DEVELOPMENT OF TRANSITION-METAL-FREE POT-ECONOMY STRATEGIES FOR ACCESSING VALUE-ADDED PYRIDINES AND 1,3-DIARYLALLYLIDENE PYRAZOLONES

Ph.D. Thesis

By

ASHVANI KUMAR PATEL



DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY INDORE

DECEMBER 2024

DEVELOPMENT OF TRANSITION-METAL-FREE POT-ECONOMY STRATEGIES FOR ACCESSING VALUE-ADDED PYRIDINES AND 1,3-DIARYLALLYLIDENE PYRAZOLONES

A THESIS

Submitted in partial fulfilment of the requirements for the award of the degree

of

DOCTOR OF PHILOSOPHY

by

ASHVANI KUMAR PATEL



DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY INDORE

DECEMBER 2024

INDIAN INSTITUTE OF TECHNOLOGY INDORE

I hereby certify that the work which is being presented in the thesis entitled **"DEVELOPMENT OF TRANSITION-METAL-FREE POT-ECONOMY STRATEGIES FOR ACCESSING VALUE-ADDED PYRIDINES AND 1,3-DIARYLALLYLIDENE PYRAZOLONES"** in the partial fulfilment of the requirements for the award of the degree of **DOCTOR OF PHILOSOPHY** and submitted in the **DEPARTMENT OF CHEMISTRY, INDIAN INSTITUTE OF TECHNOLOGY, INDORE**, is an authentic record of my work carried out during the period from **JULY 2019** to **DECEMBER 2024** under the supervision of **Prof. SAMPAK SAMANTA,** Professor, Indian Institute of Technology, Indore.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

Ashvani Kumar Patel
25/06/2025

Signature of the Student with date

(ASHVANI KUMAR PATEL)

This is to certify that the above statement made by the candidate is correct to the best of my/our knowledge.

25/06/2025

Signature of Thesis Supervisor with date

(Prof. SAMPAK SAMANTA)

Mr. ASHVANI KUMAR PATEL has successfully given his Ph.D. Oral Examination held on **25th June 2025**.

25/06/2025

Signature of Thesis Supervisor with date

(Prof. SAMPAK SAMANTA)

ACKNOWLEDGEMENT

"Interdependence is a choice only independent people can have."

This research work presented here to achieve my PhD degree is not only my individual effort but also the generous efforts of numerous benevolent people. I take this opportunity to acknowledge them and convey my sincere gratitude for making it possible for me to complete my PhD thesis.

First and foremost, I am extremely grateful to *Prof. Sampak Samanta,* Professor, Department of Chemistry, IIT Indore, for believing in me and providing me with an opportunity in his esteemed research group. His perceptive guidance, constant support, and continuous encouragement throughout the PhD program motivated me to continue my research with much more enthusiasm and freedom.

I am highly thankful to my PSPC members, *Prof. Shaikh M. Mobin* and *Dr. Dipak K. Roy,* for their valuable advice and encouragement during the Comprehensive Evaluation of Research Progress (CERP) and other research activities.

I wish to express my esteemed gratitude to *Prof. Suhas S. Joshi,* the Director of IIT Indore, for providing excellent infrastructure and facilities on the campus.

I want to extend my sincere thanks to *Prof. Tushar Kanti Mukherjee,* Head of the Department of Chemistry and other faculty members which include, *Prof. Rajneesh Misra, Prof. Suman Mukhopadhyay, Prof. Apruba K. Das, Prof. Biswarup Pathak, Prof. Sanjay Kumar Singh, Dr. Tridib Kumar Sarma, Prof. Anjan Chakraborty, Prof. Satya S. Bulusu, Prof. Chelvam Venkatesh, Dr. Amrendra Kumar Singh, Dr. Debayan Sarkar, Dr. Abhinav Raghuvanshi, Dr. Selvakumar Sermadurai, Dr. Umesh A. Kshirsagar, and Dr. Pravarthana Dhanapal,* for their guidance and help during various activities in the department and creating the proper environment for research.

Many thanks to the anonymous reviewers for their valuable suggestions and feedback during the peer review process of the article publication.

I would like to extend my gratitude to the technical staff from the Sophisticated Instrumentation Centre (SIC) and our Department of Chemistry, at IIT Indore, *Dr. Kinny Pandey, Dr. Ravinder Kumar, Mr. Atul Singh, Mr. Manish Kushwaha, Mrs. Vinita Kothari, Mr. Shouvik Debnath, Mr. P. K. Parthiban, Mr. Ghanshyam Bhavsar* and *Mr. Rameshwar Dauhare,* for their kind patience and timely technical support throughout my PhD journey. It's my pleasure to express my sincere regards to *Mr. Tapesh Parihar, Mr. Kailash Jamra* and *Mr. Rahul Shrivas* from the Academic Office, IIT Indore.

My acknowledgement will never be complete without the special mention of my lab seniors, who have taught me the importance of a healthy work-life balance. I would like to convey my deepest thanks to *Dr. Debashis Majee, Dr. Soumitra Guin, Dr. Anubha Yadav, Dr. Meher Prakash* and *Dr. Monika Ahuja* for their continuous moral support and help in laboratory work. I am thankful to my lab mates, *Mrs. Rajni Lodhi, Ms. Shikha S. Rathor* and *Mr. S. Banuprakash Goud* for giving me a favourable environment around my workplace. I am happy to thank my supportive juniors, *Ms. Poonam Goyal, Mr. Sajal Halder, Mr. Raju L, Mr. Shishupal Kushwah, Mr. Hritik Kaushal, Mr. Pundalik Baliram, Mr. Kevin Patel* and *Mr. Sanjay Yadav,* for giving me cheerful surroundings.

I want to express my heartiest gratitude to my seniors and friends, *Dr. Pankaj K. Samal, Mr. Animesh Niranjan, Mr. Natwar Singh, Dr. Rajesh Bhawale, Mr. Abhinay Chillal, Dr. Reena Kyarikwal, Dr. Argha Chakraborty, Dr. Sayantan Sarkar, Dr. Meenu Sharma, Dr. Saumya Jaiswal, Dr. Sivaparwathi Golla, Dr. Soumya Poshala, Mr. Arpan Ghosh, Dr. Yogajivan, Dr. Indresh Y, Dr. Dilip, Dr. Shivendra, Dr. Shivendu, Mr. Anrudh, Dr. Chinmaya Patel, Mr. Aditya Prasun, Dr. Avijit, Dr. Debanjan, Ms. Amrita, Ms. Vidhi, Mrs. Ekta, Ms. Achena, Ms. Ritika, Ms. Nisha, Mr. Nissar, Mr. Zahir, Mr. Rahul Y., Mr. Dilip, Mr. Abhishek, Mr. Ramakant M, Mr. Nikhil Ji, Mr. Ramakant G, Mr. Rahul S., Dr. Navdeep, Mr. Amardeep, Mr. Kalu Ram, Mr. Akshay, Mr. Lekhnath* and to all beloved friends in IIT Indore for their love and support with me.

I want to extend my deepest gratitude to all my teachers, *Prof. Sanjay Gupta*, *Prof. J. K. Agarwal*, *Prof. Shridhar Pathak* and *Prof. Rajiv K. Jain*, Banaras Hindu University, Varanasi; *Prof. I. Ajit K. Reddy*, *Prof. V. Rajeswar Rao*, *Prof. A. Ramachandraiah*, *Prof. Lakshma Reddy* and *Dr. Hari Prasad Kokatla*, National Institute of Technology, Warangal for their valuable teachings, blessings, guidance and continuous support.

The most important part of my life and each journey, i.e., my family; it would have been impossible for me to reach here without their support, care and love. I express my respect, love and gratitude to my family, especially my grandmother, *Late Kalawati Devi* and my grandfather, *Lalchand Kurmi.* I am extremely fortunate to have beloved parents, *Mr. Rajendra Kumar Singh* and *Mrs. Sushila Devi* and sisters *Reeta Patel* and *Sarita Patel,* their kindness, generosity and patience taught me invaluable lessons about life. My dearest brothers *Mr. Manish Patel* and *Shivendra Singh,* thank you for your love and unwavering support.

I am deeply thankful to the *Ministry of Education, Government of India* and *IIT Indore* for providing me with the necessary funding and fellowship to pursue research work.

Finally, I would like to *thank all the others* who supported and encouraged me directly or indirectly to make this journey successful.

Ashvani Kumar Patel

IIT Indore

Dedicated to

My Beloved Parents

and

Family

●●●●●●●●●●

TABLE OF CONTENTS

ABSTRACT	**XI-XII**
LIST OF PUBLICATIONS	**XIII-XIV**
LIST OF ABBREVIATIONS	**XV-XVII**
LIST OF FIGURES	**XVIII-XXX**
LIST OF SCHEMES	**XXXI-XXXV**
LIST OF TABLES	**XXXVI**

Chapter 1 1-34

General Introduction and Background: Pyridines and Pyrazolones

1.1	General Introduction	1
1.2	One-Pot Chemical Synthesis	1-2
1.3	Historical Background	3-7
1.3.1	Pyridine	3-5
1.3.2	Pyrazolone	6-7
1.4	Literature Study	8-25
1.4.1	Synthesis of Functionalized Pyridines	8
1.4.1.1	Classical Approaches	8-11
1.4.1.2	Modern Strategies	12-20
1.4.2	Synthesis of Pyrazolones	20-25
1.4.2.1	Synthesis of 4-alkylidene/ alkenylidene pyrazolones	20-25
1.5	Conclusion	25
1.6	The objective of my thesis	26
1.7	References	26-34

Chapter 2 35-129

A metal oxidant solvent-free pot-economy approach to access di and trisubstituted pyridines regioselectively *via* a domino reaction involving 3-chloropropiophenones

2.1	Introduction	35
2.2	Review Work	35-39
2.2.1	Synthesis of Pyridines	36-39
2.2.2	Conclusion	39
2.3	Present Work	40
2.4	Results and Discussion	40-51
2.4.1	Optimization of reaction conditions	41-43
2.4.2	Substrate Scope	44-48
2.4.3	Control Experiments	49-50
2.4.4	Plausible Mechanism	50-51
2.5	Conclusion	51-52
2.6	Experimental Section	52-67
2.7	Copies of ^{1}H and ^{13}C NMR of the described compounds	68-125
2.8	References	126-129

Chapter 3 131-252

Organocatalyzed double C(sp^3)–H alkylation of cyclic *N*-sulfonyl ketimines with 3-chloropropiophenones: for accessing value-added 2,3,6-trisubstituted pyridines

3.1	Introduction	131
3.2	Review Work	131-135
3.2.1	Synthesis of trisubstituted pyridines	132-135
3.2.2	Conclusion	135-136
3.3	Present Work	136
3.4	Results and Discussion	137-151
3.4.1	Optimization of reaction conditions	138-140
3.4.2	Substrate Scope	140-147
3.4.3	Control Experiments	148-149
3.4.4	Plausible Mechanism	149-151
3.5	Conclusion	151
3.6	Experimental Section	152-181
3.7	Copies of ^{1}H and ^{13}C NMR of the described compounds	182-249
3.8	References	250-252

Chapter 4 253-359

Organocatalyzed pot-economic three-component strategy to 1,3-diarylallylidene pyrazolones *via* consecutive double condensation reaction involving 4-unsubstituted pyrazolones

4.1	Introduction	253-254
4.2	Review Work	254-257
4.2.1	Synthesis of 4-Alkylidene/ Alkenylidene Pyrazolones	254-257
4.2.2	Conclusion	257
4.3	Present Work	258
4.4	Results and Discussion	258-270
4.4.1	Optimization of reaction conditions	260-261
4.4.2	Substrate Scope	261-266
4.4.3	Control Experiments	266-268
4.4.4	Plausible Mechanism	269-270
4.5	Conclusion	271
4.6	Experimental Section	271-295
4.7	Copies of ^{1}H and ^{13}C NMR of the described compounds	296-353
4.8	References	354-359

Conclusion and Future Outlook 360

ABSTRACT

The main objective of this thesis is to develop transition metal-free one-pot synthetic strategies to access value-added pyridines and pyrazolones in a simple, effective, pot-economical, and environment-friendly manner from readily available cost-effective reactants.

The first chapter starts with a general introduction highlighting the historical significance and medicinal impact of naturally occurring heterocycles on human life in the past centuries and later synthetic protocols documented for synthesizing the aforesaid class of derivatives through various synthetic modifications.

The second chapter demonstrates an efficient metal oxidant and solvent-free domino approach for regioselective synthesis of fascinating classes of di and trisubstituted unsymmetrical pyridines *via* a [3C + 2C + 1N] cyclization reaction between enolizable acyclic/ cyclic ketones (2C units), 3-chloropropiophenones (3C units) and NH_4OAc (N-atom source) under neat conditions in an open atmosphere. A mechanistic study reveals that the *in-situ* formed β-amino ketone from 3-chloropropiophenone and ammonium salt undergoes C=N bond formation with a ketone followed by an intramolecular cyclization process that leads to corresponding pyridine. This strategic protocol is conceptually unique and certainly offers an alternative procedure for making di- and tri-substituted pyridines regioselectively with good to high yields.

Chapter three illustrates a mild organocatalytic, one-pot, two-step sequential methodology for accessing 2-(2-hydroxyaryl/benzenesulfonamide)-3,6-disubstituted pyridines decorated with synthetically beneficial aryl ethyl ketone scaffold at C3 position. This sequential reaction proceeds through a double $C(sp^3)$–H alkylation of 4/3-methyl *N*-sulfonyl ketimines with *in-situ* generated vinyl aryl ketones triggered by DIPEA in the presence of $NaHCO_3$ as a cooperative base and subsequent [5C + 1N] aza-cyclization using ammonium acetate as a N-containing atom for pyridine ring construction. Furthermore, higher alkyl chains in place of the methyl group of *N*-sulfonyl

ketimines give only a monoalkylation product with *in-situ* formed vinyl ketones resulting in satisfactory to high yields of 3-picoline derivatives in an atom- and pot-economical manner with a tolerance of several compatible functional groups. Thus, designing a new organocatalytic cycle with a cheap and environmentally benign base $NaHCO_3$ is a crucial achievement for new C–C bond construction. Moreover, the synthetic utility of prepared pyridine derivatives provides several important classes of pyridocoumarin, 5*H*-chromenopyridine and dipyridine derivatives with good yields.

Chapter four describes an interesting organocatalytic, one-pot, pot-economical technique for the diastereoselective synthesis of various synthetically useful 1,3-diaryl-substituted pyrazolones in good to high yields (41-84%), excellent diastereoselectivity (≤ 99%) and high tolerance of diverse functional groups. This three-component consecutive double condensation reaction between 4-unsubstituted pyrazolones, aryl/heteroaryl aldehydes, and aryl methyl ketones goes effortlessly under pyrrolidine-BzOH salt as a cost-effective, robust catalytic system. Pyrrolidine-BzOH salt facilitates two consecutive C=C bond formations through the mutual swapping of aryl moieties, achieving a 100% carbon atom economy and thus, making a significant step toward sustainable synthesis.

Finally, the conclusion and future outlook of the developed protocols, accomplished throughout the work, are discussed.

LIST OF PUBLICATIONS

A. Publications from thesis work:

1. **Patel A. K.,** Rathor S. S. and Samanta S. (2022), Regioselective access to di- and trisubstituted pyridines via a metal-oxidant-solvent-free domino reaction involving 3-chloropropiophenones, *Org. Biomol. Chem.*, *20*, 6759-6765 (DOI: 10.1039/D2OB01193J)

2. **Patel A. K.** and Samanta S. (2023), Organocatalyzed Double C(sp^3)–H Alkylation of Cyclic N-Sulfonyl Ketimines with 3-Chloropropiophenones: Selective Access to 2,3,6-Trisubstituted Pyridines, *Eur. J. Org. Chem.*, *26*, e202300631 (DOI: 10.1002/ejoc.202300631)

3. **Patel A. K.** and Samanta S. (2024), Robust Organocatalytic Three-Component Approach to 1,3-Diarylallylidene Pyrazolones via Consecutive Double Condensation Reactions, *J. Org. Chem.*, *89*, 17528-17543 (DOI: 10.1021/acs.joc.4c02273)

B. Publications beyond thesis work:

1. Rathor S. S., **Patel A. K.** and Samanta S., (2024), Organocatalyzed diastereoselective cyclization of β-alkyl nitroolefins with alkylidene malononitriles: new approach to azetidine nitrones and isoxazoles, *Org. Chem. Front.*, *11*, 1782-1789 (DOI: 10.1039/D3QO01979A)

2. Lodhi R., **Patel A. K.** and Samanta S. (2022), AgOTf/Et_3N Cooperative Catalysis Enabled One-Pot Access to α-(Indolizinylethyl)-Substituted N-Sulfonyl Ketimines via an Imino-Alkyne Cyclization, *Asian J. Org. Chem.*, *11*, e202200569 (DOI: 10.1002/ajoc.202200569)

3. Majee D., Goud S. B., Guin S., Rathor S. S., **Patel A. K.** and Samanta S. (2021), Reversal Reactivity of β-Alkylnitroalkenes as 1,3-Binucleophiles: Application to Nitroarenes using Organocatalysis, *Asian J. Org. Chem.*, *10*, 1650-1654 (DOI: 10.1002/ajoc.202100216)

4. Guin S., Saha H. K., **Patel A. K.,** Gudimella S. K., Biswas S. and Samanta S. (2020), 1, 6-Aza-Michael addition of para-quinone methides with *N*-heterocycles catalyzed by Zn(OTf)2: A regioselective approach to N-diarylmethyl-substituted heterocycles, *Tetrahedron*, *76*, 131338 (DOI: 10.1016/j.tet.2020.131338)

Conferences:

- Delivered a poster presentation at the international conference on **"Sustainable Chemistry-2023"** under Indo-German Higher Education Partnerships held at the Indian Institute of Technology Indore, 22nd -23rd February 2023.

- Oral presentation in **"In-House Chemistry Symposium (CHEM 2023)"** organized by the Department of Chemistry, Indian Institute of Technology Indore, 06 March 2023.

- Oral presentation in **"In-House Chemistry Symposium (CHEM 2024)"** organized by the Department of Chemistry, Indian Institute of Technology Indore, 21 March 2024.

- Actively participated in **"RSC-IIT Indore Symposium on Materials Science towards New Horizons-2023"** organized by the Department of Chemistry, Indian Institute of Technology Indore, from 19th-20th January 2023.

- Delivered a poster presentation at the national conference on **"Frontiers in Chemistry"** organized by the Department of Chemistry, IISER Bhopal and IIT Indore under the CRSI Local Chapter on 04th May 2024, held at the Indian Institute of Science Education and Research Bhopal (Got the Best Poster Award).

LIST OF ABBREVIATIONS

$(NH_4)_2CO_3$	Ammonium carbonate
NH_4OAc	Ammonium acetate
NH_4HCO_2	Ammonium formate
NH_4HCO_3	Ammonium bicarbonate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
$(NH_4)_2SO_4$	Ammonium sulfate
NH_4SCN	Ammonium thiocyanate
$AlCl_3$	Aluminium chloride
MeCN	Acetonitrile
AcOH	Acetic acid
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
Bz	Benzoyl
2,2′-bpy	2,2'-bipyridine
$Cu(OAc)_2$	Cupper(II)acetate
CuBr	Copper(I) bromide
J	Coupling constant
Cs_2CO_3	Cesium carbonate
$CeCl_3.7H_2O$-NaI	Cerium(III) chloride heptahydrate and sodium iodide
CuI	Copper iodide
$Cu(NO_3)_2$	Copper(II) nitrate
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DMAP	4-Dimethylaminopyridine
DMSO-d_6	Deuterated dimethylsulfoxide
DMF	Dimethylformamide
DCM	Dichloromethane
$CDCl_3$	Deuterated chloroform
D_2O	Deuterium oxide

dr	Diastereomeric ratio
Et_2O	Diethylether
d	Doublet
DCE	1,2-Dichloroethane
DMSO	Dimethyl sulfoxide
$Ph_2Si(OMe)_2$	Dimethoxydiphenylsilane
ee	Enantiomeric excess
ESI-MS	Electronspray ionization mass spectrometry
EtOH	Ethanol
$AuCl_3$	Gold(III)chloride
Hz	Hertz
HRMS	High-resolution mass spectrometry
$InCl_3$	Indiumtrichloride
$In(OTf)_3$	Indium triflate
$FeCl_3$	Iron(III) chloride
$Fe(NO_3)_3$	Iron(III) nitrate
I_2	Molecular iodine
LDA	Lithiumdiisopropylamide
$LiAlH_4$	Lithium aluminium hydride
Li_2CO_3	Lithium carbonate
L-Proline	(*S*)-Pyrrolidine-2-carboxylic acid
LC-MS	Liquid chromatography-mass spectrometry
MCR	Multicomponent reaction
MHz	Megahertz
m	Multiplet
2-MeTHF	2-Methyltetrahydrofuran
DIPEA	N,N-Diisopropylethylamine (Hunig's base)
NMR	Nuclear magnetic resonance
$NbCl_5$	Niobium(V) chloride
$Pd(OAc)_2$	Palladium(II)acetate
$PdCl_2$	Palladium(II)chloride
PEG-400	Polyethylene glycol
$K_5CoW_{12}O_{40}$	Potassium dodecatungstocobaltate trihydrate

ppm	Part-per-million
KOH	Potassium hydroxide
t-BuOK	Potassium *tert*-Butoxide
K_2CO_3	Potassium carbonate
$HClO_4$	Perchloric acid
q	Quartet
R_f	Retardation factor
$[RhCl(CO_2)]_2$	Rhodium(I) dicarbonyl chloride dimer
$RuCl_3$	Ruthenium(III) chloride
s	Singlet
Ag_2CO_3	Silver carbonate
SC-XRD	Single Crystal X-ray Diffractometers
Na_2CO_3	Sodium carbonate
NaOH	Sodium hydroxide
$NaHCO_3$	Sodium bicarbonate
$NaHSO_3$	Sodium bisulfite
NaOEt	Sodium ethoxide
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
PPh_3	Triphenylphosphine
p-TSA	*p*-Toluenesulfonic acid
THF	Tetrahydrofuran
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TFA	Trifuluoroacetic acid
TOF-MS	Time of flight mass spectrometry
Et_3N	Triethylamine
TLC	Thin-layer chromatography
t	Triplet

LIST OF FIGURES

Figure 1.1	One-pot synthesis	2
Figure 1.2	The general structure of pyridine	3
Figure 1.3	Natural occurrence of pyridines	4
Figure 1.4	A few examples of marketed drugs consisting of pyridine	4
Figure 1.5	Some selected examples of agrochemicals and ligands used in catalysis contain a pyridine motif as a core	5
Figure 1.6	General representative picture showing wide applications of pyridines	5
Figure 1.7	General structure of pyrazolone	6
Figure 1.8	Selected examples of pyrazolone-based active drugs	6
Figure 1.9	Some examples of biologically relevant pyrazolone Derivatives	7
Figure 1.10	General representative sketch showing applications of pyrazolones	7
Figure 2.1	500 MHz ^{1}H Spectrum of **3aa** in $CDCl_3$	68
Figure 2.2	125 MHz ^{13}C Spectrum of **3aa** in $CDCl_3$	68
Figure 2.3	500 MHz ^{1}H Spectrum of **3ab** in $CDCl_3$	69
Figure 2.4	125 MHz ^{13}C Spectrum of **3ab** in $CDCl_3$	69
Figure 2.5	500 MHz ^{1}H Spectrum of **3ag** in $CDCl_3$	70
Figure 2.6	125 MHz ^{13}C Spectrum of **3ag** in $CDCl_3$	70
Figure 2.7	500 MHz ^{1}H Spectrum of **3ae** in $CDCl_3$	71
Figure 2.8	125 MHz ^{13}C Spectrum of **3ae** in $CDCl_3$	71
Figure 2.9	500 MHz ^{1}H Spectrum of **3af** in $CDCl_3$	72
Figure 2.10	125 MHz ^{13}C Spectrum of **3af** in $CDCl_3$	72
Figure 2.11	500 MHz ^{1}H Spectrum of **3ah** in $CDCl_3$	73
Figure 2.12	125 MHz ^{13}C Spectrum of **3ah** in $CDCl_3$	73
Figure 2.13	500 MHz ^{1}H Spectrum of **3ac** in $CDCl_3$	74
Figure 2.14	125 MHz ^{13}C Spectrum of **3ac** in $CDCl_3$	74

Figure 2.15 500 MHz ^{1}H Spectrum of **3aj** in $CDCl_3$ 75
Figure 2.16 125 MHz ^{13}C Spectrum of **3aj** in $CDCl_3$ 75
Figure 2.17 500 MHz ^{1}H Spectrum of **3ad** in $CDCl_3$ 76
Figure 2.18 125 MHz ^{13}C Spectrum of **3ad** in $CDCl_3$ 76
Figure 2.19 500 MHz ^{1}H Spectrum of **3ai** in $CDCl_3$ 77
Figure 2.20 125 MHz ^{13}C Spectrum of **3ai** in $CDCl_3$ 77
Figure 2.21 500 MHz ^{1}H Spectrum of **3al** in $CDCl_3$ 78
Figure 2.22 125 MHz ^{13}C Spectrum of **3al** in $CDCl_3$ 78
Figure 2.23 500 MHz ^{1}H Spectrum of **3am** in $CDCl_3$ 79
Figure 2.24 125 MHz ^{13}C Spectrum of **3am** in $CDCl_3$ 79
Figure 2.25 500 MHz ^{1}H Spectrum of **3ak** in $CDCl_3$ 80
Figure 2.26 125 MHz ^{13}C Spectrum of **3ak** in $CDCl_3$ 80
Figure 2.27 500 MHz ^{1}H Spectrum of **3ba** in $CDCl_3$ 81
Figure 2.28 125 MHz ^{13}C Spectrum of **3ba** in $CDCl_3$ 81
Figure 2.29 500 MHz ^{1}H Spectrum of **3bb** in $CDCl_3$ 82
Figure 2.30 125 MHz ^{13}C Spectrum of **3bb** in $CDCl_3$ 82
Figure 2.31 500 MHz ^{1}H Spectrum of **3bg** in $CDCl_3$ 83
Figure 2.32 125 MHz ^{13}C Spectrum of **3bg** in $CDCl_3$ 83
Figure 2.33 500 MHz ^{1}H Spectrum of **3ca** in $CDCl_3$ 84
Figure 2.34 125 MHz ^{13}C Spectrum of **3ca** in $CDCl_3$ 84
Figure 2.35 500 MHz ^{1}H Spectrum of **3ea** in $CDCl_3$ 85
Figure 2.36 125 MHz ^{13}C Spectrum of **3ea** in $CDCl_3$ 85
Figure 2.37 500 MHz ^{1}H Spectrum of **3eb** in $CDCl_3$ 86
Figure 2.38 125 MHz ^{13}C Spectrum of **3eb** in $CDCl_3$ 86
Figure 2.39 500 MHz ^{1}H Spectrum of **3eg** in $CDCl_3$ 87
Figure 2.40 125 MHz ^{13}C Spectrum of **3eg** in $CDCl_3$ 87
Figure 2.41 500 MHz ^{1}H Spectrum of **3ee** in $CDCl_3$ 88
Figure 2.42 125 MHz ^{13}C Spectrum of **3ee** in $CDCl_3$ 88
Figure 2.43 500 MHz ^{1}H Spectrum of **3ef** in $CDCl_3$ 89
Figure 2.44 125 MHz ^{13}C Spectrum of **3ef** in $CDCl_3$ 89
Figure 2.45 500 MHz ^{1}H Spectrum of **3fa** in $CDCl_3$ 90
Figure 2.46 125 MHz ^{13}C Spectrum of **3fa** in $CDCl_3$ 90
Figure 2.47 500 MHz ^{1}H Spectrum of **3ff** in $CDCl_3$ 91

Figure 2.48 125 MHz ^{13}C Spectrum of **3ff** in $CDCl_3$ 91
Figure 2.49 500 MHz ^{1}H Spectrum of **3ga** in $CDCl_3$ 92
Figure 2.50 125 MHz ^{13}C Spectrum of **3ga** in $CDCl_3$ 92
Figure 2.51 500 MHz ^{1}H Spectrum of **3gb** in $CDCl_3$ 93
Figure 2.52 125 MHz ^{13}C Spectrum of **3gb** in $CDCl_3$ 93
Figure 2.53 500 MHz ^{1}H Spectrum of **3ha** in $CDCl_3$ 94
Figure 2.54 125 MHz ^{13}C Spectrum of **3ha** in $CDCl_3$ 94
Figure 2.55 500 MHz ^{1}H Spectrum of **3da** in $CDCl_3$ 95
Figure 2.56 125 MHz ^{13}C Spectrum of **3da** in $CDCl_3$ 95
Figure 2.57 500 MHz ^{1}H Spectrum of **3db** in $CDCl_3$ 96
Figure 2.58 125 MHz ^{13}C Spectrum of **3db** in $CDCl_3$ 96
Figure 2.59 500 MHz ^{1}H Spectrum of **3in** in $CDCl_3$ 97
Figure 2.60 125 MHz ^{13}C Spectrum of **3in** in $CDCl_3$ 97
Figure 2.61 500 MHz ^{1}H Spectrum of **4ay** in $CDCl_3$ 98
Figure 2.62 125 MHz ^{13}C Spectrum of **4ay** in $CDCl_3$ 98
Figure 2.63 500 MHz ^{1}H Spectrum of **4dy** in $CDCl_3$ 99
Figure 2.64 125 MHz ^{13}C Spectrum of **4dy** in $CDCl_3$ 99
Figure 2.65 500 MHz ^{1}H Spectrum of **4az** in $CDCl_3$ 100
Figure 2.66 125 MHz ^{13}C Spectrum of **4az** in $CDCl_3$ 100
Figure 2.67 500 MHz ^{1}H Spectrum of **3ao** in $CDCl_3$ 101
Figure 2.68 125 MHz ^{13}C Spectrum of **3ao** in $CDCl_3$ 101
Figure 2.69 500 MHz ^{1}H Spectrum of **4ao** in $CDCl_3$ 102
Figure 2.70 125 MHz ^{13}C Spectrum of **4ao** in $CDCl_3$ 102
Figure 2.71 500 MHz ^{1}H Spectrum of **3ap** in $CDCl_3$ 103
Figure 2.72 125 MHz ^{13}C Spectrum of **3ap** in $CDCl_3$ 103
Figure 2.73 500 MHz ^{1}H Spectrum of **3aq** in $CDCl_3$ 104
Figure 2.74 125 MHz ^{13}C Spectrum of **3aq** in $CDCl_3$ 104
Figure 2.75 500 MHz ^{1}H Spectrum of **4ar** in $CDCl_3$ 105
Figure 2.76 125 MHz ^{13}C Spectrum of **4ar** in $CDCl_3$ 105
Figure 2.77 500 MHz ^{1}H Spectrum of **3ar** in $CDCl_3$ 106
Figure 2.78 125 MHz ^{13}C Spectrum of **3ar** in $CDCl_3$ 106
Figure 2.79 500 MHz ^{1}H Spectrum of **4as** in $CDCl_3$ 107
Figure 2.80 125 MHz ^{13}C Spectrum of **4as** in $CDCl_3$ 107

Figure 2.81	500 MHz ^{1}H Spectrum of **3as** in $CDCl_3$	108
Figure 2.82	125 MHz ^{13}C Spectrum of **3as** in $CDCl_3$	108
Figure 2.83	500 MHz ^{1}H Spectrum of **3at** in $CDCl_3$	109
Figure 2.84	125 MHz ^{13}C Spectrum of **3at** in $CDCl_3$	109
Figure 2.85	500 MHz ^{1}H Spectrum of **4at** in $CDCl_3$	110
Figure 2.86	125 MHz ^{13}C Spectrum of **4at** in $CDCl_3$	110
Figure 2.87	500 MHz ^{1}H Spectrum of **3au** in $CDCl_3$	111
Figure 2.88	125 MHz ^{13}C Spectrum of **3au** in $CDCl_3$	111
Figure 2.89	500 MHz ^{1}H Spectrum of **4au** in $CDCl_3$	112
Figure 2.90	125 MHz ^{13}C Spectrum of **4au** in $CDCl_3$	112
Figure 2.91	500 MHz ^{1}H Spectrum of **3du** in $CDCl_3$	113
Figure 2.92	125 MHz ^{13}C Spectrum of **3du** in $CDCl_3$	113
Figure 2.93	500 MHz ^{1}H Spectrum of **4du** in $CDCl_3$	114
Figure 2.94	125 MHz ^{13}C Spectrum of **4du** in $CDCl_3$	114
Figure 2.95	500 MHz ^{1}H Spectrum of **3aw** in $CDCl_3$	115
Figure 2.96	125 MHz ^{13}C Spectrum of **3aw** in $CDCl_3$	115
Figure 2.97	500 MHz ^{1}H Spectrum of **4av** in $CDCl_3$	116
Figure 2.98	125 MHz ^{13}C Spectrum of **4av** in $CDCl_3$	116
Figure 2.99	500 MHz ^{1}H Spectrum of **3aw** in $CDCl_3$	117
Figure 2.100	125 MHz ^{13}C Spectrum of **3aw** in $CDCl_3$	117
Figure 2.101	500 MHz ^{1}H Spectrum of **4aw** in $CDCl_3$	118
Figure 2.102	125 MHz ^{13}C Spectrum of **4aw** in $CDCl_3$	118
Figure 2.103	500 MHz ^{1}H Spectrum of **4azz** in $CDCl_3$	119
Figure 2.104	125 MHz ^{13}C Spectrum of **4azz** in $CDCl_3$	119
Figure 2.105	500 MHz ^{1}H Spectrum of **3ax** in $CDCl_3$	120
Figure 2.106	125 MHz ^{13}C Spectrum of **3ax** in $CDCl_3$	120
Figure 2.107	500 MHz ^{1}H Spectrum of **3ix** in $CDCl_3$	121
Figure 2.108	125 MHz ^{13}C Spectrum of **3ix** in $CDCl_3$	121
Figure 2.109	500 MHz ^{1}H Spectrum of **14** in $CDCl_3$	122
Figure 2.110	125 MHz ^{13}C Spectrum of **14** in $CDCl_3$	122
Figure 2.111	500 MHz ^{1}H Spectrum of **5a** in $CDCl_3$	123
Figure 2.112	125 MHz ^{13}C Spectrum of **5a** in $CDCl_3$	123

Figure 2.113	500 MHz ^{1}H Spectrum of **3-bromopropiophenone** in $CDCl_3$	124
Figure 2.114	125 MHz ^{13}C Spectrum of **3-bromopropiophenone** in $CDCl_3$	124
Figure 2.115	500 MHz ^{1}H Spectrum of **6a** in $CDCl_3$	125
Figure 2.116	125 MHz ^{13}C Spectrum of **6a** in $CDCl_3$	125
Figure 3.1	Some selected biologically active 2,3,6-trisubstituted pyridines	131
Figure 3.2	500 MHz ^{1}H Spectrum of **3aa** in $CDCl_3$	182
Figure 3.3	125 MHz ^{13}C Spectrum of **3aa** in $CDCl_3$	182
Figure 3.4	500 MHz ^{1}H Spectrum of **3ab** in $CDCl_3$	183
Figure 3.5	125 MHz ^{13}C Spectrum of **3ab** in $CDCl_3$	183
Figure 3.6	500 MHz ^{1}H Spectrum of **3ac** in $CDCl_3$	184
Figure 3.7	125 MHz ^{13}C Spectrum of **3ac** in $CDCl_3$	184
Figure 3.8	500 MHz ^{1}H Spectrum of **3ai** in $CDCl_3$	185
Figure 3.9	125 MHz ^{13}C Spectrum of **3ai** in $CDCl_3$	185
Figure 3.10	500 MHz ^{1}H Spectrum of **3aj** in $CDCl_3$	186
Figure 3.11	125 MHz ^{13}C Spectrum of **3aj** in $CDCl_3$	186
Figure 3.12	500 MHz ^{1}H Spectrum of **3ak** in $CDCl_3$	187
Figure 3.13	125 MHz ^{13}C Spectrum of **3ak** in $CDCl_3$	187
Figure 3.14	500 MHz ^{1}H Spectrum of **3ad** in $CDCl_3$	188
Figure 3.15	125 MHz ^{13}C Spectrum of **3ad** in $CDCl_3$	188
Figure 3.16	500 MHz ^{1}H Spectrum of **3ae** in $CDCl_3$	189
Figure 3.17	125 MHz ^{13}C Spectrum of **3ae** in $CDCl_3$	189
Figure 3.18	500 MHz ^{1}H Spectrum of **3af** in $CDCl_3$	190
Figure 3.19	125 MHz ^{13}C Spectrum of **3af** in $CDCl_3$	190
Figure 3.20	500 MHz ^{1}H Spectrum of **3ag** in $CDCl_3$	191
Figure 3.21	125 MHz ^{13}C Spectrum of **3ag** in $CDCl_3$	191
Figure 3.22	500 MHz ^{1}H Spectrum of **3ah** in $CDCl_3$	192
Figure 3.23	125 MHz ^{13}C Spectrum of **3ah** in $CDCl_3$	192
Figure 3.24	500 MHz ^{1}H Spectrum of **3al** in $CDCl_3$	193
Figure 3.25	125 MHz ^{13}C Spectrum of **3al** in $CDCl_3$	193
Figure 3.26	500 MHz ^{1}H Spectrum of **3am** in $CDCl_3$	194

Figure 3.27 125 MHz ^{13}C Spectrum of **3am** in $CDCl_3$ 194
Figure 3.28 500 MHz ^{1}H Spectrum of **3an** in $CDCl_3$ 195
Figure 3.29 125 MHz ^{13}C Spectrum of **3an** in $CDCl_3$ 195
Figure 3.30 500 MHz ^{1}H Spectrum of **3ba** in $CDCl_3$ 196
Figure 3.31 125 MHz ^{13}C Spectrum of **3ba** in $CDCl_3$ 196
Figure 3.32 500 MHz ^{1}H Spectrum of **3ca** in $CDCl_3$ 197
Figure 3.33 125 MHz ^{13}C Spectrum of **3ca** in $CDCl_3$ 197
Figure 3.34 500 MHz ^{1}H Spectrum of **3cb** in $CDCl_3$ 198
Figure 3.35 125 MHz ^{13}C Spectrum of **3cb** in $CDCl_3$ 198
Figure 3.36 500 MHz ^{1}H Spectrum of **3cc** in $CDCl_3$ 199
Figure 3.37 125 MHz ^{13}C Spectrum of **3cc** in $CDCl_3$ 199
Figure 3.38 500 MHz ^{1}H Spectrum of **3cj** in $CDCl_3$ 200
Figure 3.39 125 MHz ^{13}C Spectrum of **3cj** in $CDCl_3$ 200
Figure 3.40 500 MHz ^{1}H Spectrum of **3ce** in $CDCl_3$ 201
Figure 3.41 125 MHz ^{13}C Spectrum of **3ce** in $CDCl_3$ 201
Figure 3.42 500 MHz ^{1}H Spectrum of **3cl** in $CDCl_3$ 202
Figure 3.43 125 MHz ^{13}C Spectrum of **3cl** in $CDCl_3$ 202
Figure 3.44 500 MHz ^{1}H Spectrum of **3cm** in $CDCl_3$ 203
Figure 3.45 125 MHz ^{13}C Spectrum of **3cm** in $CDCl_3$ 203
Figure 3.46 500 MHz ^{1}H Spectrum of **3da** in $CDCl_3$ 204
Figure 3.47 125 MHz ^{13}C Spectrum of **3da** in $CDCl_3$ 204
Figure 3.48 471 MHz ^{19}F NMR of **3da** in $CDCl_3$ 205
Figure 3.49 500 MHz ^{1}H Spectrum of **3ea** in $CDCl_3$ 206
Figure 3.50 125 MHz ^{13}C Spectrum of **3ea** in $CDCl_3$ 206
Figure 3.51 500 MHz ^{1}H Spectrum of **3eb** in $CDCl_3$ 207
Figure 3.52 125 MHz ^{13}C Spectrum of **3eb** in $CDCl_3$ 207
Figure 3.53 500 MHz ^{1}H Spectrum of **3el** in $CDCl_3$ 208
Figure 3.54 125 MHz ^{13}C Spectrum of **3el** in $CDCl_3$ 208
Figure 3.55 500 MHz ^{1}H Spectrum of **3em** in $CDCl_3$ 209
Figure 3.56 125 MHz ^{13}C Spectrum of **3em** in $CDCl_3$ 209
Figure 3.57 500 MHz ^{1}H Spectrum of **3fa** in $CDCl_3$ 210
Figure 3.58 125 MHz ^{13}C Spectrum of **3fa** in $CDCl_3$ 210
Figure 3.59 500 MHz ^{1}H Spectrum of **3ga** in $CDCl_3$ 211

Figure 3.60 125 MHz ^{13}C Spectrum of **3ga** in $CDCl_3$ 211
Figure 3.61 500 MHz ^{1}H Spectrum of **3ha** in $CDCl_3$ 212
Figure 3.62 125 MHz ^{13}C Spectrum of **3ha** in $CDCl_3$ 212
Figure 3.63 500 MHz ^{1}H Spectrum of **3hb** in $CDCl_3$ 213
Figure 3.64 125 MHz ^{13}C Spectrum of **3hb** in $CDCl_3$ 213
Figure 3.65 500 MHz ^{1}H Spectrum of **3hc** in $CDCl_3$ 214
Figure 3.66 125 MHz ^{13}C Spectrum of **3hc** in $CDCl_3$ 214
Figure 3.67 500 MHz ^{1}H Spectrum of **3hi** in $CDCl_3$ 215
Figure 3.68 125 MHz ^{13}C Spectrum of **3hi** in $CDCl_3$ 215
Figure 3.69 500 MHz ^{1}H Spectrum of **3hj** in $CDCl_3$ 216
Figure 3.70 125 MHz ^{13}C Spectrum of **3hj** in $CDCl_3$ 216
Figure 3.71 500 MHz ^{1}H Spectrum of **3hk** in $CDCl_3$ 217
Figure 3.72 125 MHz ^{13}C Spectrum of **3hk** in $CDCl_3$ 217
Figure 3.73 500 MHz ^{1}H Spectrum of **3hd** in $CDCl_3$ 218
Figure 3.74 125 MHz ^{13}C Spectrum of **3hd** in $CDCl_3$ 218
Figure 3.75 500 MHz ^{1}H Spectrum of **3he** in $CDCl_3$ 219
Figure 3.76 125 MHz ^{13}C Spectrum of **3he** in $CDCl_3$ 219
Figure 3.77 500 MHz ^{1}H Spectrum of **3hf** in $CDCl_3$ 220
Figure 3.78 125 MHz ^{13}C Spectrum of **3hf** in $CDCl_3$ 220
Figure 3.79 500 MHz ^{1}H Spectrum of **3hg** in $CDCl_3$ 221
Figure 3.80 125 MHz ^{13}C Spectrum of **3hg** in $CDCl_3$ 221
Figure 3.81 500 MHz ^{1}H Spectrum of **3hl** in $CDCl_3$ 222
Figure 3.82 125 MHz ^{13}C Spectrum of **3hl** in $CDCl_3$ 222
Figure 3.83 500 MHz ^{1}H Spectrum of **3hm** in $CDCl_3$ 223
Figure 3.84 125 MHz ^{13}C Spectrum of **3hm** in $CDCl_3$ 223
Figure 3.85 500 MHz ^{1}H Spectrum of **3hn** in $CDCl_3$ 224
Figure 3.86 125 MHz ^{13}C Spectrum of **3hn** in $CDCl_3$ 224
Figure 3.87 500 MHz ^{1}H Spectrum of **3ia** in $CDCl_3$ 225
Figure 3.88 125 MHz ^{13}C Spectrum of **3ia** in $CDCl_3$ 225
Figure 3.89 500 MHz ^{1}H Spectrum of **3ic** in $CDCl_3$ 226
Figure 3.90 125 MHz ^{13}C Spectrum of **3ic** in $CDCl_3$ 226
Figure 3.91 500 MHz ^{1}H Spectrum of **3if** in $CDCl_3$ 227
Figure 3.92 125 MHz ^{13}C Spectrum of **3if** in $CDCl_3$ 227

Figure 3.93	500 MHz ^{1}H Spectrum of **3ii** in $CDCl_3$	228
Figure 3.94	125 MHz ^{13}C Spectrum of **3ii** in $CDCl_3$	228
Figure 3.95	500 MHz ^{1}H Spectrum of **3ig** in $CDCl_3$	229
Figure 3.96	125 MHz ^{13}C Spectrum of **3ig** in $CDCl_3$	229
Figure 3.97	500 MHz ^{1}H Spectrum of **3il** in $CDCl_3$	230
Figure 3.98	125 MHz ^{13}C Spectrum of **3il** in $CDCl_3$	230
Figure 3.99	500 MHz ^{1}H Spectrum of **3im** in $CDCl_3$	231
Figure 3.100	125 MHz ^{13}C Spectrum of **3im** in $CDCl_3$	231
Figure 3.101	500 MHz ^{1}H Spectrum of **3ja** in $CDCl_3$	232
Figure 3.102	125 MHz ^{13}C Spectrum of **3ja** in $CDCl_3$	232
Figure 3.103	500 MHz ^{1}H Spectrum of **3ka** in $CDCl_3$	233
Figure 3.104	125 MHz ^{13}C Spectrum of **3ka** in $CDCl_3$	233
Figure 3.105	500 MHz ^{1}H Spectrum of **3kc** in $CDCl_3$	234
Figure 3.106	125 MHz ^{13}C Spectrum of **3kc** in $CDCl_3$	234
Figure 3.107	500 MHz ^{1}H Spectrum of **3ki** in $CDCl_3$	235
Figure 3.108	125 MHz ^{13}C Spectrum of **3ki** in $CDCl_3$	235
Figure 3.109	500 MHz ^{1}H Spectrum of **3km** in $CDCl_3$	236
Figure 3.110	125 MHz ^{13}C Spectrum of **3km** in $CDCl_3$	236
Figure 3.111	500 MHz ^{1}H Spectrum of **3la** in $CDCl_3$	237
Figure 3.112	125 MHz ^{13}C Spectrum of **3la** in $CDCl_3$	237
Figure 3.113	500 MHz ^{1}H Spectrum of **3ma** in $CDCl_3$	238
Figure 3.114	125 MHz ^{13}C Spectrum of **3ma** in $CDCl_3$	238
Figure 3.115	500 MHz ^{1}H Spectrum of **compound 20** in $CDCl_3$	239
Figure 3.116	125 MHz ^{13}C Spectrum of **compound 20** in $CDCl_3$	239
Figure 3.117	500 MHz ^{1}H Spectrum of **compound 19** in $CDCl_3$	240
Figure 3.118	125 MHz ^{13}C Spectrum of **compound 19** in $CDCl_3$	240
Figure 3.119	500 MHz ^{1}H Spectrum of **compound 21** in $CDCl_3$	241

Figure 3.120	125 MHz ^{13}C Spectrum of **compound 21** in $CDCl_3$	241
Figure 3.121	500 MHz ^{1}H Spectrum of **compound 4** in $CDCl_3$	242
Figure 3.122	125 MHz ^{13}C Spectrum of **compound 4** in $CDCl_3$	242
Figure 3.123	500 MHz ^{1}H Spectrum of **compound 4′** in $CDCl_3$	243
Figure 3.124	125 MHz ^{13}C Spectrum of **compound 4′** in $CDCl_3$	243
Figure 3.125	500 MHz ^{1}H Spectrum of **1m** in $CDCl_3$	244
Figure 3.126	500 MHz ^{1}H Spectrum of **2h** in $CDCl_3$	244
Figure 3.127	125 MHz ^{13}C Spectrum of **2h** in $CDCl_3$	245
Figure 3.128	500 MHz ^{1}H Spectrum of **2m** in $CDCl_3$	245
Figure 3.129	125 MHz ^{13}C Spectrum of **2m** in $CDCl_3$	246
Figure 3.130	500 MHz ^{1}H Spectrum of **2l** in $CDCl_3$	246
Figure 3.131	125 MHz ^{13}C Spectrum of **2l** in $CDCl_3$	247
Figure 3.132	500 MHz ^{1}H Spectrum of **2e** in $CDCl_3$	247
Figure 3.133	125 MHz ^{13}C Spectrum of **2e** in $CDCl_3$	248
Figure 3.134	500 MHz ^{1}H Spectrum of **2g** in $CDCl_3$	248
Figure 3.135	125 MHz ^{13}C Spectrum of **2g** in $CDCl_3$	249
Figure 3.136	500 MHz ^{1}H Spectrum of **2n** in $CDCl_3$	249
Figure 4.1	Selected examples of biologically active pyrazolone derivatives	262
Figure 4.2	ORTEP plot of compound **4aba** with thermal ellipsoids drawn at the 50% probability level	276
Figure 4.3	ORTEP plot of compound **4aca** with 50% ellipsoid probability	277
Figure 4.4	500 MHz ^{1}H Spectrum of **4aaa** in $CDCl_3$	296
Figure 4.5	125 MHz ^{13}C Spectrum of **4aaa** in $CDCl_3$	296
Figure 4.6	500 MHz ^{1}H Spectrum of **4aad** in $CDCl_3$	297
Figure 4.7	125 MHz ^{13}C Spectrum of **4aad** in $CDCl_3$	297
Figure 4.8	500 MHz ^{1}H Spectrum of **4aac** in $CDCl_3$	298

Figure 4.9	125 MHz ^{13}C Spectrum of **4aac** in $CDCl_3$	298
Figure 4.10	500 MHz ^{1}H Spectrum of **4aab** in $CDCl_3$	299
Figure 4.11	125 MHz ^{13}C Spectrum of **4aab** in $CDCl_3$	299
Figure 4.12	500 MHz ^{1}H Spectrum of **4aae** in $CDCl_3$	300
Figure 4.13	125 MHz ^{13}C Spectrum of **4aae** in $CDCl_3$	300
Figure 4.14	500 MHz ^{1}H Spectrum of **4aag** in $CDCl_3$	301
Figure 4.15	125 MHz ^{13}C Spectrum of **4aag** in $CDCl_3$	301
Figure 4.16	500 MHz ^{1}H Spectrum of **4aaf** in $CDCl_3$	302
Figure 4.17	125 MHz ^{13}C Spectrum of **4aaf** in $CDCl_3$	302
Figure 4.18	500 MHz ^{1}H Spectrum of **4aah** in $CDCl_3$	303
Figure 4.19	125 MHz ^{13}C Spectrum of **4aah** in $CDCl_3$	303
Figure 4.20	500 MHz ^{1}H Spectrum of **4aai** in $CDCl_3$	304
Figure 4.21	125 MHz ^{13}C Spectrum of **4aai** in $CDCl_3$	304
Figure 4.22	471 MHz ^{19}F NMR of **4aai** in $CDCl_3$	305
Figure 4.23	500 MHz ^{1}H Spectrum of **4aaj** in $CDCl_3$	306
Figure 4.24	125 MHz ^{13}C Spectrum of **4aaj** in $CDCl_3$	306
Figure 4.25	500 MHz ^{1}H Spectrum of **4aak** in $CDCl_3$	307
Figure 4.26	125 MHz ^{13}C Spectrum of **4aak** in $CDCl_3$	307
Figure 4.27	500 MHz ^{1}H Spectrum of **4aal** in $CDCl_3$	308
Figure 4.28	125 MHz ^{13}C Spectrum of **4aal** in $CDCl_3$	308
Figure 4.29	500 MHz ^{1}H Spectrum of **4aam** in $CDCl_3$	309
Figure 4.30	125 MHz ^{13}C Spectrum of **4aam** in $CDCl_3$	309
Figure 4.31	500 MHz ^{1}H Spectrum of **4aan** in $CDCl_3$	310
Figure 4.32	125 MHz ^{13}C Spectrum of **4aan** in $CDCl_3$	310
Figure 4.33	500 MHz ^{1}H Spectrum of **4aao** in $CDCl_3$	311
Figure 4.34	125 MHz ^{13}C Spectrum of **4aao** in $CDCl_3$	311
Figure 4.35	500 MHz ^{1}H Spectrum of **4aap** in $CDCl_3$	312
Figure 4.36	125 MHz ^{13}C Spectrum of **4aap** in $CDCl_3$	312
Figure 4.37	500 MHz ^{1}H Spectrum of **4aaq** in $CDCl_3$	313
Figure 4.38	125 MHz ^{13}C Spectrum of **4aaq** in $CDCl_3$	313
Figure 4.39	500 MHz ^{1}H Spectrum of **4aas** in $CDCl_3$	314
Figure 4.40	125 MHz ^{13}C Spectrum of **4aas** in $CDCl_3$	314
Figure 4.41	500 MHz ^{1}H Spectrum of **4aat** in $CDCl_3$	315

Figure 4.42 125 MHz ^{13}C Spectrum of **4aat** in $CDCl_3$ 315
Figure 4.43 500 MHz ^{1}H Spectrum of **4aau** in $CDCl_3$ 316
Figure 4.44 125 MHz ^{13}C Spectrum of **4aau** in $CDCl_3$ 316
Figure 4.45 500 MHz ^{1}H Spectrum of **4aav** in $CDCl_3$ 317
Figure 4.46 125 MHz ^{13}C Spectrum of **4aav** in $CDCl_3$ 317
Figure 4.47 500 MHz ^{1}H Spectrum of **4aaw** in $CDCl_3$ 318
Figure 4.48 125 MHz ^{13}C Spectrum of **4aaw** in $CDCl_3$ 318
Figure 4.49 500 MHz ^{1}H Spectrum of **4aax** in $CDCl_3$ 319
Figure 4.50 125 MHz ^{13}C Spectrum of **4aax** in $CDCl_3$ 319
Figure 4.51 500 MHz ^{1}H Spectrum of **4aar** in $CDCl_3$ 320
Figure 4.52 125 MHz ^{13}C Spectrum of **4aar** in $CDCl_3$ 320
Figure 4.53 500 MHz ^{1}H Spectrum of **4aay** in $CDCl_3$ 321
Figure 4.54 125 MHz ^{13}C Spectrum of **4aay** in $CDCl_3$ 321
Figure 4.55 500 MHz ^{1}H Spectrum of **4aaz** in $CDCl_3$ 322
Figure 4.56 125 MHz ^{13}C Spectrum of **4aaz** in $CDCl_3$ 322
Figure 4.57 500 MHz ^{1}H Spectrum of **4abk** in $CDCl_3$ 323
Figure 4.58 125 MHz ^{13}C Spectrum of **4abk** in $CDCl_3$ 323
Figure 4.59 500 MHz ^{1}H Spectrum of **4ack** in $CDCl_3$ 324
Figure 4.60 125 MHz ^{13}C Spectrum of **4ack** in $CDCl_3$ 324
Figure 4.61 500 MHz ^{1}H Spectrum of **4ajk** in $CDCl_3$ 325
Figure 4.62 125 MHz ^{13}C Spectrum of **4ajk** in $CDCl_3$ 325
Figure 4.63 500 MHz ^{1}H Spectrum of **4akk** in $CDCl_3$ 326
Figure 4.64 125 MHz ^{13}C Spectrum of **4akk** in $CDCl_3$ 326
Figure 4.65 500 MHz ^{1}H Spectrum of **4aba** in $CDCl_3$ 327
Figure 4.66 125 MHz ^{13}C Spectrum of **4aba** in $CDCl_3$ 327
Figure 4.67 500 MHz ^{1}H Spectrum of **4aca** in $CDCl_3$ 328
Figure 4.68 125 MHz ^{13}C Spectrum of **4aca** in $CDCl_3$ 328
Figure 4.69 500 MHz ^{1}H Spectrum of **4ada** in $CDCl_3$ 329
Figure 4.70 125 MHz ^{13}C Spectrum of **4ada** in $CDCl_3$ 329
Figure 4.71 500 MHz ^{1}H Spectrum of **4aga** in $CDCl_3$ 330
Figure 4.72 125 MHz ^{13}C Spectrum of **4aga** in $CDCl_3$ 330
Figure 4.73 500 MHz ^{1}H Spectrum of **4aha** in $CDCl_3$ 331
Figure 4.74 125 MHz ^{13}C Spectrum of **4aha** in $CDCl_3$ 331

Figure 4.75 500 MHz ^{1}H Spectrum of **4aia** in $CDCl_3$ 332
Figure 4.76 125 MHz ^{13}C Spectrum of **4aia** in $CDCl_3$ 332
Figure 4.77 471 MHz ^{19}F NMR of **4aia** in $CDCl_3$ 333
Figure 4.78 500 MHz ^{1}H Spectrum of **4aja** in $CDCl_3$ 334
Figure 4.79 125 MHz ^{13}C Spectrum of **4aja** in $CDCl_3$ 334
Figure 4.80 500 MHz ^{1}H Spectrum of **4aka** in $CDCl_3$ 335
Figure 4.81 125 MHz ^{13}C Spectrum of **4aka** in $CDCl_3$ 335
Figure 4.82 500 MHz ^{1}H Spectrum of **4aea** in DMSO-d_6 336
Figure 4.83 125 MHz ^{13}C Spectrum of **4aea** in $CDCl_3$ 336
Figure 4.84 500 MHz ^{1}H Spectrum of **4afa** in $CDCl_3$ 337
Figure 4.85 125 MHz ^{13}C Spectrum of **4afa** in $CDCl_3$ 337
Figure 4.86 500 MHz ^{1}H Spectrum of **4ama** in $CDCl_3$ 338
Figure 4.87 125 MHz ^{13}C Spectrum of **4ama** in $CDCl_3$ 338
Figure 4.88 500 MHz ^{1}H Spectrum of **4ana** in $CDCl_3$ 339
Figure 4.89 125 MHz ^{13}C Spectrum of **4ana** in $CDCl_3$ 339
Figure 4.90 500 MHz ^{1}H Spectrum of **4aoa** in $CDCl_3$ 340
Figure 4.91 125 MHz ^{13}C Spectrum of **4aoa** in $CDCl_3$ 340
Figure 4.92 500 MHz ^{1}H Spectrum of **4daa** in $CDCl_3$ 341
Figure 4.93 500 MHz ^{1}H Spectrum of **4caa** in $CDCl_3$ 342
Figure 4.94 125 MHz ^{13}C Spectrum of **4caa** in $CDCl_3$ 342
Figure 4.95 500 MHz ^{1}H Spectrum of **4baa** in $CDCl_3$ 343
Figure 4.96 125 MHz ^{13}C Spectrum of **4baa** in $CDCl_3$ 343
Figure 4.97 500 MHz ^{1}H Spectrum of **4aqa** in $CDCl_3$ 344
Figure 4.98 125 MHz ^{13}C Spectrum of **4aqa** in $CDCl_3$ 344
Figure 4.99 500 MHz ^{1}H Spectrum of **3t** in $CDCl_3$ 345
Figure 4.100 125 MHz ^{13}C Spectrum of **3t** in $CDCl_3$ 345
Figure 4.101 500 MHz ^{1}H Spectrum of **3u** in $CDCl_3$ 346
Figure 4.102 125 MHz ^{13}C Spectrum of **3u** in $CDCl_3$ 346
Figure 4.103 500 MHz ^{1}H Spectrum of **3r** in $CDCl_3$ 347
Figure 4.104 125 MHz ^{13}C Spectrum of **3r** in $CDCl_3$ 347
Figure 4.105 500 MHz ^{1}H Spectrum of **3z** in $CDCl_3$ 348
Figure 4.106 125 MHz ^{13}C Spectrum of **3z** in $CDCl_3$ 348
Figure 4.107 500 MHz ^{1}H Spectrum of **1d** in $CDCl_3$ 349

Figure 4.108 500 MHz ^{1}H Spectrum of **1c** in $CDCl_3$ 349
Figure 4.109 500 MHz ^{1}H Spectrum of **1b** in $CDCl_3$ 350
Figure 4.110 125 MHz ^{13}C Spectrum of **1b** in $CDCl_3$ 350
Figure 4.111 500 MHz ^{1}H Spectrum of **3aa** in $CDCl_3$ 351
Figure 4.112 500 MHz ^{1}H Spectrum of **3ad** in $CDCl_3$ 351
Figure 4.113 125 MHz ^{13}C Spectrum of **3ad** in $CDCl_3$ 352
Figure 4.114 500 MHz ^{1}H Spectrum of **4ad** in $CDCl_3$ 352
Figure 4.115 500 MHz ^{1}H Spectrum of **5ad** in $CDCl_3$ 353
Figure 4.116 125 MHz ^{13}C Spectrum of **5ad** in $CDCl_3$ 353

LIST OF SCHEMES

Scheme 1.1	One-pot synthesis of tropinone	2
Scheme 1.2.	Construction of pyridine ring from acetylene and hydrogen cyanide gas	8
Scheme 1.3	Hantzsch pyridine synthesis	8
Scheme 1.4	Chichibabin reaction for pyridine synthesis	9
Scheme 1.5	Synthesis of trisubstituted pyridines *via* Bohlmann-Rahtz's method	9
Scheme 1.6	Synthesis of 2,4,6-trisubstituted pyridines	10
Scheme 1.7	One-pot reaction of enaminoketones with acetyl acetones to afford pyridines	10-11
Scheme 1.8	MCR approach to trisubstituted pyridines	11
Scheme 1.9	Regioselective synthesis of tri- and tetrasubstituted pyridines *via* a hetero-Dials-Alder reaction	12
Scheme 1.10	Rh(I)-catalyzed *ortho*-arylation of pyridines	12-13
Scheme 1.11	Ce(III)-catalyzed synthesis of 2,3,6-trisubstituted pyridines	13
Scheme 1.12	$NbCl_5$-catalyzed cycloaddition of *tert*-butyl acetylene with aryl/alkylnitriles	14
Scheme 1.13	Two-step sequential strategy to access trisubstituted pyridines	14-15
Scheme 1.14	$FeCl_3$-catalyzed hetero-cyclization reaction of ketoxime acetates and N, N-dimethyl aniline	15
Scheme 1.15	$FeCl_3$-promoted reaction of β-enamine esters with enones to offer trisubstituted pyridines	16
Scheme 1.16	$FeCl_3$-catalyzed domino reaction to the synthesis of Pyridines	17
Scheme 1.17	Synthesis of tri- and tetrasubstituted pyridines *via* a domino reaction	17

Scheme 1.18	DBU-promoted ring expansion of 2*H*-azirines to access trisubstituted pyridines	18
Scheme 1.19	Metal-free one-pot sequential technique for accessing disubstituted pyridines	18-19
Scheme 1.20	NH_4OAc-promoted synthesis of tri- and tetrasubstituted unsymmetrical pyridines	19-20
Scheme 1.21	Construction of 4-unsubstituted pyrazolones using hydrazine hydrates and alkyl acetoacetates	20
Scheme 1.22	Access to dihydro pyrazolones from pyrazolidinone	20
Scheme 1.23	Et_3N-catalyzed synthesis of pyrimidinyl pyrazolones	21
Scheme 1.24	Piperidine-catalyzed synthesis of indole derived pyrazolones	22
Scheme 1.25	Synthesis of benzylidene pyrazolones *via* Knoevenagel condensation reaction	21-22
Scheme 1.26	Au/Ag-catalyzed intramolecular cyclization/aryl migration for the synthesis of benzylidene pyrazolones	22
Scheme 1.27	DBU-promoted cycloaddition reaction for synthesizing fused pyrazoles	22-23
Scheme 1.28	Cs_2CO_3-promoted cyclopropanation of unsaturated pyrazolones with sulfur ylides	23
Scheme 1.29	DABCO-catalyzed one-pot strategy for accessing 4-arylidene pyrazolones	24
Scheme 1.30	DDQ-mediated one-pot strategy to give 1,3-diarylallylidene pyrazolones	24-25
Scheme 2.1	Rh(I)-catalyzed direct *ortho*-arylation of pyridines	36
Scheme 2.2	DBU promoted ring expansion of 2*H*-azirines	36
Scheme 2.3	Ruthenium-catalyzed synthesis of 2,4-diaryl substituted pyridines	37
Scheme 2.4	Cu-catalyzed cascade approach to pyridines	37-38

Scheme 2.5	I_2/Et_3N-promoted reaction of ketoximes with acroleins	38
Scheme 2.6	Fe-catalyzed hetero-cyclization reaction for accessing di-substituted pyridines	39
Scheme 2.7	Cu(II)-catalyzed Michael addition/cyclization of β-enaminones with ketones to construct pyridines	40
Scheme 2.8	Fe(III)/In(III)-catalyzed decarboxylative cyclization reaction to construct pyridines	41
Scheme 2.9	Domino approach to the synthesis of pyridines	41
Scheme 2.10	Metal-free regioselective synthesis of di- and tri-substituted pyridines	42
Scheme 2.11	Substrate scope of 2,4-diarylpyridines using acyclic ketones	47-48
Scheme 2.12	Metal-free domino access to carbo- and heterocycle-fused pyridines by utilizing cyclic ketones	49-50
Scheme 2.13	Regioselective access to 2,6-disubstituted nicotinates and 7,8-dihydroquinoline-5(*6H*)-one	51
Scheme 2.14	Access to the 5,6-dihydrobenzo[*b*][1,7]phenanthroline derivative	51
Scheme 2.15	Control experiments	52
Scheme 2.16	A plausible mechanism for this hetero-cyclization reaction	53
Scheme 3.1	Bohlmann-Rahtz pyridine synthesis	136
Scheme 3.2	One-pot three-component cyclization reaction for accessing to 2,3,6-trisubstituted pyridines	136-137
Scheme 3.3	$NbCl_5$-catalyzed cyclization of *tert*-butyl acetylene with aryl/alkylnitriles	137-138
Scheme 3.4	Sequential approach to 2,3,6-trisubstituted pyridines	138
Scheme 3.5	Cu-catalyzed one-pot method for synthesizing 2,4,6-trisubstituted pyridines	139

Scheme 3.6	$FeCl_3$-promoted reaction of β-enaminoesters with enones to produce trisubstituted pyridines	139-140
Scheme 3.7	Cu(II)-catalyzed one-pot method for accessing pyridines	140
Scheme 3.8	Photocatalyzed and blue-LED promoted [2+2+2] cycloaddition of aryl alkynes with nitriles	141
Scheme 3.9	Cu(II)-catalyzed three component reaction for the synthesis of 2,4,6-trisubstituted pyridines	141-142
Scheme 3.10	Phosphine-catalyzed and DDQ-promoted one-pot synthesis of trisubstituted pyridine	142-143
Scheme 3.11	Organocatalyzed synthesis of 2,3,6-trisubstituted pyridines adorned with benzenesulfonamides and phenols	144
Scheme 3.12	Organocatalyzed sequential approach to 2,3,6-trisubstituted pyridines	148-150
Scheme 3.13	One-pot access to benzenesulfonamide adorned 2,3,6-trisubstituted pyridines	151-152
Scheme 3.14	One-pot access to 3-picoline derivatives	153-154
Scheme 3.15	Access to 2-(5*H*-chromeno[4,3-*b*]pyridine-5-ylidene) derivatives **19,** 5*H*-chromeno[4,3-*b*]pyridine-5-one **20** anddi(pyridine-3-yl)methane **21**	155
Scheme 3.16	Control experiments	155-156
Scheme 3.17	A plausible mechanism of this $C(sp^3)$–H alkylation-aza-cyclization reaction	157
Scheme 4.1	Access to benzylidene pyrazolones via Knoevenagel condensation reaction	262-263
Scheme 4.2	Sodium acetate-catalyzed synthesis of arylidene prazolones	263
Scheme 4.3	Au-catalyzed intramolecular cyclization/aryl migration for accessing benzylidene pyrazolones	264
Scheme 4.4	A simple catalyst-free approach to α,β,γ,δ-unsaturated prazolones	264-265

Scheme 4.5	DABCO-catalyzed one-pot approach to 4-arylidene pyrazolones	265-266
Scheme 4.6	DDQ-mediated one-pot strategy for accessing 1,3-diarylallylidene pyrazolones	266-267
Scheme 4.7	Pyrrolidine-BzOH salt-catalyzed one-pot three-component reaction of pyrazolones	268
Scheme 4.8	NH_4OAc-mediated synthesis of 1,3-diphenylallyl pyrazolone	269
Scheme 4.9	Pot-economy access to unsaturated pyrazolones (**4aaa-4daa)**	272
Scheme 4.10	Pot-economy access to unsaturated pyrazolones (**4aab-4akk**)	274-275
Scheme 4.11	Gram-scale synthesis of **4aaa**	276
Scheme 4.12	Control experiments	277-278
Scheme 4.13	Plausible mechanistic pathways for this double-condensation reaction	280

LIST OF TABLES

Table 2.1	Optimization of reaction conditions	44-45
Table 3.1	Optimization of reaction conditions	145-146
Table 4.1	Optimization of reaction conditions	270-271

Chapter 1

General Introduction and Background: Pyridines and Pyrazolones

Chapter 1

Introduction and Background: Pyridines and Pyrazolones

1.1 General Introduction:

The field of chemistry has drawn huge attention and prestige from the scientific community and society since the last century due to its excellence in efficiently addressing therapeutic challenges and other important applications globally, which has substantially increased human life expectancy and quality of life. Nature has been a great motivator for us in setting complex targets, which are crucial in the design and synthesis of medicines, vitamins, agrochemicals, and functional materials, among others. The challenge for synthetic chemists is to synthesize these complex targets and related complex scaffolds in large amounts to feed global needs. Today, synthetic organic chemists have achieved a milestone by synthesizing almost all known natural complex targets in the laboratory on a small scale. Leaving scope for further improvements in strategies to produce them on a large scale. In the last four decades, one-pot chemical synthesis has emerged as a new strategy for synthetic chemists as a better solution to the above problems.[1-3]

1.2 One-Pot Chemical Synthesis:

One-pot synthesis is the construction of two or more bonds in a single reaction vessel without isolating intermediates. The term “one-pot” has a broader meaning; it is valid for multiple successive reactions executed in a sequence in the same reaction pot without purifying any intermediates. This strategy of bond formations has been adopted widely among synthetic chemists[2,4] due to its beneficial efficiency and sustainability in the chemical transformation process over multi-step traditional methods such as reducing tedious purification steps, minimizing solvent usage, saving time, work force, reducing cost, minimal by-products and significantly improved yields of the final synthesized products. Thus, it offers a practical applicability of

synthesized targets on a large scale to serve society's needs. Various terms like 'domino reaction', 'cascade reaction', and 'tandem reaction' are used for 'one-pot reactions' for meaningful sub-division. [5]

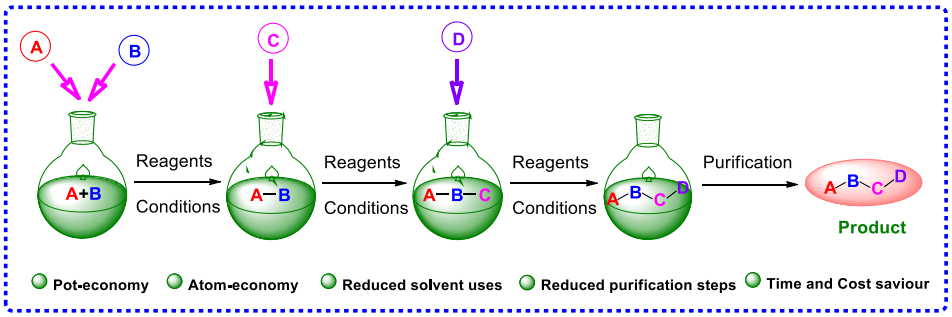
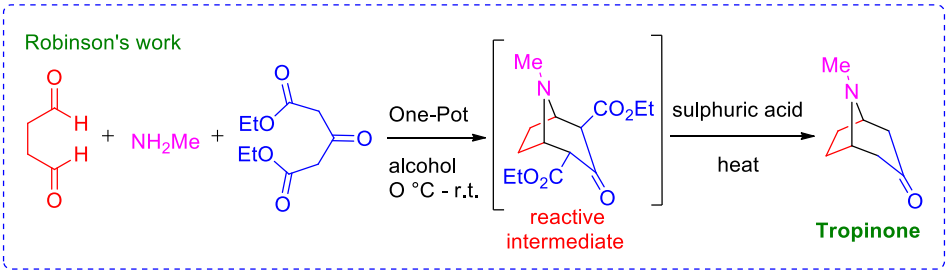


Figure 1.1 One-pot synthesis

In literature, one-pot synthesis was reported first by Robinson in 1917. He synthesized *N*-alkyl bicyclic natural alkaloid tropinone by involving succinaldehyde, ethyl acetone-dicarboxylate, and methyl amine in alcohol under at 0 °C to rt, followed by acidic treatment.[6] Later, this tropinone is utilized specifically as a building block for synthesizing anti-colic and spasmolytic drugs (class of tropine alkaloids). This method has been well-recognized as an efficient and pot-economical route for accessing many drug scaffolds, pharmaceuticals, and complex molecules since the 20th century (**Scheme 1.1**)



Scheme 1.1 One-pot synthesis of tropinone

The field of organocatalysis has evolved as a good partner for this one-pot strategy in the last three decades. Organocatalysts are compatible with setting up one-pot reactions for multi-step synthesis.[4] Our research group has developed several one-pot methods for synthesizing biologically recognized carbo- and heterocyclic scaffolds using organocatalysts and has significantly

contributed to synthetic chemistry.[7-13] As part of our continued one-pot synthesis, we are interested in exploring important aza-heterocyclic scaffolds, pyridines, and pyrazolones.

1.3 Historical Background:

1.3.1 Pyridine:

Pyridine is a six-membered aromatic aza-heterocycle with the molecular formula C_5H_5N **(Figure 1.2)**. Chemical structure-wise, it is similar to benzene with one C-H group of benzene replaced by one N-atom. In 1849, for the first time, it was isolated from bone oil by Anderson[14] and later, in 1869, Wilhelm Körner and James Dewar determined its chemical structure.[15-16]

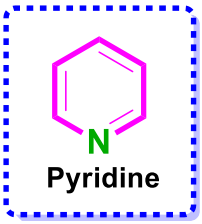


Figure 1.2. The general structure of pyridine

The pyridine motif is pivotal as a structural component in enormous bioactive natural and synthetic alkaloids, pharmaceutical precursors for drug candidates, and agrochemicals. Moreover, pyridine is present as a subunit in vitamins (niacin and pyridoxine), nicotine (a euphoriant), picoline, and redox nucleotides NADP-NADPH coenzymes, which actively take part in energy metabolism along with other biochemical antioxidant functions. In addition, synthetically incorporated pyridine scaffolds have immense practical utilization in supramolecular chemistry, functional materials, and inorganic metal-ligand complex formation to carry out catalytic symmetric and asymmetric organic transformations. [17- 30] Understanding their medicinal significance and other essential importance, chemists worldwide have made enormous contributions by constructing various structurally complex pyridine derivatives that mimic marketable drug-like molecules **(Figure 1.3-1.5** shows some important pyridine molecules). [31,32]

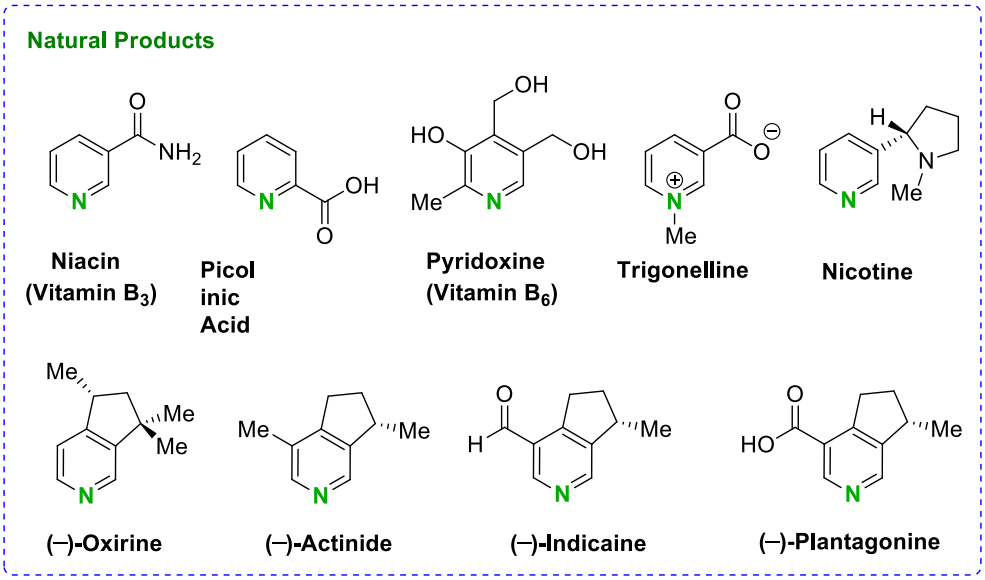


Figure 1.3. Natural occurrence of pyridines

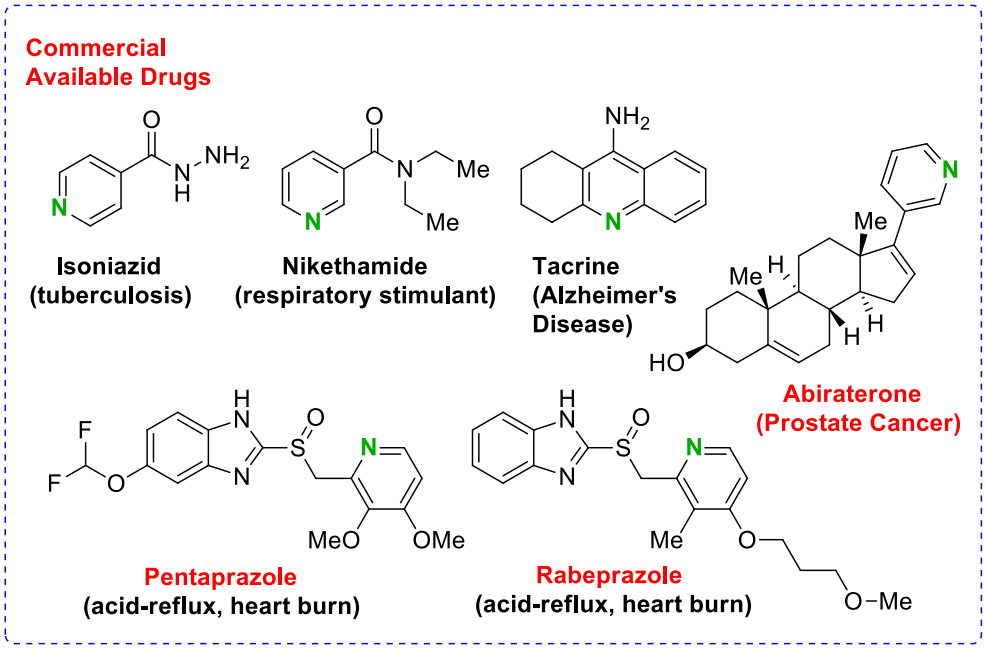


Figure 1.4 A few examples of marketed drugs consisting of pyridine

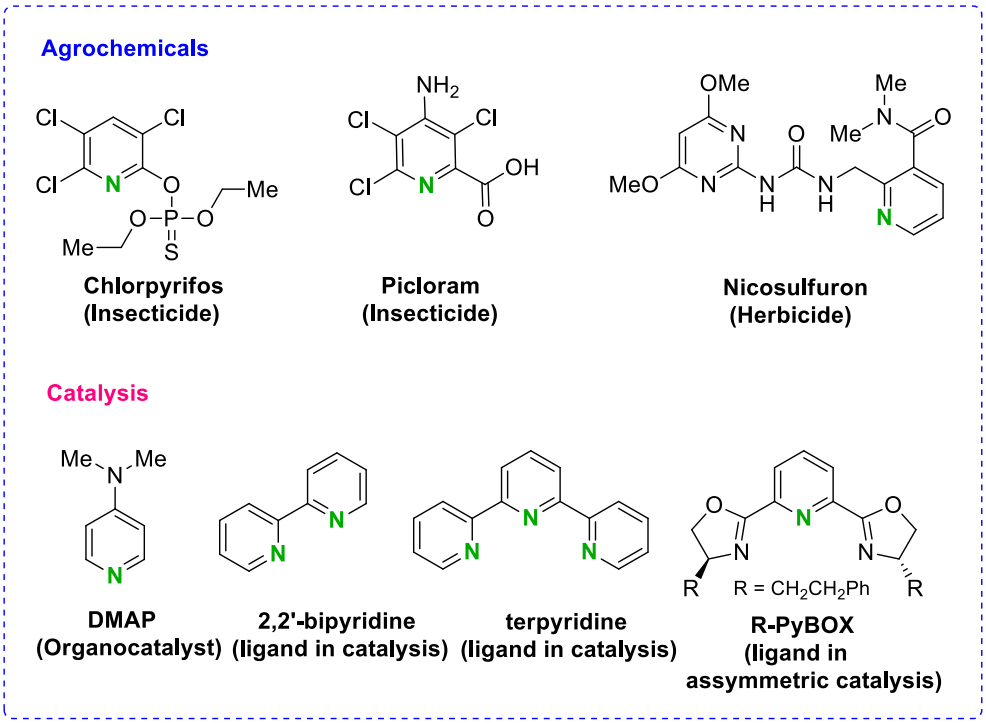


Figure 1.5 Some selected examples of agrochemicals and ligands used in catalysis contain a pyridine motif as a core

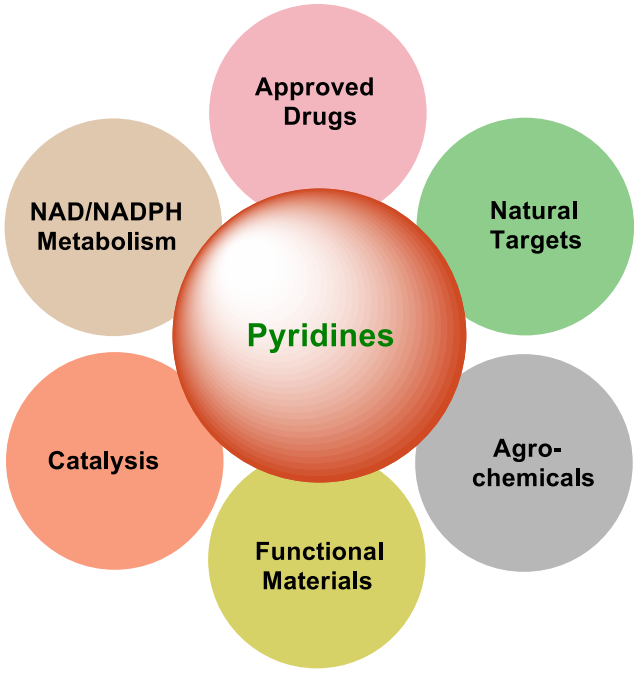


Figure 1.6 General representative picture showing wide applications of pyridines.

1.3.2 Pyrazolone:

Pyrazolone is a five-membered versatile heterocyclic molecule with structural formula $C_3H_4N_2O$ **(Figure 1.7)**. This five-membered ring consists of nitrogen-nitrogen adjacent bonds, a lactam moiety, and a reactive methylene center at C4 which is highly useful in synthetic transformation.[33-34] This aza-hetero cycle has received immense attention from different arenas because of its presence in active pharmaceuticals and

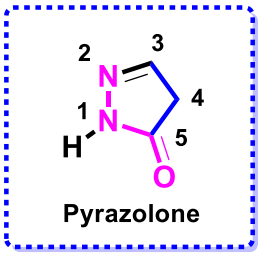


Figure 1.7 General structure of pyrazolone

approved drug molecules. These properties of pyrazolone are closely related to its structural features. Their 4-alkylidene derivatives have proven effective against many biological targets like SARS-CoV 3CL protease inhibitors, neuraminidase H1N1 and H5N1 inhibitors, farnesoid X receptor (FXR) selective antagonists, HIV-1 integrase inhibitors, anti-orthopoxvirus activity etc.[35-41] Thus, it has emerged as a highly valued reactive intermediate in the last two decades. Some relevant pyrazolone molecules are sketched in **Figures 1.8** and **1.9**.

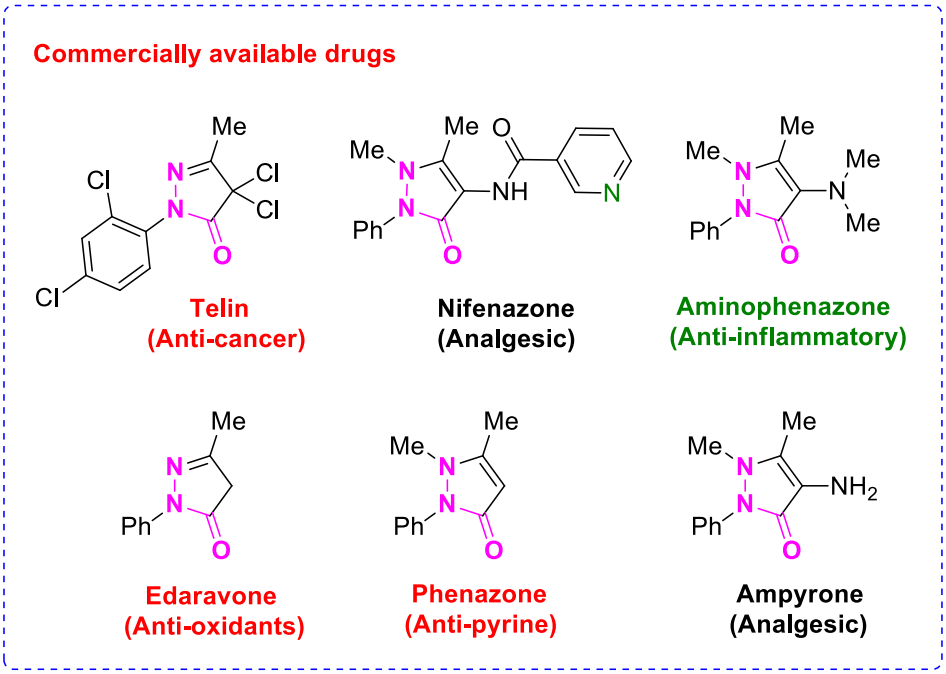


Figure 1.8. Selected examples of pyrazolone-based active drugs

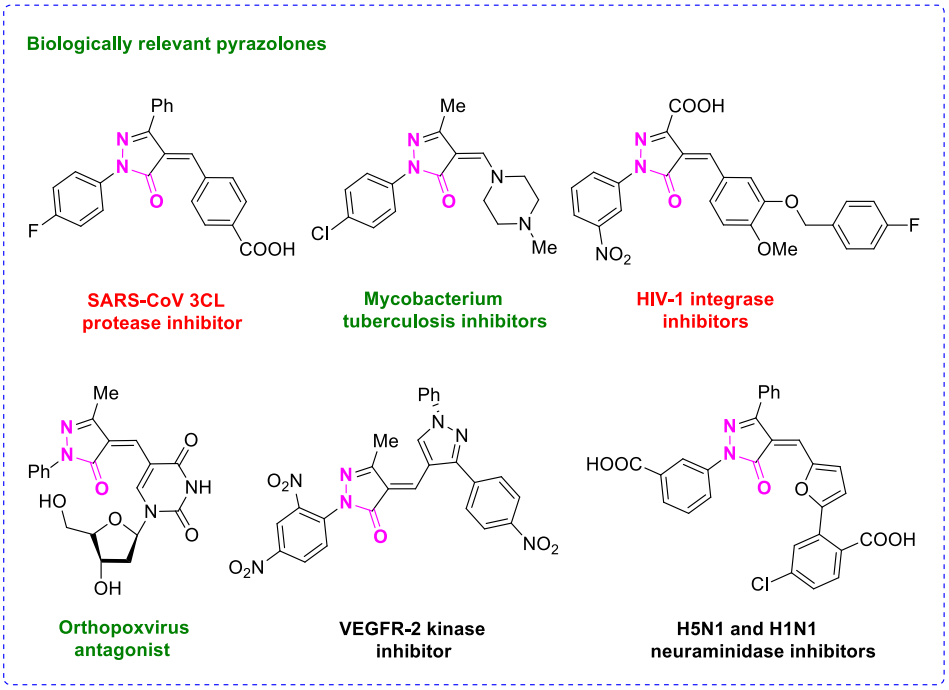


Figure 1.9. Some examples of biologically relevant pyrazolone derivatives

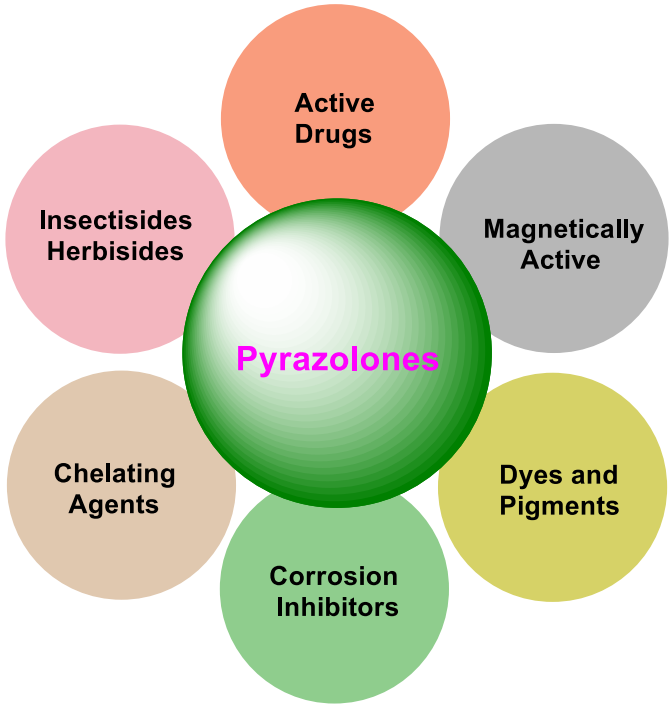
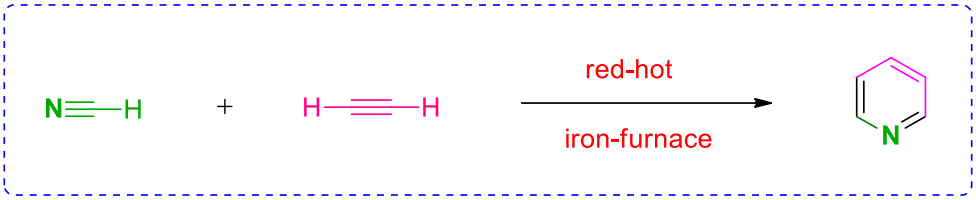


Figure 1.10. General representative sketch showing applications of pyrazolones.

1.4 Literature Study:

1.4.1 Synthesis of Functionalized Pyridines:

Pyridine was discovered for the first time in 1849, and its structure was assigned to it in 1869. Finally, Ramsay synthesized it for the first time[42] in 1876 by passing a mixture of acetylene and hydrogen cyanide gas through a red-hot iron tube **(Scheme 1.2)**.

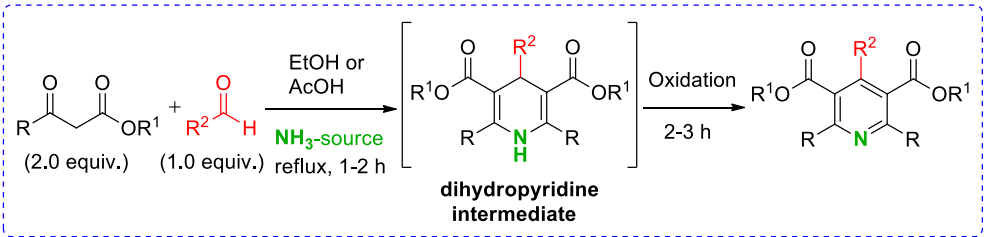


Scheme 1.2. Construction of pyridine ring from acetylene and hydrogen cyanide gas.

1.4.1.1 Classical Approaches:

Hantzsch pyridine synthesis:

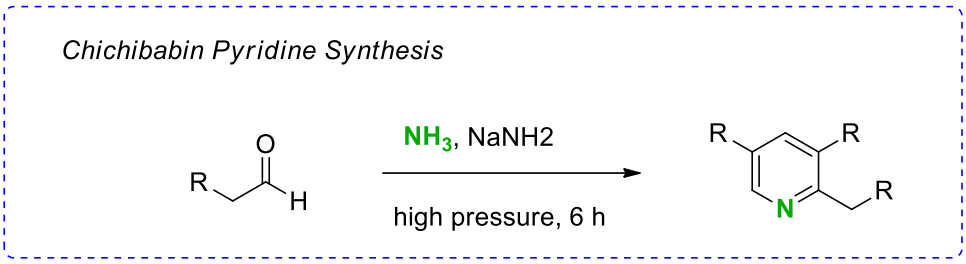
In 1881, Hantzsch developed a powerful method for synthesizing symmetrically substituted pyridines by a pseudo-four-component reaction between 1,3-dicarbonyls (2.0 equiv), aldehydes (1.0 equiv) and NH_4OAc as a good N-atom source for pyridine ring construction in alcoholic solvent to generate a dihydropyridine intermediate, which subsequently oxidized to produce the pyridines[43] **(Scheme 1.3)**.



Scheme 1.3. Hantzsch pyridine synthesis.

Chichibabin pyridine synthesis:

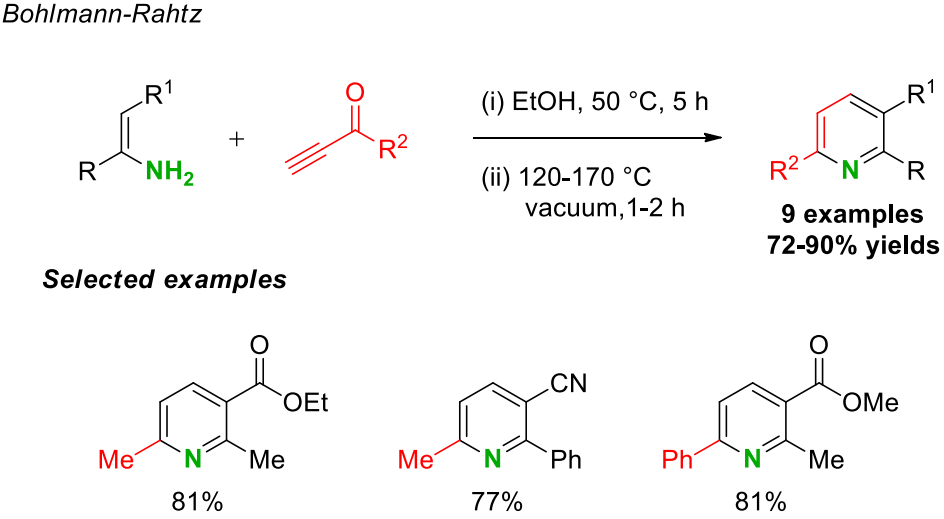
In 1924, Chichibabin disclosed a nice method for synthesizing tri-substituted pyridines involving enolizable aldehydes (3.0 equiv) and ammonia under high pressure in the presence of $NaNH_2$ **(Scheme 1.4)**.[44]



Scheme 1.4. Chichibabin reaction for pyridine synthesis.

Bohlmann-Rahtz Pyridine Synthesis:

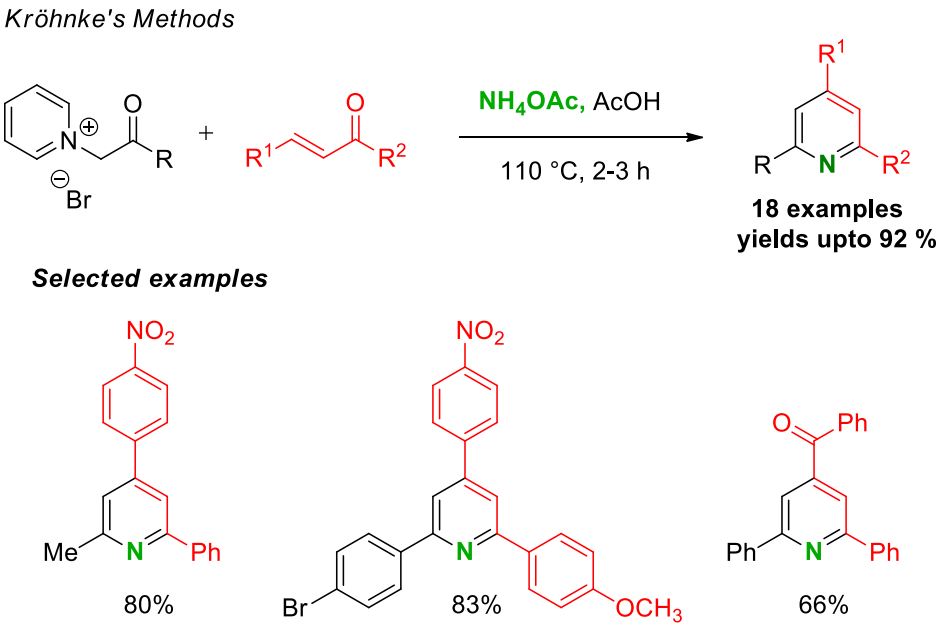
For the first time, Bohlmann and Rahtz (1957) synthesized 2,3,6-trisubstituted pyridines through a one-pot two-step sequential reaction of enamines and ethynyl ketones in EtOH at 50 °C. This reaction proceeds through Michael addition, followed by cyclization of the resulting Michael adducts at 120-170 °C under vacuum for 1-2 h. This sequential process allows the intended 2,3,6-trisubstituted pyridines in good to high yields ranging from 72% to 90% **(Scheme 1.5)**.[45]



Scheme 1.5. Synthesis of trisubstituted pyridines *via* Bohlmann-Rahtz's method.

Kröhnke pyridine synthesis:

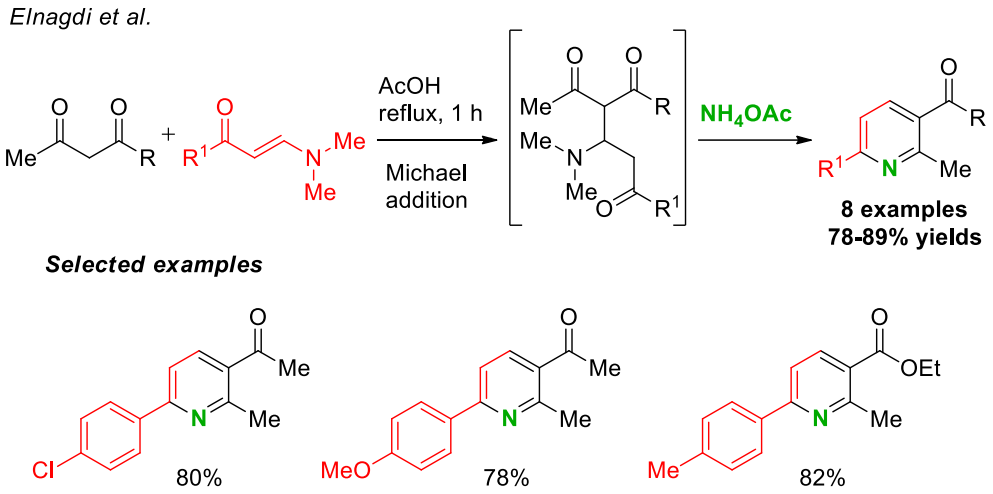
In 1976, the Kröhnke group established a powerful, one of the widely used methods for synthesizing symmetrical and unsymmetrical 2,4,6-trisubstituted pyridines involving various α,β-unsaturated ketones, pyridinium salts and NH_4OAc as N-atom source in boiling AcOH to provide good to high yields of pyridines in a reasonable time **(Scheme 1.6)**.[46]



Scheme 1.6. Synthesis of 2,4,6-trisubstituted pyridines.

Michael-reaction-based pyridine synthesis:

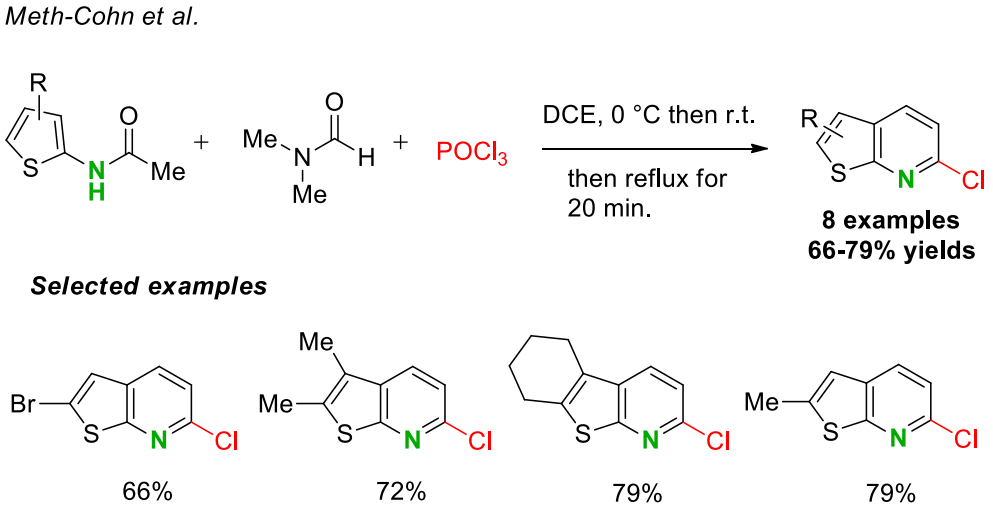
In 2002, Elnagdi *et al.* demonstrated a regioselective synthesis of 2,3,6-trisubstituted pyridines *via* a Michael addition reaction between acetyl acetones and enaminoketones followed by aza-cyclization using NH_4OAc. This strategy provides good to high yields ranging from 78% to 89% of the intended pyridines **(Scheme 1.7)**.[47]



Scheme 1.7. One-pot reaction of enaminoketones with acetyl acetones to afford pyridines.

Vilsmeier-Haack reaction-based pyridine synthesis:

In 1981, the Meth-Cohn group reported a one-pot method for accessing trisubstituted pyridines by utilizing acetamidothiophens, DMF, and $POCl_3$ *via* a Vilsmeier-Haack reaction. Interestingly, this one-pot method affords good yields (66-79%) of the targeted pyridines **(Scheme 1.8)**.[48]

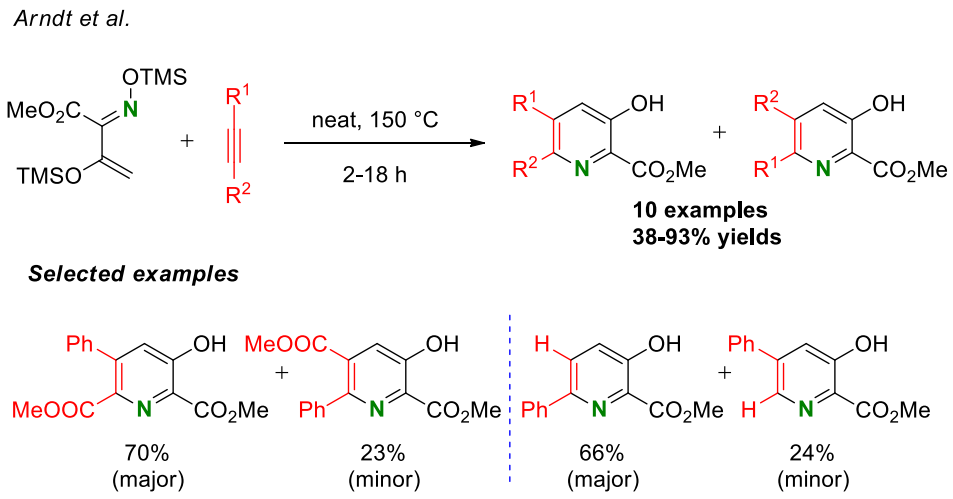


Scheme 1.8. MCR approach to trisubstituted pyridines.

1.4.1.2 Modern Strategies:

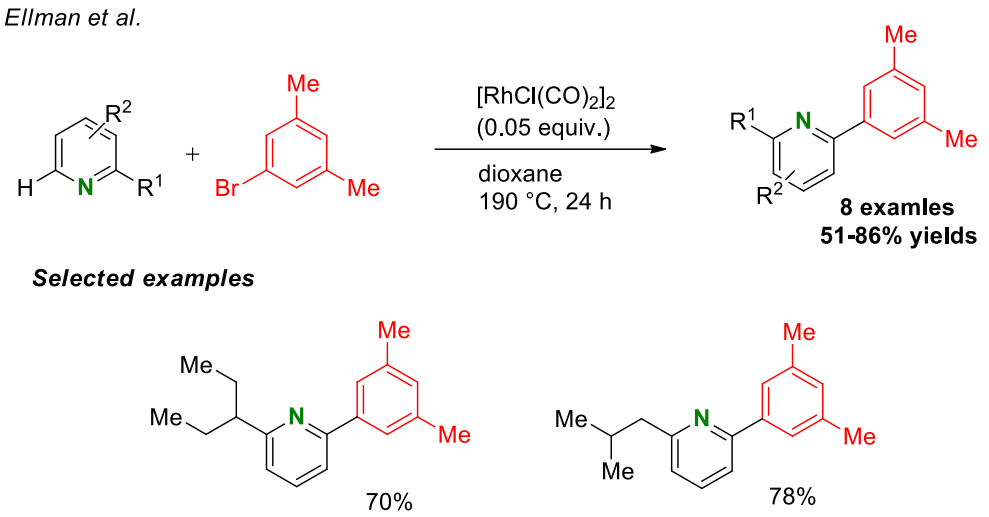
Transition metal-salts-catalyzed synthetic strategies:

In 2007, Arndt *et al.* reported a hetero-Dials-Alder reaction between silylated enol oximes (1-azadiene system) and substituted alkynes under neat conditions at 150 °C to offer tri- and tetrasubstituted pyridines regioselectively. This method provides moderate to high yields (38-93%) of the targeted pyridines **(Scheme 1.9)**.[49]



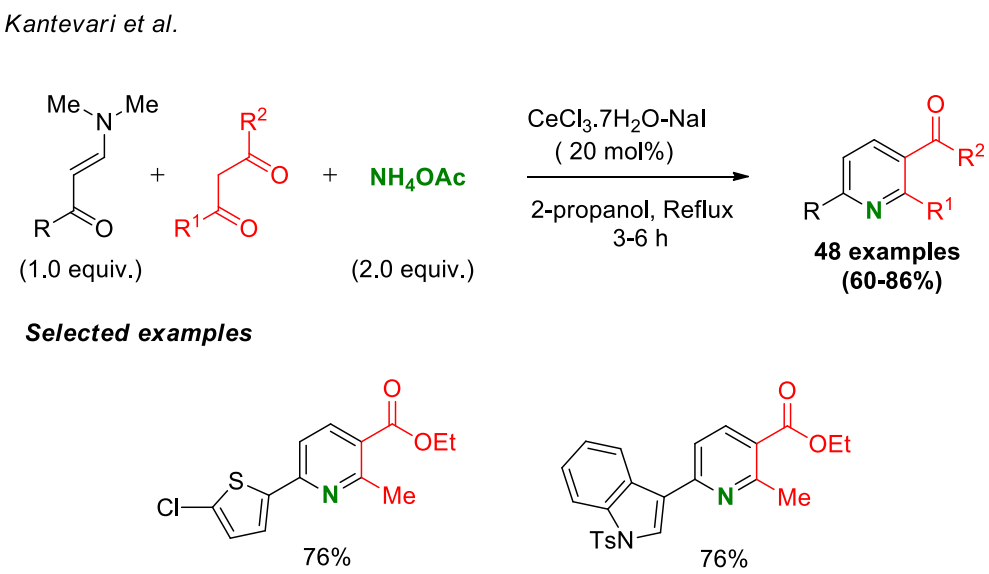
Scheme 1.9. Regioselective synthesis of tri- and tetrasubstituted pyridines via a hetero-Dials-Alder reaction.

Ellman *et al.* (2008) developed an efficient Rh(I)-catalyzed Csp^2–H ortho-arylation of pyridines using 3,5-dibromobenzene in dioxane at 190 °C for 24 h to produce di- and trisubstituted pyridines. This arylation reaction selectively provides good to high yields (51-86%) of pyridines **(Scheme 1.10)**.[50]



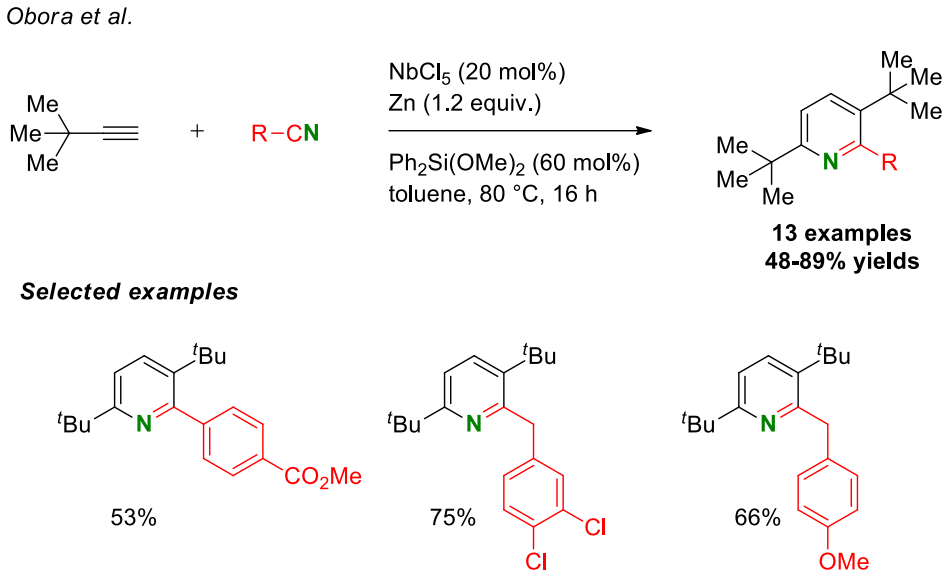
Scheme 1.10. Rh(I)-catalyzed *ortho*-arylation of pyridines.

In 2011, Kantevari *et al.* reported a new strategy for the synthesis of 2,3,6-trisubstituted pyridines from a variety of aryl/heteroaryl/cyclic/alkyl 1,3-dicarbonyl compounds, β-enaminones and ammonium acetate using a catalytic amount of $CeCl_3.7H_2O$-NaI. This process offers good to high yields (60-86%) of pyridines in **Scheme 1.11**.[51]



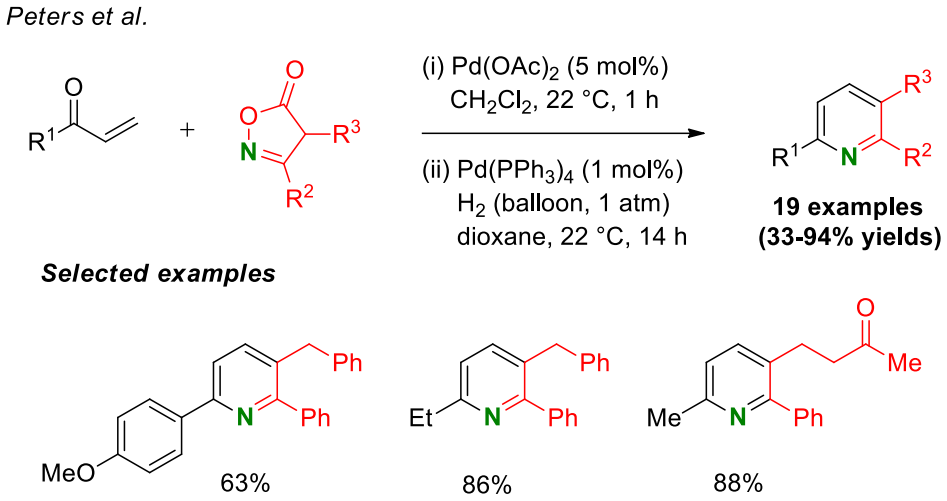
Scheme 1.11. Ce(III)-catalyzed synthesis of 2,3,6-trisubstituted pyridines.

In 2013, Obora *et al.* illustrated a simple, straightforward cycloaddition reaction of *tert*-butylacetylene with aryl nitrile using 20 mol% $NbCl_5$, Zn (1.2 equiv), and $Ph_2Si(OMe)_2$ as a combined catalytic system at 80 °C in toluene. This method provides trisubstituted pyridine derivatives in good to high yields, ranging from 48% to 89% as shown in **Scheme 1.12**.[52]



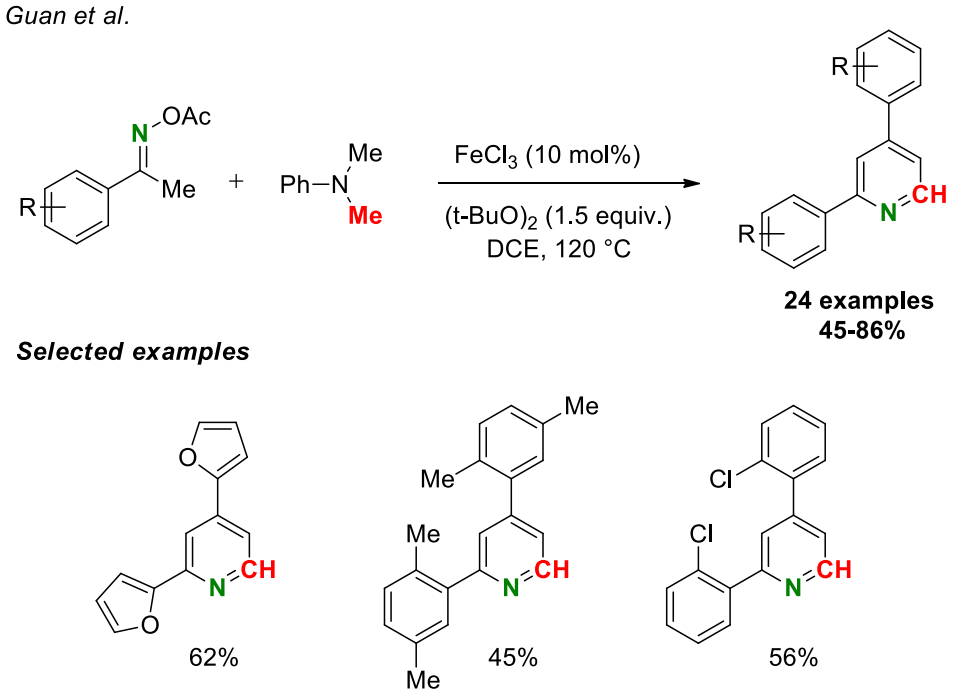
Scheme 1.12. $NbCl_5$-catalyzed cycloaddition of *tert*-butyl acetylene with aryl/alkylnitriles.

In 2015, Peters *et al.* established a mild sequential reaction involving vinyl ketones and isoxazolinones catalyzed by $Pd(OAc)_2$ to form 1,4-addition adducts, which were subjected to intramolecular cyclization in the presence of catalyst $Pd(PPh_3)_4$ under H_2-balloon. This sequential protocol endows a variable range of yields from 33% to 94% of the corresponding trisubstituted pyridines regioselectively **(Scheme 1.13)**.[53]



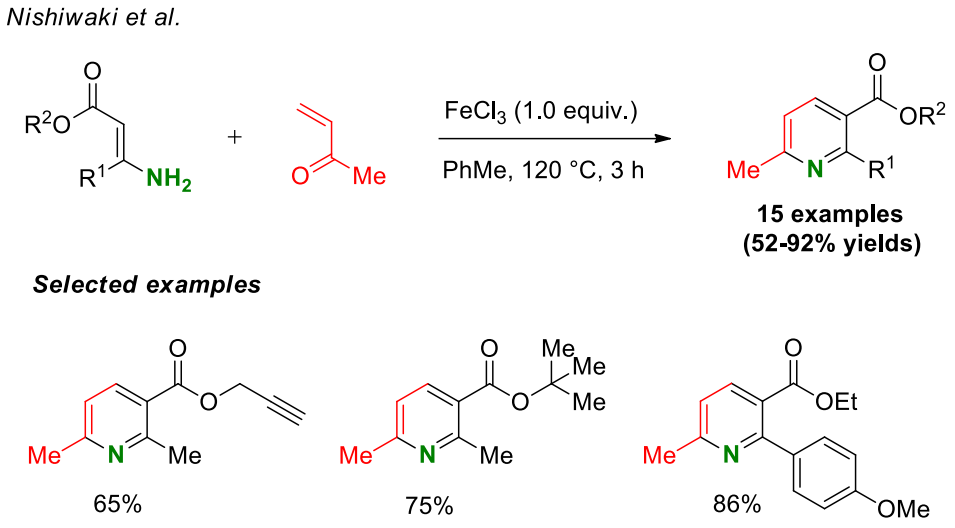
Scheme 1.13. Two-step sequential strategy to access trisubstituted pyridines.

In 2016, Guan *et al.* developed a powerful method for the construction of 2,4-disubstituted pyridines from ketoxime acetates and N, N-dimethyl aniline catalyzed by $FeCl_3$ in the presence of *tert*-butyl hydroperoxide (TBHP) as an external oxidant. This method provides moderate to high yields (45-86%) and allows a variety of functional groups in **Scheme 1.14**.[54]



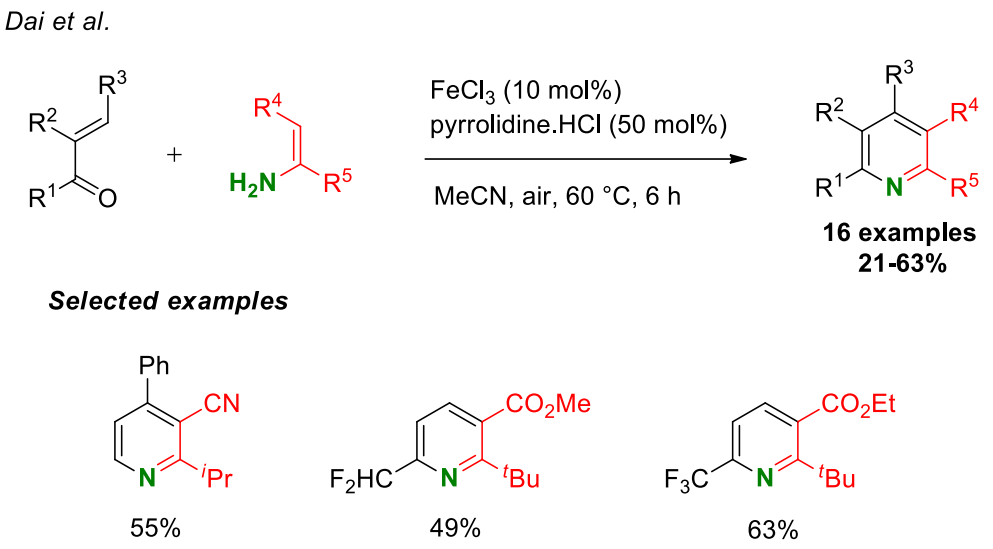
Scheme 1.14. $FeCl_3$-catalyzed hetero-cyclization reaction of ketoxime acetates and N, N-dimethyl aniline.

In 2017, Nishiwaki *et al.* developed a powerful $FeCl_3$-promoted condensation reaction of β-enamine esters with α,β-unsaturated ketones to produce the corresponding trisubstituted pyridines. This strategy offers a simple and efficient route to synthesize substituted pyridines in good to high yields (52-92%) as depicted in **Scheme 1.15**.[55]



Scheme 1.15. $FeCl_3$-promoted reaction of β-enamine esters with enones to offer trisubstituted pyridines.

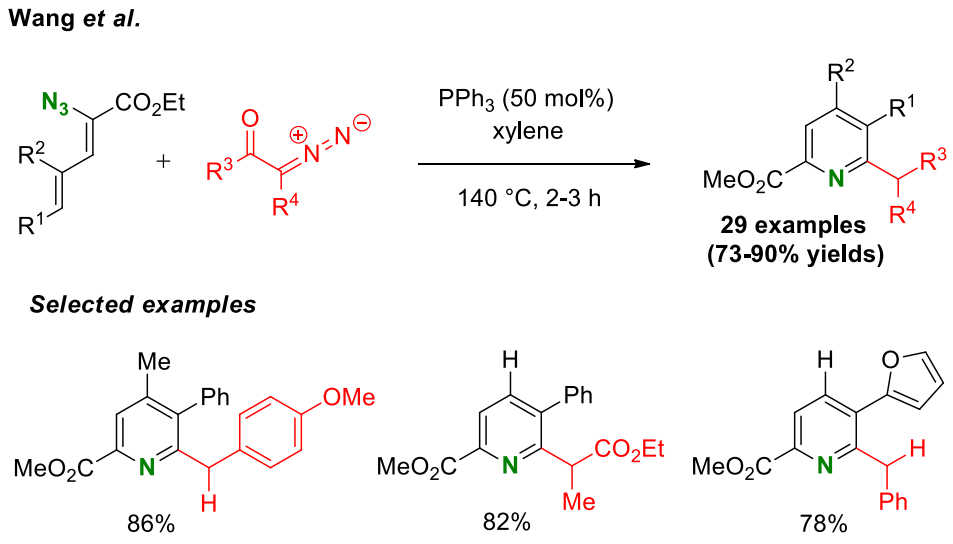
Recently, Dai *et al.* (2022) disclosed an organocatalyzed cycloaddition reaction of enamines with enone/enal derivatives using a catalytic amount of $FeCl_3$ in MeCN at 60 °C. This reaction offers a variety of trisubstituted pyridines in poor to good yields (21-63%) as illustrated in **Scheme 1.16**.[56]



Scheme 1.16. $FeCl_3$-catalyzed domino reaction to the synthesis of pyridines.

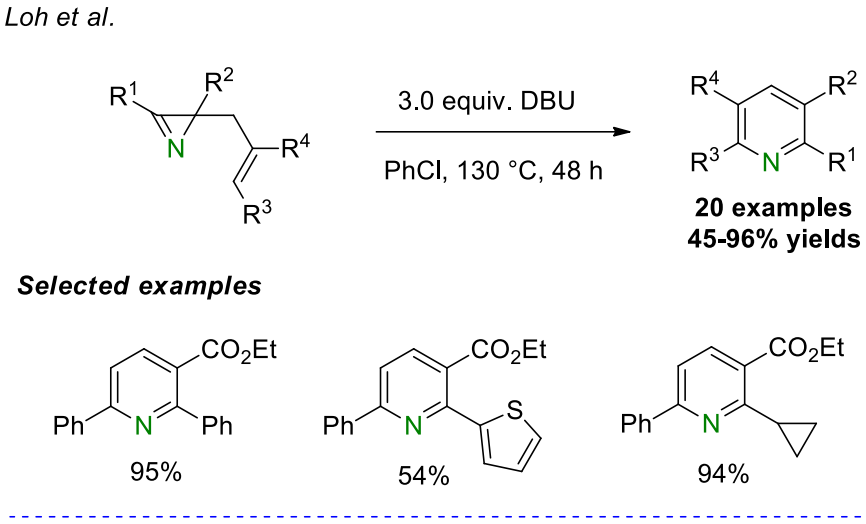
Transition metal-free strategies:

Wang *et al.* (2008) established an efficient one-pot domino reaction between 2-azido-2,4-dienoates in the catalytic amount of PPh_3 in xylene at 140 °C and α-diazo ketones to produce tri- and tetrasubstituted pyridines in good to excellent yields (73-90%) with high functional group tolerance **(Scheme 1.17)**.[57]



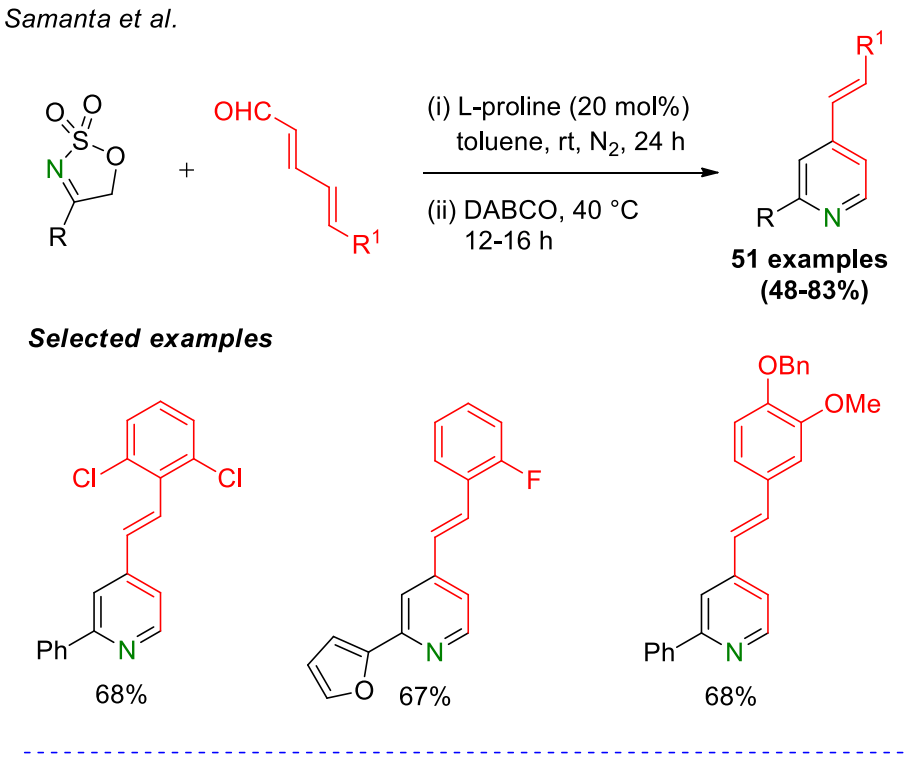
Scheme 1.17. Synthesis of tri- and tetrasubstituted pyridines *via* a domino reaction.

In 2014, Loh *et al.* accomplished a simple 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) promoted intramolecular aza-cyclization technique to open the 2-allyl-2*H*-azirines into 1-aza trienes that led to the intended pyridines *via* electro-cyclization process. This protocol offers moderate to excellent yields (45-96%) of nicotinates (**Scheme 1.18**).[58]



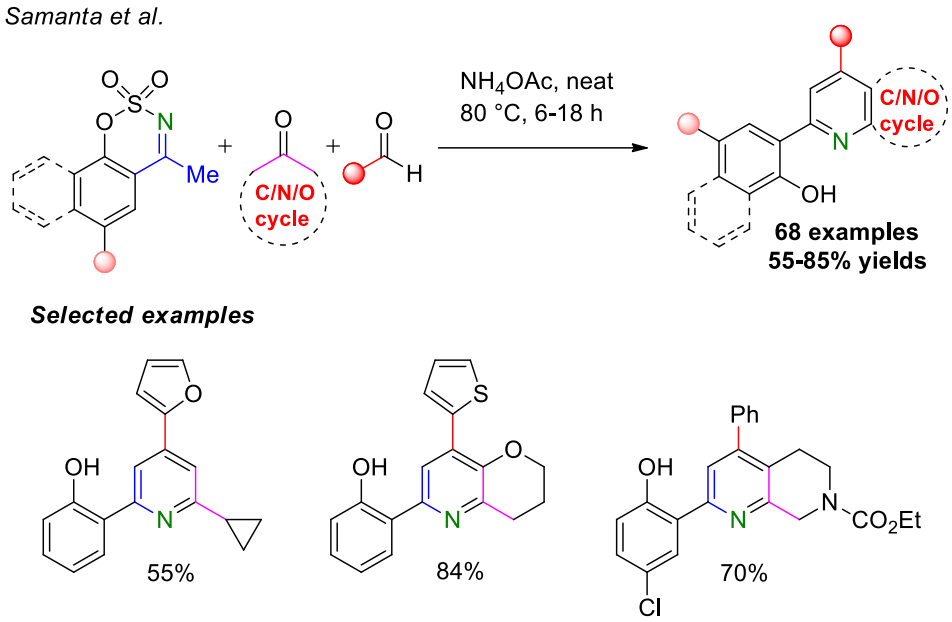
Scheme 1.18. DBU-promoted ring expansion of 2*H*-azirines to access trisubstituted pyridines.

Samanta *et al.* (2017) developed a sequential one-pot, two-step technique to access 2,4-disubstituted pyridines. This reaction uses L-proline to facilitate the Michael addition reaction between cyclic sulfamidate imines and α,β,γ,δ-substituted acroleins to give the Michael adducts, which are subsequently converted into pyridines via an elimination-imino cyclization-dehydration process in the presence of DABCO (1.5 equiv) at 40 °C. This metal-free process endows good to high yields (48-83%) of the pyridines as illustrated in **Scheme 1.19**.[59]



Scheme 1.19. Metal-free one-pot sequential technique for accessing disubstituted pyridines.

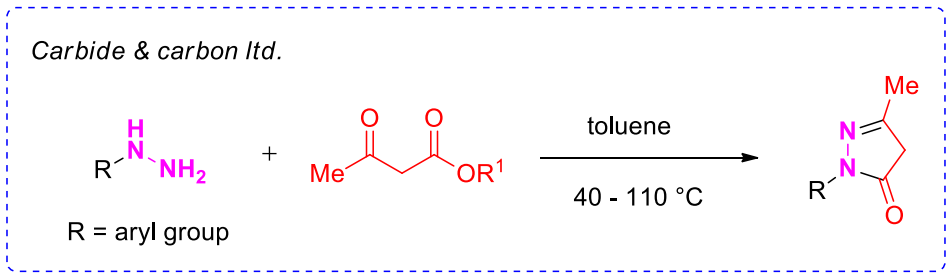
Soon after, in 2020, Samanta *et al.* again explored an ammonium acetate-promoted one-pot strategy for the synthesis of a variety of tri- and tetrasubstituted pyridines under neat conditions involving cyclic sulfamidate imines, aryl/heteroaryl ketones and aryl/heteroaryl aldehydes at 80 °C. This three-component reaction bestows good to high yields in 55-85% yields and tolerates various functional groups in **Scheme 1.20**.[60]



Scheme 1.20. NH_4OAc-promoted synthesis of tri- and tetrasubstituted unsymmetrical pyridines.

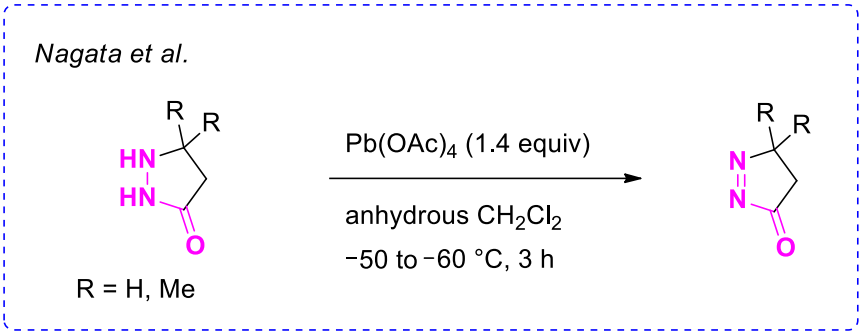
1.4.2 Synthesis of pyrazolones:

In 1935, Carbide and Carbon Ltd. developed a powerful methodology for accessing 1-aryl-3-methyl-5-pyrazolones involving aryl hydrazine hydrate and alkyl acetoacetate in equimolar mixture in toluene at 40-110°C. Later, this invention got huge attention and directed the path for synthesizing many value-added complex pyrazolones **(Scheme 1.21)**.[61]



Scheme 1.21. Construction of 4-unsubstituted pyrazolones using hydrazine hydrates and alkyl acetoacetates.

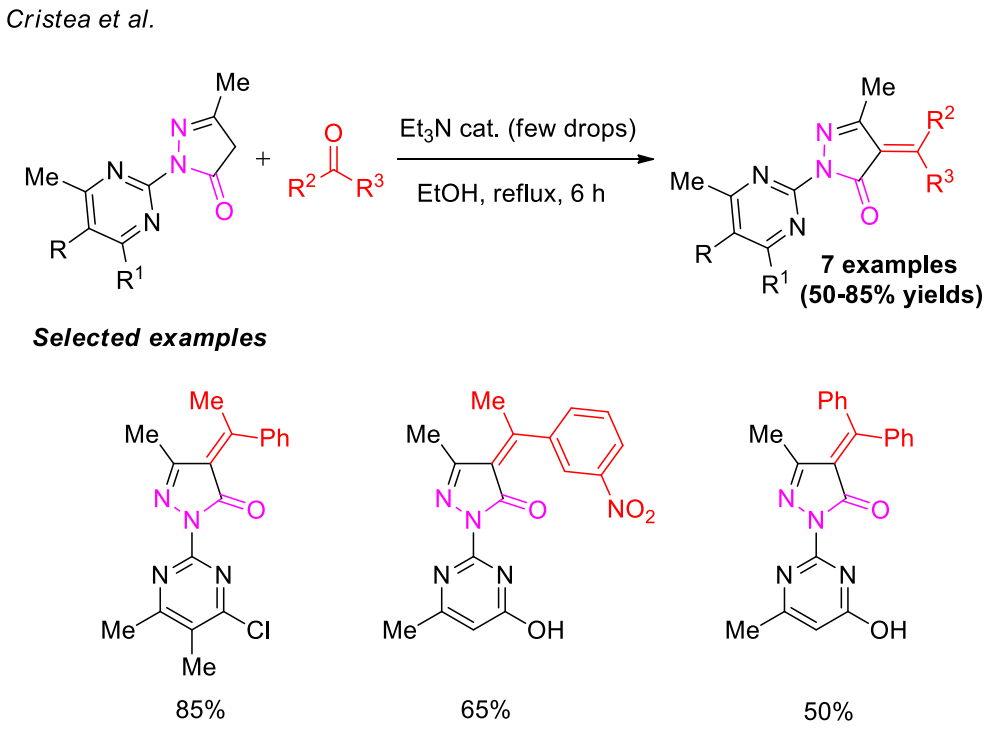
In 1970, **Nagata *et al.*** disclosed a strategy to access dihydro pyrazolones from corresponding pyrazolidin-3-one *via* dehydrogenative oxidation using lead tetra acetate in CH_2Cl_2 at –60 °C for 3 h **(Scheme 1.22)**.[62]



Scheme 1.22. Access to dihydro pyrazolones from pyrazolidinone

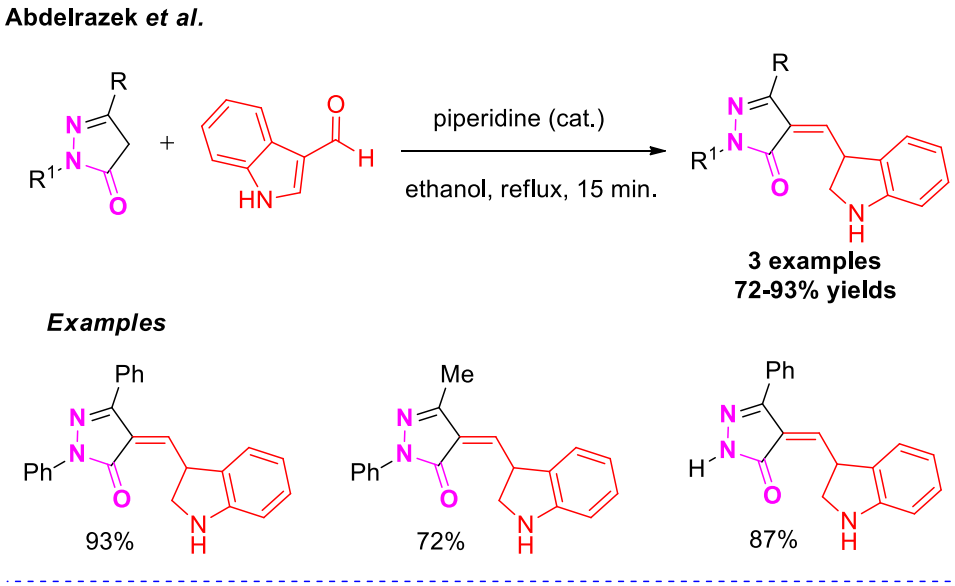
1.4.2.1 Synthesis of 4-alkylidene/ alkenylidene pyrazolones:

In 1998, Cristea *et al.* developed a strategy for the synthesis of 4-arylidene pyrimidinyl pyrazolones through a Knoevenagel condensation of 4-unsubstituted pyrimidinyl pyrazolones with aryl ketones in refluxing EtOH under basic catalysis (Et_3N) for 6 h. This protocol provides *Z*-isomer of desired pyrazolones in good to high yields ranging from 50% to 85% (**Scheme 1.23**).[63]



Scheme 1.23. Et_3N-catalyzed synthesis of pyrimidinyl pyrazolones.

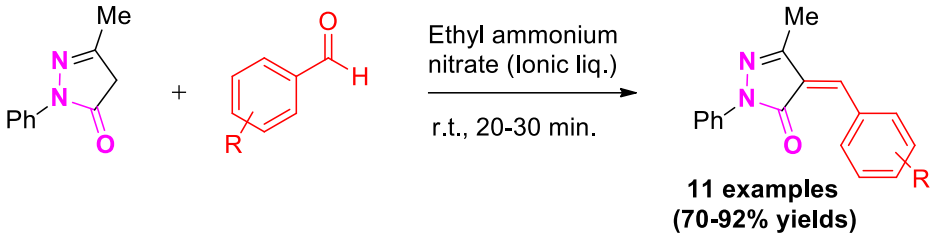
In 2007, Abdelrazek *et al.* reported an efficient procedure to synthesize indole-derived pyrazolone derivatives involving 4-unsubstituted pyrazolone and indole-3-carboxaldehyde in the catalytic amount of piperidine in refluxing ethanol for 15 min **(Scheme 1.24)**.[64]



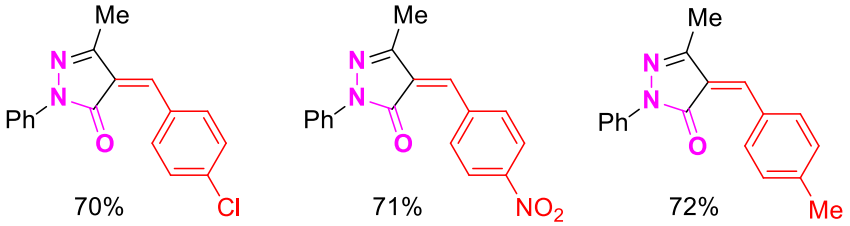
Scheme 1.24. Piperidine-catalyzed synthesis of indole derived pyrazolones.

In 2002, Shingare *et al.* established a Knoevenagel condensation reaction between 4-unsubstituted pyrazolones and aryl aldehyde in ethyl ammonium nitrate (ionic liquid) at room temperature for 30 minutes, giving access to pyrazolones in good to excellent yields of 70% to 90% (**Scheme 1.25**).[65]

Shingare et al.



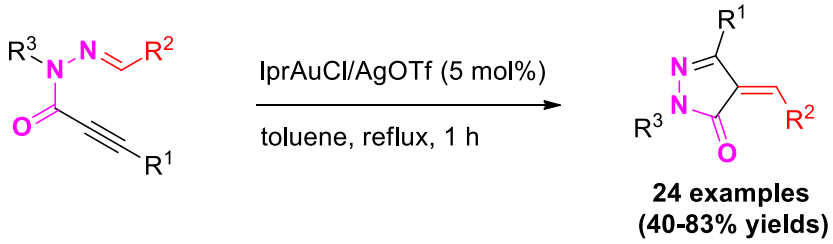
Selected examples



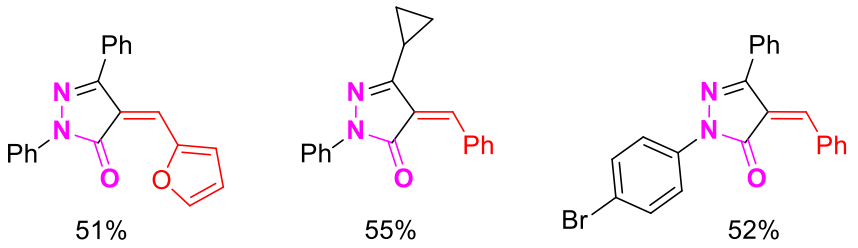
Scheme 1.25. Synthesis of benzylidene pyrazolones *via* Knoevenagel condensation reaction.

In 2015, Zhan *et al.* accomplished an intramolecular cyclization of N-propioloyal hydrazones using IprAuCl/AgOTf as a combined catalytic system, followed by 1,3-migration of aryl moieties to afford moderate to good yields from 40% to 83% of the pyrazolone derivatives as shown in **Scheme 1.26.**[66]

Zhan et al.

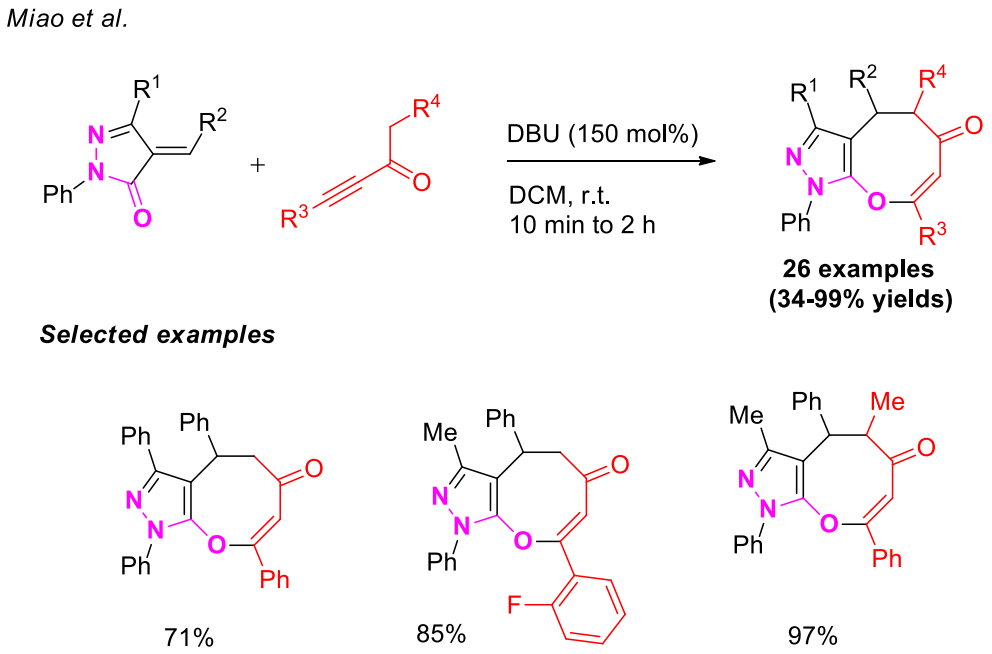


Selected examples



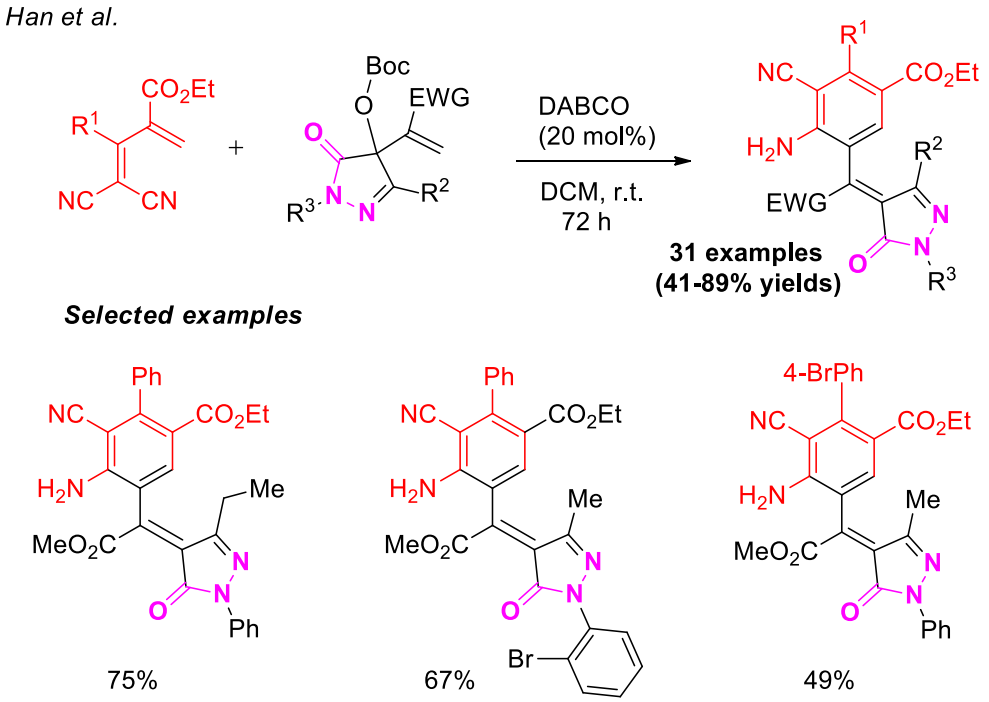
Scheme 1.26. Au/Ag-catalyzed intramolecular cyclization/aryl migration for the synthesis of benzylidene pyrazolones.

In 2018, Miao *et al.* demonstrated a DBU-promoted cycloaddition of benzylidene pyrazolones with ynones in DCM at room temperature for 2 h. This cycloaddition reaction leads to the corresponding eight-membered cyclic ethers with a variable range of yields from 34% to 99% in **Scheme 1.27**.[67]



Scheme 1.27. DBU-promoted cycloaddition reaction for synthesizing fused pyrazoles.

Recently, in 2022, Han *et al*. explored a mild DABCO-catalyzed [5 + 1] benzannulation reaction between 2-alkylidene malononitriles and Morita-Baylis-Hilman carbonates derived from pyrazolones providing multi-functionalized 4-benzylidene pyrazolones in moderate to high yields starting from 41% to 89% as shown in **Scheme 1.28**.[68]



Scheme 1.28. DABCO-catalyzed one-pot strategy for accessing 4-arylidene pyrazolones.

1.5 Conclusion:

The literature survey suggests that numerous methods have been documented for synthesizing functionalized pyridines and pyrazolones due to their medicinal properties and other applications in different sectors. However, the reported methods usually face many challenges such as the need for toxic and expensive transition metal salts, additional oxidants, volatile and hazardous organic solvents, tedious workup and harsh reaction conditions, and unsatisfactory yields preventing further large-scale synthesis for several applications. Therefore, there is a great demand to develop a simple, convenient, and eco-friendly method to offer a series of value-added pyridines and pyrazolones from simple, cost-effective, readily available starting materials.

1.6 The objective of my thesis:

This chapter illustrates the significance of aza-heterocyclic and carbocyclic scaffolds such as pyridines and pyrazolones. Considering their current demand for synthesis, we intended to develop transition metal-free one-pot synthetic strategies to access value-added pyridines and pyrazolones in a simple, effective, pot-economical, and environment-friendly manner from readily available cost-effective reactants.

1.7 References:

1. Tietze L. F. (1996), Domino Reactions in Organic Synthesis, *Chem. Rev., 96,* 115-136 (DOI: 10.1021/cr950027e)

2. Walji A. M., MacMillan D. W. C. (2007), Strategies to bypass the taxol problem. enantioselective cascade catalysis, a new approach for the efficient construction of molecular complexity, *Synlett, 10,* 1477-1489 (DOI: 10.1055/s-2007-980382)

3. Nicolaou K. C., Chena J. S. (2009), The art of total synthesis through cascade reactions, *Chem. Soc. Rev., 38,* 2993-3009 (DOI: 10.1039/B903290H)

4. Grondal C., Jeanty M. and Enders D. (2010), Organocatalytic cascade reactions as a new tool in total synthesis, *Nat. Chem., 2,* 167-178 (DOI: DOI: 10.1038/nchem.539)

5. Hayashi Y. (2016), Pot economy and one-pot synthesis, *Chem. Sci., 7,* 866-880 (DOI: 10.1039/C5SC02913A)

6. Robinson R. (1917), LXIII–A synthesis of tropinone, *J. Chem. Soc. Trans., 111, 762-768,* 762-768 (DOI: 10.1039/CT9171100762)

7. Majee D., Goud S. B., Guin S., Rathor S. S., Patel A. K., and Samanta S. (2021), Reversal Reactivity of β-Alkylnitroalkenes as 1,3-Binucleophiles: Application to Nitroarenes using Organocatalysis, *Asian J. Org. Chem., 10,* 1650-1654 (DOI: 10.1002/ajoc.202100216)

8. Biswas S., Yadav A., Majee D., Mobin S. M. and Samanta S. (2019), Diastereoselective pot-and atom-economical synthesis of densely-substituted polycyclic 1,2-and 1,2,3-fused indole scaffolds, *Tetrahedron Lett.*, *60*, 150921 (DOI: 10.1016/j.tetlet.2019.07.012)

9. Singh S., Srivastava A., Mobin S. M. and Samanta S. (2015), A remarkable solvent effect on the reaction of 4-hydroxycoumarin with (*E*)-3-aryl-2-nitroprop-2-enol: Facile synthesis of highly substituted furo/pyrano [3,2-*c*] chromenes, *RSC Adv.*, *5*, 5010-5014 (DOI: 10.1039/C4RA10610E)

10. Majee D., Biswas S., Mobin S. M. and Samanta S. (2014), An expedient one-pot sequential three-component reaction for the stereoselective synthesis of functionalized spiro-sulfamidate imine fused δ-lactone scaffold, *Tetrahedron Lett.*, *55*, 4553-4558 (DOI: 10.1016/j.tetlet.2014.06.088)

11. Majee D., Srivastava A., Mobin S. M. and Samanta S. (2013), l-Proline catalyzed highly efficient synthesis of *Z*-5-alkylidene cyclic sulfamidate imines: an easy access to 5-alkyl-substituted cyclic sulfamidate imines, *RSC Adv.*, *3*, 11502-11506 (DOI: DOI: 10.1039/c3ra40299a)

12. Arupula S. K., Guin S., Yadav A., Mobin S. M. and Samanta S. (2018), Stereoselective synthesis of 3,3-Disubstituted oxindoles and spirooxindoles via allylic alkylation of Morita–Baylis–Hillman carbonates of isatins with cyclic sulfamidate imines catalyzed by DABCO, *J. Org. Chem.*, *83*, 2660-2675 (DOI: 10.1021/acs.joc.7b03090)

13. Prakash M., Gudimella S. K., Lodhi R., Guin S. and Samanta S. (2019), NH_4OAc-Promoted Domino Route to Hydroxyarylated Unsymmetrical Pyridines under Neat Conditions, *J. Org. Chem.*, *85*, 2151-2167 (DOI: DOI: 10.1021/acs.joc.9b02896)

14. Anderson T. V. (1849), "Producte der trocknen Destillation thierischer Materien" [Products of the dry distillation of animal matter], *Annalen der Chemie und Pharmacie.*, *70*, 32-38 (DOI: 10.1002/jlac.18490700105)

15. Körner W. (1869), *Giornale academico di Palermo*, 5

16. Dewar J. (1871), *Chemical News*, 23, 38

17. Ling Y., Hao Z. Y., Liang D., Zhang C. L., Liu Y. F. and Wang Y. (2021), The expanding role of pyridine and dihydropyridine scaffolds in drug design, *Drug Des. Devel. Ther.*, *15*, 4289-4338 (DOI: 10.2147/DDDT.S329547)

18. Marinescu M. and Popa C. V. (2022), Pyridine compounds with antimicrobial and antiviral activities, *Int. J. Mol. Sci.*, *23*, 5659 (DOI: 10.3390/ijms23105659)

19. Jones R. G. (1951), Pyridine Syntheses. II. A New Pyridine Synthesis Leading to Vitamin B_6, *J. Am. Chem. Soc.*, *73*, 5244-5247 (DOI: 10.1021/ja01155a072)

20. Baumann M. and Baxendale I. R. (2013), An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles, *Beilstein J. Org. Chem.*, *9*, 2265-2319 (DOI: 10.3762/bjoc.9.265)

21. Guan A. Y., Liu C. L., Sun X. F., Xie Y. and Wang M. A. (2016), Discovery of pyridine-based agrochemicals by using intermediate derivatization methods, *Bioorg. Med. Chem.*, *24*, 342-353 (DOI: 10.1016/j.bmc.2015.09.031)

22. Sinthupoom N., Prachayasittikul V., Prachayasittikul S., Ruchirawat S. and Prachayasittikul V. (2015), Nicotinic acid and derivatives as multifunctional pharmacophores for medical applications, *Eur. Food Res. Techno.*, *240*, 1-17 (DOI: 10.1007/s00217-014-2354-1)

23. Sasabe H. and Kido J. (2011), Multifunctional materials in high-performance OLEDs: challenges for solid-state lighting, *Chem. Mater.*, *23*, 621-630 (DOI: 10.1021/cm1024052)

24. Tseberlidis G., Intrieri D. and Caselli A. (2017), Catalytic Applications of Pyridine-Containing Macrocyclic Complexes, *Eur. J. Inorg. Chem.*, *2017*, 3589-3603 (DOI: 10.1002/ejic.201700633)

25. Yazıcıoğlu E. Y. and Tanyeli C. (2012), A method for the synthesis of pyridine-based C_2-symmetrical chiral nucleophilic organocatalysts via Pd-catalyzed coupling, *Tetrahedron: Asymmetry*, *23*, 1694-1699(DOI: 10.1016/j.tetasy.2012.11.007)

26. Mishra A. and Gupta R. (2014), Supramolecular architectures with pyridine-amide based ligands: discrete molecular assemblies and their applications, *Dalton Trans.*, *43*, 7668-7682 (DOI: 10.1039/C4DT00277F)

27. Michael J. P. (2005), Quinoline, quinazoline and acridone alkaloids, *Nat. Prod. Rep.*, *22*, 627-646 (DOI: 10.1039/B413750G)

28. Sumby C. J. (2011), Bridging ligands comprising two or more di-2-pyridylmethyl or amine arms: Alternatives to 2,2′-bipyridyl-containing bridging ligands, *Coord. Chem. Rev.*, *255*, 1937-1967 (DOI: 10.1016/j.ccr.2011.03.015)

29. Wise M. D., Ruggi A., Pascu M., Scopelliti R. and Severin K. (2013), Clathrochelate-based bipyridyl ligands of nanoscale dimensions: easy-to-access building blocks for supramolecular chemistry, *Chem. Sci.*, *4*, 1658-1662 (DOI: 10.1039/C3SC50155H)

30. Wu D., Zhi L., Bodwell G. J., Cui G., Tsao N. and Müllen K. (2007), Self-assembly of positively charged discotic PAHs: from nanofibers to nanotubes, *Angew. Chem.*, *119*, 5513-5516 (DOI: 10.1002/ange.200700515)

31. Henry G. D. (2004), De novo synthesis of substituted pyridines, *Tetrahedron*, *29*, 6043-6061 (DOI: 10.1016/j.tet.2004.04.043)

32. Allais C., Grassot J. M., Rodriguez J. and Constantieux T. (2014), Metal-free multicomponent syntheses of pyridines, *Chem. Rev.*, *114*, 10829-10868 (DOI: 10.1021/cr500099b)

33. S Hamama W., G El-Gohary H., Kuhnert N. and H Zoorob H. (2012), Chemistry of pyrazolinones and their applications, *Curr. Org. Chem.*, *16*, 373-399 (DOI: 10.2174/138527212799499921)

34. Liu S., Bao X. and Wang B. (2018), Pyrazolone: a powerful synthon for asymmetric diverse derivatizations, *Chem. Comm.,* 54, 11515-11529 (DOI: 10.1039/C8CC06196C)

35. Ramajayam R., Tan K. P., Liu H. G. and Liang P. H. (2010), Synthesis and evaluation of pyrazolone compounds as SARS-coronavirus 3C-like protease inhibitors, *Bioorg. Med. Chem., 18,* 7849-7854 (DOI: 10.1016/j.bmc.2010.09.050)

36. Kumar V., Chang C. K., Tan K. P., Jung Y. S., Chen S. H., Cheng Y. S. E. and Liang P. H. (2014), Identification, synthesis, and evaluation of new neuraminidase inhibitors, *Org. Lett., 16,* 5060-5063 (DOI: 10.1021/ol502410x)

37. Huang H., Yu Y., Gao Z., Zhang Y., Li C., Xu X., Jin H., Yan W., Ma R., Zhu J. and Shen X. (2012), Discovery and optimization of 1,3,4-trisubstituted-pyrazolone derivatives as novel, potent, and nonsteroidal farnesoid X receptor (FXR) selective antagonists, *J. Med. Chem., 55,* 7037-7053 (DOI: 10.1021/jm3002718)

38. Dayam R., Al-Mawsawi L. Q., Zawahir Z., Witvrouw M., Debyser Z. and Neamati N. (2008), Quinolone 3-carboxylic acid pharmacophore: design of second generation HIV-1 integrase inhibitors, *J. Med. Chem., 51,* 1136-1144 (DOI: 10.1021/jm070609b)

39. Fan X., Zhang X., Zhou L., Keith K. A., Kern E. R. and Torrence P. F., (2006), A pyrimidine–pyrazolone nucleoside chimera with potent in vitro anti-orthopoxvirus activity, *Bioorg. Med. Chem. Lett., 16,* 3224-3228 (DOI: 10.1016/j.bmcl.2006.03.043)

40. Dawood D. H., Nossier E. S., Ali M. M. and Mahmoud A. E. (2020), Synthesis and molecular docking study of new pyrazole derivatives as potent anti-breast cancer agents targeting VEGFR-2 kinase, *Bioorg. Chem., 101,* 103916 (DOI: 10.1016/j.bioorg.2020.103916)

41. Castagnolo D., Manetti F., Radi M., Bechi B., Pagano M., De Logu A., Meleddu R., Saddi M. and Botta M. (2009), Synthesis, biological evaluation, and SAR study of novel pyrazole analogues as inhibitors of Mycobacterium tuberculosis: Part 2. Synthesis of rigid pyrazolones, *Bioorg. Med. Chem., 17*, 5716-5721 (DOI: 10.1016/j.bmc.2009.05.058)

42. W. Ramsay (1877), *Ber. Dtsch. Chem. Ges. 10* 736

43. Hantzsch A. (1881), Condensationsprodukte aus aldehydammoniak und ketonartigen verbindungen, *Ber. Dtsch. Chem. Ges.,14,* 1637-1638 (DOI: 10.1002/cber.18810140214)

44. Tschitschibabin A. E, (1924), Über Kondensationen Der Aldehyde Mit Ammonik zu Pyridinbasen, *Adv. Synth. Catal., 107,* 122-128 (DOI: 10.1002/prac.19241070110)

45. Bohlmann F. & Rahtz D. (1957), Über eine neue Pyridinsynthese, *Chem. Ber. 90,* 2265-2272 (DOI: 10.1002/cber.19570901021)

46. Krohnke, F. (1976), The specific synthesis of pyridines and oligopyridines, *Synthesis, 1976*, 1-24 (DOI: 10.1055/s-1976-23941)

47. Al-Saleh B., Abdelkhalik M. M., Eltoukhy A. M., Elnagdi M. H. (2002), Enaminones in heterocyclic synthesis: A new regioselective synthesis of 2,3,6-trisubstituted pyridines, 6-substituted-3-aroylpyridines and 1,3,5-triaroylbenzenes, *J. Heterocycl. Chem., 39,* 1035-1038 (DOI: 10.1002/jhet.5570390528)

48. Meth-Cohn O., Narine B., Tarnowski B. (1981), A versatile new synthesis of quinolines and related fused pyridines. Part 7. The conversion of acetamidothiophens into thienopyridines, *J. Chem. Soc., Perkin Trans. 1*, 1531- 1536 (DOI: 10.1039/P19810001531)

49. Lu J.-Y., Arndt H.-D. (2007), Hetero Diels-Alder synthesis of 3-hydroxypyridines: access to the Nosiheptide core, *J. Org. Chem., 72,* 4205-4212 (DOI: 10.1021/jo0703505)

50. Berman A. M., Lewis J. C., Bergman R. G. and Ellman J. A. (2008), Rh(I)-catalyzed direct arylation of pyridines and quinolines, *J. Am. Chem. Soc.*, *130*, 14926-14927 (DOI: 10.1021/ja8059396)

51. Kantevari S., Patpi S. R., Addla D., Putapatri S. R., Sridhar B., Yogeeswari P. and Sriram D. (2011), Facile Diversity-Oriented Synthesis and Antitubercular Evaluation of Novel Aryl and Heteroaryl Tethered Pyridines and Dihydro-6*H*-quinolin-5-ones Derived via Variants of the Bohlmann–Rahtz Reaction, *ACS Comb. Sci.*, *13*, 427-435 (DOI: 10.1021/co2000604)

52. Satoh Y. and Obora Y. (2013), Low-valent niobium-catalyzed intermolecular [2+2+2] cycloaddition of *tert*-butylacetylene and arylnitriles to form 2,3,6-trisubstituted pyridine derivatives, *J. Org. Chem.*, *78*, 7771-7776 (DOI: 10.1021/jo401399y)

53. Rieckhoff S., Hellmuth T. and Peters R. (2015), Regioselective Pd-Catalyzed Synthesis of 2,3,6-Trisubstituted Pyridines from Isoxazolinones, *J. Org. Chem.*, *80*, 6822-6830 (DOI: 10.1021/acs.joc.5b01065)

54. Zhao M. N., Ren Z. H., Yu L., Wang Y. Y. and Guan Z. H. (2016), Iron-catalyzed cyclization of ketoxime carboxylates and tertiary anilines for the synthesis of pyridines, *Org. Lett.*, *18*, 1194-1197 (DOI: 10.1021/acs.orglett.6b00326)

55. Hirai S., Horikawa Y., Asahara H. and Nishiwaki N. (2017), Tailor-made synthesis of fully alkylated/arylated nicotinates by $FeCl_3$-mediated condensation of enamino esters with enones, *Chem. Comm.*, *53*, 2390-2393 (DOI: 10.1039/C7CC00051K)

56. Dai X. J., Krolikowski P., Murray J. I., Wei C. S., Dornan P. K., Rotheli A. R., Caille S., Thie O. R., Smith A. G. and Parsons A. T. (2022), Synthesis of Substituted Pyridines via Formal (3+3) Cycloaddition of Enamines with Unsaturated Aldehydes and Ketones, *J. Org. Chem.*, *87*, 8437-8444 (DOI: 10.1021/acs.joc.2c00576)

57. Chen Z.-B., Hong D., Wang Y.-G. (2009), A cascade approach to pyridines from 2-azido-2,4-dienoates and γ-diazocarbonyl\ compounds, *J. Org. Chem.*, *74*, 903-905 (DOI:10.1021/jo802159g)

58. Jiang Y., Park C. M. and Loh T. P. (2014), Transition-metal-free synthesis of substituted pyridines via ring expansion of 2-allyl-2*H*-azirines, *Org. Lett.*, *16*, 3432-3435 (DOI: 10.1021/ol501010k)

59. Majee D., Guin S., Biswas S. and Samanta S. (2017), A Metal-Free Based New Approach to 2,4-Disubstituted Pyridines via One-Pot Sequential Reaction of Cyclic Sulfamidate Imines with β-Substituted Acroleins, *Chemistry Select*, *2*, 3423-3427 (DOI: 10.1002/slct.201700733)

60. Prakash M., Gudimella S. K., Lodhi R., Guin S. and Samanta S. (2019), NH_4OAc-Promoted Domino Route to Hydroxyarylated Unsymmetrical Pyridines under Neat Conditions, *J. Org. Chem.*, *85*, 2151-2167 (DOI: 10.1021/acs.joc.9b02896)

61. Carbide & Carbon Chem Corp, Preparation of 1-Phenyl-3-Methyl-Pyrazolone-5 and related Compounds, U. S. Patent 11497/35, Oct. 13, 1936 (https://worldwide.espacenet.com/patent/search/family/021938297/publication/GB455094A?q=pn%3DGB455094A)

62. Nagata W. and Kamata S. (1970), Preparation and reactions of cyclic α-monocarbonyl azo-compounds: 1-pyrazolin-3-one derivatives, *J. Chem. Soc. C.*, *1970*, 540-550 (10.1039/J39700000540)

63. Cristea L. and Panea L. (1998), Synthesis and Structural Study of Some 4-(α-Arylethylidene)-1-pyrimidinyl-2-pyrazolin-5-ones, *Heterocycl. Commun.*, *4*, 139-143 (DOI: 10.1515/HC.1998.4.2.139)

64. Abdelrazek F. M., Metz P., Kataeva O., Jager A., El-Mahrouky S. F. (2007), Synthesis and Molluscicidal Activity of New Chromene and Pyrano[2,3-*c*]pyrazole Derivatives, *Arch. Pharm. Chem. Life Sci.*, *340*, 543-548, (DOI: 10.1002/ardp.200700157)

65. Hangarge R. V., Jarikote D. V. and Shingare M. S. (2002), Knoevenagel condensation reactions in an ionic liquid, *Green Chem.*, *4*, 266-268 (DOI: 10.1039/B111634G)

66. Ding Z. C., Tang H. T., Li R. H., Ju L. C. and Zhan Z. P. (2015), Synthesis of 4-Arylidenepyrazolones by a Gold-Catalyzed Cyclization/Arylidene Group Transfer Cascade of *N*-Propioloyl Hydrazones, *J. Org. Chem.*, *80*, 9307-9313 (DOI: acs.joc.5b01366)

67. Cheng C., Zhang J., Wang X. and Miao Z. (2018), DBU-Promoted [4+4] Domino Cycloaddition of Ynones with Benzylidenepyrazolones To Access Eight-Membered Cyclic Ethers, *J. Org. Chem.*, *83*, 5450-5457 (DOI: 10.1021/acs.joc.8b00352)

68. He S., Wang J., Zheng J., Luo Q. Q., Leng H., Zheng S., Peng C., Han B. and Zhan G. (2022), Organocatalytic (5+1) benzannulation of Morita–Baylis–Hillman carbonates: synthesis of multisubstituted 4-benzylidene pyrazolones, *New J. Chem.*, *46*, 11617-11622 (DOI: 10.1039/D2NJ01949C)

Chapter 2

A Metal Oxidant Solvent-Free Pot-Economy Approach to Access Di and Trisubstituted Pyridines Regioselectively *via a* Domino Reaction involving 3-Chloropropiophenones

Chapter 2

A metal oxidant solvent-free pot-economy approach to access di and trisubstituted pyridines regioselectively *via* a domino reaction involving 3-chloropropiophenones

2.1 Introduction

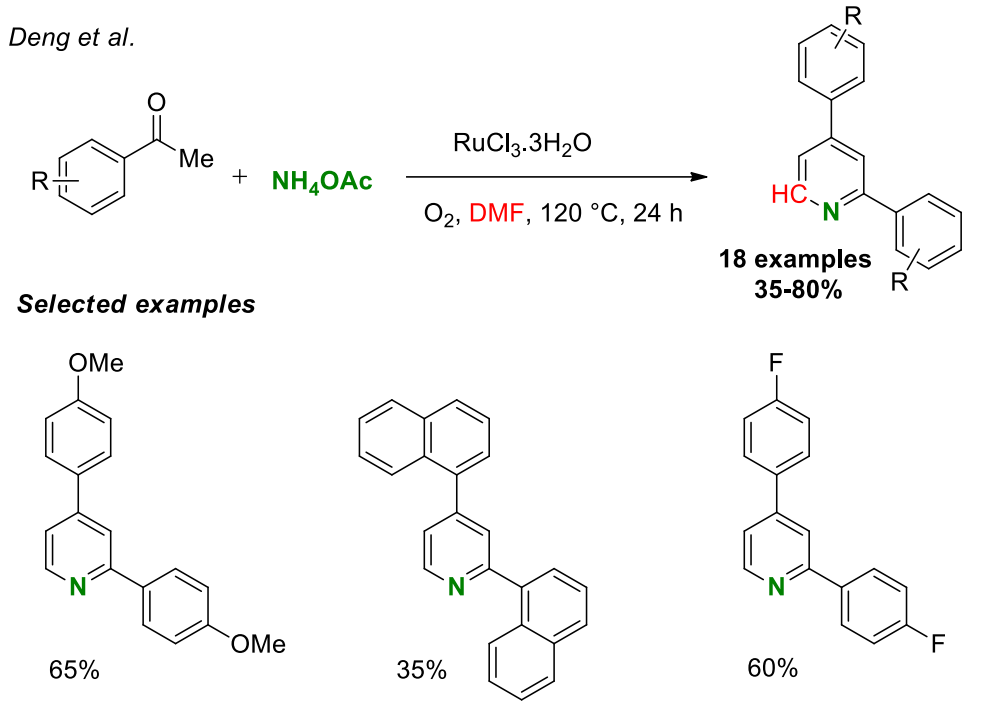
Pyridines are a fascinating class of aza-heteroaromatic building blocks.[1-3] These aza-aromatic compounds are found in many biologically active natural alkaloids,[4] clinically approved pharmaceuticals,[5,8] agrochemicals[6] and life-preserving medicines.[7] Furthermore, pyridines are the precursors for essential biochemical vitamins [B_3 (niacin), B_6(pyridoxin)], picoline, nicotine, and redox nucleotides [nicotinamide adenine dinucleotide (NAD)/NADPH as coenzyme], which plays crucial roles in energy metabolism and other critical physiological functions.[2] The chemical transformation of pyridine scaffolds has shown an extensive range of prominent applications in ligand synthesis for producing metal inorganic complexes,[11,12]new catalytic symmetric and asymmetric organocatalysis,[13,14] functional materials[9,10] and supramolecular chemistry due to their excellent π-stacking ability.[15,16] Considering their significant importance in chemical science, a simple metal-free facile protocol for accessing diversely and variously substituted pyridines using readily available inexpensive reactants under benign conditions is an enchanting research objective for organic and medicinal chemists.[17-19]

2.2 Review Work

Researchers worldwide have made immense contributions in designing and constructing a diverse set of value-added pyridines. Some of the related methods have been described in the next section **(2.2.1)**.

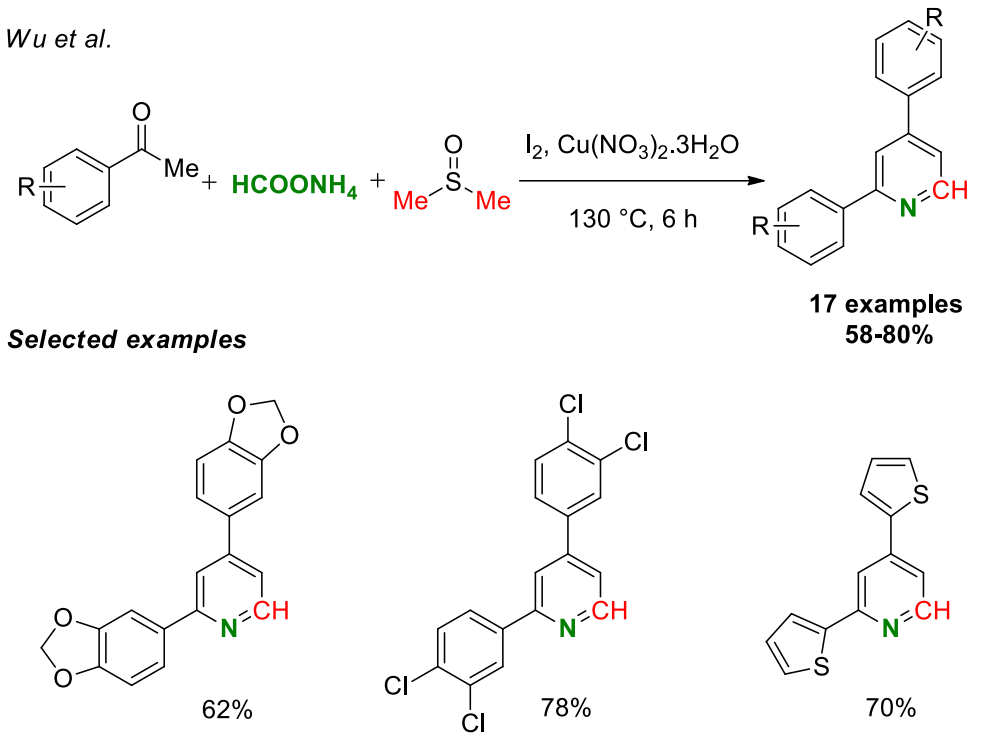
2.2.1 Synthesis of Pyridines

Deng *et al.* (2015) reported a one-pot strategy to access 2,4-disubstituted pyridines using acetophenones, ammonium acetate and DMF as a 1C unit catalyzed by $RuCl_3$ at 120 °C under an O_2 atmosphere. The presence of carbon atom at the C6 position of pyridine comes from DMF as shown in **Scheme 2.1**.[20]



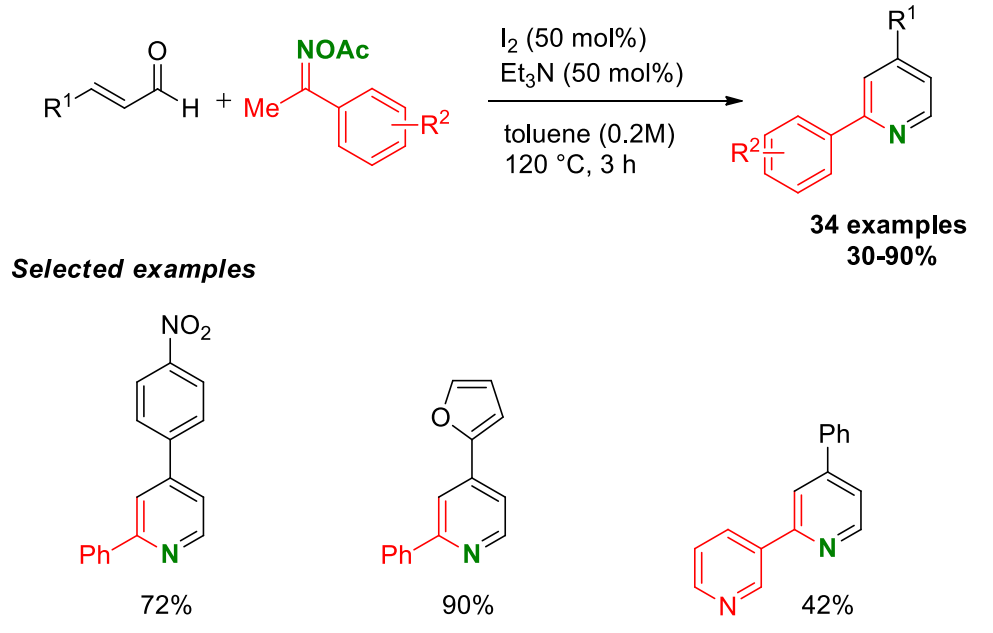
Scheme 2.1. Ruthenium-catalyzed synthesis of 2,4-diaryl substituted pyridines.

Wu *et al.* (2015) developed a Cu-catalyzed cascade reaction using aryl methyl ketones, ammonium formate, and DMSO in the presence of molecular I_2. This cyclization process affords 2,4-disubstituted pyridines in good to high yields (58-80%). Notably, DMSO acts as a solvent as well as 1C atom source for pyridine ring construction in **Scheme 2.2**.[21]



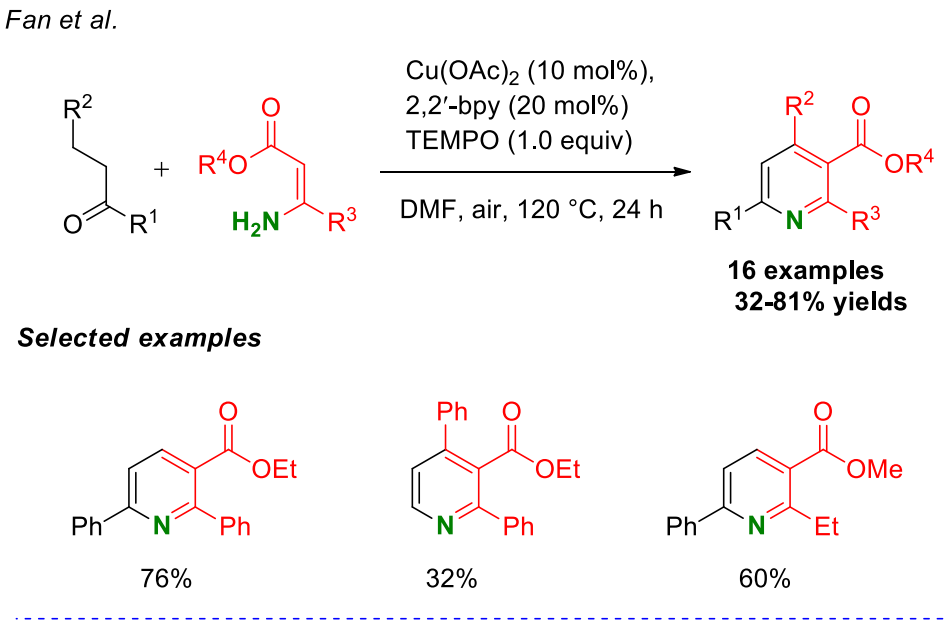
Scheme 2.2. Cu-catalyzed cascade approach to pyridines

In 2016, Deng *et al.* developed a facile I_2/Et_3N-promoted aza-cyclization reaction between *O*-acetyl ketoxime and *α,β*-unsaturated aldehydes at 120 °C to deliver di-and tri-substituted pyridines. This reaction proceeds through a radicle pathway, leading to the corresponding products in a variable range of yields (30-90%) (**Scheme 2.3**).[22]



Scheme 2.3. I_2/Et_3N-promoted reaction of ketoximes with acroleins.

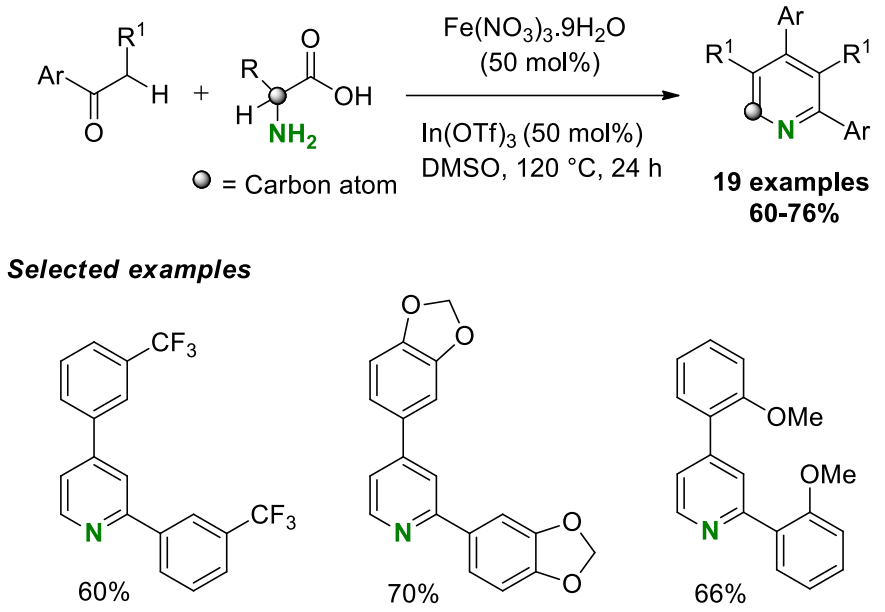
In 2017, Fan *et al.* exemplified a facile Cu(II)-catalyzed [3+3] annulation of saturated ketones with *β*-enamino esters using 20 mol% of 2,2′-bpy and 1.0 equivalent TEMPO. This reaction follows sequential pathways: oxidation, Michael addition, aldol condensation, and aerial oxidation process, leading to the corresponding nicotinates in varying yields ranging from 32% to 81% in **Scheme 2.4**.[23]



Scheme 2.4. Cu(II)-catalyzed Michael addition/cyclization of β-enaminones with ketones to construct pyridines.

Malakar *et al.* (2019) developed an interesting decarboxylative technique for the regioselective access di-arylpyridines using amino acids and enolizable ketones using Fe(III)/In(III)-salt as the combined catalytic system in DMSO under heating conditions. This method provides satisfactory yields (60-76%) of the mentioned pyridine derivatives (**Scheme 2.5)**.[24]

Malakar et al.



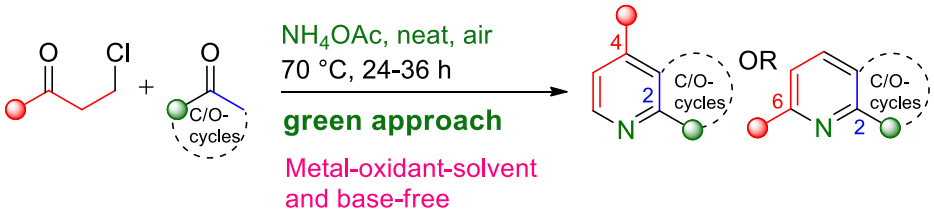
Scheme 2.5. Fe(III)/In(III)-catalyzed decarboxylative cyclization reaction to construct pyridines.

2.2.2 Conclusion

The literature survey suggests that numerous methods have been documented for synthesizing pyridines due to their wide applications in different fields. While several of the enriched methods bestow many advantages, some of them also encounter a few drawbacks, such as the consumption of non-commercial reactants, high temperatures, hazardous and volatile organic solvents, reliance on metal salts with ligands, poor functional group tolerance, poor atom economy, specific substrate scope, etc. Therefore, there is a crucial need to develop a more convenient and eco-friendly method that could produce a series of functionalized pyridines, including fused ones selectively from commercially available simple reactants.

2.3 Present Work

The importance of the pyridine moiety has been emphasized previously in the introductory Chapter 1. In this context, synthesizing various functionalized pyridine derivatives and their fused analogues remains a pivotal research focus for chemists. In addition, our continued research interest is aimed at developing new synthetic processes for making diverse pyridine scaffolds. Herein, we wish to report further a simple, convenient, metal-free, one-pot, three-component [3C+2C+1N] reaction involving 3-chloropropiophenones, cyclic/acyclic ketones and NH_4OAc as an N-containing source under neat conditions in air providing a variety of di- and tri-substituted unsymmetrical pyridines regioselectively as shown in **Scheme 2.6**.



Scheme 2.6. Metal-free regioselective synthesis of di- and tri-substituted pyridines

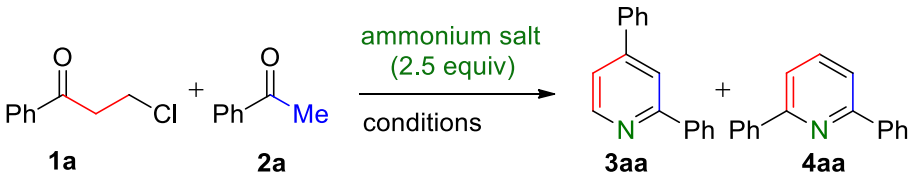
2.4 Results and Discussion

2.4.1 Optimization of reaction conditions

The optimization reaction was commenced by putting the model reaction of 3-chloropropiophenone (**1a**), acetophenone (**2a**), and NH_4OAc in dry MeCN at 50 °C in an open atmosphere. The progress of the reaction was monitored by TLC. After 24h, the expected 2,4-disubstituted pyridine **3aa** was isolated in 55% yield (**Table 2.1**, entry 1). The product **3aa** was fully characterized by its spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) and confirmed the chemical structure. The ^{1}H NMR spectrum of **3aa** shows a doublet peak at 8.47 ppm (one proton) and a singlet peak at 7.94 ppm (one proton) corresponding to the C6 and C3 protons of pyridine respectively, depicting

the occupied 2 and 4 positions of the phenyl group. In addition, other aromatic peaks appear at 8.05 ppm (doublet) for 2 protons, 7.70 ppm (doublet) for 2 protons, and aromatic region (7.53-7.43) ppm for 7 protons. In the ^{13}C NMR spectrum, 13 aromatic peaks indicate the formation of our expected 2,4-Diphenylpyridine **3aa.** Furthermore, the molecular ion peak $[M+H]^+$ appears at 232.1119 in the HRMS spectrum, corresponding to the molecular weight (231.1048) of the expected product **3aa**. Afterwards, the formation of product **4aa** i.e. 2,6-diphenylpyridine in a trace amount, was confirmed by analyzing the ^1H NMR spectrum of the crude product (not isolated). Now the conversion of this minor isomer **4aa** was calculated by integrating the corresponding proton signals between the major isomer **3aa** and minor isomer **4aa** in ^1H NMR of crude mixture. This enthusiastic result inspired us to explore the reaction in detail.

Table 2.1: Optimization of reaction conditions. [a,b,c]



Entry	Solvent	Ammonium salt	T/ °C	Time (h)	Yield (%) 3aa[b,c]	4aa[d]
1	MeCN	NH_4OAc	50	48	55	<5
2	MeCN	NH_4OAc	70	36	71	<6
3	MeCN	NH_4OAc	80	36	70	<7
4	Toluene	NH_4OAc	70	36	33	<7
5	2-MeTHF	NH_4OAc	70	36	37	<6
6	DMF	NH_4OAc	70	36	74	<5

7	DMSO	NH_4OAc	70	36	61	<8
8	EtOH	NH_4OAc	70	36	21	<7
9	PEG-400	NH_4OAc	70	36	19	<6
10	H_2O	NH_4OAc	70	36	10	nd[e]
11	Neat	NH_4OAc	70	24	72	<5
12	Neat	NH_4HCO_3	70	24	31	<5
13	Neat	NH_4HCO_2	70	24	60	<5
14	Neat	NH_4SCN	70	24	25	<5
15	Neat	$(NH_4)_2CO_3$	70	24	25	<5
16	Neat	NH_4Cl	70	24	10	nd[e]
17	Neat	$(NH_4)_2SO_4$	70	24	8	nd[e]
18	Neat	NH_4OH	70	24	33	<8
19[f]	Neat	NH_4OAc	70	24	73	<5
20[g]	Neat	NH_4OAc	70	24	74	trace

[a]Unless otherwise noted, all of the reactions were carried out with **1a** (0.3 mmol, 1.0 equiv), **2a** (0.36 mmol, 1.2 equiv.) and ammonium salt (2.5 equiv.) in the specified dry solvent (1.0 mL) or a neat condition and temperature under aerobic conditions. [b]Isolated yield of **3aa** after column chromatography. [c]Isolated yield after column chromatography, calculated with respect to the starting material **1a**. [d]Conversion of minor isomer **4aa** was calculated based on the integration values of the corresponding proton signals between the major isomer **3aa** and minor isomer in the ^{1}H NMR spectrum of the crude

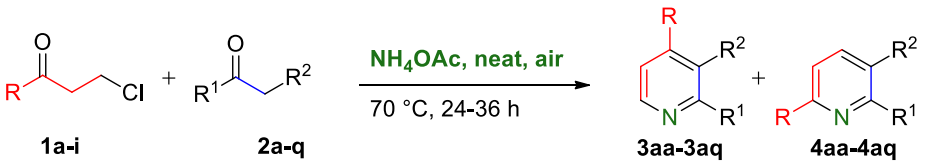
product (not isolated). [e]nd indicates not detected. [f]Under O_2-balloon. [g]Reaction was performed using 3-bromopropiophenone in place of 3-chloropropiophenenone (**1a**).

Interestingly, upon raising the reaction temperature to 70 °C (entry 2) and 80 °C (entry 3), pyridine **3aa** was obtained in good yield of 71% and 70% respectively. Since, when the reaction was either heated at a lower or higher temperature than 70 °C, the slightly lower yield of **3aa** was obtained. Thus, the optimal temperature for this conversion is 70 °C. Next, we screened various solvents such as Toluene, 2-MeTHF, DMF, DMSO, EtOH, PEG-400 and H_2O (entries 4-10). The result showed that DMF was the best (with 74% yield) among all the solvents (entries 4-10). Thus, considering the toxicity of DMF, we intended to perform this aza-cyclization reaction under neat conditions (no DMF used). The reaction performed well without DMF under neat conditions giving 72% of **3aa**. Then, we examined the effect of many commercially available ammonium salts such as NH_4HCO_3, NH_4HCO_2, NH_4SCN, $(NH_4)_2CO_3$, NH_4Cl, $(NH_4)_2SO_4$, NH_4OH and NH_4OAc on this reaction under solvent-free conditions. The result shows that NH_4OAc is the best N-source supplier for pyridine synthesis compared to other ammonium salts (entries 11-17). Further, we performed the reaction under O_2-balloon instead of air and observed a little change only (entry 19). Notably, these reactions happen with high regioselectivity, affording only 5-8% conversion of the minor isomer **4aa**.

When we used 3-bromopropiophenone instead of **1a** in this reaction, a similar yield (74%) was obtained (entry 20). However, **1a** is preferred over 3-bromopropiophenone due to the low-cost starting material.

2.4.2 Substrate Scope

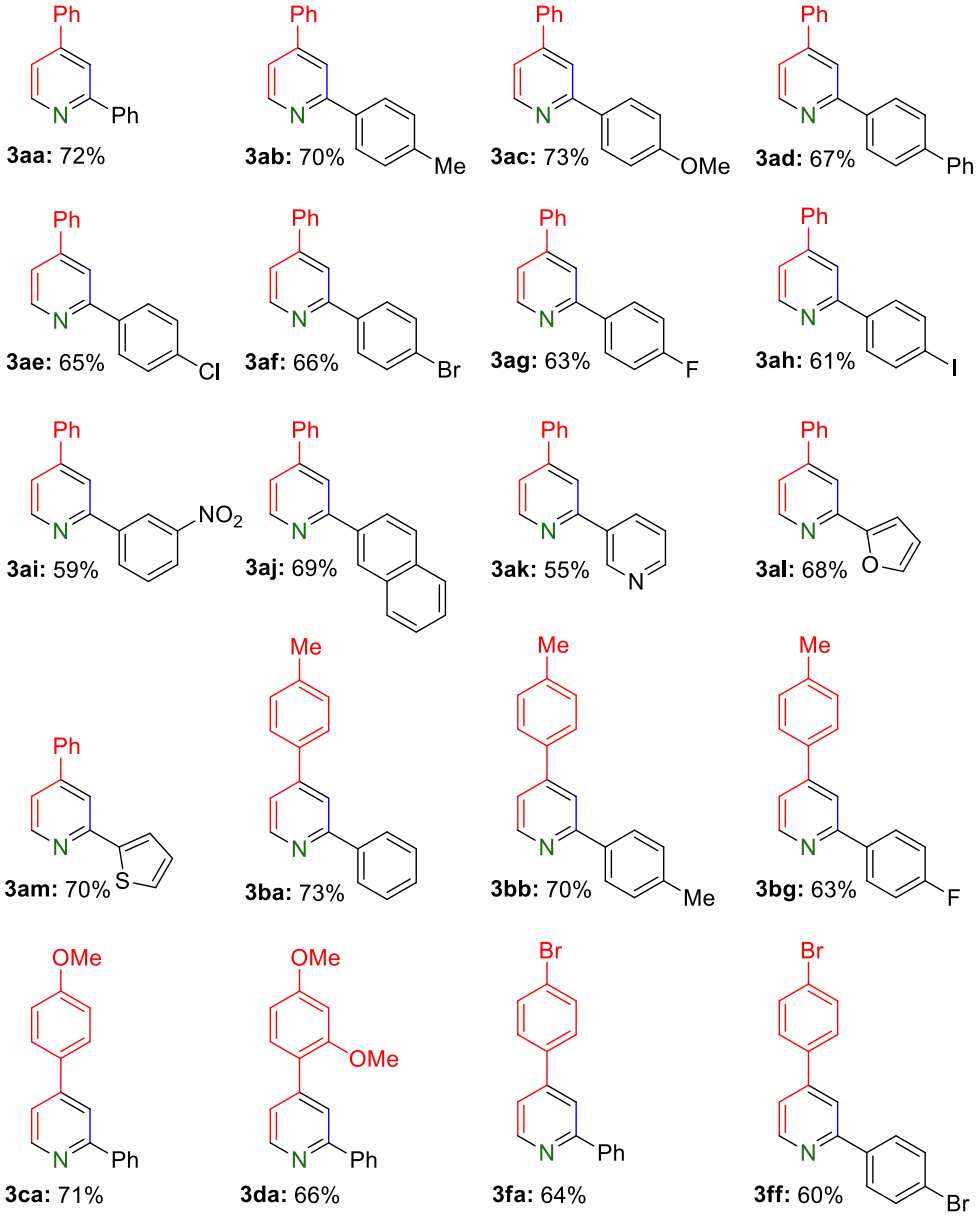
Once the best reaction parameters were established, we explored the generality and scope of this metal-oxidant- and solvent-free three-component reaction by utilizing several 3-chloropropiophenones (**1a-1h**), aryl/heteroaryl alkyl ketones and NH_4OAc under standard conditions. The results are nicely summarized in **Scheme 2.7**. It was found that several acetophenones possessing electron-donating (Me and MeO) and electron-withdrawing atoms (Cl, Br, F, I, Ph, NO_2) on the aryl rings nicely participated in this [3+2+1] aza-cyclization reaction with 3-chloropropiophenone **1a,** providing the desired 2,4-diarylpyridines (**3ab-3ai;** 59-73% yields) regioselectively over 2,6-diarylpyridines (yield of **4ab-4ai:** less than 5-6%, not isolated). However, the obtained yields of electron-withdrawing atoms attached to acetophenone afforded slightly lower yields (**3ad-3ai**; 59-67%) than those of electron-donating substituents (**3ab-3ac;** 70-73%). Interestingly, bulky ketone 2-acetonaphthone responded very well to this aza-cyclization with **1a** to give 2-(2-naphthyl)-4-phenylpyridine (**3aj**) in 69% yield. Moreover, heteroaryl methyl ketones (**2k**, **2l** and **2m**) showed promising reactivity with **1a,** offering corresponding major isomers 2-pyridinyl/2-furanyl/2-thiophenyl//4-phenylpyridines **3ak**, **3al** and **3am** in 55%, 68% and 70% yields respectively. On the other hand, many 3-chloropropiophenones (**2b-2g**) attached with Me, MeO, di-MeO, Cl, Br, and I atoms smoothly participated in this reaction with methyl ketones to give satisfactory yields (56-73%) of the corresponding 2,4-diarylpyridines (**3ba-3ga**). Moreover, when acetophenones were replaced with propiophenones **2o** and **2p** and subjected to the reaction with **1a** under standard conditions, pleasantly provided the corresponding 2,3,4-trisubstituted pyridines **3ao** and **3ap** as major regioisomer with good yields (61% and 57% respectively) along with 2,3,6-trisubstituted pyridines **4ao** (9% yield) and **4ap** (conversion: 7%, not isolated) as minor isomer. Finally, symmetrical and unsymmetrical alkyl ketones such as 3-pentanone (**2q**) and cyclopropyl methyl ketone (**2n**) were subjected to react with 3-chloropropiophenone derivatives **1a** and **1i** which led to good yields (64% and 76%, respectively) of 2-alkyl-4-arlpyridines **3aq** and **3in**.

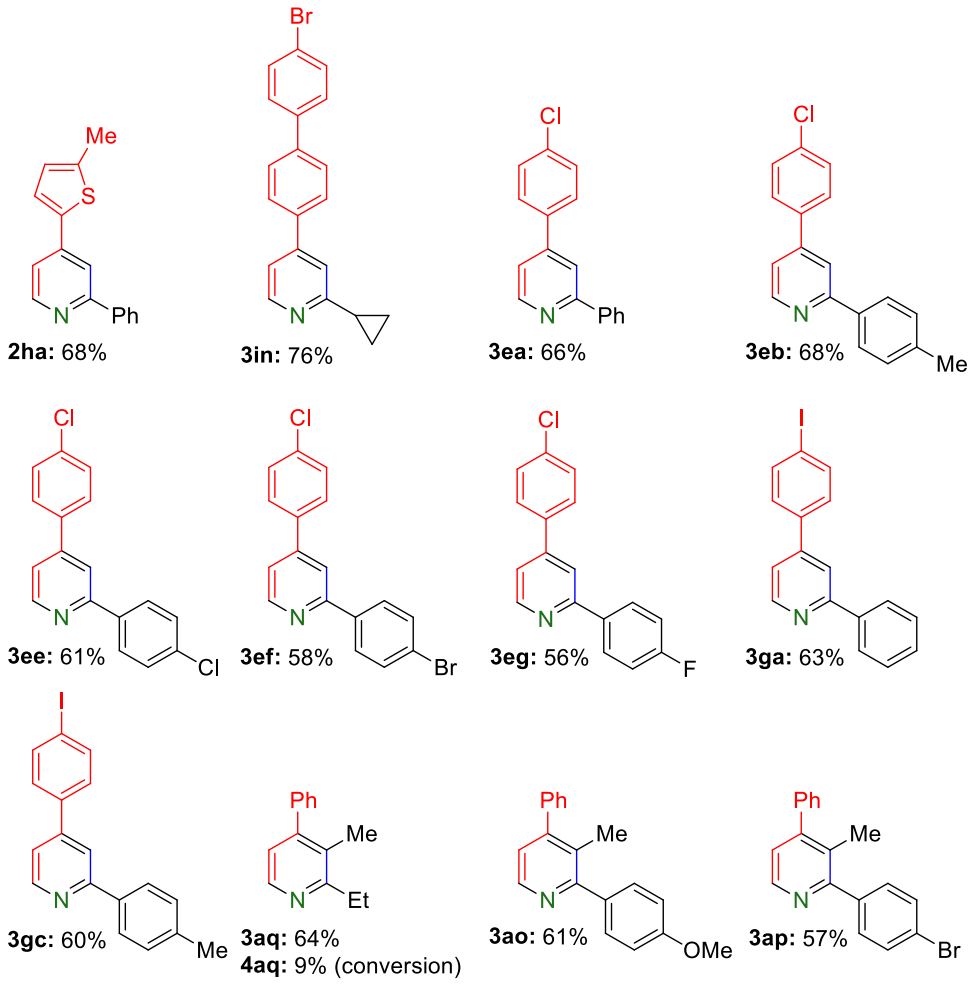


1a-i **2a-q** **3aa-3aq** **4aa-4aq**

1a: R = Ph
1b: R = 4-MeC_6H_4
1c: R = 4-$MeOC_6H_4$
1d: R = 2,4-$(MeO)_2C_6H_3$
1e: R = 4-ClC_6H_4
1f: R = 4-BrC_6H_4
1g: R = 4-IC_6H_4
1h: R = 5-methylthiophene
1i : R = 4-(4-BrC_6H_4)-C_6H_4

2a: R^1 = Ph; R^2 = H
2b: R^1 = 4-MeC_6H_4; R^2 = H
2c: R^1 = 4-$MeOC_6H_4$; R^2 = H
2d: R^1 = biphenyl; R^2 = H
2e: R^1 = 4-ClC_6H_4; R^2 = H
2f: R^1 = 4-BrC_6H_4; R^2 = H
2g: R^1 = 4-FC_6H_4; R^2 = H
2h: R^1 = 4-IC_6H_4; R^2 = H
2i: R^1 = 3-$NO_2C_6H_4$; R^2 = H
2j: R^1 = 2-naphthyl; R^2 = H
2k: R^1 = 3-pyridinyl; R^2 = H
2l: R^1 = 2-furanyl; R^2 = H
2m: R^1 = 2-thiophenyl; R^2 = H
2n: R^1 = cyclopropyl; Ph; R^2 = H
2o: R^1 = 4-$MeOC_6H_4$; R^2 = Me
2p: R^1 = 4-BrC_6H_4; R^2 = Me
2q: R^1 = Et; R^2 = Et

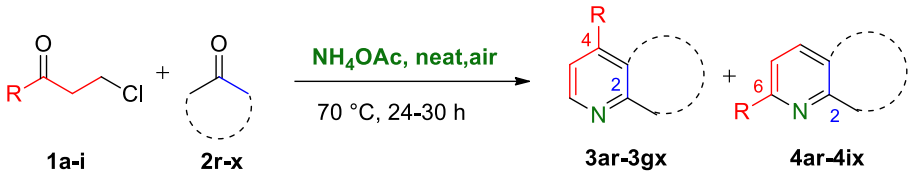




Scheme 2.7: Substrate scope of 2,4-diarylpyridines using acyclic ketones.

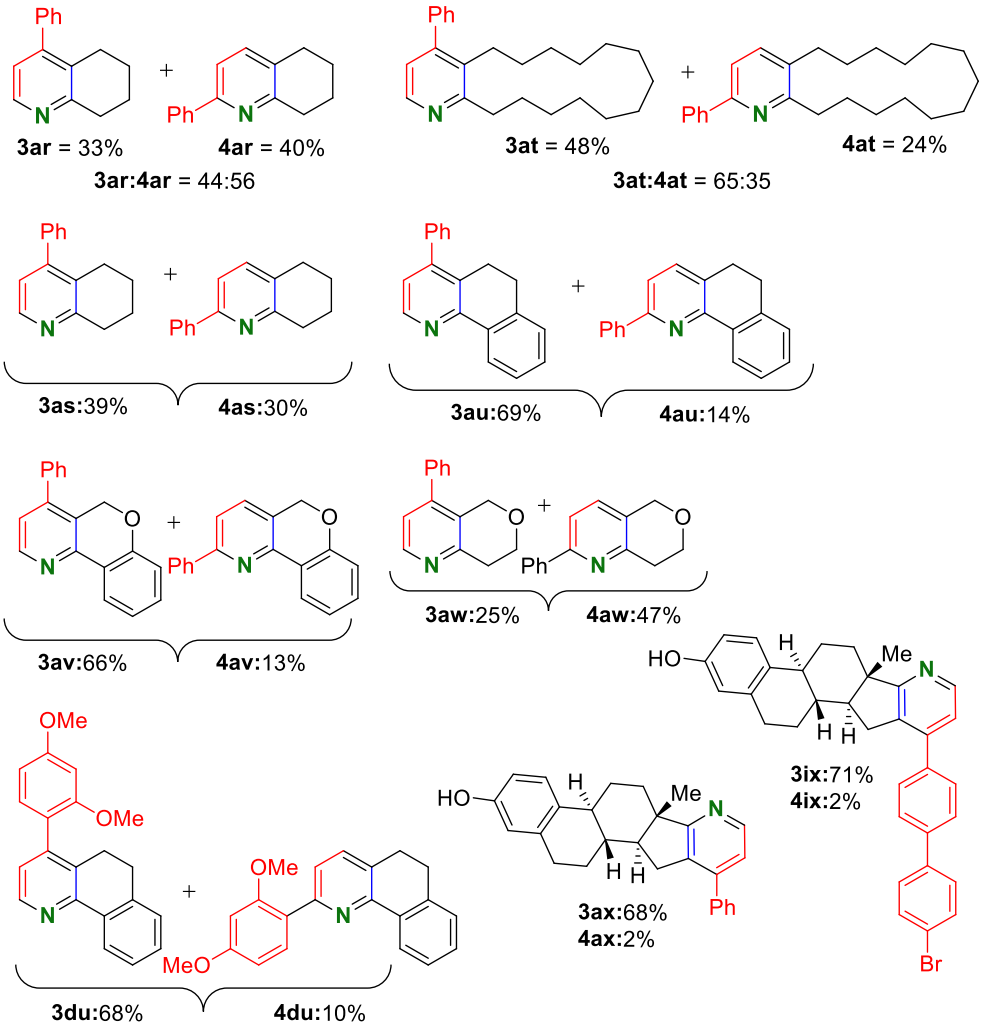
For further extension of our current method, we utilized cyclic ketones as the 2C units for pyridine synthesis. We successfully employed a range of cyclic ketones as C–H-activated donors in this aza-cyclization reaction. For example, 6-,7-, and 15-membered cyclic ketones, hexanone, heptanone and cyclopentadecanone (normuscone) respectively reacted effortlessly with 3-chloropropiophenone **1a** under standard conditions to give an interesting class of carbocyclic fused pyridine frameworks **3ar-3at** (33-48% yields) and **4ar-4at** (24-39% yields) as depicted in **Scheme 2.8**. Further, α-tetralone, 4-chromanone and dihydropyranone challenging 2C units for this aza-cyclization reaction smoothly reacted with **1a** & **1d,** providing targeted tricyclic fused pyridines (**3au-3du**) with high yields (66-69%) and minor regioisomer (**4au-4du**) in 10-14% yields. Remarkably, steroidal estrone **2x** as an enantioenriched polycyclic ketone reacted effortlessly in this domino

reaction with 3-propiophenones **1a** and **1h**, producing the pharmacologically prevalent[25] steroid-fused pyridine derivatives **3ax** and **3ix** in good yields of 68% and 71%, respectively.



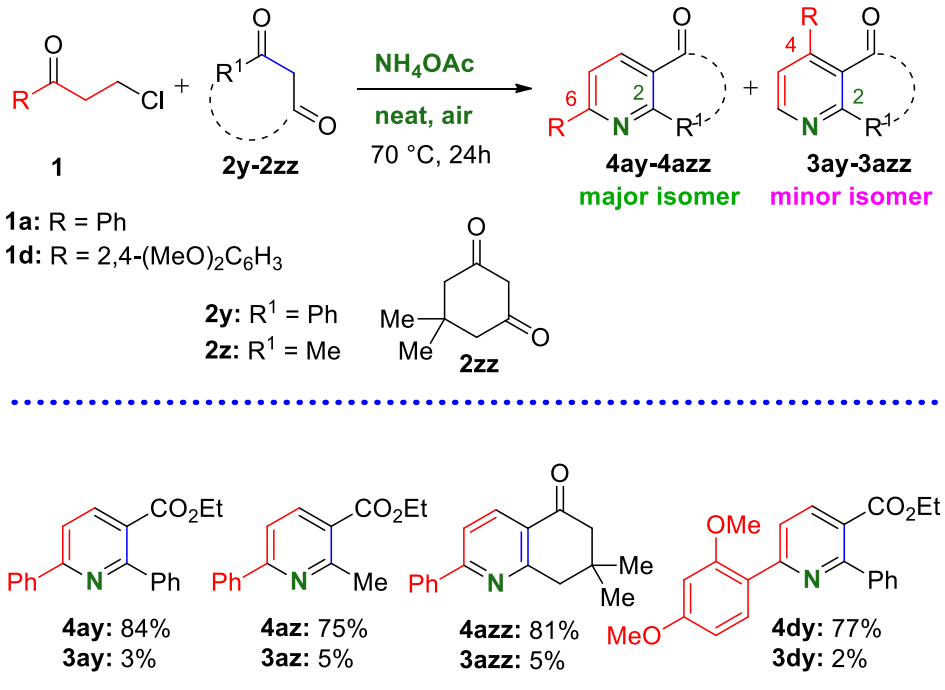
1a: R = Ph
1d: R = 2,4-$(MeO)_2C_6H_3$
1i: R = 4-(4-BrC_6H_4)-C_6H_4

2r: cyclohexanone
2s: cycloheptanone
2t: cyclopentadecanone
2u: a-tetralone
2v: 4-chromanone
2w: dihydropyranone
2x: estrone



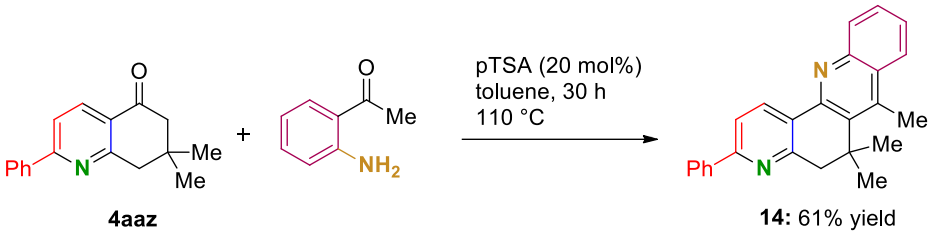
Scheme 2.8: Metal-free domino access to carbo- and heterocycle-fused pyridines using cyclic ketones.

To further extend this methodology, we employed 1,3-dicarbonyl compounds like β-keto esters (**2y** and **2z**) as reactive carbonucleophiles in this reaction with **1a-1d** under neat conditions. Surprisingly, these reactions endowed an exciting class[26] of 2,6-disubstituted nicotinates **4ay**, **4dy** and **4az** as major isomers in high yields of 84%, 77% and 75% respectively, and minor isomers **3ay**-**3az** in low conversion (3-5%, not isolated). Next, another 1,3-dicarbonyl compound **2zz** (dimedone) was also utilized in this cyclization, giving 7,8-dihydroquinoline-5(*6H*)-one in high yield (81%) as shown in **Scheme 2.9**., The formation of opposite regioisomer in the case of 1,3-dicarbonyl compounds is due to the less electrophilic nature of keto groups of 1,3-dicarbonyl compounds in comparison to methyl aryl ketones; thus, they are reluctant to participate in the imino-condensation reaction with *in-situ* generated β-aminoketone salts as illustrated in **Scheme 2.12** for minor isomer.



Scheme 2.9: Regioselective access to 2,6-disubstituted nicotinates and 7,8-dihydroquinoline-5(*6H*)-one.

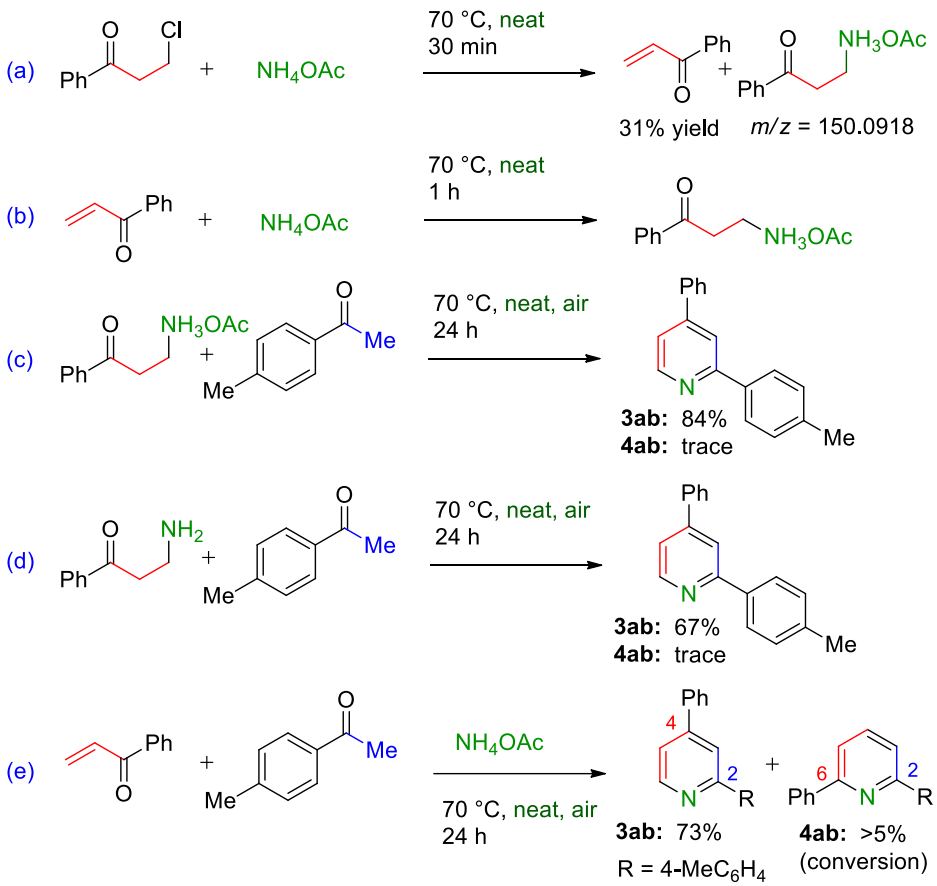
To highlight the synthetic utility of the prepared pyridines, the fused pyridine **4aaz** was reacted with 2-aminoacetophenone using 20 mol% pTSA in toluene at 110 °C. Interestingly, after 30 h, this reaction gave an interesting class[27] of 5,6-dihydrobenzo[*b*][1,7]phenanthroline building block **14** in a good yield of 61% as shown in **Scheme 2.10**.



Scheme 2.10. Access to the 5,6-dihydrobenzo[*b*][1,7]phenanthroline derivative.

2.4.3 Control Experiments

Several control experiments were performed to gain a quick insight into the pathways as illustrated in **Scheme 2.11**. When 3-chloropropiophenone (**1a**) was heated with NH_4OAc at 70 °C for 30 minutes, vinyl ketone (**5a,** 31% yield) and 3-amino-1-phenylpropan-1-one (**6a,** detected by HRMS) were formed as shown in **Scheme 2.11a**. Additionally, β-amino ketone **6a** originated with vinyl ketone **5a** and NH_4OAc under heating conditions *via* aza-Michael reaction (**Scheme 2.11b**). To illustrate the origin of major regioisomer like 2,4-diaryl pyridine **3ab,** we conducted the reaction between **6a** or **6a′** and **2b** at 70 °C under solvent-free conditions in an open atmosphere for 24 h. Interestingly, iminium salt of β-amino ketone **6a** showed a higher reactivity towards **2b,** providing a better yield (84%, **Scheme 2.11c**) of **3ab** than free amine **6a′** (67% yield, **Scheme 2.11d**). Moreover, when we took vinyl ketone in place of **6a** or **6a′,** the reaction proceeded smoothly with **2b** and NH_4OAc under standard reaction conditions to provide the major regioisomer **3ab** in 73% yield along with the minor regioisomer **4ab** (conversion: slightly greater than 5%, **Scheme 2.11e**).

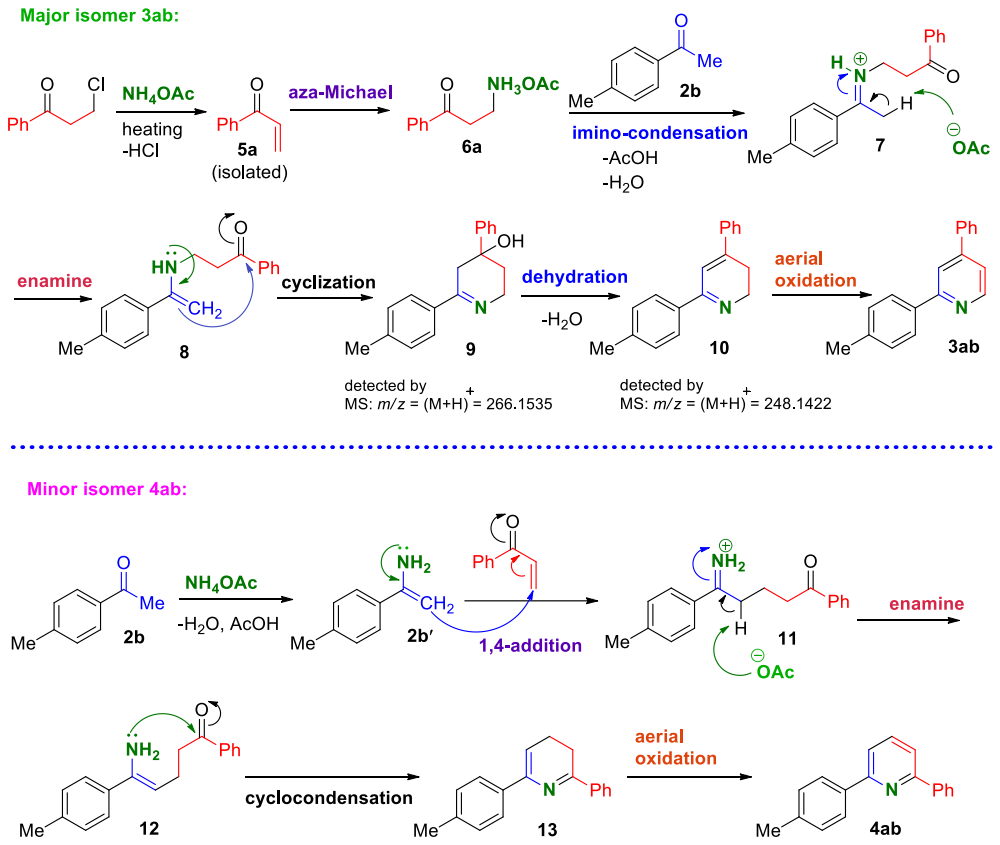


Scheme 2.11. Control experiments

2.4.4 Plausible Mechanism

We illustrated a logical mechanism for this hetero-cyclization reaction based on our control experiments as depicted in **Scheme 2.12**. Initially, the salt of β-amino ketone **6a** may be generated from *in-situ* formed vinyl ketone **5a** and NH_4OAc. Afterwards, β-amino ketone **6a** condenses with ketone **2b** leading to the reactive intermediate ketimine **7,** accompanied by an imine-enamine tautomerization in the presence of AcOH. This enamine intermediate **8** goes through intramolecular cyclization leading to tetrahydropyridine **9** (detected by HRMS). Then, water is eliminated in the presence of AcOH to form the dihydropyridine **10** (detected by HRMS), followed by aerial oxidation providing the major isomer **3ab**. However, ketone **2b** may also give an enamine intermediate **2b′** *via* a condensation reaction with ammonium acetate. After that, this enamine intermediate **2b′** attacks the β-position of vinyl ketone **5a,** followed by Michael addition adduct **11** which tautomerizes to give the enamine intermediate **12**. Ultimately, it is converted into the minor

isomer **4ab** *via* intramolecular cyclo-condensation followed by aerial oxidation of intermediate **13**.



Scheme 2.12. A Plausible mechanism for this hetero-cyclization reaction.

2.5 Conclusion

In this chapter, a one-pot, metal-free, simple reaction between 3-chloropropiophenones, different kinds of enolizable acyclic/cyclic ketones and NH_4OAc to produce a wide range of fascinating classes of di- and tri-substituted unsymmetrical pyridines regioselectively, including carbo- and heterocyclic fused aza-rings was established. Our strategic protocol is conceptually unique and certainly offers an alternative procedure for making di- and tri-substituted pyridines regioselectively with good to high yields. Additionally, our protocol has several positive points such as high substrate scope, neutral reaction conditions, excellent functional group tolerance,

operational simplicity, no requirement for volatile and hazardous organic solvents, no external oxidants and transition metal salts, mild reaction conditions, environmental friendliness and suitable for gram scale synthesis.

2.6 Experimental Section

General information: All reactions were carried out either under inert atmosphere or air and continuously monitored by TLC using Merck 60 F254 pre-coated silica gel plates and the products were visualized by UV light. Flash chromatography was done with silica gel (200-300 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance (III) 500 MHz spectrometer. ^{1}H NMR data are reported as a chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constant J (Hz), integration, and assignment, data for ^{13}C are reported as a chemical shift (δ ppm). High-resolution mass spectral analyses (HRMS) were carried out using ESI-TOF-MS. Melting points were recorded on an Electrothermal melting points apparatus and are uncorrected.

Starting materials: 3-Chloropropiophenones (**1a-1i**) and 3-bromopropiophenone were prepared according to literature procedures. Cyclic and acyclic ketones and ammonium salts were purchased from commercial suppliers and used without further purification unless otherwise stated.

Representative procedure for the Synthesis of (3aa): A mixture of compounds **1a** (0.3 mmol), **2a** (0.36 mmol) and NH_4OAc was heated at 70 °C in an open atmosphere under neat conditions. After completion of the reaction, the crude reaction mixture was extracted with ethyl acetate (3 × 10 mL), washed with water and brine, respectively, and dried over Na_2SO_4. The combined organic phases were evaporated under reduced pressure to get the crude product. Finally, the product was purified through column chromatography over silica gel using a mixture of EtOAc/hexane (1:19, v/v) as the eluent and obtained a 72% yield, and was fully characterized by its spectroscopic data (^{1}HNMR, ^{13}C NMR, and HRMS).

The prepared pyridines mentioned in **Scheme 2.7-2.9** followed the above procedure and were characterized by their corresponding spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS).

2,4-Diphenylpyridine (3aa):[28] Gummy liquid; yield = 72%; time = 24 h; R_f = 0.33 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 5.0 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 2H), 7.94 (s, 1H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.53-7.43 (m, 7H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 150.2, 149.4, 139.6, 138.6, 129.2, 129.19, 129.17, 128.9, 127.2, 127.1, 120.4, 118.9 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{14}N^+$ 232.1121, found 232.1119.

4-Phenyl-2-(4-methylphenyl)pyridine (3ab): [28] Gummy liquid; yield = 70%; time = 24 h; R_f = 0.34 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.1 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.91 (s, 1H), 7.70 (d, *J* = 7.0 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.47-7.41 (m, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 150.1, 149.3, 139.1, 138.7, 136.7, 129.6, 129.2, 129.1, 127.2, 127.0, 120.1, 118.5, 21.4 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}N^+$ 246.1277, found 246.1279.

2-(4-Fluorophenyl)-4-phenylpyridine (3ag): [28] Yellow oil; yield = 63%; time = 24 h; R_f = 0.45 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 5.1 Hz, 1H), 8.06-8.02 (m, 2H), 7.87 (s, 1H), 7.69 (d, *J* = 7.0 Hz, 2H), 7.53-7.43 (m, 4H), 7.18 (t, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 (d, J_{C-F} = 247.2 Hz), 157.2, 150.2, 149.5, 138.5, 135.7, 129.28, 129.25, 128.9 (d, J_{C-F} = 8.2 Hz), 127.2, 120.3, 118.5, 115.8 (d, J_{C-F} = 21.3 Hz) ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}FN^+$ 250.1027, found 250.1028.

2-(4-Chlorophenyl)-4-phenylpyridine (3ae):[28] Light yellow solid; yield =65%; mp 52-54 °C; time = 24 h; R_f = 0.41 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.1 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.89 (s, 1H), 7.69 (d, *J* = 7.1 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.48-7.45 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 150.3, 149.6, 138.5, 138.0, 135.3,

129.3, 129.1, 128.6, 128.4, 127.2, 120.6, 118.6 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}ClN^+$ 266.0731, found 266.0729.

2-(4-Bromophenyl)-4-phenylpyridine (3af): [28] Pale yellow solid; yield= 66%; mp 66-68 °C; time = 24 h; R_f = 0.41 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.1 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.89 (s, 1H), 7.68 (d, *J* = 7.1 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.53-7.45 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 150.3, 149.6, 138.4, 138.2, 132.0, 129.3 (2C, one overlap peak), 128.7, 127.2, 123.6, 120.7, 118.6 ppm; HRMS (ESITOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}{}^{79}BrN^+$ 310.0226, found 310.0234; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}{}^{81}BrN^+$ 312.0211, found 312.0206.

2-(4-Iodophenyl)-4-phenylpyridine (3ah):[28] Colorless solid; yield = 61%; mp 81-83 °C; time = 24 h; R_f = 0.45 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.1 Hz, 1H), 7.89 (s, 1H), 7.85-7.77 (m, 4H), 7.68 (d, *J* = 7.1 Hz, 2H), 7.53-7.40 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 150.3, 149.6, 139.0, 138.4, 138.08, 138.04, 129.3, 128.9, 127.2, 120.8, 118.6, 95.5 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}IN^+$ 358.0087, found 358.0081.

2-(4-Methoxyphenyl)-4-phenylpyridine (3ac):[28] Pale yellow solid; yield=73%; mp 52-54 °C; time = 24 h; R_f = 0.31 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 5.1 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.87 (s, 1H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.40 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 157.8, 150.0, 149.3, 138.8, 132.2, 129.2, 129.1, 128.4, 127.2, 119.7, 118.2, 114.3, 55.5 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}NO^+$ 262.1226, found 262.1224.

2-(Naphthalen-2-yl)-4-phenylpyridine(3aj): [28] Yellow oil; yield = 69%; time = 24 h; R_f = 0.28 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, *J* = 5.1 Hz, 1H), 8.55 (s, 1H), 8.21 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.08 (s, 1H), 7.98 (d, *J* = 8.7 Hz, 2H), 7.90-7.88 (m, 1H), 7.74 (d, *J* = 7.1 Hz, 2H), 7.55-7.47 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 150.3, 149.5,

138.6, 136.8, 133.8, 133.6, 129.3, 129.2, 128.8, 128.6, 127.8, 127.2, 126.7, 126.6, 126.4, 124.8, 120.4, 119.1 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}N^+$ 282.1277, found 182.1286.

2-([1, 1′-Biphenyl]-4-yl)-4-phenylpyridine (3ad): [28] Light yellow solid; yield = 67%; time = 24 h; mp 88-90 °C; R_f = 0.38 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 5.1 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 2H), 7.99 (s, 1H), 7.75-7.71 (m, 4H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 2H), 7.49-7.46 (m, 4H), 7.38 (t, *J* = 7.3 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 150.2, 149.5, 141.9, 140.7, 138.6, 138.4, 129.3, 129.2, 128.9, 128.0, 127.7, 127.6, 127.5, 127.2, 120.4, 118.8 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{23}H_{18}N^+$ 308.1434, found 308.1439.

2-(3-Nitrophenyl)-4-phenylpyridine (3ai): [28] Yellow solid; yield = 59% ; mp 109-111 °C; time = 24 h; R_f = 0.33 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.77 (d, *J* = 5.0 Hz, 1H), 8.43 (d, *J* = 7.7 Hz, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 7.98 (s, 1H), 7.71-7.64 (m, 3H), 7.54-7.47 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 150.5, 149.9, 148.9, 141.2, 138.1, 132.9, 129.8, 129.5, 129.3, 127.2, 123.7, 122.0, 121.4, 118.8 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}N_2O_2^+$ 277.0972, found 277.0970.

2-(Furan-2-yl)-4-phenylpyridine (3al): [28] Yellow oil; yield = 68%; time = 24 h; R_f = 0.32 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.1 Hz, 1H), 7.92 (br s, 1H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.55 (br s, 1H), 7.50 (t, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.37 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.12 (d, *J* = 3.3 Hz, 1H), 6.56 (dd, *J* = 3.2, 1.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 150.1, 149.9, 149.2, 143.4, 138.3, 129.2, 129.2, 127.1, 120.0, 116.6, 112.2, 108.9 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}NO^+$ 222.0913, found 222.0932.

4-Phenyl-2-(thiophen-2-yl)pyridine (3am):[28] Colorless oil; yield = 70%; time = 24 h; R_f =0.32 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.2 Hz, 1H), 7.86 (br s, 1H), 7.68 (d, *J* = 7.0 Hz, 3H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 5.0 Hz, 1H), 7.37 (dd, *J* =

5.2, 1.6 Hz, 1H), 7.14 (dd, *J* = 5.0, 3.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 150.1, 149.4, 144.9, 138.4, 129.2, 128.2, 128.0, 127.8, 127.2, 124.8, 120.2, 117.0 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}NS^+$ 238.0685, found 238.0690.

4-Phenyl-2,3′-bipyridine (3ak):[28] Pale yellow solid; yield = 55%; mp 51-53 ℃; time = 24 h; R_f = 0.20 (EtOAc/Hexane = 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.76 (d, *J* = 5.0 Hz, 1H), 8.68 (br s, 1H), 8.38 (d, *J* = 7.8 Hz, 1H), 7.94 (s, 1H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.55-7.42 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 150.6, 150.0, 149.7, 148.3, 138.2, 135.1, 134.7, 129.4, 129.3, 127.2, 123.7, 121.1, 118.9 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}N_2^+$ 233.1073, found 233.1084.

2-Phenyl-4-(4-methylphenyl)pyridine (3ba): [29] Pale yellow solid; yield = 73%; mp 73-75 ℃; time = 24 h; R_f = 0.31 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.0 Hz, 1H), 8.04 (d, *J* = 7.0 Hz, 2H), 7.92 (s, 1H), 7.61 (d, *J* = 7.1 Hz, 2H), 7.49 (t, *J* = 6.7 Hz, 2H), 7.44 (d, *J* = 5.0 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 2H), 2.43 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 150.2, 149.3, 139.7, 139.3, 135.7, 130.0, 129.1, 128.9, 127.2, 127.0, 120.1, 118.7, 21.3 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}N^+$ 246.1277, found 246.1295.

2,4-Di-(4-methylphenyl)pyridine (3bb): [29] Colorless solid; yield = 70%; mp 112-114 ℃; time = 24 h; R_f = 0.34 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.9 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 2H), 7.89 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 4.7 Hz, 1H), 7.32-7.28 (m, 4H), 2.43 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 150.1, 149.2, 139.2, 139.1, 136.9, 135.8, 129.9, 129.6, 127.05, 127.03, 119.9, 118.3, 21.4, 21.3 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}N^+$ 260.1434, found 260.1440.

2-(4-Fluorophenyl)-4-(4-methylphenyl)pyridine (3bg): Pale yellow oil; yield = 63%; time = 24 h; R_f = 0.35 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 5.1 Hz, 1H), 8.03 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.86 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.43 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.32 (d, *J* =

7.8 Hz, 2H), 7.18 (t, *J* = 8.7 Hz, 2H), 2.43 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5 (d, J_{C-F} = 246.7 Hz), 157.0, 150.0, 149.3, 139.2, 135.7, 135.4, 129.8, 128.8 (d, J_{C-F} = 8.2 Hz), 126.9, 120.0, 118.2, 115.6 (d, J_{C-F} = 21.3 Hz), 21.2 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}FN^+$ 264.1183, found 264.1184.

4-(4-Methoxyphenyl)-2-phenylpyridine (3ca):[28], [29] Yellow oil; yield = 71%; time = 24 h; R_f = 0.31 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 5.1 Hz, 1H), 8.04 (d, *J* = 7.3 Hz, 2H), 7.89 (s, 1H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.45-7.41 (m, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 158.1, 150.0, 148.9, 139.6, 130.8, 129.1, 128.9, 128.4, 127.2, 119.8, 118.4, 114.7, 55.5 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}NO^+$ 262.1226, found 262.1229.

4-(4-Chlorophenyl)-2-phenylpyridine (3ea): [29] Yellow oil; yield = 66%; time = 24 h; R_f = 0.33 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 5.0 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.88 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.51-7.39 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 150.3, 148.1, 139.4, 137.1, 135.4, 129.4, 129.3, 128.9, 128.4, 127.1, 120.1, 118.6 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}ClN^+$ 266.0731, found 266.0741.

4-(4-Chlorophenyl)-2-(4-methylphenyl)pyridine (3eb):[29] Colorless solid; yield = 68%; mp 96-98 °C; time = 24 h; R_f = 0.37 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.9 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.86 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 3.9 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 150.2, 148.1, 139.3, 137.2, 136.6, 135.3, 129.6, 129.4, 128.5, 127.0, 119.8, 118.3, 21.4 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}ClN^+$ 280.0888, found 280.0894.

4-(4-Chlorophenyl)-2-(4-fluorophenyl)pyridine (3eg): Colorless solid; yield =56%; mp 61-63 °C; time = 24 h; R_f = 0.39 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.1 Hz, 1H), 7.94 (dd, *J* = 8.7, 5.4

Hz, 2H), 7.74 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.31 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.09 (t, *J* = 8.6 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 (d, J_{C-F} = 247.3 Hz), 157.3, 150.3, 148.2, 136.9, 135.57 (d, J_{C-F} = 2.8 Hz), 135.50, 129.5, 128.9 (d, J_{C-F} = 8.4 Hz), 128.4, 120.0, 118.2, 115.8 (d, J_{C-F} = 21.3 Hz) ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{12}ClFN^+$ 284.0637, found 284.0635.

2, 4-Bis(4-chlorophenyl)pyridine (3ee): Colorless solid; yield=61%; mp 97-99 °C; time = 24 h; R_f = 0.46 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.1 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 2H), 7.85 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.48 (dd, *J* = 10.4, 8.6 Hz, 4H), 7.42 (dd, *J* = 5.1, 1.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 150.4, 148.4, 137.8, 136.9, 135.5, 135.4, 129.5, 129.1, 128.5, 128.4, 120.4, 118.4 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{12}Cl_2N^+$ 300.0341, found 300.0347.

2-(4-Bromophenyl)-4-(4-chlorophenyl)pyridine (3ef): Colorless solid; yield = 58%; mp 112-114 °C; time = 24 h; R_f = 0.47 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.1 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.85 (s, 1H), 7.62 (dd, *J* = 8.5, 3.6 Hz, 4H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.42 (dd, *J* = 5.1, 1.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 150.4, 148.4, 138.3, 136.9, 135.5, 132.1, 129.5, 128.7, 128.5, 123.8, 120.4, 118.3 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{12}{}^{79}BrClN^+$ 343.9836, found 3343.9844; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{12}{}^{81}BrClN^+$ 345.9815, found 345.9817.

4-(4-Bromophenyl)-2-phenylpyridine (3fa): *[29]* Yellow oil; yield = 64%; time = 24 h; R_f = 0.39 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, *J* = 5.1 Hz, 1H), 8.04 (d, *J* = 7.3 Hz, 2H), 7.88 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.41 (dd, *J* = 5.1, 1.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 150.3, 148.3, 139.3, 137.5, 132.4, 129.3, 128.9, 128.8, 127.2, 123.7, 120.1, 118.6 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}{}^{79}BrN^+$ 310.0226, found 310.0230; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}{}^{81}BrN^+$ 312.0207, found 312.0211.

2,4-Bis(4-bromophenyl)pyridine (3ff): Colorless solid; yield = 60%; mp 128-131 °C; time = 24 h; R_f = 0.44 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 5.1 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.83 (s, 1H), 7.63 (dd, *J* = 10.3, 8.6 Hz, 4H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.41 (dd, *J* = 5.0, 1.3 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 150.4, 148.4, 138.2, 137.3, 132.4, 132.0, 128.7, 128.7, 123.8, 123.7, 120.3, 118.2 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{12}{}^{79}Br_2N^+$ 387.9331, found 387.9349; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{12}{}^{79}Br^{81}BrN^+$ 389.9311, found 389.9325; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{12}{}^{81}Br_2N^+$ 391.9293, found 391.9291.

4-(4-Iodophenyl)-2-phenylpyridine (3ga): Gummy; yield = 63%; time = 24 h; R_f = 0.40 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, *J* = 5.1 Hz, 1H), 8.04 (d, *J* = 7.1 Hz, 2H), 7.88 (s, 1H), 7.86-7.83 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.46-7.40 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 150.3, 148.4, 139.3, 138.4, 138.1, 129.3, 128.9, 128.9, 127.2, 120.0, 118.5, 95.4 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}IN^+$ 358.0087, found 358.0087.

4-(4-Iodophenyl)-2-(4-methoxyphenyl)pyridine (3gb): Gummy; yield = 60%; time = 24 h; R_f = 0.36 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 5.1 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 3.87 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 158.0, 150.2, 148.2, 138.3, 138.3, 131.9, 128.9, 128.4, 119.3, 117.7, 114.3, 95.2, 55.5 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}INO^+$ 388.0193, found 388.0197.

4-(5-Methylthiophen-2-yl)-2-phenylpyridine (3ha): Pale yellow solid; yield = 68%; mp 84- 86 °C; time = 24 h; R_f = 0.37 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.2 Hz, 1H), 8.02 (d, *J* = 7.2 Hz, 2H), 7.82 (s, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.37-7.34 (m, 2H), 6.80 (dd, *J* = 3.5, 0.9 Hz, 1H), 2.55 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 150.2, 142.5, 142.3, 139.5, 139.0, 129.1, 128.8, 127.1, 126.8,

125.5, 118.1, 116.6, 15.7 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{16}H_{14}NS^+$ 352.0841, found 352.0847.

4-(2,4-Dimethoxyphenyl)-2-phenylpyridine (3da): Pale yellow oil; yield = 66%; time = 24 h; R_f = 0.21 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 5.1 Hz, 1H), 8.01 (d, *J* = 7.7 Hz, 2H), 7.88 (s, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.43-7.40 (m, 2H), 7.35 (d, *J* = 8.3 Hz, 1H), 6.62-6.59 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 157.9, 157.3, 149.3, 147.2, 139.9, 131.2, 128.9, 128.8, 127.2, 122.8, 121.4, 120.8, 105.2, 99.2, 55.7, 55.6 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}NO_2^+$ 292.1332, found 292.1343.

4-(4′-Bromo-[1,1′-biphenyl]-4-yl)-2-cyclopropylpyridine (3in): Pale Yellow oil; yield = 76%; time = 30 h; R_f = 0.32 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 5.2 Hz, 1H), 7.72-7.70 (m, 2H), 7.67-7.66 (m, 2H), 7.60-7.58 (m, 2H), 7.51-7.49 (m, 2H), 7.38 (s, 1H), 7.31 (dd, *J* = 5.2, 1.5 Hz, 1H), 2.18-2.13 (m, 1H), 1.13-1.04 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 149.1, 148.4, 140.8, 139.2, 137.6, 132.2, 128.8, 127.7, 127.7, 122.2, 119.2, 118.7, 17.2, 10.3 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}{}^{79}BrN^+$ 350.0539, found 350.0539; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}{}^{81}BrN^+$ 352.0520, found 352.0525.

Ethyl 2, 6-diphenylnicotinate (4ay): Pale yellow oil; yield =84%; time = 24 h; R_f = 0.34 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.1 Hz, 1H), 8.14-8.12 (m, 2H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.66-7.63 (m, 2H), 7.50-7.43 (m, 6H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 158.8, 158.5, 140.6, 139.0, 138.4, 129.8, 128.98, 128.92, 128.7, 128.1, 127.4, 125.4, 117.9, 61.5, 13.8 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}NO_2^+$ 304.1332, found 304.1341.

Ethyl 6-(2,4-dimethoxyphenyl)-2-phenylnicotinate (4dy): Yellow oil; yield = 77%; time = 24 h; R_f = 0.26 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.61 (dd, *J* = 7.6, 1.4 Hz, 2H), 7.44-7.38 (m, 3H), 6.62 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.56 (d, *J* = 2.2 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H),

3.86 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 162.0, 158.8, 158.5, 157.1, 141.0, 137.9, 132.7, 128.9, 128.4, 128.0, 124.2, 122.3, 121.1, 105.4, 98.9, 61.3, 55.7, 55.6 13.8 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}NO_4^+$ 364.1543, found 364.1541.

Ethyl 2-methyl-6-phenylnicotinate (4az): Yellow oil; yield =75%; time = 24 h; R_f = 0.58 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.2 Hz, 1H), 8.06-8.04 (m, 2H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.49-7.41 (m, 3H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.92 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 159.9, 159.0, 139.3, 138.5, 129.6, 128.8, 127.3, 123.6, 117.3, 61.1, 25.3, 14.3 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{15}H_{16}NO_2^+$ 242.1176, found 242.1182.

2-(4-Methoxyphenyl)-3-methyl-4-phenylpyridine (3ao, major isomer): Colorless oil; yield = 61%; time = 36 h; R_f = 0.24 (EtOAc/Hexane = 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.9 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.37-7.36 (m, 2H), 7.13 (d, *J* = 4.9 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 2.23 (s, 3H).ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 159.4, 151.2, 146.3, 140.0, 130.6, 129.9, 128.8, 128.7, 128.5, 128.0, 123.0, 113.7, 55.4, 18.4 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}NO^+$ 276.1383, found 276.1382.

2-(4-Methoxyphenyl)-3-methyl-6-phenylpyridine (4ao, minor isomer): Colorless oil; yield = 9%; time = 36 h; R_f = 0.28 (EtOAc/Hexane = 20:80); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.4 Hz, 2H), 7.66-7.60 (m, 4H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 157.5, 154.3, 139.7, 130.6, 129.3, 128.7, 128.6, 128.2, 127.9, 126.9, 118.5, 113.5, 55.3, 20.0 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}NO^+$ 276.1383, found 276.1388.

2-(4-Bromophenyl)-3-methyl-4-phenylpyridine (3ap): Yellow oil; yield = 57%; time = 36 h; R_f = 0.21 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.9 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.48-7.40 (m, 5H), 7.36 (d, *J* = 7.1 Hz, 2H), 7.16 (d, *J* = 4.9 Hz, 1H), 2.20 (s, 3H) ppm; ^{13}C NMR

(125 MHz, $CDCl_3$) δ 158.6, 151.3, 146.7, 140.0, 139.7, 131.4, 131.0, 128.8, 128.7, 128.6, 128.1, 123.6, 122.3, 18.1 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}{}^{79}BrN^+$ 324.0382, found 324.0383; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}{}^{81}BrN^+$ 326.0364, found 326.0366.

2-Ethyl-3-methyl-4-phenylpyridine (3aq): Pale yellow oil; yield = 64%; time = 36 h; R_f = 0.31 (EtOAc/Hexane = 10:90); ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.0 Hz, 1H), 7.45-7.42 (m, 2H), 7.40-7.37 (m, 1H), 7.29-7.27 (m, 2H), 7.00 (d, *J* = 5.0 Hz, 1H), 2.91 (q, *J* = 7.5 Hz, 2H), 2.22 (s, 3H), 1.35 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 149.9, 146.0, 140.1, 129.1, 128.8, 128.3, 127.7, 122.3, 29.2, 15.6, 12.9 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{14}H_{15}N^+$ 198.1277, found 198.1285.

2-Phenyl-5,6,7,8-tetrahydroquinoline (4ar, major isomer):[30] Pale yellow oil; yield = 40%; time = 24 h; R_f = 0.52 (EtOAc/Hexane = 10:90); ^1H NMR (500 MHz, $CDCl_3$) δ 7.95-7.93 (m, 2H), 7.46-7.35 (m, 5H), 3.01 (t, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 6.3 Hz, 2H), 1.95-1.91 (m, 2H), 1.86-1.81 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 154.8, 139.9, 137.6, 130.9, 128.7, 128.5, 126.9, 118.1, 32.9, 28.7, 23.3, 22.9 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}N^+$ 210.1277, found 210.1281.

4-Phenyl-5,6,7,8-tetrahydroquinoline (3ar, minor isomer): Pale yellow oil; yield = 33%; time = 24 h; R_f = 0.24 (EtOAc/Hexane = 15:85); ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.9 Hz, 1H), 7.44-7.37 (m, 3H), 7.29-7.27 (m, 2H), 6.99 (d, *J* = 4.9 Hz, 1H), 3.03 (t, *J* = 6.6 Hz, 2H), 2.63 (t, *J* = 6.3 Hz, 2H), 1.93-1.88 (m, 2H), 1.75-1.70 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 150.2, 146.0, 139.3, 130.3, 128.6, 128.4, 128.0, 122.2, 32.8, 27.5, 22.9, 22.9 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}N^+$ 210.1277, found 210.1278.

2-Phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine (4as, minor): Pale yellow oil; yield =30%; time = 24 h; R_f = 0.56 (EtOAc/Hexane = 10:90); ^1H NMR (500 MHz, $CDCl_3$) δ 7.97-7.96 (m, 2H), 7.46-7.43 (m, 4H), 7.37 (t, *J* = 7.3 Hz, 1H), 3.15-3.12 (m, 2H), 2.82-2.79 (m, 2H), 1.92-1.87 (m, 2H), 1.75-1.69 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 154.1, 139.9, 137.3,

136.7, 128.7, 128.4, 126.9, 118.0, 39.8, 35.1, 32.7, 28.2, 26.8 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}N^+$ 224.1434, found 224.1433.

4-Phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine (3as, major): Pale yellow oil; yield = 39%; time = 24 h; R_f = 0.30 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 5.1 Hz, 1H), 7.37-7.29 (m, 3H), 7.18 (d, *J* = 6.9 Hz, 2H), 6.91 (d, *J* = 5.1 Hz, 1H), 3.07-3.04 (m, 2H), 2.67-2.64 (m, 2H), 1.82-1.77 (m, 2H), 1.71-1.67 (m, 2H), 1.57-1.52 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 149.1, 145.2, 140.0, 135.7, 128.9, 128.4, 127.74, 122.79, 39.4, 32.3, 29.7, 27.8, 26.5 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}N^+$ 224.1434, found 224.1443.

4-Phenyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-5*H*-cyclopentadeca[*b*]pyridine (3at, major isomer): Yellow oil; yield = 48%; time = 30 h; R_f = 0.22 (EtOAc/Hexane = 05:95); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 4.9 Hz, 1H), 7.41-7.33 (m, 3H), 7.24-7.22 (m, 2H), 6.90 (d, *J* = 4.9 Hz, 1H), 2.84-2.80 (m, 2H), 2.51-2.48 (m, 2H), 1.83 – 1.77 (m, 2H), 1.60-1.55 (m, 2H), 1.46-1.39 (m, 4H), 1.36-1.31 (m, 4H), 1.28-1.20 (m, 10H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 150.3, 146.1, 140.4, 133.5, 128.4, 128.2, 127.6, 122.6, 35.3, 29.1, 29.0, 28.3, 27.7, 27.6, 26.9, 26.7, 26.5, 26.2, 26.1, 25.4, 25.2 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{24}H_{34}N^+$ 336.2686, found 336.2694.

2-[Phenyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-5*H*-cyclopentadeca[*b*]pyridine (4at, minor isomer): *[30]* Colorless solid; yield = 24%; mp 39-41 °C; time = 30 h; R_f = 0.69 (EtOAc/Hexane = 05:95); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.97 (m, 2H), 7.46-7.42 (m, 4H), 7.36 (t, *J* = 7.3 Hz, 1H), 2.88-2.84 (m, 2H), 2.65-2.62 (m, 2H), 1.86 – 1.80 (m, 2H), 1.67-1.61 (m, 2H), 1.59-1.55 (m, 2H), 1.54-1.48 (m, 2H), 1.44-1.42 (m, 4H), 1.38-1.34 (m, 10H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 154.4, 140.0, 137.9, 134.2, 128.7, 128.4, 126.9, 118.0, 35.1, 32.3, 29.7, 28.2, 27.6, 27.5, 27.1, 27.0, 26.8, 26.17, 26.13, 25.7 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{24}H_{34}N^+$ 336.2686, found 336.2699.

4-Phenyl-5,6-dihydrobenzo[*h*]quinoline (3au, major isomer):[28], [30] Yellow solid; yield = 69%; mp 89-91 °C; time = 24 h; R_f = 0.45 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.9 Hz, 1H), 8.38 (d, *J* = 7.6 Hz, 1H), 7.49-7.32 (m, 7H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 4.9 Hz, 1H), 2.92 (t, *J* = 7.0, 2H), 2.82 (t, *J* = 6.9, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 148.6, 147.2, 138.9, 138.2, 135.0, 129.5, 129.2, 128.8, 128.5, 128.1, 127.6, 127.2, 125.5, 123.4, 28.1, 25.5 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}N^+$ 258.1277, found 258.1278.

2-Phenyl-5,6-dihydrobenzo[*h*]quinoline (4au, minor isomer):[30] Pale yellow oil; yield = 14%; time = 24 h; R_f = 0.60 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 7.0 Hz, 1H), 8.16-8.14 (m, 2H), 7.61-7.55 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.42-7.38 (m, 2H), 7.34-7.30 (m, 1H), 7.23 (d, *J* = 7.1 Hz, 1H), 2.98-2.95 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 152.1, 139.7, 138.3, 136.4, 134.9, 130.4, 129.1, 128.7, 127.8, 127.2, 126.9, 125.4, 118.8, 28.2, 27.9 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}N^+$ 258.1277, found 258.1260.

4-(2,4-Dimethoxyphenyl)-5,6-dihydrobenzo[*h*]quinoline (3du, major isomer): Colorless oil; yield =68%; time = 30 h; R_f = 0.58 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.9 Hz, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 4.9 Hz, 1H), 6.52 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.49 (d, *J* = 2.1 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 2.73-2.71 (m, 3H), 2.61-2.57 (m, 1H) ppm; 13C NMR (125 MHz, $CDCl_3$) δ 161.2, 157.6, 152.4, 147.0, 145.7, 138.5, 135.2, 131.5, 131.1, 129.0, 127.5, 127.2, 125.5, 124.3, 120.7, 104.6, 98.7, 55.6, 55.5, 28.1, 25.4 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{21}H_{20}NO_2^+$ 318.1489, found 318.1495.

2-(2,4-Dimethoxyphenyl)-5,6-dihydrobenzo[*h*]quinoline (4du): Pale yellow oil; yield = 10%; time = 30 h; R_f = 0.69 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.1 Hz, 1H), 7.31-7.28 (m, 1H), 7.23 (d, *J* = 7.3 Hz, 1H), 6.67 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.96 (s, 4H) ppm; ^{13}C NMR

(125 MHz, $CDCl_3$) δ 161.1, 158.3, 153.4, 151.6, 138.0, 135.3, 132.1, 129.2, 128.7, 127.6, 127.0, 125.1, 123.2, 105.1, 98.9, 55.6, 55.4, 28.2, 27.7 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{21}H_{20}NO_2^+$ 318.1489, found 318.1496.

4-Phenyl-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine (3aw, minor isomer): Yellow oil; yield = 25%; time = 30 h; R_f = 0.16 (EtOAc/Hexane = 25:75); ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.9 Hz, 1H), 7.39-7.34 (m, 4H), 7.20 (bs, 1H), 6.97 (d, *J* = 4.9 Hz, 1H), 4.60 (s, 2H), 4.03 (t, *J* = 5.9 Hz, 2H), 3.05 (t, *J* = 5.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 147.6, 147.3, 137.6, 128.8, 128.5, 128.29, 128.25 122.4, 66.5, 65.8, 32.0 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO^+$ 212.1070, found 212.1068.

2-Phenyl-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine (4aw, major isomer): Yellow oil; yield = 47%; time = 30 h; R_f = 0.70 (EtOAc/Hexane = 25:75); ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.4 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.41-7.36 (m, 2H), 4.81 (s, 2H), 4.11 (t, *J* = 5.8 Hz, 2H), 3.11 (t, *J* = 5.7 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 153.6, 139.5, 133.1, 128.9, 128.8, 127.0 (2C, one overlap peak), 118.4, 67.2, 65.9, 32.1 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO^+$ 212.1070, found 212.1072.

4-phenyl-5*H*-chromeno[4,3-*b*]pyridine (3av, major isomer): Pale yellow solid; yield = 66%; time = 30 h; R_f = 0.62 (EtOAc/Hexane = 15:85); ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.0 Hz, 1H), 8.29 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.52-7.43 (m, 3H), 7.32 (ddd, *J* = 10.8, 8.2, 4.0 Hz, 3H), 7.17 (d, *J* = 5.0 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 5.22 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 149.3, 149.0, 146.8, 137.3, 131.5, 128.9, 128.8, 128.6, 125.2, 124.0, 123.8, 123.5, 122.7, 117.0, 66.0 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{14}NO^+$ 260.1070, found 260.1082.

2-Phenyl-5*H*-chromeno[4,3-*b*]pyridine (4av, minor isomer): Pale yellow oil; yield = 13%; time = 30 h; R_f = 0.70 (EtOAc/Hexane = 15:85); ^1H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.13 (d, *J* = 7.4 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.51-7.48 (m, 3H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.34-7.31

(m, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 5.27 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 156.6, 148.4, 139.3, 132.9, 131.3, 129.2, 128.8, 127.0, 125.0, 124.5, 123.5, 122.4, 119.1, 117.0, 68.0 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{18}H_{14}NO^+$ 260.1070, found 260.1071.

7,7-Dimethyl-2-phenyl-7,8-dihydroquinolin-5(6*H*)-one (4azz): Colorless solid; yield = 81%; mp 58-60 °C; time = 24 h; R_f = 0.38 (EtOAc/Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.2 Hz, 1H), 8.03 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.47-7.40 (m, 3H), 3.08 (s, 2H), 2.53 (s, 2H), 1.11 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 162.4, 161.0, 138.4, 135.3, 129.9, 128.8, 127.4, 125.5, 118.8, 52.0, 46.7, 32.9, 28.3 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO^+$ 252.1383, found 252.1383.

(6b*S*,8a*S*,13a*S*,13b*R*)-8a-Methyl-12-phenyl-2,6b,7,8,8a,13,13a,13b-octahydro-1*H*-naphtho[2′,1′:4,5]indeno[1,2-*b*]pyridin-4-ol (3ax): Pale yellow solid; yield = 68%; mp 211-213 °C; time = 30 h; R_f = 0.47 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.3 Hz, 1H), 7.51-7.42 (m, 5H), 7.17 (t, *J* = 7.2 Hz, 2H), 6.71 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.64 (d, *J* = 2.0 Hz, 1H), 2.94-2.79 (m, 4H), 2.52-2.44 (m, 2H), 2.36-2.32 (m, 1H), 2.00-1.96 (m, 1H), 1.86-1.67 (m, 4H), 1.48-1.39 (m, 1H), 1.14 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 154.5, 146.6, 146.4, 138.3, 137.8, 134.3, 131.7, 128.7, 128.5, 128.3, 126.2, 120.9, 115.5, 113.0, 55.1, 46.2, 44.3, 37.6, 33.7, 30.3, 29.5, 27.4, 26.3, 17.6 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{27}H_{28}NO^+$ 382.2165 , found 382.2163.

(6b*S*,8a*S*,13a*S*,13b*R*)-12-(4′-Bromo-[1,1′-biphenyl]-4-yl)-8a-methyl 2,6b,7,8,8a,13,13a,13b-octahydro-1*H*-naphtho[2′,1′:4,5]indeno[1,2-*b*]pyridin-4-ol (3ix): Yellow solid; yield =71%; mp 220-222 °C; time = 30 h; R_f = 0.43 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 8.7 Hz, 4H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.20-7.17 (m, 2H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.62 (s, 1H), 6.41 (br s, 1H), 2.91-2.82 (m, 4H), 2.48 (d, *J* = 10.2 Hz, 2H), 2.37-2.33 (m, 1H), 2.01-2.00 (m, 1H), 1.86-1.72 (m, 4H), 1.49-1.40 (m, 1H), 1.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 154.2, 147.1, 145.8, 140.3, 139.5, 138.2,

137.9, 134.3, 132.4, 132.3, 129.1, 128.9, 127.4, 126.5, 122.2, 120.9, 115.6, 113.1, 55.4, 46.4, 44.6, 37.8, 34.0, 30.6, 29.7, 27.6, 26.5, 17.8 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{33}H_{31}{}^{79}BrNO^+$ 536.1584, found 536.1586. HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{33}H_{31}{}^{81}BrNO^+$ 538.1569, found 538.1574.

6,6,7-Trimethyl-3-phenyl-5,6-dihydrobenzo[*b*][1,7]phenanthroline: Colorless solid; yield = 61%; mp 141-143 °C; time = 30 h; R_f = 0.48 (EtOAc/ Hexane = 10:90); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, *J* = 8.0 Hz, 1H), 8.10- 8.05 (m, 4H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.67 (t, *J* = 7.3 Hz, 1H), 7.54-7.48 (m, 3H), 7.43 (t, *J* = 7.1 Hz, 1H), 3.18 (s, 2H), 2.88 (s, 3H), 1.61 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 157.2, 151.2, 146.5, 141.6, 139.5, 136.5, 135.0, 129.8, 129.2, 129.1, 128.9, 128.8, 128.7, 127.2, 126.3, 123.6, 119.8, 49.4, 37.5, 28.4, 18.0 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{25}H_{23}N_2^+$ 351.1856, found 351.1860.

3-Bromo-1-phenylpropan-1-one: White solid; mp 47-50°C; R_f = 0.73 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 3.74 (t, *J* = 6.9 Hz, 2H), 3.58 (t, *J* = 6.9 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 136.3, 133.7, 128.8, 128.1, 41.6, 25.8 ppm; HRMS (ESI-TOF): *m/z* $[M+ Na]^+$ calcd for $C_9H_9{}^{79}BrONa^+$ 234.9729, found 234.9725; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_9H_9{}^{81}BrONa^+$ 236.9709, found 236.9699

2.7 Copies of ^{1}H and ^{13}C NMR of the described compounds:

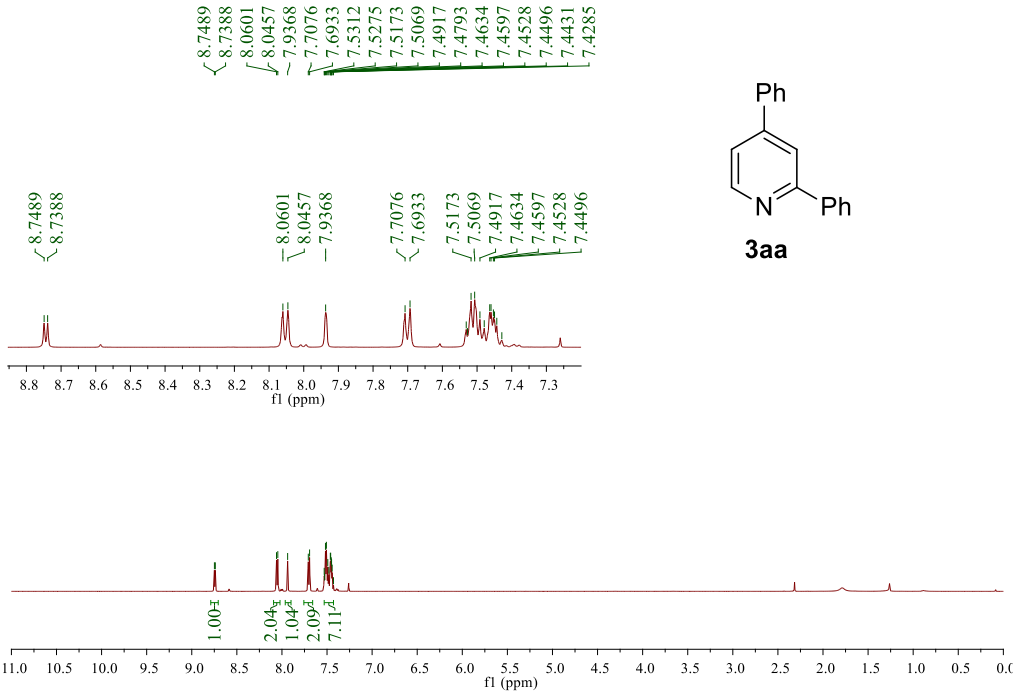


Figure 2.1. 500 MHz ^{1}H Spectrum of **3aa** in $CDCl_3$

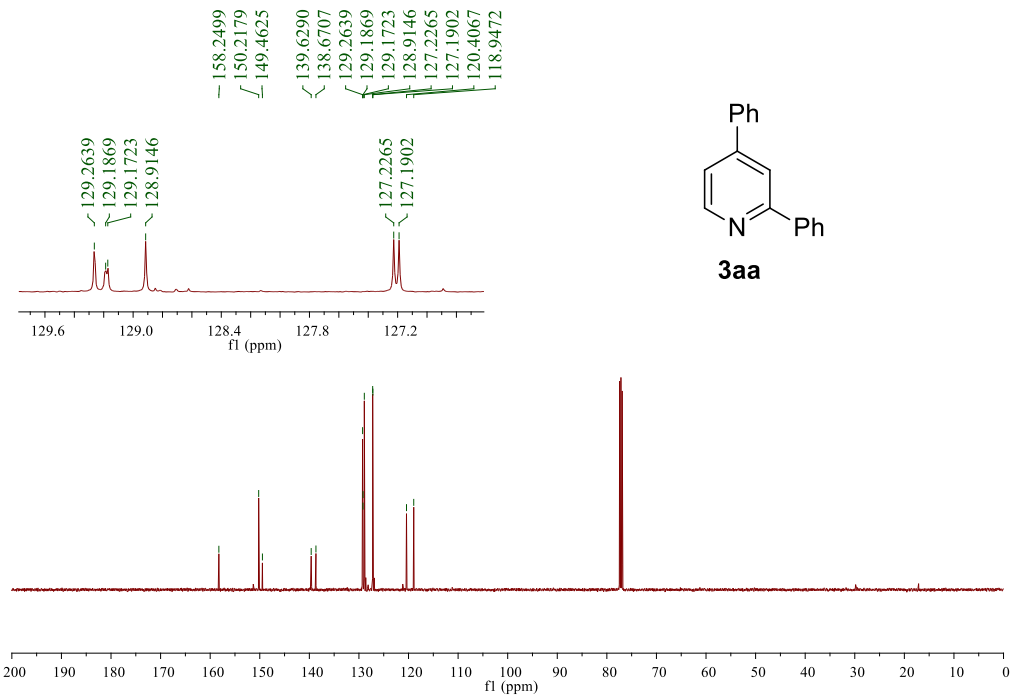


Figure 2.2. 125 MHz ^{13}C Spectrum of **3aa** in $CDCl_3$

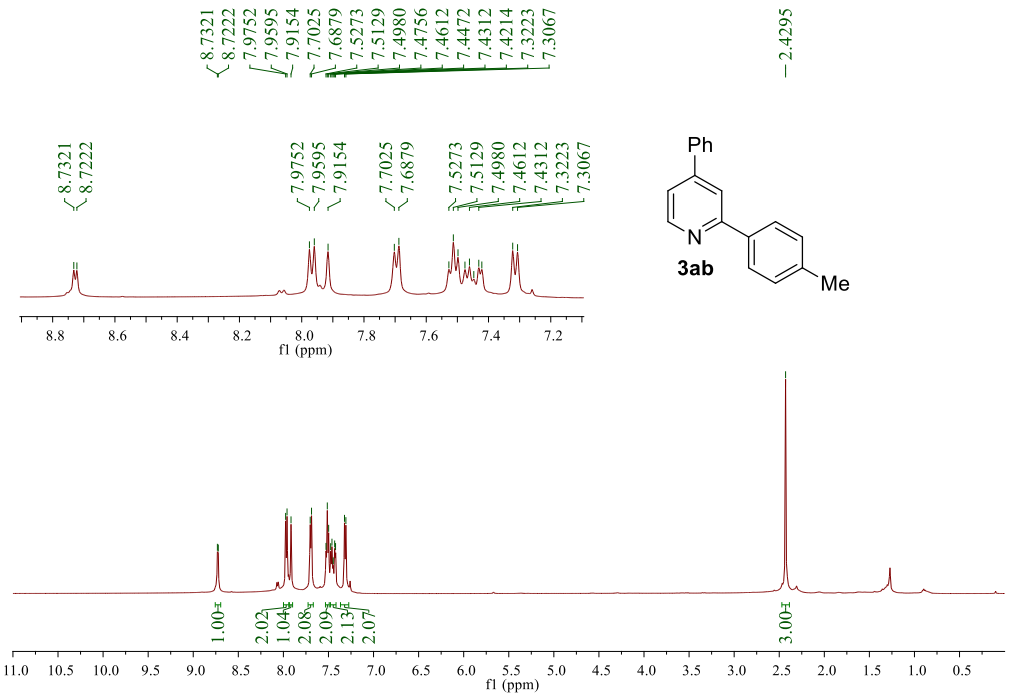


Figure 2.3. 500 MHz ^{1}H Spectrum of **3ab** in $CDCl_3$

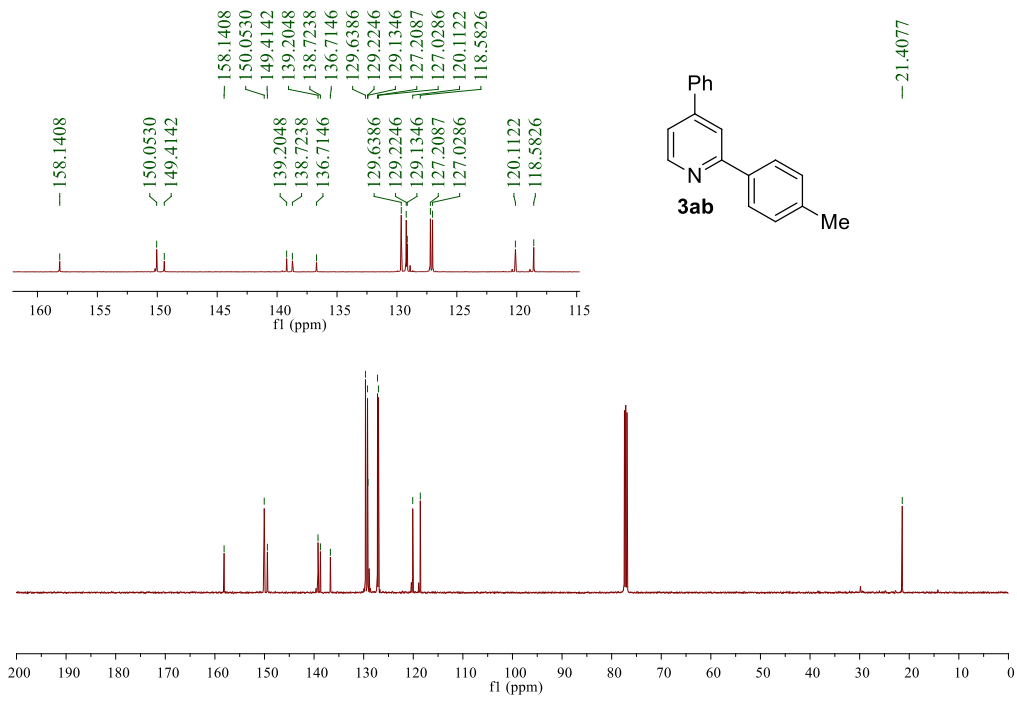


Figure 2.4. 125 MHz ^{13}C Spectrum of **3ab** in $CDCl_3$

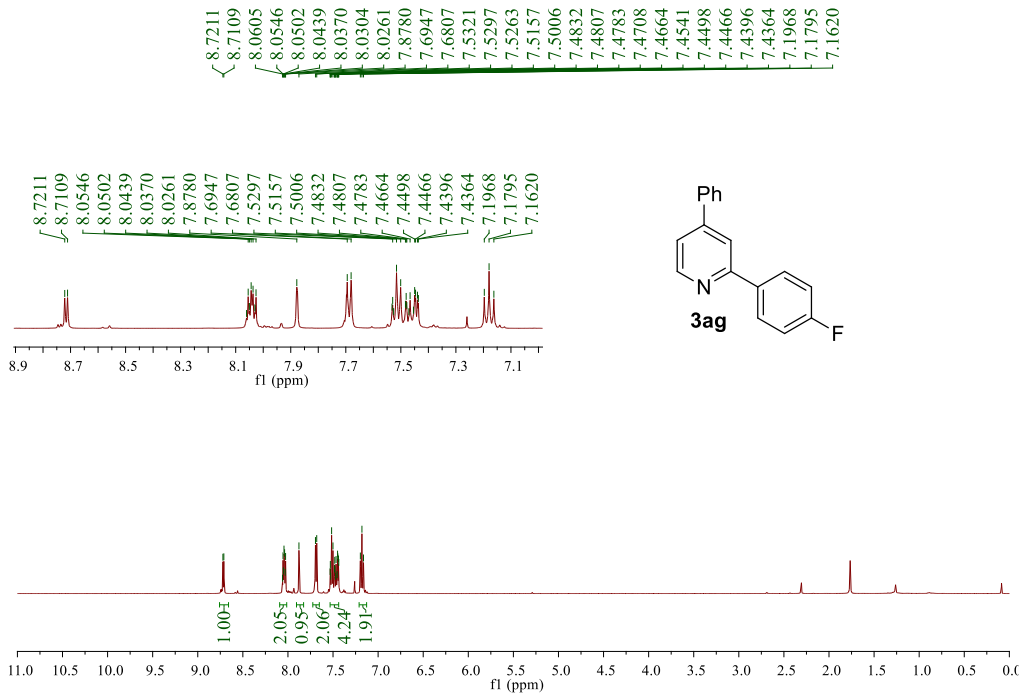


Figure 2.5. 500 MHz ^{1}H Spectrum of **3ag** in $CDCl_3$

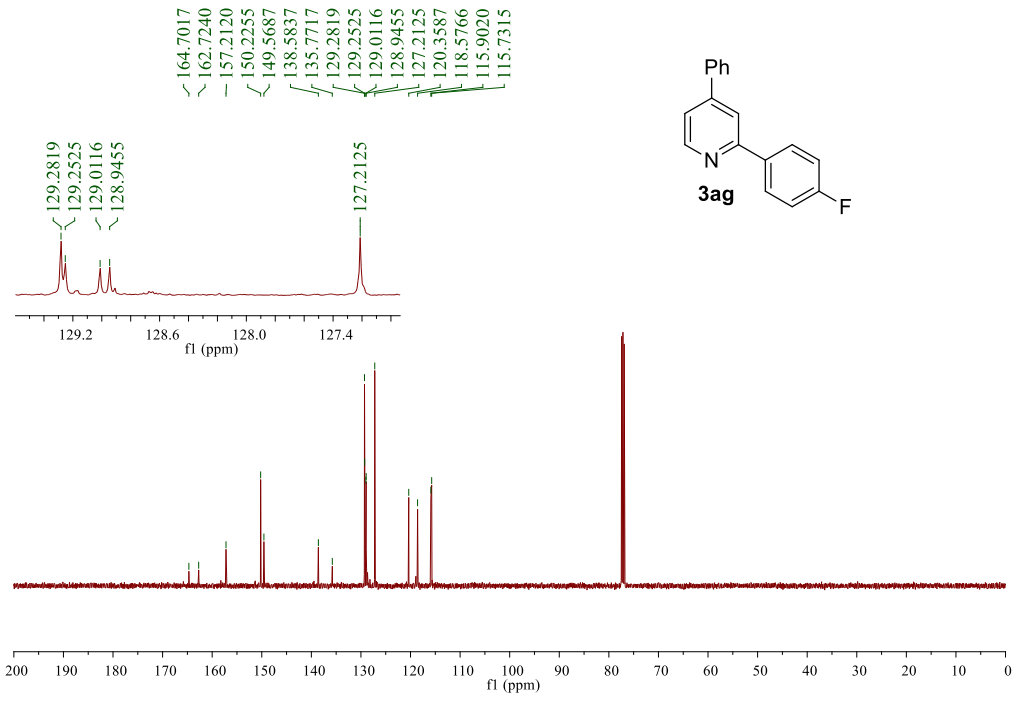


Figure 2.6. 125 MHz ^{13}C Spectrum of **3ag** in $CDCl_3$

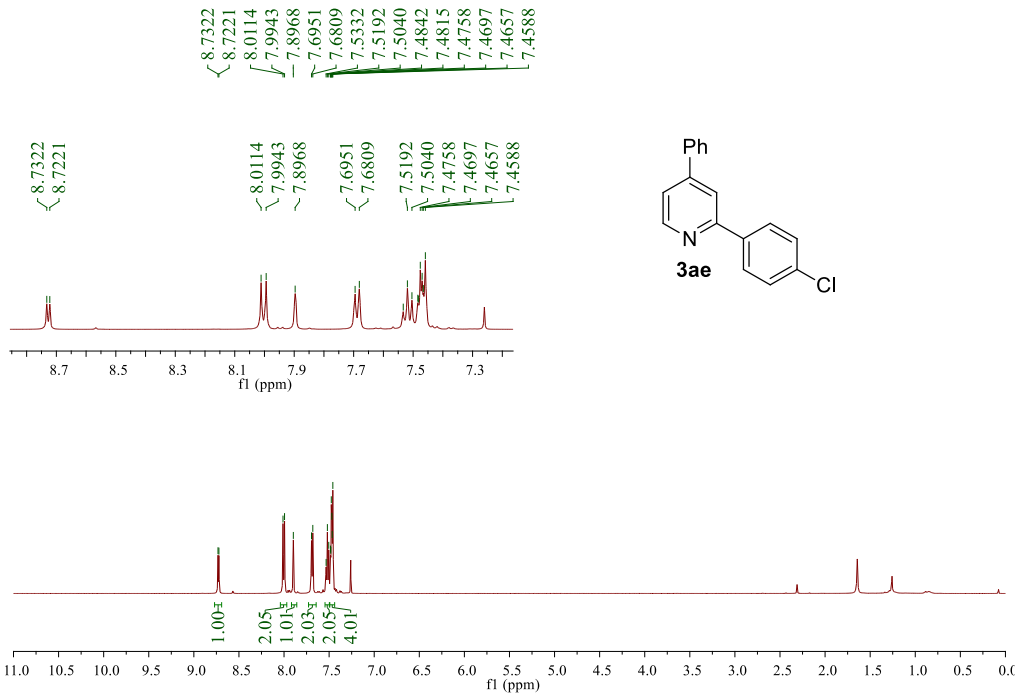


Figure 2.7. 500 MHz ^{1}H Spectrum of **3ae** in $CDCl_3$

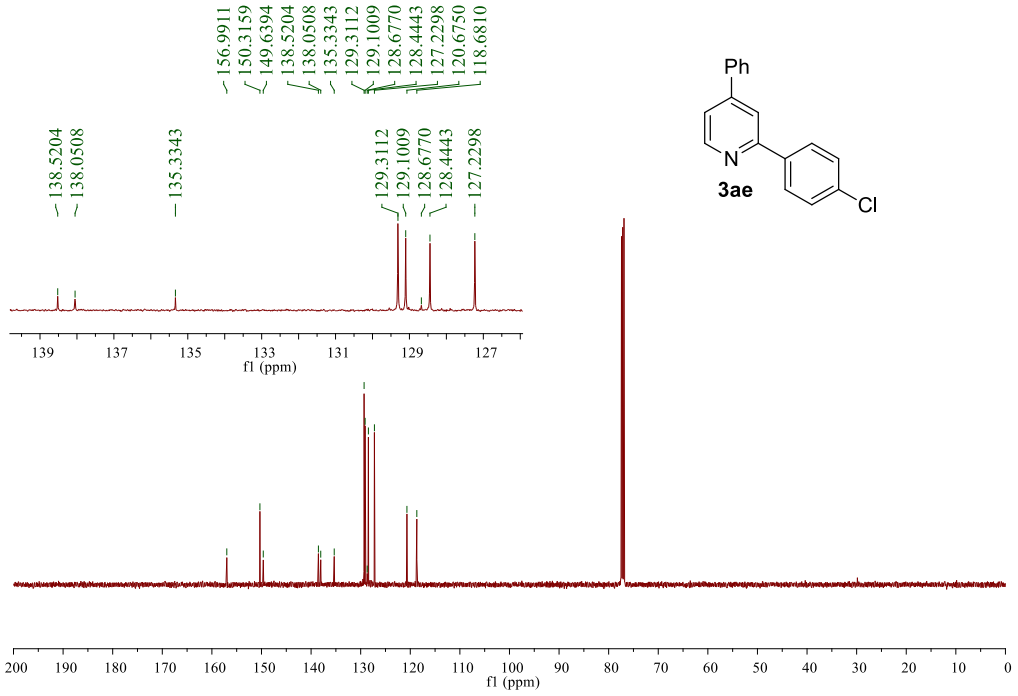


Figure 2.8. 125 MHz ^{13}C Spectrum of **3ae** in $CDCl_3$

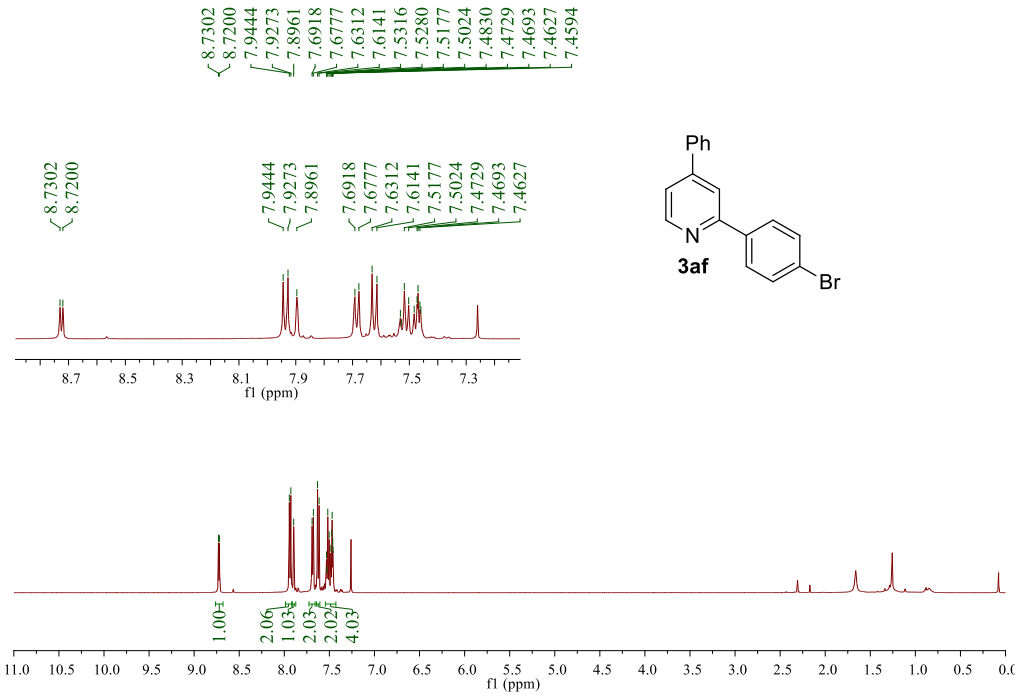


Figure 2.9. 500 MHz ^{1}H Spectrum of **3af** in $CDCl_3$

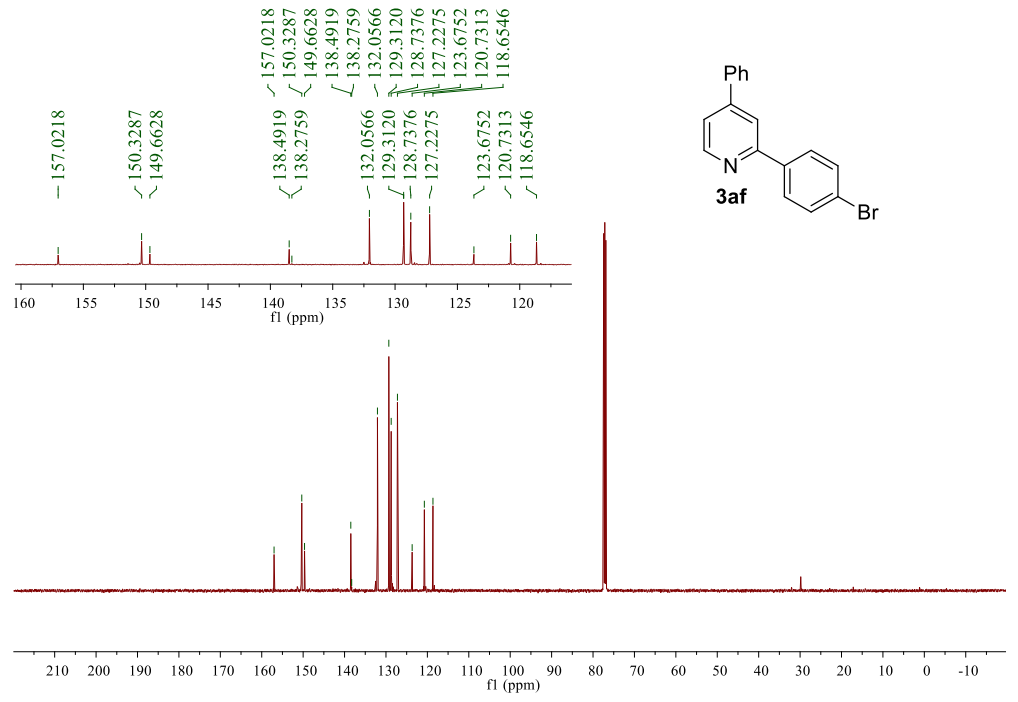


Figure 2.10. 125 MHz ^{13}C Spectrum of **3af** in $CDCl_3$

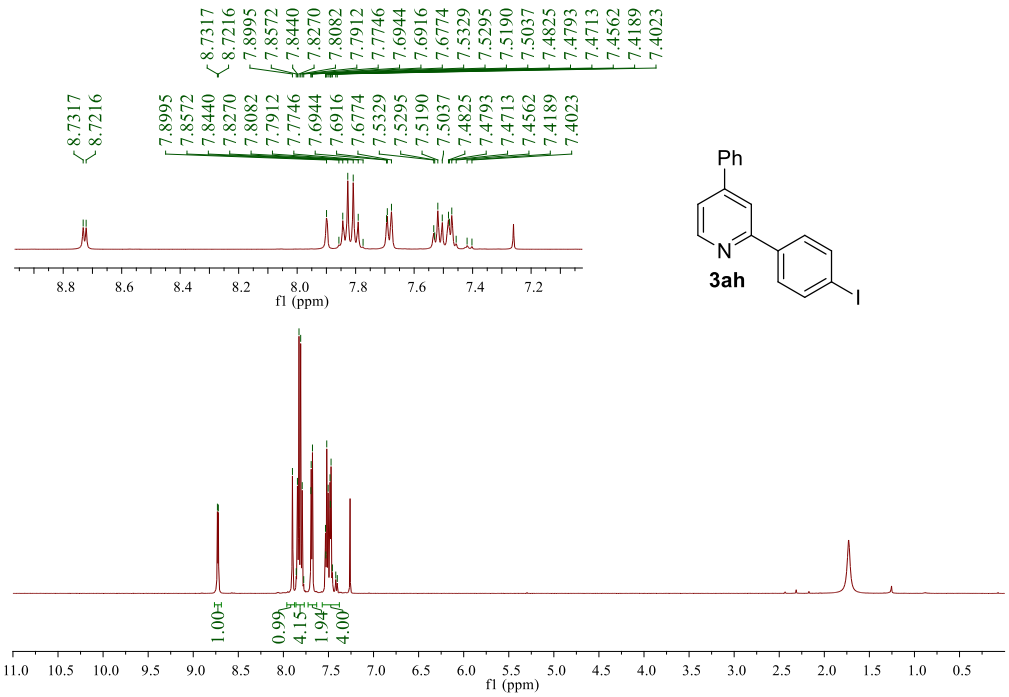


Figure 2.11. 500 MHz ^{1}H Spectrum of **3ah** in $CDCl_3$

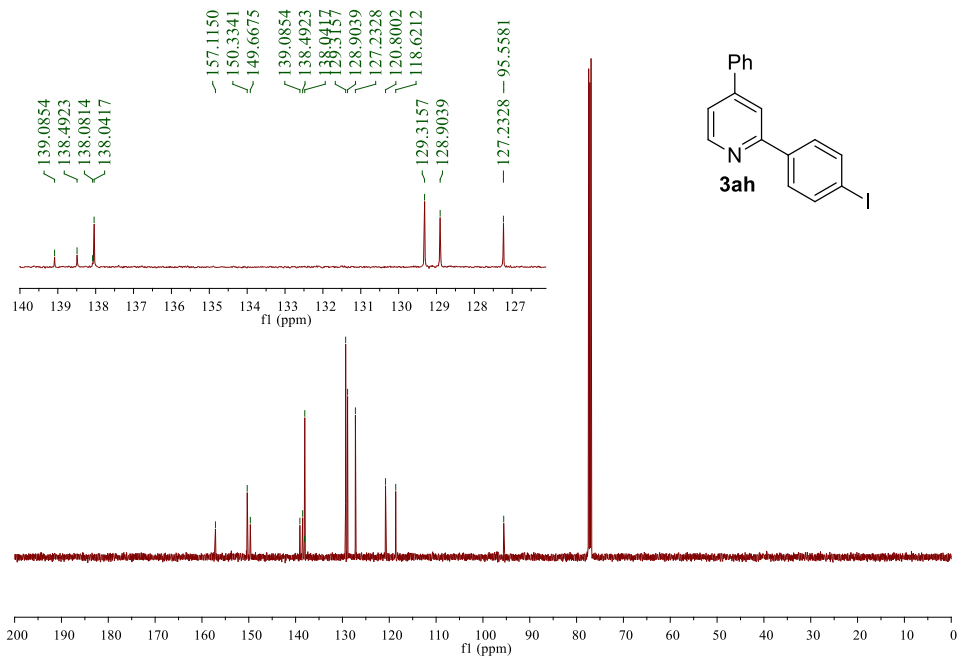


Figure 2.12. 125 MHz ^{13}C Spectrum of **3ah** in $CDCl_3$

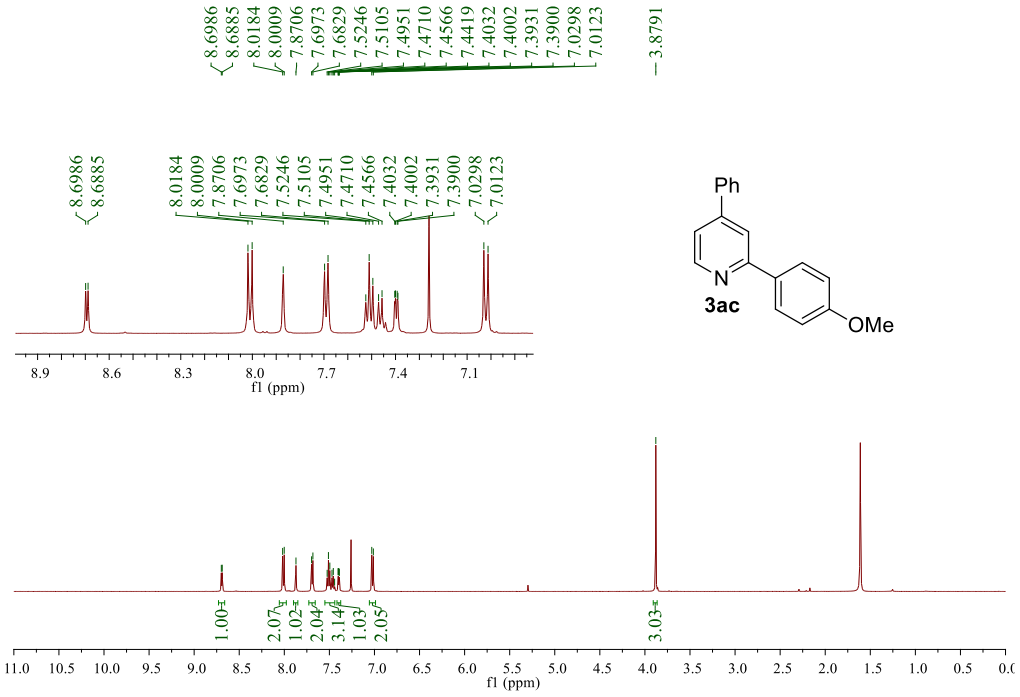


Figure 2.13. 500 MHz ^{1}H Spectrum of **3ac** in $CDCl_3$

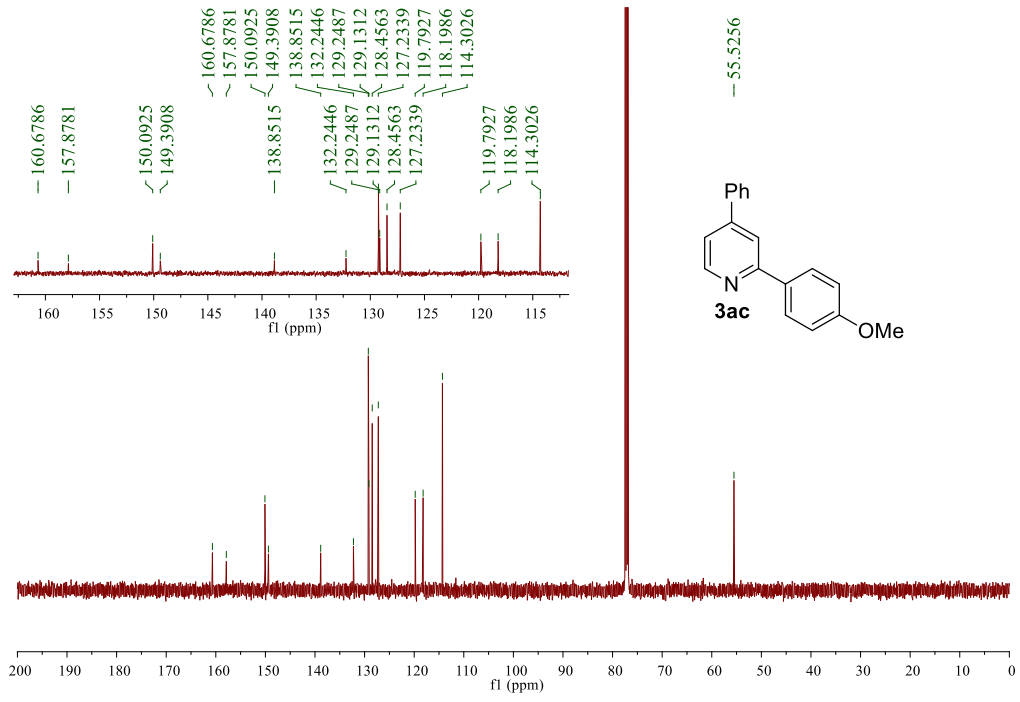


Figure 2.14. 125 MHz ^{13}C Spectrum of **3ac** in $CDCl_3$

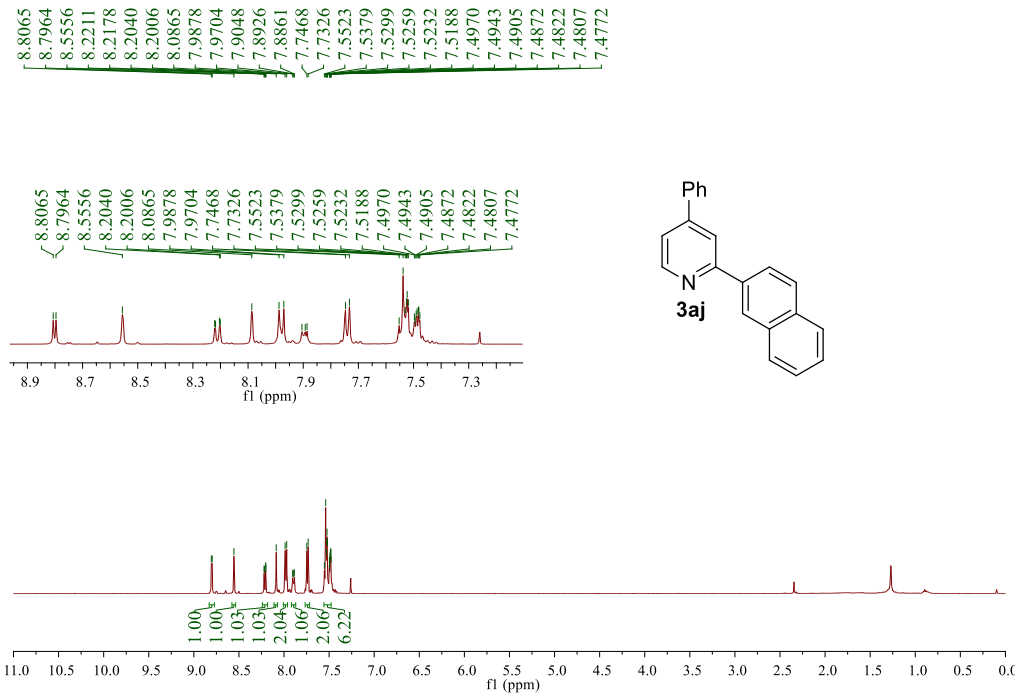


Figure 2.15. 500 MHz ^{1}H Spectrum of **3aj** in $CDCl_3$

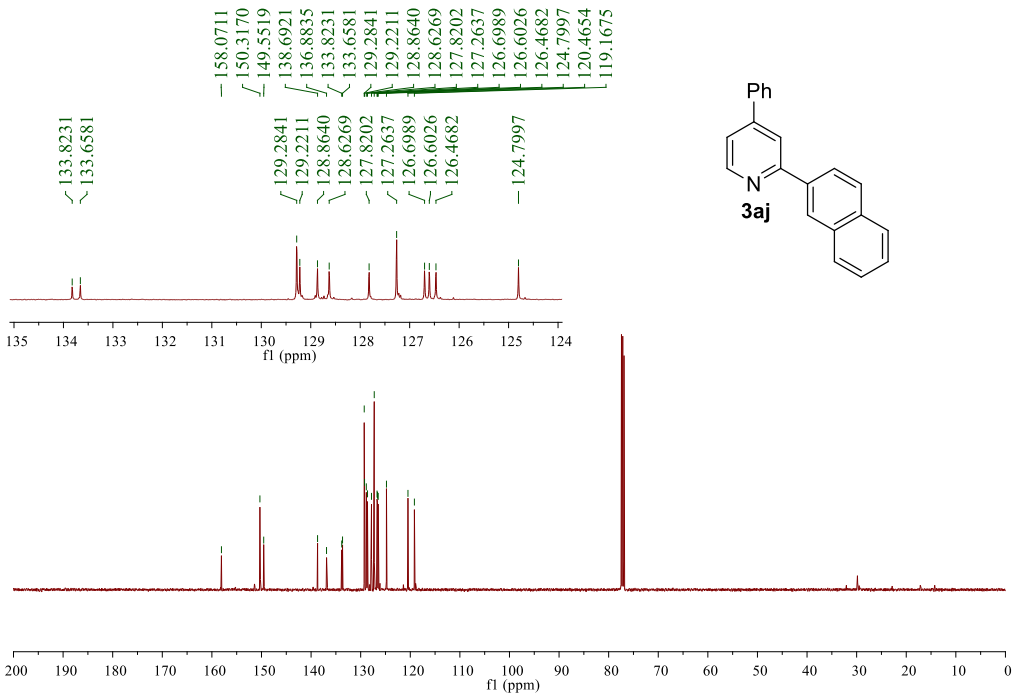


Figure 2.16. 125 MHz ^{13}C Spectrum of **3aj** in $CDCl_3$

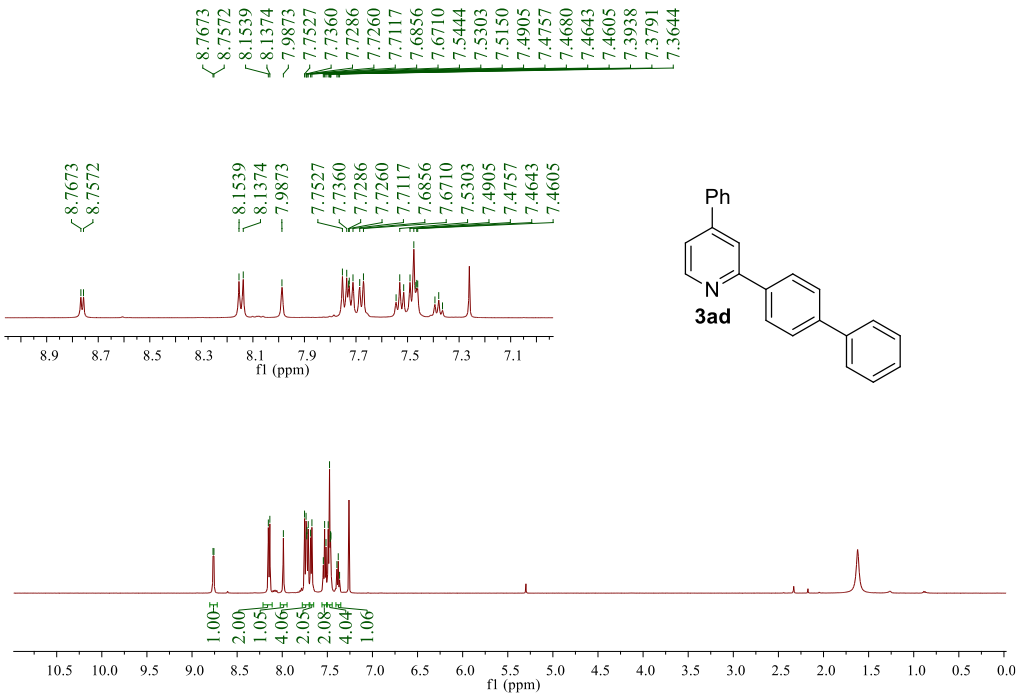


Figure 2.17. 500 MHz ^{1}H Spectrum of **3ad** in $CDCl_3$

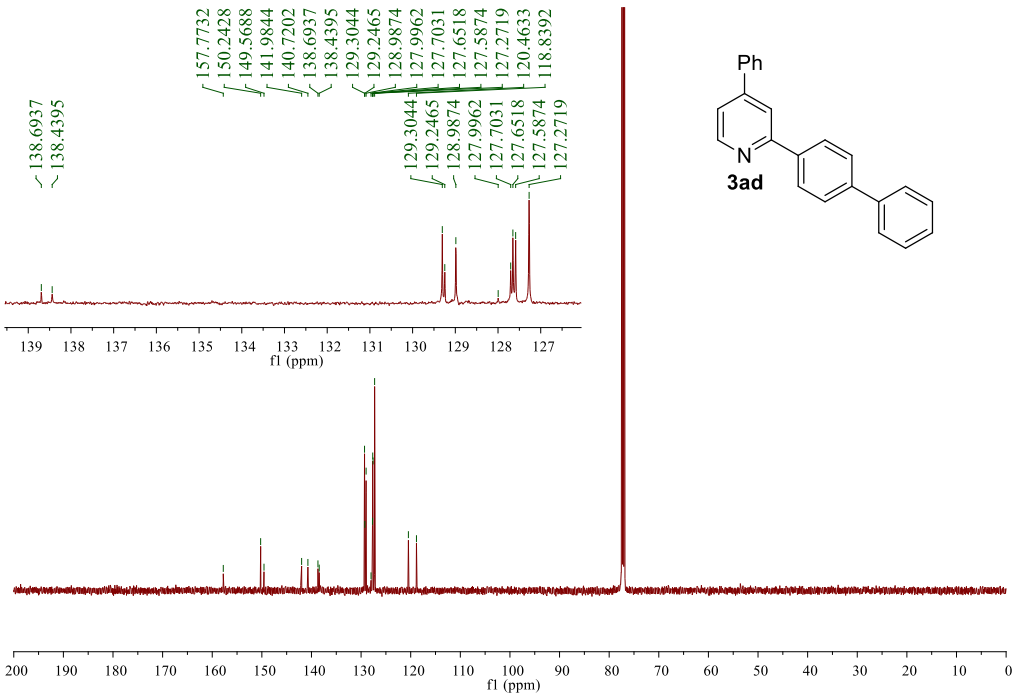


Figure 2.18. 125 MHz ^{13}C Spectrum of **3ad** in $CDCl_3$

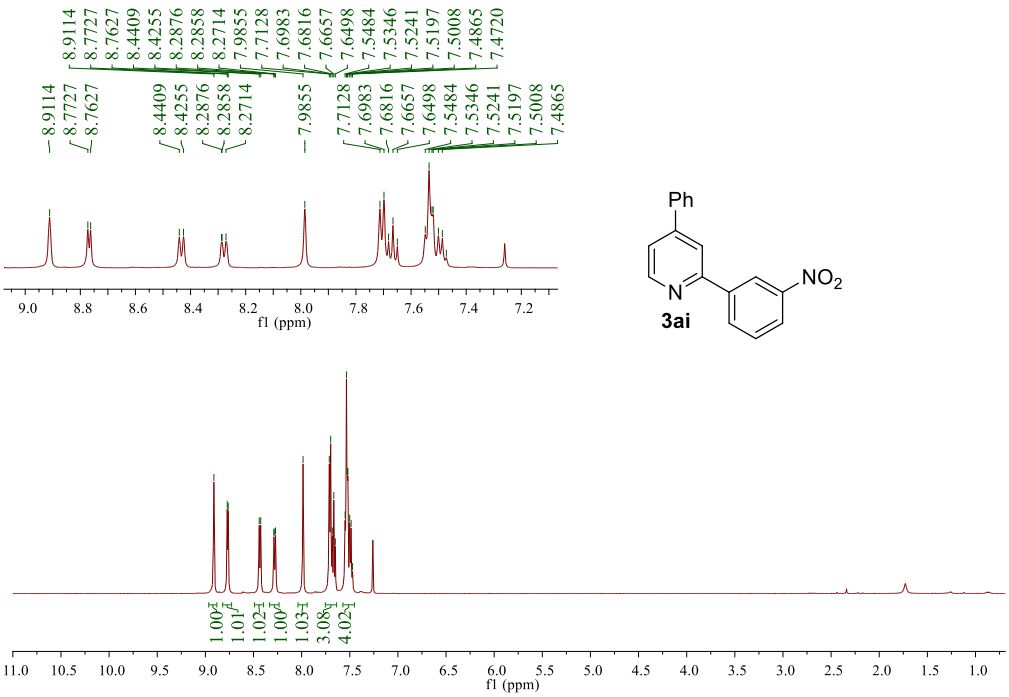


Figure 2.19. 500 MHz ^{1}H Spectrum of **3ai** in $CDCl_3$

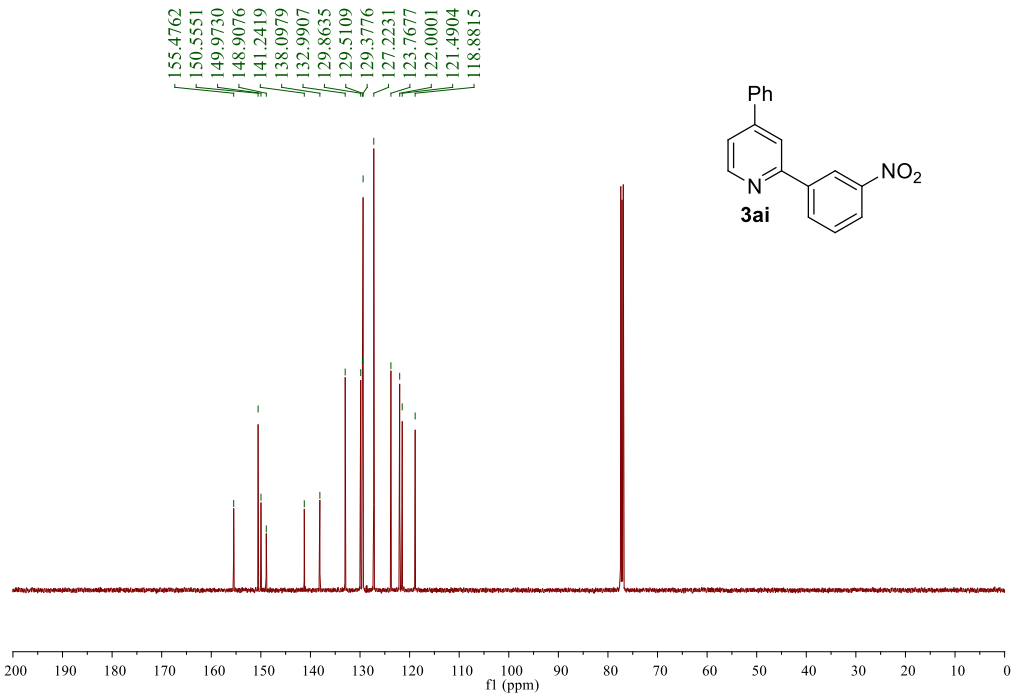


Figure 2.20. 125 MHz ^{13}C Spectrum of **3ai** in $CDCl_3$

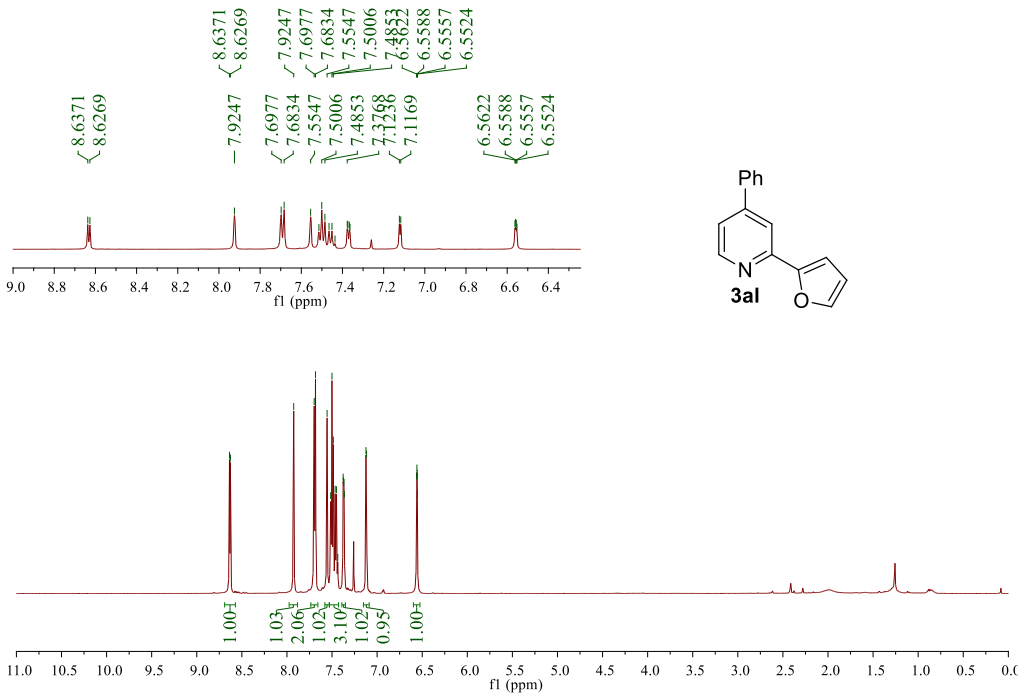


Figure 2.21. 500 MHz ^{1}H Spectrum of **3al** in $CDCl_3$

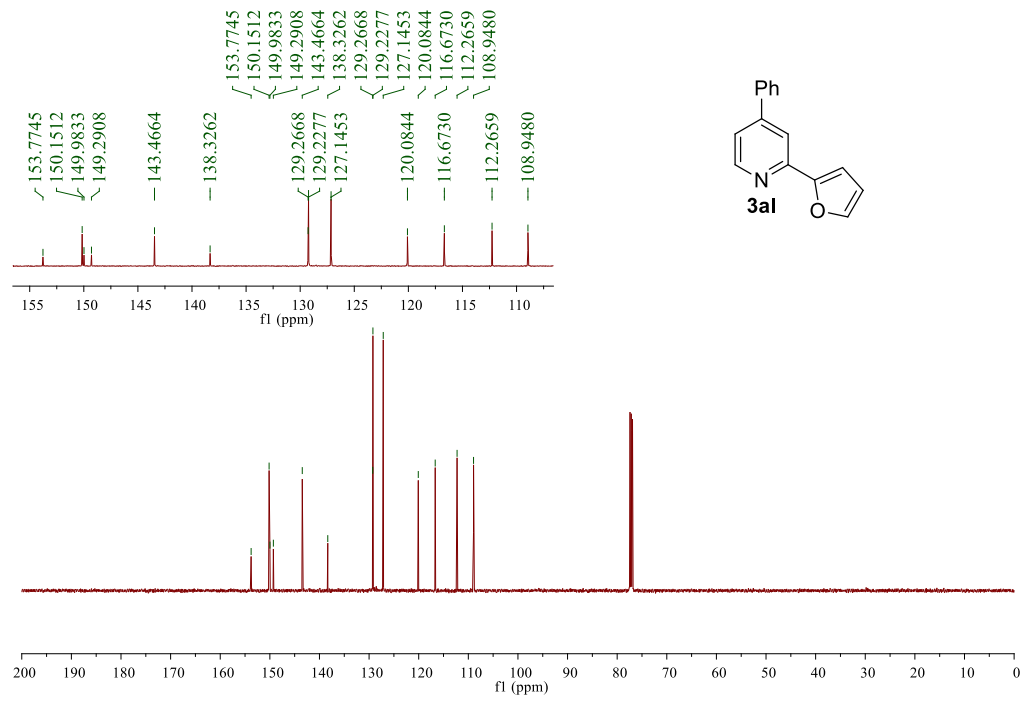


Figure 2.22. 125 MHz ^{13}C Spectrum of **3al** in $CDCl_3$

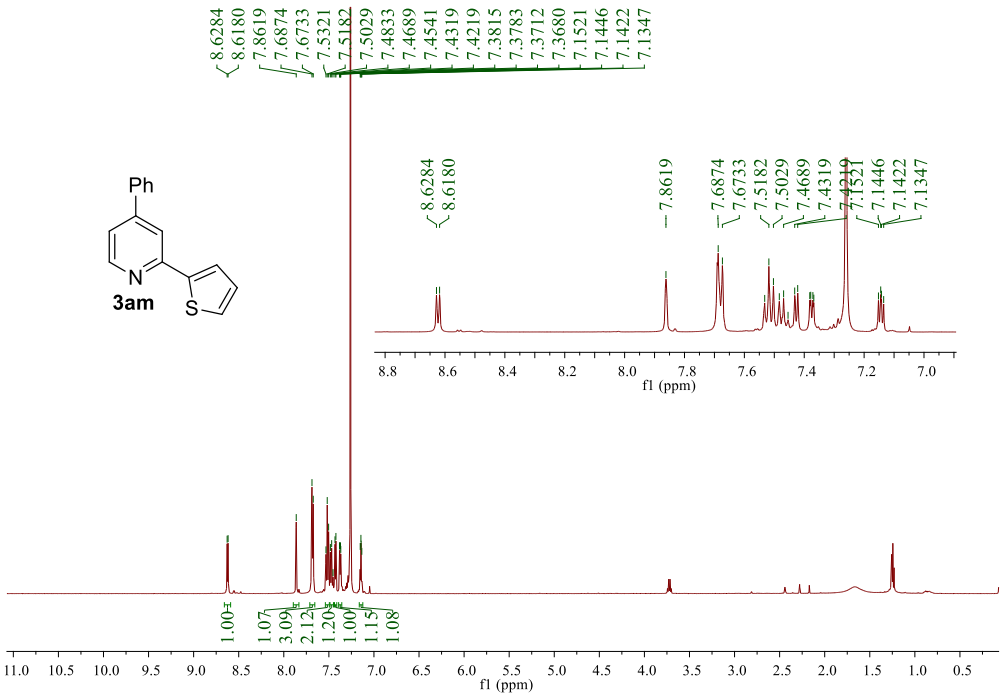


Figure 2.23. 500 MHz ^{1}H Spectrum of **3am** in $CDCl_3$

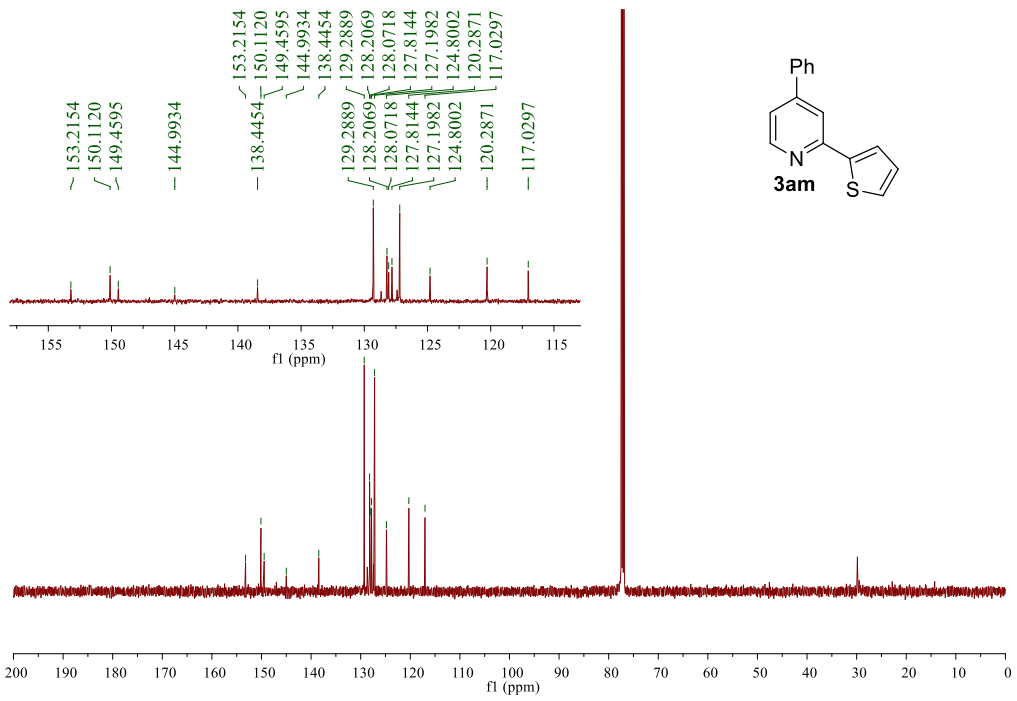


Figure 2.24. 125 MHz ^{13}C Spectrum of **3am** in $CDCl_3$

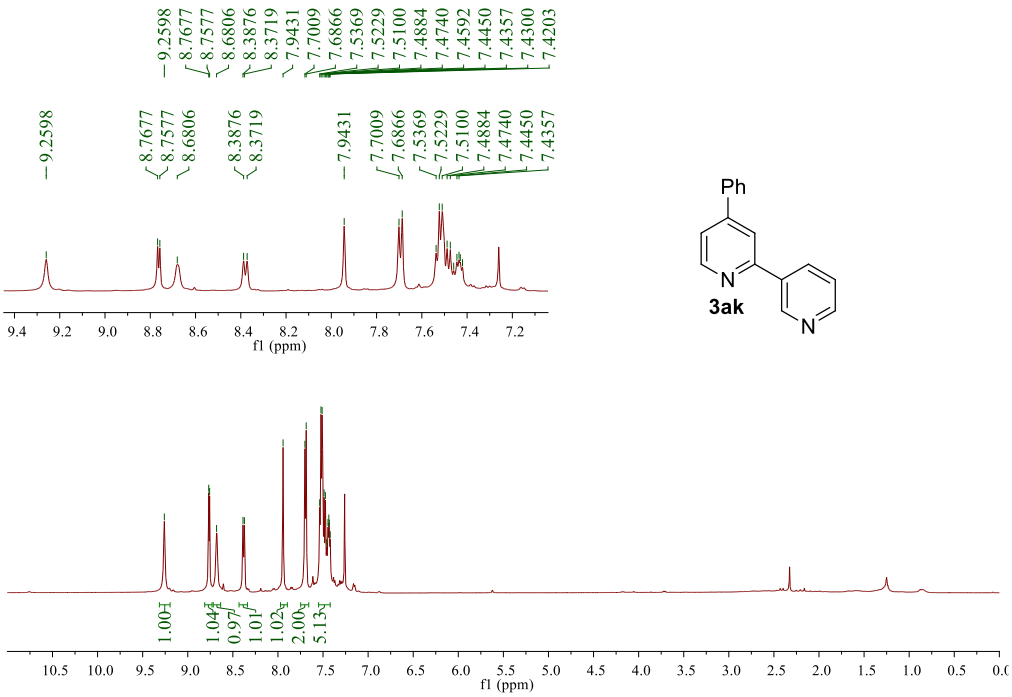


Figure 2.25. 500 MHz ^{1}H Spectrum of **3ak** in $CDCl_3$

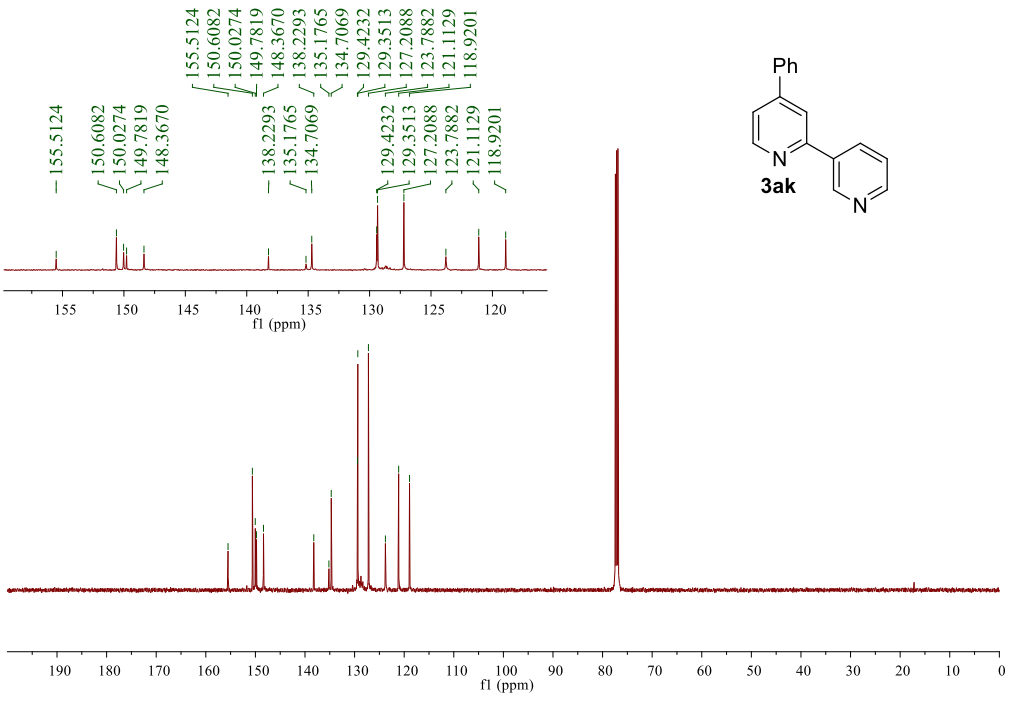


Figure 2.26. 125 MHz ^{13}C Spectrum of **3ak** in $CDCl_3$

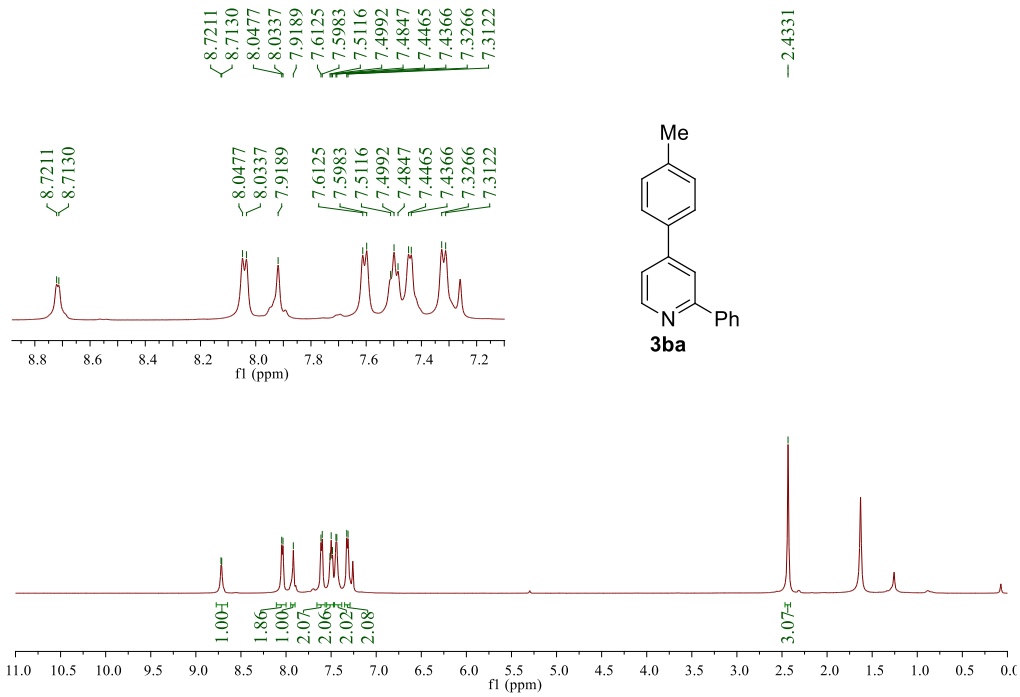


Figure 2.27. 500 MHz ^{1}H Spectrum of **3ba** in $CDCl_3$

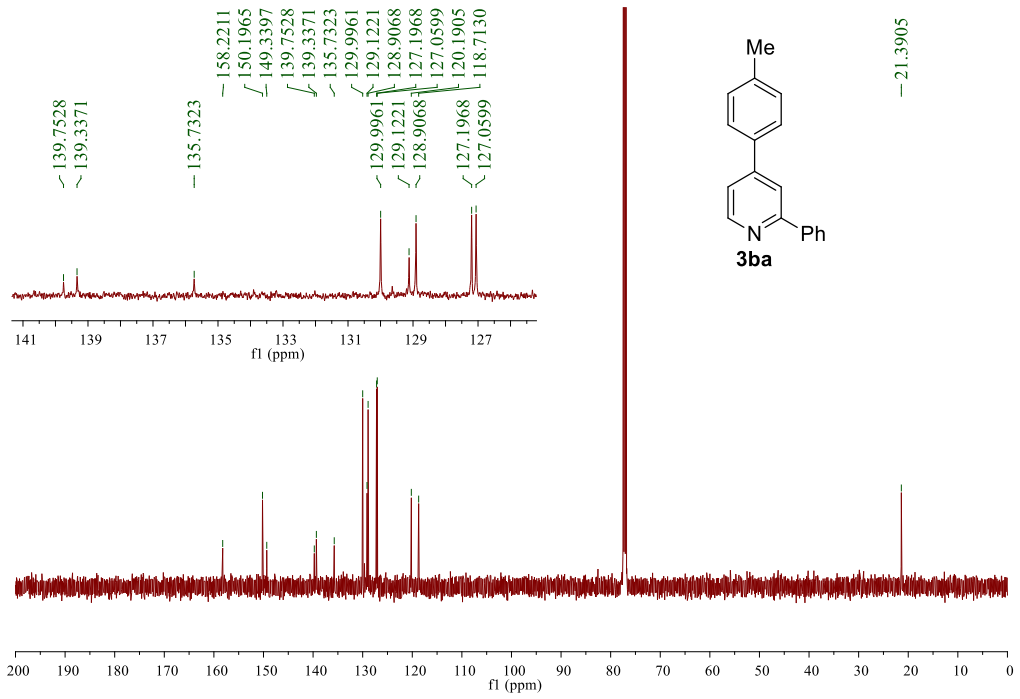


Figure 2.28. 125 MHz ^{13}C Spectrum of **3ba** in $CDCl_3$

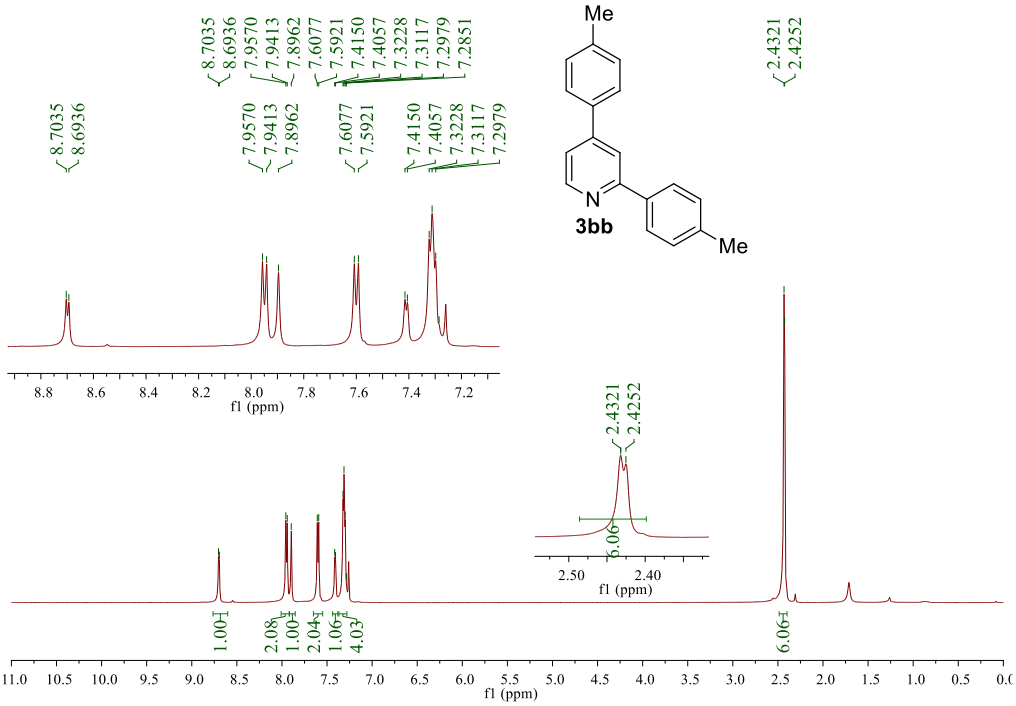


Figure 2.29. 500 MHz ^{1}H Spectrum of **3bb** in $CDCl_3$

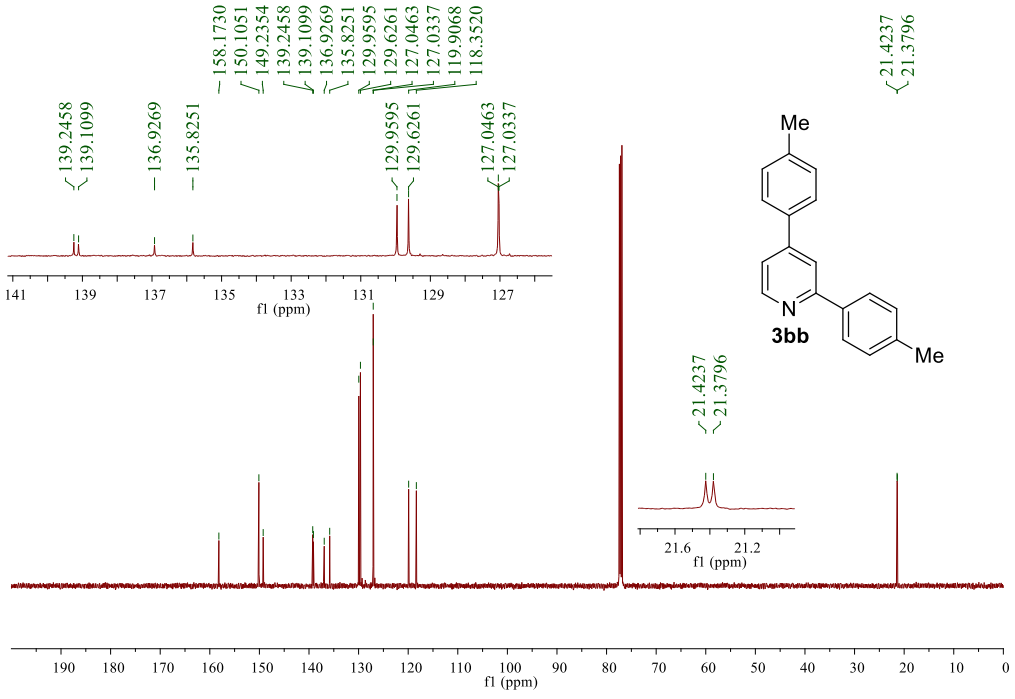


Figure 2.30. 125 MHz ^{13}C Spectrum of **3bb** in $CDCl_3$

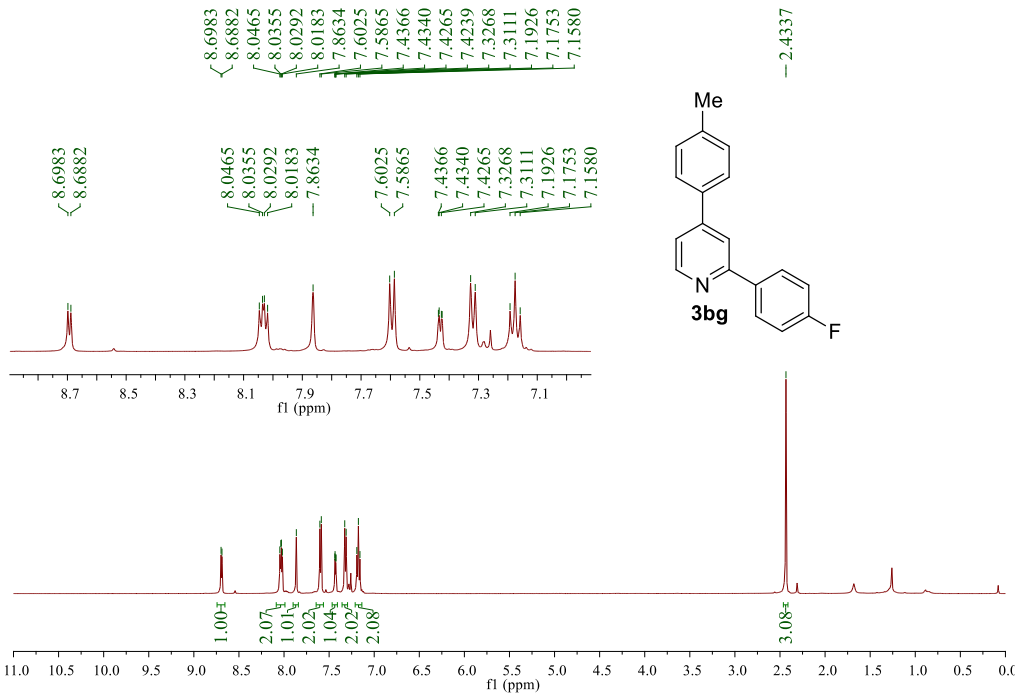


Figure 2.31. 500 MHz ^{1}H Spectrum of **3bg** in $CDCl_3$

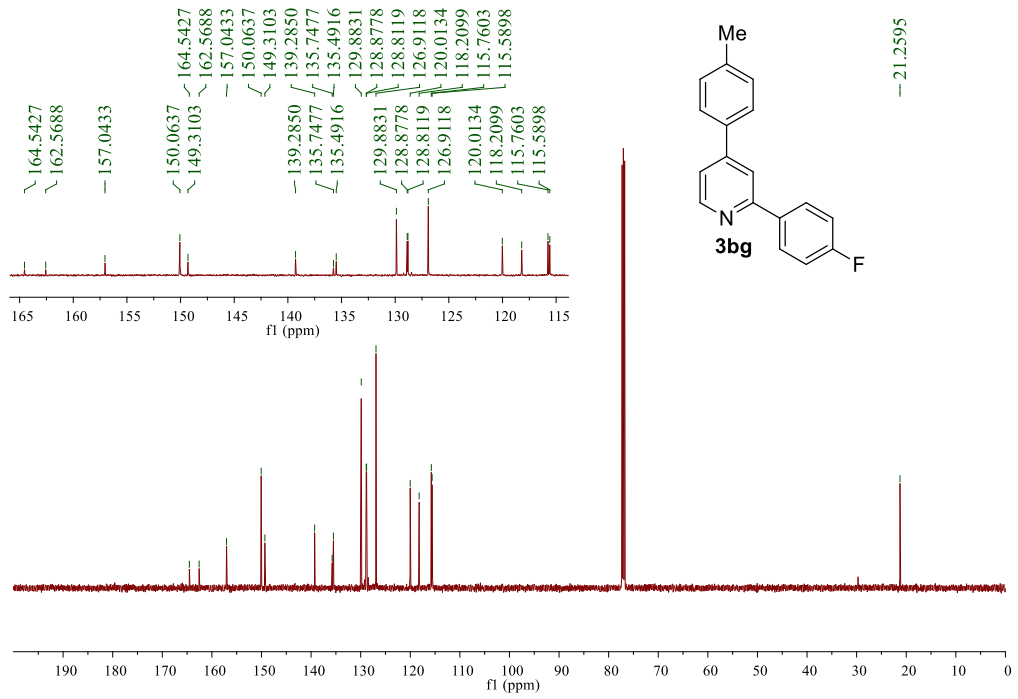


Figure 2.32. 125 MHz ^{13}C Spectrum of **3bg** in $CDCl_3$

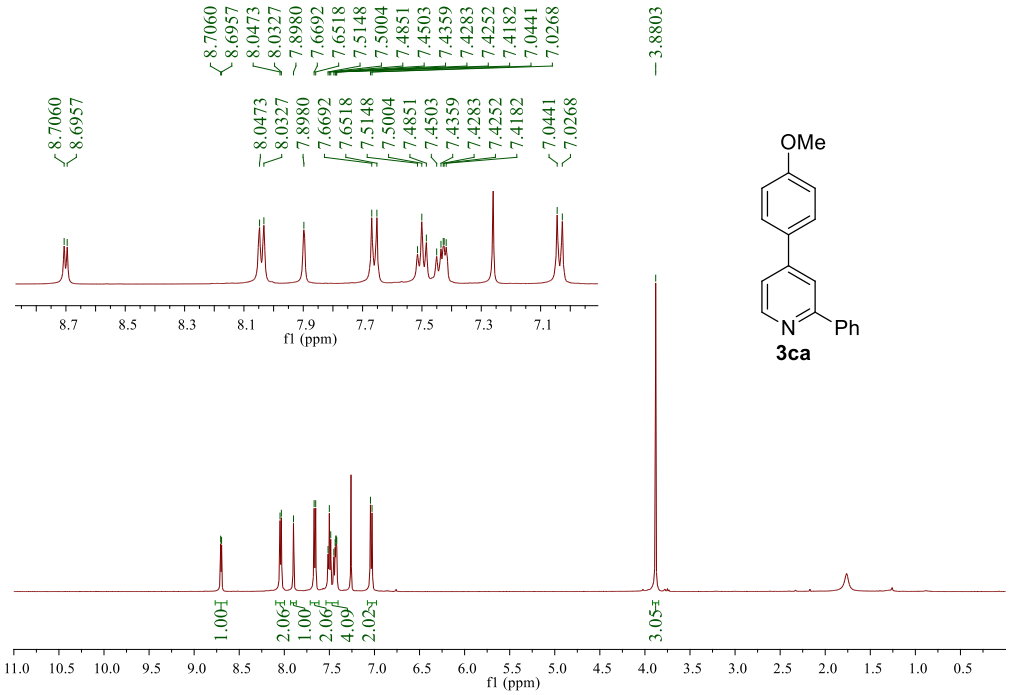


Figure 2.33. 500 MHz ^{1}H Spectrum of **3ca** in $CDCl_3$

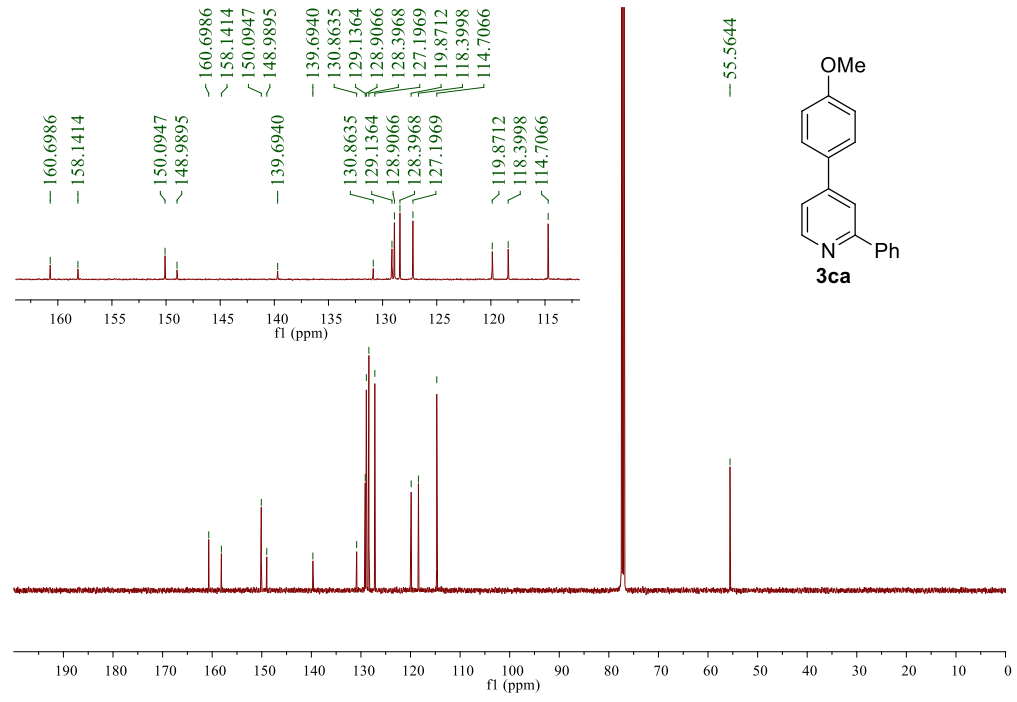


Figure 2.34. 125 MHz ^{13}C Spectrum of **3ca** in $CDCl_3$

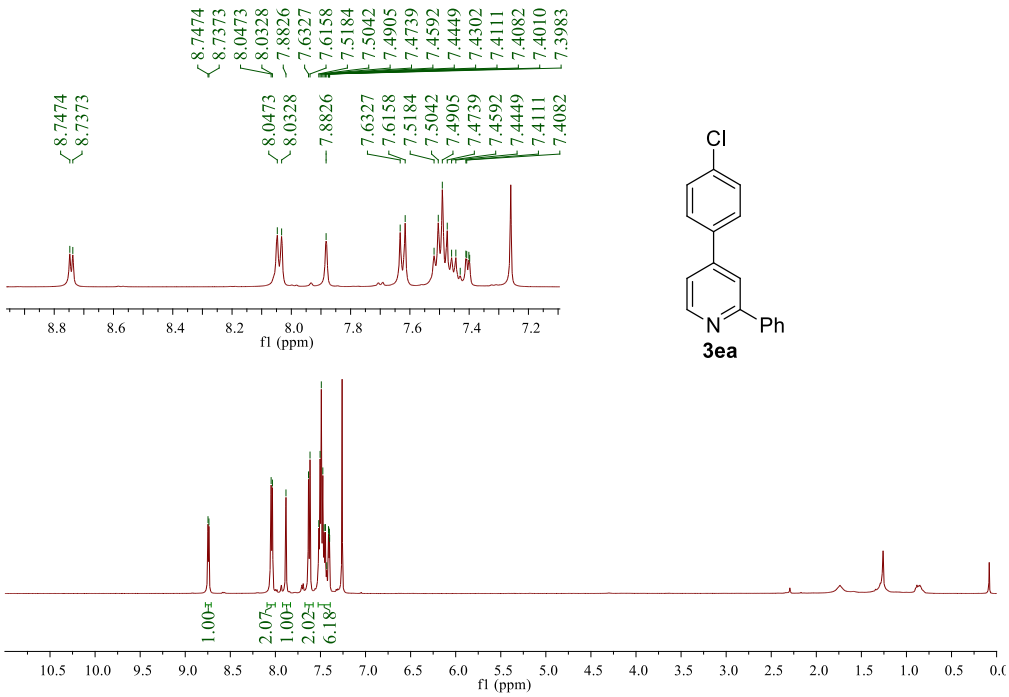


Figure 2.35. 500 MHz ^{1}H Spectrum of **3ea** in $CDCl_3$

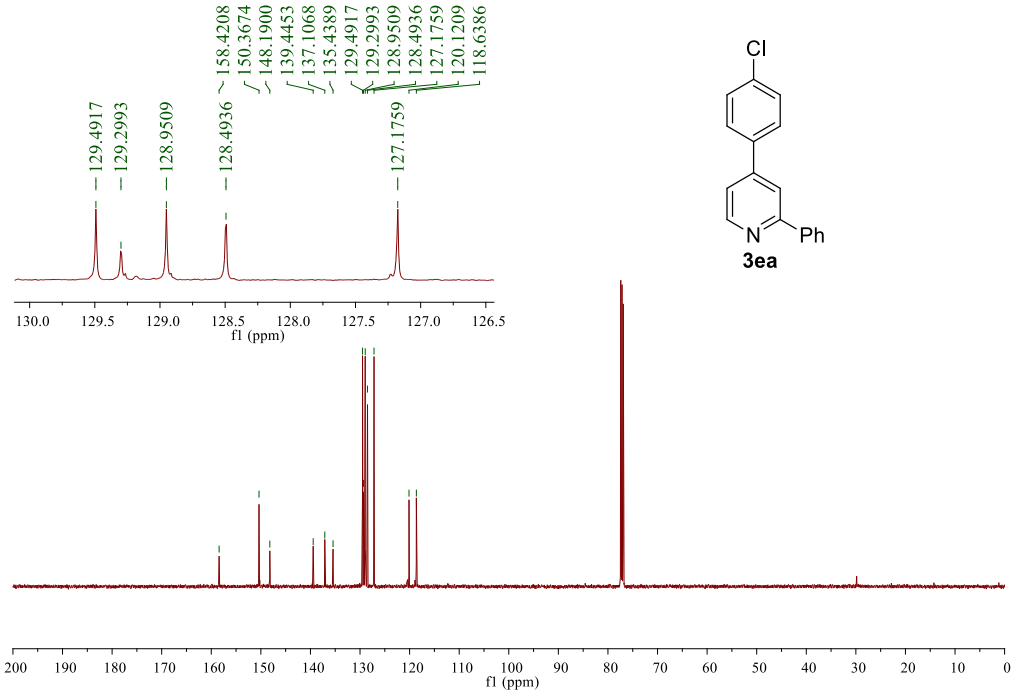


Figure 2.36. 125 MHz ^{13}C Spectrum of **3ea** in $CDCl_3$

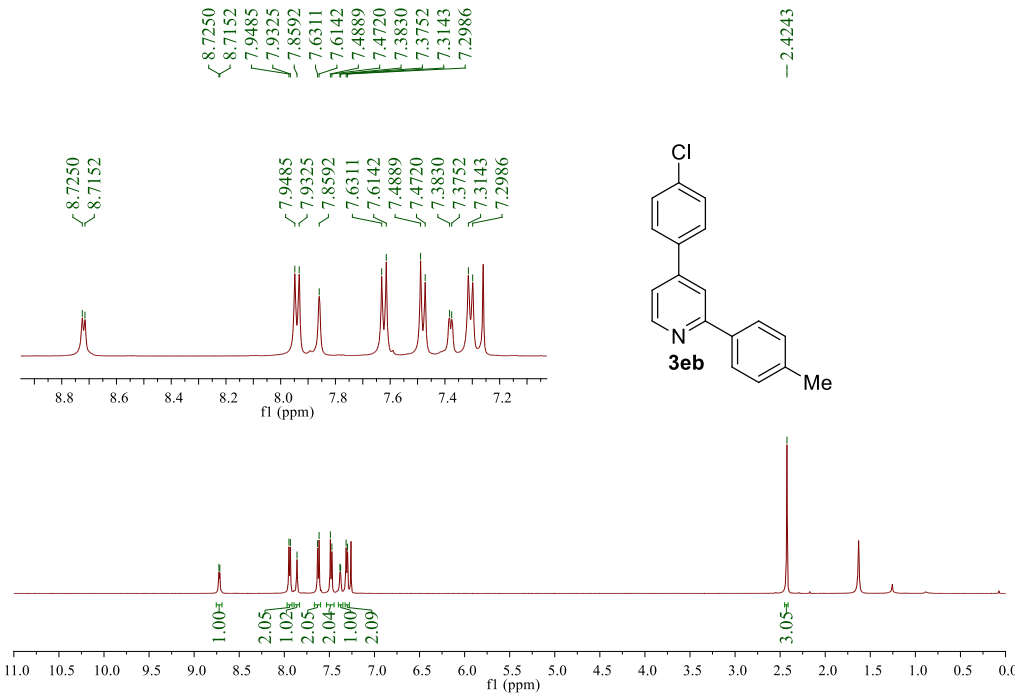


Figure 2.37. 500 MHz ^{1}H Spectrum of **3eb** in $CDCl_3$

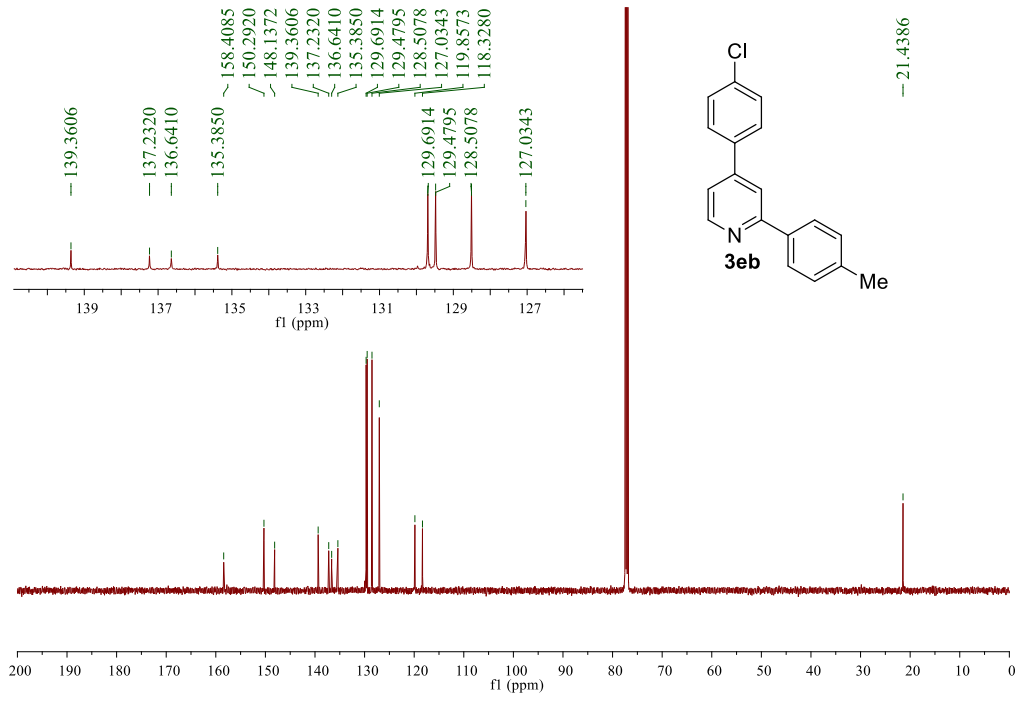


Figure 2.38. 125 MHz ^{13}C Spectrum of **3eb** in $CDCl_3$

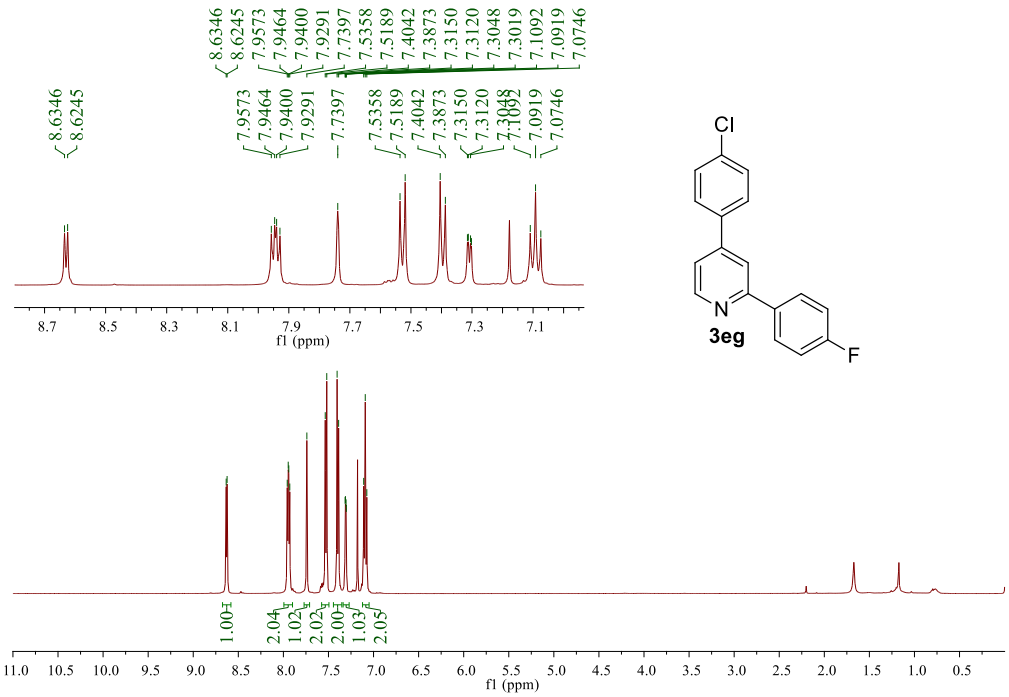


Figure 2.39. 500 MHz ^{1}H Spectrum of **3eg** in $CDCl_3$

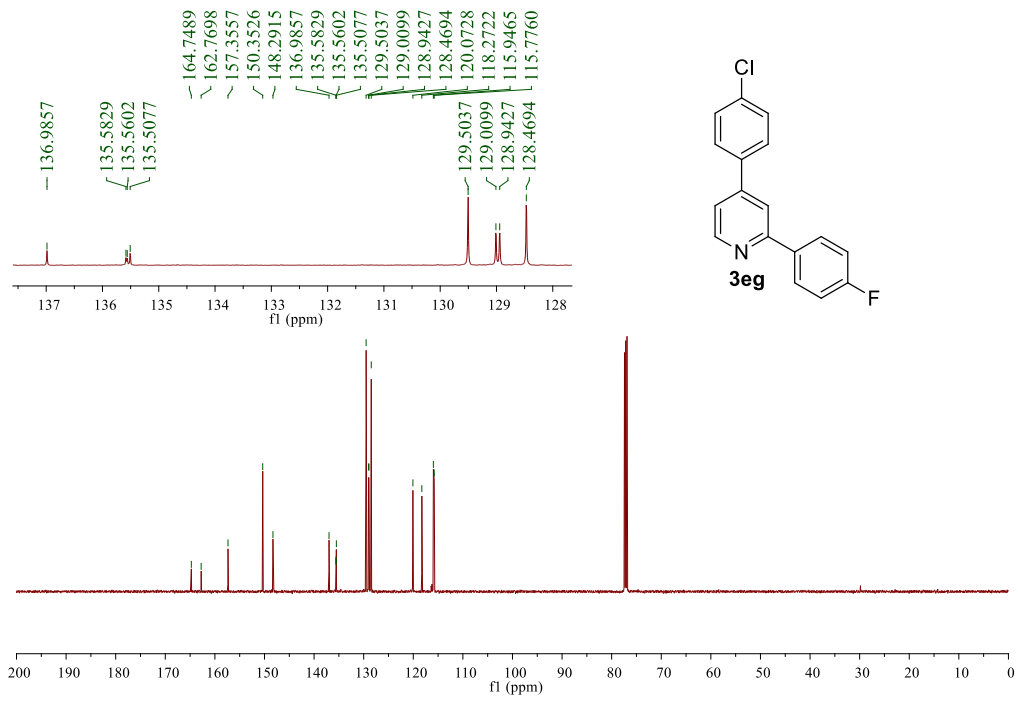


Figure 2.40. 125 MHz ^{13}C Spectrum of **3eg** in $CDCl_3$

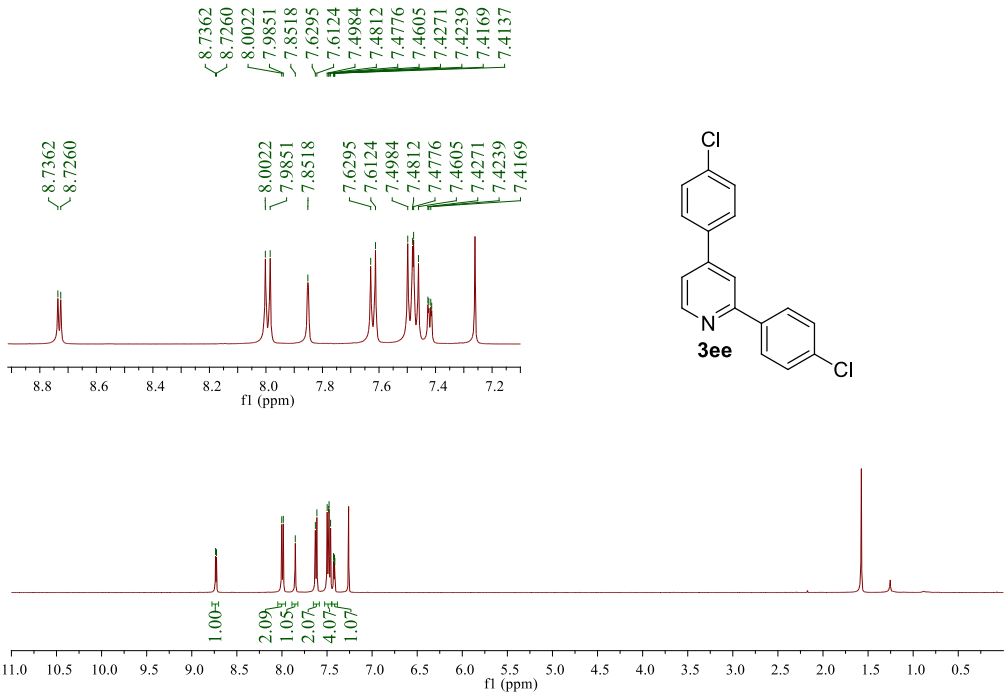


Figure 2.41. 500 MHz ^{1}H Spectrum of **3ee** in $CDCl_3$

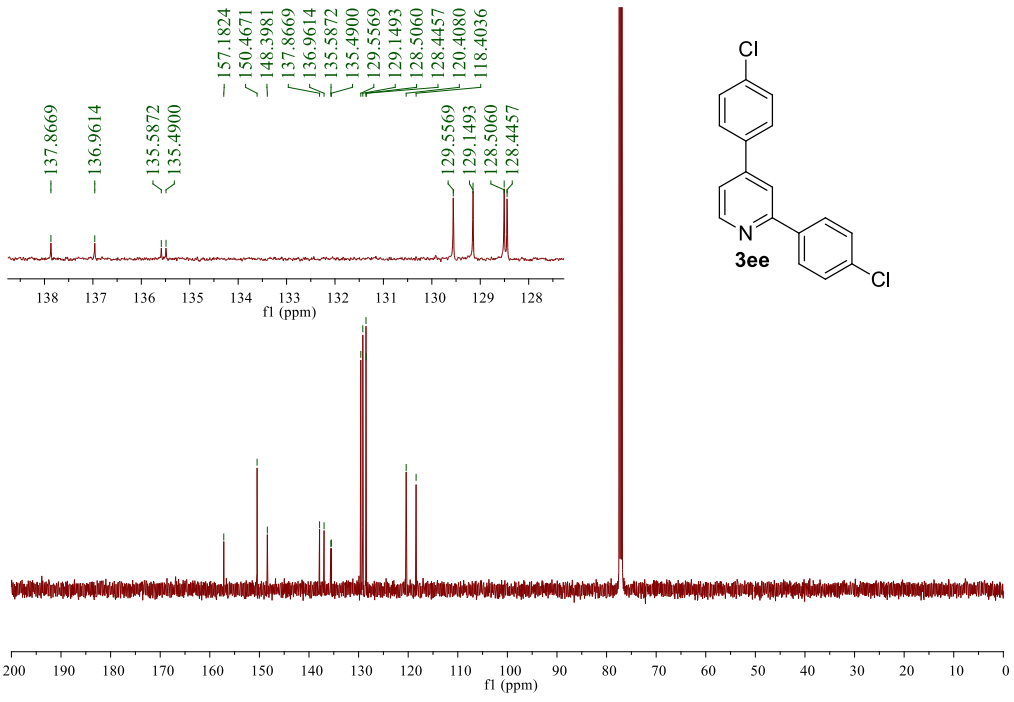


Figure 2.42. 125 MHz ^{13}C Spectrum of **3ee** in $CDCl_3$

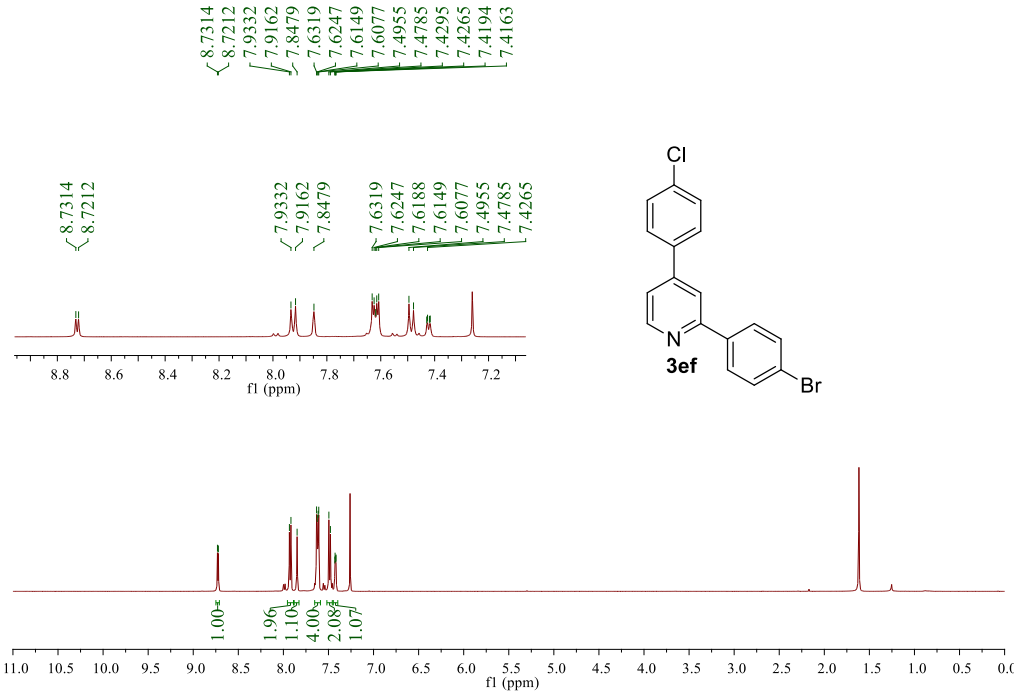


Figure 2.43. 500 MHz ^{1}H Spectrum of **3ef** in $CDCl_3$

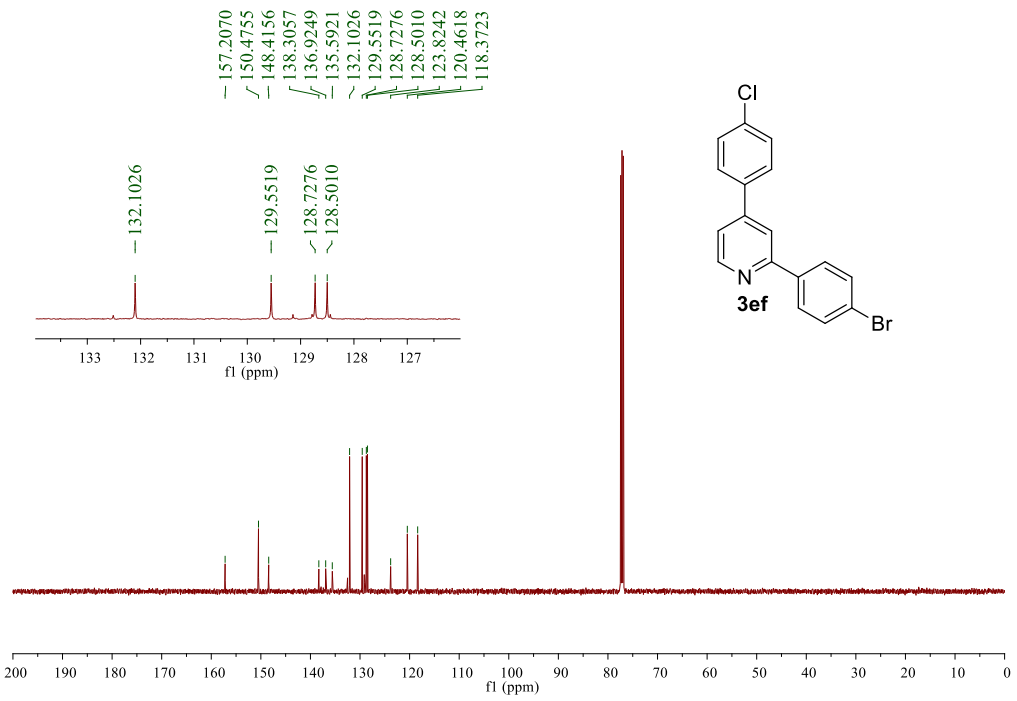


Figure 2.44. 125 MHz ^{13}C Spectrum of **3ef** in $CDCl_3$

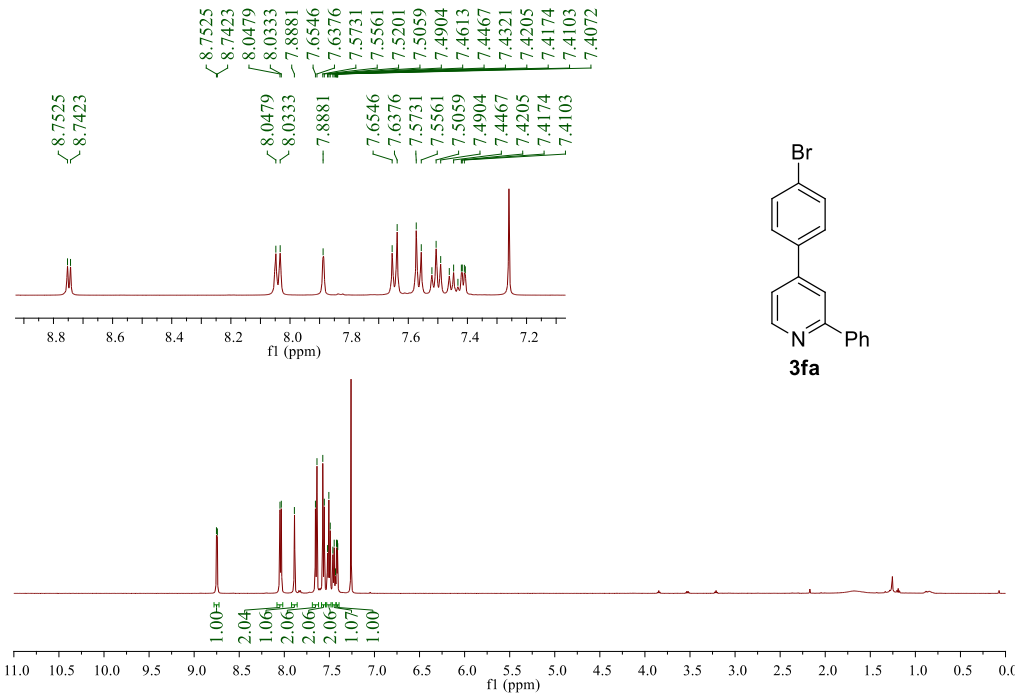


Figure 2.45. 500 MHz ^{1}H Spectrum of **3fa** in $CDCl_3$

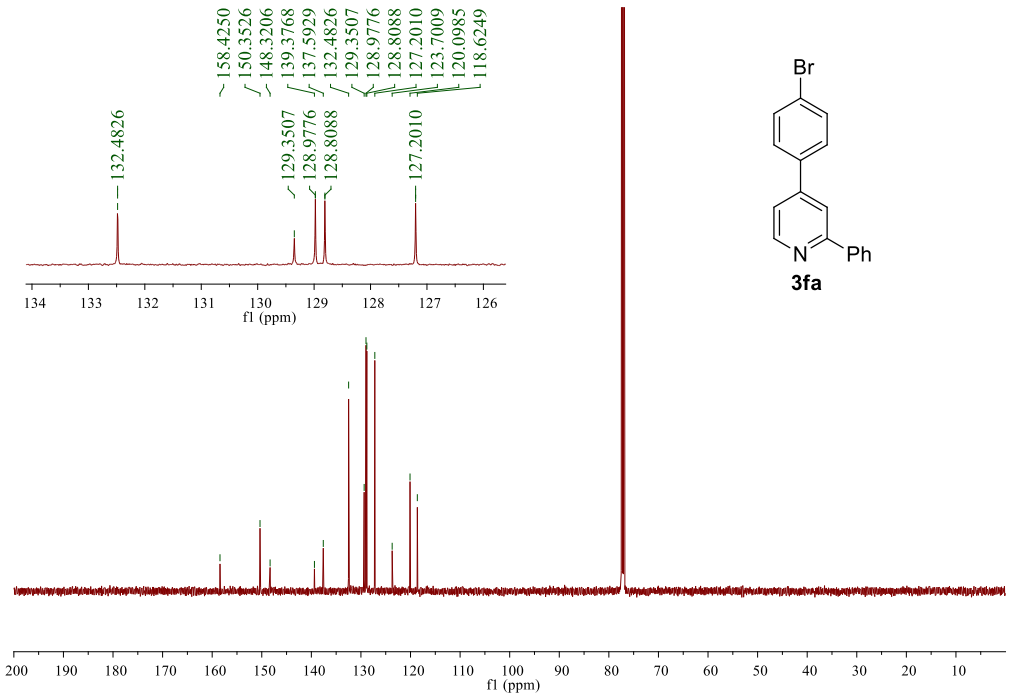


Figure 2.46. 125 MHz ^{13}C Spectrum of **3fa** in $CDCl_3$

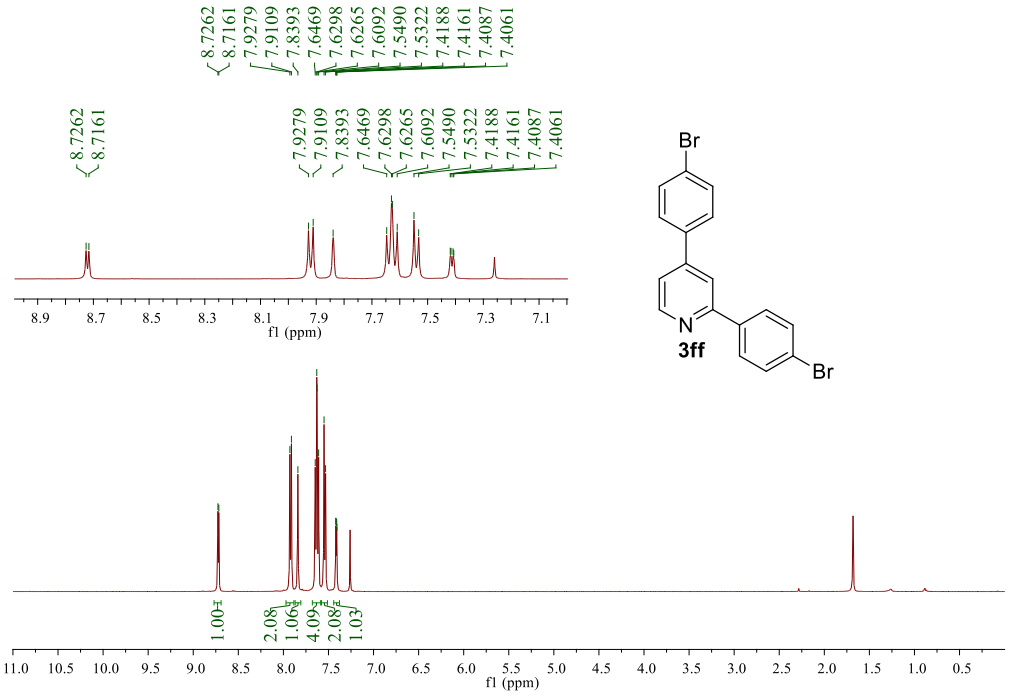


Figure 2.47. 500 MHz ^{1}H Spectrum of **3ff** in $CDCl_3$

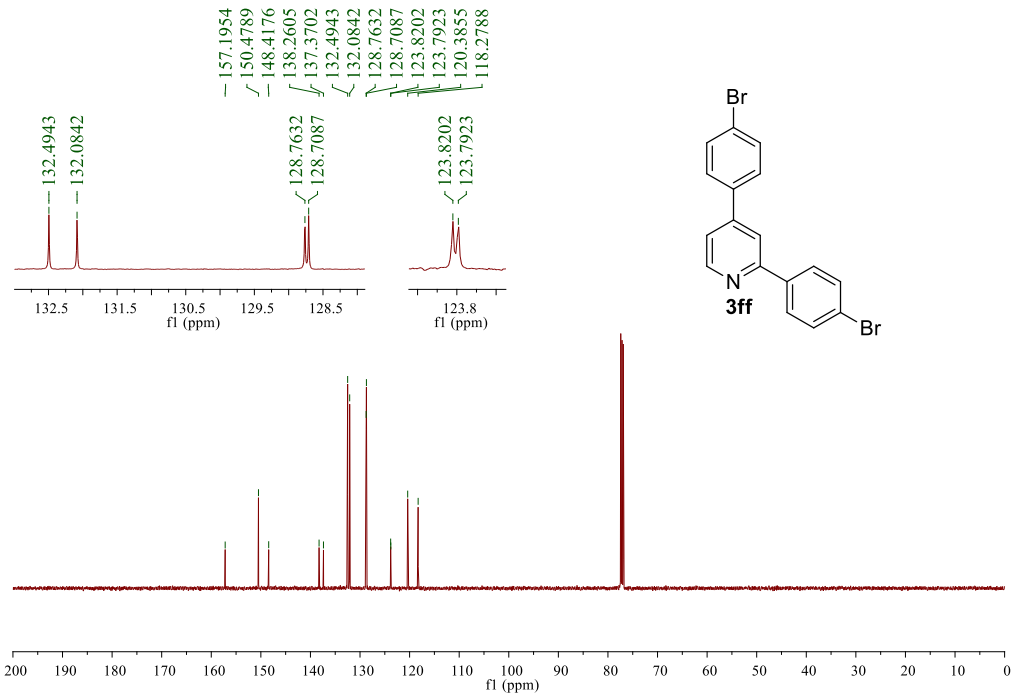


Figure 2.48. 125 MHz ^{13}C Spectrum of **3ff** in $CDCl_3$

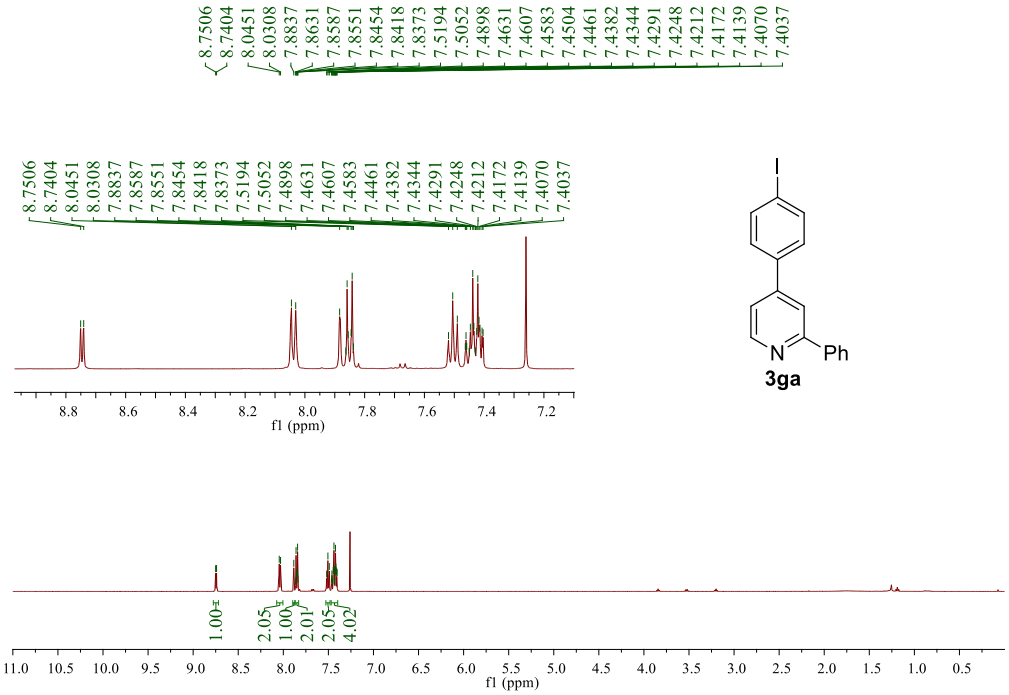


Figure 2.49. 500 MHz ^{1}H Spectrum of **3ga** in $CDCl_3$

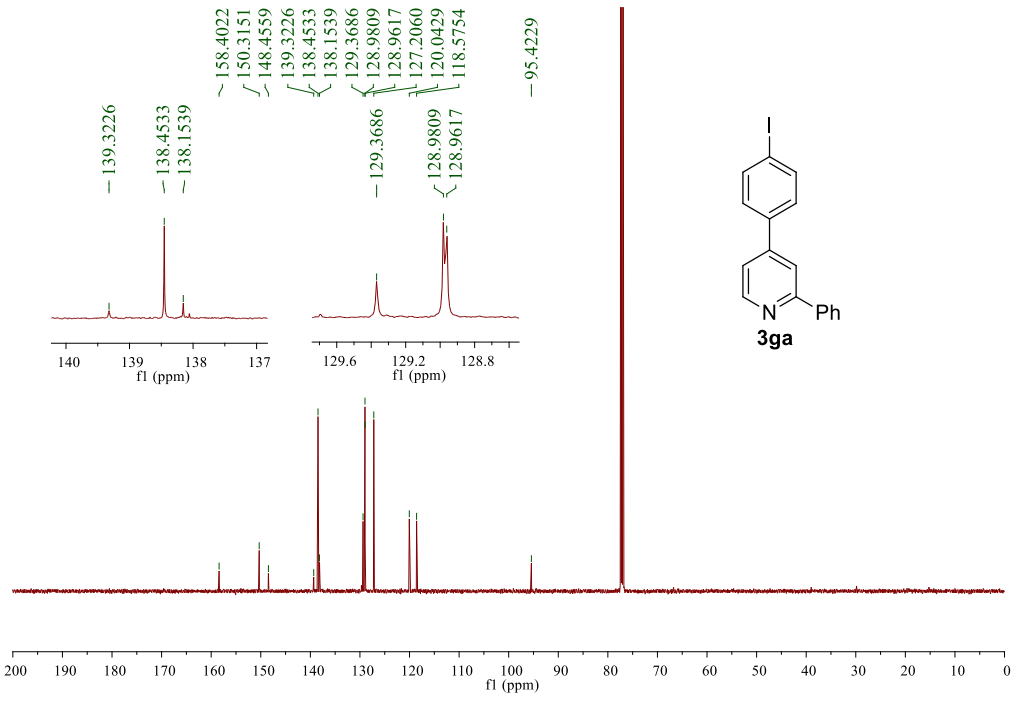


Figure 2.50. 125 MHz ^{13}C Spectrum of **3ga** in $CDCl_3$

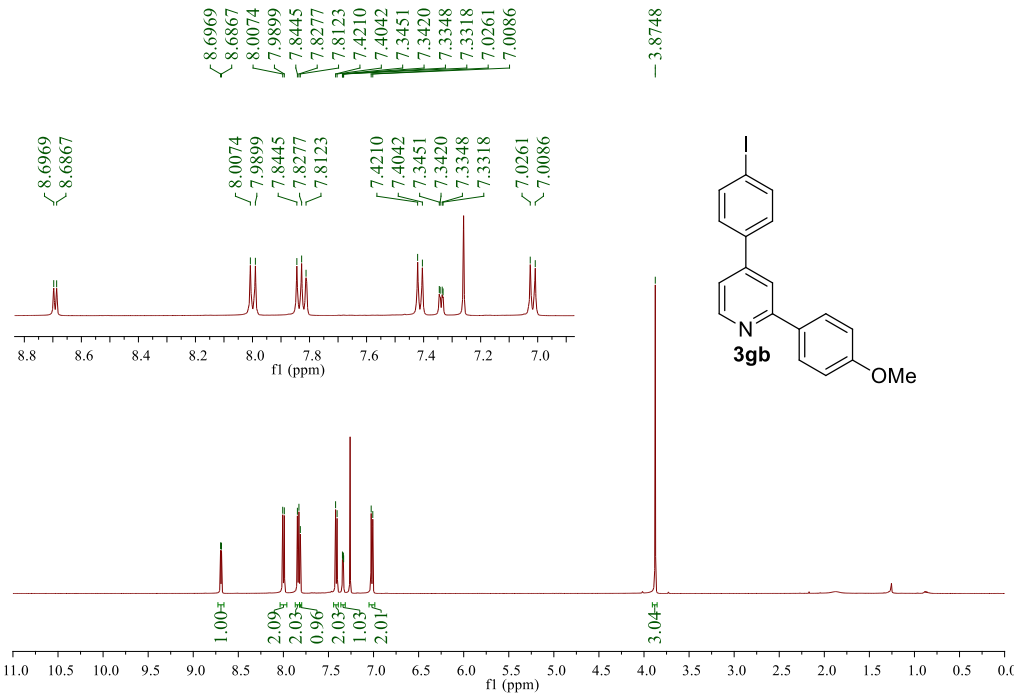


Figure 2.51. 500 MHz ^{1}H Spectrum of **3gb** in $CDCl_3$

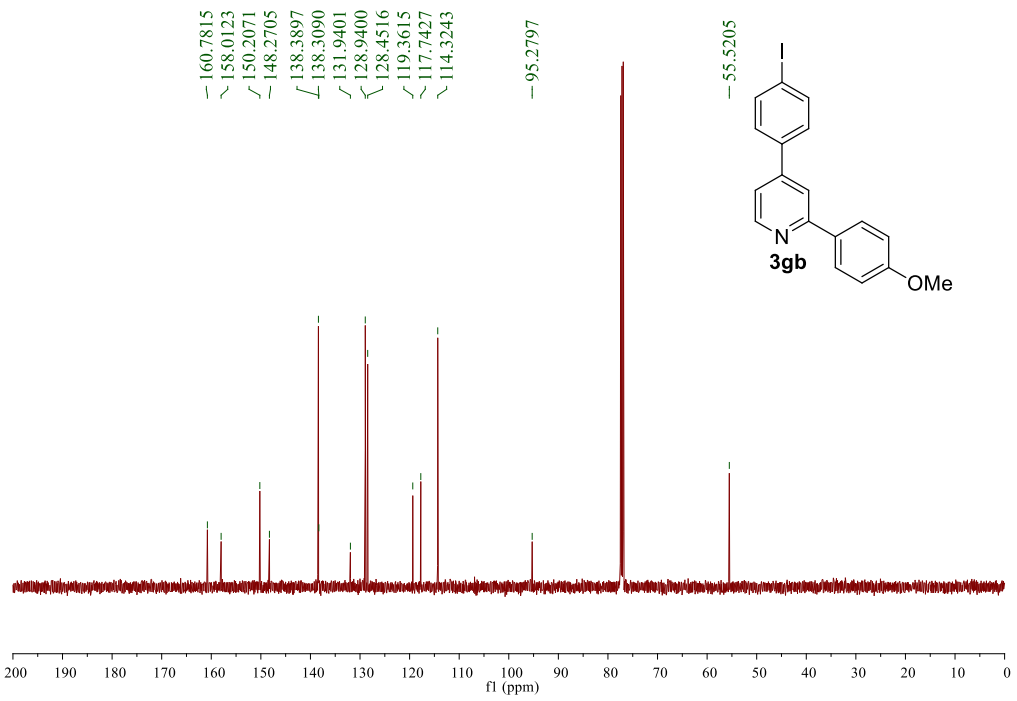


Figure 2.52. 125 MHz ^{13}C Spectrum of **3gb** in $CDCl_3$

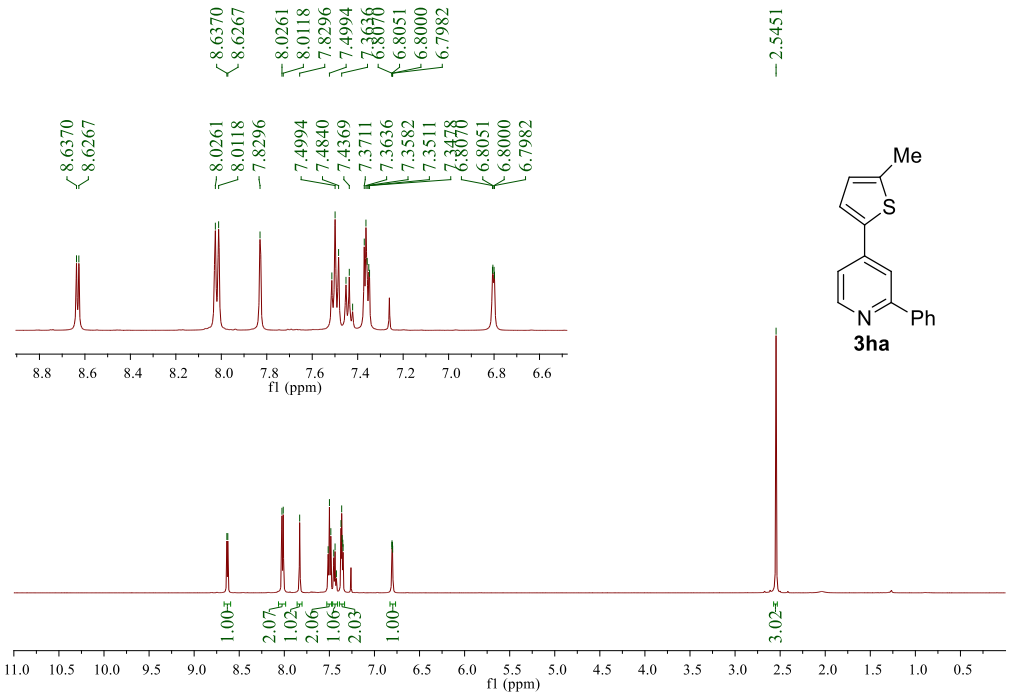


Figure 2.53. 500 MHz ^{1}H Spectrum of **3ha** in $CDCl_3$

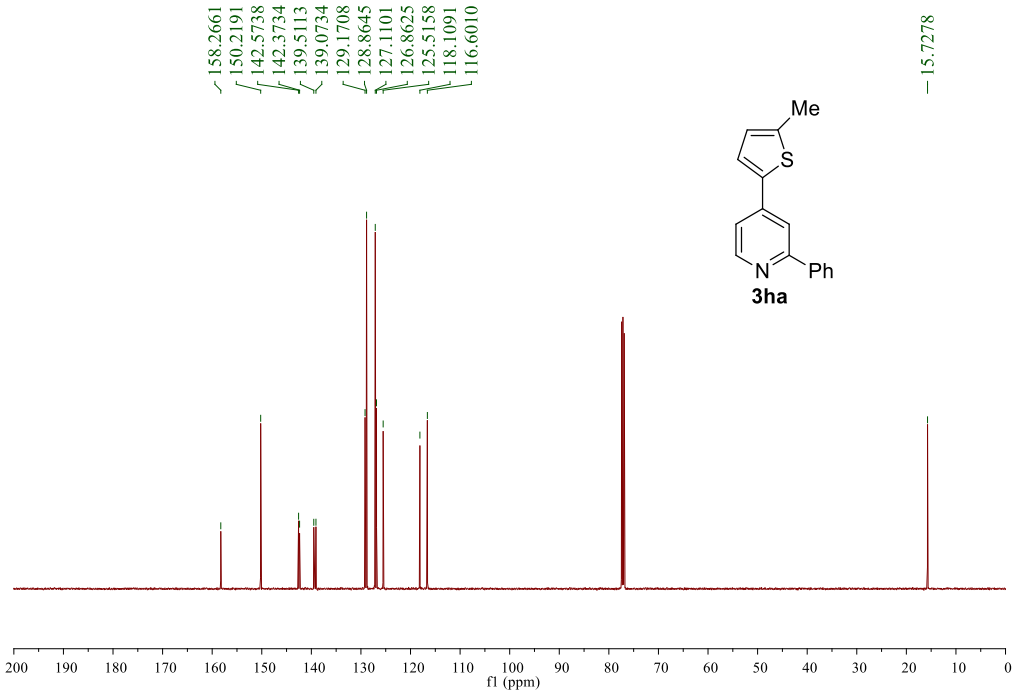


Figure 2.54. 125 MHz ^{13}C Spectrum of **3ha** in $CDCl_3$

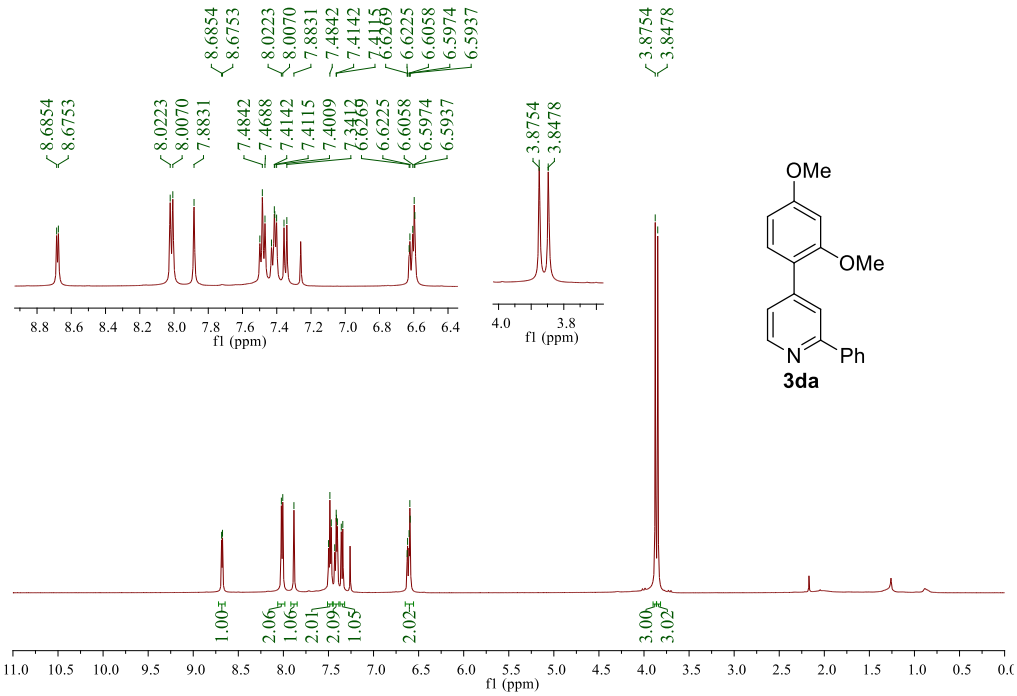


Figure 2.55. 500 MHz ^{1}H Spectrum of **3da** in $CDCl_3$

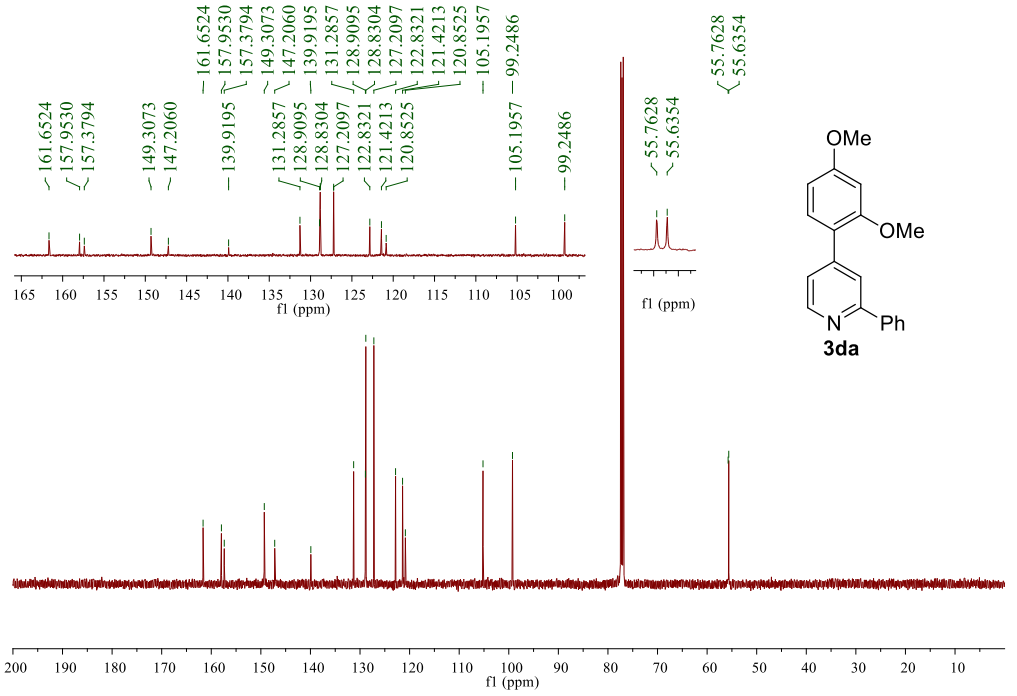


Figure 2.56. 125 MHz ^{13}C Spectrum of **3da** in $CDCl_3$

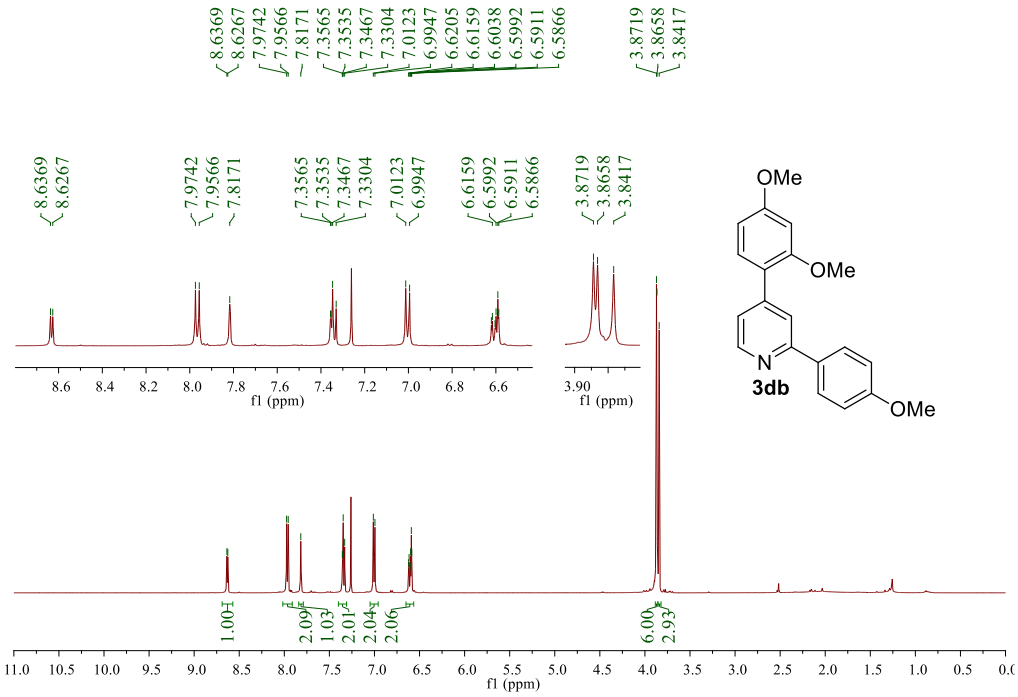


Figure 2.57. 500 MHz ^{1}H Spectrum of **3db** in $CDCl_3$

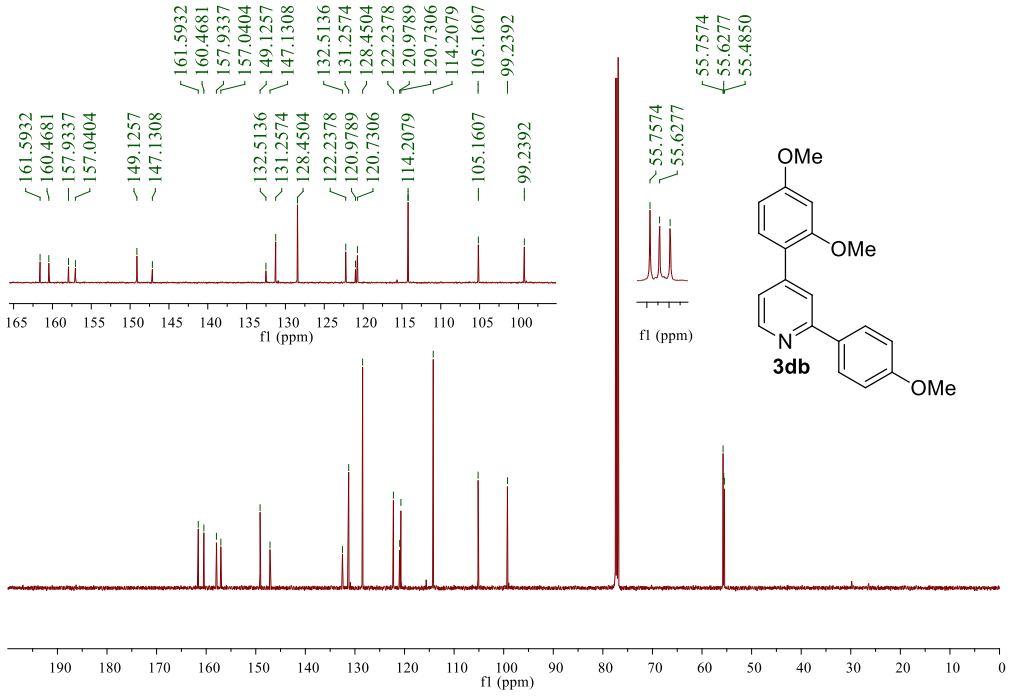


Figure 2.58. 125 MHz ^{13}C Spectrum of **3db** in $CDCl_3$

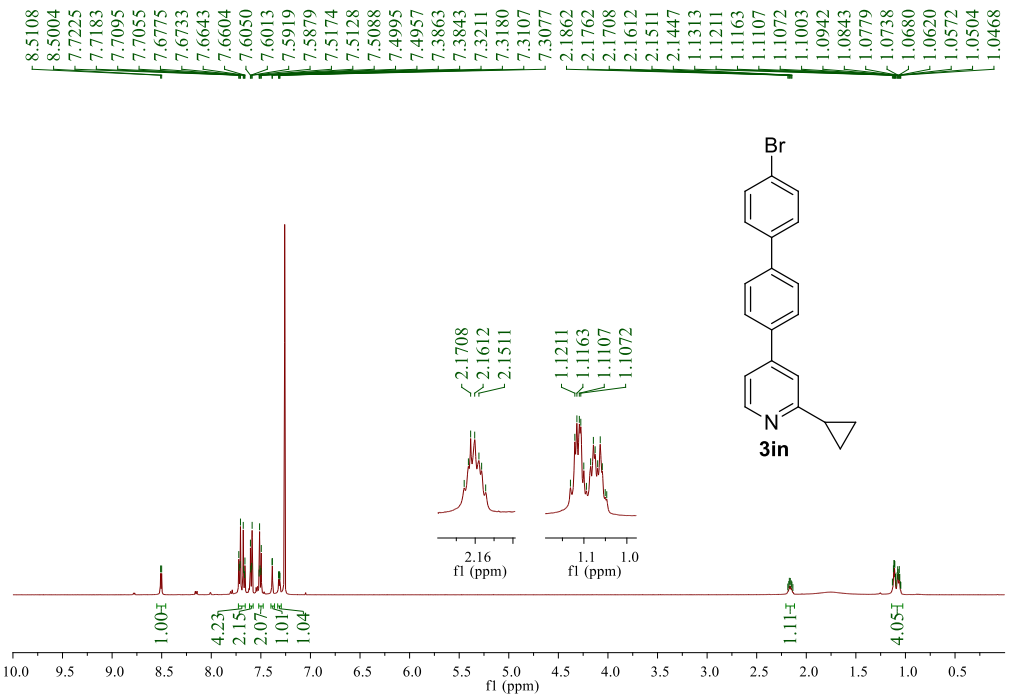


Figure 2.59. 500 MHz ^{1}H Spectrum of **3in** in $CDCl_3$

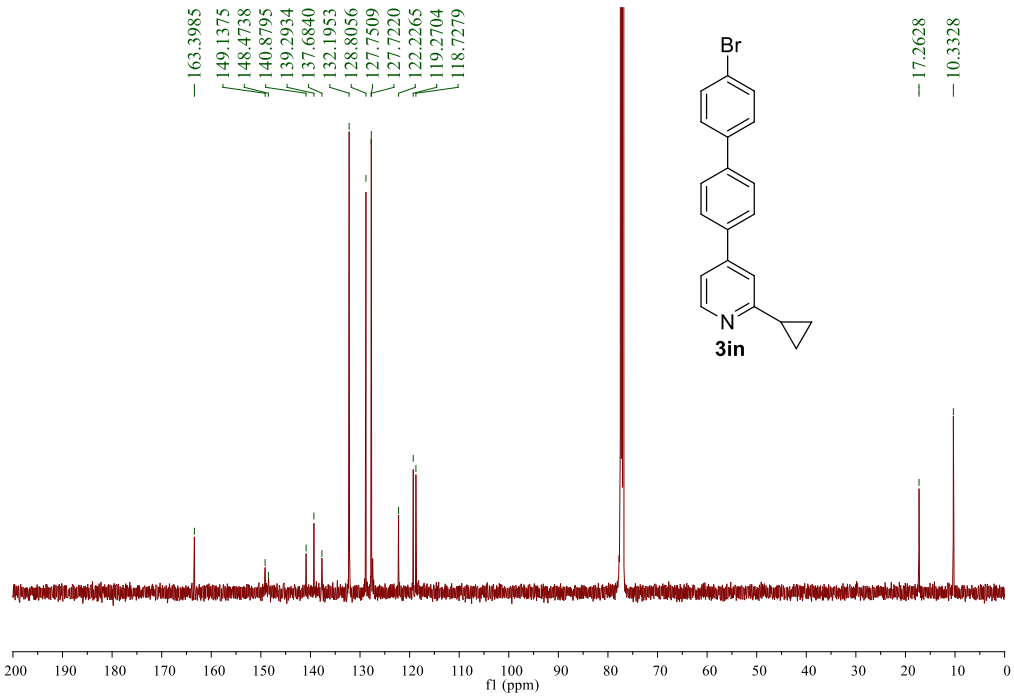


Figure 2.60. 125 MHz ^{13}C Spectrum of **3in** in $CDCl_3$

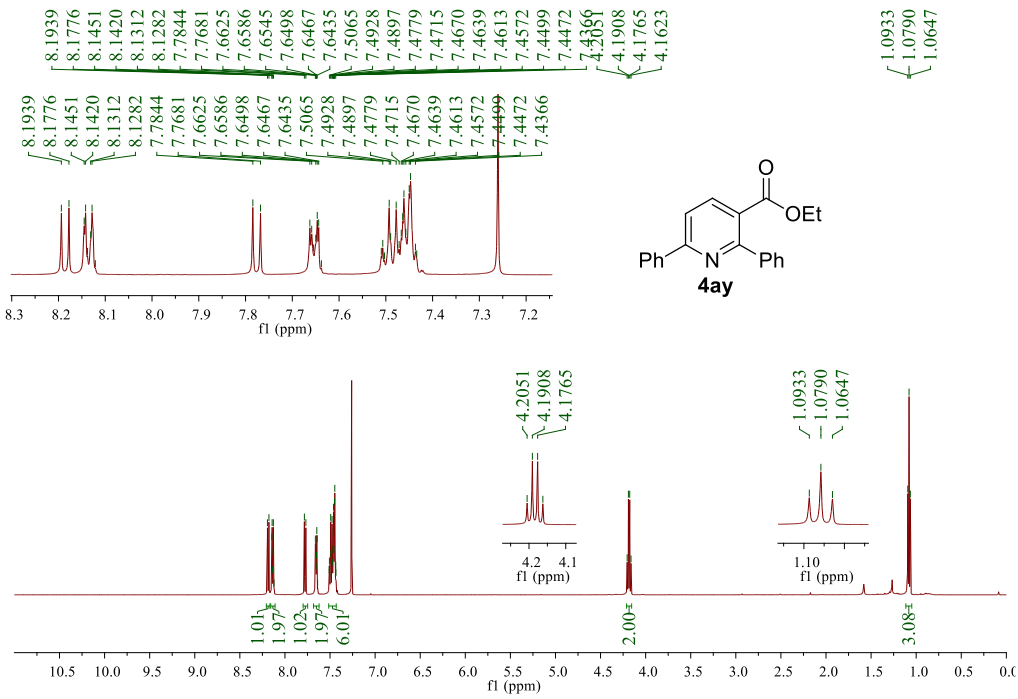


Figure 2.61. 500 MHz ^{1}H Spectrum of **4ay** in $CDCl_3$

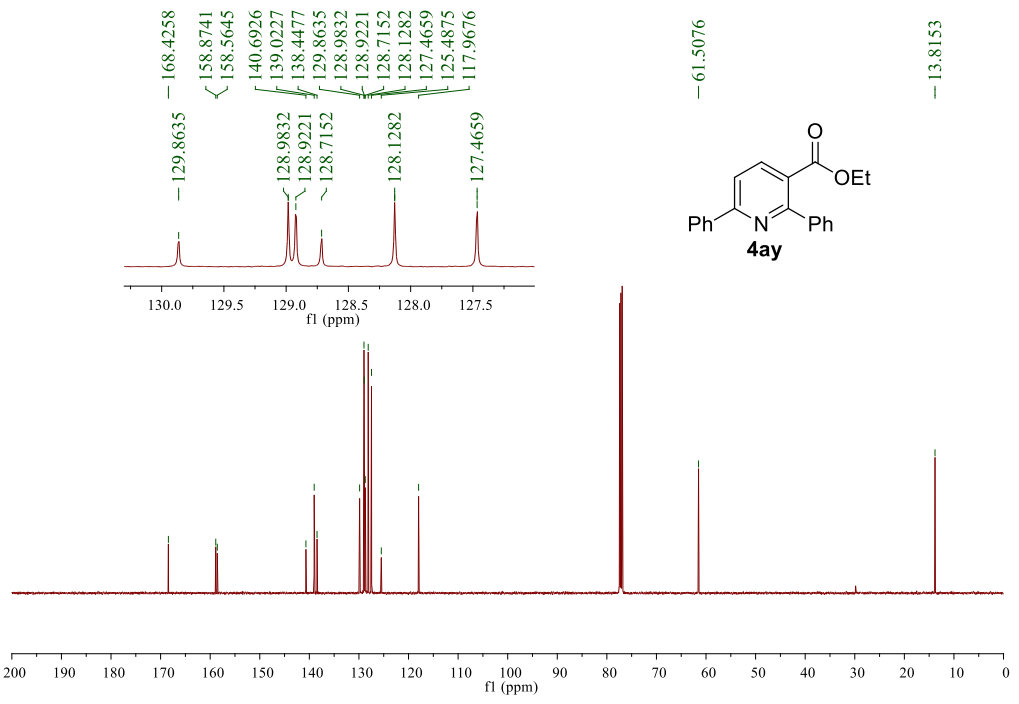


Figure 2.62. 125 MHz ^{13}C Spectrum of **4ay** in $CDCl_3$

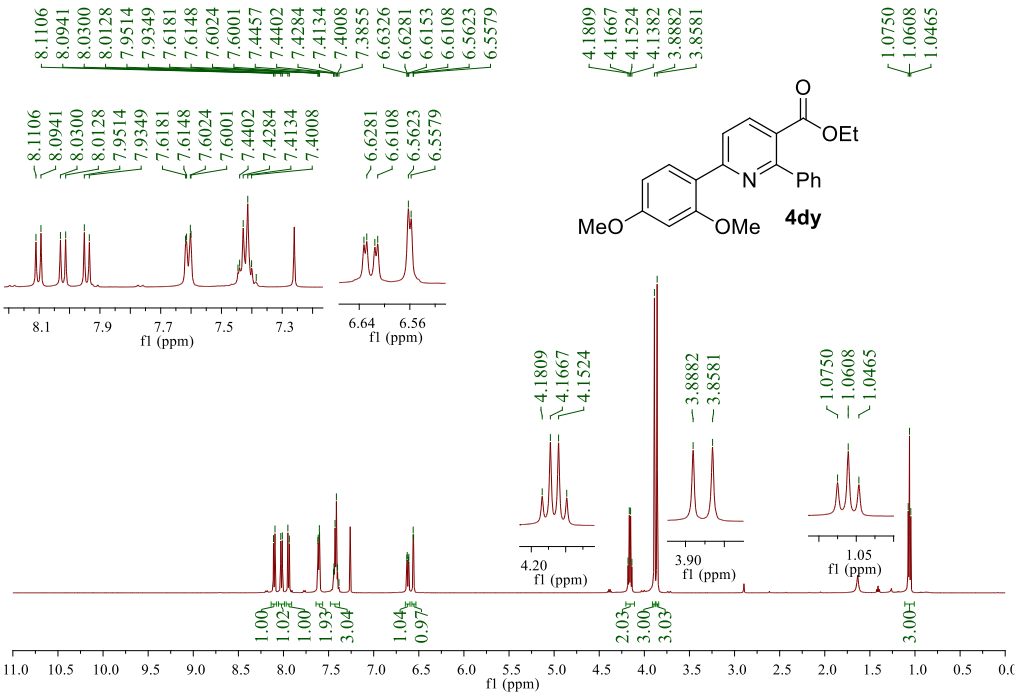


Figure 2.63. 500 MHz ^{1}H Spectrum of **4dy** in $CDCl_3$

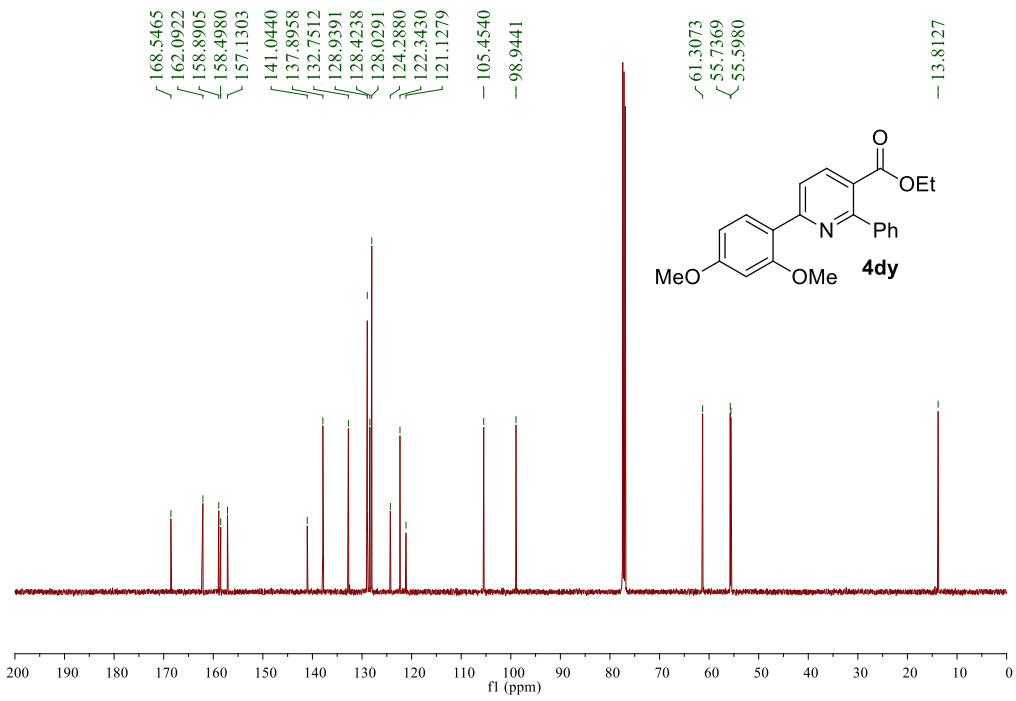


Figure 2.64. 125 MHz ^{13}C Spectrum of **4dy** in $CDCl_3$

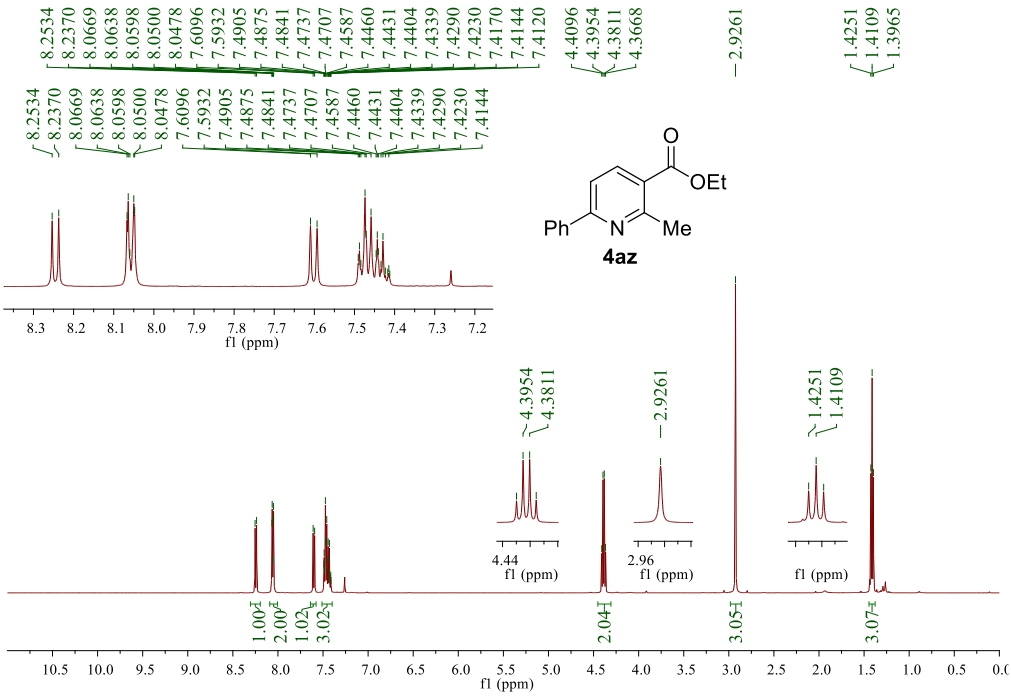


Figure 2.65. 500 MHz ^{1}H Spectrum of **4az** in $CDCl_3$

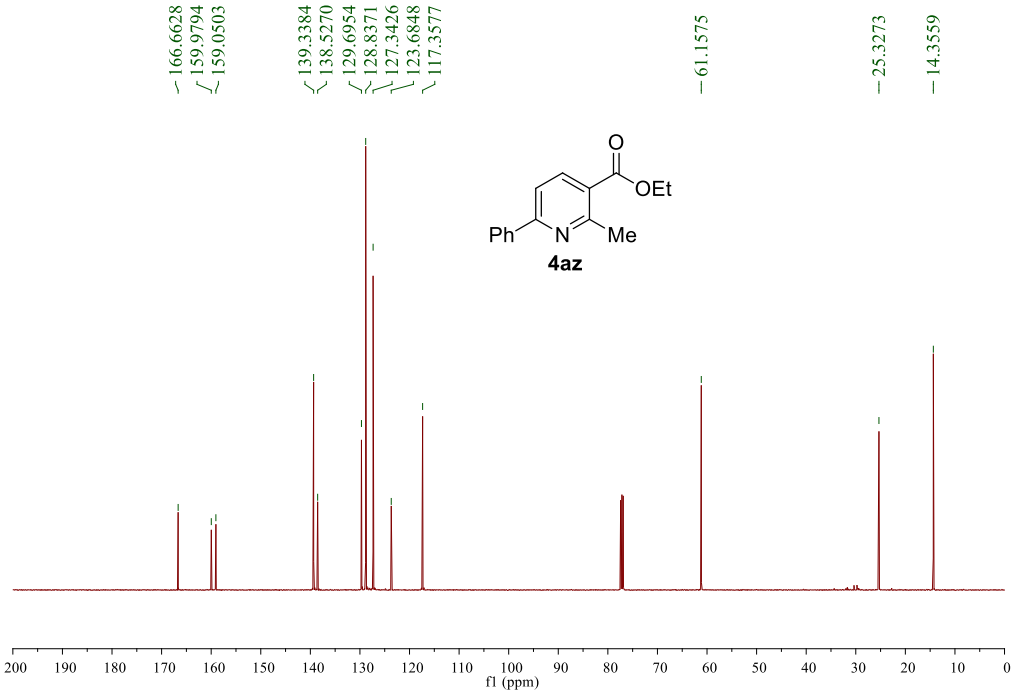


Figure 2.66. 125 MHz ^{13}C Spectrum of **4az** in $CDCl_3$

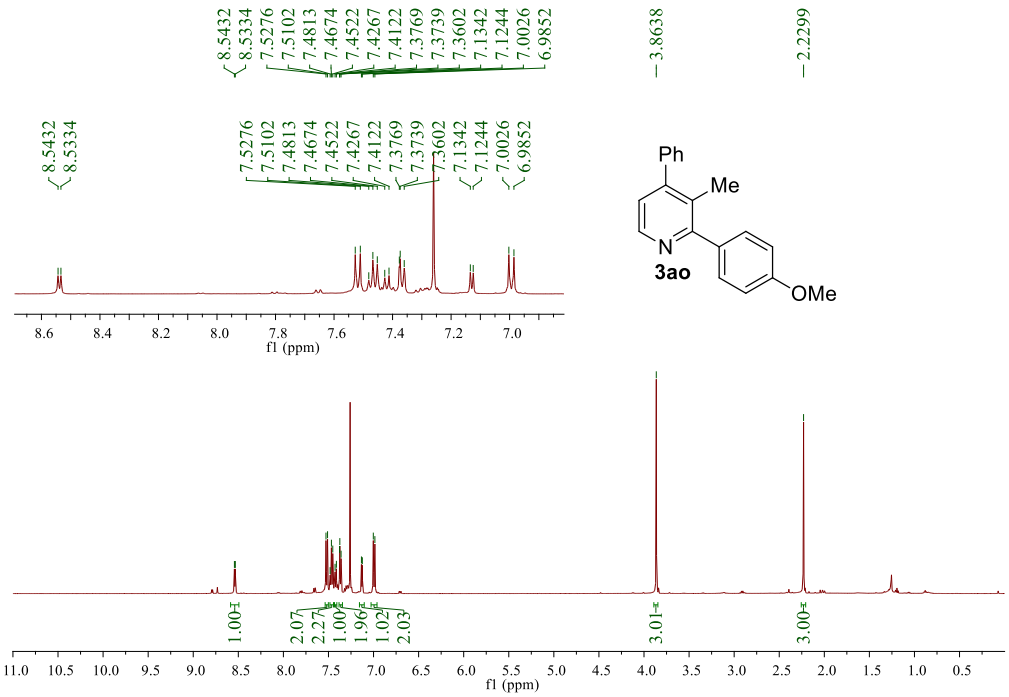


Figure 2.67. 500 MHz ^{1}H Spectrum of **3ao** in $CDCl_3$

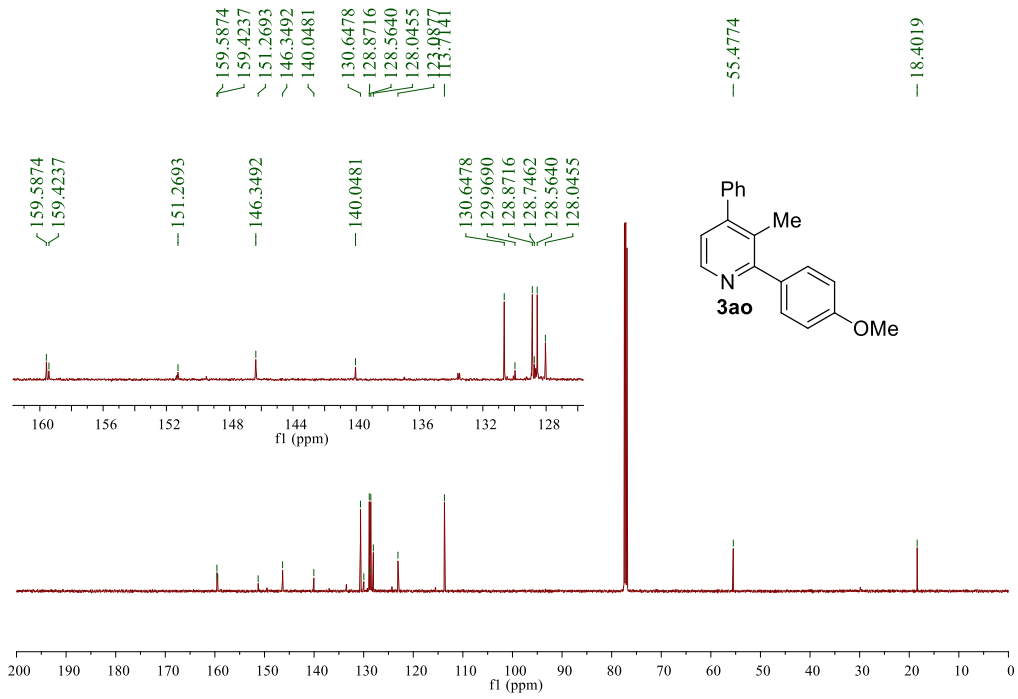


Figure 2.68. 125 MHz ^{13}C Spectrum of **3ao** in $CDCl_3$

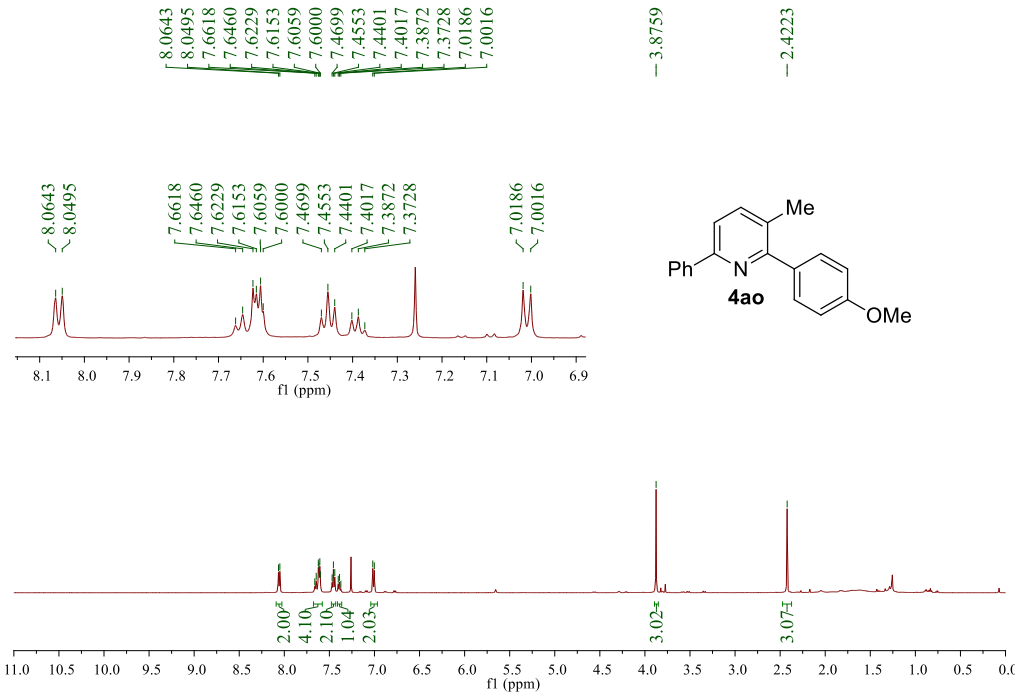


Figure 2.69. 500 MHz ^{1}H Spectrum of **4ao** in $CDCl_3$

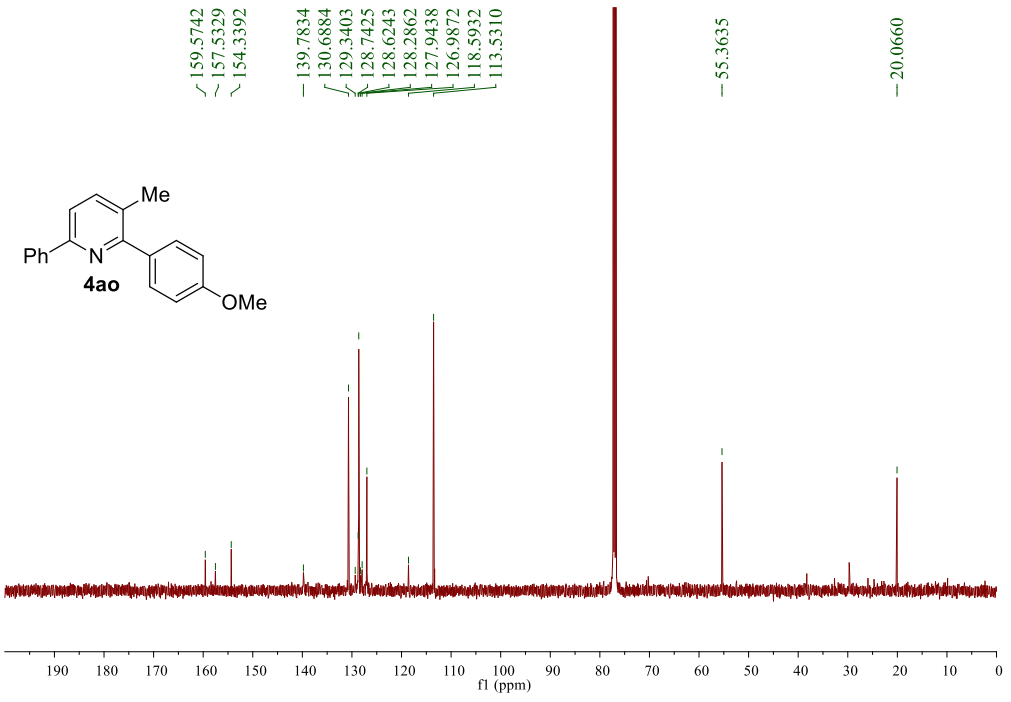


Figure 2.70. 125 MHz ^{13}C Spectrum of **4ao** in $CDCl_3$

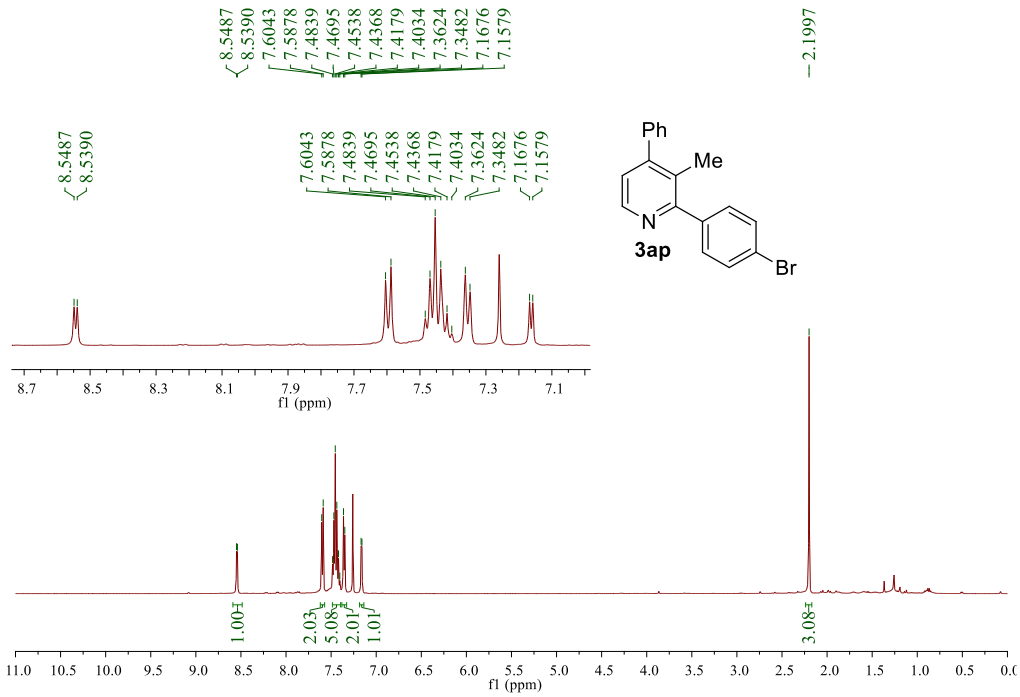


Figure 2.71. 500 MHz ^{1}H Spectrum of **3ap** in $CDCl_3$

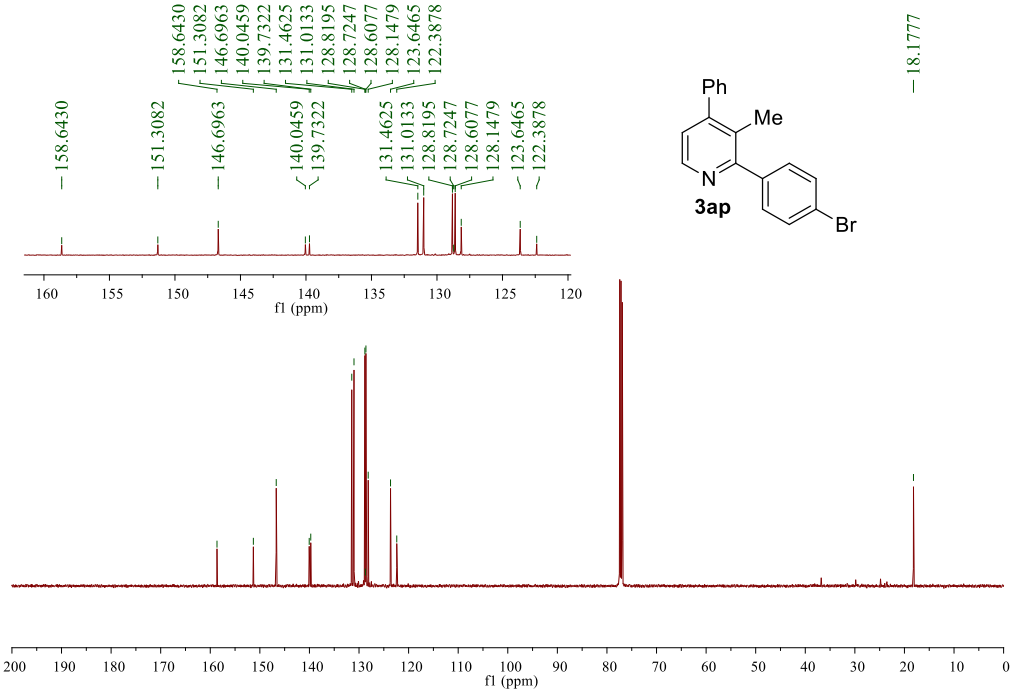


Figure 2.72. 125 MHz ^{13}C Spectrum of **3ap** in $CDCl_3$

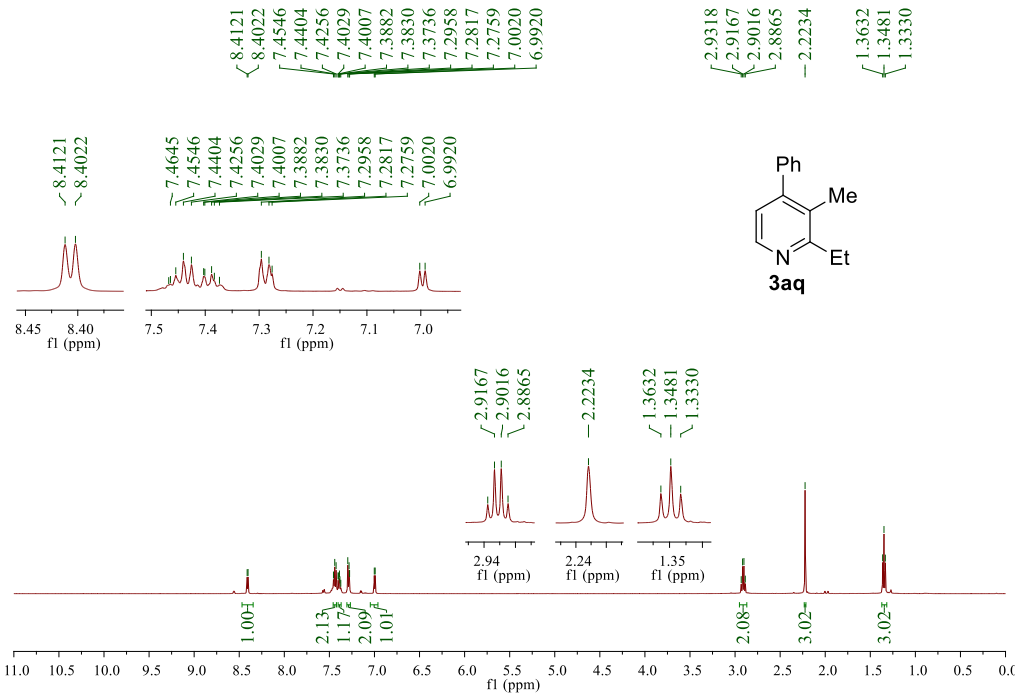


Figure 2.73. 500 MHz ^{1}H Spectrum of **3aq** in $CDCl_3$

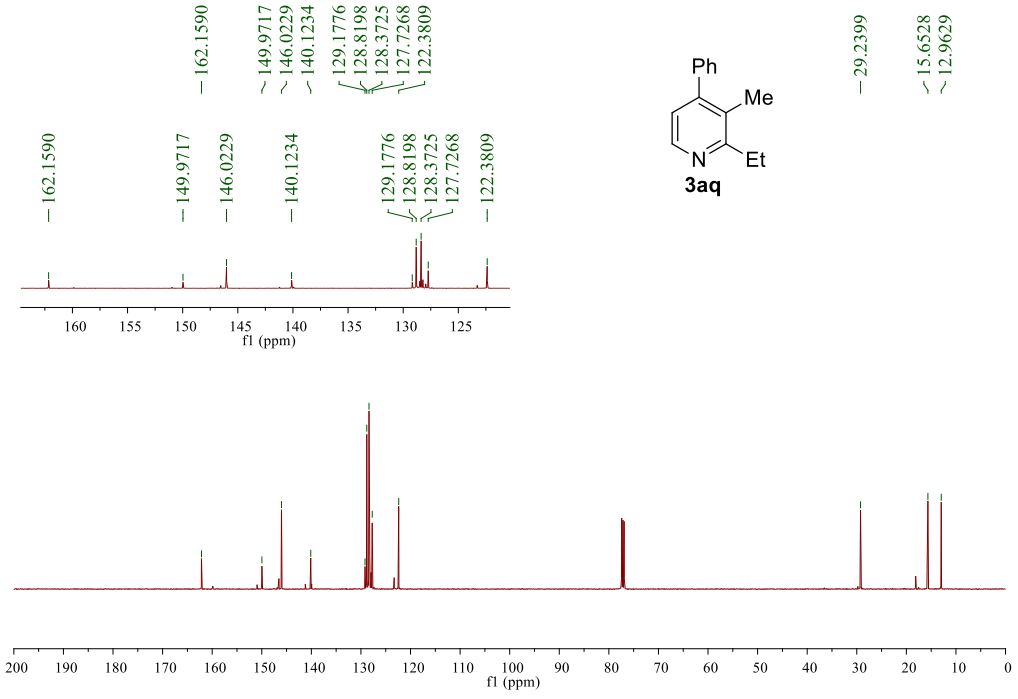


Figure 2.74. 125 MHz ^{13}C Spectrum of **3aq** in $CDCl_3$

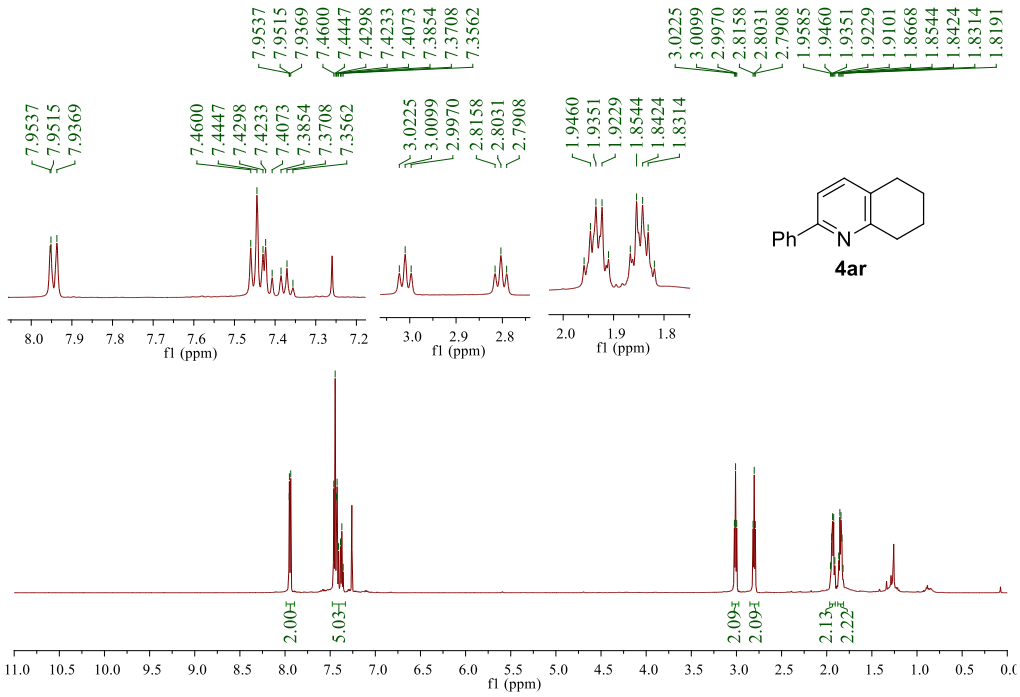


Figure 2.75. 500 MHz ^{1}H Spectrum of **4ar** in $CDCl_3$

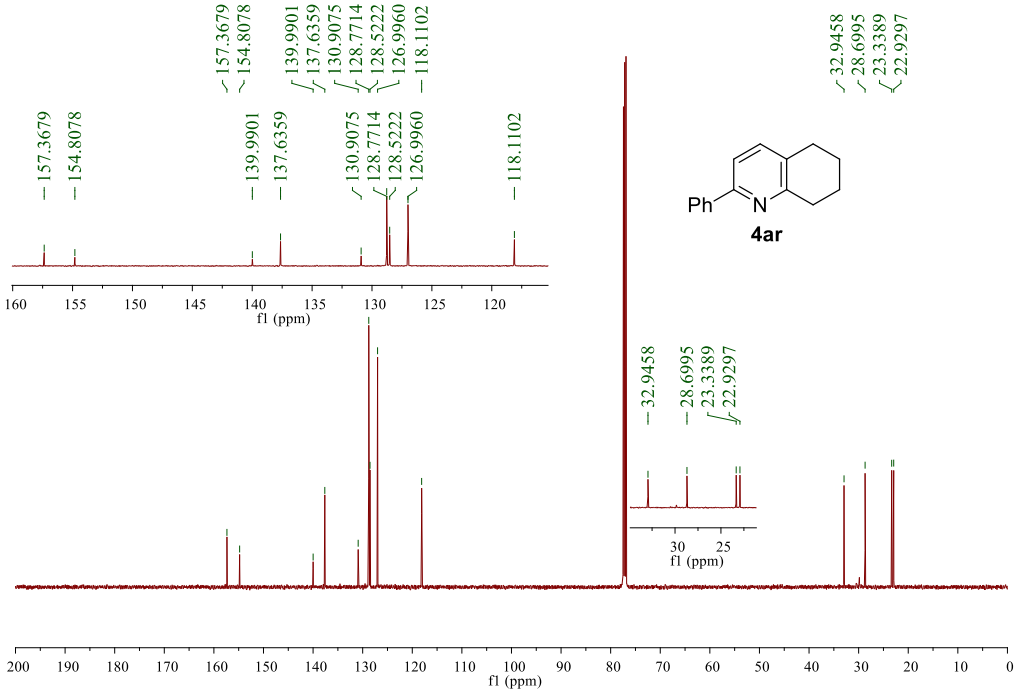


Figure 2.76. 125 MHz ^{13}C Spectrum of **4ar** in $CDCl_3$

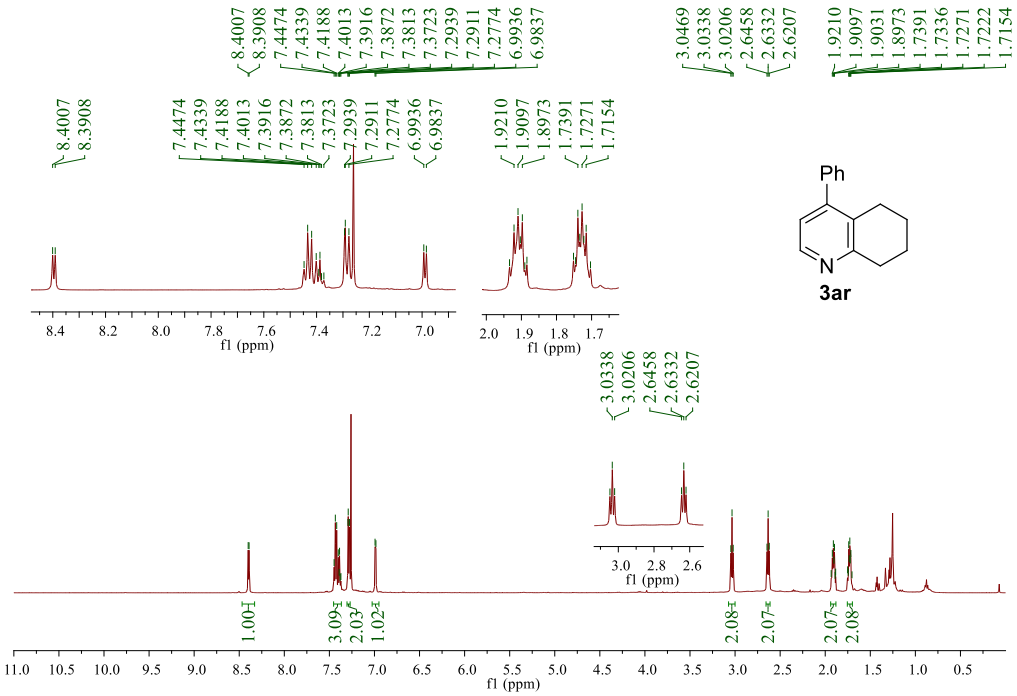


Figure 2.77. 500 MHz ^{1}H Spectrum of **3ar** in $CDCl_3$

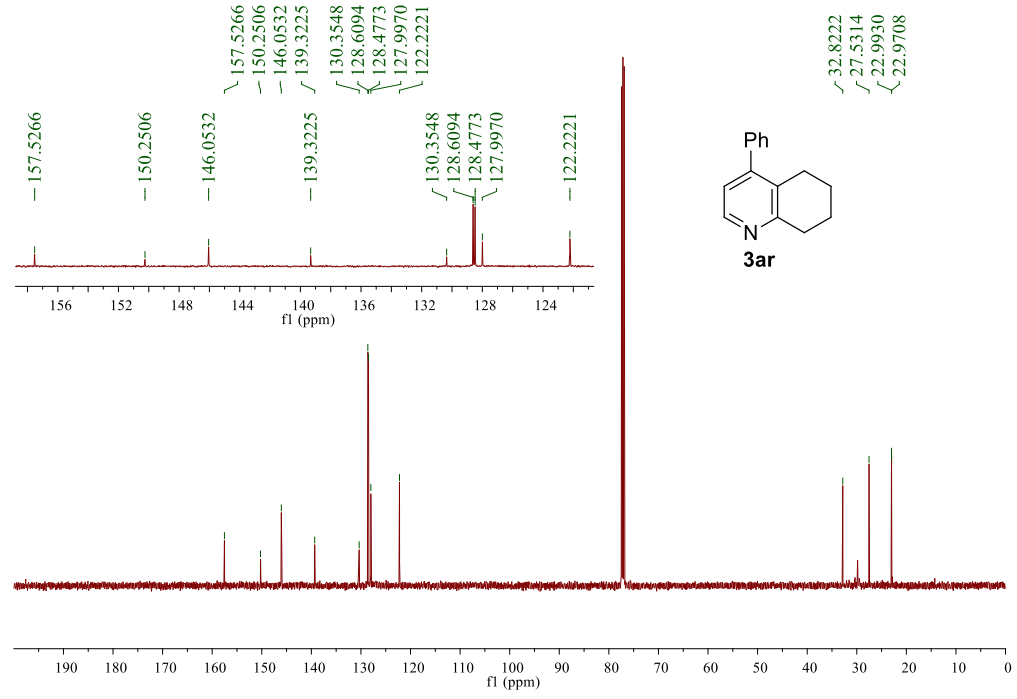


Figure 2.78. 125 MHz ^{13}C Spectrum of **3ar** in $CDCl_3$

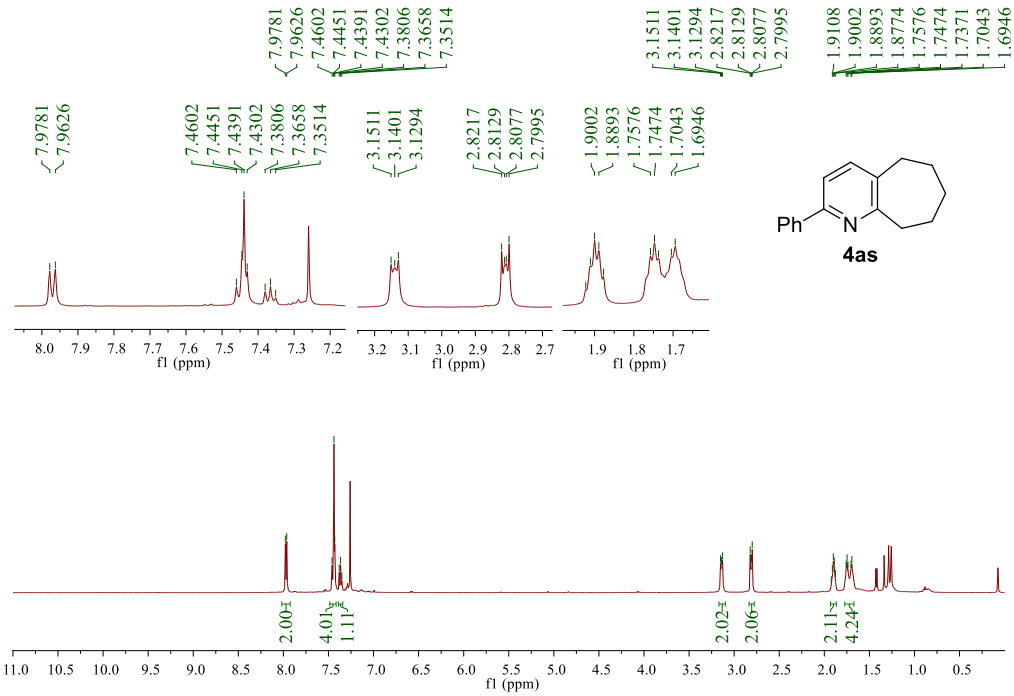


Figure 2.79. 500 MHz ^{1}H Spectrum of **4as** in $CDCl_3$

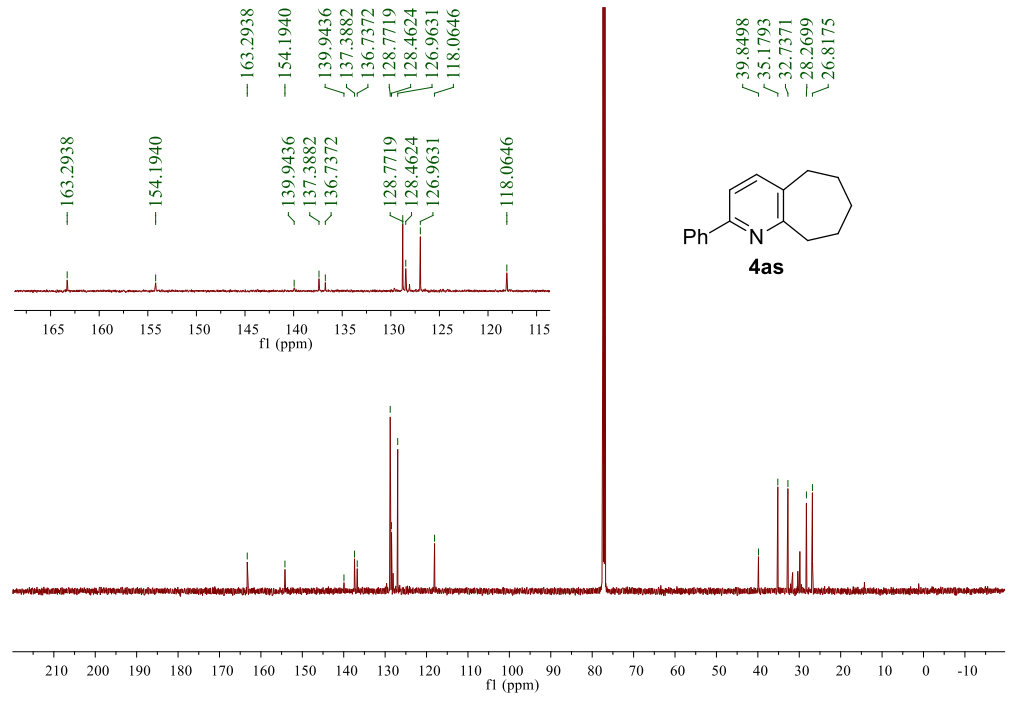


Figure 2.80. 125 MHz ^{13}C Spectrum of **4as** in $CDCl_3$

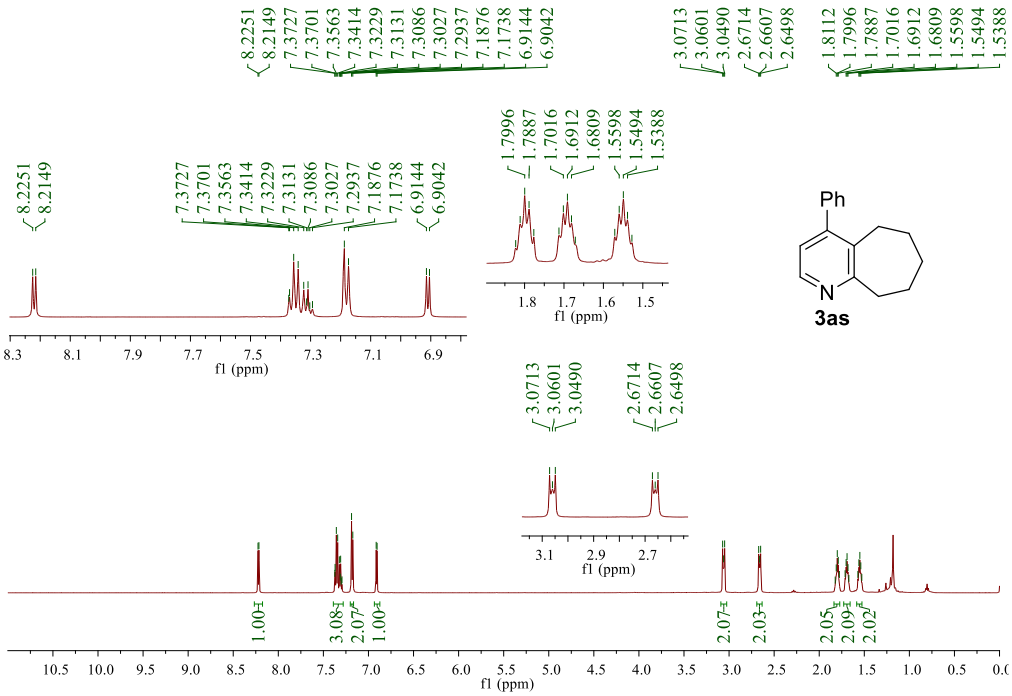


Figure 2.81. 500 MHz ^{1}H Spectrum of **3as** in $CDCl_3$

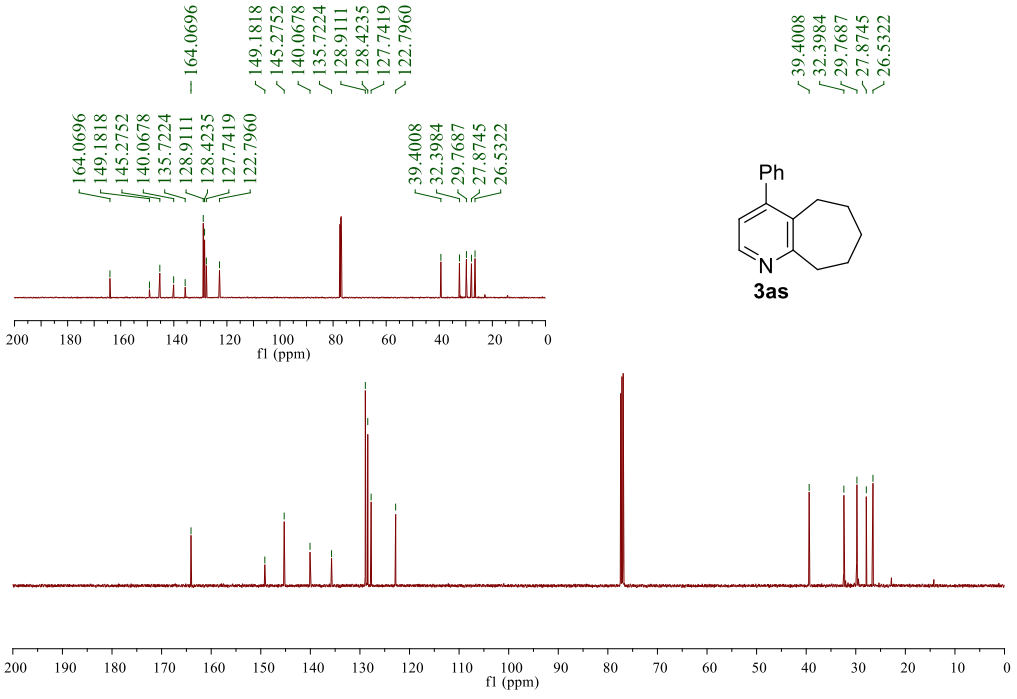


Figure 2.82. 125 MHz ^{13}C Spectrum of **3as** in $CDCl_3$

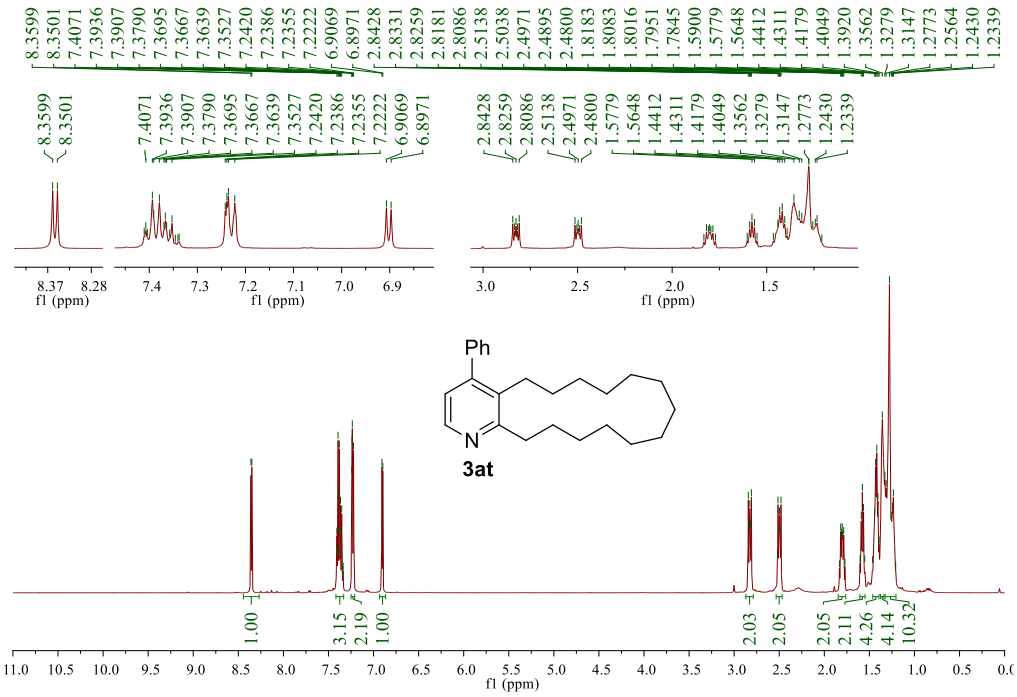


Figure 2.83. 500 MHz ^{1}H Spectrum of **3at** in $CDCl_3$

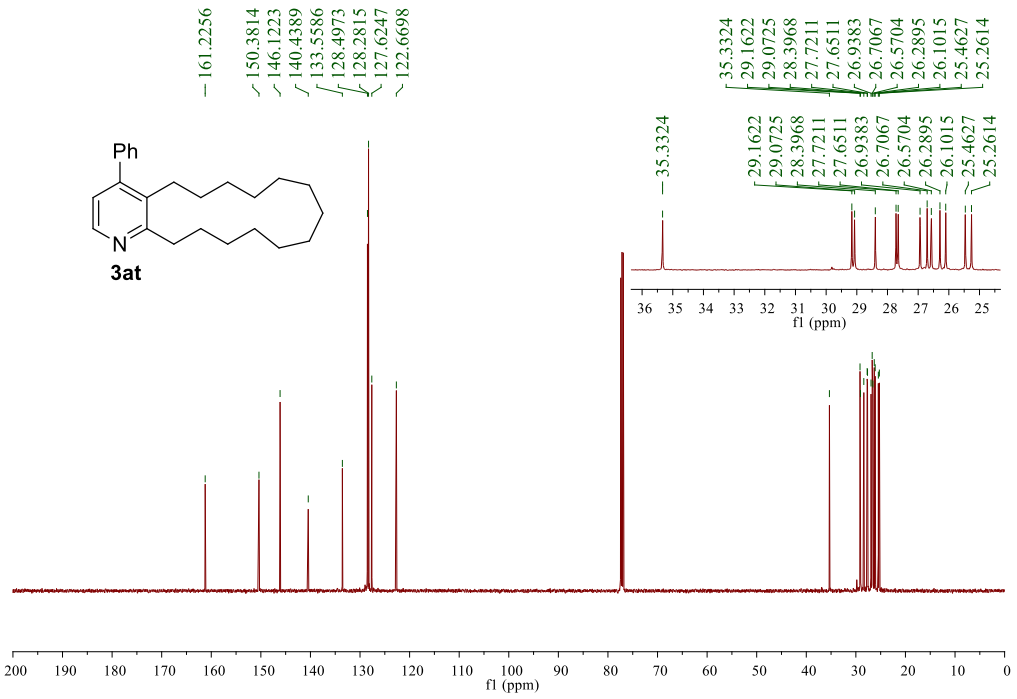


Figure 2.84. 125 MHz ^{13}C Spectrum of **3at** in $CDCl_3$

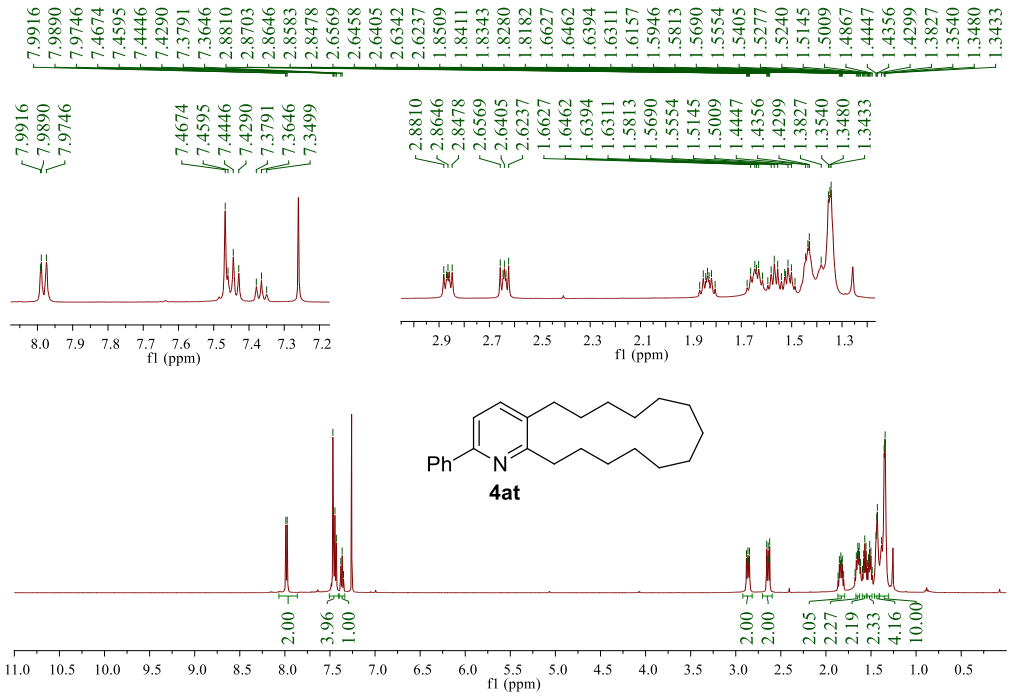


Figure 2.85. 500 MHz ^{1}H Spectrum of **4at** in $CDCl_3$

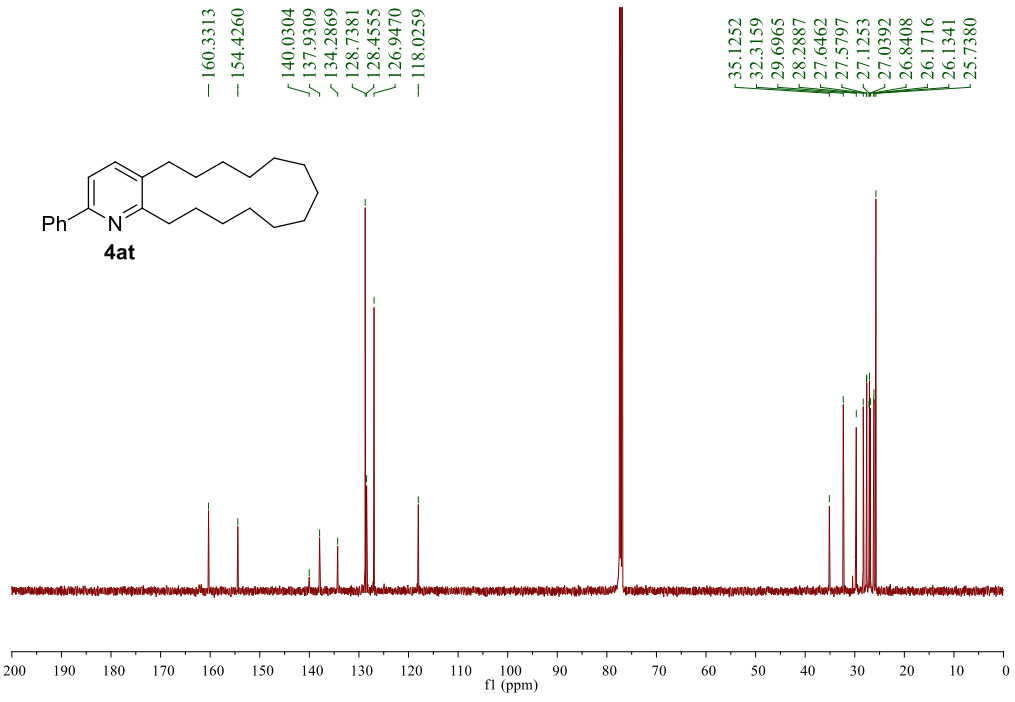


Figure 2.86. 125 MHz ^{13}C Spectrum of **4at** in $CDCl_3$

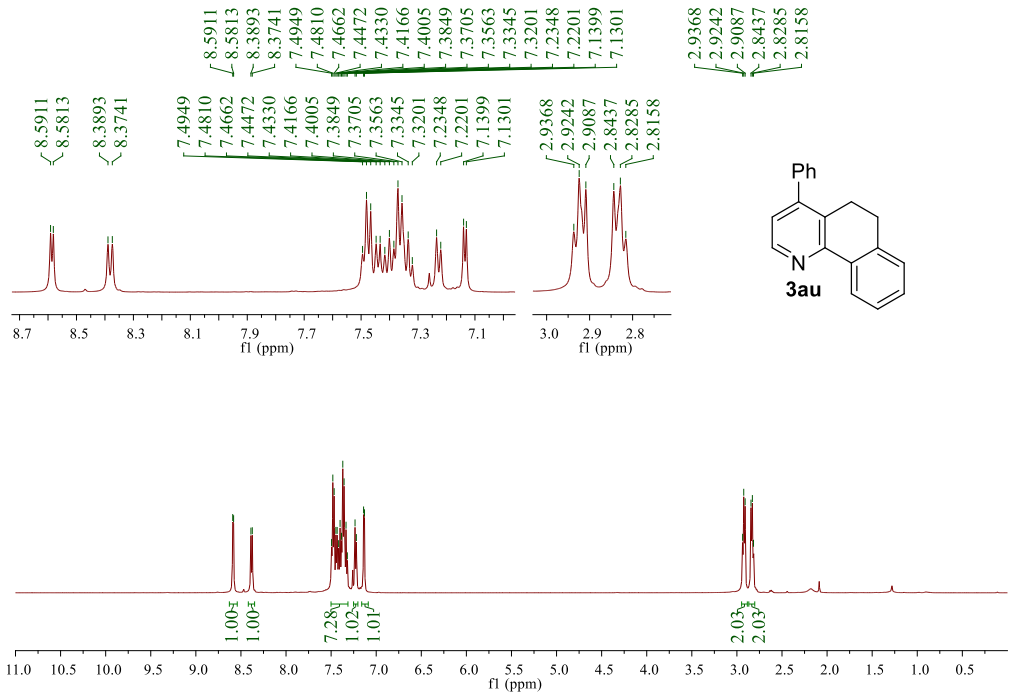


Figure 2.87. 500 MHz ^{1}H Spectrum of **3au** in $CDCl_3$

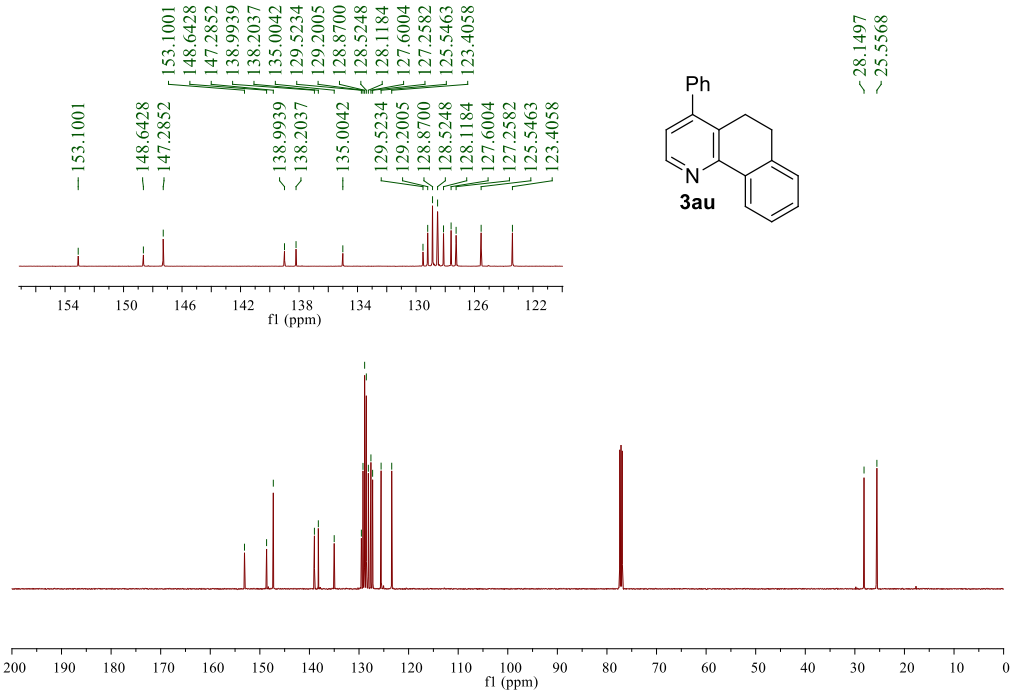


Figure 2.88. 125 MHz ^{13}C Spectrum of **3au** in $CDCl_3$

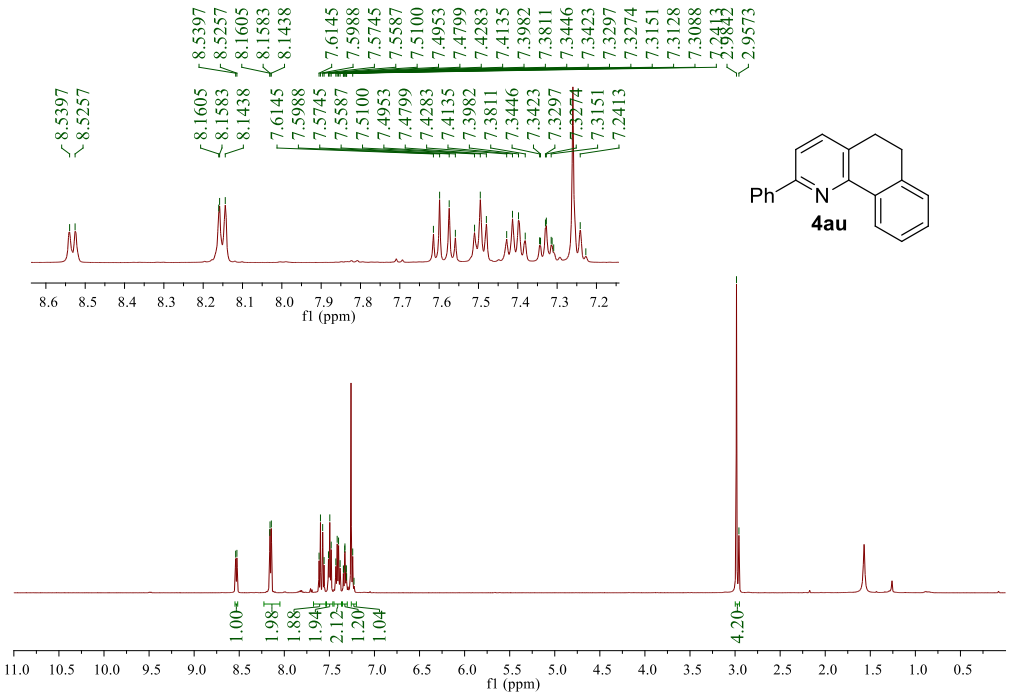


Figure 2.89. 500 MHz ^{1}H Spectrum of **4au** in $CDCl_3$

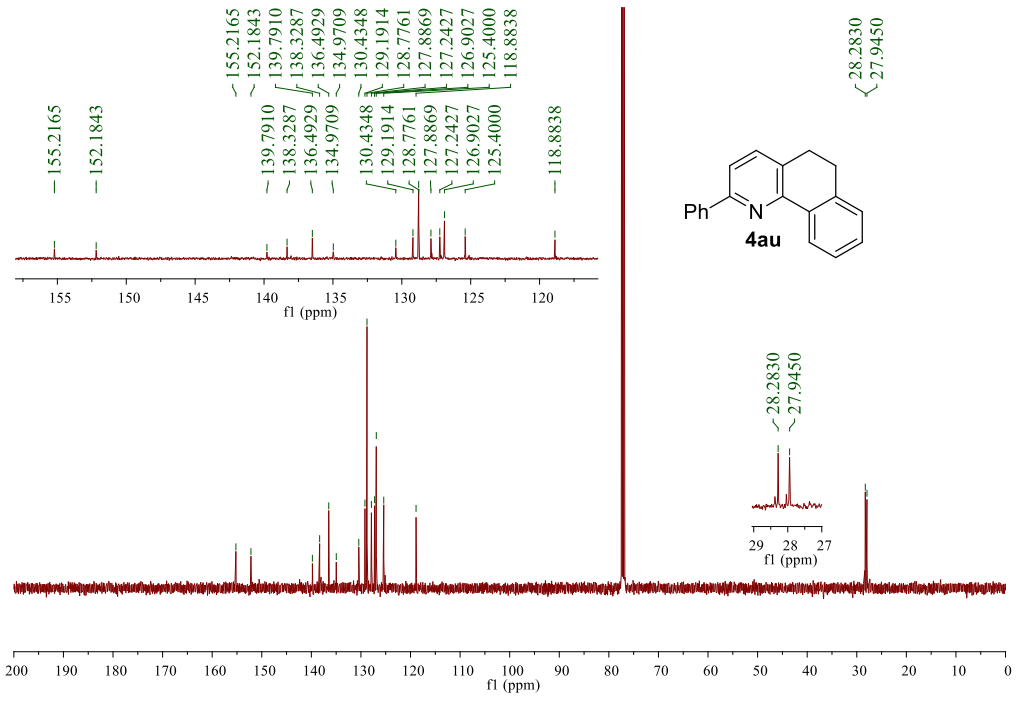


Figure 2.90. 125 MHz ^{13}C Spectrum of **4au** in $CDCl_3$

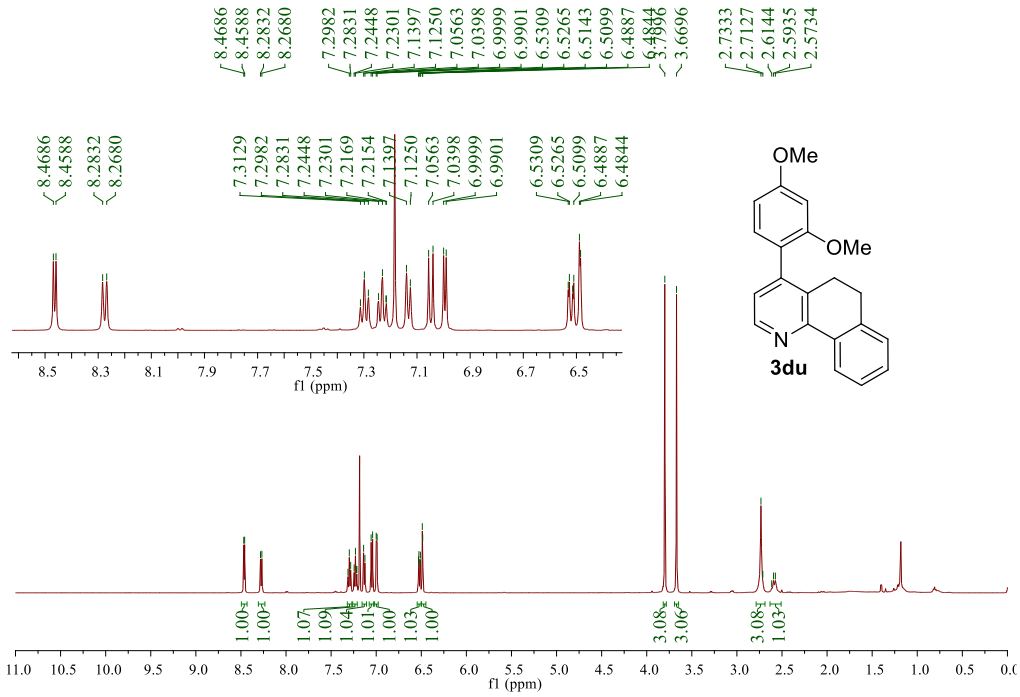


Figure 2.91. 500 MHz ^{1}H Spectrum of **3du** in $CDCl_3$

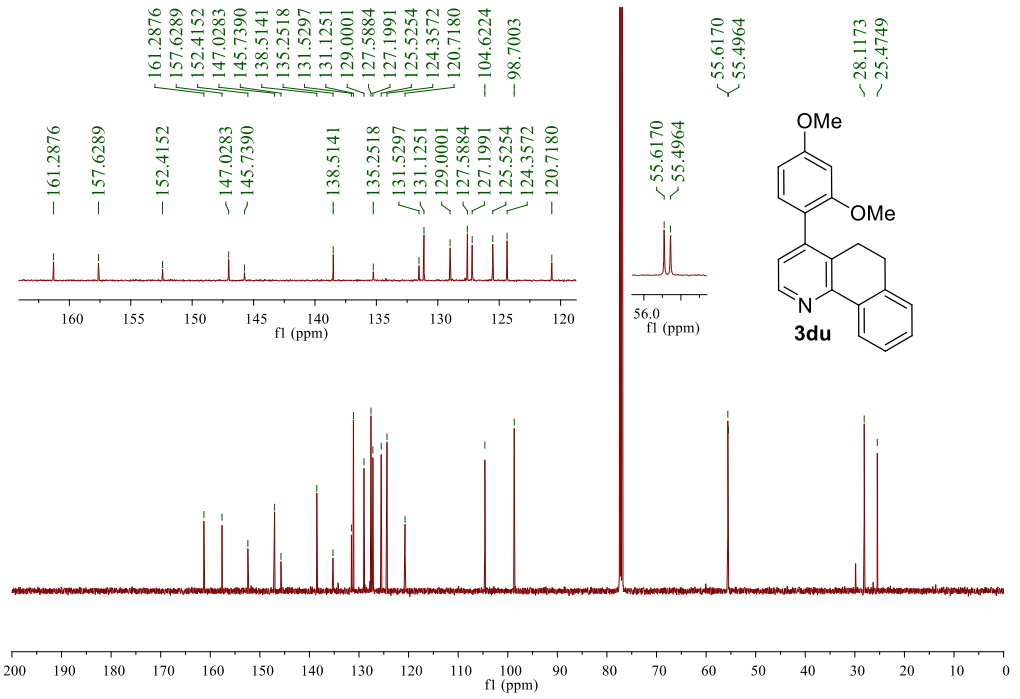


Figure 2.92. 125 MHz ^{13}C Spectrum of **3du** in $CDCl_3$

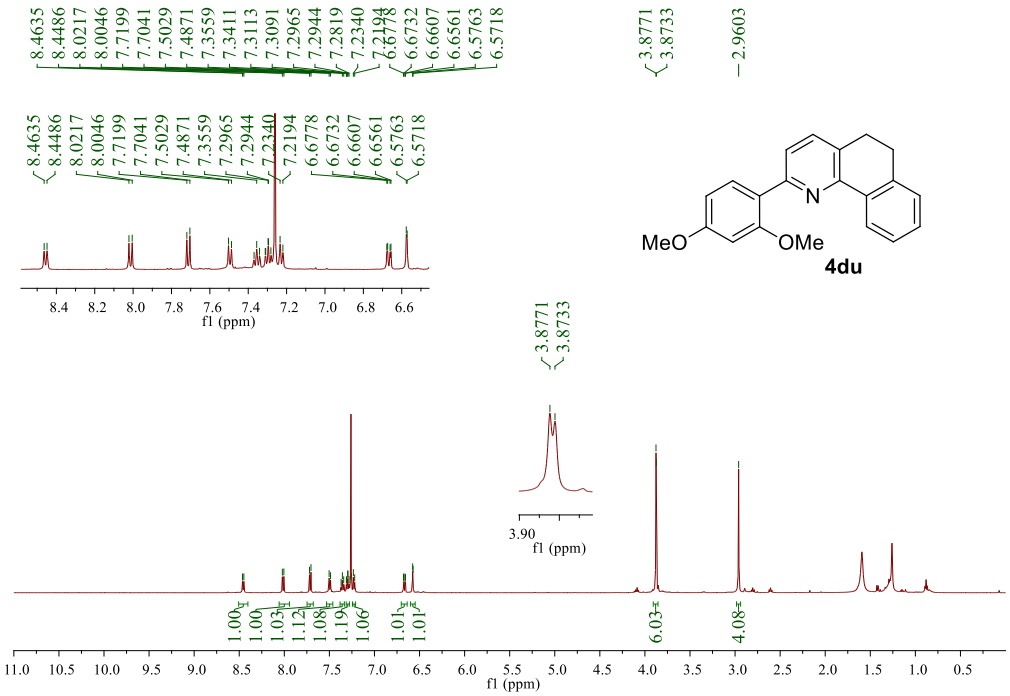


Figure 2.93. 500 MHz ^{1}H Spectrum of **4du** in $CDCl_3$

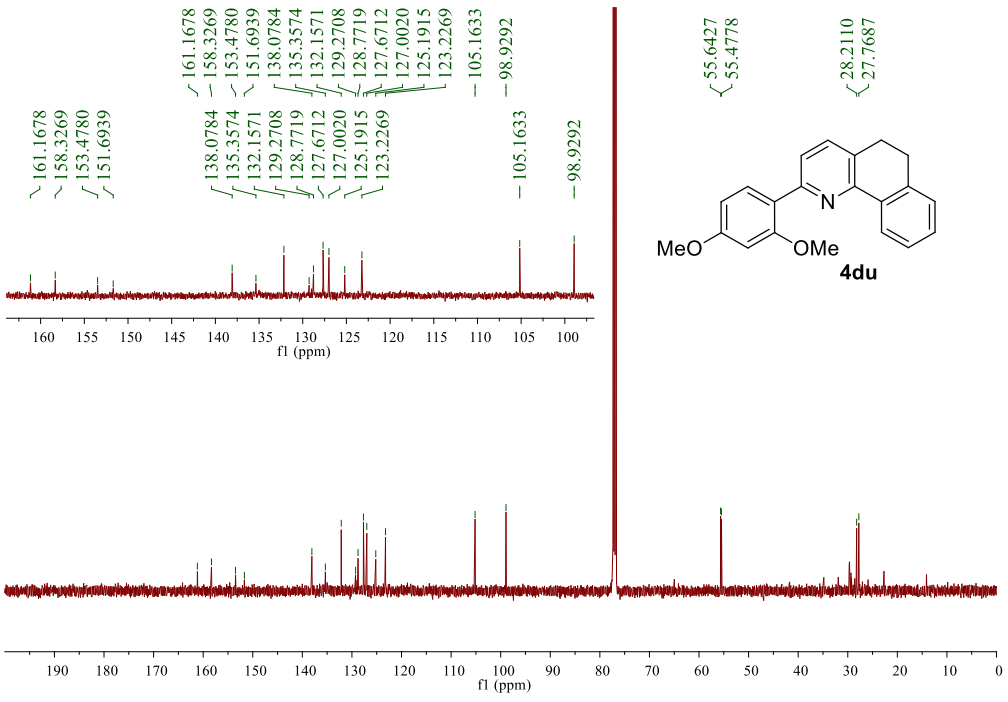


Figure 2.94. 125 MHz ^{13}C Spectrum of **4du** in $CDCl_3$

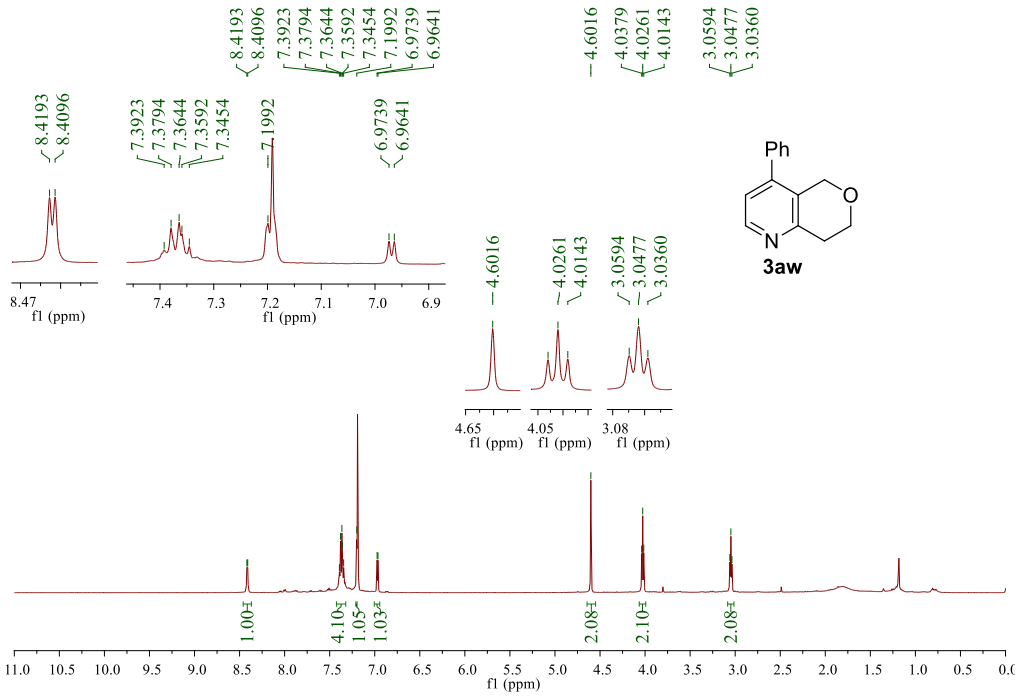


Figure 2.95. 500 MHz ^{1}H Spectrum of **3aw** in $CDCl_3$

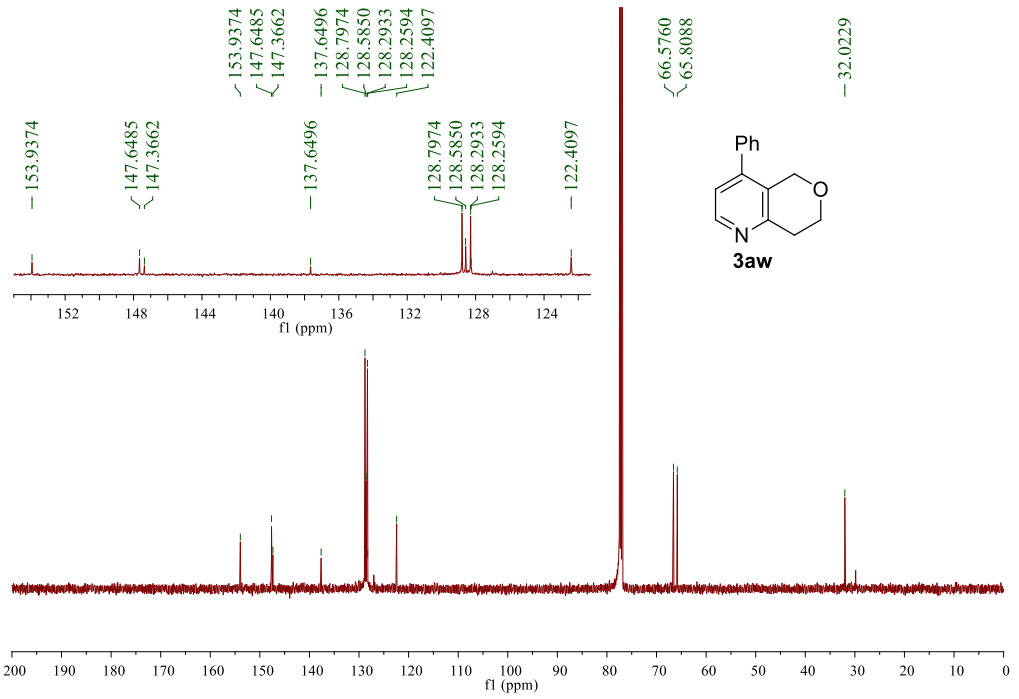


Figure 2.96. 125 MHz ^{13}C Spectrum of **3aw** in $CDCl_3$

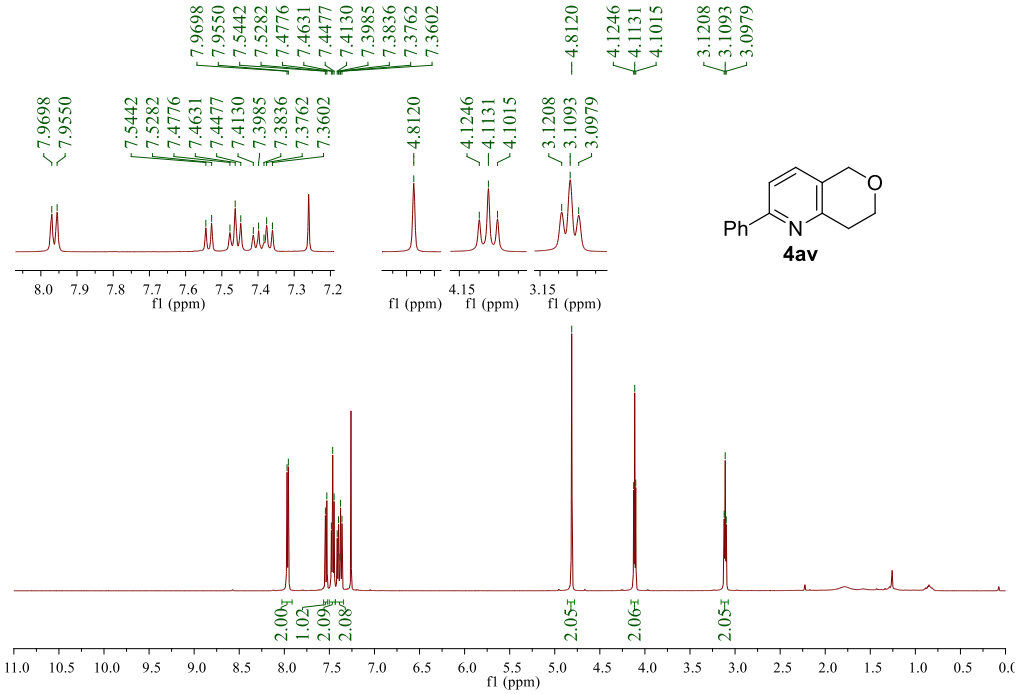


Figure 2.97. 500 MHz ^{1}H Spectrum of **4av** in $CDCl_3$

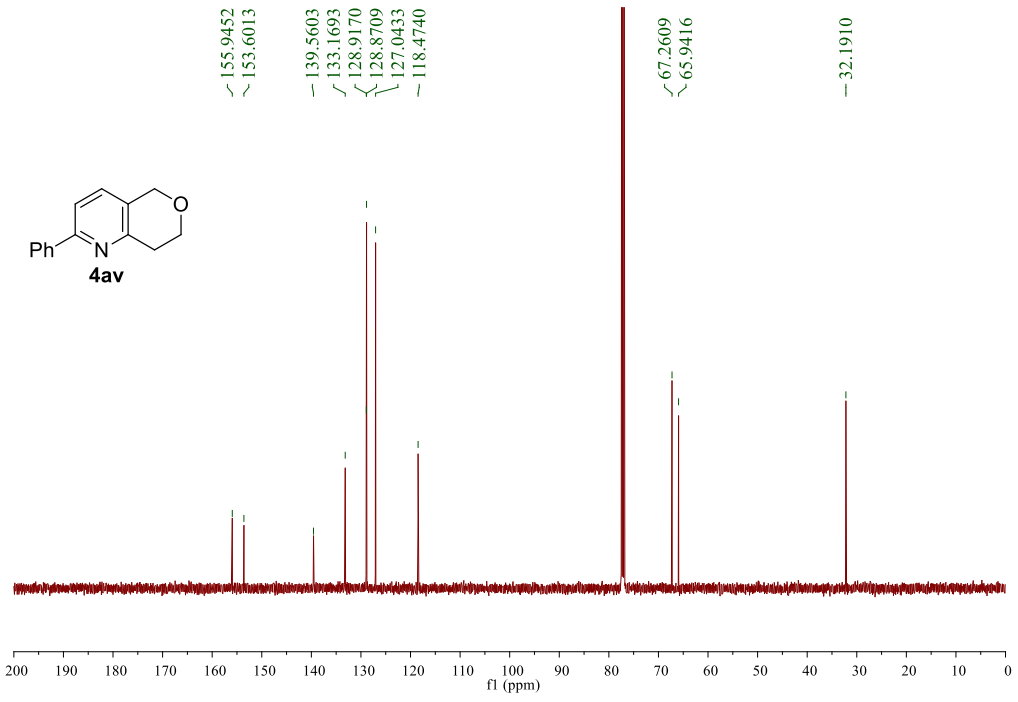


Figure 2.98. 125 MHz ^{13}C Spectrum of **4av** in $CDCl_3$

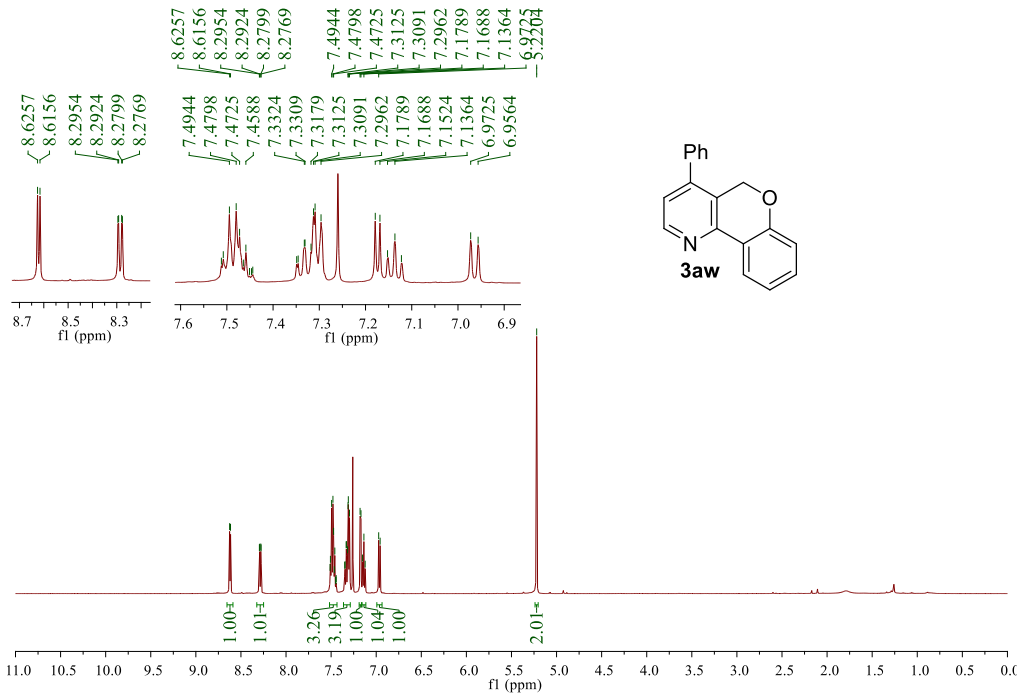


Figure 2.99. 500 MHz ^{1}H Spectrum of **3aw** in $CDCl_3$

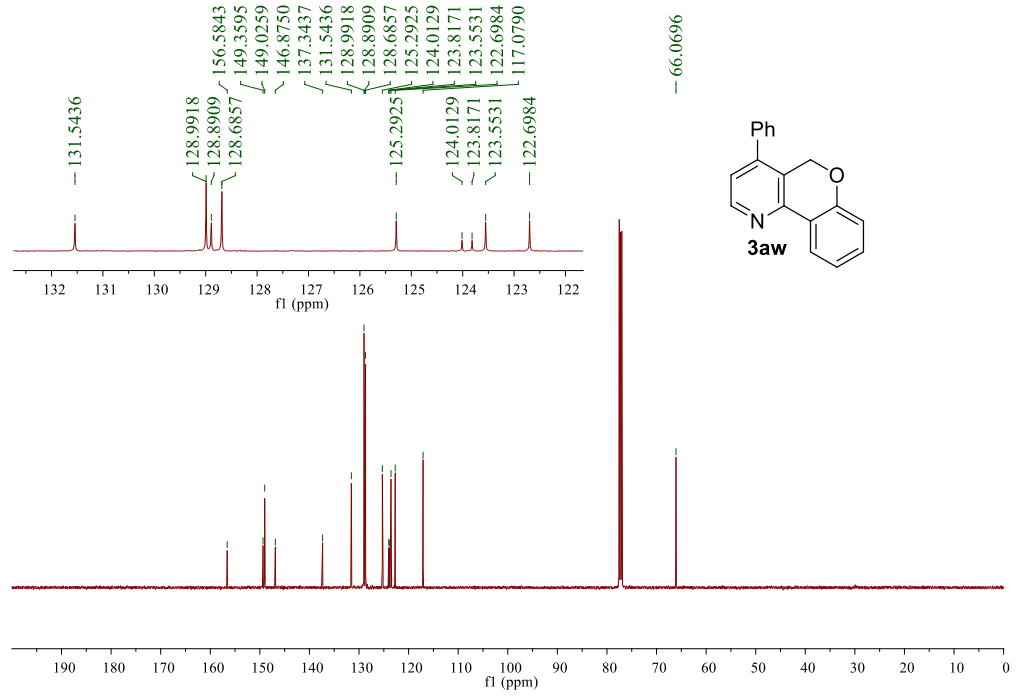


Figure 2.100. 125 MHz ^{13}C Spectrum of **3aw** in $CDCl_3$

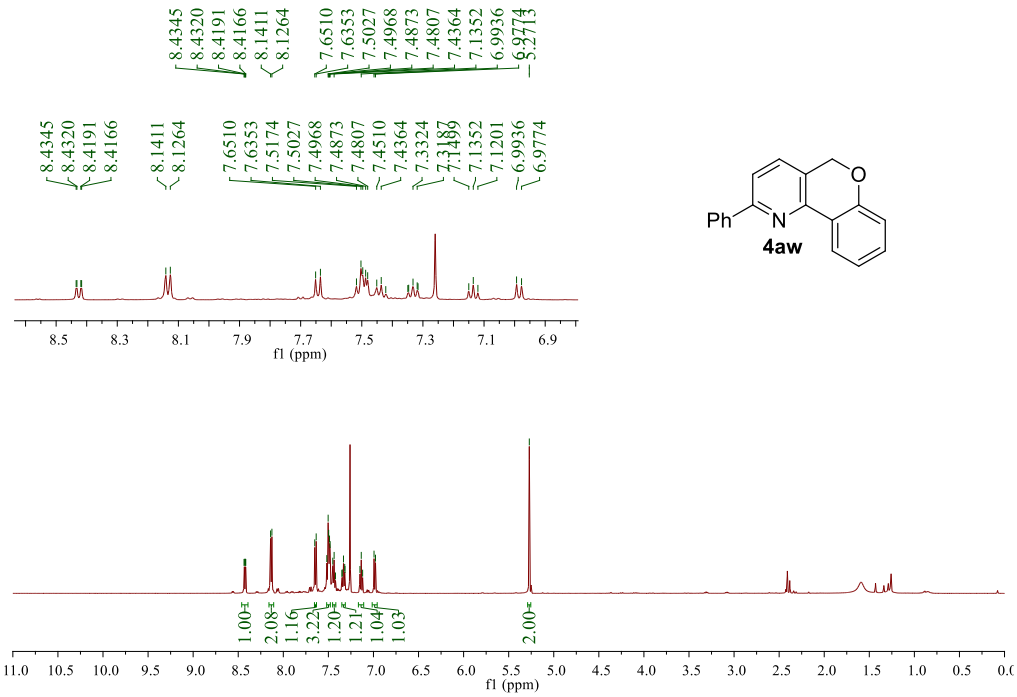


Figure 2.101. 500 MHz ^{1}H Spectrum of **4aw** in $CDCl_3$

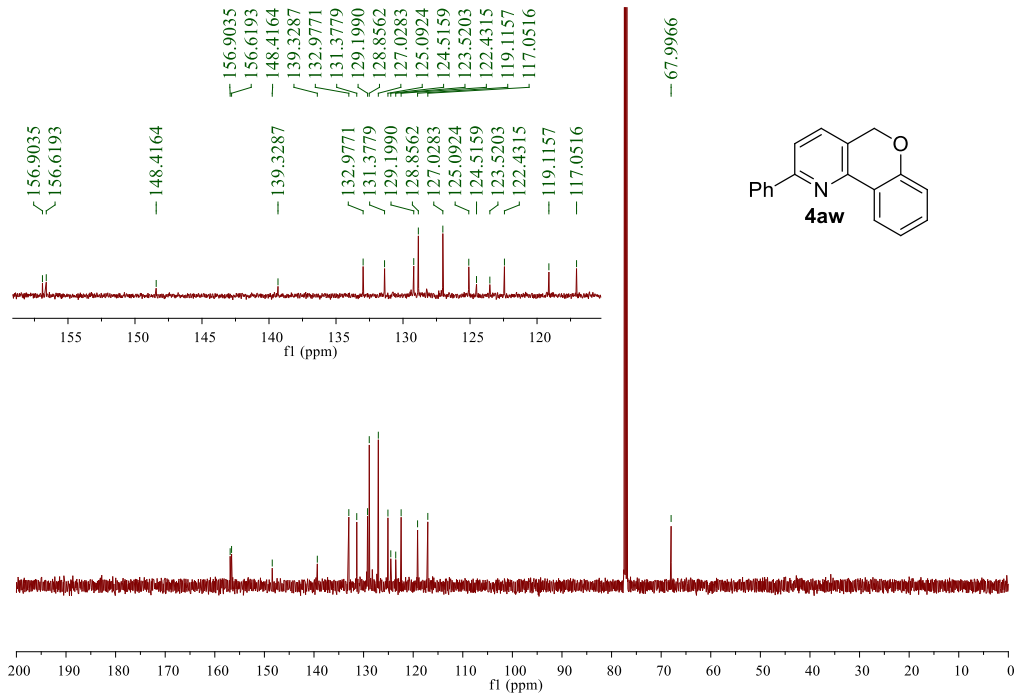


Figure 2.102. 125 MHz ^{13}C Spectrum of **4aw** in $CDCl_3$

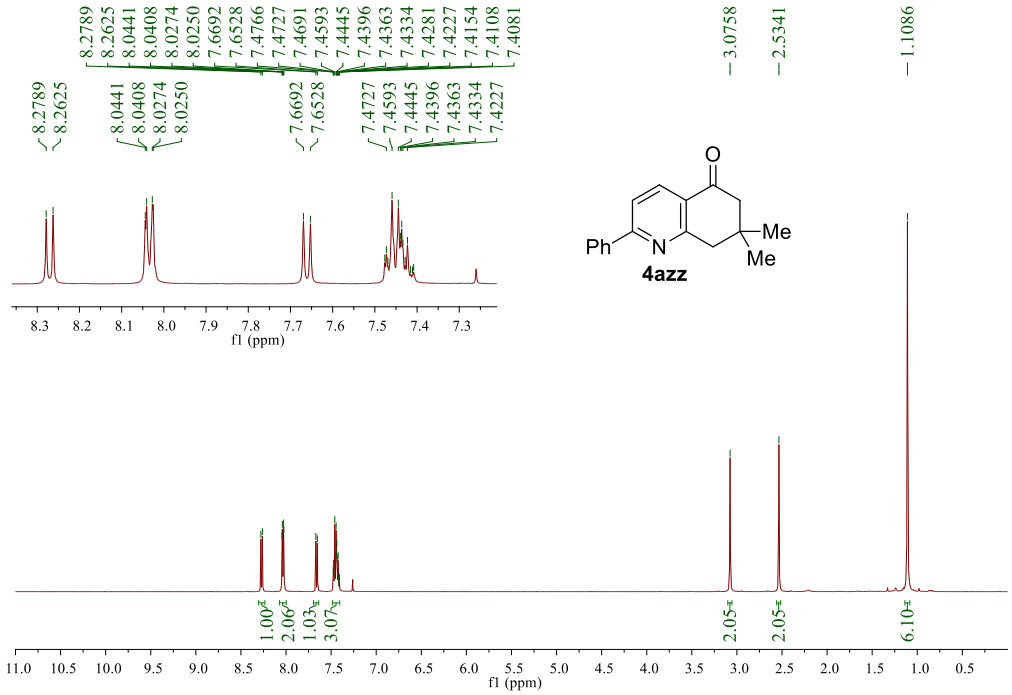


Figure 2.103. 500 MHz ^{1}H Spectrum of **4azz** in $CDCl_3$

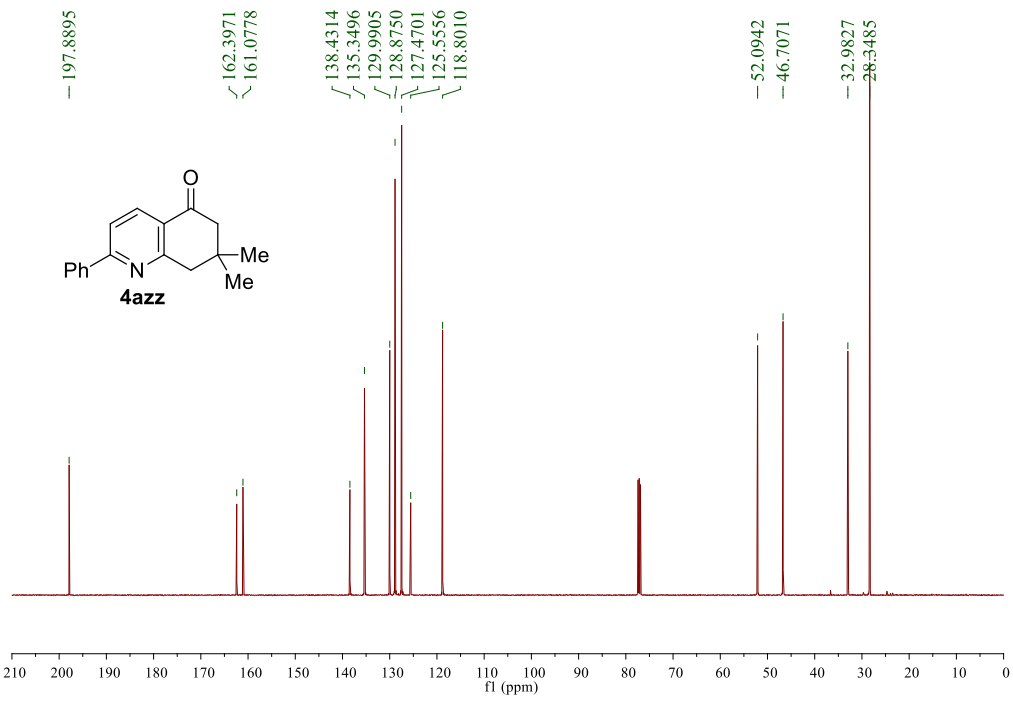


Figure 2.104. 125 MHz ^{13}C Spectrum of **4azz** in $CDCl_3$

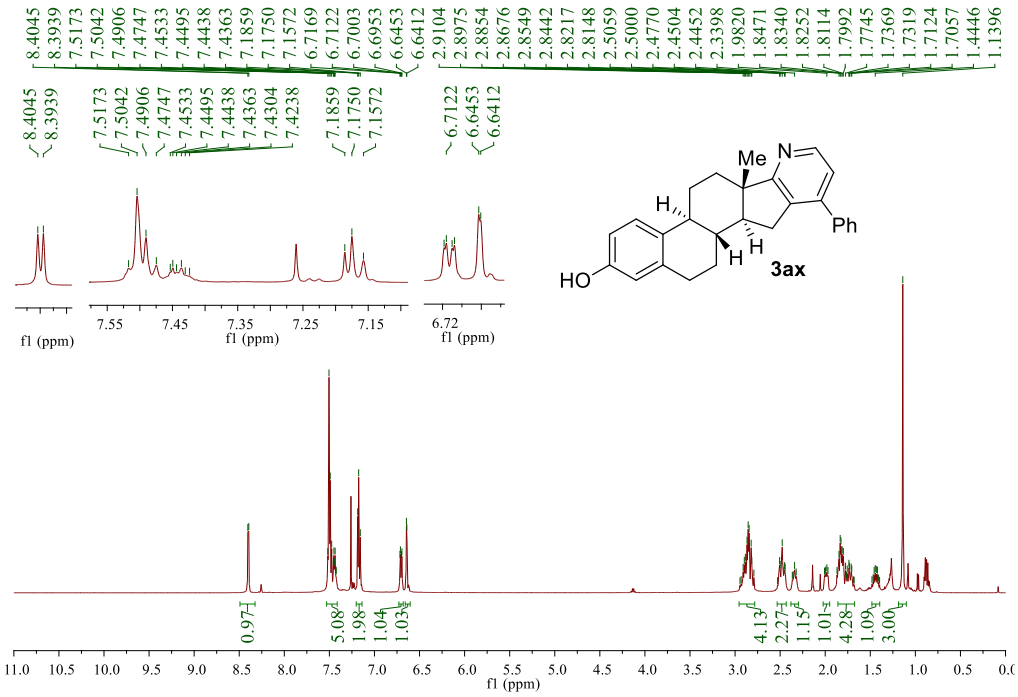


Figure 2.105. 500 MHz ^{1}H Spectrum of **3ax** in $CDCl_3$

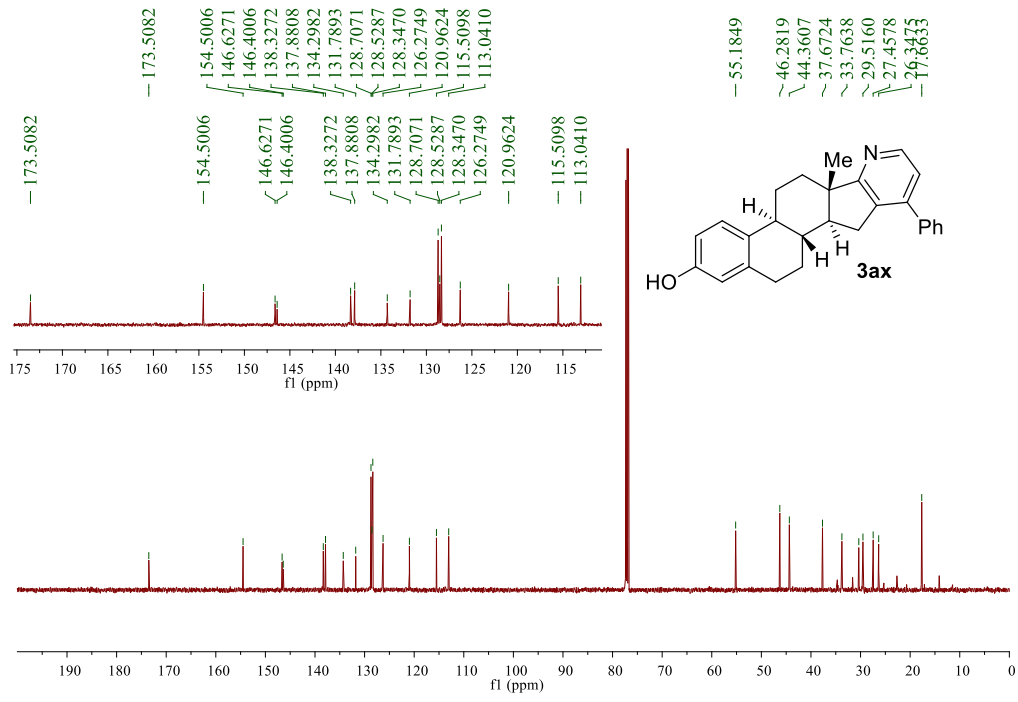


Figure 2.106. 125 MHz ^{13}C Spectrum of **3ax** in $CDCl_3$

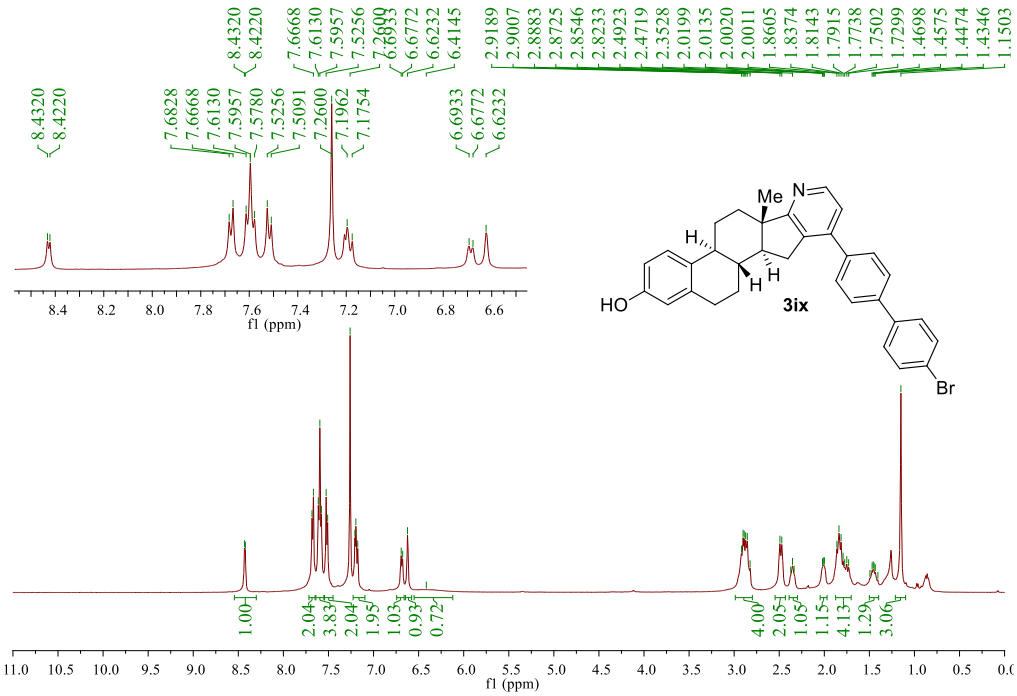


Figure 2.107. 500 MHz ^{1}H Spectrum of **3ix** in $CDCl_3$

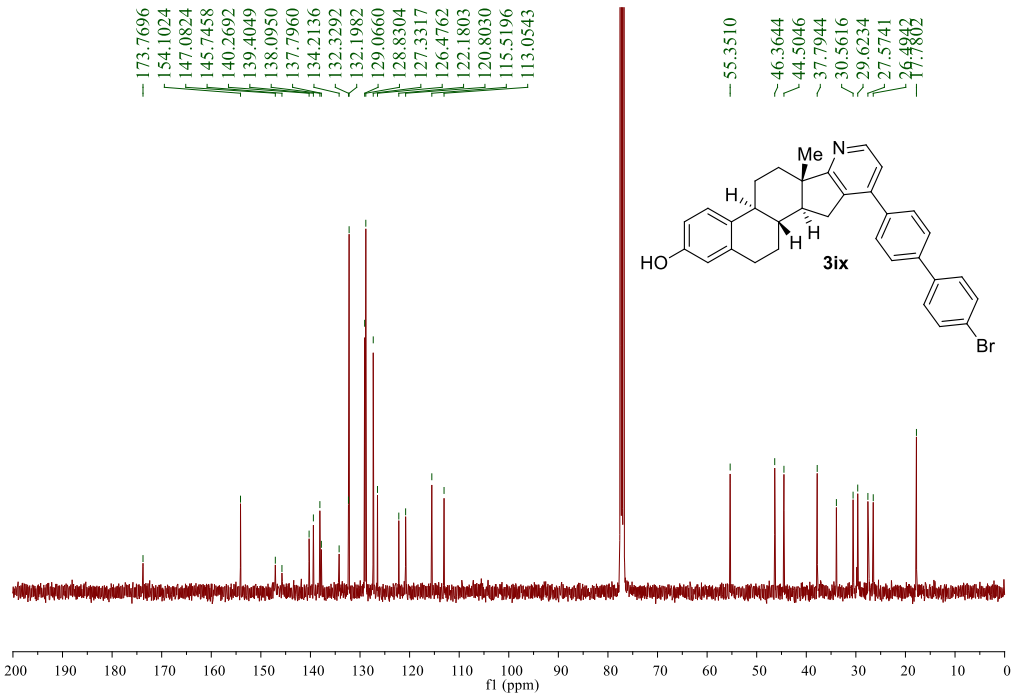


Figure 2.108. 125 MHz ^{13}C Spectrum of **3ix** in $CDCl_3$

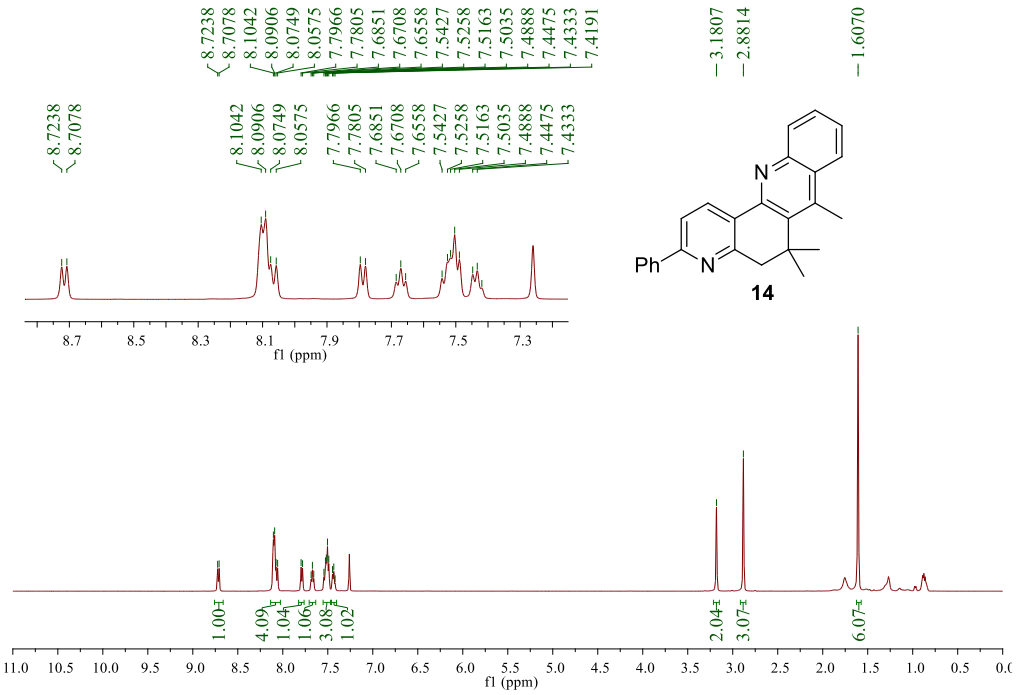


Figure 2.109. 500 MHz ^{1}H Spectrum of **14** in $CDCl_3$

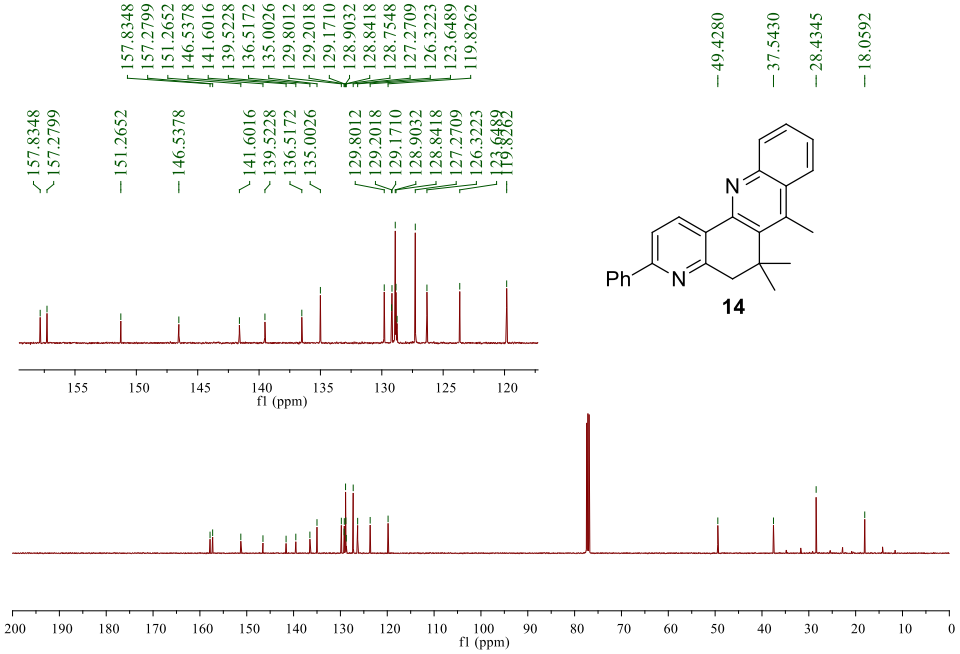


Figure 2.110. 125 MHz ^{13}C Spectrum of **14** in $CDCl_3$

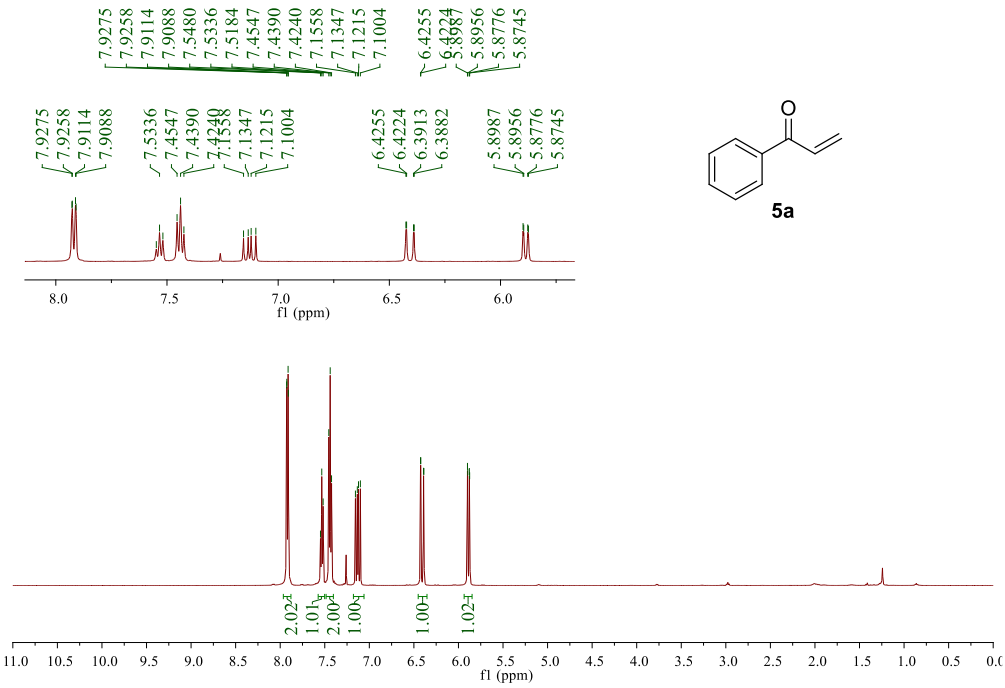


Figure 2.111. 500 MHz ^{1}H Spectrum of **5a** in $CDCl_3$

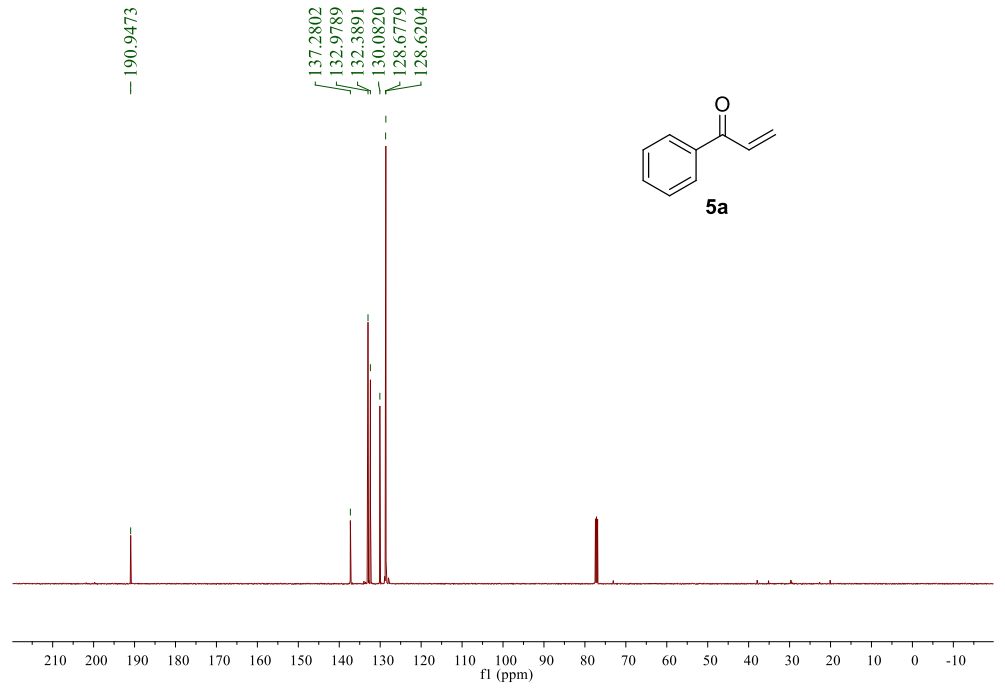


Figure 2.112. 125 MHz ^{13}C Spectrum of **5a** in $CDCl_3$

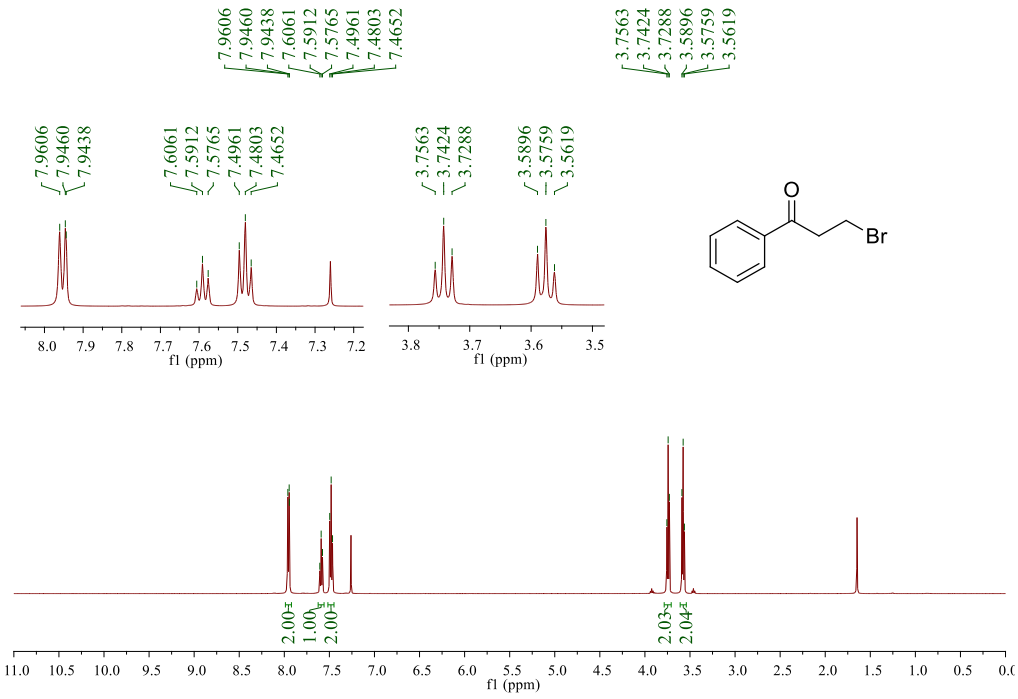


Figure 2.113. 500 MHz ^{1}H Spectrum of **3-bromopropiophenone** in $CDCl_3$

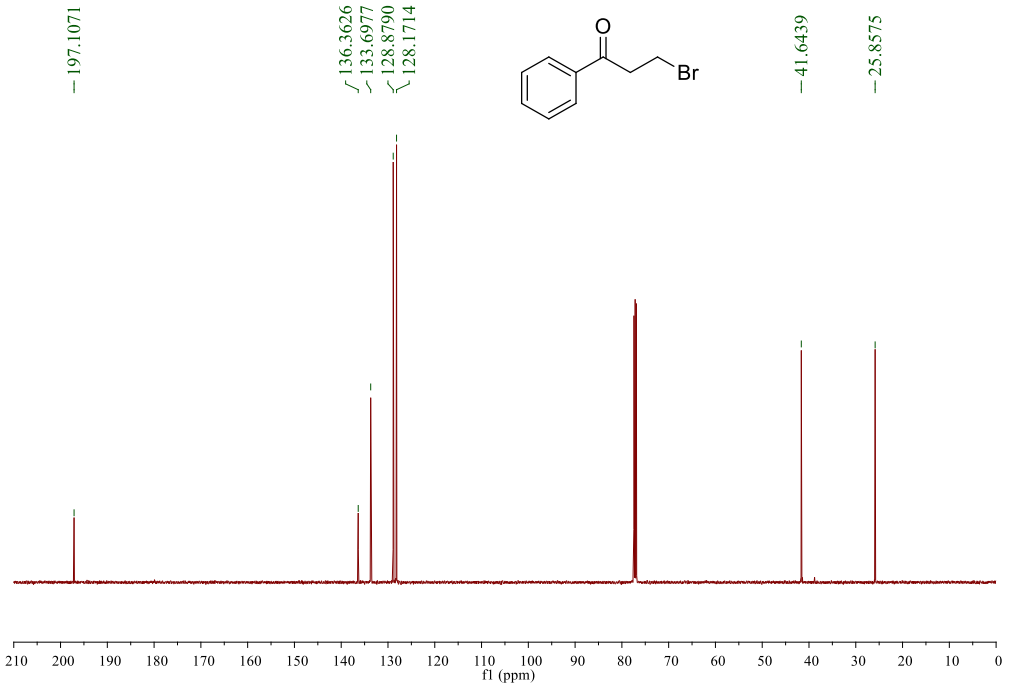


Figure 2.114. 125 MHz ^{13}C Spectrum of **3-bromopropiophenone** in $CDCl_3$

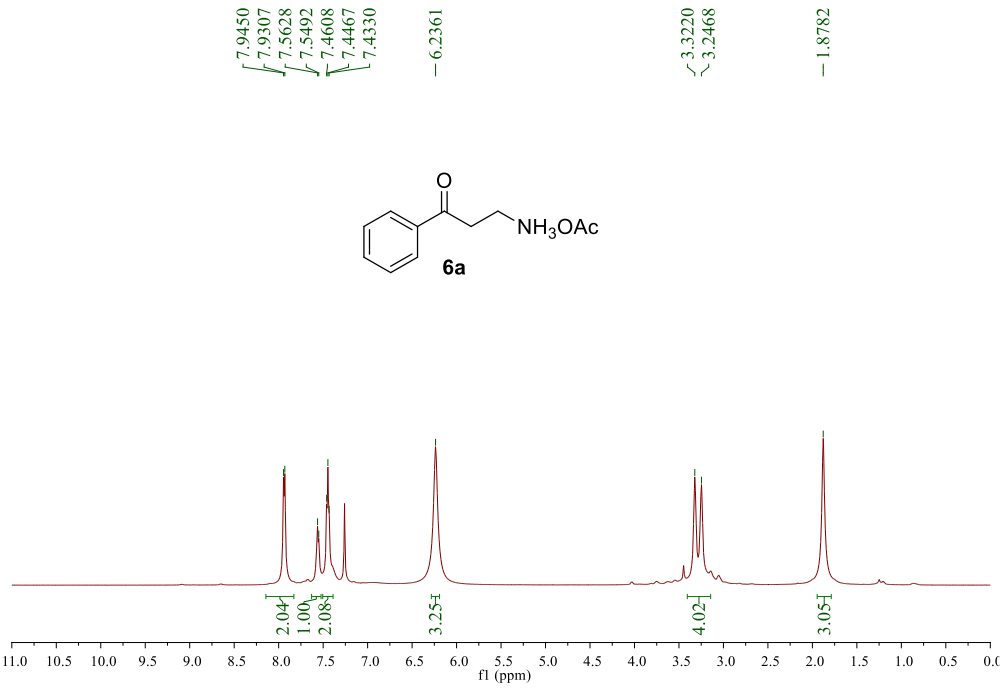


Figure 2.115. 500 MHz ^{1}H Spectrum of **6a** in $CDCl_3$

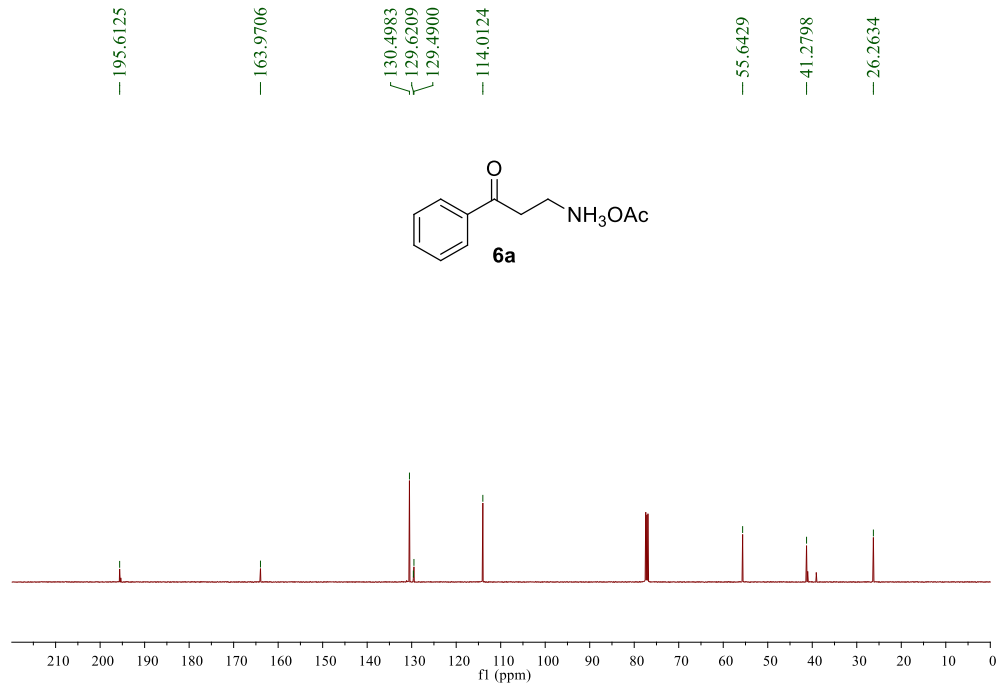


Figure 2.116. 125 MHz ^{13}C Spectrum of **6a** in $CDCl_3$

2.8 References:

1. Henry G. D. (2004), De novo synthesis of substituted pyridines, *Tetrahedron*, *29*, 6043-6061 (DOI: 10.1016/j.tet.2004.04.043)

2. Hill M. D. (2010), Recent strategies for the synthesis of pyridine derivatives, *Chem. Eur. J.*, *16*, 12052-12062 (DOI: 10.1002/chem.201001100

3. Khan E. (2021), Pyridine derivatives as biologically active precursors; organics and selected coordination complexes, *Chemistry Select*, *6*, 3041-3064 (DOI: 10.1002/slct.202100332)

4. Michael J. P. (2005), Quinoline, quinazoline and acridone alkaloids, *Nat. Prod. Rep.*, *22*, 627-646 (DOI: 10.1039/B413750G)

5. Sinthupoom N., Prachayasittikul V., Prachayasittikul S., Ruchirawat S. and Prachayasittikul V. (2015), Nicotinic acid and derivatives as multifunctional pharmacophores for medical applications, *Eur. Food Res. Technol.*, *240*, 1-17 (DOI: 10.1007/s00217-014-2354-1)

6. Guan A. Y., Liu C. L., Sun X. F., Xie Y. and Wang M. A. (2016), Discovery of pyridine-based agrochemicals by using intermediate derivatization methods, *Bioorg. Med. Chem.*, *24*, 342-353 (DOI: 10.1016/j.bmc.2015.09.031)

7. Longstreet A. R., Opalka S. M., Campbell B. S., Gupton B. F. and McQuade D. T. (2013), Investigating the continuous synthesis of a nicotinonitrile precursor to nevirapine, *Beilstein J. Org. Chem.*, *9*, 2570-2578 (DOI: 10.3762/bjoc.9.292)

8. Ling Y., Hao Z. Y., Liang D., Zhang C. L., Liu Y. F. and Wang Y. (2021), The expanding role of pyridine and dihydropyridine scaffolds in drug design, *Drug Des. Devel. Ther.*, *15*, 4289-4338 (DOI: 10.2147/DDDT.S329547)

9. Sasabe H. and Kido J. (2011), Multifunctional materials in high-performance OLEDs: challenges for solid-state lighting, *Chem. Mater.*, *23*, 621-630 (DOI: 10.1021/cm1024052)

10. Zhou G., Wong W. Y. and Yang X. (2011), New Design Tactics in OLEDs Using Functionalized 2-Phenylpyridine-Type Cyclometalates of Iridium(III) and Platinum(II), *Chem. Asian J.*, *6*, 1706-1727 (DOI: 10.1002/asia.201000928)

11. Sumby C. J. (2011), Bridging ligands comprising two or more di-2-pyridylmethyl or amine arms: Alternatives to 2,2′-bipyridyl-containing bridging ligands, *Coord. Chem. Rev.*, *255*, 1937-1967 (DOI: 10.1016/j.ccr.2011.03.015)

12. Tseberlidis G., Intrieri D. and Caselli A. (2017), Catalytic Applications of Pyridine-Containing Macrocyclic Complexes, *Eur. J. Inorg. Chem.*, *2017*, 3589-3603 (DOI: 10.1002/ejic.201700633)

13. Yazıcıoğlu E.Y. and Tanyeli C. (2012), A method for the synthesis of pyridine-based C_2-symmetrical chiral nucleophilic organocatalysts via Pd-catalyzed coupling, *Tetrahedron: Asymmetry*, *23*, 1694-1699 (DOI: 10.1016/j.tetasy.2012.11.007)

14. Mishra A. and Gupta R. (2014), Supramolecular architectures with pyridine-amide based ligands: discrete molecular assemblies and their applications, *Dalton Trans.*, *43*, 7668-7682 (DOI: 10.1039/C4DT00277F)

15. Wise M. D., Ruggi A., Pascu M., Scopelliti R. and Severin K. (2013), Clathrochelate-based bipyridyl ligands of nanoscale dimensions: easy-to-access building blocks for supramolecular chemistry, *Chem. Sci.*, *4*, 1658-1662 (DOI: 10.1039/C3SC50155H)

16. Wu D., Zhi L., Bodwell G. J., Cui G., Tsao N. and Müllen K. (2007), Self-assembly of positively charged discotic PAHs: from nanofibers to nanotubes, *Angew. Chem.*, *119*, 5513-5516 (DOI: 10.1002/ange.200700515)

17. Uredi D., Motati D. R. and Watkins E. B. (2019), A simple, tandem approach to the construction of pyridine derivatives under metal-free conditions: a one-step synthesis of the monoterpene natural product,(−)-actinidine, *Chem. Comm.*, *55*, 3270-3273 (DOI: 10.1039/C9CC01097A)

18. Hirai S., Horikawa Y., Asahara H. and Nishiwaki N. (2017), Tailor-made synthesis of fully alkylated/arylated nicotinates by $FeCl_3$-mediated condensation of enamino esters with enones, *Chem. Comm.*, *53*, 2390-2393 (DOI: 10.1039/C7CC00051K)

19. Shabalin D. A. (2021), Recent advances and future challenges in the synthesis of 2,4,6-triarylpyridines, *Org. Biomol. Chem.*, *19*, 8184-8204 (DOI: 10.1039/D1OB01310F)

20. Bai Y., Tang L., Huang H. and Deng G. J. (2015), Synthesis of 2,4-diarylsubstituted-pyridines through a Ru-catalyzed four component reaction, *Org. Biomol. Chem.*, *13*, 4404-4407 (DOI: 10.1039/C5OB00162E)

21. Wu X., Zhang J., Liu S., Gao Q. and Wu A. (2016), An Efficient Synthesis of Polysubstituted Pyridines via C–H Oxidation and C–S Cleavage of Dimethyl Sulfoxide, *Adv. Synth. Catal.*, *358*, 218-225 (DOI: 10.1002/adsc.201500683)

22. Huang H., Cai J., Tang L., Wang Z., Li F. and Deng G. J. (2016), Metal-free assembly of polysubstituted pyridines from oximes and acroleins, *J. Org. Chem.*, *81*, 1499-1505 (DOI: 10.1021/acs.joc.5b02624)

23. Chen G., Wang Z., Zhang X. and Fan X. (2017), Synthesis of functionalized pyridines via Cu(II)-catalyzed one-pot cascade reactions of inactivated saturated ketones with electron-deficient enamines, *J. Org. Chem.*, *82*, 11230-11237 (DOI: 10.1021/acs.joc.7b01901)

24. Gujjarappa R., Vodnala N. and Malakar C. C. (2020), Decarboxylative cyclization of amino acids towards the Regioselective synthesis of 2, 4-diarylpyridines via relay Fe(III)/In(III)-catalysis, *Tetrahedron Lett.*, *61*, 151495 (DOI: 10.1016/j.tetlet.2019.151495)

25. Fischer D. S., Allan G. M., Bubert C., Vicker N., Smith A., Tutill H. J., Purohit A., Wood L., Packham G., Mahon M. F. and Reed M. J. (2005), E-ring modified steroids as novel potent inhibitors of 17β-hydroxysteroid

dehydrogenase type 1, *J. Med. Chem.*, *48*, 5749-5770 (DOI: 10.1021/jm050348a)

26. Song Z., Huang X., Yi W. and Zhang W. (2016), One-pot reactions for modular synthesis of polysubstituted and fused pyridines, *Org. Lett.*, *18*, 5640-5643 (DOI: acs.orglett.6b02883)

27. Roopan S. M., Bharathi A., Palaniraja J., Anand K. and Gengan R. M. (2015), Unexpected regiospecific Michael addition product: synthesis of 5, 6-dihydrobenzo[1,7]phenanthrolines, *RSC Adv.*, *5*, 38640-38645 (DOI: 10.1039/C4RA16640J)

28. Huang H., Cai J., Tang L., Wang Z., Li F. and Deng G. J. (2016), Metal-free assembly of polysubstituted pyridines from oximes and acroleins, *J. Org. Chem.*, *81*, 1499-1505 (DOI: 10.1021/acs.joc.5b02624)

29. Wang S. W., Guo W. S., Wen L. R. and Li M. (2014), A new approach to pyridines through the reactions of methyl ketones with 1,2,4-triazines, *RSC Adv.*, *4*, 59218-59220 (DOI: 10.1039/C4RA11294F)

30. Zhan J. L., Wu M. W., Wei D., Wei B. Y., Jiang Y., Yu W. and Han B. (2019), 4-HO-TEMPO-catalyzed redox annulation of cyclopropanols with oxime acetates toward pyridine derivatives, *ACS Catal.*, *9*, 4179-4188 (DOI: 10.1021/acscatal.9b00832)

Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Published on 11 August 2022. Downloaded by IIT Indore , Central Library on 9/2/2022 10:29:31 AM.

Check for updates

Cite this: *Org. Biomol. Chem.*, 2022, **20**, 6759

Received 4th July 2022,
Accepted 10th August 2022

DOI: 10.1039/d2ob01193j

rsc.li/obc

Regioselective access to di- and trisubstituted pyridines *via* a metal-oxidant-solvent-free domino reaction involving 3-chloropropiophenones†

Ashvani Kumar Patel, Shikha Singh Rathor and Sampak Samanta *

A remarkable metal-oxidant-solvent- and base-free domino route for regioselective access to a wide range of 2,4-di- and 2,3,4/6-trisubstituted pyridines including carbo- and heterocyclic fused pyridines is reported. This [3C + 2C + 1N] cyclization reaction occurs between 3-chloropropiophenones (3C units), enolizable acyclic/cyclic ketones (2C sources) and NH_4OAc as a robust N source under neat conditions under an open atmosphere, producing new C=C and C=N–C bonds in highly chemo- and regioselective manners. Interestingly, this eco-friendly method has many positive features: excellent functional group tolerance, broad substrate scope, good to excellent regioselectivities, promising yields, no-unwanted products, neutral reaction conditions and appropriateness for large-scale synthesis. Mechanism studies reveal that the *in situ* generated β-amino ketone from 3-chloropropiophenone and an ammonium salt undergoes C=N bond formation with a ketone followed by an intramolecular cyclization process (C=C bond), which are the decisive steps for pyridine synthesis.

Pyridines are certainly one of the most cherished N-containing heteroaromatic building blocks.[1,2] These six-membered azaarenes are structural components of many biologically active natural alkaloids,[3] clinically accepted pharmaceuticals,[4] agrochemicals,[5] and lifesaving medicines.[6] Moreover, they are also the precursors of bioceuticals vitamins [B_3 (niacin), B_6 (pyridoxine)], nicotine and pyridine nucleotides [nicotinamide adenine dinucleotide (NAD)/NADPH as coenzymes], which have vital roles in energy metabolism and other biochemical processes.[7] Besides, pyridine scaffolds have a wide range of renowned applications in ligand synthesis for producing inorganic complexes,[8] novel catalytic symmetric and asymmetric organic transformations,[9] functional materials,[10] and supramolecular chemistry due to their π-stacking ability.[11] Considering their inescapable roles in chemical science, the development of a simple metal-free-based flexible protocol for accessing a myriad of pyridines with diverse functionalities using easily accessible inexpensive reactants under benign conditions is an alluring research object for organic and medicinal chemists.[12] Since the discovery of pyridine,[13] researchers worldwide have made colossal contributions to designing and constructing various value-added pyridine derivatives. For this purpose, Hantzsch,[14] Chichibabin,[15] and other groups[16] independently established a broad spectrum of classical methods based on the condensation–cyclization reactions between amines (or ammonia) and enolizable ketones/aliphatic aldehydes to prepare symmetrical and unsymmetrical pyridines. Moreover, various contemporary techniques have been extensively investigated aimed at different types of structurally complex pyridines. These methods cover several transition metal-salt-catalyzed [4 + 2][17]/[2 + 2 + 2][18,19] cycloaddition reactions between alkynes and nitriles/unsaturated oximes/enamides, 6π-electrocyclization,[20] C–H functionalization on the pyridine rings,[21] and multicomponent reactions.[22] Despite the magnificent advances, the above methods have a few practical snags: the use of non-commercial complex reactants, harsh reaction conditions, low tolerance of functionalities and unsatisfactory yields. Alternatively, many improvised methods have also been developed that afforded a variety of di- and trisubstituted pyridines from very simple and cheap reactants like ketones or ketoximes having an enolizable α-Csp^3–H group and N-sourcing agents to overcome the above shortcomings.[23,24] For example, the Wu and Deng groups independently discovered efficient transition-metal salt-assisted domino reactions between aryl methyl ketones and a large excess of ammonium salts in DMSO or DMF as the carbon source for pyridine synthesis as well as the solvent using stoichiometric amounts of $Cu(NO_3)_2{\cdot}3H_2O/I_2$ [23a] or catalytic amounts of $RuCl_3$ [23b] at 130 °C, capable of producing 2,4-diarylpyridines (Scheme 1a). Similarly, Malakar *et al.* synthesized a series of 2,4-disubstituted pyridines regioselectively by utilizing easily available α-amino acids as C–N bond sources and nonactivated aryl alkyl ketones in DMSO or DMF at 120 °C in

Department of Chemistry, Indian Institute of Technology Indore, Simrol, 453552, India. E-mail: sampaks@iiti.ac.in

†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2ob01193j

This journal is © The Royal Society of Chemistry 2022

Chapter 3

Organocatalyzed Double C(sp^3)–H Alkylation of Cyclic *N*-Sulfonyl Ketimines with 3-Chloropropiophenones: For Accessing Value-Added 2,3,6-Trisubstituted Pyridines

Chapter 3

Organocatalyzed double C(sp^3)–H alkylation of cyclic *N*-sulfonyl ketimines with 3-chloropropiophenones: for accessing value-added 2,3,6-trisubstituted pyridines

3.1 Introduction

As discussed in previous Chapters 1 and 2, the pyridine motif is pivotal as a structural component in enormous bioactive natural and synthetic alkaloids.[1-3] In this chapter, we are ready to explore a simple and convenient strategy for accessing value-added 2,3,6-trisubstituted pyridines because of their significant specific biological activity such as antitumor, antibacterial,[4] mTOR inhibitor, C-Src kinase inhibitor[5-7] etc. as shown in **Figure 3.1**.

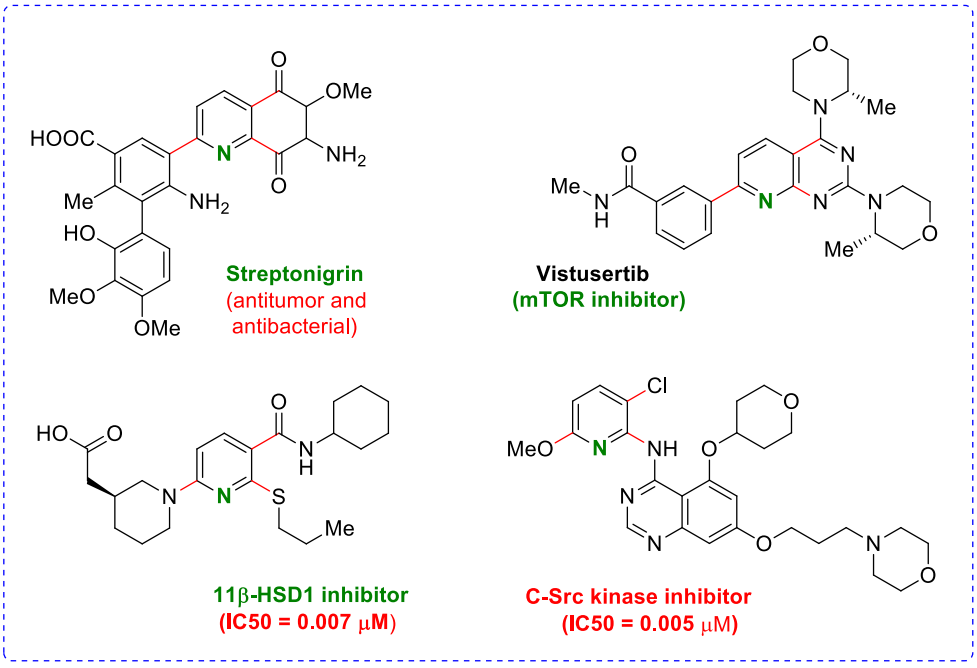


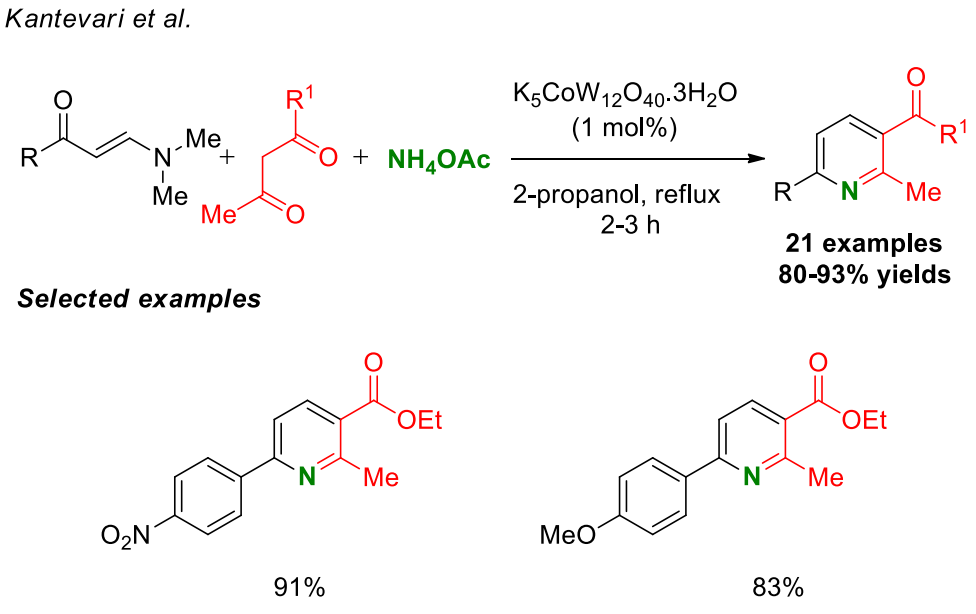
Figure 3.1. Some selected biologically active 2,3,6-trisubstituted pyridines.

3.2 Review Work

The significant applications of trisubstituted pyridines make them a beneficial target for chemists. Thus, numerous methods have been discovered to synthesize various trisubstituted pyridines. Among them, the synthetic methodologies related to the synthesis of 2,3,6-trisubstituted pyridines selectively have been delineated in the below section **(3.2.1).**

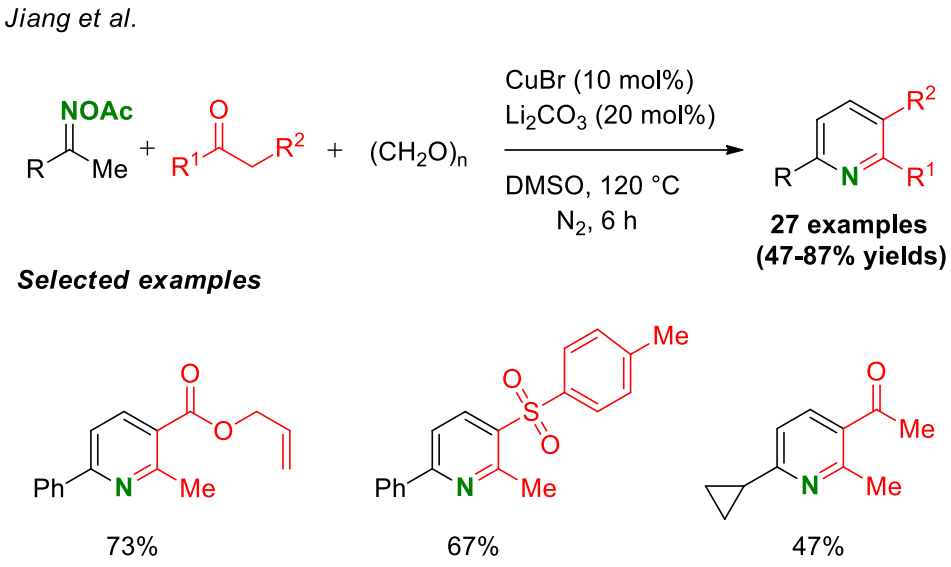
3.2.1 Synthesis of trisubstituted pyridines

In 2007, Kantevari *et al.* reported an efficient one-pot method for the synthesis of trisubstituted pyridines. This method involves using 1,3-dicarbonyls, *β*-enaminoketones, and NH_4OAc catalyzed by $K_5CoW_{12}O_{40}.3H_2O$ in isopropanol under refluxing conditions, providing high to excellent yields (80-93%) of corresponding pyridine derivatives as shown in (**Scheme 3.1**).[8]



Scheme 3.1. One-pot three-component cyclization reaction for accessing to 2,3,6-trisubstituted pyridines.

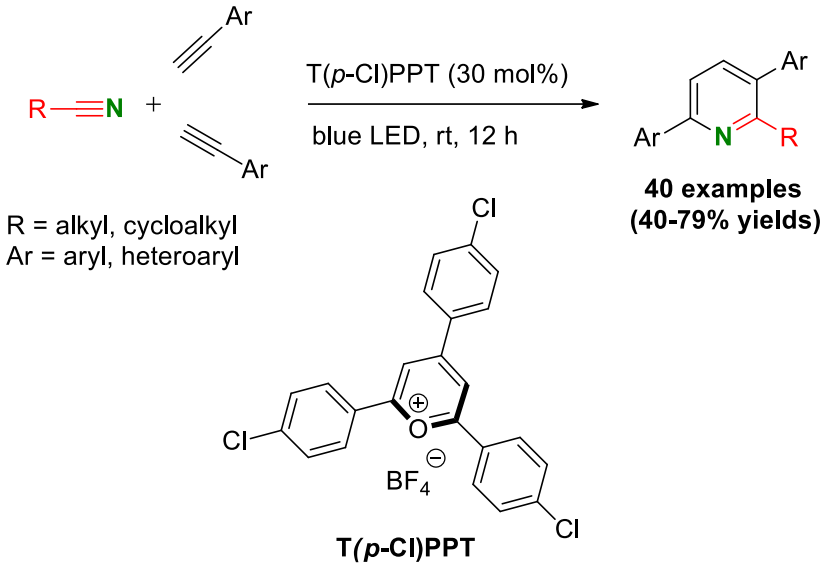
In 2015, Jiang *et al.* reported a Cu-catalyzed three-component annulation reaction between oxime acetates, enolizable ketones, and paraformaldehyde at 120 °C in DMSO to afford a wide range of aryl/heteroaryl/alkyl-substituted pyridines with good to high yields (47-87%) after 6h, as shown in **Scheme 3.2**.[9]



Scheme 3.2. Cu-catalyzed one-pot method for synthesizing 2,4,6-trisubstituted pyridines.

In 2017, Wang *et al.* demonstrated a visible-light-promoted regioselective cycloaddition of aryl alkynes and alkyl nitriles in the presence of pyrylium salt (2,4,6-tris(4-chlorophenyl)pyrylium tetrafluoroborate) as a photoredox catalyst under irradiation blue-LED light at room temperature. This single-electron-transfer process leads to moderate to high yields (40-79%) of trisubstituted pyridines as shown in (**Scheme 3.3**).[10]

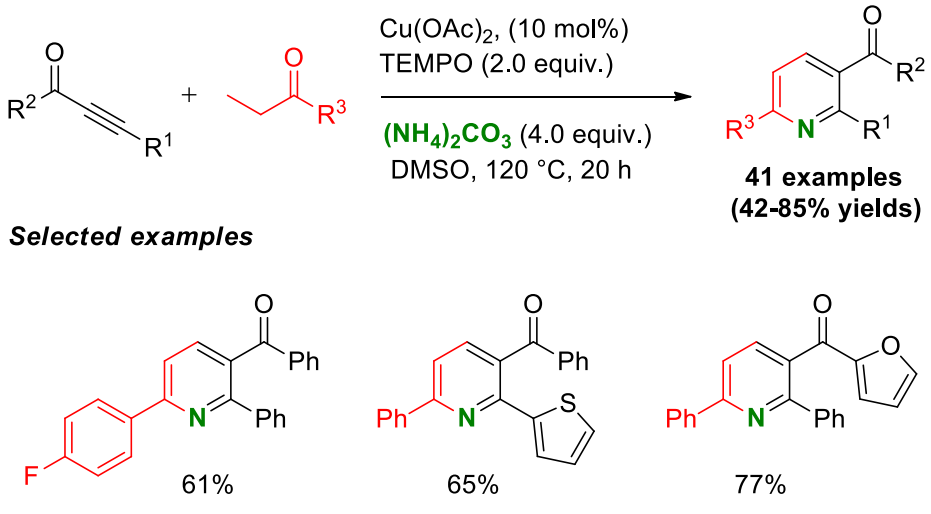
Wang et al.



Scheme 3.3. Photocatalyzed and blue-LED promoted [2 + 2 + 2] cycloaddition of aryl alkynes with nitriles.

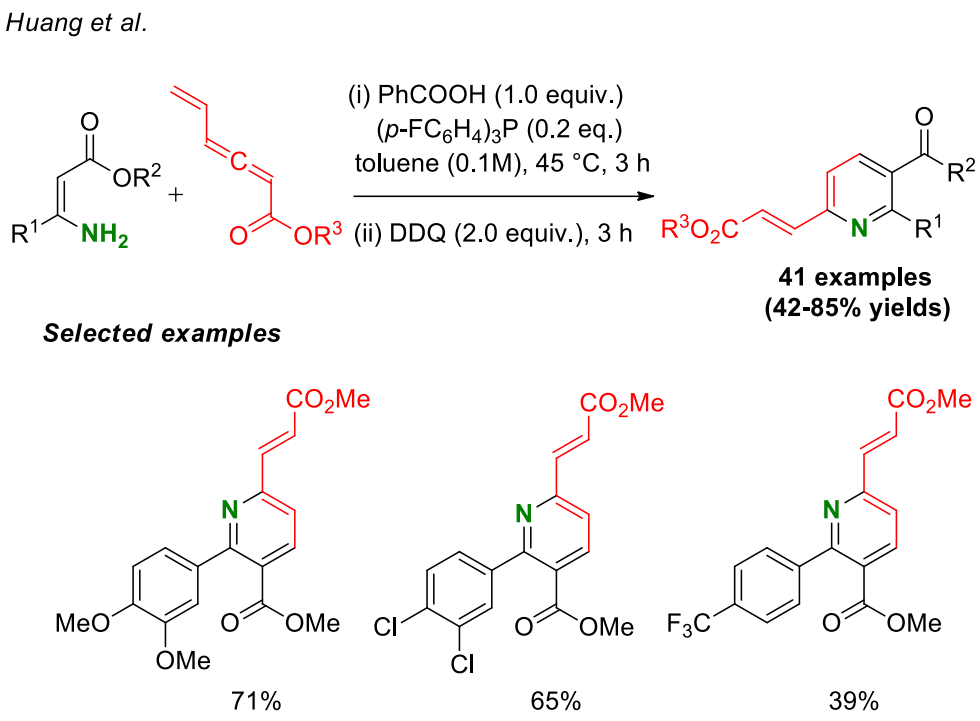
Later on, in 2021, Huang *et al.* accomplished a highly efficient one-pot synthesis of 2,3,6-trisubstituted pyridines through a Cu(II)-catalyzed three-component reaction of saturated ketones, alkynones and ammonium carbonate in the presence of TEMPO at 120 °C. This method affords moderate to good yields (42-85%) and tolerates various functional groups, as illustrated in **Scheme 3.4.**[11]

Huang et al.



Scheme 3.4. Cu(II)-catalyzed three component reaction for the synthesis of 2,4,6-trisubstituted pyridines.

Just after, in 2022, Huang *et al.* developed a one-pot phosphine-catalyzed and DDQ-promoted strategy for the synthesis of trisubstituted pyridines using γ-vinyl allenoates and enamino esters. This two-step sequential reaction proceeds *via* annulation of both the reactants in the presence of the catalyst to give the corresponding tetrahydropyridine derivatives which further oxidize in the presence of DDQ to afford 2,3,6-trisubstituted pyridines in moderate to good yields (42-85%) (**Scheme 3.5**).[12]



Scheme 3.5. Phosphine-catalyzed and DDQ-promoted one-pot synthesis of trisubstituted pyridine

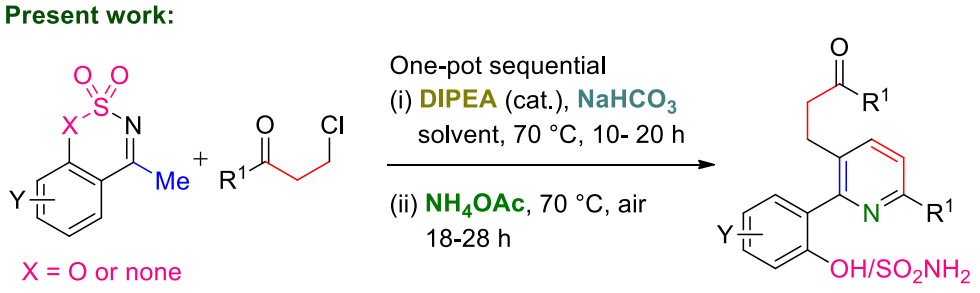
3.2.2 Conclusion

We have seen through this literature survey that several methods have been developed over the years for synthesising trisubstituted pyridines due to their significant scope in different sectors. However, the methodologies developed have a set of disadvantages, such as the use of transition-metal salts, complex

non-commercial starting materials, regioisomer along with unwanted side products, the need for external oxidants and ligands, low yields and scarcity of diverse functional groups. Thus, there is a demand to develop a simple, convenient and eco-friendly method to offer a series of value-added 2,3,6-trisubstituted pyridines from simple cost-effective reactants.

3.3 Present Work

The significance of the pyridine scaffold has been illustrated previously in Chapters 1 and 2. In this context, our immediate priority is to develop a simple metal-oxidant-free empirical approach for the synthesis of 2,3,6-trisubstituted pyridines adorned with worthwhile substituents like benzenesulfonamide, phenols, and propiophenone at relevant places. In the previous chapter, we reported a metal-oxidant-solvent-free domino approach to give access to di- and trisubstituted pyridines by utilizing commercially available 3-chloropropiophenones, enolizable ketones, and NH_4OAc. Herein, we further wish to report a one-pot sequential strategy to 2,3,6-trisubstituted pyridines *via* a double C(sp^3)–H alkylation of *N*-sulfonyl ketimines with 3-chloropropiophenones catalyzed by DIPEA together with $NaHCO_3$ as a cooperative base, followed by [5C+1N] cycloaddition/aerial oxidation in the presence of NH_4OAc as *N*-containing source for pyridine nitrogen as illustrated in **Scheme 3.6**.



Scheme 3.6. Organocatalyzed synthesis of 2,3,6-trisubstituted pyridines adorned with benzenesulfonamides and phenols.

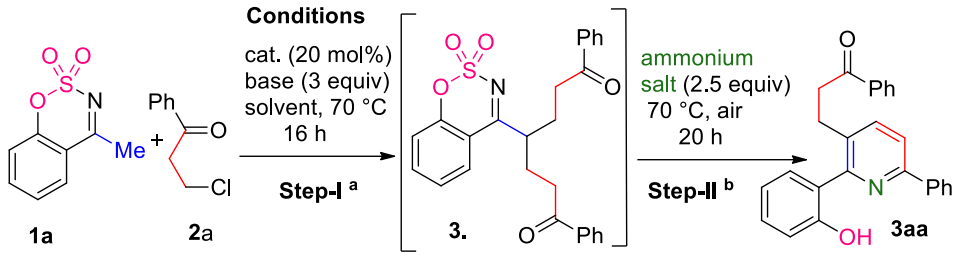
3.4 Results and Discussion

3.4.1 Optimization of reaction conditions

We have commenced the optimization studies by setting forth the model reaction between 3-methyl *N*-sulfonyl ketimine (**1a**), and 3-chloropropiophenones (**2a**) in the presence of DIPEA (3.0 equiv.) in dry 2-MeTHF at 50 °C. After 16 h, we isolated a dialkylated addition product **3** in 90% yield. Further, this dialkylated addition product **3** was subjected to react with NH_4OAc in an open atmosphere at 50 °C with the hope of an aza-cyclization/aerial oxidation reaction. Interestingly, after 30 h of reaction, we endowed a 48% yield of the product **3aa** with a synthetically applicable propiophenone moiety at the C3 position. Further, we performed this two-step reaction in one pot sequentially (without isolating dialkylated addition product **3**); just after the completion of the first step in 16 h, NH_4OAc (2.5 equiv.) was added to the reaction mixture under an open atmosphere at 50 °C. After 36 h of the reaction, same 2-(2-hydroxyphenyl) pyridine (**3aa)** in 45% yield was observed (entry 1, **Table 1**). The product **3aa** was fully characterized by its spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS) and the chemical structure was confirmed by analyzing all the spectroscopic data. The ^{1}H NMR spectrum of **3aa** shows a singlet peak at 11.63 ppm (one proton), two triplet peaks at 3.42 ppm (two protons) and 3.25 ppm (two protons), corresponding to the phenolic OH group at C2 and two consecutive methyl groups at the C3 position of the pyridine, respectively. Peaks appear at 7.98 ppm (doublet) for 2 protons, 7.67 ppm (doublet) for one proton and 7.12 ppm (doublet) for one proton, depicting the occupied position at C6 and two free positions at C4 and C5 of the pyridine, respectively. In addition, other aromatic peaks appear at 7.89-7.85 ppm (multiplet) for 3 protons, 7.58-7.53 ppm (multiplet) for 2 protons, 7.50-7.42 ppm (multiplet) for 5 protons, a triplet at 7.32 ppm for one proton and another triplet at 6.95 ppm for one proton. In the ^{13}C NMR spectrum, peaks appear at 198.7, 39.2 and 27.5 ppm, confirming the presence of the carbonyl group and two consecutive methylene groups of the compound **3aa**. The remaining aromatic peaks appear in the aromatic region (157.1-118.2 ppm) for 19 carbons. Furthermore, the molecular ion peak $[M+H]^+$ appears at 380.1654 in the HRMS spectrum corresponding to the molecular weight (MW

= 379.1572) of the desired product **3aa**, confirming the formation of 2-(2-hydroxyphenyl)pyridine **3aa**.

Table 3.1: Optimization of reaction conditions [a,b]



Entry	Catalyst	Base	Solvent	T°C	NH_4X (2.5 equiv.)	Yield (%)[c]
1[d]	DIPEA	-	2-MeTHF	50	NH_4OAc	45
2[d]	DIPEA	-	2-MeTHF	70	NH_4OAc	75
3	DIPEA	$NaHCO_3$	2-MeTHF	70	NH_4OAc	82
4	DIPEA	$NaHCO_3$	2-MeTHF	70	NH_4HCO_2	83
5	DIPEA	$NaHCO_3$	2-MeTHF	70	NH_4SCN	80
6	DIPEA	$NaHCO_3$	2-MeTHF	70	NH_4HCO_3	12
7	DIPEA	$NaHCO_3$	2-MeTHF	70	$(NH_4)_2CO_3$	10
8	DIPEA	$NaHCO_3$	2-MeTHF	70	NH_4Cl	11
9	DIPEA	$NaHCO_3$	2-MeTHF	70	$(NH_4)_2SO_4$	5
10	Et_3N	$NaHCO_3$	2-MeTHF	70	NH_4OAc	72
11	DABCO	$NaHCO_3$	2-MeTHF	70	NH_4OAc	trace
12	DBU	$NaHCO_3$	2-MeTHF	70	NH_4OAc	59
13	DIPEA	$NaHCO_3$	toluene	70	NH_4OAc	77
14	DIPEA	$NaHCO_3$	MeCN	70	NH_4OAc	74

15	DIPEA	$NaHCO_3$	DMF	70	NH_4OAc	79
16	DIPEA	$NaHCO_3$	DCE	70	NH_4OAc	62
17	DIPEA	$NaHCO_3$	EtOH	70	NH_4OAc	43

[a]Unless otherwise noted, all of the reactions were carried out with **1a** (0.2 mmol, 1.0 equiv), **2a** (0.44 mmol, 2.2 equiv.), organo-base (20 mol%) and $NaHCO_3$ (0.6 mmol) in the specified solvent (2.0 mL) and temperature for 16 h under nitrogen atmosphere. [b]Step-II, after completion of step-I, ammonium salt (0.5 mmol, 2.5 equiv.) was added at the same temperature under air for 20 h. [c]Isolated yield of **3aa** after column chromatography. [d]3.0 equiv. of DIPEA was used.

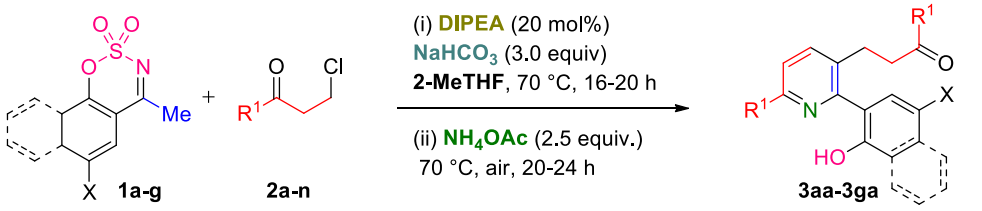
Interestingly, upon elevating the reaction temperature to 70 °C (entry 2), steps I and II progressed effortlessly to confer a 75% yield of **3aa**. However, *N*-sulfonyl ketimine **1a** slightly decomposes under excessive DIPEA. To overcome this, we simultaneously decreased the amount of DIPEA from 300 to 20 mol% for step I, which was counterbalanced by adding 3.0 equivalent of $NaHCO_3$ as a mild, cheap and harmless base for neutralizing acid. In this new cooperative system of DIPEA-$NaHCO_3$, the alkylation reaction proceeded effectively and afterwards, aza-cyclization led to a high yield of pyridine **3aa** (entry 3). After optimizing the first step, we moved toward step II optimization. We screened several common ammonium salts as *N*-containing sources for the pyridine ring formation. Results showed that the weak acid salts (NH_4OAc, NH_4SCN, and NH_4HCO_2) were more or less equally capable of the aza-cyclization reaction, providing high yields of **3aa** (82%, 83%, and 80%, respectively, entries 3-5) as compared to other basic salts [NH_4HCO_2 and $(NH_4)_2CO_3$ with 12% and 10 % yields respectively, entries 6 and 7], and acidic ammonium salts (NH_4Cl and $(NH_4)_2SO_4$) which yields 12% and 5% of **3aa** (entries 8 and 9 respectively). Now, considering the yield and cost of the first three equipotent weak acid salts for this aza-cyclization reaction, we selected NH_4OAc as the best N-containing source for step II. Now we screened for the best organo-base and for that several organo-bases (Et_3N, DBU, and

DABCO) along with $NaHCO_3$ (3.0 equiv.) in 2-MeTHF were tested under present sequential conditions. The results revealed 72% in Et_3N (entry 10) and 59% in DBU (entry 12) yields of **3aa** except DABCO (entry 11). Thus, DIPEA resulted as our best choice for further process. In the end, the screening of organic solvents (toluene, MeCN, DMF, DCE, and EtOH) resulted in moderate to high yields (43-79%, entries 13-17) of **3aa**, with 2-MeTHF (82% yield of **3aa**, entry 3) as our best green solvent for this sequential reaction.

3.4.2 Substrate Scope

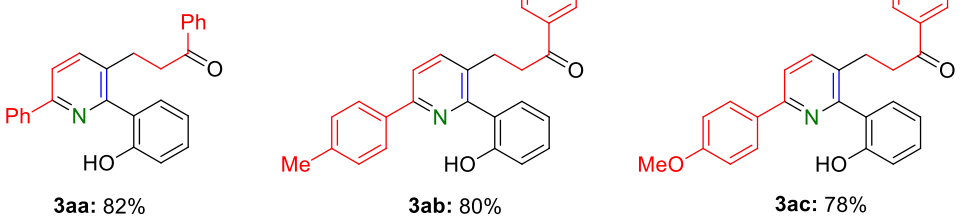
After having the best reaction conditions in hand, we explored the generality and scope of this organocatalyzed sequential reaction involving several 4-methyl *N*-sulfonyl ketimine (**1a-g**), 3-chloropropiophenones (**2a-n**) and NH_4OAc under optimized conditions. The pleasant results are summarized in **Scheme 3.7**. It was observed that ketimine **1a** underwent double Michael reaction effectively with *in-situ* formed aryl/naphthyl vinyl ketones from 3-chloropropiophenones (**2b-2n**) attached with different substituents (Me, OMe, cyclohexyl, 4-BrPh, Cl, Br, and I) on the phenyl ring under combined DIPEA-$NaHCO_3$ conditions. After completion of step II, all led to the corresponding 2-(*ortho*-hydroxyphenyl) pyridines(**3ab-3al**) in satisfactory to high yields (67-83%). On the other hand, sterically hindered 3-chloropropiophenones (**2d, 2e, 2f, 2h,** and **2l**) provided slightly lower yields (67-72%) of the products (**3ad-3al**) with a longer reaction time for step I (**20 h**) as compared to smaller 3-chloropropiophenones (**3ab, 3ac,** and **3ai-3ak;** 76-83% yields; **16 h** for step I). Moreover, propiophenones (**2g, 2m,** and **2n**) having pharmacologically O/S containing heterocycles such as 2,3-dihydro benzofuran, 5-methyl-thiophene and benzo[*b*]thiophene were pleasantly tolerated by this method, offering targeted pyridines **3ag, 3am** and **3an** in 72%, 74% and 71% yields respectively. Now, cyclic ketimines (**1d-1f**) attached with electron-poor halogen atoms (F, Cl, Br) on the phenyl part showed slightly less reactivity

towards double alkylation with a group of 1-aryl/heteroaryl/naphthyl-3-chloropropiophenones compared to electron donating (Me and MeO) propiophenones. Thus, the electron-donating substituents led to 5-8% higher yields of the corresponding 2-(hydroxyaryl) pyridines (**3ba** and **3ca-3cm;** 75-83% yields) than the former ones (**3da, 3ea-3em** and **3fa;** 69-75% yields). Additionally, cyclic imine (**1g**) having bulky 1-hydroxy naphthalene-2-carbaldehyde employed well as a good Michael donor offering 77% yields of **3ga** with a beneficial naphthyl moiety. Now, we have seen that this protocol tolerates various useful functional groups like F, Cl, Br, OH, OMe, Me C=O, thiophene, benzo[*b*]thiophene, 2,3-dihydrobezofuran etc., and offers a group of value-added pyridines which are hard to access or cannot be synthesized by before established procedures.

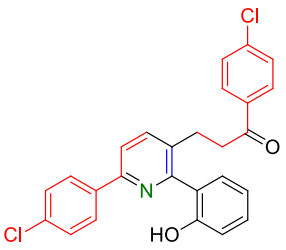


1a: X = H
1b: X = 6-Me
1c: X = 6-MeO
1d: X = 6-F
1e: X = 6-Cl
1f: X = 6-Br
1g: X = H and naphthyl core

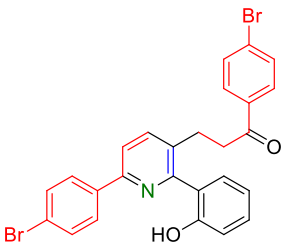
2a: R^1 = Ph
2b: R^1 = 4-MeC_6H_4
2c: R^1 = 4-$MeOC_6H_4$
2d: R^1 = 2,4-$(Me)_2C_6H_3$
2e: R^1 = 2,4-$(MeO)_2C_6H_3$
2f: R^1 = 4-$C_6H_{11}C_6H_4$
2g: R^1 = 2,3-dihydro-benzofuran
2h: R^1 = 4-(4-BrC_6H_4)C_6H_4
2i: R^1 = 4-ClC_6H_4
2j: R^1 = 4-BrC_6H_4
2k: R^1 = 4-IC_6H_4
2l: R^1 = 2-naphthyl
2m: R^1 = 4-$C_6H_{11}C_6H_4$
2n: R^1 = benzo[*b*]thiophene



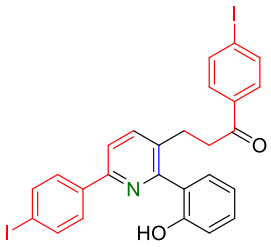
3aa: 82%
3ab: 80%
3ac: 78%



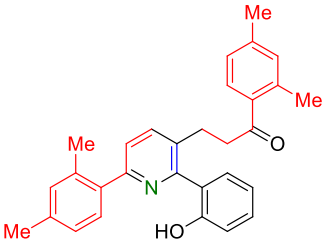
3ai: 83%



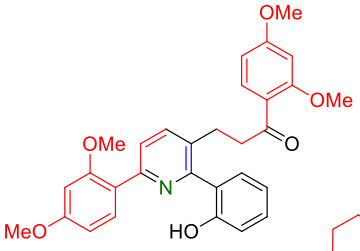
3aj: 80%



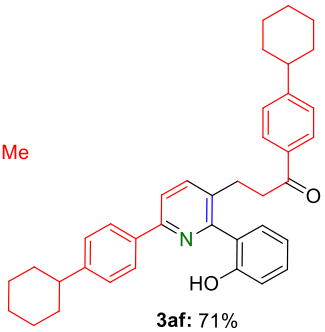
3ak: 76%



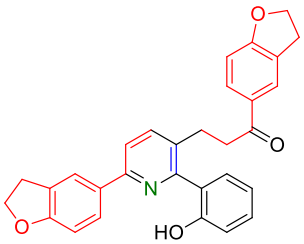
3ad: 82%



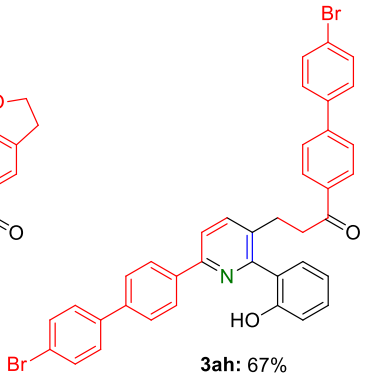
3ae: 70%



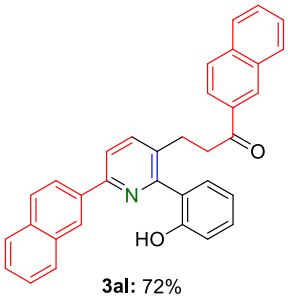
3af: 71%



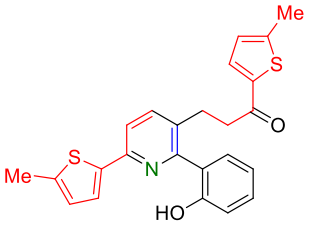
3ag: 72%



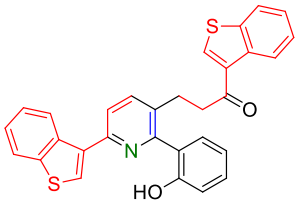
3ah: 67%



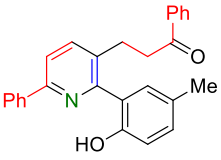
3al: 72%



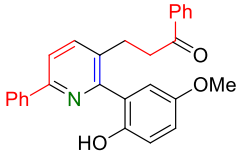
3am: 74%



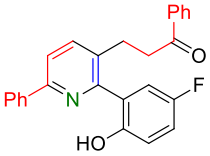
3an: 71%



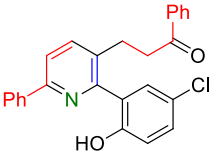
3ba: 83%



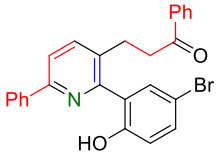
3ca: 81%



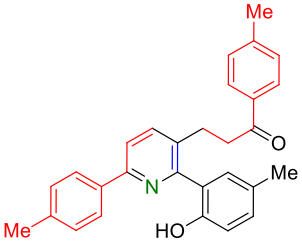
3da: 72%



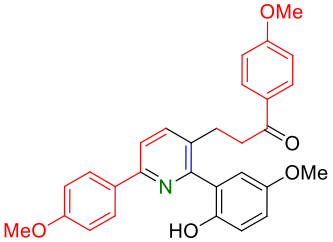
3ea: 75%



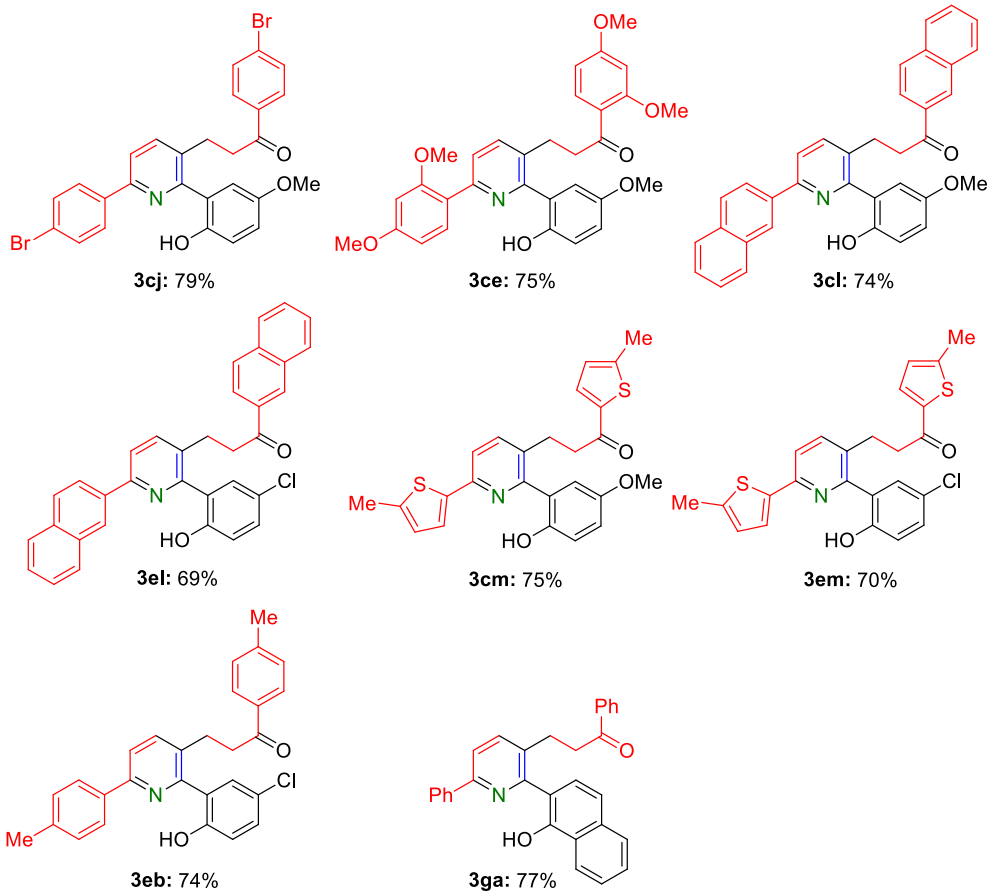
3fa: 74%



3cb: 82%



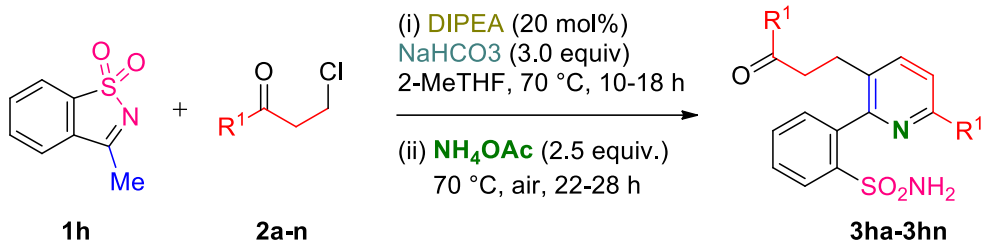
3cc: 83%



Scheme 3.7: Organocatalyzed sequential approach to 2,3,6-trisubstituted pyridines.

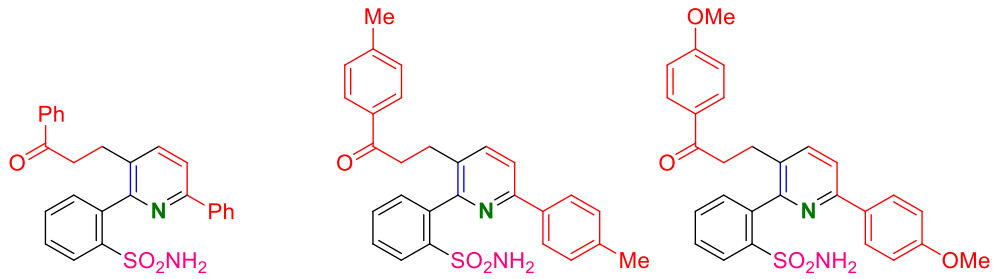
For further extension of the present methodology, we utilized saccharin-derived 3-methyl *N*-sulfonyl ketimine (**1h**) as a 2C unit for pyridine synthesis. This sulfonyl imine (**1h**) showed a high reactivity towards Michael reaction with 3-chloropropiophenone **2a** under present conditions and afterwards cycloaromatization using NH_4OAc. Interestingly, in this reaction, no cleavage of the C(sp^2)–S bond resulted in pyridine **3ha** (81 % yields) adorned with a pharmacologically well-recognized benzenesulfonamide moiety as shown in **Scheme 3.8**. Now the reaction of **1h** with 3-chloropropiophenones having Me, MeO, Cl, Br, and I on the phenyl ring occurred with no noticeable difficulty during alkylation and cycloaromatization reaction, providing the corresponding 2-(2-benzenesulfonamide)-3,6-disubstituted pyridines (**3hb-3hc** and **3hi-3hk)** with satisfactory to good yields (75-82%). However, in the case of challenging 3-chloropropiophenones (**2d, 2e, 2f,** and **2l**) attached with

sterically demanding phenyl groups like 2,4-dimethylphenyl, 2,4-dimethoxyphenyl, 4-cyclohexylphenyl, and 2-naphthyl obstruct the reaction to some extent, hence offering 72%, 75%, 72%, and 73% yields of the corresponding pyridines **3hd, 3he, 3hf** and **3hl**, respectively. Next, a few 3-chloropropiophenones attached with an interesting class of heterocyclic molecules, named 2,3-dihydrobenzofuran, 5-methylthiophene, and benzo[*b*]thiophene, bestowed biologically relevant pyridines **3hg, 3hm,** and **3hn** in 74%, 76%, and 73% yields, respectively. Notably, the above heterocyclic building blocks are still challenging for organic chemists. Thus, this transition metal-free organocatalytic technique would decisively enable their practical synthesis.

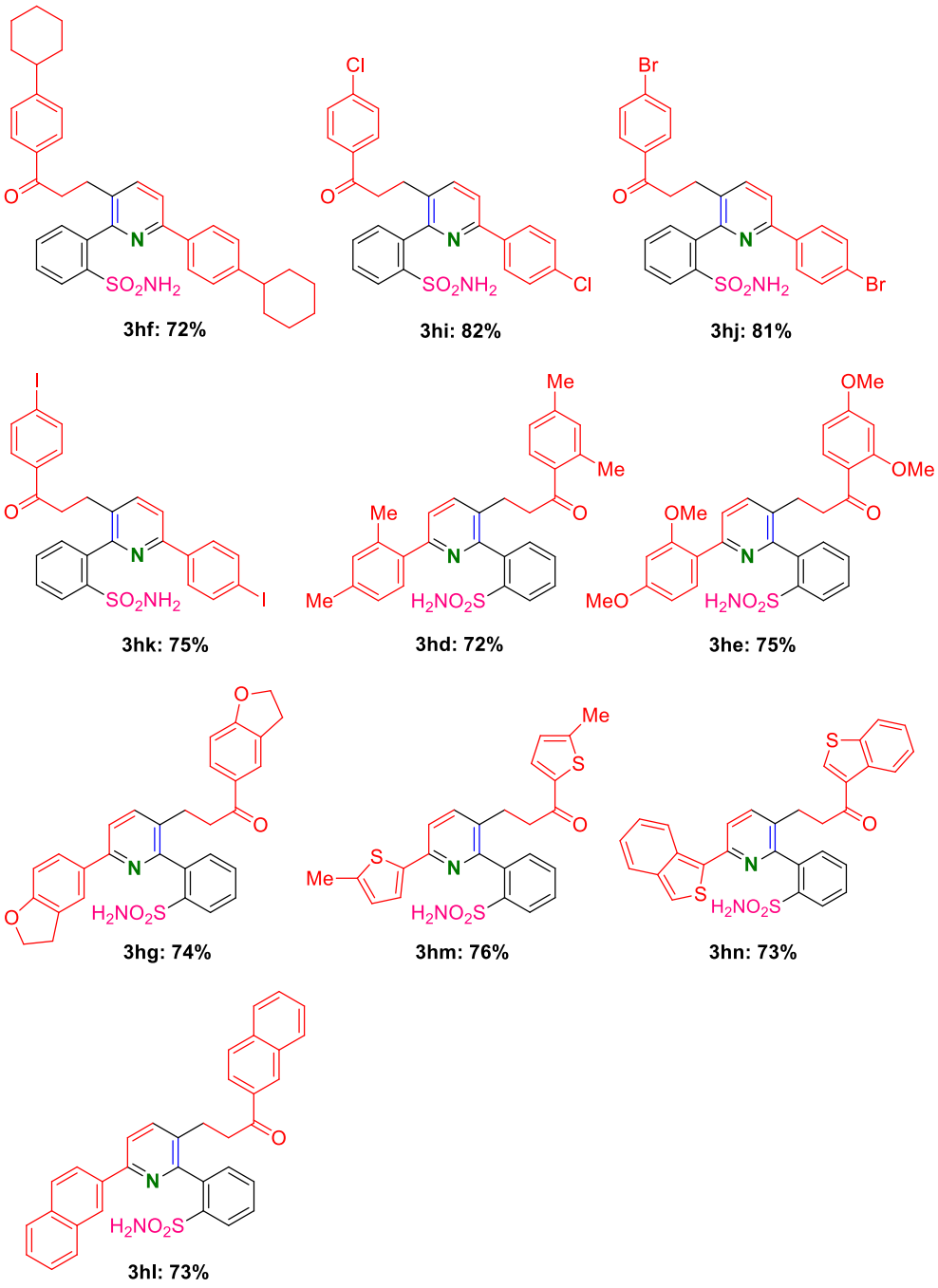


1h **2a-n** **3ha-3hn**

2a: R^1 = Ph
2b: R^1 = 4-MeC_6H_4
2c: R^1 = 4-$MeOC_6H_4$
2d: R^1 = 2,4-$(Me)_2C_6H_3$
2e: R^1 = 2,4-$(MeO)_2C_6H_3$
2f: R^1 = 4-$C_6H_{11}C_6H_4$
2g: R^1 = 2,3-dihydrobenzofuran
2i: R^1 = 4-ClC_6H_4
2j: R^1 = 4-BrC_6H_4
2k: R^1 = 4-IC_6H_4
2l: R^1 = 2-naphthyl
2m: R^1 = 4-$C_6H_{11}C_6H_4$
2n: R^1 = benzo[*b*]thiophene



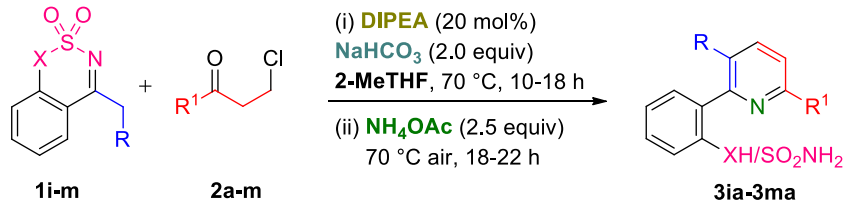
3ha: 81% **3hb: 79%** **3hc: 77%**



Scheme 3.8: One-pot access to benzenesulfonamide adorned 2,3,6-trisubstituted pyridines.

In continuation of the further substrate scope, 4-ethyl *N*-sulfonyl ketimine (**1i**) was subjected to the Michael addition reaction with **2a** (2.2 equiv.) using DIPEA/$NaHCO_3$ combined basic system followed by the addition of NH_4OAc. Remarkably, only mono-alkylation reaction occurred in place of di-alkylation as seen previously, which offered a high yield (82%) of an essential

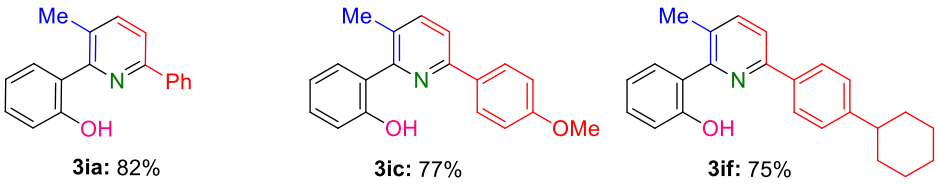
class of 3-picoline derivatives **3ia** as illustrated in **Scheme 3.9**. Next, with slightly adjusted conditions, 4- and 3-ethyl-substituted *N*-sulfonyl imines (**1i** and **1k**) reacted well with a group of 1-aryl/heteroaryl-3-chloropropiophenones (**2a-m,** 1.2 equiv.) and ammonium acetate (2.5 equiv.) at 70 °C, offering the corresponding 2-(2-hydroxyphenyl/benzenesulfonamide)-6-aryl-3-picoline derivatives (**3ic-3km**) with good to high yields (73-83%). In addition, extended alky chains (propyl and octyl) at the C4 and C3 positions of cyclic imines **1j, 1l,** and **1m** underwent mono-alkylation reaction effortlessly with **2a** leading to comparable yields of corresponding 3-alkylpyridines **3ja** (75%), **3la** (76%), and **3ma** (70%).



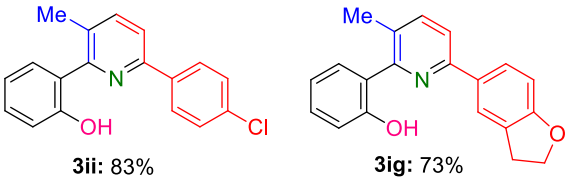
1i-m **2a-m** **3ia-3ma**

1i: X = O, R = Me
1j: X = O, R = Et
1k: X = none, R = Me
1l: X = none, R = Et
1m: X = heptyl

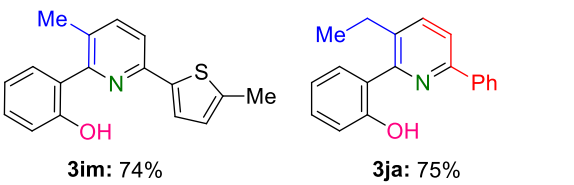
2a: R^1 = Ph
2c: R^1 = 4-$MeOC_6H_4$
2f: R^1 = 4-$C_6H_{11}C_6H_4$
2g: R^1 = 2,3-dihydrobenzofuran
2i: R^1 = 4-ClC_6H_4
2l: R^1 = 2-naphthyl
2m: R^1 = 4-$C_6H_{11}C_6H_4$



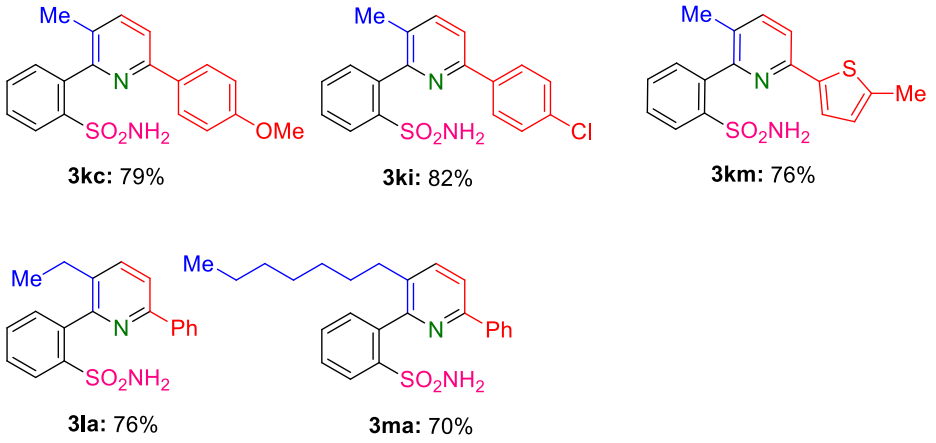
3ia: 82% **3ic:** 77% **3if:** 75%



3ii: 83% **3ig:** 73% **3il:** 75%



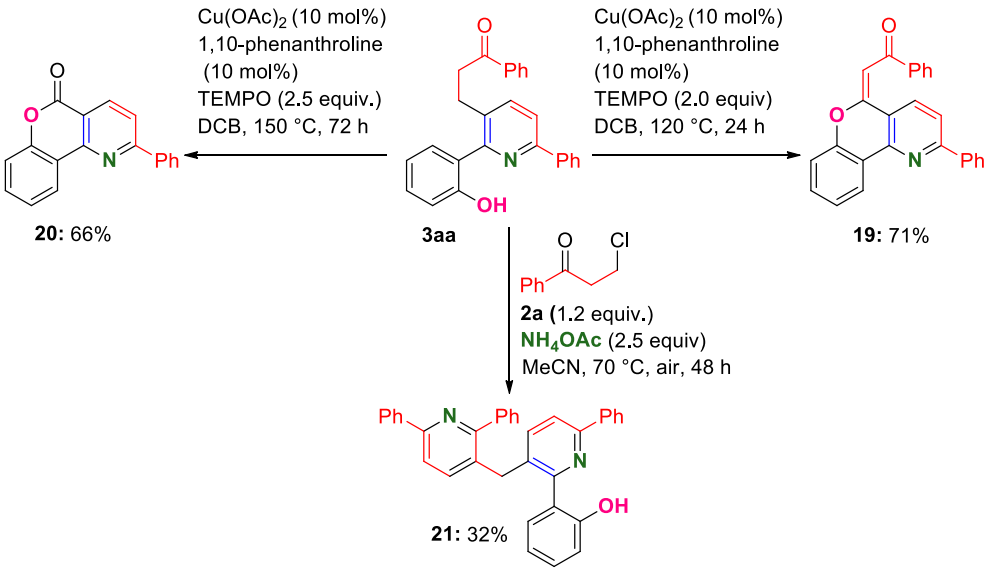
3im: 74% **3ja:** 75% **3ka:** 80%



Scheme 3.9: One-pot access to 3-picoline derivatives.

Gram-scale synthesis of pyridine: A gram-scale reaction was executed to set up the practical applicability of our fortified approach. A mixture of compound *N*-sulfonyl ketimine **1a** (986 mg, 5.0 mmol), 3-chloropropiophenone **2a** (1.86 g, 11.0 mmol), catalyst DIPEA (20 mol%, 1.0 mmol) and cooperative base $NaHCO_3$ (15.0 mmol) in 2-MeTHF (20 mL) was heated at 70 °C for 18 h, followed by addition of NH_4OAc (12.5 mmol) at the same temperature under open atmosphere. After 22 h, the pyridine **3aa** was isolated in a satisfactory yield of 77% (1.45 g).

Synthetic utility: To exhibit the synthetic utility of prepared pyridine, pyridine **3aa** was subjected to undergo oxidative dehydrogenation/annulation reaction by treatment with 10 mol% of $Cu(OAc)_2$ and 2.5 equivalent of TEMPO at 120 °C for 24, affording 71% yield of an appropriate[14] of 2-(5*H*-chromeno[4,3-*b*]pyridine-5-ylidine)-1-phenylethanone **19**. Additionally, the same reaction at an elevated temperature of 150 °C for 48 h, provided a 66% yield of pyrido-coumarin **20**. Furthermore, we performed a three-component [3C + 2C + 1N] aza-cyclization reaction using **3aa, 2a** and NH_4OAc at 70 °C for 48 h under aerobic conditions, which leads to synthetically hostile di-(pyridine-3-yl)methane derivative 21 in 32% yield as shown in **Scheme 3.10**.

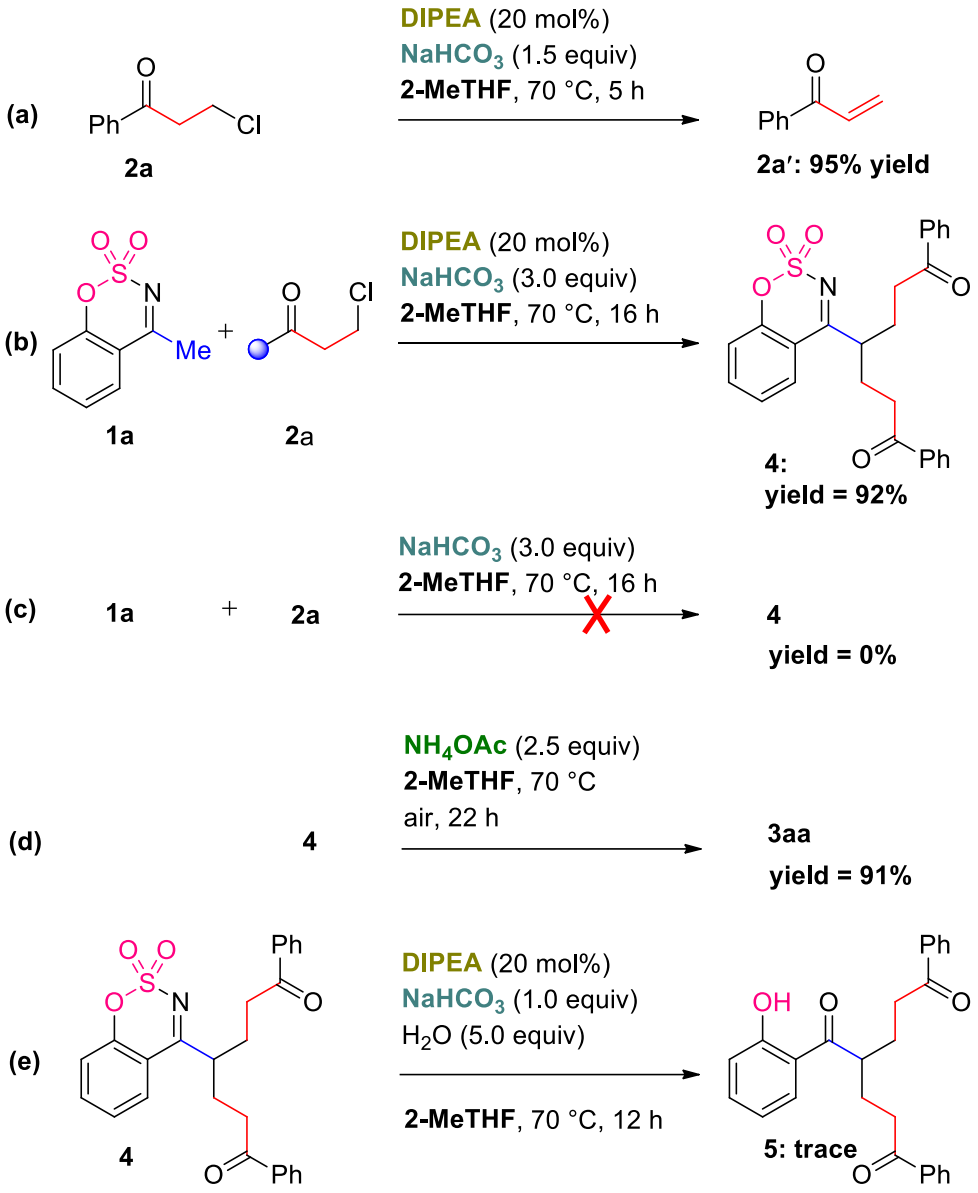


Scheme 3.10. Access to 2-(5*H*-chromeno[4,3-*b*]pyridine-5-ylidene) derivatives **19,** 5*H*-chromeno[4,3-*b*]pyridine-5-one **20** and di(pyridine-3-yl)methane **21.**

3.4.3 Control Experiments

We performed several control experiments to understand the detailed mechanism illustrated in **Scheme 3.11**. Results showed that **2a** was fully converted into vinyl phenyl ketone **2a′** by using 20 mol% of DIPEA and 1.5 equivalent $NaHCO_3$ under the present conditions in an excellent yield of 95% (**Scheme 3.11a**). Next, **1a** reacted with **2a** (2.2 equiv.) at 70 °C for 16 h, providing di-alkylated Michael addition product **4** in 92% yield (**Scheme 3.11b**). However, in the absence of DIPEA, the above double Michael reaction did not happen (**Scheme 3.11c**). Thus, DIPEA is an essential base for this C–C bond-forming reaction. Furthermore, double alkylated product **4** and ammonium acetate (2.5 equiv.) at 70 °C under aerial conditions in 2-MeTHF, undergo an aza-cyclization reaction to provide pyridine **3aa** in an excellent yield of 91%. Thus, confirming NH_4OAc as a *N*-atom source for pyridine ring construction (**Scheme 3.11d**). Importantly, double alkylated product **4** upon treatment of 20 mol% DIPEA and $NaHCO_3$ (1.0 equiv.) at 70 °C in a residual amount of water in 2-MeTHF for 16 h could not hydrolyze C=N bond of **4**

(Scheme 3.11e), which suggests that pyridine **3aa** may not originate from intermediate **5**.

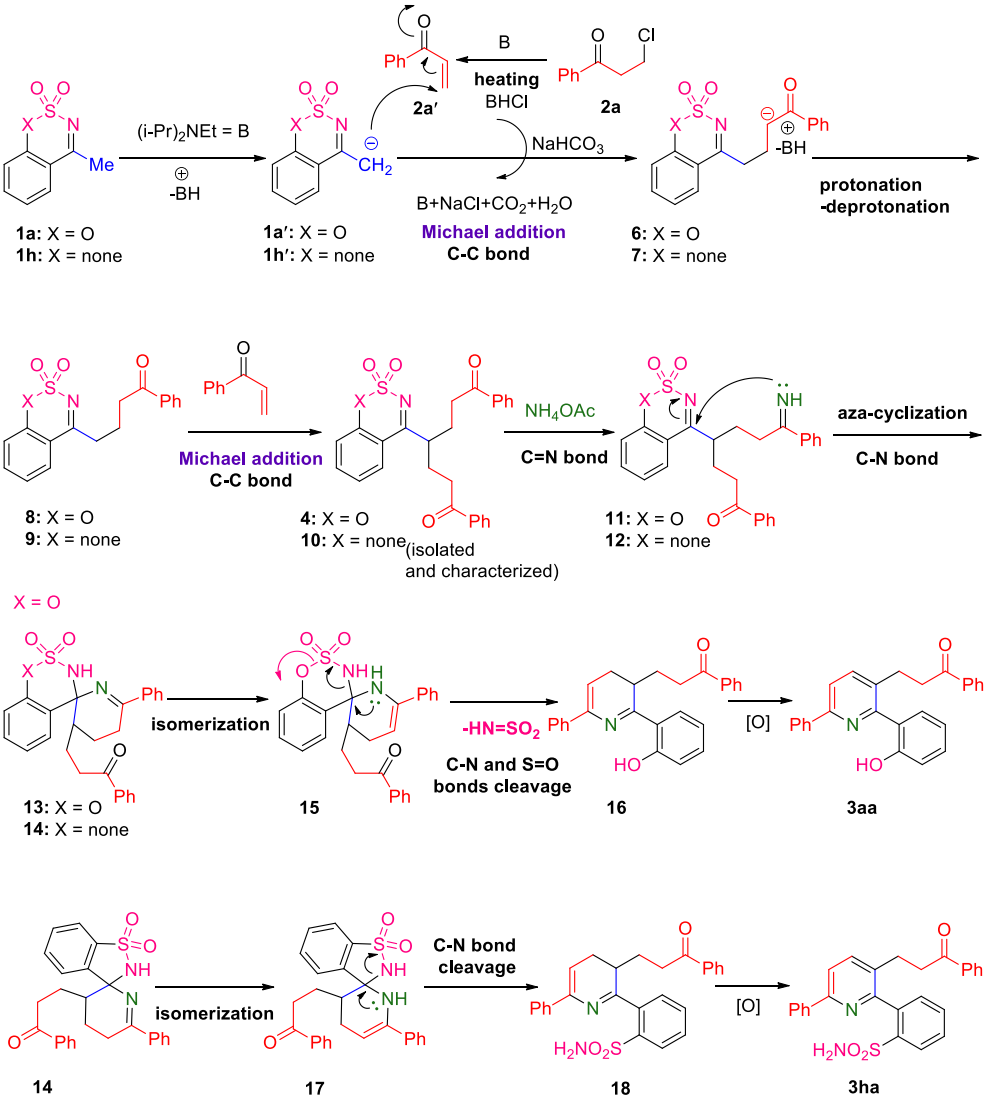


Scheme 3.11. Control experiments

3.4.4 Plausible Mechanism

Based on our control experiments, we propose a plausible mechanism for this pseudo-four-component reaction as represented in **Scheme 3.12**. Initially, the base DIPEA abstracts a C(sp^3)–H proton from cyclic imines **1a/1h** to form a carbanion intermediate **1a′/1h′.** After that, this carbanion intermediate attacks *in-situ* formed vinyl phenyl ketone **2a′,** followed by a quick protonation-

deprotonation sequence to generate another carbanion intermediate **8/9**. Remarkably, the key role of $NaHCO_3$ is to regenerate the DIPEA (B) as a catalyst for the next cycle by reacting with *in-situ* formed *N*-ethyl-*N*, *N*-di-isopropyl ammonium chloride (BHCl) and giving NaCl, CO_2 and H_2O as non-hazardous side products. Next, the carbanion intermediate **8/9** again undergoes Michael addition with **2a′** producing an isolable double alkylated product **4/10**. Further, alkylated addition product **4/10** in the presence of NH_4OAc forms ketimine **11/12**. Intramolecular aza-cyclization reaction in formed ketimine **11/12** leads to spirocyclic intermediate **13/14**. Intermediate **13** tautomerizes to



Scheme 3.12. A plausible mechanism of this C(sp^3)–H alkylation-aza-cyclization reaction.

eliminate $HN{=}SO_2$ *via* breaking C–N and S–O bonds and offers corresponding dihydropyridine **16**. Finally, this dihydropyridine oxidizes under aerobic conditions to give the desired pyridine **3aa**. In the same way, spirocyclic intermediate **14** also undergoes tautomerization/ C–N bond cleavage/ aerial oxidation in a sequence to form intended pyridine **3ha**.

3.5 Conclusion

We have developed a mild organocatalytic, one-pot, two-step sequential methodology for the synthesis of 2-(2-hydroxyaryl/benzenesulfonamide)-3,6-disubstituted pyridines decorated with synthetically beneficial aryl ethyl ketone scaffold at C3 position. The reaction proceeds through a double $C(sp^3)$–H alkylation of 4/3-methyl *N*-sulfonyl ketimines with *in-situ* generated vinyl aryl ketones triggered by DIPEA in the presence of $NaHCO_3$ as a cooperative base and subsequent [5C+1N] aza-cyclization using ammonium acetate as a *N*-containing atom for pyridine scaffold construction. Furthermore, higher alkyl chains in place of the methyl group of *N*-sulfonyl ketimines give only a monoalkylation product with *in-situ* formed vinyl ketones, resulting in satisfactory to high yields of 3-picoline derivatives in an atom- and pot-economical manner. Thus, designing a new organocatalytic cycle with a cheap and environmentally benign base $NaHCO_3$ is a crucial achievement for new C–C bond construction. The present methodology is conceptually unique with many advantages such as transition-metal-oxidant-free conditions, excellent functional group tolerance, broader substrate scope, operational simplicity and scalability to gram-level synthesis. In addition, access to numerous pharmacologically acknowledged moieties such as 2-(5*H*-chromeno[4,3-*b*]pyridine-5-ylidene, 5*H*-chromino[4,3-*b*]pyridine-5-one and di(pyridine-3-yl)methane derivatives were achieved through our current strategy.

3.6 Experimental Section

General Information: All reactions were carried out either under an inert atmosphere or air and continuously monitored by TLC using Merck 60 F254 pre-coated silica gel plates and the products were visualized by UV light. Flash chromatography was done with silica gel (200-300 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance (III) 500 MHz spectrometer. ^{1}H NMR data are reported as a chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constant *J* (Hz), integration, and assignment; data for ^{13}C are reported as a chemical shift (δ ppm). High-resolution mass spectral analyses (HRMS) were carried out using ESI-TOF-MS. Melting points were recorded on an Electrothermal melting points apparatus and are uncorrected.

Starting materials: *N*-sulfonyl ketimines (**1a-1m**)[15] and 3-chloropropiophenones **(2a-2n)**[16] were synthesized according to known literature procedures. Notably, the synthesized starting materials (**1a-1c, 1d, 1e-1i,** and **1k-1l**; **2a, 2b**, **2c, 2d, 2f, 2i, 2j,** and **2k**) are known in the literatures. The following ketimines (**1m, 2e, 2g, 2h, 2l, 2m** and **2n**) did not have the characterization data in the literature. Therefore, these *N*-sulfonyl imines were characterized by ^{1}H, ^{13}C and HRMS data. All the bases used in the reaction were purchased from commercial suppliers.

3-Octylbenzo[*d*]isothiazole 1,1-dioxide (1m): Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.88 (m, 1H), 7.74-7.67 (m, 3H), 2.96-2.93 (m, 2H), 1.89-1.83 (m, 2H), 1.49–1.43 (m, 2H), 1.37-1.27 (m, 8H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm.

3-Chloro-1-(2,4-dimethoxyphenyl)propan-1-one (2e): Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.8 Hz, 1H), 6.47 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.38 (d, *J* = 1.9 Hz, 1H), 3.83 (s, 3H), 3.81-3.78 (m, 5H), 3.37 (t, *J* = 6.9 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 165.0, 161.2, 133.0, 120.2, 105.5, 98.4, 55.7, 55.6, 46.5, 39.5 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{13}ClO_3Na^+$ 251.0445, found 251.0458.

3-Chloro-1-(2,3-dihydrobenzofuran-5-yl)propan-1-one (2g): Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.79 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 4.66 (t, *J* = 8.8 Hz, 2H), 3.90 (t, *J* = 6.9 Hz, 2H), 3.38 (t, *J* = 6.9 Hz, 2H), 3.25 (t, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 164.8, 130.2, 129.9, 128.0, 125.5, 109.2, 72.4, 41.0, 39.2, 29.0 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{11}ClO_2Na^+$ 233.0340, found 233.0365.

1-(4′-Bromo-[1,1′-biphenyl]-4-yl)-3-chloropropan-1-one (2h): Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 3.95 (t, *J* = 6.8 Hz, 2H), 3.49 (t, *J* = 6.8 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 145.0, 138.7, 135.4, 132.2, 128.9, 128.9, 127.3, 122.9, 41.4, 38.8 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{12}BrClONa^+$ 344.9652, found 344.9647.

3-Chloro-1-(naphthalen-2-yl)propan-1-one (2l): White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.03 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 3.99 (t, *J* = 6.8 Hz, 2H), 3.60 (t, *J* = 6.8 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 135.9, 133.8, 132.5, 130.0, 129.7, 128.8, 128.8, 127.9, 127.1, 123.7, 41.4, 38.9 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{11}ClONa^+$ 241.0391, found 241.0407.

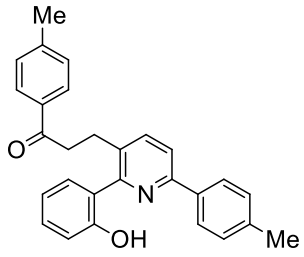
3-Chloro-1-(5-methylthiophen-2-yl)propan-1-one (2m): Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 3.8 Hz, 1H), 6.81 (d, *J* = 3.6 Hz, 1H), 3.88 (t, *J* = 6.8 Hz, 2H), 3.31 (t, *J* = 6.8 Hz, 2H), 2.54 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 150.7, 141.5, 133.1, 127.0, 41.4, 38.9, 16.1 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_8H_9ClOSNa^+$ 210.9955, found 210.9950.

1-(Benzo[*b*]thiophen-3-yl)-3-chloropropan-1-one (2n): Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 8.1 Hz, 1H), 8.28 (s, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.51-7.48 (m, 1H), 7.44-7.41 (m, 1H), 3.95 (t, *J* = 6.7 Hz, 2H), 3.45 (t, *J* = 6.7 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 139.8,

137.5, 136.4, 134.8, 126.1, 125.7, 125.7, 122.3, 42.6, 38.8 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{11}H_9ClOSNa^+$ 246.9955, found 246.9968.

Representative procedure for the synthesis of pyridine (3aa): A mixture of compound 3-methyl *N*-sulfonyl **1a** (39.45 mg, 0.2 mmol), 3-chloropropiophenone **2a** (74.2 mg, 0.44 mmol), catalyst DIPEA (5.17 mg, 7.0 µL, 20 mol%) and cooperative base $NaHCO_3$ (50.4 mg, 0.6 mmol) in dry 2-MeTHF (2.0 mL) was stirred at 70°C under an inert atmosphere. After completion of the reaction (continuously monitored by TLC), NH_4OAc (38.5 mg, 0.5 mmol) was added to the reaction mixture at the same temperature under aerobic conditions for 20 h. Afterward, the solvent was evaporated from the reaction mixture under reduced pressure to provide the solid residue of crude mixture, which was extracted with ethyl acetate (3×10 mL), followed by washing with water and brine, respectively, and dried using Na_2SO_4. The combined extracted organic phases were evaporated under reduced pressure to give the solid crude product. In the end, product **3aa** was isolated in its pure form (62.1 mg, 82% yield) by performing column chromatography over silica gel with a mixture of EtOAc/hexane (7:93 v/v) as the eluent. The product **3aa** was fully characterized by its essential spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS). The above procedure was followed for synthesizing all the pyridine derivatives illustrated in Schemes **3.7** and **3.8**. Notably, all the accessed pyridines **3aa-3hn** are unknown and characterized by their spectroscopic (^{1}H NMR, ^{13}C NMR, and HRMS).

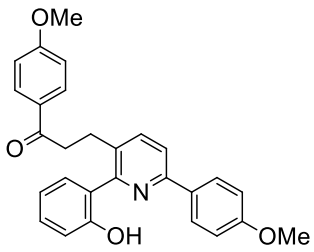
3-(2-(2-Hydroxyphenyl)-6-(4-methylphenyl)pyridin-3-yl)-1-(4-methylphenyl)propan-1-one (3ab): Colorless solid**;** yield = 80% (65.0 mg);



mp = 131-133 °C; R_f = 0.45 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.78 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.32 - 7.27 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 3.39 (t, *J* = 7.6 Hz, 2H), 3.21 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 157.1, 155.8, 153.5, 144.2, 141.1, 139.7,

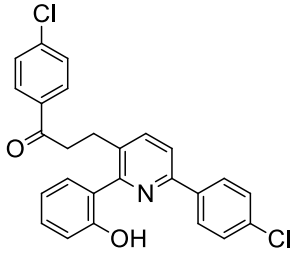
135.1, 134.2, 133.4, 130.7, 129.8, 129.4, 129.4, 128.3, 126.7, 122.2, 119.2, 118.7, 118.1, 39.1, 27.6, 21.7, 21.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{28}H_{26}NO_2^+$ 408.1958, found 408.1969.

3-(2-(2-Hydroxyphenyl)-6-(4-methoxyphenyl)pyridin-3-yl)-1-(4-methoxyphenyl)propan-1-one (3ac): Colorless solid; yield = 78% (68.5 mg);

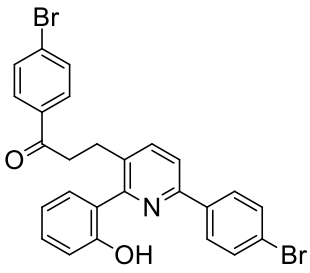


mp = 110-112 °C; R_f = 0.49 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.76 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.55 (m, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.94 – 6.88 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.38 – 3.35(m, 2H), 3.19 – 3.16 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 163.7, 160.9, 157.1, 155.7, 153.1, 141.1, 133.0, 130.7, 130.5, 130.4, 129.7, 129.4, 128.1, 122.3, 119.2, 118.3, 118.1, 114.5, 113.9, 55.6, 55.5, 38.9, 27.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{28}H_{26}NO_4^+$ 440.1856, found 440.1865.

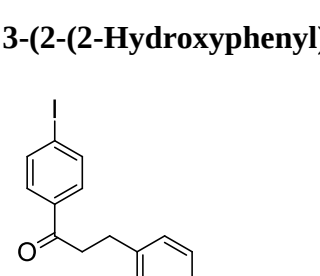
1-(4-Chlorophenyl)-3-(6-(4-chlorophenyl)-2-(2-hydroxyphenyl) pyridin-3-yl)propan-1-one (3ai): Colorless solid; yield = 83% (74.3 mg); mp = 132-134 °C; R_f = 0.26 (EtOAc/Hexane = 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 1H), 7.91 (d, *J* = 7.7 Hz, 2H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.1 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.34-7.31 (m, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.95 (t, *J* = 6.7 Hz, 1H), 3.41 - 3.37 (m, 2H), 3.19-3.15 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 156.7, 156.1, 152.5, 141.2, 139.9, 136.3, 135.8, 134.8, 133.9, 130.9, 129.6, 129.3, 129.3, 129.1, 128.1, 122.2, 119.5, 118.9, 118.2, 39.0, 27.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{20}Cl_2NO_2^+$ 448.0886 , found 448.0867.



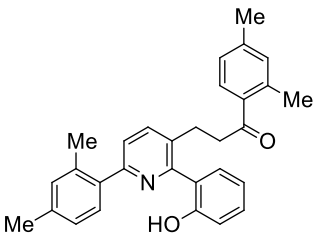
1-(4-Bromophenyl)-3-(6-(4-bromophenyl)-2-(2-hydroxyphenyl)pyridin-3-yl)propan-1-one (3aj): Colorless solid; yield = 80% (86.0 mg); mp = 137-139 °C; R_f = 0.41 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.13 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 3H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.62-7.51 (m 6H), 7.34-7.31 (m, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 3.37 (t, *J* = 7.5 Hz, 2H), 3.16 (t, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 156.7, 156.2, 152.6, 141.2, 136.8, 135.2, 133.9, 132.3, 132.1, 130.9, 129.6, 129.3, 128.6, 128.3, 124.1, 122.2, 119.5, 118.8, 118.2, 38.9, 27.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{20}{}^{79}Br_2NO_2^+$ 535.9855, found 535.9868; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{20}{}^{79}Br^{81}BrNO_2^+$ 537.9835, found 537.9847; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{20}{}^{81}Br_2NO_2^+$ 539.9814, found 539.9824.



3-(2-(2-Hydroxyphenyl)-6-(4-iodophenyl)pyridin-3-yl)-1-(4-iodophenyl)propan-1-one (3ak): Colorless solid; yield =76% (95.9 mg); mp = 95-97 °C; R_f = 0.45 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.13 (s, 1H), 7.83–7.76 (m, 5H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.55–7.51 (m, 3H), 7.34–7.30 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 3.37 (t, *J* = 7.5 Hz, 2H), 3.15 (t, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 156.7, 156.2, 152.7, 141.2, 138.2, 138.1, 137.4, 135.7, 134.0, 130.9, 129.5, 129.3, 128.5, 122.2, 119.5, 118.8, 118.2, 101.5, 96.0, 38.9, 27.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{20}I_2NO_2^+$ 631.9578, found 631.9594.

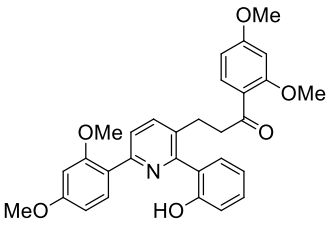


1-(2,4-Dimethylphenyl)-3-(6-(2,4-dimethylphenyl)-2-(2-hydroxyphenyl)pyridin-3-yl)propan-1-one (3ad): Colorless solid; yield = 72% (62.7 mg); mp = 106-109 °C; R_f = 0.48 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.86 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H),

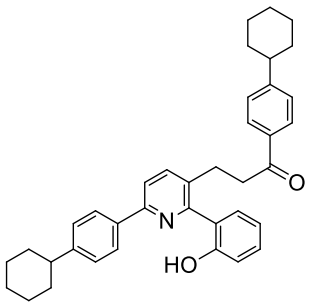


7.32 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.10 – 7.08 (m, 2H), 7.05 – 7.03 (m, 2H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.91 (t, *J* = 7.3 Hz, 1H), 3.40 – 3.37 (m, 2H), 3.20 (t, *J* = 7.5 Hz, 2H), 2.46 (s, 3H), 2.37 (s, 6H), 2.34 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 157.4, 155.6, 142.3, 140.4, 138.9, 138.6, 136.2, 135.7, 134.4, 133.1, 132.9, 131.8, 130.6, 129.8, 129.4, 129.2, 129.1, 126.9, 126.5, 122.6, 121.9, 119.0, 118.2, 41.6, 27.9, 21.7, 21.5, 21.2, 20.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{30}H_{30}NO_2^+$ 436.2271, found 436.2293.

1-(2,4-Dimethoxyphenyl)-3-(6-(2,4-dimethoxyphenyl)-2-(2-hydroxyphenyl)pyridin-3-yl)propan-1-one (3ae): Colorless solid; yield = 70% (70.0 mg); mp = 116-118 °C; R_f = 0.43 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.72 (s, 1H), 7.79 (dd, *J* = 7.9, 4.4 Hz, 2H), 7.61 – 7.57 (m, 2H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.24 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.88 (t, *J* = 7.3 Hz, 1H), 6.60 – 6.58 (m, 2H), 6.52 (d, *J* = 8.3 Hz, 1H), 6.41 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H), 3.32 – 3.27 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 164.6, 161.6, 160.9, 158.2, 157.2, 155.2, 152.3, 140.2, 133.1, 132.9, 131.5, 130.3, 129.6, 122.7, 122.5, 120.9, 120.8, 118.9, 118.0, 105.3, 105.1, 99.2, 98.4, 55.6, 55.6, 55.6, 55.5, 44.4, 27.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{30}H_{30}NO_6^+$ 500.2068, found 500.2072.

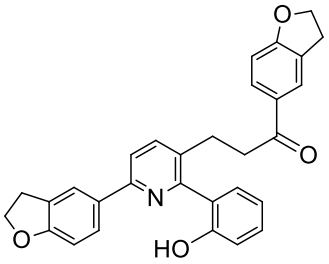


1-(4-Cyclohexylphenyl)-3-(6-(4-cyclohexylphenyl)-2-(2-hydroxyphenyl)pyridin-3-yl)propan-1-one (3af): Colorless solid; yield =71% (77.2 mg); mp = 76-78 °C; R_f = 0.42 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.82 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 3H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.54 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.29-7.21 (m, 5H), 7.08 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.91 – 6.88 (m, 1H), 3.36 (t, *J* = 7.5 Hz, 2H), 3.19 (t, *J* = 7.5 Hz, 2H), 2.55-2.50 (m, 2H), 1.88-1.81 (m, 8H), 1.74-1.72 (m, 2H), 1.46-1.31 (m, 8H), 1.28-1.21 (m, 2H) ppm; ^{13}C



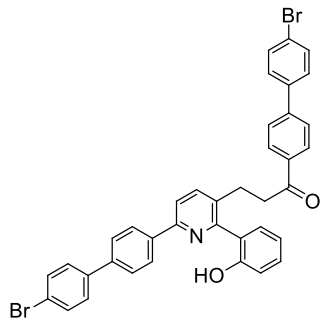
NMR (125 MHz, $CDCl_3$) δ 198.4, 157.2, 155.8, 154.1, 153.5, 149.7, 141.1, 135.5, 134.5, 133.4, 130.7, 129.4, 128.4, 127.6, 127.2, 126.8, 122.2, 119.2, 118.7, 118.1, 44.8, 44.5, 39.1, 34.4, 34.2, 27.6, 26.9, 26.8, 26.2, 26.1 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{38}H_{42}NO_2^+$ 544.3210, found 544.3199.

1-(2,3-Dihydrobenzofuran-5-yl)-3-(6-(2,3-dihydrobenzofuran-5-yl)-2-(2-hydroxyphenyl)pyridin-3-yl)propan-1-one (3ag): Pale yellow solid; yield



=72% (66.7 mg); mp = 111-113 °C; R_f = 0.22 (EtOAc/Hexane = 25:75); ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.75 (s, 1H), 7.72 (t, *J* = 9.5 Hz, 2H), 7.56-7.54 (m, 2H), 7.32-7.28 (m, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 4.64 (t, *J* = 8.7 Hz, 4H), 3.37-3.34 (m, 2H), 3.28 (t, *J* = 8.7 Hz, 2H), 3.21 (t, *J* = 8.7 Hz, 2H), 3.16-3.13 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 164.6, 161.6, 157.0, 155.6, 153.5, 141.1, 132.8, 130.7, 130.6, 130.1, 130.1, 129.4, 128.2, 127.8, 127.2, 125.5, 123.6, 122.3, 119.2, 118.3, 118.0, 109.7, 109.2, 72.3, 71.9, 38.9, 29.7, 29.1, 27.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{30}H_{26}NO_4^+$ 464.1856, found 464.1845.

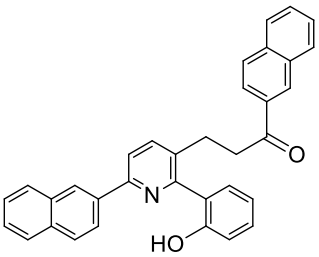
1-(4′-Bromo-[1,1′-biphenyl]-4-yl)-3-(6-(4′-bromo-[1,1′-biphenyl]-4-yl)-2-(2-hydroxyphenyl)pyridin-3-yl)propan-1-one (3ah): Yellow solid; yield =



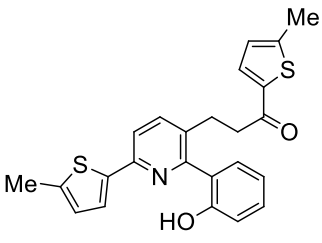
67% (92.3 mg); mp = 184-186 °C; R_f = 0.48 (EtOAc/Hexane = 15:85); ^1H NMR (500 MHz, $CDCl_3$) δ 11.54 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.61-7.57 (m, 3H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 3.44 (t, *J* = 7.5 Hz, 2H), 3.27 (t, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 156.8, 156.0, 152.9, 144.7, 141.1, 140.9, 139.2, 138.6, 137.0, 135.4, 133.7, 132.1, 132.0, 130.8, 129.3, 128.8, 128.7, 128.6, 127.5, 127.2, 127.1, 122.7, 122.1, 122.0,

119.2, 118.8, 118.1, 39.0, 27.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{38}H_{28}{}^{79}Br_2NO_2{}^+$ 688.0481, found 688.0493; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{38}H_{28}{}^{79}Br^{81}BrNO_2{}^+$ 690.0461, found 690.0479; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{38}H_{28}{}^{81}Br_2NO_2{}^+$ 692.0440, found 692.0467.

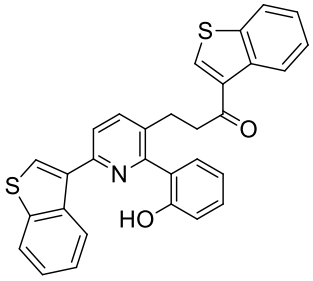
3-(2-(2-Hydroxyphenyl)-6-(naphthalen-2-yl)pyridin-3-yl)-1-(naphthalen-2-yl)propan-1-one (3al): Colorless solid; yield = 72% (69.0 mg); mp = 170-172 °C; R_f = 0.30 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.60 (s, 1H), 8.45 (s, 1H), 8.37 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.98-7.91 (m, 5H), 7.88 – 7.85 (m, 3H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.63-7.51 (m, 5H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 3.50 (t, *J* = 7.3 Hz, 2H), 3.39 (t, *J* = 7.3 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 157.0, 156.1, 153.6, 141.3, 135.8, 135.2, 134.0, 133.9, 133.8, 133.6, 132.6, 130.9, 129.9, 129.7, 129.5, 128.9, 128.9, 128.7, 128.7, 127.9, 127.8, 127.0, 126.6, 126.5, 124.2, 123.8, 122.3, 119.4, 119.4, 118.2, 39.2, 27.7 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{34}H_{26}NO_2{}^+$ 480.1958, found 480.1951.



3-(2-(2-Hydroxyphenyl)-6-(5-methylthiophen-2-yl)pyridin-3-yl)-1-(5-methylthiophen-2-yl)propan-1-one (3am): Pale yellow solid; yield = 74% (62.0 mg); mp = 76-78 °C; R_f = 0.42 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.28 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 3.5 Hz, 1H), 7.36 (d, *J* = 3.7 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.76 (dd, *J* = 15.0, 3.4 Hz, 2H), 3.33 (t, *J* = 7.6 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.51 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 156.9, 155.5, 150.2, 149.0, 143.0, 141.7, 141.0, 140.8, 132.8, 132.7, 130.8, 129.4, 126.9, 126.7, 125.3, 121.9, 119.3, 118.3, 116.9, 39.3, 27.9, 16.1, 15.7 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{22}NO_2S_2{}^+$ 420.1086, found 420.1102.

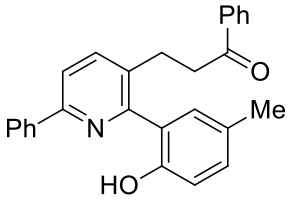


1-(Benzo[*b*]thiophen-3-yl)-3-(6-(benzo[*b*]thiophen-3-yl)-2-(2-hydroxyphenyl)pyridin-3-yl)propan-1-one (3an): Pale yellow solid; yield = 71% (69.8 mg); mp = 66-68 °C; R_f = 0.61 (EtOAc/Hexane = 25:75); ^{1}H



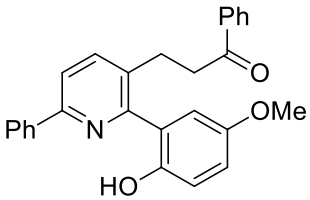
NMR (500 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.74 (d, *J* = 7.9 Hz, 1H), 8.29 (d, *J* = 7.6 Hz, 1H), 8.01 (s, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.84-7.80 (m, 3H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48-7.45 (m, 1H), 7.42-7.36 (m, 3H), 7.33-7.30 (m, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.96 (t, *J* = 7.1 Hz, 1H), 3.42-3.39 (m, 2H), 3.20-3.17 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 156.9, 156.0, 150.5, 141.0, 140.9, 139.9, 137.2, 136.8, 136.5, 135.3, 134.7, 133.5, 130.8, 129.5, 127.4, 126.0, 125.7, 125.6, 125.0, 124.8, 123.6, 123.0, 122.4, 122.3, 121.1, 119.4, 118.3, 40.4, 28.0 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{30}H_{22}NO_2S_2^+$ 492.1086, found 492.1089.

3-(2-(2-Hydroxy-5-methylphenyl)-6-phenylpyridin-3-yl)-1-phenylpropan-1-one (3ba): Colorless solid; yield = 83% (65.3 mg); mp =



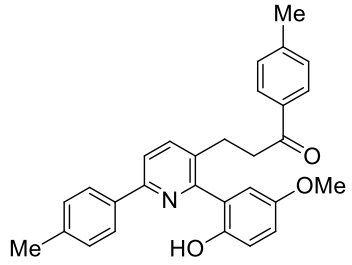
108-110 °C; R_f = 0.37 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.13 (s, 1H), 7.98 – 7.96 (m, 2H), 7.88 – 7.86 (m, 2H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.49-7.41 (m, 5H), 7.36 (s, 1H), 7.12 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 3.41 (t, *J* = 7.5 Hz, 2H), 3.23 (t, *J* = 7.5 Hz, 2H), 2.30 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 156.1, 154.5, 153.6, 141.0, 138.0, 136.6, 133.7, 133.4, 131.4, 129.7, 129.5, 129.1, 128.8, 128.3, 128.1, 126.8, 122.2, 118.9, 117.9, 39.2, 27.6, 20.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}NO_2^+$ 394.1802, found 394.1815.

3-(2-(2-Hydroxy-5-methoxyphenyl)-6-phenylpyridin-3-yl)-1-phenylpropan-1-one (3ca): Colorless solid; yield = 81% (66.3 mg); mp=114-116 °C; R_f = 0.24 EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.79 (s, 1H), 7.97 (d, *J* = 6.9 Hz, 2H), 7.88-7.84 (m, 3H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.55 (t,

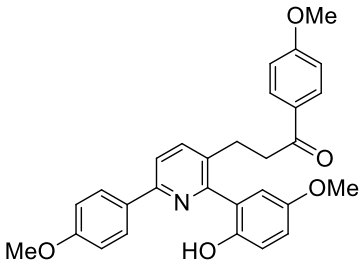


J = 6.3 Hz, 1H), 7.48-7.42 (m, 5H), 7.12 (s, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 3.77 (s, 3H), 3.42 (t, *J* = 6.7 Hz, 2H), 3.25 (t, *J* = 7.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 155.8, 153.8, 152.5, 150.7, 141.1, 137.9, 136.6, 133.7, 133.4, 129.5, 129.1, 128.8, 128.1, 126.8, 122.8, 119.1, 118.7, 116.7, 114.5, 56.0, 39.1, 27.6 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{27}H_{24}NO_3^+$ 410.1751, found 410.1752.

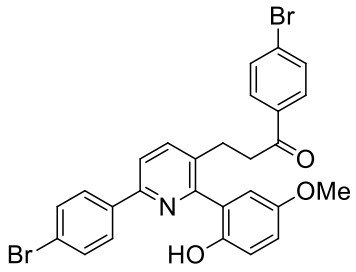
3-(2-(2-Hydroxy-5-methoxyphenyl)-6-(4-methylphenyl)pyridin-3-yl)-1-(4-methylphenyl)propan-1-one (3cb): Colorless solid; yield = 82% (71.6 mg); mp=112-114 °C; R_f = 0.35 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.93 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 3.0 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.91 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.76 (s, 3H), 3.39 (t, *J* = 7.6 Hz, 2H), 3.23-3.20 (m, 2H), 2.41 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 155.7, 153.7, 152.4, 150.8, 144.2, 141.0, 139.6, 135.1, 134.1, 133.4, 129.8, 129.4, 128.3, 126.7, 122.7, 118.8, 118.7, 116.7, 114.5, 56.0, 39.1, 27.6, 21.7, 21.4 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{29}H_{28}NO_3^+$ 438.2064, found 438.2081.



3-(2-(2-Hydroxy-5-methoxyphenyl)-6-(4-methoxyphenyl)pyridin-3-yl)-1-(4-methoxyphenyl)propan-1-one (3cc): Colorless solid; yield = 83% (77.9 mg); mp = 116-118 °C; R_f = 0.52 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.92 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.11 (s, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.91 (dd, *J* = 10.3, 5.5 Hz, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.38 (t, *J* = 7.3 Hz, 2H), 3.18 (t, *J* = 7.4 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 163.7, 160.9, 155.6, 153.4, 152.4, 150.7, 141.1, 133.0, 130.6, 130.4, 129.7, 128.1, 122.8, 118.6, 118.4, 116.7, 114.5, 114.4, 113.9, 56.0, 55.6, 55.5, 38.9, 27.7 ppm;

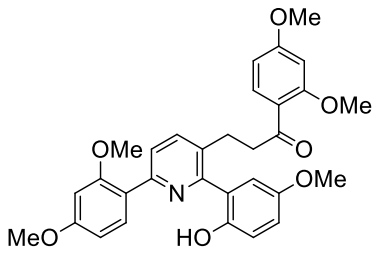


HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{29}H_{28}NO_5^+$ 470.1962, found 470.1971.

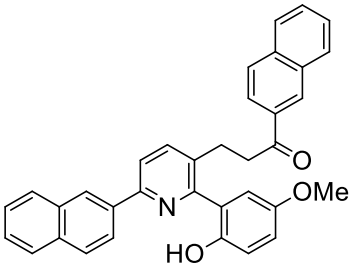


1-(4-Bromophenyl)-3-(6-(4-bromophenyl)-2-(2-hydroxy-5-methoxyphenyl)pyridin-3-yl)propan-1-one (3cj): White solid; yield = 79% (89.6 mg); mp = 128-130 °C; R_f = 0.32 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.85 – 7.82 (m, 3H), 7.71 – 7.69 (m, 2H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.57 – 7.54 (m, 2H), 7.07 (d, *J* = 3.0 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.92 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.77 (s, 3H), 3.38 (t, *J* = 7.5 Hz, 2H), 3.17 (t, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 155.9, 152.7, 152.5, 150.2, 141.0, 136.7, 135.1, 133.8, 132.1, 132.0, 129.5, 128.5, 128.2, 123.9, 122.7, 118.8, 118.6, 116.5, 114.5, 55.9, 38.8, 27.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{27}H_{22}{}^{79}Br_2NO_3^+$ 565.9961, found 565.9974; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{27}H_{22}{}^{79}Br^{81}BrNO_3^+$ 567.9943, found 567.9966; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{27}H_{22}{}^{81}Br_2NO_3^+$ 569.9928, found 569.9946.

1-(2,4-Dimethoxyphenyl)-3-(6-(2,4-dimethoxyphenyl)-2-(2-hydroxy-5-methoxyphenyl)pyridin-3-yl)propan-1-one (3ce): Pale yellow solid; yield = 75% (79.4 mg); mp = 85-87 °C; R_f = 0.21 (EtOAc/Hexane = 30:70); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.00 (s, 1H), 7.80 – 7.77 (m, 2H), 7.59 (t, *J* = 8.4 Hz, 2H), 7.08 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 6.86 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.59 – 6.57 (m, 2H), 6.52 (d, *J* = 7.6 Hz, 1H), 6.41 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 3.33 – 3.29 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 164.6, 161.6, 160.9, 158.3, 155.0, 152.5, 152.1, 151.0, 140.3, 133.1, 132.8, 131.5, 123.1, 122.6, 120.9, 120.8, 118.6, 116.6, 114.4, 105.3, 105.1, 99.2, 98.4, 56.0, 55.6, 55.6, 55.6, 55.5, 44.4, 27.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{31}H_{32}NO_7^+$ 530.2173, found 530.2194.

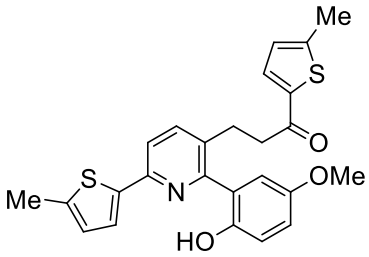


3-(2-(2-Hydroxy-5-methoxyphenyl)-6-(naphthalen-2-yl)pyridin-3-yl)-1-(naphthalen-2-yl)propan-1-one (3cl): White solid; yield = 74% (75.4 mg);



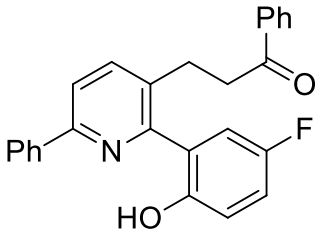
mp = 143-145 °C; R_f = 0.32 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.45 (s, 1H), 8.37 (s, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.97 – 7.90 (m, 5H), 7.87 – 7.85 (m, 3H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.55 – 7.51 (m, 3H), 7.17 (d, *J* = 2.2 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.93 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.77 (s, 3H), 3.50 – 3.48 (m, 2H), 3.40 – 3.37 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 156.0, 153.8, 152.5, 150.6, 141.2, 135.8, 135.3, 133.9, 133.9, 133.8, 133.5, 132.6, 129.9, 129.7, 128.9, 128.74, 128.72, 127.9, 127.8, 126.9, 126.6, 126.4, 124.2, 123.8, 122.9, 119.5, 118.7, 116.7, 114.6, 56.0, 39.2, 27.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{35}H_{28}NO_3^+$ 510.2064, found 510.2068.

3-(2-(2-Hydroxy-5-methoxyphenyl)-6-(5-methylthiophen-2-yl)pyridin-3-yl)-1-(5-methylthiophen-2-yl)propan-1-one (3cm): Pale yellow solid; yield

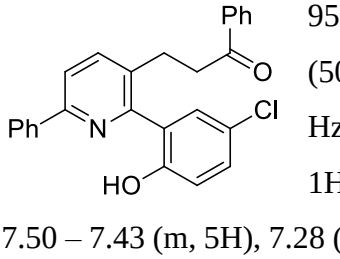


= 75% (67.4 mg); mp = 122-125 °C; R_f = 0.46 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 15.9, 3.1 Hz, 2H), 7.06 – 7.04 (m, 2H), 6.91 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.76 (dd, *J* = 13.3, 2.2 Hz, 2H), 3.77 (s, 3H), 3.34 (t, *J* = 7.5 Hz, 2H), 3.07 (t, *J* = 7.5 Hz, 2H), 2.51 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 155.4, 152.4, 150.7, 150.3, 149.2, 143.0, 141.6, 140.9, 140.9, 132.9, 132.7, 126.9, 126.7, 125.3, 122.4, 118.8, 117.1, 116.8, 114.4, 56.1, 39.3, 28.0, 16.2, 15.7 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{24}NO_3S_2^+$ 450.1192, found 450.1202.

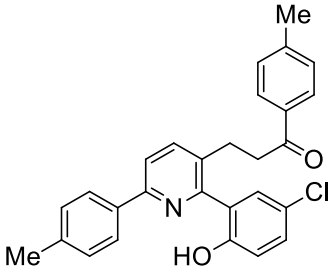
3-(2-(5-Fluoro-2-hydroxyphenyl)-6-phenylpyridin-3-yl)-1-phenylpropan-1-one (3da): Colorless solid; yield =72% (57.2 mg); mp = 79-80 °C; R_f = 0.37 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.23 (s, 1H), 7.94 (d, *J* = 7.1 Hz, 2H), 7.88 (d, *J* = 7.4 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.56-7.53 (m, 1H), 7.48-7.41 (m, 5H), 7.26 (d, *J* = 10.0 Hz, 1H), 7.03 (d, *J* = 5.5 Hz, 2H), 3.36-3.33 (m, 2H), 3.25-3.22 (m, 2H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ -124.50 (dd, *J* = 13.7, 6.7 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 155.85 (d, J_{C-F} = 235.0 Hz), 153.8, 152.9, 141.1, 137.7, 136.5, 133.68 (d, J_{C-F} = 49.9 Hz), 129.6, 129.1, 128.8, 128.1, 126.8, 122.8 (d, J_{C-F} = 7.3 Hz), 119.58, 119.0 (d, J_{C-F} = 7.7 Hz), 117.4, 117.2, 115.7, 115.5, 39.0, 27.17 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}FNO_2^+$ 398.1551, found 398.1547.



3-(2-(5-Chloro-2-hydroxyphenyl)-6-phenylpyridin-3-yl)-1-phenylpropan-1-one (3ea): Colorless solid; yield = 75% (62.0 mg); mp = 93-95 °C; R_f = 0.34 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.54 (s, 1H), 7.95 (d, *J* = 7.9 Hz, 2H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.55 (m, 2H), 7.50 – 7.43 (m, 5H), 7.28 (s, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 3.40 (t, *J* = 7.2 Hz, 2H), 3.28 (t, *J* = 7.2 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 155.7, 154.7, 153.8, 141.3, 137.7, 136.5, 133.9, 133.5, 130.5, 129.7, 129.2, 129.0, 128.8, 128.2, 126.8, 123.9, 123.4, 119.6, 39.1, 27.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}ClNO_2^+$ 414.1255, found 414.1263.

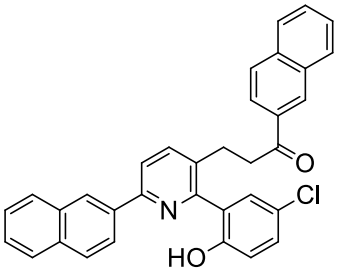


3-(2-(5-Chloro-2-hydroxyphenyl)-6-(4-methylphenyl)pyridin-3-yl)-1-(4-methylphenyl)propan-1-one(3eb): Colorless solid; yield =74% (65.4 mg); mp = 108-110 °C; R_f = 0.37 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.68 (s, 1H), 7.83 – 7.78 (m, 5H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.53 (s, 1H), 7.28 – 7.22 (m, 5H), 7.03 (d, *J* = 8.6 Hz, 1H), 3.35 (t, *J* = 6.8 Hz, 2H), 3.22 (t, *J* = 6.9

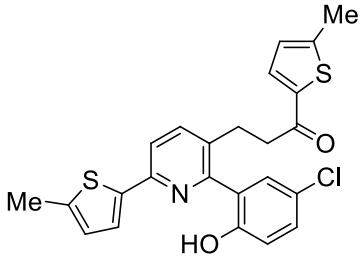


Hz, 2H), 2.40 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 155.7, 154.5, 153.7, 144.3, 141.2, 139.8, 134.9, 134.1, 133.6, 130.4, 129.8, 129.5, 129.0, 128.3, 126.7, 123.8, 123.5, 119.5, 119.2, 39.0, 27.3, 21.7, 21.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{28}H_{25}ClNO_2^+$ 442.1568, found 442.1577.

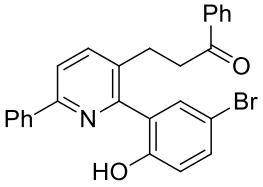
3-(2-(5-Chloro-2-hydroxyphenyl)-6-(naphthalen-2-yl)pyridin-3-yl)-1-(naphthalen-2-yl)propan-1-one (3el): Colorless solid; yield = 69% (70.9 mg); mp = 167-169 °C; R_f = 0.32 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.51 (s, 1H), 8.41 (d, *J* = 12.1 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.00-7.93 (m, 5H), 7.89-7.82 (m, 4H), 7.60-7.52 (m, 5H), 7.29 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 3.49-3.46 (m, 1H), 3.44-3.41 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 155.6, 154.8, 153.8, 141.3, 135.8, 135.0, 134.0, 133.9, 133.5, 132.6, 130.5, 129.9, 129.7, 129.1, 128.9, 128.9, 128.7, 127.9, 127.8, 127.0, 127.0, 126.7, 126.7, 126.5, 124.1, 124.0, 123.8, 123.6, 119.9, 119.6, 39.0, 27.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{34}H_{25}ClNO_2^+$ 514.1568, found 514.1586.



3-(2-(5-Chloro-2-hydroxyphenyl)-6-(5-methylthiophen-2-yl)pyridin-3-yl)-1-(5-methylthiophen-2-yl)propan-1-one(3em): Colorless solid; yield =70% (63.5 mg); mp =110-112 °C; R_f = 0.30 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.50–7.48 (m, 2H), 7.42 (d, *J* = 3.7 Hz, 1H), 7.39 (d, *J* = 3.5 Hz, 1H), 7.27 (d, *J* = 2.5 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 6.77 (t, *J* = 3.6 Hz, 2H), 3.31 (t, *J* = 7.4 Hz, 2H), 3.09 (t, *J* = 7.4 Hz, 2H), 2.52 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 155.6, 154.2, 150.4, 149.2, 143.2, 141.5, 141.1, 140.5, 132.9, 132.8, 130.5, 128.9, 127.0, 126.8, 125.6, 123.9, 123.1, 119.6, 117.5, 39.3, 27.8, 16.2, 15.7 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}ClNO_2S_2^+$ 454.0697, found 454.0699.

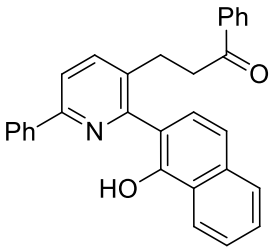


3-(2-(5-Bromo-2-hydroxyphenyl)-6-phenylpyridin-3-yl)-1-phenylpropan-1-one(3fa): Colorless solid; yield =74% (67.8 mg); mp = 109-111 °C; R_f = 0.39 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ



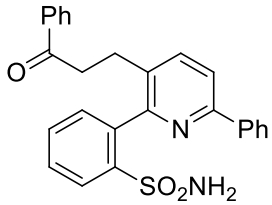
11.55 (s, 1H), 7.94 – 7.92 (m, 2H), 7.90 – 7.88 (m, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.67 – 7.65 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.49 – 7.42 (m, 5H), 7.39 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 3.36 (t, *J* = 7.3 Hz, 2H), 3.26 (t, *J* = 7.2 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 156.1, 154.6, 153.8, 141.2, 137.6, 136.5, 133.9, 133.4, 133.4, 131.9, 129.7, 129.1, 128.8, 128.2, 126.8, 124.1, 120.0, 119.6, 111.0, 39.0, 27.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}{}^{79}BrNO2^+$ 458.0750, found 458.0755; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}{}^{81}BrNO_2^+$ 460.0733, found 460.0788.

3-(2-(1-Hydroxynaphthalen-2-yl)-6-phenylpyridin-3-yl)-1-phenylpropan-1-one(3ga): Yellow color solid; yield = 77% (66.1 mg); mp =



72-74 °C; R_f = 0.32 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.28 (s, 1H), 8.46 (d, *J* = 7.0 Hz, 1H), 8.00 (d, *J* = 7.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 7.4 Hz, 2H), 7.78 (d, *J* = 7.1 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.52-7.45 (m, 6H), 7.37-7.36 (m, 3H), 3.48-3.45 (m, 2H), 3.24-3.21 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 156.6, 154.5, 153.4, 141.4, 137.9, 136.6, 134.8, 133.6, 133.3, 129.5, 129.2, 128.7, 128.1, 127.5, 127.4, 126.9, 126.1, 125.9, 125.4, 123.5, 118.8, 118.2, 114.8, 39.1, 27.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{30}H_{24}NO_2^+$ 430.1802, found 430.1817.

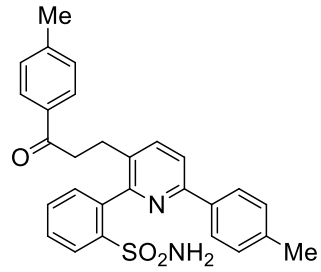
2-(3-(3-Oxo-3-phenylpropyl)-6-phenylpyridin-2-yl)benzenesulfonamide(3ha): Pale yellow solid; yield = 81% (71.7 mg); mp



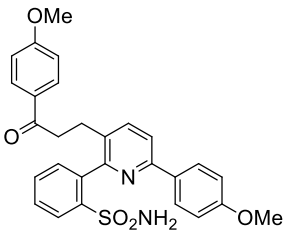
= 183-185 °C; R_f = 0.51 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.6 Hz, 1H), 7.89-7.85 (m, 3H), 7.82 (d, *J* = 7.3 Hz, 2H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.68-7.65 (m, 1H), 7.60-7.57 (m, 1H), 7.52-7.47 (m, 2H), 7.45-7.37 (m, 5H), 5.70 (s, 2H), 3.17-3.12 (m, 2H), 3.03 (t,

J = 7.2 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 157.4, 154.4, 141.0, 139.9, 138.4, 137.8, 136.4, 134.3, 133.2, 132.5, 131.8, 129.4, 129.1, 129.0, 128.7, 128.1, 128.1, 126.8, 120.6, 38.7, 26.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_3S^+$ 443.1424, found 443.1429.

2-(3-(3-Oxo-3-(4-methylphenyl)propyl)-6-(4-methylphenyl)pyridin-2-yl)benzenesulfonamide (3hb): Pale yellow solid; yield =79% (74.2 mg); mp = 208-210 °C; R_f = 0.53 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.71-7.70 (m, 3H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.25 – 7.22 (m, 3H), 7.17 (d, *J* = 7.9 Hz, 2H), 5.73 (s, 2H), 3.17 – 3.04 (m, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 2.38 (s, 3H), 2.36 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 157.2, 154.4, 144.0, 141.1, 139.8, 139.4, 137.9, 135.6, 134.0, 132.5, 131.8, 129.8, 129.4, 128.9, 128.3, 128.1, 126.7, 120.3, 38.7, 26.9, 21.7, 21.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_3S^+$ 471.1737, found 471.1719.



2-(6-(4-Methoxyphenyl)-3-(3-(4-methoxyphenyl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3hc): Yellow solid; yield =77% (77.3 mg); mp = 88-91°C; R_f = 0.48 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.7 Hz, 1H), 7.83 – 7.78 (m, 5H), 7.67 – 7.63 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.78 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.14 – 2.97 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 163.6, 160.7, 157.1, 154.0, 141.0, 139.8, 137.9, 133.6, 132.5, 131.8, 131.0, 130.4, 129.6, 128.8, 128.11,128.09 119.9, 114.4, 113.8, 55.5, 55.4, 38.4, 27.0 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_5S^+$ 503.1635 , found 503.1631.

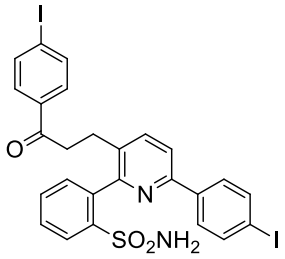


2-(6-(4-Cyclohexylphenyl)-3-(3-(4-cyclohexylphenyl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3hf): Pale yellow solid; yield =72% (87.3 mg); mp = 95-97 °C; R_f = 0.54 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.7 Hz, 1H), 7.81 (t, *J* = 9.1 Hz, 3H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 7.28 (s, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.74 (s, 2H), 3.17 – 3.07 (m, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.53 – 2.52 (m, 2H), 1.90 – 1.82 (m, 8H), 1.75 (d, *J* = 11.8 Hz, 2H), 1.47 – 1.37 (m, 8H), 1.27 – 1.25 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 157.2, 154.4, 153.9, 149.5, 141.0, 139.8, 137.9, 135.9, 134.3, 134.0, 132.5, 131.8, 128.9, 128.4, 128.1, 127.6, 127.2, 126.7, 120.3, 44.7, 44.4, 38.7, 34.4, 34.2, 27.0, 26.9, 26.8, 26.2, 26.1 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{38}H_{43}N_2O_3S^+$ 607.2989, found 607.2991

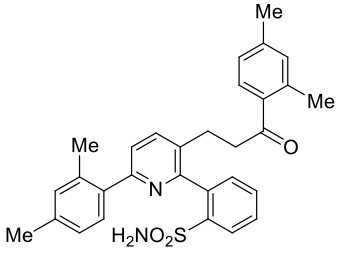
2-(6-(4-Chlorophenyl)-3-(3-(4-chlorophenyl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3hi): Pale yellow solid; yield =82% (83.8 mg); mp = 137-139 °C; R_f = 0.41 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.71 – 7.66 (m, 2H), 7.61 (t, *J* = 7.1 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 5.61 (s, 2H), 3.09 – 2.01 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 157.6, 153.3, 141.0, 140.1, 139.7, 137.6, 136.8, 135.6, 134.7, 134.5, 132.6, 131.7, 129.6, 129.3, 129.1, 129.0, 128.2, 128.1, 120.5, 38.6, 26.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}Cl_2N_2O_2^+$ 511.0644 , found 511.0626.

2-(6-(4-Bromophenyl)-3-(3-(4-bromophenyl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3hj): Pale yellow solid; yield =81% (97.2 mg); mp = 172-173°C; R_f = 0.50 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H),

7.76 (d, *J* = 8.5 Hz, 2H), 7.71 – 7.65 (m, 4H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 7.4 Hz, 1H), 5.63 (s, 2H), 3.10 – 3.05 (m, 2H), 3.02 – 2.99 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 157.6, 153.3, 141.0, 140.1, 137.5, 137.3, 135.1, 134.5, 132.6, 132.3, 132.0, 131.7, 129.7, 129.1, 128.5, 128.3, 128.2, 123.9, 120.4, 38.5, 26.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}{}^{79}Br_2N_2O_3S^+$ 598.9634, found 598.9631, HRMS (ESI-TOF); *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}{}^{79}Br^{81}BrN_2O_3S^+$ 600.9615, found 600.9613; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}{}^{81}Br_2N_2O_3S^+$ 602.9599, found 602.9594.

2-(6-(4-Iodophenyl)-3-(3-(4-iodophenyl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3hk): Colorless solid; yield =75% (104.1 mg); mp = 189-191 °C; R_f = 0.46 (EtOAc/Hexane = 25:75); 

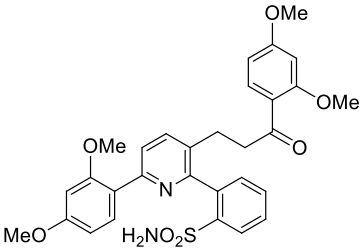
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.77 – 7.73 (m, 4H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.62 – 7.59 (m, 3H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 7.4 Hz, 1H), 5.62 (s, 2H), 3.08 – 2.98 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 157.6, 153.4, 141.0, 140.2, 138.3, 138.0, 135.7, 134.6, 134.0, 133.6, 132.6, 131.7, 129.5, 129.2, 128.5, 128.2, 123.8, 122.6, 120.5, 101.3, 95.9, 38.5, 26.8 ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}I_2N_2O_3S^+$ 694.9357, found 694.9336.

2-(6-(2,4-Dimethylphenyl)-3-(3-(2,4-dimethylphenyl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3hd): Pale yellow solid; yield 

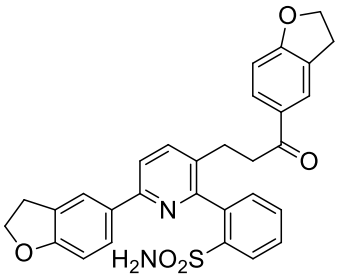
=72% (71.7 mg); mp = 155-157°C; R_f = 0.52 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.07 – 7.04 (m, 2H), 6.99 – 6.96 (m, 2H), 5.69 (s, 2H), 3.05 – 2.96 (m, 4H), 2.43 (s, 3H), 2.35 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 156.9, 156.8, 142.2, 141.1, 139.0, 138.9, 138.4, 137.6, 136.9, 135.6,

134.1, 133.6, 132.9, 132.4, 131.8, 131.5, 129.6, 129.4, 128.9, 128.1, 126.8, 126.6, 124.1, 41.0, 27.1, 21.8, 21.4, 21.2, 20.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{30}H_{31}N_2O_3S^+$ 499.2050, found 499.2034.

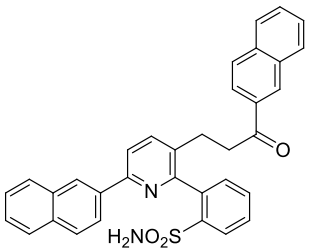
2-(6-(2,4-Dimethoxyphenyl)-3-(3-(2,4-dimethoxyphenyl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3he): Pale yellow solid; yield =75% (84.3 mg); mp = 163-165°C; R_f = 0.39 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.7 Hz, 1H), 7.77 – 7.74 (m, 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.52 – 7.43 (m, 3H), 6.53–6.51 (m, 2H), 6.47 (dd, *J* = 8.7, 1.7 Hz, 1H), 6.39 (d, *J* = 1.5 Hz, 1H), 5.75 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.82 (s, 6H), 3.20–3.07 (m, 2H), 2.95 (t, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 164.6, 161.5, 161.3, 158.2, 156.8, 153.4, 140.8, 138.8, 138.2, 133.9, 132.7, 132.4, 131.9, 131.6, 128.6, 127.9, 124.5, 121.7, 120.5, 105.2, 105.1, 99.2, 98.3, 55.6, 55.6, 55.5, 55.5, 43.4, 27.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{30}H_{31}N_2O_7S^+$ 563.1846, found 563.1843.



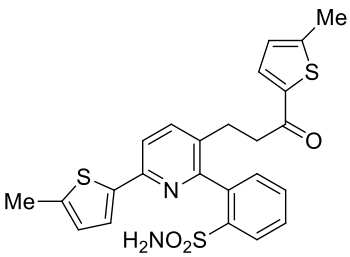
2-(6-(2,3-Dihydrobenzofuran-5-yl)-3-(3-(2,3-dihydrobenzofuran-5-yl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3hg): Gummy; yield = 74% (77.9 mg); mp = 72-74 °C; R_f = 0.41 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 10.4 Hz, 2H), 7.67 – 7.63 (m, 4H), 7.60 – 7.56 (m, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 5.74 (s, 2H), 4.62 (t, *J* = 8.7 Hz, 4H), 3.25 – 3.17 (m, 4H), 3.13 – 3.02 (m, 2H), 2.98 – 2.97 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 164.5, 161.4, 157.0, 154.5, 141.0, 139.7, 138.0, 133.4, 132.5, 131.8, 131.3, 130.1, 129.9, 128.8, 128.1, 128.0, 127.7, 127.3, 125.5, 123.5, 119.9, 109.7, 109.1, 72.3, 71.8, 38.6, 29.6, 29.0, 27.1 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}N_2O_5S^+$ 527.1635, found 527.1636.



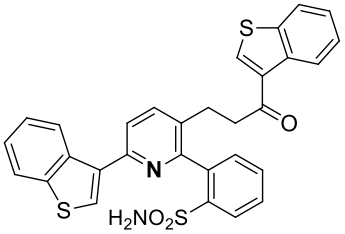
2-(6-(Naphthalen-2-yl)-3-(3-(naphthalen-2-yl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3hl): Pale yellow solid; yield =73% (79.2 mg); mp = 140-142°C; R_f = 0.43 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 2H), 8.22 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.93 – 7.81 (m, 9H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.60 7.49 (m, 6H), 5.73 (s, 2H), 3.37 – 3.25 (m, 2H), 3.11 (t, *J* = 7.2 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 157.6, 154.4, 141.1, 140.0, 137.9, 135.8, 135.7, 134.4, 133.8, 133.8, 133.6, 132.64, 132.62, 131.8, 130.2, 129.9, 129.0, 128.9, 128.7, 128.6, 128.5, 128.2, 127.8, 127.7, 126.9, 126.8, 126.7, 126.4, 124.3, 123.8, 121.0, 38.8, 27.1 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{34}H_{27}N_2O_3S^+$ 543.1737, found 543.1733.



2-(6-(5-Methylthiophen-2-yl)-3-(3-(5-methylthiophen-2-yl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3hm): Pale yellow solid; yield =76% (73.3 mg); mp = 110-112 °C; R_f = 0.37 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.65–7.62 (m, 1H), 7.59–7.56 (m, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.33–7.31 (m, 2H), 6.72 (d, *J* = 25.8 Hz, 2H), 5.75 (s, 2H), 2.97–2.88 (m, 4H), 2.47 (s, 3H), 2.46 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 157.0, 149.8, 149.7, 142.4, 141.5, 141.1, 140.8, 139.5, 137.4, 133.2, 133.1, 132.4, 131.7, 128.8, 128.0, 126.9, 126.8, 125.1, 118.3, 38.5, 27.0, 16.0, 15.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_3S_3^+$ 483.0865, found 483.0848.



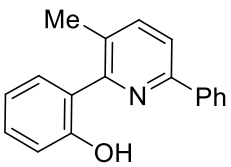
2-(6-(Benzo[*b*]thiophen-3-yl)-3-(3-(benzo[*b*]thiophen-3-yl)-3-oxopropyl)pyridin-2-yl)benzenesulfonamide (3hn): Yellow solid; yield =73% (80.9 mg); mp = 139-141 °C; R_f = 0.42 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 7.5 Hz, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 8.12 (s, 1H), 7.91–7.89 (d, *J* = 7.7 Hz, 2H), 7.83 – 7.81 (m, 2H), 7.71 – 7.67 (m, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H),

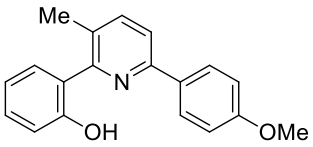


7.40–7.33 (m, 3H), 5.72 (s, 2H), 3.15–3.07 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 157.3, 151.4, 141.1, 141.1, 140.0, 140.0, 137.9, 137.5, 137.0, 136.6, 135.3, 134.6, 134.2, 132.6, 131.9, 129.1, 128.2, 127.2, 125.8, 125.5, 125.4, 124.9, 124.9, 123.6, 123.1, 122.5, 122.3, 40.1, 27.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{30}H_{23}N_2O_3S_3^+$ 555.0865, found 555.0855.

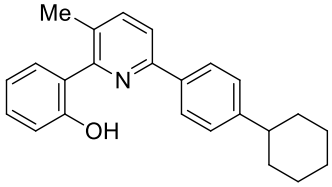
Representative procedure for the synthesis of (3ia): A mixture of compounds sulfonyl imine **1i** (0.2 mmol), 3-chloropropiophenone **2a** (0.22 mmol), catalyst DIPEA (20 mol%) and base $NaHCO_3$ (0.4 mmol) in dry 2-MeTHF (2.0 mL) was heated at 70 °C under an inert atmosphere. After completion of the reaction (continuously monitored by TLC), NH_4OAc (0.5 mmol) was added to the above reaction mixture at the same temperature under aerobic conditions for 18 h. After completion of the reaction, the solvent was evaporated from the reaction mixture under reduced pressure to give the solid crude residue, which was further extracted with ethyl acetate (3 × 10 mL), washed with water and brine, respectively, and passed through Na_2SO_4. The extracted combined organic phases were removed under reduced pressure to give the crude solid product. Finally, product **3ia** was isolated in its pure form (82% yield) by performing column chromatography over silica gel with a mixture of EtOAc/hexane (10:90 v/v) as the eluent. The pyridine **3ia** was fully characterized by its spectroscopic data (^{1}HNMR, ^{13}C NMR, and HRMS). Furthermore, all the accessed 3-picoline derivatives (**3ia-3ma)** in **Scheme 3.9** are unknown in the literature.

2-(3-Methyl-6-phenylpyridin-2-yl)phenol (3ia): Colorless solid; yield =82%; mp = 70-72 °C; R_f = 0.67 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.63 (s, 1H), 7.97–7.96 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.64–7.59 (m, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.10 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.96–6.93 (m, 1H), 2.61 (s, 3H) ppm; ^{13}C NMR (125 MHz,) δ 157.9, 156.1, 152.9, 142.3, 138.0, 130.6, 130.2, 129.9, 129.4, 129.1, 126.8, 121.8, 118.7, 118.5, 118.0, 21.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}NO^+$ 262.1226, found 262.1227.

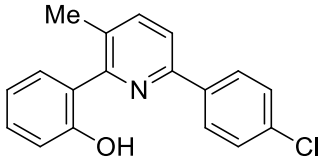


2-(6-(4-Methoxyphenyl)-3-methylpyridin-2-yl)phenol (3ic): Pale yellow solid; yield =77% (44.2 mg); mp = 101-103 °C; 

R_f = 0.70 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.75 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 2H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.31–7.29 (m, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 2H), 6.94–6.92 (m, 1H), 3.86 (s, 3H), 2.58 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 157.9, 155.8, 152.6, 142.3, 130.6, 130.5, 129.8, 129.3, 128.0, 121.8, 118.4, 118.0, 114.5, 55.5, 21.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}NO_2^+$ 292.1332, found 292.1336.

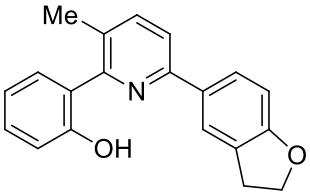
2-(6-(4-Cyclohexylphenyl)-3-methylpyridin-2-yl)phenol (3if): Yellow solid; yield =75% (51.5 mg); mp = 50-52 °C; 

R_f = 0.68 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.79 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 6.5 Hz, 2H), 7.33–7.30 (t, *J* = 8.8 Hz, 3H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.94 (t, *J* = 7.4 Hz, 1H), 2.60 (s, 3H), 1.92 (d, *J* = 10.3 Hz, 1H), 1.87 (d, *J* = 10.2 Hz, 1H), 1.78 (d, *J* = 12.5 Hz, 1H), 1.50–1.27 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 155.9, 152.9, 149.6, 142.3, 135.6, 130.5, 127.6, 126.7, 121.8, 118.4, 118.0, 44.5, 34.4, 26.9, 26.2, 21.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{26}NO^+$ 344.2009, found 344.2010.

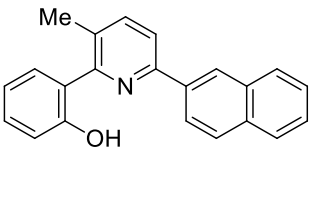
2-(6-(4-Chlorophenyl)-3-methylpyridin-2-yl)phenol (3ii): Colorless solid; yield =83% (49.0 mg); mp = 63-65°C; 

R_f = 0.61 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.34 (s, 1H), 7.90–7.88 (m, 2H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.46–7.43 (m, 2H), 7.34–7.30 (m, 1H), 7.10 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.95 (td, *J* = 7.9, 1.2 Hz, 1H), 2.59 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 156.2, 151.7, 142.4, 136.5, 135.5, 130.7, 130.6, 129.9, 129.3, 128.0, 121.7, 118.6, 118.5, 118.0, 21.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{18}H_{15}ClNO^+$ 296.0837, found 296.0843.

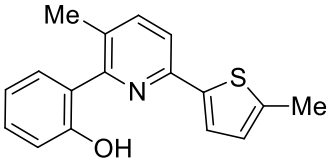
2-(6-(2,3-Dihydrobenzofuran-5-yl)-3-methylpyridin-2-yl)phenol (3ig): Colorless solid; yield = 73% (44.2 mg); mp = 121-124°C; R_f = 0.46 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.76 (s, 1H), 7.84 (s, 1H), 7.73 7.69 (m, 2H), 7.59 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.32–7.29 (m, 1H), 7.09 (dd, *J* = 8.1, 0.8 Hz, 1H), 6.95–6.92 (m, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.64 (t, *J* = 8.7 Hz, 2H), 3.28 (t, *J* = 8.7 Hz, 2H), 2.58 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 157.8, 155.7, 153.0, 142.3, 130.8, 130.5, 129.8, 129.1, 128.2, 127.1, 123.5, 121.9, 118.4, 118.0, 117.9, 109.7, 71.8, 29.7, 21.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}NO_2^+$ 304.1332, found 304.1339



2-(3-Methyl-6-(naphthalen-2-yl)pyridin-2-yl)phenol (3il): Pale yellow solid; yield = 75% (46.7 mg); mp = 175-177 °C; R_f = 0.47 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.58 (s, 1H), 8.44 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.89–7.87 (m, 1H), 7.81 7.75 (m, 2H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.53–7.51 (m, 2H), 7.34 (s, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 2.62 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 156.2, 152.8, 142.3, 135.3, 133.8, 133.5, 130.7, 130.3, 129.9, 128.9, 128.8, 127.8, 126.9, 126.6, 126.3, 124.2, 121.9, 119.0, 118.6, 118.0, 21.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{22}H_{18}NO^+$ 312.1383, found 312.1361.



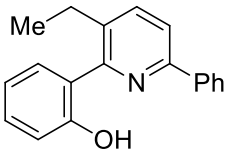
2-(3-Methyl-6-(5-methylthiophen-2-yl)pyridin-2-yl)phenol(3im):



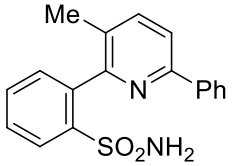
Colorless solid; yield =74% (41.6 mg); mp = 95-97 °C; R_f = 0.41 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.14 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 3.4 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 2.6 Hz, 1H), 2.55 (s, 3H), 2.52 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 155.6, 148.3, 142.7, 142.1, 140.9, 130.6, 129.9, 129.4, 126.7, 125.1, 121.6, 118.5, 118.1, 116.6,

21.5, 15.7 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{17}H_{16}NOS^+$ 282.0947, found 282.0954.

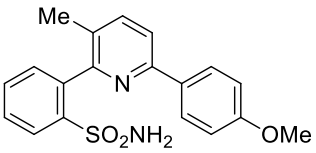
2-(3-Ethyl-6-phenylpyridin-2-yl)phenol (3ja): Colorless oil; yield =75% (41.3 mg); R_f = 0.52 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.04 (s, 1H), 7.98 (d, *J* = 7.3 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.53-7.47 (m, 3H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 2.95 (q, *J* = 7.5 Hz, 2H), 1.33 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 155.8, 152.8, 140.3, 138.1, 136.3, 130.6, 129.7, 129.4, 129.1, 126.8, 122.1, 119.0, 118.8, 118.0, 25.9, 15.3 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{19}H_{18}NO^+$ 276.1383, found 276.1388.



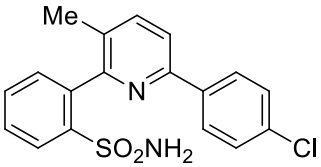
2-(3-Methyl-6-phenylpyridin-2-yl)benzenesulfonamide (3ka): Colorless solid; yield =80% (51.9 mg); mp = 140-142°C; R_f = 0.49 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.1 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.67 (t, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.44–7.37 (m, 4H), 5.65 (s, 2H), 2.22 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 153.9, 140.8, 140.3, 138.6, 138.3, 132.3, 131.5, 131.1, 129.2, 129.0, 128.7, 128.0, 126.7, 120.3, 19.4 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_2S^+$ 325.1005, found 325.0999.



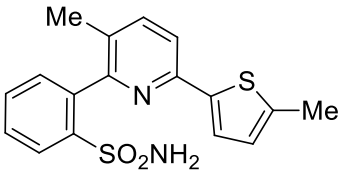
2-(6-(4-Methoxyphenyl)-3-methylpyridin-2-yl)benzenesulfonamide (3kc): Colorless solid; yield =79% (56.0 mg); mp = 159-161 °C; R_f = 0.43 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.67–7.63 (m, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.40 (d, *J* = 7.1 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 2H), 5.67 (s, 2H), 3.84 (s, 3H), 2.19 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 157.2, 153.7, 140.8, 140.3, 138.4, 132.3, 131.5, 131.2, 130.2, 128.6, 128.0, 127.9, 119.6, 114.4, 55.4, 19.3 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{19}H_{19}N_2O_3S^+$ 355.1111, found 355.1105.



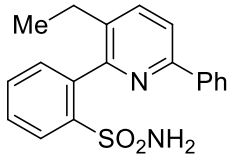
2-(6-(4-Chlorophenyl)-3-methylpyridin-2-yl)benzenesulfonamide (3ki): Colorless solid; yield =82% (58.0 mg); mp = 189-191° C; R_f = 0.45 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.67–7.65 (m, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 3H), 5.56 (s, 2H), 2.21 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 152.8, 140.8, 140.4, 138.1, 137.1, 135.3, 132.4, 131.5, 131.4, 129.2, 128.8, 128.0, 120.2, 19.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}ClN_2O_2S^+$ 359.0616, found 359.0606.



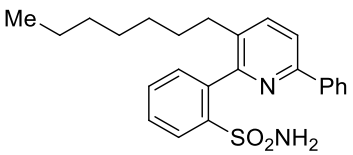
2-(3-Methyl-6-(5-methylthiophen-2-yl)pyridin-2-yl)benzenesulfonamide (3km): Pale yellow solid; yield =76% (52.3 mg); mp = 170-172 °C; R_f = 0.42 (EtOAc/Hexane = 25:75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.4 Hz, 1H), 7.65 – 7.56 (m, 4H), 7.37 – 7.32 (m, 2H), 6.75 (s, 1H), 5.65 (s, 2H), 2.47 (s, 3H), 2.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 149.5, 142.2, 141.4, 140.8, 140.1, 138.1, 132.3, 131.5, 130.4, 128.7, 128.0, 126.8, 124.9, 118.1, 19.4, 15.7 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_2S_2^+$ 345.0726, found 345.0725.



2-(3-Ethyl-6-phenylpyridin-2-yl)benzenesulfonamide (3la): Pale yellow solid; yield =76% (51.4 mg); mp = 163-165°C; R_f = 0.51 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 7.1 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 7.1 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.43–7.36 (m, 4H), 5.65 (s, 2H), 2.61–2.54 (m, 1H), 2.53 2.45 (m, 1H), 1.15 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 153.8, 141.0, 138.7, 138.6, 138.2, 136.8, 132.1, 131.5, 129.1, 129.0, 128.7, 128.0, 126.7, 120.5, 25.4, 14.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_2S^+$ 339.1162, found 339.1164.

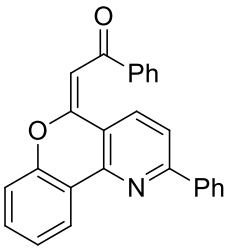


2-(3-Heptyl-6-phenylpyridin-2-yl)benzenesulfonamide (3ma): Pale yellow solid; yield =70% (57.0 mg); mp = 94-96 °C; R_f = 0.78 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.89–7.87 (m, 2H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1H), 7.59 (td, *J* = 7.7, 1.1 Hz, 1H), 7.45–7.37 (m, 4H), 5.67 (s, 2H), 2.61–2.55 (m, 1H), 2.45–2.39 (m, 1H), 1.56–1.50 (m, 2H), 1.26–1.19 (m, 8H), 0.85 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 153.7, 141.0, 139.3, 138.6, 138.1, 135.7, 132.0, 131.5, 129.1, 129.0, 128.7, 128.0, 126.7, 120.4, 32.2, 31.7, 29.9, 29.4, 28.9, 22.7, 14.1 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{29}N_2O_2S^+$ 409.1944, found 409.1951.



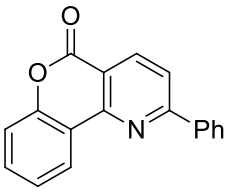
Procedure for the synthesis of (19): The mixture of compounds **3aa** (0.15 mmol), $Cu(OAc)_2$ (10 mol%), 1,10-phenanthroline (10 mol%) and TEMPO (2.0 equiv.) in 1,2-dichlorobenzene (0.5 mL) was stirred at 120 °C in an argon atmosphere for 24 h. After completion of the reaction, it was quenched with water and extracted with ethyl acetate (3 × 10 mL), washed with brine and dried over Na_2SO_4. The extracted combined organic phases were removed under reduced pressure to get the solid crude product which was further purified by column chromatography over silica gel with ethyl acetate/hexane as an eluent, offering a previously unknown compound **19** in 71% yield. The product **19** was characterized by ^{1}H, ^{13}C NMR and HRMS data.

(*E*)-1-Phenyl-2-(2-phenyl-5*H*-chromeno[*4,3-b*]pyridin-5-ylidene)ethanone (19): Yellow solid; yield =71% (40 mg); mp = 185-187°C; R_f = 0.39 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 7.8 Hz, 1H), 8.26–8.22 (m, 3H), 8.00 (d, *J* = 7.3 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.57–7.45 (m, 7H), 7.31–7.28 (m, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.81 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7, 160.0, 158.2, 152.7, 147.2, 140.5, 137.9, 133.2, 131.9, 131.8, 130.3, 128.9, 128.4, 127.9, 127.3, 124.4, 124.1, 120.1, 120.0, 118.6, 117.0, 97.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{18}NO_2^+$ 376.1332, found 376.1308.



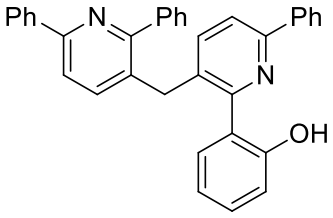
Procedure for the synthesis of (20): A mixture of compounds **3aa** (0.1 mmol), $Cu(OAc)_2$ (10 mol%), 1,10-phenanthroline (10 mol%) and TEMPO (2.0 equiv.) in 1,2-dichlorobenzene (0.5 mL) was stirred at 150 °C in argon atmosphere for 60 h. After that usual work-up and purification were done. The reaction afforded compound **20** in 60% yield. The compound **20** was known in the literature.[3]

2-Phenyl-5*H*-chromeno[*4,3-b*]pyridin-5-one (20): Pale yellow solid; yield = 66% (18 mg); mp = 195-197 °C; R_f = 0.63 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.65 (d, *J* = 8.3 Hz, 1H), 8.26 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.61–7.52 (m, 4H), 7.44 7.39 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 161.4, 153.0, 151.8, 139.1, 137.9, 132.3, 130.9, 129.1, 127.9, 125.0, 124.9, 120.5, 119.7, 117.3, 115.7 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{18}H_{12}NO_2^+$ 274.0863, found 274.0842.



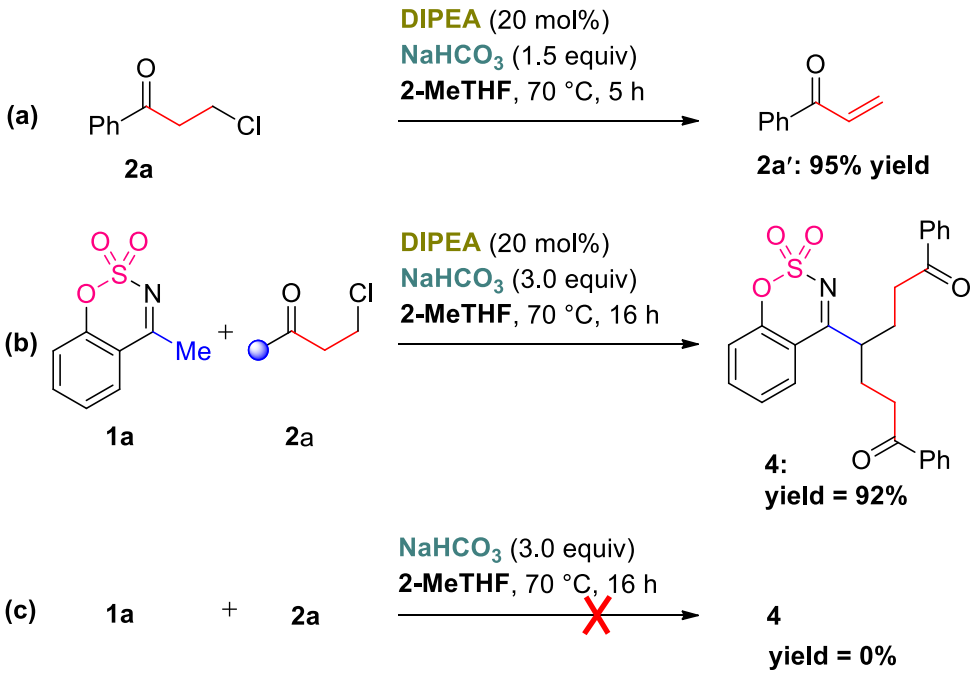
Procedure for the synthesis of (21): To a stirred solution of compound **3aa** (0.22 mmol), **2a** (0.66 mmol, 3.0 equiv.) and NH_4OAc (3.5 equiv.) in dry MeCN (2.0 mL) were kept on stirred at 70 °C for 3 days. After the usual work-up, the crude product was isolated in its pure form by performing column chromatography over silica gel with a mixture of ethyl acetate/hexane (8:92 v/v) to provide a 32% yield of previously unknown compound **21**.

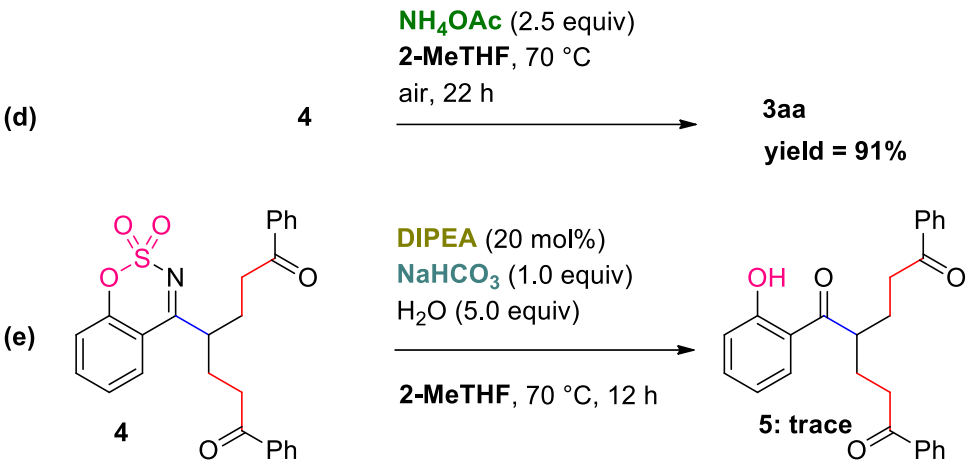
2-(3-((2,6-Diphenylpyridin-3-yl)methyl)-6-phenylpyridin-2-yl)phenol (21): Yellow solid; yield = 32% (34.5 mg); mp = 136-138 °C; R_f = 0.54 (EtOAc/Hexane = 25:75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.0 Hz, 1H), 7.84 (d, *J* = 6.7 Hz, 2H), 7.46-7.42 (m, 6H), 7.34-7.29 (m, 6H), 7.20-7.15 (m, 3H), 7.01-6.96 (m, 4H), 6.80-6.77 (m, 1H), 4.39 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 157.3, 155.9, 152.3, 151.8, 147.7, 140.2, 138.9, 137.9, 133.4, 131.9, 130.6, 129.8, 129.4, 129.1, 128.5, 128.4, 128.4, 128.4, 128.2, 128.2, 127.8, 126.7, 124.1, 120.8, 118.3, 118.1, 117.7, 33.0 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{35}H_{26}N_2O^+$ 491.2118, found 491.2114.



Scheme 3.11a: To a previously stirred solution of 3-chloropropiophenone **2a** (1.0 mmol) in 2-MeTHF (3.0 mL), catalyst DIPEA (20 mol%) and base $NaHCO_3$ (1.5 mmol) was added at 70 °C for 5 h. Afterwards, the crude reaction mixture was concentrated under reduced pressure to provide a solid product. Then it was isolated in its pure form by flash column chromatography over silica gel using diethyl ether/hexane (1:10) as an eluent to give a 95% yield of commercially available vinyl ketone **2a´**.

Scheme 3.11b: A mixture of compounds *N*-sulfonyl ketimine **1a** (0.2 mmol), 3-chloropropiophenone **2a** (0.44 mmol), catalyst DIPEA (20 mol%) and cooperative base $NaHCO_3$(0.6 mmol) in dry 2-MeHF (2.0 mL) was stirred at 70 °C in an inert atmosphere for 16 h. Then, the solvent was evaporated from the reaction mixture under reduced pressure to provide a crude solid, which was further purified by column chromatography over silica gel using a mixture of EtOAc/hexane (10:90 v/v) as the eluent to offer the unknown compound **4** in the excellent yield of 92%. Complete characterization of compound **4** was done by ^{1}H NMR, ^{13}C NMR, and HRMS, which reveals its structure as a double alkylated addition product.





Scheme 3.11. Control Experiments

4-(2,2-Dioxidobenzo[*e*][*1,2,3*]oxathiazin-4-yl)-1,7-diphenylheptane-1,7-dione (4): Colorless solid; yield = 92% (84.9 mg); R_f = 0.22 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.9 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 4H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 2H), 7.44–7.37 (m, 5H), 7.29 (d, *J* = 8.2 Hz, 1H), 3.81 (dt, *J* = 12.9, 6.3 Hz, 1H), 3.25–3.19 (m, 2H), 3.01–2.95 (m, 2H), 2.40–2.33 (m, 2H), 2.17–2.10 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 183.4, 154.0, 137.3, 136.6, 133.4, 128.8, 128.7, 128.1, 126.3, 119.4, 116.4, 41.6, 35.1, 27.2 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{23}NO_5SNa^+$ 484.1189, found 484.1193.

Scheme 3.11d: To a stirred solution of double alkylated addition product **4** (0.1 mmol) in 2-MeTHF (2.0 mL), NH_4OAc (2.5 equiv.) was added at 70 °C in an open atmosphere for 22 h. After the usual work-up, the targeted pyridine derivative **3aa** was obtained in 91% yield through column chromatography over silica gel using a mixture of EtOAc/hexane (7:93 v/v).

4-(2,2-Dioxidobenzo[*e*][*1,2,3*]oxathiazin-4-yl)-1-phenylpentan-1-one (4′): White solid; yield = 91% (**R_f** = 0.31 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.5

Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 3.70 (dd, *J* = 13.4, 6.7 Hz, 1H), 3.23-3.17 (m, 1H), 3.05-2.99 (m, 1H), 2.41 – 2.34 (m, 1H), 2.04 – 1.97 (m, 1H), 1.38 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz,) δ 199.6, 184.1, 154.1, 137.0, 136.6, 133.5, 128.8, 128.3, 128.1, 126.1, 119.5, 115.9, 37.2, 35.1, 28.8, 18.5 ppm; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{17}NO_4SNa^+$ 366.0770, found 366.0782.

3.7 Copies of ^{1}H and ^{13}C NMR of the described compounds:

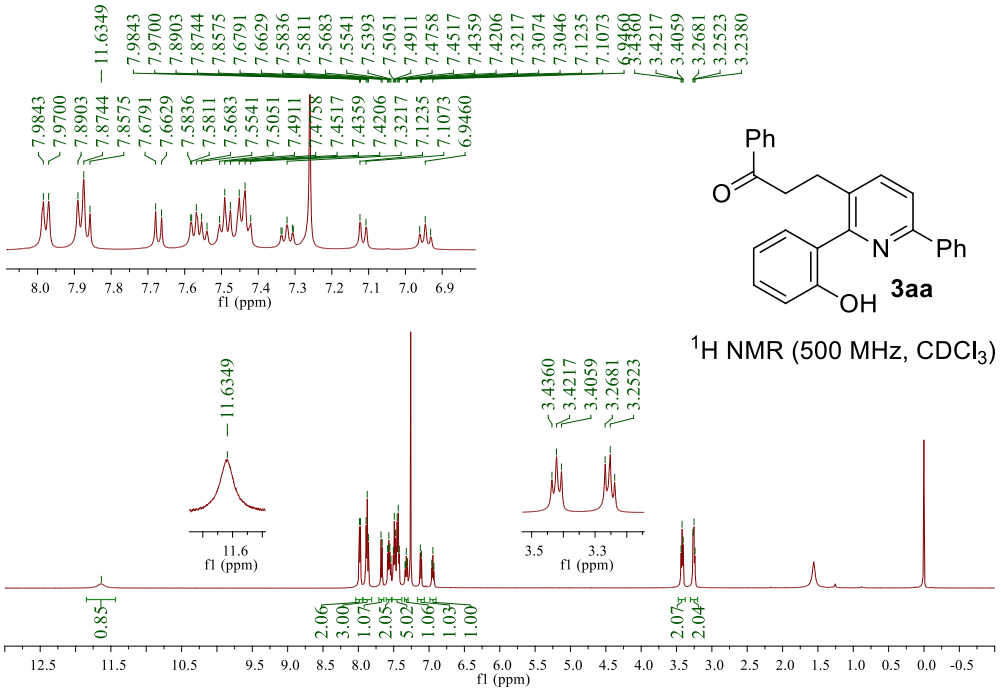


Figure 3.2. 500 MHz ^{1}H Spectrum of **3aa** in $CDCl_3$

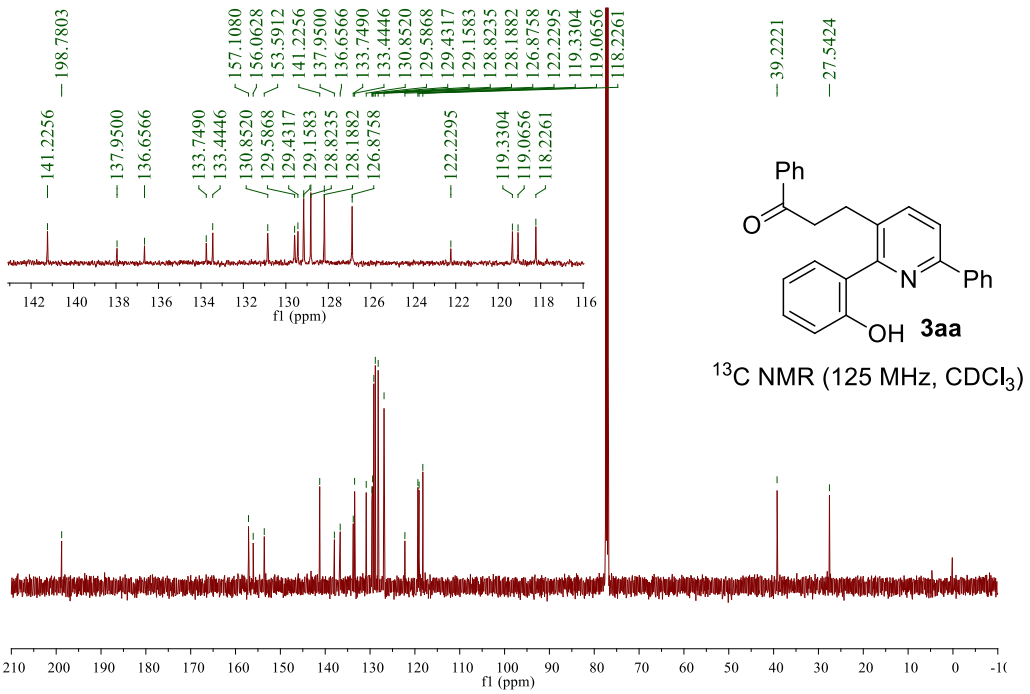


Figure 3.3. 125 MHz ^{13}C Spectrum of **3aa** in $CDCl_3$

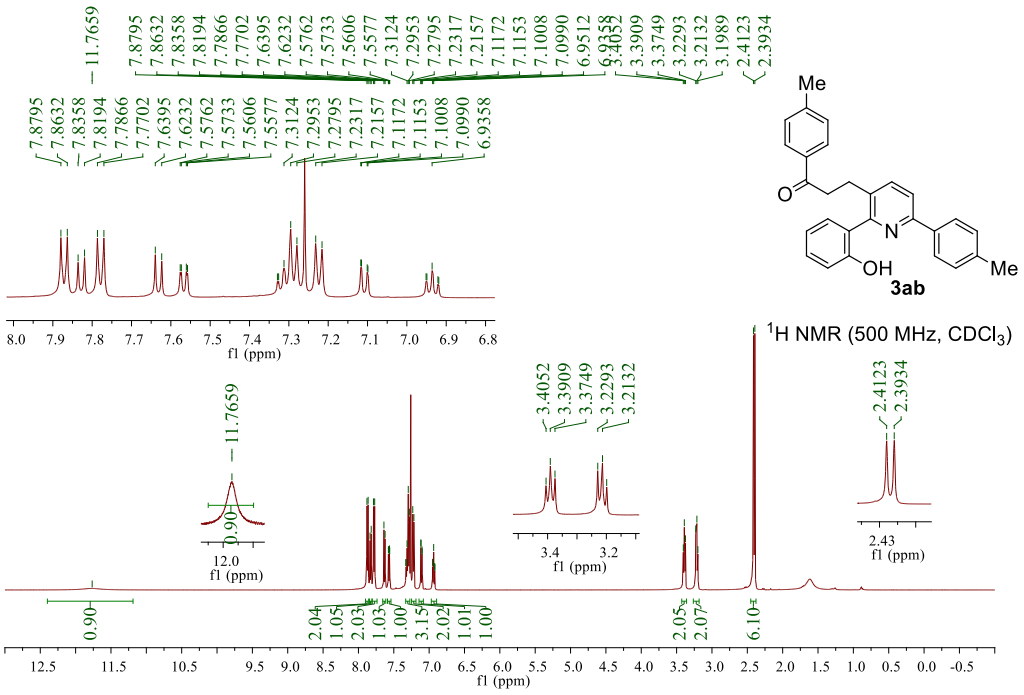


Figure 3.4. 500 MHz ^{1}H Spectrum of **3ab** in $CDCl_3$

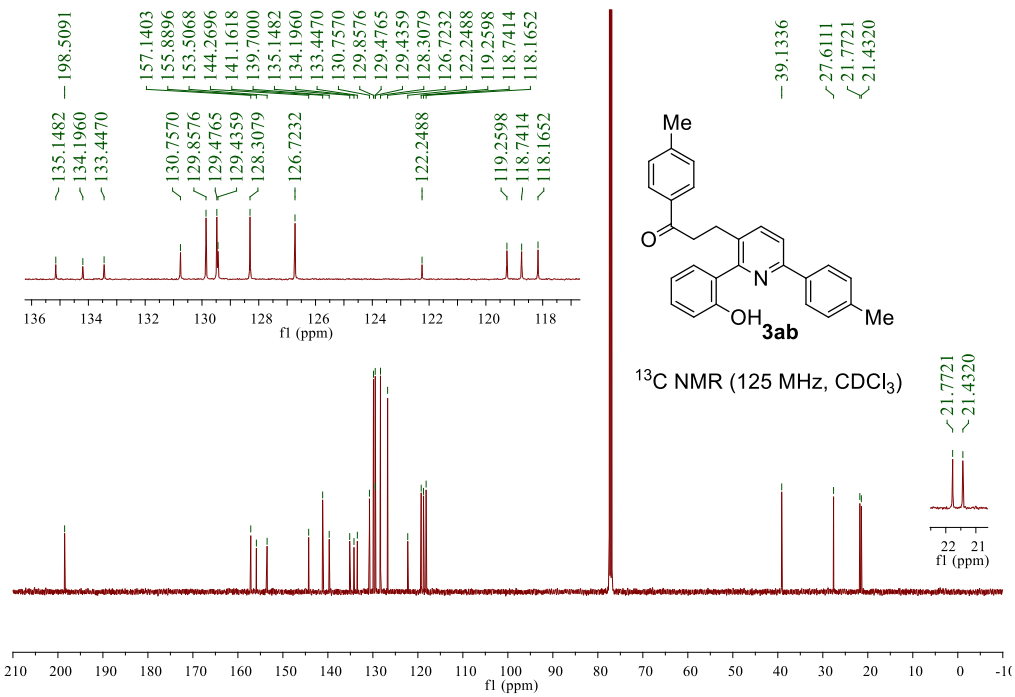


Figure 3.5. 125 MHz ^{13}C Spectrum of **3ab** in $CDCl_3$

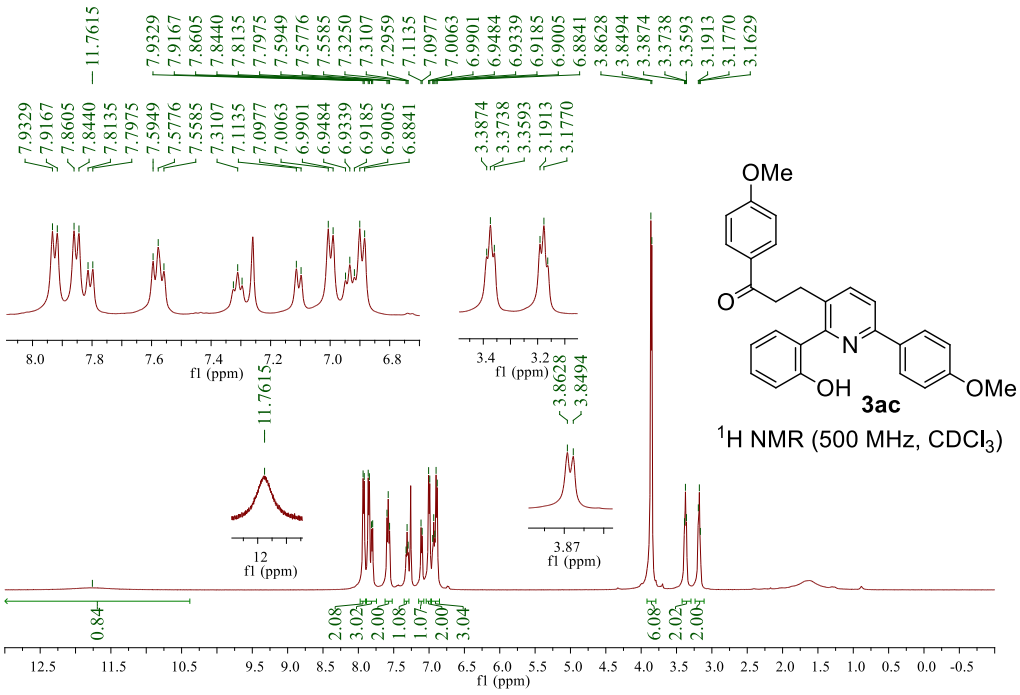


Figure 3.6. 500 MHz ^{1}H Spectrum of **3ac** in $CDCl_3$

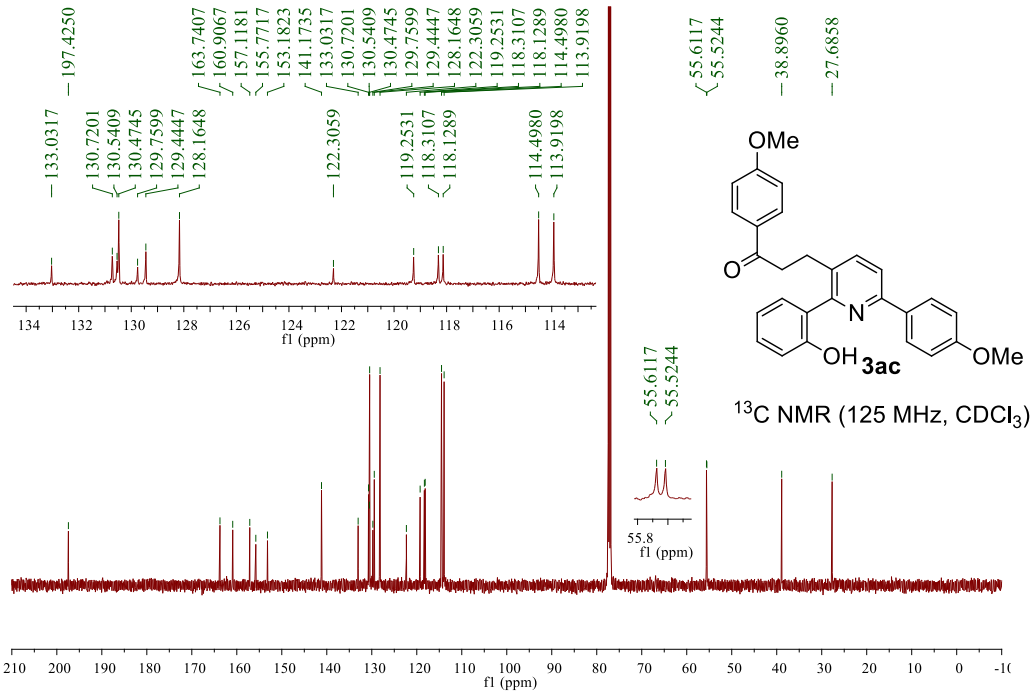


Figure 3.7. 125 MHz ^{13}C Spectrum of **3ac** in $CDCl_3$

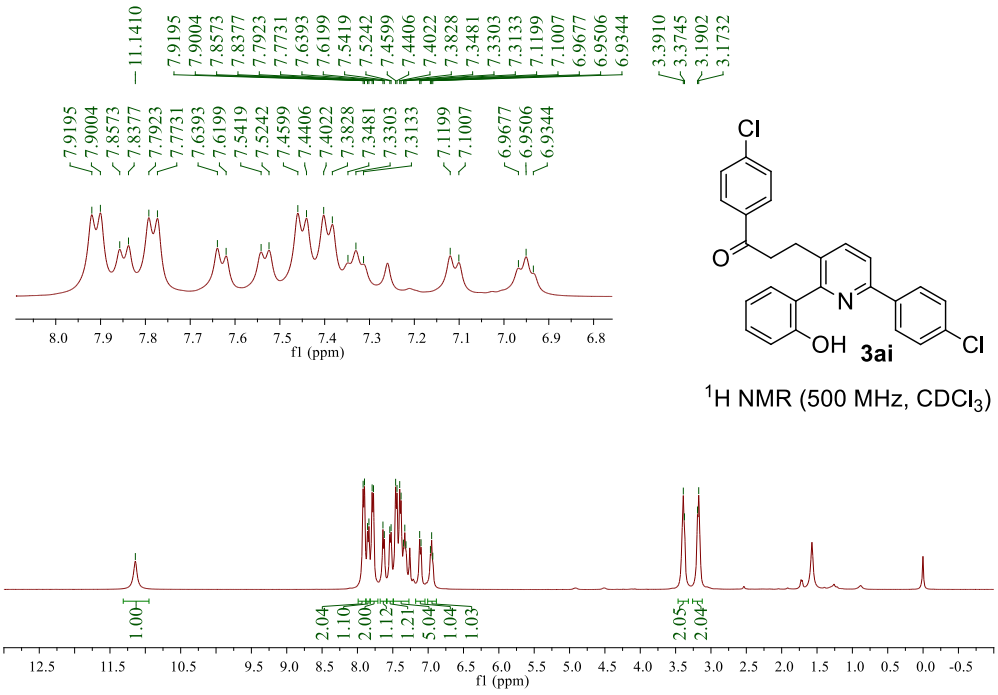


Figure 3.8. 500 MHz ^{1}H Spectrum of **3ai** in $CDCl_3$

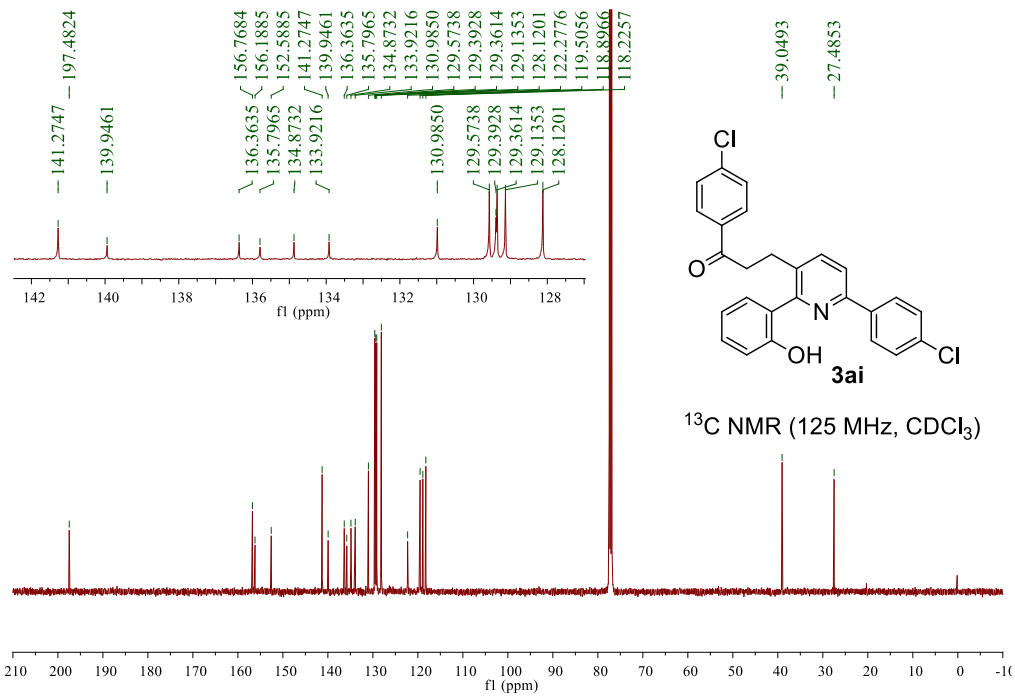


Figure 3.9. 125 MHz ^{13}C Spectrum of **3ai** in $CDCl_3$

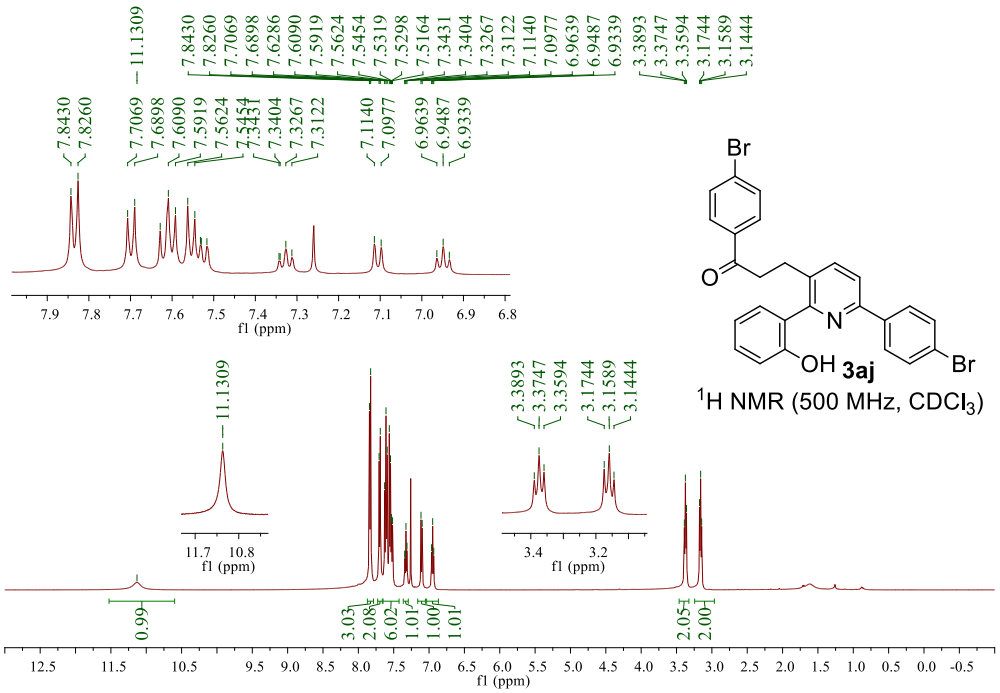


Figure 3.10. 500 MHz ^{1}H Spectrum of **3aj** in $CDCl_3$

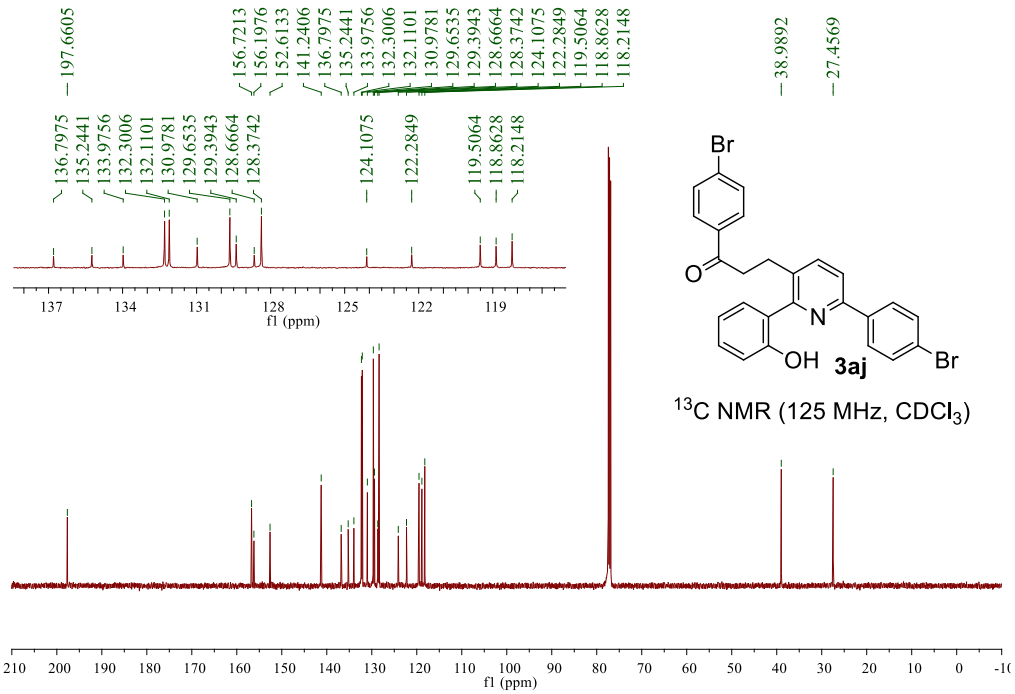


Figure 3.11. 125 MHz ^{13}C Spectrum of **3aj** in $CDCl_3$

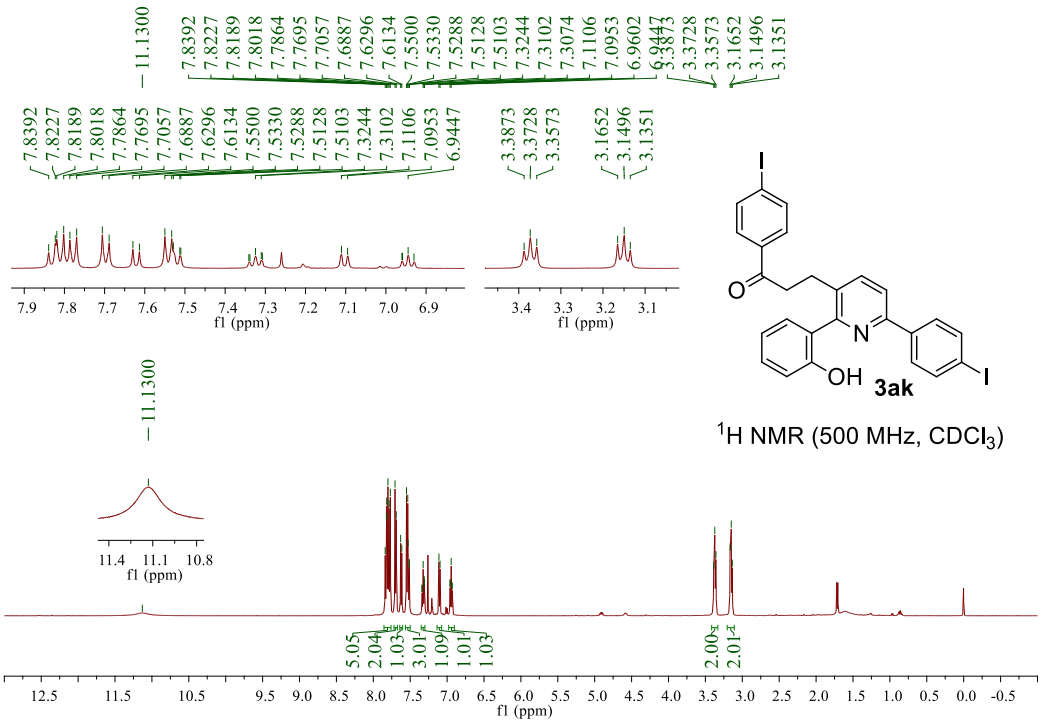


Figure 3.12. 500 MHz ^{1}H Spectrum of **3ak** in $CDCl_3$

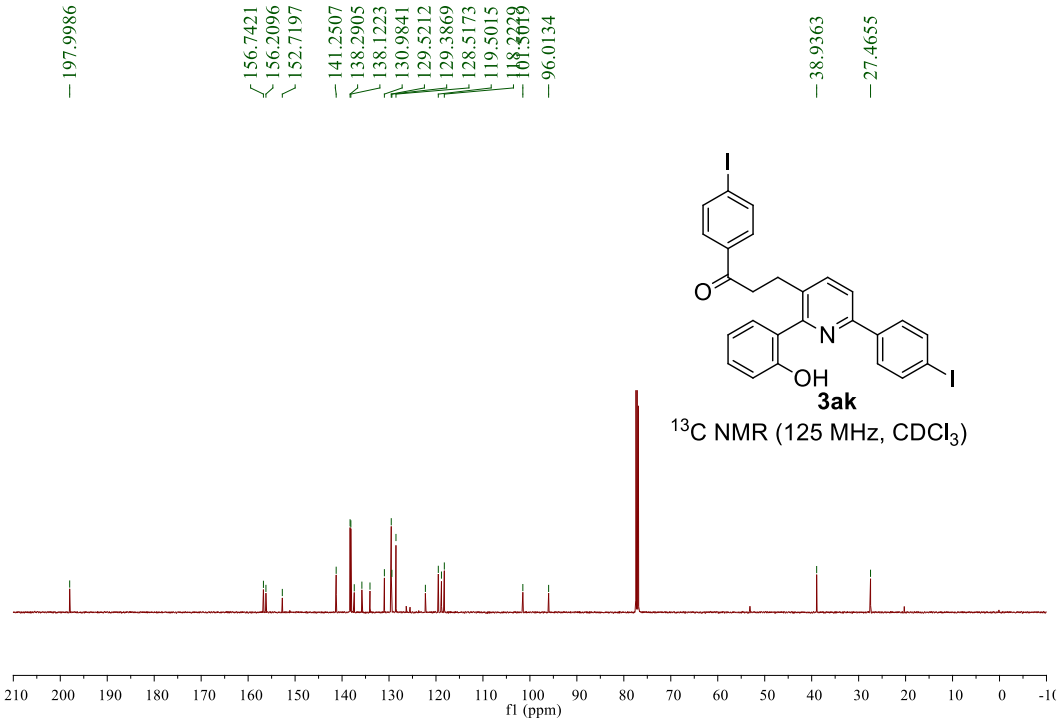


Figure 3.13. 125 MHz ^{13}C Spectrum of **3ak** in $CDCl_3$

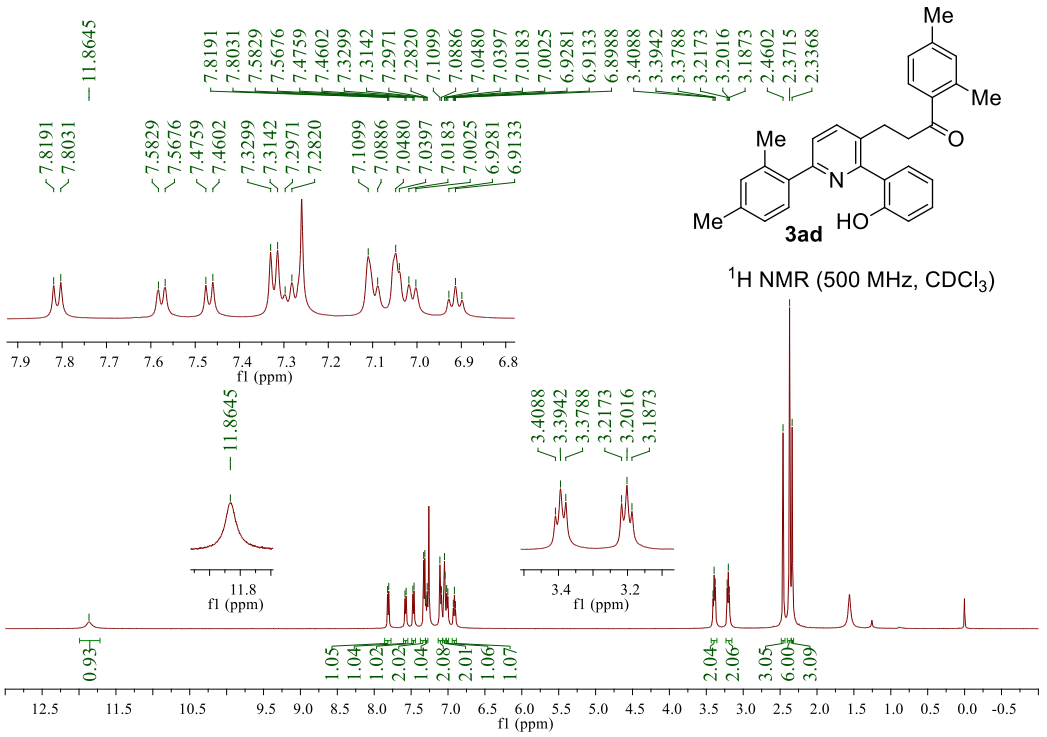


Figure 3.14. 500 MHz ^{1}H Spectrum of **3ad** in $CDCl_3$

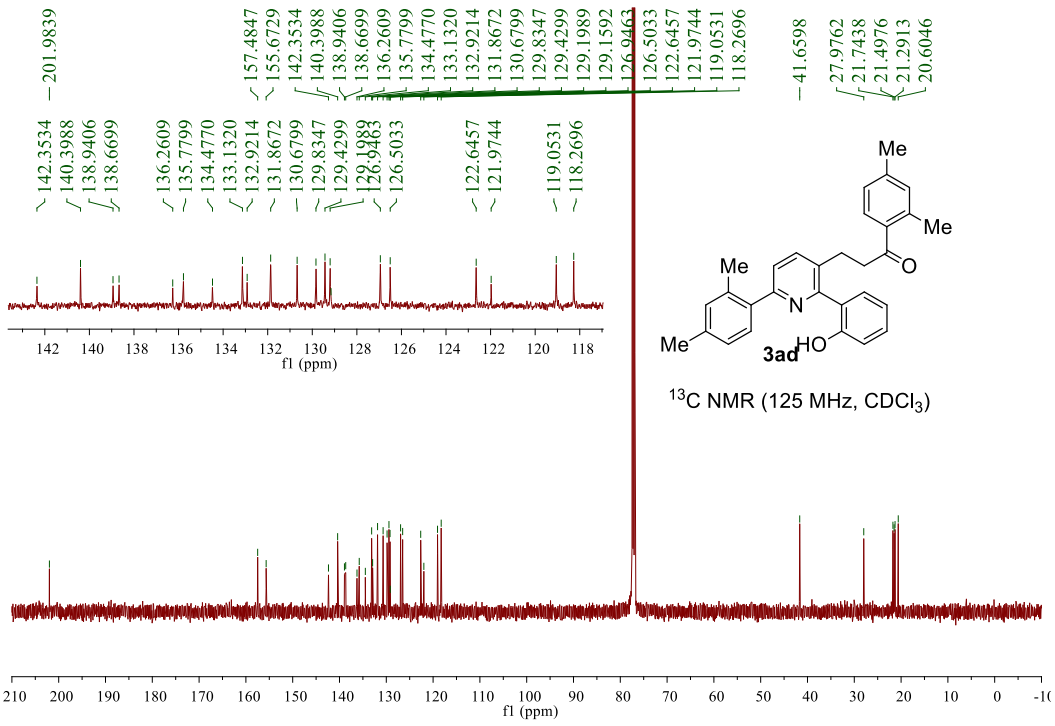


Figure 3.15. 125 MHz ^{13}C Spectrum of **3ad** in $CDCl_3$

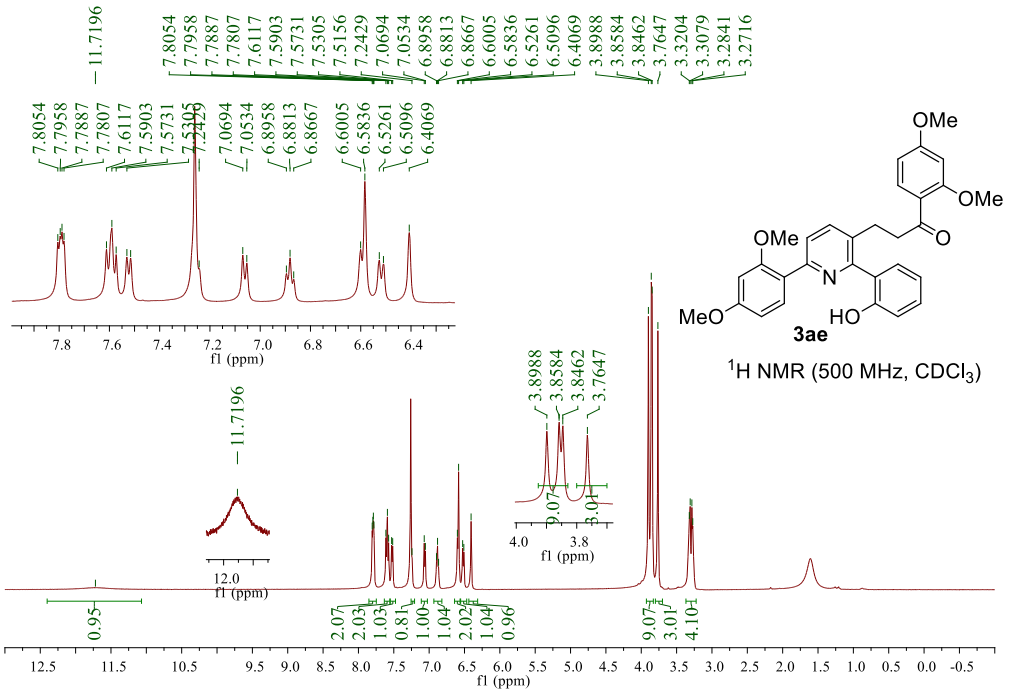


Figure 3.16. 500 MHz ^{1}H Spectrum of **3ae** in $CDCl_3$

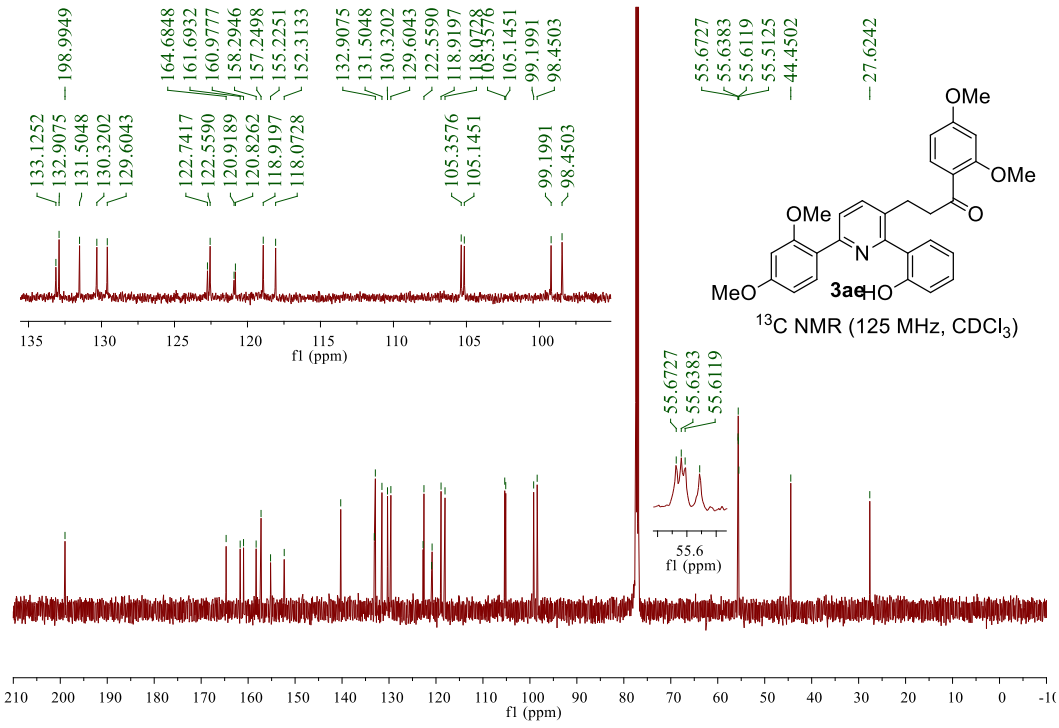


Figure 3.17. 125 MHz ^{13}C Spectrum of **3ae** in $CDCl_3$

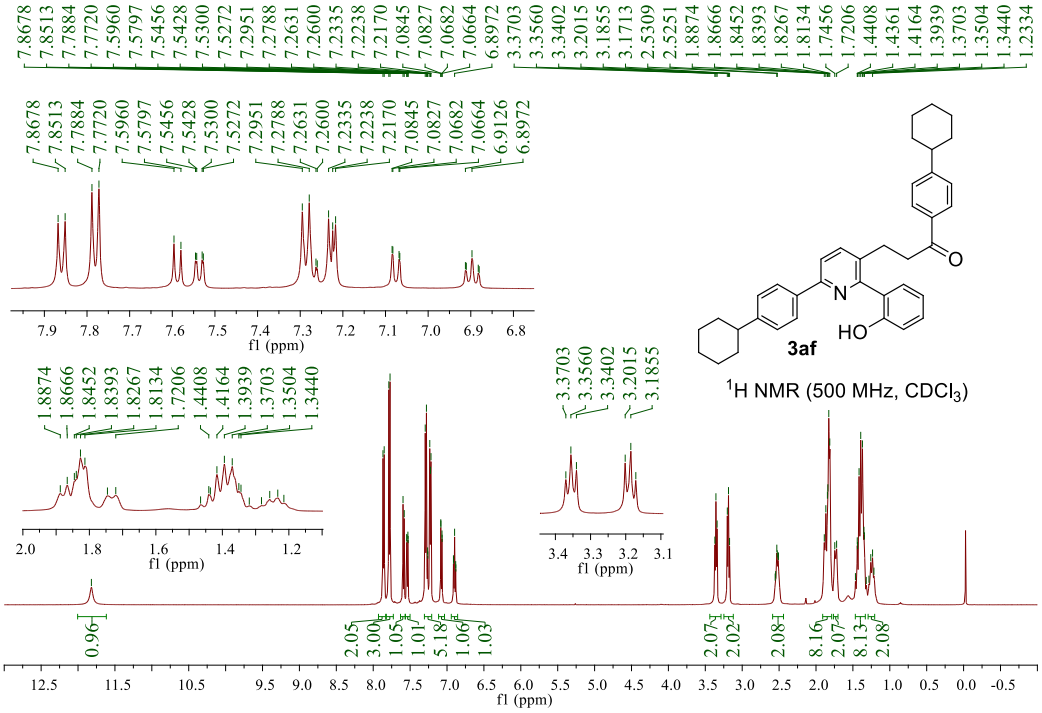


Figure 3.18. 500 MHz ^{1}H Spectrum of **3af** in $CDCl_3$

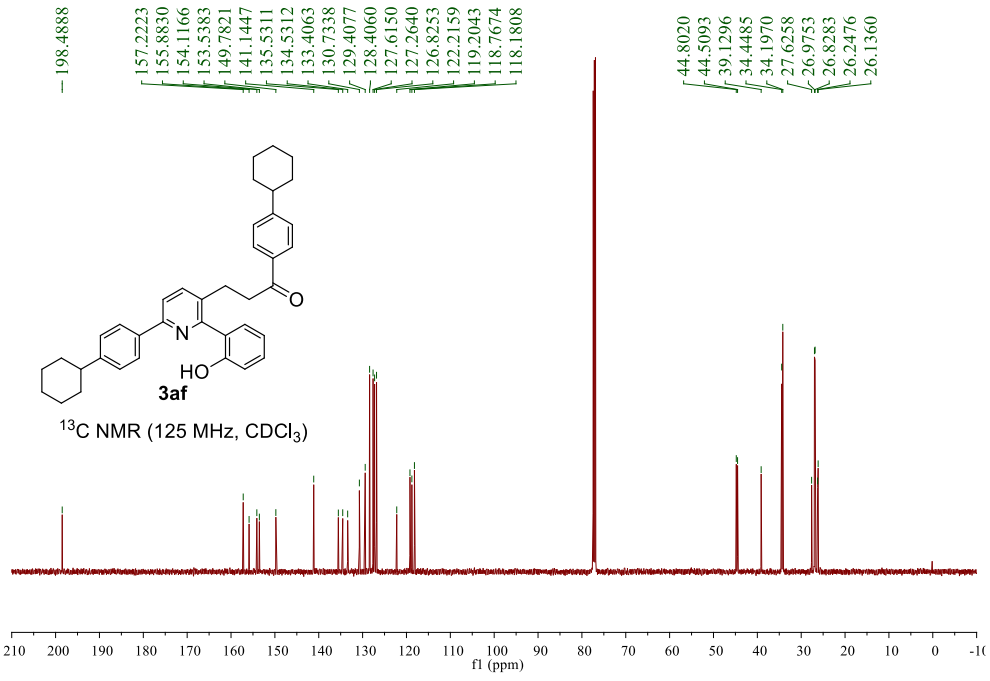


Figure 3.19. 125 MHz ^{13}C Spectrum of **3af** in $CDCl_3$

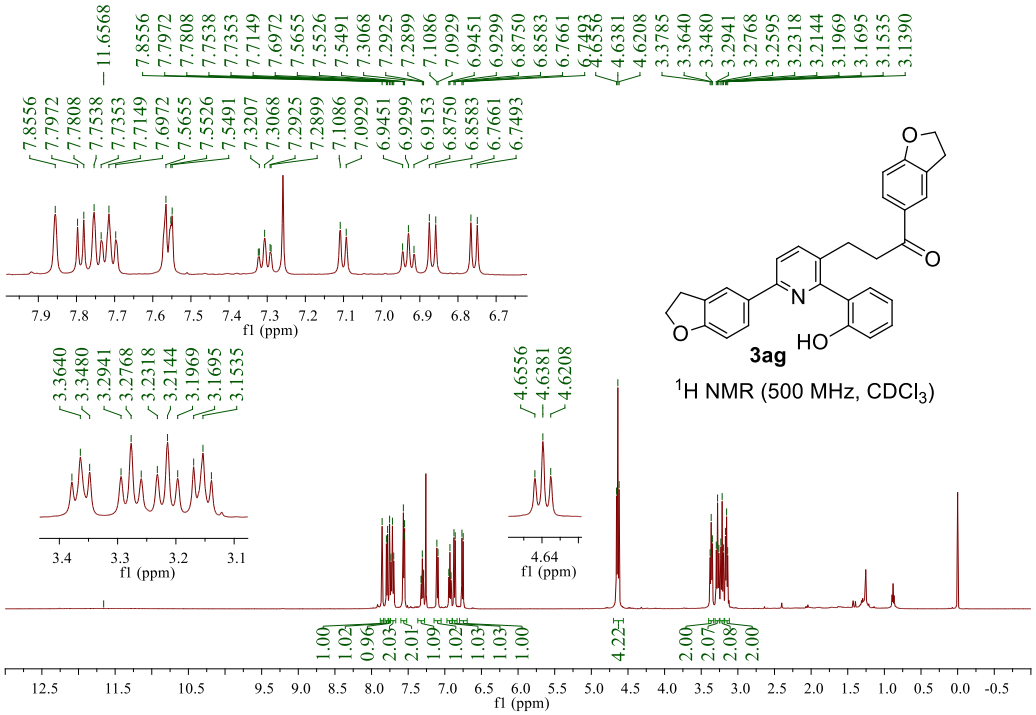


Figure 3.20. 500 MHz ^{1}H Spectrum of **3ag** in $CDCl_3$

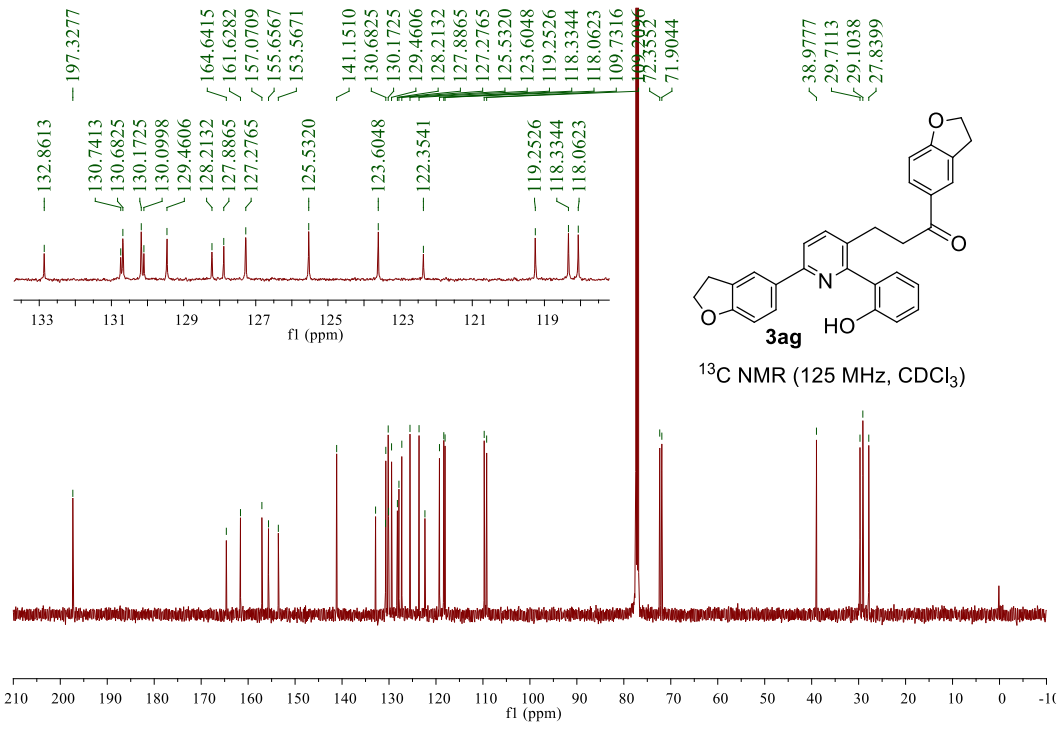


Figure 3.21. 125 MHz ^{13}C Spectrum of **3ag** in $CDCl_3$

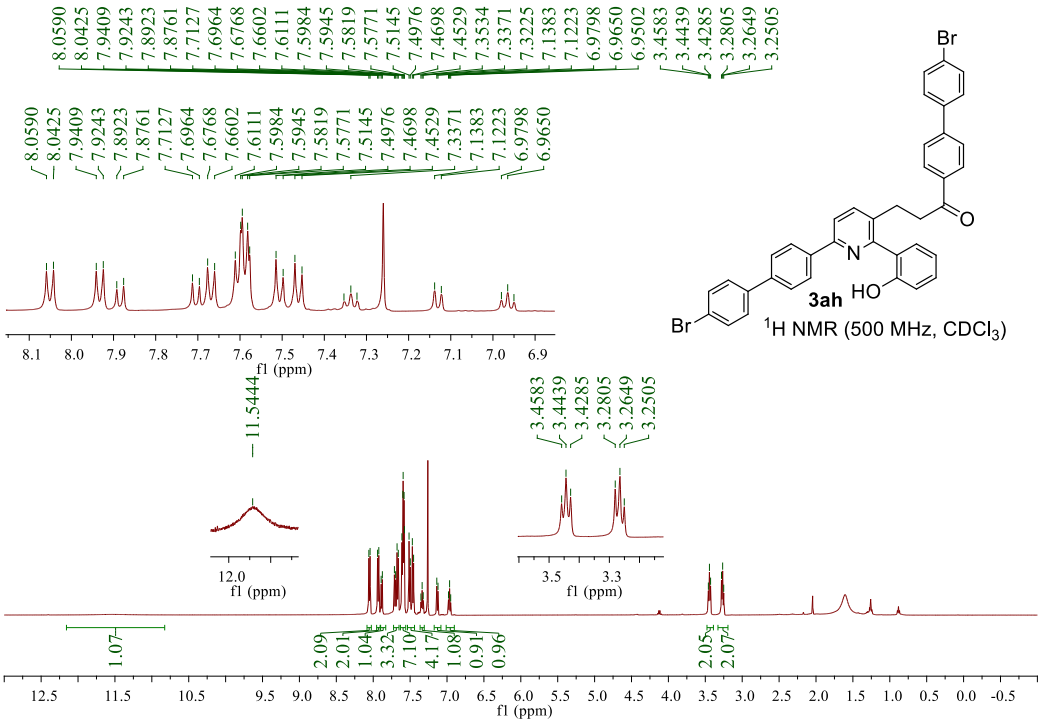


Figure 3.22. 500 MHz ^{1}H Spectrum of **3ah** in $CDCl_3$

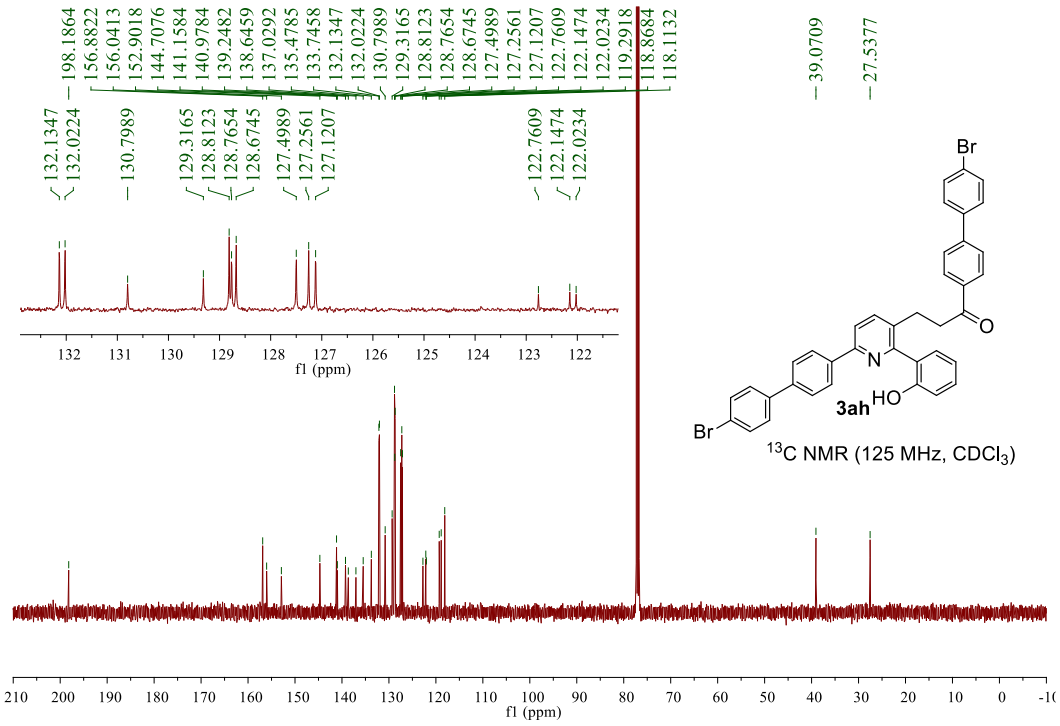


Figure 3.23. 125 MHz ^{13}C Spectrum of **3ah** in $CDCl_3$

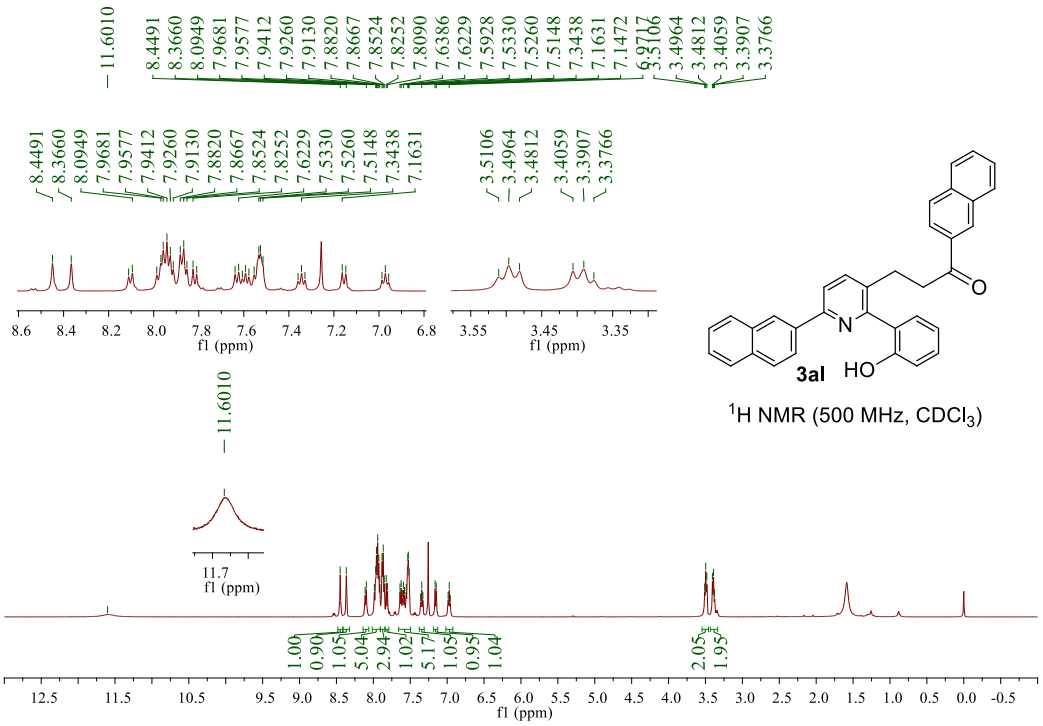


Figure 3.24. 500 MHz ^{1}H Spectrum of **3al** in $CDCl_3$

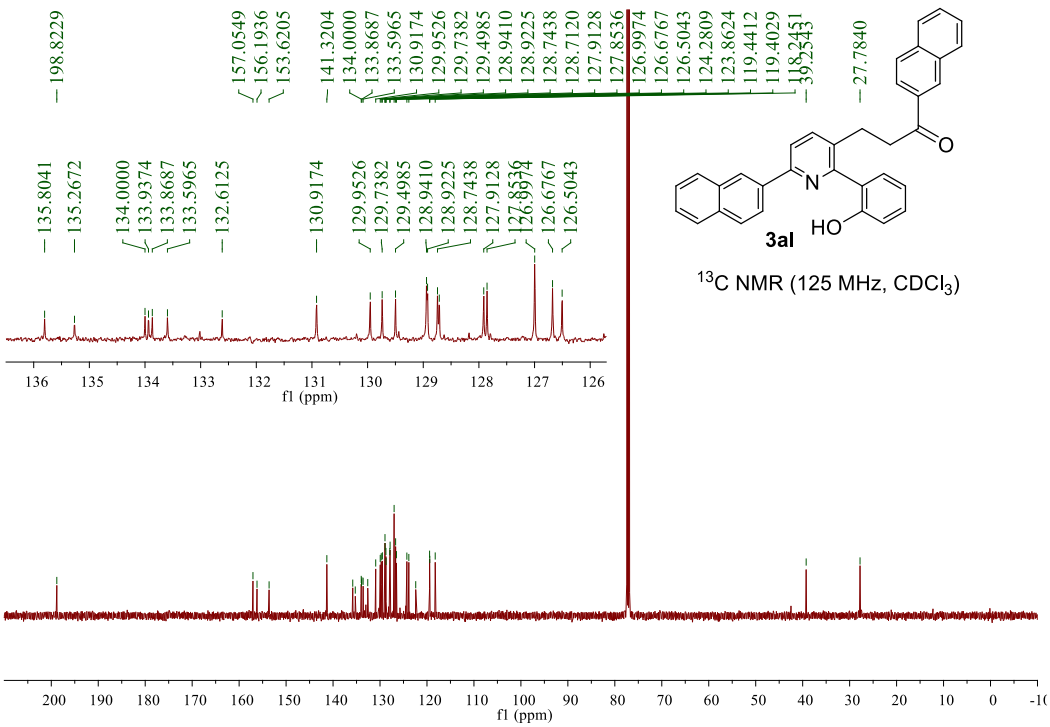


Figure 3.25. 125 MHz ^{13}C Spectrum of **3al** in $CDCl_3$

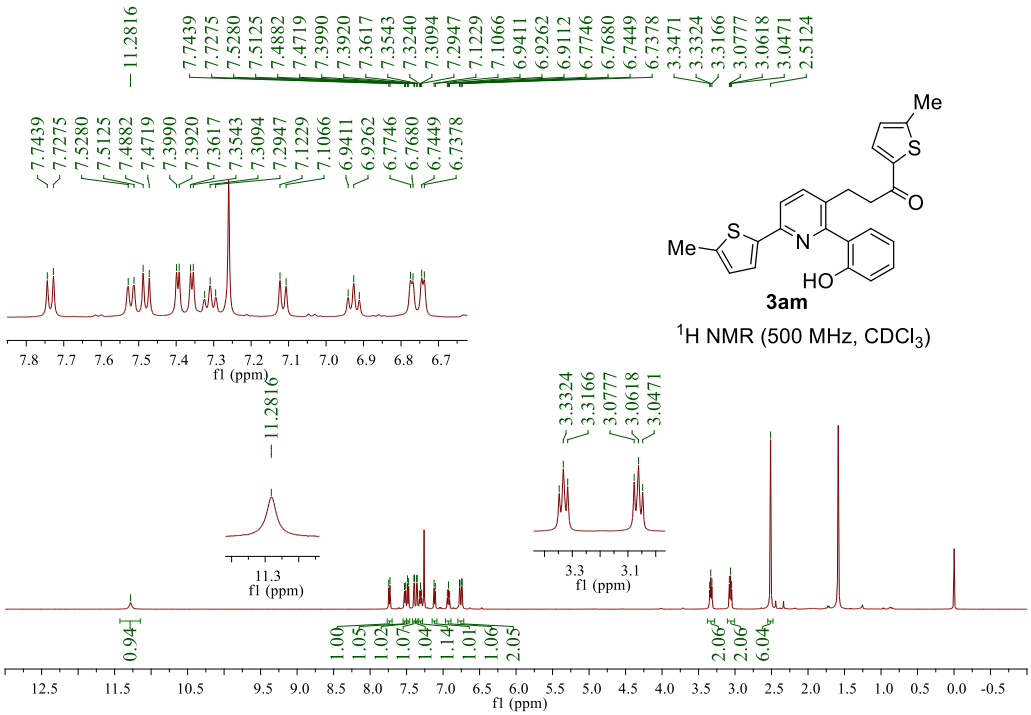


Figure 3.26. 500 MHz ^{1}H Spectrum of **3am** in $CDCl_3$

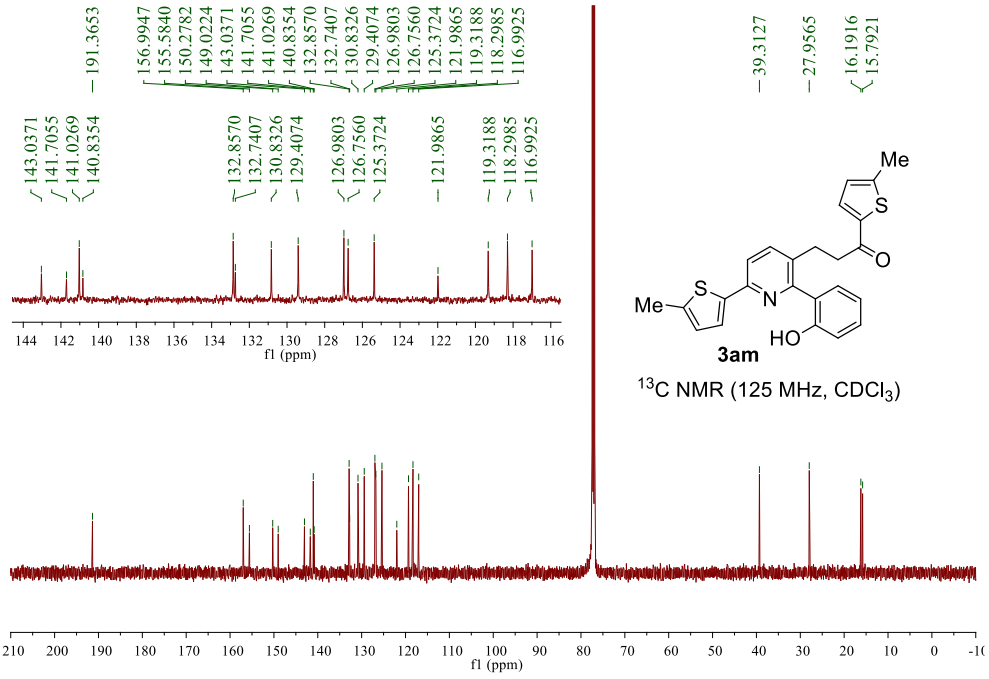


Figure 3.27. 125 MHz ^{13}C Spectrum of **3am** in $CDCl_3$

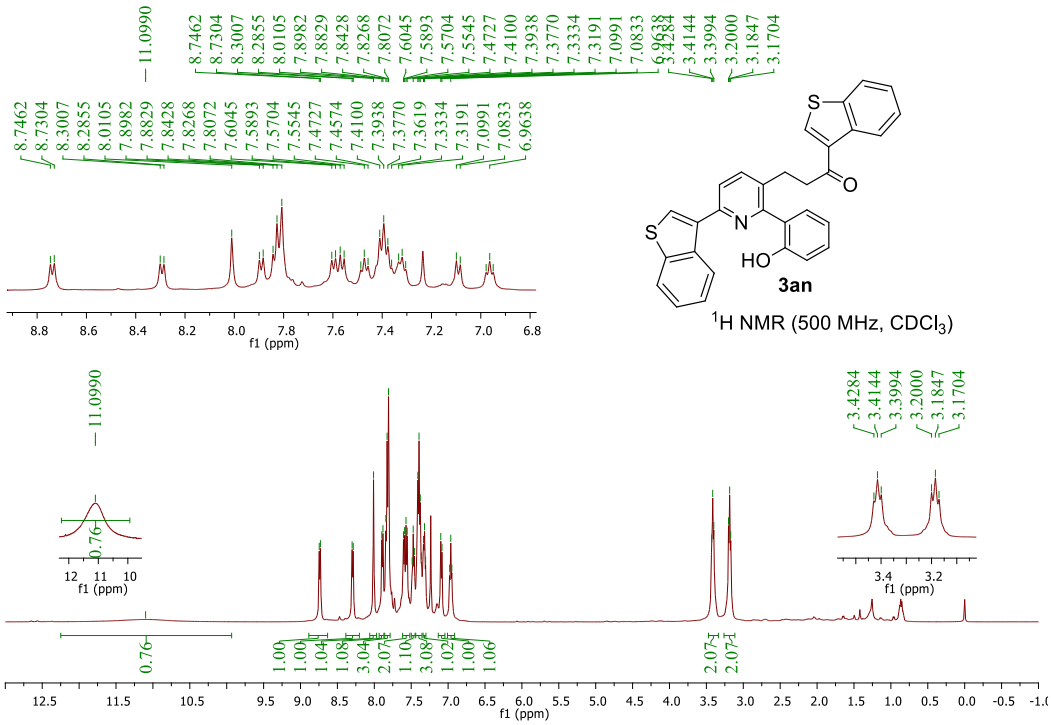


Figure 3.28. 500 MHz ^{1}H Spectrum of **3an** in $CDCl_3$

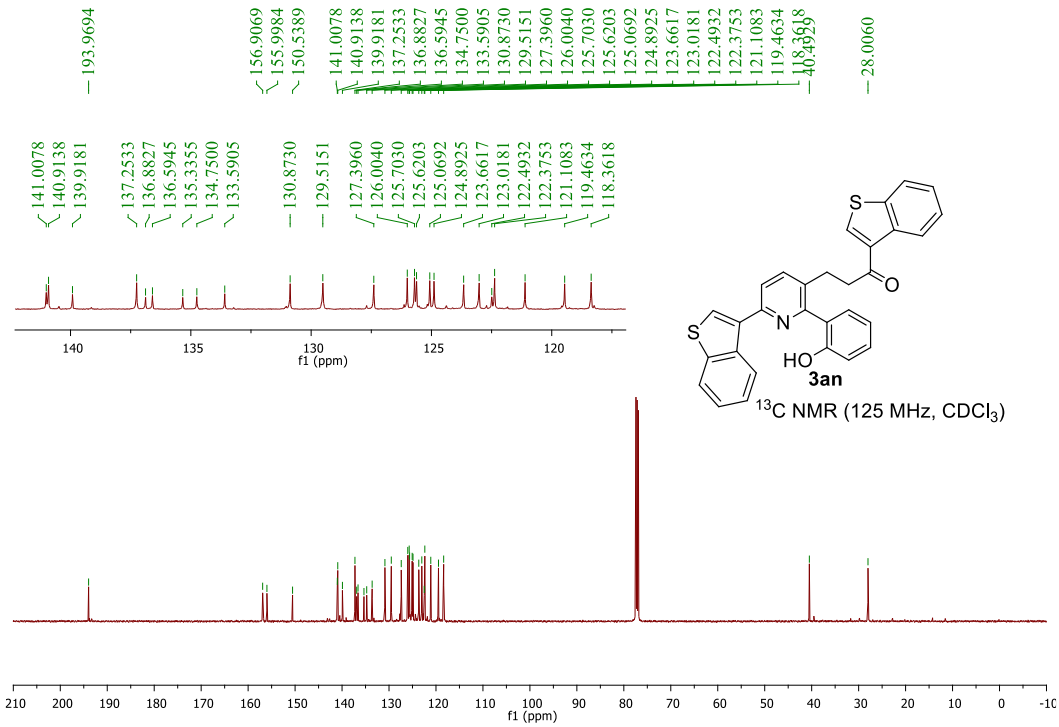


Figure 3.29. 125 MHz ^{13}C Spectrum of **3an** in $CDCl_3$

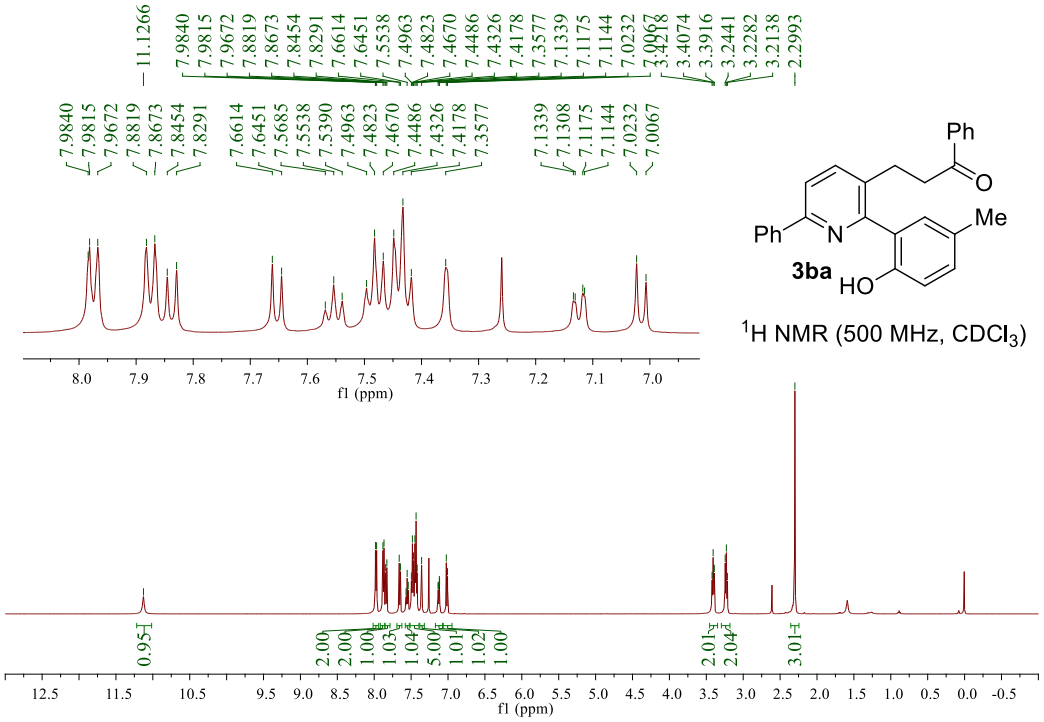


Figure 3.30. 500 MHz ^{1}H Spectrum of **3ba** in $CDCl_3$

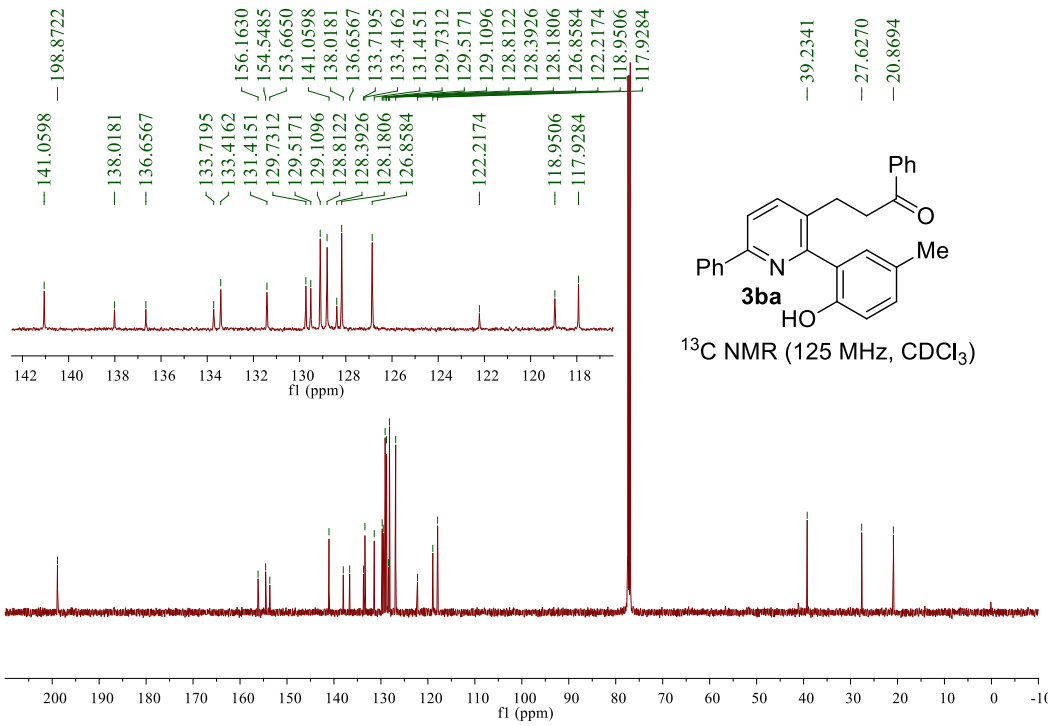


Figure 3.31. 125 MHz ^{13}C Spectrum of **3ba** in $CDCl_3$

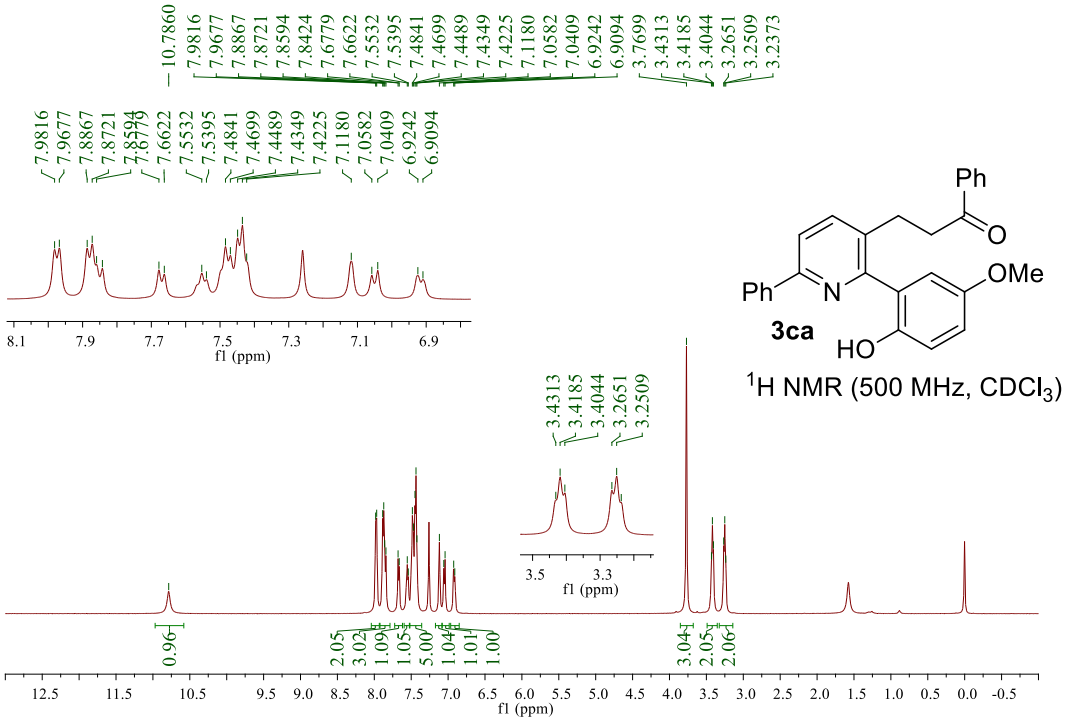


Figure 3.32. 500 MHz ^{1}H Spectrum of **3ca** in $CDCl_3$

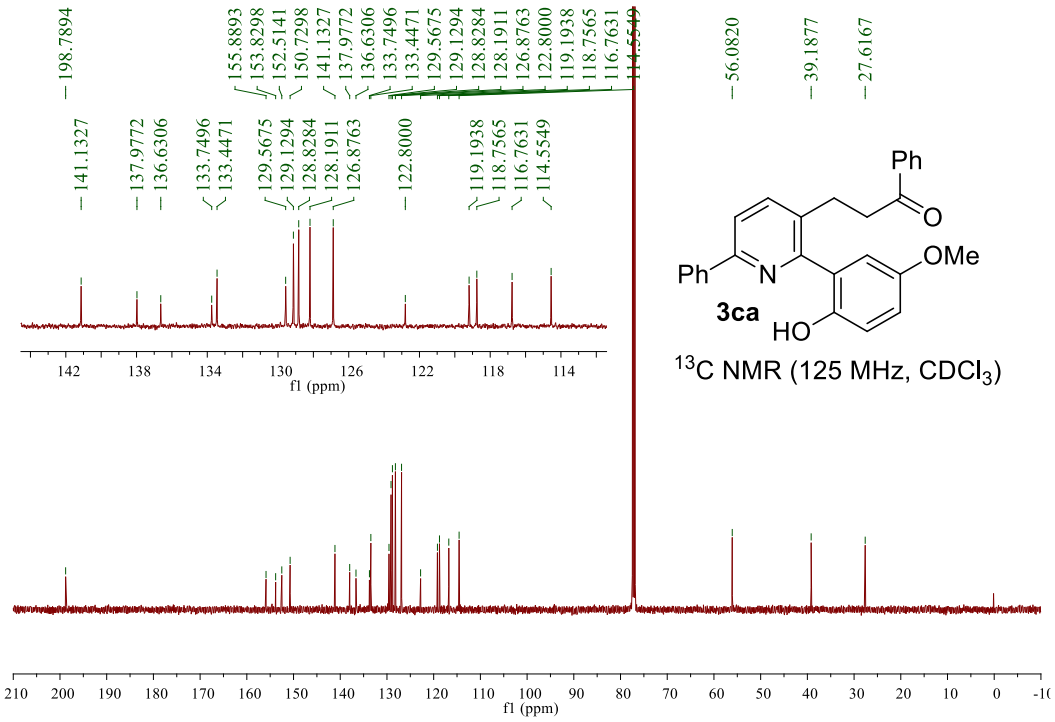


Figure 3.33. 125 MHz ^{13}C Spectrum of **3ca** in $CDCl_3$

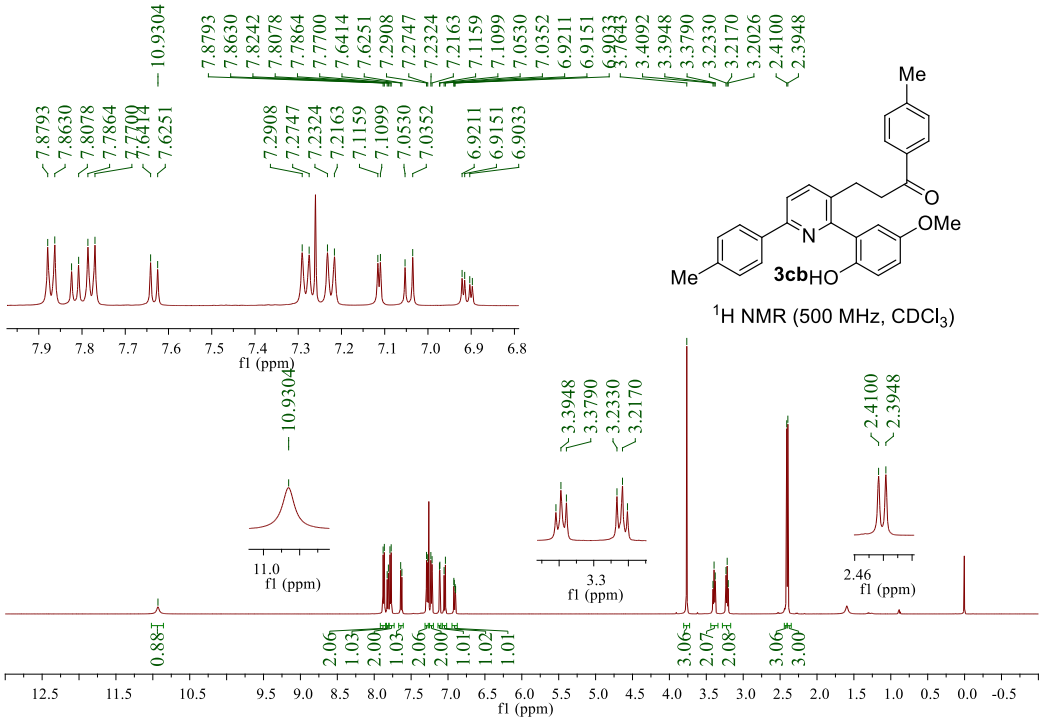


Figure 3.34. 500 MHz ^{1}H Spectrum of **3cb** in $CDCl_3$

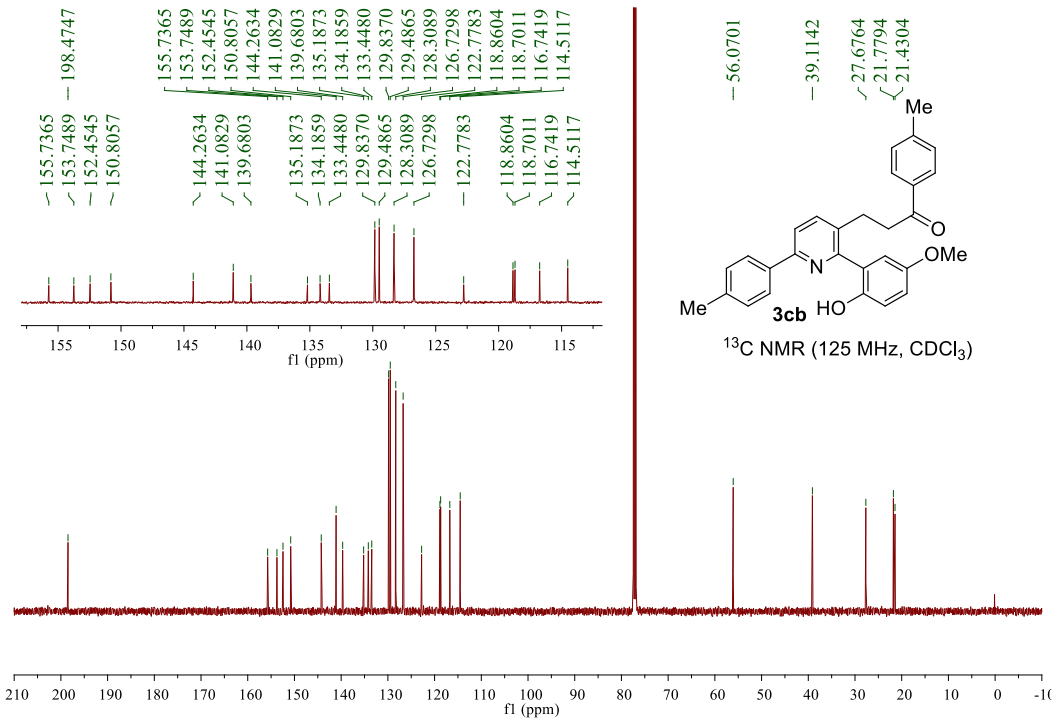


Figure 3.35. 125 MHz ^{13}C Spectrum of **3cb** in $CDCl_3$

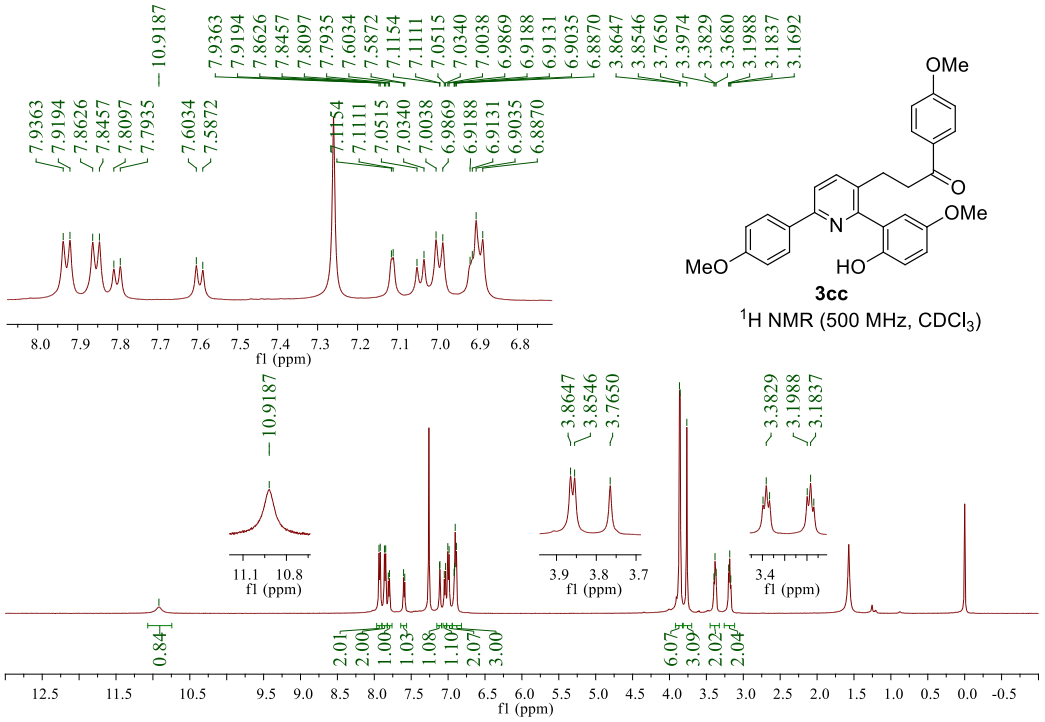


Figure 3.36. 500 MHz ^{1}H Spectrum of **3cc** in $CDCl_3$

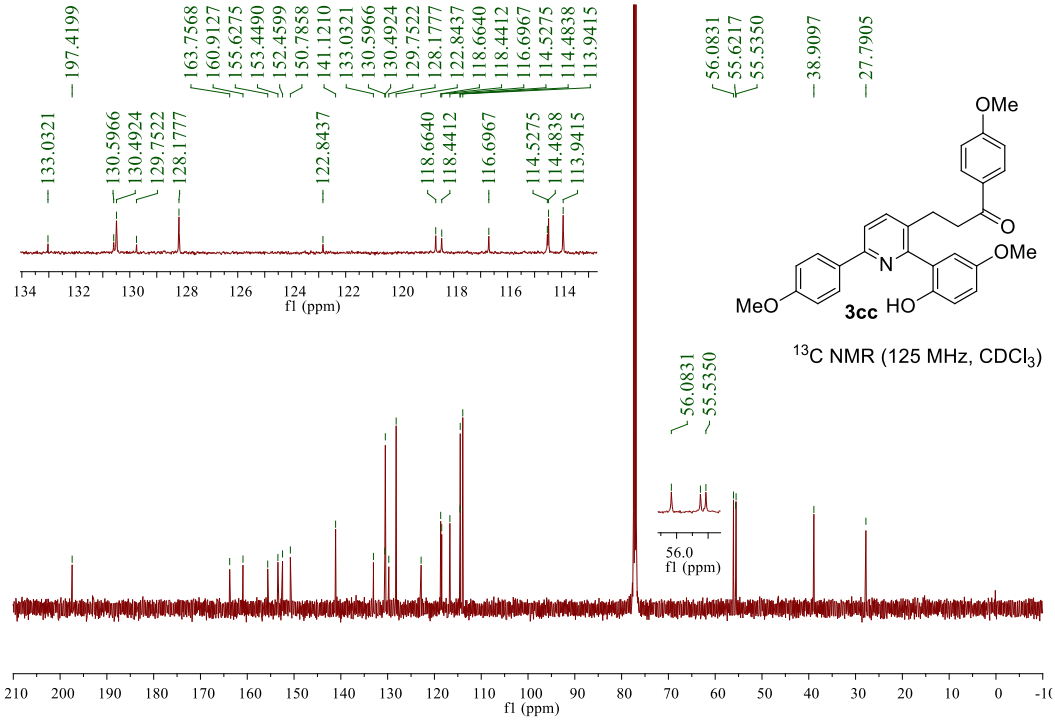


Figure 3.37. 125 MHz ^{13}C Spectrum of **3cc** in $CDCl_3$

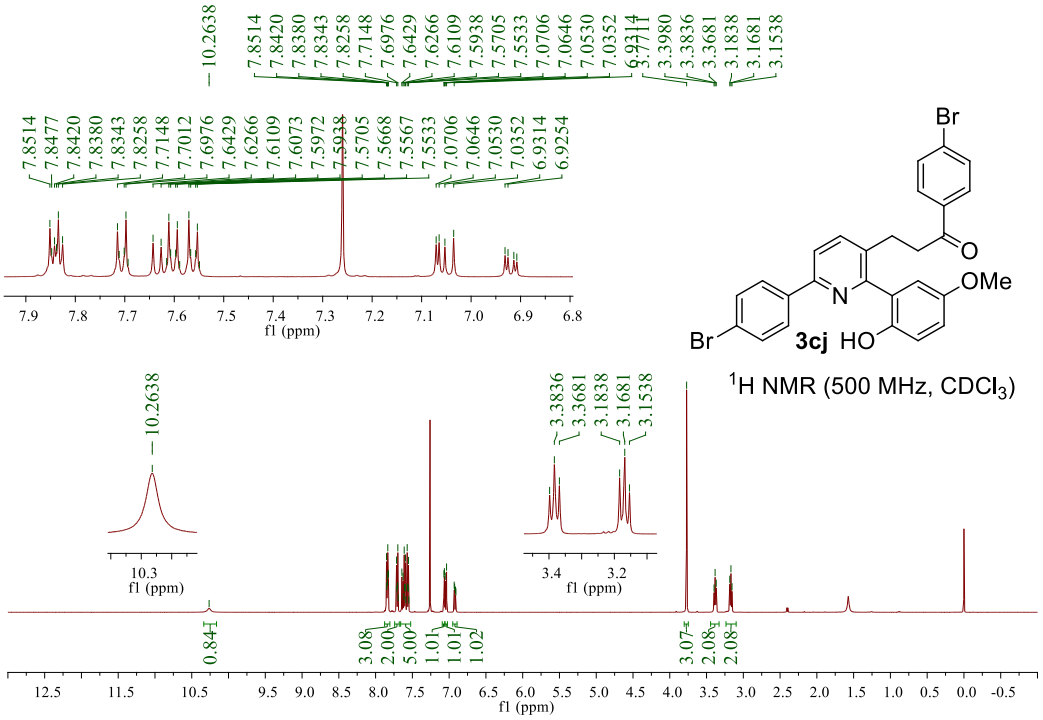


Figure 3.38. 500 MHz ^{1}H Spectrum of **3cj** in $CDCl_3$

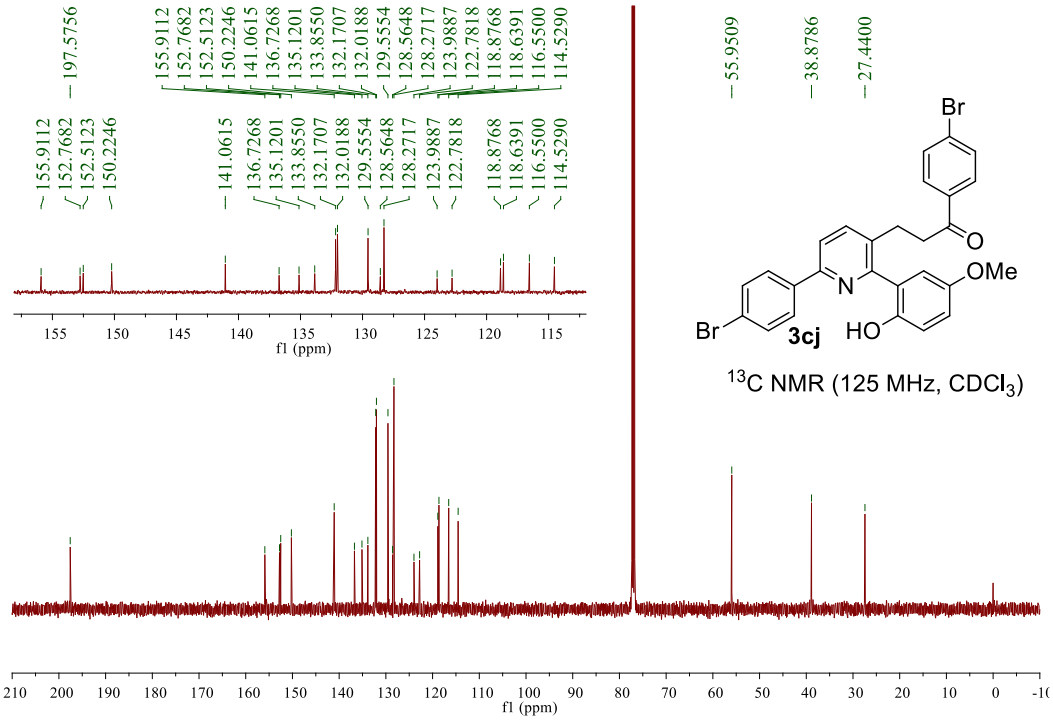


Figure 3.39. 125 MHz ^{13}C Spectrum of **3cj** in $CDCl_3$

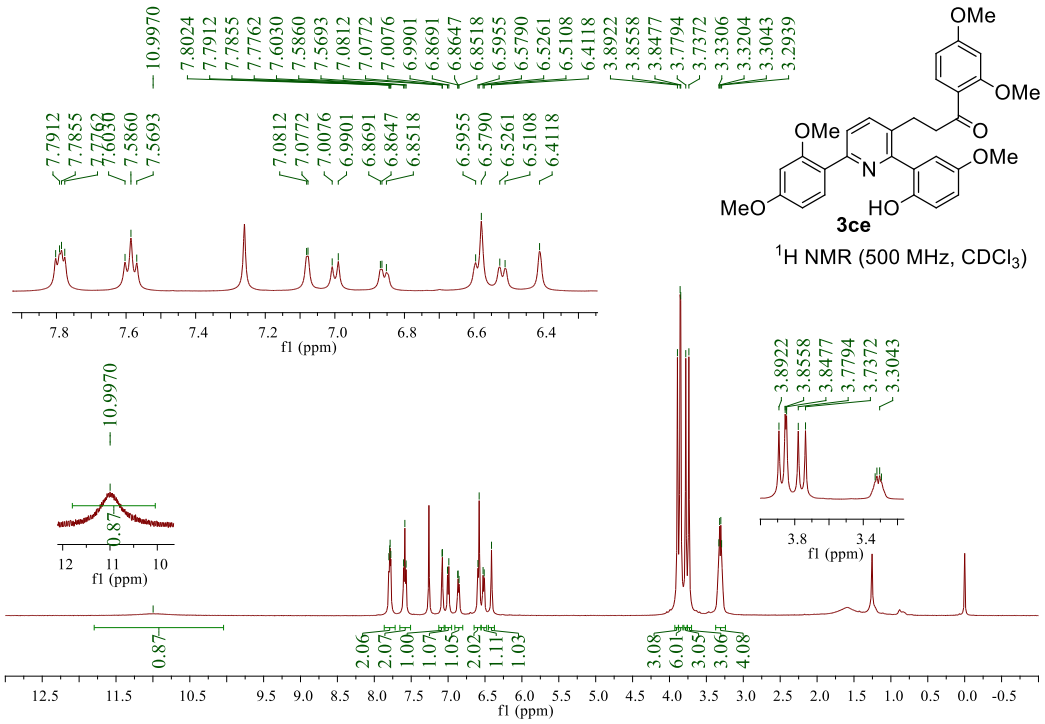


Figure 3.40. 500 MHz ^{1}H Spectrum of **3ce** in $CDCl_3$

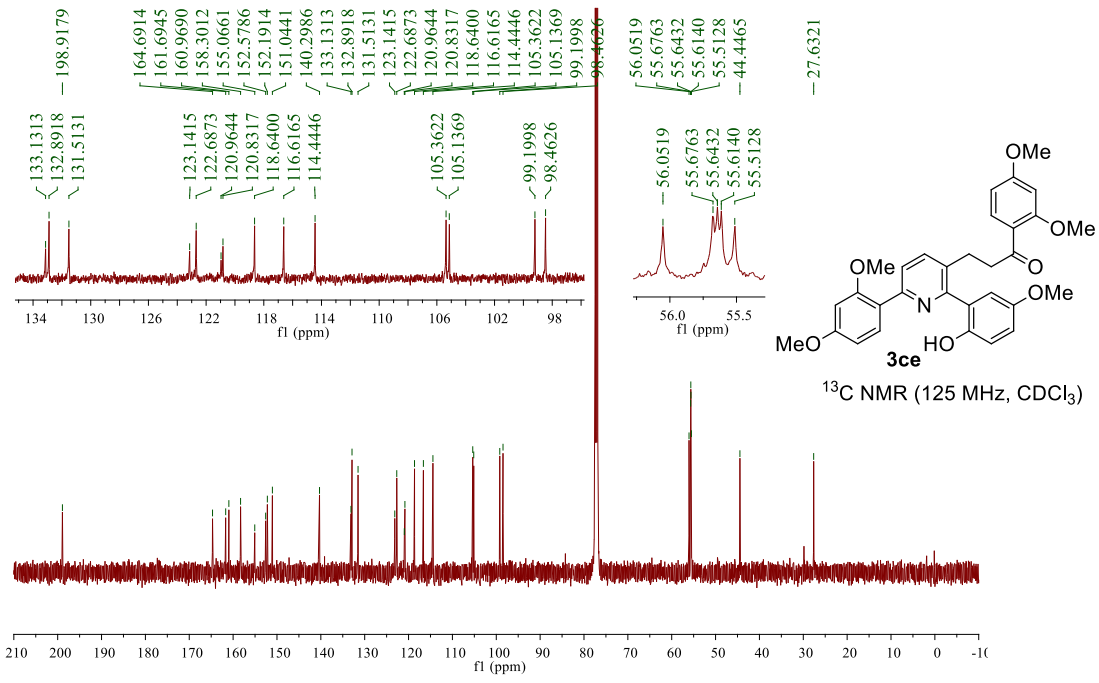


Figure 3.41. 125 MHz ^{13}C Spectrum of **3ce** in $CDCl_3$

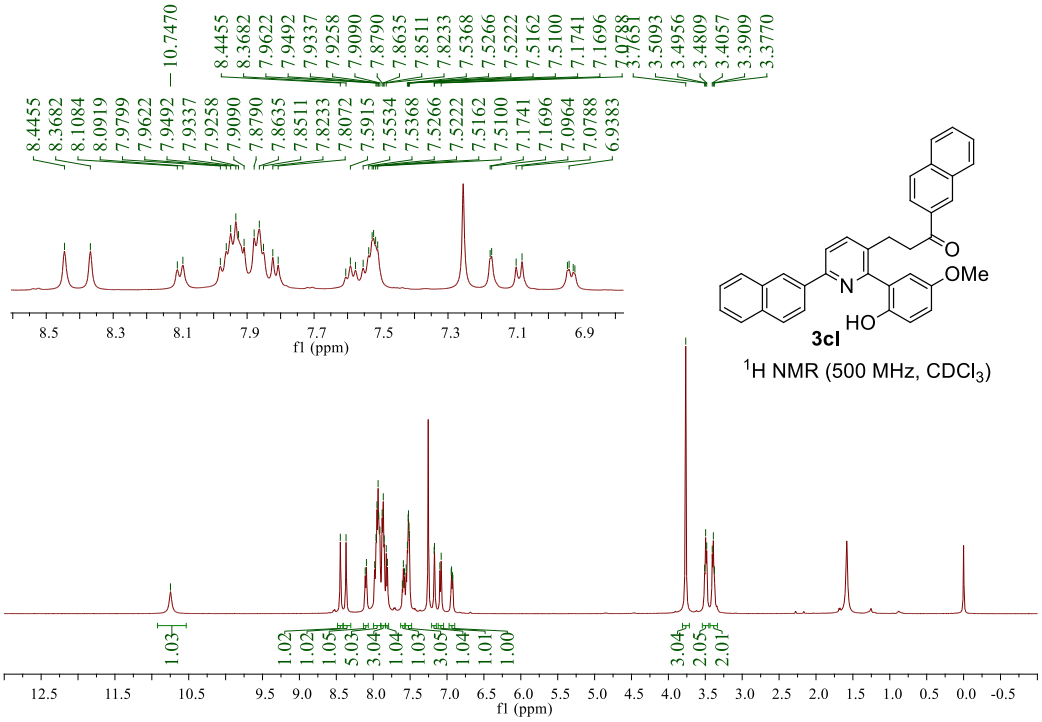


Figure 3.42. 500 MHz ^{1}H Spectrum of **3cl** in $CDCl_3$

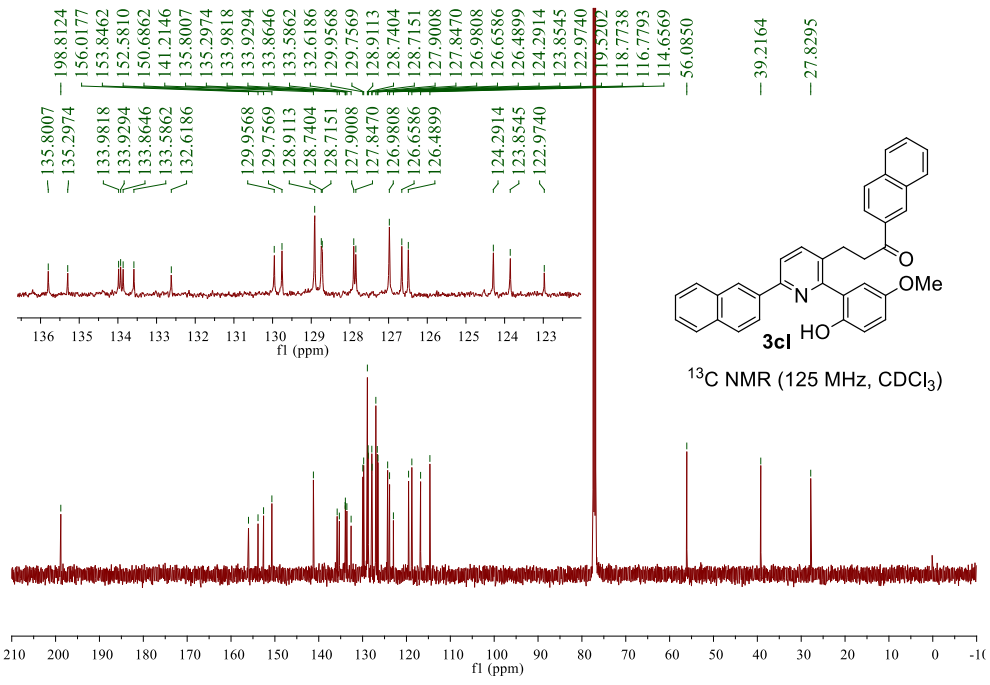


Figure 3.43. 125 MHz ^{13}C Spectrum of **3cl** in $CDCl_3$

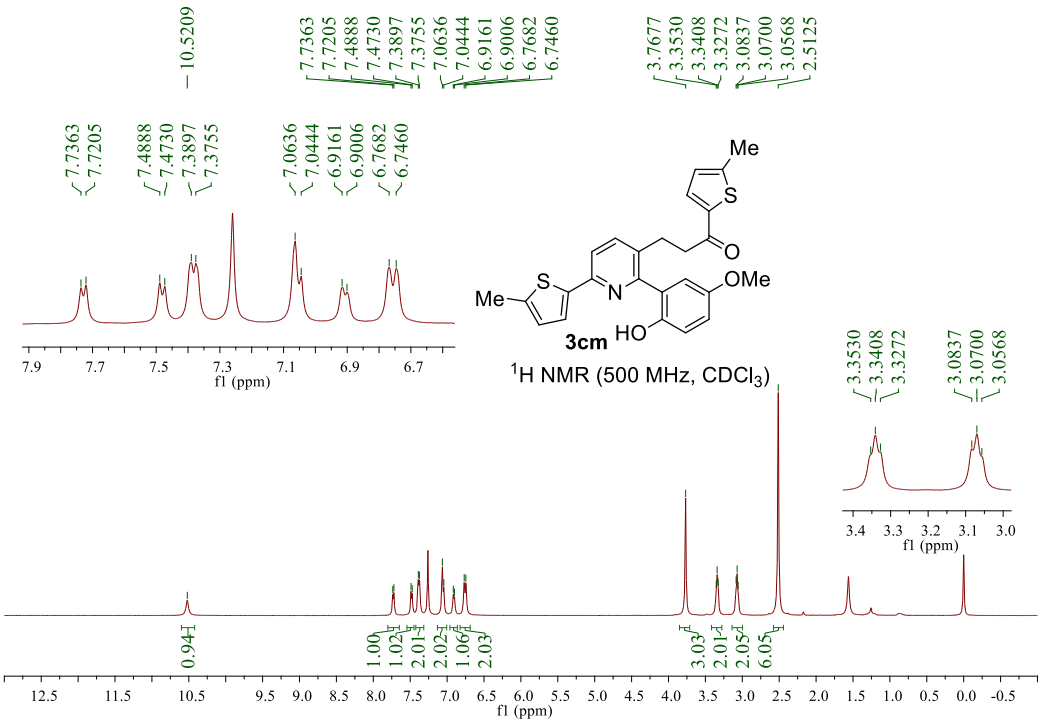


Figure 3.44. 500 MHz ^{1}H Spectrum of **3cm** in $CDCl_3$

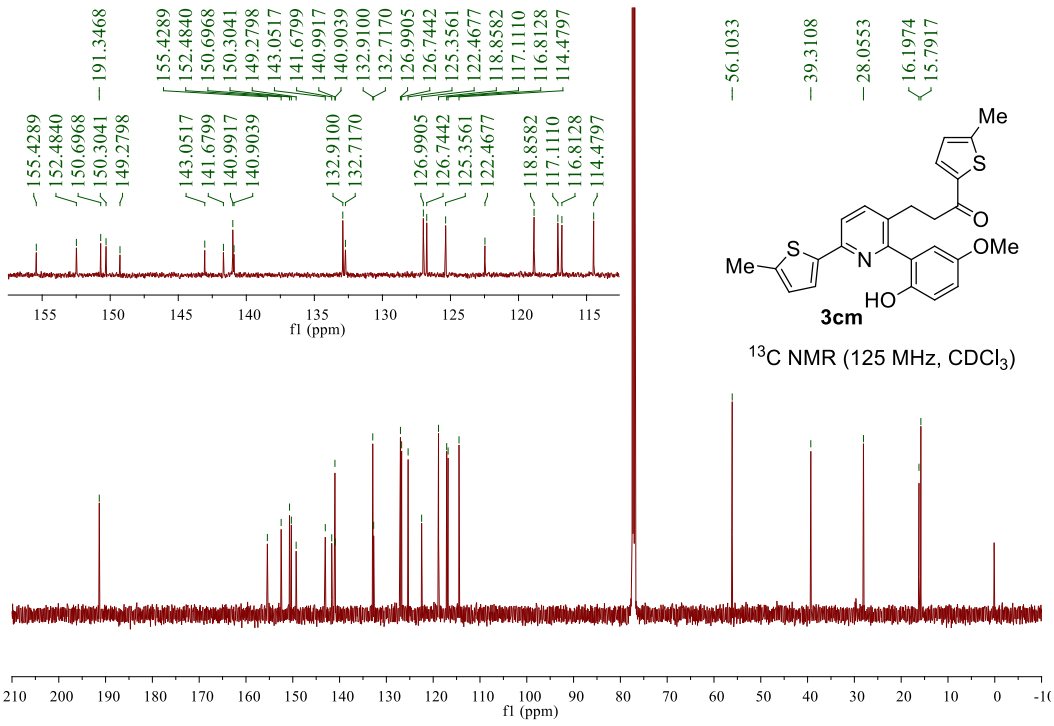


Figure 3.45. 125 MHz ^{13}C Spectrum of **3cm** in $CDCl_3$

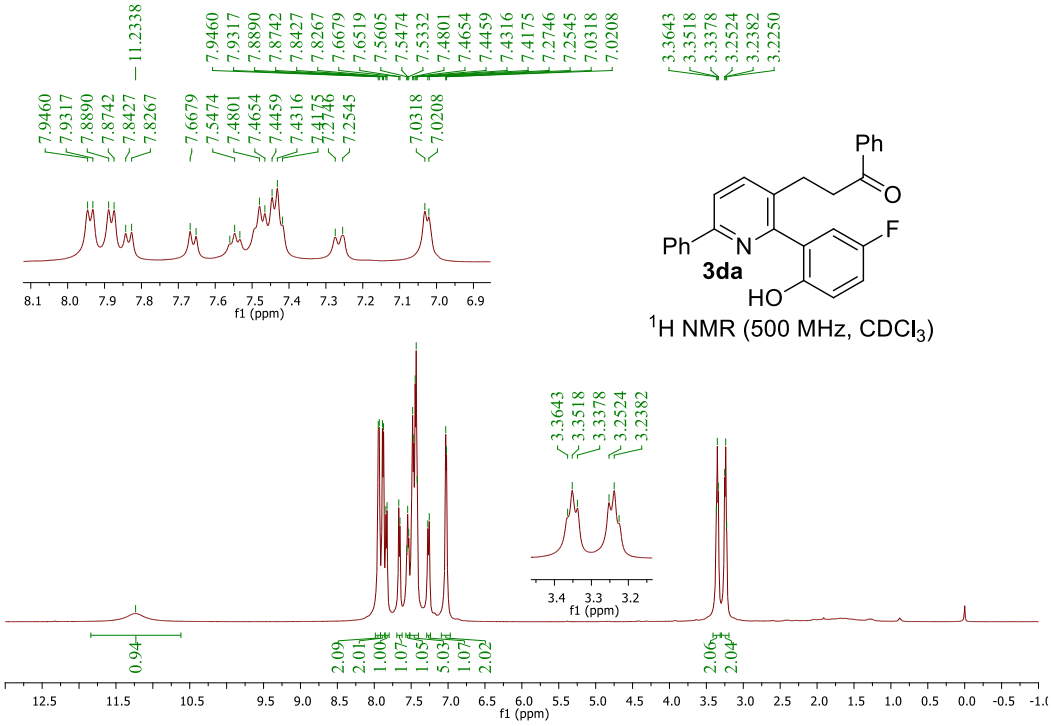


Figure 3.46. 500 MHz ^{1}H Spectrum of **3da** in $CDCl_3$

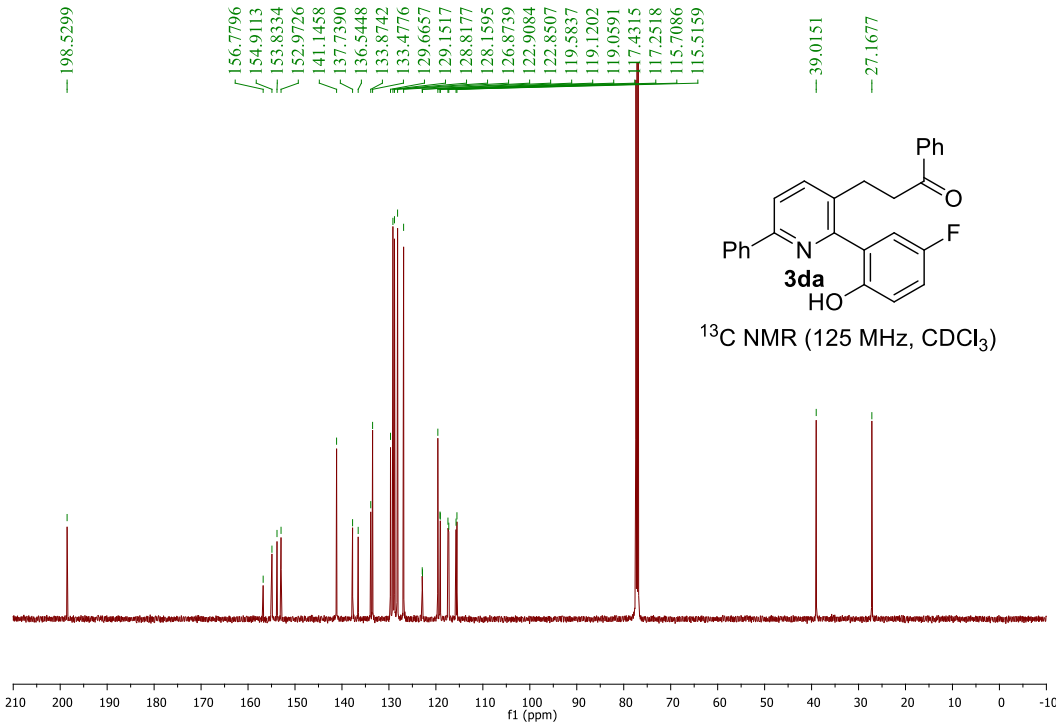


Figure 3.47. 125 MHz ^{13}C Spectrum of **3da** in $CDCl_3$

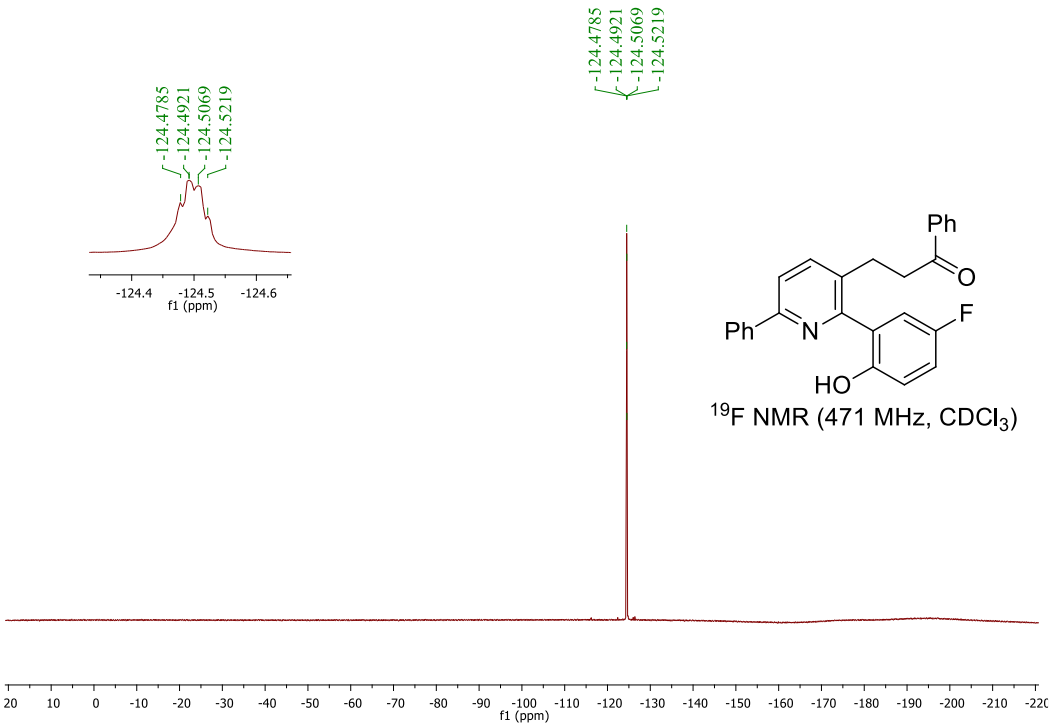


Figure 3.48. 471 MHz ^{19}F NMR of **3da** in $CDCl_3$

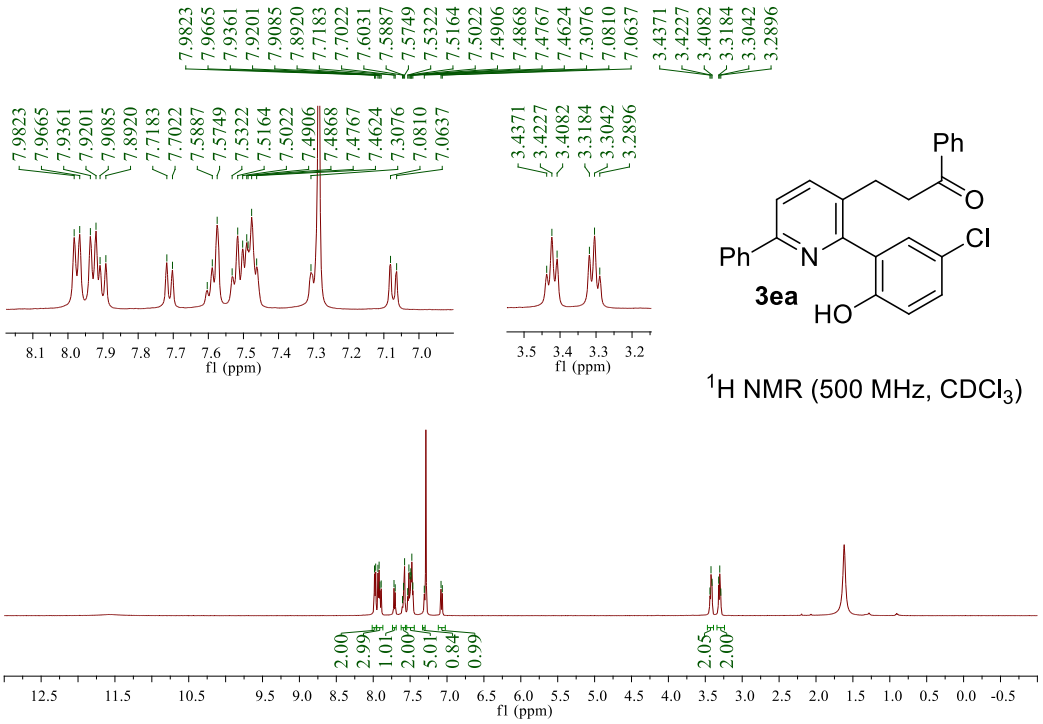


Figure 3.49. 500 MHz ^{1}H Spectrum of **3ea** in $CDCl_3$

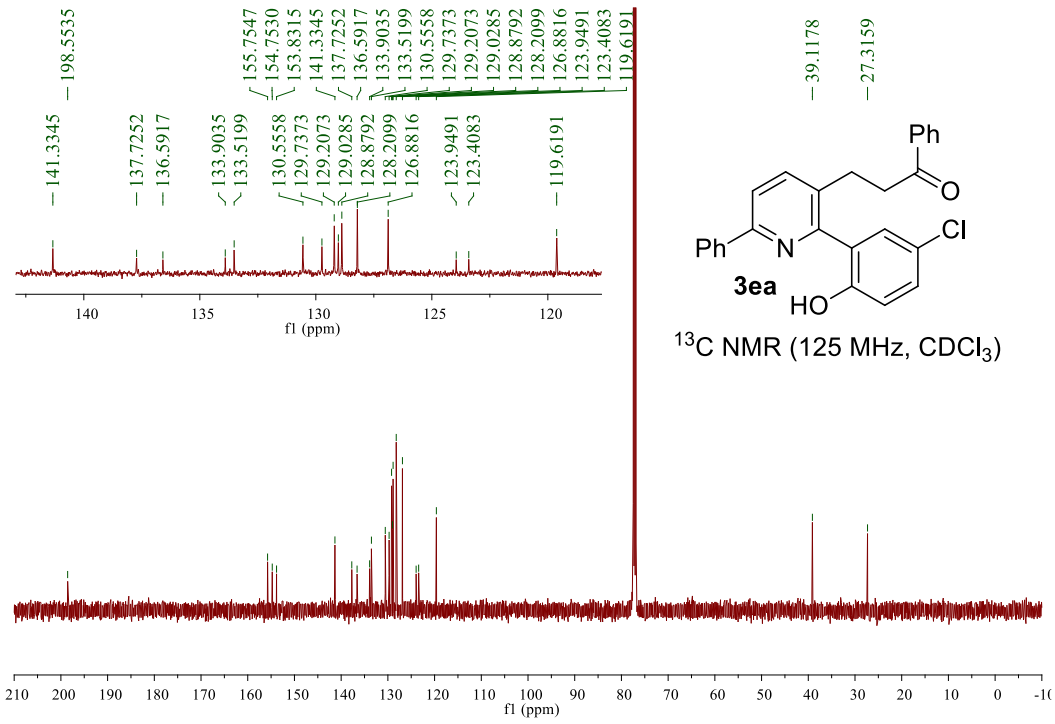


Figure 3.50. 125 MHz ^{13}C Spectrum of **3ea** in $CDCl_3$

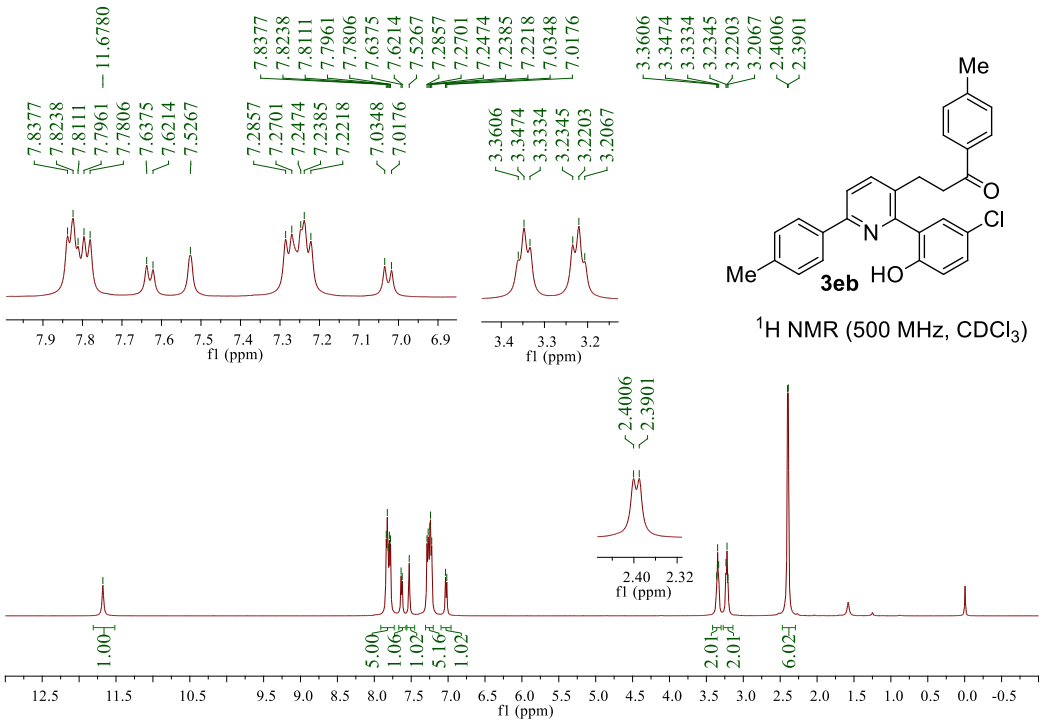


Figure 3.51. 500 MHz ^{1}H Spectrum of **3eb** in $CDCl_3$

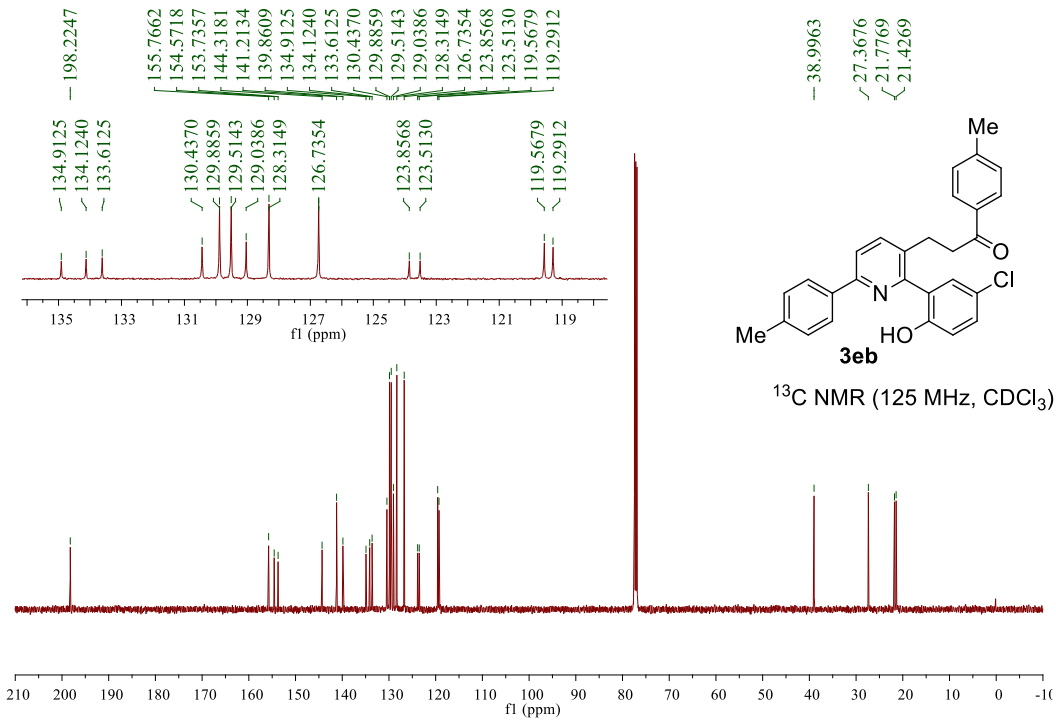


Figure 3.52. 125 MHz ^{13}C Spectrum of **3eb** in $CDCl_3$

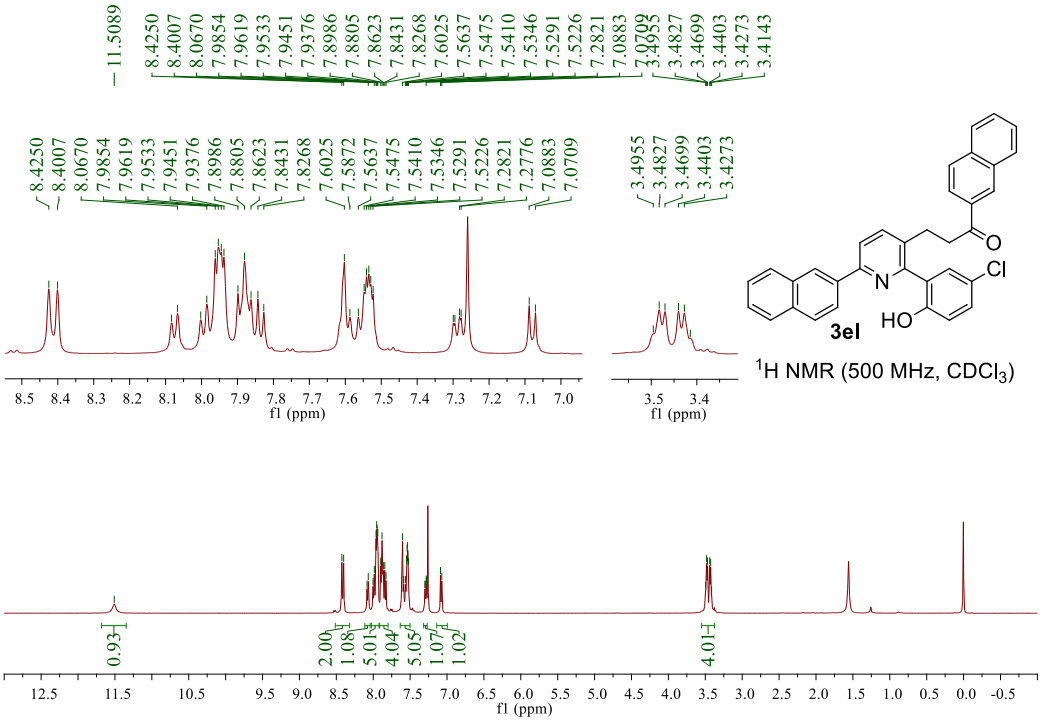


Figure 3.53. 500 MHz ^{1}H Spectrum of **3el** in $CDCl_3$

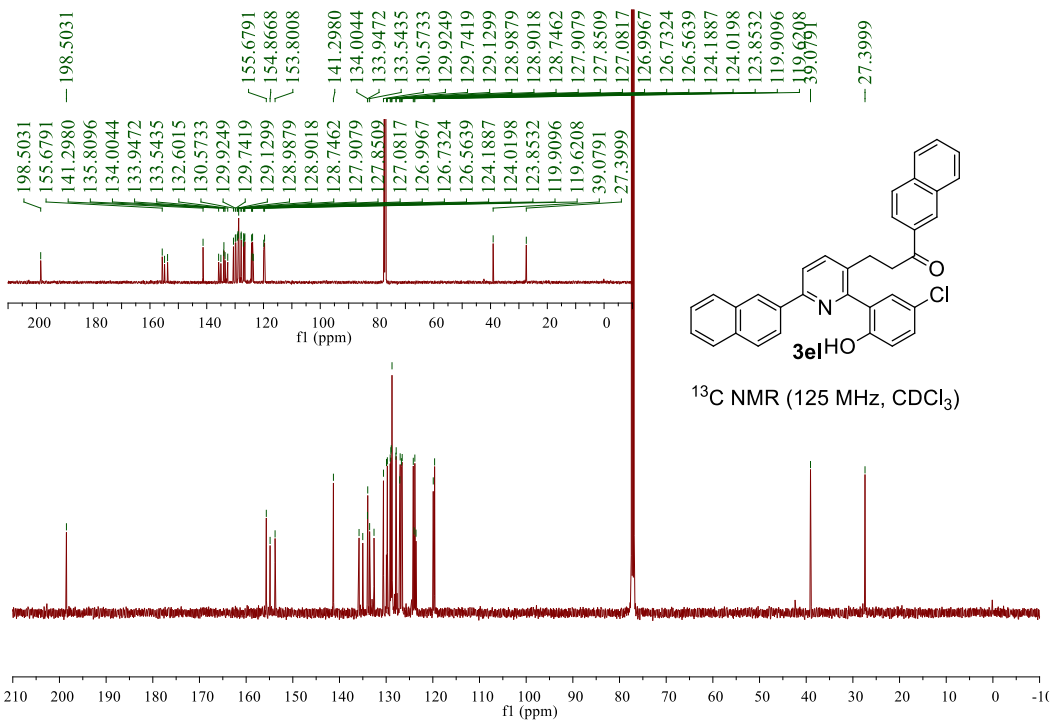


Figure 3.54. 125 MHz ^{13}C Spectrum of **3el** in $CDCl_3$

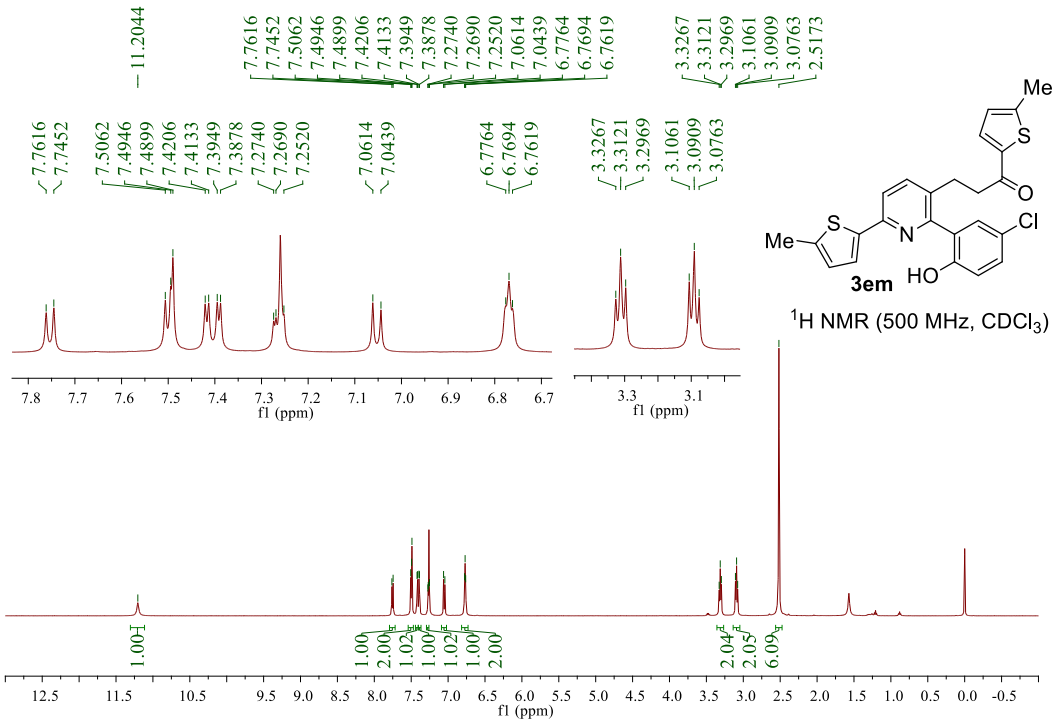


Figure 3.55. 500 MHz ^{1}H Spectrum of **3em** in $CDCl_3$

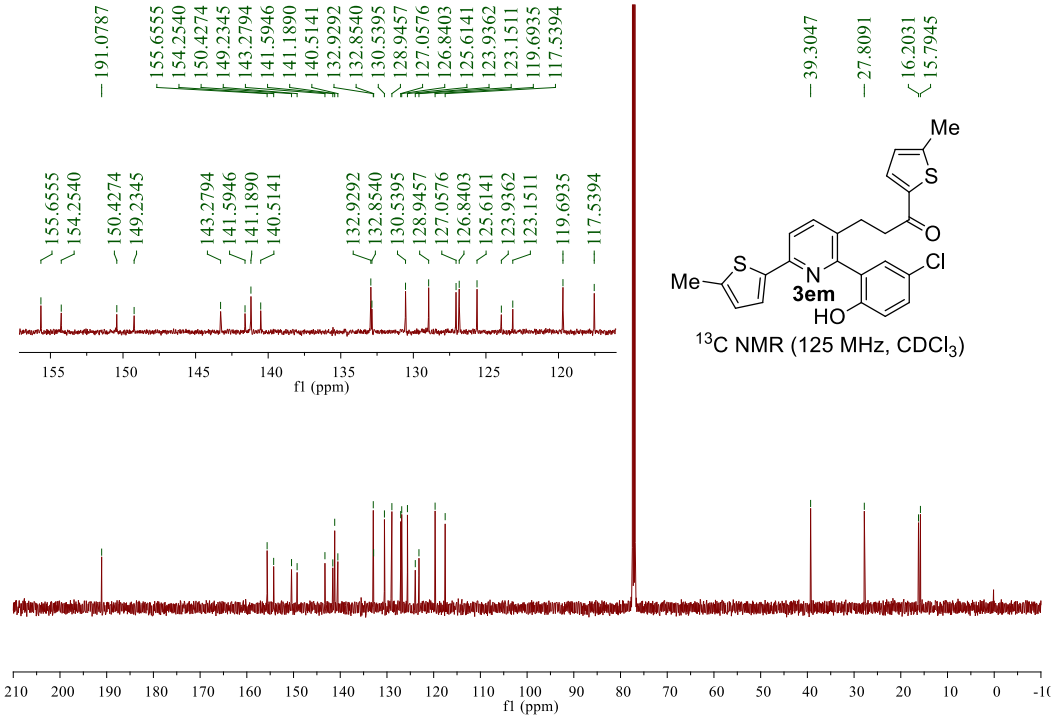


Figure 3.56. 125 MHz ^{13}C Spectrum of **3em** in $CDCl_3$

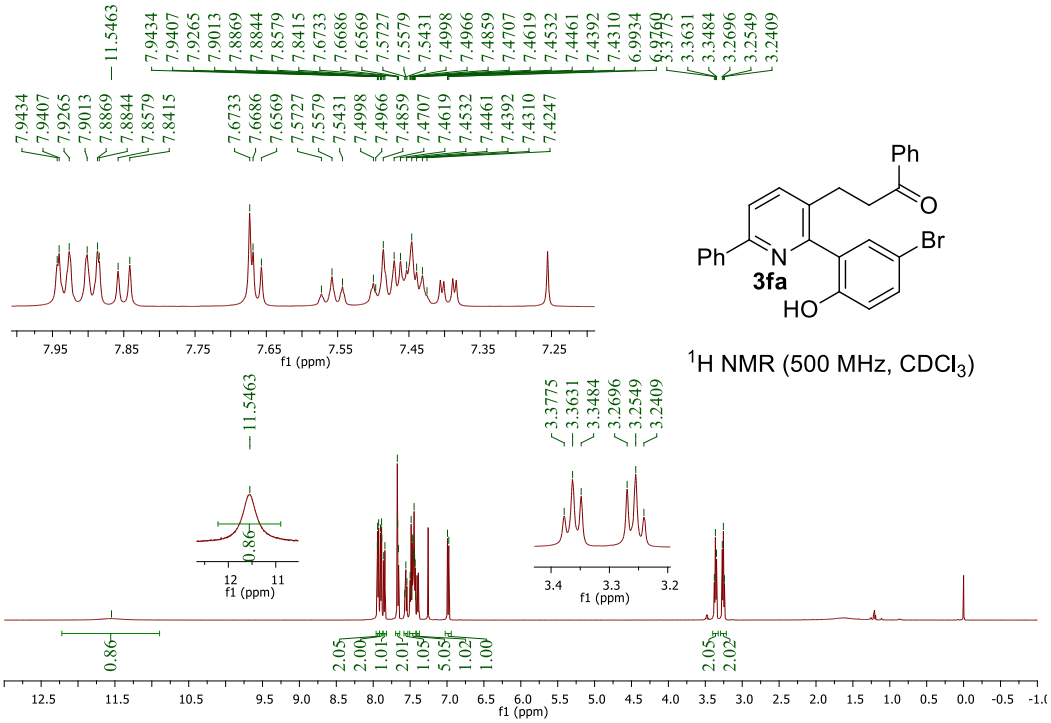


Figure 3.57. 500 MHz ^{1}H Spectrum of **3fa** in $CDCl_3$

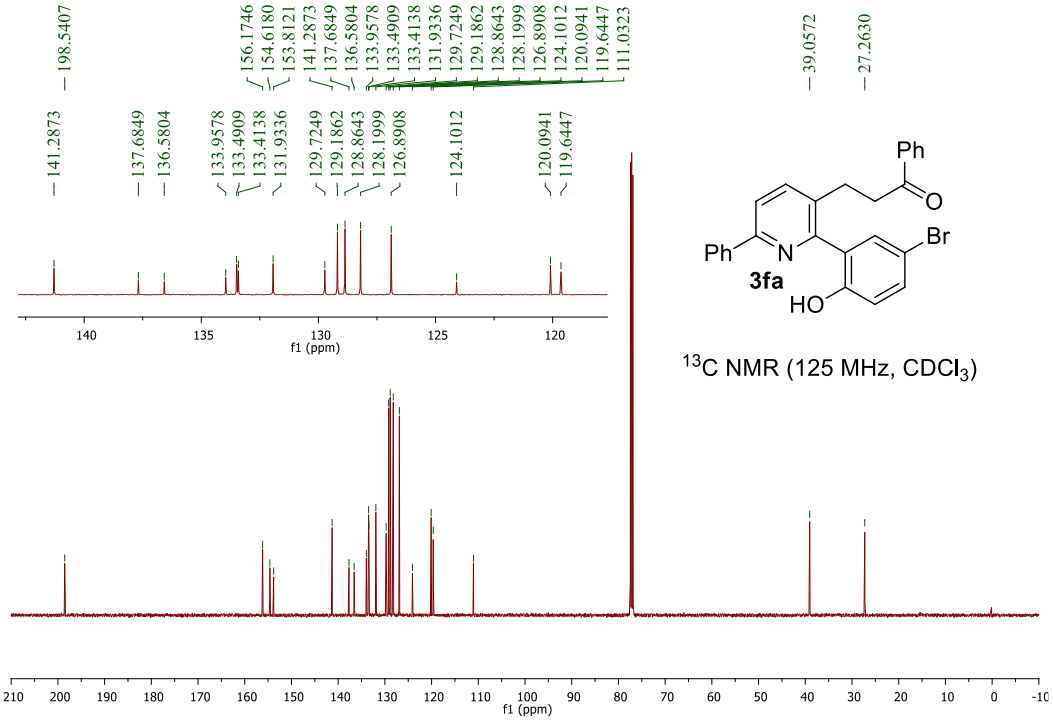


Figure 3.58. 125 MHz ^{13}C Spectrum of **3fa** in $CDCl_3$

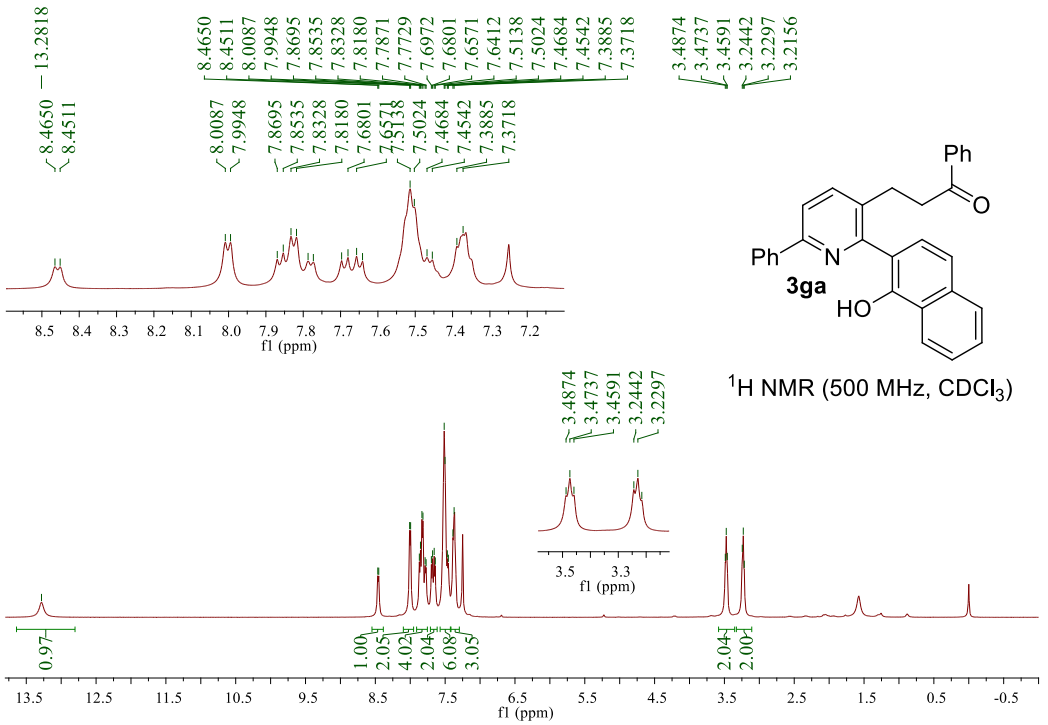


Figure 3.59. 500 MHz ^{1}H Spectrum of **3ga** in $CDCl_3$

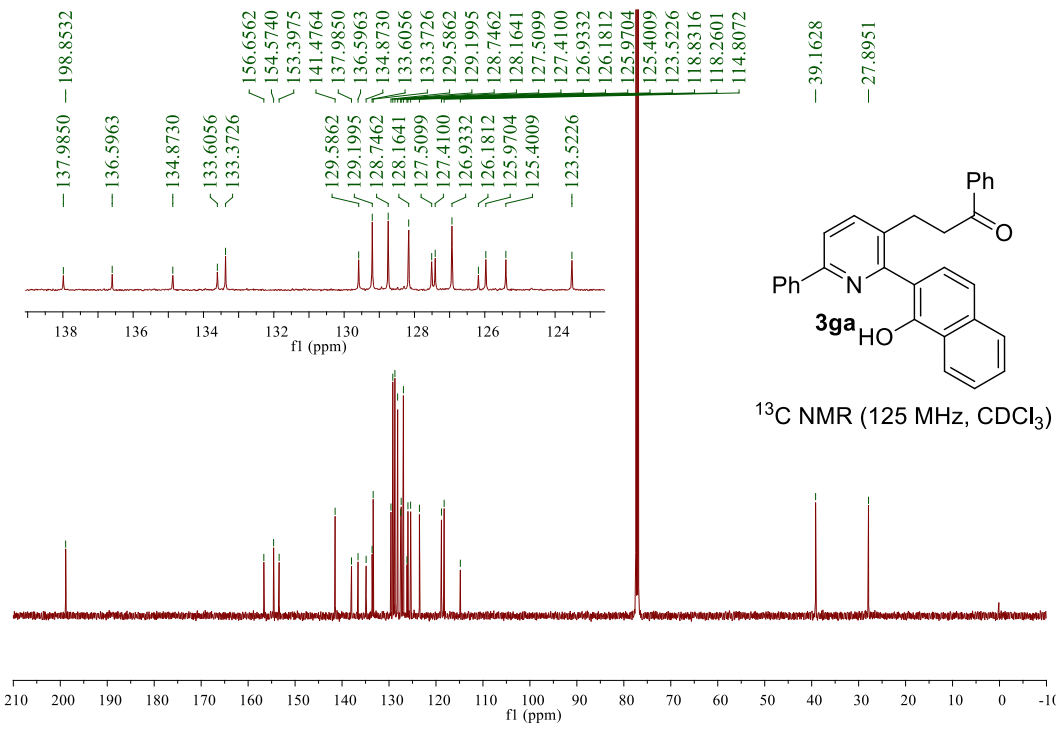


Figure 3.60. 125 MHz ^{13}C Spectrum of **3ga** in $CDCl_3$

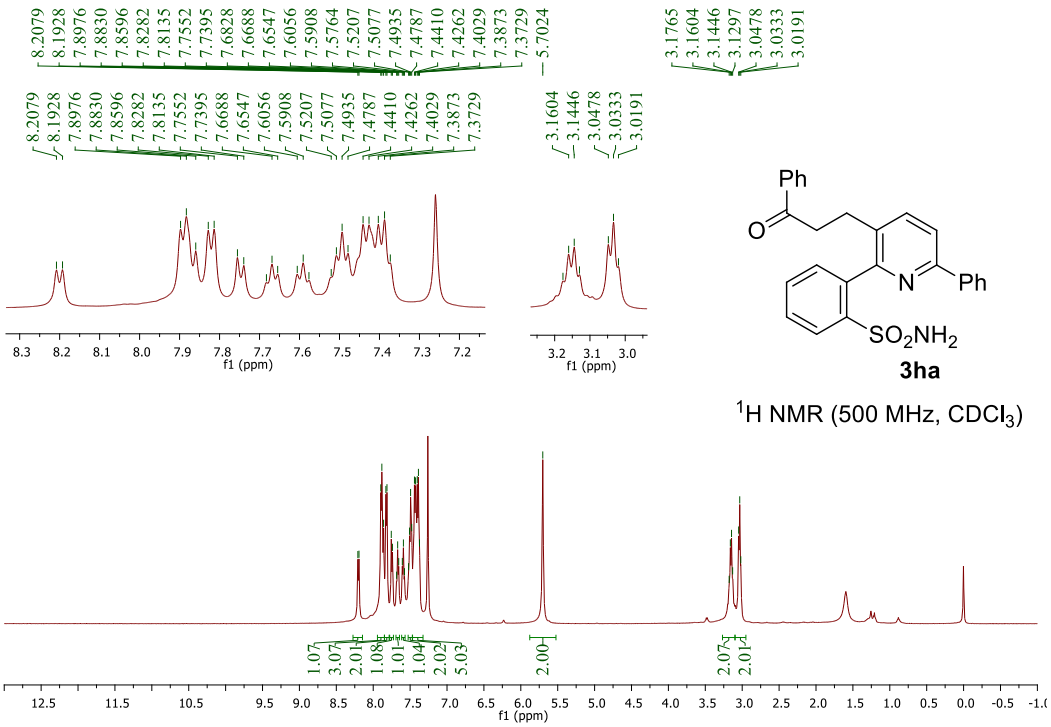


Figure 3.61. 500 MHz ^{1}H Spectrum of **3ha** in $CDCl_3$

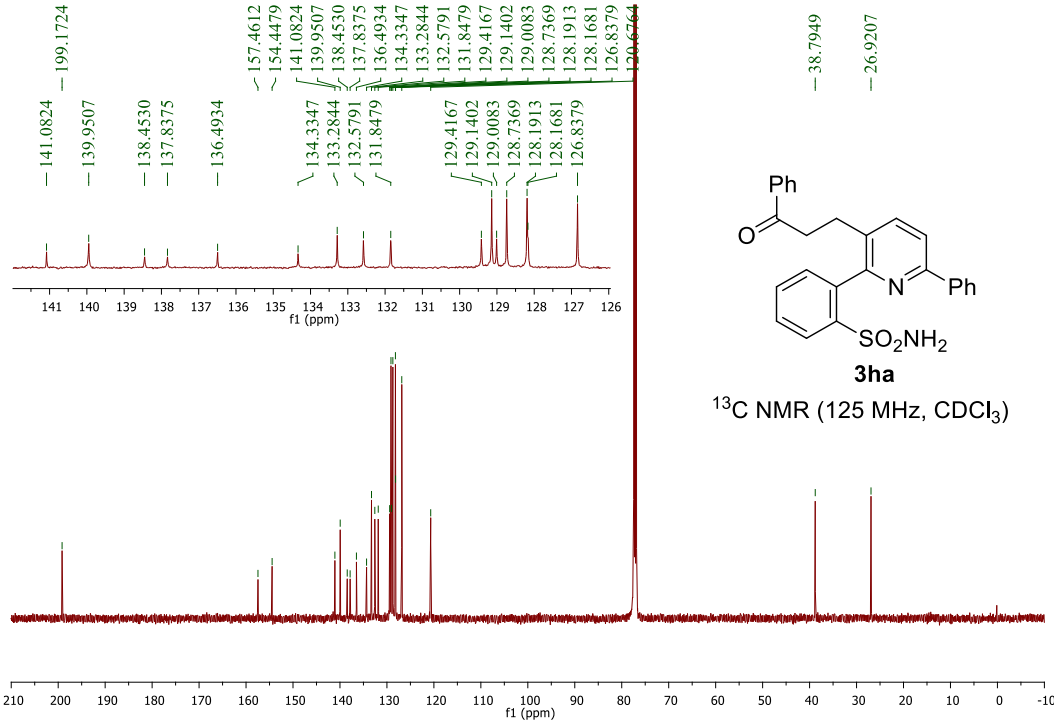


Figure 3.62. 125 MHz ^{13}C Spectrum of **3ha** in $CDCl_3$

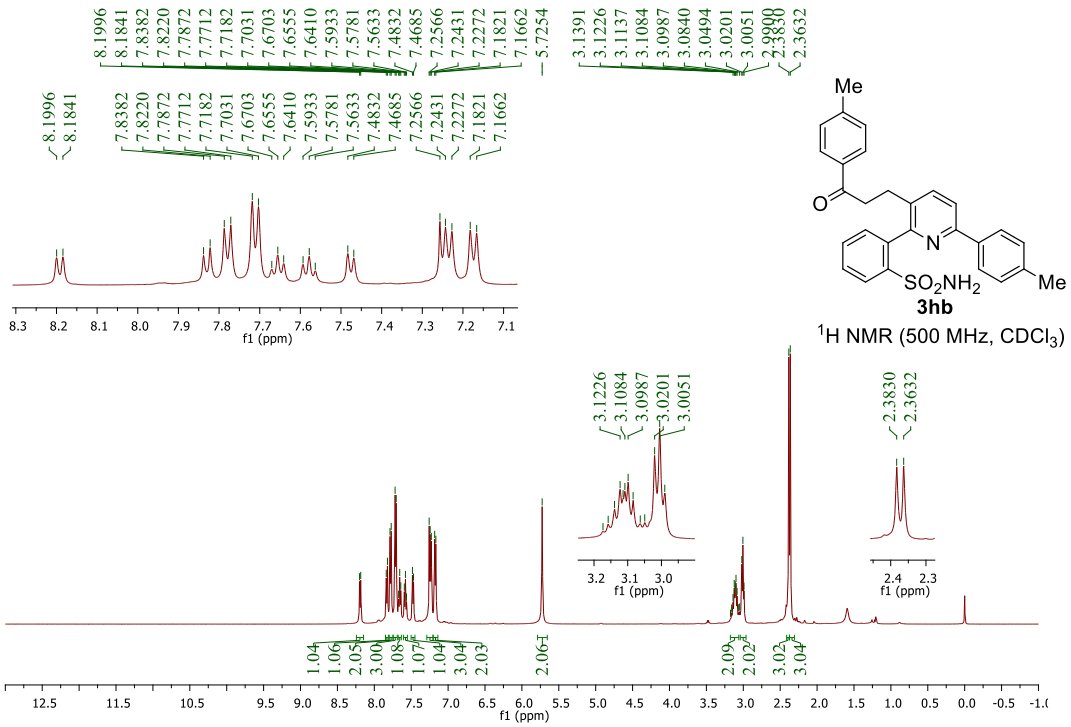


Figure 3.63. 500 MHz ^{1}H Spectrum of **3hb** in $CDCl_3$

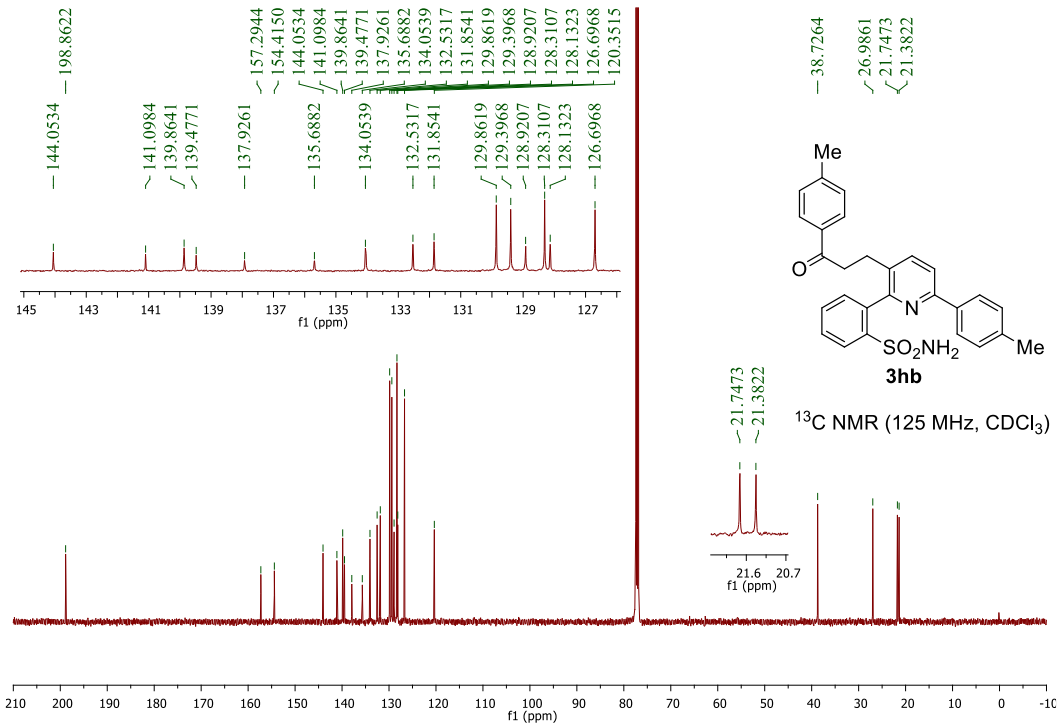


Figure 3.64. 125 MHz ^{13}C Spectrum of **3hb** in $CDCl_3$

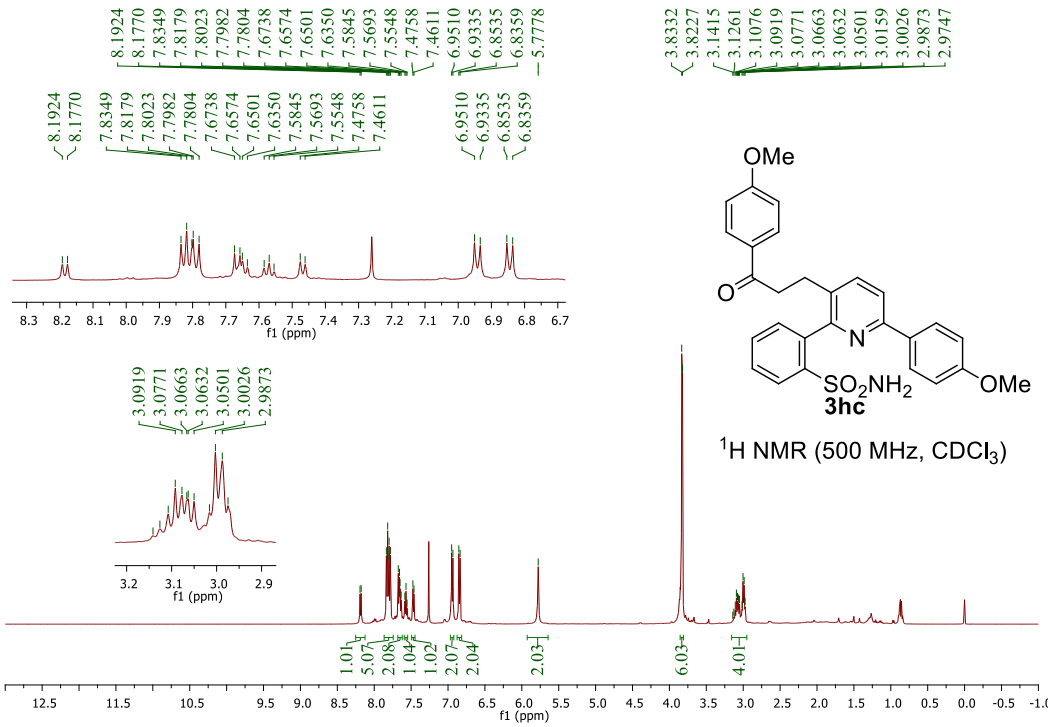


Figure 3.65. 500 MHz ^{1}H Spectrum of **3hc** in $CDCl_3$

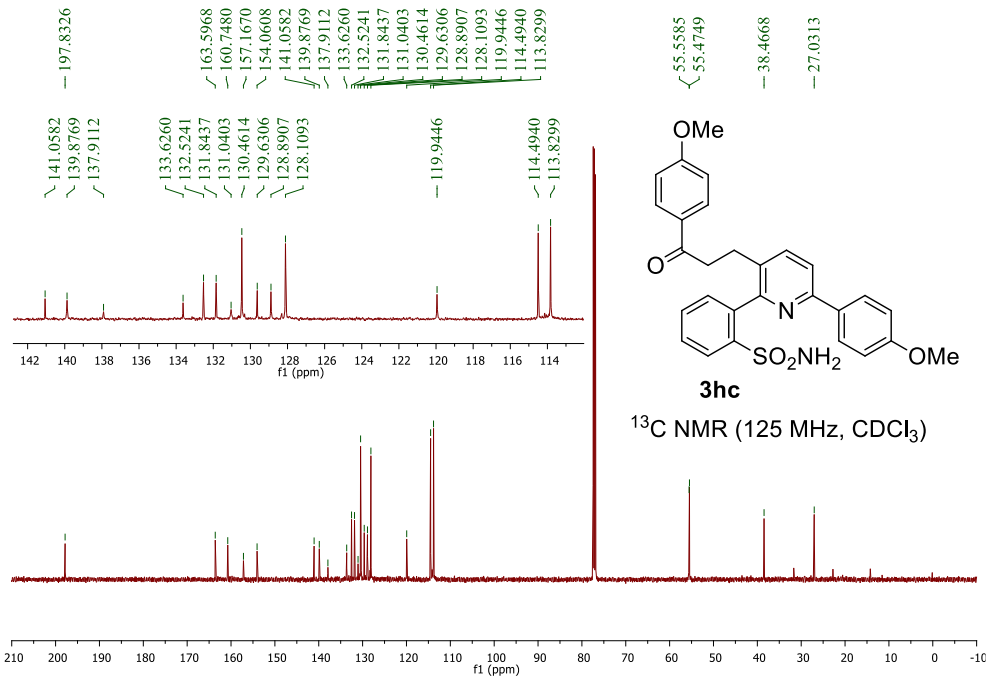


Figure 3.66. 125 MHz ^{13}C Spectrum of **3hc** in $CDCl_3$

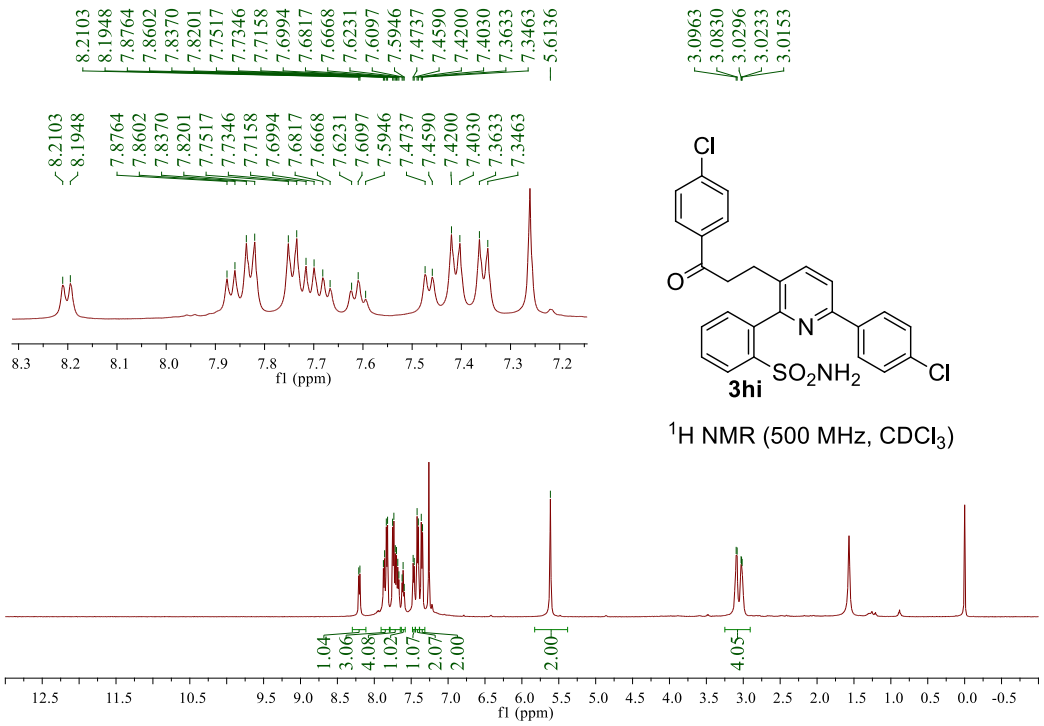


Figure 3.67. 500 MHz ^{1}H Spectrum of **3hi** in $CDCl_3$

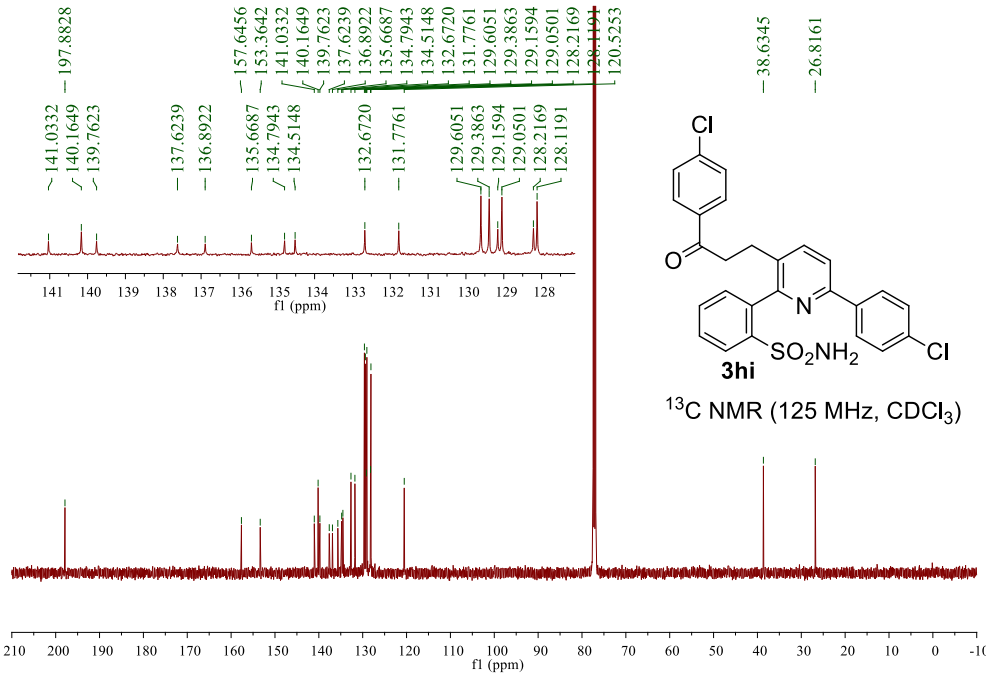


Figure 3.68. 125 MHz ^{13}C Spectrum of **3hi** in $CDCl_3$

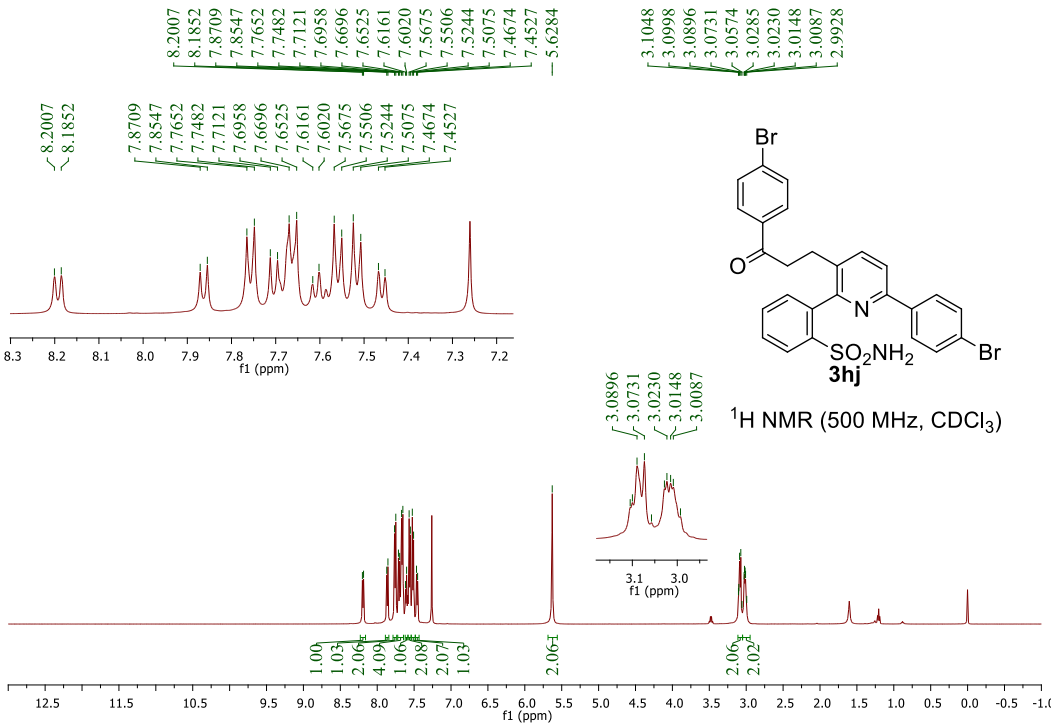


Figure 3.69. 500 MHz ^{1}H Spectrum of **3hj** in $CDCl_3$

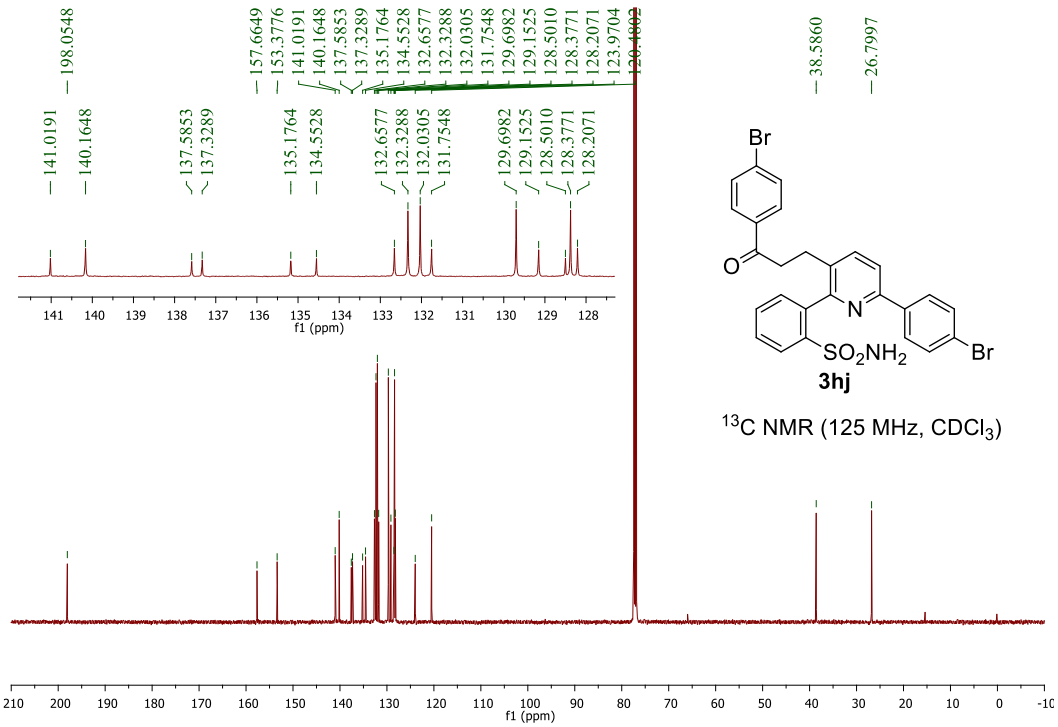


Figure 3.70. 125 MHz ^{13}C Spectrum of **3hj** in $CDCl_3$

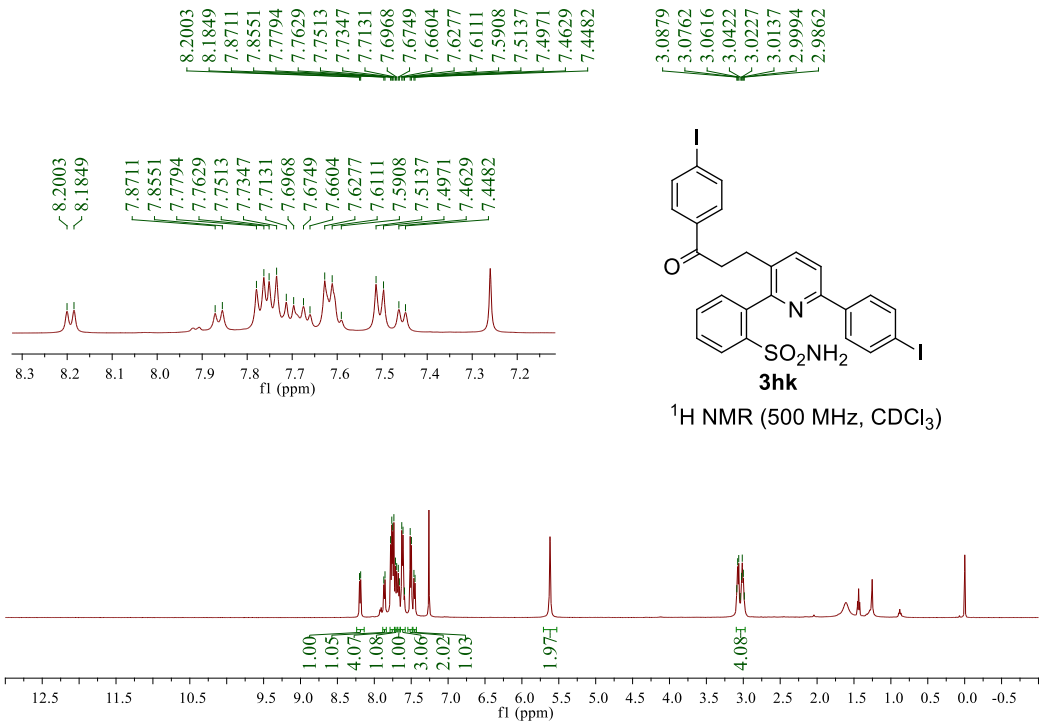


Figure 3.71. 500 MHz ^{1}H Spectrum of **3hk** in $CDCl_3$

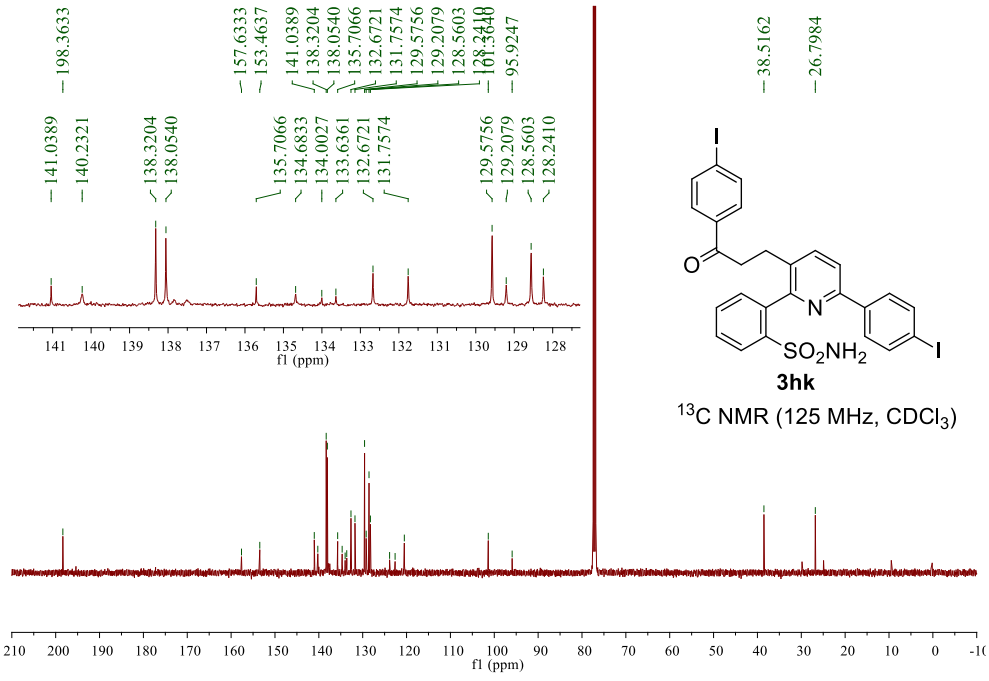


Figure 3.72. 125 MHz ^{13}C Spectrum of **3hk** in $CDCl_3$

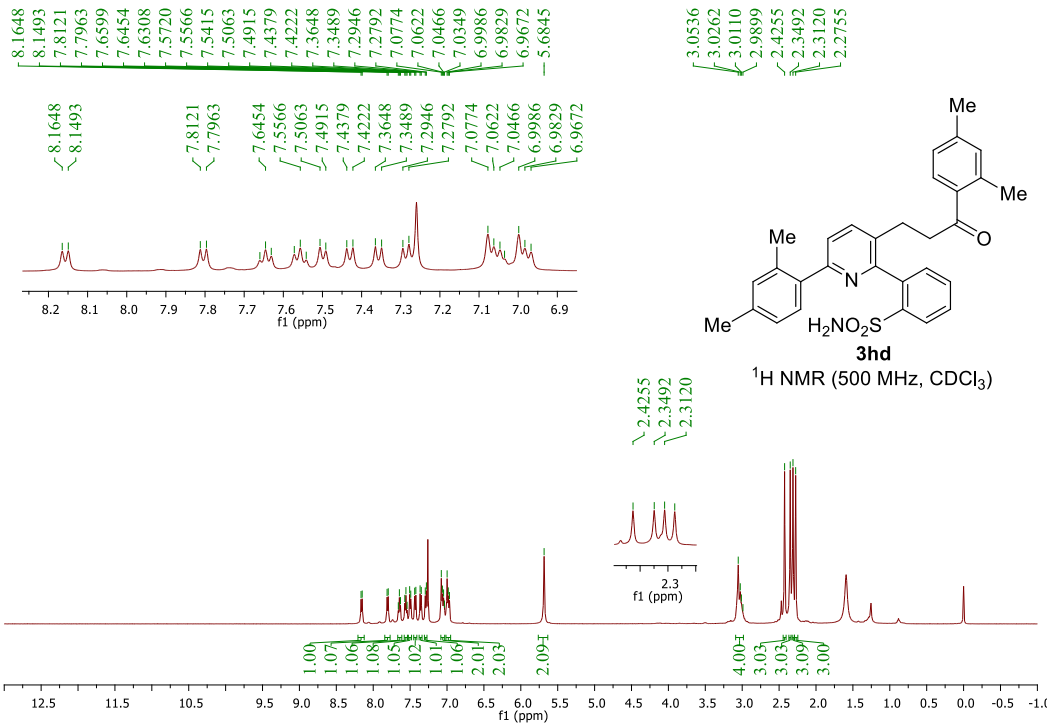


Figure 3.73. 500 MHz ^{1}H Spectrum of **3hd** in $CDCl_3$

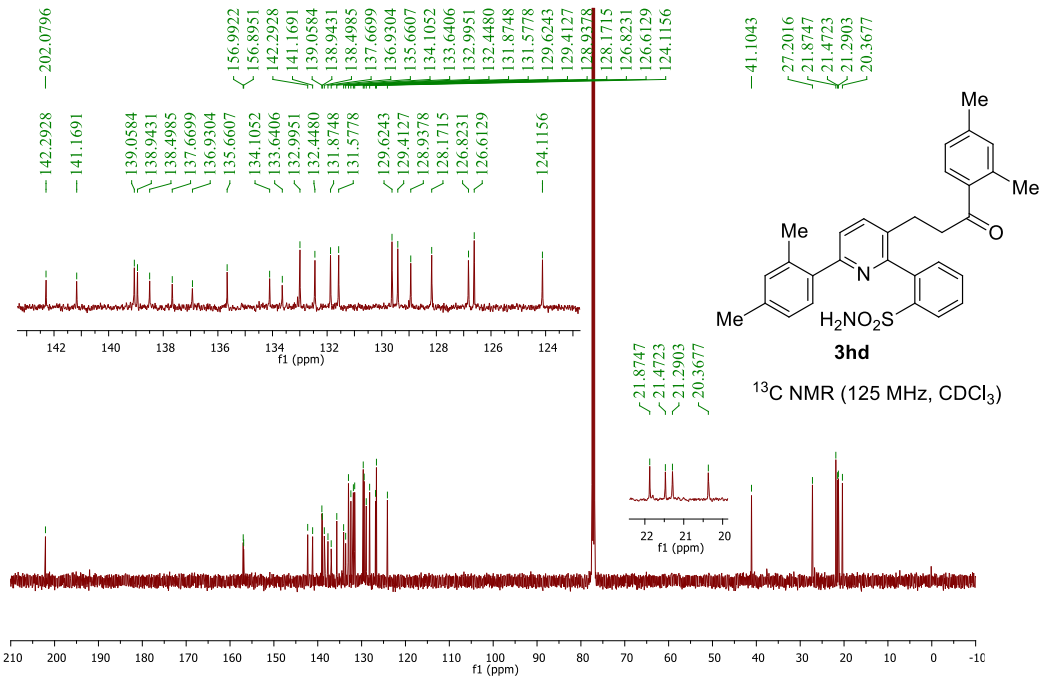


Figure 3.74. 125 MHz ^{13}C Spectrum of **3hd** in $CDCl_3$

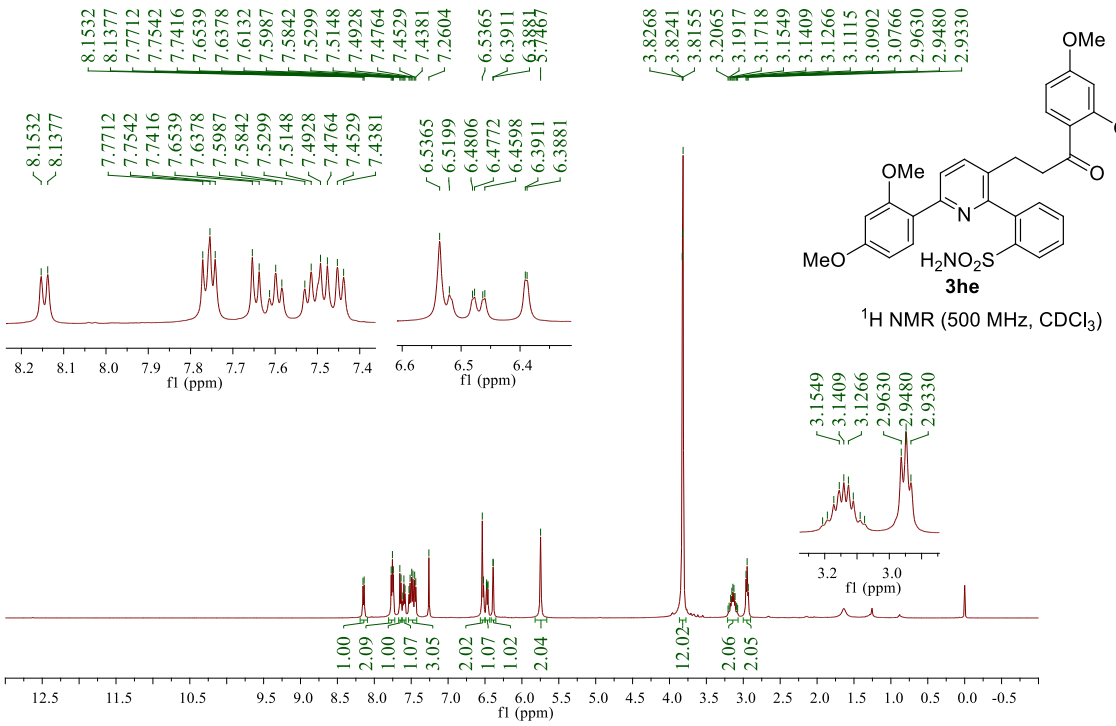


Figure 3.75. 500 MHz ^{1}H Spectrum of **3he** in $CDCl_3$

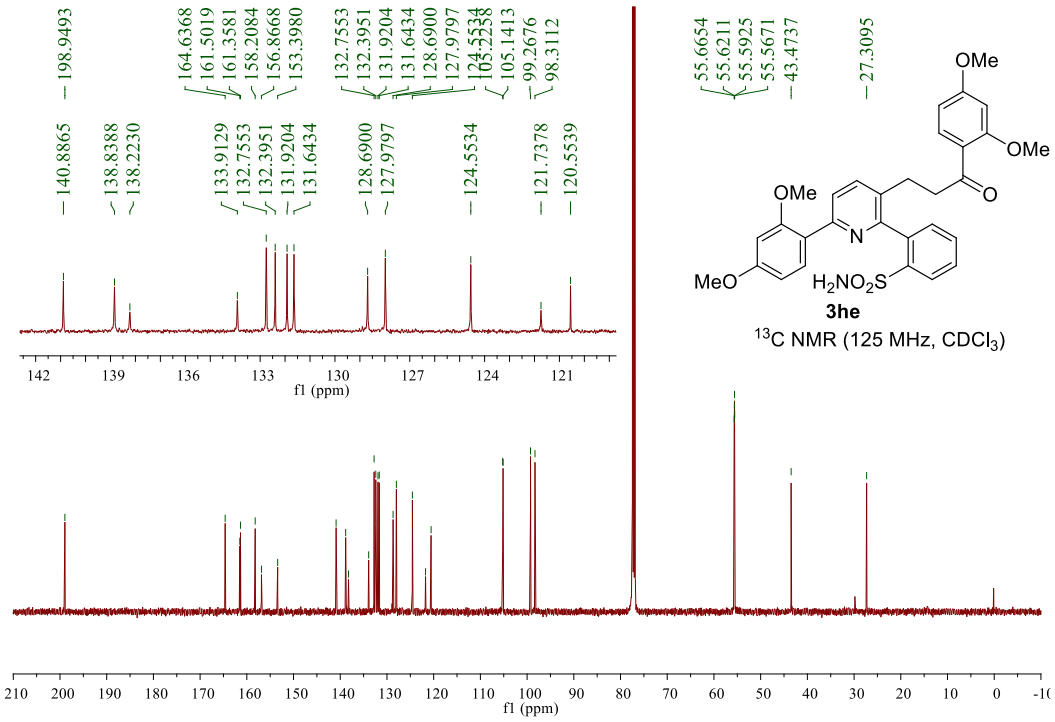


Figure 3.76. 125 MHz ^{13}C Spectrum of **3he** in $CDCl_3$

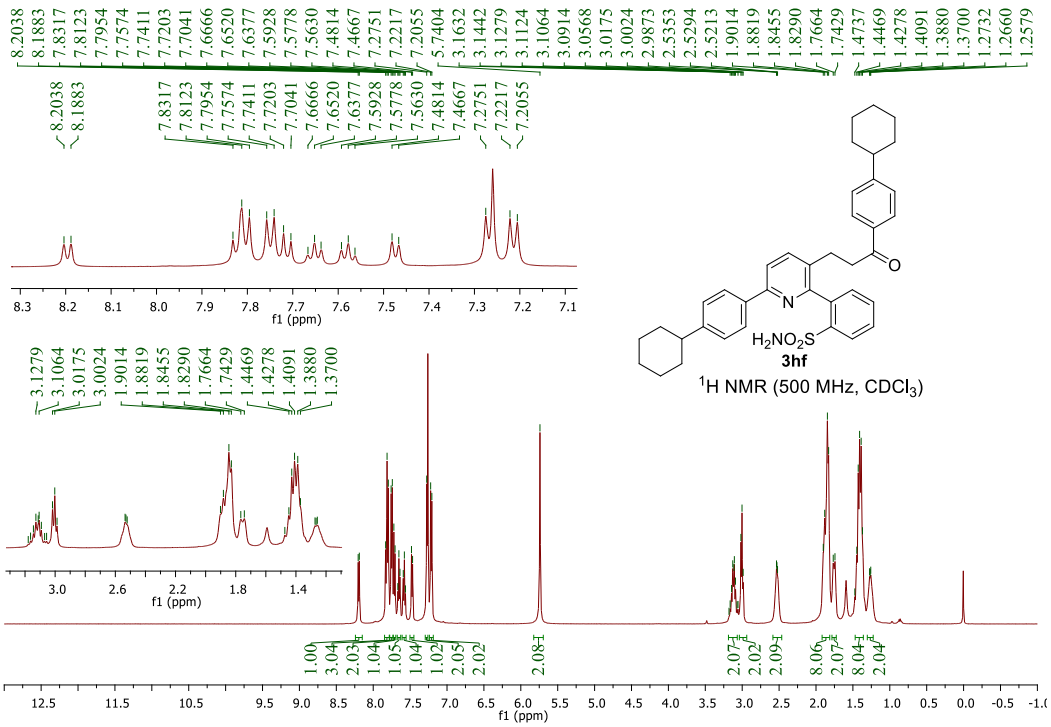


Figure 3.77. 500 MHz ^{1}H Spectrum of **3hf** in $CDCl_3$

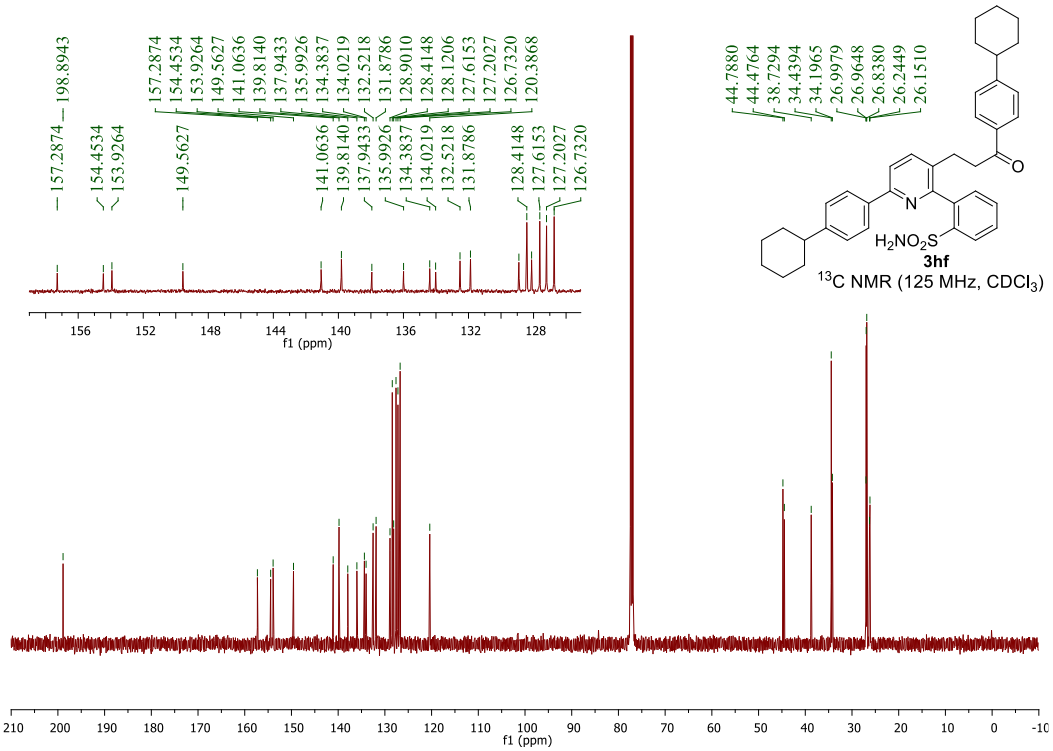


Figure 3.78. 125 MHz ^{13}C Spectrum of **3hf** in $CDCl_3$

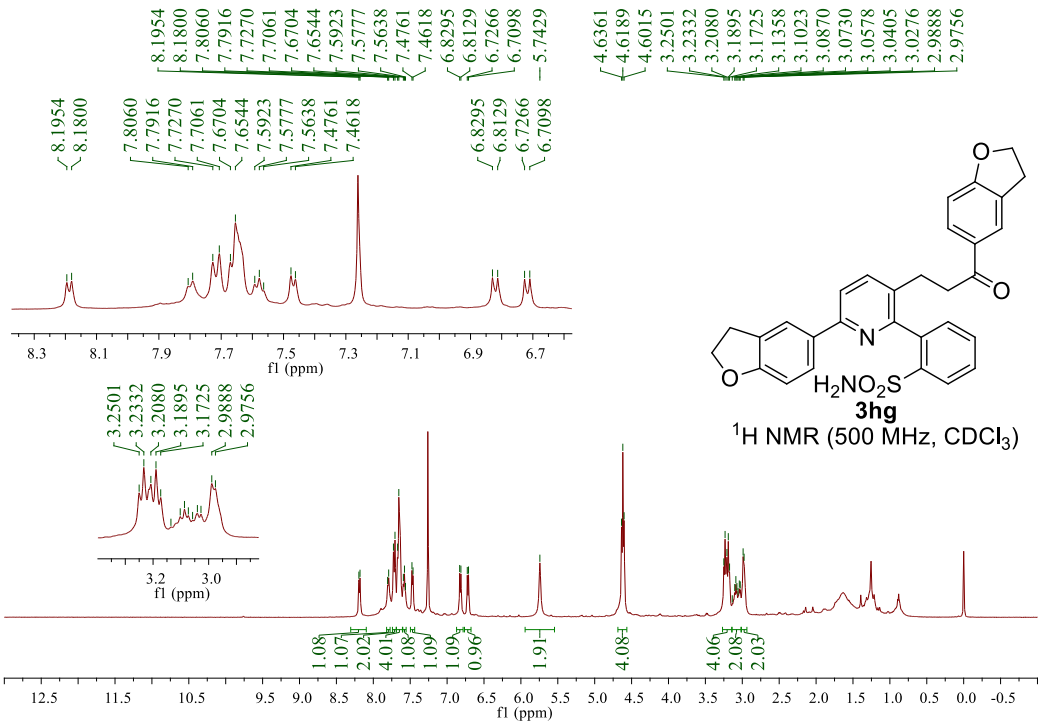


Figure 3.79. 500 MHz ^{1}H Spectrum of **3hg** in $CDCl_3$

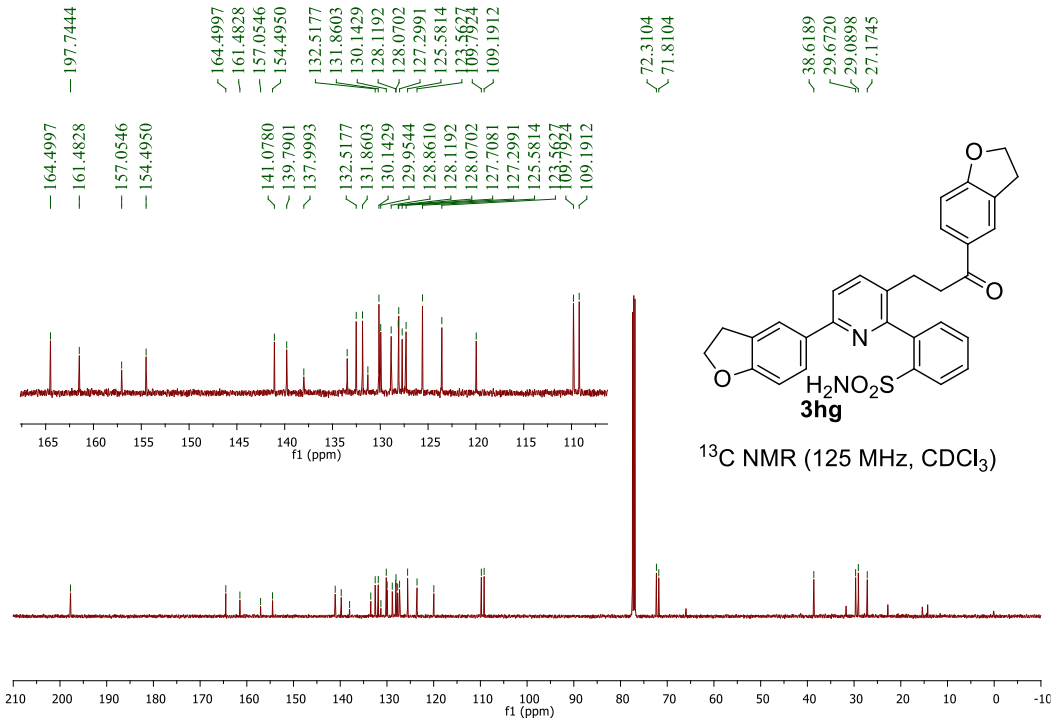


Figure 3.80. 125 MHz ^{13}C Spectrum of **3hg** in $CDCl_3$

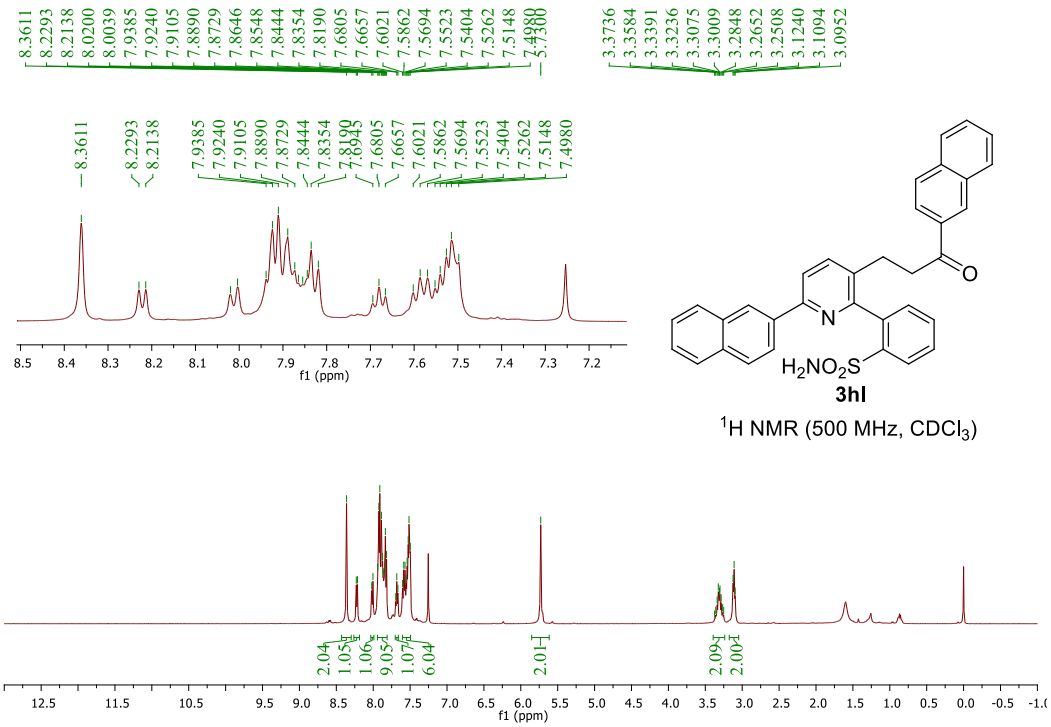


Figure 3.81. 500 MHz ^{1}H Spectrum of **3hl** in $CDCl_3$

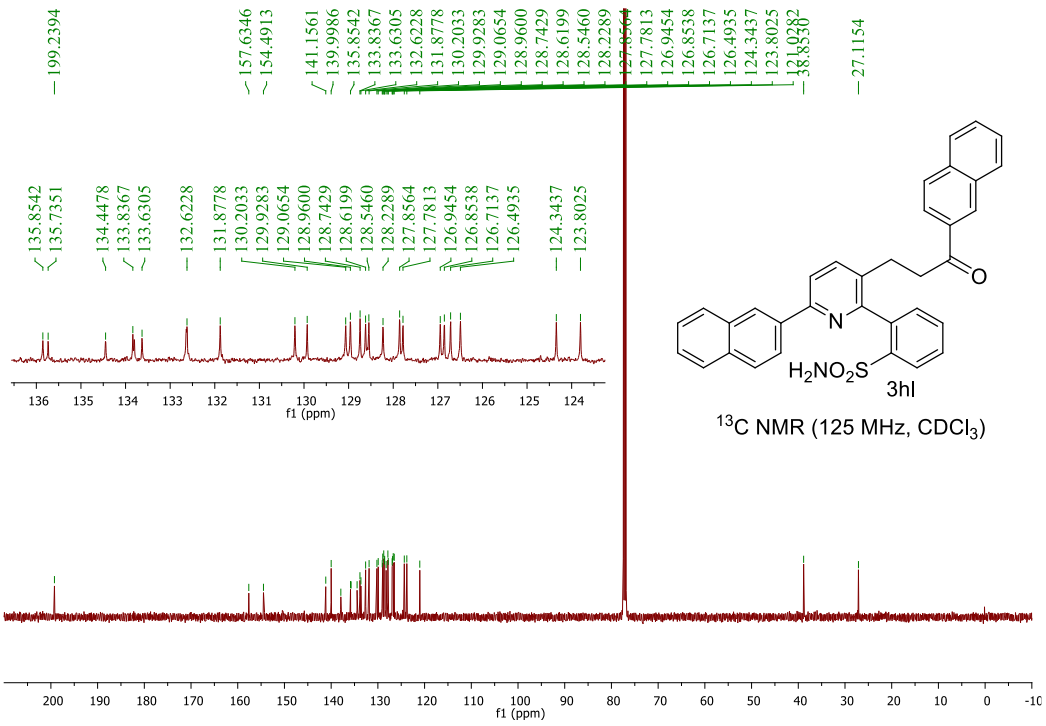


Figure 3.82. 125 MHz ^{13}C Spectrum of **3hl** in CDCl

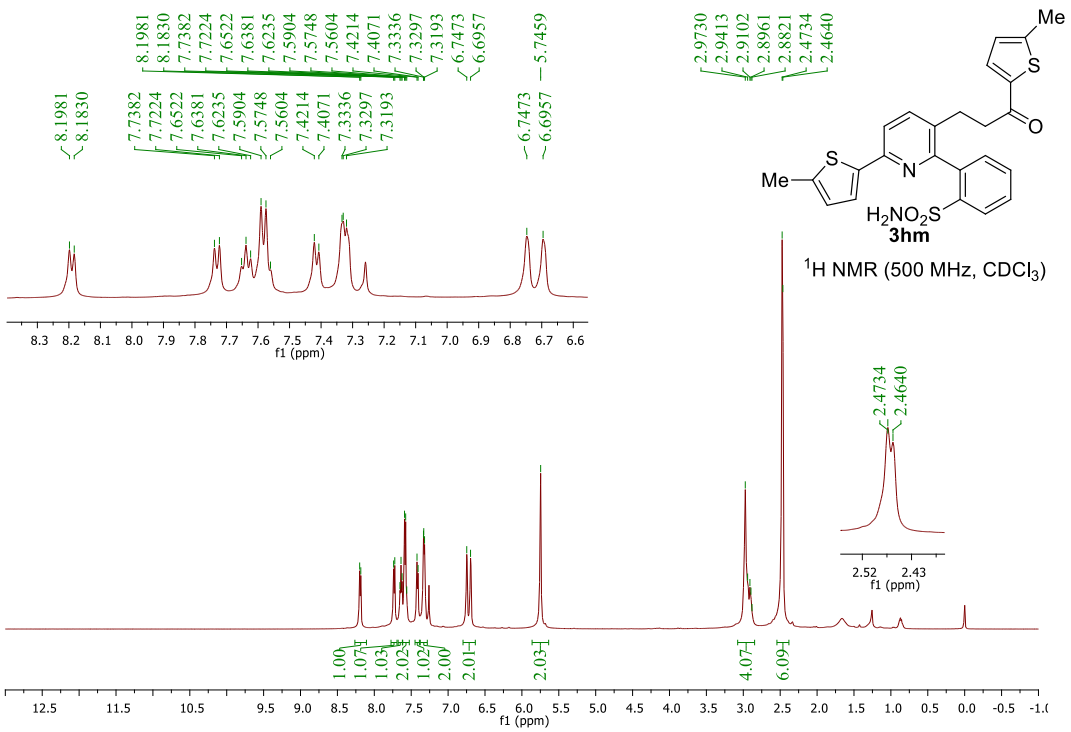


Figure 3.83. 500 MHz ^{1}H Spectrum of **3hm** in $CDCl_3$

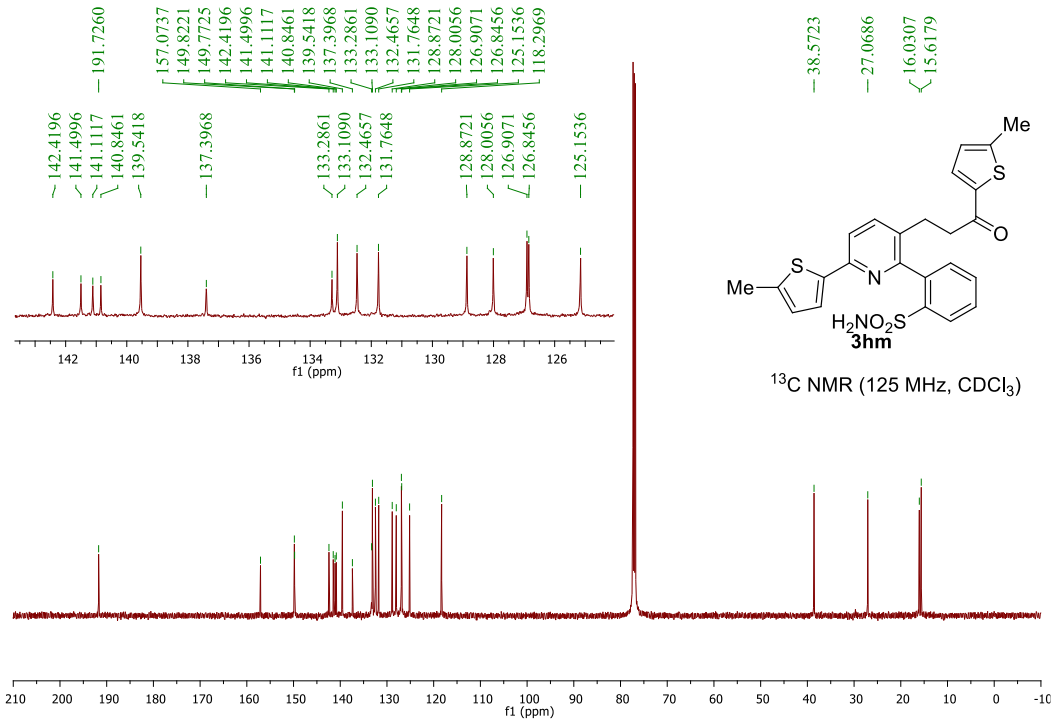


Figure 3.84. 125 MHz ^{13}C Spectrum of **3hm** in $CDCl_3$

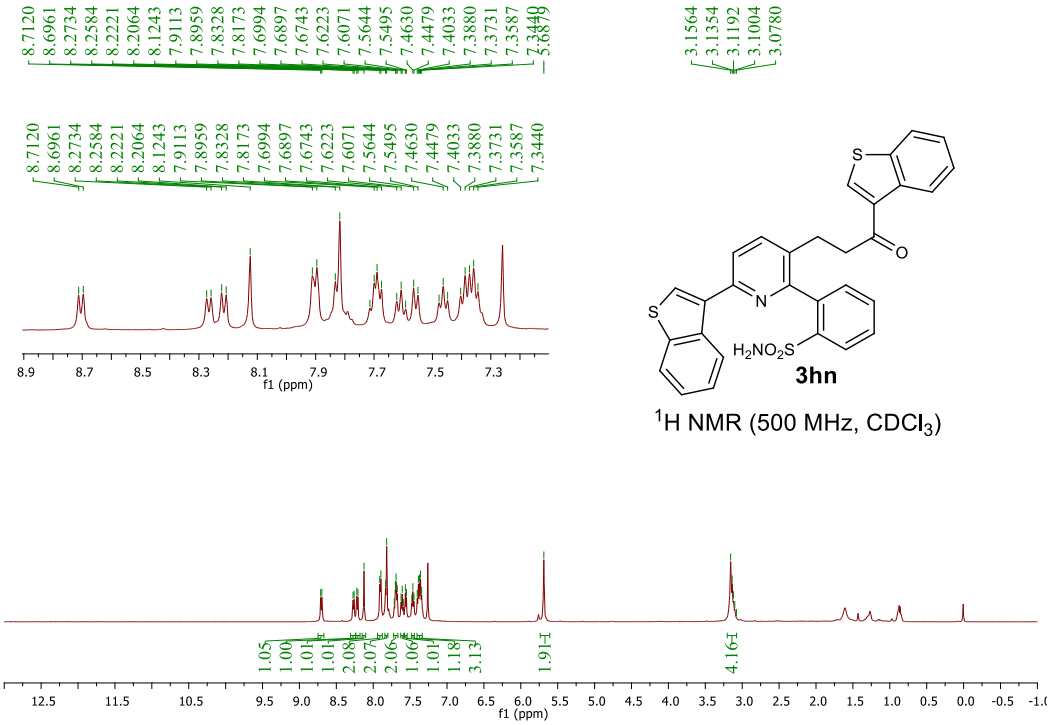


Figure 3.85. 500 MHz ^{1}H Spectrum of **3hn** in $CDCl_3$

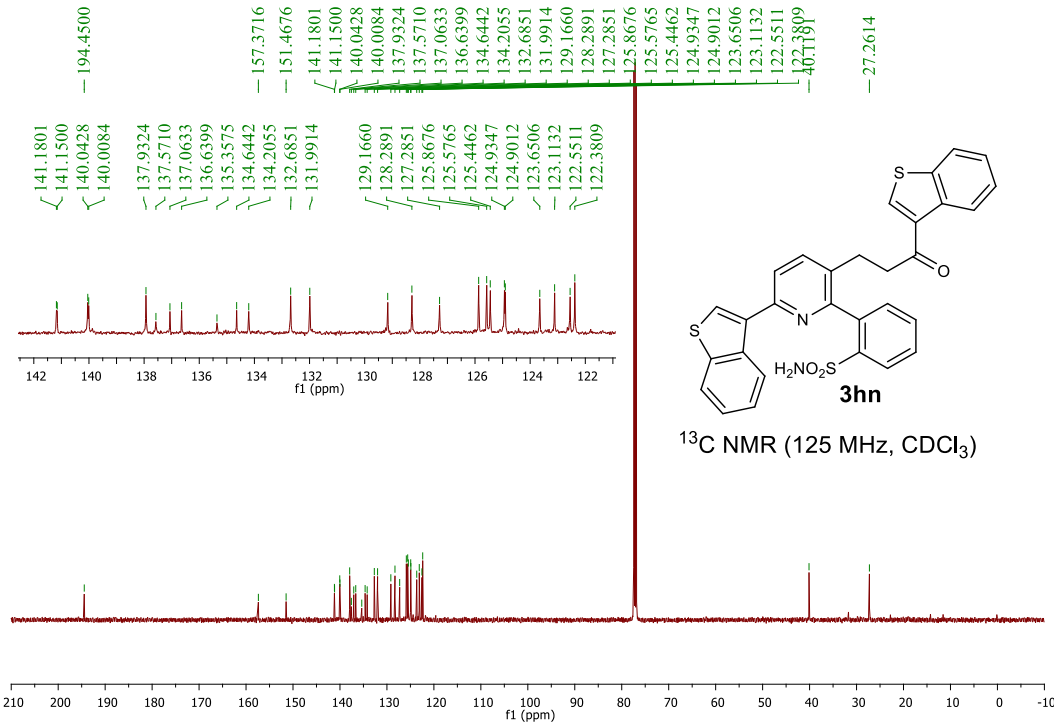


Figure 3.86. 125 MHz ^{13}C Spectrum of **3hn** in $CDCl_3$

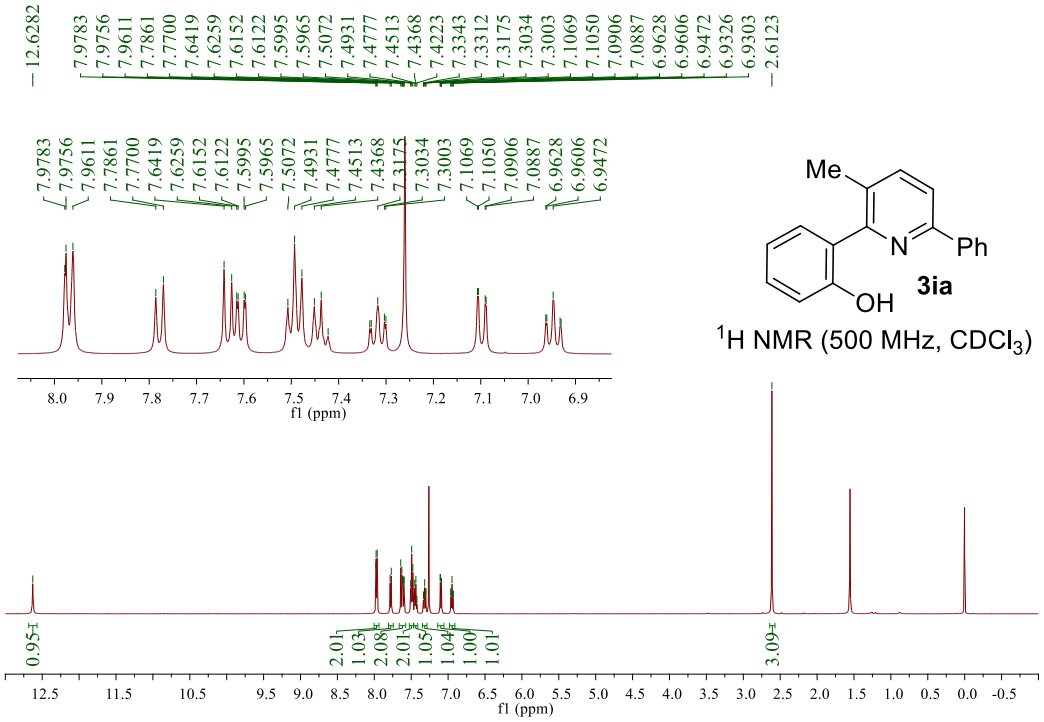


Figure 3.87. 500 MHz ^{1}H Spectrum of **3ia** in $CDCl_3$

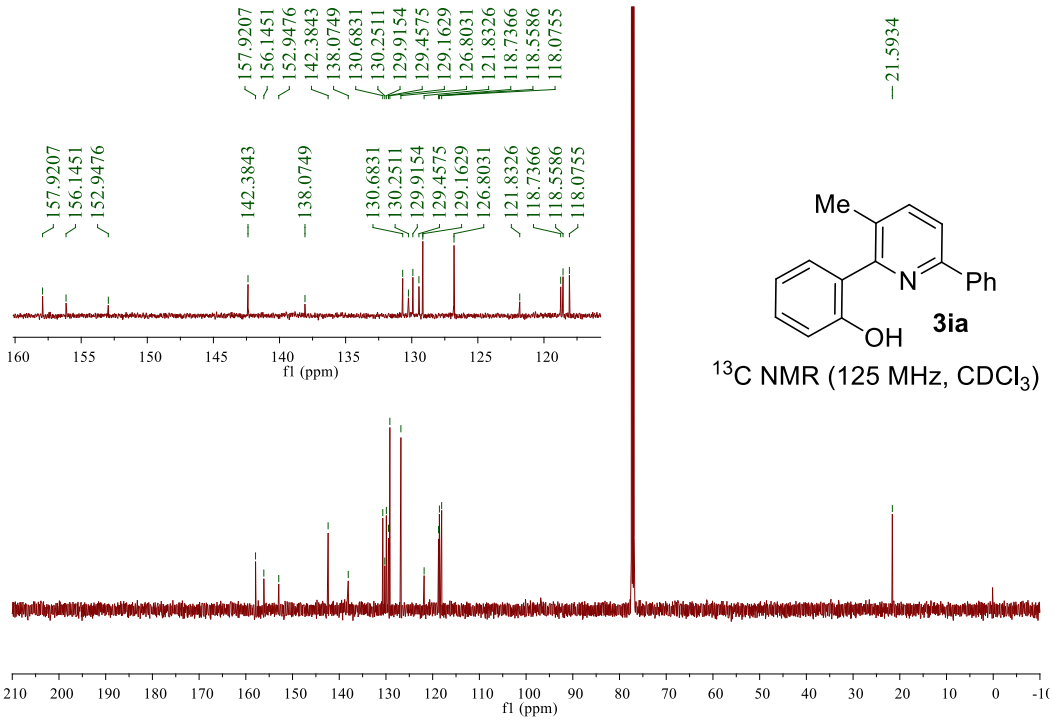


Figure 3.88. 125 MHz ^{13}C Spectrum of **3ia** in $CDCl_3$

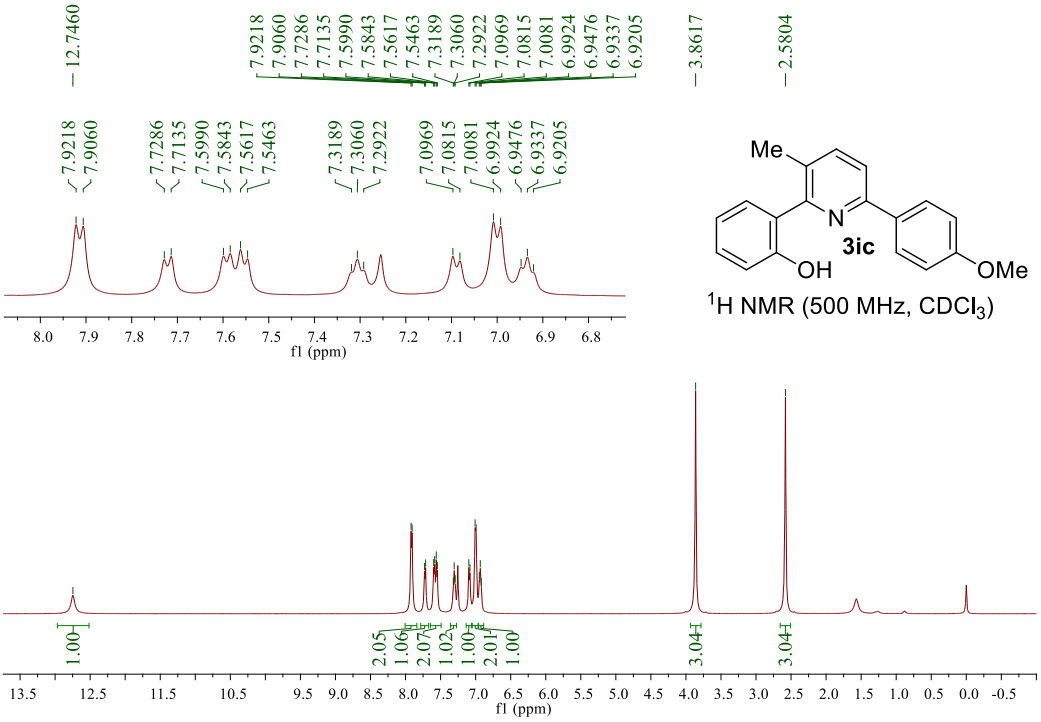


Figure 3.89. 500 MHz ^{1}H Spectrum of **3ic** in $CDCl_3$

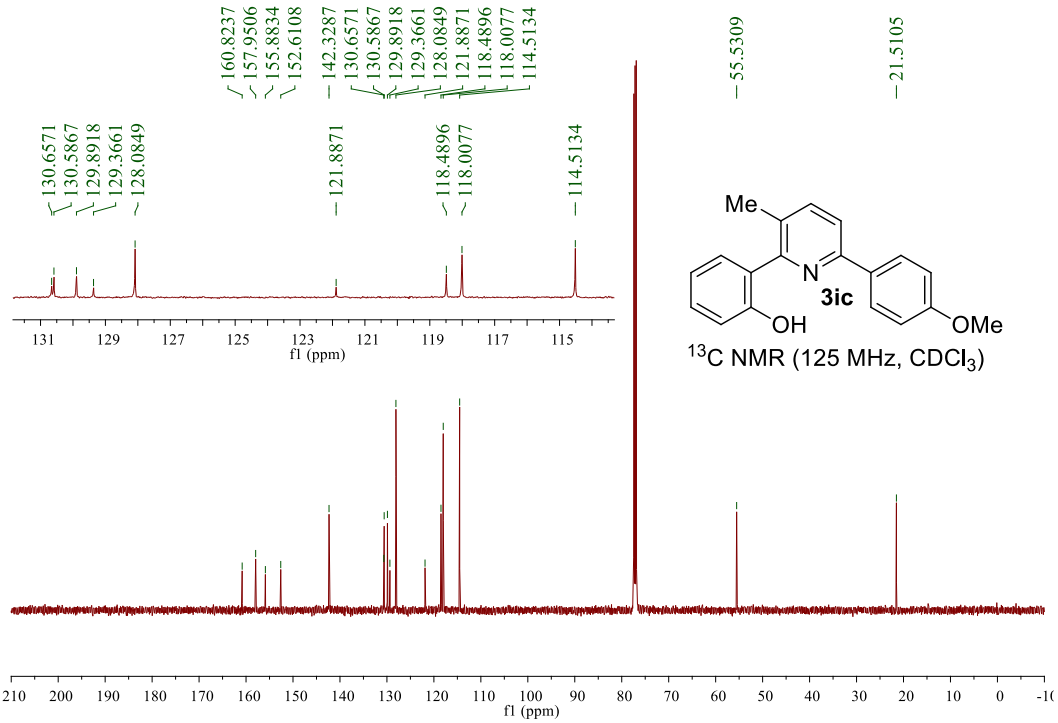


Figure 3.90. 125 MHz ^{13}C Spectrum of **3ic** in $CDCl_3$

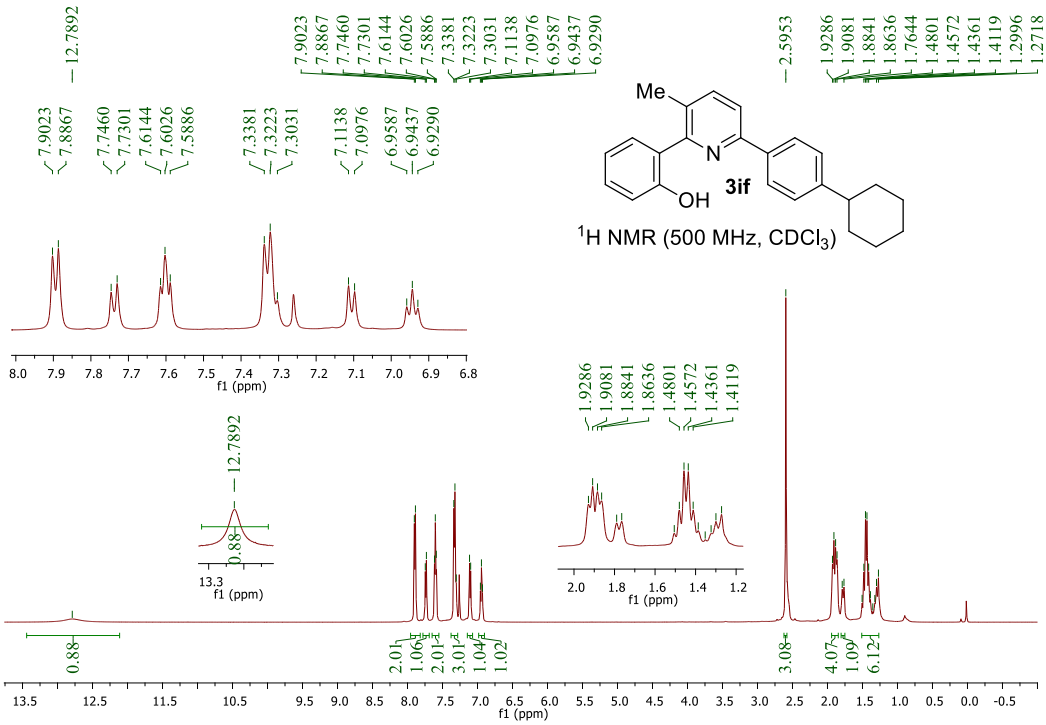


Figure 3.91. 500 MHz ^{1}H Spectrum of **3if** in $CDCl_3$

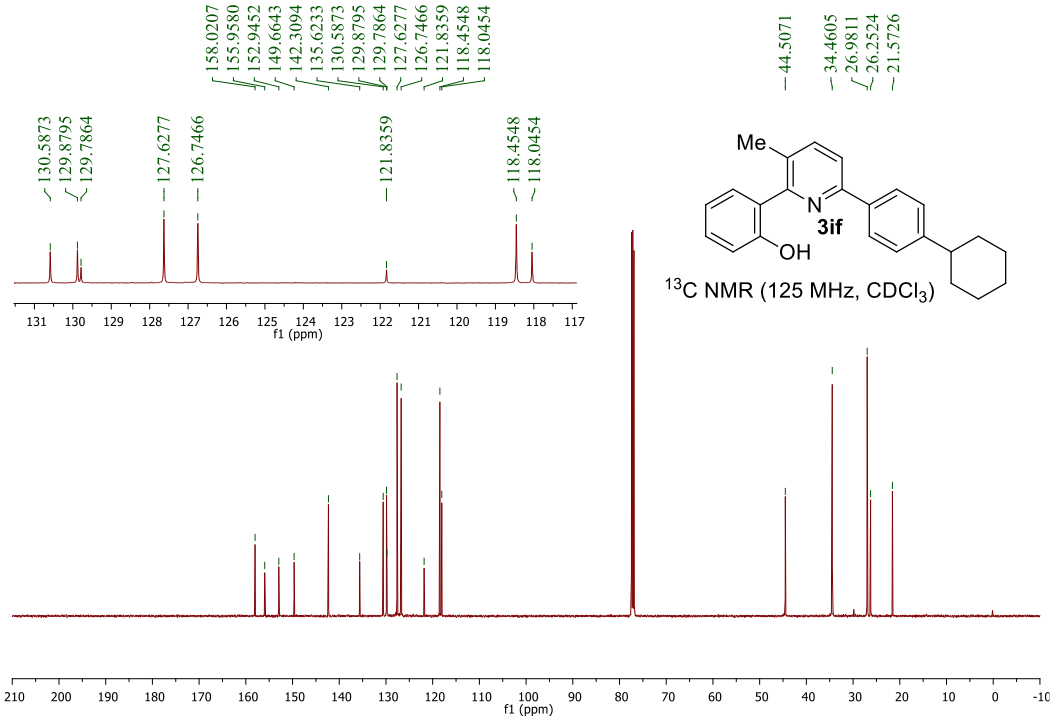


Figure 3.92. 125 MHz ^{13}C Spectrum of **3if** in $CDCl_3$

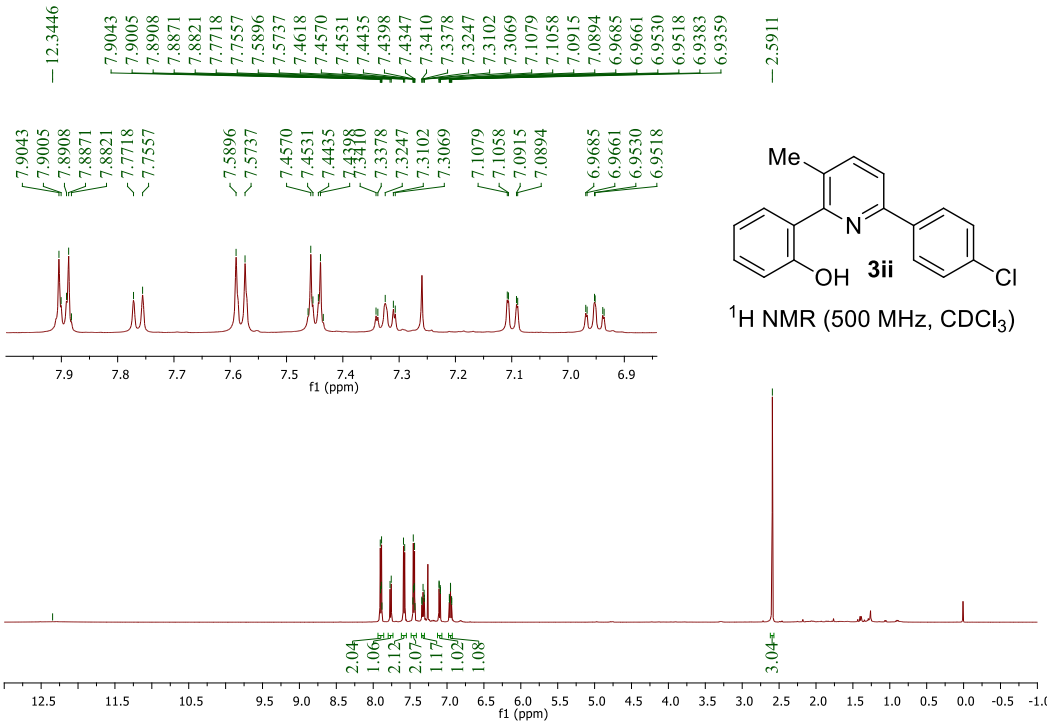


Figure 3.93. 500 MHz ^{1}H Spectrum of **3ii** in $CDCl_3$

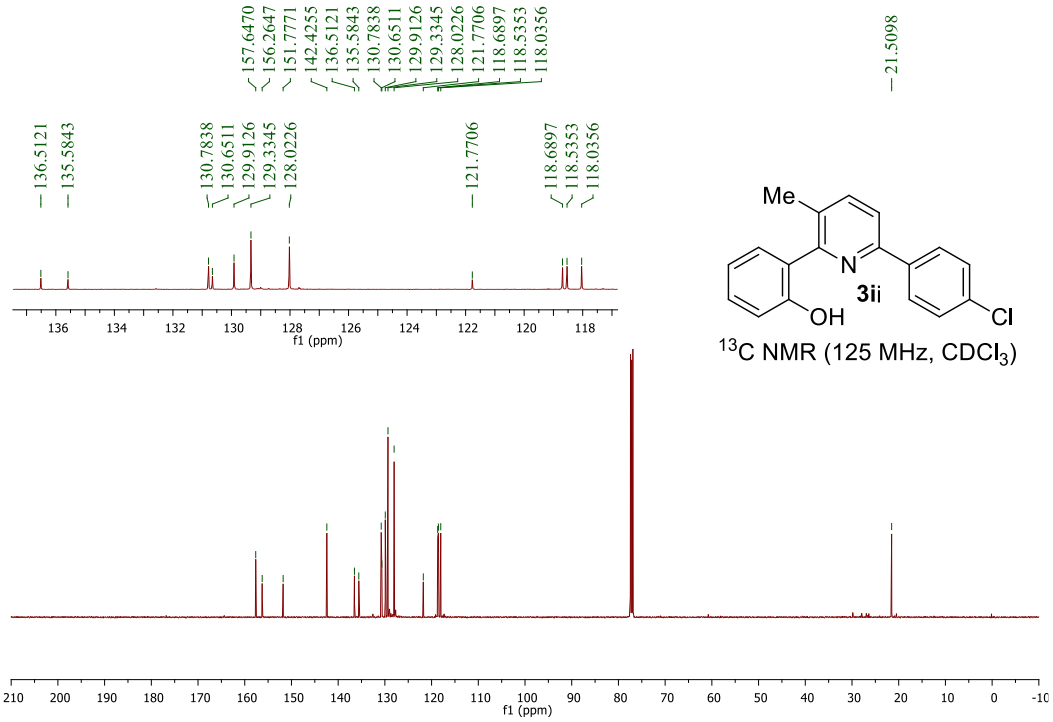


Figure 3.94. 125 MHz ^{13}C Spectrum of **3ii** in $CDCl_3$

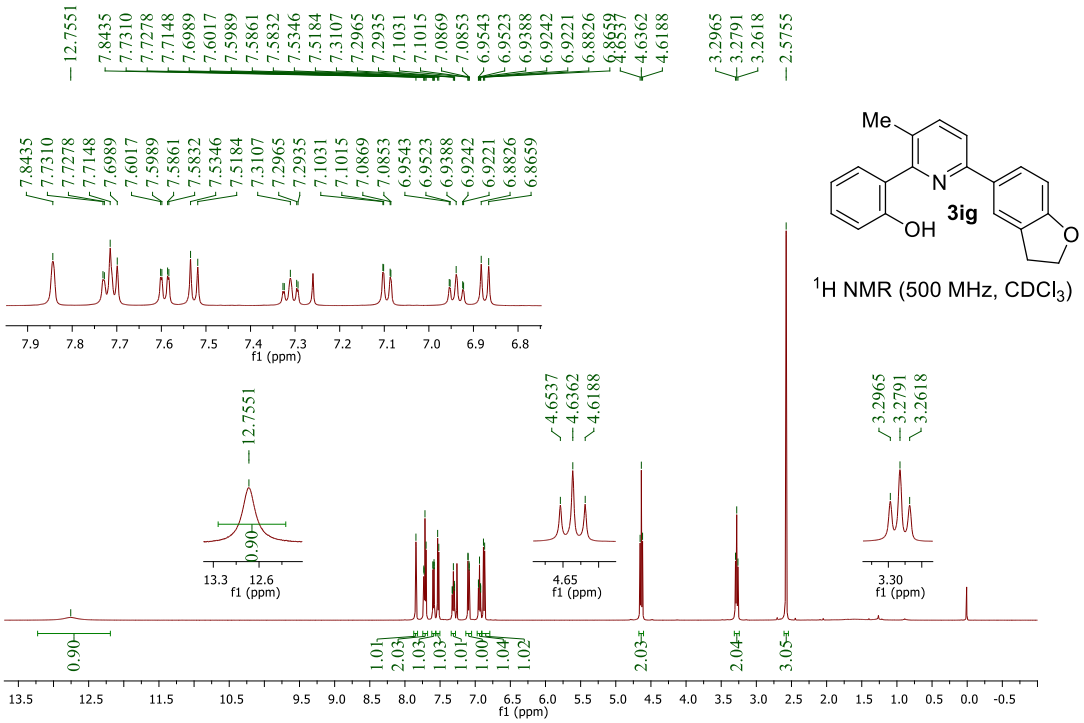


Figure 3.95. 500 MHz ^{1}H Spectrum of **3ig** in $CDCl_3$

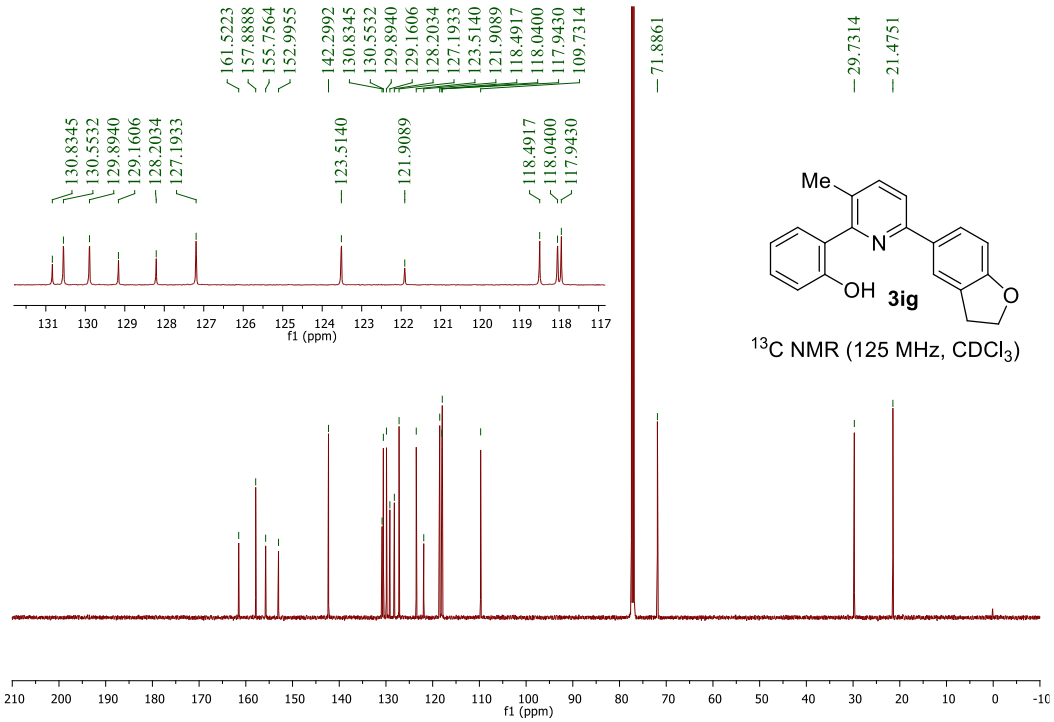


Figure 3.96. 125 MHz ^{13}C Spectrum of **3ig** in $CDCl_3$

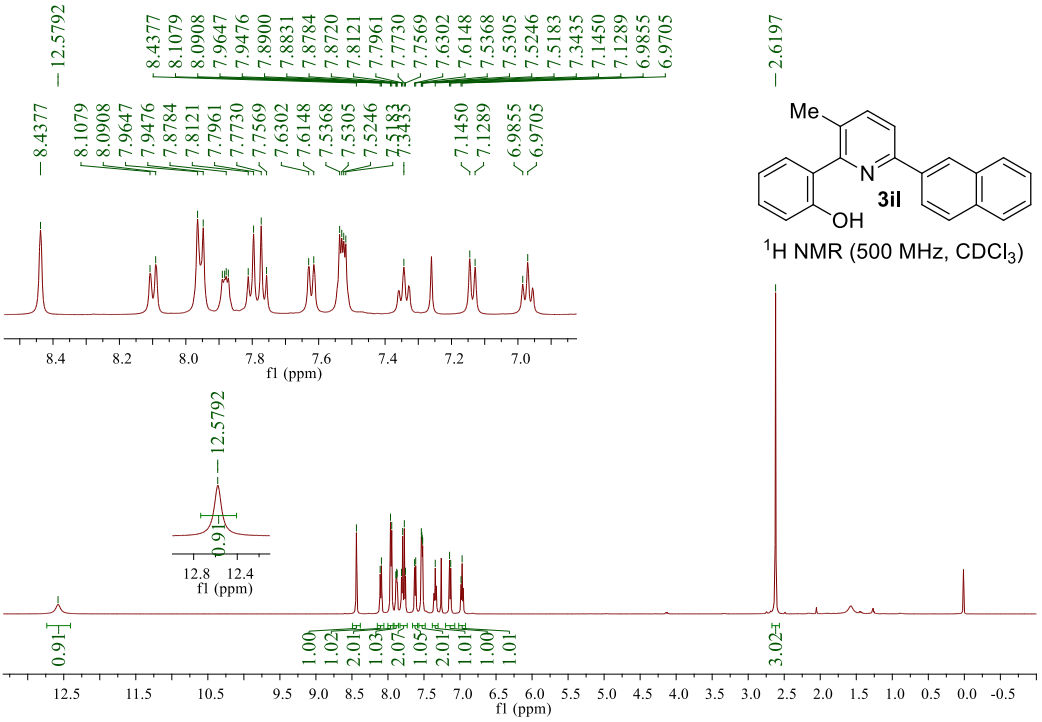


Figure 3.97. 500 MHz ^{1}H Spectrum of **3il** in $CDCl_3$

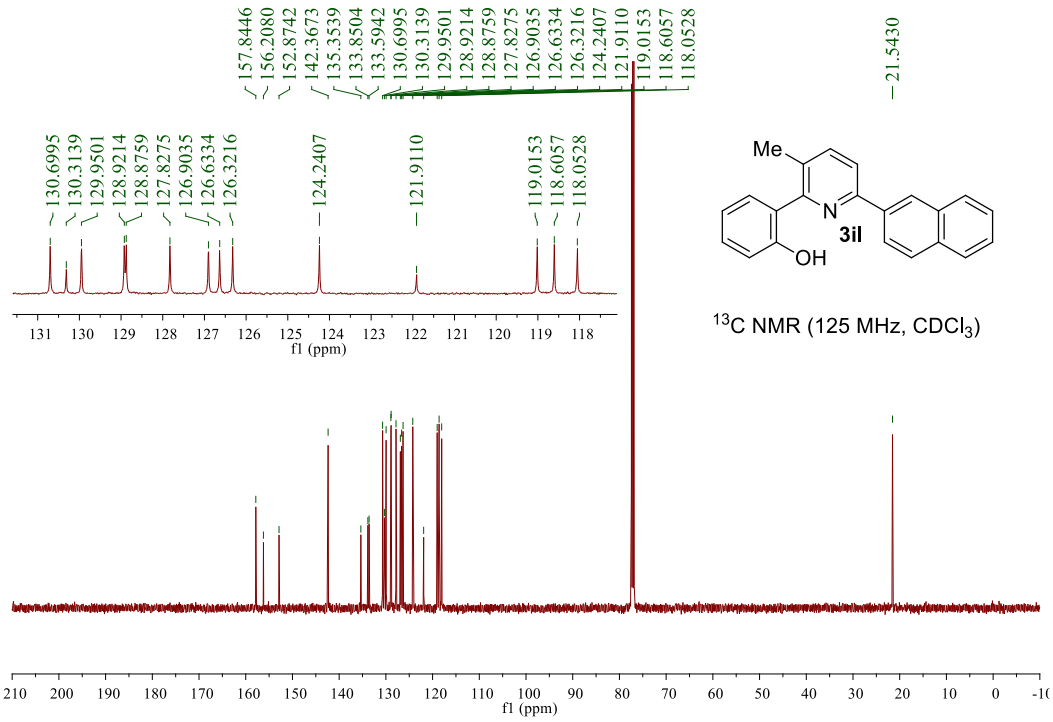


Figure 3.98. 125 MHz ^{13}C Spectrum of **3il** in $CDCl_3$

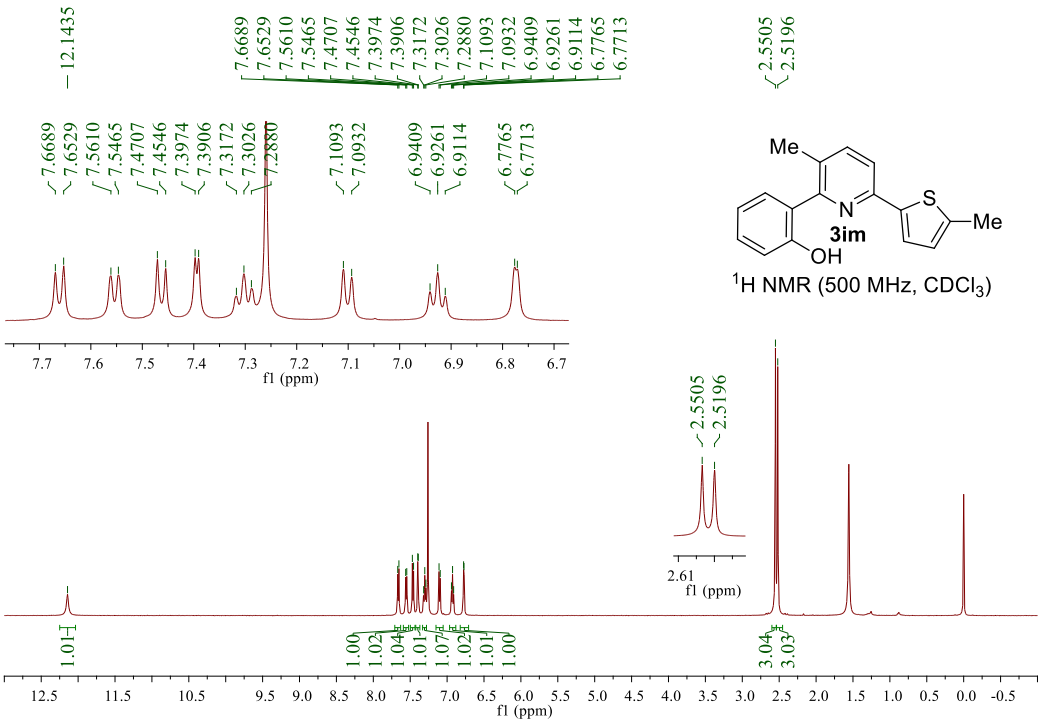


Figure 3.99. 500 MHz ^{1}H Spectrum of **3im** in $CDCl_3$

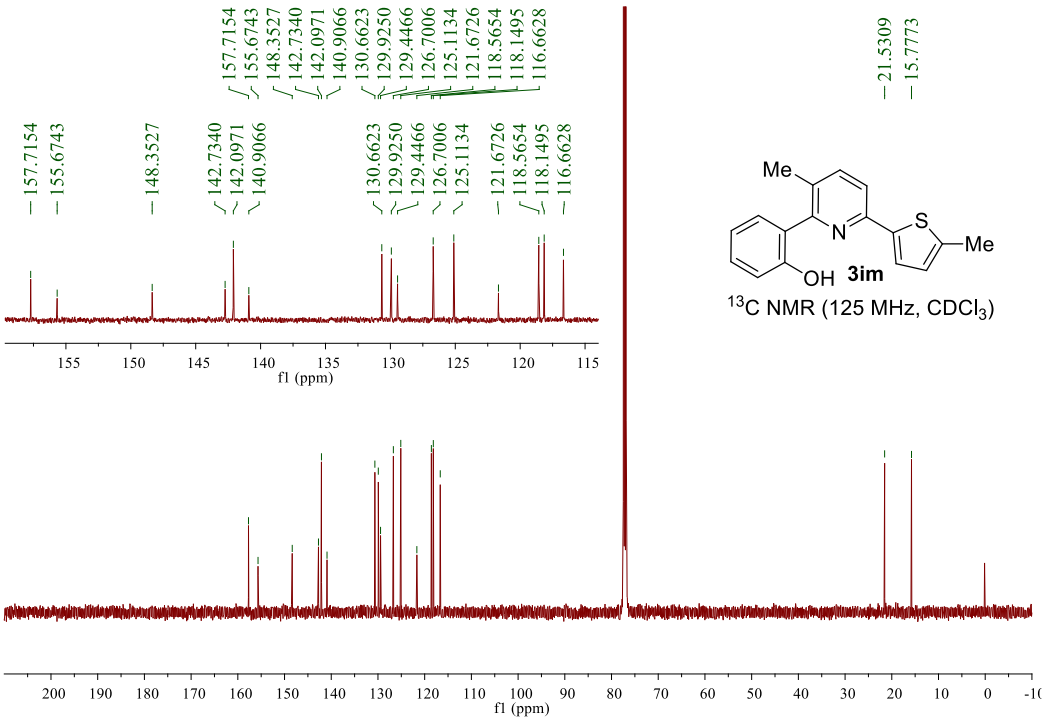


Figure 3.100. 125 MHz ^{13}C Spectrum of **3im** in $CDCl_3$

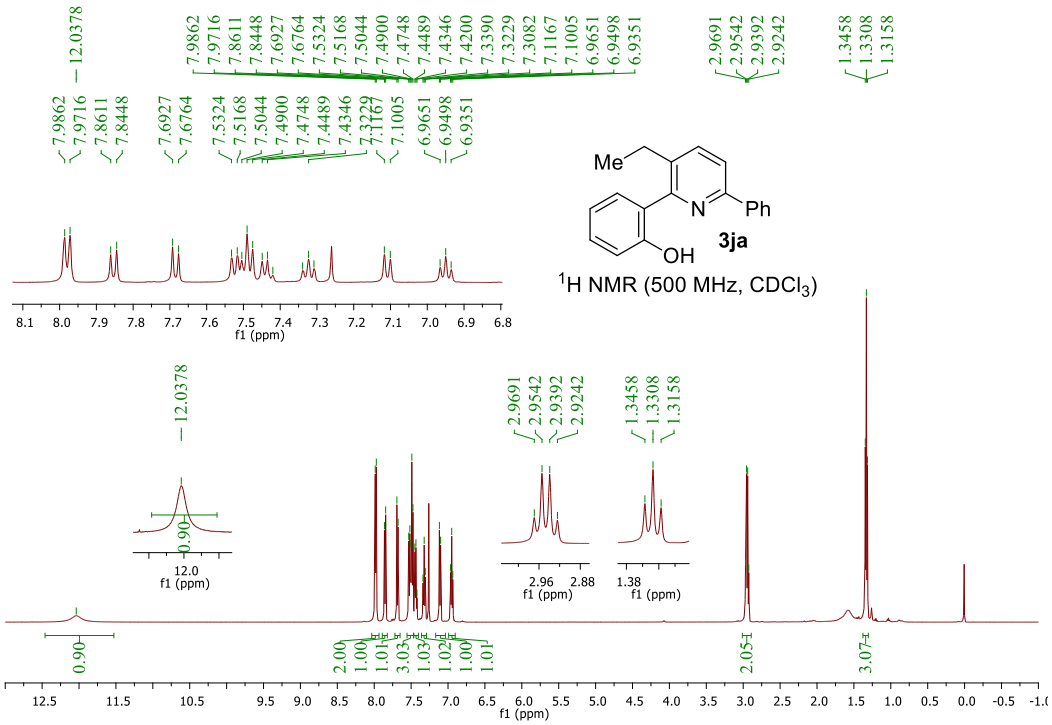


Figure 3.101. 500 MHz ^{1}H Spectrum of **3ja** in $CDCl_3$

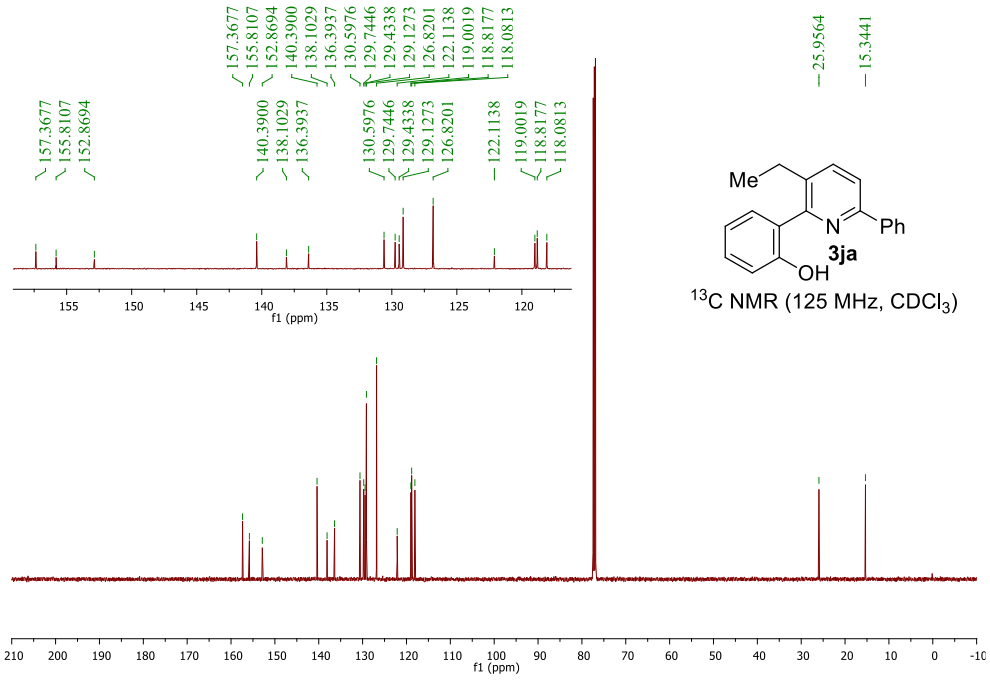


Figure 3.102. 125 MHz ^{13}C Spectrum of **3ja** in $CDCl_3$

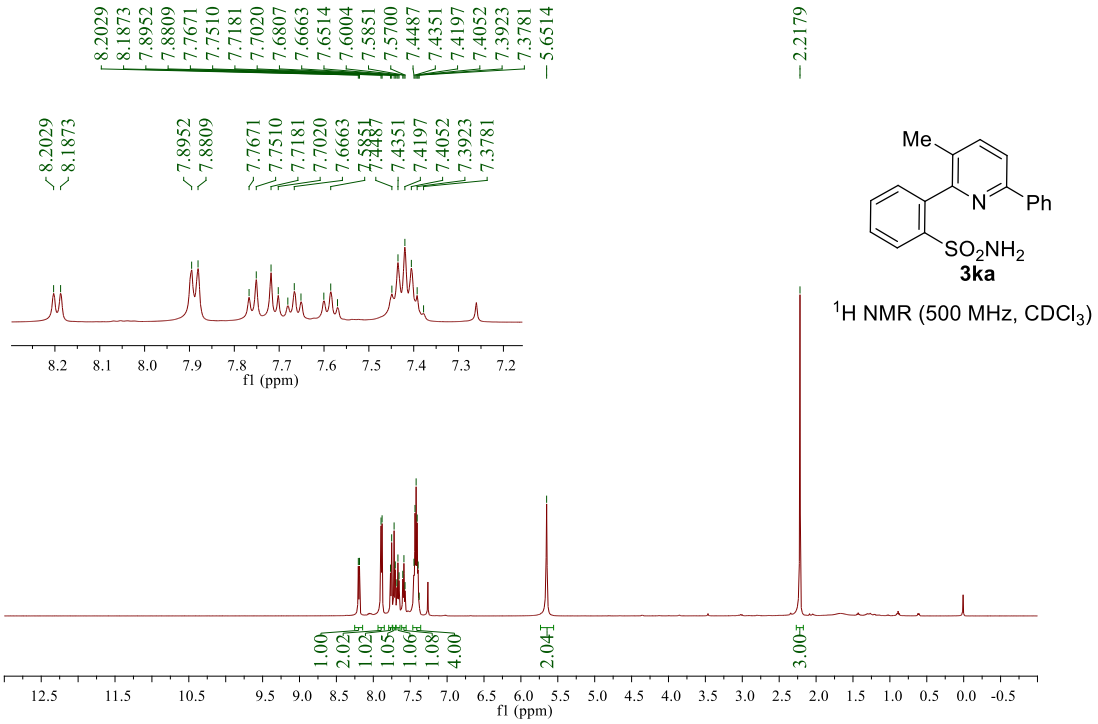


Figure 3.103. 500 MHz ^{1}H Spectrum of **3ka** in $CDCl_3$

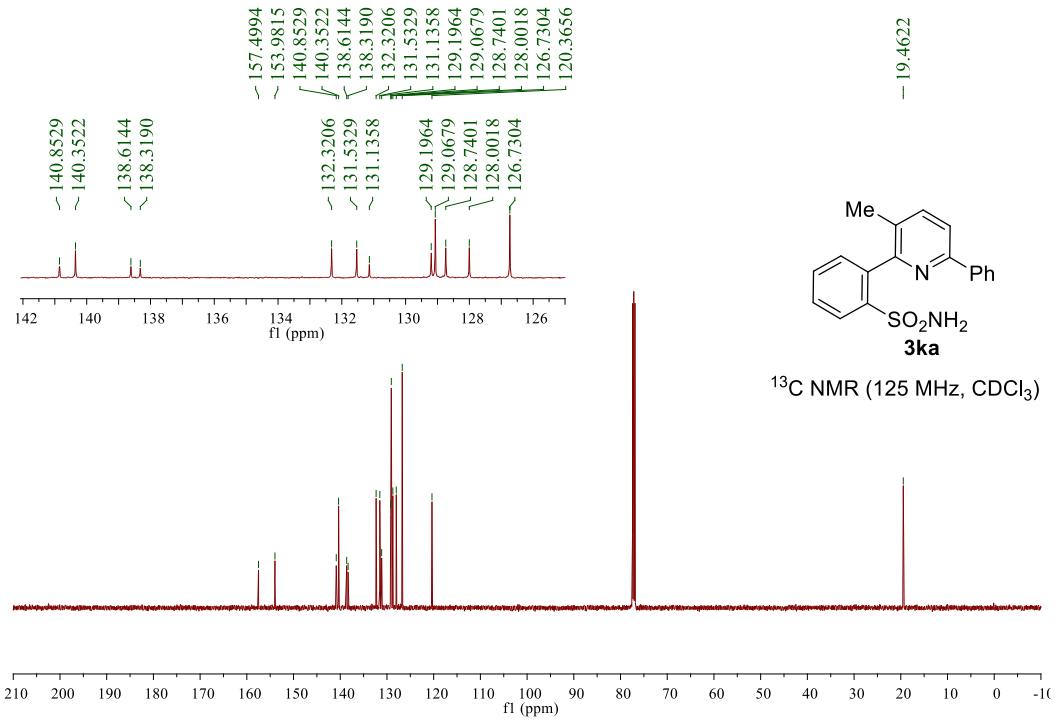


Figure 3.104. 125 MHz ^{13}C Spectrum of **3ka** in $CDCl_3$

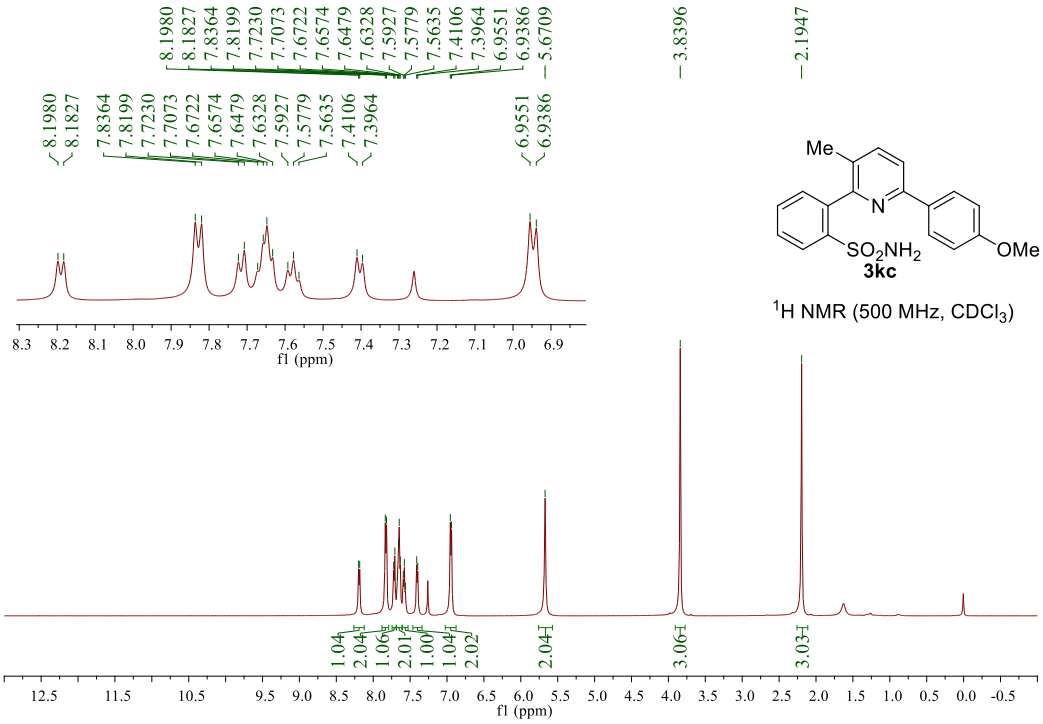


Figure 3.105. 500 MHz ^{1}H Spectrum of **3kc** in $CDCl_3$

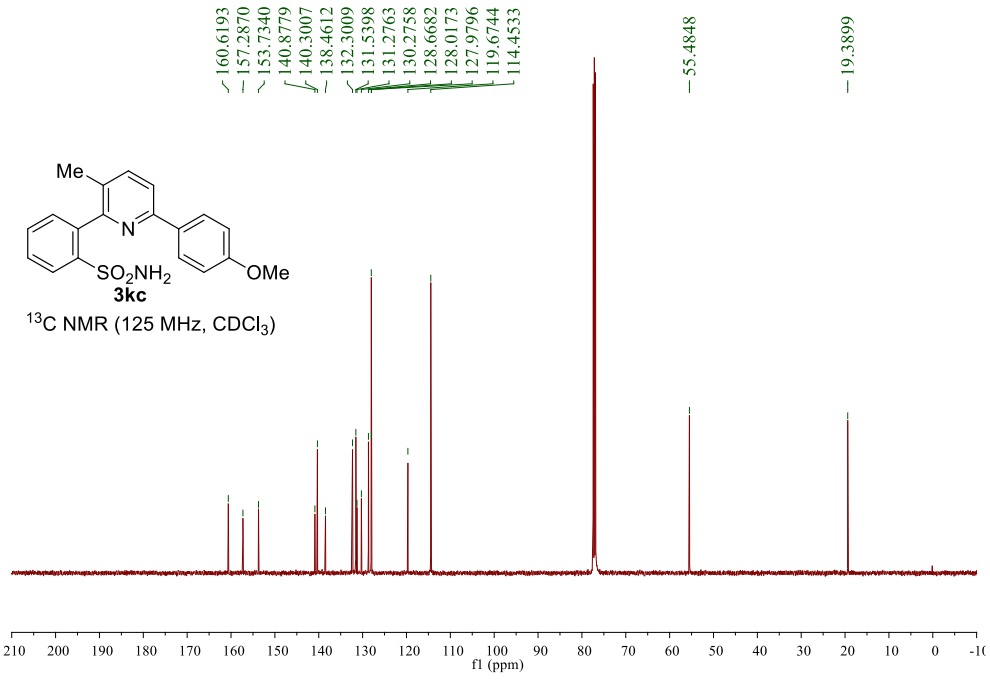


Figure 3.106. 125 MHz ^{13}C Spectrum of **3kc** in $CDCl_3$

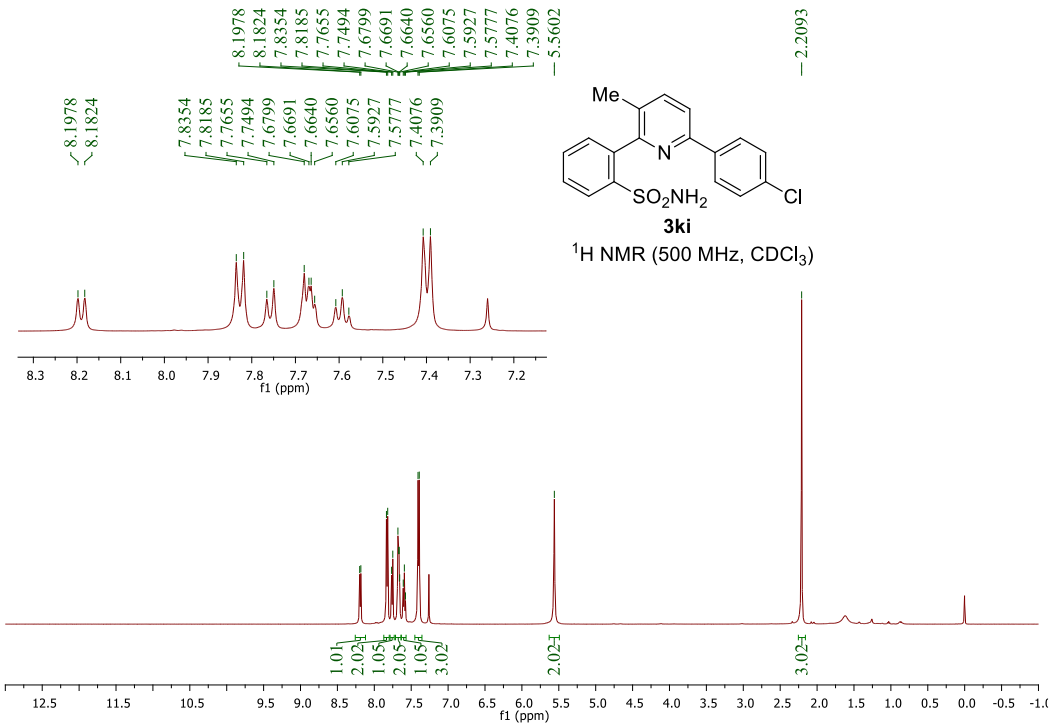


Figure 3.107. 500 MHz ^{1}H Spectrum of **3ki** in $CDCl_3$

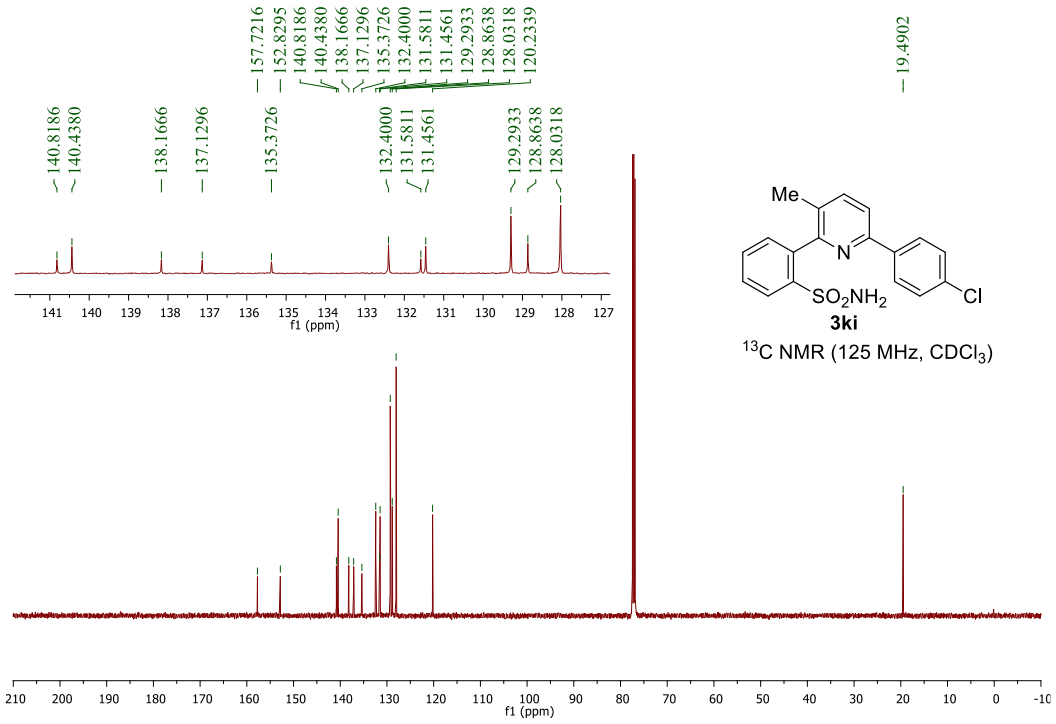


Figure 3.108. 125 MHz ^{13}C Spectrum of **3ki** in $CDCl_3$

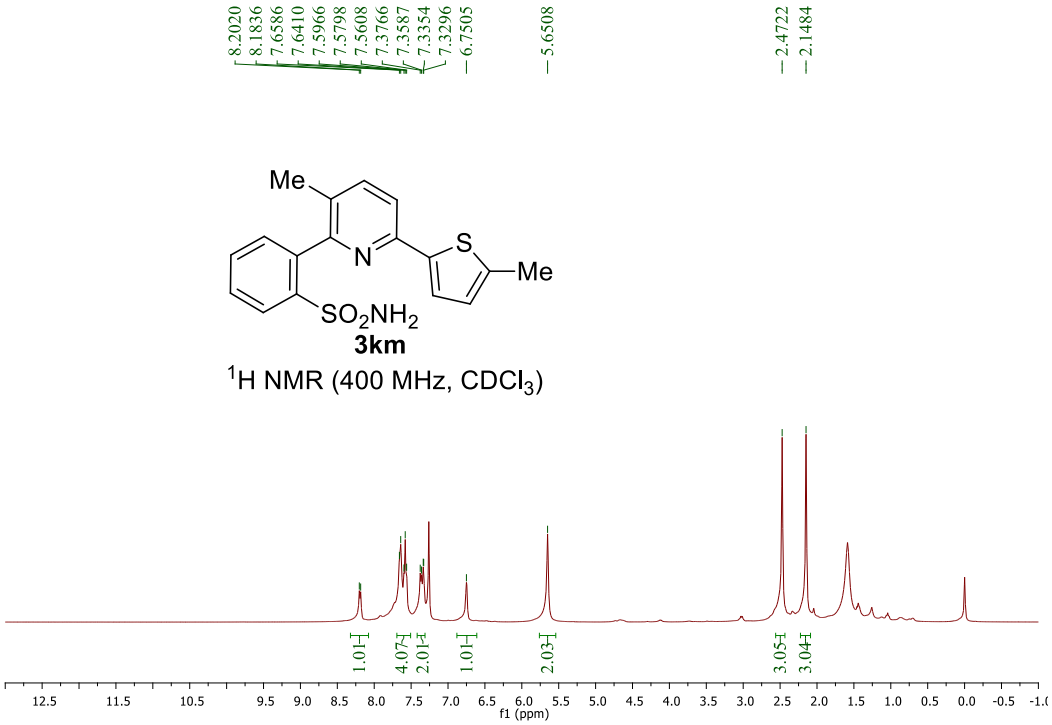


Figure 3.109. 500 MHz ^{1}H Spectrum of **3km** in $CDCl_3$

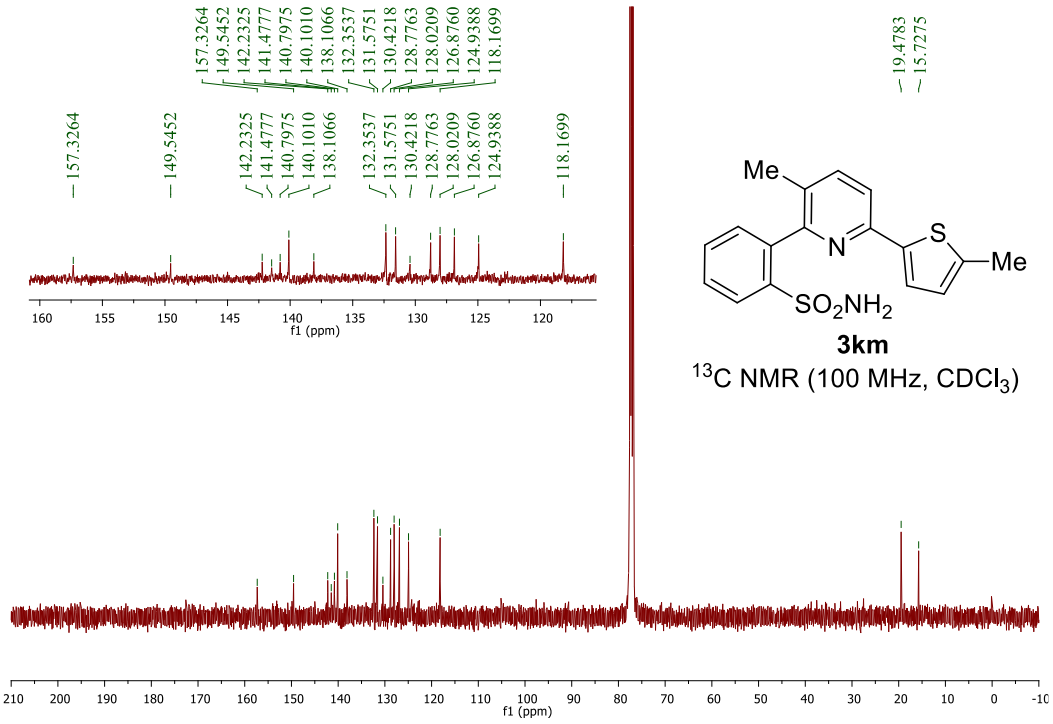


Figure 3.110. 125 MHz ^{13}C Spectrum of **3km** in $CDCl_3$

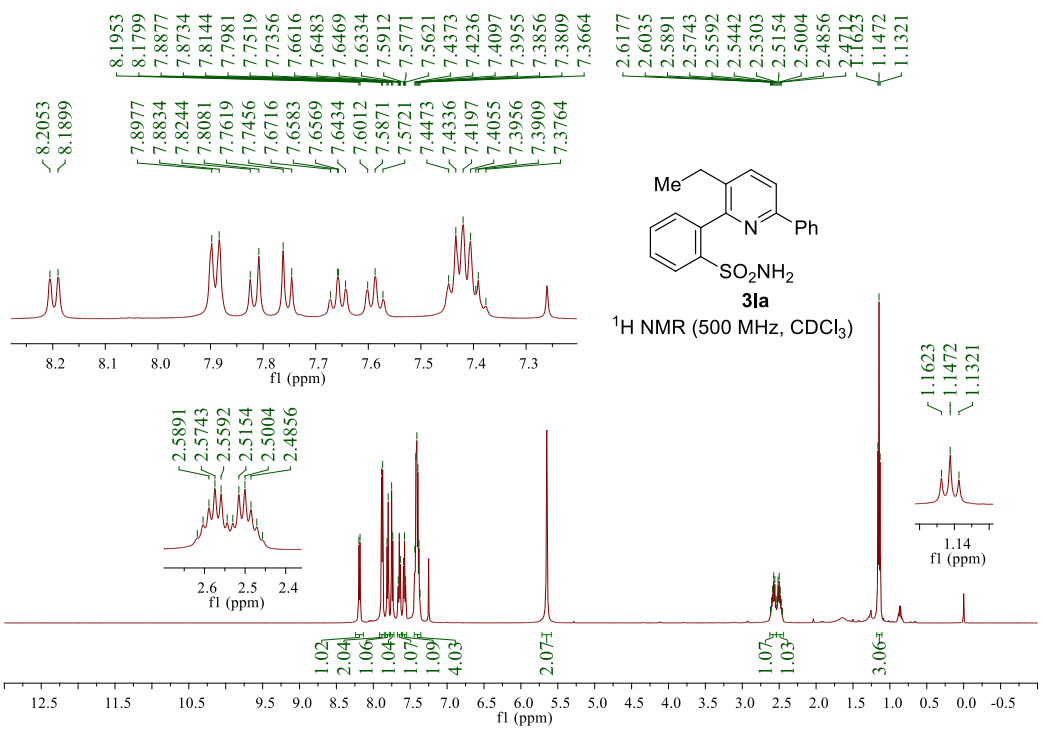


Figure 3.111. 500 MHz ^{1}H Spectrum of **3la** in $CDCl_3$

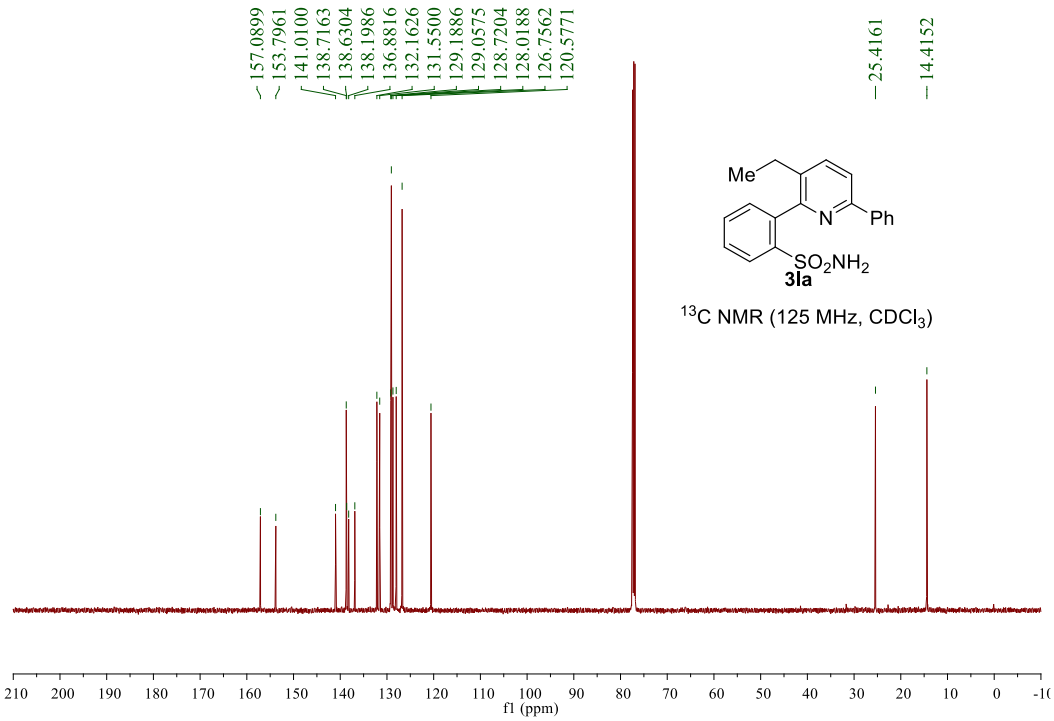


Figure 3.112. 125 MHz ^{13}C Spectrum of **3la** in $CDCl_3$

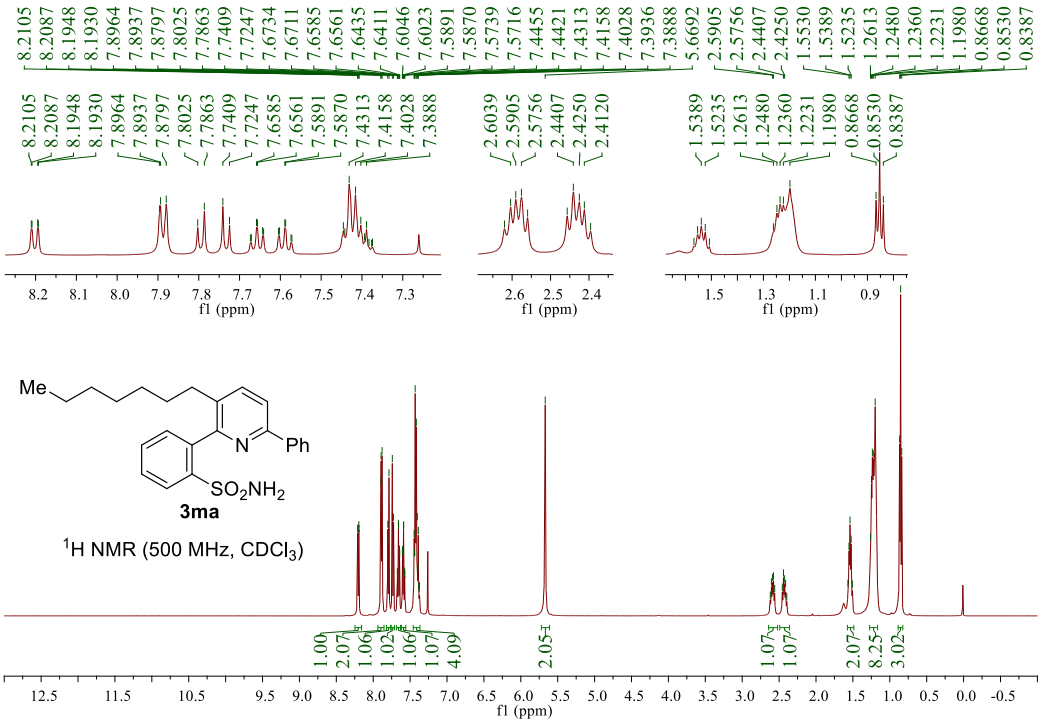


Figure 3.113. 500 MHz ^{1}H Spectrum of **3ma** in $CDCl_3$

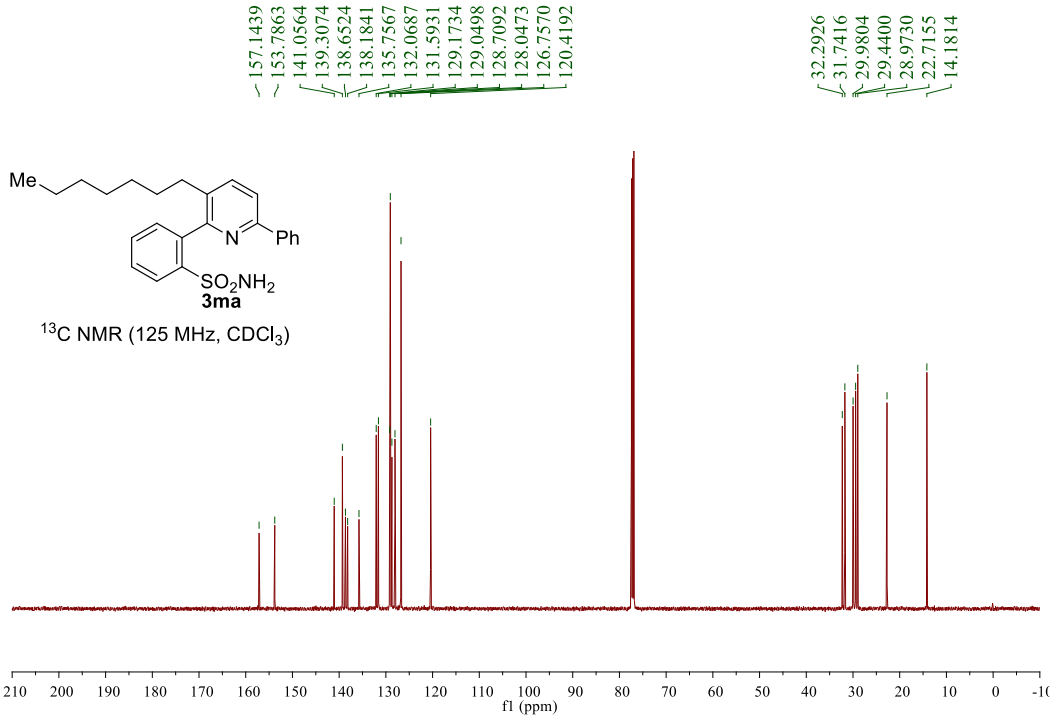


Figure 3.114. 125 MHz ^{13}C Spectrum of **3ma** in $CDCl_3$

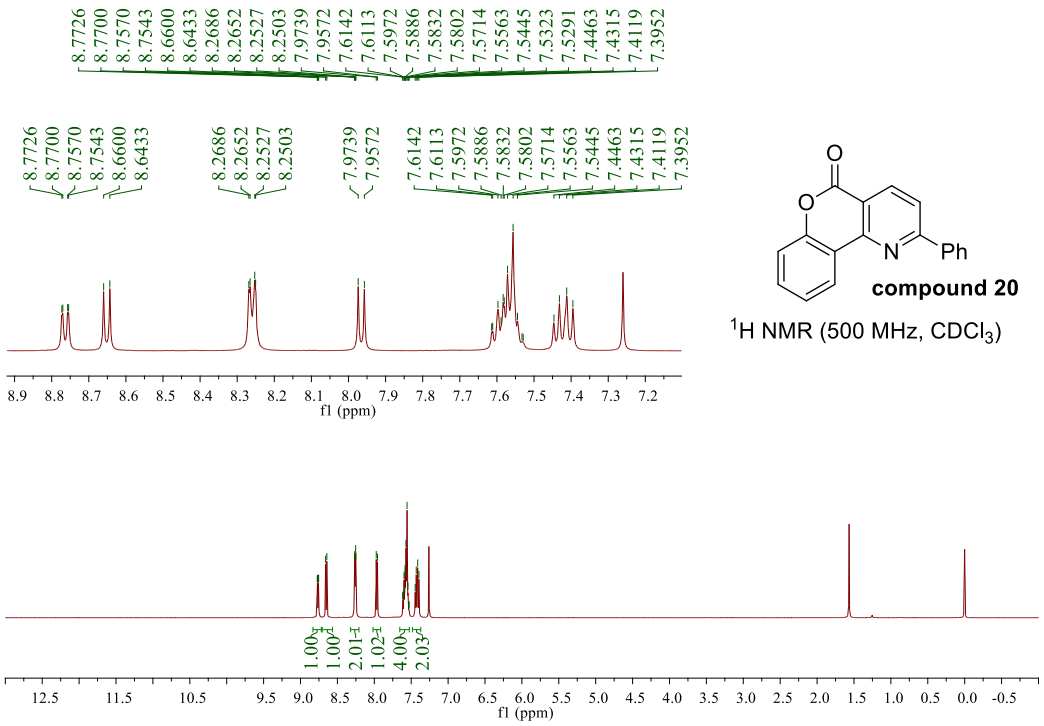


Figure 3.115. 500 MHz ^{1}H Spectrum of **compound 20** in $CDCl_3$

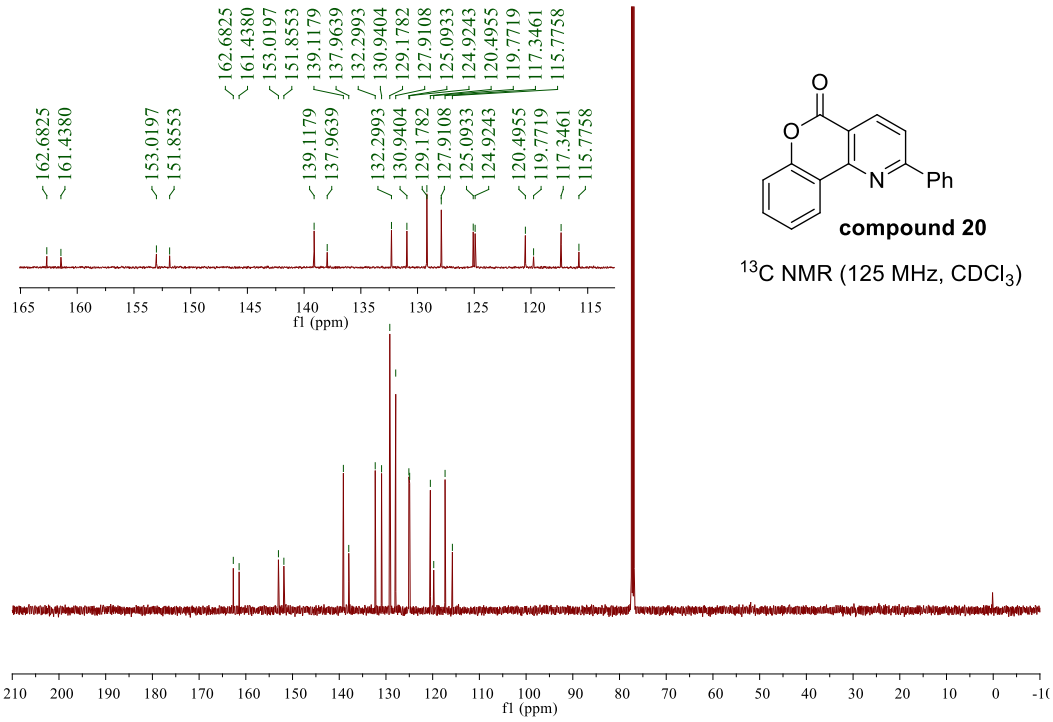


Figure 3.116. 125 MHz ^{13}C Spectrum of **compound 20** in $CDCl_3$

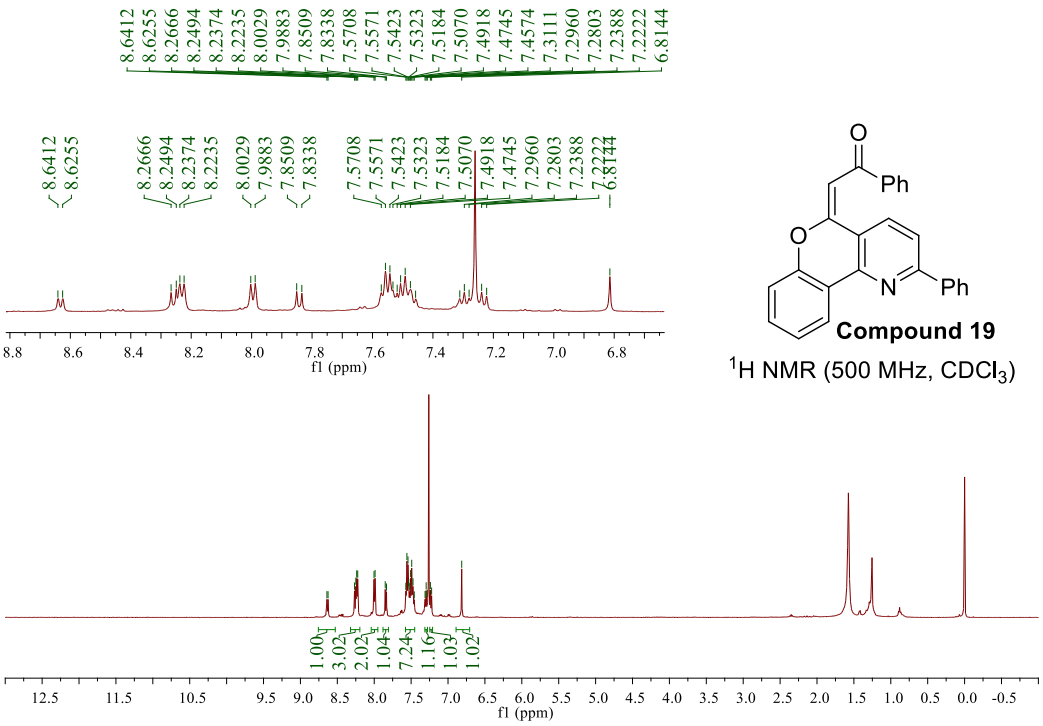


Figure 3.117. 500 MHz ^{1}H Spectrum of **compound 19** in $CDCl_3$

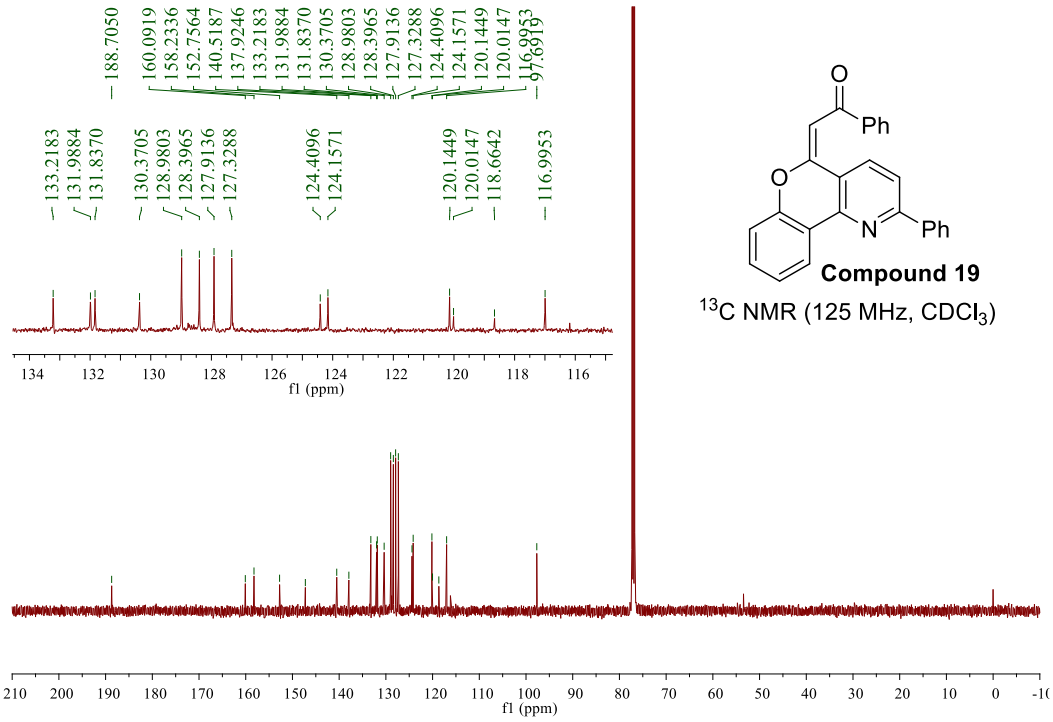


Figure 3.118. 125 MHz ^{13}C Spectrum of **compound 19** in $CDCl_3$

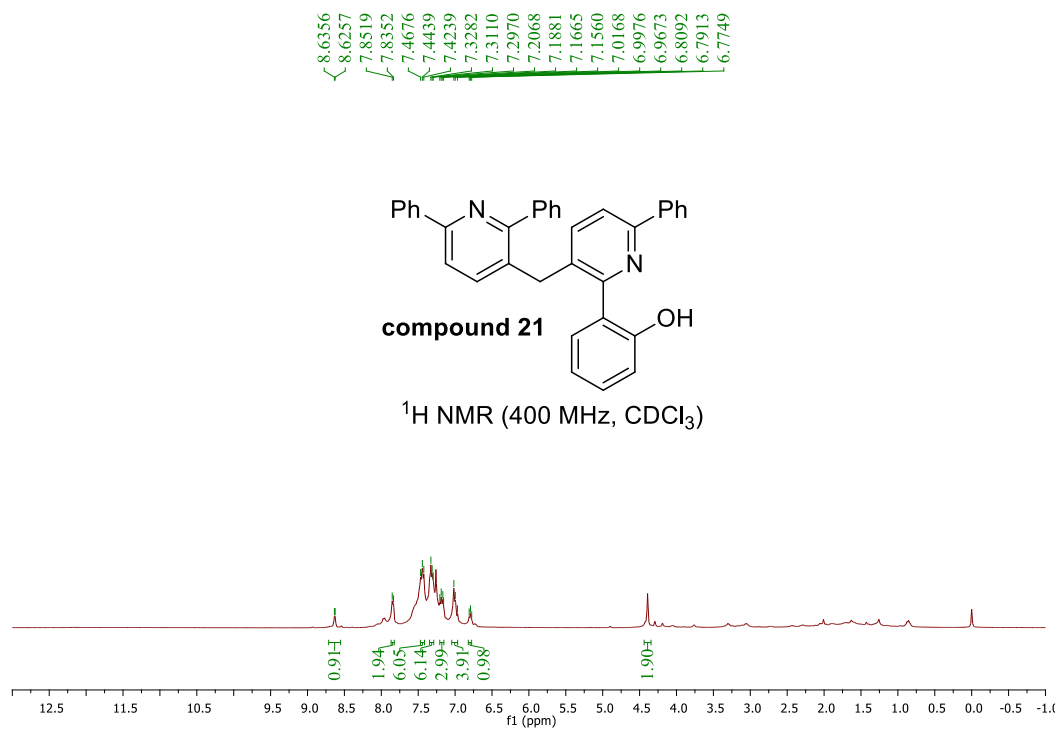


Figure 3.119. 500 MHz ^{1}H Spectrum of **compound 21** in $CDCl_3$

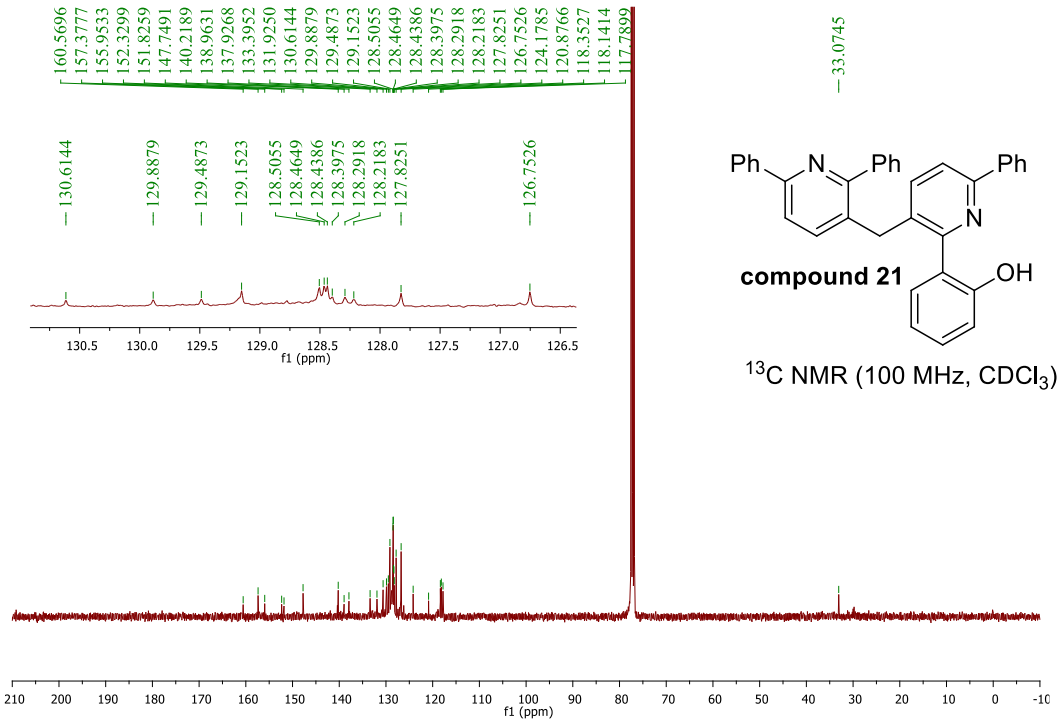


Figure 3.120. 125 MHz ^{13}C Spectrum of **compound 21** in $CDCl_3$

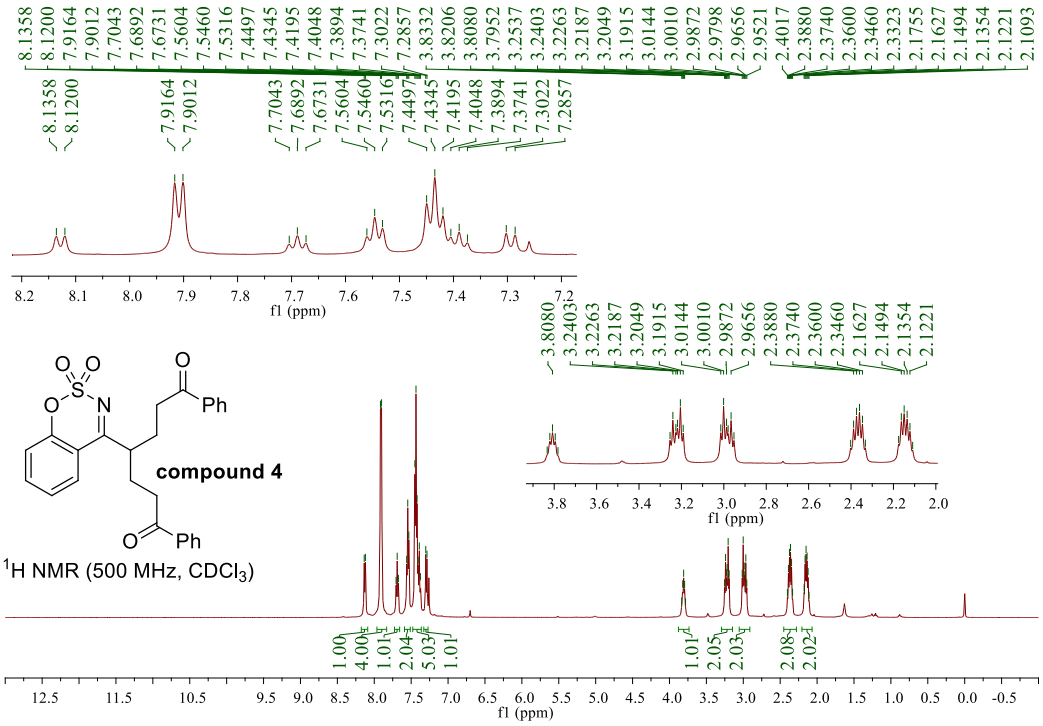


Figure 3.121. 500 MHz ^{1}H Spectrum of **compound 4** in $CDCl_3$

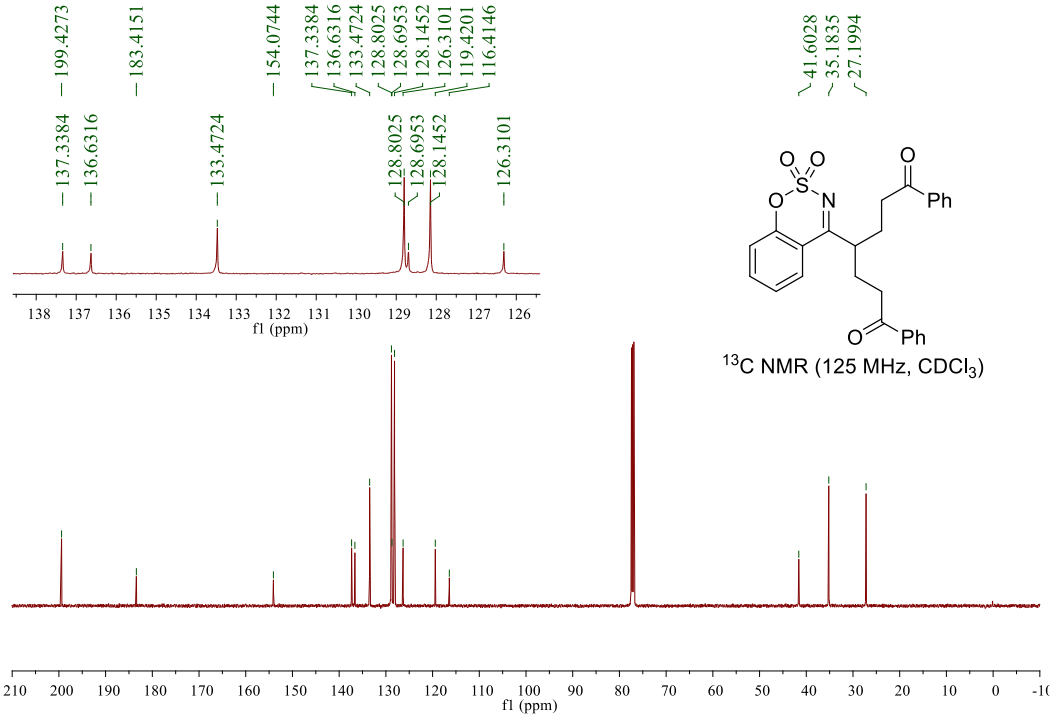


Figure 3.122. 125 MHz ^{13}C Spectrum of **compound 4** in $CDCl_3$

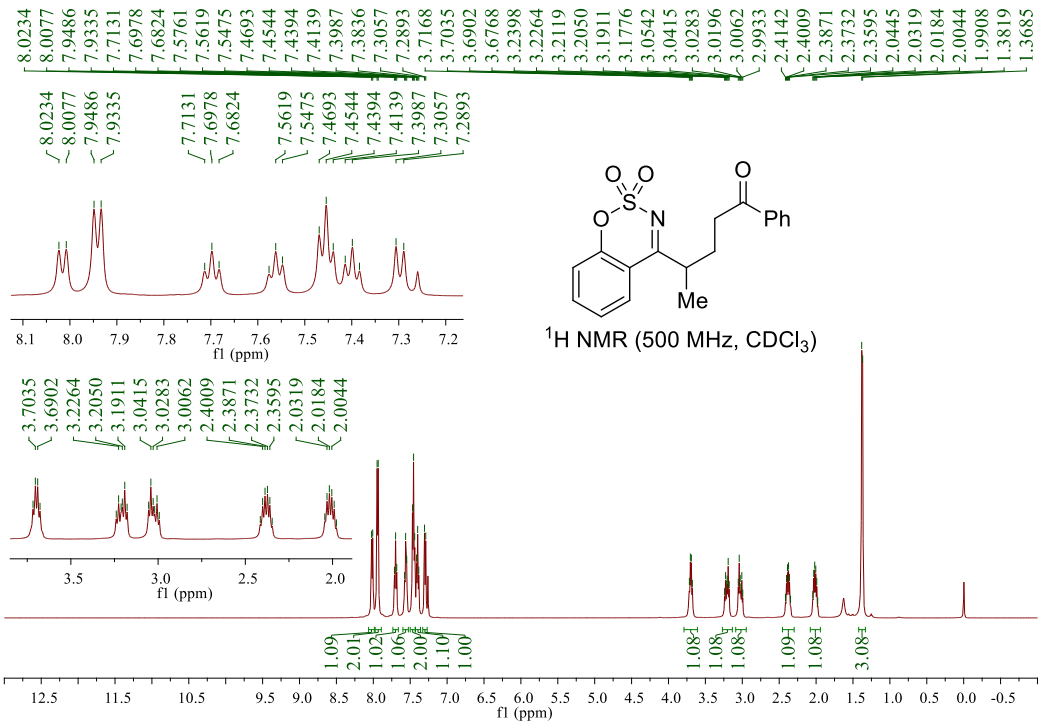


Figure 3.123. 500 MHz ^{1}H Spectrum of **compound 4′** in $CDCl_3$

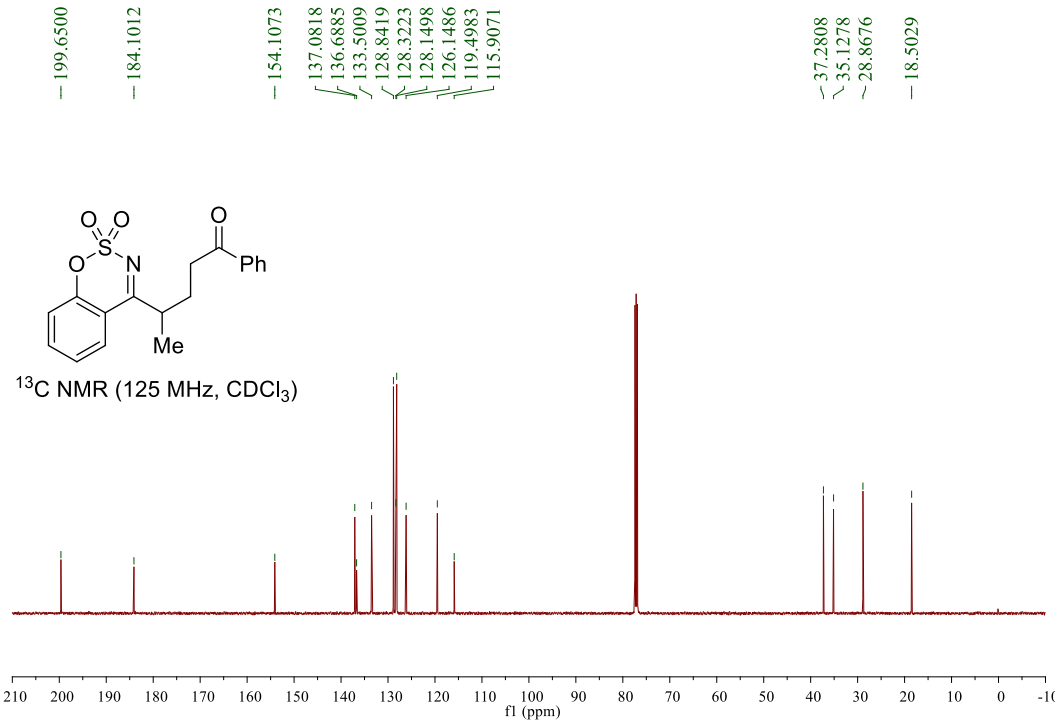


Figure 3.124. 125 MHz ^{13}C Spectrum of **compound 4′** in $CDCl_3$

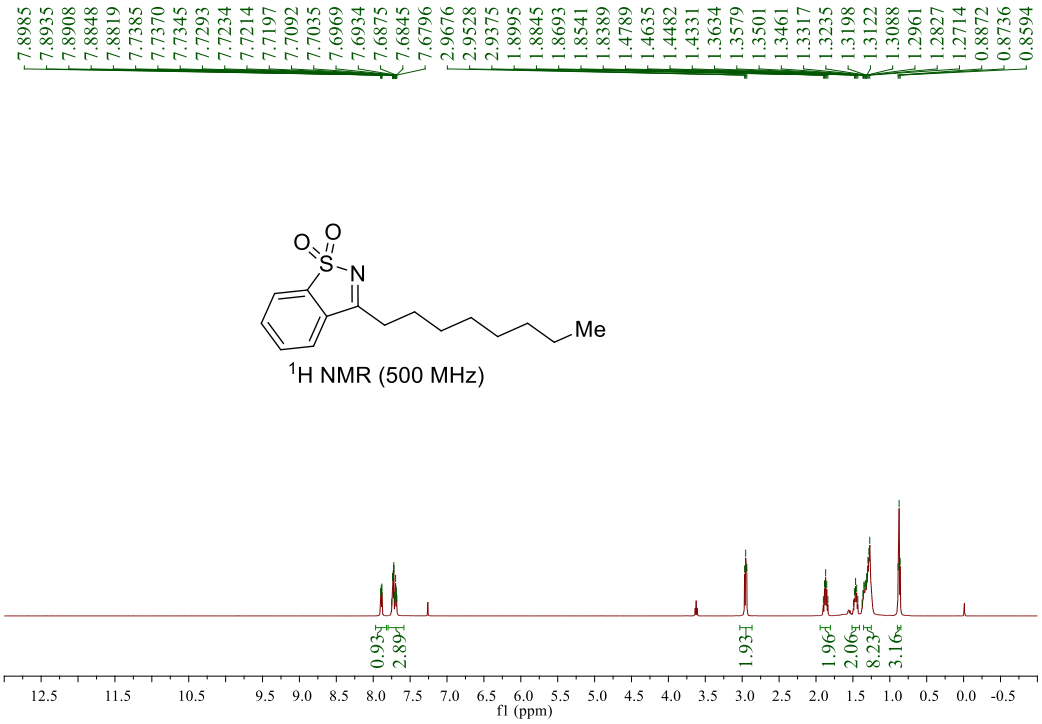


Figure 3.125. 500 MHz ^{1}H Spectrum of **1m** in $CDCl_3$

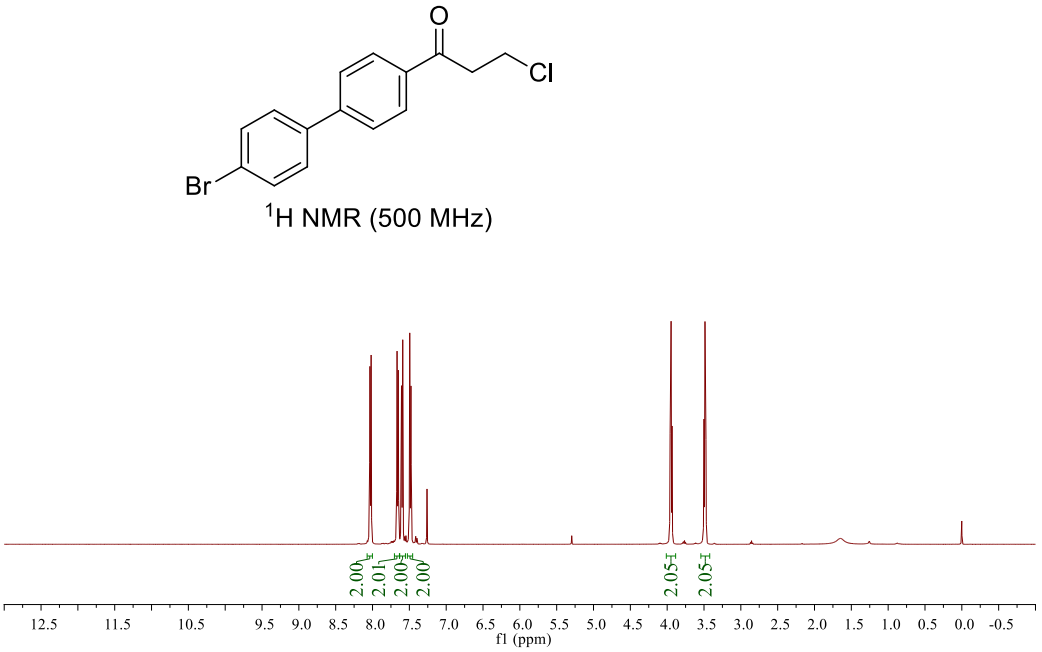


Figure 3.126. 500 MHz ^{1}H Spectrum of **2h** in $CDCl_3$

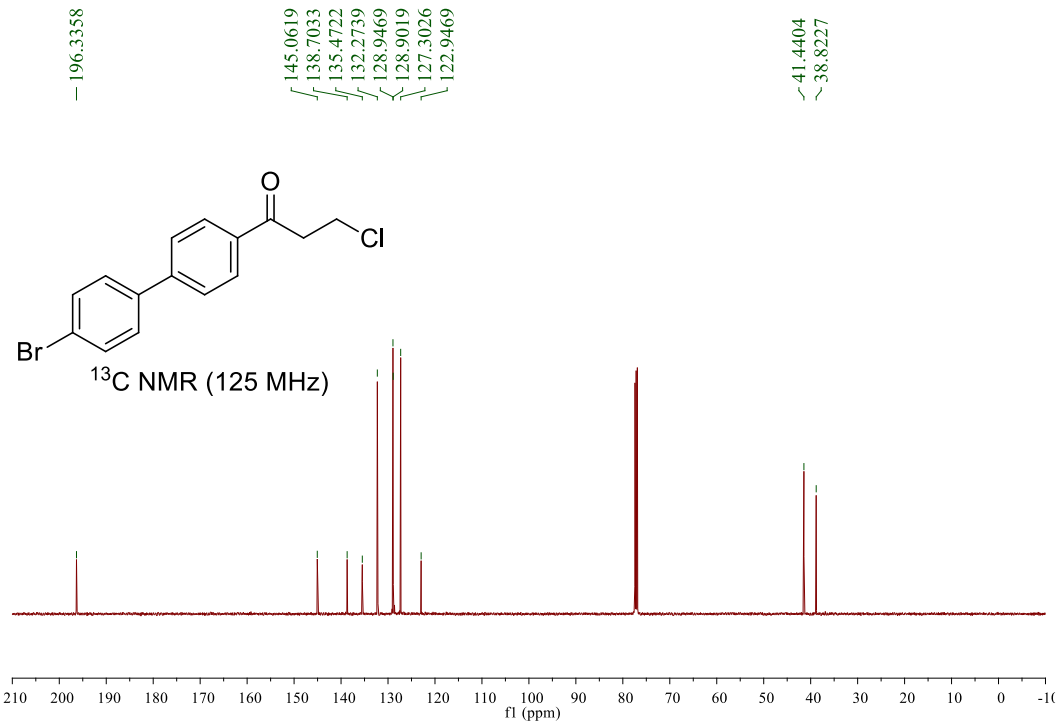


Figure 3.127. 125 MHz ^{13}C Spectrum of **2h** in $CDCl_3$

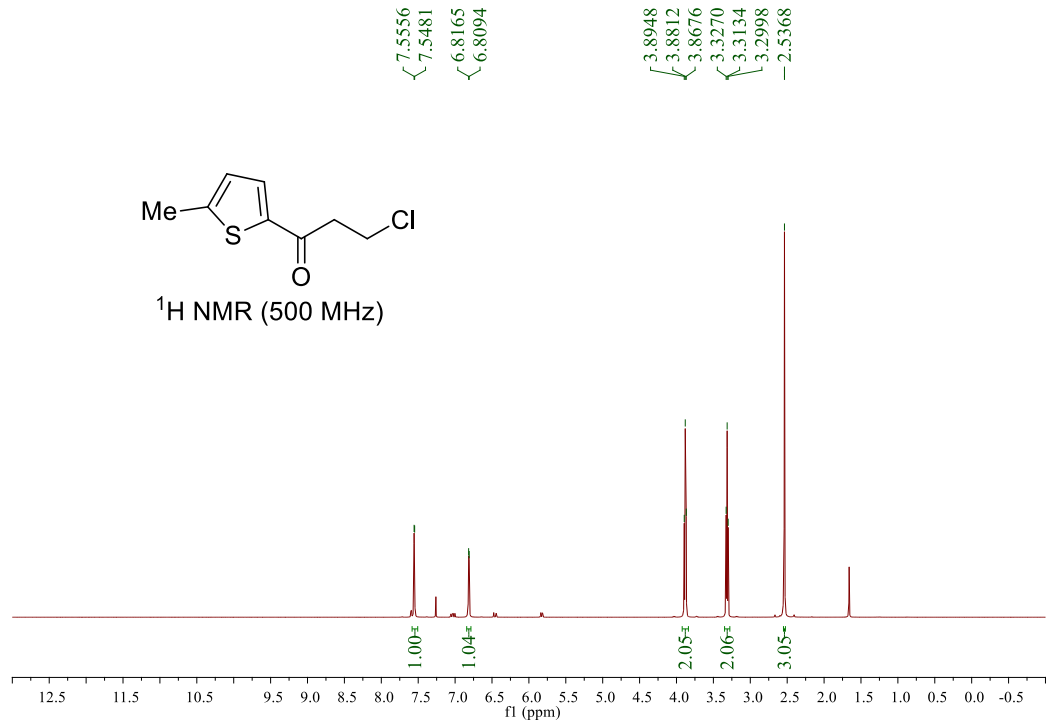


Figure 3.128. 500 MHz ^{1}H Spectrum of **2m** in $CDCl_3$

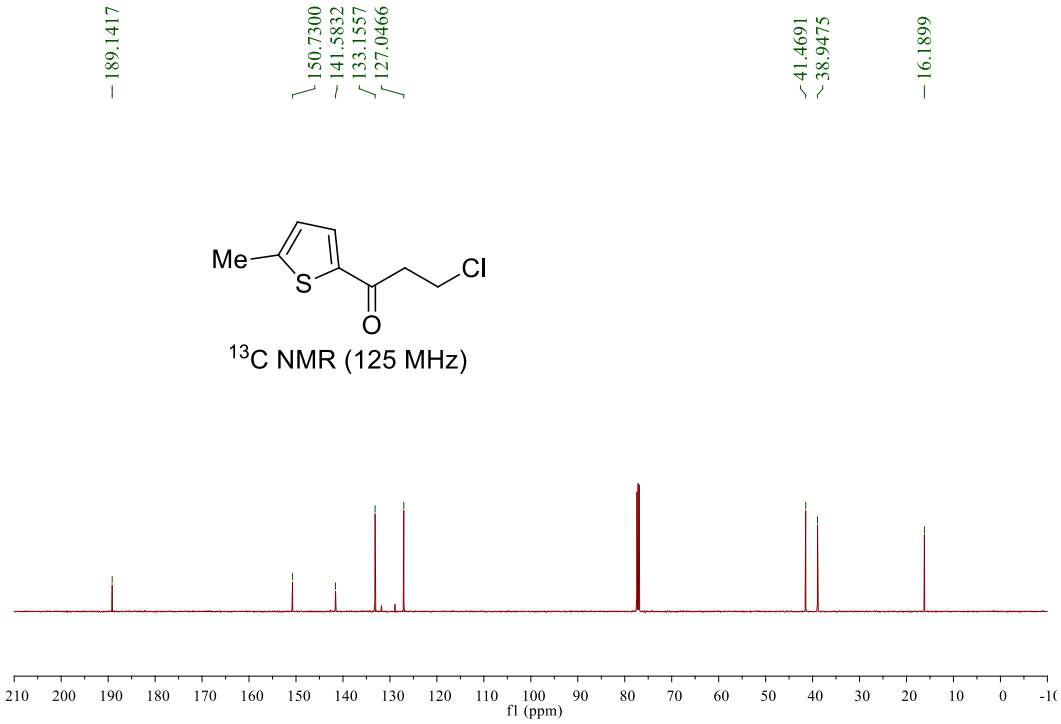


Figure 3.129. 125 MHz ^{13}C Spectrum of **2m** in $CDCl_3$

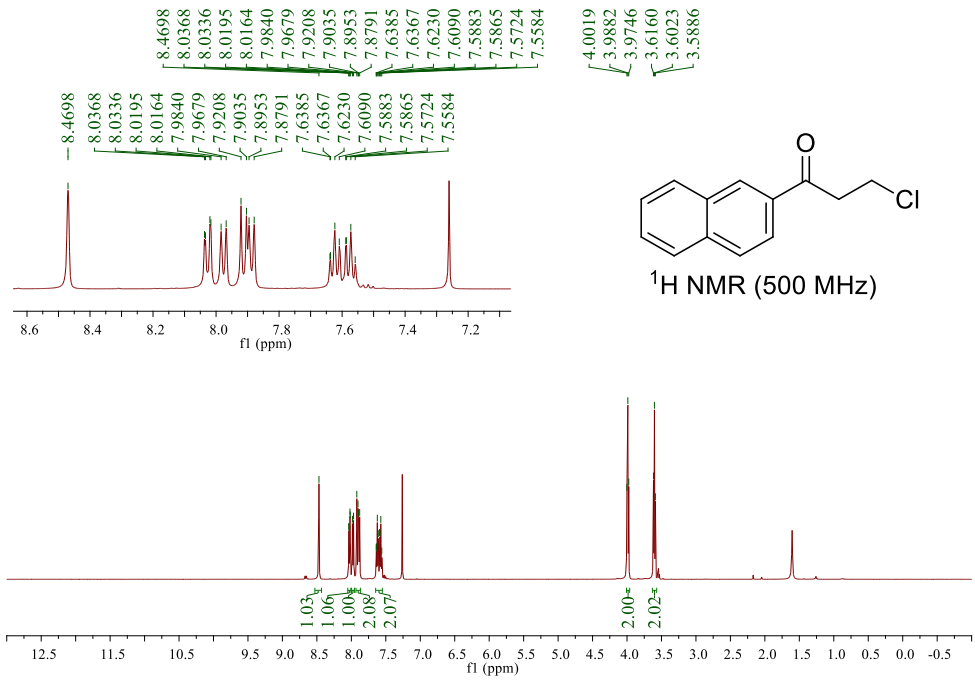


Figure 3.130. 500 MHz ^{1}H Spectrum of **2l** in $CDCl_3$

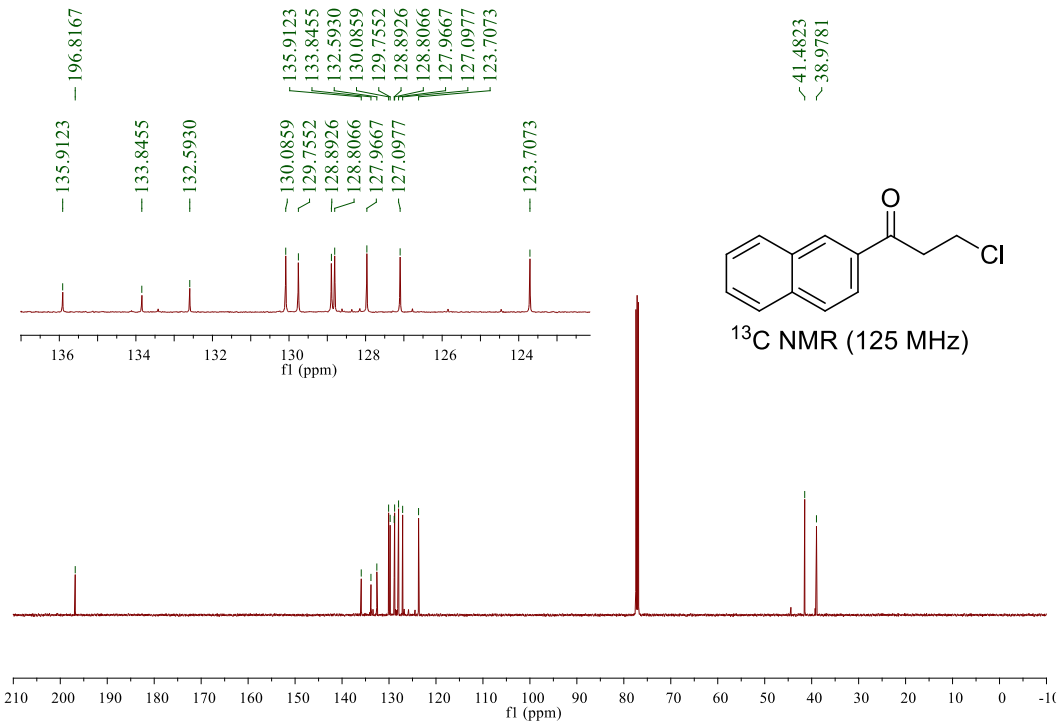


Figure 3.131. 125 MHz ^{13}C Spectrum of **2l** in $CDCl_3$

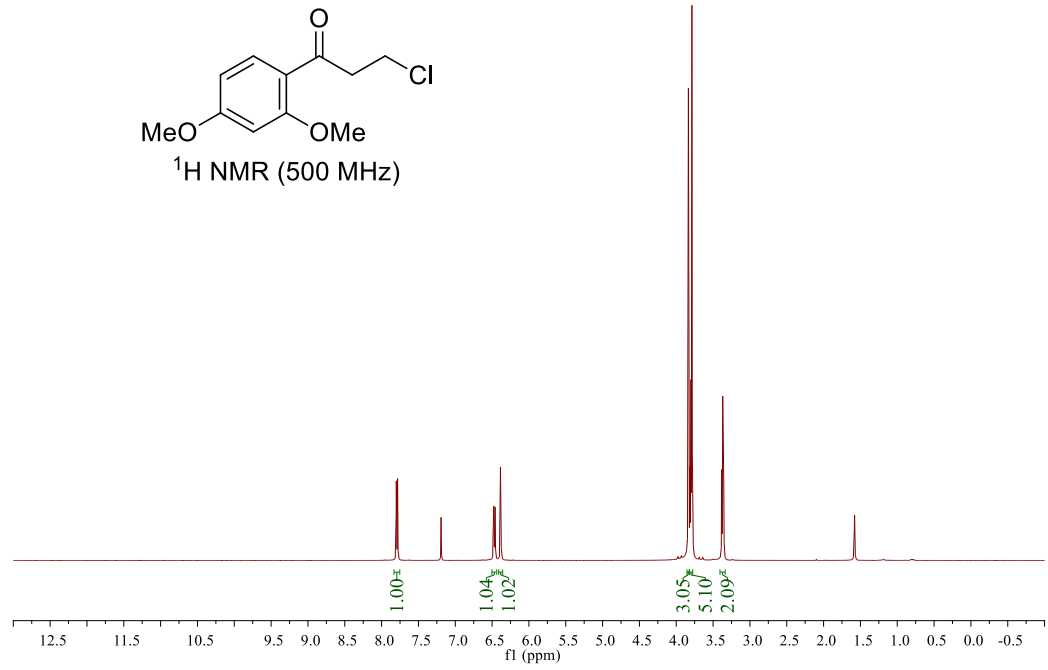


Figure 3.132. 500 MHz ^{1}H Spectrum of **2e** in $CDCl_3$

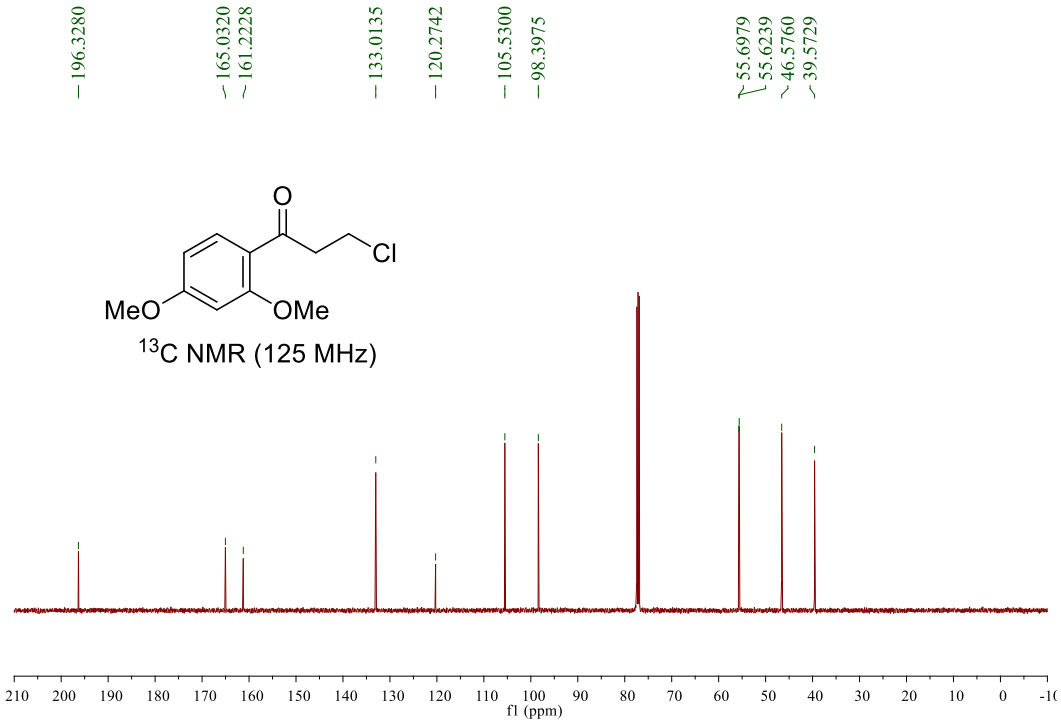


Figure 3.133. 125 MHz ^{13}C Spectrum of **2e** in $CDCl_3$

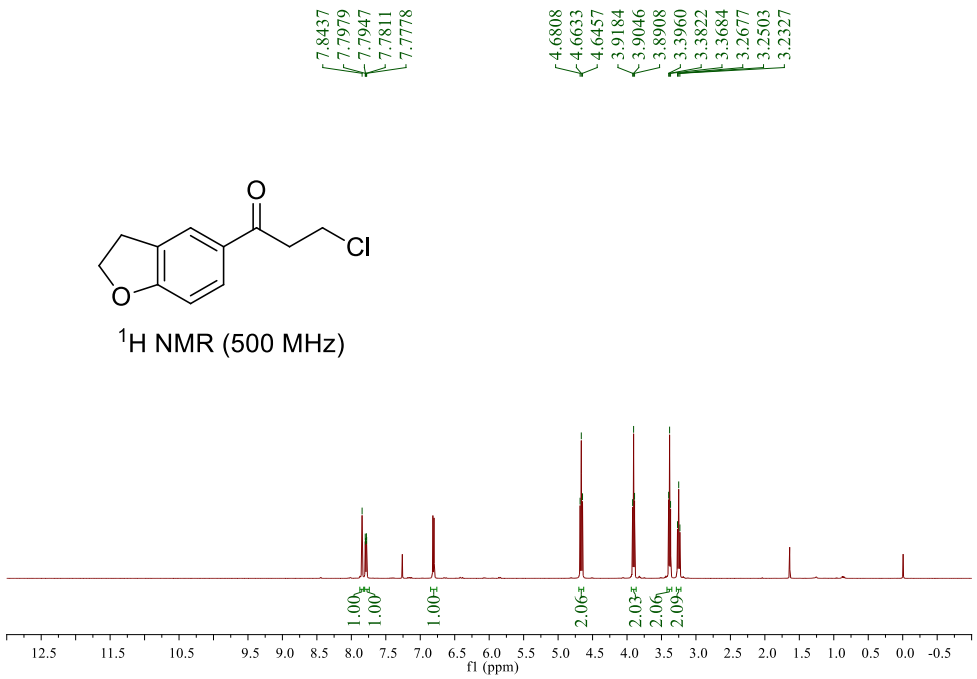


Figure 3.134. 500 MHz ^{1}H Spectrum of **2g** in $CDCl_3$

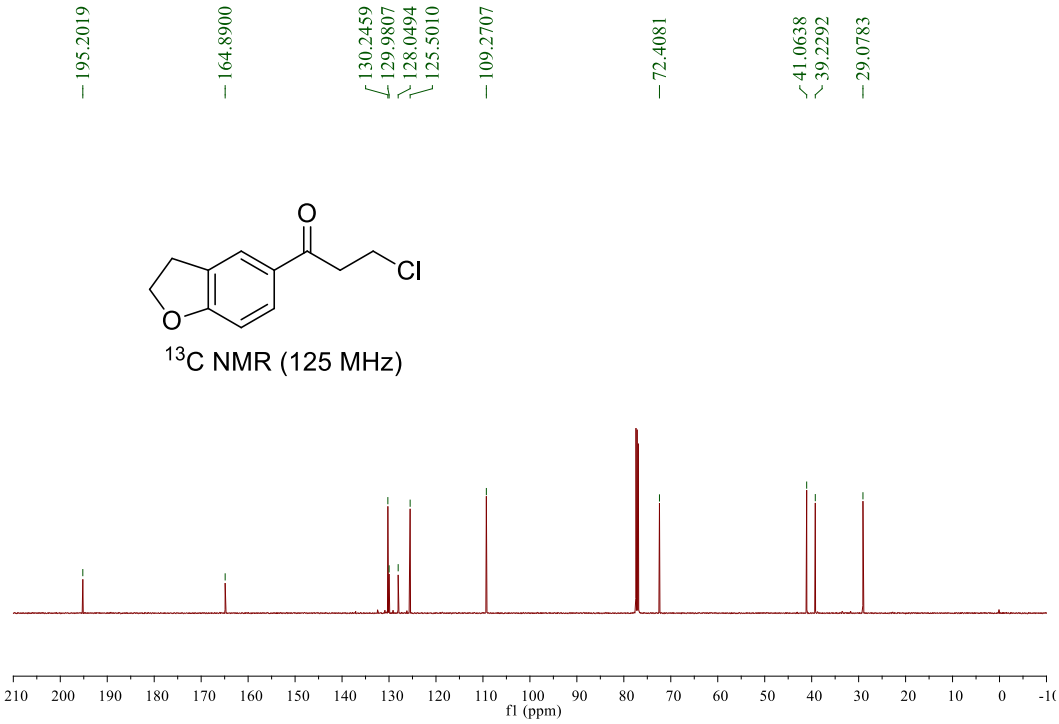


Figure 3.135. 125 MHz ^{13}C Spectrum of **2g** in $CDCl_3$

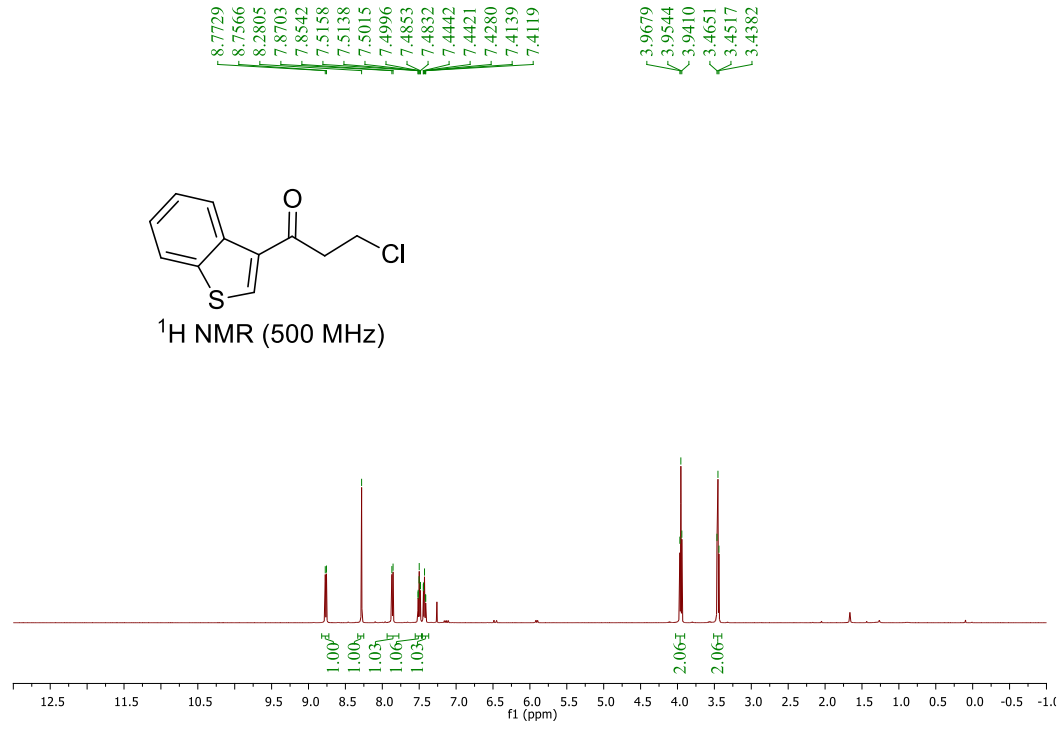


Figure 3.136. 500 MHz ^{1}H Spectrum of **2n** in $CDCl_3$

3.8 References:

1. Hill M. D. (2010), Recent strategies for the synthesis of pyridine derivatives, *Chem. Eur. J.*, *16*, 12052-12062 (DOI: 10.1002/chem.201001100)

2. Michael J. P. (2005), Quinoline, quinazoline and acridone alkaloids, *Nat. Prod. Rep.*, *22*, 627-646 (DOI: 10.1039/B413750G)

3. Khan E. (2021), Pyridine derivatives as biologically active precursors; organics and selected coordination complexes, *Chemistry Select*, *6*, 3041-3064 (DOI: 10.1002/slct.202100332)

4. Kantevari S., Patpi S. R., Addla D., Putapatri S. R., Sridhar B., Yogeeswari P. and Sriram D. (2011), Facile Diversity-Oriented Synthesis and Antitubercular Evaluation of Novel Aryl and Heteroaryl Tethered Pyridines and Dihydro-6 H-quinolin-5-ones Derived via Variants of the Bohlmann–Rahtz Reaction, *ACS Comb. Sci.*, *13*, 427-435 (DOI: 10.1021/co2000604)

5. Oleksak P., Nepovimova E., Chrienova Z., Musilek K., Patocka J. and Kuca K. (2022), Contemporary mTOR inhibitor scaffolds to diseases breakdown: A patent review (2015–2021), *Eur. J. Med. Chem.*, *238*, 114498 (DOI: 10.1016/j.ejmech.2022.114498)

6. Barlaam B., Fennell M., Germain H., Green T., Hennequin L., Morgentin R., Olivier A., Plé P., Vautier M. and Costello G. (2005), New heterocyclic analogues of 4-(2-chloro-5-methoxyanilino) quinazolines as potent and selective c-Src kinase inhibitors, *Bioorg. Med. Chem. Lett.*, *15*, 5446-5449 (DOI: 10.1016/j.bmcl.2005.08.106)

7. Scott,J. S., Bowker S. S., Deschoolmeester J., Gerhardt S., Hargreaves D., Kilgour E., Lloyd A., Mayers R. M., McCoull W., Newcombe N. J. and Ogg D. (2012), Discovery of a potent, selective, and orally bioavailable acidic 11β-hydroxysteroid dehydrogenase type 1 (11β-hsd1) inhibitor: Discovery of 2-[(3s)-1-[5-(cyclohexylcarbamoyl)-6-propylsulfanylpyridin-2-yl]-3-piperidyl]

acetic acid (azd4017), *J. Med. Chem.*, *55*, 5951-5964 (DOI: 10.1021/jm300592r)

8. Kantevari S., Chary M. V. and Vuppalapati S. V. (2007), A highly efficient regioselective one-pot synthesis of 2,3,6-trisubstituted pyridines and 2,7,7-trisubstituted tetrahydroquinolin-5-ones using $K_5CoW_{12}O_{40}\cdot 3H_2O$ as a heterogeneous recyclable catalyst, *Tetrahedron*, *63*, 13024-13031 (DOI: 10.1016/j.tet.2007.10.014)

9. Jiang H., Yang J., Tang X., Li J. and Wu W. (2015), Cu-catalyzed three-component cascade annulation reaction: an entry to functionalized pyridines, *J. Org. Chem.*, *80*, 8763-8771 (DOI: 10.1021/acs.joc.5b01621)

10. Wang K., Meng L. G. and Wang L. (2017), Visible-light-promoted [2+2+2] cyclization of alkynes with nitriles to pyridines using pyrylium salts as photoredox catalysts, *Org. Lett.*, *19*, 1958-1961 (DOI: 10.1021/acs.orglett.7b00292)

11. Zhan Z. Z., He J. P., Jiang P. B., Zhang M. M., Wang H. S., Luo N. and Huang G. S. (2021), Cu(II)-Catalyzed Synthesis of 2,3,6-Trisubstituted Pyridines from Saturated Ketone and Alkynones/1,3-Dicarbonyl Compounds, *ChemistrySelect*, *6*, 4160-4165 (DOI: 10.1002/slct.202100775)

12. Li X., Cai W. and Huang Y. (2022), One-Pot Synthesis of 2,3,6-Trisubstituted Pyridines by Phosphine-Catalyzed Annulation of γ-Vinyl Allenoates with Enamino Esters Followed by DDQ-Promoted Oxidative Aromatization, *Adv. Synth. Catal.*, *364*, 1879-1883 (DOI: 10.1002/adsc.202200071)

13. Lu Z. M., Zhang Q. J., Chen R. Y. and Yu D. Q. (2008), Four new alkaloids from Polyalthia nemoralis (Annonaceae), *J. Asian Nat. Prod. Res.*, *10*, 656-664 (DOI: 10.1080/10286020802242281)

14. Lodhi R., Patel A. K. and Samanta S. (2022), AgOTf/Et_3N Cooperative Catalysis Enabled One-Pot Access to α-(Indolizinylethyl)-Substituted *N*-

Sulfonyl Ketimines via an Imino-Alkyne Cyclization, *Asian J. Org. Chem.*, *11*, e202200569 (DOI: 10.1002/ajoc.202200569)

15. Fan X., Zhao H., Yu J., Bao X. and Zhu C. (2016), Regiospecific synthesis of distally chlorinated ketones via C–C bond cleavage of cycloalkanols, *Org. Chem. Front.*, *3*, 227-232 (DOI: 10.1039/C5QO00368G)

Check for updates

EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202300631

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Organocatalyzed Double C(sp^3)–H Alkylation of Cyclic *N*-Sulfonyl Ketimines with 3-Chloropropiophenones: Selective Access to 2,3,6-Trisubstituted Pyridines

Ashvani Kumar Patel[a] and Sampak Samanta*[a]

An efficient sequential one-pot, two-step pseudo-four-component reaction between 3/4-methyl *N*-sulfonyl ketimines with 3-chloropropiophenones triggered by DIPEA/$NaHCO_3$ as a cooperative base and subsequent aza-cyclization using NH_4OAc is reported. This transition-metal-oxidant-free technique concocts new C–C/C=C/C=N–C bonds selectively, guaranteeing acceptable yields of 2,3,6-trisubstituted pyridines possessing *ortho*-hydroxyaryl/benzenesulfonamide and propiophenone moieties at C2 and C3 positions, respectively. Interestingly, while replacing methyl-substituents with straight alkyl chains of *N*-sulfonyl ketimines, only a monoalkylation reaction happened with in situ-generated vinyl ketones to deliver promising yields of 3-picoline derivatives. Moreover, the synthetic transmutation of prepared pyridine derivative led to several important classes of pyridocoumarin, 5*H*-chromenopyridine, and di(pyridin-3-yl) methane derivatives.

Introduction

Pyridines are well-known N-containing heteroaromatic scaffolds widely distributed in a plethora of biologically natural and synthetic alkaloids,[1–2] marketable drugs,[3] pharmaceutically valuable agents,[4] and agrochemicals.[5] Additionally, this moiety is also a critical subunit of vitamins (B3 and B6) and nucleotides [nicotinamide adenine dinucleotide (NAD)/NADPH as coenzymes], and remains a convenient energy source for metabolism and other biochemical progressions.[6] In addition, they are linchpin stockpiles for accessing supramolecular scaffolds,[7] organocatalysts,[8] conjugated polymers,[9] and ligands for metal-catalyzed organic conversions,[10] making them the most lucrative targets for chemists. Given their extraordinary medicinal importance and other imperative roles, chemists have enormously contributed towards constructing structurally complex, diverse pyridine frameworks resembling drug-like molecules.[1,11] In this context, pioneering works by Hantzsch,[12] Chichibabin,[13] and other groups[14] independently developed the condensation-cyclization reactions between simple enolizable ketones/aliphatic aldehydes and amines (or ammonia), assembling a wide breadth of symmetrical and unsymmetrical pyridines. However, the described protocols are often restricted to accessing only specific substitution patterns on the pyridine rings along with unsatisfactory yields due to the side products which, in turn, limit the practical usage of the methods. Alternatively, many efficient and modern protocols, including transition metal-salts-catalyzed [2+2+2][15]/[4+2][16] cycloaddition reactions, electrocyclization,[17] and multicomponent reactions[18] have also been extensively delved, thus targeting ploy-substituted pyridines. Despite the splendid advances, selective access to synthetically[19] and medicinally useful[20] 2,3,6-trisubstituted pyridines[21–27] is a limited success compared to other trisubstituted ones[28] and remains an unmet synthetic challenge in organic chemistry. The literature study revealed that the isolated or in situ-generated β-enaminoesters as 2C1N components have been commonly utilized in the cyclization reactions with 3C Michael acceptors like ethynyl ketones,[21] β-enaminones,[22] vinyl allenoates,[23] and enones[24] or in situ generated enones from allylic alcohols[25]/propiophenones[26] using various catalytic and non-catalytic conditions [Brønsted/Lewis acid catalysts, BzOH/(*p*-$FC_6H_4)_3P$/DDQ, IBX, Cu(II)/bpy/TEMPO/air] as developed by Bohlman-Rahtz, Bagley and other groups. Furthermore, Obora and Wang's groups established a novel regioselective cyclization reaction between terminal alkynes and nitriles in the presence of either $NbCl_5$/Zn/$Ph_2Si(OMe)_2$ as a merged catalytic system[29] or pyrylium salt as the photocatalyst,[30] affording 2,3,6-trisubstituted pyridines. Moreover, Jun et al. also disclosed a Cu(II)-promoted dehydrogenation of the allylamines, followed by Rh-(III)-catalyzed [4+2] aza-cyclization of the resulting unsaturated imines with symmetrical alkynes.[31] In addition, Peters et al. brilliantly developed a one-pot, two-step sequential regioselective 1,4-addition of isoxazolinones as 2C1N sources to vinyl ketones catalyzed by Pd(II) and subsequent Pd(0)-catalyzed N–O bond cleavage-decarboxylation-cyclization reaction under H_2-atmosphere to afford the targeted pyridines.[32] However, the enriched methodologies have a set of drawbacks, such as the use of exceptional raw materials, costly transition-metal salts, high temperatures, a mixture of regioisomers with unwanted side products, poor yields, need for excess oxidants and ligands, and lack of functional group diversity. Therefore, our immediate priority is to develop a simple transition metal-oxidant-free pragmatic technique for synthesizing 2,3,6-trisubstituted pyridines deco-

[a] *A. K. Patel, Prof. S. Samanta*
Department of Chemistry
Indian Institute of Technology Indore
Simrol, 453552, Madhya Pradesh (India)
E-mail: sampaks@iiti.ac.in

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202300631

© 2023 Wiley-VCH GmbH

Chapter 4

Organocatalyzed Pot-Economic Three-Component Strategy to 1,3-Diarylallylidene Pyrazolones *via* Consecutive Double Condensation Reaction involving 4-Unsubstituted Pyrazolones

Chapter 4

Organocatalyzed pot-economic three-component strategy to 1,3-diarylallylidene pyrazolones *via* consecutive double condensation reaction involving 4-unsubstituted pyrazolones

4.1 Introduction

Pyrazolone is a versatile five-membered heterocyclic molecule enriched with consecutive nitrogen-nitrogen bonds, a lactam motif, and a synthetically useful active methylene centre, which makes it one of the most recognized reactive intermediates.[1-5] In the previous hapters 2 and 3, we discussed the pyridine motif as our continued exploration of aza-heterocycles. Now, herein, we focus on discussing another aza-heterocyclic compound like pyrazolone. This privileged aza-heterocyclic molecule has drawn great attention across diverse arenas due to its occurrence in active pharmaceuticals,[6] and synthetic drug molecules.[7-9] Moreover, pyrazolone and its derivatives are well-identified for their medicinal properties, which are closely relevant to their structural features.[10-16] Among various derivatives, 4-alkylidene pyrazolones are of particular importance in medicinal chemistry for their success against various biological targets such as SARS-CoV 3CL protease inhibitors,[10] neuraminidase H1N1 and H5N1 inhibitors,[11] farnesoid X receptor (FXR) selective antagonist,[12] HIV-1 integrase inhibitors,[13] anti-orthopoxvirus activity,[14] VEGFR-2 inhibitor as anti-breast cancer agents,[15] Mycobacterium tuberculosis (MTB) inhibitors[16] etc. Additionally, pyrazolones have also emerged as valuable reactive intermediates for synthesizing various structurally relevant pyrazoles and pyrazolones,[17-22] ligands used in bioimaging,[23,24] dyes and pigments,[25] emphasizing their vital usefulness in recent decades.

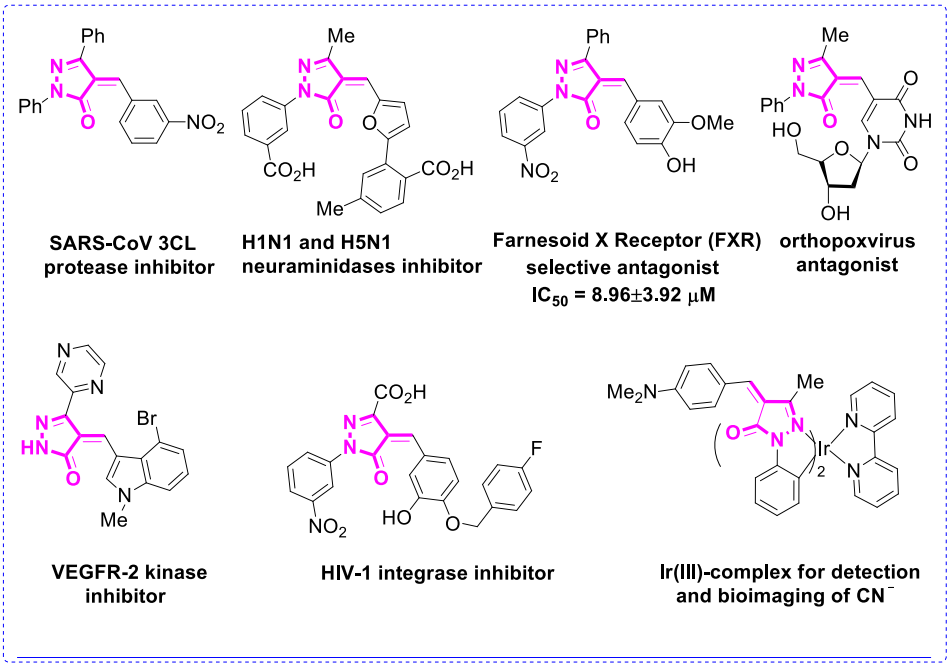


Figure 4.1. Selected examples of biologically active pyrazolone derivatives.

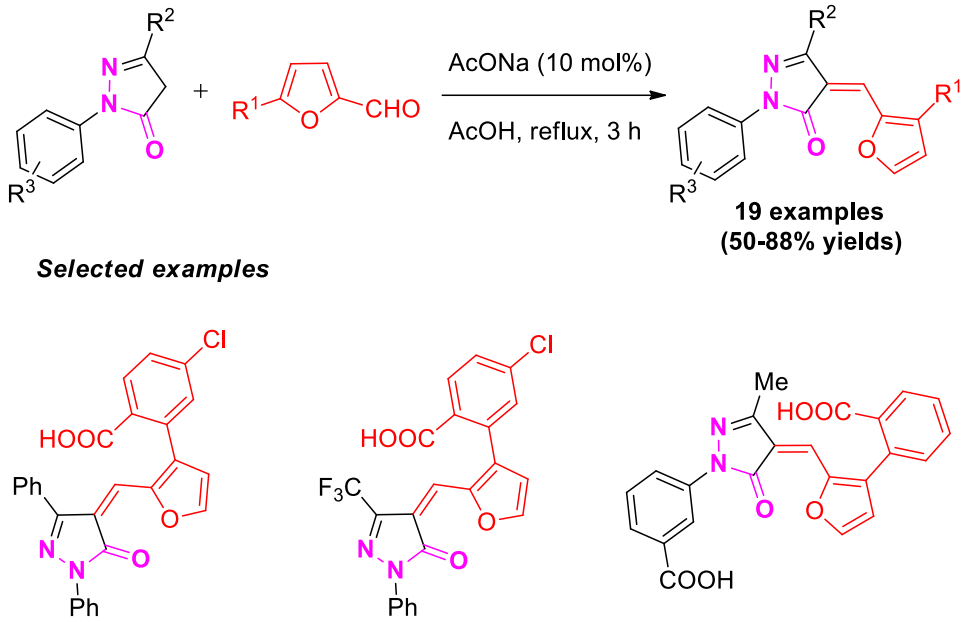
4.2 Review Work

Due to their prevalence in medicines and other applications, synthetic chemists have developed numerous powerful methods for synthesizing a broad range of 4-alkylidene pyrazolones with various substitution patterns for pharmacological usefulness.[26-32] Some relevant techniques are discussed below (**4.2.1**).

4.2.1 Synthesis of 4-Alkylidene/Alkenylidene Pyrazolones

In 2014, Liang *et al.* developed a powerful strategy for synthesizing biologically active (Neuraminidase inhibitors) 4-arylidene pyrazolone derivatives. This strategy involves Knoevenagel condensation reaction of substituted furfural with various pyrazolones in the presence of a catalytic amount of NaOAc (10 mol%) in refluxing acetic acid for 3 h, offering the corresponding pyrazolones in good to high yields (50-88%) **Scheme 4.1**.[11]

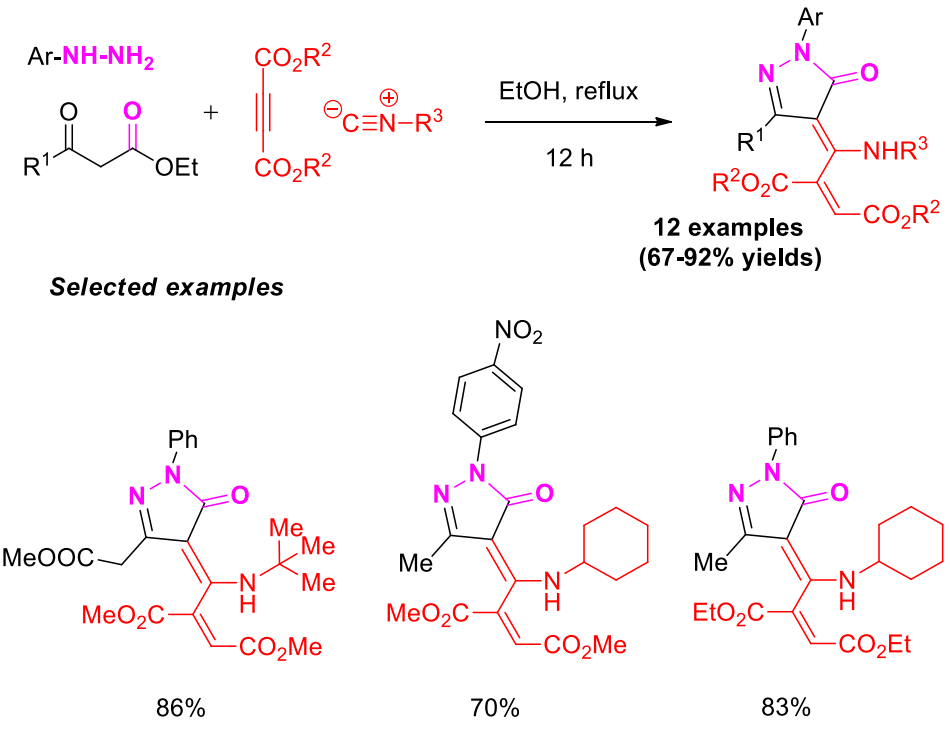
Liang et al.



Scheme 4.1. Sodium acetate-catalyzed synthesis of arylidene prazolones.

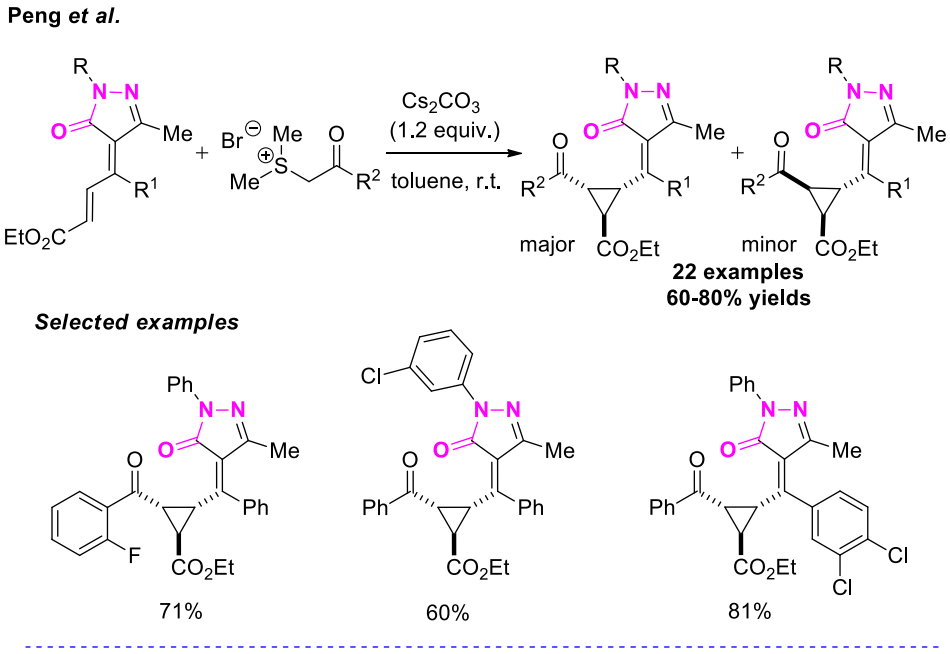
In 2018, Yavari *et al.* established a catalyst-free multicomponent reaction involving aryl hydrazine, ethyl acetoacetates, dimethyl acetylene carboxylate, and *tert*-butyl isocyanates in refluxing EtOH for 12 h to endow good to excellent yields (67-92%) of pyrazolones as illustrated in **Scheme 4.2**.[30]

Yavari et al.



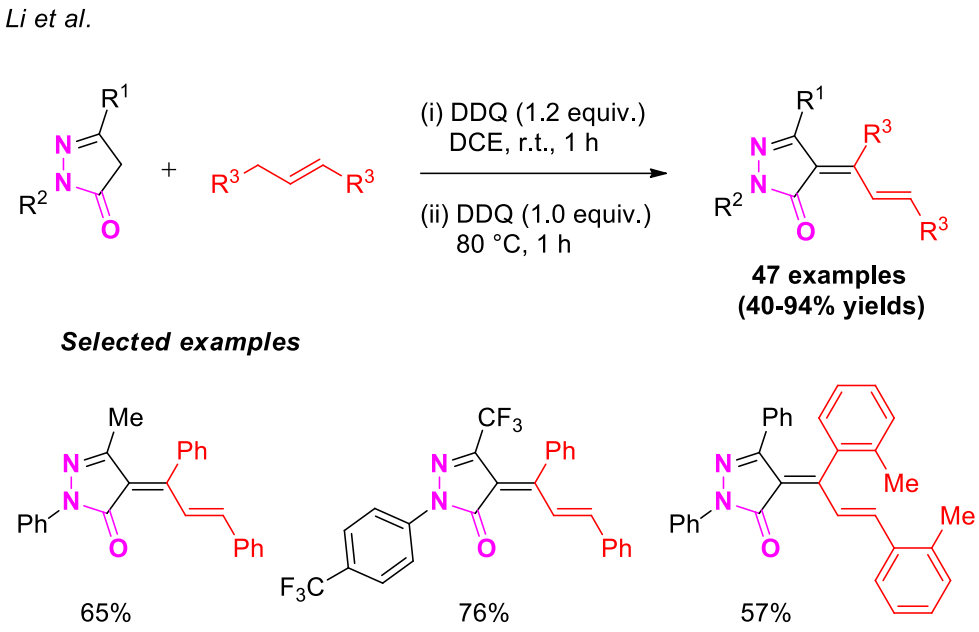
Scheme 4.2. A simple catalyst-free approach to 4-α,β,γ,δ-unsaturated prazolones.

Just after, Peng *et al.* (2018) disclosed a powerful method for accessing cyclopropyl fused pyrazolones using 4-α,β,γ,δ-unsaturated pyrazolones and sulfur ylides in the presence of strong base Cs_2CO_3 in toluene at room temperature. This regioselective process offers high yields from 60% to 80% of the targeted pyrazolones **(Scheme 4.3)**.[44]



Scheme 4.3. Cs_2CO_3-promoted cyclopropanation of 4-α,β,γ,δ-unsaturated pyrazolones with sulfur ylides.

Recently, in 2022, Li *et al.* developed a one-pot DDQ-mediated strategy to give 1,3-diarylallylidene pyrazolones through an oxidative coupling reaction of pyrazolones with 1,3-diaryl propenes. This two-step sequential reaction proceeds via ion-pair formation of 1,3-diarylallylidene through a charge-transfer mechanism in the presence of DDQ (1.2 equiv.), followed by the attack of nucleophilic pyrazolones making O-coupled and C-coupled intermediates which finally converted into the targeted pyrazolone in the presence pf DDQ (1.0 equiv.). This method provides moderate to excellent yields (40%- 94%, **Scheme 4.4**).[32]



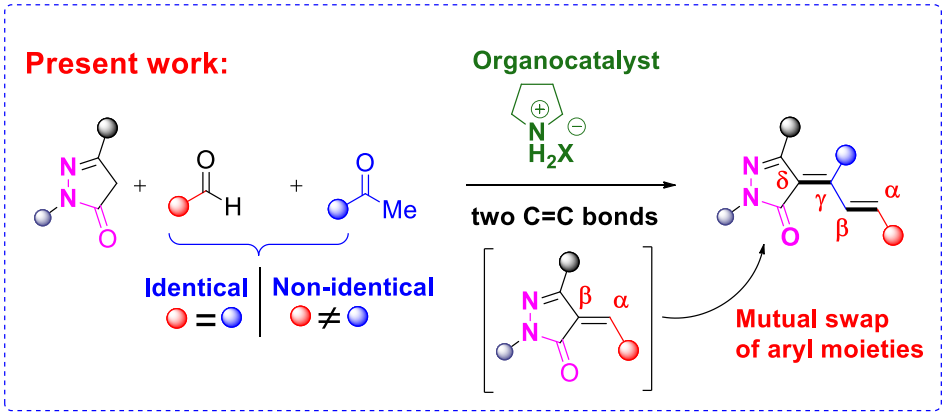
Scheme 4.4. DDQ-mediated one-pot strategy for accessing 1,3-diarylallylidene pyrazolones

4.2.2 Conclusion

The above discussion shows that considerable efforts have been devoted to synthesizing various 4-alkylidene pyrazolones due to their medicinal properties and other significant applications. However, the reported methods usually face many challenges such as the need for expensive transition metal-salts, specific substrate scope, unsatisfactory yields, less atom economy and use of excess base or oxidants which prevent their practical applicability in a large-scale synthesis. In addition, the synthesis of 4-alkenylidene pyrazolones with a diene motif at the C4 position is a limited success and remains challenging for synthetic chemists. Therefore, there is a great demand to develop a simple, organocatalytic, diastereoselective, and atom-economy method for accessing a diverse set of 1,3-diarylallylidene pyrazolones involving commercially available, cheap and modifiable reactants, showcasing a great potential to uncover precious pharmaceuticals and functional materials.

4.3 Present Work

Pyrazolones are a special class of molecules, as previously highlighted in the introduction section (4.1). Therefore, designing and developing a simple, metal-free, practical approach for accessing 1,3-diarylallylidene pyrazolones decorated with diverse substitution patterns from readily available cheap, simple reactants remains an innate challenge for chemists. In this context, herein, we wish to report further an efficient one-pot three-component organocatalytic strategy to access value-added *α,β,γ,δ*-unsaturated pyrazolones diastereoselectively involving 4-unsubstituted pyrazolones, aryl/heteroaryl aldehydes and aryl methyl ketones. This reaction proceeds *via* a sequential double-condensation of 4-unsubstituted pyrazolones with ary methyl ketones and aryl/heteroaryl aldehydes in the catalytic amount of pyrrolidine-BzOH salt (20 mol%) as illustrated in **Scheme 4.5.**

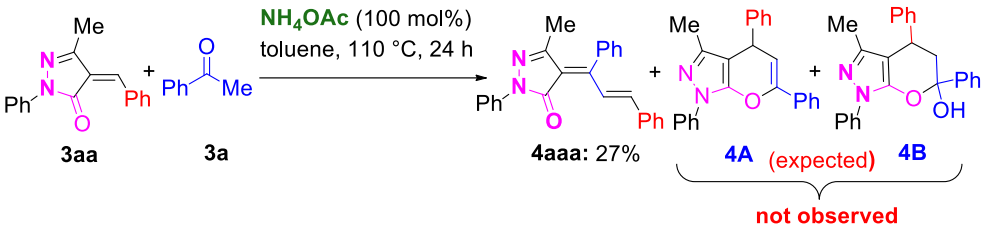


Scheme 4.5. Pyrrolidine-BzOH salt-catalyzed one-pot three-component reaction of pyrazolones.

4.4 Results and Discussion

We commenced a reaction between 4-benzylidene pyrazolone **3aa** and acetophenone **3a** using 100 mol% NH_4OAc in toluene at 110 °C. To our great pleasure, we achieved an unexpected (*E*)-4-[(*E*)-1,3-diphenylallylidene)pyrazolone **4aaa** as a single geometrical isomer (*E*, *E* > 99%) in 27% yield after 24 h of reaction as illustrated in **Scheme 4.6.** The

product **4aaa** was fully characterized by its spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS). The stereochemistry of the C=C double bonds is (*E*, *E*), as confirmed by matching it with the reported one.



Scheme 4.6. NH_4OAc-mediated synthesis of 1,3-diphenylallyl pyrazolone

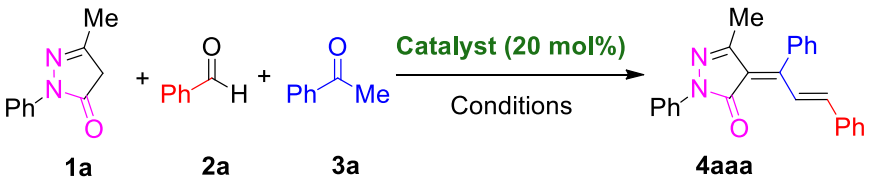
Furthermore, considering the demanding interest for one-pot multicomponent reaction (MCR) over stepwise protocol in organic and medicinal chemistry because of its proficiency in high atom economy and greener perspectives,[33-37] such as no need to isolate and purify intermediates, reducing solvent uses, cost, time, chemical waste and labor force. We thought that instead of using isolated 4-benzylidene pyrazolone **3aa,** it may form *in situ* from pyrazolone **1a** containing an active methylene group at C4 and benzaldehyde **2a** using pyrrolidine salt as a dual mode (iminium ion and enamine) of activation catalyst,[38-40] possibility of making α,β,γ,δ-unsaturated pyrazolone.

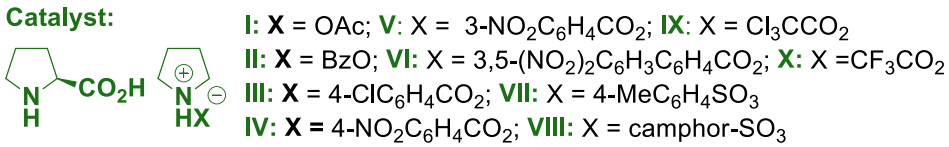
4.4.1 Optimization of reaction conditions

To verify the above hypothesis, we initiated a model reaction between **1a, 2a,** and **3a** in dry toluene at 110 °C in the presence of L-proline catalysis (20 mol%). Interestingly, we achieved the intended product **4aaa** in a 20% yield (**Table 4.1,** entry 2). We screened several pyrrolidine-acid salts (I-X, entries 3-12) based on their pK_a values, for this C=C bond-forming reaction to further improve this MCR protocol. Results showed that catalysts **II** [pyrrolidine-BzOH] and **III** [pyrrolidine/4-ClBzOH] are almost similar for this conversion, producing **4aaa** in 84% (entry 4) and 82% (entry 5) yields, respectively. These

are quite higher yields than those achieved with other catalysts **I** (71%, entry 3), **IV** (75%, entry 6), **V** (74%, entry 7), and **VI** (61%, entry 8), respectively. Furthermore, in the case of catalysts prepared from strong acids such as (±)-CSA, PTSA, TCA, and TFA, the reaction was either slow or did not occur which led to inferior results (≤ 23% yields of **4aaa,** entries 9-12). Thus, considering the cost of benzoic acid, catalyst **II** [(pyrrolidine-BzOH), 84% yield, entry 4] was an obvious choice for this diastereoselective C=C bond-making reaction. Additionally, with this exciting result, we checked the effect of common organic solvents on the yield of **4aaa.** Good yields of the desired product **4aaa** were obtained in xylene (79%, entry 16) and 1,2-dichlorobenzene (73%, entry 18). However, polar solvents like DMF, DMSO, and 1,4-dioxane (entries 13-15) afforded a negligible yield. Decreasing the reaction temperature from 110 °C to 85 °C, resulted in no conversion (entry 18) of the desired product **4aaa.** Use of 10 mol% of catalyst II, offered 65% yields (entry 19) after 24 h.

Table 4.1: Optimization of reaction conditions [a,b]





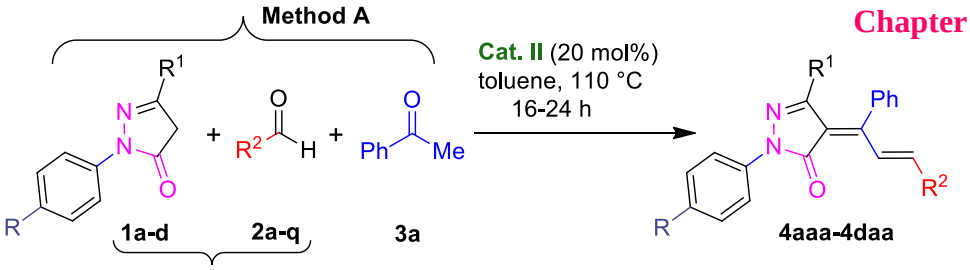
Entry	Catalyst	Solvent	Temp(°C)	Time (h)	Yield [b] (%)
1	NH_4OAc	toluene	110	24	27
2	L-Proline	toluene	110	16	20
3	**I**	toluene	110	16	71
4	**II**	toluene	110	16	84
5	**III**	toluene	110	16	82

6	**IV**	toluene	110	16	75
7	**V**	toluene	110	16	74
8	**VI**	toluene	110	16	61
9	**VII**	toluene	110	16	trace
10	**VIII**	toluene	110	16	trace
11	**IX**	toluene	110	16	21
12	**X**	toluene	110	16	23
13	**II**	DMF	110	16	trace
14	**II**	DMSO	110	16	trace
15	**II**	1,4-dioxane	110	16	15
16	**II**	xylene	110	16	79
17	**II**	1,2-$Cl_2C_6H_4$	110	16	73
18	**II**	toluene	85	24	trace
19[c]	**II**	toluene	110	24	65

[a]Unless otherwise noted, all of the reactions were carried out with **1a** (0.2 mmol, 1.0 equiv), **2a** (0.22 mmol, 1.1 equiv.), organo-base and catalyst (20 mol%) in specified dry solvent (2.0 mL) and temperature under an inert atmosphere for 16 h. [b]Isolated yield of **4aaa** after column chromatography. [c]10.0 mol% catalyst **II**.

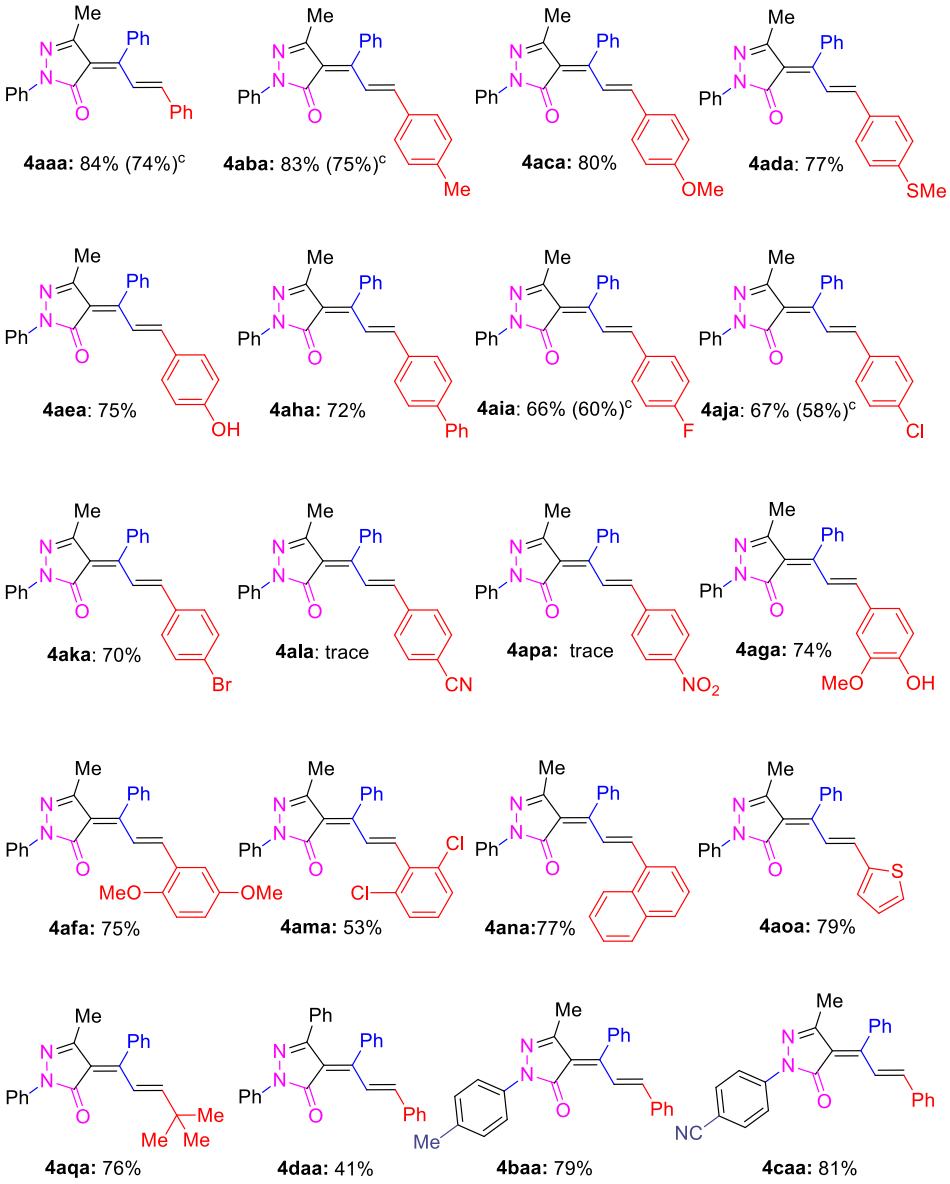
4.4.2 Substrate Scope

With the optimized conditions in hand, we explored the substrate scope using various substituted aldehydes **(2b-2p)** and pyrazolones **(1a-1d)** under the present established conditions. A set of aryl aldehydes containing electron-deficient (Ph, F, Cl, Br) and electron-rich (Me, MeO, MeS, and OH) groups on benzene rings displayed good reactivity toward the consecutive two C=C bonds forming event with pyrazolone **1a** and ketone **3a** as 2C units for this diene formation (**Scheme 4.7**). All offered the corresponding 4-alkenylidene pyrazolones (**4aba-4ala**) with single (*E, E*) isomer. Notably, the yields obtained in the case of electron-donating substituents are higher to some extent than those obtained in electron-withdrawing ones (75-83% vs 66-70%).



1a: R = H, R^1 = Me
1b: R = Me, R^1 = Me
1c: R = CN, R^1 = Me
1d: R = H, R^1 = Ph

2a: R^2 =Ph;
2b: R^2 =4-MeC_6H_4;
2c: R^2 =4-MeOC_6H_4;
2d: R^2 =4-MeSC_6H_4;
2e: R^2 = 4-HOC_6H_4;
2f: R^2 = 2,5-$(MeO)_2C_6H_3$;
2g: R^2 = 3-MeO-4-HOC_6H_3
2h: R^2 = 4-PhC_6H_4
2i: R^2 = 4-F
2j: R^2 = 4-Cl
2k: R^2 = 4-Br
2l: R^2 = NC-C_6H_4
2m: R^2 = 2,6-$Cl_2C_6H_3$
2n: R^2 = 1-naphthyl
2o: R^2 = 2-thiophene
2p: R^2 = 4-O_2N-C_6H_4
2q: R^3 = Me_3C



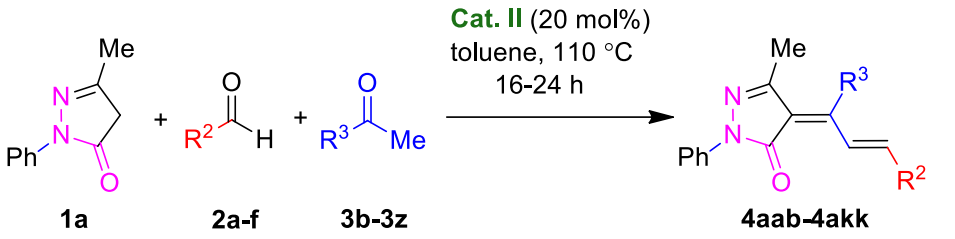
Scheme 4.7. Pot-economy access to unsaturated pyrazolones (**4aaa-4daa)**

Aldehydes with electron-deficient substituents provide diminished yields due to the difficulty of iminium ion activation.

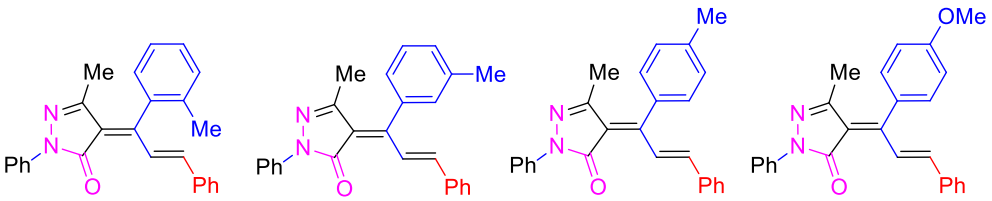
Moreover, X-ray crystallographic data showed *E*, *E*-configurations of both C=C double bonds in compound **4aba** (CCDC 2378712) and **4aca** (CCDC 2378711). Aldehydes containing strong electron-withdrawing groups such as NO_2 and CN did not yield products **4ala** and **4apa.** Disubstituted aldehydes bearing donating groups like MeO and OH, reacted well resulting in good yields of 75% and 74% of **4afa** and **4aga** and aldehydes with two Cl atoms attached yielded 53% for **4ama.** Furthermore, 1-naphthaldehyde (**2n**) and 2-thiophene aldehyde (**2o**) were good partners, resulting in 77% and 79% of **4ana** and **4aoa,** respectively. Aliphatic aldehyde like pivaldehyde (**2q**) nicely reacted with **1a** and **3a** to offer the desired alkenylidene pyrazolone **4aqa** in 76% yield. Next, *N*-arylpyrazolones containing Me and CN moieties on the phenyl rings were suitable substrates for high yields of **4baa** (79%) and **4caa** (81%), respectively. Replacing 3-methylpyrazolone **1a** with 3-phenylpyrazolone **1d,** showed poor reactivity toward this reaction due to the bulkiness of the benzene ring, affording a 41% yield of **4daa.** The yields obtained by method A were slightly higher than those obtained using method B. The yields in parentheses were obtained by method B **(Scheme 4.7).**

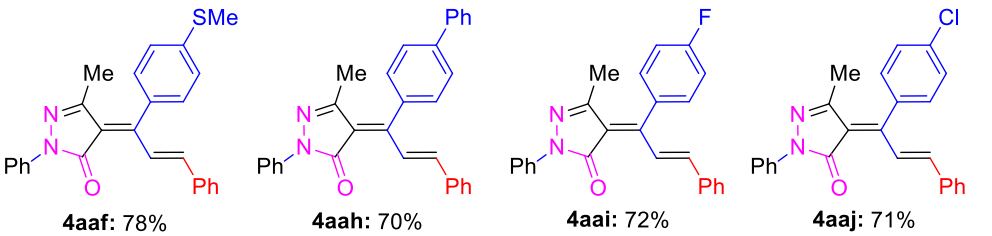
To further extend the present methodology, we varied the aryl parts of ketones in this diastereoselective C=C double bond construction process. For example, a set of electronic and structurally diverse substituents like Me, MeO, MeS, HO, Me_2N, O–CH_2–O, Ph, F, Cl, Br, I, CN and SO_2Me at the different positions of benzene rings of acetophenones were well tolerated and enabled the corresponding alkenylidene pyrazolones (**4aab-4aas**) with excellent diastereoselectivity (*E*, *E* ≥ 99%) in **Scheme 4.8.** ketones attached with electron-rich groups resulted in somewhat increased nucleophilic strength of the corresponding enamines, and furnished noticeably higher yields (72-81%; **4aab-4aag** and **4aao-4aas**) in comparison to those with electron-withdrawing ones (47-73%; **4aah-4aan**). Additionally, ketones featuring fluorenyl, tetrahydronaphthyl, and naphthyl groups underwent smoothly reaction with **1a** and **2a,** offering pyrazolones **4aat, 4aau,** and **4aav** in 76%, 73%, and 75

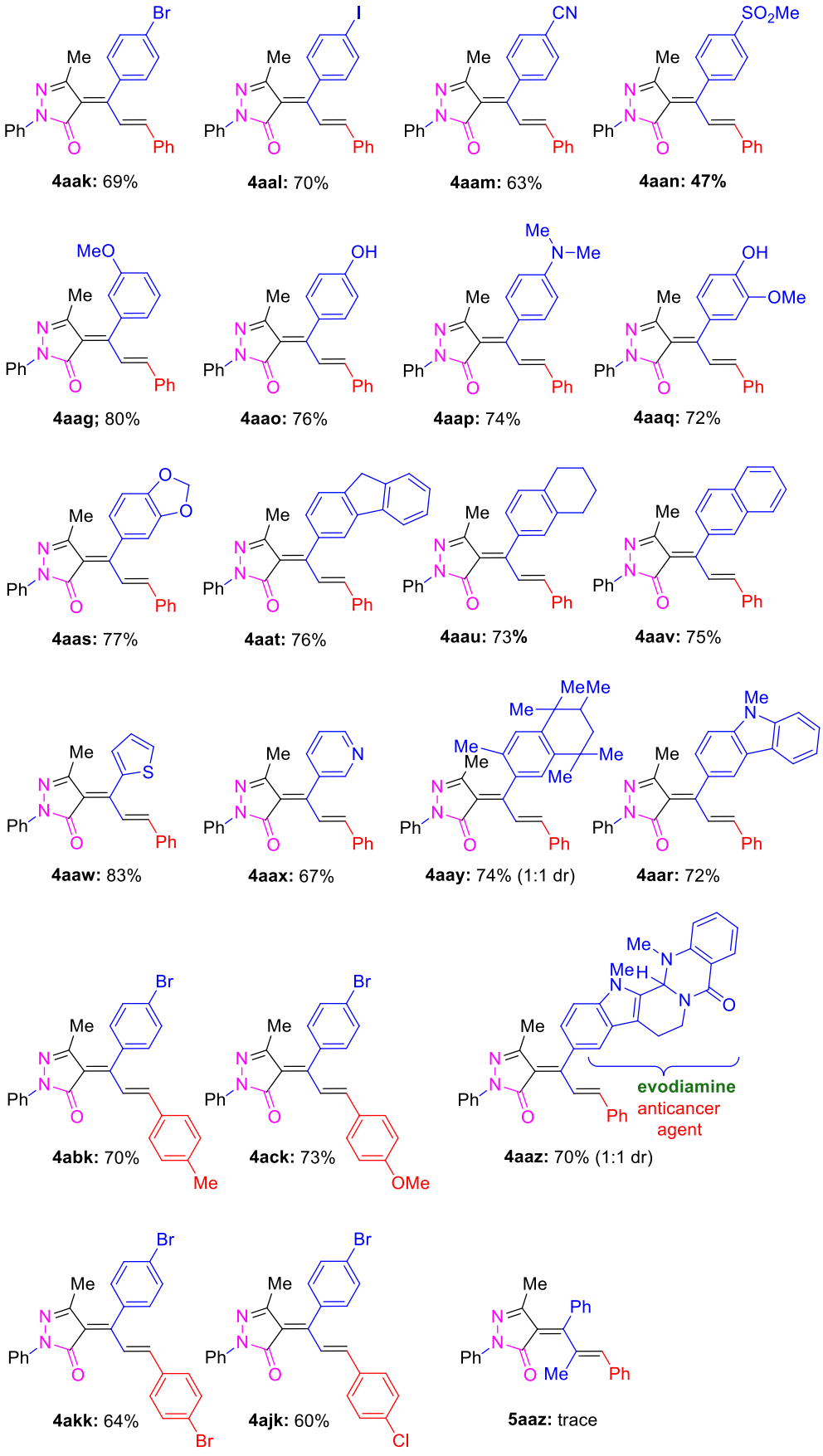
yields respectively via two consecutive C=C bonds formation. Furthermore, heteroaryl ketones such as 2-acetyl thiophene, 3-acetylpyridine, and 3-acetyl carbazole are involved efficiently in this three-component reaction, leading to heteroaryl-substituted allylidene pyrazolones **4aaw, 4aax,** and **4aar** in good yields of 67% to 83%. Notably, even bulky ketones like tonalid (a fragrance) and a racemic version of acetyl evodiamine (an anticancer agent),[41,42] which are considered challenging substrates in enamine chemistry, resulted in the desired products in satisfactory yields (74% for **4aay** and 70% for **4aaz**). Next, aryl aldehydes attached with Me, MeO, Cl, and Br atoms also displayed good reactivity with 4-bromoacetophenone (**3k**), bestowing satisfactory yields (60-73%) of corresponding 1,3-diarylallylidene pyrazolones (**4abk-4akk**).



3b: R^3 = 2-MeC_6H_4; **3i/3j/3k/3l:** R^3=4-F/Cl/Br/IC_6H_4; **3x:** R^3 = 3-pyridine
3c: R^3 = 3-MeC_6H_4; **3m/3n/3o/3p:** R^3= 4-NC/SO_2Me/HO/Me_2N-C_6H_4
3d: R^3= 4-MeC_6H_4; **3q:** R^3=3-MeO-4-HOC_6H_4; **3r:** R^3 = 3-N-methylcarbazole
3e: R^3= 4-$MeOC_6H_4$; **3s:** R^3=3,4-methylelnedioxybenzene
3f: R^3= 4-$MeSC_6H_4$; **3t:** R^3=3-(9*H*)-fluorene; **3w:** R^3 = 2-thiophene
3g: R^3= 3-$MeOC_6H_4$; **3u:** R^3= tetrahydronaphthalene
3h: R^3= 4-PhC_6H_4; **3v:** R^3= 1-naphthalene; **3y:** tonalide



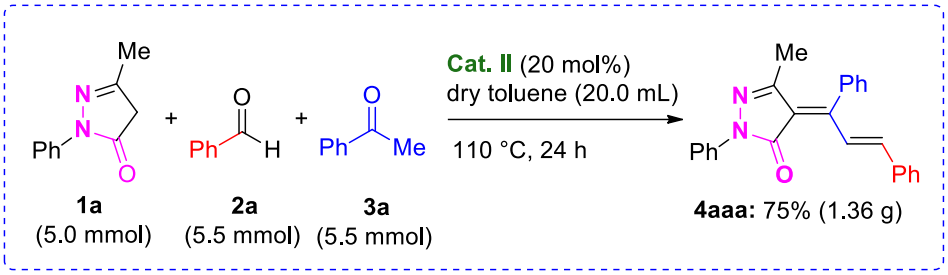




Scheme 4.8. Pot-economy access to unsaturated pyrazolones (**4aab-4akk**)

Thus, this metal-free catalytic method tolerates several hetero- and carbocyclic frameworks along with various functionalities such as Me, MeO, MeS, HO, Me_2N, O–CH_2–O, F, Cl, Br, I, CN, SO_2Me, and C=C bonds, which may be further synthetic manipulations to create new biological targets.

Gram-scale synthesis of *α,β,γ,δ*-unsaturated pyrazolone: To highlight the robustness and practical applicability of this method, a gram-scale reaction was executed for the synthesis of **4aaa** involving **1a** (5.0 mmol, 1.0 equiv.), **2a** (5.5 mmol, 1.1 equiv.), **3a** (5.5 mmol, 1.1 equiv.) using 20 mol% catalyst **II** under optimal conditions, offering 1.36 g (75% yield, **Scheme 4.9**) of the compound **4aaa.**

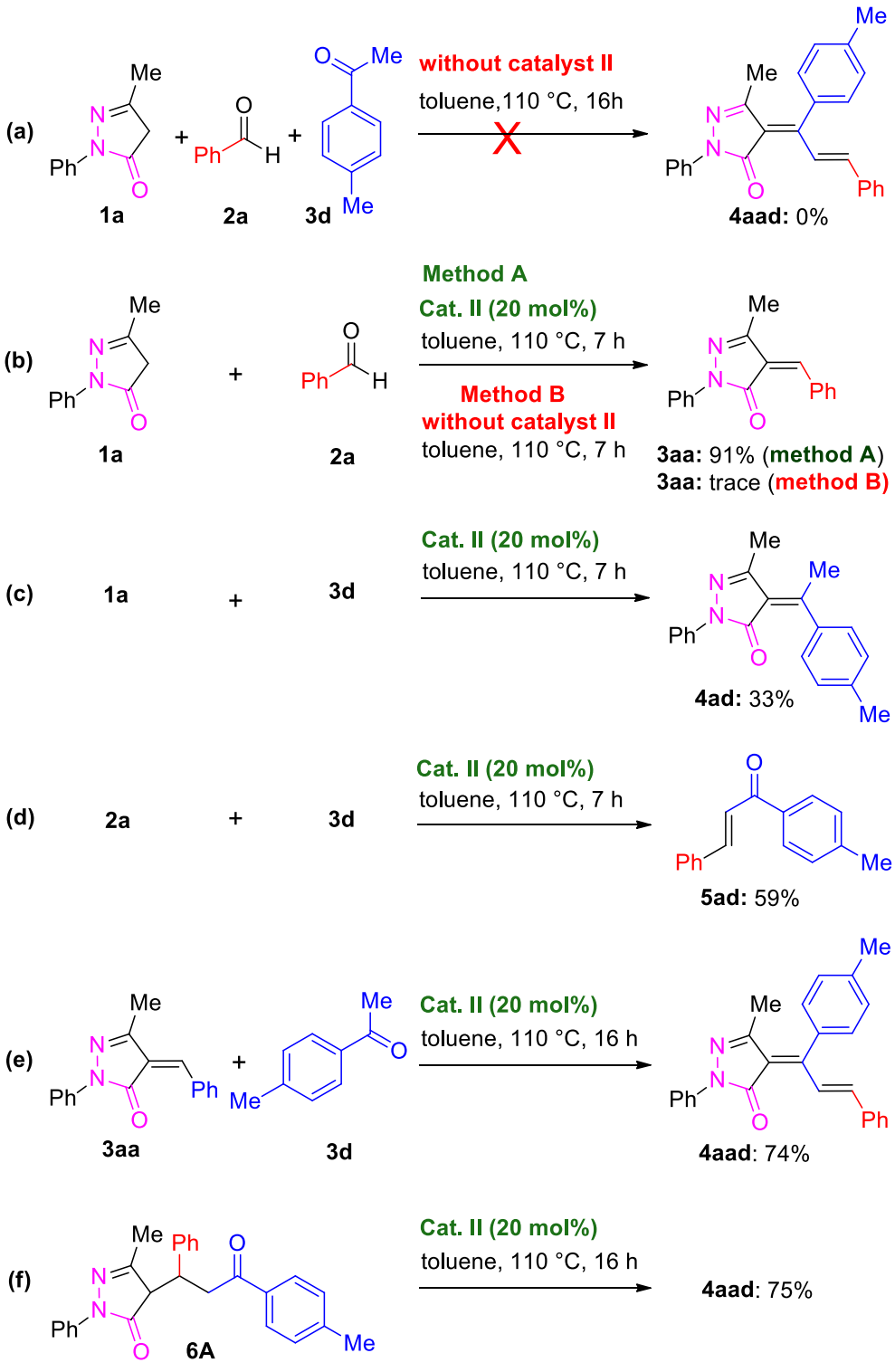


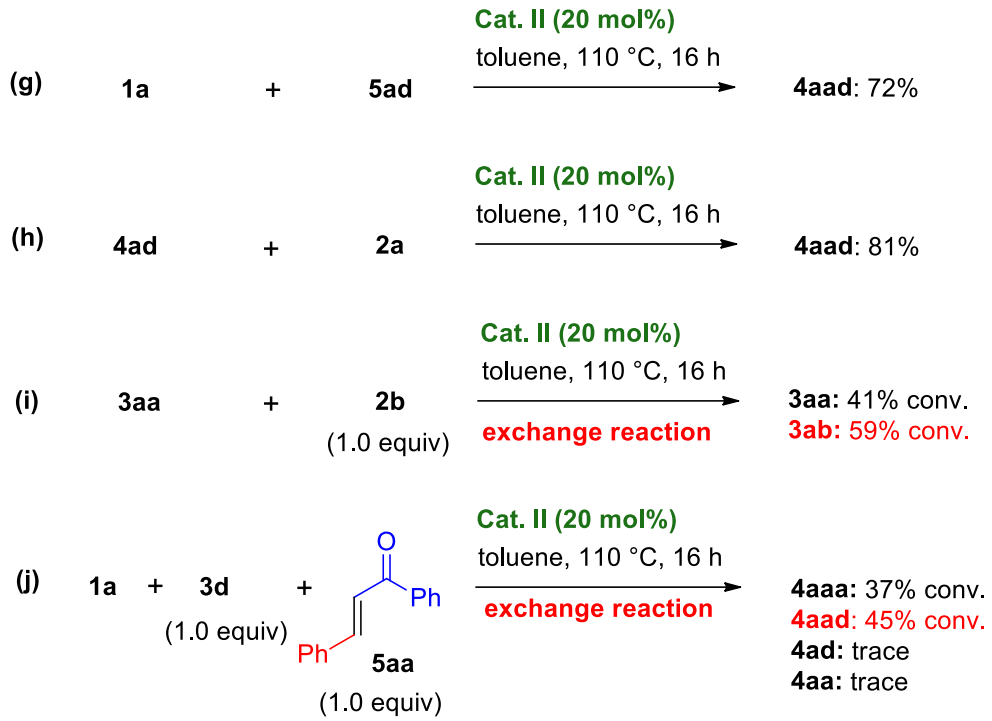
Scheme 4.9. Gram-scale synthesis of **4aaa.**

4.4.3 Control Experiments

We performed several control experiments to understand the appropriate mechanism illustrated in **Scheme 4.10**. For example, in the absence of catalyst **II** (**Scheme 4.10a**), the reaction between **1a, 2a,** and **3a** did not occur in toluene at 110 °C, suggesting that the catalyst (pyrrolidine salt) is required for this C=C double bond-making process. Further, we observed that pyrazolone **1a** condensed with reactive benzaldehyde (**2a)** much faster (providing **3aa**) than with less reactive acetophenone (**3d**) (giving **4ad** more slowly) under the aforementioned conditions. This difference in the condensation process led to 91% of **3aa** (**Scheme 4.10b**) and 33% of **4ad** (**Scheme 4.10c**) after 7 h. Additionally, the reaction between ketone **3d** and aldehyde **2a** using 20 mol% of catalyst **II** afforded 59% of chalcone **5ad** (**Scheme 4.10d**). Furthermore, ketone **3d** displayed good reactivity as an enamine doner with benzylidene pyrazolone **3aa,** heading to a 74% yield of **4aad** *via* a mutual swap of aryl

groups (**Scheme 4.10e**). Next, Michael adduct **6A** is converted into the desired product **4aad** (75% yield, **Scheme 4.10f**) under the present catalytic conditions.





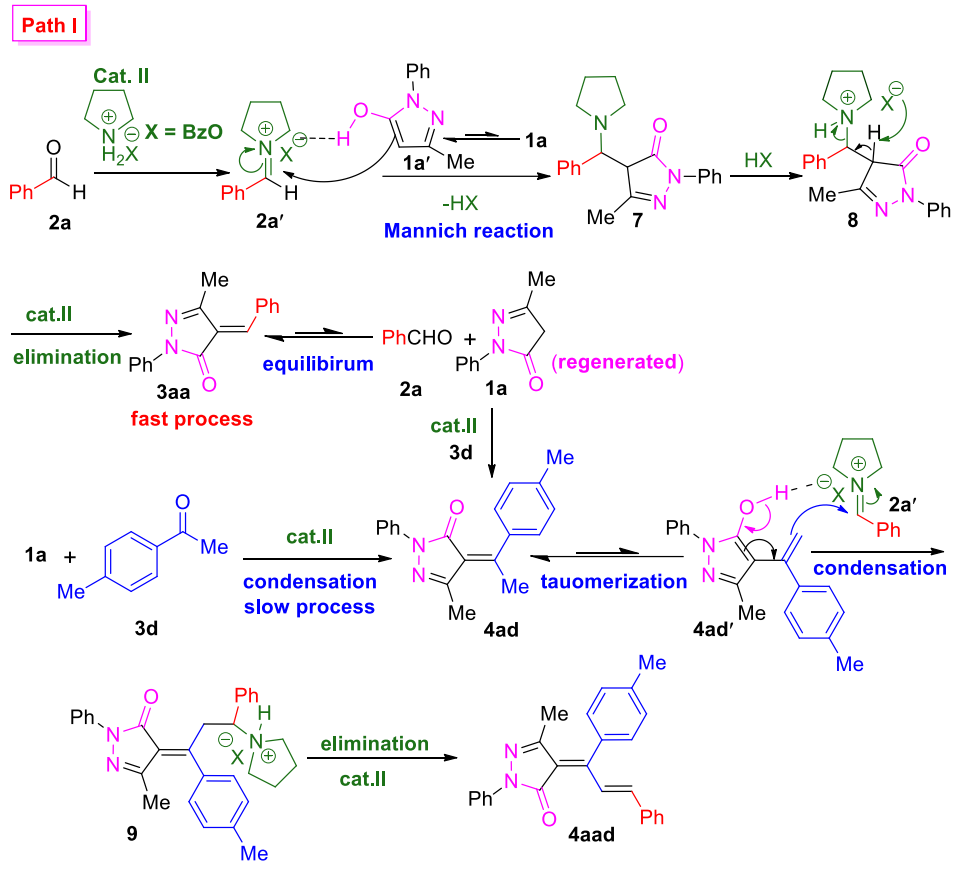
Scheme 4.10. Control experiments

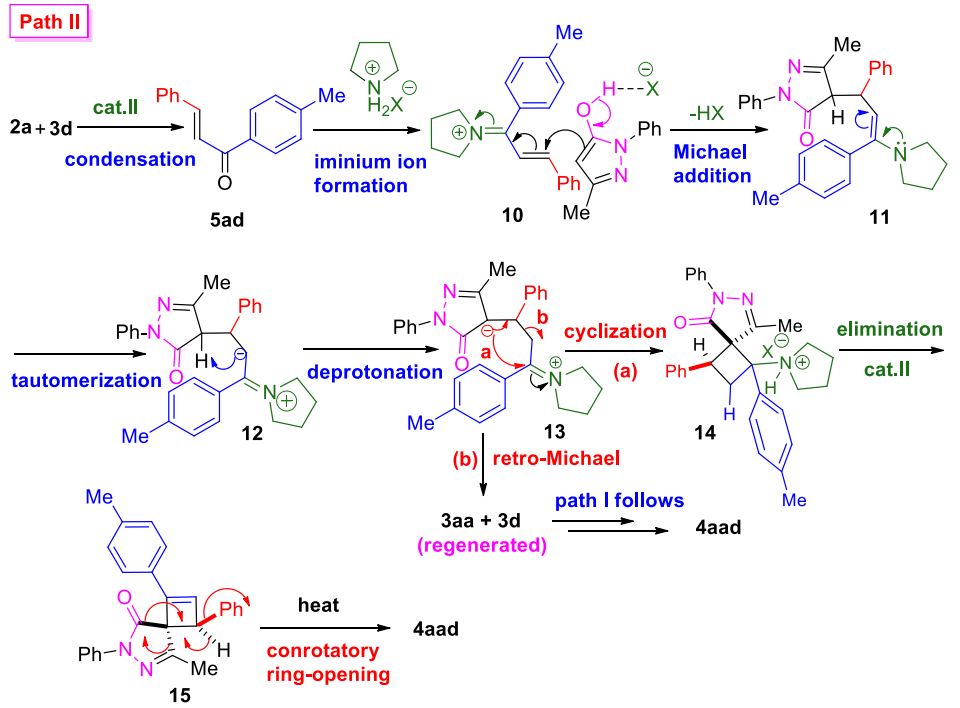
The reaction of pyrazolone **1a** with chalcone **5ad** also provided a good yield (72%, **Scheme 4.10g**) of the product **4aad,** similarly, benzylidene pyrazolone **4ad** with benzaldehyde **2a** also yielded the product **4aad** with a high yield of 81% (**Scheme 4.10h**). After thoroughly observing these findings, it is understandable that the targeted product **4aad** can be synthesized from three different intermediates: **3aa, 5ad,** and **4ad.** It should be noted that the formation rate of intermediate **3aa** exceeds that of the other intermediates, making it a vital contributor to the high yield of the intended product **4aad.** Next, we commenced the reaction between **3aa** and 4-methyl benzaldehyde (**2b**) in toluene using catalyst **II,** surprisingly, it led to **3ab** (59% conversion, **Scheme 4.10i**) along with 41% intact of **3aa.** This suggests that benzylidene pyrazolone **3aa** equilibrates with pyrazolone **1a** and benzaldehyde (**2a**) under the present catalytic conditions. Similarly, the three-component reaction between chalcone **5aa,** ketone **3d,** and pyrazolone **1a** resulted in a mixture of two products **4aaa** and **4aad,** with a conversion of 37% and 45%, respectively.

4.4.4 Plausible Mechanism

Based on our control experiments, we propose two feasible mechanistic pathways for this organocatalytic C=C bond-making reaction as depicted in **Scheme 4.11.** Initially, catalyst **II** (pyrrolidine-BzOH salt) readily reacts with benzaldehyde (**2a**) to form highly reactive iminium ion intermediate **2a′** (a LUMO-lowering energy species). Now this **2a′** goes through a Mannich addition reaction with pyrazole **1a′** (an enolic form of **1a**) and then subsequent elimination of catalyst **II,** giving **3aa.** Simultaneously, pyrazolone **1a** and ketone **3d** condenses in the presence of catalyst **II** to form intermediate **4ad,** which may further tautomerize into its enolic form **4ad′** under the present conditions. Next, this intermediate **4ad** attacks iminium ion intermediate **2a′** to give intermediate **9.** Then, the elimination of catalyst **II** from **9** for the next catalytic circle, provides our desired product **4aad.** Notably, the formation of intermediate **3aa** is much faster rate than that of another intermediate **4ad.** Interestingly, pyrazolone **1a** and benzaldehyde (**2a**) regenerate from the slow dissociation of intermediate **3aa** through a *retro*-Knoevenagel in an equilibrium state under the present catalytic system. Thus, this process continuously supplies pyrazolone **1a** which reacts with **3d,** eventually leading to **4ad.** Therefore, the major contribution toward the high yield of the intended product **4aad** comes from this proposed path **I.**

On the other hand, path **II** depicts that *in-situ* generated chalcone **5ad** in the presence of catalyst **II** converts into its iminium ion form **10**, which is then attacked by the enolic form of pyrazolone **1a′** to give intermediate **11.** Then, it undergoes tautomerization to give iminium ion intermediate **13.** Further, this intermediate subsequently converts into its spiro-cyclobutane intermediate **14** as a single diastereomer, followed by the elimination of catalyst **II** from **14**, leading to an unstable spiro-cyclobutene intermediate **15.** Finally, it may undergo a conrotatory process to open the electrocyclic ring under heating conditions to fortify **4aad** with the intended stereochemistry (rout **a**). Besides, pyrazolone **3aa** and ketone **3d** may regenerate from intermediate **13** through a *retro*-Michael reaction as route **b**, and then follows path **I** again to give the desired product **4aad (Scheme 4.11).**





Scheme 4.11. Plausible mechanistic pathways for this double-condensation reaction

4.5 Conclusion

In this chapter, we have presented a new facile, organocatalytic, one-pot, pot-economical technique for the diastereoselective synthesis of various 1,3-diaryl-substituted pyrazolones, which are either difficult to synthesize or inaccessible using traditional methods. This three-component consecutive double condensation reaction between pyrazolones, aryl/heteroaryl aldehydes, and aryl methyl ketones goes effortlessly under pyrrolidine-BzOH salt as a cost-effective, robust catalytic system. Furthermore, 4-benzylidene pyrazolone with unaltered aryl methyl ketones under established conditions provides the same pyrazolone derivatives through a *retro*-Knoevenagel/ sequential double condensation reaction. Moreover, it possesses notable features such as good chemical yields, excellent diastereoselectivity (≤ 99%), and high tolerance of diverse functional groups. Additionally, this metal-free catalytic approach has many advantages, such as being operationally simple, applicable to gram-scale synthesis, 100% carbon-atom economy, water as the only by-product, and no need for toxic oxidants. This unique catalytic concept will further open the door for more challenging synthetic transformations for medicinal and other relevant applications.

4.6 Experimental Section:

General Information: All the above reactions were executed under an inert atmosphere or in the open air. The progress of the reaction was continuously monitored by TLC using Merck 60 F_{254} pre-coated silica-gel plates and the products were visualized by UV detection lamp. Flash chromatography was performed in silica gel (200-300 mesh). ^{1}H and ^{13}C NMR spectra were recorded on 500 MHz and 400 MHz spectrometers with ^{13}C operating frequencies of 100 and 125 MHz. Final data for ^{1}H NMR are reported as a chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant *J* (Hz), integration, and assignment, data for $^{13}C\{^{1}H\}$ are reported as a chemical shift. High-resolution mass spectral analyses (HRMS) were accomplished using ESI-TOF-MS. Single crystal X-ray diffraction data was recorded on the Bruker D8 quest single

crystal-XRD instrument. Melting points were recorded on an Electro thermal melting points apparatus and are uncorrected.

Starting materials: All the pyrazolones **1a** (commercial); **1b-1d**,[11,43] aldehydes **2a-q** (commercial sources) and ketones **3r, 3t, 3u** and **3z** (**3a-q, 3s, 3v-3y** and **4z** commercial sources) were prepared by following literature known procedures and being fully characterized. Pyrrolidine, NH_4OAc, L-proline and all utilized acids were purchased from commercial suppliers.

3-Methyl-1-(4-methylphenyl)-1*H*-pyrazol-5(4*H*)-one (1b):[43] Colorless gummy; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 3.40 (s, 2H), 2.33 (s, 3H), 2.17 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.4, 156.1, 135.6, 134.7, 129.3, 118.9, 43.0, 20.9, 17.0 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2O^+$ 189.1022, found 189.1011.

4-(3-Methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)benzonitrile (1c):[11] Pale yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 3.47 (s, 2H), 2.22 (s, 3H) ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{11}H_{10}N_3O^+$ 200.0818, found 200.0817.

1,3-Diphenyl-1*H*-pyrazol-5(4*H*)-one (1d):[11] Off white solid; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.7, 1.0 Hz, 2H), 7.80-7.7 (m, 2H), 7.48-7.41 (m, 5H), 7.25 – 7.20 (m, 1H), 3.85 (s, 2H) ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2O^+$ 237.1022, found 237.1020.

1-(9-Methyl-9*H*-carbazol-3-yl)ethanone (3r): Off white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.11 (t, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.34-7.27 (m, 2H), 3.80 (s, 3H), 2.70 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.7, 143.6, 141.7, 128.8, 126.5, 126.4, 123.1, 122.5, 121.7, 120.5, 120.0, 109.0, 108.0, 29.2, 26.7 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{13}NONa^+$ 246.0889, found 246.0890.

1-(9*H*-Fluoren-3-yl)ethanone (3t): Off white solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.84 (t, *J* = 7.3 Hz, 2H), 7.59

(d, *J* = 7.2 Hz, 1H), 7.44-7.35 (m, 2H), 3.95 (s, 2H), 2.66 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 198.1, 146.5, 144.6, 143.4, 140.6, 135.7, 128.1, 127.8, 127.1, 125.3, 125.0, 121.0, 119.7, 37.0, 26.9 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{12}ONa^+$ 231.0780, found 231.0779.

1-(5,6,7,8-Tetrahydronaphthalen-2-yl)ethanone (3u): Pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.62 (m, 2H), 7.12 (d, *J* = 8.3 Hz, 1H), 2.83-2.77 (m, 4H), 2.55 (s, 3H), 1.83-1.77 (m, 4H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 198.1, 143.1, 137.4, 134.7, 129.3, 129.2, 125.4, 29.6, 29.3, 26.5, 22.9, 22.8 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{14}ONa^+$ 197.0937, found 197.0927.

10-Acetyl-13,14-dimethyl-7,8,13*b*,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5(13*H*)-one (3z): Off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.29 – 7.20 (m, 2H), 5.98 (s, 1H), 4.95 (dd, *J* = 12.8, 4.7 Hz, 1H), 3.92 (s, 3H), 3.21 (td, *J* = 12.3, 3.8 Hz, 1H), 3.09 (d, *J* = 15.3 Hz, 1H), 2.99 – 2.89 (m, 1H), 2.70 (s, 3H), 2.45 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 198.1, 164.6, 150.7, 140.4, 133.1, 130.6, 129.7, 129.0, 125.2, 124.3, 123.9, 123.1, 123.0, 121.1, 114.9, 109.3, 67.9, 39.3, 36.5, 30.4, 26.7, 20.3 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{22}H_{21}N_3O_2Na^+$ 382.1526, found 382.1510.

(*Z*)-4-Benzylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3aa): Red solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.56-7.48 (m, 3H), 7.56-7.49 (m, 3H), 7.44-7.38 (m, 1H), 2.36 (s, 3H) ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{17}H_{15}N_2O^+$ 263.1179, found 263.1157.

(*Z*)-3-Methyl-4-(4-methylbenzylidene)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3ab): Red solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.1 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.34 (s, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 2.43 (s, 3H), 2.33 (s, 1H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 162.1, 151.0, 147.1, 144.5, 138.5, 134.1, 130.6, 129.6,

128.8, 126.8, 124.9, 119.2, 22.1, 13.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O^+$ 277.1335, found 277.1354.

(*Z*)-3-Methyl-1-phenyl-4-(1-(*p*-methylphenyl)ethylidene)-1*H*-pyrazol-5(4*H*)-one (4ad): A mixture of pyrazolone **1a** (87.1 mg, 0.5 mmol), ketone **3d** (67.0 mg, 0.5 mmol), and catalyst **II** (20 mol%, 19.3 mg) in dry toluene (4.0 mL) was heated at 110 °C in oil bath for 7 hours. The reaction mixture was then extracted with ethyl acetate (3 × 10 mL), washed with water, and treated with Na_2SO_4. The combined solvents were evaporated to leave the crude solid product. Then it was purified by silica-gel column chromatography using ethyl acetate/hexane as an eluent, which resulted in a pure product **4ad** (33%, 47.1 mg)**.** Brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.6, 0.9 Hz, 2H), 7.42 – 7.38 (m, 2H), 7.26-7.24 (m, 2H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 2.84 (s, 3H), 2.42 (s, 3H), 1.62 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 163.9, 148.6, 139.8, 138.4, 138.4, 129.3, 128.8, 127.2, 126.1, 124.8, 119.0, 23.2, 21.4, 17.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2O^+$ 291.1492, found 291.1488.

(*E*)-3-Phenyl-1-(*p*-methylphenyl)prop-2-en-1-one (5ad): A solution of freshly distilled benzaldehyde (**2a**, 53.0 mg, 0.5 mmol), ketone **3d** (67.0 mg, 0.5 mmol), and catalyst **II** (20 mol%, 19.3 mg) in dry toluene (4.0 mL) was heated at 110 °C under an argon atmosphere for 7 hours. The reaction mixture was then extracted with ethyl acetate, washed with water, and treated with Na_2SO_4. After removing the solvent under reduced pressure by rotary evaporation, the crude mass was purified by silica-gel column chromatography using ethyl acetate/hexane as an eluent, resulting in a pure chalcone derivative **5ad** in a 59% (65.4 mg) yield**.** Off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.9 Hz, 2H), 7.82 (d, *J* = 15.7 Hz, 1H), 7.67-7.62 (m, 2H), 7.55 (d, *J* = 15.7 Hz, 1H), 7.44-7.39 (m, 3H), 7.31 (d, *J* = 7.8 Hz, 2H), 2.43 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 190.1, 144.4, 143.7, 135.7, 135.0, 130.5, 129.4, 129.0, 128.7, 128.5, 122.1, 21.7 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{14}ONa^+$ 245.0937, found 245.0930.

General Procedure for the Synthesis of *α,β,γ,δ*-Unsaturated Pyrazolone 4aaa: A mixture of pyrazolone **1a** (0.2 mmol, 1.0 equiv), aldehyde **2a** (22.0 mmol, 1.1 equiv), ketone **3a** (0.22 mmol, 1.1 equiv) and catalyst **II** (0.04 mmol, 20 mol%, 0.2 equiv) in dry toluene (2.0 mL) was heated at 110 °C in a preheated oil-bath under an argon-atmosphere. The progress of the reaction was monitored by TLC (thin-layer chromatography). After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 ×10 mL). The combined organic solvents were washed with brine and treated with anhydrous Na_2SO_4. Afterwards, evaporation of the organic solvent under reduced pressure left the crude solid product which was further purified by silica-gel column chromatography using ethyl acetate/hexane as an eluent to afford the corresponding substituted unsaturated pyrazolone **4aaa**. The molecular structures of all the synthesized products in **Schemes 4.7** and **4.9** were determined by their ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HRMS data.

(*E*)-4-((*E*)-1,3-Diphenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aaa): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.35 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aaa** as a red solid; yield = 84% (61.2 mg); mp = 128-130 °C; R_f = 0.74 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (d, *J* = 15.9 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.58 – 7.56 (m, 2H), 7.53– 7.49 (m, 3H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.34 (m, 3H), 7.30 – 7.28 (m, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 15.9 Hz, 1H), 1.48 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.8, 158.8, 149.3, 148.0, 138.4, 136.1, 136.0, 130.5, 129.3, 129.1, 129.0, 128.9, 128.7, 128.5, 126.8, 124.8, 123.4, 119.2, 16.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_2O^+$ 365.1648, found 365.1640.

(*E*)-4-((*E*)-1-Phenyl-3-(4-methylphenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aba): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2b** (26.4 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aba** as a deep orange red solid; yield = 83% (62.8 mg); mp = 92-94 °C; R_f = 0.75 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (d, *J* = 15.9 Hz,

1H), 7.98 (d, *J* = 7.6 Hz, 2H), 7.54 – 7.45 (m, 5H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.21 – 7.13 (m, 3H), 6.70 (d, *J* = 15.9 Hz, 1H), 2.36 (s, 3H), 1.47 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 163.9, 159.1, 149.38, 148.34, 141.2, 138.5, 136.1, 133.4, 129.7, 129.2, 129.1, 128.8 (2C, one overlap peak), 128.4, 125.9, 124.8, 122.9, 119.2, 21.6, 16.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O^+$ 379.1805, found 379.1799.

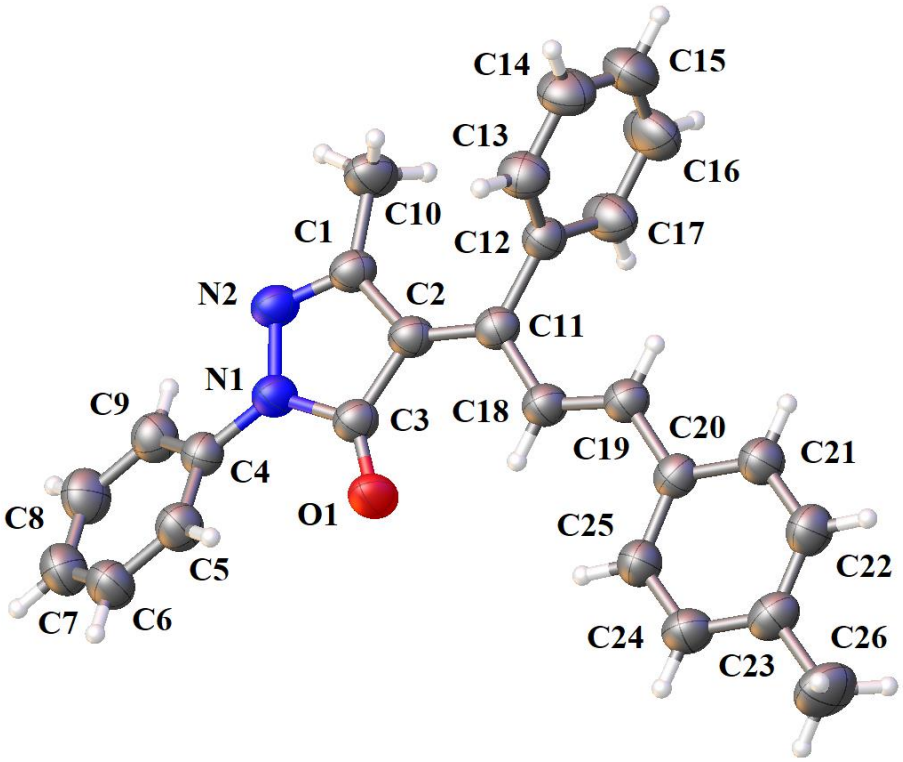


Figure 4.2. ORTEP plot of compound **4aba** with thermal ellipsoids drawn at the 50% probability level.

The single crystal of **4aba** was grown in a mixture of solvents hexane/ethyl acetate (9:1) by slow evaporation of solvents at room temperature. The stereochemistry of major diastereomer **4aba** (*E, E*) was confirmed by its single crystal X-ray diffraction data (**CCDC 2378712)** shown in **Figure 4.2.**

(*E*)-4-((*E*)-1-Phenyl-3-(4-methoxyphenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aca): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2c** (29.95 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aca** as a red solid;

yield = 80% (63.1 mg); mp = 114-116 °C; R_f = 0.62 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (d, *J* = 15.8 Hz, 1H), 7.98 (d, *J* = 7.7 Hz, 2H), 7.56 – 7.48 (m, 5H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 15.8 Hz, 1H), 3.82 (s, 3H), 1.46 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.0, 161.9, 159.4, 149.3, 148.1, 138.5, 136.2, 130.6, 129.2 (2C), 129.1, 129.0, 128.8, 128.4, 124.7, 122.2, 119.2, 114.5, 55.5, 16.9 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{26}H_{23}N_2O_2^+$ 395.1754, found 395.1758.

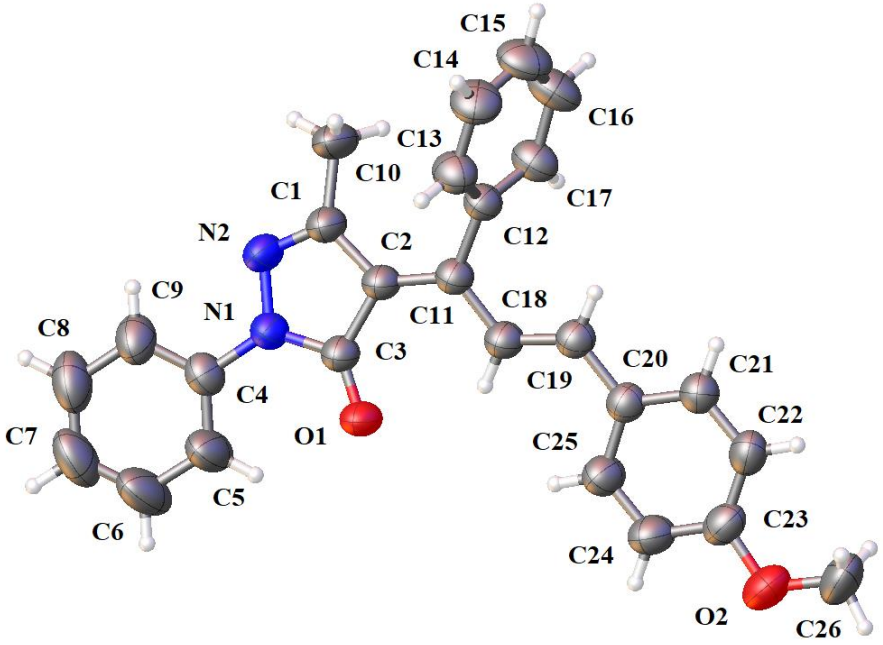


Figure 4.3. ORTEP plot of compound **4aca** with 50% ellipsoid probability.

The single crystal of **4aca** was grown in a mixture of solvents hexane/ethyl acetate (9:1) by slow evaporation of solvents at room temperature. The stereochemistry of major diastereomer **4aca** (*E, E*) was assigned by its single crystal X-ray diffraction data (**CCDC 2378711)** shown in **Figure 4.3.**

(*E*)-4-((*E*)-1-Phenyl-3-(4-thiomethylphenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4ada): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2d** (30.44 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4ada** as a red solid; yield = 77% (63.0 mg); mp = 94-96 °C; R_f = 0.75 (EtOAc/Hexane

= 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.53 – 7.46 (m, 5H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.20 – 7.16 m, 3H), 6.66 (d, *J* = 15.9 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 158.9, 149.3, 147.6, 142.6, 138.5, 136.0, 132.7, 129.3, 129.1, 129.1, 128.9, 128.5, 125.94, 125.93, 124.8, 122.9, 119.2, 16.9, 15.1 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2OS^+$ 411.1526, found 411.1533.

(*E*)-4-((*E*)-1-Phenyl-3-(4-hydroxyphenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aea): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2e** (26.86 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aea** as a red solid; yield = 75% (62.7 mg); mp = 202-204 °C; R_f = 0.30 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.05 (d, *J* = 15.8 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.58-7.54 (m, 3H), 7.47-7.40 (m, 4H), 7.37-7.34 (m, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 15.8 Hz, 1H), 1.36 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.3, 161.3, 159.9, 150.0, 138.0, 136.3, 131.1, 130.3, 129.4, 129.2, 129.0, 128.5, 128.3, 125.6, 124.2, 121.8, 120.4, 116.5, 16.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_2^+$ 381.1598, found 381.1577.

(*E*)-4-((*E*)-1-Phenyl-3-(2,5-dimethoxyphenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4afa): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2f** (36.54 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4afa** as a red solid; yield = 75% (63.5 mg); mp = 150-152 °C; R_f = 0.62 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (d, *J* = 16.0 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.54 – 7.47 (m, 3H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.33 – 7.26 (m, 3H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 16.1 Hz, 1H), 6.89 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 1.47 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 159.6, 153.9, 153.1, 149.4, 143.2, 138.5, 136.3, 129.2, 129.2, 128.9, 128.4, 127.3, 125.8, 124.8, 123.0, 119.3, 118.2, 112.7, 112.6, 56.3, 56.0, 17.0 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{27}H_{25}N_2O_3^+$ 425.1860, found 425.1851.

(*E*)-4-((*E*)-1-Phenyl-3-(4-hydroxyphenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aga): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2g** (33.46 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aga** as a red solid; yield = 74% (60.7 mg); mp = 180-182 °C; R_f = 0.32 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (d, *J* = 15.7 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.55 – 7.46 (m, 3H), 7.41 (t, *J* = 7.1 Hz, 2H), 7.31 – 7.25 (m, 2H), 7.18 (t, *J* = 6.8 Hz, 1H), 7.11 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 15.7 Hz, 1H), 6.11 (s, 1H), 3.91 (s, 3H), 1.46 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.0, 159.5, 149.4, 148.8, 148.7, 147.0, 138.5, 136.2, 131.5, 129.2, 129.1, 128.98, 128.90, 128.4, 124.8, 124.5, 124.4, 122.1, 119.4, 114.9, 109.8, 56.2, 16.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_3^+$ 411.1703, found 411.1698.

(*E*)-4-((*E*)-3-([1,1′-Biphenyl]-4-yl)-1-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aha): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2h** (40.0 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aha** as a red solid; yield = 72% (63.4 mg); mp = 125-127 °C; R_f = 0.70 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (d, *J* = 15.9 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 2H), 7.67 – 7.58 (m, 6H), 7.55 – 7.51 (m, 3H), 7.47 – 7.41 (m, 4H), 7.38 – 7.34 (m, 1H), 7.33 – 7.28 (m, 2H), 7.22 – 7.17 (m, 1H), 6.75 (d, *J* = 15.9 Hz, 1H), 1.49 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 158.7, 149.3, 147.5, 143.2, 140.1, 138.5, 136.0, 135.1, 129.35, 129.34, 129.1, 129.0, 128.9, 128.5, 128.0, 127.6, 127.1, 126.8, 124.8, 123.3, 119.2, 16.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{31}H_{25}N_2O^+$ 441.1961, found 441.1960.

(*E*)-4-((*E*)-1-Phenyl-3-(4-fluorophenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aia): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2i** (27.3 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aia** as a red solid; yield = 66% (48.1 mg); mp = 118-120 °C; R_f = 0.73 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 2H),

7.58 -7.49 (m, 5H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 8.3 Hz, 2H), 6.66 (d, *J* = 15.9 Hz, 1H), 1.48 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, CDCl3) δ 164.1 (d, J_{C-F} = 252.3 Hz), 163.9, 158.6, 149.3, 146.5, 138.4, 135.9, 132.4 (d, J_{C-F} = 3.5 Hz), 130.6 (d, J_{C-F} = 8.3 Hz), 129.3, 129.1, 128.9, 128.5, 126.6 (d, J_{C-F} = 2.3 Hz), 124.9, 123.4, 119.2, 116.2 (d, J_{C-F} = 21.9 Hz), 16.9 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -108.77 – -108.97 (m); HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}FN_2O^+$ 383.1554, found 383.1544.

(*E*)-4-((*E*)-1-Phenyl-3-(4-chlorophenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aja): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2j** (30.9 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aja** as an orange solid; yield = 67% (53.4 mg); mp = 96-98 °C; R_f = 0.72 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (d, *J* = 15.9 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 2H), 7.55 – 7.46 (m, 5H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.26 (m, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 1.48 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 163.8, 158.3, 149.3, 146.2, 138.4, 136.4, 135.8, 134.6, 129.8, 129.4, 129.3, 129.1, 128.9, 128.6, 127.3, 125.0, 123.7, 119.2, 16.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}ClN_2O^+$ 399.1259, found 399.1253.

(*E*)-4-((*E*)-1-Phenyl-3-(4-bromophenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aka): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2k** (40.7 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aka** as an orange solid; yield = 70% (62.0 mg); mp = 124-126 °C; R_f = 0.74 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (d, *J* = 15.9 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 2H), 7.52 (d, *J* = 5.8 Hz, 3H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.44 – 7.39 (m, 4H), 7.30-7.26 (m, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 1.48 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 163.8, 158.2, 149.3, 146.3, 138.3, 135.8, 135.0, 132.2, 130.0, 129.4, 129.1, 128.9, 128.6, 127.4, 125.0, 124.8, 123.8, 119.2, 16.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd

for $C_{25}H_{20}{}^{79}BrN_2O^+$ 443.0754, found 443.0752; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{25}H_{20}{}^{81}BrN_2O^+$ 445.0736, found 445.0743.

(*E*)-4-((*E*)-1-Phenyl-3-(2,6-dichlorophenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4ama): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2m** (38.5 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4ama** as a red solid; yield = 53% (45.8 mg); mp = 116-118 °C; R_f = 0.72 (EtOAc/Hexane = 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, *J* = 16.3 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.55 – 7.50 (m, 3H), 7.42 – 7.30 (m, 6H), 7.21 – 7.08 (m, 2H), 6.81 (d, *J* = 16.3 Hz, 1H), 1.52 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.4, 157.6, 149.2, 141.5, 138.3, 135.4, 135.0, 134.4, 133.5, 129.7, 129.5, 129.3, 128.89, 128.87, 128.5, 124.9, 124.8, 119.2, 17.0 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{25}H_{19}Cl_2N_2O^+$ 433.0869, found 433.0866.

(*E*)-4-((*E*)-1-Phenyl-3-(1-naphthylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4ana): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2n** (34.34 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4ana** as a deep orange solid; yield = 77% (63.8 mg); mp = 132-134 °C; R_f = 0.72 (EtOAc/Hexane = 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, *J* = 15.9 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.89 – 7.76 (m, 5H), 7.58 – 7.41 (m, 7H), 7.37 – 7.29 (m, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 15.9 Hz, 1H), 1.49 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.9, 158.8, 149.3, 148.1, 138.4, 136.0, 134.4, 133.7, 133.4, 130.6, 129.3, 129.1, 128.9, 128.8, 128.7, 128.5, 127.9, 127.5, 127.0, 126.7, 124.9, 124.2, 123.3, 119.2, 16.9 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{29}H_{23}N_2O^+$ 415.1805, found 415.1803.

(*E*)-4-((*E*)-1-Phenyl-3-((thiophen-2-yl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aoa): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2o** (24.64 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aoa** as an orange solid; yield = 79% (58.4 mg); mp = 130-132 °C; R_f = 0.64 (EtOAc/Hexane = 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, *J* = 15.6 Hz, 1H), 7.97 (d, *J* = 7.9 Hz,

2H), 7.54 – 7.49 (m, 3H), 7.45 – 7.39 (m, 3H), 7.31 – 7.26 (m, 2H), 7.18 (t, *J* = 7.2 Hz, 2H), 7.05 – 6.99 (m, 1H), 6.81 (d, *J* = 15.6 Hz, 1H), 1.46 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.8, 158.2, 149.1, 142.2, 140.1, 138.5, 135.9, 131.2, 130.0, 129.3, 129.1, 128.8, 128.56, 128.52, 126.2, 124.8, 122.7, 119.2, 16.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2OS^+$ 371.1213, found 371.1212.

(*E*)-4-((*E*)-4,4-Dimethyl-1-phenylpent-2-en-1-ylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aqa): Following the general procedure, the reaction of pyrazolone **1a** (39.64 mg, 0.2 mmol), **2q** (20.67 mg, 0.24 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aqa** as an orange solid; yield = 76% (52.0 mg); mp = 102-104 °C; R_f = 0.78 (EtOAc/Hexane = 15:85); ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 15.8 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.47-7.36 (m, 5H), 7.22-7.13 (m, 3H), 6.03 (d, *J* = 15.8 Hz, 1H), 1.44 (s, 3H), 1.09 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.0, 163.7, 159.9, 149.3, 138.4, 136.3, 129.1, 129.0, 128.7, 128.2, 124.7, 122.7, 120.2, 119.1, 35.2, 29.0, 16.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O^+$ 345.1961, found 345.1956.

(*E*)-4-((*E*)-1,3-Diphenylallylidene)-3-methyl-1-(4-methylphenyl-1*H*-pyrazol-5(4*H*)-one (4baa): Following the general procedure, the reaction of pyrazolone **1b** (37.64 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4baa** as a dark red solid; yield = 79 % (59.7 mg); R_f = 0.5 (EtOAc/Hexane = 5:95); ^1H NMR (500 MHz, $CDCl_3$) δ 9.33 (d, J = 15.9 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.57-7.56 (m, 2H), 7.53 – 7.49 (m, 3H), 7.35-7.33 (m, 3H), 7.29-7.28 (m, 2H), 7.22 (d, J = 8.3 Hz, 2H), 6.70 (d, J = 15.9 Hz, 1H), 2.36 (s, 3H), 1.47 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.6, 158.4, 149.0, 147.7, 136.0, 135.9, 134.4, 130.4, 129.3, 129.2, 129.0, 128.8, 128.6, 128.4, 126.7, 123.4, 119.1, 21.0, 16.8 ppm; HRMS (ESI-TOF): m/z $[M+Na]^+$ calcd for $C_{26}H_{22}N_2NaO^+$: 401.1624, found 401.1612.

(*E*)-4-((*E*)-1,3-Diphenylallylidene)-3-methyl-1-(4-cyanophenyl-1*H*-pyrazol-5(4*H*)-one (4caa): Following the general procedure, the reaction of pyrazolone **1c** (39.64 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3a** (26.4 mg,

0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4caa** as a red solid; yield = 81% (63.0 mg); mp = 146-148 °C; R_f = 0.69 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (d, *J* = 15.9 Hz, 1H), 8.20 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.58 – 7.50 (m, 5H), 7.39 – 7.35 (m, 3H), 7.30 – 7.25 (m, 2H), 6.75 (d, *J* = 15.9 Hz, 1H), 1.48 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.3, 160.0, 150.7, 149.2, 141.9, 135.8, 135.6, 133.1, 130.9, 129.6, 129.1, 129.0, 128.9, 128.6, 126.5, 122.6, 119.2, 118.3, 107.2, 17.0 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{26}H_{20}N_3O^+$ 390.1601, found 390.1614.

(*E*)-4-((*E*)-1,3-Dihenylallylidene)-3-methyl-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (4daa): Following the general procedure, the reaction of pyrazolone **1d** (39.64 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3a** (26.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4daa** as a red solid; yield = 41% (34.8 mg); mp = 155-157 °C; R_f = 0.76 (EtOAc/Hexane = 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, *J* = 15.9 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 7.66 – 7.63 (m, 2H), 7.48 – 7.44 (m, 3H), 7.42-7.38 (m, 3H), 7.27 – 7.22 (m, 2H), 7.17-7.14 (m, 1H), 7.10 – 7.05 (m, 5H), 7.00 – 6.97 (m, 2H), 6.89 (d, *J* = 15.9 Hz, 1H) ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{30}H_{23}N_2O^+$ 427.1805, found 427.1797.

(*E*)-3-Methyl-1-phenyl-4-((*E*)-3-phenyl-1-(2-methylphenyl)allylidene)-1*H*-pyrazol-5(4*H*)-one (4aab): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3b** (29.5 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aab** as a deep orange solid; yield = 79% (59.7 mg); mp = 82-84 °C; R_f = 0.75 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (d, *J* = 15.9 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.59 – 7.57 (m, 2H), 7.42 (t, *J* = 7.9 Hz, 3H), 7.37–7.30 (m, 5H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 2.22 (s, 3H), 1.43 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 158.6, 149.4, 147.0, 138.4, 136.1, 135.6, 135.5, 130.6, 130.5, 129.2, 128.85, 128.84, 126.0, 125.7, 124.9, 123.3, 119.2, 19.5, 16.2 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{26}H_{23}N_2O^+$ 379.1805, found 379.1810.

(*E*)-3-Methyl-1-phenyl-4-((*E*)-3-phenyl-1-(3-methylphenyl)allylidene)-1*H*-pyrazol-5(4*H*)-one (4aac): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3c** (29.5 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aac** as a deep orange solid; yield = 80% (60.4 mg); mp = 108-110 °C; R_f = 0.75 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (d, *J* = 15.9 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 2H), 7.59 – 7.57 (m, 2H), 7.43 – 7.34 (m, 7H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.10 – 7.08 (m, 2H), 6.75 (d, *J* = 15.9 Hz, 1H), 2.45 (s, 3H), 1.50 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 159.1, 149.4, 147.9, 138.4, 138.2, 136.1, 135.9, 130.5, 130.0, 129.6, 128.9, 128.8, 128.7, 128.3, 126.8, 126.2, 124.8, 123.2, 119.2, 21.5, 16.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O^+$ 379.1805, found 379.1817.

(*E*)-3-Methyl-1-phenyl-4-((*E*)-3-phenyl-1-(4-methylphenyl)allylidene)-1*H*-pyrazol-5(4*H*)-one (4aad): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3d** (29.5 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aad** as a deep orange solid; yield = 81% (61.1 mg); mp = 112-114 °C; R_f = 0.76 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.58–7.57 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.36–7.34 (m, 3H), 7.31 (d, *J* = 7.7 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 3H), 6.74 (d, *J* = 15.9 Hz, 1H), 2.48 (s, 3H), 1.52 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 159.3, 149.5, 147.9, 139.4, 138.5, 136.2, 133.0, 130.5, 129.2 (2C, one peak overlap), 129.0, 128.9, 128.8, 127.1, 124.8, 123.4, 119.2, 21.5, 17.12 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O^+$ 379.1805, found 379.1811.

(*E*)-3-Methyl-1-phenyl-4-((*E*)-3-phenyl-1-(4-methoxyphenyl)allylidene)-1*H*-pyrazol-5(4*H*)-one (4aae): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3e** (33.0 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aae** as a deep orange solid; yield = 80% (63.1 mg); mp = 119-121 °C; R_f = 0.65 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (d, *J* = 15.9 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 2H), 7.60-7.57 (m, 2H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.36-7.34 (m, 3H),

7.22 (d, *J* = 8.5 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 15.9 Hz, 1H), 3.92 (s, 3H), 1.56 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 163.9, 160.7, 159.0, 149.4, 147.9, 138.5, 136.2, 130.9, 130.5, 129.0, 128.9, 128.7, 128.2, 127.4, 124.8, 123.6, 119.2, 113.9, 55.5, 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_2^+$ 395.1754, found 395.1778.

(*E*)-3-Methyl-1-phenyl-4-((*E*)-3-phenyl-1-(4-thiomethylhenyl)allylidene)-1*H*-pyrazol-5(4*H*)-one (4aaf): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3f** (36.57 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aaf** as a deep orange solid; yield = 78% (64.0 mg); mp = 121-123 °C; R_f = 0.77 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 3.6 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.38 – 7.34 (m, 5H), 7.23 – 7.17 (m, 3H), 6.74 (d, *J* = 15.9 Hz, 1H), 2.58 (s, 3H), 1.56 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 163.8, 158.3, 149.2, 147.9, 140.8, 138.4, 136.1, 132.3, 130.6, 129.7, 129.0, 128.9, 128.8, 127.0, 125.6, 124.9, 123.5, 119.2, 17.3, 15.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2OS^+$ 411.1526, found 411.1537.

(*E*)-3-Methyl-1-phenyl-4-((*E*)-3-phenyl-1-(3-methoxyphenyl)allylidene)-1*H*-pyrazol-5(4*H*)-one (4aag): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3g** (33.0 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aag** as a deep orange solid; yield = 80% (63.1 mg); mp = 62-64 °C; R_f = 0.62 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (d, *J* = 15.9 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 2H), 7.60 – 7.56 (m, 2H), 7.42 (t, *J* = 7.3 Hz, 3H), 7.37 – 7.32(m, 3H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 6.83 (s, 1H), 6.77 (d, *J* = 15.9 Hz, 1H), 3.86 (s, 3H), 1.56 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 163.9, 159.6, 158.5, 149.3, 148.0, 138.4, 137.2, 136.1, 130.6, 129.7, 129.0, 128.9, 128.8, 126.6, 124.9, 123.2, 121.5, 119.2, 114.78, 114.74, 55.5, 16.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_2^+$ 395.1754, found 395.1750.

(*E*)-4-((*E*)-1-([1,1′-Biphenyl]-4-yl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aah): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3h** (43.16 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aah** as a deep orange solid; yield = 70% (61.6 mg); mp = 170-172 °C; R_f = 0.72 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (d, *J* = 15.9 Hz, 1H), 7.99 (d, *J* = 7.7 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 3.5 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 3H), 7.39 – 7.34 (m, 5H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 15.9 Hz, 1H), 1.57 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 158.6, 149.3, 148.0, 142.2, 140.0, 138.4, 136.1, 134.9, 130.6, 129.7, 129.1, 129.0, 128.9, 128.8, 128.1, 127.2, 127.0, 126.9, 124.9, 123.5, 119.2, 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{31}H_{25}N_2O^+$ 441.1961, found 441.1973.

(*E*)-4-((*E*)-1-(4-Fluorophenyl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aai): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3i** (30.38 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aai** as an orange solid; yield = 72% (55.0 mg); mp = 135-137 °C; R_f = 0.75 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 3.3 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.34 (m, 3H), 7.31 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 6.68 (d, *J* = 15.9 Hz, 1H), 1.52 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.7, 163.4 (d, J_{C-F} = 248.1), 157.4, 148.9, 147.9, 138.4, 135.9, 131.9 (d, J_{C-F} = 3.3 Hz), 131.1 (d, J_{C-F} = 8.2 Hz), 130.7, 129.0, 128.9, 128.8, 126.9, 124.9, 123.7, 119.2, 115.8 (d, J_{C-F} = 21.8 Hz), 17.2 ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.17 – -111.42 (m). HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}FN_2O^+$ 383.1554, found 383.1566.

(*E*)-4-((*E*)-1-(4-Chlorophenyl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aaj): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3j** (34.0 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aaj** as an orange solid; yield = 71% (56.6 mg); mp = 140-142 °C; R_f = 0.73 (EtOAc/Hexane =

15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (d, *J* = 15.9 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.63 – 7.58 (m, 2H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.41 – 7.37 (m, 3H), 7.31 – 7.26 (m, 2H), 7.22 (t, *J* = 7.0 Hz, 1H), 6.70 (d, *J* = 15.9 Hz, 1H), 1.56 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.6, 157.1, 148.8, 147.9, 138.3, 135.9, 135.6, 134.4, 130.7, 130.5, 129.0, 128.9 (2C, one overlap peak), 128.8, 126.6, 125.0, 123.6, 119.2, 17.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}ClN_2O^+$ 399.1259, found 399.1260.

(*E*)-4-((*E*)-1-(4-Bromophenyl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aak): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3k** (43.78 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aak** as an orange solid; yield = 69% (61.1 mg); mp = 143-145 °C; R_f = 0.74 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (d, *J* = 16.0 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.60 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.40 – 7.36 (m, 3H), 7.20 – 7.23 (m, 3H), 6.70 (d, *J* = 16.0 Hz, 1H), 1.56 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.7, 157.1, 148.8, 148.0, 138.3, 135.9, 134.9, 131.8, 130.8, 130.8, 129.1, 128.9, 128.8, 126.5, 125.0, 123.7, 123.5, 119.2, 17.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}{}^{79}BrN_2O^+$ 443.0754, found 443.0756; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}{}^{81}BrN_2O^+$ 445.0736, found 445.0736.

(*E*)-4-((*E*)-1-(4-Iodophenyl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aal): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3l** (54.12 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aal** as an orange solid; yield = 70% (68.6 mg); mp = 135-137 °C; R_f = 0.76 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (d, *J* = 16.0 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 2H), 7.78 (d, *J* = 7.9 Hz, 2H), 7.51 – 7.46 (m, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.29 – 7.26 (m, 3H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 2H), 6.59 (d, *J* = 16.0 Hz, 1H), 1.45 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.6, 157.1, 148.8, 147.9, 138.3, 137.7, 135.9, 135.4, 130.9, 130.7, 129.0,

128.9, 128.8, 126.4, 124.9, 123.4, 119.2, 95.4, 17.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}IN_2O^+$ 491.0615, found 491.0600.

4-((1*E*,2*E*)-1-(3-Methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)-3-phenylallyl)benzonitrile (4aam): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3m** (31.92 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aam** as an orange solid; yield = 63% (49.0 mg); mp = 195-197 °C; R_f = 0.60 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (d, *J* = 16.1 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 7.9 Hz, 2H), 7.57 – 7.54 (m, 2H), 7.47 – 7.40 (m, 4H), 7.39 – 7.34 (m, 3H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 16.1 Hz, 1H), 1.47 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.4, 155.4, 148.1, 148.0, 140.8, 138.2, 135.6, 132.3, 131.0, 130.0, 129.1, 128.9, 128.8, 125.9, 125.1, 123.5, 119.2, 118.1, 113.5, 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{20}N_3O^+$ 390.1601, found 390.1605.

(*E*)-3-Methyl-4-((*E*)-1-(4-(methylsulfonyl)phenyl)-3-phenylallylidene)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aan): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3n** (43.60 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aan** as an orange solid; yield = 47% (41.6 mg); mp = 126-128 °C; R_f = 0.21 (EtOAc/Hexane = 25:75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 16.1 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.59 – 7.53 (m, 3H), 7.46 – 7.40 (m, 3H), 7.40 – 7.35 (m, 3H), 7.22 – 7.18 (m, 2H), 6.57 (d, *J* = 16.1 Hz, 1H), 3.19 (s, 3H), 1.46 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.4, 155.4, 148.1, 141.7, 141.6, 138.2, 135.7, 131.0, 130.2, 129.1, 128.9, 128.8, 128.8, 127.7, 126.0, 125.2, 123.6, 119.2, 44.6, 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_3S^+$ 443.1424, found 443.1422.

(*E*)-4-((*E*)-1-(4-Hydroxyphenyl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aao): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3o** (29.94 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aao** as an orange solid; yield = 76% (57.8 mg); mp = 194-196 °C; R_f = 0.28 (EtOAc/Hexane =

25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (d, *J* = 15.9 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.60 – 7.55 (m, 2H), 7.42 (s, 2H), 7.36 – 7.32 (m, 3H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 15.8 Hz, 1H), 5.81 (s, 1H), 1.56 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 159.4, 157.1, 149.6, 148.2, 138.4, 136.1, 131.0, 130.6, 129.0, 128.9, 128.8, 128.2, 127.3, 125.0, 123.5, 119.4, 115.5, 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_2^+$ 381.1598, found 381.1602.

(*E*)-4-((*E*)-1-(4-(Dimethylamino)phenyl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aap): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3p** (35.9 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aao** as an orange solid; yield = 74% (60.2 mg); mp = 156-158 °C; R_f = 0.52 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (d, *J* = 15.8 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 6.2 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.38 – 7.32 (m, 3H), 7.20 – 7.15 (m, 3H), 6.88 (d, *J* = 15.8 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 2H), 3.07 (s, 6H), 1.66 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.2, 160.5, 151.5, 149.7, 147.5, 138.7, 136.4, 131.6, 130.2, 128.9, 128.8, 128.6, 128.1, 124.6, 123.5, 122.8, 119.2, 111.4, 40.3, 17.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{27}H_{26}N_3O^+$ 408.2070, found 408.2072.

(*E*)-4-((*E*)-1-(4-Hydroxy-3-methoxyphenyl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aaq): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3q** (36.5 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aaq** as an orange solid; yield = 72% (59.0 mg); mp = 126-128 °C; R_f = 0.30 (EtOAc/Hexane = 25:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (d, *J* = 15.8 Hz, 1H), 7.97 (d, *J* = 7.9 Hz, 2H), 7.62 – 7.58 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.38 – 7.34 (m, 3H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.84 – 6.76 (m, 3H), 5.89 (s, 1H), 3.92 (s, 3H), 1.60 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.0, 159.0, 149.4, 148.0, 146.8, 146.6, 138.5, 136.1, 130.5, 129.0, 128.9, 128.8, 127.9, 127.2, 124.9, 123.5, 123.0, 119.2, 114.6, 112.0, 56.3, 17.0 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_3^+$ 411.1703, found 411.1698.

(*E*)-4-((*E*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aas): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3s** (36.1 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aas** as an orange solid; yield = 77% (62.8 mg); mp = 100-102 °C; R_f = 0.61 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.62 – 7.56 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.39 – 7.32 (m, 3H), 7.18 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 15.9 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.10 (d, *J* = 8.6 Hz, 2H), 1.64 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 158.4, 149.3, 148.7, 147.9, 147.8, 138.4, 136.1, 130.6, 129.5, 129.0, 128.9, 128.8, 127.0, 124.9, 123.6, 123.4, 119.2, 109.9, 108.5, 101.7, 17.1 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_3^+$ 409.1547, found 409.1562.

(*E*)-4-((*E*)-1-(9*H*-Fluoren-3-yl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aat): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3t** (45.8 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aat** as an orange solid; yield = 76% (68.7 mg); mp = 70-72 °C; R_f = 0.76 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (d, *J* = 15.9 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 2H), 7.91 (dd, *J* = 15.5, 7.6 Hz, 2H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.58 (dd, *J* = 6.7, 2.7 Hz, 2H), 7.49 – 7.33 (m, 8H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 15.9 Hz, 1H), 4.02 (s, 2H), 1.53 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 159.38, 149.4, 148.0, 143.6, 143.3, 143.0, 140.9, 138.5, 136.2, 134.4, 130.5, 129.0, 128.9, 128.8, 128.1, 127.7, 127.2, 127.2, 126.0, 125.4, 124.8, 123.5, 120.4, 119.8, 119.2, 37.1, 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{32}H_{25}N_2O^+$ 453.1961, found 453.1950.

(*E*)-3-Methyl-1-phenyl-4-((*E*)-3-phenyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)allylidene)-1*H*-pyrazol-5(4*H*)-one (4aau): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3u** (38.3 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aau** as a reddish solid; yield = 73% (61.1 mg); mp = 112-114 °C; R_f = 0.68

(EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (d, *J* = 15.9 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 2H), 7.62 – 7.57 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.37 – 7.33 (m, 3H), 7.18 (t, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.97 – 6.94 (m, 1H), 6.80 (d, *J* = 15.9 Hz, 1H), 2.87 (s, 2H), 2.81 (s, 2H), 1.88 (s, 4H), 1.54 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.0, 159.7, 149.6, 147.9, 138.6, 138.5, 137.3, 136.3, 133.0, 130.4, 129.8, 129.1, 129.0, 128.9, 128.8, 127.1, 126.3, 124.8, 123.3, 119.3, 29.4, 29.4, 23.2, 17.2 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{29}H_{27}N_2O^{+}$ 419.2118, found 419.2125.

(*E*)-3-Methyl-4-((*E*)-1-(naphthalen-2-yl)-3-phenylallylidene)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aav): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3v** (37.4 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aav** as an orange solid; yield = 75% (62.0 mg); mp = 156-158 °C; R_f = 0.70 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (d, *J* = 15.9 Hz, 1H), 7.98 (t, *J* = 7.7 Hz, 4H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.79 (s, 1H), 7.65 – 7.58 (m, 2H), 7.56 – 7.53 (m, 2H), 7.42 (dd, *J* = 15.0, 7.5 Hz, 3H), 7.36 – 7.31 (m, 3H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 15.9 Hz, 1H), 1.43 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.9, 158.7, 149.3, 148.2, 138.4, 136.1, 133.4, 132.7, 130.6, 129.0, 128.9, 128.8, 128.6, 128.4, 128.3, 128.1, 127.3, 127.2, 126.9, 126.7, 124.9, 123.7, 119.2, 17.2 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{29}H_{23}N_2O^{+}$ 415.1805, found 415.1790.

(*E*)-3-Methyl-1-phenyl-4-((*E*)-3-phenyl-1-(thiophen-2-yl)allylidene)-1*H*-pyrazol-5(4*H*)-one (4aaw): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3w** (27.72 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aaw** as an orange solid; yield = 83% (61.3 mg); mp = 97-99 °C; R_f = 0.59 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (d, *J* = 15.8 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 2H), 7.62 – 7.58 (m, 3H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.39 – 7.34 (m, 3H), 7.22 – 7.16 (m, 2H), 7.14 (d, *J* = 2.3 Hz, 1H), 6.98 (d, *J* = 15.8 Hz, 1H), 1.71 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.4, 151.1, 149.1, 147.7, 138.4, 136.0, 135.7, 130.7, 130.3, 129.0, 128.9, 128.8, 128.6, 127.5, 127.4,

125.0, 124.9, 119.2, 16.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2OS^+$ 371.1213, found 371.1218.

(*E*)-3-Methyl-1-phenyl-4-((*E*)-3-phenyl-1-(pyridin-3-yl)allylidene)-1*H*-pyrazol-5(4*H*)-one (4aax): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3x** (26.6 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aax** as an orange solid; yield = 67% (48.9 mg); mp = 108-110 °C; R_f = 0.24 (EtOAc/Hexane = 25:75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 16.0 Hz, 1H), 8.81 (d, *J* = 3.5 Hz, 1H), 8.59 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.53 – 7.47 (m, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.39 – 7.34 (m, 3H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 1.50 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.4, 154.1, 150.6, 149.3, 148.4, 148.1, 138.2, 136.7, 135.8, 132.0, 130.9, 129.1, 128.9, 128.8, 126.6, 125.1, 124.3, 123.3, 119.3, 17.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}N_3O^+$ 366.1601, found 366.1605.

(*E*)-3-Methyl-4-((*E*)-1-(9-methyl-9*H*-carbazol-3-yl)-3-phenylallylidene)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aar): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), **3r** (26.6 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aar** as an orange solid; yield = 72% (46.0 mg); mp = 238-240 °C; R_f = 0.66 (EtOAc/Hexane = 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 15.8 Hz, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 8.06 – 8.0 (m, 3H), 7.60 – 7.38 (m, 8H), 7.37 – 7.26 (m, 4H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 15.8 Hz, 1H), 3.95 (s, 3H), 1.46 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.0, 160.5, 149.8, 148.2, 141.6, 141.5, 138.6, 136.2, 130.4, 128.9, 128.8, 128.7, 128.0, 127.3, 126.7, 126.5, 124.7, 123.8, 122.7, 122.4, 121.8, 120.6, 119.8, 119.2, 109.0, 108.4, 29.4, 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{32}H_{26}N_3O^+$ 468.2070, found 468.2057.

(*E*)-4-((*E*)-1-(1,5,5,6,8,8-Hexamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-3-phenylallylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4aay): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), racemic **3y** (56.8 mg, 0.22 mmol) and

catalyst (7.73 mg, 0.04 mmol) gave **4aay** as an orange solid; yield = 74% (74.3 mg); mp = 128-130 °C; dr = 1:1; R_f = 0.75 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ (mixture of dr = 1:1) 9.34 (d, *J* = 15.9 Hz, 0.5H), 9.31 (d, *J* = 15.9 Hz, 0.5H), 7.97 (2d, *J* = 7.8 Hz, 2H), 7.62 – 7.58 (m, 2H), 7.41 (2t, *J* = 7.8 Hz, 2H), 7.36-7.33 (m, 3H), 7.25 (2s, 1H), 7.18 (2t, *J* = 7.3 Hz, 1H), 7.00 (s, 0.5H), 6.99 (s, 0.5H), 6.77 (d, *J* = 15.9 Hz, 0.5H), 6.70 (s, *J* = 15.9 Hz, 0.5H), 2.13 (s, 3H), 1.97 – 1.89 (m, 1H), 1.71 – 1.61 (m, 2H), 1.41 (2s, 3H), 1.36 (2s, 3H), 1.27 (2s, 3H), 1.25 (2s, 3H), 1.17 (s, 1.5 H), 1.10 (s, 1.5 H), 1.04 (2s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ (dr = 1:1) 163.99 (163.98)*, 159.84 (159.82), 149.8, 147.33 (147.30), 147.2(147.0) 142.6 (142.5), 138.5, 136.4 (136.3), 132.6 (132.5), 132.3 (132.2), 130.4, 129.0, 128.9, 128.8, 128.6, 127.0 (126.9), 126.1, 124.8, 123.5 (123.4), 119.2, 43.7 (43.6), 37.8, 34.73(34.70), 34.3 (34.2), 32.6 (32.5), 32.3 (32.1), 29.2 (28.5), 25.4 (25.1), 19.4 (19.37), 17.0, 16.0 (15.9) ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{35}H_{39}N_2O^+$ 503.3057, found 503.3029.

*In parentheses indicate the peaks of another isomer.

13,14-Dimethyl-10-((1*E*, 2*E*)-1-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)-3-phenylallyl)-7,8,13*b*,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5(13*H*)-one (4aaz): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2a** (23.55 mg, 0.22 mmol), racemic **3z** (79.0 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4aaz** as an orange solid; yield = 70% (84.5 mg); mp = 134-136 °C; dr = 1:1, R_f = 0.44 (EtOAc/Hexane = 25:75); ^{1}H NMR (400 MHz, $CDCl_3$) δ (dr = 1:1) 9.30 (d, *J* = 15.8 Hz, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 8.03 – 7.98 (m, 2H), 7.60-7.47 (m, 5H), 7.44 –7.40 (m, 3H), 7.33 (br s, 3H), 7.27 – 7.16 (m, 3H), 6.83 (d, *J* = 15.8 Hz, 0.5H), 6.74 (d, *J* = 15.8 Hz, 0.5H), 6.02 (s, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 3.96 (s, 3H), 3.25 (t, *J* = 11.9 Hz, 1H), 3.04 – 2.89 (m, 2H), 2.53 (s, 1.5H), 2.51 (s, 1.5H), 1.50 (s, 1.5H), 1.45 (s, 1.5H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.8, 164.0, 160.6, 150.8, 149.7, 148.1, 138.6, 138.3, 136.33(136.30), 133.2, 131.6, 130.4, 129.1, 129.0, 128.9, 128.7, 128.0, 127.4, 125.4(125.3), 124.8, 124.4, 124.31 (124.27), 124.0, 123.8 (123.7), 123.1, 120.5 (120.4), 119.3, 113.6 (113.5),

109.3, 68.2, 39.5, 36.84 (36.78), 30.4, 20.44(20.41), 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{39}H_{34}N_5O_2^+$ 604.2707, found 604.2698.

*In parentheses indicate the ^{13}C peaks of another isomer.

(*E*)-4-((*E*)-1-(4-Bromophenyl)-3-(*p*-methylphenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4abk): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2b** (26.4 mg, 0.22 mmol), **3k** (43.78 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4abk** as an orange solid; yield = 70% (64.0 mg); mp = 125-127 °C; R_f = 0.72 (EtOAc/Hexane = 15:85); ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.22 – 7.15 (m, 5H), 6.65 (d, *J* = 15.9 Hz, 1H), 2.36 (s, 3H), 1.53 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.7, 157.4, 148.8, 148.3, 141.5, 138.4, 135.0, 133.3, 131.8, 130.8, 129.8, 128.9, 125.5, 124.9, 123.6, 123.0, 119.2, 21.7, 17.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}{}^{79}BrN_2O^+$ 457.0910, found 457.0916; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}{}^{81}BrN_2O^+$ 459.0893, found 459.0895.

(*E*)-4-((*E*)-1-(4-Bromophenyl)-3-(4-methoxyphenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4ack): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2c** (29.95 mg, 0.22 mmol), **3k** (43.78 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4ack** as an orange solid; yield = 73% (69.1 mg); mp = 130-132 °C; R_f = 0.70 (EtOAc/Hexane = 15:85); ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.20 – 7.14 (m, 3H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 15.9 Hz, 1H), 3.83 (s, 3H), 1.51 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.8, 162.0, 157.6, 148.8, 148.0, 138.4, 135.1, 131.7, 130.8, 130.7, 128.9, 128.8, 124.8, 124.3, 123.5, 122.3, 119.2, 114.6, 55.5, 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}{}^{79}BrN_2O_2^+$ 473.0859, found 473.0881; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}{}^{81}BrN_2O_2^+$ 475.0842, found 475.0866.

(*E*)-4-((*E*)-1-(4-Bromophenyl)-3-(4-chlorophenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4ajk): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2j** (30.9 mg, 0.22 mmol), **3k** (43.78 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4ajk** as an orange solid; yield = 60% (57.3 mg); mp = 124-126 °C; R_f = 0.74 (EtOAc/Hexane = 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 16.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.21 – 7.15 (m, 3H), 6.59 (d, *J* = 16.0 Hz, 1H), 1.52 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.6, 156.5, 148.8, 146.1, 138.2, 136.6, 134.6, 134.4, 131.9, 130.7, 129.8, 129.3, 128.9, 126.9, 125.0, 123.8, 123.8, 119.2, 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}{}^{79}BrClN_2O^+$ 477.0364, found 477.0349; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}{}^{81}BrClN_2O^+$ 479.0344, found 479.0332.

(*E*)-4-((*E*)-1,3-Bis(4-bromophenyl)allylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (4akk): Following the general procedure, the reaction of pyrazolone **1a** (34.84 mg, 0.2 mmol), **2k** (40.7 mg, 0.22 mmol), **3k** (43.78 mg, 0.22 mmol) and catalyst (7.73 mg, 0.04 mmol) gave **4akk** as an orange solid; yield = 64% (66.8 mg); mp = 132-134 °C; R_f = 0.71 (EtOAc/Hexane = 15:85); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (d, *J* = 15.9 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.44 – 7.39 (m, 4H), 7.21 – 7.15 (m, 3H), 6.58 (d, *J* = 16.0 Hz, 1H), 1.53 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.6, 156.5, 148.8, 146.2, 138.2, 134.8, 134.6, 132.3, 131.9, 130.7, 130.0, 128.9, 127.0, 125.1, 123.8, 119.2, 17.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}{}^{79}Br_2N_2O^+$ 520.9859, found 520.9866; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}{}^{79}Br\,{}^{81}BrN_2O^+$ 522.9840, found 522.9829; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}\,{}^{81}Br_2N_2O^+$ 524.9812, found 524.9757.

4.7 Copies of ^{1}H and ^{13}C NMR of the described compounds:

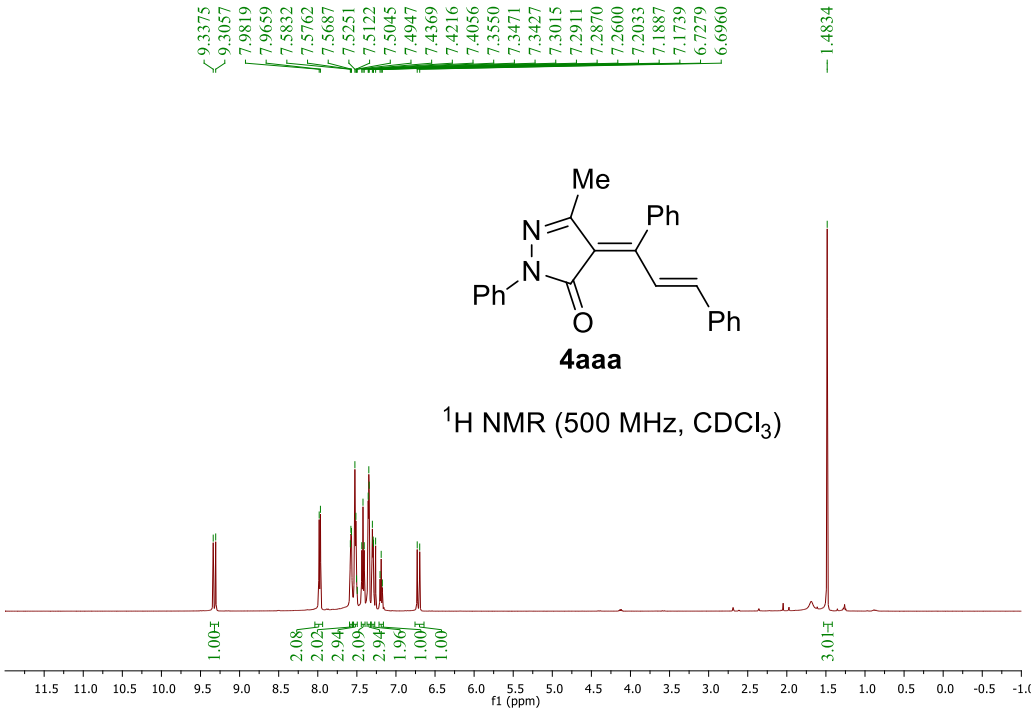


Figure 4.4 500 MHz ^{1}H Spectrum of **4aaa** in $CDCl_3$

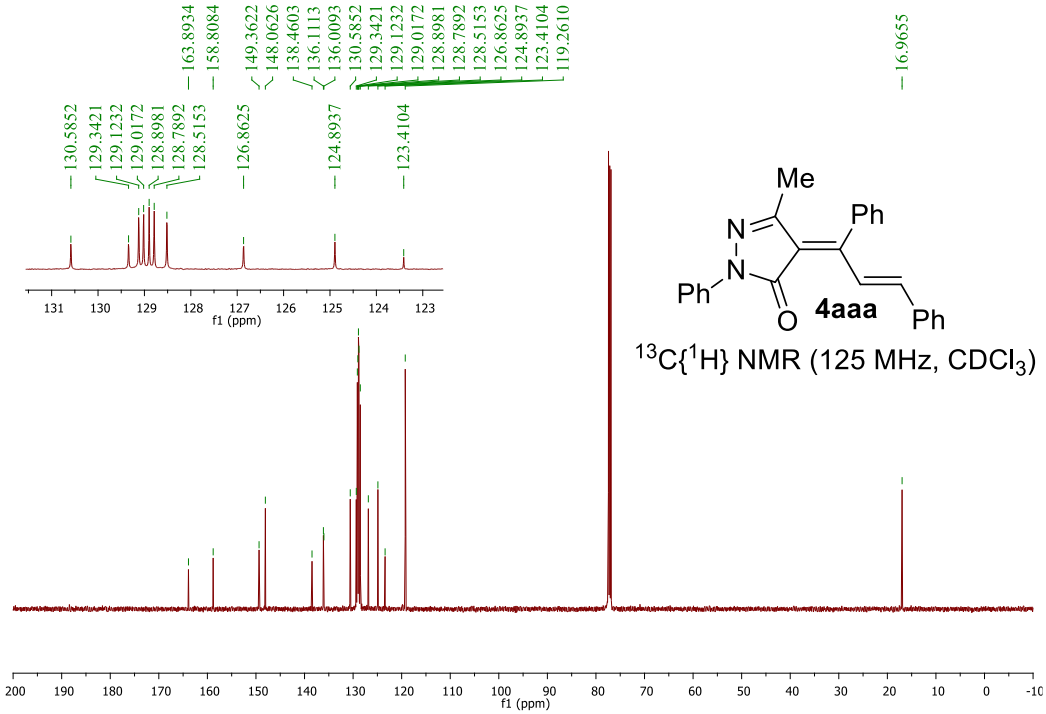


Figure 4.5 125 MHz ^{13}C Spectrum of **4aaa** in $CDCl_3$

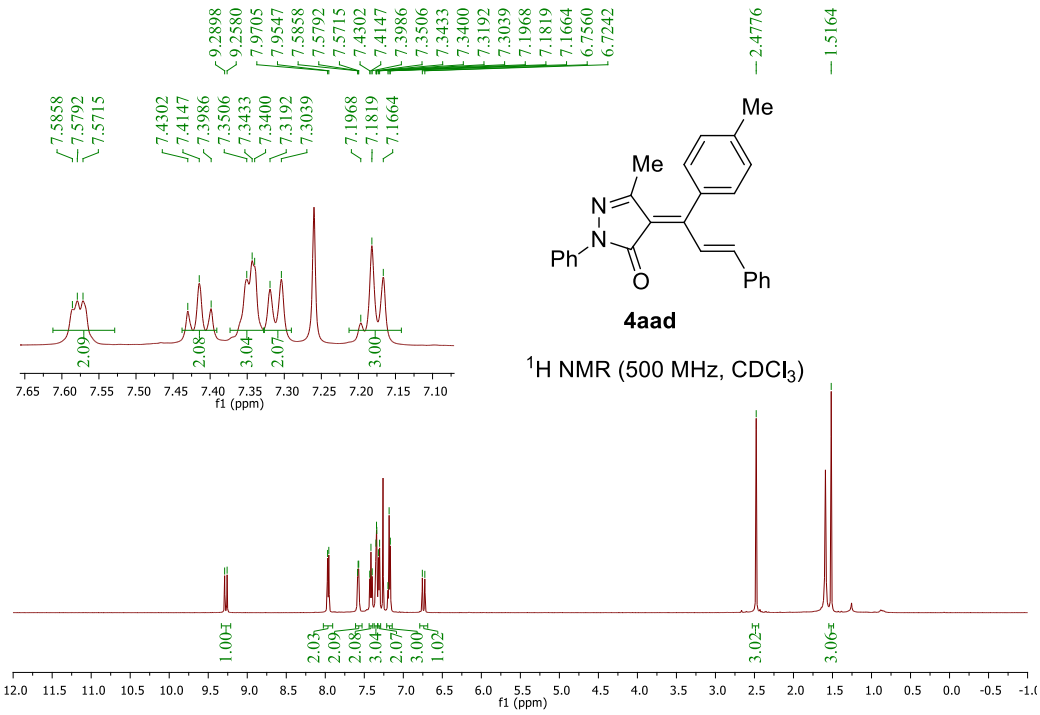


Figure 4.6 500 MHz ^{1}H Spectrum of **4aad** in $CDCl_3$

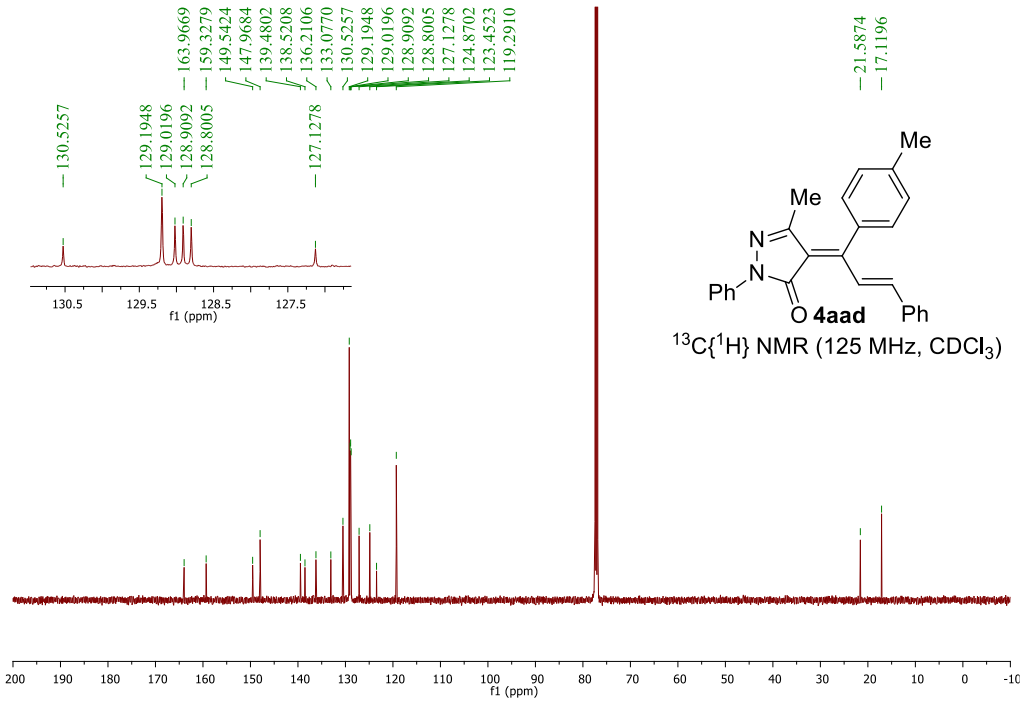


Figure 4.7 125 MHz ^{13}C Spectrum of **4aad** in $CDCl_3$

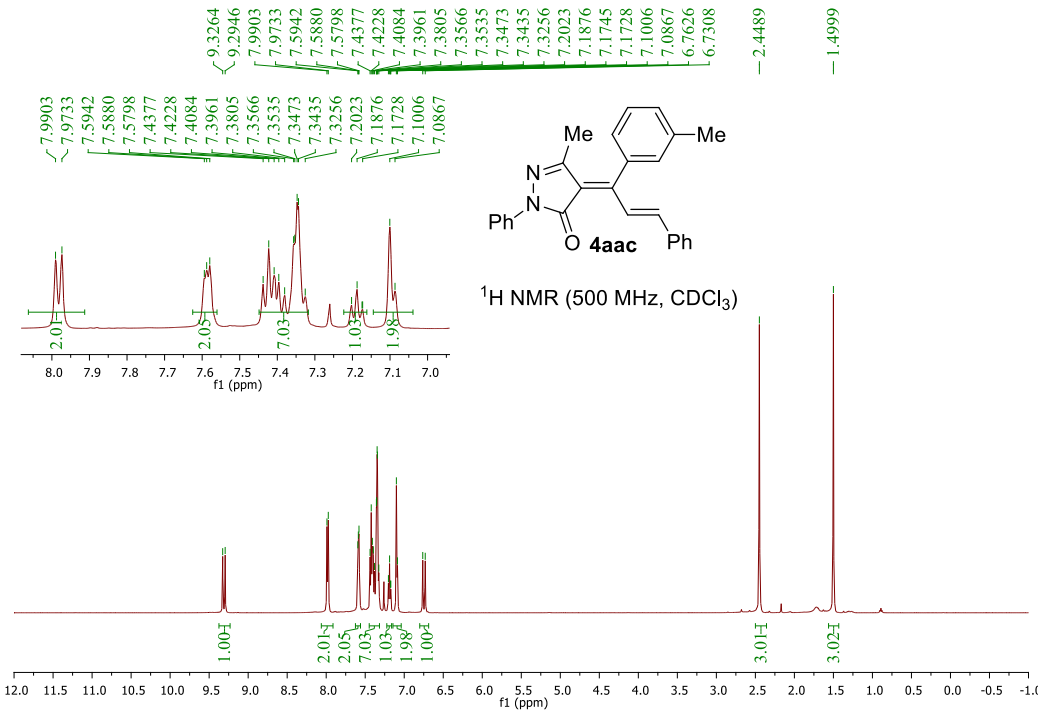


Figure 4.8 500 MHz ^{1}H Spectrum of **4aac** in $CDCl_3$

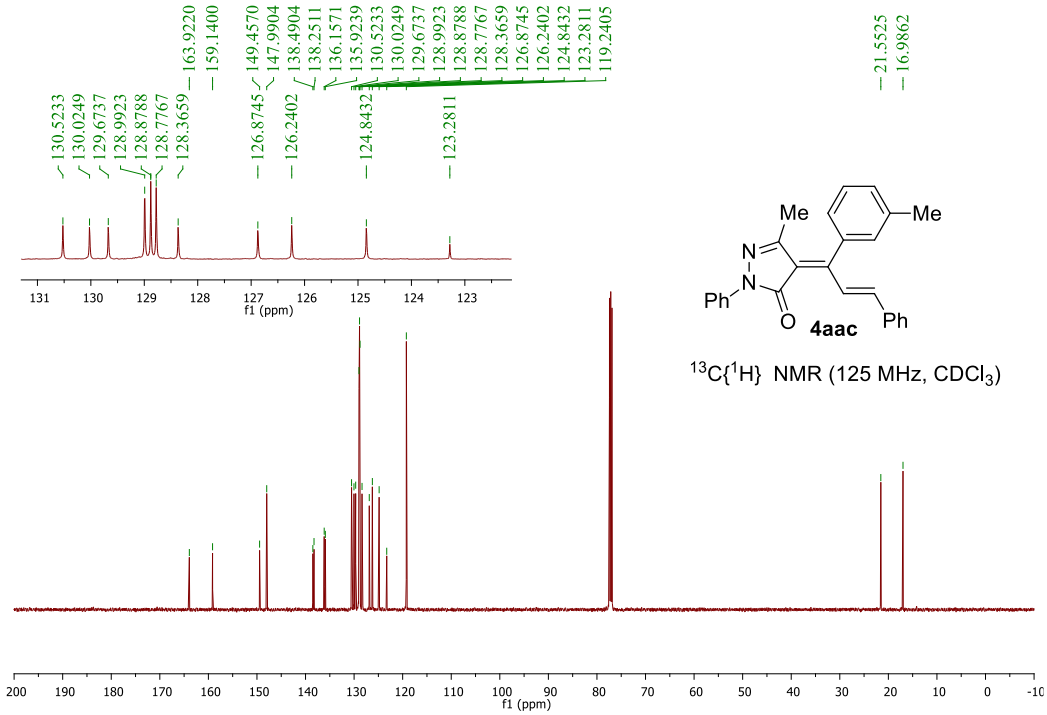


Figure 4.9 125 MHz ^{13}C Spectrum of **4aac** in $CDCl_3$

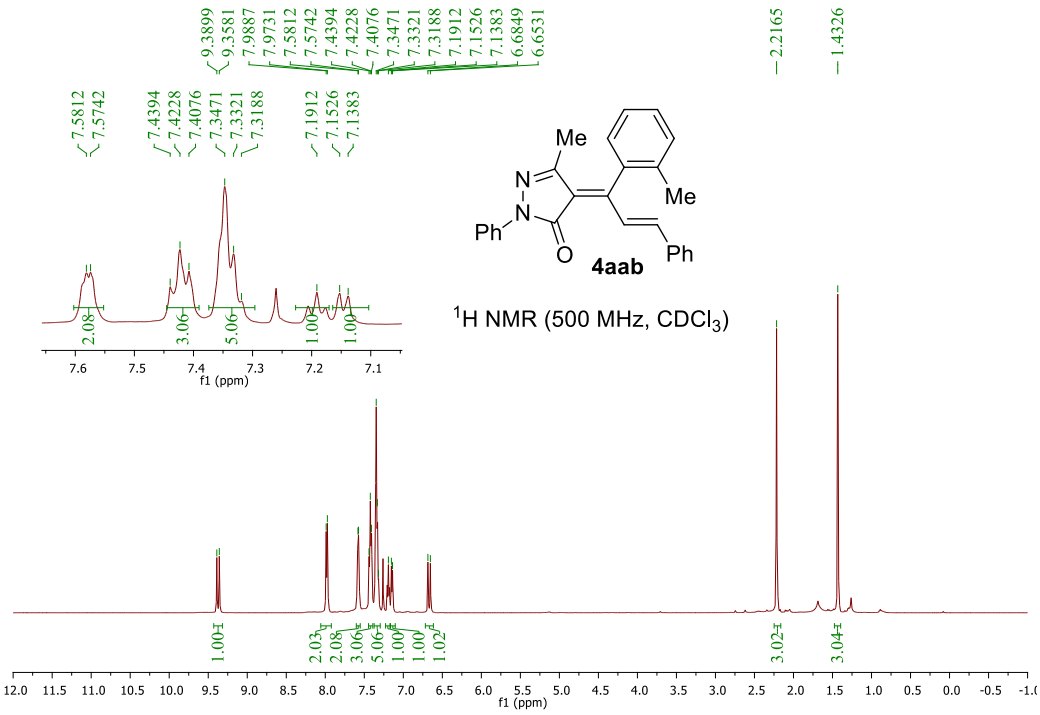


Figure 4.10 500 MHz ^{1}H Spectrum of **4aab** in $CDCl_3$

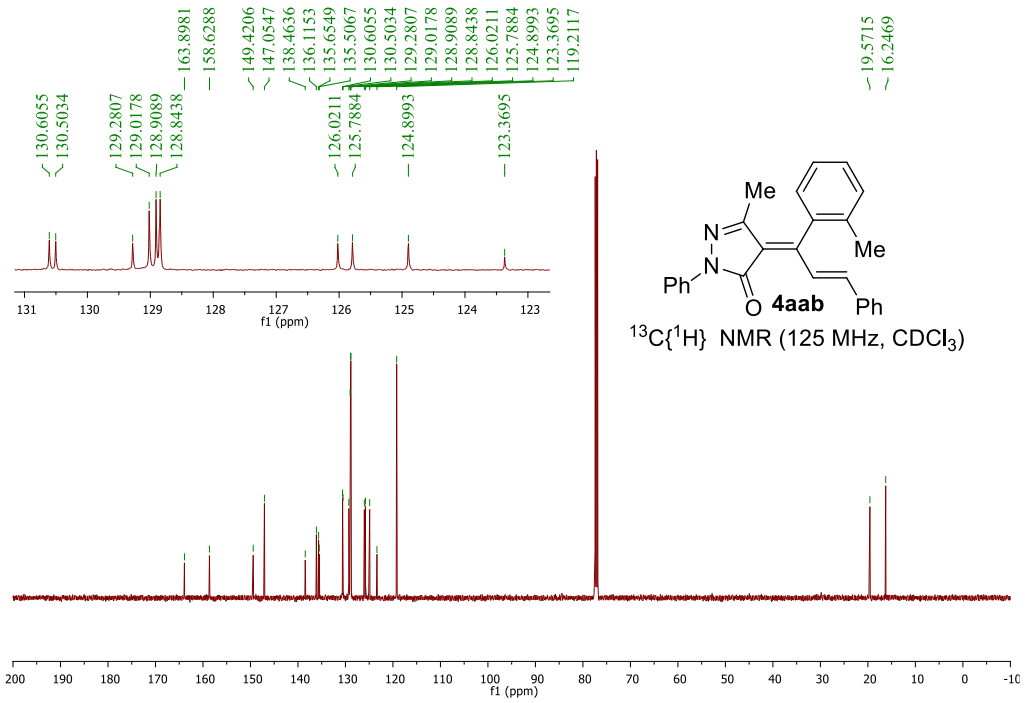


Figure 4.11 125 MHz ^{13}C Spectrum of **4aab** in $CDCl_3$

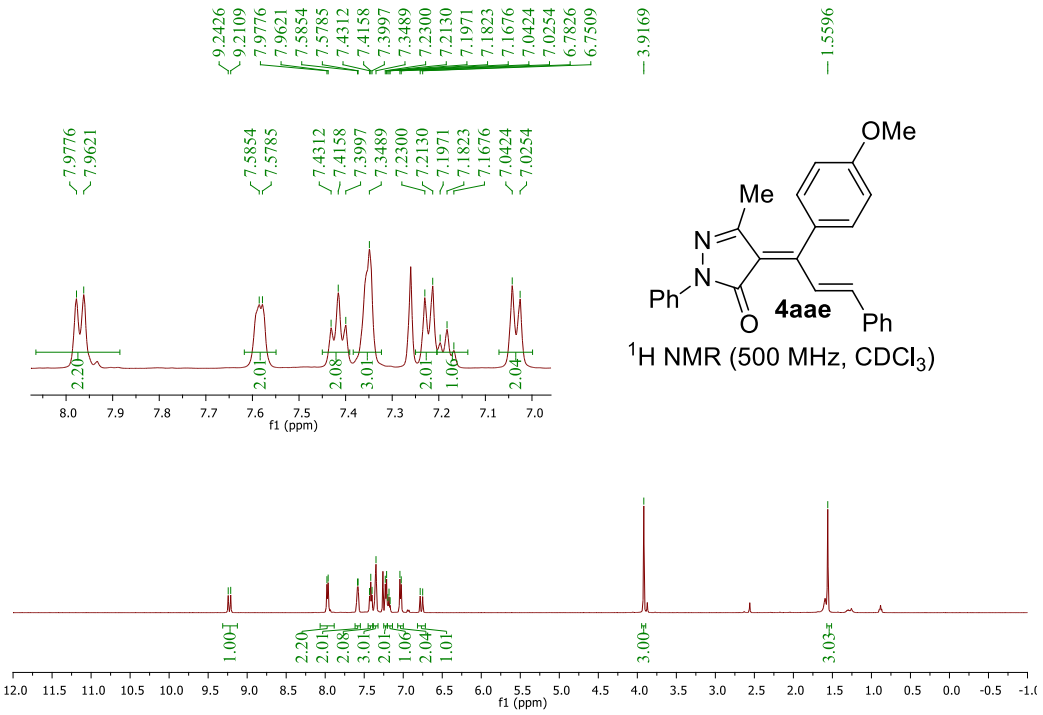


Figure 4.12 500 MHz ^{1}H Spectrum of **4aae** in $CDCl_3$

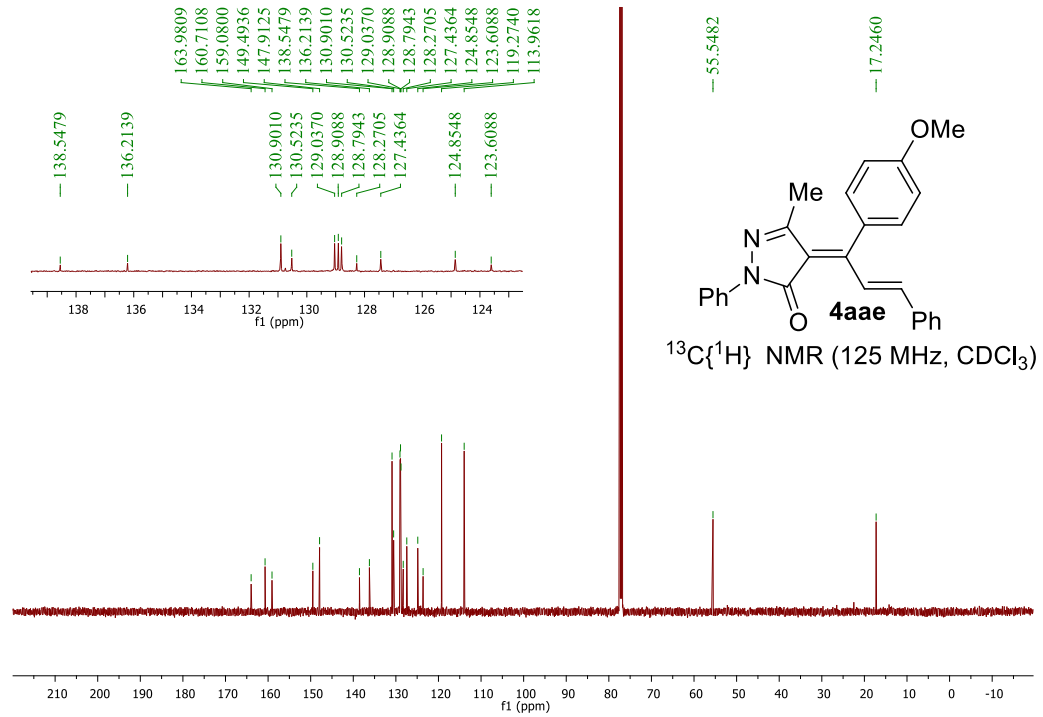


Figure 4.13 125 MHz ^{13}C Spectrum of **4aae** in $CDCl_3$

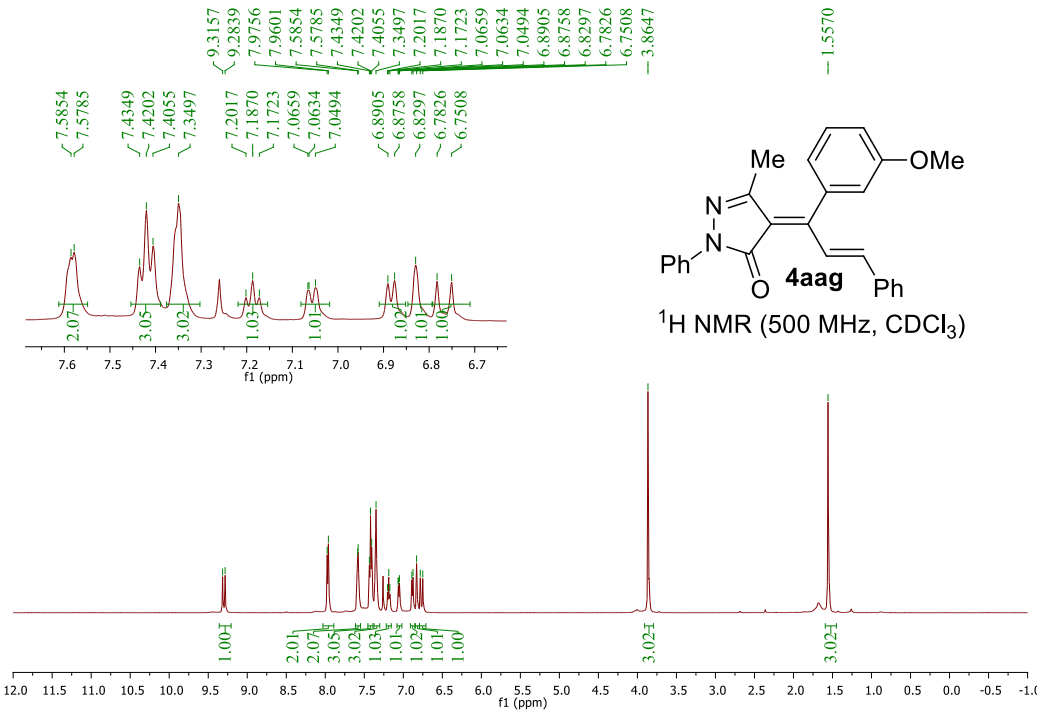


Figure 4.14 500 MHz ^{1}H Spectrum of **4aag** in $CDCl_3$

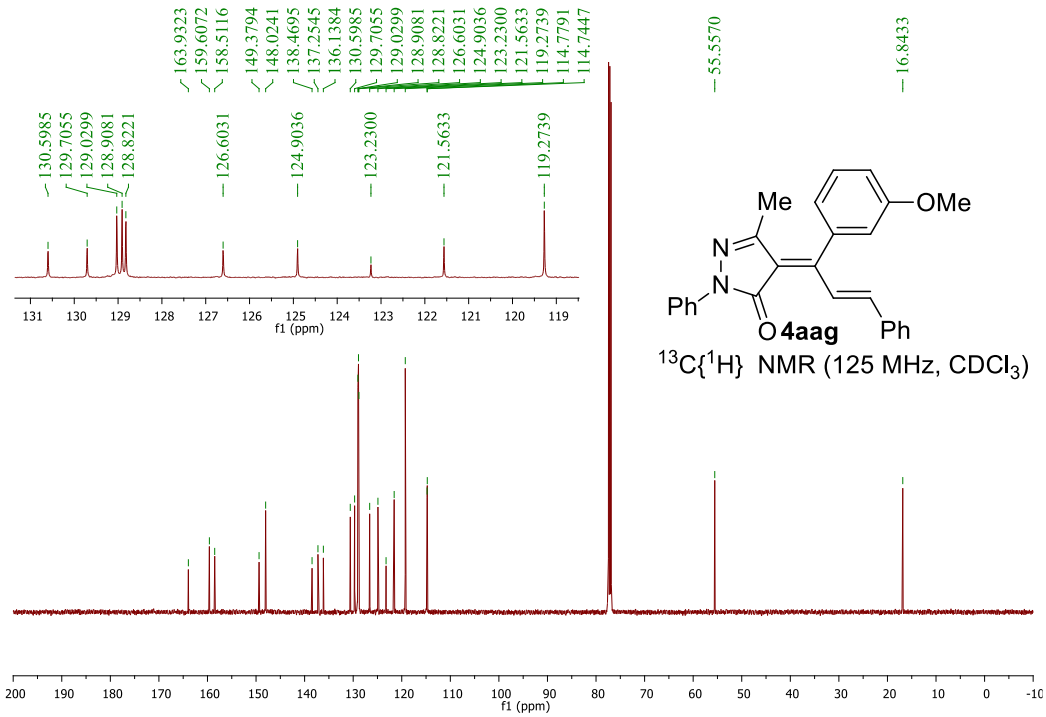


Figure 4.15 125 MHz ^{13}C Spectrum of **4aag** in $CDCl_3$

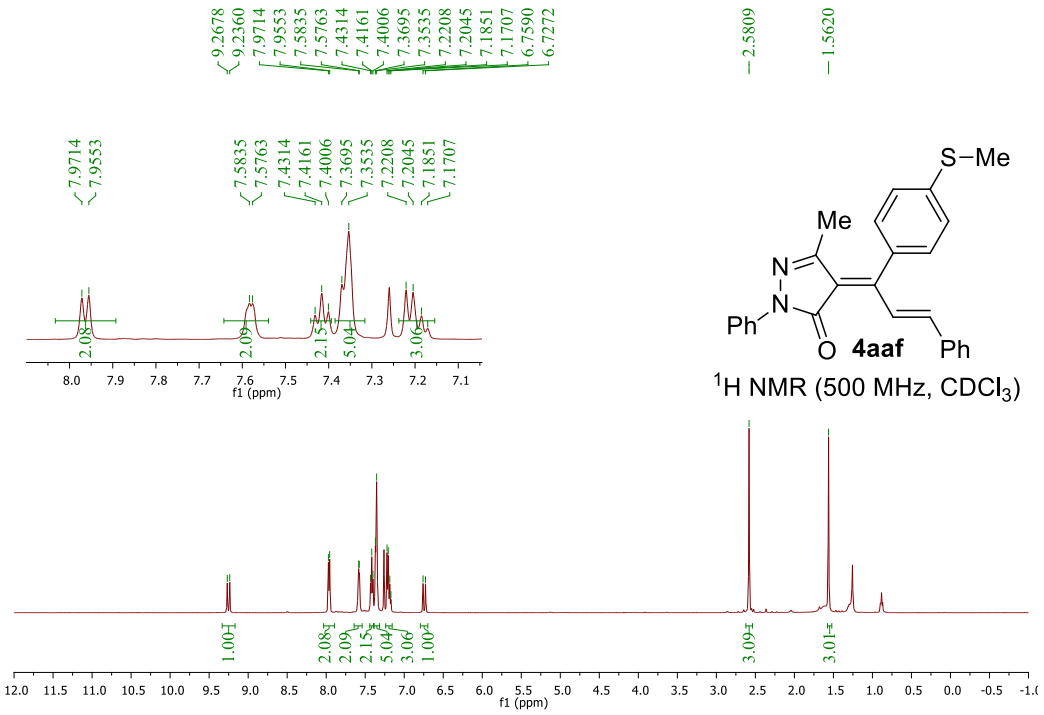


Figure 4.16 500 MHz ^{1}H Spectrum of **4aaf** in $CDCl_3$

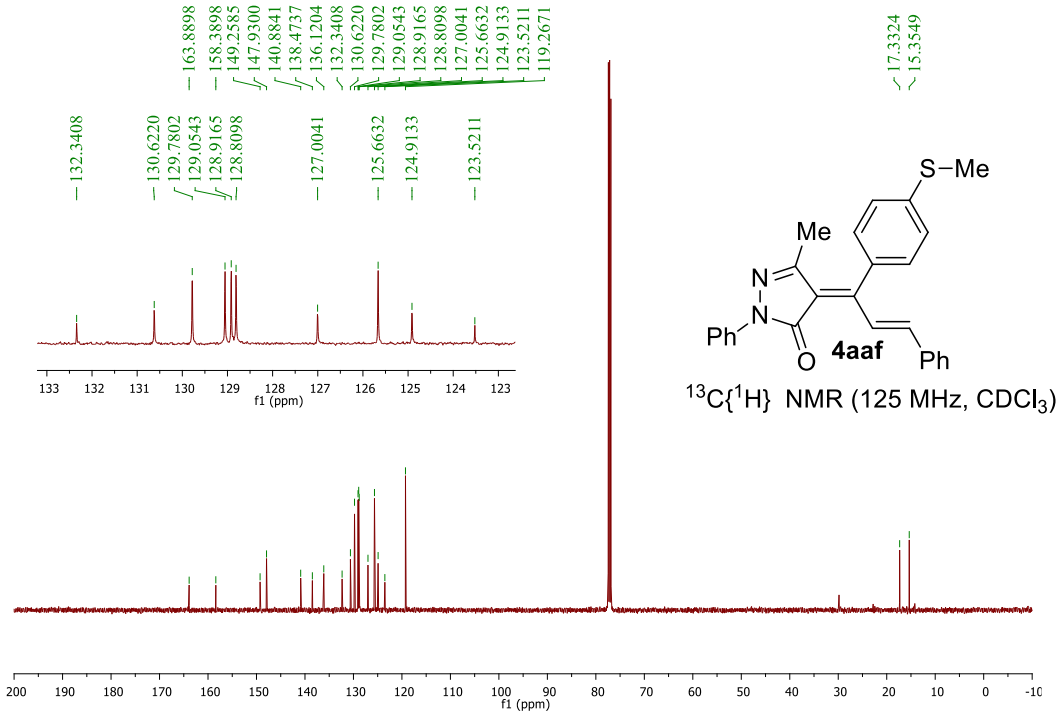


Figure 4.17 125 MHz ^{13}C Spectrum of **4aaf** in $CDCl_3$

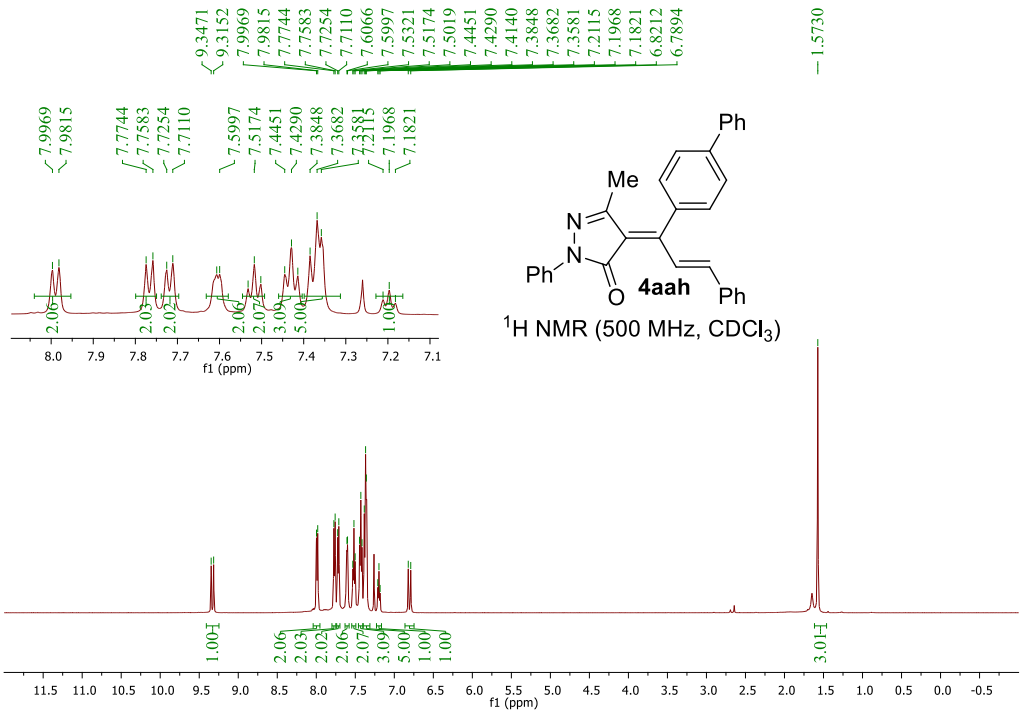


Figure 4.18 500 MHz ^{1}H Spectrum of **4aah** in $CDCl_3$

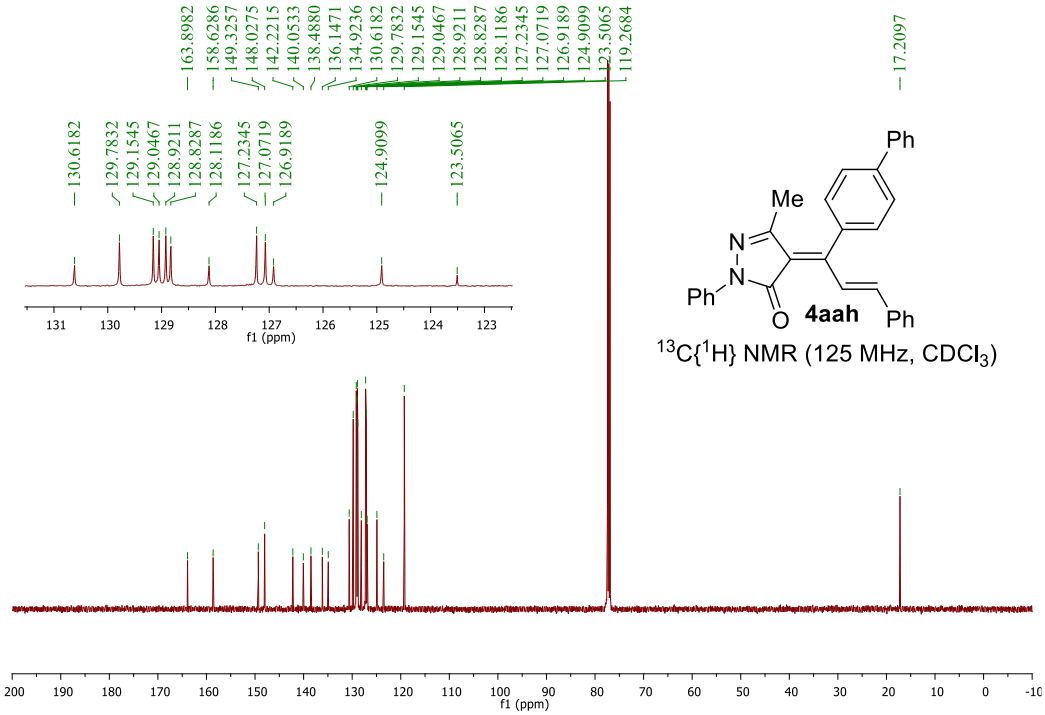


Figure 4.19 125 MHz ^{13}C Spectrum of **4aah** in $CDCl_3$

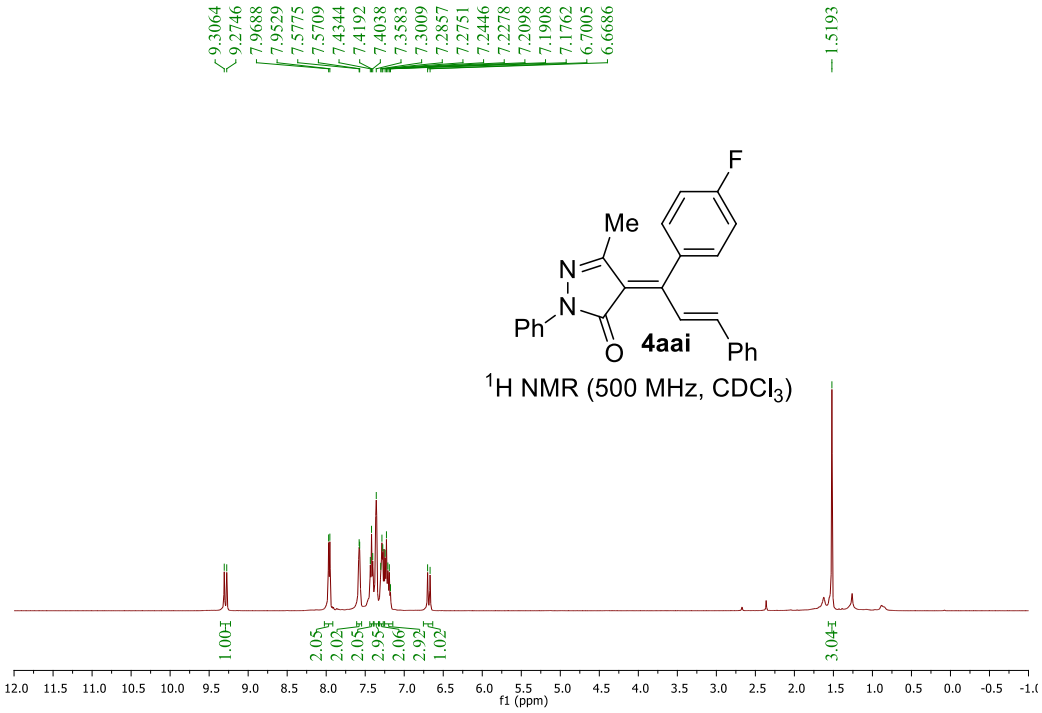


Figure 4.20 500 MHz ^{1}H Spectrum of **4aai** in $CDCl_3$

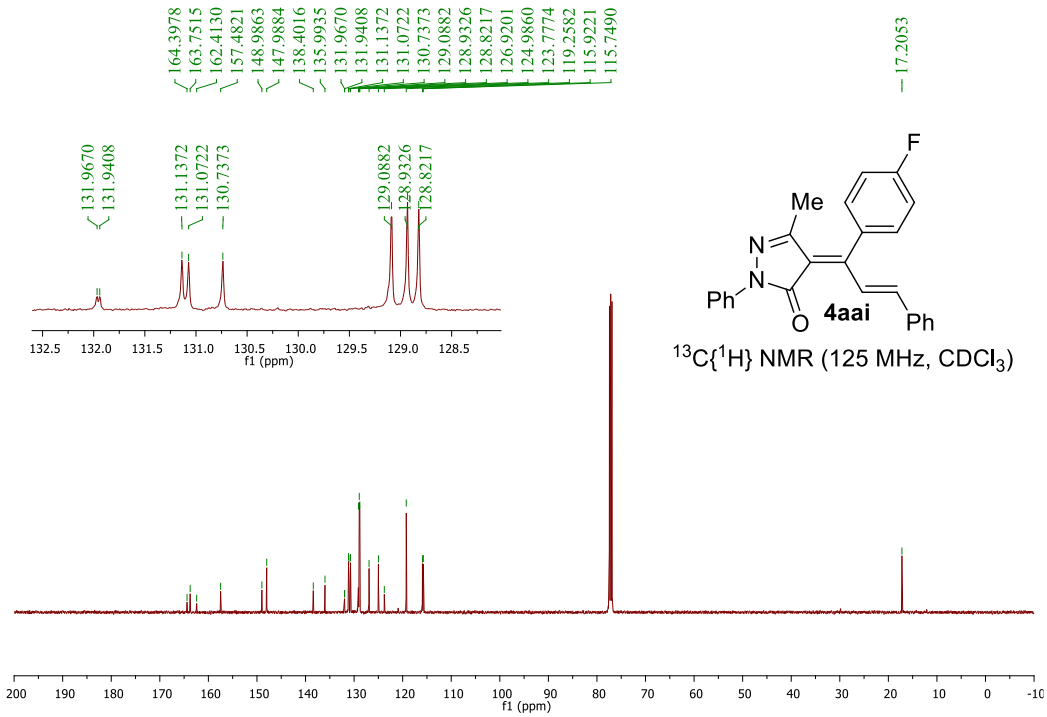


Figure 4.21 125 MHz ^{13}C Spectrum of **4aai** in $CDCl_3$

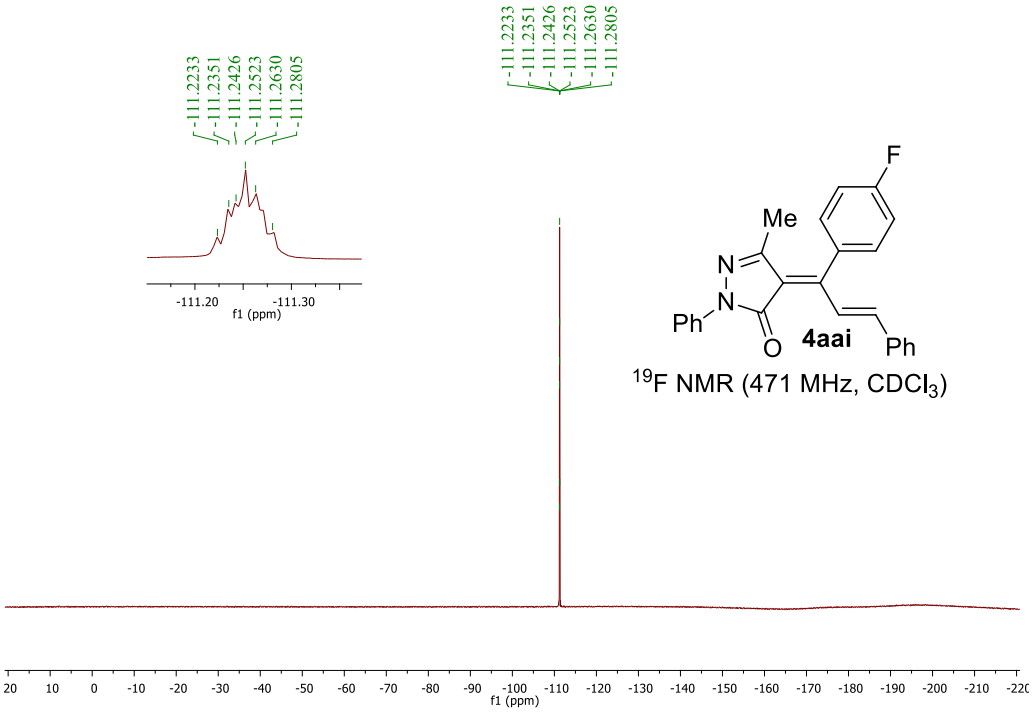


Figure 4.22 471 MHz ^{19}F NMR of **4aai** in $CDCl_3$

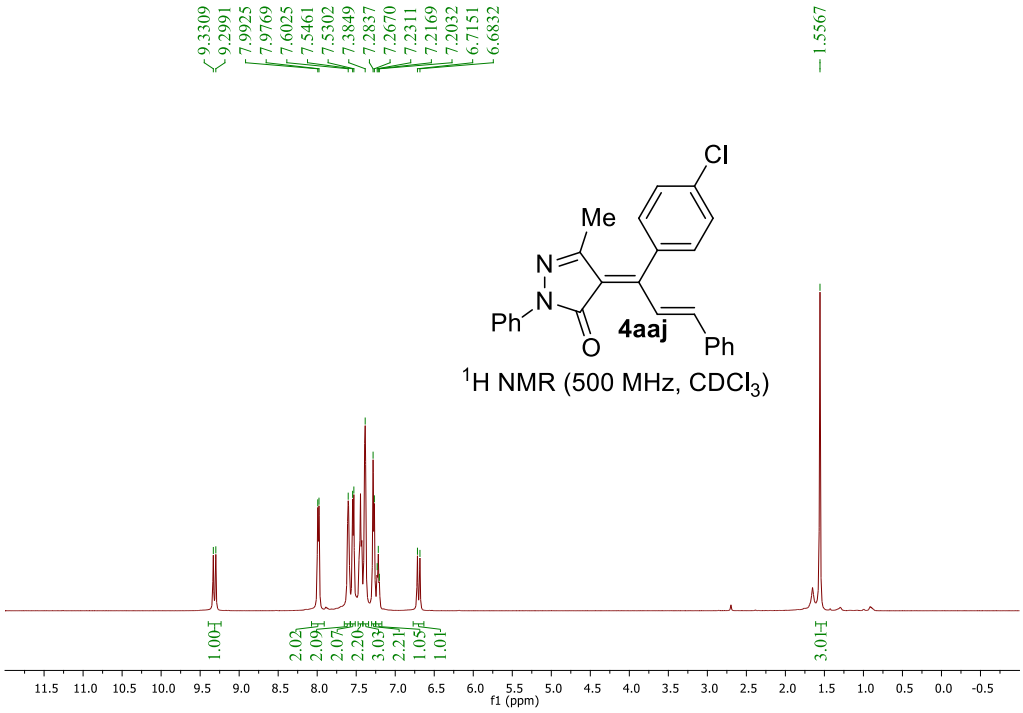


Figure 4.23 500 MHz ^{1}H Spectrum of **4aaj** in $CDCl_3$

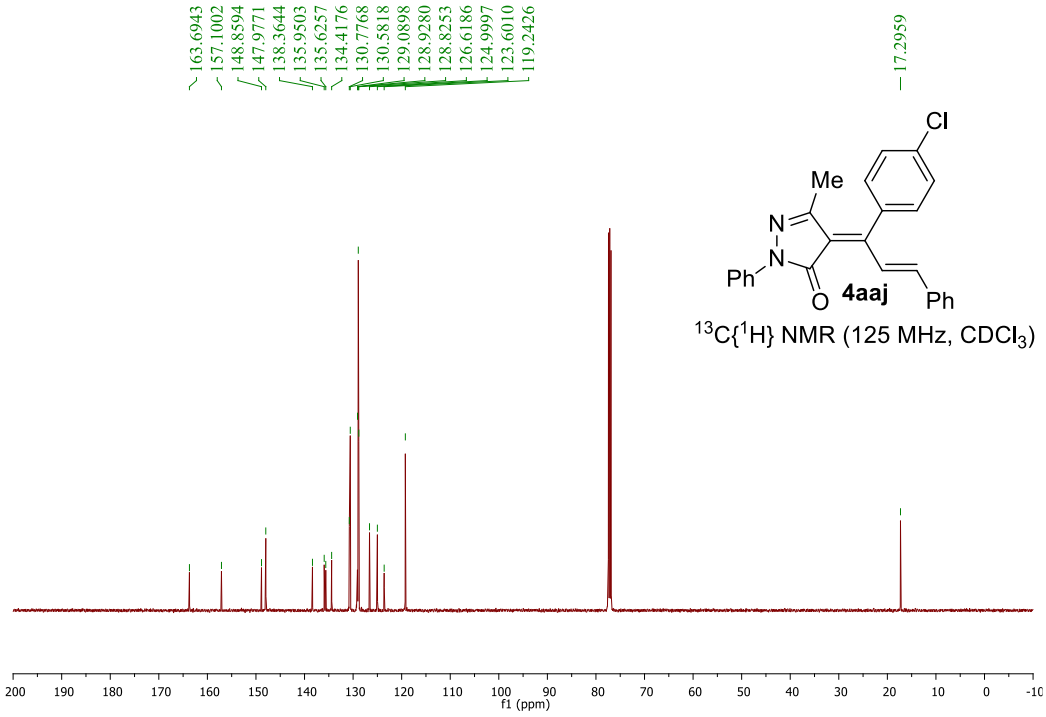


Figure 4.24 125 MHz ^{13}C Spectrum of **4aaj** in $CDCl_3$

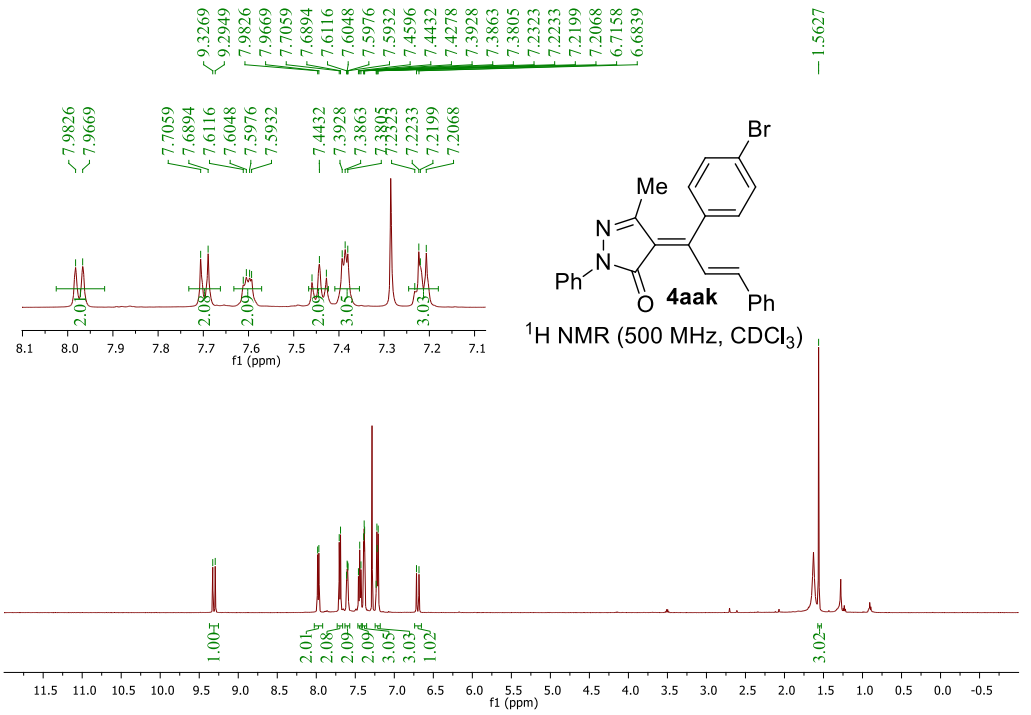


Figure 4.25 500 MHz ^{1}H Spectrum of **4aak** in $CDCl_3$

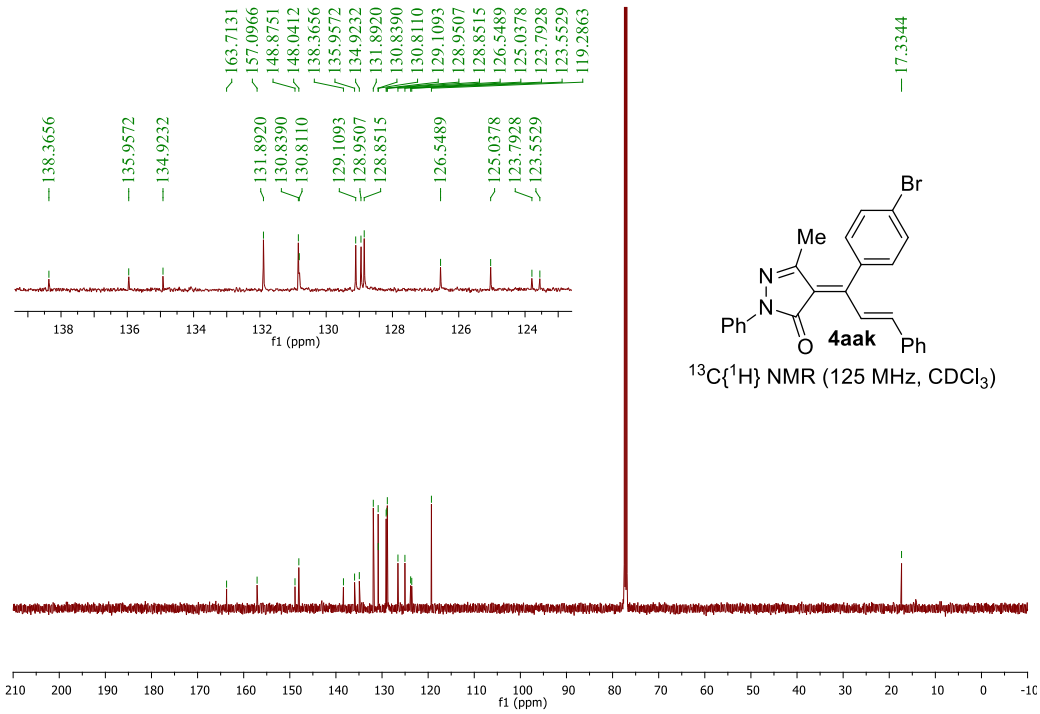


Figure 4.26 125 MHz ^{13}C Spectrum of **4aak** in $CDCl_3$

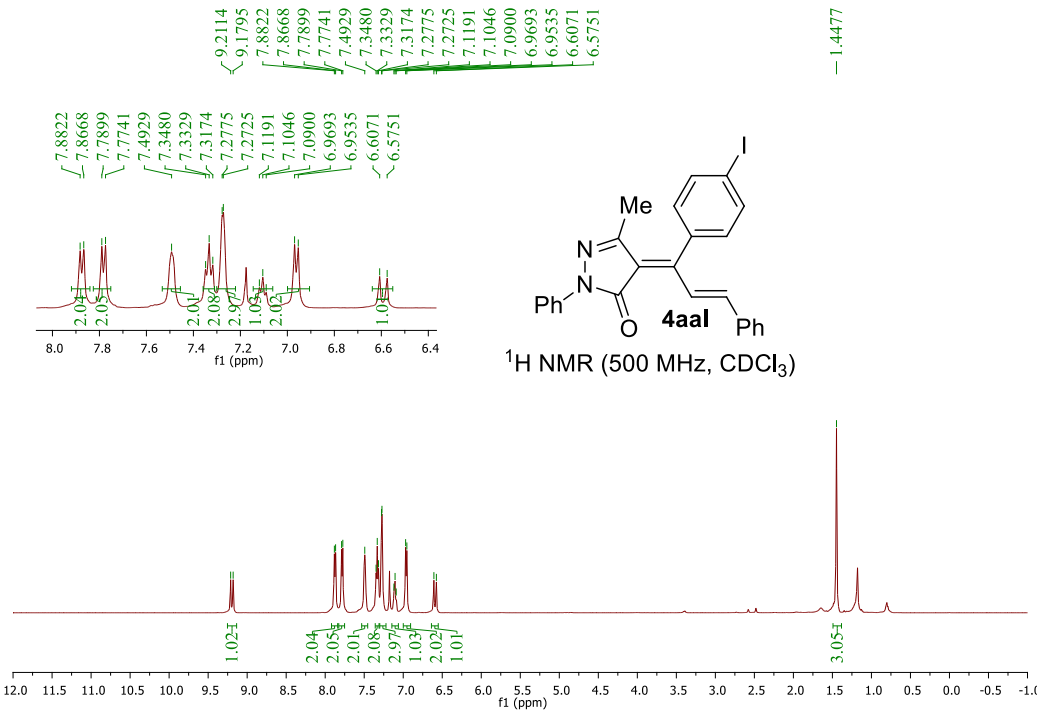


Figure 4.27 500 MHz ^{1}H Spectrum of **4aal** in $CDCl_3$

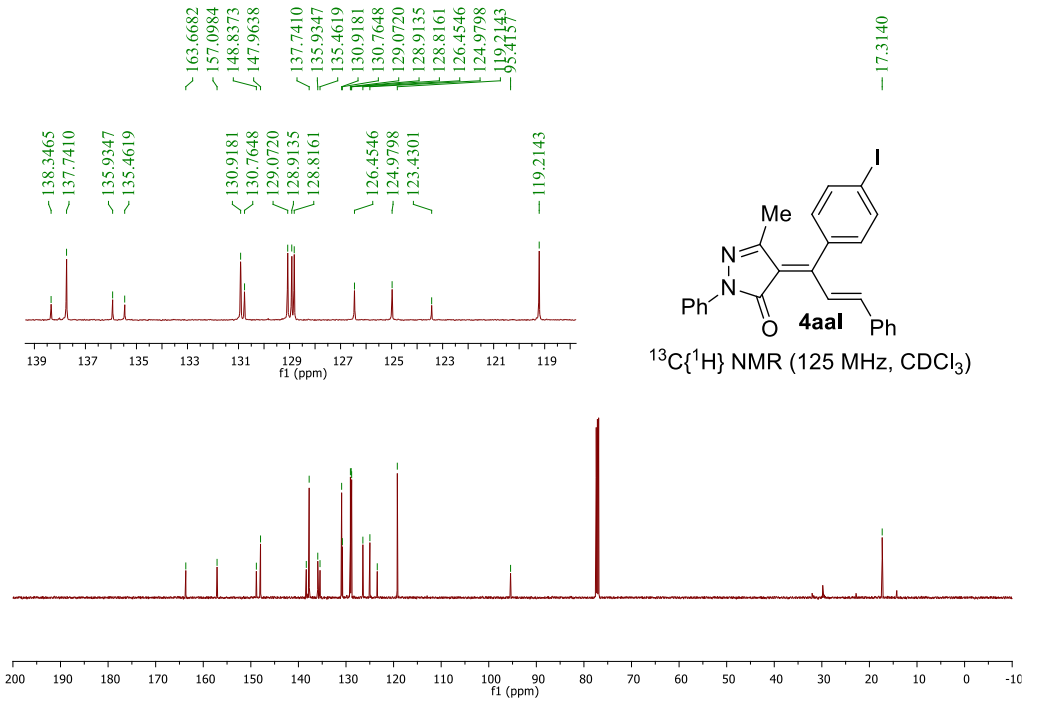


Figure 4.28 125 MHz ^{13}C Spectrum of **4aal** in $CDCl_3$

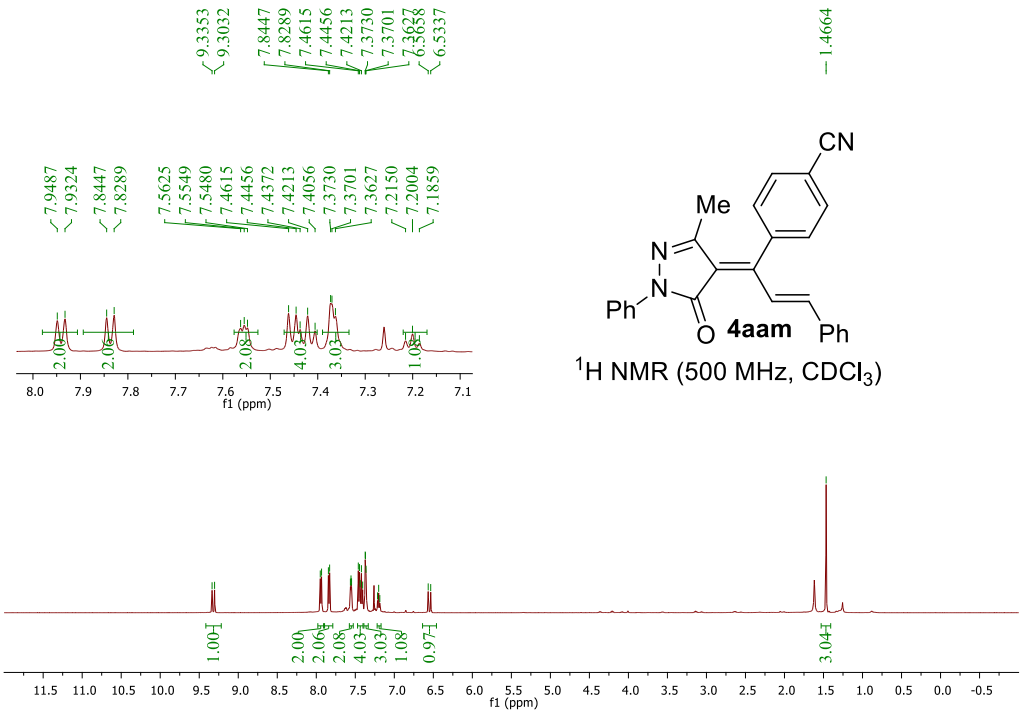


Figure 4.29 500 MHz ^{1}H Spectrum of **4aam** in $CDCl_3$

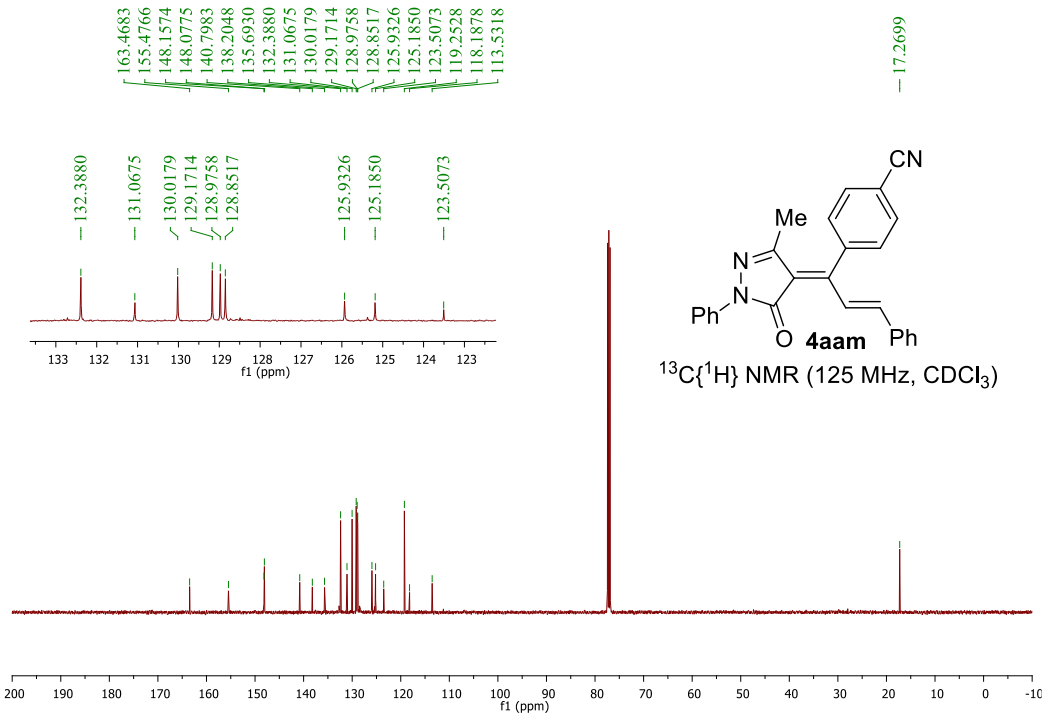


Figure 4.30 125 MHz ^{13}C Spectrum of **4aam** in $CDCl_3$

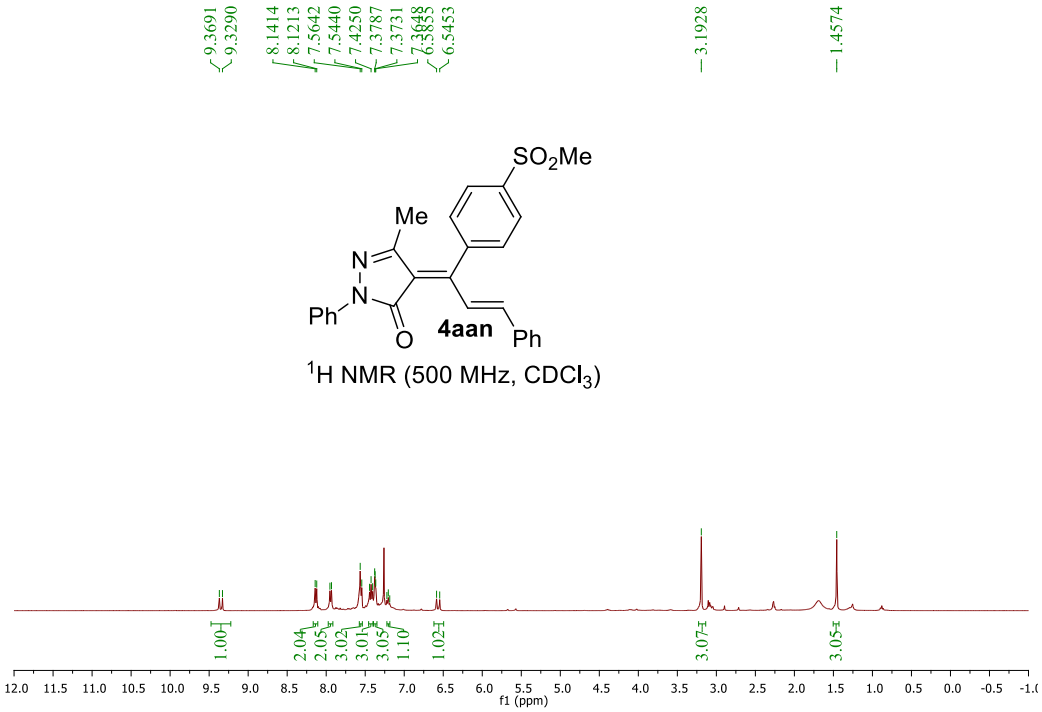


Figure 4.31 500 MHz ^{1}H Spectrum of **4aan** in $CDCl_3$

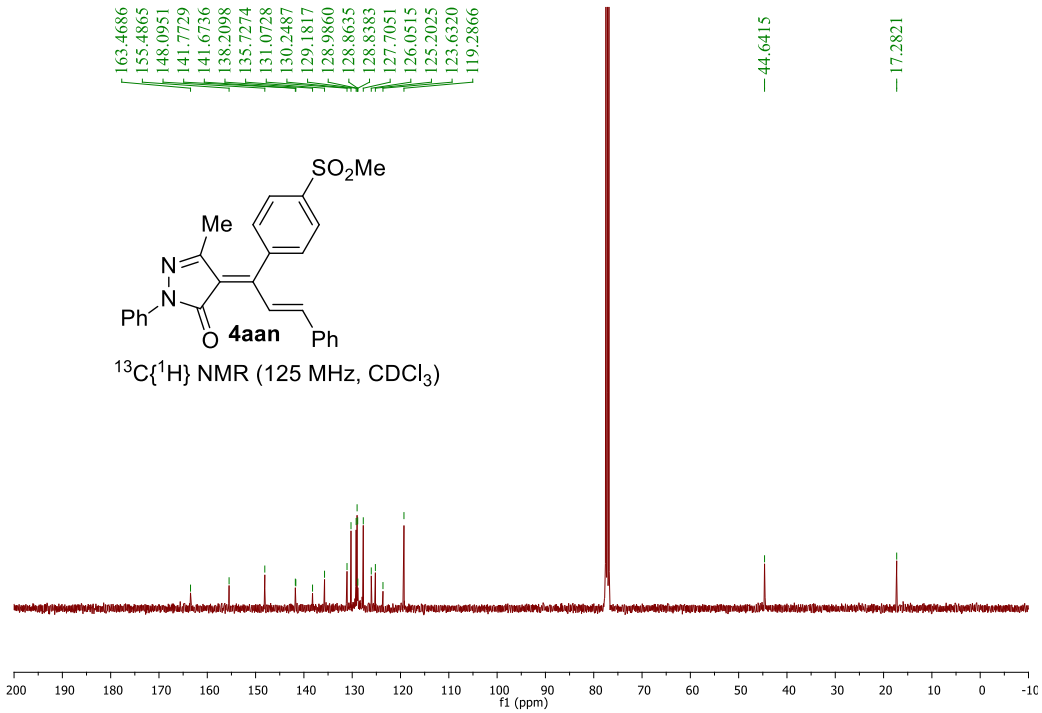


Figure 4.32 125 MHz ^{13}C Spectrum of **4aan** in $CDCl_3$

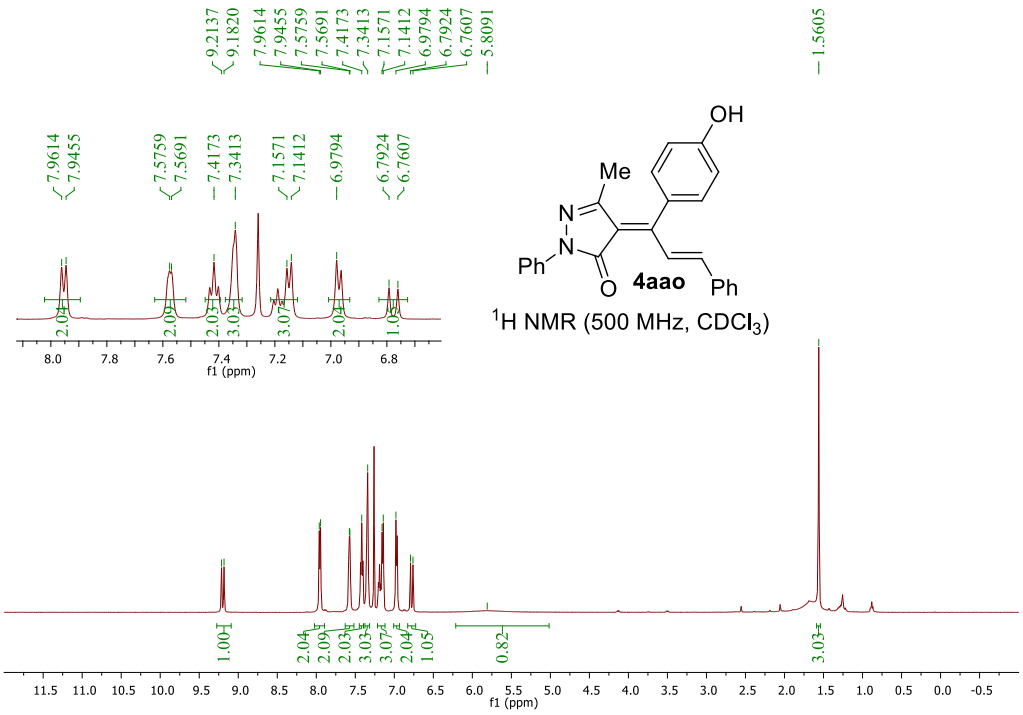


Figure 4.33 500 MHz ^{1}H Spectrum of **4aao** in $CDCl_3$

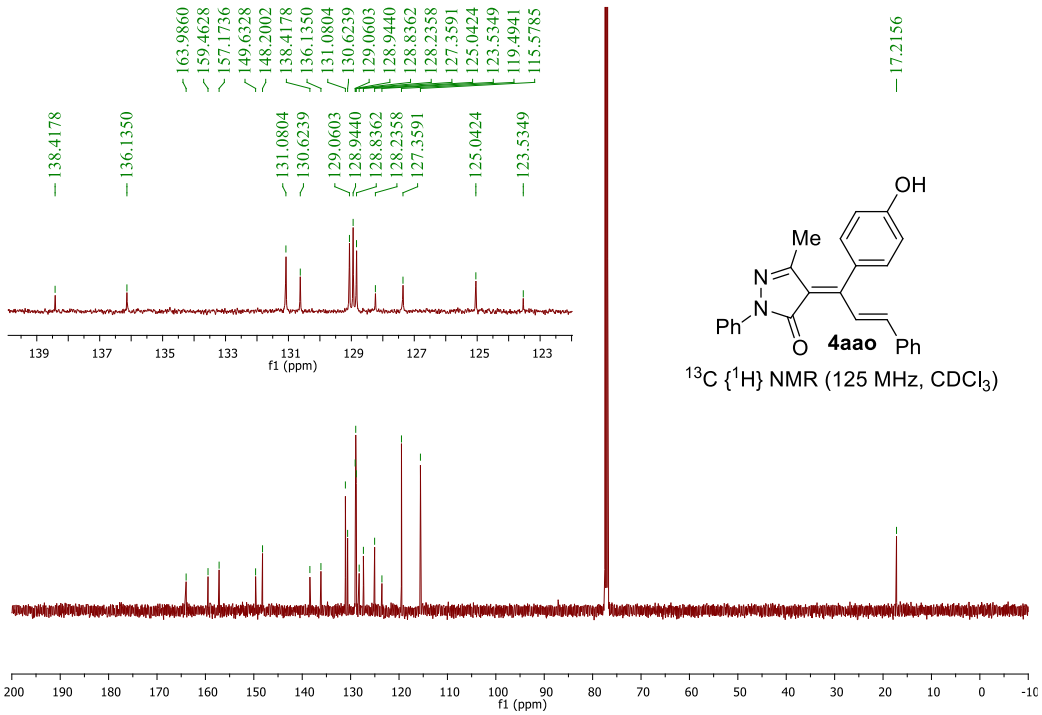


Figure 4.34 125 MHz ^{13}C Spectrum of **4aao** in $CDCl_3$

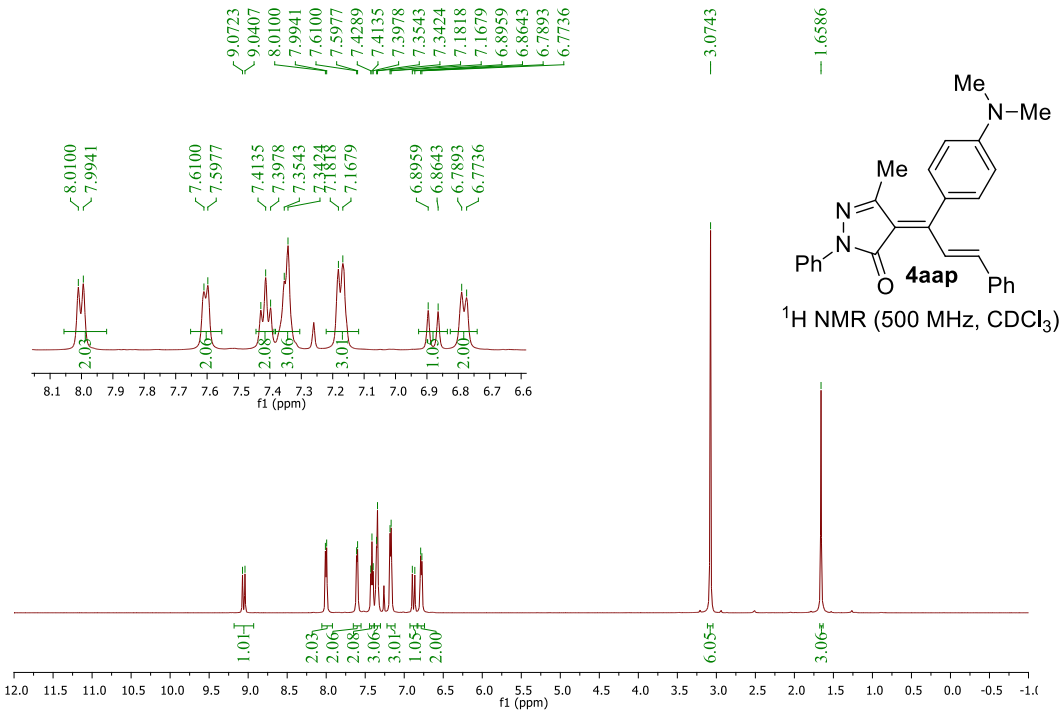


Figure 4.35 500 MHz ^{1}H Spectrum of **4aap** in $CDCl_3$

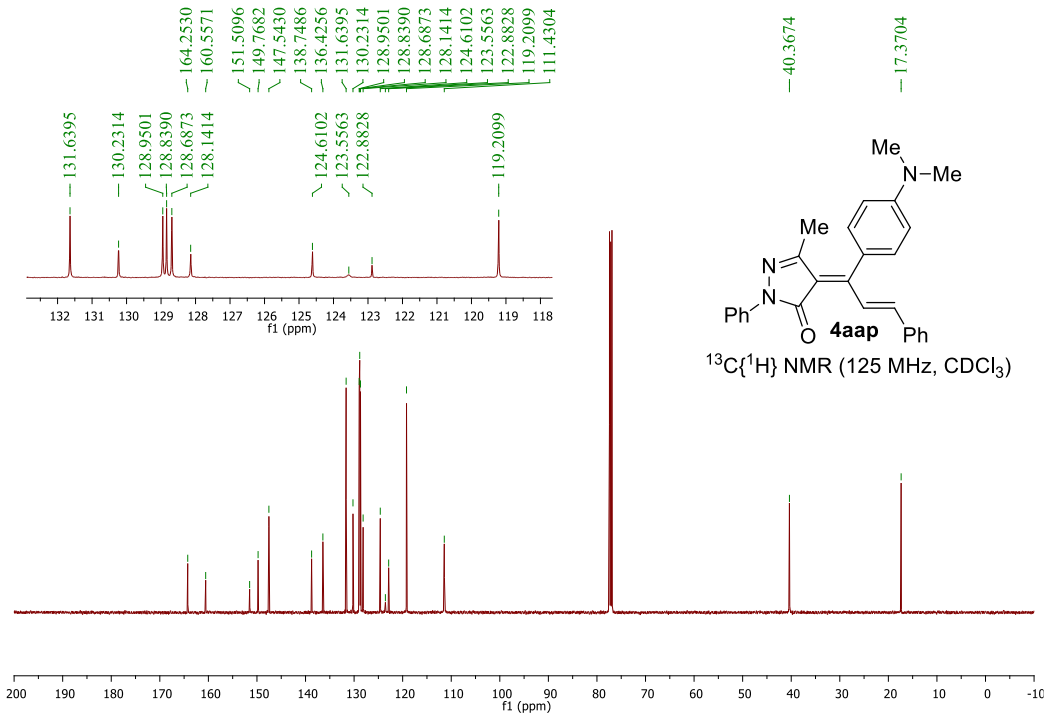


Figure 4.36 125 MHz ^{13}C Spectrum of **4aap** in $CDCl_3$

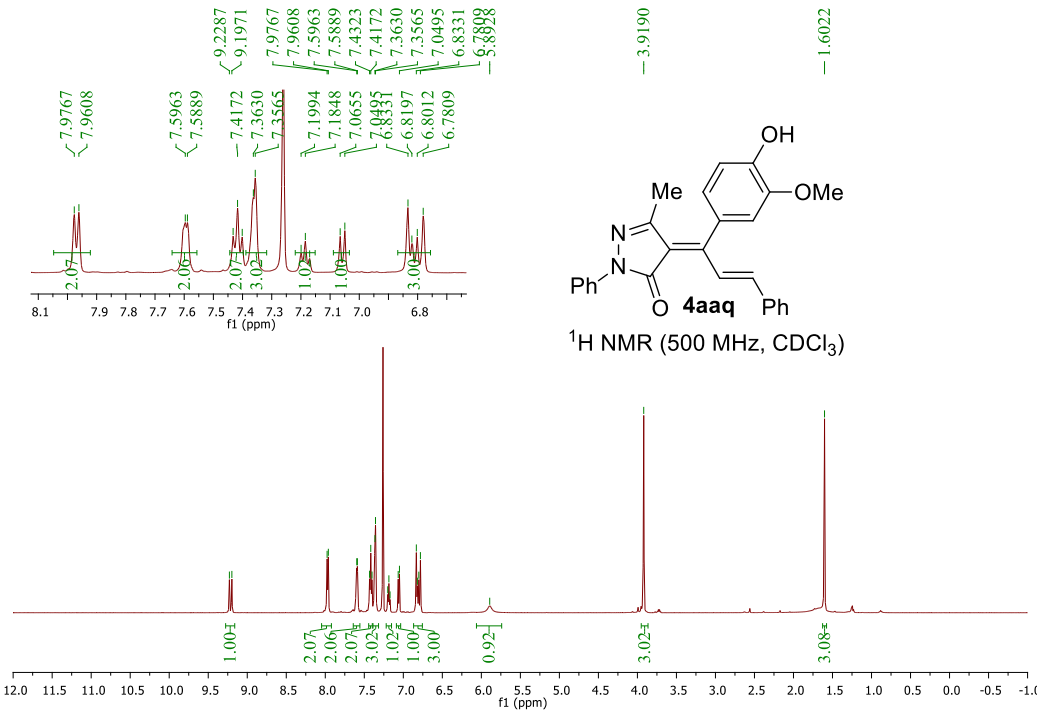


Figure 4.37 500 MHz ^{1}H Spectrum of **4aaq** in $CDCl_3$

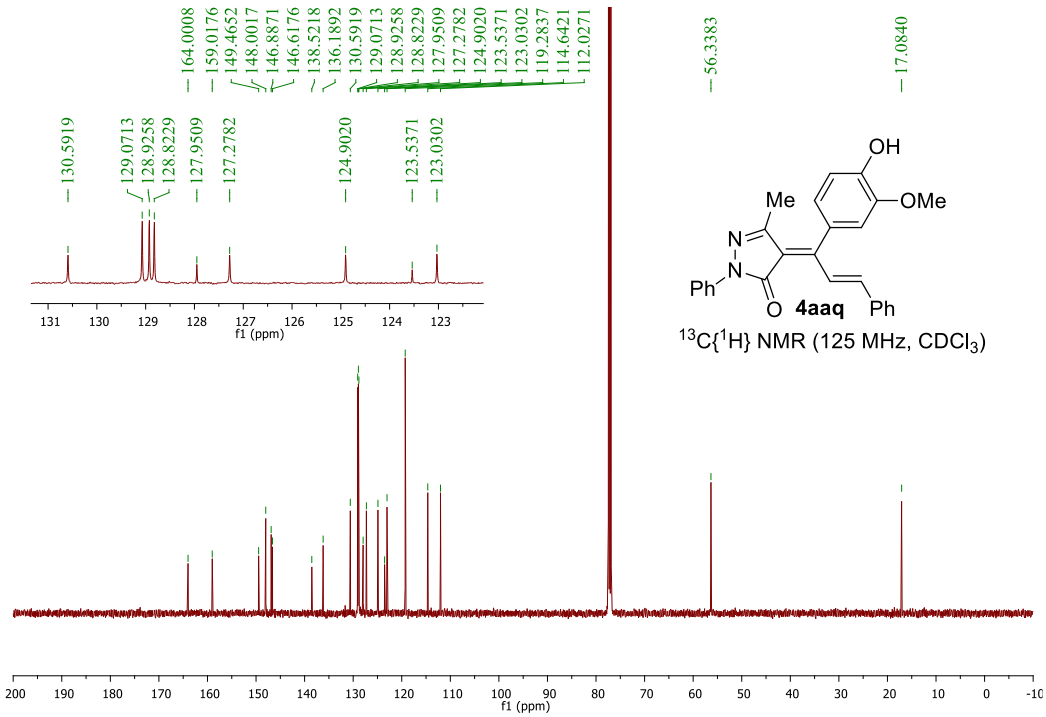


Figure 4.38 125 MHz ^{13}C Spectrum of **4aaq** in $CDCl_3$

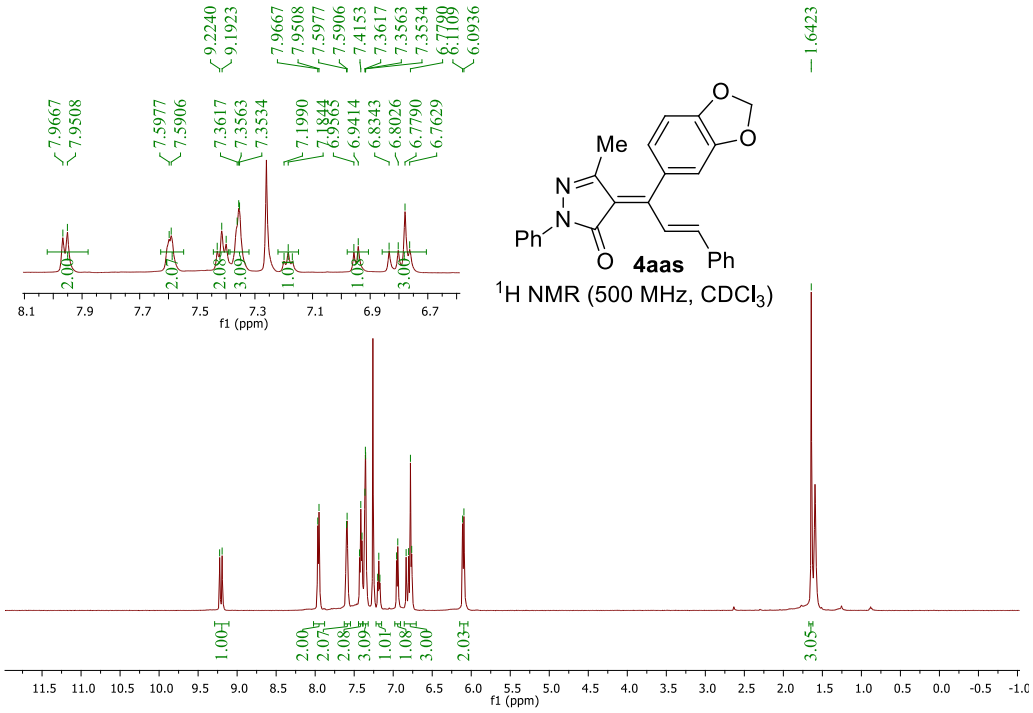


Figure 4.39 500 MHz ^{1}H Spectrum of **4aas** in $CDCl_3$

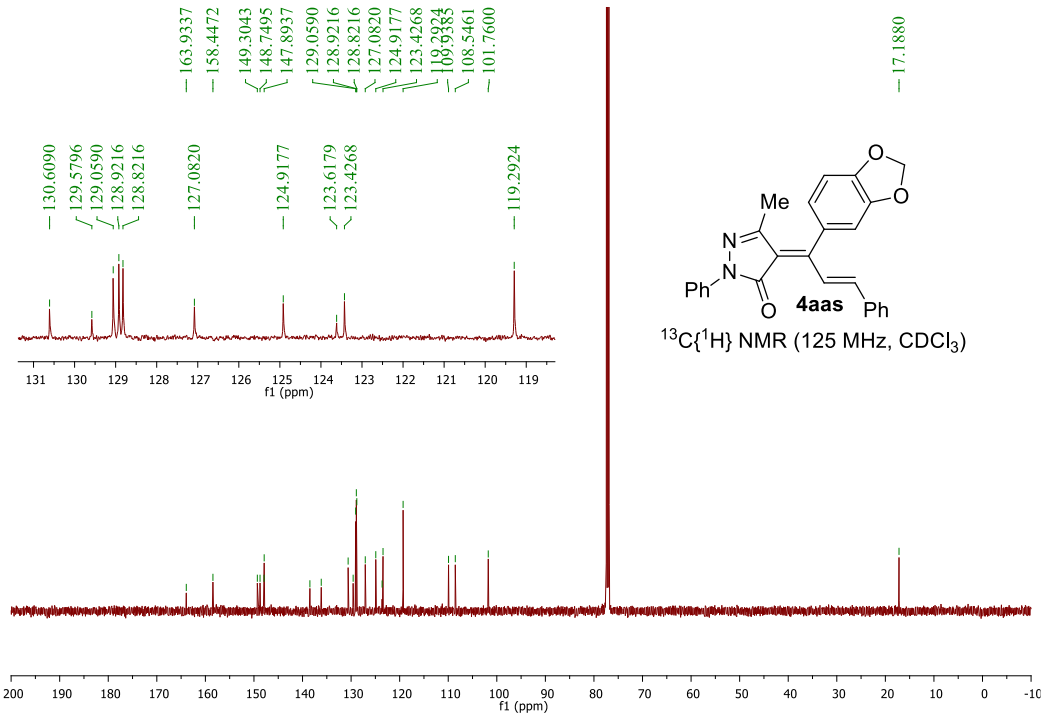


Figure 4.40 125 MHz ^{13}C Spectrum of **4aas** in $CDCl_3$

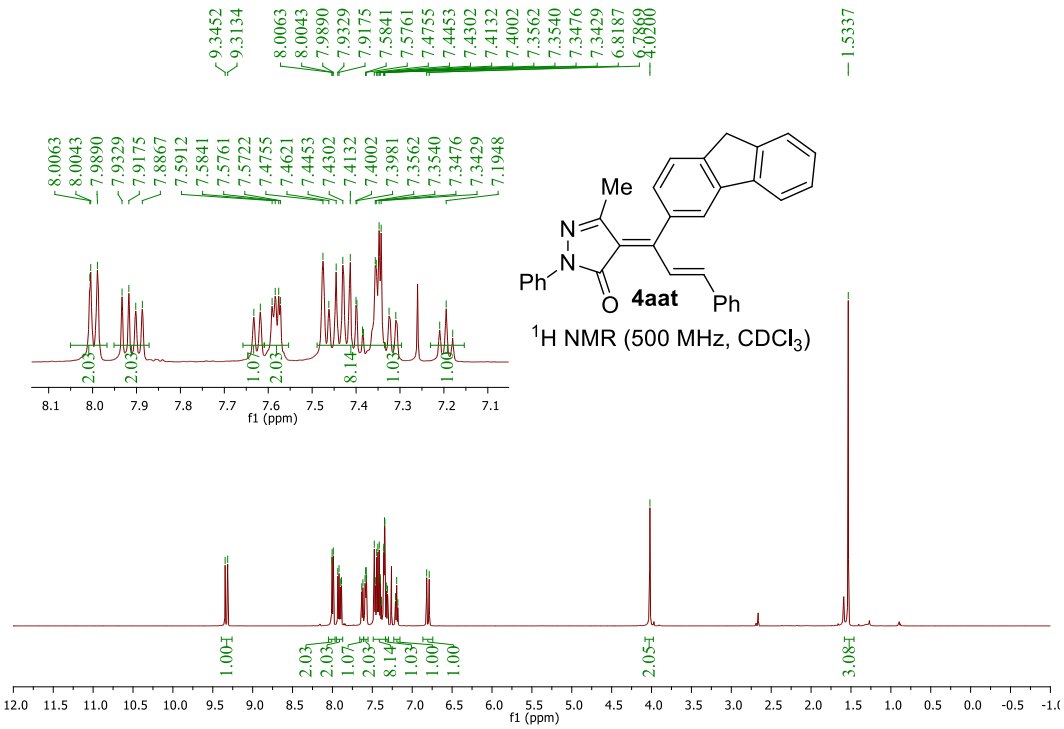


Figure 4.41 500 MHz ^{1}H Spectrum of **4aat** in $CDCl_3$

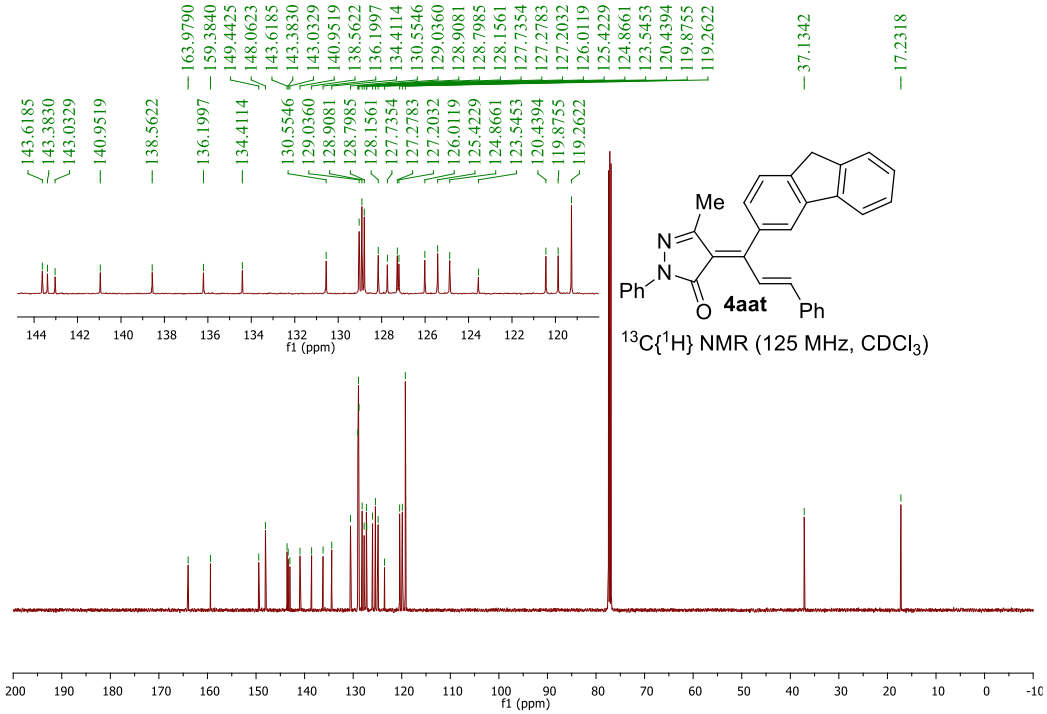


Figure 4.42 125 MHz ^{13}C Spectrum of **4aat** in CDCl

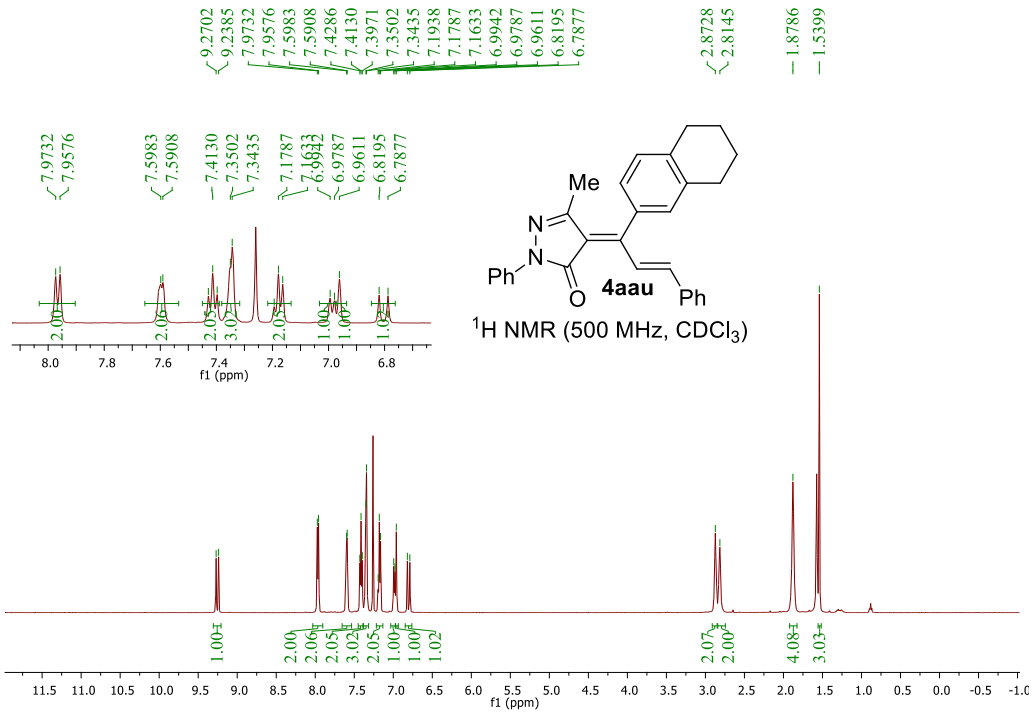


Figure 4.43 500 MHz ^{1}H Spectrum of **4aau** in $CDCl_3$

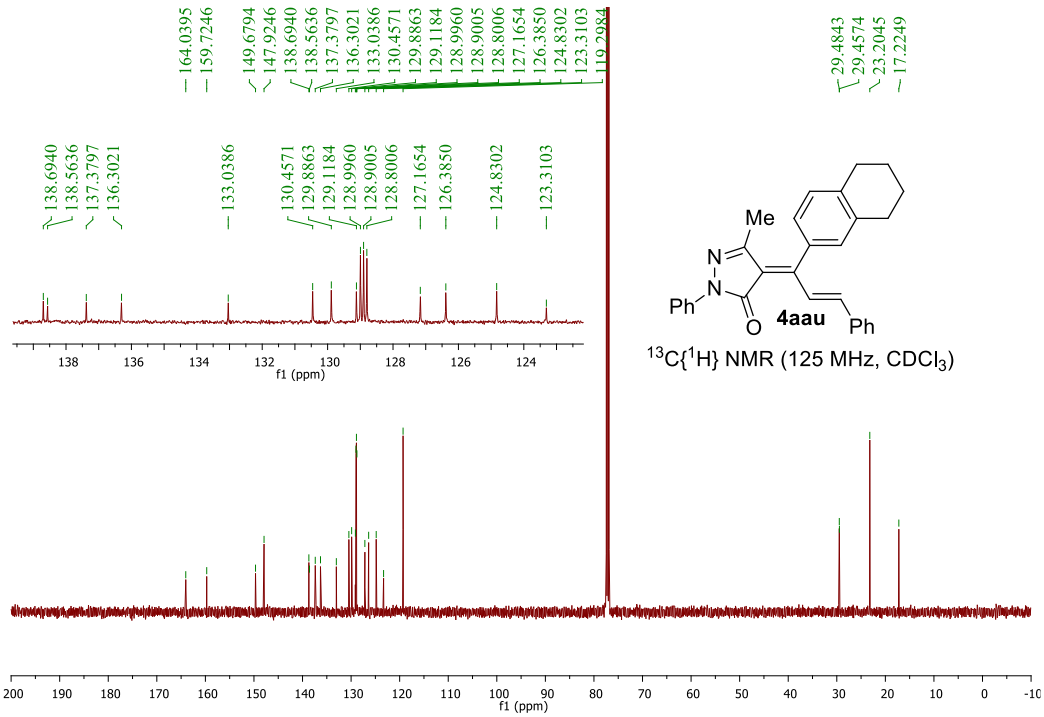


Figure 4.44 125 MHz ^{13}C Spectrum of **4aau** in $CDCl_3$

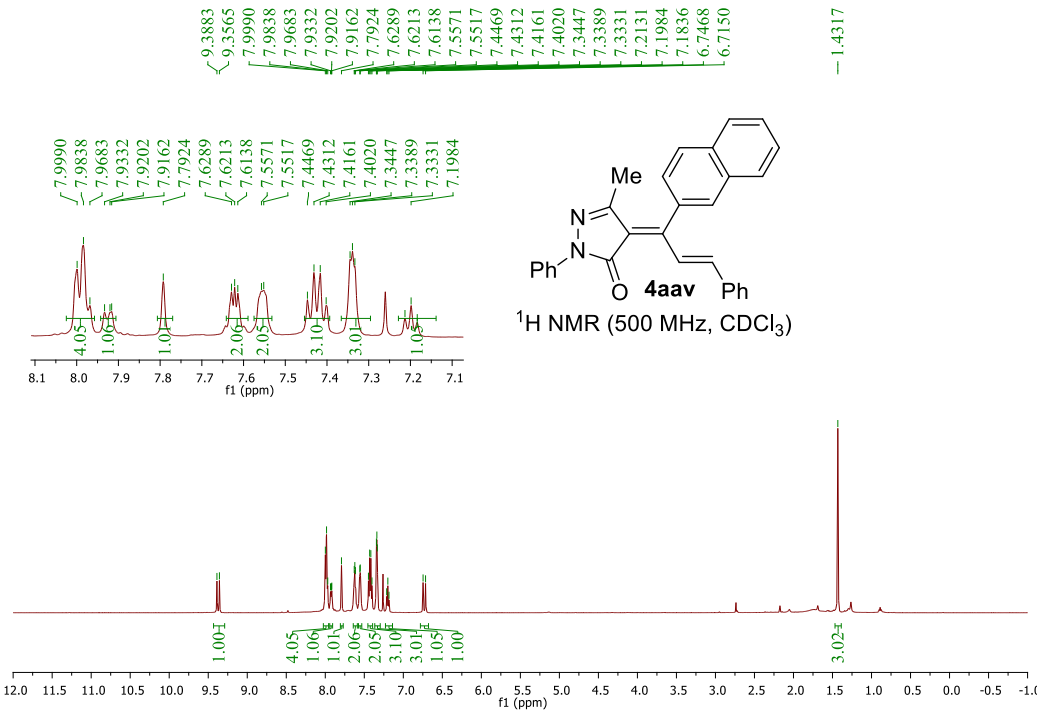


Figure 4.45 500 MHz ^{1}H Spectrum of **4aav** in $CDCl_3$

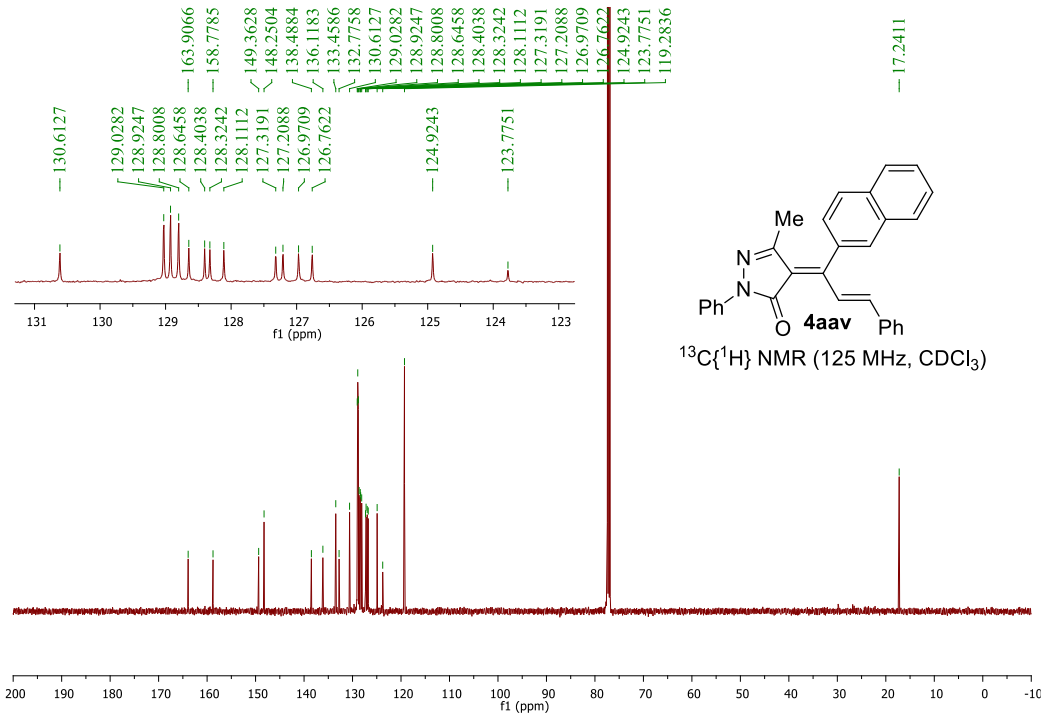


Figure 4.46 125 MHz ^{13}C Spectrum of **4aav** in $CDCl_3$

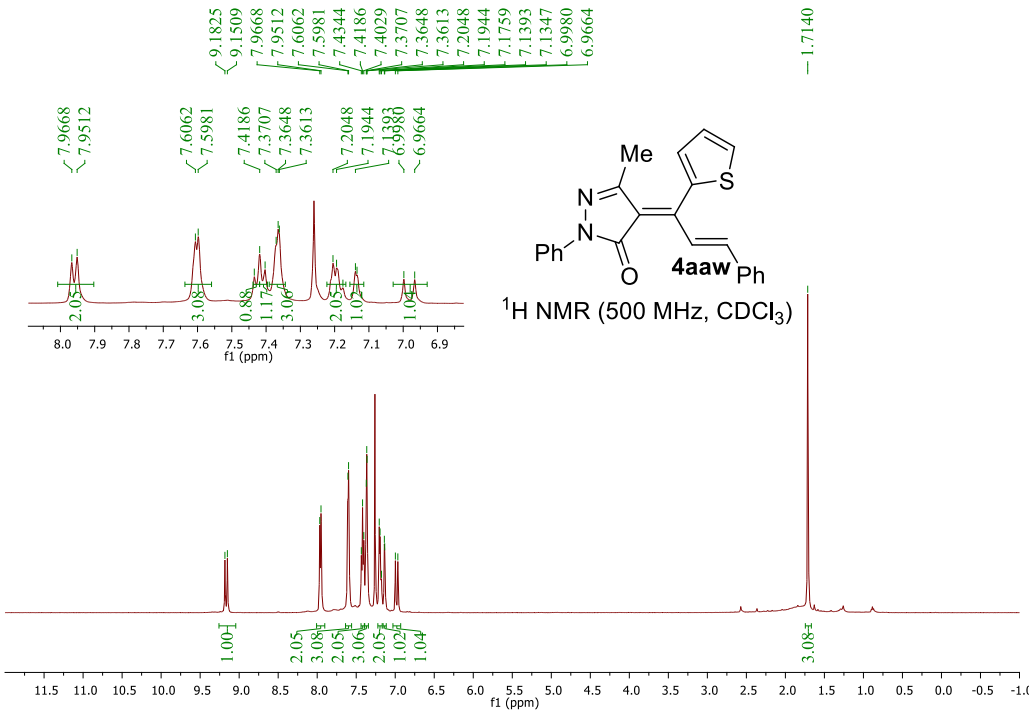


Figure 4.47 500 MHz ^{1}H Spectrum of **4aaw** in $CDCl_3$

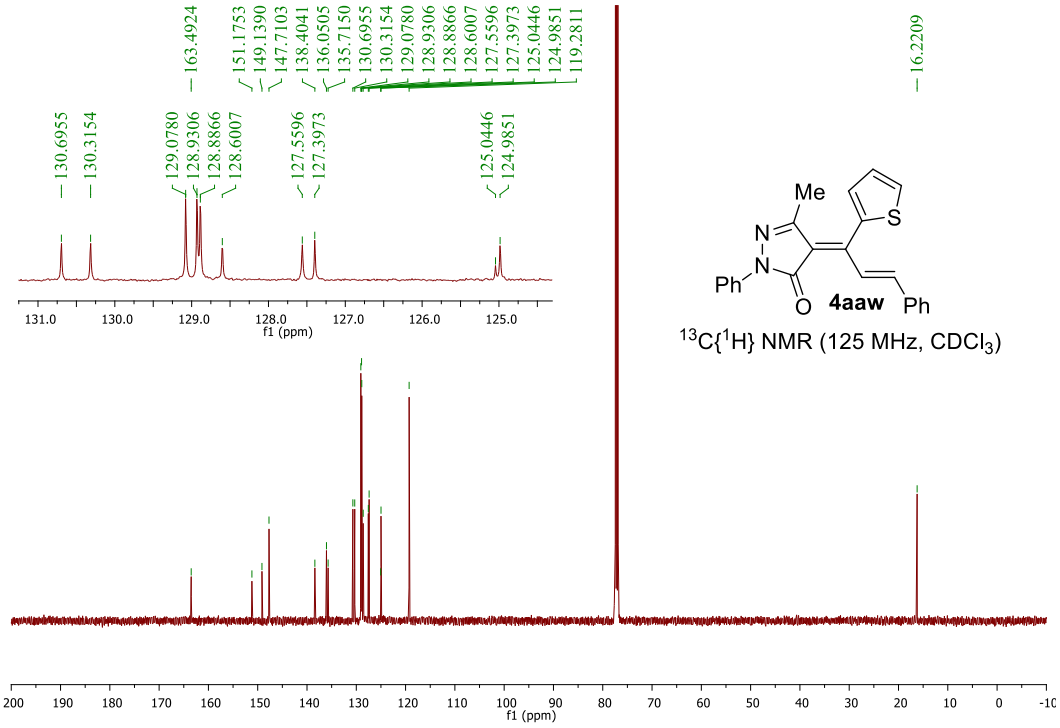


Figure 4.48 125 MHz ^{13}C Spectrum of **4aaw** in $CDCl_3$

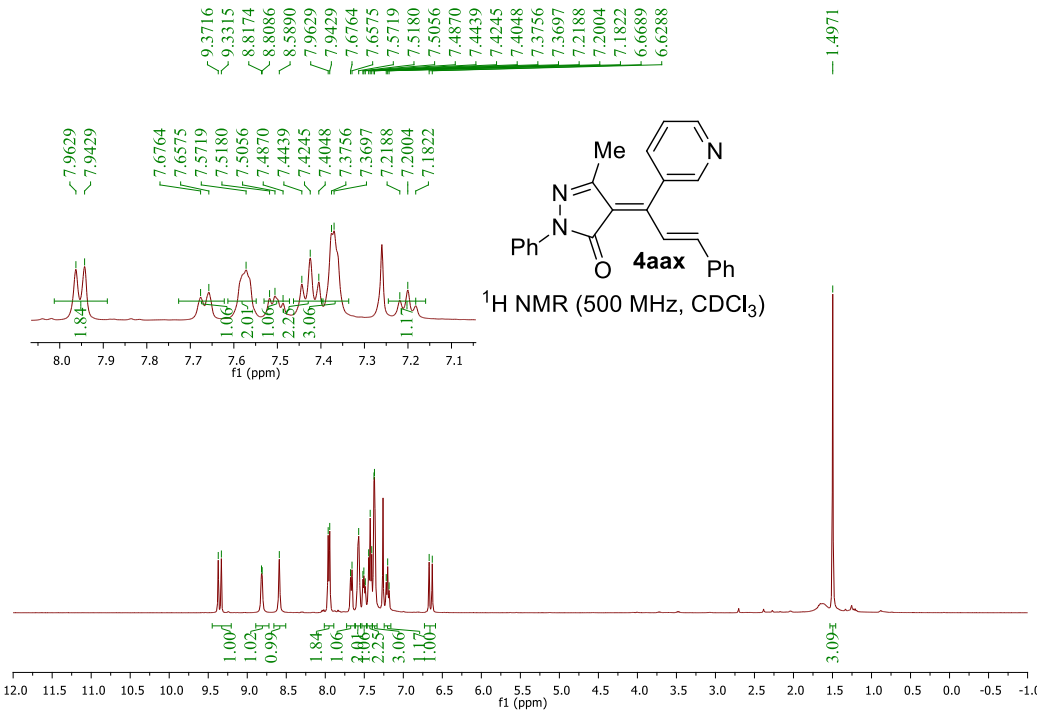


Figure 4.49 500 MHz ^{1}H Spectrum of **4aax** in $CDCl_3$

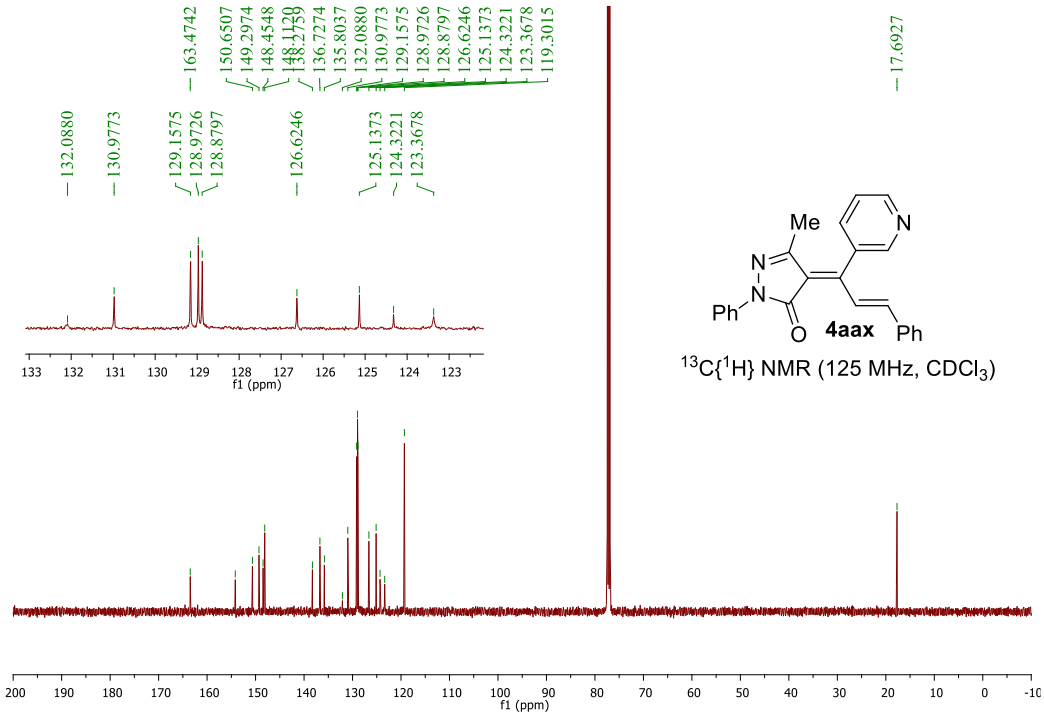


Figure 4.50 125 MHz ^{13}C Spectrum of **4aax** in $CDCl_3$

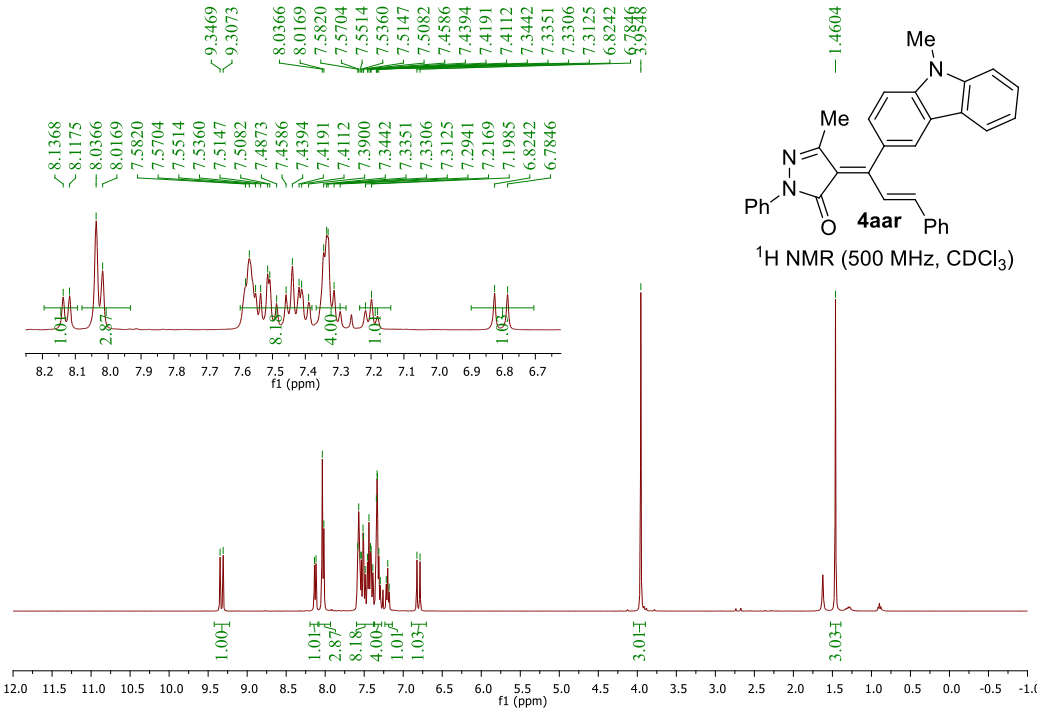


Figure 4.51 500 MHz ^{1}H Spectrum of **4aar** in $CDCl_3$

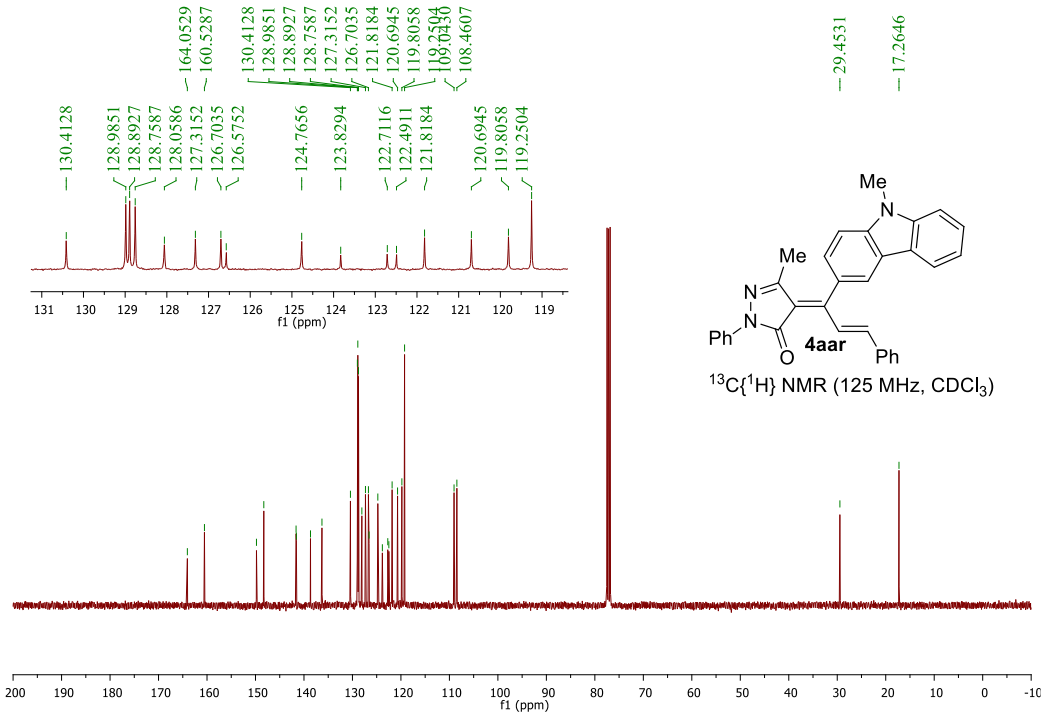


Figure 4.52 125 MHz ^{13}C Spectrum of **4aar** in $CDCl_3$

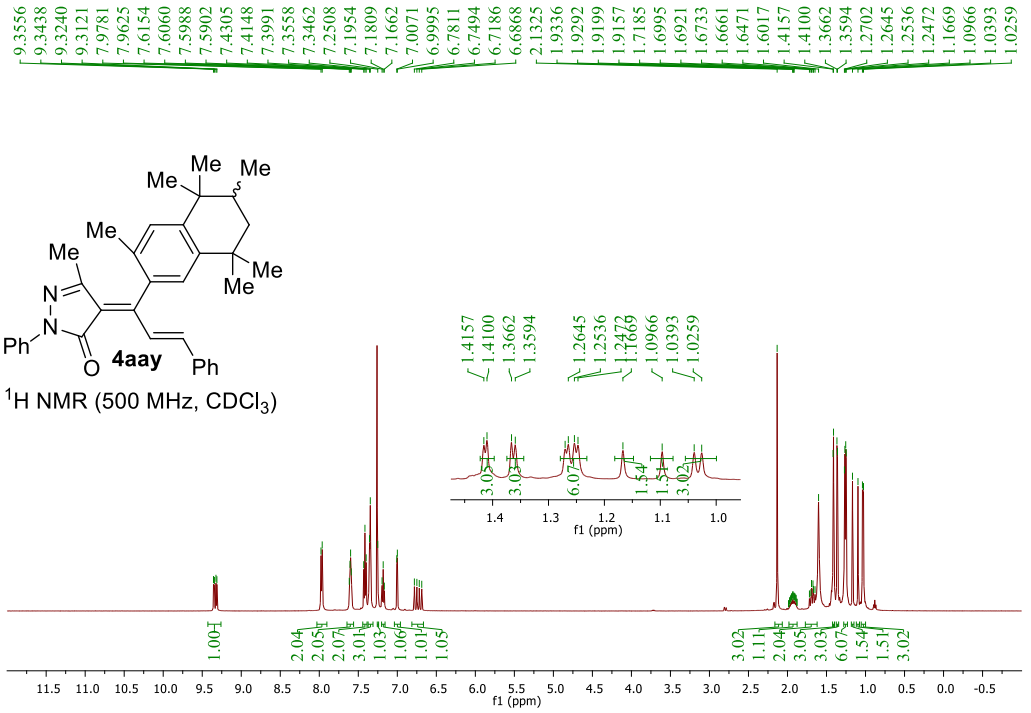


Figure 4.53 500 MHz ^{1}H Spectrum of **4aay** in $CDCl_3$

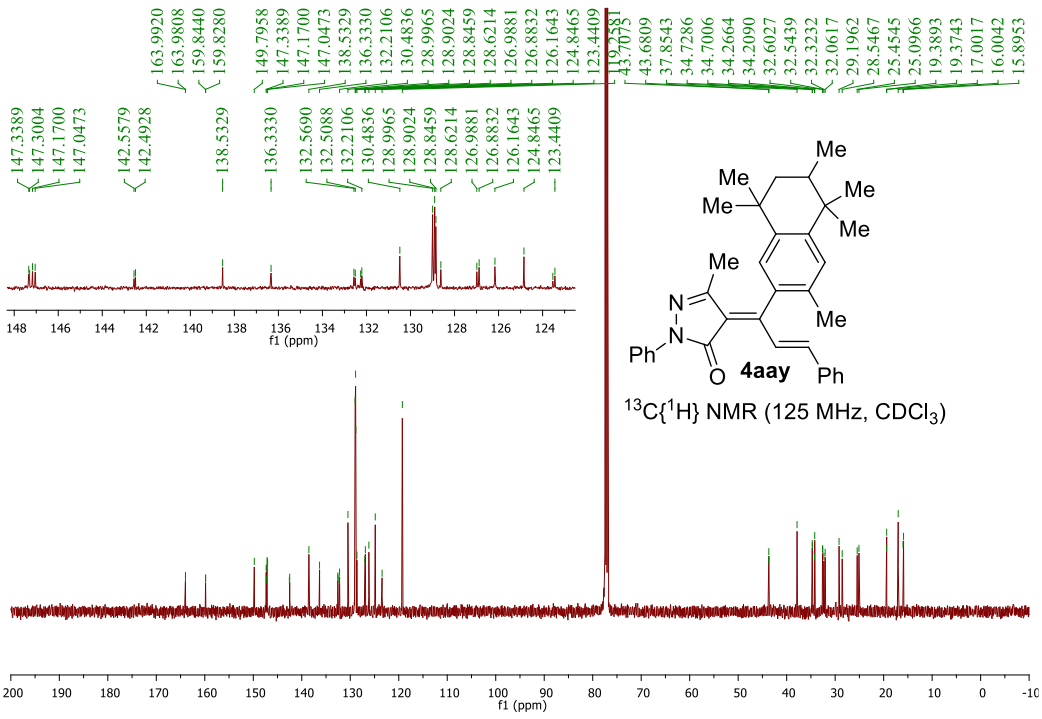


Figure 4.54 125 MHz ^{13}C Spectrum of **4aay** in $CDCl_3$

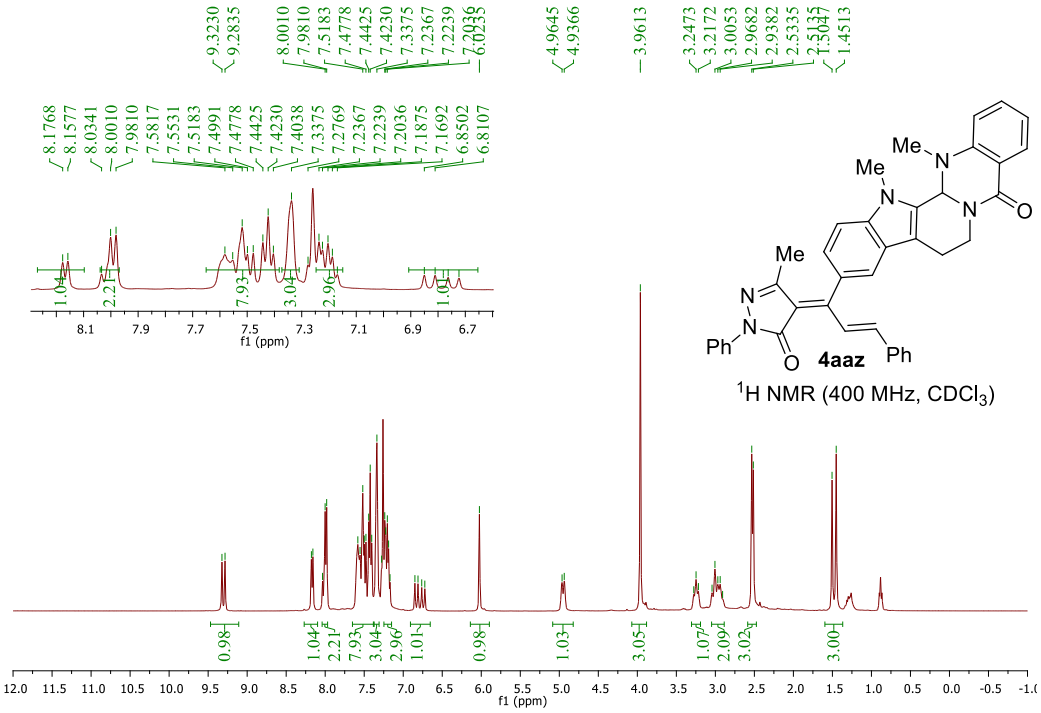


Figure 4.55 500 MHz ^{1}H Spectrum of **4aaz** in $CDCl_3$

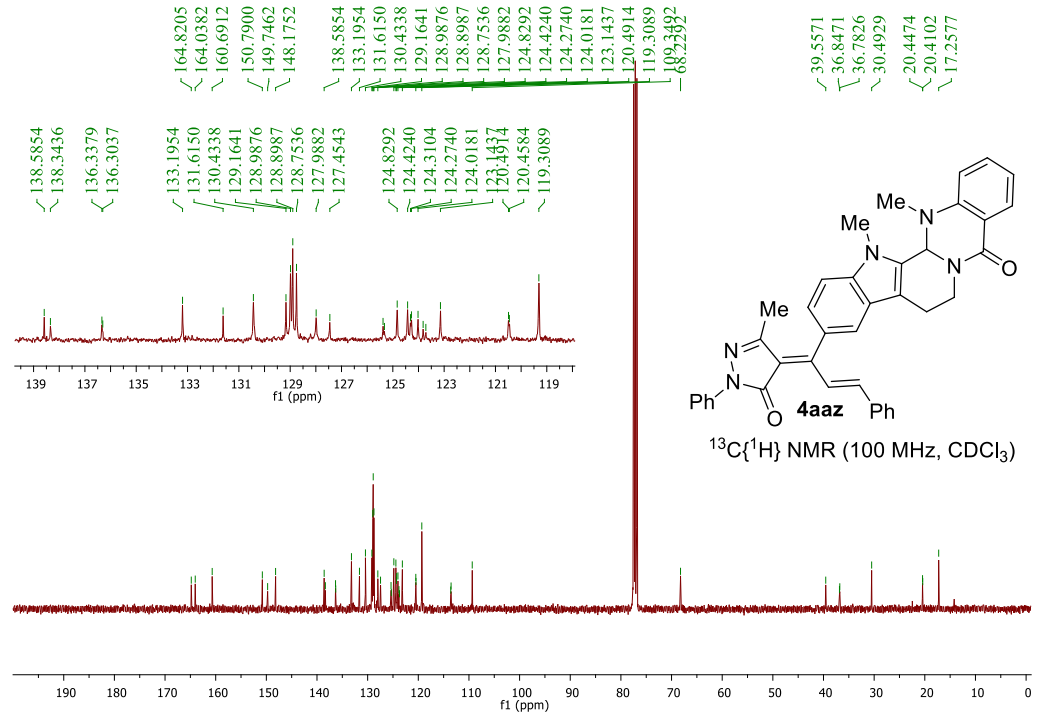


Figure 4.56 125 MHz ^{13}C Spectrum of **4aaz** in $CDCl_3$

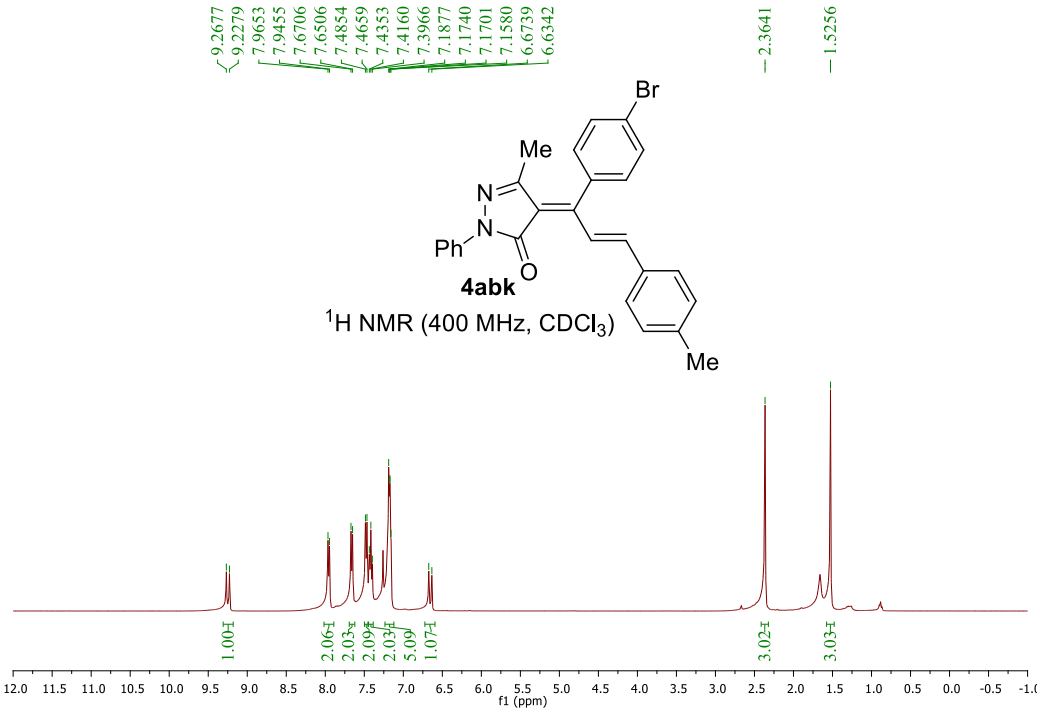


Figure 4.57 500 MHz ^{1}H Spectrum of **4abk** in $CDCl_3$

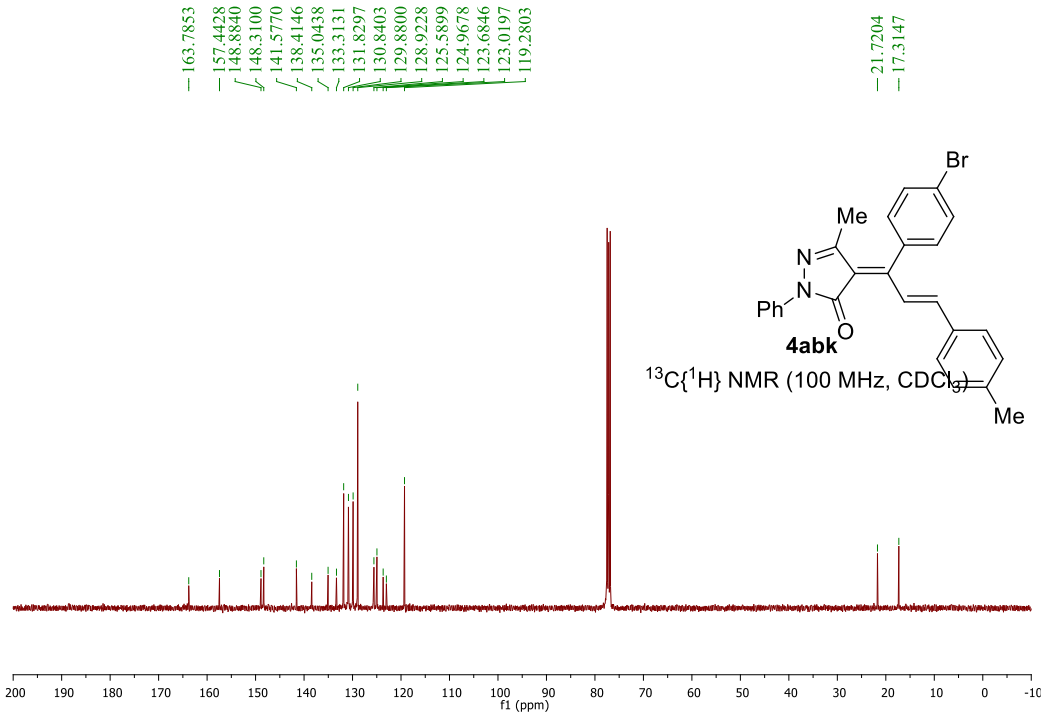


Figure 4.58 125 MHz ^{13}C Spectrum of **4abk** in $CDCl_3$

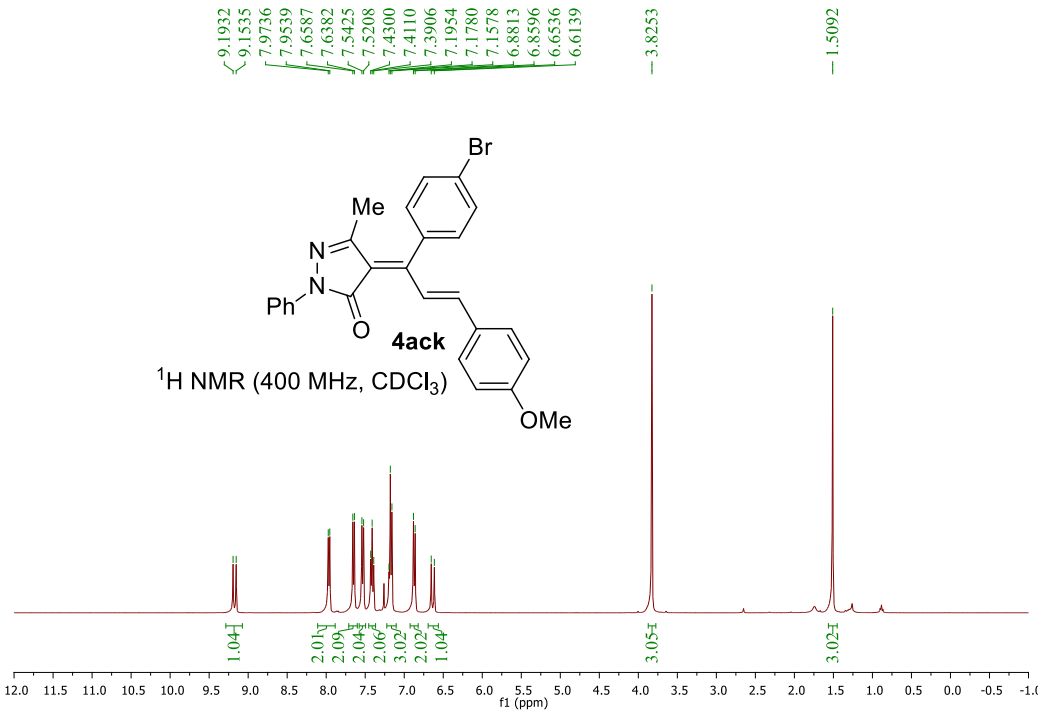


Figure 4.59 500 MHz ^{1}H Spectrum of **4ack** in $CDCl_3$

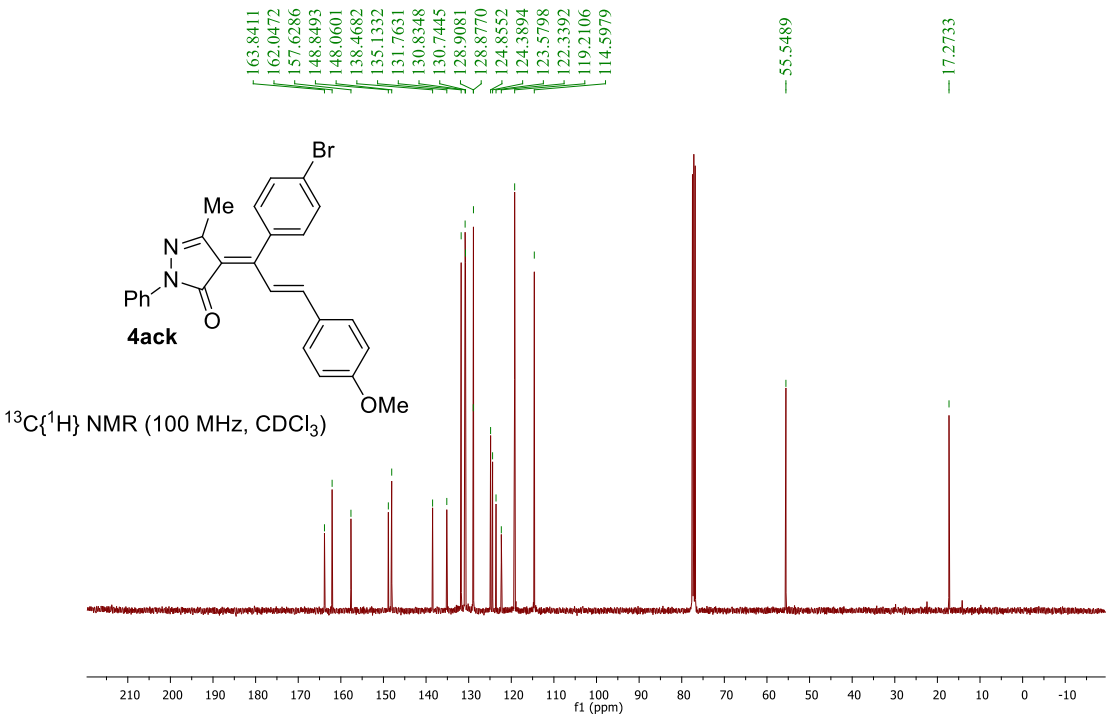


Figure 4.60 125 MHz ^{13}C Spectrum of **4ack** in $CDCl_3$

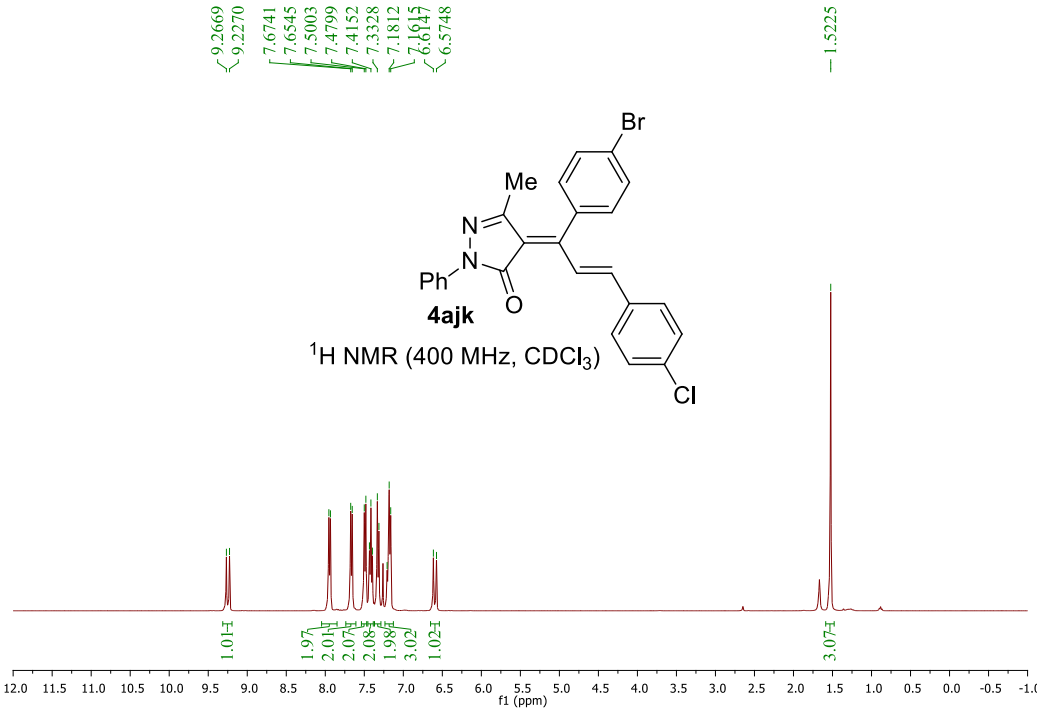


Figure 4.61 500 MHz ^{1}H Spectrum of **4ajk** in $CDCl_3$

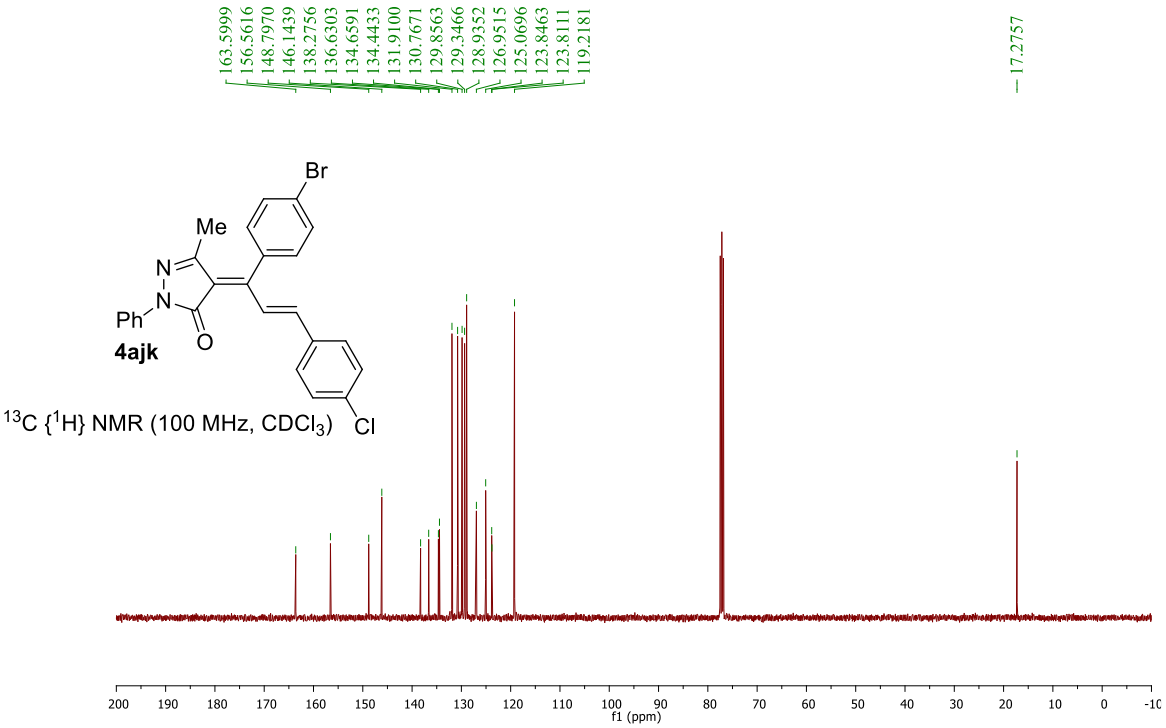


Figure 4.62 125 MHz ^{13}C Spectrum of **4ajk** in $CDCl_3$

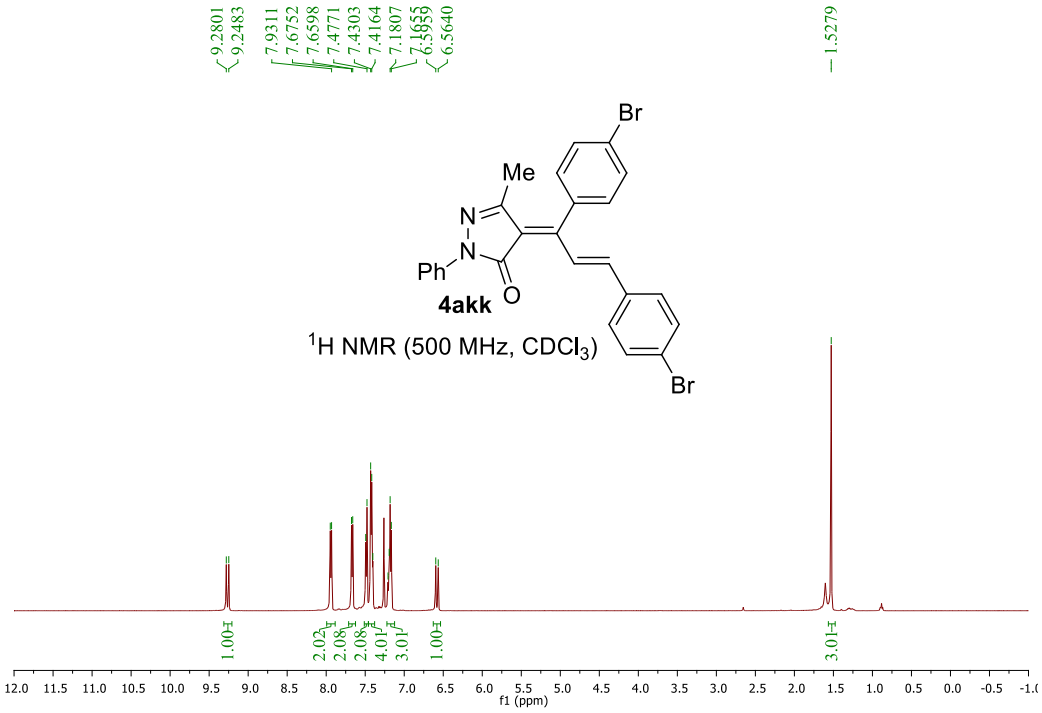


Figure 4.63 500 MHz ^{1}H Spectrum of **4akk** in $CDCl_3$

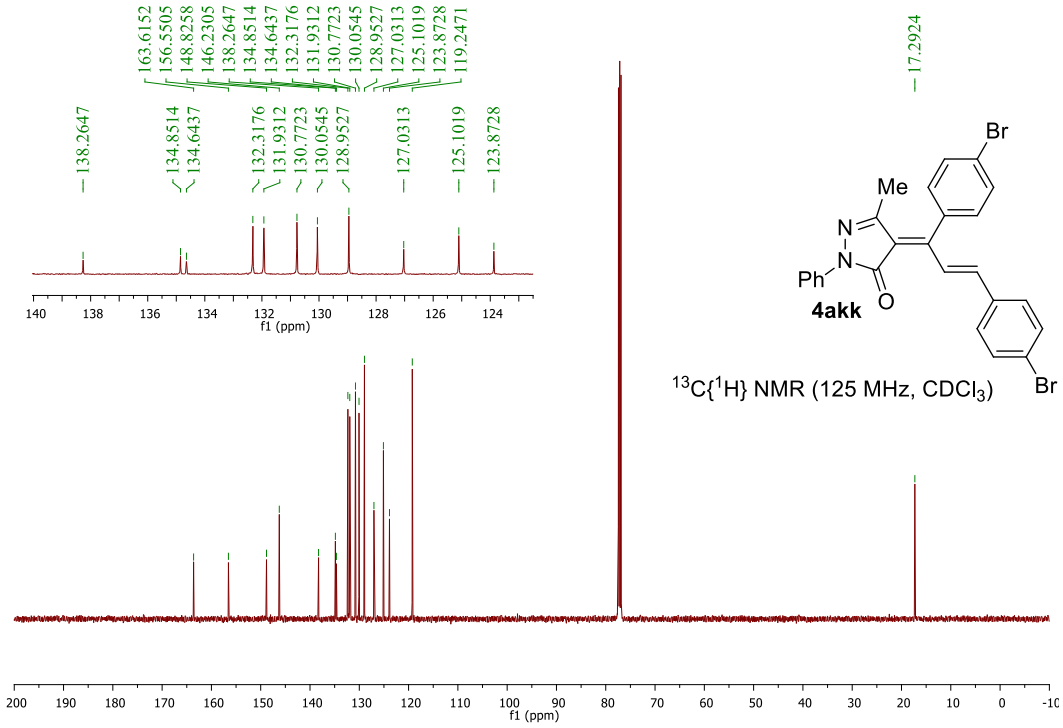


Figure 4.64 125 MHz ^{13}C Spectrum of **4akk** in $CDCl_3$

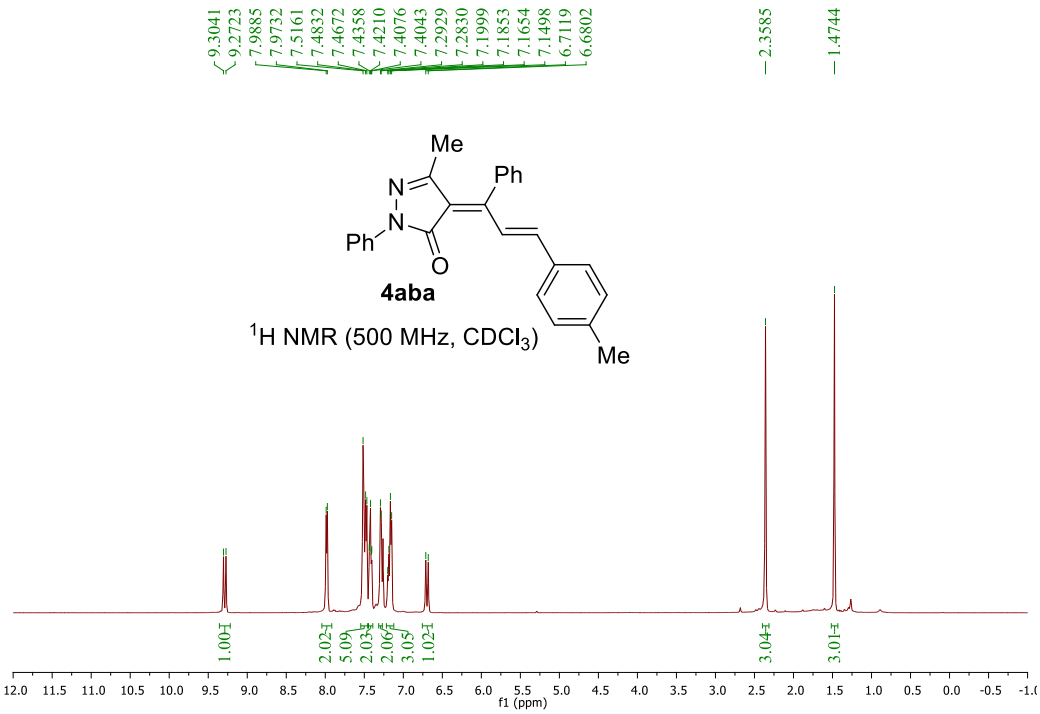


Figure 4.65 500 MHz ^{1}H Spectrum of **4aba** in $CDCl_3$

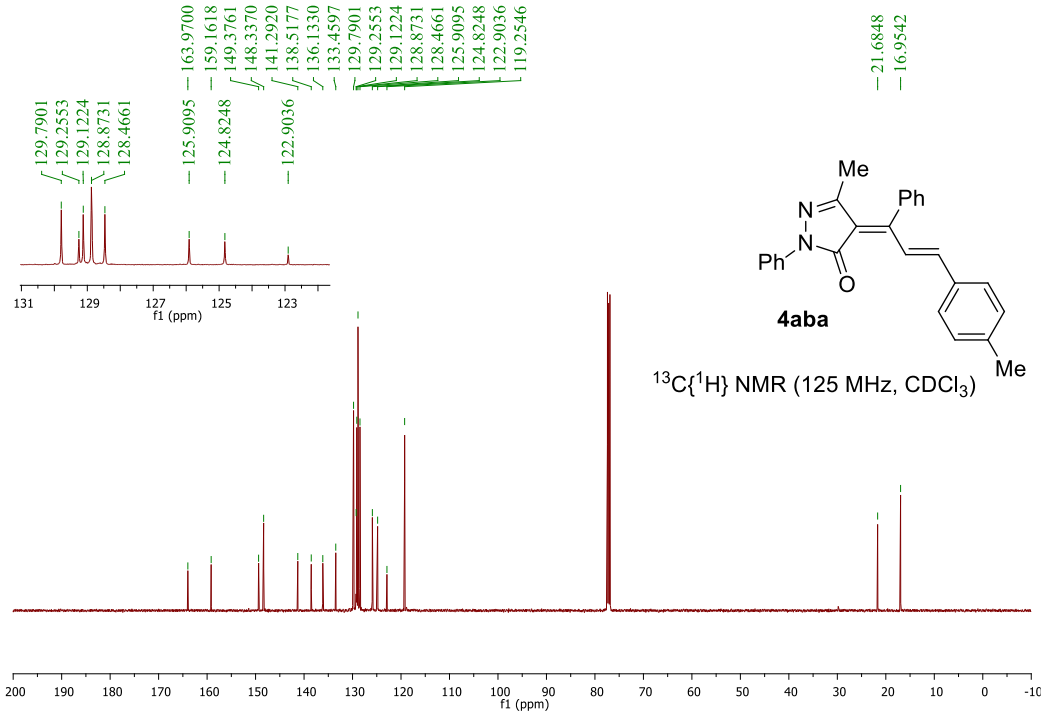


Figure 4.66 125 MHz ^{13}C Spectrum of **4aba** in $CDCl_3$

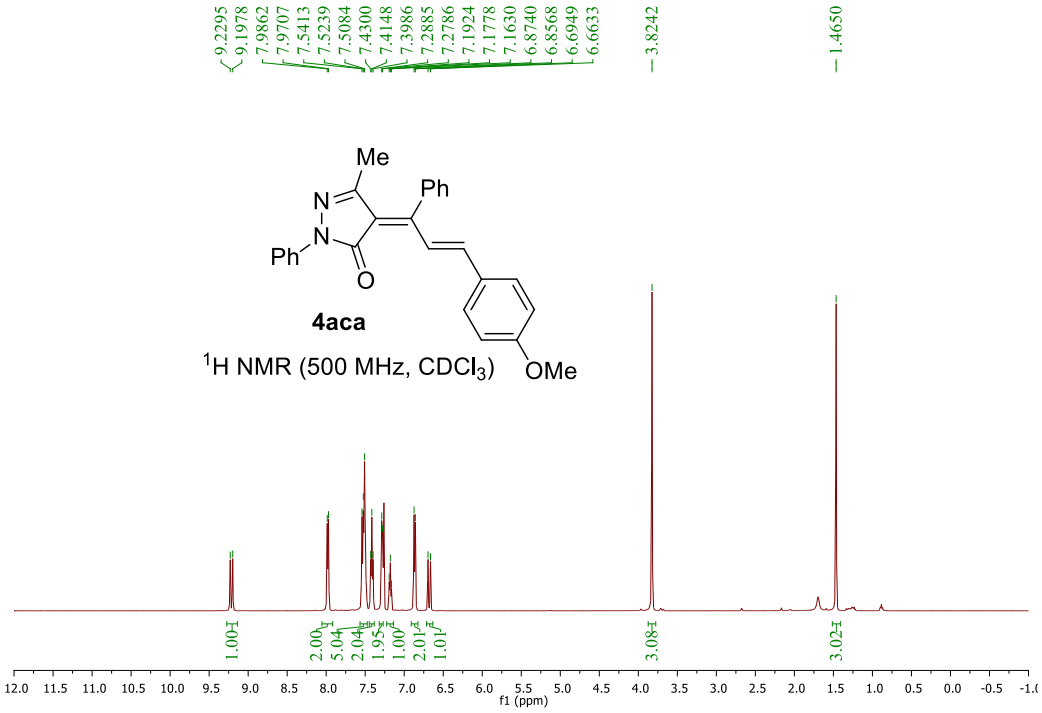


Figure 4.67 500 MHz ^{1}H Spectrum of **4aca** in $CDCl_3$

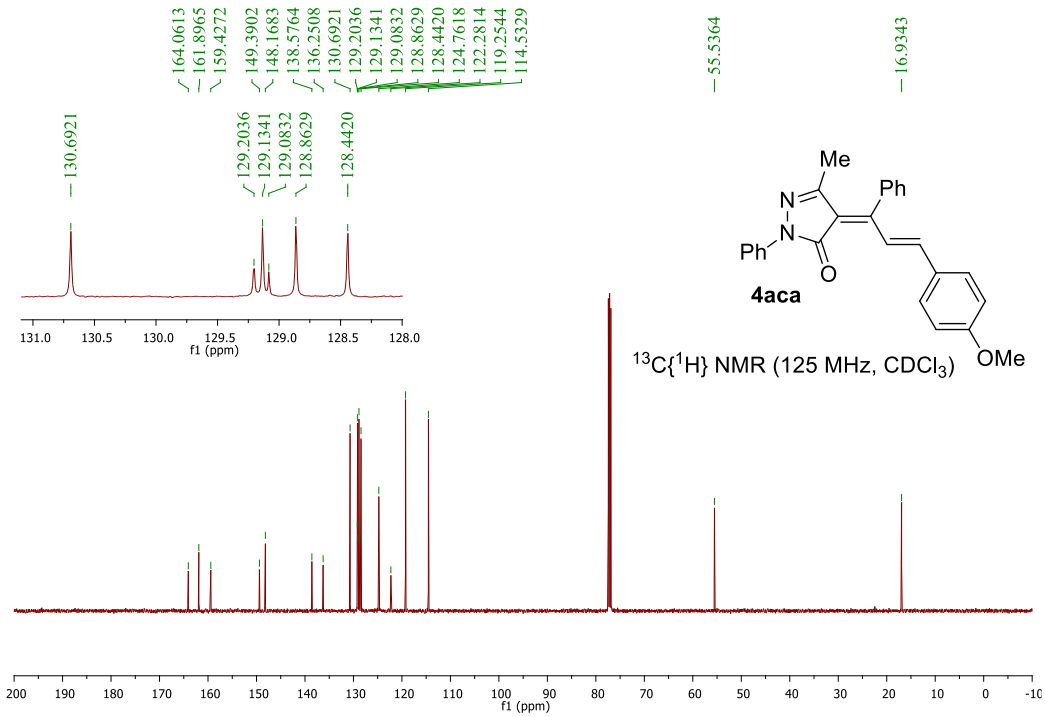


Figure 4.68 125 MHz ^{13}C Spectrum of **4aca** in $CDCl_3$

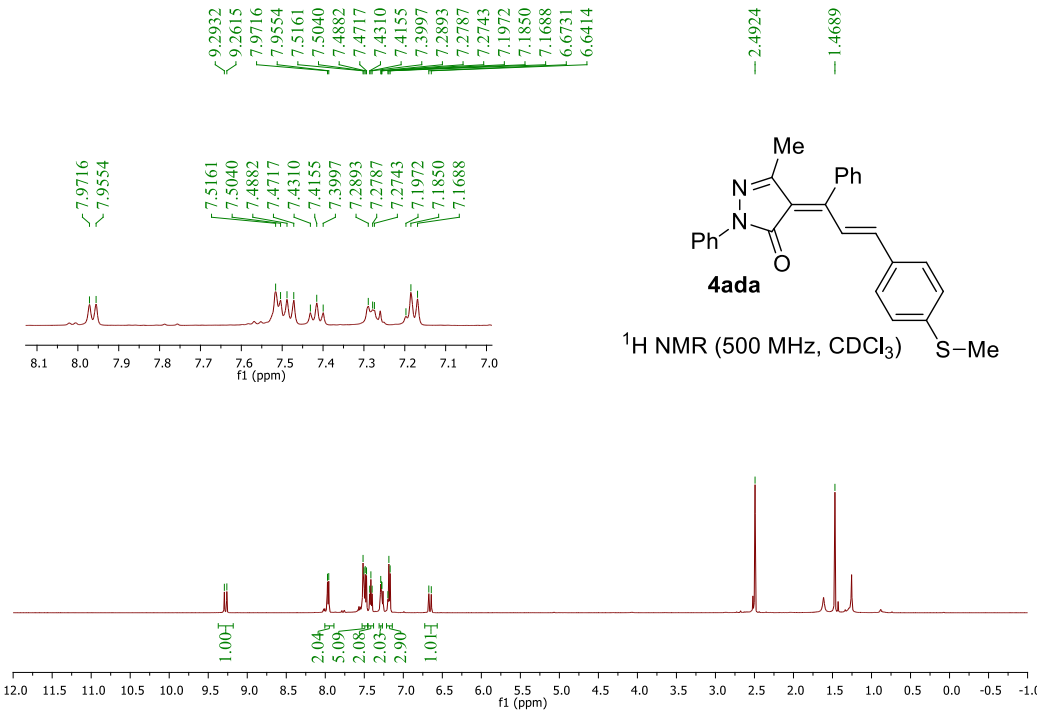


Figure 4.69 500 MHz ^{1}H Spectrum of **4ada** in $CDCl_3$

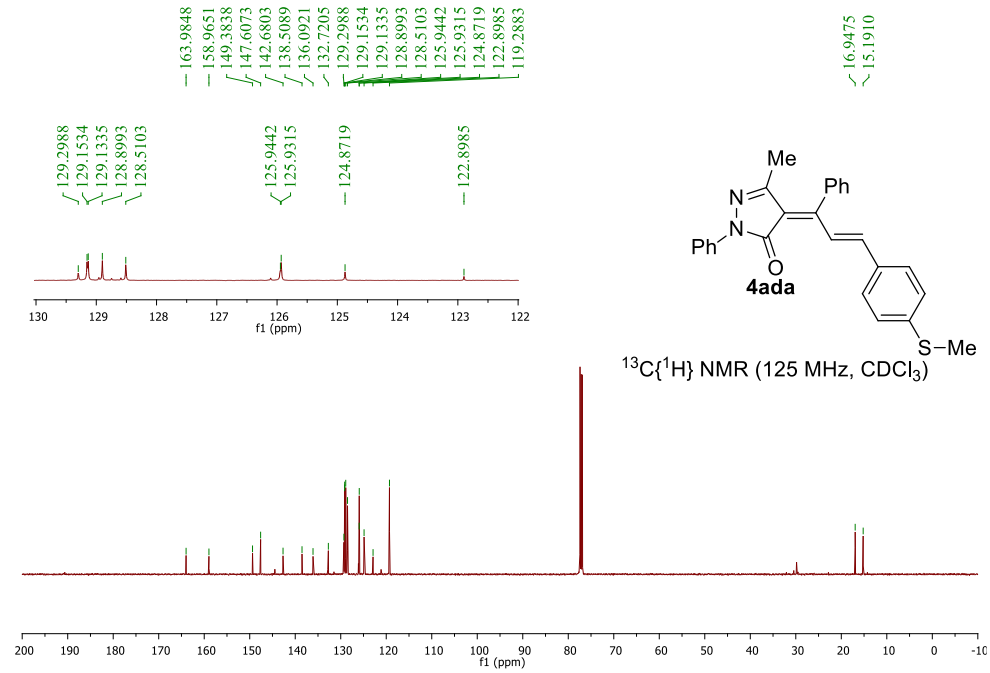


Figure 4.70 125 MHz ^{13}C Spectrum of **4ada** in $CDCl_3$

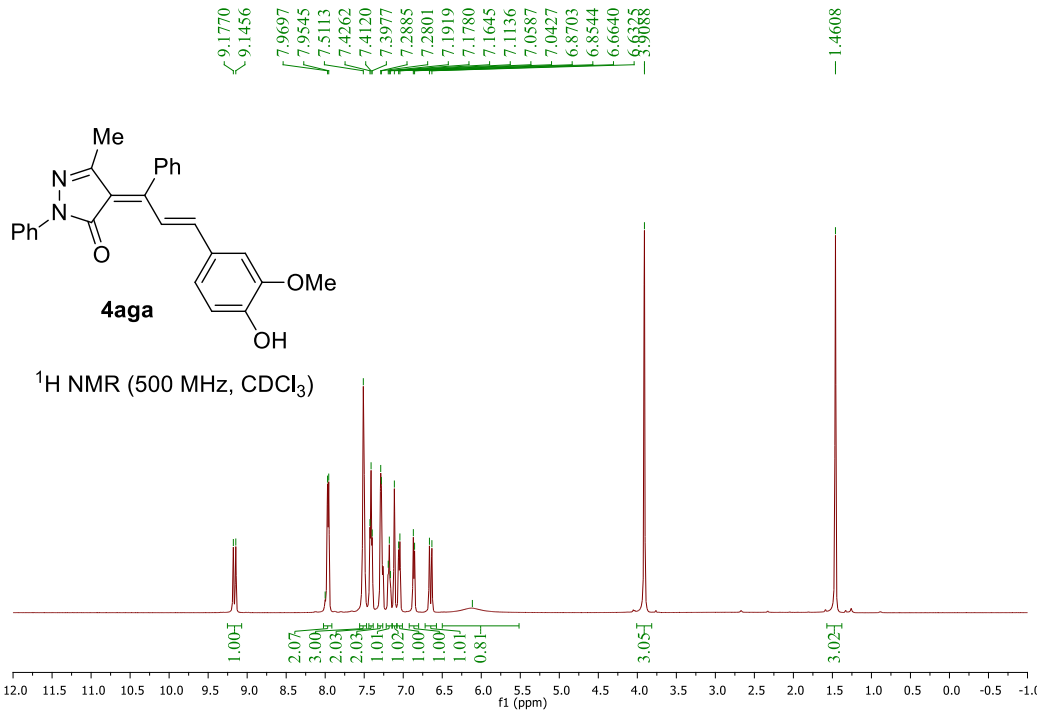


Figure 4.71 500 MHz ^{1}H Spectrum of **4aga** in $CDCl_3$

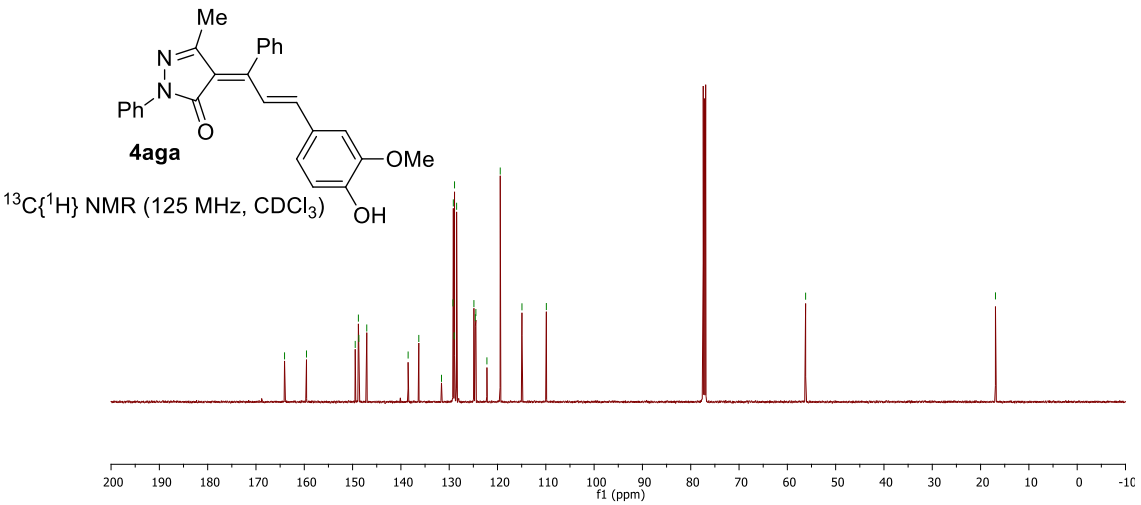


Figure 4.72 125 MHz ^{13}C Spectrum of **4aga** in $CDCl_3$

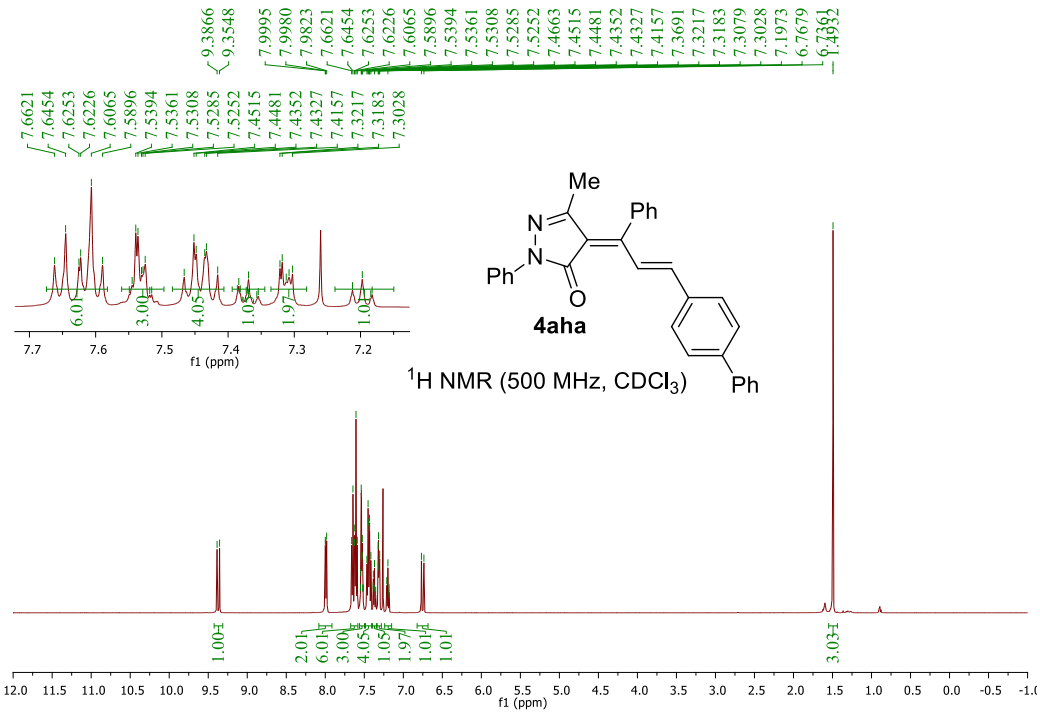


Figure 4.73 500 MHz ^{1}H Spectrum of **4aha** in $CDCl_3$

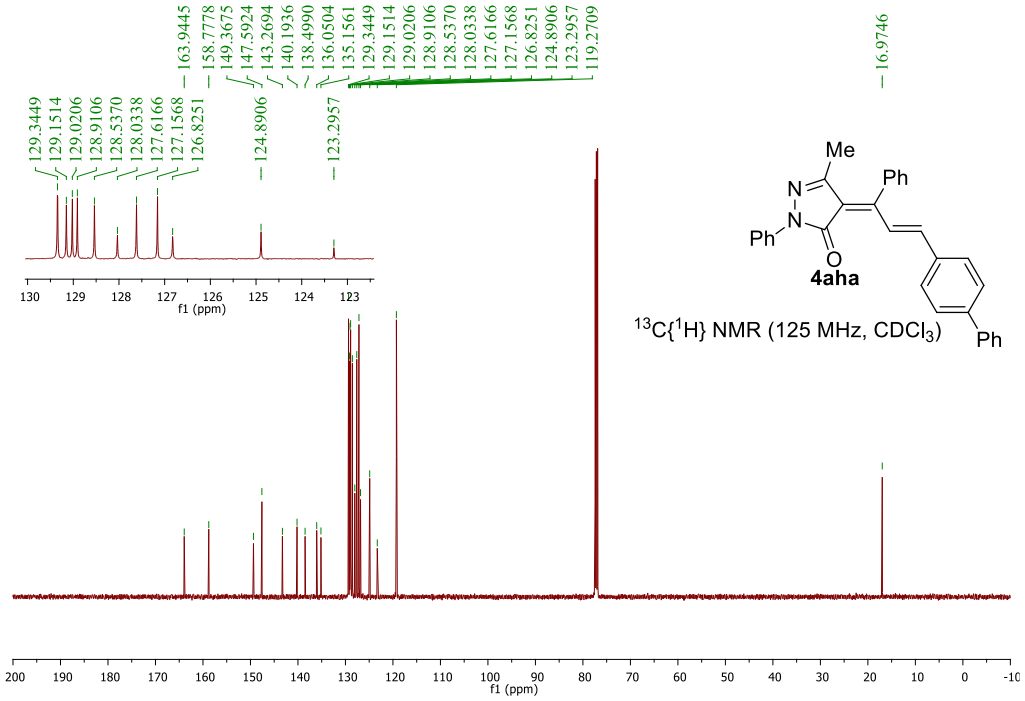


Figure 4.74 125 MHz ^{13}C Spectrum of **4aha** in $CDCl_3$

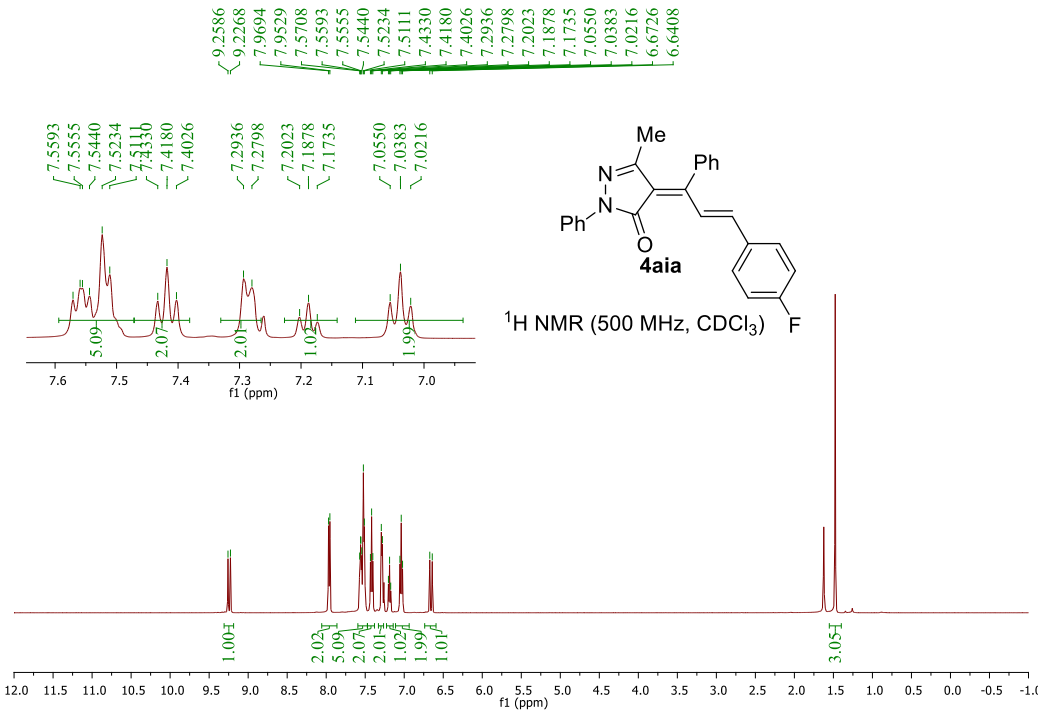


Figure 4.75 500 MHz ^{1}H Spectrum of **4aia** in $CDCl_3$

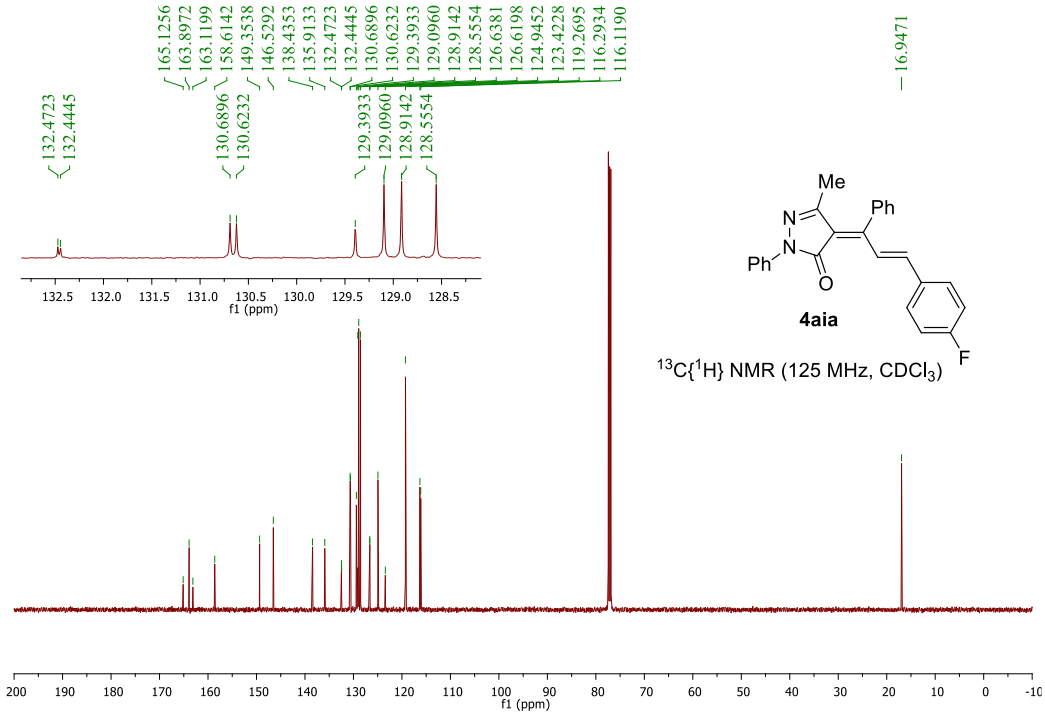


Figure 4.76 125 MHz ^{13}C Spectrum of **4aia** in $CDCl_3$

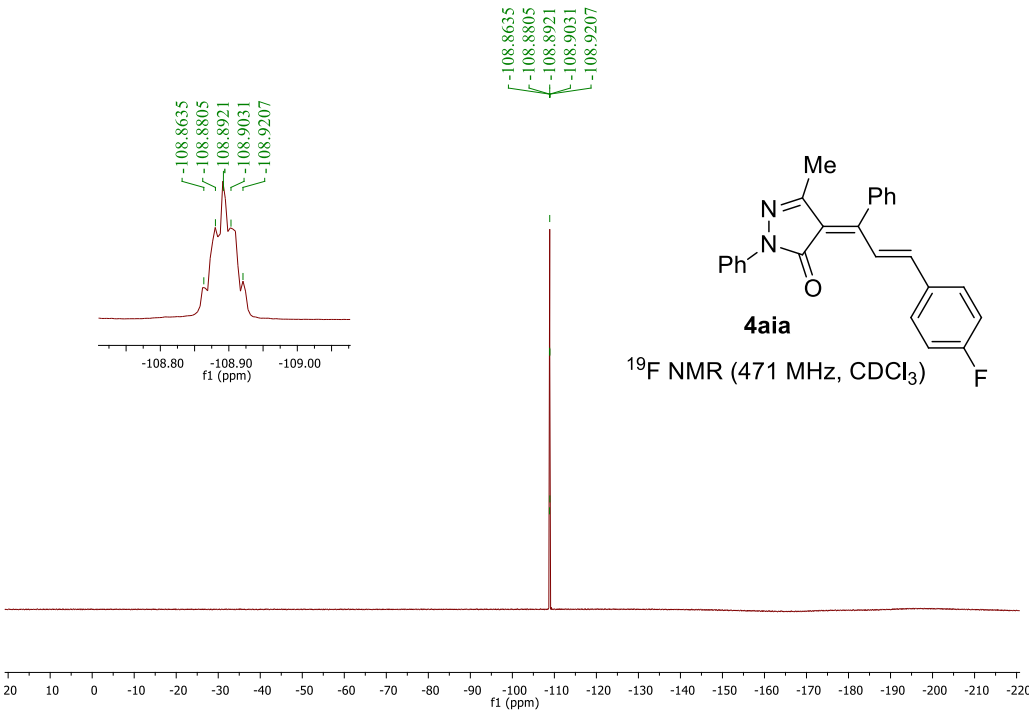


Figure 4.77 471 MHz ^{19}F NMR of **4aia** in $CDCl_3$

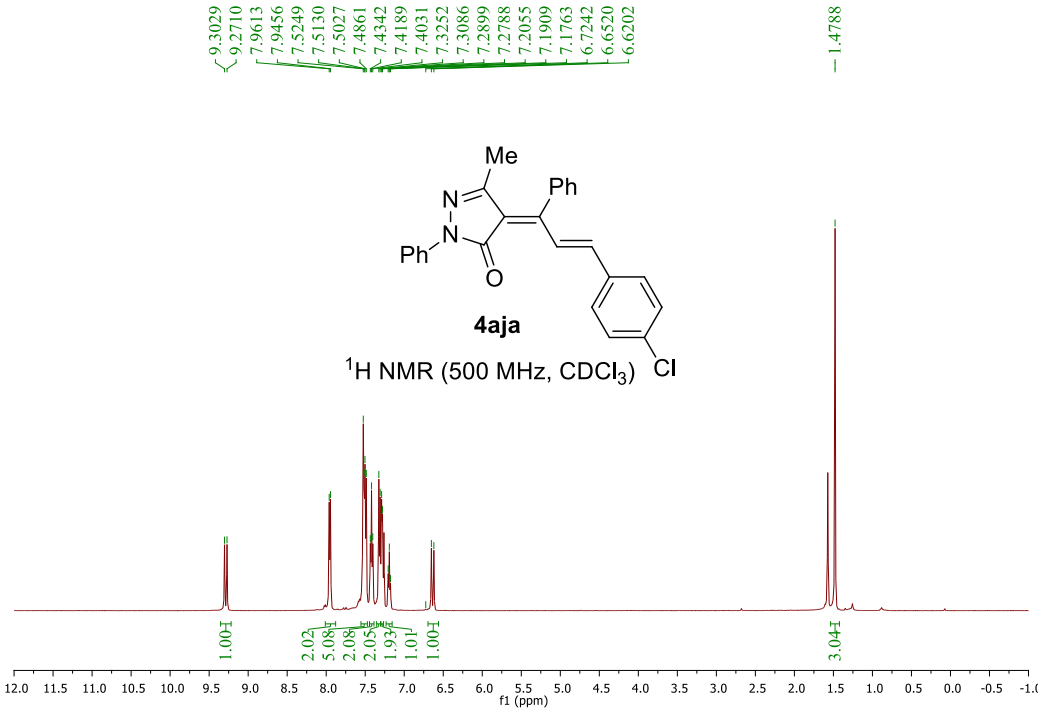


Figure 4.78 500 MHz ^{1}H Spectrum of **4aja** in $CDCl_3$

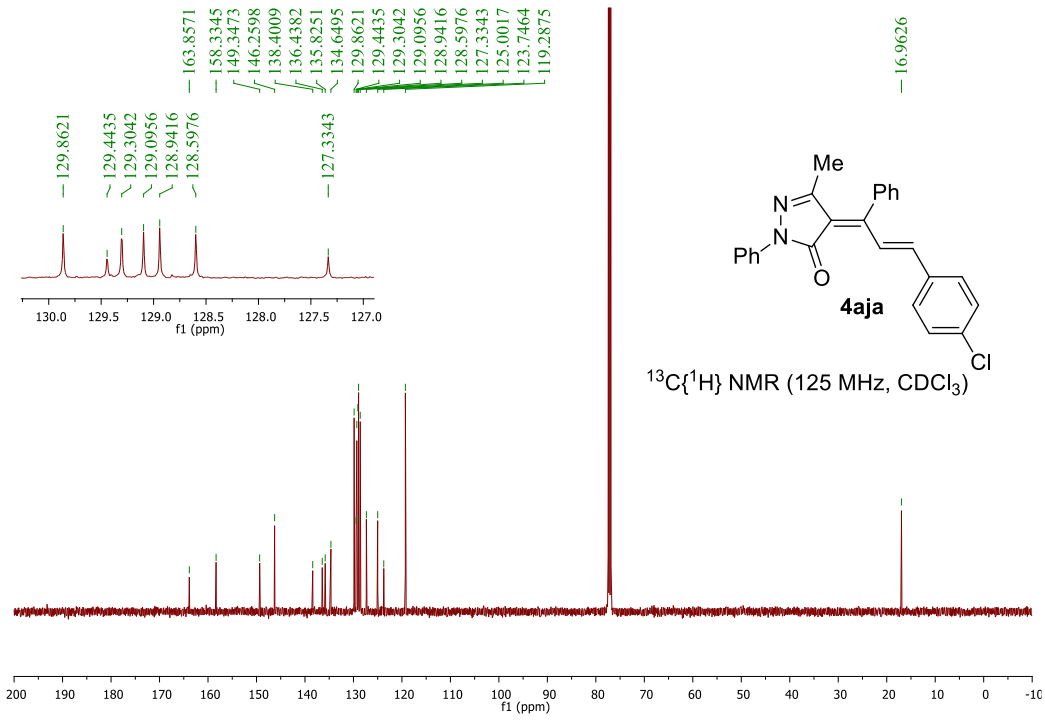


Figure 4.79 125 MHz ^{13}C Spectrum of **4aja** in $CDCl_3$

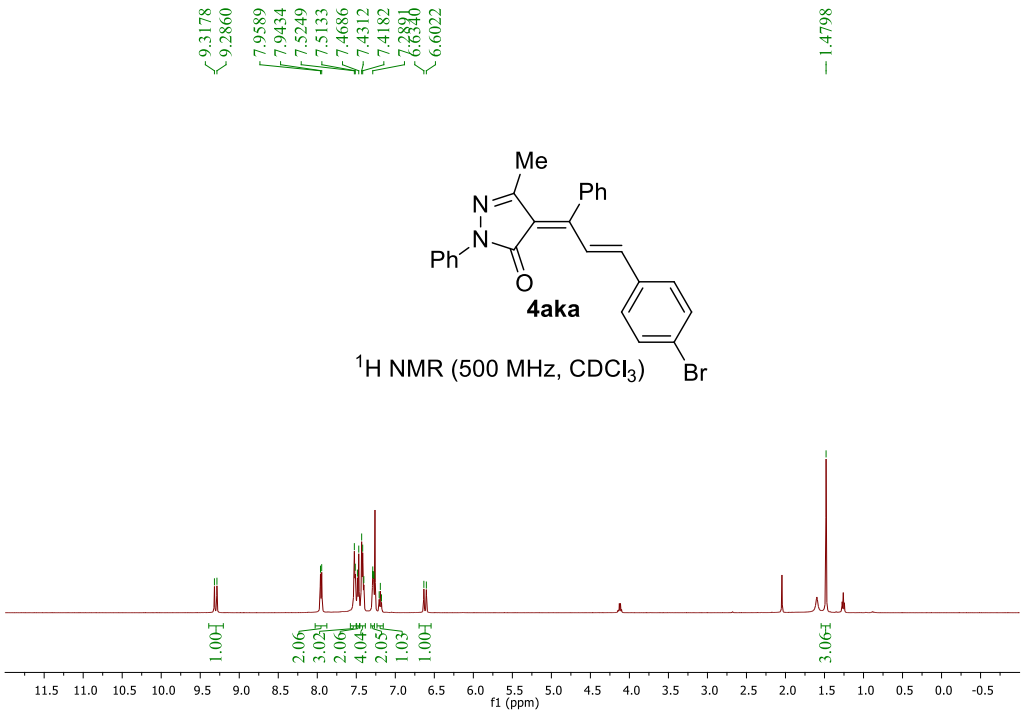


Figure 4.80 500 MHz ^{1}H Spectrum of **4aka** in $CDCl_3$

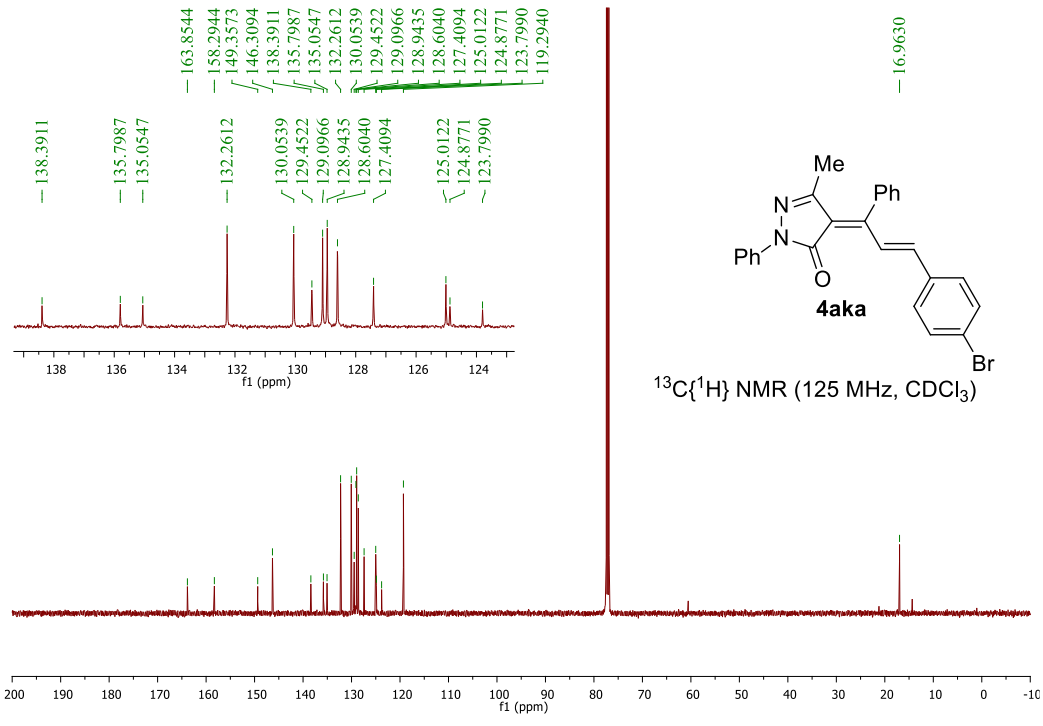


Figure 4.81 125 MHz ^{13}C Spectrum of **4aka** in $CDCl_3$

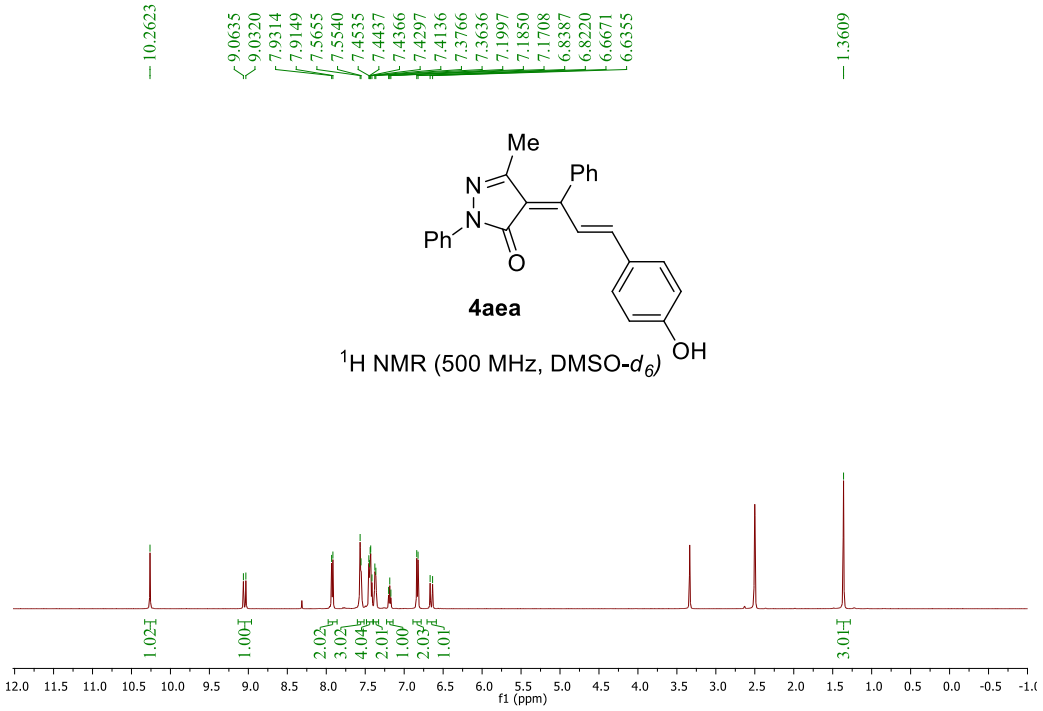


Figure 4.82 500 MHz ^{1}H Spectrum of **4aea** in DMSO-d_6

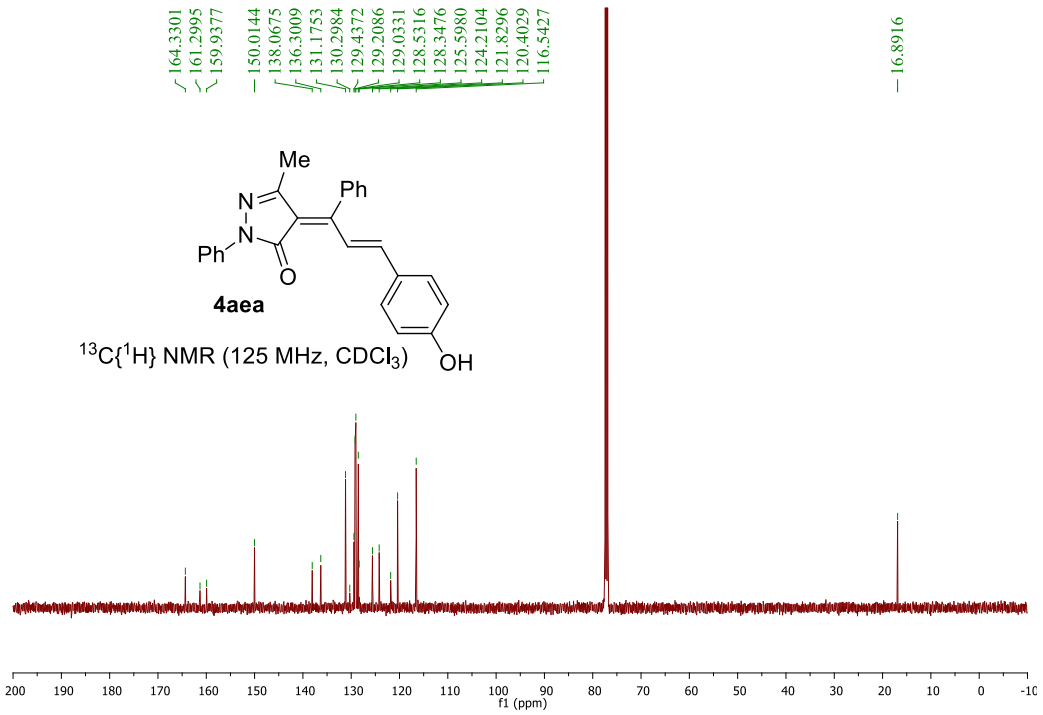


Figure 4.83 125 MHz ^{13}C Spectrum of **4aea** in $CDCl_3$

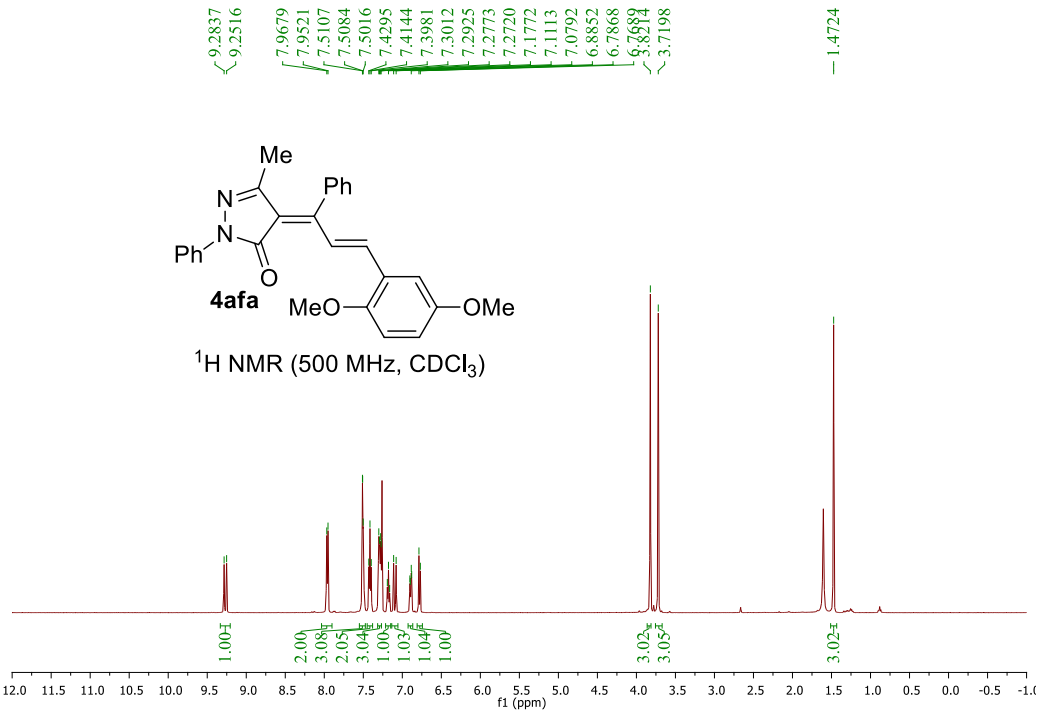


Figure 4.84 500 MHz ^{1}H Spectrum of **4afa** in $CDCl_3$

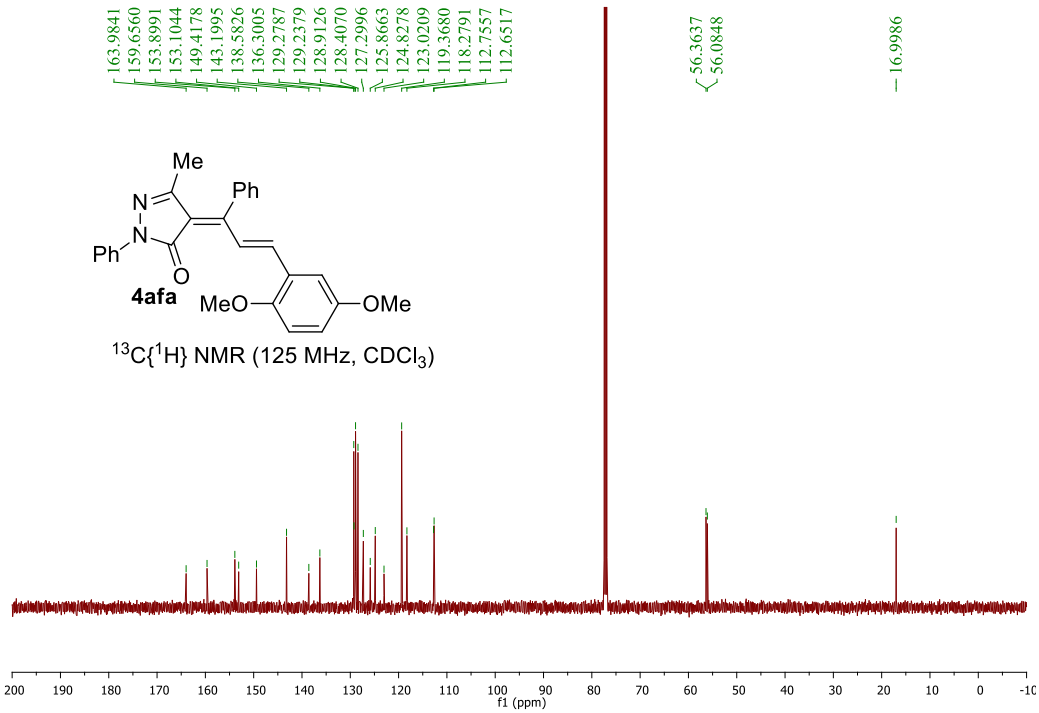


Figure 4.85 125 MHz ^{13}C Spectrum of **4afa** in $CDCl_3$

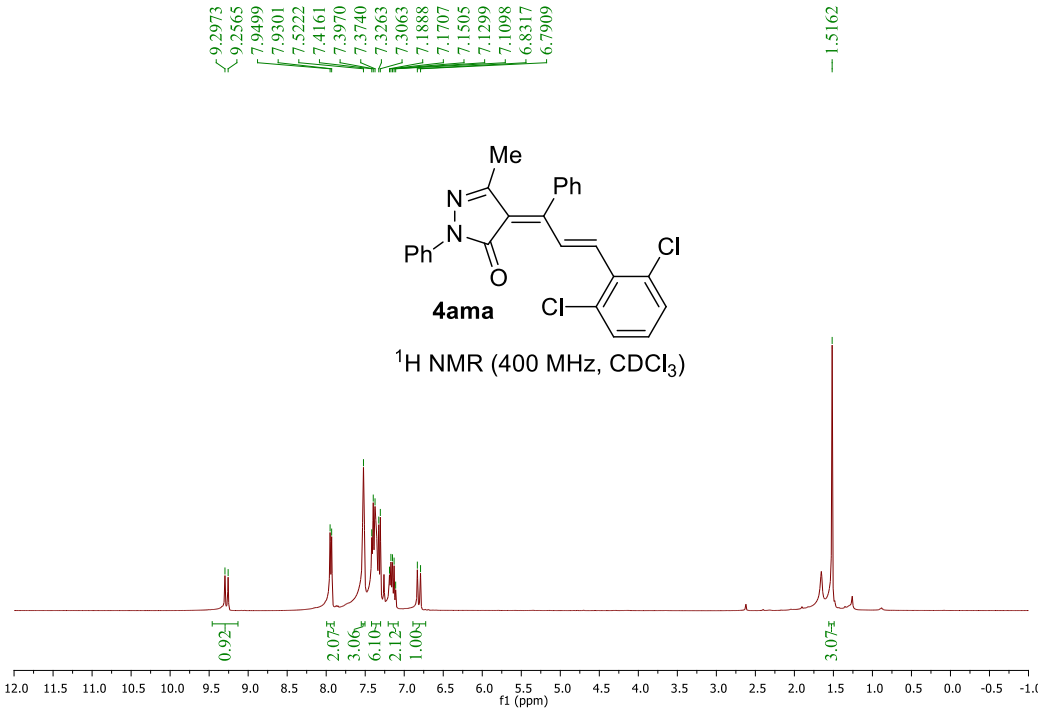


Figure 4.86 500 MHz ^{1}H Spectrum of **4ama** in $CDCl_3$

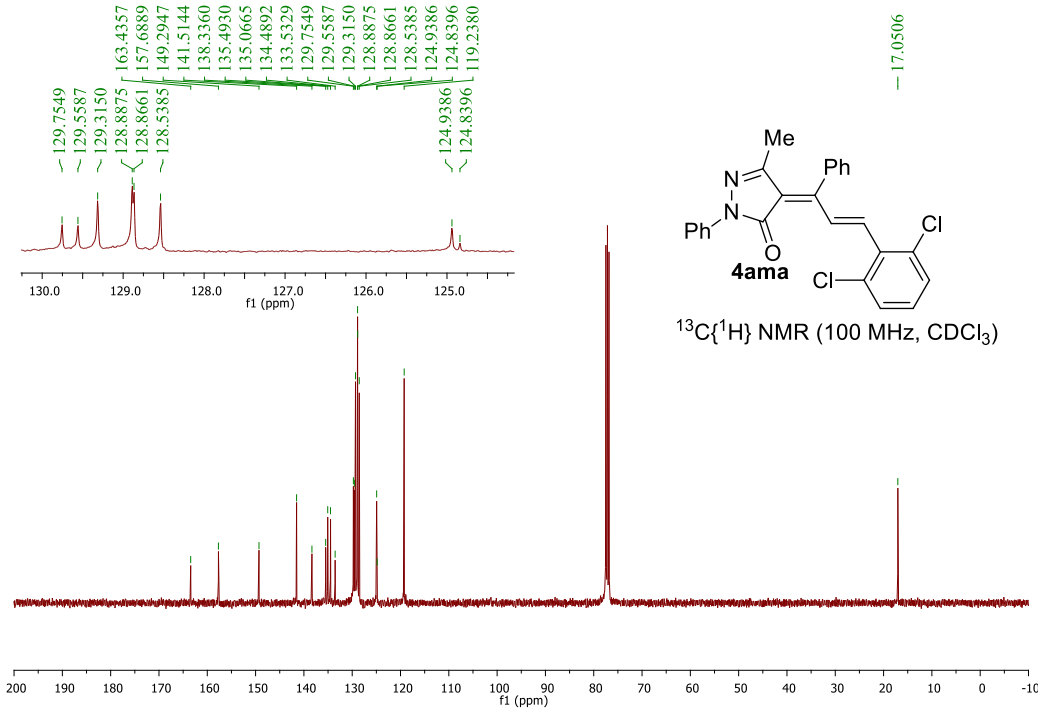


Figure 4.87 125 MHz ^{13}C Spectrum of **4ama** in $CDCl_3$

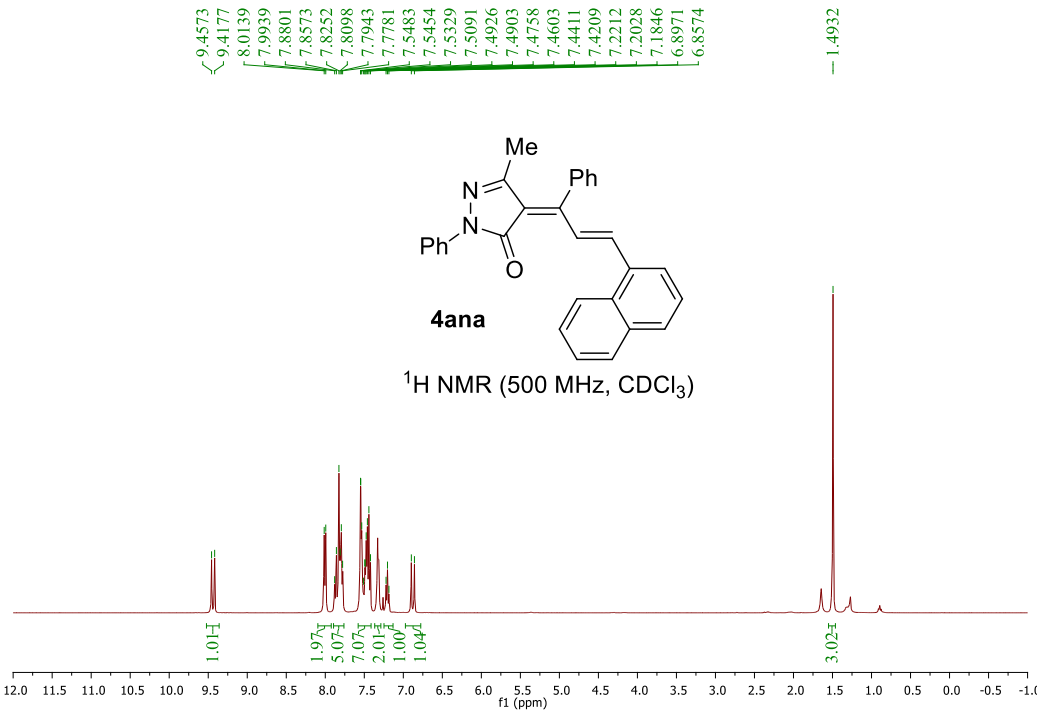


Figure 4.88 500 MHz ^{1}H Spectrum of **4ana** in $CDCl_3$

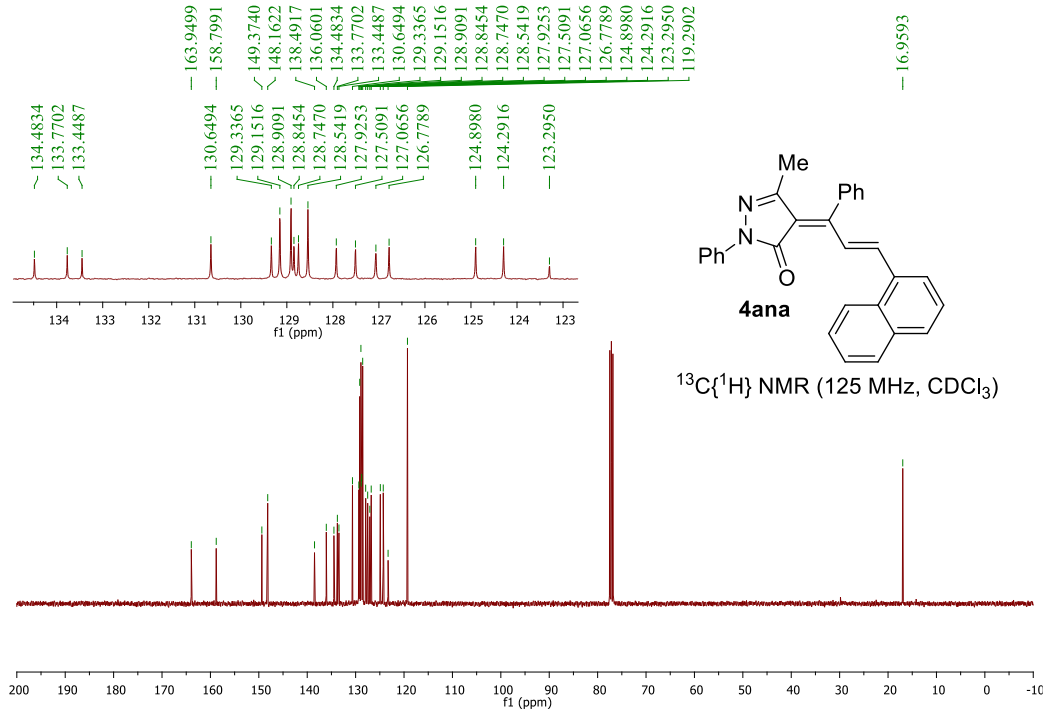


Figure 4.89 125 MHz ^{13}C Spectrum of **4ana** in $CDCl_3$

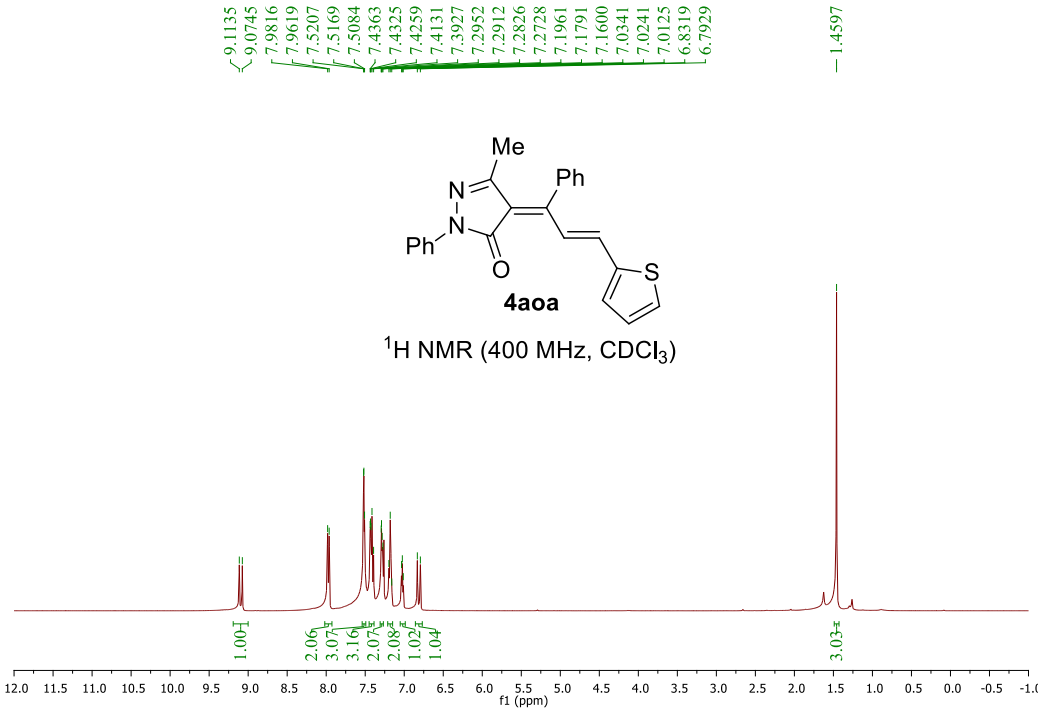


Figure 4.90 500 MHz ^{1}H Spectrum of **4aoa** in $CDCl_3$

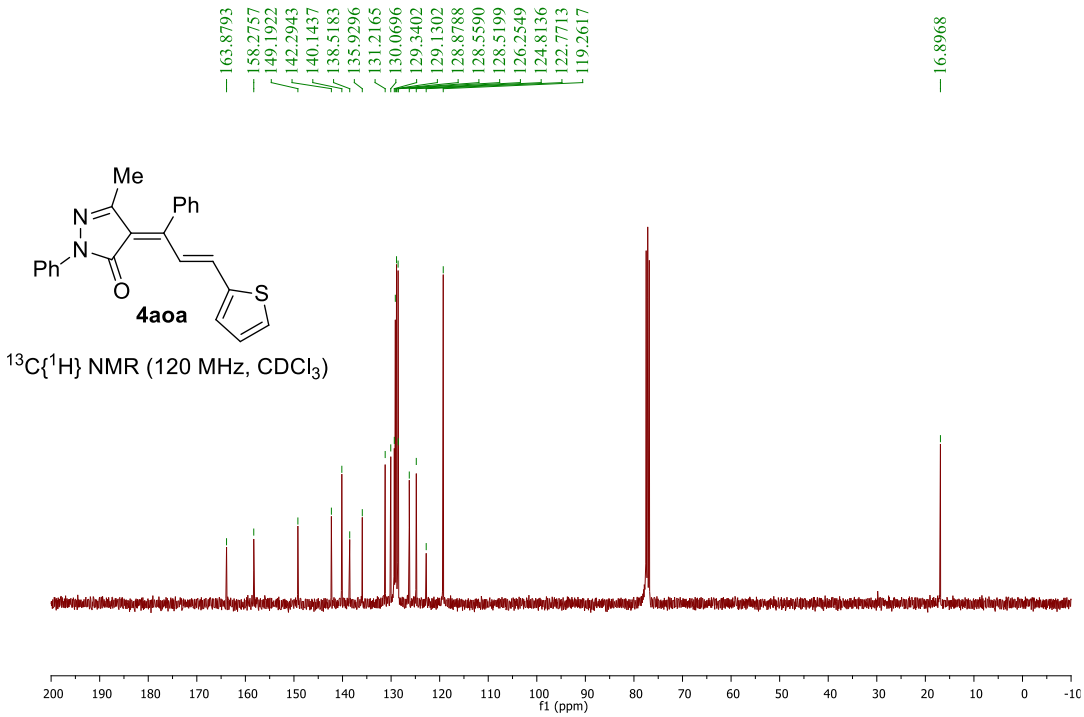


Figure 4.91 125 MHz ^{13}C Spectrum of **4aoa** in $CDCl_3$

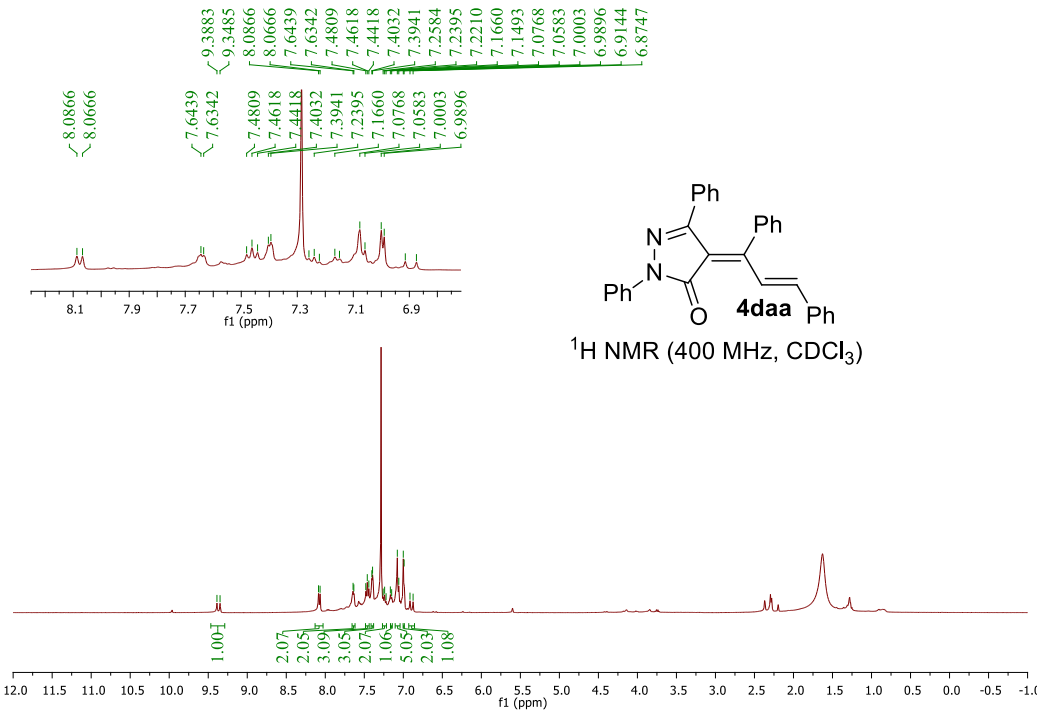


Figure 4.92 500 MHz ^{1}H Spectrum of **4daa** in $CDCl_3$

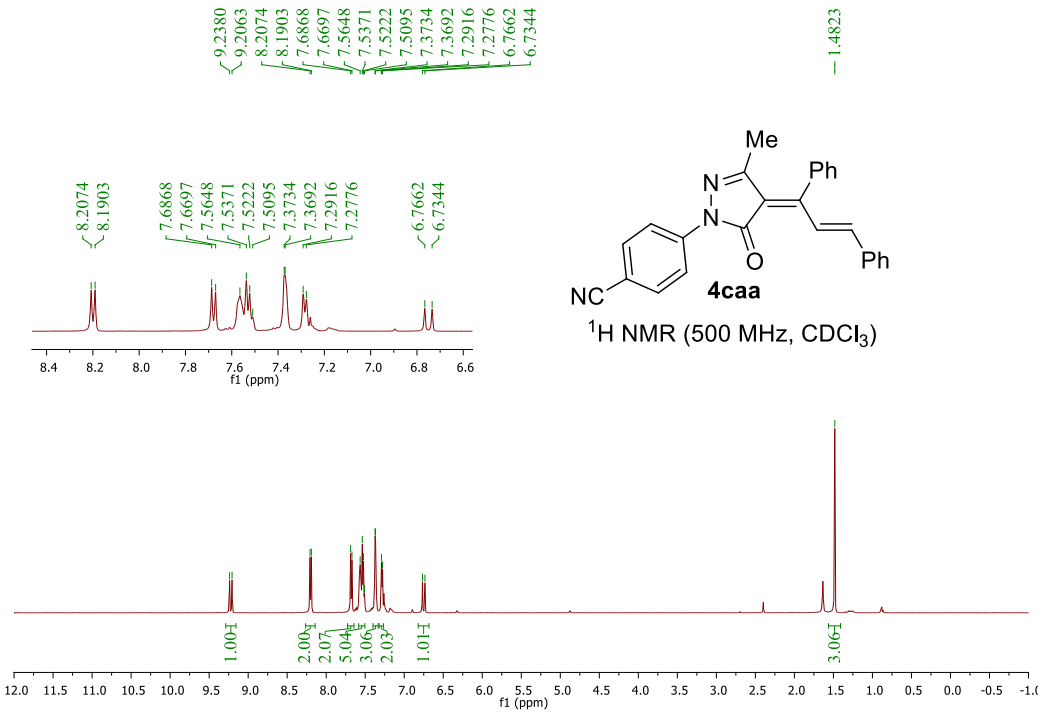


Figure 4.93 500 MHz ^{1}H Spectrum of **4caa** in $CDCl_3$

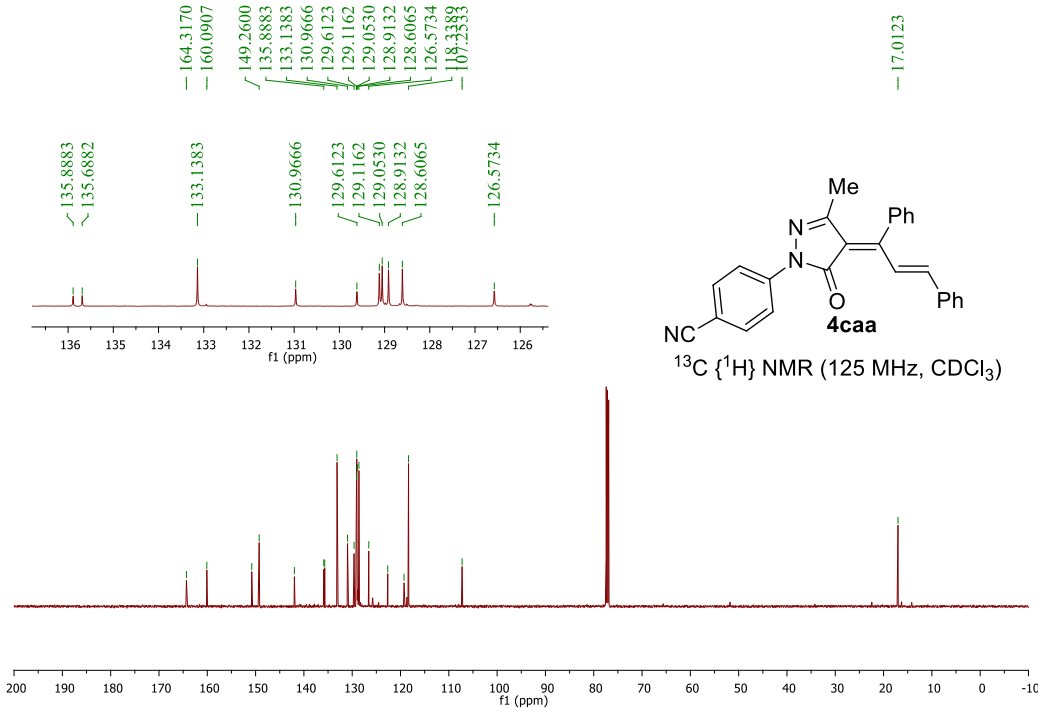


Figure 4.94 125 MHz ^{13}C Spectrum of **4caa** in $CDCl_3$

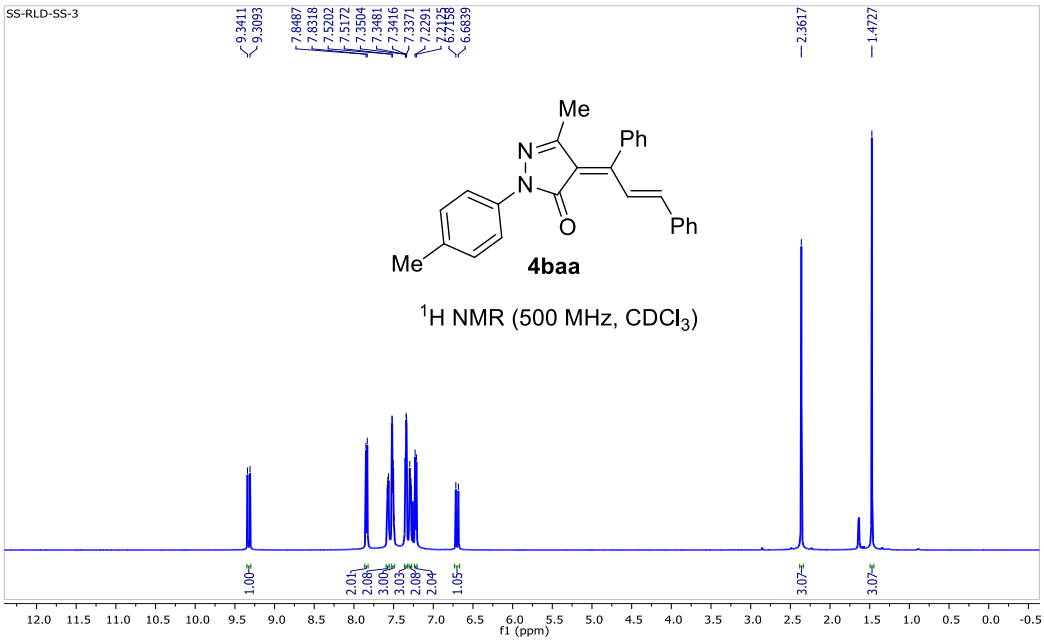


Figure 4.95 500 MHz ^{1}H Spectrum of **4baa** in $CDCl_3$

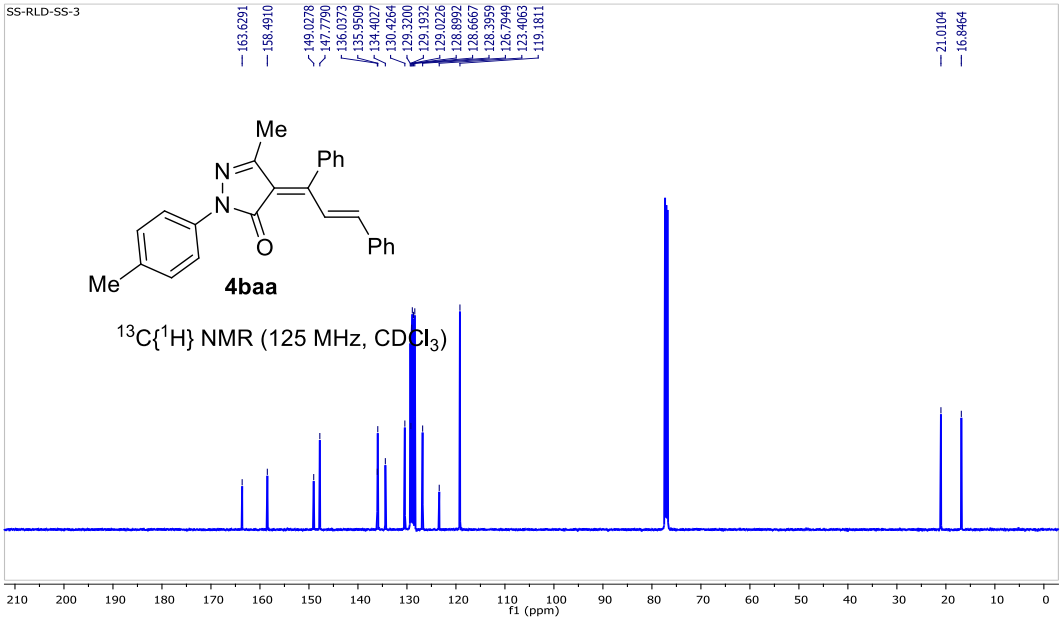


Figure 4.96 125 MHz ^{13}C Spectrum of **4baa** in $CDCl_3$

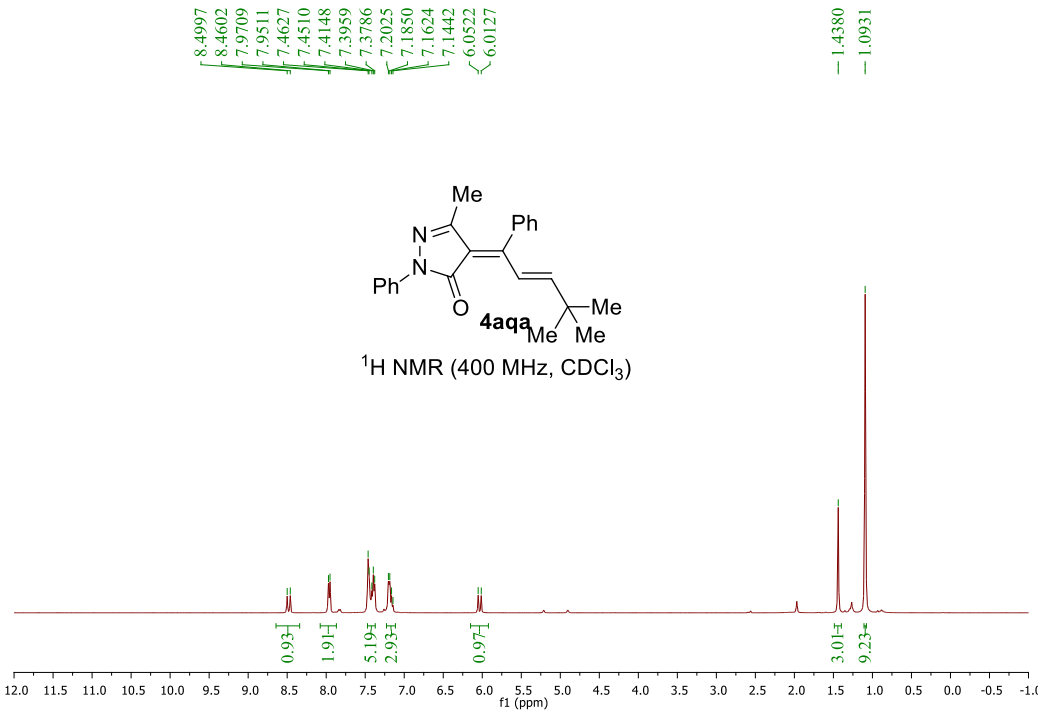


Figure 4.97 500 MHz ^{1}H Spectrum of **4aqa** in $CDCl_3$

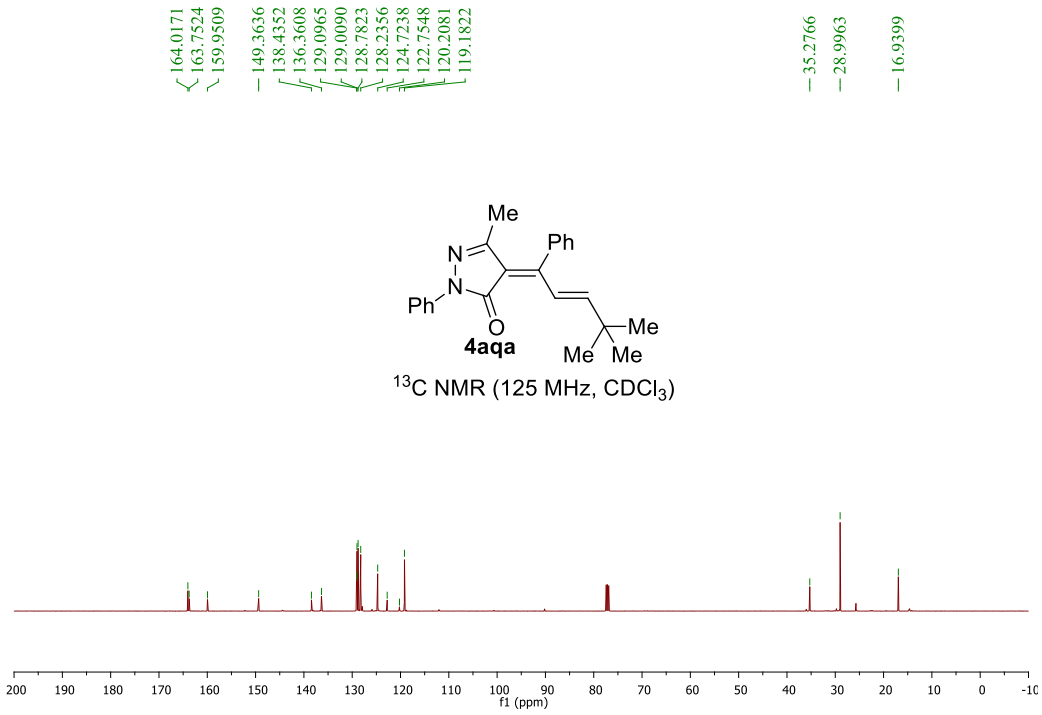


Figure 4.98 125 MHz ^{13}C Spectrum of **4aqa** in $CDCl_3$

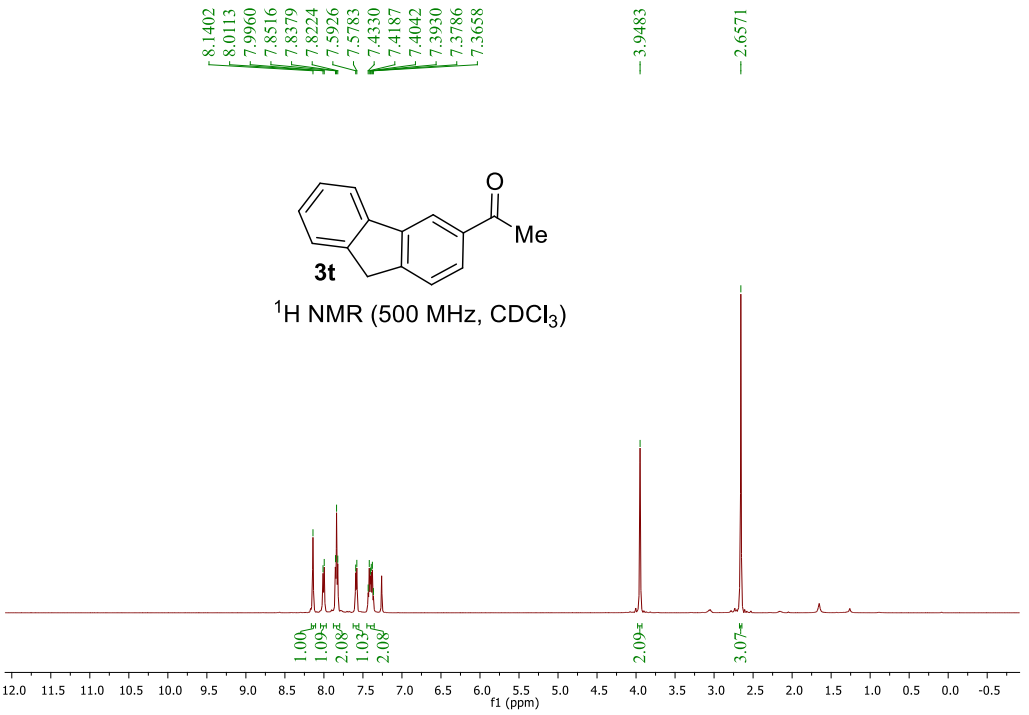


Figure 4.99 500 MHz ^{1}H Spectrum of **3t** in $CDCl_3$

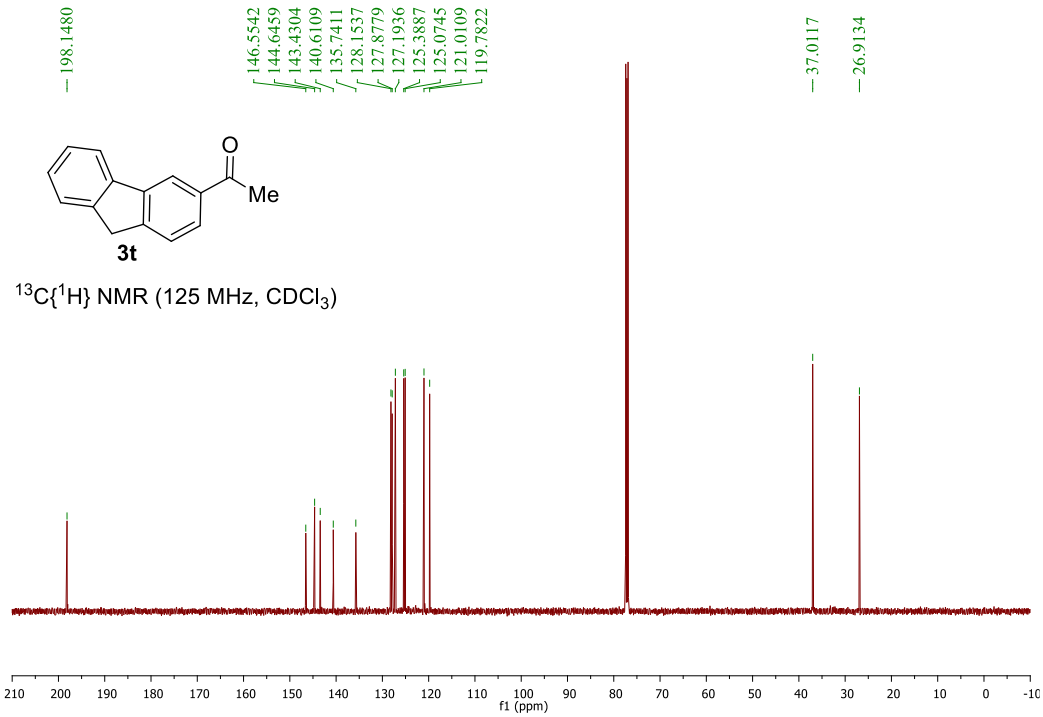


Figure 4.100 125 MHz ^{13}C Spectrum of **3t** in $CDCl_3$

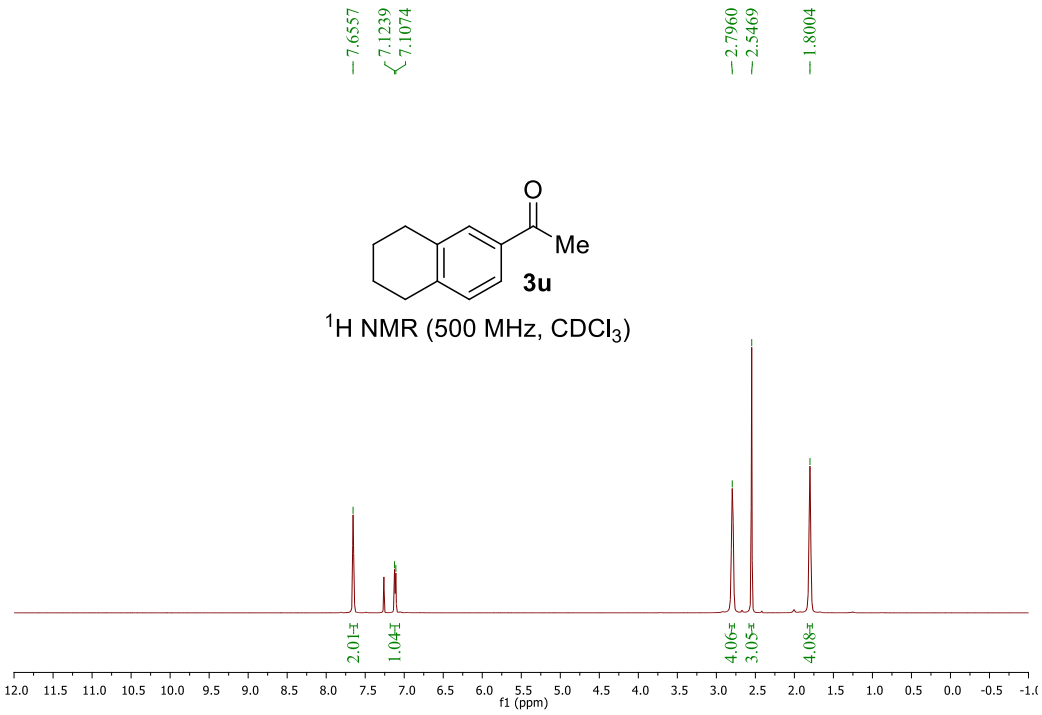


Figure 4.101 500 MHz ^{1}H Spectrum of **3u** in $CDCl_3$

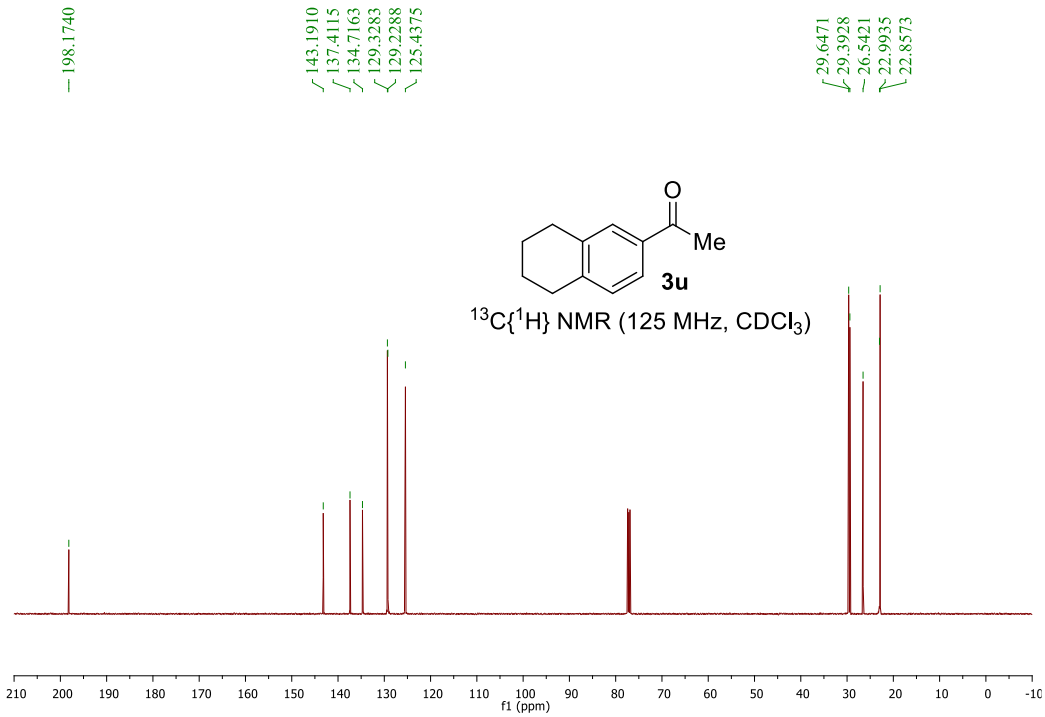


Figure 4.102 125 MHz ^{13}C Spectrum of **3u** in $CDCl_3$

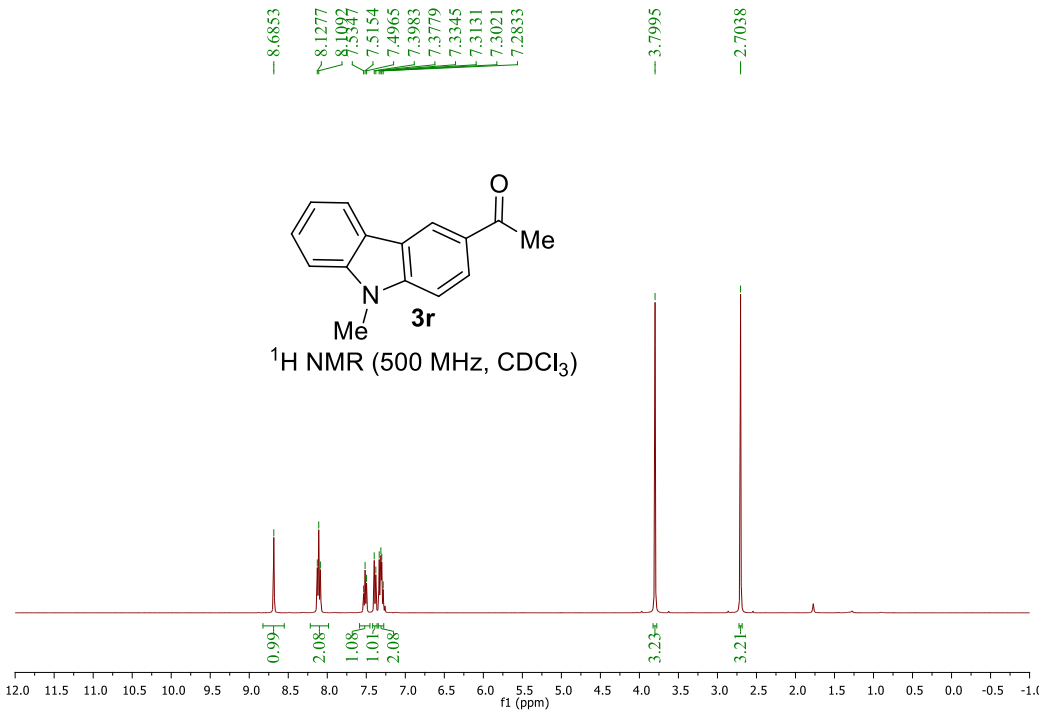


Figure 4.103 500 MHz ^{1}H Spectrum of **3r** in $CDCl_3$

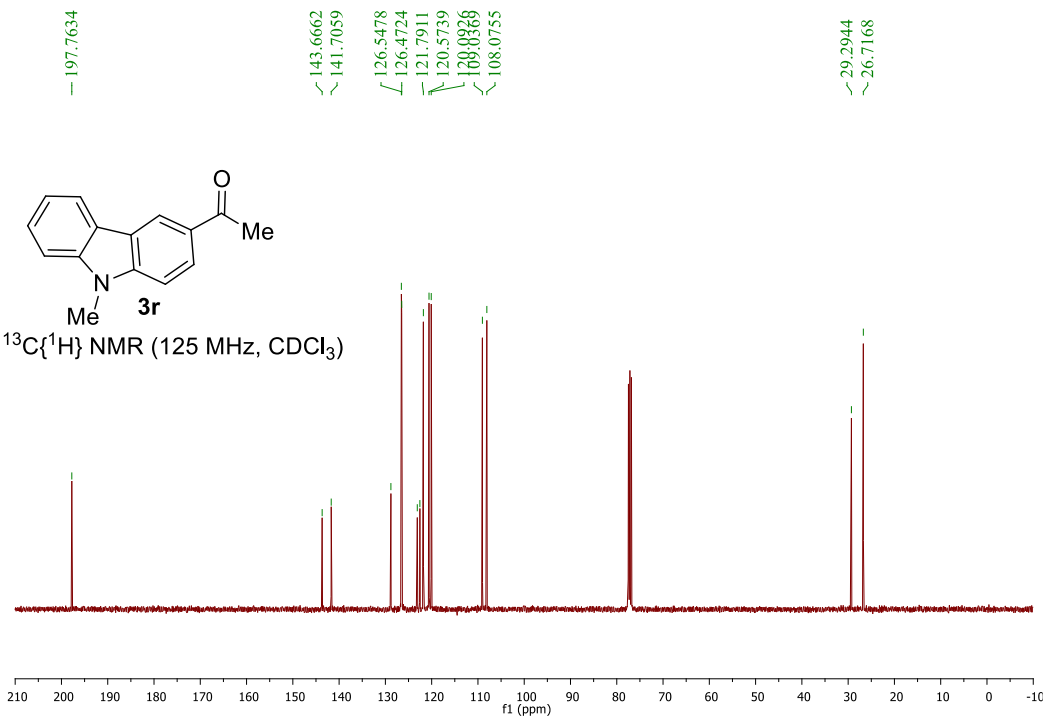


Figure 4.104 125 MHz ^{13}C Spectrum of **3r** in $CDCl_3$

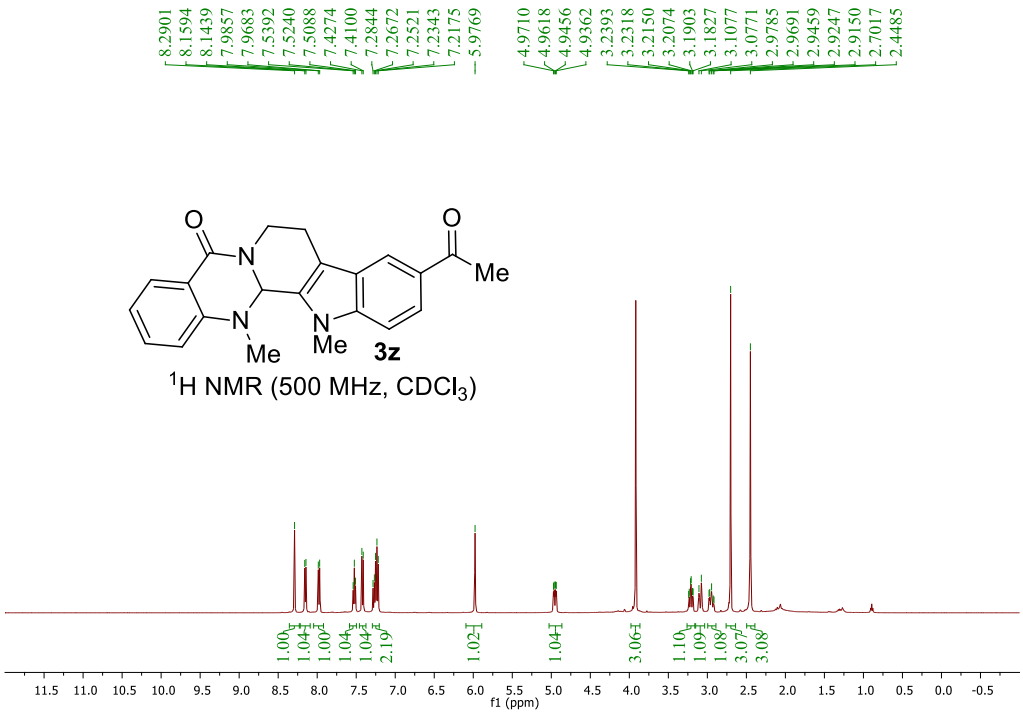


Figure 4.105 500 MHz ^{1}H Spectrum of **3z** in $CDCl_3$

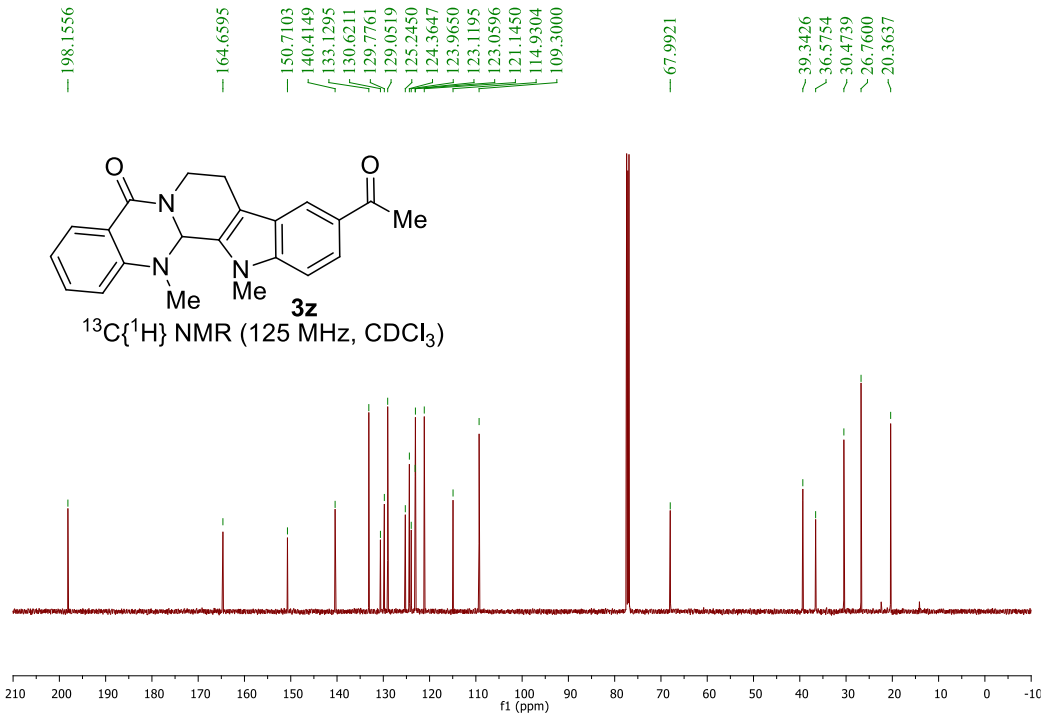


Figure 4.106 125 MHz ^{13}C Spectrum of **3z** in $CDCl_3$

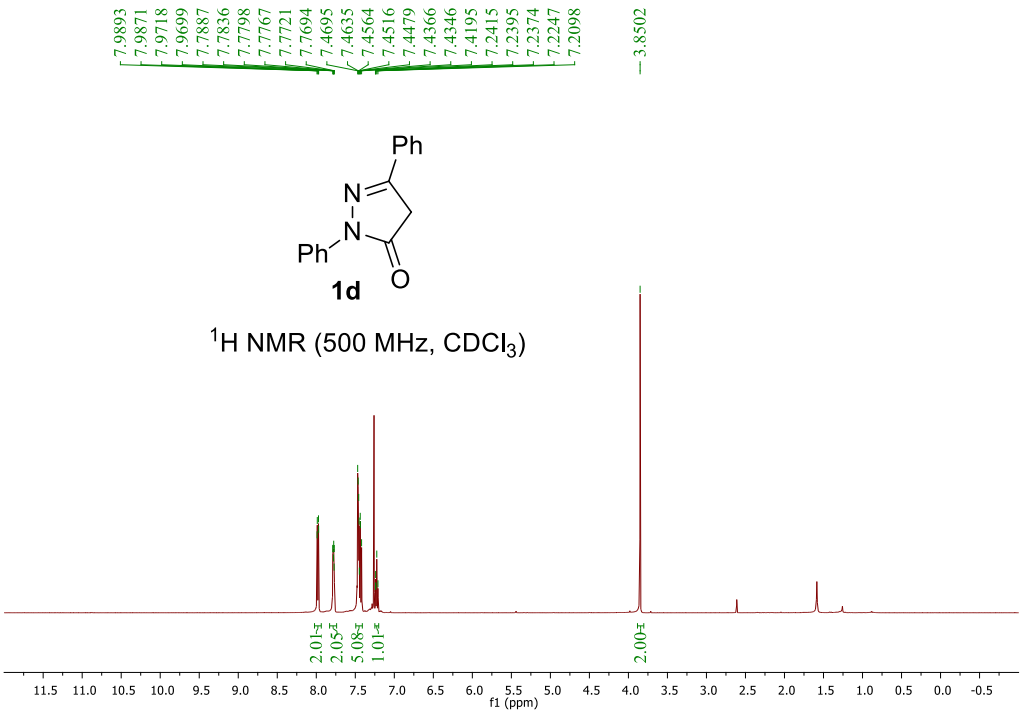


Figure 4.107 500 MHz ^{1}H Spectrum of **1d** in $CDCl_3$

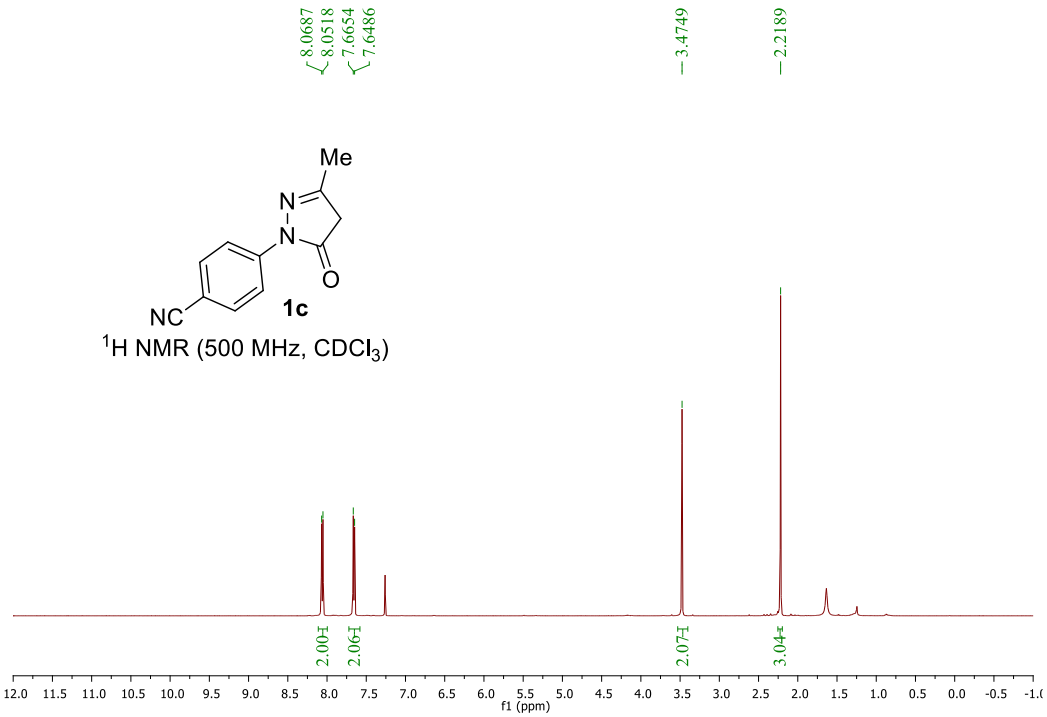


Figure 4.108 500 MHz ^{1}H Spectrum of **1c** in $CDCl_3$

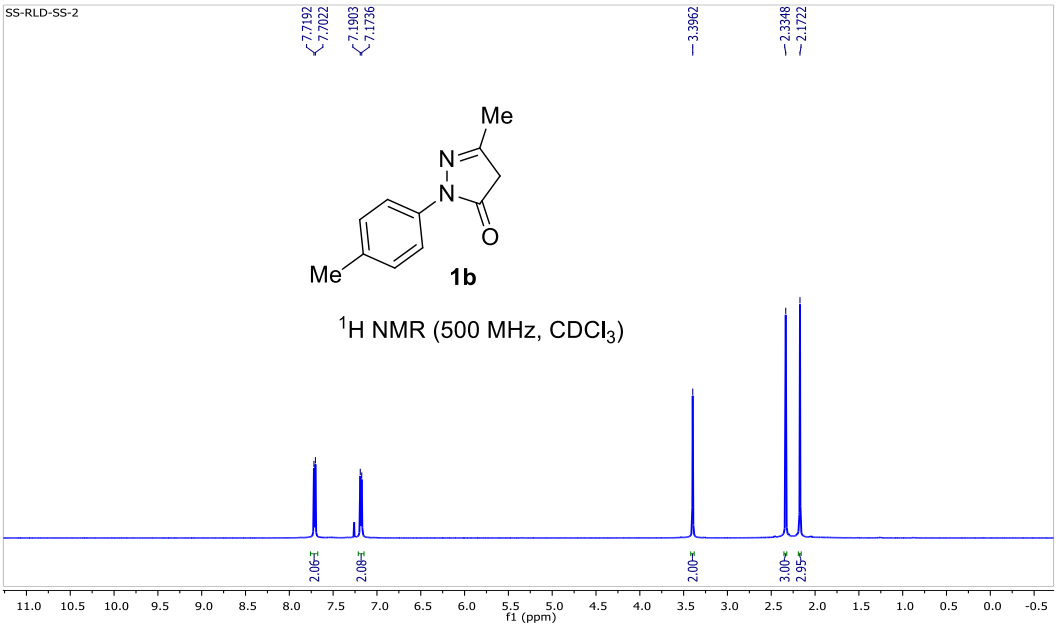


Figure 4.109 500 MHz ^{1}H Spectrum of **1b** in $CDCl_3$

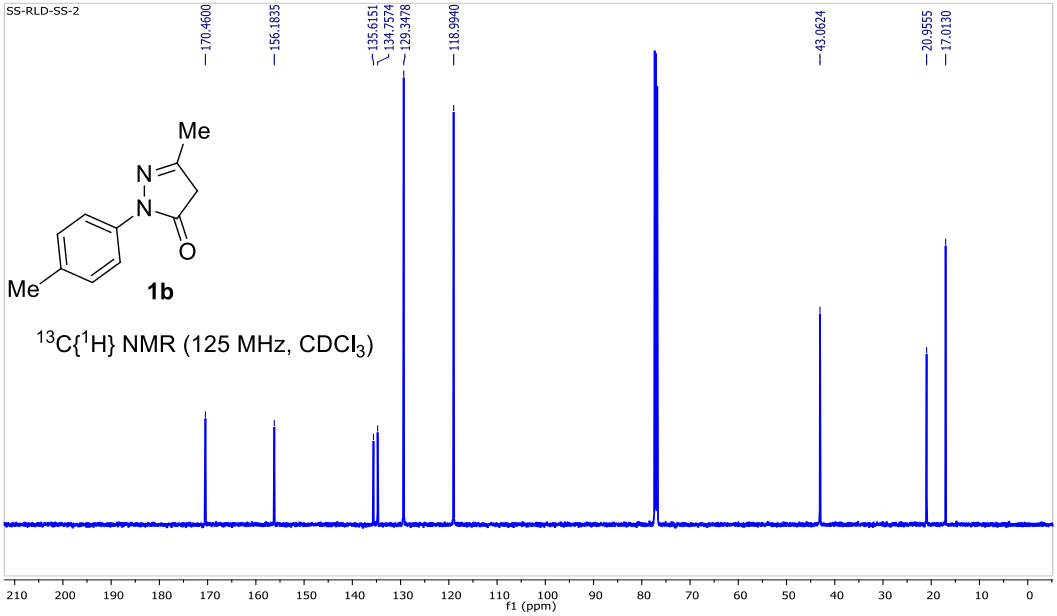


Figure 4.110 125 MHz ^{13}C Spectrum of **1b** in $CDCl_3$

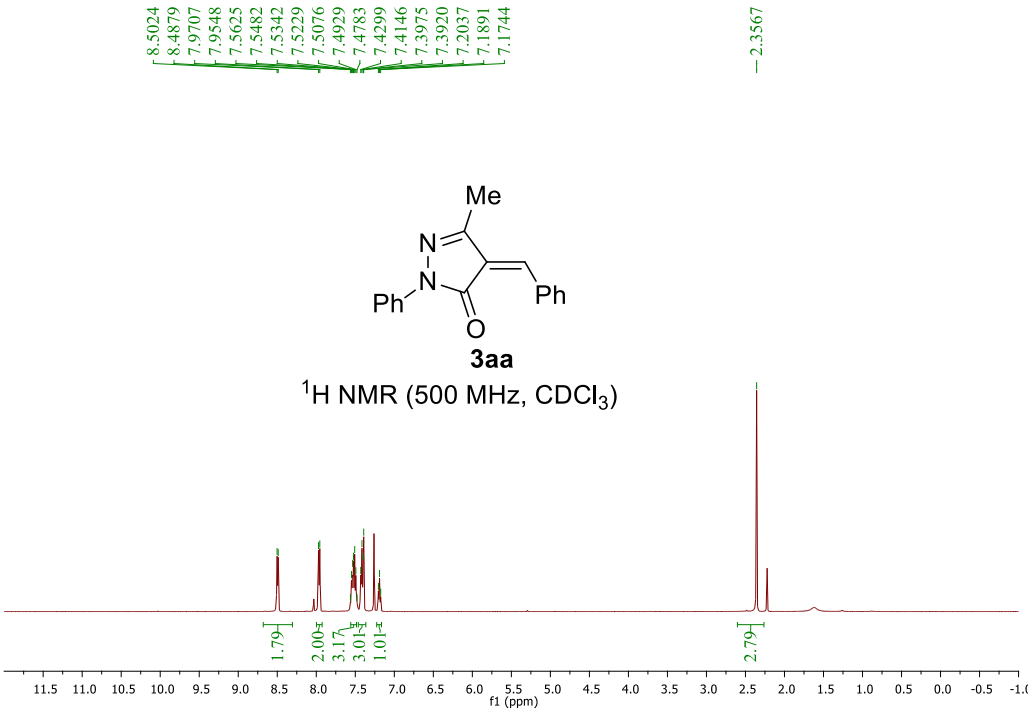


Figure 4.111 500 MHz ^{1}H Spectrum of **3aa** in $CDCl_3$

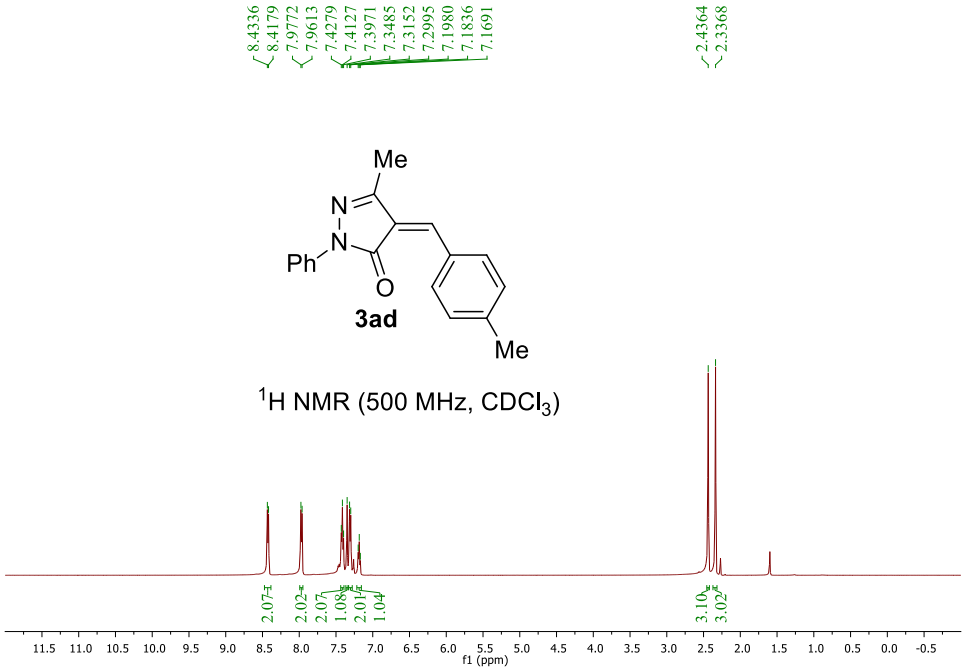


Figure 4.112 500 MHz ^{1}H Spectrum of **3ad** in $CDCl_3$

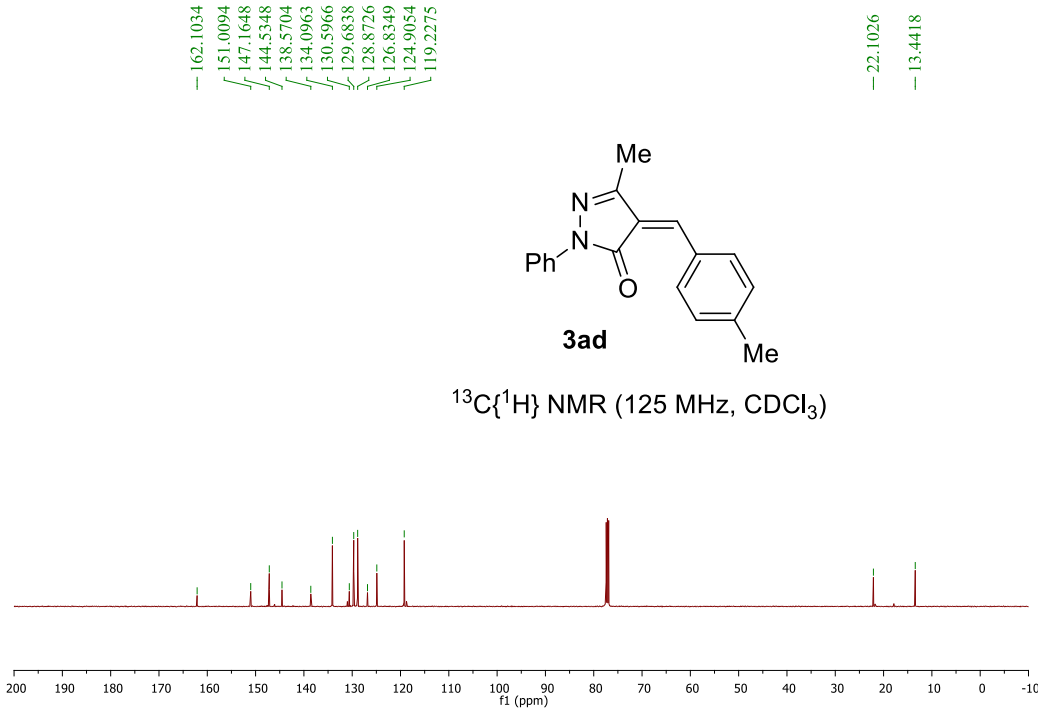


Figure 4.113 125 MHz ^{13}C Spectrum of **3ad** in $CDCl_3$

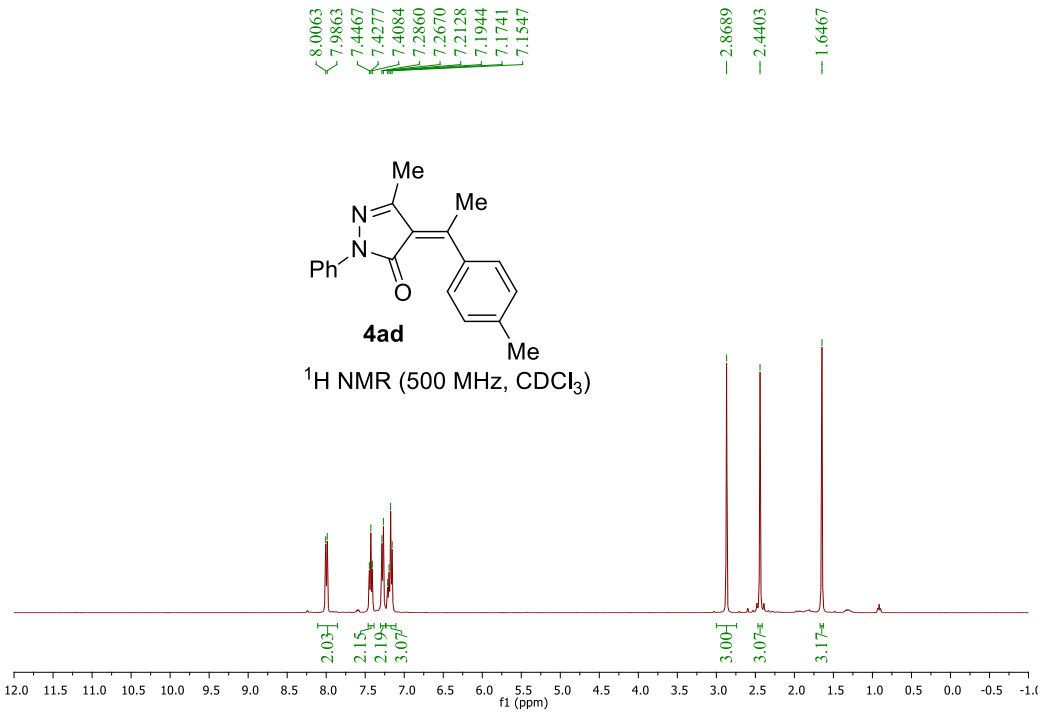


Figure 4.114 500 MHz ^{1}H Spectrum of **4ad** in $CDCl_3$

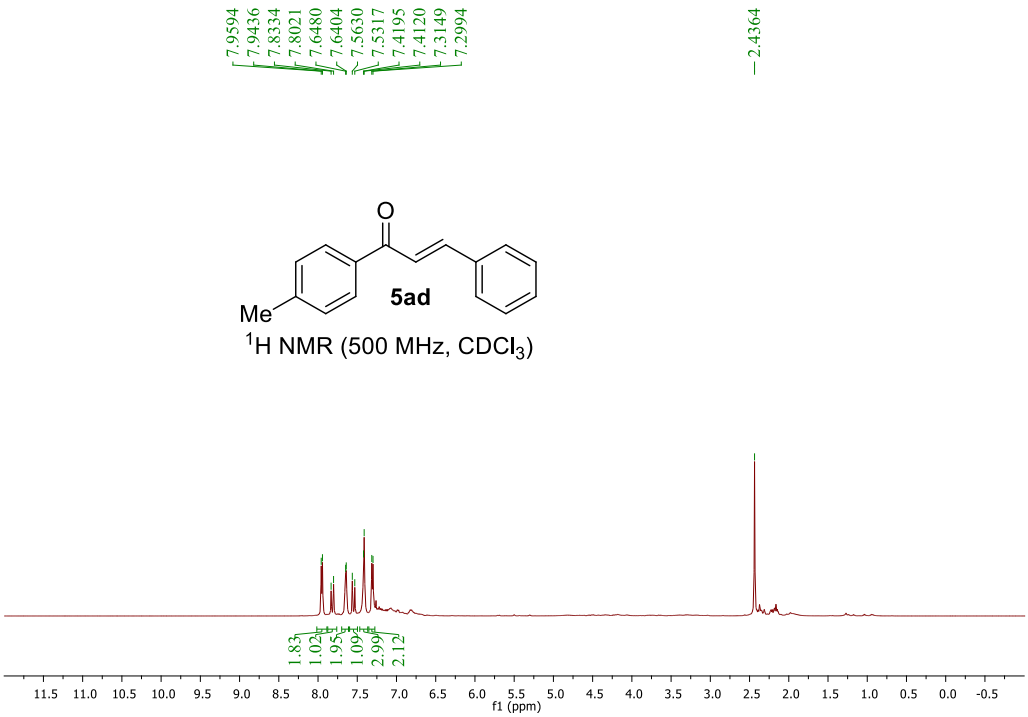


Figure 4.115 500 MHz ^{1}H Spectrum of **5ad** in $CDCl_3$

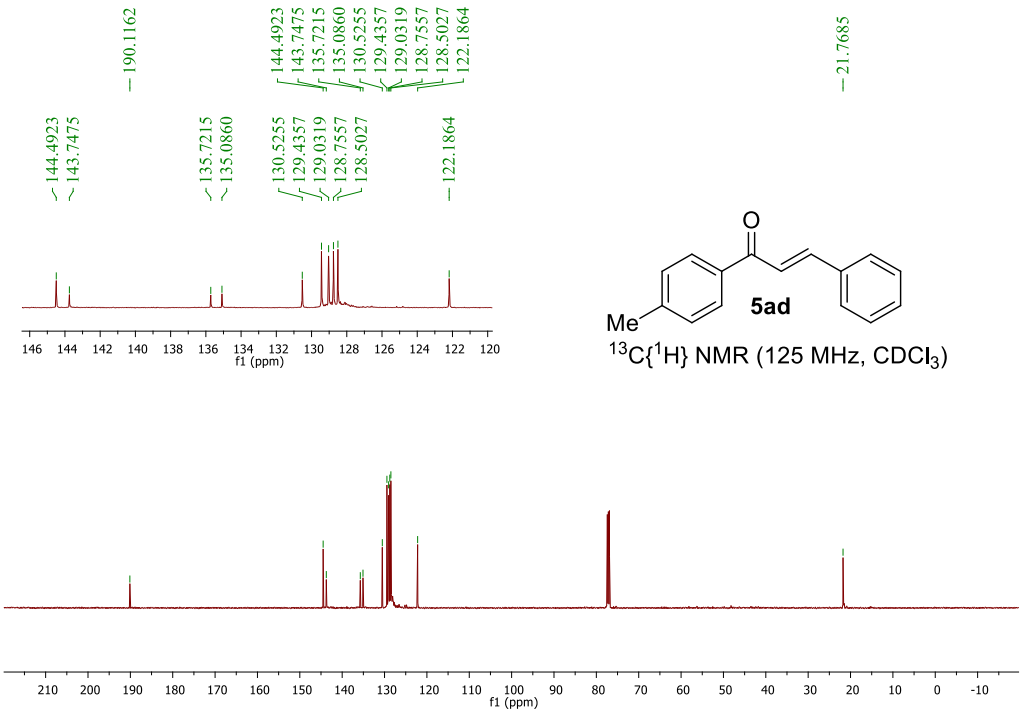


Figure 4.116 125 MHz ^{13}C Spectrum of **5ad** in $CDCl_3$

4.8 References:

1. S Hamama W., G El-Gohary H., Kuhnert N. and H Zoorob H. (2012), Chemistry of pyrazolinones and their applications, *Curr. Org. Chem.*, *16*, 373-399 (DOI: 10.2174/138527212799499921)

2. Ji D. W., Yang F., Chen B. Z., Min X. T., Kuai C. S., Hu Y. C. and Chen Q. A. (2020), Rhodium-catalyzed regio-and enantioselective allylic alkylation of pyrazol-5-ones with alkynes, *Chem. Comm.*, *56*, 8468-8471 (DOI: 0.1039/D0CC04002A)

3. Liu S., Bao X. and Wang B. (2018), Pyrazolone: a powerful synthon for asymmetric diverse derivatizations, *Chem. Comm.*, 54, 11515-11529 (DOI: 10.1039/C8CC06196C)

4. Bao X., Wang X., Tian J. M., Ye X., Wang B. and Wang H. (2022), Recent advances in the applications of pyrazolone derivatives in enantioselective synthesis, *Org. Biomol. Chem.*, *20*, 2370-2386 (DOI: 10.1039/D1OB02426D)

5. Bao X., Wang B., Cui L., Zhu G., He Y., Qu J. and Song Y. (2015), An organocatalytic asymmetric Friedel–Crafts addition/fluorination sequence: construction of oxindole−pyrazolone conjugates bearing vicinal tetrasubstituted stereocenters, *Org. Lett.*, *17*, 5168-5171 (DOI: 10.1021/acs.orglett.5b02470)

6. Mustafa G., Zia-ur-Rehman M., Sumrra S. H., Ashfaq M., Zafar W. and Ashfaq M. (2022), A critical review on recent trends on pharmacological applications of pyrazolone endowed derivatives, *J. Mol. Struct.*, *1262*, 133044 (DOI: 10.1016/j.molstruc.2022.133044)

7. Sharma R., Chawla P. A., Chawla V., Verma R., Nawal N. and Gupta V. (2021), A therapeutic journey of 5-pyrazolones as a versatile scaffold: a review, *Mini Rev. Med. Chem.*, *21*, 1770-1795 (DOI: 10.2174/1389557521999210101224058)

8. Zhao Z., Dai X., Li C., Wang X., Tian J., Feng Y., Xie J., Ma C., Nie Z., Fan P. and Qian M. (2020), Pyrazolone structural motif in medicinal

chemistry: Retrospect and prospect. *Eur. J. Med. Chem.*, *186*, 111893 (DOI: 10.1016/j.ejmech.2019.111893)

9. Zhang J., Yang Y., Qian X. K., Song P. F., Zhao Y. S., Guan X. Q., Zou L. W., Bao X. and Wang H. (2021) Design, Synthesis, and Structure-Activity Relationship Study of Pyrazolones as Potent Inhibitors of Pancreatic Lipase, *ChemMedChem*, *16*, 1600-1604 (DOI: 10.1002/cmdc.202000850)

10. Ramajayam R., Tan K. P., Liu H. G. and Liang P. H. (2010), Synthesis and evaluation of pyrazolone compounds as SARS-coronavirus 3C-like protease inhibitors, *Bioorg. Med. Chem.*, *18*, 7849-7854 (DOI: 10.1016/j.bmc.2010.09.050)

11. Kumar V., Chang C. K., Tan K. P., Jung Y. S., Chen S. H., Cheng Y. S. E. and Liang P. H. (2014), Identification, synthesis, and evaluation of new neuraminidase inhibitors, *Org. Lett.*, *16*, 5060-5063 (DOI: 10.1021/ol502410x)

12. Huang H., Yu Y., Gao Z., Zhang Y., Li C., Xu X., Jin H., Yan W., Ma R., Zhu J. and Shen X. (2012), Discovery and optimization of 1,3,4-trisubstituted-pyrazolone derivatives as novel, potent, and nonsteroidal farnesoid X receptor (FXR) selective antagonists, *J. Med. Chem.*, *55*, 7037-7053 (DOI: 10.1021/jm3002718)

13. Dayam R., Al-Mawsawi L. Q., Zawahir Z., Witvrouw M., Debyser Z. and Neamati N. (2008), Quinolone 3-carboxylic acid pharmacophore: design of second generation HIV-1 integrase inhibitors, *J. Med. Chem.*, *51*, 1136-1144 (DOI: 10.1021/jm070609b)

14. Fan X., Zhang X., Zhou L., Keith K. A., Kern E. R. and Torrence P. F., (2006), A pyrimidine–pyrazolone nucleoside chimera with potent in vitro anti-orthopoxvirus activity, *Bioorg. Med. Chem. Lett.*, *16*, 3224-3228 (DOI: 10.1016/j.bmcl.2006.03.043)

15. Dawood D. H., Nossier E. S., Ali M. M. and Mahmoud A. E. (2020), Synthesis and molecular docking study of new pyrazole derivatives as potent

anti-breast cancer agents targeting VEGFR-2 kinase, *Bioorg. Chem.*, *101*, 103916 (DOI: 10.1016/j.bioorg.2020.103916)

16. Castagnolo D., Manetti F., Radi M., Bechi B., Pagano M., De Logu A., Meleddu R., Saddi M. and Botta M. (2009), Synthesis, biological evaluation, and SAR study of novel pyrazole analogues as inhibitors of Mycobacterium tuberculosis: Part 2. Synthesis of rigid pyrazolones, *Bioorg. Med. Chem.*, *17*, 5716-5721 (DOI: 10.1016/j.bmc.2009.05.058)

17. Maity R. and Pan S. C., (2017), Enantioselective aminocatalytic synthesis of tetrahydropyrano [2,3-*c*] pyrazoles *via* a domino Michael-hemiacetalization reaction with alkylidene pyrazolones, *Org. Biomol. Chem.*, *15*, 8032-8036 (DOI: 10.1039/C7OB02170D)

18. Li J. H. and Du D. M. (2015), Phosphine-Catalyzed Cascade Reaction of Unsaturated Pyrazolones with Alkyne Derivatives: Efficient Synthesis of Pyrano [2,3-*c*] pyrazoles and Spiro-cyclopentanone-pyrazolones, *Adv. Synth. Catal.*, *357*, 3986-3994 (DOI: 10.1002/adsc.201500675)

19. Cheng C., Zhang J., Wang X. and Miao Z. (2018), DBU-Promoted [4+4] Domino Cycloaddition of Ynones with Benzylidenepyrazolones To Access Eight-Membered Cyclic Ethers, *J. Org. Chem.*, *83*, 5450-5457 (DOI: 10.1021/acs.joc.8b00352)

20. Mao B., Liu H., Yan Z., Xu Y., Xu J., Wang W., Wu Y. and Guo H. (2020), Palladium-Catalyzed Asymmetric [4+2] Cycloaddition of 2-Methylidenetrimethylene Carbonate with Alkenes: Access to Chiral Tetrahydropyran-Fused Spirocyclic Scaffolds, *Angew. Chem. Int. Ed.*, *59*, 11316-11320 (DOI: 10.1002/anie.202002765)

21. Li X., Chen F. Y., Kang J. W., Zhou J., Peng C., Huang W., Zhou M. K., He G. and Han B. (2019), Stereoselective assembly of multifunctional spirocyclohexene pyrazolones that induce autophagy-dependent apoptosis in colorectal cancer cells, *J. Org. Chem.*, *84*, 9138-9150 (DOI: 10.1021/acs.joc.9b01098)

22. Kumari A., Patanvadiya D. J., Jain A., Patra R., Paranjothy M. and Rana N. K. (2024), Pyridinium Ylide-Mediated Diastereoselective Synthesis of Spirocyclopropanyl-pyrazolones *via* Cascade Michael/Substitution Reaction, *J. Org. Chem.*, *89*, 8230-8242 (DOI: 10.1021/acs.joc.3c02879)

23. Zhao L., Peng J., Chen M., Liu Y., Yao L., Feng W. and Li F. (2014), Yolk–shell upconversion nanocomposites for LRET sensing of cysteine/homocysteine, *ACS Appl. Mater. Interfaces.*, *6*, 11190-11197 (DOI: 10.1021/am501249p)

24. Liu J., Liu Y., Liu Q., Li C., Sun L. and Li F. (2011), Iridium (III) complex-coated nanosystem for ratiometric upconversion luminescence bioimaging of cyanide anions, *J. Am. Chem. Soc.*, *133*, 15276-15279 (DOI: 10.1021/ja205907y)

25. Sun Y. F. and Cui Y. P. (2009), The synthesis, structure and spectroscopic properties of novel oxazolone-, pyrazolone- and pyrazoline-containing heterocycle chromophores, *Dyes Pigm.*, *81*, 27-34 (DOI: 10.1016/j.dyepig.2008.08.010)

26. Cristea L. and Panea L. (1998), Synthesis and Structural Study of Some 4-(α-Arylethylidene)-1-pyrimidinyl-2-pyrazolin-5-ones, *Heterocycl. Commun.*, *4*(2), 139-143 (DOI: 10.1515/HC.1998.4.2.139)

27. Abdelrazek,F. M., Metz P., Kataeva O., Jäger A. and El-Mahrouky S.F. (2007), Synthesis and molluscicidal activity of new chromene and pyrano [2,3-*c*] pyrazole derivatives, *Arch. Pharm. Chem. Life Sci.*, *340*, 543-548 (DOI: 10.1002/ardp.200700157)

28. Hangarge R. V., Jarikote D. V. and Shingare M. S. (2002), Knoevenagel condensation reactions in an ionic liquid, *Green Chem.*, *4*, 266-268 (DOI: 10.1039/B111634G)

29. Ding Z. C., Tang H. T., Li R. H., Ju L. C. and Zhan Z. P. (2015), Synthesis of 4-Arylidenepyrazolones by a Gold-Catalyzed Cyclization/Arylidene Group

Transfer Cascade of *N*-Propioloyl Hydrazones, *J. Org. Chem.*, *80*, 9307-9313 (DOI: acs.joc.5b01366)

30. Yavari I., Sheykhahmadi J., Saffarian H., Zahedi N., Bahemmat S. and Halvagar M. R. (2018), A convenient synthesis of functionalized pyrazolones bearing a highly twisted 1,3-butadiene moiety with skew geometry, *Synth. Commun.*, *48*, 2608-2614 (DOI: 10.1080/00397911.2018.1516292)

31. He S., Wang J., Zheng J., Luo Q. Q., Leng H., Zheng S., Peng C., Han B. and Zhan G. (2022), Organocatalytic (5+1) benzannulation of Morita–Baylis–Hillman carbonates: synthesis of multisubstituted 4-benzylidene pyrazolones, *New J. Chem.*, *46*, 11617-11622 (DOI: 10.1039/D2NJ01949C)

32. Tao Y., Gu H., Xia H., Yang H., Li J., Xu X. and Cheng D. (2023), Synthesis of 4-Alkenylated Pyrazolinones by 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-Mediated Oxidative Coupling Reaction, *Eur. J. Org. Chem.*, *26*, e202201480 (10.1002/ejoc.202201480)

33. Graebin C. S., Ribeiro F. V., Rogério K. R. and Kümmerle A. E. (2019), Multicomponent reactions for the synthesis of bioactive compounds: A review, *Curr. Org. Synth.*, 16, 855-899 (DOI: 10.2174/1570179416666190718153703)

34. Neto B. A., Rocha R. O. and Rodrigues M. O. (2021), Catalytic approaches to multicomponent reactions: A critical review and perspectives on the roles of catalysis, *Molecules*, *27*, 132 (DOI: 10.3390/molecules27010132)

35. Nandi S., Jamatia R., Sarkar R., Sarkar F. K., Alam S. and Pal A. K. (2022), One-Pot Multicomponent Reaction: A Highly Versatile Strategy for the Construction of Valuable Nitrogen-Containing Heterocycles, *ChemistrySelect*, *7*, 202201901 (DOI: 10.1002/slct.202201901)

36. Domling A., Wang W. and Wang K. (2012), Chemistry and biology of multicomponent reactions, *Chem. Rev.*, *112*, 3083-3135 (DOI: 10.1021/cr100233r)

37. Hayashi Y. (2016), Pot economy and one-pot synthesis, *Chem. Sci.*, *7*, 866-880 (DOI: 10.1039/C5SC02913A)

38. Quintavalla A., Carboni D. and Lombardo M. (2023), Recent advances in asymmetric synthesis of pyrrolidine-based organocatalysts and their application: a 15-year update, *Molecules*, *28*, 2234 (DOI: 10.3390/molecules28052234)

39. Oliveira V. D. G., Cardoso M. F. D. C. and Forezi L. D. S. M. (2018) Organocatalysis: A brief overview on its evolution and applications, *Catalysts*, *8*, 605 (DOI: 10.3390/catal8120605)

40. List B., Lerner R. A. and Barbas C. F. (2000), Proline-catalyzed direct asymmetric aldol reactions, *J. Am. Chem. Soc.*, *122*, 2395-2396 (DOI: DOI: 10.1021/ja994280y)

41. Yu H., Jin H., Gong W., Wang Z. and Liang H. (2013), Pharmacological actions of multi-target-directed evodiamine, *Molecules*, *18*, 1826-1843 (DOI: 10.3390/molecules18021826)

42. Li L., Zhang C., Huang C., Tian X., Sun W. and Jiang S. (2022), Research advances in antitumor mechanism of evodiamine, *J. Chem.*, *2022*, 2784257 (DOI: DOI: 10.1155/2022/2784257)

43. Xu X. H., Wang X., Liu G. K., Tokunaga E. and Shibata N. (2012), Regioselective synthesis of heteroaryl triflones by LDA (lithium diisopropylamide)-mediated anionic thia-Fries rearrangement, *Org. Lett.*, *14*, 2544-2547 (DOI: 10.1021/ol300842d)

44. Li X., Liu Y. Q., Kang J. W., Chen F. Y., He X. G., Yuan S. S., Guo L., Peng C. and Huang W. (2018), Synthesis of Vinylcyclopropane-Fused Pyrazolone Derivatives by Sulfur Ylide-Initiated 1,6-Michael Addition-Cyclization Reactions, *Eur. J. Org. Chem.*, *2018*, 4723-4730 (DOI: 10.1002/ejoc.201800710)

JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

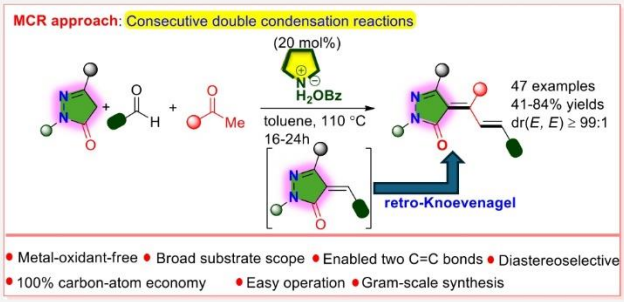
Robust Organocatalytic Three-Component Approach to 1,3-Diarylallylidene Pyrazolones via Consecutive Double Condensation Reactions

Ashvani K. Patel and Sampak Samanta*

Cite This: https://doi.org/10.1021/acs.joc.4c02273 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A robust pyrrolidine-BzOH salt-catalyzed one-pot three-component reaction involving 4-unsubstituted pyrazolones, aryl/heteroarylaldehydes, and aryl methyl ketones is reported for the first time. This catalytic process fortifies an efficient method, allowing for the practical synthesis of a wide array of synthetically useful 1,3-diarylallylidene pyrazolones in good to high yields exclusively in their single geometrical isomer forms. Furthermore, this catalyst facilitates a sequential double condensation reaction under thermal conditions, thereby enabling two consecutive C═C bonds through displacement of aryl groups. Moreover, this organocatalytic technique achieves a 100% carbon atom economy, marking a significant step forward toward efficient and sustainable synthesis.



INTRODUCTION

Pyrazolone is a historically recognized top class heterocyclic molecule adorned with a unique composition of two adjacent N atoms, a lactam function and an active methylene group, making it a commendable reactive intermediate.[1,2] This reputable molecular structure has garnered significant interest across various arenas due to its incorporation of numerous active pharmaceuticals[3] and synthetic drug molecules.[4] Moreover, they are known for their assorted biological activities which are closely linked to their structures.[5−11] Among these derivatives, 4-alkylidene pyrazolones are of particular interest in medicinal chemistry for their effectiveness against various biological targets such as Farnesoid X Receptor (FXR) antagonists,[5] SARS-CoV 3CL inhibitors,[6] H1N1 and H5N1 neuraminidase inhibitors,[7] orthopoxvirus,[8] HIV-1 integrase inhibitors,[9] VEGFR-2 kinase inhibitors,[10] etc. Beyond their medicinal applications, these compounds serve as versatile electrophiles, useful in synthesizing complex pyrazolone and pyrazole structures,[12] ligands,[13] dyes, and pigments,[14] highlighting their significant utility in recent decades (see Figure 1).

Therefore, considerable efforts have been devoted to establishing various powerful methods for accessing a wide breadth of 4-alkylidene pyrazolones with diverse substitution patterns for pharmacological importance.[15−19] Commonly, the base-assisted Knoevenagel condensation of pyrazolones with aldehydes, their acetals and imines, or phenyl ketones has been employed (Scheme 1a).[7,15] Furthermore, Zhan et al. also brilliantly developed an innovative cascade cyclization/1,3-migration reaction of *N*-propionyl hydrazones using IprAuCl/AgOTf as a combined π-philic Lewis acid catalytic system to afford 4-alkylidene pyrazolones (Scheme 1b).[17] Nevertheless, Han et al. introduced a mild [5 + 1] benzannulation reaction between Morita−Baylis−Hillman carbonate derived from pyrazolones and 2-allylidenemalononitriles catalyzed by DABCO to produce 4-benzylidene pyrazolones.[18] However, the delineated methods often face challenges such as the need for expensive catalysts, limited substrate scopes, unsatisfactory yields, longer reaction times, less atom economy, and the need for excess bases, which might alleviate their practical applicability on a large scale practice. In addition, synthesizing synthetically resourceful unsaturated pyrazolones bearing a diene moiety at C4 positions is a meager success and remains challenging.[20−22] Despite these hurdles, Li et al. recently divulged an appealing technique for making 1,3-diarylallylidene pyrazolones via an oxidative coupling reaction of pyrazolones with 1,3-diarylpropenes in the presence of DDQ.[20] Although, this method is limited by its specificity to identical aryl groups and the use of excess DDQ, slacking the process's future growth. Therefore, the pursuit of a robust, organocatalytic, diastereoselective, and atom-economical method for synthesiz-

Received: September 11, 2024
Revised: October 23, 2024
Accepted: November 1, 2024

Downloaded via INDIAN INST OF TECH INDORE on November 16, 2024 at 14:59:01 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

© XXXX American Chemical Society

Conclusion and Future Outlook

The research work of this thesis encompasses the development of simple, efficient, transition-metal-free, practical, pot-economic approaches for the synthesis of a wide range of high-value pyridines and 1,3-diarylallylidene pyrazolones in an atom-economical and eco-friendly manner from readily available raw materials. Under enriched conditions, the developed methodologies afforded satisfactory chemical yields and excellent diastereoselectivities of the intended heterocycles and carbocycles adorned with various valuable functionalities.

It should be noted that the described methods bestow multiple benefits, such as avoiding costly and toxic metal salts, reducing the need for additional oxidants, minimizing the use of volatile and hazardous organic solvents, and preventing tedious workups. Consequently, the developed protocols may be helpful in both synthetic and medicinal chemistry, providing practical strategies for efficiently making value-added aza-heterocyclic scaffolds.

Therefore, we hope that all the developed methodologies in this thesis will offer potential applications in heterocyclic chemistry, material science, and drug discovery processes. Furthermore, many new concepts would be generated, which will facilitate the future growth of heterocyclic chemistry.





Dr. Ashvani Patel was born in Varanasi, Uttar Pradesh, India. He was raised multilingual during his schooling, speaking Hindi, English, Bhojpuri and Sanskrit, and developed an interest in writing *self-help books.* He received his *Bachelor's degree in Physics and Chemistry from Mahatma Gandhi Kashi Vidyapith University, Varanasi,* in 2016, and achieved his *MSc in Organic Chemistry from the National Institute of Technology, Warangal,* in 2018. He joined the *Department of Chemistry at IIT Indore, India,* in July 2019 and obtained his PhD in June 2025 under the supervision of *Prof. Sampak Samanta.*

His exceptional synthetic capability has resulted in the publication of three papers directly stemming from his thesis work, in addition to four other related publications listed in his CV. All were published in peer-reviewed international journals with decent impact factors, underscoring the novelty and relevance of the work. In summary, Dr. Patel's thesis demonstrates ingenuity, productivity, and quality.

He can be contacted at ashvaniiitian@gmail.com

You may visit: https://beingspiritualscientific.org