T.R.
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INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY

SYNTHESIS OF SOME NEW THIAZOLIDINE SUBSTITUTED COMPOUNDS

MASTER OF SCIENCE

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Havva ACAR

ABSTRACT

SYNTHESIS OF SOME THIAZOLIDINE SUBTITUTED COMPOUNDS
MSC THESIS
HAVVA ACAR
BOLU ABANT IZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY
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BOLU, JULY 2023
(xvii + 90)

A fragrance is a blend of diverse volatile organic compounds (VOC) that can be perceived through the olfactory sense. These VOC mixtures find frequent application in a wide range of consumer goods (perfumes, cosmetics, laundry detergents, cleaning agents). Fragrance compounds encompass both simple and complex substances utilized in the fragrance industry. Various N,S-heterocyclic compounds find application in this field. Sulfur-containing molecules are particularly known for their potent odors and their odorants are present in various fruits, essential oils, and resins. Thiazolines and thiazoles, which contain both S and N atoms in their structures, hold significant importance in the fragrance and flavor industry. Both thiazoles and thiazolines impart sulfurous or earthy nuances to the fragrances they are employed in. Their aromatic characteristics and capacity to enhance complex scent profiles make them useful in the fragrance industry.

In this thesis, we focused on the synthesis of some new substituted thiazoline- and thiazole-4-carboxylates (**78,79**). Therefore, variety of thiazoline-4-carboxylates (**78a-k**) were synthesized using a very effective methodology which contains multistep transformations starting from fragrant aldehydes giving nitriles, then their imino ethers (imidates) and the condensations of imidates with (L)-cysteine methyl ester. Finally, thiazoles (**79a-j**) were obtained from corresponding thiazolines (**78**) by a simple but effective oxidation reaction. All the target compounds (**78,79**) were characterized by means of FTIR, NMR and HRMS analyses. Besides, olfactory tests of the compounds were performed by some expert noses.

KEYWORDS: Odor, fragrance, imidate, thiazole, oxidation.

ÖZET

BAZI YENİ TİYAZOLİDİN SÜBSTİTÜE BİLEŞİKLERİNİN SENTEZİ
YÜKSEK LİSANS TEZİ
HAVVA ACAR
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
KİMYA ANABİLİM DALI

BOLU, TEMMUZ - 2023
(xvii + 90)

Bir koku, koku alma duyusuyla algılanabilen çeşitli uçucu organik bileşiklerin (UOB) bir karışımıdır. Bu UOB karışımları, çok çeşitli tüketim mallarında (parfümler, kozmetikler, çamaşır deterjanları, temizlik maddeleri) sıklıkla uygulama bulmaktadır. Koku bileşikleri, koku endüstrisinde kullanılan hem basit hem de karmaşık maddeleri kapsar. Çeşitli N,S-heterosiklik bileşikler bu alanda uygulama bulmaktadır. Kükürt içeren moleküller özellikle güçlü kokularıyla bilinirler ve koku vericileri çeşitli meyvelerde, uçucu yağlarda ve reçinelerde bulunur. Yapılarında hem S hem de N atomu bulunduran tiazolinler ve tiyazoller, koku ve aroma endüstrisinde büyük önem taşımaktadır. Hem tiazoller hem de tiazolinler, kullanıldıkları kokulara kükürtlü veya topraksı nüanslar verirler. Aromatik özellikleri ve karmaşık koku profillerini geliştirme kapasiteleri, onları koku endüstrisinde faydalı kılar.

Bu tezde, bazı yeni ikame edilmiş tiyazolin- ve tiyazol-4-karboksilatların (**78,79**) sentezine odaklandık. Bu nedenle, çeşitli tiyazolin-4-karboksilatlar (**78a-k**), nitril veren kokulu aldehitlerden başlayarak imino eterler (imidatlar) ve imidatların (L)-sistein metil ester ile yoğunlaştırılmasıyla çok aşamalı dönüşümleri içeren çok etkili bir metodoloji kullanılarak sentezlendi. Son olarak, tiyazoller (**79a-j**) basit fakat etkili bir oksidasyon reaksiyonuyla tiyazolinlerden (**78**) elde edildi. Tüm hedef bileşikler (**78,79**) FTIR, NMR ve HRMS analizleri ile karakterize edildi. Ayrıca bazı uzman parfümörler tarafından bileşiklerin koku alma testleri yapılmıştır.

ANAHTAR KELİMELER: Koku, parfüm, imidat, tiyazol, yükseltgenme.

TABLE OF CONTENT

Page

LIST OF FIGURES

Page

LIST OF TABLE

LIST OF SCHEMES

LIST OF ABBREVIATIONS AND SYMBOLS

^{13}C NMR : Carbon-13 nuclear magnetic resonance

^{1}H NMR : Proton nuclear magnetic resonance

ASTM : American society for testing and materials

Br_2 : Bromine

$BrCCl_3$: Bromotrichlorimethane

C_6H_5Cl : Chlorobenzene

CCl_4 : Carbon tetrachloride

$CDCl_3$: Deuerated chloroform

CH_3CN : Acetonitrile

CMD : Chemical manganese dioxide

CS_2 : Carbon disulfide

d : Doublets

DBC : Dimethyl benzyl carbinol

DBU : 1,8-Diazabicyclo (5.4.0) undec-7-ene

DCM : Dichloromethane

dd : Doublet of doublets

DMF : N,N-Dimethylformamide

DMSO : Dimethyl sulfoxide

DPC : Dimethyl phenethyl carbinol

Et_2O : Diethylether

Et_3N : Triethylamine

Et_3OPF_6 : Triethyloxonium hexafluorophosphate

EtOAc : Ethyl acetate

EtOH : Ethanol

FEMA : Flovor and extract manufacturers association

FTIR : Fourier transform infrared

GC : Gas chromatography

GC-MS : Gas chromatography-mass chromatography

H_2O : Water

HCl : Hydrogen chloride

IFRA : International fragrance association

J : Coupling constant

K_2CO_3 : Potassium carbonate

$KHCO_3$: Potassium bicarbonate

L-Cys-OMe : L-cysteine methyl ester

m : Multiplets

M.p : Melting point

MeOH : Methanol

MHz : Megahertz

MnO_2 : Manganese dioxide

N : Nitrogen

Na_2SO_4 : Sodium sulphate

PPh_3 : Triphenylphosphine

ppm : Parts per million

Pyr : Pyridine

q : Quartets

s : Singlet

S : Sulfur

t : Triplets

Tf_2O : Trifluoromethhanesulfonic anhydride

TLC : Thin-layer-chromatography

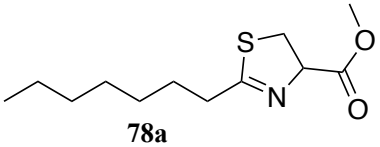
TMS : Tetramethylsilane

UV : Ultraviolet spectra

VOCs : Volatile organic compounds

$ZnCl_2$: Zinc chloride

FORMULAE



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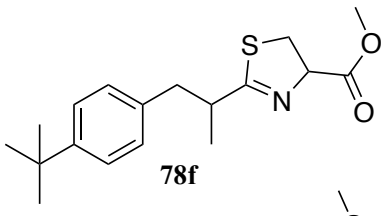

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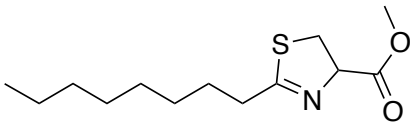

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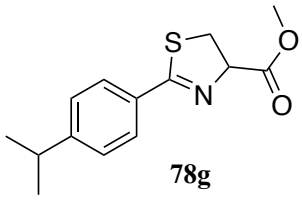

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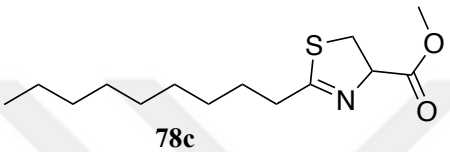

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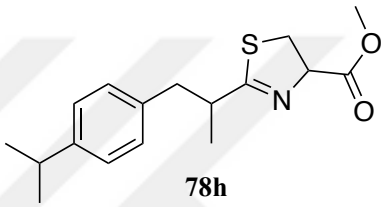

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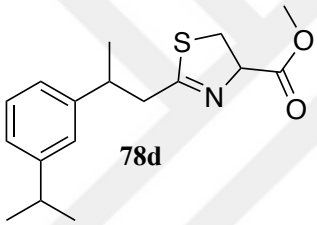

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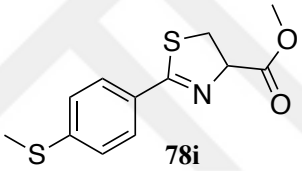

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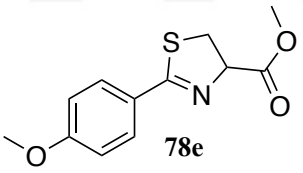

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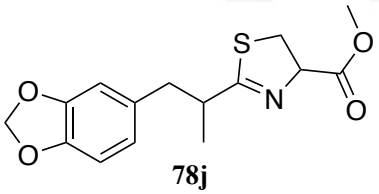

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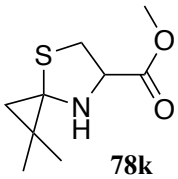

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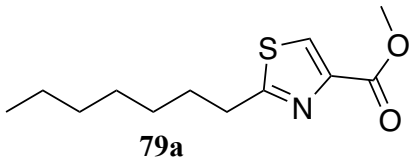

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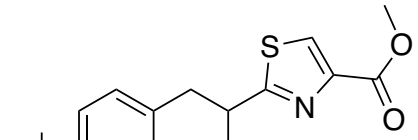

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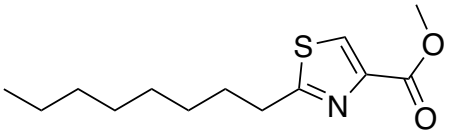

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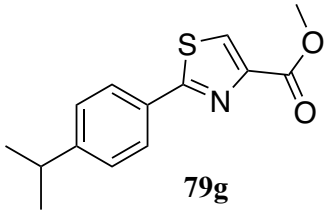

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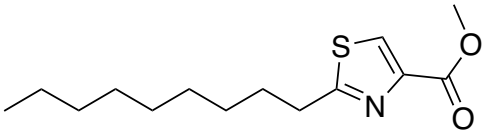

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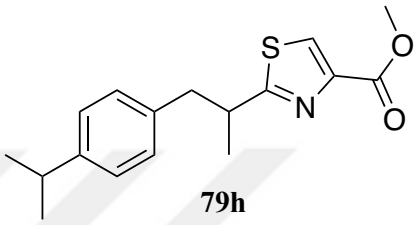

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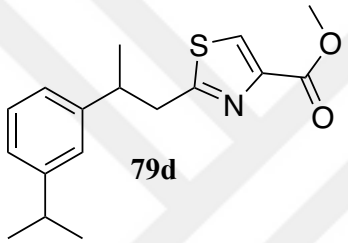

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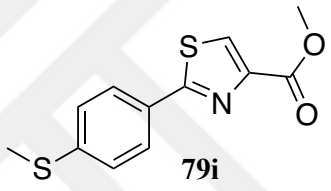

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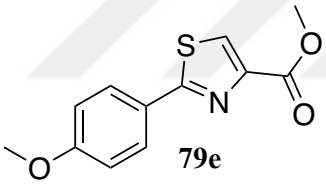

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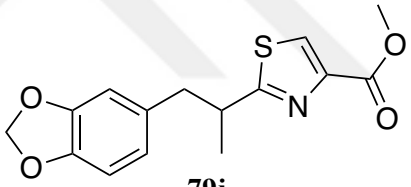

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1. INTRODUCTION

1.1 Fragrance

1.1.1 Definition and History of Odor

A scent or aroma, commonly known as a fragrance, is a combination of various volatile organic compounds (VOCs) that can be detected through our sense of smell. These VOC mixtures are frequently utilized in an assortment of consumer goods, including perfumes, cosmetics, detergents, and cleaning agents, to add a pleasing or unique odor. Fragrance substances are highly aromatic organic compounds that possess distinctive and often pleasing odors. These compounds serve as the primary constituents in perfumed products (1).

Since the dawn of recorded history, humans have used on an array of plant- and animal-derived spices and resins for their odor properties. Throughout time, the materials employed in fragrance creation have varied, ranging from intricate blends to individual compounds (1).

The exploration of fragrance molecules began when individuals discovered that the olfactory characteristics of natural substances could be enhanced through simple techniques. During the sixteenth and seventeenth centuries, distillation methods were employed by pharmacists to produce numerous essential oils that are still utilized by perfumers today. The early part of the nineteenth century, industrialization revolutionized production as the demand for these oils grew. By the 1950s, single organic compounds were employed to achieve specific fragrance profiles (1). In fact, this improvement emerged when Jean-Baptiste Dumas and Eugène-Melchior Pèligot isolated cinnamaldehyde from cinnamon oil in 1834 and benzaldehyde from bitter almond oil by Justus Liebig and Friedrich Wöhler in 1837 (2).

Over time, the number of fragrance molecules has steadily expanded, owing to systematic research on fragrant substances and essential oils. At first, only the main component was isolated from natural substances. However, advancements in modern analytical techniques enabled the isolation and identification of characteristic odor molecules present in natural products (1).

In the middle of the 19th century, the advancement of organic chemistry increased the use of synthetic chemicals, thus enabling the use of synthetic products in fragrances. At first, perfumes were mostly for personal use. The ingredients of these perfumes consisted of natural materials with high cost, so only the wealthy part of the society used it. The production of synthetic ingredients cost much less than natural ingredients, thus making perfume accessible to everyone.

Combining synthetic products with perfumery received a great deal of attention in 1921 when COCO Chanel launched perfume N°5. The popularity of this fragrance inspired work with synthetic materials, thus beginning the modern era of perfumery (3).

Moreover, strong molecules can be produced that can remain intact longer in acidic or basic environments, even in oxidizing environments. It was not preferred to be used in household products as the components of natural oils undergo odor and color changes due to decomposition in a short time, and it became easier to add perfume to household products thanks to synthetic molecules (3).

1.1.2 Odor Types and Their Classification

Scent note characterization and identification is a psychophysical process that requires particular techniques and uses two separate approaches. In the first method, a semantic approach is used to derive the qualitative description of the smell notes. The other method is to find it by comparison with a number of odorants known as reference substances (benchmark odorants) (2).

By examining the common structural components of the odorants as well as the interrelatedness of the most prevalent odorant types, Harder U. of the German company Haarmann & Reimer (now symrise) regulated the significant odor groups into a circular incessantness of similarity (4). This Fragrance Circle (Fig. 1) is arranged in 14 main fragrance themes and the related notes are arranged to be adjacent and at the same time to blend with each other smoothly (2).

Figure 1.1. Symrise Fragrance Circle (2).

The top notes (Citrus, Aldehydic, Marine, Green, Aromatic) are in the upper right area, whereas the base notes (Powdery, Musky, Woody, Ambery, Balsamic) are in the upper left area in the fragrance circle. The lower portion of the Fragrance Circle displays the major heart notes (Edible, Fruity, Spicy, Floral) (2).

With regards to the progression of fragrance characteristics, perfume ingredients are conventionally classified into three categories: top notes, heart notes (also known as middle notes), and base notes. Even though the first perceived scents are the top notes, the bottom notes are the notes that are perceived when they are dry and that add durability to the composition.

Table 1.1. Typical top notes (1).

Citrus	Fresh, stimulating odor of citrus fruits such as lemon, lime, orange, bergamot
Aldehyde	Odor note of the long-chained fatty aldehyde: faty-sweaty, ironed laundry, metallic, fresh seawater, ozone-like, marine fragrances
Fruity	Light fruity notes: typical notes of aliphatic esters: found, for example, in odors of apples, pears, melons Dark (heavy, sweet) Fruity notes: found, for example, in odors of strawberries, raspberries, lactone odor of peaches and coconuts
Green	Typical odor of green vegetation: green leaves and freshly cut grass
Herbal	Odor of green herbs and spices, for example, sage, mint, eucalyptus; camphoraceous such as rosemary; coniferous such as fir needles; earthy agrestic

Table 1.2. Typical heart notes (1).

Floral Light	Rose
Floral Green	Lily of the Valley (muguet)
Floral Fresh	Geranium, lavender
Floral Fruity	For example, damascones
Floral Heavy	Narcotic flower fragrances such as jasmine, tuberose
Floral Woody	For example, methylionones

Table 1.3. Typical base Notes (1).

Aromatic	Sweet aromatic to aromatic spicy odors, for example, of honey, almond, aniseed, woodruff, nutmeg, clove. This segment also contains the so-called gourmand notes having pronounced culinary properties, for example, vanilla, tonka, lovage
Balsamic	Heavy sweet odors, such as chocolate and vanilla, cinnamon with resinous element
Moss	Dry, algae-like, tar-like, phenolic, oak moss
Leather, Animalic	Odor of cresol, isobutyl quinoline, and so on; fecal such as indole
Musk	Warm soft odor reminding of freshly washed and ironed laundry, often with skin-like and animalic-erogenous facets
Amber	Warm, slightly earthy-camphoraceous woody note, reminding natural ambergris, represented typically by amber oxide
Wood	Clear cool radiant odor found in natural materials such as cedarwood (pencil note), patchouli, sandalwood, and vetiver

Many fragrances that were sold between 1990 and 1975 were first categorized in the Haarman & Reimer genealogy using broad scent notes rather than brand names (4). Afterwards, these fragrance notes were then split into two groups, one for feminine and one for masculine (5).

Table 1.4. Feminine fragrance type (5).

Floral	Green, Fruity, Fresh, Floral, Aldehydic, Sweet
Oriental	Ambery, Spicy
Chypre	Fruity, Animalic, Woody, Fresh, Green

Table 1.5. Masculine fragrance type (5).

Fougere	Fresh, Woody, Ambery
Oriental	Ambery, Spicy
Chypre	Woody, Leather, Fresh, Citrusy

1.1.3 Odor Compounds

Fragrance compounds include some of the simple and complex ones used in the fragrance industry (6). It is seen that those with the identical functional group in fragrance compound has same odors. For instance esters contain fruity and floral odor. Amines display animal odor, thiols contain a sour to rancid odor. Lactones also have nutmeg or apricot nuance of odor (7). Of course, there are substances that share the similar functional group but have distinct scent notes. Some lactones have fragrant notes such as mint, butter, terben-like and camphorous (8).

1.1.3.1 Alcohols

Alcohols are substances that include the -OH group is also referred to, hydroxyl, or hydroxyl group (9). Ethanol **1**, one of the simplest saturated alkyl alcohols, is a common solvent used for fine fragrances. The 3,4,5,6,6-trimethyl-2-heptanol **2**, which has a "woody-amber" fragrance, is an intriguing branched alcohol utilized in perfumes. A powerful synthetic substance called 4-methyl-3-decen-5-ol **3** is utilized for give scents green flowery characteristics (6).

Naturally occurring scent substances contain many complex alcohols as odorants. Santanol **4**, one of the complex fragrance alcohols is the important fragrance in sandalwood (6).

Benzyl alcohol **5** is utilized for sweet aroma. However, far bigger portion of it is employed as a transport solvent, particularly for odors. Saturated side-chain aromatic alcohols are very stable and useful for incorporating floral notes in domestic perfumes and soaps. For example, DBC **6** and DPC (Dimethylphenethyl carbinol) **7** (6).

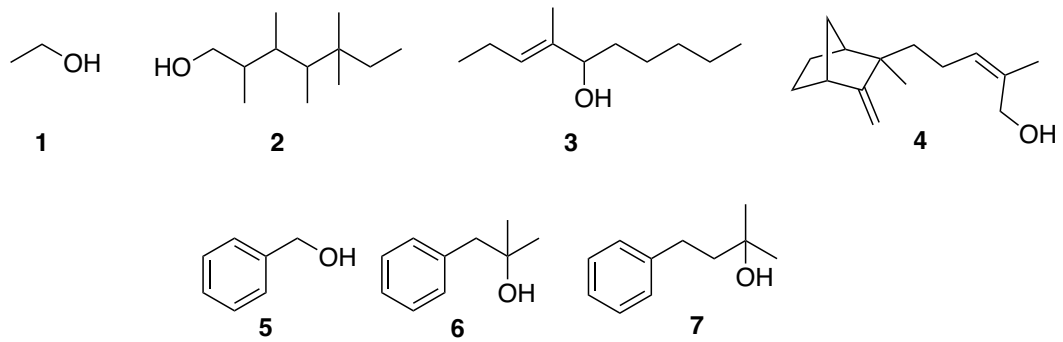
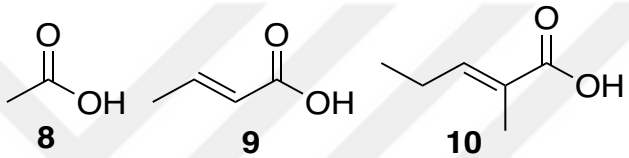


Figure 1.2. Odorant alcohol molecules.

1.1.3.2 Carboxylic acids

Numerous carboxylic acids' odor characteristics change with dilution. The concentrated acid is generally unlikeable and sweaty or stinky, however, when diluted, they lose some of their unpleasant and frequently exhibit fruity character (9).

Acetic acid **8**, which is also saturated aliphatic acids, has the smell of vinegar as its fragrance note (9). Trans-2-butenoic acid **9**, which is one of the unsaturated acids, has a cheesy odor. 2-methyl-2-pentenoic acid **10** has a fruity scent. These unsaturated acids have stronger, more pungent odors than their native acid counterparts (6).



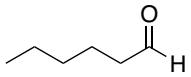
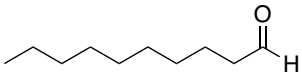
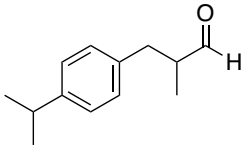
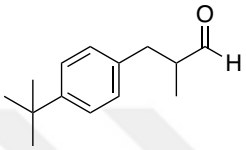
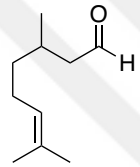
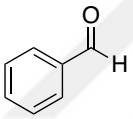
8 **9** **10**

Figure 1.3. Odorant carboxylic acid molecules.

1.1.3.3 Aldehydes

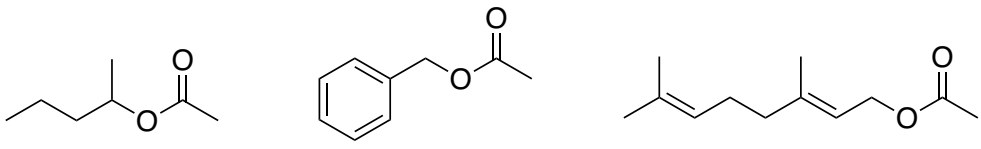
Aldehydes are crucial to the perfume industry as they generally have powerfull scents. The most well-known of all odors, Chanel No.5 has a top note aldehydes. After the launch in 1921, this top note started a fashion trend and thus the family of aldehydic fragrances was created (9). Table 1.6 presents several examples of aldehydes along with their corresponding odor notes (10).

Table 1.6. Example of some aldehyde with fragrance note (10).

Compound	Name	Odor notes
	Hexanal (Aldehyde C-6)	Very powerful fatty green grassy odor.
	Decanal (Aldehyde C-10)	Very powerful sweet waxy odor.
	Crylamen Aldehyde	Powerful green floral stem with pronounced cucumber, melon.
	Lilial	Sweet yet refreshing floral green.
	Citronellal	Powerful fresh green citrusy, slight woody odor.
	Benzaldehyde	Powerful sweet odor of freshly cut bitter almonds.

1.1.3.4 Esters

Carboxylic esters generally have a fruity odor character. Amyl acetate **11** smells like fruit, including banana and pears. Geranyl acetate **12** has a fruity, rosy scent, while Benzyl acetate **13** has a fruity note (9).

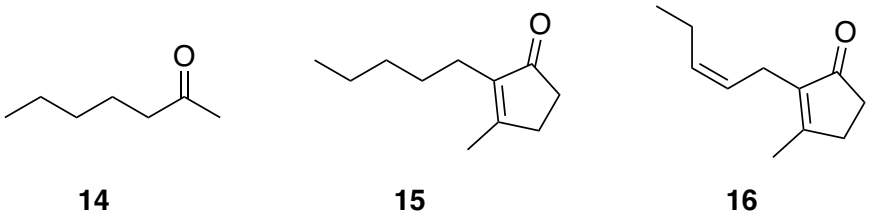


11 **12** **13**

Figure 1.4. Odorant ester molecules.

1.1.3.5 Ketones

Ketones are other significant class of substances in the fragrance industry. 2-Heptanone **14** has a fruity and spicy note (9). Cis-jasmone **15** is an important scent of jasmine, also this substance is not found in nature. However dihydrojasmone **16** is easier to synthesize and has jasmine note (6).

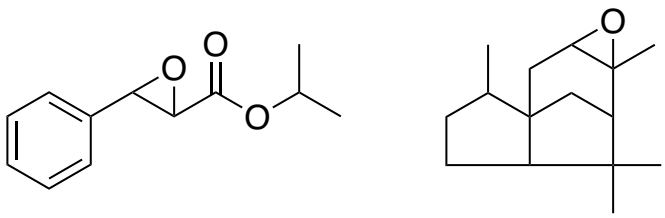


14 **15** **16**

Figure 1.5. Odorant ketone molecules.

1.1.3.6 Heterocyclic Compounds

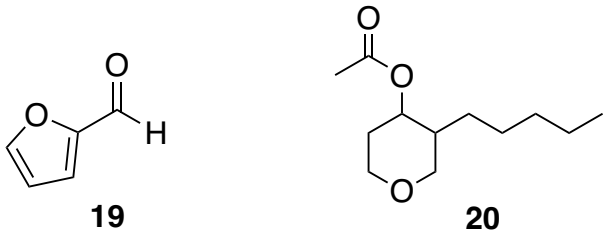
Heterocyclic compounds are separated into two groups as aromatic or non-aromatic structures (11). Some of the oxiranes (epoxides) derivatives, which are members of the oxygen-containing heterocyclic family and also non-aromatic, have odor notes. Ethyl 3-phenylglycidate **17** smells like honey, strawberries, and fruit odour (12). Alpha-cedrene epoxide **18** one of the other epoxides, has a priceless woodsy scent, resembles of ambergris and sandalwood (13).



17 **18**

Figure 1.6. Odorant epoxide molecules.

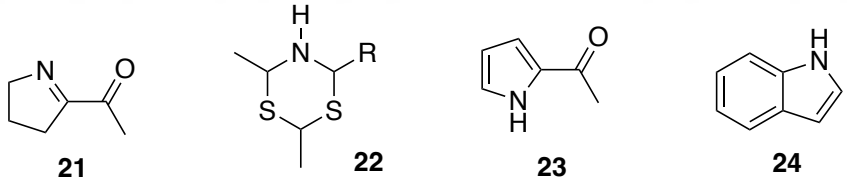
Furfural **19** has a odor that sweet caramel-like, nutlike, smell of freshly-baked bread, and almond (14). The smell of tetrahydro-3-pentyl-2H-pyran-4-yl acetate (Jasmine acetate) **20** is oily, lavender-like, slightly mushroom-like, and has a floral tea-like jasmine odor of character. Jasmine acetate is cheaper alternatives to jasmonates in floral substances. (6).



19 **20**

Figure 1.7. Odorant furan and pyran derivatives.

Various heterocyclic compuound include nitrogen and/or sulfur are used in the fragrance industry (6). Sulfur-containing molecules are known to have strong odor properties. There are many sulfur-containing odorants in various fruits, essential oils and resins. (15). Similarly, nitrogen-containing compounds have odor characteristics. 2-acetyl-3,4-dihydro-5H-pyrrole **21** which is non-aromatic molecule possesses the distinctive smell of white bread crust, its application is constrained by its short half-life. Another non-aromatic compound 2-Isobutyl-4,6-dimethyldihydro-1,3,5-dithiazine (R=i-Pr) **22** is formed in the essence of yeasts and has fruity, cocoa-like, tropical fruit note, odours (6). 2-Acetylpyrrole **23** which has aromatic cyclic structure, include sweet musty, walnut and bread odour (16). The odor of indole **24**, which is erogen-floral, animalic, and cheese-like, become slightly faecal when diluted (17).



21 **22** **23** **24**

Figure 1.8. Odorant pyrrole, dithiazine and indole molecule.

Thiazolines and thiazoles that contain both sulfur and nitrogen atoms in their structures occupy an significant place in the fragrance and flavour industry. The most important types of thiazolines used in the fragrance industry are alkylthiazoles, acetylthiazoles and hydroxyethylthiazoles (6). For instance, 2-ethyl-4-methylthiazole **25**, which is one of the alkylthiazolines, is found in coffee and has the smell of coffee, cocoa and nutty (18). 4-Vinyl-5-methylthiazole **26** is another instance of this kind of thiazole and has it has nutty, roasted peanut, bread crust-like and popcorn scent (19).

2,4-Dimethyl-5-acetylthiazole **27** is an example of acetylthiazolines, has not available in nature, but it may be possibly found in meat. It has a meaty, roasted and nutty odour (6). 4-Methyl-5-thiazoleethanol (Sulfurol) **28**, which is an example of hydroxyethylthiazoles has meaty, beef juice, brothy, nutty, yeasty and sulfurous odor (20). 2-Acetyl-2-thiazoline **29**, one of the dihydrothiazoles, has the smell of roasty, popcorn (21).

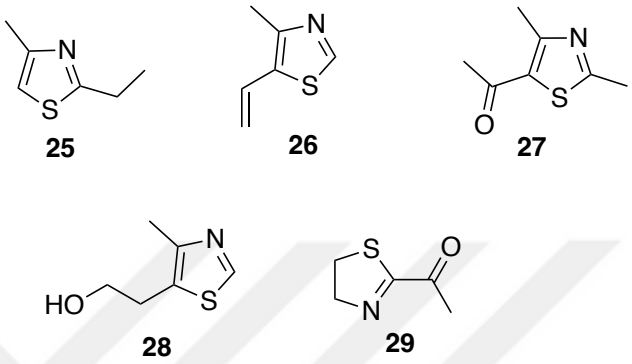


Figure 1.9. Odorant thiazole and thiazoline molecule.

1.1.4 Analysis of Odor

The identification and quantification of plant-derived products (natural or synthetic) has begun to attract more attention by the scientific and economic sectors (22). Although in the past (since the mid-1990s) attempts were made to discover the chemical structure of fragrance and flavor compounds and even to identify the main components, today this has become a necessity with international security and restrictions.Various regulatory and advisory organizations have been established, such as IFRA (International Fragrance Association) and FEMA (Flavor and Extract Manufacturers Association), to monitor the manipulation of raw materials to be used in the food and cosmetics industry (23).

Analysis of a fragrance and/or aroma compounds is not an easy process. Most of these compounds mentioned are in a complex and mixed state, there is currently no single analytical technique that guarantees all successful results. Since traditional analytical techniques are not complete and sufficient to meet such requirements, new sample preparation techniques, advanced chromatographic and spectoscopic instrumentation are needed. Modern analytical techniques provide higher sensitivity and selectivity, the ability to automate, and more accurate results (23).

1.1.4.1 Instrumental Methods of Analysis

Infrared spectroscopy is an significant analytical method used in the fragrance industry. IR spectroscopy measures the vibrational frequency of bonds in a molecule and provides information about which functional groups the molecule contains (24).

Nuclear Magnetic Resonance (NMR) spectroscopy utilizes radiofrequency radiation and the influence of powerful magnetic fields on specific atomic nuclei (25). NMR spectroscopy gives information about the number of hydrogens in a molecule, the possible structure of the molecule, which atoms bond, which are close together (26). At the same time, using MNR spectroscopy in the analysis of odor molecules is very helpful in understanding the structure of the molecule (9).

Mass spectroscopy is one of the spectroscopic methods that precisely measures the molecular masses of compounds and atoms in the gas phase by converting them into charged ions. The resulting ion fragmentation model gives information about the molecular structure (27).

Gas chromatography is a widely used technique in the field of flavor and fragrance to investigate the complexity and composition of samples. By virtue of its ability to separate individual components, GC has been instrumental in identifying new and often trace compounds that contribute to odor, and in determining their molecular structures. As a result, this technique has played a key role in advancing the field of sensory analysis, providing researchers with the data needed to better understand the chemistry of odors and fragrances (28).

GC-MS is an analytical method which separates the components of a substance from each other, and also identifies the components of a substance (29). GC-MS is probably the best technique for odor analysis. Because most known fragrance compounds are volatile (30). In gas chromatography, identification is made according to the retention times of the compounds. However, this chromatography alone is not sufficient for complex compounds as compounds may have similar retention times. Combined with mass spectroscopy, each analyte is separated into ionized fragments. Thanks to this process, the total masses of the compounds, similar fragmentation patterns are obtained. Thus, the analysis of the sample gives more accurate and clear results (29).

1.1.4.2 Sensory Method of Analysis

Sensory analysis is a method used to define, evaluate and improve the characteristics of the analysis sample, by utilizing one or more sense organs, in accordance with the conditions, requirements and methods suitable for the task given by the person performing the analysis (31). The senses allow us to receive signals originating from the external world and/or from within the body. The senses of smell and taste can be referred to as chemical senses since the interaction between chemical compounds and chemoreceptors is the initial stage in the process of obtaining olfactory stimuli through the senses (32).

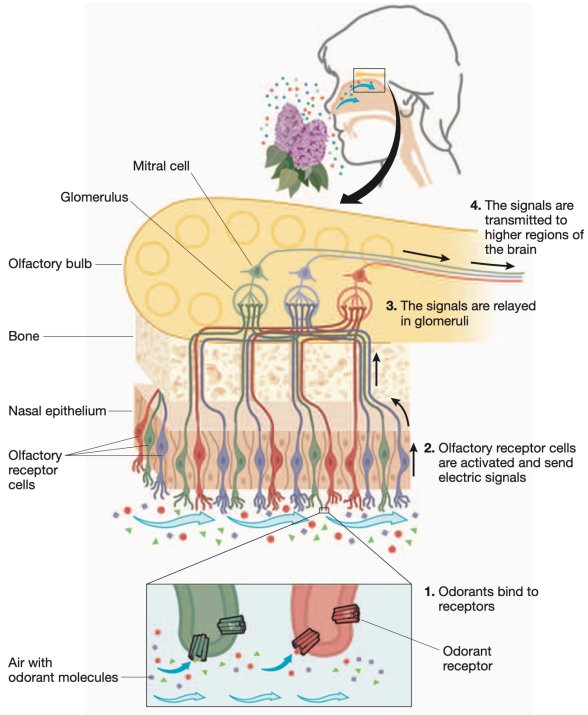


Figure 1.10. The human olfactory system (33).

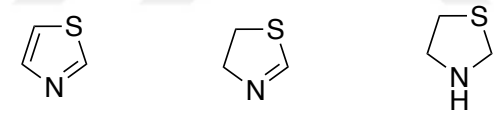
1.1.4.2.1 Expert Nose

The use of a human nose may be seen as an alternative method that may be used instead of high-priced and time-consuming analysis methods and can be considered as a microanalytical laboratory (33). There are experts who can analyze using the experience and the development of the sense of smell given by years and professional knowledge. Even some organic chemists are in a position to be proficient (34). The expert nose has the ability of detecting and identifying so many different notes that are much lower in intensity than the dominant components of a scent sample (35).

1.2 Thiazoline and Thiazole

1.2.1 Definition

Thiazole belongs to the group of heterocyclic compound having a 5-membered unsaturated ring with a S atom at position 1 and N atom in the position 3. Thiazoles that have undergone partial reduction are referred to as thiazolines, while a thiazole that has been fully reduced is known as a thiazolidine and the dihydro- and tetrahydro- 1,3-thiazoles are named thiazoline and thiazolidine, respectively (11).



thiazole 4,5-dihydrothiazole thiazolidine

Figure 1.11. Thiazole, thiazoline and thiazolidine molecule.

2-Thiazolines, classified as 1,3-azoles, are heterocyclic compounds with a five-membered ring structure composed of a S atom with a N atom (36). It has a general formula of C_3H_5NS and colorless liquid.

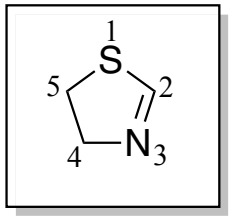


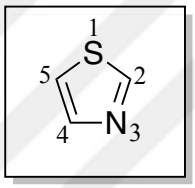
Figure 1.12. General structure of the 2-thiazolines.

1.2.2 Physical and Spectroscopic Properties

Thiazole general formula of C_3H_3NS (37) and has both an electron-donating group (-S-) as well as an electron-withdrawing group (C=N), thus making them a stable heterocyclic compound (38). Thiazole has a boiling point around 116-118 °C and is a transparent, pale-yellow liquid and completely soluble in ether and alcohol, but slightly soluble in H_2O (39). Thiazole has a smell that is similar to pyridine (40). The thiazole heterocyclic ring has a delocalization of 6π electrons according to Huckel's rule from the sulfate atom's lone pair of electrons (41).

The C-S bond length of the thiazole is 171.3 pm. The dipole moment is 161 D and its ionization potential is 9.50 eV. The table below includes UV and NMR data.

Table 1.7. Spectroscopic data of thiazole (42) .



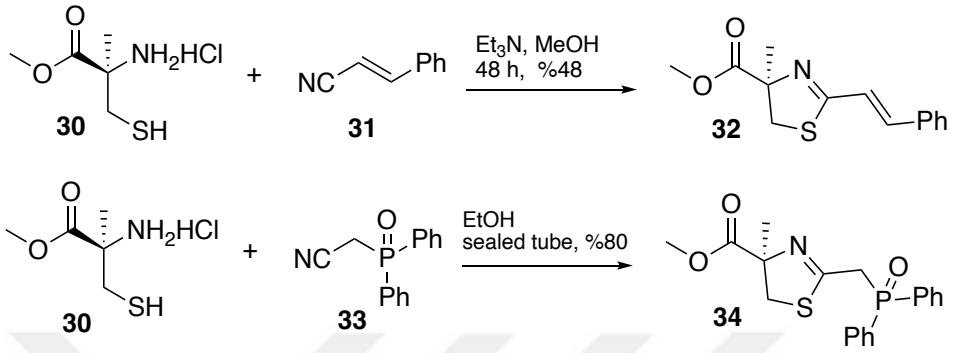
UV (EtOH) λ (nm) (ε)	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
207.5 (3.41)	H-2 : 8.77	C-2 : 153.6
233.0 (3.57)	H-4 : 7.86	C-4 : 154.3
	H-5 : 7.27	C-5 : 119.6

1.2.3 Synthesis of Thiazolines and Thiazoles

Various methods can be applied for the synthesis of thiazolines and thiazoles. Since thiazoles are the dehydration product of thiazolines, in the practical synthesis of thiazoline, various ways of oxidation of thiazolines are widely used. Moreover, various techniques for directly producing thiazoles have also been devised (43).

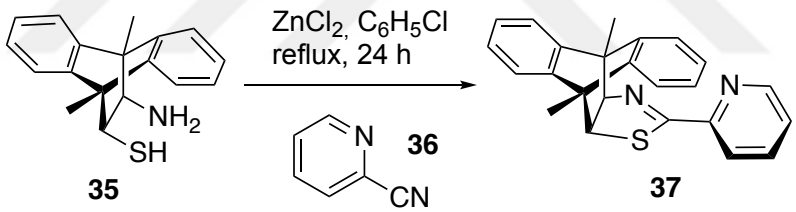
1.2.3.1 Thiazolines via condensations of vicinal-amino thiols

Since nitriles are electrophilic, they are easily attacked by thiol and amine groups (44). Ehrler and co-workers used nitriles **31, 33** to condense with the α-methyl cysteine methyl ester HCl **30** to generate thiazolines during the complete synthesis of thiangazole **32, 34** (45).



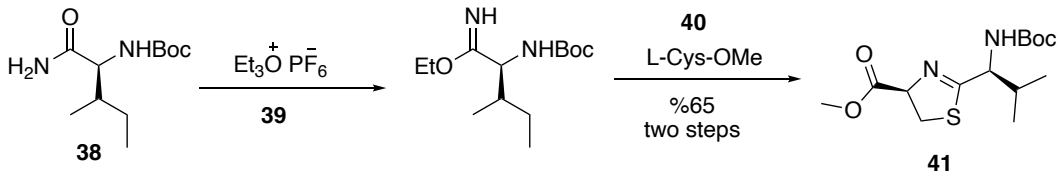
Scheme 1.1. Condensation of vicinal-amino thiols and nitriles.

In addition, a Lewis acid can be used in amino thiol **35** and nitrile **36** condensation to afford thiazolines. For instance, Kunieda and colleagues used zinc chloride as a catalyst in the synthesis of thiazolines **37** (46).



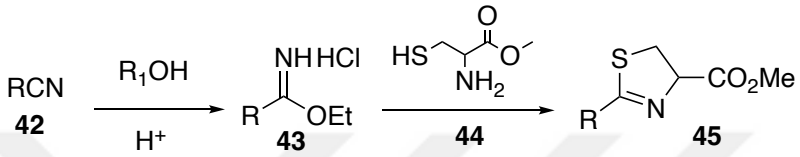
Scheme 1.2. Lewis acid-catalyzed thiazoline formation.

Iminoethers are more reactive to the condensation process with vicinal-aminothiols than nitriles. vic-aminothiols are readily condensed with imino ethers for synthesis of thiazoline derivatives directly in hot MeOH or EtOH or without a base. For instance, Pattenden and Thorn synthesized (-)-didehydromirabazole A using this approach. The corresponding iminoether was obtained by treating the primary amide **38** with triethyloxonium hexafluorophosphate **39**, which was then condensed with L-Cys-OMe **40** to generate the thiazoline **41** (47).



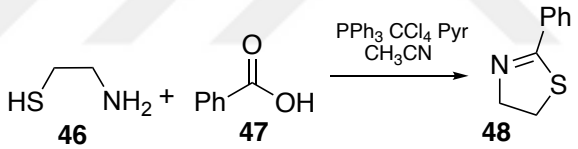
Scheme 1.3. Condensation of amino thiol with iminoether.

In 1976, Mayers and co-workers developed athe method for the synthesis of thiazolines (48)(49). This methodology is very effective since nitriles **42**, via their corresponding imino ethers (imidates) **43**, can be condensed with (L)-cysteine methyl ester hydrochloride **44** to synthesis of thiazoline derivatives **45** (50).



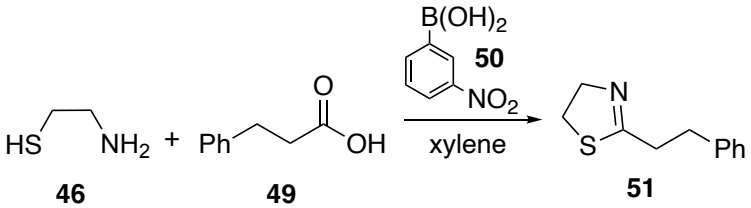
Scheme 1.4. Synthesis of thiazoline with amino thiol and iminoether.

Besides, Vorbriiggen and Krolikiewicz published the synthesis of thiazoline in the early 1980s. In this method, benzoic acid (carboxylic acid) **47** and aminoethanethiol **46** were reacted in the presence of PPh_3, CCl_4, and pyridine to generate the thiazoline **48** (51).



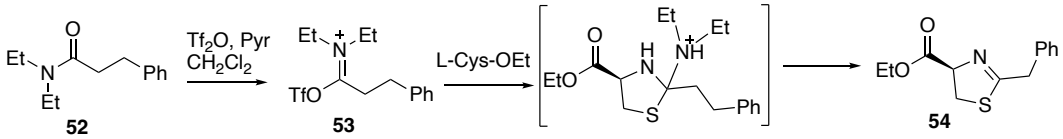
Scheme 1.5. Condensation of amino thiol with carboxylic acid.

Also, thiazolines **51** were made using a sequential condensation-cyclodehydration of 3-phenylpropanoic acid **49** with aminoethanethiol **46** utilizing 3-nitrophenylboronic acid **50** as a catalys by Peter Wipf (52).



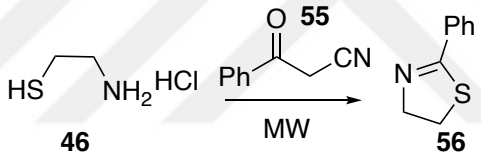
Scheme 1.6. Condensation with propanoic acid and aminoethanethiol.

Iminium triflate reacts more readily when condensed with an aminothiol. It is quickly prepared by reacting primary or secondary amide with Tf_2O in the presence pyridine. Charette and Chua synthesized of 2-alkyl-thiazolines and 2-aryl-thiazolines **54** from L-Cys-OEt and secondary or tertiary amides **52** using reactive electrophilic species of the iminium triflates **53**. The mild conditions employed allow for the generation of highly functionalized chiral species in high yield while tolerating the majority of functional groups (53).



Scheme 1.7. Iminium triflate-mediated thiazoline formation.

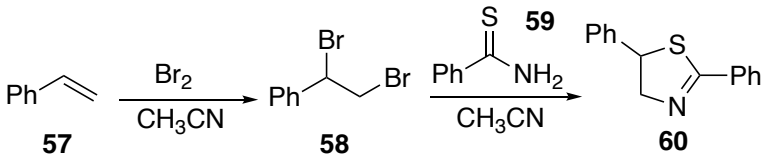
Kamila and Biehl have discovered an effective approach to obtain 2-aryl-thiazolines **56** from aminoethanethiol **46** and aryl ketonitriles **55** in the absence of a solvent under microwave irradiation (54).



Scheme 1.8. Condensation of amino thiol with aryl ketonitriles.

1.2.3.2 Thiazolines via direct coupling of thiamides and alkenes

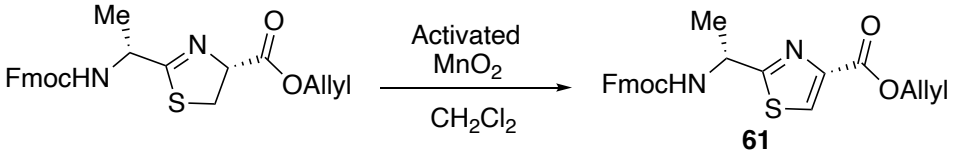
Wei Li and co-workers published a suitable one-pot reaction of alkenes with thioamides for the synthesis of various thiazolines. In this study, (1,2-dibromoethyl)benzene **58** produced via a dibromation of styrene **57** in CH_3CN. Thiobenzamide **59** treatment of (1,2-dibromoethyl)benzene was resulted in thiazoline formation **60** (55).



Scheme 1.9. One-pot reaction of alkenes with thioamides.

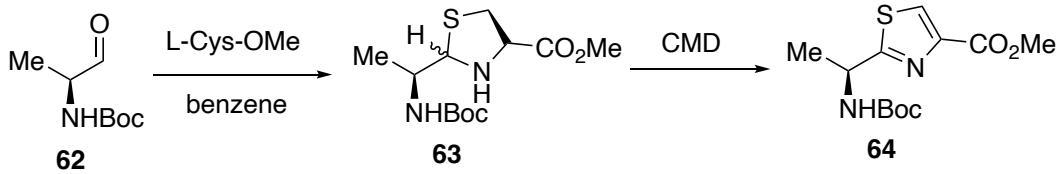
1.2.3.3 Thiazoles via oxidation of thiazolines

The most common oxidant for converting thiazolines into the thiazoles is manganese dioxide (MnO_2) in the DCM at room temperature. The term "activated MnO_2" refers to a molecule that has been synthesized in a laboratory (56), often in its gamma form (57). MnO_2 purity is essential in the reaction (58). Shu-Li and Jeffery used this method in the synthesis of thiazole-containing amino acids **61** (59).



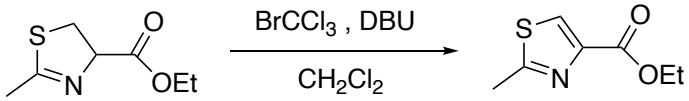
Scheme 1.10. Oxidation with actiated MnO_2.

Commercially, chemical manganese dioxide is available as an effective oxidizing agent both benzylic and allylic alcohols (60) as well as for converting thiazolines and thiazolidines to the thiazoles. For the synthesis of optically pure thiazole-containing amino acids **64**, Shioiri and co-workers first produced thiazolidines **63** by condensation of *L*-cystenine ester and amino aldehydes **62**, then converted into thiazoles by CMD oxidation (61).



Scheme 1.11. Oxidation with chemical manganese dioxide.

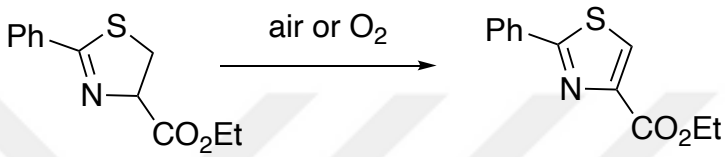
In another study, Williams and co-workers synthesized thiazoles in high yields by oxidation thiazolines with bromotrichloromethane and DBU at 0°C in DCM (62).



Scheme 1.12. Oxidation with Williams method.

For oxidation, although the above-mentioned reagents are highly efficient, high amounts of their activated form are required, and $CBrCl_3$ is an environmentally harmful reagent. Until now, several environmentally friendly methods and researches have been made on this subject (63).

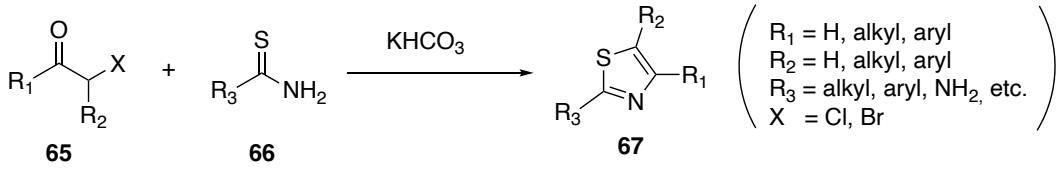
Xiaoming Wu and co-workers described utilization of molecular oxygen as an oxidizing agent to convert thiazolines into thiazoles under different conditions using K_2CO_3 in anhydrous DMF. Thiazole derivatives were obtained in medium-high yields in an environmentally-friendly way (64).



Scheme 1.13. Oxidation with molecular oxygen.

1.2.3.4 Thiazoles via condensation of α-halocarbonyl compounds with thioamides

In 1887, Hantzsch and Weber first published the synthesis of thiazoles **67** by condensation of α-halo ketones (or aldehyde) **65** along with thioamides **66** (65). This process is usually known to as the Hantzsch thiazole synthesis (66).

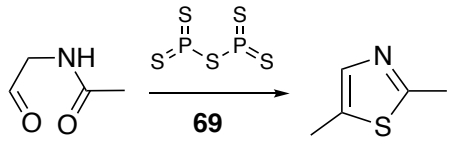


Scheme 1.14. Hantzsch thiazole synthesis.

Through this reaction, several thiazoles containing substituents at positions 2, 4, or 5 that are alkyl, aryl, or heteroaryl can be produced (67).

1.2.3.5 Via cyclization reaction of α-acylamino ketones with P_2S_5

Another way of thiazole synthesis is Robinson-Gabriel synthesis. The name of this synthesis comes from Sir Robert Robinson (68) and Siegmund Gabriel (69), who reported the reaction. 2,5-disubstituted thiazole derivatives **70** are obtained by the cyclization reaction of α-cylamino-ketone **68** with phosphoruspentasulfide **69** (70).



68 70

Scheme 1.15. Robinson-Gabriel thiazole Synthesis (72).

1.2.3.6 Thiazoles from α-Aminonitriles

The other method, known as Cook-Heilbron synthesis, is used to synthesize thiazole **73** as a result of the reaction of α-aminonitrile **71** or α-aminoamide with carbon disulfide **72** (71). This method was published in 1947 by Cook and Heilbron (72).

71 72 73

Scheme 1.16. Cook-Heilbron thiazole synthesis (75).

1.2.4. Thiazoles and thiazolines as fragrant compound

Thiazoles have a diverse range of applications, including their use as fragrances in perfumes and colognes. These compounds often contribute to the overall odor profile of a fragrance and can provide unique and desirable scent characteristics. Thiazolines are closely related to thiazoles but contain a saturated nitrogen atom in the ring instead of an aromatic nitrogen atom. This substitution results in a reduced aromatic character compared to thiazoles.While thiazolines are less commonly used as fragrant compounds compared to thiazoles, they can still contribute to the overall scent profile of a fragrance due to their distinct aroma.

Both thiazoles and thiazolines possess sulfur atoms in their structures, which can introduce sulfurous or earthy notes to the fragrances in which they are used. Their aromatic properties and ability to contribute to complex odor profiles make them valuable ingredients in the fragrance industry. However, the specific scents associated with these compounds can vary depending on their chemical structure and other fragrance components used in combination (73–75).

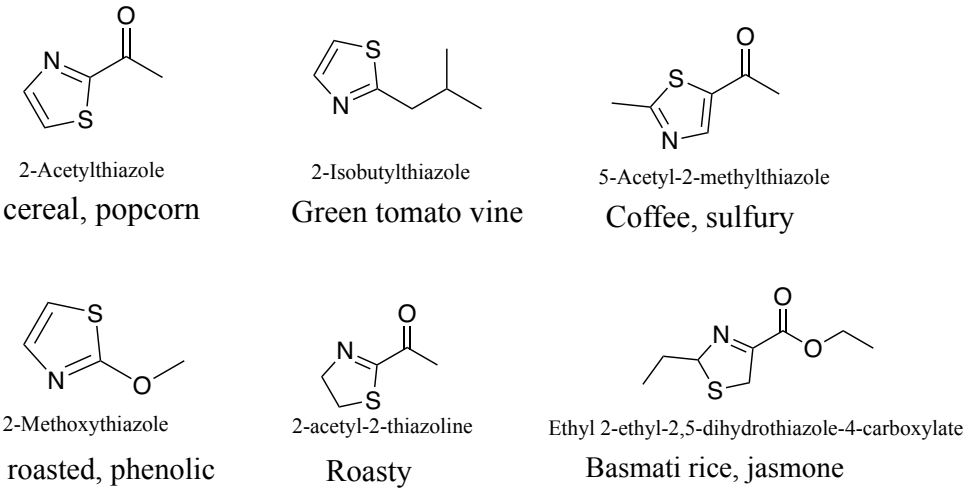


Figure 1.13. Some thiazole and thiazoline with olfactory properties.

2. AIM AND SCOPE OF THE STUDY

Considering the aforementioned fragrance properties of thiazole and thiazoline derivatives present in recent literature, we prompted for the synthesis of novel thiazoline (**78**) and thiazole compounds (**79**) by following a multistep synthetic route and then focused the investigation of fragrant properties of target products. For this purpose, new thiazoline-based molecules with many different alkyl and aryl groups were prepared starting from fragrant aldehyde precursors and several imidate derivatives. After purification of target compounds, their structures were elucidated using IR, NMR, Mass measurements. Finally, odor characteristics and nuances of all products were analyzed and determined by expert noses.

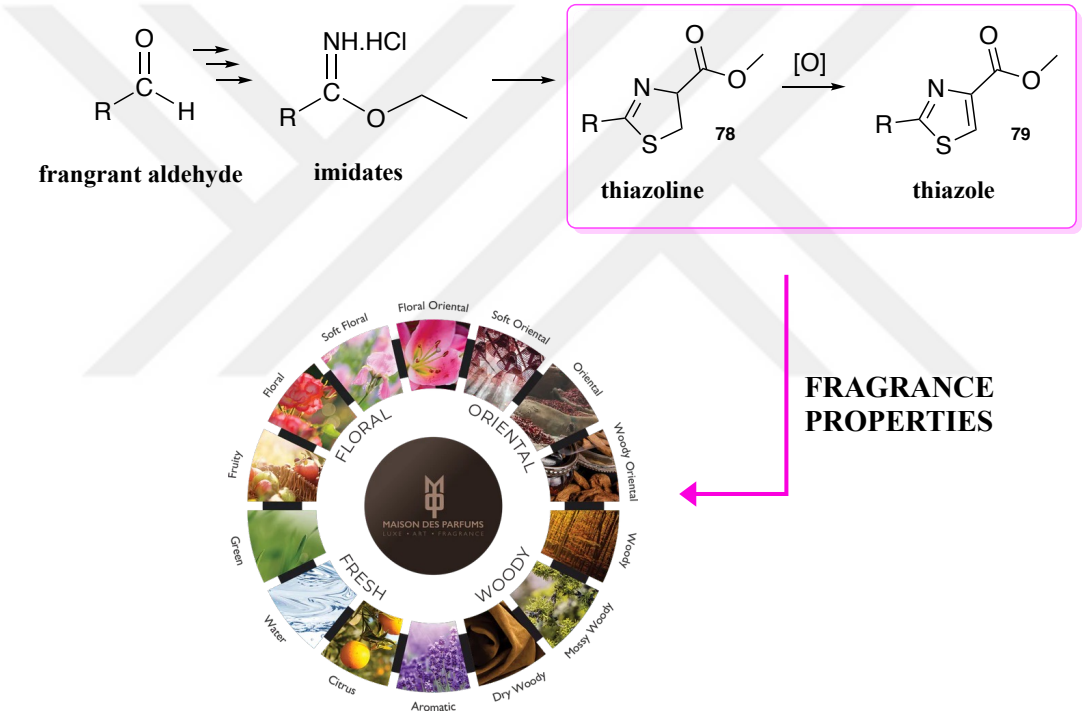


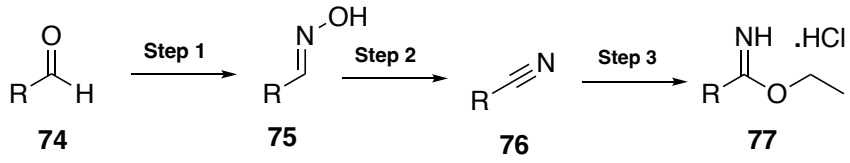
Figure 2.1. Work plan to access new fragrant thiazolines and thiazoles **78, 79**.

3. MATERIALS AND METHODS

During the synthesis, all reagents and solvents utilized were obtained commercially with analytical grade from Merck and Sigma-Aldrich and used without further purification. Nuclear magnetic resonance (NMR) spectra, including ^{1}H-NMR and ^{13}C-NMR, were obtained at room temperature using a Bruker DPX400 spectrometer with 400 MHz for proton and 100 MHz for carbon. Chemical shifts (δ) were reported in parts per million (ppm) downfield from tetramethylsilane (TMS), and J values were expressed in Hz. The NMR signal abbreviations used were s for singlet, d for doublet, t for triplet, q for quartet, sep for septet, and m for multiplet. Infrared (IR) spectra were measured using a Thermo Nicolet iS20 FTIR spectrometer, and high-resolution mass spectra were obtained using a Waters Lct Premier XE oa-TOF Mass Spectrometer. Melting points were determined using an uncorrected MELTEMP apparatus. TLC was monitored using precoated plates with a fluorescent indicator (Merck 5735). Column chromatographic separations were conducted using silica gel (Merck, 230–400 mesh ASTM) with an eluent of either ethyl acetate (EA) and hexanes (H) or only ethyl acetate. Potassium permanganate staining solutions and a UV lamp with wavelengths of 254-366 nm were used to visualize the TLC spots.

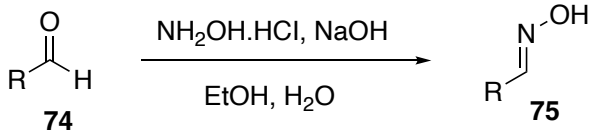
3.1 Experimental

3.1.1 Preparation of Precurcors



74 75 76 77

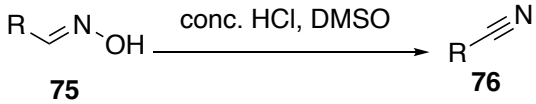
1st Step : General method for Preparation of Oximes (76,77)



74 75

Hydroxylamine hydrochloride (30 mmol, 1,2 equiv.) was dissolved in 50 mL of pure ethanol. Following this, a solution containing sodium hydroxide (30 mmol, 1,2 equiv.) and 10 mL of distilled water was introduced. Subsequently, aldehyde (25 mmol, 1 equiv.) was carefully added drop by drop. The resulting mixture was stirred at room temperature for one hour, progress of the reaction was monitored using thin-layer chromatography (TLC). Once the reaction is completed, reaction mixture was extracted using ethyl acetate (3*50 mL). The organic phase from each extraction was combined, and Na_2SO_4 was employed to dry it. The mixture was then filtered, and the solvent was removed using a rotary evaporator.

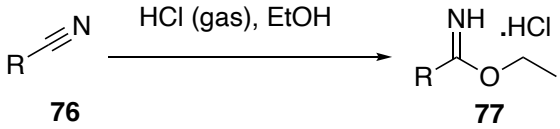
2nd Step: General Method for Preparation of Nitrile



75 76

Oxime (18 mmol) was dissolved in 45 mL of DMSO. Subsequently, concentrated HCl (60 drops) was added to the solution in a gradual manner. The resulting mixture was then subjected to reflux at 90°C for one hour, while monitoring the reaction progress using TLC. Upon completion, the solution was carefully poured into an ice-water mixture and extracted with Et_2O (3x50mL). The organic phase was combined, dried using Na_2SO_4, and subsequently filtered. Finally, the solvent was removed using a rotary evaporator.

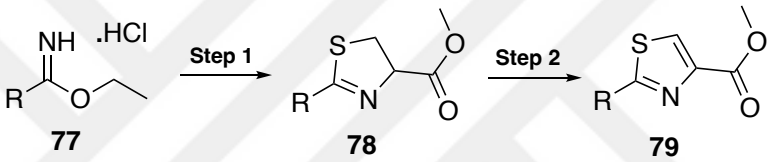
3rd Step: General Method for Preparation of Carboximidate hydrochlorides



76 **77**

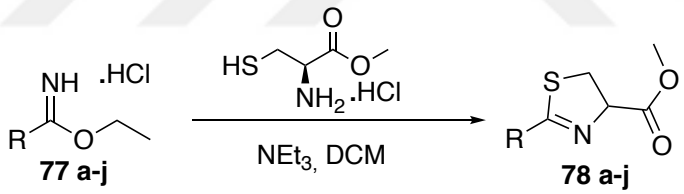
Nitrile (16 mmol) was dissolved in 15 mL of ethanol (EtOH). Subsequently, the reaction mixture was exposed to HCl gas overnight at 0°C. Once the reaction reached completion, the ethanol was evaporated, and the resulting solution was subjected to extraction using a mixture of DCM and water (3x50 mL). The combined organic phase was then dried using Na_2SO_4, filtered, and evaporated.

3.1.2 Synthesis of Final Product



77 **78** **79**

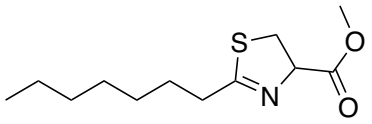
1st Step : General method for Preparation of Thiazoline



77 a-j **78 a-j**

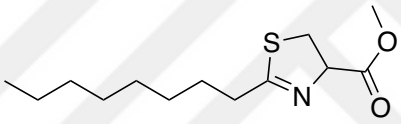
At 0°C, triethylamine (8,4 mmol, 1,32 equiv.) was carefully introduced to a suspension of L-cysteine methyl ester hydrochloride (8,5 mmol, 1,34) equiv.) in dry CH_2Cl_2. Following a 20-minute interval, a suspension of carboximidate hydrochloride **77** (6,4 mmol, 1 equiv.) in CH_2Cl_2 was added to the mixture, and it was then left to reach room temperature overnight. Upon completion of the reaction, the mixture was diluted with DCM and subjected to washing with $NaHCO_3$ and brine. The organic phase was subsequently combined, dried using Na_2SO_4, filtered, and evaporated. The thiazoline products **78** was purified through column chromatography using hexane-EtOAc mixtures.

Methyl 2-heptyl-4,5-dihydrothiazole-4-carboxylate 78a



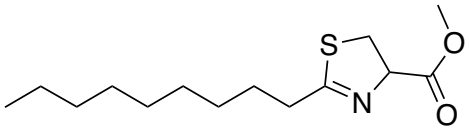
Column chromatography (3% EtOAc/hexane) afforded yellow oil. Yield: (57%), R_f (33% EtOAc/hexane) 0.45. IR (ATR, cm^{-1}): v = 2952-2854 (aliph.CH str.), 1740 (ester C=O), 1620 (C=N str.), 1174 (C-O-C), 931 (C-S str.). ^1H NMR (400 MHz, $CDCl_3$) δ 5.06 (t, J = 9.2 Hz, 1H, CH), 3.80 (s, 3H, OCH_3), 3.64 – 3.46 (m, 2H, S-CH_2), 2.55 (t, J = 7.7 Hz, 2H), 1.64 (p, J = 7.4 Hz, 2H), 1.35 – 1.19 (m, 8H), 0.87 (t, J = 6.7 Hz, (3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 175.27 (C=O), 171.46 (C=N), 77.73 (C-N), 61.65, 52.66 (O-CH_3), 35.50 (C-S), 34.50, 31.66, 28.93, 27.70, 22.63, 14.08.

Methyl 2-octyl-4,5-dihydrothiazole-4-carboxylate 78b



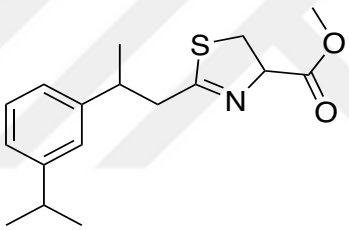
Column chromatography (3% EtOAc/hexane) afforded colorless oil. Yield: (75%), R_f (33% EtOAc/hexane) 0.52. IR (ATR, cm^{-1}): v = 2952-2853 (aliph. CH), 1737 (ester C=O), 1620 (C=N str.), 1435 (C-H bend.), 1274, 1175 (C-O-C), 739 (C-S). ^1H NMR (400 MHz,$CDCl_3$) δ 5.03 (t, J = 9.2 Hz, 1H, CH), 3.77 (s, 3H, OCH_3), 3.60 – 3.38 (m, 2H, S-CH_2), 2.52 (t, J = 7.6 Hz, 2H), 1.69 – 1.55 (m, 2H), 1.23 (s, 10H), 0.84 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.33 (C=O), 170.96 (C=N), 77.68 (C-N), 52.76 (O-CH_3), 35.38 (C-S), 34.45, 31.77, 29.18, 29.09, 29.06, 27.66, 22.62, 14.09.

Methyl 2-nonyl-4,5-dihydrothiazole-4-carboxylate 78c



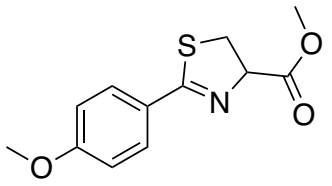
Column chromatography (3% EtOAc/hexane) afforded yellow oil. Yield: (53%), R_f (%33 EtOAc/hexane) 0.56. IR (ATR, cm^{-1}): ν = 2922, 2853 (aliph. CH), 1742 (ester C=O), 1621 (C=N str.), 1435 (C-H bend.), 1175 (C-O-C), 739 (C-S str). ^{1}H NMR (400 MHz, cdcl$_3$) δ 5.04 (t, J = 9.1 Hz, 1H, CH), 3.79 (s, 3H, O-CH_3), 3.60 – 3.43 (m, 2H, S-CH_2), 2.53 (t, J = 7.7 Hz, 2H), 1.62 (p, J = 7.1 Hz, 2H), 1.34 – 1.21 (m, 12H), 0.85 (t, J = 6.8 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 175.19 (C=O), 171.41(C=N), 77.84 (C-N), 77.79, 52.67 (O-CH_3), 35.36 (C-S), 34.47, 31.85, 29.40, 29.24, 29.06, 27.67, 22.66, 14.11.

Methyl 2-(2-(3-isopropylphenyl)propyl)-4,5-dihydrothiazole-4-carboxylate 78d



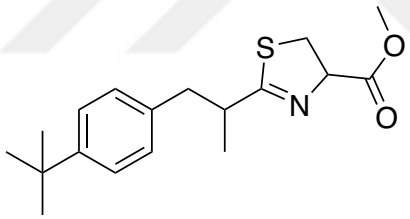
Column chromatography (3-10% EtOAc/hexane) afforded colorless oil. Yield: (90%), R_f (%33 EtOAc/hexane) 0.43. IR (ATR, cm^{-1}): ν = 2957, 2957 (aliph. CH), 1738 (C=O), 1619 (C=N), 1434 (C-H bend.), 1274, 1175 (C-O-C), 962, 739, 703. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 6.98 (m, 4H, arom. CH), 5.07 (q, J = 9.7 Hz, 1H, CH), 3.80 (d, J = 8.4 Hz, 3H, O-CH_3), 3.54 (dddd, J = 35.8, 11.3, 9.1, 2.4 Hz, 2H, S-CH_2), 3.27 – 3.11 (m, 1H), 2.95 – 2.81 (m, 3H), 1.33 (dd, J = 6.9, 1.9 Hz, 3H), 1.25 (d, J = 6.8 Hz, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.47 (C=O), 171.21 (C=N), 149.02, 145.44, 145.41 (arom. CH), 128.44, 125.20, 124.52, 124.15, 77.34 (C-N), 52.79 (O-CH_3), 42.68, 38.80, 35.55(S-CH_2), 34.15, 24.07, 21.46.

Methyl 2-(4-methoxyphenyl)-4,5-dihydrothiazole-4-carboxylate 78e



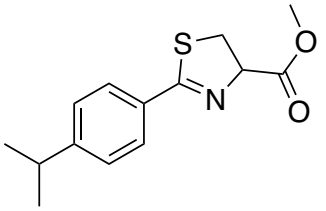
Column chromatography (5-10% EtOAc/hexane) afforded white solid. Yield: (71%), R_f (%33 EtOAc/hexane) 0.33. IR (ATR, cm^{-1}): ν = 3008 (arom. CH), 2953-2833 (aliph. CH), 1733 (ester C=O), 1588 (C=N str.), 1432 (C-H bend.), 1170 (C-O-C), 845 (C-S str). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 9.0 Hz, 2H, arom. CH), 6.89 (d, J = 9.0 Hz, 2H, arom. CH), 5.24 (t, J = 9.0 Hz, 1H, CH), 3.83 (d, J = 5.3 Hz, 6H, O-CH_3), 3.73 – 3.55 (m, 2H, S-CH_2).^{13}C NMR (101 MHz, $CDCl_3$) δ 171.55(C=O), 170.29 (C=N), 162.39, 130.41, 125.41 (arom. CH), 113.76 (arom. CH), 78.35 (C-N), 77.09, 55.39, 52.74 (O-CH_3), 35.43 (C-S), 29.72.

Methyl 2-(1-(4-(*tert*-butyl)phenyl)propan-2-yl)-4,5-dihydrothiazole-4-carboxylate 78f



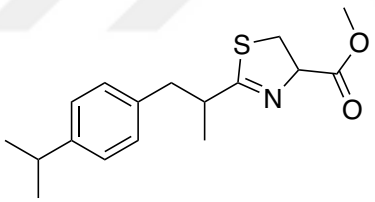
Column chromatography (1.5-5% EtOAc/hexane) afforded yellow oil. Yield: (67%), R_f (%33 EtOAc/hexane) 0.48. IR (ATR, cm^{-1}): ν = 2957, 2868 (aliph. CH), 1736 (ester C=O), 1615 (C=N str.), 1435 (C-H bend.), 1173 (C-O-C), 833 (C-S str). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 6.7 Hz, 2H, arom. CH), 7.11 (d, J = 8.4 Hz, 2H, arom. CH), 5.04 (td, J = 9.1, 6.2 Hz, 1H, CH), 3.78 (d, J = 8.6 Hz, 3H, O-CH_3), 3.57 – 3.38 (m, 2H, S-CH_2), 3.13 – 2.97 (m, 2H, CH_2), 2.73 – 2.60 (m, 1H, CH), 1.29 (s, 9H, CH_3), 1.17 (t, J = 6.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.51(C=O), 179.45, 171.37(C=N), 171.30, 148.99, 136.08, 136.05, 128.72 (arom. CH), 125.17 (arom. CH), 77.70 (C-N), 77.60, 52.75 (O-CH_3), 52.65, 40.98, 34.79 (C-S), 34.37, 31.38, 18.69.

Methyl 2-(4-isopropylphenyl)-4,5-dihydrothiazole-4-carboxylate 78g



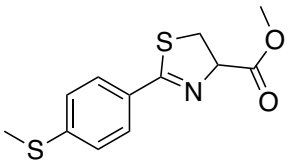
Column chromatography (3-5% EtOAc/hexane) afforded colorless oil. Yield: (54%), R_f (%33 EtOAc/hexane) 0.55. IR (ATR, cm^{-1}): v = 2958, 2872 (aliph. CH), 1740 (ester C=O), 1598 (C=N str.), 1435 (C-H bend.), 1175 (C-O-C), 840 (C-S str).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2H, arom. CH), 7.28 (s, 2H, arom. CH), 5.28 (t, J = 9.1 Hz, 1H, CH), 3.83 (s, 3H, O-CH_3), 3.70 – 3.57 (m, 2H S-CH_2), 2.94 (p, J = 6.8 Hz, 1H), 1.25 (d, J = 6.8 Hz, 6H, CH_3).^{13}C NMR (101 MHz, $CDCl_3$) δ 171.40 (C=O), 170.74 (C=N), 152.96, 130.31, 128.71 (arom. CH), 126.56 (arom. CH), 78.40 (C-N) , 77.52, 77.20, 76.88, 52.71(O-CH_3), 35.27 (C-S), 34.12, 23.74.

Methyl 2-(1-(4-isopropylphenyl)propan-2-yl)-4,5-dihydrothiazole-4-carboxylate 78h



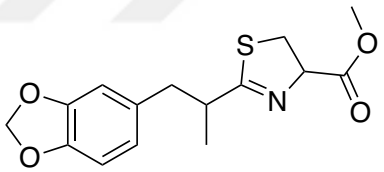
Column chromatography (3-5% EtOAc/hexane) afforded yellow oil. Yield: (73%), R_f (%33 EtOAc/hexane) 0.49. IR (ATR, cm^{-1}): v = 2957-2870 (aliph. CH), 1738 (ester C=O), 1615 (C=N str.), 1435 (C-H bend.), 1172 (C-O-C), 809 (C-S str). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 6.99 (m, 4H, arom. CH), 5.04 (td, J = 9.0, 6.9 Hz, 1H, CH), 3.78 (d, J = 9.8 Hz, 3H, O-CH_3), 3.60 – 3.40 (m, 2H, S-CH_2), 3.04 (dddd, J = 13.4, 9.7, 6.4, 3.6 Hz, 2H, CH_2), 2.84 (h, J = 6.9 Hz, 1H), 2.74 – 2.55 (m, 1H), 1.21 (d, J = 6.9 Hz, 6H, CH_3), 1.16 (t, J = 6.0 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.51 (C=O), 171.38 (C=N), 146.76, 136.46, 129.02, 128.98 (arom. CH), 126.34 (arom. CH), 77.64 (C-N) , 52.71 (O-CH_3), 41.12, 41.08, 34.78 (C-S), 33.70, 29.72, 24.05, 18.70, 18.54.

Methyl 2-(4-(methylthio)phenyl)-4,5-dihydrothiazole-4-carboxylate 78i



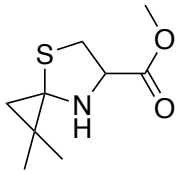
Column chromatography (6-20% EtOAc/hexane) afforded light orange solid. Yield: (64%), R_f (%33 EtOAc/hexane) 0.35. IR (ATR, cm^{-1}): v = 2953-2844 (aliph. CH str.), 1739 (ester C=O), 1599 (C=N str.), 1433 (C-H bend.), 1173 (C-O-C), 818 (C-S str). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 2H, arom. CH), 7.21 (d, J = 8.6 Hz, 2H arom. CH), 5.25 (t, J = 9.1 Hz, 1H, CH), 3.82 (s, 3H, O-CH_3), 3.73 – 3.57 (m, 2H, S-CH_2), 2.49 (s, 3H S-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.37 (C=O), 170.36 (C=N), 143.75 (quart C), 129.82 (quart. C), 128.96 (arom. CH), 125.19 (arom. CH), 78.35 (C-N), 60.85, 52.79 (O-CH_3), 35.35 (C-S), 29.70, 15.01 (S-CH_3).

Methyl 2-(1-(benzo[d][1,3]dioxol-5-yl)propan-2-yl)-4,5-dihydrothiazole-4-carboxylate 78j



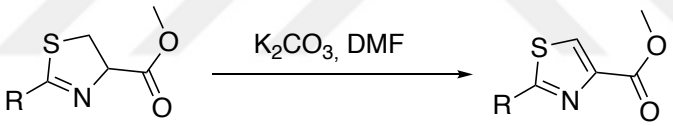
Column chromatography (4% EtOAc/hexane) afforded yellow solid. Yield: (72%), R_f (%33 EtOAc/hexane) 0.31. IR (ATR, cm^{-1}): v = 2934,2915 (aliph. CH str.), 1739 (ester C=O), 1609 (C=N str.), 1439 (C-H bend.), 1034 (C-O-C), 782 (C-S str). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 – 6.47 (m, 3H, arom. CH), 5.88 (s, 2H, O-CH_2), 5.02 (td, J = 9.0, 3.6 Hz, 1H, CH), 3.76 (d, J = 9.1 Hz, 3H, O-CH_3), 3.63 – 3.34 (m, 2H, S-CH_2), 3.04 – 2.87 (m, 2H, CH_2), 2.70 – 2.55 (m, 1H), 1.15 (t, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.07 (C=O), 171.25 (C=N), 147.47, 145.93, 132.93, 122.06 (arom. CH), 109.39, 108.11, 100.88 (O-C-O), 77.69 (C-N) , 77.58, 52.64 (O-CH_3), 41.28, 34.85 (C-S), 18.51.

Methyl 1,1-dimethyl-4-thia-7-azaspiro[2.4]heptane-6-carboxylate 78k



Column chromatography (4-5% EtOAc/hexane) afforded dark yellow oil. Yield (42%), R_f (%33 EtOAc/hexane) 0.41. IR (ATR, cm^{-1}): v = 3305 (N-H str.), 2954-2855 (aliph. CH str.), 1739 (ester C=O), 1229 (C-O-C), 790 (C-S str). ^1H NMR (400 MHz, $CDCl_3$) δ 4.06 (dd, J = 9.2, 7.0 Hz, 1H, N-H), 3.76 (s, 3H, O-CH_3), 3.40 (dd, J = 10.5, 7.0 Hz, 1H, CH), 3.00 (t, J = 9.8 Hz, 2H, S-CH_2), 2.48 (s, 2H), 1.67 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.97 (C=O), 77.07 (C-N), 64.34 (S-C-N), 52.51 (O-CH_3), 40.23, 32.61 (C-S), 30.45, 29.67, 22.67.

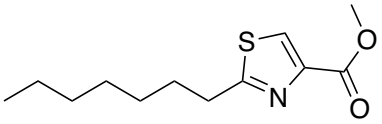
2nd Step: General Method for Preparation of Thiazole 79 (63)



78 a-j **79 a-j**

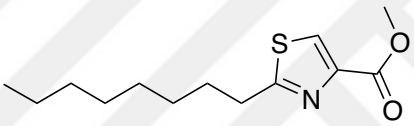
A solution of thiazoline **78** was prepared by dissolving it in dry DMF (7 mL). Subsequently, molecular sieves (4 Å, 280 mg, 200 wt %) and K_2CO_3 (6 mmol, 3 equiv.) were introduced to the solution. The resulting reaction mixture was stirred at 100°C for 1 hours. Upon completion, the solution was diluted with ethyl acetate and subjected to washing with water and brine. Following the washes, the solution was dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The thiazole products **79** was purified through column chromatography using hexane-EtOAc mixtures.

Methyl 2-heptylthiazole-4-carboxylate 79a



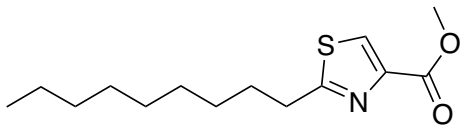
Column chromatography (2% EtOAc/hexane) afforded yellow oil. Yield: (53%), R_f (%33 EtOAc/hexane) 0.50. IR (ATR, cm^{-1}): v = 2952-2852 (aliph. CH str.), 1720 (ester C=O), 1484 (C=N str.), 1206 (C-O-C), 749 (C-S str.). ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H, =CH), 3.89 (s, 3H, OCH_3), 3.06 – 2.88 (m, 2H), 1.75 (p, J = 7.7 Hz, 2H), 1.46 – 1.11 (m, 8H), 0.82 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.59 (C=N) , 161.95 (C=O), 146.24, 127.08 (S-CH=), 52.67 (O-CH_3), 52.27, 33.61, 31.60, 30.16, 28.88, 22.56, 14.02.

Methyl 2-octylthiazole-4-carboxylate 79b



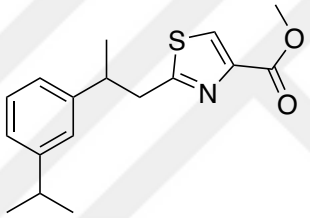
Column chromatography (10% EtOAc/hexane) afforded white solid. Yield: (67%), R_f (%33 EtOAc/hexane) 0.62. IR (ATR, cm^{-1}): v = 2923, 2853 (aliph. CH str.), 1720 (ester C=O), 1484 (C=N str.), 1206 (C-O-C), 748 (C-S str.).^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H, =CH), 3.93 (s, 3H, OCH_3), 3.09 – 2.97 (m, 2H), 1.78 (p, J = 7.6 Hz, 2H), 1.43 – 1.16 (m, 10H), 0.86 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.63 (C=N), 161.96 (C=O), 146.26, 127.11 (S-CH=), 52.48 (O-CH_3), 52.34, 33.63, 31.77, 30.17, 29.19, 29.07, 22.63, 14.09.

Methyl 2-nonylthiazole-4-carboxylate 79c



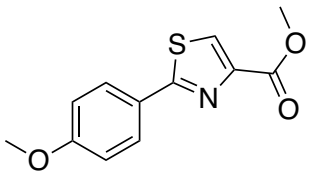
Column chromatography (5% EtOAc/hexane) afforded yellow oil. Yield: (74%), R_f (1:3 EtOAc/hexane) 0.59. IR (ATR, cm^{-1}): ν = 2922, 2853 (aliph. CH str.), 1720 (ester C=O), 1484 (C=N str.), 1206 (C-O-C), 748 (C-S str.). ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H, =CH), 3.93 (s, 3H, OCH_3), 3.04 (t, J = 7.8 Hz, 2H), 1.78 (p, J = 7.7 Hz, 2H), 1.35 – 1.22 (m, 12H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.67 (C=N), 162.00 (C=O), 146.29, 127.16 (S-CH=), 52.51(O-CH_3), 33.66, 31.85, 30.19, 29.41, 29.40, 29.24, 29.08, 22.67, 14.12.

Methyl 2-(2-(3-isopropylphenyl)propyl)thiazole-4-carboxylate 79d



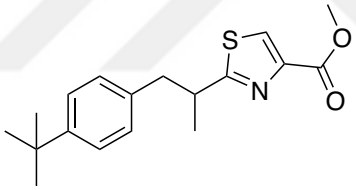
Column chromatography (6-10% EtOAc/hexane) afforded yellow oil. Yield: (78%), R_f (%33 EtOAc/hexane) 0.46. IR (ATR, cm^{-1}): ν = 2958-2868 (aliph. CH str.), 1720 (ester C=O), 1603 (C=N str.), 1207 (C-O-C), 733 (C-S str.). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H, =CH), 7.22 (t, J = 7.7 Hz, 1H, arom. CH), 7.14 – 6.95 (m, 3H, arom. CH), 3.93 (s, 3H, OCH_3), 3.30 (dddd, J = 28.1, 17.8, 11.9, 5.0 Hz, 3H), 2.85 (hept, J = 7.0 Hz, 1H), 1.41 – 1.15 (m, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 170.41 (C=N), 161.98 (C=O), 149.18 (arom. CH), 146.14, 144.90, 128.63, 127.44 (S-CH=), 125.51 (arom. CH), 53.47, 52.34 (O-CH_3), 42.06, 40.86, 34.11, 29.71, 24.02, 21.63, 14.15.

Methyl 2-(4-methoxyphenyl)thiazole-4-carboxylate 79e



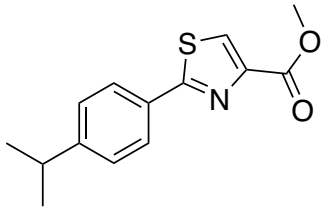
Column chromatography (3-10% EtOAc/hexane) afforded white solid. Yield: (77%), R_f (%33 EtOAc/hexane) 0.36. IR (ATR, cm^{-1}): ν = 3125 (arom. CH), 2922-2852 (aliph. CH str.), 1702 (ester C=O), 1609 (C=N str.), 1232 (C-O-C), 837 (C-S str.). ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H, =CH), 7.94 (d, J = 8.5 Hz, 2H, arom. CH), 6.95 (d, J = 8.6 Hz, 2H, , arom. CH), 3.97 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.95 (C=N), 162.10 (C=O), 161.71(arom. CH), 147.45, 128.53 (arom. CH), 126.76 (S-CH=), 126.53, 125.65 (arom. CH), 114.50 (arom. CH), 114.14, 55.63 (O-CH_3), 52.43 (O-CH_3).

Methyl 2-(1-(4-(*tert*-butyl)phenyl)propan-2-yl)thiazole-4-carboxylate 79f



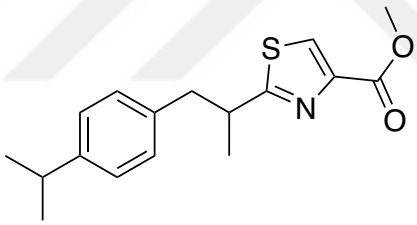
Column chromatography (6-10% EtOAc/hexane) afforded yellow oil. Yield: (74%), R_f (%33 EtOAc/hexane) 0.55. (ATR, cm^{-1}): ν = 2958,2868 (aliph. CH str.), 1719 (ester C=O), 1480 (C=N str.), 1239 (C-O-C), 749 (C-S str.). ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H, =CH), 7.28 (d, J = 8.1 Hz, 2H, arom. CH), 7.08 (d, J = 7.9 Hz, 2H, arom. CH), 3.94 (s, 3H, OCH_3), 3.58 (dt, J = 8.9, 6.6 Hz, 1H), 3.21 (dd, J = 13.6, 5.9 Hz, 1H), 2.82 (dd, J = 13.6, 9.0 Hz, 1H), 1.36 (d, J = 6.9 Hz, 3H), 1.29 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 177.49 (C=N), 162.07 (C=O), 149.23 (arom. CH), 146.2, 135.78, 128.76 (S-CH=), 126.85, 125.35 (arom. CH), 53.47, 52.38 (O-CH_3), 43.16, 40.36, 34.39, 31.41, 29.71, 22.71, 20.48, 14.16.

Methyl 2-(4-isopropylphenyl)thiazole-4-carboxylate 79g



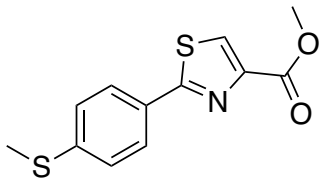
Column chromatography (10% EtOAc/hexane) afforded yellow solid. Yield: (83%), R_f (%33 EtOAc/hexane) 0.61. (ATR, cm^{-1}): ν = 3125 (arom. CH), 2950 (aliph. CH str.), 1724 (ester C=O), 1611 (C=N str.), 1204 (C-O-C), 835 (C-S str.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H, =CH), 7.96 – 7.84 (m, 2H, arom. CH), 7.28 (d, J = 8.3 Hz, 2H, arom. CH), 3.95 (s, 3H, OCH_3), 2.93 (hept, J = 7.0 Hz, 1H), 1.25 (d, J = 6.9 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 169.16 (C=N), 162.00 (C=O), 151.98 (arom. CH), 147.50, 130.38, 127.08 (S-CH=), 127.00 (arom. CH), 52.53, 52.43 (O-CH_3), 34.07, 23.76.

Methyl 2-(1-(4-isopropylphenyl)propan-2-yl)thiazole-4-carboxylate 79h



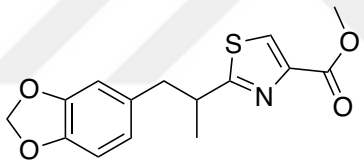
Column chromatography (10-20% EtOAc/hexane) afforded yellow oil. Yield: (95%), R_f (1:3 EtOAc/hexane) 0.55. (ATR, cm^{-1}): ν = 2957-2869 (aliph. CH str.), 1719 (ester C=O), 1481 (C=N str.), 1239 (C-O-C), 749 (C-S str.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H, =CH), 7.13 (d, J = 8.0 Hz, 2H, arom. CH), 7.07 (d, J = 7.9 Hz, 2H, arom. CH), 3.96 (s, 3H, O-CH_3), 3.63 – 3.52 (m, 1H), 3.21 (dd, J = 13.5, 5.9 Hz, 1H), 2.92 – 2.75 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.29 – 1.19 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.50 (C=N), 162.10 (C=O), 146.99 (arom. CH), 146.22, 136.16, 129.09 (S-CH=), 126.89, 126.45 (arom. CH), 52.48 (O-CH_3), 43.32, 40.39, 33.72, 31.46, 29.74, 24.05, 20.50, 14.19

Methyl 2-(4-(methylthio)phenyl)thiazole-4-carboxylate 79i



Column chromatography (3-10% EtOAc/hexane) afforded light orange solid. Yield: (71%), R_f (%33 EtOAc/hexane) 0.45. (ATR, cm^{-1}): *v* = 3109 (arom. CH), 2953-2852 (aliph. CH str.), 1703 (ester C=O), 1570 (C=N str.), 1238 (C-O-C), 765 (C-S str.) ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H, =CH), 7.91 (d, *J* = 8.4 Hz, 2H, arom. CH), 7.28 (d, *J* = 8.4 Hz, 2H, arom. CH), 3.97 (s, 3H, O-CH_3), 2.52 (s, 3H, S-CH_3).^{13}C NMR (101 MHz, $CDCl_3$) δ 168.63 (C=N), 161.98 (C=O), 147.61 (arom. CH), 142.54, 129.25 , 127.03 (S-CH=), 126.90, 126.04, 52.67 (O-CH_3), 29.75, 15.27, 15.07 (S-CH_3).

Methyl 2-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)thiazole-4-carboxylate 79j



Column chromatography (6-16% EtOAc/hexane) afforded white solid. Yield: (71%), R_f (33% EtOAc/hexane) 0.45. (ATR, cm^{-1}): *v* = 3121 (arom. CH), 2953-2926 (aliph. CH str.), 1732 (ester C=O), 1488 (C=N str.), 1243 (C-O-C), 751 (C-S str.) ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, =CH), 6.68 (d, *J* = 7.9 Hz, 2H, arom CH), 6.56 (dd, *J* = 8.0, 1.7 Hz, 1H, arom CH), 5.90 (s, 2H, O-CH_2), 3.94 (s, 3H, O-CH3), 3.56 – 3.44 (m, 1H), 3.13 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.79 (dd, *J* = 13.7, 8.5 Hz, 1H), 1.35 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 177.01 (C=N), 162.01 (C=O), 147.55 (arom. CH), 146.24, 146.06, 132.57, 126.83 (S-CH=), 122.18, 109.41, 108.13, 100.85, 52.39 (O-CH3), 43.32, 40.53, 20.44.

3.2 Olfactory Studies

Once the synthesis and characterization studies of the target compounds **78**,**79** were completed, an initial evaluation was conducted to assess the olfactory properties of all the products.

General Method

For the initial level test, a 10% solution of each sample in dipropylene glycol was prepared and applied onto perfume test sticks. The olfactory evaluation of each sample was conducted to assess its scent characteristics, both when initially applied and after 4 hours and 24 hours. Expert perfumers were involved in the assessment process to identify the fragrance classes of the samples. Additionally, the perfumers determined the molecules with the highest fragrance density and examined whether these could potentially serve as new essential compounds. The olfactory studies of the compounds produced in this thesis were carried out by experienced perfumers at Parkim Perfume Plastic and Chemical Industry LC, and a detailed report of the results was provided to us.

4. RESULT AND DISCUSSION

4.1. Synthesis of Precursor Compounds

Imidates, also referred to as imino-ethers, hold significant importance as organic motifs due to their versatile electronic properties. It is noteworthy that the term "imidates" originates from imidic acids, which are derived from amide-iminol tautomerism. In general, imidate motifs play a crucial role as both electrophiles and nucleophiles, in contrast to their corresponding amides (figure. 4.1) (78).

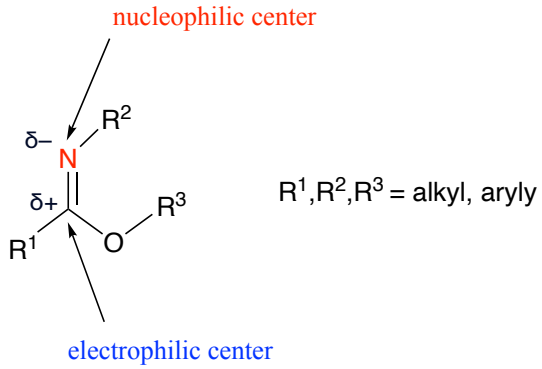


Figure 3.1. General electronic structure of imidates.

The utilization of imidate functionality extends beyond functional group transformations, such as the synthesis of esters, orthoesters, and amidines. It also encompasses the synthesis of various structurally diverse functionalized heterocyclic molecules, including saturated and unsaturated heterocycles. Functionalized heterocyclic compounds, whether saturated or unsaturated, are crucial structural frameworks found in a wide range of natural products, physiologically active agents, ligands, and pharmaceutical active ingredients. Due to its convenient synthesis, the imidate functionality has been extensively employed in the synthesis of N-heterocycles. Early reports showcased the successful use of imidates as a synthon for directly synthesizing various compounds, including imidazoles or imidazolones, imidazolines, benzimidazoles, oxazoles, oxazolines, benzoxazoles, thiazolines, and azines (Figure 4.2) (79,80).

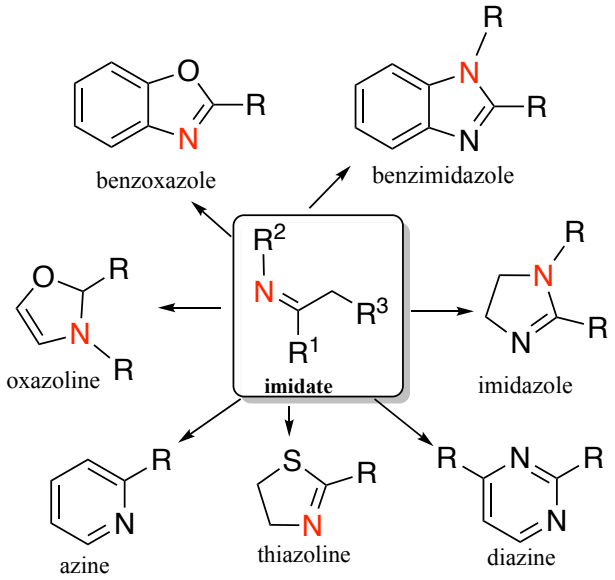
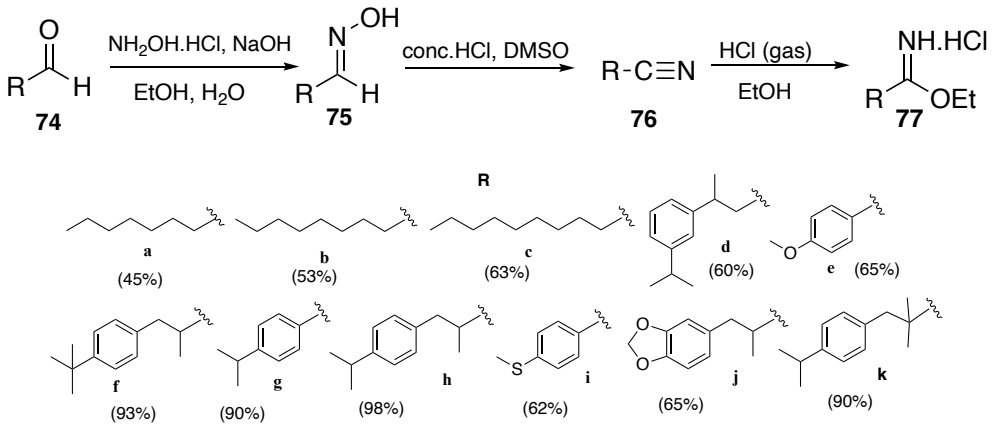


Figure 3.2. Different heterocycles starting with imidates.

The synthesis of imidate functionality typically involves the reaction of nitriles with alcohols under appropriate acidic conditions, known as the Pinner reaction, or through the alkylation of amides using ortho-esters (81). So, in the current study, we first prompted for the synthesis of imidates derivates as suitable precursors using this efficient technique. Firstly, commercially valuable aldehydes in cosmetic industry **74** were converted into corresponding oximes **75**, subsequently the oximes were reduced into nitrile derivatives **76**. Lastly, nitriles were transformed into related imidate hydrochlorides **77** in moderate to good yields (45-98%). In general, reaction yields of long chain alkyl substituted imidates **77a-c** were observed at moderate levels, but in contrast, phenyl or phenylpropanyl substitutions on imidates **78f,g,h,k** caused an increase in reaction yields up to 98%. So, the highest yield (98%) were attained in 1-(4-isopropylphenyl)propan-2-yl imidate **78h** among other products. However, the lowest yield (45%) was observed in heptyl substituted imidate derivative **78a** (Scheme 4.1). The reason of such low yields in alkyl substituted imidates would be a decrease in positive charge on nitrile C atom, hence the attack of ethanol molecule to electrophilic center has become more difficult. All the synthetic transformations from aldehydes toward the imidates **74-77** were monitored and characterized by FTIR analysis in each step. Also, main precursors, ethyl imidate hydrochlorides **77** were simply characterized using FT-IR spectroscopy.



Scheme 3.1 Route to access precursor compounds **77**.

For instance, in IR spectrum of **77d**, NH, CH, C=N, C-O-C stretching vibration peaks are seen around at 3385, 2959-2871, 1659 and 1094 cm^{-1}, respectively (figure 4.3).

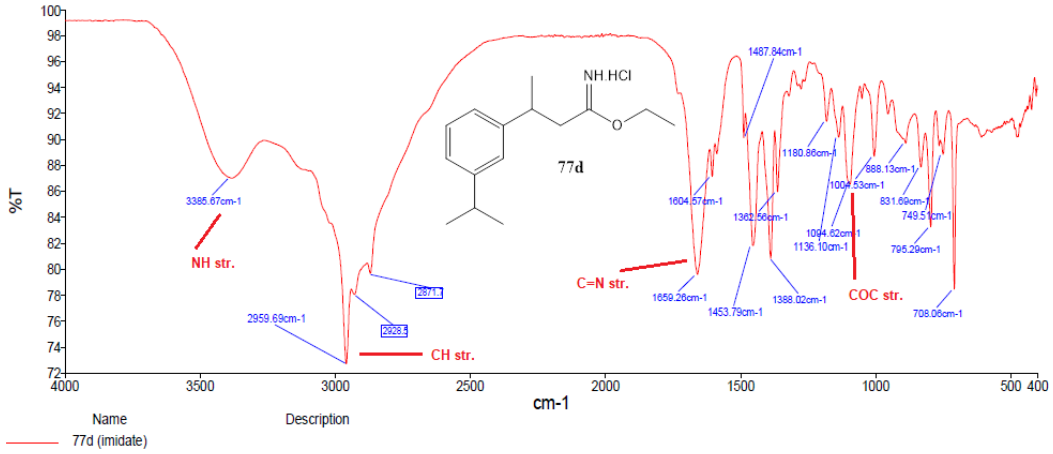
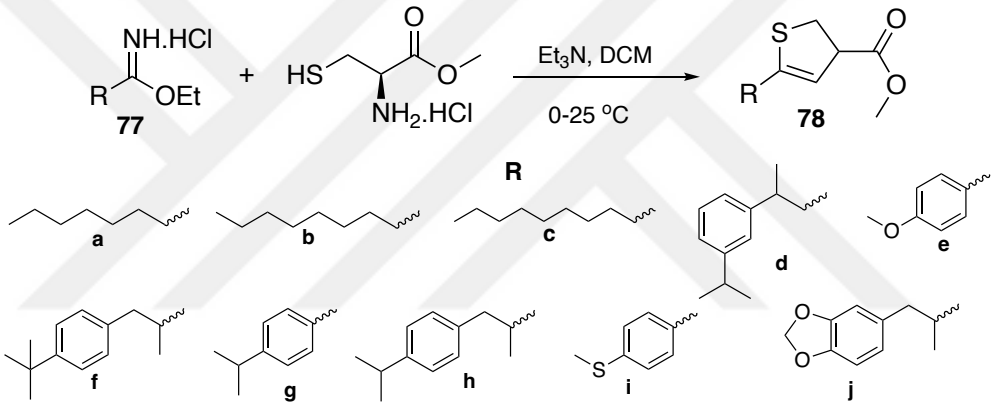


Figure 3.3. Important IR stretching vibrations in imidate **77d**.

4.2. Synthesis and characterization of thiazolines and thiazoles

After synthesis and characterization of imidate precursors **77**, they were reacted with L-cysteine methyl ester hydrochloride to get target products, 2-substituted-thiazoline-4-carboxylates **78a-j**. At the beginning of this reaction, Et_3N was added dropwise to a suspension of L-cysteine methyl ester hydrochloride in dry CH_2Cl_2 at 0°C and strirred at this temperature for 20 min. After that, a suspension of imidate hydrochlorides **77** in CH_2Cl_2 was added and resulting mixture was stirred at room temperature overnight. After a simple workup, thiazoline-4-carboxylates **78a-j** were purified by column chromatography using varying elution mixtures of EtOAc-Hexane (1.5-20%) and isolated in moderate to good yields (53-90%) (Table 4.1).



(**a**) hept: heptyl; (**b**) oct: octyl; (**c**) nony: nonyl; (**d**) 2-(3-iPr-Ph)Pr : 2-(3-isopropylphenyl)propyl; (**e**) 4-MeOPh: 4-methoxyphenyl; (**f**) 1-(4-t-Bu)Ph: 1-(4-(*tert*-butyl)phenyl; (**g**) 4-iPr-Ph: 4-isopropylphenyl; (**h**) 1-(4-iPrPh)-2-Pr: 1-(4-isopropylphenyl)propan-2-yl; (**i**) 4-MeS-Ph: 4-(methylthio)phenyl; (**j**) 1-Benzodioxoyl-2-Pr: 1-(benzo[d][1,3]dioxol-5-yl)propan-2-yl; (**k**) 3-(4-iPr-Ph)-2,2-diMePr: 3-(4-isopropylphenyl)-2,2-dimethylpropan.

Scheme 3.2. Synthesis of thiazolidine-4-carboxylates **(78)**.

Best yield (90%) was obtained in preparation of 2-(3-isopropylphenyl) propyl substituted thiazoline **78d** (Table 4.1, entry 4). However, the lowest yields (53-54%) were observed in nonyl **78c** and 4-isopropylphenyl substituted **78g** thiazolines, respectively. All alkyl substituted products were isolated in moderate-good yields (53-75%) but also propylaryl or phenyl substituted thiazolines had slightly better yields (54-90%). Moreover, 3-(4-isopropylphenyl)-2,2-dimethylpropanyl thiazoline product **78k** was not obtained as expected but a kind of rearrangement product was thought to be isolated (Table 4.1, entry 11).

Table 3.1. Physical data, reaction yields, times for thiazoline **78a-k**.

Entry	**78**	**R**	Physical form	Rf [a]	Time (h)	Yield (%)[b]
1	**a**	hept	YO	0.45	16	57
2	**b**	oct	CO	0.52	11	75
3	**c**	nony	YO	0.56	9	53
4	**d**	2-(3-iPr-Ph)Pr	CO	0.43	17	**90**
5	**e**	4-MeOPh	WS	0.33	19	71
6	**f**	1-(4-t-Bu)Ph	YO	0.48	15	67
7	**g**	4-iPr-Ph	CO	0.55	17	54
8	**h**	1-(4-iPrPh)-2-Pr	YO	0.49	18	73
9	**i**	4-MeS-Ph	LOS	0.35	18	64
10	**j**	1-Benzodioxoyl-2-Pr	YS	0.31	17	72
11	**k***	3-(4-iPr-Ph)-2,2-diMePr	DYO	0.41	12	42

[a] Mobile phase: %33 EtOAc/hexane; [b] yields after CC; * Unexpected rearrangement product.
YO: yellow oil; CO:colorless oil; WS:white solid; LOS: light orange solid; YS: yellow solid; DYO: dark yellow oil.

The structures of thiazoline-4-carboxylates **78a-j** were determined by means of IR, NMR and MS data. In the IR spectra of **78a-j**, C=O, C=N, C-S stretching vibration peaks appeared around 1733-1740, 1588-1621, 739-931 cm^{-1}, respectively (Table 4.2). Indicative proton NMR signals supported the expected structures of products **78**, they belong to SCH_2 and CH protons resonating at around 374-3.34 and 4.99-5.28 ppm. Also, C=N and C=O carbon signals of **78** derivatives at around 170-171 and 171-179 ppm supported the formation of expected products (Table 4.2) (see experimental and appendices). Some representative IR, NMR spectra for **78a** were illustrated below (Figure 4.4-4.6).

Table 3.2. IR and NMR data for thiazoline-4-carboxylates **78**.

	IR (ν_{max}/cm^{-1})			^{1}H-NMR (δ,ppm)		^{13}C-NMR (δ,ppm)	
78	C=O	C=N	C-S	SCH_2	-C**H**	**C**=N	**C**=O
a	1740	1620	931	3.74-3.40	4.99	171.4	175.2
b	1737	1620	739	3.60-3.38	5.03	170.9	175.3
c	1742	1621	739	3.60-3.43	5.04	171.4	175.1
d	1738	1619	739	3.74-3.54	5.07	171.2	174.4
e	1733	1588	845	3.73-3.55	5.24	170.2	171.5
f	1736	1615	833	3.57-3.38	5.04	171.3	179.5
g	1740	1598	840	3.70-3.57	5.28	170.7	171.4
h	1738	1615	809	3.60-3.40	5.04	171.3	179.5
i	1739	1599	818	3.73-3.57	5.25	170.3	171.3
j	1739	1609	782	3.63-3.34	5.02	171.2	179.0

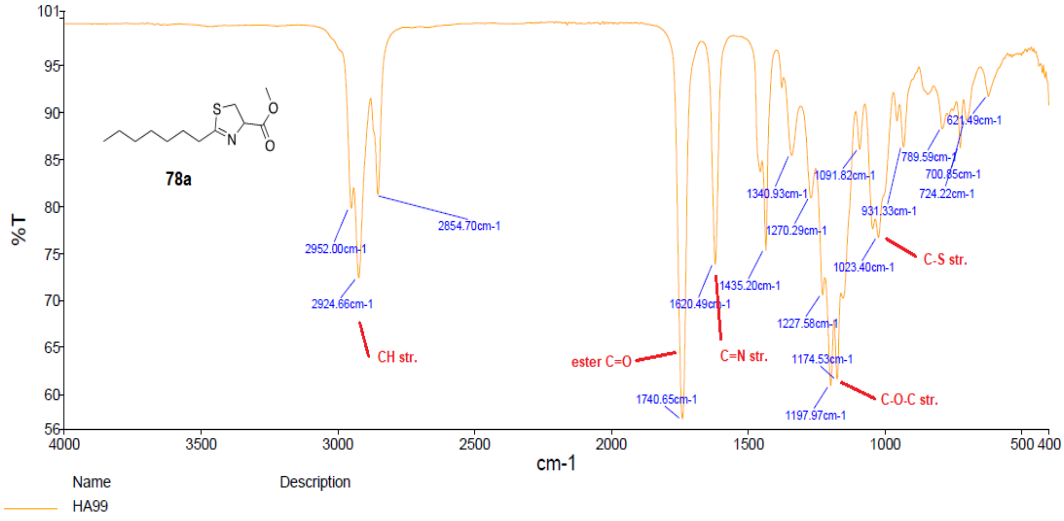


Figure 3.4. IR spectrum of compound **78a**.

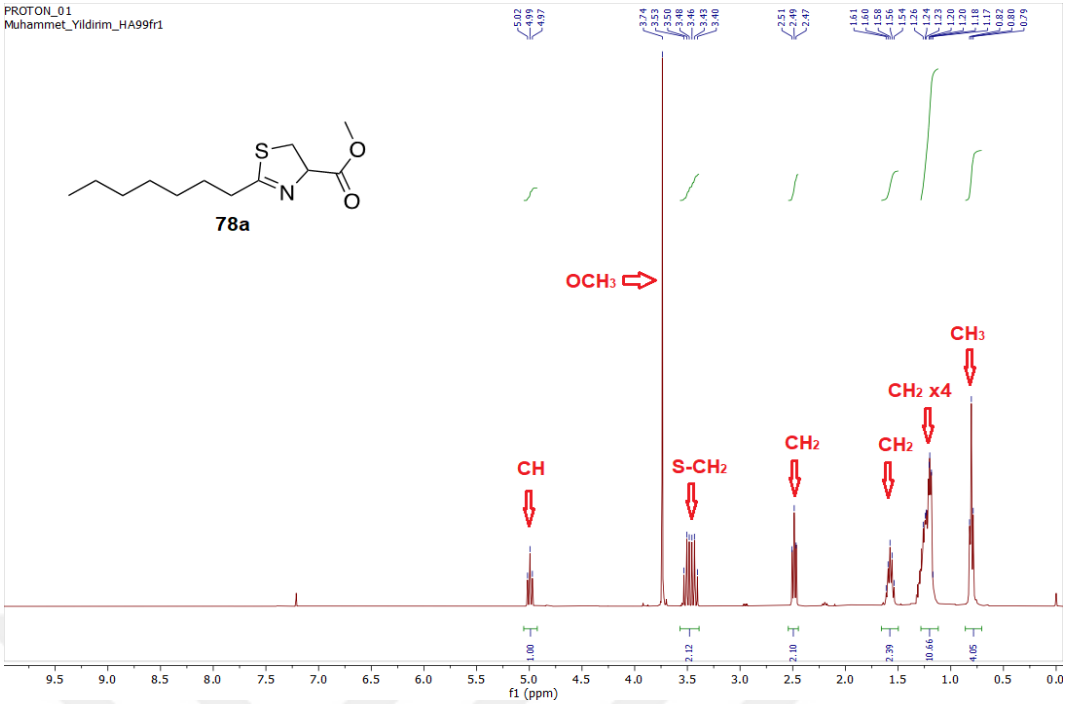


Figure 3.5. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78a**.

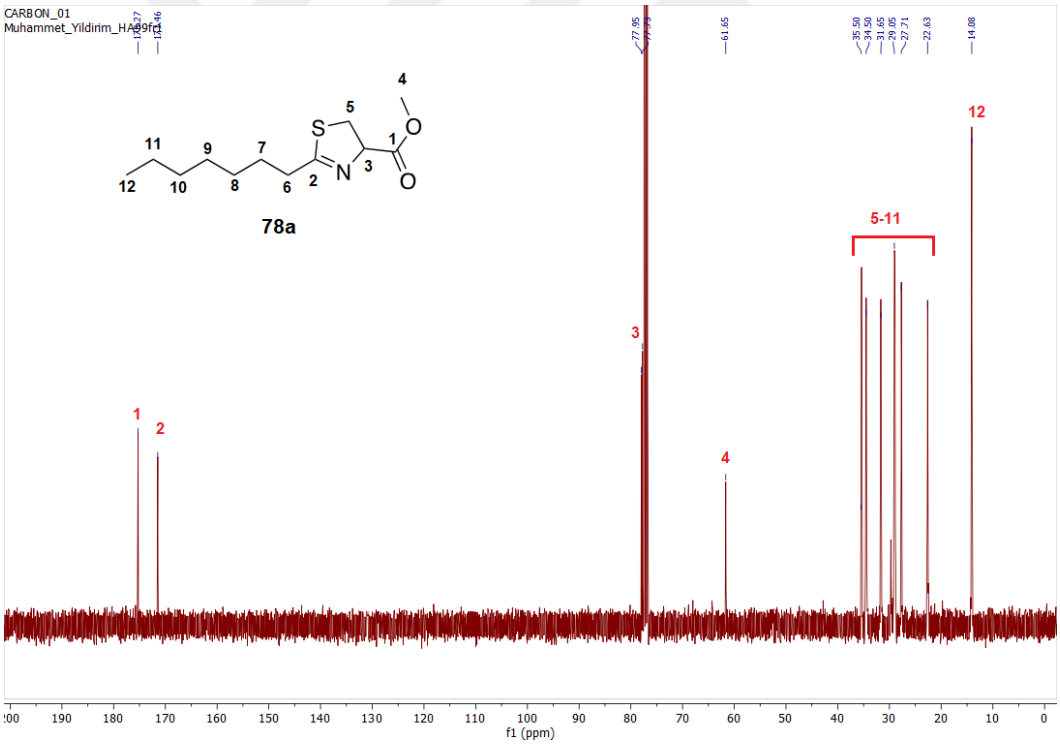
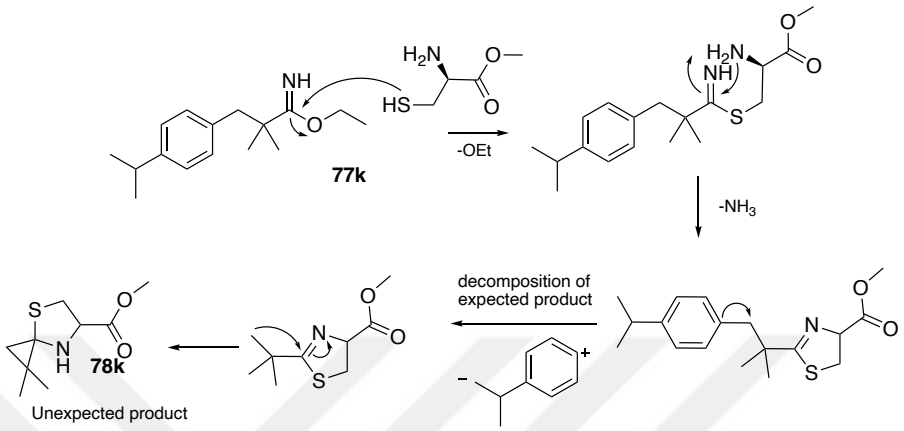


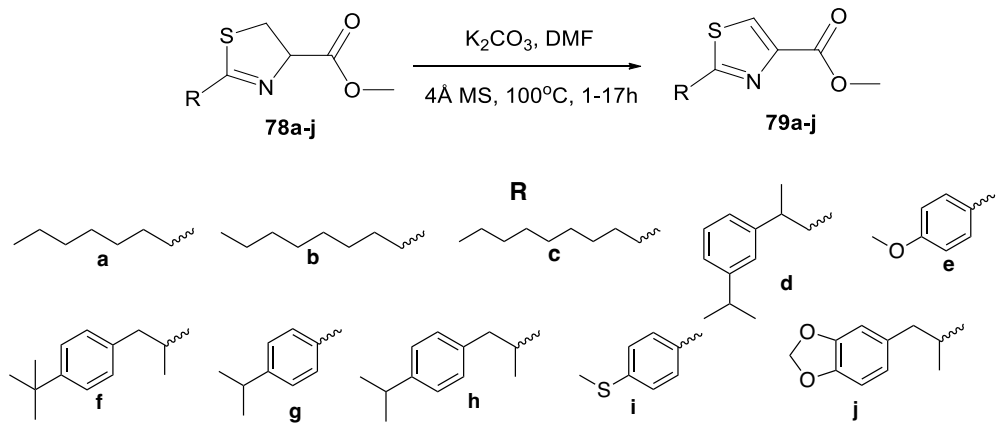
Figure 3.6. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78a**.

Other than the target thiazoline products, one unexpected product **78k** was also isolated from the reaction of 3-(4-isopropylphenyl)-2,2-dimethylpropanimidate **77k** with L-cysteine methyl ester hydrochloride. Regarding the proton NMR of product **78k**, a structure was proposed through the mechanism as given below.



Scheme 3.3. Proposed mechanism for the unexpected product **78k**.

Another series of target compounds, thiazole-4-carboxylates **79** were also prepared through oxidation reactions of corresponding thiazoline-4-carboxylates **78** with K_2CO_3 in DMF at 100°C. Even dry DMF was used as solvent, use of molecular sieve was found beneficial to increase the reaction yields. Thiazole-4-carboxylate products (**79**) were generally obtained with moderate-good yields (53-95%) within 1 to 5 hour. The best yield was found as 95% in the formation of product **79h** in 4 hour, however the lowest yield was obtained in the formation of product **79a** (Table 4.3). All the thiazole-4-carboxylate products **79a-j** were isolated in high purity by column chromatography using EtOAc-hexane (2-20%) mixtures (Table 4.3).



Scheme 3.4. Method for the synthesis of thiazole-4-carboxylates **79**.

Table 3.3. Physical data, reaction yields, times for thiazoles **79**.

79	Physical form	Rf [a]	Time (h)	Temp. (C°)	Yield (%)[b]
a	Yellow oil	0.50	1	100	53
b	White solid	0.62	4	80	67
c	Yellow oil	0.59	5	100	74
d	Yellow oil	0.46	3	90	78
e	White solid	0.36	1	90	77
f	Yellow oil	0.55	3	90	74
g	Yellow solid	0.61	3	80	83
h	Yellow oil	0.55	4	100	95
i	Light orange solid	0.45	1	90	71
j	White solid	0.35	4	80	71

[a] Mobile phase: %33 EtOAc/hexane; [b] yields after CC.

The structures of new thiazole-4-carboylates **77a-j** were primarily identified by ester C=O and C=N IR stretching vibrations at around 1703-1732 and 1480-1611 cm^{-1}, respectively (Table 4.4). In proton NMR spectra, =CH and OCH_3 proton signals at around 7.98-8.14 (singlet) and 3.86-3.97 (singlet) ppm supoorted the structue of target thizole-4-carboxylate derivatives **77a-j**. Moreover, in ^{13}C-NMR spectra of **79** derivatives, quarternary carbon signals resonated at 168-177 (-C=N) and 161.9-162.1 (C=O) ppm also confirmed for the expected structures or products (**79**) (Table 4.4). Finally, the expected structures of **79** derivatives will be also confirmed by accurate mass data (HRMS) by using LC-MS analysis, however the HRMS analysis of samples are underway now. Representative IR and NMR spectra of **79b** are given in Figures 4.6-4.9.

Table 3.4. Important IR and NMR data for thiazole-4-carboxylates (**79**).

	IR (ν_{max}/cm^{-1})		^{1}H-NMR (δ,ppm)		^{13}C-NMR (δ,ppm)	
79	C=O	C=N	=C**H**	OCH_3	**C**=N	**C**=O
a	1720	1484	8.03	3.89	172.5	161.9
b	1720	1484	8.06	3.93	172.6	161.9
c	1720	1484	8.06	3.93	172.6	162.0
d	1720	1603	7.98	3.89	170.4	161.9
e	1702	1609	8.11	3.86	168.9	162.1
f	1719	1480	8.07	3.94	177.4	162.0
g	1724	1611	8.12	3.95	169.1	162.0
h	1719	1481	8.08	3.96	177.5	162.1
i	1703	1570	8.14	3.97	168.6	161.9
j	1732	1488	8.05	3.94	177.0	162.0

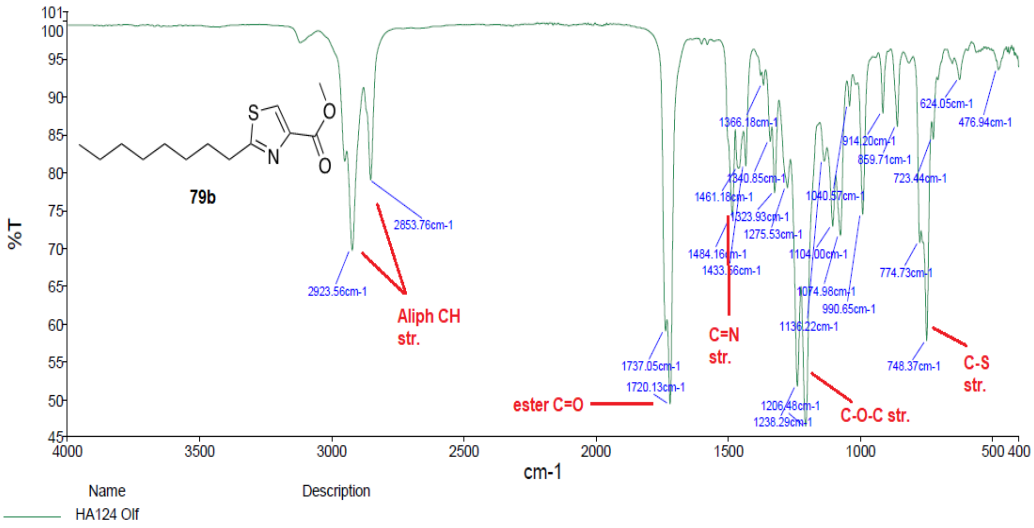


Figure 3.7. IR spectrum of thiazole-4-carboxylates **79b**.

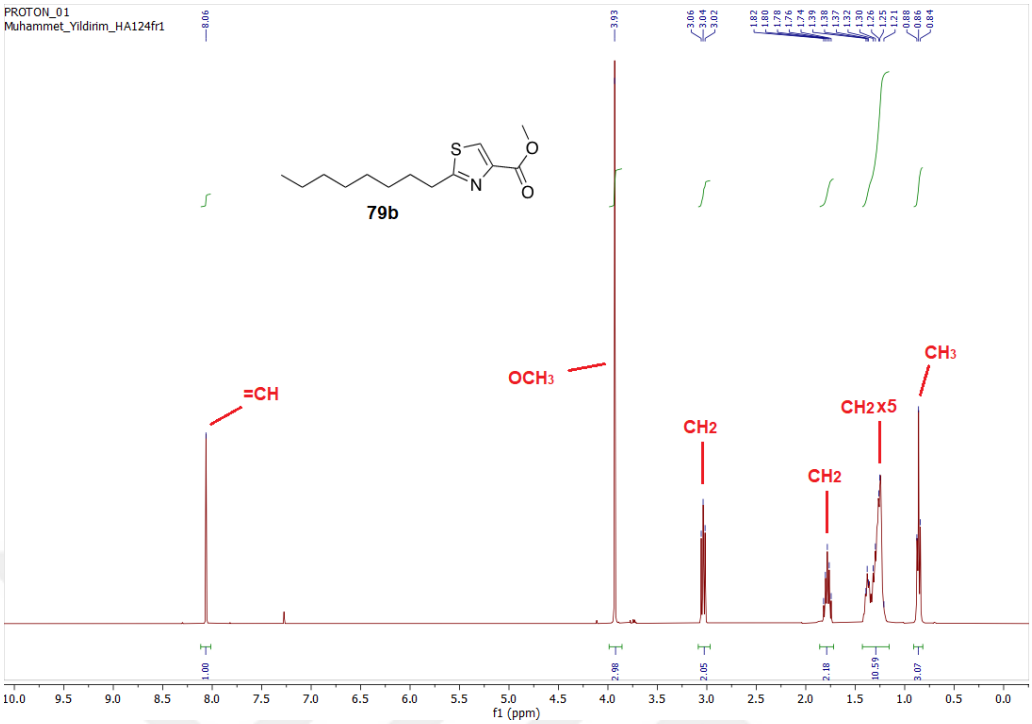


Figure 3.8. ^{1}H-NMR spectrum of thiazole-4-carboxylates **79b**.

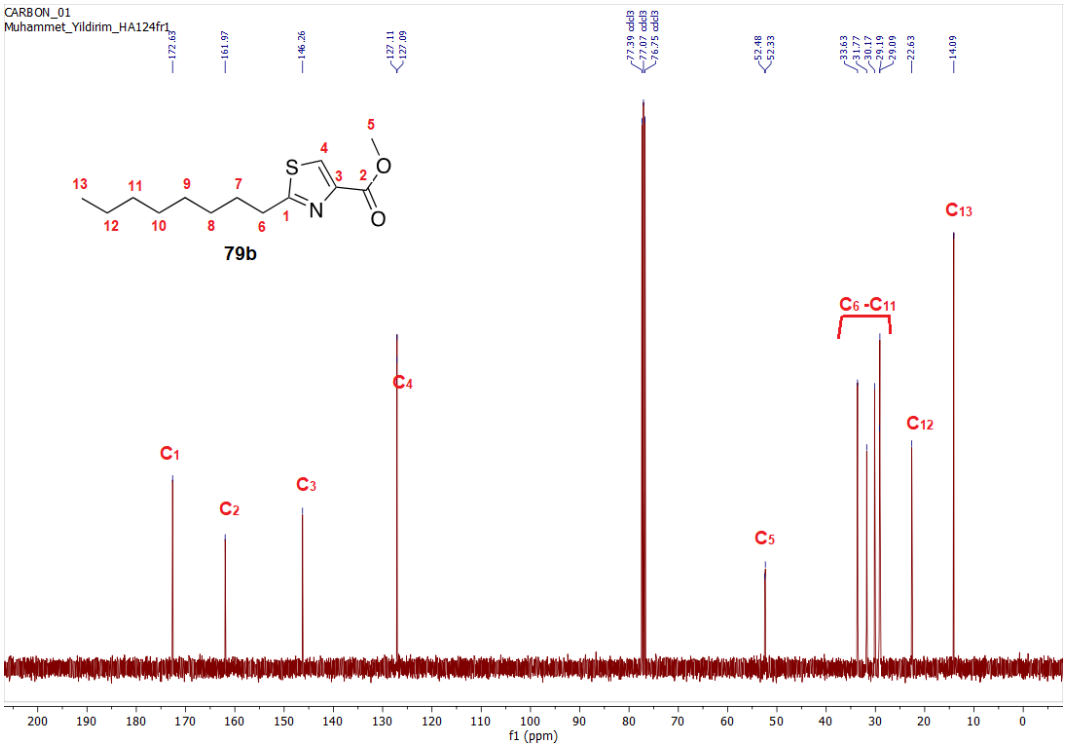


Figure 3.9. ^{13}C-NMR spectrum of thiazole-4-carboxylates **79b**.

4.3. Olfactory studies of thiazoline- and thiazole-4-carboxylates

In the final part of the this dissertation study, the olfactory analysis was conducted on all thiazoline **78a-k** and thiazole derivatives **79a-j** that had been previously synthesized, purified, and characterized. The evaluation was performed by experienced olfactory experts employed at a partner cosmetic company, Parkim LLC. Subsequently, detailed descriptions of the odors associated with each tested compound were recorded and are presented in the table 4.5-4.6 below.

When the olfactory tests results of products **78a-k** were evaluated, it is understood that some of the compounds **78a,c,d,I** had sulfox-like odor (unpleasant odor), some others **78b,f,g,h,j,k** had solvent-like odor and compound **78e** had no odor when they are fresh. Besides, as time passed (4-24h) all the products presented no odor and they are quite volatile compounds (figure 4.5). In general, although some of **78** derivatives presented some type of odors but they cannot be considered as potential fragrant compounds.

Table 3.5. Olfactory test results for thiazoline-4-carboxylates **78a-k**.

Test sample	**Odor description**		
78	Fresh	4 hour	24 hour
a	Like sulfox	Like sulfox	-[a]
b	Solvent-like	-[a]	-[a]
c	Like sulfox	-[a]	-[a]
d	Like sulfox	Like sulfox	-[a]
e	-[a]	-[a]	-[a]
f	Solvent-like	-[a]	-[a]
g	Solvent-like	-[a]	-[a]
h	Solvent-like	-[a]	-[a]
i	Like sulfox	-[a]	-[a]
j	Solvent-like	-[a]	-[a]
k	Solvent-like	-[a]	-[a]

[a] no odor.

However, we can say that the olfactory test results of thiazole-4-carboxylates **79a-j** are slightly much better than those of **78** derivatives. When they are tested fresh, the products **79a,d,h,i**,**j** exhibited solvent-like odor type and products **78b,c,e** had no specific odor. Besides, when fresh or tested after 4-24 hour, the products **79f** and **79g** presented earthy and heliotropine-vanilic type odors, respectively and it is understood that they are not volatile compounds.

Only two thiazole-4-carboxylate products **79f**, **79g** have a potentialto be some fragrant compounds (Figure 4.10).

Table 3.6. Olfactory test results for thiazole-4-carboxylates **79a-j**.

Test sample	Odor description		
79	Fresh	4 hour	24 hour
a	Solvent like	-[a]	-[a]
b	-[a]	-[a]	-[a]
c	-[a]	-[a]	-[a]
d	Solvent like	-[a]	-[a]
e	-[a]	-[a]	-[a]
f	Earthy	Earthy	Earthy
g	heliotropine, vanillic	heliotropine, vanillic	-[a]
h	Solvent like	-[a]	-[a]
i	Solvent like	-[a]	-[a]
j	Solvent like	-[a]	-[a]

[a] No odor.

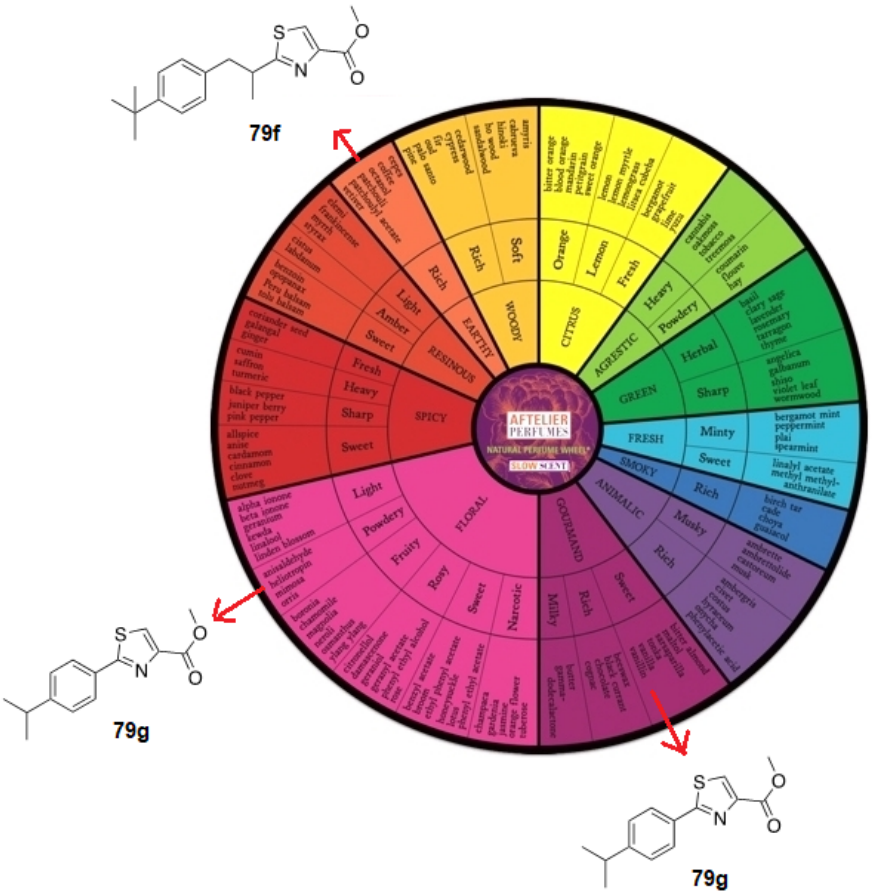


Figure 3.10. Odor characteristics of products **79f, 79g** on fragrance wheel.

5. CONCLUSIONS

In summary, some conclusions can be drawn for this thesis study as given below.

In the first part of the study, starting from fragrant aldehydes, a variety of main precursors, imidate compounds **77a-k** have been prepared in moderate to good yields over a reaction series including oxime and nitrile formation and imidate synthesis, respectively. And their structures were characterized using IR spectroscopy and also supported by physical analysis data.

In the second part of the study, target compounds, thiazoline-4-carboxylates **78a-j** and one unexpected product **78k** were synthesized and isolated in moderate to good yields via the base-catalyzed cyclocondensation reactions of imidates **77a-k** with L-cysteine methyl ester. The structures of thiazoline products **78a-k** were characterized by means of physical data and IR, ^{1}H-NMR, ^{13}C-NMR and HRMS analyses.

Subsequently, in the third part of study, thiazoline-4-carboxylates **78** were converted into corresponding thiazole-4-carboxylates **79a-j** efficiently via an oxidation reaction under basic conditions. The structures of thiazole-4-carboxylates **79a-k** were also characterized by means of physical data and IR, ^{1}H-NMR, ^{13}C-NMR and HRMS analyses.

In the last part of the study, all the products **78**,**79** were subjected to olfactory tests by expert noses to specify their odor types and scent compound potential. Result of olfactory tests showed that thiazoline-4-carboxylates **78** had no significant odor characteristics, however, two of thiazole-4-carboxylates **79f,79g** presented some top and heart notes like earthy, heliotropine, vanillic and also seen that these compounds have not much volatile characteristic

6. REFERENCES

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7. APPENDICES

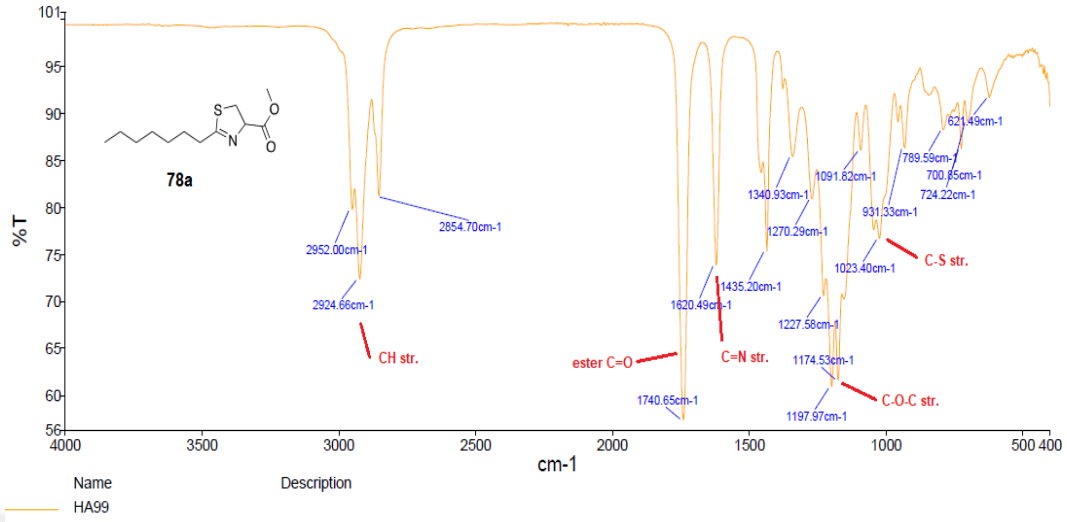

Figure 7.1. IR spectrum of thiazoline-4-carboxylates **78a**.

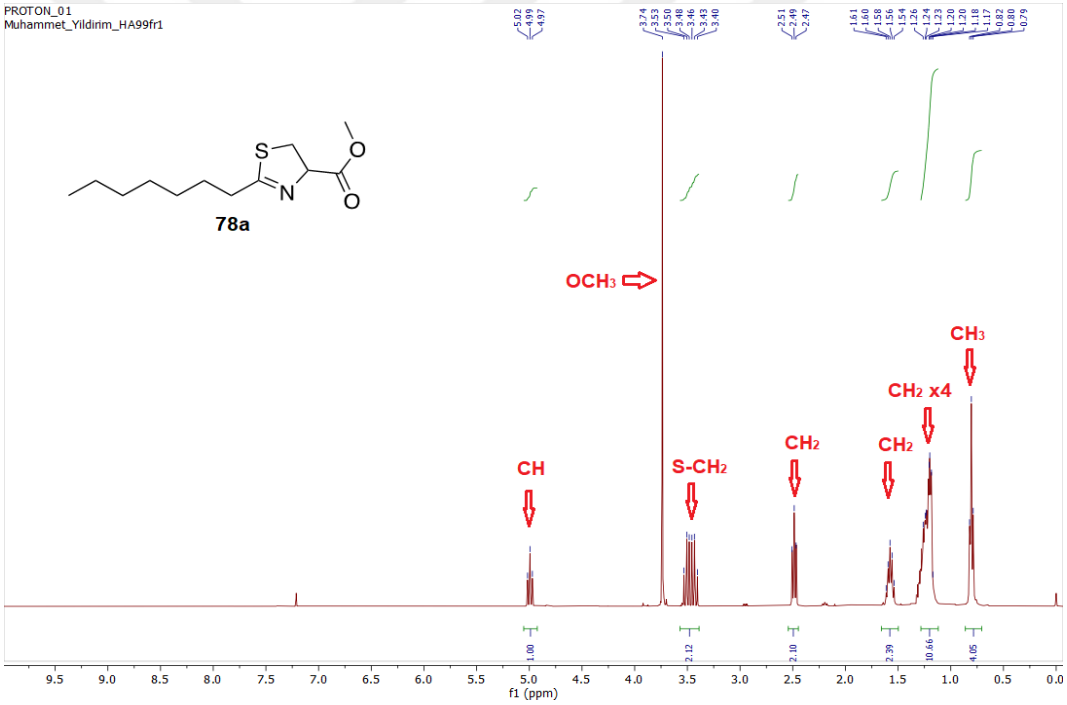

Figure 7.2. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78a**.

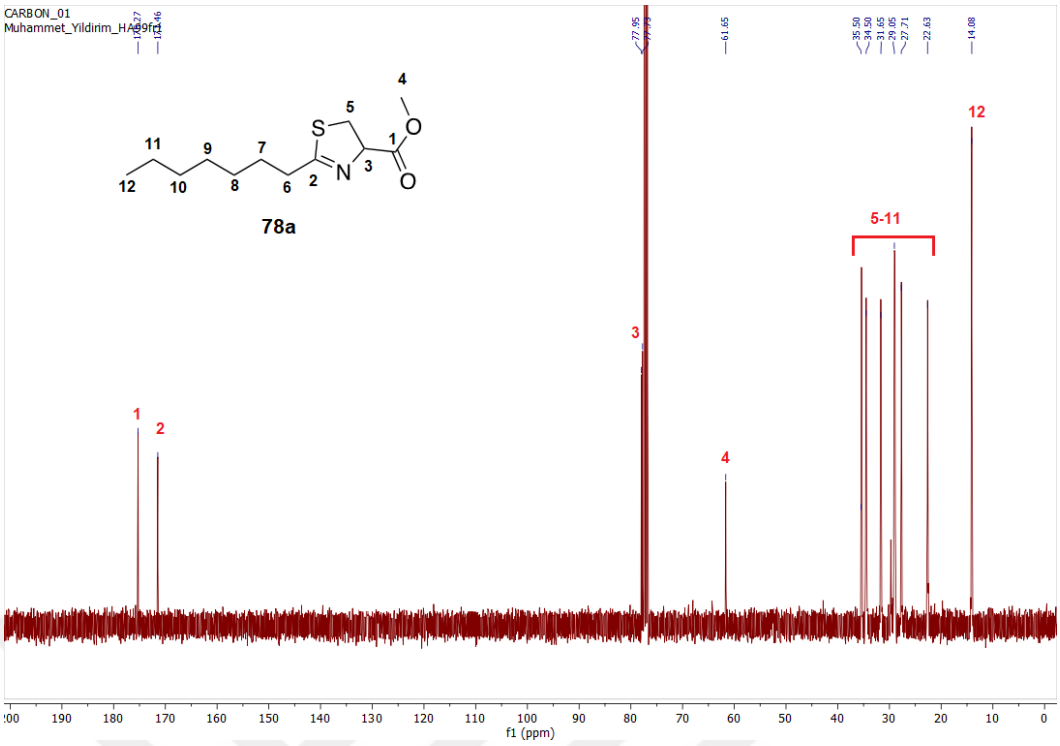

Figure 7.3. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78a**.

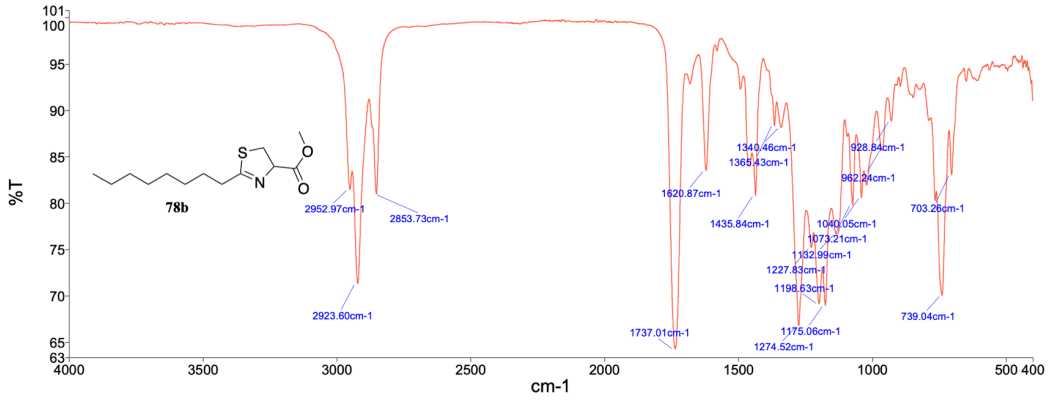

Figure 7.4 IR spectrum of thiazoline-4-carboxylates **78b**.

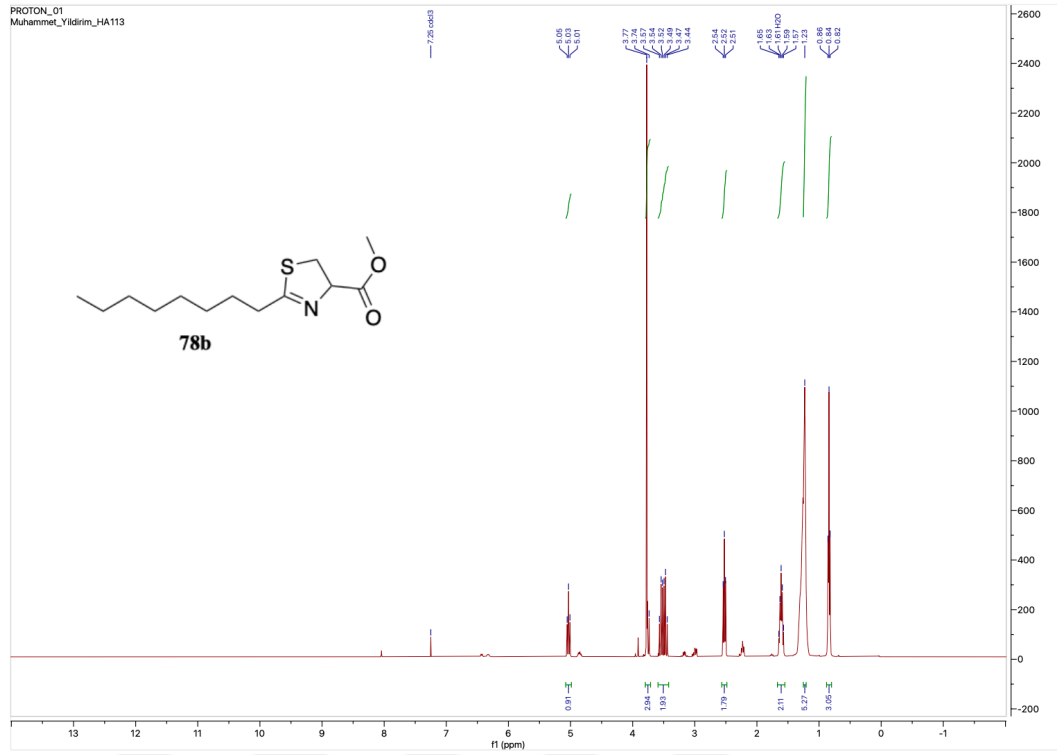

Figure 7.5. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78b**.

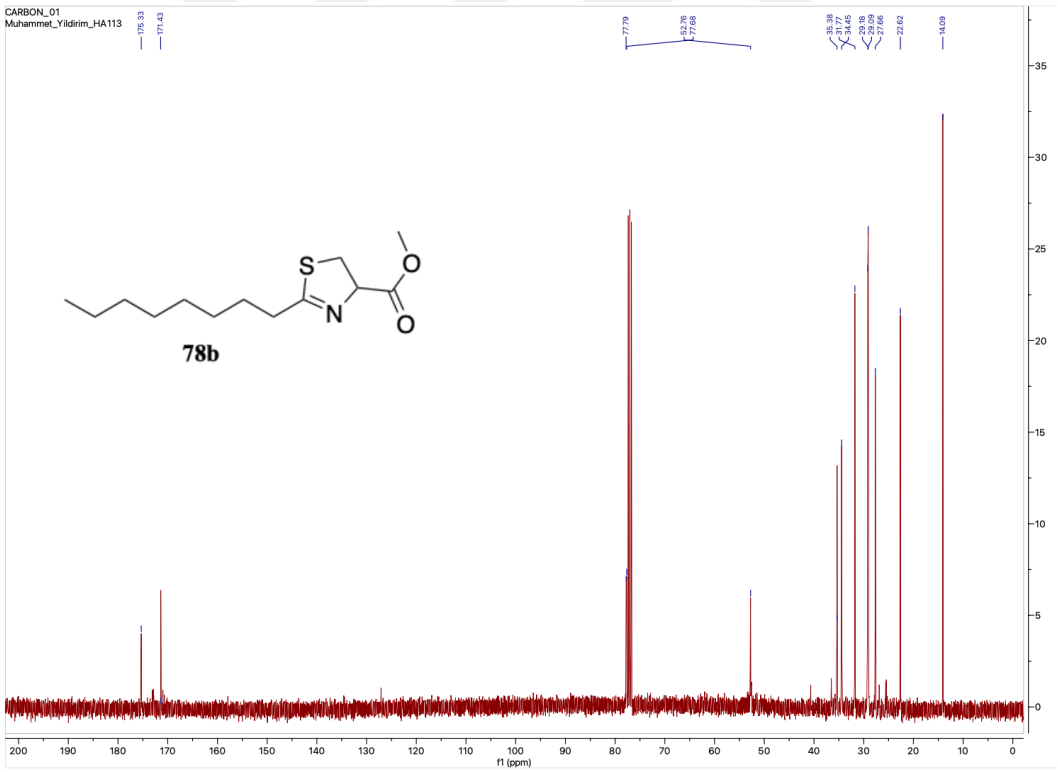

Figure 7.6. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78b**.

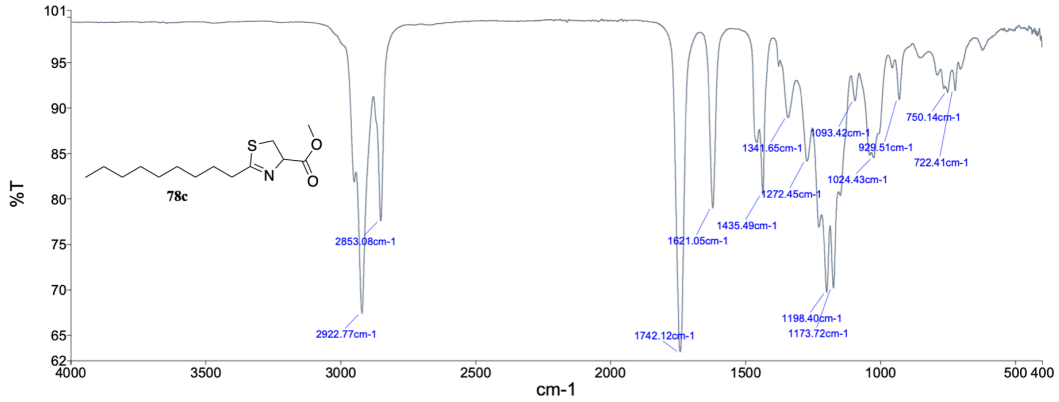

Figure 7.7. IR spectrum of thiazoline-4-carboxylates **78c**.

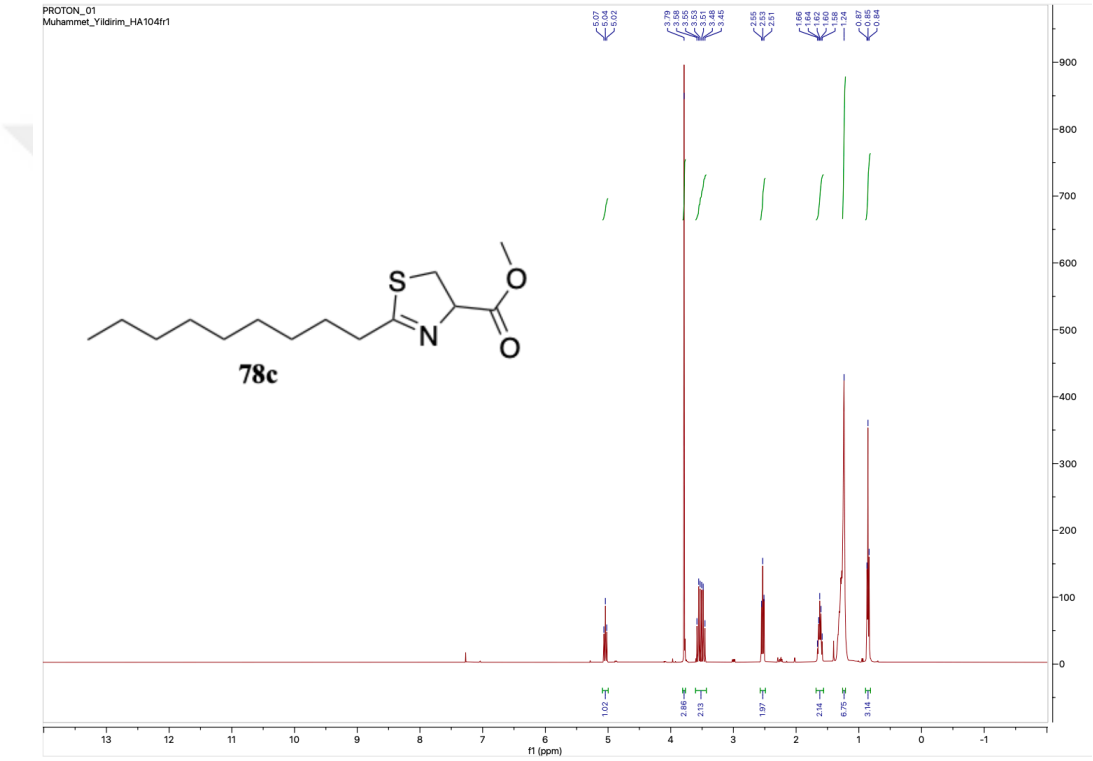

Figure 7.8. [1]H-NMR spectrum of thiazoline-4-carboxylates **78c**.

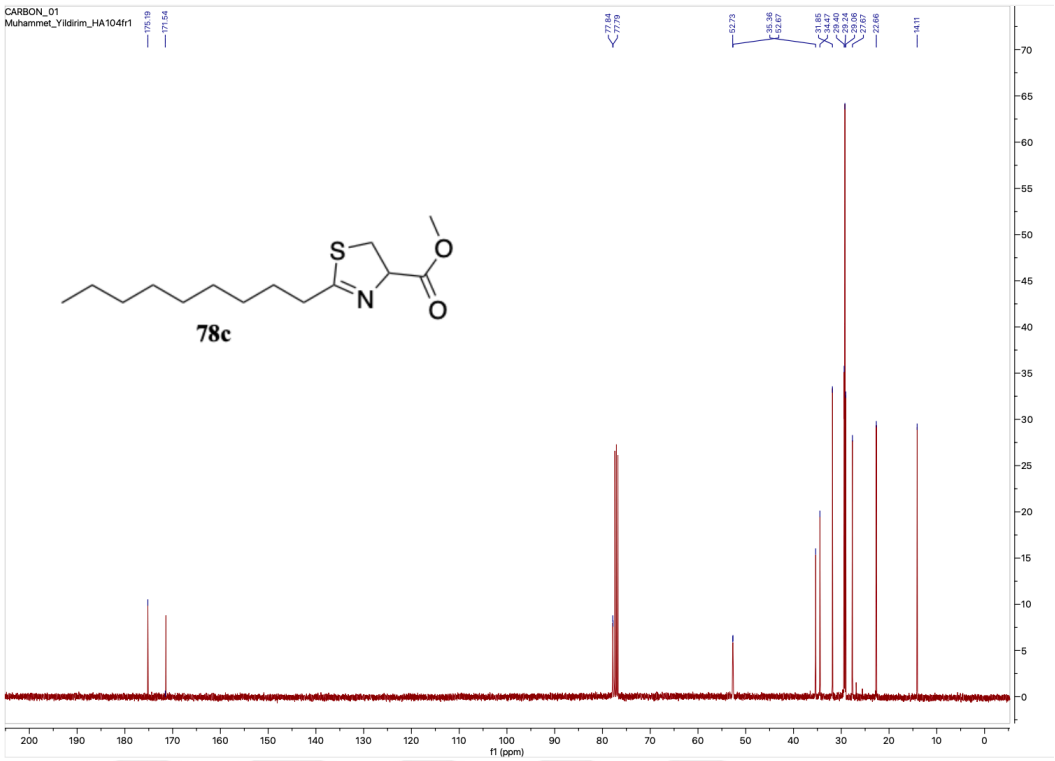

Figure 7.9. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78c**.

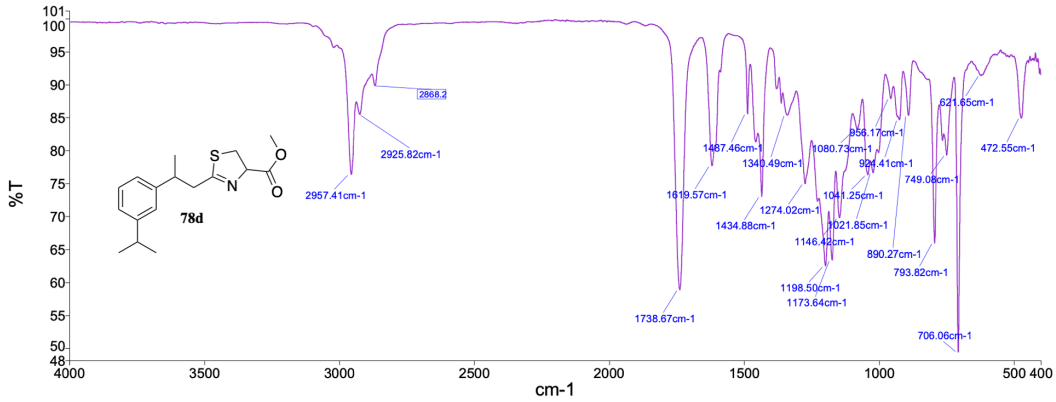

Figure 7.10 IR spectrum of thiazoline-4-carboxylates **78d**.

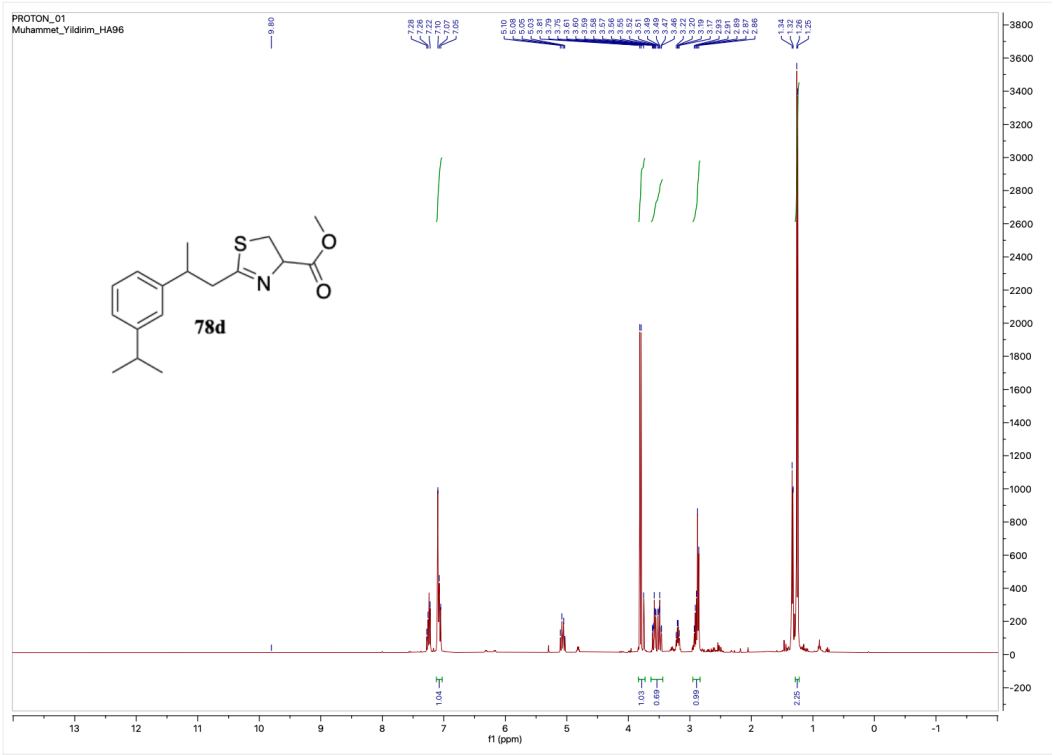

Figure 7.11. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78d**.

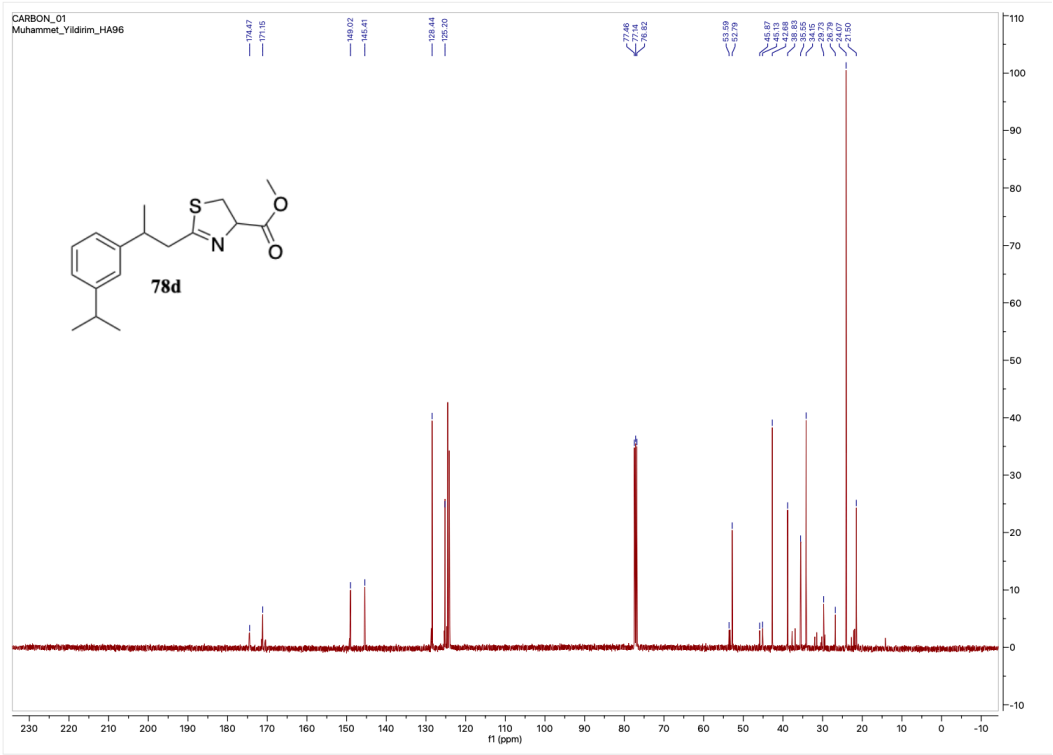

Figure 7.12. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78d**.

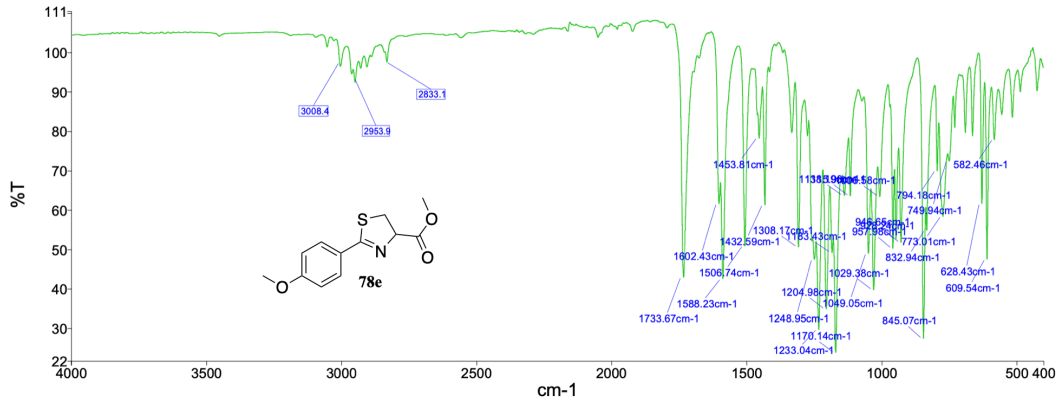

Figure 7.13. IR spectrum of thiazoline-4-carboxylates **78e**.

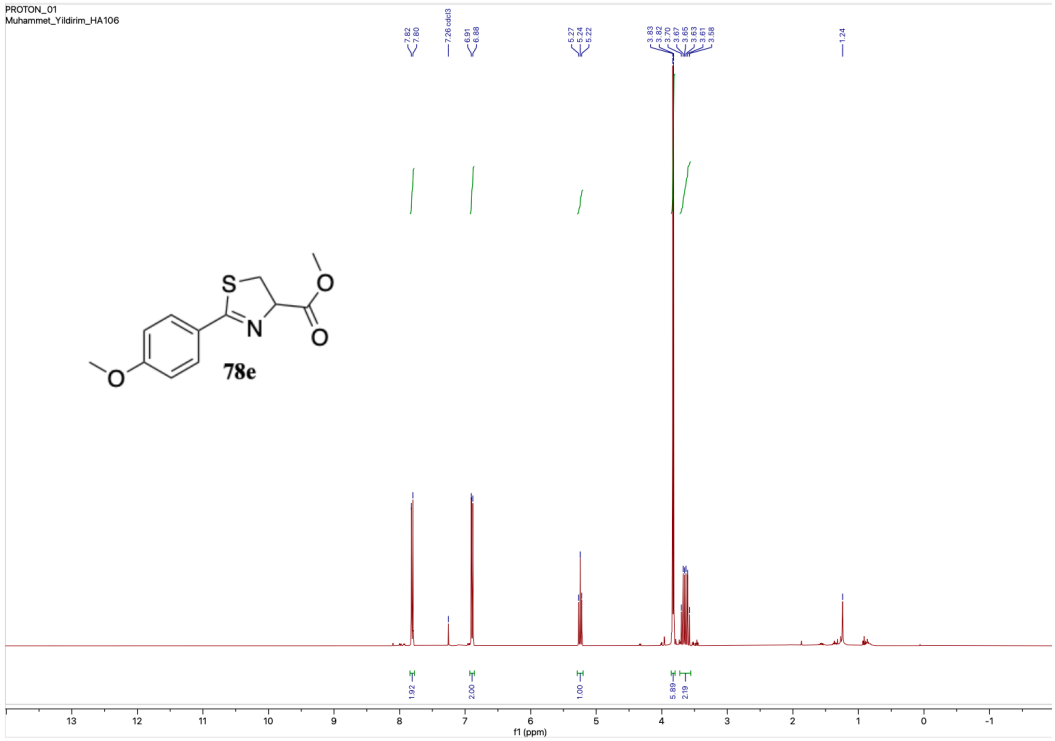

Figure 7.14. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78e**.

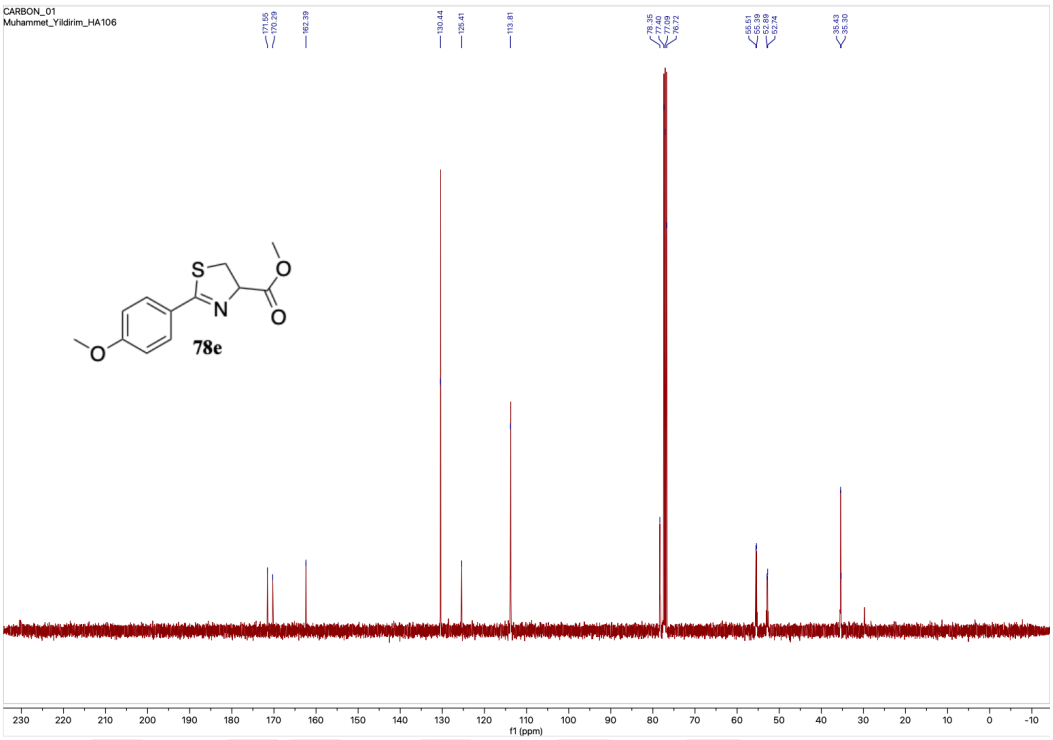

Figure 7.15. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78e**.

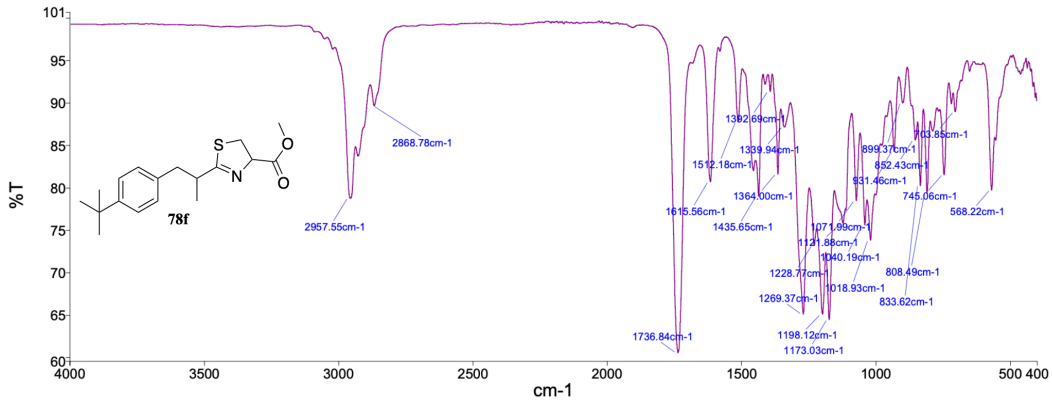

Figure 7.16. IR spectrum of thiazoline-4-carboxylates **78f**.

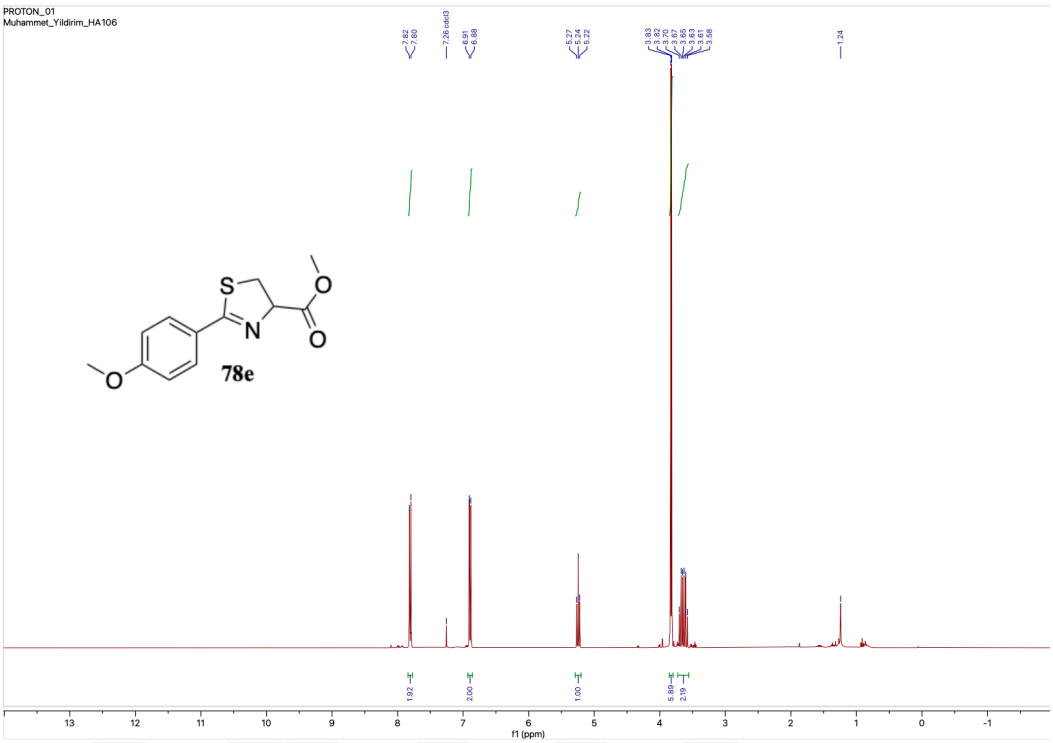

Figure 7.17. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78f**.

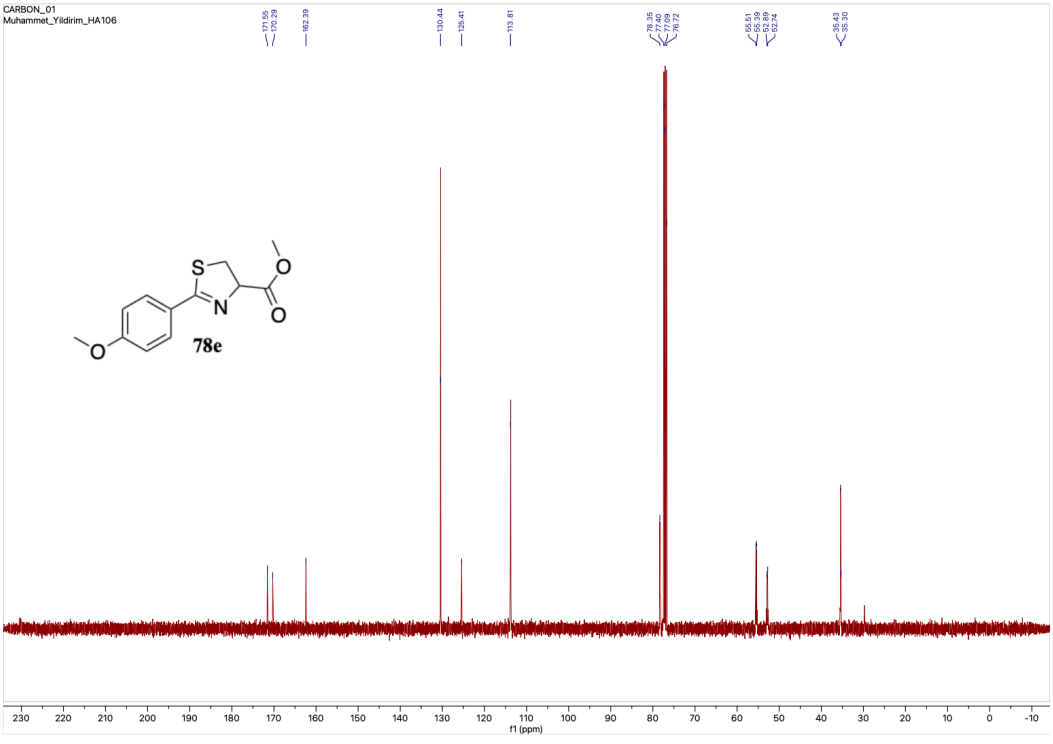

Figure 7.18. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78e**.

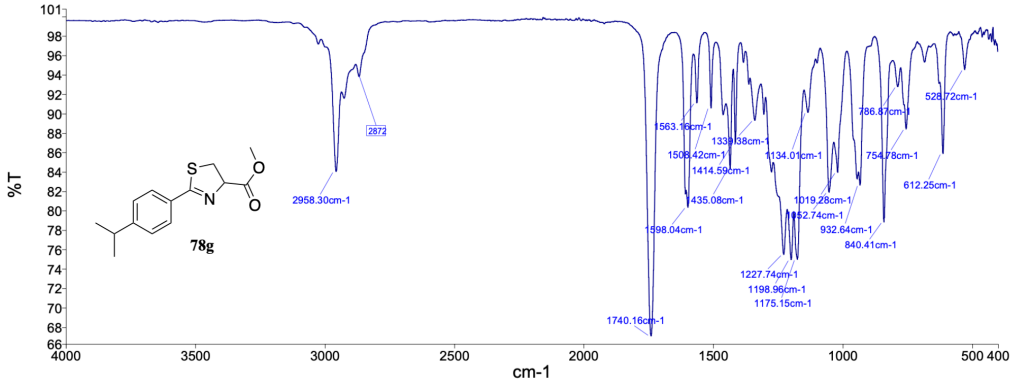

Figure 7.19. IR spectrum of thiazoline-4-carboxylates **78g**.

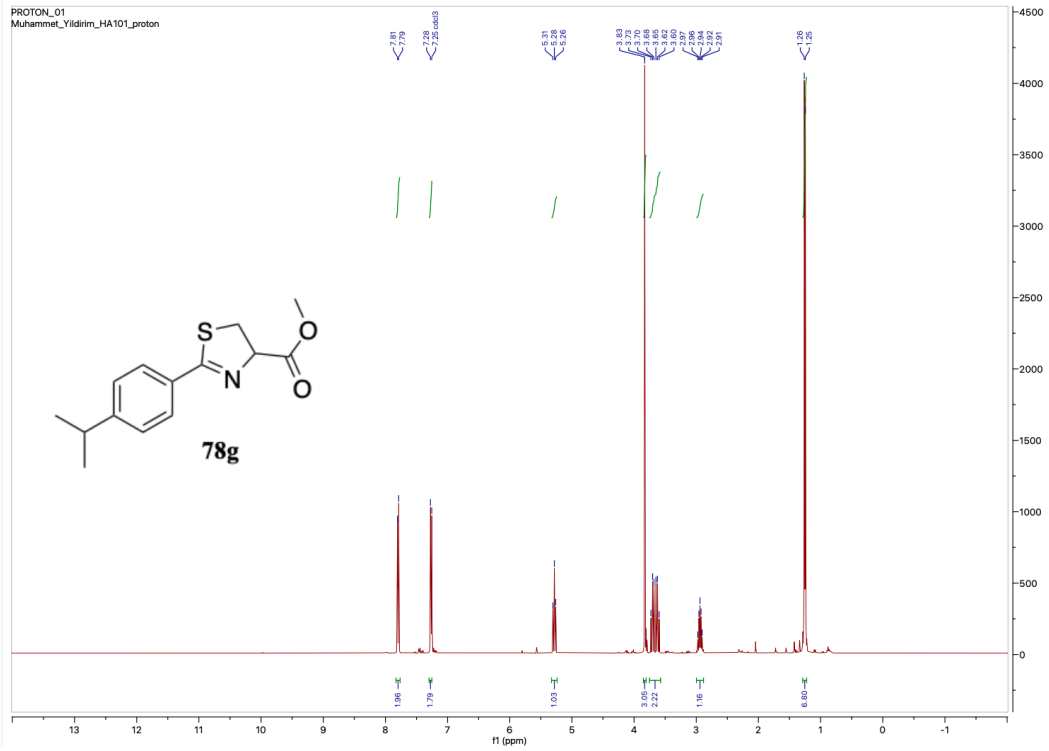

Figure 7.20. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78g**.

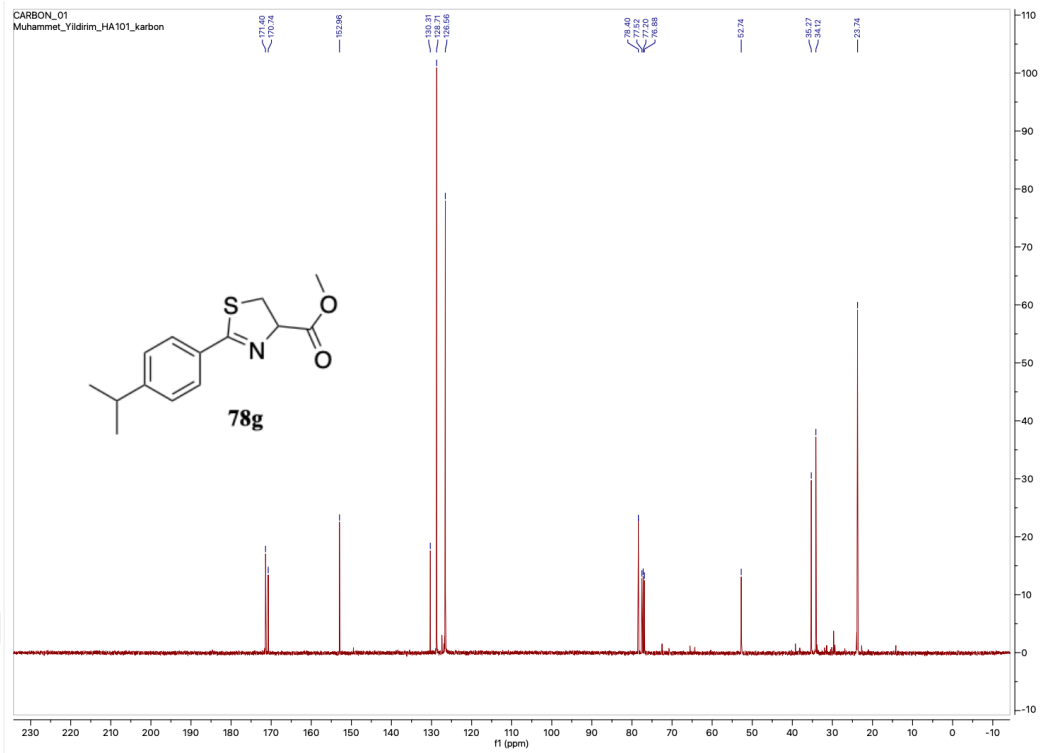

Figure 7.21. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78g**.

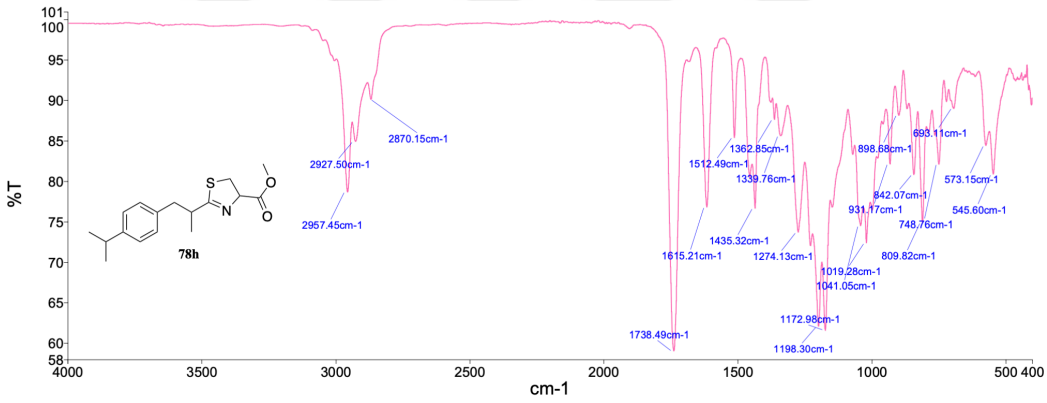

Figure 7.22. IR spectrum of thiazoline-4-carboxylates **78h**.

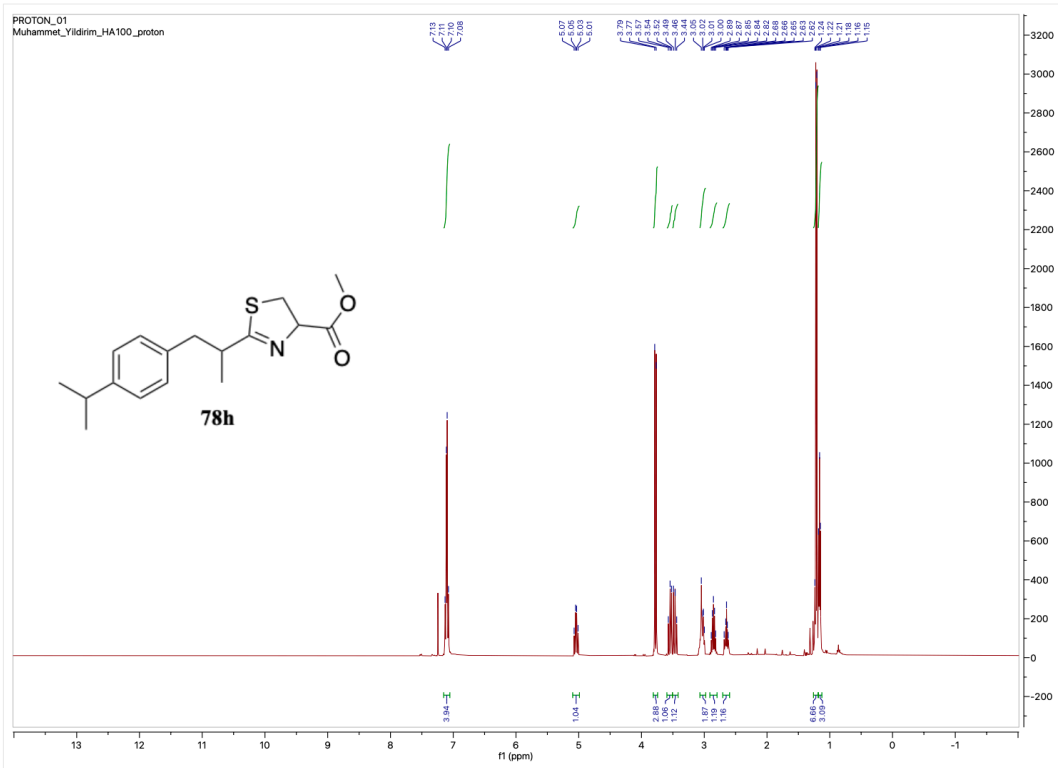

Figure 7.23. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78h**.

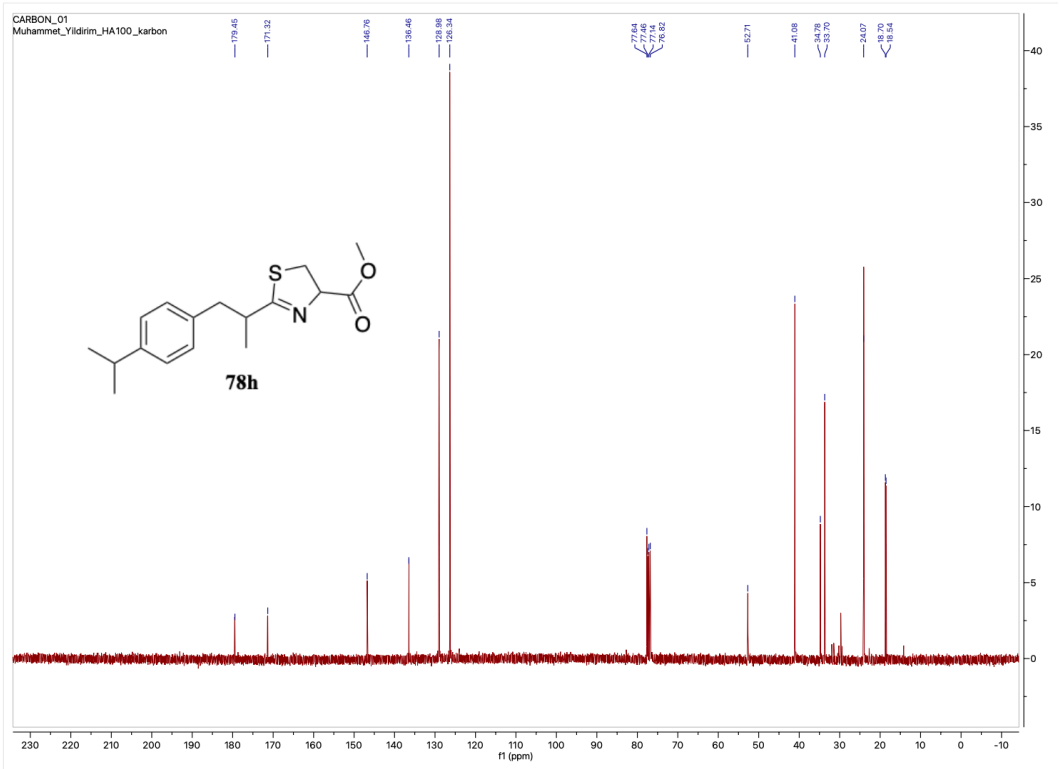

Figure 7.24. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78h**.

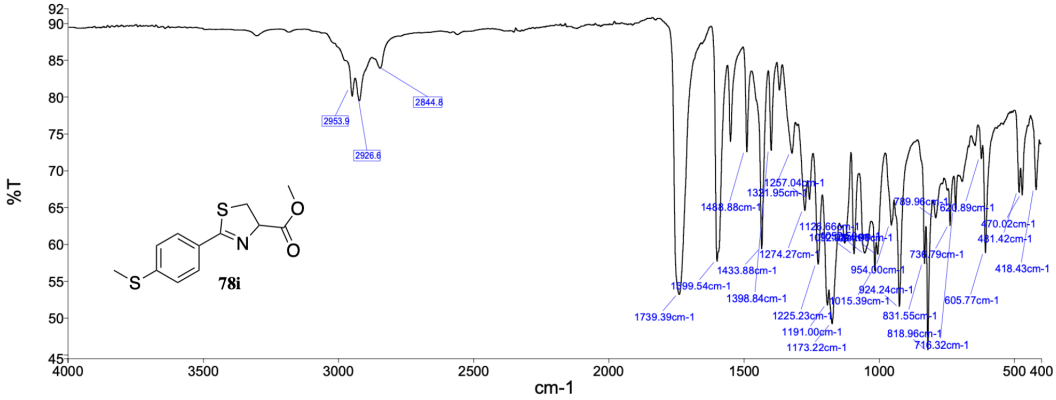

Figure 7.25. IR spectrum of thiazoline-4-carboxylates **78i**.

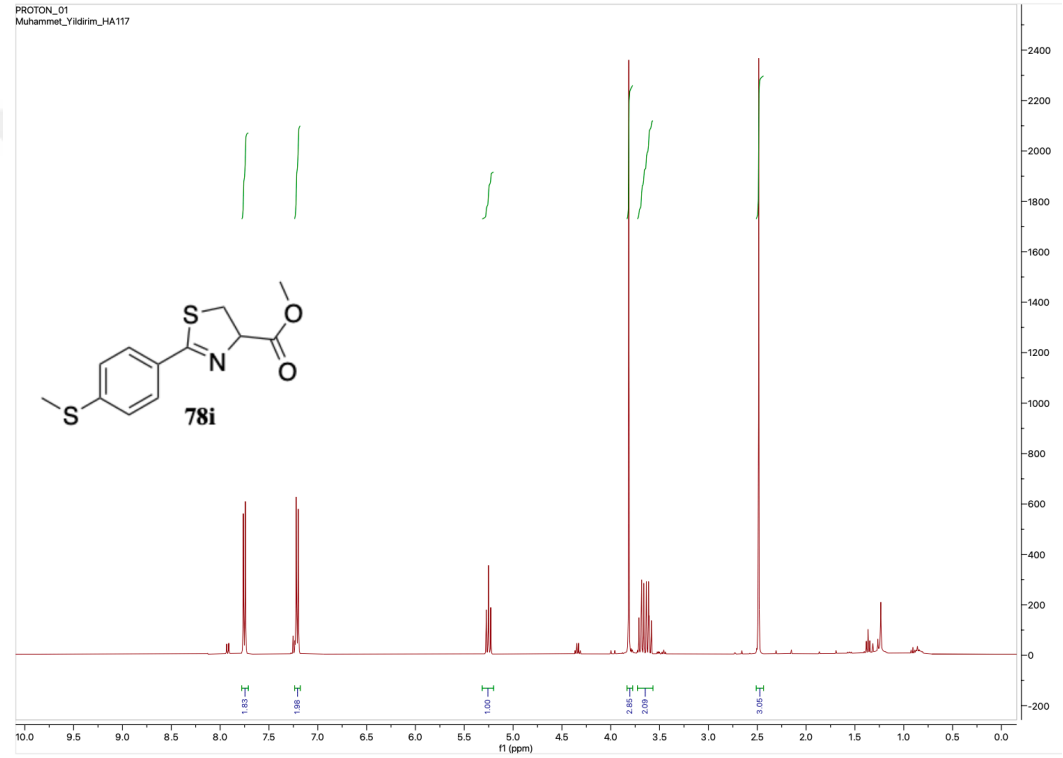

Figure 7.26. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78i**.

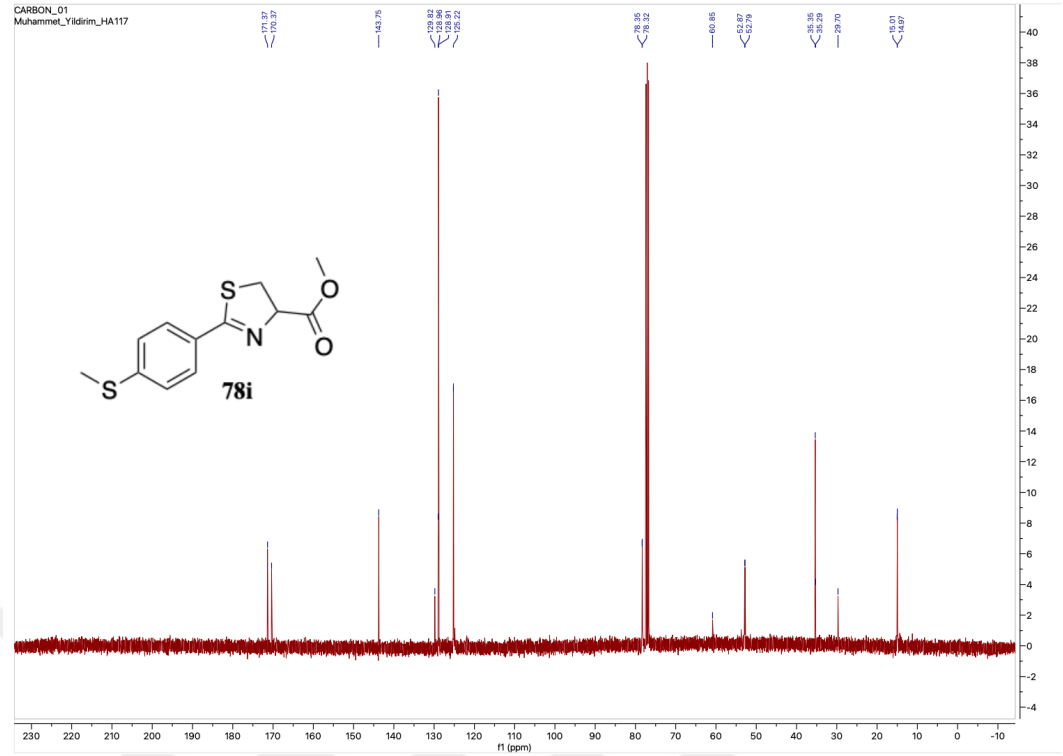

Figure 7.27. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78i**.

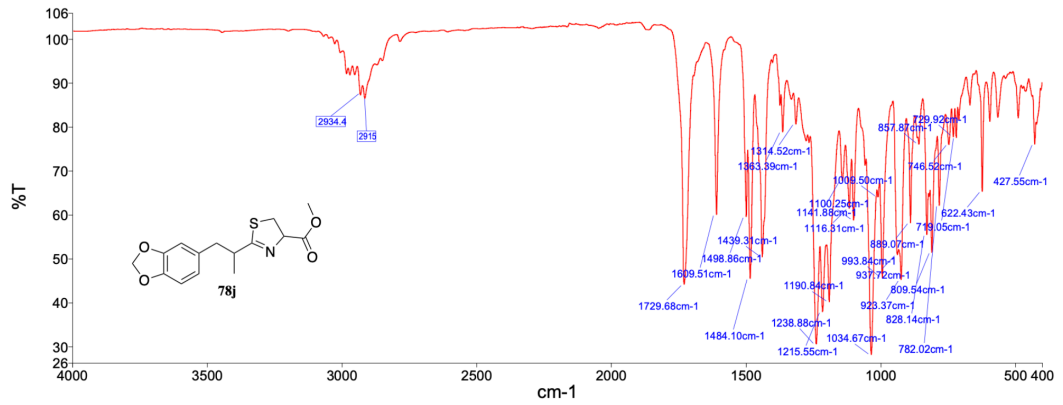

Figure 7.28. IR spectrum of thiazoline-4-carboxylates **78j**.

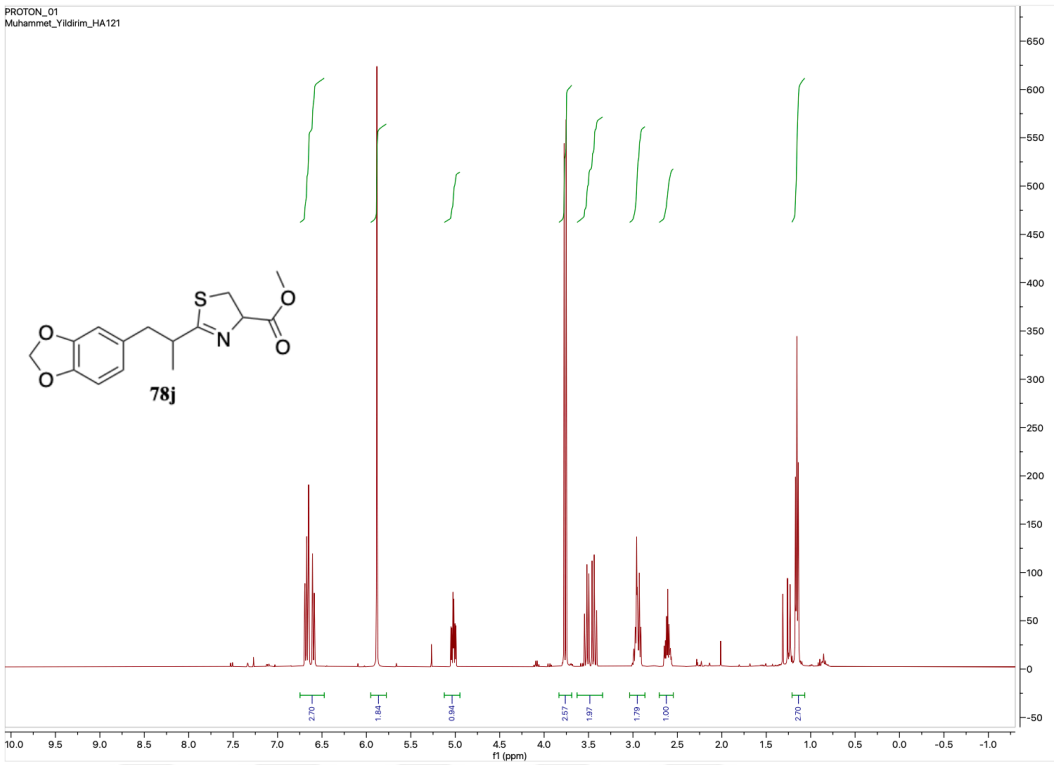

Figure 7.29. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78j**.

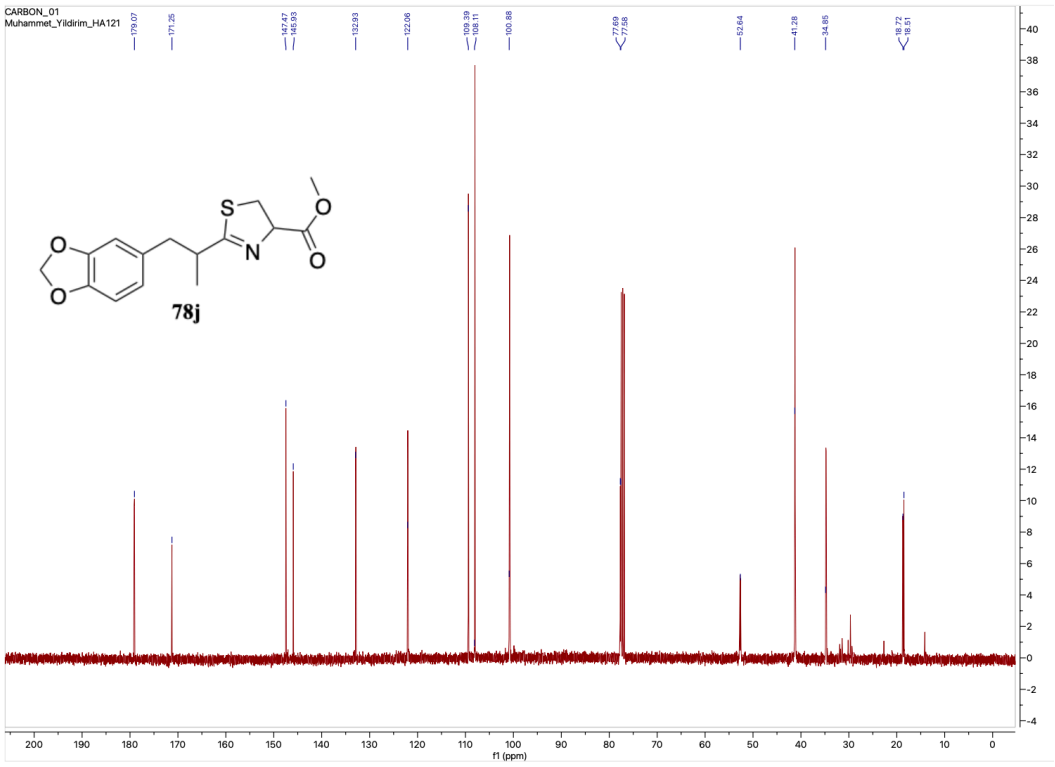

Figure 7.30. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78j**.

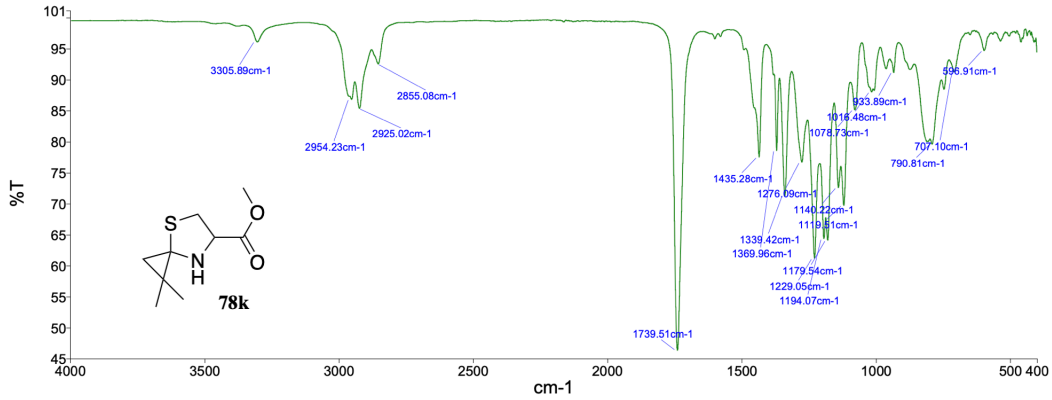

Figure 7.31. IR spectrum of thiazoline-4-carboxylates **78k**.

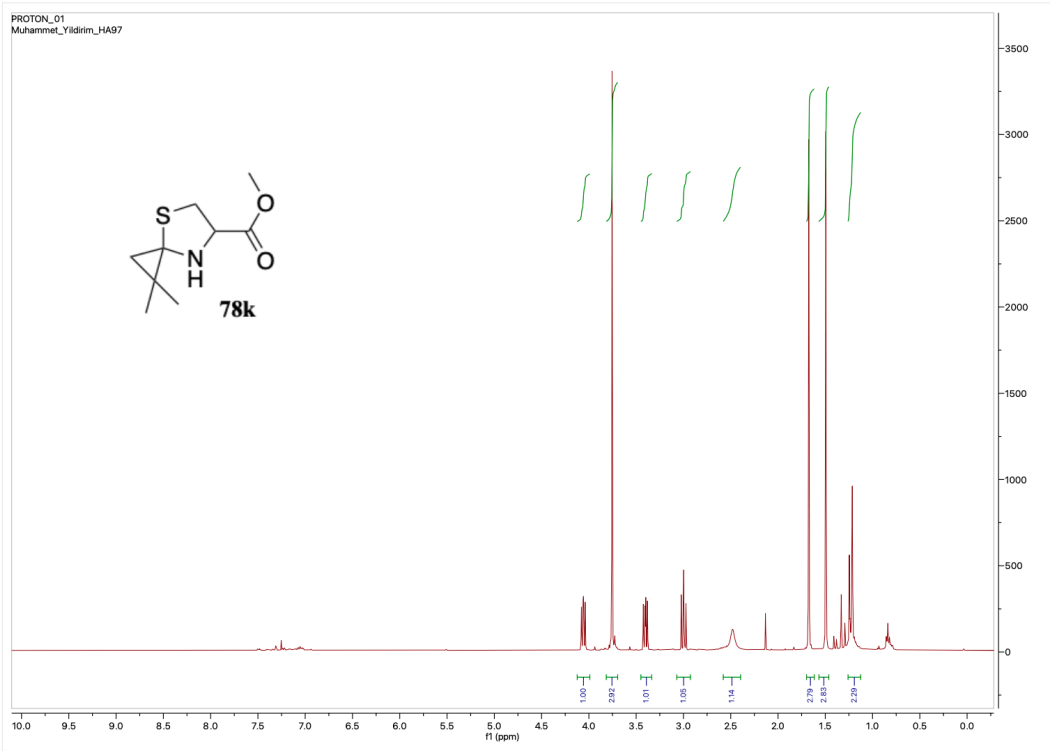

Figure 7.32. ^{1}H-NMR spectrum of thiazoline-4-carboxylates **78k**.

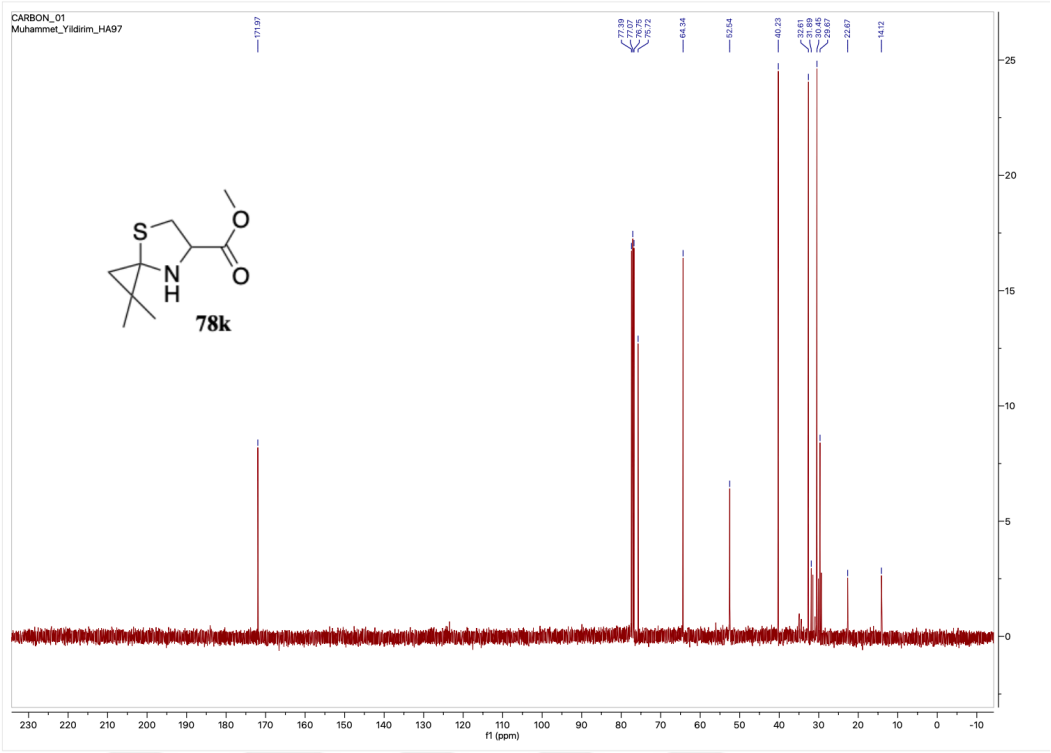

Figure 7.33. ^{13}C-NMR spectrum of thiazoline-4-carboxylates **78k**.

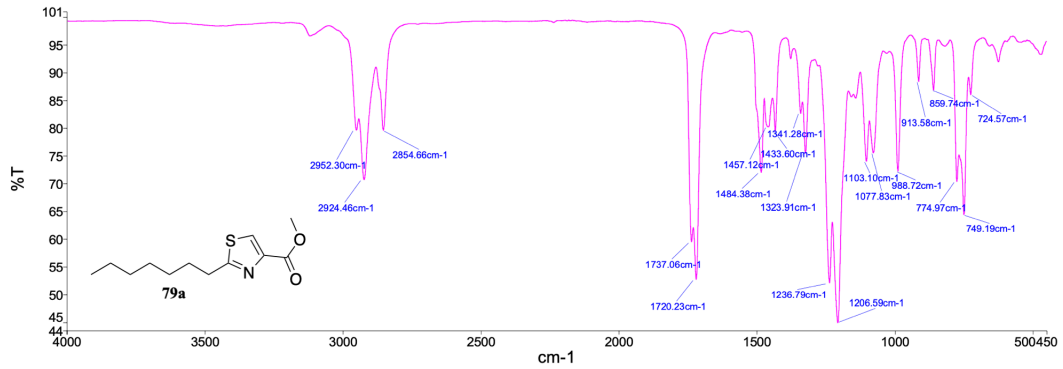

Figure 7.34. IR spectrum of thiazole-4-carboxylates **79a**.

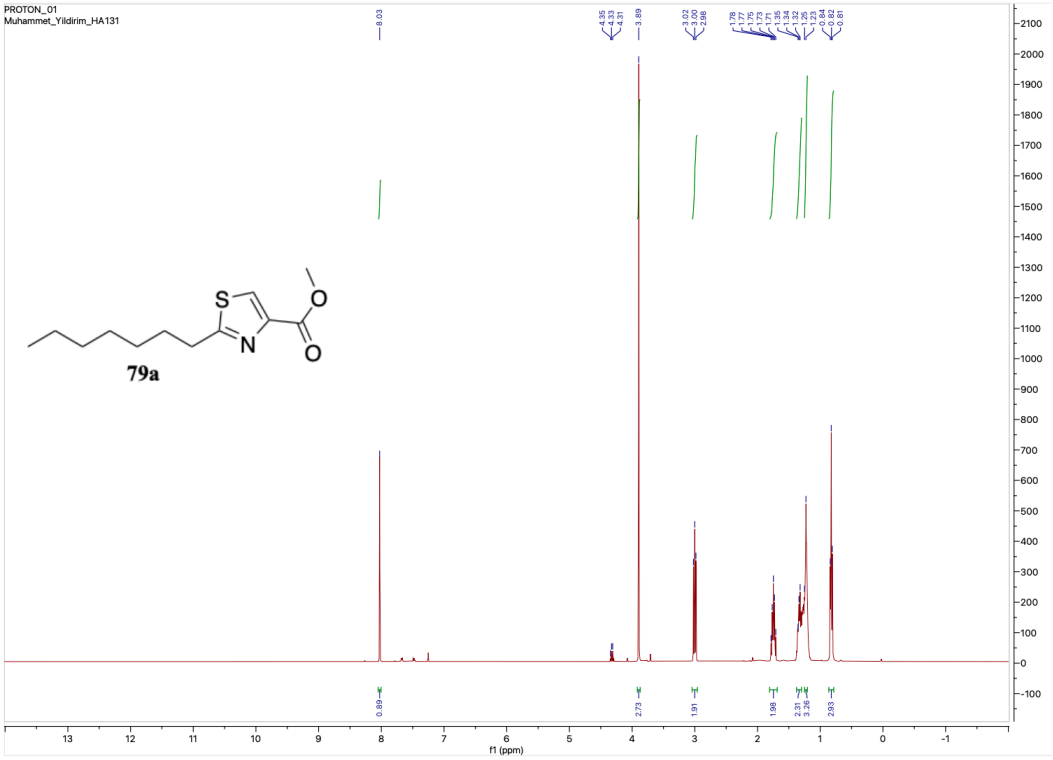

Figure 7.35. ^{1}H-NMR spectrum of thiazole-4-carboxylates **79a**.

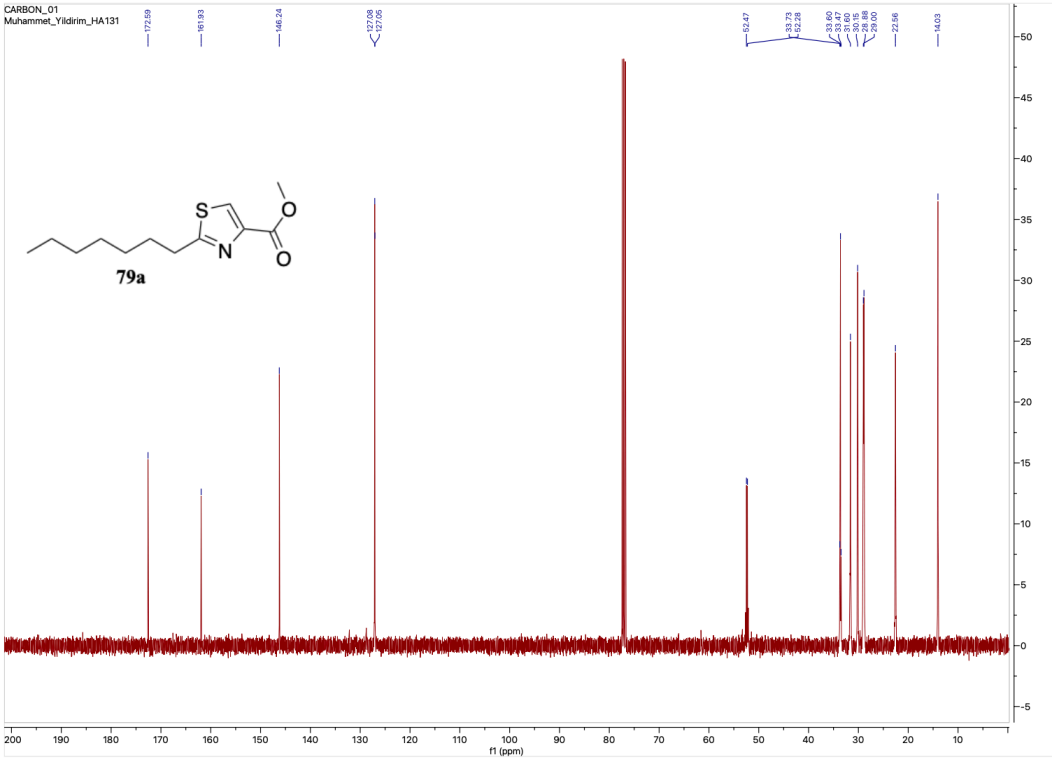

Figure 7.36. ^{13}C-NMR spectrum of thiazole-4-carboxylates **79a**.

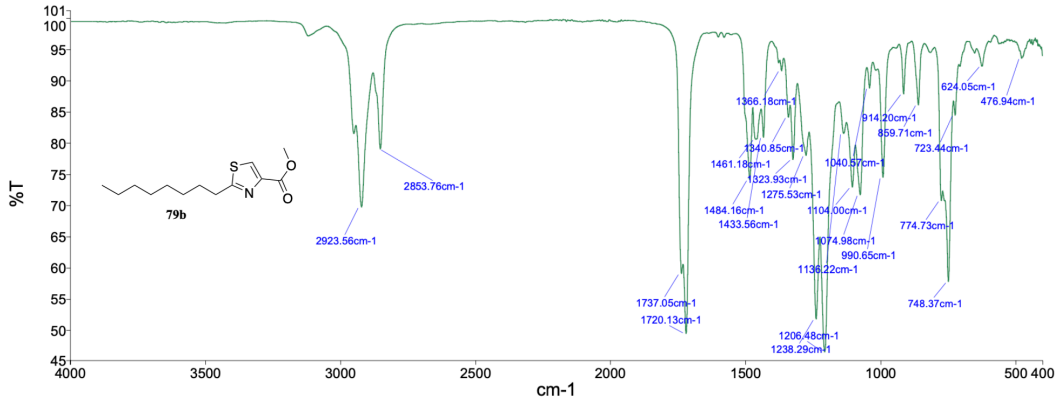

Figure 7.37. IR spectrum of thiazole-4-carboxylates **79b**.

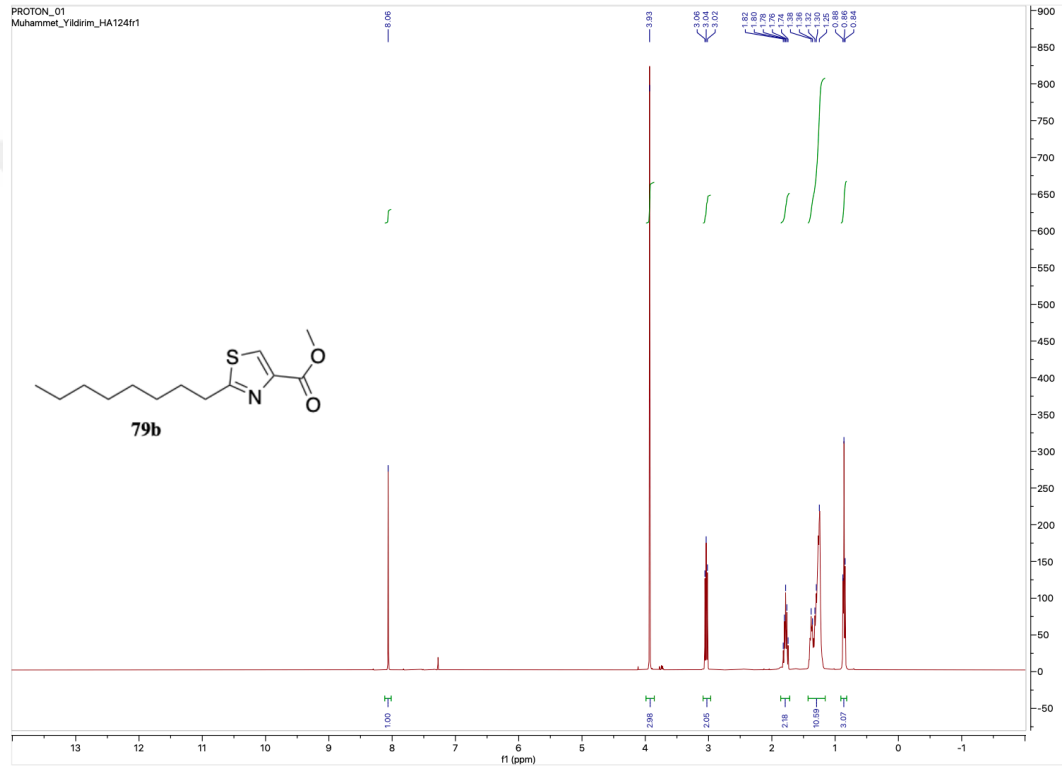

Figure 7.38. ^{1}H-NMR spectrum of thiazole-4-carboxylates **79b**.

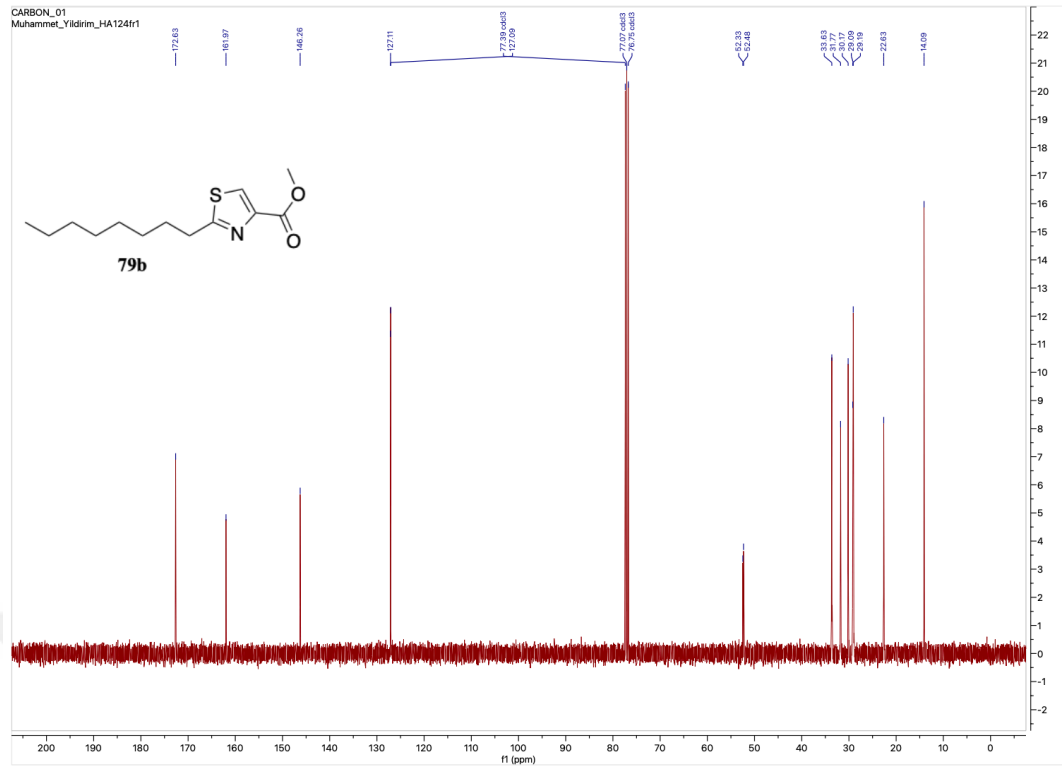

Figure 7.39. ^{13}C-NMR spectrum of thiazole-4-carboxylates **79b**.

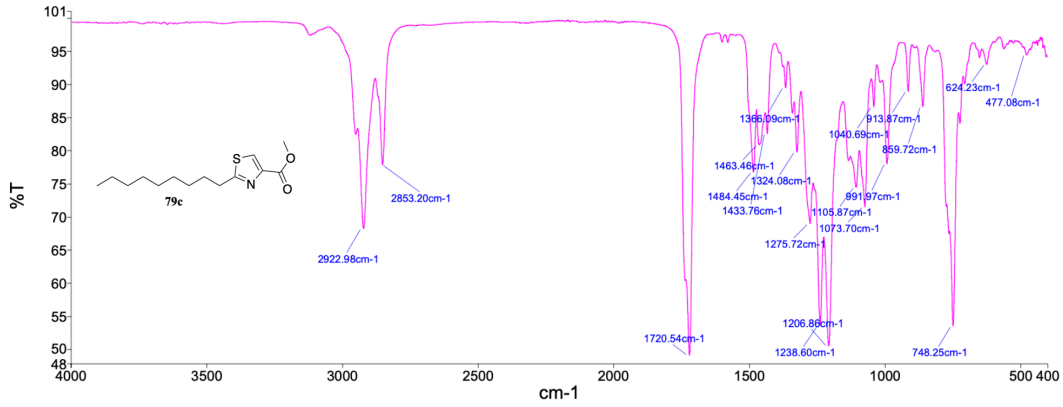

Figure 7.40. IR spectrum of thiazole-4-carboxylates **79c**.

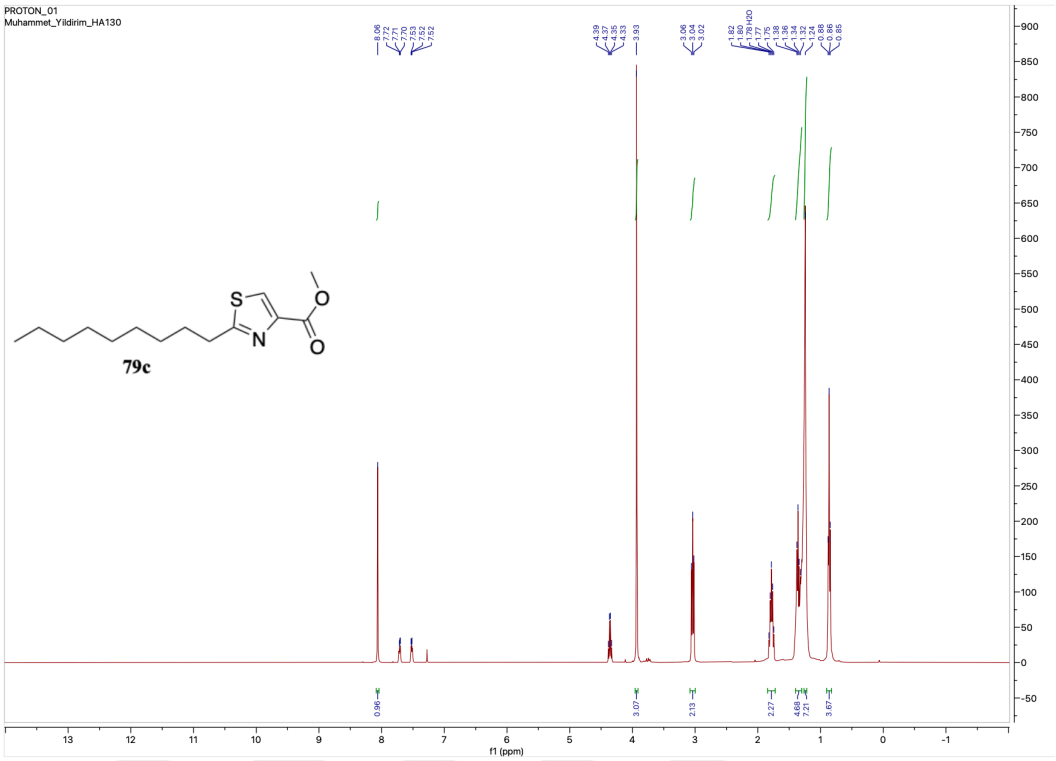

Figure 7.41. ^{1}H-NMR spectrum of thiazole-4-carboxylates **79c**.

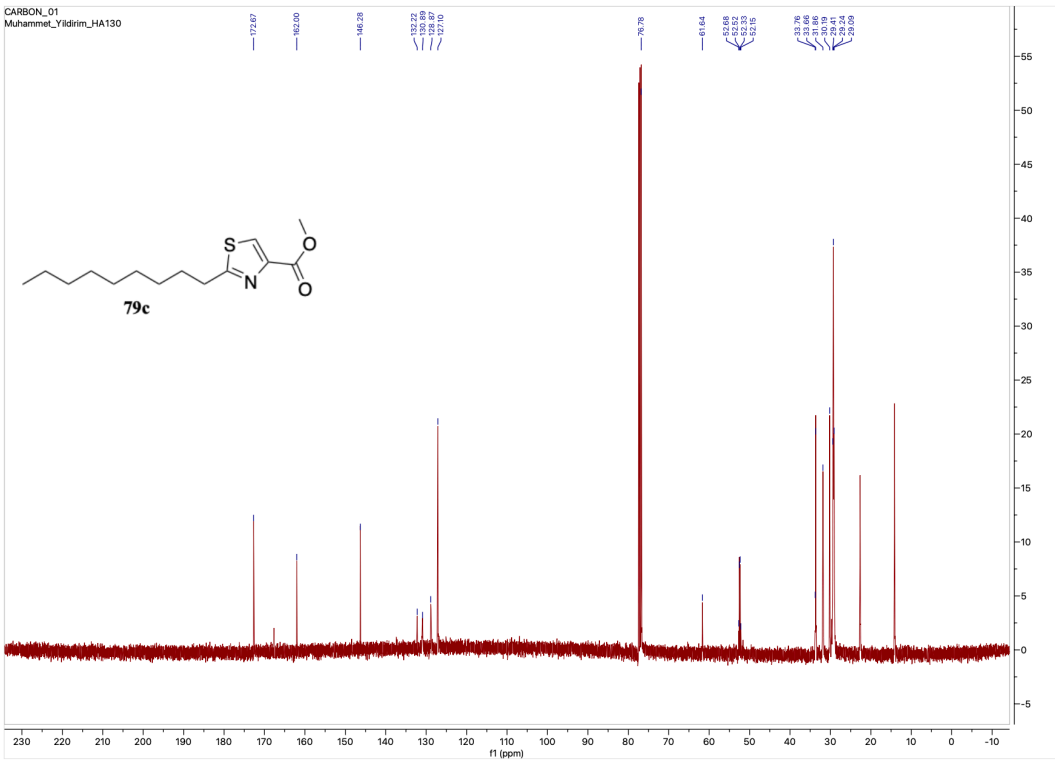

Figure 7.42. ^{13}C-NMR spectrum of thiazole-4-carboxylates **79c**.

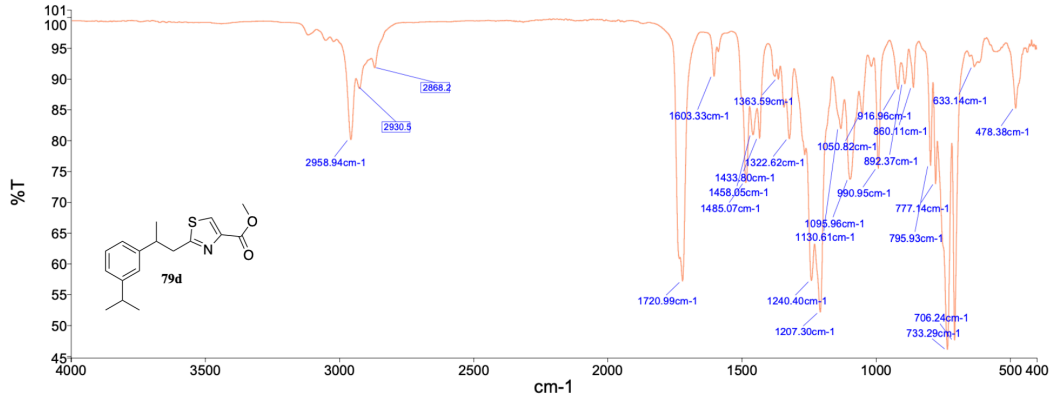

Figure 7.43. IR spectrum of thiazole-4-carboxylates **79d**.

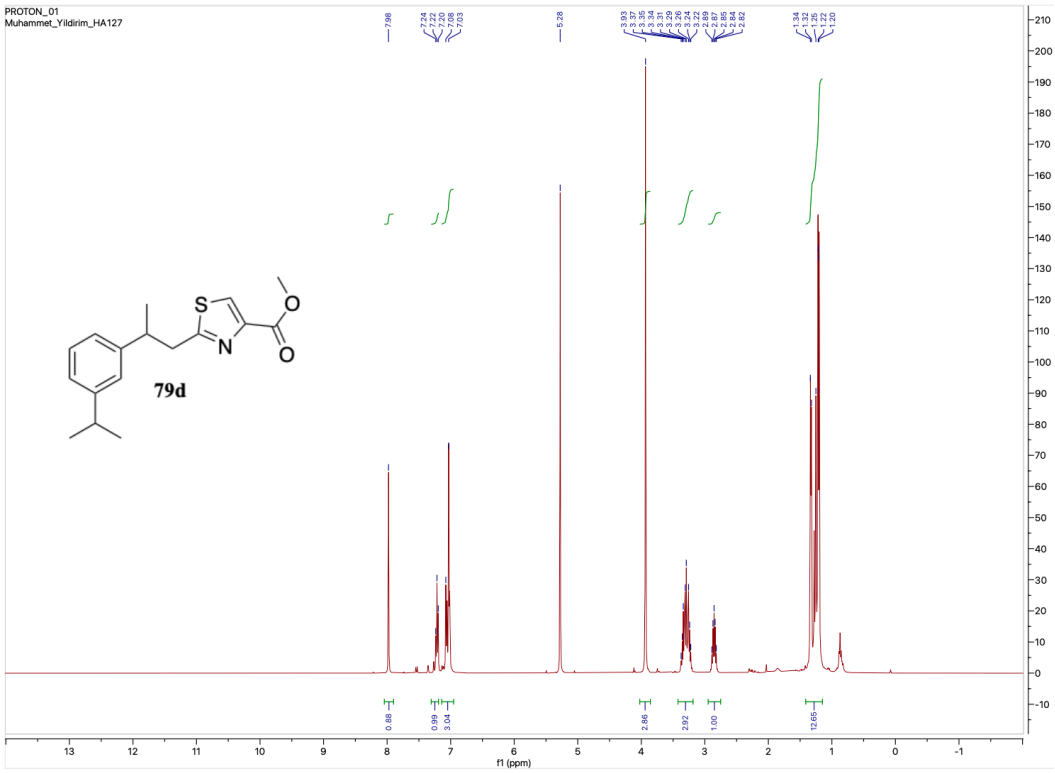

Figure 7.44. ^{1}H-NMR spectrum of thiazole-4-carboxylates **79d**.

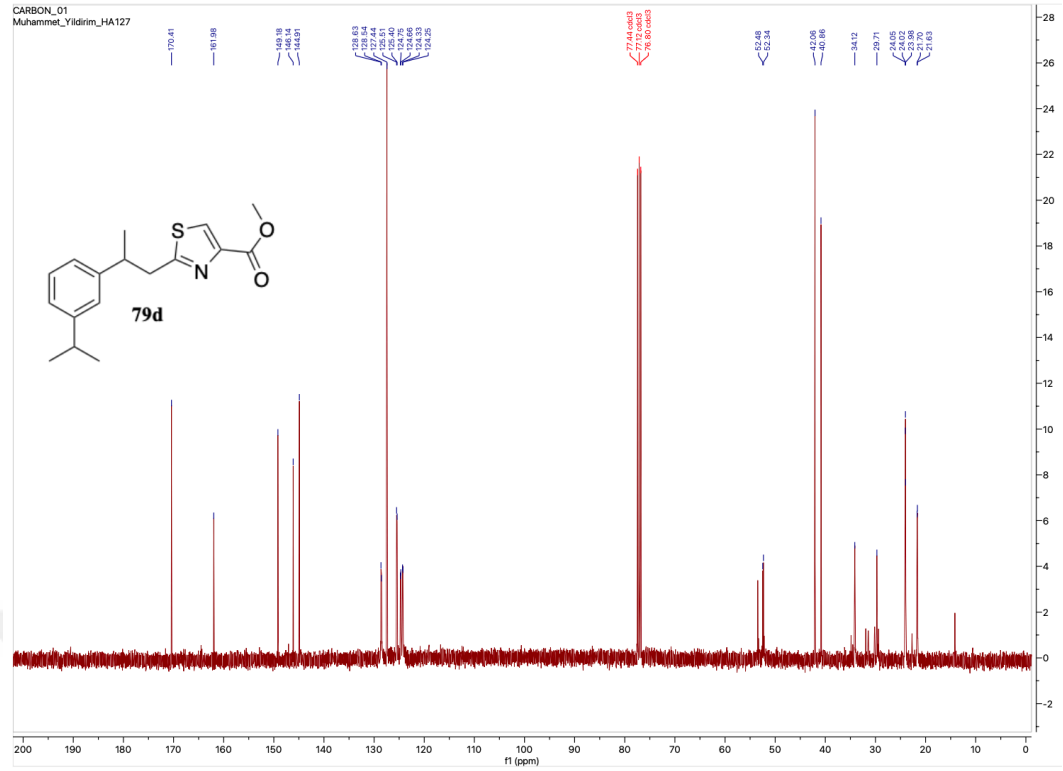

Figure 7.45. ^{13}C-NMR spectrum of thiazole-4-carboxylates **79d**.

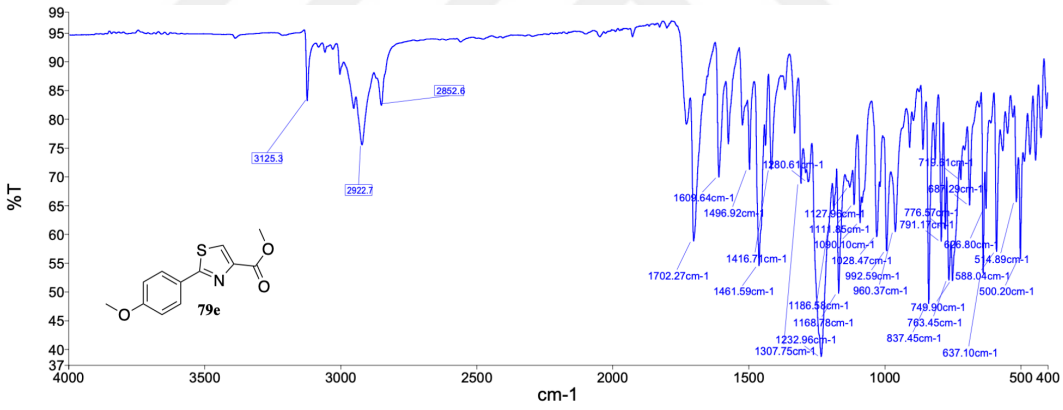

Figure 7.46. IR spectrum of thiazole-4-carboxylates **79e**.

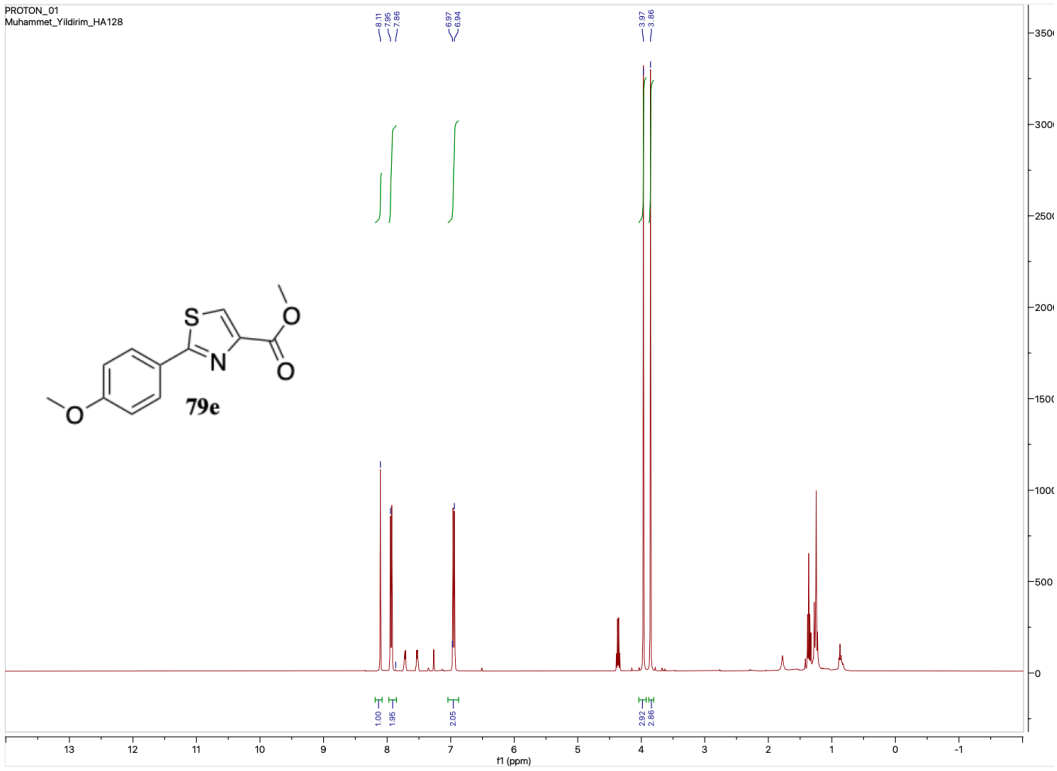

Figure 7.47. ^{1}H-NMR spectrum of thiazole-4-carboxylates **79e**.

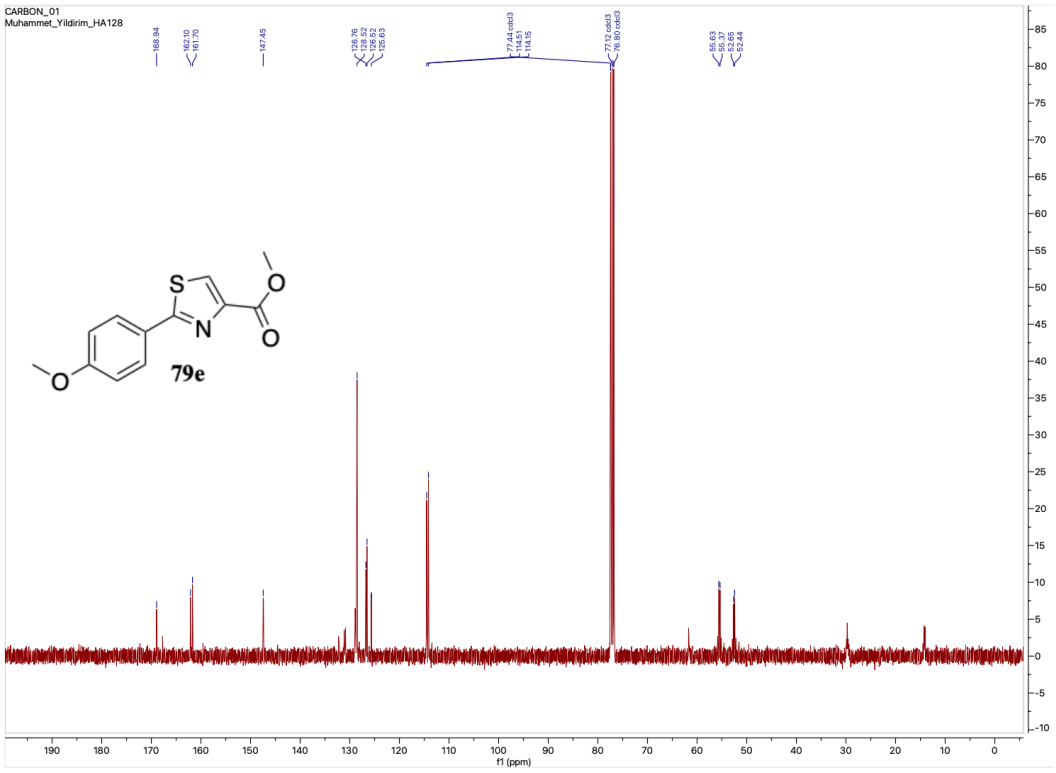

Figure 7.48. ^{13}C-NMR spectrum of thiazole-4-carboxylates **79e**.

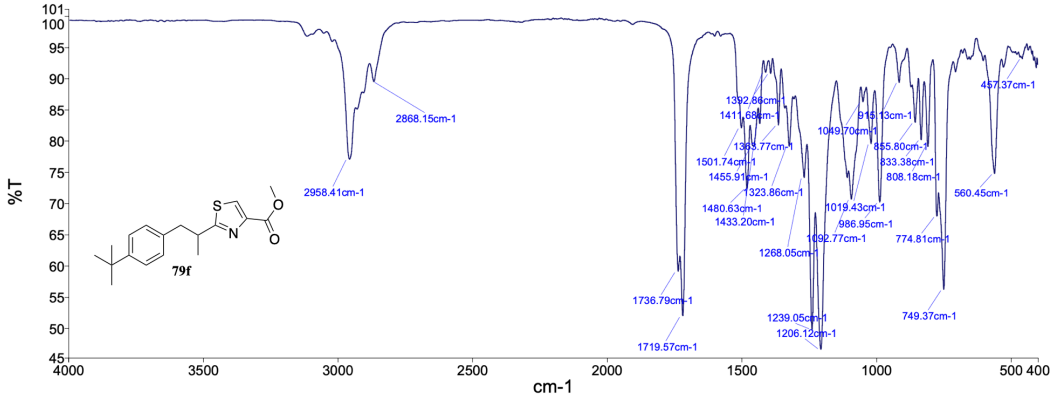

Figure 7.49. IR spectrum of thiazole-4-carboxylates **79f**.

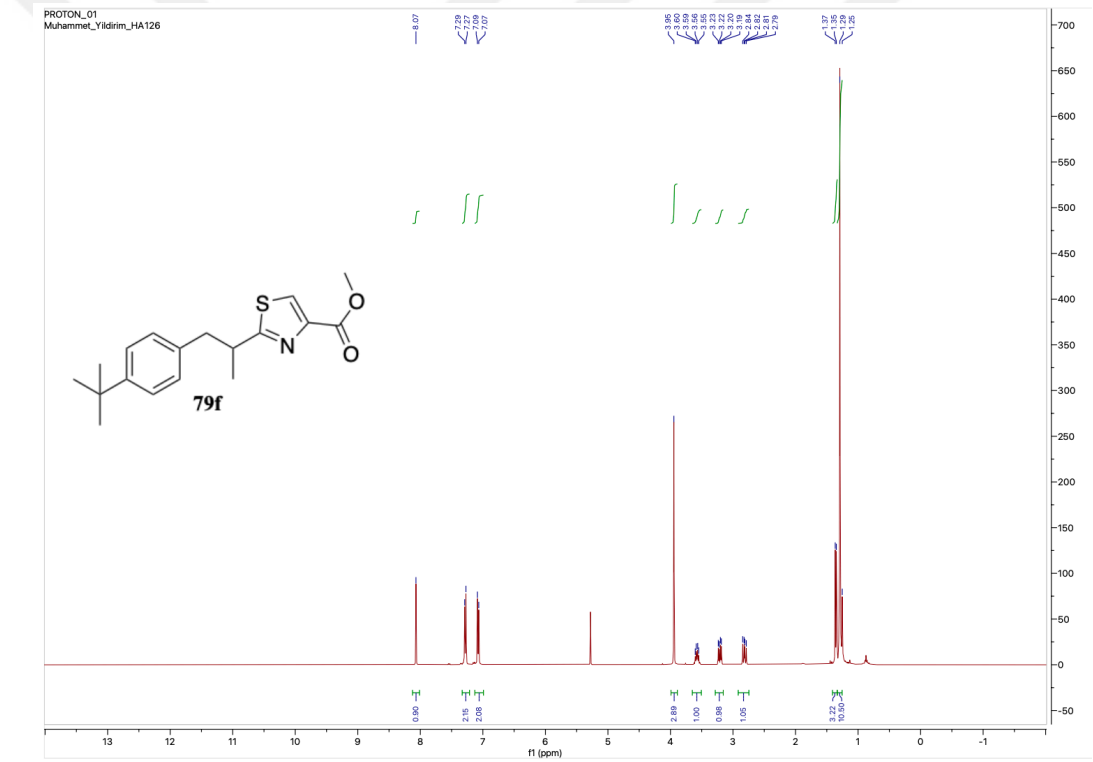

Figure 7.50. [1]H-NMR spectrum of thiazole-4-carboxylates **79f**.

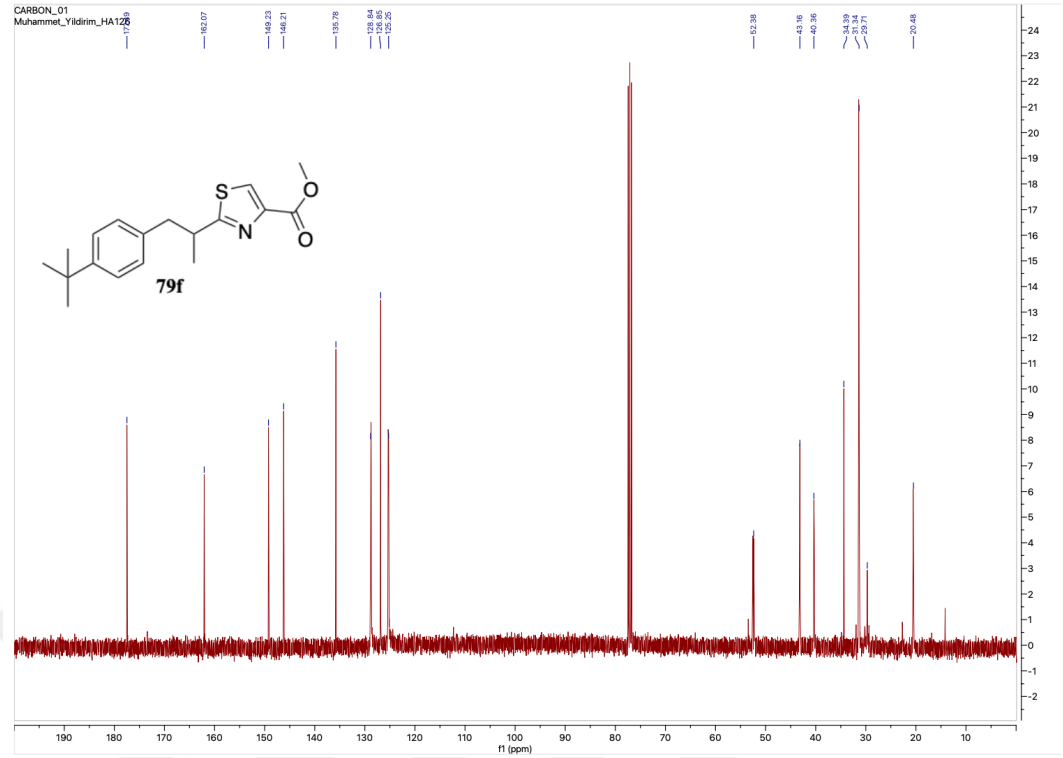

Figure 7.51. ^{13}C-NMR spectrum of thiazole-4-carboxylates **79f**.

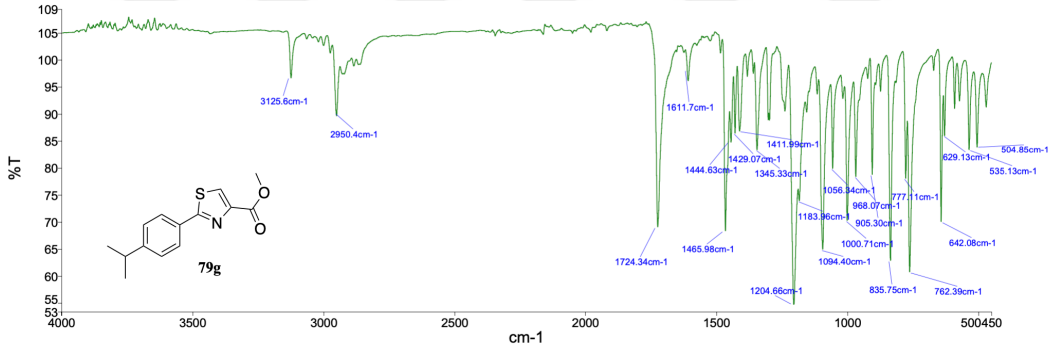

Figure 7.52. IR spectrum of thiazole-4-carboxylates **79g**.

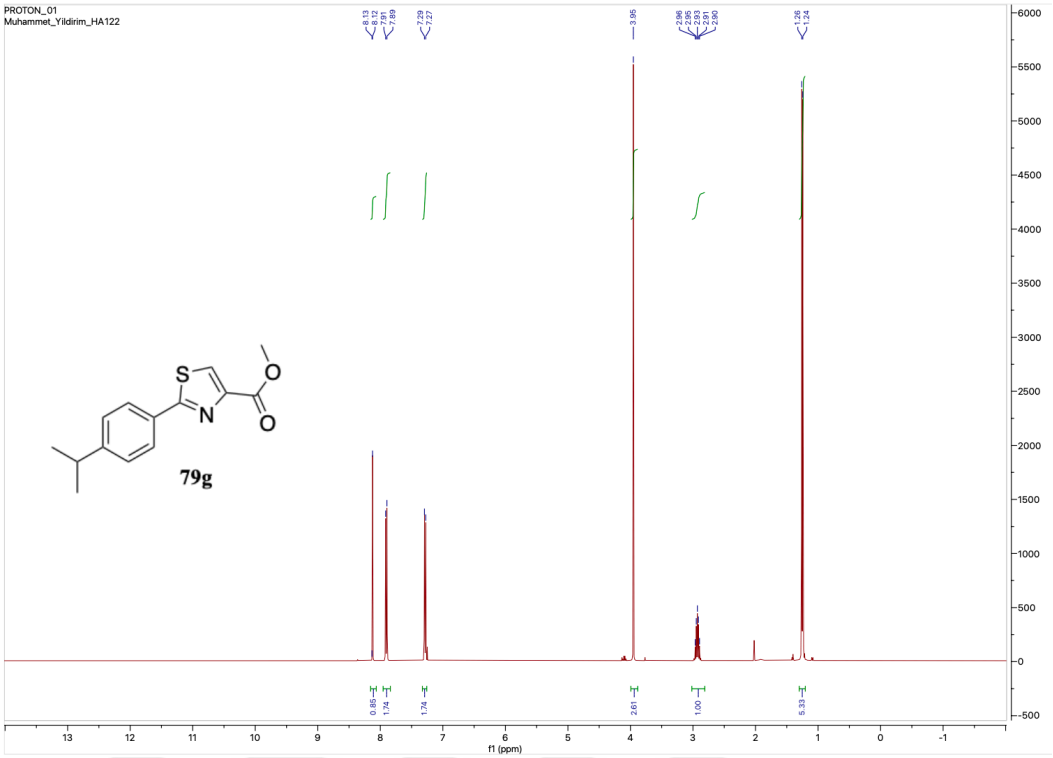

Figure 7.53. [1]H-NMR spectrum of thiazole-4-carboxylates **79g**.

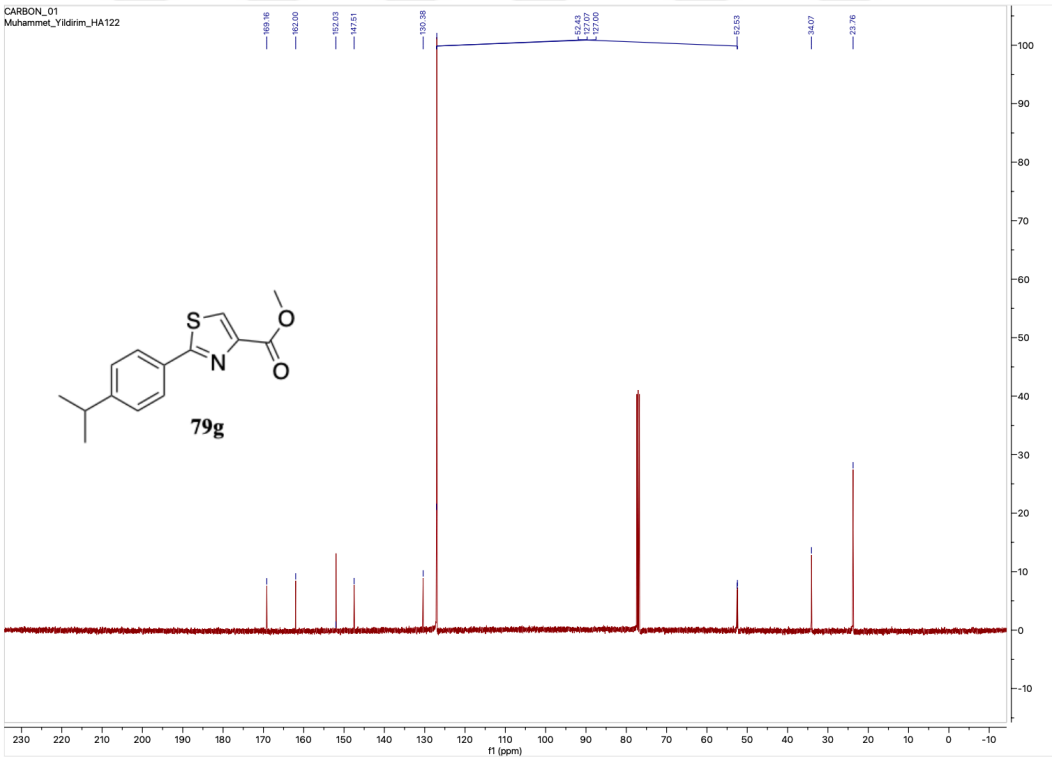

Figure 7.54. [13]C-NMR spectrum of thiazole-4-carboxylates **79g**.

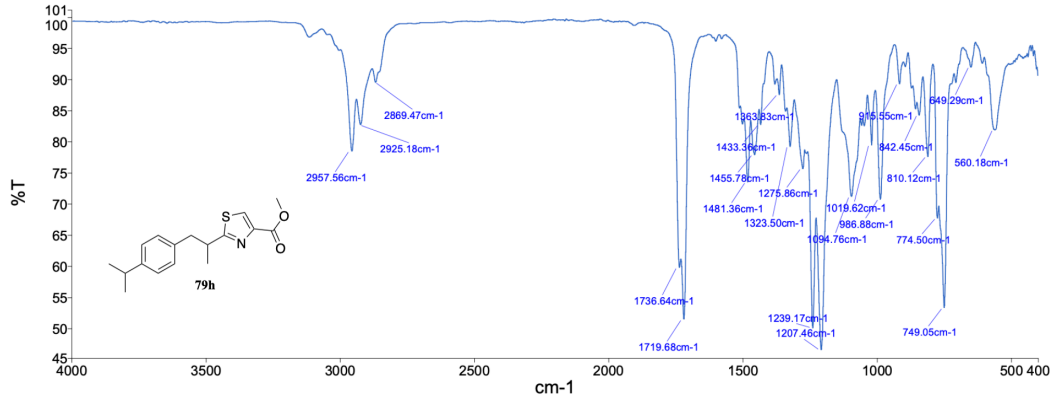

Figure 7.55. IR spectrum of thiazole-4-carboxylates **79h**.

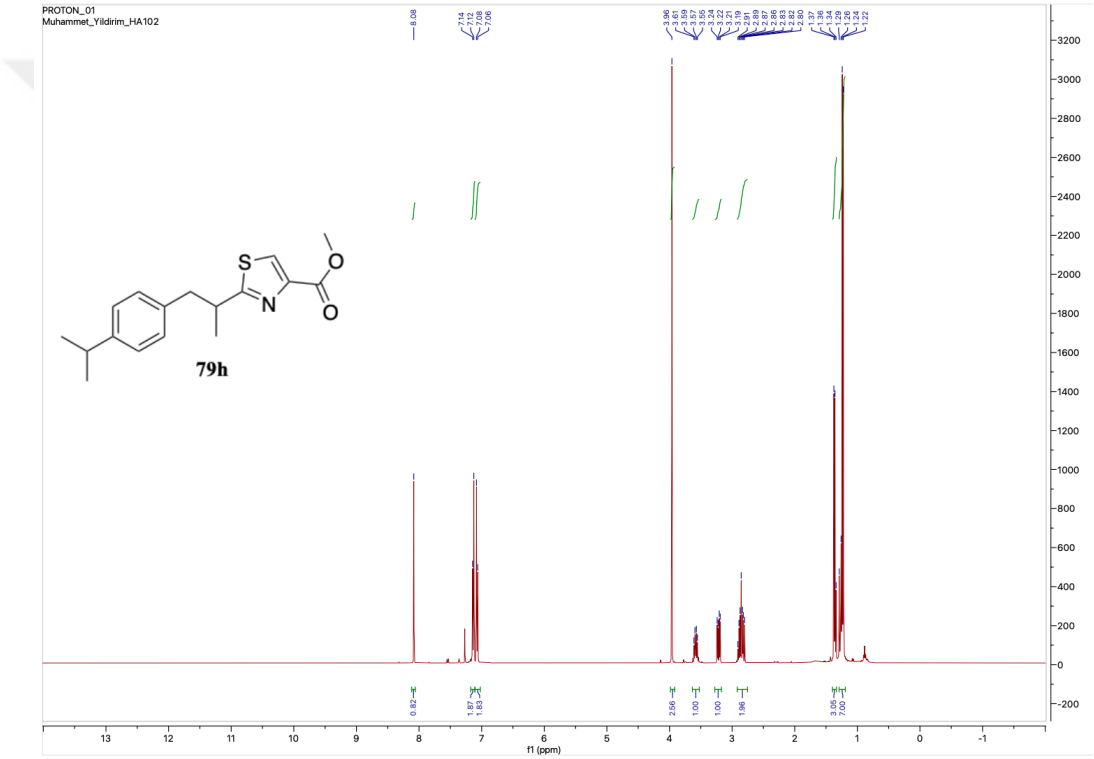

Figure 7.56. 1H-NMR spectrum of thiazole-4-carboxylates **79h**.

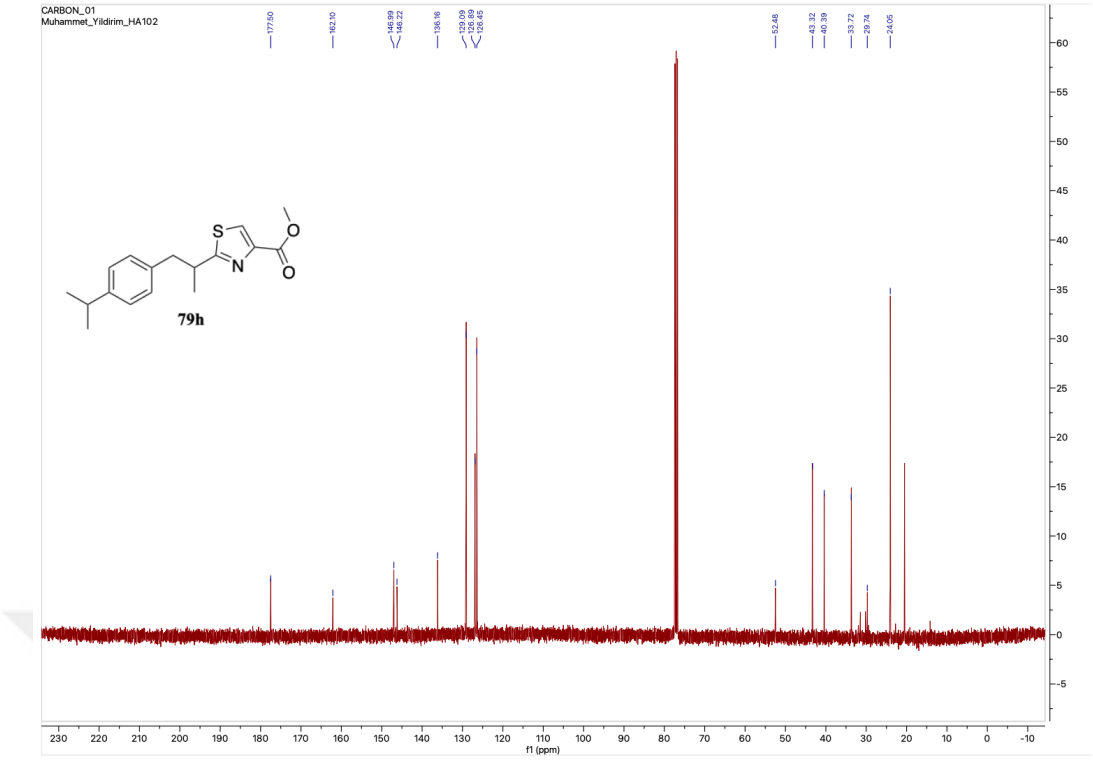

Figure 7.57. ^{13}C-NMR spectrum of thiazole-4-carboxylates **79h**.

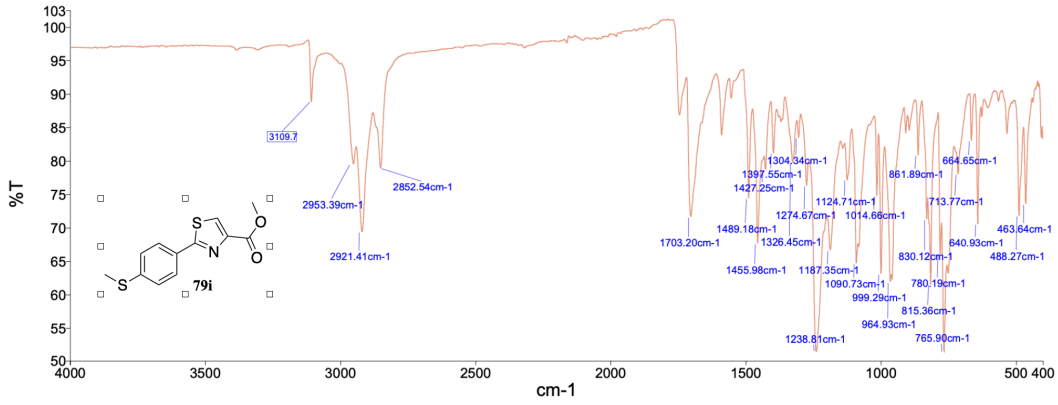

Figure 7.58. IR spectrum of thiazole-4-carboxylates **79i**.

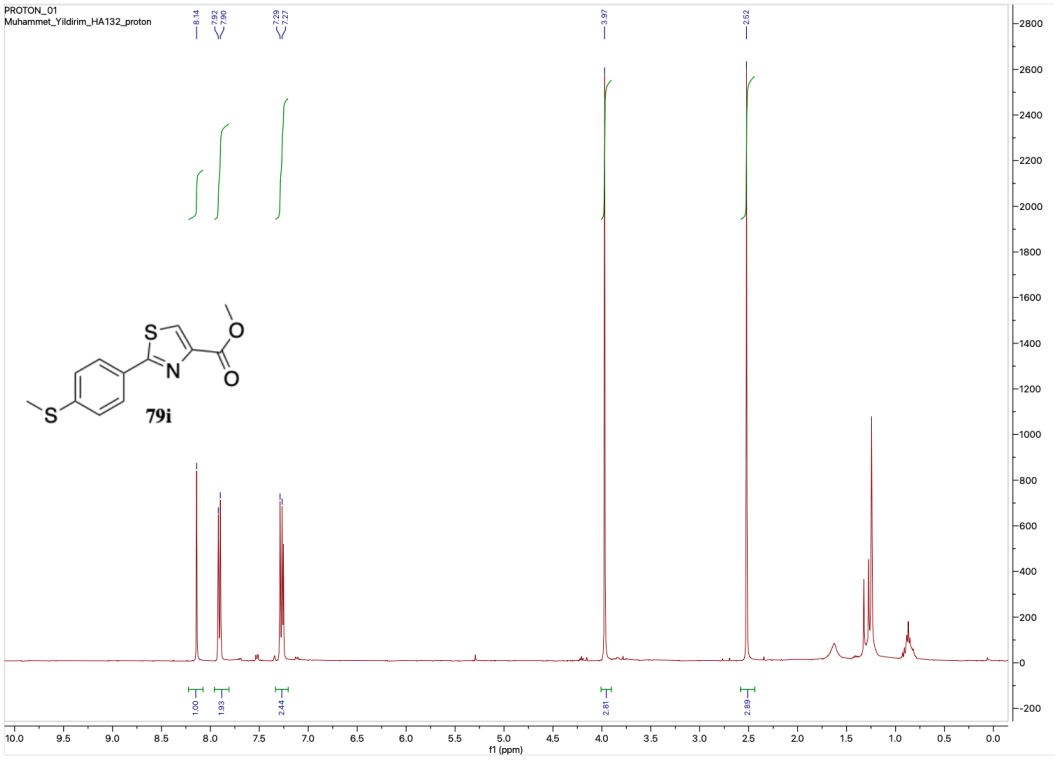

Figure 7.59. ^{1}H-NMR spectrum of thiazole-4-carboxylates **79i**.

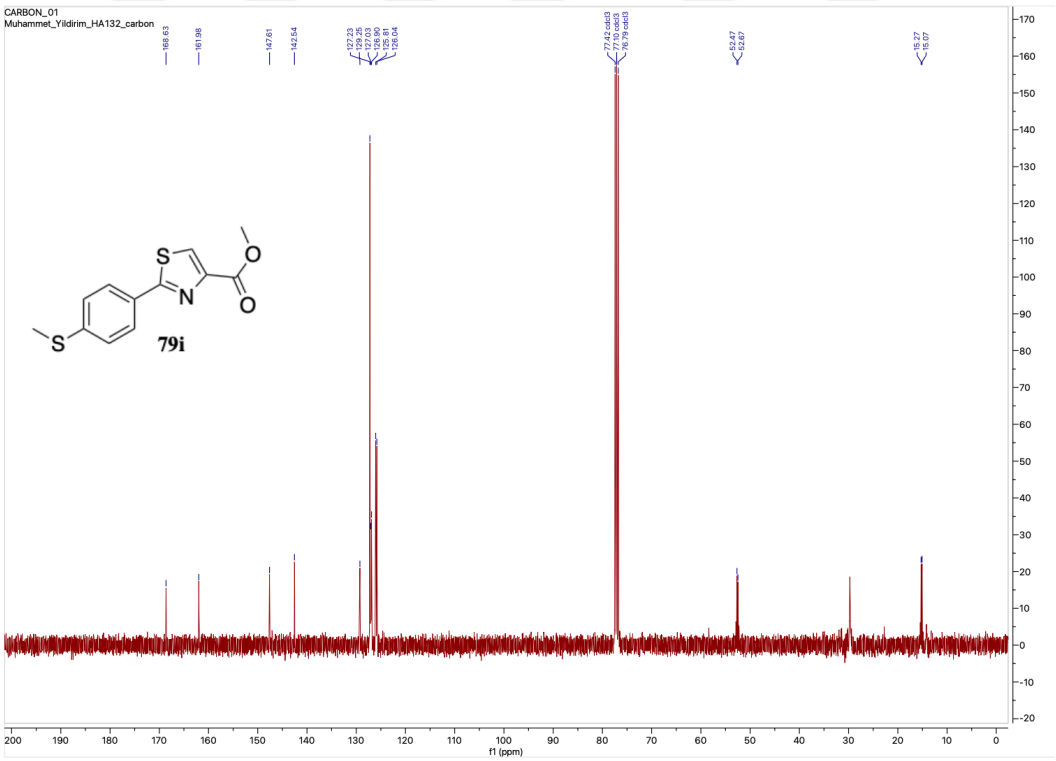

Figure 7.60. ^{13}C-NMR spectrum of thiazole-4-carboxylates **79i**.

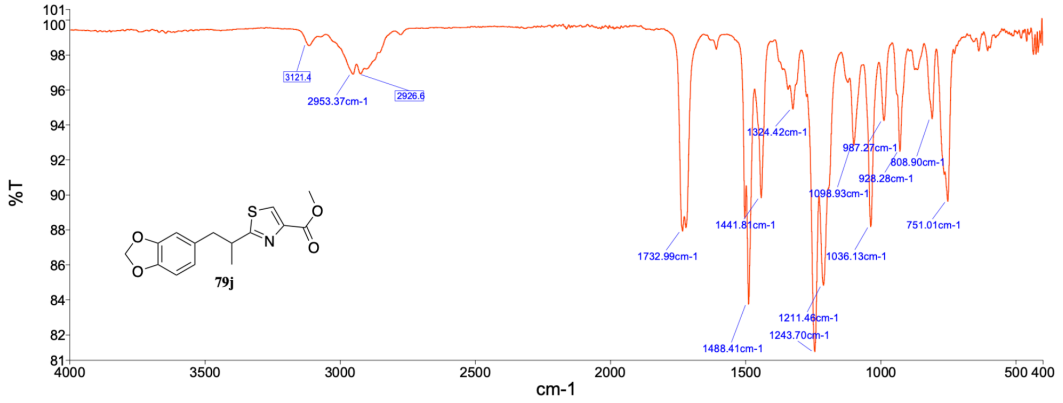

Figure 7.61. IR spectrum of thiazole-4-carboxylates **79j**.

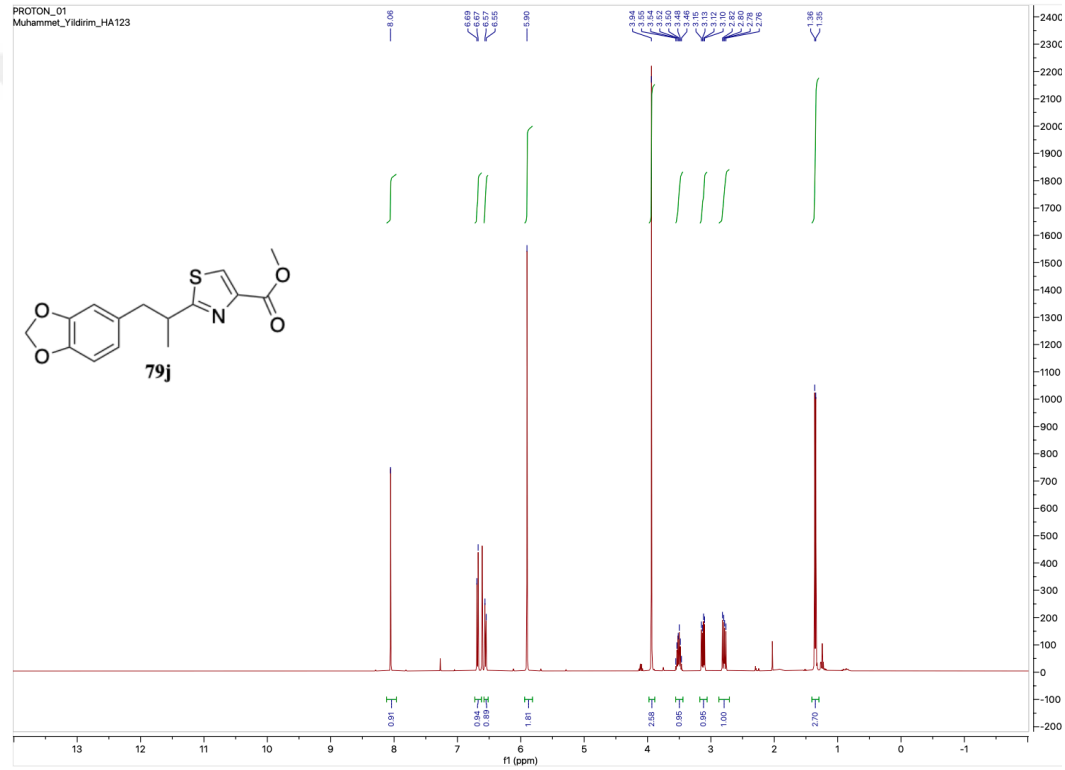

Figure 7.62. ^{1}H-NMR spectrum of thiazole-4-carboxylates **79j**.

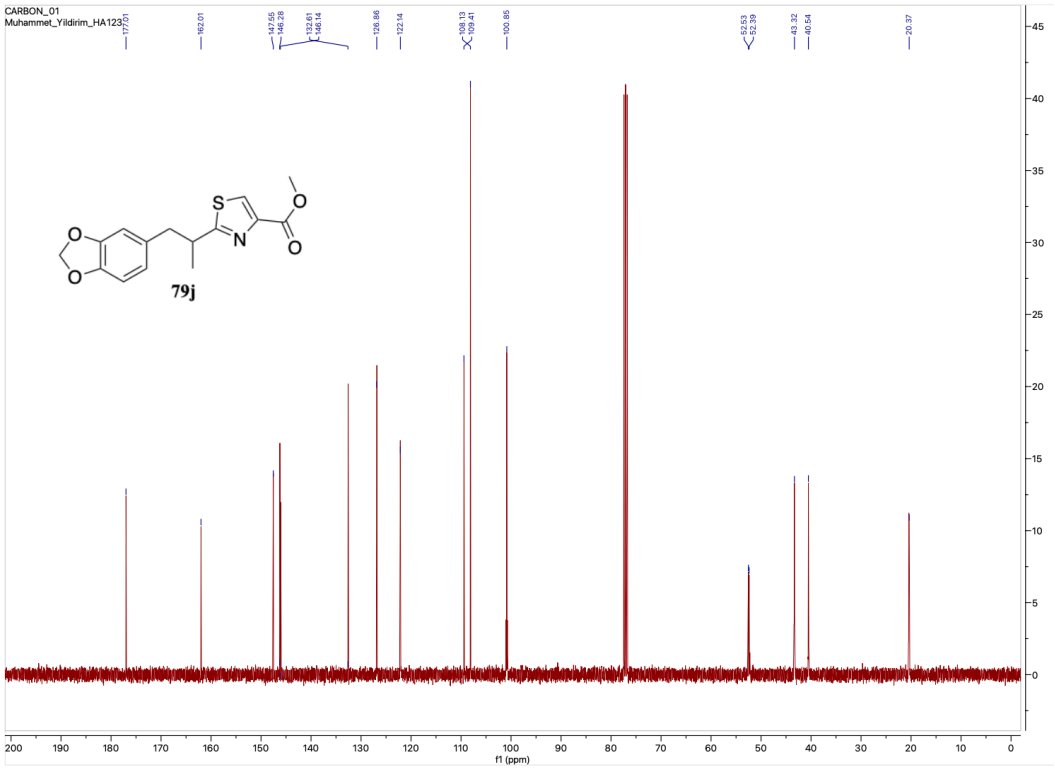

Figure 7.63. ^{13}C-NMR spectrum of thiazole-4-carboxylates **79j**.