Quinoline Syntheses *via* Copper-Catalyzed Domino Reaction of 2-Halogenated Benzaldehydes and Enaminones

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Science in Organic Chemistry

Prince of Songkla University

2018

Thesis Title	Quinoline Syntheses *via* Copper-Catalyzed Domino Reaction of 2-Halogenated Benzaldehydes and Enaminones
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ชื่อวิทยานิพนธ์ การสังเคราะห์อนุพันธ์ควิโนลีนด้วยปฏิกิริยาการเกิดแบบหลายขั้นตอน โดยใช้คอปเปอร์เป็นตัวเร่งปฏิกิริยาของสารตั้งต้น 2-halogenated benzaldehydes และ enaminones

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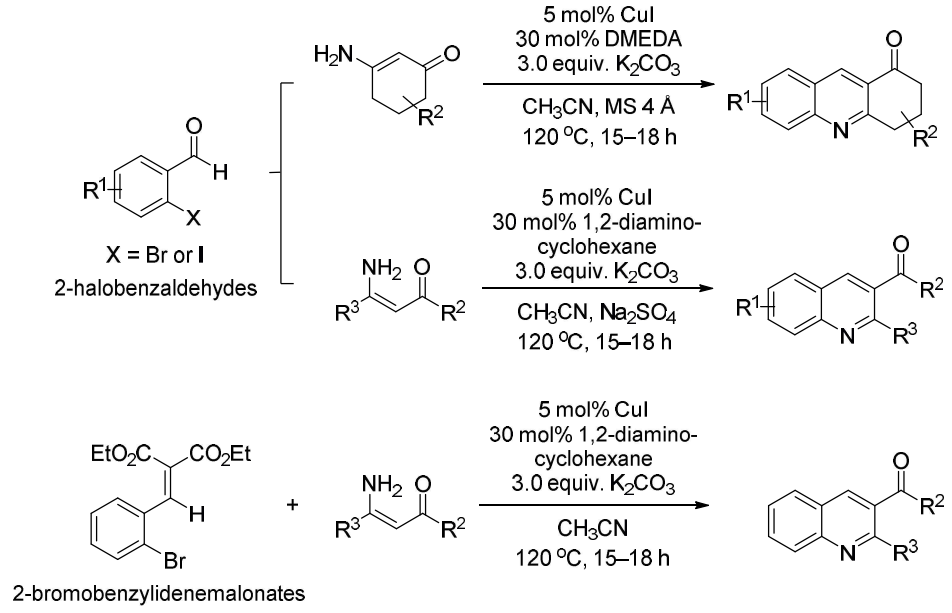
บทคัดย่อ



ควิโนลีนเป็นผลิตภัณฑ์ธรรมชาติที่มีไนโตรเจนเป็นองค์ประกอบ ซึ่งแสดงฤทธิ์ทางชีวภาพที่น่าสนใจ สามารถสังเคราะห์ได้จากปฏิกิริยาที่เกิดแบบหลายขั้นตอนโดยใช้คอปเปอร์เป็นตัวเร่ง ระหว่างสารตั้งต้น enaminone และ 2-bromo หรือ 2-iodobenzaldehyde กลไกการเกิดปฏิกิริยาประกอบด้วย 1. aldol reaction 2. C(aryl)–N bond formation และ 3. elimination ผลอิเล็กทรอนิกส์บน aldehyde และการใช้ drying agent มีผลเป็นอย่างมากต่อร้อยละผลิตภัณฑ์ของอนุพันธ์ควิโนลีน ผู้วิจัยสามารถสังเคราะห์ควิโนลีนได้ในร้อยละผลิตภัณฑ์ที่สูง จาก cyclic และ acyclic enaminone นอกจากนี้อนุพันธ์ควิโนลีนยังสามารถสังเคราะห์ได้จากการทำปฏิกิริยาระหว่าง diethyl-2-(2-bromobenzylidine)malonate และ acyclic enaminone ซึ่งวิธีการนี้ให้ผลการทดลองที่ดีกว่าการใช้ aldehyde เป็นสารตั้งต้น

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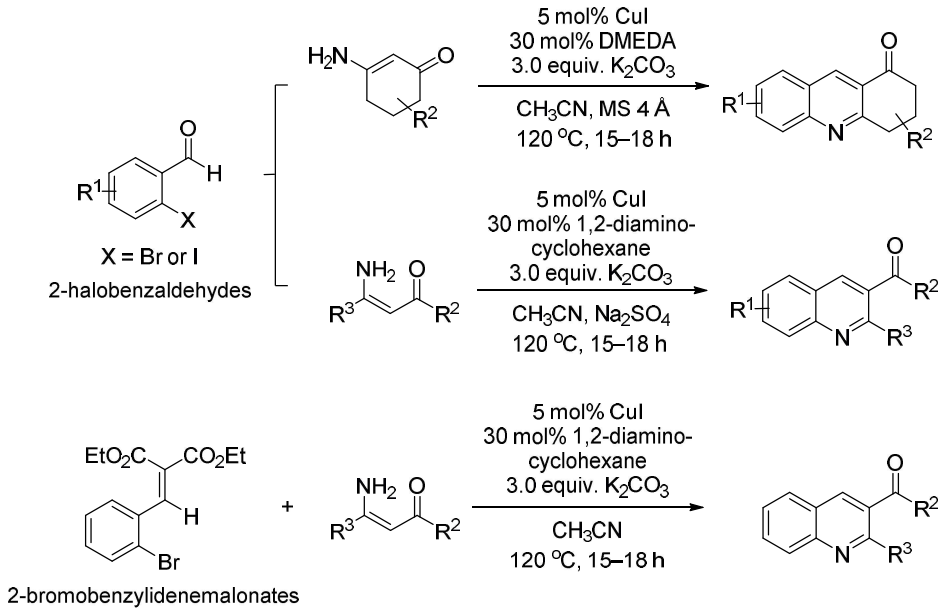
Academic Year	2017

Abstract



Quinolines showing broad range of biological activities were obtained from enaminones and 2-bromo- or 2-iodobenzaldehyde *via* copper-catalyzed tandem reaction. The domino processes consisted of aldol reaction, C(aryl)–N bond formation and elimination. The electronic effect of aldehydes and drying agent displayed a huge impact on product yield. Both 2-bromo- and 2-iodobenzaldehydes provided a library of quinolines from cyclic and acyclic enaminones in good yields. Diethyl-2-(2-bromobenzylidine)malonate was introduced to the reaction instead of aldehyde as a better coupling partner of non-active enaminones.

ACKNOWLEDGEMENT

I feel deeply impressive by many people whose help made my graduate study successful. First of all, I would like to sincerely thank my advisor, Asst. Prof. Dr. Juthanat Kaeobamrung for his dedication, commitment and motivation encouraging me to achieve my educational goals. Through his guidance and useful advice, I've learned to grow both personally and academically.

I also would like to thank the following people; my committee members, Assoc. Prof. Dr. Sumrit Wacharasindhu, Asst. Prof. Dr. Juthanat Kaeobamrung, Prof. Dr. Vatcharin Rukachaisirikul, Asst. Prof. Dr. Kwanruthai Tadpetch and Dr. Chittreeya Tansakul for their assistance, valuable discussions, reviewing my dissertation and guidance throughout this project.

I am grateful and appreciated to the Development and Promotion of Science and Technology Talents Project (DPST) for a scholarship and Graduate School, Prince of Songkla University.

My heartfelt thanks to my family, members of laboratory, and friends who have been supported, encouraged and assisted me to overcome all obstacles.

Benyapa Kaewmee

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LIST OF ABBREVATIONS AND SYMBOLS

General

ν	=	absorption
Å	=	angstrom (10^{-10} meters)
aq	=	aqueous
atm	=	atmosphere
br	=	broad
calcd.	=	calculated
cat.	=	catalyst
δ	=	chemical shift relative to TMS
J	=	coupling constant
^{o}C	=	degree Celsius
d	=	doublet
dd	=	doublet of doublets
equiv.	=	equivalent
ESI	=	electrospray ionization
FT-IR	=	Fourier transform Infrared
g	=	gram
Hz	=	hertz
HRMS	=	high-resolution mass spectroscopy
h	=	hour
m/z	=	mass-to-charge ratio
MHz	=	megahertz
μ	=	micro
mg	=	milligram
mL	=	milliliter
mmol	=	millimole
M	=	molar
mol%	=	mole percent

LIST OF ABBREVATIONS AND SYMBOLS (Continued)

m	=	multiplet
NMR	=	nuclear magnetic resonance
Nu	=	nucleophile
ppm	=	part per million
H	=	proton
psi	=	pound per square inch
q	=	quartet
cm^{-1}	=	reciprocal centimeter (wavenumber)
sat.	=	saturated
Temp	=	temperature
TLC	=	thin-layer chromatography
t	=	triplet

Chemical

Ac	=	acetyl
AcOH	=	acetic acid
$CDCl_3$	=	deuterochloroform
$CHCl_3$	=	chloroform
CH_2Cl_2	=	dichloromethane
CH_3CN	=	acetonitrile
Cs_2CO_3	=	cesium carbonate
Cy	=	cyclohexyl
DMEDA	=	*N*,*N*′-dimethylethylenediamine
DMF	=	dimethylformamide
DMSO	=	dimethylsulfoxide

LIST OF ABBREVATIONS AND SYMBOLS (Continued)

DMSO-d_6	=	dimethyl sulfoxide-*d6*
Et	=	ethyl
EtOAc	=	ethyl acetate
EtOH	=	ethanol
H_2SO_4	=	sulfuric acid
MeOH	=	methanol
MS	=	molecular sieves
NaOH	=	sodium hydroxide
Na_2SO_4	=	sodium sulfate
NH_4Cl	=	ammonium chloride
Ph	=	phenyl
$PhCH_3$	=	toluene
$Ph_2(CO)$	=	benzoquinone
PMP	=	*p*-methoxyphenyl
K_2CO_3	=	potassium carbonate
K_3PO_4	=	potassium phosphate
TMS	=	tetramethylsilane

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Kaewmee, B.; Kaeobamrung, J.; Rukachaisirikul, V. 2017. Synthesis of Quinolines *via* Copper-catalyzed Domino Reactions from Enaminones.. Org. Biomol. Chem. 15, 7387–7395.

CHAPTER 1

INTRODUCTION

1.1 Structure and Isolation of Quinoline

Quinoline (1-aza-napthalene or benzo[b]pyridine) is a nitrogen-containing heterocyclic aromatic compound composing of a rigid heterocyclic core of benzene *ortho*-fused with a pyridine ring with a molecular formula C_9H_7N. Quinoline was first extracted from coal tar in 1834 by Friedlieb Ferdinand Runge (Bharate *et al*., 2015) (**Figure 1**).

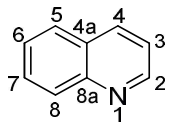


Figure 1 Quinoline Core Structure

1.2 Application of Quinoline Derivatives

Heterocyclic compounds, being widespread in nature and essential for human life, are ubiquitous in pharmaceutical, agrochemical and many other chemical industries (Liao *et al*., 2014). A prominent aza-heterocycle is one of the most important and omnipresent compounds in all branches of chemistry. In particular, quinolines are well-known structural scaffolds as building blocks of many biologically active compounds (Anand *et al*., 2015). For instance, quinine (**1**) being used as a multipurpose treatment since the 17th century has showed antimalarial, antipyretic, analgesic, and anti-inflammatory activities (Neuhaus *et al*., 2016). Quinmerac (**2**) has been used in agricultural area as a herbicide. Quinolobactin (**3**) and mefloquine (**4**) have been applied to the treatment of *Plasmodium falciparum*

(malaria) (Jiang *et al*., 2002). Quinoline **5**, ethyl 2-methylquinoline-3-carboxylate (**6**) and 3,4-dihydroacridin-1(2H)-one (**7**) showing anticancer activity against various human tumour cell lines (chronic myeloid leukemia K562 cells, colon carcinoma Colo-205 cells, breast cancer MDA-MB 231 cells and neuroblastoma IMR32 cells). Marinoquinolines B (**8**) and F (**9**) showed moderate antimalarial activity (Okanya *et al*., 2011). 6-Hydroxyquinoline-8-carboxylic acid (**10**) and 4-amino-6-hydroxyquinoline-8-carboxylic acid (**11**) exhibited antibacterial activity (Teichert *et al*., 2008). Moreover, harmine (**12**) and 10-iodo-11H-indolo[3,2-c]quinoline-6-carboxylic acid (**13**) presented DYRK1A inhibitors associating with Down syndrome and Alzheimer's disease (Falke *et al*., 2015). Kynurenate (**14**) and xanthurenate (**15**) have been implicated to treat chronic neurodegenerative diseases (Carrigan *et al*., 2002) (**Figure 2**).

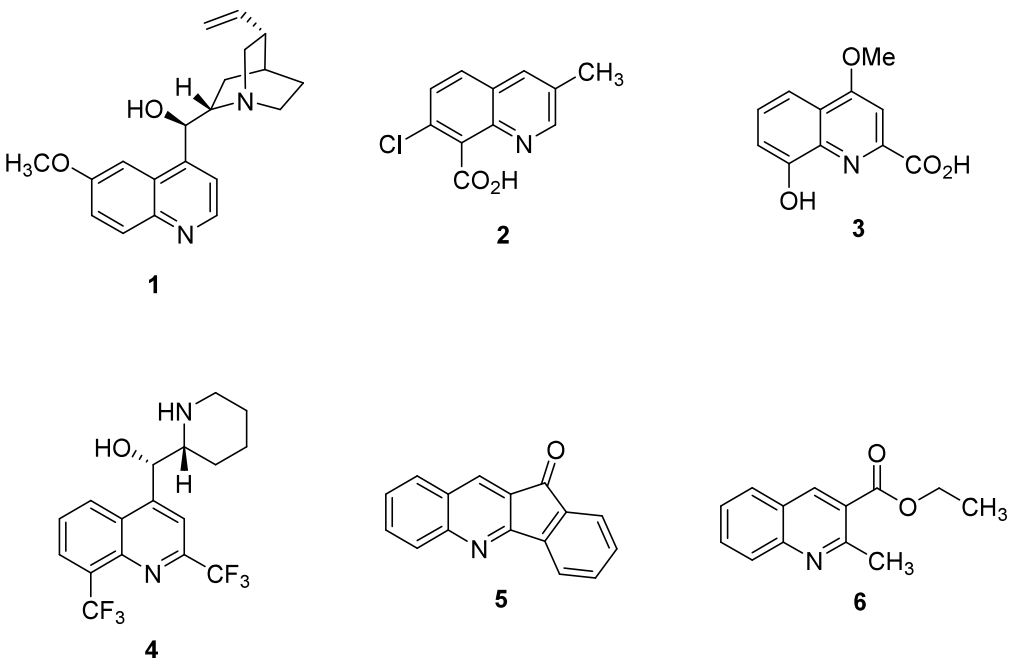


Figure 2 Quinoline Derivatives in Pharmaceutical and Agrochemical Chemistry

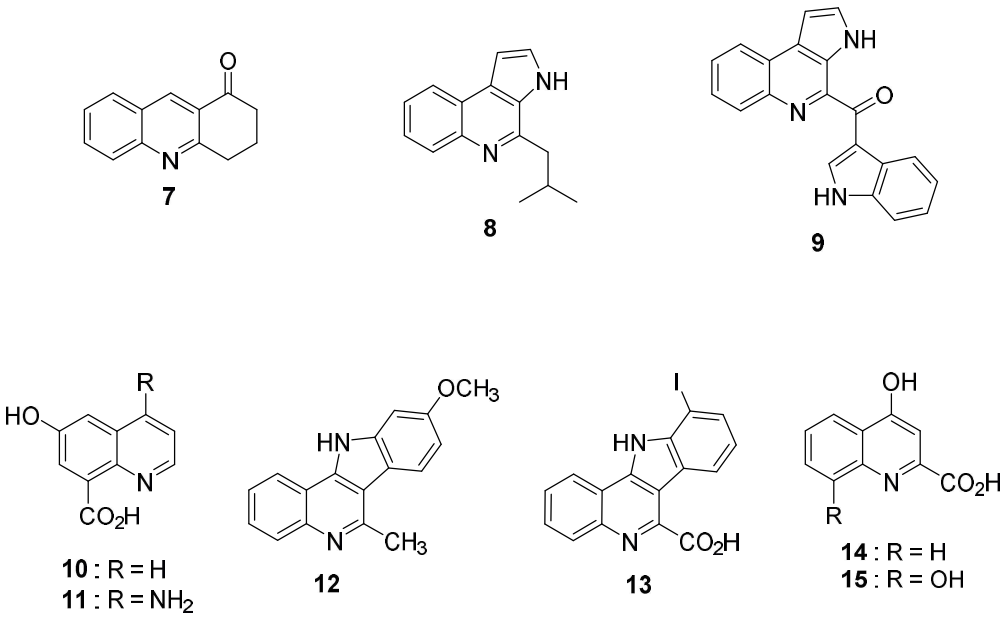


Figure 2 (Continued)

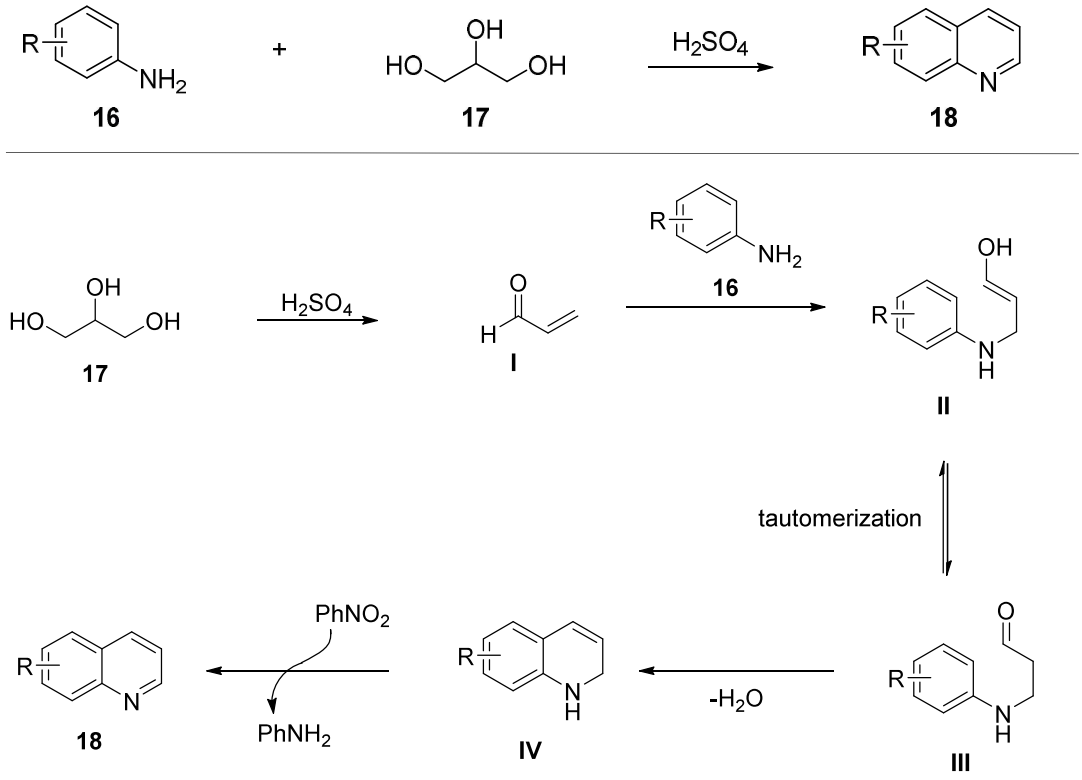
1.3 Synthetic-Classical Approaches to Access Quinoline Derivatives

In the past century, many researchers have paid great attention on the study of quinoline derivatives which showed a broad range of biological activities. Due to such significance, the developments of practical methodologies for the synthesis of quinolines were increased continuously. A large number of traditional synthetic strategies have been reported consistently, for example, Friedländer, Skraup, Döebner-Miller, Conrad-Limpach and Combes methods to obtain quinolines based on type of the starting materials (Batista *et al*., 2016).

1.3.1 The Skraup synthesis

In 1880, Zdenko Hans Skraup reported the first formal synthesis of quinoline derivatives whereby the reaction involved heating aniline derivatives **16** with glycerol (**17**), sulfuric acid and nitrobenzene as an oxidizing agent. The mechanism initially

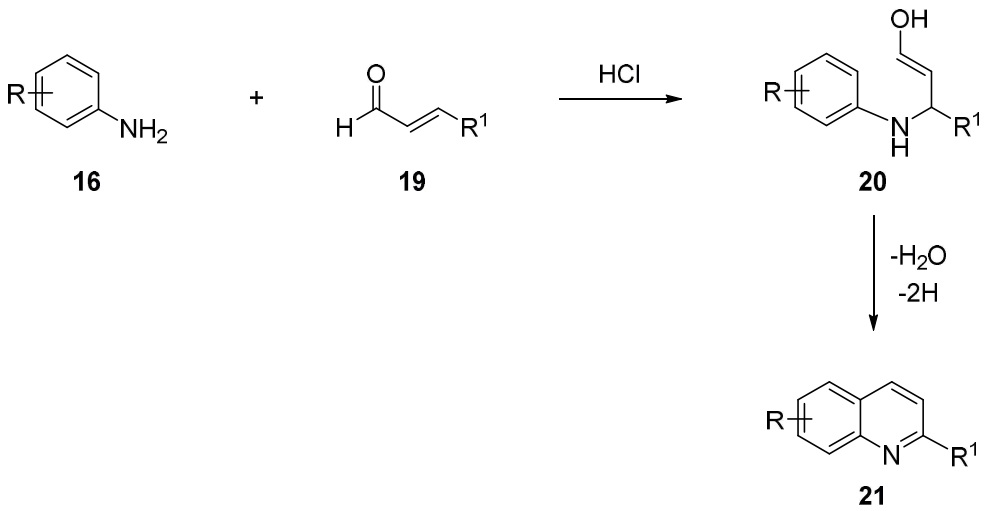
started with the formation of acrolein (**I**) from a dehydration of glycerol. Then a conjugate addition by aniline **16** resulted in a formation of a *β*-anilinopropionaldehyde intermediate **III** which underwent ring closure and dehydration affording dihydroquinoline **IV**. Finally, **IV** was oxidized by nitrobenzene to provide the quinoline **18**. (**Scheme 1**) (Batista *et al.*, 2016).



Scheme 1 Traditional Synthetic Routes toward the Quinolines by Skraup

1.3.2 The Döebner-Miller Synthesis

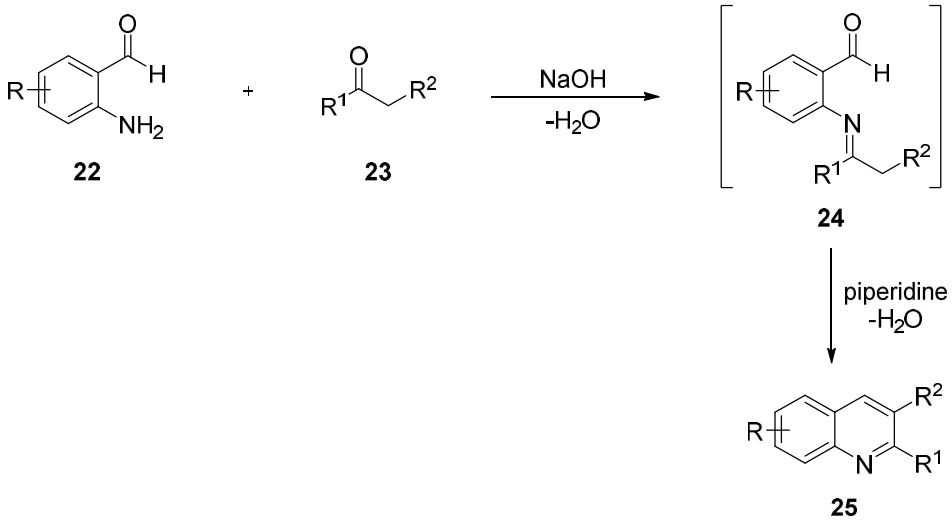
In 1881, Oscar Döebner and Wilhelm von Miller modified the Skraup quinoline synthesis by heating an aniline **16** with an *α*,*β*-unsaturated carbonyl compound **19** treated with hydrochloric acid (HCl). However, unlike the Skraup quinoline synthesis, no oxidizing agent was applied. The proposed mechanism was similar to that of the Skraup synthesis (**Scheme 2**) (Wu *et al.*, 2006).



Scheme 2 Traditional Synthetic Routes toward the Quinolines by Döebner-Miller

1.3.3 The Friedländer Synthesis

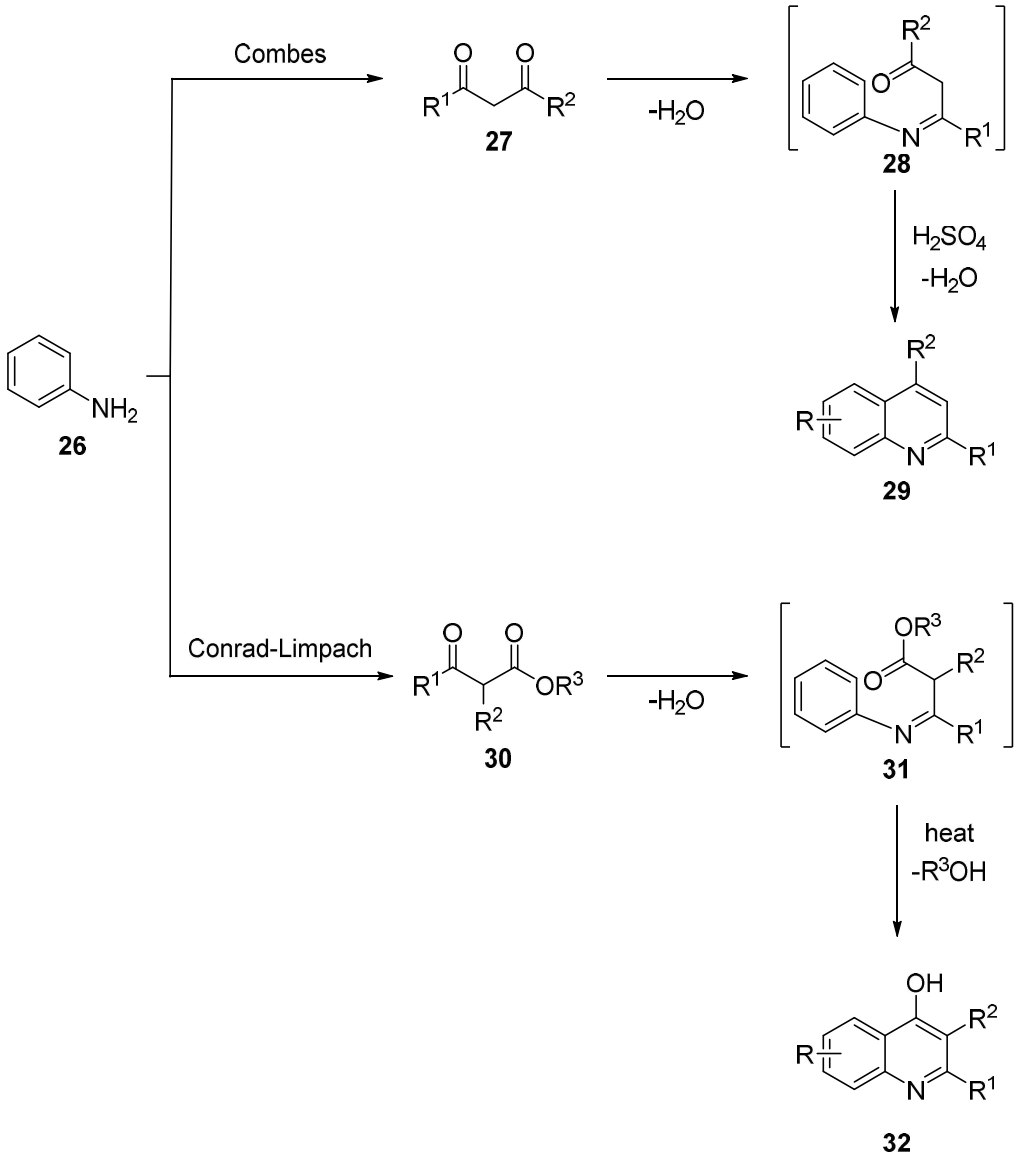
In 1882, Paul Friedländer reported the synthesis of quinoline which was achieved by the condensation of *o*-aminobenzaldehyde **22** and ketone **23**. The Friedländer ring closure was described in two steps. Firstly, the Schiff base **24** was obtained from base-catalyzed condensation of *o*-aminobenzaldehyde **22** and ketone **23**. Then, quinoline annulation by using piperidine as a condensing agent occurred (**Scheme 3**) (Batista *et al.*, 2016).



Scheme 3 Traditional Synthetic Routes toward the Quinolines by Friedländer

1.3.4 The Combes and Conrad-Limpach Synthesis

Alphonse-Edmond Combes reported the synthesis of 2,4-disubstituted quinolines in 1888 utilizing unsubstituted aniline **26** and *β*-diketones **27** to form enamine intermediate **28**. The last step involved acid-catalyzed cyclization of Schiff base **28** to provide quinoline **29**. Similar to Combes method, the Conrad-Limpach synthesis involved the reaction of *β*-keto esters **30** and anilines to achieved 2,3,4-trisubstituted quinolines **32** (**Scheme 4**) (Bharate *et al.*, 2015).



Scheme 4 Traditional Synthetic Routes toward the Quinolines by Combes and Conrad-Limpach

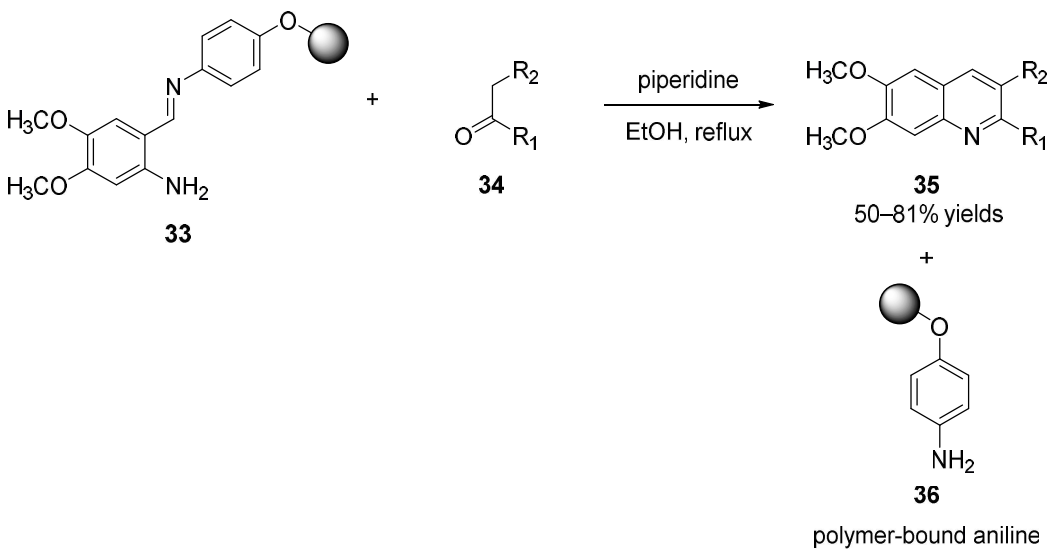
All these mentioned methods afforded quinolines *via* intermolecular or intramolecular annulation of aniline derivatives with carbonyls under acidic or basic condition starting from *o*-acetophenones or anilines. Although, the synthesis of quinolines through the classical routes was easily accessible, all methods associated with tedious reaction conditions (highly acidic media, high temperature and prolonged

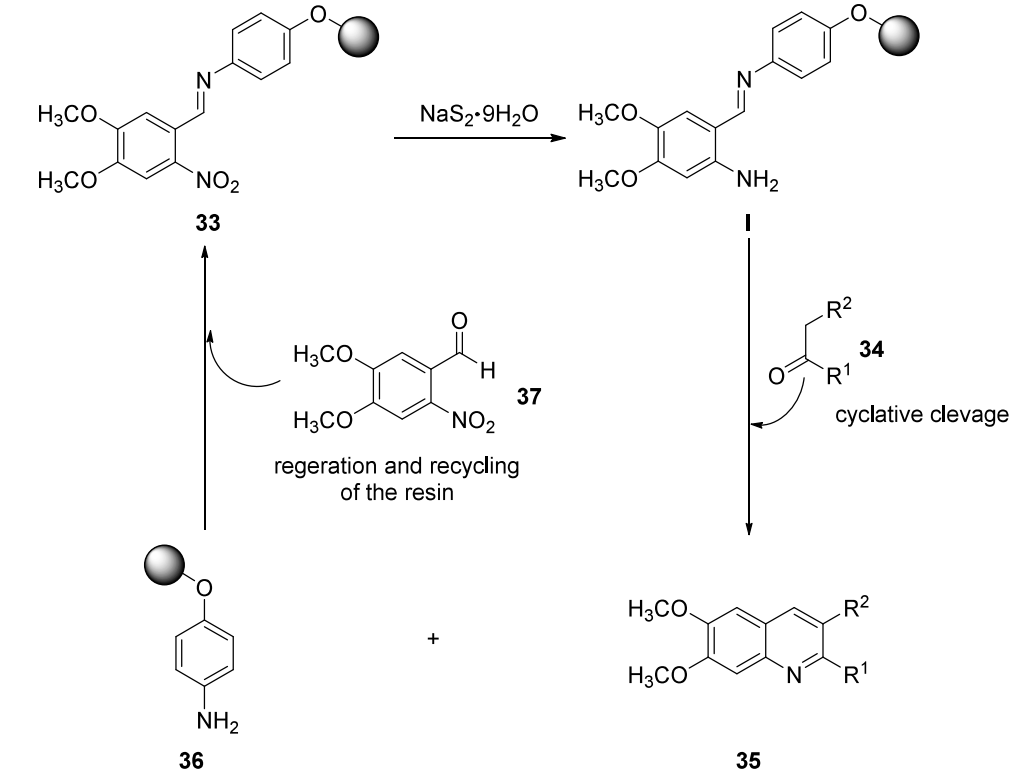
reaction time). Furthermore, in most of cases the regioselectivity and scope of functionality on the quinolines were limited. Thus, chemistry for the development of quinoline synthesis has constituted as the one of the largest areas in organic synthesis.

1.4 Metal-Free Protocols for Quinoline Synthesis

Practically, the Friedländer reaction has been still considered as a popular method for quinoline construction because the procedure is simple and rapid to provide quinolines. However, poor stability of *o*-aminobenzaldehyde, undergoing self-condensation, is a major limitation. Consequently, methodologies relating the use of synthetic equivalent have been extensively explored.

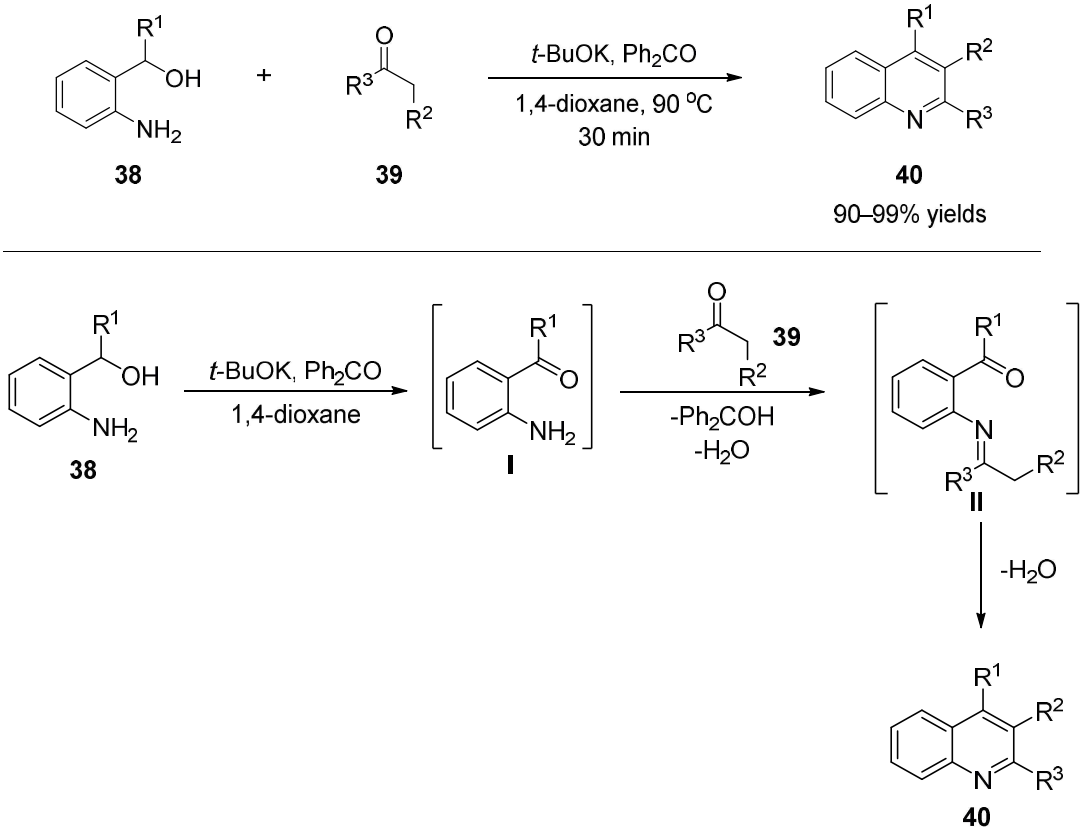
In 2003, Levacher and co-workers developed solid-phase synthesis of quinolines based on Friedländer-type reaction by designing resin bound azomethine **I** which was prepared in two steps. Firstly, the condensation of *p*-toluidine **36** and an *o*-nitrobenzaldehyde **37** to form azomethine **33**, followed by sodium sulfide reduction to generate aniline **I**. The azomethine **33** acted as a more proper starting material than aminobenzaldehydes since it minimized self-condensation reaction. The azomethine **I** smoothly reacted with ketone **34** under basic conditions releasing desired quinoline **35** through cyclative cleavage. Moreover, the resin-bound aniline **36** was recyclable. This approach afforded quinolines in fairly good to excellent yields (50–81%) (**Scheme 5**) (Patteux *et al*., 2003).





Scheme 5 A Novel Traceless Solid-Phase Friedländer Synthesis by Levacher

In 2008, Ramón and co-workers reported the quinoline construction from *o*-aminobenzyl alcohols **38** and ketones **39** in the presence of strongly basic condition and benzophenone as a hydride scavenger at 90 ^{o}C to accomplish quinolines in excellent yields in a very short period of time under metal free reaction conditions. The mechanism was proposed in which intermediate **I** was formed *in situ* through the oxidation of benzyl alcohol. Subsequenct imination and annulation of **II** provided 2,3,4-trisubstituted quinolines **40** (**Scheme 6**) (Martínez *et al*., 2008).



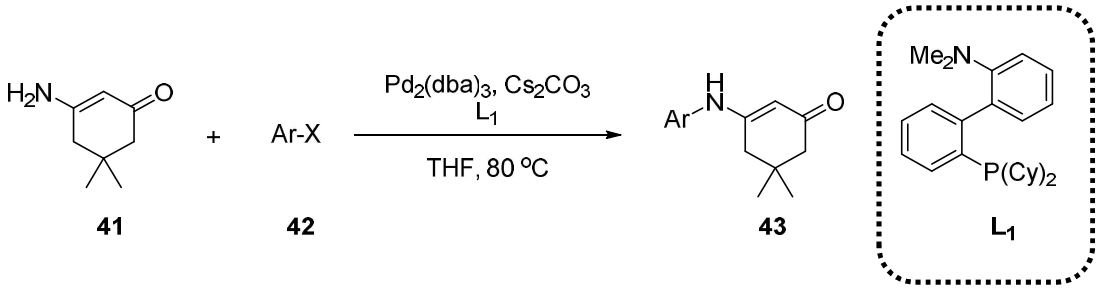
Scheme 6 The Synthesis of Quinoline from 2-Aminobenzyl Alcohols **38**

1.5 Metal-Catalyzed Reaction for Quinoline Synthesis

In the past decades, transition-metal-catalyzed reactions have become popular in synthetic organic molecules due to their abilities to shorten reaction procedures, reduce waste, and use milder conditions. Moreover, a development of new methods for efficient synthetic quinoline is an ongoing subject for many research groups.

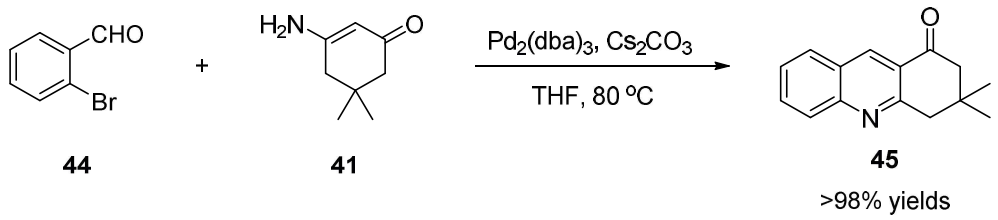
Palladium catalyst is one of the most frequently used transition metal catalysts due to its low toxicity and broad reactivity. The palladium-catalyzed formation of nitrogen-aryl bonds has been selectively used for the synthesis of N-containing heterocycles.

In 2000, Edmondson and co-workers have reported the application of Hartwig-Buchwald couplings to the synthesis of *N*-aryl vinylogous amides (enaminones) **41** and aryl halide **42** under palladium catalysis with commercially available ligand $\mathbf{L_1}$ to afford *N*–aryl products **43** in high yields (up to 98%) (**Scheme 7**).



Scheme 7 Palladium-Catalyzed Coupling of **41** with Aryl Halides **42**

Interestingly, this methodology was employed in a cascade fashion to synthesize heterocyclic compounds. They demonstrated that quinoline **45** could be synthesized under palladium catalysis from 2-bromobenzaldehyde **(44)** and enaminone **41** in quantitative yield (**Scheme 8**) (Edmondson *et al*., 2010).



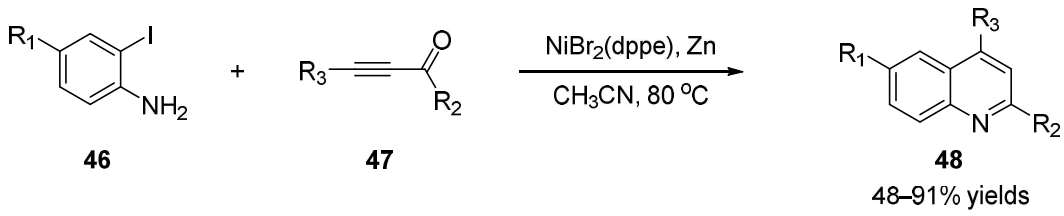
44 **41** **45**

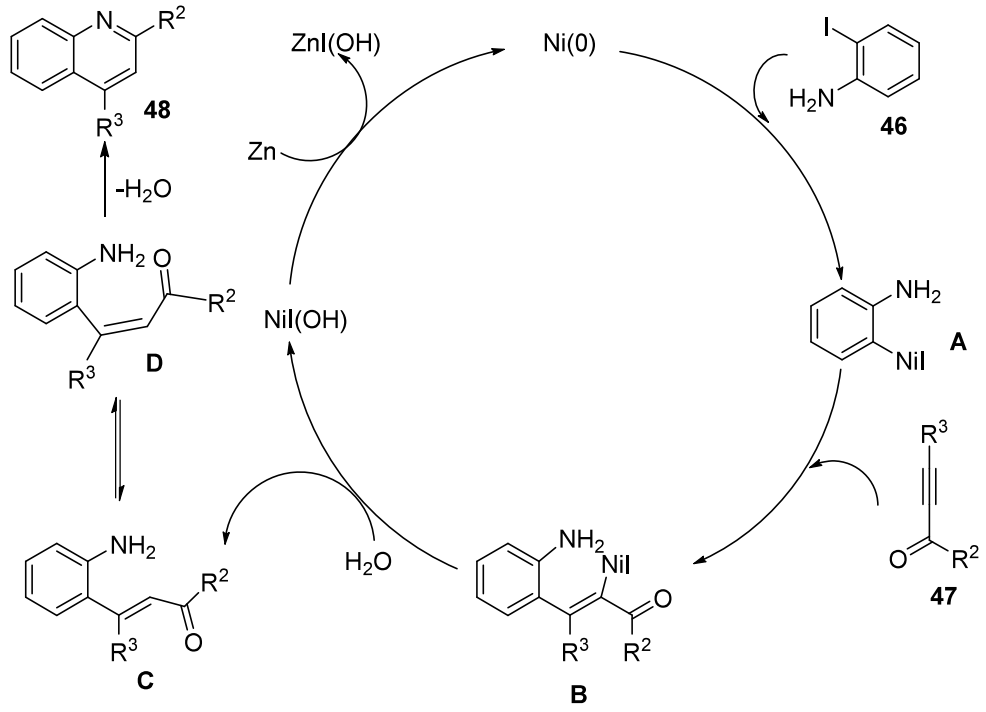
>98% yields

Scheme 8 Palladium-Catalyzed Coupling of 2-Bromobenzaldehyde (**44**) with Enaminone **41**

In 2006, a novel cascade formation of nickel-catalyzed reaction was developed by the Korivi group to achieve 2,4-disubstituted quinoline products **48** in moderate to high yields (48–91%) from *o*-iodoaniline (**46**) and aroylalkynes (**47**).

They explained possible mechanism as shown in **Scheme 9**. The catalytic cycle was likely initiated by the reduction of Ni(II) to Ni(0) by zinc metal powder, followed by the oxidative addition to afford complex **A**. Next, intermediate **A** reacted with an alkyne to generate intermediate **B**. Subsequent protonation yielded a corresponding chalcone **C**. Presumably, **C** underwent *trans-cis* isomerization, followed by cyclization to give final product **48** (**Scheme 9**) (Korivi *et al*., 2006).

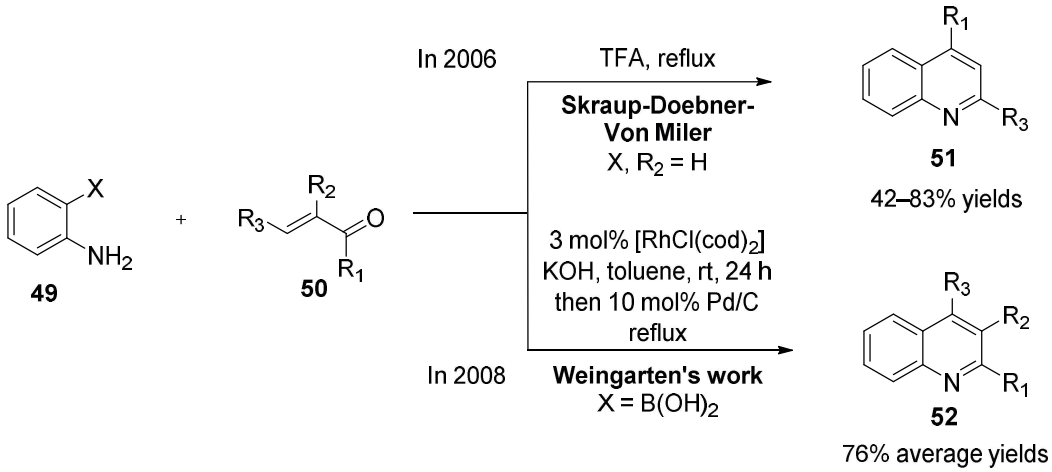




Scheme 9 Nickel-Catalyzed Cyclization of 2-Iodoanilines **46** with Aroylalkynes **47**

The Skraup-Doebner-Von Miller quinoline synthesis has been a great value for constructing the quinoline system using *α,β*-unsaturated carbonyls and aniline as starting materials. In 2006, Chen and co-workers reported the synthesis of quinoline *via* Skraup-Doebner-Von Miler synthesis from enones **50** in the presence of TFA to give quinolines **51** in 42–83% yields (**Scheme 10**). Despite the good outcome of this reaction, strongly acidic condition was required.

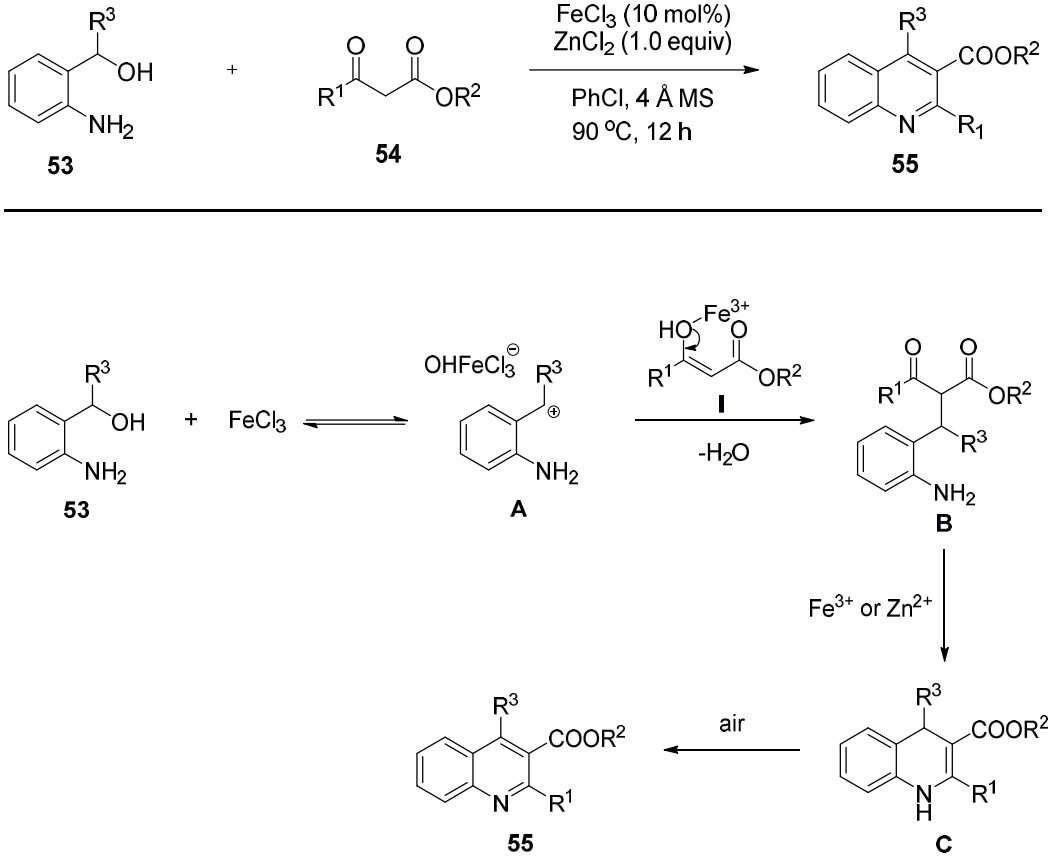
On the other hand, non-acidic conditions was introduced by Weingarten and co-workers in 2008. They reported rhodium-catalyzed reaction for quinoline synthesis from *o*-amino arylboronic acids **49** and enones **50** to give 2,3,4-trisubstituted quinolines **52** in 76% average yields. Significantly, this reaction gave quinolines with high regioselectivity (**Scheme 10**).



Scheme 10 Synthesis of Quinolines **51**, **52** from *o*-Aminophenylboronic Acids **49** and *α,β*-Unsaturated Ketones **50**

In 2008, Wang and co-workers introduced a useful cascade synthesis of substituted 3-quinolinecarboxylic esters **55** *via* $FeCl_3$-catalyzed benzylation/ propargylation-cyclization reaction from 2-aminobenzyl alcohols **53** and 1,3-diketones **54**. They obtained quinolines in excellent yield (up to 94 % yield) (**Scheme 11**).

A tentative mechanism of reaction of 2-aminobenzyl alcohols **53** and 1,3-ketoester **54** was proposed in **Scheme 11** starting with a formation of a carbocation intermediate **A** from 2-aminobenzyl alcohols **53** by $FeCl_3$. Next, a nucleophilic addition of Fe-ketoester complex **I** occurred to form an intermediate **B**. Subsequently, the cyclization of **B** took place to give dihydroquinoline **C**, followed by an oxidation to generate quinoline products **55** (Fan *et al.*, 2008).

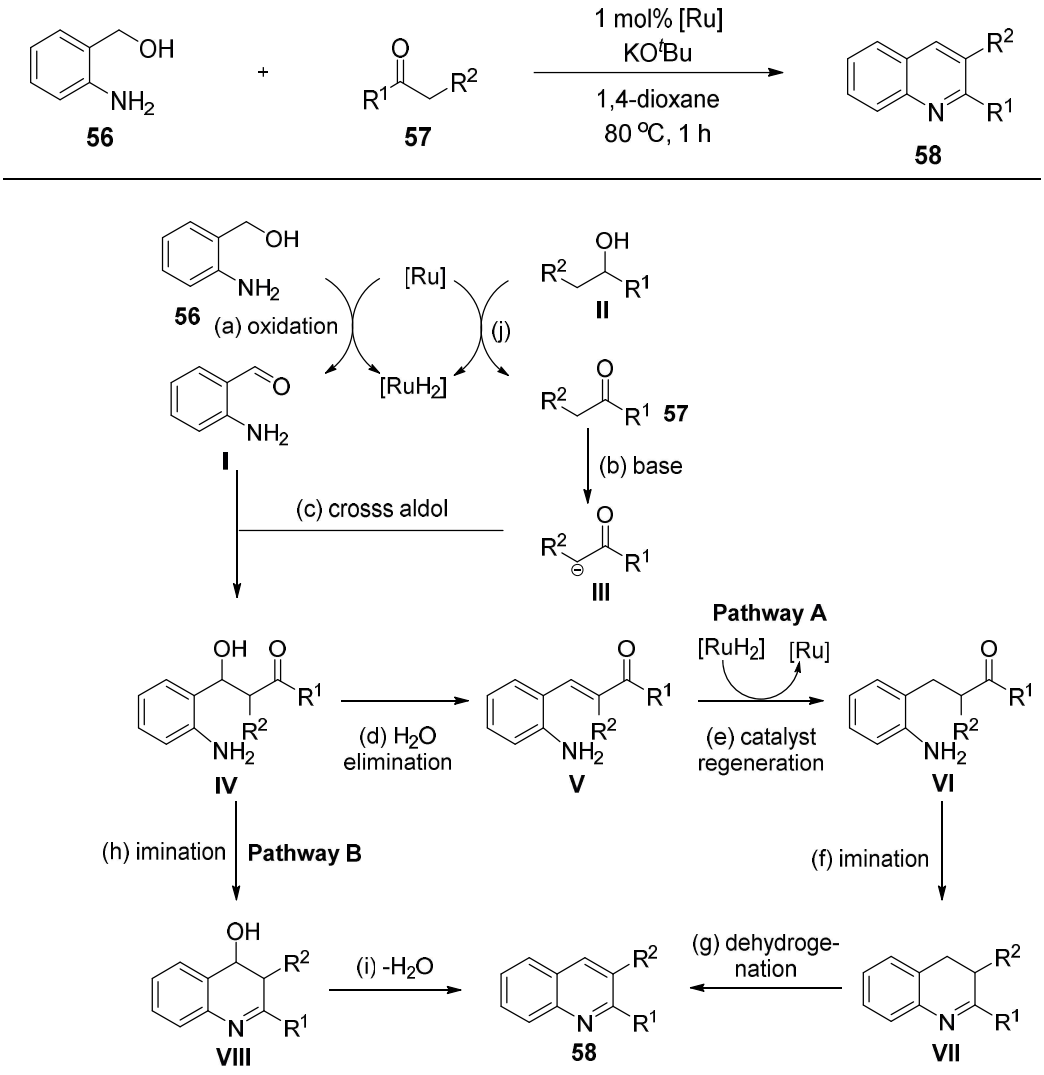


Scheme 11 The Metal-Catalyzed Reaction from 2-Aminobenzyl Alcohol **53** and 1,3-Diketone **54** for Quinoline Synthesis

In the same year, Verpoort and co-workers also used 2-aminobenzyl alcohols **56** in ruthenium-catalyzed reaction to accomplish quinolines **58**. The second generation Grubbs' catalysts showed the best result in the oxidative cyclization of 2-aminobenzyl alcohol **56** and a variety of ketones **57** in the presence of KO^{t}Bu (**Scheme 12**).

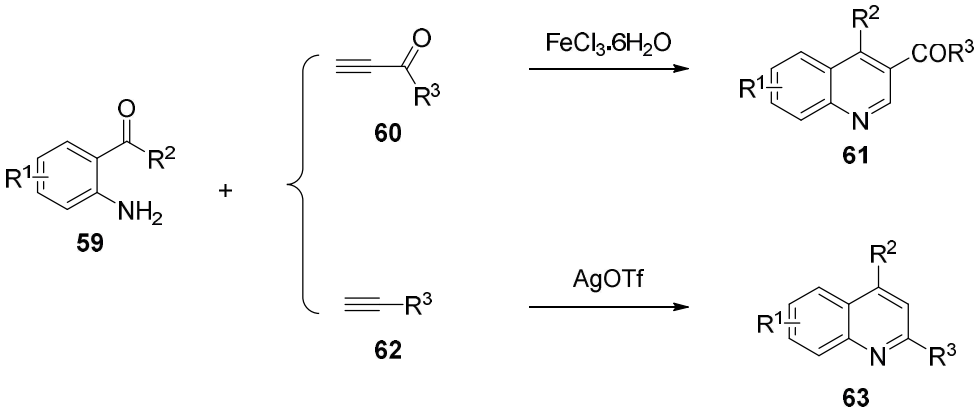
The mechanism began with the oxidation of 2-aminobenzyl alcohols **56** to a corresponding benzaldehyde **I**. Cross aldol reaction occurred to generate compound **IV**. To form a quinoline product, they proposed two plausible pathways from the intermediated **IV**. Pathway **A**, the elimination of water took place, followed by

hydrogenation to provide compound **VI**. The desired quinoline **58** was produced through imination and dehydrogenation from aniline **4**. Pathway **B** involved imination and elimination of water to generate adduct **58** (Mierde *et al.,* 2008).



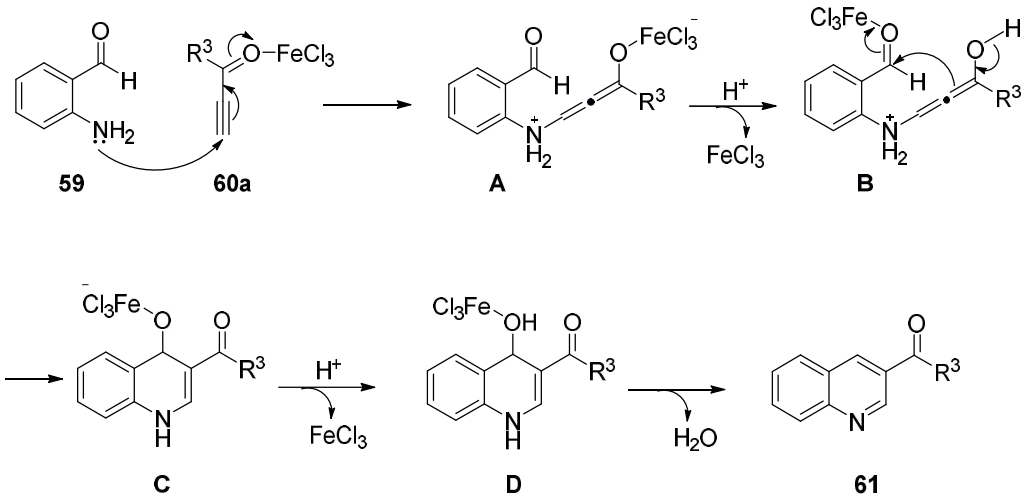
Scheme 12 The Synthesis of 2,3-Disubstituted Quinolines *via* Ruthenium-Catalyzed Reaction from 2-Aminobenzyl Alcohols **56** and Ketone **57**

In 2011, the Liu group reported two strategies for the synthesis of quinolines. The first was Fe-catalyzed reaction of *o*-acylanilines **59** and alkynones **60** to obtain 2,4-disubstituted quinolines **61**. The second involved Ag-catalyzed reaction of **59** and alkynes **62** to give corresponding 3,4-substituted quinolines **63** (**Scheme 13**).



Scheme 13 Metal-Catalyzed Synthesis of Substituted Quinolines **62**, **63** from *ortho*-Acylanilines **59**

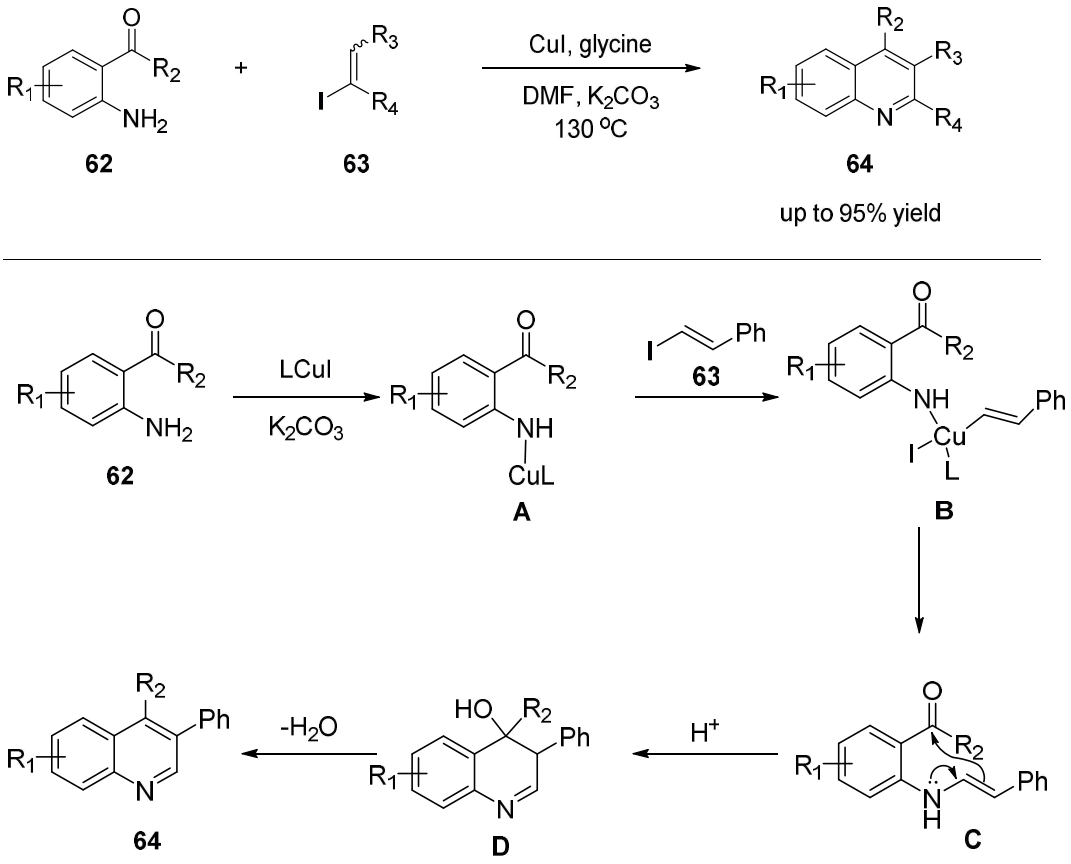
A plausible reaction mechanism of iron-catalyzed reaction of *o*-acylanilines **59** and alkynones **60** was shown in **Scheme 14**. The first transformation was 1,4-addition of anilines **59** and alkynones **60a** to generate intermediate **A**. Then, intramolecular aldol cyclization of **B** occurred to form dihydroquinoline **C**, followed by protonation to give intermediate **D**. The last step was dehydration yielding the target quinolines **61** (Li *et al*., 2011).



Scheme 14 A Propose Reaction Mechanism of Iron-Catalyzed Reaction of Acylanilines **59** and Alkynones **60**

On the basis of economy and easy-handle-catalyst of copper-catalyzed reaction and the discovery of copper/ligand system, Ullmann type coupling was the powerful method in the synthesis of C–heteroatom bond. In 2014, Liu's group also reported an alternative method for multisubstituted quinoline synthesis from *o*-acylanilines **62** and alkenyl iodides **63**. They utilized the copper-catalyzed reaction in which the intermolecular Ullmann-type C–N coupling and enamine condensation reaction demonstrated as key transformations (**Scheme 15**).

The reaction mechanism pathway for quinoline formation was proposed with model substrates **62** and **63** as outlined in **Scheme 15**. The process started with the ligand exchange with *o*-acylaniline **62** affording a copper-coordinated intermediate **A** in the presence of K_2CO_3. An oxidative addition of alkenyl iodides **63** by intermediate **A** gave copper complex **B**, followed by reductive elimination to furnish aniline **C**. Intramolecular enamine addition occurred to form dihydroquinoline **D**. Then, a dehydration took place to yield target quinolines **64** (Kong *et al*., 2014).

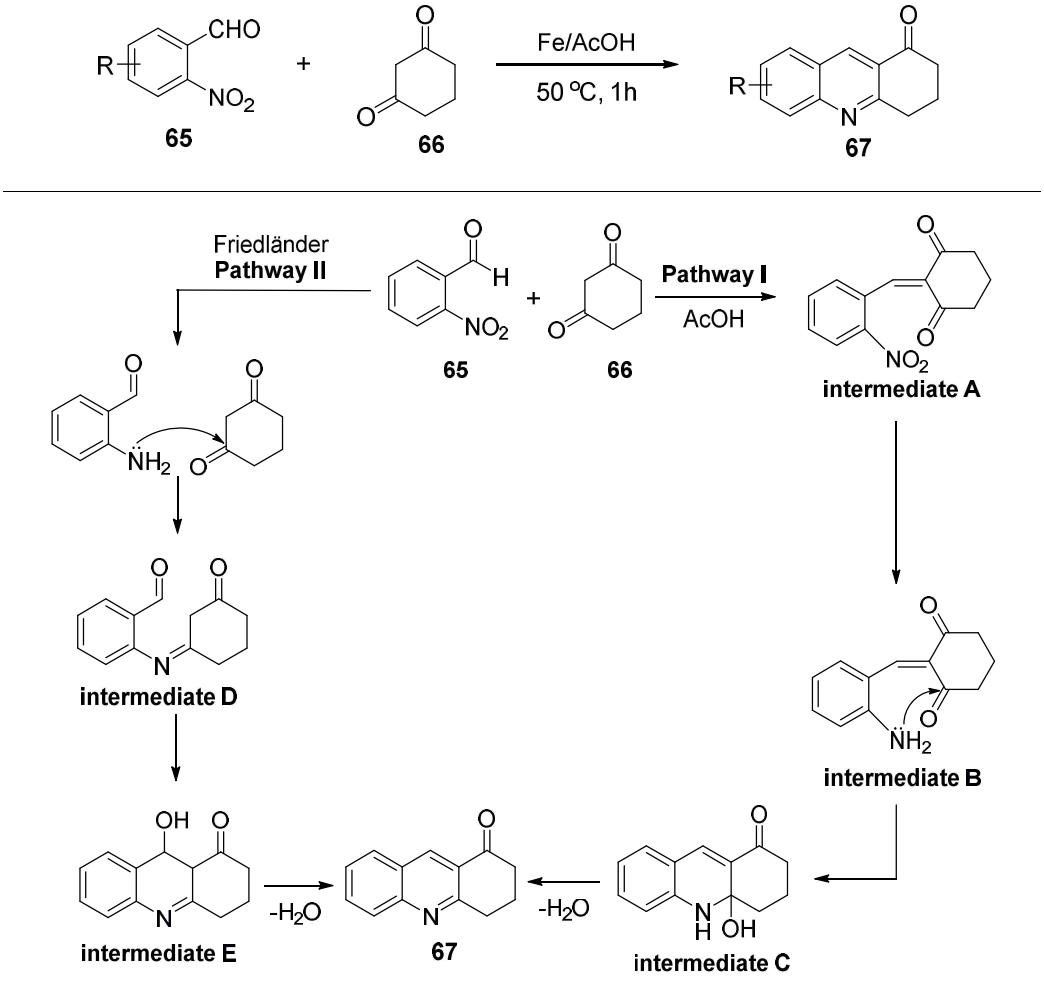


Scheme 15 Copper-Catalyzed Reaction of 2-Aminobenzaldehydes **62** and Alkenyl Iodides **63**

In 2014, Lui and co-workers reported iron/acetic acid mediated reaction for the synthesis of quinoline derivatives. The reaction protocol provided several advantages, such as broad availability of starting materials, environmental safety and low cost. The corresponding quinolines **67** were accomplished in 72–92% yields from 2-nitrobenzaldehydes **65** and 1,3-cyclohexanedione **66** (**Scheme 16**).

The two plausible mechanisms for the construction of quinoline with iron/acetic acid condition were proposed as shown in **Scheme 16**. For pathway I, the first step was aldol condensation of *o*-nitroaldehydes **65** and 1,3-cyclohexanone **66** to give intermediate **A**. Then, reductive cyclization mediated by iron/acetic occurred to

generate intermediate **C**, followed by dehydration to afford the desired quinoline **67**. For the pathway II, the reaction of nitro functionality to corresponding amine was the first transformation, followed by condensation to give a corresponding imine **D**. Then cyclization and dehydration took place, respectively, to generate the quinoline products **67** (Rajawinslin *et al*. 2014).

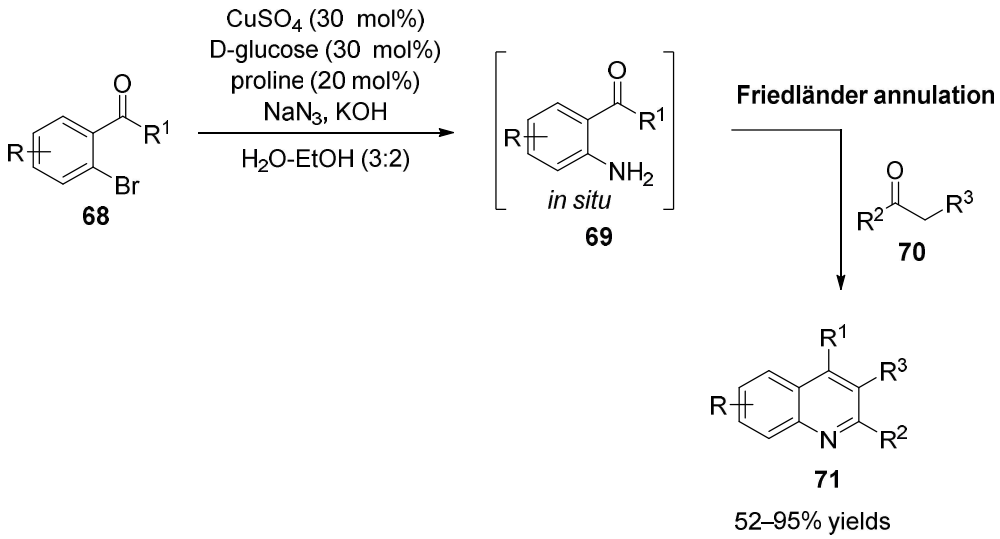


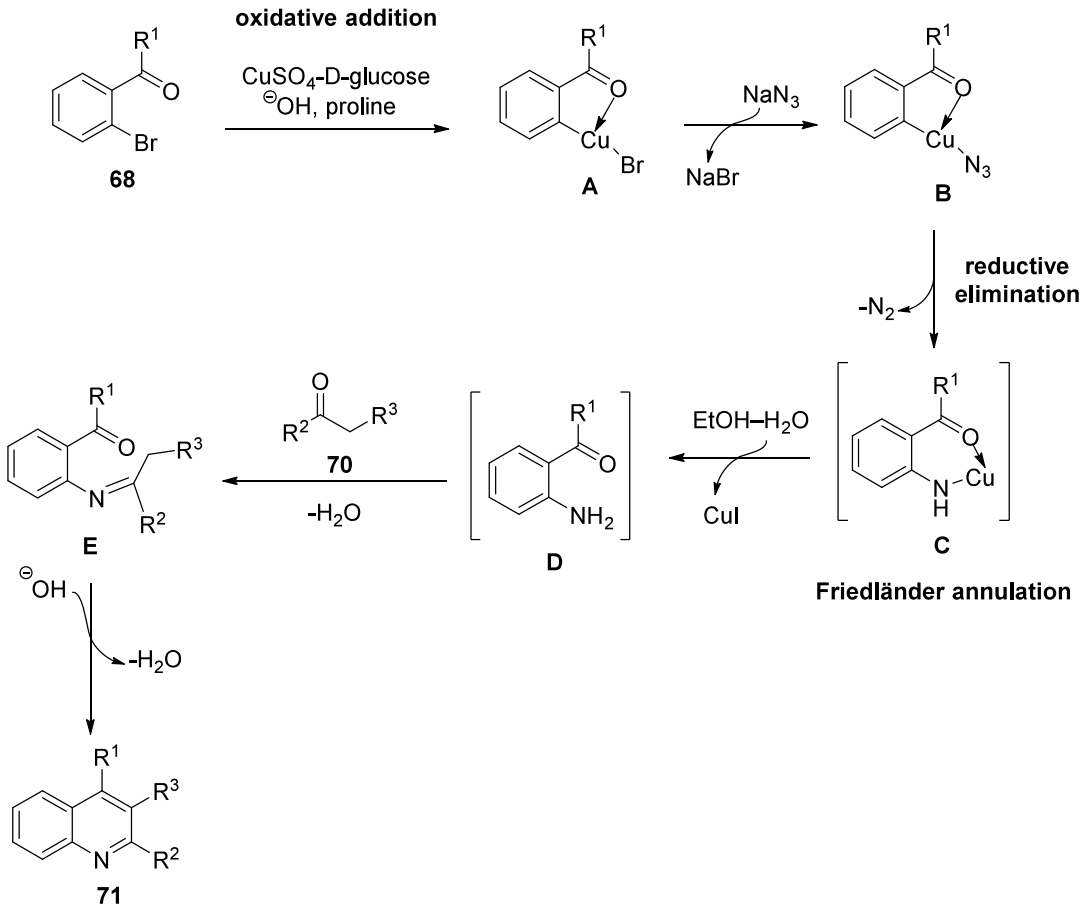
Scheme 16 The Iron/Acetic Acid Catalyzed Reaction for Quinoline Formation

In 2015, Singh and co-workers reported the modified Friedländer annulation on the concept of eco-efficient strategies and green conditions. They designed *o*-bromoaromatic aldehydes/ketones **68** as a mimic of *o*-aminobenzaldehyde. The

desired quinolines **71** were accomplished in moderate to excellent yield *via* copper(II)-catalyzed reaction. The cascade reaction consisted of S_NAr reaction, reduction and heteroannulation (Friedländer annulation). This methodology could be useful for an industrial scale because of inexpensive and easily prepared $CuSO_4$-D-glucose (**Scheme 17**) (Anand *et al*., 2015).

The proposed mechanism was initially involved Cu (I) by the reduction of $CuSO_4$ in presence of D-glucose, base and proline. Next, an oxidative addition with aldehydes **68** gave copper complex **A**, followed by a ligand exchange to give the azido Cu complex **B**. Then reductive elimination took place to generate complex **C**, which was readily converted to *ortho*-aminoaldehyde/ketone **D**. The intermediate **D** underwent dehydrative coupling with ketone **E**, followed by Friedländer annulation to produce the desired quinolines **71**.

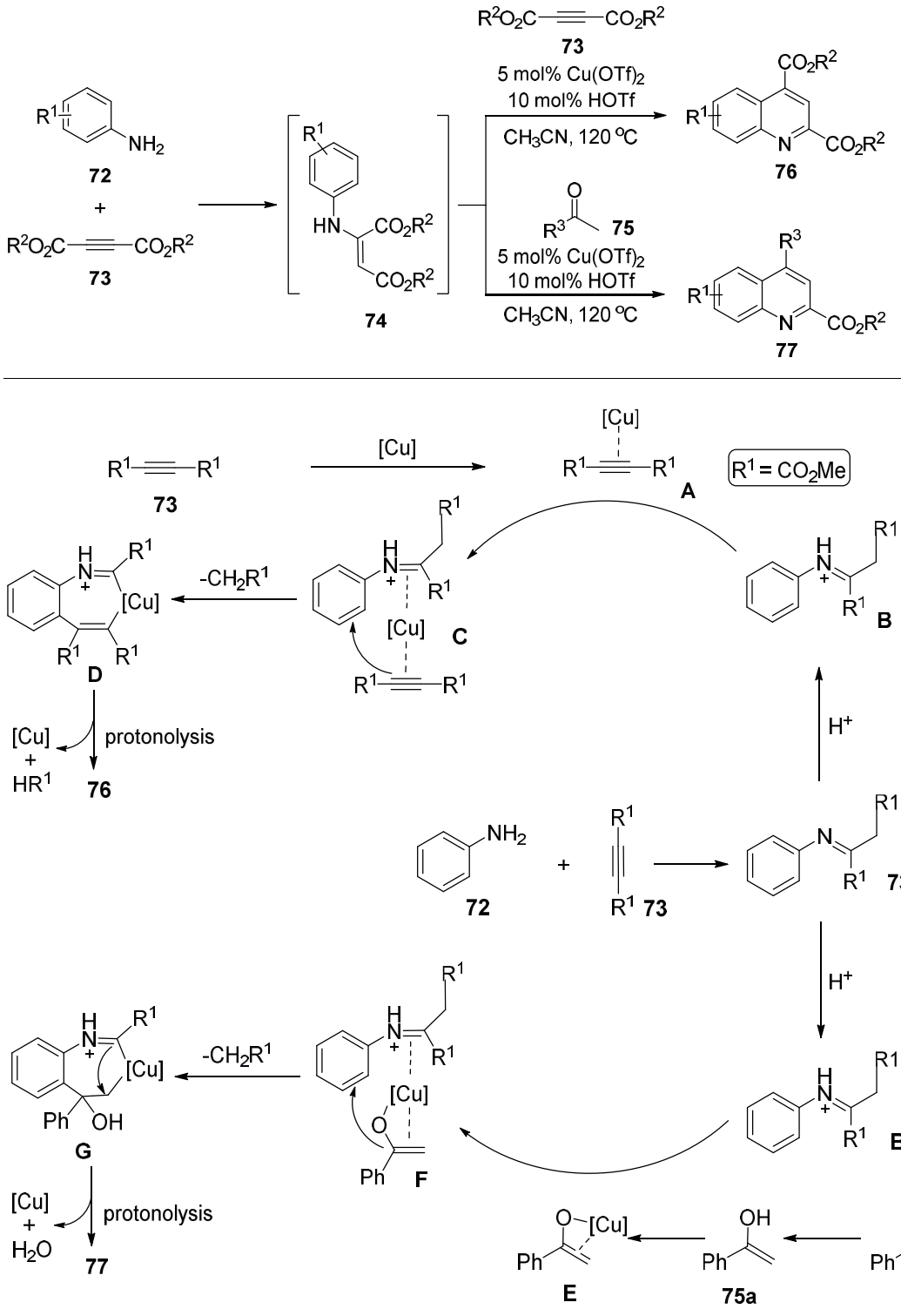




Scheme 17 The Quinolines through Modified Friedländer Approach

More recently, Yia and co-workers have been reported copper(II)-catalyzed cascade annulation of quinoline in 2018. They have developed method for 2,4-disubstituted quinolines **76** from simple anilines and two molecules of alkyne esters **73**. The first step was the formation of imine **73a** from aniline **72** and alkyne **73**, followed by the protonation of **73a** to provide iminium **B**. Next, The copper(II)-catalyzed reaction to produce copper-acetylide **A**. Subsequently, the coordination of complex **A** with iminium **B** to generate copper complex **C**. Species **D** was generated from regioselective migratory insertion of alkyne **73** with the C−C bond cleavage. Then, the protonolysis of intermediate **D** delivered the desired product **76** and the active Cu(II) catalyst.

For the ketone substrates, an alternative reaction pathway was adopted after the formation of the imine species **B**. Firstly, the coordination of the enol form of **75** with Cu(II) catalyst afforded the intermediate **E**, followed by further coordination with B to generate the intermediate **F**. Regioselective migratory insertion of the enol form of **E** gave the intermediate **G** with a similar C−C bond cleavage as shown in above. Protonolysis of **G** delivered the product **77** (**Scheme 18**) (Wu *et al*., 2018).

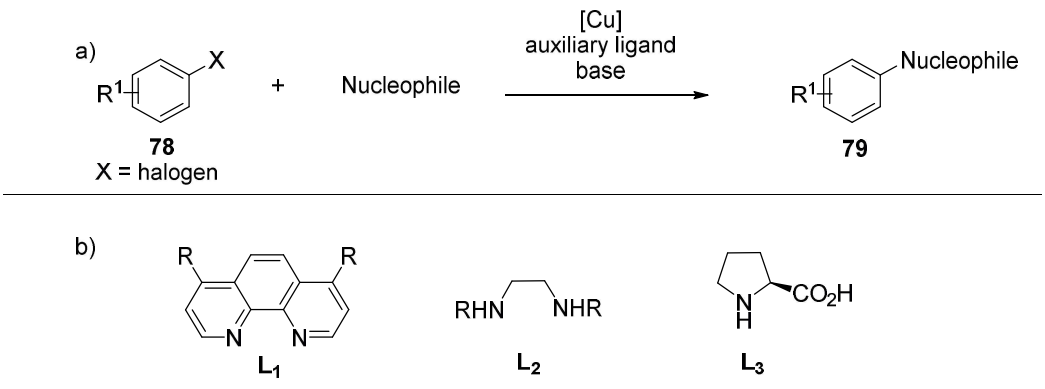


Scheme 18 Novel Cu(II)-Catalyzed Cascade Process for Quinoline Synthesis

1.6 Ullmann-Type Coupling Chemistry

Based on examination of literatures, most of starting materials for quinoline formation were *ortho*-amino carbonyl in which the C(aryl)–N bonds were originally installed. Therefore, synthesis of quinolines by initially forming a the C(aryl)–N bond was a challenge task and practically provided alternative tools to accomplish quinolines.

Copper, eco-friendly, low-cost and easy-handling catalyst, displays a great catalytic potential in many reactions, such as bimetallic-catalyzed Sonogashira coupling, click reaction (cycloaddition with azides) and nucleophilic aromatic substitution. Historically, copper-catalyzed nucleophilic aromatic substitutions have been discovered by Ullmann and Goldberg that applied stoichiometric amount of copper, highly temperature and prolonging reaction time. Then, Buchwald and Taillefer developed the Ullmann-type coupling reaction for C–heteroatom bond formations by adding inorganic bases and auxiliary ligands, resulting in enhancing reaction rates, milder temperature and reduced amounts of copper. They assumed that auxiliary ligands increased solubility and stability of copper complexes. In consequence, ligands were a key component to develop Ullmann-type coupling reactions. There were several ligands to promote copper-catalyzed cross-coupling reactions, for instance, phenanthrolines $\mathbf{L_1}$, 1,2-diamines $\mathbf{L_2}$ and α-aminoacids $\mathbf{L_3}$ (Casitas *et al*. 2013) (**Scheme 19**).

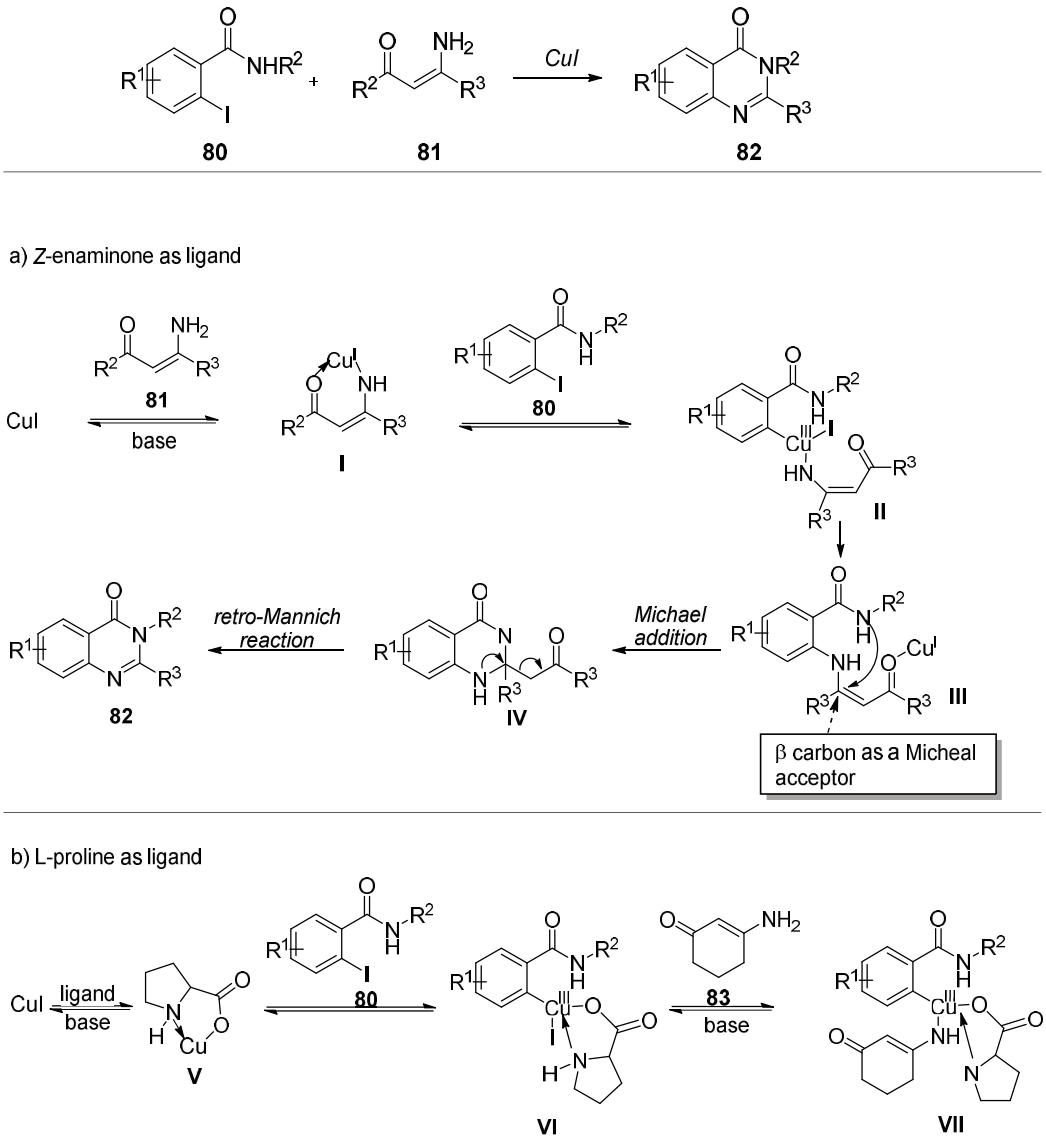


Scheme 19 Ullmann Reaction: a) General Reaction of Aryl Halide Cross Coupling with Nucleophile and b) Some Representative Auxiliary Ligands Used

Hence, copper-catalyzed reaction toward heterocyclic compounds has received more attention these days. Cu-catalyzed reactions devoting to the formation of C–heteroatom bonds (Ullmann-type couplings) have acquired a great attention from synthetic organic chemists.

1.7 Exploring an Alternative Approach for Quinoline Synthesis

In 2014, our research group reported the methodology of copper-catalyzed reaction for the synthesis of quinazolinones **82**. We have demonstrated the C–N bond formation *via* Ullmann-type coupling reaction between 2-iodobenzamides **80** and enaminones **81**. The nitrogen atom of enaminones acted as a nucleophile in Ullmann-type coupling, while the carbon at the beta position acted as a Michael acceptor (**Scheme 20**) (Songsichan *et al*., 2014). The roles of enaminones make us fascinated in their reactivity.



Scheme 20 Copper-Catalyzed Quinazolinone Synthesis

Enlightened by our previous work, we envisioned that enaminones have more than one reactive site. Carbonyl carbon can occur 1,2-addition, while the α-carbon, the high electron density position, can acts as carbon nucleophile. In addition, the β-carbon demonstrates the ability to be a Michael acceptor (1,4-addition). For amino group shows efficiency in Ullmann-type coupling as a nitrogen nucleophile. This is still challenge to us to utilize enaminones in Ullmann-type coupling due to low

electron density on nitrogen atom of vinylogous amides (enaminones). We then tried to introduce other applications of enaminones. To obtain desired quinoline, we envisioned that we could use nitrogen as a nitrogen nucleophile for Ullmann-type coupling, and α-carbon as a nucleophile to form carbon–carbon bond (**Figure 3**).

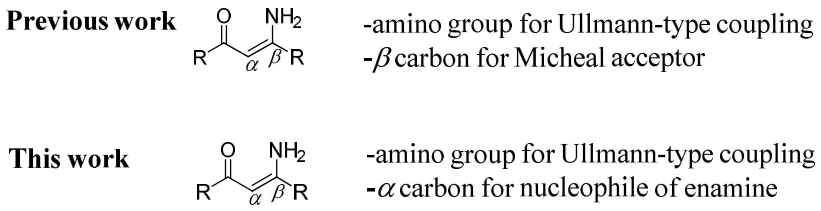
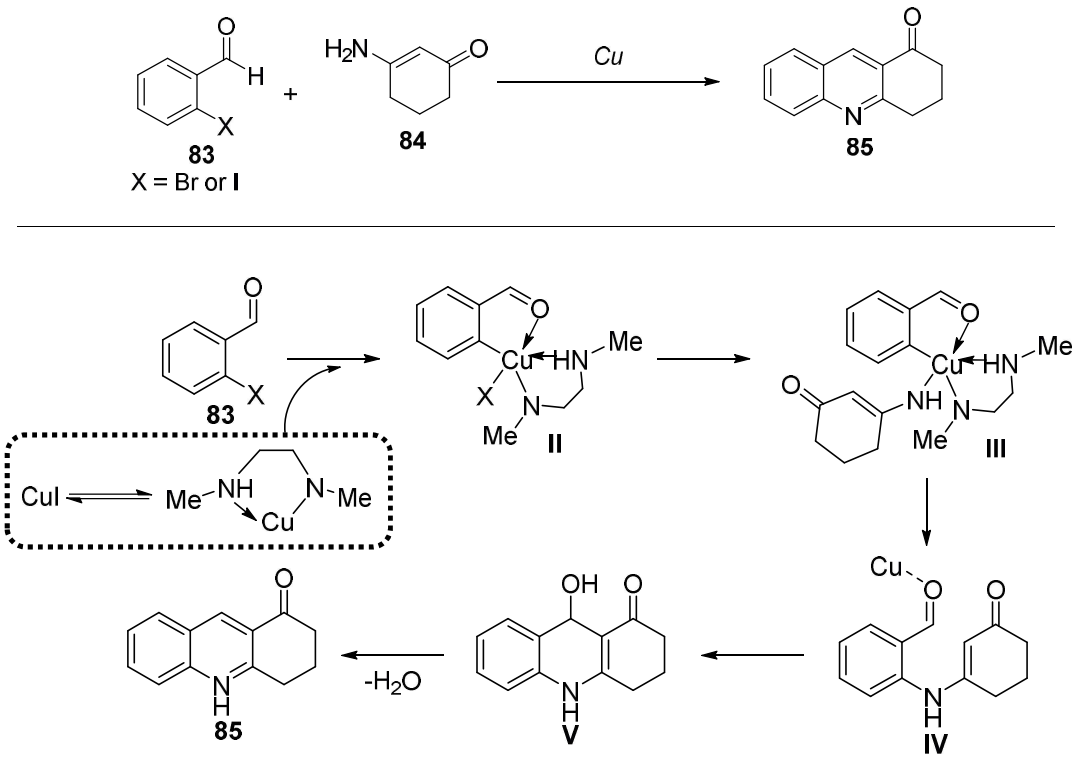


Figure 3 Reactive Modes of Enaminones

In order to accomplish desired quinolines from enaminones, we designed 2-halobenzaldehydes as a reaction partners. The reasons were that 2-halobenzaldehyde provided aryl-halogen site for C(aryl)–N bond coupling, and aldehyde functionality for nucleophilic addition of enaminone. The last transformation was dehydration to accomplish quinoline (**Scheme 21**).



Scheme 21 The Reaction Model of Quinoline Syntheses

1.8 The Objective

To find alternative methods of copper(I)-catalyzed reaction for the synthesis of quinoline derivatives under simple and mild conditions.

CHAPTER 2

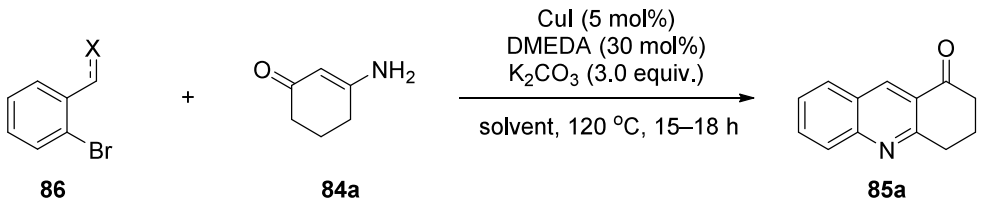
RESULTS AND DISCUSSION

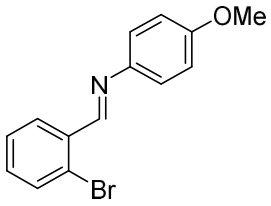
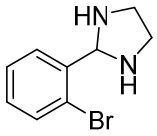
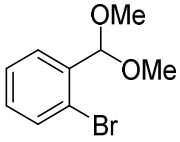
Practically, the copper-catalyzed Ullmann-type coupling has been selected as a great tool to promote C–heteroatom bond formation. In this dissertation, we demonstrated the utility of enaminones in copper-catalyzed domino reaction to accomplish quinolines. Our synthetic strategy involved C–N bond formation by Ullmann-type coupling, C–C bond construction by enamine addition and aromatization by elimination.

2.1 The Study of Suitable Coupling Partner for the Synthesis of Quinoline from 3-Aminocyclohex-2-en-1-one (84a)

We started our investigation with an exploration of coupling partners for the synthesis of quinolines. At the beginning, the reaction was performed with **86** and 3-aminocyclohex-2-en-1-one (**84a**) under Cu-catalyzed reaction in the presence of 5 mol% of CuI as a copper salt, 30 mol% of DMEDA (*N,N'*-dimethylethylenediamine) as a ligand, 3.0 equiv. of K_2CO_3 as a base at 120 ^{o}C in sealed tube (**Table 1**).

Table 1. Copper(I)-Catalyzed Synthesis of Quinoline **85a** from 3-Aminocyclohex-2-en-1-one **(84a)** and Various Coupling Partners **86**[a]



Entry	Starting Material	Additive	Solvent	%Yield[b]
1	 **86a**	-	toluene	16
2	 **86b**	-	CH_3CN	16
3	 **86c**	-	CH_3CN	0
4	 **86d**	-	**toluene**	**49**

[a] Reaction conditions: **84a** (0.5 mmol), **86** (0.6 mmol), CuI (5 mol%), DMEDA (30 mol%), additive (20 mol%), K_2CO_3 (1.5 mmol), solvent (0.5 M) at 120 °C for 15–18 h in sealed tube.

[b] Isolated yield.

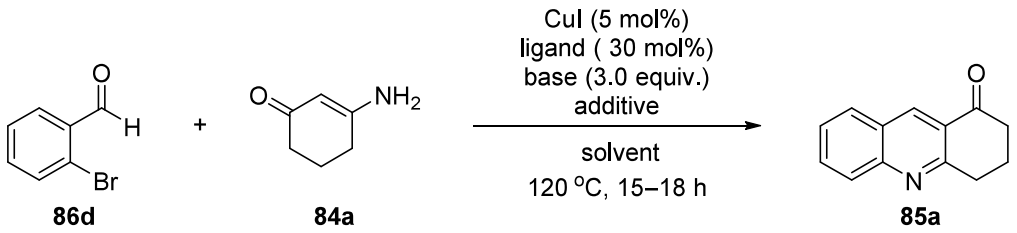
The Preliminary studies showed that quinoline **85a** could be achieved from 3-aminocyclohex-2-en-1-one (**84a**) and various coupling partners such as imine, aminal and aldehyde. The reaction with imine **86a** afforded quinoline **85a** in 16% yield (entry 1, **Table 1**). The equal yield was obtained from the reaction of aminal **86b** (entry 2). On the contrary, no product was observed when the reaction was carried out with acetal **86c** (entry 3). Interestingly, 49% yield of quinoline, was obtained from 2-bromobenzaldehyde (**86d**) (entry 4). These results suggested that the aldehyde functionality was preferably suitable for our domino reaction. Therefore, 2-bromobenzaldehyde was chosen as a coupling partner of enaminones for the synthesis of quinolines via copper-catalyzed domino reaction.

2.2 The Study of Copper-Catalyzed Coupling of 2-Bromobenzaldehyde and Cyclic Enaminone

2.2.1 The Optimization of Reaction Condition (Ligand, Base, Additive, Solvent and Temperature)

The optimization of copper-catalyzed domino reaction was investigated including ligand, base, additive, solvent, and reaction temperature. We selected the reaction of 2-bromobenzaldehyde (**86d**) and 3-aminocyclohex-2-en-1-one (**84a**) as model substrates (**Table 2**).

Table 2. Optimization of Reaction Conditions for Ullmann-Type Coupling[a]



86d **84a** **85a**

Entry	Ligand	Base	Additive	Solvent	Yield[b] (%)
1	DMEDA	K_2CO_3	-	toluene	49
2	DMEDA	Cs_2CO_3	-	toluene	14
3	DMEDA	K_3PO_4	-	toluene	trace[c]
4	DMEDA	*t*-BuOK	-	toluene	0
5	DMEDA	NEt_3	-	toluene	5
6	**DMEDA**	**K_2CO_3**	**Na_2SO_4**	**toluene**	**58**
7	L-proline	K_2CO_3	Na_2SO_4	toluene	23
8	1,10-phenanthroline	K_2CO_3	Na_2SO_4	toluene	26
9	1,2- diamino-cyclohexane	K_2CO_3	Na_2SO_4	toluene	34
10	TMEDA	K_2CO_3	Na_2SO_4	toluene	34
11	PPh_3	K_2CO_3	Na_2SO_4	toluene	12

Table 2. (Continued)

Entry	Ligand	Base	Additive	Solvent	Yield[b] (%)
12	DMEDA	K_2CO_3	Na_2SO_4	dioxane	trace
13	DMEDA	K_2CO_3	Na_2SO_4	CH_3CN	33
14	DMEDA	K_2CO_3	Na_2SO_4	DMF	4
15	DMEDA	K_2CO_3	Na_2SO_4	DMSO	trace
16	DMEDA	K_2CO_3	Na_2SO_4	*i*-PrOH	trace
17	DMEDA	K_2CO_3	Na_2SO_4	*t*-BuOH	7
18	DMEDA	K_2CO_3	reflux	toluene	43
19	DMEDA	K_2CO_3	MS	toluene	56

[a] Reaction conditions: **84** (0.5 mmol), **86d** (0.6 mmol), CuI (5 mol%), ligand (30 mol%), additive (500 mg), base (1.5 mmol), solvent (0.5 M) at 120 ^oC for 15–18 h in sealed tube.
[b] Isolated yield.
[c] Trace amount of product observed from the ^1H NMR spectrum of the crude reaction mixture.

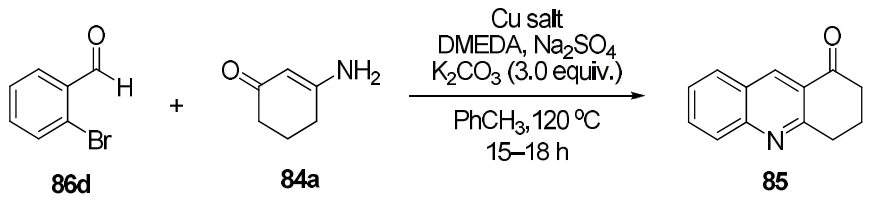
We began our optimization with the reaction of **84a** (0.50 mmol) and **86d** (0.60 mmol) in the presence of CuI (2.50×10^{-2} mmol), K_2CO_3 (1.50 mmol) and DMEDA (0.15 mmol) in toluene at 120 ^oC for 15–18 h affording the desired product **85** in 49% yield (entry 1, **Table 2**). We turned our attention to various bases. When the reaction was performed with Cs_2CO_3, the yield was diminished to 14% (entry 2). Changing base to K_3PO_4 provided trace amount of quinoline **85a** (entry 3), while a stronger base, *t*-BuOK, and common organic base, NEt_3, gave low yields (entries 4–

5). A satisfactory result was obtained when Na_2SO_4 was added as an additive giving the corresponding product in 58% yield (entry 6). No improvement in yields was observed when the reaction was carried out in the presence of various ligands, such as L-proline, 1,10-phenanthroline, 1,2-diaminocyclohexane, PPh_3 and TMEDA (entries 7–11). DMEDA, a bidentate ligand, was still the suitable ligand. A variety of solvents were studied. The low yields were obtained from polar solvents, such as dioxane, CH_3CN, DMF, DMSO, *i*-PrOH and *t*-BuOH (entries 12–17). Next, the role of Na_2SO_4 was examined. Refluxing condition without Na_2SO_4 diminished yield to 43% (entry 18) whereas a comparable yield was achieved from the reaction in the presence of 4 Å molecular sieves (MS) (entry 19). The results suggested that using Na_2SO_4 possibly acted as a drying agent in our reaction. Moreover, the high temperature at 120 ^oC and long reaction time (15–18 h) were necessary for completion of the reaction. In conclusion, the optimal condition was the use of 1.2 equiv. of 2-bromobenzaldehyde (**86d**), 1.0 equiv. of 3-aminocyclohex-2-enone (**84a**), 5 mol% of CuI, drying agents (Na_2SO_4 or MS) in toluene at 120 ^oC in sealed tube for 15–18 h.

2.2.2 The Optimization of Reaction Condition (Copper Salt, Amount of Ligand and Catalyst Loading)

Due to the moderate yield of desired product, we attempted to improve the product yield by further investigation. Copper salts, amount of ligand and catalyst loading were subjected to the further optimized study (**Table 3**).

Table 3. The Optimization Study of Copper Salt and Catalyst Loading[a]



Entry	Cu	Cu (mol%)	DMEDA (mol%)	Yield[b] (%)
1	CuI	5	10	25
2	CuI	5	20	31
3	**CuI**	**5**	**30**	**58**
4	CuI	5	40	34
5	CuI	5	50	53
6	CuI	10	30	27
7	CuI	20	30	23
8	CuI	30	30	21
9	CuCl	5	30	37
10	Cu_2O	5	30	50
11	CuBr	5	30	49
12	$Cu(OAc)_2$	5	30	0

[a] Reaction conditions: **86d** (0.5 mmol), **84a** (0.6 mmol), Na_2SO_4 (500 mg), toluene (0.5 M) at 120 °C for 15–18 h in sealed tube.
[b] Isolated yield.

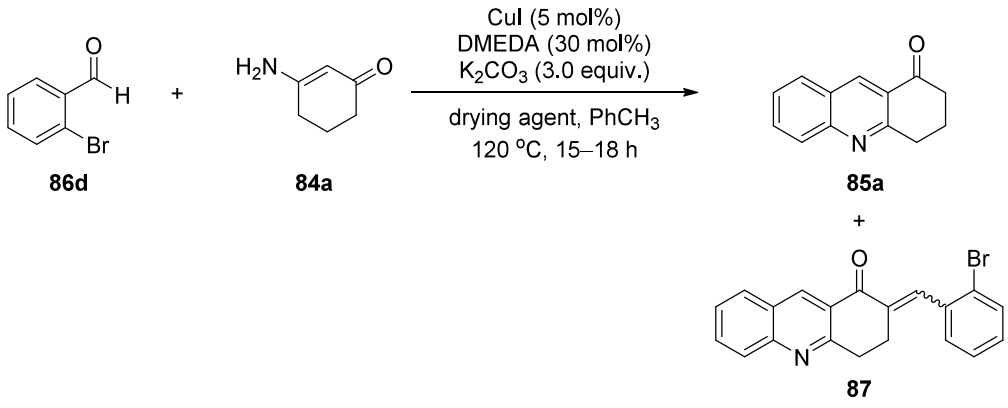
We started with 5 mol% of CuI and enhancing a number of DMEDA from 10 to 50 mol% (entries 1–5, **Table 3**). Based on the results, the reaction with 30 mol% of ligand and 5 mol% of CuI gave the best yield in 58% (entry 3). We then varied amount of copper(I) loading from 5 to 30 mol%. The results suggested that excessive

amount of copper could not develop the yields (entries 6–8). Subsequently, the study of various copper salts was investigated. CuCl provided low yield, 37% (entry 9). Cu_2O and CuBr gave comparable yield of product, 50% and 49%, respectively (entries 10–11). Different result was found, when $Cu(OAc)_2$ was used as a catalyst yielding 0% of quinoline (entry 12).

2.2.3 The Optimization of Reaction Condition (Ratio of Substrates)

Based on no improvement of product yield from varying amount of copper and ligand, we attempted to increase yield by varying the ratio of starting materials showing in **Table 4**.

Table 4. The Optimization Study of the Ratio of Aldehyde **86d** and Enaminone **84a**[a]



86d **84a** **85a** **87**

Entry	Additive	Ratio 86d:84a	Yield[b] of 85a:87 (%)
1	Na_2SO_4	1.2:1.0	58:14
2	MS	1.2:1.0	57:13
3	**MS**	**1.0:2.0**	**77:7**

Table 4. (Continued)

Entry	Additive	Ratio 86d:84a	Yield[b] of 85a:87 (%)
4	None (reflux)	1.2:1.0	43:21

[a] Reaction conditions: CuI (5 mol%), DMEDA (30 mol%), Na_2SO_4 (500 mg), toluene (0.5 M) at 120 ^oC for 15–18 h in sealed tube.
[b] Isolated yield.

In this experiment, we began with the use of 1.2 equiv. of 2-bromobenzaldehyde (**86d**), 1.0 equiv. of 3-aminocyclohex-2-en-1-one (**84a**), 5 mol% of CuI in toluene at 120 ^oC in sealed tube for 15–18 h (entries 1–2). We found that using Na_2SO_4 or MS as a drying agent gave a comparable yield. Importantly, we obtained quinoline **87** as a by-product presumably generated from the excess amount of aldehyde. Therefore, we switched the ratio of **86d** and **84a**. Significantly, the yield of product was greatly improved to 77% (entry 3). Lastly, we tried to apply reflux condition instead of adding drying agent. The desired product **85a** was obtained relatively moderate (entry 4).

We concluded that the optimal condition was as follows: 1.0 equiv. of 2-bromobenzaldehyde (**86d**) and 2.0 equiv. of 3-aminocyclohex-2-en-1-one (**84**), 5 mol% of CuI as the catalyst, 30 mol% of DMEDA as the ligand, and 3.0 equiv. of K_2CO_3 as the base in toluene at 120 ^oC under air in sealed tube.

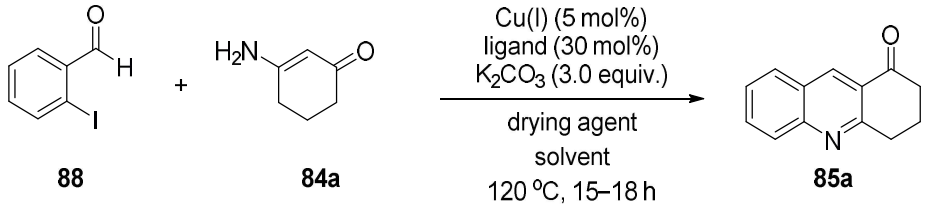
2.3 The Study of Copper-Catalyzed Coupling between 2-Iodobenzaldehyde and Cyclic Enaminone

A satisfactory result of quinoline formation from aryl bromides encouraged us to extend the study. In considering the availability of 2-halobenzaldehydes, we found that both bromine and iodine were commonly substituents of benzaldehyde and applicable to copper-catalyzed Ullmann-type coupling (Beletskaya *et al.*, 2012). With

this idea in mind, 2-iodobenzaldehyde **88** was subjected to our quinoline formation study (**Table 5**).

2.3.1 The Optimization of Reaction Condition (Copper, Ligand, Base, Ratio, Additive and Solvent)

Table 5. The Optimization Studies for the Synthesis of **85a**[a]



88 **84a** **85a**

Entry	Catalyst	Ligand	Ratio 88:84a	Additive	Solvent	Yield[b] (%)
1	CuI	DMEDA	1.2:1.0	Na_2SO_4	toluene	30
2	CuI	DMEDA	1.0:2.0	Na_2SO_4	toluene	45
3	CuI	DMEDA	1.0:2.0	Na_2SO_4	DMF	trace[c]
4	CuI	DMEDA	1.0:2.0	Na_2SO_4	DMSO	trace
5	CuI	DMEDA	1.0:2.0	Na_2SO_4	CH_3CN	49
6	CuI	DMEDA	1.0:2.0	MS	CH_3CN	50
7	CuCl	DMEDA	1.0:2.0	MS	CH_3CN	33
8	CuBr	DMEDA	1.0:2.0	MS	CH_3CN	35
9	**CuI**	**1,2-diamino-cyclohexane**	**1.0:2.0**	**MS**	**CH_3CN**	**75**

Table 5. (Continued)

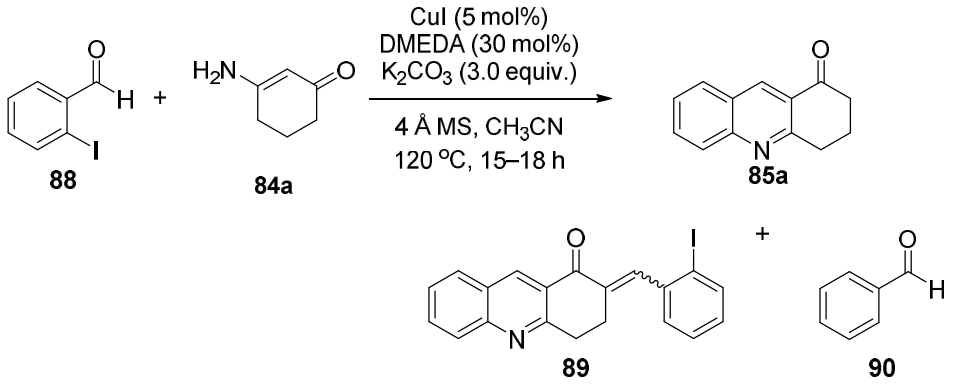
Entry	Catalyst	Ligand	Ratio 88:84a	Additive	Solvent	Yield[b] (%)
10	CuI	L-proline	1.0:2.0	MS	CH_3CN	69
11	CuI	1,10-phenan-throline	1.0:2.0	MS	CH_3CN	43
12	CuI	2,2'-bipyridine	1.0:2.0	MS	CH_3CN	64
13	CuI	1,2-diamino-cyclohexane	1.2:1.0	MS	CH_3CN	47

[a] Reaction conditions: **88** (0.5 mmol), **84a** (0.6 mmol), Cu(I) (5 mol%), ligand (30 mol%), additive (500 mg), K_2CO_3 (1.5 mmol), solvent (0.5 M) at 120 ^oC for 15-18 h in sealed tube.
[b] Isolated yield.
[c] Trace amount of product observed from the ^1H NMR spectrum of the crude reaction mixture.

Firstly, we subjected 1.2 equiv. of 2-iodobenzaldehyde (**88**) and 1.0 equiv. of enaminone **84a** to the similar condition used for the reaction of 2-bromobenzaldehyde (**86d**) and enaminone **84a**. The desired quinoline **85** was obtained in low yield, 30% (entry 1). Switching the ratio of starting materials improved the yield up to 45% (entry 2). Based on the results, the reaction of 2-iodobenzaldehyde (**88**) and enaminones **84** was required an optimization in order to improve the yield of quinolines. Consequently, variety of solvents was subjected to our study (entries 3, 4 and 5). Fortunately, CH_3CN gave the best yield of quinoline, 49% (entry 5). Employing 4 Å molecular sieves as the drying agent was no significance in yield improvement (entry 6). The study of other copper salts was examined; CuCl and CuBr gave product yield in 33% and 35%, respectively (entries 7–8). Next, a variety of common ligands was subjected to our study (entries 9–12). The best yield, 75%, was obtained from the 1,2-diaminocyclohexane (entry 9). In addition, switching ratio of 2-iodobenzaldehyde and enaminone to 1.2:1.0 providing 47% yield of the quinoline

(entry 13). Note that, the excess amount of enaminone was crucial in the domino reaction. Consequently, the optimal condition was 1.0 equiv. of 2-iodobenzaldehyde, 2.0 equiv. of enaminone, 30 mol% of 1,2-diaminocyclohexane, 3.0 equiv. of K_2CO_3 in CH_3CN at 120 ^oC under air in sealed tube.

As for the result, two simple protocols were achieved for the synthesis of quinoline **85** from both 2-bromo- and 2-iodobenzaldehydes, 77% and 75% yields, respectively. However, we still observed amount of by-product **89** and benzaldehyde **90** from the ^1H NMR of the crude reaction mixture (**Scheme 22**).



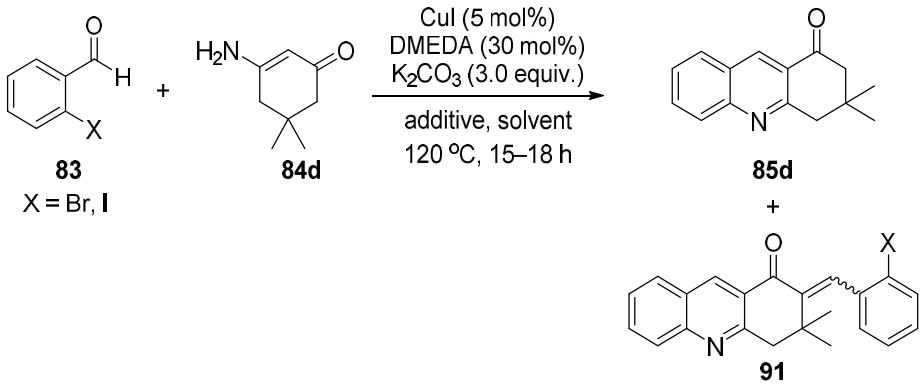
Scheme 22 The Product and By-Products from Copper-Catalyzed Reaction of 2-Iodobenzaldehyde **88** and Enaminone **84a**

2.4 The Reactions of 2-Haloginated Benzaldehydes 83 with 5,5-Dimethylcyclohex-2-enone (84d)

Next, we explored a derivative of enaminone (**85d**) for our domino reaction. We found that the yield of quinoline **85d** from 3-amino-5,5-dimethylcyclohex-2-enone (**84b**) was generally higher than that of 3-aminocyclohex-2-en-1-one (**84a**) with both 2-bromo or 2-iodobenzaldehyde **83** (**Table 6**). More importantly, the 2.0 equiv. of enaminone **84a** was not required (entries 1–5). The high yields of quinoline were

obtained. Based on these result, we believed that having geminal dimethyl substituents increased the reactivity of the enaminone in the synthesis of quinoline.

Table 6. The Reactions of 2-Halobenzaldehydes **83** and 3-Amino-5,5-Dimethylcyclo-hex-2-enone (**84d**)[a]



83
X = Br, **I**

84d

85d
+

91

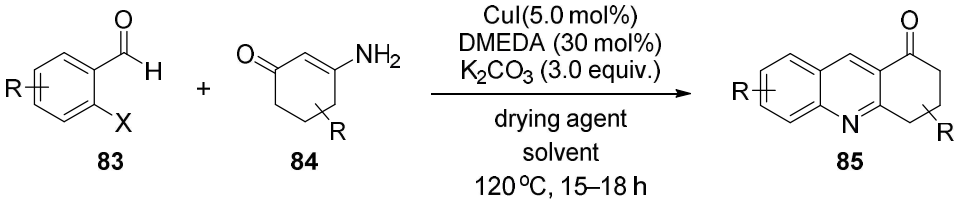
Entry	X	Solvent	Additive	Ratio 83:84d	%Yield[b] of 85d:91
1	Br	$PhCH_3$	Na_2SO_4	1.2:1.0	70:0
2	**Br**	**$PhCH_3$**	**MS**	**1.2:1.0**	**83:0**
3	I	CH_3CN	Na_2SO_4	1.2:1.0	74:0
4	**I**	**CH_3CN**	**MS**	**1.2:1.0**	**75:0**
5	I	CH_3CN	MS	2.0:1.0	78:0

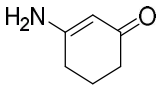
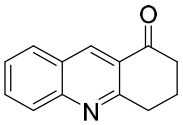
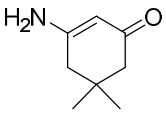
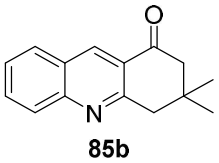
[a] Reaction conditions: Cu(I) (5 mol%), DMEDA (30 mol%), additive (500 mg), K_2CO_3 (1.5 mmol), solvent (0.5 M) at 120 °C for 15–18 h in sealed tube.
[b] Isolated yield.

2.5 The Summary of Optimization Reaction Condition between 2-Halobenzaldehydes and Cyclic Enaminones

Based on reaction optimizations, we summarized the practical protocols for quinoline synthesis from 2-bromo- or 2-iodobenzaldehyde and cyclic enaminones (**Table 7**)

Table 7. The Summary of the Optimization Conditions of Copper-Catalyzed Domino Reaction[a]



Entry	X	Enaminone	Ratio 83:84	Solvent	Drying agent	Product	Yield[b] (%)
1	Br	 **84a**	1.0:2.0	$PhCH_3$	Na_2SO_4	 **85a**	77
2	Br	 **84d**	1.2:1.0	$PhCH_3$	MS	 **85b**	83
3	I	**84a**	1.0:2.0	CH_3CN	Na_2SO_4	**85a**	75
4	I	**84d**	1.2:1.0	CH_3CN	MS	**85b**	75

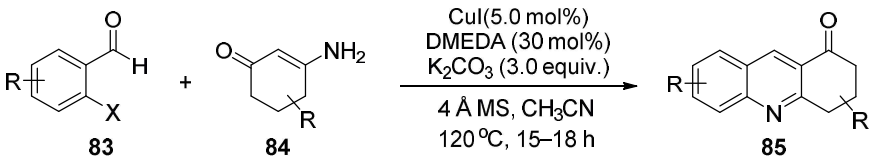
[a] Reaction conditions: Cu(I) (5 mol%), DMEDA (30 mol%), additive (500 mg), K_2CO_3 (1.5 mmol), solvent (0.5 M) at 120 ^oC for 15–18 h in sealed tube.
[b] Isolated yield.

To accomplish quinolines from 2-halobenzaldehydes and cyclic enaminones, the reaction of 2-bromobenzaldehyde with both cyclic enaminones required toluene as an optimal solvent. Meanwhile, acetonitrile was the optimal solvent when 2-iodobenzaldehyde was used as a starting material. As for an effect of drying agent, all reactions from cyclic enaminone **84a** could proceed with Na_2SO_4 (entries 1 and 3). On the other hand, the reaction of enaminone **84b** worked well in the presence of molecular sieves (entries 2 and 4). The ratio of 2-halobenzaldehydes had a great effect on yield. The excess amount of enaminone was very crucial when low-reactive enaminone **84a** was employed.

2.6 The Substrate Scopes of the Cu-Catalyzed Reaction of Quinoline Derivatives from Cyclic Enaminones

After having established suitable reaction conditions, we explored the substrate scope of Cu-catalyzed domino reaction of quinoline derivatives from various 2-halobenzaldehydes (**83**) and *E*-enaminones (**84**) (**Table 8**).

Table 8. Copper-Catalyzed Synthesis of Quinolines **85** from 2-Halobenzaldehydes **83** and *E*-Enaminones **84**[a]



83 **84** **85**

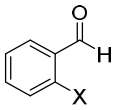
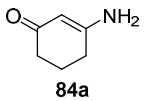
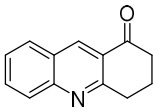
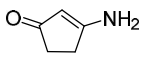
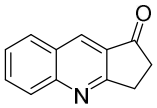
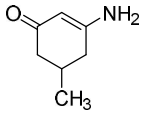
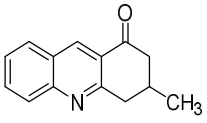
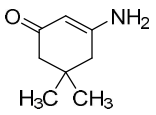
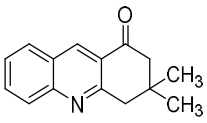
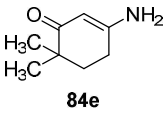
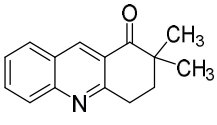
Entry	2-Haloben-zaldehydes	*E*-Enaminone	Product	Yield[b] (%) Br	Yield[b] (%) I
1	 **83a**	 **84a**	 **85a**	77[d,f]	75[d,f]
2	**83a**	 **84b**	 **85b**	0[e,f]	0[e,f]
3	**83a**	 **84c**	 **85c**	30[e]	41[e]
4	**83a**	 **84d**	 **85d**	83	75
5	**83a**	 **84e**	 **85e**	68	76

Table 8. (Continued)

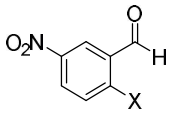
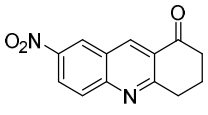
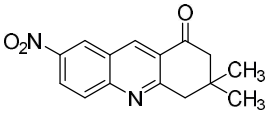
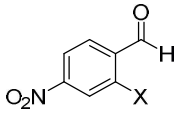
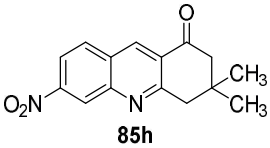
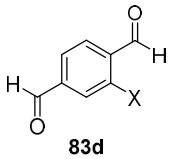
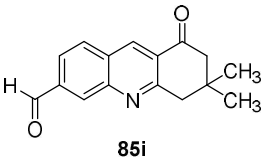
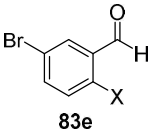
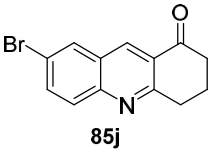
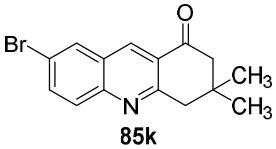
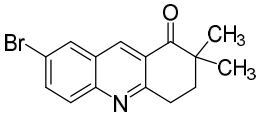
Entry	2-Haloben-zaldehydes	*E*-Enaminone	Product	Yield[b] (%) Br	Yield[b] (%) I
6	 **83b**	**84a**	 **85f**	28[e, f]	0[e, f]
7	**83b**	**84d**	 **85g**	57	51
8	 **83c**	**84d**	 **85h**	51	ND[c]
9	 **83d**	**84d**	 **85i**	ND[c]	74
10	 **83e**	**84a**	 **85j**	ND[c]	trace[e, f, g]
11	83e	**84d**	 **85k**	54	70[e]
12	83e	**84e**	 **85l**	44[e]	65[e]

Table 8. (Continued)

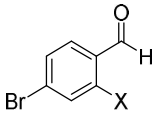
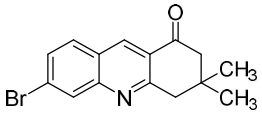
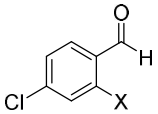
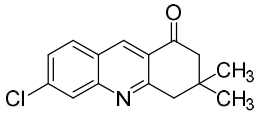
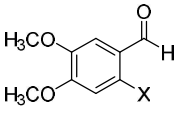
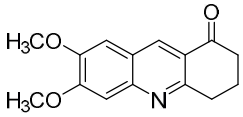
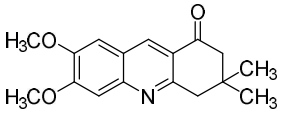
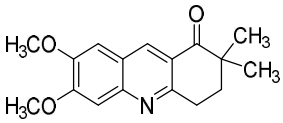
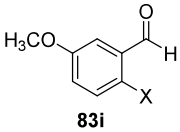
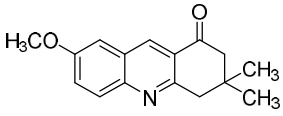
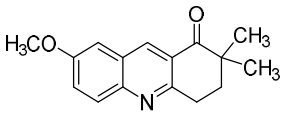
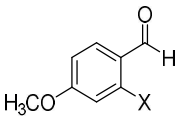
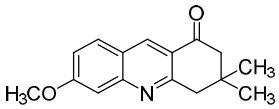
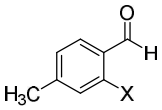
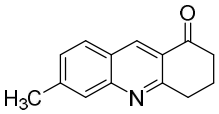
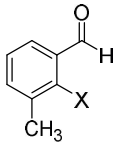
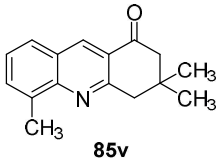
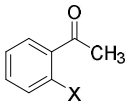
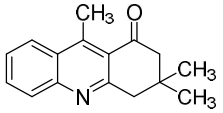
Entry	2-Haloben-zaldehydes	*E*-Enaminone	Product	Yield[b] (%) Br	Yield[b] (%) I
13	 **83f**	**84d**	 **85m**	56[e]	ND[c]
14	 **83g**	**84d**	 **85n**	ND[c]	65[e]
15	 **83h**	**84a**	 **85o**	0[e, f]	12[e, f]
16	**83h**	**84d**	 **85p**	0[e]	56
17	**83h**	**84e**	 **85q**	0[e]	39[e]
18	 **83i**	**84d**	 **85r**	82	70

Table 8. (Continued)

Entry	2-Haloben-zaldehydes	*E*-Enaminone	Product	Yield[b] (%) Br	Yield[b] (%) I
19	**83i**	**84e**	 **85s**	65 [e]	ND[c]
20	 **83j**	**84d**	 **85t**	65	ND[c]
21	 **83k**	**84a**	 **85u**	61	ND[c]
22	 **83l**	**84d**	 **85v**	ND[c]	42 [e]
23	 **83m**	**84d**	 **85w**	0 [e]	27 [e]

[a] Reaction conditions: **84** (0.5 mmol), **83** (0.6 mmol),Cu(I) (5 mol%), DMEDA (30 mol%), additive (500 mg), K_2CO_3 (1.5 mmol), solvent (0.5 M) at 120 ^oC for 15–18 h in sealed tube.

[b] Isolated yield.

[c] ND: not determined.

[d] The quantity of starting materials was **83** (0.5 mmol), **84** (1.0 mmol),

[e] Drying agent was with Na_2SO_4.

[f] The reaction proceeded in toluene.

[g] Trace amount of product observed from the ^{1}H NMR spectrum of the crude reaction mixture.

Following the data, the experimental results revealed that the nature substituents on benzaldehyde ring had effect on yields of quinolines. The neutral aldehyde smoothly produced the desired product in great yields (**85a**, **85d–e**, **Table 8**). Both the reactions of 2-bromo- and 2-iodobenzaldehydes and 3-aminocyclohex-2-en-1-one (**84a**) provided corresponding quinoline **85a** in high yields, 77% and 75%, respectively (entry 1). Using 3-aminocyclopent-2-enone (**84b**) with 2-halobenzaldehydes **83** didn't provide quinoline (**85b**) (entry 2). It seems that the ring size of cyclic enaminone has much effect on the tandem process. The low yield was obtained when 3-amino-5-methylcyclohex-2-enone (**84c**) was used (entry 3). On the contrary, having geminal dimethyl substituents on the 3-aminocyclohex-2-enone increased the yield of quinoline products (entries 4–5). The results illustrated that geminal dimethyl substituents enhanced the reaction reactivity of enaminones. Unfortunately, an aldehyde having nitro substituent generally gave low to moderate yields of the corresponding quinolines (entries 6–7). Different result was found when 4-formal-2-iodobenzaldehyde (**83d**) was subjected to the reaction. The yield of quinoline was obtained in 74% (entry 9). 3-Aminocyclohex-2-enone (**84b**) was not suitable to reaction when 5-bromo-2-iodobenzaldehyde (**83e**) was used (entry 10). On the other hand, cyclic enaminone with geminal dimethyl substituents provided moderate to good yield of quinolines (entries 11–13). 4-Chloro-2-iodobenzaldehyde was also suitable to reaction giving good yield of product (entry 14). 2-Bromobenzaldehyde with dimethoxy substituents gave 0% yield of quinoline. While in case of 2-iodobenzaldehyde gave low to moderate yields (entries 15–17). These results suggested that the electronic property played a huge role in this reaction in which high electron density on benzaldehydes was not applicable to our protocols. Interestingly, the yield was dramatically increased when monomethoxy substituent on aromatic aldehydes **83i**, **83j** was used (entries 18–20). In addition, the yields were slightly dropped from the reaction of enaminones **84a** or **84d** when reacting with monomethyl substituted benzaldehyde (entries 21–22). Unfortunately, the low or no

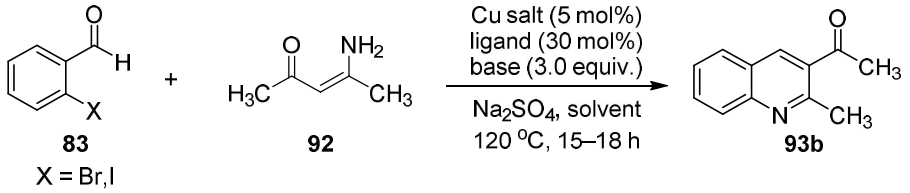
yield was obtained when the reaction performed with 2-haloacetophenones **83m** (entry 23).

2.7 The Study of Copper-Catalyzed Coupling of 2-Halobenzaldehydes and Acyclic Enaminone

2.7.1 The Optimization of Reaction Condition (Ligand, Base, Additive and Solvent)

To extend this protocol, we would like to include acyclic enaminones (*Z*-enaminones) in our substrate scope. However, cyclic and acyclic enaminones showed different reactivity for chemical reactions. Therefore, the optimization of the reaction was required. We performed reaction optimization by using 2-halobenzaldehydes and (*Z*)-4-aminopent-3-en-2-one as a model (**Table 9**).

Table 9. The Optimization Condition of Quinoline **93b** from 2-Halobenzaldehydes **83** and (*Z*)-4-Aminopent-3-en-2-one (**92**)[a]



Entry	X	Catalyst	Ligand	Base	Solvent	Yield[b] (%)
1	Br	CuI	1,2-diaminocyclohexane	K_2CO_3	CH_3CN	43
2	Br	CuI	1,2-diaminocyclohexane	K_2CO_3	$PhCH_3$	0
3	Br	CuI	1,2-diaminocyclohexane	K_2CO_3	DMF	0
4	Br	CuI	1,2-diaminocyclohexane	K_2CO_3	DMSO	0
5	Br	CuI	1,2-diaminocyclohexane	K_2CO_3	*i*PrOH	0

Table 9. (Continued)

Entry	X	Catalyst	Ligand	Base	Solvent	Yield[b] (%)
6	Br	CuI	1,10-phenanthroline	K_2CO_3	CH_3CN	0
7	Br	CuI	2,2'-bipyridine	K_2CO_3	CH_3CN	0
8	Br	CuI	L-proline	K_2CO_3	CH_3CN	0
9	Br	CuI	DMEDA	K_2CO_3	CH_3CN	0
10	Br	CuI	TMEDA	K_2CO_3	CH_3CN	0
11	Br	CuI	PPh_3	K_2CO_3	CH_3CN	0
12	Br	CuI	1,2-diaminocyclohexane	Cs_2CO_3	CH_3CN	0
13	Br	CuI	1,2-diaminocyclohexane	K_3PO_4	CH_3CN	0
14	Br	CuI	1,2-diaminocyclohexane	Et_3N	CH_3CN	0
15	Br	CuBr	1,2-diaminocyclohexane	K_2CO_3	CH_3CN	trace[c]
16	Br	Cu_2O	1,2-diaminocyclohexane	K_2CO_3	CH_3CN	trace
17	Br	CuCl	1,2-diaminocyclohexane	K_2CO_3	CH_3CN	trace
18	I	CuI	DMEDA	K_2CO_3	CH_3CN	0
19	**I**	**CuI**	**1,2-diaminocyclohexane**	**K_2CO_3**	**CH_3CN**	**55**

[a] Reaction conditions: **92** (0.5 mmol), **83** (0.6 mmol),Cu(I) (5 mol%), ligand (30 mol%), additive (500 mg), base (1.5 mmol), solvent (0.5 M) at 120 ^oC for 15–18 h in sealed tube.
[b] Isolated yield.
[g] Trace amount of product observed from the ^1H NMR spectrum of the crude reaction mixture.

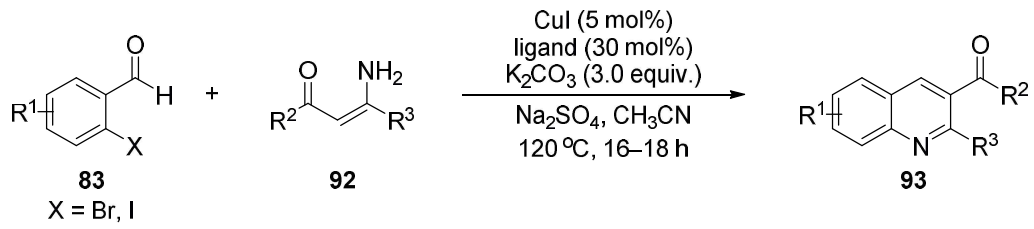
The results showed that the reaction of 2-bromobenzaldehyde **86d** (0.60 mmol), (*Z*)-4-Aminopent-3-en-2-one (**92**) (0.50 mmol) in the present of CuI (2.50×10^{-2} mmol), K_2CO_3 (1.50 mmol) and 1,2-diaminoyclohexane (0.15 mmol) in

acetonitrile at 120 ^{o}C for 15-18 h affording the desired product **93** in 43% yield (entry 1, **Table 11**). Then, we began exploring solvents, ligands, bases and copper salts. Trace amount or no product was observed (entries 2–17). Additionally, we tested the reaction with 2-iodobenzaldehyde (**88**) and (*Z*)-4-aminopent-3-en-2-one (**92**). 1,2-Diaminocyclohexane was still the optimal ligand to provide quinoline **93b** in 55% yield. The optimal condition was concluded that both 2-bromo- and 2-iodobenzaldehydes worked well in the use of 1.2 equiv. of 2-halobenzaldehydes, 1.0 equiv. of enaminone, 30 mol% of 1,2-diaminocyclohaxane, 3.0 equiv. of K_2CO_3 in CH_3CN at 120 ^{o}C under air in sealed tube.

2.7.2 The Cu-catalyzed Reaction to Synthesize Quinoline Derivatives

With these optimized conditions in hand, we surveyed the substrate scopes of of CuI-catalyzed domino reaction for synthesis of quinoline derivatives from 2-halobenzaldehydes **83** and *Z*-enaminones **92** (**Table 10**).

Table 10. Copper-Catalyzed Reaction of 2-Halobenzaldehydes **83** and *Z*-Enaminones **92**[a]



83 X = Br, I **92** **93**

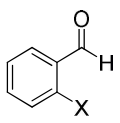
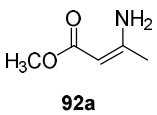
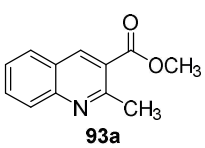
Entry	2-Haloben-zaldehydes	*E*-Enaminones	Product	%Yield[b] X = Br	%Yield[b] X = I
1		 **92a**	 **93a**	58	42

Table 10. (Continued)

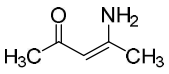
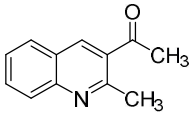
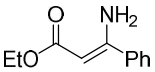
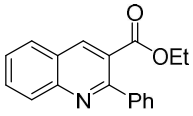
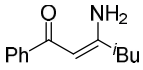
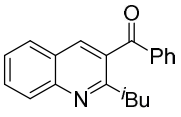
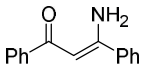
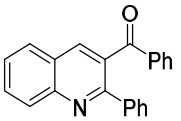
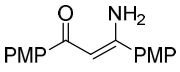
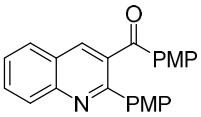
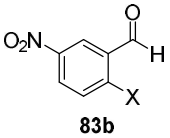
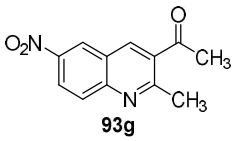
Entry	2-Haloben-zaldehydes	*E*-Enaminones	Product	%Yield[b] X = Br	%Yield[b] X = I
2	**83a**	 **92b**	 **93b**	43	55
3	**83a**	 **92c**	 **93c**	34 (96% brsm)	0
4	**83a**	 **92d**	 **93d**	29 (99% brsm)	33 (92% brsm)
5	**83a**	 **92e**	 **93e**	0	34 (98% brsm)
6	**83a**	 **92f**	 **93f**	0	0
7	 **83b**	**92b**	 **93g**	0	0

Table 10. (Continued)

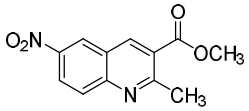
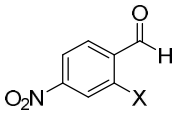
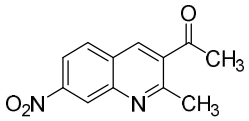
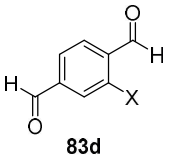
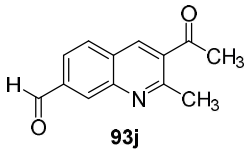
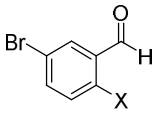
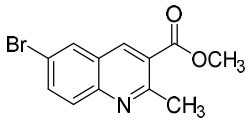
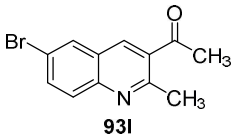
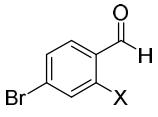
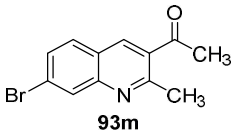
Entry	2-Haloben-zaldehydes	*E*-Enaminones	Product	%Yield[b] X = Br	%Yield[b] X = I
8	**83b**	**92a**	 **93h**	0	ND[c]
9	 **83c**	**92b**	 **93i**	0	ND[c]
10	 **83d**	**92b**	 **93j**	ND[c]	0
11	 **83e**	**92a**	 **93k**	ND[c]	27
12	**83e**	**92b**	 **93l**	0	0
13	 **83f**	**92b**	 **93m**	0	ND[c]

Table 10. (Continued)

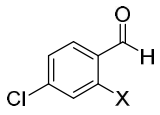
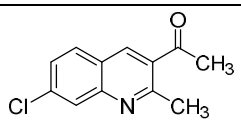
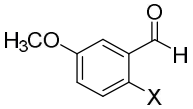
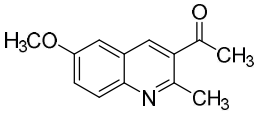
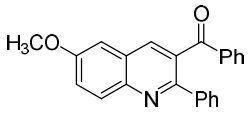
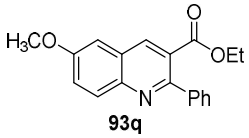
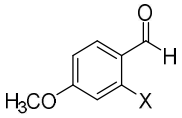
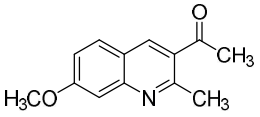
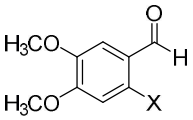
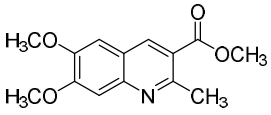
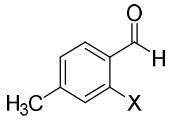
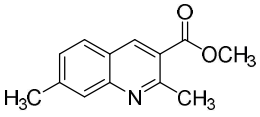
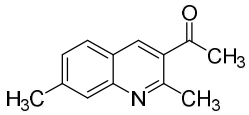
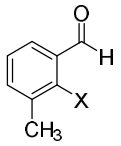
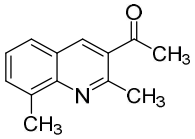
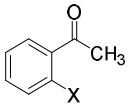
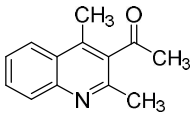
Entry	2-Haloben-zaldehydes	*E*-Enaminones	Product	%Yield[b] X = Br	%Yield[b] X = I
14	 **83g**	**92b**	 **93n**	ND[c]	0
15	 **83i**	**92b**	 **93o**	73	ND[c]
16	**83i**	**92e**	 **93p**	27 (74% brsm)	ND[c]
17	**83i**	**92c**	 **93q**	37 (86% brsm)	ND[c]
18	 **83j**	**92b**	 **93r**	89	ND[c]
19	 **83h**	**92a**	 **93s**	ND[c]	0
20	 **83k**	**92a**	 **93t**	52	ND[c]

Table 10. (Continued)

Entry	2-Haloben-zaldehydes	*E*-Enaminones	Product	%Yield[b] X = Br	%Yield[b] X = I
21	**83k**	**92b**	 **93u**	84	ND[c]
22	 **83l**	**92b**	 **93v**	ND[c]	0
23	 **83m**	**92b**	 **93w**	0	0

[a] Reaction conditions: **92** (0.5 mmol), **83** (0.6 mmol), CuI (5 mol%), 1,2-diaminocyclohexane (30 mol%), Na_2SO_4 (500 mg), K_2CO_3 (1.5 mmol), CH_3CN (0.5 M) at 120 ^oC for 15-18 h in sealed tube.
[b] Isolated yield.
[c] ND: no determined.

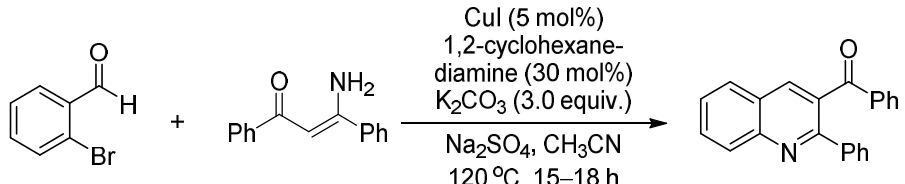
Generally, the yields of quinoline from a variety of 2-halobenzaldehydes with acyclic enaminones were low or 0% yields. We believed that low reactivity of acyclic enaminone was a major factor. However, with no substituents on aldehyde, the yields of quinolines were moderate (entries 1 and 2). Low or no yields were obtained when phenyl-substituted acyclic enaminoester **92c** reacted with 2-bromo or 2-iodo benzaldehyde, respectively (entry 3). Electron-withdrawing substituted benzaldehydes were not applicable to the reaction (entries 7–10). Likewise, 2-bromo or 2-iodobenzaldehyde bearing bromine or chlorine was not suitable to the reaction yielding low or 0% yields of product (entries 11–14). Different results were formed when mono-methoxy substituted benzaldehyde was used. High yield, 73%, was

obtained when aryl-substituted enaminone were subjected to the reaction (entries 16 and 17). The similar result was obtained from the reaction of **83j** and **92b**. The results indicated that acyclic enaminones having aryl substituent was not suitable to the reaction. Similar to cyclic enaminone, high electron density aldehyde was not applicable to the reaction. 3,4-Dimethoxy-2-iodobenzaldehyde gave no yield of product (entry 19). Methyl-substituted 2-bromobenzaldehyde gave moderate to high yield of quinolines (entries 20 and 21). However, having methyl next to an iodine atom of benzaldehyde enhanced a steric enhanced a steric effect resulting in yield of quinoline (entry 22). Neither 2-bromo- or 2-iodoacetophenone was suitable to our process (entry 23).

2.7.3 The Optimization of Reaction Condition (Copper loading)

Since we got the low yield of quinolines from **93p** and **93q**. We assume that increasing catalyst loading could improve the product yield. Hence, we planed the reaction with varying amount of copper at 5, 15 and 30 mol% (**Table 11**).

Table 11. The Study of Catalyst Loading[a]



Entry	Cu (mol%)	%Yield[b]
1	5	27 (74% brsm)
2	15	33 (66% brsm)
3	30	41

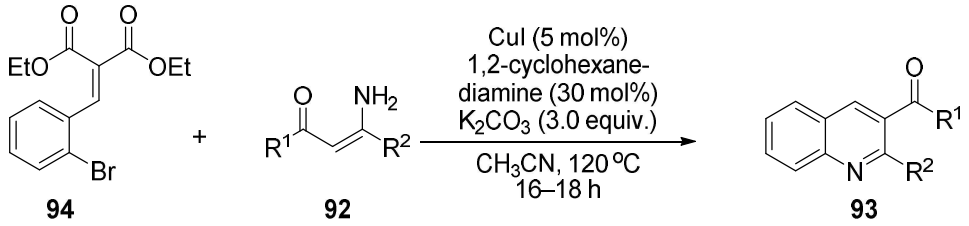
[a] Reaction conditions: **92d** (0.5 mmol), **86d** (0.6 mmol), CuI (5 mol%), 1,2-diaminocyclohexane (30 mol%), Na_2SO_4 (500 mg), K_2CO_3 (1.5 mmol), CH_3CN (0.5 M) at 120 ^oC for 15-18 h in sealed tube.
[b] Isolated yield.

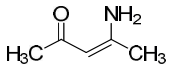
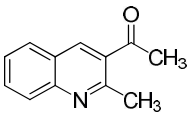
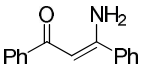
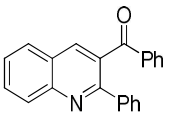
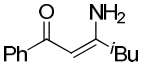
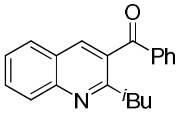
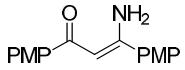
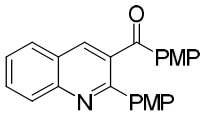
The reaction was subjected to 5, 15 and 30 mol% of CuI under optimal condition. At 5 mol% of CuI, the quinoline **93e** was observed in 27%. The yield was slightly increased to 33% when 15 mol% of copper was used (entry 2). The 30 mol% of CuI gave the best yield of the product at 41% (entry 3). However, when we considered the conversion of the enaminone, we found that at 30 mol%, enaminone **92d** was completely consumed. The results suggested that high amount of copper increased the rate of decomposition of enaminones.

2.8 The Alternative Coupling Partner of Enaminone

Since mostly low yields of quinolines were achieved from the reaction of halobenzaldehydes and *Z*-enaminones. We further designed a new substrate to use instead of the aldehyde with the concept of increasing carbon electrophilicity. Recently, we have reported the copper-catalyzed reaction for the synthesis of chromene using 2-bromobenzylidenemalonate as the substrate (Saebang *et al*., 2017). They reported that 2-bromobenzylidenemalonate was reactive to Micheal addition. However, the diester moiety could undergo elimination. Based on these two functions, the benzylidenemalonate could be an alternative coupling partner for less-reactive acyclic enaminone (**Table 12**).

Table 12. Reaction of 2-Bromobenzylidene Malonate with *Z*-Enaminones[a]



Entry	*Z*-Enaminone	Product	Yield[b] (%)
1			99
2			64 (99% brsm)
3			65 (97% brsm)
4			74 (98% brsm)

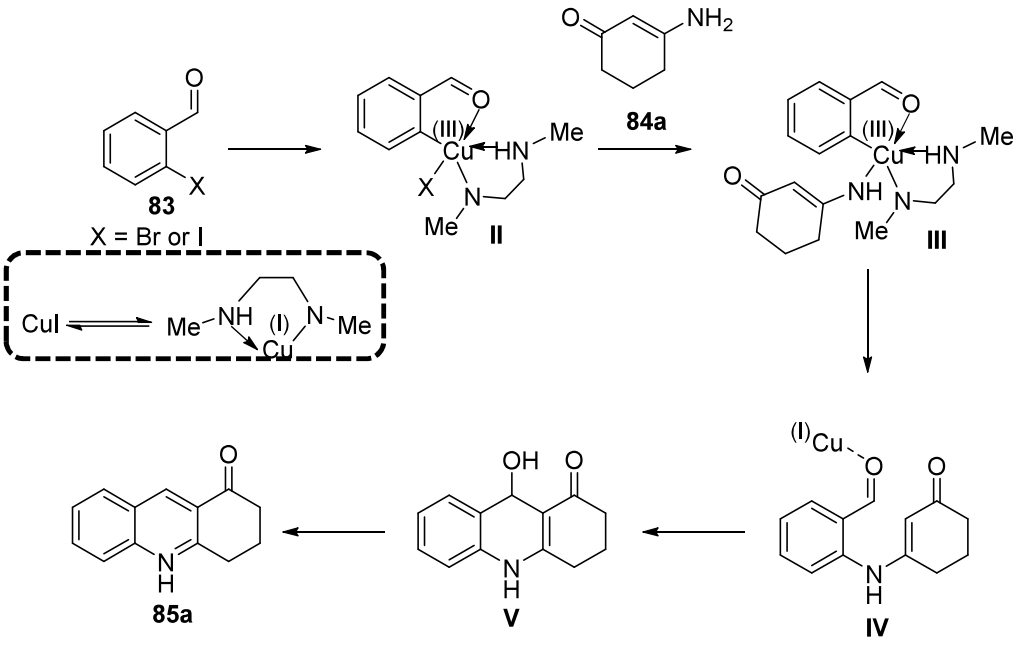
[a] Reaction conditions: **92** (0.5 mmol), **94** (0.6 mmol), CuI (5 mol%), 1,2-diaminocyclohexane (30 mol%), K_2CO_3 (1.5 mmol), CH_3CN (0.5 M) at 120 °C for 15–18 h in sealed tube.
[b] Isolated yield.

Greatly, the yield was tremendously increased up to 99% from dimethyl enaminones **92a** (entry 1, **Table 12**). Significant improvement of the product yields from aryl substituted enaminones was obtained (entries 2–4). The quinoline was obtained in 64% yield from diphenyl enaminone **92e** (entry 2). Comparable yield was found when phenyl alkyl substituted enaminone was used (entry 3). High yield, 74%, was obtained from diaryl bearing electron donating group enaminone (entry 4).

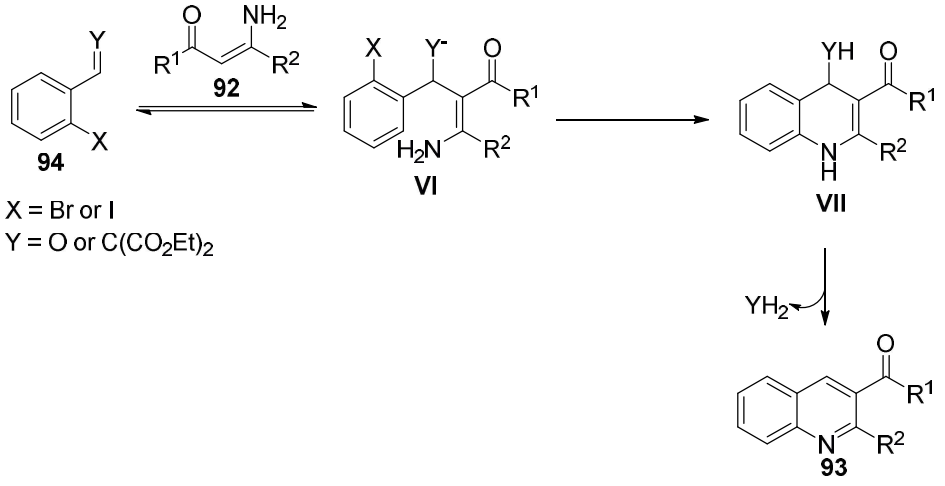
2.9 Proposed reaction mechanism

Based on the results from benzaldehydes and benzylidinemalonates. We proposed two plausible mechanism pathways (**Scheme 23**). The pathway **A** began with oxidative addition with 2-halobezaldehydes **83** to give copper complex **II** in which the aldehyde oxygen played a directing group role. Next, the nucleophilic substitution of halide with enaminone **84a** provided the copper complex **III** followed by reductive elimination to give complex **IV**. Subsequently, an intramolecular Aldol and isomerization took place to afford alcohol **V** which further underwent dehydration to provide the desired quinoline **85a**. The other pathway involved enamine addition of aldehyde or benzylidenemalonate to form carbon-carbon bond generating intermediate **VI**. The next transformation was an intramolecular copper-catalyzed Ullmann-type coupling to form dihydroquinoline **VII**, followed by an elimination to give desired quinoline.

Pathway A



Pathway B



Scheme 23 Tentative Mechanism for the Synthesis of Quinoline via Copper-Catalyzed Domino Reaction

CHAPTER 3

CONCLUSION

In summary, our study on copper-catalyzed Ullmann-type coupling of 2,3-disubstituted quinoline derivatives under mild and simple reaction conditions from 2-halobenzaldehydes and enaminones provided quinolines in good yields. The domino processes consisted of C–N bond formation *via* Ullmann-type coupling, C–C bond construction by enamine addition and elimination. The study results from cyclic and acyclic enaminones suggested that cyclic enaminones mostly displayed higher activity than acyclic one. The electronic effect of aldehyde played a huge role in which mostly electron-donating substituent on aldehydes gave great results, while benzaldehyde with electron-withdrawing group provided low yield or no reaction. Importantly, drying agent is necessary in improving product yields. An alternative approach to synthesize quinolines was investigated by using diethyl-2-(2-bromobenzylidene)malonate to react with less-reactive acyclic enaminones. All approaches are expected to provide a new perspective for the synthesis of quinoline and related N-heterocycle moieties.

CHAPTER 4

EXPERIMENTAL

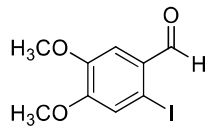
4.1 General Information

Both toluene and CH_3CN were dried over 4 Å molecular sieves. Solvent for extraction and column chromatograph were distilled at their boiling point ranges prior to use. Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} (Merck) and were visualized by fluorescence quenching under UV light. Column chromatography was performed on SilicaFlash® G60 (70-230 Mesh). ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a 300 MHz Bruker FTNMR Ultra Shield spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ 0.00) and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet. Infrared spectra (IR) were measured on a Perkin Elmer Spectrum GX FT-TR system and recorded on wavenumber (cm^{-1}). Mass spectra were obtained from a liquid chromatograph-mass spectrometer (2090, LCT, Waters, Micromass).

4.2 Preparation of Starting Materials

4.2.1 Synthesis of 2-Halobenzaldehydes

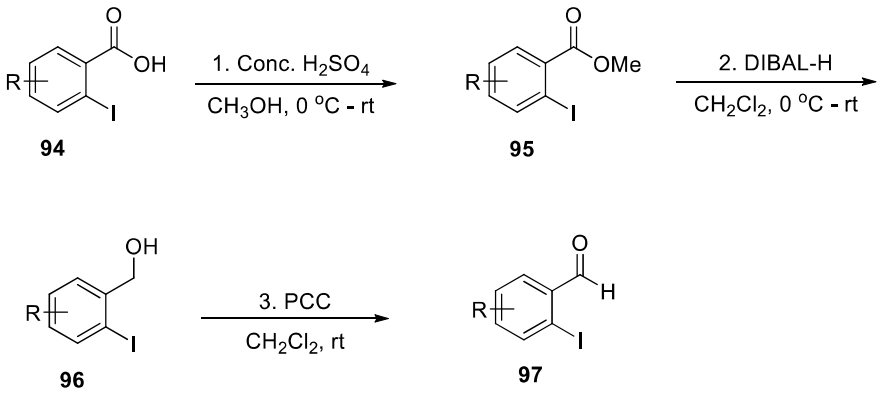
4.2.1.1 2-Iodo-4,5-dimethoxybenzaldehyde (**83h**)



83h
$C_9H_9IO_3$
Mw = 292.0725 g/mol

Prepared according to literature procedure (Songsichan *et al*., 2014). A solution of 3,4-dimethoxybenzaldehyde (369 mg, 2.2 mmol) in MeOH (13 mL) was added silver nitrate (377 mg, 2.2 mmol) and iodine (650 mg, 2.6 mmol). The reaction was stirred at room temperature for overnight under argon. The yellow participate of silver iodide was filtered off and washed with methanol. The filtrate was evaporated and diluted with EtOAc (20 mL), then washed with Sat. $Na_2S_2O_3$ (3×15 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (4:1 hexanes:EtOAc) to afford **83h** as a yellow solid (660 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 194.7, 154.4, 149.7, 128.3, 121.7, 111.0, 92.7, 56.5, 56.0; IR (thin film) ν 2840, 1669, 1584, 1501, 1377, 1265, 1153 cm^{-1}. Other data was identical to the literature values (Hathaway *et al*., 2007).

General Procedure for the Synthesis of 2-Iodobenzaldehyde



Method A

Step 1: Preparation of 2- iodobenzoic acid methyl ester **95**

To a solution of 2-iodobenzoic acid **94** (2.48 g, 10 mmol) in methanol (59 mL) was added concentrated H_2SO_4 (6 mL) cautiously. The reaction mixture was heat at reflux for 4 h, then cooled to room temperature and removed MeOH by vacuum evaporation. The resulting was diluted with EtOAc (50 mL) and then washed with H_2O (2×30 mL), saturated $NaHCO_3$ solution (50 mL), and brine (30 mL). The organic layer was dried

over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford **95** as a pale yellow oil without further purification (2.62 g, 99%).

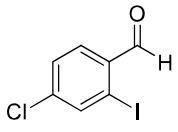
Step 2: Preparation of 2-iodobenzyl alcohol **96**

To a solution of **95** (2.2 g, 8.5 mmol) in dry CH_2Cl_2 (15 mL) was slowly added DIBAL-H (1M in THF, 18 mL) at 0 ^oC under argon. The reaction was gradually warmed up to room temperature. After being stirred for 4 h, the mixture was quenched with Sat. NH_4Cl (10 mL) and kept stirred for 1 h, then extracted with CH_2Cl_2 (3×15 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4. Evaporation *in vacuo* yielded **96** as a white solid without further purification (1.87 g, 99%).

Step 3: Preparation of 2-iodobenzaldehyde **97**

To a stirred solution of 2-iodobenzyl alcohol **96** (1.83 g, 7.9 mmol) in CH_2Cl_2 (30 mL) was added pyridinium chlorochromate (2.10 g, 9.74 mmol) in portionwise. The reaction mixture was stirred at room temperature under argon for 4 h, then filtered through a pad of Celite and concentrated *in vacuo*. Purification of the crude mixture by silica-gel chromatography (hexane:EtOAc, 9:1) yielded the product as a light yellow sold (1.44 g, 79%).

4.2.1.2 4-Chloro-2-iodobenzaldehyde (**83g**)

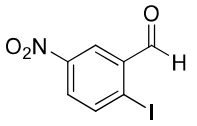


83g
C_7H_4ClIO
Mw = 266.4625 g/mol

4-Chloro-2-iodobenzaldehyde (**83g**) was synthesized from commercially available 4-chloro-2-iodobenzoic acid and using *Method A*. Yielded 52% (over 3 steps) as a light yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.85 (d, J = 1.6 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.76 (dd, J = 8.3, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

190.7, 136.3, 132.3, 131.4, 130.8, 129.8, 127.4.; IR (thin film) ν 2863, 1690, 1573, 1458, 1370, 1200, 828 cm^{-1}. Other data was identical to the literature values (Takaya *et al*., 2016).

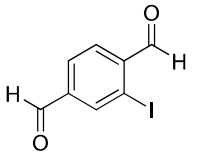
4.2.1.3 2-Iodo-5-nitrobenzaldehyde (**83b**)



83b
$C_7H_4INO_3$
Mw = 277.0175 g/mol

2-Iodo-5-nitrobenzaldehyde (**83b**) was synthesized from 2-iodo-5-nitrobenzoic acid[3] and using *Method A*. Yielded 70 % (over 3 steps) as an orange-brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.65 (d, *J* = 2.7 Hz, 1H), 8.21 (d, *J* = 8.6 Hz, 1H), 8.12 (dd, *J* = 8.6, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 148.6, 142.0, 136.2, 128.6, 124.6, 107.3; IR (thin film) ν 3089, 1683, 1602, 1568, 1531, 1349, 1188 cm^{-1}. Other data was identical to the literature values (Barbasiewicz *et al*., 2013).

4.2.1.4 2-Iodoterephthalaldehyde (**83d**)



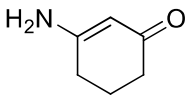
83d
$C_8H_5IO_2$
Mw = 260.0305 g/mol

Prepared according to literature procedure and followed by *method A*. Yielded 66% (over 3 steps) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1H), 10.05 (s, 1H), 8.44 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 189.9, 141.5, 140.5, 138.7, 130.7, 129.3, 100.2; IR (thin film)

ν 2845, 1685, 1469, 1365, 1195, 1184, 787 cm^{-1}.Other data was identical to the literature values (Wu *et al*., 2011).

4.2.2 Synthesis of Enaminones

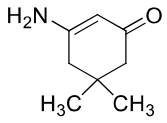
4.2.2.1 3-Aminocyclohex-2-enone (**84a**)



84a
C_6H_9NO
Mw = 111.1440 g/mol

Prepared according to literature procedure. To a solution of 1.0 equiv of 1,3cyclohexanedione in EtOH (0.5 M) was added 1.2 equiv of NH_4OAc. The reaction mixture was heat at reflux for overnight, then cooled to room temperature and removed EtOH by vacuum evaporation. The crude product was purified by column chromatography (6:1 EtOAc:MeOH) to give **84a** as a pale yellow solid. ^1H NMR (300 MHz, DMSO-*d6*) δ 6.70 (brs, 2H), 4.90 (s, 1H), 2.23 (t, *J* = 6.3 Hz, 2H), 2.00 (t, *J* = 6.3 Hz, 2H), 1.75 (q, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 194.9, 167.7, 97.9, 36.4, 28.4, 22.0; IR (thin film) ν 3135, 1674, 1539, 1258, 1189, 1143, 828 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

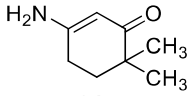
4.2.2.2 3-Amino-5,5-dimethylcyclohex-2-enone (**84d**)



84d
$C_8H_{13}NO$
Mw = 139.1980 g/mol

Prepared according to procedure described for **84a**. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 6.75 (brs, 2H), 4.91 (s, 1H), 2.11 (s, 2H), 1.89 (s, 2H), 0.94 (s, 6H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 194.5, 166.1, 96.4, 50.2, 42.1, 32.7, 28.5; IR (thin film) ν 3080, 1539, 1260, 1153, 1129, 772, 751 cm^{-1}. Other data was identical to the literature values(Al-Mousawi *et al*., 2003).

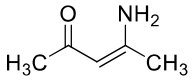
4.2.2.3 3-Amino-6,6-dimethylcyclohex-2-enone (**84e**)



84e
$C_8H_{13}NO$
Mw = 139.1980 g/mol

Prepared according to procedure described for **84a**. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 6.59 (brs, 2H), 4.79 (s, 1H), 2.26 (t, *J* = 6.3 Hz, 2H), 1.16 (t, *J* = 6.3 Hz, 2H), 0.92 (s, 6H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 199.9, 166.0, 96.4, 38.7, 35.7, 25.5; IR (thin film) ν 3353, 3147, 1652, 1539, 1215, 769 cm^{-1}.Other data was identical to the literature values (Bergmana *et al*. 2014).

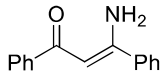
4.2.2.4 (*Z*)-4-Aminopent-3-en-2-one (**92b**)



92b
C_5H_9NO
Mw = 99.1330 g/mol

Prepared according to literature procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (brs, 1H), 5.84 (brs, 1H), 4.92 (s, 1H), 1.92 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 161.7, 95.1, 28.7, 21.7; IR (thin film) ν 3346 1621, 1538, 1414, 1357, 1291, 896 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

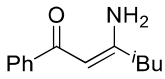
4.2.2.5 (*Z*)-3-Amino-1,3-diphenylprop-2-en-1-one (**92e**)



92e
$C_{15}H_{13}NO$
Mw = 223.2750 g/mol

Prepared according to literature procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.44 (brs, 1H), 7.99-7.96 (m, 2H), 7.67-7.64 (m, 2H), 7.53-7.42 (m, 6H), 6.17 (s 1H), 5.72 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 163.0, 140.2, 137.4, 130.9, 130.6, 128.9, 128.2, 127.1, 126.3, 91.7; IR (thin film) ν 3060, 1601, 1567, 1526, 1484, 1327, 741 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

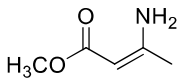
4.2.2.6 (*Z*)-3-Amino-5-methyl-1-phenylhex-2-en-1-one (**92d**)



92d
$C_{13}H_{17}NO$
Mw = 203.2850 g/mol

Prepared according to literature procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (brs, 1H), 7.89-7.86 (m ,2H), 7.43-7.39 (m, 2H), 5.71 (s, 1H), 2.10 (d, *J* = 7.4 Hz, 2H), 2.03-1.90 (m, 1H), 0.98 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 166.4, 140.4, 130.8, 128.2, 127.1, 126.3, 92.3, 46.3, 28.1, 22.8, 22.4; IR (thin film) ν 3380, 1603, 1574, 1527, 1320, 1216, 745 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

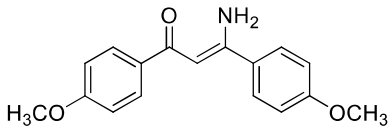
4.2.2.7 (*Z*)-Methyl-3-aminobut-2-enoate (**92a**)



92a
$C_5H_9NO_2$
Mw = 115.1320 g/mol

Prepared according to literature procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (s, 1H), 3.60 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 160.0, 83.3, 49.9, 22.1; IR (thin film) ν 3410, 3318, 1654, 1558, 1298, 1166, 1006 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

4.2.2.8 (*Z*)-3-Amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**92f**)



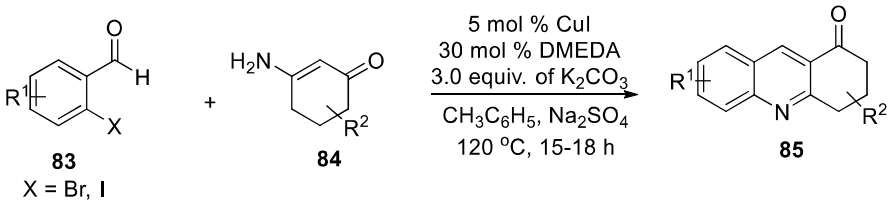
92f
$C_{17}H_{17}NO_3$
Mw = 283.3270 g/mol

Prepared according to literature procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 7.62-7.59 (m, 2H), 7.00-6.93 (m, 4H), 6.10 (s, 1H), 3.87 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 162.1, 161.9, 161.5, 133.2, 129.8, 129.0, 127.7, 114.3, 113.4, 90.8, 55.4, 55.3; IR (thin film) ν 2840, 1600, 1494, 1257, 1230, 1173, 1029 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

4.2.3 Synthesis of Quinoline Derivatives

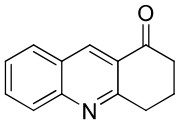
General Procedure for Copper-Catalyzed Domino Reaction for Synthesis of Quinoline Derivatives.

General Procedure A: For the Reaction of *E*-Enaminone



The reaction of 2-bromobenzaldehyde (**1a**) and 3-aminocyclohex-2-enone (**2**) is representative: A sealed-tube was charged with 2-bromobenzaldehyde (1a) (0.60 mmol), 3-aminocyclohex-2-enone (**2a**) (0.50 mmol), CuI (0.03 mmol), DMEDA (0.15 mmol), Na_2SO_4 (500 mg) and K_2CO_3 (1.50 mmol) in toluene (1.0 mL). The reaction mixture was allowed to stir at 120 ^oC for 15-18 h. After completion of reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15:1 CH_2Cl_2:EtOAc) to provide **3a** in 60.1 mg (61% yield) as a light yellow solid.

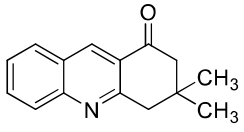
4.2.3.1 3,4-Dihydroacridin-1(2*H*)-one (**85a**)



85a
$C_{13}H_{11}NO$
Mw = 197.2370 g/mol

Prepared according to general procedure A from 2-bromobenzaldehyde and 3-aminocyclohex-2-enone (**84a**). Yield 60.1 mg (61 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$); 8.84 (s, 1H), 8.05 (d, *J* = 8.1 Hz,1H), 8.93 (d, *J* = 8.1 Hz, 1H), 7.81 (td, *J* = 8.1, 1.0 Hz), 7.55 (t, *J* = 8.1 Hz, 1H), 3.32 (t, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.28 (qn, *J* = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 161.9, 149.6, 137.1, 132.4, 129.7, 128.5, 126.8, 126.7, 126.3, 39.1, 33.4, 21.8; IR (thin film) ν 3060, 2951, 2867, 1688, 1593, 1206, 754 cm^{-1}. Other data was identical to the literature values (Rajawinslin *et al*., 2014).

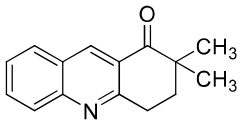
4.2.3.2 3,3-Dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85d**)



85d
$C_{15}H_{15}NO$
Mw = 225.2910 g/mol

Prepared according to general procedure A from 2-bromobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 72.1 mg (64 %) as a dark brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.78 (t, *J* = 6.9 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 3.18 (s, 2H), 2.63 (s, 2H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 160.5, 149.7, 136.1, 131.9, 129.5, 128.3, 126.4 (126.44), 126.4 (126.39), 125.0, 52.2, 46.9, 32.5, 28.1; IR (thin film) ν 3052, 2956, 2871, 1689, 1617, 1593, 1212, 760 cm^{-1}. Other data was identical to the literature values (Anand *et al*., 2015).

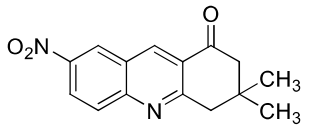
4.2.3.3 2,2-Dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85e**)



85e
$C_{15}H_{15}NO$
Mw = 225.2910 g/mol

Prepared according to general procedure A from 2-bromobenzaldehyde and 3-amino-6,6-dimethylcyclohex-2-enone (**84e**). Yield 76.5 mg (68 %) as a dark brown gum.[1]H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.52 (t, 8.1 Hz, 1H), 3.33 (t, *J* = 6.3 Hz, 2H), 2.10 (t, *J* = 6.3, 2H), 1.29 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 161.0, 149.3, 137.8, 132.0, 129.4, 128.2, 126.7, 126.4, 125.1, 41.7, 34.9, 29.2, 24.1; IR (thin film) ν 3062, 2963, 2929, 1687, 1619, 1180, 753 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{15}NO$ 226.1232, found 226.1232.

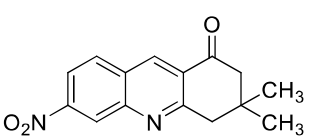
4.2.3.4 3,3-Dimethyl-7-nitro-3,4-dihydroacridin-1(2*H*)-one (**85g**)



85g
$C_{15}H_{14}N_2O_3$
Mw = 270.2880 g/mol

Prepared according to general procedure A from 2-bromo-5-nitro-benzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 50.0 mg (37 %) as an orange solid. [1]H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.88 (d, *J* = 2.7 Hz, 1H), 8.53 (dd, *J* = 9.3, 2.7 Hz, 1H), 8.17 (d, *J* = 9.3 Hz, 1H), 3.24 (s, 2H), 2.70 (s, 2H), 1.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 164.7, 151.6, 145.5, 138.0, 130.5, 126.6, 126.2, 125.5, 125.2, 52.2, 47.3, 32.7, 28.3; IR (thin film) ν 3087, 2959, 2872, 1699, 1603, 1567, 735 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{14}N_2O_3$ 271.1082, found 271.1082.

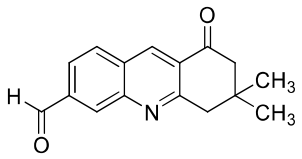
4.2.3.5 3,3-Dimethyl-6-nitro-3,4-dihydroacridin-1(2*H*)-one (**85h**)



85h
$C_{15}H_{14}N_2O_3$
Mw = 270.2880 g/mol

Preparation according to general procedure A from 2-bromo-4-nitrobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 69.0 mg (51 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90-8.88 (m, 2H), 8.30 (dd, *J* = 8.9, 1.9 Hz, 1H), 8.13 (d, *J* = 8.9 Hz, 1H), 3.27 (s, 2H), 2.73 (s, 2H), 1.20 (s, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 163.1, 149.3, 148.7, 135.8, 131.2, 129.6, 127.0, 124.5, 119.8, 52.2, 47.0, 32.5, 28.2; IR (thin film) 2965, 1695, 1596, 1530, 1348, 1182, 836 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{14}N_2O_3$ 271.1082, found 271.1082.

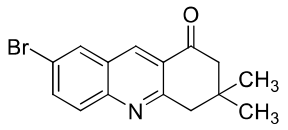
4.2.3.6 6,6-Dimethyl-8-oxo-5,6,7,8-tetrahydroacridine-2-carbaldehyde (**85i**)



85i
$C_{16}H_{15}NO_2$
Mw = 253.3010 g/mol

A sealed-tube was charged with 4-iodoisophthaldehyde (**83d**) (0.60 mmol), 3-amino-5,5-dimethylcyclohex-2-enone (**84d)** (0.50 mmol), CuI (0.03 mmol), DMEDA (0.15 mmol), Na_2SO_4 (500 mg) and K_2CO_3 (1.50 mmol) in CH_3CN (1.0 mL). The reaction mixture was allowed to stir at 120 ^{o}C for 15-18 h. After completion of reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15:1 CH_2Cl_2:EtOAc) to provide **85i** in 68.2 mg (54 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.86 (s, 1H), 8.51 (s, 1H), 8.05-8.04 (m, 2H), 3.00 (s, 2H). 2.70 (s, 2H), 1.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 191.8, 162.1, 149.7, 138.7, 136.2, 134.2, 130.8, 130.2, 126.8, 123.3, 52.4, 47.1, 32.7, 28.4; IR (thin film) ν 2957, 2861, 1697, 1596, 1371, 1241, 769 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{16}H_{15}NO_2$ 254.1181, found 254.1181.

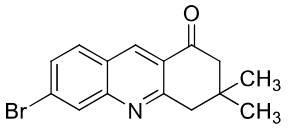
4.2.3.7 7-Bromo-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85k**)



85k
$C_{15}H_{14}BrNO$
Mw = 304.1870 g/mol

Prepared according to general procedure A from 2,5-dibromobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 80.9 mg (54 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.84 (dd, *J* = 9.0, 1.8 Hz, 1H), 3.17 (s, 2H), 3.34 (s, 2H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 161.2, 148.5, 135.5, 135.4, 131.4, 130.3, 127.9, 125.8, 120.4, 52.4, 47.1, 32.7, 28.4; IR (thin film) ν 2958, 2870, 1690, 1590, 1479, 1372, 1209 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{14}BrNO$ 304.0336, found 304.0337.

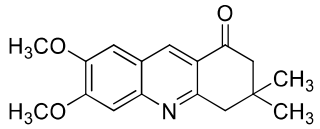
4.2.3.8 6-Bromo-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85m**)



85m
$C_{15}H_{14}BrNO$
Mw = 304.1870 g/mol

Preparation according to general procedure A from 2,4-dibromobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 85.1 mg (56 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.22 (s, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.62 (dd, *J* = 8.7, 1.5 Hz, 1H), 3.17 (s, 2H), 2.65 (s, 2H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 161.9, 150.2, 136.2, 131.0, 130.7, 130.3, 126.7, 125.4, 125.2, 52.3, 47.0, 32.6, 28.3; IR (thin film) ν 2962, 2872, 1684, 1608, 1486, 1069, 708 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{14}BrNO$ 304.0337 found 304.0335.

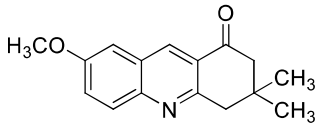
4.2.3.9 3,4-Dimethoxy-3,3-dimethyl-3,4-dihydro-2*H*-acridin-1-one one (**85p**)



85p
$C_{17}H_{19}NO_3$
Mw = 285.3430 g/mol

Prepared according to general procedure described for **85i** from 2-iodo-4,5-dimethoxybenzaldehyde (**83h**) and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 51.3 mg (36 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.34 (s, 1H), 7.10 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 2.58 (s, 2H), 1.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 158.9, 154.8, 149.8, 147.6, 134.1, 123.7, 122.4 107.1, 106.3, 56.2, 56.0, 52.3, 46.8, 32.8, 28.3; IR (thin film) ν 3014, 2957, 1682, 1621, 1590, 1504, 1257 cm^{-1}. Other data was identical to the literature values (Patteux *et al*., 2003).

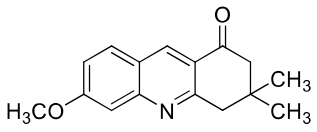
4.2.3.10 7-Methoxy-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85r**)



85r
$C_{16}H_{17}NO_2$
Mw = 255.3170 g/mol

Preparation according to general procedure described for **85i** from 2-bromo-5-methoxybenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 92.8 mg (73 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.44 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.15 (d, *J* = 2.6 Hz, 1H), 3.93 (s, 3H), 3.14 (s, 2H), 2.63, (s, 2H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 158.2, 157.7, 146.2, 134.9, 129.8, 127.6, 125.2, 106.3, 55.5, 52.4, 46.8, 32.7, 28.3; IR (thin film) ν 2956, 2867, 1686, 1623, 1593, 1495, 1236 cm^{-1}. Other data was identical to the literature values (Anand *et al*., 2015).

4.2.3.11 6-Methoxy-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85t**)



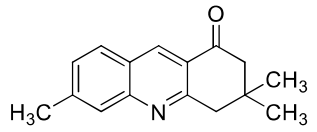
85t

$C_{16}H_{17}NO_2$

Mw = 255.3170 g/mol

Preparation according to general procedure described for **85i** from 2-bromo-4-methoxybenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 70.2 mg (55 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.31 (d, *J* = 2.1 Hz, 1H), 7.13 (dd, *J* = 9.0, 2.1 Hz, 1H), 3.92 (s, 3H), 3.09 (s, 2H), 2.57 (s, 2H), 1.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 163.0, 161.3, 151.9, 135.9, 130.7, 123.4, 121.9, 120.2, 106.4, 55.6, 52.2, 47.0, 32.7, 28.3; IR (thin film) ν 2956, 2870, 1685, 1619, 1594, 1498, 1207 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{17}H_{20}NO_2$ 256.1388 found 256.1388.

4.2.3.12 3,3,7-Trimethyl-3,4-dihydroacridin-1(2*H*)-one (**85u**)



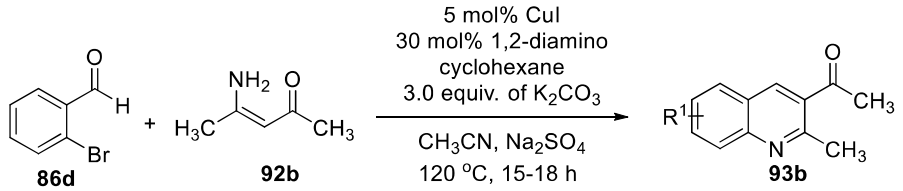
85u

$C_{16}H_{17}NO$

Mw = 239.3180 g/mol

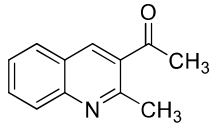
Preparation according to general procedure described for **85i** from 2-bromo-3-methylbenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d)**. Yield 52.6 mg (44 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.86-7.83 (m, 2H), 7.43 (d, *J* = 1.1 Hz, 1H), 3.02 (s, 2H), 2.66 (s, 2H), 2.60 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 160.8, 150.1, 143.2, 136.2, 129.3, 129.0, 127.5, 124.8, 124.6, 52.4, 47.1, 32.7, 28.3, 22.2; IR (thin film) ν 2956, 2861, 1687, 1626, 1594, 1498, 1372 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{16}H_{17}NO$ 240.1388, found 240.1389.

General Procedure B: For the Reaction of *Z*-Enaminone



The reaction of 2-bromobenzaldehyde (**86d**) and (*Z*)-4-aminopent-3-en-2-one (**92b**) is representative: A sealed-tube was charged with 2-bromobenzaldehyde (**1a**) (0.60 mmol), (*Z*)-4-aminopent-3-en-2-one (**92b**) (0.50 mmol), CuI (0.03 mmol), cyclohexane-1,2-diamine (0.15 mmol), Na_2SO_4 (500 mg) and K_2CO_3 (1.50 mmol) in CH_3CN (1.0 mL). The reaction mixture was allowed to stir at 120 ^oC for 15-18 h. After completion of reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15:1 CH_2Cl_2:EtOAc) to provide x in 54.4 mg (55% yield) as a light yellow solid.

4.2.3.13 1-(2-Methylquinolin-3-yl)ethanone (**93b**)



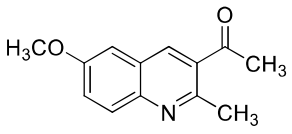
93b

$C_{12}H_{11}NO$

Mw = 185.2260 g/mol

Prepared according to general procedure B from 2-bromobenzaldehyde (**86d**) and (*Z*)-4-aminopent-3-en-2-one (**92b**). Yield 39.8 mg (43 %) as a light brown solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.77 (ddd, *J* = 9.3, 6.9, 1.5 Hz, 1H), 7.53 (ddd, *J* = 9.3, 6.9, 1.5 Hz, 1H), 2.91 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 157.5, 148.2, 138.1, 131.7, 131.1, 128.5, 128.3, 126.6, 125.6, 29.2, 25.6; IR (thin film) ν 3058, 2990, 2967, 1682, 1620, 1562, 1420 cm^{-1}. Other data was identical to the literature values (Anand *et al*., 2015).

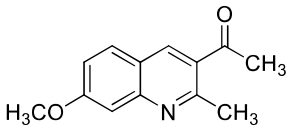
4.2.3.14 1-(6-Methoxy-2-methylquinolin-3-yl)ethanone (**93o**)



93o
$C_{13}H_{13}NO_2$
Mw = 215.2520 g/mol

Preparation according to general procedure B from 2-bromo-5-methoxylbenzaldehyde and (*Z*)-4-aminopent-3-en-2-one (**92b**). Yield 77.7 mg (72 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.41 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.08 (d, *J* = 2.6 Hz, 1H), 3.92 (s, 3H), 2.86 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 157.6, 154.6, 144.0, 136.8, 131.0, 129.6, 126.4, 124.2, 105.4, 55.4, 29.0, 25.0; IR (thin film) ν 2997, 1683, 1595, 1493, 1227, 1030, 834. HRMS (ESI) $[M+H]^+$ calcd. for $C_{13}H_{13}NO_2$ 216.1025 found 216.1025.

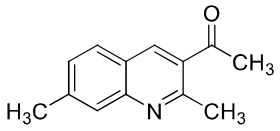
4.2.3.15 1-(7-Methoxy-2-methylquinolin-3-yl)ethanone (**93r**)



93r
$C_{13}H_{13}NO_2$
Mw = 215.2520 g/mol

Preparation according to general procedure B from 2-bromo-4-methoxylbenzaldehyde and (*Z*)-4-aminopent-3-en-2-one (**92b**). Yield 95.7 mg (89 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.64 (d, *J* = 8.9 Hz, 1H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.11 (dd, *J* = 8.9, 2.2 Hz, 1H), 3.88 (s, 3H), 2.82 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 162.8, 158.4, 150.3, 138.3, 129.5, 128.7, 120.6, 120.0, 106.7, 55.7, 29.0, 25.8; IR (thin film) ν 2965, 1675, 1623, 1612, 1488, 1210, 1193 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{13}H_{13}NO_2$ 216.1025 found 216.1025.

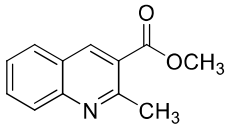
4.2.3.16 1-(2,7-Dimethylquinolin-3-yl)ethanone (**93u**)



93u
$C_{13}H_{13}NO$
Mw = 199.2530 g/mol

Preparation according to general procedure B from 2-bromo-4-methylbenzaldehyde and (*Z*)-4-aminopent-3-en-2-one (**92b**). Yield 83.7 mg (84 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.83 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 2.91 (s, 3H), 2.71 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 157.7, 148.5, 142.6, 138.1, 130.3, 128.9, 128.0, 127.6, 123.6, 29.1, 25.7, 22.1; IR (thin film) ν 3031, 1682, 1666, 1427, 1240, 1129, 778 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{13}H_{13}NO$ 200.1075 found 200.1075.

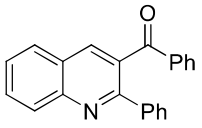
4.2.3.17 Methyl-2-methylquinoline-3-carboxylate (**93a**)



93a
$C_{12}H_{11}NO_2$
Mw = 201.2250 g/mol

Preparation according to general procedure B from 2-bromobenzaldehyde (**86d**) and (*Z*)-Methyl-3-aminobut-2-enoate (**92a**) Yield 51.2 mg (52 %) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.77 (td, *J* = 8.1, 1.2 Hz, 1H), 7.53 (td, *J* = 8.1, 1.2 Hz), 3.98 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 158.5, 148.6, 140.0, 131.7, 128.5, 128.4, 126.5, 125.7, 123.5, 52.3, 25.6; IR (thin film) ν 3063, 2999, 2952, 1727, 1622,1201, 789 cm^{-1}. Other data was identical to the literature values (Anand *et al*., 2015).

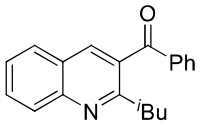
4.2.3.18 Phenyl(2-phenylquinolin-3-yl)methanone (**93e**)



93e
$C_{22}H_{15}NO$
Mw = 309.3680 g/mol

Prepared according to general procedure B from 2-iodobenzaldehyde and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**92e**). Yield 52.5 mg (34 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s,1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.83 (ddd, *J* = 8.4, 7.5, 1.5 Hz, 1H), 7.73-7.70 (m, 2H), 7.64-7.58 (m, 3H), 7.47 (tt, *J* = 7.5, 1.0 Hz, 1H), 7.35-7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 157.5, 148.4, 139.7, 137.6, 137.1, 133.3, 132.9, 131.2, 130.0, 129.7, 129.3, 128.8, 128.4, 128.1, 127.3, 125.8; IR (thin film) ν 3059, 3020, 1662, 1595,1270, 1234, 770 cm^{-1}. Other data was identical to the literature values (Rajawinslin *et al*., 2014).

4.2.3.19 2-Isobutylquinolin-3-yl(phenyl)methanone (**93d**)

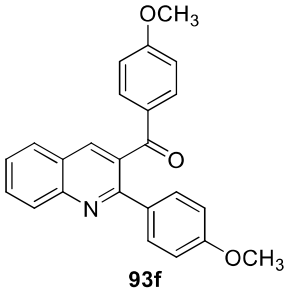


93d
$C_{20}H_{19}NO$
Mw = 289.3780 g/mol

Prepared according to general procedure B from 2-bromobenzaldehyde (**86d**) and (*Z*)-3-amino-5-methyl-1-phenylhex-2-en-1-one (**92d**). Yield 41.9 mg (29 %) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 1H), 8.08 (s, 1H), 7.86-7.76 (m ,4H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.57-7.47 (m, 3H), 2.97 (s, 3H), 2.96 (d, *J* = 7.3 Hz, 2H), 2.22-2.12 (m, 1H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 160.0, 148.0, 137.5, 136.7, 133.7, 132.6, 130.9, 130.2, 129.0, 128.7, 128.0, 126.7, 125.2, 45.4, 29.3, 22.5; IR (thin film) ν 3061, 2957, 1667, 1619, 1595,

1450, 1262 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{20}H_{19}NO$ 290.1545, found 290.1546.

4.2.3.20 (4-Methoxyphenyl)(2-(4-methoxyphenyl)quinolin-3-yl)methanone (**93f**)



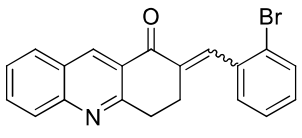
93f

$C_{24}H_{19}NO_3$

Mw =369.4200 g/mol

A sealed-tube was charged with 2-(2-bromobenzylidene)malonate (0.60 mmol), (*Z*)-3-amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**92f**) (0.50 mmol), CuI (0.03 mmol), cyclohexane-1,2-diamine (0.15 mmol), Na_2SO_4 (500 mg) and K_2CO_3 (1.50 mmol) in CH_3CN (1.0 mL). The reaction mixture was allowed to stir at 120 ^oC for 15-18 h. After completion of reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15:1 CH_2Cl_2:EtOAc) to provide x in 81.7 mg (74 % yield) as a light yellow solid. Yield 136.6 mg (74 %) as a light yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.80 (ddd, *J* = 8.5, 7.0, 1.2 Hz, 1H), 7.76-7.72 (m, 2H), 7.65-7.56 (m, 3H), 6.85-6.81 (m, 4H), 3.83 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 163.6, 160.1, 156.6, 148.1, 136.9, 132.9, 132.3, 132.1, 130.7, 129.8, 129.3, 127.8, 126.8, 125.5, 113.8, 113.6, 55.3, 55.1; IR (thin film) ν 3008, 2838, 1660, 1599, 1253, 1024, 758 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{24}H_{19}NO_3$ 370.1443 found 340.1440.

4.2.3.21 2-(2-Bromobenzylidene)-3,4-dihydroacridin-1(2H)-one (**91**)



91

$C_{20}H_{14}BrNO$

Mw = 364.2420 g/mol

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.99-7.97 (m, 2H), 7.82 (td, *J* = 7.2, 1.2 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.38-7.34 (m. 2H), 7.21-7.22 (m, 1H), 3.31 (t, *J* = 6.0 Hz, 2H), 3.16 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 160.9, 149.5, 138.3, 137.0, 136.0, 135.9, 133.1, 132.4, 130.5, 130.1, 129.8, 128.6, 127.1, 126.9, 126.8, 125.0, 32.7, 26.2; IR (thin film) ν 3448, 3059, 2958, 2853, 1617, 1492 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for CHNO 364.0337, found 364.0337.

CHAPTER 4

EXPERIMENTAL

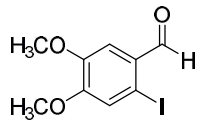
4.1 General Information

Both toluene and CH_3CN were dried over 4 Å molecular sieves. Solvent for extraction and column chromatograph were distilled at their boiling point ranges prior to use. Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} (Merck) and were visualized by fluorescence quenching under UV light. Column chromatography was performed on SilicaFlash® G60 (70-230 Mesh). ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a 300 MHz Bruker FTNMR Ultra Shield spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ 0.00) and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet. Infrared spectra (IR) were measured on a Perkin Elmer Spectrum GX FT-TR system and recorded on wavenumber (cm^{-1}). Mass spectra were obtained from a liquid chromatograph-mass spectrometer (2090, LCT, Waters, Micromass).

4.2 Preparation of Starting Materials

4.2.1 Synthesis of 2-Halobenzaldehydes

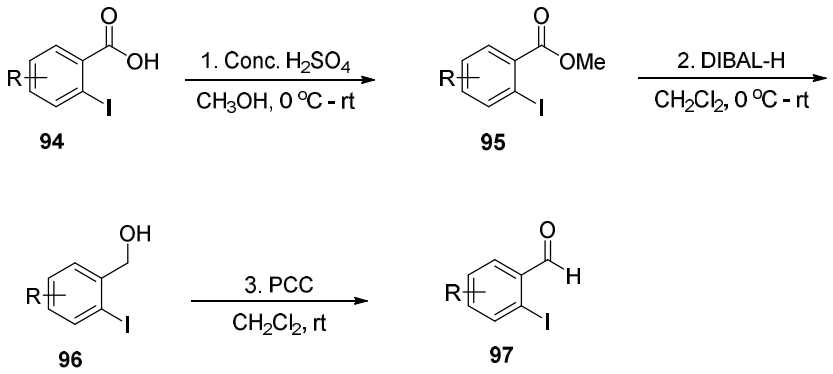
4.2.1.1 2-Iodo-4,5-dimethoxybenzaldehyde (**83h**)



83h
$C_9H_9IO_3$
Mw = 292.0725 g/mol

Prepared according to literature procedure (Songsichan *et al*., 2014). A solution of 3,4-dimethoxybenzaldehyde (369 mg, 2.2 mmol) in MeOH (13 mL) was added silver nitrate (377 mg, 2.2 mmol) and iodine (650 mg, 2.6 mmol). The reaction was stirred at room temperature for overnight under argon. The yellow participate of silver iodide was filtered off and washed with methanol. The filtrate was evaporated and diluted with EtOAc (20 mL), then washed with Sat. $Na_2S_2O_3$ (3×15 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (4:1 hexanes:EtOAc) to afford **83h** as a yellow solid (660 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 194.7, 154.4, 149.7, 128.3, 121.7, 111.0, 92.7, 56.5, 56.0; IR (thin film) ν 2840, 1669, 1584, 1501, 1377, 1265, 1153 cm^{-1}. Other data was identical to the literature values (Hathaway *et al*., 2007).

General Procedure for the Synthesis of 2-Iodobenzaldehyde



Method A

Step 1: Preparation of 2- iodobenzoic acid methyl ester **95**

To a solution of 2-iodobenzoic acid **94** (2.48 g, 10 mmol) in methanol (59 mL) was added concentrated H_2SO_4 (6 mL) cautiously. The reaction mixture was heat at reflux for 4 h, then cooled to room temperature and removed MeOH by vacuum evaporation. The resulting was diluted with EtOAc (50 mL) and then washed with H_2O (2×30 mL), saturated $NaHCO_3$ solution (50 mL), and brine (30 mL). The organic layer was dried

over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford **95** as a pale yellow oil without further purification (2.62 g, 99%).

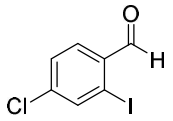
Step 2: Preparation of 2-iodobenzyl alcohol **96**

To a solution of **95** (2.2 g, 8.5 mmol) in dry CH_2Cl_2 (15 mL) was slowly added DIBAL-H (1M in THF, 18 mL) at 0 ^oC under argon. The reaction was gradually warmed up to room temperature. After being stirred for 4 h, the mixture was quenched with Sat. NH_4Cl (10 mL) and kept stirred for 1 h, then extracted with CH_2Cl_2 (3×15 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4. Evaporation *in vacuo* yielded **96** as a white solid without further purification (1.87 g, 99%).

Step 3: Preparation of 2-iodobenzaldehyde **97**

To a stirred solution of 2-iodobenzyl alcohol **96** (1.83 g, 7.9 mmol) in CH_2Cl_2 (30 mL) was added pyridinium chlorochromate (2.10 g, 9.74 mmol) in portionwise. The reaction mixture was stirred at room temperature under argon for 4 h, then filtered through a pad of Celite and concentrated *in vacuo*. Purification of the crude mixture by silica-gel chromatography (hexane:EtOAc, 9:1) yielded the product as a light yellow sold (1.44 g, 79%).

4.2.1.2 4-Chloro-2-iodobenzaldehyde (**83g**)

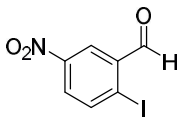


83g
C_7H_4ClIO
Mw = 266.4625 g/mol

4-Chloro-2-iodobenzaldehyde (**83g**) was synthesized from commercially available 4-chloro-2-iodobenzoic acid and using *Method A*. Yielded 52% (over 3 steps) as a light yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.85 (d, J = 1.6 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.76 (dd, J = 8.3, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

190.7, 136.3, 132.3, 131.4, 130.8, 129.8, 127.4.; IR (thin film) ν 2863, 1690, 1573, 1458, 1370, 1200, 828 cm^{-1}. Other data was identical to the literature values (Takaya *et al*., 2016).

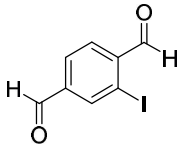
4.2.1.3 2-Iodo-5-nitrobenzaldehyde (**83b**)



83b
$C_7H_4INO_3$
Mw = 277.0175 g/mol

2-Iodo-5-nitrobenzaldehyde (**83b**) was synthesized from 2-iodo-5-nitrobenzoic acid[3] and using *Method A*. Yielded 70 % (over 3 steps) as an orange-brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.65 (d, *J* = 2.7 Hz, 1H), 8.21 (d, *J* = 8.6 Hz, 1H), 8.12 (dd, *J* = 8.6, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 148.6, 142.0, 136.2, 128.6, 124.6, 107.3; IR (thin film) ν 3089, 1683, 1602, 1568, 1531, 1349, 1188 cm^{-1}. Other data was identical to the literature values (Barbasiewicz *et al*., 2013).

4.2.1.4 2-Iodoterephthalaldehyde (**83d**)



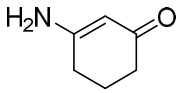
83d
$C_8H_5IO_2$
Mw = 260.0305 g/mol

Prepared according to literature procedure and followed by *method A*. Yielded 66% (over 3 steps) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1H), 10.05 (s, 1H), 8.44 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 189.9, 141.5, 140.5, 138.7, 130.7, 129.3, 100.2; IR (thin film)

ν 2845, 1685, 1469, 1365, 1195, 1184, 787 cm^{-1}.Other data was identical to the literature values (Wu *et al*., 2011).

4.2.2 Synthesis of Enaminones

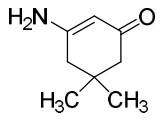
4.2.2.1 3-Aminocyclohex-2-enone (**84a**)



84a
C_6H_9NO
Mw = 111.1440 g/mol

Prepared according to literature procedure. To a solution of 1.0 equiv of 1,3cyclohexanedione in EtOH (0.5 M) was added 1.2 equiv of NH_4OAc. The reaction mixture was heat at reflux for overnight, then cooled to room temperature and removed EtOH by vacuum evaporation. The crude product was purified by column chromatography (6:1 EtOAc:MeOH) to give **84a** as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 6.70 (brs, 2H), 4.90 (s, 1H), 2.23 (t, *J* = 6.3 Hz, 2H), 2.00 (t, *J* = 6.3 Hz, 2H), 1.75 (q, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 194.9, 167.7, 97.9, 36.4, 28.4, 22.0; IR (thin film) ν 3135, 1674, 1539, 1258, 1189, 1143, 828 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

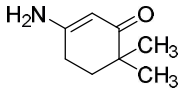
4.2.2.2 3-Amino-5,5-dimethylcyclohex-2-enone (**84d**)



84d
$C_8H_{13}NO$
Mw = 139.1980 g/mol

Prepared according to procedure described for **84a**. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 6.75 (brs, 2H), 4.91 (s, 1H), 2.11 (s, 2H), 1.89 (s, 2H), 0.94 (s, 6H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 194.5, 166.1, 96.4, 50.2, 42.1, 32.7, 28.5; IR (thin film) ν 3080, 1539, 1260, 1153, 1129, 772, 751 cm^{-1}. Other data was identical to the literature values(Al-Mousawi *et al*., 2003).

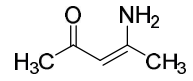
4.2.2.3 3-Amino-6,6-dimethylcyclohex-2-enone (**84e**)



84e
$C_8H_{13}NO$
Mw = 139.1980 g/mol

Prepared according to procedure described for **84a**. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 6.59 (brs, 2H), 4.79 (s, 1H), 2.26 (t, *J* = 6.3 Hz, 2H), 1.16 (t, *J* = 6.3 Hz, 2H), 0.92 (s, 6H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 199.9, 166.0, 96.4, 38.7, 35.7, 25.5; IR (thin film) ν 3353, 3147, 1652, 1539, 1215, 769 cm^{-1}.Other data was identical to the literature values (Bergmana *et al*. 2014).

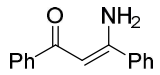
4.2.2.4 (*Z*)-4-Aminopent-3-en-2-one (**92b**)



92b
C_5H_9NO
Mw = 99.1330 g/mol

Prepared according to literature procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (brs, 1H), 5.84 (brs, 1H), 4.92 (s, 1H), 1.92 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 161.7, 95.1, 28.7, 21.7; IR (thin film) ν 3346 1621, 1538, 1414, 1357, 1291, 896 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

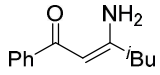
4.2.2.5 (*Z*)-3-Amino-1,3-diphenylprop-2-en-1-one (**92e**)



92e
$C_{15}H_{13}NO$
Mw = 223.2750 g/mol

Prepared according to literature procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.44 (brs, 1H), 7.99-7.96 (m, 2H), 7.67-7.64 (m, 2H), 7.53-7.42 (m, 6H), 6.17 (s 1H), 5.72 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 163.0, 140.2, 137.4, 130.9, 130.6, 128.9, 128.2, 127.1, 126.3, 91.7; IR (thin film) ν 3060, 1601, 1567, 1526, 1484, 1327, 741 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

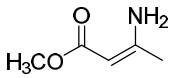
4.2.2.6 (*Z*)-3-Amino-5-methyl-1-phenylhex-2-en-1-one (**92d**)



92d
$C_{13}H_{17}NO$
Mw = 203.2850 g/mol

Prepared according to literature procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (brs, 1H), 7.89-7.86 (m ,2H), 7.43-7.39 (m, 2H), 5.71 (s, 1H), 2.10 (d, *J* = 7.4 Hz, 2H), 2.03-1.90 (m, 1H), 0.98 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 166.4, 140.4, 130.8, 128.2, 127.1, 126.3, 92.3, 46.3, 28.1, 22.8, 22.4; IR (thin film) ν 3380, 1603, 1574, 1527, 1320, 1216, 745 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

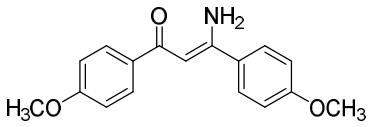
4.2.2.7 (*Z*)-Methyl-3-aminobut-2-enoate (**92a**)



92a
$C_5H_9NO_2$
Mw = 115.1320 g/mol

Prepared according to literature procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (s, 1H), 3.60 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 160.0, 83.3, 49.9, 22.1; IR (thin film) ν 3410, 3318, 1654, 1558, 1298, 1166, 1006 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

4.2.2.8 (*Z*)-3-Amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**92f**)



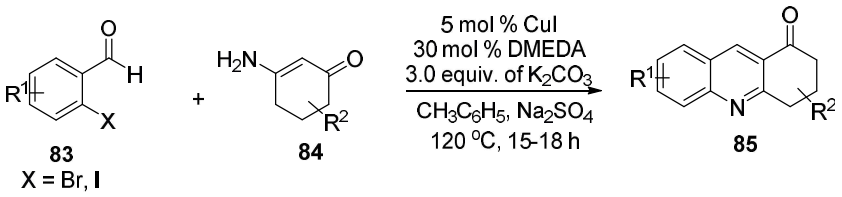
92f
$C_{17}H_{17}NO_3$
Mw = 283.3270 g/mol

Prepared according to literature procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 7.62-7.59 (m, 2H), 7.00-6.93 (m, 4H), 6.10 (s, 1H), 3.87 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 162.1, 161.9, 161.5, 133.2, 129.8, 129.0, 127.7, 114.3, 113.4, 90.8, 55.4, 55.3; IR (thin film) ν 2840, 1600, 1494, 1257, 1230, 1173, 1029 cm^{-1}. Other data was identical to the literature values (Songsichan *et al*., 2014).

4.2.3 Synthesis of Quinoline Derivatives

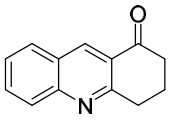
General Procedure for Copper-Catalyzed Domino Reaction for Synthesis of Quinoline Derivatives.

General Procedure A: For the Reaction of *E*-Enaminone



The reaction of 2-bromobenzaldehyde (**1a**) and 3-aminocyclohex-2-enone (**2**) is representative: A sealed-tube was charged with 2-bromobenzaldehyde (1a) (0.60 mmol), 3-aminocyclohex-2-enone (**2a**) (0.50 mmol), CuI (0.03 mmol), DMEDA (0.15 mmol), Na_2SO_4 (500 mg) and K_2CO_3 (1.50 mmol) in toluene (1.0 mL). The reaction mixture was allowed to stir at 120 ^oC for 15-18 h. After completion of reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15:1 CH_2Cl_2:EtOAc) to provide **3a** in 60.1 mg (61% yield) as a light yellow solid.

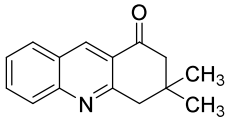
4.2.3.1 3,4-Dihydroacridin-1(2*H*)-one (**85a**)



85a
$C_{13}H_{11}NO$
Mw = 197.2370 g/mol

Prepared according to general procedure A from 2-bromobenzaldehyde and 3-aminocyclohex-2-enone (**84a**). Yield 60.1 mg (61 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$); 8.84 (s, 1H), 8.05 (d, *J* = 8.1 Hz,1H), 8.93 (d, *J* = 8.1 Hz, 1H), 7.81 (td, *J* = 8.1, 1.0 Hz), 7.55 (t, *J* = 8.1 Hz, 1H), 3.32 (t, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.28 (qn, *J* = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 161.9, 149.6, 137.1, 132.4, 129.7, 128.5, 126.8, 126.7, 126.3, 39.1, 33.4, 21.8; IR (thin film) ν 3060, 2951, 2867, 1688, 1593, 1206, 754 cm^{-1}. Other data was identical to the literature values (Rajawinslin *et al*., 2014).

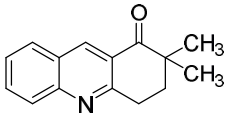
4.2.3.2 3,3-Dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85d**)



85d
$C_{15}H_{15}NO$
Mw = 225.2910 g/mol

Prepared according to general procedure A from 2-bromobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 72.1 mg (64 %) as a dark brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.78 (t, *J* = 6.9 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 3.18 (s, 2H), 2.63 (s, 2H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 160.5, 149.7, 136.1, 131.9, 129.5, 128.3, 126.4 (126.44), 126.4 (126.39), 125.0, 52.2, 46.9, 32.5, 28.1; IR (thin film) ν 3052, 2956, 2871, 1689, 1617, 1593, 1212, 760 cm^{-1}. Other data was identical to the literature values (Anand *et al*., 2015).

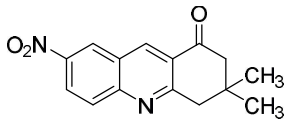
4.2.3.3 2,2-Dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85e**)



85e
$C_{15}H_{15}NO$
Mw = 225.2910 g/mol

Prepared according to general procedure A from 2-bromobenzaldehyde and 3-amino-6,6-dimethylcyclohex-2-enone (**84e**). Yield 76.5 mg (68 %) as a dark brown gum.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.78 (t, J = 8.1 Hz, 1H), 7.52 (t, 8.1 Hz, 1H), 3.33 (t, J = 6.3 Hz, 2H), 2.10 (t, J = 6.3, 2H), 1.29 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 161.0, 149.3, 137.8, 132.0, 129.4, 128.2, 126.7, 126.4, 125.1, 41.7, 34.9, 29.2, 24.1; IR (thin film) ν 3062, 2963, 2929, 1687, 1619, 1180, 753 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{15}NO$ 226.1232, found 226.1232.

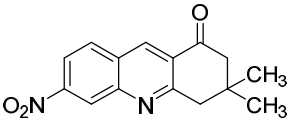
4.2.3.4 3,3-Dimethyl-7-nitro-3,4-dihydroacridin-1(2*H*)-one (**85g**)



85g
$C_{15}H_{14}N_2O_3$
Mw = 270.2880 g/mol

Prepared according to general procedure A from 2-bromo-5-nitro-benzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 50.0 mg (37 %) as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.88 (d, J = 2.7 Hz, 1H), 8.53 (dd, J = 9.3, 2.7 Hz, 1H), 8.17 (d, J = 9.3 Hz, 1H), 3.24 (s, 2H), 2.70 (s, 2H), 1.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 164.7, 151.6, 145.5, 138.0, 130.5, 126.6, 126.2, 125.5, 125.2, 52.2, 47.3, 32.7, 28.3; IR (thin film) ν 3087, 2959, 2872, 1699, 1603, 1567, 735 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{14}N_2O_3$ 271.1082, found 271.1082.

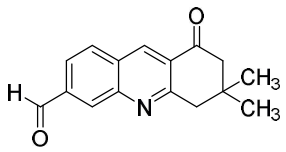
4.2.3.5 3,3-Dimethyl-6-nitro-3,4-dihydroacridin-1(2*H*)-one (**85h**)



85h
$C_{15}H_{14}N_2O_3$
Mw = 270.2880 g/mol

Preparation according to general procedure A from 2-bromo-4-nitrobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 69.0 mg (51 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90-8.88 (m, 2H), 8.30 (dd, *J* = 8.9, 1.9 Hz, 1H), 8.13 (d, *J* = 8.9 Hz, 1H), 3.27 (s, 2H), 2.73 (s, 2H), 1.20 (s, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 163.1, 149.3, 148.7, 135.8, 131.2, 129.6, 127.0, 124.5, 119.8, 52.2, 47.0, 32.5, 28.2; IR (thin film) 2965, 1695, 1596, 1530, 1348, 1182, 836 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{14}N_2O_3$ 271.1082, found 271.1082.

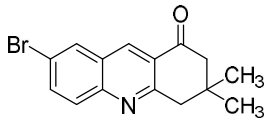
4.2.3.6 6,6-Dimethyl-8-oxo-5,6,7,8-tetrahydroacridine-2-carbaldehyde (**85i**)



85i
$C_{16}H_{15}NO_2$
Mw = 253.3010 g/mol

A sealed-tube was charged with 4-iodoisophthaldehyde (**83d**) (0.60 mmol), 3-amino-5,5-dimethylcyclohex-2-enone (**84d)** (0.50 mmol), CuI (0.03 mmol), DMEDA (0.15 mmol), Na_2SO_4 (500 mg) and K_2CO_3 (1.50 mmol) in CH_3CN (1.0 mL). The reaction mixture was allowed to stir at 120 ^{o}C for 15-18 h. After completion of reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15:1 CH_2Cl_2:EtOAc) to provide **85i** in 68.2 mg (54 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.86 (s, 1H), 8.51 (s, 1H), 8.05-8.04 (m, 2H), 3.00 (s, 2H). 2.70 (s, 2H), 1.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 191.8, 162.1, 149.7, 138.7, 136.2, 134.2, 130.8, 130.2, 126.8, 123.3, 52.4, 47.1, 32.7, 28.4; IR (thin film) ν 2957, 2861, 1697, 1596, 1371, 1241, 769 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{16}H_{15}NO_2$ 254.1181, found 254.1181.

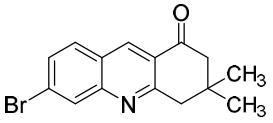
4.2.3.7 7-Bromo-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85k**)



85k
$C_{15}H_{14}BrNO$
Mw = 304.1870 g/mol

Prepared according to general procedure A from 2,5-dibromobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 80.9 mg (54 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.84 (dd, *J* = 9.0, 1.8 Hz, 1H), 3.17 (s, 2H), 3.34 (s, 2H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 161.2, 148.5, 135.5, 135.4, 131.4, 130.3, 127.9, 125.8, 120.4, 52.4, 47.1, 32.7, 28.4; IR (thin film) ν 2958, 2870, 1690, 1590, 1479, 1372, 1209 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{14}BrNO$ 304.0336, found 304.0337.

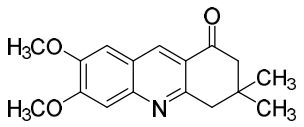
4.2.3.8 6-Bromo-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85m**)



85m
$C_{15}H_{14}BrNO$
Mw = 304.1870 g/mol

Preparation according to general procedure A from 2,4-dibromobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 85.1 mg (56 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.22 (s, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.62 (dd, *J* = 8.7, 1.5 Hz, 1H), 3.17 (s, 2H), 2.65 (s, 2H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 161.9, 150.2, 136.2, 131.0, 130.7, 130.3, 126.7, 125.4, 125.2, 52.3, 47.0, 32.6, 28.3; IR (thin film) ν 2962, 2872, 1684, 1608, 1486, 1069, 708 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{14}BrNO$ 304.0337 found 304.0335.

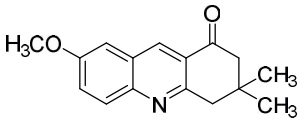
4.2.3.9 3,4-Dimethoxy-3,3-dimethyl-3,4-dihydro-2*H*-acridin-1-one one (**85p**)



85p
$C_{17}H_{19}NO_3$
Mw = 285.3430 g/mol

Prepared according to general procedure described for **85i** from 2-iodo-4,5-dimethoxybenzaldehyde (**83h**) and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 51.3 mg (36 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.34 (s, 1H), 7.10 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 2.58 (s, 2H), 1.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 158.9, 154.8, 149.8, 147.6, 134.1, 123.7, 122.4 107.1, 106.3, 56.2, 56.0, 52.3, 46.8, 32.8, 28.3; IR (thin film) ν 3014, 2957, 1682, 1621, 1590, 1504, 1257 cm^{-1}. Other data was identical to the literature values (Patteux *et al*., 2003).

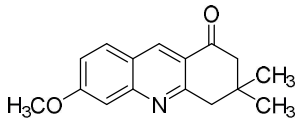
4.2.3.10 7-Methoxy-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85r**)



85r
$C_{16}H_{17}NO_2$
Mw = 255.3170 g/mol

Preparation according to general procedure described for **85i** from 2-bromo-5-methoxybenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 92.8 mg (73 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.44 (dd, J = 9.2, 2.4 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 3.93 (s, 3H), 3.14 (s, 2H), 2.63, (s, 2H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 158.2, 157.7, 146.2, 134.9, 129.8, 127.6, 125.2, 106.3, 55.5, 52.4, 46.8, 32.7, 28.3; IR (thin film) ν 2956, 2867, 1686, 1623, 1593, 1495, 1236 cm^{-1}. Other data was identical to the literature values (Anand *et al*., 2015).

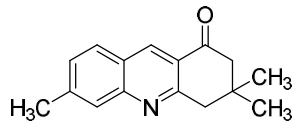
4.2.3.11 6-Methoxy-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (**85t**)



85t
$C_{16}H_{17}NO_2$
Mw = 255.3170 g/mol

Preparation according to general procedure described for **85i** from 2-bromo-4-methoxybenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d**). Yield 70.2 mg (55 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.31 (d, *J* = 2.1 Hz, 1H), 7.13 (dd, *J* = 9.0, 2.1 Hz, 1H), 3.92 (s, 3H), 3.09 (s, 2H), 2.57 (s, 2H), 1.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 163.0, 161.3, 151.9, 135.9, 130.7, 123.4, 121.9, 120.2, 106.4, 55.6, 52.2, 47.0, 32.7, 28.3; IR (thin film) ν 2956, 2870, 1685, 1619, 1594, 1498, 1207 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{17}H_{20}NO_2$ 256.1388 found 256.1388.

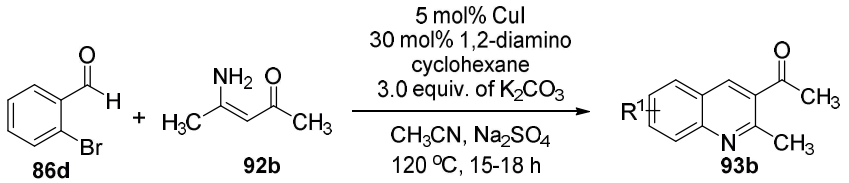
4.2.3.12 3,3,7-Trimethyl-3,4-dihydroacridin-1(2*H*)-one (**85u**)



85u
$C_{16}H_{17}NO$
Mw = 239.3180 g/mol

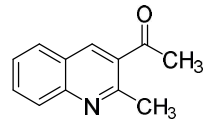
Preparation according to general procedure described for **85i** from 2-bromo-3-methylbenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone (**84d)**. Yield 52.6 mg (44 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.86-7.83 (m, 2H), 7.43 (d, *J* = 1.1 Hz, 1H), 3.02 (s, 2H), 2.66 (s, 2H), 2.60 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 160.8, 150.1, 143.2, 136.2, 129.3, 129.0, 127.5, 124.8, 124.6, 52.4, 47.1, 32.7, 28.3, 22.2; IR (thin film) ν 2956, 2861, 1687, 1626, 1594, 1498, 1372 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{16}H_{17}NO$ 240.1388, found 240.1389.

General Procedure B: For the Reaction of *Z*-Enaminone



The reaction of 2-bromobenzaldehyde (**86d**) and (*Z*)-4-aminopent-3-en-2-one (**92b**) is representative: A sealed-tube was charged with 2-bromobenzaldehyde (**1a**) (0.60 mmol), (*Z*)-4-aminopent-3-en-2-one (**92b**) (0.50 mmol), CuI (0.03 mmol), cyclohexane-1,2-diamine (0.15 mmol), Na_2SO_4 (500 mg) and K_2CO_3 (1.50 mmol) in CH_3CN (1.0 mL). The reaction mixture was allowed to stir at 120 ^oC for 15-18 h. After completion of reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15:1 CH_2Cl_2:EtOAc) to provide x in 54.4 mg (55% yield) as a light yellow solid.

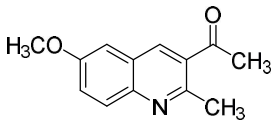
4.2.3.13 1-(2-Methylquinolin-3-yl)ethanone (**93b**)



93b
$C_{12}H_{11}NO$
Mw = 185.2260 g/mol

Prepared according to general procedure B from 2-bromobenzaldehyde (**86d**) and (*Z*)-4-aminopent-3-en-2-one (**92b**). Yield 39.8 mg (43 %) as a light brown solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.77 (ddd, *J* = 9.3, 6.9, 1.5 Hz, 1H), 7.53 (ddd, *J* = 9.3, 6.9, 1.5 Hz, 1H), 2.91 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 157.5, 148.2, 138.1, 131.7, 131.1, 128.5, 128.3, 126.6, 125.6, 29.2, 25.6; IR (thin film) ν 3058, 2990, 2967, 1682, 1620, 1562, 1420 cm^{-1}. Other data was identical to the literature values (Anand *et al.*, 2015).

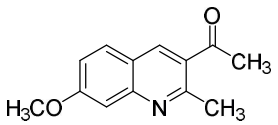
4.2.3.14 1-(6-Methoxy-2-methylquinolin-3-yl)ethanone (**93o**)



93o
$C_{13}H_{13}NO_2$
Mw = 215.2520 g/mol

Preparation according to general procedure B from 2-bromo-5-methoxylbenzaldehyde and (*Z*)-4-aminopent-3-en-2-one (**92b**). Yield 77.7 mg (72 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.41 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.08 (d, *J* = 2.6 Hz, 1H), 3.92 (s, 3H), 2.86 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 157.6, 154.6, 144.0, 136.8, 131.0, 129.6, 126.4, 124.2, 105.4, 55.4, 29.0, 25.0; IR (thin film) ν 2997, 1683, 1595, 1493, 1227, 1030, 834. HRMS (ESI) $[M+H]^+$ calcd. for $C_{13}H_{13}NO_2$ 216.1025 found 216.1025.

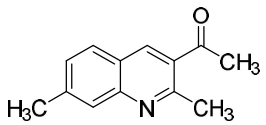
4.2.3.15 1-(7-Methoxy-2-methylquinolin-3-yl)ethanone (**93r**)



93r
$C_{13}H_{13}NO_2$
Mw = 215.2520 g/mol

Preparation according to general procedure B from 2-bromo-4-methoxylbenzaldehyde and (*Z*)-4-aminopent-3-en-2-one (**92b**). Yield 95.7 mg (89 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.64 (d, *J* = 8.9 Hz, 1H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.11 (dd, *J* = 8.9, 2.2 Hz, 1H), 3.88 (s, 3H), 2.82 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 162.8, 158.4, 150.3, 138.3, 129.5, 128.7, 120.6, 120.0, 106.7, 55.7, 29.0, 25.8; IR (thin film) ν 2965, 1675, 1623, 1612, 1488, 1210, 1193 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{13}H_{13}NO_2$ 216.1025 found 216.1025.

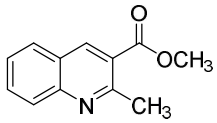
4.2.3.16 1-(2,7-Dimethylquinolin-3-yl)ethanone (**93u**)



93u
$C_{13}H_{13}NO$
Mw = 199.2530 g/mol

Preparation according to general procedure B from 2-bromo-4-methylbenzaldehyde and (*Z*)-4-aminopent-3-en-2-one (**92b**). Yield 83.7 mg (84 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.83 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 2.91 (s, 3H), 2.71 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 157.7, 148.5, 142.6, 138.1, 130.3, 128.9, 128.0, 127.6, 123.6, 29.1, 25.7, 22.1; IR (thin film) ν 3031, 1682, 1666, 1427, 1240, 1129, 778 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{13}H_{13}NO$ 200.1075 found 200.1075.

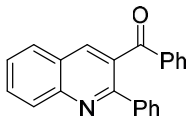
4.2.3.17 Methyl-2-methylquinoline-3-carboxylate (**93a**)



93a
$C_{12}H_{11}NO_2$
Mw = 201.2250 g/mol

Preparation according to general procedure B from 2-bromobenzaldehyde (**86d**) and (*Z*)-Methyl-3-aminobut-2-enoate (**92a**) Yield 51.2 mg (52 %) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.77 (td, *J* = 8.1, 1.2 Hz, 1H), 7.53 (td, *J* = 8.1, 1.2 Hz), 3.98 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 158.5, 148.6, 140.0, 131.7, 128.5, 128.4, 126.5, 125.7, 123.5, 52.3, 25.6; IR (thin film) ν 3063, 2999, 2952, 1727, 1622,1201, 789 cm^{-1}. Other data was identical to the literature values (Anand *et al*., 2015).

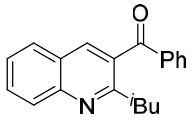
4.2.3.18 Phenyl(2-phenylquinolin-3-yl)methanone (**93e**)



93e
$C_{22}H_{15}NO$
Mw = 309.3680 g/mol

Prepared according to general procedure B from 2-iodobenzaldehyde and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**92e**). Yield 52.5 mg (34 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s,1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.83 (ddd, *J* = 8.4, 7.5, 1.5 Hz, 1H), 7.73-7.70 (m, 2H), 7.64-7.58 (m, 3H), 7.47 (tt, *J* = 7.5, 1.0 Hz, 1H), 7.35-7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 157.5, 148.4, 139.7, 137.6, 137.1, 133.3, 132.9, 131.2, 130.0, 129.7, 129.3, 128.8, 128.4, 128.1, 127.3, 125.8; IR (thin film) ν 3059, 3020, 1662, 1595,1270, 1234, 770 cm^{-1}. Other data was identical to the literature values (Rajawinslin *et al*., 2014).

4.2.3.19 2-Isobutylquinolin-3-yl(phenyl)methanone (**93d**)

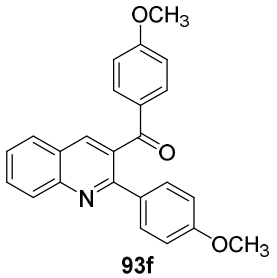


93d
$C_{20}H_{19}NO$
Mw = 289.3780 g/mol

Prepared according to general procedure B from 2-bromobenzaldehyde (**86d**) and (*Z*)-3-amino-5-methyl-1-phenylhex-2-en-1-one (**92d**). Yield 41.9 mg (29 %) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 1H), 8.08 (s, 1H), 7.86-7.76 (m ,4H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.57-7.47 (m, 3H), 2.97 (s, 3H), 2.96 (d, *J* = 7.3 Hz, 2H), 2.22-2.12 (m, 1H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 160.0, 148.0, 137.5, 136.7, 133.7, 132.6, 130.9, 130.2, 129.0, 128.7, 128.0, 126.7, 125.2, 45.4, 29.3, 22.5; IR (thin film) ν 3061, 2957, 1667, 1619, 1595,

1450, 1262 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{20}H_{19}NO$ 290.1545, found 290.1546.

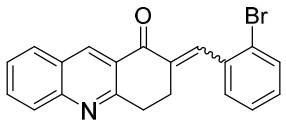
4.2.3.20 (4-Methoxyphenyl)(2-(4-methoxyphenyl)quinolin-3-yl)methanone (**93f**)



93f
$C_{24}H_{19}NO_3$
Mw =369.4200 g/mol

A sealed-tube was charged with 2-(2-bromobenzylidene)malonate (0.60 mmol), (*Z*)-3-amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**92f**) (0.50 mmol), CuI (0.03 mmol), cyclohexane-1,2-diamine (0.15 mmol), Na_2SO_4 (500 mg) and K_2CO_3 (1.50 mmol) in CH_3CN (1.0 mL). The reaction mixture was allowed to stir at 120 ^oC for 15-18 h. After completion of reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15:1 CH_2Cl_2:EtOAc) to provide x in 81.7 mg (74 % yield) as a light yellow solid. Yield 136.6 mg (74 %) as a light yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.80 (ddd, *J* = 8.5, 7.0, 1.2 Hz, 1H), 7.76-7.72 (m, 2H), 7.65-7.56 (m, 3H), 6.85-6.81 (m, 4H), 3.83 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 163.6, 160.1, 156.6, 148.1, 136.9, 132.9, 132.3, 132.1, 130.7, 129.8, 129.3, 127.8, 126.8, 125.5, 113.8, 113.6, 55.3, 55.1; IR (thin film) ν 3008, 2838, 1660, 1599, 1253, 1024, 758 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{24}H_{19}NO_3$ 370.1443 found 340.1440.

4.2.3.21 2-(2-Bromobenzylidene)-3,4-dihydroacridin-1(2H)-one (**91**)



91

$C_{20}H_{14}BrNO$

Mw = 364.2420 g/mol

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.99-7.97 (m, 2H), 7.82 (td, *J* = 7.2, 1.2 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.38-7.34 (m. 2H), 7.21-7.22 (m, 1H), 3.31 (t, *J* = 6.0 Hz, 2H), 3.16 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 160.9, 149.5, 138.3, 137.0, 136.0, 135.9, 133.1, 132.4, 130.5, 130.1, 129.8, 128.6, 127.1, 126.9, 126.8, 125.0, 32.7, 26.2; IR (thin film) ν 3448, 3059, 2958, 2853, 1617, 1492 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for CHNO 364.0337, found 364.0337.

APPENDIX

Organic & Biomolecular Chemistry

PAPER

Cite this: *Org. Biomol. Chem.*, 2017, **15**, 7387

Synthesis of quinolines *via* copper-catalyzed domino reactions of enaminones†

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Received 27th July 2017,
Accepted 18th August 2017

DOI: 10.1039/c7ob01867c

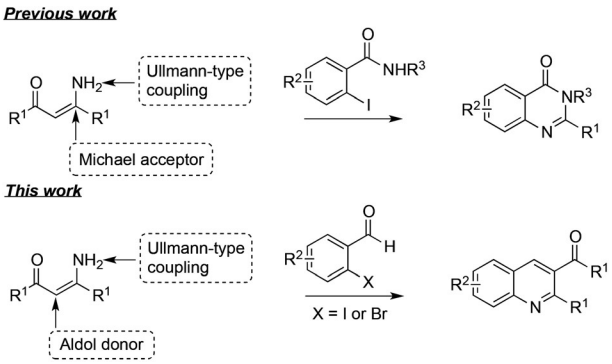
rsc.li/obc

Quinoline derivatives were obtained from enaminones and 2-bromo- or 2-iodobenzaldehydes *via* copper-catalyzed domino reactions consisting of the aldol reaction, C(aryl)–N bond formation and elimination. The electronic effect of aldehydes played a major role in the reaction outcome. Two simple protocols are disclosed to achieve various quinolines from both cyclic and acyclic enaminones in good yields. With the less-reactive acyclic enaminones, diethyl-2-(2-bromobenzylidene)malonate was shown to be more compatible than the benzaldehydes.

Introduction

Copper-catalyzed domino reactions have been one of the most useful and powerful synthetic tools in organic synthesis. In particular, tandem processes involving C–N bond formations from aryl halides and nitrogen nucleophiles have attracted most attention among copper-catalyzed reactions in synthesizing heterocycles in which a variety of nitrogen nucleophiles and aryl halide derivatives have been introduced to obtain the corresponding N-heterocyclic molecules.[1]

In continuation of our research interest in seeking new methodologies to construct N-heterocycles *via* a tandem process from readily accessible starting materials under mild and simple reaction conditions as well as practical preparations, we have found that enaminones are useful substrates for a domino process since they have more than one reactive site.[2] We previously documented the use of enaminones in the synthesis of quinazolinones in Ullmann-type coupling.[2a] Alternatively, we envisioned that we could utilize the enamine moiety as a carbon nucleophile for the aldol reaction with 2-halobenzaldehyde followed by dehydration to obtain 4*H*-quinolines (Scheme 1). Similarly, Edmondson introduced this concept of the C–N bond formation of aryl halides and enaminones catalyzed by palladium.[3] Recently, Singh also reported a one-pot, three-component reaction for the synthesis of quinolines *via* the copper-catalyzed C–N bond formation of 2-bromobenzaldehyde and sodium azide, followed by the intermolecular annulation of 1,3-dicarbonyls.[4]



Scheme 1 The uses of enaminones.

Quinolines are one of the most important N-heterocycles due to their common occurrence in natural products and biologically active molecules.[5] In addition, they are key structures in materials and synthetic chemistry as ligands.[6] Several classical methods are known, for example Friedländer, Skraup, Conrad–Limpach, Combes, and Doebner–Miller reactions, to obtain quinolines.[7] All these methods provide quinolines *via* intermolecular or intramolecular annulation of aniline derivatives with carbonyls. The developments in classical methods to overcome drawbacks, such as harsh reaction conditions, noble and/or toxic metal catalysts and problems associated with the 2-amino carbonyl compounds, have been consistently introduced.[8] However, most of them were based on aniline derivatives in which the C(ary)–N bonds were originally installed. Another development by using a rearrangement of azide derivatives in quinoline formations has also been reported.[9] Herein, we introduced the copper-catalyzed domino reactions of 2-halobenzaldehydes and cyclic enaminones to accomplish dihydroacridines, and acyclic enaminones to achieve quinolines.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ob01867c

Results and discussion

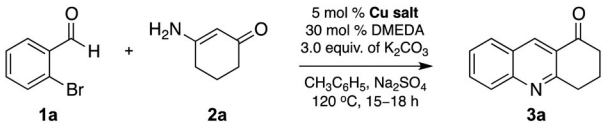
We began our study by investigating the reaction conditions. We selected a reaction of commercially available 2-bromobenzaldehyde and readily prepared 3-aminocyclohex-2-enone as a model (Table 1).

A variety of bases were used in the reaction (entries 1–5) with toluene as an initial solvent and *N*,*N*′-dimethylethylenediamine (DMEDA) as a ligand at 120 °C. High temperature was required in order to complete the reaction. K_2CO_3 gave the highest yield, 49%, whereas a stronger base, *t*-BuOK, and a common organic base, NEt_3, gave low yield. Fortunately, in the presence of Na_2SO_4 as an additive, the yield of the product increased to 58% (entry 6). The attempts to improve the product yield by varying common ligands, such as L-proline, 1,10-phenanthroline, 1,2-diaminocyclohexane and PPh_3, were made (entries 7–10), but the reaction with DMEDA still gave the best yield. Other common solvents were also investigated. Dioxane gave only a trace amount of the product (entry 11). Changing the solvent to acetonitrile (ACN) gave quinoline in 33% yield (entry 12). Highly polar solvents, such as DMF, DMSO, isopropanol and *t*-BuOH, gave low yield or a trace amount of quinoline product (entries 13–16). Next, we examined the role of Na_2SO_4. The reaction with reflux conditions without Na_2SO_4 gave low yield (entry 17). Importantly, in the presence of molecular sieves (MS), the reaction gave a comparable yield to that of Na_2SO_4 (entry 18). The result suggested that the role of Na_2SO_4 was a drying agent. In addition, good yield was obtained when we switched the ratio of **1a** : **2a** from 1.2 : 1.0 to 1.0 : 2.0 (entry 19).

Next, we explored various copper salts (Table 2). The reaction was applicable to various copper salts. CuCl provided low yield, 37% (entry 1). Similar yields were obtained from the reaction using Cu_2O or CuBr (entries 2 and 3). $Cu(OAc)_2$ was not suitable for the reaction (entry 4).

By considering the availability of 2-halobenzaldehydes, we found that 2-iodobenzaldehyde was also applicable in the reaction. However, when we subjected 2-iodobenzaldehyde and **2a** to the optimal conditions, the yield of **3a** dramatically reduced to 30%. Based on this result, further optimization reaction of

Table 2 Quinoline from various copper salts[a]

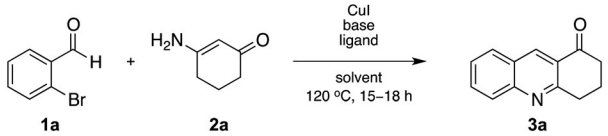


1a 2a 3a

Entry	Copper salt	Yield[b]
1	CuCl	37
2	Cu_2O	50
3	CuBr	49
4	$Cu(OAc)_2$	0

[a] Reaction conditions: All reactions were performed with 0.5 mmol of **2a**, 1.2 equiv. of **1a** and 1.0 mL of solvent in a sealed tube. [b] Isolated yield.

Table 1 Screening of reaction conditions[a]

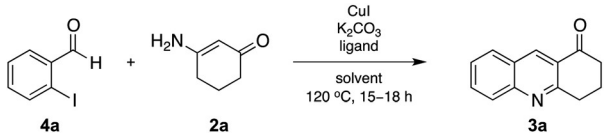


1a 2a 3a

Entry	Ligand	Base	Additive	Solvent	Yield[b]
1	DMEDA	K_3PO_4	—	Toluene	Trace[c]
2	DMEDA	Cs_2CO_3	—	Toluene	14
3	DMEDA	K_2CO_3	—	Toluene	49
4	DMEDA	^{t}BuOK	—	Toluene	Trace
5	DMEDA	NEt_3	—	Toluene	5
6	DMEDA	K_2CO_3	Na_2SO_4	Toluene	58
7	L-Proline	K_2CO_3	Na_2SO_4	Toluene	23
8	1,10-Phenanthroline	K_2CO_3	Na_2SO_4	Toluene	26
9	1,2-Diaminocyclohexane	K_2CO_3	Na_2SO_4	Toluene	34
10	PPh_3	K_2CO_3	Na_2SO_4	Toluene	12
11	DMEDA	K_2CO_3	Na_2SO_4	Dioxane	Trace
12	DMEDA	K_2CO_3	Na_2SO_4	ACN	33
13	DMEDA	K_2CO_3	Na_2SO_4	DMF	4
14	DMEDA	K_2CO_3	Na_2SO_4	DMSO	Trace
15	DMEDA	K_2CO_3	Na_2SO_4	i-PrOH	Trace
16	DMEDA	K_2CO_3	Na_2SO_4	*t*-BuOH	7
17	DMEDA	K_2CO_3	Reflux	Toluene	34
18	DMEDA	K_2CO_3	MS[d]	Toluene	56
19[e]	DMEDA	K_2CO_3	MS	Toluene	77

[a] Reaction conditions: All reactions were performed with 0.5 mmol of **2a**, 5 mol% of Cu salt, 30 mol% of ligand, 1.2 equiv. of **1a**, 3.0 equiv. of base and 1.0 mL of solvent in a sealed tube. [b] Isolated yield. [c] The ^{1}H NMR of the crude reaction mixture. [d] Molecular sieves 4 Å. [e] The reaction was performed with 1.0 equiv. of **1a** and 2.0 equiv. of **2a**.

Table 3 Screening the conditions of the reaction of 2-iodobenzaldehyde[a]



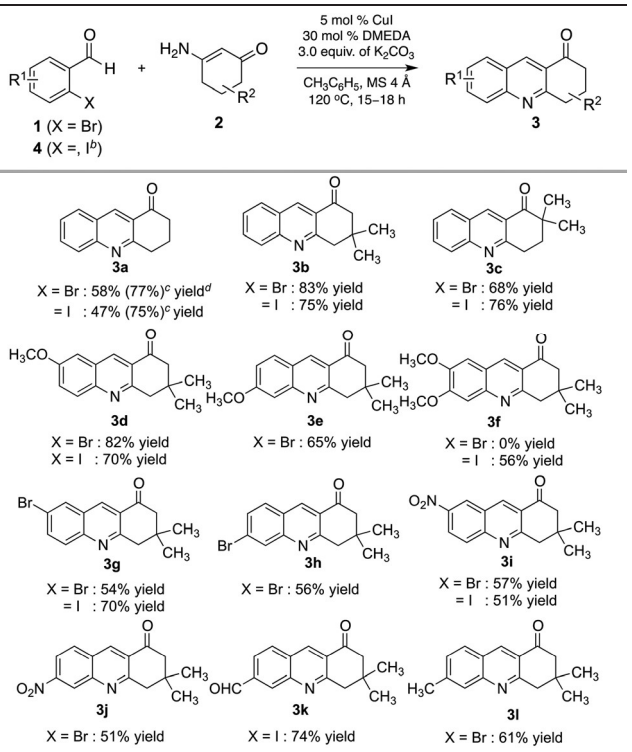
Entry	Cu	Ligand	Ratio **4a** : **2a**	Additive	Solvent	Yield[b]
1	CuI	DMEDA	1.2 : 1.0	Na_2SO_4	Toluene	30
2	CuI	DMEDA	1.0 : 2.0	Na_2SO_4	Toluene	45
3	CuI	DMEDA	1.0 : 2.0	Na_2SO_4	DMF	Trace[c]
4	CuI	DMEDA	1.0 : 2.0	Na_2SO_4	DMSO	Trace
5	CuI	DMEDA	1.0 : 2.0	Na_2SO_4	ACN	49
6	CuI	DMEDA	1.0 : 2.0	MS[d]	ACN	50
7	CuCl	DMEDA	1.0 : 2.0	MS	ACN	33
8	CuBr	DMEDA	1.0 : 2.0	MS	ACN	35
9	CuI	1,2-Diaminocyclohexane	1.0 : 2.0	MS	ACN	75
10	CuI	L-Proline	1.0 : 2.0	MS	ACN	69
11	CuI	1,10-Phenanthroline	1.0 : 2.0	MS	ACN	43
12	CuI	2,2′-Dipyridine	1.0 : 2.0	MS	ACN	64
13	CuI	1,2-Diaminocyclohexane	1.2 : 1.0	MS	ACN	47

[a] Reaction conditions: All reactions were performed on a 0.5 mmol scale of the limiting starting material, 5 mol% of Cu salt, 30 mol% of ligand, 3.0 equiv. of base and 1.0 mL of solvent in a sealed tube. [b] Isolated yield. [c] The ^{1}H NMR spectrum of the crude reaction mixture. [d] Molecular sieves 4 Å.

2-iodobenzaldehyde was required (Table 3). We observed the remaining 2-iodobenzaldehyde and undesired byproducts from the ^{1}H NMR spectrum of the crude reaction mixture of the reaction (entry 1). We then switched the ratio of 2-iodobenzaldehyde and **2a** from 1 : 1.2 to 1.0 : 2.0. Significantly, the reaction yield increased to 45% (entry 2). Next, we explored polar solvents. We found that both DMSO and DMF provided a trace amount of the desired quinoline (entries 3 and 4). Satisfactorily, changing the solvent to ACN increased the product yield to 49% (entry 5). The comparable yield of quinoline was found when we changed the drying agent to MS (entry 6). Other common copper salts showed low efficiency, such as CuCl and CuBr (entries 7 and 8). Subsequently, a range of common ligands, such as 1,2-diaminocyclohexane, L-proline, 1,10-phenanthroline and 2,2′-dipyridine, were examined, producing quinoline in 75%, 69%, 43% and 64% yields, respectively (entries 9–12). In addition, we switched the ratio of 2-iodobenzaldehyde and **2a** back to 1.2 : 1.0 providing quinoline in 47% yield (entry 13). Therefore, the optimal conditions were 1.0 equiv. of **4a**, 2.0 equiv. of **2a**, 30 mol% of 1,2-diaminocyclohexane, and 3.0 equiv. of K_2CO_3 in ACN at 120 °C under air in a sealed tube.

After having optimal reaction conditions, we explored the scope of the substrates (Table 4). Both the reactions of 2-bromo- and 2-iodobenzaldehydes and 3-aminocyclohex-2-enone gave good yields, 77% and 75%, respectively (**3a**). Interestingly, with the geminal dimethyl substituents on the 3-aminocyclohex-2-enone, the yields of products increased (**3b** and **3c**). We found that 2.0 equivalents of 3-amino-5,5-dimethylcyclohex-2-enone were not necessary for this reaction with 2-bromo- and 2-iodobenzaldehydes (**3b**). In addition, changing the drying agent to MS increased the yield of quino-

Table 4 Quinolines from cyclic enaminones[a]



[a] Reaction conditions: All reactions were performed with 0.5 mmol of **2**, 5 mol% of Cu salt, 1.2 equiv. of **1** or **4**, and 1.0 mL of $CH_3C_6H_5$ in a sealed tube. [b] The solvent and ligand were changed to ACN and 1,2-diaminocyclohexane, respectively. [c] The reaction was performed with 1.0 equiv. of aldehyde and 2.0 equiv. of **2a**. [d] Isolated yield.

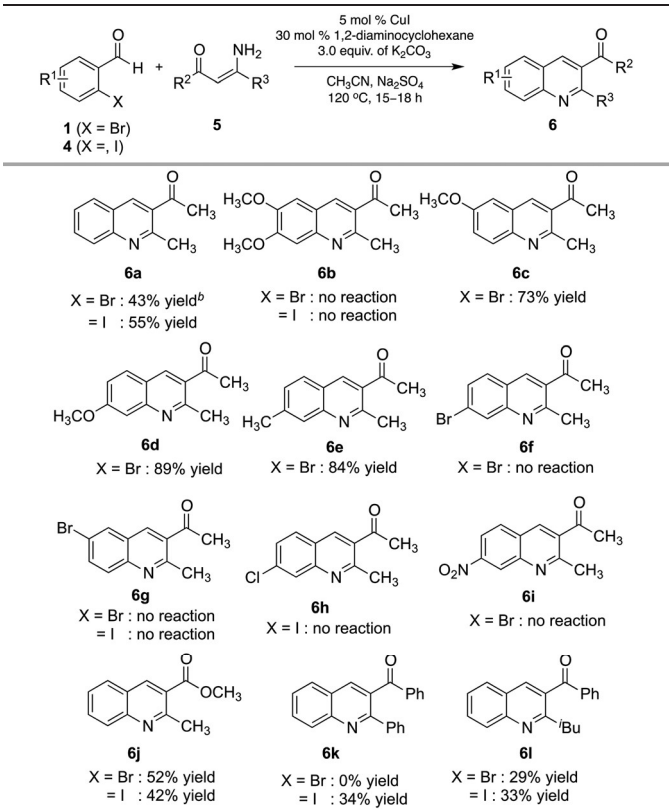
lines. 3-Amino-6,6-dimethylcyclohex-2-enone also provided a good yield of quinoline from both 2-bromo- and 2-iodobenzaldehydes, 68% and 76% yields, respectively (**3c**). These results suggested that 3-amino-5,5-dimethyl- and 3-amino-6,6-dimethylcyclohex-2-enones were more reactive than unsubstituted enaminones. A variety of substituents of benzaldehydes, such as electron-withdrawing groups, electron-donating groups and halogen atoms, are applicable to the reaction, providing the corresponding quinolines in moderate to good yields. Significantly, we found that the reaction depended on the position and number of electron-donating substituents of benzaldehydes. 2-Iodo-5-methoxybenzaldehyde gave quinoline in good yield, 70% (**3d**). On the other hand, 2-bromo-4-methoxybenzaldehye provided the corresponding quinoline in moderate yield, 65% (**3e**). Different results were found from the reaction of dimethoxy-substituted benzaldehydes: 2-bromo-4,5-dimethoxybenzaldehye gave no product, whereas 2-iodo-4,5-dimethoxybenzaldehyde gave 56% yield of the corresponding quinoline (**3f**). A halogen substituent was also suitable for the reaction. Both 2,5-dibromo- and 2,4-dibromobenzaldehydes gave moderate yields of quinolines, 54% and 56%, respectively (**3g** and **3h**).

A high yield, 70%, was obtained from 2-iodo-5-bromobenzaldehyde (**3g**). Having nitro as a substituent provided moderate yields of the corresponding quinolines from both 2-bromo- and 2-iodobenzaldehydes (**3i** and **3j**). The formyl group was applicable resulting in quinoline in 74% yield from 2-iodoterephthalaldehyde (**3k**). Lastly, an alkyl substituent was also suitable providing quinoline in 61% yield (**3l**).

Next, we considered acyclic enaminones. The yield of quinolines was moderate, possibly resulting from the low reactivity of *Z*-enaminones (Table 5). With the reaction of acyclic enaminones, having an electron-donating group at the *para* or *meta*-position of the aldehydes resulted in exceptionally high yields of quinolines: 73–89% (**6c–e**). In contrast, having electron-withdrawing or halogen substituents of aldehydes gave no products (**6f–i**). A variety of acyclic enaminones were explored. However, the yields of quinoline products were low to moderate. Particularly, (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one gave quinolines in low yield from 2-iodobenzaldehyde and no reaction occurred from 2-bromobenzaldehyde (**6k**). In addition, the reaction of (*Z*)-3-amino-4,4-dimethyl-1-phenylpent-2-en-1-one gave a low yield of quinoline with both 2-iodo- and 2-bromobenzaldehydes (**6l**). The results suggested that the acyclic enaminones with aryl substituents are relatively low in reactivity of the reactions.

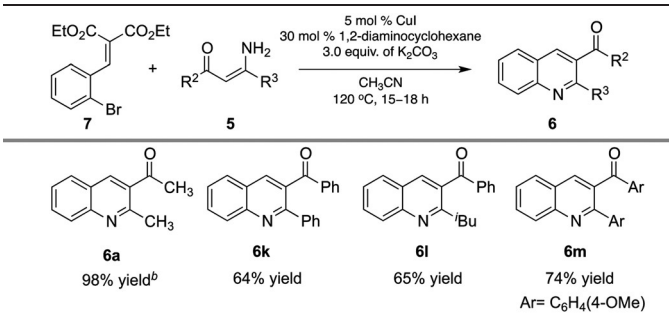
Recently, we have reported the use of 2-bromobenzylidenemalonates as the starting material for copper-catalyzed chromene synthesis.[10] Benzylidenemalonates not only showed high reactivity for Michael addition, but the malonate moiety was also significantly active as a leaving group. Therefore, we anticipated that 2-bromobenzylidenemalonate would also be a suitable coupling partner with less-reactive acyclic enaminones. We subjected 2-bromobenzylidenemalonate to the reaction conditions of acyclic enaminones. In this case, Na_2SO_4 was not required as an additive. The yield of quinoline was significantly increased to 98% (Table 6, **6a**). Consequently, the benzylidenemalonate could be an alternative coupling partner for less-reactive acyclic enaminones. Therefore, we conducted the reactions of 2-bromobenzylidenemalonate with acyclic enaminones (Table 6). Significantly, the yields of quinolines derived from benzylidenemalonate and less-reactive acyclic enaminones greatly increased compared to those from benz-

Table 5 Quinolines from acyclic enaminones[a]

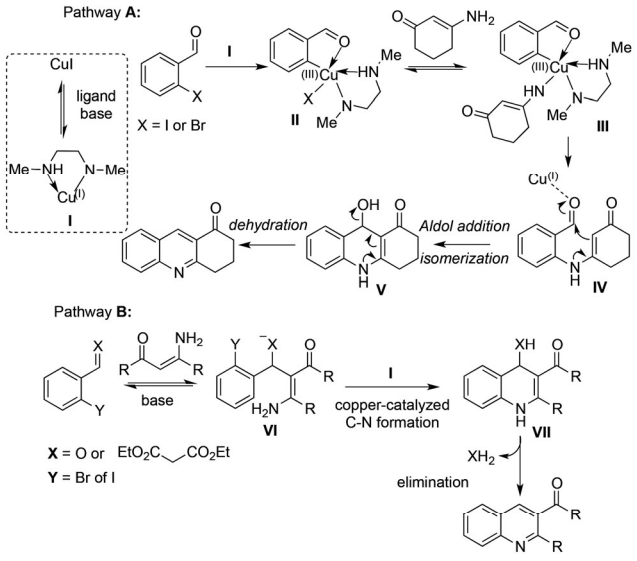


[a] Reaction conditions: All reactions were performed with 0.5 mmol of **5**, 5 mol% of Cu salt, 1.2 equiv. of **1** or **4**, 3.0 equiv. of K_2CO_3 and 1.0 mL of CH_3CN in a sealed tube. [b] Isolated yield.

Table 6 Quinolines from 2-bromobenzylidenemalonate[a]



[a] Reaction conditions: All reactions were performed with 0.5 mmol of **5**, 5 mol% of Cu salt, 1.2 equiv. of **7**, 3.0 equiv. of K_2CO_3 and 1.0 mL of CH_3CN in a sealed tube. [b] Isolated yield.



Scheme 2 Proposed reaction mechanism.

aldehydes. The reactions from the aryl substituents of enaminones gave good yields (**6k–m**).

Based on the results from both aldehydes and benzylidenemalonate, we proposed two possible pathways (Scheme 2). The pathway **A** involved the coordination of aldehyde carbonyl and the copper–ligand complex to undergo oxidative addition to form the complex **II**, followed by ligand exchange with enaminones to form intermediate **III**. Then, a reductive elimination took place to form the C(ary)–N bond of intermediate **IV**. Subsequently, intramolecular aldol and isomerization occurred to give dihydroquinoline alcohol **V**. The last step was dehydration to give the desired quinoline.

Alternatively, the pathway **B** involved the carbon–carbon bond formation of aldehydes or benzylidenemalonate and enaminones to generate intermediate **VI** in which the aldehydes underwent aldol reaction, whereas benzylidenemalonate possibly underwent Michael addition. The next transformation was an intramolecular copper-catalyzed Ullmann type C(aryl)–N bond formation to give dihydroquinoline **VII**, followed by an elimination to provide a desired quinoline. Although we could not yet clarify which pathway was more favorable, we postulated that aldehydes could undergo both pathways since the carbonyl group could function as a directing group and an electrophile.

Conclusions

We have herein reported the facile syntheses of quinoline derivatives *via* copper-catalyzed domino reactions under mild and simple reaction conditions. We have demonstrated both 2-bromo- and 2-iodobenzaldehydes as our starting materials. The choice of ligand played a key role in providing the best yield of the reactions from both aldehydes. In addition, we also showcased both cyclic and acyclic enaminones. These results suggested that cyclic enaminones generally displayed higher reactivity than acyclic ones. The electronic effect of aldehydes played a major role in the reaction. The aldehydes with electron-withdrawing substituents gave low reaction yield or no reaction. On the other hand, aldehydes with electron-donating substituents, especially at the *meta*-position, gave quinolines in high yields. Nonetheless, by replacing the aldehydes with diethyl-2-(2-bromobenzylidene)malonate, the reactions with less-reactive acyclic enaminones gave high yields. We hope that our one-pot protocols will provide alternative simple methods in the syntheses of quinolines and related N-heterocycle formations.

Experimental section

General information

Commercially available reagents and reaction solvents were used without further purification. The solvents for extraction and column chromatography were distilled in their boiling point ranges prior to use. Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} (Merck) and was visualized by fluorescence quenching under UV light. Column chromatography was performed on SilicaFlash®G60 (70–230 Mesh). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a 300 MHz Bruker FTNMR Ultra Shield spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ 0.00) and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra (IR) were recorded on a PerkinElmer Spectrum GX FT-IR system in wavenumber (cm^{-1}).

Synthesis of quinoline derivatives from cyclic enaminones

General procedure A. A sealed tube was charged with 2-bromobenzaldehyde (0.60 mmol), cyclic enaminone (**2**) (0.50 mmol), CuI (0.03 mmol), DMEDA (0.15 mmol), K_2CO_3 (1.50 mmol), and MS in toluene (1.0 mL). The reaction mixture was allowed to stir at 120 °C for 15–18 h.

General procedure B. A sealed tube was charged with 2-iodobenzaldehyde (0.60 mmol), cyclic enaminone (**2**) (0.50 mmol), CuI (0.03 mmol), 1,2-diaminocyclohexane (0.15 mmol), K_2CO_3 (1.50 mmol), and MS in ACN (1.0 mL). The reaction mixture was allowed to stir at 120 °C for 15–18 h.

After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with 1 M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15 : 1 CH_2Cl_2 : EtOAc) to provide the corresponding quinoline.

3,4-Dihydroacridin-1(2*H*)-one (3a). Prepared according to general procedure **A** from 2-bromobenzaldehyde and 3-aminocyclohex-2-enone yielding **3a** in 57.14 mg (58%) as a light yellow solid. Prepared according to procedure **B** from 2-iodobenzaldehyde and 3-aminocyclohex-2-enone yielding **3a** in

46.30 mg (47%). ^{1}H NMR (300 MHz, $CDCl_3$); 8.84 (s, 1H), 8.05 (d, J = 8.1 Hz, 1H), 8.93 (d, J = 8.1 Hz, 1H), 7.81 (td, J = 8.1, 1.0 Hz), 7.55 (t, J = 8.1 Hz, 1H), 3.32 (t, J = 6.4 Hz, 2H), 2.80 (t, J = 6.4 Hz, 2H), 2.28 (qn, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 161.9, 149.6, 137.1, 132.4, 129.7, 128.5, 126.8, 126.7, 126.3, 39.1, 33.4, 21.8; IR (thin film) ν 3060, 2951, 2867, 1688, 1593, 1206, 754 cm^{-1}. Other data were identical to the literature values.[11]

3,3-Dimethyl-3,4-dihydroacridin-1(2*H*)-one (3b). Prepared according to general procedure **A** from 2-bromobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3b** in 93.50 mg (83%) as a dark brown solid. Prepared according to procedure **B** from 2-iodobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3b** in 84.49 mg (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.78 (t, J = 6.9 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 3.18 (s, 2H), 2.63 (s, 2H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 160.5, 149.7, 136.1, 131.9, 129.5, 128.3, 126.4 (126.44), 126.4 (126.39), 125.0, 52.2, 46.9, 32.5, 28.1; IR (thin film) ν 3052, 2956, 2871, 1689, 1617, 1593, 1212, 760 cm^{-1}. Other data were identical to the literature values.[4]

2,2-Dimethyl-3,4-dihydroacridin-1(2*H*)-one (3c). Prepared according to general procedure **A** from 2-bromobenzaldehyde and 3-amino-6,6-dimethylcyclohex-2-enone yielding **3c** in 76.5 mg (68%) as a dark brown gum. Prepared according to procedure **B** from 2-iodobenzaldehyde and 3-amino-6,6-dimethylcyclohex-2-enone yielding **3c** in 85.5 mg (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.78 (t, J = 8.1 Hz, 1H), 7.52 (t, 8.1 Hz, 1H), 3.33 (t, J = 6.3 Hz, 2H), 2.10 (t, J = 6.3, 2H), 1.29 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 161.0, 149.3, 137.8, 132.0, 129.4, 128.2, 126.7, 126.4, 125.1, 41.7, 34.9, 29.2, 24.1; IR (thin film) ν 3062, 2963, 2929, 1687, 1619, 1180, 753 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{15}NO$ 226.1232, found 226.1232.

7-Methoxy-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (3d). Prepared according to general procedure **A** from 2-bromo-5-methoxybenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3d** in 86.81 mg (68%) as a light yellow solid and 104.68 mg (82%) in ACN. Prepared according to procedure **B** from 2-iodobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3d** in 89.36 mg (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.44 (dd, J = 9.2, 2.4 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 3.93 (s, 3H), 3.14 (s, 2H), 2.63 (s, 2H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 158.2, 157.7, 146.2, 134.9, 129.8, 127.6, 125.2, 106.3, 55.5, 52.4, 46.8, 32.7, 28.3; IR (thin film) ν 2956, 2867, 1686, 1623, 1593, 1495, 1236 cm^{-1}. Other data were identical to the literature values.[4]

6-Methoxy-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (3e). Prepared according to general procedure **A** in ACN from 2-bromo-4-methoxybenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3e** in 82.98 mg (65%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.13 (dd, J = 9.0, 2.1 Hz, 1H), 3.92 (s, 3H), 3.09 (s, 2H), 2.57 (s, 2H), 1.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 163.0, 161.3, 151.9, 135.9, 130.7, 123.4, 121.9, 120.2, 106.4, 55.6, 52.2, 47.0, 32.7, 28.3; IR (thin film) ν 2956, 2870, 1685, 1619, 1594, 1498, 1207 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{17}H_{20}NO_2$ 256.1388 found 256.1388.

3,4-Dimethoxy-3,3-dimethyl-3,4-dihydro-2*H*-acridin-1-one (3f). Prepared according to procedure **B** from 2-iodo-4,5-dimethoxybenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3f** in 79.90 mg (56%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.34 (s, 1H), 7.10 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 2.58 (s, 2H), 1.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 158.9, 154.8, 149.8, 147.6, 134.1, 123.7, 122.4, 107.1, 106.3, 56.2, 56.0, 52.3, 46.8, 32.8, 28.3; IR (thin film) ν 3014, 2957, 1682, 1621, 1590, 1504, 1257 cm^{-1}. Other data were identical to the literature values.[12]

7-Bromo-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (3g). Prepared according to general procedure **A** in ACN from 2,5-dibromobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3g** in 82.13 mg (54%) as a light yellow solid. Prepared according to procedure **B** from 5-bromo-2-iodobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3g** in 106.46 mg (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.07 (d, J = 1.8 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.84 (dd, J = 9.0, 1.8 Hz, 1H), 3.17 (s, 2H), 3.34 (s, 2H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 161.2, 148.5, 135.5, 135.4, 131.4, 130.3, 127.9, 125.8, 120.4, 52.4, 47.1, 32.7, 28.4; IR (thin film) ν 2958, 2870, 1690, 1590, 1479, 1372, 1209 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{14}BrNO$ 304.0337, found 304.0337.

6-Bromo-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one (3h). Prepared according to general procedure **A** in ACN from 2,4-dibromobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3h** in 85.17 mg (56%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.22 (s, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.62 (dd, J = 8.7, 1.5 Hz, 1H), 3.17 (s, 2H), 2.65 (s, 2H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 161.9, 150.2, 136.2, 131.0, 130.7, 130.3, 126.7, 125.4, 125.2, 52.3, 47.0, 32.6, 28.3; IR (thin film) ν 2962, 2872, 1684, 1608, 1486, 1069, 708 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{14}BrNO$ 304.0337 found 304.0335.

3,3-Dimethyl-7-nitro-3,4-dihydroacridin-1(2*H*)-one (3i). Prepared according to general procedure **A** in ACN from 2-bromo-5-nitro-benzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3i** in 77.03 mg (57%) as an orange solid. Prepared according to procedure **B** from 2-iodo-5-nitro-benzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3i** in 68.92 mg (51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.88 (d, J = 2.7 Hz, 1H), 8.53 (dd, J = 9.3, 2.7 Hz, 1H), 8.17 (d, J = 9.3 Hz, 1H), 3.24 (s, 2H), 2.70 (s, 2H), 1.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 164.7, 151.6, 145.5, 138.0, 130.5, 126.6, 126.2, 125.5, 125.2, 52.2, 47.3, 32.7, 28.3; IR (thin film) ν 3087, 2959, 2872, 1699, 1603, 1567, 735 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{14}N_2O_3$ 271.1082, found 271.1082.

3,3-Dimethyl-6-nitro-3,4-dihydroacridin-1(2*H*)-one (3j). Prepared according to general procedure **A** from 2-bromo-4-nitrobenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3j** in 68.92 mg (51%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90–8.88 (m, 2H), 8.30 (dd, J = 8.9, 1.9 Hz,

1H), 8.13 (d, J = 8.9 Hz, 1H), 3.27 (s, 2H), 2.73 (s, 2H), 1.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 163.1, 149.3, 148.7, 135.8, 131.2, 129.6, 127.0, 124.5, 119.8, 52.2, 47.0, 32.5, 28.2; IR (thin film) 2965, 1695, 1596, 1530, 1348, 1182, 836 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{15}H_{14}N_2O_3$ 271.1082, found 271.1082.

6,6-Dimethyl-8-oxo-5,6,7,8-tetrahydroacridine-2-carbaldehyde (3k). Prepared according to procedure **B** from 4-iodoisophthaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3k** in 93.72 mg (74%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.86 (s, 1H), 8.51 (s, 1H), 8.05–8.04 (m, 2H), 3.00 (s, 2H). 2.70 (s, 2H), 1.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 191.8, 162.1, 149.7, 138.7, 136.2, 134.2, 130.8, 130.2, 126.8, 123.3, 52.4, 47.1, 32.7, 28.4; IR (thin film) ν 2957, 2861, 1697, 1596, 1371, 1241, 769 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{15}NO_2$ 254.1181, found 254.1181.

3,3,7-Trimethyl-3,4-dihydroacridin-1(2*H*)-one (3l). Prepared according to general procedure **A** from 2-bromo-3-methylbenzaldehyde and 3-amino-5,5-dimethylcyclohex-2-enone yielding **3l** in 72.99 mg (61%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.86–7.83 (m, 2H), 7.43 (d, J = 1.1 Hz, 1H), 3.02 (s, 2H), 2.66 (s, 2H), 2.60 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 160.8, 150.1, 143.2, 136.2, 129.3, 129.0, 127.5, 124.8, 124.6, 52.4, 47.1, 32.7, 28.3, 22.2; IR (thin film) ν 2956, 2861, 1687, 1626, 1594, 1498, 1372 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{17}NO$ 240.1388, found 240.1389.

Synthesis of quinoline derivatives from acyclic enaminones

General procedure C. A sealed tube was charged with 2-halobenzaldehyde (0.60 mmol), acyclic enaminone (**5**) (0.50 mmol), CuI (0.03 mmol), 1,2-diaminocyclohexane (0.15 mmol), Na_2SO_4 (500 mg) and K_2CO_3 (1.50 mmol) in CH_3CN (1.0 mL). The reaction mixture was allowed to stir at 120 °C for 15–18 h.

General procedure D. A sealed tube was charged with 2-(2-bromobenzylidene)malonate (0.60 mmol), acyclic enaminone (**5**) (0.50 mmol), CuI (0.03 mmol), 1,2-diaminocyclohexane (0.15 mmol), and K_2CO_3 (1.50 mmol) in CH_3CN (1.0 mL). The reaction mixture was allowed to stir at 120 °C for 15–18 h.

After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with 1 M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15 : 1 CH_2Cl_2 : EtOAc) to provide the corresponding quinoline in 54.4 mg (55% yield) as a light yellow solid.

1-(2-Methylquinolin-3-yl)ethanone (6a). Prepared according to general procedure **C** from (*Z*)-4-aminopent-3-en-2-one and 2-bromobenzaldehyde yielding **6a** in 39.8 mg (43%), and 2-iodobenzaldehyde yielding **6a** in 50.94 mg (55%) as a light brown solid. Prepared according to general procedure **D** from (*Z*)-4-aminopent-3-en-2-one and diethyl 2-(2-bromobenzylidene)malonate (**7**) yielding **6a** in 90.76 mg (98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.77 (ddd, J = 9.3, 6.9, 1.5 Hz, 1H), 7.53 (ddd, J = 9.3, 6.9, 1.5 Hz, 1H), 2.91 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 157.5, 148.2, 138.1, 131.7, 131.1, 128.5, 128.3, 126.6, 125.6, 29.2, 25.6; IR (thin film) ν 3058, 2990, 2967, 1682, 1620, 1562, 1420 cm^{-1}. Other data were identical to the literature values.[4]

1-(6-Methoxy-2-methylquinolin-3-yl)ethanone (6c). Prepared according to general procedure **C** from (*Z*)-4-aminopent-3-en-2-one and 2-bromo-5-methoxylbenzaldehyde yielding **6c** in 78.56 mg (73%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.41 (dd, J = 9.0, 2.6 Hz, 1H), 7.08 (d, J = 2.6 Hz, 1H), 3.92 (s, 3H), 2.86 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 157.6, 154.6, 144.0, 136.8, 131.0, 129.6, 126.4, 124.2, 105.4, 55.4, 29.0, 25.0; IR (thin film) ν 2997, 1683, 1595, 1493, 1227, 1030, 834. HRMS (ESI) $[M + H]^+$ calcd for $C_{13}H_{13}NO_2$ 216.1025 found 216.1025.

1-(7-Methoxy-2-methylquinolin-3-yl)ethanone (6d). Prepared according to general procedure **C** from (*Z*)-4-aminopent-3-en-2-one and 2-bromo-4-methoxylbenzaldehyde yielding **6d** in 95.7 mg (89%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.28 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 8.9, 2.2 Hz, 1H), 3.88 (s, 3H), 2.82 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 162.8, 158.4, 150.3, 138.3, 129.5, 128.7, 120.6, 120.0, 106.7, 55.7, 29.0, 25.8; IR (thin film) ν 2965, 1675, 1623, 1612, 1488, 1210, 1193 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{13}H_{13}NO_2$ 216.1025 found 216.1025.

1-(2,7-Dimethylquinolin-3-yl)ethanone (6e). Prepared according to general procedure **C** from (*Z*)-4-aminopent-3-en-2-one and 2-bromo-4-methylbenzaldehyde yielding **6e** in 83.7 mg (84%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.83 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 2.91 (s, 3H), 2.71 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 157.7, 148.5, 142.6, 138.1, 130.3, 128.9, 128.0, 127.6, 123.6, 29.1, 25.7, 22.1; IR (thin film) ν 3031, 1682, 1666, 1427, 1240, 1129, 778 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{13}H_{13}NO$ 200.1075 found 200.1075.

Methyl-2-methylquinoline-3-carboxylate (6j). Prepared according to general procedure **C** from (*Z*)-methyl-3-aminobut-2-enoate and 2-bromobenzaldehyde yielding **6j** in 51.2 mg (52%), and 2-iodobenzaldehyde yielding **6j** in 42.26 mg (42%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.77 (td, J = 8.1, 1.2 Hz, 1H), 7.53 (td, J = 8.1, 1.2 Hz), 3.98 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 158.5, 148.6, 140.0, 131.7, 128.5, 128.4, 126.5, 125.7, 123.5, 52.3, 25.6; IR (thin film) ν 3063, 2999, 2952, 1727, 1622, 1201, 789 cm^{-1}. Other data were identical to the literature values.[4]

Phenyl(2-phenylquinolin-3-yl)methanone (6k). Prepared according to general procedure **C** from (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one and 2-iodobenzaldehyde yielding **6k** in 52.5 mg (34%) as a light yellow solid. Prepared according to general procedure **D** from (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one and diethyl 2-(2-bromobenzylidene)malonate yielding **6k** in 99.00 mg (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.83 (ddd, J = 8.4, 7.5, 1.5 Hz, 1H), 7.73–7.70 (m, 2H), 7.64–7.58 (m, 3H), 7.47

(tt, J = 7.5, 1.0 Hz, 1H), 7.35–7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 157.5, 148.4, 139.7, 137.6, 137.1, 133.3, 132.9, 131.2, 130.0, 129.7, 129.3, 128.8, 128.4, 128.1, 127.3, 125.8; IR (thin film) ν 3059, 3020, 1662, 1595, 1270, 1234, 770 cm^{-1}. Other data were identical to the literature values.[11]

2-Isobutylquinolin-3-yl(phenyl)methanone (6l). Prepared according to general procedure **C** from (*Z*)-3-amino-5-methyl-1-phenylhex-2-en-1-one and 2-bromobenzaldehyde yielding **6l** in 41.9 mg (29%), and 2-iodobenzaldehyde yielding **6l** in 47.75 (33%) as a light yellow oil. Prepared according to general procedure **D** from (*Z*)-3-amino-5-methyl-1-phenylhex-2-en-1-one and diethyl 2-(2-bromobenzylidene)malonate yielding **6l** in 94.05 mg (65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 8.8 Hz, 1H), 8.08 (s, 1H), 7.86–7.76 (m, 4H), 7.64 (t, J = 7.2 Hz, 1H), 7.57–7.47 (m, 3H), 2.97 (s, 3H), 2.96 (d, J = 7.3 Hz, 2H), 2.22–2.12 (m, 1H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 160.0, 148.0, 137.5, 136.7, 133.7, 132.6, 130.9, 130.2, 129.0, 128.7, 128.0, 126.7, 125.2, 45.4, 29.3, 22.5; IR (thin film) ν 3061, 2957, 1667, 1619, 1595, 1450, 1262 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{20}H_{19}NO$ 290.1545, found 290.1546.

(4-Methoxyphenyl)(2-(4-methoxyphenyl)quinolin-3-yl)methanone (6m). Prepared according to general procedure **D** from (*Z*)-3-amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one and diethyl 2-(2-bromobenzylidene)malonate yielding **6m** in 136.68 mg (74%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.20 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.80 (ddd, J = 8.5, 7.0, 1.2 Hz, 1H), 7.76–7.72 (m, 2H), 7.65–7.56 (m, 3H), 6.85–6.81 (m, 4H), 3.83 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 163.6, 160.1, 156.6, 148.1, 136.9, 132.9, 132.3, 132.1, 130.7, 129.8, 129.3, 127.8, 126.8, 125.5, 113.8, 113.6, 55.3, 55.1; IR (thin film) ν 3008, 2838, 1660, 1599, 1253, 1024, 758 cm^{-1}. HRMS (ESI) $[M + H]^+$ calcd for $C_{24}H_{19}NO_3$ 370.1443 found 370.1440.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the Development and Promotion of Science and Technology Talents Project (DPST) (grant no. 012/2558) for support of this research. B. K. also is a graduate fellow of DPST and partly supported by The Center of Excellence for Innovation in Chemistry (PERCH-CIC). We also thank Dr Jessada Mahatthananchai for helpful discussions.

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^{1}H and ^{13}C NMR Spectra of Aldehyde Derivatives

Figure 4 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **83h** in $CDCl_3$

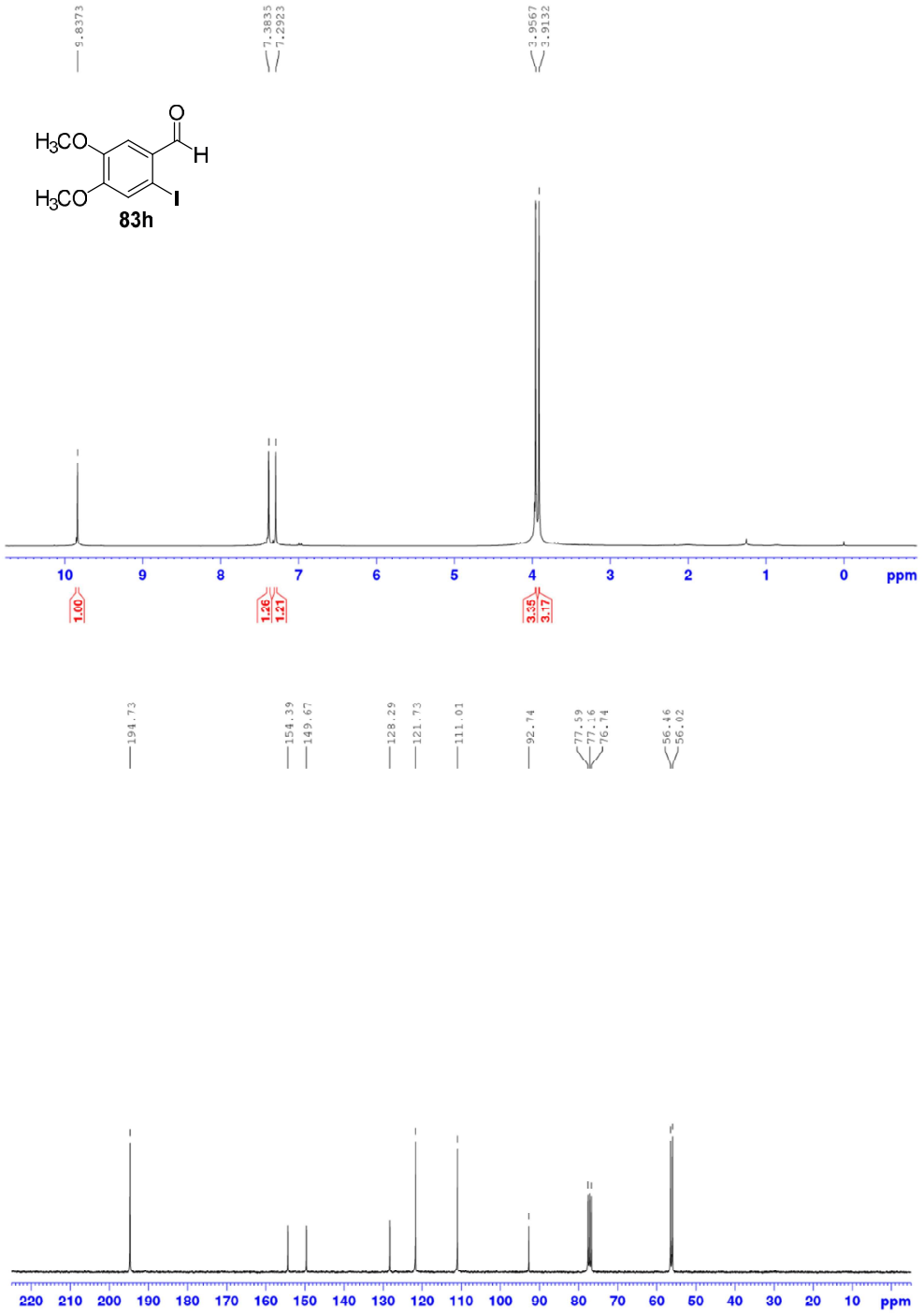


Figure 5 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **83g** in $CDCl_3$

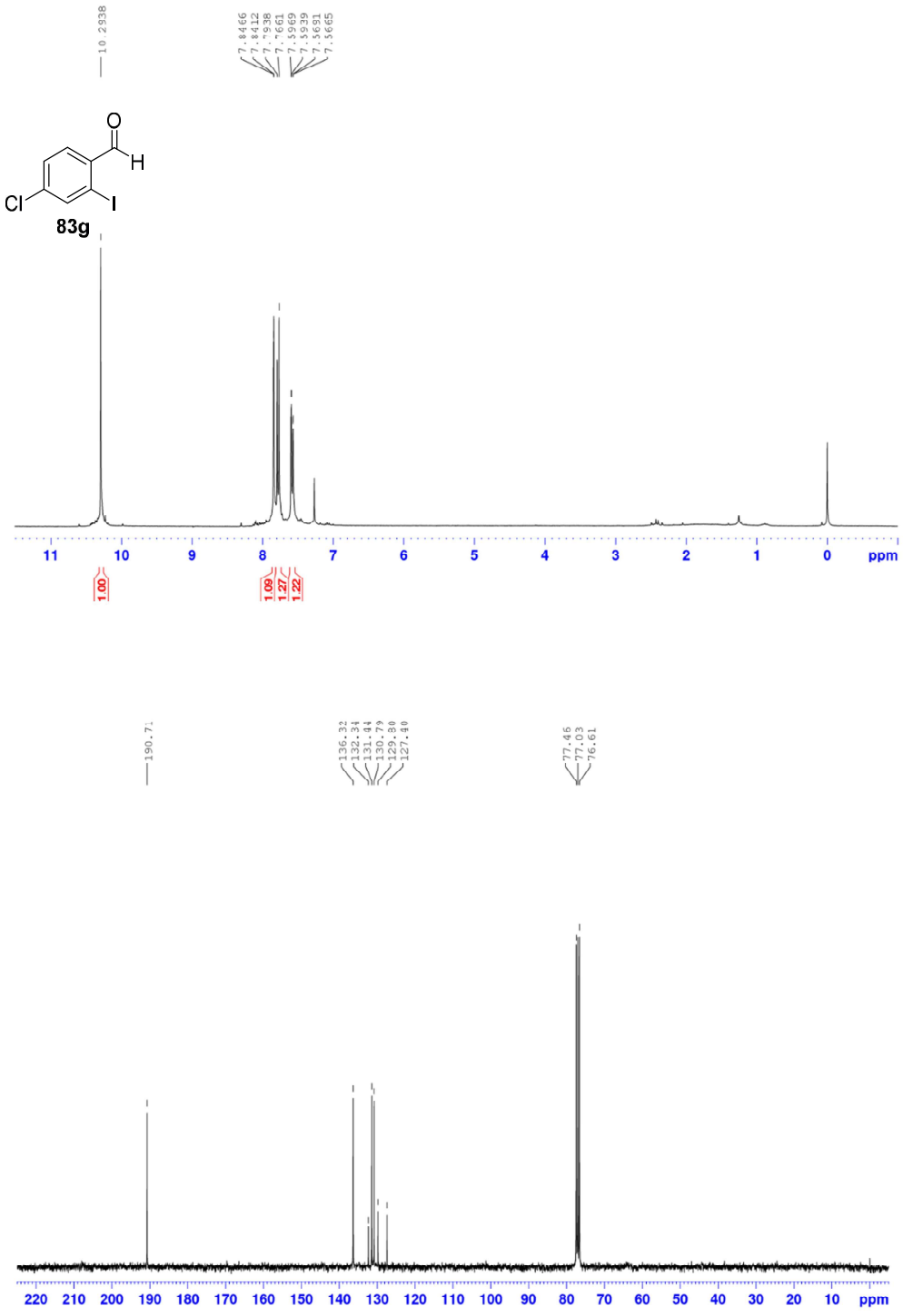


Figure 6 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **83b** in $CDCl_3$

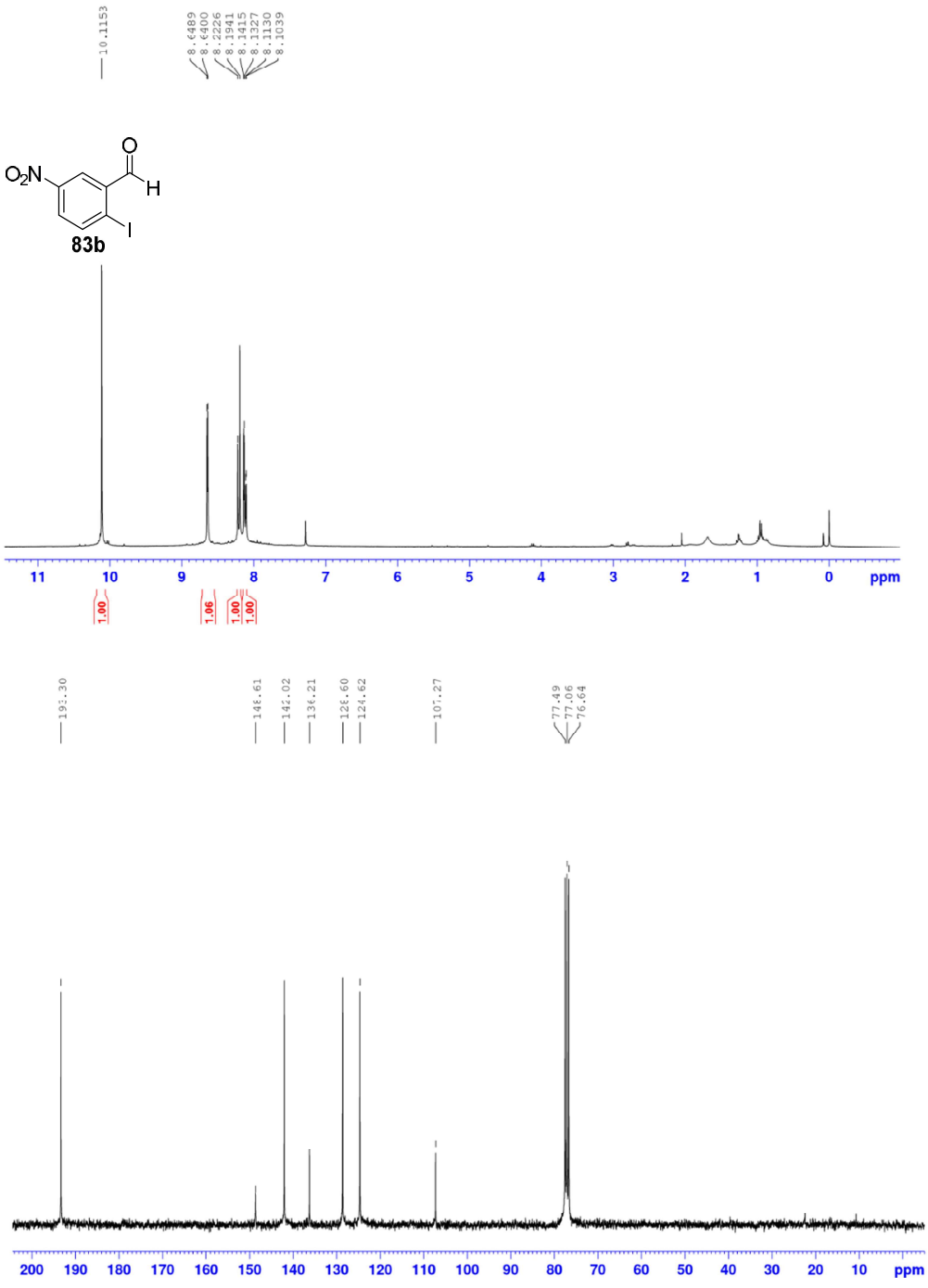
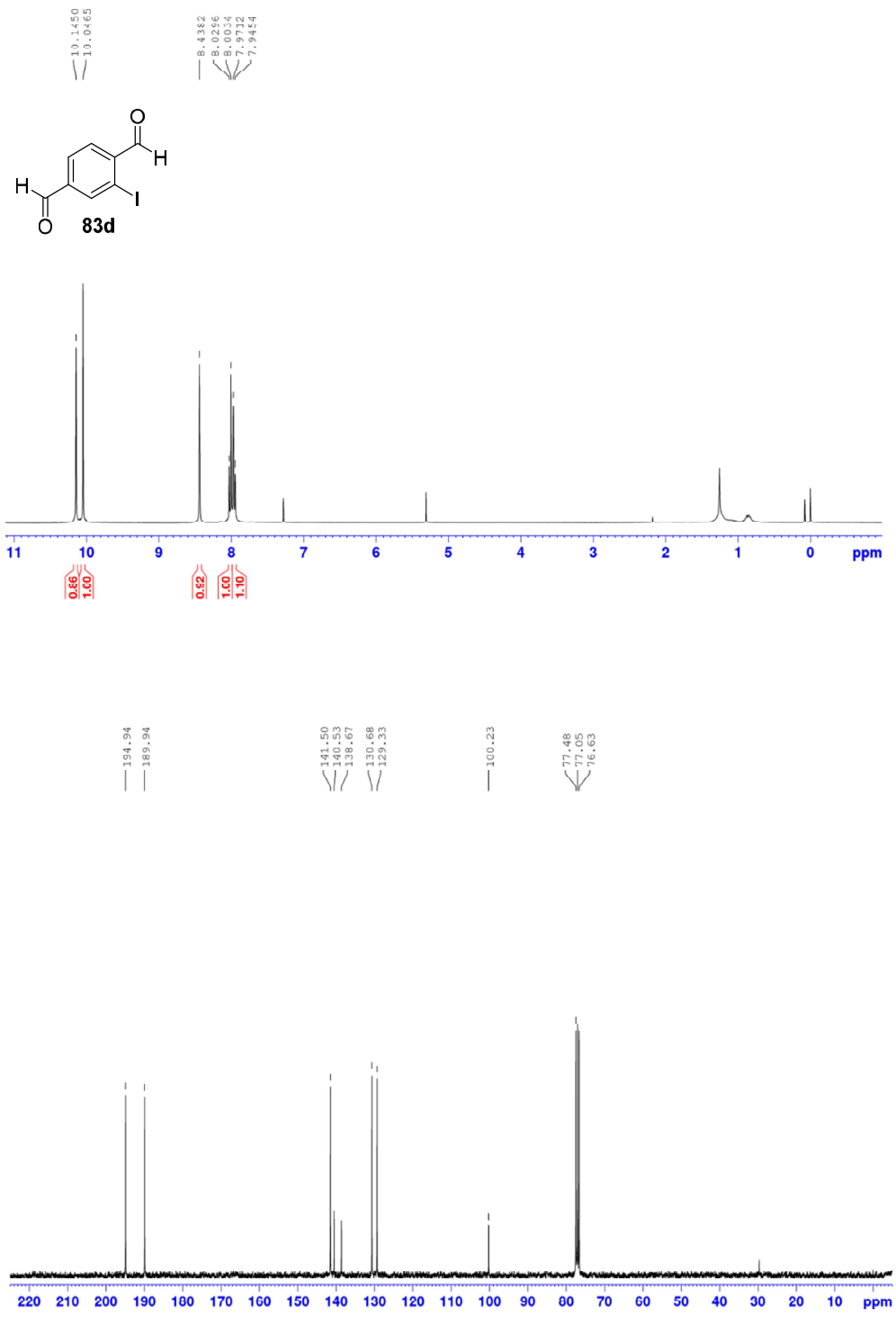


Figure 7 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **83d** in $CDCl_3$



^{1}H and ^{13}C NMR Spectra of Enaminone Derivatives

Figure 8 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **84a** in DMSO-*d6*

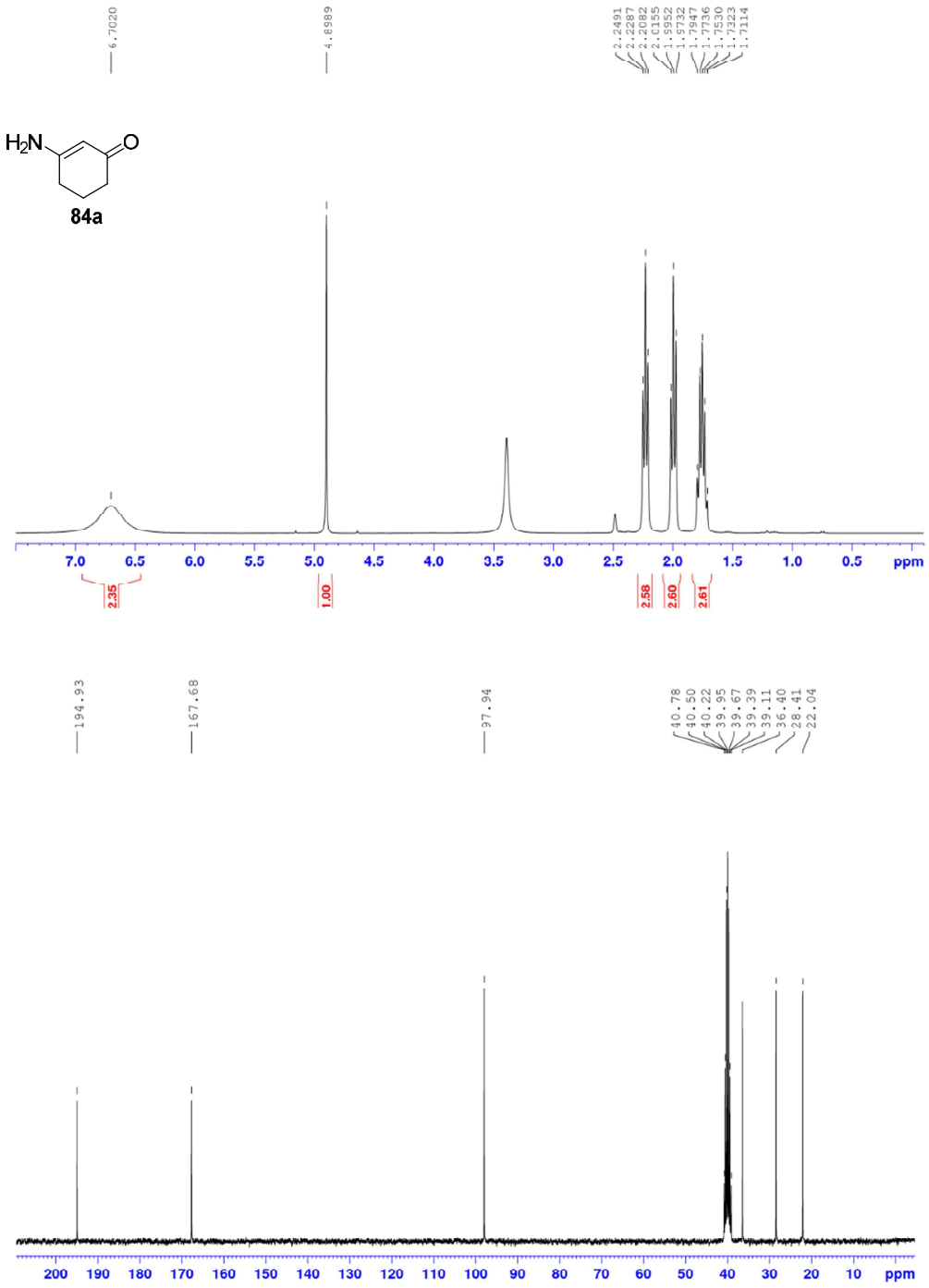


Figure 9 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **84d** in DMSO-*d6*

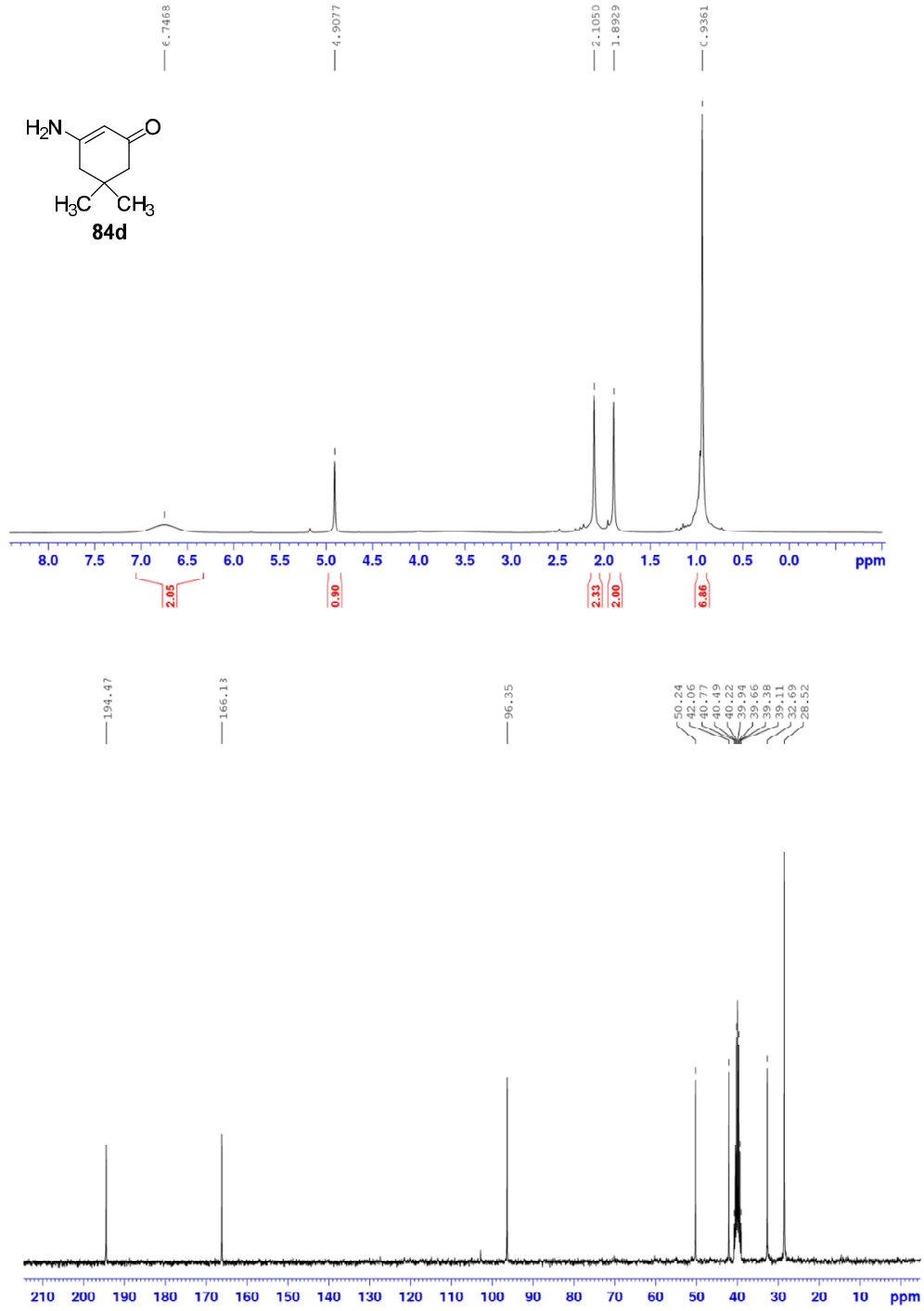


Figure 10 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **84e** in DMSO-*d6*

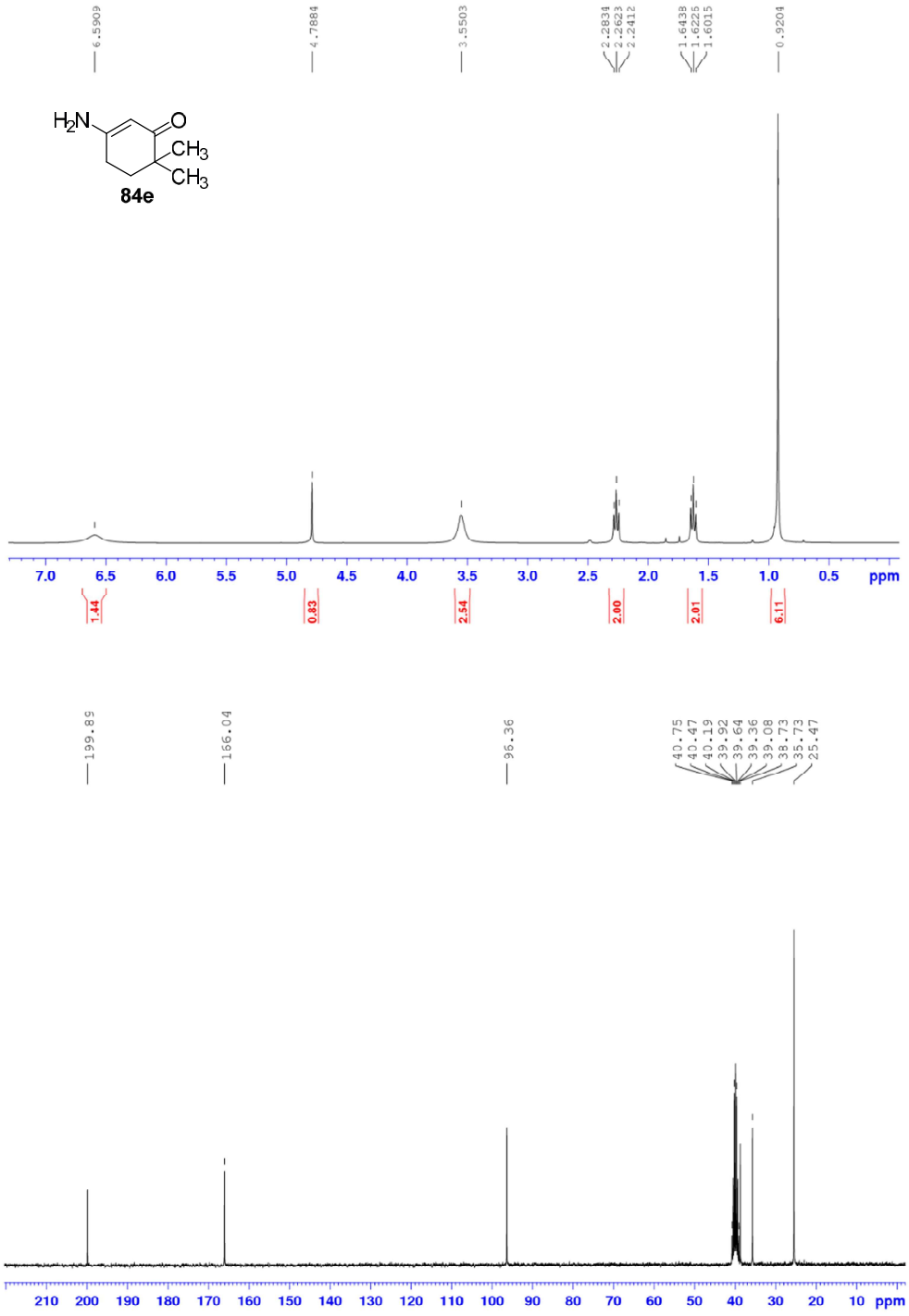


Figure 11 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **92b** in $CDCl_3$

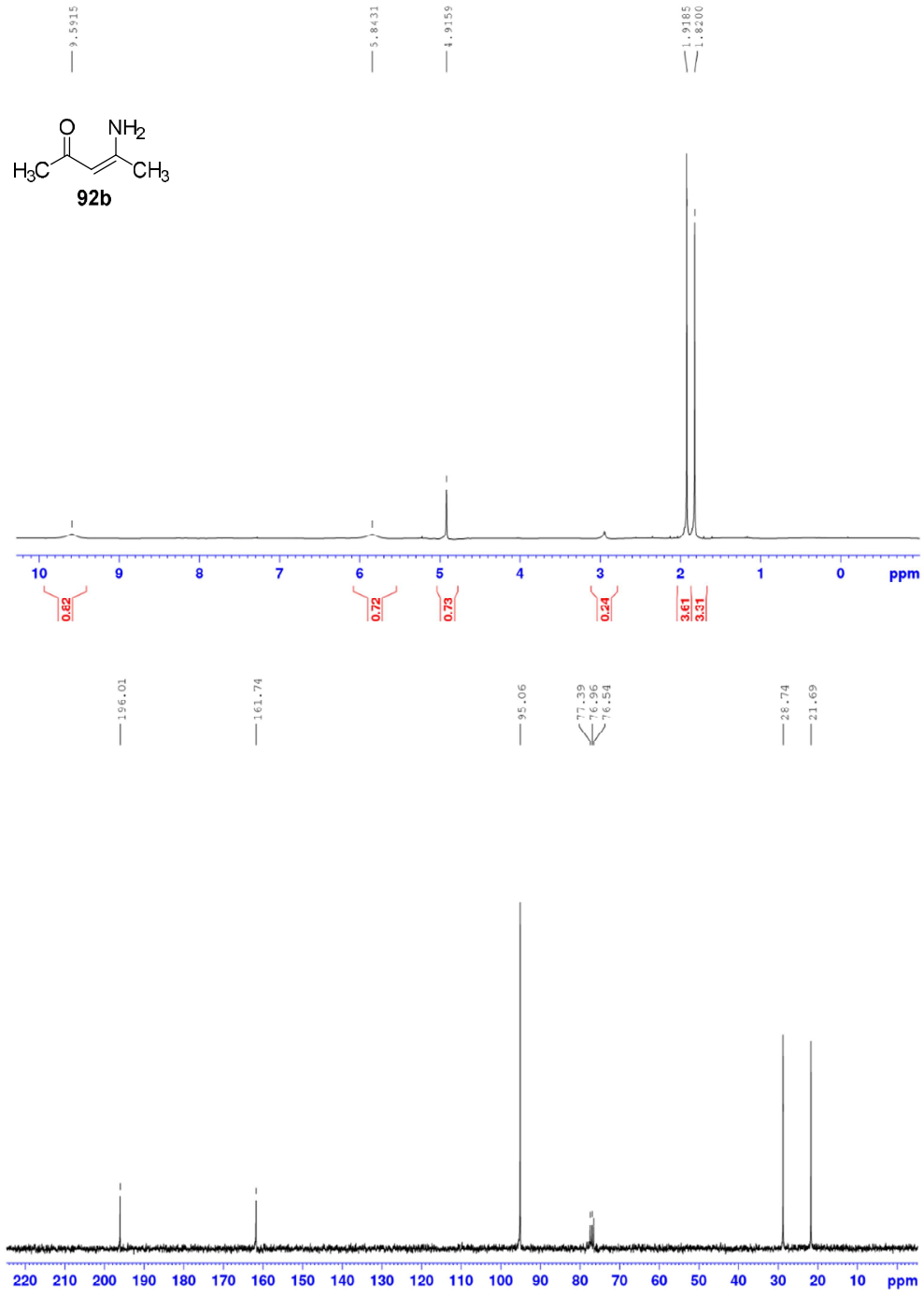


Figure 12 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **92e** in $CDCl_3$

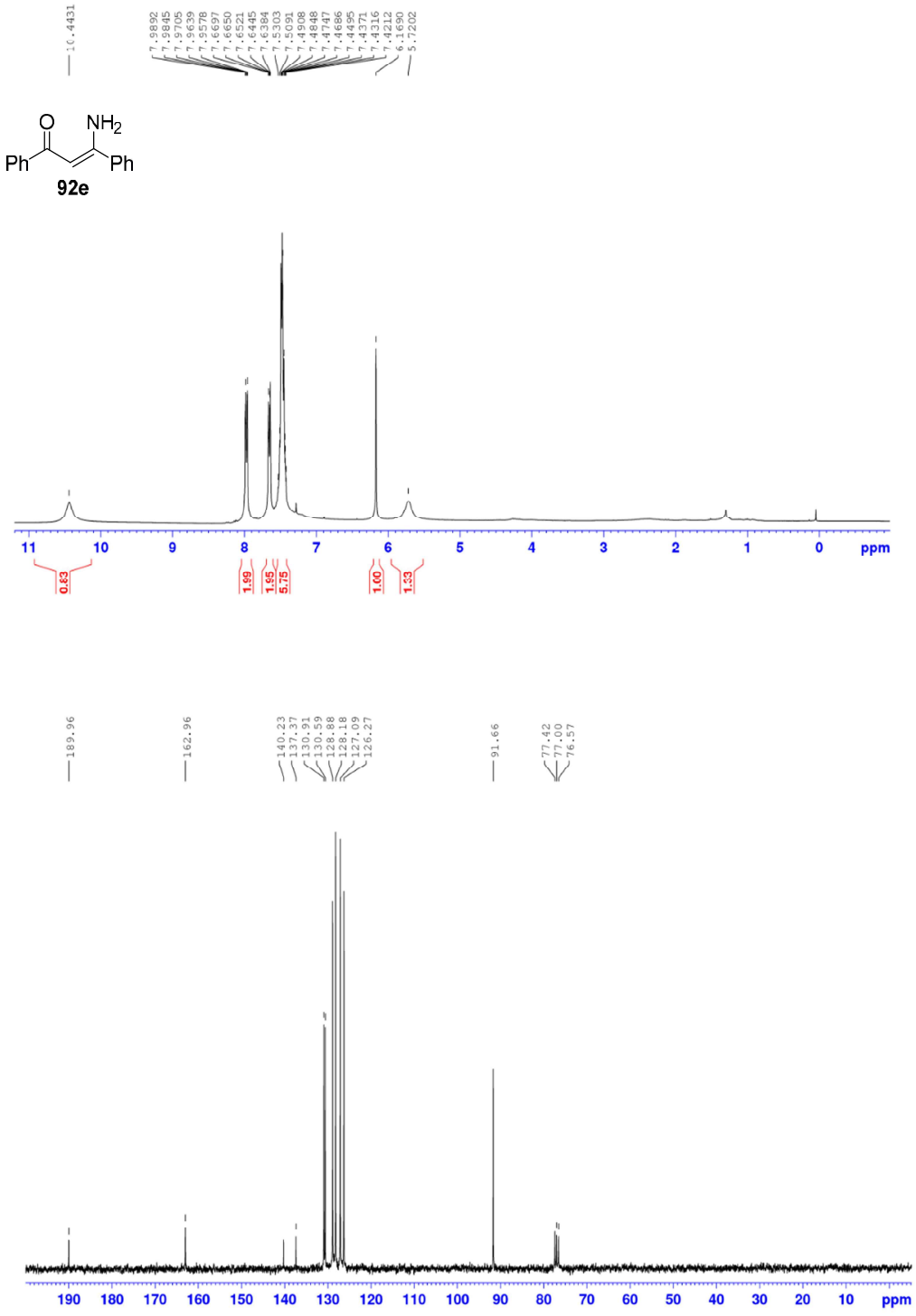


Figure 13 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **92d** in $CDCl_3$

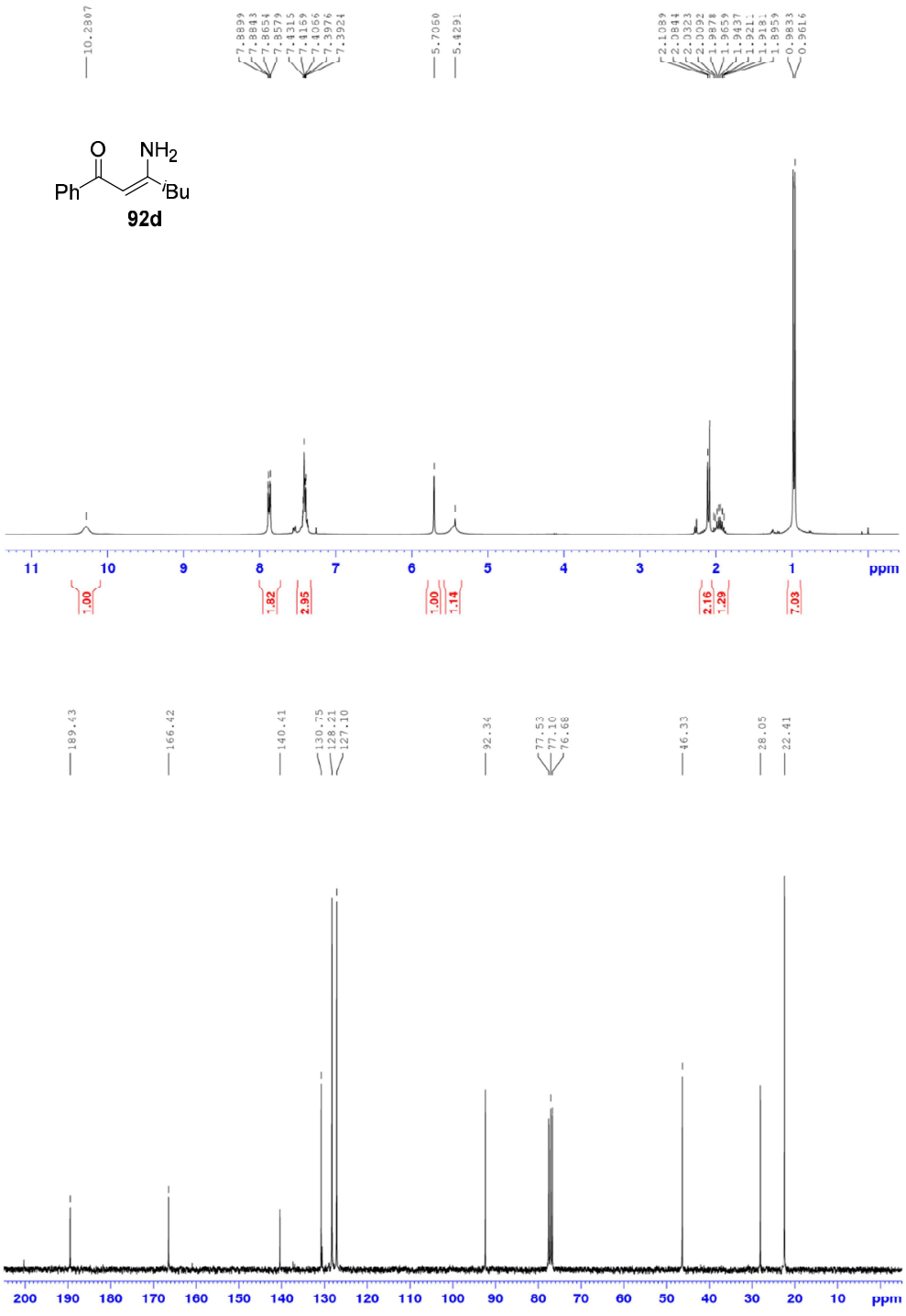


Figure 14 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **92a** in $CDCl_3$

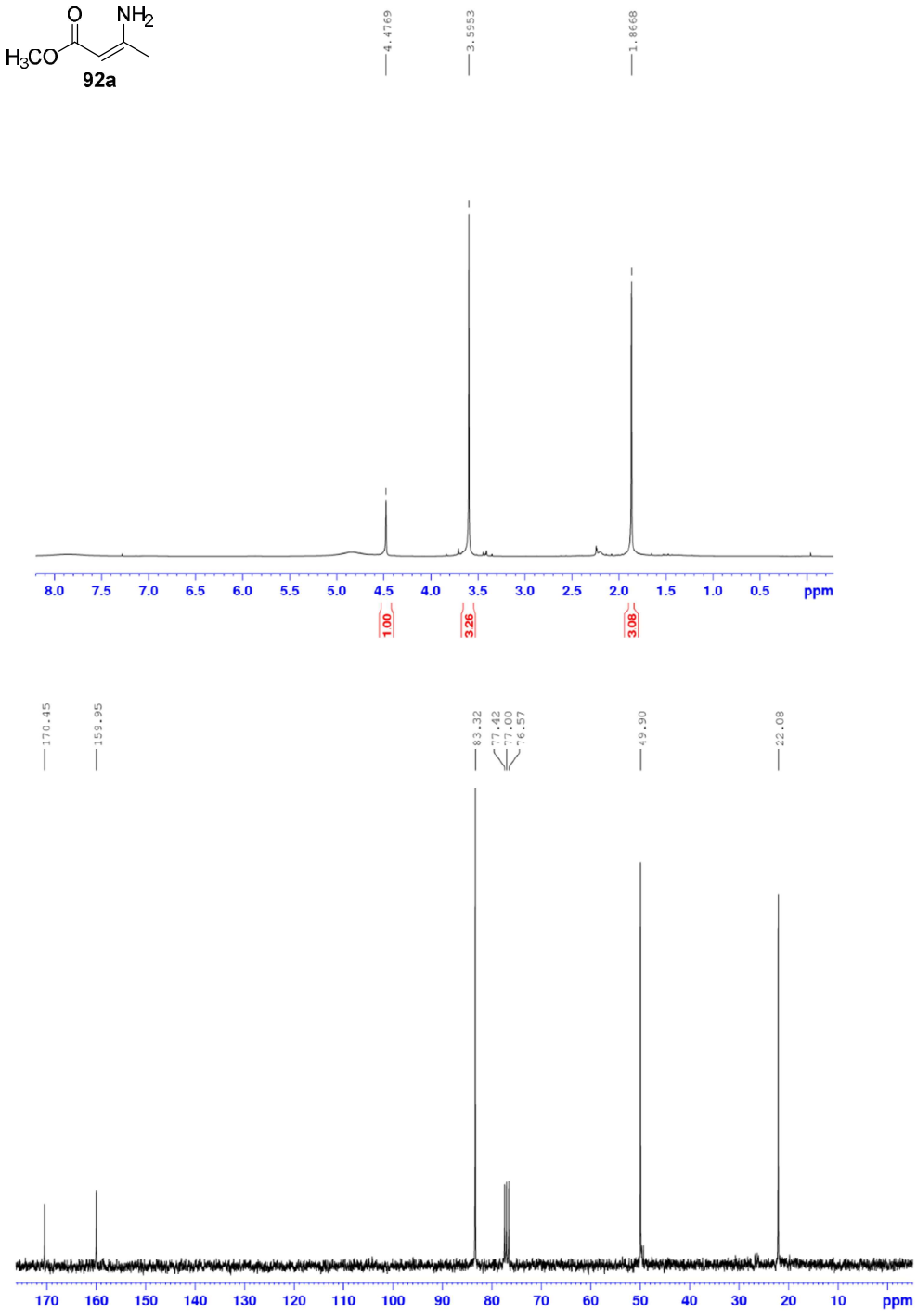
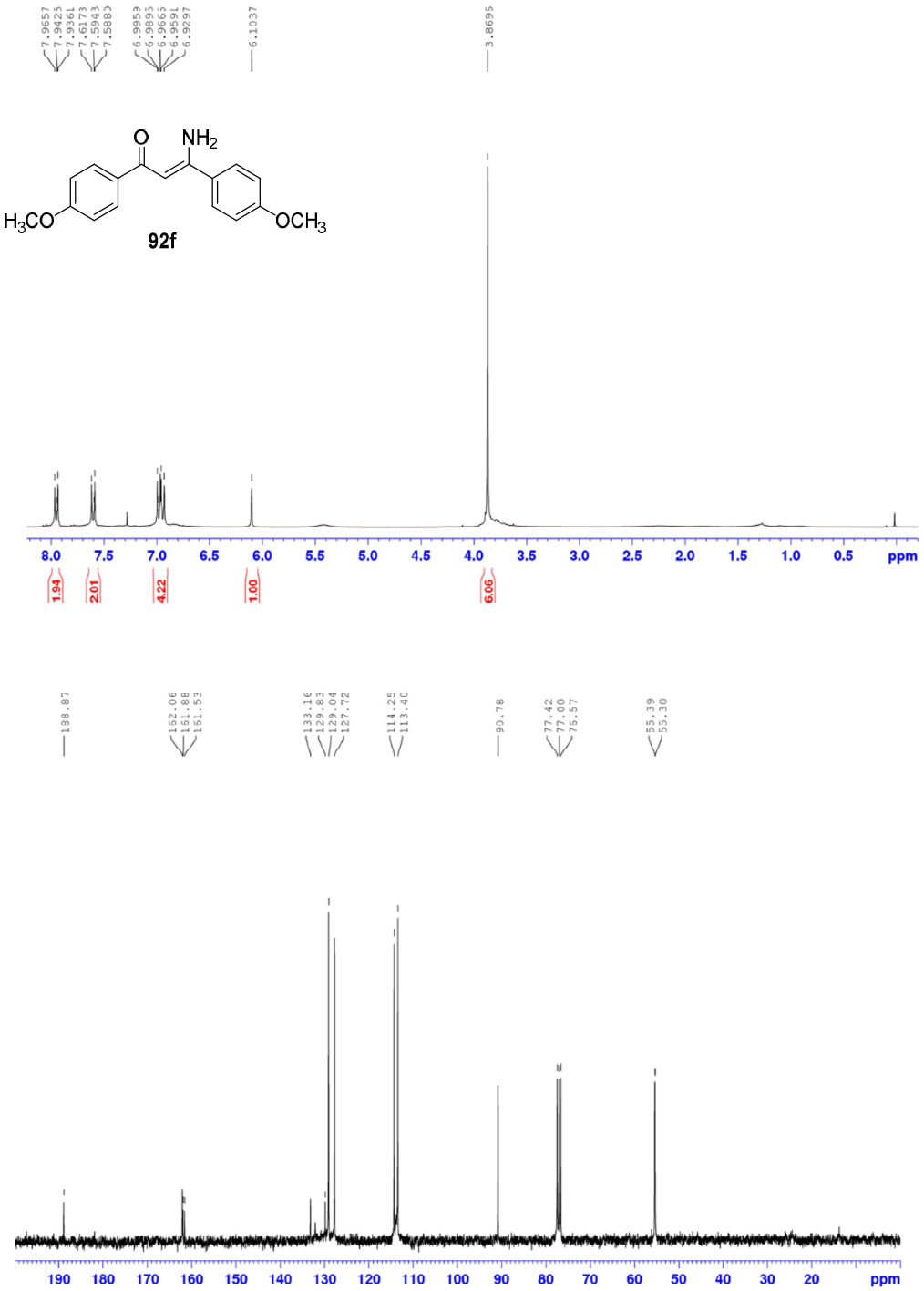


Figure 15 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **92f** in $CDCl_3$



^{1}H and ^{13}C NMR Spectra of Quinoline Derivatives

Figure 16 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85a** in $CDCl_3$

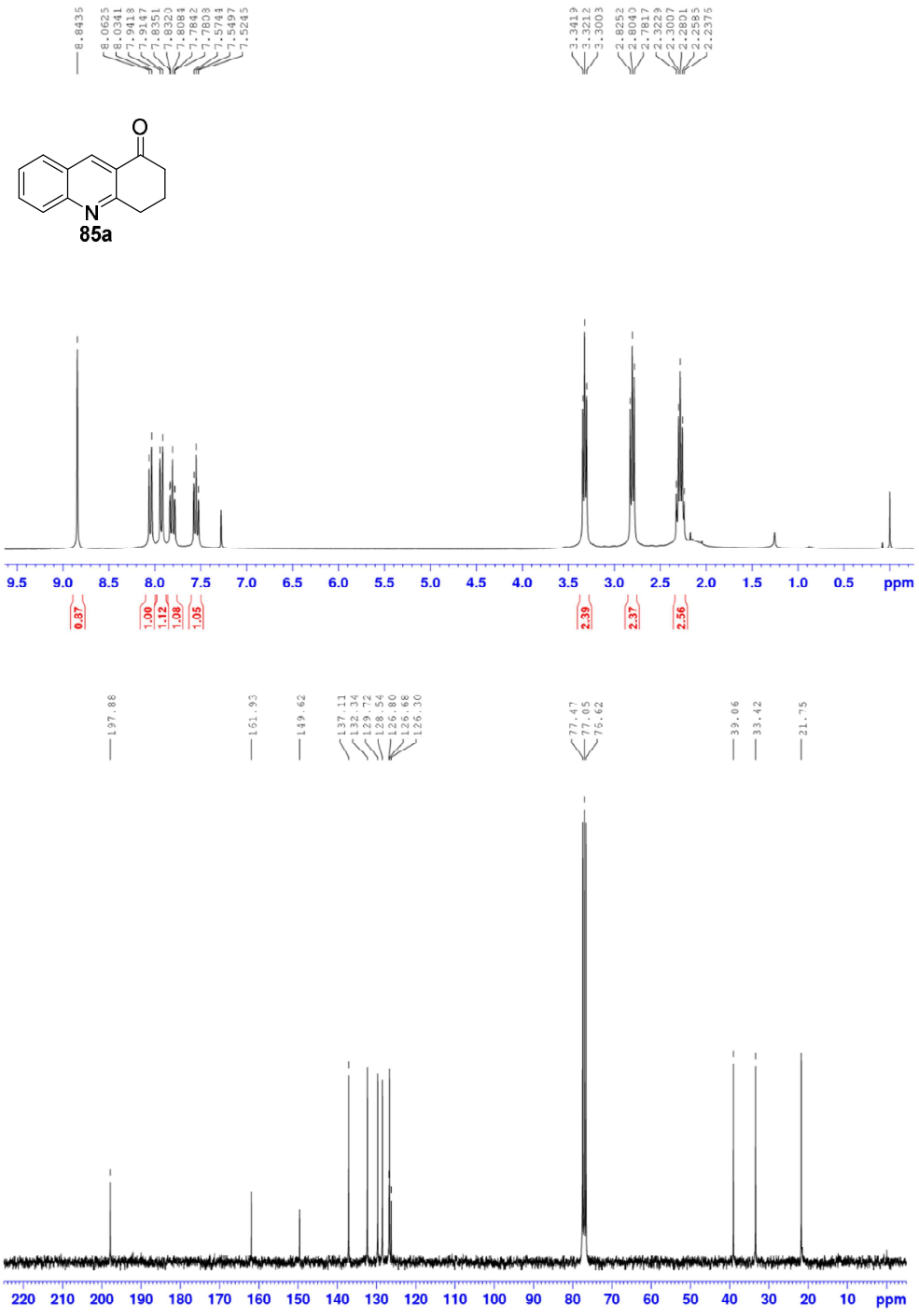


Figure 17 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85d** in $CDCl_3$

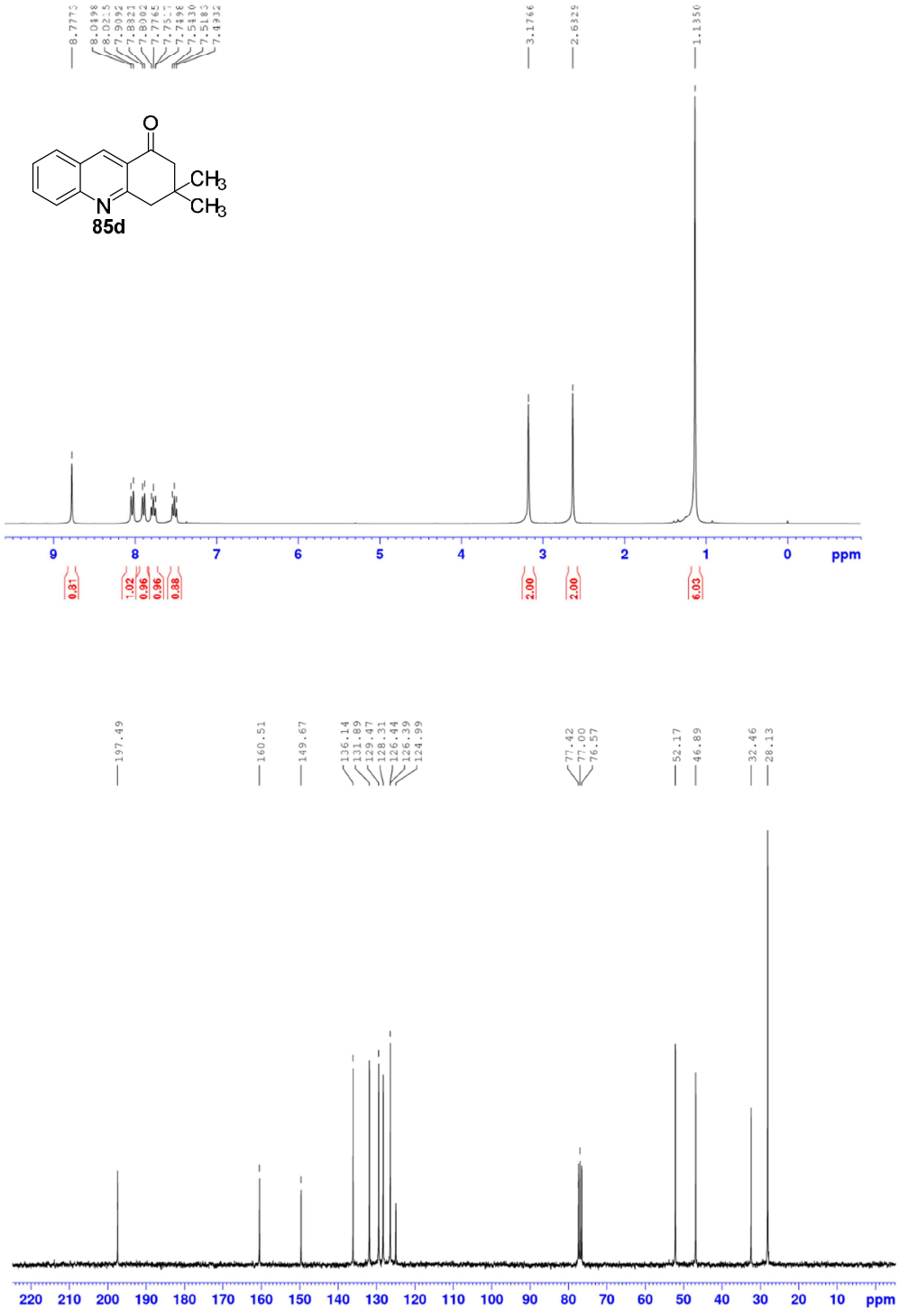


Figure 18 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85e** in $CDCl_3$

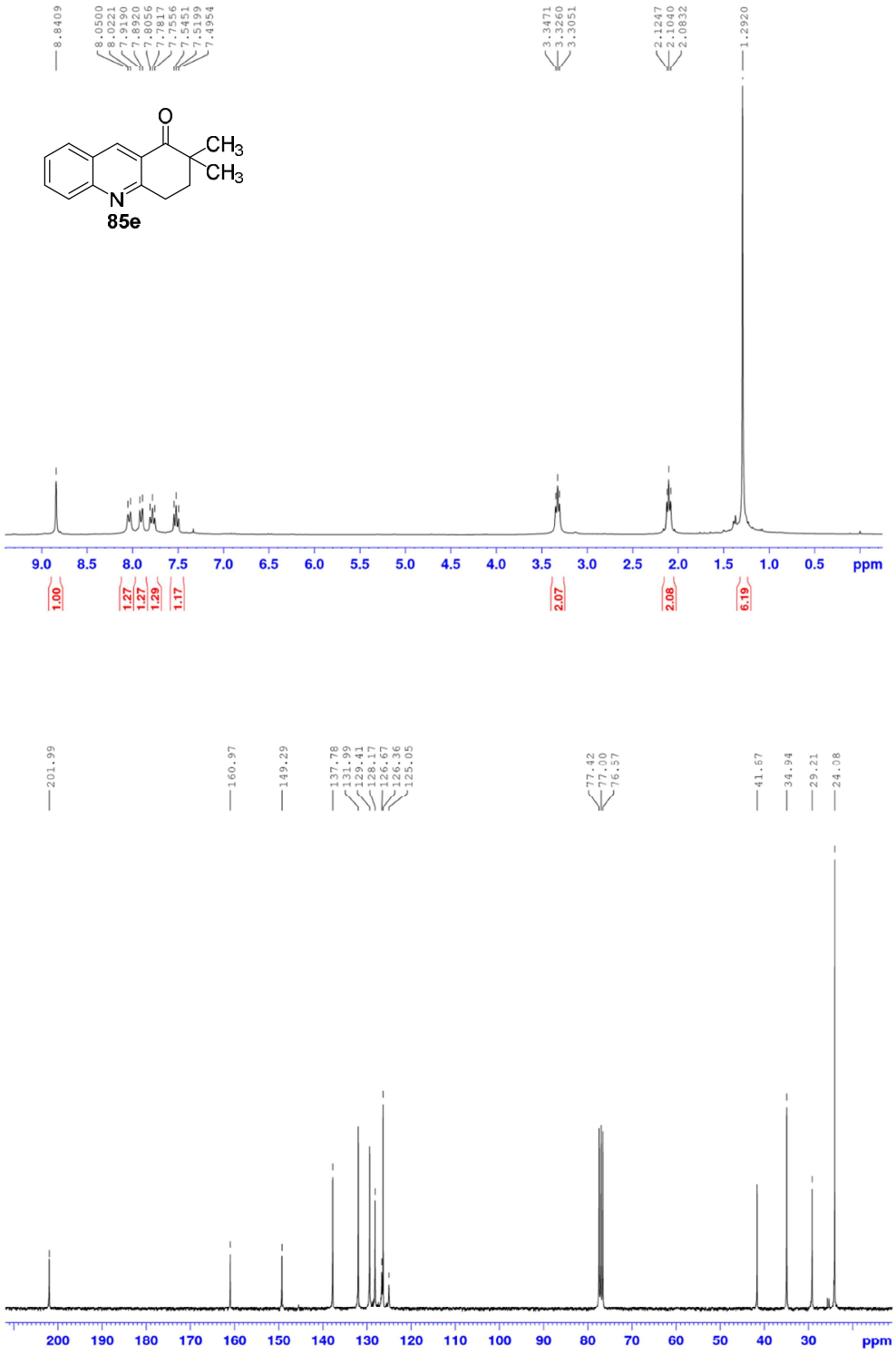


Figure 19 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85g** in $CDCl_3$

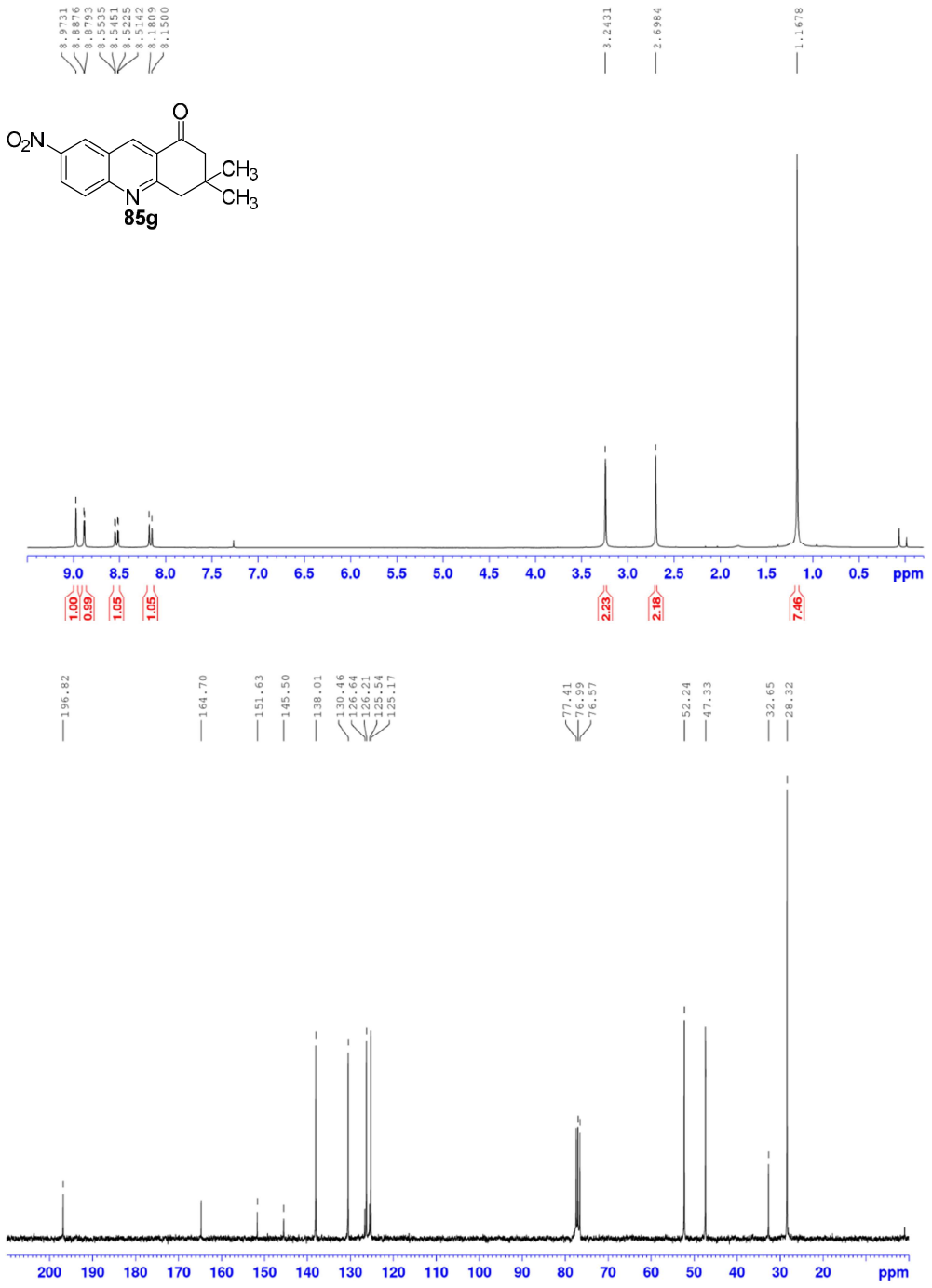


Figure 20 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85h** in $CDCl_3$

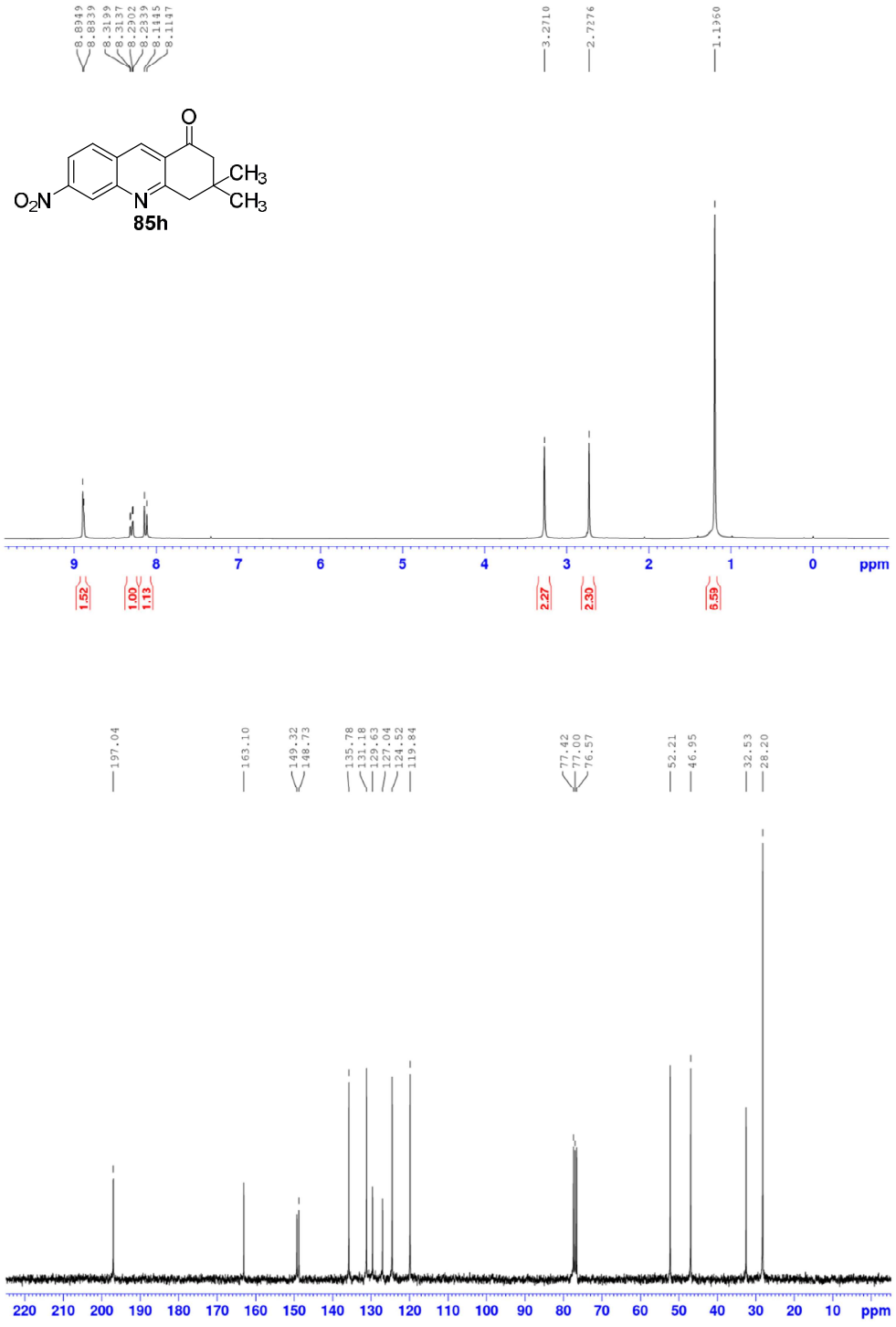


Figure 21 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85i** in $CDCl_3$

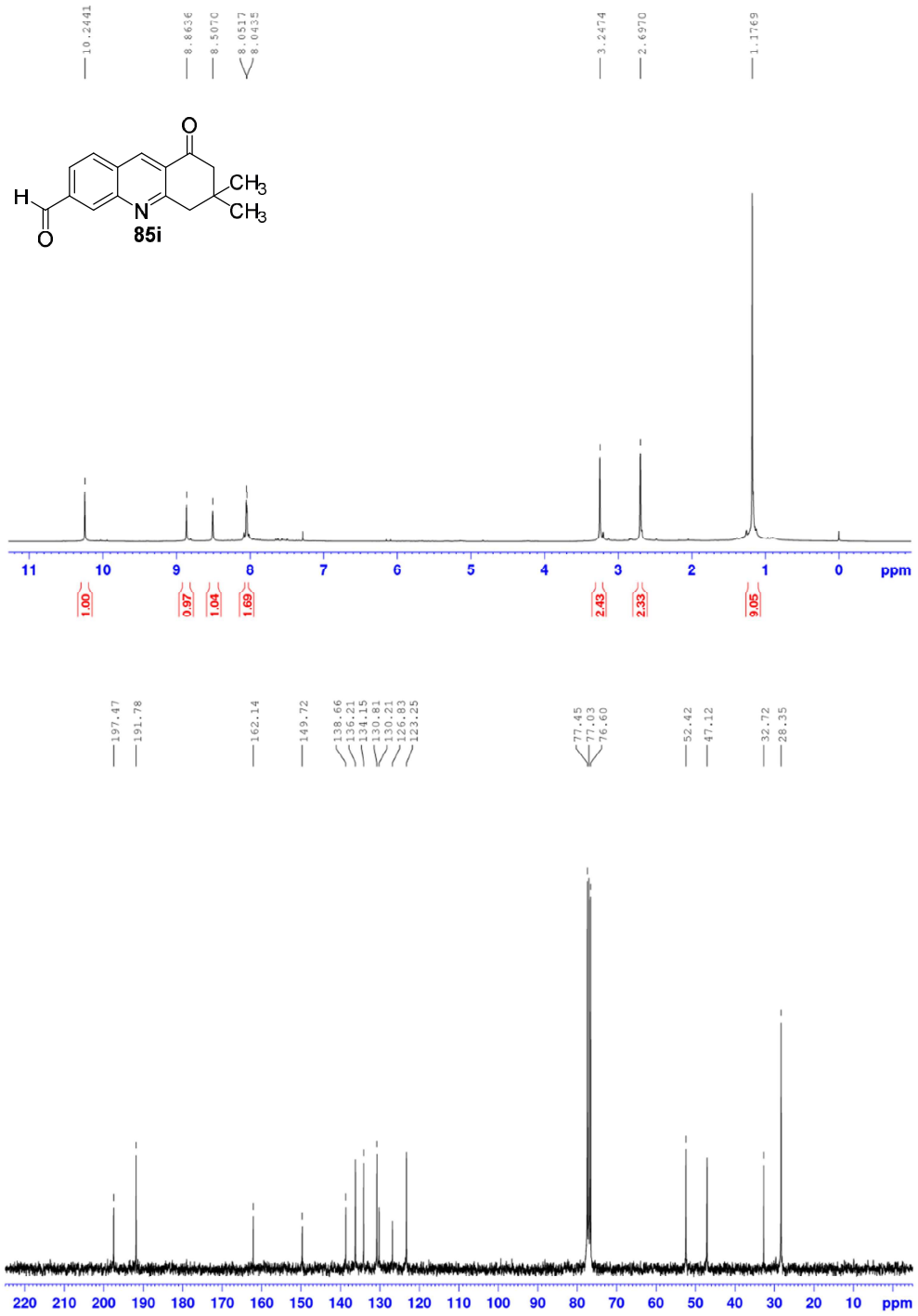


Figure 22 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85k** in $CDCl_3$

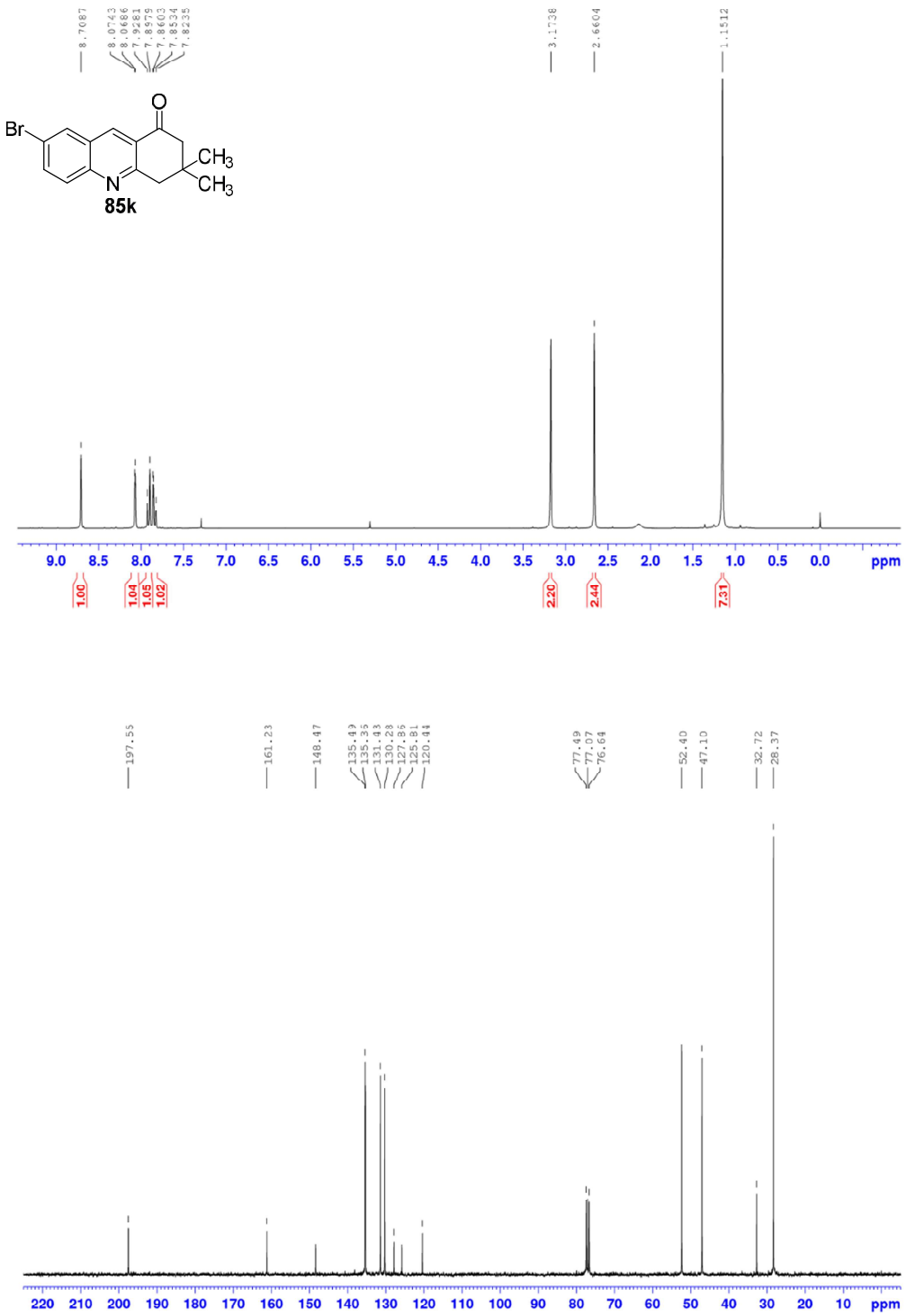


Figure 23 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85m** in $CDCl_3$

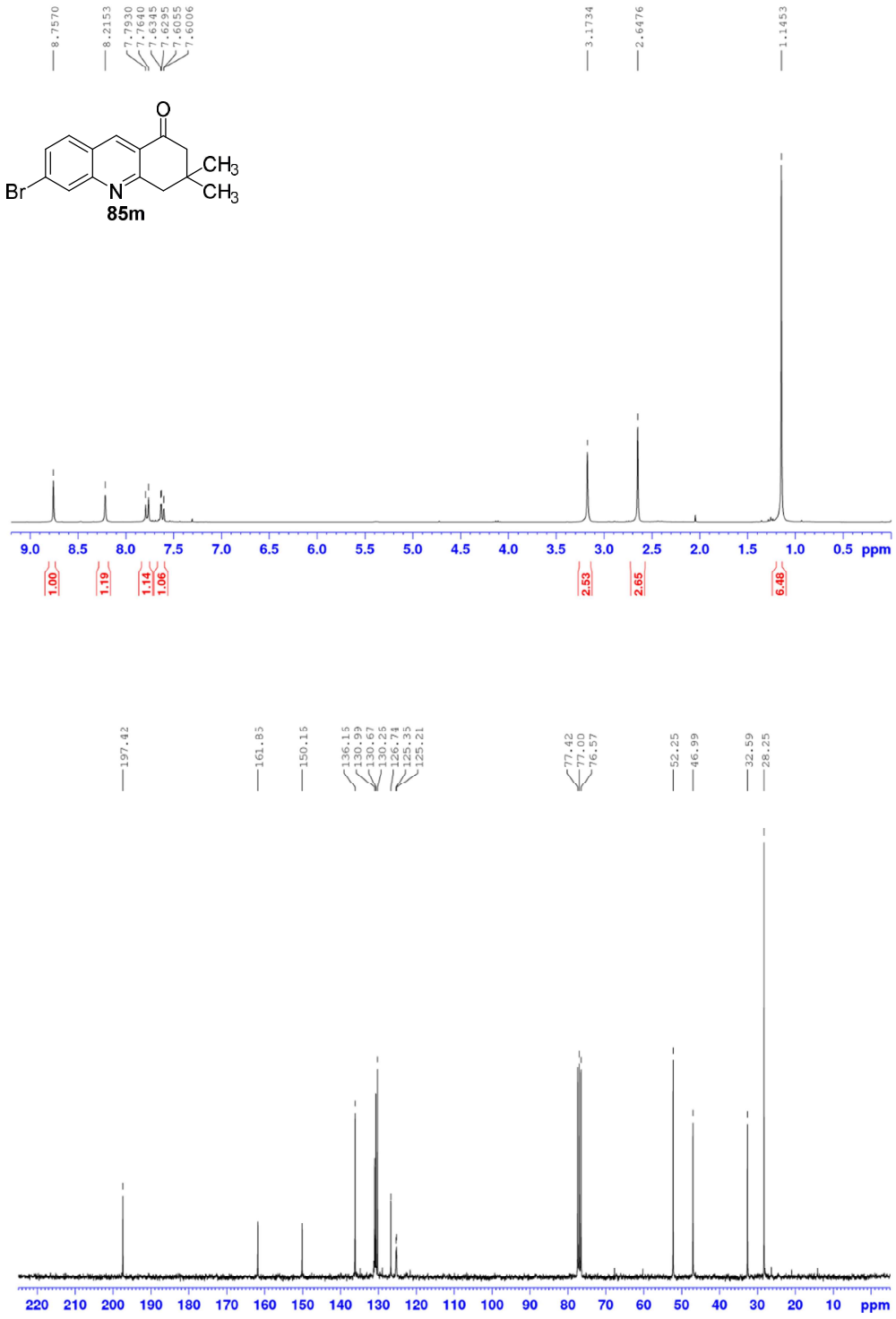


Figure 24 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85p** in $CDCl_3$

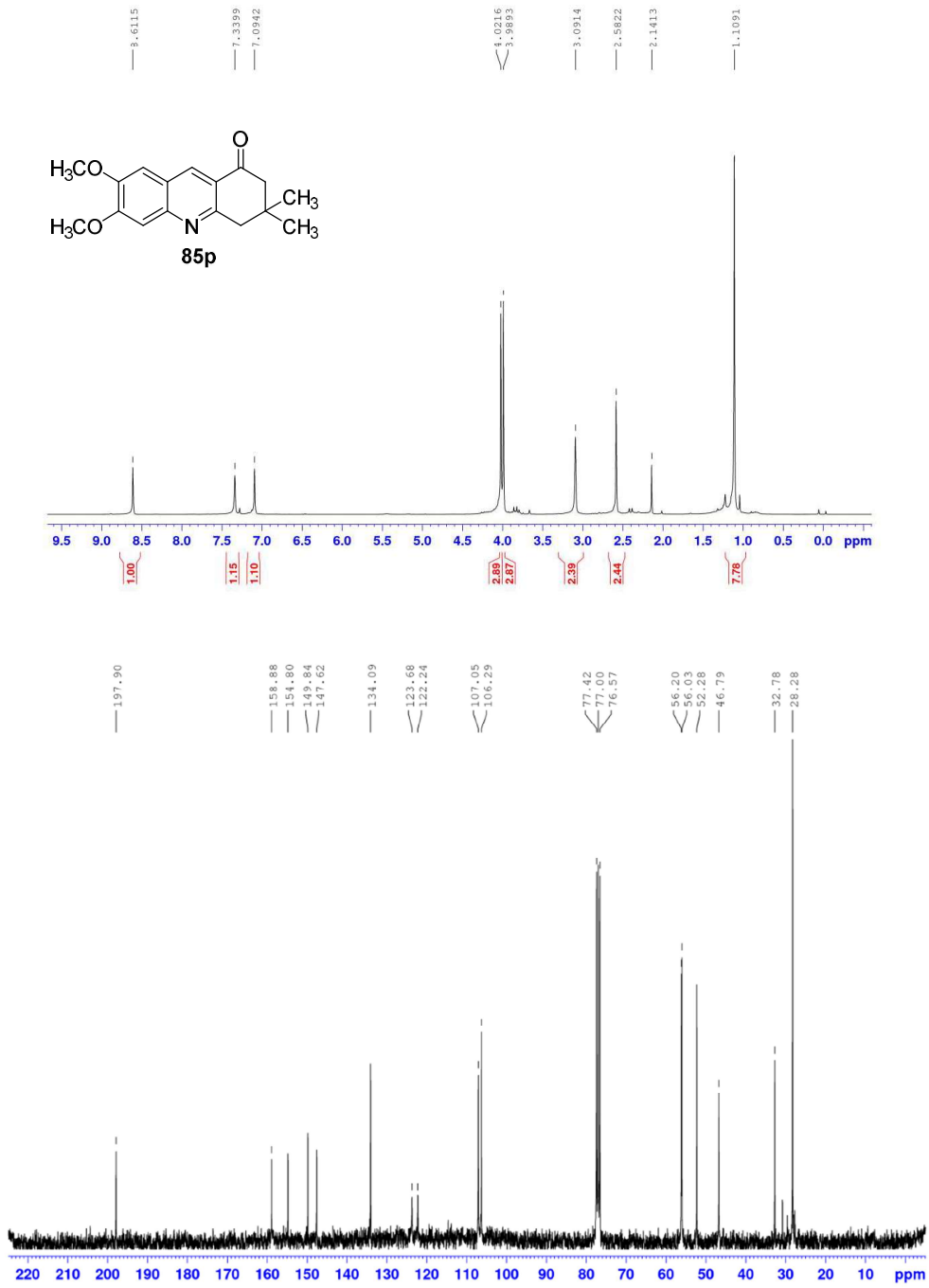


Figure 25 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85r** in $CDCl_3$

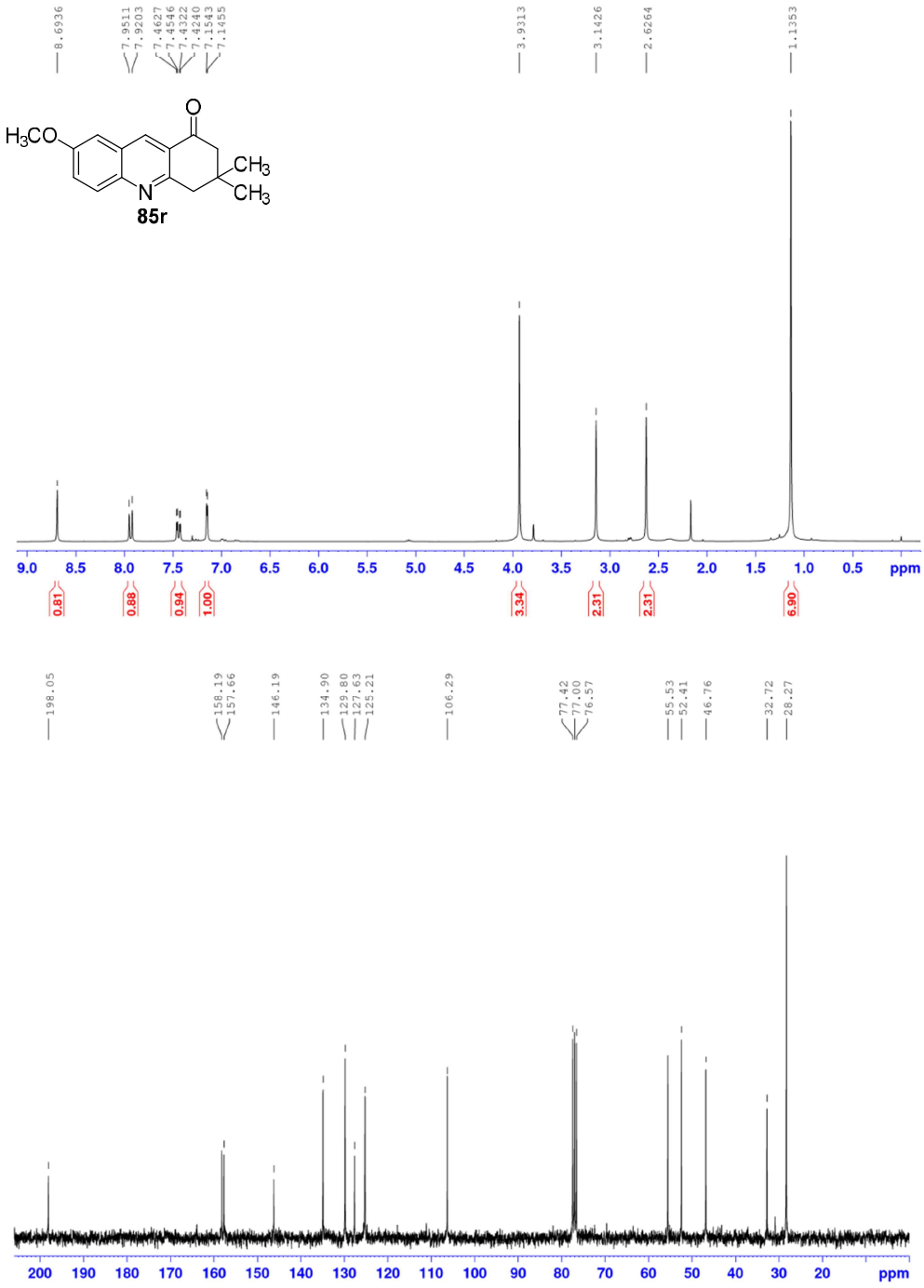


Figure 26 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85t** in $CDCl_3$

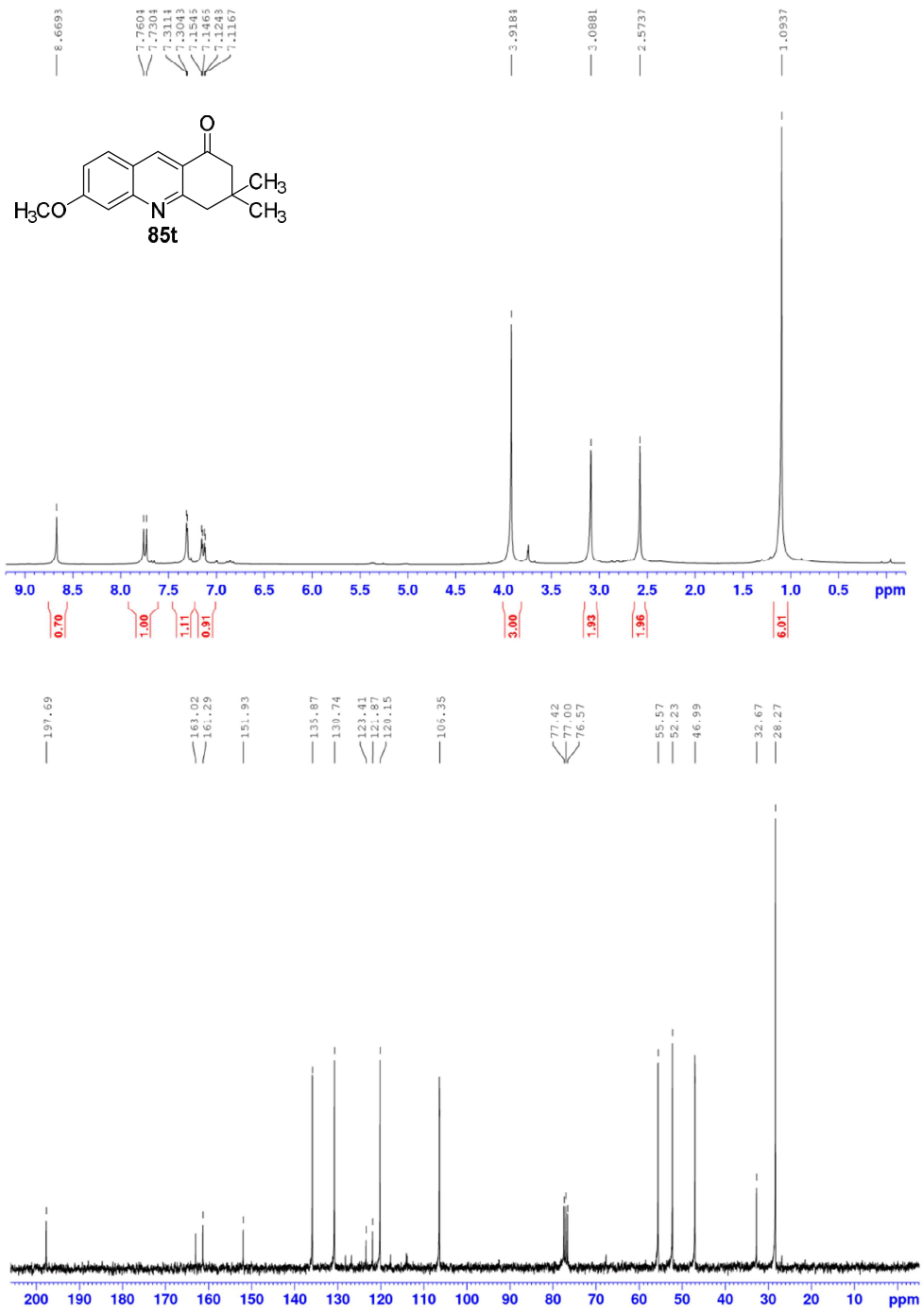


Figure 27 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **85u** in $CDCl_3$

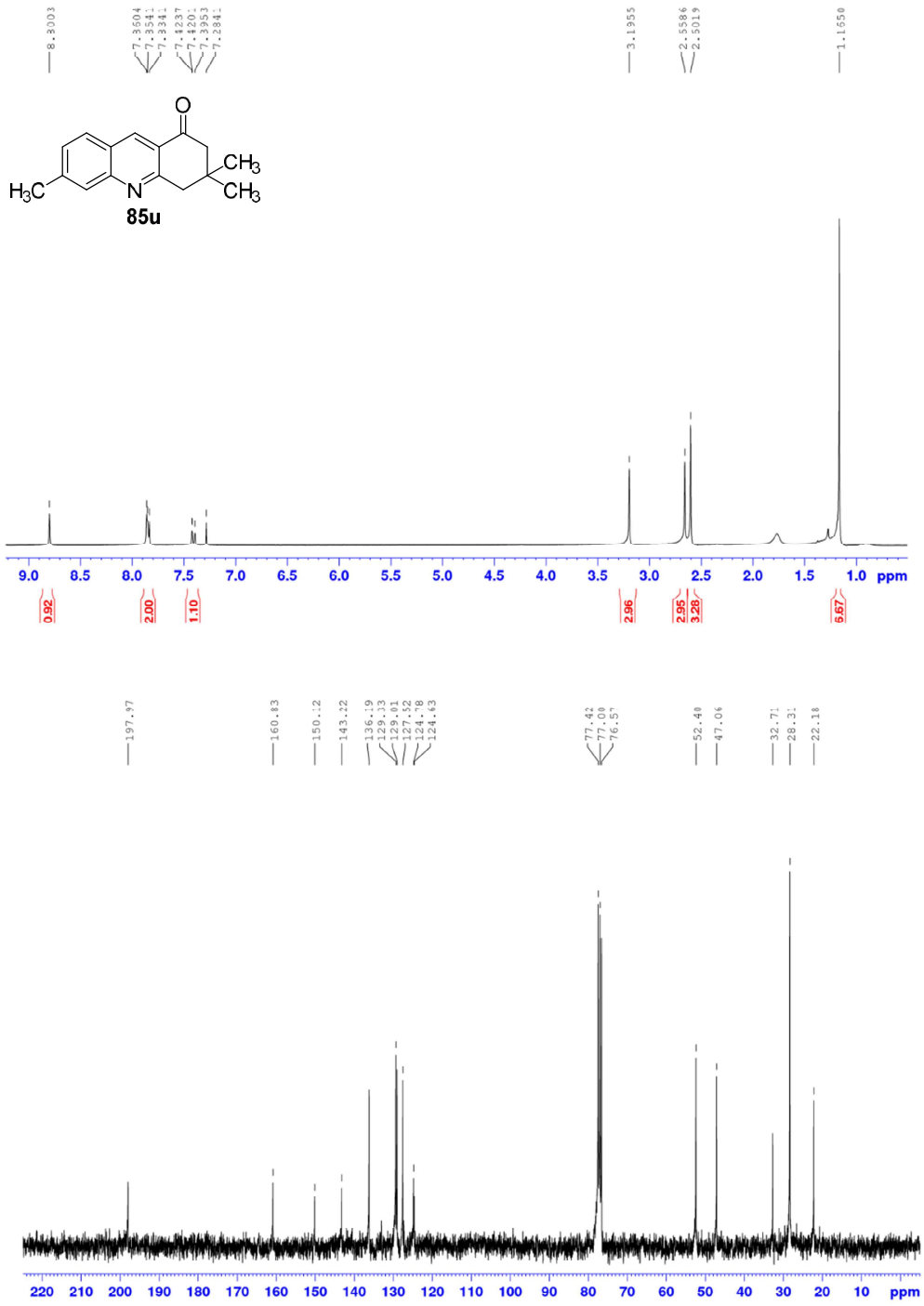


Figure 28 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **93b** in $CDCl_3$

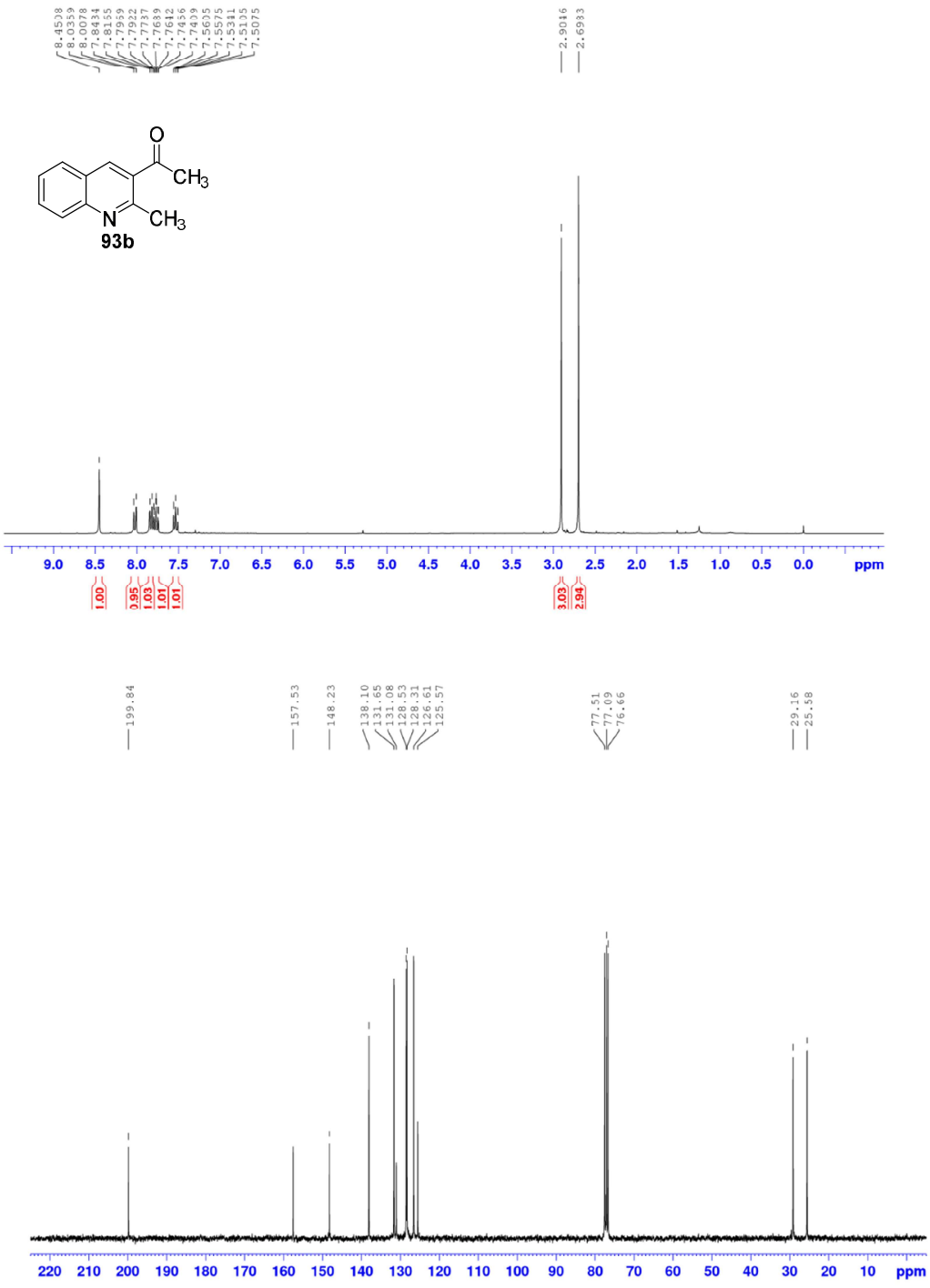


Figure 29 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **93o** in $CDCl_3$

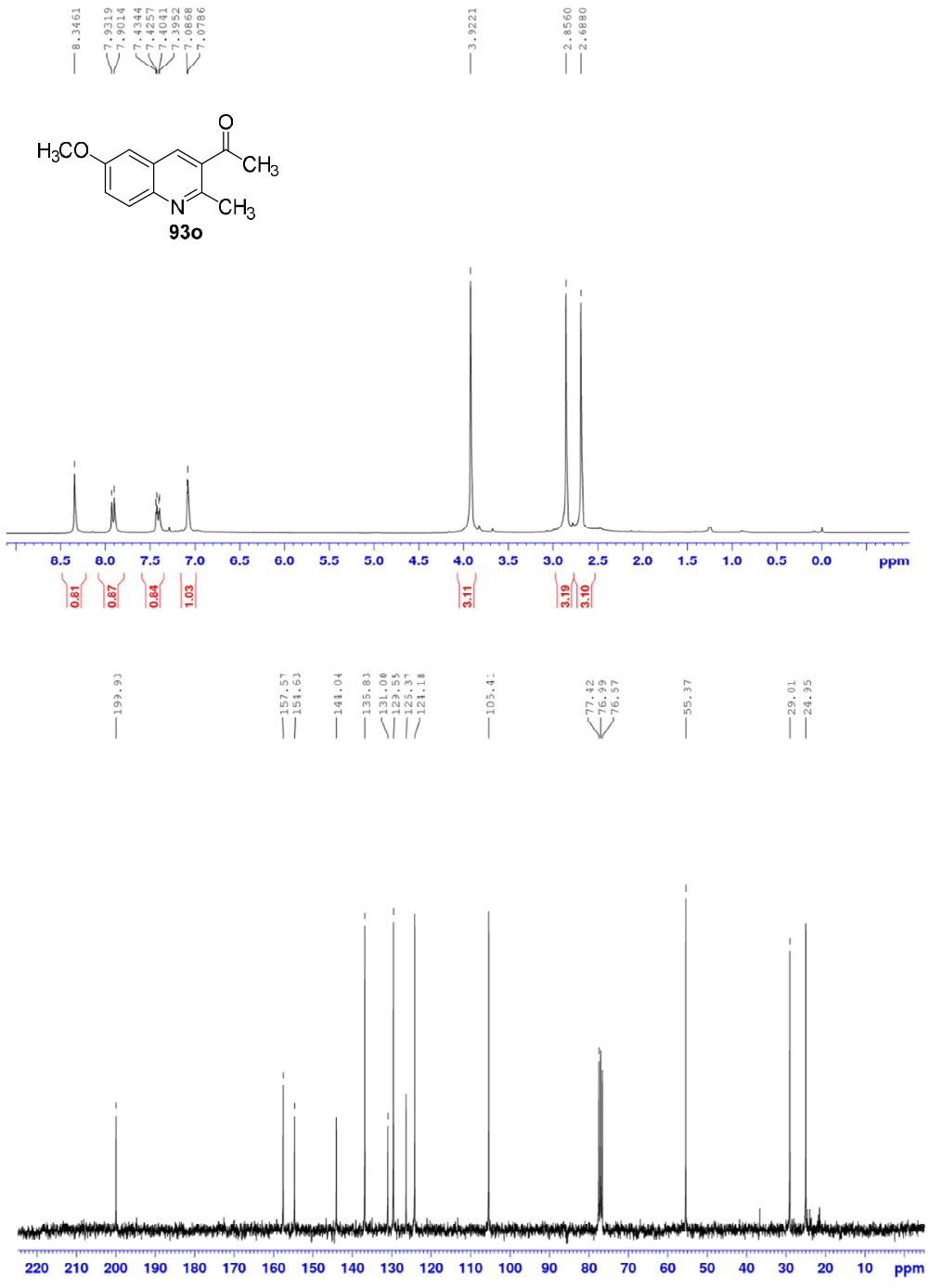


Figure 30 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **93r** in $CDCl_3$

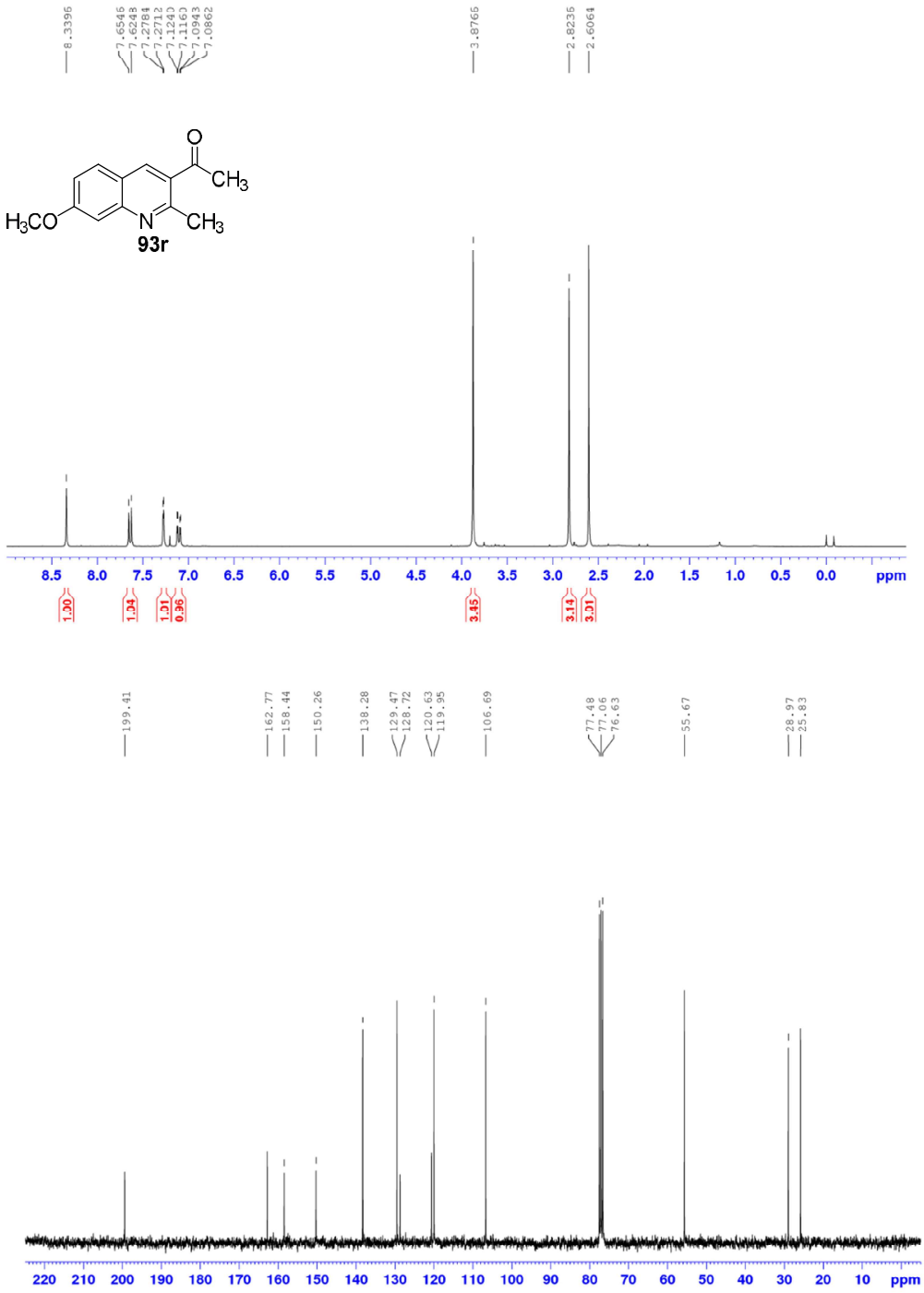


Figure 31 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **93u** in $CDCl_3$

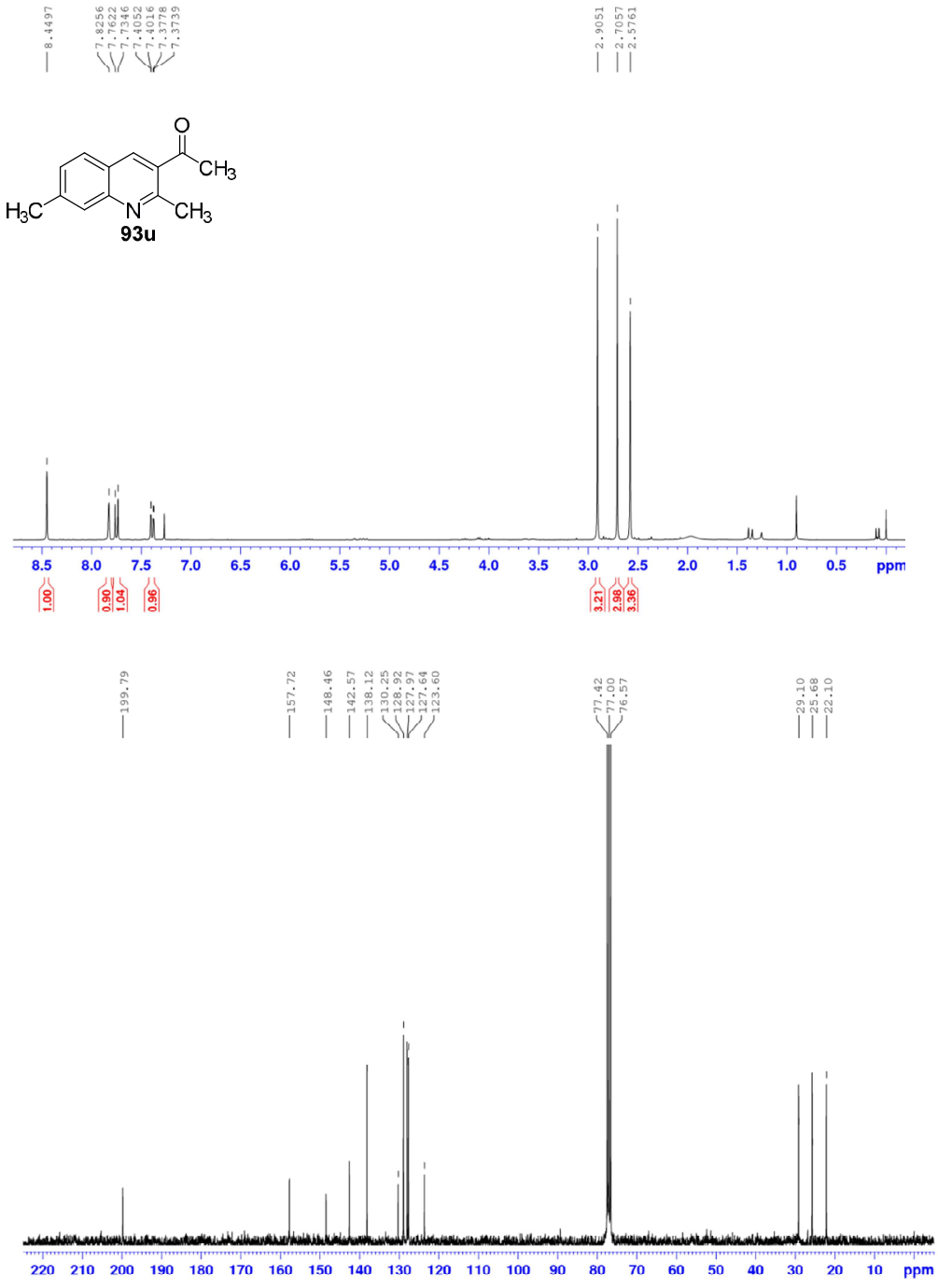


Figure 32 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **93a** in $CDCl_3$

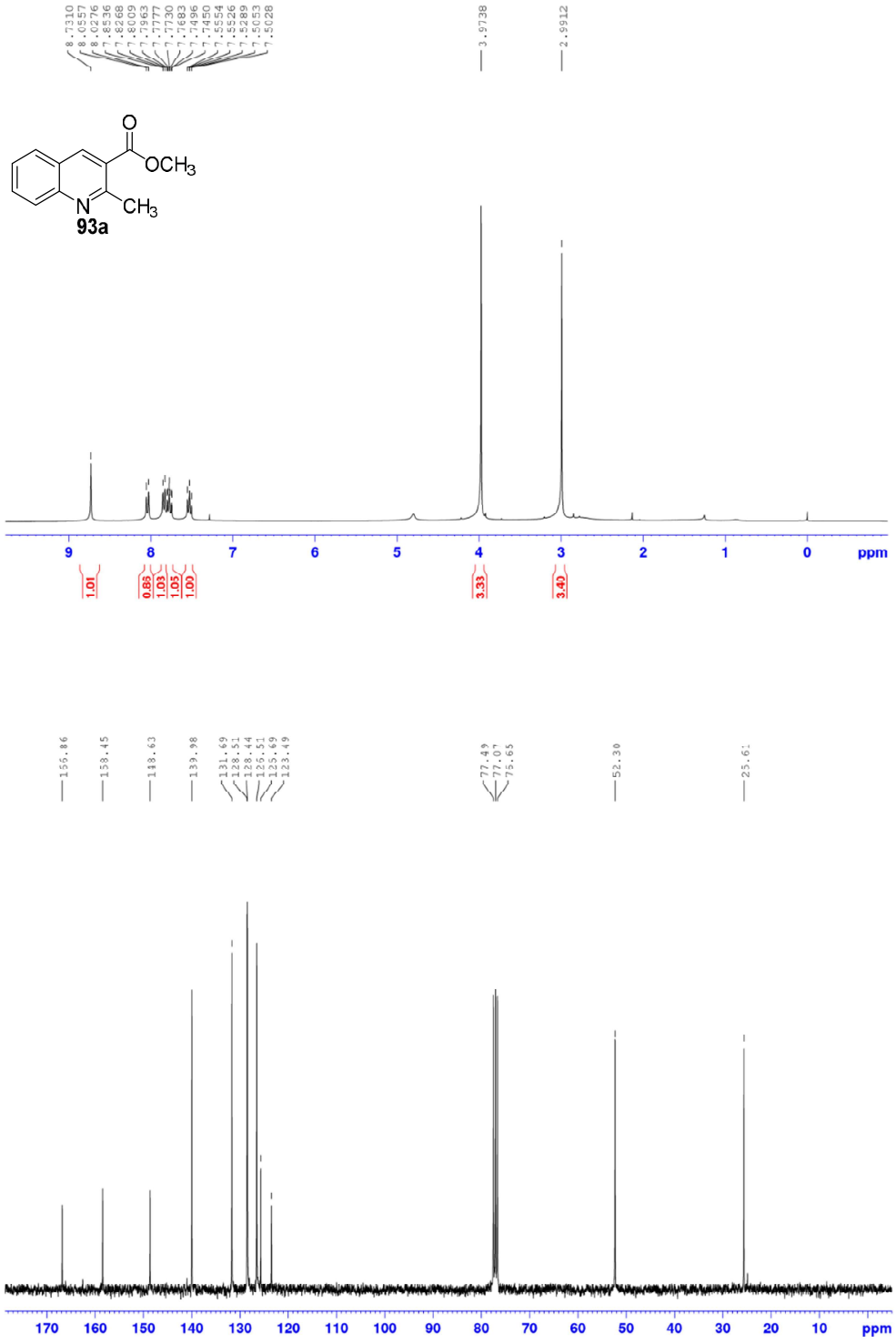


Figure 33 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **93e** in $CDCl_3$

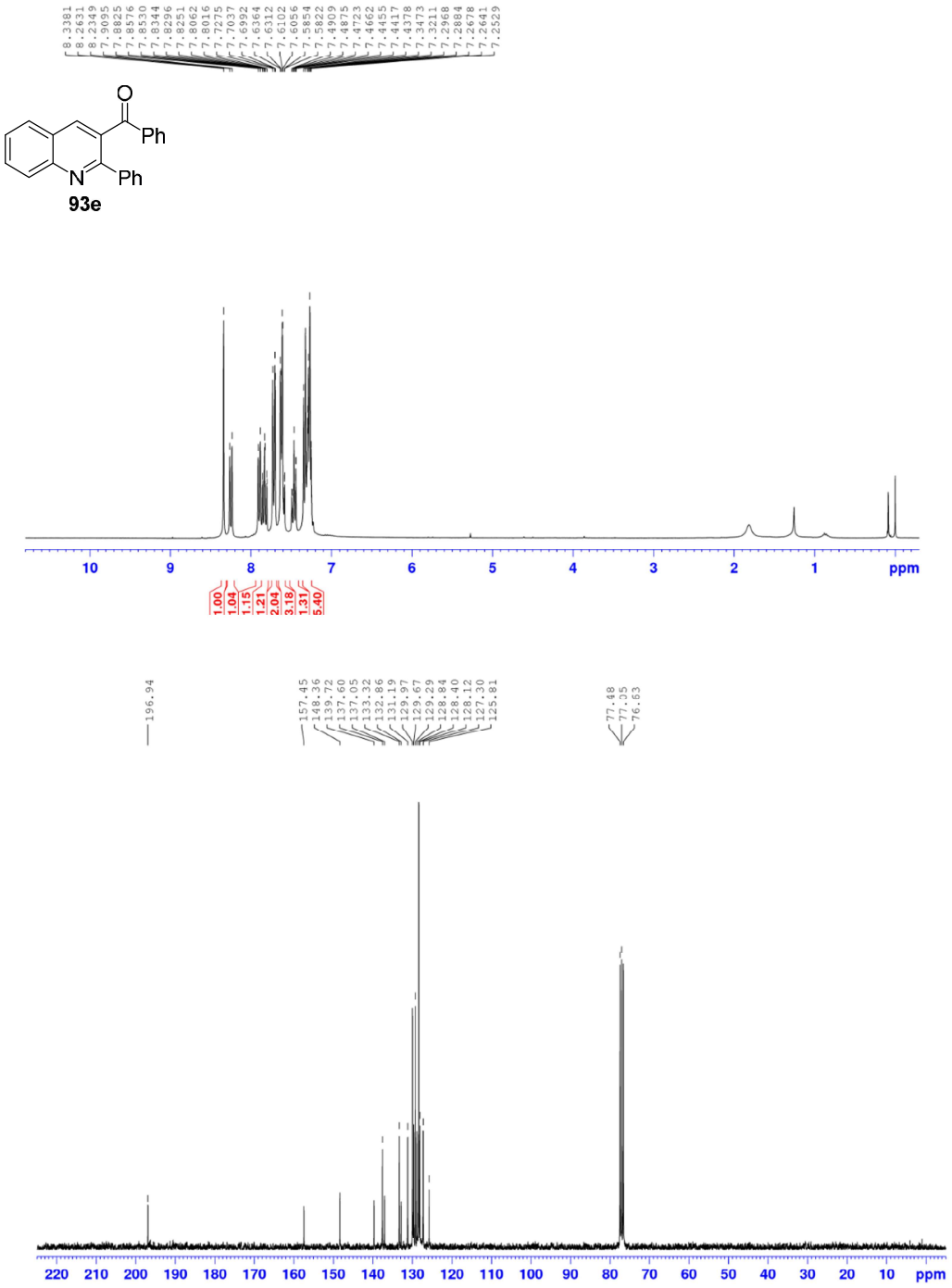


Figure 34 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **93d** in $CDCl_3$

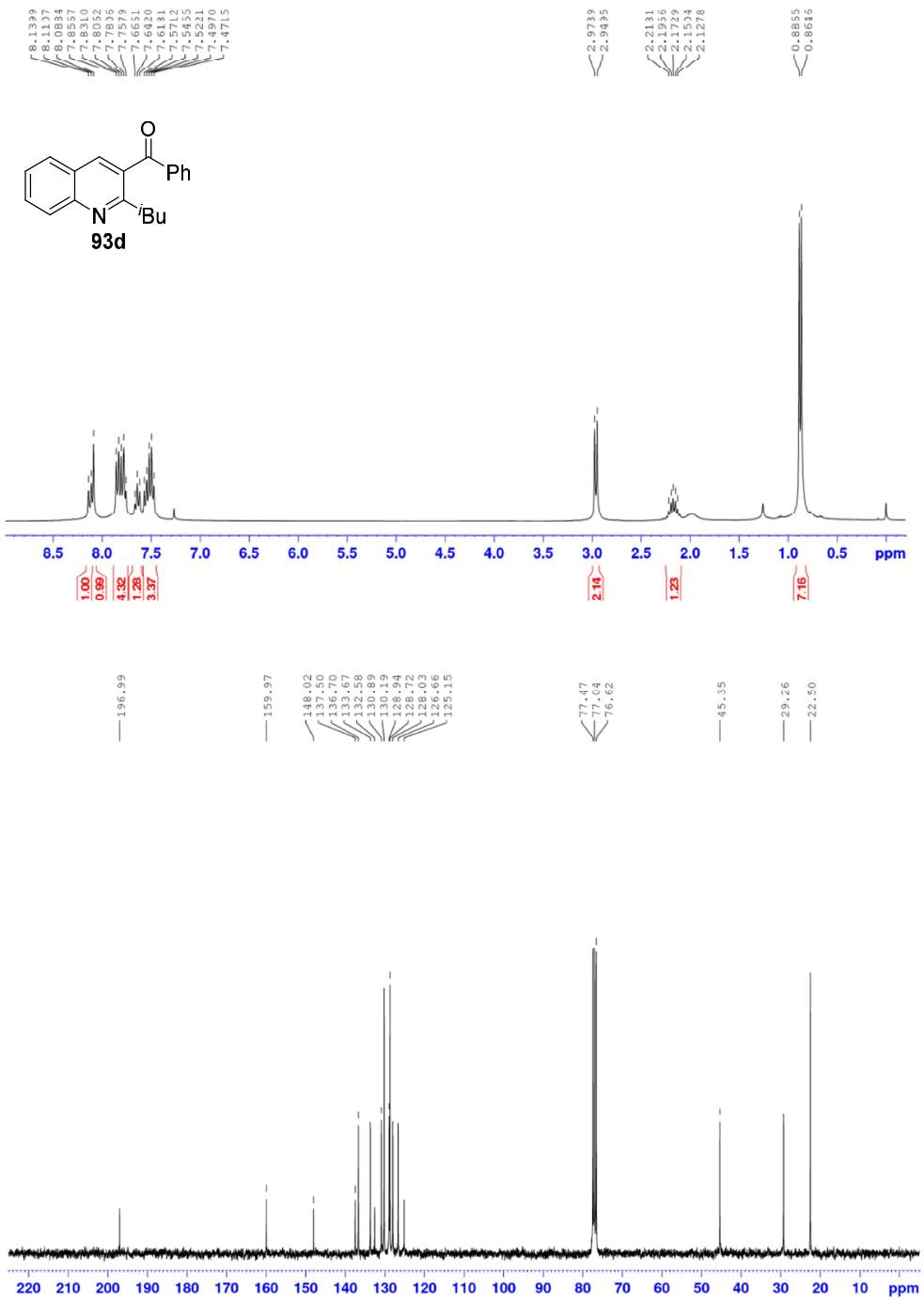


Figure 35 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **93f** in $CDCl_3$

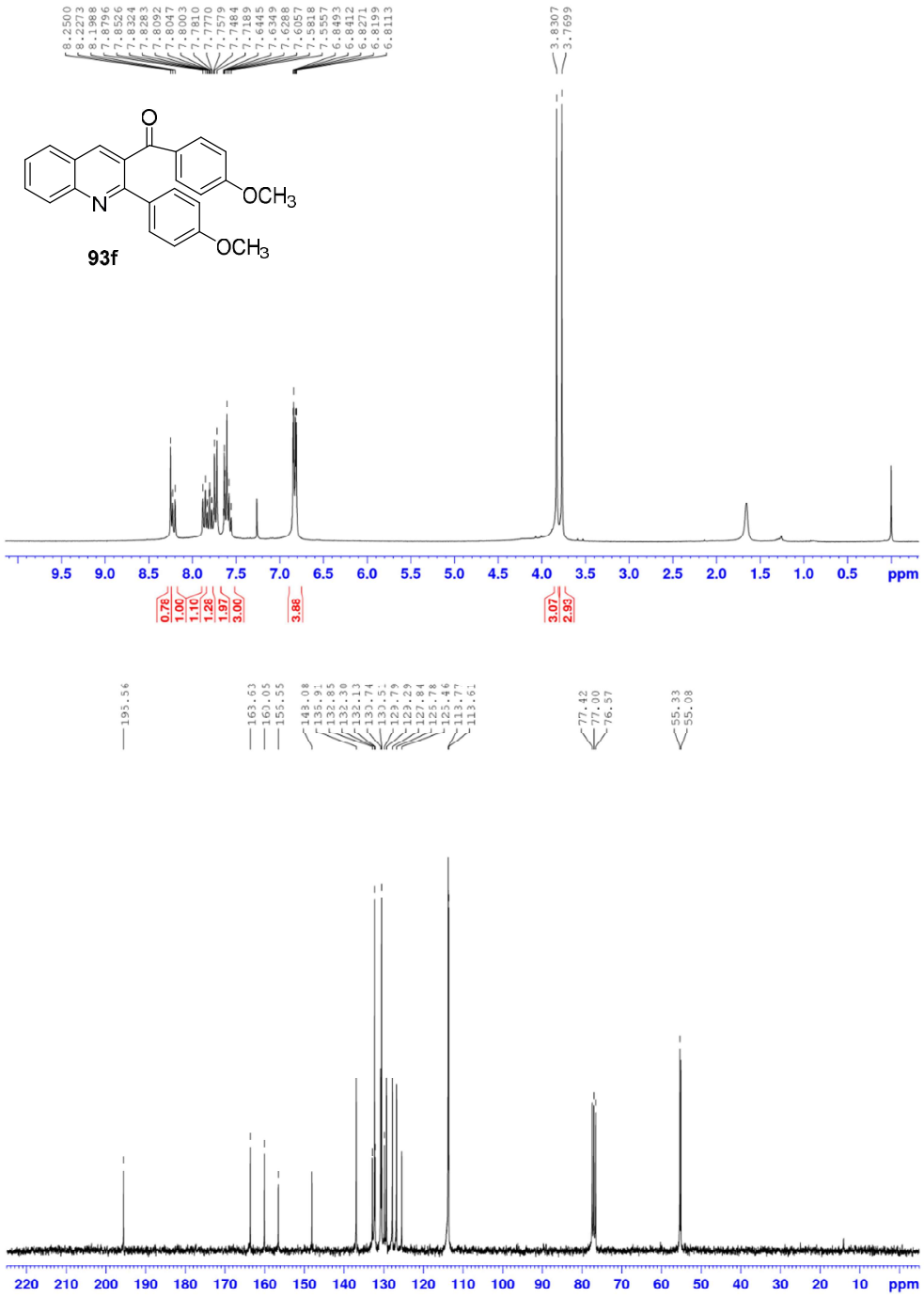
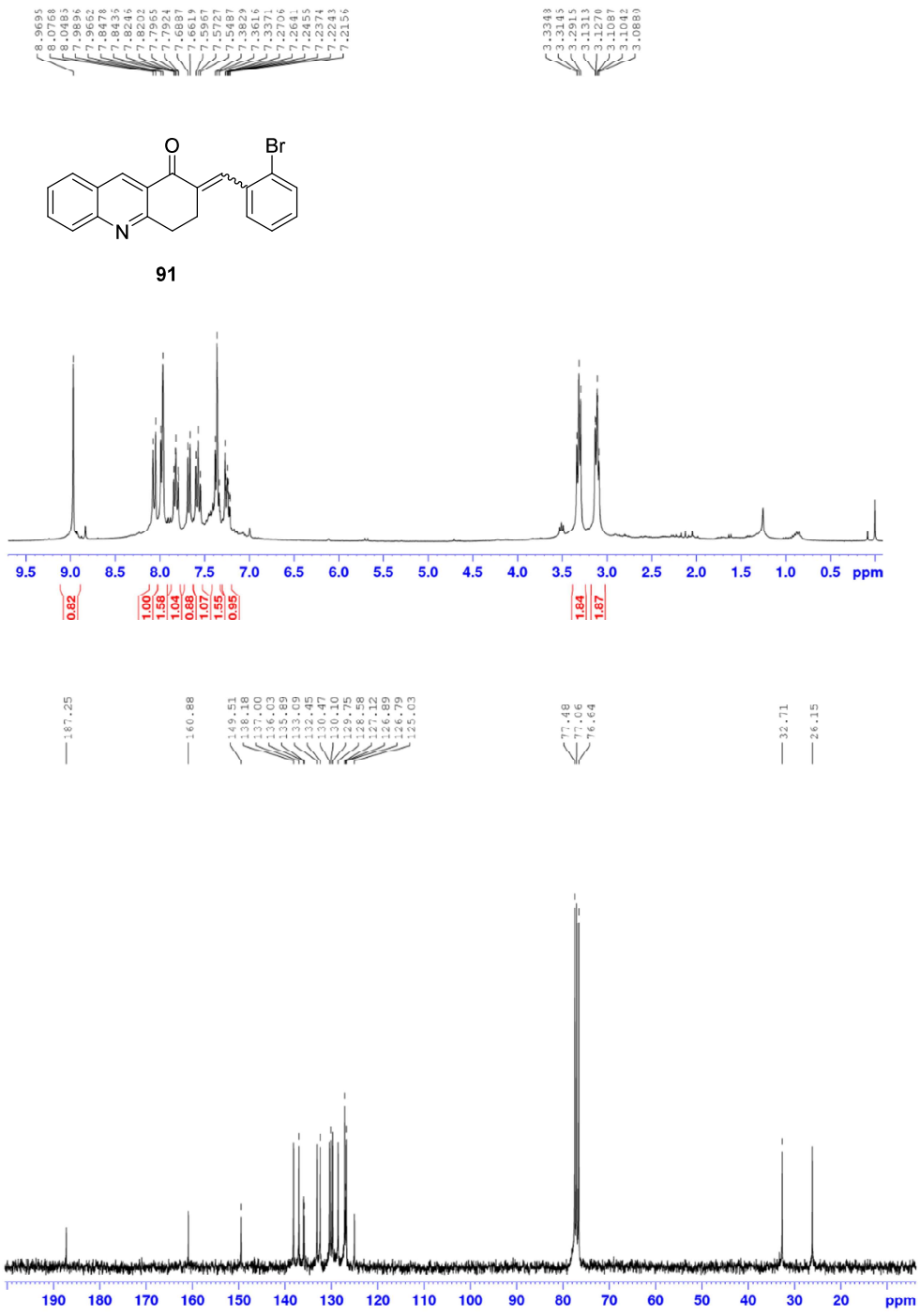


Figure 36 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **91** in $CDCl_3$



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Scholarship Award during Enrolment

Development and Promotion of Science and Technology Talents Project (DPST)

List of Publications

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