การจัดเป็นวงภายในโมเลกุลของแอลคิลบีตา-อะมิโนอะคริเลตที่เร่งปฏิกิริยาด้วยกรด

นายถิรวัฒน์ ศิริจินดาเลิศ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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ACID-CATALYZED INTRAMOLECULAR CYCLIZATION OF ALKYL BETA-AMINOACRYLATES

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ถิรวัฒน์ ศิริจินดาเลิศ : การจัดเป็นวงภายในโมเลกุลของแอลคิลบีตา-อะมิโนอะคริเลตที่เร่งปฏิกิริยาด้วยกรด (ACID-CATALYZED INTRAMOLECULAR CYCLIZATION OF ALKYL BETA-AMINO ACRYLATES). อ. ที่ปรึกษาวิทยานิพนธ์หลัก : อ.ดร.อนวัช อาชวาคม, อ. ที่ปรึกษาวิทยานิพนธ์ร่วม ผศ.ดร.ไพฑูรย์ รัชตะสาคร และ รศ.ดร.มงคล สุขวัฒนาสินิทธิ์ 148 หน้า.

วิทยานิพนธ์นี้ได้ศึกษาปฏิกิริยาภายใต้ภาวะที่มีกรดเป็นตัวเร่งปฏิกิริยาของสารประกอบแอลคิล บีตา-อะมิโน อะคริเลต (อีนามีน) ที่มีคุณสมบัติแบบแอมฟิฟิลิก อีนามีนที่ขาดอิเล็กตรอนนี้ถูกใช้เป็นสารมัธยันต์ในการสร้างพันธะคาร์บอน-คาร์บอนอย่างกว้างขวางในงานสังเคราะห์โมเลกุลขนาดใหญ่ ซึ่งโมเลกุลบีต้า-อะมิโนอคริเลตที่ออกแบบนี้ประกอบด้วยระบบคอนจูเกตของหมู่อะมิโน หมู่แอลคีน และหมู่เอสเทอร์ตามลำดับ ส่งผลให้โมเลกุลนี้ มีคุณสมบัติทั้งนิวคลีโอฟิลิก และ อิเล็กโทรฟิลิกในโมเลกุลเดียวกัน การเตรียมสารประกอบอะลิฟาติก บีต้า-อะมิโน อคริเลต สามารถเตรียมได้ง่ายด้วยปฏิกิริยา 1,4-ไมเคิลแอดดิชันระหว่างสารประกอบอะลิฟาติกเอมีนและเอทิลโพรพิโอเลต ในตัวทำละลายไดคลอโรมีเทน ที่อุณหภูมิห้อง ขณะที่อะโรมาติกเอมีนจำเป็นต้องใช้สารประกอบคอปเปอร์(I) ไอโอไดด์ ที่อุณหภูมิ 60 °C เพื่อขับเคลื่อนปฏิกิริยา เอทิล บีต้า-อะมิโนอะคริเลต ที่ไม่เสถียรนี้ถูกนำไปใช้เป็นสารตั้งต้นในขั้นตอนการทำปฏิกิริยากับกรดชนิดต่างๆ เช่น กรดไฮโดรคลอริก กรดซัลฟิวริก กรดไตรฟลูออโรอะซิติก รวมทั้งกรดลิวอิส เช่นอลูมิเนียมไตรคลอไรด์ ไดเมทิลอลูมิเนียมคลอไรด์ โบรอนไตรฟลูออไรด์ ไททาเนียมเททระคลอไรด์ ในปริมาณน้อยกว่าปริมาณสมมูลของสารตั้งต้น ภายใต้ภาวะที่เหมาะสมที่สุด โดยตลอดการศึกษาการปฏิกิริยาของสารประกอบบีต้า-อะมิโนอะคริเลต ในภาวะกรดต่างๆ เหล่านี้ เราได้ประสบความสำเร็จในการพัฒนาวิธีการใหม่ 2 วิธี สำหรับเตรียมอนุพันธ์ของสารประกอบออกซาโซลิดิโนน และ อนุพันธ์ของสารประกอบ 1,4-ไดไฮโดรพีรีดีน

ในรายละเอียด อนุพันธ์ของสารประกอบออกซาโซลิดิโนนสามารถเตรียมได้ในร้อยละผลิตภัณฑ์ที่สูงภายใต้ภาวะเร่งปฏิกิริยาของกรดไตรฟลูออโรอะซิติก ของสารประกอบคาร์บาเมตที่มีปลายเป็นหมู่อะซิทาลและมีหมู่ป้องกันอะตอมไนโตรเจนคือหมู่เทอร์เชียรีบิวทอกซีคาร์บอนิล ขณะที่สารประกอบไดไฮโดรพีรีดีนสามารถเตรียมได้จากการเติมไทเทเนียม(IV) คลอไรด์ 0.2 – 0.5 เท่าเพื่อเร่งให้บีต้า-อะมิโน อคริเลตเกิดปฏิกิริยาปิดวงภายใต้ภาวะไม่รุนแรง ซึ่งก็เกิดร้อยละผลิตภัณฑ์ที่สูงมากเช่นเดียวกัน และช่วงท้ายการวิจัยนี้ได้เสนอกลไกการเกิดปฏิกิริยา พร้อมทั้งสามารถระบุและแยกสารมัธยันต์ที่เป็นหลักฐานสำคัญในการสนับสนุนกลไกการเกิดปฏิกิริยาปิดวงเป็นอนุพันธ์ของสารประกอบ 1,4-ไดไฮโดรพีรีดีน

ภาควิชา	เคมี	ลายมือชื่อนิสิต	
สาขาวิชา	เคมี	ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก	
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OXAZOLIDINONE /1,4-DIHYDROPYRIDINE / TITANIUM(IV) CHLORIDE

THIRAWAT SIRIJINDALERT : ACID-CATALYZED INTRAMOLECULAR CYCLIZATION OF ALKYL BETA-AMINOACRYLATES. ADVISOR : ANAWAT AJAVAKOM, Ph. D., CO-ADVISOR: ASST. PROF. PAITOON RASHATASAKHON, Ph. D., ASSOC. PROF. MONGKOL SUKWATTANASINITT, Ph. D., 148 pp.

The acid-induced reaction of the amphiphilic β-amino acrylates (enamines) was thoroughly investigated in this work. The electron-deficient enamines have been widely used as the important intermediates for C-C formation in total synthesis. The structure of these enamines contains three conjugated functional groups exhibiting both nucleophilic and electrophilic properties. The simple Michael addition between aliphatic amines and ethyl propiolate in DCM was used to prepare ethyl β-amino acrylates to provide aliphatic enamines in quantitative yields. For aromatic enamines, addition of the copper(I) iodide at 60 °C was required to push the reaction forward. In the cyclization step, the unstable ethyl β-amino acrylates were immediately treated as a substrate *in situ* with acid in an optimized condition. Several acids and Lewis acid e.g. HCl, H_2SO_4, TFA, $BF_3{\cdot}OEt_2$, $AlCl_3$, $AlMe_2Cl$, and $TiCl_4$ were used in sub-stoichiometric amount. Along with the study of reaction under several acidic conditions, the novel synthetic methods for a couple sets of new compounds, oxazolidin-2-ones and 1,4-dihydropyridines were successfully developed.

In details, a set of oxazolidin-2-ones were synthesized in very good yield by intramolecular cyclization for the case of Boc-enamides bearing dialkyl acetal moiety. On the other hand, 1,4-dihydropyridine containing various *N*-substituents were synthesized by treatment of β-amino acrylates with 0.2 - 0.5 equivalent of $TiCl_4$ under mild condition resulted in excellent yields. The cyclization reaction mechanism was proposed base on the separation of dimeric intermediate.

Department : CHEMISTRY Student's Signature .....
Field of Study : CHEMISTRY Advisor's Signature .....
Academic Year : 2011 Co-advisor's Signature .....
Co-advisor's Signature .....

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CONTENTS

Page

Page

Page

List of Tables

Page

List of Figures

Page

Page

Page

Page

Page

Page

Page

Page

Page

Page

List of Schemes

Page

Page

List of Abbreviations and Signs

δ	chemical shift (NMR)
ν	wave number (IR)
°C	degree celsius
Φ_F	fluorescent quantum yield
^{13}C-NMR	carbon nuclear magnetic resonance
^{1}H-NMR	proton nuclear magnetic resonance
Å	angstrom
$AlCl_3$	aluminium trichloride
$AlMe_2Cl$	dimethylalumium chloride
Ar	aromatic
$BF_3{\cdot}OEt_2$	borontrifluoride·diethyletherate
Boc	tertiarybutoxycarbonyl
br	broad (NMR)
$CDCl_3$	deuterated chloroform
cm^{-1}	per centimeter
CuI	copper(I) iodide
d	doublet (NMR)
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublet (NMR)
DHP	1,4-dihydropyridine
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
E	electrophile
EN	enamine
equiv	equivalent
EtOAc	ethyl acetate
FTIR	fourier transform infrared spectroscopy
g	gram
HRMS	high resolution mass spectrum
Hz and MHz	hertz and megahertz

IR	infrared
J	coupling constant (NMR)
L.A.	Lewis acid
M	molar
m.p.	melting point
m/z	mass per charge
mL	millilitre
mmol	millimole
NMR	nuclear magnetic resonance
Nu	nucleophile
o/n	overnight
OX	oxazolidin-2-one
ppm	part per million (NMR)
q	quartet (NMR)
R_f	retardation factor
rt	room temperature
s	singlet (NMR)
S_N2	nucleophilic substitution-2
t	triplet (NMR)
TEA	triethylamine
TFA	trifluoroacetic acid
$TiCl_4$	titanium tetrachloride
TLC	thin layer chromatography
TMSOTf	trimethylsilyl trifluoromethanesulfonate

List of Numbered Compound

1	*ethyl β-amino acrylates containing acetal terminus*
2	*ethyl β-amino acrylates containing O-methyl oxonium cation terminus*
3	*ethyl-3-(2,2-dimethoxyethylamino)acrylate*
4	*ethyl 3-((tert-butoxycarbonyl)(2,2-dimethoxyethyl)amino)acrylate*
5	*ethyl 3-(alkylamino)acrylate*
5a	*ethyl-3-(butylamino)acrylate*
5b	*ethyl-3-(octadecylamino)acrylate*
5c	*ethyl-3-(benzylamino)acrylate*
5d	*ethyl-3-(2-hydroxyethylamino)a*crylate
5e	*ethyl-3-(phenylamino)acrylate*
5f	*ethyl-3-(4-methoxyphenylamino)acrylate*
5g	*ethyl-3-(4-iodophenylamino)acrylate*
5h	*ethyl-3-(4-fluorophenylamino)acrylate*
5i	*ethyl-3-(3-chlorophenylamino)acrylate*
6	*tert-butyl alkyl(2,2-dimethoxyethyl)carbamates*
6a	*tert-butyl benzyl(2,2-dimethoxyethyl)carbamates*
6b	*tert-butyl (2,2-dimethoxyethyl)(4-nitrophenyl)carbamate*
6c	*tert-butyl (2,2-dimethoxyethyl)(naphthalen-1-ylmethyl)carbamate*
7	*3-alkyl-5-methoxyoxazolidin-2-one*
7a	*(E)-ethyl 3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate*
7b	*3-benzyl-5-methoxyoxazolidin-2-one*
7c	*5-methoxy-3-(4-nitrobenzyl)oxazolidin-2-on*
7d	*5-methoxy-3-(naphthalen-1-ylmethyl)oxazolidin-2-one*
8	*diethyl-1-alkyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate*
8a	*diethyl-1-(2,2-dimethoxyethyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate*
8b	*diethyl-1-butyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate*
8c	*diethyl-4-(2-ethoxy-2-oxoethyl)-1-octadecyl-1,4-dihydropyridine-3,5dicarboxylate*

8d	*diethyl-1-benzyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate*
8e	*diethyl-4-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl)-1,4-di-hydropyridine-3,5-dicarboxylate*
8f	*diethyl-4-(2-ethoxy-2-oxoethyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxyl*
8g	*diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate*
8h	*diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-iodophenyl)-1,4-dihydropyridine-3,5-dicarboxylate*
8i	*diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate*
8j	*diethyl-1-(3-chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate*
9	*diethyl 4-((phenylamino)methylene)pent-2-enedioate*

List of Equation

Page

CHAPTER I

INTRODUCTION

Alkyl β-amino acrylates (enamines) are widely applied to the effective intermediates for C-C bond formation in total synthesis of many natural products and drug candidates. [1-4] The multifunctional enamine carboxylate (NH-C=C-COOEt) containing three conjugated functional groups exhibiting both nucleophilic and electrophilic properties. One of the most classic examples of enamine reaction is Mannich reaction [5-6] in which the enamines are generated from carbonyl compounds and amines. Enamines can be used for the cyclization to allow an efficient synthesis of various heterocyclic compounds such as pyrroles. [7-8] In this work, alkyl β-amino acrylates which are the enamines bearing an carboxylate group were synthesized and isolated. The treatments of these enamines with several acids i.e. mineral acid, organic acid and Lewis acid were undertaken in order to develop the novel synthetic methods.

1.1 Synthesis of heterocyclic compounds

A heterocyclic organic compound is a carbon-based cyclic molecule containing at least one or more non-carbon elements (e.g. N, O and S) in its ring. Heterocyclic compounds have been applied for wide range of synthesis and biologically active compounds. There are many ways of achieving the synthesis of heterocyclic compounds, such as intramolecular cyclization, cycloaddition, and rearrangement. One of the most important routes to heterocyclic compound formation is the intramolecular ring-closing reaction, because heterocyclic compounds have one or more heteroatom that can usually served as the nucleophile in intramolecular substitution and addition. Concept of ring-closing reaction may be typically divided into two groups. The first one is intramolecular cyclization of molecule designed to bear both nucleophilic and electrophilic sites. Under appropriate treatment with acid, or base or heat, this molecule will react within itself to form a ring product. The ring formation of more than two components proceeding step by step in one pot reaction without the separation of any intermediates can be defined as the intermolecular cyclization. Here are some classic examples of such intramolecular ring-closing reaction. First, the 3-membered-ring compound such as epoxide or aziridine could be

prepared from halohydrin or 2-haloethanamine by using nucleophilic heteroatom (oxygen or nitrogen) to directly attack to adjacent electrophilic carbon. [9-10] Second example is the synthesis of lactones by esterification such as Keck macrolactonization that used DCC and DMAP as catalysts for esterification. [11-12] Next, intramolecular version of Chichibabin amination reaction [13] is also another example that its side chain aliphatic amine adds to an α-position of pyridine (**Figure 1.1**). For the cases of the intermolecular cyclization, heterocyclic compounds were generally prepared by mixing two or more components together to obtain a ring. There are several well-known named reactions featured in this type of cyclization i.e. Biginelli reaction, [14] Knorr pyrrole synthesis, [15] Feist-Bénary furan synthesis [16-18] Hantzsch dihydropyridine synthesis, [19-22] (**Figure 1.2**).

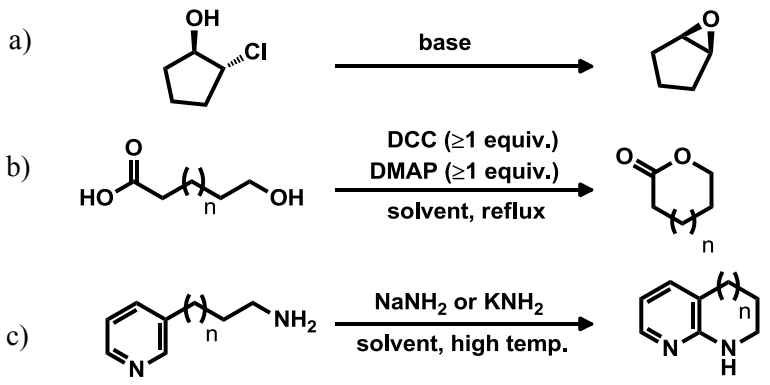


Figure 1.1 Synthesis of heterocyclic compounds through intramolecular cyclization: a) epoxide formation from halohydrin [9] b) Keck macrolactonization [11-12] c) Intramolecular Chichibabin reaction [13]

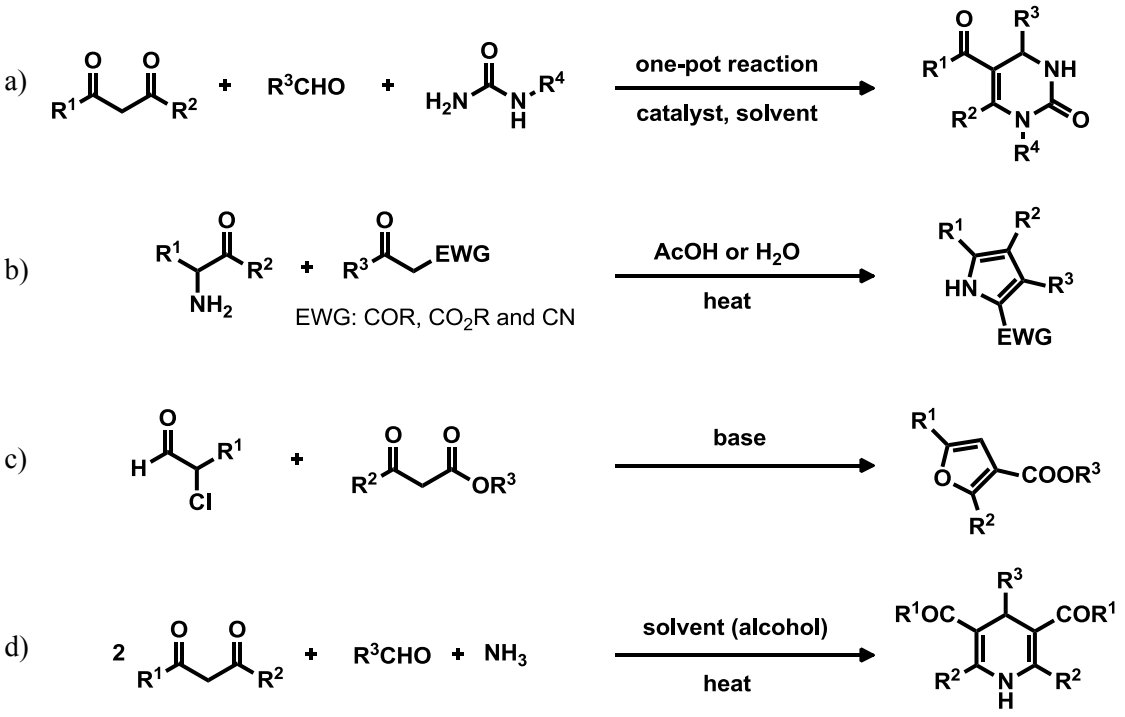


Figure 1.2 Synthesis of heterocyclic compounds through intermolecular cyclization:
a) Biginelli reaction [14] b) Knorr pyrrole synthesis [15]
c) Feist-Bénary furan synthesis [16-18]
d) Hantzsch dihydropyridine synthesis [19-22]

1.2 Baldwin's rules

In 1976, ring-closing possibility of organic reaction has been suggested by Sir Jack E. Baldwin [23-25]. Baldwin's rules formulated a set of guidelines of ring closure reactions that described in term of three features of the reaction which are the number of atoms within the ring being formed (*X*), trajectories of the bond breaking (*exo* or *endo*), and hybridization of electrophilic carbon (sp-*dig*, sp^2-*trig*, sp^3-*tet*). The abbreviation term of each cyclization can be expressed in the order of no. of atoms within the ring-trajectories of the bond breaking – hybridization of electrophilic carbon; for example *5-exo-trig*. Favored/disfavored processes are summarized in **Table 1.1.**

Table 1.1 Summary of cyclization probability of Baldwin's rule [23-25], the cyclizing abilities of the system

No. of atoms	*dig*		*trig*		*tet*	
	exo	***endo***	***exo***	***endo***	***exo***	***endo***
3	disfavored	favored	favored	disfavored	favored	
4	disfavored	favored	favored	disfavored	favored	
5	favored	favored	favored	disfavored	favored	disfavored
6	favored	favored	favored	favored	favored	disfavored
7	favored	favored	favored	favored	favored	

The reaction of ethyl 4-amino-2-methylenebutanoate is one of the very good cyclization examples that supported the guideline of Baldwin's rule. [25] There are two possible routes to form different 5-membered ring products which are *5-exo-trig* and *5-endo-trig* to form lactam and pyrrole, respectively. Only lactam product was detected as a regioselective product through *5-exo-trig* process, the favored cyclization pathway in Baldwin's rule, but not through the disfavored *5-endo-trig* (**Figure 1.3a**).

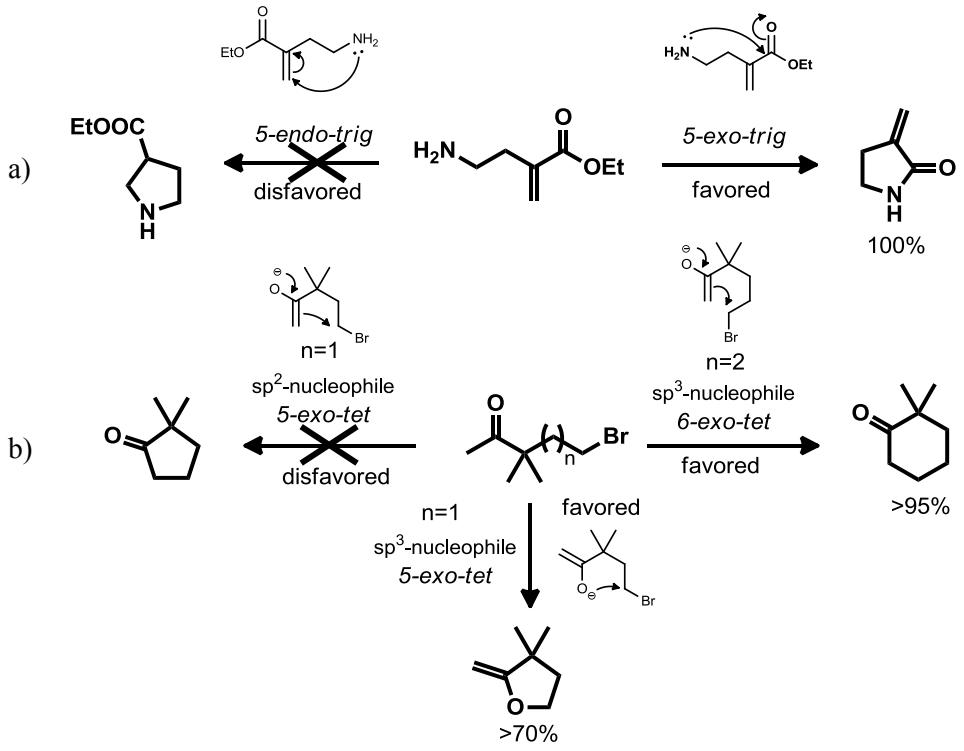


Figure 1.3 a) Cyclization process of ethyl 4-amino-2-methylenebutanoate
b) Cyclization process of n = 1; 5-bromo-3,3-dimethylpentan-2-one, n = 2; 6-bromo-3,3-dimethylhexan-2-one

In specific case, the 5-membered or smaller ring closing reaction operated from sp^2 nucleophile (π-bond), such as enolate anion and enamine, is disfavored comparing to the sp^3 nucleophile, because the stereoelectronic effect on this type of nucleophile is rather improper to be arranged its attack position toward the electrophile. Therefore, only (*6* or *7*)-exo-(*trig* or *tet*) are favored for these kinds of ring closing reaction. For example, the cyclization of 5-bromo-3,3-dimethylpentan-2-one and 6-bromo-3,3-dimethylhexan-2-one in basic conditions are very good exceptional examples for Baldwin's rule (**Table 1.1**). [25] In the former case, no cyclopentanone product from the attack of sp^2 nucleophile (enolate carbon) but only 5-membered cyclic ether from the attack of sp^3 nucleophile (oxide anion) was generated. However, in the latter case of the longer substrate, 6-bromo-3,3-dimethylhexan-2-one, only cyclohexanone was produced from sp^2 nucleophile through *6-exo-tet* process (**Figure 1.3b**).

1.3 β-Amino acrylates

β-Amino acrylates are multifunctional molecules consisting of nitrogen atom and ester group directly attached to the alkene in the opposite side (**Figure 1.4**). β-Amino acrylate can also be defined as enamine (ene + amine) that possesses ester group. This β-amino acrylate or enamine is unstable because it can be oxidized easily and decomposed to amine and acrylate. Generally, β-amino acrylate is often used as intermediate for C-C bond formation and can be generated *in situ*. To prepare a series of ethyl β-amino acrylates, addition between various amines and ethyl propiolate was developed in the previous work among our research group [26]. Other enamines can be exemplified such as the preparation methods for condensation of amine and acetoacetate ester [7] and Mannich's reaction in which the β-amino acrylates were prepared from amines, formaldehyde, and carbonyl compounds [5-6].

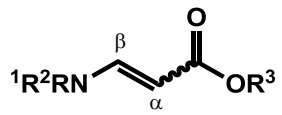


Figure 1.4 Structure of β-amino acrylates

β-Amino acrylate contains three functional groups which are amine, alkene, and ester conjugated to each other. The reason for interesting reactivity in its molecule

comes from its four active sites. Two of these active sites are nucleophilic sites including nitrogen atom for the direct attack to an electrophile (Nu-1) and α-carbon for the attack through conjugation (Nu-2), while the other two active sites are electrophilic sites that are carbonyl group for the attack through 1,2-addition (E-1) and β-carbon for the attack through 1,4-addition (E-2). Basically, the chemoselectivity usually depends on the reaction conditions. For example, hard nucleophilic reagents such as sodium ethoxide, thionyl chloride prefers to undergo the *trans*-esterification with hard electrophilic carbonyl of ester (E-1). On the other hand, soft electrophilic 1,4-Michael acceptor (E-2) would habitually couple with soft nucleophile such as malonate anion. The kind of substrate that combines both nucleophile and electrophile within, such as this β-amino acrylate, is commonly called amphiphilic molecule (**Figure 1.5**).

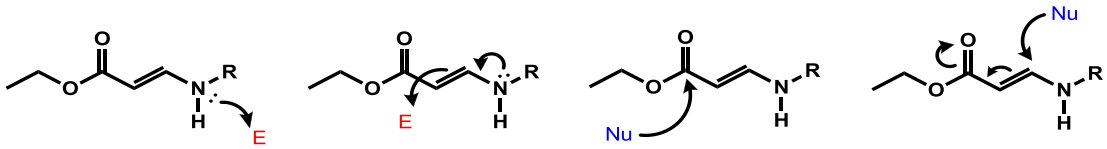


Figure 1.5 Amphiphilic property of ethyl β-amino acrylate

1.4 Designed molecule

According to the previous research results [26], ethyl β-amino acrylates containing acetal terminus with different number of carbons (n = 1 - 3) (**1**) were designed and synthesized for the cyclizing study. The expected products are three- to seven-membered rings depending on the number of carbons (n). Basically, acetal group is a protected version of aldehydes or ketones and under the acidic aqueous condition such as hydrochloric acid, it will be converted back to carbonyl group. However, in the case of non-aqueous acidic condition such as TFA, the acetal group moves to the equilibrium with oxonium cation (**2**), which can accept electron either from through route of nucleophile a) or b) producing the corresponding heterocyclic compounds (**Figure 1.6**).

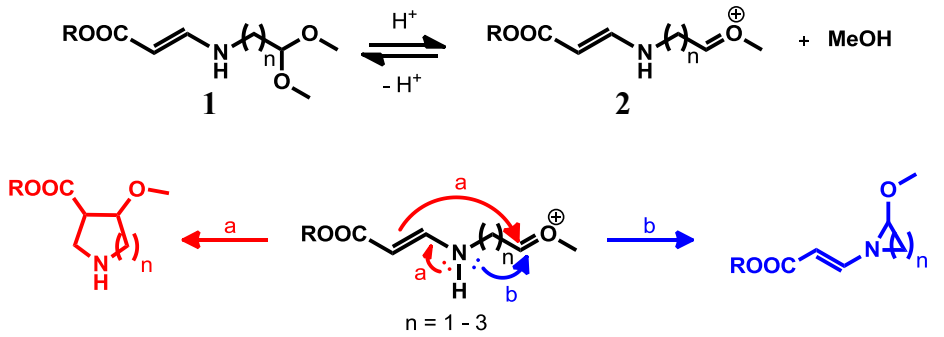


Figure 1.6 Designated molecules: β-amino acrylates containing acetal terminus with different number of carbons (n = 1 - 3)

As far as Baldwin's rules concern in the case of β-amino acrylates using oxonium cation (sp^2) as an electrophilic site, including the exceptional case in **Figure 1.3b**, all cyclization operated by direct attack process are favored, on the other hand, indirect attack patterns favored ring closures only in the case of 6 and 7 membered formation (**Figure 1.7**).

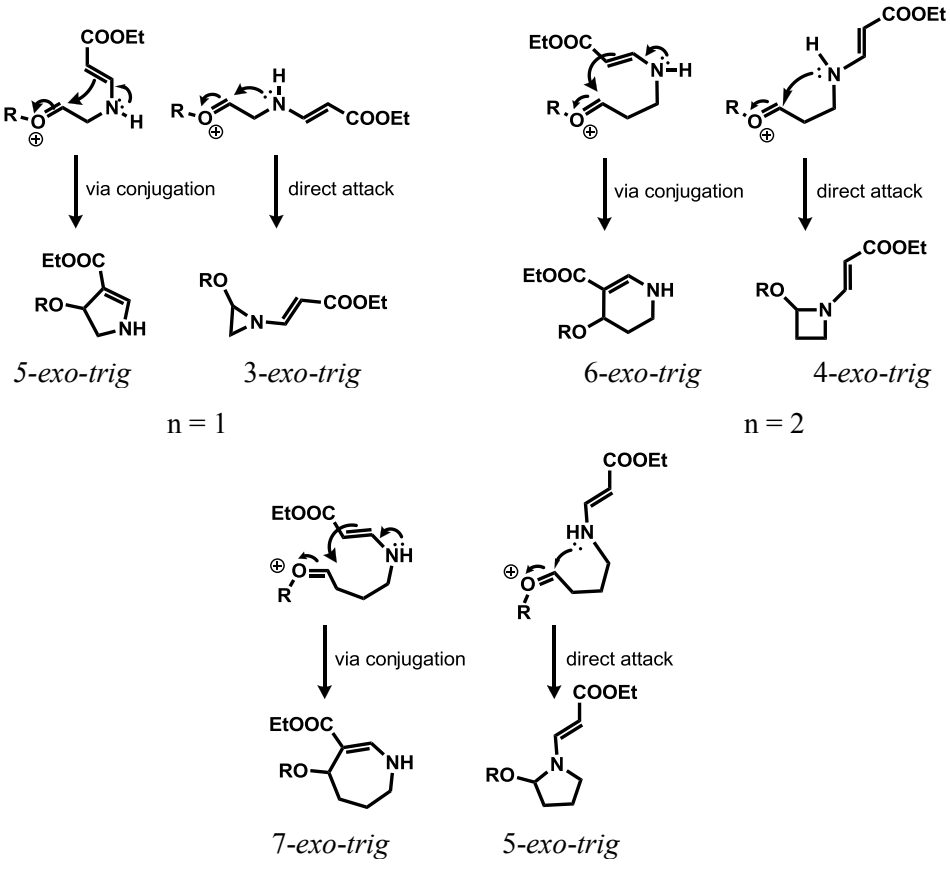


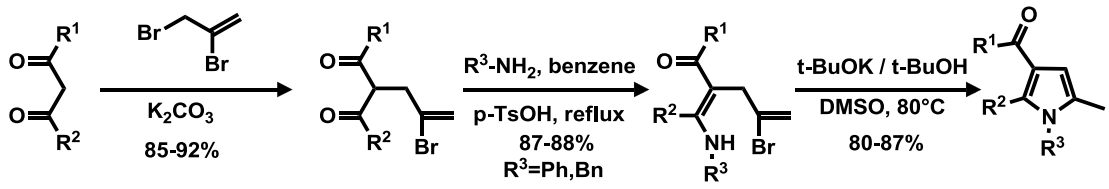
Figure 1.7 Cyclization of designated β-amino acrylates (**1**)

1.5 Cyclization examples

1.5.1 Intramolecular cyclization

Recently, there are many related reports concerning the intramolecular cyclization of β-amino acrylates to various heterocyclic compounds. Most of them used β-amino acrylates as an intermediate and handled the reaction as one pot reaction. Some enamines were isolated prior to use as substrates for cyclization. And some of these interesting examples of reaction of enamines under different conditions are shown as followed.

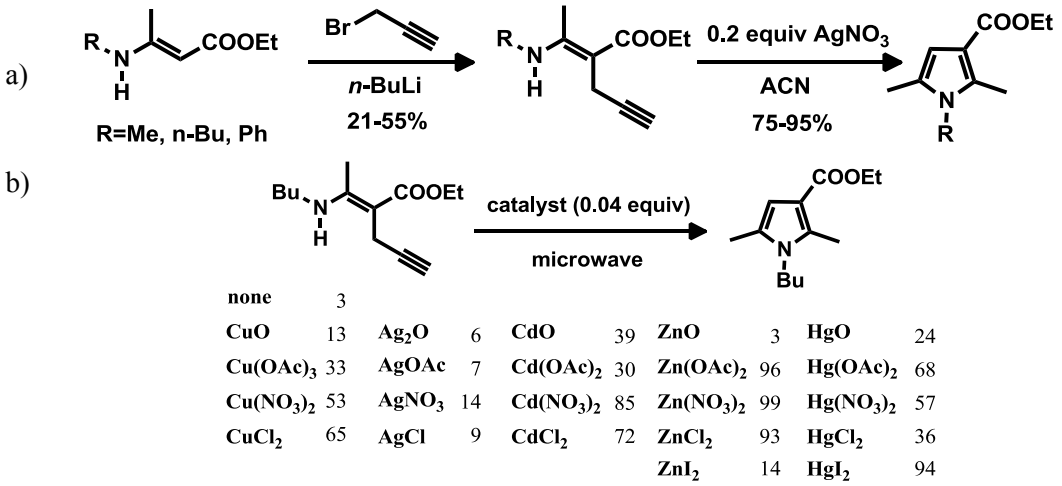
In 2002, Demir and his team [7] reported the synthesis of pyrrole derivative via β-amino acrylate intermediate (**Scheme 1.1**). In the ring closure step, this work designed the nitrogen atom to directly attack to the vinyl bromide in *5-exo-trig* manner, and then isomerize to pyrrole target molecule after the bromide elimination. Although, Turkish scientists successfully synthesized the pyrrole derivatives in excellent yield but the reaction required very strong and bulky base *tert*-butoxide in the solution of DMSO.



Scheme 1.1 Cyclization of designed enamines reported by Demir [7]

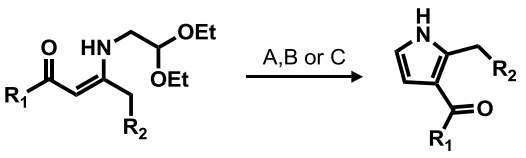
In 2004, Robinson and colleagues [8] presented the synthesis of pyrrole derivative similar to those of Demir in which the alkyne substrate was used as electrophilic site instead of vinyl bromide. In cyclization step, the catalyst $AgNO_3$ induces the lone pair of nitrogen atom to couple with alkyne, followed by isomerization to obtain the target pyrroles in very good yield. The limitation of this research was the low to moderate yielding in the step of intermediate synthesis (**Scheme 1.2a**).

Four years later, Robinson's team [27] developed alternative reagents such as the compounds of Zn, Cu, Hg, and Cd instead of air sensitive $AgNO_3$. Moreover, not only new catalysts but the conditions in microwave atmosphere have been developed to accomplish the reaction by using lower catalytic amount and lower reaction time. The best condition was the use of $Zn(NO_3)_2$ or $Zn(OAc)_2$ in only 0.04 equivalent under microwave atmosphere (**Scheme 1.2b**).



Scheme 1.2 Cyclization of designed β-amino acrylate reported by Robinson [8, 27] in a) 2004 b) 2008

In 2006, Bellur and Langer [28] have found three different methods for pyrrole synthesis from enamines. Under very large excess of TFA condition (method A) only enamines substituted by ketone (R^1 = alkyl) did cyclize in excellent product yields (**Scheme 1.3**). However, the harsh condition 150°C was required for method C to push the reaction of enamines substituted by ester or β-amino acrylate (R^1 = alkoxy), while steric effect at R^2-position was essentially needed to operate at -78 °C in a present of TMSOTf (method B).



R^1	R^2	method	%yield
alkoxy	H	C	40 - 58
alkoxy	alkyl	B	37 - 58
alkyl	H	A	up to 82

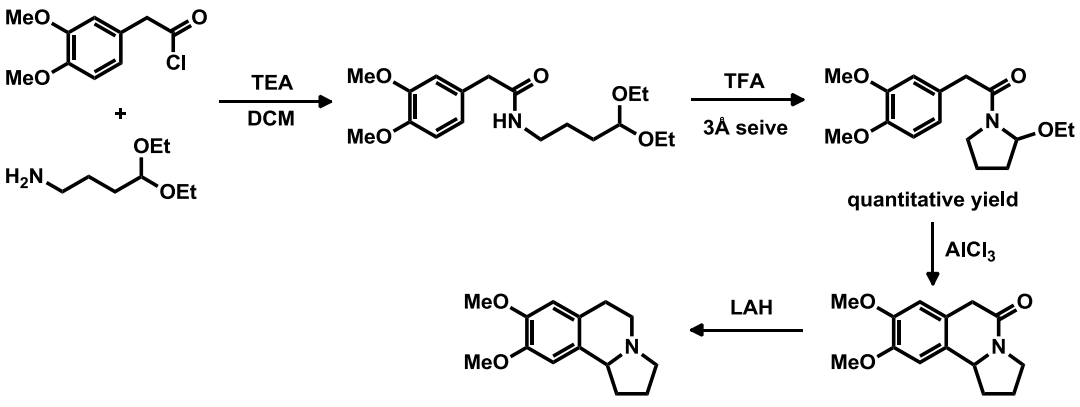
Scheme 1.3 Three cyclization methods of the designed enamines reported by Bellur and Langer [28]

A: TFA (10 equivalent), DCM, 0 °C to 20 °C

B: TMSOTf (1 equivalent), DCM, -78 °C to 20 °C

C: DMSO, 150 °C, 24 h

In 2007, King and coworker [29] designed the amide substrate consisting of acetal group, amide, and three carbons linker between these groups, to be cyclized into pyrrole derivatives (**Scheme 1.4**). Under acidic condition of TFA, oxonium cation converted from acetal was attacked by amide to provide the pyrrole derivatives in quantitative yield. Furthermore, in the final step, the amido group in lactam ring was reduced to amino group by $LiAlH_4$. This example provided the concept of using protected amine in the cyclization step in order to control the reaction by decrease the reactivity of amino group.



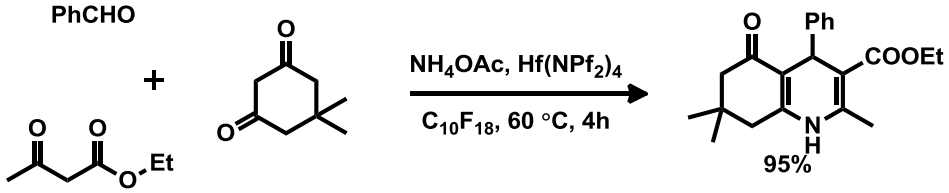
Scheme 1.4 Cyclization of designed amide reported by King [29]

The structure of β-amino acrylates was designed as described above to react within their molecules and the most popular cyclized products are pyrrole derivatives. β-Amino acrylates, however, could combine with some reactive species in most cases aldehydes, to provide other aza-heterocyclic compound such as 1,4-dihydropyridine (1,4-DHP). This type of intermolecular cyclization will be described in details in section 1.5.2.

1.5.2 Intramolecular cyclization

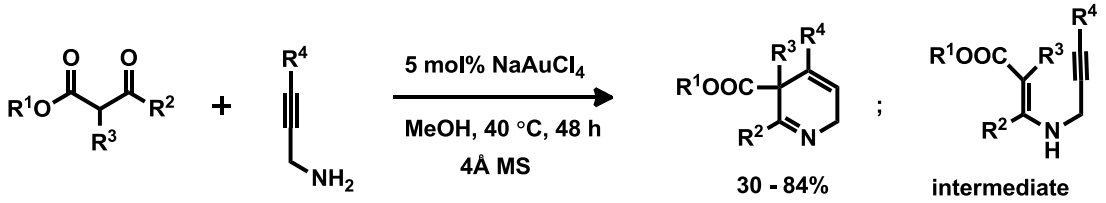
The intramolecular cyclizations of enamines with several conditions were already exemplified. Here are some examples of Lewis acid induced intermolecular cyclizations between other substrates to form such heterocyclic rings.

In 2010, Hong's team [30] developed the modified Hantzsch's reaction that combined benzaldehyde, acetoacetate ester, 1,3-cyclohexadione, and ammonium acetate in a presence of several Lewis acid such as $Hf(NPf_2)_4$, $Sn(NPf_2)_4$, $Sc(NPf_2)_4$, and $Sc(OTf)_3$ (**Scheme 1.5**). The most effective catalyst is $Hf(NPf_2)_4$ under the optimized conditions, perfluorodecalin at 60 °C, obtaining fused ring DHP in excellent yields together with other fifteen related products in 83 - 96% yields.



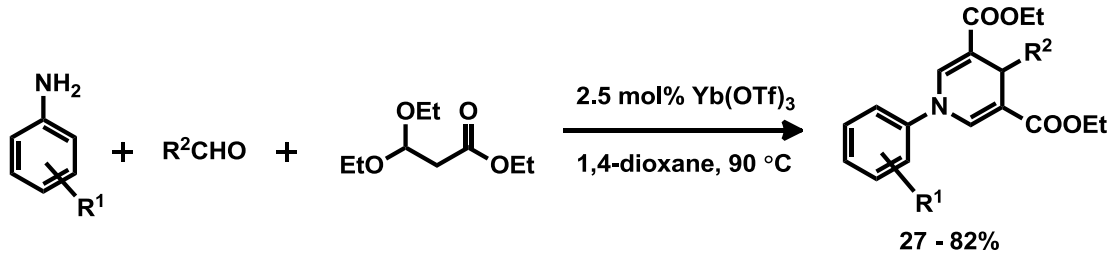
Scheme 1.5 Synthesis of 1,4-DHPs reported by Hong [30]

In the same year, Fananas and his colleges [31] reported gold-catalyzed synthesis of 2,5-DHP derivatives from ketoesters and propagylamines. Treatment of 0.05 equivalent of $NaAuCl_4$ in methanol at 40 °C for 48 hours was used as the condition to synthesize fifteen variations of 2.5-DHP derivatives (**Scheme 1.6**). They also declared the β-amino acrylate bearing alkyne terminus as the key intermediate.



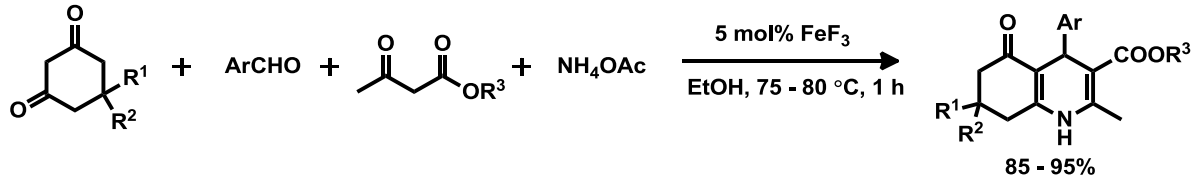
Scheme 1.6 Synthesis of 1,4-DHPs reported by Fananas and his team [31]

In 2011, Sueke and his team [32] demonstrated the one pot synthesis of 1,4-DHPs catalyzed by $YbOTf_3$. In their work, several Lewis acids were attempted for the condensation reaction of aniline, aldehyde, and acetal protected β-ketoester. A series of 1,4-DHPs were synthesized by using 2.5 mol% $YbOTf_3$ in 1,4-dioxane at 90 °C for 16 hours in moderate to good yields (**Scheme 1.7**).



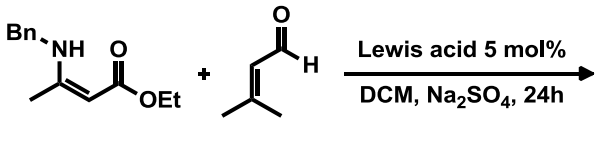
Scheme 1.7 Synthesis of 1,4-DHPs reported by Sueka and his team [32]

In 2012, using FeF_3 as a catalyst for 1,4-DHP synthesis was reported by Surasani's team. [33] Again under this modified Hantzsch's reaction, four components which are 1,3-cyclokexadione, aromatic aldehyde, β-ketoester, and ammonium acetate, reacts in a presence of 5 mol% FeF_3 under reflux temperature of ethanol for 1 hour to provide 1,4-DHP in excellent yields. Though CaF_2, CsF, KF, NH_4F, and TBAF were attempted as catalysts, none of these ionic compounds could produce the target DHP in more than 40% yield (**Scheme 1.8**).



Scheme 1.8 Synthesis of 1,4-DHPs reported by Surasani's team [33]

Coupling reaction in a presence of Lewis acid between β-amino acrylates and α,β-unsaturated aldehyde to give 1,4-DHP derivatives was reported in 2006 by Vohra and coworkers [34]. They modified the well known reaction, Hantzsch reaction, by using Lewis acid as a catalyst. Four Lewis acids which are $Zn(OAc)_2$, $CeCl_3$, $FeCl_3$, and $Sc(OTf)_3$ in catalytic amount were attempted to this coupling reaction (**Scheme 1.9**). The best catalyst that promoted the 1,4-DHP formation in moderate yield under mild condition without heat is $Sc(OTf)_3$.

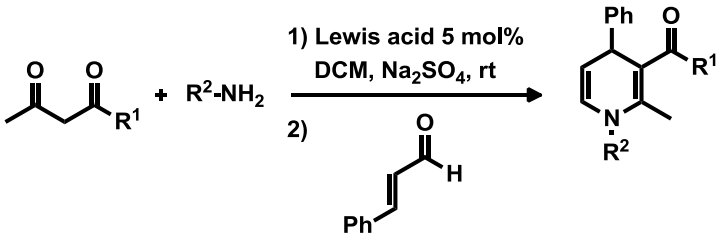


Lewis acid	%yield
$Zn(OAc)_2 \cdot 6H_2O$	no reaction *
$CeCl_3 \cdot 7H_2O$	15
$FeCl_3 \cdot 6H_2O$	53*
$Sc(OTf)_3$	54

* after reflux

Scheme 1.9 Synthesis of 1,4-DHPs reported by Vohra [34]

Continuously, in the same paper, Vohra also reported the one pot reaction to 1,4-DHP without the separation of such enamine intermediate (**Scheme 1.10**). According to the %yield presented in **Scheme 1.9**, $FeCl_3$ and $Sc(OTf)_3$ were selected for this reaction. Under this condition, coupling reaction between β-ketoester and primary aliphatic amine, followed by addition of α,β-unsaturated aldehyde was successfully operated in one pot and gave the target 1,4-DHPs in very good yields.



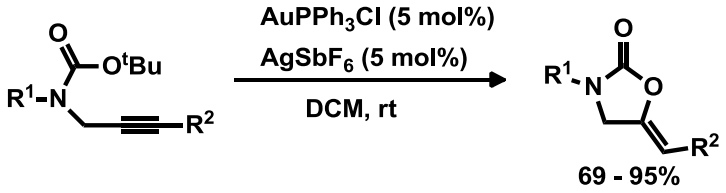
Lewis acid	R^1	R^2	%yield
$FeCl_3 \cdot 6H_2O$	OEt	Bn	98
$Sc(OTf)_3$	OEt	Bn	75
	OEt	*n*-Bu	80
	Me	*n*-Bu	80

Scheme 1.10 One pot synthesis of 1,4-DHPs reported by Vohra [34]

1.6 The use of protecting group as reacting site in acidic condition

In general, protecting groups may be used to avoid unwanted side reactions or prevent some important groups from reacting with reagents. As previously mentioned, selected β-amino acrylates contain five active sites (acetal + 4 active sites from β-amino acrylates, see **Section 1.4**), so that it is easy to give the side reaction for example dimerization and polymerization. According to the structure of selected β-amino acrylates, using nitrogen protecting group such as Boc-group seems to be the best choice to handle under acidic condition. Although the Boc-group is sensitive to acids, it can help preventing such dimerization and polymerization effect. Also during the deprotection process, Boc-group may act like the nucleophile itself to intramolecularly attack the electrophilic site within the molecule.

Interestingly, Robles-Machin and his team found a cyclization example which Boc-group participated in cyclization step. [35] In 2006, Spanish researchers used 5 mol% of $AuPPh_3Cl$ and 5 mol% of $AgSbF_6$ as a co-catalyst system for oxazolidin-2-one synthesis (**Scheme 1.11**). Under ordinary condition, gold-silver catalyst induces carbonyl oxygen to cyclize with activated alkyne to form 5-membered ring, oxazolidin-2-one product in up to 91% (5-*exo*-dig).



Scheme 1.11 Synthesis of oxazolidi-2-one derivatives reported by Robles-Machin [35]

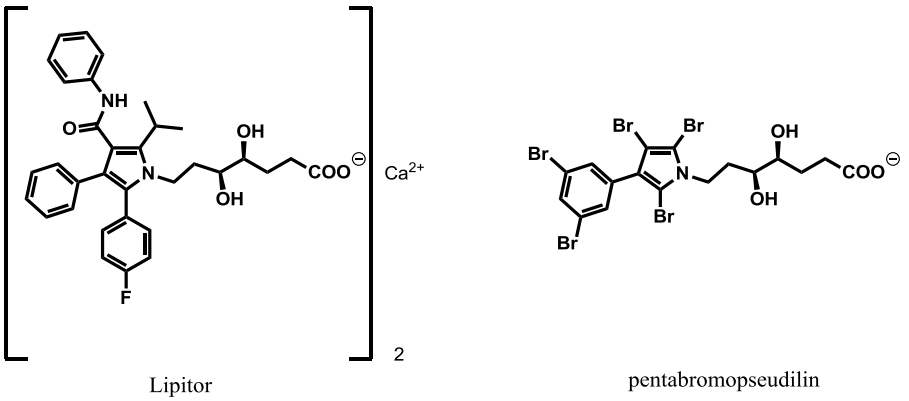
1.7 Target products

In accordance with several reviews above, the potential products of β-amino acrylates or *N*-protected β-amino acrylates from both intermolecular and intramolecular cyclization process are various *N*-heterocyclic compounds such as pyrrolidine, pyrrole, oxazolidin-2-one, and 1,4-DHP. All of these products can also be the main products of the research. Hopefully, the reaction of β-amino acrylates under acidic condition is possibly a novel route to the novel derivative of the product compounds that typically used for total synthesis of the high significance molecule.

1.7.1 Pyrroles

Pyrroles are very considerable heterocyclic compound because they have extensive biological activities, pharmaceutical properties. They also present in various natural products such as heme, chlorophyll, and vitamin B_{12}. The ring-closing reaction usually occurs *via* C-N formation between nucleophilic nitrogen and electrophilic moieties such as acetal, allyl bromide. Some examples of pyrrole derivatives that were used as commercial products are Lipitor and pentabromopseudilin (**Figure 1.8**). Lipitor has been used as a drug for lowering the cholesterol [(36)], and pentabromopseudilin as an antibacterial medicine [(37)].

Although, there are several effective methods to generate the pyrrole ring but some limitations such as requirement of strong base *tert*-BuOK, bad yield in the precursor preparation step are still very much problematic.



Lipitor pentabromopseudilin

Figure 1.8 Commercial medicines contain pyrrole moiety in their structure

1.7.2 Oxazolidin-2-ones

Oxazolidin-2-one is a heterocyclic compound containing nitrogen, carbonyl group and oxygen in a five-membered ring. For designed substrates, β-amino acrylates protected by Boc-protecting group could be cyclized itself in the same way by using acetal end as an electrophilic site instead of alkyne.

Ozaolidin-2-ones are very useful as both in organic synthetic field and pharmaceutical field. In the synthetic site, oxaolidin-2-ones are widely applied as chiral auxiliaries [38]. One of the famous chiral catalyst is Evans' type oxazolidinone for the asymmetric synthesis. For pharmaceutical site, oxazolidin-2-ones are familiarly to the use as antimicrobials that work as protein inhibitors [39-45]. Some derivatives are now available as the commercial medicines such as Linezolid [46-48] Posidolid [49], and Radezolid [50] (**Figure 1.9**).

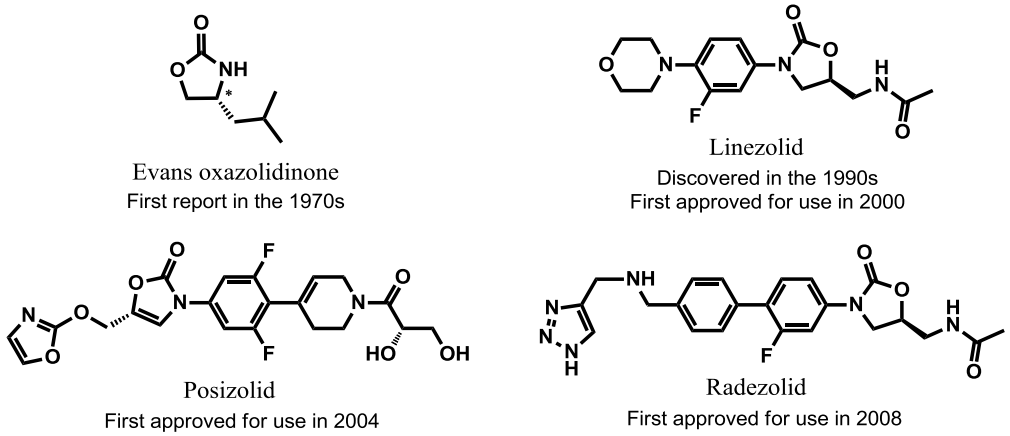
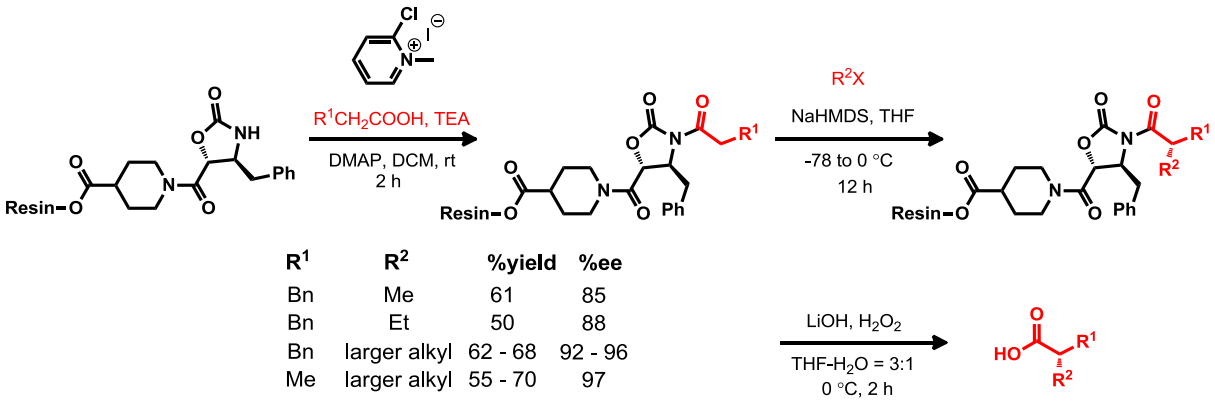


Figure 1.9 Commercial products contain oxazolidinone moiety in their structure

In 2005, Kotake and co-worker [51] reported the application of modified Evans-type oxazolidinone as chiral auxilliary in the solid-phase asymmetric alkylation reactions. In their research, they initially condensed R^1CH_2COOH to oxazolidinone nitrogen and then stereoselectively inserted R^2 at α-position of the amide carbonyl adjacent to R^1 via simple S_N2 mechanism under very strong and steric base. Finally, the reaction in a presence of $LiOH/H_2O_2$ dissociated the corresponding chiral carboxylic acid in excellent %ee (**Scheme 1.12**).

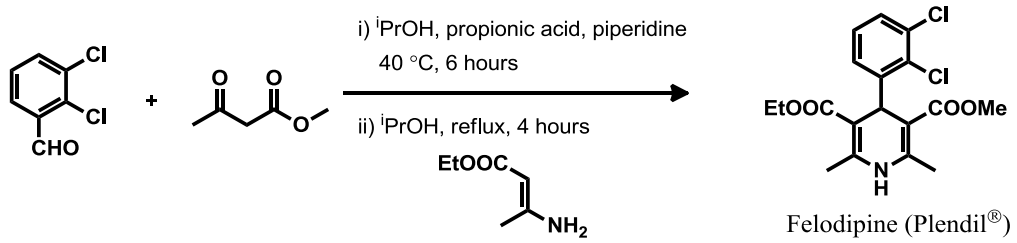


R^1	R^2	%yield	%ee
Bn	Me	61	85
Bn	Et	50	88
Bn	larger alkyl	62 - 68	92 - 96
Me	larger alkyl	55 - 70	97

Scheme 1.12 Modifying Evans-type oxazolidinone as a solid state chiral auxiliary for asymmetric alkylation reported by Kotake [51]

1.7.3 1,4-Dihydropyridines (1,4-DHP)

1,4-DHP is a 6-membered ring molecule based upon pyridine that one of three double bonds was substituted by two hydrogen atoms at 1 and 4-positions. The classic method for synthesizing DHP is Hantzsch's reaction (since 1881) [19], which condensed ammonia, aldehydes, and acetoacetate ester together (**Figure 1.2d**). Since then more than a century passed, there are numerous modified versions of Hantzsch's reaction. These modified methods were utilized for the synthesis of calcium channel blocker compounds containing 1,4-DHP as the core unit such as Felodipine or commercial name 'Plendil', as reported by Che and co-worker [52] in 2005 (**Scheme 1.13**). They treated the 2,3-dichlorobenzaldehyde with methyl acetoacetate in isopropanol solution. The adduct was then refluxed with β-amino acrylate to obtain target Felodipine in good yield.



Scheme 1.13 Synthesis of 'Plendil'reported by Che and co-worker [52]

In addition, over twenty 1,4-DHP derivatives are now commercially available for using as calcium antagonist [53-57]. Amongst them Plendil [58], Cleviprex [59], DynaCirc [60], Nifedipine [61], Nilvadil [62], and Nitrepin [63] are sold for more than million US dollars per year (**Figure 1.10**)

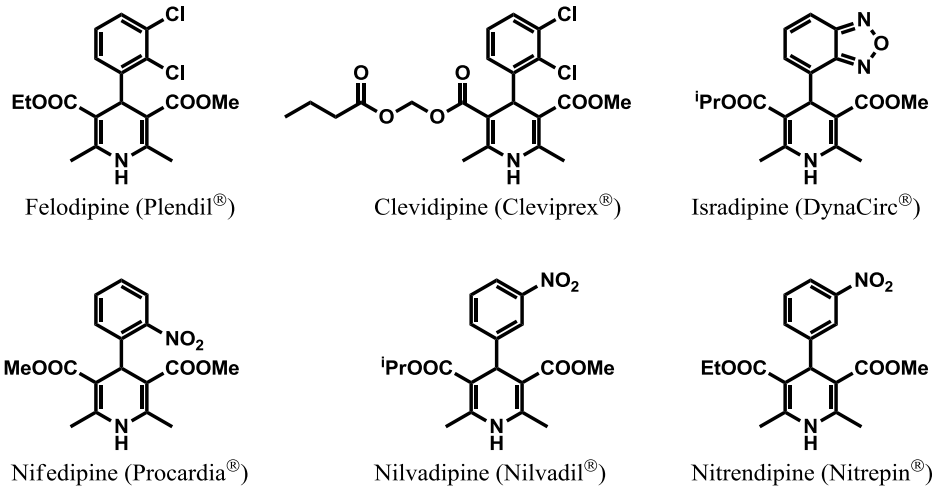


Figure 1.10 Commercial medicines containing 1,4-DHP moiety in their structures

This dissertation presents the reaction of β-amino acrylates contains aliphatic acetal terminus (n = 1) (**3**) in a present of mineral acids, non-protic acids, and Lewis acids, the reaction of *N*-protected β-amino acrylates (or β-amido acrylates) (**4**) under acidic conditions and the reaction of β-amino acrylates under acidic conditions (**Scheme 1.14**). The cyclization process will be attempted to use for the related substrates (**5**) and applied to use for the synthesis of some bioactive molecules or selective chemosensor.

Scheme 1.14 Investigation plan of this dissertation

The outline of this research include 1) preparation of β-amino acrylates and β-amido acrylates 2) cyclization of β-amino acrylates and β-amido acrylates under acidic conditions 3) characterization of the synthesized compound 4) optimization of cyclization method 5) utilization of synthetic method for synthesis of some bioactive molecules or selective chemosensor.

CHAPTER II

EXPERIMENTAL

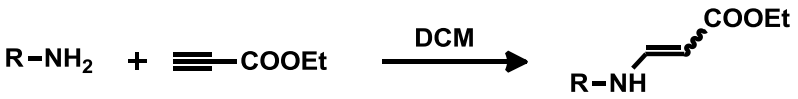
Materials: All reagents were obtained from Sigma-Aldrich, Merck® (Germany). For general reaction, solvents as follow: DCM, toluene, and methanol were reagent grade stored over 3Å or 4Å molecular sieves. For anhydrous reactions, DCM was dried over calcium hydride and distilled before use and THF was dried over Na/benzophenone and distilled prior to use. Column chromatography was operated using Merck silica gel 60 (SiO_2, 70-230 mesh, no. 7734) and extraction solvent such as hexane, EtOAc, and DCM were commercial grade and simply distilled before use. Deionized water was used in all experiments. For air-sensitive conditions, coverage gas was high purity nitrogen gas obtained from Thai Industrial Gases Public Company Limited.

Analytical instruments:

1D and 2D NMR spectra were recorded with a Varian Mercury 400 NMR spectrometer and a Bruker Avance 400 at 400 MHz and 100 MHz for ^{1}H and ^{13}C respectively. Chemical shifts (δ) were reported in ppm and coupling constants (J) were given in Hz. Spectra were referenced with respect to the residual peak for the deuterated solvent. FTIR spectra were recorded with the Nicolet 6700 FT-IR spectrometer equipped with a global source and DTGS detector in region 4000 – 400 cm^{-1}. High resolution mass spectra were obtained on a micrOTOF, Bruker Daltonics electronspray ionization mass spectrometer.

2.1 Preparation of enamine substrates

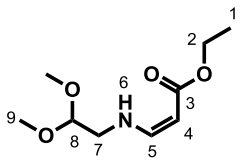
2.1.1 Preparation of aliphatic enamine



5

Ethyl propiolate (1.2 equivalent) was added dropwise to a solution of aliphatic amine in DCM (0.2 – 0.5 M). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 10 hours and concentrated under vacuum. Purification was accomplished by flash chromatography on silica gel eluting with 1 : 10 EtOAc/hexane to provide the corresponding aliphatic enamines (**3, 5a - 5d**)

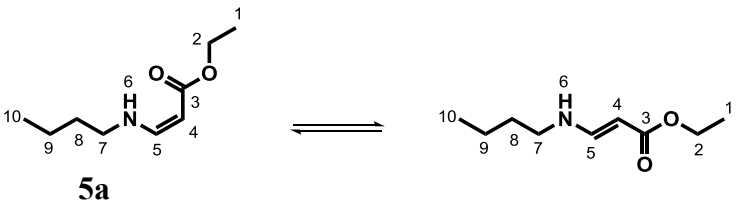
Ethyl-3-(2,2-dimethoxyethylamino)acrylate (**3**)



3

The product was synthesized starting from aminoacetaldehyde dimethylacetal (500 mg, 4.76 mmol) following to the procedure 2.1.1 as a pale yellow oil (880 mg, 91%) as a *cis*-isomer; R_f (25% EtOAc/Hexane) = 0.25; ν_{max} (neat) 3350, 2986, 2937, 2837, 1663, 1618, 1476, 1372, 1194, 1125, 1070 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.79 (1H, s (br), H-6), 6.57 (1H, dd, J = 8.1, 1.4 Hz, H-5), 4.46 (1H, dd, J = 8.1, 1.7 Hz, H-4), 4.30 (1H, dt, J = 5.3, 1.6 Hz, H-8), 4.08 (2H, dq, J = 7.1, 1.7 Hz, H-2), 3.38 (6H, 2s, H-9), 3.21 (2H, t, J = 5.8 Hz, H-7), 1.23 (3H, dt, J = 7.1, 1.7 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 170.6, 152.3, 103.9, 82.8, 58.6, 54.6 (2C), 50.3, 14.5; HRMS (ESI): M+Na^+, found 226.1042. $C_9H_{17}NNaO_4^+$ requires 226.1050.

***Ethyl-3-(butylamino)acrylate* (5a)**



5a

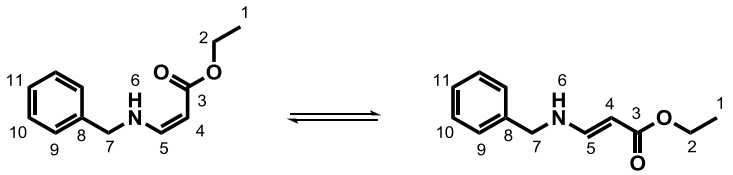
The product was synthesized starting from *n*-butylamine (450 mg, 6.15 mmol) following to the procedure 2.1.1 as a pale yellow oil (917 mg, 87%) as a 1:3 mixture of *trans*- and *cis*-isomers; R_f (25% EtOAc/Hexane) = 0.45; ν_{max} (neat) 3332, 2960, 2929, 2873, 1667, 1625, 1479, 1198, 1149, 1052 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.94 - 7.64 (0.75H, br, H-6 *(cis)*), 7.46 (0.25H, dd, *J* = 13.1, 8.1 Hz, H-5 *(trans)*), 6.58 (0.75H, dd, *J* = 13.2, 8.0 Hz, H-5 *(cis)*), 4.67 (0.50H, d (br), *J* = 13.2 Hz, H-6 *(trans),* H-4 *(trans)*), 4.39 (0.75H, d, *J* = 8.0 Hz, H-4 *(cis)*), 4.11-4.00 (2H, m, H-7), 3.11 (1.50H, dd, *J* = 13.2, 6.6 Hz, H-2 *(cis)*), 2.99 (0.50H, dd, *J* = 12.6, 6.7 Hz, H-2 *(trans)*), 1.59- 1.39 (2H, m, H-8), 1.32 (2H, dq, *J* =14.6, 7.2 Hz, H-9), 1.21 (3H, t, *J* = 7.1 Hz, H-1), 0.88 (3H, t, *J* = 7.3 Hz, H-10); δ_C (100 MHz, $CDCl_3$): 170.8 *(cis)*, 169.6 *(trans)*, 152.3, 85.1 *(trans)*, 81.2 *(cis)*, 58.8 *(trans)*, 58.4 *(cis)*, 48.2, 33.2, 19.6, 14.5, 13.6; HRMS (ESI): M+Na^+, found 194.1159. $C_9H_{17}NNaO_2^+$ requires 194.1151.

Ethyl-3-(octadecylamino)acrylate **(5b)**

5b

The product was synthesized starting from octadecylamine (200 mg, 0.74 mmol) following to the procedure 2.1.1 as a yellow solid (254 mg, 93%) as a *cis*-isomer; m.p. 59 - 63 °C; R_f (25% EtOAc/Hexane) = 0.75; ν_{max} (neat) 3332, 2920, 2851, 1665, 1614, 1466, 1194, 1149, 1039 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.90-7.75 (1H, m, H-6), 6.61 (1H, dd, *J* = 13.2, 8.0 Hz, H-5), 4.43 (1H, d, *J* = 8.0 Hz, H-4), 4.10 (2H, td, *J* = 14.2, 5.0 Hz, H-7), 3.13 (2H, q, *J* = 6.7 Hz, H-2), 1.51 (2H, td, *J* = 14.1, 7.0 Hz, H-8), 1.35 - 1.13 (33H, m, H-1 and H-9 to H-23), 0.87 (3H, t, *J* = 6.8 Hz, H-24); δ_C (100 MHz, $CDCl_3$): 152.4, 81.2, 58.6, 48.7, 31.9, 31.3, 29.7-29.6 (10C, br), 29.5, 29.4, 29.3, 26.5, 22.7, 14.6, 14.1; HRMS (ESI): $M+H^+$, found 368.3523. $C_{23}H_{46}NO_2^+$ requires 368.3523.

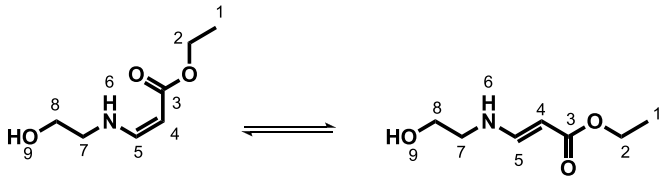
Ethyl-3-(benzylamino)acrylate **(5c)**



5c

The product was synthesized starting from benzyl amine (500 mg, 4.67 mmol) following to the procedure 2.1.1 as a pale yellow oil (862 mg, 90%) as a 1 : 2 mixture of *trans*- and *cis*-isomers; R_f (25% EtOAc/Hexane) = 0.35; ν_{max} (neat) 3333, 3056, 3023, 2977, 2937, 2900, 1668, 1612, 1483, 1452, 1191, 1142, 1055 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 8.20 - 8.00 (0.67H, br, H-6 *(cis)*), 7.58 (0.33H, dd, *J* = 13.2, 8.0 Hz, H-5 *(trans)*), 7.40 - 7.19 (5H, m, H-9 to H-11), 6.69 (0.67H, dd, *J* = 13.0, 8.1 Hz, H-5 *(cis)*), 4.90 - 4.70 (0.66H, d (br), *J* = 13.3 Hz, H-6 *(trans)* and H-4 *(trans)*), 4.54 (0.67H, d, *J* = 8.1 Hz, H-4 *(cis)*), 4.34 (0.67H, d, *J* = 6.0 Hz, H-7 *(cis)*), 4.21 (0.33H, d, *J* = 5.3 Hz, H-7 *(trans)*), 4.12 (2H, q, *J* = 7.1 Hz, H-2), 1.25 (3H, dt, *J* = 7.1, 3.3 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 170.8 *(cis)*, 169.5 *(trans)*, 152.0, 138.5, 128.8 *(trans)*, 128.7 *(cis)*, 127.8 *(trans)*, 127.5 *(cis)*, 127.1, 86.8 *(trans)*, 82.8 *(cis)*, 59.0 *(trans)*, 58.7 *(cis)*, 52.1, 14.5; HRMS (ESI): $M+Na^+$, found 228.0993. $C_{12}H_{15}NNaO_2^+$ requires 228.0995.

***Ethyl-3-(2-hydroxyethylamino)a*crylate (5d)**



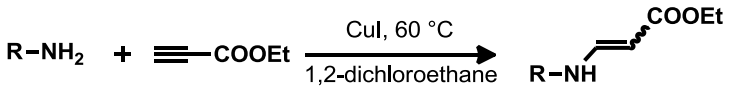
5d

The product was synthesized starting from 2-hydroxyethylamine (200 mg, 3.27 mmol) following to the procedure 2.1.1 as a pale yellow solid (494 mg, 95%) as a 1:1 mixture of *trans*- and *cis*-isomers; m.p. 36 - 38 °C; R_f (50% EtOAc/Hexane) = 0.20; ν_{max} (neat) 3346, 2976, 2930, 1666, 1606, 1162, 1050 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 8.00-7.80 (0.5H, br, H-6 (*cis*)), 7.53 (0.5H, dd, *J* = 13.3, 8.3 Hz, H-5 (*trans*)), 6.66 (0.5H, dd, *J* = 13.1, 8.0 Hz, H-5 (*cis*)), 5.10 - 5.00 (0.5H, br, H-6 (*trans*)), 4.74 (0.5H, d, *J* = 13.3 Hz, H-4 (*trans*)), 4.50 (0.5H, d, *J* = 8.0 Hz, H-4 *(cis*)), 4.11 (2H, 2q, *J* = 7.1 Hz, H-8), 3.77 (1H, t, *J* = 5.0 Hz, H-7 (*cis*)), 3.69 (1H, t, *J* = 4.7 Hz, H-7 (*trans*)), 3.30 (1H, dd, *J* = 11.2, 5.5 Hz, H-8 (*cis*)), 3.20 (1H, dd, *J* = 10.5, 5.3 Hz, H-8 (*trans*)), 2.43 - 2.32 (0.5H, br, H-9 (*cis*)), 2.32 - 2.20 (0.5H, br, H-9 (*trans)*), 1.25 (3H, dt, *J* = 7.1, 2.5 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 171.0 *(cis)*, 169.9 *(trans)*, 152.6, 86.1 (*trans*), 82.6 (*cis*), 62.6, 59.1 (*cis*), 58.8 (*trans*), 50.7, 14.5; HRMS (ESI): $M+Na^+$, found 182.0798. $C_7H_{13}NNaO_3^+$ requires 182.0788.

2.1.2 Scanning and optimization of the catalysts for aromatic enamine preparation by NMR experiment

4-Iodoaniline (0.2 g, 0.91 mmol) and ethyl propiolate (1.5 equivalent) were dissolved into chloroform-d (10 mL) under the nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 10 minutes and then injected to the NMR tubes by syringe (0.8 mL). To the mixed solution in each tube, a small piece of different catalysts (~2 - 5 mg) which are $CuSO_4$, CuI, $Zn(OAc)_2$, $AgNO_3$, and $BF_3{\cdot}OEt_2$ were weighted and added individually. The reaction was monitored by ^{1}H-NMR at the same time every day until the signals of the product stopped increasing. After that, the reaction tube was heated statically around 50 °C for one more day before the last ^{1}H-NMR monitoring.

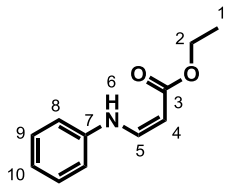
2.1.3 Preparation of aromatic enamine



5

To a solution of aniline in 1,2-dichloroethane (DCE), ethyl propiolate (1.2 equivalent) and CuI (0.5 equivalent) were added stepwise to a solution of anilines in 1,2-dichloroethane. The reaction mixture was stirred at 60 °C under nitrogen atmosphere for 10 hours, filtered out and concentrated under vacuum. Purification was accomplished by flash column chromatography on silica gel eluting with 1 : 10 EtOAc/hexane to provide the corresponding aromatic enamines (**5e - 5i**).

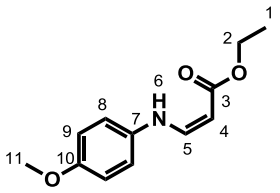
Ethyl-3-(phenylamino)acrylate **(5e)**



5e

The product was synthesized from aniline (500 mg, 5.37 mmol) following to the procedure 2.1.3 as a colorless oil (564 mg, 55%) as a *cis*-isomer; R_f (10% EtOAc/Hexane) = 0.50; ν_{max} (neat) 3307, 3054, 3031, 2982, 1667, 1628, 1598, 1488, 1453, 1242, 1190 cm-1; δ_H (400 MHz, $CDCl_3$): 9.92 (1H, d (br), *J* = 11.7 Hz, H-6), 7.36 - 7.18 (3H, m, H-5 and H-8), 7.05 - 6.88 (3H, m, H-9 and H-10), 4.85 (1H, d, *J* = 8.3 Hz, H-4), 4.19 (2H, q, *J* = 7.1 Hz, H-2), 1.31 (3H, t, *J* = 7.1 Hz, H-1) δ_C (100 MHz, $CDCl_3$): 170.3, 142.9, 140.6, 129.6 (2C), 122.4, 115.2 (2C), 87.3, 59.2, 14.4; HRMS (ESI): $M+Na^+$, found 214.0715. $C_{11}H_{13}NNaO_2^+$ requires 214.0838.

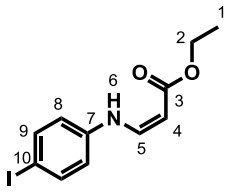
Ethyl-3-(4-methoxyphenylamino)acrylate **(5f)**



5f

The product was synthesized from 4-methoxyaniline (500 mg, 4.05 mmol) following to the procedure 2.1.3 as a yellow oil (296 mg, 33%) as a *cis*-isomer; R_f (17% EtOAc/Hexane) = 0.38; ν_{max} (neat) 3274, 3073, 3037, 2976, 2950, 1615, 1589, 1508, 1482, 1277, 1164 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.81 (1H, d (br), *J* = 12.6 Hz, H-6), 7.15 (1H, dd, *J* = 12.8, 8.3 Hz, H-5), 6.91 (2H, d, *J* = 9.0 Hz, H-9), 6.85 (2H, d, *J* = 9.0 Hz, H-8), 4.77 (1H, d, *J* = 8.2 Hz, H-4), 4.17 (2H, q, *J* = 7.1 Hz, H-2), 3.78 (3H, s, H-11), 1.30 (3H, t, *J* = 7.1 Hz, H-1) δ_C (100 MHz, $CDCl_3$): 170.5, 155.4, 144.1, 134.4, 116.9 (2C), 114.9 (2C), 86.0, 59.1, 55.5, 14.5; HRMS (ESI): $M+Na^+$, found 244.0828. $C_{12}H_{15}NNaO_3^+$ requires 244.0944.

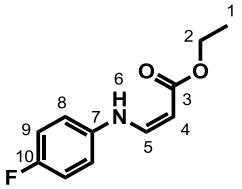
Ethyl-3-(4-iodophenylamino)acrylate **(5g)**



5g

The product was synthesized following to the procedure 2.1.3 from 4-iodoaniline (1.01 g, 4.61 mmol) in DCM solution at room temperature as a white solid (1.21 g, 83%) as a *cis*-isomer; m.p. 90 - 95 °C; R_f (20% EtOAc/Hexane) = 0.50; ν_{max} (neat) 3294, 3084, 2971, 1666, 1625, 1584, 1470, 1196 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 9.89 (1H, d (br), *J* = 11.6 Hz, H-6), 7.57 (2H, d, *J* = 8.7 Hz, H-9), 7.17 (1H, dd, *J* = 12.5, 8.4 Hz, H-5), 6.73 (2H, d, *J* =8.7 Hz, H-8), 4.87 (1H, d, *J* = 8.4 Hz, H-4), 4.17 (2H, q, *J* 7.1 Hz, H-2), 1.30 (3H, t, *J* 7.1 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 170.2, 142.2, 140.4, 138.4 (2C), 117.2 (2C), 88.4, 84.6, 59.4, 14.4; HRMS (ESI): $M+H^+$, found 317.9985. $C_{12}H_{15}NNaO_3^+$ requires 317.9986.

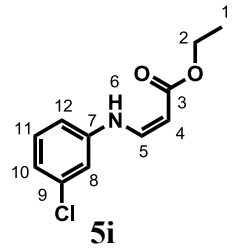
Ethyl-3-(4-fluorophenylamino)acrylate **(5h)**



5h

The product was synthesized from 4-fluoroaniline (500 mg, 4.50 mmol) following to the procedure 2.1.3 as a yellow solid (556 mg, 59%) as a *cis*-isomer; m.p. 35 - 38 °C; R_f (10% EtOAc/Hexane) = 0.50; ν_{max} (neat) 3305, 3275, 3071, 3948, 2980, 1665, 1624, 1600, 1509, 1478, 1197 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 9.87 (1H, d (br), *J* = 11.5 Hz, H-6), 7.15 (1H, dd, *J* = 12.6, 8.3 Hz, H-5), 7.06 - 6.95 (2H, m, H-9), 6.95 - 6.85 (2H, m, H-8), 4.82 (1H, d, *J* = 8.3 Hz, H-4), 4.17 (2H, q, *J* = 7.1 Hz, H-2), 1.34 - 1.27 (3H, m, H-3); δ_C (100 MHz, $CDCl_3$): 170.4, 158.5 (d, *J* = 241.3 Hz, C-10), 143.4, 137.0, 116.7 (2C, d, *J* = 7.9 Hz, C-8), 116.3 (2C, d, *J* = 23.0 Hz, C-9), 87.3, 59.3, 14.4; HRMS (ESI): $M+Na^+$, found 232.0663. $C_{11}H_{12}FNNaO_2^+$ requires 232.0744.

Ethyl-3-(3-chlorophenylamino)acrylate **(5i)**

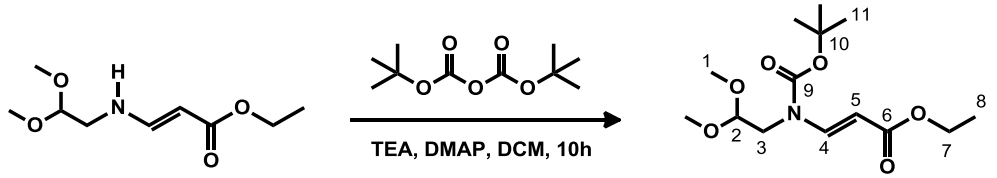


5i

The product was synthesized from 3-chloroaniline (411 mg, 3.22 mmol) following to the procedure 2.1.3 as a yellow solid (392 mg, 54%) as a *cis*-isomer; m.p. 51 - 52 °C; R_f (10% EtOAc/Hexane) = 0.48; ν_{max} (neat) 3067, 2982, 2927, 2898, 1670, 1635, 1599, 1469, 1203 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 9.91 (1H, d (br), *J* = 11.8 Hz, H-6), 7.19 (2H, td, *J* = 12.5, 7.2 Hz, H-5 and H-8), 6.95 (2H, d, *J* = 6.7 Hz, H-10 and H-12), 6.81 (1H, d, *J* = 7.8 Hz, H-11), 4.88 (1H, d, *J* = 8.4 Hz, H-4), 4.18 (2H, q, *J* = 7.1 Hz, H-2), 1.30 (3H, t, *J* = 7.1 Hz,H-1); δ_C (100 MHz, $CDCl_3$): 170.2, 142.2, 141.9, 135.4, 130.6, 122.3, 115.1, 113.6, 88.7, 59.5, 14.4; HRMS (ESI): $M+Na^+$, found 248.0346. $C_{11}H_{12}{}^{35}ClNNaO_2^+$ requires 248.0449.

2.2 Synthesis of a series of oxazolidinone derivatives (7a - 7d)

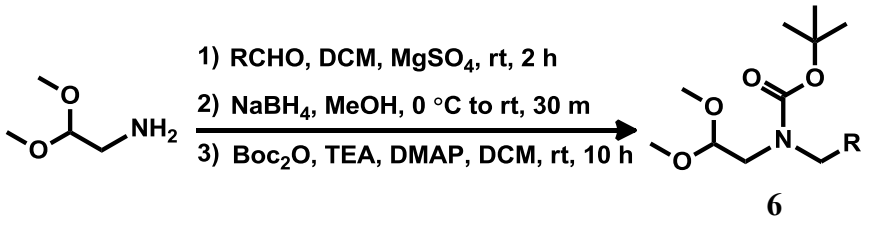
*2.2.1 Preparation of β-amido acrylate (**4**) from β-amino acrylate (**3**)*



3 **4**

TEA (2 equivalent), Boc_2O (1.2 equivalent) and DMAP (0.5 equivalent) were added to a solution of enamine (**3**) (667 mg, 3.28 mmol) in DCM (0.5 M), respectively. The reaction was stirred at room temperature under nitrogen atmosphere for 10 hours and concentrated under vacuum. Purification was accomplished by flash chromatography on silica gel eluting with 1 : 10 EtOAc/Hexane to provide the corresponding β-amido acrylate (**4**) as pale yellow oil. R_f (25% EtOAc/Hexane) = 0.45; δ_H (400 MHz, $CDCl_3$): 8.20 (1H, d, *J* = 14.0 Hz, H-4), 5.29 (1H, d, *J* = 14.0 Hz, H-5), 4.52 (1H, t, *J* = 5.2 Hz, H-2), 4.17 (2H, q, *J* = 7.2 Hz, H-7), 3.66 (2H, d, *J* = 5.2 Hz, H-3), 3.37 (6H, s, H-1), 1.52 (9H, s, H-11), 1.22 (3H, t, *J* = 7.2 Hz, H-8).

*2.2.2 Preparation of carbamate (**6**)*



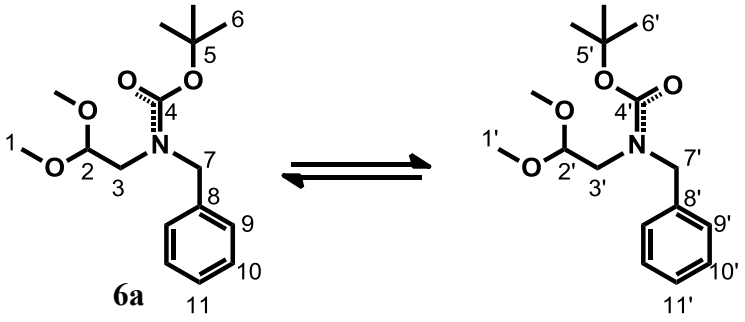
6

First step, aldehyde and aminoacetaldehyde dimethylacetal (1.2 equiv) were dissolved in DCM (0.2 – 0.5 M). After 10 minutes, $MgSO_4$ (4 equivalents) was then added to the solution. The reaction mixture was stirred at room temperature for 2 hours and concentrated under vacuum, filtered, washed by DCM (2 × 10 mL) and evaporated to give an imine intermediate.

Second step, the intermediate was dissolved in methanol (10 mM). The reaction was cooled in the ice bath and $NaBH_4$ (2 equivalent) was then added to the solution. The reaction mixture was stirred for 30 minutes, quenched by water (20 mL), extracted with EtOAc (2 × 10 mL), washed with brine (2 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated to obtain the corresponding secondary amine.

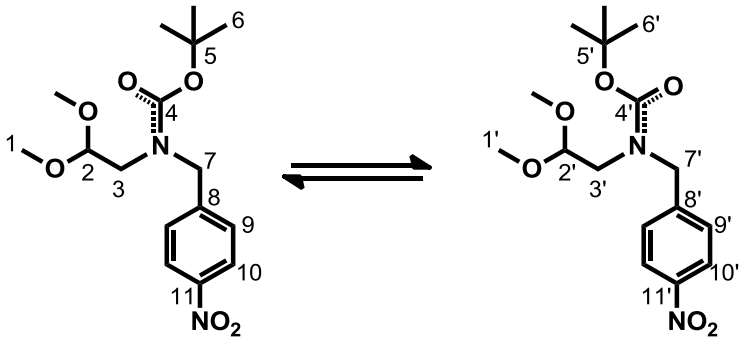
Third step, the obtained secondary amine was used in the reaction described previously as in the procedure 2.2.1.

tert-Butyl benzyl(2,2-dimethoxyethyl)carbamates (**6a**)



The product was synthesized from benzaldehyde (1.11 g, 10.5 mmol) following to the procedure 2.1.3 as a colorless oil (1.71 g, 55%); R_f (25% EtOAc/Hexane) = 0.40; δ_H (400 MHz, $CDCl_3$): 7.33 – 7.20 (5H, m, H-9, H-10, H-11, H-9', H-10' and H-11'), 4.54 – 4.43 (3H, m, H-2, H-7, H-2' and H-7'), 3.40 (3H, s, H-1), 3.36 (3H, s, H-1'), 3.31 (1H, d, J = 4.4 Hz , H-1), 3.20 (1H, d, J = 4.4 Hz , H-1), 3.38 (4.5. s. H-6), 3.38 (4.5. s. H-6').

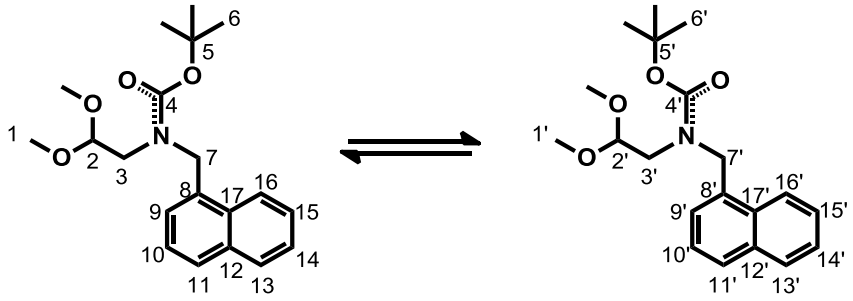
tert-Butyl (2,2-dimethoxyethyl)(4-nitrophenyl)carbamate (**6b**)



6b

The product was synthesized from 4-nitrobenzaldehyde (200 mg, 1.32 mmol) following to the procedure 2.1.3 as a pale yellow oil (286 mg, 64%); R_f (25% EtOAc/Hexane) = 0.40; δ_H (400 MHz, $CDCl_3$): 8.15 (2H, dd (br), *J* =7.3, 4.7 Hz, H-10 and H-10'), 7.35 (2H, t, *J* = 9.5 Hz, H-9 and H-9'), 4.60 (1H, s, H-7'), 4.56 (H, s, H-7), 4.49 (0.5H, t, *J* = 4.9 Hz, H-2), 4.40 (0.5H, t, *J* = 4.8 Hz, H-2'), 3.36 (7H, 2s, H-1, H-1' and H-3), 3.21 (1H, d, *J* = 4.9 Hz, H-3'), 1.49 (4.5H, s, H-6), 1.36 (4.5H, s, H-6'); δ_C (100 MHz, $CDCl_3$): 155.7, 155.5, 147.1, 146.8, 146.3, 128.2, 127.5, 123.8, 123.7, 104.3, 103.7, 80.7, 54.9, 51.9, 50.9, 49.4, 49.2, 28.5, 28.3.

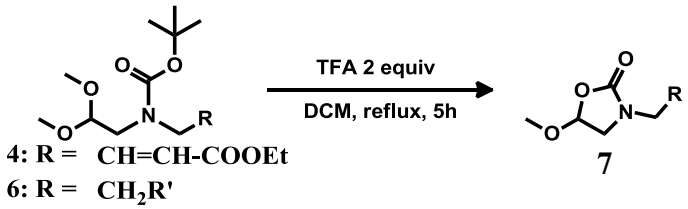
tert-Butyl (2,2-dimethoxyethyl)(naphthalen-1-ylmethyl)carbamate (**6c**)



6c

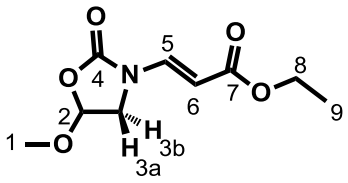
The product was synthesized from 1-naphthaladehyde (216 mg, 1.38 mmol) following to the procedure 2.1.3 as a colorless oil (311 mg, 65%); R_f (25% EtOAc/Hexane) = 0.50; δ_H (400 MHz, $CDCl_3$): 8.17 (0.5H, d, *J* = 7.8 Hz, H-16), 8.04 (0.5H, d, *J* = 6.8 Hz, H-16'), 7.86 (1H, m, H-13 and H-13'), 7.79 (1H, d, *J* = 8.2 Hz, H-11 and H-11'), 7.57 – 7.30 (4H, m, H-9, H-10, H-14, H-15, H-9', H-10', H-14' and H-15'), 5.08 (3.4H, s, H-7'), 5.05 (2.6H, s, H-7), 4.61 (0.9H, m, H-2) , 4.55 (1.1H, m, H-2'), 3.38 (7H, 2s, H-1, H-1' and H-3), 3.19 (1H, d, *J* = 4.5 Hz, H-3'), 1.52 (5H, s, H-6) , 1.48 (4H, s, H-6'); δ_C (100 MHz, $CDCl_3$): 155.8, 155.6, 133.9, 133.4, 131.9, 131.4, 128.8, 128.6, 128.2, 127.7, 126.8, 126.2, 126.0, 125.7, 125.3, 124.7, 124.0, 123.1, 104.5, 103.7, 80.1, 54.7, 49.4, 48.5, 48.1, 47.3, 28.5.

*2.2.3 Synthesis of a series of oxazolidinone derivatives (**7a - 7d**)*



To a solution of amide (**4** and **6**) in DCM (0.2 M), TFA (2 equivalents) was slowly added and the reaction mixture was refluxed for 5 hours, quenched by 0.2 M $NaHCO_3$ (20 mL), extracted with DCM (2 × 20 mL) and concentrated under vacuum. Purification was accomplished by flash column chromatography on silica gel eluting with 1 : 7 EtOAc/hexane to provide the corresponding oxazolidinone derivatives (**7a – 7d**).

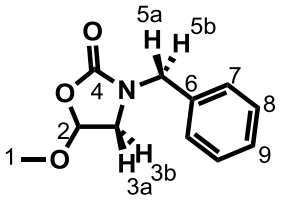
(E)-ethyl 3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate (**7a**)



7a

The product was synthesized from enamide **4** (98 mg, 0.32 mmol) following to the procedure 2.2.3 as a yellow solid (58 mg, 81%); R_f (25% EtOAc/Hexane) = 0.10; δ_H (400 MHz, $CDCl_3$): 7.93 (1H, d, *J* = 14.2 Hz, H-5), 5.55 (1H, dd, *J* = 6.4, 2.5 Hz, H-2), 5.13 (1H, d, *J* = 14.1 Hz, H-6), 4.20 (2H, q, *J* = 7.1 Hz, H-8), 3.84 (1H, dd, *J* = 10.6, 6.4 Hz, H-3a), 3.57 (3H, s, H-1), 3.53 (1H, dd, *J* = 10.6, 2.5 Hz, H-3b), 1.26 (3H, t, *J* = 7.1 Hz, H-9); δ_C (100 MHz, $CDCl_3$): 166.9, 153.2, 137.9, 100.2, 97.8, 65.7, 51.2, 48.9, 14.8. All data are identical to those reported in the literature. [64]

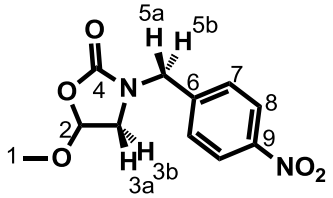
3-benzyl-5-methoxyoxazolidin-2-one (**7b**)



7b

The product was synthesized from amide **6a** (500 mg, 1.69 mmol) following to the procedure 2.2.3 as a yellow oil (295 mg, 84%); R_f (25% EtOAc/Hexane) = 0.10; δ_H (400 MHz, $CDCl_3$): 7.37 - 7.25 (5H, m, H-7, H-8 and H-9), 5.34 (1H, dd, *J* = 6.4, 2.3 Hz, H-2), 4.48 (1H, d, *J* = 15.0 Hz, H-5a), 4.42 (1H, q, *J* = 15.0 Hz, H-5b), 3.90 – 3.45 (4H, dd, *J* = 10.6, 6.4 Hz, H-1 and H-3a), 3.21 (1H, dd, *J* = 10.0, 2.3 Hz, H-3b); δ_C (100 MHz, $CDCl_3$): 156.3, 135.1, 128.4, 127.6, 127.5, 97.8, 55.8, 49.8,47.3; HRMS (ESI): $M+H^+$, found 208.0973. $C_{11}H_{14}NO_3^+$ requires 208.0968.

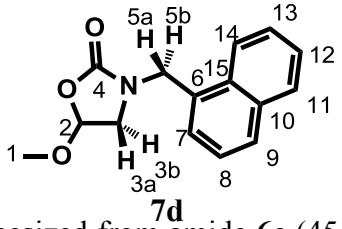
5-methoxy-3-(4-nitrobenzyl)oxazolidin-2-one (**7c**)



7c

The product was synthesized from amide **6b** (66 mg, 0.19 mmol) following to the procedure 2.2.3 as a colorless oil (45 mg, 92%); R_f (50% EtOAc/Hexane) = 0.13; ν_{max} (neat) 3099, 3073, 2916, 2845, 1746, 1525, 1345 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 8.21 (2H, d, *J* = 8.6 Hz, H-7), 7.44 (2H, d, *J* = 8.4 Hz, H-8), 5.39 (1H, dd, *J* = 6.3, 2.1 Hz, H-2), 4.61 (1H, d, *J* = 15.9 Hz, H-5a), 4.48 (1H, d, *J* = 15.9 Hz, H-5b), 3.60 (1H, dd, *J* = 9.9, 6.3 Hz, H-3a), 3.52 (3H, s, H-1), 3.25 (1H, dd, *J* = 9.9, 2.1 Hz, H-3b); δ_C (100 MHz, $CDCl_3$): 156.6, 147.6, 142.9, 128.4 (2C), 124.0 (2C), 98.1, 56.3, 50.4, 47.0; HRMS (ESI): $M+Na^+$, found 275.0664. $C_{11}H_{12}N_2NaO_5^+$ requires 275.0638.

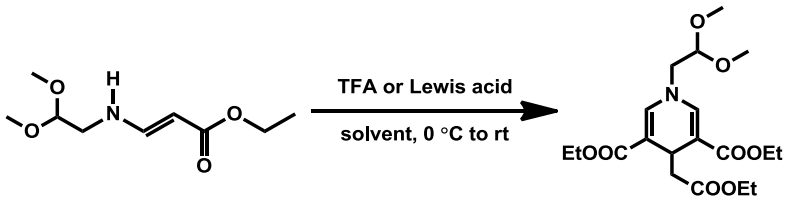
5-methoxy-3-(naphthalen-1-ylmethyl)oxazolidin-2-one (**7d**)



7d

The product was synthesized from amide **6c** (45 mg, 0.13 mmol) following to the procedure 2.2.3 as a colorless oil (28 mg, 84%); R_f (50% EtOAc/Hexane) = 0.50; ν_{max} (neat) 3049, 3001, 2933, 2837, 1745, 1481, 1217 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 8.12 (1H, d, *J* = 8.3 Hz, H-14), 7.86 (2H, dd, *J* = 16.2, 7.8 Hz, H-9 and H-11), 7.62 – 7.49 (2H, m, H-7 and H-8), 7.48 – 7.35 (2H, m, H-12 and H-13), 5.32 – 5.24 (1H, m, H-2), 5.00 (1H, d, *J* = 14.8 Hz, H-5a), 4.80 (1H, d, *J* = 14.8 Hz, H-5b), 3.47 (3H, s, H-1), 3.39 (1H, dd, *J* = 10.1, 6.5 Hz, H-3a), 3.15 (1H, dd, *J* = 10.1, 2.4 Hz, H-3b); δ_C (100 MHz, $CDCl_3$): 156.2, 133.8, 131.4, 130.9, 129.1, 128.7, 127.2, 126.9, 125.1, 123.4, 98.0, 56.1, 50.2, 46.1; HRMS (ESI): $M+Na^+$, found 280.0970. $C_{15}H_{15}NNaO_3^+$ requires 280.0944.

2.3 Optimization for 1,4-DHP formation with several Lewis acid

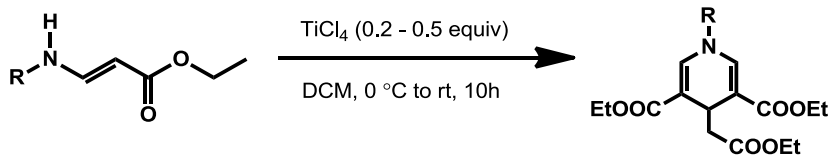


3 **8a**

Brønsted acid or Lewis acid was slowly added to the cold solution of ethyl β-amino acrylates (**3**) (100 mg, 0.25 mmol) in dry solvent (0.01 M). The reaction was allowed to stay at room temperature under nitrogen atmosphere and monitored by using TLC until the starting material spot disappeared. If the reaction was incomplete after one hour, reagent (0.2 equivalent) was added. When the reaction finished, it was quenched with ice (25 mL), extracted with DCM (25 mL), The combined organic portions were neutralized by 0.1 M $NaHCO_3$ (25 mL), washed with DI water (25 mL × 3), concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (EtOAc/hexane = 1:50 to 1:3) to provide the 1,4-DHP (**8a**) as a pale yellow oil, R_f (25 % EtOAc/Hexane) = 0.38

Lewis acid (solvent)	**Amount of Lewis acid (equivalent)**	**Reaction time**
TFA (DCM)	0.5 – 2	10 hours
$AlCl_3$ (THF)	0.3	3 hours
	0.5	3 hours
	1	3 hours
$AlCl_3$ (DCM)	0.3	3 hours
$AlMeCl_2$ (THF)	0.2 - 0.5	10 hours
$BF_3{\cdot}OEt_2$ (THF)	0.3	10 hours
	0.3	2 days
	0.5	2 days
$TiCl_4$ (DCM)	0.2	10 hours

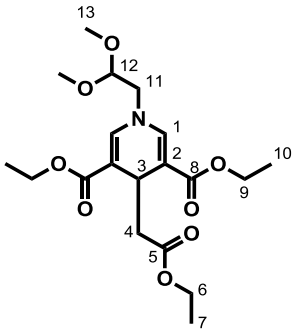
2.4 Synthesis of a series of 1,4-DHP derivatives (8a - 8j)



5 **8**

Titanium tetrachloride (0.2 equivalent for *N*-aliphatic enamine substrates or 0.5 equivalent for *N*-aromatic enamine substrates) was quickly injected to the cold solution of enamine (**5**) (1 equivalent) in anhydrous DCM (0.2 M). The reaction mixture was allowed to stir at room temperature under nitrogen atmosphere for 10 hours, quenched with ice (25 mL), extracted with DCM (25 mL). Combined organic portions were neutralized by 0.1 M $NaHCO_3$ (25 mL), washed with DI water (25 mL × 3), concentrated under vacuum. The crude oil was then purified by flash column chromatography on silica gel (EtOAc/hexane = 1 : 50 to 1 : 3) to provide the analogous DHPs (**8a - 8j**).

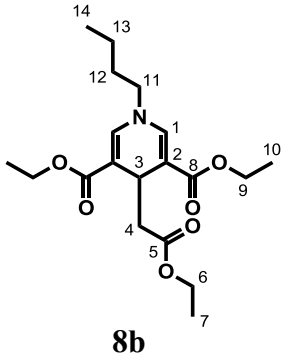
Diethyl-1-(2,2-dimethoxyethyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8a**)



8a

The product was synthesized from ethyl-3-(2,2-dimethoxyethylamino) acrylate (**3**) (577 mg, 2.84 mmol) following to the procedure 2.4 as a pale yellow oil (307 mg, 81%); R_f (25% EtOAc/Hexane) = 0.38; ν_{max} (neat) 2981, 2934, 1731, 1705, 1583, 1415, 1250, 1184, 1079 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.15 (2H, s, H-1), 4.39 (1H, t, *J* = 5.1 Hz, H-12), 4.23 - 4.16 (5H, m, H-3, H-9), 4.03 (2H, q, *J* = 7.1 Hz, H-6), 3.43 (6H, s, H-13), 3.37 (2H, d, *J* = 5.1 Hz, H-11), 2.47 (2H, d, *J* = 5.0 Hz, H-4), 1.29 (6H, t, *J* = 7.1 Hz, H-10), 1.21 (3H, t, *J* = 7.1 Hz, H-7); δ_C (100 MHz, CDCl3): 171.7, 166.9 (2C), 139.8 (2C), 106.1 (2C), 103.4, 60.1 (2C), 59.9, 56.4, 55.1 (2C), 40.7, 29.2, 14.4 (2C), 14.1; HRMS (ESI): $M+H^+$, found 400.1971. $C_{19}H_{30}NO_8^+$ requires 400.1967.

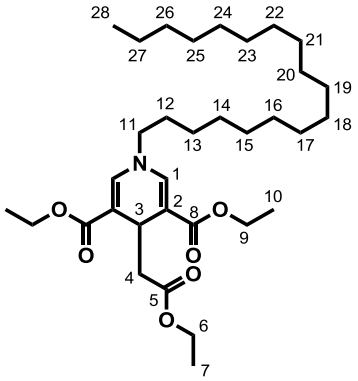
Diethyl-1-butyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8b**)



8b

The product was synthesized following to the procedure 2.4 from ethyl-3-(butylamino) acrylate (**5a**) (450 mg, 2.63 mmol) as a pale yellow oil (262 mg, 81%); R_f (25% EtOAc/Hexane) = 0.28; ν_{max} (neat) 2975, 2957, 2932, 1731, 1699, 1580, 1196, 1081 cm^{-1}; δ_H (400 MHz, $CDCl_3$: 7.12 (2H, s, H-1), 4.23 - 4.15 (5H, m, H-3, H-9), 4.03 (2H, q, *J* = 7.1 Hz, H-6), 3.30 (2H, t, *J* = 7.2 Hz, H-11), 2.45 (2H, d, *J* = 5.0 Hz, H-4), 1.66-1.53 (2H, m, H-12), 1.41 - 1.31 (2H, m, H-13), 1.29 (6H, t, *J* = 7.1 Hz, H-10), 1.20 (3H, t, *J* = 7.2 Hz, H-7), 0.95 (3H, t, *J* = 7.3 Hz, H-7); δ_C (100 MHz, $CDCl_3$): 171.7, 166.9 (2C), 139.3 (2C), 105.7 (2C), 60.0 (2C), 59.9, 54.7, 40.9, 32.3, 29.5, 19.5, 14.4 (2C), 14.1, 13.6; HRMS (ESI): $M+Na^+$, found 390.1887. $C_{19}H_{29}NNaO_6^+$ requires 390.1887.

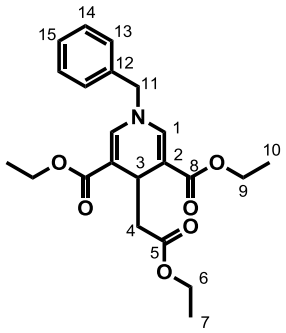
Diethyl-4-(2-ethoxy-2-oxoethyl)-1-octadecyl-1,4-dihydropyridine-3,5dicarboxylate (**8c**)



8c

The product was synthesized from ethyl-3-(octadecylamino) acrylate (**5b**) (318 mg, 0.87 mmol) following to the procedure 2.4 as a pale yellow oil (134 mg, 83%); R_f (25% EtOAc/Hexane) = 0.20; ν_{max} (neat) 2929, 2850, 1736, 1697, 1211, 1175, 1072 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.12 (2H, s, H-1), 4.23 - 4.15 (5H, m, H-3, H-9), 4.02 (2H, q, *J* = 7.1 Hz, H-6), 3.28 (2H, t, *J* = 7.3 Hz, H-11), 2.45 (2H, d, *J* = 5.0 Hz, H-4), 1.65 - 1.55 (2H, m, H-12), 1.43-1.11 (39H, m, H-7, H-10, H-13 to H-27), 0.87 (3H, t, *J* = 6.8 Hz, H-28); δ_C (100 MHz, $CDCl_3$): 171.7, 166.9 (2C), 139.3 (2C), 105.7 (2C), 60.0 (2C), 59.9, 54.9, 40.9, 31.9, 30.3, 29.8-29.6 (11C, br), 29.5, 29.3, 26.2, 22.7, 14.4 (2C), 14.2, 14.1; HRMS (ESI): $M+H^+$, found 564.4259. $C_{33}H_{58}NO_6^+$ requires 564.4259.

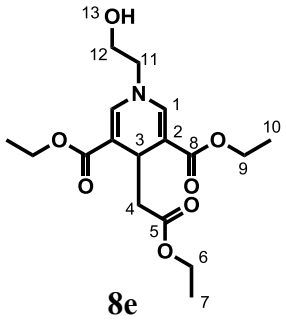
***Diethyl-1-benzyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate* (8d)**



8d

The product was synthesized from ethyl-3-(benzylamino) acrylate (**5c**) (401 mg, 1.95 mmol) following to the procedure 2.4 as a pale yellow oil (207 mg, 79%); R_f (25% EtOAc/Hexane) = 0.25; ν_{max} (neat) 3060, 3029, 2979, 2928, 1731, 1698, 1582, 1241, 1186, 1077 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.47 - 7.21 (5H, m, H-13 to H-15), 7.19 (2H, s, H-1), 4.50 (2H, s, H-11), 4.23-4.13 (5H, m, H-3, H-9), 3.99 (2H, q, *J* = 7.1 Hz, H-6), 2.50 (2H, d, *J* = 5.0 Hz, H-4), 1.27 (6H, t, *J* = 7.1 Hz, H-10), 1.16 (3H, t, *J* = 7.1 Hz, H-7); δ_C (100 MHz, $CDCl_3$): 171.7, 166.7 (2C), 139.4 (2C), 129.0 (2C), 128.2 (2C), 127.1, 109.9, 106.4 (2C), 60.1 (2C), 59.9, 58.0, 40.8, 29.5, 14.3 (2C), 14.1; HRMS (ESI): $M+H^+$, found 402.1916. $C_{22}H_{28}NO_6^+$ requires 402.1911.

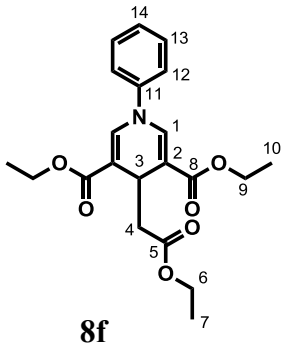
Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl)-1,4-di-hydropyridine-3,5-dicarboxylate (**8e**)



8e

The product was synthesized from ethyl-3-(2-hydroxyethylamino) acrylate (**5d**) (500 mg, 3.14 mmol) following to the procedure 2.4 as a pale yellow solid (303 mg, 81%); m.p. 73-75 °C; R_f (50% EtOAc/Hexane) = 0.20; ν_{max} (neat) 3625 - 3200 (br), 2981, 2940, 1724, 1699, 1579, 1229, 1185, 1069 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.17 (2H, s, H-1), 4.27 - 4.10 (4H, m,H-9), 4.07 (1H, t, *J* = 3.7 Hz, H-3), 4.02 (2H, q, *J* = 7.1 Hz, H-6), 3.88 - 3.81 (1H, m, H-13), 3.78 - 3.70 (2H, m, H-12), 3.49 - 3.37 (2H, m, H-11), 2.64 (2H, d, *J* = 3.7 Hz, H-4), 1.28 (6H, t, *J* = 7.1 Hz, H-10), 1.18 (3H, t, J 7.1 Hz, H-7); δ_C (100 MHz, $CDCl_3$): 173.9, 166.8 (2C), 140.3 (2C), 105.3 (2C), 61.7, 60.3 (2C), 60.1, 57.6, 39.1, 28.6, 14.4 (2C), 14.0; HRMS (ESI): $M+H^+$, found 356.1704. $C_{17}H_{26}NO_7^+$ requires 356.1704.

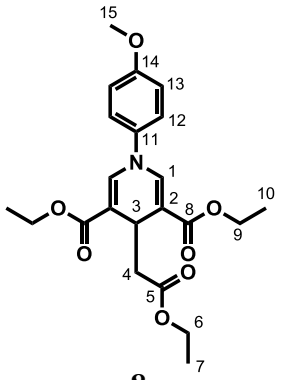
Diethyl-4-(2-ethoxy-2-oxoethyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**8f**)



8f

The product was synthesized from ethyl-3-(phenylamino) acrylate (**5e**) (480 mg, 2.51 mmol) following to the procedure 2.4 as a pale yellow oil (265 mg, 82%); R_f (17% EtOAc/Hexane) 0.25; ν_{max} (neat) 3063, 2975, 2935, 1734, 1704, 1596, 1586, 1495, 1235, 1204, 1072 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.58 (2H, s, H-1), 7.42 (2H, t, *J* = 7.9 Hz, H-13), 7.30 - 7.19 (3H, m, H-12, H-14), 4.30 - 4.17 (5H, m, H-3, H-9), 4.03 (2H, q, *J* = 7.1 Hz, H-6), 2.59 (2H, d, *J* = 4.8 Hz, H-4), 1.30 (6H, t, *J* = 7.1 Hz, H-10), 1.17 (3H, t, J 7.1 Hz, H-7); δ_C (100 MHz, $CDCl_3$): 171.7, 166.7 (2C), 143.0, 137.6 (2C), 129.8 (2C), 126.4, 120.8 (2C), 108.2 (2C), 60.3 (2C), 60.1, 40.5, 29.6, 14.4 (2C), 14.2; All data are identical to those reported in the literature. [65]

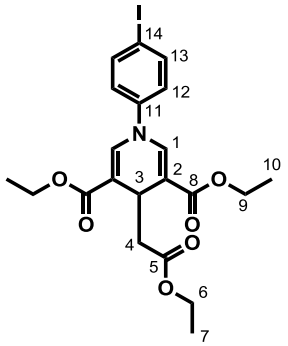
Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8g**)



8g

The product was synthesized from ethyl-3-(4-methoxyphenylamino) acrylate (**5f**) (356 mg, 1.61 mmol) following to the procedure 2.4 as a pale yellow oil (170 mg, 76%), R_f (25% EtOAc/Hexane) = 0.30; ν_{max} (neat) 3079, 3039, 2977, 2934, 1738, 1702, 1599, 1582, 1518, 1229, 1205, 1079 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.46 (2H, s, H-1), 7.15 (2H, d, *J* = 9.0 Hz, H-13), 6.92 (2H, d, *J* = 9.0 Hz, H-12), 4.28 - 4.17 (5H, m, H-3, H-9), 4.04 (2H, q, *J* = 7.1 Hz, H-6), 3.82 (3H, s, H-15), 2.57 (2H, d, *J* = 4.8 Hz, H-4), 1.29 (6H, t, *J* = 7.1 Hz, H-10), 1.18 (3H, t, *J* = 7.1 Hz, H-7); δ_C (100 MHz, $CDCl_3$): 171.7, 166.8 (2C), 158.2, 138.3 (2C), 136.6, 122.9 (2C), 114.8 (2C), 107.5 (2C), 60.3 (2C), 60.0, 55.6, 40.6, 29.5, 14.4 (2C), 14.2; HRMS (ESI): $M+H^+$, found 418.1860. $C_{22}H_{28}NO_7^+$, requires 418.1860.

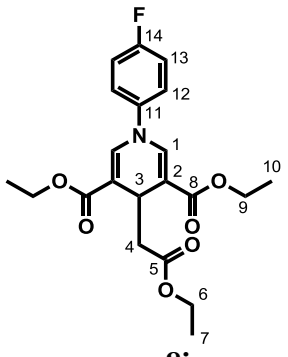
Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-iodophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8h**)



8h

The product was synthesized from ethyl-3-(4-iodophenylamino) acrylate (**5g**) (928 mg, 2.93 mmol) following to the procedure 2.4 as a pale yellow solid (396 mg, 79%); m.p. 61 – 66 °C; R_f (20% EtOAc/Hexane) = 0.20; ν_{max} (neat) 3083, 3063, 2974, 2931, 1731, 1704, 1625,1582, 1494, 1229 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.72 (2H, d, *J* = 8.4 Hz, H-13), 7.51 (2H, s, H-1), 6.98 (2H, d, *J* = 8.4 Hz, H-12), 4.30 - 4.14 (5H, m, H-3, H-9), 4.01 (2H, q, *J* = 7.1 Hz, H-6), 2.59 (2H, d, *J* = 4.7 Hz, H-4), 1.30 (6H, t, *J* = 7.1 Hz, H-10), 1.16 (3H, t, *J* = 7.1 Hz, H-7); δ_C (100 MHz, $CDCl_3$): 171.5, 166.5 (2C), 142.7, 138.8 (2C), 136.9 (2C), 122.4 (2C), 108.9 (2C), 90.2 , 60.4 (2C), 60.1, 40.3, 29.5, 14.3 (2C), 14.2; HRMS (ESI): $M+Na^+$, found 536.0541. $C_{21}H_{24}INNaO_6^+$, requires 536.0540.

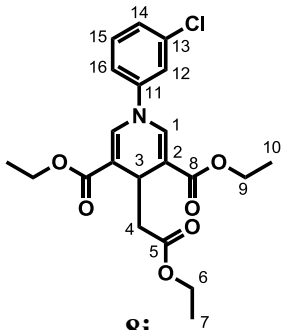
Diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8i**)



8i

The product was synthesized from ethyl-3-(4-fluorophenylamino) acrylate (**5h**) (556 mg, 2.66 mmol) following to the procedure 2.4 as a pale yellow solid (251 mg, 69%); m.p. 75-76°C; R_f (25% EtOAc/Hexane) = 0.38; ν_{max} (neat) 3071, 2982, 2940, 1732, 1707, 1594, 1516, 1219, 1085 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.48 (2H, s, H-1), 7.24 - 7.16 (2H, m, H-13), 7.11 (2H, t, *J* = 8.5 Hz, H-12), 4.28 - 4.18 (5H, m, H-3, H-9), 4.03 (2H, q, *J* = 7.1 Hz, H-6), 2.59 (2H, d, *J* = 4.8 Hz, H-4), 1.30 (6H, t, *J* = 7.1 Hz, H-10), 1.18 (3H, t, *J* = 7.1 Hz, H-7); δ_C (100 MHz, $CDCl_3$): 171.7, 166.6 (2C), 160.9 (d, *J* = 246.7 Hz, C-14), 139.4, 137.8 (2C), 123.1 (2C, d, *J* = 8.4 Hz, C-12), 116.6 (2C, d, *J* = 23.0 Hz, C-13), 108.2 (2C), 60.4 (2C), 60.0, 40.4, 29.5, 14.4 (2C), 14.2; HRMS (ESI): MNa^+, found 428.1480. $C_{21}H_{24}FNNaO_6^+$, requires 428.1480.

Diethyl-1-(3-chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8j**)

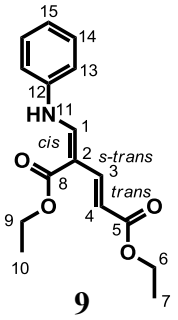


8j

The product was synthesized from ethyl-3-(3-chlorophenylamino) acrylate (**5i**) (346 mg, 1.53 mmol) following to the procedure 2.4 as a pale yellow oil (164 mg, 76%); R_f (25% EtOAc/Hexane) = 0.30; ν_{max} (neat) 3072, 2976, 2935, 1729, 1707, 1594, 1483, 1207, 1081 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.54 (2H, s, H-1), 7.40 - 7.10 (4H, m, H-13, H-14 to H-16), 4.29 - 4.20 (5H, m, H-3, H-9), 4.03 (2H, q, *J* = 7.1 Hz, H-6), 2.60 (2H, d, *J* = 4.8 Hz, H-4), 1.31 (6H, t, *J* = 7.1 Hz, H-10), 1.18 (3H, t, *J* = 7.1 Hz, H-7); δ_C (100 MHz, $CDCl_3$): 171.5, 166.4 (2C), 143.9, 136.9 (2C), 135.5, 130.8, 126.3, 120.8, 118.6, 109.0 (2C), 60.4 (2C), 60.0, 40.2, 29.5, 14.3 (2C), 14.1; HRMS (ESI): $M+Na^+$, found 444.1184. $C_{21}H_{24}{}^{35}ClNNaO_6^+$, requires 444.1184.

2.5 Preparation of dimeric intermediate of 1,4-DHP formation

Diethyl 4-((phenylamino)methylene)pent-2-enedioate (**9**)



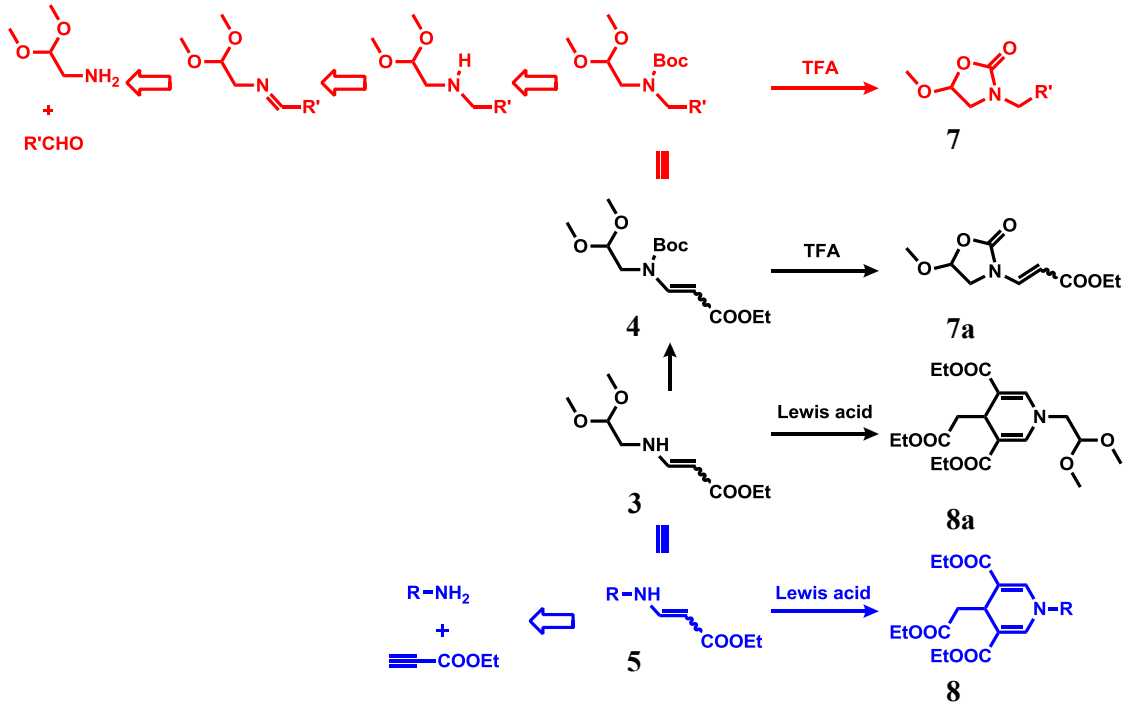
9

Aniline (265 mg, 2.15 mmol) and CuI (409 mg, 2.15 mmol) were stepwise added to the solution of ethyl propiolate (651 mg, 6.64 mmol) in dried 1.2-dichloroethane (20 mL). The reaction mixture was allowed to reflux for 10 hours.The CuI was filtered out and the reaction solution was concentrated under vacuum and purified by flash column chromatography on silica gel (EtOAc/hexane = 1:50 to 1:3) to give the dimer (**9**) as a yellow oil (261 mg, 42%); R_f (25% EtOAc/Hexane) = 0.50; ν_{max} (neat) 3271, 3220, 3047, 2981, 1659, 1597, 1582, 1278, 1179, 1157,1029 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 10.78 (1H, d, *J* = 13.2 Hz, H-11), 7.76 (1H, d, *J* = 13.2 Hz, H-1), 7.48 (1H, d, J 15.7 Hz, H-4), 7.36 (2H, t, *J* = 7.6 Hz, H-14), 7.19-7.00 (3H, m, H13, H-15), 6.18 (2H, d, *J* = 15.7 Hz, H-3), 4.33 (1H, q, *J* = 7.1 Hz, H-9), 4.22 (2H, q, *J* = 7.1 Hz, H-6), 1.40 (3H, t, *J* = 7.1 Hz, H-10), 1.31 (3H, t, *J* = 7.1 Hz, H-7); HRMS (ESI): $M+Na^+$, found 312.1205. $C_{16}H_{19}NNaO_4^+$, requires 312.1206. This data are fully identical to that of compound isolated in trace amount from the previous procedure 2.4 for synthesis of (**8f**).

CHAPTER III

RESULTS AND DISCUSSION

An overview of discovery of novel compounds named 1,4-dihydropyridines (1,4-DHPs) will be discussed throughout the dissertation as shown in **Scheme 3.1**. Originally, the designed multifunctional molecule, alkyl β-amino acrylate or enamine containing acetal end (**3**), was prepared in excellent yield and used as a substrate for appropriate cyclization within its molecule under TFA condition. No characterizable product was observed because of too many active sites worked concurrently. To solve this problem, there are two conceivable ideas which are using *t*-Boc protecting group to inhibit the reactivity of a lone pair of nitrogen before treating with TFA and using Lewis acid instead of TFA. The first route, treatment of Boc-enamide (**4**) with TFA, provided an oxazolidin-2-one (**7a**) in good to excellent yield. The series of oxazolidin



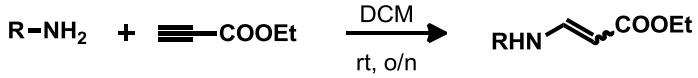
Scheme 3.1 An overview of discovery of oxazolidin-2-ones and 1,4-DHPs

-2-one derivatives (**7**) were also synthesized from the corresponding Boc-enamides by the same condition. While the other route appeared to surprisingly construct a novel products, 1,4-DHP derivatives (**8**), including the DHP which contains the acetal end (**8a**), from the enamines (**3, 5**) in a presence of Lewis acid such as $AlCl_3$, $TiCl_4$, and $BF_3{\cdot}OEt_2$.

3.1. Preparation of ethyl β-amino acrylates (enamines)

3.1.1. Preparation of N-alkyl enamines

As previously mentioned, the simple 1,4-Michael addition of the aliphatic amines to carbonyl-conjugated alkyne, ethyl propiolate, in DCM at room temperature for 10 hours provided a series of ethyl (*N*-alkyl)-amino acrylates in excellent yields (81 – 95 %) (**Scheme 3.2**).



3: R = $(MeO)_2CHCH_2$; 91 %
5a: n-C_4H_9; 81 %
5b: n-$C_{18}H_{37}$; 83 %
5c: $PhCH_2$; 90 %
5d: $HOCH_2CH_2$; 95 %

Scheme 3.2 Preparation of *N*-alkyl ethyl β-amino acrylates

3.1.2. Scanning the catalysts for the N-aryl enamine preparation by using ^{1}H-NMR experiment

N-Aliphatic substituted enamine was easily prepared by the method described above (**section 1.3**). However, in the case of aromatic amine, for instance, simple addition of aniline to ethyl propiolate resulted in no reaction at all, because the nitrogen atom of aromatic amine is less nucleophilic than that of the aliphatic one. Some possible ways to push the reaction forward were attempted to solve this problem such as increasing the reaction time, raising the reaction temperature, using higher concentration and varying catalysts. Although the reaction was forced by heat or using higher concentration, both substrates did not show any changes in the ^{1}H-NMR spectra. Addition of catalysts often being used for coupling reaction such as $CuSO_4$, CuI, $Zn(OAc)_2$, $AgNO_3$, $BF_3{\cdot}OEt_2$, and $InCl_4$ were tried. The progress of the stimulated reactions was investigated in the NMR tube, by analyzing the chemical shift of ^{1}H-NMR signals. To monitor the reaction progress, conversion of the alkyne proton represented in ‘c’ proton at 2.90 ppm to alkene protons (black arrow) and the downfield shift of aromatic protons which are ‘a’ and ‘b’ to the higher ppm direction (white arrow) can be checked **(Figure 3.1)**. The ^{1}H-NMR investigation, 4-iodoaniline was used throughout as an aromatic amine substrate because its simple splitting pattern in aromatic region will not hide the generated alkene protons.

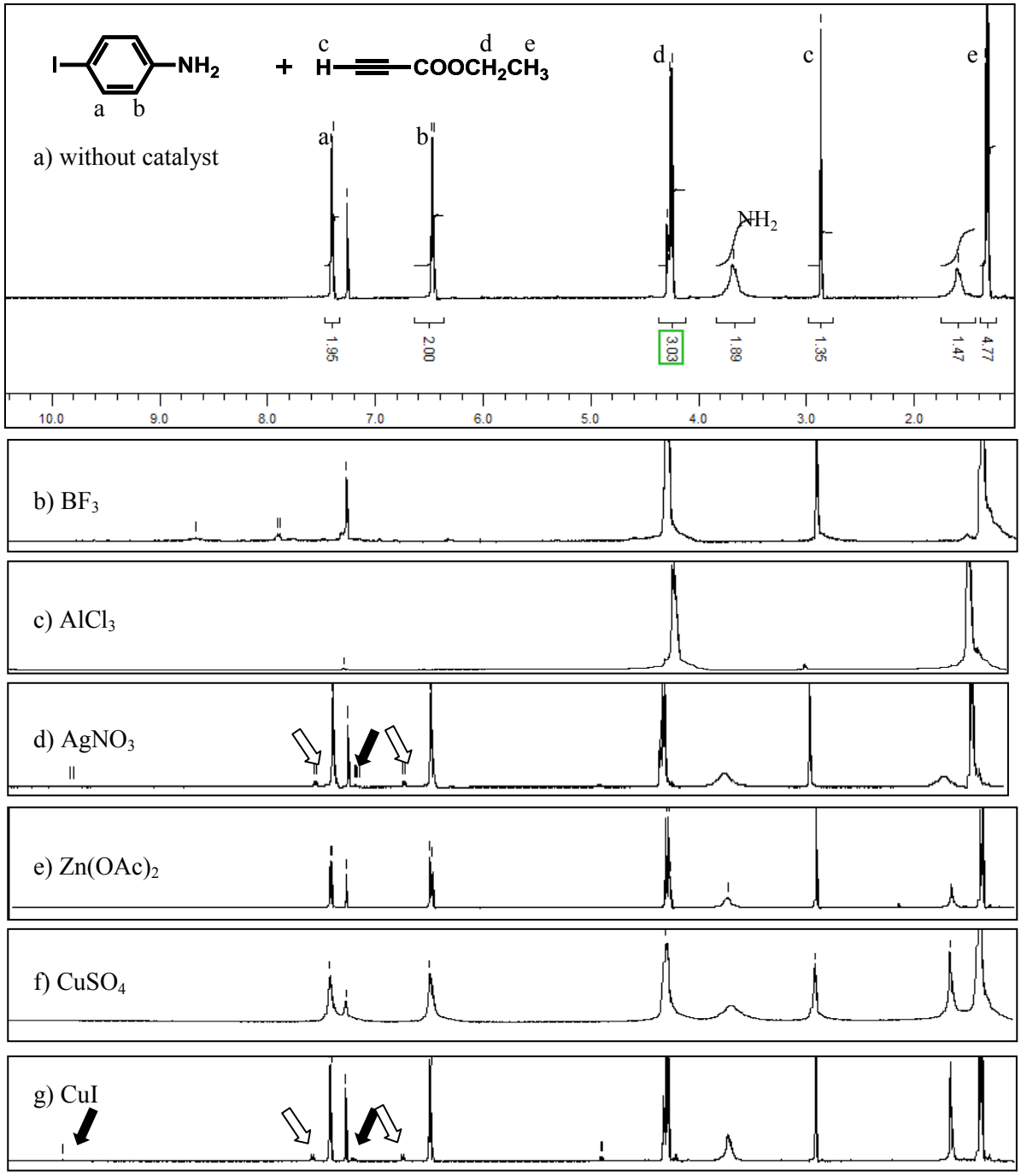


Figure 3.1 Scanning of the catalysts for aromatic enamine preparation by NMR experiment a) without catalyst, b) BF_3, c) $AlCl_3$, d) $AgNO_3$, e) $Zn(OAc)_2$, f) $CuSO_4$,g) CuI after 1 day

According to the ^{1}H-NMR spectra, the reactions in the presence of $BF_3{\cdot}OEt_2$ and $AlCl_3$ showed no aromatic signals, which is likely due to the precipitation of the insoluble complex between aniline and Lewis acid, while the use of $CuSO_4$ and $Zn(OAc)_2$ gave no reaction. Moreover, in the case of $AlCl_3$, terminal alkyne proton (4.3 ppm) disappeared may be because ethyl propiolate was also decomposed.

In the case of $AgNO_3$ and CuI, more than four new signals were observed in the NMR spectra which probably matched with two new aromatic protons (6.70 and 7.55 ppm) and new alkene protons (7.20 and 10.0 ppm). Moreover, the reaction in a presence of CuI was monitored continuously. The results shown the integration of the new signal increased as the reaction time increased or with heat (**Figure 3.2**).

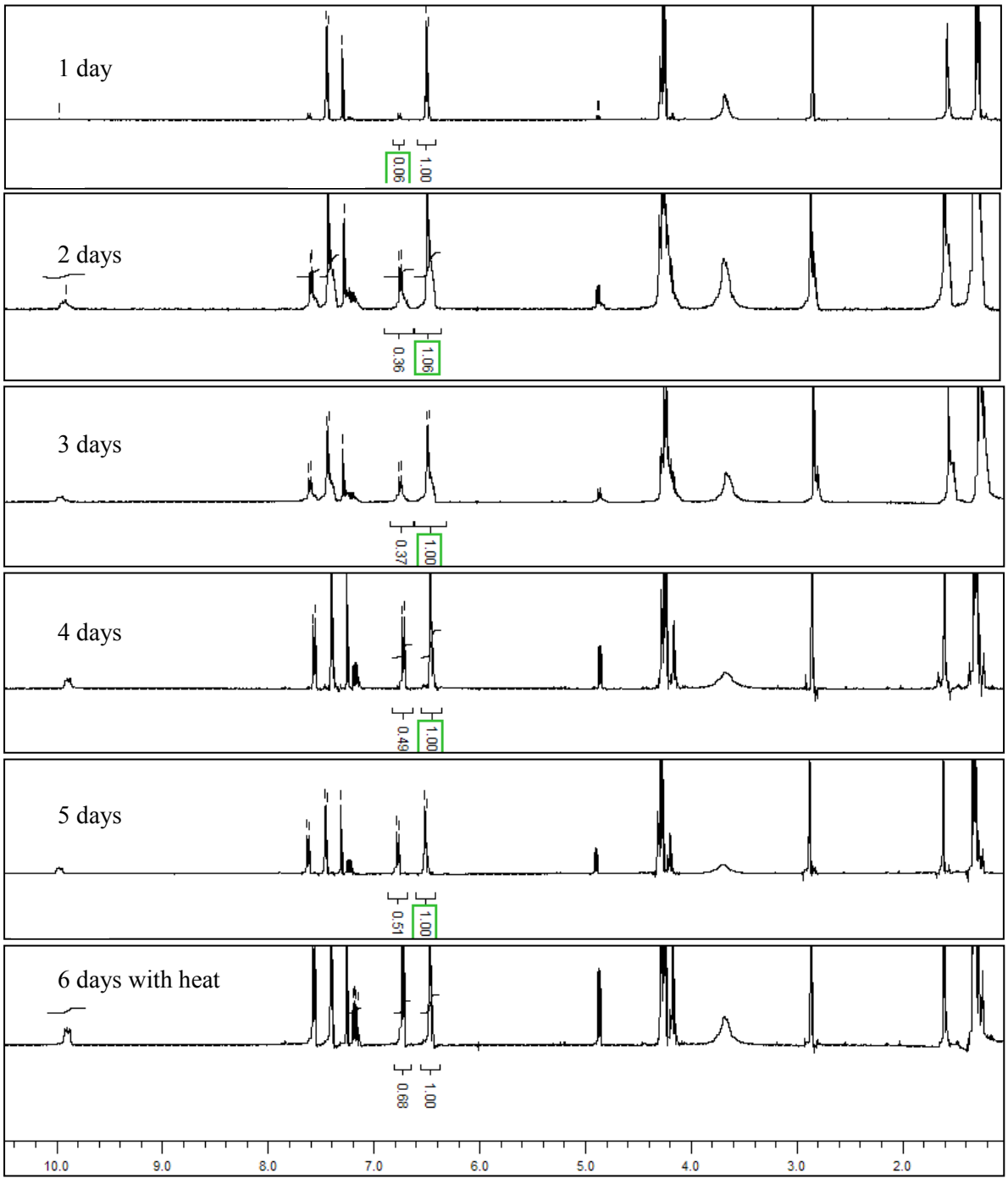


Figure 3.2 ^{1}H-NMR of aromatic enamine preparation with CuI

In order to calculate the product yields through ^{1}H-NMR experiment, the integration area under the clear peaks of both substrate and product were used for the analysis. In this case, comparison of the selected protons, for those belonging to aniline substrate (6.45 ppm) and enamine product (6.70 ppm) were calculated by using the equation below.

$$\%\ yield = \frac{\frac{area\ of\ product\ peak}{No.of\ protons\ of\ product\ peak}}{\frac{area\ of\ product\ peak}{No.of\ protons\ of\ product\ peak} + \frac{area\ of\ substrate\ peak}{No.of\ protons\ of\ substrate\ peak}} \times 100$$

Equation 3.1 The percentage yield calculation using ^{1}H-NMR spectrum

As previously mentioned, only CuI and $AgNO_3$ could promote the reaction between aniline and ethyl propiolate. They were selected to study for a longer period of time until the reaction reaches equilibrium. After the time extension, the NMR tubes were kept in the water bath at 50 °C to check the effect of temperature on the rates of reaction. The percentages of product yields were reported in the **Table 3.1 – 3.2**. In the case of CuI, the product peak rapidly increased from 6% to 26% between the first and second day and slightly increased until the fifth day from 26% to 34%. After that, the reaction was heated for one day and the product peak went up to 40%. For the silver nitrate case, the product peak slowly rose from 6% to 11% among the first two-day and moved up gradually to 32% on the day #10. After heating the reaction, the product peak dramatically increased to 54%.

Table 3.1 The ^{1}H-NMR yields of aromatic enamine preparation catalyzed by CuI

Conditions	Integration of signal (arbitrary unit)		% Yield [a]
	Substrate (6.45 ppm)	Product (6.70 ppm)	
1 day	1.00 [b]	0.06	6
2 days	1.00 [b]	0.36	26
3 days	1.00 [b]	0.37	27
4 days	1.00 [b]	0.49	32
5 days	1.00 [b]	0.51	34
6 days [c]	1.00 [b]	0.68	40

[a] calculated from Equation 3.1

[b] this value was set as an integration reference.

[c] the reaction was heated at 50 °C after the day #5.

Table 3.2 The NMR yields of aromatic enamine preparation catalyzed by $AgNO_3$

Conditions	Integration of signal (arbitrary unit)		% Yield [a]
	Substrate (6.45 ppm)	Product (6.70 ppm)	
1 day	1.00 [b]	0.06	6
2 days	1.00 [b]	0.12	11
6 days	1.00 [b]	0.38	28
8 days	1.00 [b]	0.40	29
9 days	1.00 [b]	0.44	31
10 days [c]	1.00 [b]	0.47	32
11 days [c]	1.00 [b]	1.17	54

[a] calculated from Equation 3.1

[b] this value was set as an integration reference

[c] the reaction was heated at 50 °C after the day #9

The effects of several variables such as inorganic salts, reaction temperature and reaction time were studied through ^{1}H-NMR experiment. The catalyst activity was found to be highly dependent on type of catalyst, temperature and reaction time. After the optimization, for this addition reaction the catalyst that showed best activity is CuI and the condition at 50 °C could produce the product in higher yield. However, the product peaks obtained from these initial results are quite low, because this heterogeneous reaction within the NMR tube seems to be not efficiency enough.

3.1.3. Preparation of N-aryl enamines

1,4-Michael addition between 4-iodoaniline and ethyl propiolate in a presence of CuI satisfactorily provided the aromatic enamines, ethyl-3-(4-iodophenylamino)acrylate (**5g**). Nevertheless this reaction needed a large amount of CuI (0.5 - 1 equivalent), because this heterogeneous reaction required CuI to be dispersed thoroughly. Interestingly, by using this condition at room temperature only *cis*-isomeric product was separated as a white plate-shaped crystal. In a polar aprotic solvent, the hydrogen bonding between C=O of ethyl propiolate and hydrogen atom of amino group plays an important role to induce two molecules closer to each other (**Figure 3.3**). The lone pair of nitrogen consecutively attacked to copper-activated alkyne to provide a geometrical (*cis*) selective product. It is worth nothing that the complexation of CuI with the terminal alkyne gives a π-complex of copper(I) acetylide, which acts as an activated species for the coupling reactions. [66] According to the ^{1}H-NMR spectrum of this product, the important peak implying the existence of the intramolecular hydrogen bonding was found at 9.89 ppm (**Figure 3.4**).

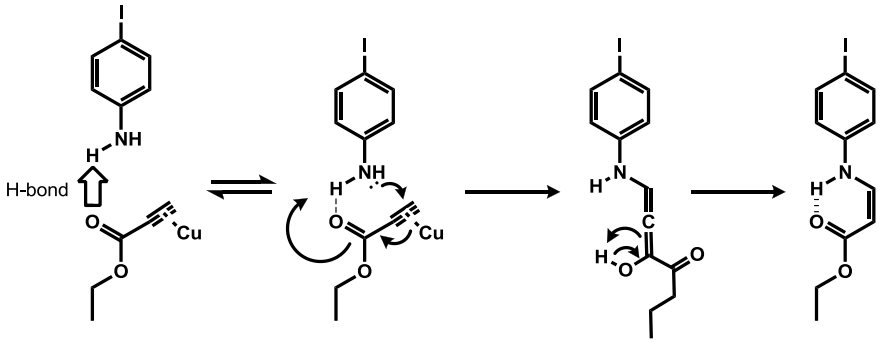


Figure 3.3 Mechanistic proposal of Michael addition between 4-iodoaniline and ethyl propiolate

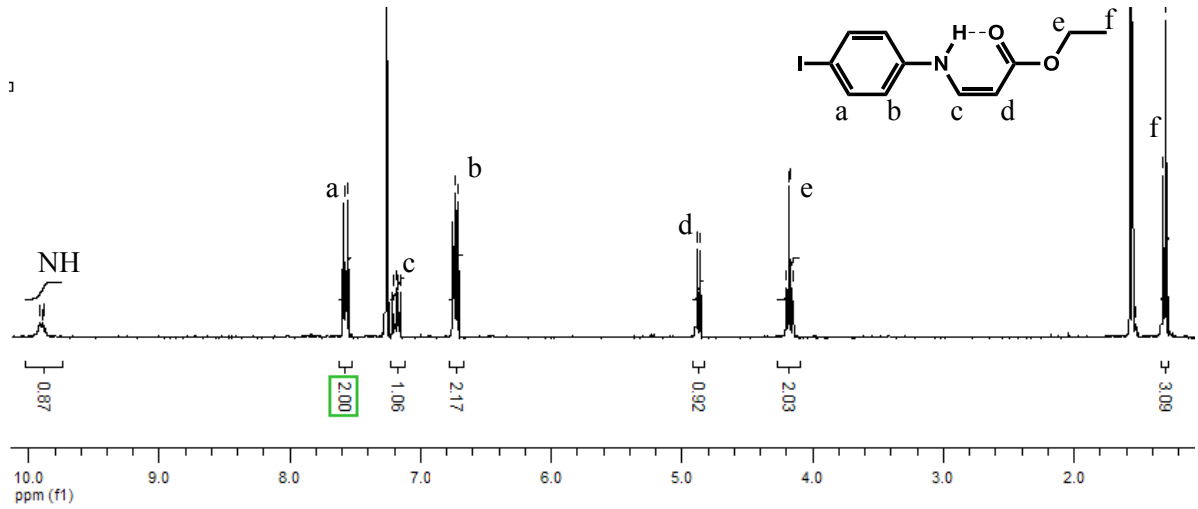


Figure 3.4 ^{1}H-NMR of ethyl-3-(4-iodophenylamino)acrylate (**5g**)

Unfortunately, the Michael addition of other anilinyl derivatives, such as aniline, 4-methoxyaniline, were not successful at room temperature. Only addition of CuI was not efficient enough to push the reaction forward, raising the reaction temperature was chosen to improve the reaction. Therefore, 1,2-dichloroethane (DCE), with higher boiling point (81 °C) was used instead of lower boiling point DCM which generally used throughout the project, in order to be able to tune up the reaction temperature. The reaction temperatures for the operation were 40 °C, 60 °C, and 80 °C adjustable by reflux action of DCM, constant heat in DCE and reflux action of DCE, respectively. Following these conditions, unsubstituted aniline and 4-methoxylaniline that used as a substrate reacted with ethyl propiolate and the reaction was tracked by ^{1}H-NMR after solvent removal. Initially, the reaction undertaken at 40 °C slightly raised up the product signal but not well enough (30 - 36%). The reaction under DCE reflux also disappointingly gave no target product but only the decomposed residue or di-/polymerized by products. The condition processed at 60 °C could improve the yield of product together with almost disappearance of the substrate (**Table 3.3**). Also with high temperature condition, some kinetic *cis*-isomeric products isomerize into *trans*-isomer. Unfortunately, the leftover substrate and *trans*-product have nearly the same R_f value, therefore the loss during separation could be one of the low yield reasons. Although, almost aniline substrate was converted to the product, but only 55% isolated yield was achieved presumably due to

the decomposition during the purification by column chromatography. The results of the addition of series of aliphatic amines and anilines with ethyl propiolate were summarized as shown in **Scheme 3.3** and **Table 3.4**.

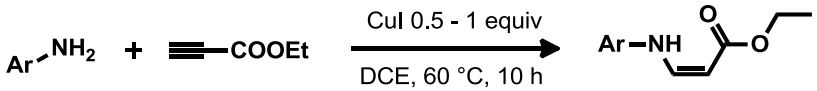
Table 3.3 The product yields of CuI (0.5 equivalent) assisted or catalyzed aromatic enamine prepared at room temperature, 40 °C, 60 °C, and 80 °C

Substrates	**Reaction temperature**	**% yield** [a]
Aniline	room temperature	<10
	40 °C	36
	60 °C	88 (55 [b])
	80 °C	0 [c]
4-Methoxy aniline	room temperature	<10
	40 °C	30
	60 °C	62 (33 [b])

[a] calculated by ^{1}H-NMR without isolation

[b] isolated yield by column chromatography

[c] no target product detected



5e: Ar = C_6H_5; 55 %
5f: p-MeO-C_6H_4; 33 %
5g: p-I-C_6H_4; 93 %
5h: p-F-C_6H_4; 59 %
5i: m-Cl-C_6H_4; 54 %

Scheme 3.3 Preparation of *N*-aryl ethyl β-amino acrylates (**5e - 5i**)

Table 3.4 The isolated yields of alkyl β-amino acrylates or enamines

Aliphatic amine			Aromatic amine		
compound	**R-group**	**% isolated yield**	**compound**	**R-group**	**% isolated yield**
3	$(MeO)_2CHCH_2$	91[a]	**5e**	C_6H_5	55[c]
5a	*n*-C_4H_9	81[a]	**5f**	*p*-MeO-C_6H_4	33[c]
5b	*n*-$C_{18}H_{37}$	83[a]	**5g**	*p*-I-C_6H_4	93[b]
5c	$PhCH_2$	90[a]	**5h**	*p*-F-C_6H_4	59[c]
5d	$HOCH_2CH_2$	95[a]	**5i**	*m*-Cl-C_6H_4	54[c]

[a] without catalyst, DCM, room temperature, 10 hours

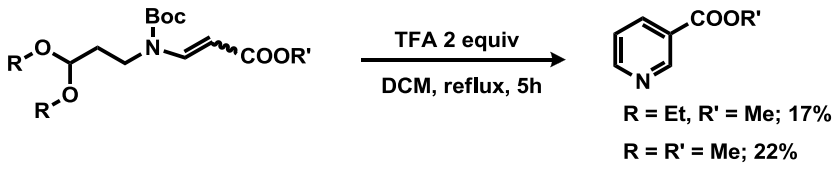
[b] CuI 0.5 equivalent, DCM, room temperature, 10 hours

[c] CuI 0.5 equivalent, DCE, 60 °C, 10 hours

3.2. Acid-induced intramolecular cyclization of the alkyl β-amino acrylates

3.2.1. Reaction of alkyl β-amino acrylates with protic acid

As previous results in our research group, the acid induced intramolecular cyclization of a structure of multifunctional molecules, alkyl β-amino acrylates containing acetal end with different alkyl chain lengths, was investigated. Some heterocyclic compounds such as pyridine were produced in relatively low yield by Hansuthirakul [26] (**Scheme 3.4**). This very interesting topic was then carried on in the dissertation by treating ethyl 3-(2,2-dimethoxyethylamino) acrylate (**3**) with several acids. Initially, a group of mineral acids such as hydrochloric acid and phosphoric acid were used as a reagent but substrates were completely decomposed without the evidence of any characterizable product (**Table 3.5**). Treatment of TFA (an organic acid), gave the same result. This multifunctional substrate seemed to be too highly reactive making the acid treatment of it uncontrollable. Some interesting ideas to control the reaction were attempted to solve this problem such as using the nitrogen protecting group to inhibit the reactivity of the substrate and using Lewis acid instead of Brønsted acid.



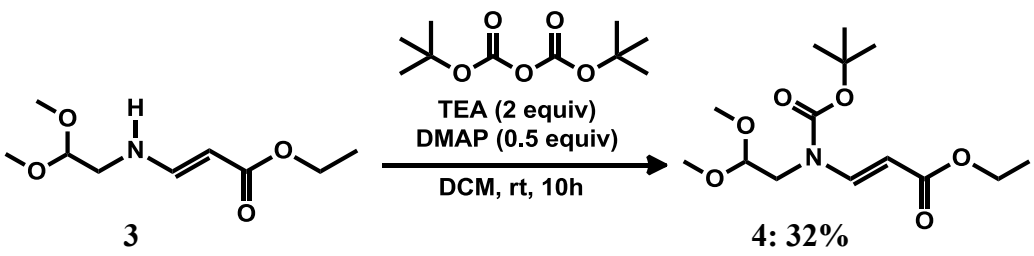
Scheme 3.4 Synthesis of pyridine derivatives reported by Kunlayanee [26]

Table 3.5 The result of treating alkyl β-amino acrylates with HCl, H_3PO_4, and TFA

Acid	Conditions	Results
HCl	THF, room temp, 10 hours	No product detected
H_3PO_4	THF, room temp, 10 hours	No product detected
TFA	2 equivalent, DCM, room temp, 2 hours	No product detected
	2 equivalent, DCM, reflux, 2 hours	No product detected
	2 equivalent, DCM, reflux, 10 hours	No product detected
	2 equivalent, DCM, room temperature, 10 hours	No product detected

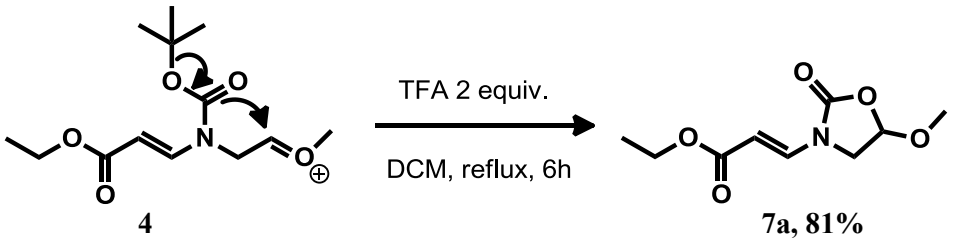
3.2.2. Reaction of alkyl β-amido acrylates with protic acid

Since the reaction of ethyl 3-(2,2-dimethoxyethylamino) acrylate (**3**) under acidic condition was uncontrollable. The decomposed products were found at the base line of TLC referring to oligo-/polymerization of the substrates. High dilution condition and slow releasing of enamine might possibly prevent the reaction from oligo-/polymerization. Protection of enamine nitrogen with *tert*-butoxycarbonyl group (Boc-group) as a protecting group was carried out to create less reactive substrate for the next acid-induced reaction. Under acidic and high dilution condition, the enamine substrate was expected to slowly release from protected version and then react individually. Basically, amide formation was prepared by coupling the amine with di-*tert*-butyl dicarbonate (Boc-anhydride) in the presence of triethylamine (TEA) as a base and DCM as a solvent providing β-amido acrylates (**4**) in 32% (**Scheme 3.5**).



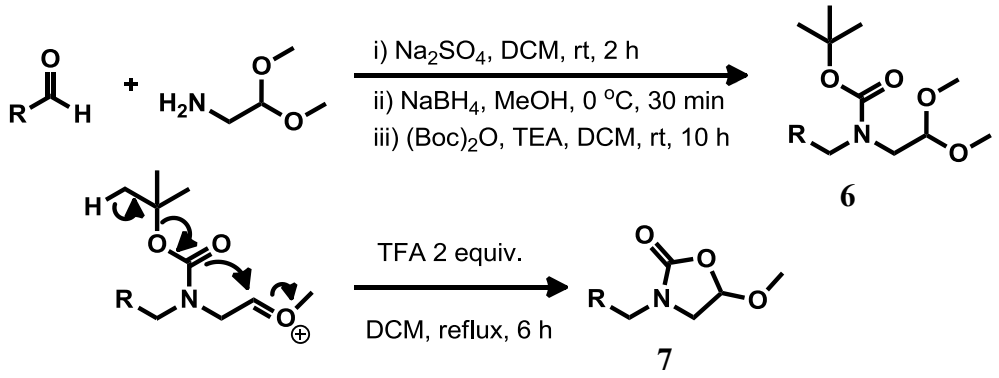
Scheme 3.5 Preparation of alkyl β-amido acrylate (**4**)

Followed the condition optimized by Hansuthirakul [26], under the conventional Boc-group deprotection conditions by treatment of 2 equivalent of TFA, individual cyclization within molecule of β-amido acrylate (**4**) was expected during the deprotection process. Interestingly, a novel compound was constructed mechanistically. While the acetal group converted to oxonium cation, the O=C-O group of Boc-group was not removed but it directly attacked to the oxonium carbon to form oxazolidin-2-nones in excellent yield (81%) (**Scheme 3.6**).



Scheme 3.6 Cyclization of methyl 3-(*tert*-butoxycarbonyl(2,2-dimethoxyethyl)amino) acrylate (**7a**)

A series of carbamates (**7b – 7d**) were synthesized by reductive amination between aldehydes and 2,2-dimethoxy ethanamine without separation by column chromatrography, followed by insertion of Boc-group *via* amide formation to give the substrates for TFA induced cyclization (**Scheme 3.7**). Though the overall yield of the first three steps was not satisfactory due to the reason as previously discussed, they worked very well in the cyclization step (**Table 3.6**). These successful results lead to the new method to synthesize a number of oxazolidin-2one derivatives.



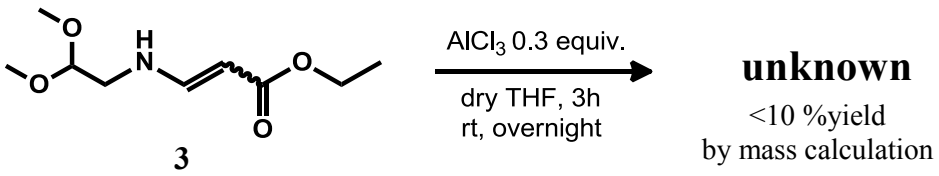
Scheme 3.7 Cyclization of alkyl carbamates (**6**) to the corresponding oxazolidin-2-ones (**7**)

Table 3.6 The product yields of synthesis of a series of oxazolidin-2-ones

R-group	% Yield	
	Substrate (6) (overall from step i, ii, iii)	**Product (7)**
Ph	**6a:** 55	**7b:** 84
4-nitrophenyl	**6b:** 64	**7c:** 92
Naphthalenyl	**6c:** 65	**7d:** 84

*3.2.3. Reaction of ehtyl β-amino acrylate (**3**) with Lewis acid*

Due to the unexpected participation of Boc-group, the reaction in a presence of Lewis acids was used as alternative. Hard acid, in principle, prefers to coordinate with the hard base functional groups. In this reaction, hard acidic species such as $AlCl_3$, $BF_3{\cdot}OEt_2$ may bind with hard functional groups for example carbonyl group, acetal group, and nitrogen atom in this substrate and binding activity depends on type of Lewis acid catalyst. To begin with, the first chosen Lewis acid for the reaction of β-amino acrylate (**3**) was $AlCl_3$. Interestingly, by using $AlCl_3$ as a catalyst, the novel compound was isolated in low yield (**Scheme 3.8**). The NMR spectra including ^1H, ^{13}C, HSQC, HMBC, COSY, and NOESY are very clean. Any expected products such as cyclization products, dimer, and polymers did not match with both ^1H- and ^{13}C-NMR spectra.



Scheme 3.8 Treatment of β-amino acrylate (**3**) with $AlCl_3$ in THF

A bunch of small signals ranged from 2.0 - 5.5 ppm appeared closely to the baseline in ^1H-NMR spectrum of the substrate, are signals of *trans*-isomer enamine substrate that can be easily isomerized from major *cis*-isomer. To avoid the isomerization, room temperature evaporation and immediate purification prior to the NMR experiment are required. Therefore some solvent peaks such as TEA or EtOAc might be found in spectrum. To clarify the structural difference by ^1H-NMR spectrum, there are some significant differences between the spectrum of enamine

substrate (**3**) and the unknown spectrum (**Figure 3.5**). Firstly, the alkene peaks of substrate which represented as ‘d’ and ‘e’ disappeared, while the new singlet signal was found at 7.15 ppm. This fact might be implying to aromatic-like tri-substituted alkene proton. Also there was an appearance of two similar sets of ethyl ester signals with an exact ratio of 1 : 2. The signals belonging to the acetal group which represented as ‘a’, ‘b’, and ‘c’ still remained with small shifts and smaller integration values. All of these data suggested the new compound still possesses the moieties of the starting materials which are an acetal group, tri-substituted alkene, two sets of ester group.

Moreover, the doublet signal around 2.5 ppm was detected only in the product spectrum corresponding to new aliphatic proton(s) with correlation with one proton nearby. In COSY spectrum (**Figure 3.6a**), this aliphatic proton(s) reveals the relation with the multiplet signal at 4.20 ppm (yellow line). Thus, the 2.5 ppm signal and its pair of unknown product presumably matched with CH_2-CH that CH situated in low field environment. The COSY 1D-graphical view (**Figure 3.6b**) also confirmed the existence of two groups of ethyl ester (red and green lines) and acetal moiety (blue line).

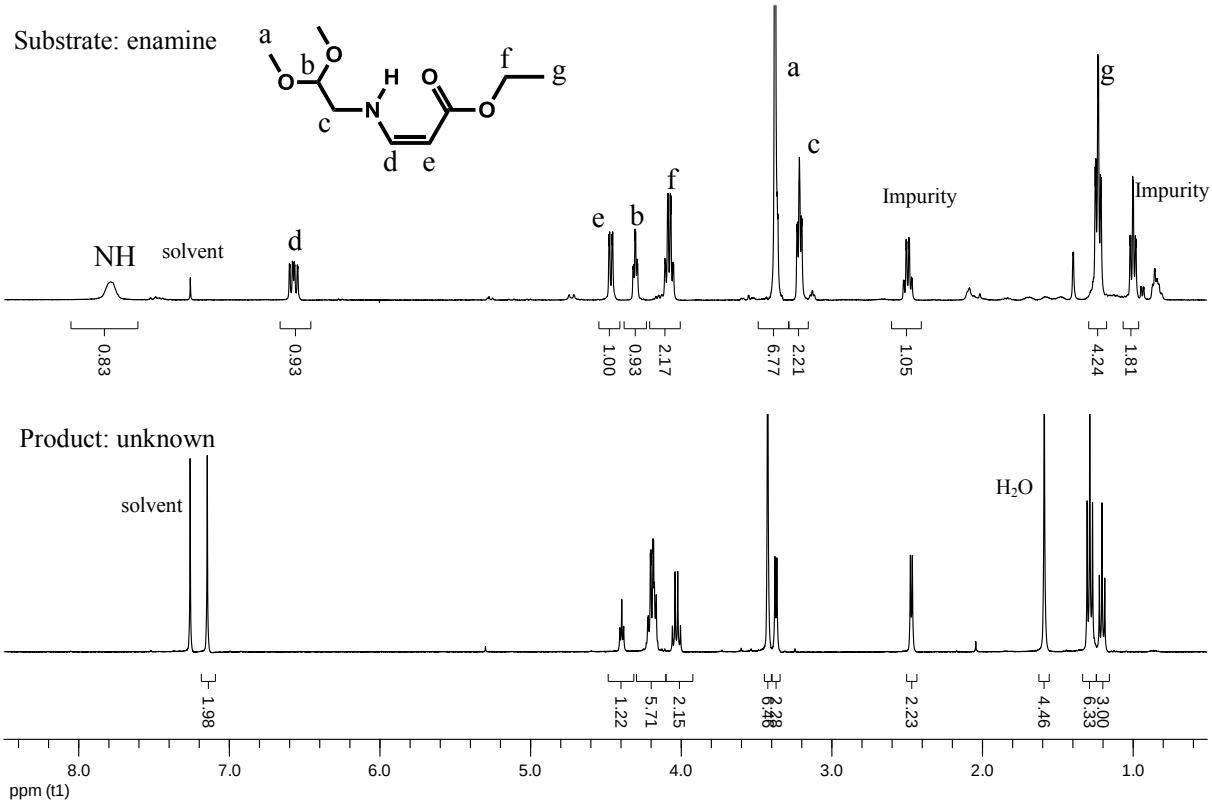


Figure 3.5 ^{1}H-NMR comparison between enamine substrate (**3**) and its product

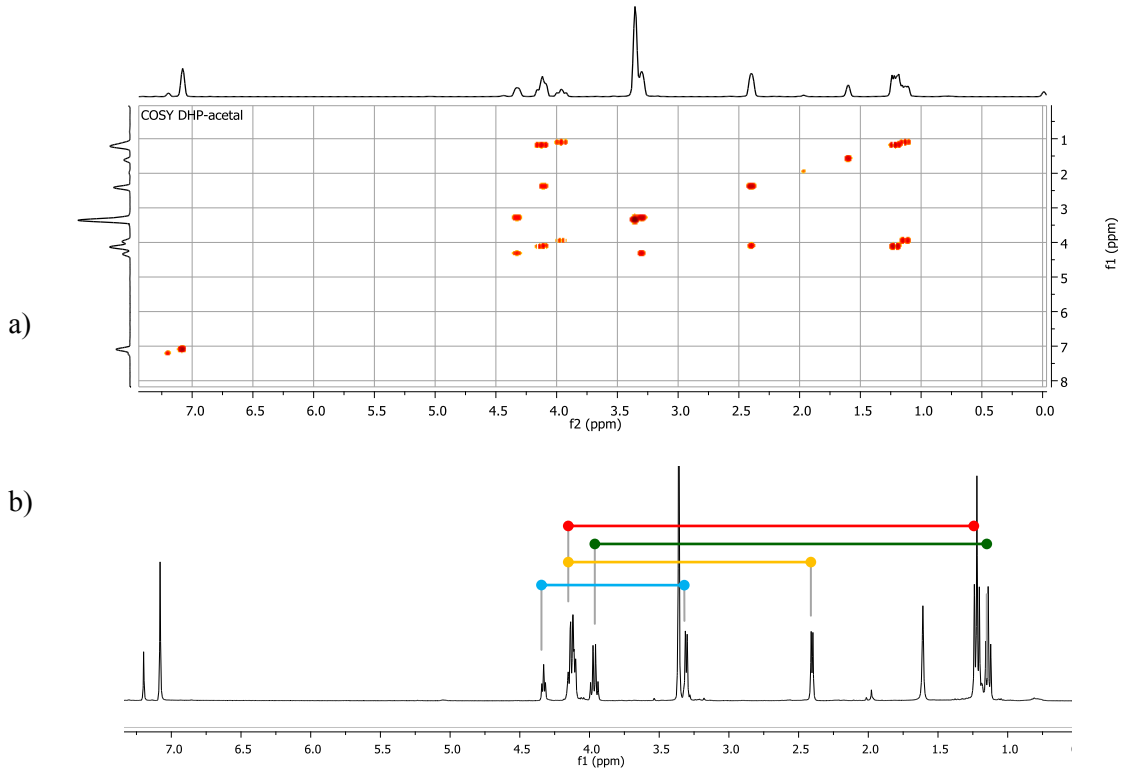


Figure 3.6 COSY spectrum of unknown
a) 2D-COSY b) graphical illustration for COSY results

More information came with the ^{13}C-NMR spectrum (**Figure 3.7**). The unknown has at least thirteen different carbons. When compared to the ^{13}C-NMR spectrum of enamine substrate (**3**) to verify the structural differences, two carbonyl carbon signals were found to support the occurrence of more than one ethyl ester group in the molecule. At the same time, the new aliphatic signals were found in relatively downfield region around 30 and 40 ppm.

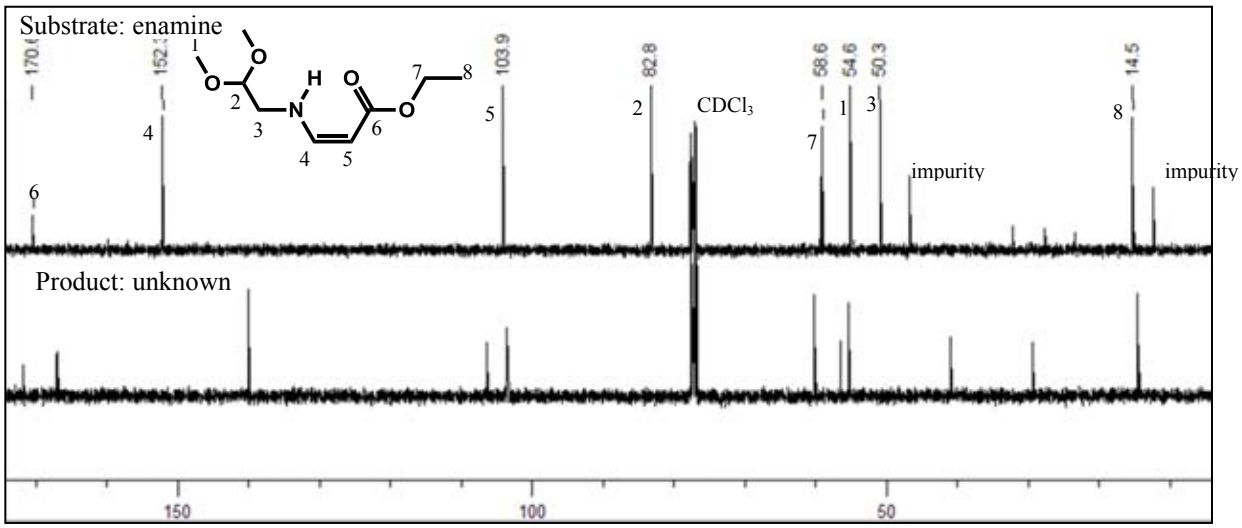


Figure 3.7 ^{13}C-NMR comparison between enamine substrate (**3**) and its product

The ^{1}H - ^{13}C correlations NMR technique, HSQC, was used to figure out the exact structure of the unknown. In principle, HSQC spectrum shows the correlation between proton (s) and its carbon. More than the specification of proton-carbon pair, HSQC also delivers another important information separated in positive (blue spot) or negative signal (red spot). The positive signal corresponds with primary (CH_3) or tertiary carbon (CH). On the other hand, the negative signal corresponds with secondary carbon (CH_2). The original 2D-HSQC-spectrum (**Figure 3.8a**) was simplified to ^{1}H-^{13}C stacking view (**Figure 3.8b**) and positive signals (CH or CH_3) represent as ( ) and negative signal (CH_2) represents as ( ). One important information from HSQC spectrum is that there is one quaternary carbon (excluding two carbonyl carbons). Occurrence of two overlap signals around 4.20 ppm and existence of acetal group, two ester groups trisubstituted alkene were also confirmed.

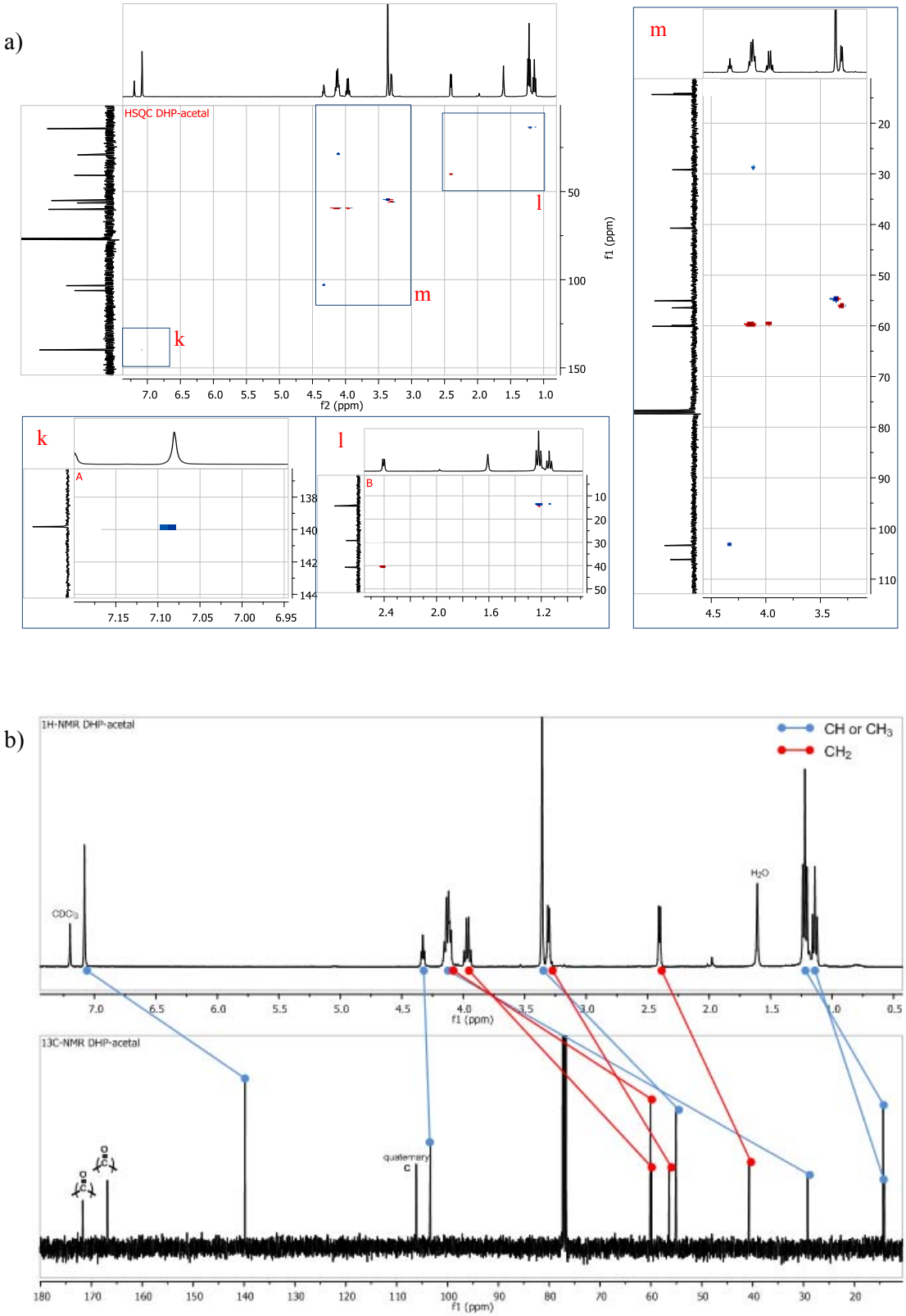


Figure 3.8 HSQC spectrum of unknown

a) 2D-HSQC b) graphical illustration for ^{1}H-^{13}C pair specification

To assemble the structure of unknown, all data was analyzed to gain the possible components **Figure 3.9**. Together with the results of the COSY and the calculation of the integration numbers, this molecule seems to contain five types of fragment as followed; one dimethoxy ethamine unit, two symmetric trisubstituted alkene units, three ethyl ester units that separated to 2 : 1 equivalent and one CH_2-CH linker unit.

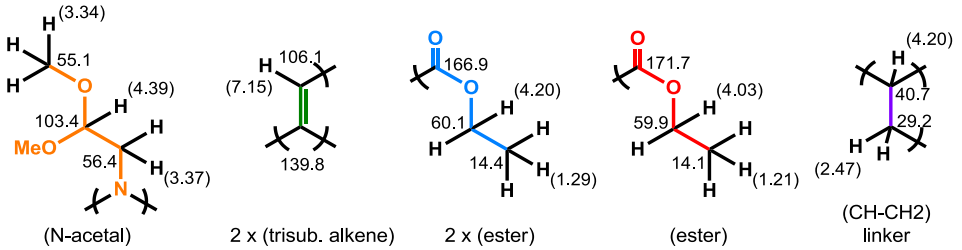
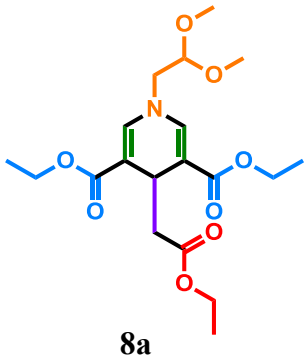


Figure 3.9 Possible fragments of unknown compound analyzed from ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC

As a result from thorough consideration, this unknown product that once was very hard to identify, starts to show its exact structure. 1,4-DHP is expected to be the core of the structure (**Figure 3.10**) and its formation consumes three substrate molecules. Therefore, the product yield were calculated based on this consumption of the substrate; for instant, 100% yield for one mole enamine substrate means that 1/3 mole of product was produced. ^{1}H-NMR and ^{13}C-NMR with full assignment are demonstrated in **Figures 3.11 - 3.12**. More techniques such as HMBC, IR, and HRMS also completely supported and confirmed the structure of 1,4-DHP (**see Appendix)**. Although, there was no substrate spot found on TLC, below 10% yield was unsatisfactory and the optimization of reaction was needed. The cyclization mechanism will be proposed in the next section.



8a

Figure 3.10 Structure of unknown product (1,4-DHP (**8a**))

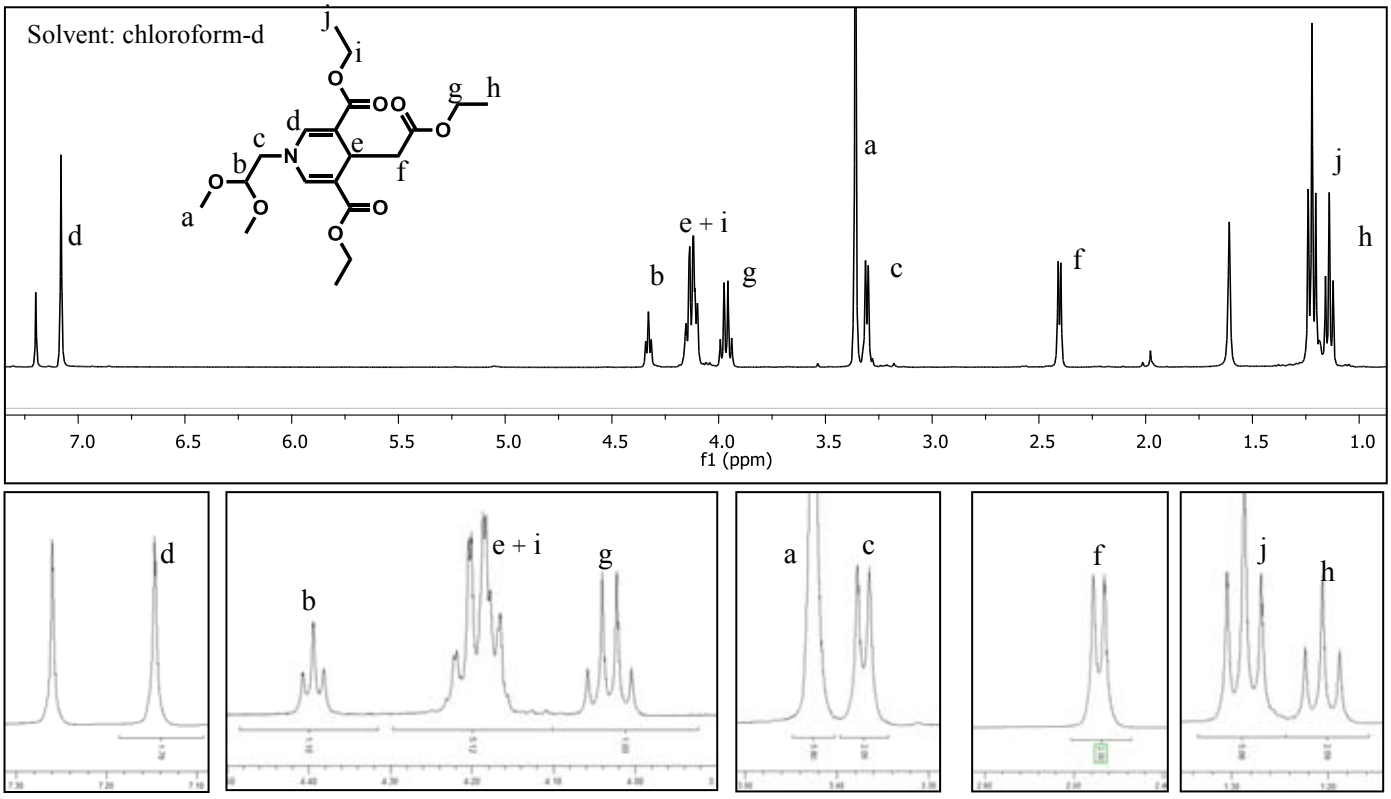


Figure 3.11 ^{1}H-NMR of 1,4-DHP (**8a**)

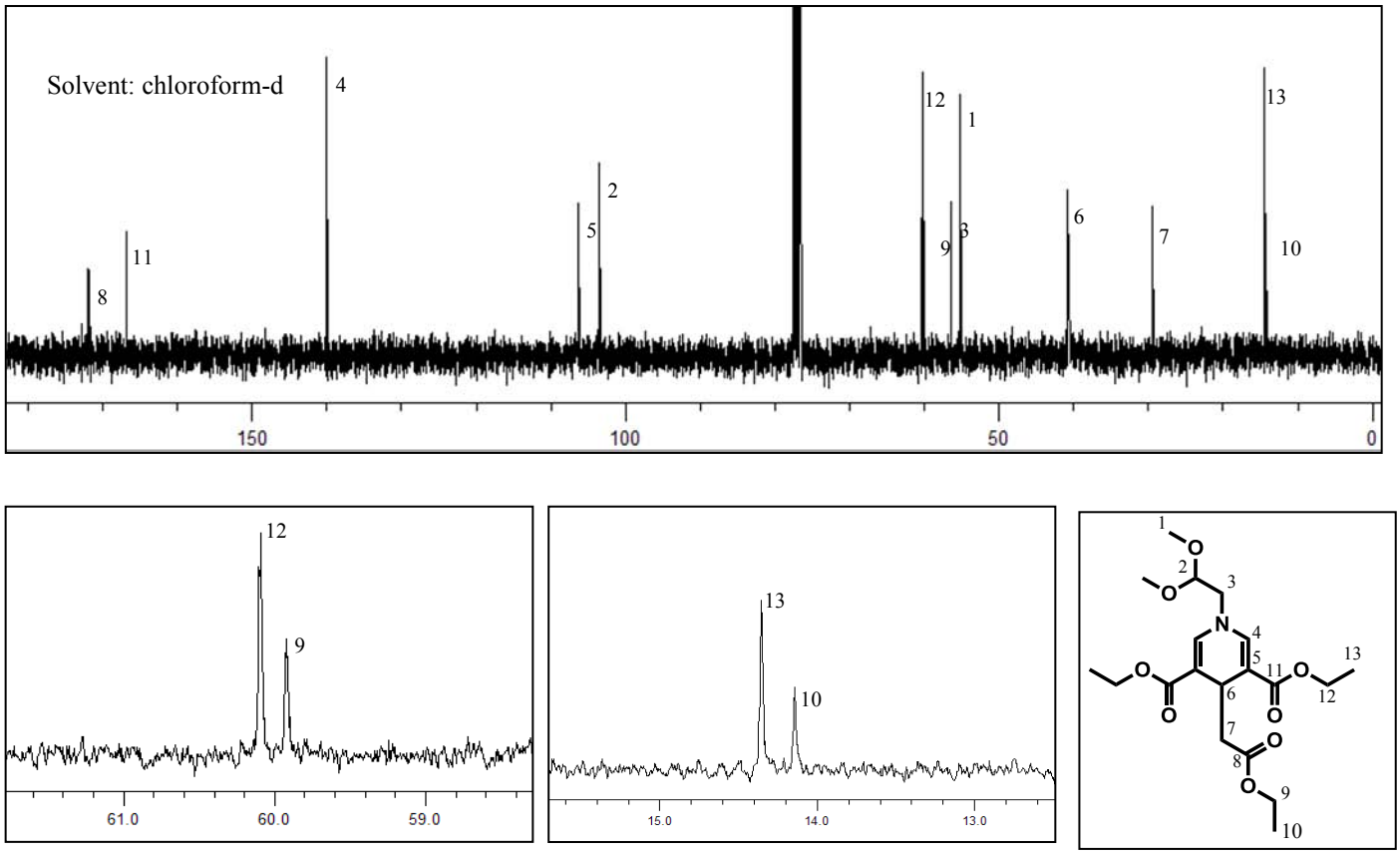
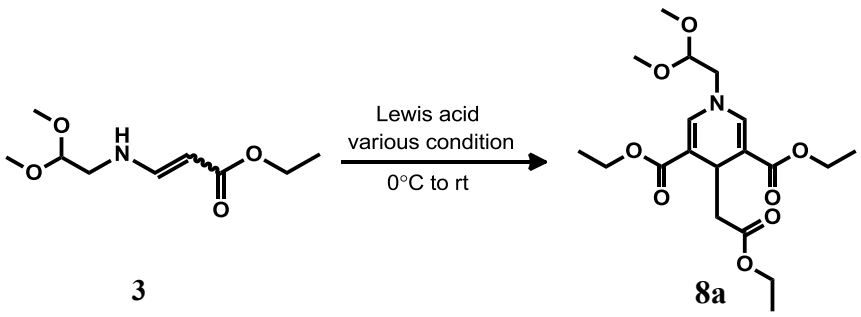


Figure 3.12 ^{13}C-NMR of 1,4-DHP (**8a**)

Though symmetric 1,4-DHP was found, below 10% product yield was unsatisfactory. In order to improve the product yield, tuning up the temperature, extending the reaction time and varying Lewis acids such as $AlMe_2Cl$, $BF_3{\cdot}OEt_2$ were attempted (**Scheme 3.9 and Table 3.7**). Firstly, adding more $AlCl_3$ to the reaction slightly increased the yield but catalyst overload led to the lower yield. Weaker Lewis acid, $AlMe_2Cl$ was then used as an alternative for the reaction. Unfortunately, several trials with various adding amount of Lewis acid (0.2 - 0.5 equivalent) were attempted, but less reactive acid gave no reaction and substrates were almost recovered. Using $BF_3{\cdot}OEt_2$ as a Lewis acid under the same condition provided 17% product yield. Although $BF_3{\cdot}OEt_2$ seemed to work more efficiently than previous Lewis acid, the extension of reaction time to two days resulted in the product yield of only 34% and there was no significant effect on higher amount addition (0.5 equivalent). Lastly, under the condition of 0.2 equivalent of $TiCl_4$, 1,4-DHP product was obtained in 33%, which is the best yield occurred for the same reaction time and the amount of Lewis acid.



3 **8a**

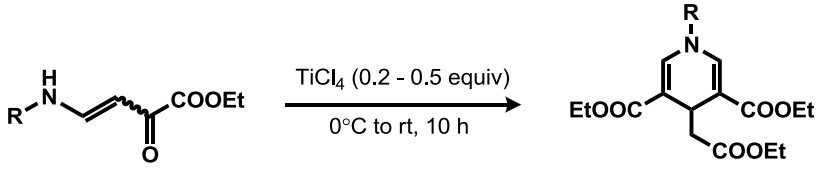
Scheme 3.9 Optimization of 1,4-DHP (**8a**)

Table 3.7 Variation of several Lewis acids and conditions for 1,4-DHP synthesis

Lewis acid (solvent)	Amount of Lewis acid (equivalent)	Reaction time	% Yield
TFA (DCM)	0.5 – 2	10 h	0
$AlCl_3$ (THF)	0.3	3 h	< 10
	0.5	3 h	24
	1	3 h	14
$AlCl_3$ (DCM)	0.3	3h	<10
$AlMeCl_2$ (THF)	0.2 - 0.5	10 h	0 [a]
$BF_3{\cdot}OEt_2$ (THF)	0.3	10 h	17
	0.3	2 days	34
	0.5	2 days	38
$TiCl_4$ (DCM)	0.2	10 h	33

The reaction of this enamine (**3**) with Lewis acid suggested that the acetal group could survive under the Lewis acid condition. However, at the quenching process, the acetal group might be converted to the unstable aldehyde and could be destroyed by amine co-product eliminated along the reaction process or any impurities. This might be one of the reasons that caused the low product yields. From this hypothesis, a series of enamine substrates without acetal moiety were prepared and used as substrates. According to the yields presented in **Table 3.7**, $TiCl_4$ was selected as Lewis acid for further elaboration.

Treatment of ethyl β-amino acrylates with 0.2 equivalent $TiCl_4$ in DCM solution at room temperature provided a number of 1,4-DHPs in excellent yield (70 – 83%). In the case of *N*-aryl amino acrylates, the higher amount of $TiCl_4$ is required for the higher % product yields (see the case of *para*-I-Ph and *para*-MeO-Ph) (**Scheme 3.10** and **Table 3.8**). With high yielding property, this Lewis acid-induced cyclization of enamine under mild conditions can thus be an attractive alternative method for the construction of 1,4-DHP derivatives.

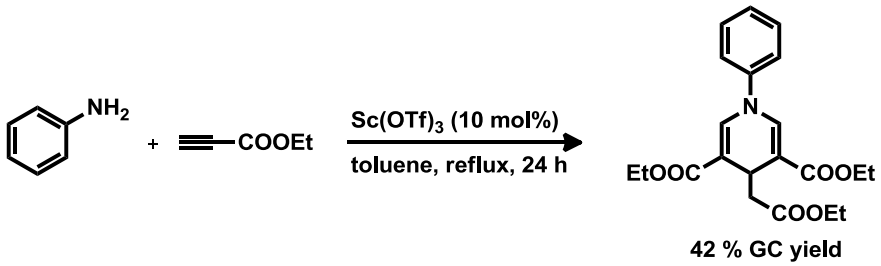


Scheme 3.10 Synthesis of 1,4-DHP (**8a - 8j**)

Table 3.8 Synthesis of a series of 1,4-DHP derivatives (**8**) in DCM at 0 °C to room temperature for 10 hours

Aliphatic enamine			Aromatic enamine		
R-group (compound)	**$TiCl_4$ amount (equivalent)**	**% isolated yield**	**R-group (compound)**	**$TiCl_4$ amount (equivalent)**	**% isolated yield**
$(MeO)_2CHCH_2$ (8a)	0.2	33	**C_6H_5 (8f)**	0.5	82
***n*-C_4H_9 (8b)**	0.2	81	***para*-MeO-C_6H_4 (8g)**	0.2 0.5	52 76
***n*-$C_{18}H_{37}$ (8c)**	0.2	83	***para*-I-C_6H_4 (8h)**	0.2 0.5	58 79
$PhCH_2$ (8d)	0.2	79	***para*-F-C_6H_4 (8i)**	0.5	70
$HOCH_2CH_2$ (8e)	0.2	81	***m*eta-Cl-C_6H_4 (8j)**	0.5	76

During the dissertation progress, one of 1,4-DHP derivatives (R = Ph) had been discovered by Kikuchi and his team [64]. It was synthesized from the reaction of aniline and ethyl propiolate in a presence of $Sc(OTf)_2$ under reflux temperature of toluene for 24 hours in 42 % GC yield (**Scheme 3.11**). Even though the synthesis of 1,4-DHP containing triester groups has already reported, some important information such as variation of *N*-substituted group, possible mechanism have not been studied and propsed yet. Furthermore, the reaction processed under reflux temperature of toluene (110 °C) may destroy or decompose the unstable substrates especially heat-sensitive compound.



Scheme 3.11 Synthesis of 1,4-DHP (**8f**) reported by Kikuchi and his team [64]

3.2.4. Mechanistic Proposal

Since the 1,4-DHP cyclization was constructed unexpectedly from three units of multifunctional enamine, we then turned to focus on the consideration of its mechanism. Obviously, three molecules of ethyl β-amino acrylate properly react with each other by using both of their nucleophilic and electrophilic sites to create the stable 6-membered ring 1,4-DHP compound. During the condition optimization, a minor product was isolated which was identified as the dimer (**9**). This is the very important evidence suggesting that the cyclotrimerization occurs via the formation of this dimeric intermediate (**Figure 3.13**). The structure of this intermediate was fully characterized by ^{1}H-NMR as shown in **Figure 3.14** and IR, HRMS (**see appendix**). According to the analysis results, this dimer contains two alkenes which arranged itself into *2E,4Z*-isomer as the major form. From the consideration of coupling constant (*J*) in ^{1}H-NMR, the vicinal coupling between the C2 proton and the C3 proton reveals $J = 15.7$ Hz which compliance to the coupling constant of *trans*-alkene protons. In the case of trisubstituted alkene (C4=C5), the exact configuration cannot be derived directly from coupling constant of C5. However, the large down field chemical shift of the N-H proton (10.8 ppm) is consistent with the H-bonding interaction between N-H proton and carbonyl oxygen, therefore the configuration of this trisubstituted alkene could be determined as *Z*-configuration.

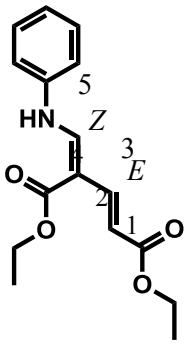


Figure 3.13 Structure of dimer (**9**)

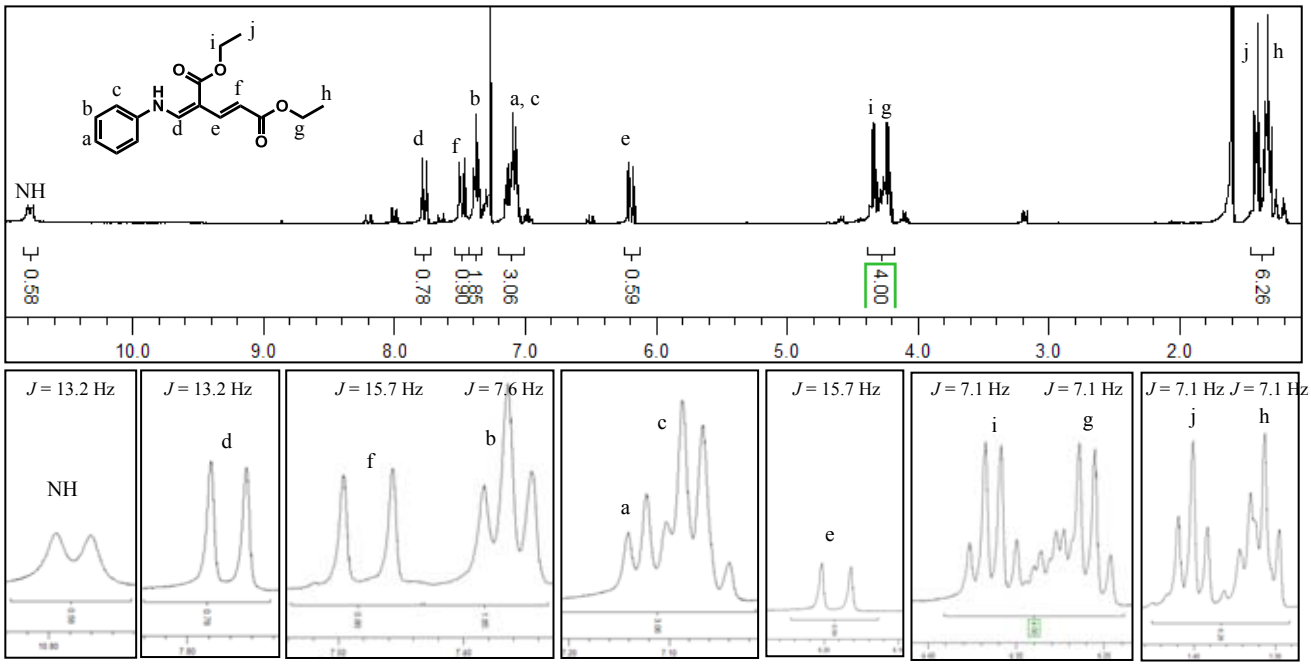


Figure 3.14 ^{1}H-NMR spectrum of dimer (**9**)

The mechanism is proposed based on the discovery of the key intermediate, dimer (**9**) (**Figure 3.15**). To start with, the first enamine (**5**) labeled on the ester group with 'COOEt1' acts as nucleophile to attack through conjugation to the second enamine labeled with 'COOEt2' at the electrophilic Michael accepter position. This adductive intermediate has undertaken the elimination of the quaternary ammonium group of the second enamine obtaining the dimeric intermediate. After that, the third enamine labeled as 'COOEt3' attacks the second Michael acceptor of COOEt2 system of dimeric intermediate. This regioselectivity was conducted by binding nature of

Lewis acid, while prefers to coordinate with COOEt2 carbonyl more than COOEt1 due to the existence of the intramolecular H-bonding between NH and COOEt1 carbonyl. The trimeric adduct has adjusted itself by proton transferring process into dienamyl intermediate, which intramolecularly cyclizes in 6-*exo*-trig manner to form 6-membered ring 1,4-DHP. This cyclic formation starts from the direct attack of lone pair electron of nitrogen at 1,4-Michael accepter position of the third alkene, followed by, the exclusion of amine co-product from the ring once again to obtain the target 1,4-DHP. The proposed mechanism suggested that overall, the reaction was processed from three molecules of substrate and catalyzed by Lewis acid through three Michael additions with two eliminations of amine leaving group.

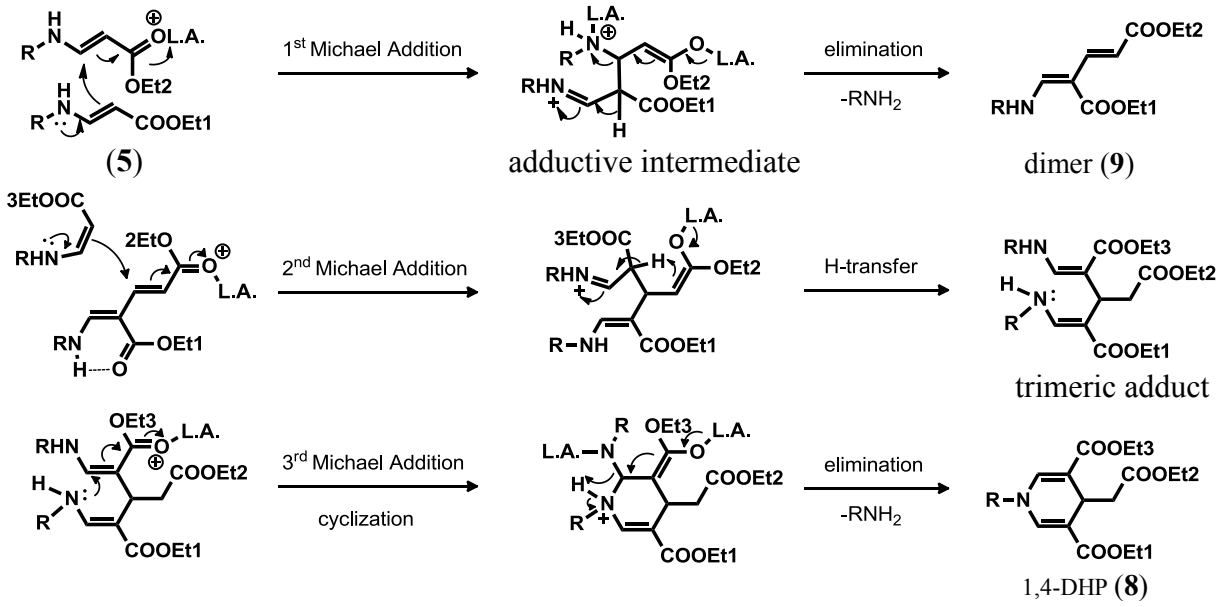


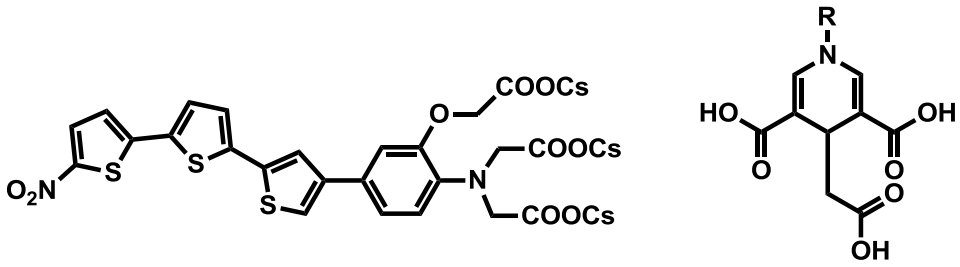
Figure 3.15 Proposed mechanism of 1,4-DHP (**8**) formation

3.3. Using 1,4-DHPs as a fluorescent sensor

The construction of the acid-induced cyclization not only surprisingly established a unique method for 1,4-DHP, but also provided the product which has fluorescent property. The existence of fluorescent property among nine conjugated atoms within its structure (O=C-C=C-N-C=C-C=O) was discovered during the purification by column chromatography (**Figure 3.16**).

Figure 3.16 Fluorescence emission of 1,4-DHPs under black light lamp

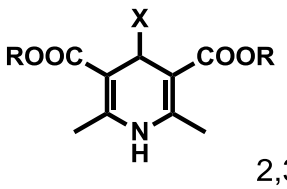
For the application of 1,4-DHPs, they were tested as fluorescent chemosensor. In general, most applications of fluorescent sensor will be developed mainly in two parts which are detecting unit and fluorophore unit. One of many researchs reported by Boens [66], the fluorescence sensor molecule containing terthiophene unit as a fluorophore and tricarboxylate chelator as a detecting unit was successfully synthesized and developed as Cu^{2+} indicator (**Figure 3.17**). Fortunately, this 1,4-DHP derivative contains both fluorophore and tricarboxylic (hydrolyzed from triester) detecting unit. Thus, these molecules are now readily being investigated as a fluorescent chemosensor.



Noël Boens' fluorescence sensor for Ca^{2+} hydrolyzed 1,4-DHP

Figure 3.17 Comparison of Boen's Ca^{2+} fluorescence sensor and hydrolyzed 1,4-DHP

Interestingly, fluorescence property of related 1,4-DHP have been reported in 2007 by Chilean scientists, Pávez and Encinas [67]. They studied photophysics and photochemical properties of 1,4-DHP derivatives (**Figure 3.18**). However, variation of X group of these derivatives did not have a direct effect to the fluorophore unit, as previously mentioned (O=C-C=C-N-C=C-C=O). In contrast, the new 1,4-DHPs that developed in the dissertation can be tuned *N*-substituted group by using different amine starting materials.

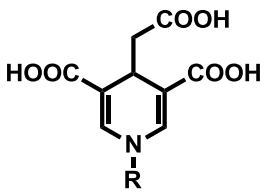


X	R	λ_{abs} nm	λ_{flu} nm	Φ_F
Me	Me	354	436	0.010
Ph	Et	358	430	0.012
4-OHPh	Me	358	430	0.011
2,3-diClPh	Et	367	430	0.029

Figure 3.18 Fluorescence study of 1,4-DHP derivatives reported by Pávez and Encinas [67] measured in water pH 5.8

The fluorescent property of new 1,4-DHPs tricarboxylic acids has been already measured by one of research group members, Homraruen [68]. Triester groups were hydrolyzed by saturated KOH to tricarboxylate groups in order to develop as the water soluble chemosensor. According to the fluorescence quantum yield, 1,4-DHP containing electron donating group (R = 4-MeOPh) yields the best fluorescence emission and was selected to be applied as a fluorescence sensor (**Figure 3.19a**). Finally, after several metal ions (50 μM) were tested in phosphate buffer solution of the 1,4-DHP (1 μM), only Hg^{2+} quenched the fluorescence signal. This is the first 1,4-DHP that was used as a fluorescence chemosensor in our group (**Figure 3.19b**).

a)



R	λ_{abs} nm	λ_{flu} nm	Φ_F
Ph	347	435	0.08
4-MeOPh	352	443	0.14
4-IPh	353	432	0.07
Bn	357	439	0.09

b)

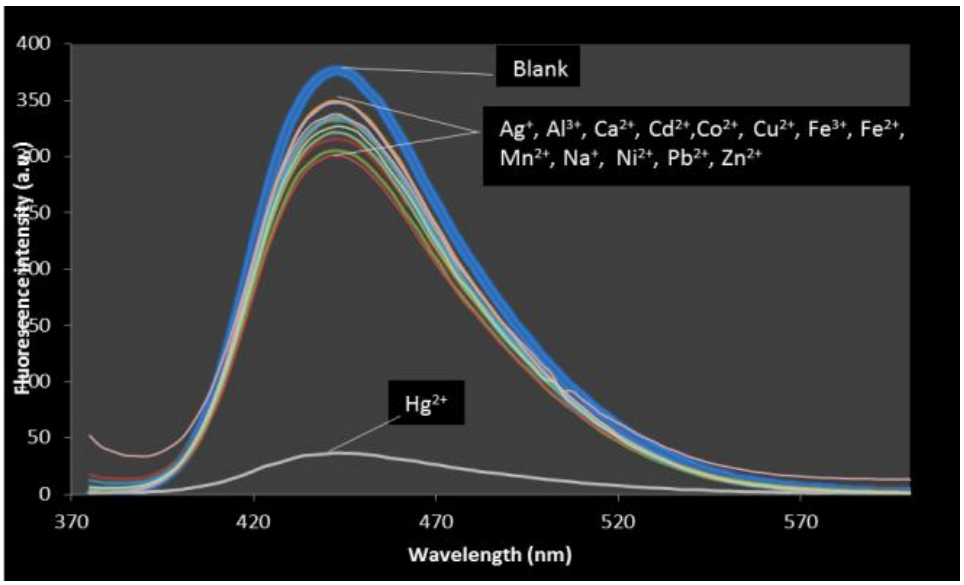
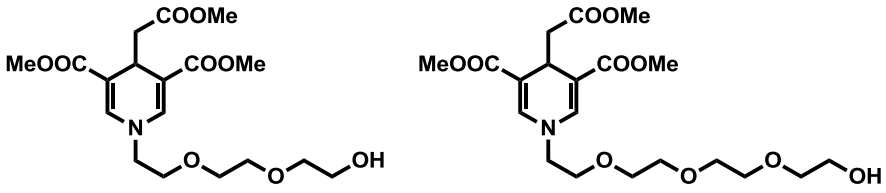


Figure 3.19 a) Absorption and fluorescent emission property of new 1,4-DHP derivatives

b) Fluorescence quenching profile of 1μM of hydrolyzed 1,4-DHP (R = 4-MeOPh) in Phosphate buffer solution pH 8.0 (excitation at 352 nm, emission at 443 nm), metal ion 100 μM reported by Homraruen [68]

According to Homraruen's results of the fluorescent property study of hydrolyzed 1,4-DHP, the fluorescent signal significantly decreased compared to those of triester derivatives likely due to the newly generated carboxyl group, that might have some impacts on the conjugated system. To solve this problem, attaching of water soluble group such as oligoethylene glycol to 1,4-DHPs at the *N*-substituent was tried instead of hydrolysis of ester group. In 2010, Miss Dokbua and Miss Hompetchrungrueng [(69)] synthesized and studied the fluorescence properties of di-/triethyleneglycol 1,4-DHP containing triester groups in phosphate buffer solution pH 8.0, but there was no selective metal ion response (**Figure 3.20a**). Bis(1,4-DHP) linked by ethylene glycol chains have also been synthesized and studied as a fluorescence sensor by Bookong and Jaipong [(70)] (**Figure 3.20b**). Auspiciously, the fluorescent signal of bis(1,4-DHP) linked by tetraethyleneglycol (1 μM) was completely quenched by Au(III) (100μM) in Milli-Q water medium (**Figure 3.21**).

a)



b)

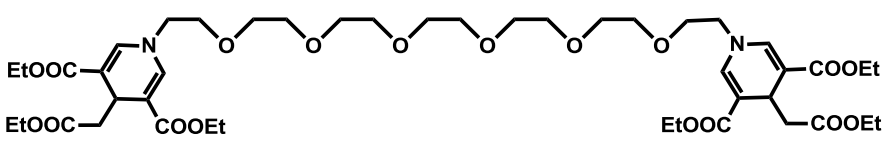


Figure 3.20 a) di-/triethyleneglycol 1,4-DHP reported by Dokbua and Hompetchrungrueng [(69)]

b) bis(1,4-DHP) connecting with tetraethyleneglycol reported by Bookong and Jaipong [(70)]

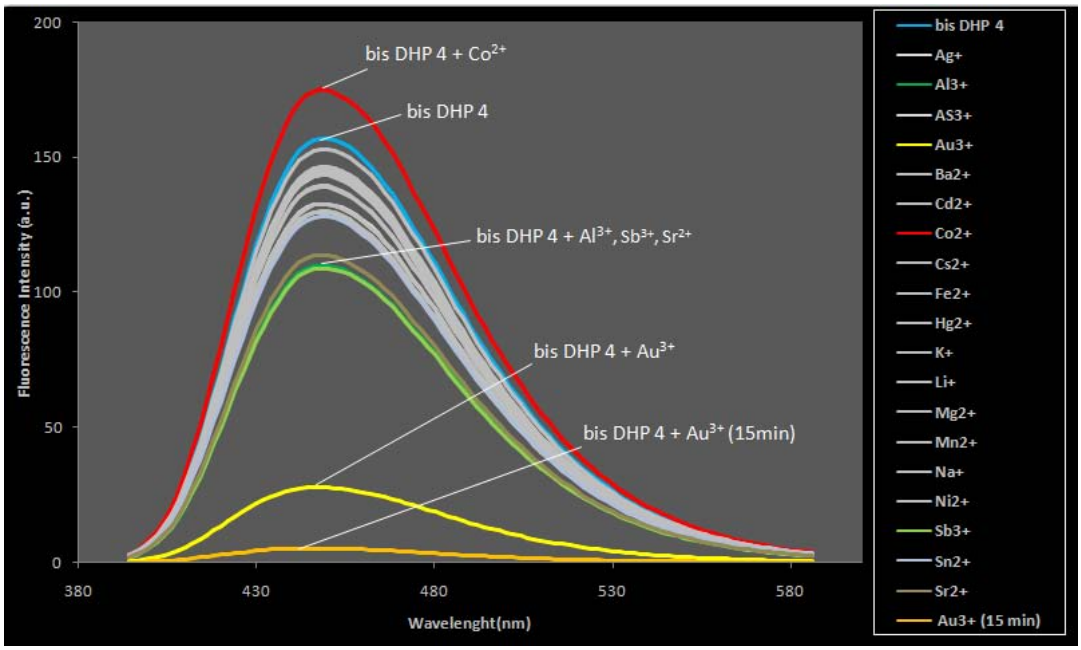


Figure 3.21 Fluorescence quenching profile of bis(1,4-DHP) (1μM) in MilliQ water (excitation at 350 nm, emission at 450 nm), metal ion (100 μM) reported by Bookong and Jaipong [70]

CHAPTER IV

CONCLUSION AND SUGGESTION

4.1. Conclusion

According to the results of the acid-induced reaction of the electron deficient enamines (β-amino acrylates), three sets of new compounds, β-amino acrylates, oxazolidin-2-ones, and 1,4-DHPs were synthesized through the developed novel synthetic methods.

Preparation of ethyl β-amino acrylate, the simple Michael addition between aliphatic amines and ethyl propiolate in DCM was used to provide aliphatic enamines in very good yields (81 – 95%). CuI (0.5 equivalent) was confirmed to assist the reaction to obtain aromatic substrates in moderate to excellent yield (33 - 93%) after scanning the catalytic effect of inorganic salts such as $CuSO_4$, CuI, $Zn(OAc)_2$, $AgNO_3$, $BF_3{\cdot}OEt_2$, and $InCl_4$ was achieved by the reaction in NMR tubes. The obtained ethyl β-amino acrylates were unstable, so they were immediately treated as a substrate *in situ* with acid. Several Lewis acids, e.g. $BF_3{\cdot}OEt_2$, $AlCl_3$, $AlMe_2Cl$, and $TiCl_4$, were tested in the acid-induced reaction of ethyl β-amino acrylate series in sub-stoichiometric amount.

The novel synthesis of oxazolidin-2-ones was developed by TFA-induced intramolecular cyclization of Boc-enamides bearing dialkyl acetal moiety. Mechanistically, instead of the deprotection of Boc-group by TFA, carbonyl oxygen attacked the activated oxonium cation to form the oxazolidinone ring in excellent yields (81 – 92 %).

After the optimization during the development period, treatment of β-amino acrylates with 0.2 equivalent of $TiCl_4$ at 0 °C to room temperature for 10 hours was proven to be the best condition. It could successfully provide a series of 1,4-DHP containing various *N*-substituents in very good yields (70 – 83 %). The reaction proceded through three Michael additions and an intramolecular cyclization. Dimeric intermediate was detected and separated during the product purification confirming the mechanism for this kind of reaction.

4.2. Suggestion

Followed to the successful results of the fluorescence chemosensor cases, the future work should be therefore mainly focused in sensing applications as following;

1) Study the fluorescent property of bis(1,4-DHP) linked tetraethyleneglycol, and its quenching mechanism with Au^{3+}.
2) Apply bis(1,4-DHP)-Au^{3+} complex as a switch on mode sensor for sulfur-based biomolecule.
3) Design and synthesis of the novel water soluble cationic fluorescent sensors containing one or more 1,4-DHP unit within their structures.

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APPENDIX

APPENDIX

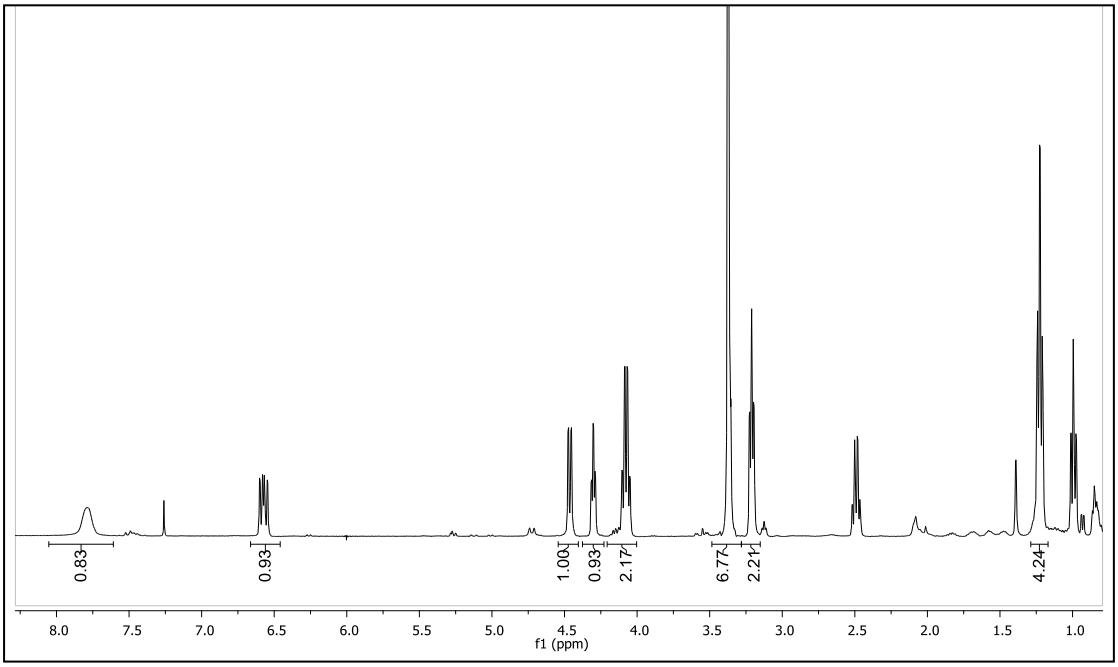

Figure A.1 ^{1}H-NMR of ethyl-3-(2,2-dimethoxyethylamino)acrylate (**3**)

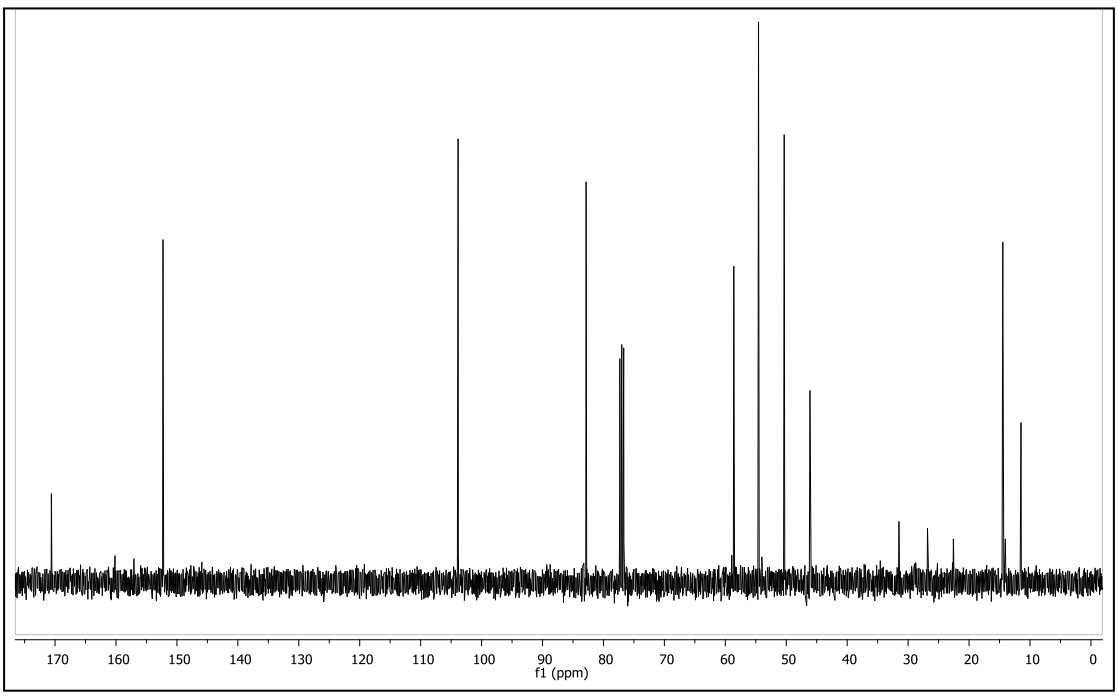

Figure A.2 ^{13}C-NMR of ethyl-3-(2,2-dimethoxyethylamino)acrylate (**3**)

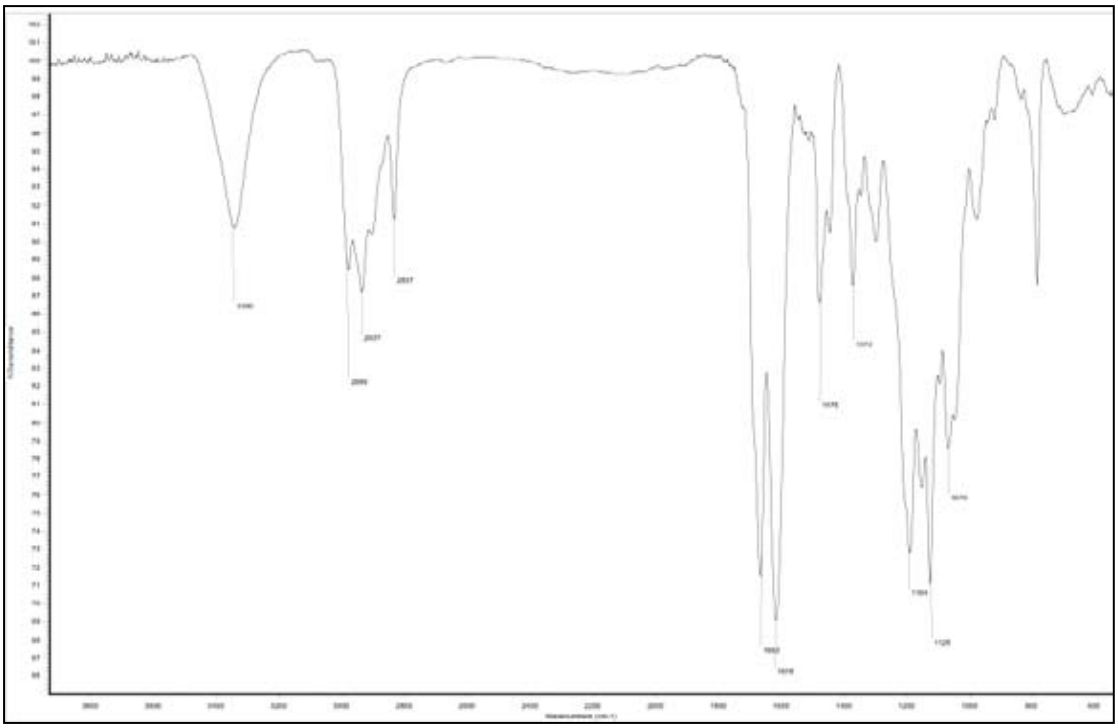

Figure A.3 IR of ethyl-3-(2,2-dimethoxyethylamino)acrylate (**3**)

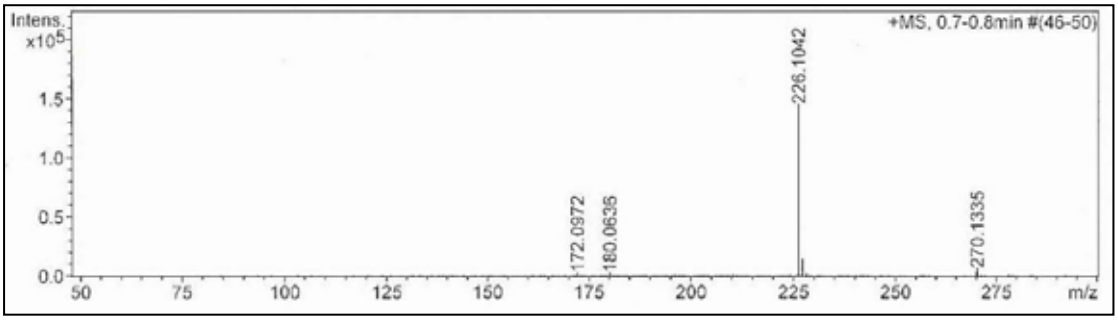

Figure A.4 HRMS of ethyl-3-(2,2-dimethoxyethylamino)acrylate (**3**)

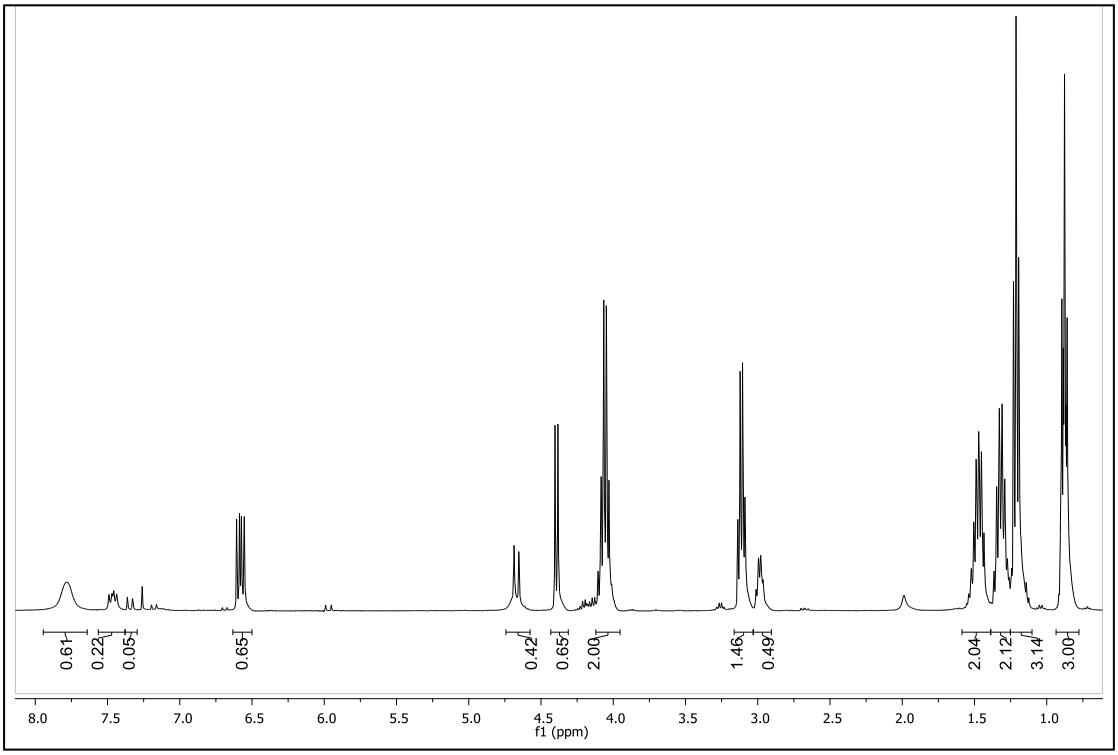

Figure A.5 ^{1}H-NMR of ethyl-3-(butylamino)acrylate **(5a)**

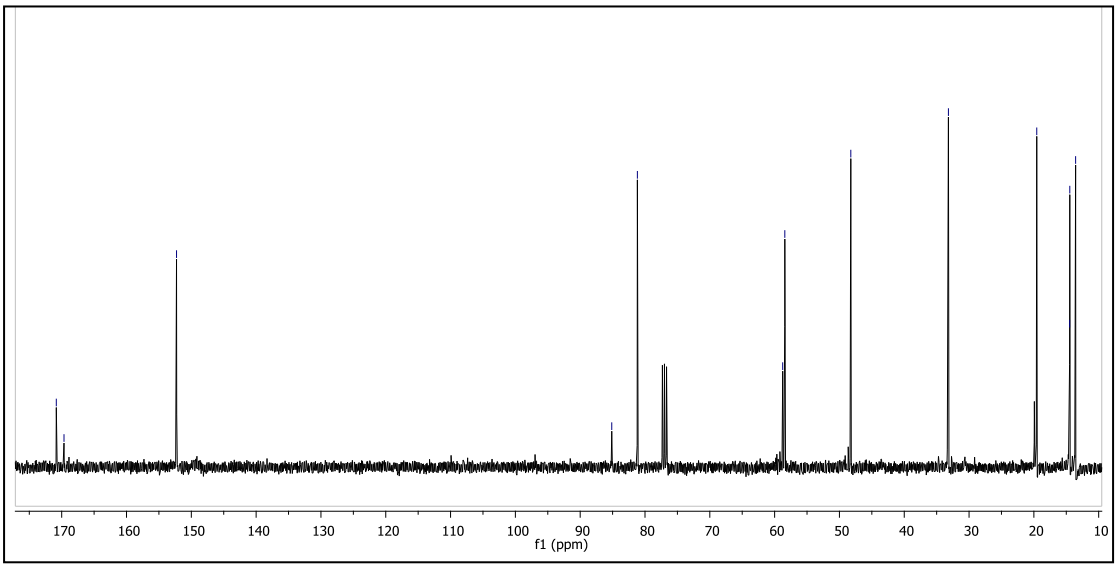

Figure A.6 ^{13}C-NMR of ethyl-3-(butylamino)acrylate **(5a)**

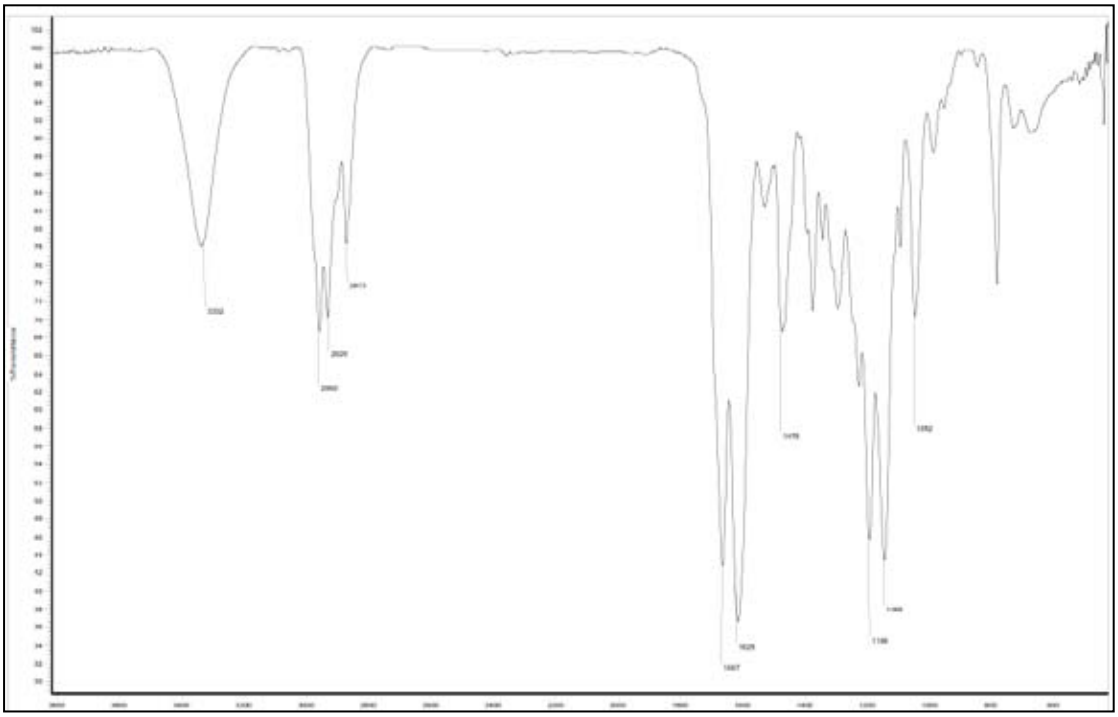

Figure A.7 IR of ethyl-3-(butylamino)acrylate **(5a)**

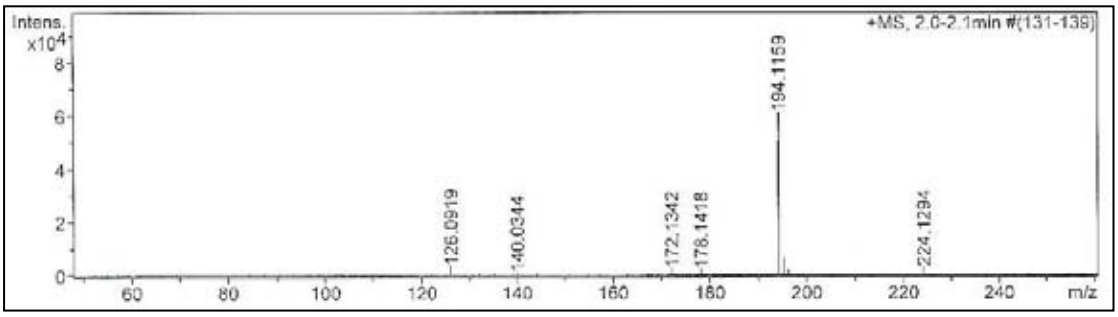

Figure A.8 HRMS of ethyl-3-(butylamino)acrylate **(5a)**

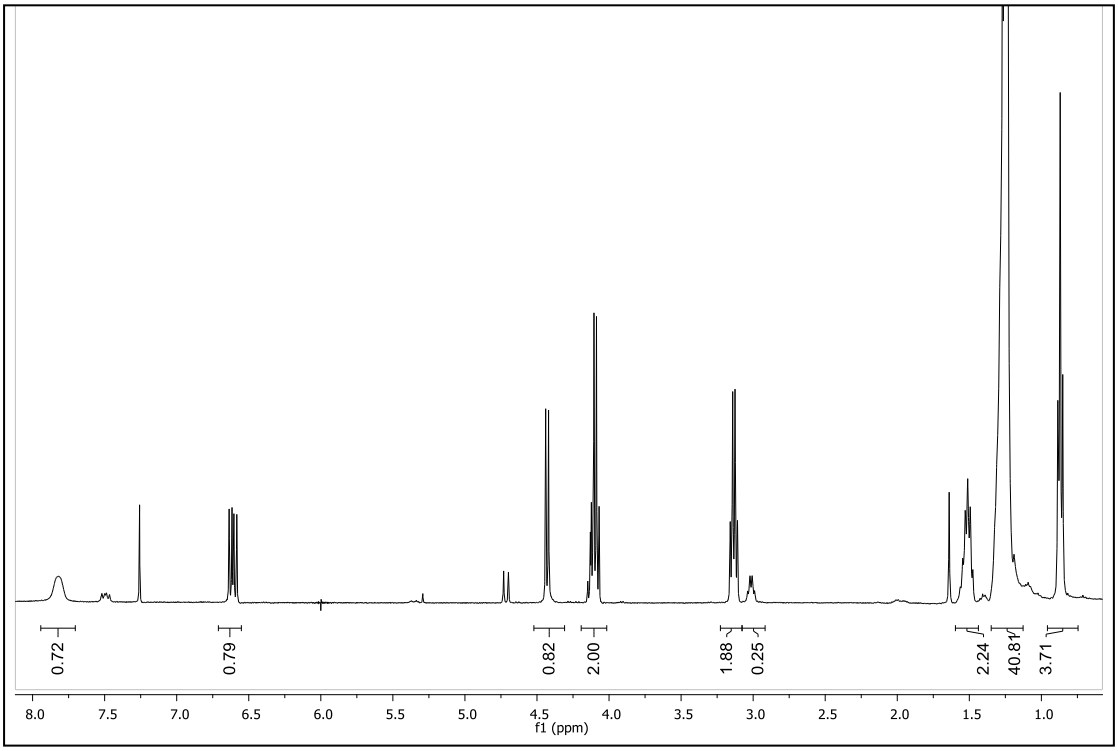

Figure A.9 ^{1}H-NMR of ethyl-3-(octadecylamino)acrylate **(5b)**

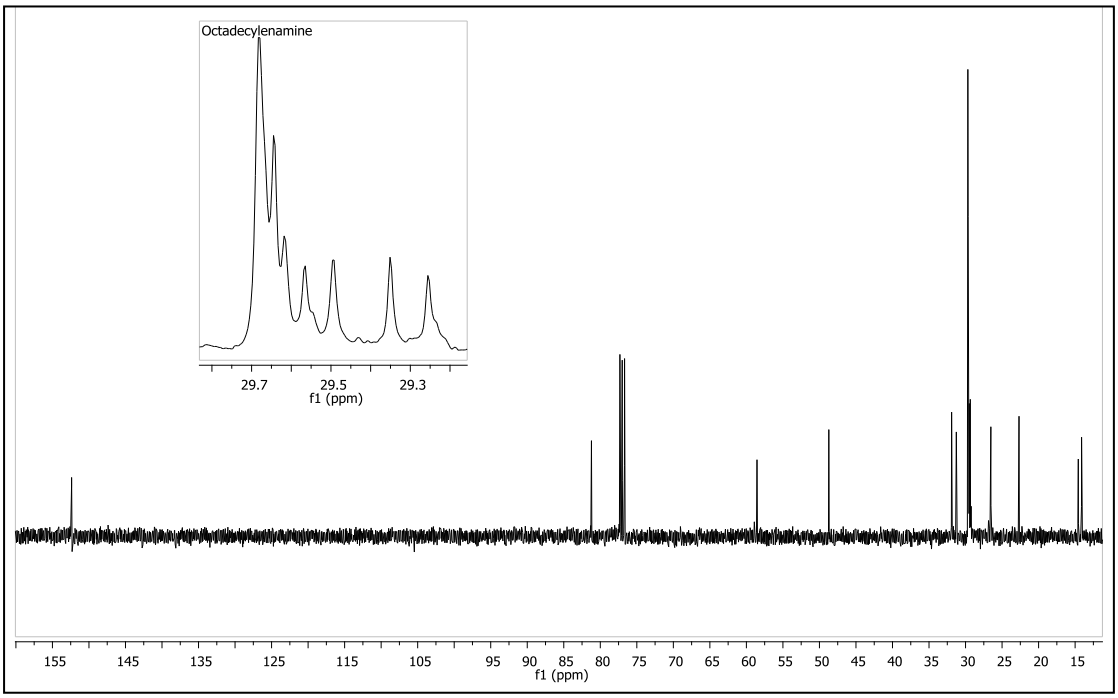

Figure A.10 ^{13}C-NMR of ethyl-3-(octadecylamino)acrylate **(5b)**

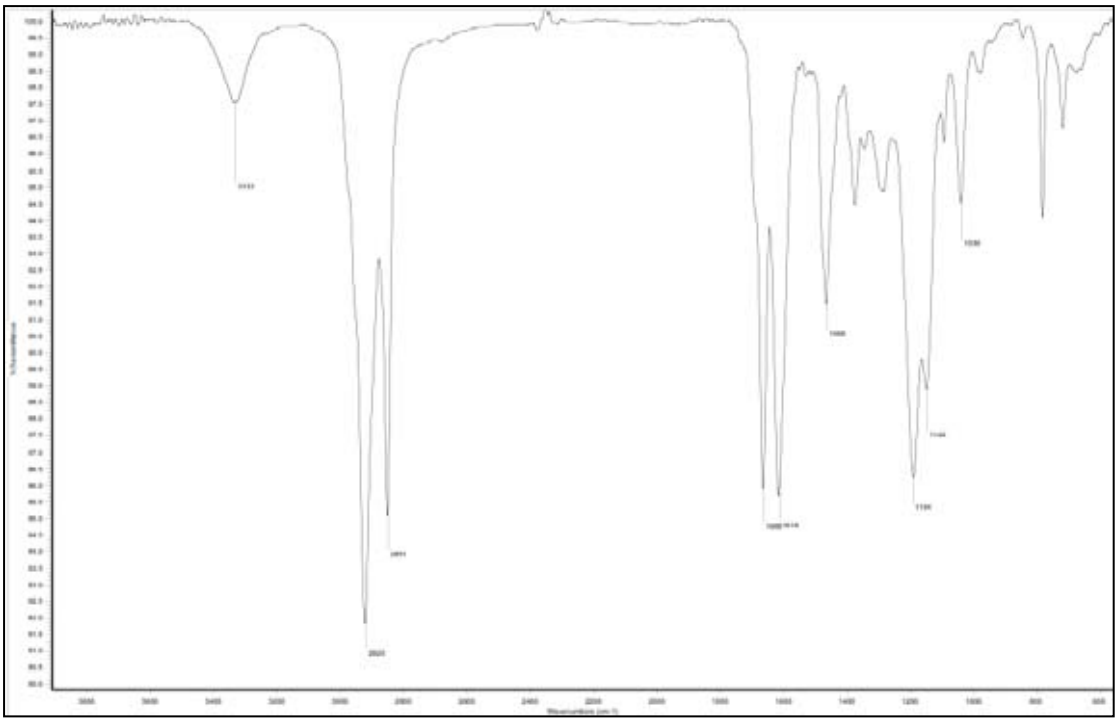

Figure A.11 IR of ethyl-3-(octadecylamino)acrylate **(5b)**

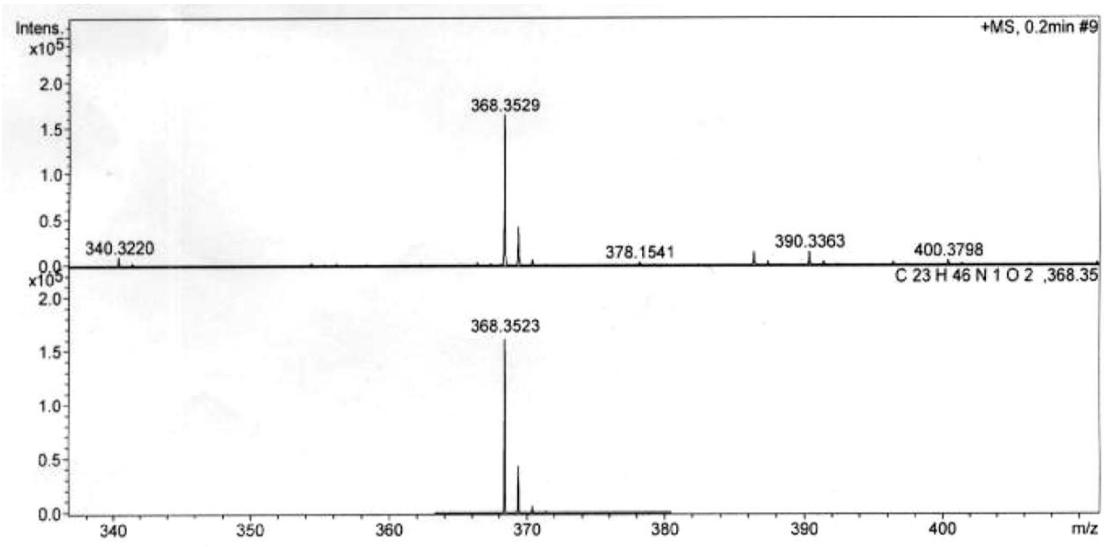

Figure A.12 HRMS of ethyl-3-(octadecylamino)acrylate **(5b)**

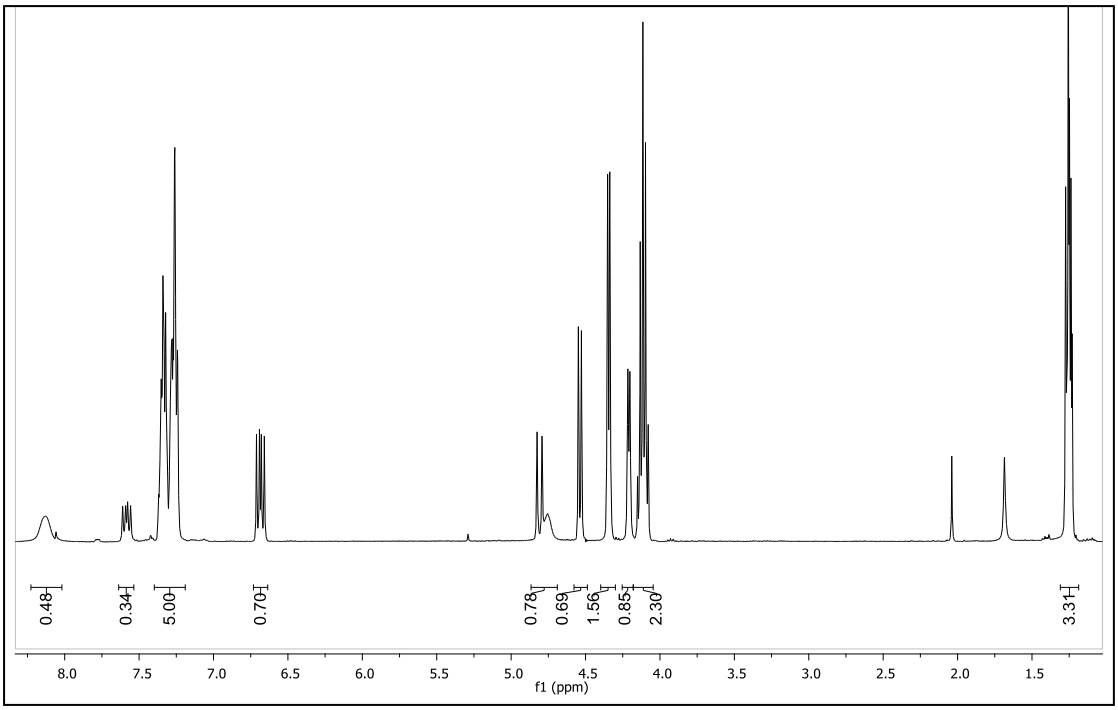

Figure A.13 ^{1}H-NMR of ethyl-3-(benzylamino)acrylate **(5c)**

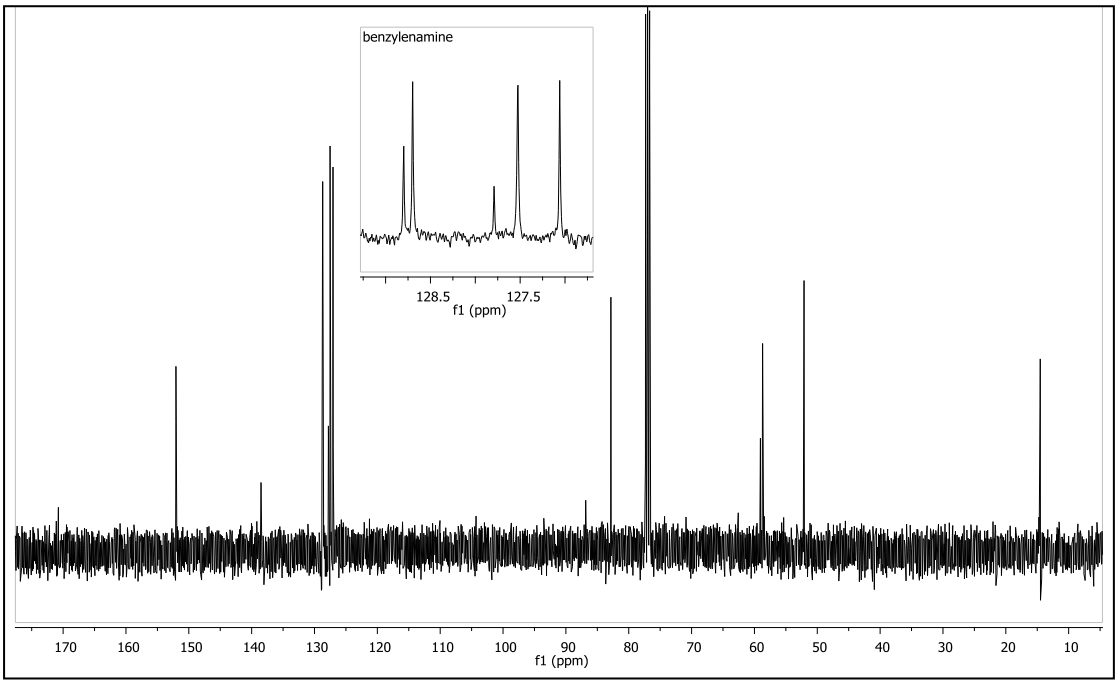

Figure A.14 ^{13}C-NMR of ethyl-3-(benzylamino)acrylate **(5c)**

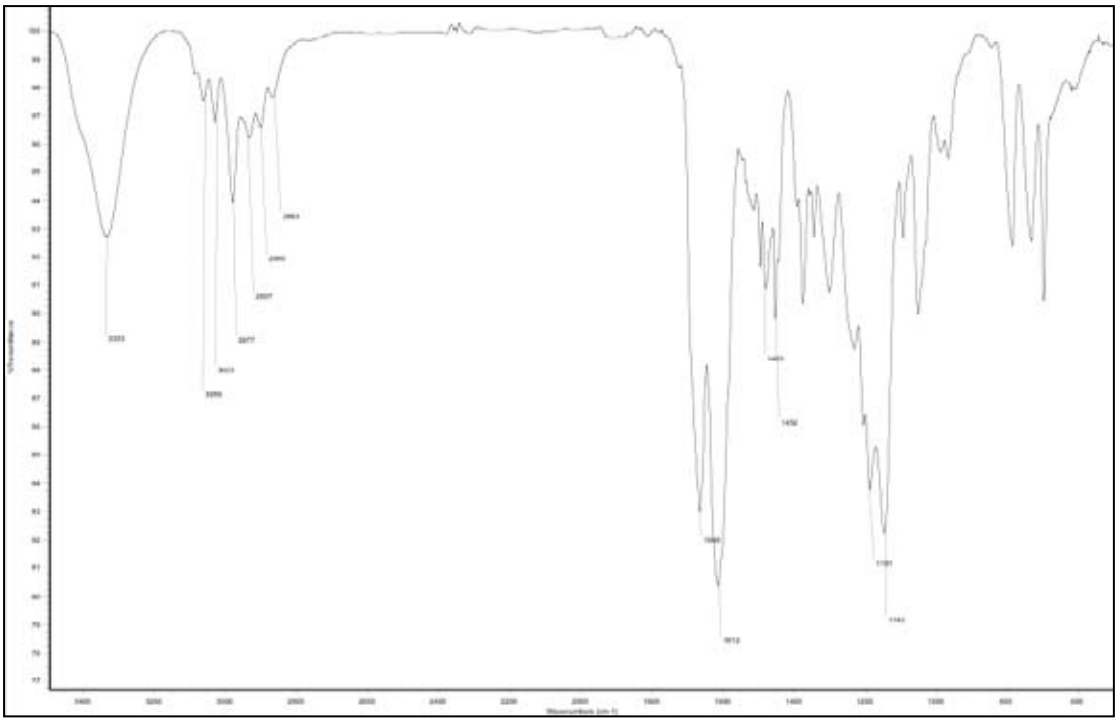

Figure A.15 IR of ethyl-3-(benzylamino)acrylate **(5c)**

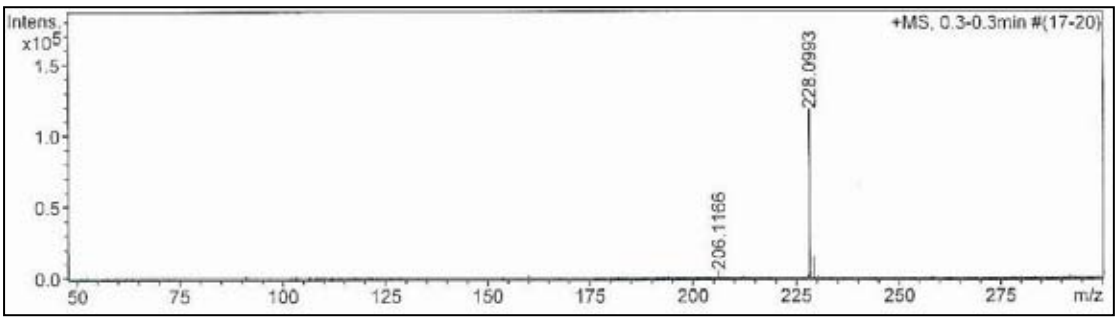

Figure A.16 HRMS of ethyl-3-(benzylamino)acrylate **(5c)**

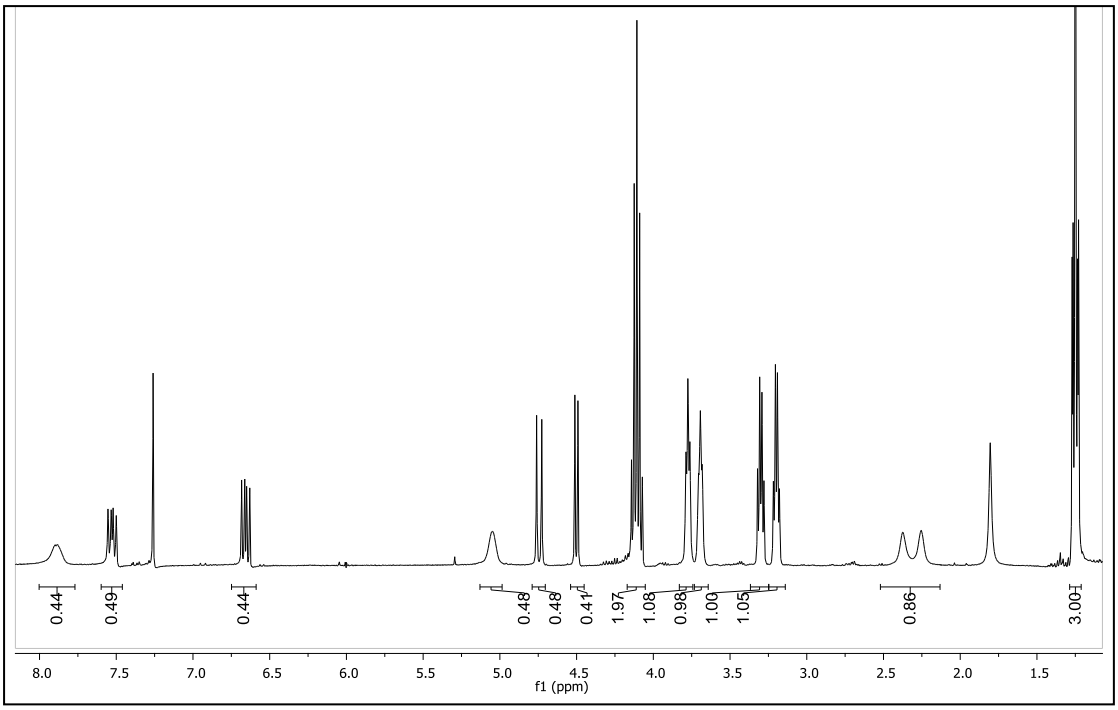

Figure A.17 ^{1}H-NMR of ethyl-3-(2-hydroxyethylamino)acrylate **(5d)**

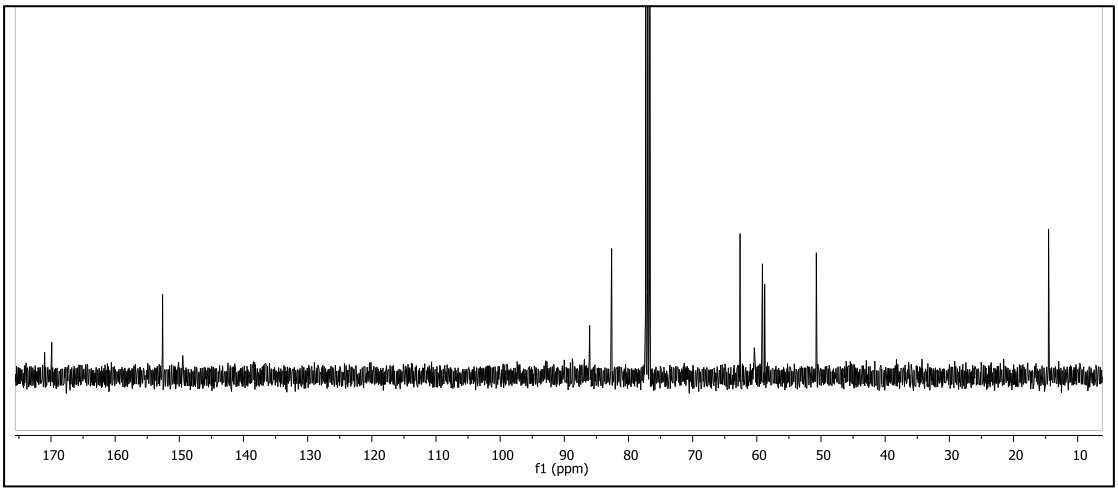

Figure A.18 ^{13}C-NMR of ethyl-3-(2-hydroxyethylamino)acrylate **(5d)**

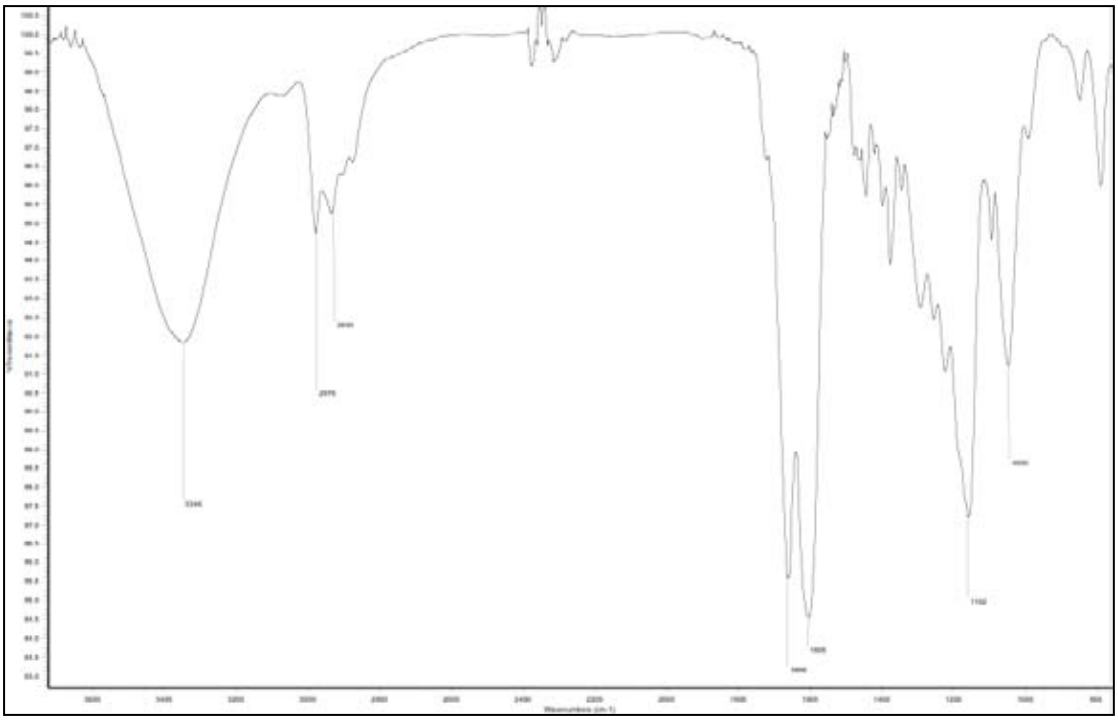

Figure A.19 IR of ethyl-3-(2-hydroxyethylamino)acrylate **(5d)**

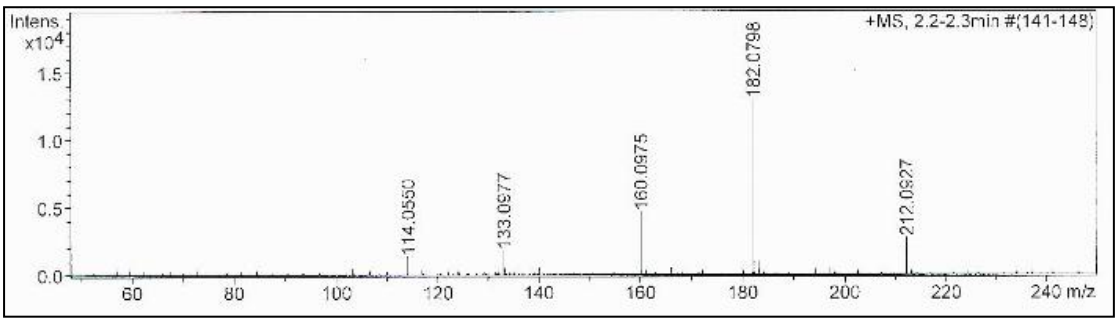

Figure A.20 HRMS of ethyl-3-(2-hydroxyethylamino)acrylate **(5d)**

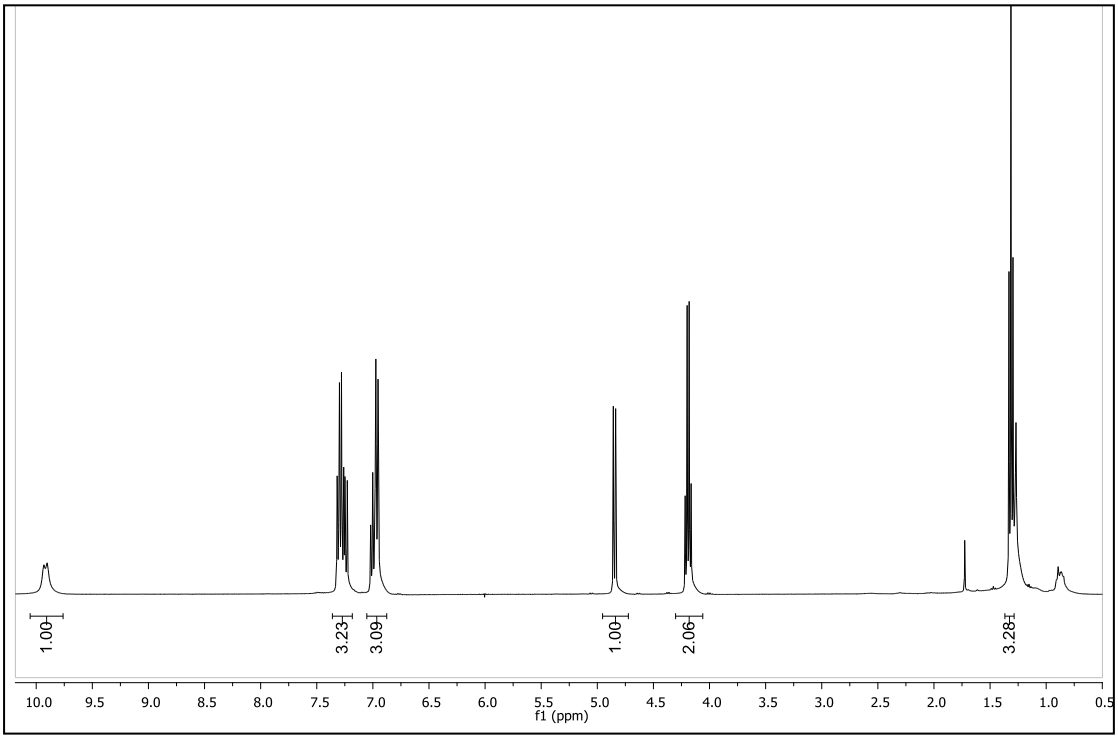

Figure A.21 ^{1}H-NMR of ethyl-3-(phenylamino)acrylate **(5e)**

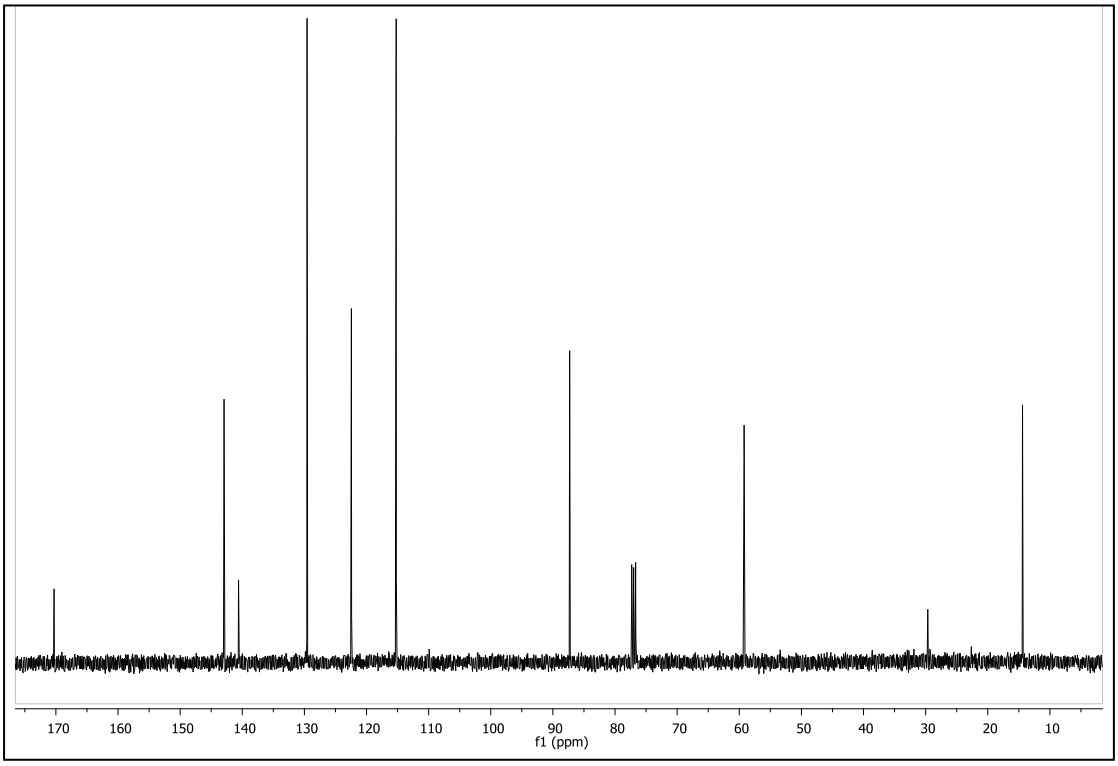

Figure A.22 ^{13}C-NMR of ethyl-3-(phenylamino)acrylate **(5e)**

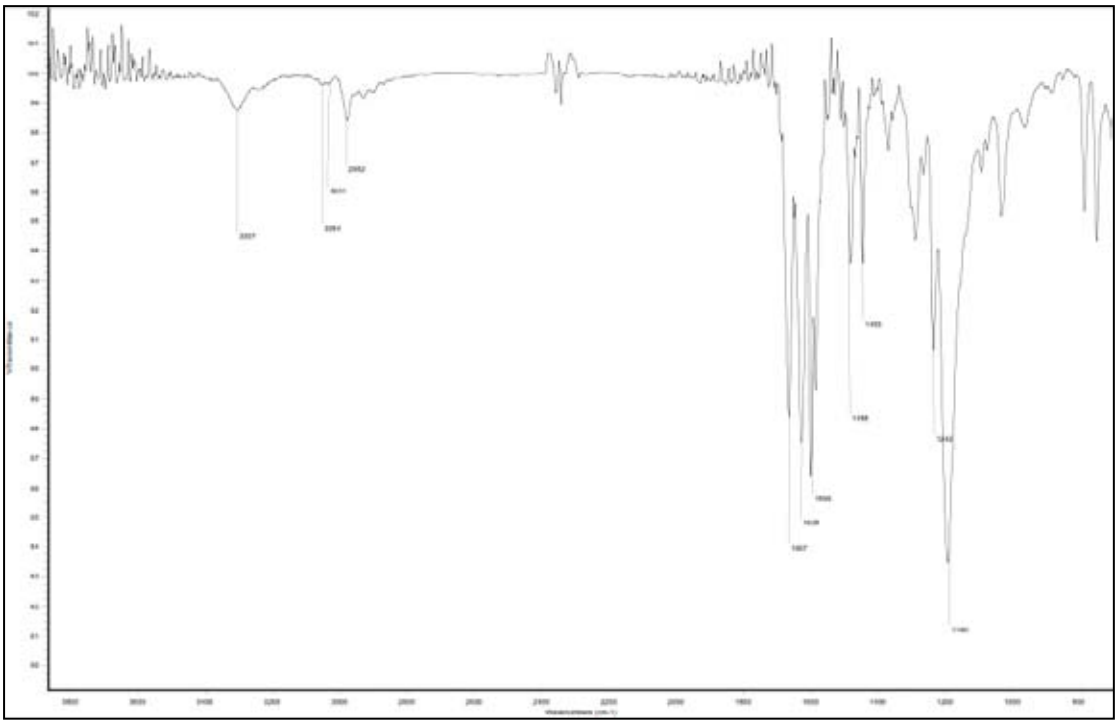

Figure A.23 IR of ethyl-3-(phenylamino)acrylate **(5e)**

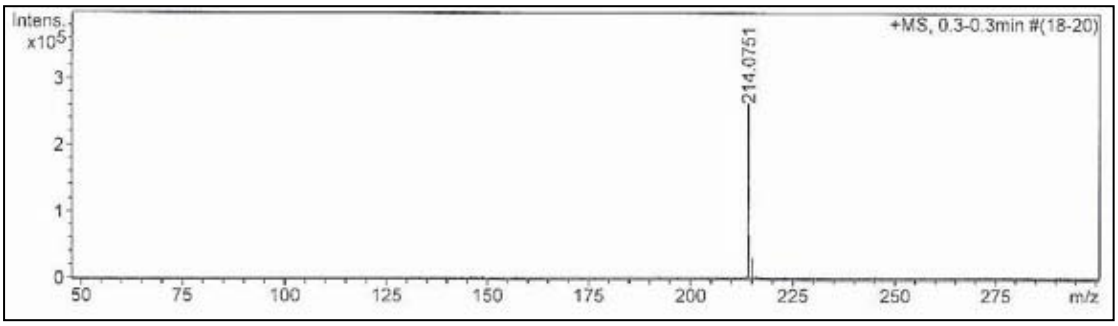

Figure A.24 HRMS of ethyl-3-(phenylamino)acrylate **(5e)**

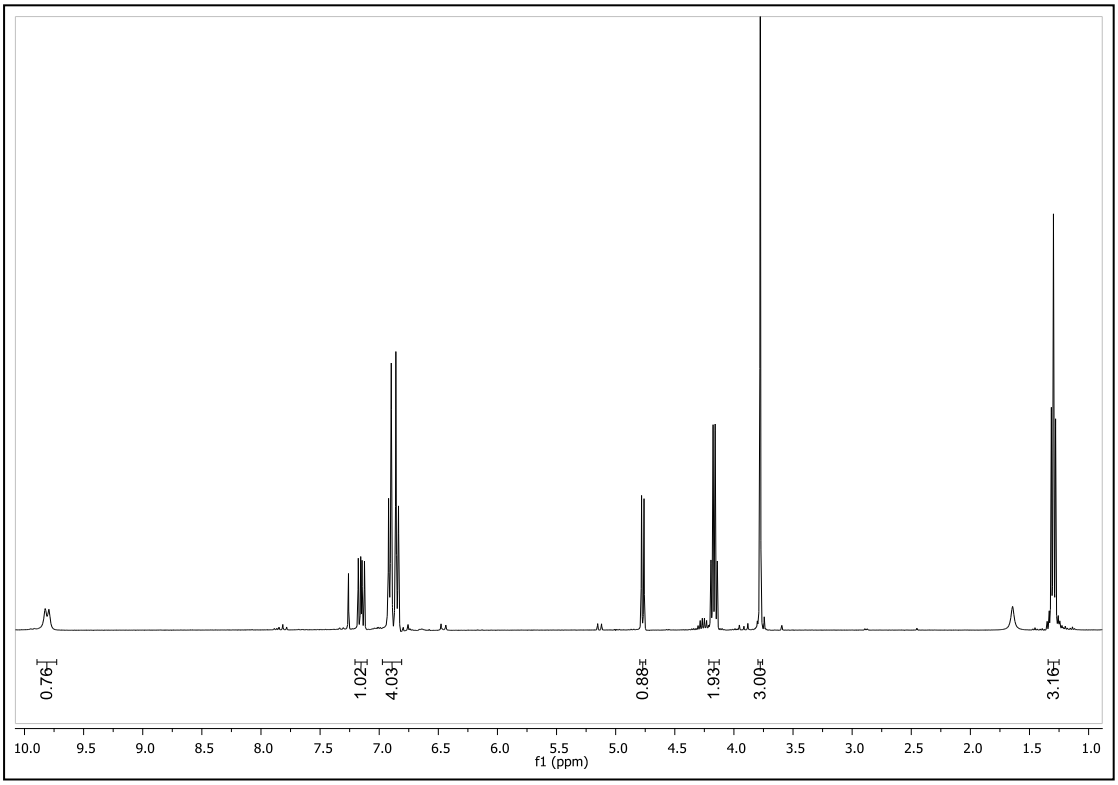

Figure A.25 ^{1}H-NMR of ethyl-3-(4-methoxyphenylamino)acrylate **(5f)**

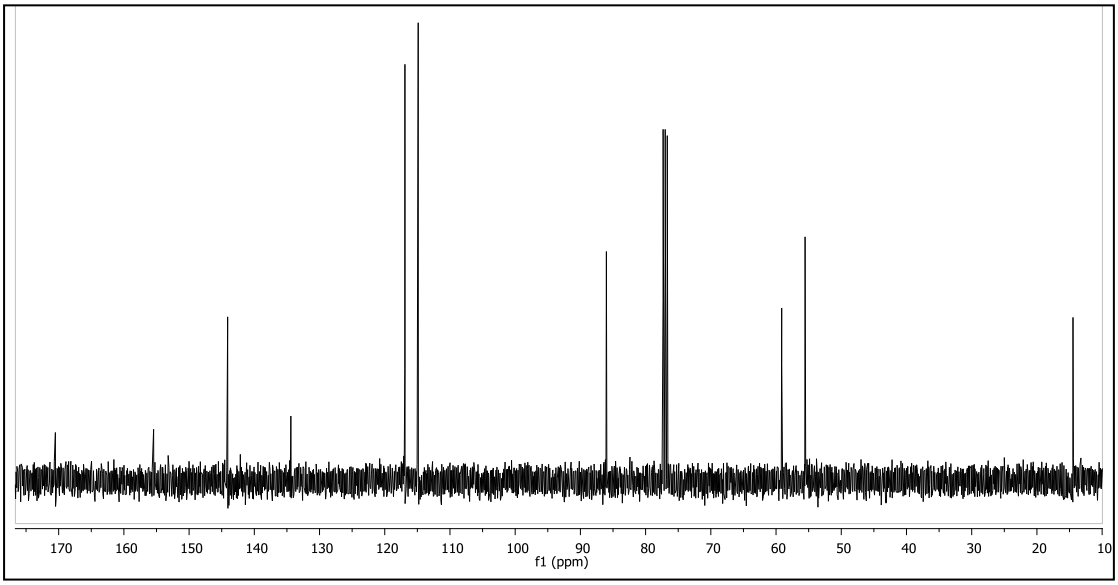

Figure A.26 ^{13}C-NMR of ethyl-3-(4-methoxyphenylamino)acrylate **(5f)**

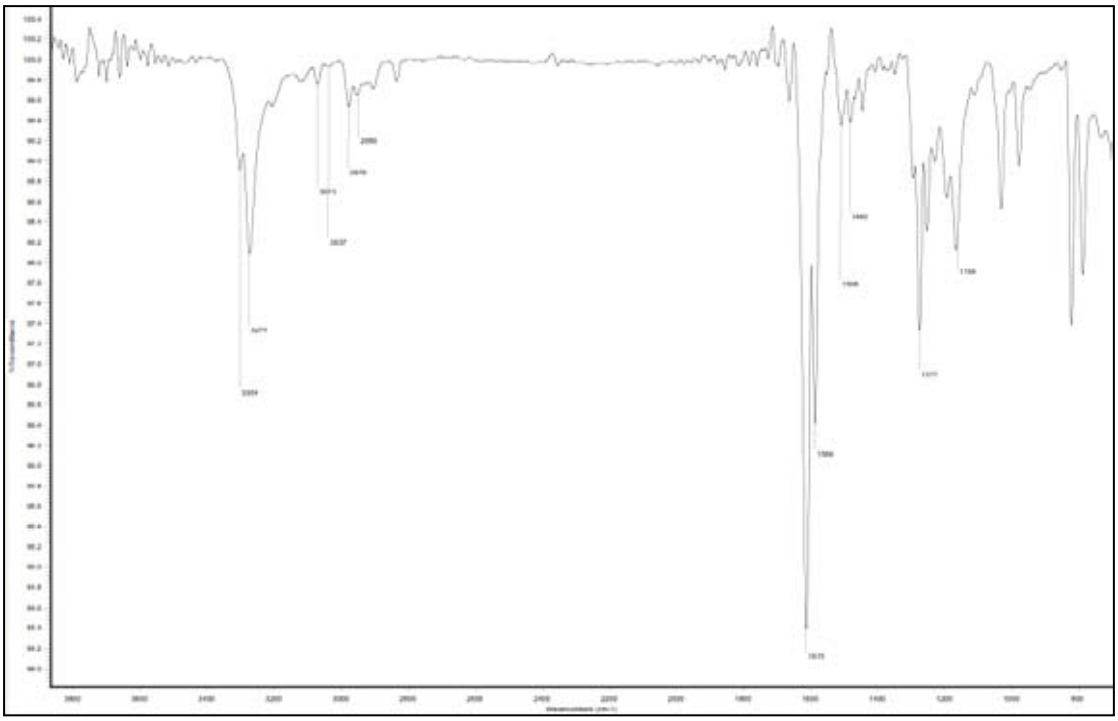

Figure A.27 IR of ethyl-3-(4-methoxyphenylamino)acrylate **(5f)**

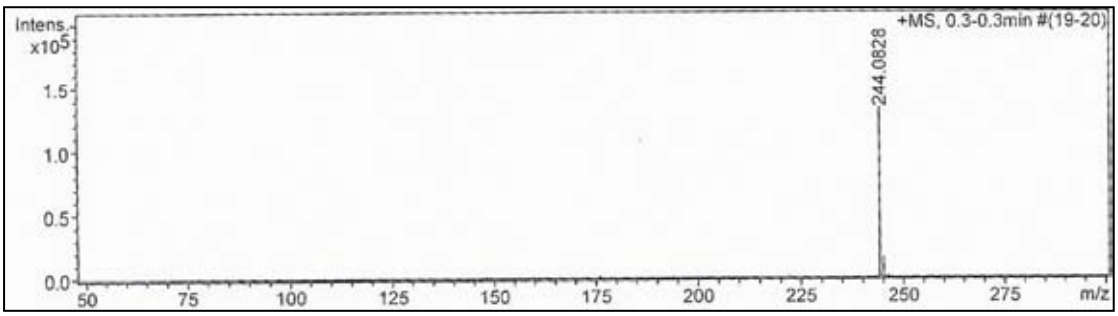

Figure A.28 HRMS of ethyl-3-(4-methoxyphenylamino)acrylate **(5f)**

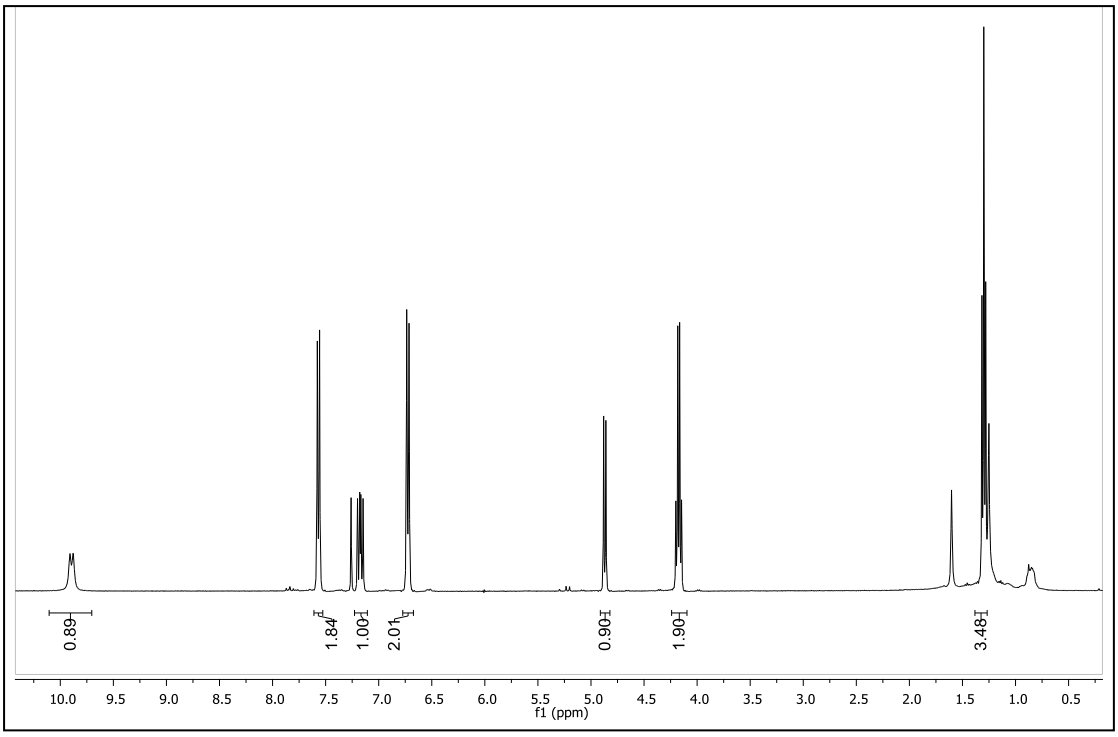

Figure A.29 ^{1}H-NMR of ethyl-3-(4-iodophenylamino)acrylate **(5g)**

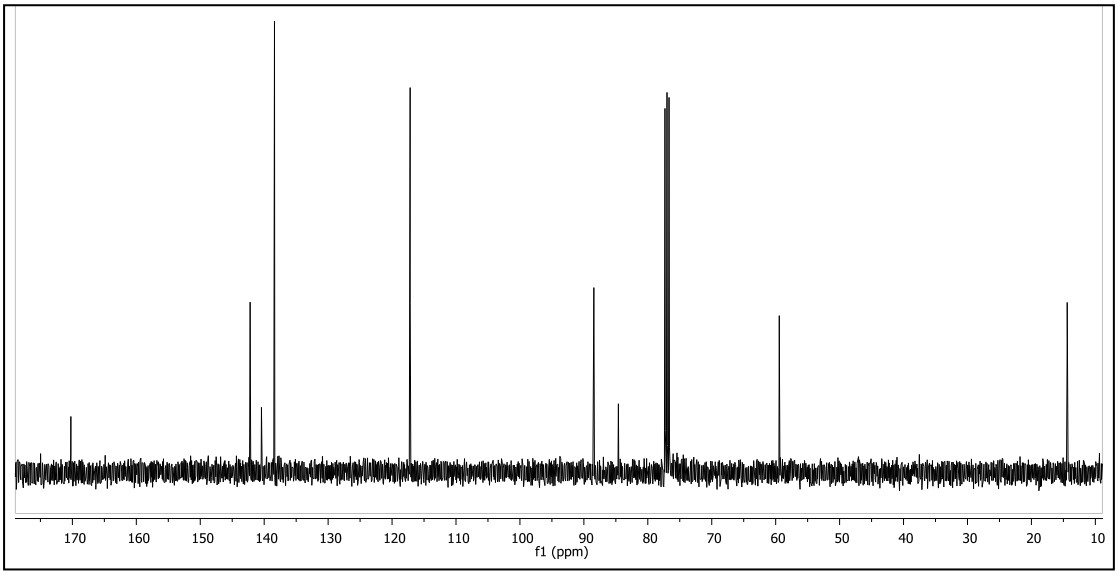

Figure A.30 ^{13}C-NMR of ethyl-3-(4-iodophenylamino)acrylate **(5g)**

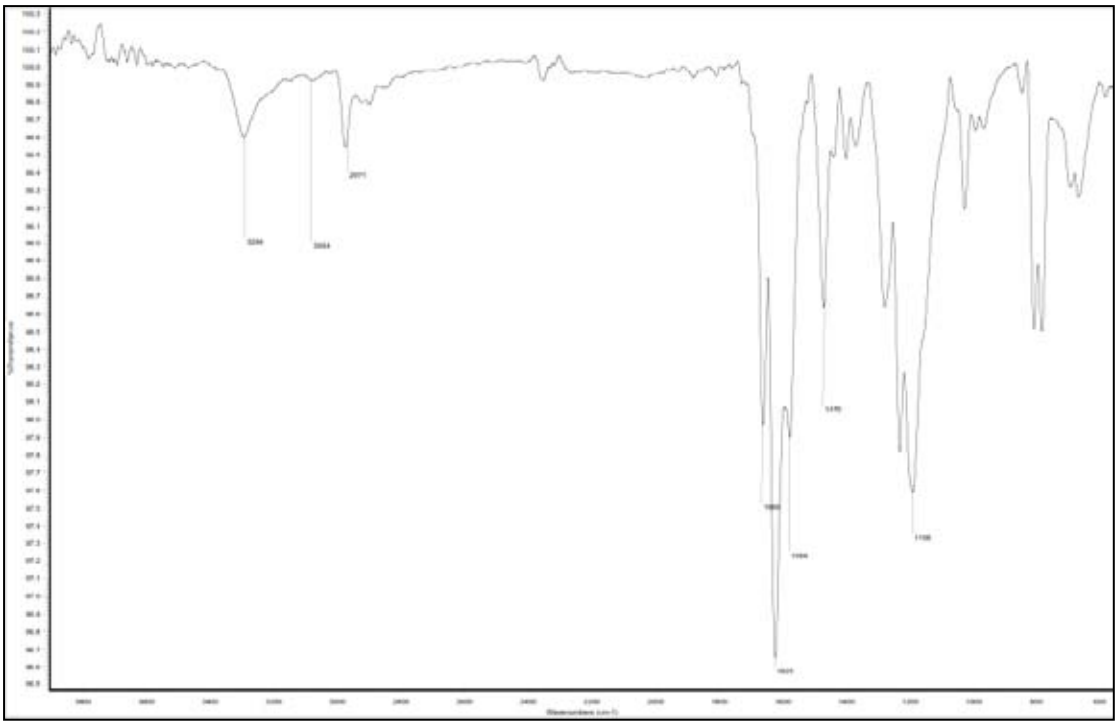

Figure A.31 IR of ethyl-3-(4-iodophenylamino)acrylate **(5g)**

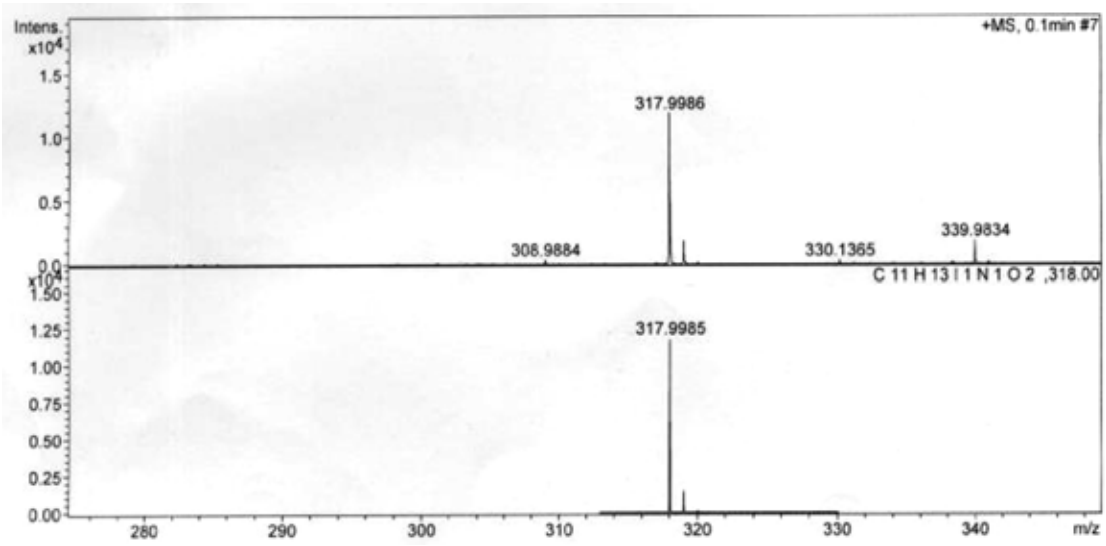

Figure A.32 HRMS of ethyl-3-(4-iodophenylamino)acrylate **(5g)**

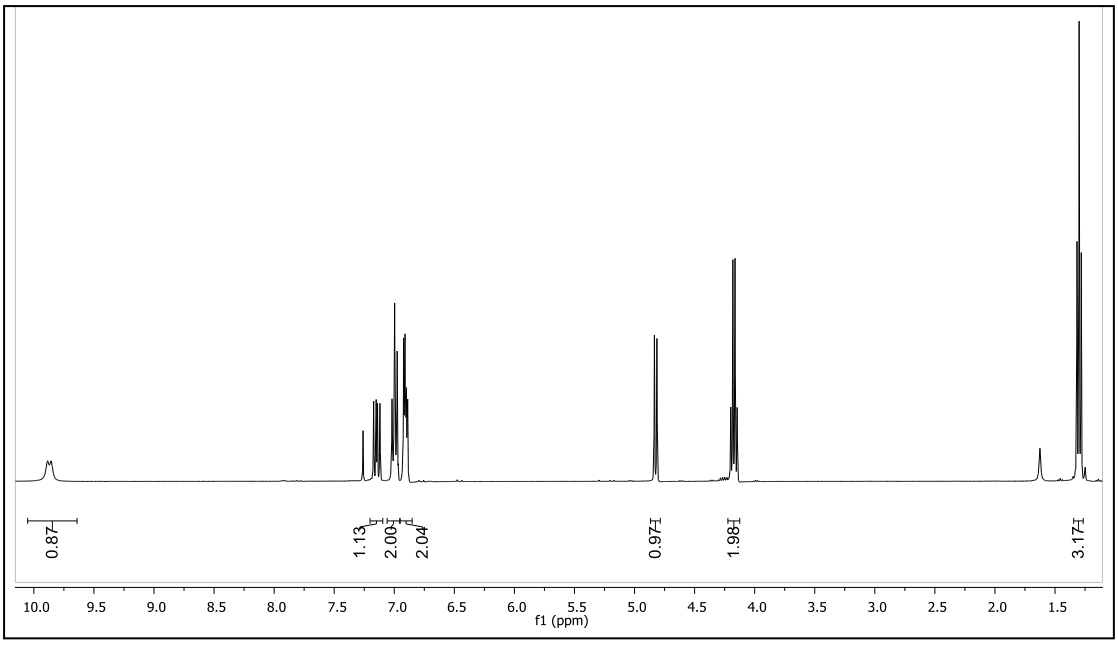

Figure A.33 ^{1}H-NMR of ethyl-3-(4-fluorophenylamino) acrylate **(5h)**

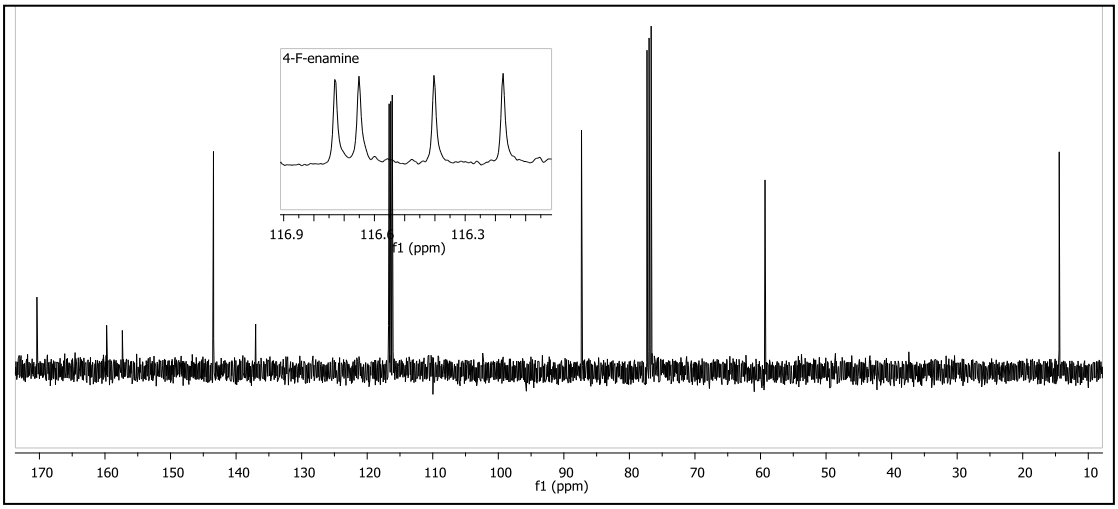

Figure A.34 ^{13}C-NMR of ethyl-3-(4-fluorophenylamino) acrylate **(5h)**

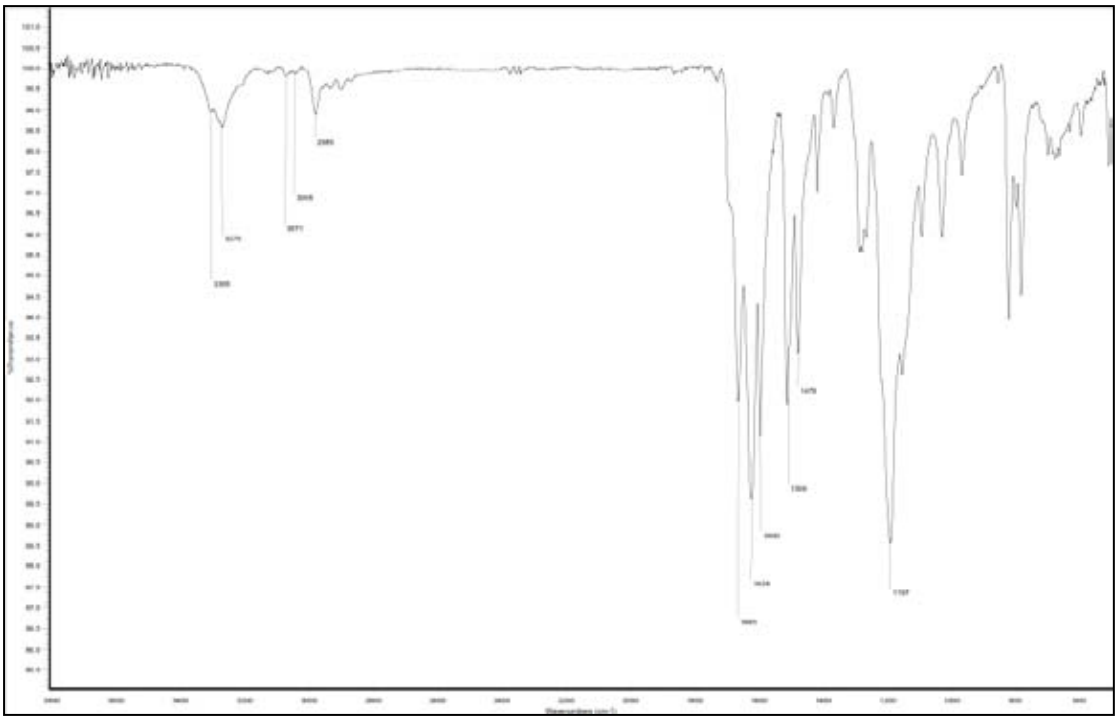

Figure A.35 IR of ethyl-3-(4-fluorophenylamino) acrylate **(5h)**

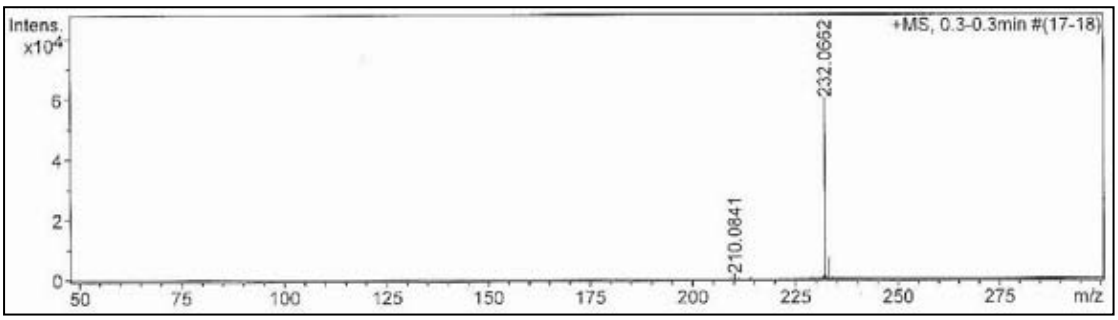

Figure A.36 HMRS of ethyl-3-(4-fluorophenylamino) acrylate **(5h)**

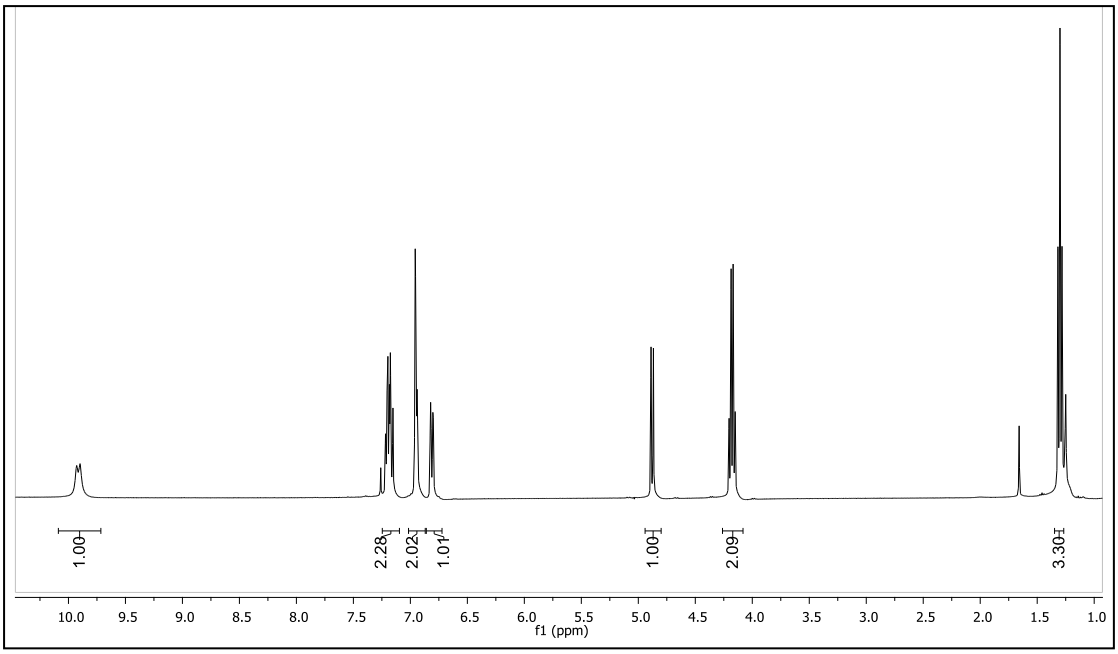

Figure A.37 ^{1}H-NMR of ethyl-3-(3-chlorophenylamino)acrylate **(5i)**

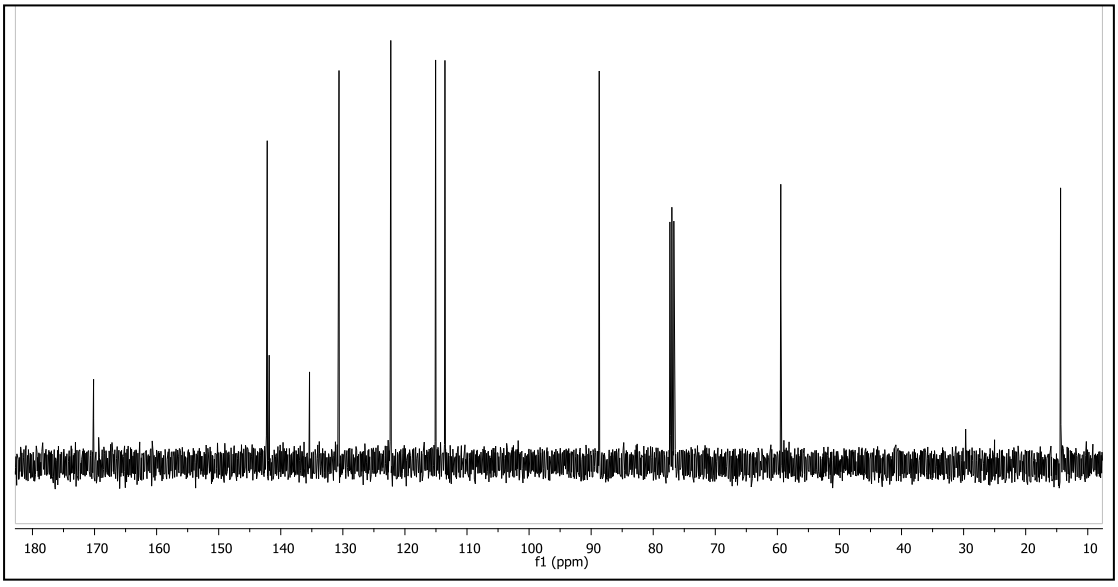

Figure A.38 ^{13}C-NMR of ethyl-3-(3-chlorophenylamino)acrylate **(5i)**

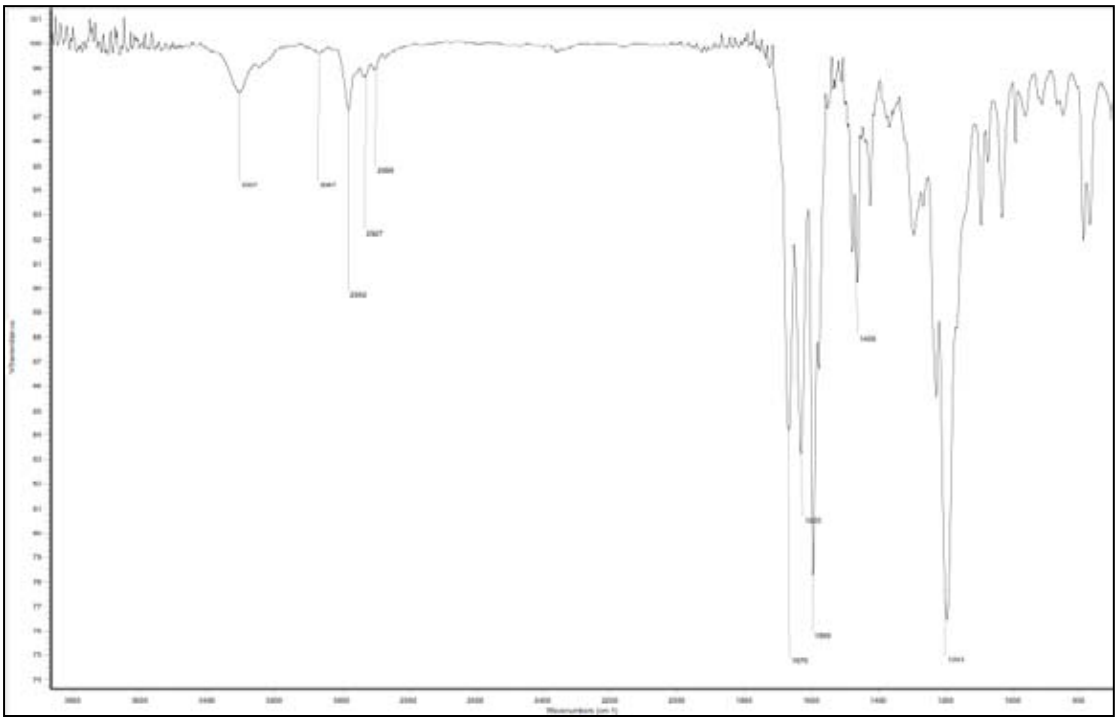

Figure A.39 IR of ethyl-3-(3-chlorophenylamino)acrylate **(5i)**

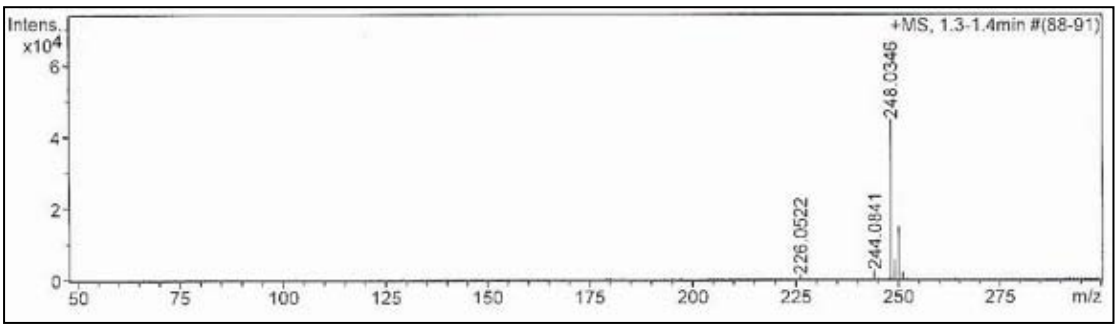

Figure A.40 HRMS of ethyl-3-(3-chlorophenylamino)acrylate **(5i)**

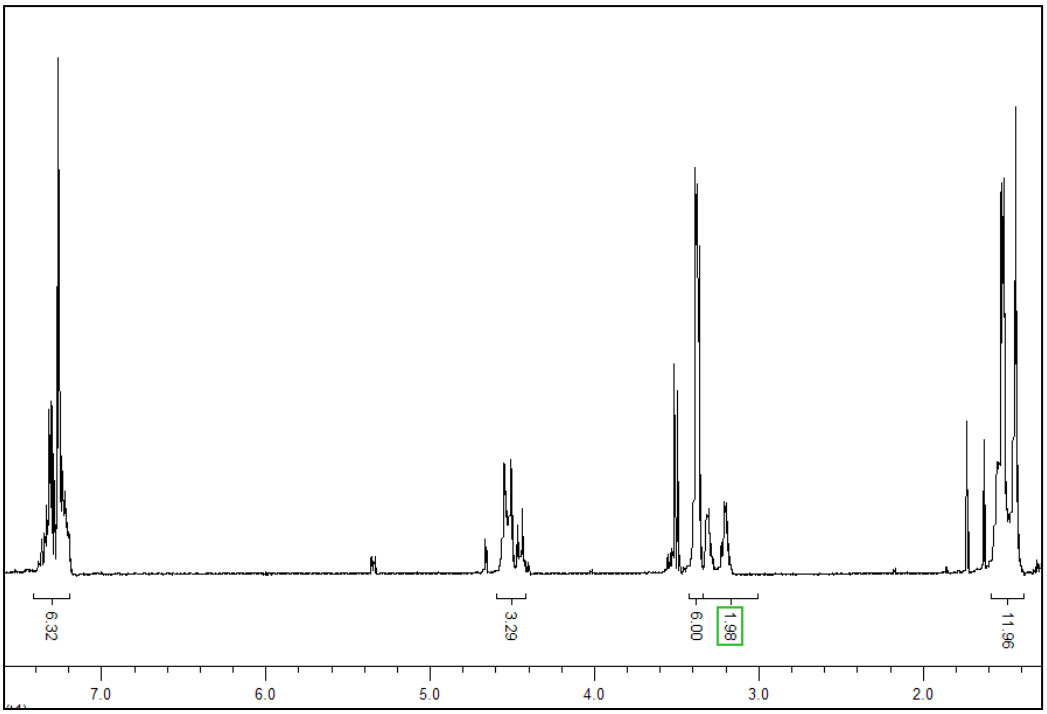

Figure A.41 ^{1}H-NMR of *tert*-butyl benzyl(2,2-dimethoxyethyl)carbamates (**6a**)

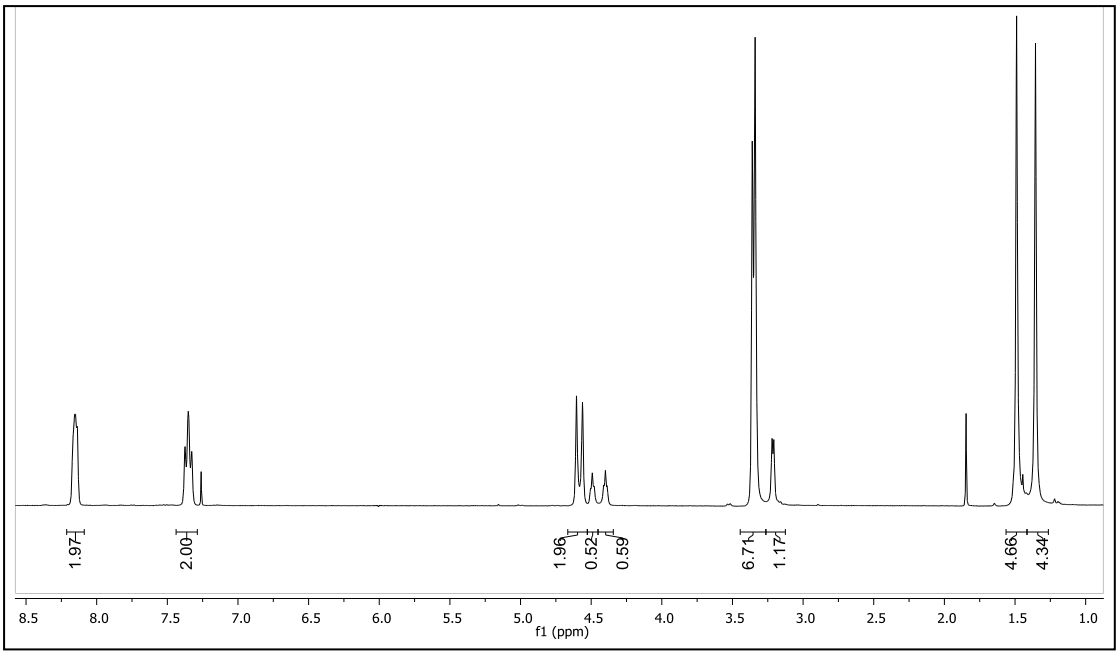

Figure A.42 ^{1}H-NMR of *tert*-butyl (2,2-dimethoxyethyl)(4-nitrophenyl) carbamate (**6b**)

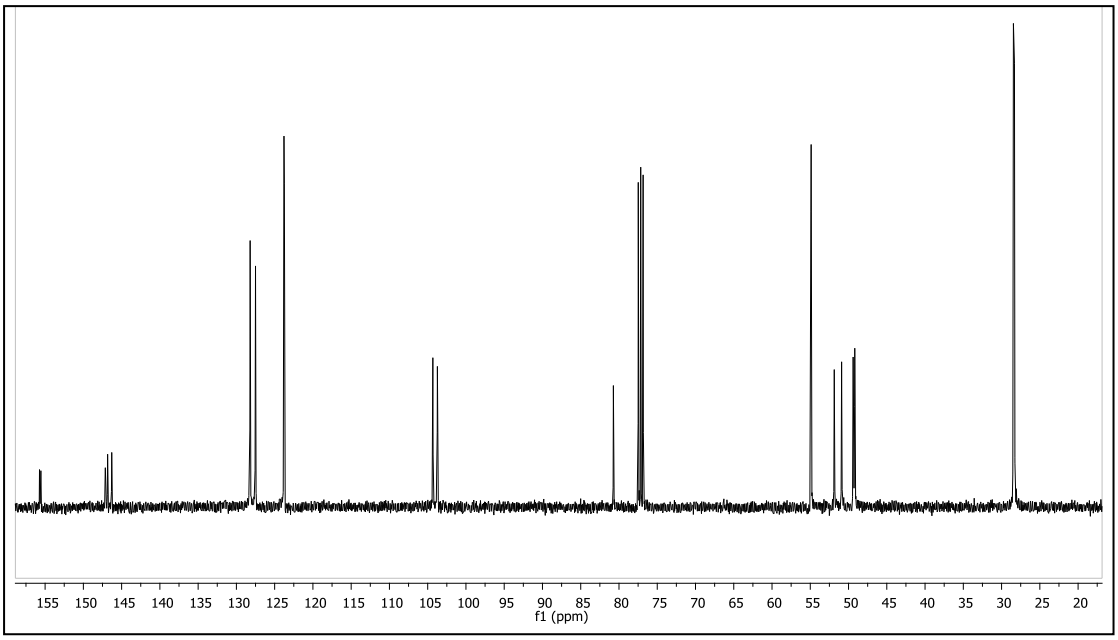

Figure A.43 ^{13}C-NMR of *tert*-butyl (2,2-dimethoxyethyl)(4-nitrophenyl) carbamate (**6b**)

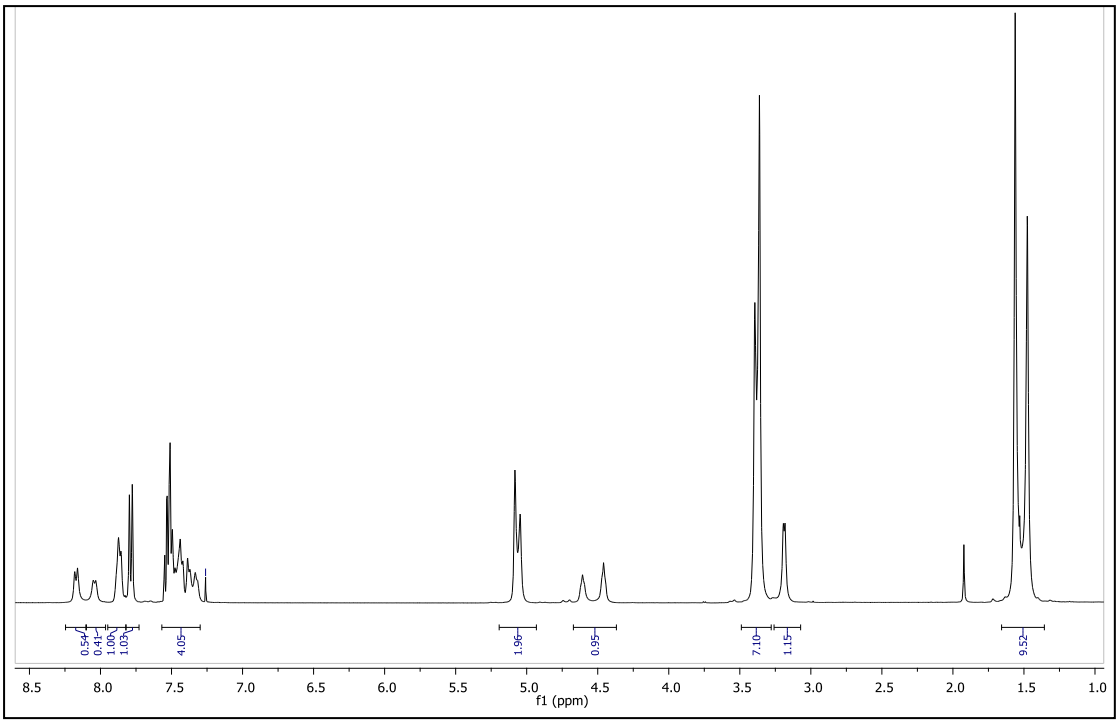

Figure A.44 ^{1}H-NMR of *tert*-butyl (2,2-dimethoxyethyl)(naphthalen-1-ylmethyl)carbamate (**6c**)

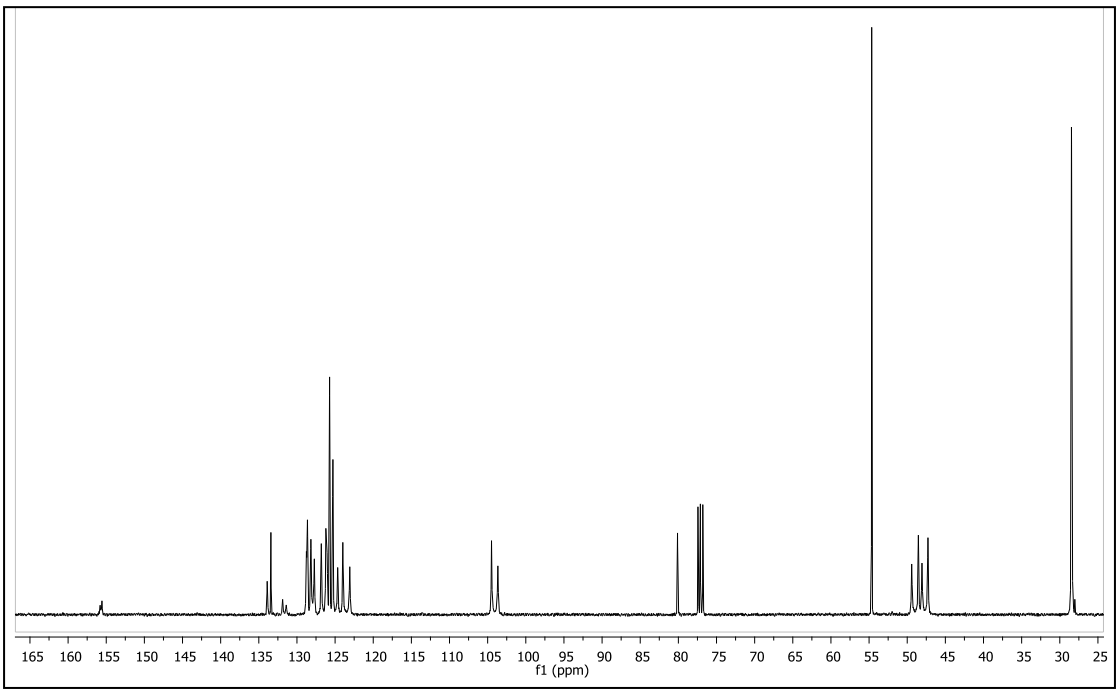

Figure A.45 ^{13}C-NMR of *tert*-butyl (2,2-dimethoxyethyl)(naphthalen-1-ylmethyl)carbamate (**6c**)

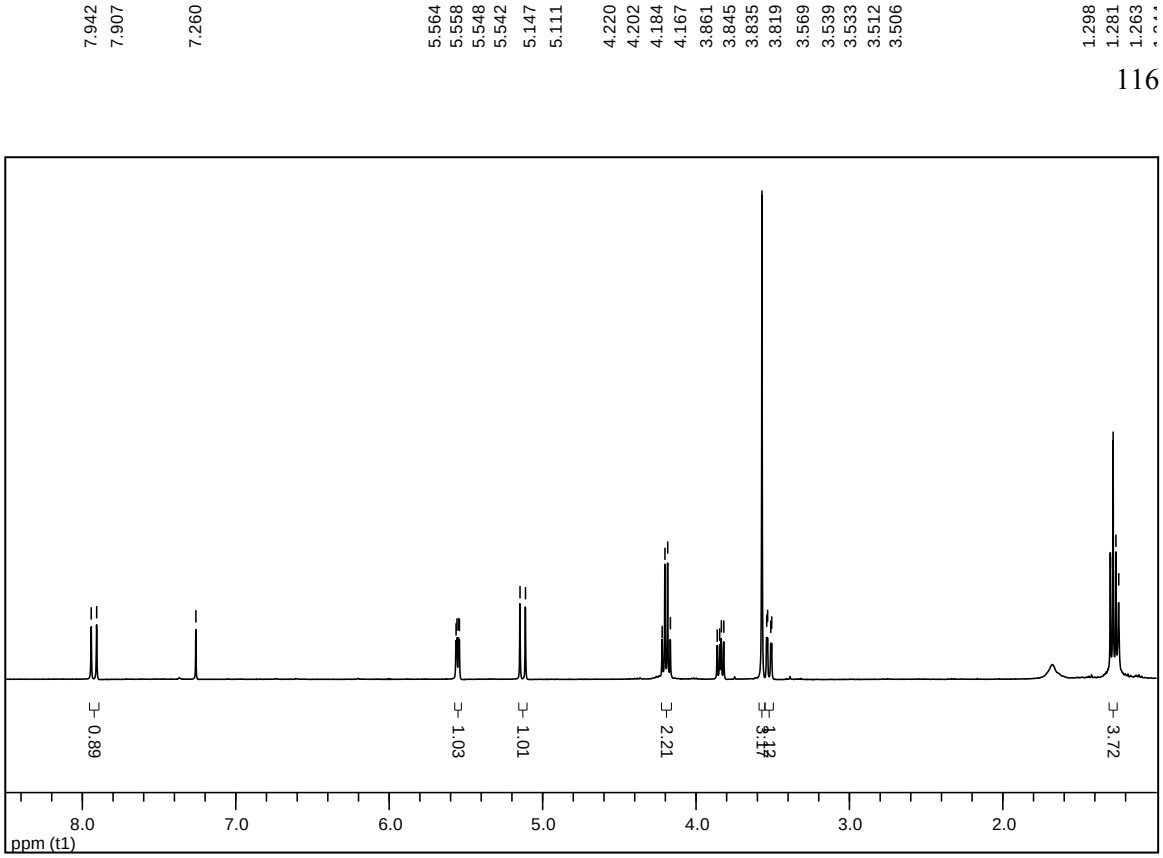

Figure A.46 ^{1}H-NMR of *(E)*-ethyl 3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate (**7a**)

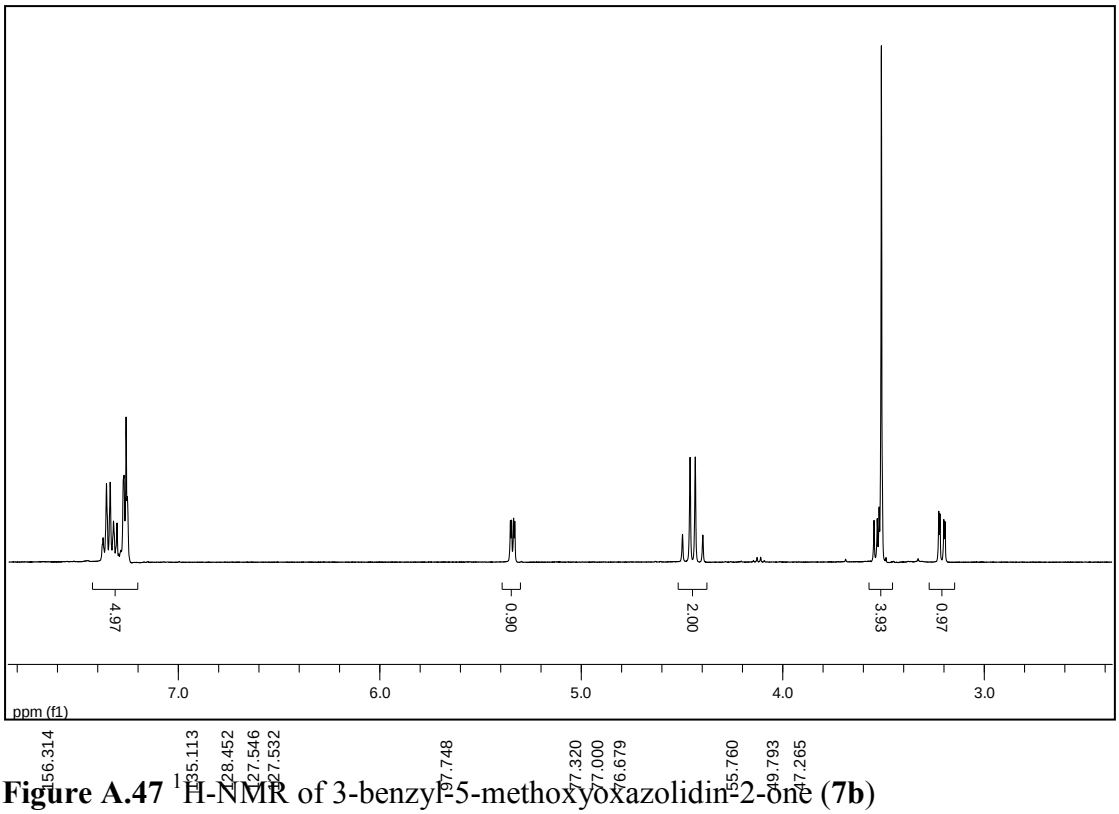

Figure A.47 ^{1}H-NMR of 3-benzyl-5-methoxyoxazolidin-2-one (**7b**)

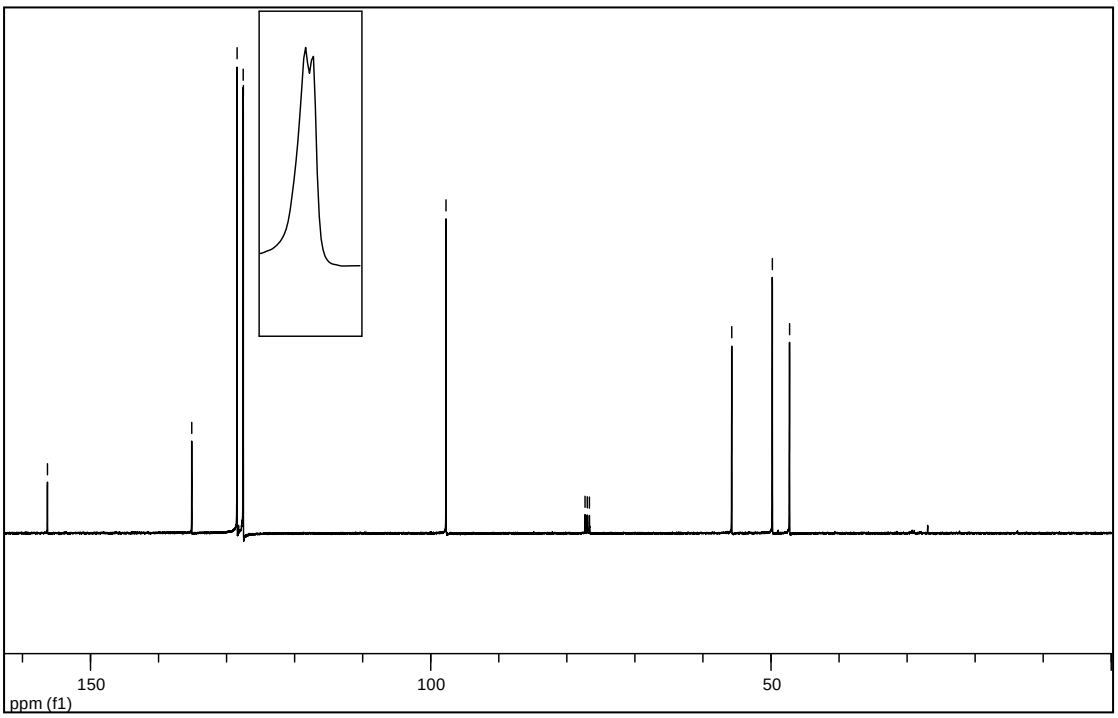

Figure A.48 ^{13}C-NMR of 3-benzyl-5-methoxyoxazolidin-2-one (**7b**)

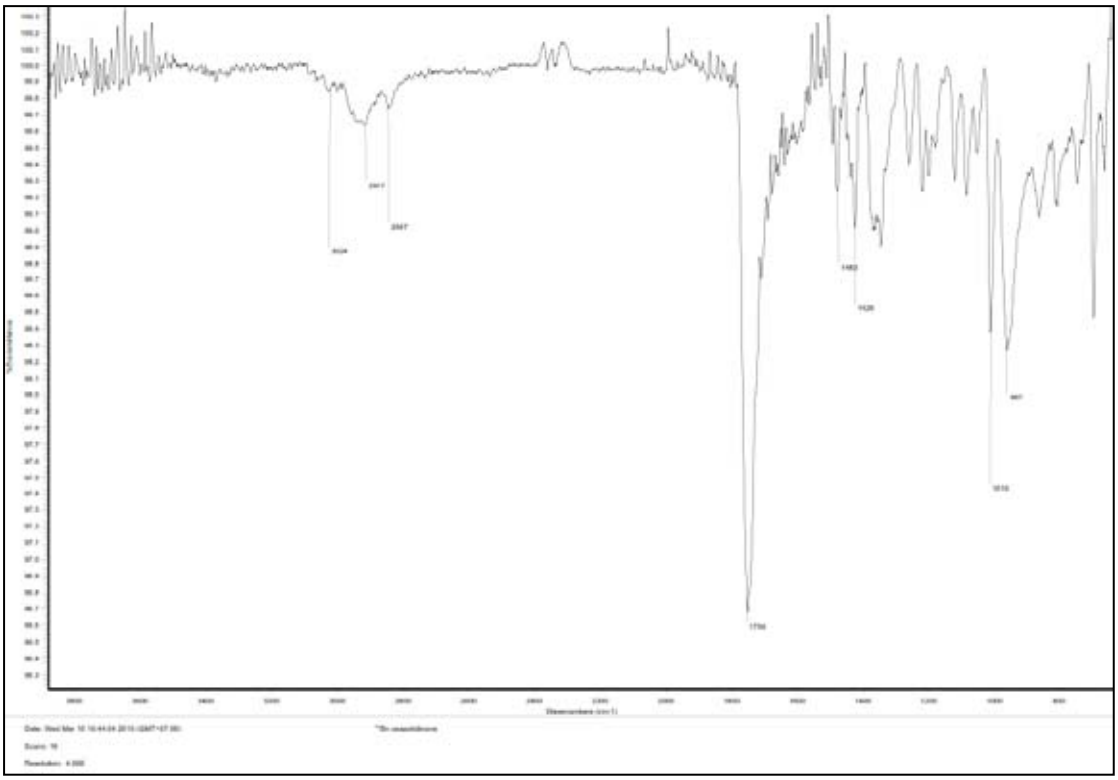

Figure A.49 IR of 3-benzyl-5-methoxyoxazolidin-2-one (**7b**)

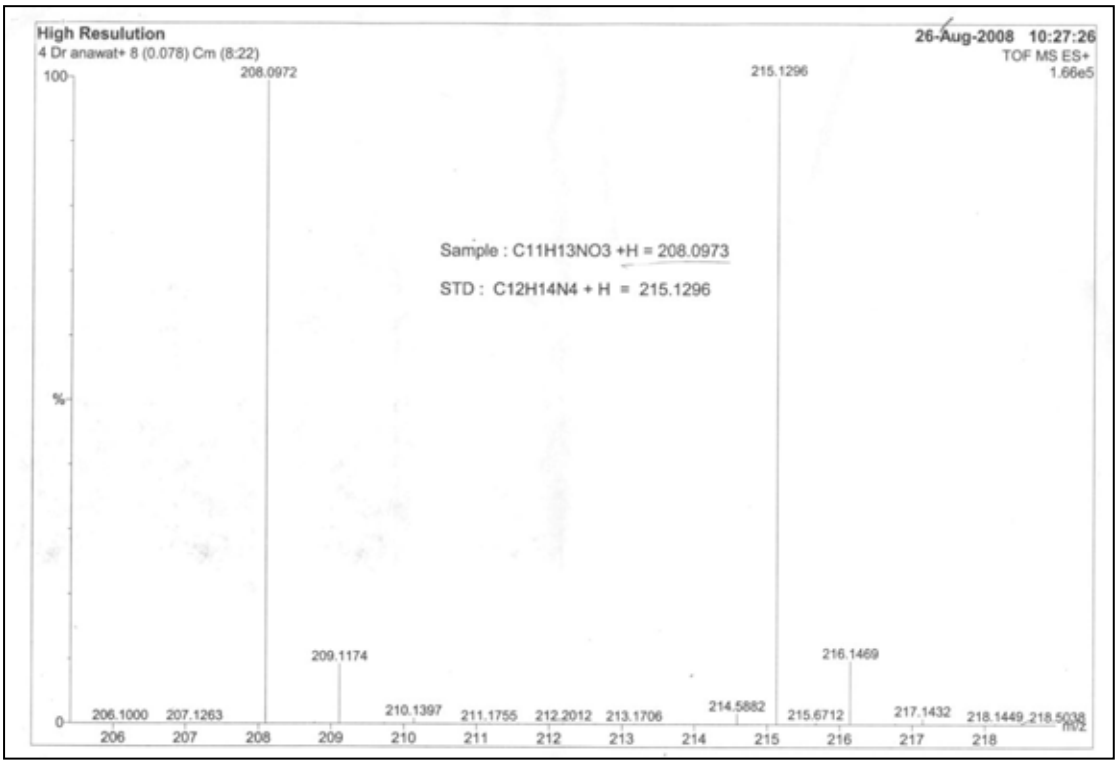

Figure A.50 HRMS of 3-benzyl-5-methoxyoxazolidin-2-one (**7b**)

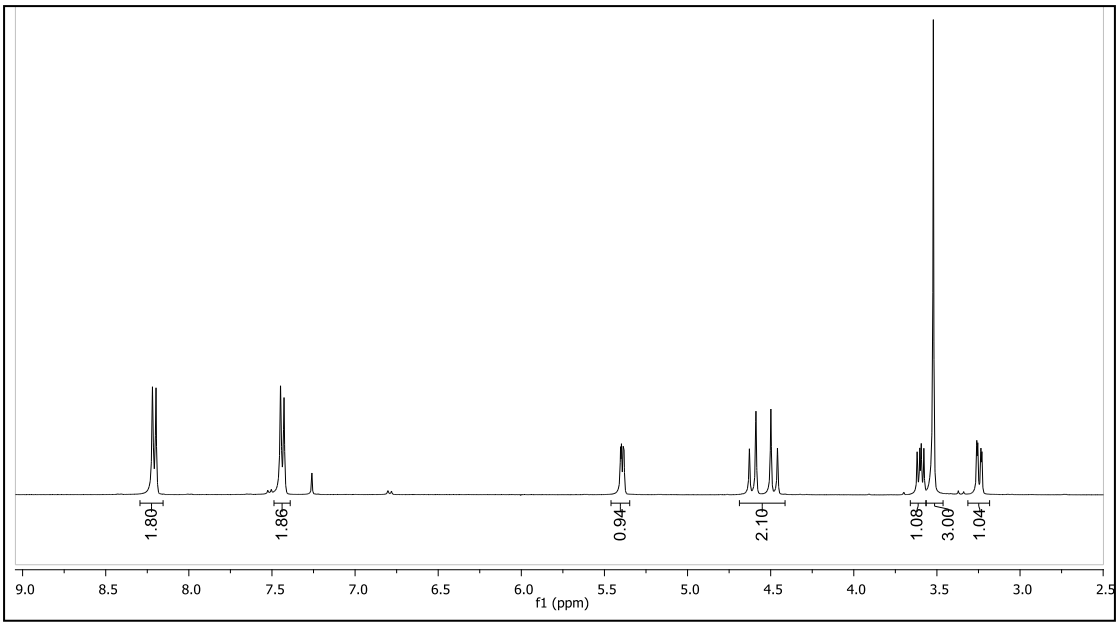

Figure A.51 ^{1}H-NMR of 5-methoxy-3-(4-nitrobenzyl)oxazolidin-2-one (**7c**)

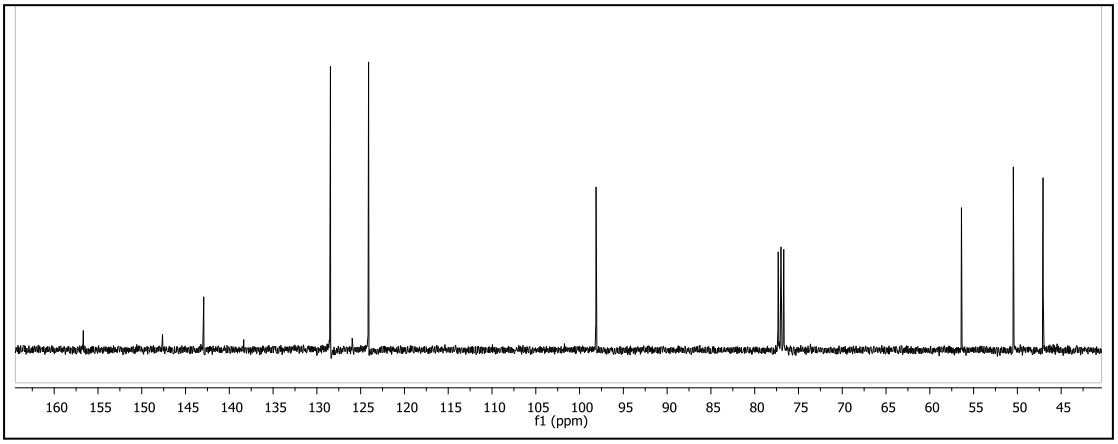

Figure A.52 ^{13}C-NMR of 5-methoxy-3-(4-nitrobenzyl)oxazolidin-2-one (**7c**)

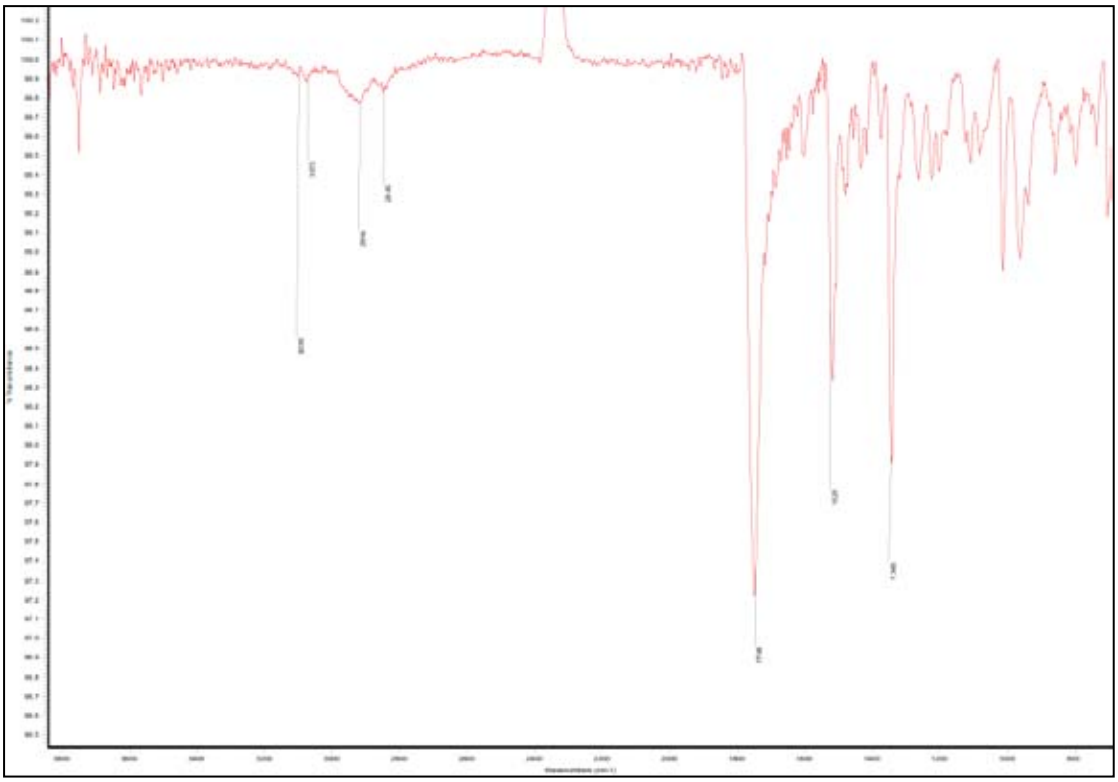

Figure A.53 IR of 5-methoxy-3-(4-nitrobenzyl)oxazolidin-2-one (**7c**)

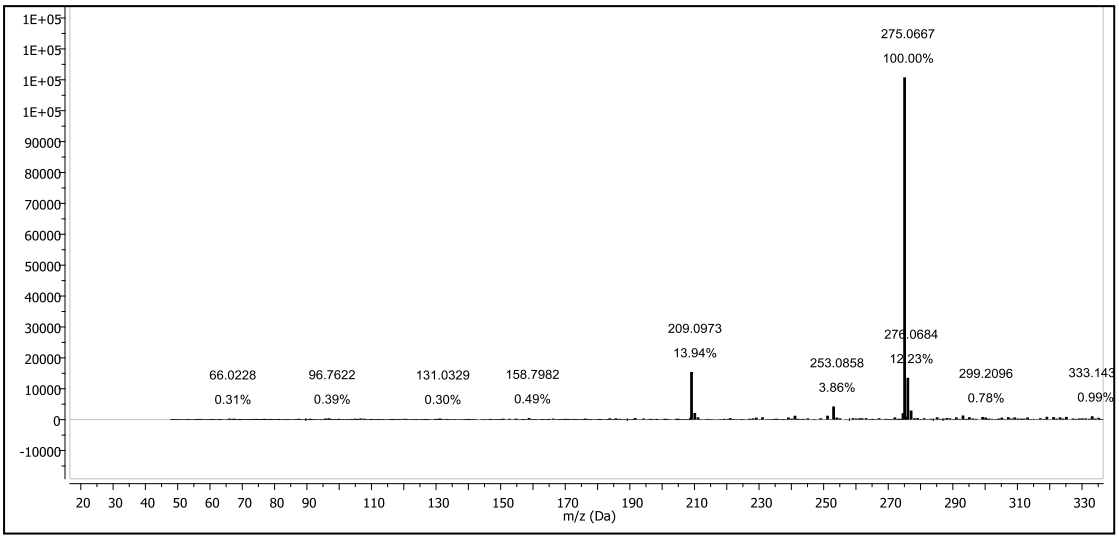

Figure A.54 HRMS of 5-methoxy-3-(4-nitrobenzyl)oxazolidin-2-one (**7c**)

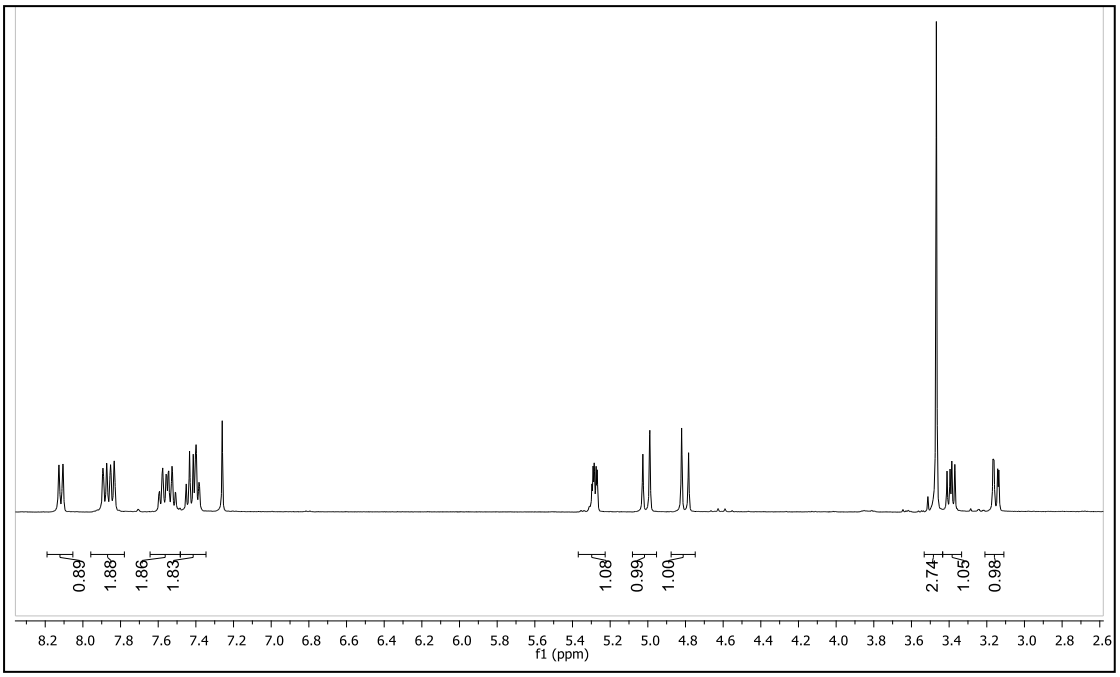

Figure A.55 ^{1}H-NMR of 5-methoxy-3-(naphthalen-1-ylmethyl)oxazolidin-2-one (**7d**)

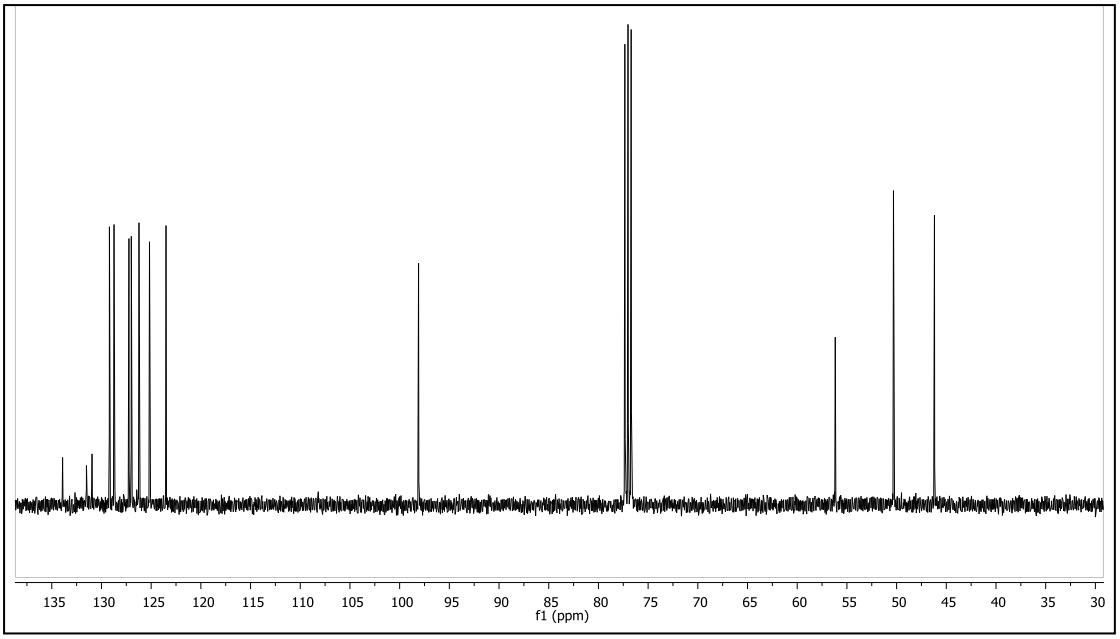

Figure A.56 ^{13}C-NMR of 5-methoxy-3-(naphthalen-1-ylmethyl)oxazolidin-2-one (**7d**)

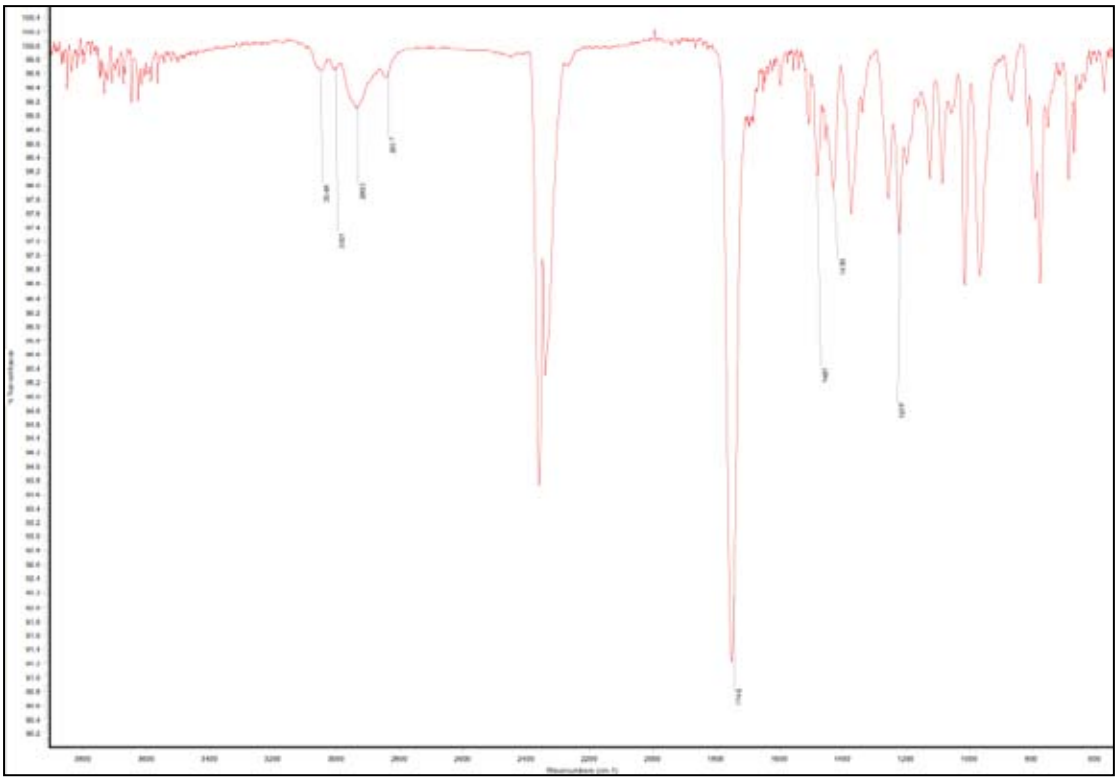

Figure A.57 IR of 5-methoxy-3-(naphthalen-1-ylmethyl)oxazolidin-2-one (**7d**)

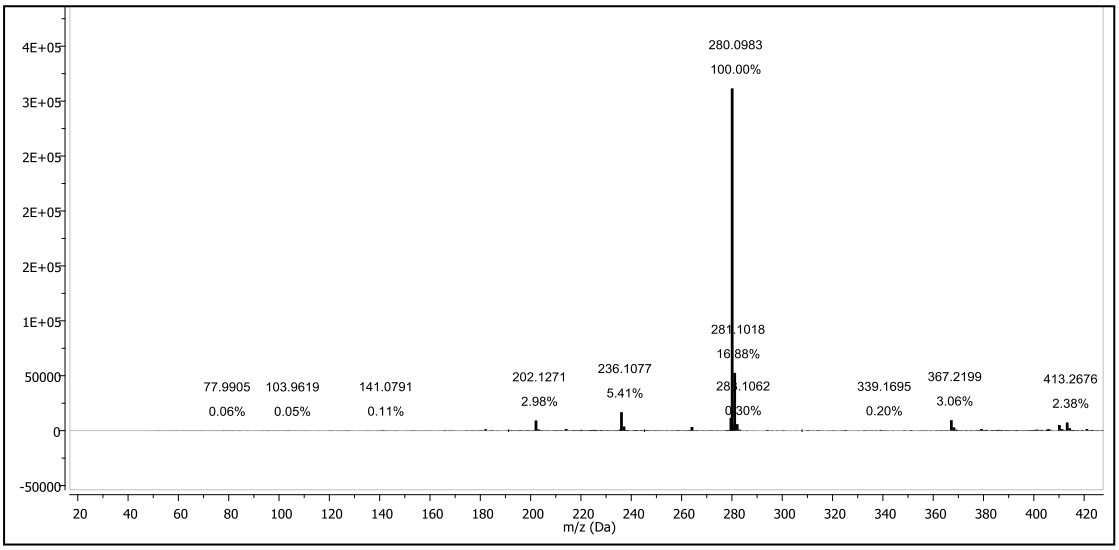

Figure A.58 HRMS of 5-methoxy-3-(naphthalen-1-ylmethyl)oxazolidin-2-one (**7d**)

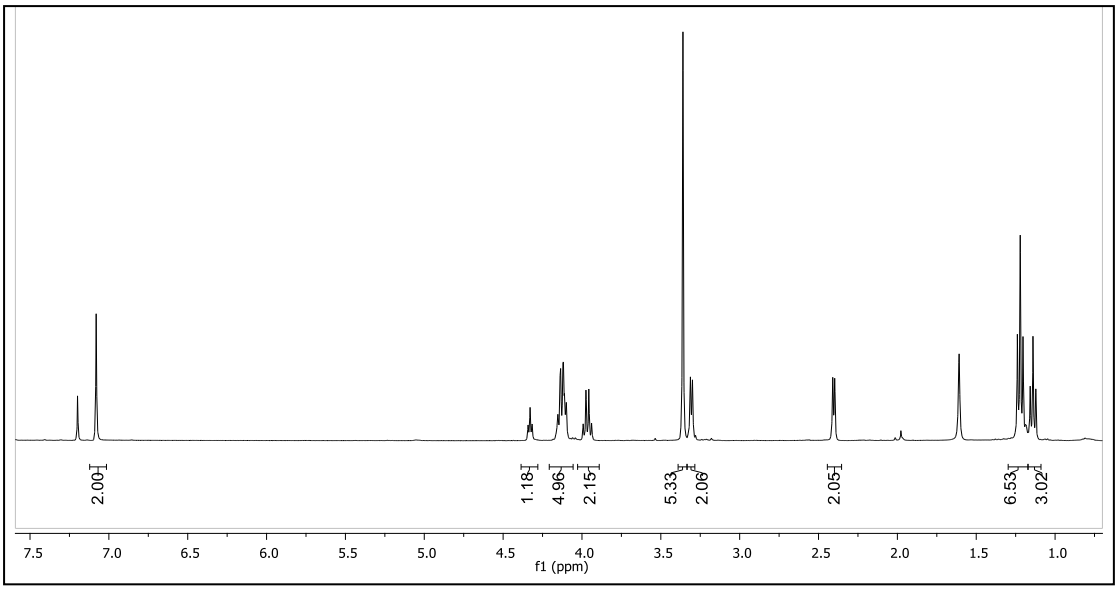

Figure A.59 ^{1}H-NMR of diethyl-1-(2,2-dimethoxyethyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8a**)

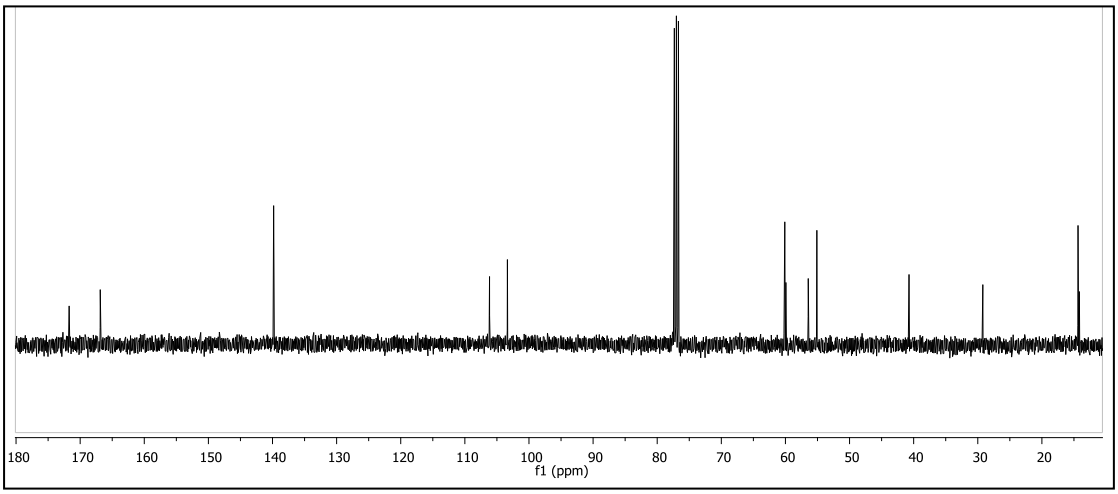

Figure A.60 ^{13}C-NMR of diethyl-1-(2,2-dimethoxyethyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8a**)

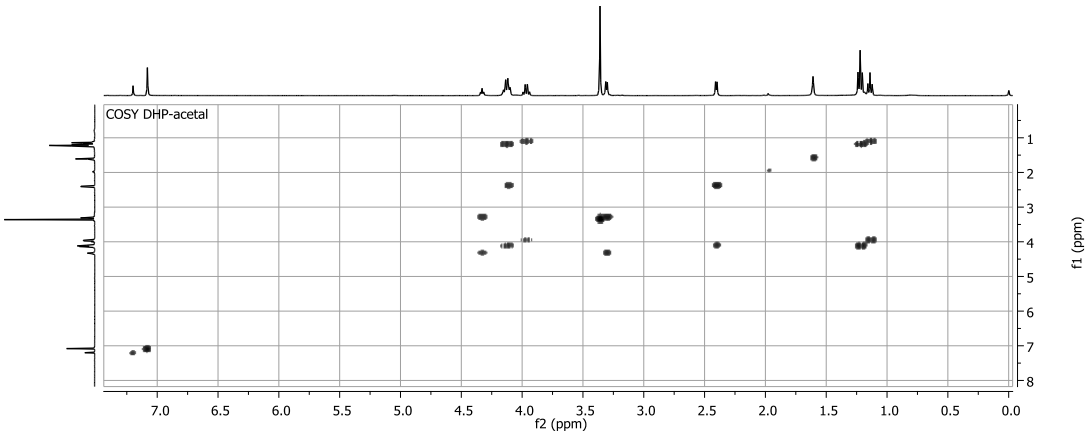

Figure A.61 COSYof diethyl-1-(2,2-dimethoxyethyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8a**)

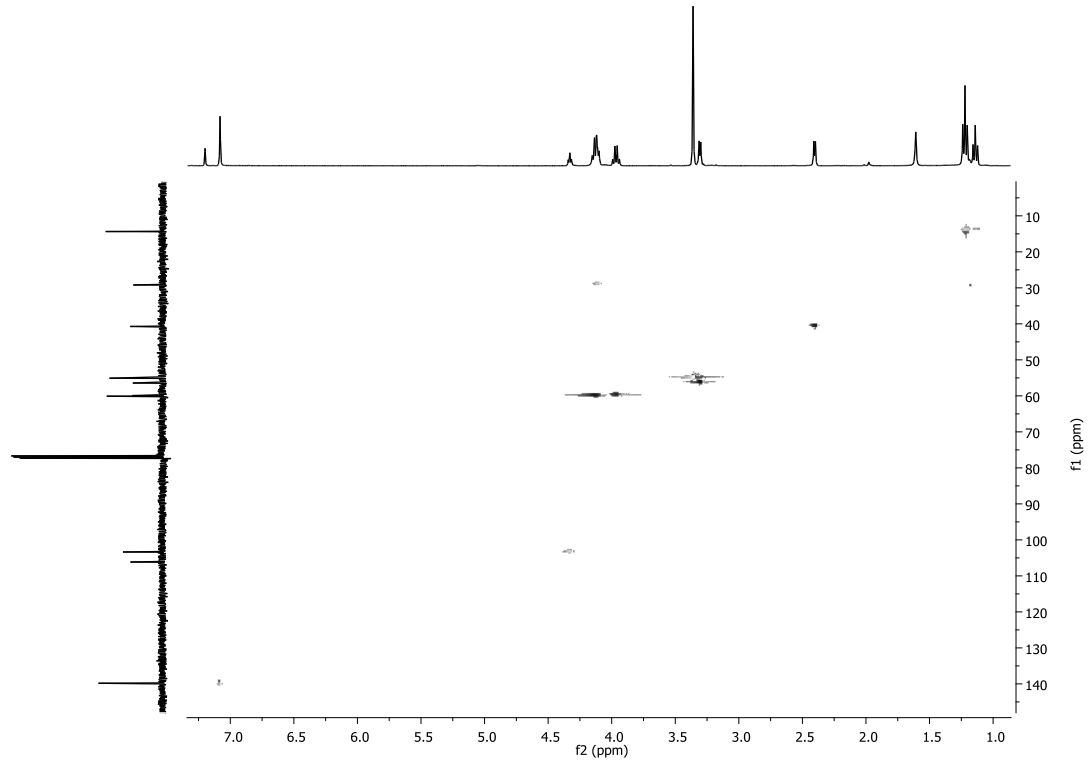

Figure A.62 HSQC of diethyl-1-(2,2-dimethoxyethyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8a**)

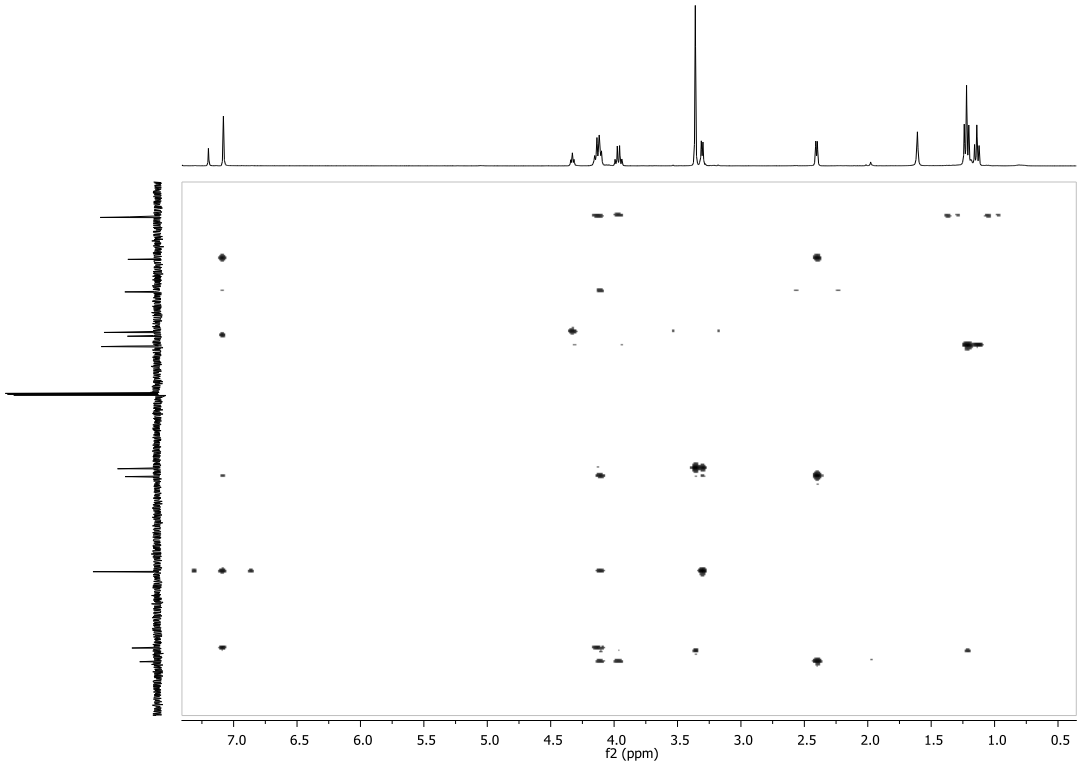

Figure A.63 HMBC of diethyl-1-(2,2-dimethoxyethyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8a**)

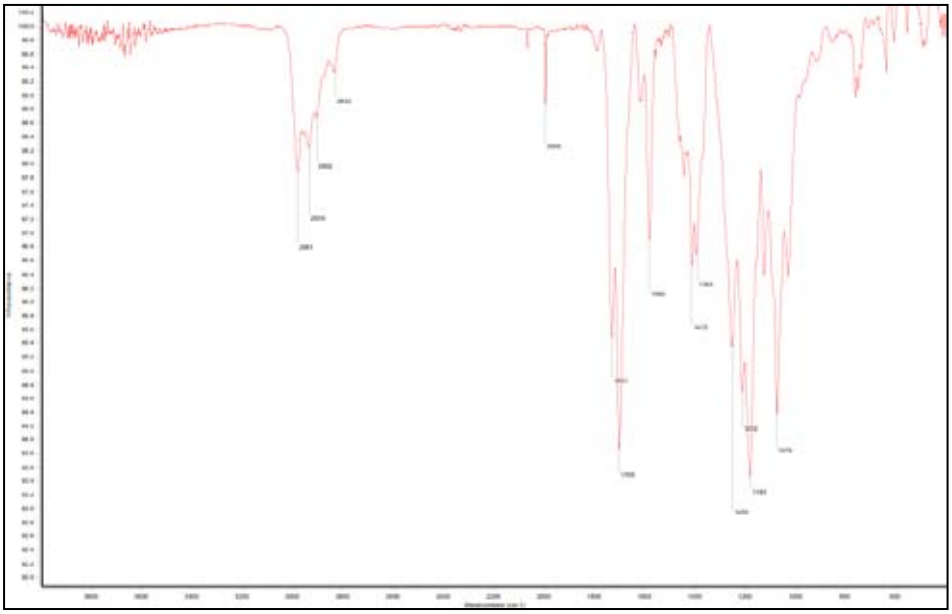

Figure A.64 IR of diethyl-1-(2,2-dimethoxyethyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8a**)

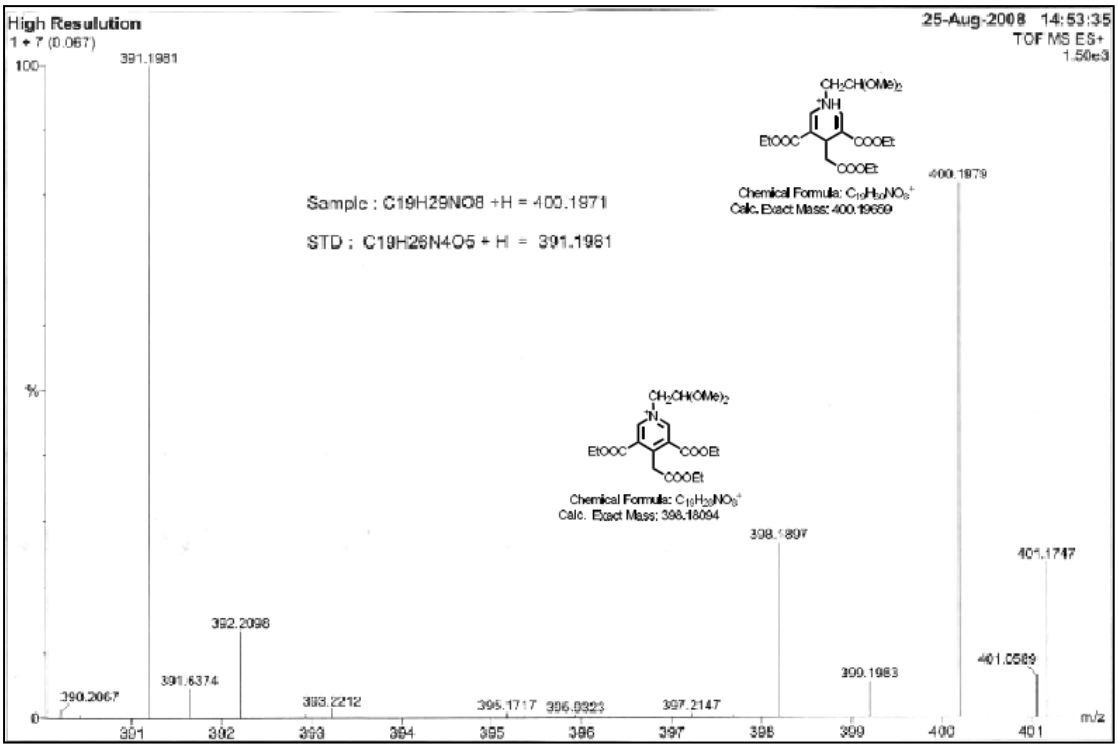

Figure A. 65 HRMS of diethyl-1-(2,2-dimethoxyethyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8a**)

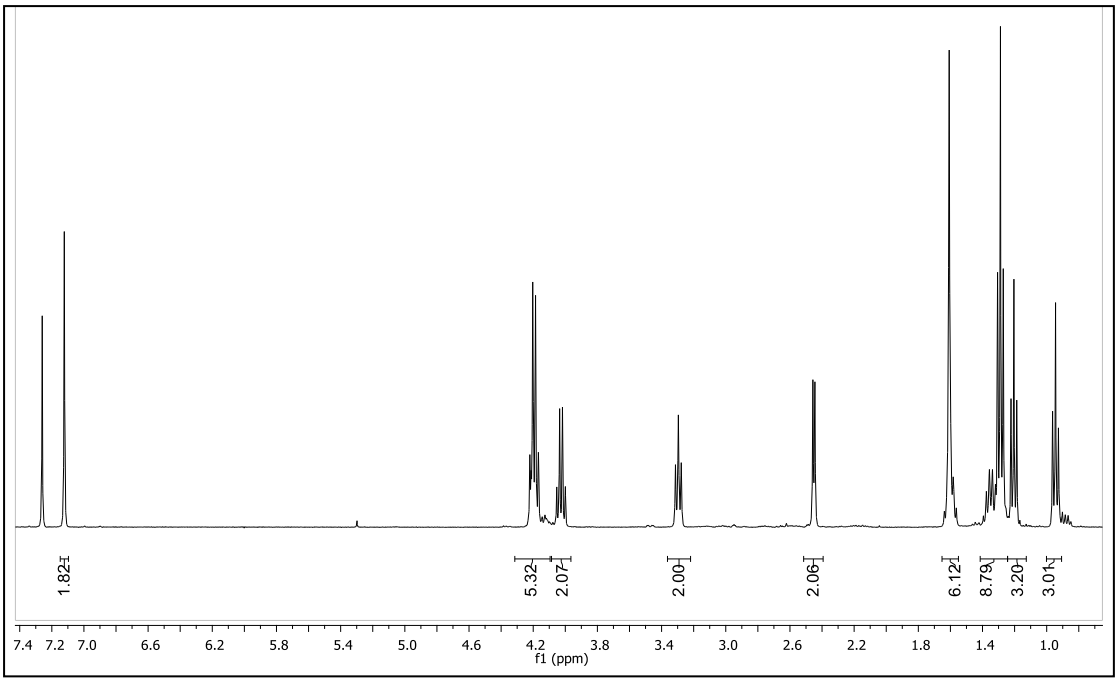

Figure A.66 ^{1}H-NMR of diethyl-1-butyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8b**)

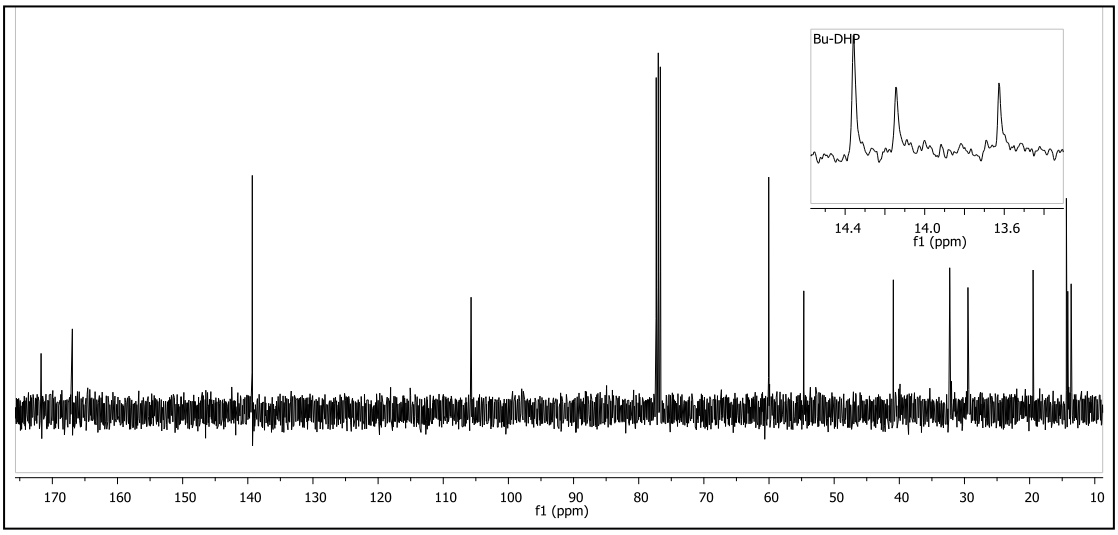

Figure A.67 ^{13}C-NMR of diethyl-1-butyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8b**)

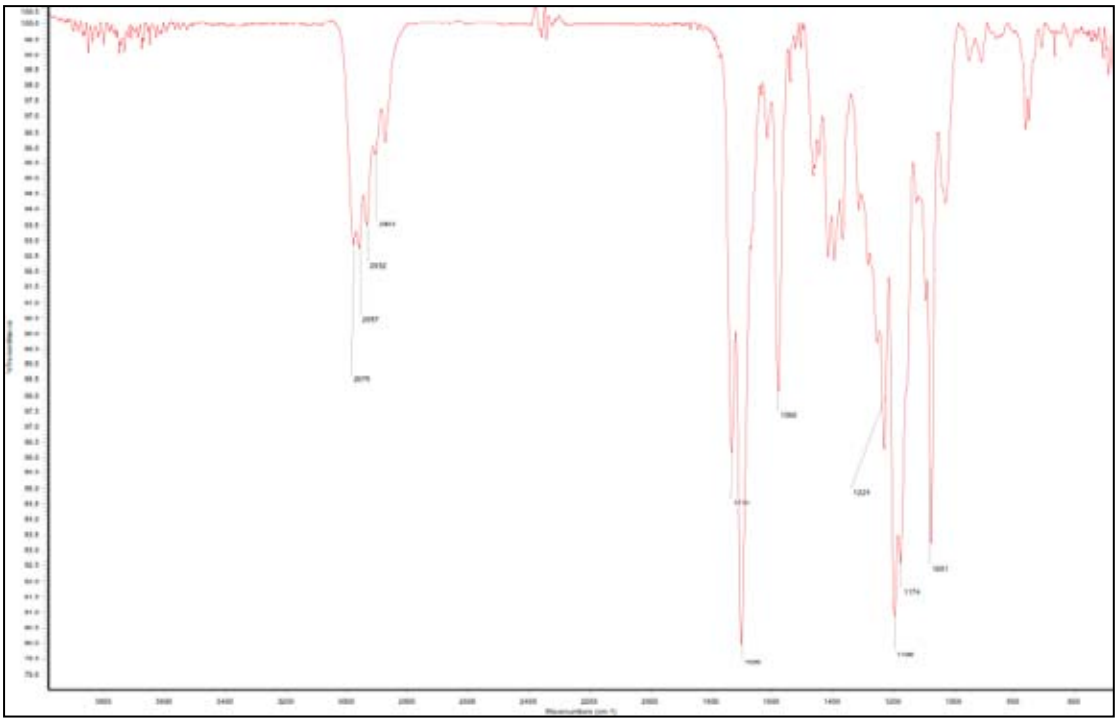

Figure A.68 IR of diethyl-1-butyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8b**)

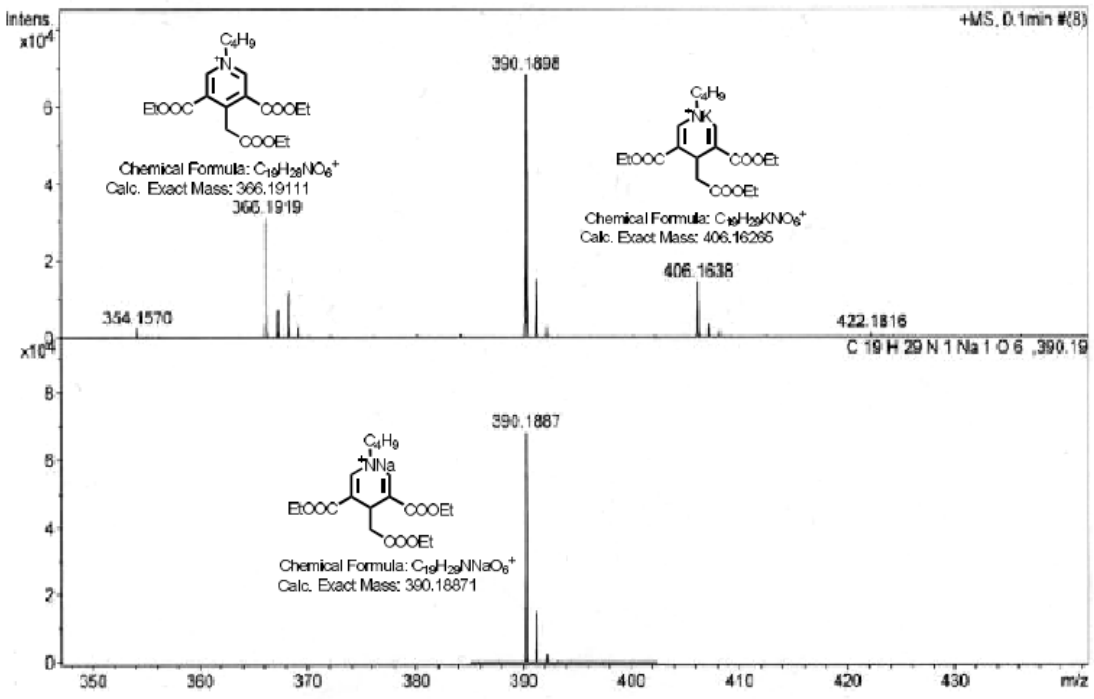

Figure A.69 HRMS of diethyl-1-butyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8b**)

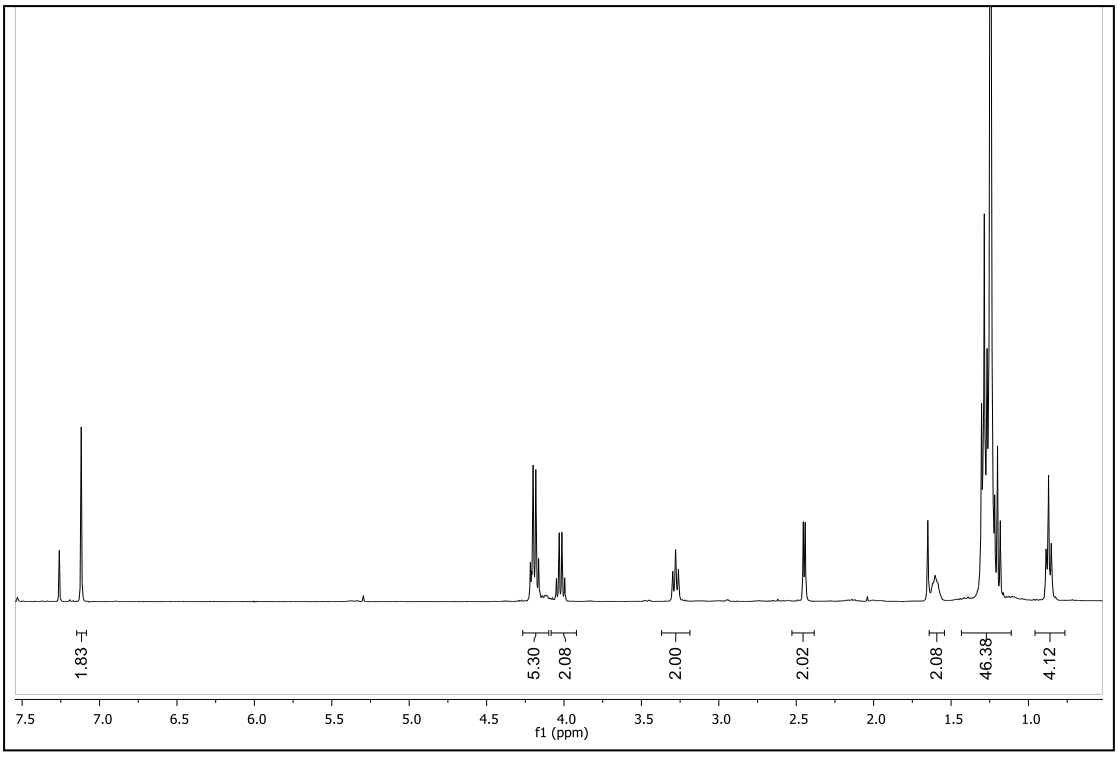

Figure A.70 ^{1}H-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-octadecyl-1,4-dihydropyridine-3,5dicarboxylate (**8c**)

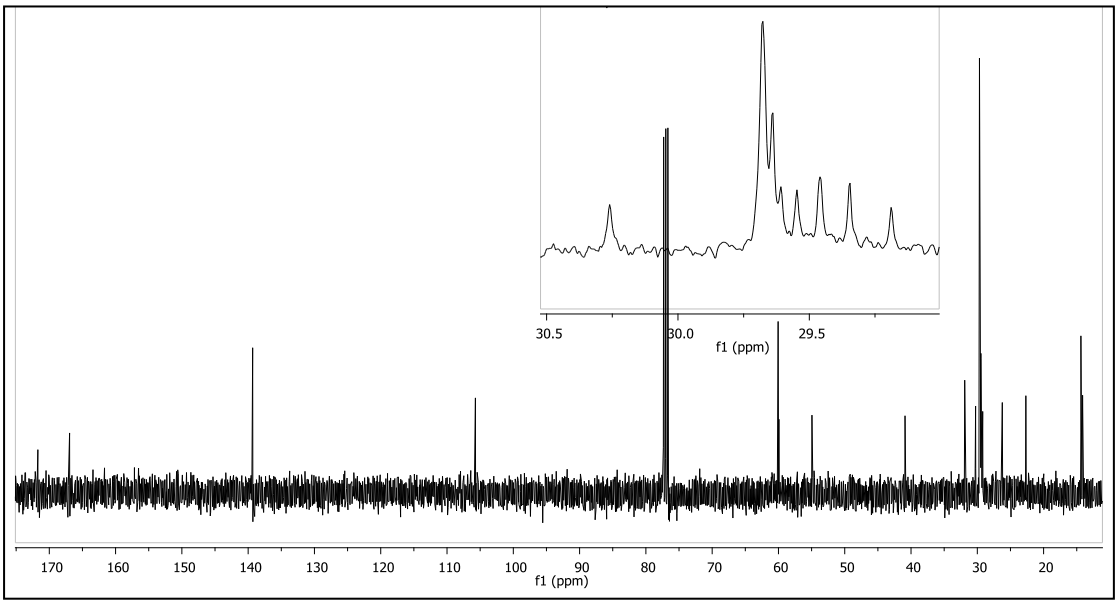

Figure A.71 ^{13}C-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-octadecyl-1,4-dihydropyridine-3,5dicarboxylate (**8c**)

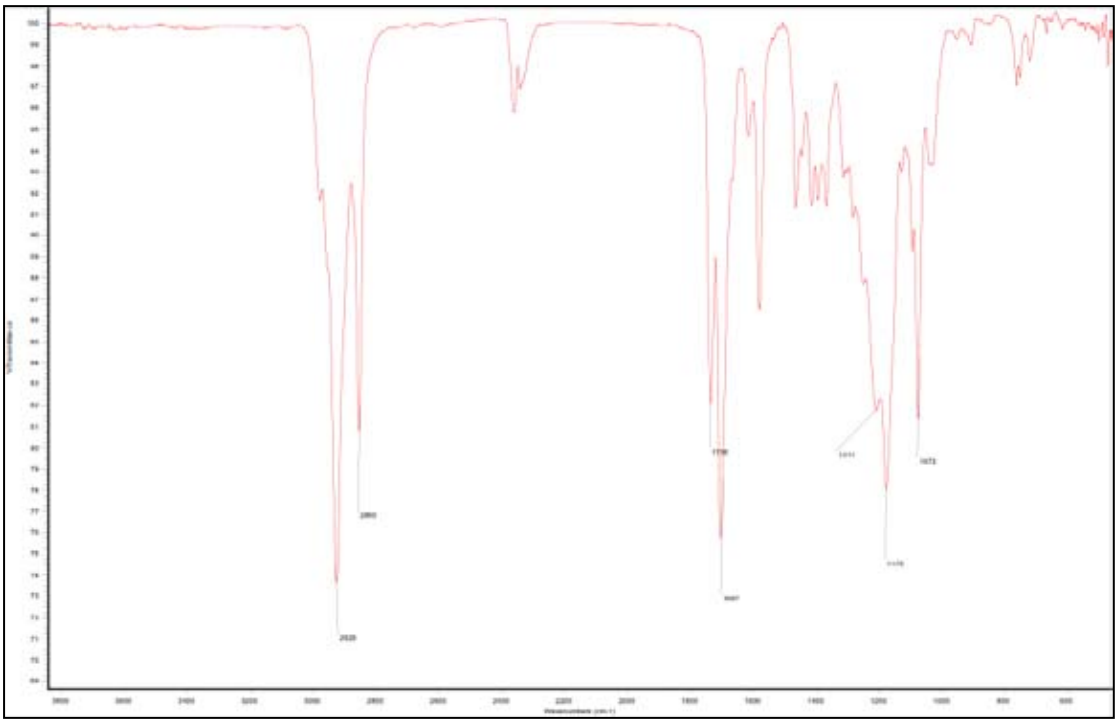

Figure A.72 IR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-octadecyl-1,4-dihydropyridine-3,5dicarboxylate (**8c**)

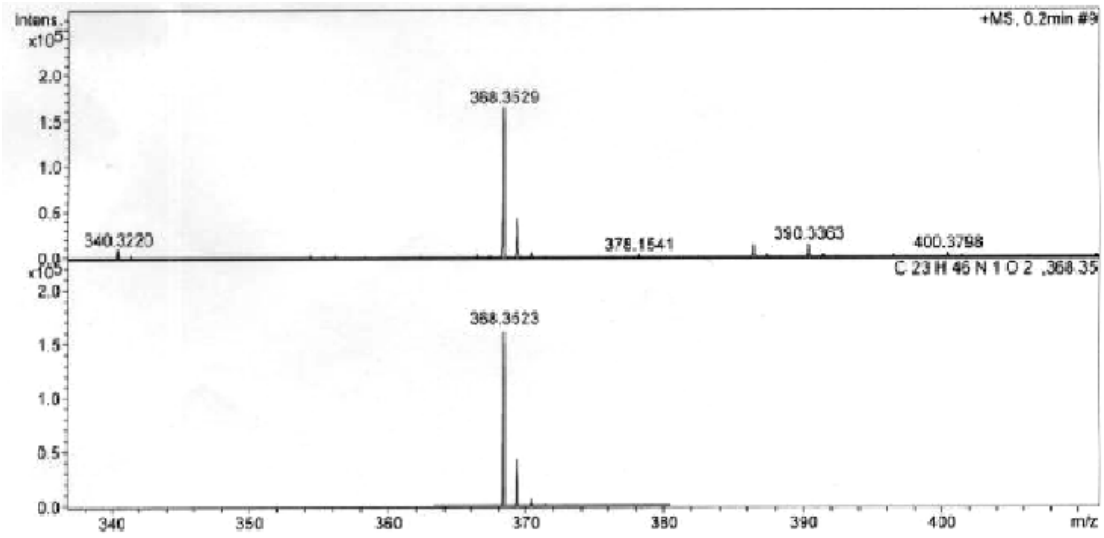

Figure A.73 HRMS of diethyl-4-(2-ethoxy-2-oxoethyl)-1-octadecyl-1,4-dihydropyridine-3,5dicarboxylate (**8c**)

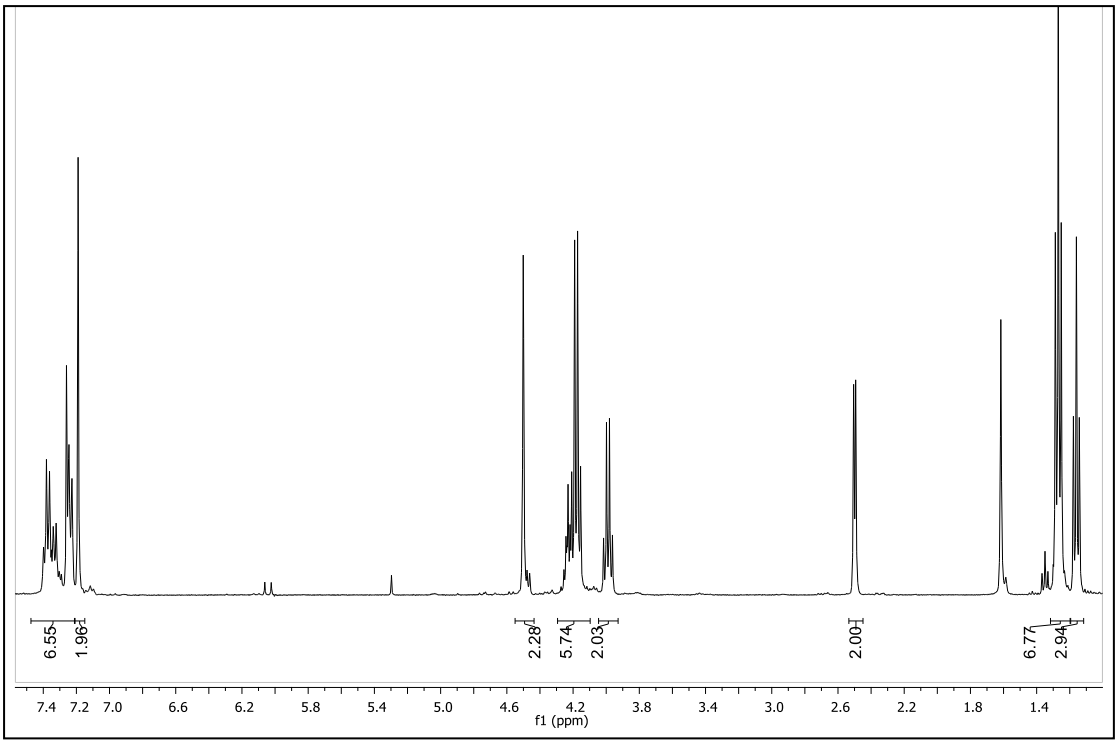

Figure A.74 ^{1}H-NMR of diethyl-1-benzyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate **(8d)**

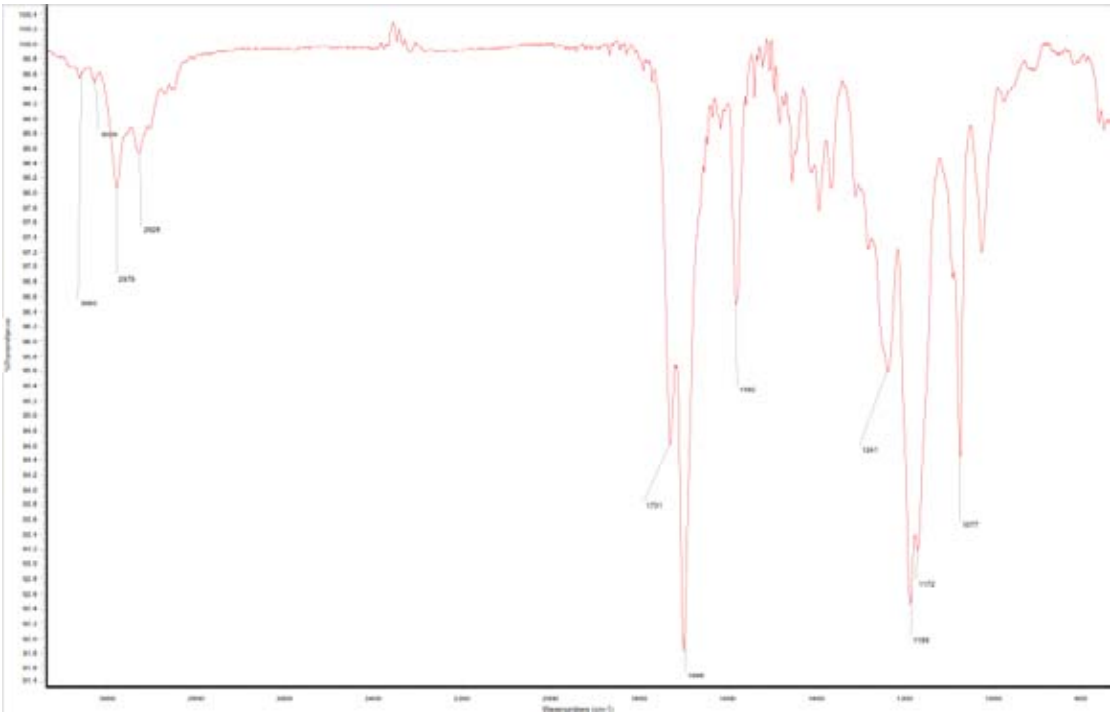

Figure A.75 IR of diethyl-1-benzyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate **(8d)**

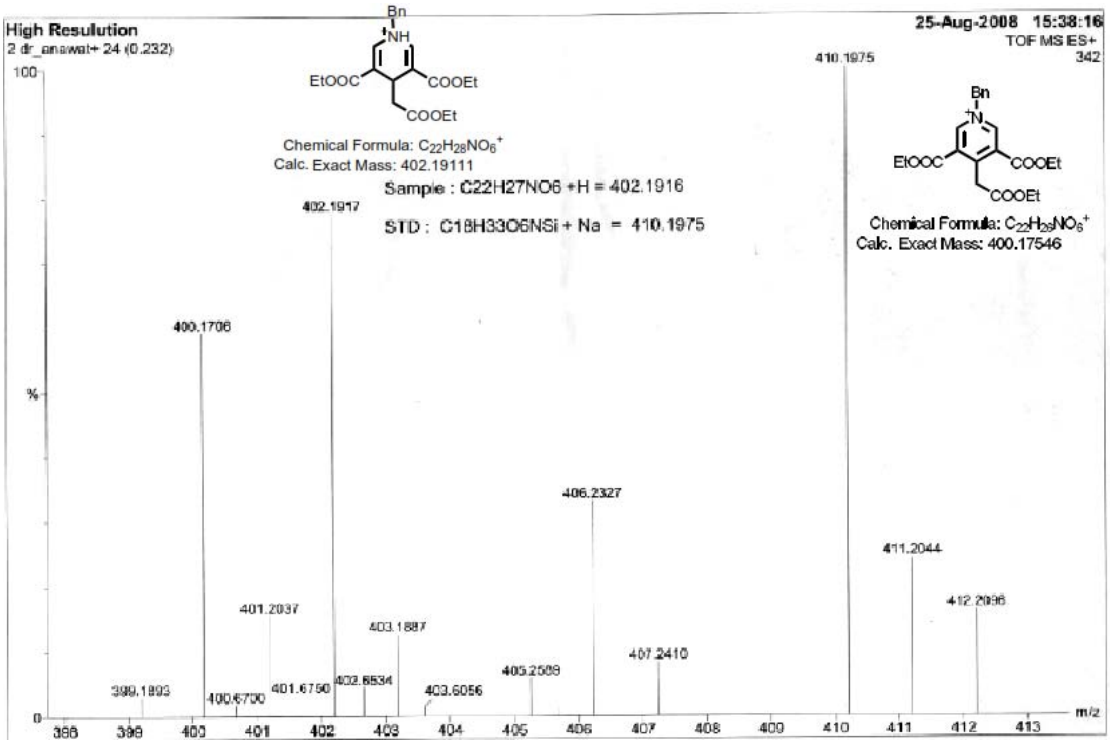

Figure A.76 HRMS of diethyl-1-benzyl-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate **(8d)**

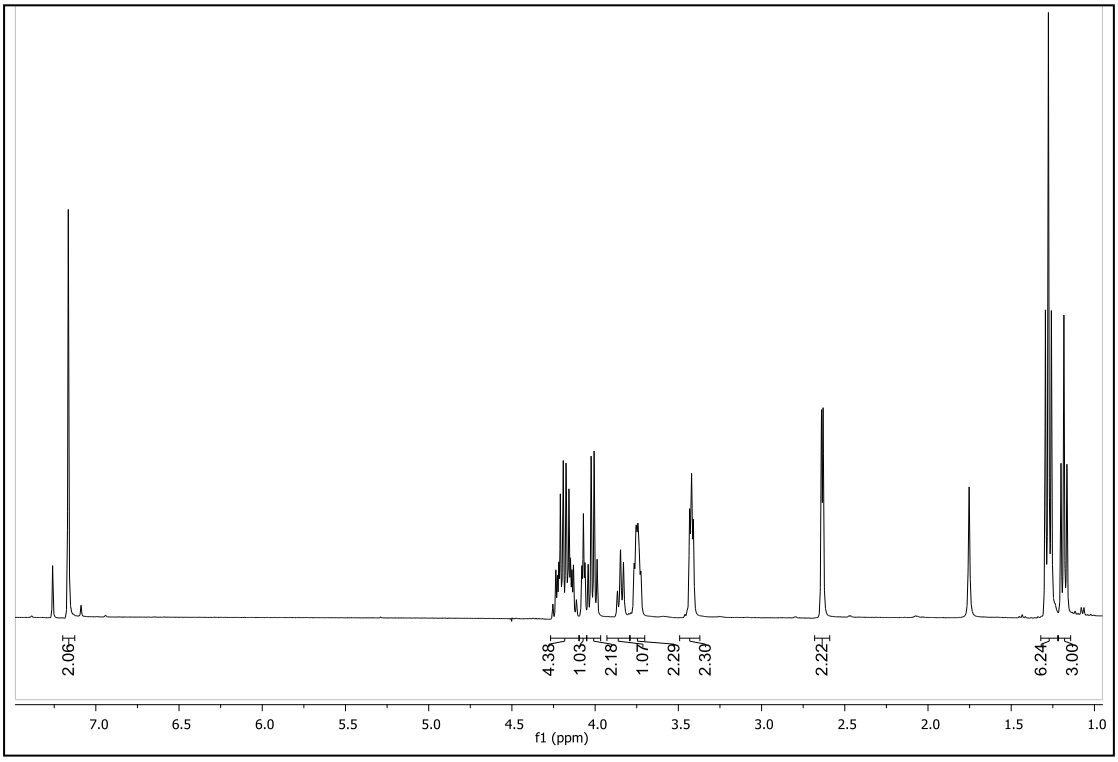

Figure A.77 ^{1}H-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8e**)

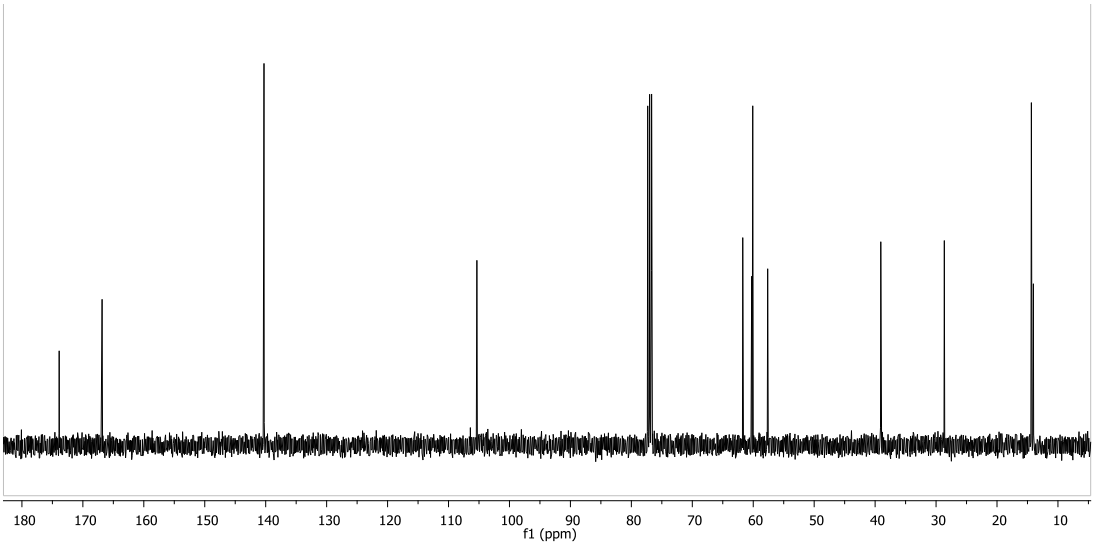

Figure A.78 ^{13}C-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8e**)

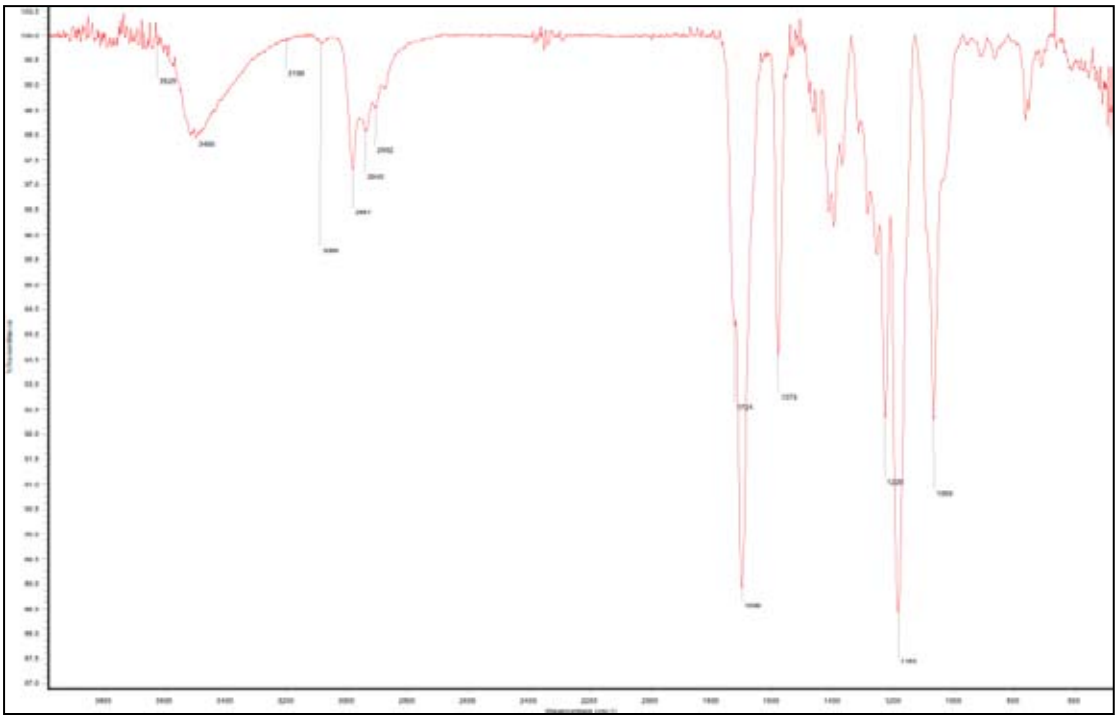

Figure A.79 IR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8e**)

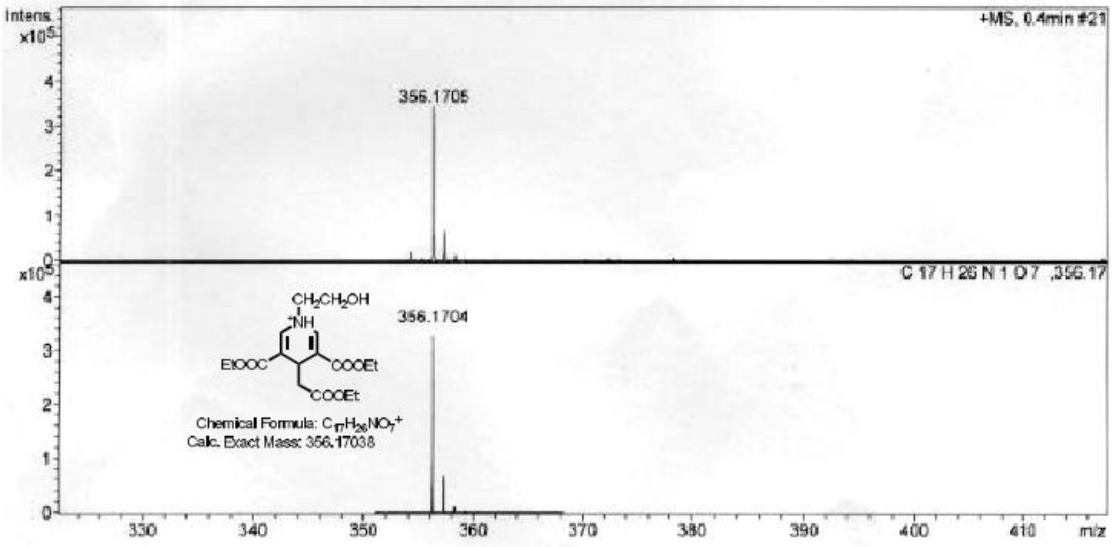

Figure A.80 HRMS of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(2-hydroxyethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8e**)

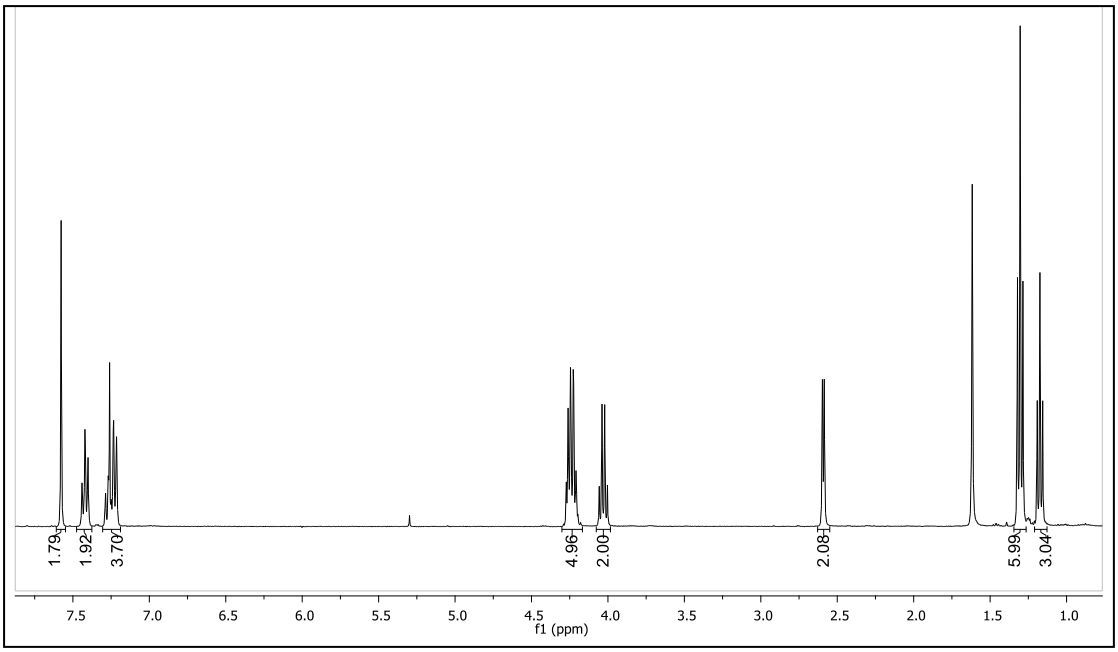

Figure A.81 ^{1}H-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**8f**)

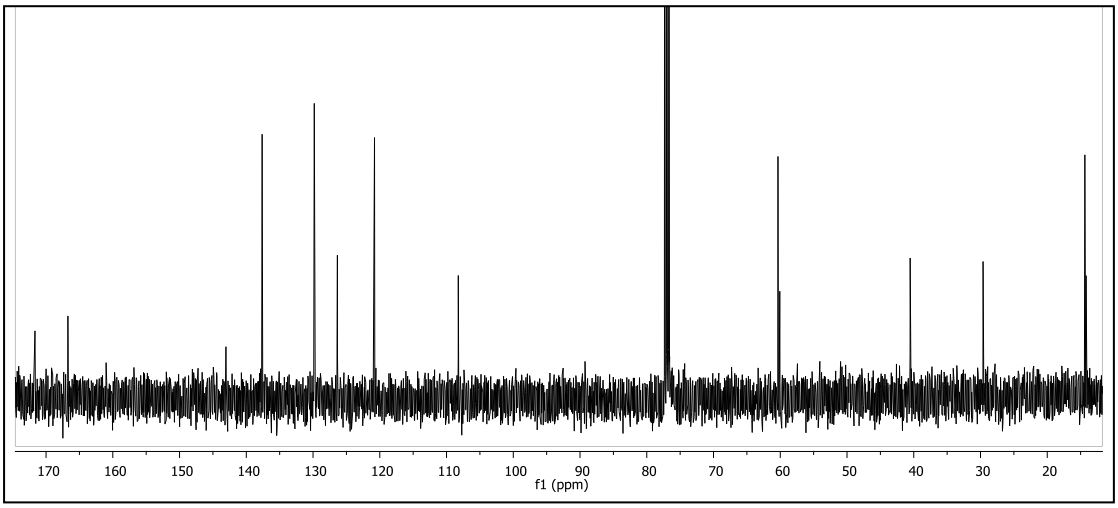

Figure A.82 ^{13}C-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**8f**)

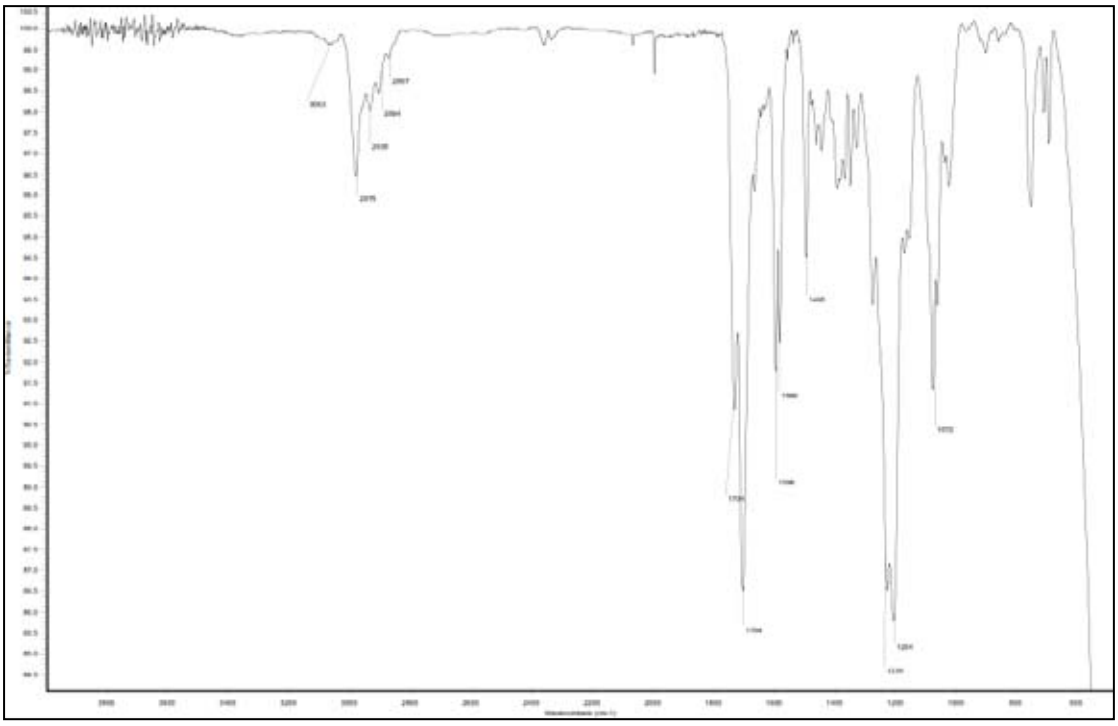

Figure A.83 IR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**8f**)

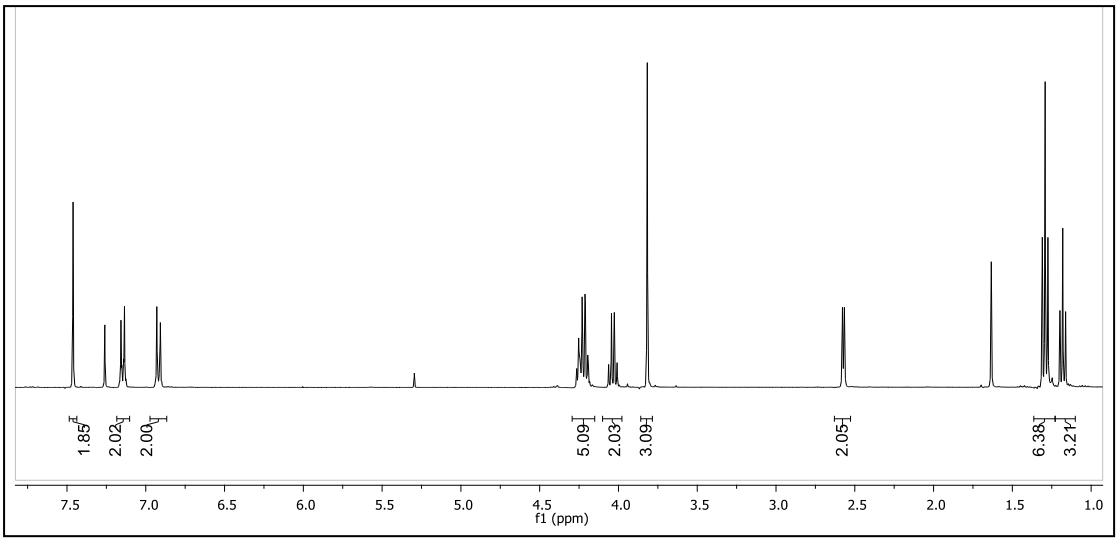

Figure A.84 ^{1}H-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8g**)

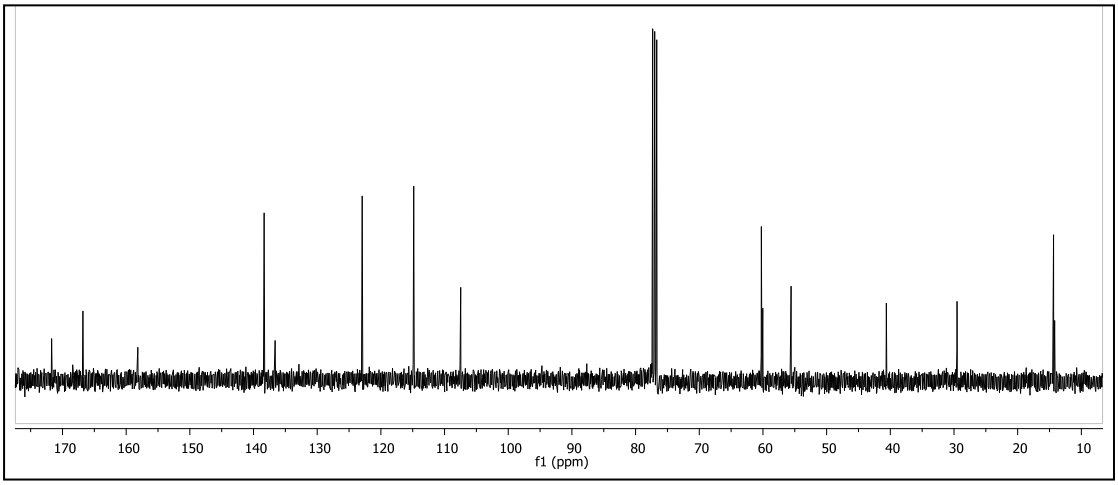

Figure A.85 ^{13}C-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8g**)

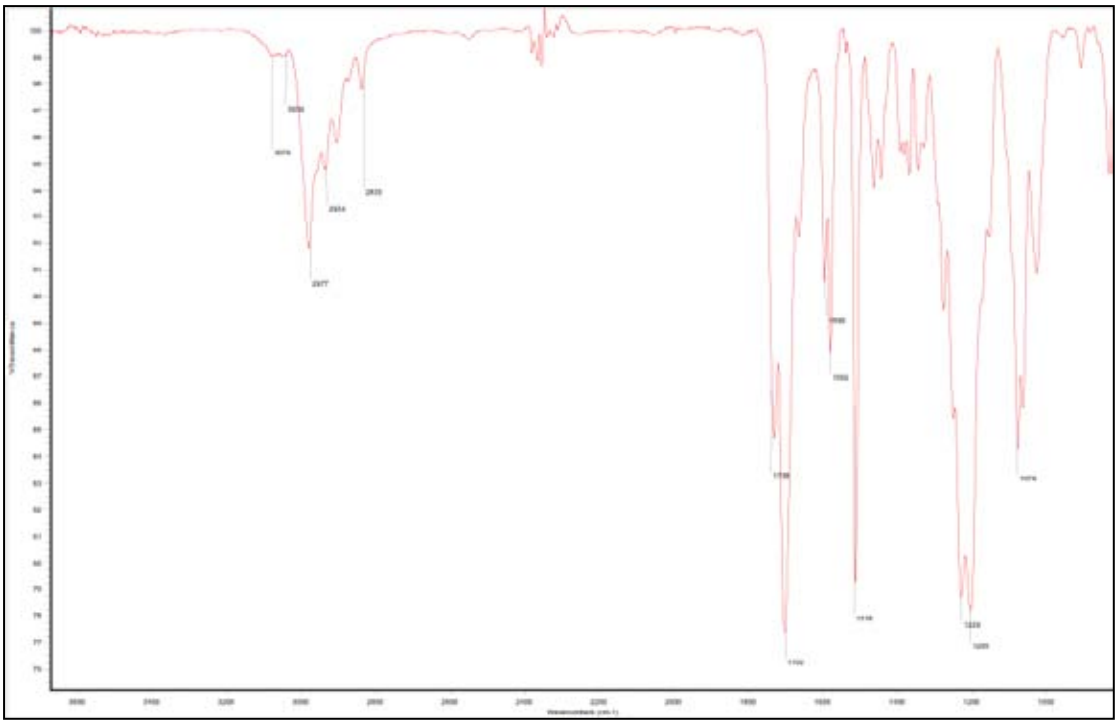

Figure A.86 IR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8g**)

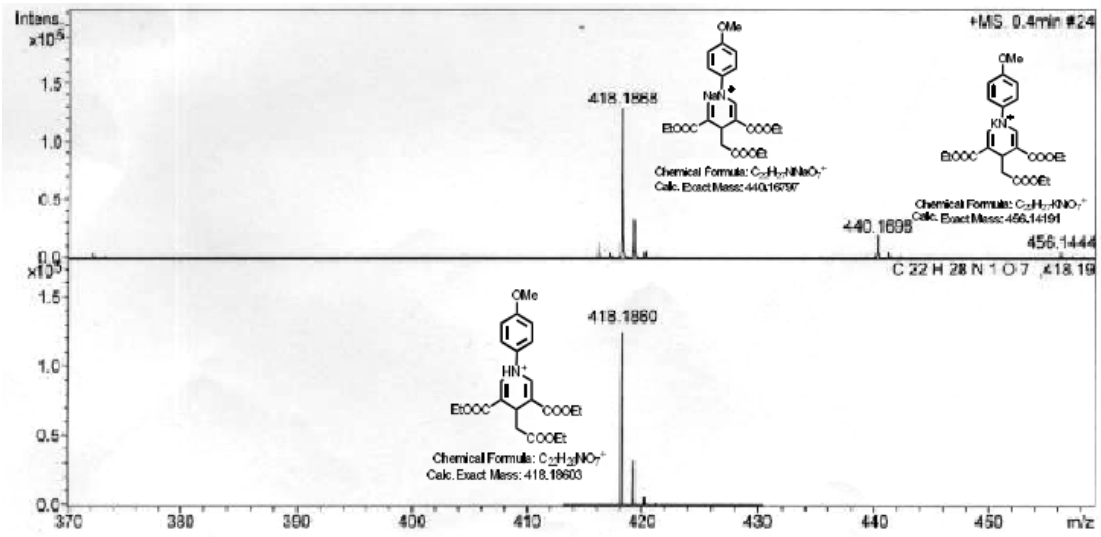

Figure A.87 HRMS of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8g**)

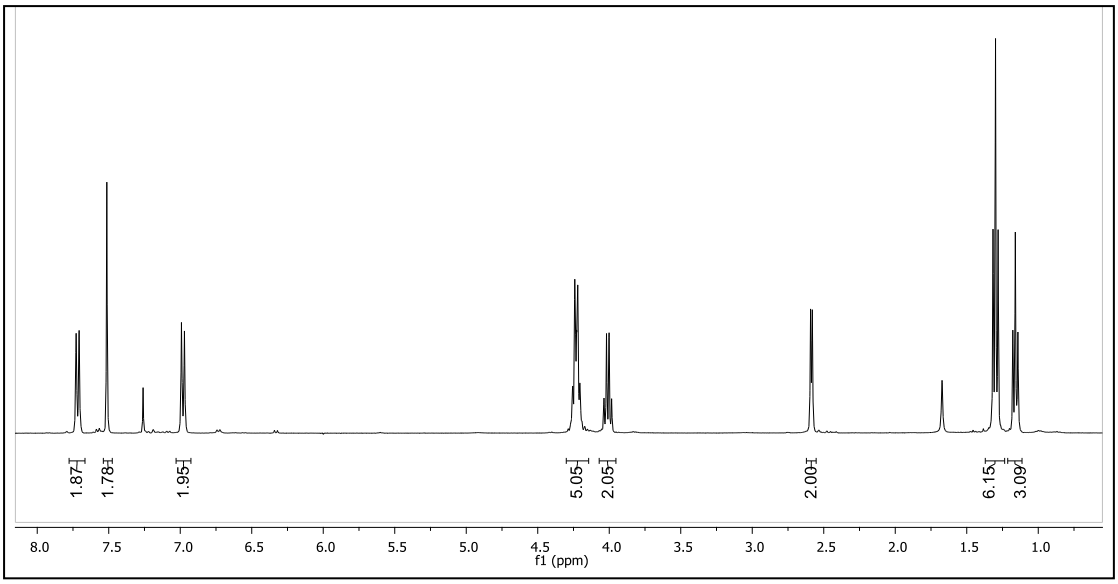

Figure A.88 ^{1}H-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-iodophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8h**)

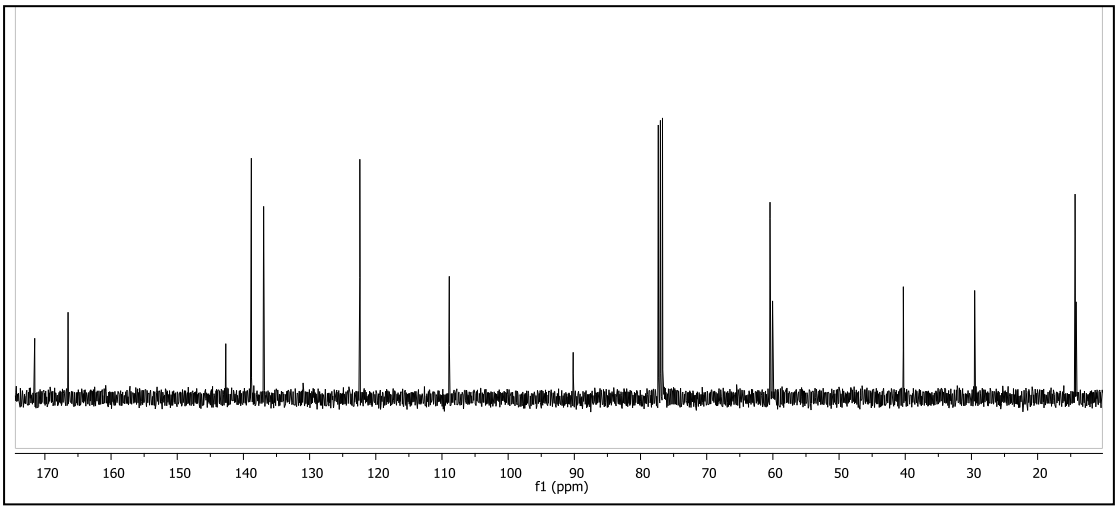

Figure A.89 ^{13}C-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-iodophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8h**)

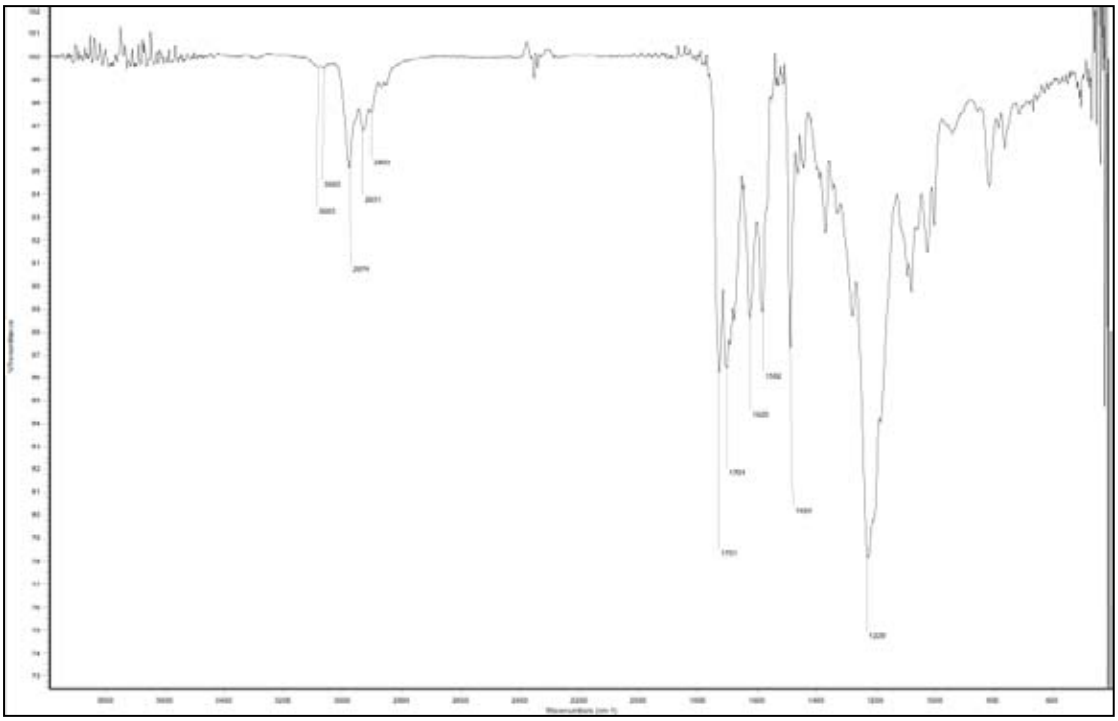

Figure A.90 IR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-iodophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8h**)

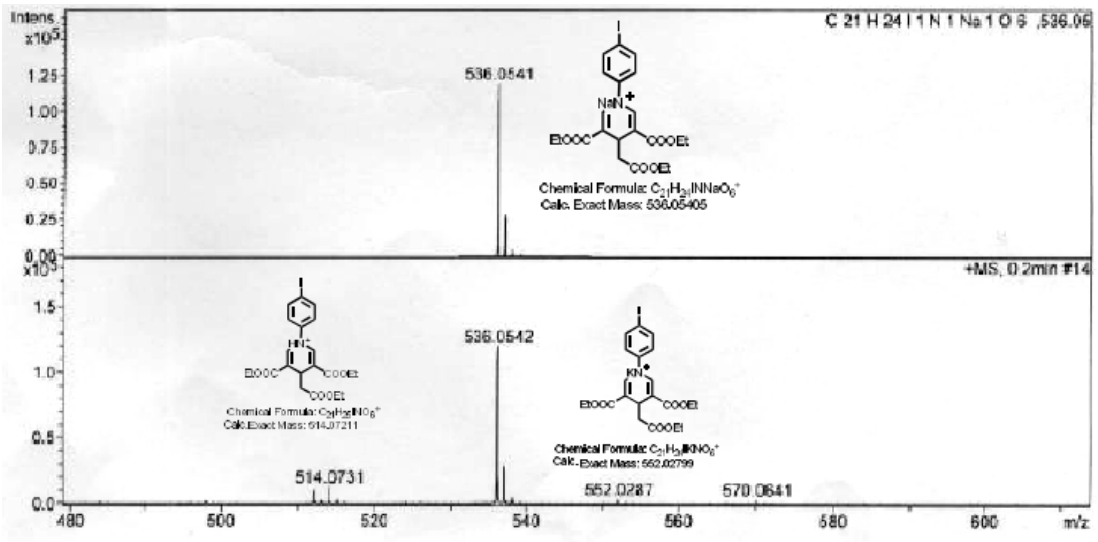

Figure A.91 HRMS of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-iodophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8h**)

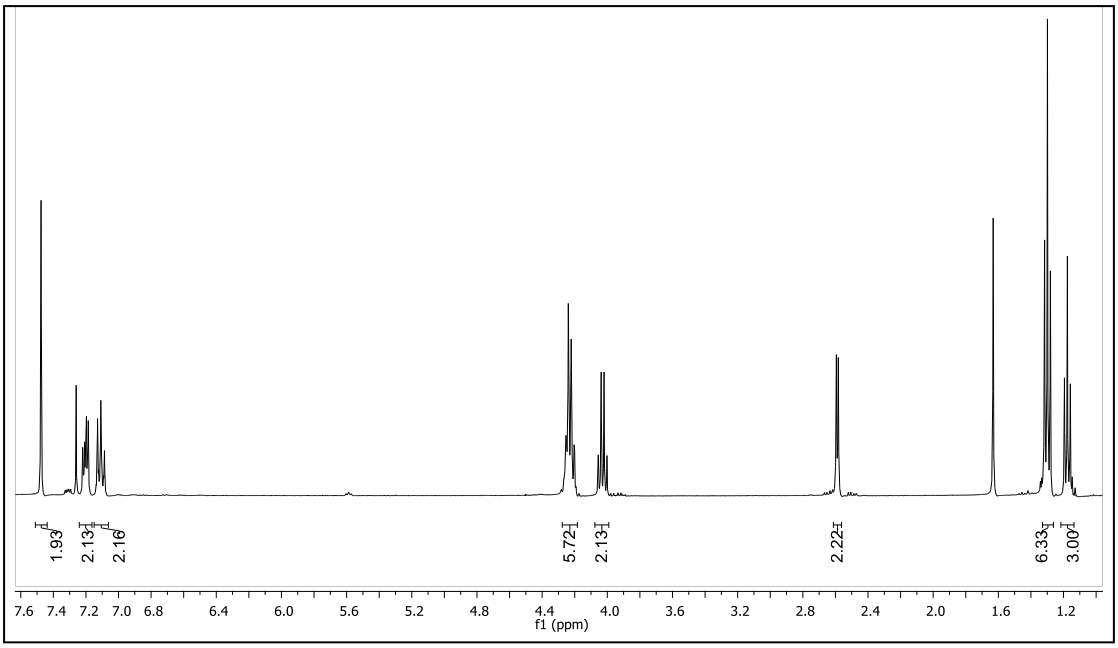

Figure A.92 ^{1}H-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8i**)

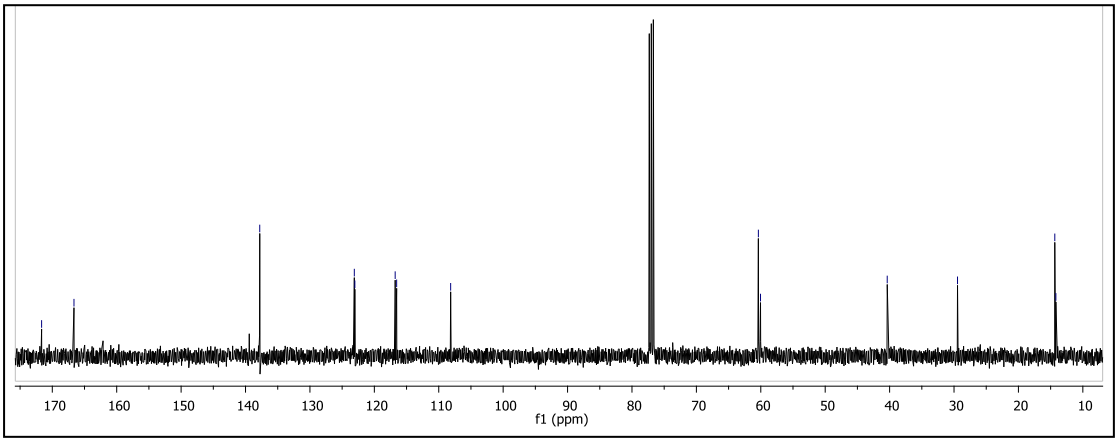

Figure A.93 ^{13}C-NMR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8i**)

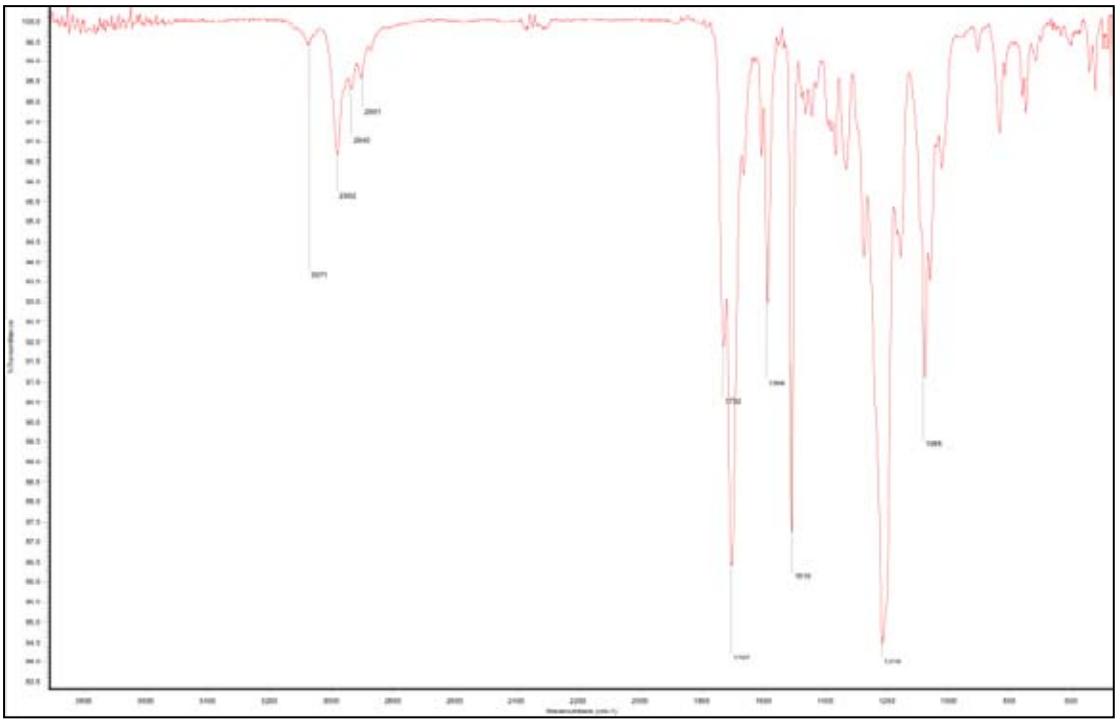

Figure A.94 IR of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8i**)

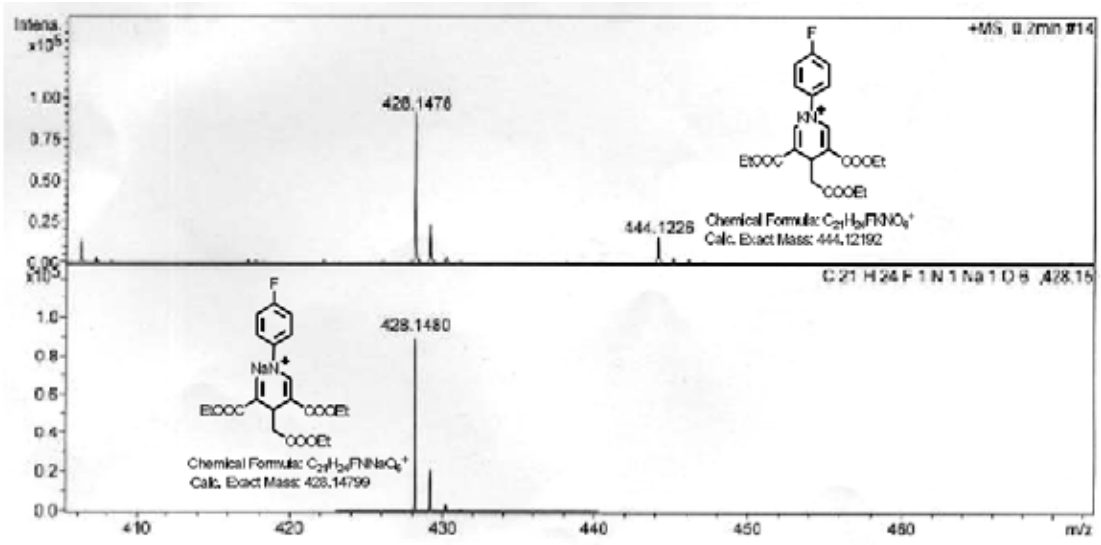

Figure A.95 HRMS of diethyl-4-(2-ethoxy-2-oxoethyl)-1-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8i**)

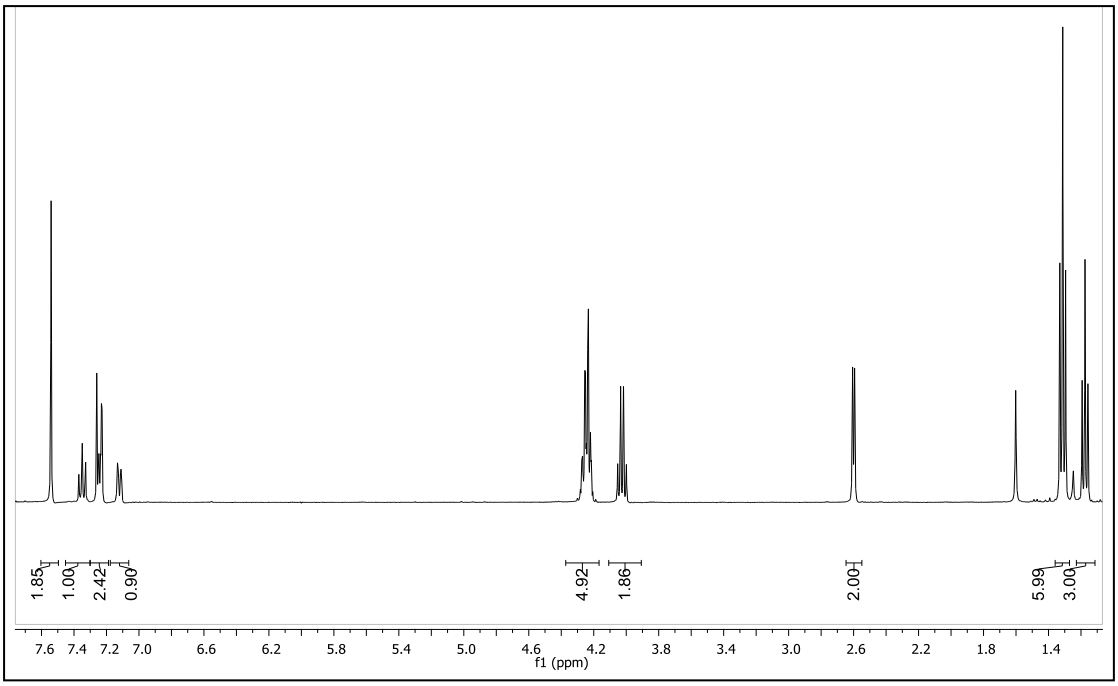

Figure A.96 ^{1}H-NMR of diethyl-1-(3-chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8j**)

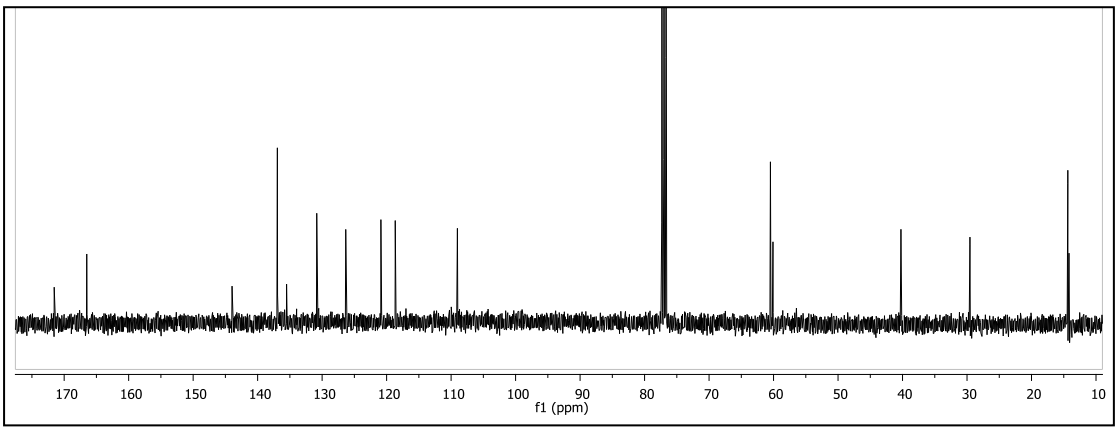

Figure A.97 ^{13}C-NMR of diethyl-1-(3-chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8j**)

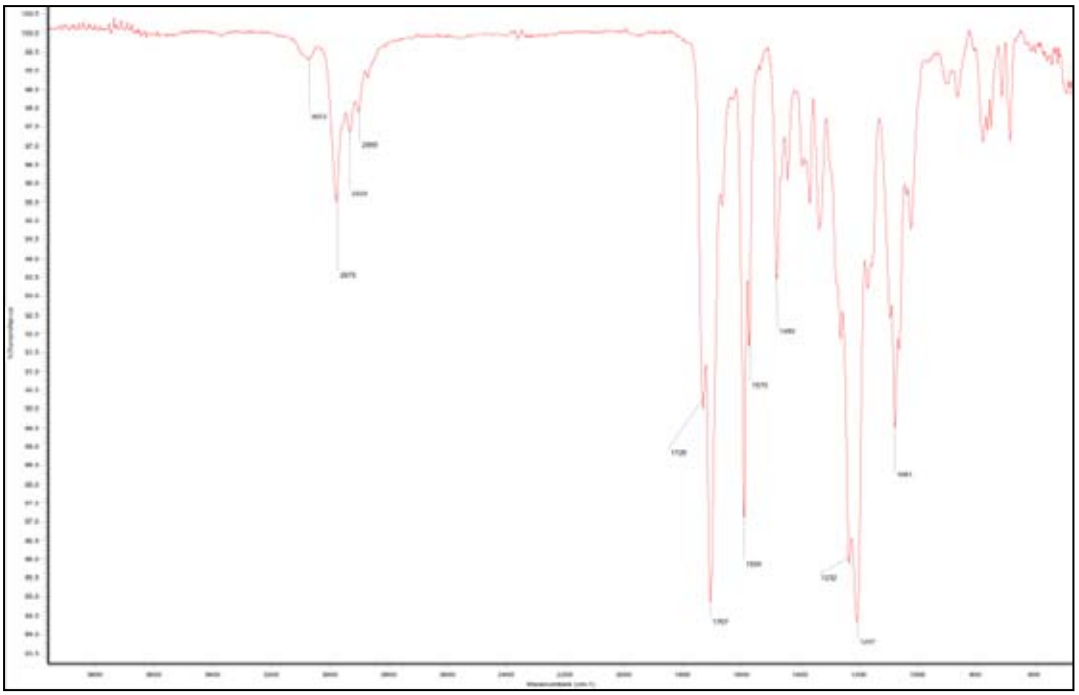

Figure A.98 IR of diethyl-1-(3-chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8j**)

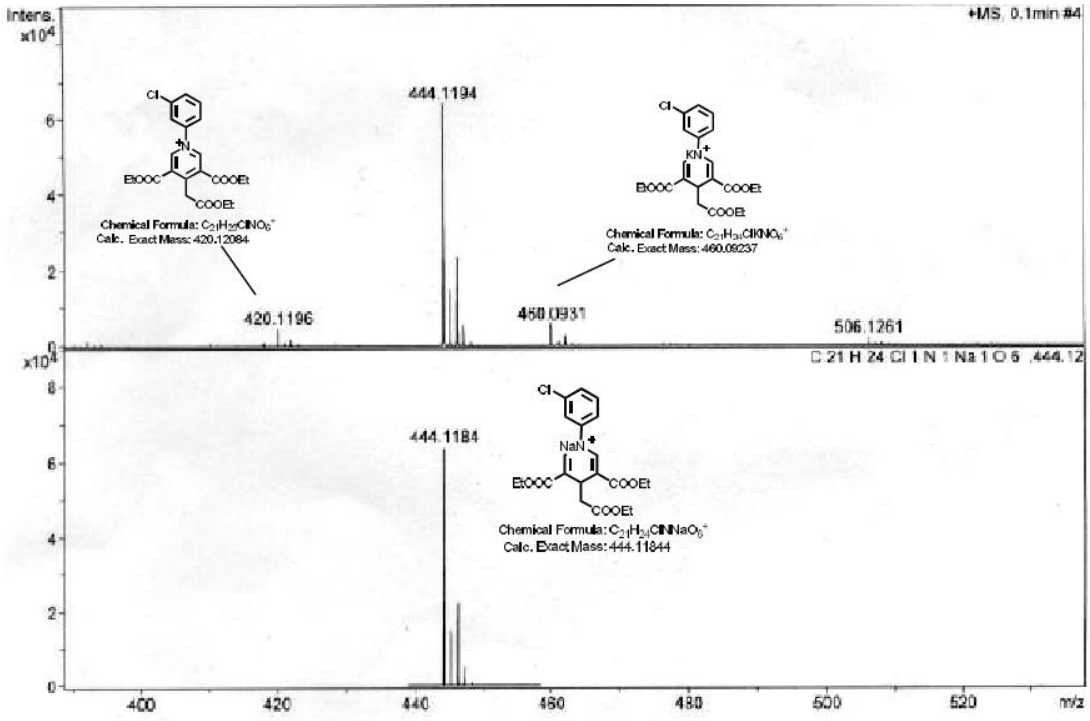

Figure A.99 HRMS of diethyl-1-(3-chlorophenyl)-4-(2-ethoxy-2-oxoethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8j**)

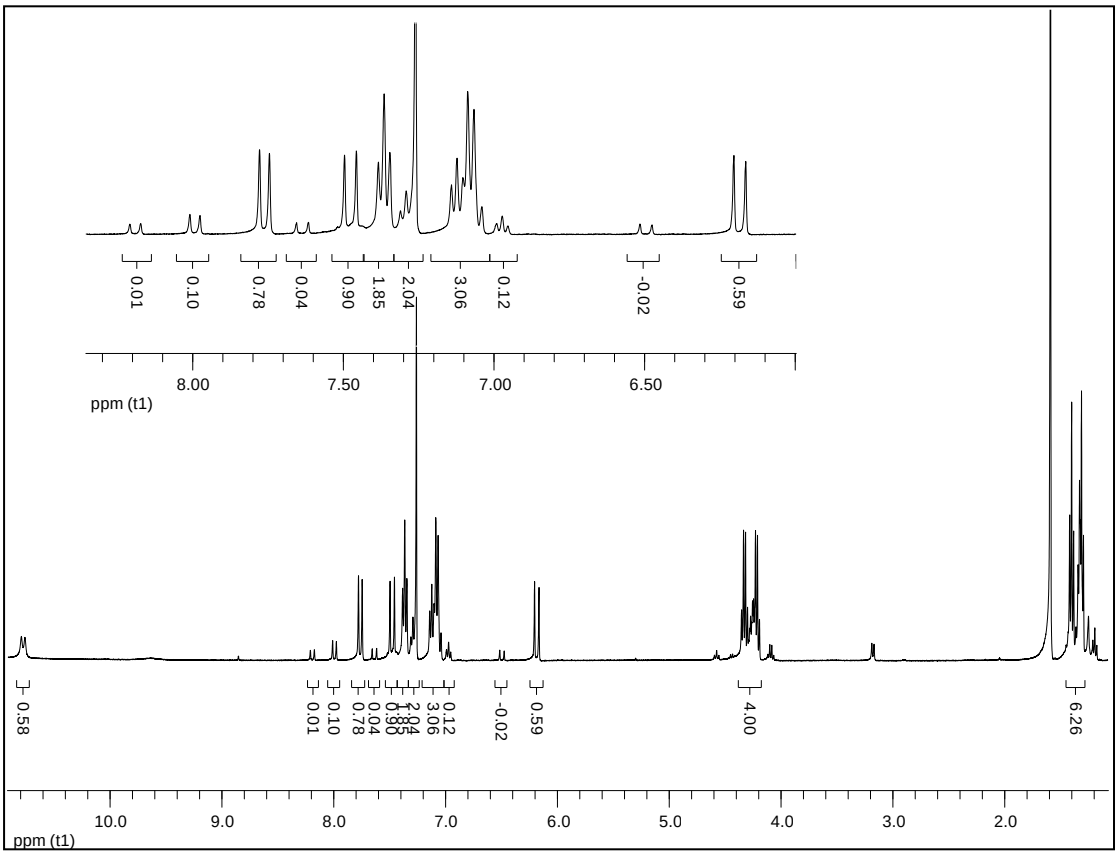

Figure A.100 ^{1}H-NMR of diethyl 4-((phenylamino)methylene)pent-2-enedioate (**9**)

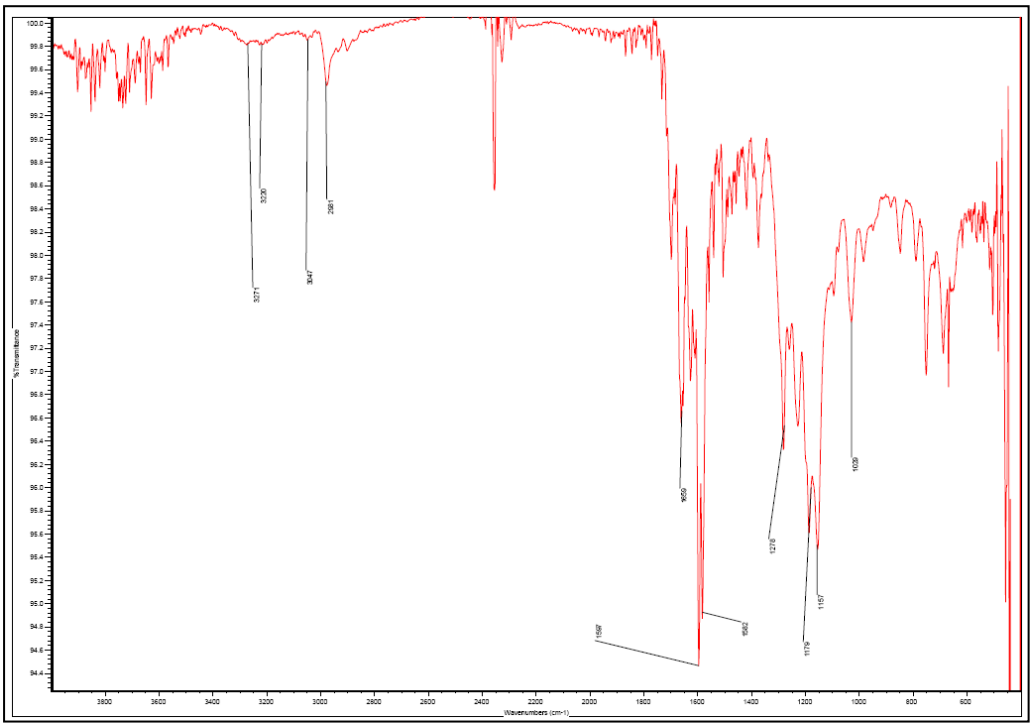

Figure A.101 IR of diethyl 4-((phenylamino)methylene)pent-2-enedioate (**9**)

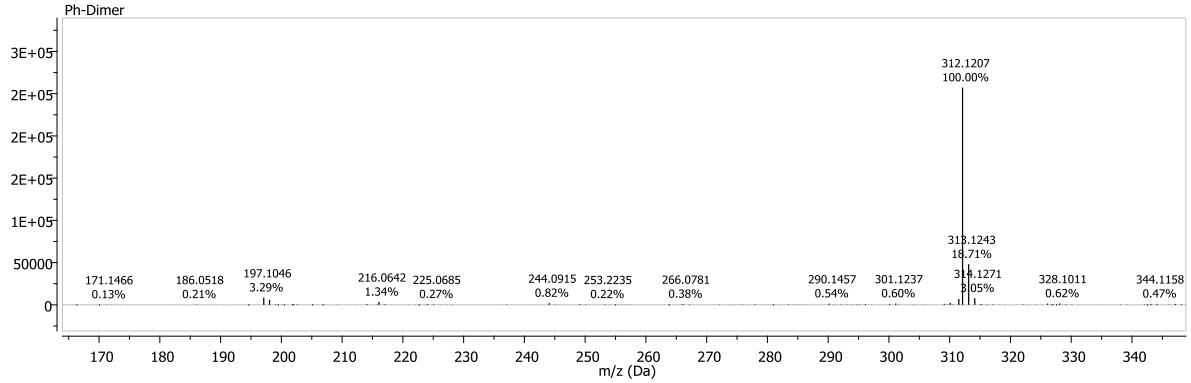

Figure A.102 HRMS of diethyl 4-((phenylamino)methylene)pent-2-enedioate (**9**)

VITA

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Publication

Sirijindalert, T.; Hansuthirakul, K.; Rashatasakhon, P.; Sukwattanasinitt, M.; and Ajavakom, A. Novel synthetic route to 1,4-dihydropyridines from β-amino acrylates by using titanium(IV) chloride under facile conditions *Tetrahedron* (66) 2010: 5161-5167.