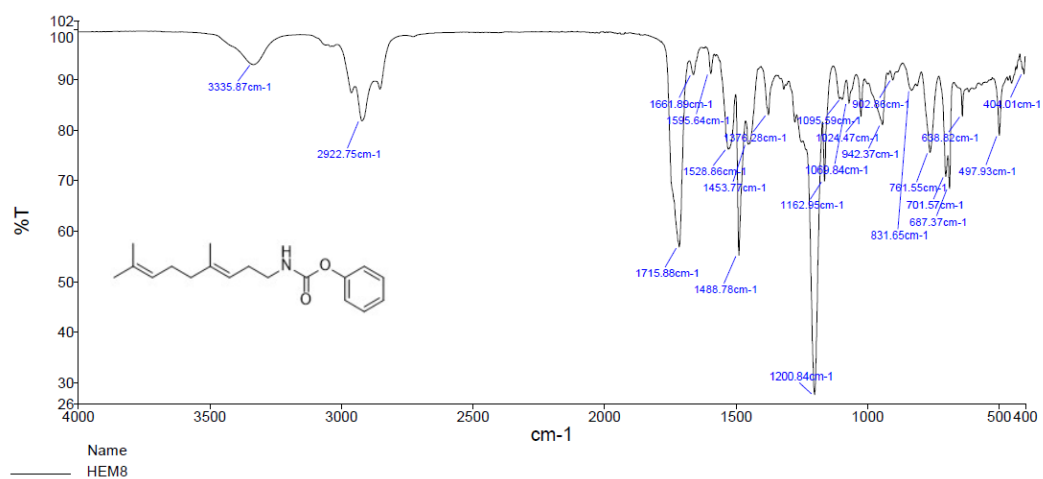


Figure 7.41. IR spectrum of phenyl homogeranyl carbamate **193k**.

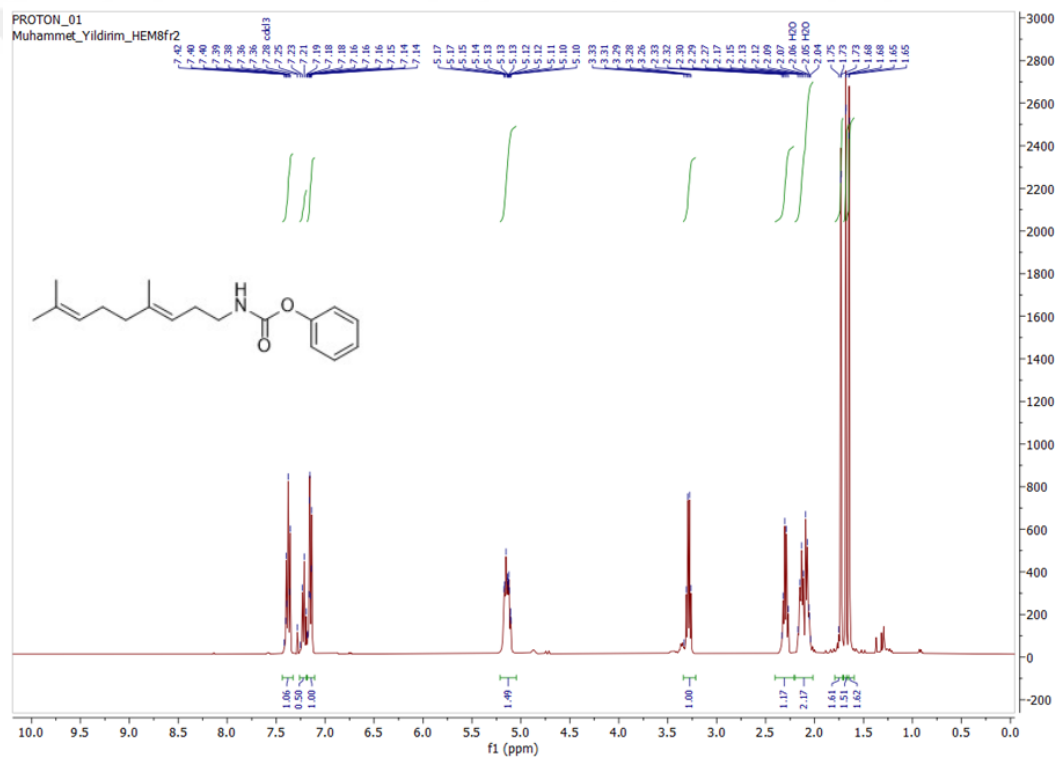


Figure 7.42. ¹H NMR spectrum of phenyl homogeranyl carbamate **193k**.

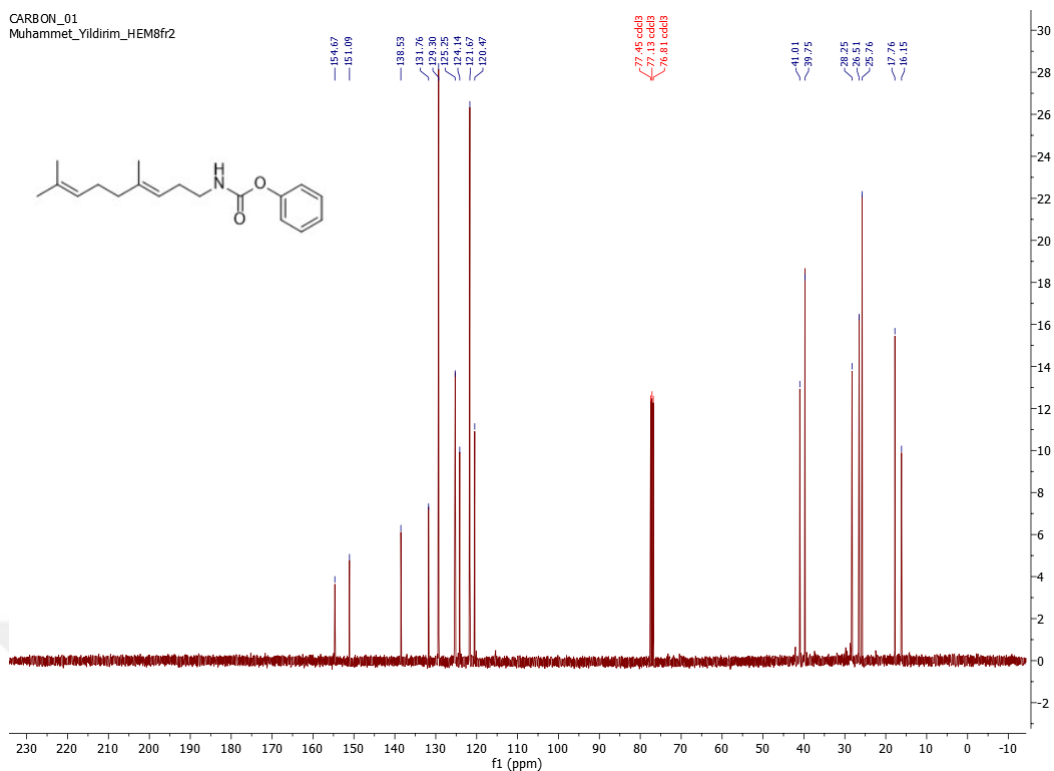


Figure 7.43. ¹³C NMR spectrum of phenyl homogreranyl carbamate **193k**.

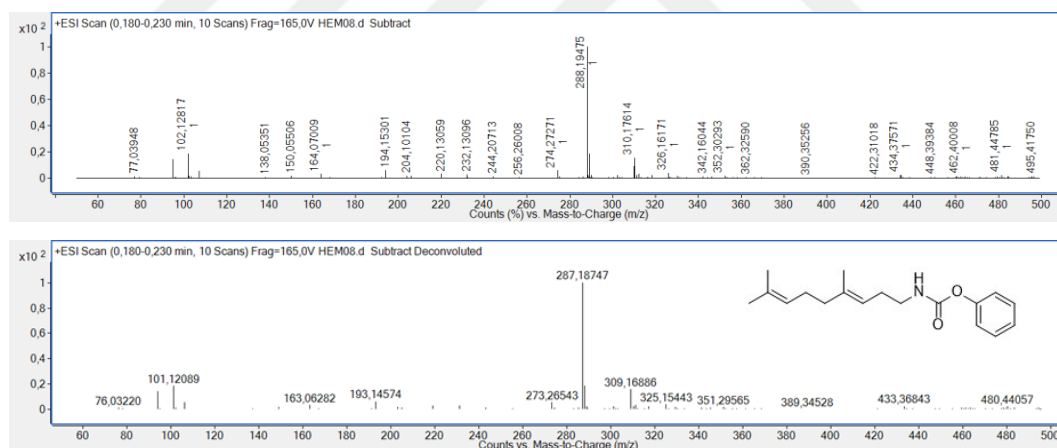


Figure 7.44. Exact mass (HRMS) spectrum of phenyl homogreranyl carbamate **193k**.

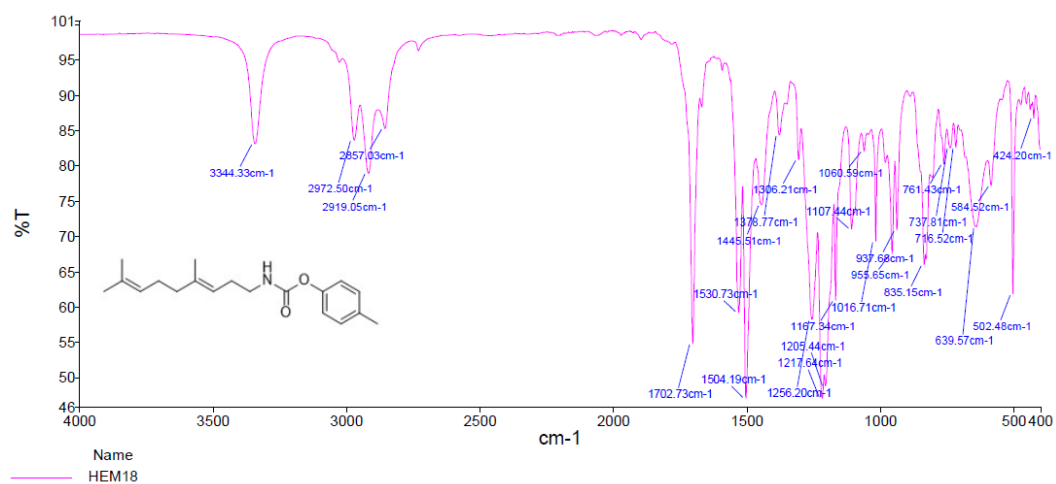


Figure 7.45. IR spectrum of p-tolyl homogreranyl carbamate **193l**.

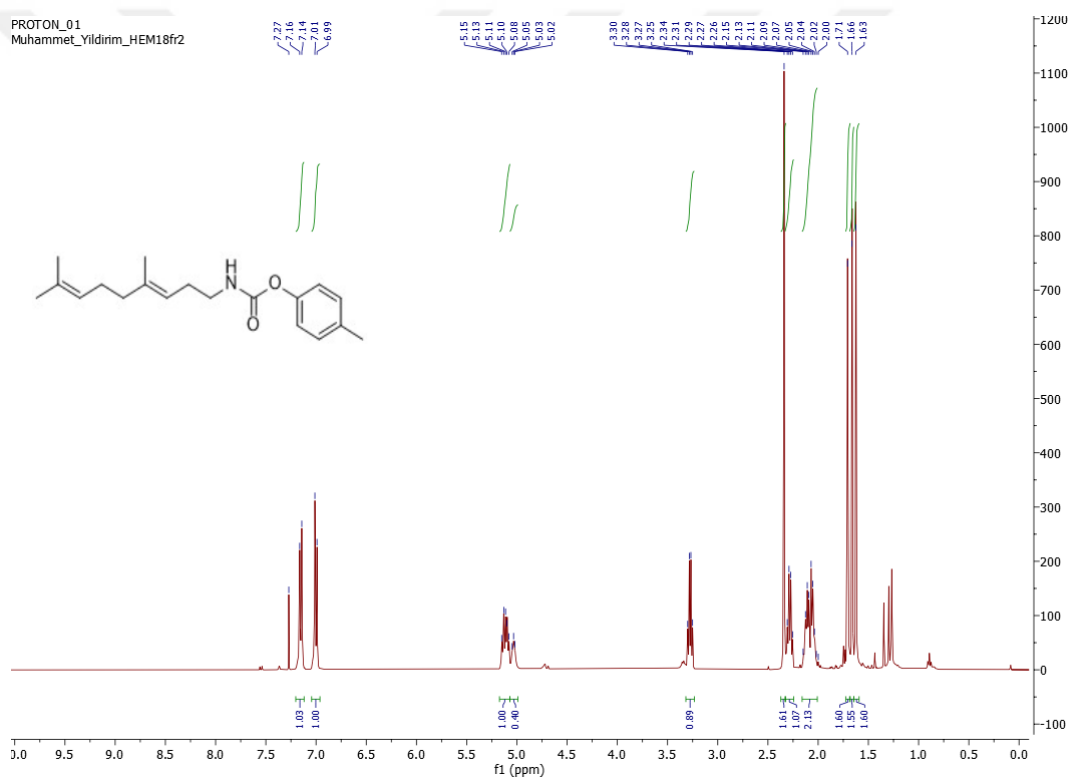


Figure 7.46. ¹H NMR spectrum of p-tolyl homogreranyl carbamate **193l**.

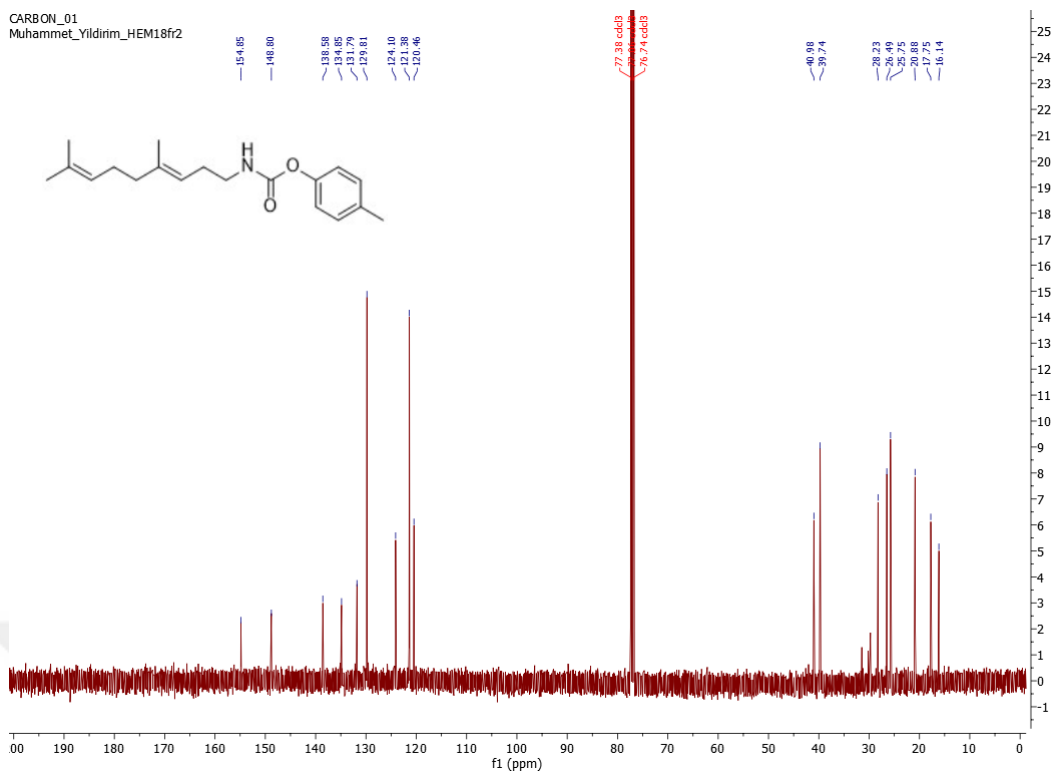


Figure 7.47. ^{13}C NMR spectrum of p-tolyl homogreranyl carbamate **193l**.

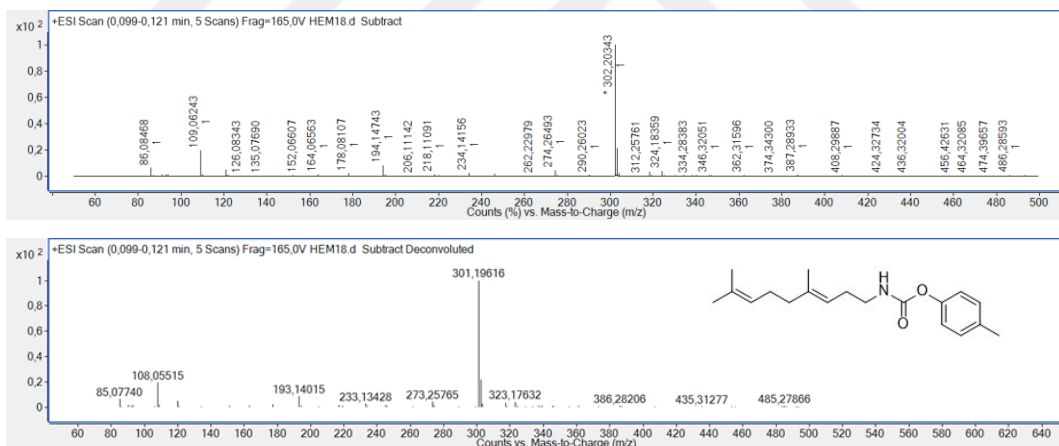


Figure 7.48. Exact mass (HRMS) spectrum of p-tolyl homogreranyl carbamate **193l**.

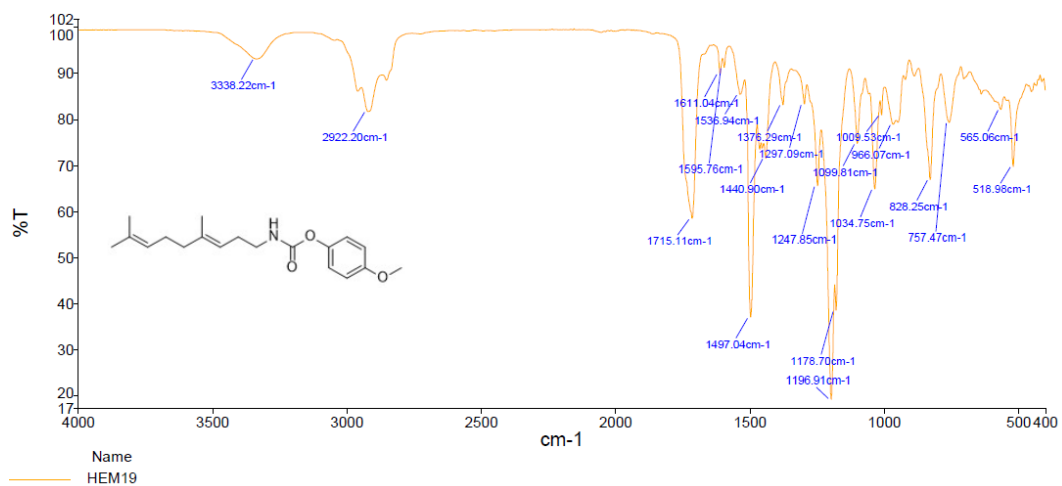


Figure 7.49. IR spectrum of p-methoxyphenyl homogeranyl carbamate **193m**.

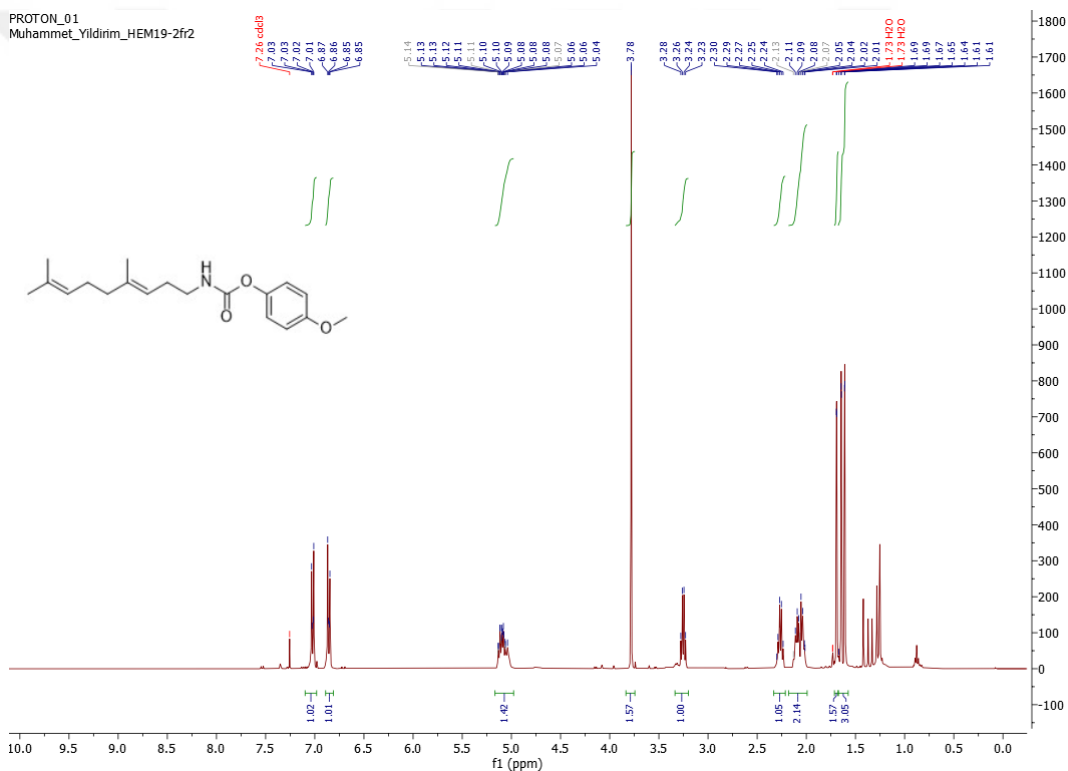


Figure 7.50. ¹H NMR spectrum of p-methoxyphenyl homogeranyl carbamate **193m**.

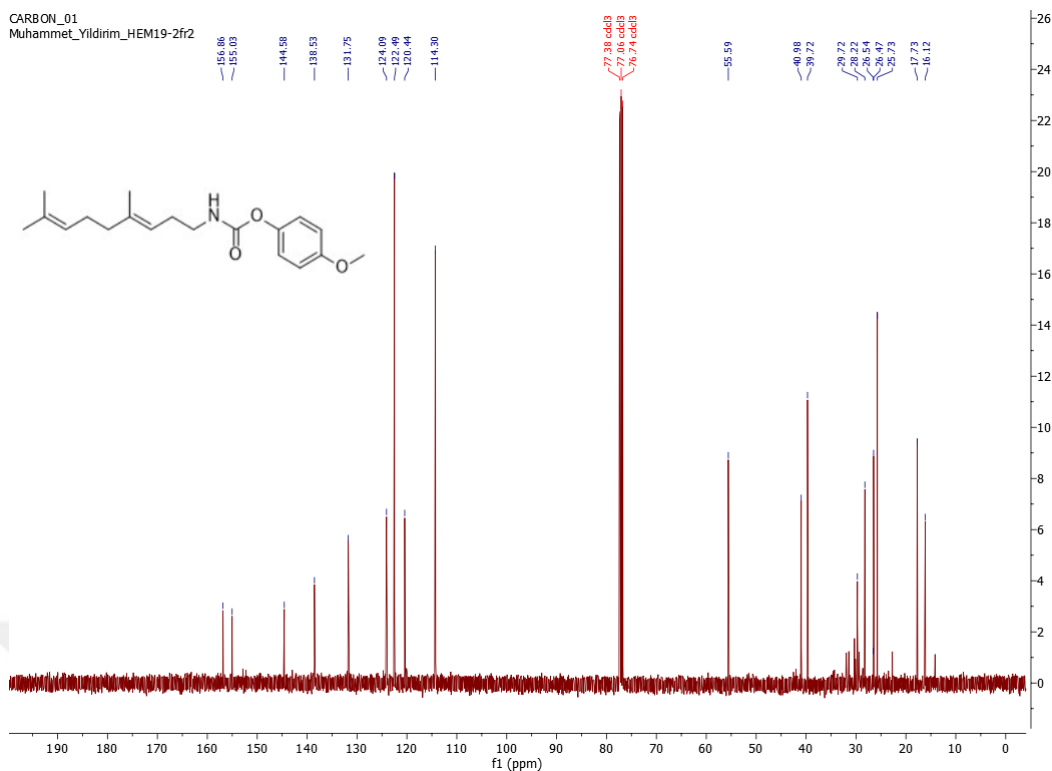


Figure 7.51. ¹³C NMR spectrum of p-methoxyphenyl homogeranyl carbamate **193m**.

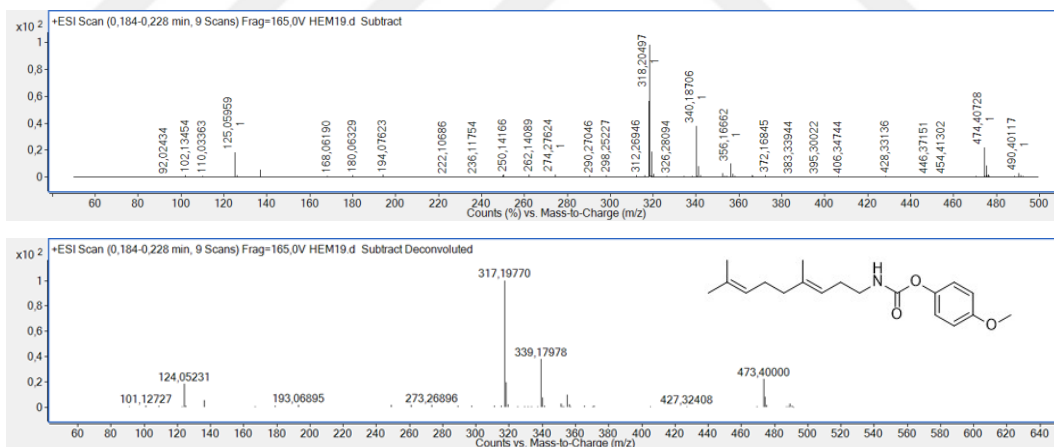


Figure 7.52. Exact mass (HRMS) spectrum of p-methoxyphenyl homogeranyl carbamate **193m**.

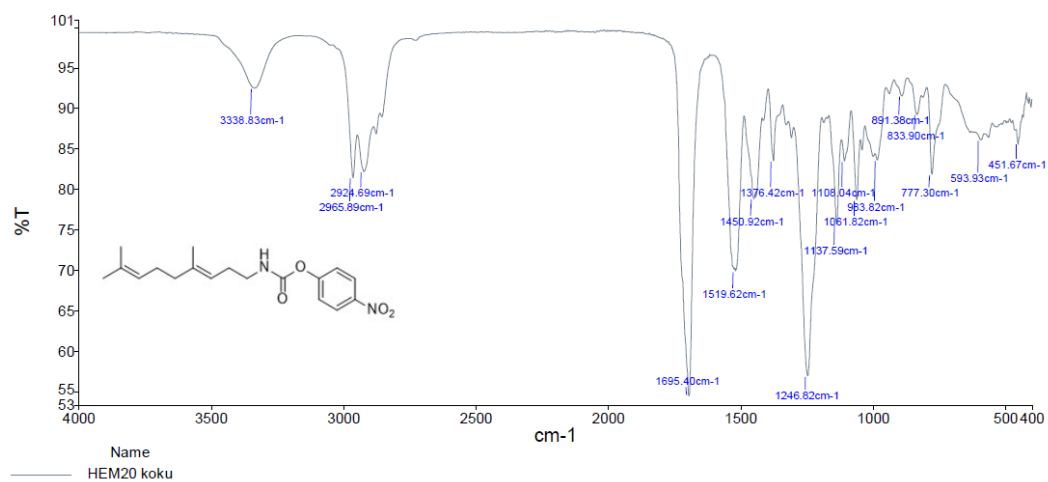


Figure 7.53. IR spectrum of p-nitrophenyl homogteranyl carbamate **193n**.

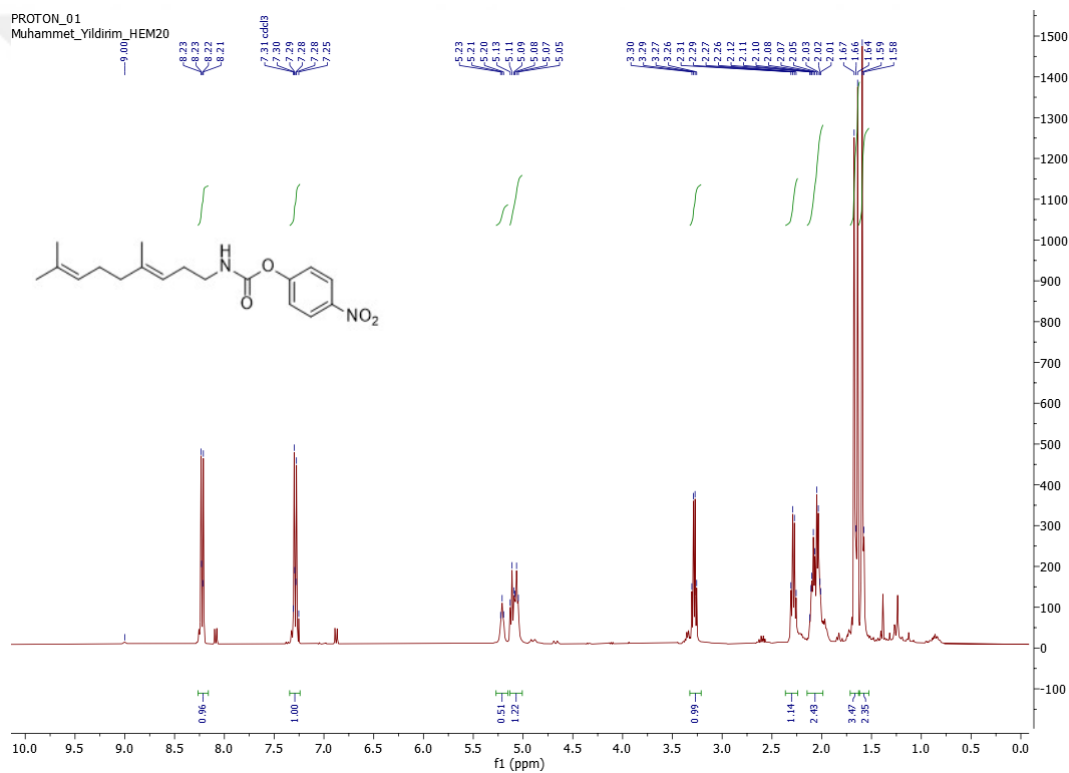


Figure 7.54. ¹H NMR spectrum of p-nitrophenyl homogteranyl carbamate **193n**.

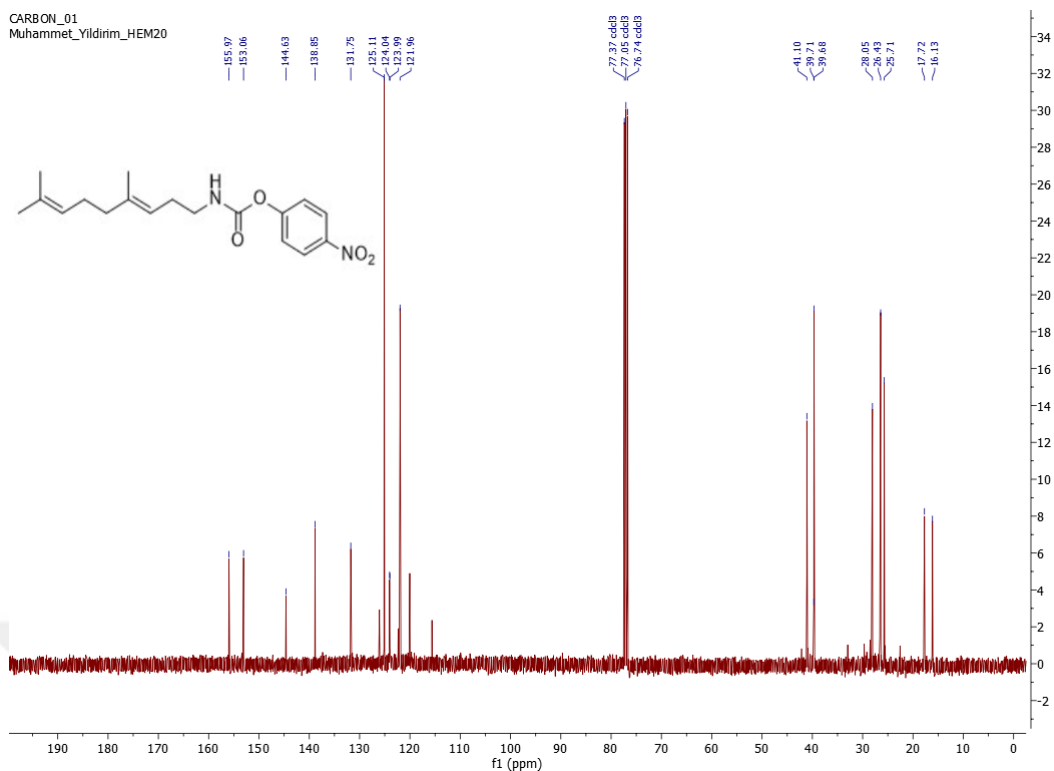


Figure 7.55. ^{13}C NMR spectrum of p-nitrophenyl homogeranyl carbamate **193n**.

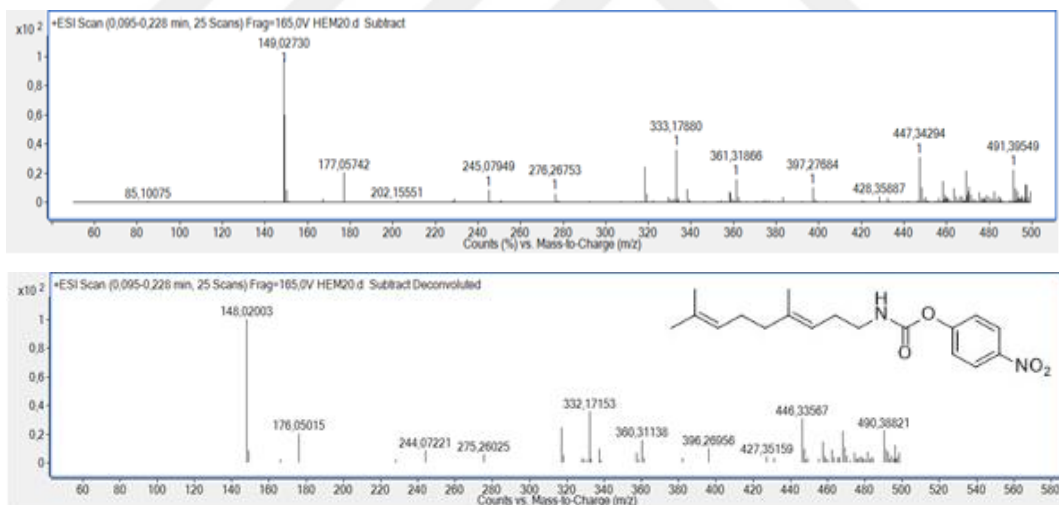


Figure 7.56. Exact mass (HRMS) spectrum of p-nitrophenyl homogeranyl carbamate **193n**.

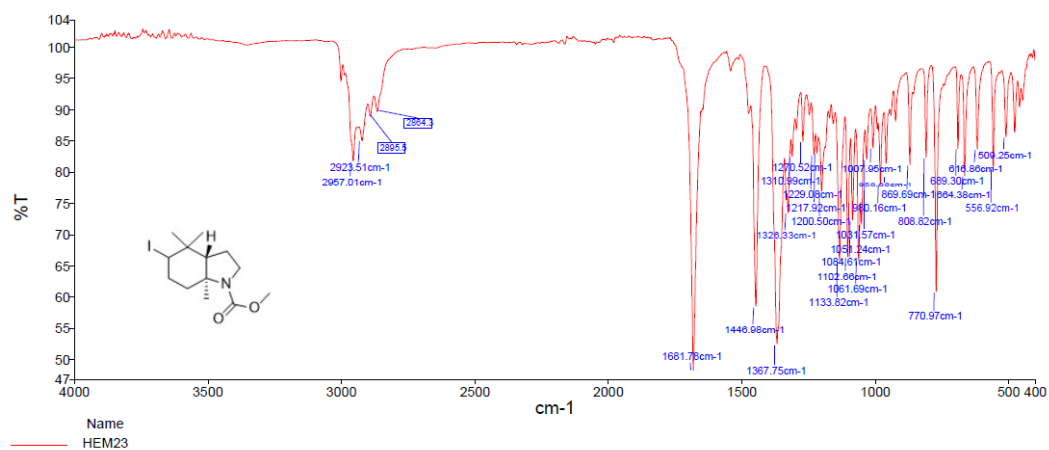


Figure 7.57. IR spectrum of methyl 5-iodotrimethyloctahydroindole carbamate **194a**.

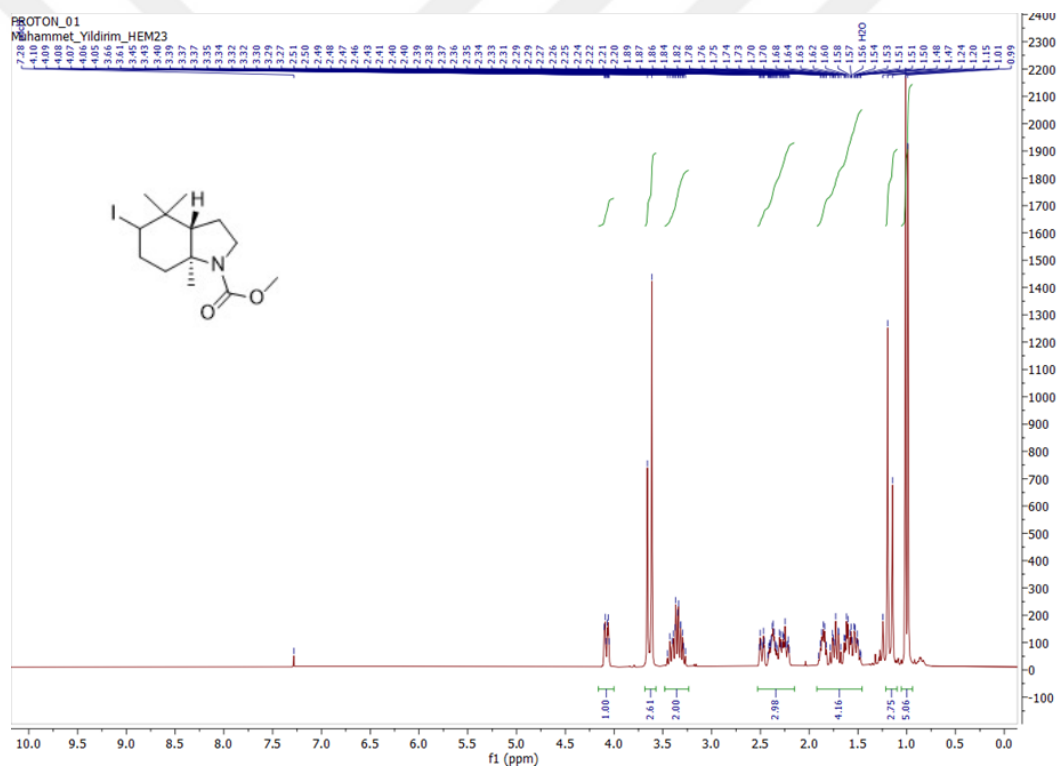


Figure 7.58. ¹H NMR spectrum of methyl 5-iodotrimethyloctahydroindole carbamate **194a**.

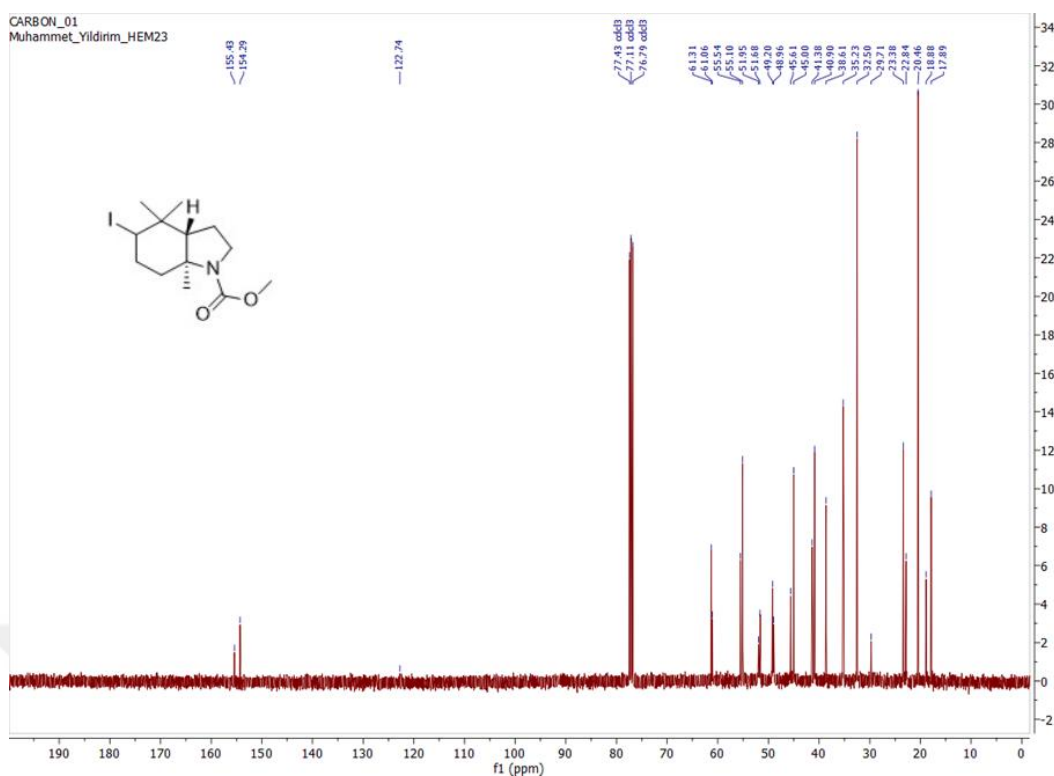


Figure 7.59. ^{13}C NMR spectrum of methyl 5-iodotrimethyloctahydroindole carbamate **194a**.

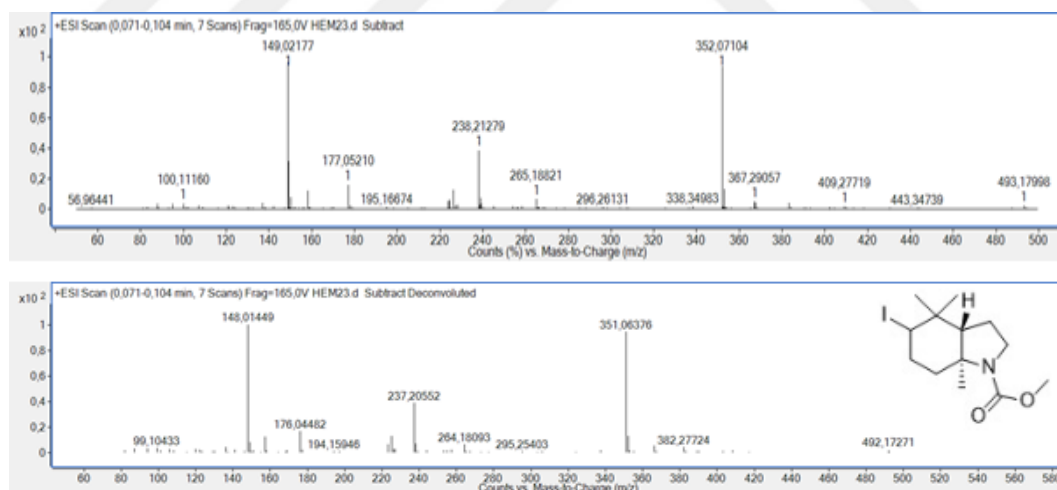


Figure 7.60. Exact mass (HRMS) spectrum of methyl 5-iodotrimethyloctahydroindole carbamate **194a**.

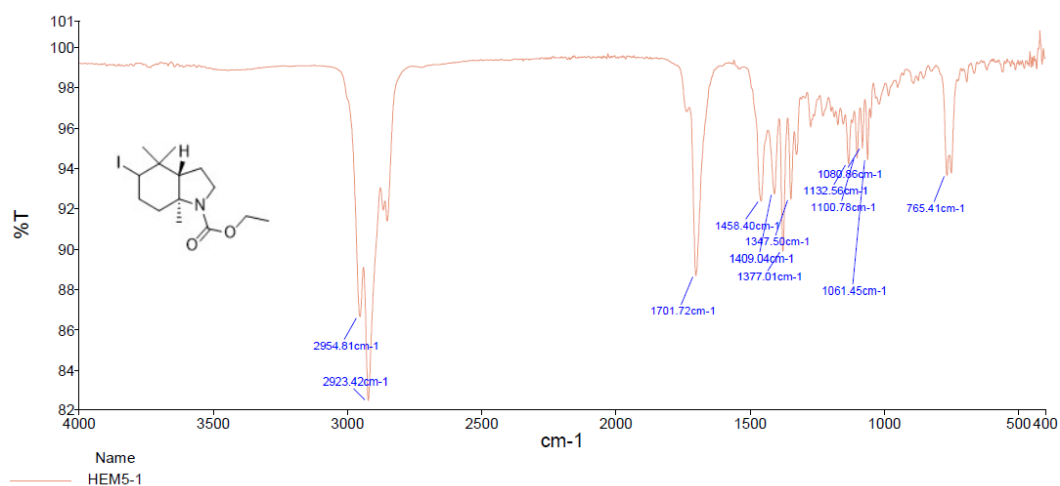


Figure 7.61. IR spectrum of ethyl 5-iodotrimethyloctahydroindole carbamate **194b**.

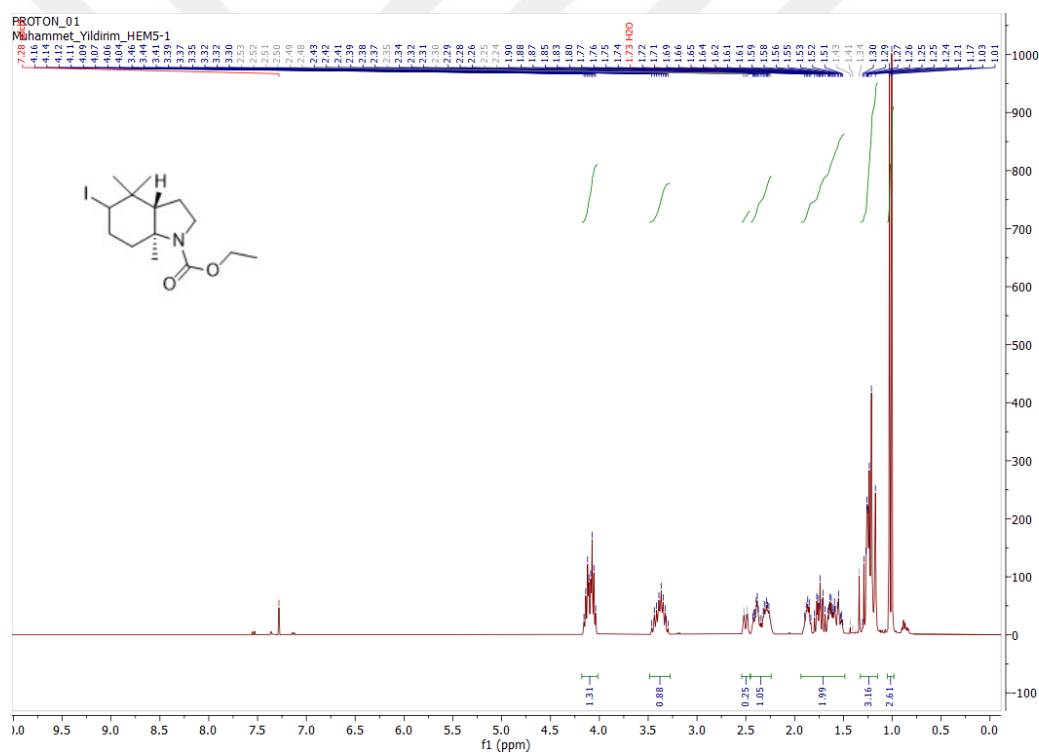


Figure 7.62. ¹H NMR spectrum of ethyl 5-iodotrimethyloctahydroindole carbamate **194b**.

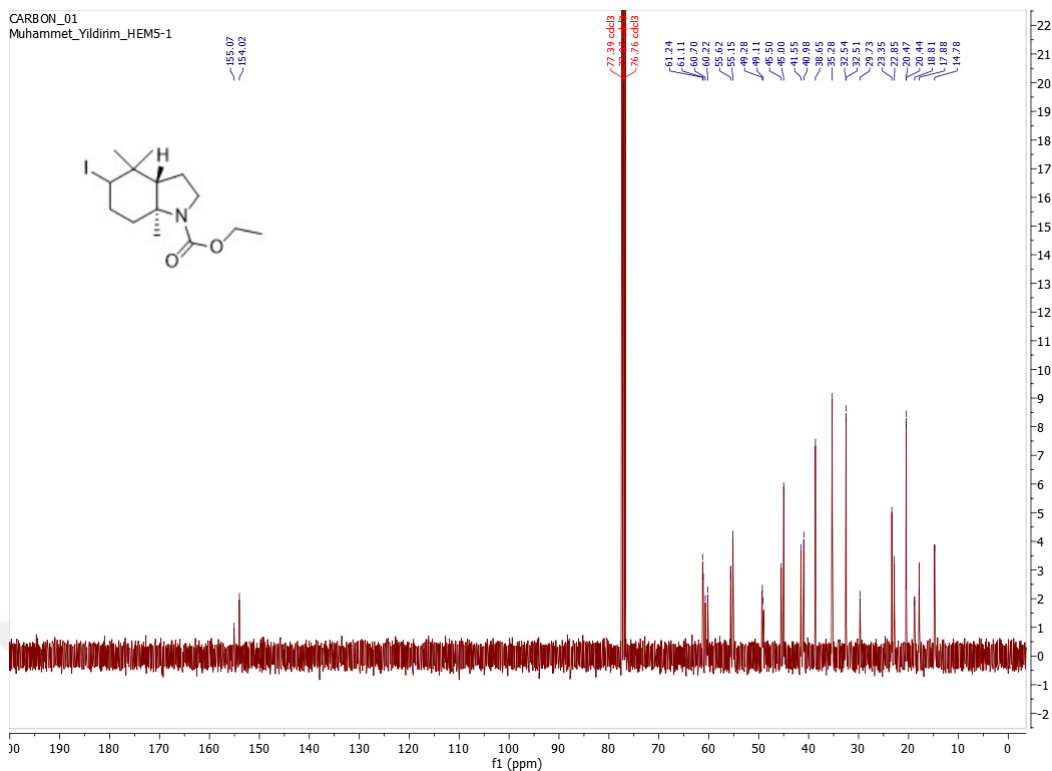


Figure 7.63. ¹³C NMR spectrum of ethyl 5-iodotrimethyloctahydroindole carbamate **194b**.

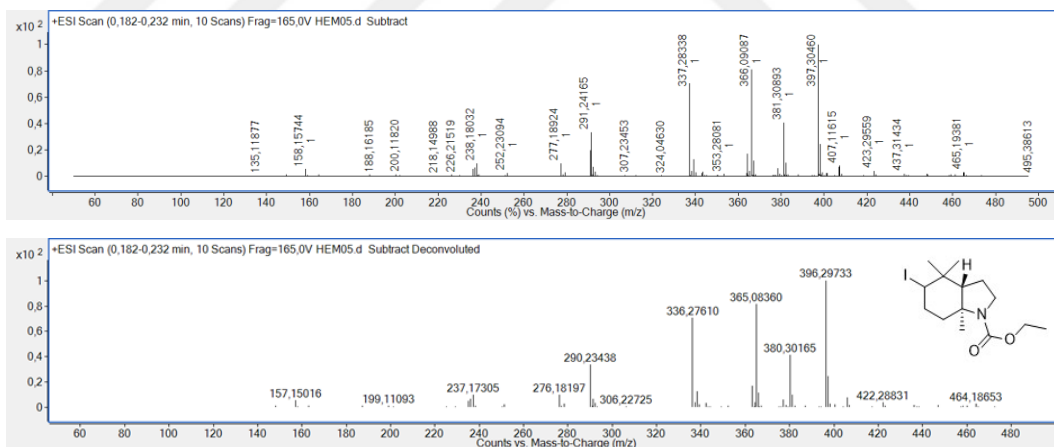


Figure 7.64. Exact mass (HRMS) spectrum of ethyl 5-iodotrimethyloctahydroindole carbamate **194b**.

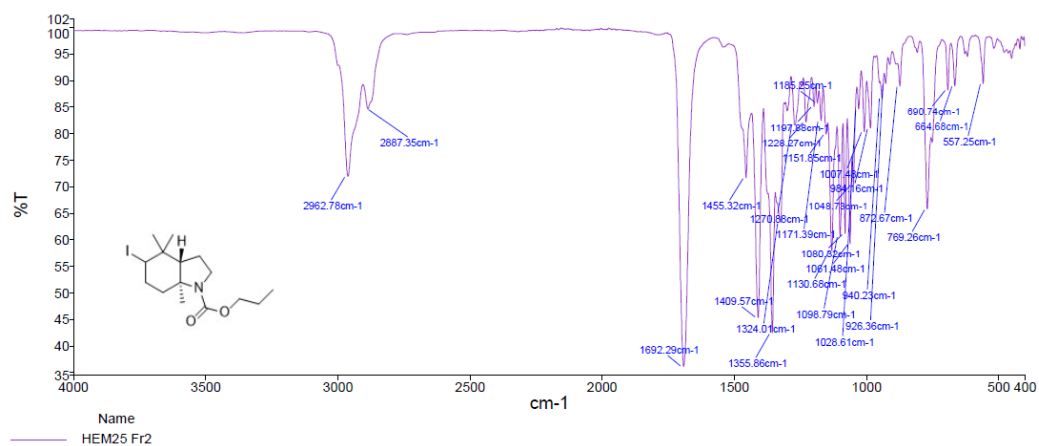


Figure 7.65. IR spectrum of propyl 5-iodotrimethyloctahydroindole carbamate **194c**.

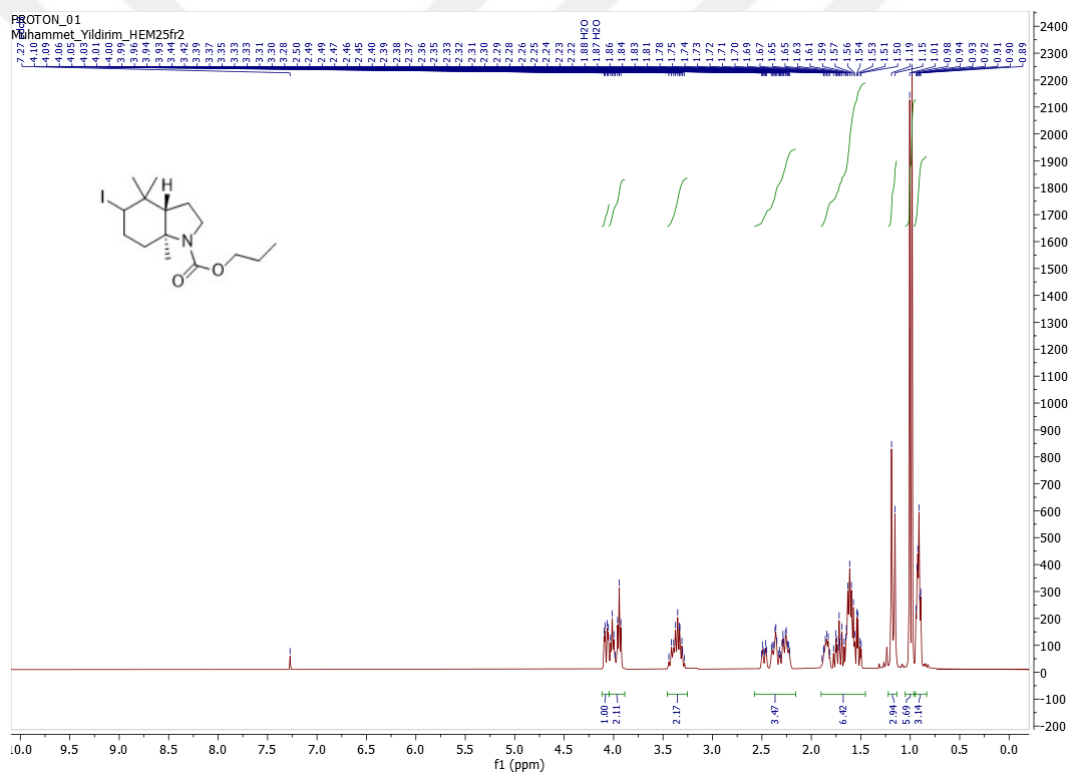


Figure 7.66. ¹H NMR spectrum of propyl 5-iodotrimethyloctahydroindole carbamate **194c**.

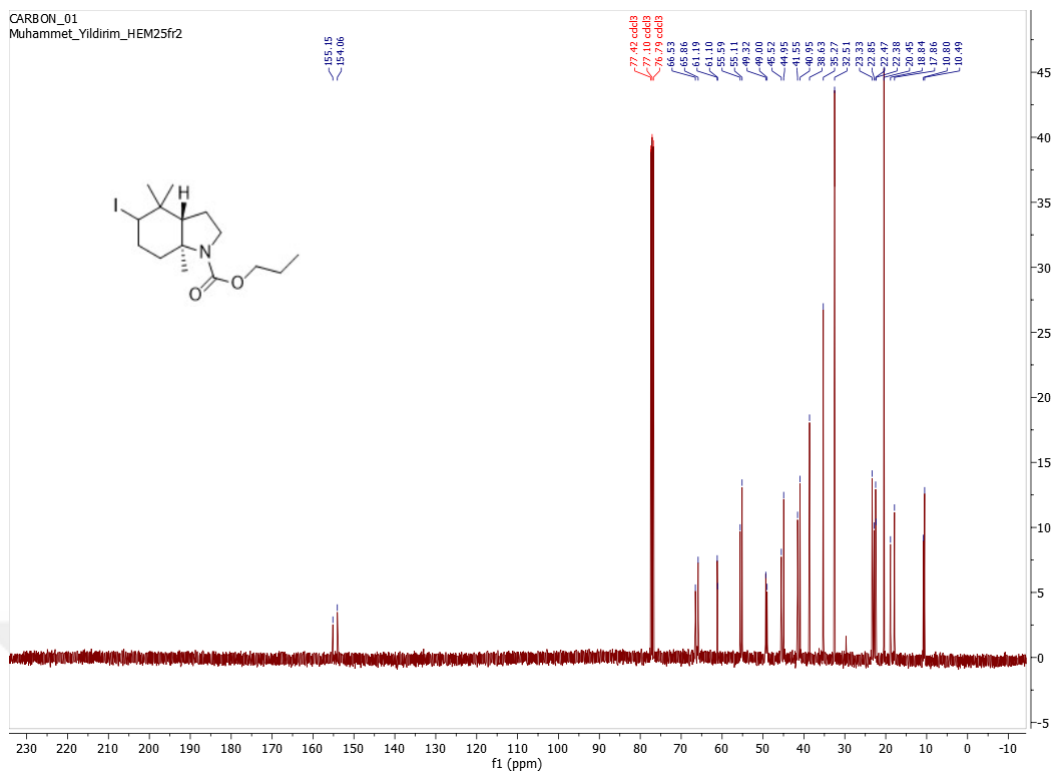


Figure 7.67. ^{13}C NMR spectrum of propyl 5-iodotrimethyloctahydroindole carbamate **194c**.

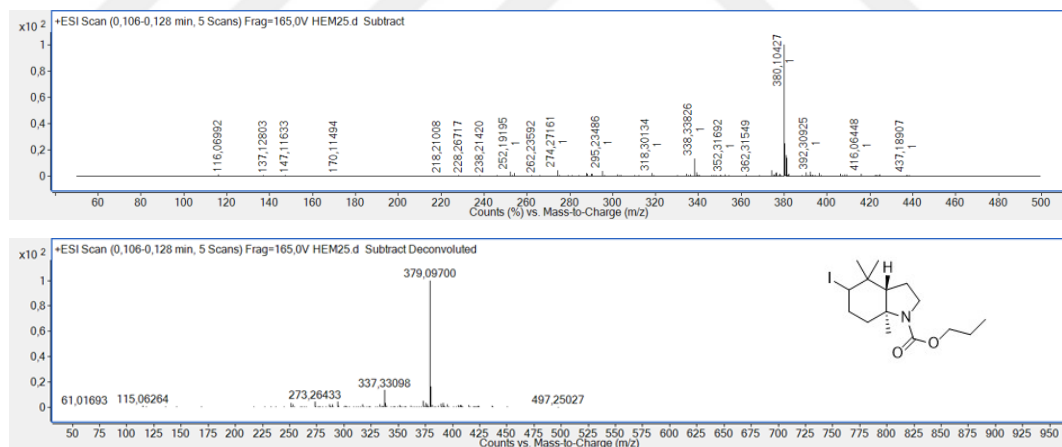


Figure 7.68. Exact mass (HRMS) spectrum of propyl 5-iodotrimethyloctahydroindole carbamate **194c**.

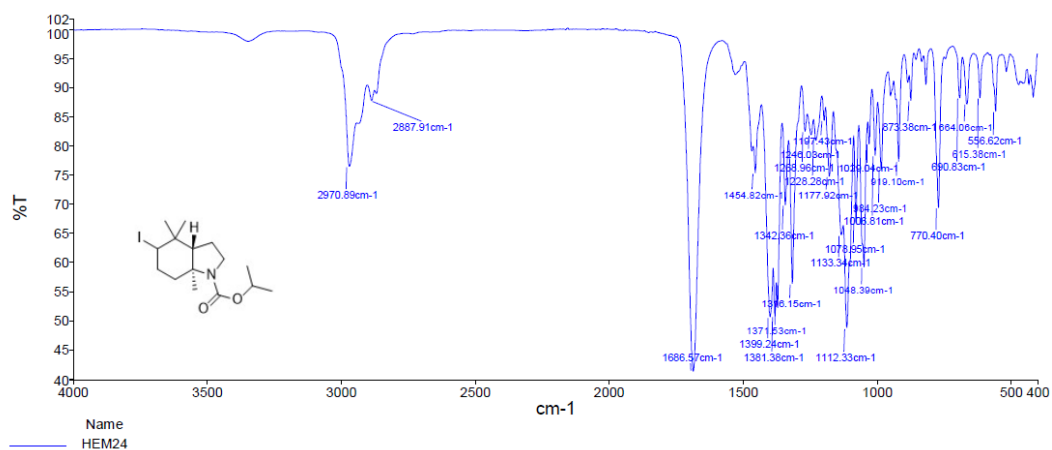


Figure 7.69. IR spectrum of *i*-propyl 5-iodotrimethyloctahydroindole carbamate **194d**.

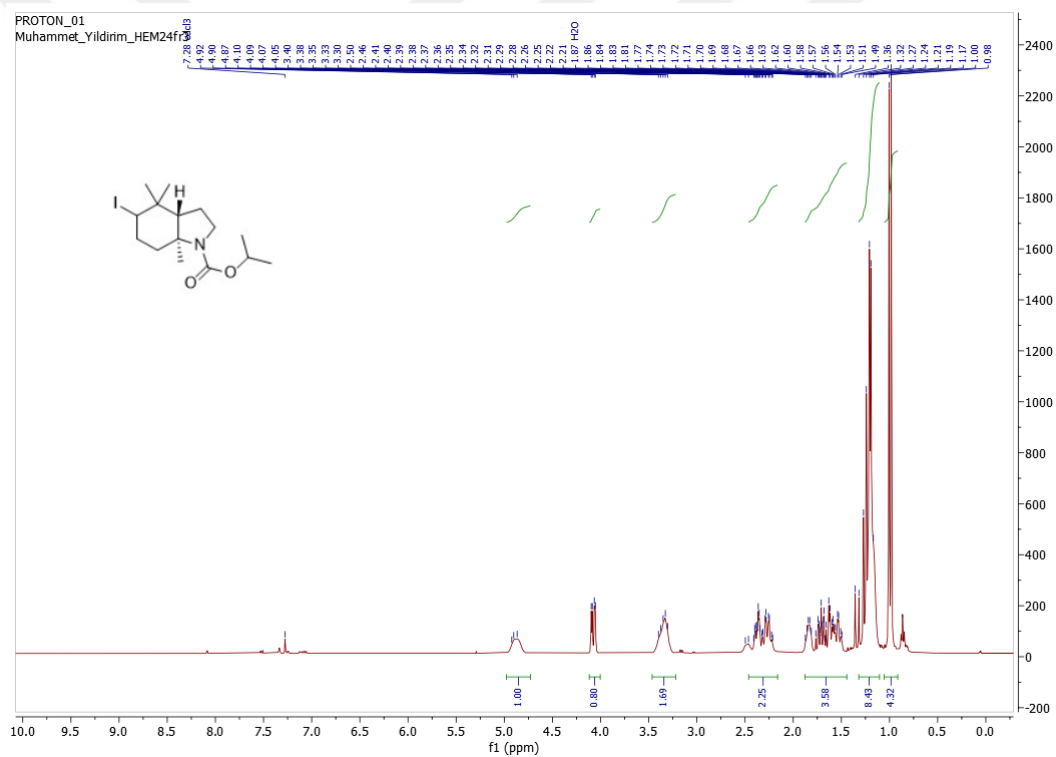


Figure 7.70. ¹H NMR spectrum of *i*-propyl 5-iodotrimethyloctahydroindole carbamate **194d**.

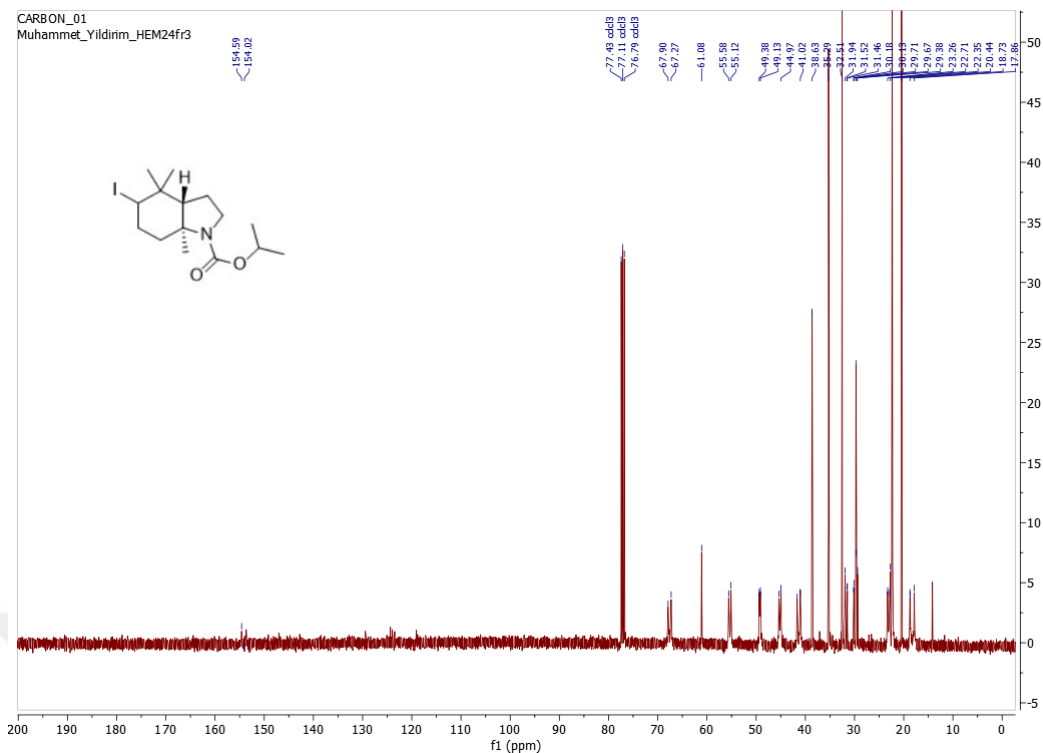


Figure 7.71. ^{13}C NMR spectrum of *i*-propyl 5-iodotrimethyloctahydroindole carbamate **194d**.

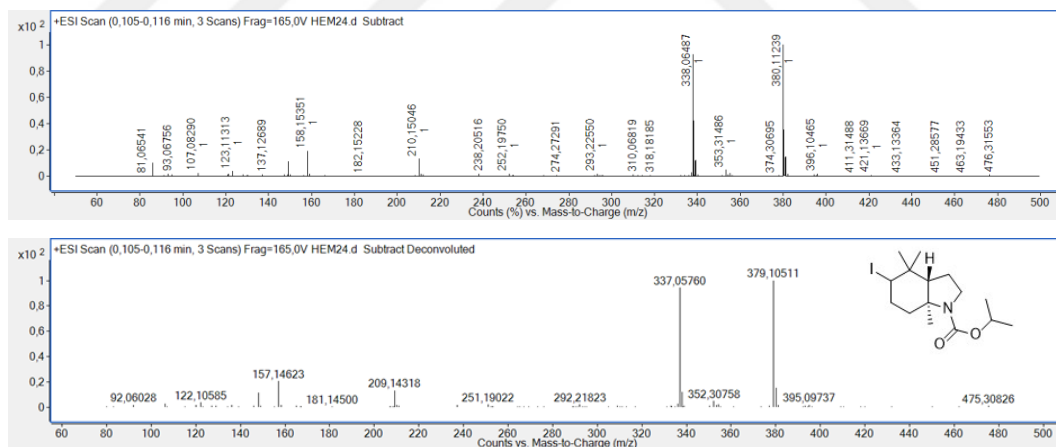


Figure 7.72. Exact mass (HRMS) spectrum of *i*-propyl 5-iodotrimethyloctahydroindole carbamate **194d**.

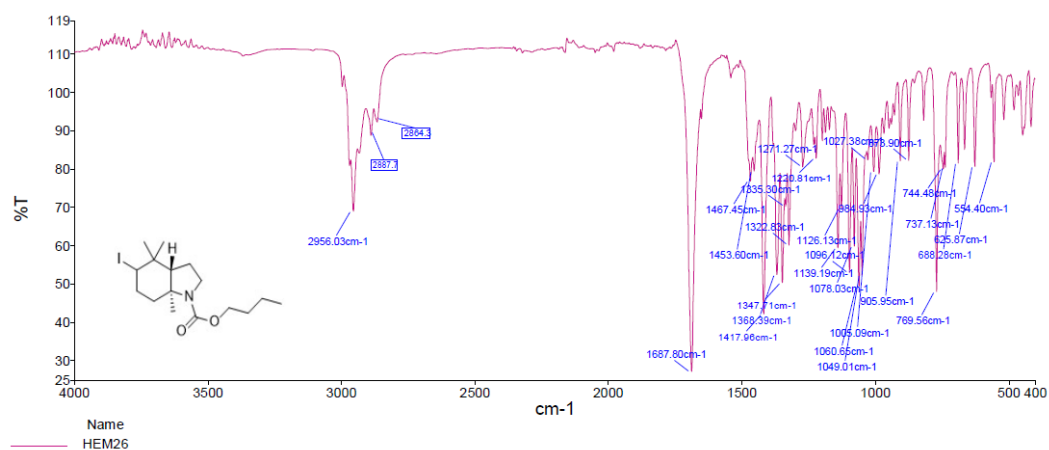


Figure 7.73. IR spectrum of butyl 5-iodotrimethyloctahydroindole carbamate **194e**.

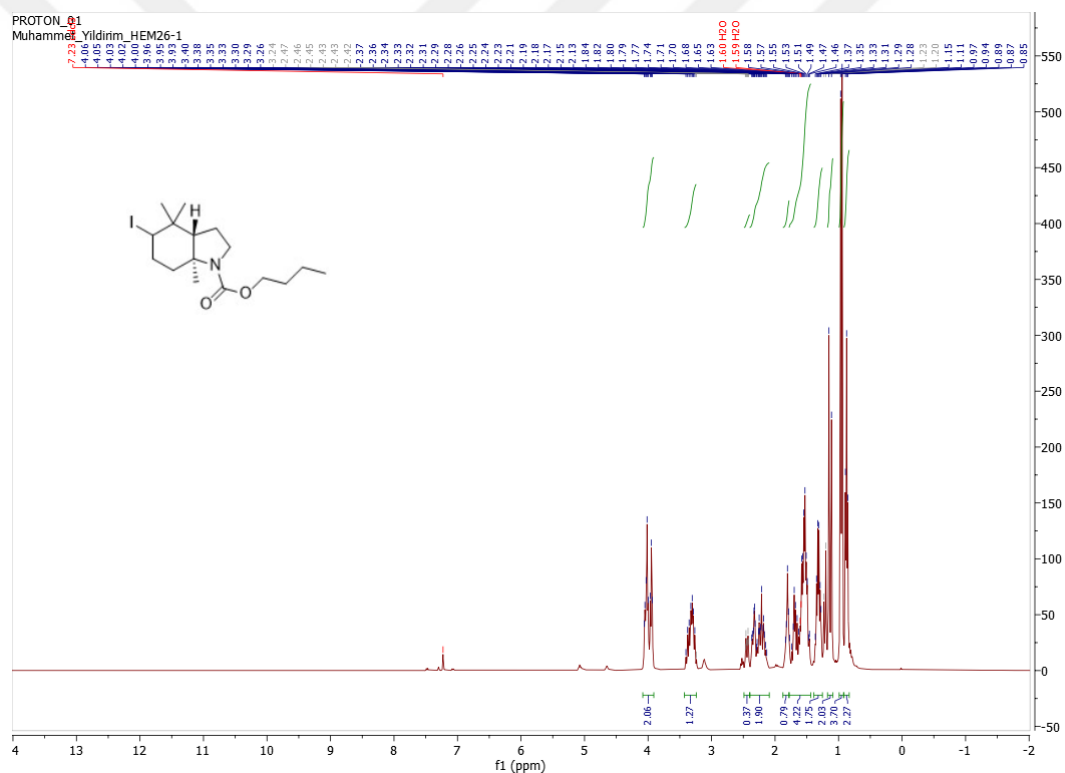


Figure 7.74. ¹H NMR spectrum of butyl 5-iodotrimethyloctahydroindole carbamate **194e**.

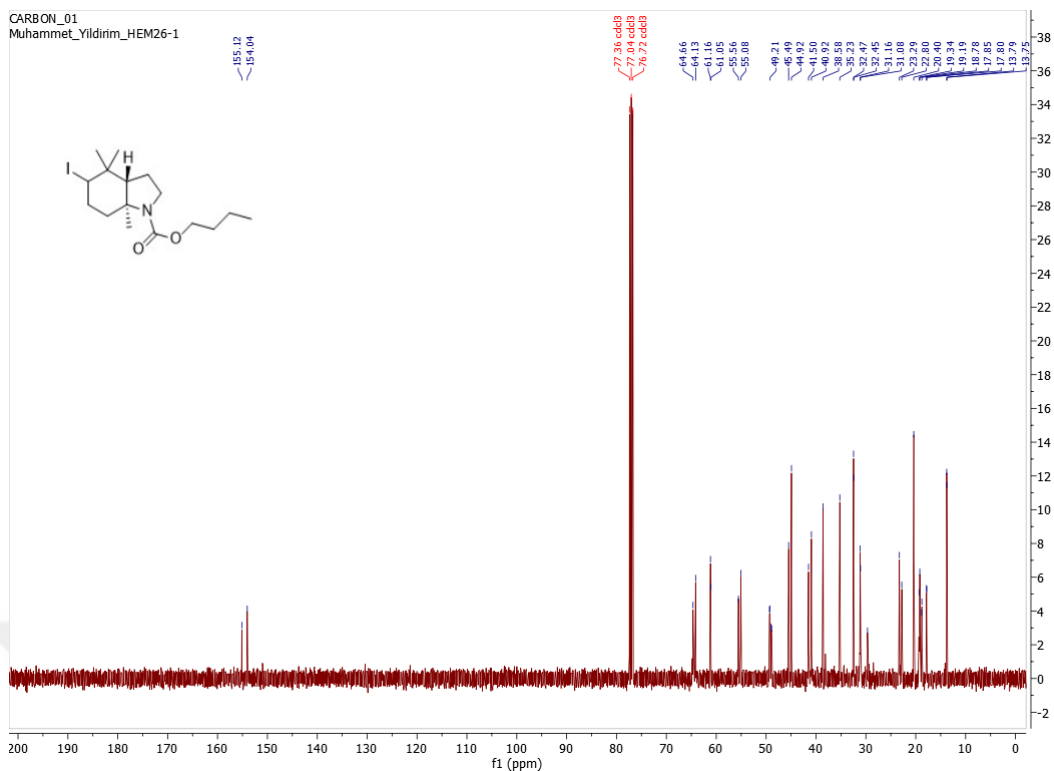


Figure 7.75. ^{13}C NMR spectrum of butyl 5-iodotrimethyloctahydroindole carbamate **194e**.

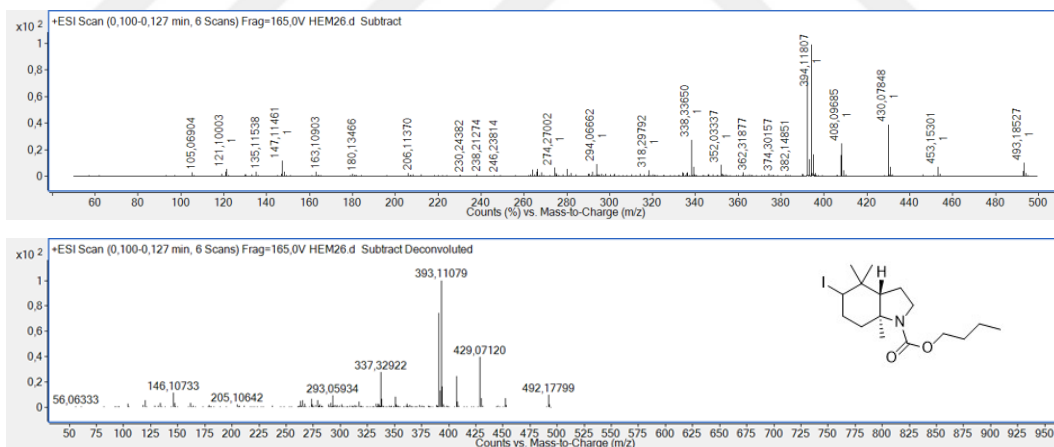
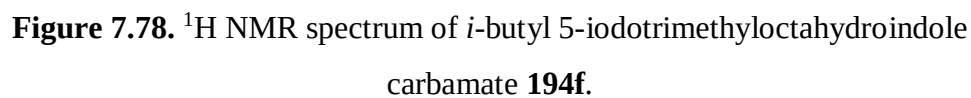
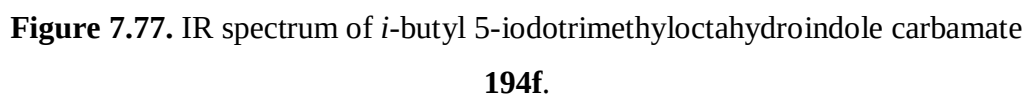


Figure 7.76. Exact mass (HRMS) spectrum of butyl 5-iodotrimethyloctahydroindole carbamate **194e**.



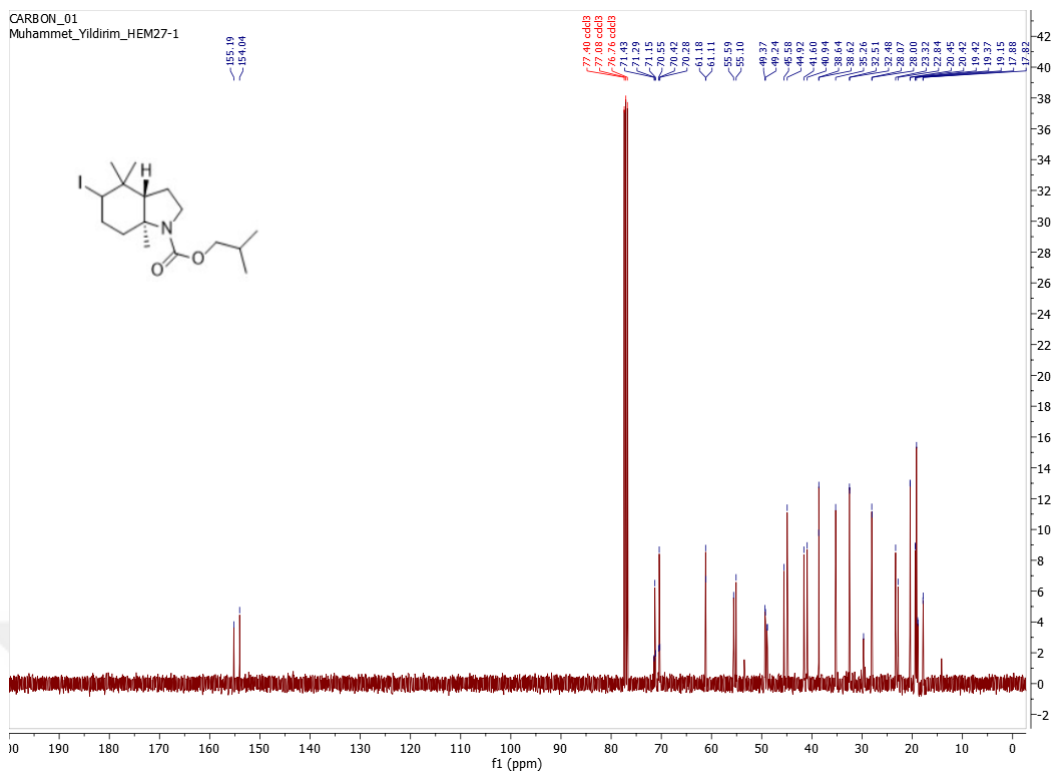


Figure 7.79. ¹³C NMR spectrum of *i*-butyl 5-iodotrimethyloctahydroindole carbamate **194f**.

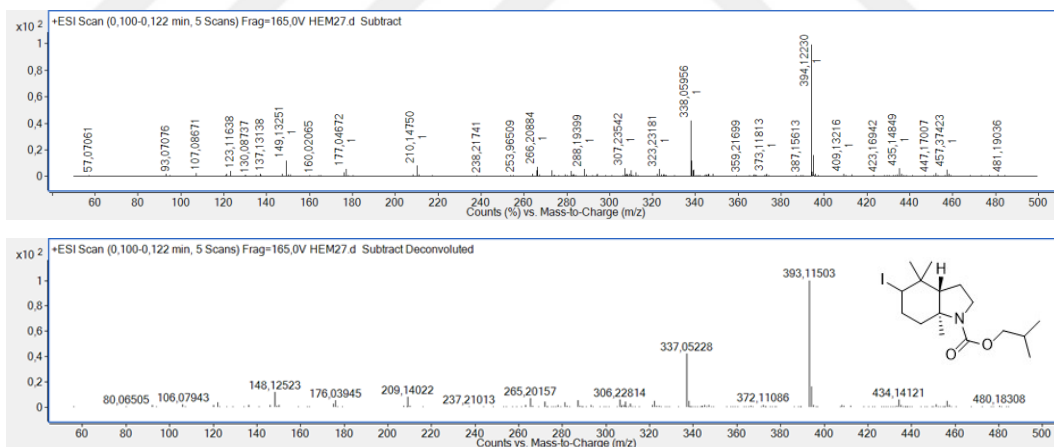


Figure 7.80. Exact mass (HRMS) spectrum of *i*-butyl 5-iodotrimethyloctahydroindole carbamate **194f**.

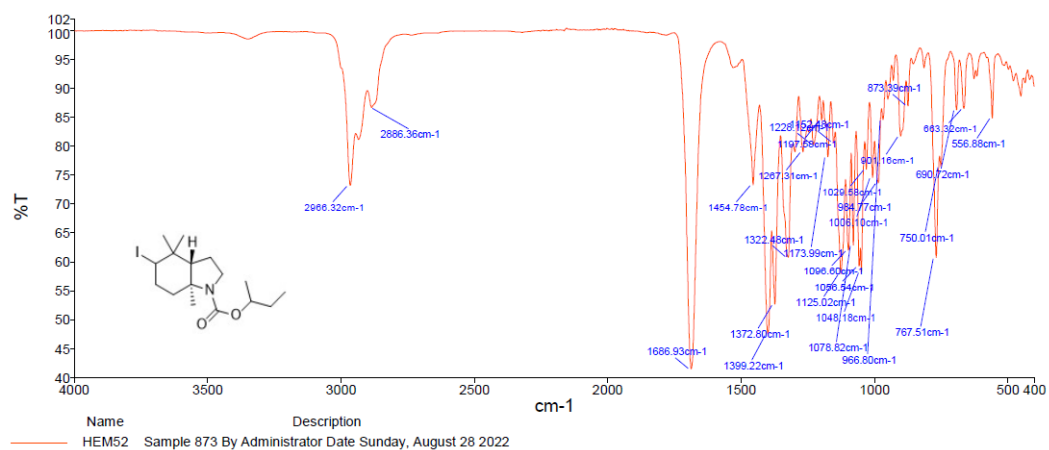


Figure 7.81. IR spectrum of sec-butyl 5-iodotrimethyloctahydroindole carbamate **194g**.

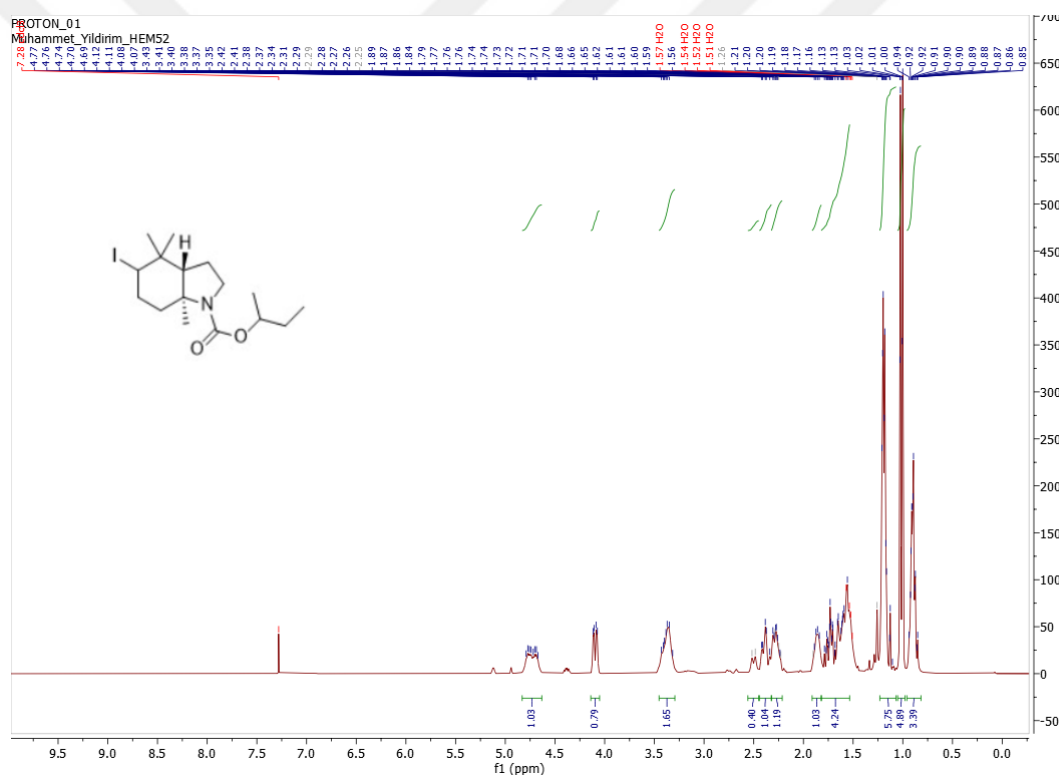


Figure 7.82. ¹H NMR spectrum of sec-butyl 5-iodotrimethyloctahydroindole carbamate **194g**.

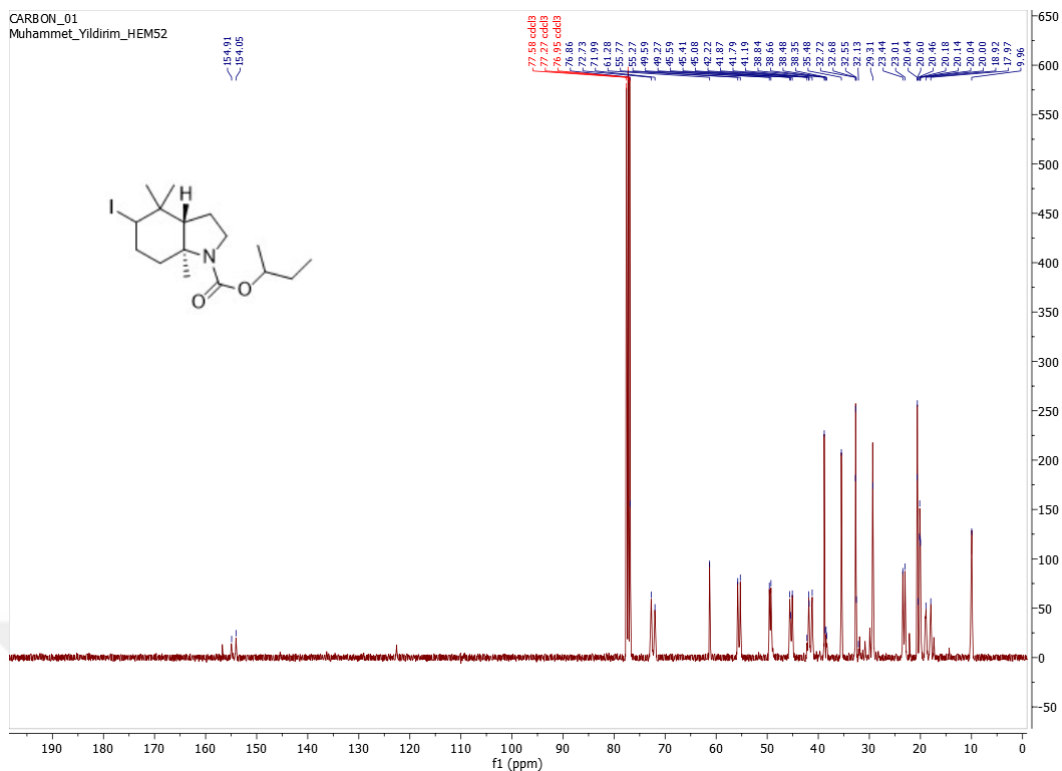


Figure 7.83. ^{13}C NMR spectrum of sec-butyl 5-iodotrimethyloctahydroindole carbamate **194g**.

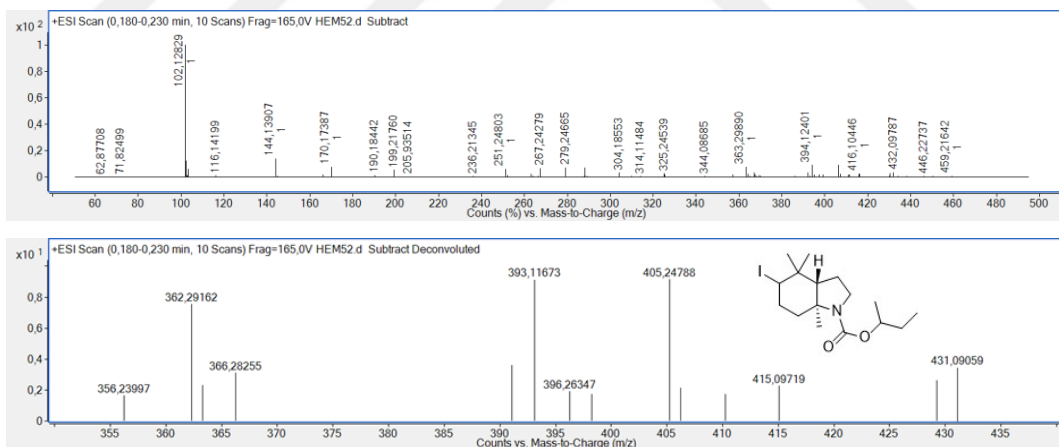


Figure 7.84. Exact mass (HRMS) spectrum of sec-butyl 5-iodotrimethyloctahydroindole carbamate **194g**.

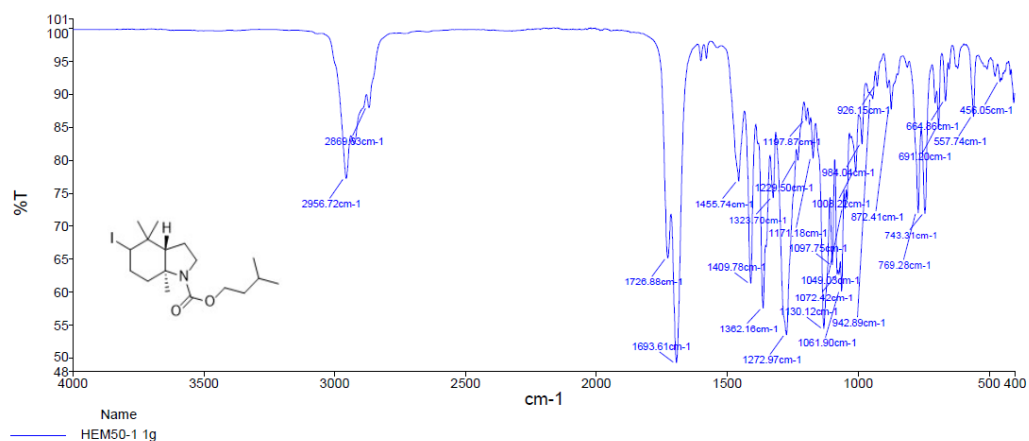


Figure 7.85. IR spectrum of *i*-amyl 5-iodotrimethyloctahydroindole carbamate **194h**.

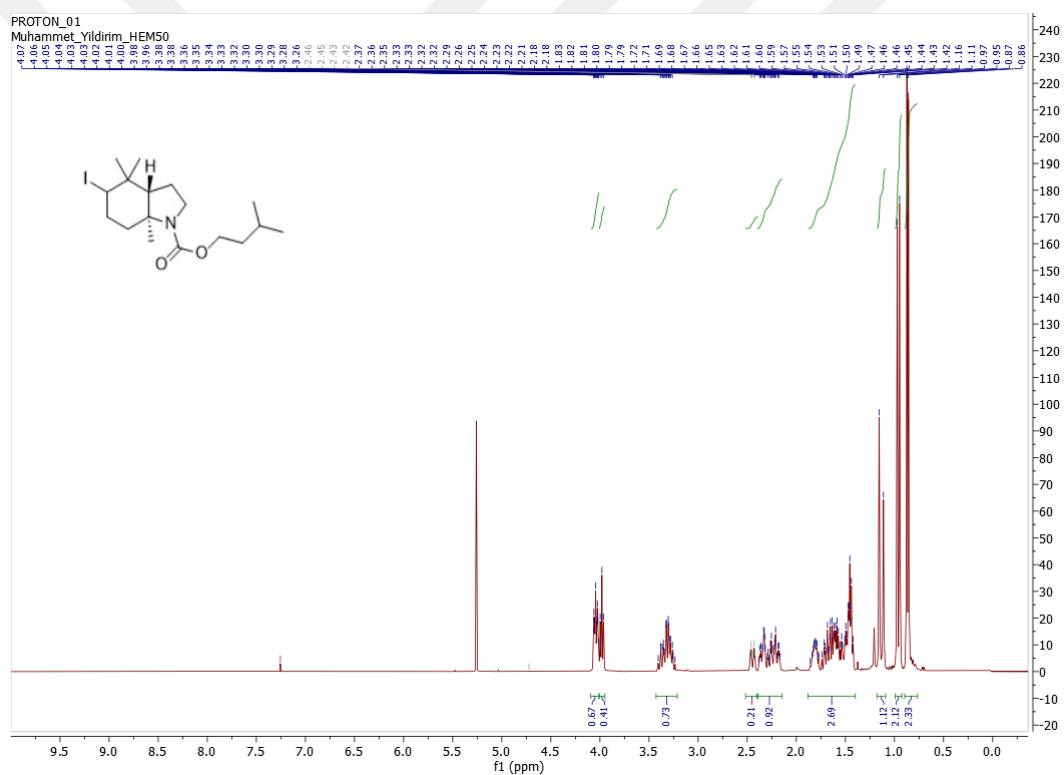


Figure 7.86. ¹H NMR spectrum of *i*-amyl 5-iodotrimethyloctahydroindole carbamate **194h**.

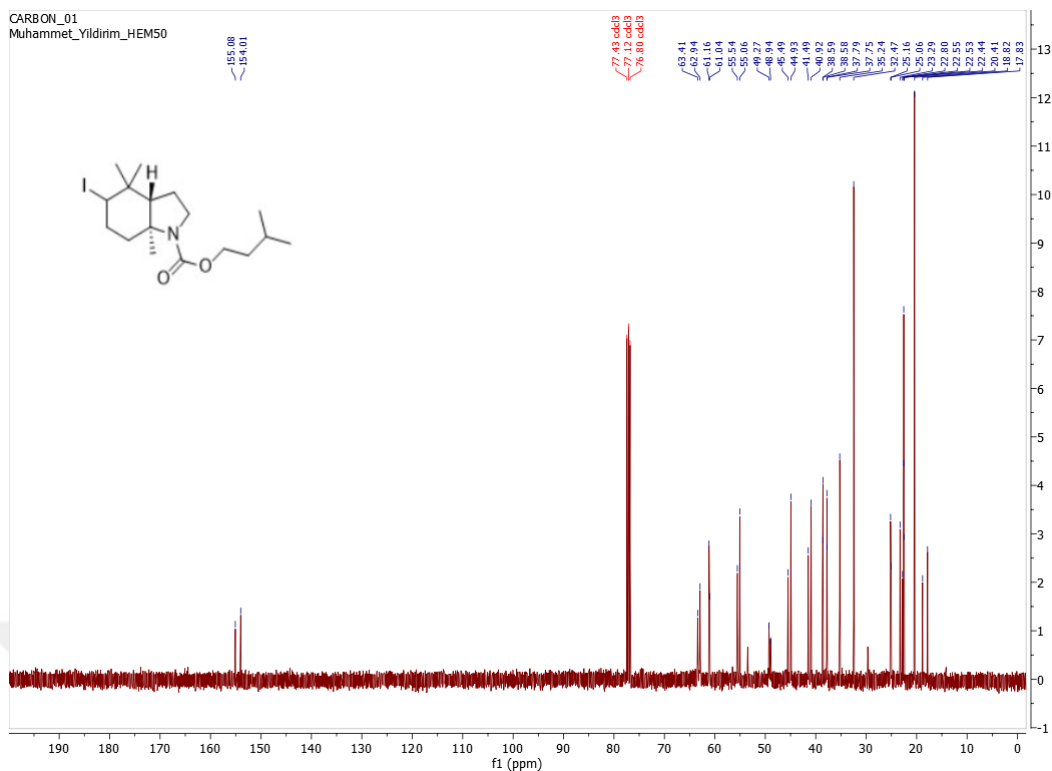


Figure 7.87. ¹³C NMR spectrum of *i*-amyl 5-iodotrimethyloctahydroindole carbamate **194h**.

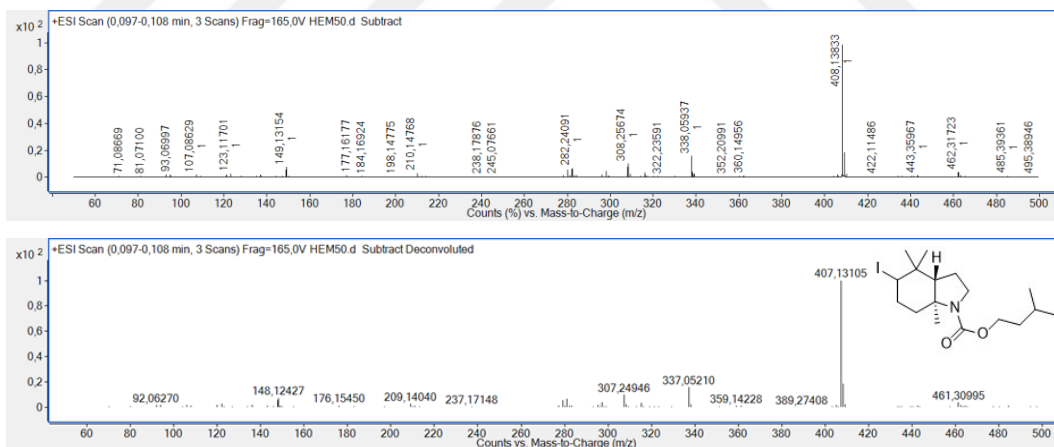


Figure 7.88. Exact mass (HRMS) spectrum of *i*-amyl 5-iodotrimethyloctahydroindole carbamate **194h**.

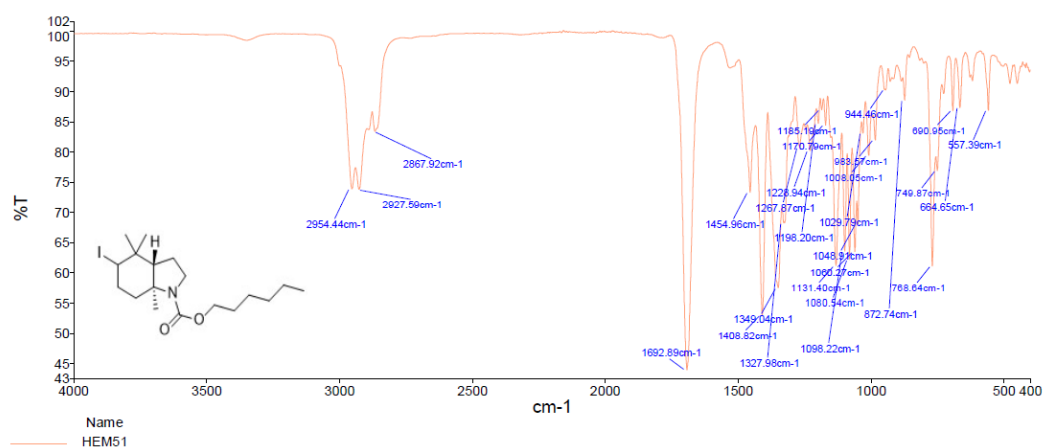


Figure 7.89. IR spectrum of hexyl 5-iodotrimethyloctahydroindole carbamate **194i**.

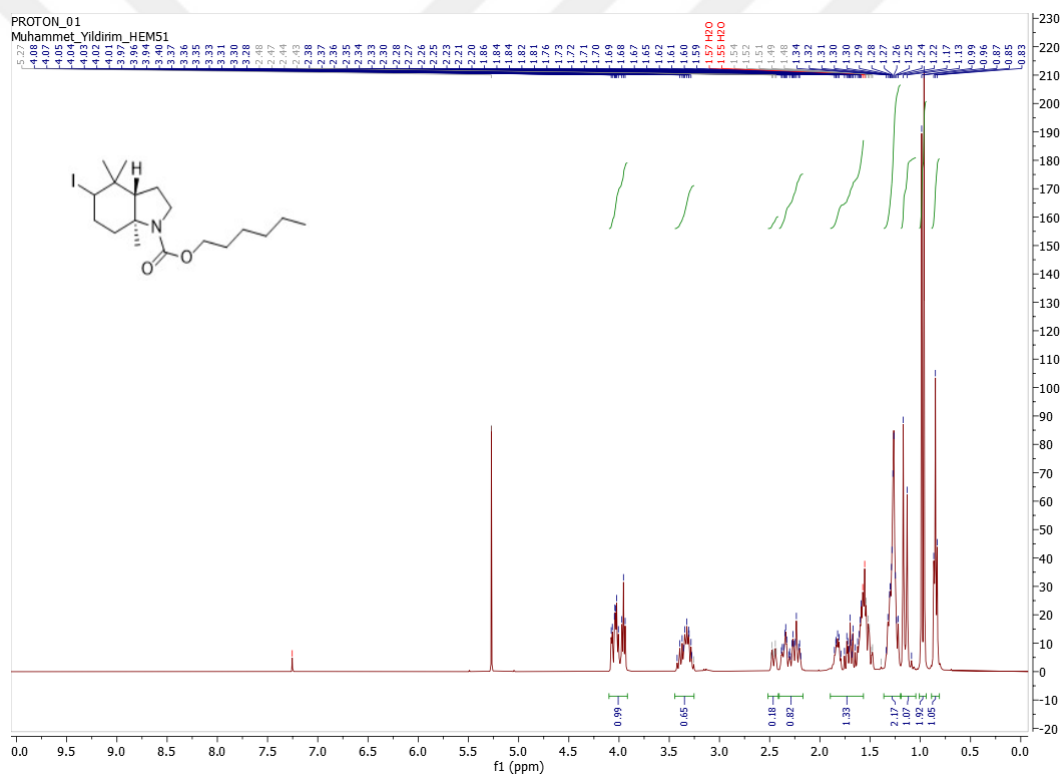


Figure 7.90. ¹H NMR spectrum of hexyl 5-iodotrimethyloctahydroindole carbamate **194i**.

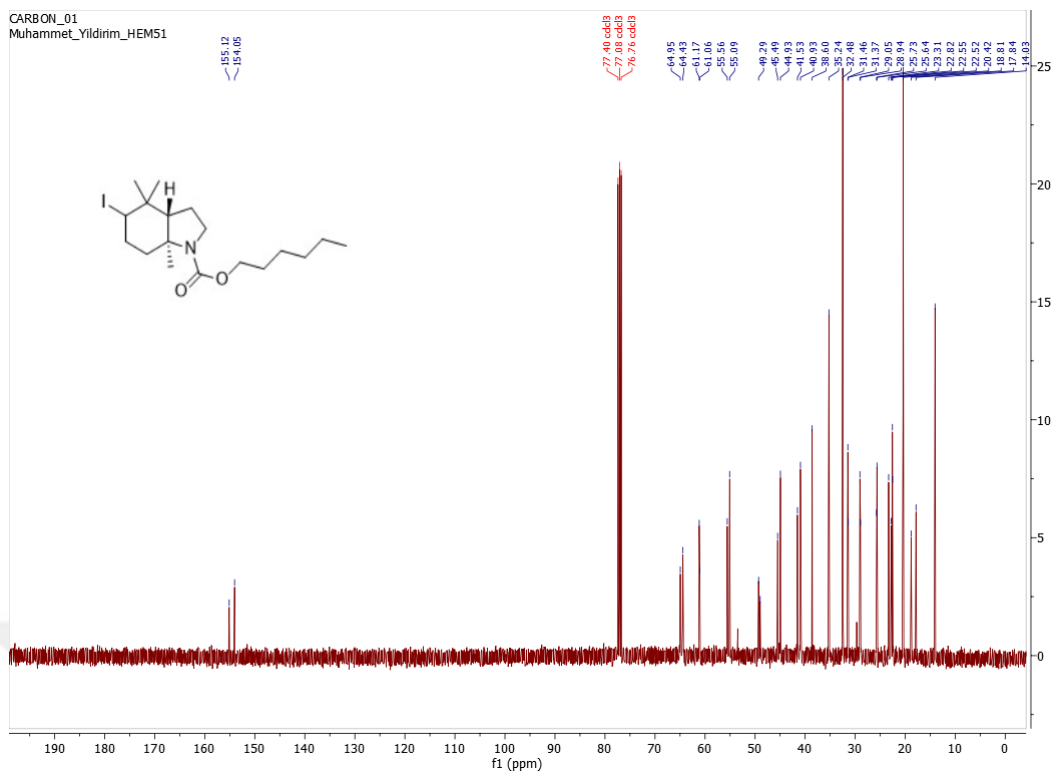


Figure 7.91. ^{13}C NMR spectrum of hexyl 5-iodotrimethyloctahydroindole carbamate **194i**.

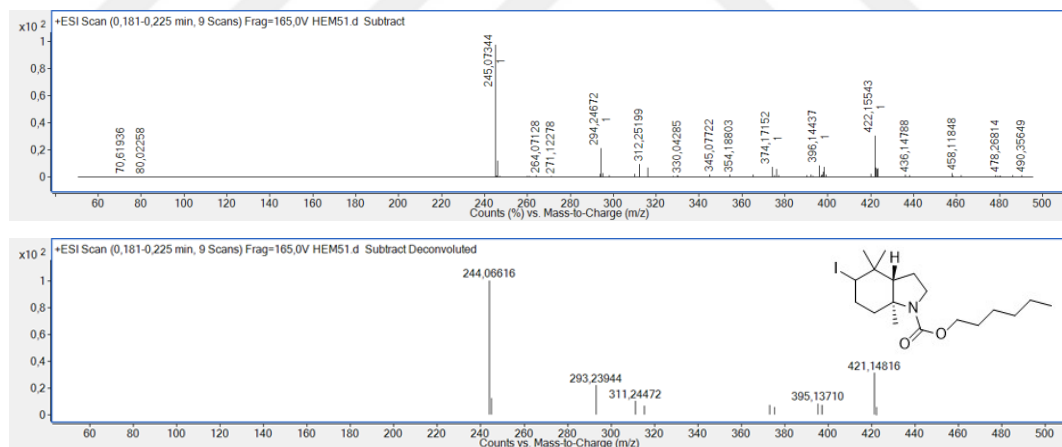


Figure 7.92. Exact mass (HRMS) spectrum of hexyl 5-iodotrimethyloctahydroindole carbamate **194i**.

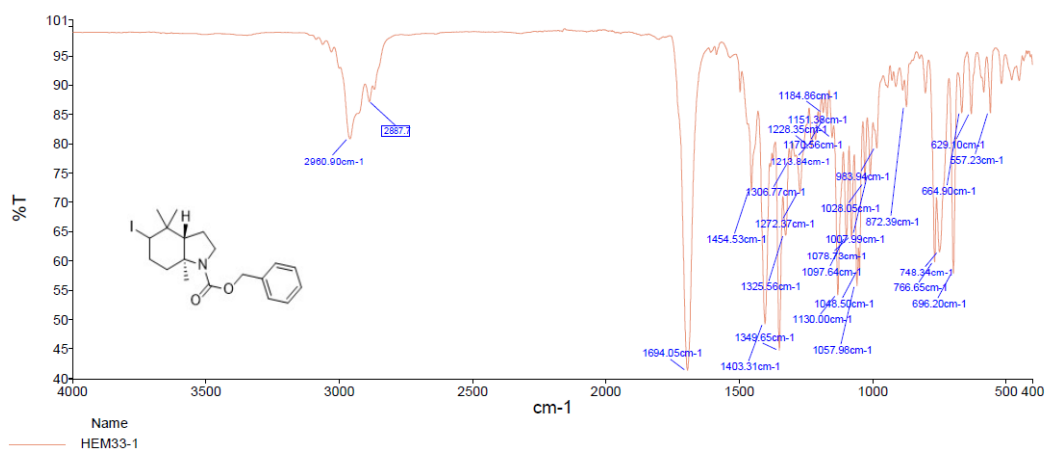
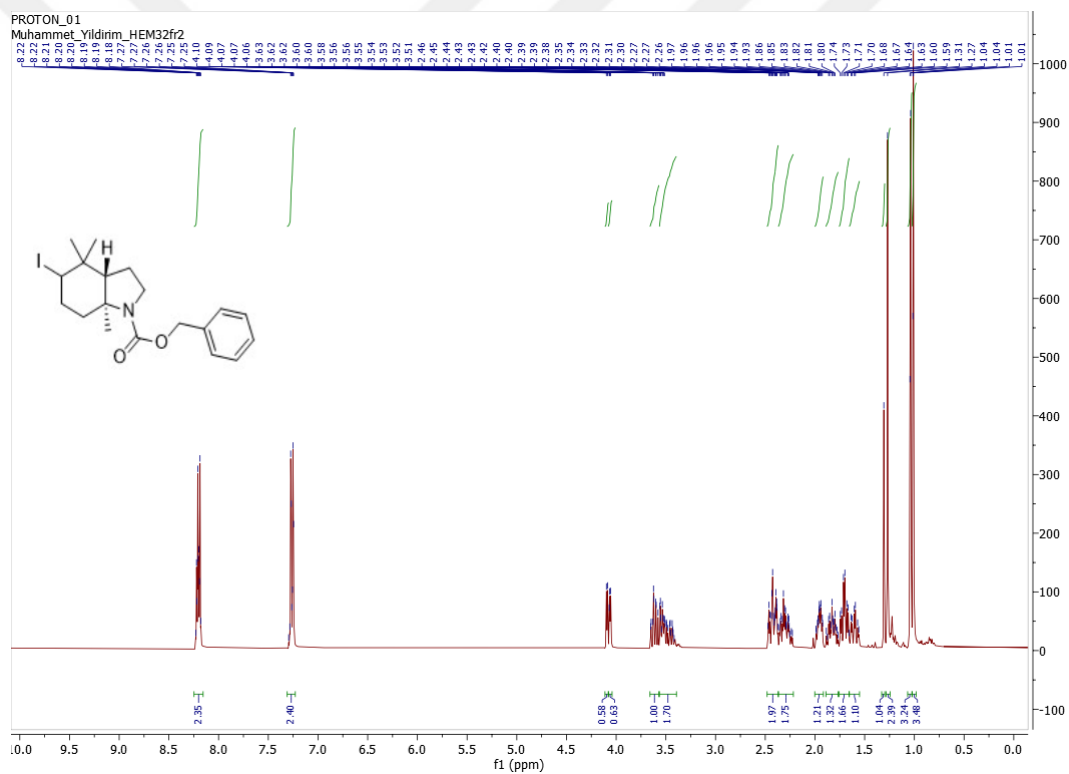


Figure 7.93. IR spectrum of benzyl 5-iodotrimethyloctahydroindole carbamate **194j**.



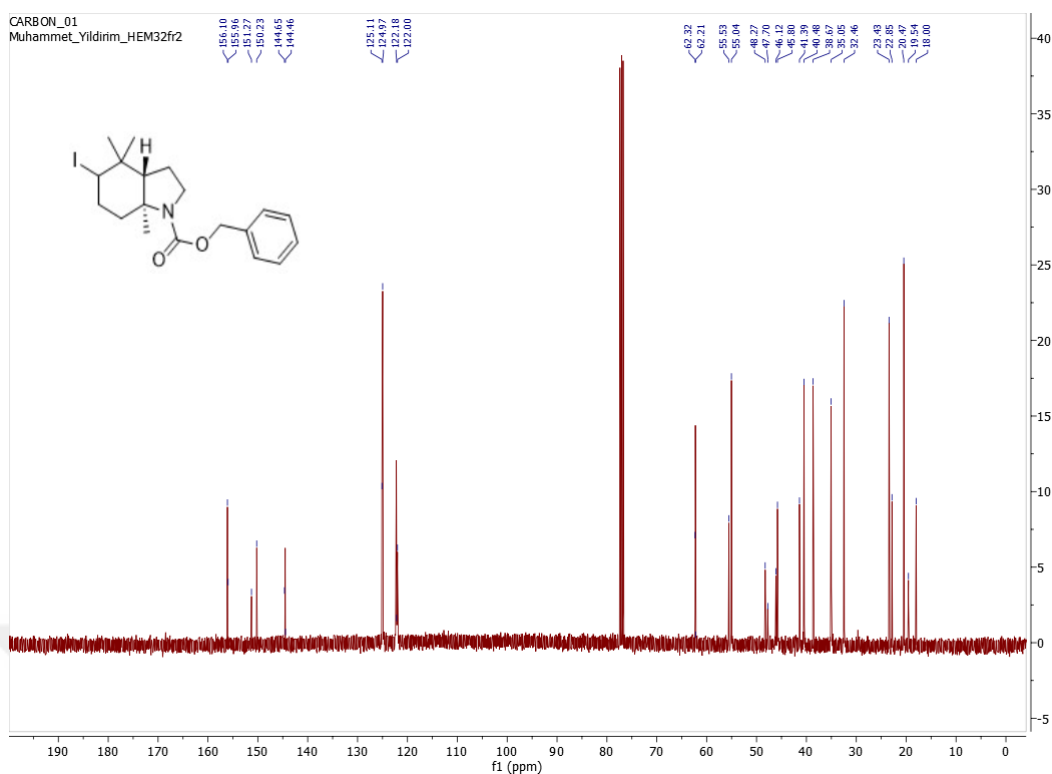


Figure 7.95. ^{13}C NMR spectrum of benzyl 5-iodotrimethyloctahydroindole carbamate **194j**.

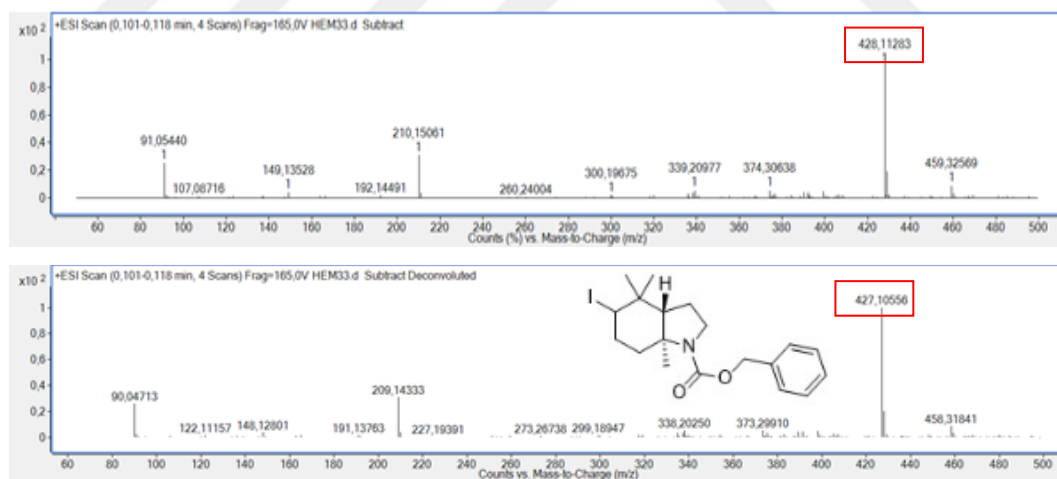


Figure 7.96. Exact mass (HRMS) spectrum of benzyl 5-iodotrimethyloctahydroindole carbamate **194j**.

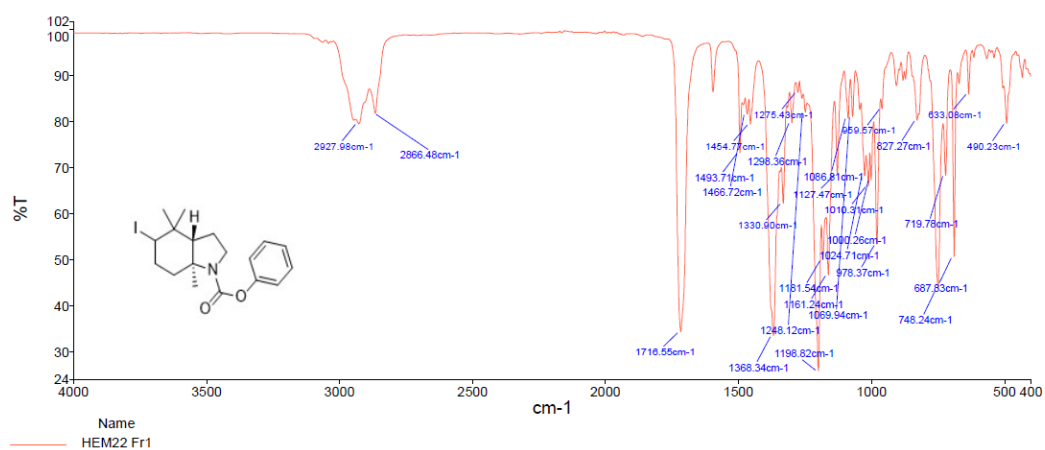


Figure 7.97. IR spectrum of phenyl 5-iodotrimethyloctahydroindole carbamate **194k**.

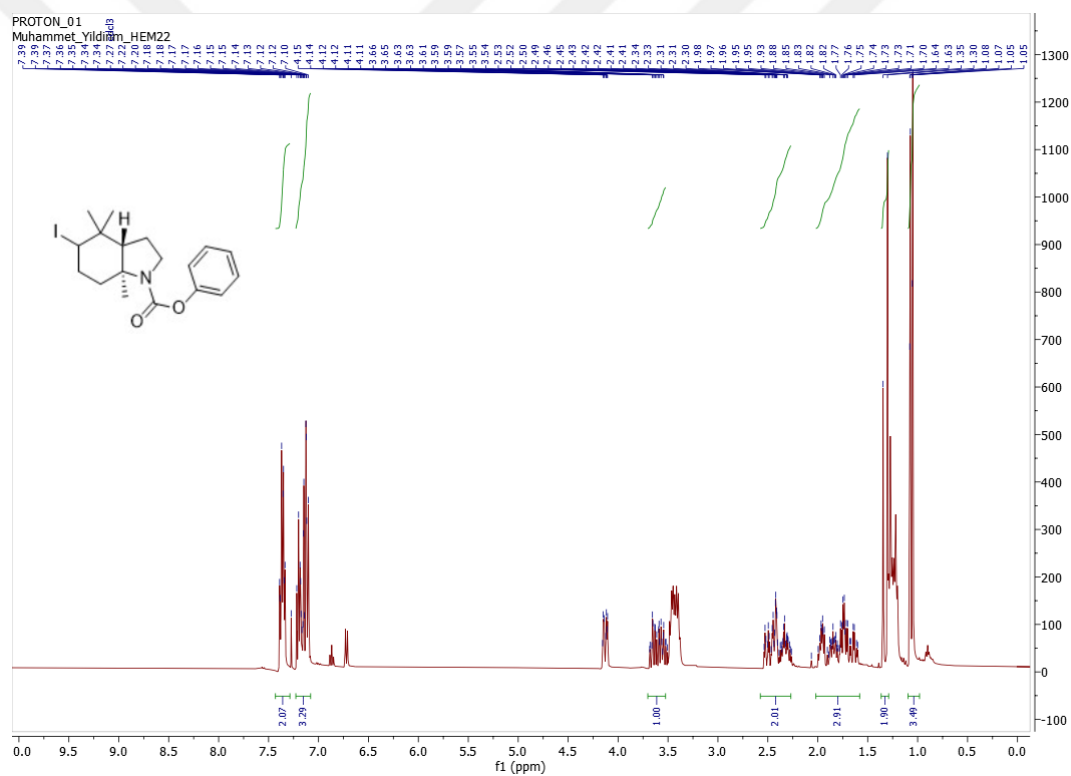


Figure 7.98. ¹H NMR spectrum of phenyl 5-iodotrimethyloctahydroindole carbamate **194k**.

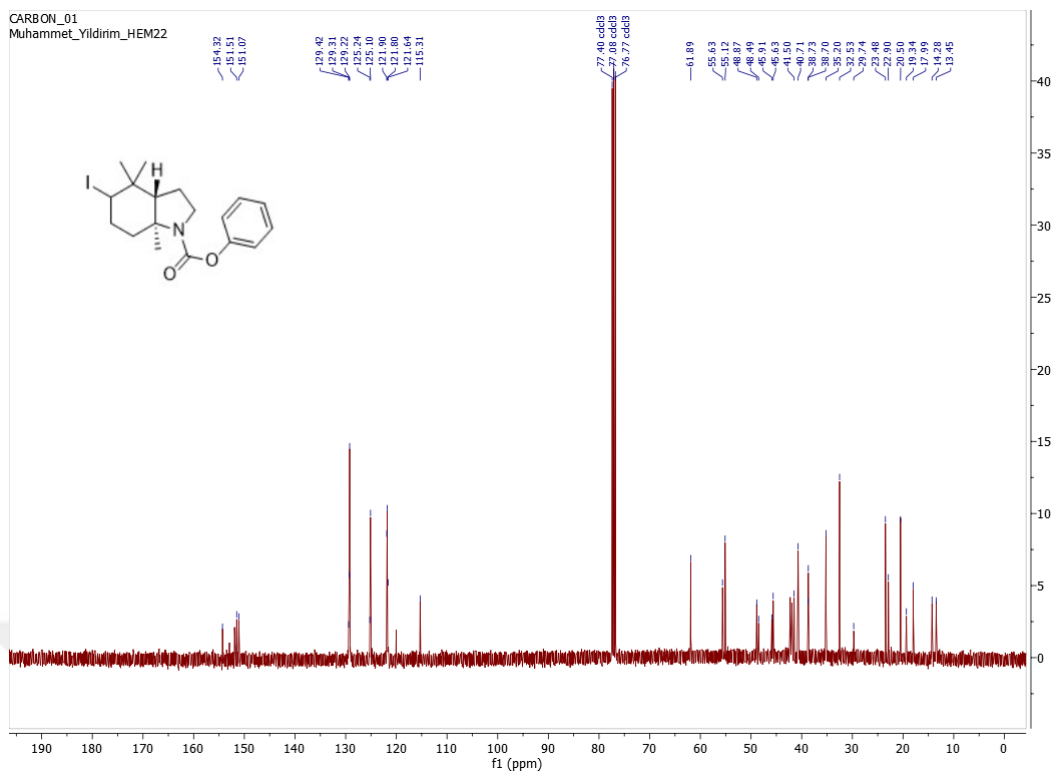


Figure 7.99. ^{13}C NMR spectrum of phenyl 5-iodotrimethyloctahydroindole carbamate **194k**.

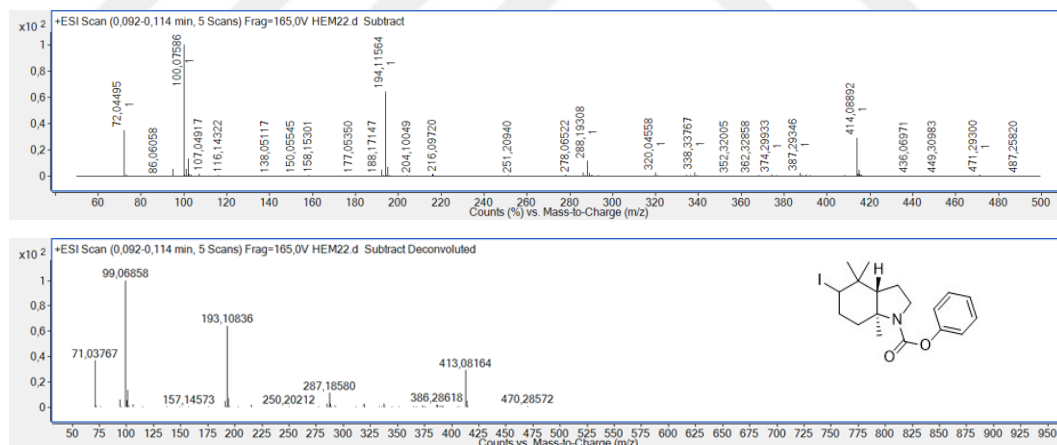
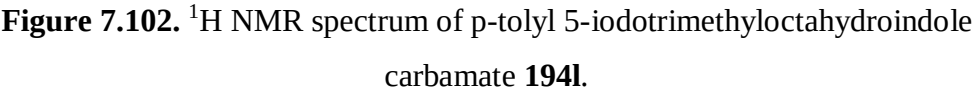
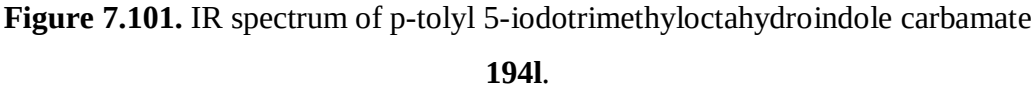


Figure 7.100. Exact mass (HRMS) spectrum of phenyl 5-iodotrimethyloctahydroindole carbamate **194k**.



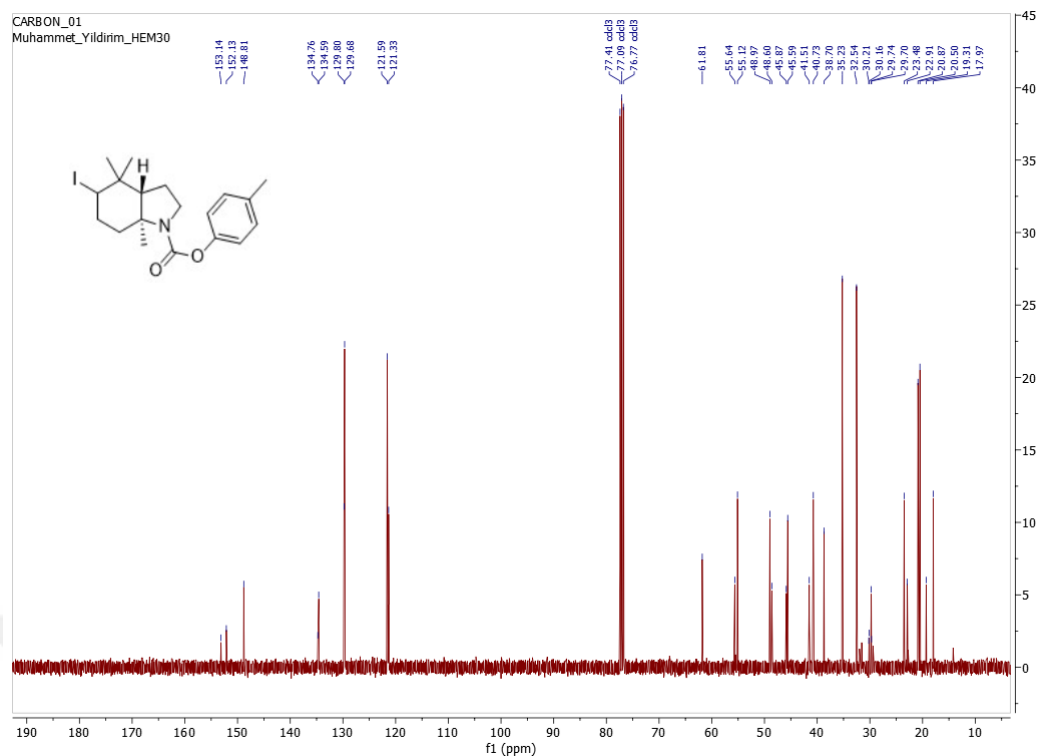


Figure 7.103. ^{13}C NMR spectrum of p-tolyl 5-iodotrimethyloctahydroindole carbamate **194I**.

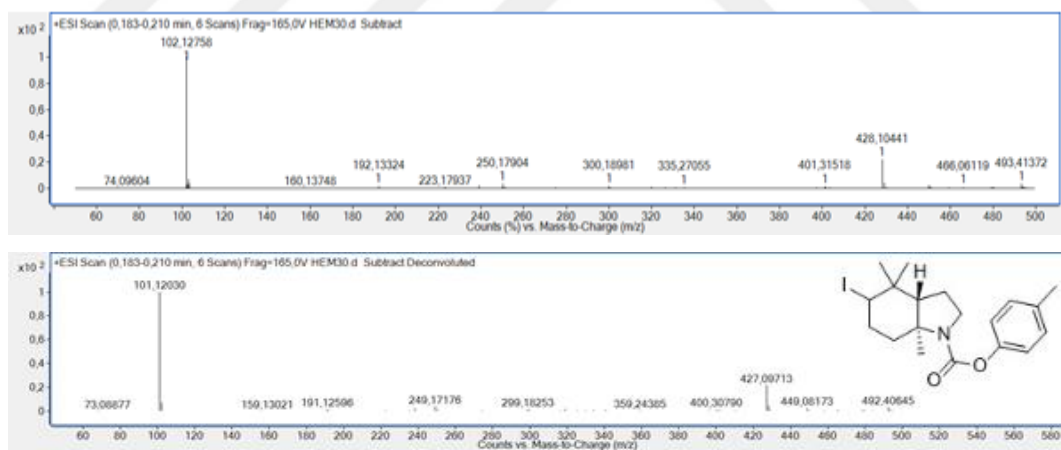


Figure 7.104. Exact mass (HRMS) spectrum of p-tolyl 5-iodotrimethyloctahydroindole carbamate **194I**.

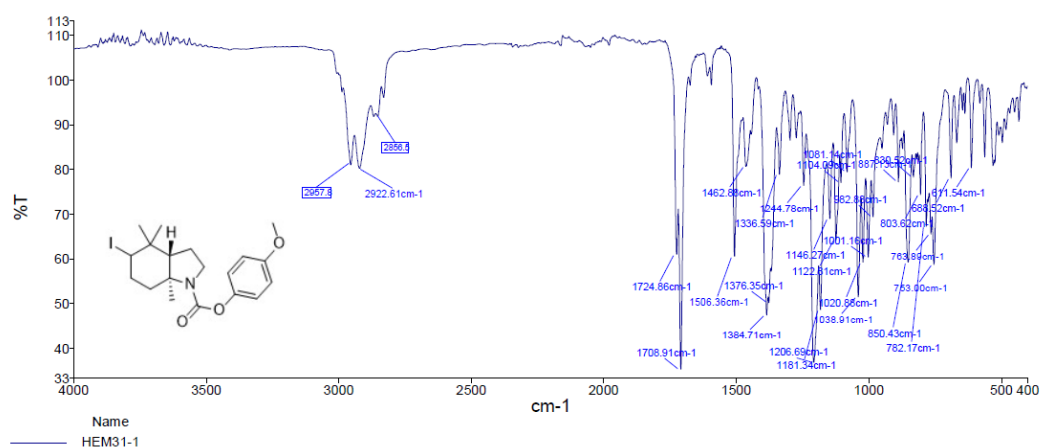


Figure 7.105. IR spectrum of p-methoxyphenyl 5-iodotrimethyloctahydroindole carbamate **194m**.

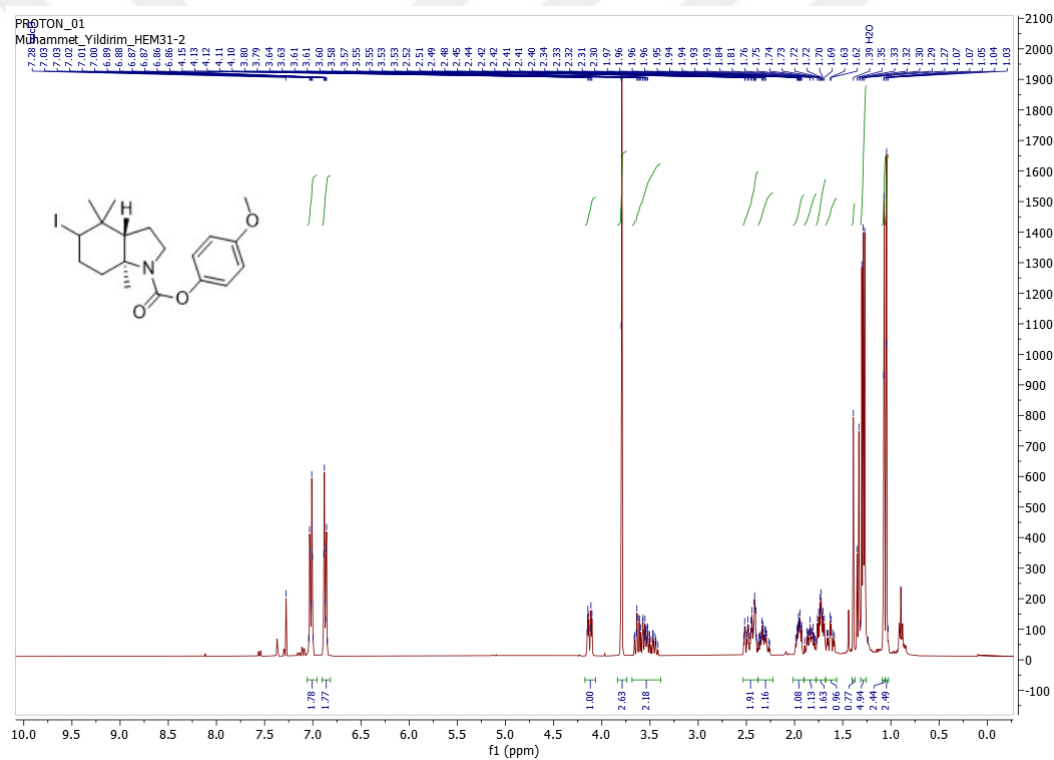


Figure 7.106. ¹H NMR spectrum of p-methoxyphenyl 5-iodotrimethyloctahydroindole carbamate **194m**.

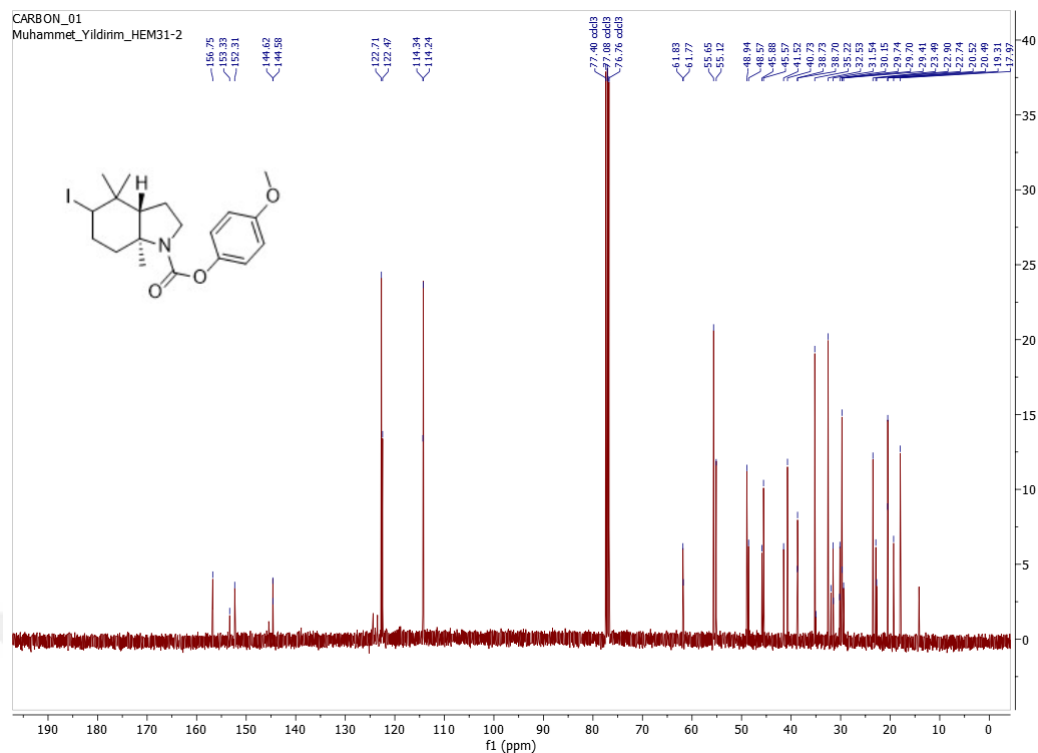


Figure 7.107. ^{13}C NMR spectrum of p-methoxyphenyl 5-iodotrimethyloctahydroindole carbamate **194m**.

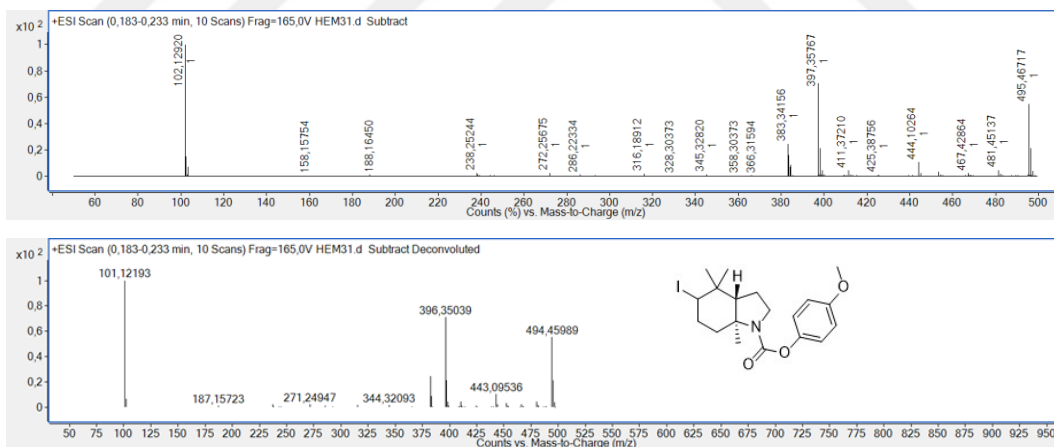


Figure 7.108. Exact mass (HRMS) spectrum of p-methoxyphenyl 5-iodotrimethyloctahydroindole carbamate **194m**.

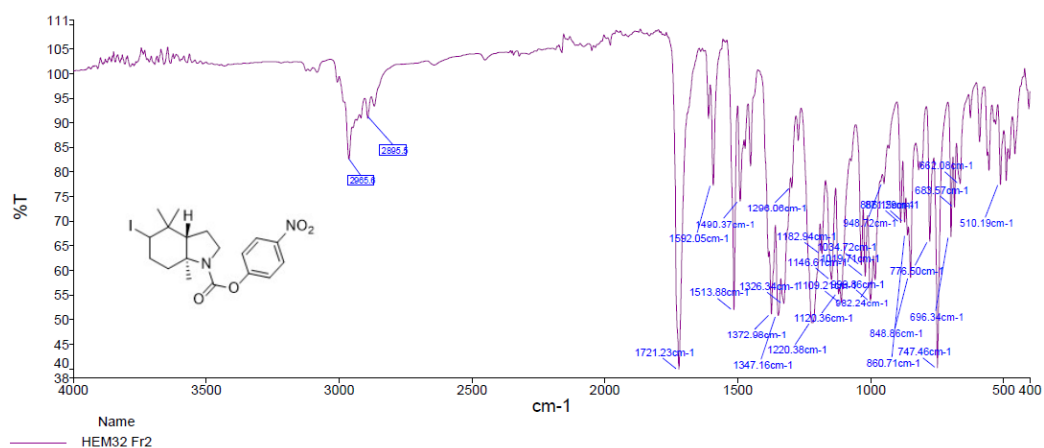


Figure 7.109. IR spectrum of p-nitrophenyl 5-iodotrimethyloctahydroindole carbamate **194n**.

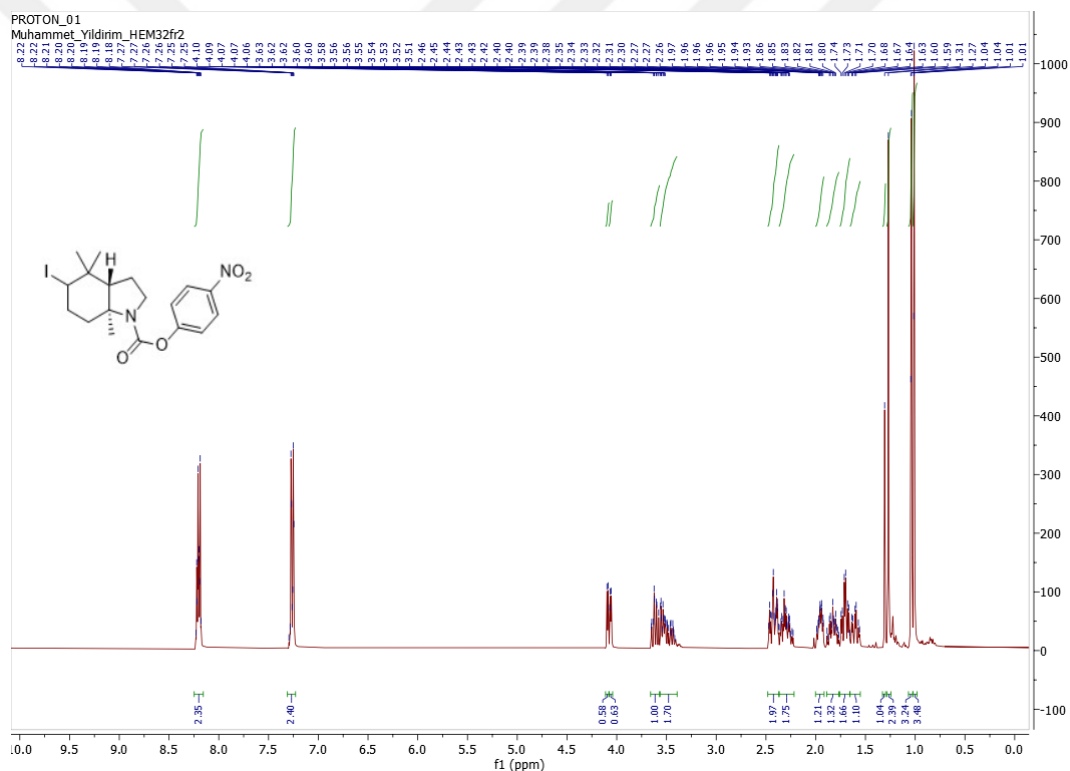


Figure 7.110. ^1H NMR spectrum of p-nitrophenyl 5-iodotrimethyloctahydroindole carbamate **194n**.

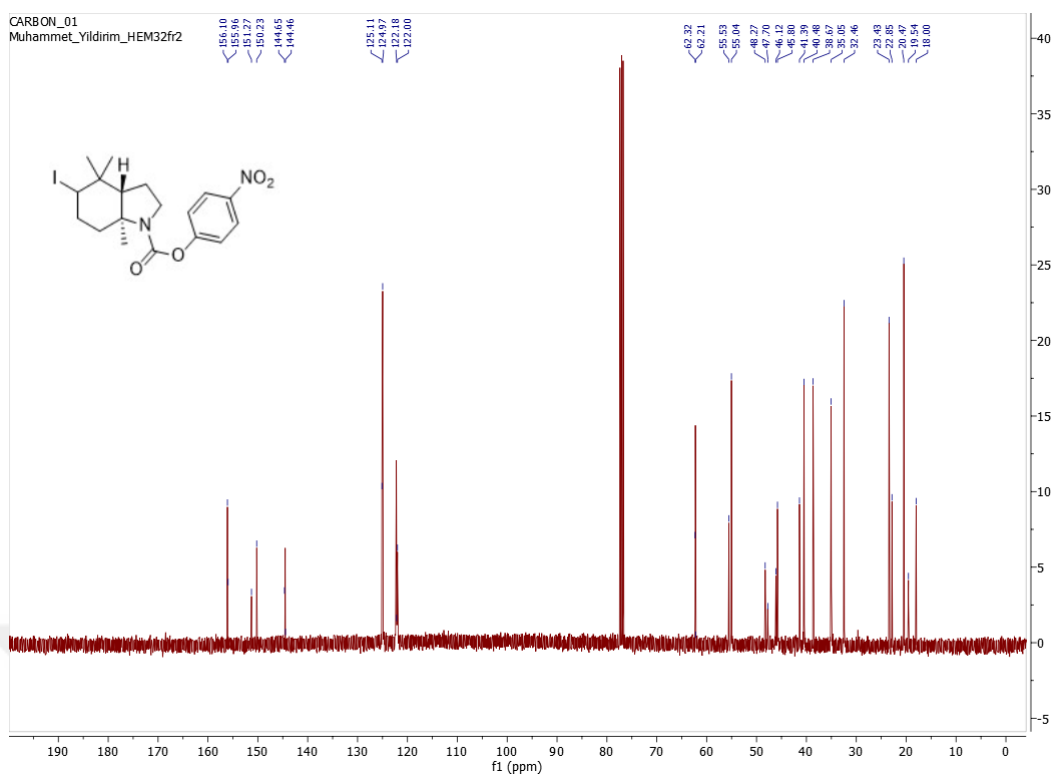


Figure 7.111. ¹³C NMR spectrum of p-nitrophenyl 5-iodotrimethyloctahydroindole carbamate **194n**.

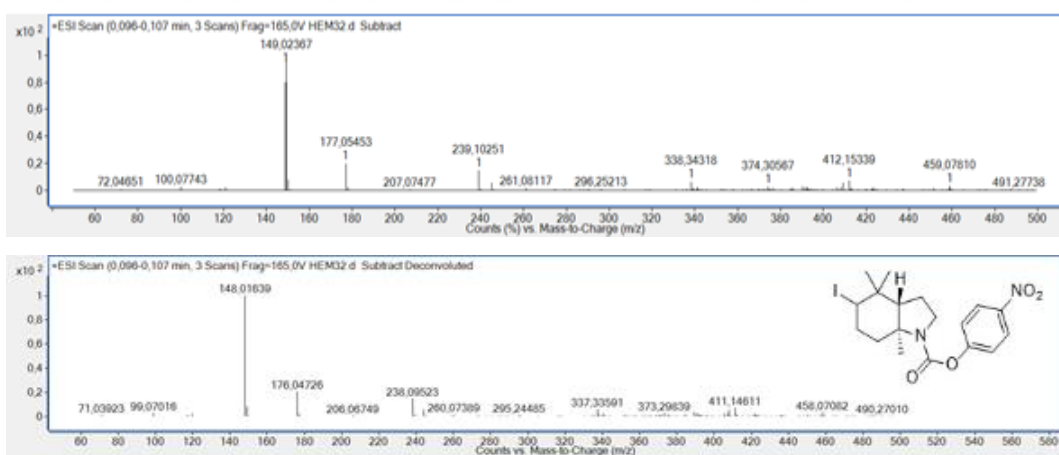


Figure 7.112. Exact mass (HRMS) spectrum of p-nitrophenyl 5-iodotrimethyloctahydroindole carbamate **194n**.

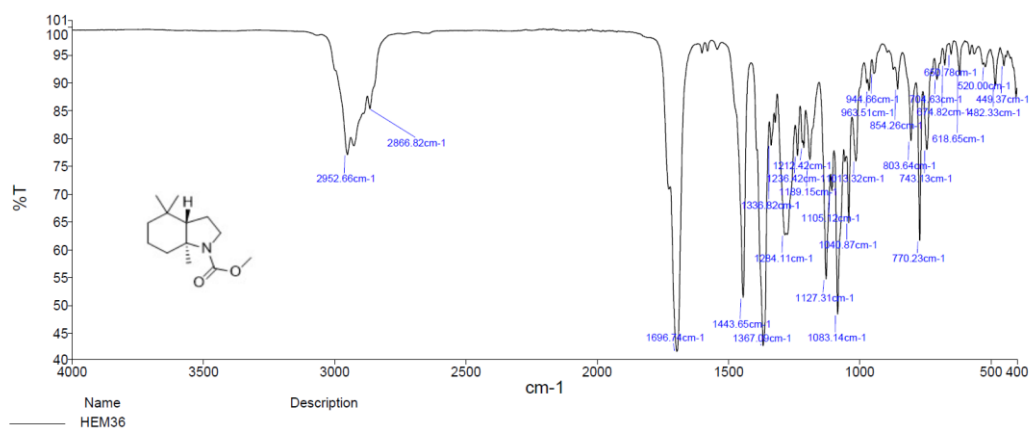


Figure 7.113. IR spectrum of methyl trimethyloctahydroindole carbamate **195a**.

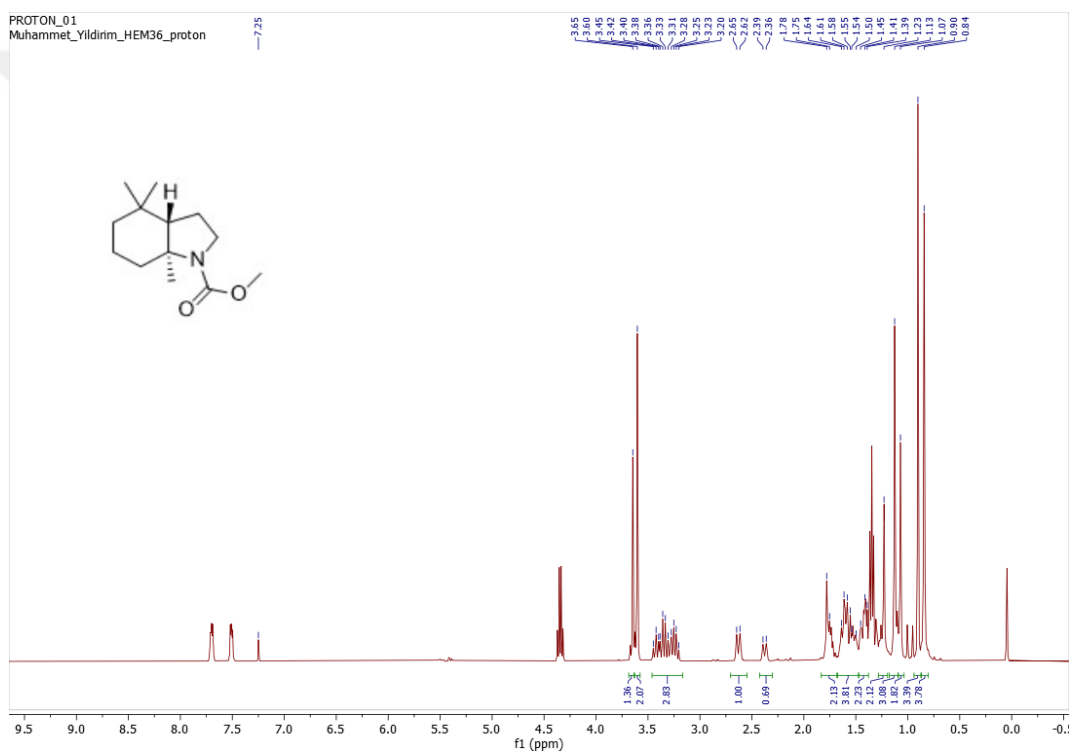


Figure 7.114. ¹H NMR spectrum of methyl trimethyloctahydroindole carbamate **195a**.

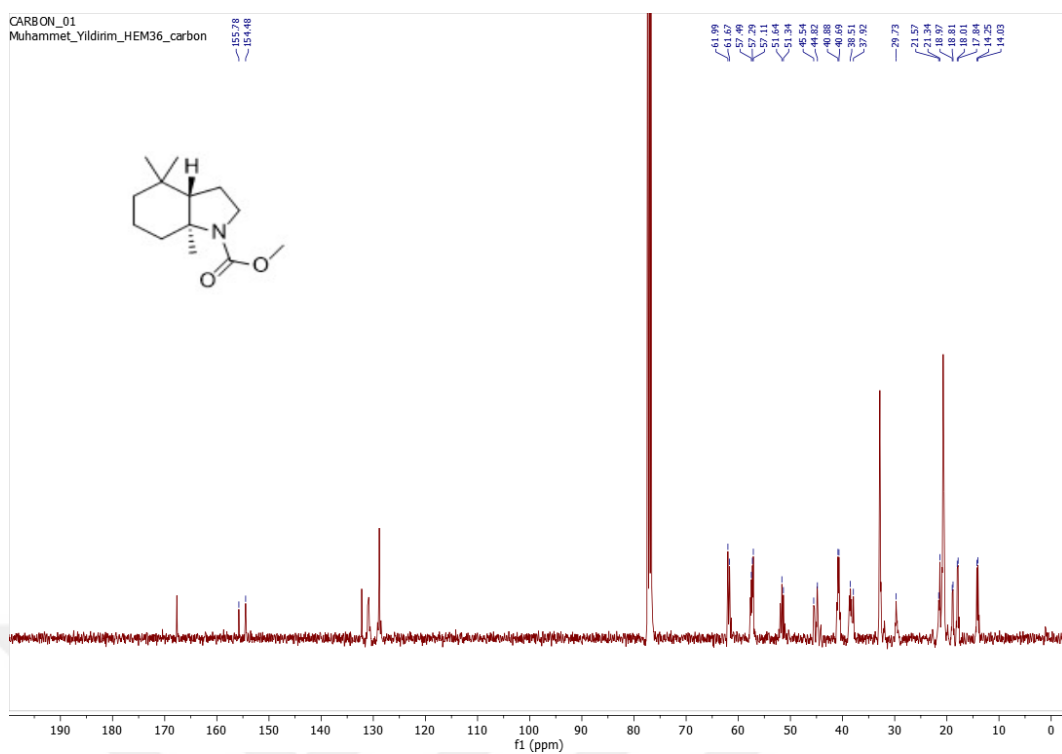


Figure 7.115. ^{13}C NMR spectrum of methyl trimethyloctahydroindole carbamate **195a**.

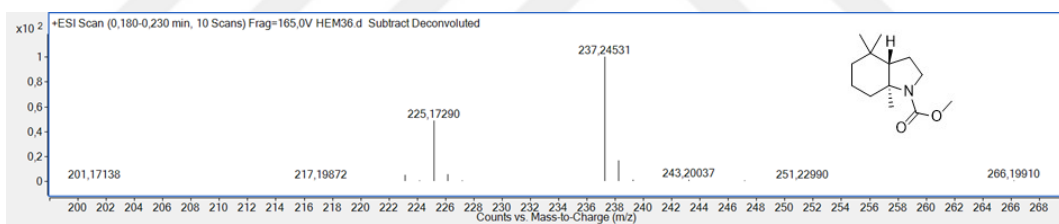


Figure 7.116. Exact mass (HRMS) spectrum of methyl trimethyloctahydroindole carbamate **195a**.

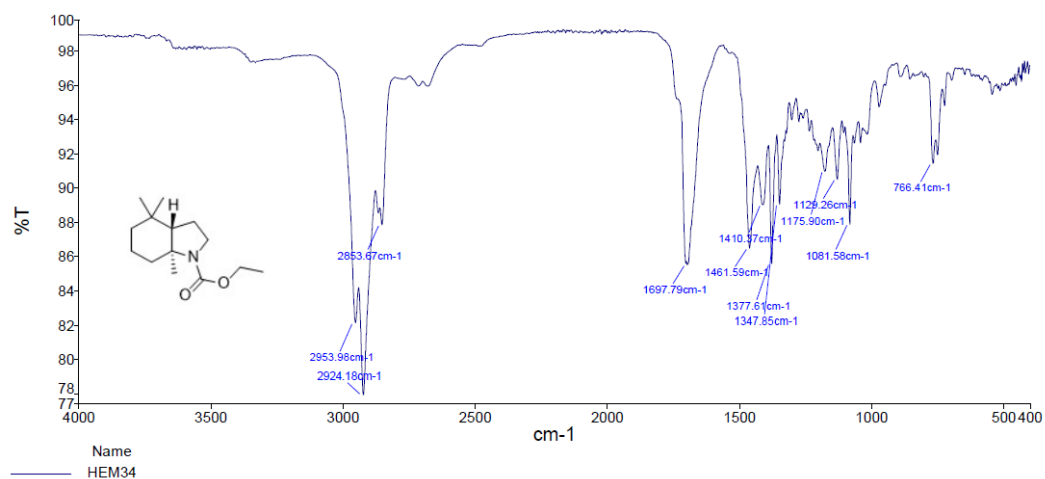


Figure 7.117. IR spectrum of ethyl trimethyloctahydroindole carbamate **195b**.

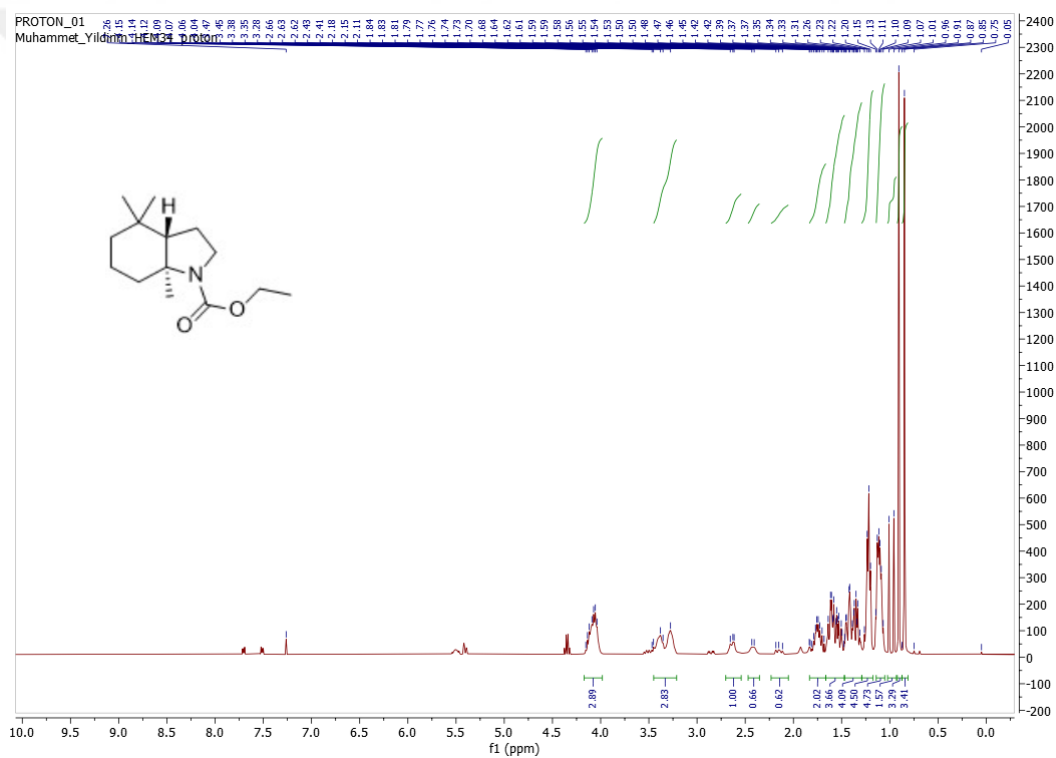


Figure 7.118. ¹H NMR spectrum of ethyl trimethyloctahydroindole carbamate **195b**.

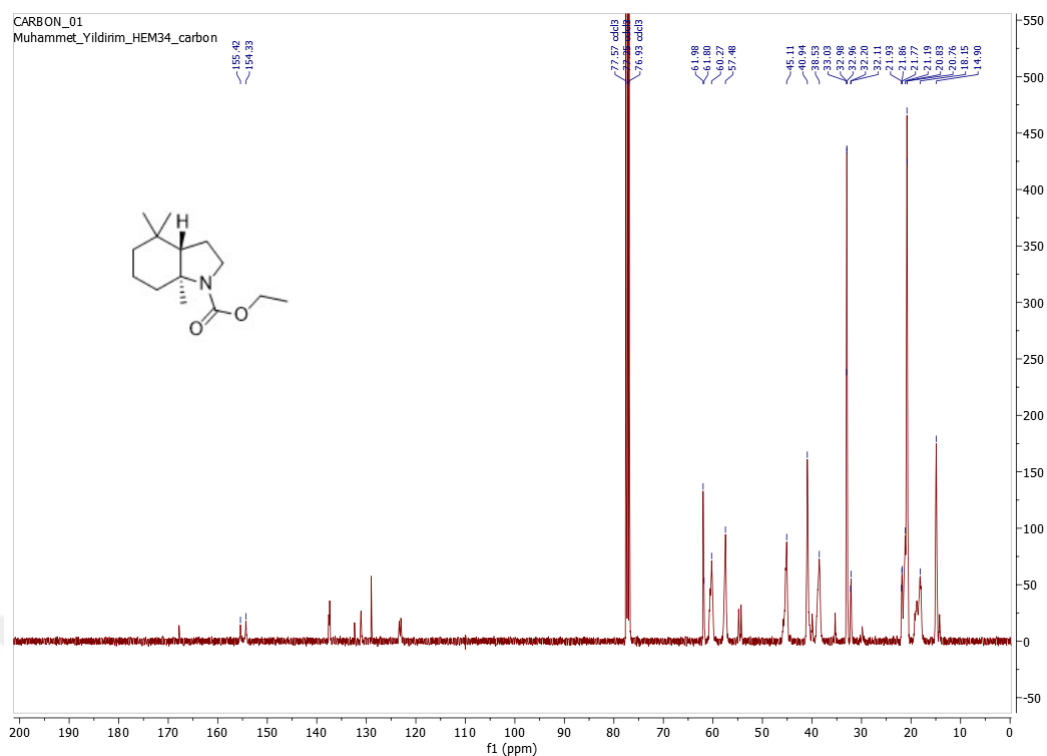


Figure 7.119. ^{13}C NMR spectrum of ethyl trimethyloctahydroindole carbamate **195b**.

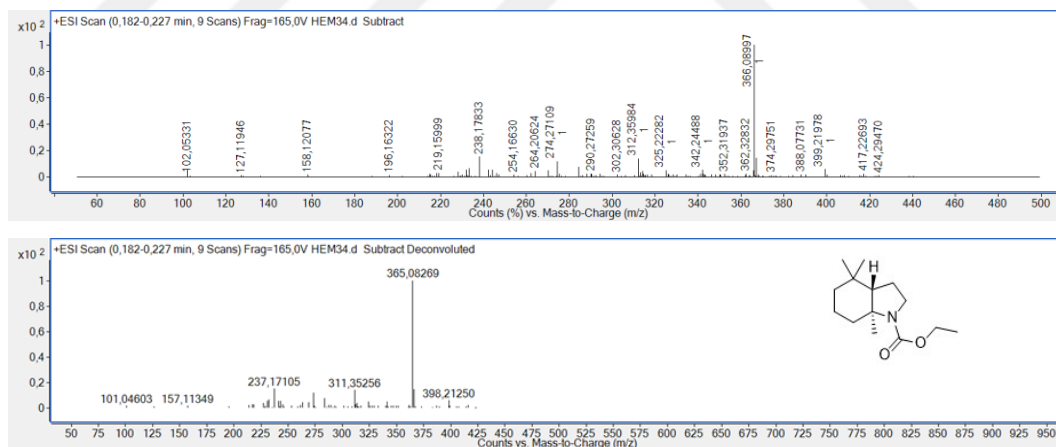


Figure 7.120. Exact mass (HRMS) spectrum of ethyl trimethyloctahydroindole carbamate **195b**.

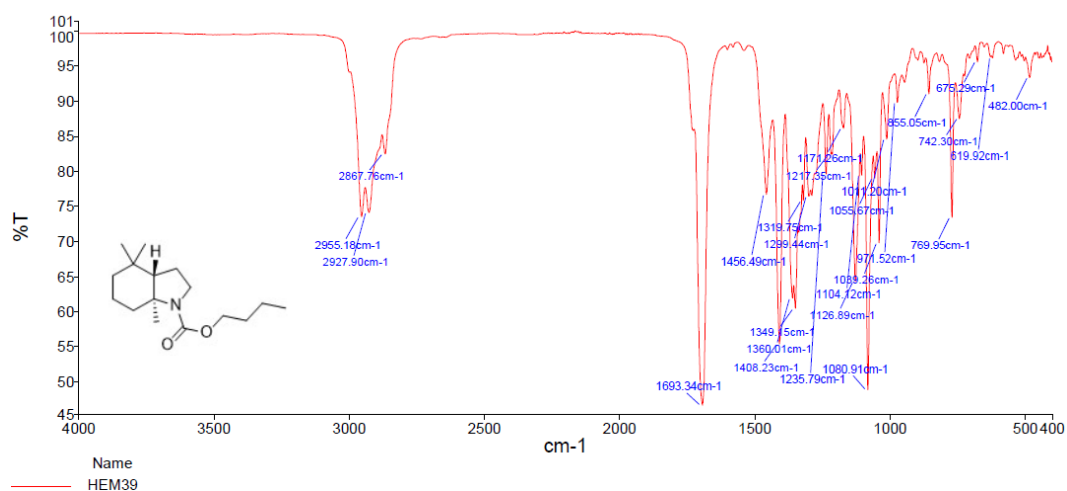


Figure 7.121. IR spectrum of butyl trimethyloctahydroindole carbamate **195e**.

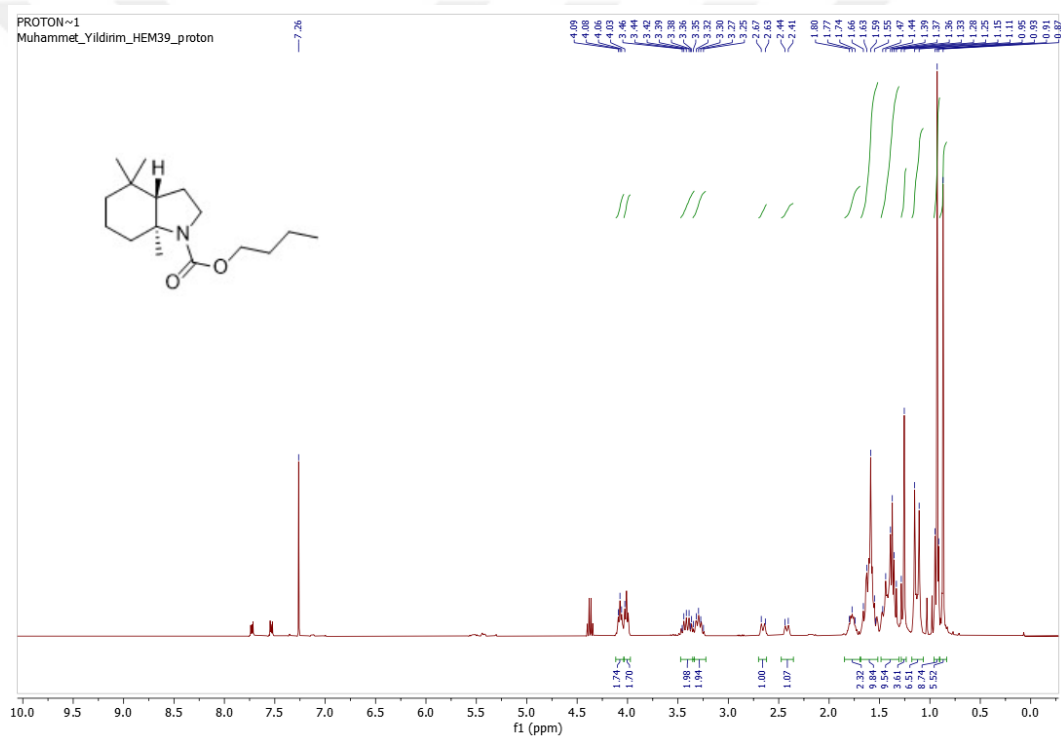


Figure 7.122. ¹H NMR spectrum of butyl trimethyloctahydroindole carbamate **195e**.

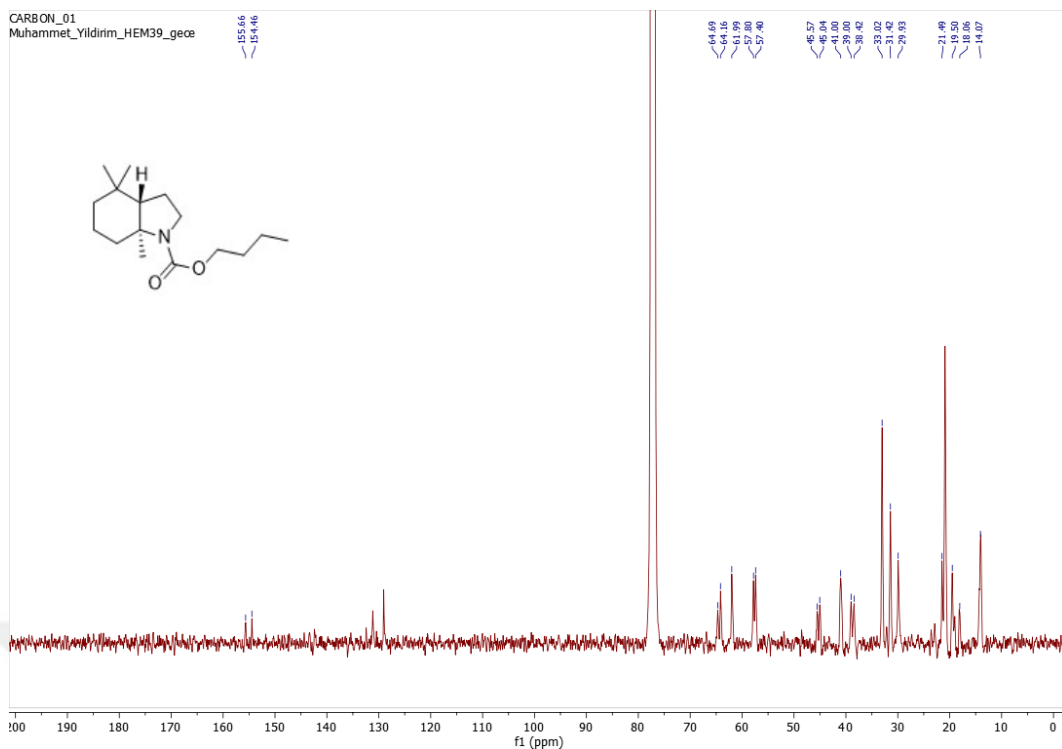


Figure 7.123. ^{13}C NMR spectrum of butyl trimethyloctahydroindole carbamate **195e**.

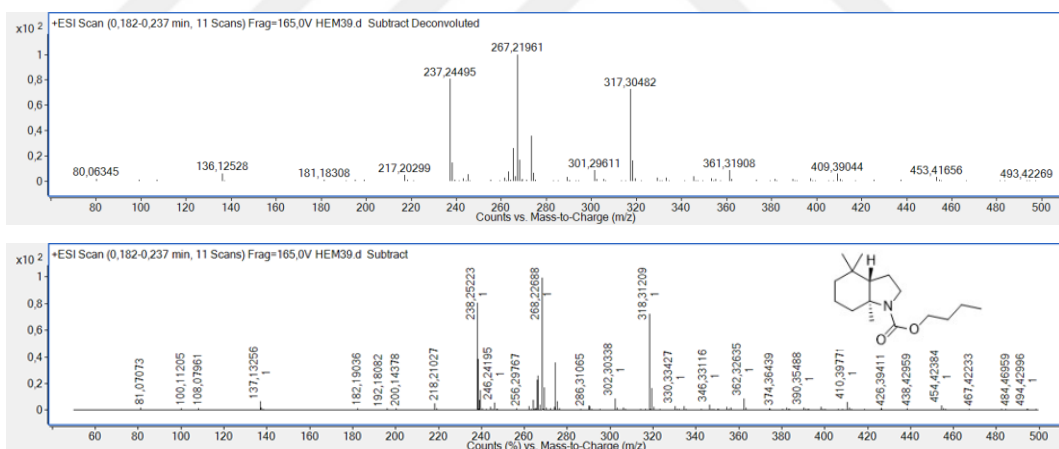


Figure 7.124. Exact mass (HRMS) spectrum of butyl trimethyloctahydroindole carbamate **195e**

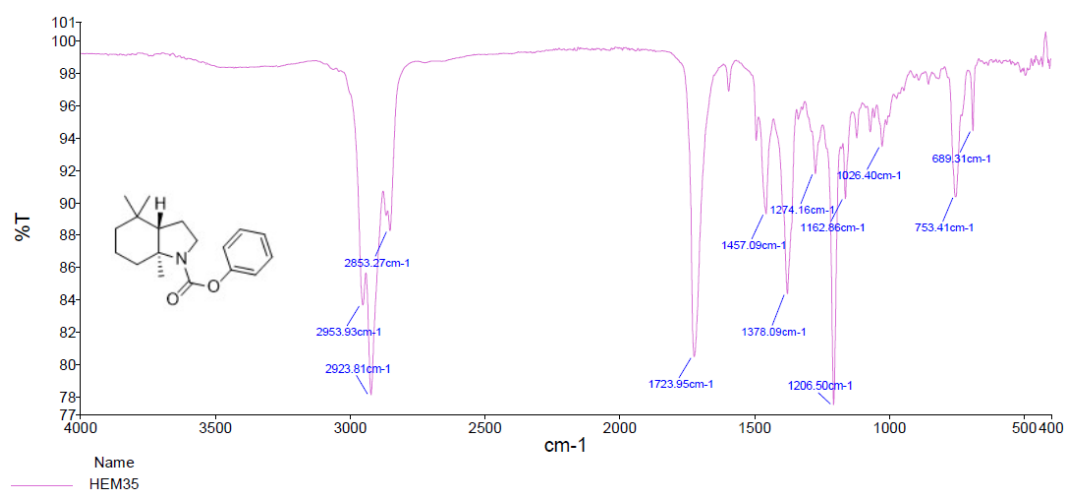


Figure 7.125. IR spectrum of phenyl trimethyloctahydroindole carbamate **195k**.

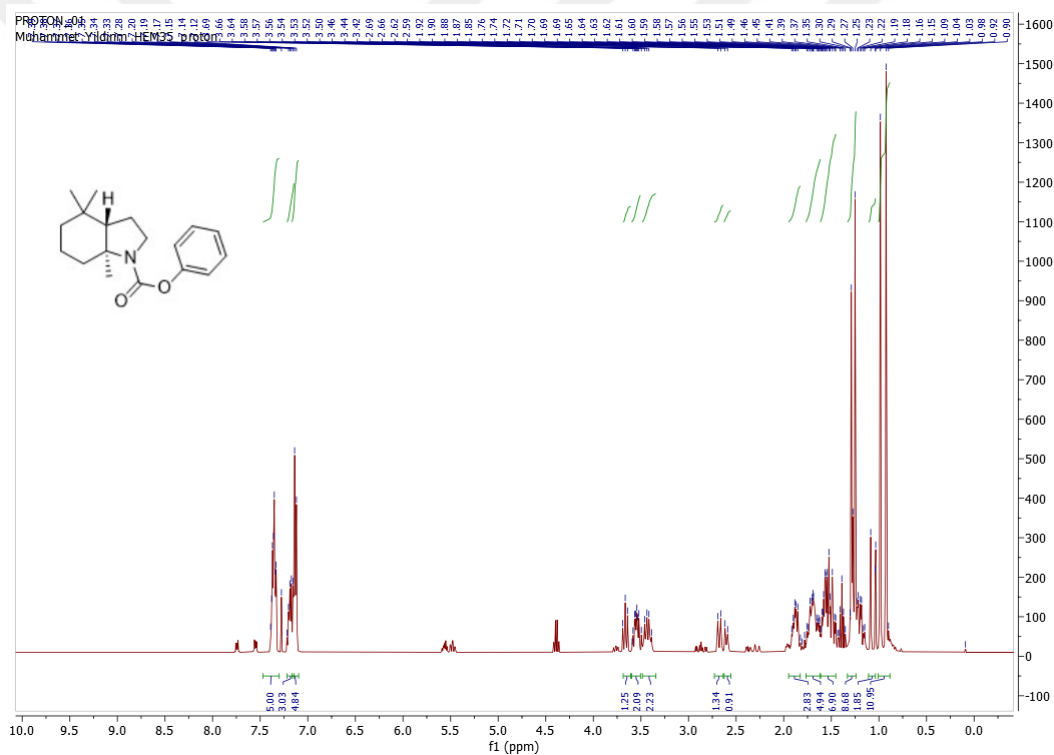


Figure 7.126. ¹H NMR spectrum of phenyl trimethyloctahydroindole carbamate **195k**.

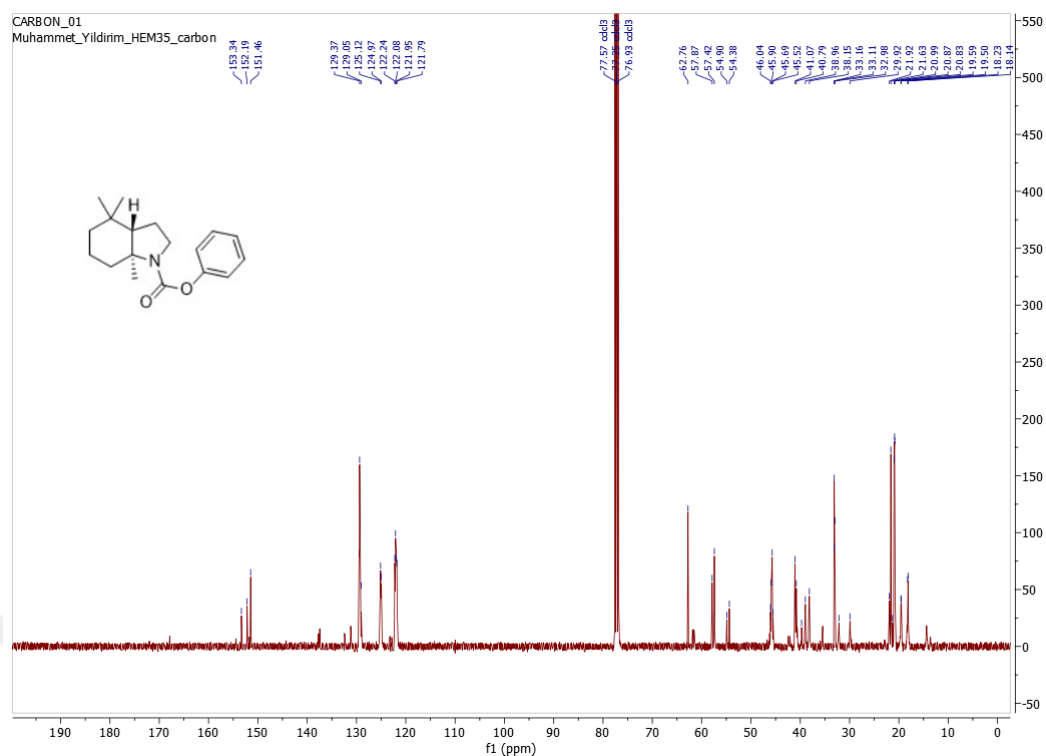


Figure 7.127. ^{13}C NMR spectrum of phenyl trimethyloctahydroindole carbamate **195k**.

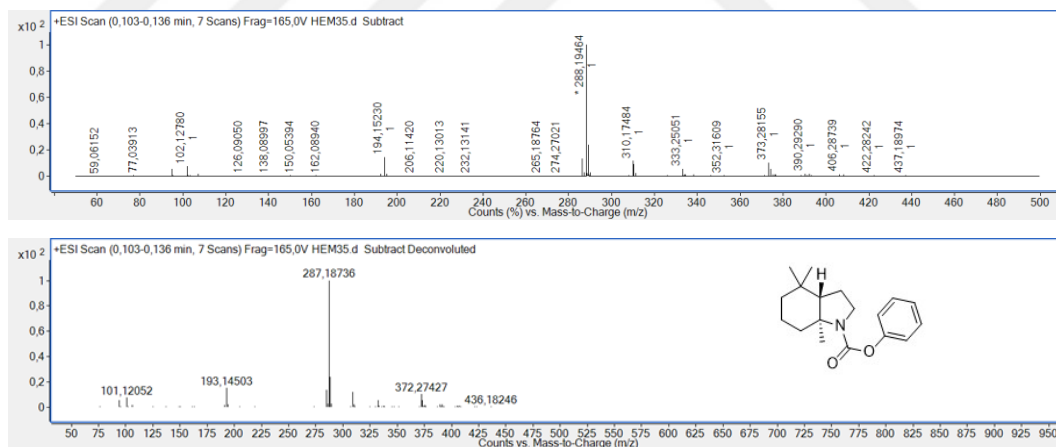


Figure 7.128. Exact mass (HRMS) spectrum of phenyl trimethyloctahydroindole carbamate **195k**.

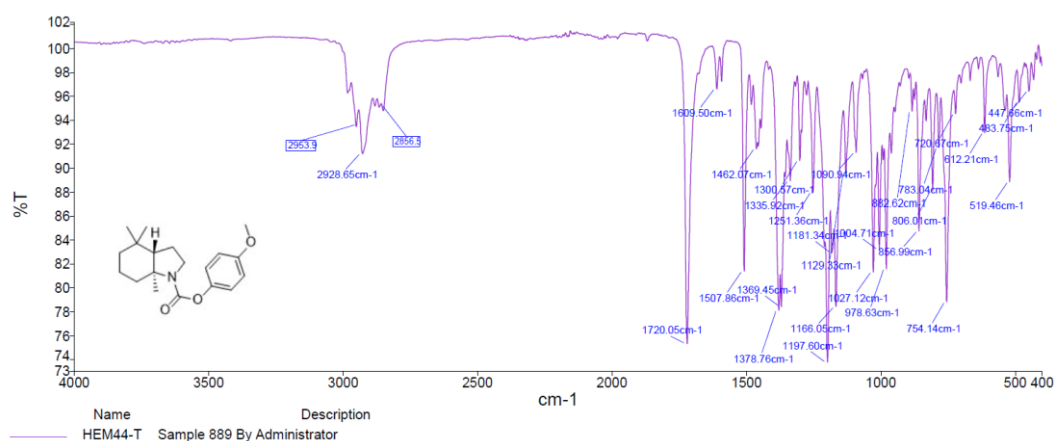


Figure 7.129. IR spectrum of p-methoxyphenyl trimethyloctahydroindole carbamate **195m**.

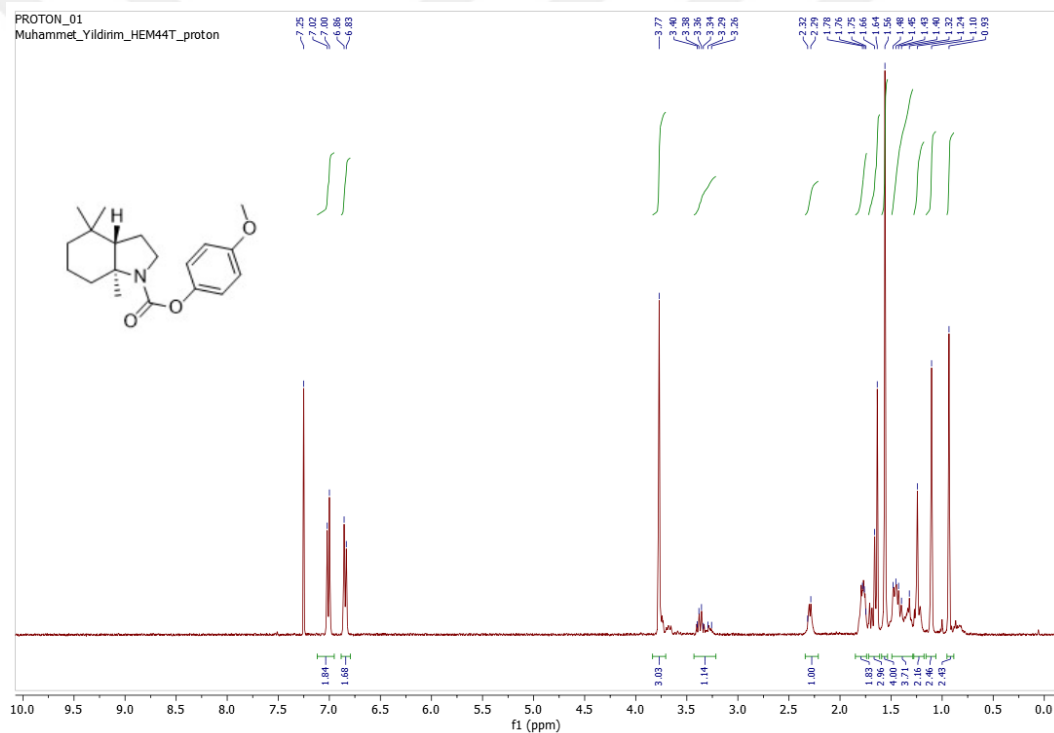


Figure 7.130. ¹H NMR spectrum of p-methoxyphenyl trimethyloctahydroindole carbamate **195m**.

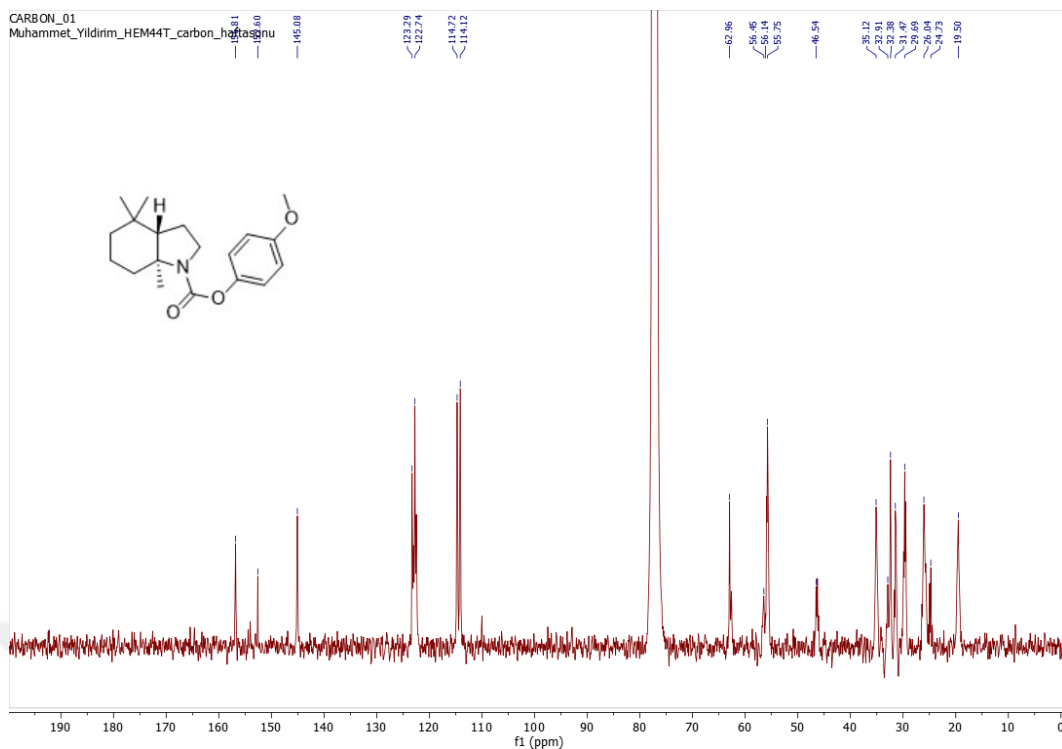


Figure 7.131. ^{13}C NMR spectrum of p-methoxyphenyl trimethyloctahydroindole carbamate **195m**.

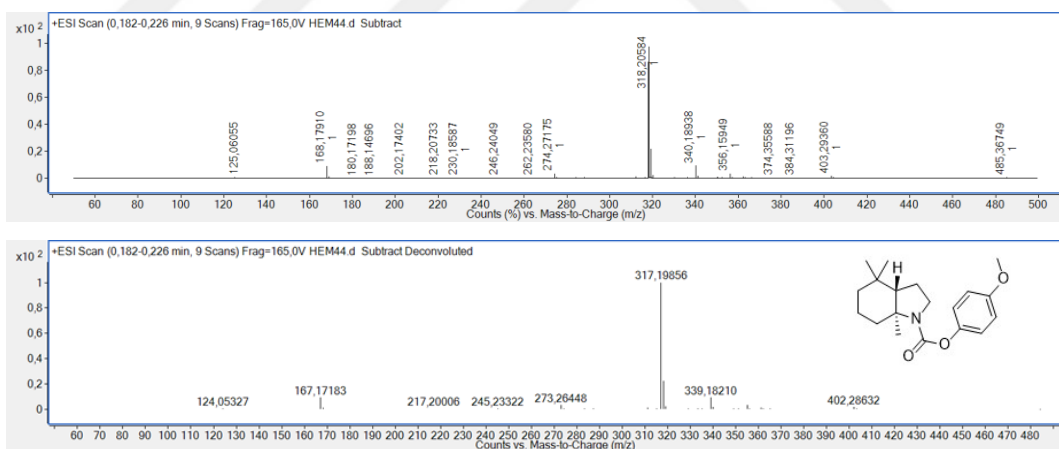


Figure 7.132. Exact mass (HRMS) spectrum of p-methoxyphenyl trimethyloctahydroindole carbamate **195m**.