Copper-Catalyzed Domino Reactions for the Synthesis of Chromenes and Quinazolinones

Yotsakorn Saebang

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Science in Organic Chemistry

Prince of Songkla University

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Author	Mr. Yotsakorn Saebang
Major Program	Organic Chemistry

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Dean of Graduate School

This is to certify that the work here submitted is the result of the candidate's own investigations. Due acknowledgement has been made of any assistance received.

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(Mr. Yotsakorn Saebang)
Candidate

I hereby certify that this work has not been accepted in substance for any degree, and is not being currently submitted in candidature for any degree.

……...…..Signature
(Mr. Yotsakorn Saebang)
Candidate

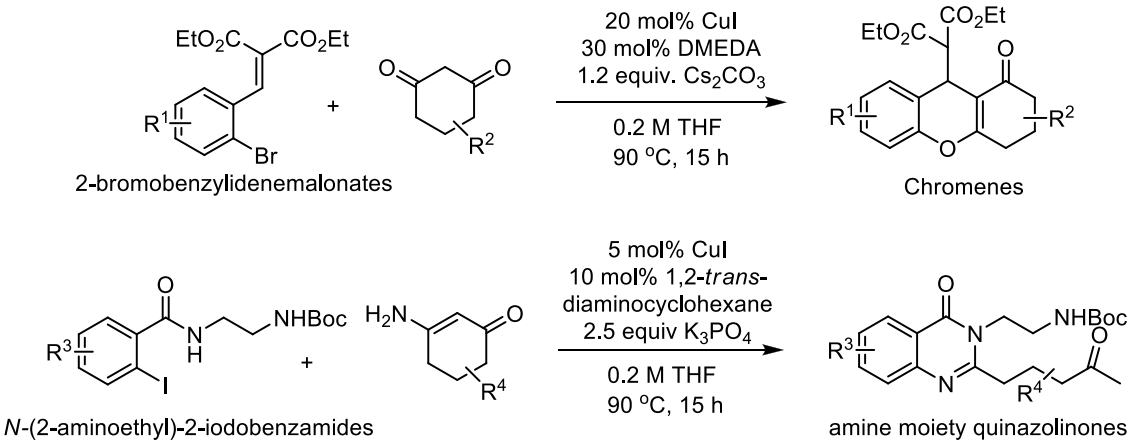
ชื่อวิทยานิพนธ์ การสังเคราะห์โครมีนและควินาโซลิโนนด้วยปฏิกิริยาการเกิดแบบหลายขั้นตอนโดยใช้คอปเปอร์เป็นตัวเร่งปฏิกิริยา

ผู้เขียน นายยศกร แซ่บ้าง

สาขาวิชา เคมีอินทรีย์

ปีการศึกษา 2559

บทคัดย่อ



คอปเปอร์ถูกใช้เป็นตัวเร่งปฏิกิริยาในการสร้างพันธะเช่น C(aryl)–C C(aryl)–O C(aryl)–N และ C(aryl)–S เนื่องจากมีราคาถูก มีความเป็นพิษต่ำและมีปริมาณเยอะในธรรมชาติ โครมีนเป็นหนึ่งในสารผลิตภัณฑ์ธรรมชาติที่มีอะตอมของออกซิเจนเป็นองค์ประกอบและมีฤทธิ์ทางชีวภาพที่น่าสนใจ ผู้วิจัยได้สังเคราะห์โครมีนซึ่งมีหมู่แทนที่บนคาร์บอนตำแหน่งที่ 4 จากสารตั้งต้น 2-bromobenzylidenemalonates และ 1,3-diketones ผ่านปฏิกิริยา Cu(I)-catalyzed domino reactions โดยมีกลไกปฏิกิริยาคือ 1. Michael addition 2. tautomerization และ 3. intramolecular C(aryl)–O formation ควินาโซลิโนนเป็นสารผลิตภัณฑ์ธรรมชาติประเภทอัลคาลอยด์ที่สำคัญซึ่งแสดงฤทธิ์ทางชีวภาพที่หลากหลายและใช้เป็นยารักษาโรค ควินาโซลิโนนที่มีหมู่อะมิโนเป็นองค์ประกอบถูกสังเคราะห์ได้ร้อยละของผลผลิตในระดับปานกลางจนถึงสูงจากสารตั้งต้น *N*-amino moiety-2-iodobenzamides และ cyclic enaminones ผ่านปฏิกิริยา Cu(I)-catalyzed domino reactions ภายใต้เงื่อนไขปฏิกิริยาที่ไม่รุนแรง นอกจากนี้หมู่ diamino ของ 2-iodobenzamides สามารถทำหน้าที่เป็น internal ligand ซึ่งสามารถสังเคราะห์ควินาโซลิโนนได้ในระดับดี โดยมีกลไกการเปิดปฏิกิริยาคือ 1. C(aryl)–N bond formation 2. intramolecular Michael addition และ 3. retro-Mannich reaction

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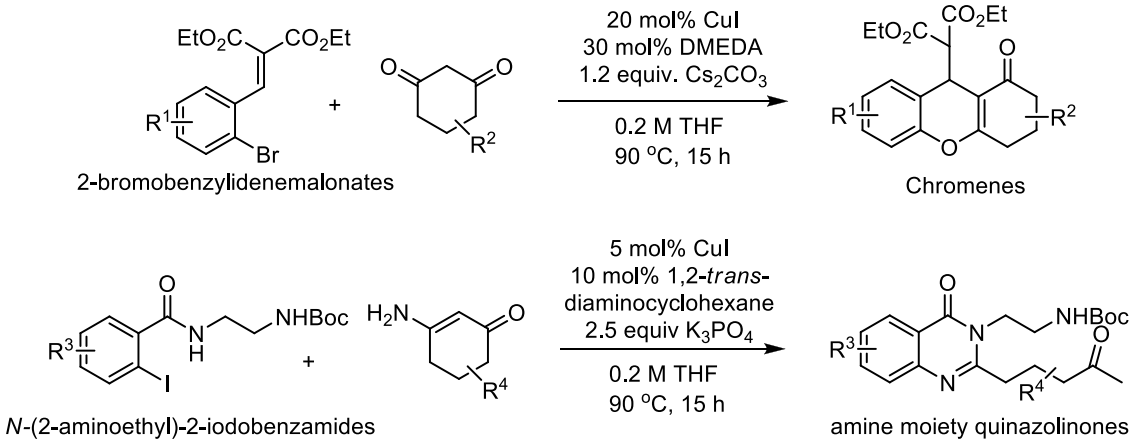
ABSTRACT



Copper has been widely used as a catalyst for bond formation, such as C(aryl)–C, C(aryl)–O, C(aryl)–N and C(aryl)–S due to their inexpensive, low toxicity and high natural abundance. Chromenes are one of the most important O-containing natural products with a wide range of biological activities. A various chromenes, having a functionality at the fourth carbon, were achieved from 2-bromobenzylidenemalonates and 1,3-diketones *via* Cu(I)-catalyzed domino reactions. The domino reactions consisted of Michael addition, a tautomerization and an intramolecular C(aryl)–O formation. Quinazolinones are important alkaloids showing a variety of biological and pharmalogical activities. The amine moiety quinazolinone derivatives were synthesized from *N*-(2-aminoethyl)-2-iodobenzamides and cyclic enaminones *via* Cu(I)-catalyzed domino reactions under mild reaction conditions. Interestingly, diamino moiety of 2-iodobenzamides operated as an internal ligand to assist the reaction process occurring smoothly. The domino processes underwent sequential a C(aryl)–N bond formation, an intramolecular Michael addition and retro-Mannich reaction.

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Yotsakorn Saebang

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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
ACN	=	acetonitrile
AcOH	=	acetic acid
$CDCl_3$	=	deuterochloroform
$CHCl_3$	=	chloroform
CH_2Cl_2	=	dichloromethane
CH_3CN	=	acetonitrile
Cs_2CO_3	=	cesium carbonate
DABCO	=	1,4-diazabicyclo[2.2.2]octane
DMA	=	dimethylacetamide
DMEDA	=	*N*,*N*'-dimethylethylenediamine
DMF	=	dimethylformamide

LIST OF ABBREVATIONS AND SYMBOLS (Continued)

DMSO	=	dimethylsulfoxide
DMSO-d_6	=	dimethyl sulfoxide-*d6*
DTBM	=	5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
Et	=	ethyl
EtOAc	=	ethyl acetate
EtOH	=	ethanol
Me	=	methyl
MS	=	molecular sieve
$NaBAr_F$	=	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Na_2SO_4	=	sodium sulfate
NH_4Cl	=	ammonium chloride
NMP	=	*N*-methyl-2-pyrrolidone
Ph	=	phenyl
Piv	=	pivaloyl
PPh_3	=	triphenylphosphine
K_2CO_3	=	potassium carbonate
K_3PO_4	=	potassium phosphate
Tf	=	triflyl
THF	=	tetrahydrofuran
TMS	=	tetramethylsilane

LIST OF PUBLICATION

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CHAPTER 1

Cu(I)-Catalyzed Domino Reactions of Chromene Syntheses

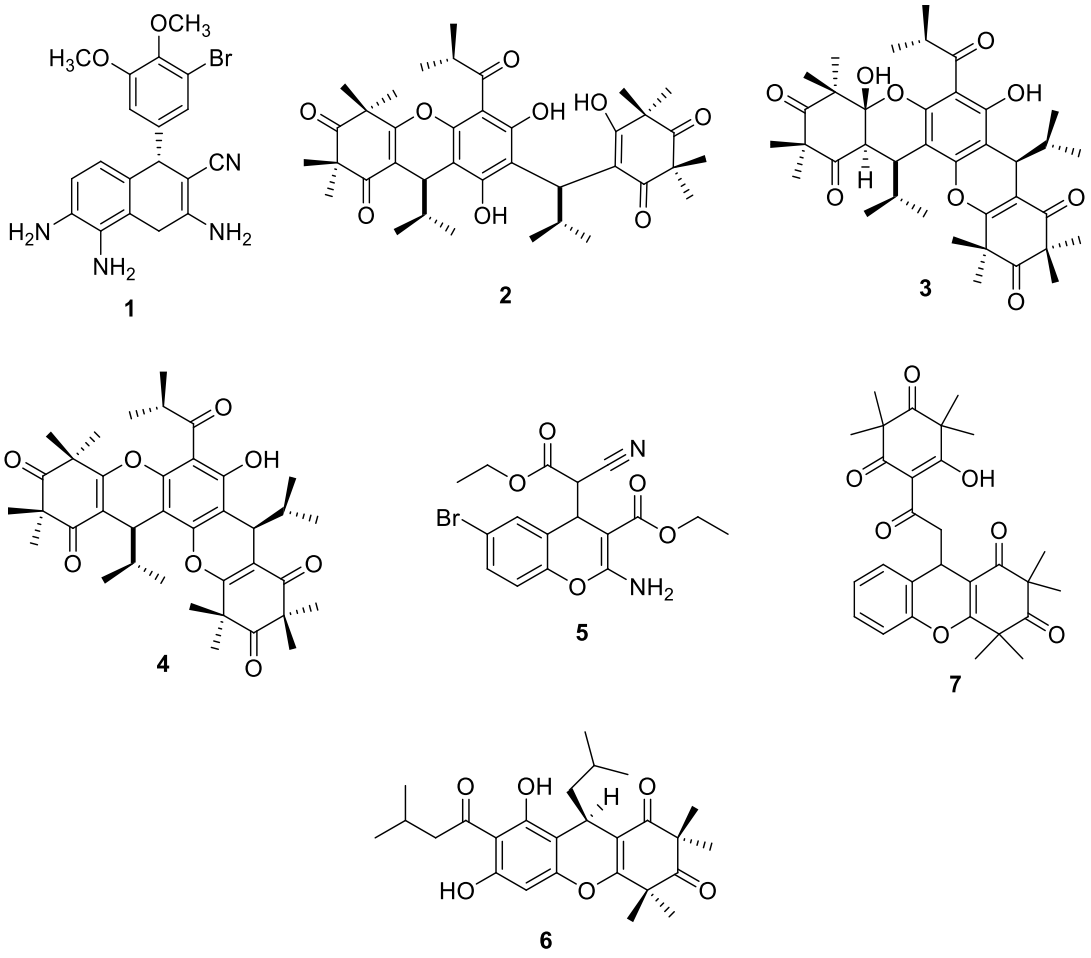
1.1 INTRODUCTION

1.1.1 Introduction

Metal-catalyzed domino reactions have been one of the most useful and powerful procedures for the construction of complex organic compounds from simple starting materials (Guo *et al*., 2015). Especially, copper-catalyzed domino reactions have been widely used for the formation of C(aryl)–C, C(aryl)–N, C(aryl)–O and C(aryl)–S bonds because of their low cost, low toxicity and high natural abundance (Liu *et al*., 2011).

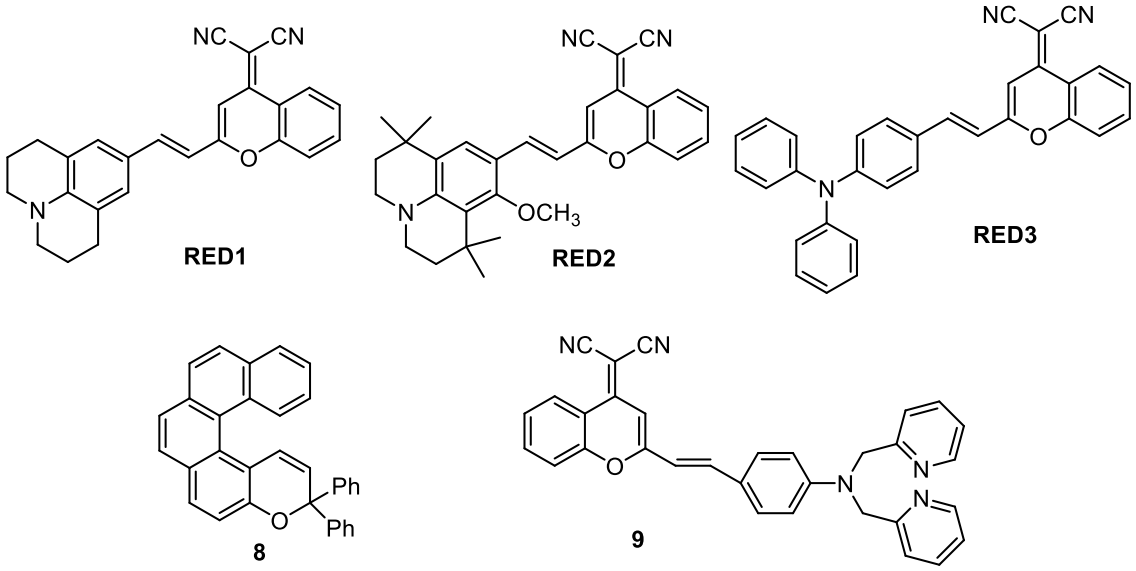
Chromenes or benzopyrans are heterocyclic molecules consisting of a benzene ring fused to a pyran ring. It is one of the most important O-containing heterocyclic compounds, widely presented in natural products and biologically active molecules. Chromenes exhibited a variety of biological properties, for example (**Figure 1**), EPC2407 or crolibulin (**1**) displayed potentially antitumor activity, and it is currently in a phase II clinical test for anaplastic thyroid cancer for the National Cancer Institute (NCI) (Patil *et al*., 2013). In addition, myrtucomulone-C (**2**), myrtucomulone-D (**3**) and myrtucomulone-E (**4**) from *Myrtus communis L*. exhibited α-glucosidase inhibitory and antibacterial activites (Shaheen *et al*., 2006). HA 14-1 (**5**) has emerged as a potent antagonis of the antiapoptotic Bcl-2 protein for the treatment of various cancer (Doshi *et al*., 2006). Rhodomyrtone (**6**), isolated from *Rhodomyrtus tomentosa* leaves, displayed antibacterial activity against key antibiotic-resistant pathogens including epidemic methicillin-resistant *Staphylococcus aureus* (EMRSA) (Limsuwan *et al*., 2009). In addition, Uvafzlefin (**7**), isolated from the stem of *Uvaria ufielii*, showed antimicrobial activity against gram-positive and acid-fast bacteria (Thomas *et al*., 2013).

Figure 1 Examples of bioactive chromenes



Moreover, chromene derivatives have been applied to material sciences. For example (**Figure 2**), red dopants (**RED1**, **RED2**, **RED3**), containing a 4-dicyano-methylene chromene moiety, have been presented as a π-electron acceptor in red fluorescent dye molecules for organic electroluminescent devices (Zhang *et al*., 2001). Helical chromenes (**8)** displayed helicity-dependent fluorescence and photochromism (Moorthy *et al*., 2006). DCCP (**9**), consisting of 4*H*-chromene, showed turn-on a colorimetric and fluorescent (Huang *et al*., 2008).

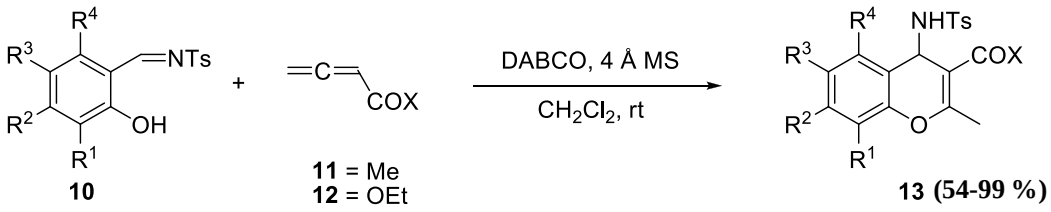
Figure 2 Examples of chromenes are applied to material sciences



Over the last decade, chromene derivatives have been synthesized *via* one-pot coupling reaction by using a variety of catalysts such as 1,4-diazabicyclo[2.2.2]octane (DABCO) (Peng *et al*., 2013) and tetrahydrothiophene (Ye *et al*., 2006). Transition metals have been introduced as powerful-alternative catalysts for synthesis of chromenes such as, gold (Au) (Chen *et al*., 2011), zinc (Zn) (Ghosh *et al*., 2013) and copper (Cu) (Fang *et al*., 2006).

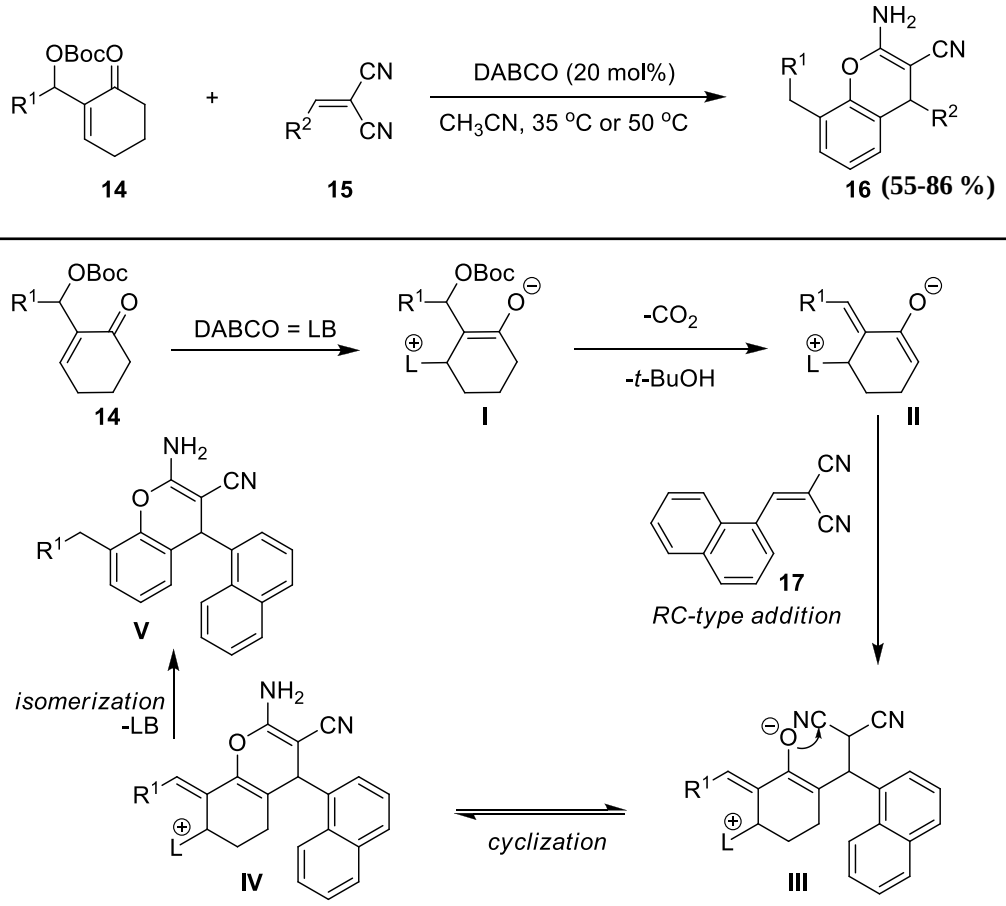
In 2005, Shi and co-workers reported a DABCO-catalyzed reactions of salicyl *N*-tosylimines (**10**) with penta-3,4-diene-2-one (**11**) and ethyl 2,3-butadienoate (**12**) in dichloromethane at room temperature to give highly functionalized chromenes in good to excellent yields (**Scheme 1**) (Shi *et al*., 2005).

Scheme 1 The DABCO-catalyzed reaction of ketones **11** and allenic ester **12** with alicyl *N*-tosylimines **10**



Rauhut–Currier-type reaction has been utilized for the synthesis of chromenes. In 2013, Peng and co-workers synthesized chromenes from Morita–Baylis–Hillman (MBH) carbonates **14** and benzylidenemalononitrile **15**. The key Rauhut–Currier-type zwitterionic dienoates **II** were generated from MBH carbonates **14** *in situ* by using DABCO. Then, **II** underwent the domino Rauhut–Currier-type reaction with alkylidenemalonitriles **17**, followed by cyclization and isomerization to provide chromenes in moderate to good yields under mild condition (**Scheme 2**) (Peng *et al*., 2013).

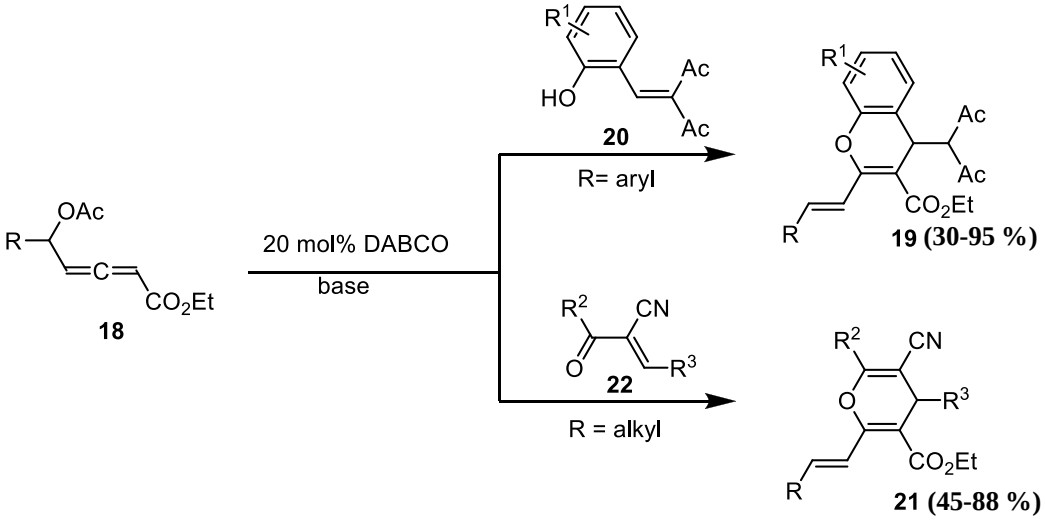
Scheme 2 The Rauhut–Currier-type reaction with MBH carbonates **14** and alkylidenemalonitriles **15**



In 2015, Gu and co-workers also reported a DABCO-catalyzed (4+2) annulations of *δ*-acetoxy allenoates **18** for the synthesis of 4*H*-chromenes **19** from

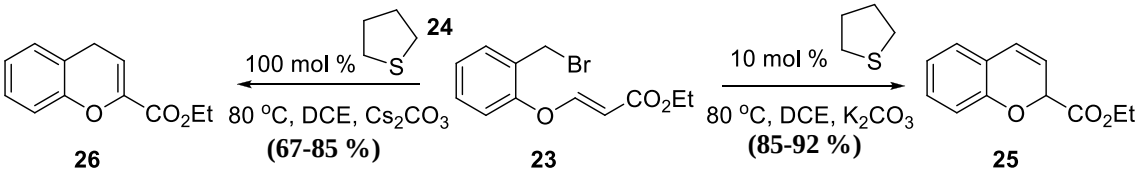
salicylaldehydes **20**, and 4*H*-pyrans **21** from oxo dienes **22**. The reactions were performed in the presence of 20 mol% of DABCO and 1.2 equiv of K_2CO_3 in $CHCl_3$ at room temperature for 12 h to give chromenes in a good yield. On the other hand, allenoates **18** underwent 4+2 cycloaddition with oxo diene **22** by using 20 mol% of DABCO and 1.2 equiv of Cs_2CO_3 in dioxane at room temperature for 12 h, providing pyrans in good yields (**Scheme 3**) (Gu *et al*., 2015).

Scheme 3 The DABCO-catalyzed (4+2) annulations of *δ*-acetoxy allenoates **18**



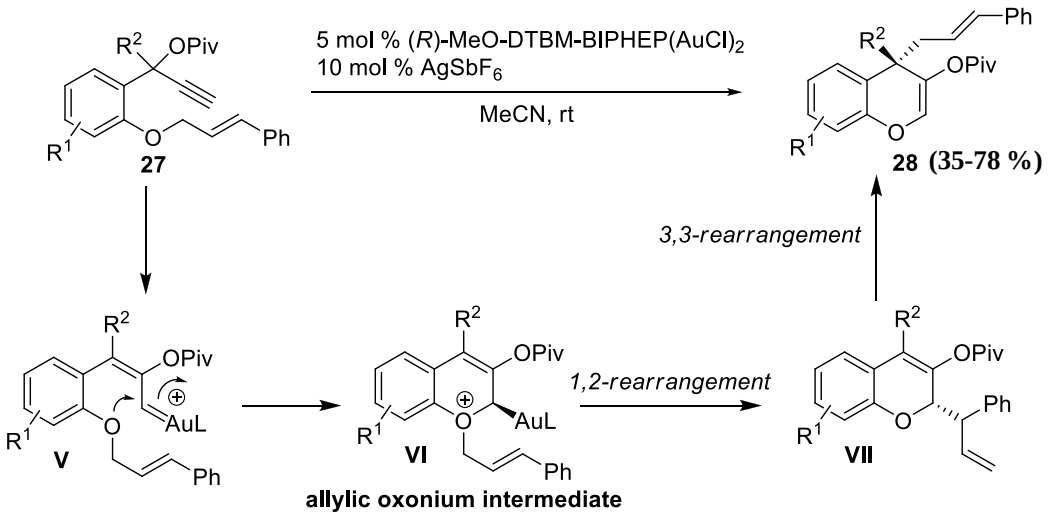
Tetrahydrothiophene (**24**) is one of organic catalysts for a construction of chromenes. In 2006, Ye and co-workers reported the synthesis of 2*H*-chromenes **25** and 4*H*-chromenes **26** in the presence of tetrahydrothiophene (**24**). The reaction process consisted of tetrahydrothiophene-catalyzed ylide annulation reaction *via* tandem Michael addition, elimination and substitution. They found that base played a crucial role in the reaction. The reaction with K_2CO_3 provided 2*H*-chromenes. On the other hand, in the presence of Cs_2CO_3, 2*H*-chromenes were isomerized to form 4*H*-chromenes due to the basicity of Cs_2CO_3 (**Scheme 4**) (Ye *et al*., 2006).

Scheme 4 The tandem ylide annulation reaction for the synthesis of chromenes



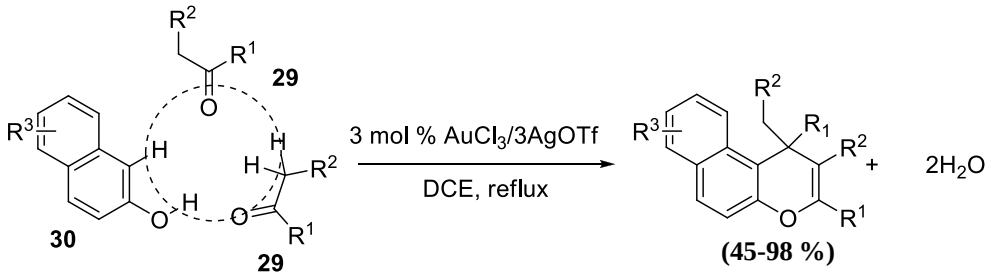
Moreover, efficient approaches for the synthesis of chromenes have been developed *via* metal-catalyzed reactions. Interestingly, all procedures were performed under mild condition. For example, in 2009, Uemura and co-workers used gold(I) as a catalyst to synthesize chromene derivatives *via* a rearrangement of allylic oxonium intermediate **VI**. This intermediate was generated *in situ* from gold-catalyzed rearrangement of propargyl ester **27**. Then, intermediate **VI** underwent 1,2-rearrangement and 3,3-rearrangement to provide chromene **28** in excellent yield (**Scheme 5**) (Uemura *et al*., 2009).

Scheme 5 The gold(I)-catalyzed enantioselective synthesis of chromenes *via* the rearrangement of allylic oxonium intermediates **VI**



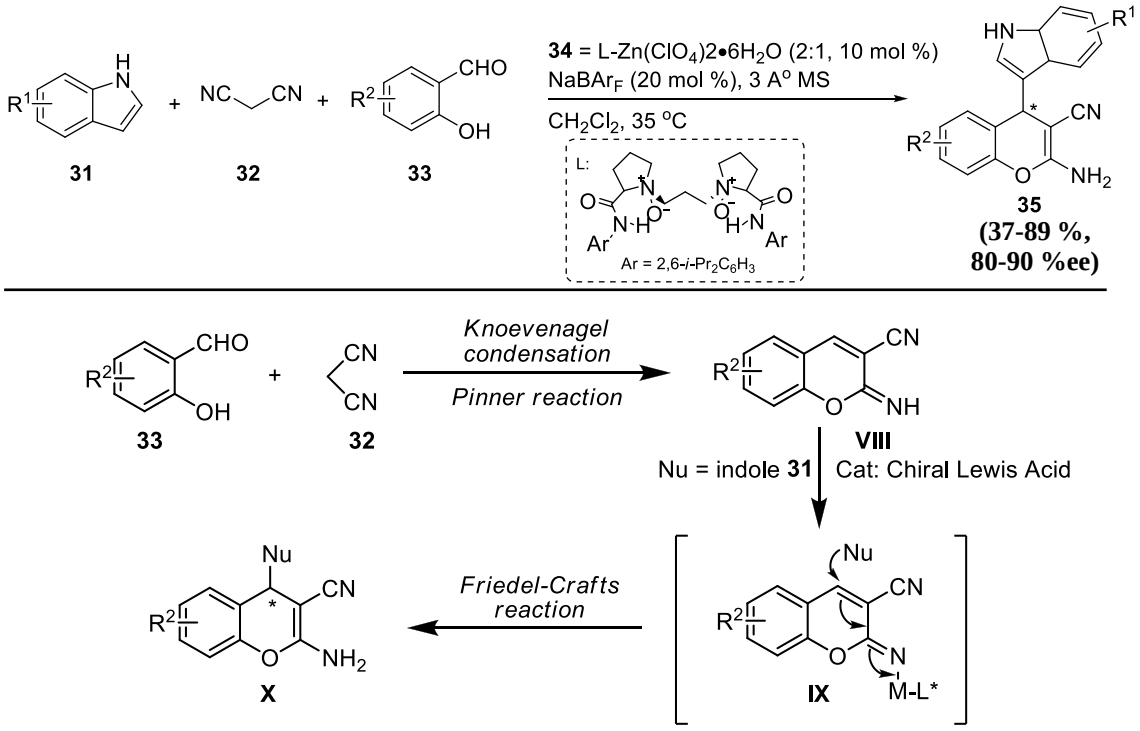
In 2010, Liu and co-workers demonstrated a gold(III)-catalyzed tandem reactions of two molecules of acetophenone derivatives **29** and phenol derivatives **30**. The reactions were accomplished in one-pot fashion involving condensation and annulation reaction in the presence of $AuCl_3$/3AgOTf in dichloroethane at reflux for 6 h to give the desired chromenes in moderate to excellent yields (**Scheme 6**) (Liu *et al*., 2009).

Scheme 6 Gold(III)-catalyzed tandem reaction of ketones **29** with phenols **30** for the synthesis of chromenes



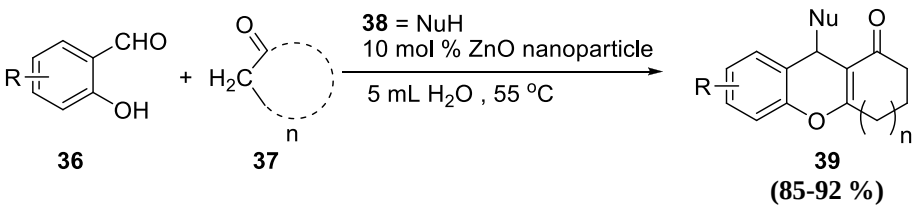
In 2011, Chen and co-workers reported a one-pot synthesis of 2-amino-4-(indol-3-yl)-4*H*-chromenes (**35**) by the use of an *N*,*N'*-dioxide–Zn(II) complex **34** as the catalyst. The transformation occurred *via* the Knoevenagal condensation of salicylaldehydes **33** and malononitrile **32** followed by Pinner reaction to give iminochromene intermediate **VIII**. Then, *N*,*N'*-dioxide–Zn(II) complex coordinated with amino moiety of intermediate **VIII** to provide intermediate **IX**. The last operation was the Friedel-Crafts reaction of indoles **31** to give chromenes **35** in moderate to good yields, up to 89%, with high enantioselectivities, up to 90% ee (**Scheme 7**) (Chen *et al*., 2011).

Scheme 7 The Zn(II) complex-catalyzed of three components for the synthesis of chromenes



In addition, ZnO nanoparticle has been used to synthesize chromenes. In 2013, Ghosh and Das reported a one-pot three component ZnO nanoparticle-mediated synthesis of 4*H*-chromenes **39** from salicylaldehydes **36**, active methylene compounds **37** and various nucleophiles **38**. The reaction condition used 10 mol% of ZnO nanoparticle as a catalyst in water under thermal condition to give desired product in 85 to 92% yields (**Scheme 8**) (Ghosh *et al*., 2013).

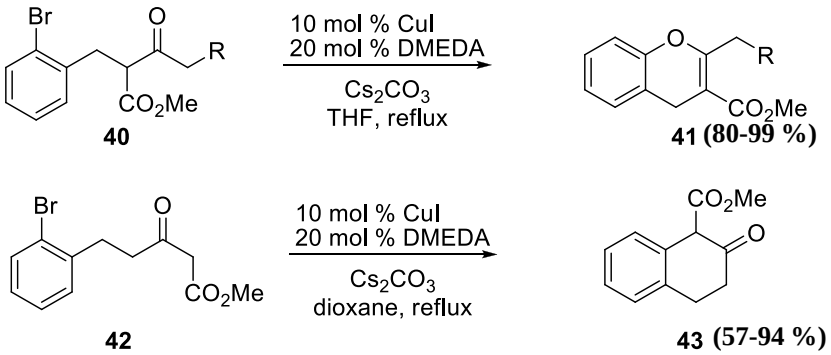
Scheme 8 The one-pot three component ZnO nanoparticle-mediated synthesis of 4*H*-chromenes from salicylaldehydes **36**



Mostly mentioned methods above, substrates were originally contained C(aryl)–O bond. Next, we introduced the reactions cooperated with C(aryl)–O bond construction for the synthesis of chromenes *via* Cu(I)-catalyzed reaction.

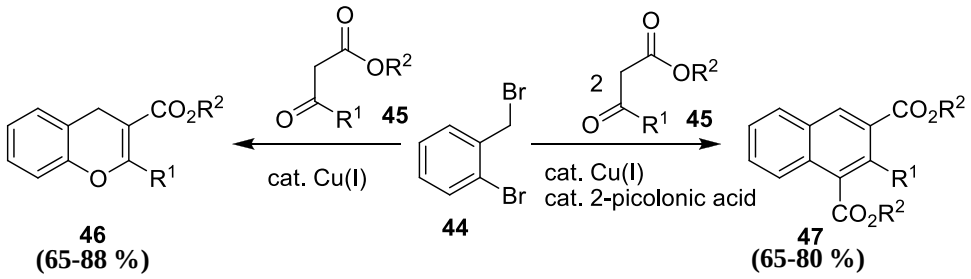
Copper is one of the most selective transition metal catalysts. The syntheses of chromenes *via* copper-catalyzed coupling have been developed consistently. In 2006, Fang and Li synthesized chromene derivatives *via* Cu(I)-catalyzed intramolecular coupling of aryl bromide having 1,3-dicarbonyl moiety. The reaction of *α*-(2-bromobenzyl)-*β*-keto esters **40** with 10 mol% of CuI as a catalyst, 20 mol% of DMEDA as a ligand, Cs_2CO_3 as a base in THF at refluxing temperature provided the corresponding chromenes **41** in high yields *via* O-arylation. In addition, the reaction of *δ*-(2-bromophenyl)-*β*-keto esters **42** in dioxane at reflux afforded the 3,4-dihydronapthalen-2(1*H*)-one **43** derivatives in moderate to good yields *via* C-arylation (**Scheme 9**). They showed that chemoselective O-arylation or C-arylation could be implemented by the appropriate choice of substrates, in which this finding should be important in the further development of copper-catalyzed Ullmann coupling reaction (Fang *et al*., 2006).

Scheme 9 The Cu(I)-catalyzed intramolecular coupling of aryl bromide with 1,3-dicarbonyl moiety



In 2011, Malakar and co-workers reported the Cu(I)-catalyzed domino reactions of 2-bromobenzyl bromide (**44**) with *β*-keto esters **45** to provide chromenes **46** and napthalenes **47**. With CuI as a catalyst, K_3PO_4 as a base, and DMF or DMA as a solvent at 110 ^oC for 24 h, the reaction of bromobenzyl bromides and *β*-keto esters (1.0 equiv.) in the absence of ligand provided the chromenes in good yields. On the other hand, the reaction of *β*-keto esters (2.0 equiv.) with 2-picolinic acid as a ligand, CuI as a catalyst, and Cs_2CO_3 as a base in NMP as a solvent at 100 ^oC for 24 h afforded the napthalenes in moderate to good yields (**Scheme 10**). The results suggested that this reaction depended on the ratio of the substrates and the presence of ligand (Malakar *et al*., 2011).

Scheme 10 The Cu(I)-catalyzed domino reaction of 2-bromobenzyl bromide (**44**) with *β*-keto esters **45**

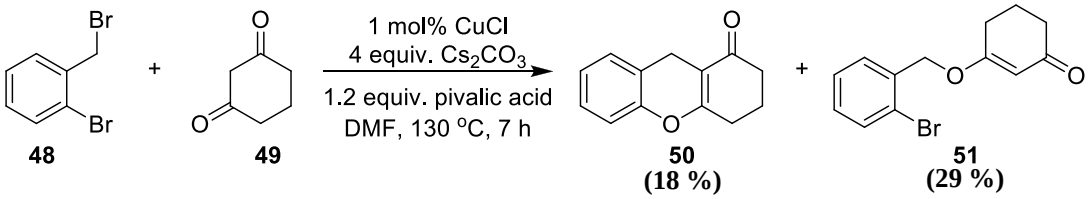


In 2012, Sudheenran and co-workers attempted to synthesize chromenes from 2-bromobenzyl bromide (**48**) with 1,3-cyclohexanedione (**49**) *via* copper-catalyzed reaction in one step (**Scheme 11a**). Unfortunately, they found that the reaction provided a low yield of chromene **50** due to the competition between C- and O-benzylation to give benzyl ether **51** as a side product. For avoiding the O-benzylation, they readily changed the one-pot procedure to two-step procedures for chromene synthesis. First step was a preparation of the C-benzylated 1,3-diones **54** from 2-bromobenzyl bromides **52** with 1,3-diketones **53** under basic conditions with yields ranging from 45% to 83% (**Scheme 11b**). Then, Cu(I)-catalyzed intramolecular O-arylation of **54** was performed by the use of 0.5 mol% of CuCl as a catalyst,

1.2 equiv. of pivalic acid as a ligand, and Cs_2CO_3 as a base in DMF at 130 ^oC for 7 h to give chromenes in good yields (**Scheme 11c**) (Sudheenran *et al.*, 2012).

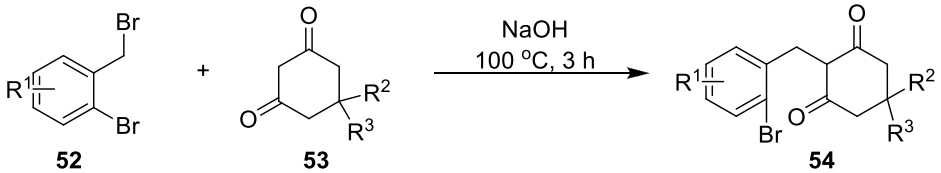
Scheme 11 a) The one-pot copper-catalyzed reaction of 2-bromobenzyl bromide (**48**) with 1,3-cyclohexanedione (**49**); b) Benzylation of cyclic 1,3-dione **53** with 2-bromobenzyl bromide **52**; C) Cu(I)-catalyzed intramolecular O-arylation of the C-benzylated 1,3-diones **54**

a)



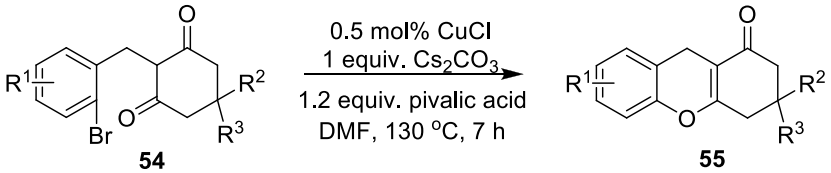
48 **49** **50 (18 %)** **51 (29 %)**

b)



52 **53** **54 (45-83 %)**

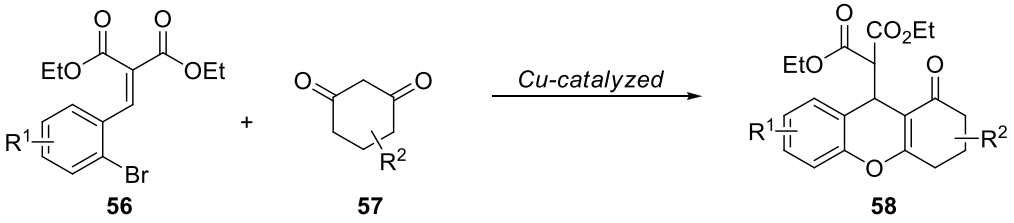
c)



54 **55 (83-99 %)**

Based on the above works, most of methodologies of chromene syntheses were heavily based on phenol derivatives in which the C(aryl)–O bond was originally installed. In this investigation, we reported a synthesis of 4*H*-chromenes **58** containing a functionality at the C-4 position via domino processes, Michael addition and C–O Ullmann type coupling reaction from 2-bromobenzylidenemalonates **56** and 1,3-diketones **57** (Scheme **12**).

Scheme 12 The Cu(I)-catalyzed domino reactions between 2-bromobenzylidene-malonates **56** and 1,3-diketones **57**



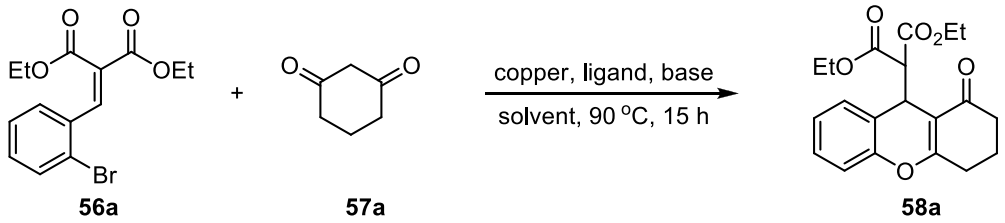
1.1.2 Objective

To find a new method of copper-catalyzed reaction for the synthesis of 4*H*-chromenes under mild conditions.

1.2 RESULTS AND DISCUSSION

Our study toward Cu(I)-catalyzed domino reactions for the synthesis of chromenes started with reaction optimization including catalysts, ligands, bases and solvents. The reaction of diethyl 2-(2-bromobenzylidene)malonate **(56a)** and cyclohexane-1,3-dione **(57a)** was selected as a model study (**Table 1**).

Table 1 Optimization of reaction conditions[a]



Entry	Cu	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	proline	K_2CO_3	ACN	Trace[c]
2	CuI	1,10-phenanthroline	K_2CO_3	ACN	10
3	CuI	DMEDA	K_2CO_3	ACN	52
4	CuI	picolinic acid	K_2CO_3	ACN	42
5	CuI	PPh_3	K_2CO_3	ACN	0
6	CuI	ethylene diamine	K_2CO_3	ACN	Trace
7	CuI	2,2′-bipyridine	K_2CO_3	ACN	12
8	CuBr	DMEDA	K_2CO_3	ACN	15
9	CuCl	DMEDA	K_2CO_3	ACN	0
10	$Cu(OAc)_2$	DMEDA	K_2CO_3	ACN	32
11	-	DMEDA	K_2CO_3	ACN	0
12	CuI	DMEDA	K_3PO_4	ACN	58
13	CuI	DMEDA	Cs_2CO_3	ACN	56
14	CuI	DMEDA	^{t}BuOK	ACN	43

Table 1 (continued)

Entry	Cu	Ligand	Base	Solvent	Yield (%)
15	CuI	DMEDA	NEt_3	ACN	0
16	CuI	DMEDA	K_3PO_4	THF	50
17	**CuI**	**DMEDA**	**Cs_2CO_3**	**THF**	**68**
18	CuI	DMEDA	Cs_2CO_3	Toluene	30
19	CuI	DMEDA	Cs_2CO_3	DMSO	0
20	CuI	DMEDA	Cs_2CO_3	dioxane	15

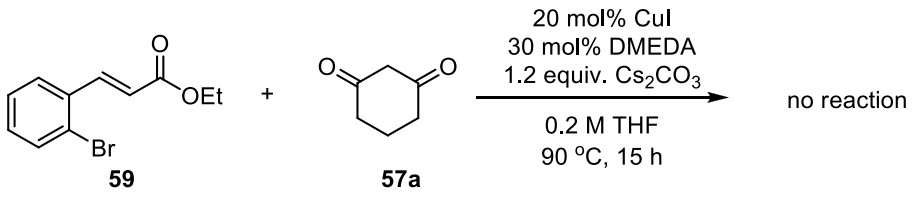
[a] Reaction conditions: **56a** (0.5 mmol), **57a** (0.75 mmol), catalyst (20 mol%), ligand (30 mol%), solvent (0.1 M) at 90 ^oC for 15 h in sealed tube.
[b] Isolated yield.
[c] Trace amount of product observed from the ^1H NMR spectrum of the crude reaction mixture.

The optimization processes were started with a variety of ligands (entries 1-7). With proline, the reaction gave chromene product only trace amount observed from the ^1H NMR spectrum of the crude reaction mixture (entry 1). The yield of chromene was obtained in 10% yield with 1,10-phenanthroline (entry 2). Significantly, changing ligand to DMEDA, the yield of chromene was dramatically improved to 52% (entry 3). We found that the use of picolinic acid as a ligand was also applicable to this reaction, giving the desired chromene in 42 % yield (entry 4). Triphenylphosphine and ethylene diamine were not suitable to the reaction resulting in no product and trace amount of chromene, respectively (entries 5 and 6). Low yield, 12%, was obtained when 2,2'-bipyridine was used (entry 7). Next, we investigated a variety of copper salts. We found that the reaction depended on type of copper salts (entries 3 and 8-10). Chromene was obtained in low yield, 15%, when CuBr was used as a catalyst (entry 8). Furthermore, the reaction with CuCl and $Cu(OAc)_2$ gave no product and low yield, 32% (entries 9 and 10), respectively. Based on these results, the counter ion of copper played a role in this reaction. As we expected, no chromene was observed when the reaction was carried out without a copper catalyst (entry 11). A various bases were also explored (entries 3 and 12-15). With K_3PO_4 and Cs_2CO_3, as a weak inorganic bases, chromene was obtained in 58% and 56% yields, respectively

(entries 12 and 13). Switching to strong base, ^{t}BuOK, the yield of product was slightly decreased to 43% (entry 14). On the other hand, chromene was not observed when NEt_3, an organic base, was used (entry 15). Next, various solvents were investigated. The yield of reaction with K_3PO_4 in THF was 50% (entry 16), slightly lower than that of ACN (entry 12). However, when changing the base to Cs_2CO_3 in THF, the yield increased to 68% (entry 17). These results suggested that the combination of base and solvent affected this reaction. We moved our focus to polarity of solvent. The less polar solvent, toluene, and the more polar solvent, DMSO, were used. The yields dropped dramatically to 30% and 0%, respectively (entries 18 and 19). For the higher boiling point solvent dioxane, the yield decreased to 15% (entry 20). Based on the optimazation, we concluded that the optimized conditions were 20 mol% of CuI as a catalyst, 30 mol% of DMEDA as a ligand, Cs_2CO_3 as a base in THF as a solvent at 90 ^{o}C for 15 hours.

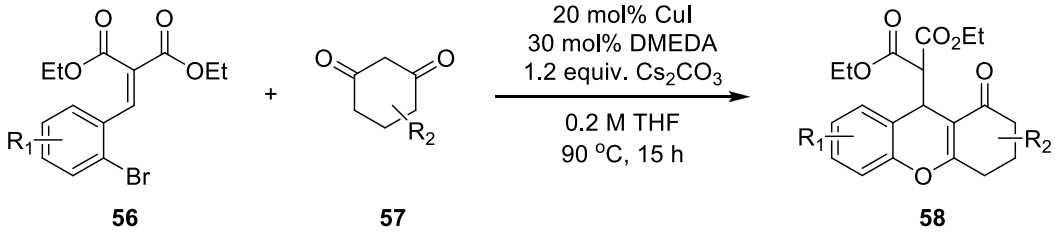
Interestingly, the corresponding chromene was not obtained when we subjected ethyl-3-(2-bromophenyl)acrylate (**59**) to the optimal reaction conditions (**Scheme 13**). We only observed both starting materials **59** and **57a** from the ^{1}H NMR spectrum of the crude reaction mixture. Based on this result, we believed that the diester moiety of benzylidene was required due to the high level of electrophilicity.

Scheme 13 Reaction of ethyl-3-(2-bromophenyl)acrylate (**59**) and cyclohexane-1,3-dione (**57a**)



After having the optimal reaction condition, we next studied an efficiency of the reaction by exploring various starting materials (**Table 2**).

Table 2 The synthesis of chromenes from 2-bromobenzylidenemalonates **56** and 1,3-diketones **57**[a]



56 **57** **58**

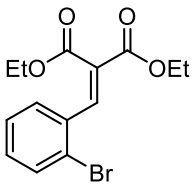
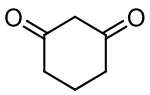
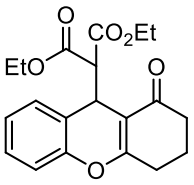
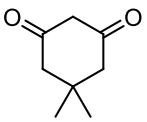
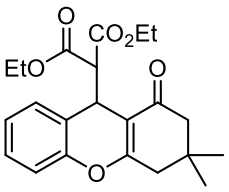
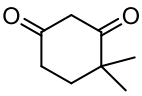
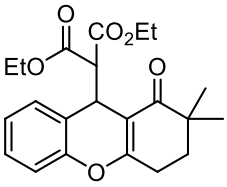
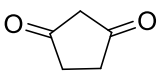
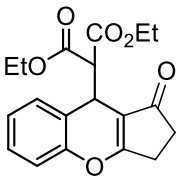
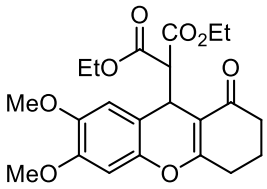
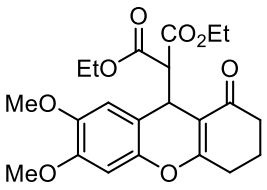
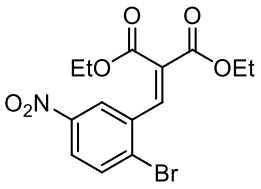
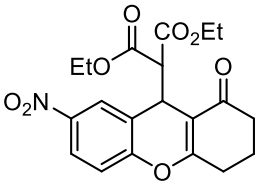
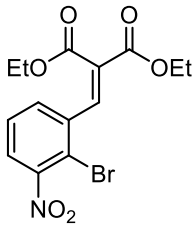
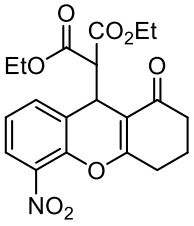
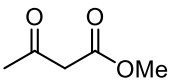
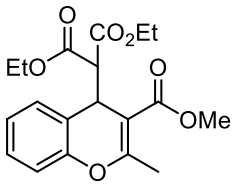
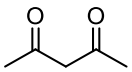
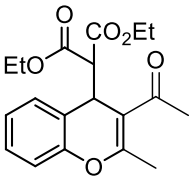
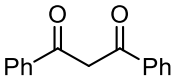
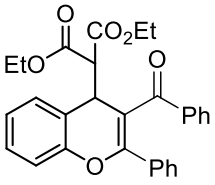
Entry	Benzylidene malonate	1,3-Diketone	Chromene	Yield (%)[b]
1	 **56a**	 **57a**	 **58a**	68
2	**56a**	 **57b**	 **58b**	66
3	**56a**	 **57c**	 **58c**	62
4	**56a**	 **57d**	 **58d**	NR[c]

Table 2 (continued)

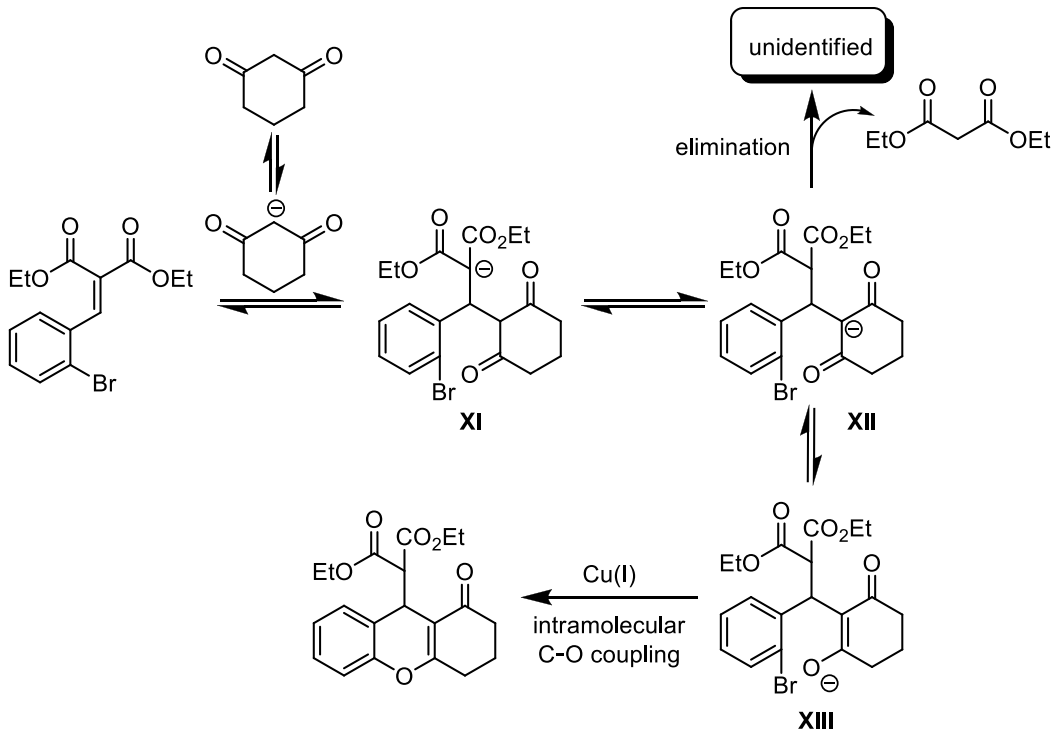
Entry	Benzylidene malonate	1,3-Diketone	Chromene	Yield (%)[b]
5	 **56b**	**57a**	 **58e**	48
6	 **56c**	**57a**	 **58f**	65
7	 **56d**	**57a**	 **58g**	56
8	**56a**	 **57e**	 **58h**	50
9	**56a**	 **57f**	 **58i**	0
10	**56a**	 **57g**	 **58j**	0

[a] Reaction conditions : **56** (0.5 mmol), **57** (0.75 mmol).
[b] Isolated yield.
[c] No reaction.

We firstly considerated various cyclic diketones. The reaction with cyclohexane-1,3-dione (**57a**) provided desired product in 68% yield (entry 1). The similar results were found in the reaction of 5,5-dimethylcyclohexane-1,3-dione (**57b**) and 4,4-dimethylcyclohexane-1,3-dione (**57c**) (entries 2 and 3). These results suggested that the geminal-dimethyl substituents on cyclic diketones had no effect on the reaction. The position of the geminal-dimethyl moiety of chromene **58c** was confirmed by heteronuclear multiple correlation (HMBC) spectroscopy (**Fig 14**). Unfortunately, the five-membered ring diketone was not suitable to the reaction. The reaction of 1,3-cyclopentanedione (**57d**) gave no reaction (entry 4). Only starting material **56a** and **57d** were observed from the ^{1}H NMR spectrum of the crude reaction mixture. Next, the effect of electron density on the benzene ring of the benzylidenemalonates was explored (entries 5 – 7). Both electron-donating and electron-withdrawing groups on the aromatic ring were applicable to the reaction. However, the reaction of benzylidenemalonate with dimethoxy substituents **56b** gave product **58e** in only 48% yield (entry 5). This result was possibly rationalized that increasing electron density on benzene ring reduced the efficiency of Michael acceptor. On the other hand, the reaction of benzylidenemalonate with electron-withdrawing group, nitro group, yielded the corresponding chromenes in 65% and 56% depending on the position of nitro group. The nitro group at the *para*-position to the bromine gave chromene in 65% yield (entry 6). On the other hand, the nitro group at the *ortho*-position gave lower yield, 56% (entry 7), due to a steric hindrance. The results suggested that the electronic effect of benzene ring affected the reaction. Next, we moved to the scope of acyclic dicarbonyls. The reaction of methyl acetoacetate **57e** gave chromenes in moderated yield of 50% (entry 8). Unfortunately, the corresponding chromenes were not obtained when acetylacetone **57f** or 1,3-diphenyl-1,3-propanedione (**57g**) was subjected in the optimal condition (entries 9 and 10).

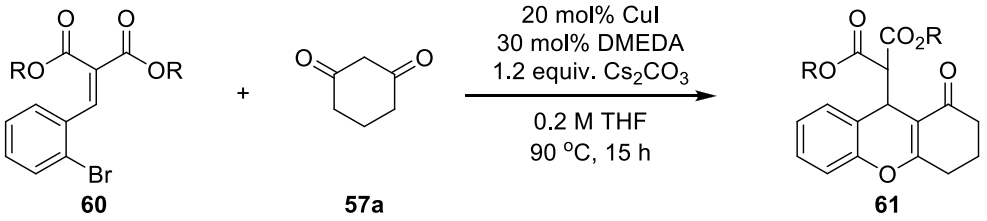
Next, we turned our interested to a possible reaction mechanism (**Scheme 14**). We rationalized the mechanism based on two value information. The first was that an isochromene has never been observed in this reaction, implying that a C(aryl)–C coupling was not formed. The second information was that the diethyl malonate was always found in the ^{1}H NMR spectrum of the crude reaction mixture, resulting in low to moderate yields of chromenes. Based on the information above, the first transformation was possibly the C–C bond formation *via* Michael addition of 1,3-dicarbonyl and benzylidenemalonate to generate the intermediate **XI**. The following step was the isomerization of stabilized carbanion **XI** to the intermediate **XII**. Based on the loss of diethylmalonate and the report from Mayr and co-workers (Mayr *et al*.; 2008), **XII** could alternatively undergo both elimination, resulting in the observation of diethylmalonate, and tautomerization to generate alkoxide intermediate **XIII**. Then, the last transformation was the intramolecular C(aryl)–O coupling to give chromene product.

Scheme 14 The proposed mechanism of Cu(I)-catalyzed domino synthesis of chromenes

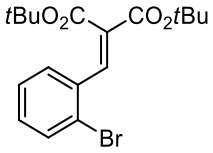
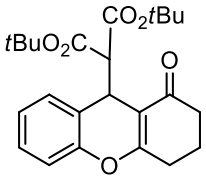
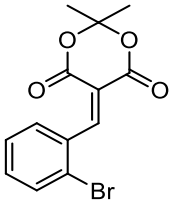
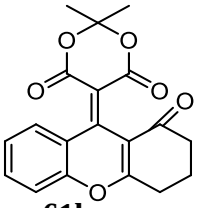
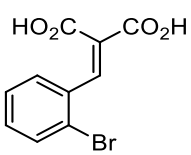
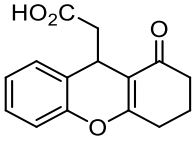


Based on our proposed mechanism, the elimination step was a major competitive reaction causing low yields of the desired chromenes. The result suggested that the nature of benzylidenemalonate was a major impact of the reaction. Therefore, we moved our focus on the diester substituents of benzylidenemalonates in order to avoid undesired elimination pathway (**Table 3**).

Table 3 The chromene formation from a variety of diester substituted benzylidenemalonates.[a]



60 **57a** **61**

Entry	Benzylidene malonate	Chromene	Yield (%)[b]
1	 **60a**	 **61a**	10
2	 **60b**	 **61b**	0
3	 **60c**	 **61c**	65

[a] Reaction condition: **60** (0.5 mmol), **57a** (0.75 mmol).
[b] Isolated yield.

We firstly examined the larger size of the diester group. The reaction of di-*tert*-butyl benzylidene malonate (**60a**) afforded a low yield of a chromene product (entry 1). In addition, the ^{1}H NMR spectrum of the crude reaction displayed the ratio of **60a** and **61a** was 10:1. This result suggested that the bulky diester group was less reactive toward the Cu(I)-catalyzed domino reaction. Next, we considered the geometry of benzylidenemalonate. The representative of *s-cis* benzylidene was 5-(2-bromo- benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**60b**), derived from a Meldrum's acid. The reaction gave no expected product (entry 2). The decomposition of **60b** was observed from the ^{1}H NMR spectrum of the crude reaction mixture. Our last attempt was using benzylidenemaloic acid (**60c**) as a substrate. We hoped that the intermediate **XII** (**Scheme 14**) would undergo decarboxylation instead of elimination after the Michael addition to give a mono acid substitution of intermediate **XIII** (**Scheme 14**). We assumed that with only one carboxylic acid substituent the rate of the elimination was significantly slow. The last step was an intramolecular coupling to provide a corresponding mono acid substituted chromene. We found that the reaction of **60c** provided expected chromene **61c** in 65% yield (entry 3) which was comparable to the yield from **58a** (entry1, **Table 2**). Additionally, the ^{1}H NMR spectrum of the crude reaction, after quenching with acid, showed a mixture of mono- and di-acid chromenes. The result suggested that decayboxylation occurred after C–O coupling had been formed.

1.3 CONCLUSION

We accomplished to synthesize 4*H*-chromene derivatives *via* copper-catalyzed domino reactions from 2-bromobenzylidenemalonates and 1,3-dicarbonyl compounds under simple and mild reaction conditions. The domino processes consisted of Michael addition and intramolecular C(aryl)–O formation. Unfortunately, acyclic dicarbonyls were not applicable. However, the reaction of 1,3-ketoester gave satisfactory yield of chromene. The high level of Michael acceptor of benzylidenemalonate starting materials was required for the domino reaction, resulting in no reaction from ethyl-3-(2-bromophenyl)acrylate. The diacid moiety of benzylidene starting material was also suitable of this reaction, giving a mono acid functionality of a corresponding chromene. Although the yields of our chromenes were low to moderate due to the competing elimination step, this method could provide an alternative way to access to 4*H*-chromene having the functionality at the fourth carbon.

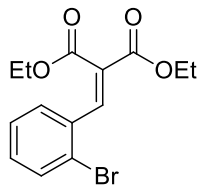
1.4 EXPERIMENTAL

1.4.1 General Information

THF was dried over 4 Å molecular sieves. Solvents for extraction and column chromatography 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). ^{1}H 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 constantsare reported as Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra (IR) were measured on a Perkin Elmer Spectrum GX FT-IR system and recorded on wavenumber (cm^{-1}).

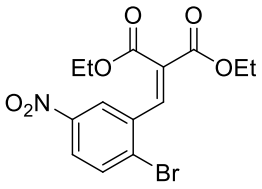
1.4.2 Preparation of Starting Materials

Synthesis of 2-bromobenzylidinemalonates

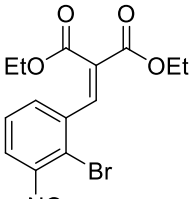


diethyl 2-(2-bromobenzylidene)malonate (56a). Prepared according to literature procedure. Diethyl malonate (10.00 mmol, 1.0 equiv) was added 2-bromobenzaldehyde (12.00 mmol, 1.2 equiv) in EtOH (15.00 mL), then a catalytic amount of HOAc and pyrrolidine were added, the resulting mixture was refluxed overnight. EtOH was removed under reduced pressure. The residue was purified by column chromatography (5:1 Hexanes:DCM) to provide **56a** in 68% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.62 (dd, J = 7.5, 1.2 Hz, 1H), 7.42 (dd, J = 7.5, 1.8 Hz, 1H), 7.29-7.21 (m, 2H), 4.33 (q, J = 7.2 Hz, 2H), 4.22 (q, J = 7.2

Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 163.6, 141.6, 134.0, 133.0, 131.1, 129.4, 128.9, 127.4, 124.5, 61.8, 61.6, 14.1, 13.8. Other data was identical to the literature values (Wang *et al*., 2013).

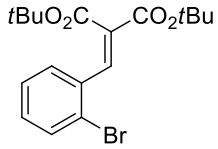


56c

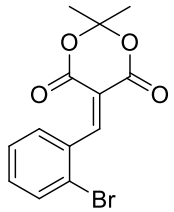


56d

Diethyl 2-(2-bromobenzylidene)malonate **(56a)** (1g, 3.00 mmol, 1.0 equiv.) was slowly added a mixture of HNO_3 (0.40 mL) and H_2SO_4 (2.00 mL) at 0 ^{o}C. The resulting mixture was stirred at 0 ^{o}C for 15 min, then at room temperature for 2 h. The mixture was poured into cool water. The yellow solid mixture was filtered and purified by column chromatography (5:1 Hexanes:EtOAc) to provide **diethyl 2-(2-bromo-5-nitrobenzylidene)malonate (56c)** in 66% yield as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 2.4 Hz, 1H), 8.09 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.89 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 163.0, 147.1, 138.9, 135.4, 134.1, 131.5, 131.3, 125.2, 124.2, 62.2, 62.1, 14.1, 13.9; IR (thin film) ν 2983, 1730, 1528, 1346, 1253, 1066, 740 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{14}BrNO_6$ 393.9902, found 393.9902 and **diethyl 2-(2-bromo-3-nitrobenzylidene)malonate (56d)** in 30% yield as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.74 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.59 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 163.1, 151.0, 140.3, 137.5, 132.3, 131.1, 128.0, 125.6, 115.6, 62.2, 61.9, 14.1, 13.8; IR (thin film) ν 2984, 1731, 1538, 1372, 1241, 1066, 706 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{14}BrNO_6$ 393.9902, found 393.9902.



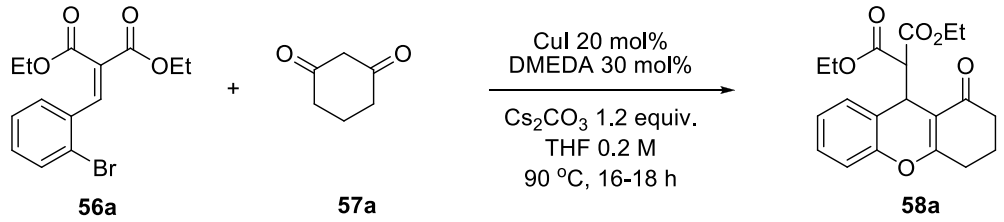
di-tert-butyl 2-(2-bromobenzylidene)malonate (60a). Prepared according to the procedure describe for **56a**. Purification by column chromatography (5:1 Hexanes:EtOAc) to provide **60a** in 65% yield as a white solid.[1]H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.21-7.16 (m, 2H), 1.55 (s, 9H), 1.42 (s, 9H); [13]C NMR (75 MHz, $CDCl_3$) δ 165.0, 163.0, 139.2, 134.3, 132.9, 131.7,130.8, 129.7, 127.1, 124.5, 82.4, 82.3, 28.1, 27.8; IR (thin film) ν 2978, 1723, 1368, 1256, 1157, 1066, 844, 756 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{18}H_{23}BrO_4$ 405.0677, found 405.0677.



5-(2-bromobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (60b). Prepared according to literature procedure.To a solution of Meldrum acid (0.56g, 3.00 mmol) and 2-bromobenzaldehyde in water (15.00 mL) was heated at 75 ^oC for 2 h. The resulting mixture was cooled to room temperature, then the solid mixture was filtered and washed with water (3×20.00 mL). The residue was purified by column chromatography (5:1 Hexanes : EtOAc) to provide **60b** in 60% yield as a white solid. [1]H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 1.83 (s, 6H); [13]C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.9, 156.6, 133.8, 132.9, 131.7, 127.0, 124.9, 118.0, 105.5, 27.8. Other data was identical to the literature values (Mohite *et al*., 2013).

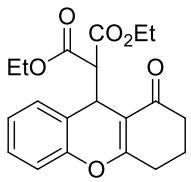
1.4.3 Synthesis of Chromene Derivatives

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



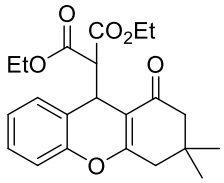
56a **57a** **58a**

A sealed tube equipped with a magnetic stirring bar was charged with diethyl 2-(2-bromobenzylidene)malonate **(56a)** (0.5 mmol), cyclohexane-1,3-dione **(57a)** (0.75 mmol), CuI (0.1 mmol), DMEDA (0.15 mmol) and Cs_2CO_3 (0.6 mmol) in THF (2.5 mL). The resulting mixture was stirred at 90^{o}C for 15 h. After that, the resulting mixture was cooled to room temperature, quenched with NH_4Cl and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (4:2:0.5 Hexanes:CH_2Cl_2:EtOAc) to provide **58a** in 68% yield as a yellow oil.

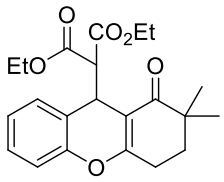


diethyl 2-(1-oxo-2,3,4,9-tetrahydro-1H-xanthen-9-yl)malonate (58a). Yield 68% as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 4.75 (d, *J* = 3.3 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.92 (q, *J* = 7.2 Hz, 2H), 3.69 (d, *J* = 3.3 Hz, 1H), 2.76-2.31 (m. 4H), 2.14-2.01 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 169.0, 168.2, 167.8, 151.0, 129.7, 128.3, 124.7, 121.6, 116.2, 111.6, 61.4, 61.0, 57.7, 36.9, 31.5, 28.0, 20.4, 14.0, 13.7; IR (thin film)

ν 2981, 1731, 1644, 1386, 1238, 760 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{20}H_{22}O_6$ 381.1314, found 381.1314.

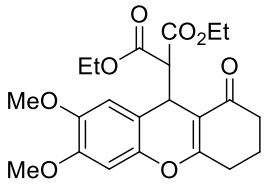


diethyl 2-(3,3-dimethyl-1-oxo-2,3,4,9-tetrahydro-1H-xanthen-9-yl)malonate (58b). Prepared according to the general procedure described for **58a**. Yield 66% as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.21 (td, *J* = 7.0, 1.5 Hz, 1H), 7.08 (td, *J* = 7.0, 1.5 Hz, 1H), 7.00 (dd, *J* = 7.0, 1.5 Hz, 1H), 4.72 (d, *J* = 3.1 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.90 (q, *J* = 7.2 Hz, 2H), 3.77 (d, *J* = 3.1 Hz, 1H), 2.49 (s, 2H), 2.32 (s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.16 (s, 3H), 1.13 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 168.3, 167.9, 167.6, 151.0, 129.9, 128.4, 124.8, 121.4, 116.2, 110.3, 61.2, 61.1, 57.3, 50.7, 41.7, 32.0, 31.4, 29.8, 26.7, 14.0, 13.7; IR (thin film) ν 2960, 1731, 1647, 1384, 1234, 761 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{26}O_6$ 409.1627, found 409.1627.

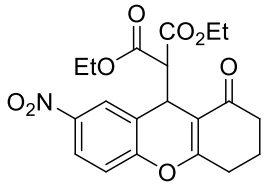


diethyl 2-(2,2-dimethyl-1-oxo-2,3,4,9-tetrahydro-1H-xanthen-9-yl)malonate (58c). Prepared according to the general procedure described for **58a**. Yield 62% as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.22 (td, *J* = 7.8, 1.3 Hz, 1H), 7.08 (td, *J* = 7.8, 1.3 Hz, 1H), 7.00 (dd, *J* = 7.8, 1.3 Hz, 1H), 4.73 (d, *J* = 3.3 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.90 (q, *J* = 7.2 Hz, 2H), 3.67 (d, *J* = 3.3 Hz, 1H), 2.72-2.51 (m, 2H), 1.98-1.82 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.18 (s, 3H), 1.12 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 168.2, 167.8, 167.1, 150.9, 129.9, 128.3, 124.6, 121.3, 116.1, 109.6, 61.4, 60.9, 57.5, 40.3,

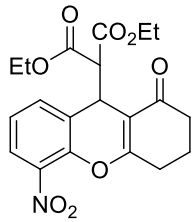
34.0, 31.7, 24.9, 24.8, 24.1, 14.0, 13.7; IR (thin film) ν 2979, 1731, 1645, 1385, 1238, 760 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{26}O_6$ 409.1627, found 409.1627.



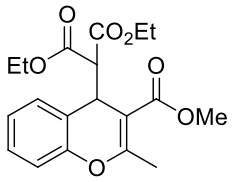
diethyl 2-(6,7-dimethoxy-1-oxo-2,3,4,9-tetrahydro-1H-xanthen-9-yl)malonate (58e). Prepared according to the general procedure described for **58a**. Yield 48% as a brown oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.57 (s, 1H), 4.66 (d, *J* = 3.5 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.92 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 6H), 3.66 (d, *J* = 3.5 Hz, 1H), 2.69-2.30 (m, 4H), 2.12-1.99 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 169.0, 168.5, 167.9, 148.8, 146.0, 144.8, 112.2, 111.8, 111.2, 100.1, 61.4, 61.0, 57.6, 56.2, 56.0, 37.0,31.3, 28.0, 20.5, 14.0, 13.8; IR (thin film) ν 2940, 1729, 1644, 1513, 1385, 1226, 862 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{26}O_8$ 441.1525, found 441.1525.



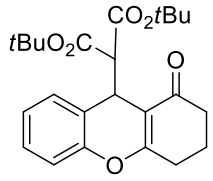
diethyl 2-(7-nitro-1-oxo-2,3,4,9-tetrahydro-1H-xanthen-9-yl)malonate (58f). Prepared according to the general procedure described for **58a**. Yield 65% as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 2.4 Hz, 1H), 8.13 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 1H), 4.77 (d, *J* = 3.6 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.99 (q, *J* = 7.2 Hz, 2H), 3.84 (d, *J* = 3.6 Hz, 1H), 2.77-2.35 (m, 4H), 2.17-1.99 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 168.2, 167.6, 167.4, 155.4, 144.3, 125.9, 124.2, 122.8, 117.0, 111.0, 62.0, 61.3, 56.9, 36.8, 31.5, 27.7, 20.3, 14.0, 13.8; IR (thin film) ν 2982, 1731, 1651, 1527, 1344, 1283, 1043, 749 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{20}H_{21}NO_8$ 426.1164, found 426.1164.



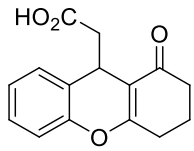
diethyl 2-(5-nitro-1-oxo-2,3,4,9-tetrahydro-1H-xanthen-9-yl)malonate (58g). Prepared according to the general procedure described for **58a**. Yield 56% as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 4.79 (d, *J* = 3.6 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.96 (q, *J* = 7.2 Hz, 2H), 3.70 (d, *J* = 3.6 Hz, 1H), 2.80-2.36 (m, 4H), 2.15-2.07 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 168.1, 167.8, 167.3, 144.0, 138.9, 135.0, 124.5, 124.2, 112.0, 61.8, 61.5, 57.4, 36.8, 31.1, 27.6, 20.3, 14.0, 13.7; IR (thin film) ν 2983, 1731, 1651, 1537, 1384, 1242, 1032, 744 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{20}H_{21}NO_8$ 426.1165, found 426.1164.



diethyl 2-(3-(methoxycarbonyl)-2-methyl-4H-chromen-4-yl)malonate (58h). Prepared according to the general procedure described for **58a**. Yield 50% as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 4.75 (d, *J* = 4.5 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.92 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 3.64 (d, *J* = 4.5 Hz, 1H), 2.46 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 167.8, 167.2, 164.0, 151.5, 129.2, 128.2, 124.3, 121.6, 115.9, 103.3, 61.4, 61.1, 58.8, 51.5, 35.2, 19.7, 14.0, 13.7; IR (thin film) ν 2984, 2953, 1731, 1644, 1221, 760 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{19}H_{22}O_7$ 385.1263, found 385.1263.



di-tert-butyl 2-(1-oxo-2,3,4,9-tetrahydro-1H-xanthen-9-yl)malonate (61a). Prepared according to the general procedure described for **58a**. Yield 10% as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 4.71 (d, *J* = 2.1 Hz, 1H), 3.53 (d, *J* = 2.1 Hz, 1H), 2.72-2.32 (m, 4H), 2.13-2.03 (m, 2H), 1.47 (s, 9H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 168.6, 167.8, 167.2, 151.0, 130.7, 128.1, 124.5, 121.9, 116.1, 112.1, 81.6, 81.0, 59.5, 37.0, 30.9, 28.0, 27.4, 20.5; IR (thin film) ν 2978, 2934, 1722, 1645, 1386, 1233, 842, 757 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{24}H_{30}O_6$ 437.1940, found 437.1940.



2-(1-oxo-2,3,4,9-tetrahydro-1H-xanthen-9-yl)acetic acid (61c). Prepared according to the general procedure described for **58a** but after reaction was completed, quenched with 1M HCl, extracted with EtOAc and concentrated under reduced pressure then the residue was decarboxylated with 1M HCl under refluxed at 90 ^{o}C. After that extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (5:1 Hexanes:EtOAc) to provide **61** in 65% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 4.31 (t, *J* = 5.2 Hz, 1H), 2.66 (d, *J* = 5.2 Hz, 2H), 2.64-2.34 (m, 4H), 2.20-1.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 176.4, 168.6, 150.0, 129.0, 128.0, 125.1, 124.1, 116.4, 112.6, 42.4, 36.8, 28.4, 27.9, 20.5; IR (thin film) ν 2951, 1728, 1389, 1233, 1186, 757 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{15}H_{14}O_4$ 281.0790, found 281.0790.

CHAPTER 2

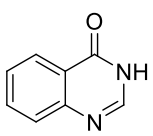
Cu(I)-Catalyzed Domino Reactions of Quinazolinone Syntheses

2.1 INTRODUCTION

2.1.1 Introduction

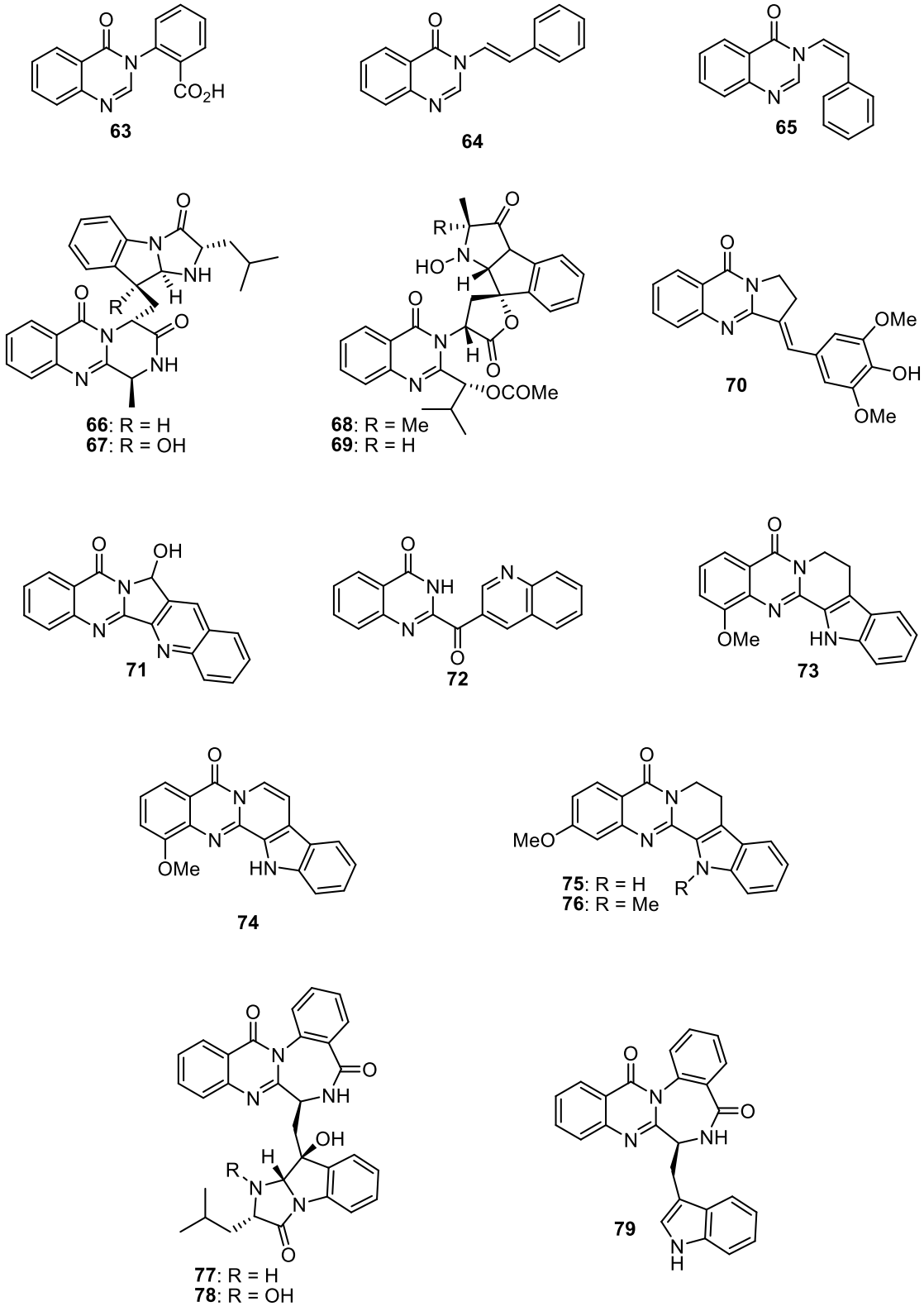
Quinazolinones with a 4*H* skeletons **62** (**Figure 3**), are one of the most important N-containing alkaloid natural products. They were isolated from a number of families of animals, microorganisms and plants (Rashmi *et al*., 2011). Quinazolinones and their derivatives are known to show a broad spectrum of biological and pharmalogical activities. Based on literature research, there are more than 40,000 biologically active compounds (Li *et al*., 2013). Examples of bioactive quinazolinones are shown in **Figure 4**. 3-(2-Carboxyphenyl)-4(3*H*)-quinazolinone (**63**) exhibited anti-endotoxic activity. (*E*)-bogorin (**64**), (*Z*)-bogorin (**65**), (–)-fumiquinazoline H (**66**) and (–)-fumiquinazoline I (**67**) displayed anti-fungal activity. 27-epi-tryptoquivaline (**68**) and 27-epinortryptoquivaline (**69**) showed tremorgenic property. isaindigotone (**70**) displayed antioxidant activity. luotonin B (**71**) and luotonin F (**72**) were active toward leukemia P388 cells and anti-tumor activity, respectively. 1-methoxyrutaecarpine (**73**) showed anti-platelet aggregation activity. 1-methoxy-7,8-dehydrorutaecarpine (**74**) showed cytotoxic activity against P-388 and HT-29 cell lines in *vitro*. 2-methoxyrutaecarpine (**75**) and 2-methoxy-13-methylrutaecarpine (**76**) exhibited anti-malarial. Furthermore, (–)-asperlicin (**77**), asperlicin B (**78**) and asperlicin C (**79**) displayed agonist of the peptide hormone CCK (Mashke *et al*., 2006).

Figure 3 Core structure of 4*H*-quinazolinone



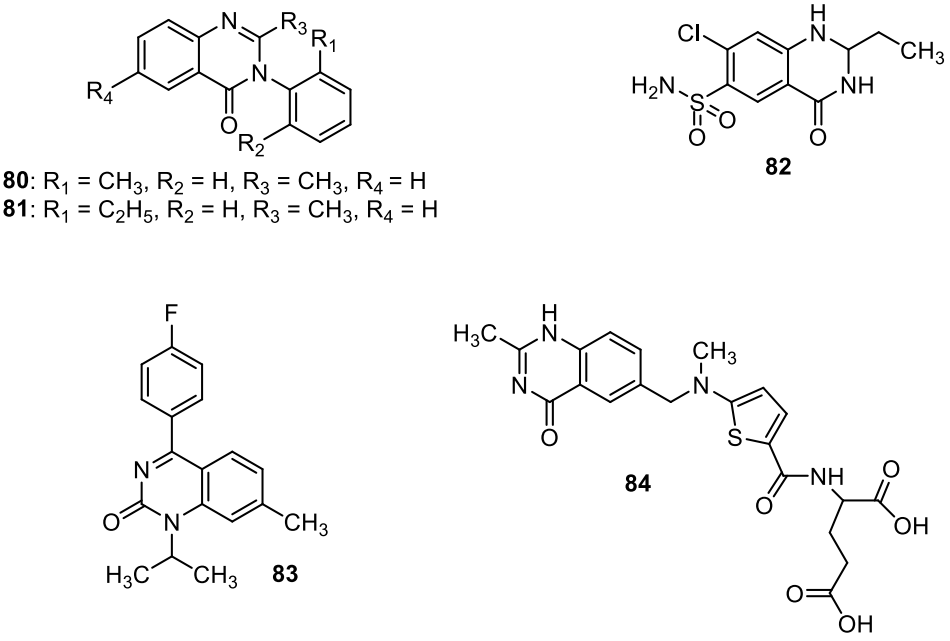
62

Figure 4 Examples of bioactive quinazolinines



Moreover, quinazolinone derivatives have been developed for clinical treatments. Some of them are shown in **Figure 5**. Methaqualone (**80**) and etaqualone (**81**) are used as sedative-hypnotic drug. Quinithazone (**82**) is used for antihypertensive. Fluproquazone (**83**) is used as NSAID drug. In addition, raltitrexed (**84**) is applied to treat cancer cells (Rashmi *et al.*, 2011).

Figure 5 Examples of quinazolinones in clinical treatment



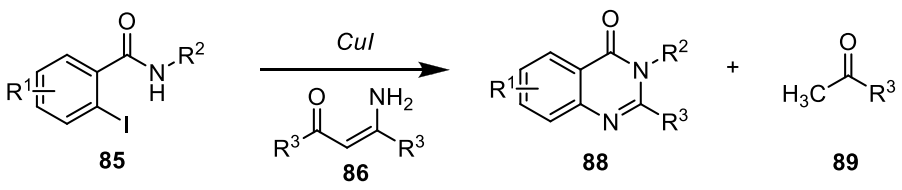
Due to the wide range of biological activities of quinazolinones and their common occurs in natural products, a number of synthetic methodologies have been introduced consistenly (Hikawa *et al.*, 2012).

As a part of our research group targets, we have been interested in finding new methods to synthesize a variety of N-containing heterocycles. In 2014, our group reported the copper-catalyzed synthesis of quinazolinone derivatives from 2-iodobenzamides **85** with acyclic enaminones **86** and cyclic enaminones **87a** to give desired quinazolinones in low to good yields (**Scheme 15**) (Songsichan *et al.*, 2014).

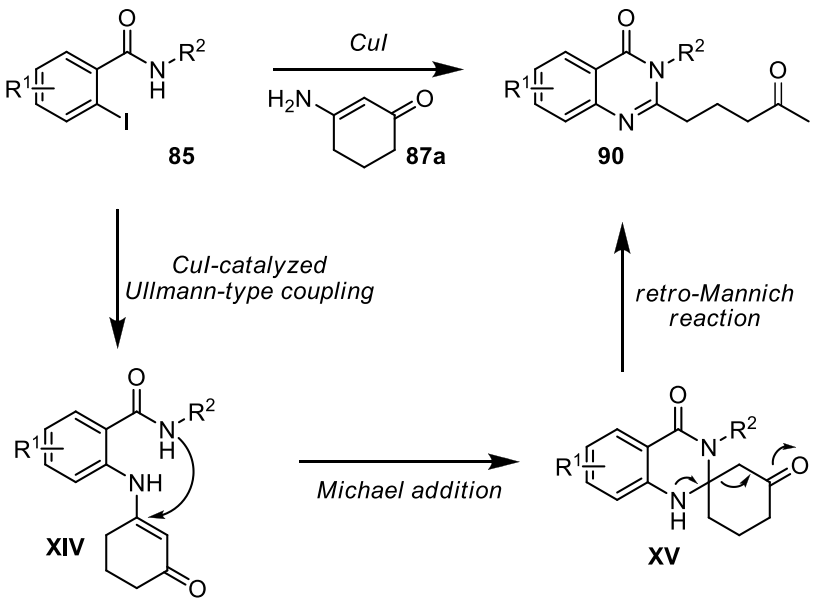
This reaction was completely operated *via* domino reaction consisting of Cu(I)-catalyzed C(aryl)–N bond formation, Michael addition and retro-Mannich reaction. We found that the reaction could carry out in the absence of external ligand for acyclic enaminones. However, the product yields were moderate. On the other hand, the ligand was required for the reaction of cyclic enaminone.

Scheme 15 Copper-catalyzed domino reactions of *N*-benzyl 2-iodobenzamide **85** with a) acyclic enaminones **86** and b) cyclic enaminone **87a**

a)

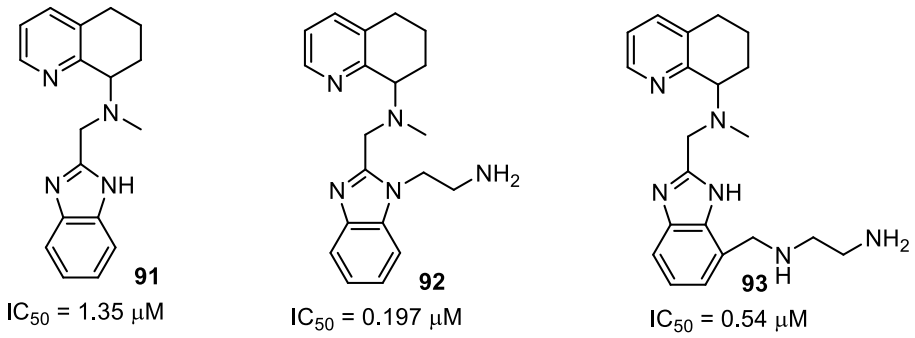


b)



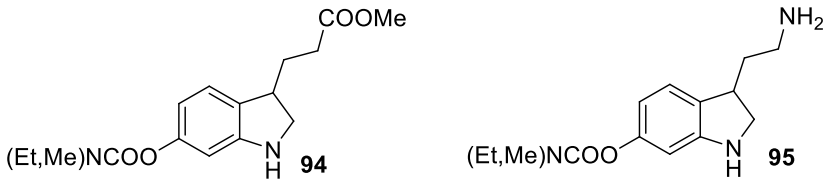
Based on this work, we are interested in the reaction of 2-iodobenzamides with cyclic enaminones because the quinazolinone products contained ketone functional group which could be further modified to obtain various quinazolinones. A terminal amine side chain has been a very important moiety which was embedded in a variety of bioactive compounds. For example, in 2009, Gudmundsson and co-workers synthesized benzimidazole derivatives with amine side chain attached to the N-1 and C-4 position for an activity against HIV-1 evalutions. They found that compounds with amine side chain **92** and **93** displayed a good activity against HIV-1 with IC_{50} values of 0.197 and 0.54 µM, respectively, comparing to a simple benzimidazole **91** (**Figure 6**) (Gudmundsson *et al*., 2009).

Figure 6 The structure and IC_{50} value of benzimidazole



In 2014, Furman and co-workers showed that an indoline with amino side chain **95** displayed an anti-inflammatory activity with an IC_{50} value of 0.40 µM, while compound **94** with a propionic ester showed an IC_{50} values of 7.40 µM (**Figure 7**) (Furman *et al*., 2014).

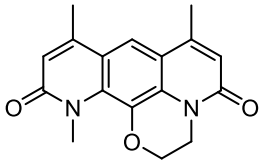
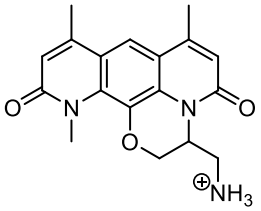
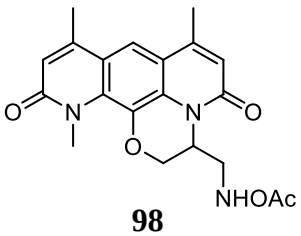
Figure 7 The structures and IC_{50} values of ester and amine derivatives of indoline



IC_{50} = 7.40 μM IC_{50} = 0.40 μM

In addition, Richter and co-workers recently reported compounds that are able to traverse to the outer membrane of gram-negative bacteria, containing two cellular membranes which are very difficult for small molecules to cross (**Table 4**) (Richter *et al.*, 2017).

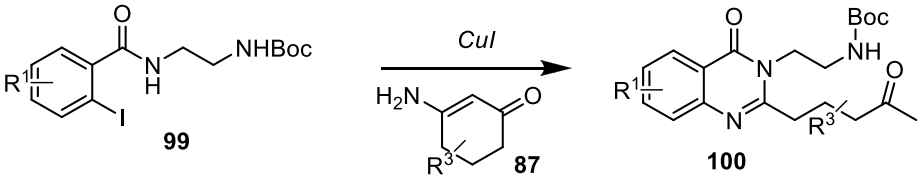
Table 4 The structures and IC_{50} values of 6DNM (**96**), 6DNM-NH_3 (**97**) and 6DNM-amide (**98**)

Entry	Compound	Rotatable bond value	Globularity value	IC_{50} value (μM)
1	 **96**	0	0.04	>32
2	 **97**	1	0.09	0.5
3	 **98**	1	0.13	>32

They evaluated the IC_{50} values against *E*.coli. They found that the 6DNM (**96**) and 6DNM-amide (**98**) showed weak activity (entries 1 and 3). Interestingly, 6DNM-NH_3 (**97**) displayed an activity with the lowest values of IC_{50} at 0.5 µM. Based on their findings, the key factors of compounds in order to cross the membrane of gram-negative bacteria were amine moiety and low globularity.

According to the importance of the amine moiety and quinazolinones, we are interested in synthesis of quinazolinone derivatives having free amine moiety (**Scheme 16**).

Scheme 16 Plan for the synthesis of quinazolinone derivatives *via* Cu(I)-catalyzed domino reactions



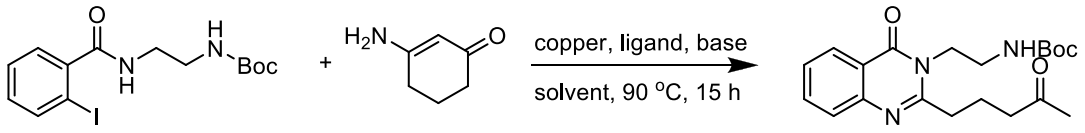
2.1.2 Objective

To synthesize quinazolinone derivatives having free amine moiety *via* copper-catalyzed domino reactions.

2.2 RESULTS AND DISCUSSION

The 2-iodobenzamide **99a** and cyclic enaminone **87a** were selected as a reaction model for the optimization of quinazolinone synthesis *via* copper-catalzed domino reaction (**Table 5**). A variety of variables, such as copper salts, ligands, bases and solvents, were investigated.

Table 5 Optimization of reaction conditions[a]



99a **87a** **100a**

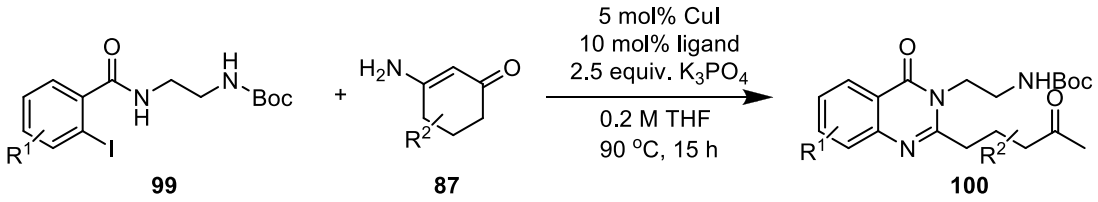
Entry	Cu	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	proline	Cs_2CO_3	ACN	63
2	CuI	proline	Cs_2CO_3	Toluene	72
3	CuI	proline	Cs_2CO_3	THF	83
4	CuI	proline	Cs_2CO_3	DMF	0
5	CuI	proline	Cs_2CO_3	DMSO	0
6	CuI	proline	K_2CO_3	THF	0
7	CuI	proline	K_3PO_4	THF	85
8	CuI	DMEDA	K_3PO_4	THF	82
9	**CuI**	**1,2-*trans*-diaminocyclohexane**	**K_3PO_4**	**THF**	**88**
10	CuI	picolinic acid	K_3PO_4	THF	78
11	CuI	no ligand	K_3PO_4	THF	72
12	CuCl	1,2-*trans*-diaminocyclohexane	K_3PO_4	THF	67
13	CuBr	1,2-*trans*-diaminocyclohexane	K_3PO_4	THF	70
14	$Cu(OAc)_2$	1,2-*trans*-diaminocyclohexane	K_3PO_4	THF	54

[a] Reaction conditions: **99a** (0.5 mmol), **87a** (0.6 mmol), catalyst (5mol%), ligand (10 mol%), Base (2.5 equiv), solvent (0.2 M), 90 °C, 15 h in sealed tube.
[b] Isolated yield.

For the initially optimization condition, we began, based on our previous work, with 5 mol% of CuI as a catalyst, 10 mol% of proline as a ligand, and 2.5 equiv. of Cs_2CO_3 as a base in 0.2 M of ACN at 90 ^oC for 15 h. The reaction gave an expected quinazolinone in 63% yield (entry 1). The reaction in toluene, non-polar solvent, gave product in moderate yield, 72% (entry 2). With slightly higher polar solvent, the yield of quinazolinone was increased to 83% yield in THF (entry 3). In contrast polar solvents, DMF and DMSO, gave no reaction (entries 4 and 5). Next, we focused on a variety of common bases for copper-catalyzed reaction. Surprisingly, the reaction with K_2CO_3 gave no product (entry 6). On the other hand, with K_3PO_4 the reaction gave a comparable yield to that of Cs_2CO_3 (entry 7). Some commercially available ligands were subjected to our investigation, such as DMEDA, 1,2-*trans*-diaminocyclohexane and picolinic acid (entries 8-10). Our domino reaction was applicable to various ligands, resulting in high yields of product. With DMEDA the yield was 82% (entry 8). Changing ligand to 1,2-*trans*-diaminocyclohexane, the yield was slightly increased to 88% (entry 9). Picolinic acid also gave product in good yield, 78% (entry 10). As the result from our previous quinazolinone formation, we reported that the reaction of cyclic enaminone and 2-iodobenzamide required the assist of a ligand. Interestingly, without an external ligand the reaction also proceeded well giving quinazolinone in good yield 72% (entry 11). Based on these results, the diamino moiety of the 2-iodobenzamide **99a** could possibly function as a ligand allowing the reaction to occur smoothly. Our last variable was copper salts. The reaction with CuCl gave moderate yield, 67% (entry 12). The similar result was found in the reaction with CuBr (entry 13). The $Cu(OAc)_2$ also catalyzed this reaction. However, the yield of product was moderate yield, 54% (entry 14).

The substrate scopes for the Cu(I)-catalyzed domino synthesis of quinazolinones were examined under the optimal condition which was the use of 5 mol% of CuI as a catalyst, 10 mol% of 1,2-*trans*-diaminocyclohaxane as a ligand, and K_3PO_4 as a base in THF 0.2 M at 90 ^oC for 15 h (**Table 6**).

Table 6 Substrate scope for the CuI-catalyzed synthesis of quinazolinones from 2-iodobenzamides **99** and cyclic enaminones **87** [a]



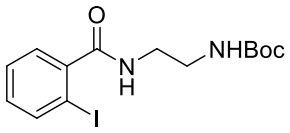
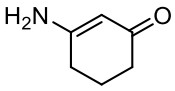
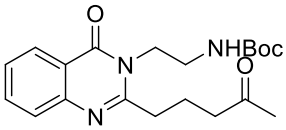
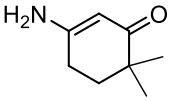
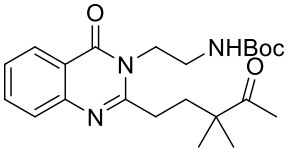
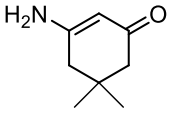
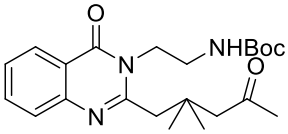
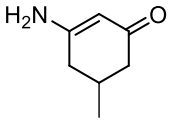
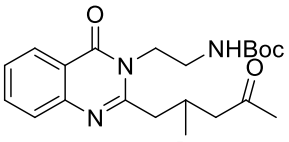
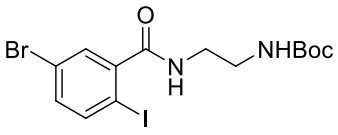
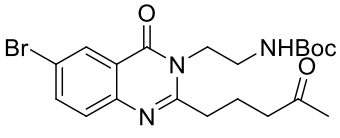
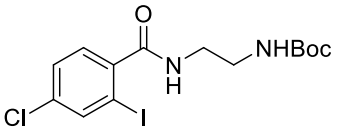
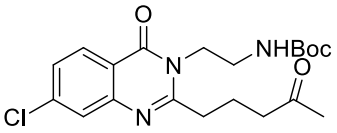
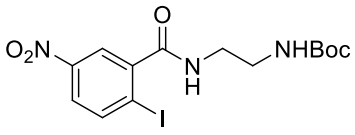
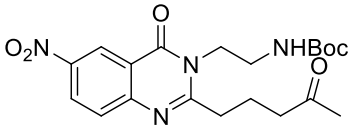
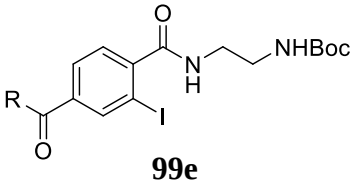
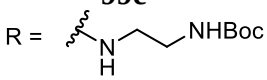
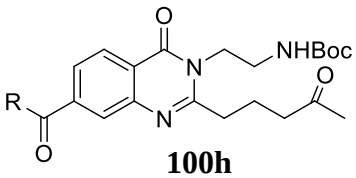
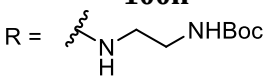
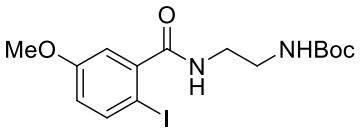
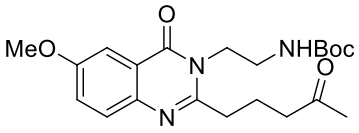
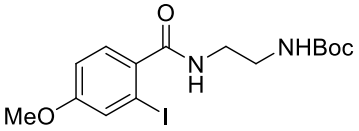
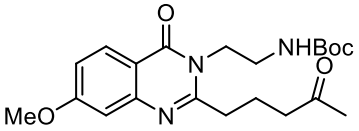
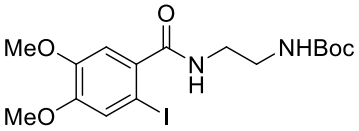
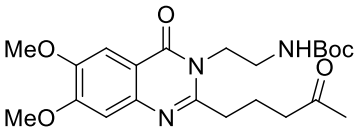
Entry	2-iodobenzamide	Enaminone	Quinazolinone	Yield (%)[b]
1	 **99a**	 **87a**	 **100a**	88
2	**99a**	 **87b**	 **100b**	74
3	**99a**	 **87c**	 **100c**	0
4	**99a**	 **87d**	 **100d**	77
5	 **99b**	**87a**	 **100e**	80
6	 **99c**	**87a**	 **100f**	70

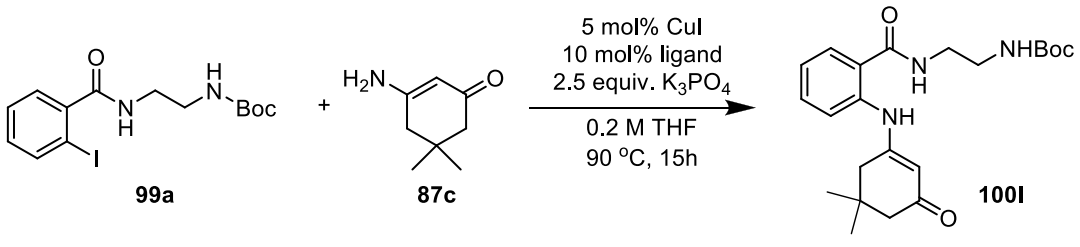
Table 6 (continued)

Entry	2-iodobenzamide	Enaminone	Quinazolinone	Yield (%)[b]
7	 **99d**	**87a**	 **100g**	54
8	 **99e** 	**87a**	 **100h** 	77
9	 **99f**	**87a**	 **100i**	78
10	 **99g**	**87a**	 **100j**	74
11	 **99h**	**87a**	 **100k**	80

[a] Reaction conditions: 0.5 mmol of **99**, 0.6 mmol of **87**, 1,2-*trans*-diaminocyclohexane as a ligand.
[b] Isolated yield.

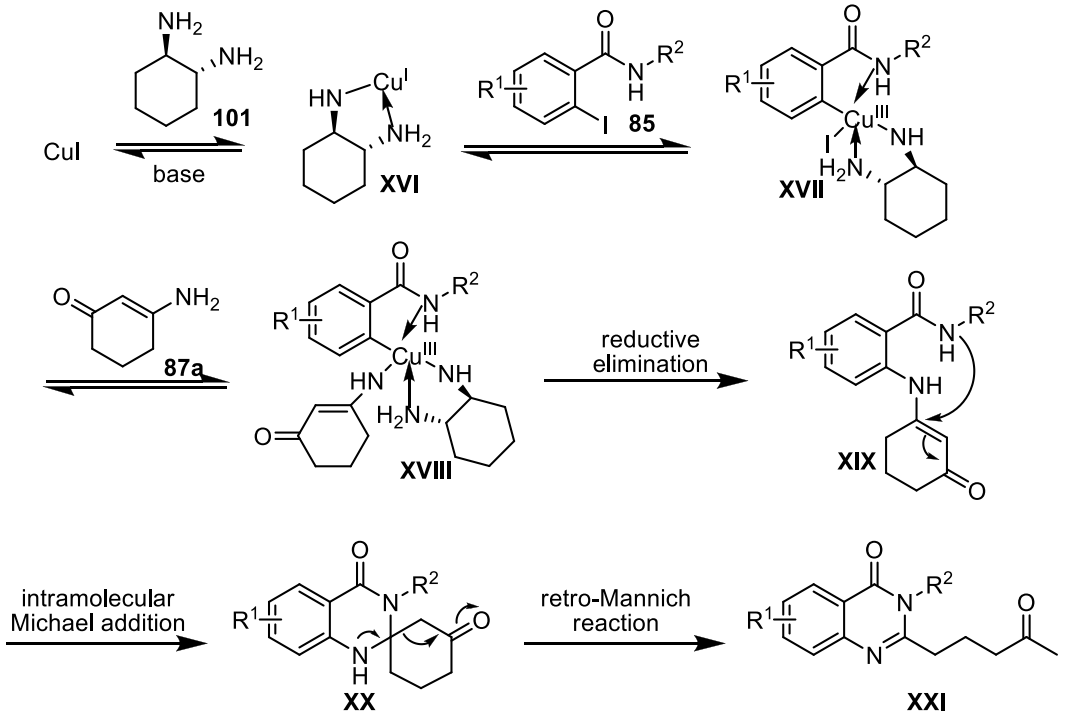
Firstly, we considered a series of six-membered cyclic enaminones (entries 1-4). The 3-amino-6,6-dimethycyclohex-2-enone (**87b**) was applicable to the reaction, resulting in good yield 74% (entry 2). Unfortunately, with 3-amino-5,5-dimethylcyclohex-2-enone (**87c**) the reaction gave no yield of quinazolinone (entry 3). However, we found that the major product was an intermediate adduct **100l** of C(aryl)–N bond formation in 88% yield (**Scheme 17**). The different result was found when we subjected 3-amino-5-methylcyclohex-2-enone (**87d**) to the optimal condition. The yield of product was 77% (entry 4). The results from the cyclic enaminone **87c** and **87d** suggested that the steric hindrance of geminal dimethyl blocked the intramolecular Michael addition of the intermediate adduct. The 2-iodobenzamides with halogen substituents, Br and Cl, were suitable in this reaction. Good yield, 80%, was obtained from the reaction of 5-bromo-2-iodobenzamide (**99b**) (entry 5). The 4-chloro-2-iodobenzamide (**99c**) also gave product in similar yield, 70%, of quinazolinone product (entry 6). The 2-iodobenzamides having electron-withdrawing substituents were also applicable to the reaction. However, the yields of quinazolinone were slightly decreased. The reaction of the 5-nitro-2-iodobenzamide (**99d**) provided quinazolinone in moderate yield, 54% (entry 7). On the other hand, having electron-withdrawing substituent at the fourth position slightly affected the yield. The 4-amido-2-iodobenzamide (**99e**) gave a corresponding quinazolinone in good yield (entry 8). Next, we explored the electron-donating group of 2-iodobenzamide. Delightfully, we found that 2-iodobenzamides with mono- (**99f** and **99g**) or dimethoxy (**99h**) substituent generally gave good yield of the corresponding quinazolinones (entries 9-11).

Scheme 17 The reaction of 2-iodobenzamide **99a** with 3-amino-5,5-dimethyl-cyclohex-2-enone (**87c**)



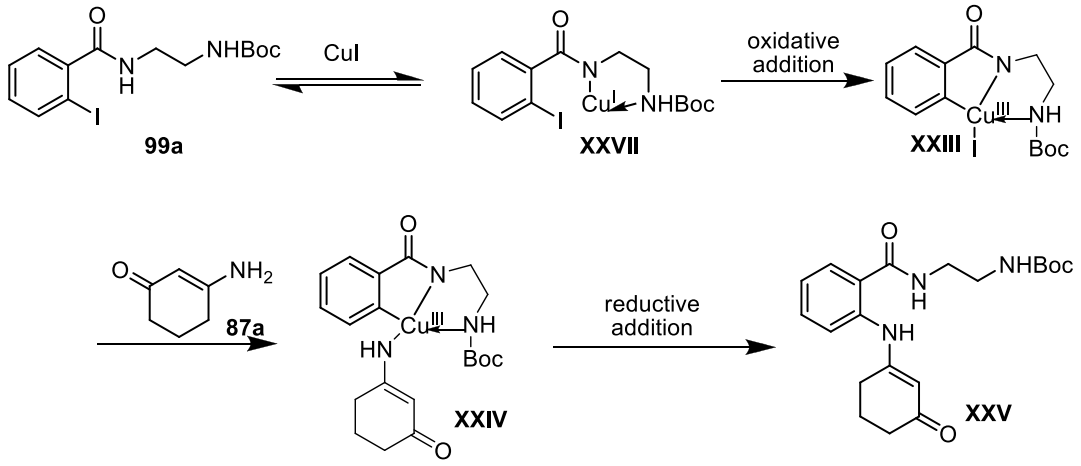
Based on the results from **Scheme 17** and previous report, The possible mechanism suggested that the C(aryl)–N bond was the first bond formation of the reaction. The initial mechanism involves the association of CuI and 1,2-*trans*-diaminocyclohexane (**101**) to form the active Cu(I) complex **XVI** (Ma *et al*., 2008). Then, the oxidative addition of **XVI** and 2-iodobenzamide **85** gave a complex **XVII**, followed by the ligand exchange with enaminone **87a** to generate complex **XVIII**. The reductive elimination of **XVIII** took place to form the *N*-arylation intermediate **XIX**. Subsequently, the Michael addition of **XIX** provided a dihydroquinazolinone intermediate **XX**. The last step was the retro-Mannich reaction, giving a corresponding quinazolinone product **XXI** (**Scheme 18**).

Scheme 18 The proposed mechanism of the Cu(I)-catalyzed domino reactions for the synthesis of quinazolinones



For a possible mechanism of the reaction without an external ligand (**Scheme 19**), diamino moiety of 2-iodobenzamide **99a** played the role of a ligand which coordinated with CuI to generate complex **XXII**. Then, the oxidative addition of **XXII** formed the complex **XXIII**. The enaminone **87a** performed as the nitrogen nucleophile to form complex **XXIV**, and then underwent reductive elimination to give intermediate **XXV**, followed by the sequential mechanism described in **Scheme 18**.

Scheme 19 The possible mechanism of the reaction without external ligand



2.3 CONCLUSION

The quinazolinone derivatives with amine moiety were obtained from 2-iodobenzamides and cyclic enaminones *via* Cu(I)-catalyzed domino reactions under mild conditions. The domino process consisted of C(aryl)–N bond formation, intramolecular Michael addition and retro-Mannich reaction. The domino reactions were suitable to a wide range of *N*-(2-aminoethyl)-2-iodobenzamides, starting materials, to accomplish the corresponding quinazolinones in moderate to high yields. Interestingly, the copper-catalyzed domino reactions of six-membered enaminones and *N*-(2-aminoethyl)-2-iodobenzamides could be carried out smoothly without external ligand to obtain product in good yield. The reasonable rationale was that the diamino moiety of 2-iodobenzamides possibly operated as a ligand assisting the domino processes. We have also found that the steric hindrance of enaminone, the geminal dimethyl groups at the fifth position, highly affected the reaction, resulting in no quinazolinone formation. Only the C(aryl)–N coupling intermediate was obtained in high yield. Although other ring size of cyclic enaminones were not included in this work due to the limited of research time, the basic knowledge of this domino reactions could be highly useful for further application.

2.4 EXPERIMENTAL

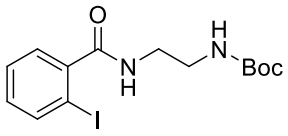
2.4.1 General Information

THF was dried over 4 Å molecular sieves. Solvents for extraction and column chromatography 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). ^{1}H 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 constantsare reported as Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra (IR) were measured on a Perkin Elmer Spectrum GX FT-IR system and recorded on wavenumber (cm^{-1}).

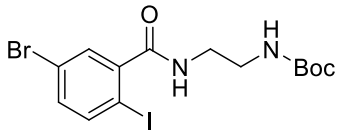
2.4.2 Preparation of Starting Materials

General Procedure A : Synthesis of 2-Iodobenzamides

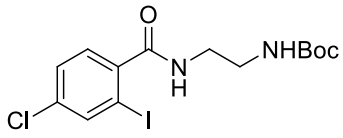
Prepared according to literature procedure (Kitching *et al*., 2012). A flame-dried round bottom flask was charged with 1.0 equiv of 2-iodobenzoic acid derivatives in CH_2Cl_2 (0.3 M) and DMF (2 drops), followed by the addition of 1.25 equiv. of oxalyl chloride at 0 ^{o}C. The reaction mixture was allowed to stir at room temperature for 4 hours. After that, the mixture was evaporated to dryness. The prepared acid chloride was dissolved in CH_2Cl_2 (0.3 M). The solution of Boc-amine (1.5 equiv.) and triethylamine (3.0 equiv.) was added at 0 ^{o}C. The reaction mixture was allowed to stir at room temperature for 15 hours. The reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to afford the title compound.



***tert*-butyl 2-(2-iodobenzamido)ethylcarbamate (99a).** Prepared according to general procedure A. Yield 88% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.41-7.29 (m, 2H), 7.13-7.02 (m, 1H), 6.59 (brs, 1H), 5.11 (brs, 1H), 3.55 (q, *J* = 5.6 Hz, 2H), 3.39 (q, *J* = 5.6 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 156.8, 142.0, 139.8, 131.1, 128.1, 128.0, 92.5, 79.8, 40.9, 40.1, 28.4; IR (thin film) ν 3318, 2976, 2930, 1693, 1640, 1253, 1015, 751 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{19}IN_2O_3$ 413.0338, found 413.0338.

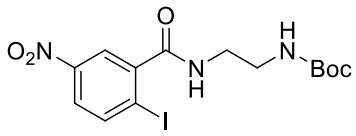


***tert*-butyl 2-(5-bromo-2-iodobenzamido)ethylcarbamate (99b).** Prepared according to general procedure A. Yield 75% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.55 (brs, 1H), 4.97 (brs, 1H), 3.56 (q, *J* = 5.6 Hz, 2H), 3.42 (q, *J* = 5.6Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.4, 155.7, 144.8, 140.9, 133.4, 130.6, 121.4, 92.3, 77.7, 39.9, 39.8, 28.3; IR (thin film) ν 3349, 3295, 2926, 1689, 1650, 1529, 1345, 1170, 841 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{18}BrIN_2O_3$ 490.9443, found 490.9443.

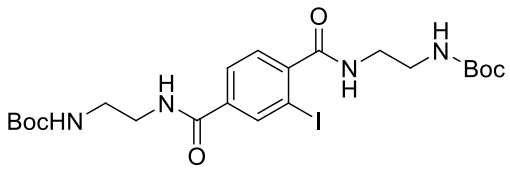


***tert*-butyl 2-(4-chloro-2-iodobenzamido)ethylcarbamate (99c)**. Prepared according to general procedure A. Yield 70% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.39-7.35 (m, 2H), 6.62 (brs,1H), 5.03 (brs, 1H), 3.60 (q, *J* = 5.6 Hz, 2H), 3.45 (q, *J* = 5.6 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.6, 156.1, 142.3, 138.4, 134.5, 129.7, 128.4, 95.0, 78.2, 39.8, 39.7, 28.7; IR (thin film) ν

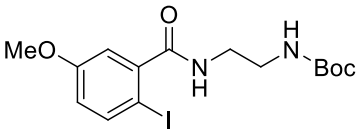
3263, 2971, 2927, 1629, 1599, 1252, 1168, 773 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{12}H_{18}ClIN_2O_3$ 446.9948, found 446.9948.



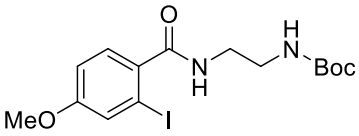
***tert*-butyl 2-(2-iodo-5-nitrobenzamido)ethylcarbamate (99d)**. Prepared according to general procedure A. Yield 78% as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 2.6 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.91 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.96 (brs, 1H), 5.07 (brs, 1H), 3.59 (q, *J* = 5.8 Hz, 2H), 3.42 (q, *J* = 5.8 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.7, 156.2, 147.6, 144.7, 141.3, 125.1, 122.6, 103.8, 78.2, 40.0, 39.7 28.7; IR (thin film) ν 3349, 3295, 2926, 1689, 1650, 1529, 1345, 1170, 841 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{18}IN_3O_5$ 458.0189, found 458.0189.



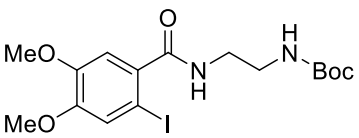
***tert*-butyl 2-(2-iodo-4-(2-(*tert*-butoxycarbonylamino)ethylcarbamoyl)benzamido) ethylcarbamate (99e)** Prepared according to general procedure A. Yield 68% as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 8.60 (brs, 1H), 8.45 (brs, 1H), 8.26 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 6.96-6.82 (m, 2H), 3.38-3.20 (m, 4H), 3.19-3.06 (m, 4H), 1.38 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.0, 164.8, 156.2, 156.1, 145.6, 138.0, 136.7, 128.2, 127.3, 93.7, 78.2, 39.8, 39.7, 31.1, 28.7; IR (thin film) ν 3345, 2923, 1691, 1640, 1547, 1274, 1168, 668 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{33}IN_4O_6$ 599.1342, found 599.1342.



***tert*-butyl 2-(2-iodo-5-methoxybenzamido)ethylcarbamate (99f)**. Prepared according to general procedure A. Yield 80% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.7 Hz, 1H), 6.96 (d, *J* = 3.0 Hz, 1H), 6.68 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.39 (brs, 1H), 4.99 (brs, 1H), 3.79 (s, 3H), 3.56 (q, *J* = 5.8 Hz, 2H), 3.40 (q, *J* = 5.8 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 159.6, 156.7, 142.8, 140.3, 117.4, 114.0, 80.8, 79.5, 55.5, 40.7, 40.1, 28.4; IR (thin film) ν 3296, 2975, 2935, 1690, 1648, 1529, 1169, 818 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{15}H_{21}IN_2O_4$ 443.0444, found 443.0444.



***tert*-butyl 2-(2-iodo-4-methoxybenzamido)ethylcarbamate (99g)**. Prepared according to general procedure A. Yield 78% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38, (d, *J* = 2.4 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.43 (brs, 1H), 5.02 (brs, 1H), 3.80 (s, 3H), 3.56 (q, *J* = 5.8 Hz, 2H), 3.40 (q, *J* = 5.8 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 160.6, 156.8, 134.0, 129.2, 125.3, 113.9, 93.1, 79.7, 55.6, 40.9, 40.2, 28.4; IR (thin film) ν 3340, 2953, 1687, 1641, 1594, 1232, 1026, 668 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{15}H_{21}IN_2O_4$ 443.0444, found 443.0444.

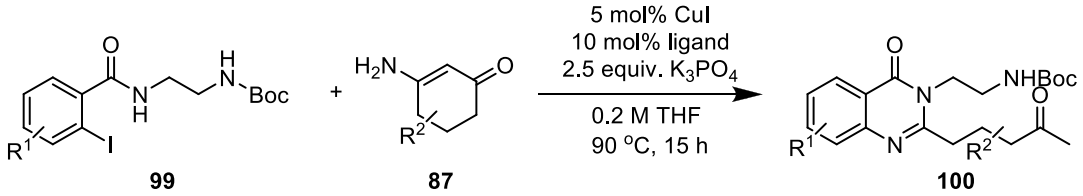


***tert*-butyl 2-(2-iodo-4,5-dimethoxybenzamido)ethylcarbamate (99h).** Prepared according to general procedure A. Yield 77% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.01 (s, 1H), 6.46 (brs, 1H), 5.01 (brs, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.57 (q, *J* = 5.5 Hz, 2H), 3.41 (q, *J* = 5.5 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (75

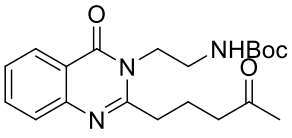
MHz, $CDCl_3$) δ 169.4, 156.8, 150.5, 149.2, 134.0, 122.0, 111.7, 81.1, 79.8, 56.3, 56.1, 41.0, 41.3, 28.4; IR (thin film) ν 3270, 2933, 2841, 1682, 1644, 1504, 1256, 1022, 866 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{16}H_{23}IN_2O_5$ 473.0549, found 473.0549.

2.4.3 Synthesis of Quinazolinone Derivatives

General Procedure B : Synthesis of Quinazolinones

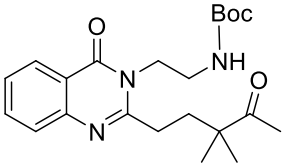


A sealed tube equipped with a magnetic stirring bar was charged with 2-iodobenzamides **99** (0.5 mmol), cyclic enaminones **87** (0.6 mmol), CuI (5 mol%), 1,2-*trans*-diaminocyclohexane (10 mol%) and K_3PO_4 (1.25 mmol) in THF (2.5 mL). The resulting mixture was stirred at 90°C for 15 h. After that, the resulting mixture was cooled to room temperature, quenched with sat. NH_4Cl and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (5:1 CH_2Cl_2:EtOAc) to provide quinazolinone products **100**.

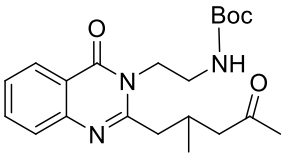


***tert*-butyl 2-(4-oxo-2-(4-oxopentyl)quinazolin-3(4H)-yl) ethyl-carbamate (100a).** Prepared according to general procedure B. Yield 87% as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 5.24 (brs, 1H), 4.27 (t, *J* = 6.2 Hz, 2H), 3.48 (q, *J* = 6.2,

2H), 2.92 (t, *J* = 6.8 Hz, 2H) 2.66 (t, *J* = 6.8 Hz, 2H), 2.28-2.04 (m, 5H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 162.6, 156.4, 156.2, 147.2, 134.2, 126.9, 126.6, 126.4, 120.3, 79.6, 43.1, 42.4, 39.2, 33.8, 30.0, 28.3, 21.0; IR (thin film) ν 3258, 2935, 1710, 1666, 1593, 1366, 1250, 1170, 774 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{20}H_{27}N_3O_4$ 396.1899, found 396.1899.

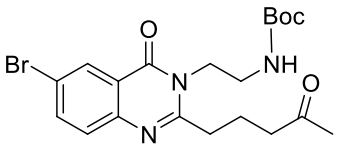


***tert*-butyl 2-(2-(3,3-dimethyl-4-oxopentyl)-4-oxoquinazolin-3(4H)yl)ethylcarbamate (100b)**. Prepared according to general procedure B. Yield 74% as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.9 Hz, 1H), 7.72 (t, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 4.97 (brs, H), 4.30 (t, *J* = 6.4 Hz, 2H), 3.48 (q, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 8.2 Hz, 2H), 2.19 (s, 3H), 2.04 (t, *J* = 8.2 Hz, 2H), 1.37 (s, 9H), 1.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 162.7, 157.1, 156.1, 147.3, 134.2, 126.8, 126.7, 126.4, 120.3, 79.6, 47.3, 43.3, 39.3, 36.6, 30.7, 28.2, 25.3, 24.5; IR (thin film) ν 3355, 2972, 1702, 1665, 1593, 1365, 1250, 1171, 775 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{31}N_3O_4$ 424.2212, found 424.2212.

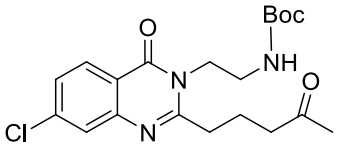


***tert*-butyl 2-(2-(2-methyl-4-oxopentyl)-4-oxoquinazolin-3(4H)-yl)ethylcarbamate (100d)**. Prepared according to general procedure B. Yield 77% as a pale brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (d, *J* = 7.6 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 5.7 Hz, 1H), 4.20-3.97 (m, 2H), 3.24 (q, *J* = 5.7 Hz, 2H), 2.86-2.55 (m, 4H), 2.35 (dd, *J* = 16.0, 6.4 Hz, 1H),

2.00 (s, 3H), 1.30 (s, 9H), 0.98 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 208.1, 161.9, 156.7, 156.2, 147.3, 134.6, 127.1, 126.6, 126.5, 120.6, 78.4, 49.9, 43.6, 41.3, 38.4, 30.5, 28.6, 27.5, 20.5; IR (thin film) ν 3355, 2974, 1707, 1672, 1591, 1508, 1365, 1250, 1169, 774 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{29}N_3O_4$ 410.2056, found 410.2056.

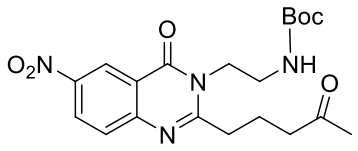


***tert*-butyl 2-(6-bromo-4-oxo-2-(4-oxopentyl)quinazolin-3(4H)-yl)ethylcarbamate (100e)**. Prepared according to general procedure B. Yield 80% as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 1.9 Hz, 1H), 7.78 (dd, J = 8.7, 1.9 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 5.02 (brs, 1H), 4.27 (t, J = 6.2 Hz, 2H), 3.46 (q, J = 6.2 Hz, 2 H), 2.90 (t, J = 7.2 Hz, 2H), 2.66 (t, J = 7.2 Hz, 2H), 2.19-2.03 (m, 5H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 161.5, 157.0, 156.1, 146.0, 137.4, 129.2, 128.8, 121.7, 119.9, 79.8, 43.3, 42.3, 39.1, 33.8, 30.0, 28.2, 20.8; IR (thin film) ν 3356, 2975, 1706, 1677, 1590, 1468, 1365, 1167, 833 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{20}H_{26}BrN_3O_4$ 474.1004, found 474.1004.

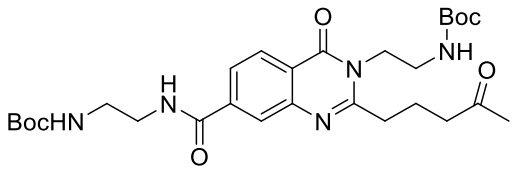


***tert*-butyl 2-(7-chloro-4-oxo-2-(4-oxopentyl)quinazolin-3(4H)-yl)- ethylcarbamate (100f)**. Prepared according to general procedure B. Yield 70% as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 1.9 Hz, 1H), 7.39 (dd, J = 8.5, 1.9 Hz, 1H), 5.03 (brs, 1H), 4.27 (t, J = 6.7 Hz, 2H), 3.47 (q, J = 6.7 Hz, 2H), 2.93 (t, J = 7.1 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H), 2.18-2.07 (m, 5H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 162.0, 157.8, 156.2, 148.1, 140.3, 128.1, 127.0, 126.4, 118.7, 79.6, 43.2, 42.3, 39.0, 33.7, 30.0, 28.2, 20.7; IR (thin film) ν 3356,

2929, 1706, 1683, 1592, 1365, 1250, 1170, 784 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{20}H_{26}ClN_3O_4$ 430.1510, found 430.1511.

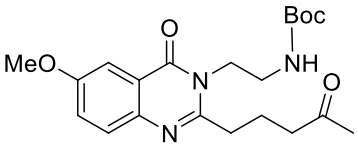


***tert*-butyl 2-(6-nitro-4-oxo-2-(4-oxopentyl)quinazolin-3(4H)-yl)ethylcarbamate (100g)**. Prepared according to general procedure B. Yield 54% as a brown solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.11 (d, *J* = 2.6 Hz, 1H), 8.50 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 4.99 (brs, 1H), 4.33 (t, *J* = 6.4 Hz, 2H), 3.50 (q, *J* = 6.4 Hz, 2H), 2.99 (t, *J* = 7.0 Hz, 2H), 2.70 (t, *J* = 7.0 Hz, 2H), 2.26-2.10 (m, 5H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 161.5, 160.4, 156.2, 151.2, 145.2, 128.5, 128.2, 123.4, 120.3, 79.8, 43.6, 42.2, 38.8, 34.0, 30.0, 28.2, 20.6; IR (thin film) ν 3371, 2975, 1699, 1684, 1575, 1340, 1166, 752 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{20}H_{26}N_4O_6$ 441.1750, found 441.1750.

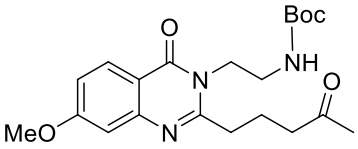


***tert*-butyl 2-(4-oxo-2-(4-oxo-pentyl)-7-(2-(*tert*-butoxycarbonylamino)ethylcarbamoyl)quinazolin-3(4H)-yl)-ethylcarbamate (100h)** Prepared according to general procedure B. Yield 77% as a dark brown solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.99 (s, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.62 (brs, 1H), 5.22 (brs, 2H), 4.25 (t, *J* = 6.3 Hz, 2H), 3.60 (q, *J* = 6.3 Hz, 2H), 3.53-3.30 (m, 4H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.66 (t, *J* = 6.9 Hz, 2H), 2.17 (s, 3H), 2.17-2.01 (m, 2H), 1.44 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 166.9, 162.2, 157.1, 156.2, 147.0, 139.5, 127.0, 125.8, 124.6, 122.0, 80.1, 79.7, 43.3, 42.3, 42.1, 40.0, 39.0, 33.6, 30.1, 29.7, 28.4, 28.3, 20.6; IR (thin film) ν 3337, 2931,

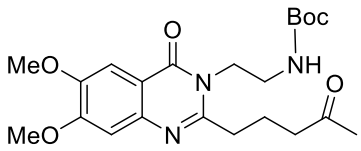
1698, 1682, 1541, 1522, 1251, 1169, 756 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{41}N_5O_7$ 560.3084, found 560.3085.



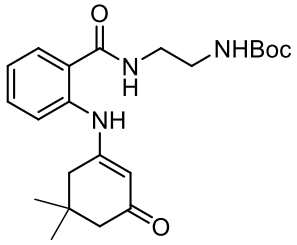
***tert*-butyl 2-(6-methoxy-4-oxo-2-(4-oxopentyl)quinazolin-3(4H)-yl)ethylcarbamate (100i)**. Prepared according to general procedure B. Yield 78% as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.9 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.27 (dd, *J* = 8.8, 2.9 Hz, 1H), 5.14 (brs, 1H), 4.24 (t, *J* = 6.4 Hz, 2H), 3.86 (s, 3H), 3.44 (q, *J* = 6.4 Hz, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.11 (s, 3H), 2.13-2.00 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 162.4, 158.0, 156.2, 154.0, 141.8, 128.4, 124.5, 120.9, 105.8, 79.5, 55.7, 43.2, 42.4, 39.1, 33.6, 29.9, 28.2, 21.0; IR (thin film) ν 3356, 2974, 1706, 1670, 1593, 1491, 1251, 1167, 837 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{29}N_3O_5$ 426.2205, found 426.2205.



***tert*-butyl 2-(7-methoxy-4-oxo-2-(4-oxopentyl)quinazolin-3(4H)-yl)ethylcarbamate (100j)**. Prepared according to general procedure B. Yield 74% as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.5 Hz, 1H), 7.09-7.01 (m, 2H), 5.05 (brs, 1H), 4.29 (t, *J* = 6.5 Hz, 2H), 3.94 (s, 3H), 3.50 (q, *J* = 6.5 Hz, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.20 (s, 3H), 2.20-2.07 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 164.6, 162.1, 157.2, 156.2, 149.3, 128.2, 116.8, 113.8, 107.3, 79.6, 55.7, 42.9, 42.4, 39.3, 33.9, 30.0, 28.2, 21.1; IR (thin film) ν 3356, 2925, 1706, 1670, 1610, 1364, 1164, 1032, 782 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{29}N_3O_5$ 426.2005, found 426.2005.



***tert*-butyl 2-(6,7-dimethoxy-4-oxo-2-(4-oxopentyl)quinazolin-3(4H)-yl)ethylcarba-mate (100k)**. Prepared according to general procedure B. Yield 80% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 6.88 (s, 1H), 5.41 (brs, 1H), 4.18 (t, *J* = 5.9 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.42 (q, *J* = 5.9 Hz, 2H), 2.80 (t, *J* = 6.9 Hz, 2H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.08 (s, 3H), 2.01 (qn, *J* = 6.9 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 161.7, 156.2, 155.1, 154.8, 148.6, 143.3, 113.4, 107.1, 105.3, 79.4, 56.1, 43.2, 42.4, 39.1, 33.7, 29.9, 28.3, 21.0; IR (thin film) ν 3367, 2924, 1706, 1654, 1499, 1249, 1168, 1002, 754 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{31}N_3O_6$ 434.2291, found 434.2291.



***tert*-butyl2-(2-(5,5-dimethyl-3-oxocyclohex-1-enylamino)benzamido)ethylcarba-mate (100l)**. Yield 88% as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.39 (t, *J* = 8.5 Hz, 1H), 7.04 (t, *J* = 8.5 Hz, 1H), 5.88 (s, 1H), 5.14 (s, 1H), 3.52 (q, *J* = 5.7 Hz, 2H), 3.42 (q, *J* = 5.7 Hz, 2H), 2.39 (s, 1H), 2.25 (s, 1H), 1.43 (s, 9H), 1.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ198.8, 169.1, 158.2, 157.6, 140.1, 131.9, 127.8, 122.8, 122.3, 100.2, 80.3, 50.4, 44.4, 42.2, 39.7, 32.6, 29.7, 28.3, 28.2; IR (thin film) ν 3293, 2930, 1698, 1522, 1271, 1167, 755 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{31}N_3O_4$ 402.2393, found 402.2393.

REFERENCES

Chen, W.; Cai, Y.; Fu, X.; Liu, X.; Lin, L.; Feng, X. 2011. Enantioselective One-Pot Synthesis of 2-Amino-4-(indol-3-yl)-4*H*-chromenes. Org. Lett. 13 (18), 4910–4913.

Doshi, J. M.; Tian, D.; Xing, C. 2006. Structure–Activity Relationship Studies of Ethyl 2-Amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (HA 14-1), an Antagonist for Abtiapoptotic Bcl-2 Proteins To Over come Drug Resistance in Cancer. J. Med. Chem. 49, 7731–7739.

Fang, Y.; Li, C. 2006. O-arylation versus C-Arylation: Copper-Catalyzed Intramolecular Coupling of Aryl Bromides with 1,3-Dicarbonyls. J. Org. Chem. 71, 6427–6431.

Furman, S.; Nissim-Bardugo, E.; Zeeli, S.; Weitman, M.; Nudelman, A.; Finkin-Groner, E.; Moradov, D.; Shifrin, H.; Schorer-Apelbaum, D.; Weinstock, M. 2014. Synthesis and in vitro evaluation of anti-inflammatory activity of ester and amine derivatives of indolin in RAW 264.7 and peritoneal macrophages. Bioorg. Med. Chem. 24, 2283–2287.

Ghosh, P. P.; Das, A. R. 2013. Nanocrystalline and Reusable ZnO Catalyst for the Assembly of Densely Functionlized 4H-Chromenes in Aqueous Medium via One-Pot Three Component Reactions: A Greener “NOES” Approach. J. Org. Chem. 78, 6170–6181.

Gu, Y.; Li, F.; Hu, P.; Liao, D.; Tong, X. 2015. Tertiary Amine-Catalyzed (4+2) Annulations of δ-Acetoxy Allenoates: Synthesis of Multisubstitued 4*H*-Pyran and 4*H*-Chromene. Org. Lett. 17, 1106–1109.

Gudmundsson, K. S.; Sebahar, P. R.; Richardson, L. D.; Miller, J. F.; Turner, E. M.; Catalano, J. G.; Spaltenstein, A.; Lawrence, W.; Thomson, M.; Jenkinson, S. 2009. Amine substituted *N*-(1*H*-benzimidazol-2ylmethyl)-5,6,7,8-tetrahydro-

8-quino-linamines as CXCR4 antagonists with potent activity against HIV-1. Bioorg. Mrd. Chem. Lett. 19, 5048–5052.

Guo, X, -X.; Gu, D. -W.; Wu, Z.; Zhang, W. 2015. Copper-Catalyzed Functionalization Reactions: Efficient Synthesis of Heterocycles. Chem. Rev. 115, 1622–1651.

Hikawa, H.; Ino, Y.; Suzuki, H.; Yokotama, Y. 2012. Pd-catalyzed Benzylic C–H Amidation with Benzyl Alcohols in water: A Strategy To Construct Quinazolinones. J. Org. Chem. 77 (16), 7046–7051.

Huang, X.; Guo, Z.; Zhu, W.; Xie, Y.; Tian, H. 2008. A colorimetric and fluorescent turn-on sensor for pyrophosphate anion based on a dicyanomethylene-4H-Chromene framework. Chem.Commun. 5143–5145.

Kaumanns, O.; Lucius, R.; Mayr, H. 2008. Determination of the Electrophilicity Parameters of Diethyl Benzylidenemalonates in Dimethyl Sulfoxide: Reference Electrophiles for Characterizing Strong Nucleophiles. Chem. Eur. J. 14, 9675–9682.

Kitching, M. O.; Hurst, T. E.; Snieckus, V. 2012. Copper-Catalyzed Cross-Coupling Interrupted by an Opportunistic Smiles Rearrangement: An Efficient Domino Approach to Dibenzoxazepinones. Angew. Chem. Int. Ed. 51 (12), 2925–2929.

Li, B.; Samp, L.; Sagal, J.; Hayward, C. M.; Yang, C.; Zhang, Z. 2013. Synthesis of Quinazolin-4(3*H*)-ones via Amidine N-Arylation. J. Org. Chem. 78 (3), 1273–1277.

Limsuwan, S.; Trip, E. N.; Kouwen, T. R.H.M.; Piersma, S.; Hiranrat, A.; Mahabusarakam, W.; Voravuthikunchai, S. P.; Dijl, J. M.; Kayser, O. 2009. Rhodomyrtone: A new candidate as natural antibacterial drug from *Rhodomyrtus tomentosa*. Phytomedicine. 16, 645–651.

Liu, Y.; Qian, J.; Lou, S.; Zhu, J.; Xu, Z. 2009. Gold(III)-Catalyzed Tandem Reaction of Ketones with Phenols: Effifient and Highly Selective Synthesis of Functionalized 4*H*-Chromenes. J. Org. Chem. 75, 1309–1312.

Liu, Y.; Wan, J. -P. 2011. Tandem reactions initiated by copper-catalyzed cross-coupling: A new strategy toeards heterocycle synthesis. Org. Biomol. Chem. 9, 6873–6894.

Ma, D.; Cai, Q. 2008. Copper/Amino Acid Catalyzed Cross-Couplings of Aryl and Vinyl Halides with Nucleophiles. Acc. Chem. Res. 41 (11), 1450–1460.

Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. 2011. Cu(I)-Catalyzed Domino Reactions: Efficient and Selective Synthesis of 4*H*-Chromenes and Napthalenes. Org. Lett. 13 (8), 1972–1975.

Mhaske, S. B.; Argade, N. P. 2006. The chemistry of recently isolated naturally occurring quinazolinone alkaloids. Tetrahedron. 62, 9787–9826.

Mohite, A.; Bhat, R. G. 2013. A Practical and Convenient Protocol for the Synthesis of (*E*)-α,β-Unsaturated Acids. Org. Lett. 15 (17), 4564–4567.

Moorthy, J. N.; Venkatakrishnan, P.; Sengupta, S.; Baidya, M. 2006. Facile Synthesis, Fluorescence, and Photochromism of Novel Helical Pyrones and Chromenes. Org. Lett. 8 (21), 4891–4894.

Patil, S. A.; Patil, R.; Pfeffer, L. M.; Miller, D. D. 2013. Chromenes: potential new chemotherapeutic agents for cancer. Future Med. Chem. 5(14), 1647–1660.

Peng, J.; Huang, X.; Zheng, P. -F.; Chen, Y. -C. 2013. Rauhut–Currier-Type Reaction with Morita–Baylis–Hillman Carbonates of 2-Cyclohexenone and Alkylidenemalononitriles To Access Chromene Derivatives. Org. Lett. 25 (21), 5534–5537.

Rashmi, A.; Ashish, K.; N.S, G.; A.C, R. 2011. QUINAZOLINONE: An Overview. IRJP. 2 (12), 22–28.

Richter, M. F.; Drown, B. S.; Riley, A. P.; Garcia, A.; Shirai, T.; Svec, R. L.; Hergenrother, P. J. 2017. Predictive compound accumulation rules yield a broad-spectrum antibiotic. Nature. 545 (7654), 299–304.

Shaheen, F.; Ahmad, M.; Khan, S. N.; Hussain, S. S.; Anjum, S.; Tashkhodjaev, B.; Turgunov, K.; Sultankhodzhaev, M. N.; Choudhary, M. I.; Rahman, A. 2006. New α-Glucosidase Inhibitors and Antibacterial Compounds from *Myrtus communis* L. Eur. J. Org. Chem. 2371–2377.

Shi, Y. -L.; Shi, M. 2005. DABCO-Catalyzed Reaction of Allenic Esters and Ketones with Salicyl N-tosylimines: Synthesis of Highly Functionalized Chromenes. Org. Lett. 7 (14), 3057–3060.

Songsichan, T.; Promsuk, J.; Rukachaisirikul, V.; Kaeobamrung, J. 2014. Syntheses of quinazolinones from 2-iodobenzamides and enaminones *via* copper-catalyzed domino reactions. Org. Biomol. Chem. 12 (26), 4571–4575.

Sudheenran, K.; Malakar, C. C.; Conrad, J.; Beifuss, U. 2012. Copper(I)-Catalyzed Intramolecular O-Arylation for the Synthesis of 2,3,4,9-Tetrahydro-1*H*-xanthen-1-ones with Low loads of CuCl. J. Org. Chem. 77, 10194–10210.

Thomas, N.; Zachariah, S. M. 2013. PHARMACOLOGICAL ACTIVITIES OF CHROMENE DEVATIVES: AN OVERVIEW. Asian J. Pharm. Clin. Res. 6 (2), 11–15.

Uemura, M.; Watson, I. D. G.; Katsukawa, M.; Toste F. D. 2009. Gold(I)-Catalyzed Enantioselective Synthesis of Benzopyrans *via* Rearrangement of Allylic Oxonium Intermediates. J. Am. Chem. Soc. 131, 3464–3465.

Wang, J.; Zhou, Y.; Zhang, L.; Li, Z.; Chen, X.; Liu, H. 2013. Asymmetric Michael Addition of *N*-*tert*-Butanesulfinyl Imidate with α,β-Unsaturated Diesters: Scope and Application to the Synthesis of Indanone Derivatives. Org. Lett. 15 (7), 1508–1511.

Ye, L. -W.; Sun, X. -L.; Zhu, C. -Y.; Tang, Y. 2006. Unexpected Tandem Ylide Annulation Reaction For Controllable Synthesis of 2*H*-Chromenes and 4*H*-Chromenes. Org. Lett. 8 (17), 3853–3856.

Zhang, X. H.; Chen, B. J.; Lin, X. Q.; Wong, O. Y.; Lee, C. S.; Kwong, H. L.; Lee, S. T.; Wu, S. K. 2001. A New Family of Red Dopants Based on Chromene-Containing Compounds for Organic Electroluminescent Devices. Chem. Mater. 13, 1565–1569.

APPENDIX

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Copper-catalysed domino reaction of 2-bromobenzylidenemalonates and 1,3-dicarbonyls for the synthesis of chromenes

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ABSTRACT

4*H*-Chromenes were synthesized from 2-bromobenzylidenemalonates and 1,3-dicarbonyls under mild and simple reaction conditions *via* copper-catalysed domino reactions involving Michael addition and intramolecular Ullmann-type C(aryl)–O bond formation. Although a competitive elimination affected these reactions, this catalytic system readily provided chromenes with functionality at the C-4 position.

Introduction

Metal-catalysed domino reactions have drawn significant attention from synthetic chemists for more than a century, especially reactions catalysed by copper due to its low toxicity and high natural abundance. Therefore, copper-catalysed domino reactions have been developed for the formation of C(aryl)–N, C(aryl)–C and C(aryl)–O bonds.[1] Unlike C(aryl)–N bond formation, tandem reactions for C(aryl)–O formation offer considerably less reaction diversity due to the lower valence of the oxygen atom.[2] In continuation of our research interest in copper-catalysed domino reactions for the synthesis of heterocyclic molecules, we were inspired by the work of Li and Fang for the formation of 4*H*-chromenes *via* copper-catalysed intramolecular coupling of aryl bromides and 1,3-dicarbonyls.[3] Their results suggested that C(aryl)–O Ullmann-type coupling occurred smoothly in an intramolecular fashion. Furthermore, Beifuss and co-workers recently took advantage of intramolecular C(aryl)–O coupling to furnish 4*H*-chromene derivatives *via* tandem process from 2-bromobenzyl bromides and 1,3-ketoesters.[4] These domino reactions involved substitution of a stabilized carbanion, generated from a 1,3-ketoester, with a bromine atom at the benzylic position, followed by tautomerization and intramolecular Ullmann-type C–O bond formation. In order to introduce functionality at the C-4 position of 4*H*-chromenes, we alternatively envisioned that the 2-bromobenzylidenemalonates would undergo C–C bond formation *via* Michael addition with 1,3-dicarbonyls, followed by intramolecular copper-catalysed C(aryl)–O bond formation to afford the desired 4*H*-chromenes (Fig. 1).

Chromenes are one of the most important *O*-containing heterocyclic systems due to their common occurrence as a structural motif in natural products[5] as well as their biological activities which include antitumor, antimicrobial, antioxidant, anticancer and estrogenic properties[6] (Fig. 2). Chromene derivatives also play important roles in material science, for example as fluorescent dyes, synthetic fibers, daylight fluorescent pigments and electroluminescent devices.[7] Due to their wide range of utilities, the syntheses of chromene have been consistently developed; most reported methods involve phenol derivatives.[8] Herein, we reported a synthesis of 4*H*-chromenes containing a functionality pendent at the C-4 position *via* domino, Michael addition and C–O Ullmann type coupling reactions.

Our investigation initially began with optimization of the reaction conditions. The reaction of diethyl 2-(2-bromobenzylidene) malonate (**1a**) and cyclohexane-1,3-dione (**2a**) was selected as a model (Table 1).

Various ligands were examined using CuI as the copper source, K_2CO_3 as a base and ACN as a solvent. The reactions were heated at 90 °C for 15 h (Entries 1–7). The reaction with DMEDA as ligand gave the best yield (Entry 3), while PPh_3 afforded none of the desired product (Entry 5). On the other hand, proline and ethylenediamine were not effective in this reaction (Entries 1 and 6) and only trace amounts of the product were observed from the ^1H

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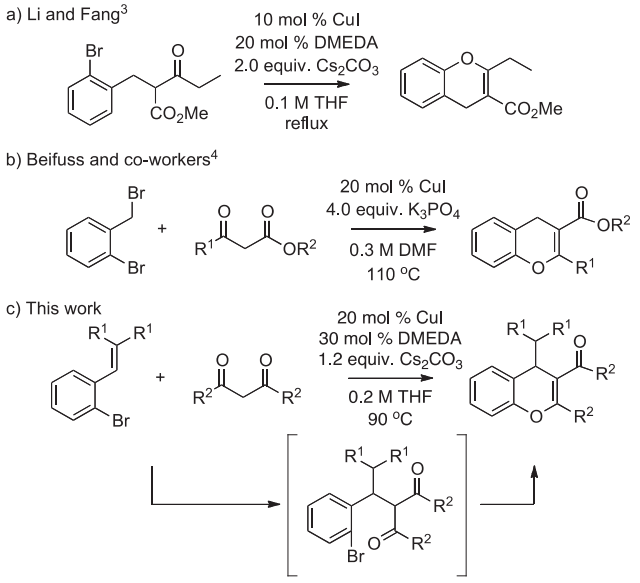


Fig. 1. Copper-catalysed reactions for the synthesis of 4*H*-chromenes.

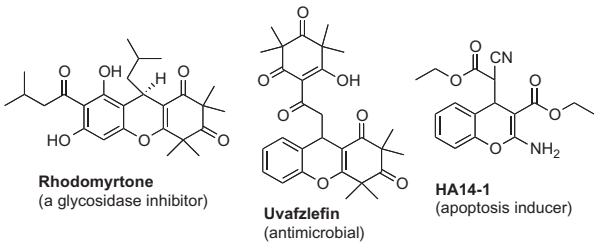


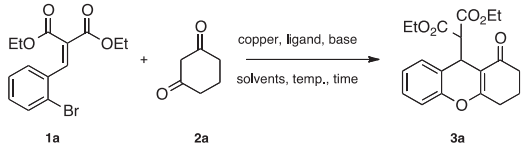
Fig. 2. Representative biologically active molecules containing the chromene moiety.

NMR spectrum of the crude reaction mixture. Next, various copper salts were explored. With $Cu(OAc)_2$, chromene **3a** was obtained in 32% yield (Entry 10) while CuBr and CuCl were not applicable to this system, resulting in low yield and no reaction, respectively (Entries 8 and 9). Without copper there was no reaction (Entry 11). Accordingly, the choice of copper was CuI. A variety of bases were then examined. NEt_3, an organic base, was not effective and no reaction was observed according to the ^{1}H NMR spectrum of the crude reaction mixture (Entry 14). The reactions with weak inorganic bases, K_3PO_4 or Cs_2CO_3 (Entries 12 and 13), gave comparable yields to the reaction with K_2CO_3 (Entry 3). The yield was slightly decreased when the stronger base ^{t}BuOK was used (Entry 15). We then conducted an exploration of solvents. The yield of reaction in THF with K_3PO_4 as a base was 50% (Entry 16), slightly lower than that of ACN (Entry 12). However, upon changing the base to Cs_2CO_3, the yield increased to 68% (Entry 17). These results suggested that the combination of base and solvent affected this catalytic reaction. Upon using the less polar solvent, toluene, or the more polar solvent, DMSO, the yield dropped dramatically to 30% and 15%, respectively (Entries 18 and 20). Finally, the higher boiling point solvent dioxane was used, resulting in a much lower yield (Entry 19). Subsequently, the optimal reaction conditions were DMEDA as a ligand, CuI as a copper source, Cs_2CO_3 as a base and THF as a solvent. Notably, the use of 20 mol% of copper and 30 mol% of ligand was required to complete the reaction.

Interestingly, the diester moiety of benzylidene was required. Upon subjecting ethyl-3-(2-bromophenyl)acrylate, an α,β-unsaturated monoester, to the optimal conditions (Scheme 1), we only observed both starting materials from the ^{1}H NMR spectrum of the crude reaction mixture.

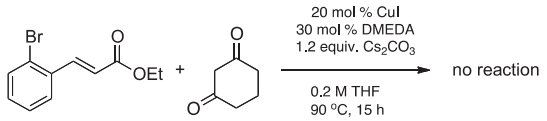
Based on this result, the electrophilicity of the Michael acceptor was deemed crucial in this system. Having established the optimal reaction conditions, we explored the substrate scope in the copper-catalysed domino reaction (Table 2).

Table 1
Reaction optimization.[a]



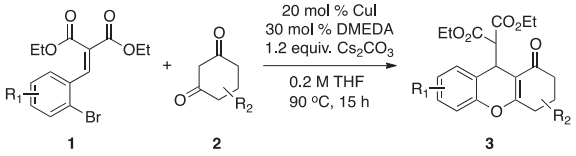
Entry	Cu	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	Proline	K_2CO_3	ACN	Trace[c]
2	CuI	1,10-Phenan throline	K_2CO_3	ACN	10
3	CuI	DMEDA	K_2CO_3	ACN	52
4	CuI	Picolinic acid	K_2CO_3	ACN	42
5	CuI	PPh_3	K_2CO_3	ACN	0
6	CuI	Ethylene diamine	K_2CO_3	ACN	Trace
7	CuI	2,2′-Bipyridine	K_2CO_3	ACN	12
8	CuBr	DMEDA	K_2CO_3	ACN	15
9	CuCl	DMEDA	K_2CO_3	ACN	0
10	$Cu(OAc)_2$	DMEDA	K_2CO_3	ACN	32
11	–	DMEDA	K_2CO_3	ACN	0
12	CuI	DMEDA	K_3PO_4	ACN	58
13	CuI	DMEDA	Cs_2CO_3	ACN	56
14	CuI	DMEDA	NEt_3	ACN	0
15	CuI	DMEDA	^{t}BuOK	ACN	43
16	CuI	DMEDA	K_3PO_4	THF	50
17	CuI	DMEDA	Cs_2CO_3	THF	68
18	CuI	DMEDA	Cs_2CO_3	Toluene	30
19	CuI	DMEDA	Cs_2CO_3	Dioxane	15
20	CuI	DMEDA	Cs_2CO_3	DMSO	0

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (20 mol%), ligand (30 mol%), solvent (0.1 M), 90 °C, 15 h.
[b] Isolated yield.
[c] Trace amount of product observed from the ^{1}H NMR spectrum of the crude reaction mixture.



Scheme 1. Reaction of ethyl-3-(2-bromophenyl)acrylate and 1,3-cyclicdiketone.

Table 2
Formation of chromenes **3a–g** from 1,3-dicarbonyls.[a]



Entry	Benzylidene malonate	Chromene	Yield (%)[b]
1	**1a**	**3a**	68
2	**1a**	**3b**	66
3	**1a**	**3c**	62
4	**1b**	**3d**	48
5	**1c**	**3e**	65
6	**1d**	**3f**	56
7	**1a**	**3g**	50

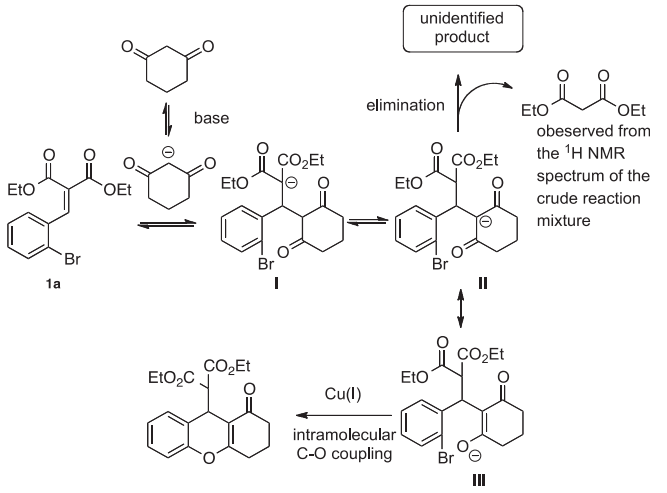
[a] Reaction conditions: **1a–d** (0.5 mmol), **2** (0.75 mmol).
[b] Isolated yield.

Cyclohexane-1,3-diones, with and without the geminal-dimethyl substituent, gave the desired chromenes in moderate yield (Entries 1–3). The results showed that the presence of the active geminal-dimethyl substituent had no effect on the reaction. Additionally, we confirmed the location of the geminal-dimethyl unit of chromene **3c** using heteronuclear multiple bond correlation (HMBC) spectroscopy (see ESI). Based on the structure of **3c**, the less sterically hindered oxygen nucleophile was postulated to undergo C(aryl)–O bond formation faster than the more sterically hindered one. This indicated that in the catalytic cycle, the rate determining step was possibly the Ullmann-type coupling.

We then explored the effect of electron density on the aromatic ring of the benzylidenemalonates. Benzylidenemalonates bearing both electron-donating and electron-withdrawing groups on the benzene ring were applicable to the reaction. However, dimethoxy substituents gave the desired chromene in only 48% yield (Entry 4). On the other hand, the reaction of benzylidenemalonates with a nitro group at the *para*-position to the bromine on the benzene ring gave a slightly better yield than that at the *ortho*-position (Entries 5 and 6), resulting from a steric effect. Next, acyclic dicarbonyls were subjected to the reaction. Unfortunately, acetylacetone and 1,3-diphenyl-1,3-propanedione were unreactive in this system. However, the reaction of methyl acetoacetate gave a moderate yield (Entry 7). These results suggested that the nucleophilicity of the dicarbonyls was crucial.

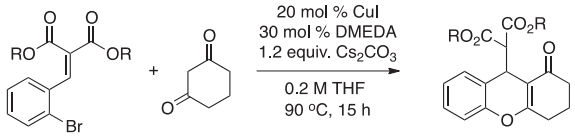
We hypothesized that the first transformation was intermolecular Michael addition, followed by intramolecular C–O bond formation since an isochromene had not been observed. Furthermore, we observed the loss of diethylmalonate from the ^{1}H NMR spectrum of the crude reaction, resulting in the low to moderate product yield obtained for the domino reaction. Our findings were consistent with a report from Mayr and co-workers regarding the reactivity of benzylidenemalonates in the Michael addition of carbanion nucleophiles.[9] We postulated that the stabilized carbanion added to the benzylidenemalonate to form the carbanion intermediate **I** which further underwent proton transfer to generate carbanion intermediate **II**. Based on the loss of diethylmalonate and reports from Mayr[10] and Li,[4] we rationalized that **II** could alternatively undergo elimination, resulting in the elimination of diethylmalonate to give an unidentified product or tautomerization to form the enolate **III**. Subsequently, Ullmann-type C–O bond formation takes place to give desired chromene (Scheme 2).

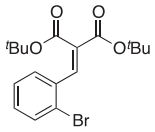
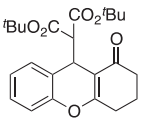
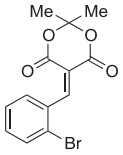
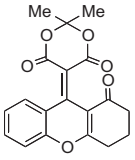
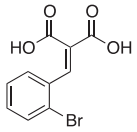
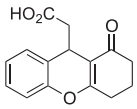
In this catalytic system, the product yields were limited by the nature of benzylidenemalonates in the Michael addition. Alternatively, Beifuss and co-workers elegantly designed a domino process[4] utilizing the nucleophilic substitution reactions of benzylbromide and 1,3-ketoesters, followed by C–O Ullmann-type coupling yielding 4*H*-chromene derivatives in moderate to high yields. Based on our proposed mechanism, the yields were diminished *via* an elimination step. Next, we explored the ester substituents of benzylidenemalonates in order to possibly avoid undesired elimination (Table 3).



Scheme 2. Possible reaction mechanism.

Table 3
4*H*-Chromene formation from a variety of ester substituted benzylidenemalonates.[a]



Entry	Benzylidene malonate	Chromene	Yield (%)[b]
1	**1e** 	**3h** 	10
2	**1f** 	**3i** 	0
3	**1g** 	**3j** 	65

[a] Reaction conditions: benzylidenemalonate (0.5 mmol), cyclohexane-1,3-dione (0.75 mmol).
[b] Isolated yield.

Increasing the size of the ester group was initially examined. Unfortunately, the reaction of di-*tert*-butyl benzylidenemalonate (**1e**) gave a low yield of the desired chromene (Entry 1). Additionally, the ^{1}H NMR spectrum of the crude reaction mixture showed that the ratio of **1e** and **3h** was 10:1. The result suggested that the bulky ester group resulted in low reactivity. We next considered the geometry of benzylidenemalonate. 5-(2-Bromobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1f**), derived from Meldrum's acid, was selected, however, the expected chromene **3i** was not observed (Entry 2). Moreover, **1f** decomposed throughout the reaction course. In order to overcome the undesired elimination, we speculated that benzylidenemalonic acid (**1g**) would undergo decarboxylation after the addition of **2a**, instead of elimination to give the mono acid substituent on the chromene. Based on our proposal, the yield of chromene would be improved. However, the reaction of diacid **1g** and **2a** gave chromene **3j** in comparable yield to the reaction of diethyl ester **1a** (Entry 3). Furthermore, the ^{1}H NMR spectrum of the crude reaction mixture prior to being quenched with acid showed a mixture of mono- and di-acid chromenes (see ESI).

Conclusion

We have demonstrated the domino synthesis of 4*H*-chromene derivatives *via* a copper-catalysed Michael addition and C–O Ullmann-type coupling reaction under mild and simple reaction conditions. The 1,3-cyclic diketones were shown to be a better reaction partner than 1,3-acyclic diketones which were not suitable in this domino system. Nonetheless, the reaction with 1,3-diketo ester gave satisfactory yields.

Acknowledgments

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A. Supplementary data

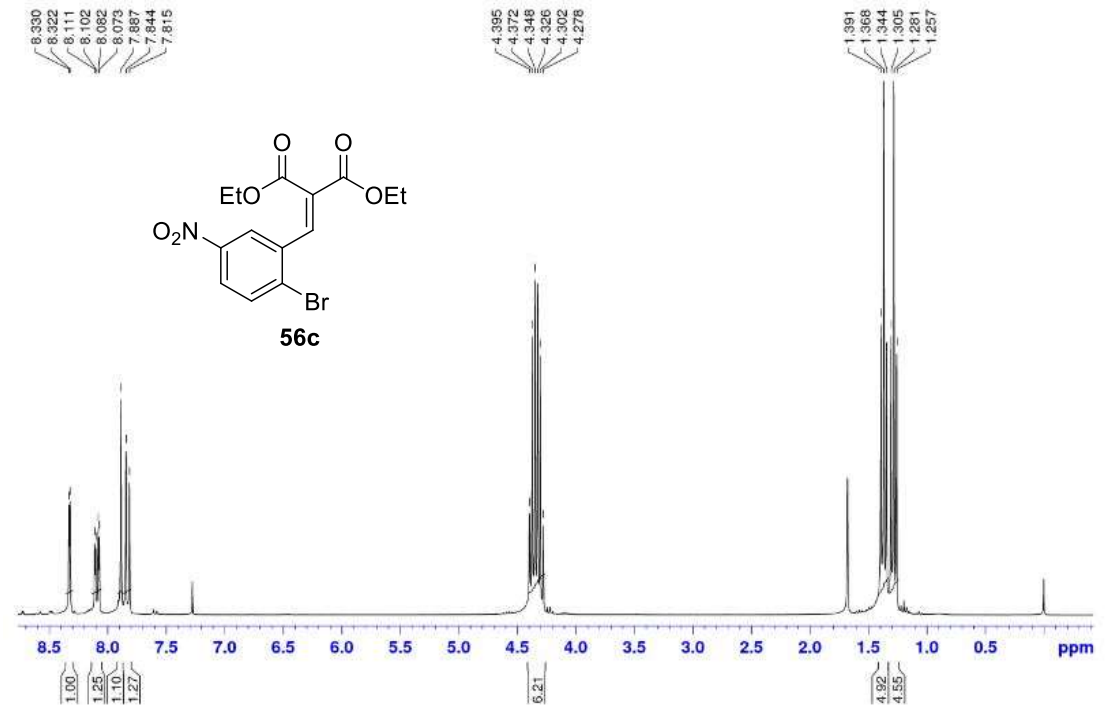
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.12.006.

References

1. (a) For selected reviews, see: Liu Y, Wan J-P. *Org Biomol Chem*. 2011;9:6873;
(b) Liao Q, Yang X, Xi C. *J Org Chem*. 2014;79:8507;
(c) Monnier F, Taillefer M. *Angew Chem Int Ed*. 2009;48:6954;
(d) Surry DS, Buchwald SL. *Chem Sci*. 2010;1:13;
(e) Evano G, Blanchard N, Toumi M. *Chem Rev*. 2008;108:3054;
(f) Zhu X, Chiba S. *Chem Soc Rev*. 2016;45:4504;
(g) Sambiaqio C, Marsden SP, Blacker AJ, McGowan PC. *Chem Soc Rev*. 2014;43:3525;
(h) Zhang C, Tang C, Jiao N. *Chem Soc Rev*. 2012;41:3464.
2. (a) For recent studies, see: Bao W, Liu Y, Lv X, Qian W. *Org Lett*. 2008;10:3899;
(b) Bhadrat S, Adak L, Samanta S, Islam AKMM, Mukherjee M, Ranu BC. *J Org Chem*. 2010;75:8533;
(c) Liu Y, Bao W. *Org Biomol Chem*. 2010;8:2700;
(d) Viirre RD, Evindar G, Batey RA. *J Org Chem*. 2008;73:3452.
3. Fang Y, Li C. *J Org Chem*. 2006;71:6427.
4. Malakar CC, Schmidt D, Conrad J, Beifuss U. *Org Lett*. 2011;13:1972.
5. (a) Joulain D, Tabacchi R. *Phytochemistry*. 1994;37:1769;
(b) Demyttenaera, Syngel JKV, Markusse AP, Vervisch S, Debenedetti S, De Kimpe N. *Tetrahedron*. 2002;58:2163;
(c) Hufford CD, Oguntimein BO, Engen DV, Muthard D, Clardy J. *J Am Chem Soc*. 1980;102:7365.
6. (a) Ellis GP, Lockhart IM. In: Ellis GP, editor. *The Chemistry of Heterocyclic Compounds: Chromenes, Chromones and Chromones*, Vol. 31. Weinheim Germany: Wiley-VCH; 2007:1;
(b) Ohemeng KA, Schwender CF, Fu KP, Barrett JF. *Bioorg Med Chem Lett*. 1993;3:225;
(c) Bonsignore L, Loy G, Secci D, Calignano A. *Eur J Med Chem*. 1993;28:517.
7. (a) Zhang XH, Chen BJ, Lin XQ, et al. *Chem Mater*. 2001;13:1565;
(b) Moorthy JN, Venkatakrishnan P, Sengupta S, Baidya M. *Org Lett*. 2006;8:4891;
(c) Huang X, Guo Z, Zhu W, Xie Y, Tian H. *Chem Commun*. 2008;5143;
(d) Huang S-T, Jian J-L, Peng H-C, et al. *Dyes Pigm*. 2010;86:6;
(e) Hobley J, Malatesta V, Millini R, et al. *Chem Commun*. 2000;1339.
8. (a) For recent studies from phenol derivatives, see: Ghosh PP, Das AR. *J Org Chem*. 2013;78:6170;
(b) Chen W, Cai Y, Fu X, Liu X, Lin L, Feng X. *Org Lett*. 2011;13:4910;
(c) van Otterlo WAL, Ngidi EL, Kuzyidza S, Morgans GL, Moleele SS, de Koning CB. *Tetrahedron*. 2005;61:9996;
(d) Liu Y, Qian J, Lou S, Zhu J, Xu Z. *J Org Chem*. 2010;75:1309;
(e) Uemura M, Watson IDG, Katsukawa M, Toste FD. *J Am Chem Soc*. 2009;131:3464;
(f) Shi Y-L, Shi M. *Org Lett*. 2005;7:3057;
(g) Ye L-W, Sun X-L, Zhu C-Y, Tang Y. *Org Lett*. 2006;71:6427;
(h) Enders D, Urbanietz G, Hahn R, Raabe G. *Synthesis*. 2012;44:773.
9. Kaumanns O, Lucius R, Mayr H. *Chem Eur J*. 2008;14:9675.

^{1}H and ^{13}C NMR Spectra of New Compounds of Chromenes

Figure 8 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **56c** in $CDCl_3$



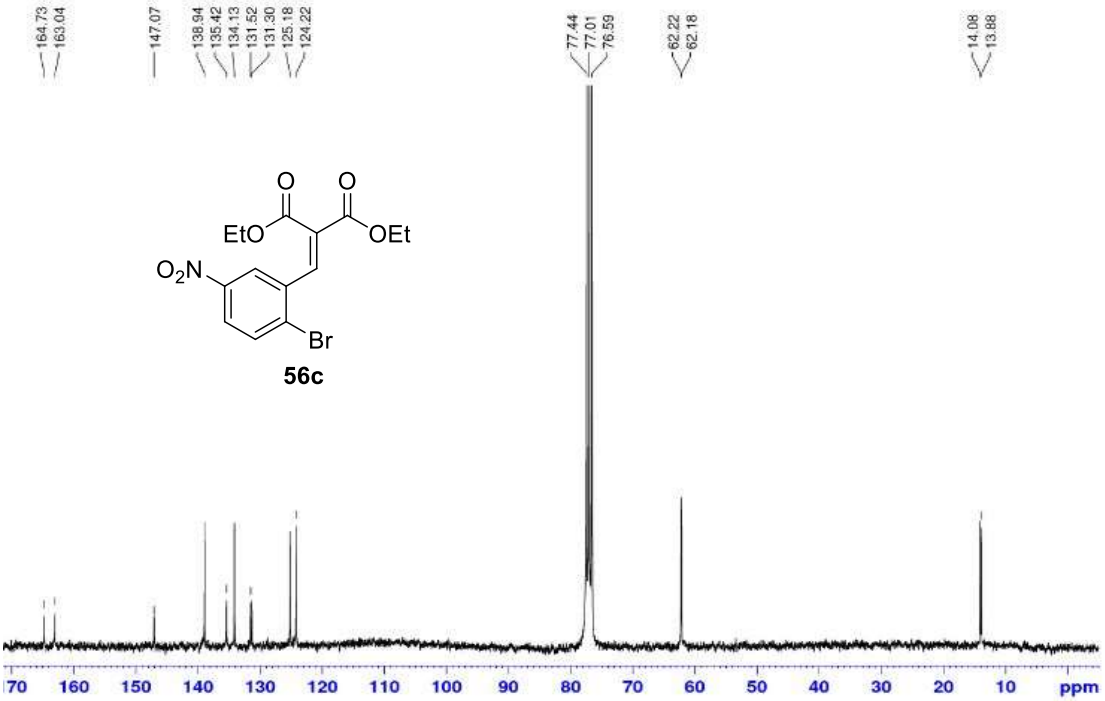


Figure 9 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **56d** in $CDCl_3$

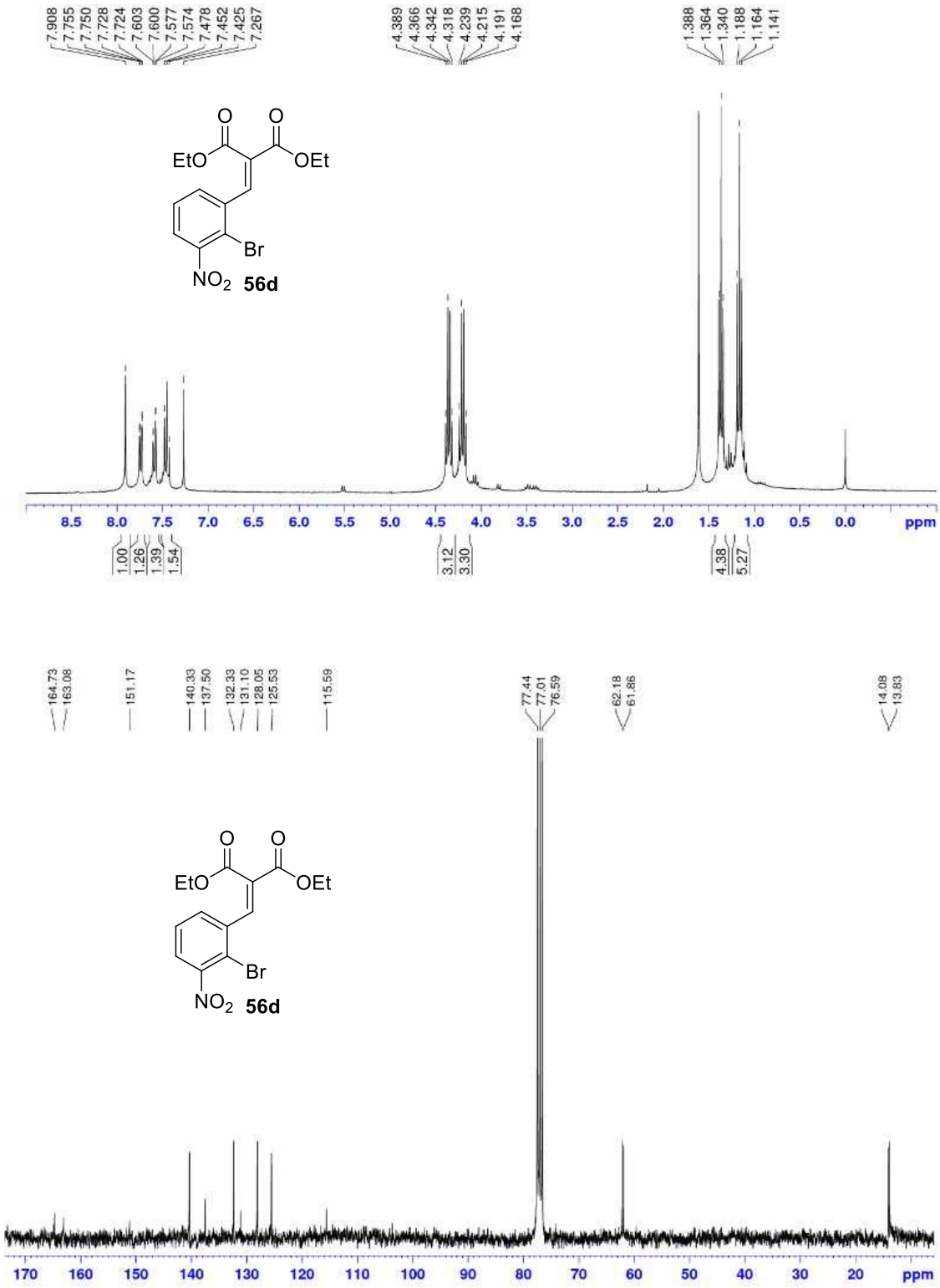


Figure 10 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **60a** in $CDCl_3$

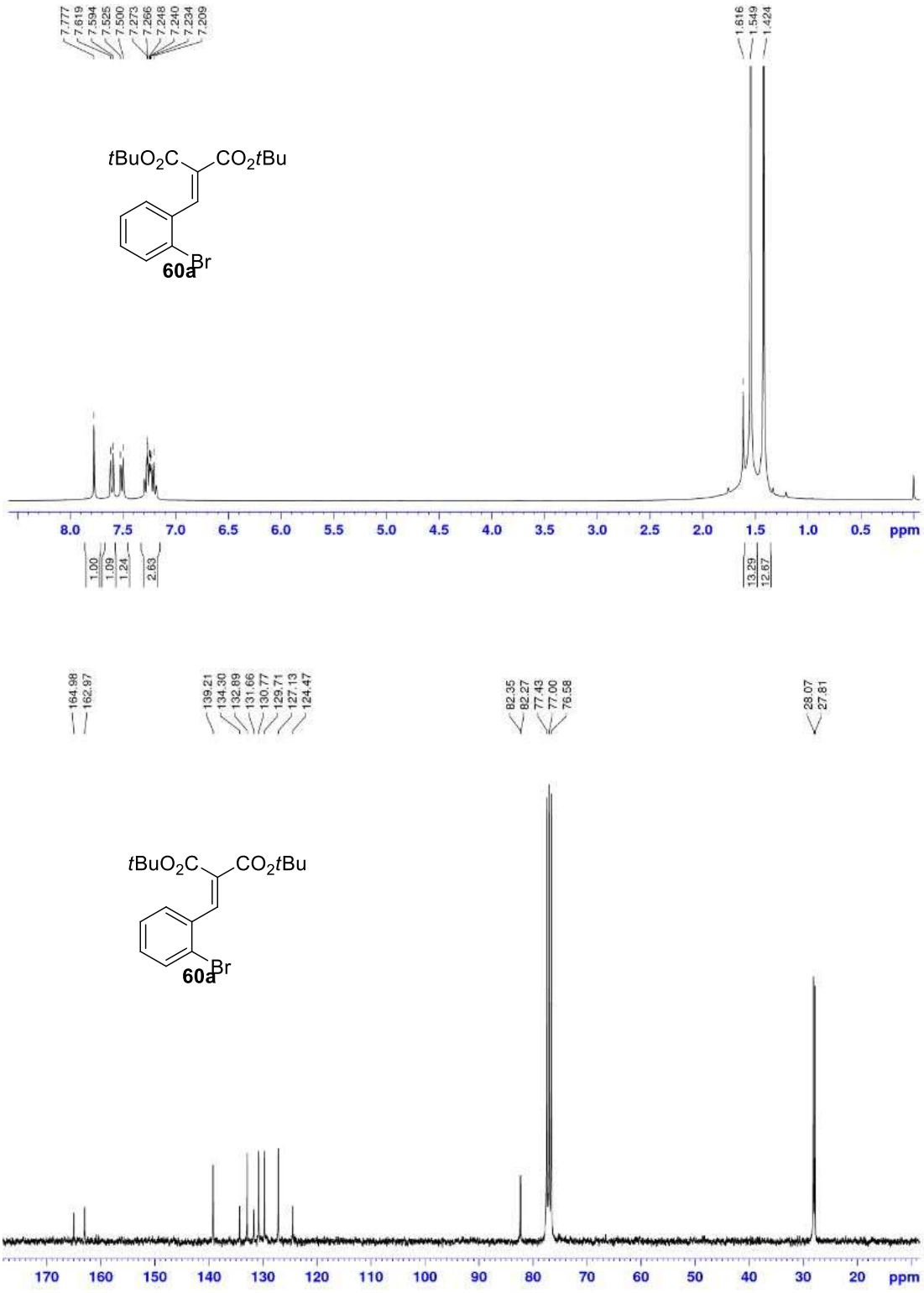


Figure 11 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **58a** in $CDCl_3$

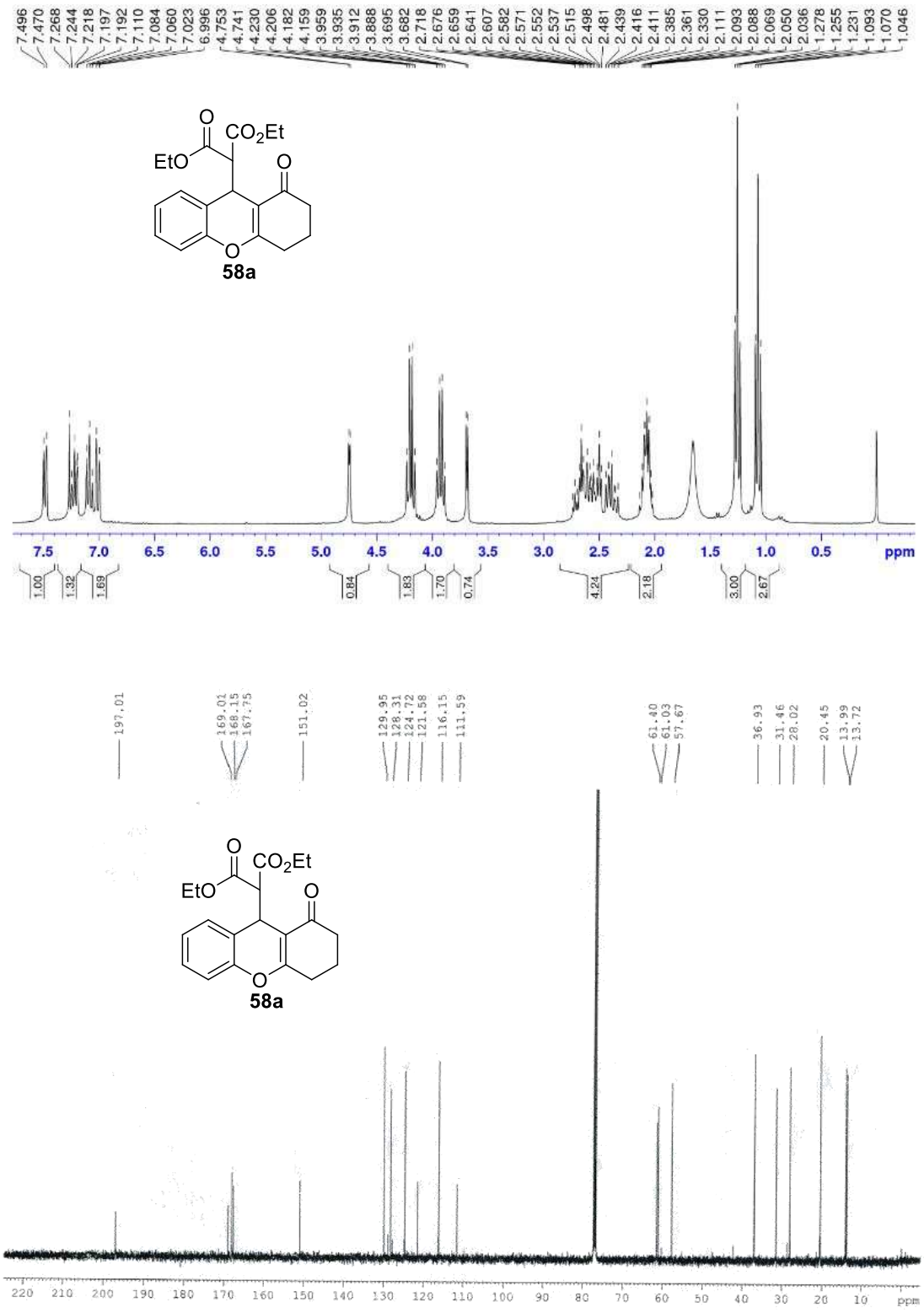


Figure 12 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **58b** in $CDCl_3$

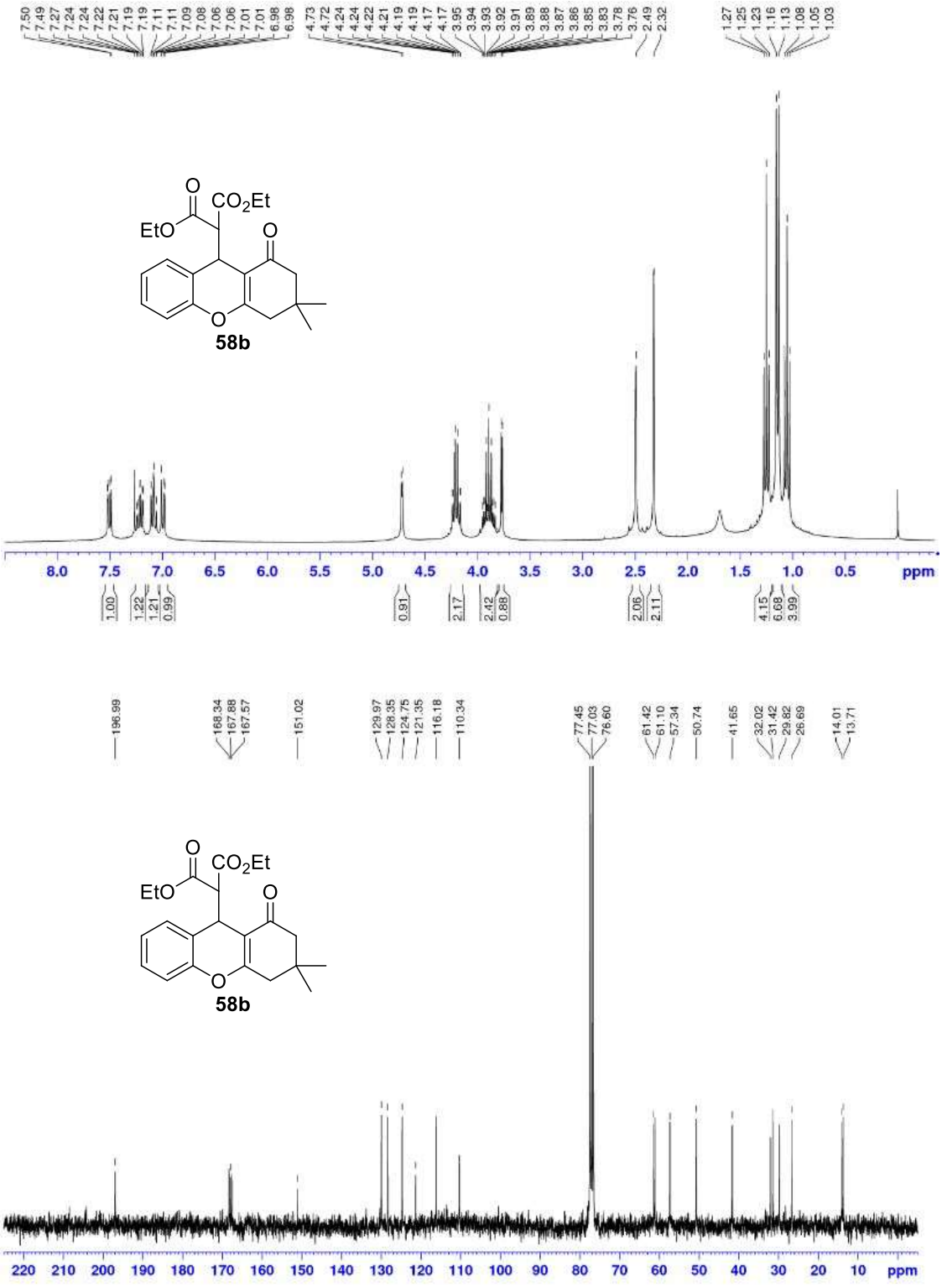


Figure 13 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **58c** in $CDCl_3$

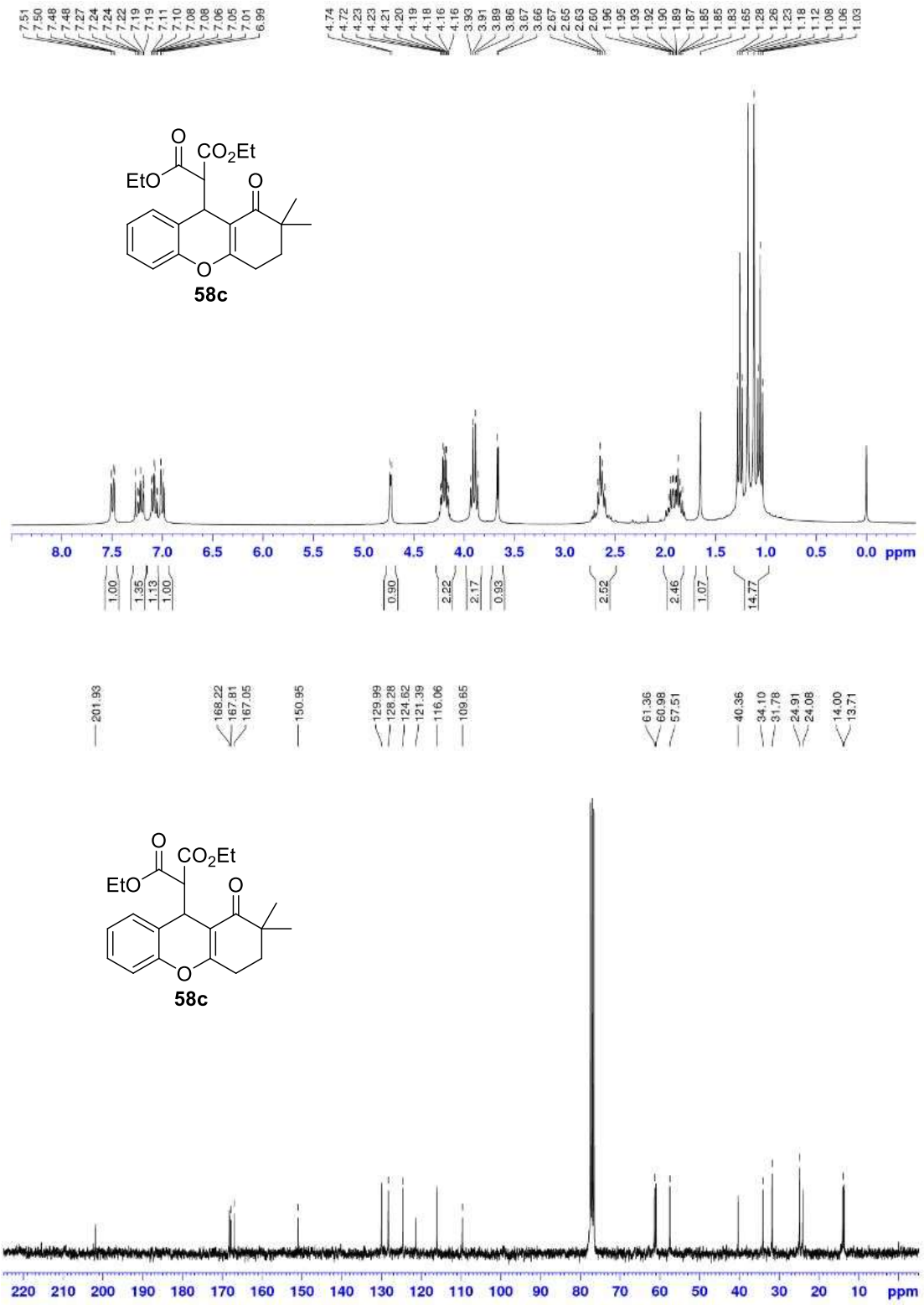


Figure 14 The heteronuclear multiple correlation (HMBC) spectroscopy of **58c** in $CDCl_3$

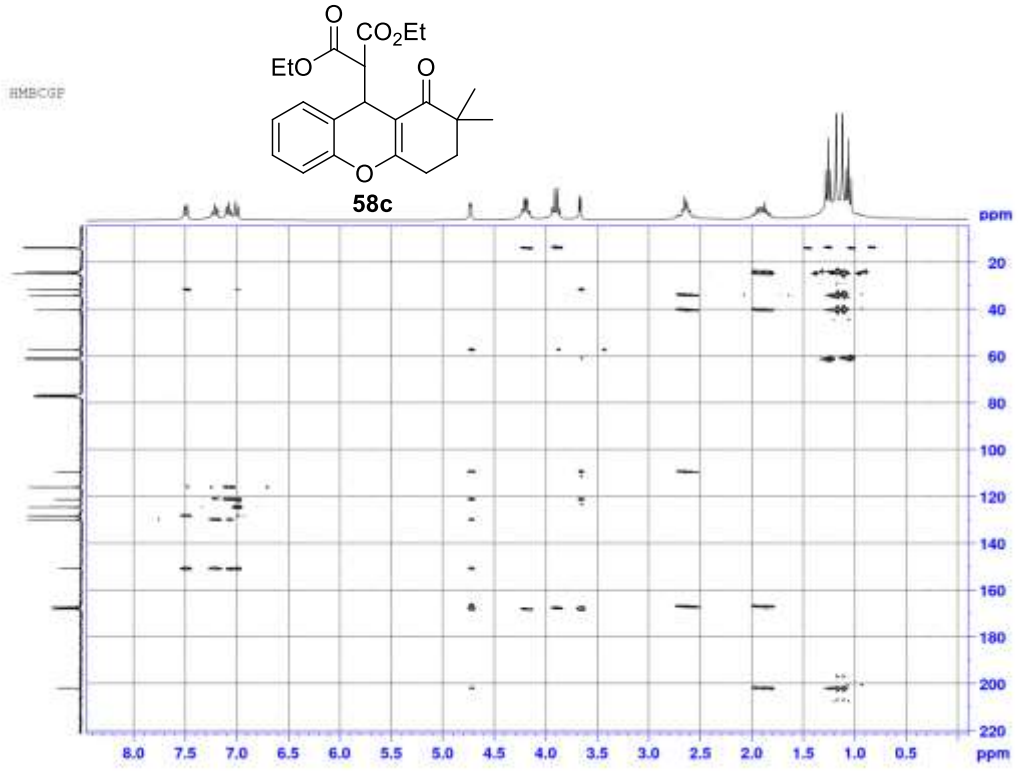


Figure 15 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **58e** in $CDCl_3$

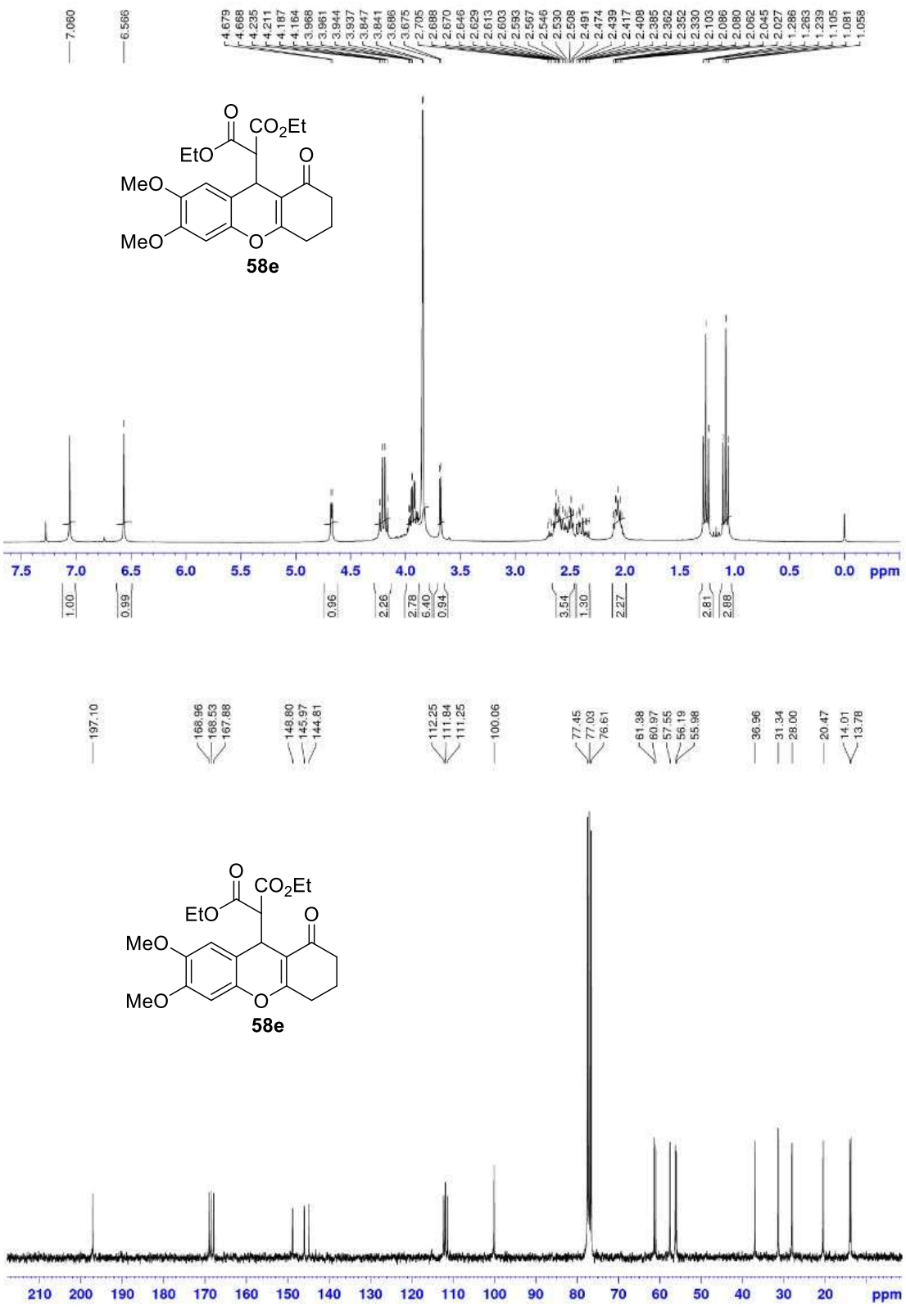


Figure 16 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **58f** in $CDCl_3$

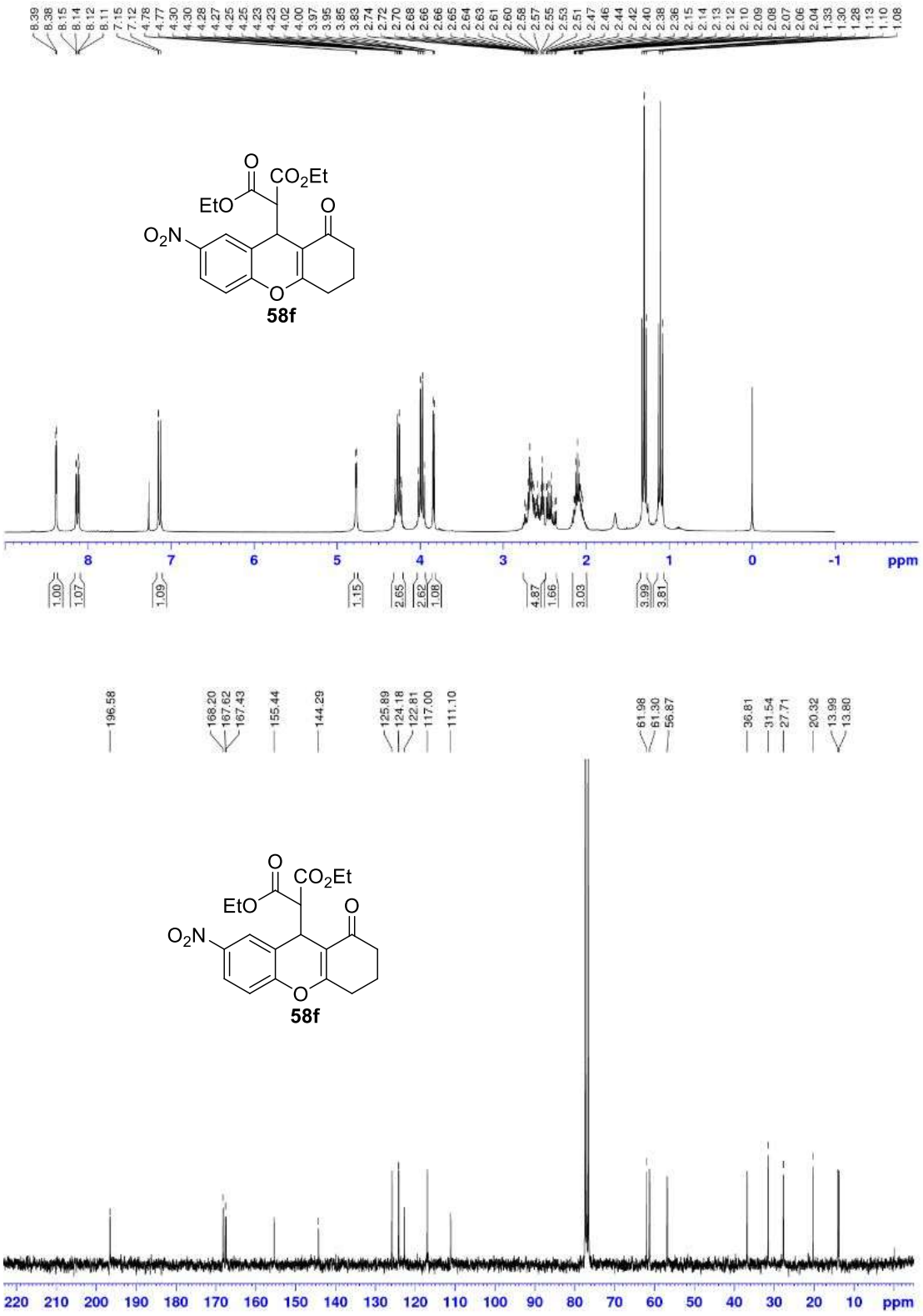


Figure 17 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **58g** in $CDCl_3$

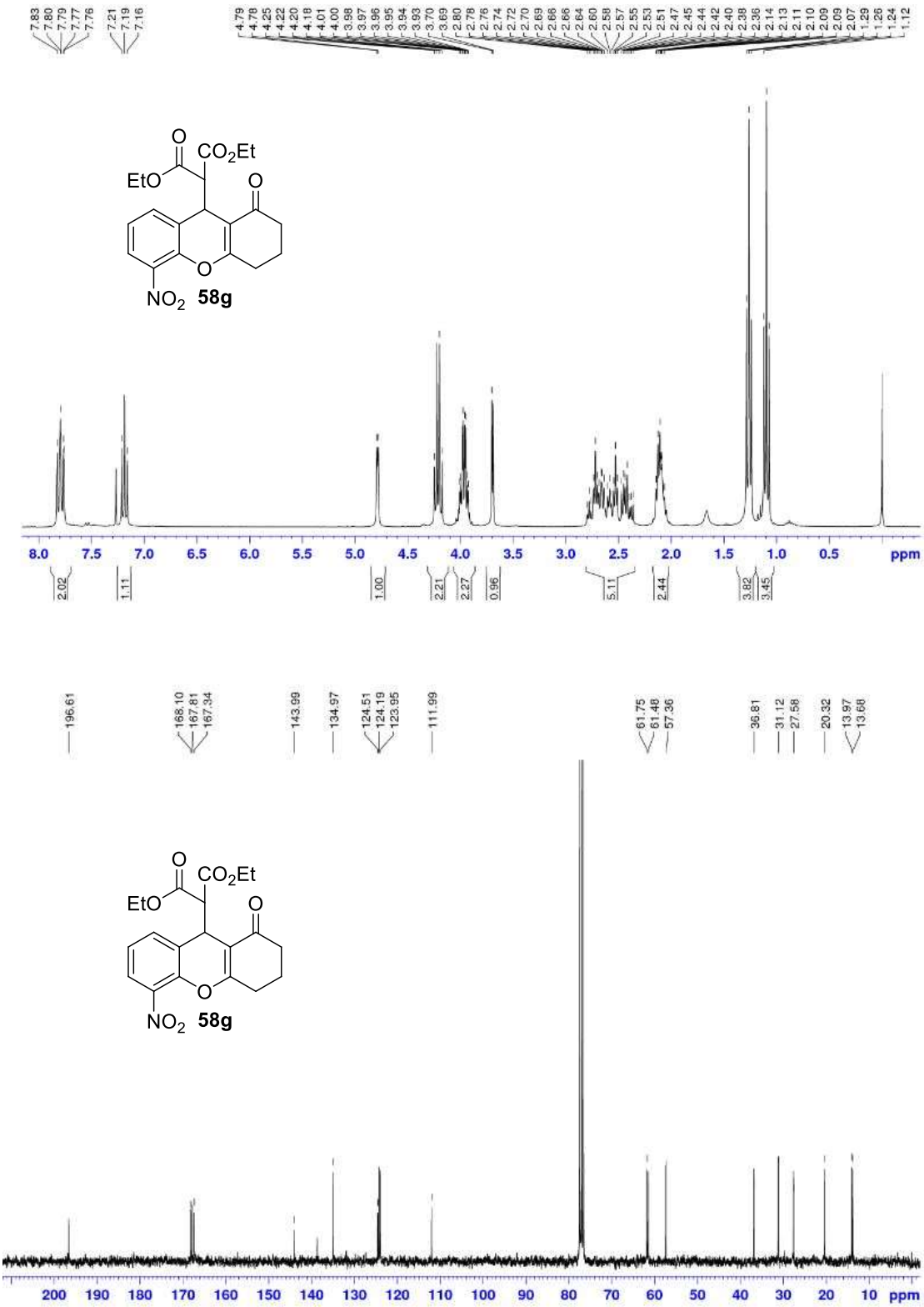


Figure 18 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **58h** in $CDCl_3$

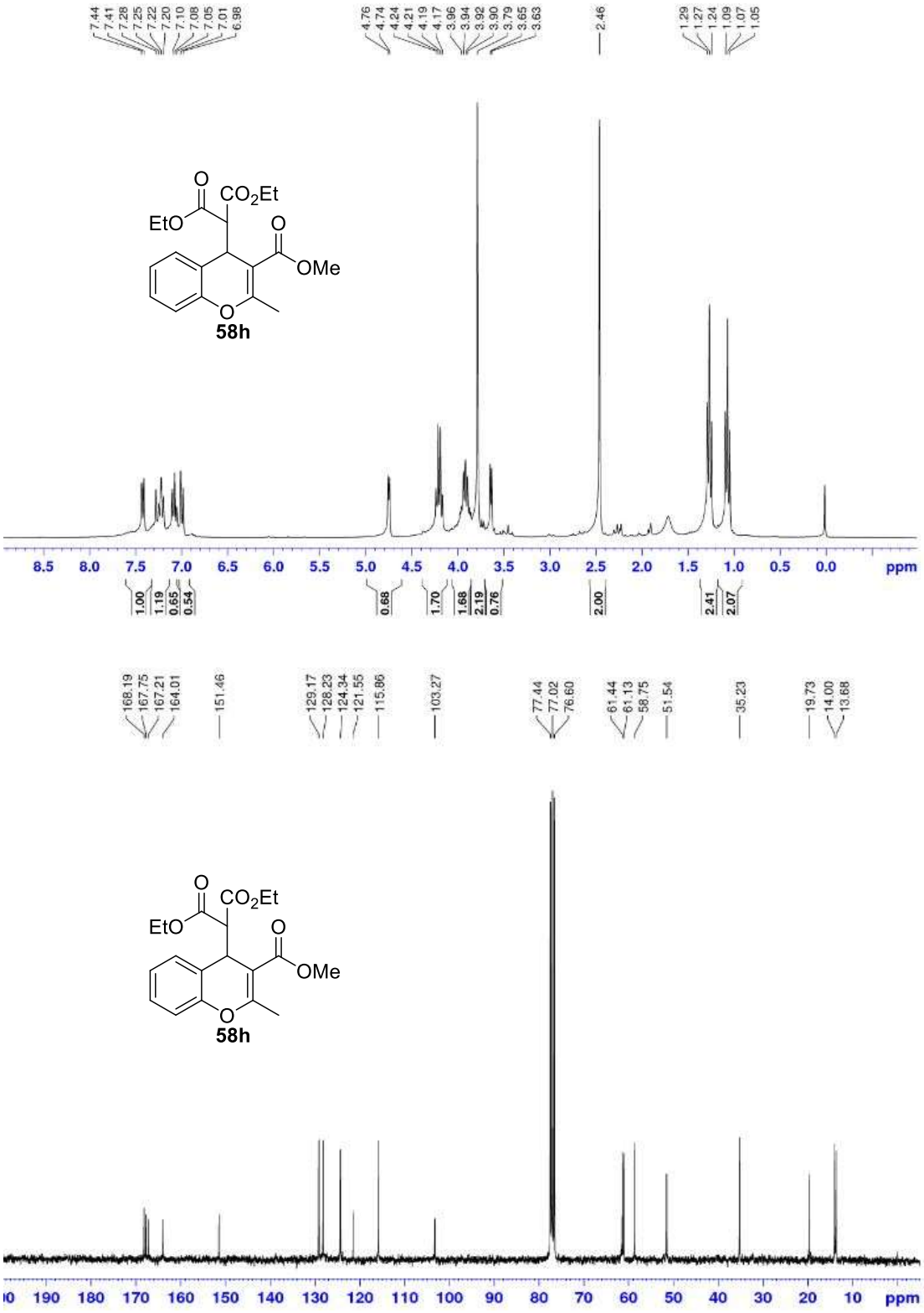


Figure 19 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **61a** in $CDCl_3$

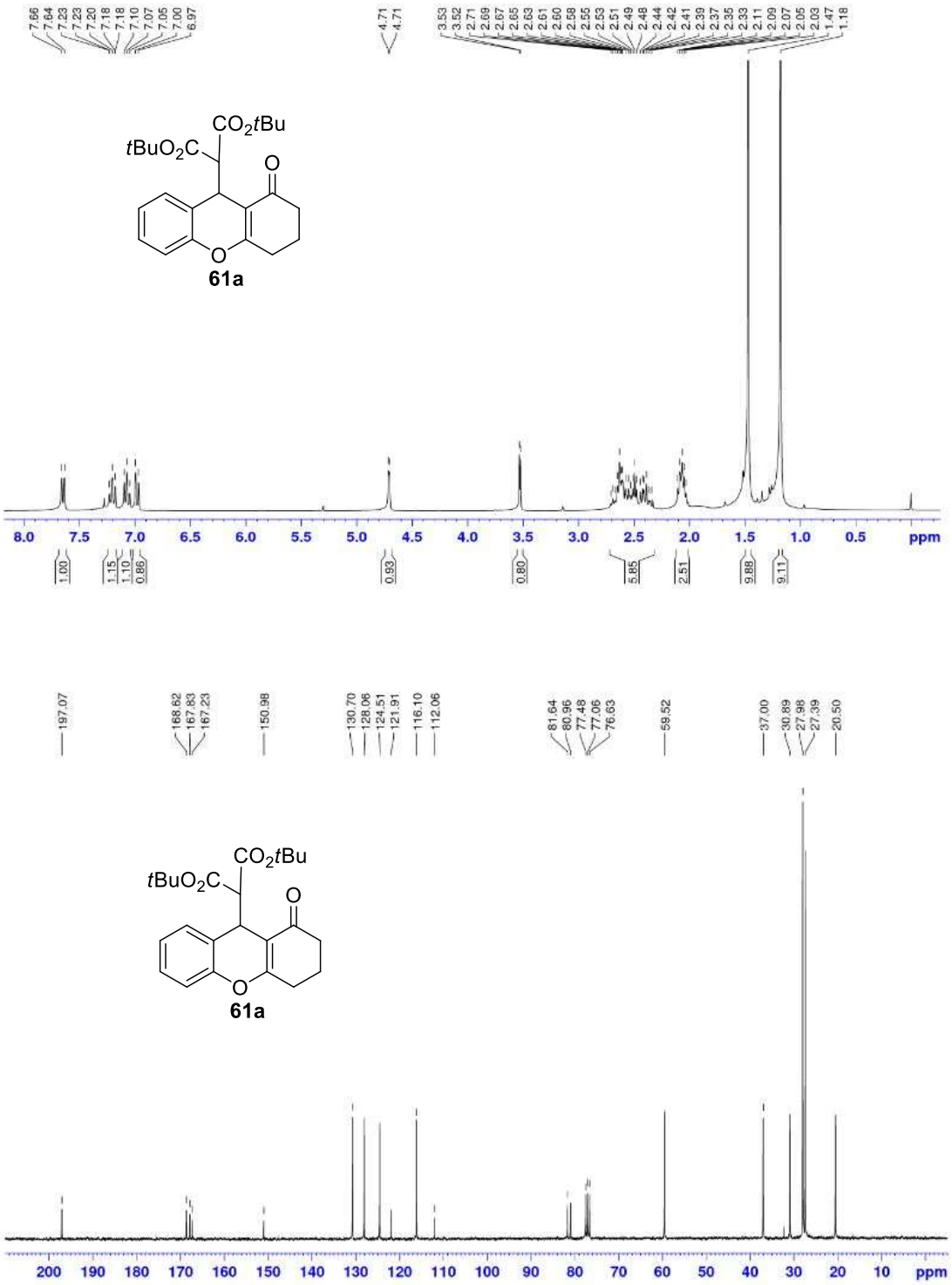
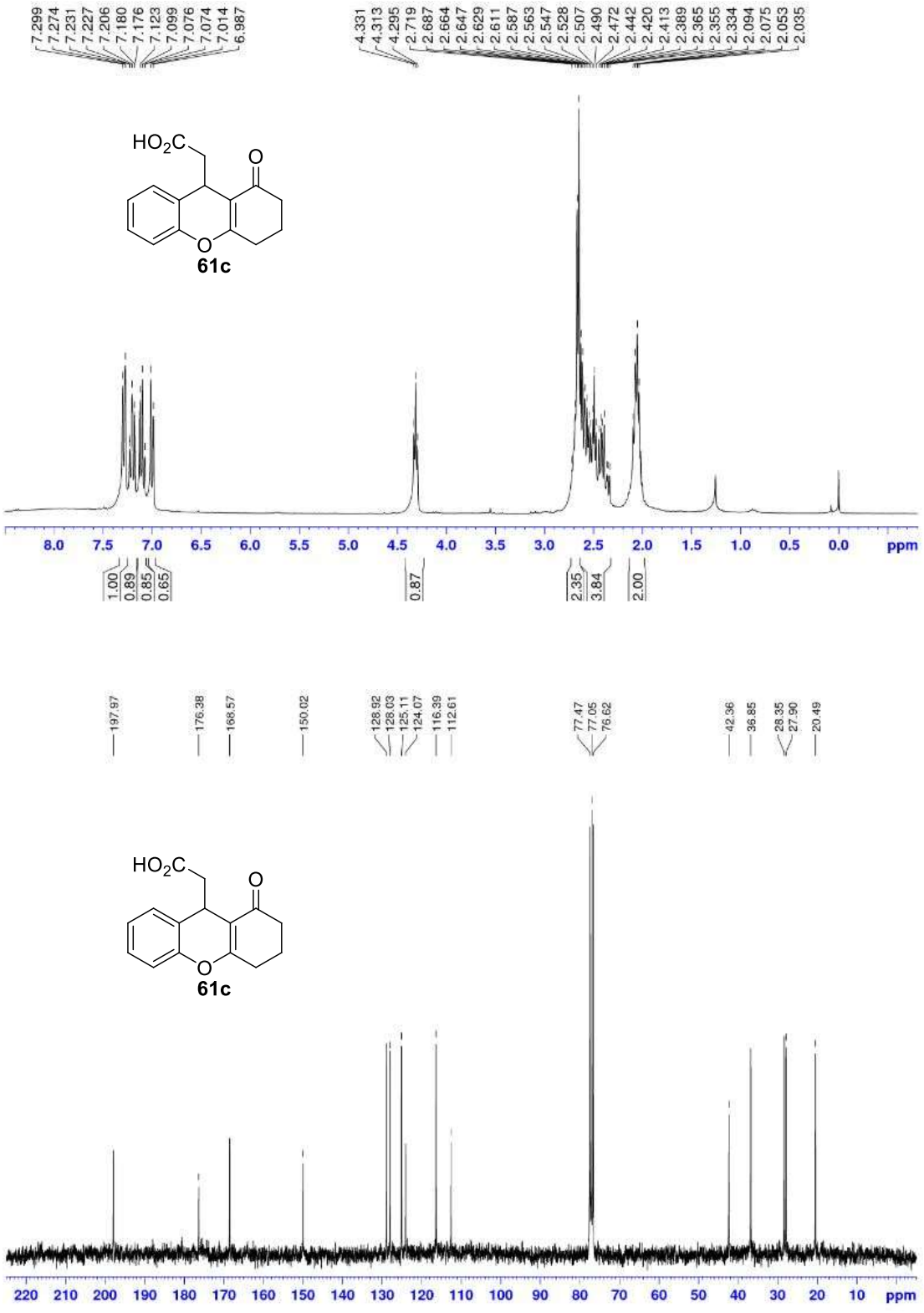


Figure 20 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **61c** in $CDCl_3$



^{1}H and ^{13}C NMR Spectra of New Compounds of Quinazolinones

Figure 21 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **99a** in $CDCl_3$

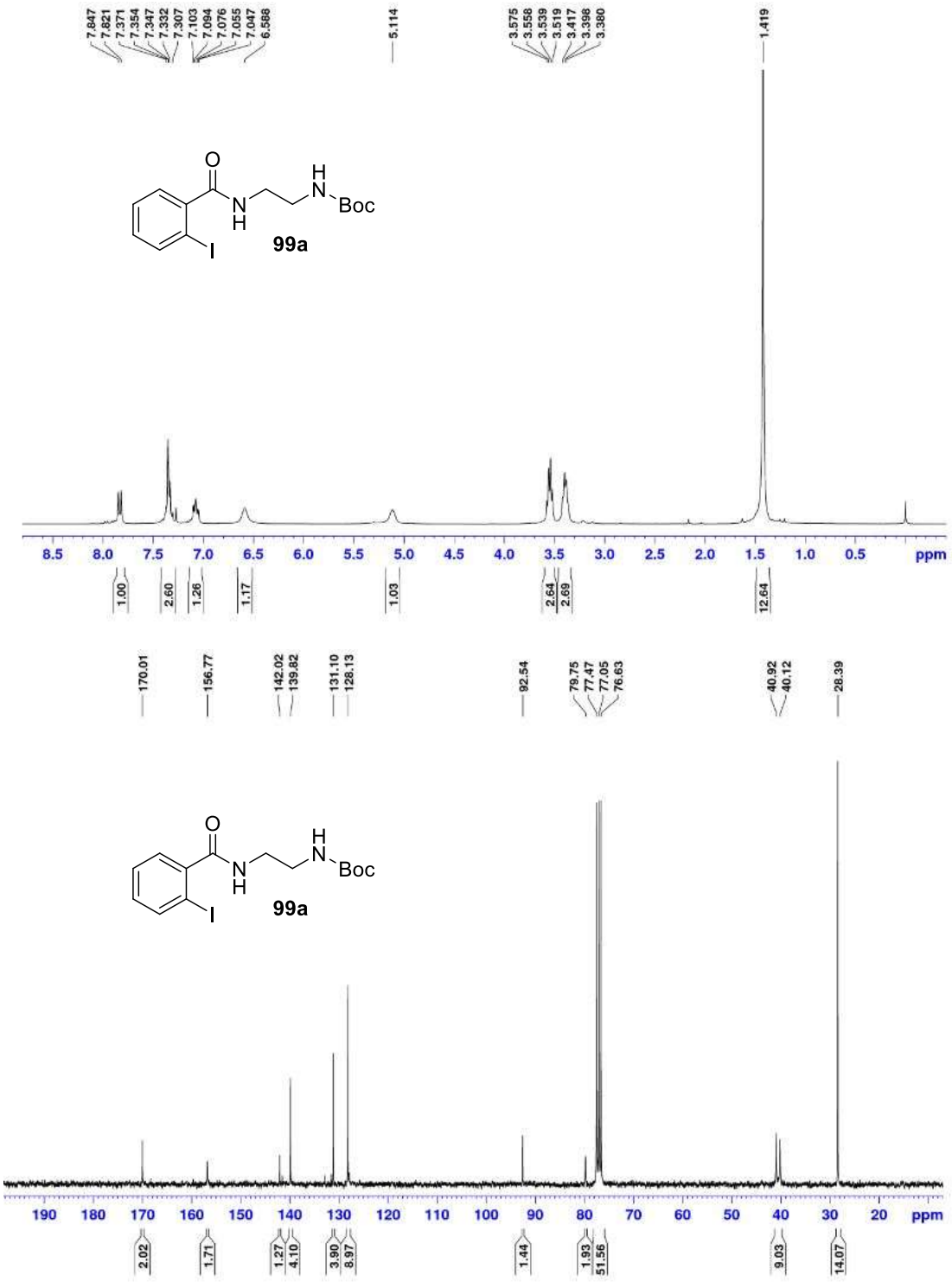


Figure 22 The ^{1}H (300 MHz) in $CDCl_3$ and ^{13}C NMR (75 MHz) in DMSO-d_6 spectra of compound **99b**

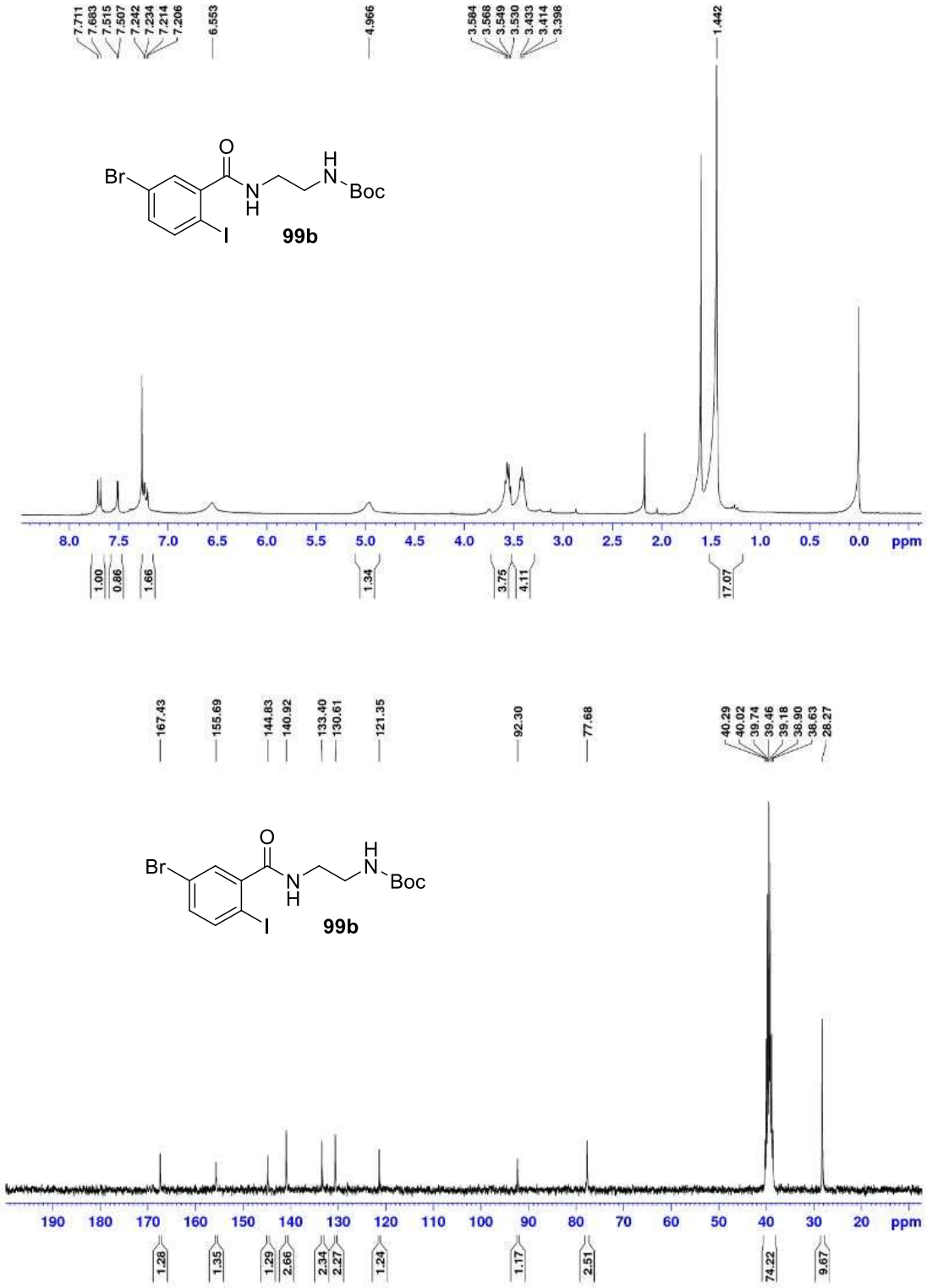


Figure 23 The ^{1}H (300 MHz) in $CDCl_3$ and ^{13}C NMR (75 MHz) in DMSO-d_6 spectra of compound **99C**

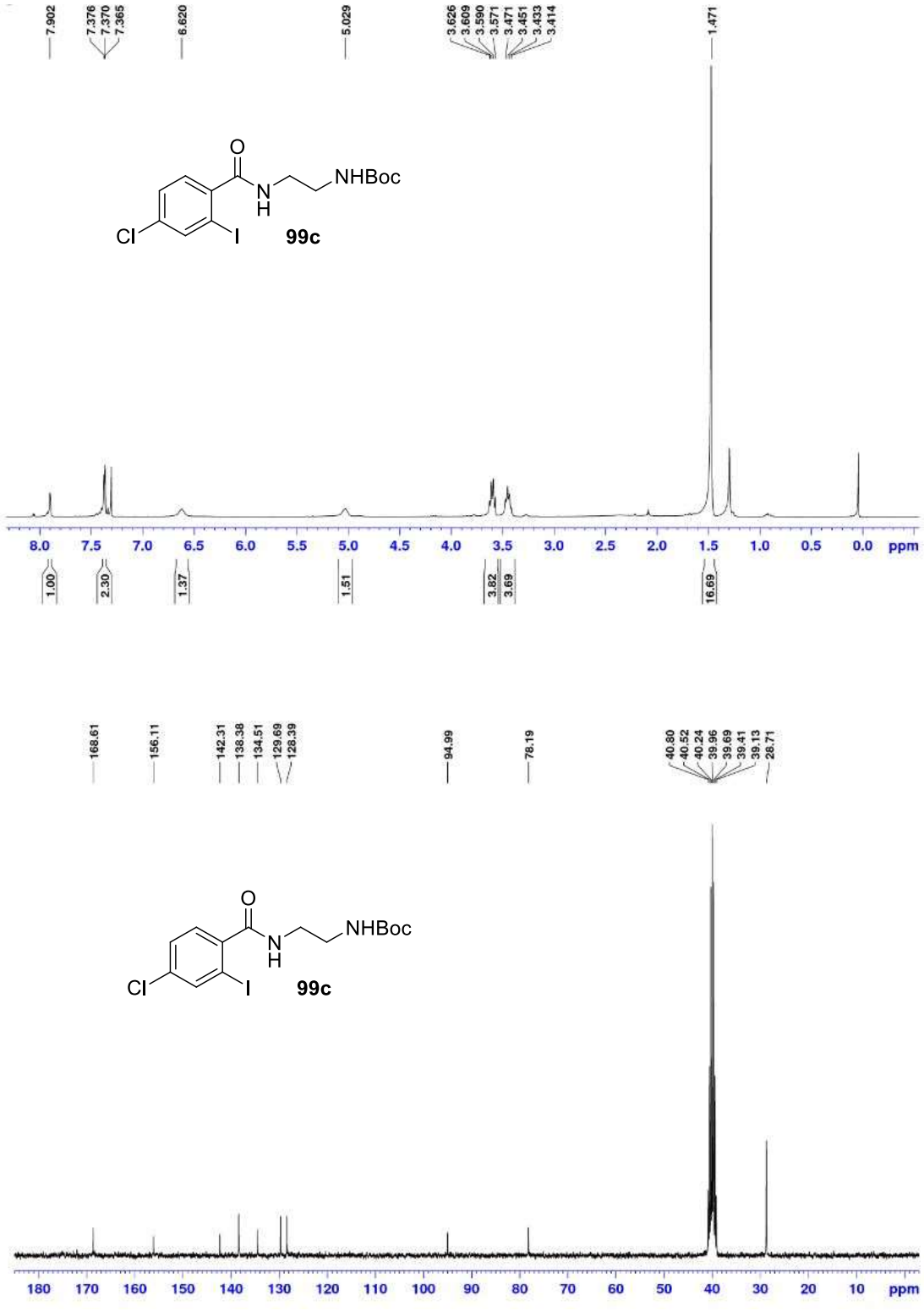


Figure 24 The ^{1}H (300 MHz) in $CDCl_3$ and ^{13}C NMR (75 MHz) in DMSO-d_6 spectra of compound **99d**

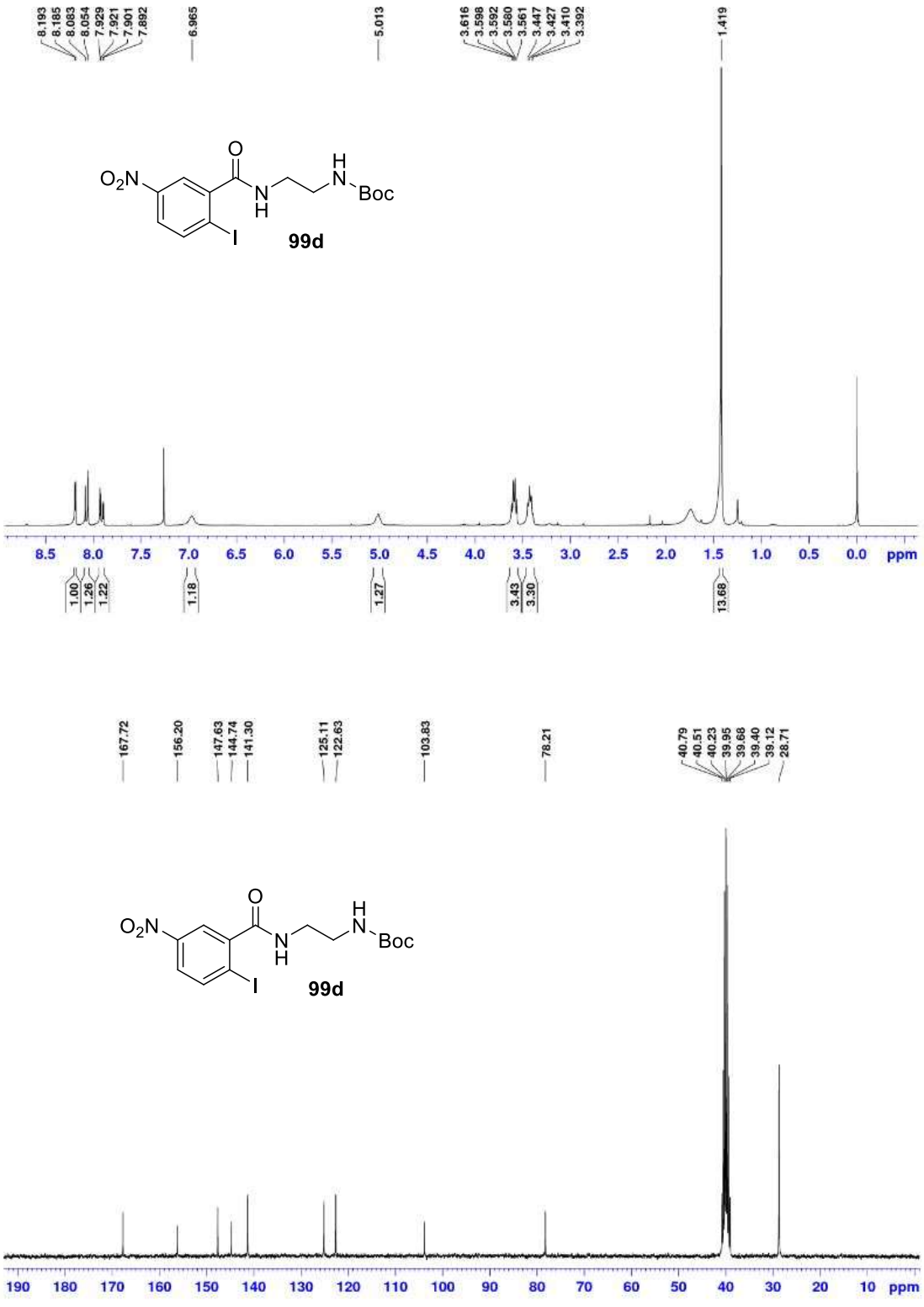


Figure 25 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **99e** in DMSO-d_6

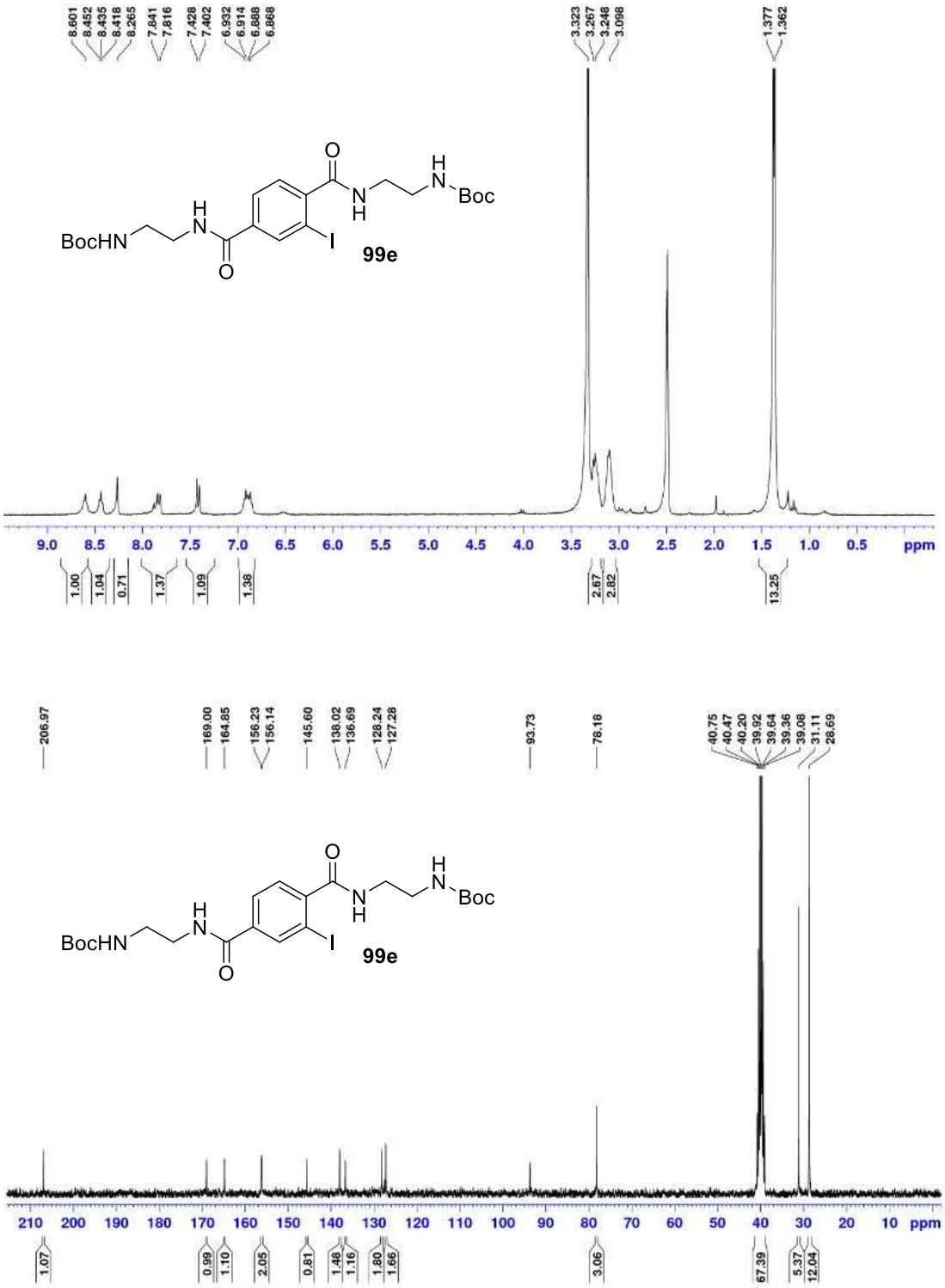


Figure 26 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **99f** in $CDCl_3$

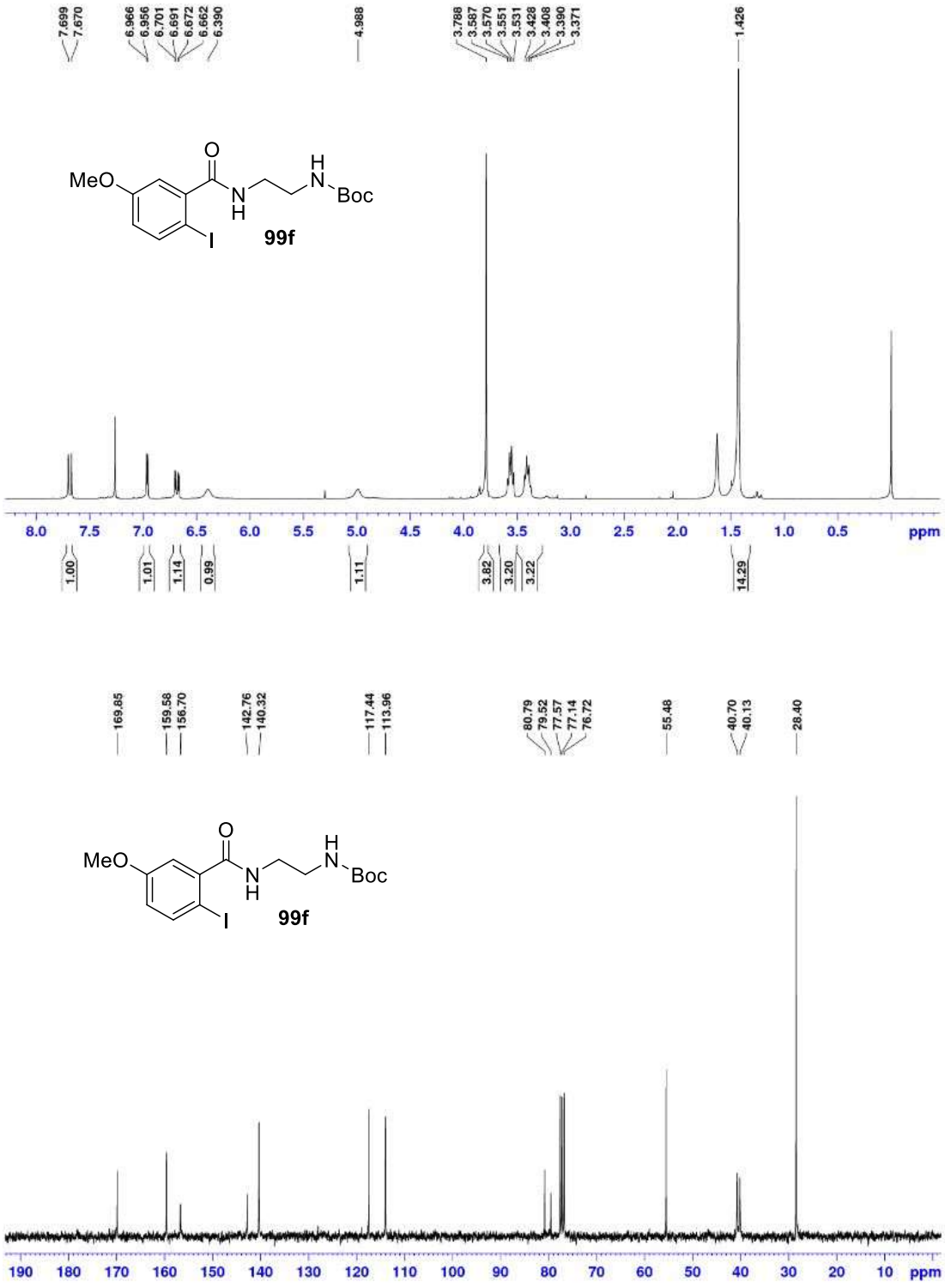


Figure 27 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **99g** in $CDCl_3$

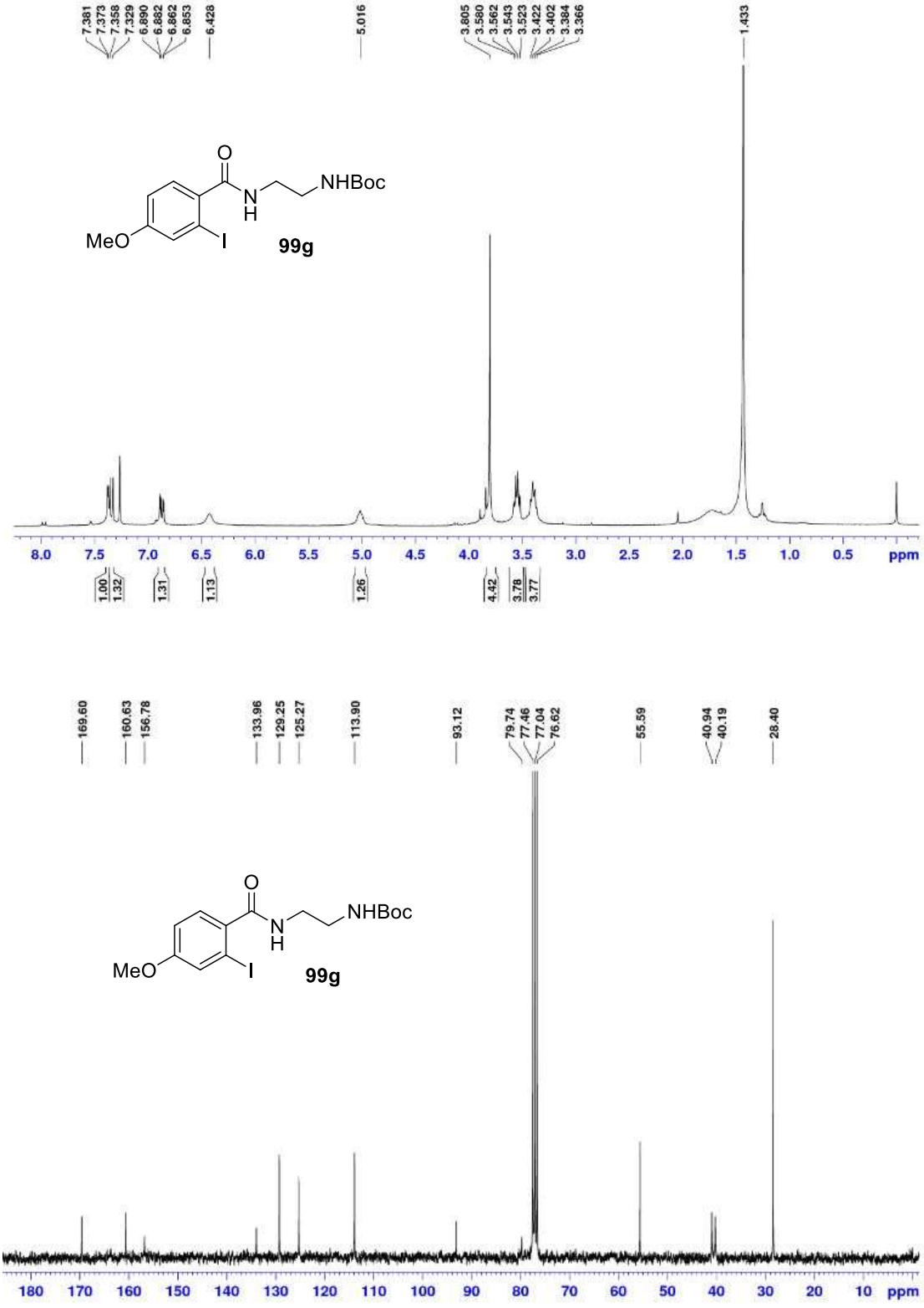


Figure 28 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **99h** in $CDCl_3$

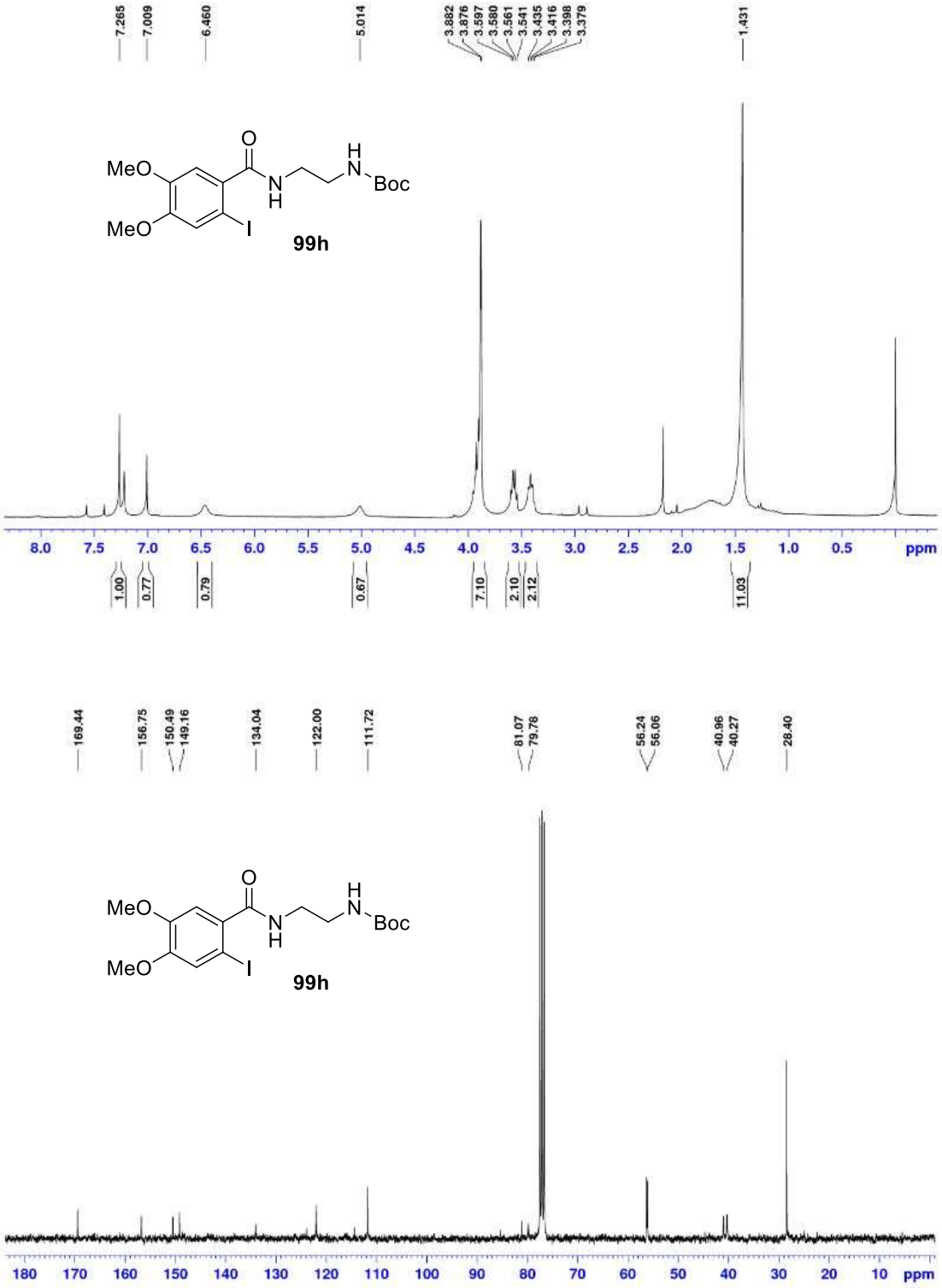


Figure 29 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100a** in $CDCl_3$

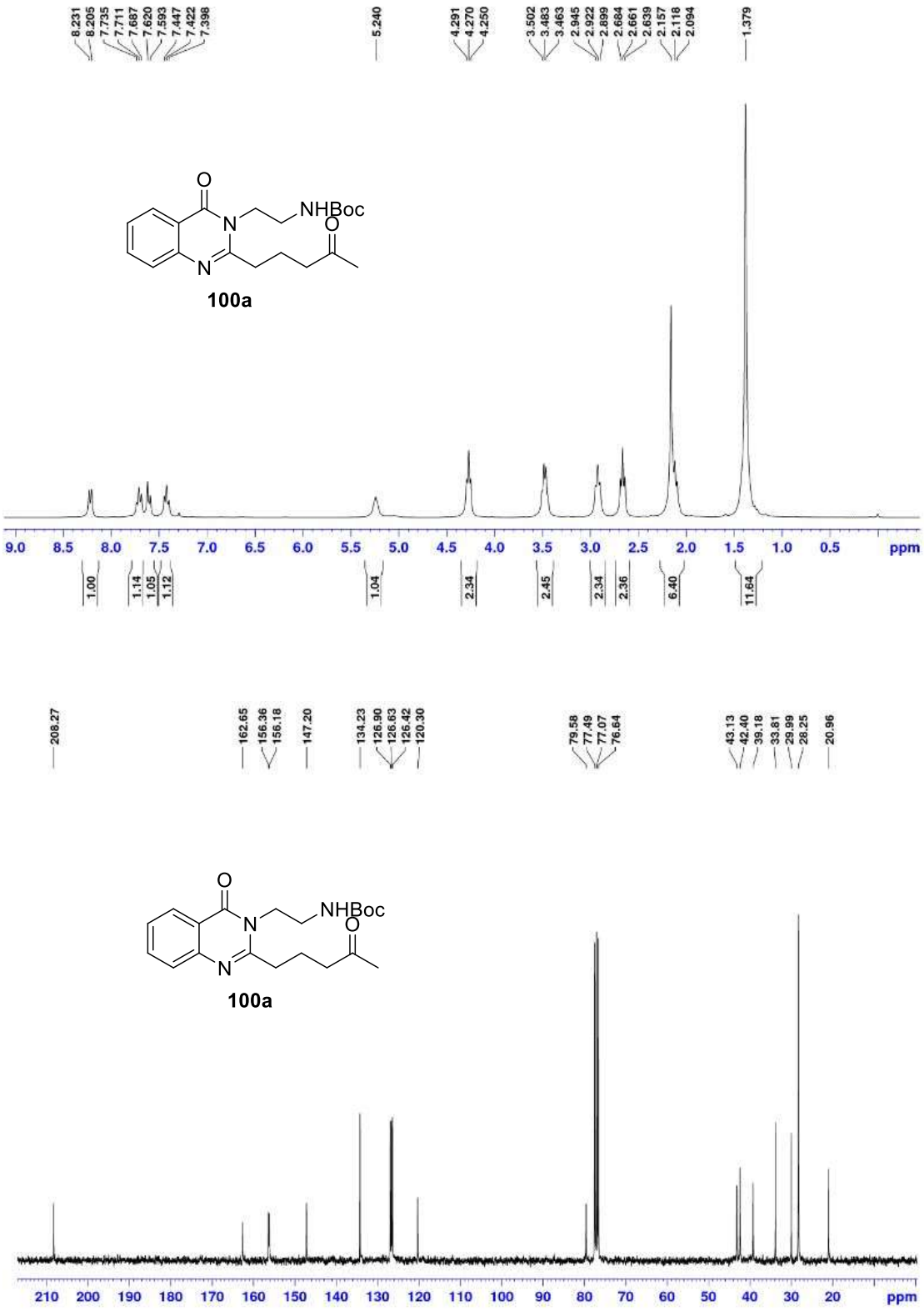


Figure 30 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100b** in $CDCl_3$

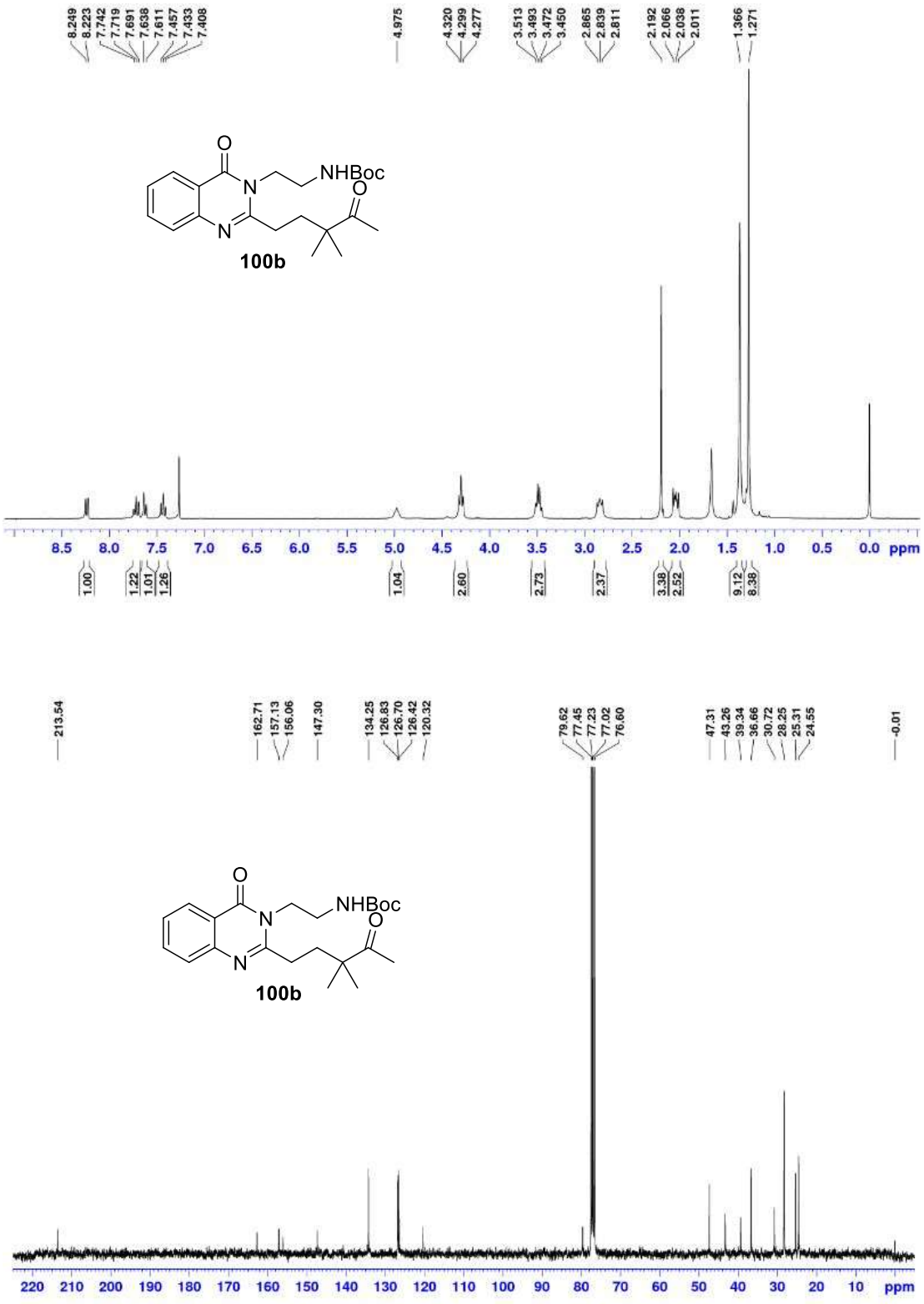
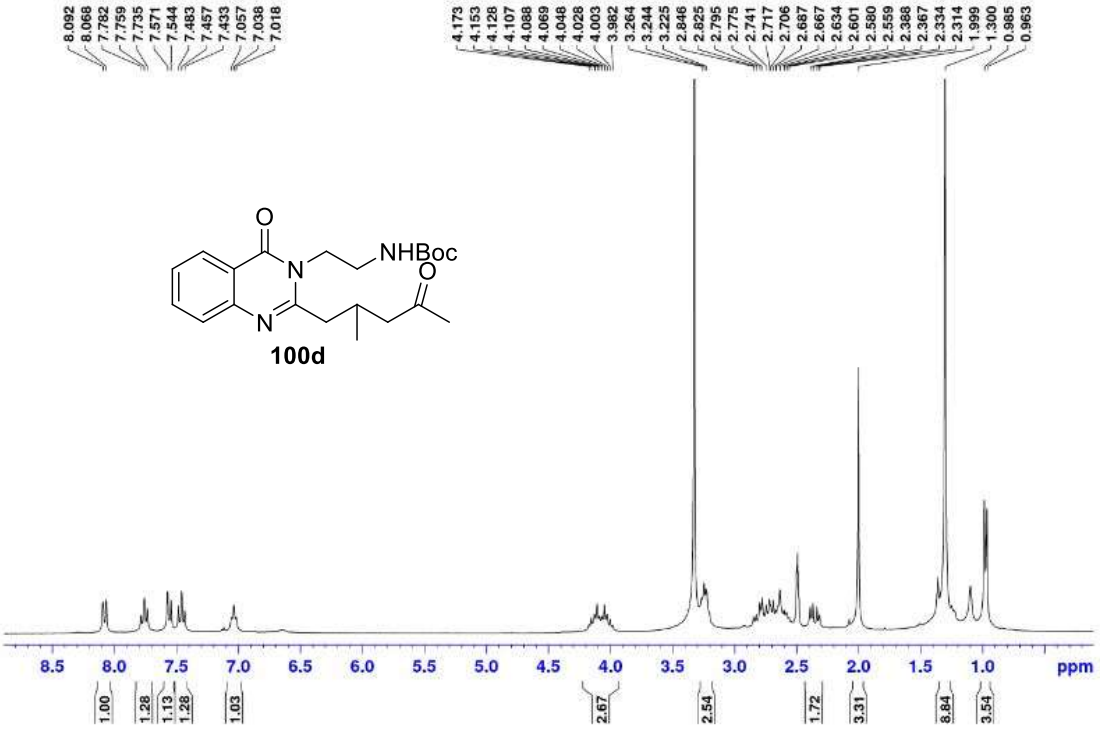


Figure 31 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100d** in DMSO-d_6



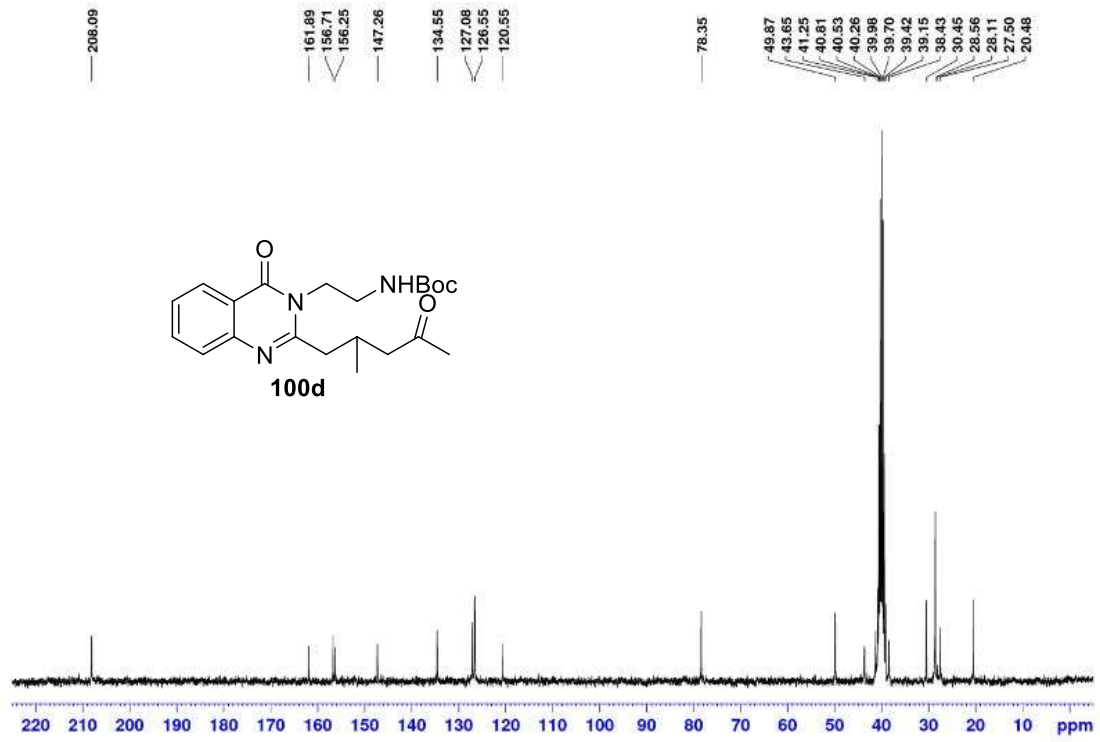


Figure 32 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100e** in $CDCl_3$

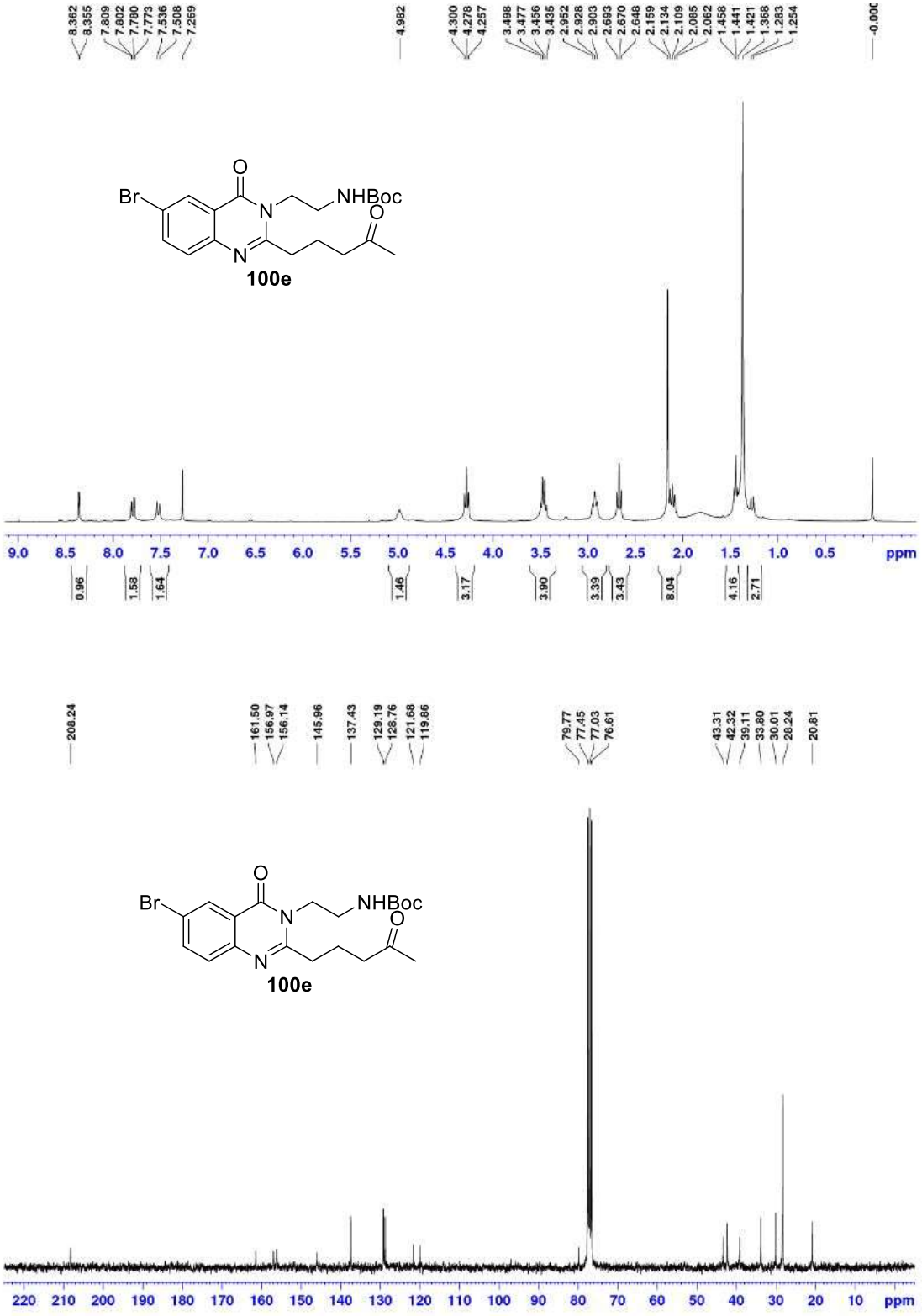


Figure 33 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100f** in $CDCl_3$

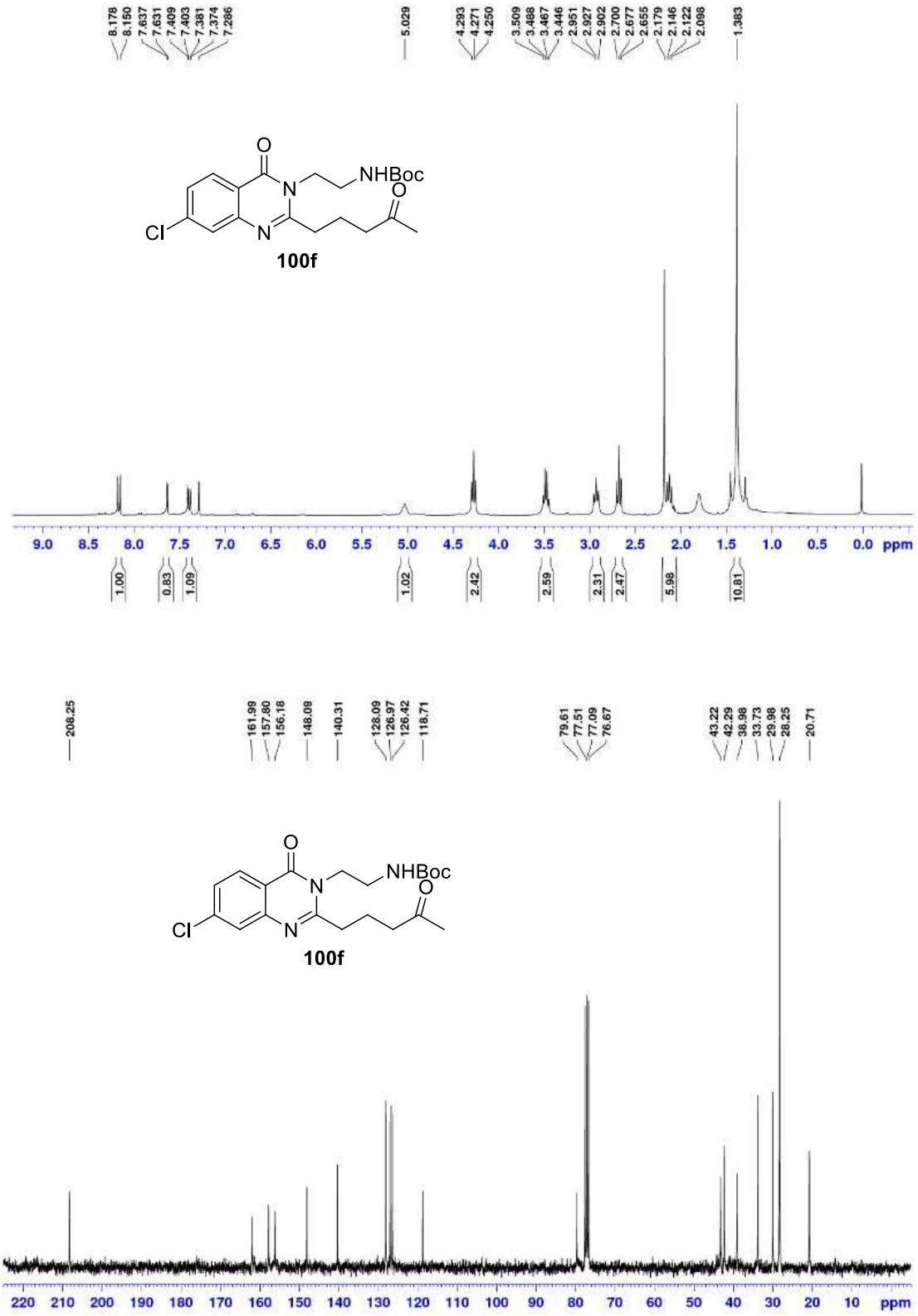


Figure 34 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100g** in $CDCl_3$

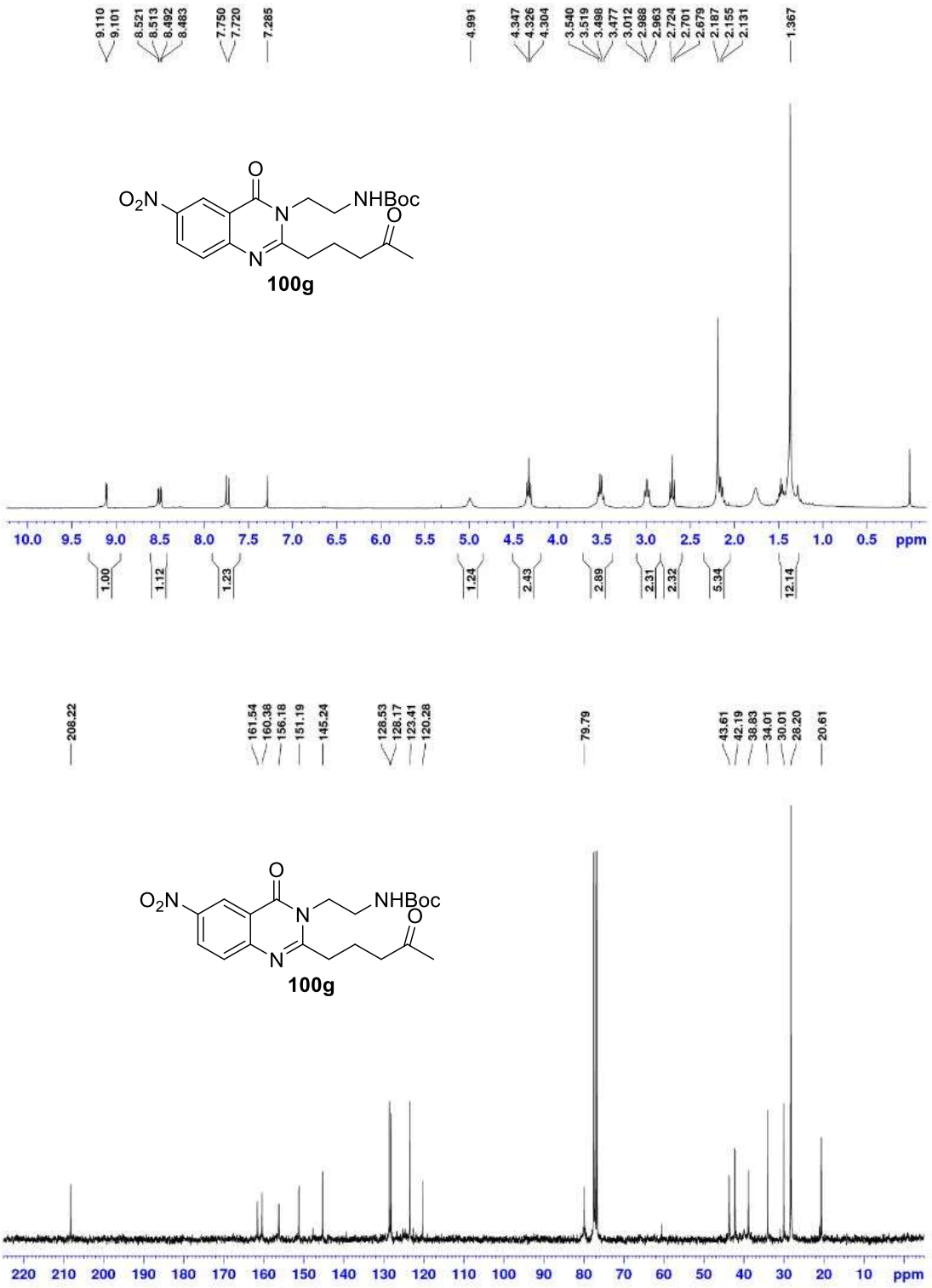


Figure 35 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100h** in $CDCl_3$

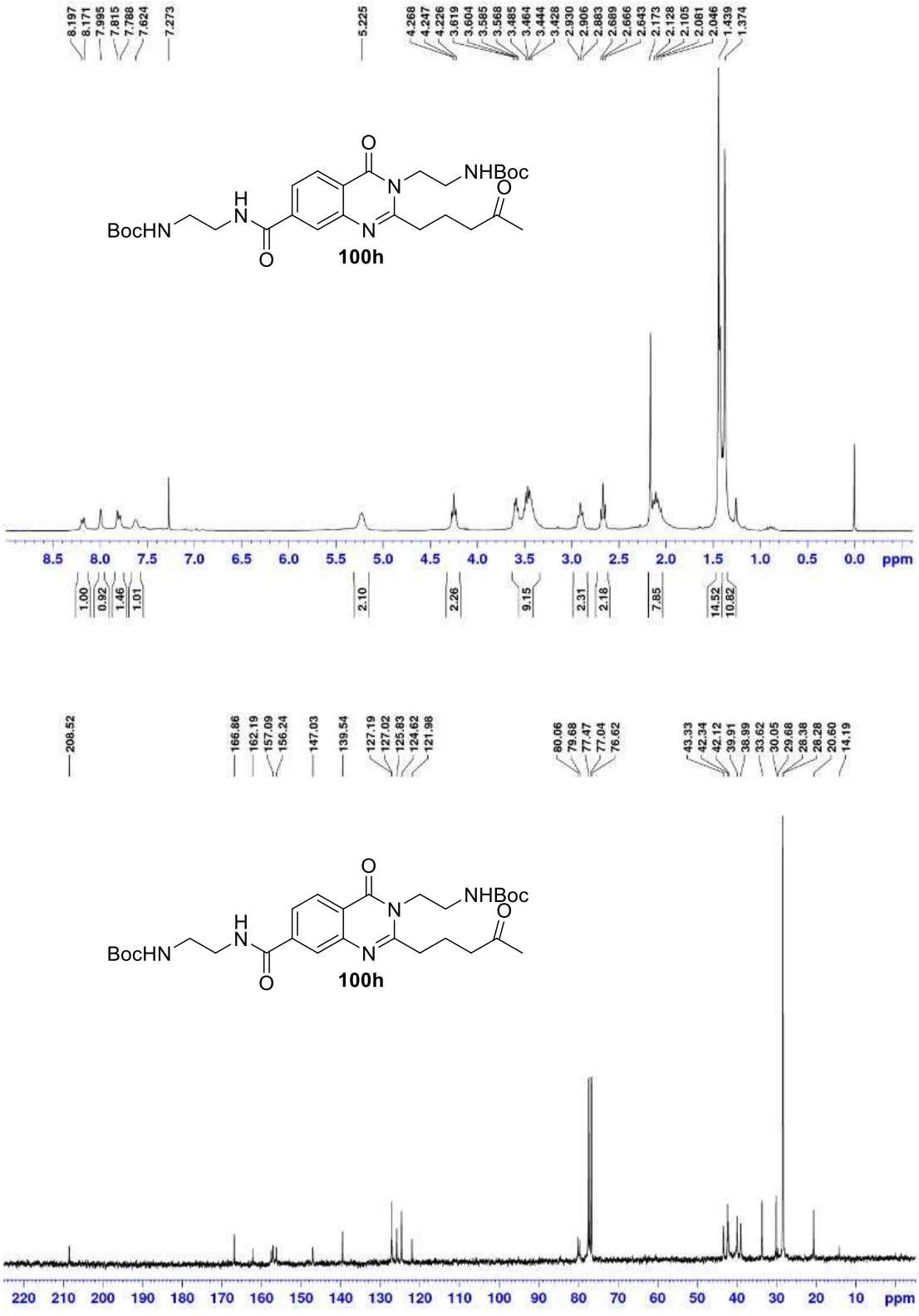


Figure 36 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100i** in $CDCl_3$

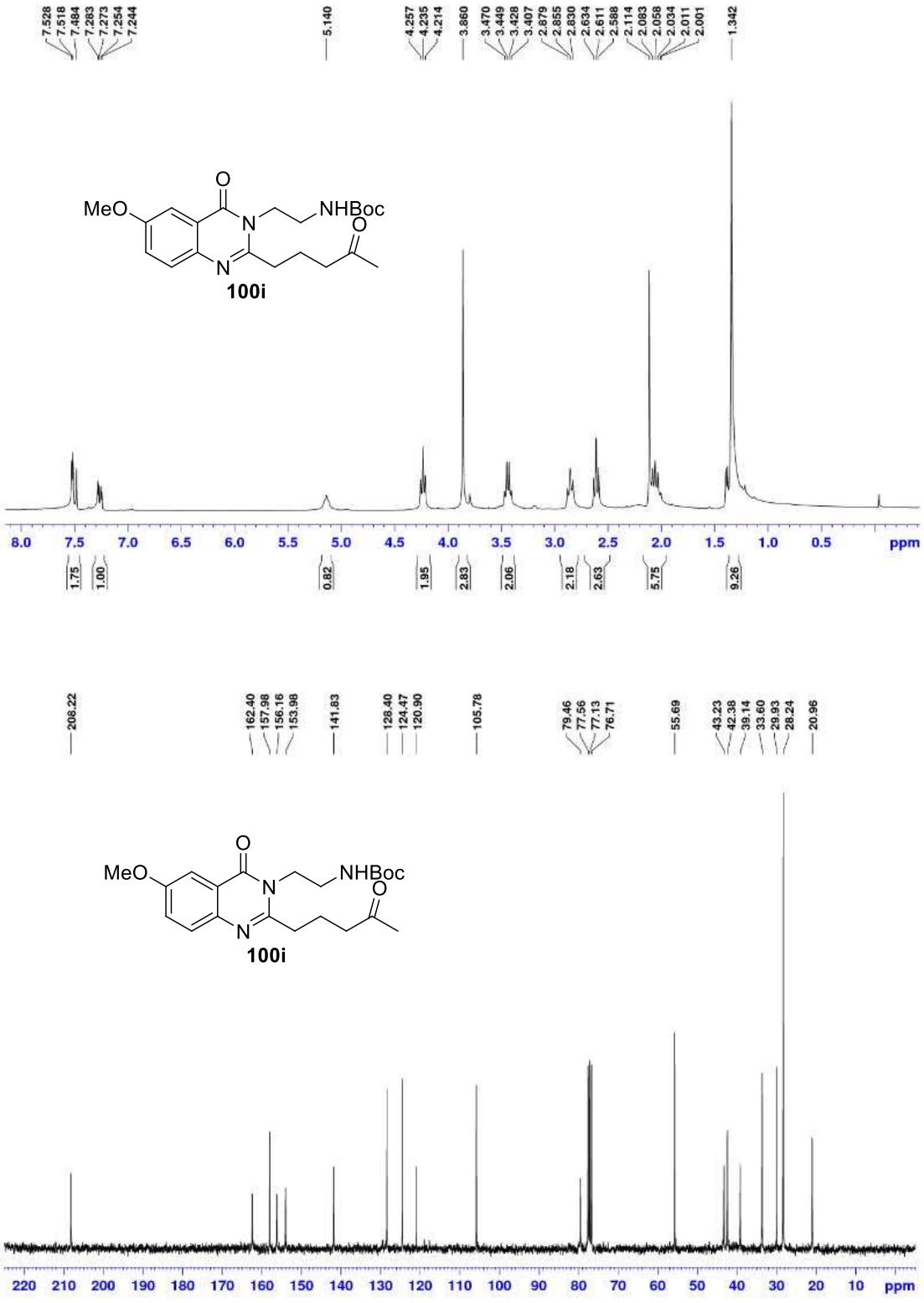


Figure 37 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100j** in $CDCl_3$

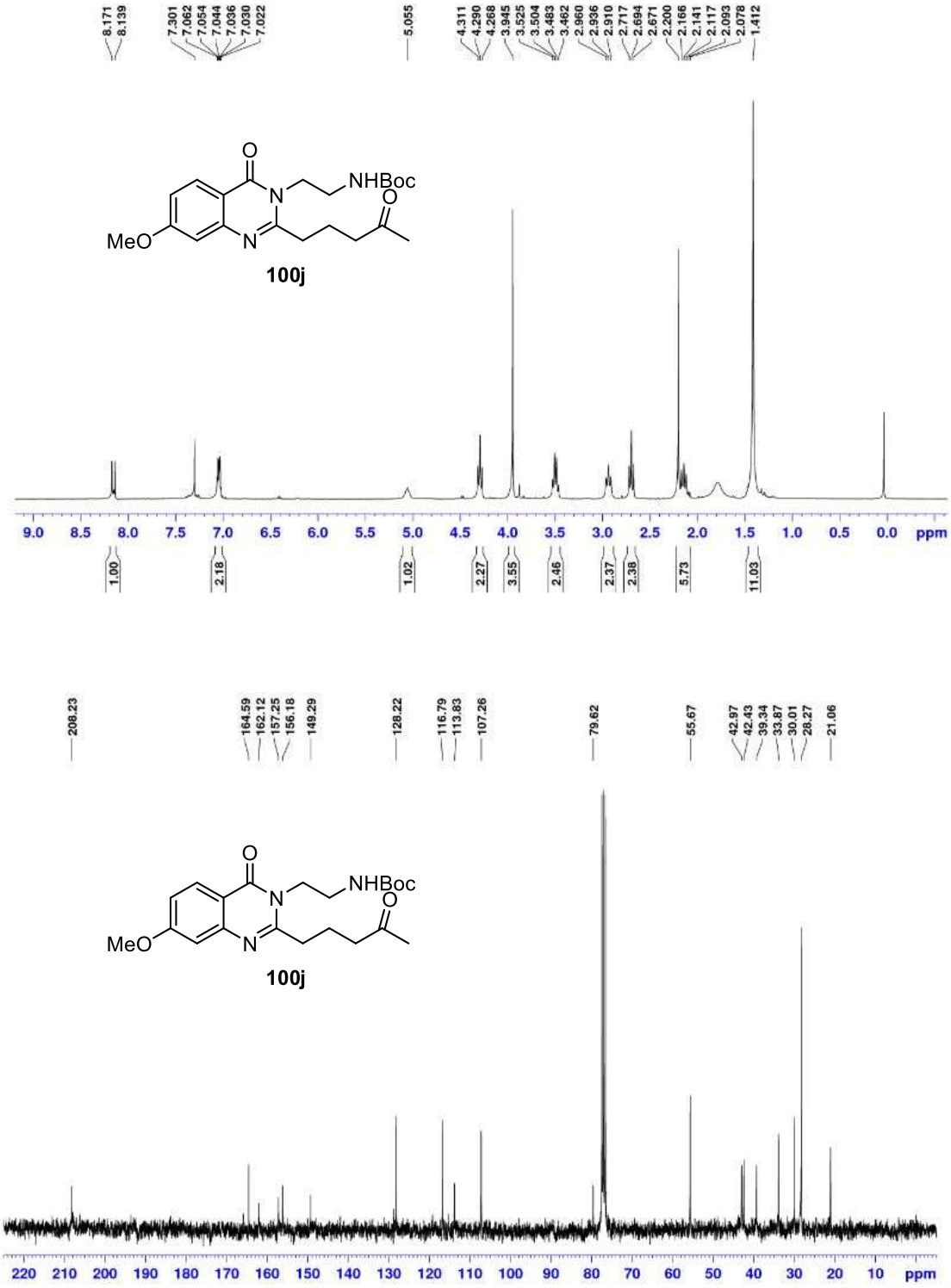


Figure 38 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100k** in $CDCl_3$

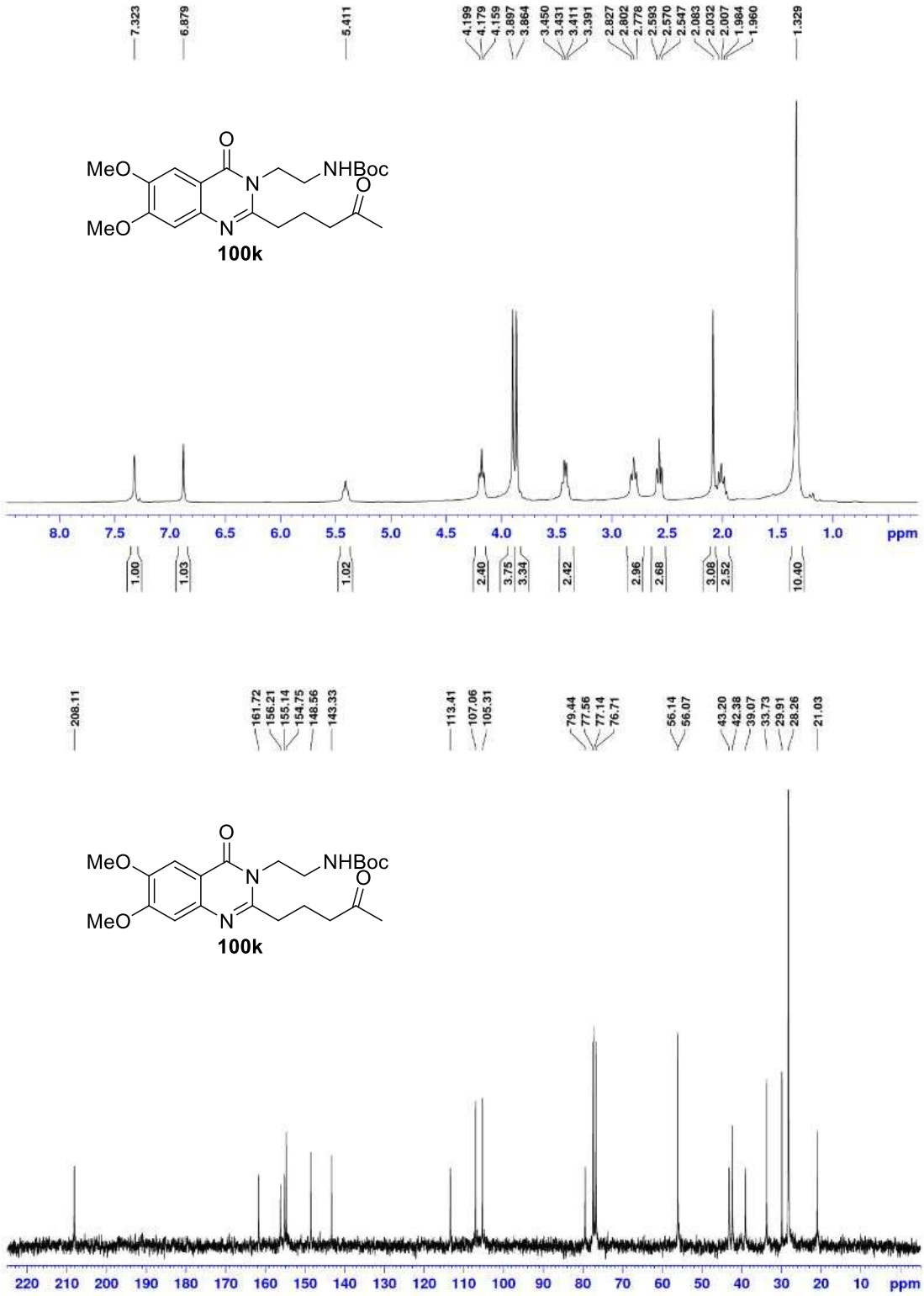
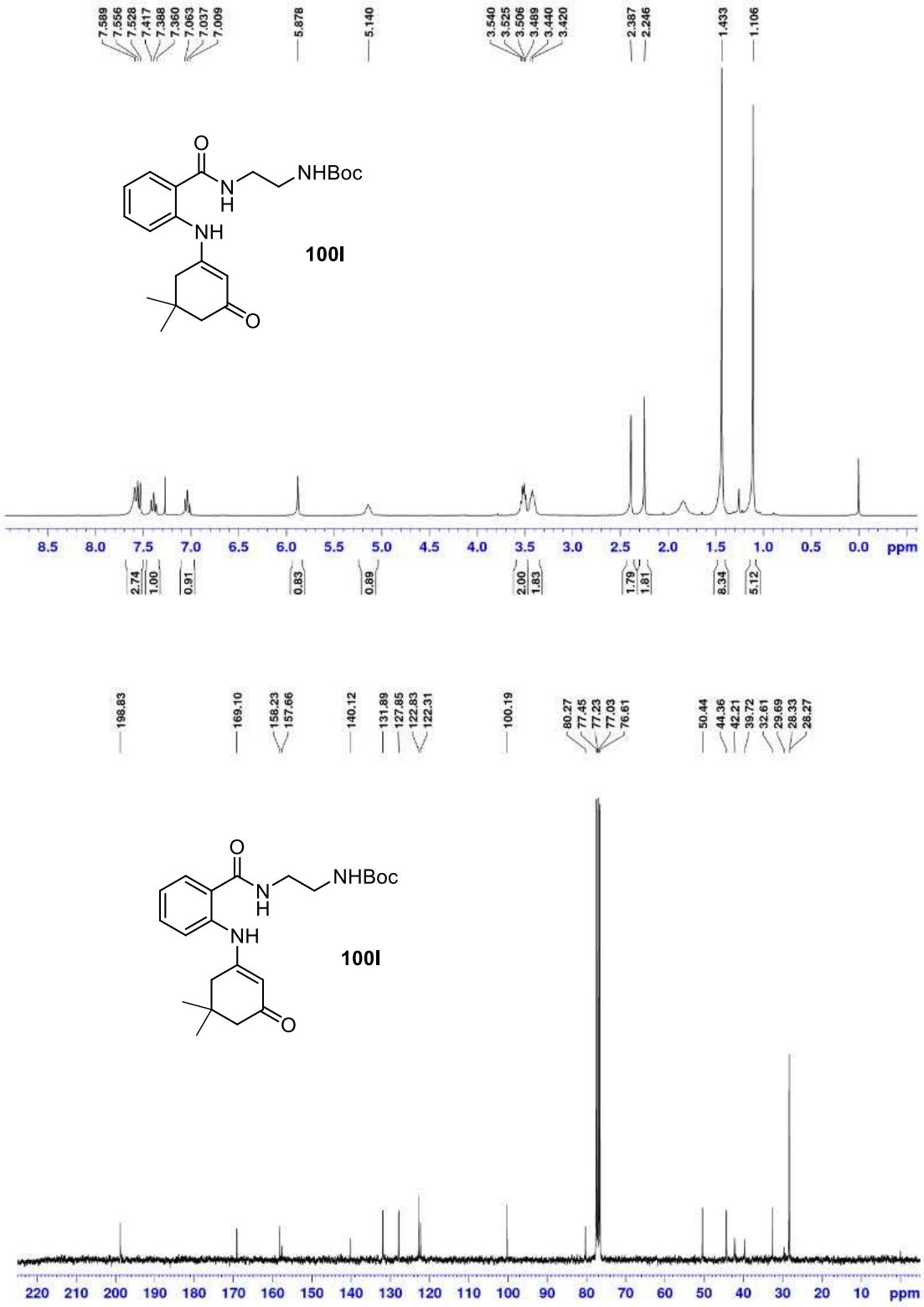


Figure 39 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **100l** in $CDCl_3$



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List of Publication

Saebang, Y.; Rukachaisirikul, V.; Kaeobamrung, J. 2017. Copper-catalyzed domino reaction of 2-bromobenzylidenemalonates and 1,3-dicarbonyls for the synthesis of chromenes. Tetrahedron Lett. 58, 168–171.