Base Promoted 5-*endo*-*dig* cyclization: A Facile Approach Towards Pyrrolizidine Core

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Certificate of Examination

This is to certify that the dissertation titled "Base Promoted 5-*endo*-*dig* cyclization: A Facile Approach Towards Pyrrolizidine Core" submitted by Mr. Manish Pareek (Reg. No. MS08031) for the partial fulfillment of BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

Dr. S. A. Babu Dr. S.V. Rama Sastry Sripada Dr. R. Vijaya Anand

(Supervisor)

Dated: April 26, 2013

Declaration

The work presented in this dissertation has been carried out by me under the guidance of Dr. R. Vijaya Anand at the Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Manish Pareek (MS08031)

(Candidate)

Dated: April 26, 2013

In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. R. Vijaya Anand

(Supervisor)

Acknowledgement

Foremost, I would like to express my sincere gratitude to my thesis supervisor Dr. R. Vijaya Anand for the continuous support throughout my project, for his patience, motivation, enthusiasm, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. My sincere thanks also goes to Mr. Mahesh Sriram with whom I worked in this project, his valueable advises and discussions helped me in inculcating a proper understanding of the subject. I would also like to thank my other lab members Mr. B.T Ramanjaneyulu, Mr. Panjab, Mr. Vir, Mr Abhijit for their valuable advises and help at various steps of my project and to maintain a knowledgable environment in the lab. It would have been tough for me to complete this thesis without any characterzation technique; I would like to thank IISER Mohali NMR facility and Prof. Guptasarma's lab for the FTIR measurements. IISER Mohali liabrary for providing me essential books. IISER Mohali computing facility for providing Top-Spin software and internet connection.

Last but not the least I would like to thank my parents, sisters and friends for their moral and emotional support without them I was not able to complete it smoothly.

-Manish

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Abbreviations

PA	Pyrrolizidine alkaloid
LD	Lethal dose
AIBN	2,2′-Azobis(2-methylpropionitrile)
NMR	Nuclear magnetic resonance
FT-NMR	Fourier transform nuclear magnetic resonance
TMS	Tetramethylsilane
HRMS	High resolution mass spectometry
FT-IR	Fourier Transform Infrared
TLC	Thin layer chromatograohy
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
THF	Tetrahydrofuran
DMF	Dimethylformamide
KO^tBu	Potassium tertiarybutoxide
LiO^tBu	Lithium tertiarybutoxide
Equiv.	Equivalents
NaH	Sodium Hydride

Contents

Abstract

Pyrrolizidine scaffolds are having many biological activities in plants as well as in human body; hence these scaffolds are of great interest on synthetic perspectives. A base facilitated 5-*endo*-*dig* cyclization strategy has been developed to obtain the pyrrolizidine scaffold. This protocol allowed us to approach a diverse range of alkyl and aryl substituted pyrrolizidine scaffolds in moderate yields from *N*-propargyl-L-proline ester derivatives under mild conditions. Synthesis of indolizidine alkaloid from *N*-propargyl-L-pipecolinic esters using this strategy was also attempted.

CHAPTER 1

Introduction:

1.1 Overview

Indolizidine and pyrrolizidine alkaloids are large classes of natural products.[1] A common feature of these compounds is that they contain a bicyclic ring with nitrogen at the bridging position. Pyrrolizidines contain two five membered rings whereas indolizidines comprise of a five and a six membered ring (Fig. 1).

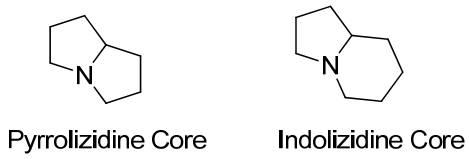


Figure 1. Pyrrolizidine and indolizidine core

Pyrrolizidine alkaloids (PAs) encompass a large family of natural products.[1] They exhibit various biological properties. Generally, PAs are hepatotoxic hence cause damage to liver and related organs.[1,2] Although these alkaloids are found to be toxic, few of them have shown some applications in the cancer treatment and viral infections like human immunity virus (HIV).[2] Some of the PAs exhibit anti-feedant activity, *i.e.* it prevents herbivores to eat the various parts of the plant, thus used in the agricultural industry as an insecticide.[2] For example, PAs **1** and **2** isolated from *Achusa Strigosa* exhibit antifeedant activity against the *Spodoptera Exigua* herbivore insect (Fig. 2).

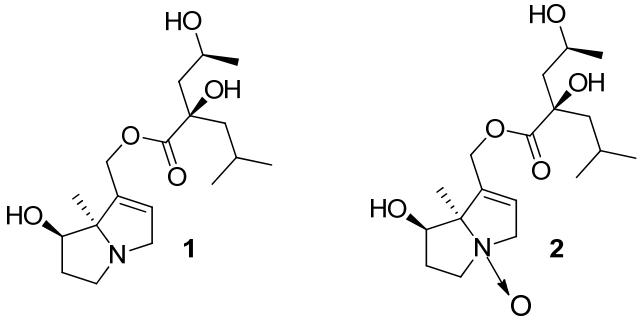


Figure 2. Pyrrolizidine alkaloids isolated from *Achusa Strigosa*.

Some of the important pyrrolizidine and indolizidine alkaloids are shown in Figure 3. Lasiocarpine **3** and europine **4**, which are extracted from *Heliotropium Bovei*, also function as deterrents to insect feeding (Fig. 3).[3] Alexine **5**, isolated from *Alexa Canaracunensis*, was found to have some potential in the treatment of HIV.[4] Casuarine **6**, which was isolated from *Casuarina Equisetifolia* and *Eugenia Jambolana*, had shown good activity for the treatment of breast cancer, bacterial infections, and diabetes.[4,5]

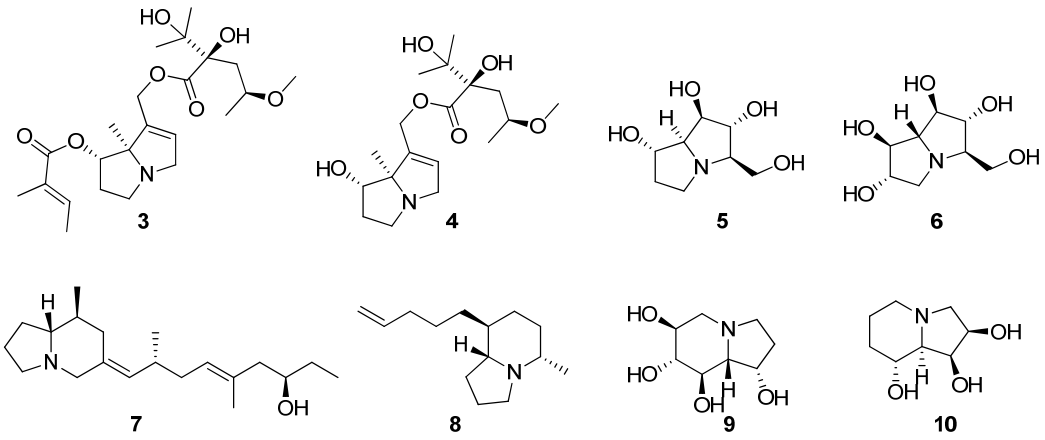


Figure 3. Various pyrrolizidine and indolizidine alkaloids; lasiocarpine (**3**), europine (**4**), alexine (**5**), casuarine (**6**), pumiliotoxin A (**7**), indolizidine 205A (**8**), castanospermine (**9**), swainsonine (**10**).

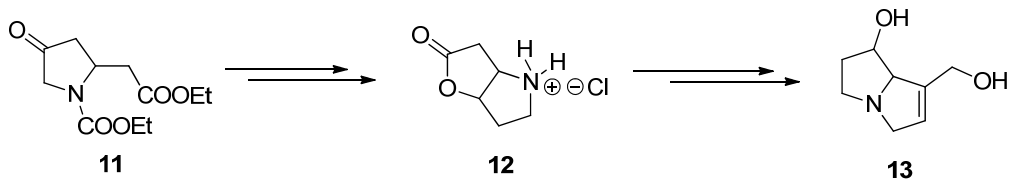
Indolizidine alkaloids generally work as an alleochemical deterrent to herbivores due to their bitter taste. They exhibit biological activity in insects, mammals and humans. Pumiliotoxins, found in many frog species like *Dendrobates*, *Minyobae*, *Mantella* etc (Fig. 3). Pumiliotoxin A (**7**) is toxic and has a LD 50 value of 2.5 mg/kg [6]. Indolizidine 205A **8** were also isolated from the frog species *Mantella*. These contains 5,8-disubstituted indolizidine moiety. These alkaloids are found to be quite toxic and their therapeutic use is still under investigation. Castanospermine **9**, isolated from *Castanospermum Austral,* and is a powerful inhibitor of several glucosidases. Swainsonine **10** is another example of an indolizidine alkaloid which also works as a glycosidase inhibitor, and has anti-tumor properties.[1]

There has been a great interest in these compounds and their derivatives, because of their biological activities described above. Extraction of these compounds

from plant sources is expensive, time consuming and low-yielding. Hence a simple and efficient synthetic route to these privileged molecules is highly desired.

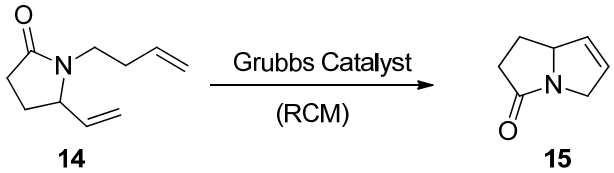
1.2 Synthetic strategies toward pyrrolizidine core:

Many synthetic strategies for the construction of the bicyclic core of these molecules have been reported in the literature. The first synthesis of (+)-retronecine, which contains the pyrrolizidine core, was performed by Geissman and Waiss in 1962.[7] This approach involves Geissman lactone **12** as an intermediate for the synthesis of the bicyclic core (Scheme 1). Since many synthetic steps are involved in the approach, less yield of final product was obtained.



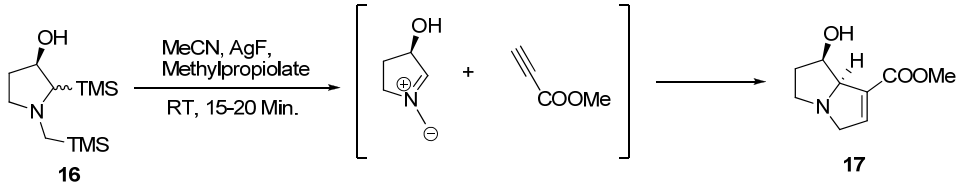
Scheme 1. Pyrrolizidine core synthesis using Geissman lactone

In another approach, ring closing metathesis (RCM)[8] was used as a key step for the construction of the bicyclic core (Scheme 2). This strategy has been elaborated to the synthesis of few pyrrolizidine natural products.



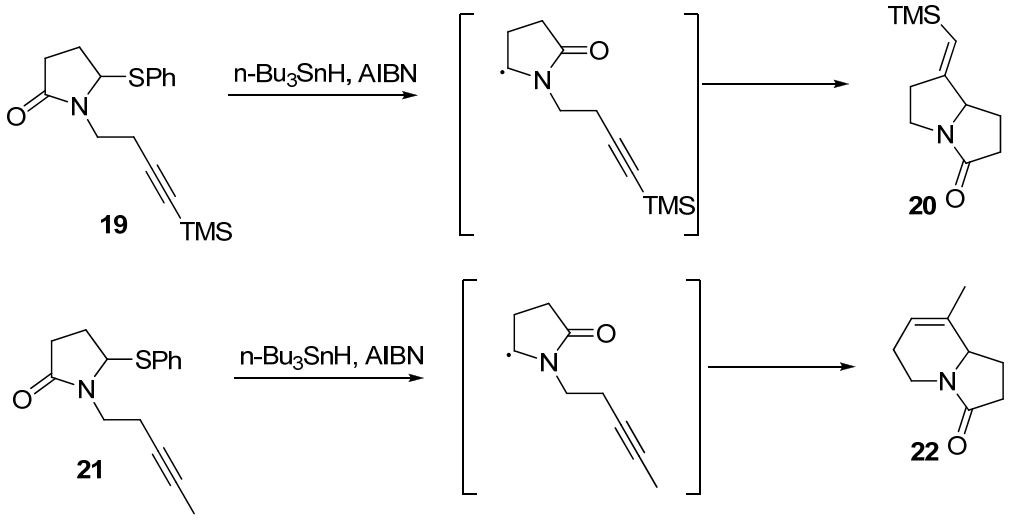
Scheme 2. Synthesis of pyrrolizidine core using ring closing metathesis

[3+2] cycloaddition strategy has also been reported for the assembly of bicyclic core. Panday and co-workers reported an efficient method for building the bicyclic core **17** by [3+2]- cycloaddition of non-stabilized azomethine ylide with a terminal alkyne (Scheme 3).[9]



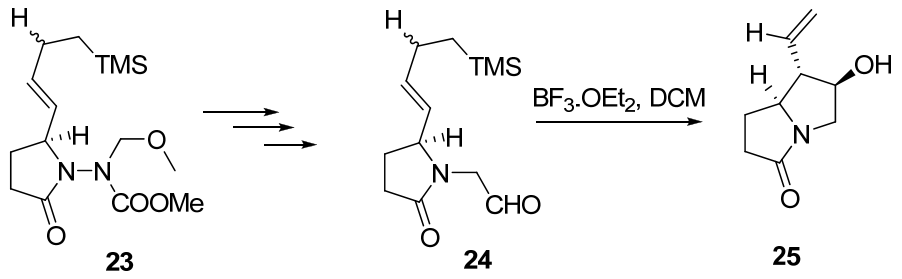
Scheme 3. Synthesis of pyrrolizidine core using [3+2] cycloaddition

Free radical Cyclization strategy was utilized by Hart and co-workers for the assembly of bicyclic core.[11] Treatment of phenylthiolactam **19** with tri-n-butyltin hydride and AIBN gave mixtures of reduction and cyclization products. Both indolizidinones and pyrrolizidinones cores were obtained depending upon the terminal alkyne substituent. When the terminal substituent was a trimethylsilyl group, pyrrolizidinone **20** was obtained and indolizidinone **22** was obtained when the terminal group was a methyl group **21** (Scheme 4).



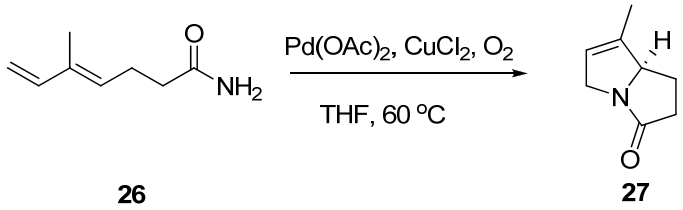
Scheme 4. Synthesis of pyrrolizidine core by free radical cyclization

Sarkar and co-workers described an intramolecular allylsilane ring closure strategy for the formation of the bicyclic core of pyrrolizidine alkaloids **25** (Scheme 5).[12]



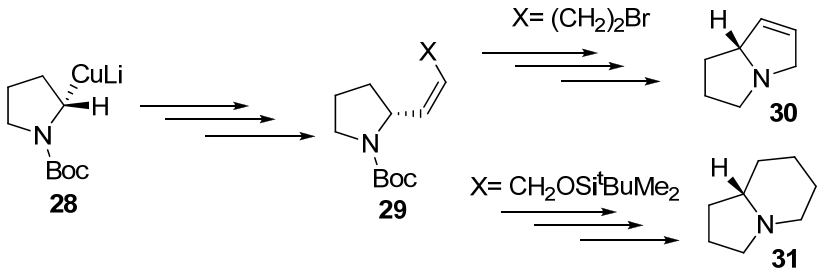
Scheme 5. Synthesis of pyrrolizidine core using intramolecular allylsilane ring closure

Transition metal catalysts including gold, copper and platinum were also employed in order to get the pyrrolizidine core. Backwall's group has reported palladium-catalyzed tandem cyclization of 4,6- and 5,7-diene amides which opened a new route toward the pyrrolizidine and indolizidine alkaloids **27** (Scheme 6).[13]



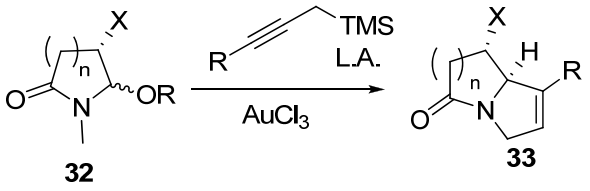
Scheme 6. Synthesis of pyrrolizidine core using palladium-catalyzed tandem cyclization

Dieter's group has synthesized scalemic 2-pyrrolidinylcuprates **28**, generated *via* asymmetric deprotonation of *N*-Boc pyrrolidine followed by treatment with CuCN.2LiCl, and reacted with functionalized vinyl halides to give 2-alkenyl-*N*-Boc-pyrrolidines. *N*-Boc deprotection and cyclization *via* intramolecular *N*-alkylation generated the pyrrolizidine or indolizidine skeletons **30** and **31** (Scheme 7).[14]



Scheme 7. Copper catalyzed synthesis of pyrrolizidine core

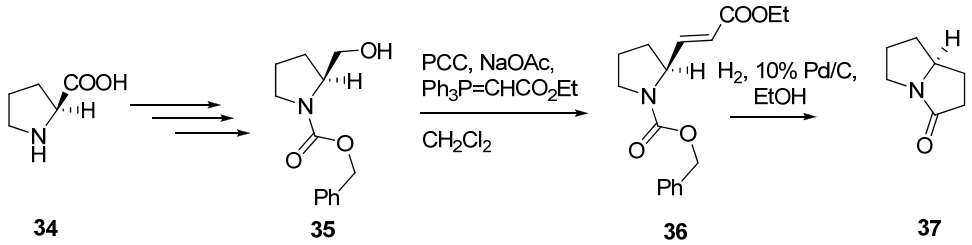
Kinderman and Hiemstra reported a reaction sequence involving the addition of propargylsilanes to lactam-derived *N*-acyliminium ion **32** followed by gold-catalyzed cyclization is applied in the syntheses of pyrrolizidine alkaloids **33** (Scheme 8).[15]



32 **33**

Scheme 8. Gold catalyzed synthesis of pyrrolizidine core

Tilve's group has achieved the synthesis of (*S*)-pyrrolam A **37** starting from *N* (benzyloxycarbonyl)-L-prolinol **35** through primary alcohol oxidation–Wittig reaction sequence (Scheme 9) .[16]

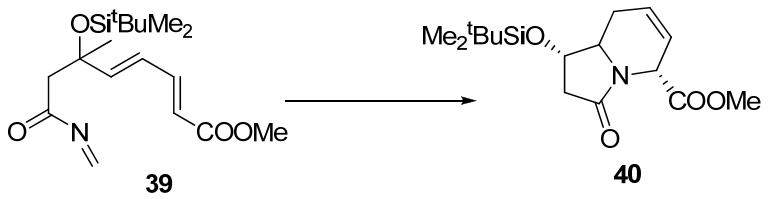


34 **35** **36** **37**

Scheme 9. Synthesis of pyrrolizidine core using domino oxidation–Wittig reaction

1.3 Synthetic strategies toward indolizidine core:

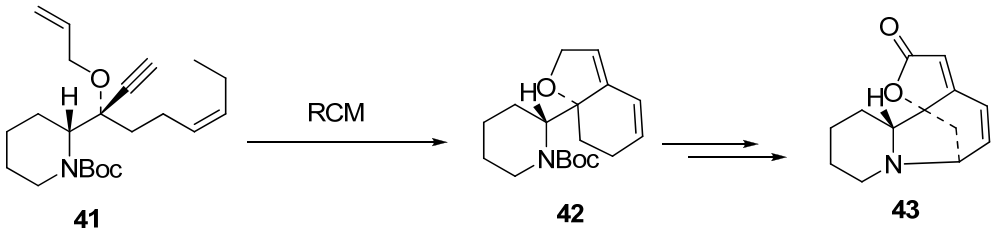
Several synthetic approaches toward indolizidine core have been reported in the literature. Weinreb's group has reported the synthesis of indolizidine core **40** from diene amide **39** *via* an intramolecular imino Diels-Alder reaction (Scheme 10).[17] The indolizidine skeleton was synthesized with required stereochemistry.



39 **40**

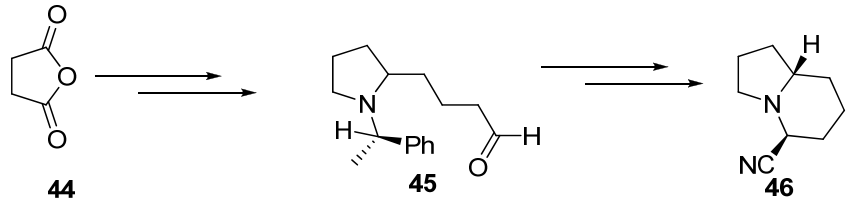
Scheme 10. Synthesis of indolizidine core using Diels-Alder reaction

Honda and co-workers reported a competent synthesis of indolizidine core **43** by applying domino enyne metathesis as a key step (Scheme 11).[18]



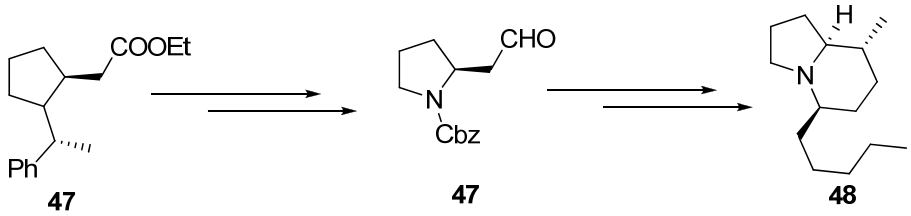
Scheme 11. Synthesis of indolizidine core using domino enyne metathesis

Polniaszek *et al.* has reported a 10 step synthesis of indolizidine core **46** starting from (S)-(-)-a-phenethylamine.[19] This method involves intramolecular imine formation followed by addition of cyanide (Scheme 12).



Scheme 12. Synthesis of indolizidine core using intramolecular imine formation

Lhommet's group has developed a highly diastereoselective synthesis of indolizidine (-)-209B **48** through diastereoselective alkylation of a chiral cyclic β-amino ester **47** (Scheme 13).[20]



Scheme 13. Synthesis of indolizidine core using diastereoselective alkylation

CHAPTER 2

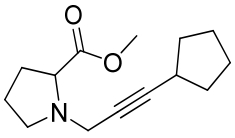
Experimental Section:

2.1 General Methods: All reactions were carried out under inert atmosphere. All the reagents used were purchased from commercial sources and used as such. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using 400 MHz and 100 MHz Bruker FT-NMR spectrometer respectively. Chemical shift values are reported in parts per million relative to TMS. High resolution mass spectra (HRMS) were recorded on a waters-Q-Tof spectrometer. IR spectra were recorded on a Brucker FT-IR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates using EtOAc/Hexane mixture as an eluent. Chromatographic separation was carried out through neutral alumina column.

2.2 General procedure for the synthesis of N-propargyl proline ester Derivatives:

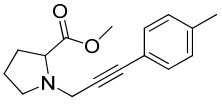
Formaldehyde (0.25 mmol), Terminal alkyne (0.25 mmol), sodium bicarbonate (0.2 mmol), and CuCl (0.02 mmol) were stirred over night with proline methyl ester hydrochloride (0.2 mmol) at 35°C under argon. After completion, the reaction mixture was directly loaded on a silica gel column and purified using hexane/EtOAc mixture (15%) as an eluent.

*Methyl -1-(3-cyclopentylprop-2-yn-1-yl)pyrrolidine-2-carboxylate (**49**):*



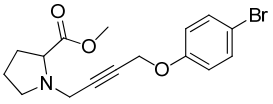
70% Yield; light yellow liquid; FT IR 2358 (C≡C), 1747 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.52 (d, J = 2.0 Hz, 2H), 3.39 (dd, J = 9.0 Hz, 6.4 Hz, 1H), 3.06-3.01 (m, 1H), 2.70-2.55 (m, 2H), 2.17-2.07 (m, 1H), 2.00-1.85 (m, 4H), 1.80-1.75 (m, 1H), 1.72-1.64 (m, 2H), 1.60-1.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 90.1, 73.8, 62.9, 52.4, 52.1, 42.0, 34.2, 30.3, 29.9, 25.0, 23.5; HRMS (ESI) calculated for $C_{14}H_{22}NO_2$ 236.1650, found 236.1651 $[M+H]^+$.

*Methyl-1-(3-(p-tolyl)prop-2-yn-1-yl)pyrrolidine-2-carboxylate (**50**)*:



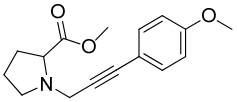
93% Yield; brown liquid; FT IR 2367 (C≡C), 1745 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 3.78 (d, J = 1.7 Hz, 2H), 3.72 (s, 3H), 3.50 (dd, J = 9.1 Hz, 6.5 Hz, 1H), 3.15-3.10 (m, 1H), 2.80-2.74 (m, 1H), 2.33 (s, 3H), 2.22-2.13 (m, 1H), 2.02-1.81 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 138.3, 131.7, 129.1, 120.0, 85.6, 83.4, 63.0, 52.6, 52.2, 42.4, 29.8, 23.5, 21.5; HRMS (ESI) calculated for $C_{16}H_{20}NO_2$ 258.1494, found 258.1497 $[M+H]^+$.

*Methyl-1-(4-(4-bromophenoxy)but-2-yn-1-yl)pyrrolidine-2-carboxylate (**51**):*



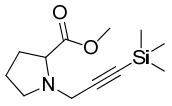
60% Yield; light yellow liquid; FT IR 2348 (C≡C), 1740 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 9.1 Hz, 2H), 6.84 (d, J = 9.1 Hz, 2H), 4.68 (t, J = 1.9 Hz, 2H), 3.70 (s, 3H), 3.60 (t, J = 1.9 Hz, 2H), 3.31 (dd, J = 9.0 Hz, 6.6 Hz, 1H), 3.03-3.00 (m, 1H), 2.60 (m, 1H), 2.11-2.01 (m, 1H), 2.00-1.82 (m, 2H), 1.77-1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 156.7, 132.3, 117.0, 113.8, 82.8, 79.8, 62.7, 56.4, 52.4, 52.1, 41.5, 29.6, 23.3; HRMS (ESI) calculated for $C_{16}H_{19}BrNO_3$ 352.0548, found 352.0549 $[M+H]^+$.

*Methyl-1-(3-(4-methoxyphenyl)prop-2-ynyl)pyrrolidine-2-carboxylate (**52**):*



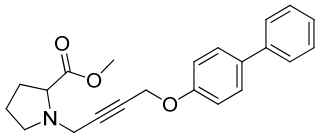
54% Yield; Light yellow liquid; FT IR 2355 (C≡C), 1738 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 3.78 (s, 3H), 3.76 (d, J = 1.9 Hz, 2H), 3.71 (s, 3H), 3.48 (dd, J = 6.5 Hz, 3.3 Hz, 1H), 3.14-3.09 (m, 1H), 2.79-2.72 (m, 1H), 2.21-2.12 (m, 1H), 2.03-1.88 (m, 2H), 1.86-1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 159.5, 133.2, 115.2, 113.9, 85.3, 82.6, 63.0, 55.3, 32.6, 42.3, 29.8, 23.4; HRMS (ESI) calculated for $C_{16}H_{20}NO_3$ 274.1443, found 274.1440 $[M+H]^+$.

*Methyl-1-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidine-2-carboxylate(**53**):*



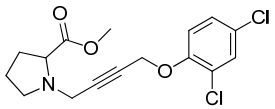
52% Yield; Light yellow liquid; FT IR 2355 (C≡C), 1738 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.58 (s, 2H), 3.40 (dd, J = 9.1 Hz, 3.3 Hz, 1H), 3.08-3.03 (m, 1H), 2.73-2.66 (m, 1H), 2.19-2.09 (m, 1H), 2.02-1.85 (m, 2H), 1.83-1.75 (m, 1H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 100.8, 90.1, 62.8, 52.5, 52.1, 42.6, 29.8, 23.5, 0.2; HRMS (ESI) calculated for $C_{12}H_{22}NO_2Si$ 240.1420, found 240.1427 $[M+H]^+$.

*Methyl-1-(4-(biphenyl-4-yloxy)but-2-ynyl)pyrrolidine-2-carboxylate(**54**):*



45% Yield; light yellow liquid; FT IR 2349 (C≡C), 1739 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.51 (m, 4H), 7.44-7.39 (m, 2H), 7.33-7.28 (m, 1H), 7.04 (d, J = 8.8 Hz, 2H), 4.76 (t, J = 1.8 Hz, 2H), 3.70 (s, 3H), 3.64 (t, J = 1.8 Hz, 2H), 3.37 (dd, J = 9.0 Hz, 6.6 Hz, 1H), 3.05-3.00 (m, 1H), 2.67-2.60 (m, 1H), 2.11-2.02 (m, 1H), 1.98-1.82 (m, 2H), 1.76-1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 157.2, 140.8, 134.6, 128.9, 128.2, 126.9, 126.9, 115.4, 82.5, 80.2, 62.7, 56.3, 52.4, 52.1, 41.6, 29.7, 23.3; HRMS (ESI) calculated for $C_{22}H_{24}NO_3$ 350.1756, found 350.1756 $[M+H]^+$.

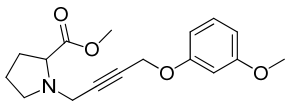
*Methyl-1-(4-(2,4-dichlorophenoxy)but-2-ynyl)pyrrolidine-2-carboxylate(**55**):*



65% Yield; light yellow liquid; FT IR 2337 (C≡C), 1739 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 2.6 Hz, 1H), 7.19 (dd, J = 8.8 Hz, 2.6 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.79 (t, J = 1.9 Hz, 2H), 3.71 (s, 3H), 3.60 (t, J = 1.9 Hz, 2H), 3.30 (dd, J = 9.0 Hz, 6.6 Hz, 1H), 3.03-2.98 (m, 1H), 2.60-2.54 (m, 1H), 2.12-2.03 (m, 1H), 1.98-1.85 (m, 2H), 1.81-1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 157.0,

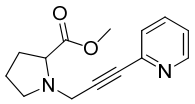
130.2, 127.5, 126.8, 124.3, 115.5, 83.6, 79.2, 62.8, 57.5, 52.5, 52.2, 41.6, 29.7, 23.3; HRMS (ESI) calculated for $C_{16}H_{19}Cl_2NO_3$ 342.0664, found 342.0666 $[M+H]^+$.

*Methyl-1-(4-(3-methoxyphenoxy)but-2-ynyl)pyrrolidine-2-carboxylate (**56**):*



48% Yield; light yellow liquid; FT IR 2344 (C≡C), 1738 (C=O), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12-7.07 (m, 1H), 6.49-6.44 (m, 3H), 4.61 (t, J = 1.9 Hz, 2H), 3.67 (s, 3H), 3.63 (s, 3H), 3.54 (t, J = 1.8 Hz, 2H), 3.26 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 2.98-2.91 (m, 1H), 2.56-1.52 (m, 1H), 2.03-1.94 (m, 1H), 1.90-1.74 (m, 2H), 1.69-1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 160.8, 158.9, 129.9, 107.2, 107.0, 101.7, 82.4, 80.2, 62.6, 56.2, 55.3, 52.3, 52.0, 41.6, 29.7, 23.3.

*Methyl-1-(3-(pyridin-2-yl)prop-2-ynyl)pyrrolidine-2-carboxylate(**57**):*

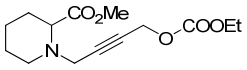


48% yield, FT IR 2350 (C≡C), 1739 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 4.9 Hz, 1H), 7.64 (td, J = 7.8 Hz, 1.9 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.23 (ddd, J = 7.6 Hz, 4.9 Hz, 1.2 Hz, 1H), 3.68 (d, J = 2.8 Hz, 2H), 3.72 (s, 3H), 3.56 (dd, J = 9.1 Hz, 6.8 Hz, 1H), 3.13-3.11 (m, 1H), 2.87-2.80 (m, 1H), 2.24-2.14 (m, 1H), 2.05-1.87 (m, 2H), 1.86-1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 149.6, 142.6, 136.5, 127.3, 123.3, 84.8, 84.8, 62.5, 52.3, 52.1, 41.5, 29.5, 23.2.

2.3 General procedure for the synthesis of N-propargyl pipecolinic ester derivatives:

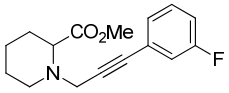
Formaldehyde (0.50 mmol), phenylacetylene (0.25 mmol), sodium bicarbonate (0.2 mmol) and CuCl (0.02 mmol) were stirred over night with pipecolinic methyl ester hydrochloride (0.2 mmol) at 35°C under argon. After completion, the Reaction mixture was directly loaded on a silica gel column and purified using Hexane/EtOAc mixture (15%) as an eluent.

*Methyl-1-(4-ethoxy-4-oxobut-2-ynyl)piperidine-2-carboxylate (**58**):*



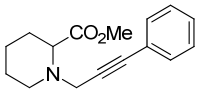
40% yield; Light yellow liquid; FT IR 2362 (C≡C), 1738 (C=O), 1730 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, J = 7.2 Hz, 2H), 3.72 (s, 3H), 3.59 (dd, J = 67.7 Hz, 18.1 Hz, 2H), 3.23 (dd, J = 10.2 Hz, 3.4 Hz, 1H), 2.87 (dt, J = 11.3 Hz, 3.5 Hz, 1H), 2.56-2.50 (m, 1H), 1.93-1.88 (m, 1H), 1.73-1.59 (m, 4H), 1.38-1.31 (m, 1H), 1.29 (t, J = 4.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 153.4, 82.6, 78.2, 63.0, 52.1, 51.5, 44.6, 30.1, 25.2, 22.8, 14.1; HRMS (ESI) calculated for $C_{14}H_{23}NO_4$ 254.1392, found 254.1393 $[M+H]^+$.

*Methyl-1-(3-(3-fluorophenyl)prop-2-ynyl)piperidine-2-carboxylate (**59**):*



52% yield; Light yellow liquid; FT IR 2363 (C≡C), 1738 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.18 (m, 2H), 7.1 (d, J = 9.5 Hz, 1H), 6.99 (t, J = 8.6 Hz, 1H), 3.74 (s, 3H), 3.63 (dd, J = 46.2 Hz, 17.4 Hz, 2H), 3.27 (dd, J = 10.2 Hz, 3.3 Hz, 1H), 2.98 (dt, J = 11.2 Hz, 3.8 Hz, 1H), 2.57-2.50 (m, 1H), 1.95-1.89 (m, 1H), 1.76-1.64 (m, 4H), 1.37-1.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 161.2, 129.6 (d, $J_{C\text{-}F}$ = 8.7 Hz), 127.7 (d, $J_{C\text{-}F}$ = 2.9 Hz), 124.9 (d, $J_{C\text{-}F}$ = 9.5 Hz), 118.8 (d, $J_{C\text{-}F}$ = 22.6), 85.0, 84.9, 63.5, 52.1, 51.6, 45.5, 30.1, 25.3, 23.1; HRMS (ESI) calculated for $C_{16}H_{19}FNO_2$ 276.1400, found 276.1403 $[M+H]^+$.

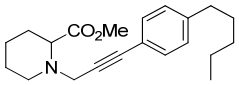
*Methyl-1-(3-phenylprop-2-ynyl)piperidine-2-carboxylate (**60**):*



50% yield, FT IR 2357 (C≡C), 1738 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.31-7.27 (m, 3H), 3.75 (s, 3H), 3.65 (dd, J = 53.4Hz, 17.4 Hz, 2H), 3.31 (dd, J = 10.3 Hz, 3.3 Hz, 1H), 3.00 (dt, J = 10.9 Hz, 3.7 Hz, 1H), 2.60-2.53 (m, 1H), 1.95-1.90 (m, 1H), 1.77-1.65 (m, 4H), 1.40-1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 131.9, 128.3, 128.2, 123.2, 86.1, 83.7, 63.5, 52.1, 51.6, 45.5,

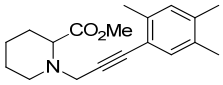
30.2, 25.4, 23.2; HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ 258.1494, found 258.1491 $[M+H]^+$.

*Methyl-1-(3-(4-pentylphenyl)prop-2-ynyl)piperidine-2-carboxylate (**61**):*



39.4% yield, FT IR 2365 (C≡C), 1738 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.3 Hz, 2H), 7.1 (d, J = 8.3 Hz, 2H), 3.75 (s, 3H), 3.64 (dd, J = 49.8 Hz, 17.4, 2H), 3.31 (dd, J = 10.3 Hz, 3.3 Hz, 1H), 2.99 (dt, J = 11.0 Hz, 3.7 Hz, 1H), 2.58 (t, J = 7.7 Hz, 3H), 1.94-1.89 (m, 1H), 1.76-1.64 (m, 4H), 1.62-1.55 (m, 2H), 1.36-1.28 (m, 5H), 0.87 (t, J = 6.84 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 143.35, 131.8, 128.5, 120.3, 86.2, 83.0, 63.5, 60.5, 52.1, 51.6, 45.6, 35.5, 31.1, 30.2, 25.4, 23.2, 22.6; HRMS (ESI) calculated for $C_{21}H_{30}NO_2$ 328.2276, found 328.2274 $[M+H]^+$.

*Methyl-1-(3-(2,4,5-trimethylphenyl)prop-2-ynyl)piperidine-2-carboxylate (**62**):*

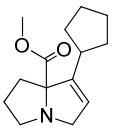


39.4% yield, FT IR 2356 (C≡C), 1739 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.96 (s, 1H), 3.75 (s, 3H), 3.67 (dd, J = 73.76Hz, 17.44 Hz, 2H), 3.35 (dd, J = 10.6 Hz, 3.3 Hz, 1H), 2.95 (dt, J = 11.1 Hz, 3.9 Hz, 1H), 2.65-2.58 (m, 1H), 2.35 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 1.94-1.86 (m, 1H), 1.77- 1.63 (m, 4H), 1.36-1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1734.0, 137.5, 137.0, 133.7, 133.1, 131.0, 120.1, 86.2, 85.3, 63.3, 52.0, 51.6, 45.6, 30.2, 25.4, 23.3, 20.4, 19.8, 19.2; HRMS (ESI) calcd for $C_{19}H_{26}NO_2$ 300.1963, found 300.1967 $[M+H]^+$.

2.4 General procedure for synthesis of pyrrolizidine scaffold :

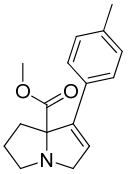
A solution of LiHMDS (0.75 mmol) in hexane was added in a drop-wise manner to a solution of *N*-propargyl proline ester (0.5 mmol) in dry THF (5 mL) at RT under inert atmosphere and the resulting solution was stirred vigorously until the starting material was completely consumed. The solvent was evaporated under reduced pressure and the residue was purified through neutral alumina column using EtOAc/Hexane mixture as an eluent.

*Methyl-7-cyclopentyl-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate (**63**)*:



50% Yield; light yellow liquid; FT IR 2949 (=CH), 1730 (C=O), 1452 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (d, J = 1.5 Hz, 1H), 3.92 (td, J = 15.3 Hz, 1.6 Hz, 1H), 3.65 (s, 3H), 3.30 (td, J = 15.3 Hz, 2.0 Hz, 1H), 3.24-3.20 (m, 1H), 2.61-2.55 (m, 1H), 2.44-2.40 (m, 1H) 2.30-2.21 (m, 1H), 1.88-1.81 (m, 1H), 1.80-1.71 (m, 3H), 1.68-1.47 (m, 5H), 1.42-1.32 (m, 1H), 1.27-1.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 147.3, 120.3, 85.2, 61.6, 57.8, 52.4, 38.8, 33.2, 33.0, 26.0, 24.9; HRMS (ESI) calculated for $C_{14}H_{22}NO_2$ 236.1650, found 236.1653 $[M+H]^+$.

*Methyl-7-(p-tolyl)-2,3,5,7a-tetrahydro-1H-pyrrolizine-7a-carboxylate (**64**)*:

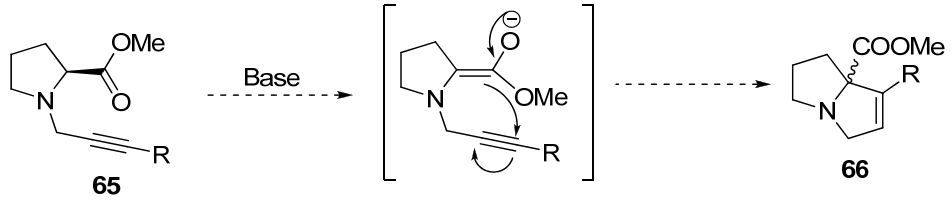


60% Yield; yellow semi solid; FT IR 2949 (=CH), 1730 (C=O), 1433 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 7.13-7.11 (m, 2H), 6.19 (t, J = 2.2 Hz, 1H), 4.12 (dd, J = 16.5 Hz, 1.8 Hz, 1H), 3.67 (s, 3H), 3.52 (dd, J = 16.5 Hz, 2.4 Hz, 1H), 3.32-3.28 (m, 1H), 2.91 (ddd, J = 12.3 Hz, 6.8 Hz, 2.5 Hz, 1H), 2.56-2.49 (m, 1H), 2.33 (s, 3H), 2.01-1.90 (m, 1H), 1.87-1.81 (m, 1H), 1.72-1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 142.2, 137.6, 130.3, 129.4, 126.3, 123.2, 83.2, 61.4, 57.7, 52.8, 33.4, 26.5, 21.3; HRMS (ESI) calculated for $C_{16}H_{20}NO_2$ 258.1494, found 258.1492 $[M+H]^+$.

CHAPTER 3

Results and Discussion:

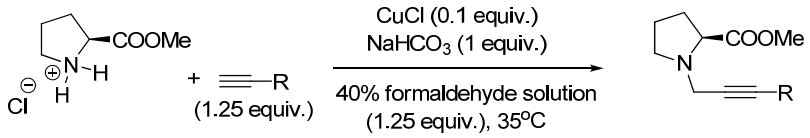
For the past two decades, the *5-endo-dig* cyclization strategy has been utilized as a powerful strategy for the assembly of bicyclic core of many valuable molecules.[21] While searching for a suitable and novel method for the assembly of bicyclic core of pyrrolizidine and indolizidine alkaloids, we thought of employing *5-endo-dig* cyclization approach for the same. Our proposed synthetic approach towards the pyrrolizidine bicyclic core is represented in Scheme 14, which clearly reveals that the bicyclic core of pyrrolizidine **66** could be easily assembled from *N*-propargyl-L-proline ester **65** through base facilitated *5-endo-dig* cyclization. The *N*-propargyl-L-proline ester **65** could be readily accessed from L-proline through a precedented method.[22] To the best of our knowledge, this strategy towards pyrrolizidine core remains unknown in the literature.

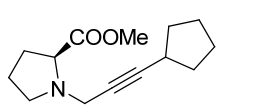


Scheme 14

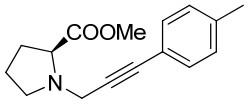
Before starting the actual optimization of *5-endo-dig* cyclization, we have synthesized a wide variety of starting materials starting from L-proline and a range of terminal alkynes following the literature procedure (Table 1).[22] As one can observe that *p*-tolyl propargyl group derived starting material **50** was obtained in maximum yield. Other starting materials were formed in moderate yields. The reaction condition was semi-neat as 40% HCHO solution was used in the reaction. *N*-Propargyl-L-proline derivatives **51**, **55**, **54**, **56** were synthesized from terminal acetylenes, which in turn were prepared by the treatment of propargyl bromide with the corresponding phenol under basic conditions (K_2CO_3, DMF).

Table 1. Preparation of *N*-propargyl-L-proline derivatives

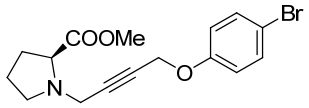




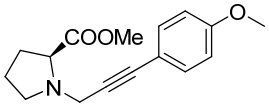
49, 12 hr, 50%



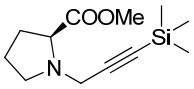
50, 12 hr, 92%



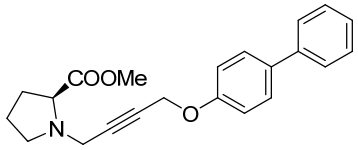
51, 12 hr, 60%



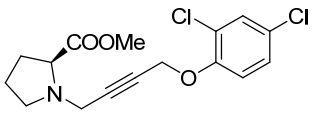
52, 12 hr, 54%



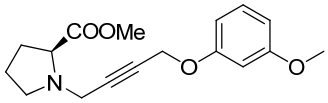
53, 12 hr, 52%



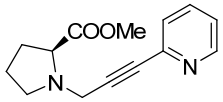
54, 12 hr, 45%



55, 12 hr, 65%



56, 12 hr, 48%



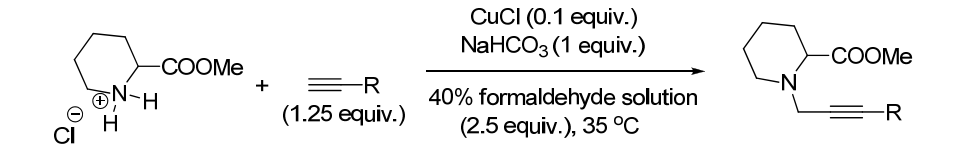
57, 12 hr, 48%

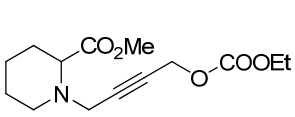
Similarly, the starting materials for the synthesis of indolizidine derivatives were prepared using the same strategy from pipecolinic acid methyl ester. In case of six membered ring containing starting material excess (2.5 equiv.) of formaldehyde was used, because the pipecolinic acid methyl ester is a solid. Hence more amount of formaldehyde was required in order to homogenize the reaction mixture. We have made few *N*-propargyl pipecolinic acid derivatives, which are listed in Table 2.

The optimization studies were performed using **67** as the starting material. Various bases and solvents were screened in order to get the final product **68** (Table 3). Our initial efforts to get the expected product **68** were discouraging as the bases NaH, KO^{t}Bu, Et_3N and LiO^{t}Bu did not yield any product. LDA and KO^{t}Bu gave either decomposed product or the complex mixtures. Many solvents like DMF, THF, toluene, and ether were also screened. The required product **68** was observed

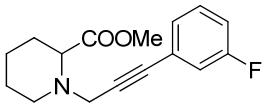
when LiHMDS was used as a base in DMF with 10% yield. So the reaction was performed under various solvents using LiHMDS as a base. Best result was obtained when we used 1.5 equiv of LiHMDS and THF as a solvent, thus chosen as the standard condition.

Table 2 Synthesis of *N*-propargyl pipecolinic ester derivatives

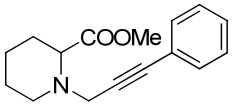




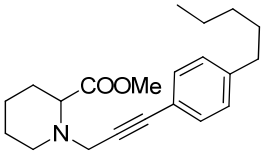
58, 12 hr, 40%



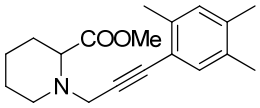
59, 12 hr, 52%



60, 12 hr, 50%



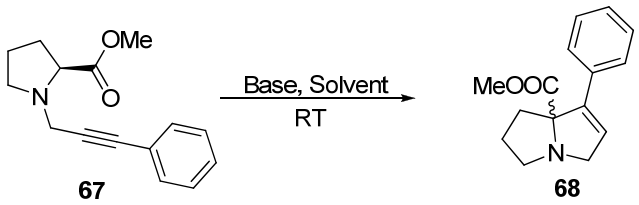
61, 12 hr, 39%



62, 12 hr, 43%

The structure of **68** was characterized via various characterization techniques like NMR, FTIR and HRMS. Since the concept of *'memory of chirality'* is often observed in *α*-alkylation chemistry of amino acids, we expected transfer of chirality in our products also. But, unfortunately, we did not observe any optical rotation in the final product. It has been well documented in the literature that the phenomena of *'memory of chirality'* was observed, when the experiments were performed at low temperatures. But in our case, all reactions were carried out at room temperature hence we observed racemic mixtures only. When we carried out the experiment at -78 ^{o}C using LDA or LiHMDS as a base in THF, we did not observe product **68** even after 12 hours. This observation clearly denotes that at this low temperature the enolate didn't react with the alkyne as it is not sufficiently electrophilic at lower temperature.

Table 3 Optimization studies



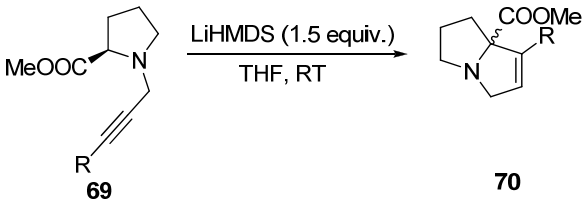
67 **68**

S. No.	Base(Equiv.)	Solvent	Temperature(^{0}C)	Yield
1	NaH (1.2)	DMF	RT	0
2	KO^{t}Bu (1.2)	Toluene	RT	Decomposed
3	LDA (1.2)	THF	-40^{0}C-RT	Complex mix.
4	Et_3N (1.5)	THF	RT	NR
5	LiHMDS (1.5)	ETHER	RT	50
6	LiHMDS (2.5)	DMF	RT	10
7	**LiHMDS (1.5)**	**THF**	**RT**	**70**

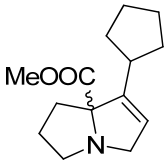
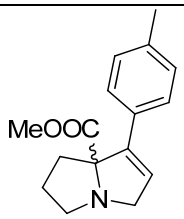
Having this optimized condition in hand, we shifted our attention towards synthesis of pyrrolizidine and indolizidine core. In this regard, two *N*-propargyl-L-proline derivatives **71**, **72** containing aliphatic and aromatic substituent at the alkyne were tested for the cyclization reaction. In both the cases **71**, **72** the required products were obtained in moderate yields (Table 4). Although, in both the cases, the conversion was more than 90% (by TLC), the products were isolated only in moderate yields after purification through column chromatography. It is well documented in the literature that pyrrolizidine derivatives are prone to undergo decomposition during column chromatography.[23] This explains the reason for getting lower yield of products in our case after chromatographic purification.

The similar reaction condition was applied for the synthesis of indolizidine derivative **58**, **60** using as a starting material. Unfortunately, the required product was not observed, and the reaction mixture was decomposed in most conditions. The optimization is still under progress.

Table 4. Base promoted 5-*endo-dig* cyclization



69 **70**

 **71,** 2 hr, 50%	 **72,** 2 hr, 60%

3.1 *Conclusion*:

An efficient, base promoted *5-endo-dig* cyclization strategy has been developed for the synthesis of bicyclic core of pyrrolizidine alkaloids. A diverse range of *N*-propargy-L-proline esters, prepared from aliphatic and aryl substituted terminal alkynes, underwent smooth conversion to the respective cyclized products under the reaction conditions. Further exploration of this methodology to prepare indolizidine core is currently under investigation.

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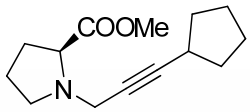
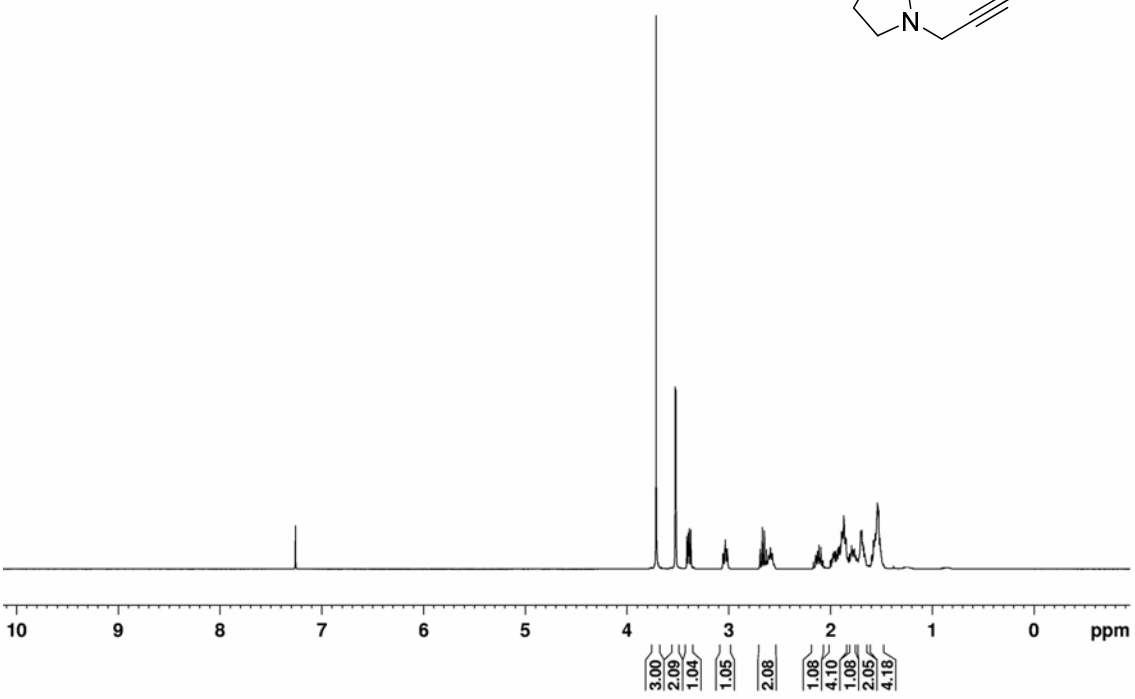
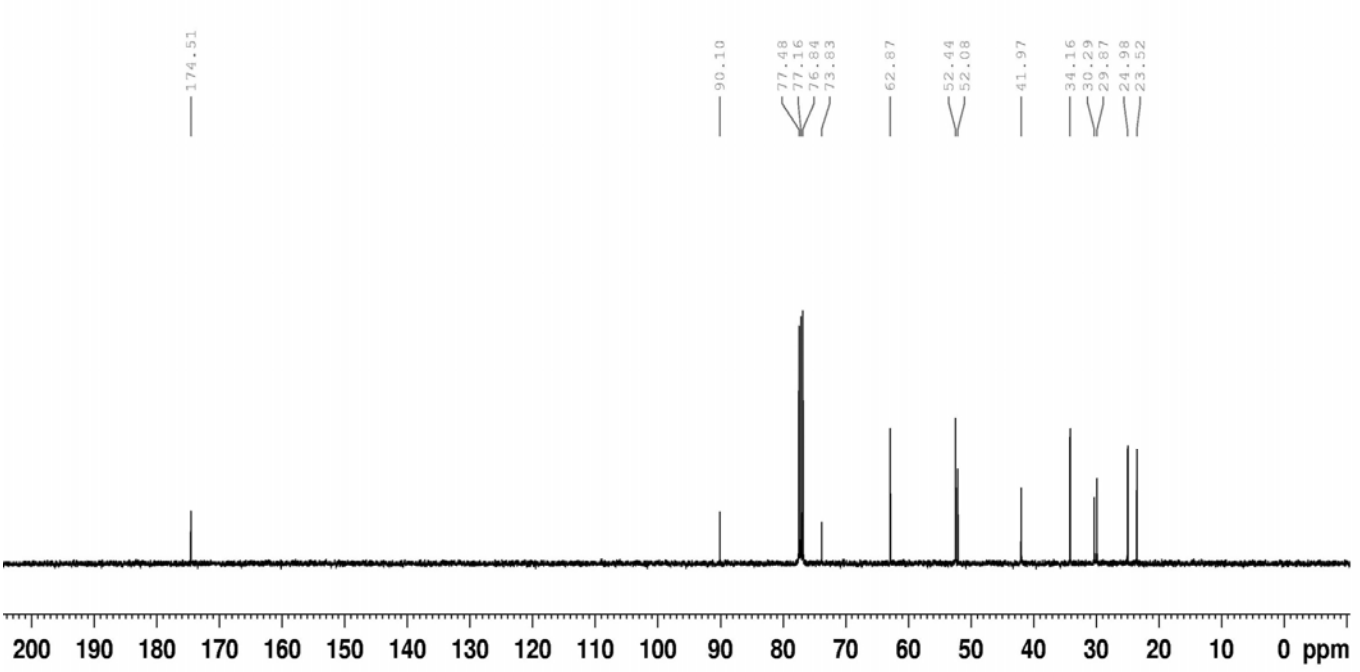
Chapter 4
Spectral Data

^{1}H and ^{13}C NMR spectra for **49**







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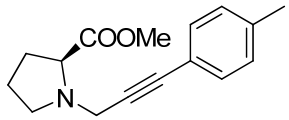

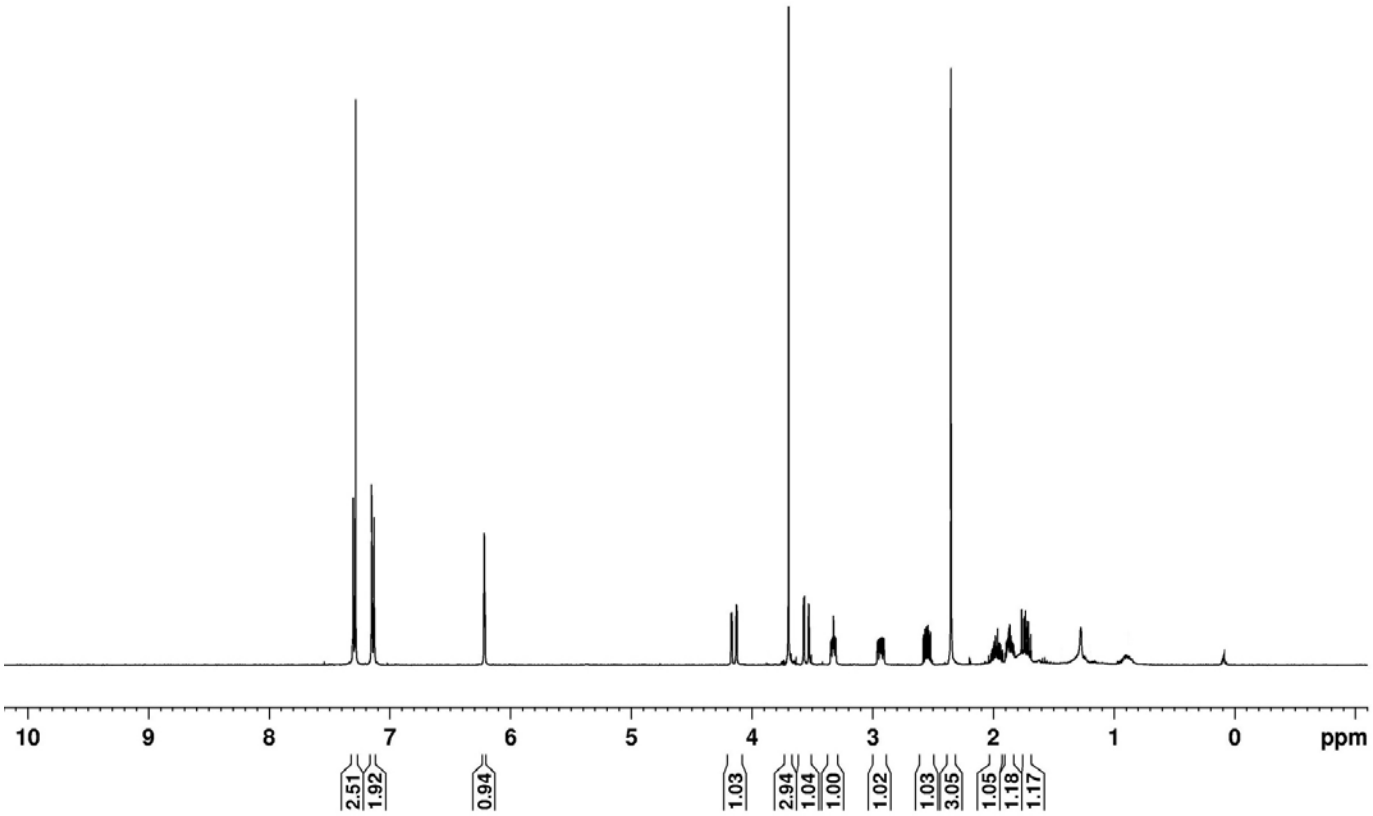

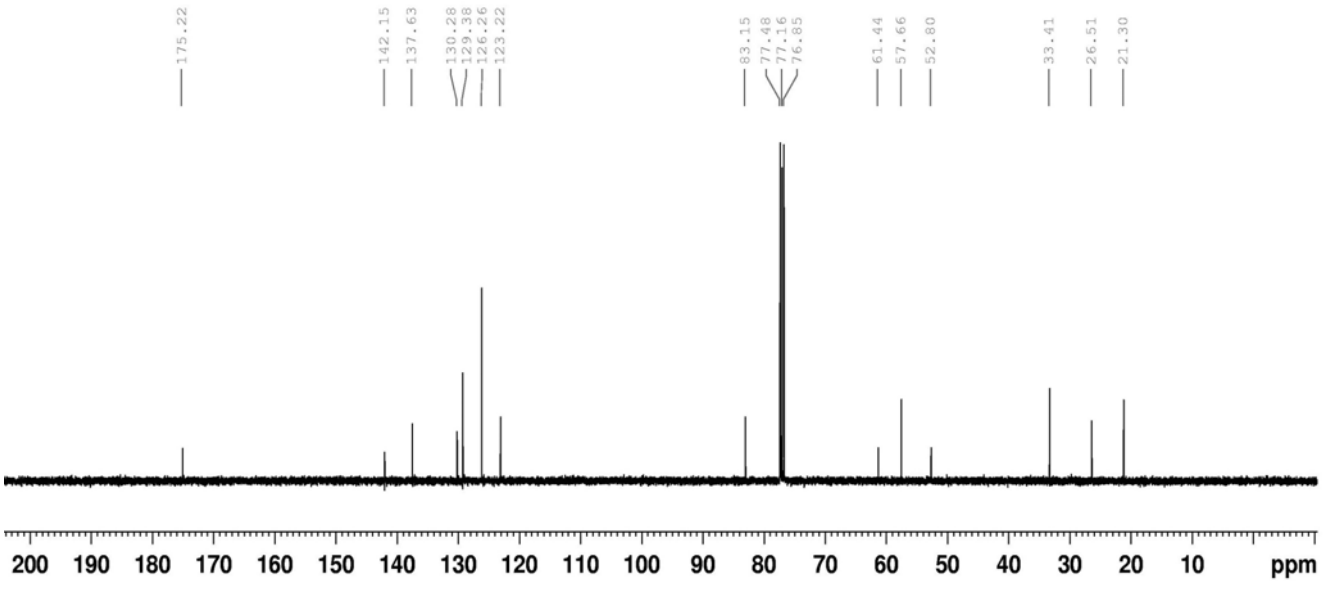

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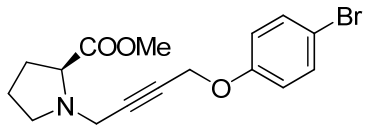

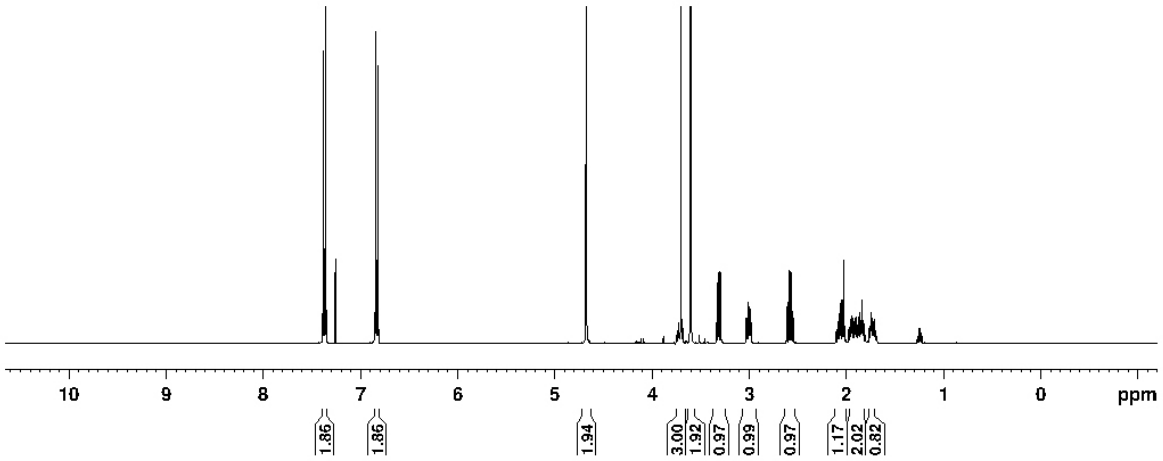

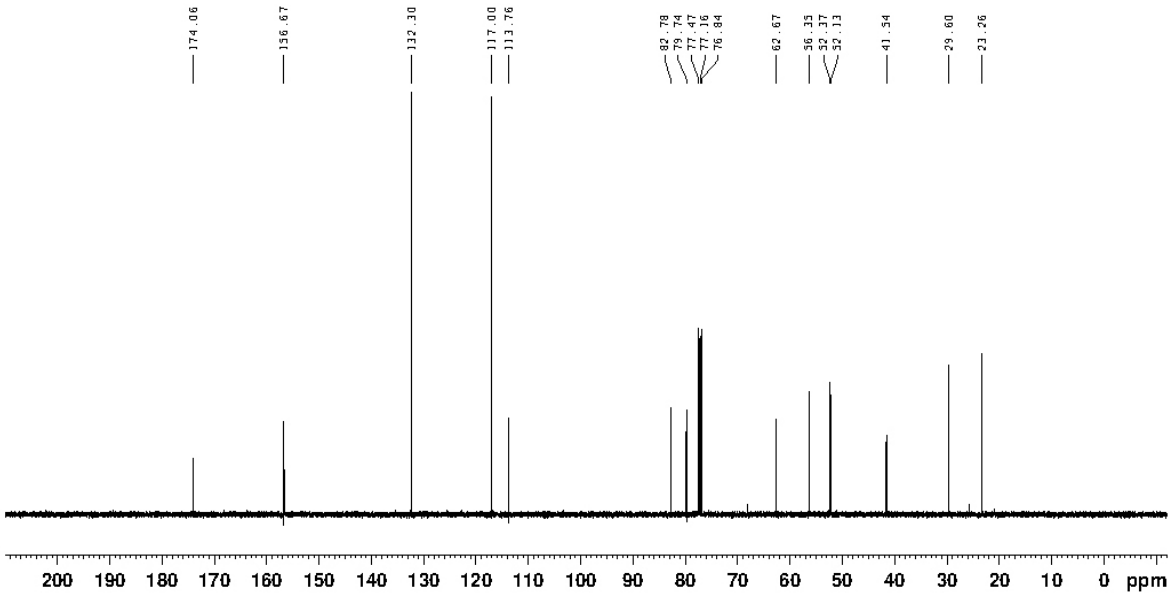

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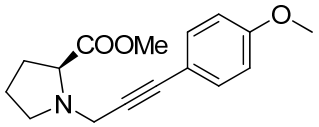

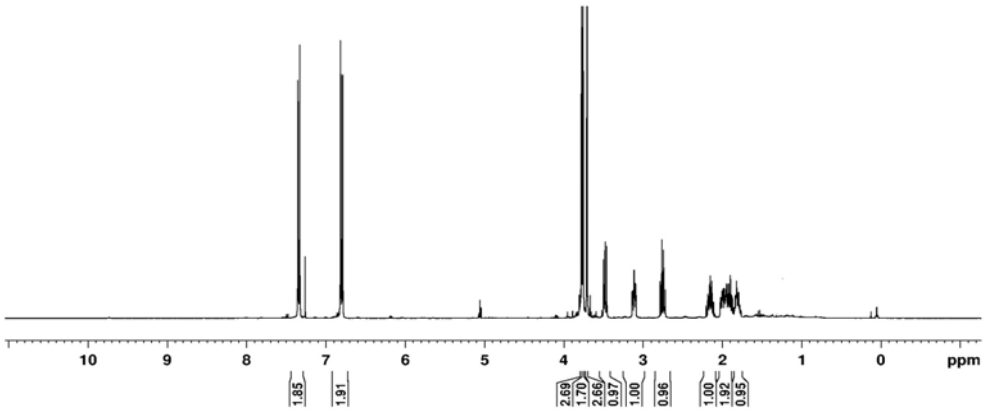

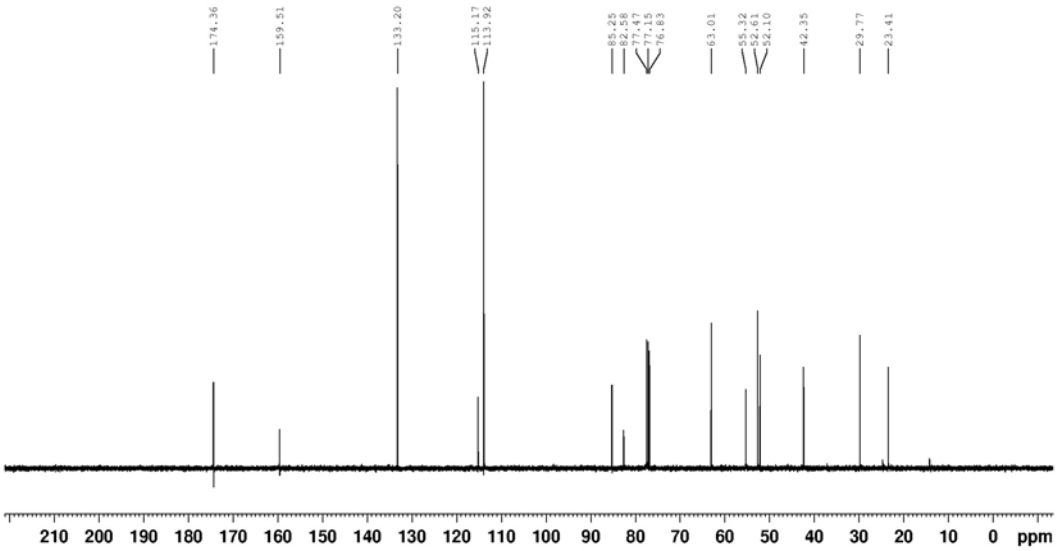

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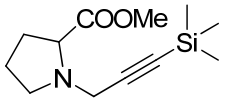

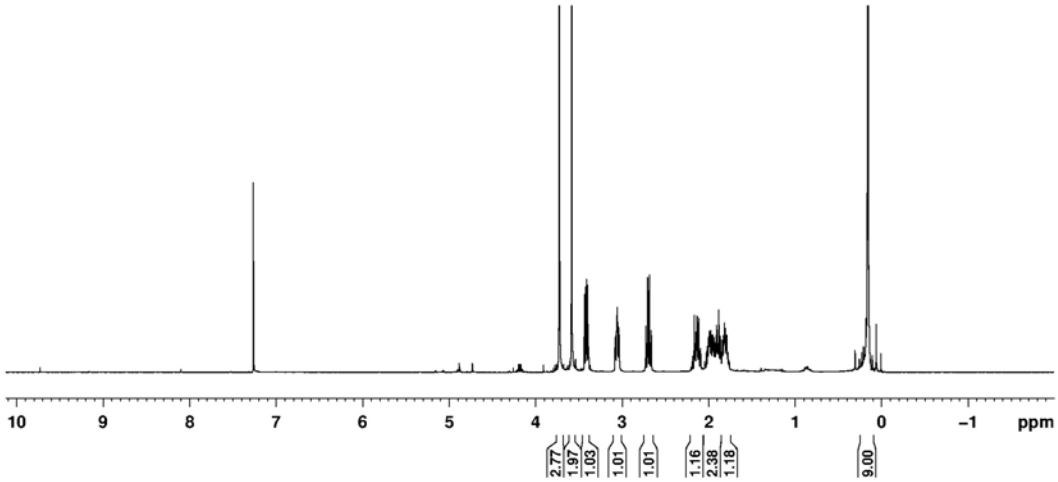

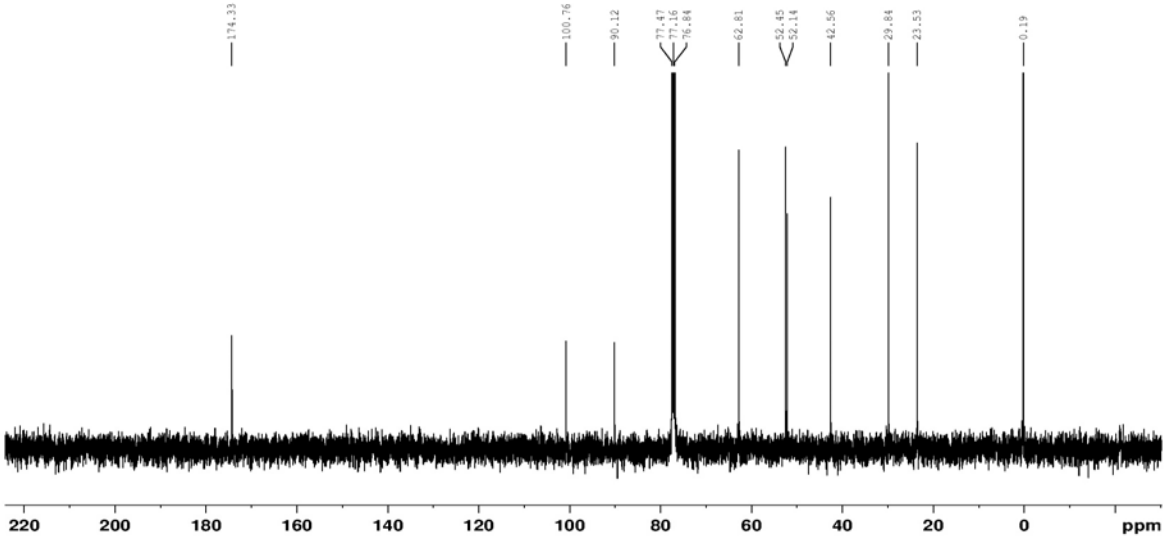

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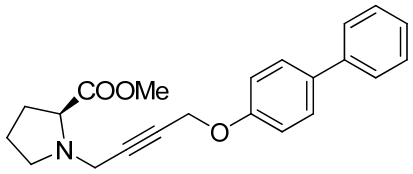

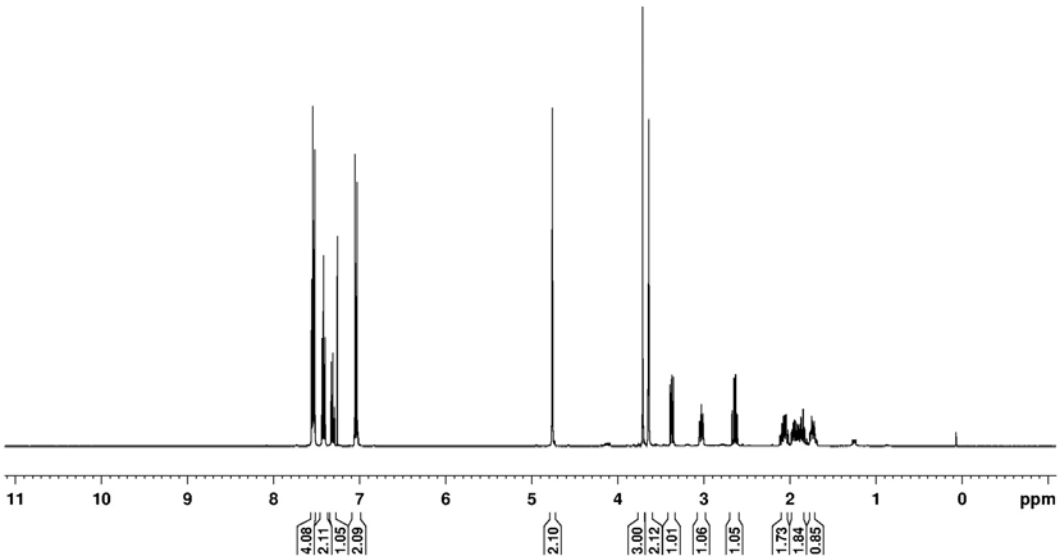

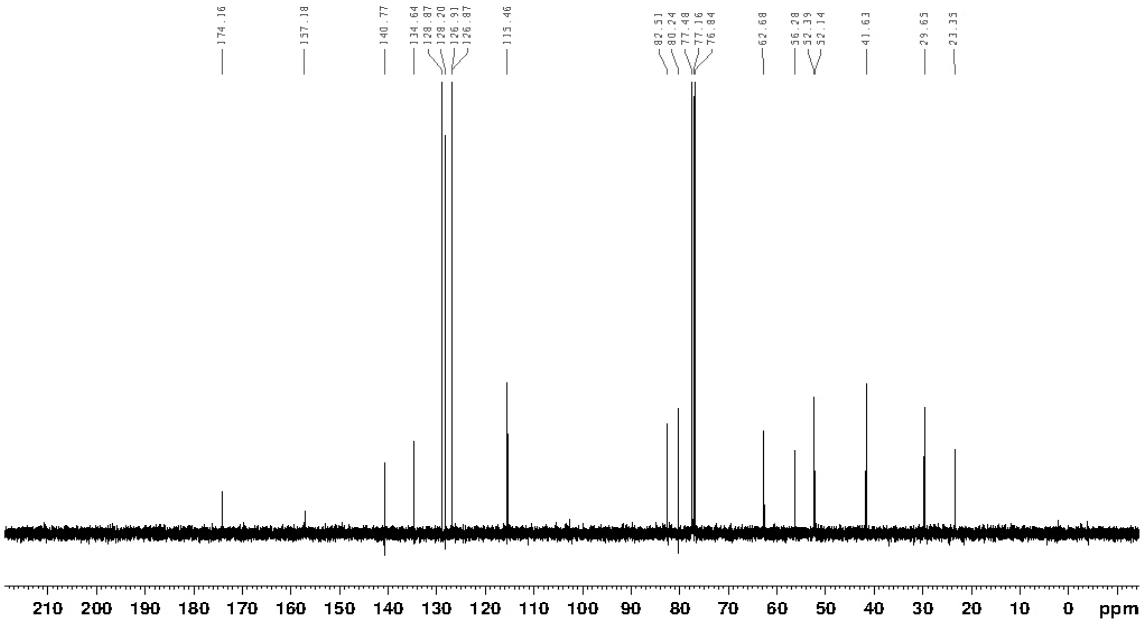

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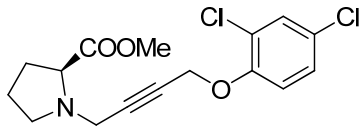
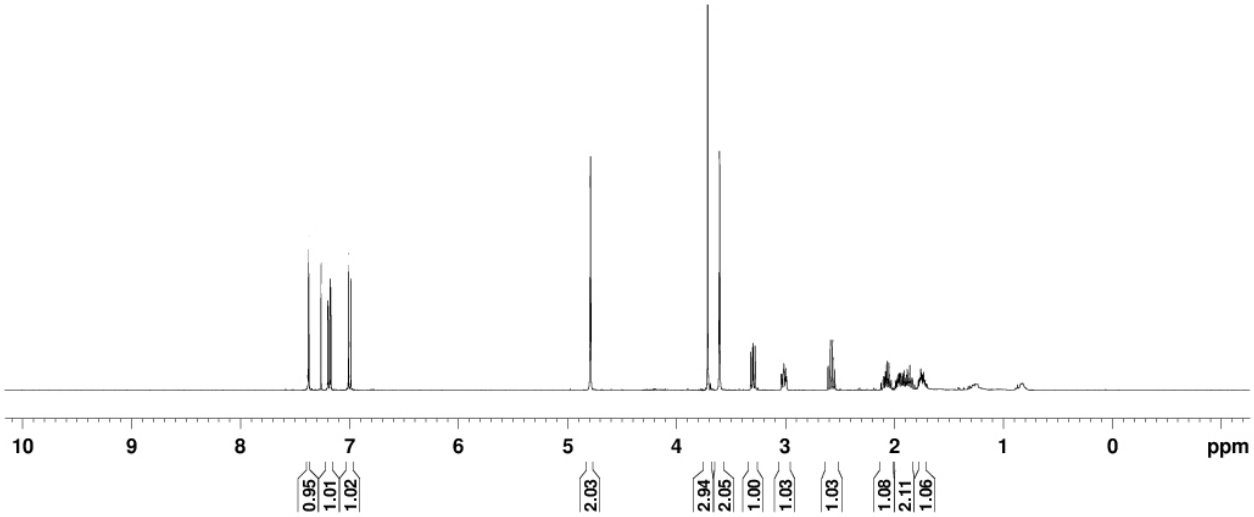
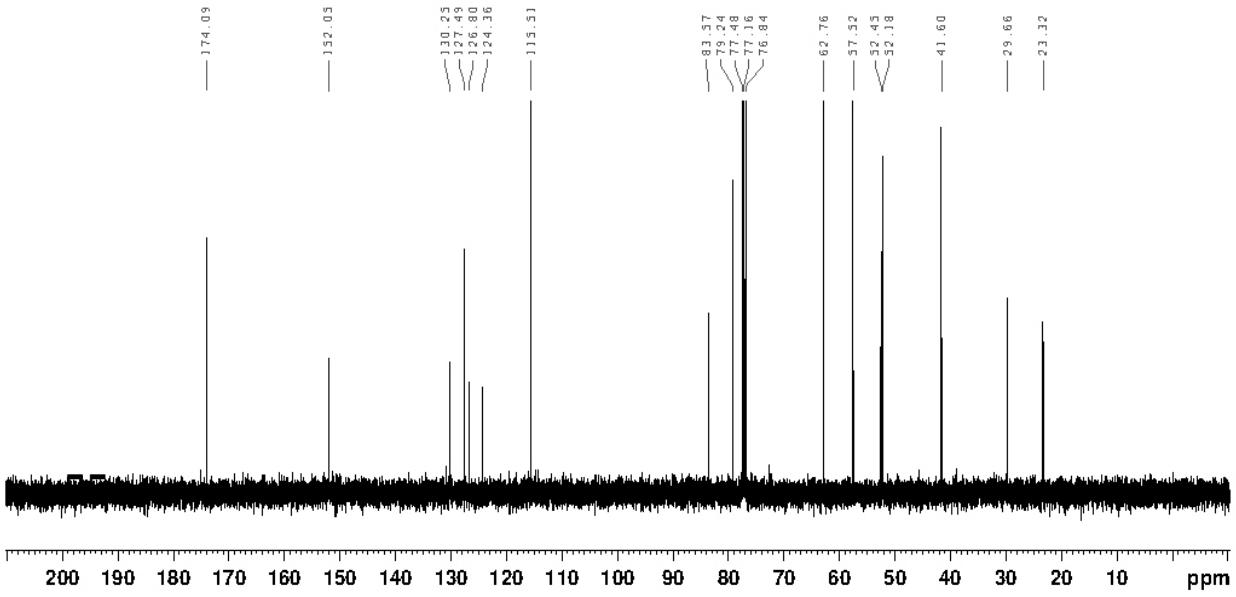
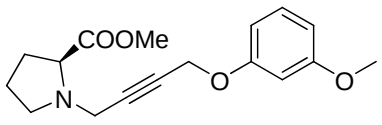
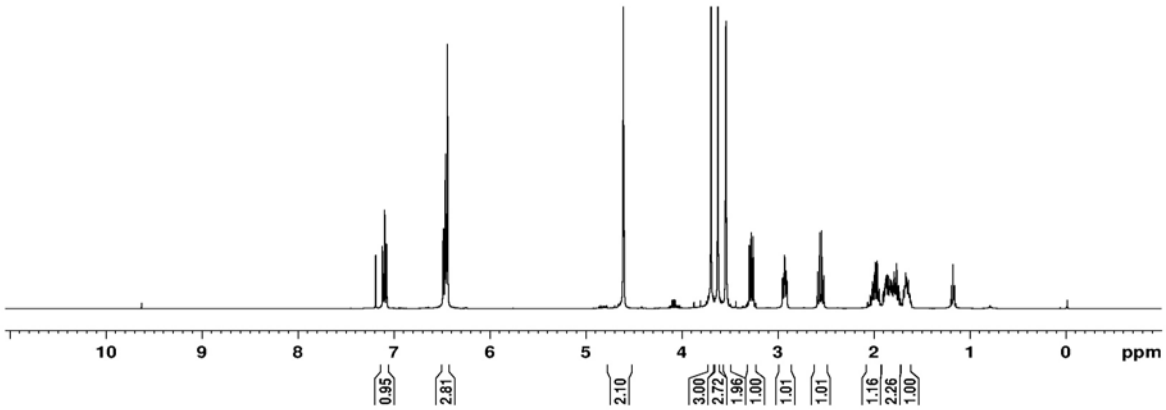


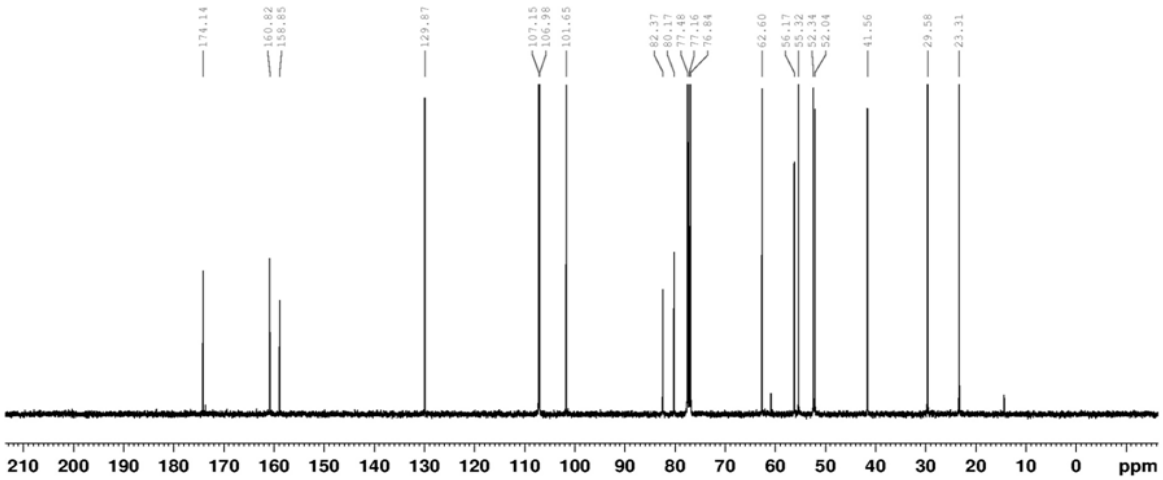




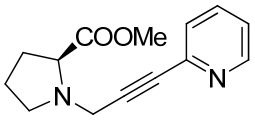
^{1}H and ^{13}C NMR spectra for **56**

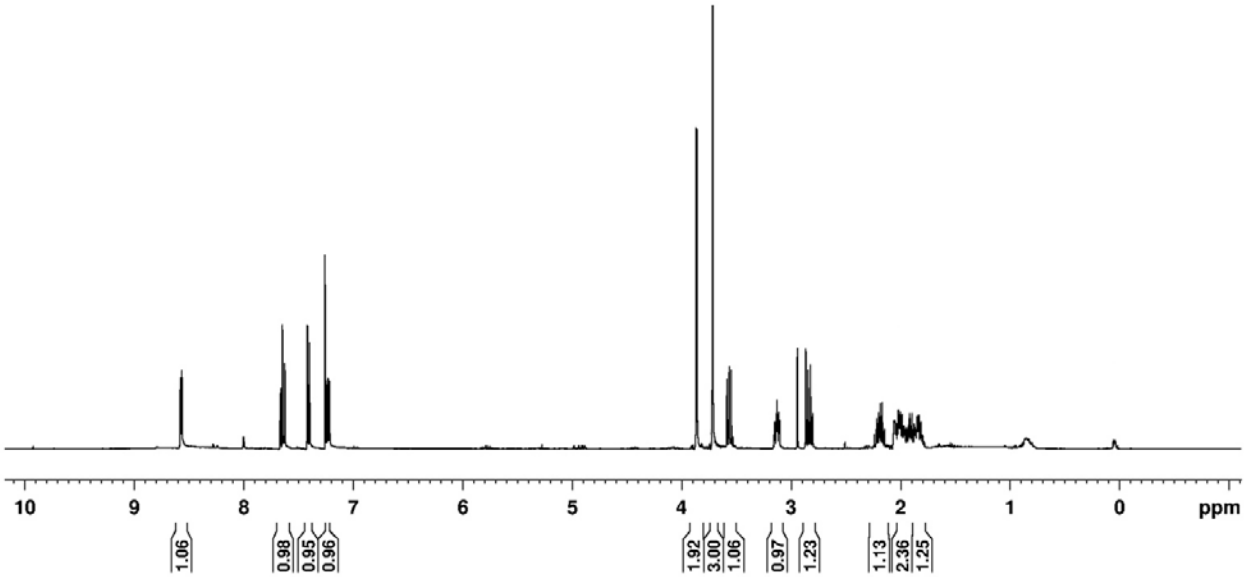


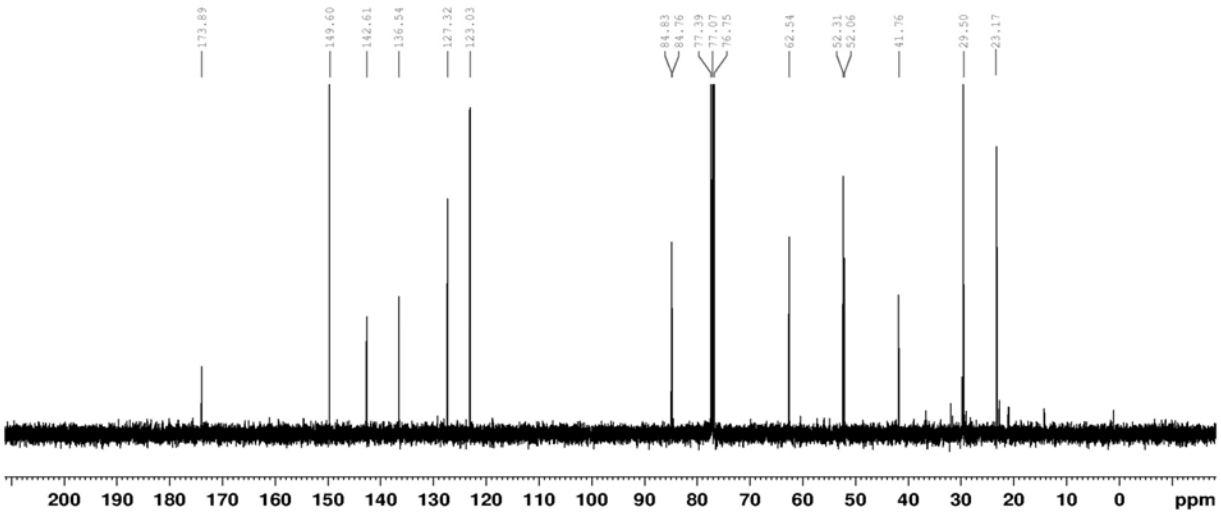




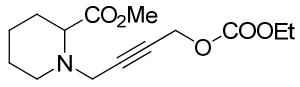
^{1}H and ^{13}C NMR spectra for **57**

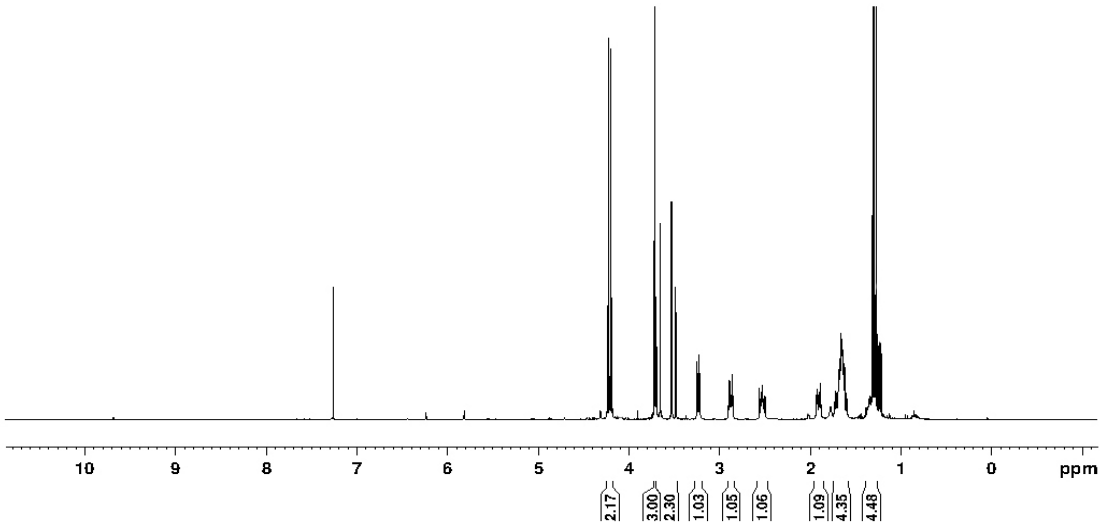


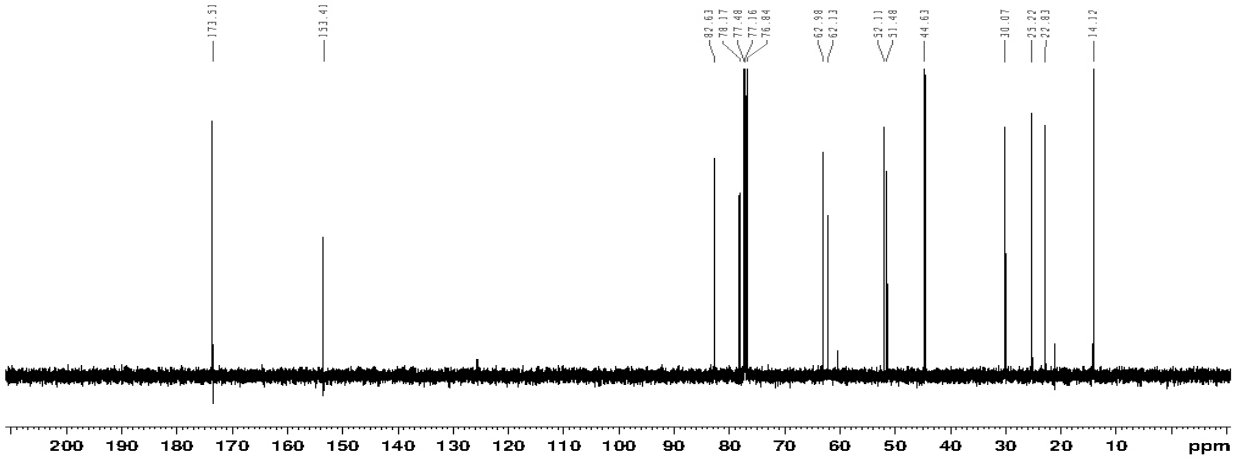




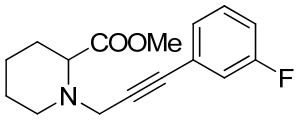
^{1}H and ^{13}C NMR spectra for **58**

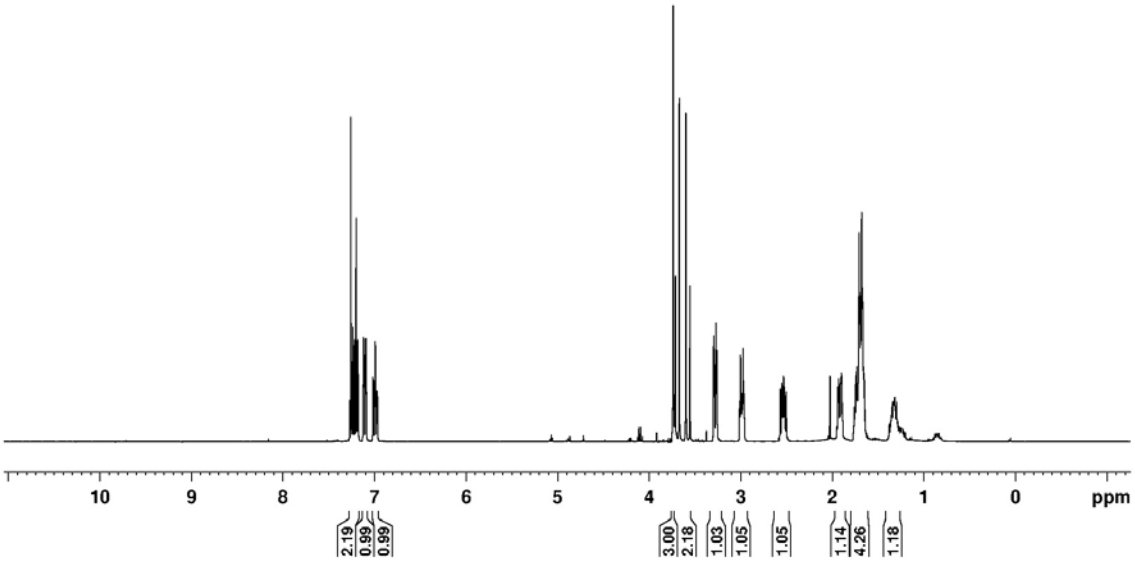


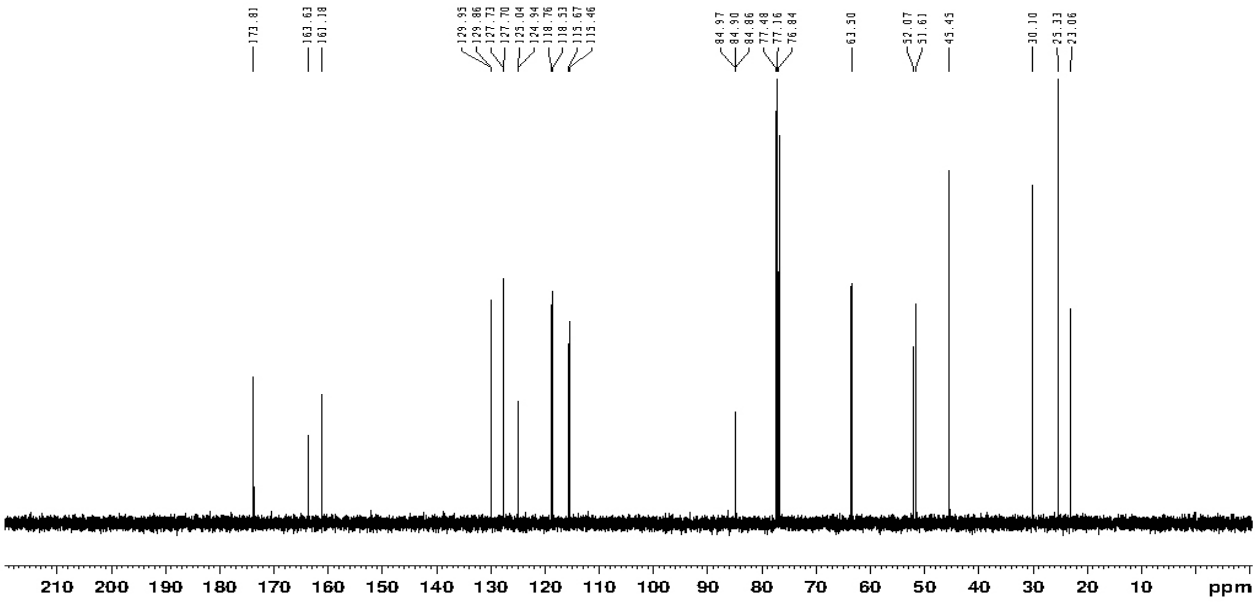




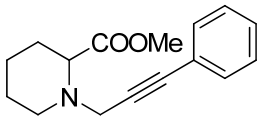
^{1}H and ^{13}C NMR spectra for **59**

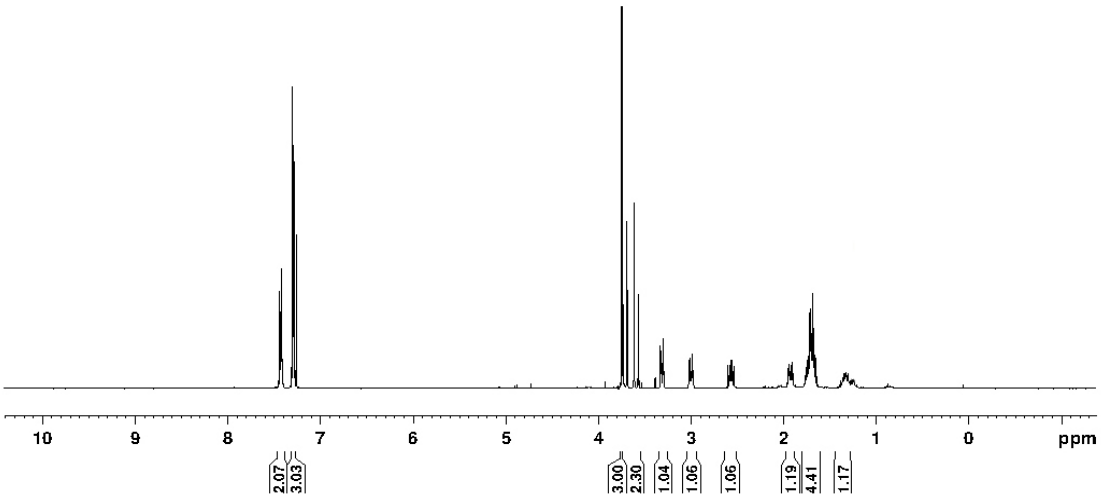


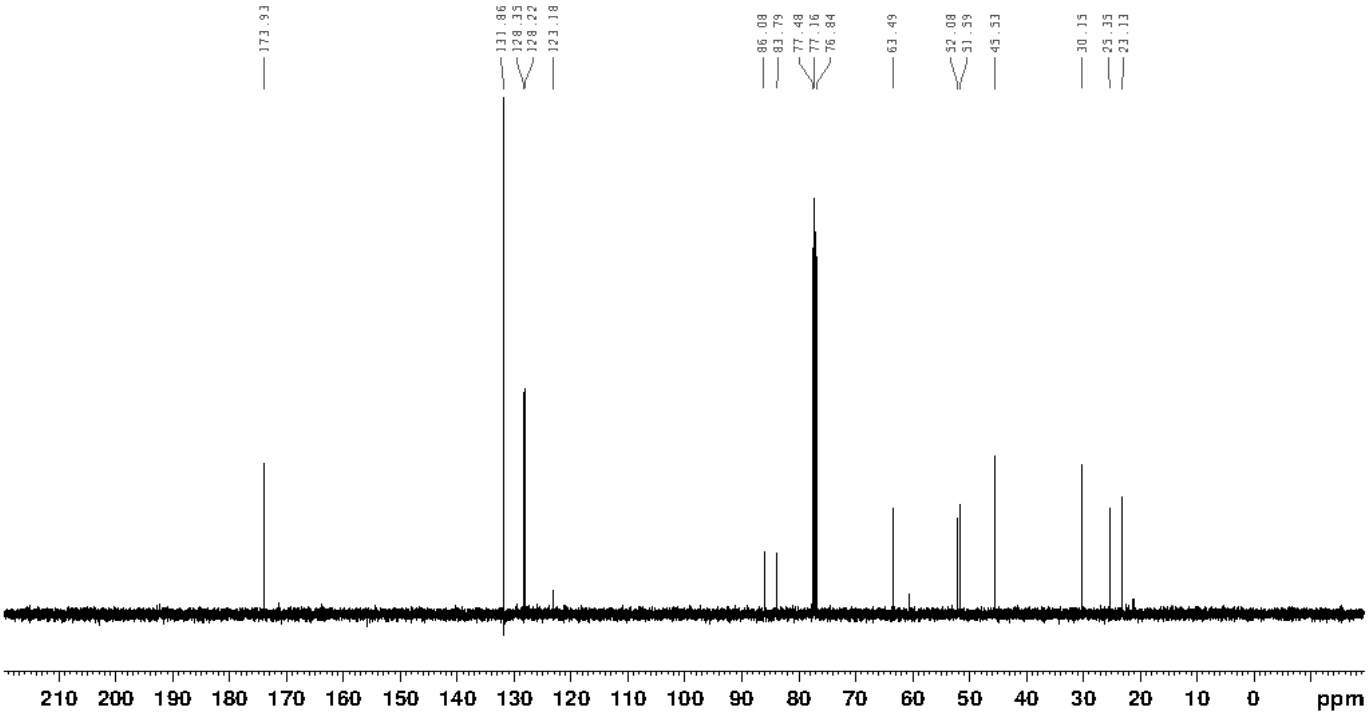




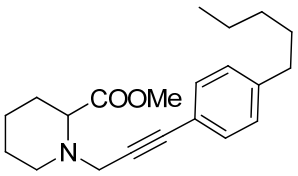
^{1}H and ^{13}C NMR spectra for **60**

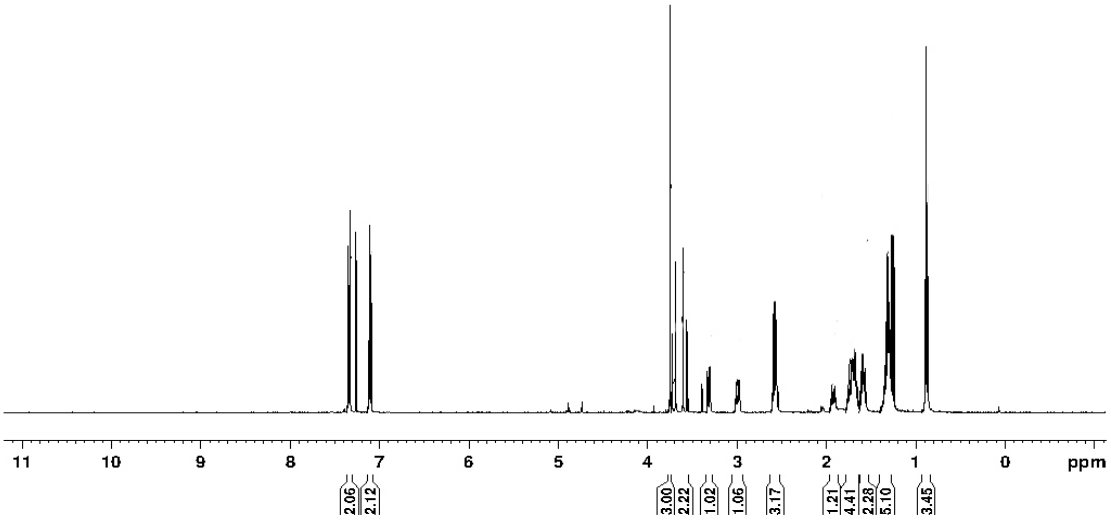


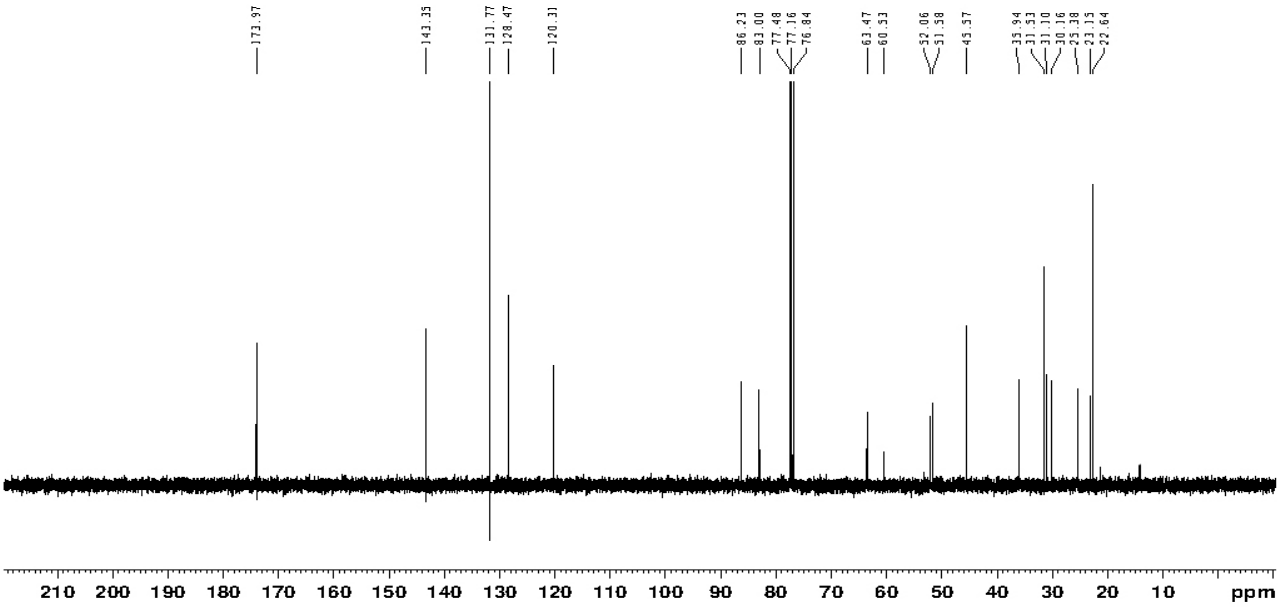




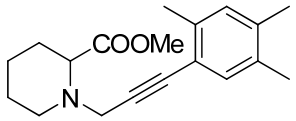
^{1}H and ^{13}C NMR spectra for **61**

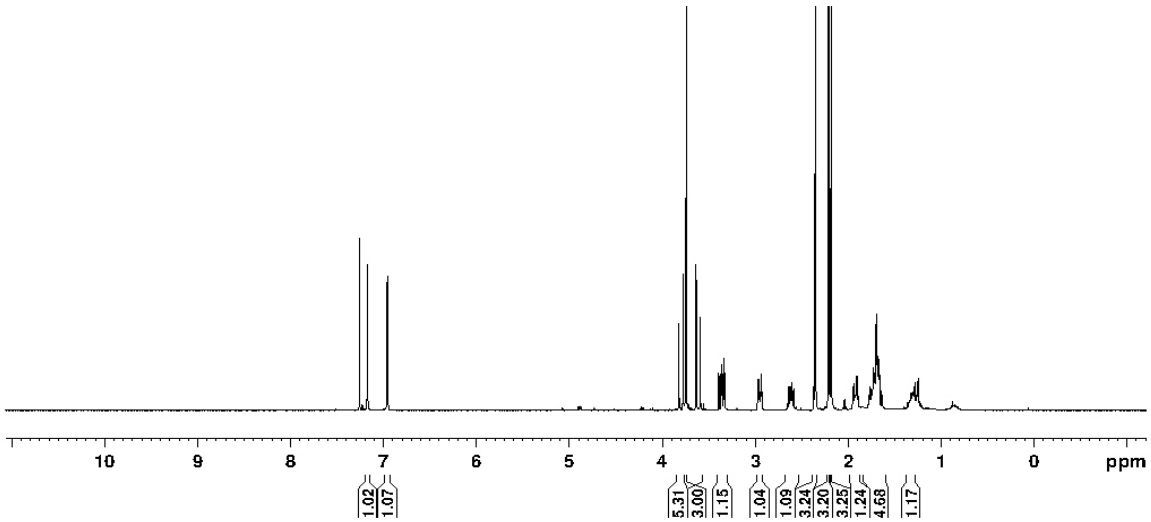


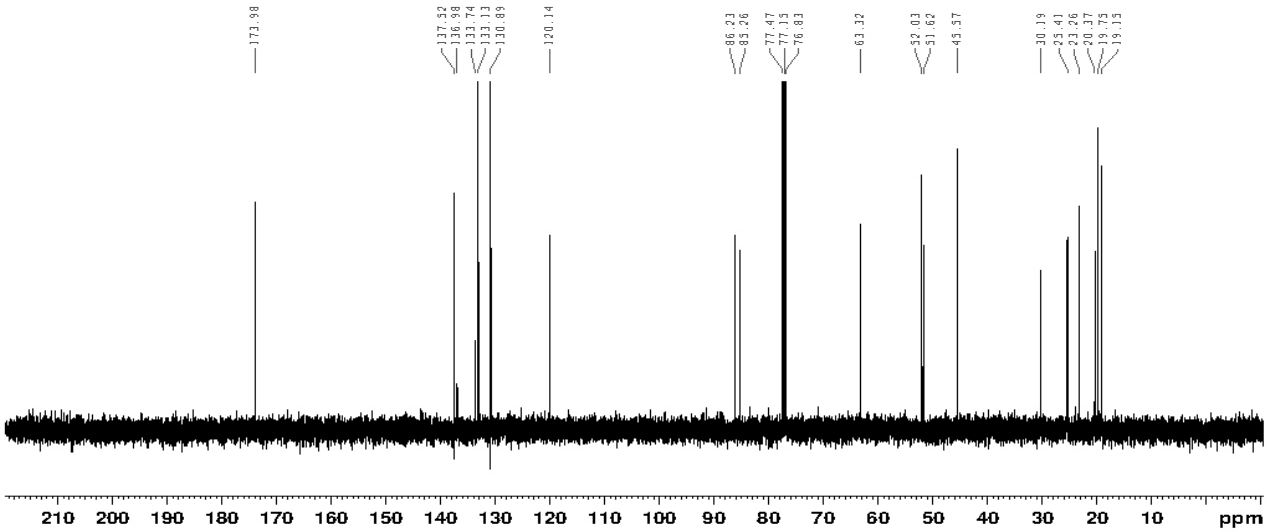




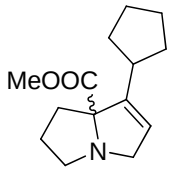
^{1}H and ^{13}C NMR spectra for **62**

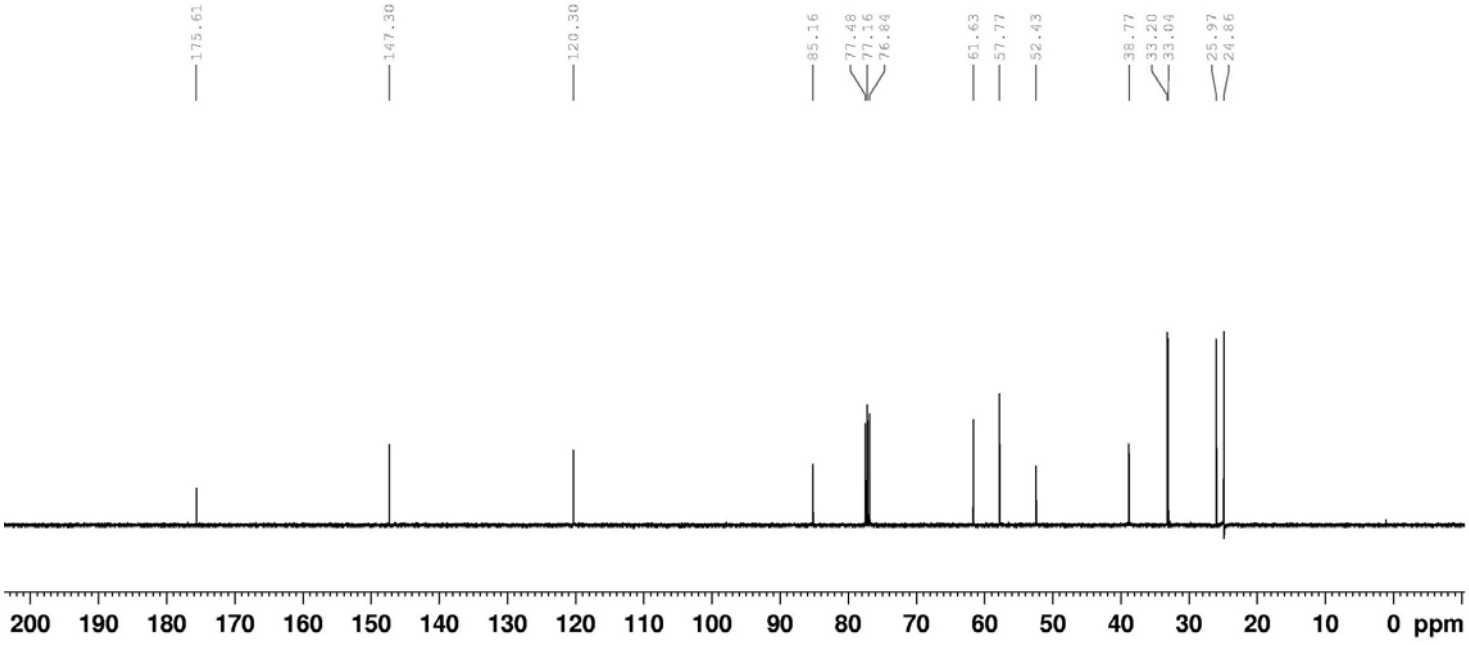




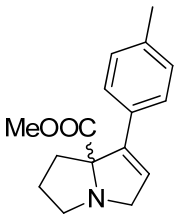


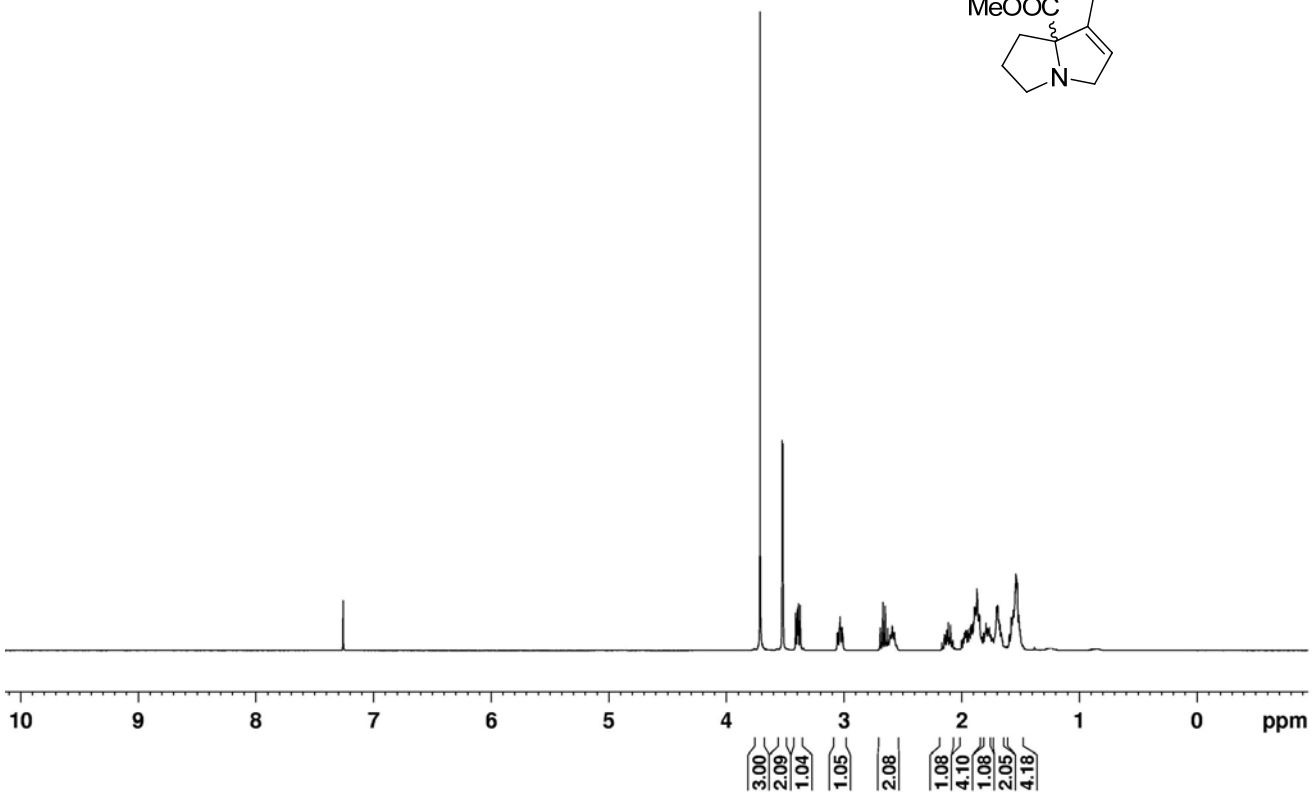
^{1}H and ^{13}C NMR spectra for **71**

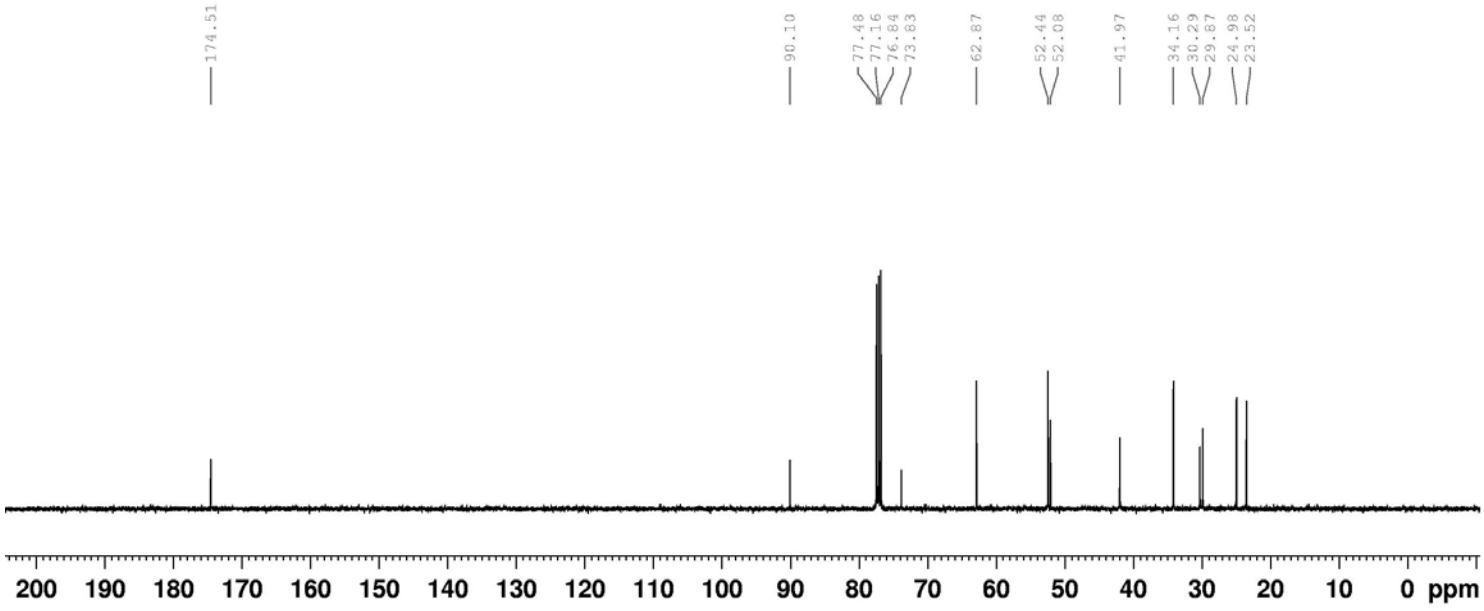




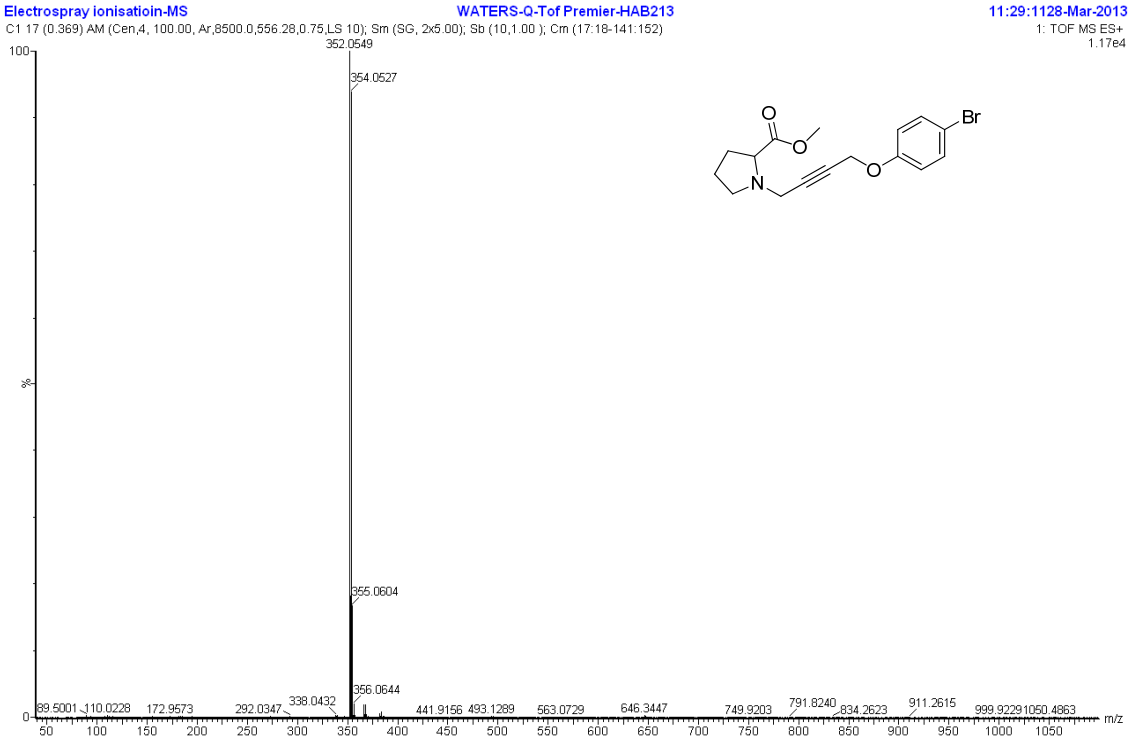
^{1}H and ^{13}C NMR spectra for **72**



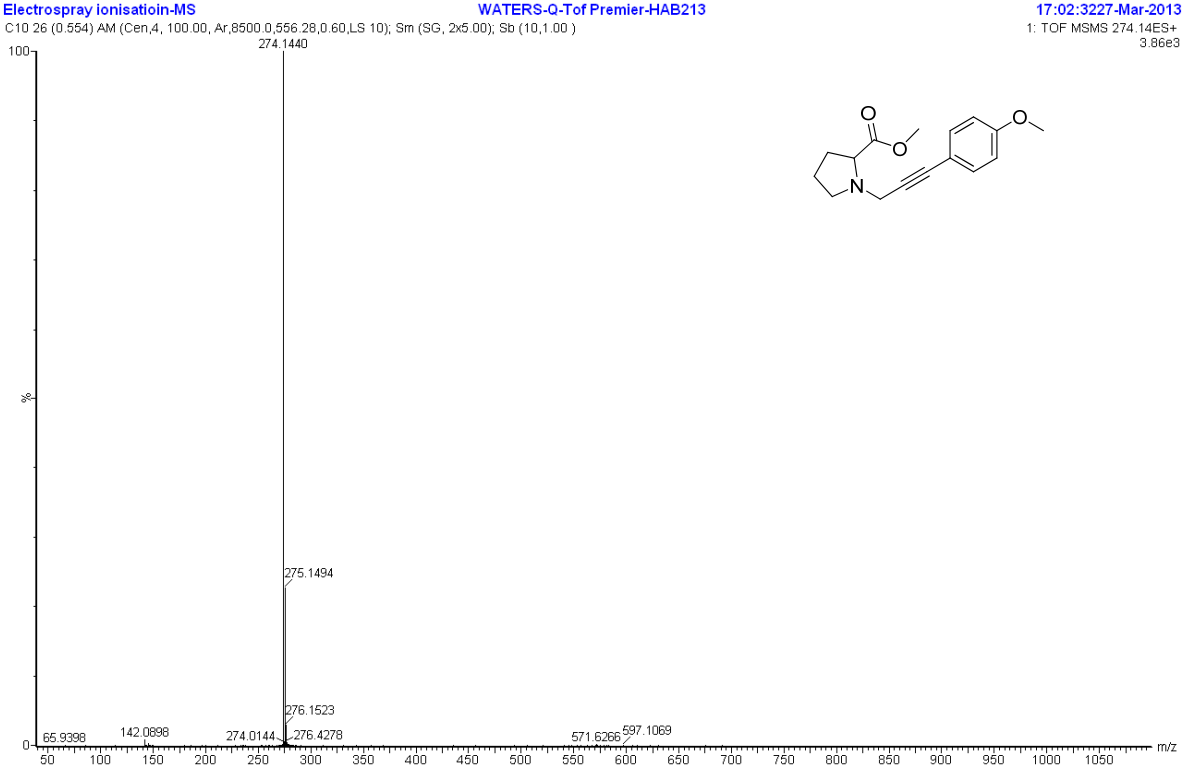




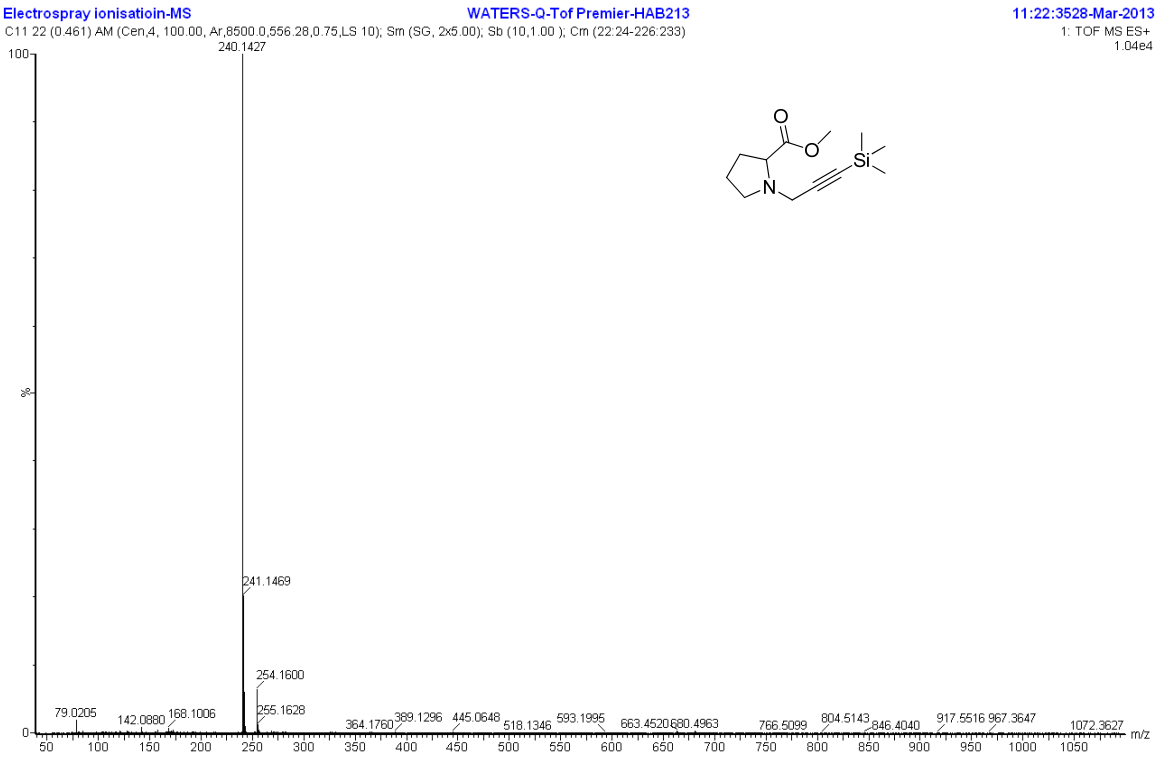
High resolution mass spectrum for **51**



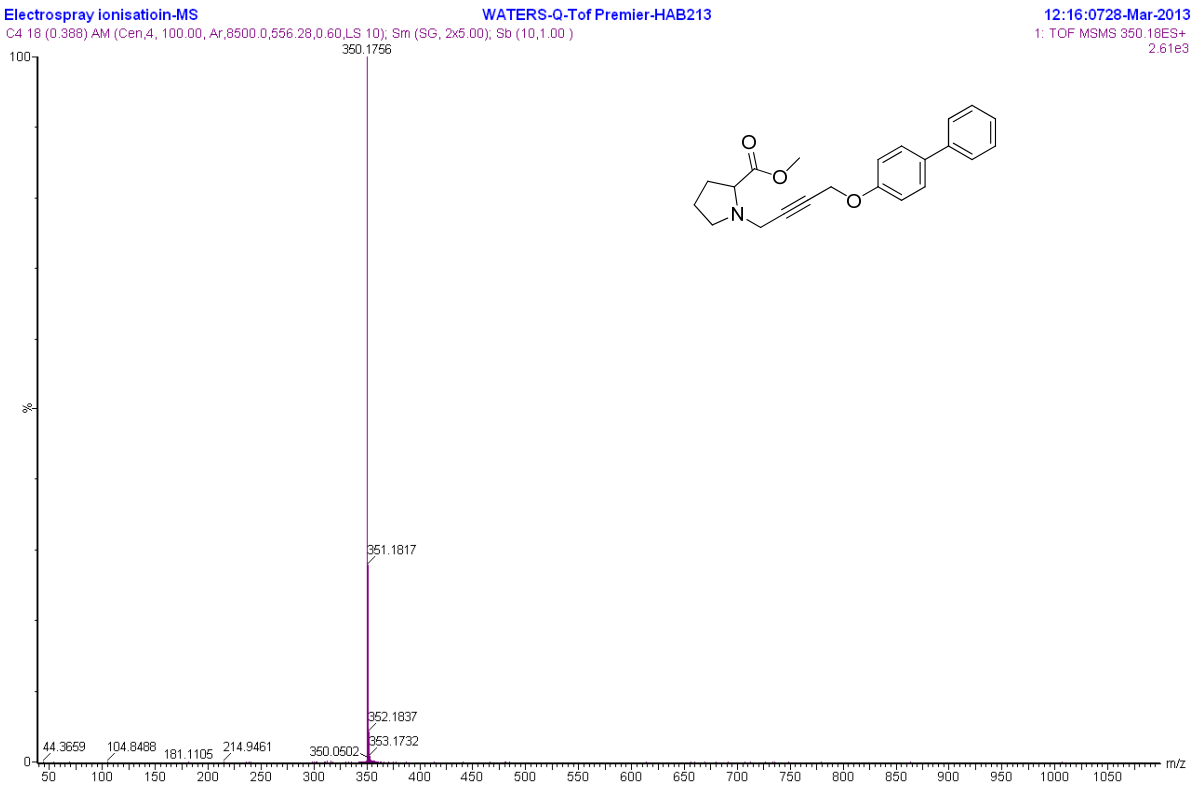
High resolution mass spectrum for **for 52**



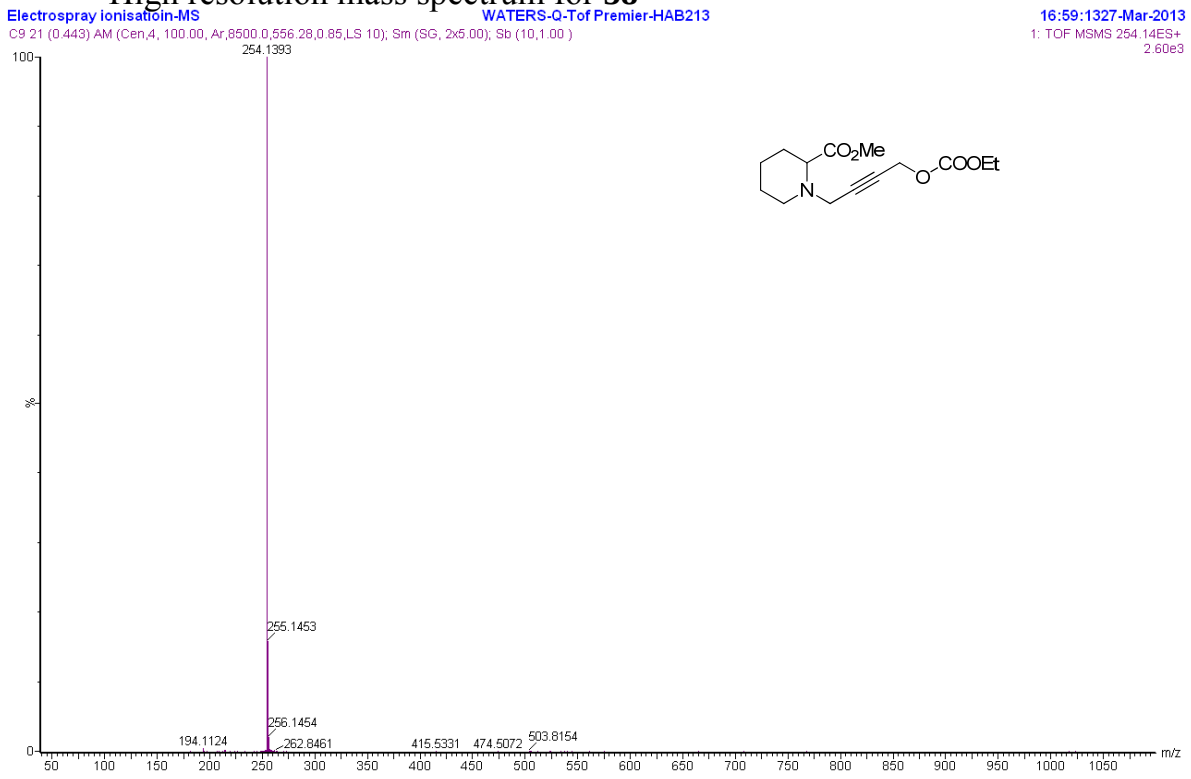
High resolution mass spectrum for **53**



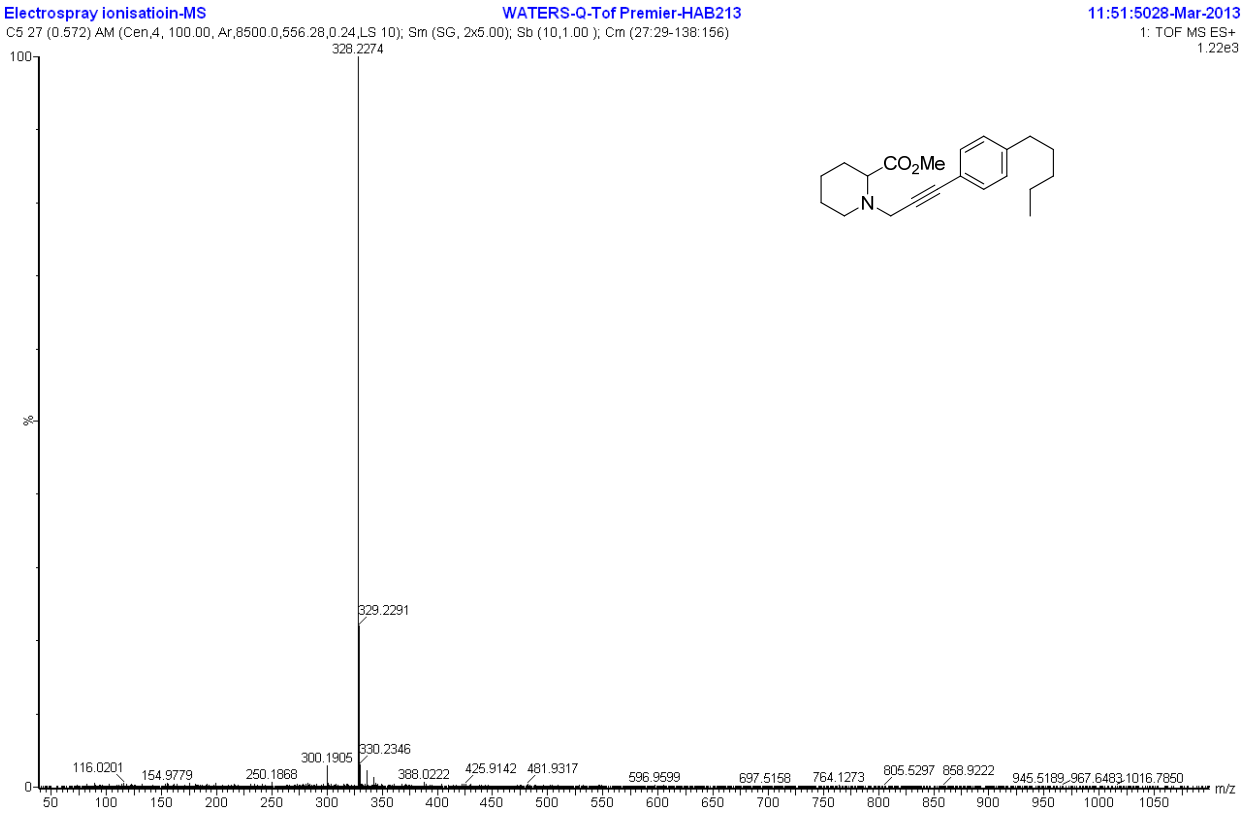
High resolution mass spectrum for **54**



High resolution mass spectrum for **58**



High resolution mass spectrum for **61**



High resolution mass spectrum for **60**