Synthesis of Small and Medium-Sized Ring Fused Quinazolinones

Yotsakorn Saebang

A Thesis Submitted in Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Chemistry (International Program)
Prince of Songkla University
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Thesis Title	Synthesis of Small and Medium-Sized Ring Fused Quinazolinones
Author	Mr. Yotsakorn Saebang
Major Program	Chemistry (International Program)

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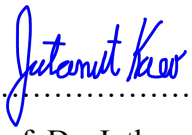
Acting Dean of Graduate School

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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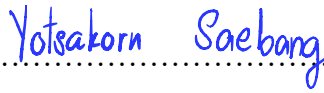

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Yotsakorn Saebang……..Signature

(Mr. Yotsakorn Saebang)

Candidate

ชื่อวิทยานิพนธ์ การสังเคราะห์วงขนาดเล็กและขนาดกลางที่เชื่อมต่อกับควินาโซลิโนน

ผู้เขียน นายยศกร แซ่บ้าง

สาขาวิชา เคมี (นานาชาติ)

ปีการศึกษา 2566

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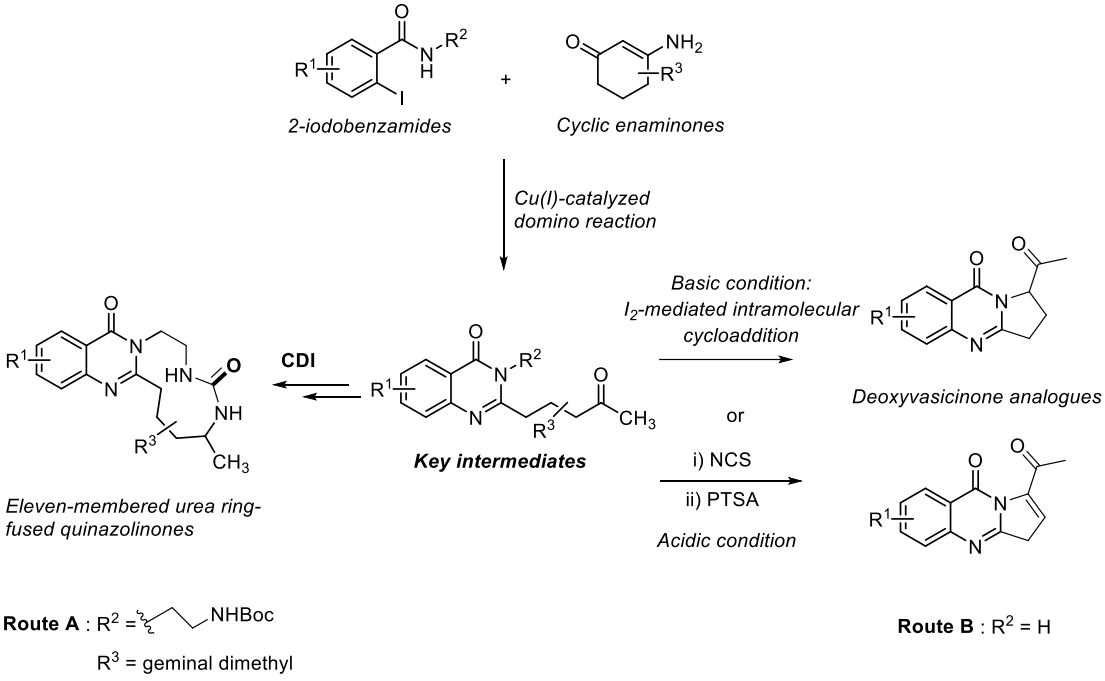

ควินาโซลิโนนเป็นสารผลิตภัณฑ์ทางธรรมชาติประเภทแอลคาลอยด์แสดงฤทธิ์ทางชีวภาพที่น่าสนใจ โดยเฉพาะควินาโซลิโนนที่เชื่อมต่อกับวงต่างๆมักพบได้หลากหลายในสารผลิตภัณฑ์ทางธรรมชาติและสารสังเคราะห์ ในงานวิจัยนี้ ผู้วิจัยได้ศึกษาการสังเคราะห์อนุพันธ์ของควินาโซลิโนนที่เชื่อมต่อกับวงขนาดกลาง และวงขนาดเล็ก จากสารตัวกลางควินาโซลิโนนที่สังเคราะห์จากวิธีที่พัฒนาภายในกลุ่มวิจัย โดยใช้คอปเปอร์เป็นตัวเร่งปฏิกิริยา ควินาโซลิโนนที่เชื่อมต่อกับวงยูเรียขนาดกลาง (11 เหลี่ยม) สามารถสังเคราะห์ได้จากสารตัวกลาง (key intermediate) ที่มีหมู่ R^2 เป็นสายโซ่ *tert*-butyl ethylcarbamate โดยผ่านปฏิกิริยา reductive amination ปฏิกิริยาการกำจัดหมู่ป้องกัน *tert*-butyl ethylcarbamate และปฏิกิริยาการปิดวงภายในโมเลกุลโดยมี 1,1'-carbonyldiimidazole (CDI) เป็นแหล่งกำเนิดของหมู่ฟังก์ชันคาร์บอนิลของยูเรีย นอกจากนี้ได้สังเคราะห์อนุพันธ์ deoxyvasicinone ซึ่งเป็นควินาโซลิโนนที่เชื่อมต่อกับวงเอมีนขนาดเล็ก

(5 เหลี่ยม) โดยสังเคราะห์ได้จากสารตัวกลางที่มีหมู่ R^2 เป็นอะตอมไฮโดรเจน ผ่านปฏิกิริยาที่แตกต่างกัน 2 เงื่อนไข ทั้งในสภาวะที่เป็นเบส และในสภาวะที่เป็นกรด สำหรับภายใต้เงื่อนไขปฏิกิริยาที่เป็นเบส สังเคราะห์อนุพันธ์ deoxyvasicinone ได้จากสารตัวกลาง 1-acetyl-2,3-dihydro pyrrolo[2,1-b]quinazolin-9(1*H*)-one ผ่านปฏิกิริยาการปิดวงภายในแบบโดยตรง โดยมีไอโอดีนเป็นตัวกลางในการปิดวง สำหรับภายใต้เงื่อนไขปฏิกิริยาที่เป็นกรด สังเคราะห์อนุพันธ์ deoxyvasicinone ได้จาก 1-acetyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1*H*)-one ผ่านปฏิกิริยา 2 ขั้นตอน ประกอบด้วย α,α-dichlorination และ intramolecular C–N bond cyclization โดยมี *para*-toluenesulfonic acid (PTSA) เป็นตัวเร่งปฏิกิริยา

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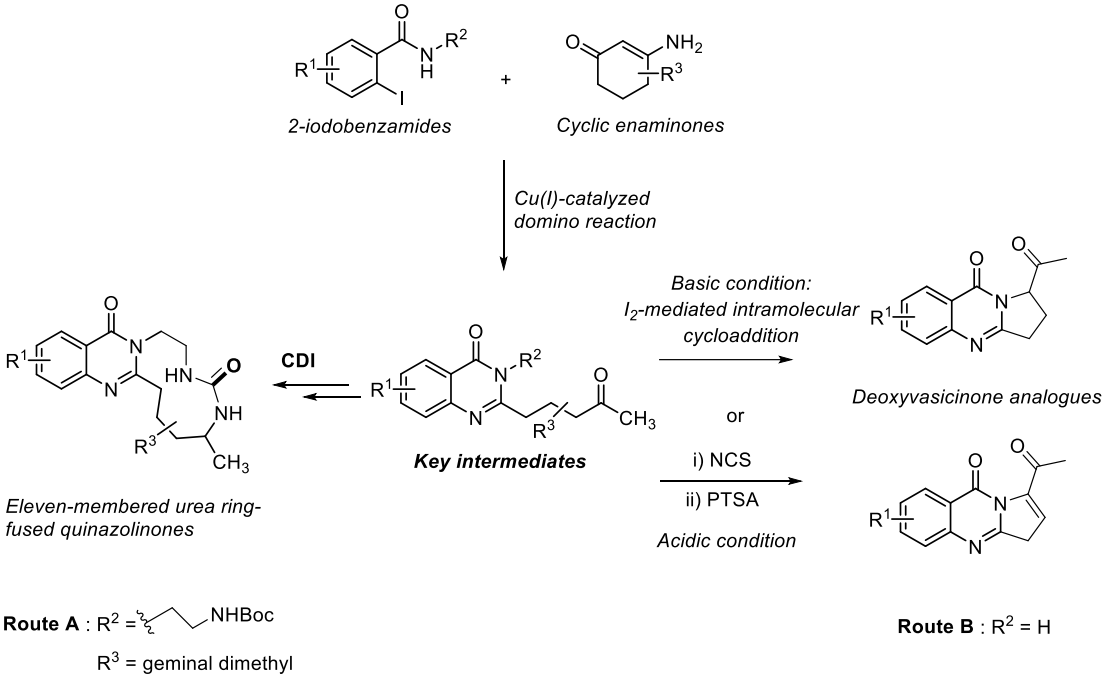
Major Program	Chemistry (International Program)
Academic Year	2023

ABSTRACT



Quinazolinones are natural alkaloids that play a crucial role in exhibiting a wide range of biological and pharmacological activities. Among them, ring-fused quinazolinones are commonly found in various natural alkaloids and synthetic molecules, showcasing a diverse array of bioactivities. In this study, we focused on synthesizing tricyclic quinazolinones. Medium and small-sized ring fused quinazolinones were achieved via direct cyclization of quinazolinone intermediates having *tert*-butyl ethylcarbamate and H as nitrogen substituents, respectively. Firstly, we focused on cyclic amine and urea moieties to fuse with quinazolinone skeletons to obtain novel 11-membered ring fused quinazolinones. Key intermediates were prepared through a copper-catalyzed domino reaction. We successfully incorporated an alkyl side chain with a functionalized amine moiety. The construction of the

11-membered ring urea moiety involved direct cyclization using 1,1'-carbonyldiimidazole (CDI) of a diamino quinazolinone intermediate, which was generated through a series of steps including reductive amination and Boc-deprotection. Secondly, we explored the synthesis of deoxyvasicinone derivatives, which are smaller-sized ring fused quinazolinones. The cyclization process for forming the smaller-sized ring was carried out under both basic and acidic conditions, resulting in the formation of two deoxyvasicinone analogues. Under basic conditions, 1-acetyl-2,3-dihydro pyrrolo[2,1-b]quinazolin-9(1*H*)-one analogues were synthesized via direct cyclization in the presence of I_2. Under acidic conditions, we synthesized 1-acetylpyrrolo[2,1-b]quinazolin-9(3*H*)-one analogues through a two-step process involving α,α-dichlorination followed by intramolecular C–N bond cyclization, with *para*-toluene sulfonic acid (PTSA) serving as a catalyst. The developed synthetic strategies provide valuable insights into the preparation and modification of quinazolinone derivatives.

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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
Boc	=	*tert*-butyloxycarbonyl
$CDCl_3$	=	deuterochloroform
$CHCl_3$	=	chloroform
CDI	=	1,1'-carbonyldiimidazole
CH_2Cl_2	=	dichloromethane
CH_3CN	=	acetonitrile
Cs_2CO_3	=	cesium carbonate
DABCO	=	1,4-diazabicyclo[2.2.2]octane
DCP	=	dicumyl Peroxide
DEAD	=	diethyl azodicarboxylate
DMAP	=	4-Dimethylaminopyridine

LIST OF ABBREVATIONS AND SYMBOLS (Continued)

DMEDA	=	*N*,*N'*-dimethylethylenediamine
DMF	=	dimethylformamide
DMSO	=	dimethylsulfoxide
DMSO-d_6	=	dimethyl sulfoxide-*d6*
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
NBS	=	*N*-bromosuccinimide
NCS	=	*N*-chlorosuccinimide
NIS	=	*N*-iodosuccinimide
NMP	=	*N*-methyl-2-pyrrolidone
Ph	=	phenyl
Piv	=	pivaloyl
PMP	=	*p*-methoxyphenol
PPh_3	=	triphenylphosphine
PTSA	=	*p*-toluenesulfonic acid
K_2CO_3	=	potassium carbonate
K_3PO_4	=	potassium phosphate
TEA	=	triethylamine
Tf	=	triflyl
TFA	=	trifluoroacetic acid
TBDPS	=	*tert*-Butyldiphenylsilyl
THF	=	tetrahydrofuran
TMS	=	tetramethylsilane
Ts	=	tosyl

LIST OF PUBLICATION

Saebang, Y.; Kaeobamrung, J.; Rukachaisirikul, V. 2022. Synthesis of Eleven-Membered Cyclic Urea Fused Quinazolinones. Synlett. 33(14), 1371–1376.

Saebang, Y.; Rukachaisirikul, V.; Kaeobamrung, J. 2023. Synthesis of acetyl deoxyvasicinone analogues from 2-(4-oxopentyl)quinazolin-4(3*H*)-ones *via* linear cyclizations. Tetrahedron Lett. 120, 154484.

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CHAPTER 1

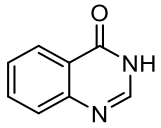
INTRODUCTION

1.1 Introduction

N-containing heterocyclic compounds are well known for their highly bioactivity potentials. A variety of N-heterocycles have been used for clinical drugs (Taylor *et al.*, 2014). Nowadays, pathogens, which are a major cause of newly emerging diseases, have evolved to grow within humans (Mougari *et al.*, 2020). To increase the opportunity for treatment, the development of new strategies for the synthesis of new biologically active molecules is significantly important and has drawn great attention from synthetic chemists.

Quinazolinones with a 4*H* skeleton **1** (**Figure 1**), are one of the most important N-containing natural products. They were isolated from a diverse range of families of plants, microorganisms and animals (Rashmi *et al.*, 2011).

Figure 1 Core structure of 4*H*-quinazolinone

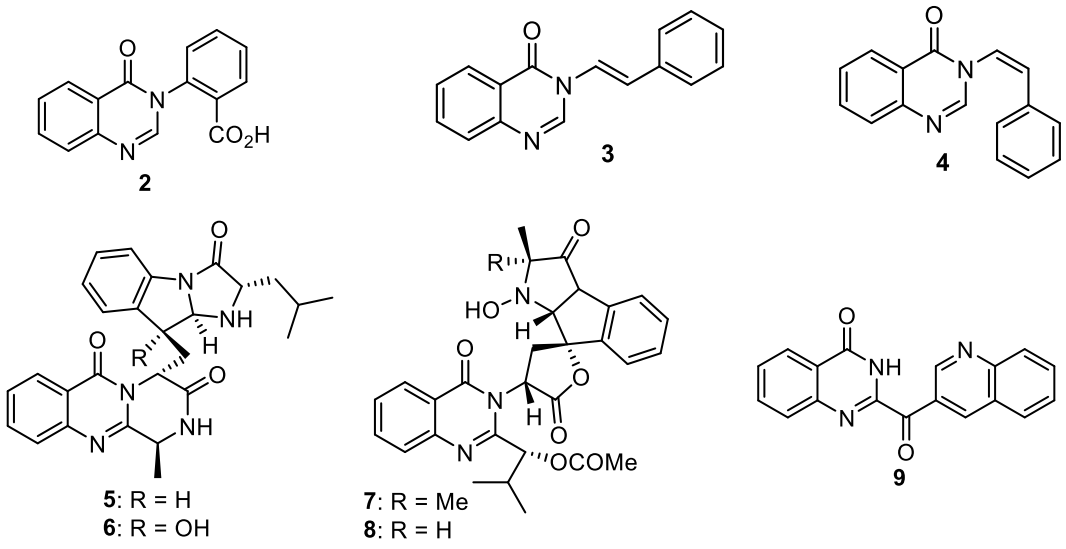


1

These derivatives of quinazolinones are well known to display a wide range of biological and pharmacological activities. Based on literature research, over 40,000 biologically active quinazolinones have been reported (Li *et al.*, 2013). As shown in Figure 2, several examples of bioactive quinazolinones were evaluated for their specific properties. 3-(2-Carboxyphenyl)-4(3*H*)-quinazolinone (**2**) was found to exhibit anti-endotoxic activity. (*E*)-bogorin (**3**), (*Z*)-bogorin (**4**), (–)-fumiquinazoline H (**5**), and (–)-fumiquinazoline I (**6**) were observed to display antifungal activity. The thermogenic property was exhibited by 27-epi-tryptoquivaline (**7**) and

27-epinortryptoquivaline (**8**). Furthermore, luotonin F (**9**) showed anti-leukemia activity against P388 cell and anti-tumor activity. (Mashke *et al.*, 2006).

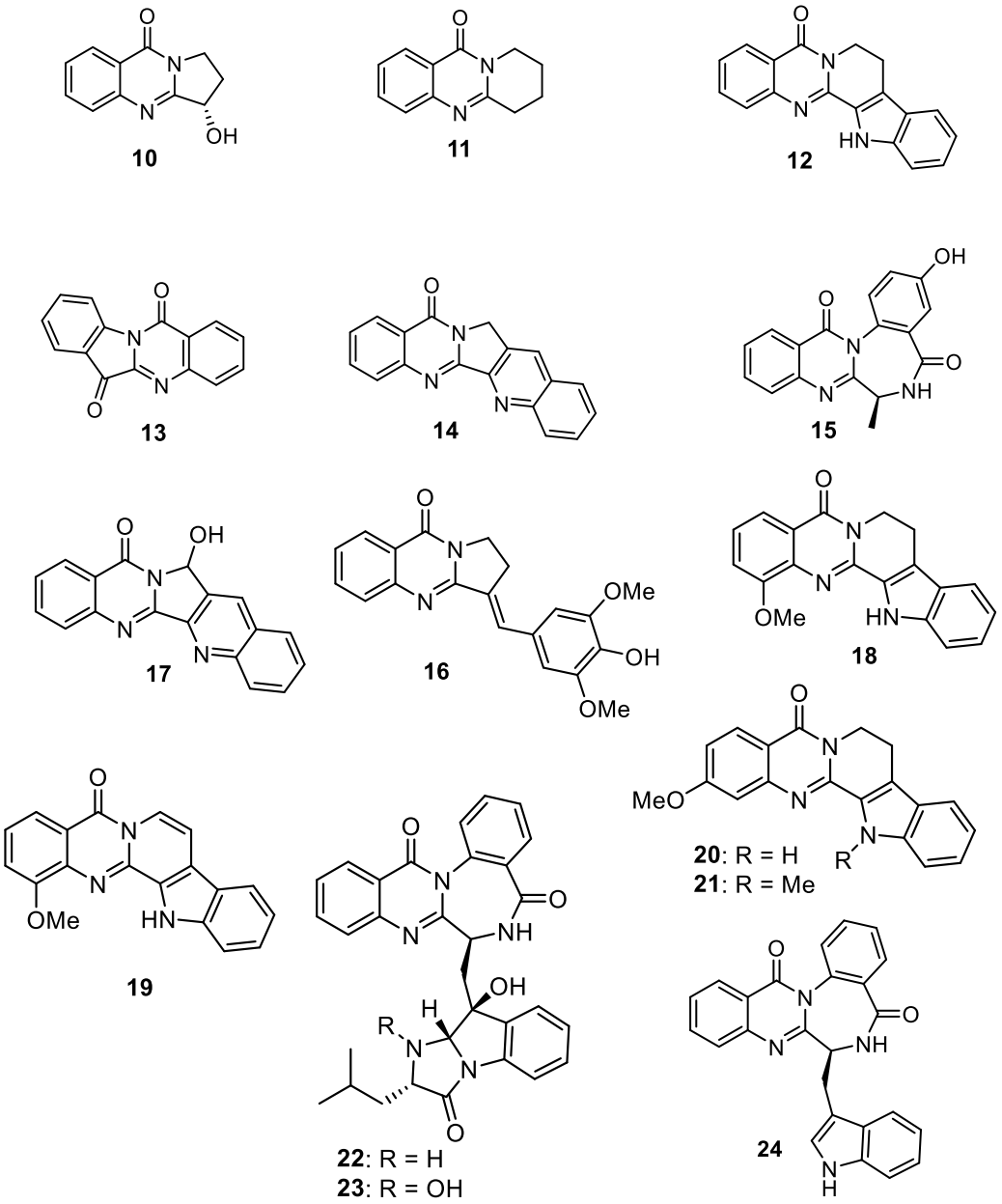
Figure 2 Examples of bioactive quinazolinones



In addition, ring-fused quinazolinones are commonly found in a variety of natural alkaloids and synthetic compounds, which exhibit a broad spectrum of biological and pharmacological activities. Some examples are shown in **Figure 3**. (-)-vasicinone (**10**), a 5-membered ring fused quinazolinone, demonstrates bronchodilatory activity. Mackinazolinone (**11**), isolated from a species of *Mackinlaya*, has been shown to exhibit antidepressant activity. Rutaecarpine (**12**), isolated from *Evodia rutaecarpa*, has demonstrated antithrombotic activity and has been traditionally used in China as a medicinal herb to treat conditions such as abdominal pain, headache, amenorrhea and dysentery. Tryptanthrin (**13**), isolated from *Candida lypolica*, is well-known for its anti-inflammatory property. Luotonin A (**14**), a pyrroloquinazolinoquinoline alkaloid isolated from *Peganum nigellastrum Bunge*, has been found to possess inhibitory activity against topoisomerase I and topoisomerase II. Circumdatin C (**15**), isolated from a culture of the fungus *Aspergillus ochraceus*, showed radical scavenging activity. Isaindigotone (**16**) displayed antioxidant activity. Luotonin B (**17**) showed anti-leukemia activity against

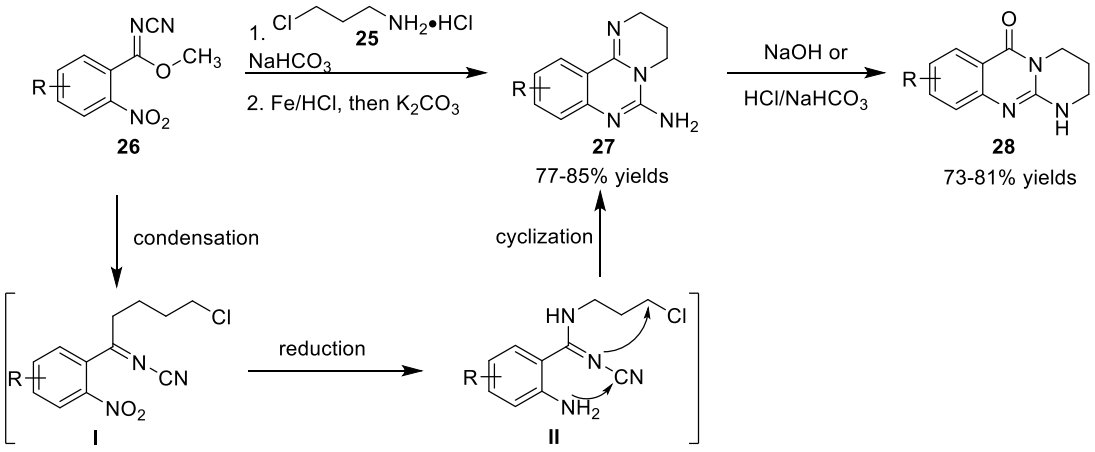
P388 cell and anti-tumor activity1-methoxyrutaecarpine (**18**) exhibited anti-platelet aggregation activity, while 1-Methoxy-7,8-dehydrorutaecarpine (**19**) showed in vitro cytotoxicity against P-388 and HT-29 cell lines. Antimalarial activity was observed for 2-methoxyrutaecarpine (**20**) and 2-methoxy-13-methylrutaecarpine (**21**). Furthermore, (–)-asperlicin (**22**), asperlicin B (**23**) and asperlicin C (**24**) were found to act as agonists for the peptide hormone cholecystokinin (CCK) (Demeunynck *et al.*, 2013).

Figure 3. Example of ring-fused quinazolinone alkaloids



Since we are interested in the synthesis of ring-fused quinazolinones, we will begin by introducing recent developments in the preparation of quinazolinone-containing heterocycles. In 2012, He and co-workers reported a method for synthesizing tricyclic quinazolinones **28** from methyl *N*-cyano-2-nitrobenzimidates **26**. This method involved a condensation reaction of **26** with amine **25** to form cyanoimidate-amine **I** followed by reductive cyclization in an iron-HCl system, resulting in high yields of tricyclic quinazolinones **27**. Moreover, these compounds could be reorganized into tricyclic quinazolinones **28** in good yields via the ring-opening/ring-closing cascade under selective hydrolysis in basic or acidic conditions. (**Scheme 1**) (Yin *et al*., 2012).

Scheme 1 The synthesis of tricyclic quinazolinones from methyl *N*-cyano-2-nitro-benzimidates **26** by He and co-workers

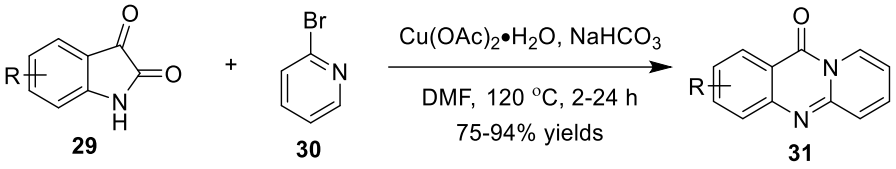


In 2016, Huang and co-workers developed a one-pot copper-catalyzed domino reaction for synthesizing pyrido-fused quinazolinones from isatins **29** and 2-bromopyridine (**30**) (**Scheme 2a**). The tandem features involved C–N/C–C bond cleavage and two C–N bond formations in a one-pot reaction. Ullmann-type coupling of isatins **29** and 2-bromopyridine (**30**), catalyzed by the low-cost catalyst $Cu(OAc)_2 \cdot H_2O$ gave intermediate **I** followed by hydrolysis in the presence of base to cleave C–N bond provided a keto-acid intermediate **II**, which was isomerized to form imine **III**. Subsequently, addition-cyclization provided six-membered ring

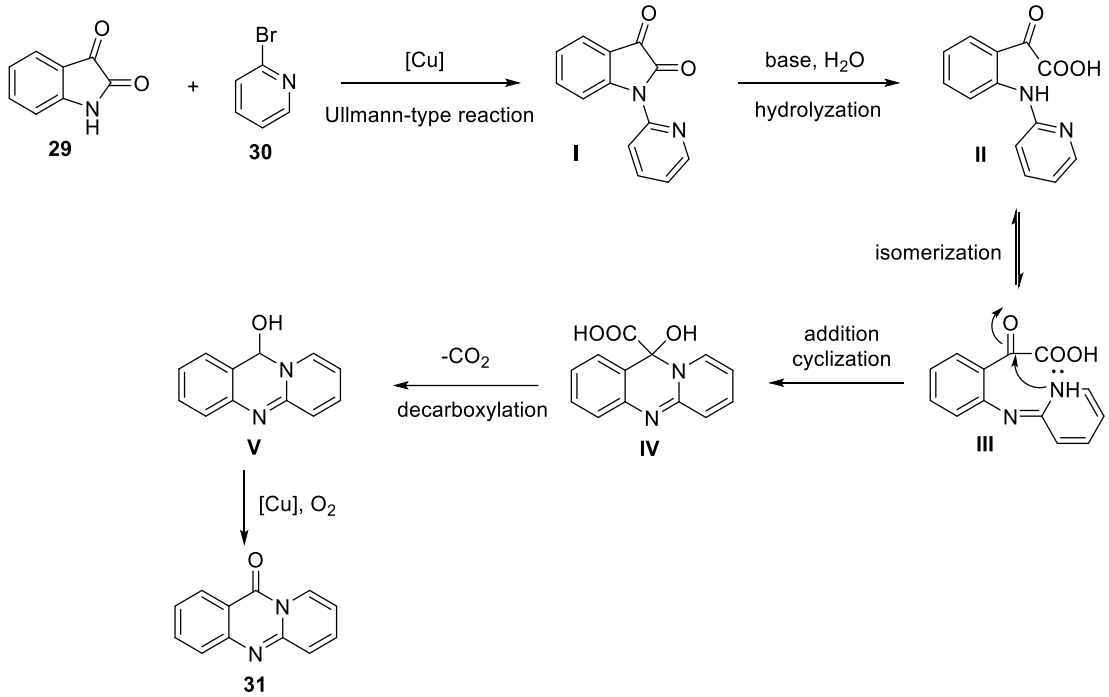
intermediate **IV** via Pfitzinger-type reaction, followed by decarboxylation gave hydroxy intermediate **V**. Finally, the hydroxyl group of **V** was oxidized via copper-mediated oxidation to afford expected quinazolinones **31**, as shown in **Scheme 2b**. This method could be applied to a wide range of substrates having functional group-tolerant, resulting in good to excellent yields (Liu *et al*., 2016).

Scheme 2 A one-pot copper-catalyzed domino reaction for the synthesis of pyrido-fused quinazolinones by Huang and co-workers

a)



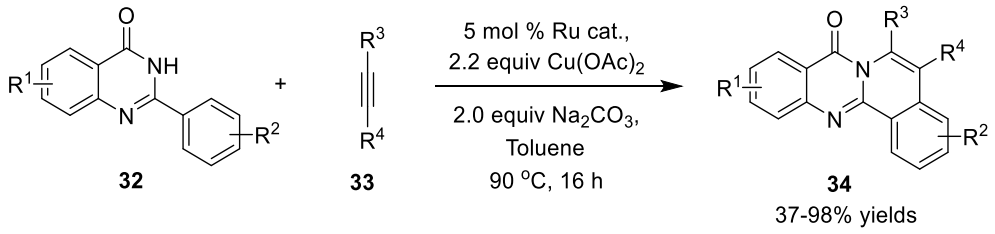
b)



In 2014, Peng and co-workers reported the development for direct synthesis of quinazolinone-fused polycyclic heteroarenes **34** from phenyl-4-quinazolinones **32** and symmetric diphenylacetylenes **33** via a ruthenium-catalyzed C–H functionalization (**Scheme 3a**). This procedure demonstrated regioselectivity in the presence of unsymmetric acetylenes, caused by the influence of steric hindrance (**Scheme 3b**). This reaction was successful with various substrate scopes and proceeded under mild conditions, resulting in moderate to high yields of 37-98%. Furthermore, they also found that the reaction did not occur when the amide group was blocked by the methyl group on **35b**. This result indicated that the amide-directing group played a crucial role in the transition metal-catalyzed transformation (**Scheme 3c**) (Lu *et al*., 2014).

Scheme 3 Ruthenium-catalyzed reaction for the synthesis of quinazolinone containing polycyclic heteroarenes by Peng and co-workers

a)



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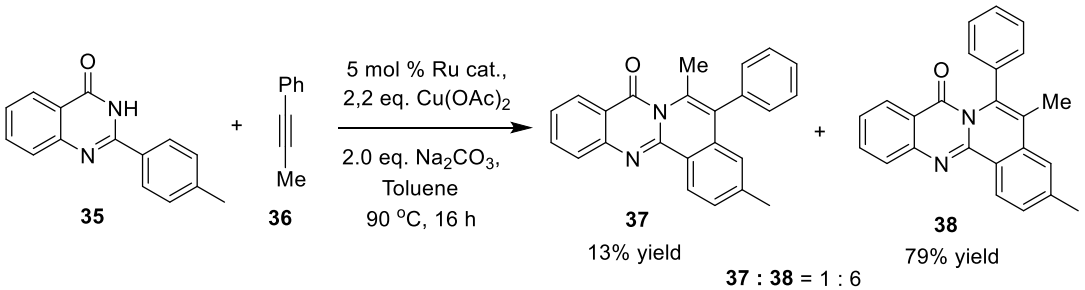

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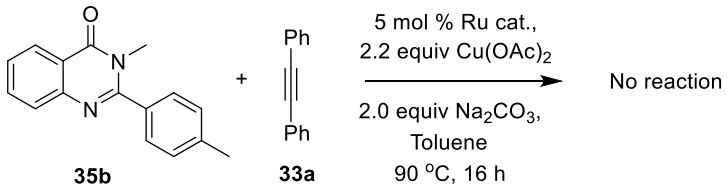
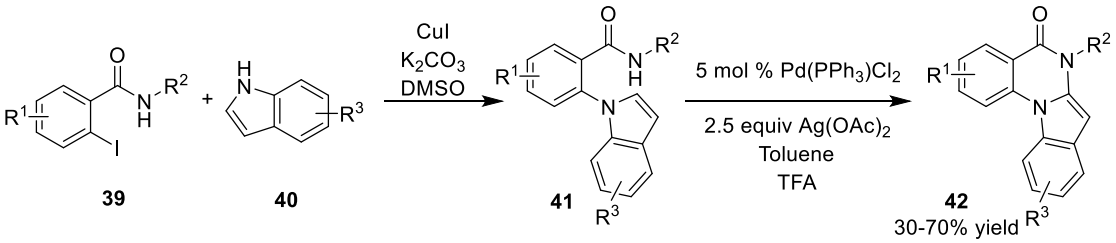


In 2014, Yao and co-workers reported a novel two-step process for synthesizing indolo[1,2-a]quinazolinones. The first step involves a copper-catalyzed Ullmann coupling between 2-iodobenzamides **39** and indole derivatives **40**, while the second step involves a palladium-catalyzed intramolecular C–H amidation. Remarkably, this reaction proceeded under mild conditions without the need for a ligand, due to the ortho effect caused by *N*-phenylamide (**Scheme 4**) (Kotipalli *et al*., 2014).

Scheme 4 The synthesis of indolo[1,2-a]quinazolinones from 2-iodobenzamides and indole derivatives by Yao and co-workers

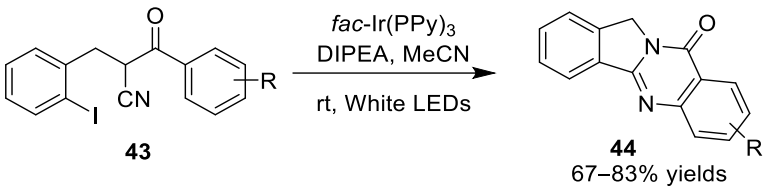


In 2016, Yu and co-workers developed a photoredox strategy for the synthesis of tetracyclic pyrroloquinazolines **44**. This reaction was accomplished through a visible light-promoted intramolecular single-electron transfer process between photocatalyst, *fac*-Ir(PPy)$_3$, and *N*-(2-iodobenzyl)-*N*-acylcyanamides **43** (**Scheme 5a**). The key transformation involves a single-electron transfer of *N*-

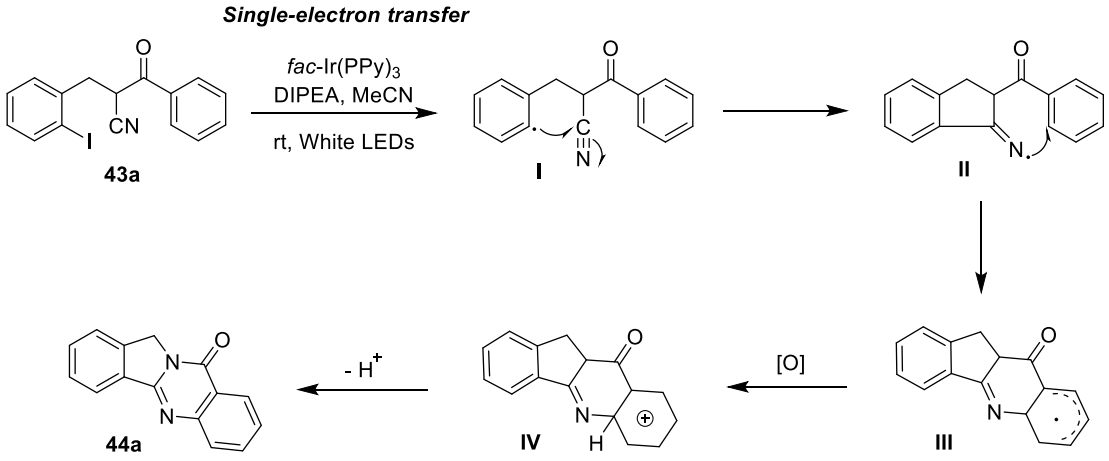
acylcyanamide **43a** to generate a radical intermediate **I**, following intramolecular radical cyclization to give a radical intermediate **III**. Then, one electron oxidation of **III** provides cation intermediate **IV**, which undergoes aromatization to form tetracyclic pyrroquinazoline **44a** (**Scheme 5b**). This photoredox strategy proceeded under visible light irradiation at room temperature, providing pyrroloquinazoline derivatives **44** in good yields and avoiding the hazardous radical initiator AIBN and toxic *n*-Bu_3SnH (Yu *et al*., 2016).

Scheme 5 A photoredox strategy for the synthesis of tetracyclic pyrroloquinazolines by Yu and co-workers

a)



b)

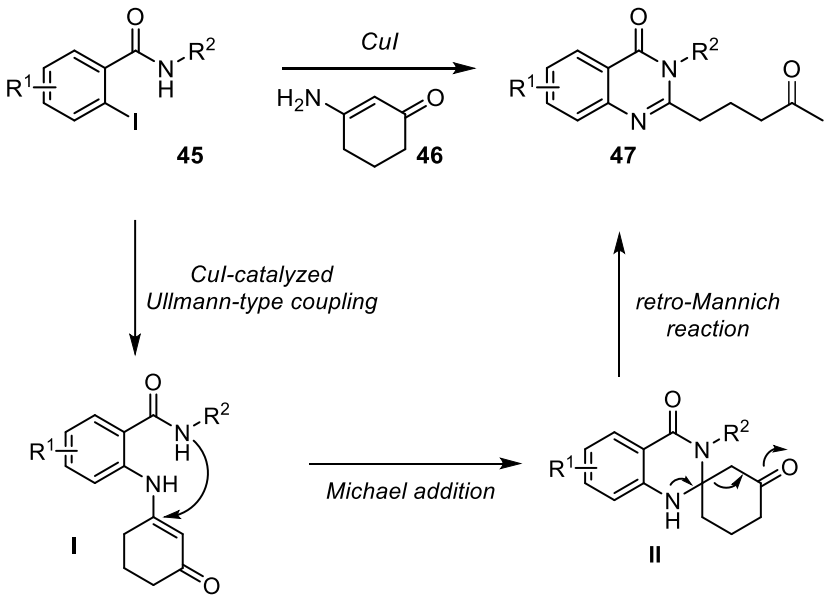


Based on the previous works, most of the quinazolinone syntheses are constructed with small-sized rings (5- and 6-membered ring) fused with a quinazolinone scaffold through coupling synthesis and linear cyclization. In addition,

a small-sized ring unit was set before coupling with the quinazolinone skeleton. Moreover, we found that quinazolinones fused with medium-sized rings are rarely presented in the literature. Therefore, we are interested in the construction of them in order to expand the variety of quinazolinone systems.

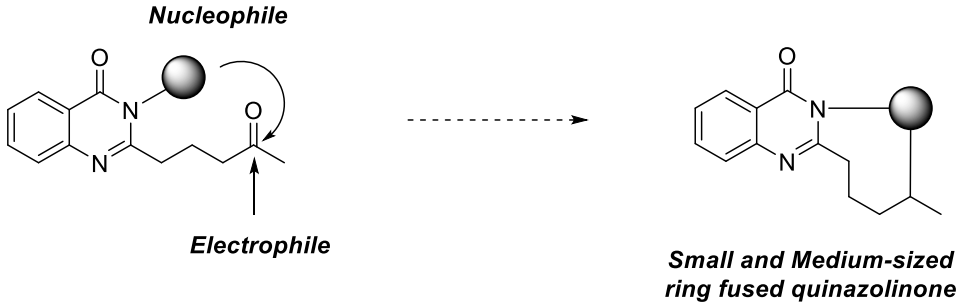
As part of our research group's targets, we have been interested in discovering new methods for synthesizing a variety of N-containing heterocycles. In 2014, our research group reported the copper-catalyzed synthesis of quinazolinone derivatives using 2-iodobenzamides **45** and cyclic enaminone **46** as starting materials. This synthesis resulted in the desired quinazolinones ranging from low to good yields. (Songsichan *et al*., 2014). This reaction likely operated through a domino process involving Cu(I)-catalyzed C(aryl)–N bond formation, Michael addition, and retro-Mannich reaction, as shown in **Scheme 6**.

Scheme 6 Copper-catalyzed domino reactions of *N*-benzyl 2-iodobenzamide **45** with cyclic enaminone **46** by our group



In this procedure, we could prepare quinazolinone scaffolds that feature a tethered ketone at the C-2 position. The ketone moiety in **47** could be further functionalized with other functional groups. We envisioned that we could take advantage of this method by designing quinazolinones with nucleophile moiety in the structure and would synthesize ring-fused systems including small and medium-sized ring fused quinazolinones (**Scheme 7**).

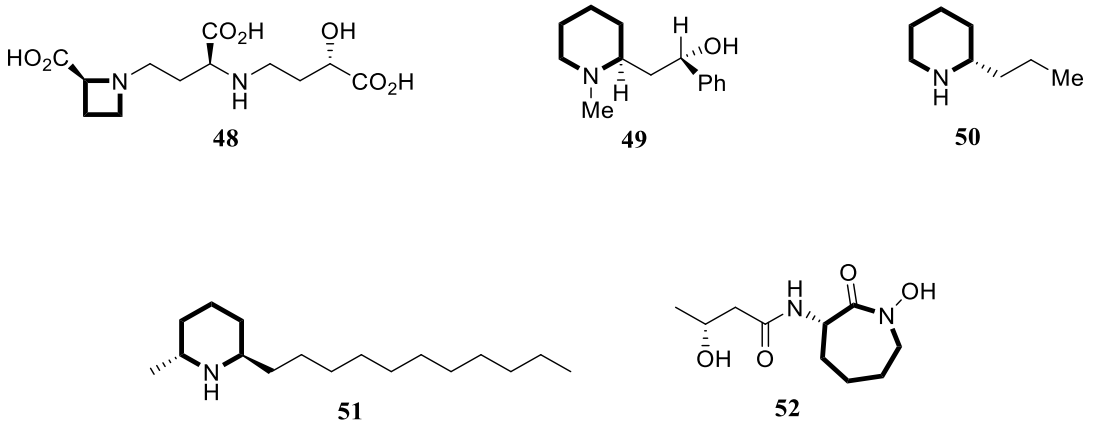
Scheme 7 The possible synthetic pathway of small and medium-sized ring-fused quinazolinones



According to various types of cyclic moieties presented in organic molecules, particularly interesting moieties are cyclic amines, carbamates and ureas in ring-fused quinazolinones. These three types are widely encountered in natural products and bioactive molecules. Additionally, quinazolinones fused with these moieties are rarely presented in the literature, and their synthesis is a very challenging task.

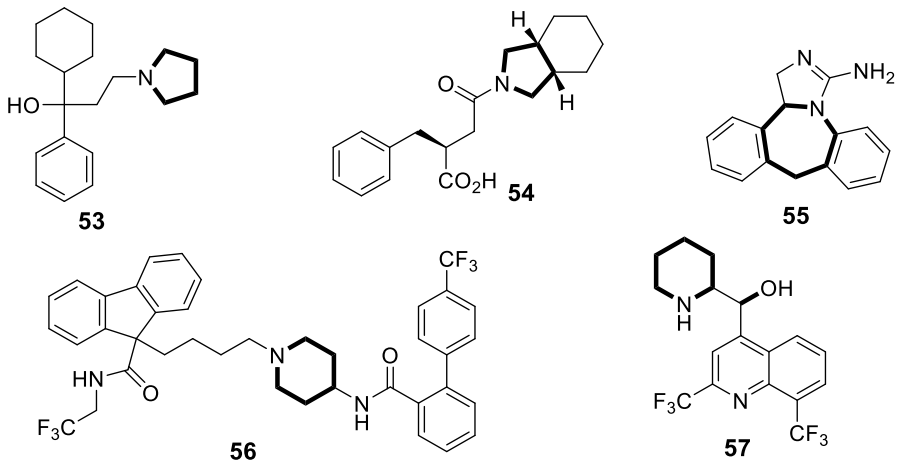
Some natural products that contain cyclic amines are shown in **Figure 4**. Mugenic acid (**48**) contains an azetidine ring with three carboxylic functional groups. Sedamine (**49**), coniine (**50**), and solenopsin A (**51**) are composed of a piperidine ring. On the other hand, (–)-cobacin T (**52**) contains a 7-membered azepane ring.

Figure 4 Some natural compounds containing cyclic amines



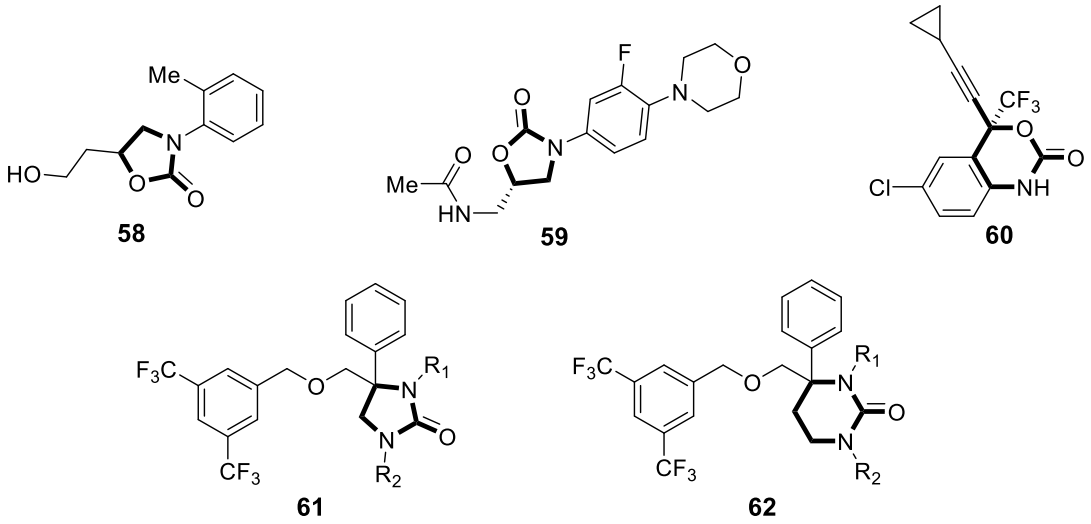
Cyclic amines are not only found in natural products but also play a role in clinical drugs as shown in **Figure 5** (Hameed *et al.*, 2017). For example, procyclidine (**53**) is used in the treatment of drug-induced parkinsonism, akathisia, and acute dystonia. Mitiglinide (**54**), a succinic acid derivative, is a medication for the treatment of type 2 diabetes. In addition, epinastine (**55**), an antihistamine, is used to prevent itching in the eyes caused by allergic conjunctivitis. Lomitapide (**56**) is used as a lipid-lowering agent that operates by inhibiting the microsomal triglyceride transfer protein. Moreover, mefloquine (**57**), also known as mefloquine hydrochloride, is used as an antimalarial drug.

Figure 5 Clinical drugs containing cyclic amines



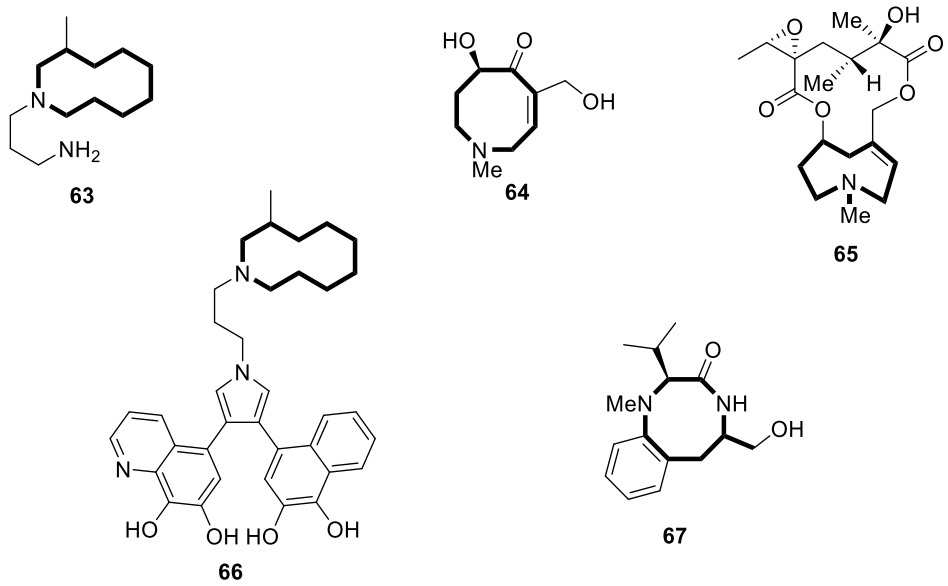
Cyclic carbamates and ureas play a significant role in pharmaceutical chemistry, as shown in **Figure 6**. Tolxatone (**58**) shows antidepressant activity, while linezolid (**59**) displays antibiotic activity. Efavirons (**60**) is a synthetic antiretroviral drug for the treatment of HIV. Additionally, 5- and 6-membered cyclic ureas (**61** and **62**) play an important role as potent and selective NK1 antagonists for the treatment of cough, inflammation, asthma, migraine, and depression (Shue *et al*., 2005).

Figure 6 Potential drugs containing cyclic carbamate and urea structures



Furthermore, medium-ring (8- to 12-membered) N-heterocycles have been found to exhibit a wide range of biological activities. These structural units are important parts of pharmaceutical compounds (Hussain *et al*., 2014). Haliclorensin (**63**) and halitulin (**64**) containing azacyclodecane ring display cytotoxic activity against mouse leukemia cells (Heinrich *et al*., 2001). Otonecine (**65**) and otosenine (**66**), containing eight-membered rings, have been shown to exhibit remarkable hepatotoxic and carcinogenic properties. Benzolactam-V8 **67** having an eight-membered lactam ring is a potent activator of protein kinase C (PKC) and exhibits a distinct pattern of tissue-specific expression, as shown in **Figure 7** (Hall *et al*., 2016).

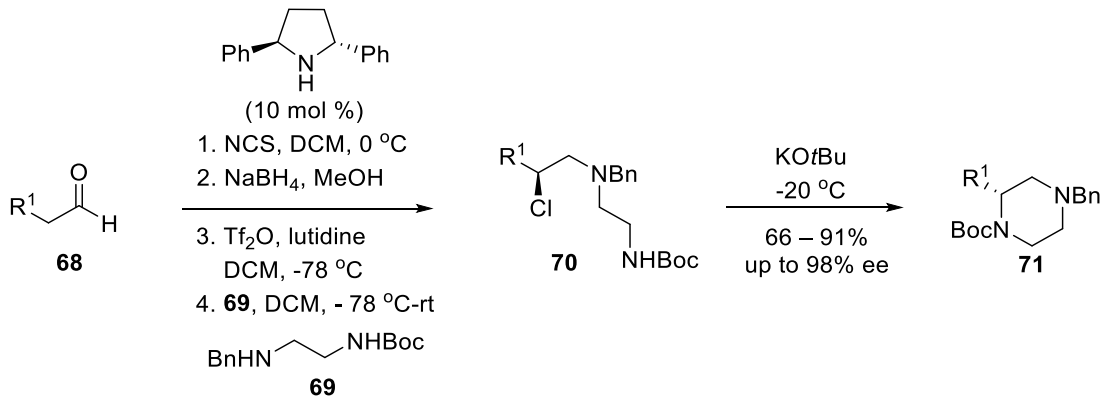
Figure 7 Medium-sized ring N-heterocycles



As a result of their interesting biological activities and structural diversity of small and medium-sized ring amines, ureas, or carbamates, we then listed selected methodologies for their synthesis.

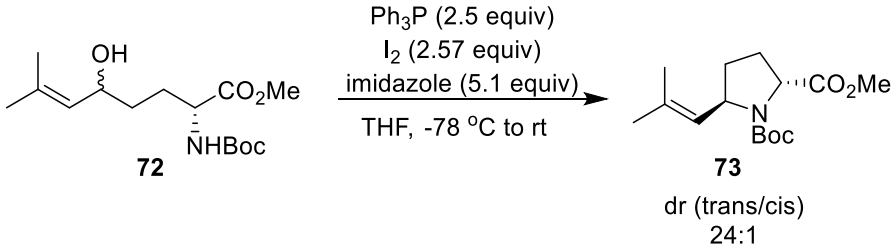
Over the past decades, several methods for the formation of the C–N bond in the synthesis of cyclic amines have received considerable attention. For example, Lindsley and co-workers applied a base-induced cyclization for the construction of *N,N'*-protected piperazines **71** from intermediates **70** which were prepared from aldehyde **68** via enantioselective chlorination and chemoselective displacement of the primary leaving group. The late stage of cyclization was carried out under the basic condition with KO*t*Bu, resulting in good yields and high enantioselectivities, as shown in **Scheme 8** (O'Reilly *et al*., 2012).

Scheme 8 Base-induced cyclization of *N,N'*-protected piperazine syntheses **71**



In addition, Chamberlin et al. reported an intramolecular cyclization of allylic alcohol **72** in 2008. This reaction smoothly occurred in the presence of Ph_3P, I_2, and imidazole to provide *trans*-pyrrolidine **73** in high yield and diastereomeric ratio (**Scheme 9**) (Vaswani *et al*., 2008).

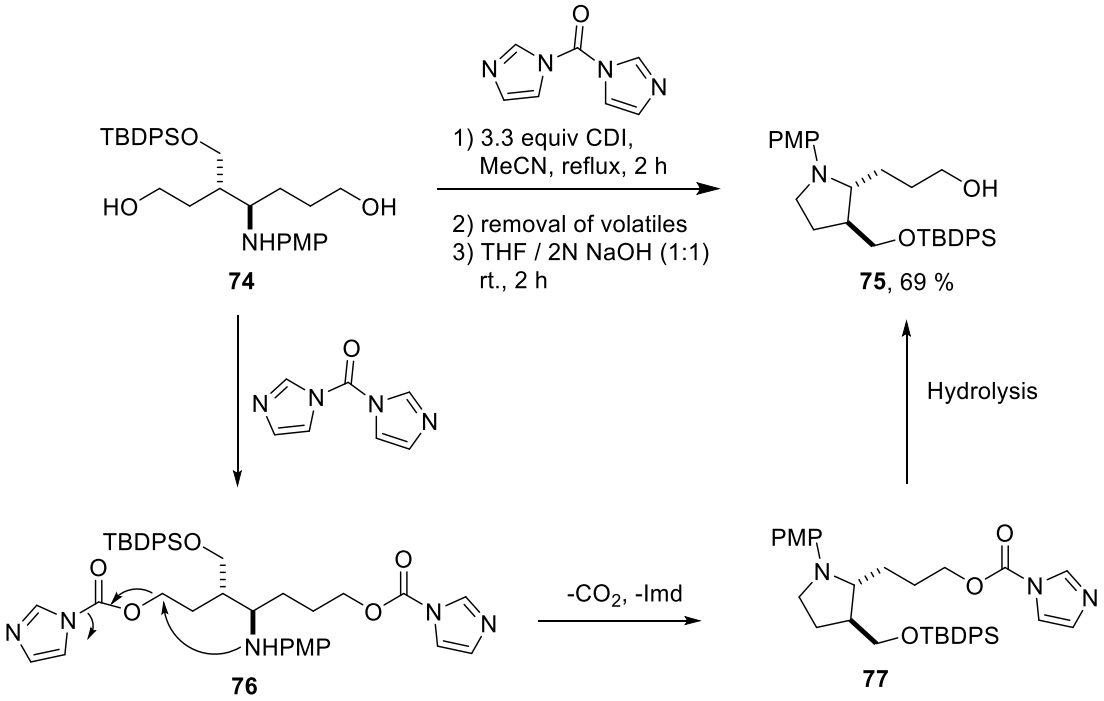
Scheme 9 Synthesis of *trans*-pyrrolidine **73** via intramolecular cyclization by Chamberlin and co-workers



In 2006, de Figueiredo and co-workers developed an efficient method for the synthesis of functionalized PMP-protected 4-, 5- and 6-membered N-heterocycles **75** through the activation of the hydroxyl group with carbonyldiimidazole (CDI) as an activating reagent. Both primary alcohols of amino alcohol **74** were activated by CDI generating carbamate **76**, which was nicely cyclized along with decarbonylation to produce disubstituted pyrrolidine **75** resulting in 69% yield. In this strategy, a variety

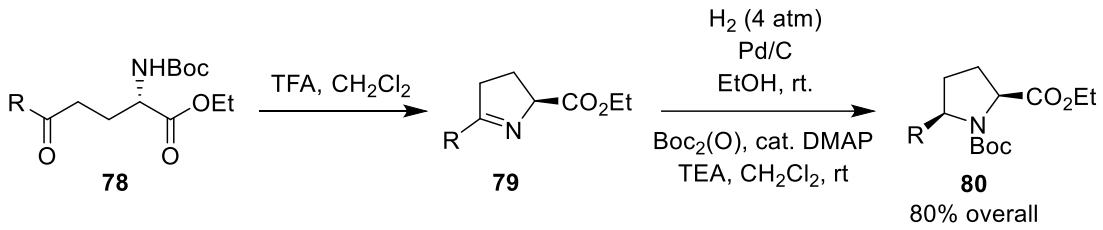
of functional groups were tolerated in good yields. This reaction makes it a versatile and useful method for the synthesis of functionalized N-heterocycles (**Scheme 10**) (de Figueiredo *et al*., 2006).

Scheme 10 The synthesis of functionalized PMP-protected N-heterocycles **75** by de Figueiredo and co-workers



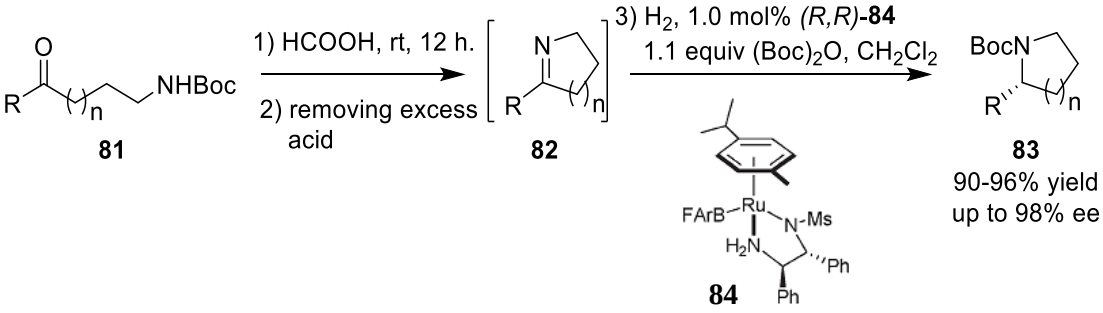
Moreover, *N*-Boc-protected aminoketones have been subjected to an intramolecular reductive amination. In 2006, Pei and co-workers reported the synthesis of *cis*-5-substituted prolines **79** from dicarbonyls **78** via TFA-mediated Boc deprotection and intramolecular cyclization in a one-pot reaction to form imines **79**. Subsequently, hydrogenation of **79** followed by Boc-protection provided proline esters **80**, yielding in overall 80%. However, this hydrogenation step must be performed under high pressure using 4 atm of hydrogen gas (**Scheme 11**) (Pei *et al*., 2006).

Scheme 11 An intramolecular reductive amination for proline ester syntheses by Pei and co-workers



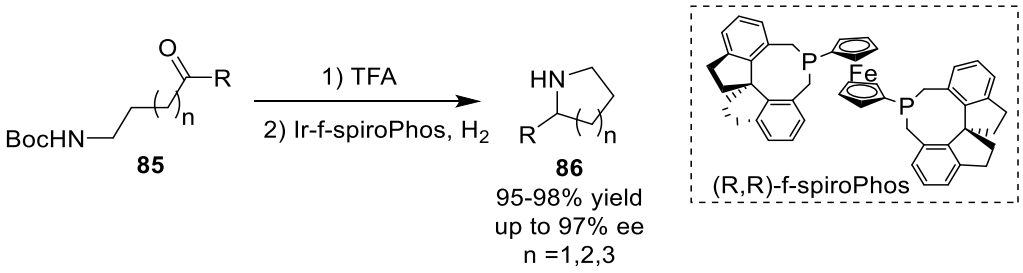
In 2011, Fan and co-workers presented an excellent asymmetric hydrogenation of cyclic *N*-alkyl imines using a chiral cationic Ru-MsDPEN catalyst. This one-pot direct asymmetric reductive amination of **81** involves deprotection of Boc-group, intramolecular imine formation, and asymmetric reduction to produce cyclic amines **83** with excellent isolated yields and enantioselectivities (up to 98% ee) (**Scheme 12**) (Chen *et al*., 2011).

Scheme 12 The one-pot direct asymmetric reductive amination of **81** by Fan and co-workers



In 2017, Hou et al. also reported a one-pot enantioselective procedure for synthesizing cyclic amines through intramolecular reductive amination of *N*-Boc-protected aminoketones **85**. This methodology allowed for the synthesis of 5-, 6-, and 7-membered N-heterocycles **86** with excellent yields and high enantioselectivities (up to 97% ee), as shown in **Scheme 13** (Zhang *et al*., 2017).

Scheme 13 A one-pot enantioselective synthesis of *N*-Boc-protected aminoketones **85** via intramolecular reductive amination by Hou and co-workers

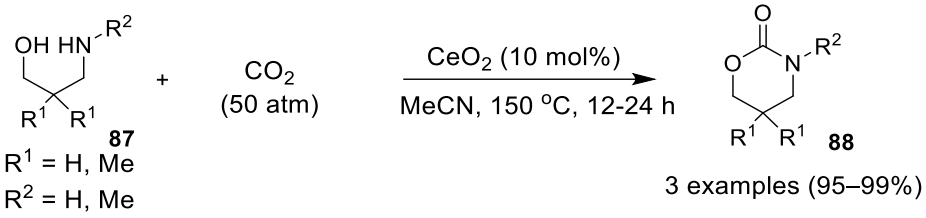


Next, we focused on the synthesis of cyclic carbamates and ureas. Generally, these compounds are synthesized by utilizing hazardous and toxic reagents such as isocyanates, carbamoyl chloride, and phosgene. Accordingly, the discovery of cheap and mild reagents has been subjected to replace highly harmful procedures. Carbon dioxide (CO_2) and 1,1'-carbonyldiimidazole (CDI), mild and the most widely used reagents, were presented as the C1 source of carbamate and urea syntheses.

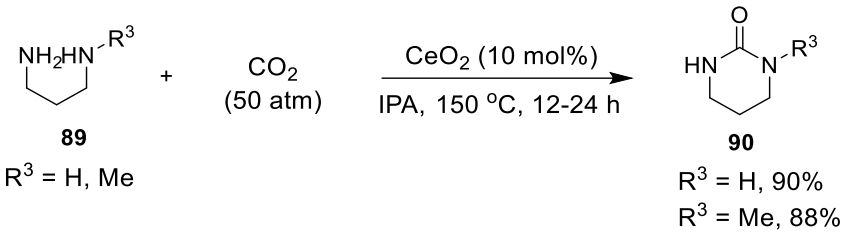
In 2014, Tomishige and co-workers reported the direct conversion of CO_2 with amino alcohols and diamines to cyclic carbamates and cyclic ureas using heterogeneous catalysts. 1,3-Oxazinan-2-one **88** was synthesized in excellent yields via CeO_2-catalyzed carbonylative cyclization of amino alcohols **87** with high pressure of CO_2. Both primary and secondary amines are allowed to undergo these conditions (**Scheme 14a**) (Tamura *et al*., 2014). Moreover, diamines **89** were also transformed to cyclic ureas **90** in these conditions (**Scheme 14b**).

Scheme 14 a) CeO_2-catalyzed carbonylative cyclization for the synthesis of cyclic carbamates **88** b) for the synthesis of cyclic ureas **90** by Tomishige and co-workers

a)



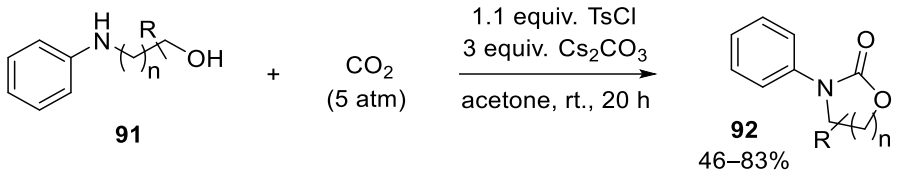
b)



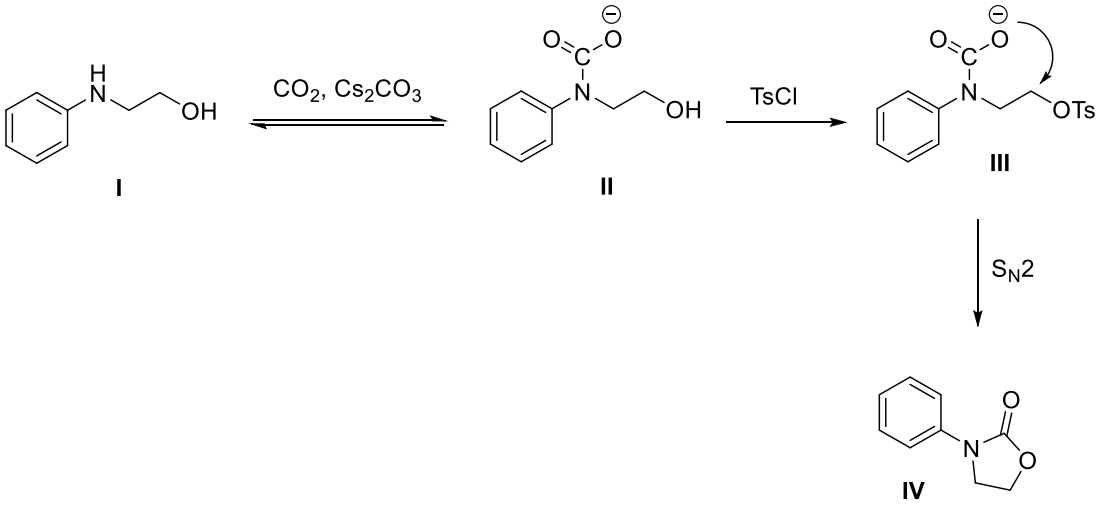
In addition, Repo et al. also reported a facile method for synthesizing cyclic carbamates from amino alcohols **91** and carbon dioxide in the presence of an external base and *p*-toluenesulfonyl chloride (TsCl) as a hydroxyl group activating reagent. This procedure proceeded under mild conditions and produced various 5- and 6-membered ring carbamates **92** in moderate to good yields (**Scheme 15a**). The one-pot transformation involves the formation of carbamate salt from amino alcohol **I** and CO_2 in the presence of Cs_2CO_3, followed by the tosylation of primary alcohol to create a leaving group, and a late-stage cyclization of **III** via intramolecular substitution (**Scheme 15b**) (Niemi *et al*., 2018).

Scheme 15 a) Carbon dioxide-based synthesis of cyclic carbamate **92** b) The one-pot transformation utilizing *p*-toluenesulfonyl chloride (TsCl) as an activating reagent by Repo and co-workers

a)



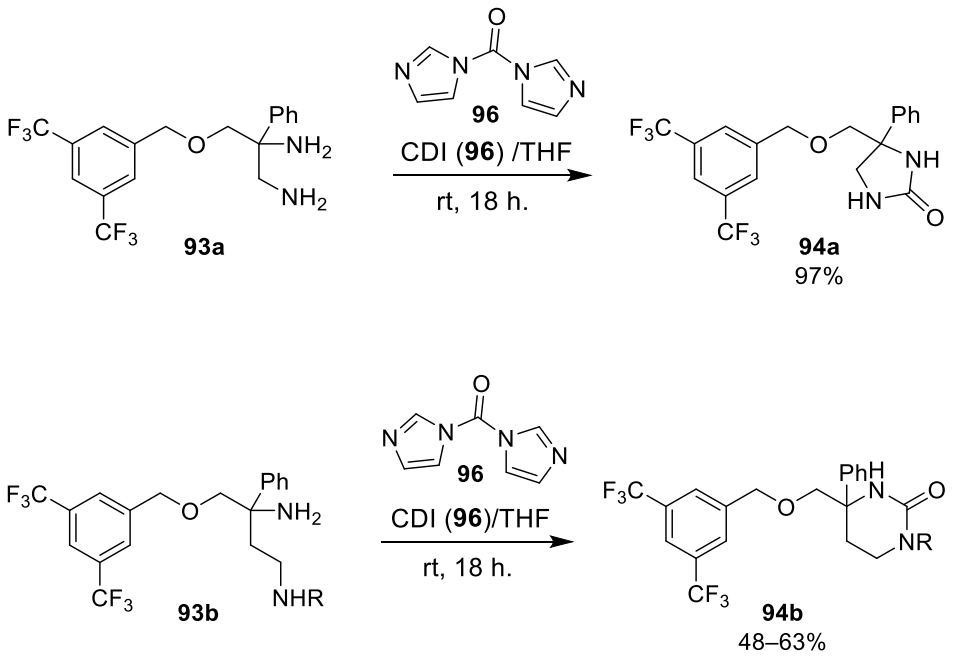
b)



From the utilization of CO_2 as a carbonyl source, the reaction conditions typically require the high-pressure system of CO_2 to install C1-carbonyl in the target molecules. As an alternative carbon source, carbonyl diimidazole (CDI) was reported.

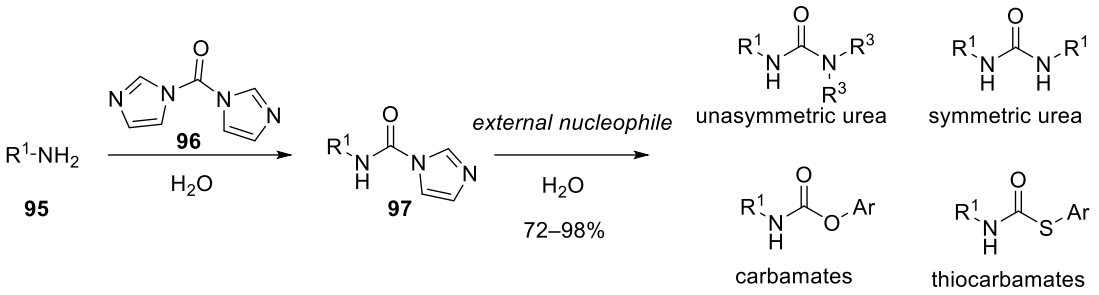
In 2005, Reichard et al. successfully synthesized cyclic urea **94a** from diamine **93a** using CDI as a carbonylating reagent in tetrahydrofuran. The reaction resulted in the desired products with high yield (**Scheme 16**) (Shue *et al*., 2005). This reaction proceeded under mild conditions and can be utilized for the synthesis of five- and six-membered ring urea derivatives **94b**.

Scheme 16 CDI cyclization of cyclic urea



Moreover, in 2012, Padiya et al. reported the use of CDI (**96**) as a carbonyl source for the preparation of ureas, carbamates, and thiocarbamates via imidazole carbonylation of amines in water. Amines **95** reacted with CDI to generate carbonyl imidazoles **97** which were stable in the water system. Subsequently, the nucleophilic substitution with various external nucleophiles provided a variety of ureas, carbamates and thiocarbamates. In addition, the products could be easily purified by filtration in high purity, making the method simple and scalable (Padiya *et al*., 2012) (**Scheme 17**).

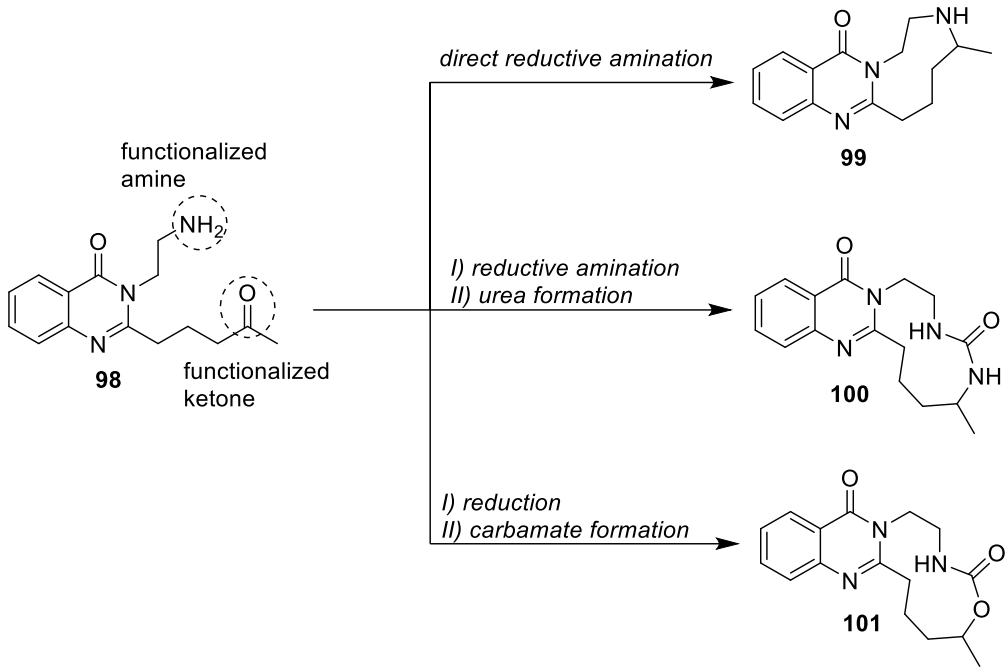
Scheme 17 Unprecedented “in water” imidazole carbonylation



To the best of our knowledge, the formation of cyclic amines, cyclic carbamates and cyclic ureas can be achieved using simple and scalable methods. Moreover, the synthesis of quinazolinones fused with medium-sized rings such as amines, ureas, or carbamates, are rare in literature. These medium-sized rings have been demonstrated as important moieties for biological activities. To expand the variety of quinazolinone systems, we plan to synthesize novel structural quinazolinones containing medium-sized rings of amines, ureas, or carbamates using the versatile quinazolinone adducts prepared by our developed method.

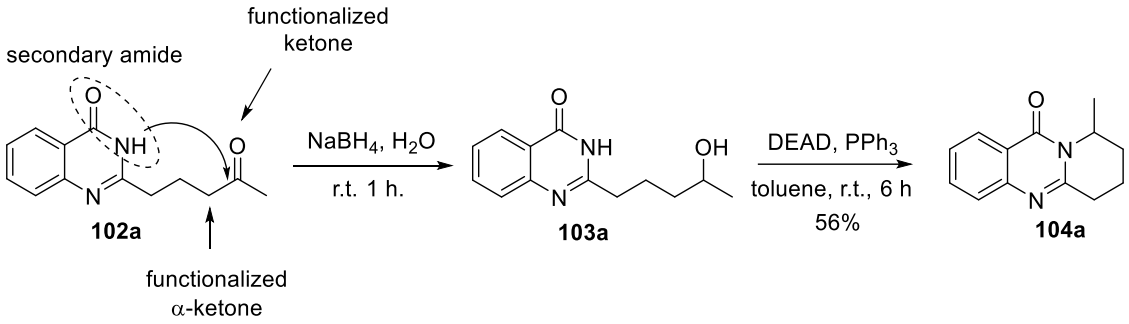
With these plans in mind, N-containing medium-sized ring fused quinazolinones could be synthesized by applying the cyclization reaction of ketone **98** having functionalized amine (**Scheme 18**), for example, A) medium-sized ring amine **99** could be obtained via a direct reductive amination, B) medium-sized ring urea **100** could be accomplished through a reductive amination with other nitrogen molecules to form an amine moiety, followed by urea formation with a carbonylating agent, and C) medium-sized ring carbamate **101** could be obtained via a reduction to provide alcohol, followed by a carbamate formation with a carbonylating agent.

Scheme 18 Plausible N-containing medium-sized ring fused quinazolinones



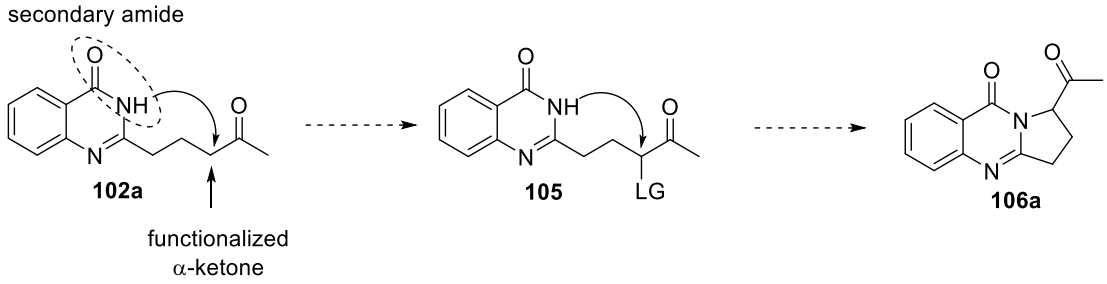
In addition, we envisioned that not only medium-sized ring fused quinazolinones could be synthesized, but also 5- or 6-membered ring fused quinazolinone could be constructed from quinazolinone intermediate **102a** having secondary amide, functionalized ketone, and α-ketone. For the formation of 6-membered ring fused quinazolinones, linear cyclization could be obtained from secondary amide and functionalized ketone. This procedure was reported by Chern and co-workers in 1998 (**Scheme 19**). Tricyclic quinazolinone **104** was synthesized from quinazolinone precursor **102a** through two linear steps including a reduction of ketone moiety to get secondary alcohol **103** followed by Mitsunobu reaction to form C–N bond of ring-fused quinazolinone **104**, resulting in 56% yield (Chern *et al*., 1998).

Scheme 19 The synthesis of 6-membered ring fused quinazolinone **104** by Chern and co-workers



Secondly, the compound **102a** containing functionalized α-ketone could be formed by setting a leaving group on α-ketone followed by intramolecular C–N bond cyclization with secondary amide providing 5-membered ring fused quinazolinone **106a** (**Scheme 20**).

Scheme 20 The plausible synthetic pathway of 5-membered ring fused quinazolinone

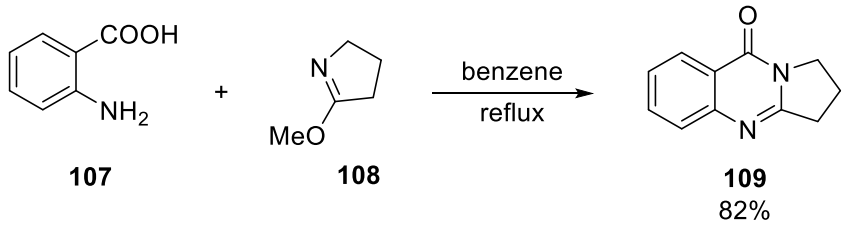


Based on our synthetic plan, the resulting products **106a** are deoxyvasicinone analogues. These analogues are quinazolinone fused with a pyrrolidine ring, which have been isolated from aerial parts of an evergreen subherbaceous bush *Adhatoda vasica*. These compounds exhibit a range of bioactivities, including antianapthylactic, antitumor, anthelmintic, brochodilating and hypotensive activities (Lee *et al*., 2003). Due to their biological activities, numerous methodologies to synthesize deoxyvasicinone have been developed. Traditionally, the preparation of these derivatives involved the reaction of anthranilic acids and pyrrolidones or γ-aminobutyric acids, as shown in **Scheme 21**. Condensation of anthranilic acid (**107**) and *O*-methylbutyrolactim (**108**) under refluxing temperature in benzene solution

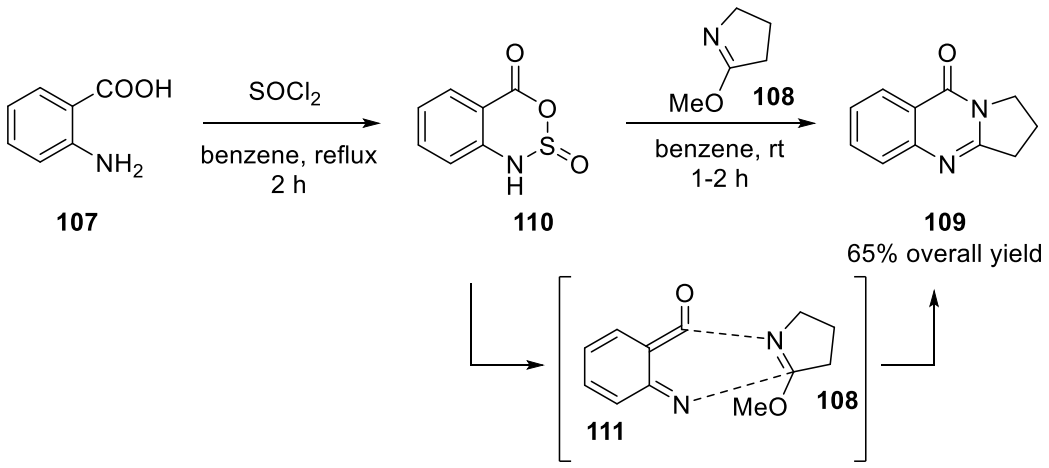
provided the desired product **109** in the yield as high as 82% (Onaka, 1971) (**Scheme 21a**). In 1976, Kametani and co-workers synthesized deoxyvasicinone from the reaction of unstable sulfonamide anhydride with *O*-methylbutyrolactim. Anthranilic acid (**107**) was heated with thionyl chloride to provide unstable sulfonamide anhydride **110** which was condensed with *O*-methylpyrrolidone (**108**) to regiospecifically give deoxyvasicinone (**109**) in good yield. In this reaction, the unstable sulfonamide anhydride **110** was transformed to the iminoketene **111** which was condensed with **108** via (4+2) cycloaddition reaction (Kametani *et al*., 1976) (**Scheme 21b**). In addition, in 2003, Jahng and co-workers reported the synthesis of deoxyvasicinone utilizing lactam **112** and methy anthranilate **114** in the presence of $POCl_3$. This procedure stared with treatment 2-pyrrolidone (**112**) with either 37.5% HCl or dry HCl to generate cyclic iminochloride **113** as an active intermediate followed by directly condensed with methyl anthranilate **114** to form deoxyvasicinone (**109**) in 88% yield (Lee *et al*., 2003) (**Scheme 21c**).

Scheme 21 Traditional procedure for the preparation of deoxyvasicinone derivatives

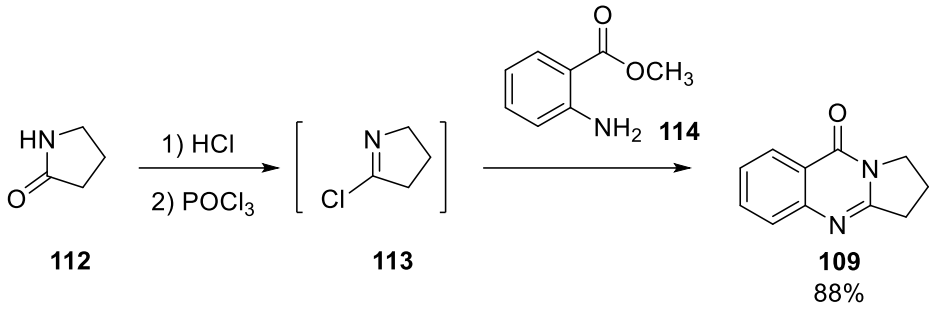
a) By Onaka



b) By Kametani and co-workers

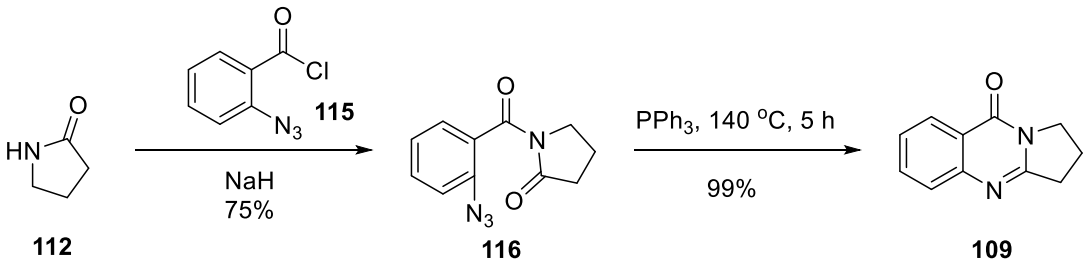


c) By Jahng and co-workers



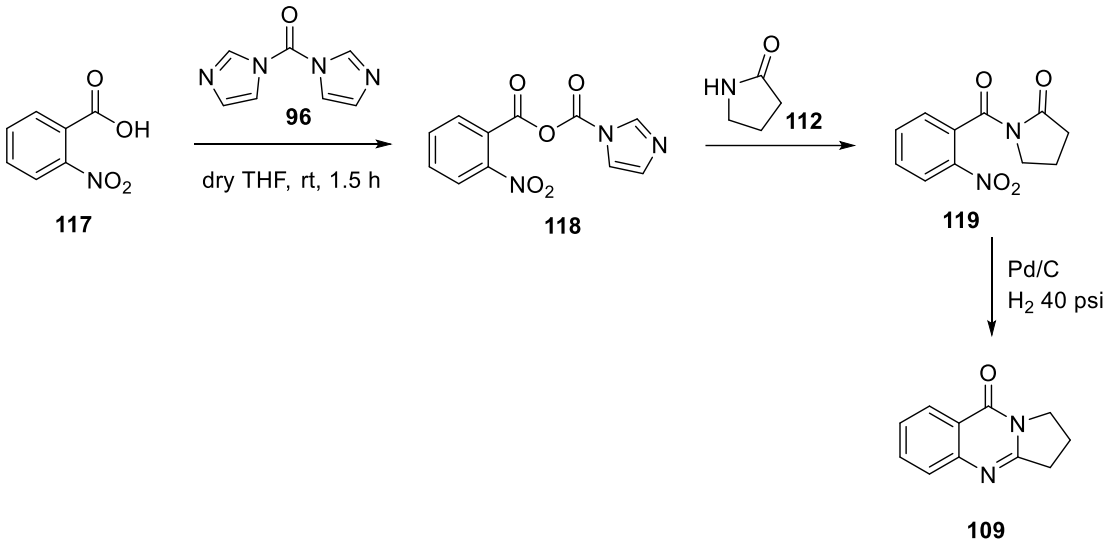
Furthermore, the aza-Wittig reaction was used as a key step to synthesize deoxyvasicinone reported by Eguchi and co-workers in 1989. The synthesis started with the reaction of 2-pyrrolidone (**112**) and acid chloride **115** in the presence of NaH as a base at room temperature followed by intramolecular aza-Wittig reaction to convert azide **116** providing deoxyvasicinone (**109**) in 99% yield. However, the cyclization step required heating at a higher temperature for 5 h (Takeuchi *et al*., 1986) (**Scheme 22**).

Scheme 22 Intramolecular aza-Wittig reaction for the synthesis of deoxyvasicinone



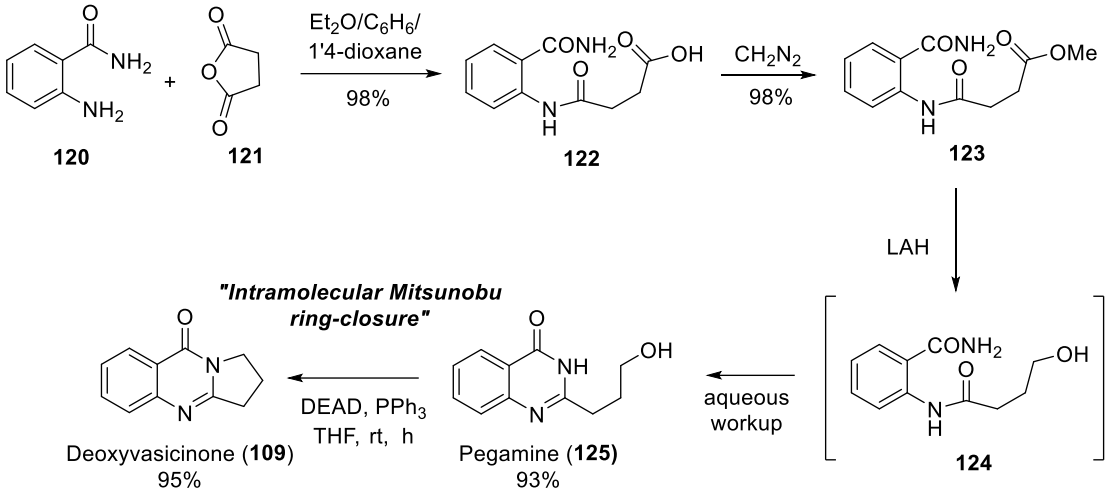
In addition, in 2004, Shafiee and co-workers synthesized deoxyvasicinone through intramolecular reductive cyclization as a key step. The reaction involved the coupling of 2-nitrobenzoic acid (**117**) with carbonyldiimidazole **96** to give compound **118** followed by condensation with 2-pyrrolidone (**112**) providing nitro **119**. Subsequently, reductive cyclization of nitro **119** in the presence of 10% Pd/C under 40 psi of H_2 gas provided deoxyvasicinone (**109**) in 98% (Ziaee *et al*., 2004) (**Scheme 23**).

Scheme 23 The intramolecular reductive cyclization for the synthesis of deoxyvasicinone



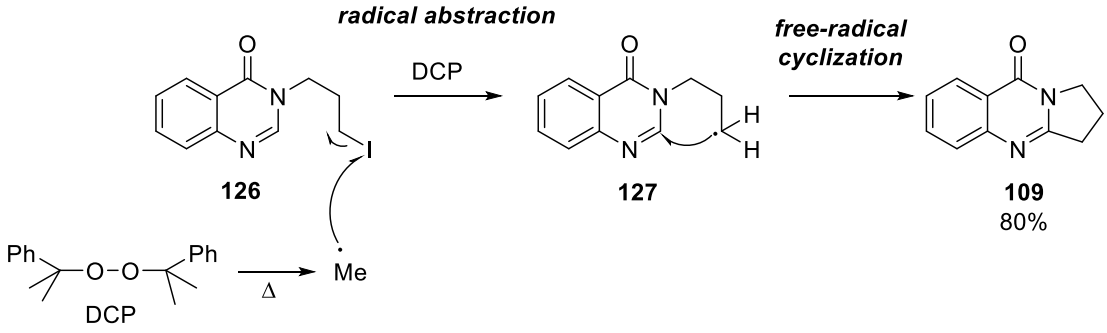
Alternatively, tricyclic quinaolinones involved the direct cyclization could be accomplished. In 2001, Argade and co-workers applied the intramolecular Mitsunobu ring-closure reaction as a key step to form ring-fused system of deoxyvasicinone. The condensation of anthranilamide (**120**) and succinic anhydride (**121**) provided *o*-amidosuccinanilic acid (**122**) in quantitative yield. The succinanilic **122** was treated with diazomethane in ether at room temperature afforded the ester **123** in quantitative yield. The ester **123** was then transformed to intermediate **124** via chemoselective reduction in the presence of LAH in THF at room temperature, followed by dehydrative ring closure under the aqueous workup catalyzed by LiOH to give pegamine (**125**) in 93% yield. Finally, pegamine (**125**) was transformed to deoxyvasicinone via intramolecular Mitsunobu ring-closure, yielding in 95% (**Scheme 24**) (Mhaske *et al*., 2001).

Scheme 24 Mitsunobu ring-closure reaction for the synthesis of deoxyvasicinone



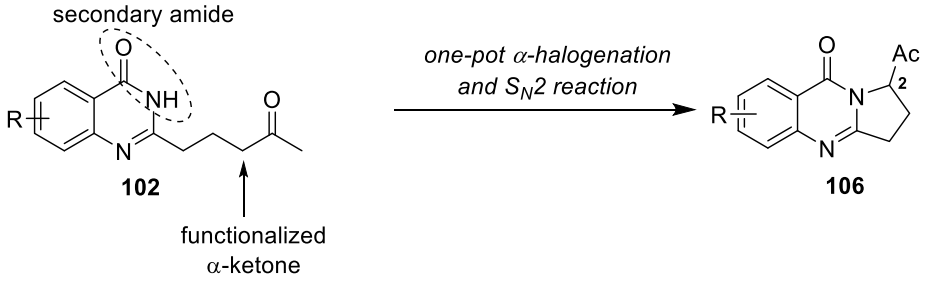
In 2020, Ramirez and co-workers reported the formation of deoxyvasicinone through a free radical cyclization of *N*-alkyl iododе **126** utilizing dicumyl peroxide (DCP) as the sole reagent. Under the conditions, the thermal decomposition of DCP resulted in the formation of a methyl radical, which abstracted the iodine atom and released the alkyl radical **127**. Subsequently, the cyclization of free-radical intermediate **127** afforded the deoxyvasicinone (**109**) in 80% yield. Moreover, this method can be used to prepare other fused-ring systems of quinazolinone derivatives (**Scheme 25**).

Scheme 25 Peroxide-mediated radical cyclization of deoxyvasicinone



Based on presented literatures, mostly deoxyvasicinone was obtained from the condensation reaction of corresponding anthranilic acids and pyrrolidone derivatives. The direct cyclization of parent quinazolinones were less explored compared to the mentioned condensation. Therefore, with our quinazolinones **102** having a long alkyl chain containing ketone functionality will be ready for direct cyclization. The direct cyclization consists of α-halogenation followed by S_N2-type cyclization. Hopefully, the cyclization would be accomplished in one-pot fashion (**Scheme 26**). In addition, the resulting product **106** will have acetyl moiety at the C2 carbon in which this analogue of deoxyvasicinones has not been much explored. Therefore, our method will provide alternative ways to prepare deoxyvasicinones having functionality at C2 carbon.

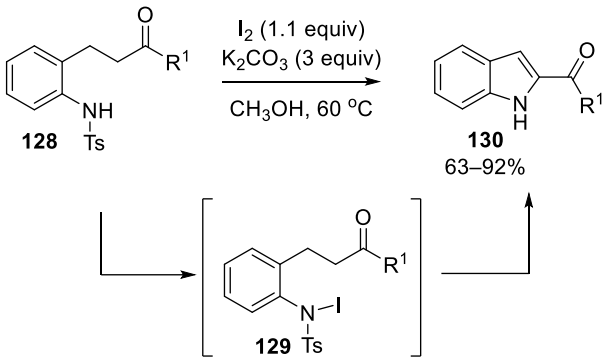
Scheme 26 Possible reaction for the synthesis of the small-sized ring fused quinazolinones



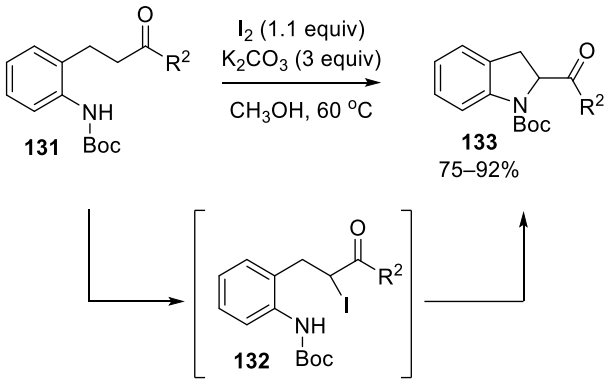
Nicely, in 2013, Zhang and co-workers reported the construction of 2-acylindoles **130** and 2-acylindolines **133** via iodine-mediated intramolecular amination of α-ketone. This method was efficiently performed under mild and basic conditions. Additionally, this process was modified by tuning the N-protecting groups of aminophenyl ketones. For the *N*-Ts protecting group, it was transformed to 2-acylindoles **130** in high yields through the intramolecular α-iodination of ketone to form the *N*–I intermediate **129**, followed by cyclization to give **130** (**Scheme 27a**). In the case of the N-Boc protecting group, it was converted to 2-acylindolines **133** via direct α-iodination of ketone **131** to form intermediate **132**, which then underwent cyclization to afford **133** in high yields (**scheme 27b**).

Scheme 27 Iodine-mediated intramolecular amination of ketones

a)



b)



Based on Zhang's finding and our quinazolinone **106**, I_2-mediated cyclizaton will be subjected to our study for direct cyclization for tryicyclic quinazolinone formation.

1.2 Objectives

1. To synthesize tricyclic quinazolinone having medium-sized cyclic amines, ureas or carbamates from *tert*-butyl 2-(4-oxo-2-(4-oxopentyl)quinazolin-3(4*H*)-yl)ethylcarbamate.

2. To synthesize five-membered ring fused quinazolinone, deoxyvasicinone derivatives, from 2-(4-oxopentyl)quinazolin-4(3*H*)-one

CHAPTER 2

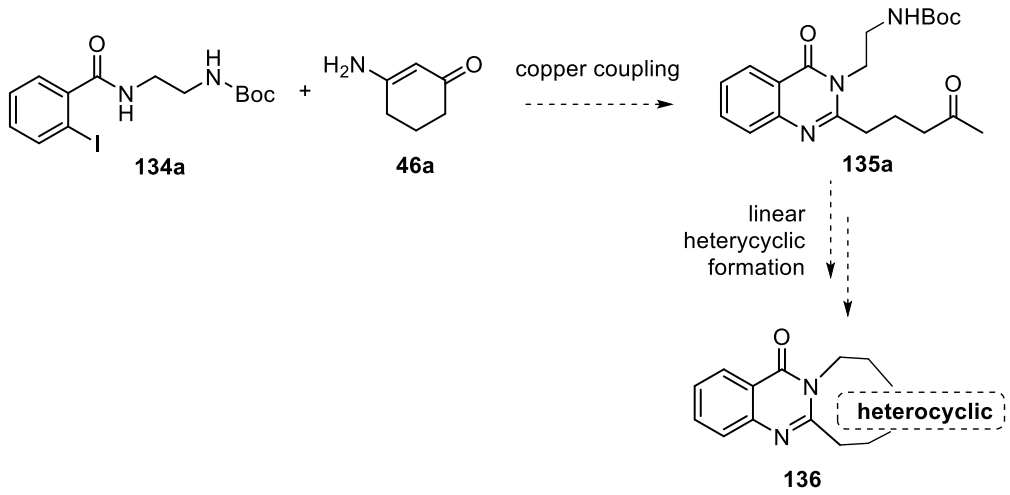
RESULTS AND DISCUSSION

To focus on the two core structures of quinazolinones, we separated this section into two parts. The first part discussed the synthesis of quinazolinones containing medium-sized N-heterocycles, while the second part investigated the synthesis of quinazolinones containing small-sized N-heterocycles.

2.1 Synthesis of quinazolinones containing medium-sized N-heterocycles

In accordance with this plan, the synthetic approach will be initiated by copper coupling of 2-iodobenzamide **134a** and cyclic enaminone **46a** providing quinazolinone intermediate **135a**. Subsequently, the medium-sized heterocycle will be synthesized through the linear heterocyclic formation, resulting in the generation of quinazolinone **136** fused with a medium-sized ring (**Scheme 28**).

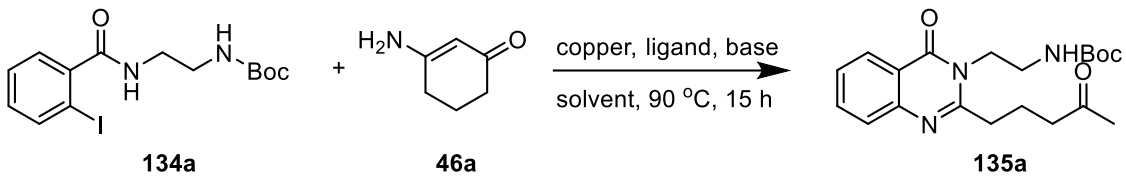
Scheme 28 The synthetic approach for the synthesis of medium-sized ring fused quinazolinone **136**



2.1.1 Optimization of quinazolinone synthesis via copper-catalyzed domino reaction

In this section, we began with the optimization of reaction conditions for the formation of quinazolinones **135a**. 2-Iodobenzamide **134a** and cyclic enaminone **46a** were chosen as model substrates for the copper-catalyzed domino reaction as shown in **Table 1**. A variety of variables were investigated, including copper salts, ligands, bases and solvents.

Table 1 Optimization of reaction conditions[a]



134a **46a** **135a**

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: **134a** (0.5 mmol), **46a** (0.6 mmol), catalyst (5 mol%), ligand (10 mol%), Base (2.5 equiv), solvent (0.2 M), 90 ^{o}C, 15 h in a sealed tube.

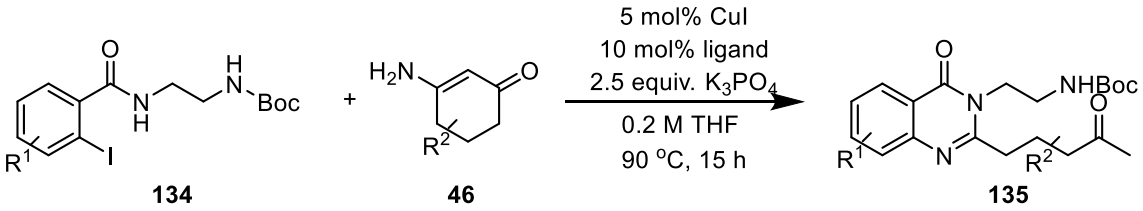
[b] Isolated yield.

Initially, we began 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 ^{o}C for 15 h, based on our previous work. The reaction gave an expected quinazolinone **135a** in 63% yield (entry 1). The reaction in toluene, a non-polar solvent, gave the product in a moderate yield, 72% (entry 2). With a slightly polar solvent, THF, the yield of quinazolinone was increased to 83% yield (entry 3). In contrast, more polar solvents, DMF and DMSO, gave no reaction (entries 4 and 5). Based on the results from the solvent experiments, it can be observed that the solubility affected the reaction. In the case of more polar solvents, the reactants were more soluble, however, due to the separation between molecules, the formation of new bonds was less likely to occur. In the case of a non-polar solvent, the non-polar solvents likely exhibited limited solubility for both the reactants and the polar transition state. We then investigated various common bases for copper-catalyzed reactions. Surprisingly, the reaction with K_2CO_3 gave no product (entry 6). On the other hand, with K_3PO_4 the reaction produced a yield of comparable to that of Cs_2CO_3 (entry 7). Notably, the solubility of the base significantly influenced the reaction by facilitating the formation of a copper-complex intermediate and assisting the addition and cyclization steps. 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 the ligand to 1,2-*trans*-diaminocyclohexane, the yield was slightly increased to 88% (entry 9). Picolinic acid also gave a good yield (78%) of product (entry 10). Noteworthy, we reported that the reaction of cyclic enaminone and 2-iodobenzamide required the assistance of a ligand from previous quinazolinone formation. Interestingly, without an external ligand, the reaction also proceeded well giving quinazolinone with a good yield of 72% (entry 11). Based on these results, the diamino moiety of the 2-iodobenzamide **134a** could function as a ligand allowing the reaction to perform smoothly. Lastly, we found that the counter ion of copper was crucial to the

reaction based on the dissociation and association of the counter ion and ligand in THF. The reaction with CuCl gave a moderate yield of 67% (entry 12). A similar result was found in the reaction with CuBr (entry 13). The $Cu(OAc)_2$ also catalyzed this reaction. However, the yield of the product was moderate, 54% (entry 14).

The substrate scopes for the Cu(I)-catalyzed domino synthesis of quinazolinones were examined under the optimal condition, 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 2**).

Table 2 Substrate scopes for the CuI-catalyzed synthesis of quinazolinones from 2-iodobenzamides **134** and cyclic enaminones **46** [a]



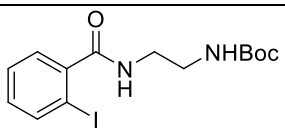
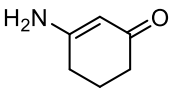
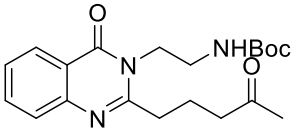
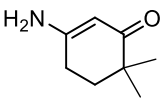
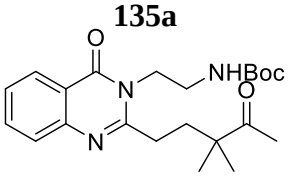
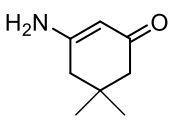
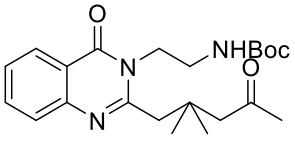
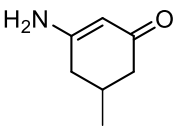
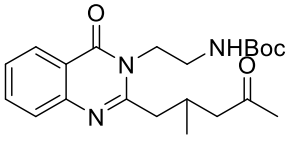
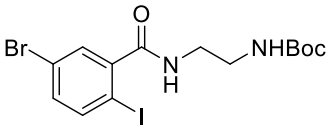
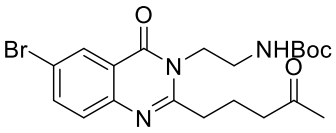
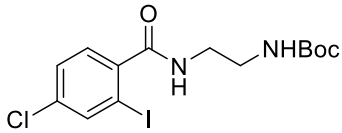
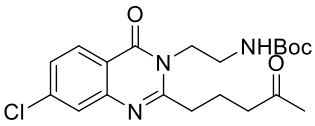
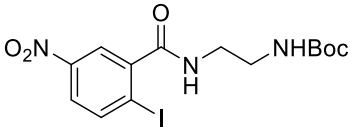
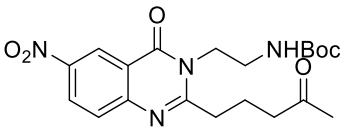
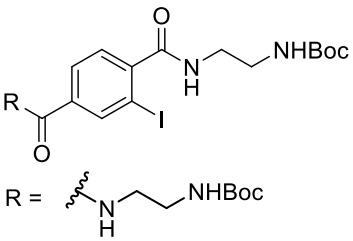
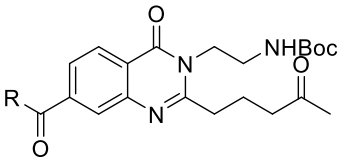
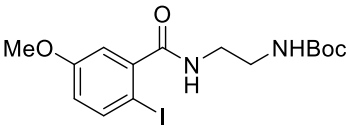
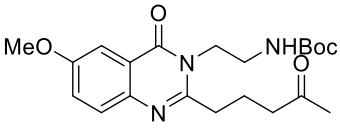
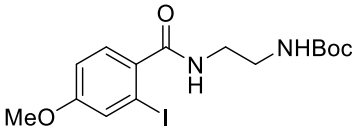
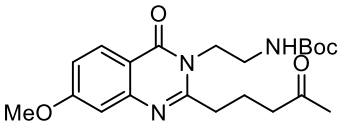
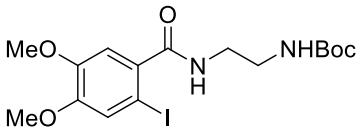
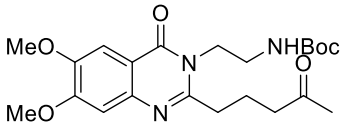
Entry	2-Iodobenzamide	Enaminone	Quinazolinone	Yield (%)[b]
1	 **134a**	 **46a**	 **135a**	88
2	**134a**	 **46b**	 **135b**	74
3	**134a**	 **46c**	 **135c**	0
4	**134a**	 **46d**	 **135d**	77

Table 2 (continued)

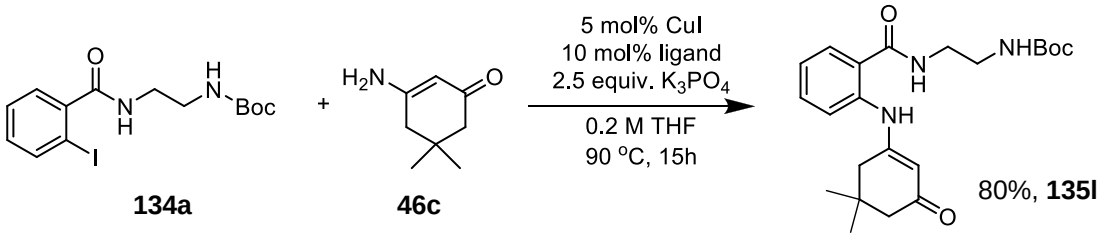
Entry	2-Iodobenzamide	Enaminone	Quinazolinone	Yield (%)[b]
5	 **134b**	**46a**	 **135e**	80
6	 **134c**	**46a**	 **135f**	70
7	 **134d**	**46a**	 **135g**	54
8	 **134e**	**46a**	 **135h**	77
9	 **134f**	**46a**	 **135i**	78
10	 **134g**	**46a**	 **135j**	74

11	 **134h**	**46a**	 **135k**	80

[a] Reaction conditions: 0.5 mmol of **134**, 0.6 mmol of **46**, 1,2-*trans*-diaminocyclohexane as a ligand.
[b] Isolated yield.

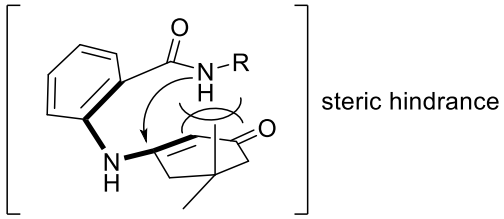
Firstly, we considered a series of six-membered cyclic enaminones (entries 1-4). The 3-amino-6,6-dimethycyclohex-2-enone (**46b**) was applied to the reaction, resulting in good yield, 74% (entry 2), whereas no quinazolinone was formed with 3-amino-5,5-dimethylcyclohex-2-enone (**46c**) (entry 3). Instead, an adduct **135l** of C(aryl)–N bond formation was obtained in 88% yield (**Scheme 29**). A different result was found when we subjected 3-amino-5-methylcyclohex-2-enone (**46d**) to the reaction. The yield of the product was 77% (entry 4). The results from the cyclic enaminone **46b** and **46d** suggested that the steric hindrance of geminal dimethyl blocked the intramolecular Michael addition of the intermediate adduct (**Figure 8**).

Scheme 29 The reaction of 2-iodobenzamide **134a** with 3-amino-5,5-dimethyl-cyclohex-2-enone (**46c**)



134a **46c**

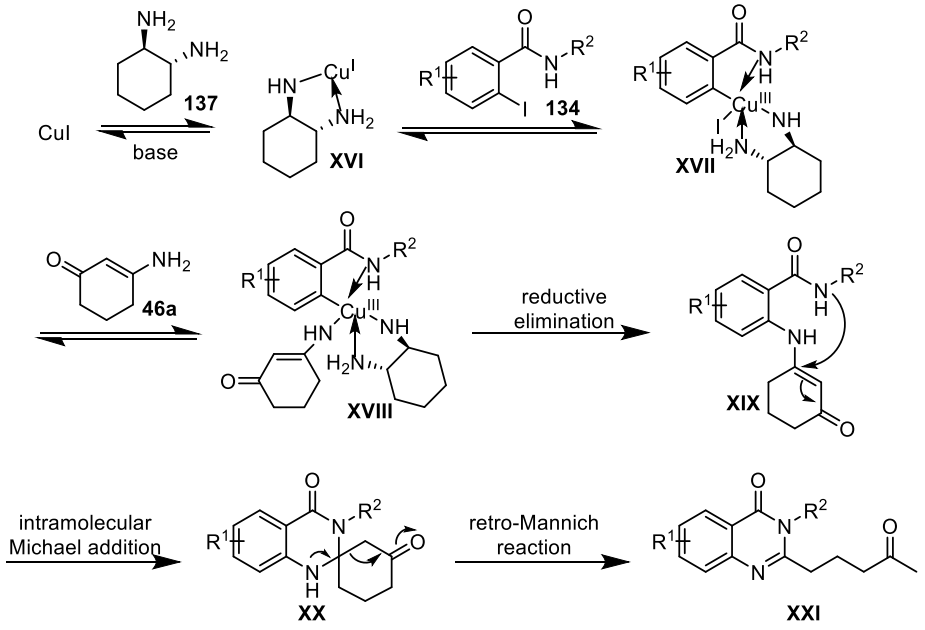
Figure 8 The steric effect of geminal dimethyl for the intramolecular Michael addition of the intermediate adduct



The 2-iodobenzamides with halogen substituents, Br and Cl, were suitable in this reaction. A good yield, 80%, was obtained from the reaction of 5-bromo-2-iodobenzamide (**134b**) (entry 5). 4-Chloro-2-iodobenzamide **134c** also gave a product with a similar yield of 70% (entry 6). The 2-iodobenzamides having electron-withdrawing substituents were also applicable to the reaction, although the yields of quinazolinone were slightly decreased. The reaction of 5-nitro-2-iodobenzamide **134d** provided quinazolinone with a moderate yield, 54% (entry 7). Different results were found from the reaction of 4-amido-2-iodobenzamide **134e** providing a corresponding quinazolinone **135h** in a good yield, 77% (entry 8). Notably, the presence of electron-withdrawing substituents at *para*-position had an effect to reduce the electron density of iodine, leading to decrease the efficiency of the coupling process. Next, we explored the effect of electron-donating groups on 2-iodobenzamide. Encouragingly, we found that 2-iodobenzamides with mono- (**134f** and **134g**) or dimethoxy (**134h**) substituents generally produced the corresponding quinazolinones with good yields, 78-80% (entries 9-11).

Based on the results of **Scheme 29** and the previous report (Songsichan *et al*., 2014), the possible mechanism suggested that the C(aryl)–N(enamine) bond was initially formed in the domino process. Therefore, the mechanism involves the association of CuI and 1,2-*trans*-diaminocyclohexane (**137**) to form the active Cu(I) complex **XVI** (Ma *et al*., 2008). Then, the oxidative addition of **XVI** and 2-iodobenzamide **134** gave a complex **XVII**, followed by the ligand exchange with enaminone **46a** to generate complex **XVIII**. The reductive elimination of **XVIII** took place to form the *N*-arylation intermediate **XIX**, followed by the intramolecular Michael addition providing a dihydroquinazolinone intermediate **XX**. The last step was the retro-Mannich reaction, giving a corresponding quinazolinone product **XXI** (**Scheme 30**).

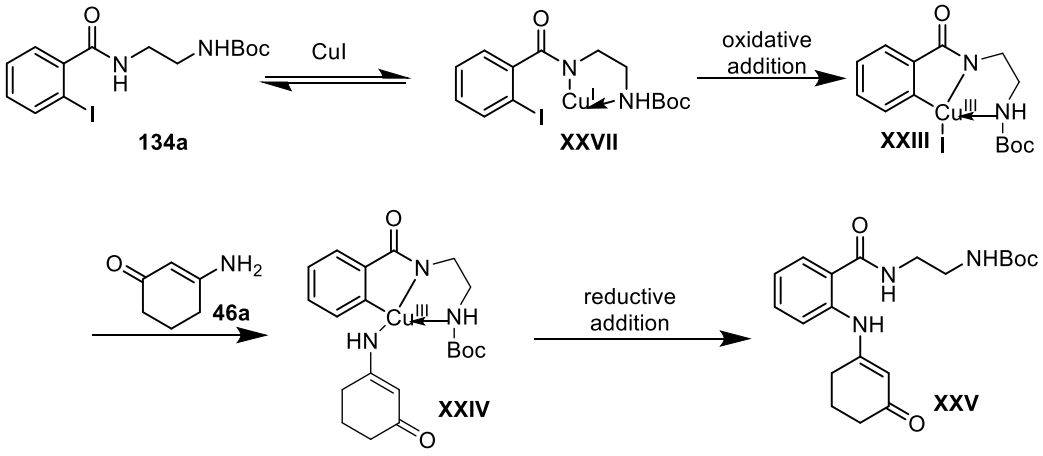
Scheme 30 The proposed mechanism of the Cu(I)-catalyzed domino reactions for the synthesis of quinazolinones



Since the reaction could perform without the additional ligand, the result suggested that the diamino moiety could function as internal ligand. Therefore, the possible mechanism of the reaction without an external ligand was described in **Scheme 31**. The diamino moiety of 2-iodobenzamide **134a** played the role of a ligand that

coordinated with CuI to generate complex **XXII**. Then, the oxidative addition of **XXII** formed the complex **XXIII**. Enaminone **46a** 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 30**.

Scheme 31 The possible mechanism of the reaction without an external ligand



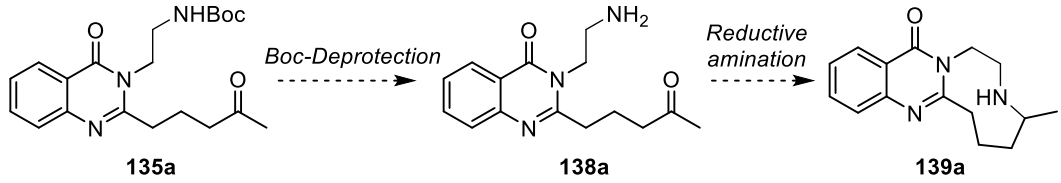
2.1.2 Synthesis of medium-sized cyclic amine fused quinazolinone

Based on the structure of **135a**, having both amine and ketone moieties. A series of attempts to install heterocycles will be discussed.

2.1.2.1 The formation of 4-methyl-2,3,4,5,6,7-hexahydro-[1,4]diazonino[9,1-b]quinazolin-13(1*H*)-one (116a).

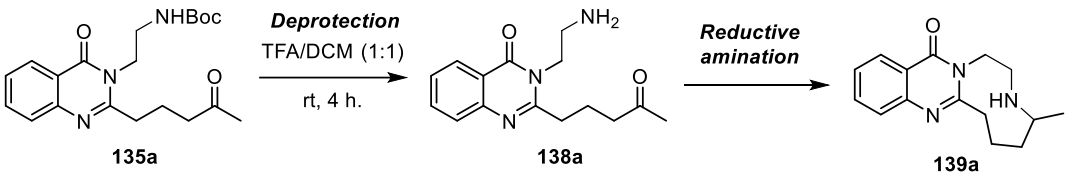
We initiated the synthesis of 9-membered cyclic amine fused with quinazolinone scaffold **139a**. The synthetic route would be started with Boc-deprotection of **135a**, followed by reductive amination to form desired product (**Scheme 32**).

Scheme 32 The plausible approach for the synthesis of 9-membered cyclic amine fused with a quinazolinone scaffold



We started with deprotection of the Boc-protecting group under acidic conditions using a 1:1 ratio of trifluoroacetic acid (TFA) in dichloromethane (DCM), which resulted in the formation of free amine **138a** in an excellent yield of 95%. After having **138a** in hand, we investigated the reductive amination of **138a** using sodium triacetoxyborohydride (STABH), and sodium borohydride ($NaBH_4$) as reducing agents (Abdel-Magid *et al*., 1996) (**Table 3**). Based on the screening test in **Table 3**, the desired product **139a** was not obtained using the selected reducing agent, sodium triacetoxyborohydride (STABH) (entry 1) and sodium borohydride ($NaBH_4$) (entry 3). Instead, we only obtained unidentified products without recovering starting material **135a**. Additionally, we also got the same result when acetic acid was added as a catalyst (entries 2 and 4). Presumably, the formation of a 9-membered cyclic imine is unfavorable.

Table 3 The screening reaction conditions of reductive amination to form **139a**

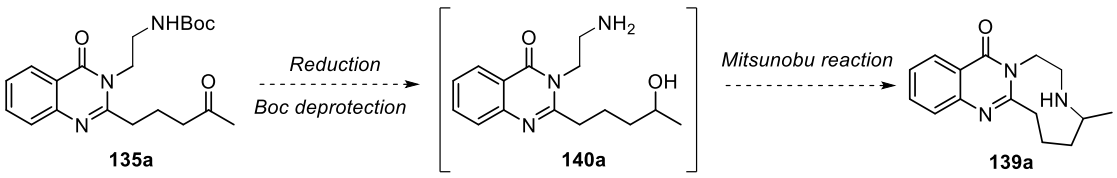


Entry	Conditions	Result
1	STABH (2.0 equiv), DCM, 0 ^{o}C to rt, 16 h.	unidentified product

2	STABH (2.0 equiv), CH_3COOH, DCM, 0 ^oC to rt, 16 h.	unidentified product
3	$NaBH_4$ (2.0 equiv), DCM, 0 ^oC to rt, 16 h.	unidentified product
4	$NaBH_4$ (2.0 equiv), CH_3COOH, DCM, 0 ^oC to rt, 16 h.	unidentified product

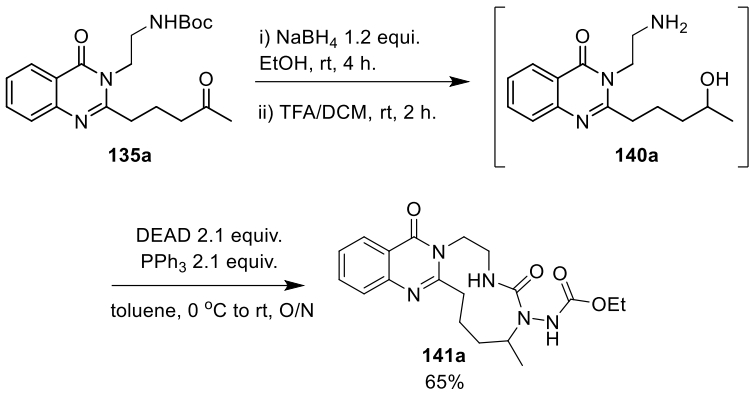
Then, we decided to apply the Mitsunobu reaction to construct the cyclic amine moiety (**Scheme 33**) as an alternative approach. The quinazolinone adduct **135a** would be converted to amino alcohol **140a** with reduction and deprotection. Lastly, **140a** could readily undergo an intramolecular cyclization, providing the desired quinazolinone **139a**.

Scheme 33 An alternative cyclization of a medium-sized ring via the Mitsunobu reaction



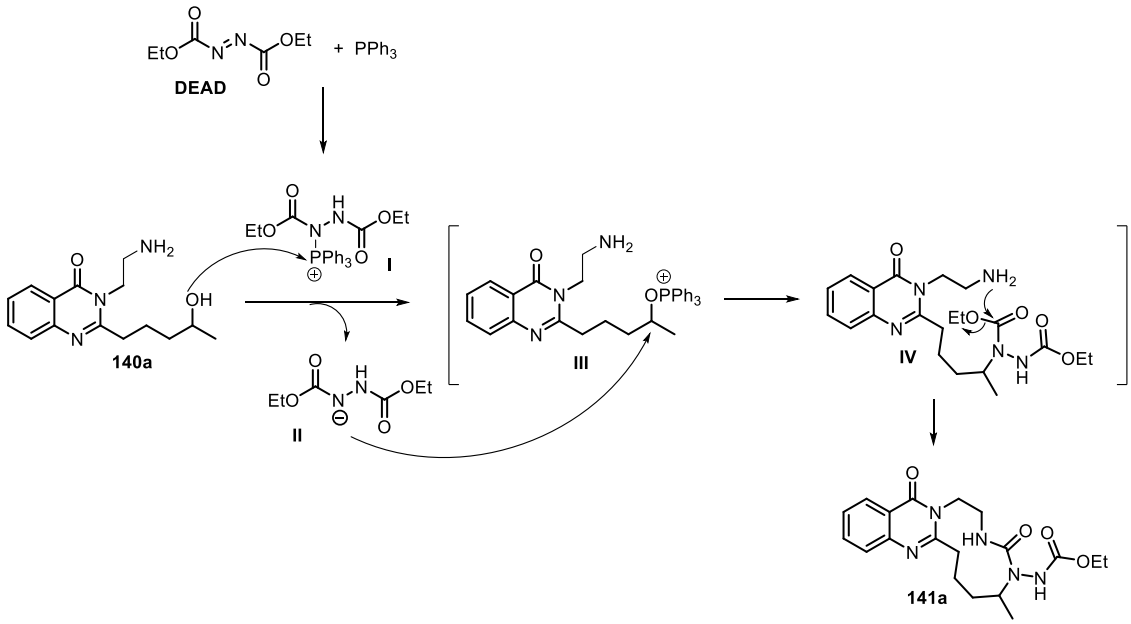
The reduction of quinazolinone adduct **135a** was performed using 1.2 equiv of $NaBH_4$ as a reducing agent at room temperature. Then, the crude reaction mixture was subjected to Boc-deprotection using TFA in DCM to produce the amino alcohol **140a** in a quantitative yield. The crude mixtures of **140a** underwent Mitsunobu reaction in the presence of 2.1 equiv of diethyl azodicarboxylate (DEAD) and 2.1 equiv of triphenylphosphine (PPh_3) in toluene at room temperature for 16 h. Surprisingly, we found that DEAD moiety took into the part of undesired product **141a**, while desired product **139a** was not observed (**Scheme 34**).

Scheme 34 The ring formation of amino alcohol **140a** via the Mitsunobu reaction



The plausible transformation of the undesired product **141a** was shown in **Scheme 35**, based on Somfai's finding (Olofsson *et al*., 2002). The triphenylphosphine (PPh_3) combines with DEAD to form phosphonium intermediate **I**, which then binds to the oxygen of alcohol, resulting in the formation of oxyphosphonium **III**. This activates alcohol as a leaving group and eliminates nucleophilic intermediate **II** as a byproduct. The attack of intermediate **II** on intermediate **III** probably leads to the formation of intermediate **IV** followed by intramolecular 1,2-addition and subsequent elimination of an ethoxide ion yielding the undesired product **141a**. Notice that the cyclization of a larger ring, an 11-membered ring, was more favorable than a smaller ring, a 9-membered ring.

Scheme 35 The possible mechanism of the undesired tricyclic quinazolinone via the Mitsunobu reaction

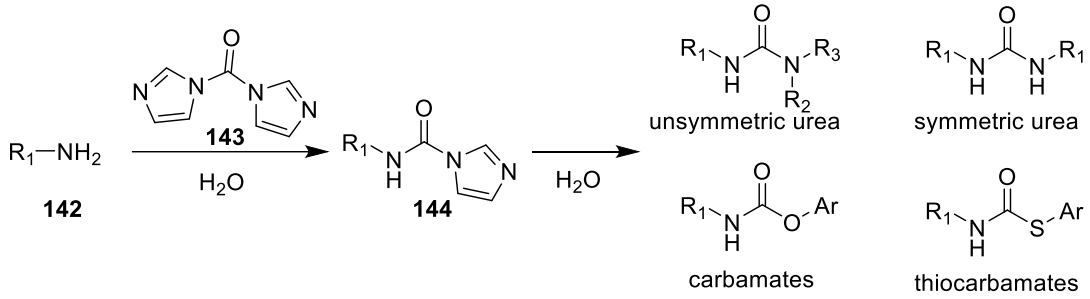


2.1.2.2 Synthesis of medium-sized cyclic carbamate fused quinazolinone

Since, we could not accomplish the 9-membered ring amine fused quinazolinone, we then moved our interest to apply a concept of inter/intra-molecular cyclization to enlarge ring size. Presumably, the flexibility of the larger ring size would allow a linear cyclization to take place. Additionally, based on the unexpected 11-membered ring fused quinazolinone **141a** from the reaction of quinazolinone **140a** and DEAD, we then moved our focus to the formation of 11-membered ring fused carbamate or urea moiety.

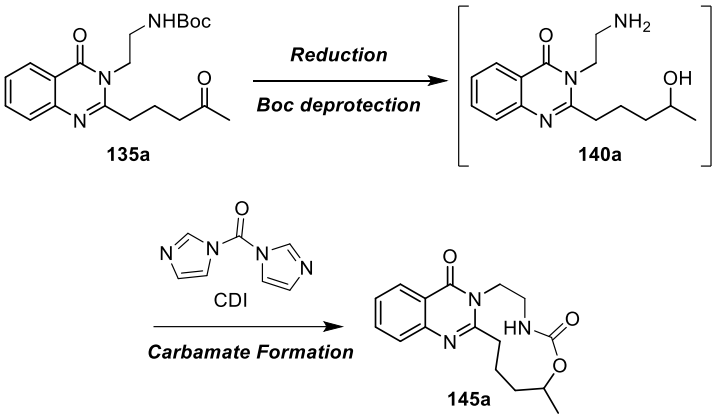
In 2012, Padiya and co-workers reported the synthesis of unsymmetrical urea, symmetric urea, carbamates, and thiocarbamates from simple amines **142** and other nucleophiles using a carbonyl diimidazole (CDI, **143**) as a green and efficient carbonylating reagent (**Scheme 36**) (Padiya *et al*, 2012). This reaction could be performed in a water system and allowed the synthesis of various acyclic ureas, carbamates, and thiocarbamates in good yields.

Scheme 36 Unprecedented “in water” imidazole carbonylation using CDI as a carbonylating reagent



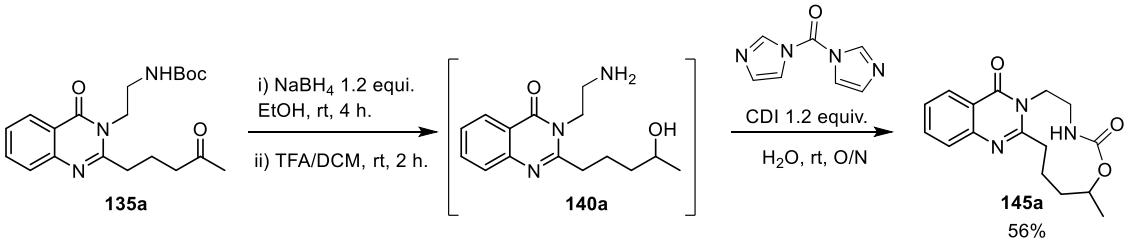
We then selected CDI as a carbonyl source to sew between tethered amine and alcohol moiety of quinazolinone **140a** providing an 11-membered ring fused quinazolinone **145a** (**Scheme 37**).

Scheme 37 The synthetic plan for synthesis of cyclic carbamate fused quinazolinone



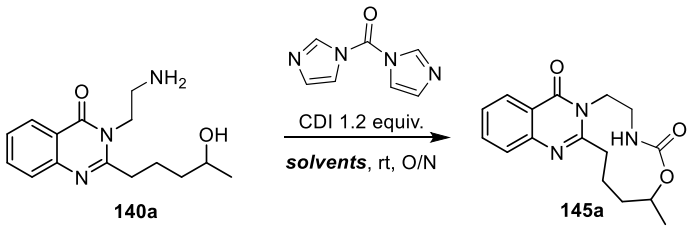
A reduction of **135a** followed by Boc-deprotection afforded the amino-alcohol quinazolinone **140a** in high yield without a purification process. We then tested an intramolecular cyclization of **140a** according to procedure reported by Padiya. Treatment **140a** with 1.2 equivalents of CDI in water at room temperature gave medium-sized cyclic carbamate fused quinazolinone **145a** in 56 %yield (**Scheme 38**).

Scheme 38 The synthesis of medium-sized cyclic carbamate fused quinazolinone **145a**



In addition, various solvents, MeOH, ^{t}BuOH, DMSO, and DMF, were investigated (**Table 4**). Unfortunately, no desired products were obtained. We only observed the decomposition of the starting material, forming the unidentified product with high polarity.

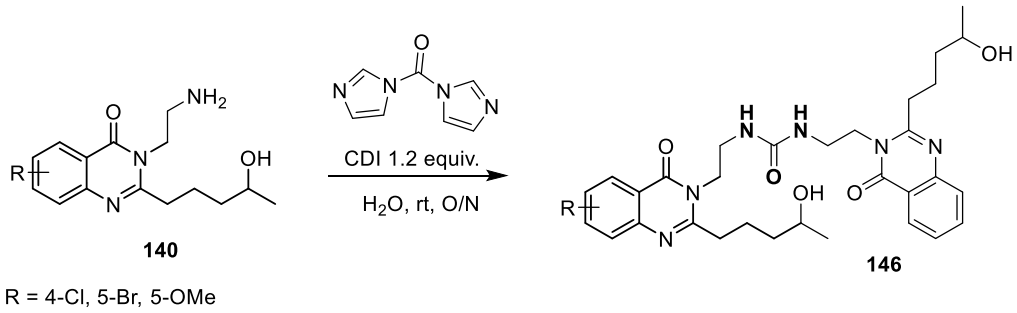
Table 4 The optimization of solvents for the synthesis of medium-sized cyclic carbamate fused quinazolinone



Entry	Solvent	Yield of 145a (%)
1	Water	56
2	MeOH	unidentified product
3	*tert*-butanol	unidentified product
4	DMSO	unidentified product
5	DMF	unidentified product
Reaction conditions: all reactions were performed with 0.3 mmol, 15 ml of solvent.		

Based on the 56% yield of **145a**, we then investigated the variety of substrate scopes by screening substituent on the phenyl ring (**Scheme 39**). Unfortunately, cyclic carbamates were not observed. Only dimer products **146** were produced in this reaction. The dimer was confirmed by mass spectroscopy. This result suggested that O-nucleophile may have less reactivity to cyclize the medium-sized ring and the formation of the urea moiety was readily achieved in this reaction.

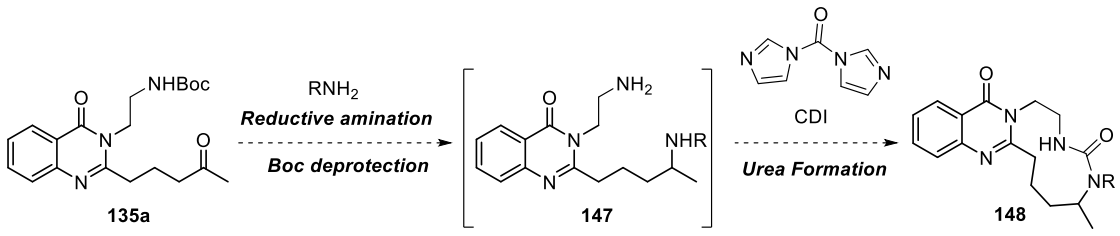
Scheme 39 The formation of undesired dimer **146**



2.1.2.3 Synthesis of medium-sized cyclic urea fused quinazolinone

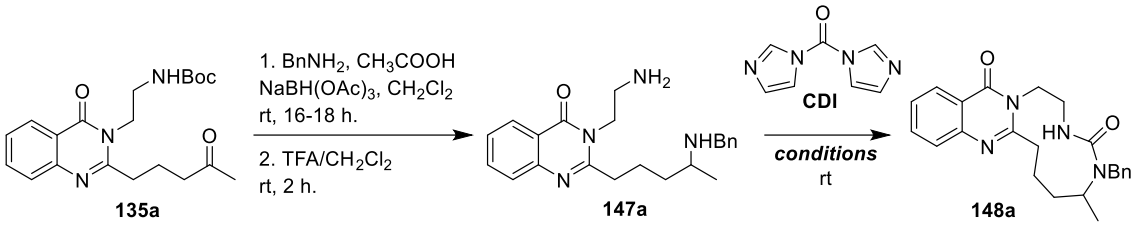
Due to uncertainty of the 11-membered carbamate formation, we turned our interest to sew up the third ring with urea moiety to obtain a 11-membered ring fused quinazolinones Due to their unique molecular structures, 11-membered rings are found in biologically active compounds and medicinally significant compounds (Hussain *et al*., 2014) The synthesis started with reductive amination with external amines, Boc-deprotection followed by urea formation (**Scheme 40**).

Scheme 40 The synthetic plan for the synthesis of medium-sized cyclic urea fused quinazolinone



Diamino precursor **147** was smoothly formed by the reductive amination with benzylamine using sodium triacetoxyborohydride as a reducing agent (Abdel-Magid *et al*., 1996), followed by Boc-deprotection mediated by trifluoroacetic acid (TFA). To cyclize diamino adduct, we applied a modified method using CDI as a carbonyl source with a variety of solvents under room temperature (**Table 5**).

Table 5 The solvents screening for the synthesis of medium-sized cyclic urea fused quinazolinone



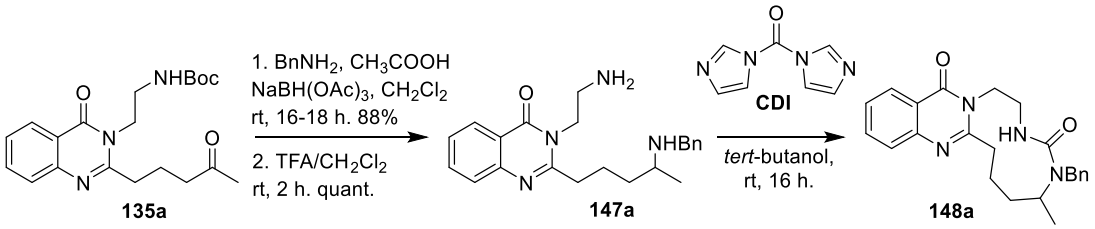
Entry	Solvent	Time	Yield (%)
1	Water	16 h	trace
2	MeOH	16 h	unidentified product
3	*tert*-butanol	16 h	65[b]
4	DMSO	16 h	unidentified product
5	DMF	16 h	unidentified product
6	CH_3CN	16 h	unidentified product
7	toluene	16 h	unidentified product

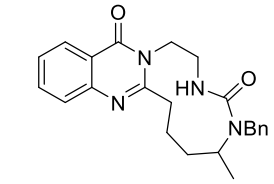
[a] Reaction conditions: **147a** (0.5 mmol), CDI (1.2 mmol), solvent (0.02 M), room temperature. [b] Isolated yield.

The results revealed that the corresponding quinazolinone fused with medium-sized ring urea **148a** was formed in 65% yield by using *tert*-butanol as a solvent (entry 3) over three steps from **135a**, whereas other solvents led to the formation of

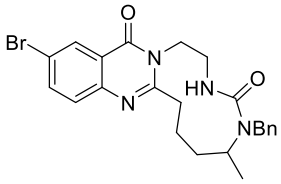
unidentified products. We then used this condition to access the tricyclic quinazolinones with various substituents. The substrate scopes with halogen substituents, Br and Cl, were suitable in this reaction. The reaction yielded a respective 58% and 52% for these substrates. For the electron-donating groups on the aryl ring, either 4-OMe or 5-OMe gave moderate yields of 57%, and 55%, respectively. On the other hand, having the nitro group at the fifth position on the aryl ring, the yield slightly decreased to 48% due to their high polarity and reduced solubility in the solvent used for the reaction. (**Scheme 41**).

Scheme 41 Substrate scopes of medium-sized cyclic urea fused quinazolinone

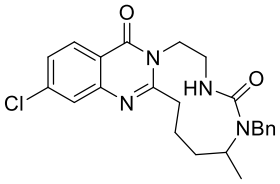




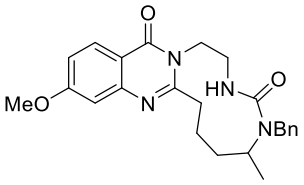
148a, 65%



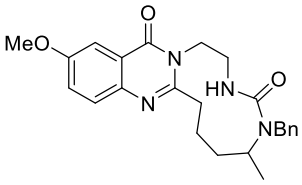
148b, 58%



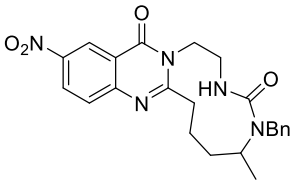
148c, 62%



148d, 57%



148e, 55%



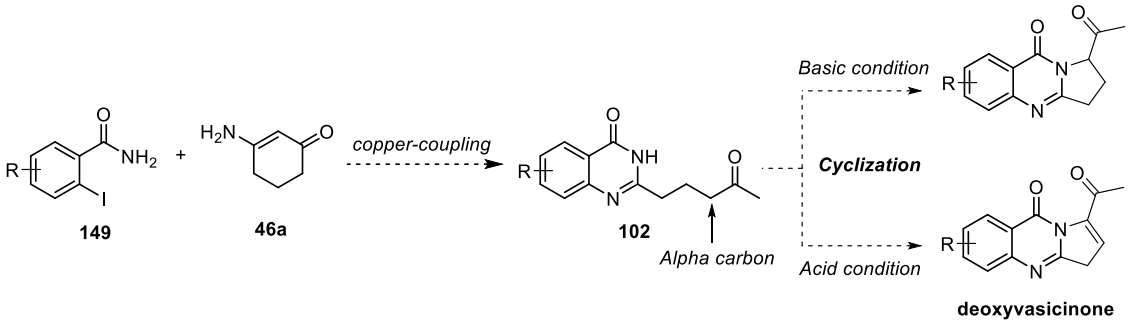
148f, 48%

Reaction conditions: **135a** (0.5 mmol), CDI (1.2 mmol), *tert*-butanaol (0.02 M).

2.2 Synthesis of Quinazolinones Containing Small-Sized N-Heterocycles

In this section, we focused on the synthesis of the small-sized ring fused quinazolinone. A small-sized ring refers to a ring that contains 3-7 carbon atoms and is fused with a quinazolinone core, forming a variety of quinazolinone derivatives found in various natural compounds. The synthetic pathway started with the preparation of quinazolinone intermediate **102** from 2-iodobenzamides **149** and cyclic enaminones **46a** via a copper-catalyzed coupling reaction. Then, the intermediate **102** could be transformed into two different deoxyvasicinones (**Scheme 42**) based on the C–N bond formation between N (amide) and C (alpha carbon)

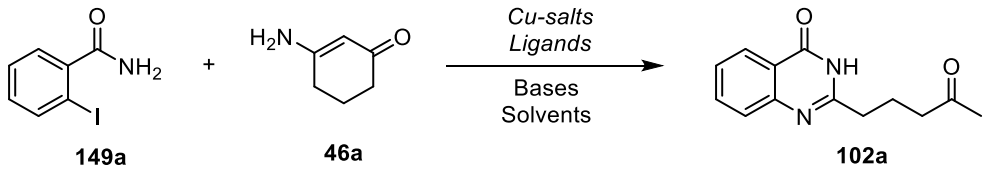
Scheme 42 The synthetic pathway for synthesizing Small-Sized N-Heterocycles fused quinazolinone



2.2.1 Optimization and Substrate Scopes of Quinazolinone Adduct via Copper-Catalyzed Domino Reaction

We started this section with the preparation of model quinazolinone core **102**, cyclized precursor, via Cu-catalyzed cascade reaction reported by our group in 2014 (Songsichan *et al*., 2014).

Table 6 Optimization of reaction conditions for the copper-catalyzed domino reaction of 2-iodobenzamide (**149a**) with cyclic enaminone **46a** to form quinazolinone adduct **102a**[a]



149a **46a** **102a**

Entry	Cu-salt	Ligand	Base	Solvent	Yield[b] (%)
1	CuI	1,2-diamino cyclohexane	Cs_2CO_3	THF	29
2	CuI	1,2-diamino cyclohexane	K_3PO_4	THF	22
3	CuI	1,2-diamino cyclohexane	K_2CO_3	THF	trace
4	CuI	1,2-diamino cyclohexane	Et_3N	THF	0
5	CuI	1,2-diamino cyclohexane	Cs_2CO_3	DMSO	22
6	CuI	1,2-diamino cyclohexane	Cs_2CO_3	DMF	16
7	CuI	1,2-diamino cyclohexane	Cs_2CO_3	MeCN	16
8	CuI	1,2-diamino cyclohexane	Cs_2CO_3	Toluene	trace
9	CuI	Proline	Cs_2CO_3	THF	52
10	CuI	DMEDA	Cs_2CO_3	THF	20
11	CuI	1,10-phenanthroline	Cs_2CO_3	THF	54
12	CuCl	1,10-phenanthroline	Cs_2CO_3	THF	47
13	CuBr	1,10-phenanthroline	Cs_2CO_3	THF	53
14	$Cu(OAc)_2$	1,10-phenanthroline	Cs_2CO_3	THF	58

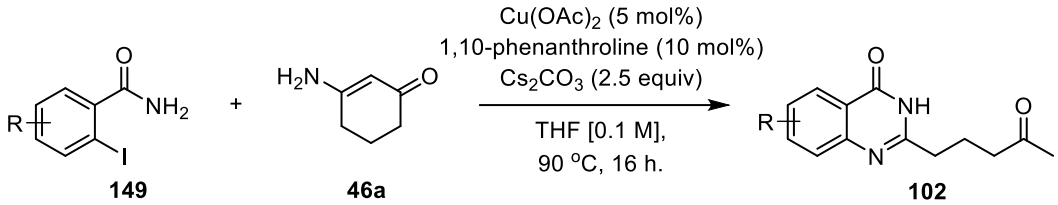
[a] Reaction conditions; all reactions were performed with 0.3 mmol of amide **149a**, 1.5 equiv of cyclic enaminone **46a**, 5 mol % of Cu salt, 10 mol % of ligand, 2.5 equiv of base, 1.5 mL of solvent, for 18 h.

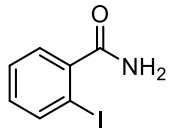
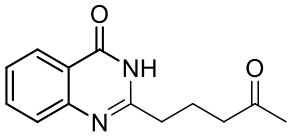
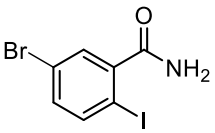
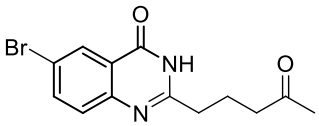
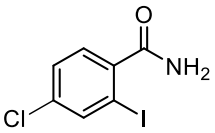
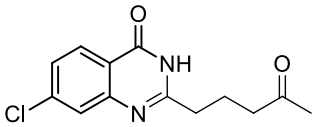
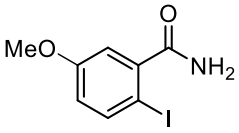
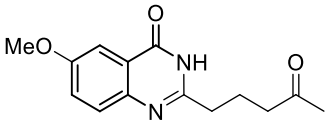
[b] Isolated yield.

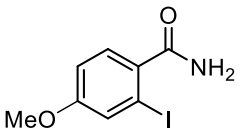
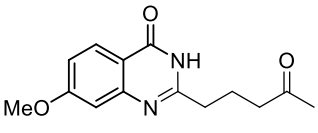
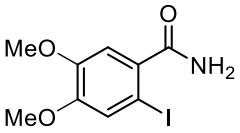
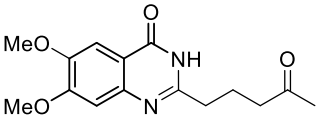
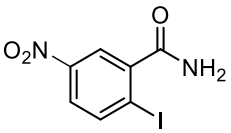
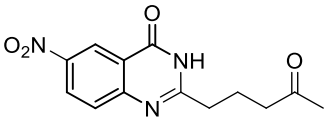
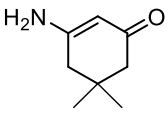
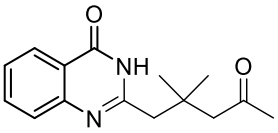
Our investigation commenced with reaction optimization using iodobenzamide **149a** and cyclic enaminone **46a** as model substrates (**Table 6**). Various bases were screened in the presence of 5 mol % of CuI as the copper source, 10 mol % of 1,2-diaminocyclohexane as a ligand and THF as a solvent by heating at 90 ^{o}C for 15 h. According to the report from our previous work, THF was a solvent of choice for this type of 2-iodobenzamide coupling reaction. The reaction with Cs_2CO_3 as the base gave **102a** in 29% yield (entry 1), whereas using K_3PO_4 and K_2CO_3 provided low yields of **102a**, 22% and trace amount, respectively (entries 2–3). Presumably, the low solubility of K_2CO_3 in THF results in a trace amount of product. Unfortunately, changing the base to an organic base, Et_3N, no product was observed (entry 4). Switching the solvents from THF to the more polar solvents, DMSO, DMF, and MeCN, for enhancing the solubility of the base, did not significantly improve the yields (entries 5–7). In addition, a trace amount of product was observed from the reaction using a nonpolar solvent, toluene (entry 8). Based on solvent exploration, the solubility of substances and reagents play a crucial role in the reaction. In nonpolar solvents, the reagents remained undissolved, resulting in a trace amount of product formation. Next, we turned our focus to a variety of common ligands for a copper coupling reaction. The utilization of proline as a ligand gave the product 52% yield, whereas the yield was slightly dropped with DMEDA, 20% yield (entry 10). Gratifyingly, the yield was improved to 54% when using 1,10-phenanthroline as a ligand (entry 11). Other copper salts were also investigated (entries 12–14). Comparable yields were found from CuCl and CuBr, giving the product in 47% and 53% yields, respectively (entries 13 and 14). Interestingly, $Cu(OAc)_2$ provided the expected product **102a** with the best result, 58% yield (entry 15). Possibly, the dissociation of Cu-counter ions and association of Cu-ligand played a certain role in the reaction in THF resulting in the best result from $Cu(OAc)_2$. Based on the exploration of the reaction condition, we summarized that the use of 5 mol % of $Cu(OAc)_2$ as the catalyst, 10 mol % of 1,10-phenanthroline as the ligand, 2.5 equiv of Cs_2CO_3 as the base and THF as the solvent at 90 ^{o}C for 16 hours was the optimal conditions for this reaction.

The broad spectrum of 2-iodobenzamides was applicable to the reaction and the results were summarized in **Table 7**.

Table 7 Substrate scopes for the copper-catalyzed reaction of quinazolinone from 2-iodobenzamides **149** and cyclic enaminones **46a**[a]



Entry	2-Iodobenzamide	Enaminone	Quinazolinone	Yield (%)[b]
1	 **149a**	**46a**	 **102a**	58
2	 **149b**	**46a**	 **102b**	52
3	 **149c**	**46a**	 **102c**	62
4	 **149d**	**46a**	 **102d**	55

5	 **149e**	**46a**	 **102e**	56
6	 **149f**	**46a**	 **102f**	52
7	 **149g**	**46a**	 **102g**	22
8	**149a**	 **46c**	 **102h**	54

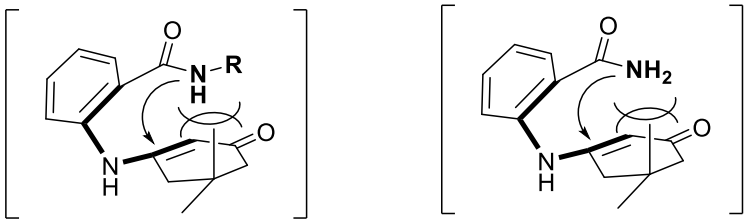
[a] Reaction conditions; all reactions were performed with 0.5 mmol of amide **149**, 1.5 equiv of cyclic enaminone **46**, 5 mol % of Cu salt, 10 mol % of ligand, 2.5 equiv of base, 2.5 mL of solvent, for 16 h.

[b] Isolated yield.

2-Iodobenzamide, which contains halogen atoms on an aryl ring, were suitable in this reaction. The reaction of 5-bromo-2-iodobenzamide (**149b**) gave the yield of 52% (entry 2). In addition, 4-Chloro-2-iodobenzamide (**149c**) yielded the corresponding quinazolinone in 62% (entry 3). The presence of the halogen atom enhances the reactivity of the coupling adduct by increasing the electron density of coupling carbon. An investigation was conducted on various 2-iodobenzamides with electron-donating or electron-withdrawing on an aromatic ring. The reaction of 5-methoxy-2-iodobenzamide (**149d**) and 4-methoxy-2-iodobenzamide (**149e**) gave the yield of the coupling product in 55% (entry 4) and 56% (entry 5), respectively, while the 4,5-diOMe quinazolinone provided a yield of 52% (entry 6). The electron-donating groups on an aryl ring have influenced the reaction by increasing the electron density

of coupling carbon resulting in increasing the product yield. On the other hand, 5-nitro-2-iodobenzamide (**149g**), which contains an electron-withdrawing group, resulted in a low yield of a corresponding quinazolinone **102g**, 22% (entry 7). This can be ascribed to the electron-withdrawing group reducing the electron density and affecting the coupling process. Next, we turned our focus to cyclic enaminones. In addition, having geminal dimethyl on C-6 provided the desired product in 54% (entry 8). Interestingly, based on the previous work (Saebang *et al.,* 2022), the cyclic enaminone having geminal dimethyl on C-6 could not undergo intramolecular Michael addition due to the steric hindrance. On the contrary, the cyclic enaminone performed intramolecular Michael addition smoothly with primary amide substances (-$CONH_2$). Presumably, primary amide reduced steric hindrance between geminal dimethyl groups and the *N*-alkyl side chain (**Figure 9**).

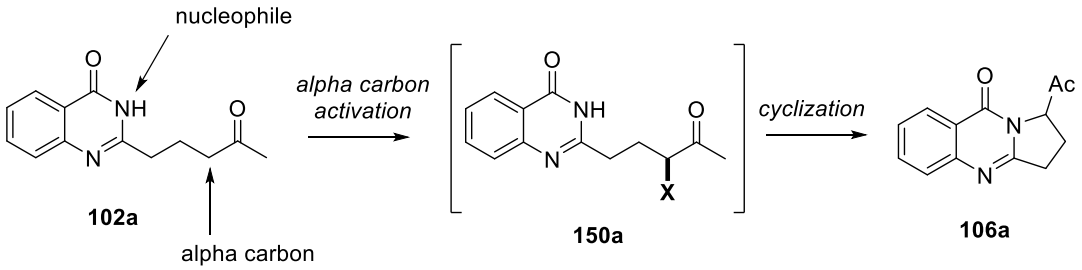
Figure 9 The steric effect of geminal dimethyl of cyclic enaminone with *N*-alkyl amide



2.2.2 Synthesis of Deoxyvasicinone Derivatives

After we had quinazolinone **102a** in hand, we focused on the construction of the third ring via linear cyclization. One of the most common methods to construct N–C(alpha) bond is alpha carbon activation. The alpha carbon activation could be accomplished from both basic and acidic conditions. Therefore, we explored both conditions for the formation of five-membered fused quinazolinones (**Scheme 43**).

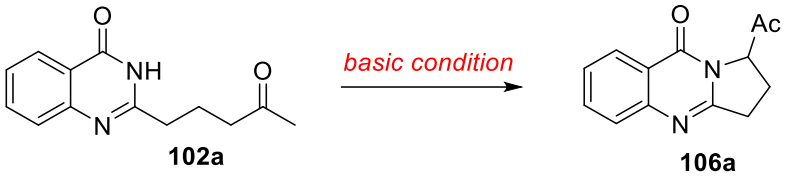
Scheme 43 The synthetic route for the formation of five-membered fused quinazolinones



2.2.2.1 Synthesis of Deoxyvasicinone Derivatives under Basic Conditions

Having the idea of alpha functionalization followed by cyclization in mind, we commenced our investigation of the intramolecular cyclization process by conducting a screening of reactions under basic conditions with common halogenating reagent. This screening aimed to explore the intramolecular cyclization of quinazolinones (**Table 8**).

Table 8 Screening halogenating reagent in basic conditions

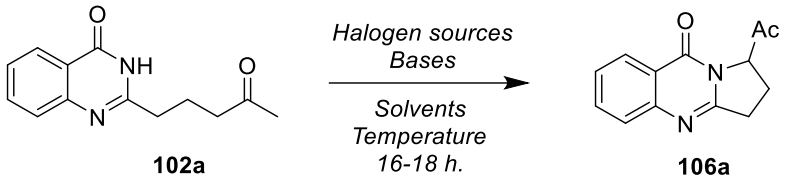


Entry	Conditions[a]	Result[b]
1	I_2 (1.5 equiv), K_2CO_3 (3.0 equiv), MeOH (0.1 M), 60 °C, 16 h	**106a** (32%)
2	NIS (1.5 equiv), K_2CO_3 (3.0 equiv), MeOH (0.1 M), 60 °C, 16 h	**106a** (22%)
3	NBS (1.5 equiv), K_2CO_3 (3.0 equiv), MeOH (0.1 M), 60 °C, 16 h	**106a** (15%)
4	NCS (1.5 equiv), K_2CO_3 (3.0 equiv), MeOH (0.1 M), 60 °C, 16 h	**106a** (trace)
[a] Reaction conditions: all reactions were performed with 0.5 mmol of **102a** [b] Isolated yield		

Based on Zhang's findings, we applied their procedure in our study which involved the screening of reactions to further explore the reaction conditions. The screening reaction was initiated by subjecting **102a** to I_2 (1.2 equiv) and K_2CO_3 (3.0 equiv) in MeOH, resulting in the desired product **106a** with a yield of 32% (entry 1). The halogen sources, NIS, NBS, and NCS, were subjected to investigation. The reaction with NIS and NBS exhibited a slight decrease in yield, resulting in 22% and 15%, respectively (entries 2 and 3). Conversely, the reaction involving NCS yielded a trace amount of the desired quinazolinone product (entry 4). Based on these findings, I_2 was chosen as the halogen source for this transformation.

In order to investigate the reaction conditions for the iodine-mediated intramolecular cyclization, a range of bases, solvents, and temperatures were examined (**Table 9**). 2-(4-oxopentyl)quinazolin-4(3*H*)-one (**102a**) was chosen as a model substrate.

Table 9 Optimization of reaction conditions of iodine-mediated intramolecular cyclization of 2-(4-oxopentyl)quinazolin-4(3*H*)-one (**102a**)[a]



102a **106a**

Entry	Halogen-source	Base	Solvent	Temp. (ºC)	Yield (%)[b]
1	I_2	K_2CO_3	MeOH	60	32
2	I_2	Cs_2CO_3	MeOH	60	39
3	I_2	K_3PO_4	MeOH	60	trace
4	I_2	^{t}BuOK	MeOH	60	trace
5	I_2	DBU	MeOH	60	0
6	I_2	Cs_2CO_3	DMSO	90	72
7	I_2	Cs_2CO_3	DMF	90	0
8	I_2	Cs_2CO_3	MeCN	90	trace
9	I_2	Cs_2CO_3	$CHCl_3$	90	0
10	I_2	Cs_2CO_3	DMSO	110	68
11	NIS	Cs_2CO_3	DMSO	90	45
12	NBS	Cs_2CO_3	DMSO	90	40
13	NCS	Cs_2CO_3	DMSO	90	0

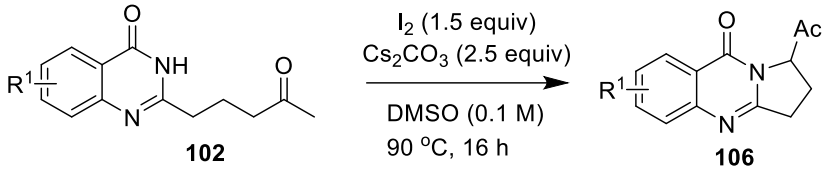
[a] Reaction conditions; all reactions were performed with 0.5 mmol of **102a**, 1.5 equiv of halogen source, 2.5 equiv of base, 5.0 mL of solvent, for 16-18 h.

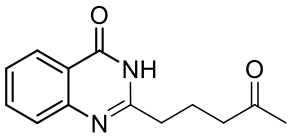
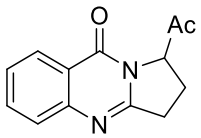
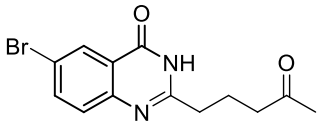
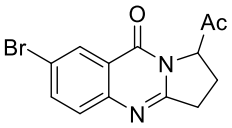
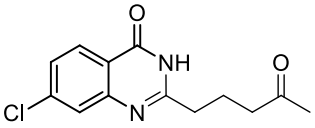
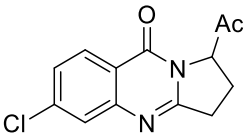
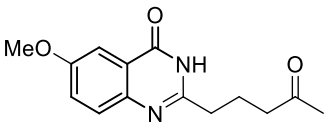
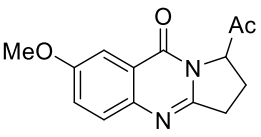
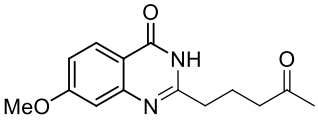
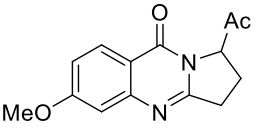
[b] Isolated yield.

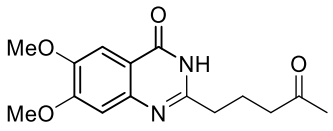
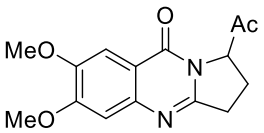
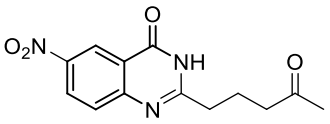
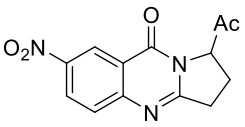
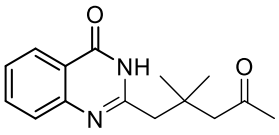
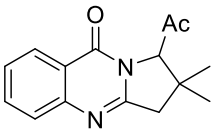
As mentioned in Table 8, the tricyclic quinazolinone product **106a** was obtained in 32% from modified Zhang's procedure using 1.5 equivalents of I_2 2.5 equivalents of K_2CO_3 in MeOH (entry 1). Next, we focused on various common bases. The yield of **106a** slightly increased to 39% by using Cs_2CO_3 (entry 2). Trace amounts of the desired product were obtained from the reaction using K_3PO_4 and *t*-BuOK as the bases (entries 3 and 4). This suggested that the solubility of bases in solvent influenced the reaction. Unfortunately, the organic base, DBU, was not suitable for the reaction giving no product (entry 5). We then attempted to increase the yield by exploring other common solvents and increasing the reaction temperature to 90 ^oC. Changing the solvents to DMSO dramatically increased the product yield by 72% (entry 6). Less polar solvents, such as DMF, MeCN, and $CHCl_3$ as solvents provided trace amounts or no product (entries 7–9). Additionally, the attempt to increase the product by elevating the reaction temperature failed. A comparable yield of product was obtained from the reaction with 110 ^oC in DMSO (entry 10). Lastly, halogenating reagents, such as NIS, NBS, and NCS, were subjected to the investigation. The yields were diminished to 45 and 40% from the reactions using NIS (entry 11) or NBS (entry 12), respectively. No product was obtained from NCS (entry 13).

With the optimized reaction conditions in hand, we then turned our focus on the substrate scope (**Table 10**).

Table 10 Substrate scopes of iodine-mediated intramolecular cyclization for the synthesis of deoxyvasicinone derivatives **106**



Entry	Quinazolinone intermediate	Deoxyvasicinone	Yield (%)[b]
1	 **102a**	 **106a**	72
2	 **102b**	 **106b**	59
3	 **102c**	 **106c**	64
4	 **102d**	 **106d**	60
5	 **102e**	 **106e**	60

6	 **102f**	 **106f**	66
7	 **102g**	 **106g**	trace
8	 **102h**	 **106h**	58

[a] Reaction conditions; all reactions were performed with 0.5 mmol of **102**, 1.5 equiv of I_2 , 2.5 equiv of Cs_2CO_3, 5.0 mL of DMSO under 90 ^oC, for 16-18 h.

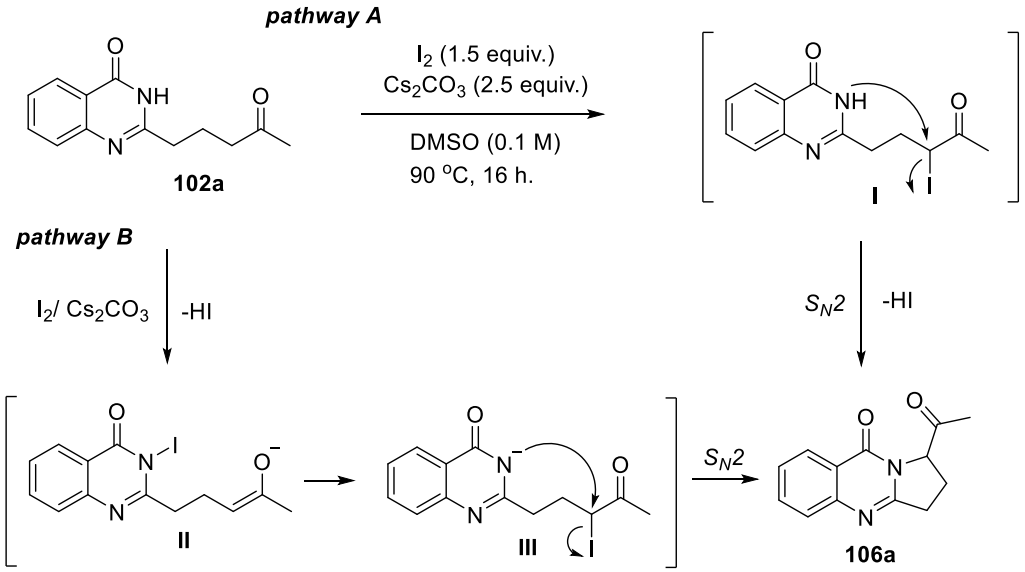
[b] Isolated yield.

For this study we mainly focused on the substituents on the aryl ring of quinazolinone **102** (**Table 10**). Halogen substituents on the aryl ring resulted in moderate yields of the desired product. The introduction of a 5-Br substituent on the aryl ring yielded 59% of the corresponding product **106b** (entry 2). Comparable yield of 64% was obtained from a reaction of 4-chloro substituted quinazolinone **106c** (entry 3). The substrates with electron-donating substituents also gave moderate yields of products. Both 5-OMe (entry 4) and 4-OMe (entry 5) quinazolinones yielded the same results, giving the corresponding products in 60% yield (**106d** and **106e**). Having two methoxy groups were also applicable to the reaction. The 4,5-diOMe quinazolinone provided product **106f** in 66% yield (entry 6). In addition, the presence of an electron-withdrawing group in the substrate resulted in a lower yield compared to those of substrates having an electron-donating group. The 5-NO_2 quinazolinone **106g** gave trace amount of product (**106g**, entry 7). Based on the results, we believed that the electronic effect of the aryl ring played a certain role in the nucleophilicity of primary amide nitrogen. Furthermore, a steric hindrance of the alpha carbon side chain affected

the reaction. The product was obtained in 58% from quinazolinone having geminal dimethyl substituents on the side chain (**106h**, entry 8) when comparing to 72% of product **106a** (**Table 10**).

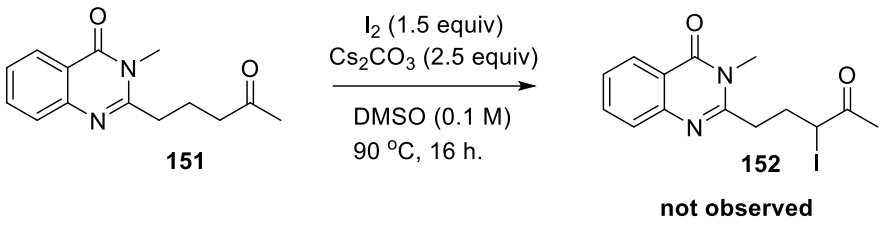
Next, we turned our interest to possible mechanism transformation. We initially suggested that iodoform **I**, resulting from iodination, served as a key intermediate for cyclization (**Scheme 44**, **pathway A**). The transformation began with the formation of iodoform **I** as a key intermediate from iodination of **102a** followed by an intramolecular cyclization providing desired quinazolinone **106a**. Alternatively, Komatsu and co-workers reported that they observed the presence of a N-iodinated intermediate during the cyclization of *N*-alkenylamides (Minakata *et al.*, 2006). Additionally, Zhang and co-workers reported the formation of a N-iodinated intermediate in the synthesis of 2-acylindoles (Gao et al., 2013). This intermediate was formed through intramolecular iodination. Based on these previous studies, we proposed an alternative mechanism for the reaction, as depicted in **Scheme 44** (**pathway B**). Initially, the nitrogen of the secondary amide undergoes iodination, forming the N-iodinated intermediate **II**. Subsequently, intramolecular iodination of the enolate leads to the formation of α-iodo ketone **III**, which smoothly undergoes intramolecular cyclization to yield acetyl deoxyvasicinone **106a**.

Scheme 44 Initially proposed mechanism of iodine-mediated intramolecular cyclization



In order to prove the proposed mechanism, we conducted a control experiment of the reaction using *N*-methylamide quinazolinone **151** as a substrate (**Scheme 45**). We introduced the methyl substituent on amide nitrogen. Hopefully, we could observe the formation of intermediate **151** to assure the possibility of the first mechanism pathway. However, iodinated intermediate **152** was not observed in the control experiment. We observed only substrate **151**.

Scheme 45 Iodine-mediated intramolecular cyclization of *N*-methylamide quinazolinone



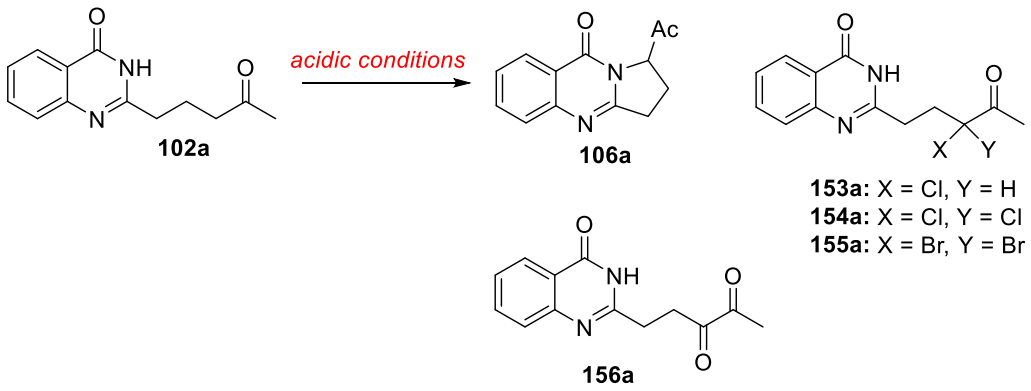
Based on the control experiment, the presence of the nitrogen atom in the 0amide moiety played a crucial role in facilitating this transformation. Therefore, we believed that the chemical transformation underwent through the second pathway.

We mentioned that the alpha-carbon could get activated by both basic and acidic conditions. We already described how the third rings of 2-acetyldeoxyvasicinone were installed via basic conditions. Next, we introduced the formation of the third ring from acidic conditions.

2.2.2.2 Synthesis of Deoxyvasicinone Derivatives under Acidic Conditions

We began the investigation with exploration of halogenation reagents in the presence of trifluoroacetic acid (**Table 11**). The exploration reaction with acidic conditions was begun with a modified condition reported from Marigo and co-workers (Marigo *et al*., 2004). Marigo showed that in the presence of 4,5-diphenylimidazolidine as a catalyst, NCS as a chlorinating agent and trifluoroacetic acid (TFA) as an additive, the corresponding *alpha*-chlorinated products were formed smoothly. Our first exploration, we used L-proline as catalyst. Unfortunately, we did not observe the expected tricyclic quinazolinone **106a**. We only observed the formation of mono chlorination at *alpha*-carbon (**153a**) together with the remaining starting material **102a** with the ratio of 0.3:1.0 (**102a**:**154a**) (entry 1). Interestingly, without L-proline, we did not observe **154a** or tricyclic **106a**. Instead, we observed the formation of geminal dichloro quinazolinone **154a** together with the remaining **102a** in the ratio of 0.4:1.0 (entry 2). These results indicated that having mono chloro substituent at the *alpha*-carbon enhanced reactivity in the formation of geminal dichlorination under the acid condition. Based on these results, we envisioned that the tricyclic **106a** could not be formed in the presence of acid, since we could not observe the **106a** from both entries 1 and 2. Presumably, in the TFA condition, the nitrogen of the quinazolinone ring would be low nucleophilicity due to protonation by acid media.

Table 11 Screening halogenating reagent in acidic conditions



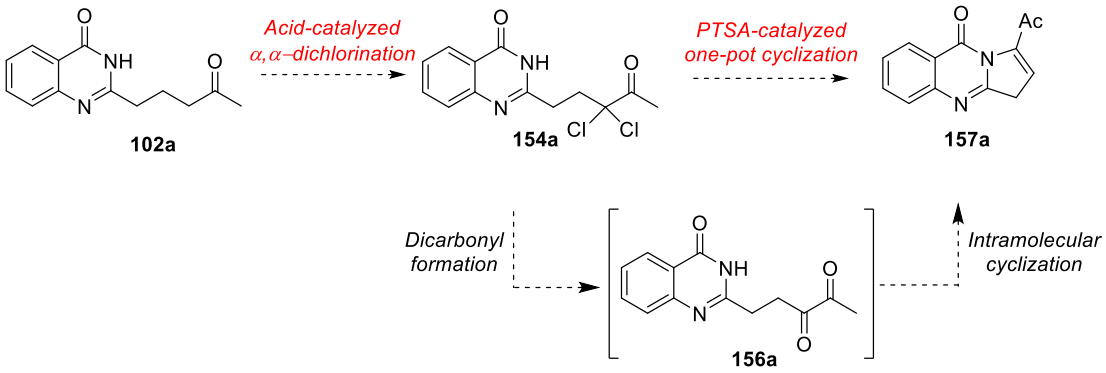
Entry	Conditions	Result
1	NCS (1.2 equiv), L-proline (20 mol%), TFA (20 mol%), CH_2Cl_2 (0.1 M), 40 °C, 16 h.	**102a** : **153** (1 : 0.3)
2	NCS (1.2 equiv), TFA (20 mol%), CH_2Cl_2 (0.1 M), 40 °C, 16 h.	**102a** : **154** (1: 0.4)
3	NCS (2.0 equiv), TFA (20 mol%), CH_2Cl_2 (0.1 M), 40 °C, 16 h.	**154a** (78%)[b]
4	NBS (2.0 equiv), TFA (20 mol%), CH_2Cl_2 (0.1 M), 40 °C, 16 h.	**155**a (66%)
5	NIS (2.0 equiv), TFA (20 mol%), CH_2Cl_2 (0.1 M), 40 °C, 16 h.	**156**a (65%)
6	I_2 (2.0 equiv), TFA (20 mol%), CH_2Cl_2 (0.1 M), 40 °C, 16 h.	**156**a (60%)

[a] Reaction conditions; all reactions were performed with 0.5 mmol of **102a**,

[b] Isolated yield for entries 3-6

Although we failed to form **106a**, we obtained a geminal dichloro adduct (entry 2). Luckily, we found that Sharon and co-workers used H_2SO_4 as an acid catalyst to transform geminal dichlorinated compound into 1,2-diketone (Sharon *et al.*, 1995). Based on Sharon's finding, we hypothesized that the α,α-dichlorinated quinazolinone **154a** could be converted into the 1,2-diketone **156a**, which would subsequently undergo intramolecular cyclization to form a 5-membered ring fused quinazolinone **157a** (**Scheme 46**).

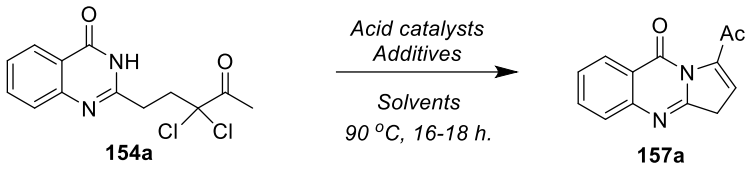
Scheme 46 The proposed alternative route to synthesize deoxyvasicinone derivatives under acidic conditions



With the idea of utilization of geminal dichloro quinazolinones, we then turned our focus on the reaction optimization in order to obtain the highest yield of geminal dichloro **154a**. The yield of geminal dichlorinated product **154a** increased to 78% by employing 2.0 equivalents of NCS (entry 3). Additionally, various halogen sources were investigated. Substituting NCS with NBS under similar conditions resulted in the formation of the geminal dibrominated product **155a** with a yield of 66% (entry 4). Surprisingly, the utilization of NIS or I_2 as halogen sources provided the 1,2-dicarbonyl product **156a** in 65% and 60% yield, respectively (entries 5 and 6).

After the condition of geminal dichloro formation was achieved, we explored reaction conditions for linear cyclization to obtain tricyclic quinazolinone **157a** including acid catalyst, additives, solvents, and reaction temperatures (**Table 12**). The 2-(3,3-dichloro-4-oxopentyl)quinazolin-4(3*H*)-one (**154a**) was selected as a model substrate.

Table 12 Optimization of reaction conditions for the acid-catalyzed intramolecular cyclization of 2-(3,3-dichloro-4-oxopentyl)quinazolin-4(3*H*)-one (**154a**) to form 1-acetylpyrrolo[2,1-b]quinazolin-9(3*H*)-one (**157a**)



Entry	Acid	Additive	Solvent	Yield (%)[c]
1[a]	H_2SO_4(98%)	-	DMSO	44
2	TFA	-	DMSO	41
3	HCl	-	DMSO	38
4	CH_3COOH	-	DMSO	trace
5	PTSA	-	DMSO	51
Entry	**Acid**	**Additive**	**Solvent**	**Yield (%)[c]**
6[b]	PTSA 50 mol%	H_2O 1.0 equiv	DMSO	57
7	PTSA	H_2O 1.0 equiv	DMF	37
8	PTSA	H_2O 1.0 equiv	MeCN	trace
9	PTSA	H_2O 1.0 equiv	$CHCl_3$	trace
10	PTSA	H_2O 1.0 equiv	toluene	0
11	PTSA	H_2O 1.0 equiv	dioxane	0
12	PTSA 50 mol %	H_2O 2.0 equiv	DMSO	62
13	PTSA 1.0 equiv	H_2O 2.0 equiv	DMSO	67
14	PTSA 1.0 equiv	H_2O 5.0 equiv	DMSO	55
15	PTSA 1.0 equiv	H_2O 10.0 equiv	DMSO	50

16	PTSA 1.0 equiv	H_2O 2.0 equiv	DMSO	48[d]

[a] Reaction condition: 0.5 mmol of **154a**, 50 mol % of acid catalyst without additive, 2.5 mL of solvent at 90 °C for 16-18 h.

[b] 1.0 equiv of H_2O was added as an additive.

[c] Isolated yield.

[d] Yield calculated over 2 steps from preparation of α,α-dichlorination without purification.

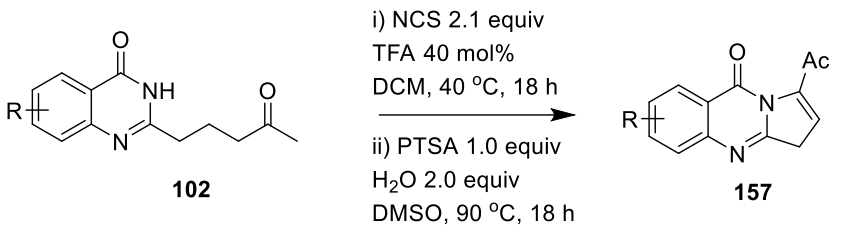
Firstly, we conducted an optimization of various acids. Gratefully, with modified Sharon's conditions, the use of H_2SO_4 as a catalyst in DMSO at 90 °C provided the desired product **157a** in a 44% yield (entry 1). The yields were slightly dropped when using TFA, HCl, and CH_3COOH as catalysts (entries 2–4). The reaction with TFA gave the desired product with a yield of 41% (entry 2). The use of HCl resulted in a decreased yield to 38% (entry 3). Surprisingly, a trace amount of **157a** was obtained when employing CH_3COOH as a catalyst (entry 4). Additionally, the increased yield of **157a**, reaching 51%, was achieved when using *p*-toluenesulfonic acid (PTSA) as the catalyst (entry 5). The addition of 1.0 equiv of H_2O as an additive was implemented to increase the polarity of the system (entry 6). This resulted in an improved yield of **157a**, reaching 57%. Other solvents were also investigated. The yield dramatically dropped to 37%, in DMF (entry 7), whereas a trace amount was obtained when using MeCN or $CHCl_3$ as solvents (entries 8 and 9). No product was observed in nonpolar solvents such as toluene and dioxane (entries 10 and 11). These observations suggested that the reaction required a high polarity of the solvent system. It can be presumed that the transition states that occurred during the reaction were high polarity.

Subsequently, the amount of the PTSA and H_2O was investigated. Upon adding 2.0 equivalents of H_2O, a slight increase in yield to 62% was observed (entry 12). Notably, when using 1.0 equivalent of PTSA and 2.0 equivalents of H_2O, the yield was further improved to 67% (entry 13). However, upon increasing the amount of H_2O to 5.0 or 10.0 equivalences, the yields dropped to 55% and 50%, respectively. Based on these results, the appropriate amount of H_2O played a crucial role in the cyclization process. In order to provide a practical procedure, we examined the reaction without

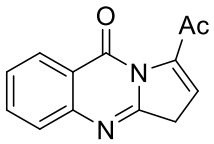
purifying the formation of the geminal dichlorination step resulting in a comparable yield of product, 48% (entry 16).

With the optimal reaction conditions, the substrate scopes were investigated from quinazolinone precursors **102** without purification of α,α-dichlorinated compounds (**Table 13**).

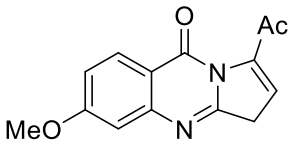
Table 13 Substrate scopes for an acid-catalyzed intramolecular of quinazolinone adducts **102** to form 5-membered ring fused quinazolinones **157**



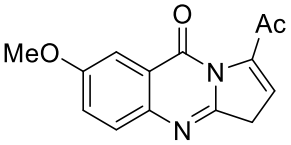
102 **157**



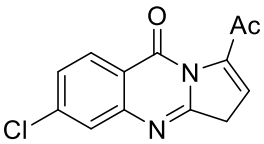
157a, 48%



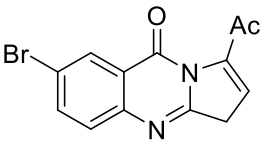
157b, 34%



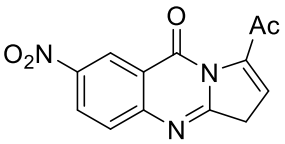
157c, 33%



157d, 34%



157e, 31%



157f, trace

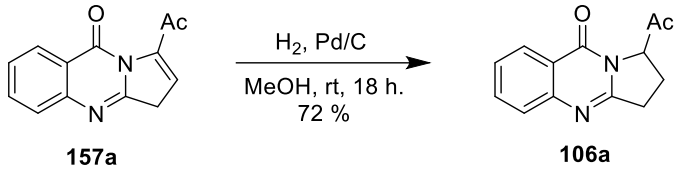
[a] Reactions were performed with 0.5 mmol of **102**.

The quinazolinone intermediate **102** with electron-donating groups on the aryl ring, 4-OMe and 5-OMe, provided the corresponding product **157b** in 34% and **157c** in 33%, respectively. Similarly, the presence of a 4-Cl substituent on the aryl ring resulted in a yield of 34% (**157d**). Notably, the introduction of a 5-Br substituent yielded a comparable result, 31% (**157e**). Trace amount of product was observed for the

quinazolinone intermediate with a 5-NO_2 group (**157f**). Although mostly isolated yield was low, this method provided accessibility to functional enriched tricyclic quinazolinone **157**.

Next, we preliminary confirmed the structure of **157a** which one oxidation state higher than that of **106a**. Nicely, **157a** underwent hydrogenation to yield the deoxyvasicinone derivative **106a** in 72% (**Scheme 47**).

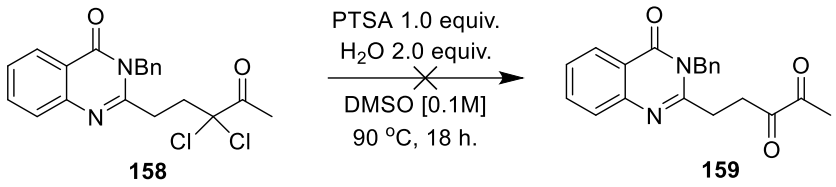
Scheme 47 The hydrogenation of 1-acetylpyrrolo[2,1-b]quinazolin-9(3*H*)-one (**157a**) to form 1-acetyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (**106a**)



157a 106a

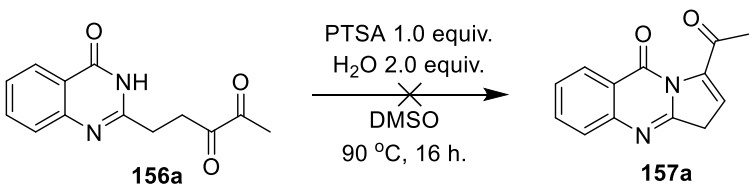
We turned our focus to chemical transformation. Based on the proposed formation of tricyclic quinazolinone **157a** (**Scheme 46**), the reaction was anticipated to proceed via the formation of the diketone intermediate **156a**. Therefore, two experiments were designed to preliminary investigate the reaction formation. Firstly, we designed to observe the diketone intermediate **159** (**Scheme 48**). Consequently, a *N*-benzylamide quinazolinone **158** was prepared. Hopefully, having benzyl protection group the nitrogen would not undergo cyclization. Unfortunately, we did not observe the formation of vicinal diketone **159**. We only observed substrate **158**.

Scheme 48 Acid-catalyzed intramolecular cyclization of 3-benzyl-2-(3,3-dichloro-4-oxopentyl)quinazolin-4(3*H*)-one (**158**)



Secondly, in an attempt to support the hypothesis that diketone could serve as an intermediate for cyclization, we conducted experiments using diketone **156a** ,prepared from the procedure as shown in entry 5 of Table 11, as a model substrate (**Scheme 49**). However, under similar conditions, the formation of the corresponding quinazolinone **157a** did not occur. The results indicated that the reaction did not proceed through an vicinal diketone intermediate.

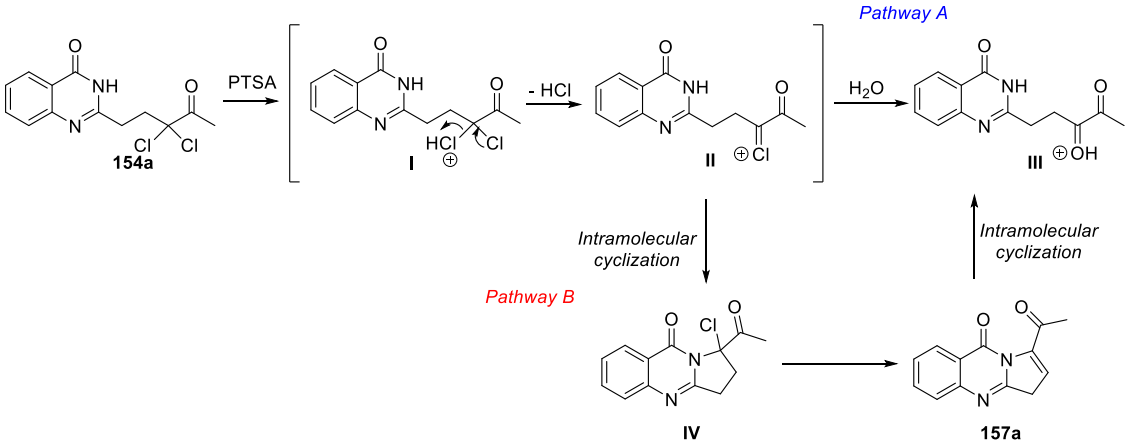
Scheme 49 Attempted acid-catalyzed intramolecular cyclization of 5-(4-oxo-3,4-dihydroquinazolin-2-yl)pentane-2,3-dione (**156a**)



According to Kappe's work, they reported the formation of C–N bond from di-halogenated compound and secondary amine under acidic conditions (Kappe *et al*., 1968). Inspired by their work together with our control experiments, we proposed a plausible mechanism for the reaction (**Scheme 50**). In acidic conditions, the chlorine atom possibly undergoes protonation and subsequent elimination, leading to the

formation of a chloronium ion (**II**). There are two plausible pathways for cyclization: **pathway A** involves water attacking the chloronium ion and subsequent elimination of chloride ion due to the result of the presence of water, resulting in the formation of an oxonium intermediate (**III**). This intermediate rapidly undergoes cyclization facilitated by the nitrogen atom, followed by dehydration to yield deoxyvasicinone **157a**. **Pathway B** involves the cyclization of the chloronium ion with the nitrogen atom of the amide moiety, leading to the formation of intermediate **IV**. This intermediate can then undergo chloride ion elimination forming an iminium followed by tautomerization to yield the desired product **157a**.

Scheme 50 The plausible mechanism of an acid-catalyzed intramolecular cyclization of **154a**



CHAPTER 3

CONCLUSION

We successfully synthesized small and medium-sized ring fused quinazolinones through a series of reactions starting from quinazolinone intermediates. Our methodology relied on a Cu(I)-catalyzed domino reaction of 2-iodobenzamides and cyclic enaminones. The domino transformation involved C(aryl)–N bond formation, intramolecular Michael addition, and retro-Mannich reaction. To facilitate the cyclization process and formation of the desired ring fused quinazolinones, we strategically positioned functionalized amine and ketone groups on the key intermediates. These intermediates readily underwent direct cyclization, resulting in the formation of small and medium-sized ring fused quinazolinones. Specifically, the synthesis of 11-membered ring fused quinazolinones was achieved by employing quinazolinone intermediates having *tert*-butyl ethylcarbamate as a nitrogen substituent. The 11-membered ring urea moiety was synthesized via direct cyclization using 1,1'-carbonyldiimidazole (CDI) of a diamino intermediate generated via reductive amination and Boc-deprotection. This synthetic strategy yielded their analogues in moderate yields. Additionally, we synthesized deoxyvasicinone derivatives, which are small-sized ring fused quinazolinones from *N*-H quinazolinones. We obtained two deoxyvasicinone analogues through cyclization performed under basic and acidic conditions. The formations of a small-sized ring were achieved by intramolecular cyclizations. Analogues of 1-acetyl-2,3-dihydro pyrrolo[2,1-b]quinazolin-9(1*H*)-one were synthesized by direct cyclization in the presence of iodine (I_2) under basic conditions, providing moderate yields for a variety of substrates. This reaction proceeded via an N–I quinazolinone intermediate, followed by intramolecular cyclization. This synthetic strategy yielded their analogues in moderate to good yields. Furthermore, analogues of 1-acetyl pyrrolo[2,1-b]quinazolin-9(3*H*)-one were synthesized through a two-step procedure. The process began with α,α-dichlorination under acidic conditions, followed by intramolecular

C–N bond cyclization in the presence of *para*-toluene sulfonic acid (PTSA) as a catalyst. This synthetic procedure yielded their analogues in moderate yields. Notably, purification of the intermediate was unnecessary for this approach. Consequently, this method provided an efficient and selective synthesis of the desired ring-fused quinazolinone compounds.

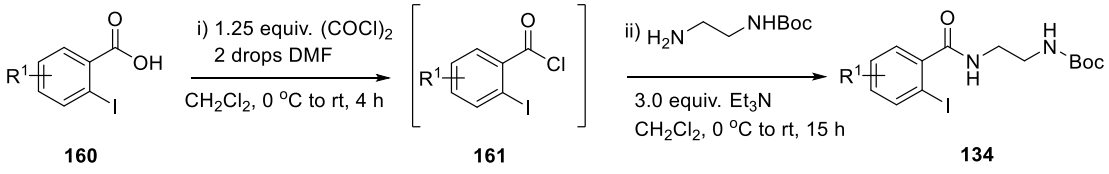
CHAPTER 4

EXPERIMENTAL

4.1 General Information

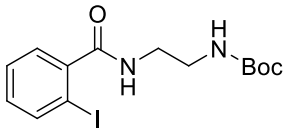
Solvents for extraction and column chromatography were distilled at their boiling point ranges prior to use. Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} (Merck) and was visualized by fluorescence quenching under UV light. Column chromatography was performed on SilicaFlash® G60 (70-230 Mesh). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a 300 MHz Bruker FTNMR Ultra Shield spectrometer using tetramethyl silane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ 0.00) and coupling constants are reported as Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra (IR) were measured on a Thermo Scientific Nicolet iS5 FTIR Spectrometer and recorded on a wavenumber (cm^{-1}). High-resolution mass spectra (HRMS) were obtained by the ESI ionization sources.

4.2 General Procedure A: Synthesis of 2-Iodobenzamides

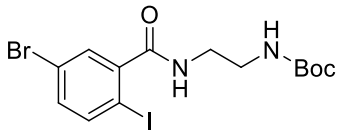


Prepared according to the literature procedure reported by Kitching (Kitching *et al.*, 2012). A flame-dried round bottom flask was charged with 1.0 equiv. of 2-iodobenzoic acid derivatives in CH_2Cl_2 (0.3 M) and DMF (2 drops), followed by the addition of 1.25 equiv. of oxalyl chloride at 0 °C. The reaction mixture was allowed to stir at room temperature for 4 h. 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-

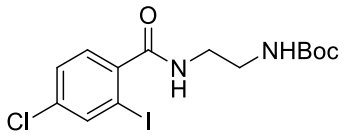
amine (1.5 equiv.) and triethylamine (3.0 equiv.) was added at 0 ^{o}C. The reaction mixture was allowed to stir at room temperature for 15 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to afford the title compound.



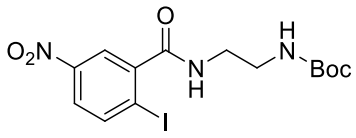
***tert*-butyl 2-(2-iodobenzamido)ethylcarbamate (134a).** Prepared according to general procedure A. Yield 88% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.41-7.29 (m, 2H), 7.13-7.02 (m, 1H), 6.58 (brs, 1H), 5.10 (brs, 1H), 3.55 (q, *J* = 5.6 Hz, 2H), 3.39 (q, *J* = 5.6 Hz, 2H), 1.41 (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.



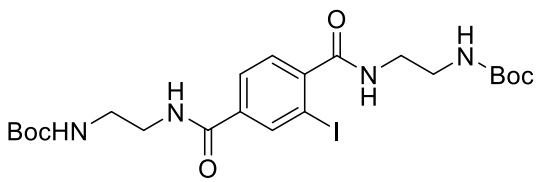
***tert*-butyl 2-(5-bromo-2-iodobenzamido)ethylcarbamate (134b).** Prepared according to general procedure A. Yield 75% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.55 (brs, 1H), 4.97 (brs, 1H), 3.56 (q, *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 (134c)**. 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.

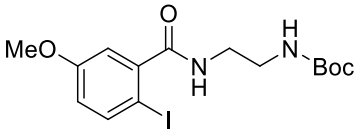


***tert*-butyl 2-(2-iodo-5-nitrobenzamido)ethylcarbamate (134d)**. Prepared according to general procedure A. Yield 78% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 2.6 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.91 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.96 (brs, 1H), 5.07 (brs, 1H), 3.59 (q, *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.

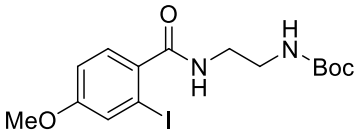


***tert*-butyl 2-(2-iodo-4-(2-(*tert*-butoxycarbonylamino)ethylcarbamoyl)benzamido) ethylcarbamate (134e)** Prepared according to general procedure A. Yield 68% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.60 (brs, 1H), 8.45 (brs, 1H), 8.26 (s,

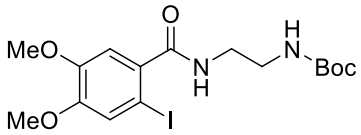
1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 6.96-6.82 (m, 2H), 3.38-3.20 (m, 4H), 3.19-3.06 (m, 4H), 1.38 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 169.0, 164.8, 156.2, 156.1, 145.6, 138.0, 136.7, 128.2, 127.3, 93.7, 78.2, 39.8, 39.7, 31.1, 28.7; IR (thin film) ν 3345, 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 (134f)**. 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.

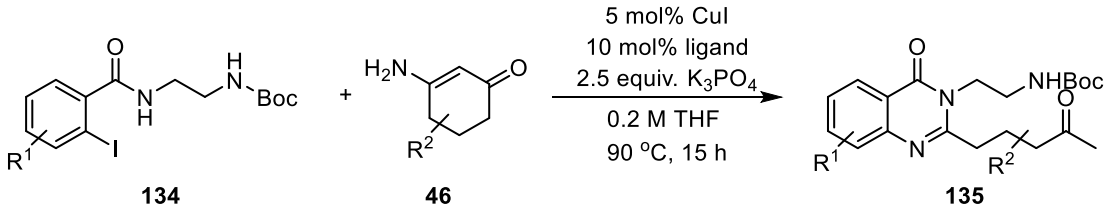


***tert*-butyl 2-(2-iodo-4-methoxybenzamido)ethylcarbamate (134g)**. Prepared according to general procedure A. Yield 78% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38, (d, *J* = 2.4 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.43 (brs, 1H), 5.02 (brs, 1H), 3.80 (s, 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.



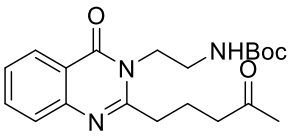
***tert*-butyl 2-(2-iodo-4,5-dimethoxybenzamido)ethylcarbamate (134h).** Prepared according to general procedure A. Yield 77% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.01 (s, 1H), 6.46 (brs, 1H), 5.01 (brs, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.57 (q, *J* = 5.5 Hz, 2H), 3.41 (q, *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.

4.3 General Procedure B: Synthesis of Quinazolinones Derivatives

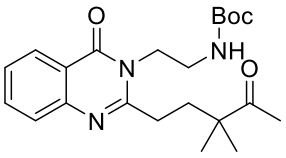


Prepared according to literature procedure reported by Songsichan (Songsichan *et al*., 2014). A sealed tube equipped with a magnetic stirring bar was charged with 2-iodobenzamides **134** (0.5 mmol), cyclic enaminones **46** (0.6 mmol), CuI (5 mol%), 1,2-*trans*-diaminocyclohexane (10 mol%) and K_3PO_4 (1.25 mmol) in THF (2.5 mL). The resulting mixture was stirred at 90^{o}C for 15 h. After that, the resulting mixture was cooled to room temperature, and quenched with sat. NH_4Cl and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered

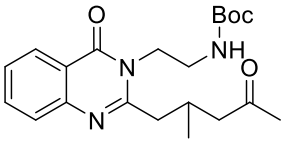
and concentrated. The residue was purified by column chromatography (5:1 CH_2Cl_2:EtOAc) to provide quinazolinone products **135**.



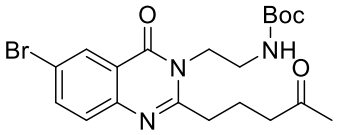
***tert*-butyl 2-(4-oxo-2-(4-oxopentyl)quinazolin-3(4*H*)-yl) ethyl-carbamate (135a).** Prepared according to general procedure B. Yield 88% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 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.



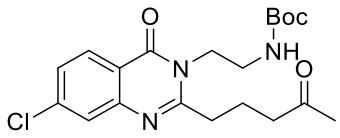
***tert*-butyl 2-(2-(3,3-dimethyl-4-oxopentyl)-4-oxoquinazolin-3(4*H*)yl)ethylcarbamate (135b)**. Prepared according to general procedure B. Yield 74% as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.9 Hz, 1H), 7.72 (t, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 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.



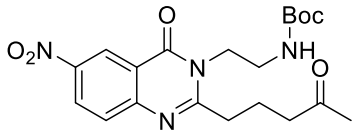
***tert*-butyl 2-(2-(2-methyl-4-oxopentyl)-4-oxoquinazolin-3(4*H*)-yl)ethylcarbamate (135d)**. Prepared according to general procedure B. Yield 77% as a pale brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (d, *J* = 7.6 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 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.



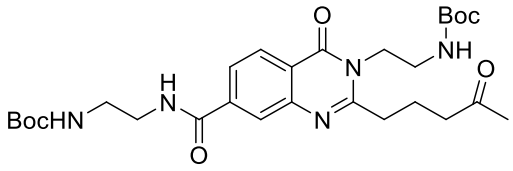
***tert*-butyl 2-(6-bromo-4-oxo-2-(4-oxopentyl)quinazolin-3(4*H*)-yl)ethylcarbamate (135e)**. Prepared according to general procedure B. Yield 80% as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 1.9 Hz, 1H), 7.78 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 5.02 (brs, 1H), 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.



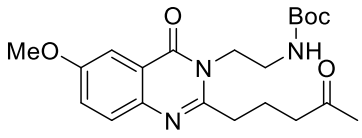
***tert*-butyl 2-(7-chloro-4-oxo-2-(4-oxopentyl)quinazolin-3(4*H*)-yl)- ethylcarbamate (135f)**. Prepared according to general procedure B. Yield 70% as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 1.9 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.9 Hz, 1H), 5.03 (brs, 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.



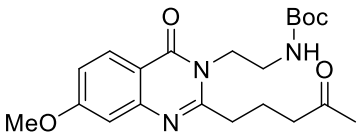
***tert*-butyl 2-(6-nitro-4-oxo-2-(4-oxopentyl)quinazolin-3(4*H*)-yl)ethylcarbamate (135g)**. Prepared according to general procedure B. Yield 54% as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (d, *J* = 2.6 Hz, 1H), 8.50 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 4.99 (brs, 1H), 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.



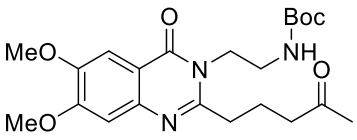
***tert*-butyl 2-(4-oxo-2-(4-oxo-pentyl)-7-(2-(*tert*-butoxycarbonylamino)ethylcarbamoyl)quinazolin-3(4H)-yl)-ethylcarbamate (135h)** Prepared according to general procedure B. Yield 77% as a dark brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.99 (s, 1H), 7.80 (d, *J* = 7.9 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.



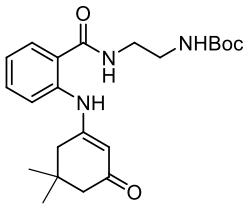
***tert*-butyl 2-(6-methoxy-4-oxo-2-(4-oxopentyl)quinazolin-3(4*H*)-yl)ethylcarbamate (135i)**. Prepared according to general procedure B. Yield 78% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.9 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.27 (dd, *J* = 8.8, 2.9 Hz, 1H), 5.14 (brs, 1H), 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(4*H*)-yl)ethylcarbamate (135j)**. Prepared according to general procedure B. Yield 74% as a white solid. ^{1}H 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.



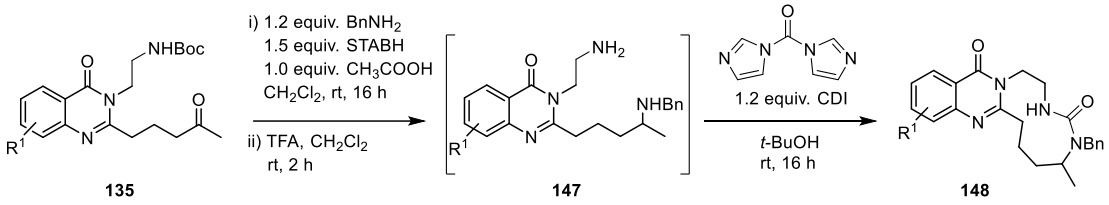
***tert*-butyl 2-(6,7-dimethoxy-4-oxo-2-(4-oxopentyl)quinazolin-3(4*H*)-yl)ethylcarba-mate (135k)**. Prepared according to general procedure B. Yield 80% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 6.88 (s, 1H), 5.41 (brs, 1H), 4.18 (t, *J* = 5.9 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 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)ethylcarbamate** (**135l**). Prepared according to general procedure B. Yield 75% 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.

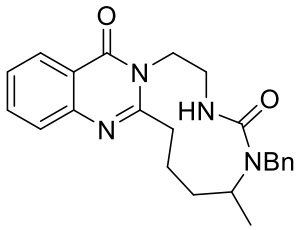
4.4 Synthesis of Quinazolinone-fused eleven membered ring ureas

General Procedure C: Synthesis of Quinazolinone-fused eleven membered ring ureas

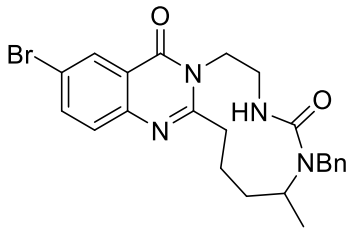


To a solution of quinazolinone **135** (0.6 mmol) and benzylamine (0.9 mmol) in CH_2Cl_2 (6 mL) was added sodium triacetoxyborohydride (STABH, 1.2 mmol) and acetic acid (18 µL). The resulting mixture was stirred at room temperature under a N_2 atmosphere for 24 h. After that, the resulting mixture was quenched by adding 1 N NaOH and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Then, the crude mixture in CH_2Cl_2 (3 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at room

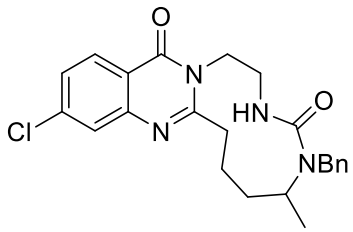
temperature under a N_2 atmosphere for 2 h. After that, the resulting mixture was quenched by adding 1 N NaOH and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give amine crude. Then, the crude mixture in ^{t}BuOH (30 mL) was stirred at room temperature. CDI (0.72 mmol) was added in reaction mixture at room temperature and stirred at room temperature for 18 h. After that, *t*BuOH was evaporated in vaccu. The resulting mixture was quenched with sat. NH_4Cl and extracted with EtOAc (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (9:1 EtOAc:MeOH) to provide quinazolinone-fused eleven membered ring ureas **148**.



5-benzyl-6-methyl-2,3,6,7,8,9-hexahydro-[1,3,6]triazacycloundecino[7,6-*b*]quinazoline-4,15(1*H*,5*H*)-dione (**148a**). Yield 60% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD 2 drops) δ 8.25 (d, *J* = 7.5 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.42-7.45 (m, 5H), 4.78 (d, *J* = 14.7 Hz, 1H), 4.58 (d, *J* = 14.4 Hz, 1H), 4.45 (m, 1H), 4.30 (d, *J* = 14.7 Hz, 1H), 4.20-4.05 (m, 2H), 3.53-3.38 (m, 1H), 3.36-3.20 (m, 1H), 2.96-2.80 (m, 1H), 2.63-2.52 (m, 1H), 2.45-2.28 (m, 1H), 1.70-1.52 (m, 1H), 1.51-1.38 (m, 1H), 1.20-1.11 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD 2 drops) δ 162.7, 158.2, 158.0, 147.3, 139.0, 134.5, 129.0, 128.6(3C), 127.7, 126.8(2C), 126.5, 120.2, 54.5, 52.8, 43.8, 40.3, 31.4, 30.8, 24.5, 20.1; IR (thin film) ν 3351, 2931, 1661, 1537, 1453, 1305, 1167, 769, 728, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{26}N_4O_2$ 391.2129, found 391.2129.

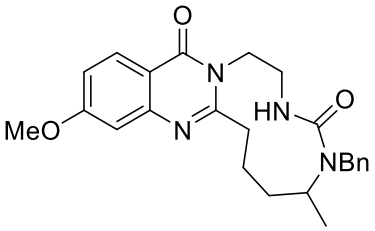


5-benzyl-13-bromo-6-methyl-2,3,6,7,8,9-hexahydro-[1,3,6]triazacycloundecino [7,6-*b*]quinazoline-4,15(1*H*,5*H*)-dione (**148b**). Yield 65% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 2.4 Hz, 1H), 7.68 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.35-7.17 (m, 5H), 4.69 (d, *J* = 14.7, 1H), 4.46 (d, *J* = 14.4 Hz, 1H), 4.21 (d, *J* = 14.7 Hz, 1H), 4.15-3.93 (m. 2H), 3.48-3.29 (m, 1H), 3.28-3.11 (m, 1H), 2.89-2.72 (m, 1H), 2.53-2.40 (m. 1H), 2.34-2.18 (m, 1H), 1.60-1.30 (m, 2H), 1.18-1.00 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 158.4, 158.1, 146.1, 139.0, 137.5, 129.2, 129.0(2C), 128.7(2C), 128.6, 127.7, 121.5, 119.8, 54.4, 52.8, 43.9, 40.2, 31.4, 30.7, 24.4, 20.1; IR (thin film) ν 3369, 2931, 1665, 1618, 1541, 1467, 1330, 1182, 830, 725, 694 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{25}BrN_4O_2$ 469.1234, found 469.1239

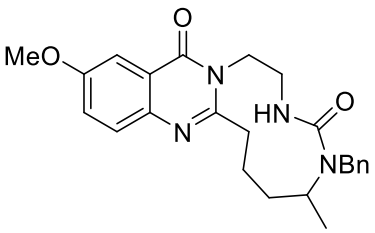


5-benzyl-12-chloro-6-methyl-2,3,6,7,8,9-hexahydro-[1,3,6]triazacycloundecino-[7,6-*b*]quinazoline-4,15(1*H*,5*H*)-dione (**148c**). Yield 67% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD 2 drops) δ 8.05 (d, *J* = 8.7 Hz, 1H), 7.51 (s, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.26-7.18 (m, 5H), 4.69 (d, *J* = 14.7 Hz, 1H), 4.45 (d, *J* = 14.4 Hz, 1H), 4.16 (d, *J* = 14.7 Hz, 1H), 4.04 (d, *J* = 14.4 Hz, 1H), 4.00-3.91 (m, 1H), 3.50-3.33 (m, 1H), 3.32-3.26 (m, 1H), 2.89-2.70 (m, 1H), 2.57-2.42 (m. 1H), 2.28-2.09 (m, 1H), 1.55-1.35 (m, 2H), 1.12-1.02 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD 2 drops) δ 162.1, 159.5, 158.3, 148.1, 140.6, 138.8, 128.8, 128.5(3C), 128.1, 127.6, 127.1, 126.1, 118.4, 54.2, 52.1, 43.9, 40.0, 31.4, 30.5, 24.3,

19.7; IR (thin film) ν 3366, 2923, 1674, 1618, 1578, 1544, 1306, 1164, 781, 742, 696 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{25}ClN_4O_2$ 425.1739, found 425.1739.

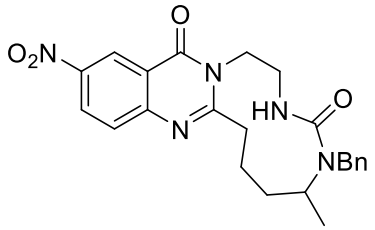


5-benzyl-12-methoxy-6-methyl-2,3,6,7,8,9-hexahydro-[1,3,6]triazacycloundecino-[7,6-*b*]quinazoline-4,15(1*H*,5*H*)-dione (**148d**). Yield 57% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.0 Hz, 1H), 7.41-7.22 (m, 5H), 6.99 (d, *J* = 9.0 Hz, 1H), 6.96 (s, 1H), 4.74 (d, *J* = 14.7 Hz, 1H), 4.54 (d, *J* = 14.7 Hz, 1H), 4.50-4.42 (m, 1H), 4.29 (d, *J* = 14.7 Hz, 1H), 4.18-4.01 (m, 2H), 3.88 (s, 3H), 3.52-3.36 (m, 1H), 3.34-3.20 (m, 1H), 2.92-2.80 (m, 1H), 2.60-2.50 (m, 1H), 2.51-2.45 (m, 1H), 2.40-2.23 (m, 1H), 1.68-1.40 (m, 2H), 1.20-1.10 (m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 162.0, 158.7, 158.2, 149.4, 139.1, 129.0(2C), 128.6(2C), 128.3, 127.7, 116.9, 113.8, 107.0, 55.8, 54.4, 52.8, 43.6, 40.4, 31.4, 30.9, 24.5, 20.1; IR (thin film) ν 3348, 2943, 1662, 1607, 1548, 1486, 1158, 1035, 779, 742, 700 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{28}N_4O_3$ 421.2239, found 421.2234.



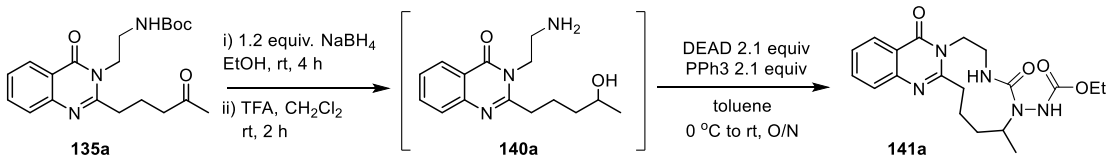
5-benzyl-13-methoxy-6-methyl-2,3,6,7,8,9-hexahydro-[1,3,6]triazacyclo-undecino[7,6-*b*]quinazoline-4,15(1*H*,5*H*)-dione (**148e**). Yield 55% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD 2 drops) δ 7.56-7.52 (m, 2H), 7.51 (s, 1H), 7.40-7.20 (m, 5H), 4.74 (d, *J* = 14.7 Hz, 1H), 4.54 (d, *J* = 14.1 Hz, 1H), 4.25 (d, *J* =

14.7, 1H), 4.20-4.39 (m, 2H), 3.89 (S, 3H), 3.58-3.30 (m, 1H), 3.40-3.25 (m, 1H), 2.94-2.80 (m, 1H), 2.63-2.50 (m, 1H), 2.35-2.14 (m, 1H), 1.63-1.40 (m, 2H), 1.38-1.20 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD 2 drops) δ 162.5, 158.4, 158.3, 155.7, 141.8, 138.9, 128.8(2C), 128.5(2C), 128.1, 127.6, 125.0, 120.7, 105.8, 55.8, 54.3, 52.3, 44.0, 40.0, 31.0, 30.7, 24.5, 19.8; IR (thin film) ν 3359, 2938, 1654, 1540, 1491, 1454, 1359, 1029, 831, 728, 629 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{28}N_4O_3$ 421.2234, found 421.2239.



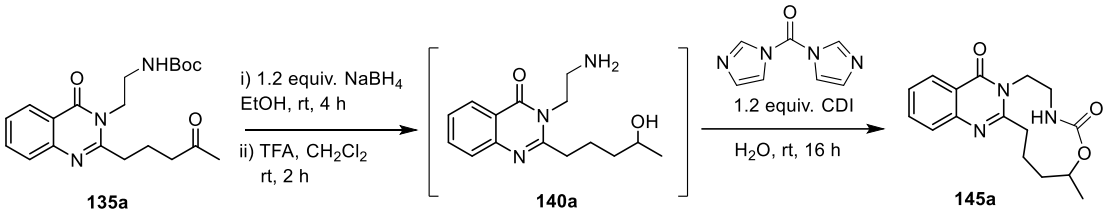
5-benzyl-6-methyl-13-nitro-2,3,6,7,8,9-hexahydro-[1,3,6]triazacycloundecino[7,6-*b*]quinazoline-4,15(1*H*,5*H*)-dione (**148f**). Yield 48% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.05 (d, *J* = 2.4 Hz, 1H), 8.46 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.43-7.27 (m, 5H), 4.80 (*J* = 14.4 Hz, 1H), 4.59 (d, *J* = 14.4 Hz, 1H), 4.45-4.52 (m, 1H), 4.26 (d, *J* = 14.4 Hz, 1H), 4.30-4.11 (m, 2H), 3.54-3.40 (m, 1H), 3.38-3.21 (m, 1H), 3.38-3.21 (m, 1H), 3.60-2.88 (m, 1H), 2.68-2.57 (m, 1H), 1.70-1.51 (m, 2H), 1.20-1.10 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.8, 161.0, 158.3, 151.1, 144.4, 140.4, 128.2, 128.0(3C), 127.6, 126.6, 122.4, 119.5, 52.0(2C), 45.1, 38.9, 31.3(2C), 24.2, 19.6; IR (thin film) ν 3362, 2933, 1673, 1617, 1560, 1522, 1338, 1158, 848, 723, 695 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{31}N_3O_4$ 436.1979, found 439.1974.

4.5 Synthesis of ethyl (6-methyl-4,15-dioxo-1,2,3,4,7,8,9,15-octahydro-[1,3,6]triaza-cycloundecino[7,6-*b*]quinazolin-5(6*H*)-yl)carbamate



To a solution of quinazolinone **135a** (0.6 mmol) in EtOH (6 mL) was added sodium borohydride (0.72 mmol). The resulting mixture was stirred at room temperature under a N_2 atmosphere for 4 h. After that, EtOH was removed by evaporation in vacuum. Then, the residue was quenched by NH_4Cl and extracted with EtOAc (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Then, the crude mixture in CH_2Cl_2 (3 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at room temperature under N_2 atmosphere for 2 h. After that, the resulting mixture was quenched by adding 1 N NaOH and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give amine crude. Then, the crude mixture in toluene (12 mL) was stirred at 0 ^oC. DEAD (1.26 mmol) and PPh_3 (1.26 mmol) were added to the reaction mixture and stirred at 0^o C to rt for 18 h. After that, the organic solvent was concentrated under a vacuum, quenched with NH_4Cl, and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to provide undesired product **141a** as a white solid in 65%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 5.47 (s, 1H), 4.50-4.30 (m, 3H), 3.94-3.86 (m, 1H), 3.70-3.60 (m, 2H), 3.02-2.90 (m, 2H), 2.07-1.92 (m, 4H), 1.67-1.59 (m, 2H), 1.43 (t, *J* = 13.2 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 160.7, 159.1, 157.3, 147.1, 134.5, 126.8, 126.6, 126.6, 120.1, 68.4, 66.9, 42.8, 41.2, 38.3, 34.6, 23.7, 23.2, 14.3; IR (thin film) ν 3045, 2928, 1707, 1665, 1442, 1310, 1128, 770 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{25}N_5O_4$ 388.1979, found 388.1980.

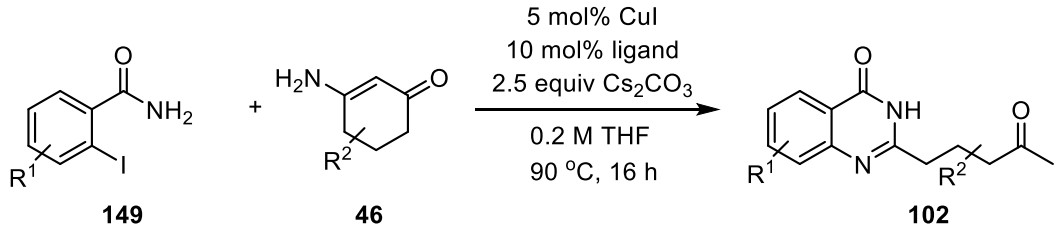
4.6 Synthesis of 6-methyl-2,3,6,7,8,9-hexahydro-15*H* [1]oxa[3,6]diazacyclo-undecino[7,6-*b*]quinazoline-4,15(1*H*)-dione (145a)



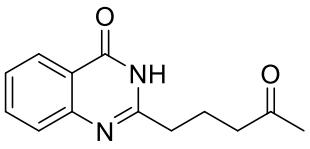
To a solution of quinazolinone **135a** (0.6 mmol) in EtOH (6 mL) was added sodium borohydride (0.72 mmol). The resulting mixture was stirred at room temperature under a N_2 atmosphere for 4 h. After that, EtOH was removed by evaporation in vacuum. Then, the residue was quenched by NH_4Cl and extracted with EtOAc (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Then, the crude mixture in CH_2Cl_2 (3 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at room temperature under N_2 atmosphere for 2 h. After that, the resulting mixture was quenched by adding 1 N NaOH and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give amine crude. Then, the crude mixture in water (30 mL) was stirred at room temperature. CDI (0.72 mmol) was added to the reaction mixture and stirred at room temperature for 18 h. After that, the reaction mixture was filtered; the precipitate obtained was washed with cold water and dried to provide quinazolinone-fused cyclic carbamate **145a** as a white solid in 56%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 (d, J = 7.5 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 6.35 (s, 1H), 4.04-4.00 (m, 2H), 3.68-3.61 (m, 1H), 3.29-3.24 (m, 2H), 2.96-2.72 (m, 2H), 2.19-1.70 (m, 2H), 1.47-1.44 (m, 2H), 1.06 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.4, 158.4, 157.7, 147.1, 134.2, 126.7, 126.1, 126.1, 120.0, 65.6, 43.5, 38.5, 37.8, 33.9, 23.8, 23.1; IR (thin film) ν 3332, 2969, 1650, 1613, 1098, 772, 695 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{19}N_3O_3$ 302.1505, found 302.1504.

4.7 Synthesis of 4(3*H*)-quinazolinone intermediates 102

General Procedure D

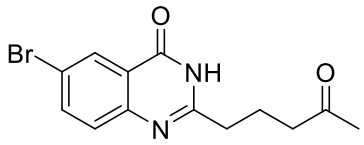


A sealed tube equipped with a magnetic stirring bar was charged with 2-iodobenzamides **149** (0.5 mmol), cyclic-enaminones **46** (0.6 mmol), CuI (5 mol%), 1,10-phenanthrolene (10 mol%) and Cs_2CO_3 (1.25 mmol) in THF (2.5 mL). The resulting mixture was stirred at 90^{o}C for 16 h. After that, the resulting 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 product **102**.



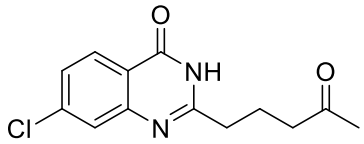
2-(4-oxopentyl)quinazolin-4(3*H*)-one (102a).

Prepared according to general procedure D. Yield 58% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 1.2, 8.1 Hz, 1H), 7.74 (dt, *J* = 1.2, 8.1 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.45 (dt, *J* = 1.2, 8.1 Hz, 1H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.23-2.10 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 164.4, 156.1, 149.4, 134.9, 127.3, 126.6, 126.4, 120.6, 42.6, 34.8, 30.1, 21.3. These data matched to the literature values (Shen *et al*., 2016).



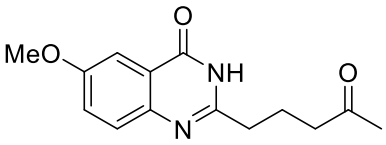
6-bromo-2-(4-oxopentyl)quinazolin-4(3*H*)-one (102b)

Prepared according to general procedure D. Yield 52% as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.4 Hz, 1H), 7.82 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 2.74 (t; *J* = 7.2 Hz, 2H), 2.63 (t; *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 2.12 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 208.0, 160.7, 157.8, 147.8, 137.0, 129.2, 127.8, 122.5, 118.3, 41.7, 33.6, 29.8, 20.6; IR (thin film) ν 3158, 3028, 2889, 1677, 1613, 1462, 1163, 837, 602 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{13}H_{13}BrN_2O_2$ 331.0053, found 331.0053.



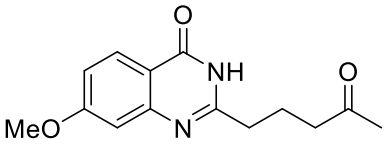
7-chloro-2-(4-oxopentyl)quinazolin-4(3*H*)-one (102c)

Prepared according to general procedure D. Yield 62% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.85 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 1.2 Hz, 1H), 7.41 (dd, *J* = 1.2, 8.4 Hz, 1H), 2.79 (t; *J* = 7.2 Hz, 2H), 2.63 (t; *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 2.20-2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 163.6, 157.4, 150.4, 141.3, 127.9, 127.3, 127.0, 119.2, 42.4, 34.6, 30.2, 21.0; IR (thin film) ν 3324, 2942, 2831, 1677, 1603, 1447, 1021, 630 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{13}ClN_2O_2$ 265.0741, found 265.0744.



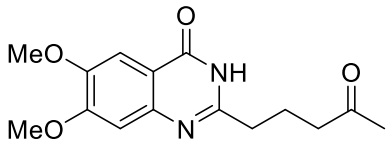
6-methoxy-2-(4-oxopentyl)quinazolin-4(3*H*)-one (102d)

Prepared according to general procedure D. Yield 55% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.63 (m 2H), 7.36 (dd, *J* = 2.7, 9.0 Hz, 1H), 3.93 (s, 3H), 2.78 (t; *J* = 7.2 Hz, 2H), 2.64 (t; *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 2.16-2.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 163.7, 158.3, 153.6, 144.0, 128.9, 125.1, 121.5, 105.9, 56.0, 42.5, 34.6, 30.2, 21.3; IR (thin film) ν 3161, 2941, 2897, 1671, 1621, 1489, 1252, 836, 650 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{16}N_2O_3$ 261.1234, found 265.1235.



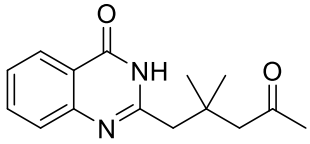
7-methoxy-2-(4-oxopentyl)quinazolin-4(3*H*)-one (102e)

Prepared according to general procedure D. Yield 56% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.57 (s, 1H), 8.16 (d, *J* = 8.7 Hz, 1H), 7.06 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 3.92 (s, 3H), 2.77 (t; *J* = 7.2 Hz, 2H), 2.63 (t; *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 2.20-2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 165.0, 163.3, 156.7, 151.6, 127.8, 116.7, 114.0, 107.8, 55.7, 42.4, 34.7, 30.0, 21.2; IR (thin film) ν 3320, 2943, 2831, 1683, 1611, 1444, 1021, 605 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{16}N_2O_3$ 261.1234, found 265.1235.



6,7-dimethoxy-2-(4-oxopentyl)quinazolin-4(3*H*)-one (102f)

Prepared according to general procedure D. Yield 52% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s 1H), 7.10 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 2.79 (t; *J* = 7.2 Hz, 2H), 2.62 (t; *J* = 7.2 Hz, 2H), 2.16 (s, 3H), 2.21-2.10 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 208.0, 161.0, 155.6, 154.6, 148.2, 144.3, 113.6, 107.3, 105.0, 55.9, 55.7, 41.8, 33.3, 29.7, 20.7; IR (thin film) ν 3155, 3024, 2941, 1667, 1610, 1489, 1273, 1108, 867, 662 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{18}N_2O_4$ 291.1339, found 291.1340.

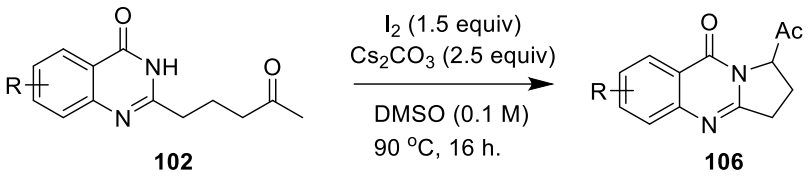


2-(2,2-dimethyl-4-oxopentyl)quinazolin-4(3*H*)-one (102h)

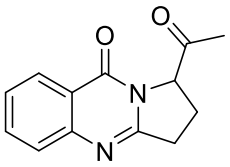
Prepared according to general procedure D. Yield 54% as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.8 Hz, 1H), 7.78-7.68 (m, 2H), 7.45 (dd, *J* = 1.5, 7.8 Hz, 1H), 2.78 (s, 2H), 2.50 (s, 2H), 2.26 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 162.6, 154.7, 148.6, 134.7, 127.0, 126.7, 126.5, 121.0, 52.0, 45.4, 35.5, 33.4, 28.9, 28.9; IR (thin film) ν 3034, 2948, 2880, 1680, 1609, 1468, 1157, 768, 602 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{18}N_2O_2$ 259.1441, found 259.1442.

4.8 Synthesis of deoxyvasicinone derivatives 106

General Procedure E

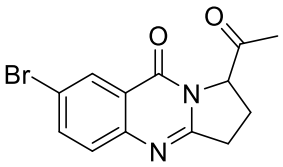


A sealed tube equipped with a magnetic stirring bar was charged with quinazoinone precursors **102** (0.3 mmol) and Cs_2CO_3 (0.9 mmol) in DMSO (2 mL). The resulting mixture was added iodine (0.63 mmol) and stirred at 90^{o}C for 16 h. After that, the resulting mixture was cooled to room temperature, quenched with sat. NH_4Cl and extracted with EtOAc. The organic layer was washed with water followed by brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (4:1 CH_2Cl_2:EtOAc) to provide deoxyvasicinone derivatives **106**.



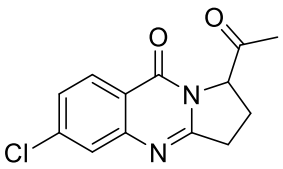
1-acetyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (106a).

Prepared according to general procedure E. Yield 72% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.8 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J*; 7.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 5.24 (dd, *J* = 2.7, 9.6 Hz, 1H), 3.28-3.10 (m, 2H), 2.61-2.48 (m, 1H), 2.47 (s, 3H), 2.30-2.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 160.6, 159.1, 149.2, 134.7, 127.0, 126.7, 126.7, 120.5, 65.0, 31.2, 27.5, 23.1; IR (thin film) ν 2973, 2899, 1720, 1662, 1628, 1471, 1171, 801, 697 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{12}N_2O_2$ 229.0972, found 229.0976.



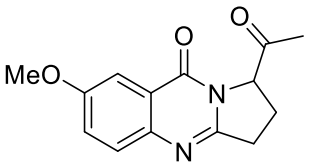
1-acetyl-7-bromo-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (106b)

Prepared according to general procedure E. Yield 59% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.4 Hz, 1H), 7.82 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.54 (d, *J*; 8.7 Hz, 1H), 5.26 (dd, *J* = 2.7, 9.6 Hz, 1H), 3.26-3.06 (m, 2H), 2.63-2.51 (m, 1H), 2.39 (s, 3H), 2.27-2.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 159.5, 159.5, 148.2, 137.8, 129.3, 128.9, 122.0, 120.1, 65.0, 31.2, 27.5, 23.0; IR (thin film) ν 3335, 2923, 2833, 1673, 1465, 1019, 664 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. For $C_{13}H_{11}BrN_2O_2$ 307.0077, found 307.0079.



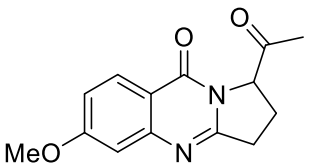
1-acetyl-6-chloro-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (106c)

Prepared according to general procedure E. Yield 64% as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.41 (dd, *J* = 1.8, 8.4 Hz, 1H), 5.25 (dd, *J* = 3.0, 9.9 Hz, 1H), 3.22-3.13 (m, 2H), 2.63-2.51 (m, 1H), 2.39 (s, 3H), 2.29-2.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 160.4, 160.0, 150.4, 140.9, 128.1, 127.2, 126.8, 119.1, 65.0, 31.2, 27.5, 23.0; IR (thin film) ν 3332, 2944, 2832, 1668, 1601, 1423, 1019, 604 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{11}ClN_2O_2$ 263.0584, found 263.0582.



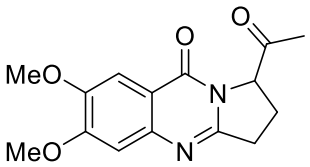
1-acetyl-7-methoxy-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (106d)

Prepared according to general procedure E. Yield 60% as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.7 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.34 (dd, *J*; 2.7, 8.7 Hz, 1H), 5.24 (dd, *J* = 3.3, 9.9 Hz, 1H), 3.90 (s, 3H), 3.26-3.05 (m, 2H), 2.62-2.56 (m, 1H), 2.38 (s, 3H), 2.28-2.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 160.6, 158.4, 156.7, 144.0, 128.6, 124.8, 121.3, 106.3, 65.0, 55.9, 30.9, 27.5, 23.3; IR (thin film) ν 2919, 2832, 1668, 1620, 1148, 1031, 826, 748 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{14}N_2O_3$ 259.1077, found 259.1080.



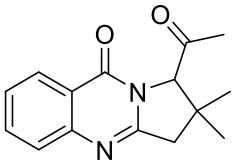
1-acetyl-6-methoxy-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (106e)

Prepared according to general procedure E. Yield 60% as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.7 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.04 (dd, *J*; 2.4, 8.7 Hz, 1H), 5.26 (d, *J* = 7.2 Hz, 1H), 3.92 (s, 3H), 3.26-3.22 (m, 2H), 2.60-2.56 (m, 1H), 2.39 (s, 3H), 2.24-2.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 165.1, 160.1, 160.0, 150.7, 128.3, 116.7, 113.9, 107.6, 65.1, 55.9, 31.2, 27.5, 23.1; IR (thin film) ν 2922, 2830, 1677, 1620, 1148, 1027, 824, 741 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{14}N_2O_3$ 259.1077, found 259.1080.



1-acetyl-6,7-dimethoxy-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (106f)

Prepared according to general procedure E. Yield 66% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.44 (s, 1H), 5.41 (d, *J* = 7.2 Hz, 1H), 4.16 (s, 3H), 4.13 (s, 3H), 3.41-3.27 (m, 2H), 2.76-2.68 (m, 1H), 2.55 (s, 3H), 2.44-2.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 160.0, 157.8, 155.3, 149.0, 145.5, 113.7, 107.6, 105.8, 65.1, 56.4, 56.4, 31.2, 27.5, 23.3; IR (thin film) ν 2936, 2927, 1657, 1609, 1266, 1174, 874, 824 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{15}H_{15}N_2O_4$ 289.1183, found 289.1189.

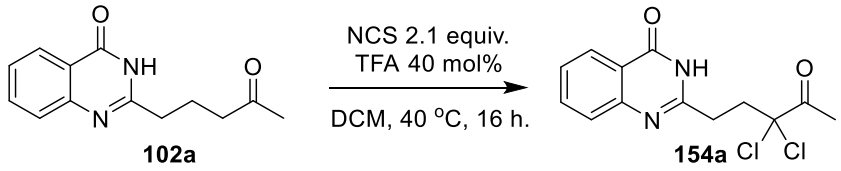


1-acetyl-2,2-dimethyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (106h).

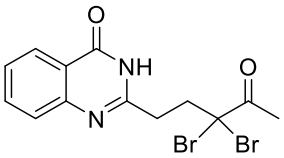
Prepared according to general procedure E. Yield 58% as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.73 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.66 (dd, *J*; 1.2, 7.8 Hz, 1H), 7.43 (dt, *J* = 1.2, 7.8 Hz, 1H), 4.86 (s, 1H), 3.14 (d, *J* = 16.8 Hz, 1H), 2.81 (d, *J* = 16.8 Hz, 1H), 2.37 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2, 160.6, 158.6, 148.9, 134.7, 126.9, 126.6, 126.6, 120.6, 73.3, 45.6, 38.5, 30.6, 29.9, 23.4; IR (thin film) ν 3338, 2964, 1672, 1626, 1468, 773, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{16}N_2O_2$ 257.1285, found 257.1284.

4.9 Synthesis of 2-(3,3-dichloro-4-oxopentyl)quinazolin-4(3*H*)-one (4a)

General Procedure F

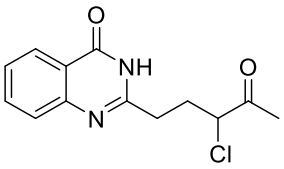


A round bottom flask equipped with a magnetic stirring bar was charged with 2-(4-oxopentyl)quinazolin-4(3*H*)-one (**102a**) (1.0 mmol) and *N*-chlorosuccinimide (2.1 equiv.) in DCM (5 mL). The resulting mixture was added TFA (40 mol%) and stirred at 40^{o}C for 15 h. After that, the resulting mixture was cooled to room temperature, neutralized with sat. $NaHCO_3$, extracted with DCM. The organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (9:1 CH_2Cl_2:EtOAc) to provide 2-(3,3-dichloro-4-oxopentyl)quinazolin-4(3*H*)-one (**154a**) (78%), brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.32 (dd, *J* = 0.9, 6.9 Hz, 1H), 7.85-7.74 (m, 2H), 7.58 (dt, *J* = 0.9, 6.9 Hz, 1H), 3.20-3.14 (m, 2H), 3.04-2.98 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 161.7, 151.1, 147.0, 135.2, 128.7, 128.7, 126.9, 121.7, 86.5, 39.9, 38.5, 30.2; IR (thin film) ν 3032, 1668, 1605, 780, 767, 651, 531 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{13}H_{12}Cl_2N_2O_4$ 321.0168, found 321.0168.



2-(3,3-dibromo-4-oxopentyl)quinazolin-4(3*H*)-one (155a),

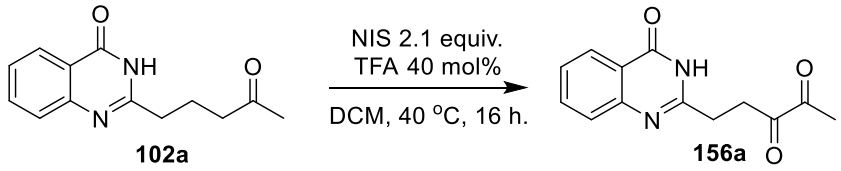
Prepared according to general procedure F. Using *N*-bromosuccinimide (2.1 equiv) brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.31 (dd, *J* = 0.9, 8.1 Hz, 1H), 7.80 (dt, *J* = 0.9, 8.1 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.57 (dt, *J* = 0.9, 8.1 Hz, 1H), 3.33-3.27 (m, 2H), 3.07-3.02 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 161.6, 152.0, 146.8, 135.2, 128.8, 128.7, 126.8, 121.5, 62.0, 42.5, 40.4, 30.3; IR (thin film) ν 3036, 1672, 1604, 1400, 1162, 780 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{12}Br_2N_2O_2$ 386.9338, found 386.9339.



2-(3-chloro-4-oxopentyl)quinazolin-4(3*H*)-one (153a),

Prepared according to general procedure F. L-proline 20 mol% was added as a catalyst. white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.11 (d, *J* = 7.5 Hz, 1H), 7.82 (t, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 4.89 (t, *J* = 7.5 Hz, 1H), 2.75-2.54 (m, 2H), 2.44-2.26 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 207.2, 161.6, 154.2, 148.0, 134.6, 127.4, 127.3, 125.9, 121.5, 58.6, 39.7, 29.7, 28.5; IR (thin film) ν 3133, 1682, 1622, 1400, 895, 774 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{13}ClN_2O_2$ 265.0739, found 265.0738.

4.10 Synthesis of 5-(4-oxo-3,4-dihydroquinazolin-2-yl)pentane-2,3-dione (156a)

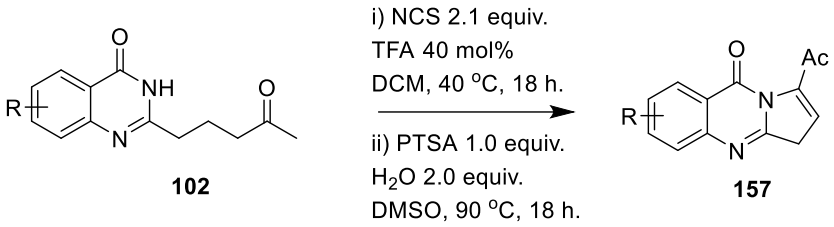


102a **156a**

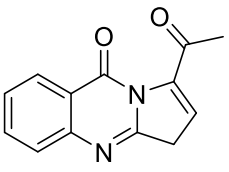
A round bottom flask equipped with a magnetic stirring bar was charged with 2-(4-oxopentyl)quinazolin-4(3*H*)-one (**102a**) (1.0 mmol) and *N*-iodosuccinimide (2.1 equiv.) in DCM (5 mL). The resulting mixture was added TFA (40 mol%) and stirred at 40°C for 16 h. After that, the resulting mixture was cooled to room temperature, neutralized with sat. $NaHCO_3$, extracted with DCM. The organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (9:1 CH_2Cl_2:EtOAc) to provide 5-(4-oxo-3,4-dihydroquinazolin-2-yl)pentane-2,3-dione (**156**) (65%) ; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.37 (dd, *J* = 1.2, 7.5 Hz, 1H), 7.92-7.82 (m, 2H), 7.64 (dt, *J* = 1.2. 7.5 Hz, 1H), 3.50 (t, *J* = 6.3 Hz, 2H), 2.97 (t, *J* = 6.3 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.3, 195.0, 160.6, 147.7, 144.9, 134.9, 129.4, 129.2, 126.9, 123.6, 37.2, 30.3, 29.8; IR (thin film) ν 3040, 2922, 1707, 1626, 1597, 1137, 776, 690 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{12}N_2O_3$ 245.0921, found 245.0922.

4.11 Synthesis of acetylpyrroloe quinazolinones 157

General Procedure G



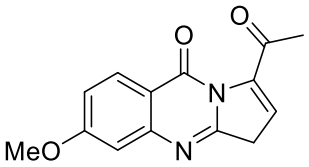
A round bottom flask equipped with a magnetic stirring bar was charged with 2-(4-oxopentyl)quinazolin-4(3*H*)-one (**102**) (1.0 mmol) and *N*-chlorosuccinimide (2.1 equiv.) in DCM (5 mL). The resulting mixture was added TFA (40 mol%) and stirred at 40^{o}C for 15 h. After that, the resulting mixture was cooled to room temperature, neutralized with sat. $NaHCO_3$, extracted with DCM. The organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. Then, the residue mixture was charged with *p*-toluenesulfonic acid (1.0 equiv.) in DMSO (2 mL). The resulting mixture was added H_2O (2.0 equiv.) and stirred at 90^{o}C for 18 h. After that, the resulting mixture was cooled to room temperature, neutralized with sat.$NaHCO_3$, extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (4:1 CH_2Cl_2:EtOAc) to provide acetylpyrroloe quinazolinones **157**.



1-acetylpyrrolo[2,1-*b*]quinazolin-9(3*H*)-one (157a).

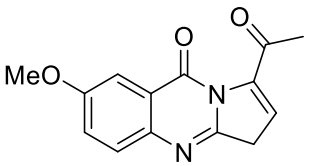
Prepared according to general procedure G. Yield 67% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.90 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.84 (dd,

J; 1.2, 7.2 Hz, 1H), 7.57 (dt, *J* = 1.2, 7.2 Hz, 1H), 5.16 (dd, *J* = 4.5, 8.4 Hz, 1H), 3.40 (dd, *J* = 8.4, 14.4 Hz, 1H), 3.26 (dd, *J* = 4.5, 14.4 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 159.8, 154.7, 148.6, 135.3, 128.6, 128.4, 126.9, 121.1, 81.4, 61.9, 47.3, 27.8; IR (thin film) ν 3032, 2920, 1686, 1631, 1465, 1165, 770, 691 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{13}H_{10}N_2O_2$ 249.0634, found 249.0637.



1-acetyl-6-methoxypyrrolo[2,1-*b*]quinazolin-9(3*H*)-one (157b)

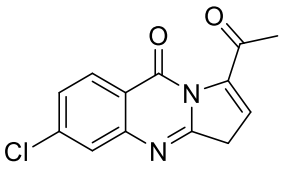
Prepared according to general procedure F. Yield 51% as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.0 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.13 (dd, *J*; 2.4, 9.0 Hz, 1H), 5.13 (dd, *J* = 4.8, 8.1 Hz, 1H), 3.94 (s, 3H), 3.40 (dd, *J* = 8.1, 14.4 Hz, 1H), 3.26 (dd, *J* = 4.8, 14.4 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 165.4, 159.4, 155.5, 151.1, 128.4, 118.4, 114.4, 109.5, 81.6, 61.9, 56.0, 47.4, 27.7; IR (thin film) ν 2942, 2831, 1679, 1610, 1446, 1110, 1021, 619 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{12}N_2O_3$ 279.0740, found 279.0745.



1-acetyl-7-methoxypyrrolo[2,1-*b*]quinazolin-9(3*H*)-one (157c)

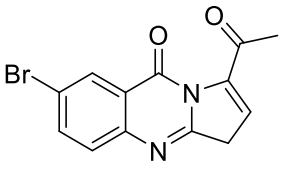
Prepared according to general procedure F. Yield 51% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 2.7 Hz, 1H), 7.43 (dd, *J*; 2.7, 9.0 Hz, 1H), 5.15 (dd, *J* = 4.8, 8.1 Hz, 1H), 3.94 (s, 3H), 3.39 (dd, *J* = 8.1, 14.1 Hz, 1H), 3.27 (dd, *J* = 4.8, 14.1 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1,

159.8, 159.7, 152.6, 143.1, 130.2, 125.3, 122.2, 106.7, 81.5, 62.0, 56.1, 47.6, 27.8; IR (thin film) ν 2943, 2832, 1674, 1448, 1113, 1021, 620 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{12}N_2O_3$ 279.0745, found 279.0740.



1-acetyl-6-chloropyrrolo[2,1-*b*]quinazolin-9(3*H*)-one (157d)

Prepared according to general procedure F. Yield 56% as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 1.5 Hz, 1H), 7.51 (dd, *J* = 1.5, 8.4 Hz, 1H), 5.14 (dd, *J* = 4.5, 8.4 Hz, 1H), 3.40 (dd, *J* = 8.4, 14.4 Hz, 1H), 3.25 (dd, *J* = 4.5, 14.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 159.2, 156.0, 149.6, 141.7, 129.0, 128.3, 128.2, 120.0, 81.3, 62.0, 47.2, 27.8; IR (thin film) ν 3065, 1683, 1598, 1379, 921, 837, 770, 682 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{13}H_9ClN_2O_2$ 283.0245, found 283.0251.



1-acetyl-7-bromopyrrolo[2,1-*b*]quinazolin-9(3*H*)-one (157e)

Prepared according to general procedure F. Yield 53% as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.1 Hz, 1H), 7.91 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.76 (d, *J*; 8.7 Hz, 1H), 5.15 (dd, *J* = 4.5, 8.1 Hz, 1H), 3.40 (dd, *J* = 8.1, 14.4 Hz, 1H), 3.26 (dd, *J* = 4.5, 14.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 158.6, 155.1, 147.5, 138.5, 130.2, 129.6, 122.5, 122.3, 81.3, 62.1, 47.2, 27.7; IR (thin film) ν 2942, 2831, 1687, 1633, 1465, 1021, 644 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{13}H_9BrN_2O_2$ 326.9740, found 326.9732.

REFERENCES

Abdel-Magid, A. F., Carson, K. G., Harris, B. D., Maryanoff, C. A., Shah, R. D. 1996. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydrides. Studies on Direct and Indirect Reductive Amination Procedures. J. Org. Chem. 61, 3849–3862

Chen, F., Ding, Z., Qin, J., Wang, T., He, Y., Fan, Q.-H. 2011. Highly Effective Asymmetric Hydrogenation of Cyclic *N*-Alkyl Imines with Chiral Cationic Ru-MsDPEN Catalysts. Org. Lett. 13, 4348–4351.

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.

de Figueiredo, R.M., Fröhlich, R., Christmann, M. 2006. *N*,*N*‘-Carbonyldiimidazole-Mediated Cyclization of Amino Alcohols to Substituted Azetidines and Other *N*-Heterocycles. J. Org. Chem. 71, 4147-4154.

Demeunynck, M., Baussanne I. 2013. Survey of recent literature related to the biologically active 4(3H)-quinazolinones containing fused heterocycles. Curr Med Chem. 20, 794–814.

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.

Gao, W.-C.; Jiang, S.; Wang, R.-L.; Zhang, C. 2013. Iodine-mediated intramolecular amination of ketones: the synthesis of 2-acylindoles and 2-acylindolines by tuning *N*-protecting groups. Chem. Commun. 49, 4890–4892.

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.

Hall, J. E., Matlock, J. V., Ward, J. W., Gray, K. V., Clayden, J. 2016. Medium-Ring Nitrogen Heterocycles through Migratory Ring Expansion of Metalated Ureas. Angew. Chem. Int. Ed. 55, 11153–11157.

Hameed, A., Javed, S., Noreen, R., Huma, T., Iqbal, S., Umbreen, H., Gulzar, T., Farooq, T. 2017. Facile and Green Synthesis of Saturated Cyclic Amines. Molecules. 22, 1691.

Han, Y.-Y., Jiang, H., Wang, R., Yu, S. 2016. Synthesis of Tetracyclic Quinazolinones Using a Visible-Light-Promoted Radical Cascade Approach. J. Org. Chem. 81, 7276–7281.

Heinrich, M.R., Steglich, W. 2001. Synthesis of (−)-(3S)-1-(3-aminopropyl)-3-methylazacyclodecane, the structure proposed for the marine alkaloid haliclorensin. Tetrahedron Lett. 42, 3287–3289.

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.

Hussain, A., Yousuf, S.K., Mukherjee, D. 2014. Importance and synthesis of benzannulated medium-sized and macrocyclic rings (BMRs). RSC Adv. 4, 43241–43257.

Kametani, T.; Higa, T.; Loc, C. V.; Ihara, M.; Koizumi, M.; Fukumoto, K. 1975. Imnoketene Cycloaddition. 1. A Facile Synthesis of Quinazolone System by Condensation of Iminoketene with Imines–A Total Synthesis of Evodiamine and Rutecarpine by Retro Mass-Spectral Synthesis. 98(20), 6186–6188.

Kappe, T., Hariri, M., Pongratz, E. 1968. Ylide von Heterocyclen, III[1] Pyridinium-Ylide von Malonylheterocyclen. Monatshefte für Chemie. 99, 2157–2166

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.

Kotipalli, T., Kavala, V., Janreddy, D., Kuo, C.-W., Kuo, T.-S., Huang, H.-N., He, C.-H., Yao, C.-F. 2014. Syntheses of indolo[1,2-a]quinazolinone derivatives via palladium catalyzed intramolecular C–H amidation. RSC Adv. 4, 2274–2283.

Lee, E. S.; Park, J,-G.; Jahng, Y. 2003. A facile synthesis of simple alkaloids-synthesis of 2,3-polymethylene-4(3H)-quinazolinones and related alkaloids. Tetrahedron Lett. 44, 1883–1886.

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.

Liu, M., Shu, M., Yao, C., Yin, G., Wang, D., Huang, J. 2016. Synthesis of Pyrido-Fused Quinazolinone Derivatives via Copper-Catalyzed Domino Reaction. Org. Lett. 18, 824–827.

Lu, H., Yang, Q., Zhou, Y., Guo, Y., Deng, Z., Ding, Q., Peng, Y. 2014. Cross-coupling/annulations of quinazolones with alkynes for access to fused polycyclic heteroarenes under mild conditions. Org. Biomol. Chem. 12, 758–764.

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. 2001. Concise and Efficient Synthesis of Bioactive Natural Products Pegamine, Deoxyvasicinone, and (–)-Vasicinone. J. Org. Chem. 66, 9038–9040.

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

Minakata, S., Morino, Y., Oderaotoshi, Y., Komatsu, M. 2006. Practical and Convenient Synthesis of *N*-Heterocycles: Stereoselective Cyclization of *N*-Alkenylamides with *t*-BuOI under Neutral Conditions Org. Lett. 8, 3335–3337.

Garcia-Ramirez, J.; Miranda, L. D. 2020. Peroxide-Mediated Oxidative Radical Cyclization to the Quinazolinone System: Efficient Syntheses of Deoxyvasicinone, Mackinazolinone and (±)-Leucomidine C. Synthesis 52, 1471–1477.

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.

Mougari, S., Chelkha, N., Sahmi-Bounsiar, D., Pinto, F. D., Colson, P., Abrahao, J., Scola, B. L. 2020. A virophage cross-species infection through mutant selection represses giant virus propagation, promoting host cell survival. Commun Biol. 3, 1–13.

Niemi, T., Fernández, I., Steadman, B., Mannisto, J.K., Repo, T. 2018. Carbon dioxide-based facile synthesis of cyclic carbamates from amino alcohols. Chem. Commun. 54, 3166–3169.

Olofsson, B., Wijtmans, R., Somfai, P. 2002. Synthesis of *N*-H vinylaziridines: a comparative study. Tetrahedron. 58, 5979–5982.

Onaka, T. 1971. General Three-Step Synthesis of Pyrrolidino[2,1-b]quinazolone Alkaloids via Biogenetically Patterned Path. Tetrahedron Lett. 46, 4387–4390.

O'Reilly, M.C., Lindsley, C.W. 2012. A General, Enantioselective Synthesis of Protected Morpholines and Piperazines. Org. Lett. 14, 2910–2913.

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.

Padiya, K.J., Gavade, S., Kardile, B., Tiwari, M., Bajare, S., Mane, M., Gaware, V., Varghese, S., Harel, D., Kurhade, S. 2012. Unprecedented "In Water" Imidazole Carbonylation: Paradigm Shift for Preparation of Urea and Carbamate. Org. Lett. 14, 2814–2817.

Pei, Z., Li, X., Longenecker, K., von Geldern, T.W., Wiedeman, P.E., Lubben, T.H., Zinker, B.A., Stewart, K., Ballaron, S.J., Stashko, M.A., Mika, A.K., Beno, D.W.A., Long, M., Wells, H., Kempf-Grote, A.J., Madar, D.J., McDermott, T.S., Bhagavatula, L., Fickes, M.G., Pireh, D., Solomon, L.R., Lake, M.R., Edalji, R., Fry, E.H., Sham, H.L., Trevillyan, J.M. 2006. Discovery, Structure−Activity Relationship, and Pharmacological Evaluation of (5-Substituted-pyrrolidinyl-2-carbonyl)-2-cyanopyrrolidines as Potent Dipeptidyl Peptidase IV Inhibitors. J. Med. Chem. 49, 3520–3535.

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.

Rutjes, F.P.J.T., Schoemaker, H.E. 1997. Ruthenium-catalyzed ring closing olefin metathesis of non-natural α-amino acids. Tetrahedron Lett. 38, 677–680.

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.

Sharon, M.; Parker, A.; Rizzo, C. J. 1995. Facile Addition of Dichloroketene to Acetylenes Mediated by Zinc and Ultrasound. Synth. Commun. 25, 2781–2789.

Shen, G.; Zhou, H.; Sui, Y.; Liu, Q.; Zou, K. 2016 $FeCl_3$-catalyzed tandem condensation/intramolecular nucleophilic addition/C–C bond cleavage: a concise synthesis of 2-substitued quinazolinones from 2-aminobenzamides and 1,3-diketones in aqueous media. Tetrahedron Lett. 57, 587–590.

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.

Shue, H.-J., Chen, X., Shih, N.-Y., Blythin, D.J., Paliwal, S., Lin, L., Gu, D., Schwerdt, J.H., Shah, S., Reichard, G.A., Piwinski, J.J., Duffy, R.A., Lachowicz, J.E., Coffin, V.L., Liu, F., Nomeir, A.A., Morgan, C.A., Varty, G.B. 2005. Cyclic urea derivatives as potent NK1 selective antagonists. Bioorg. Med. Chem. Lett. 15, 3896–3899.

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.

Takeuchi, H.; Hagiwara, S.; Eguchi, S. 1989. A New Efficient of Imidazolinones and Quinazolinone by Intramolecular Aza-Wittig Reaction. Tetrahedron 45 (20), 6375–6386.

Tamura, M., Honda, M., Nakagawa, Y., Tomishige, K. 2014. Direct conversion of CO2 with diols, aminoalcohols and diamines to cyclic carbonates, cyclic carbamates and cyclic ureas using heterogeneous catalysts. J. Chem. Technol. Biotechnol. 89, 19–33.

Taylor, R.D., MacCoss, M., Lawson, A.D.G. 2014. Rings in Drugs. J. Med. Chem. 57, 5845–5859.

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.

Vaswani, R.G., Chamberlin, A.R. 2008. Stereocontrolled Total Synthesis of (−)-Kaitocephalin. J. Org. Chem. 73, 1661–1681.

Ziaee, V.; Jalalizadeh, H.; Iranshahi, M.; Shafiee, A. 2004. Improved Synthesis of Vasicinone. Iran. J. Chem. & Chem. Eng. 23 (2), 33–36.

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.

Yin, P., Liu, N., Deng, Y.-X., Chen, Y., Deng, Y., He, L. 2012. Synthesis of 2,4-Diaminoquinazolines and Tricyclic Quinazolines by Cascade Reductive Cyclization of Methyl N-Cyano-2-nitrobenzimidates. J. Org. Chem. 77, 2649–2658.

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.

Zhang, Y., Yan, Q., Zi, G., Hou, G. 2017. Enantioselective Direct Synthesis of Free Cyclic Amines via Intramolecular Reductive Amination. Org. Lett. 19, 4215–4218.

APPENDIX

Synlett Y. Saebang et al. Cluster

Synthesis of Eleven-Membered Cyclic Urea Fused Quinazolinones

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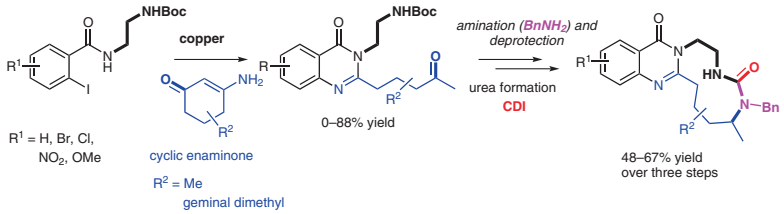

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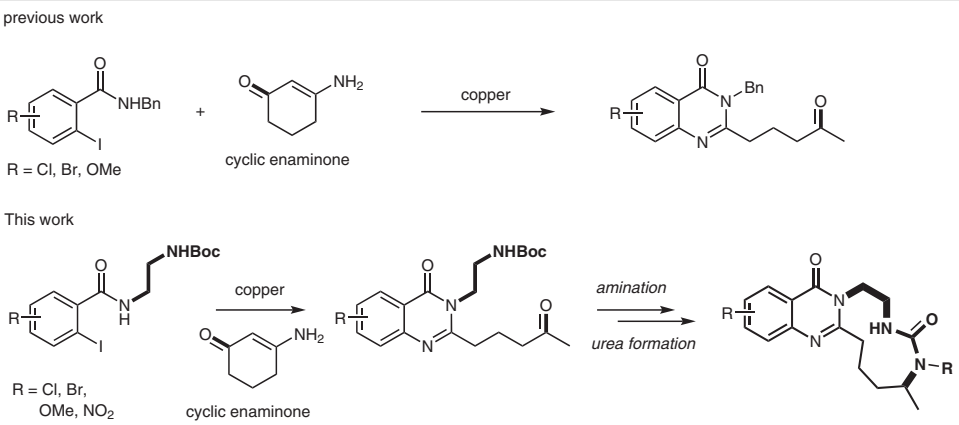
Abstract Straightforward synthesis of quinazolinones having N-fused medium-sized ring urea was accomplished. Key intermediates were *tert*-butyl [2-[4-oxo-2-(4-oxopentyl)quinazolin-3(4*H*)-yl]ethyl]carbamates derived from copper-catalyzed domino reaction of *tert*-butyl [2-(2-iodobenzamido)ethyl]carbamates and cyclic enaminones. Steric hindrance of cyclic enaminones played an important role in the formation of quinazolinone ring. The eleven-membered ring urea moiety was readily achieved by direct cyclization using 1,1′-carbonyldiimidazole (CDI) of diamino intermediate generated by readily reductive amination and deprotection of *tert*-butyl [2-[4-oxo-2-(4-oxopentyl)quinazolin-3(4*H*)-yl]ethyl]carbamates.

Key words tricyclic quinazolinones, copper-catalyzed domino reaction, C–N bond formation, medium-sized ring heterocycles, cyclic ureas

The development of methodologies for the synthesis of novel core structures remains a significant challenge for organic chemists especially involving the discovery of pharmaceutical candidates. Quinazolinones are one of the most important N-containing heterocycles due to their presence in natural products and a broad range of biological properties, such as anticancer, anti-inflammatory, antihypertensive, antitumor, antihypertensive, and antidiabetic among others.[1] Additionally, N-fused cyclic quinazolinones also disclosed a variety of biological properties from both natural and synthetic products.[2] Therefore, the development of methodologies in constructing N-fused quinazolinones including novel core structure remains important.[3] Previously we reported the synthesis of quinazolinones from 2-iodobenzamides and cyclic enaminone (Scheme 1). The corresponding quinazolinones could be potentially further functionalized due to the generation of a ketone functionality.[4] In this work, we envisioned that having extra nitrogen nucleophile on the 2-iodobenzamide would allow us to construct a new cyclic structure derived from the nitrogen and ketone providing new core structure of quinazolinones fused with medium-sized-ring heterocycles (Scheme 1). Based on our knowledge, the medium-sized-ring heterocycles were unique molecular structures and commonly found in bioactive natural products and therapeutically important molecules.[5] Therefore, the exploration of drug candidates containing medium-sized ring N-containing heterocycles have been remained important, especially cyclic urea moiety.[6] Here, we report a straightforward method for the synthesis of quinazolinones fused with an eleven-membered ring urea.



Scheme 1 Copper-catalyzed domino reaction of cyclic enaminone

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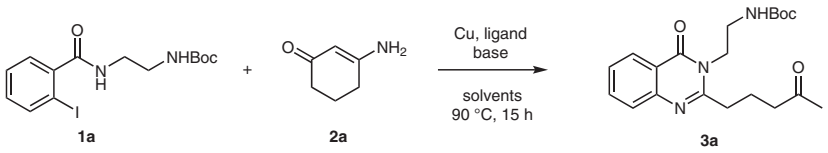
To investigate the reaction of *tert*-butyl [2-(2-iodobenzamido)ethyl]carbamate **1a** and cyclic enaminone **2a**, we initially used the reaction conditions previously reported.[4] A resulting product yield was moderate giving a corresponding quinazolinone in 63% (entry 1, Table 1). Therefore, further optimization conditions were required (Table 1). We began with a variety of solvents. Significantly, low polar solvent, tetrahydrofuran (THF), provided high yield of the product (83%, entry 3, Table 1). On the contrary, high polar solvents such as DMF and DMSO gave low yields of product, 32% and 46%, respectively (entries 4 and 5, Table 1). In addition, fairly good yield was observed (72%), when toluene was used (entry 2, Table 1). Next, common weak bases were applied. We found that K_3PO_4 gave a slight increase of the product yield (85%, entry 7, Table 1), while K_2CO_3 surprisingly gave no product (entry 6, Table 1). Generally, the reaction was applicable to a wide range of common ligands such as dimethylethylendiamine (DMEDA), 1,2-*trans*-diaminocyclohexane, and picolinic acid resulting in 82%, 88%, and 78% yields of product, respectively (entries 8–10, Table 1). Interestingly, without an external ligand the reaction still gave a good yield of the product (72%, entry 11, Table 1). This finding implicitly suggested that the diamino moiety of the amide starting material could act as ligand in the reaction, since in our previous work the copper coupling reaction of cyclic enaminone required the presence of ligand.[4] Other copper salts were also applicable to the reaction giving the product in moderate yields (entries 12–14, Table 1). Based on these results the use of CuI as a catalyst, 1,2-*trans*-diaminocyclohexane as a ligand, and K_3PO_4 as a base in THF were the optimal conditions (entry 9, Table 1).

After the optimized conditions had been obtained, we investigated a variety of *tert*-butyl [2-(2-iodobenzamido)ethyl]carbamates (2-iodobenzamides, **1**) and **2a** (Scheme 2). A broad spectrum of 2-iodobenzamide derivatives were applicable to the reaction. Having an electron-withdrawing group, the 2-iodobenzamides provided moderate yields of the corresponding products **3b**. 2-Iodobenzamides having halogen substituents also provided good yields of products; 3-bromo-2-iodobenzamides gave 80% yield (**3c**), and 4-chloro-2-iodobenzamide also gave good yield (70%, **3d**). Moreover, the reaction proceeded well with 2-iodobenzamides having electron-donating-group substituents. The 3-methoxy- and 4-methoxy-substituted 2-iodobenzamides gave a yield of 78% and 74% (**3e** and **3f**), respectively. A similar result was obtained from the reaction of 3,4-dimethoxy-substituted 2-iodobenzamide giving 80% yield of product **3g**.

Next, we turned our interest to the steric effect of cyclic enaminones. Therefore, we selected three cyclic enaminones having methyl substituent on different carbon; 3-amino-5,5-dimethylcyclohex-2-enone (**2b**), 3-amino-5-

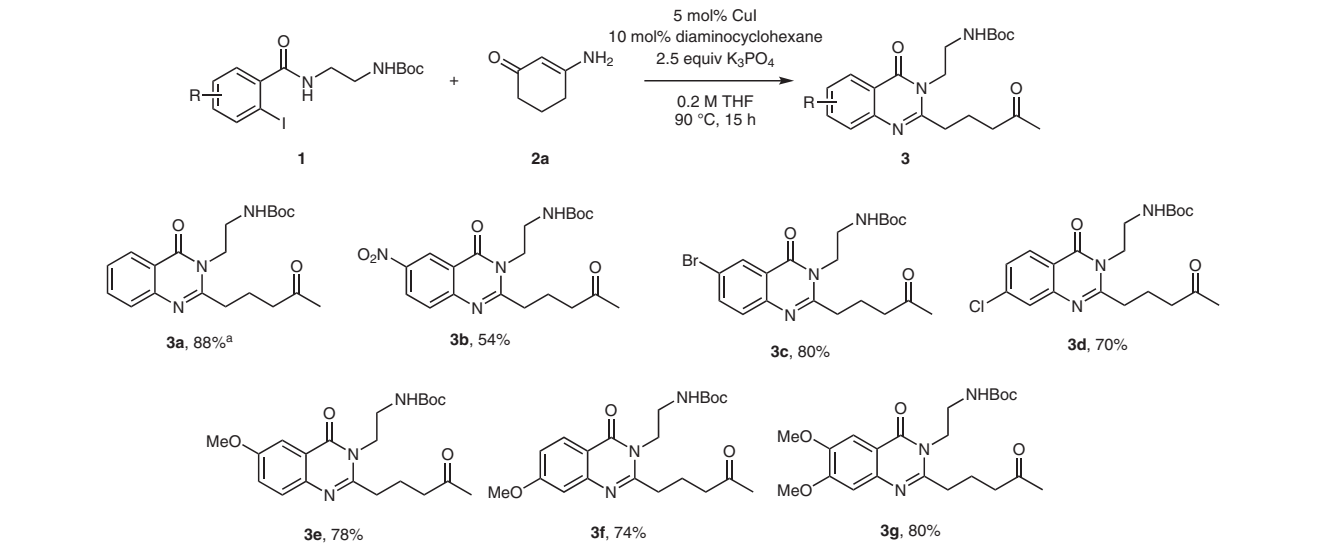
Table 1 Optimization Reaction of *tert*-Butyl [2-(2-Iodobenzamido)ethyl]carbamate **1a** and Cyclic Enaminone **2a**[a]



1a **2a** **3a**

Entry	Cu salts	Ligands	Bases	Solvents	Yield (%)[b]
1	CuI	L-proline	Cs_2CO_3	MeCN	63
2	CuI	L-proline	Cs_2CO_3	toluene	72
3	CuI	L-proline	Cs_2CO_3	THF	83
4	CuI	L-proline	Cs_2CO_3	DMF	32
5	CuI	L-proline	Cs_2CO_3	DMSO	46
6	CuI	L-proline	K_2CO_3	THF	0
7	CuI	L-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	–	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: **1a** (0.5 mmol), **2a** (0.6 mmol), cat. (5 mol%), ligand (10 mol%), base (2.5 equiv), solvent (0.2 M), and 90 °C for 15 h in sealed tube.
[b] Isolated yield.

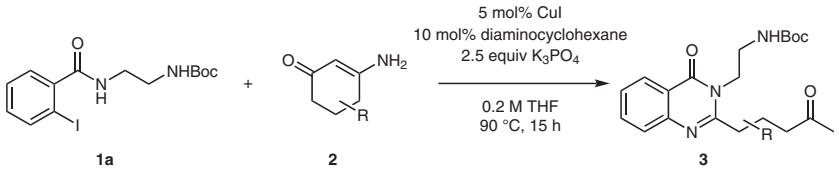


Scheme 2 Reactions of *tert*-butyl [2-(2-iodobenzamido)ethyl]carbamates **1** and **2a**. *Reagents and conditions*: **1** (0.5 mmol) and **2a** (0.6 mmol) in sealed tube. [a] Isolated yield.

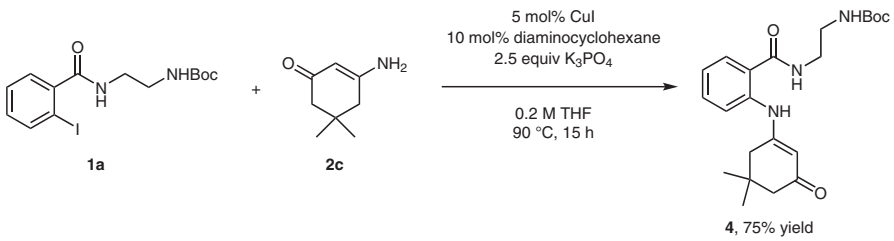
methylcyclohex-2-enone (**2c**), and 3-amino-6,6-dimethylcyclohex-2-enone (**2d**). We performed the reaction with those three enaminones under the optimal conditions (Table 2).

Having geminal dimethyl substituents at carbon 6 provided the corresponding quinazolinone in good yield (74%, entry 1, Table 2). On the contrary, no corresponding quinazolinone product was isolated when the 3-amino-5,5-dimethylcyclohex-2-enone was subjected to the reactions (entry 2, Table 2). Instead, the *N*-aryl adduct intermediate **4** was isolated in high yield (75%, Scheme 3)

Table 2 Reaction of Methyl-Substituted Cyclic Enaminones[a]



Entry	Cyclic enaminone	Product (yield, %)[b]
1	**2b**	**3h** 74
2	**2c**	**3i** 0
3	**2d**	**3j** 77



Scheme 3

On the other hand, the reaction performed smoothly with one methyl substituent giving the corresponding quinazolinone in 77% yield (entry 3, Table 2). Based on these results we rationally hypothesized that the key chemical transformation, in which a nucleophile nitrogen approached to an electrophile carbon, underwent through possibly planar conformation of the adduct intermediate **4**. The reaction of **2c** gave no quinazolinone product because the geminal dimethyl substituents prevented the electrophile carbon from the approaching of the nucleophile nitrogen (Figure 1).

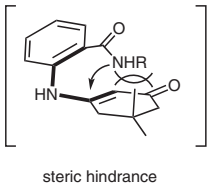
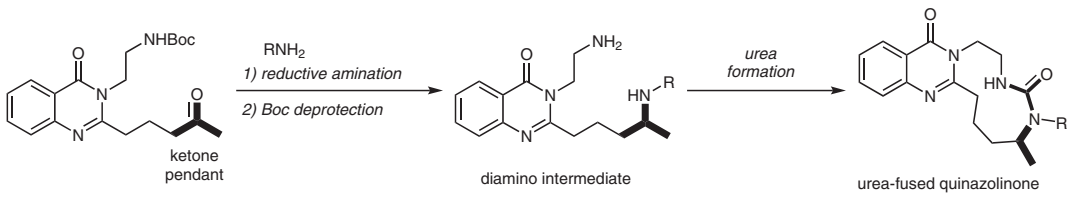


Figure 1 Possible conformation of the adduct intermediate for intramolecular Michael addition

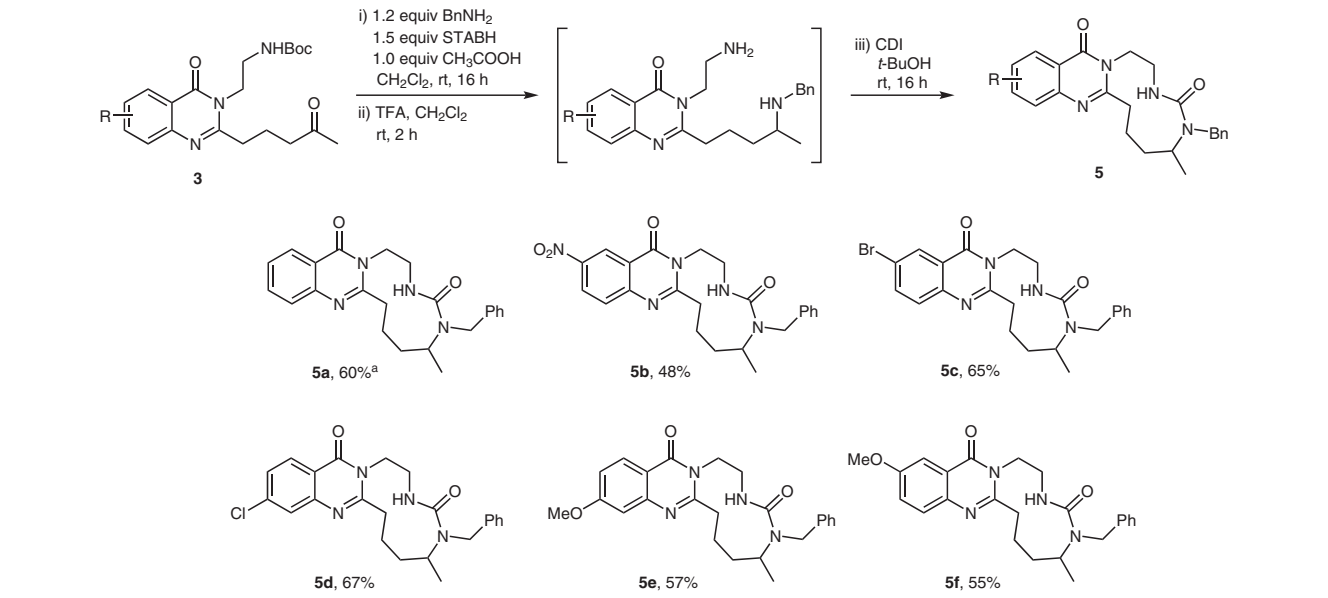
Next, we turned our interest to utilize the quinazolinone products to achieve the synthesis of a novel core structure. In this case, we envisioned that having the ketone functionality and also the amine moiety in the molecule would allow us to construct a new ring readily. The medium-sized urea rings caught our attention since they have been commonly found in both bioactive natural products and synthetic molecules.[6] Therefore, we aimed our target to accomplish the synthesis of quinazolinone fused with a medium-sized ring urea.

The synthesis was straightforward and simple, starting with reductive amination and Boc deprotection followed by urea formation (Scheme 4). The diamino intermediate was smoothly obtained under mild conditions from the reductive amination using sodium triacetoxyborohydride[7] as a reducing agent, followed by Boc deprotection with traditional trifluoroacetic acid (TFA) method. To construct the medium-sized ring with urea moiety, we selected a modified method from Padiya using 1,1′-carbonyldiimidazole (CDI) as a carbonyl source since CDI was comparatively mild and not toxic like other reagents.[8] To our delight, Lam and coworkers reported the use of CDI to directly construct a core seven-membered cyclic urea from the corresponding diamino starting material.[9] Nicely, the corresponding quinazolinones fused with eleven-membered ring urea were obtained with moderate to good yields over three steps (Scheme 5). Although we did not exhaustively explore the scope of medium-sized ring urea, we found that our copper-catalyzed domino reaction of cyclic enaminones to form quinazolinones with amino and ketone moieties have shown great potential to access other heterocycle-fused quinazolinones.

In summary, we have accomplished the synthesis of quinazolinone having amino and ketone moieties.[10–13] The key reaction was the Cu-catalyzed domino reaction of cyclic enaminone and *tert*-butyl [2-(2-iodobenzamido)ethyl]carbamate. Based on the reaction, we found that the cyclic enaminone having disubstituent at C5 was not suitable to obtain the corresponding quinazolinones due to the steric hindrance of the *N*-aryl adduct intermediate. Noteworthy, the reaction could perform smoothly without the addition of ligand. It is noteworthy that the diamino moiety of the amide starting material could act as ligand. In addition, we have demonstrated the straightforward utilization of the corresponding quinazolinones to obtain the unique core structure, a medium-sized ring urea-fused quinazolinone. The chemical transformations include reductive amination,



Scheme 4 Synthesis of quinazolinone fused with an eleven-membered ring urea



Scheme 5 Eleven-membered-ring urea fused quinazolinones. *Reagents and conditions*: i) **3** (0.6 mmol) and $BnNH_2$ (0.9 mmol) in CH_2Cl_2 (6.0 mL); ii) TFA (3.0 mL) and CH_2Cl_2 (3.0 mL); iii) CDI (0.72 mmol) in *t*-BuOH (30.0 mL). [a] Isolated yield for three steps. STABH: sodium triacetoxyborohydride; TFA: trifluoroacetic acid; CDI: 1,1′-carbonyldiimidazole.

deprotection, and urea transformation to obtain the corresponding products in moderate to good yields over three steps.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1793-1321.

References and Notes

(1) (a) Rohokale, R. S.; Kshirsagar, U. A. *Synthesis* **2016**, *48*, 1253. (b) Kshirsagar, U. A. *Org. Biomol. Chem.* **2015**, *13*, 9336. (c) Tiwary, B. K.; Pradhan, K.; Nanda, A. K.; Chakraborty, R. *J. Chem. Biol. Ther.* **2015**, *1*, 104. (d) Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. *Eur. J. Med. Chem.* **2015**, *90*, 124. (e) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787. (f) Mahdavi, M.; Pedrood, K.; Safavi, M.; Saeedi, M.; Pordeli, M.; Ardestani, S. K.; Emami, S.; Adib, M.; Foroumadi, A.; Shafiee, A. *Eur. J. Med. Chem.* **2015**, *95*, 492.

(2) (a) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1999**, *51*, 1883. (b) Elban, M. A.; Sun, W.; Eisenhauer, B. M.; Gao, R.; Hecht, S. M. *Org. Lett.* **2006**, *8*, 3513. (c) Thomas, C. J.; Rahier, N. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 1585.

(3) (a) Han, Y.-Y.; Jiang, H.; Wang, R.; Yu, S. *J. Org. Chem.* **2016**, *81*, 7276. (b) Shen, C.; Man, N. Y. T.; Stewart, S.; Wu, X.-F. *Org. Biomol. Chem.* **2015**, *13*, 4422. (c) Servais, A.; Azzouz, M.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 576. (d) Viveki, A. B.; Mhaske, S. B. *J. Org. Chem.* **2018**, *83*, 8906.

(4) Songsichan, T.; Promsuk, J.; Rukachaisirikul, V.; Kaeobamrung, J. *Org. Biomol. Chem.* **2014**, *12*, 4571.

(5) (a) Clarke, A. K.; Unsworth, W. P. *Chem. Sci.* **2020**, *11*, 2876. (b) Hussain, A.; Yousuf, S. K.; Mukherjee, D. *RSC Adv.* **2014**, *4*, 43241. (c) Sumi, K.; Inoue, Y.; Nishio, M.; Naito, Y.; Hosoya, T.; Suzuki, M.; Hidaka, H. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 831. (d) Kurouchi, H.; Ohwada, T. *J. Org. Chem.* **2020**, *85*, 876. (e) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251. (f) Hussain, A. S.; Yousuf, K.; Mukherjee, D. *RSC Adv.* **2014**, *4*, 43241. (g) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. (h) Hill, J. E.; Matlock, J. V.; Lefebvre, Q.; Cooper, K. G.; Clayden, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 5788. (i) Chinthapally, K.; Massaro, N. P.; Ton, S.; Gardner, E. D.; Sharma, I. *Tetrahedron Lett.* **2019**, *60*, 151253. (j) Stephens, T. C.; Lodi, M.; Steer, A. M.; Lin, Y.; Gill, M. T.; Unsworth, W. P. *Chem. Eur. J.* **2017**, *23*, 13314.

(6) (a) Hall, J. E.; Matlock, J. V.; Ward, J. W.; Gray, K. V.; Clayden, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 11153. (b) Yang, Y.; Ying, H.; Li, Z.; Wang, J.; Chen, Y.; Luo, B.; Gray, D. L.; Ferguson, A.; Chen, Q. Z. Y.; Cheng, J. *Nat. Commun.* **2021**, *12*, 1572.

(7) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(8) Padiya, K. J.; Gavade, S.; Kardile, B.; Tiwari, M.; Bajare, S.; Mane, M.; Gaware, V.; Varghese, S.; Harel, D.; Kurhade, S. *Org. Lett.* **2012**, *14*, 2814.

(9) Lam, P. Y. S.; Ru, Y.; Jadhav, P. K.; Aldrich, P. E.; Delucca, G. V.; Eyermann, C. J.; Chang, C.-H.; Emmett, G.; Holler, E. R.; Daneker, W. F.; Li, L.; Confalone, P. N.; McHugh, R. J.; Han, Q.; Li, R.; Markwalder, J. A.; Seitz, S. P.; Sharpe, T. R.; Bacheler, L. T.; Rayner, M. M.; Klabe, R. M.; Shum, L.; Winslow, D. L.; Kornhauser, D. M.; Jackson, D. A.; Erickson-Viitanen, S.; Hodge, C. N. *J. Med. Chem.* **1996**, *39*, 3514.

(10) **General Procedure B: Synthesis of Quinazolinones**

Prepared according to modified procedure reported by Songsichan.[4] A sealed tube equipped with a magnetic stirring bar was charged with 2-iodobenzamides **1** (0.5 mmol), cyclic enaminones **2** (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 (CH_2Cl_2/EtOAc, 5:1) to provide quinazolinone products **3**.

(11) **Analytical Data for *tert*-Butyl {2-[4-Oxo-2-(4-oxopentyl)quinazolin-3(4*H*)-yl]ethyl}carbamate 3a**

Prepared according to general procedure **B**. Yield 88% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 7.6 Hz, 1 H), 7.71 (t, *J* = 7.6 Hz, 1 H), 7.61 (d, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 5.24 (br s, 1 H), 4.27 (t, *J* = 6.2 Hz, 2 H), 3.48 (q, *J* = 6.2 Hz, 2 H), 2.92 (t, *J* = 6.8 Hz, 2 H) 2.66 (t, *J* = 6.8 Hz, 2 H), 2.28–2.04 (m, 5 H), 1.38 (s, 9 H). ^{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.

(12) **General Procedure C: Synthesis of Quinazolinone-Fused Eleven-Membered Ring Ureas**

To a solution of quinazolinone **3** (0.6 mmol) and benzylamine (0.9 mmol) in CH_2Cl_2 (6 mL) was added sodium triacetoxyborohydride (STABH, 1.2 mmol) and acetic acid (18.0 µL). The resulting mixture was stirred at room temperature under a N_2 atmosphere for 24 h. After that, the resulting mixture was quenched by adding 1.0 N NaOH and extracted with CH_2Cl_2 (3 × 10.0 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. Then, to the crude mixture in CH_2Cl_2 (3.0 mL) was added trifluoroacetic acid (3.0 mL). The mixture was stirred at room temperature under a N_2 atmosphere for 2 h. After that, the resulting mixture was quenched by adding 1.0 N NaOH and extracted with CH_2Cl_2 (3 × 10.0 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give amine crude. Then, the crude mixture in *t*-BuOH (30.0 mL) was stirred at room temperature. CDI (0.72 mmol) was added in the reaction mixture at room temperature and stirred at room temperature for 18 h. After that, *t*-BuOH was evaporated in vacuo. The resulting mixture was quenched with sat. NH_4Cl and extracted with EtOAc (3 × 10.0 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (EtOAc/MeOH, 9:1) to provide quinazolinone-fused eleven-membered-ring ureas **5**.

(13) **Analytical Data for 5-Benzyl-6-methyl-2,3,6,7,8,9-hexahydro-[1,3,6]triazacycloundecino[7,6-*b*]quinazoline-4,15(1*H*,5*H*)-dione (5a)**

Prepared according to general procedure **C**. Yield 60% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD 2 drops): δ = 8.25 (d, *J* = 7.5 Hz, 1 H), 7.71 (t, *J* = 7.5 Hz, 1 H), 7.59 (d, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 1 H), 7.42–7.45 (m, 5 H), 4.78 (d, *J* = 14.7 Hz, 1 H), 4.58 (d, *J* = 14.4 Hz, 1 H), 4.45 (m, 1 H), 4.30 (d, *J* = 14.7 Hz, 1 H), 4.20–4.05 (m, 2 H), 3.53–3.38 (m, 1 H), 3.36–3.20 (m, 1 H), 2.96–2.80 (m, 1 H), 2.63–2.52 (m, 1 H), 2.45–2.28 (m, 1 H), 1.70–1.52 (m, 1 H), 1.51–1.38 (m, 1 H), 1.20–1.11 (m, 1 H), 1.07 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD 2 drops): δ = 162.7, 158.2, 158.0, 147.3, 139.0, 134.5, 129.0, 128.6 (3 C), 127.7, 126.8 (2 C), 126.5, 120.2, 54.5, 52.8, 43.8, 40.3, 31.4, 30.8, 24.5, 20.1. IR (thin film): ν = 3351, 2931, 1661, 1537, 1453, 1305, 1167, 769, 728, 698 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{26}N_4O_2$: 391.2129; found: 391.2129..

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Synthesis of acetyl deoxyvasicinone analogues from 2-(4-oxopentyl) quinazolin-4(3*H*)-ones *via* linear cyclizations

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ABSTRACT

Two deoxyvasicinone analogues were obtained from 2-(4-oxopentyl)quinazolin-4(3*H*)-ones *via* different process of linear cyclizations. The first was 1-acetyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one analogue derived from direct cyclization in the presence of I_2 in basic condition. The other was 1-acetylpyrrolo[2,1-*b*]quinazolin-9(3*H*)-one analogue obtained from two-step procedures beginning with geminal dichlorination in acidic condition, followed by intramolecular C—N bond formation in the presence of para-toluenesulfonic acid.

Introduction

Quinazolione alkaloids are one of important *N*-heterocyclic compounds commonly found in natural products and pharmaceuticals that display a wide range of biological activities.[1] Quinazolinones containing fused-ring systems have been drawn attention due to their molecular structure challenging or biological activities (Scheme 1). [2] Vasicinone and deoxyvasicinone are the quinazolinone fused with pyrrolidine ring isolated from aerial parts of an evergreen subherbaceous bush *Adhatoda vasica*. [3] They and their derivatives exhibit antitumor, [4] hypotensive, [5] anthelmintic, [6] antianaphylactic [7] and brochodilating [8] activities. Therefore, syntheses of deoxyvasicinone, vasicinone and their derivatives have been developed consistently (Fig. 1). [9]

Generally, the preparation of deoxyvasicinone derivertives was conducted with the reaction of anthranilic derivatives and derivatives of pyrrolidones [10] or γ-aminobutyric acids. [11] Direct cyclization of corresponding quinazolinones was an alternative method to construct linear tricyclic quinazolinones. [12] Both 2 and 3-substituted quinazoliones with derivatives of propyl substituents underwent to ring closure to form the pyrrolidine readily. For an example, 2-(3-hydroxypropyl)quinazolin-4(3*H*)-one, pegamine, provided a corresponding deoxyvasicinone via intramolecular Mitsunobu ring-closure reaction. [1a,13] On the other hand, 3-(3-halopropyl)quinazolinon-4-(3*H*)-one underwent peroxide-mediated radical cyclization to obtain a corresponding deoxyvasicinone. [14] Previously, we reported the synthesis of quinazolinones with an alkyl pendent of ketone moiety from copper-catalyzed domino reaction of *N*-benzyl 2-iodobenzamide and cyclic enaminones (Fig. 2, **A**). [15] Based on the reaction, we envisioned that changing the *N*-benzyl to *N*-hydrogen we could obtain the corresponding quinazolinone **1** (Fig. 2, **B**). Next, with the ketone functionality we could directly functionalize an alpha position, such as introducing halogen atom to obtain halogenated quinazolinone (**2**). Having free nitrogen as a nucleophile and alpha halogenated moiety as an electrophile, **2** could possibly undergo to intramolecular cyclization to give 1-acetyl deoxyvasicinone (**3**).

Based on our knowledge, a few derivatives of 1-substituted-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one have been reported. For examples, 1-Methyl deoxyvasicinone was introduced by Nishiyama and co-workers from the selenium-catalyzed reductive *N*-heterocyclization of 5-methyl-1-(2-nitrobenzoyl)pyrrolidin-2-one with CO_2. [16] Deoxyvasicinone having carboxylic acid functionality was reported by Liu and co-workers via the reaction of anthranilic acid and 2-*tert*-butoxycarbonylamino-pentanedioic acid 1-*tert*-butylester in the presence of $P(OPh)_3$ under microwave irradiation. [9e] The Laufersweiler's research group also reported the synthesis of 1-carboxyl deoxyvasicinone as their key intermediate for their evaluation of tricyclic pyrrolopyrimidones as dipeptide mimetics: Inhibition of interleukin-1β-converting enzyme. [17] Herein, we introduce two straightforward protocols to obtain

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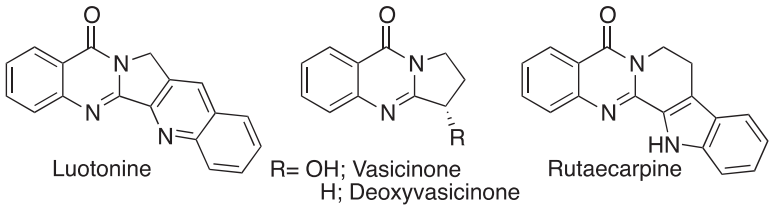


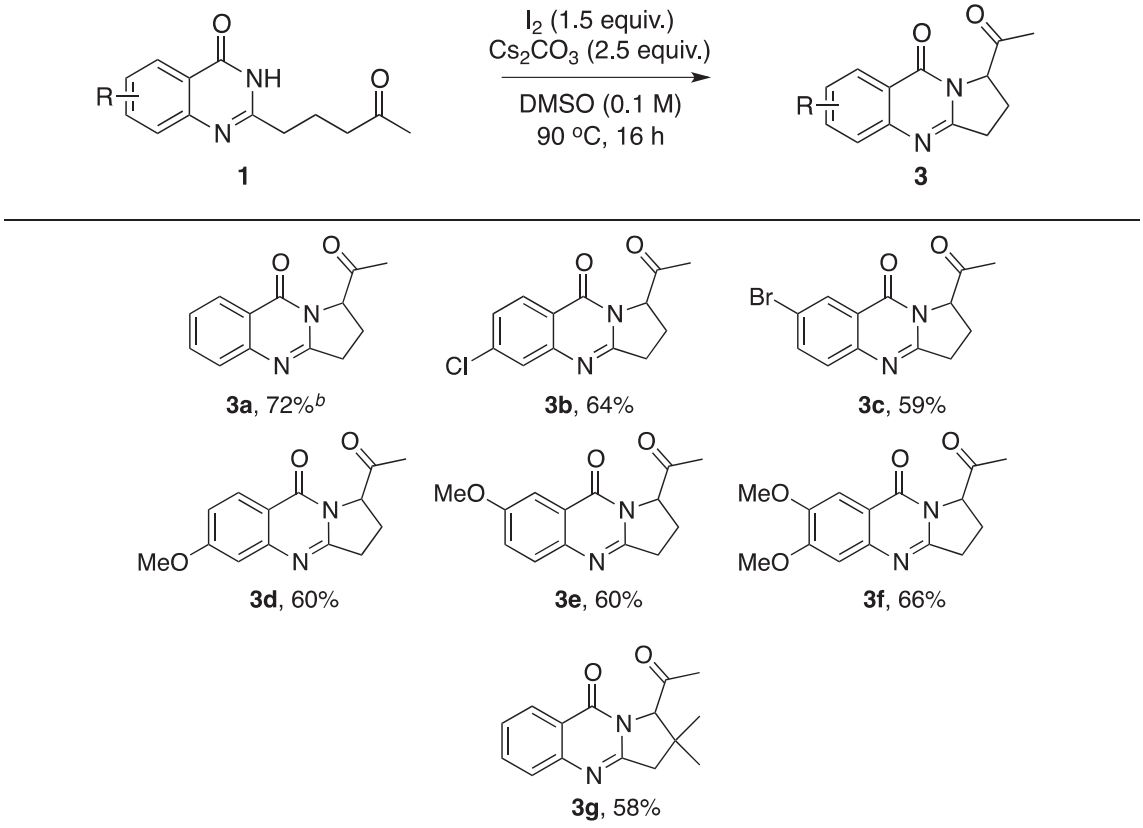
Fig. 1. Selected biological active quinazolinones containg fused ring.

two analogues of deoxyvasicinone derivatives from 2-(4-oxopentyl)quinazolin-(4(3*H*)-ones (**1**).

Results and discussions

We began our investigation with an exploration of common halogenating reagents, such as iodine, *N*-iodosuccinimide, *N*-bromosuccinimide, *N*-chlorosuccinimide and 1,3-dichloro-5,5-dimethylhydantoin in both basic and acidic conditions. A reaction of 2-(4-oxopentyl)quinazolin-4(3*H*)-one (**1a**) was selected as the reaction model (Table 1).

The exploration was started with the basic condition. To our delight, Zhang and co-worker elegantly reported an intramolecular C—N bond formation mediated by I_2 of 2′-*tert*-butyloxycarbonylamino-1,3-diphenylpropanones to obtain a corresponding *N*-Boc-2-benzoylindolines. [18] Therefore, we applied their conditions to the reaction. Nicely, we obtained the acetyl deoxyvasicinone (**3a**) in 32% with 58% recovery yield of starting material **1a** (entry 1). Next, other halogenating reagents, such as NIS, NBS and NCS, were subjected to the exploration. All of them gave low yields of **3a** and high recovery yields of starting material (entries 2–4). Next, we turned our focus on an acidic condition. We began the exploration with 1.2 equiv. of NCS and 20 mol% TFA in CH_2Cl_2. We did not find **3a**. Instead a monochloro **2a** and germinal dichloro **4a** were obtained in 23% and 20% yield, respectively (entry 5). The regioselectivity of **4a** was favorable due to possibly the formation of more stable chloro enol intermediate in acidic condition. In addition we also isolated the quinazolinone **1a** in 20% recovery yield. The attempt to obtain **3a** was made by adding L-proline. Unfortunately, **3a** was not observed. The yield of **2a** was slightly increased to 35% (entry 6). Although in the presence of L-proline we did not obtain the geminal dichloro **4a**, the recovery yield of **1a** was high at 40%. The results suggested that **1a** was not reactive to the reaction condition. However, to drive the reaction to completion, we increased the amount of NCS to 2.1 equivalent resulting in yielding geminal dichlo **4a** in 78% as an isolable-single product (entry 7). Changing halogenating reagent to NBS with 2.1 equivalent



Scheme 1. Synthesis of acetyl deoxyvasicinone derivatives.[a] Reaction condition: **1** (0.6 mmol). [b]Isolated yield.

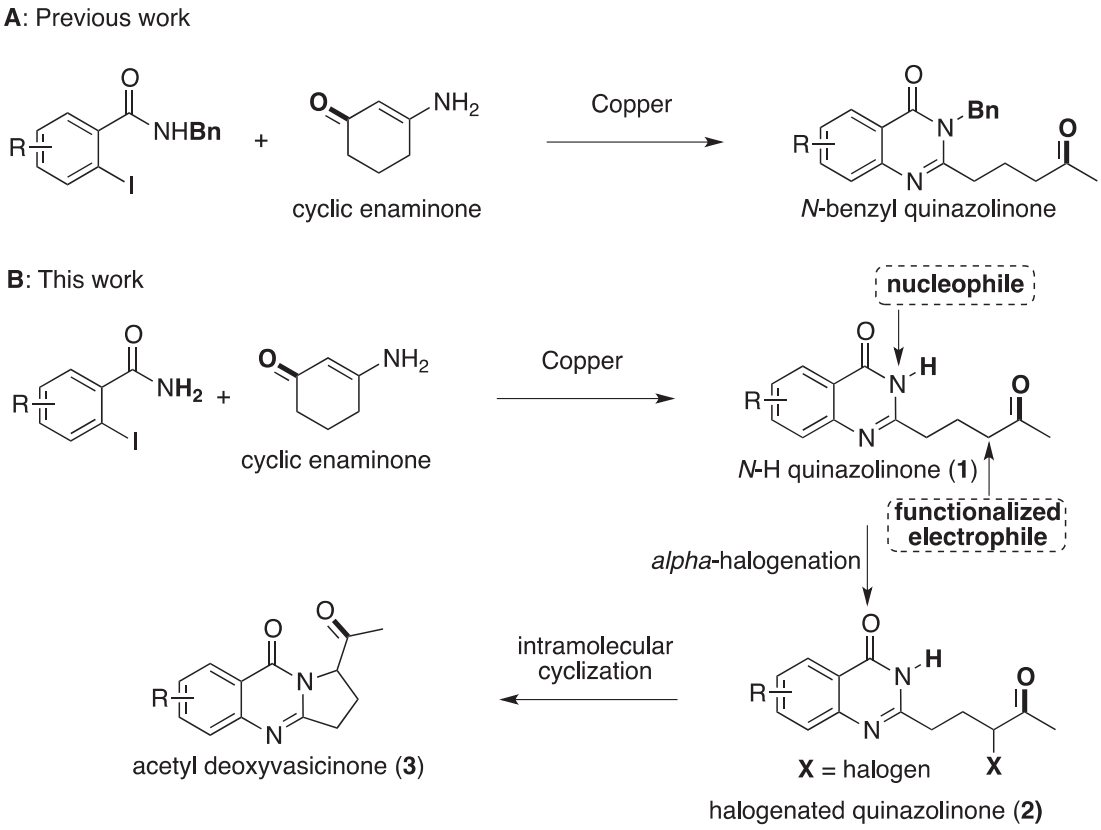
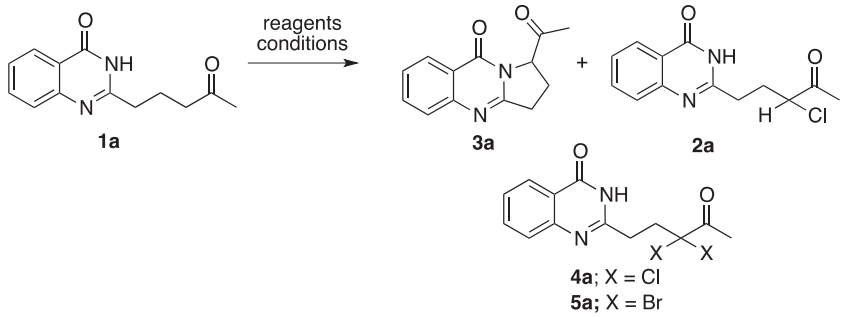


Fig. 2. Quinazolinone synthesis.

Table 1
Exploration of common halogenating reagents.[a]



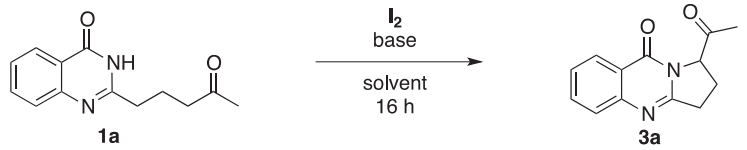
Entry	Reagent	Conditions	Product	% Yield[b]
1	I_2 [1.5 equiv.]	**A**	**3a**:**1a**	32:58[c]
2	NIS [1.5 equiv.]	**A**	**3a**:**1a**	22:69[c]
3	NBS [1.5 equiv]	**A**	**3a**:**1a**	15:77[c]
4	NCS [1.5 equiv.]	**A**	**3a**:**1a**	5:91[c]
5	NCS [1.2 equiv.]	**B**	**2a**:**4a**:**1a**	23:20:20[c]
6	NCS [1.2 equiv.]	**B**[d]	**2a**:**4a**:**1a**	35:0:40[c]
7	NCS [2.1 equiv.]	**B**	**4a**	78
8	NBS [2.1 equiv.]	**B**	**5a**	66

[a] Condition: **1a** (0.6 mmol); **A**: K_2CO_3 (3.0 equiv.), MeOH (0.1 M), 60 °C, 16 h; **B**: TFA (20 mol%), CH_2Cl_2 (0.1 M), 40 °C, 16 h.
[b] Isolated yield.
[c] Recovery yield.
[d] L-proline (20 mol%) was added.

provided geminal dibromo **5a** in 66% (entry 8). In addition, the reactions using NIS or I_2 with 2.1 equivalent gave no germinal diiodo product. Based on the results of acidic conditions, the nitrogen nucleophile of quinazolinone could not directly replace the halogen.

Based on the results from the Table 1, the condition with iodine in basic condition provided the desired product with the highest yield. Therefore, we further optimized the reaction condition with iodine as a halogenating reagent (Table 2).

Table 2
Optimization reaction with I_2.



Entry	base	Solvent	Temperature	Yield (%)[b]
1	K_2CO_3	MeOH	60	32
2	Cs_2CO_3	MeOH	60	39
3	K_3PO_4	MeOH	60	22
4	^{t}BuOK	MeOH	60	trace
5	DBU	MeOH	60	18
6	Cs_2CO_3	DMSO	90	72
7	Cs_2CO_3	DMF	90	0
8	Cs_2CO_3	MeCN	90	trace
9	Cs_2CO_3	$CHCl_3$	90	0
12	Cs_2CO_3	DMSO	110	68

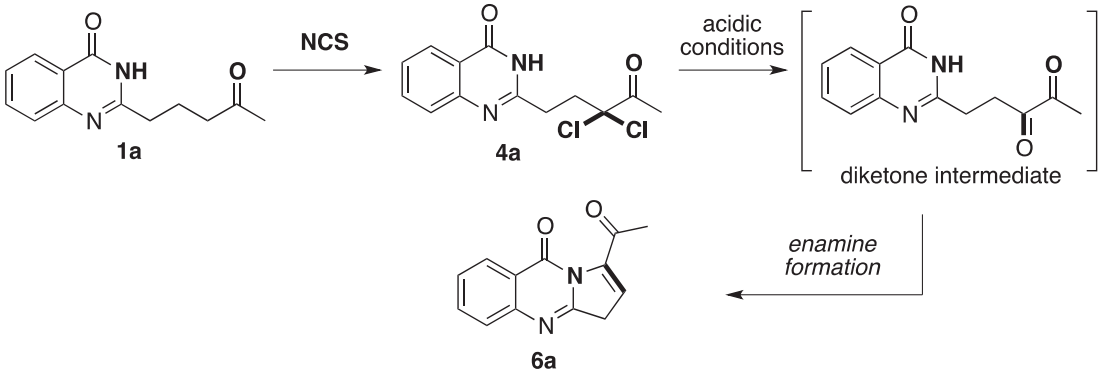
[a]Reaction condition: **1a** (0.6 mmol), I_2 (1.5 equiv.), base (2.5 equiv.), solvent (0.1 M).
[b]Isolated yield.

A variety of bases were applied to the reaction (entries 2–5). The yield of product was slightly increased to 39% when Cs_2CO_3 was used (entry 2). Trace amount of product was observed from reactions with ^{t}BuOK (entry 4). Comparable low yields, 22% or 18%, were observed from the reaction with K_3PO_4 or DBU, respectively (entries 3 and 5). Weak bases were favored for the reaction. Next we varied the solvent and also heated the reaction to 90 °C. We found that DMSO was more effective than other solvents providing the product in 72% yield (entry 6). Other solvents, such as DMF, MeCN or $CHCl_3$ gave 0% or trace amount of product (entries 7–9). Increasing the reaction temperature to 110 °C diminished yield of product to 68% (entry 12). Therefore the optimal condition was the use of I_2 and Cs_2CO_3 in DMSO at 90 °C for 16 h. Note that: we also explored other halogenating reagents, such as NIS, NBS and NCS for the optimal condition resulting in 45%, 40% and 0%, respectively.

With the optimal reaction condition, we next explored a variety of **1** (Scheme 1). The moderate yields of products were obtained. The 72% yield was obtained from non-substituted benzene ring of quinazolinone (**3a**). The yield of product was slightly diminished when halogen-substituted quinazolinones were used giving 64% and 59% yields from Cl and Br, respectively (**3b** and **3c**). The 60% was obtained from quinazolinones having 4-methoxy- or 5-methoxy substituent (**3d** and **3e**). Comparable yield was found in dimethoxy-substituted quinazolinone providing 66% yield of product (**3f**). The quinzalinone with beta geminal dimethyl underwent to the reaction giving a corresponding product in moderate yield, 58% (**3g**). Although we did not exhaustively explore the substrate, we found that both electronic effect of quinzolinone ring and steric effect of alkyl chain played some certain role in the reaction.

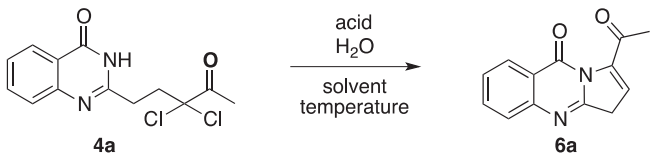
Since we found the condition to provide geminal dichlorinated adduct (**4a**) (Table 1, entry 7), we next focused on the utilization of **4a**. Greatly, the α-geminal dichlorinated carbonyls could be converted to 1,2-diones efficiently in acidic conditions. [19] Therefore, we envisioned that we could synthesize an alternative acetyl deoxyvasicinone having enone functionality (Scheme 2).

We then focused on the formation of the acetyl deoxydehydrovasicinone from dichloro adduct. The chemical transformation was projected to be the formation of diketone followed by the intramolecular enamine formation in one reaction process. The conversions of dichloro moiety to the corresponding diketones were carried out via both basic [20] and acidic [19] conditions. However, the basic condition consisted of two processes, formation of dialkoxy and acidic hydrolysis. On the other hand, the acidic condition could provide the corresponding diketone in one reaction process via acidic hydrolysis. However, the 80 °C – 90 °C of the reaction temperature was required. Based on these findings, we selected the acidic condition. Not only the reaction could provide diketone in one process, but also the diketone intermediate could undergo to enamine cyclization in the presence of acid. The reaction of 2-(3,3-dichloro-4-oxopentyl)quinazolin-4(3*H*)-one (**4a**) was selected as a reaction model (Table 3).



Scheme 2. The synthesis strategy of 1-acetylpyrrolo[2,1-*b*]quinazolin-9(3*H*)-one (**6a**).

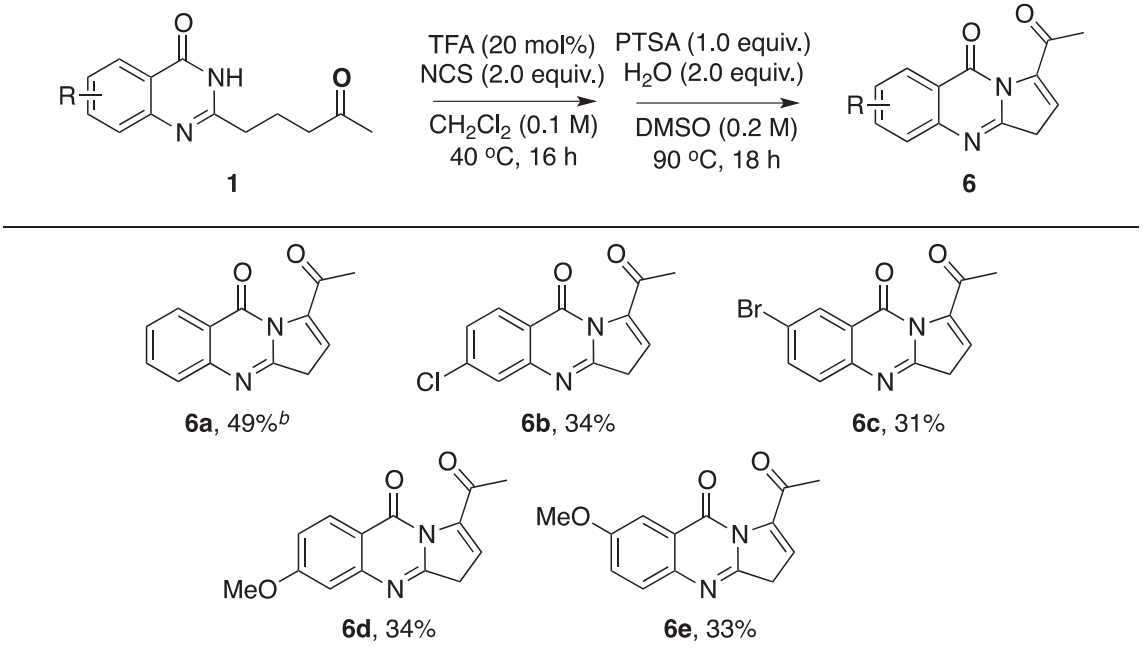
Table 3
The reaction condition of 1-acetylpyrrolo[2,1-*b*]quinazolin-9(3*H*)-one formation.[a]



4a **6a**

Entry	Acid [mol%]	Equiv. of H_2O	Solvent [M]	Temperature	Yield[b]
1	Conc. H_2SO_4 [50]	–	DMSO [0.2]	90	44
2	Conc. HCl [50]	–	DMSO [0.2]	90	38
3	CH_3COOH [50]	–	DMSO [0.2]	90	trace
4	CF_3COOH [50]	–	DMSO [0.2]	90	41
5	PTSA [50]	–	DMSO [0.2]	90	51
6	PTSA [50]	1.0	DMSO [0.2]	90	57
7	PTSA [50]	1.0	CH_3CN [0.2]	90	trace
8	PTSA [50]	1.0	CH_3Ph [0.2]	90	NR[c]
9	PTSA [50]	1.0	$CHCl_3$ [0.2]	60	trace
10	PTSA [50]	1.0	DMF [0.2]	90	37
11	PTSA [50]	2.0	DMSO [0.2]	90	62
12	PTSA [50]	10.0	DMSO [0.2]	90	50
13	PTSA [100]	2.0	DMSO [0.2]	90	67

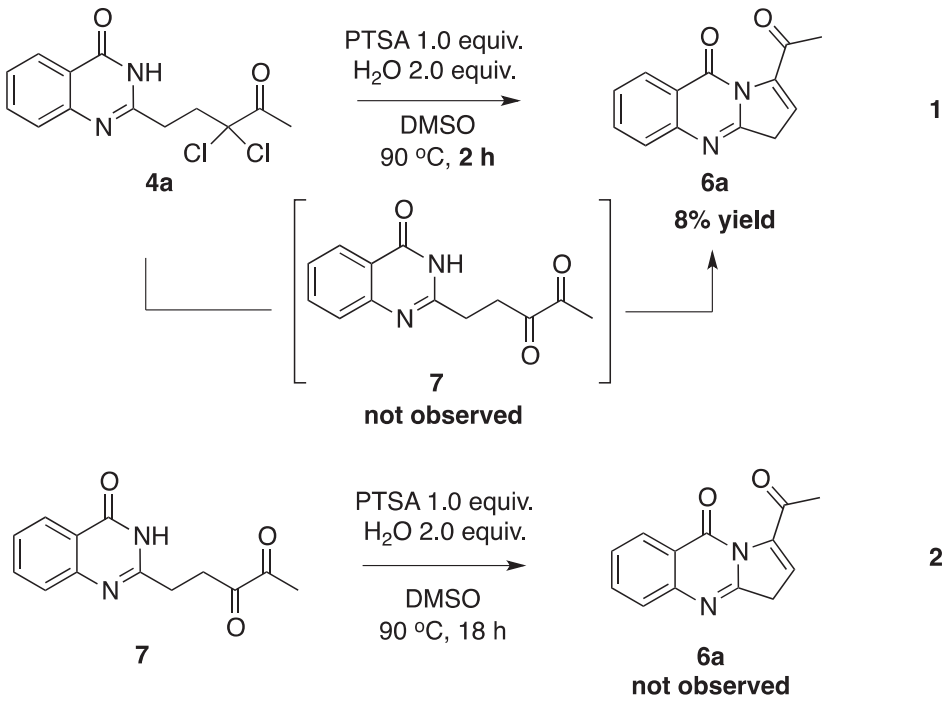
[a] Reaction condition: **4a** (0.6 mmol) and 16 h.
[b] Isolated yield.
[c] No reaction.



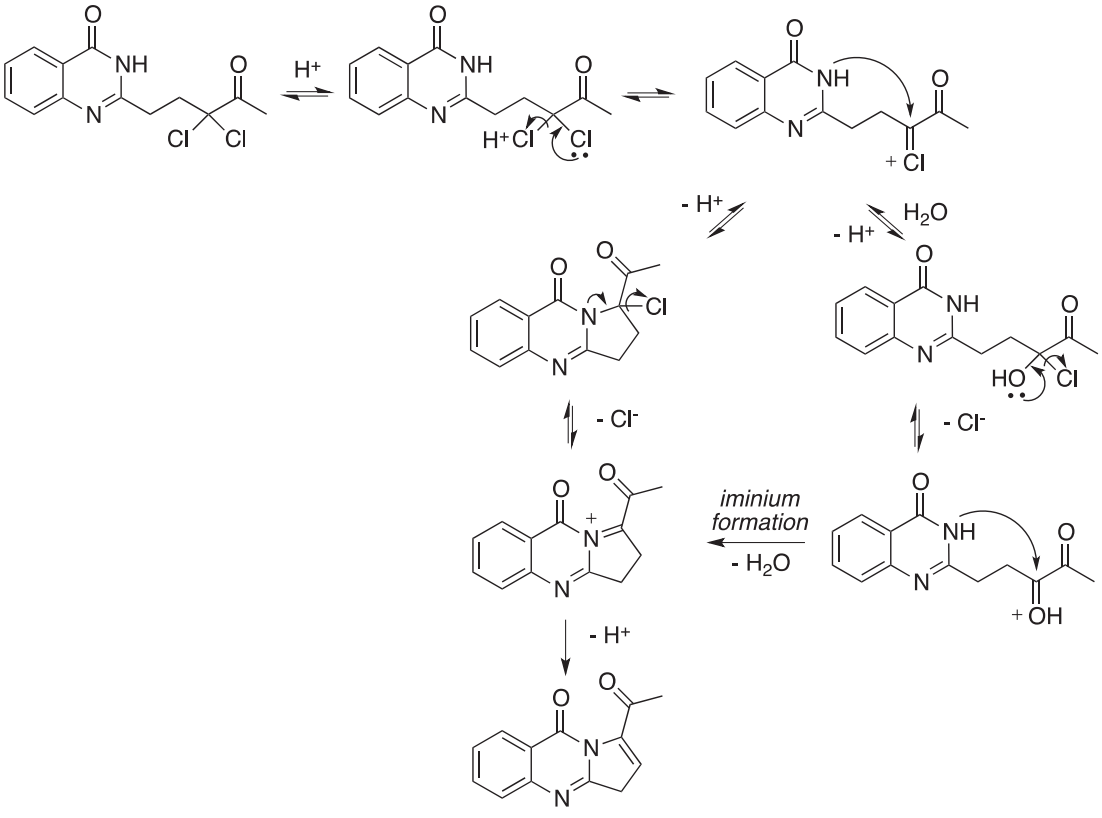
Scheme 3. Two step processes of 1-acetylpyrrolo[2,1-*b*]quinazolin-9(3*H*)-one formations[a] Reaction condition: **1** (0.6 mmol). [b]Isolated yield over two steps.

We began with the common acids, such as conc. H_2SO_4, conc. HCl, acetic acid, trifluoroacetic acid (TFA) and *p*-toluenesulfonic acid (entries 1–5). Moderate yields of product were observed except acetic acid giving trace amount of product. The yield of product was slightly increased when the 1.0 equivalent of H_2O was added (entry 6). Next, we found that polar solvent was crucial for the reaction. The use of $CHCl_3$, CH_3Ph or CH_3CN provided no reaction or trace amount of product (entries 7–9). DMF also provided moderate yield of product, 37% (entry 10). The amount of H_2O also played a key role in the reaction (entries 11 and 12). The yield of product was increased to 62% with 2.0 equivalent of H_2O (entry 11). On the contrary, increasing the amount of H_2O to 10.0 equivalent provided decreasing of product yield (entry 12). The results suggested that the small amount of H_2O was necessary to improve the product yield. A better yield, 67%, was obtained when 1.0 equivalent of PTSA was used (entry 13). Therefore, the use of 1.0 equivalent of PTSA and 2.0 equivalent of H_2O in DMSO at 90 °C for 18 h was optimal condition.

After the conditions of both reactions, dichlorination and cyclization, were optimized, we explored a variety of substrates (Scheme 3). Satisfactorily, we found that we could accomplish the product (**6**) via two-step procedures.



Scheme 4. Control experiments.



Scheme 5. The possible chemical transformation.

Non-substituted quinazolinone provided the acetyl deoxydehydrovasicinone in 49% yield (**6a**). Both chloro and bromo-substituted quinazolinone gave 34% and 31% yields, respectively (**6b** and **6c**). Methoxy-substituted quinazolinones at C7 and C6 gave corresponding product in 34% and 33% yields, respectively (**6d** and **6e**). Although the yields of the products over two steps were low to moderate, we could simply access to the acetyl deoxyvasicinone analogues readily. In addition, having enone moiety the 1-

acetylpyrrolo[2,1-*b*]quinazolin-9(3*H*)-one could be further functionalized to provide more a variety of deoxyvasicinones.

Next, we preliminarily investigated a chemical transformation from the geminal dichlorinated adduct to the corresponding deoxyvasicinone product. We conducted a set of control experiments (Scheme 4).

Firstly, we shorted the reaction time to one hour (Scheme 4, eq 1). We hoped that we might find the reaction intermediate, dione **7** in this case. Unfortunately, we did not observe dione **7** from a ^{1}H NMR of the crude reaction mixture. Instead, **6a** was obtained in 8% yield with 85% recovery yield of **4a**. Based on the result, we hypothesized that having nitrogen nucleophile the *in situ* intramolecular cyclization occurred to form **6a** rapidly. Next, we prepared the dione adduct **7**. Then, we subjected the adduct **7** to the reaction (Scheme 4, eq 2). Interestingly, no expected product **6a** was observed.

Based on the control experiment and the presence of H_2O in the reaction, we proposed the possible reaction transformation that an acid initially activated the geminal dichloro moiety to form the chloronium intermediate (Scheme 5). The intermediate could possibly undergo intramolecular cyclization to form C—N bond, followed by an elimination of Cl and isomerization to obtain the 2-acetyl dehydrodeoxyvasicinone product. Since the reaction went smoothly in the presence of water, we alternatively proposed that the chloronium intermediate possibly reacted with water to form chloro hydrin intermediate, followed by elimination of chloride ion to generate oxonium intermediate, in which this intermediate might not be generated when **7** was subjected to the reaction according to the control experiment. Finally, the cyclization and isomerization took place to form the product.

Conclusion

We have herein reported the facile syntheses of two deoxyvasicinone analogues, 1-acetyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones and 1-acetylpyrrolo[2,1-*b*]quinazolin-9(3*H*)-ones, from 2-(4-oxopentyl)quinazolin-4(3*H*)-one derivatives via two reaction procedures. Firstly, the 1-acetyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones were obtained smoothly via alpha iodination followed by intramolecular C—N bond formation to form the five-membered ring in basic conditions. The corresponding products were obtained in moderate to good yields. On the other hand, the other procedure providing 1-acetylpyrrolo[2,1-*b*]quinazolin-9(3*H*)-ones consisted of two processes, geminal dichlorination and cyclization. The geminal dichlorination was obtained from the reaction of *N*-chlorosuccinimide in acidic condition. The cyclization was achieved in the presence of PTSA. Although the yields of acetyl deoxydehydrovasicinones were moderate, we readily could access to the deoxyvasicinones having rich functional group on the pyrrole ring. Interestingly, having enone moiety the product could be potentially further functionalized.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2023.154484.

References

[1] (a) S.B. Mhaske, N. Argade, P. Tetrahedron 62 (2006) 9787–9826;
(b) S.L. Cao, Y.P. Feng, Y.Y. Jiang, S.Y. Liu, G.Y. Ding, R. Li, T, Bioorg. Med. Chem. Lett. 15 (2005) 1915–1917;
(c) J.P. Michael, Nat. Prod. Rep. 21 (2004) 650–668;
(d) I. Khan, A. Ibrar, N. Abbas, A. Saeed, Eur. J. Med. Chem. 76 (2004) 193–224;
(e) U.A. Kshirsagar, Org. Biomol. Chem. 13 (2015) 9336–9352.
[2] (a) M. Demeunynck, I. Baussanne, Curr. Med. Chem. 2 (2013) 794–814;
(b) R. Arora, A. Kapoor, N.S. Gill, A. Rana, C. Int. Res. J. Pharm. 2 (2011) 21–28;
(c) P.C. Sharma, G. Kaur, R. Pahwa, A. Sharma, H. Rajak, Curr. Med. Chem. 18 (2011) 4786–4812;
(d) Y. Saebang, J. Kaeobamrung, V. Rukachaisirikul, Synlett 33 (2022) 1371–1376.
[3] (a) A.H. Amin, D. Mehta, Nature 183 (1959) 1317;
(b) D.R. Mehta, J.S. Naravane, R. Desai, J. Org. Chem. 28 (1963) 445–448;
(c) M.P. Jain, S.K. Koul, K.L. Dhar, C. Atal, Phytochemistry 19 (1980) 1880–1882.
[4] C.-H. Wang, H. Zeng, Y.-H. Wang, C. Li, J. Cheng, Z.-J. Ye, X.-J.-J. He, Asian Nat. Prod. 17 (2015) 595–600.
[5] (a) T. Jen, B. Dienel, F. Dowalo, H.V. Hoeven, P. Bender, B. Love, J. Med. Chem. 16 (1973) 633–637;
(b) O.P. Gupta, M.L. Sharma, B.J. Ray-Ghatak, C. Atal, Indian J. Med. Res. 66 (1977) 680–691.
[6] A.H.M.M. Rahman, M. Anisuzzaman, S.A. Haider, F. Ahmed, A.K.M.R. Islam, A. Naderuzzaman, T. M. *J. Agric. Biol. Sci.* 4 (2008) 70–74.
[7] M.B. Bhide, P.Y. Naik, R. Ghooi, B. *Bull Haffkin Inst.* 4 (1976) 45–50.
[8] A. Zabeer, A. Bhaget, O.P. Gupta, G.D. Singh, M.S. Youssouf, K.L. Dhar, O.P. Suri, K.A. Suri, N.K. Satti, B.D. Gupta, G.N. Qazi, Eur. J. Med. Chem. 41 (2006) 429–434.
[9] (a) R.C. Morris, W.E. Hanford, A. Roger, J. Am. Chem. Soc. 57 (1935) 951–954;
(b) T. Kametani, T. Higa, C.V. Loc, M. Ihara, M. Koizumi, K. Fukumoto, J. Am. Chem. Soc. 98 (1976) 6186–6188;
(c) A. Kamal, K.V. Ramana, H.B. Ankati, A.V. Ramana, Tetrahedron Lett. 43 (2002) 6861–6863;
(d) V. Ziaee, H. Jalalizadeh, M. Iranshahi, A. Shafiee, Iran. J. Chem. Chem. Eng. 23 (2004) 33–36;
(e) J.-F. Liu, P. Ye, K. Sprague, K. Sargent, D. Yohannes, C.M. Baldino, C.J. Wilson, S.-C. Ng, Org. Lett. 7 (2005) 3363–3366;
(f) R.S. Rohokale, U. Kshirsagar, A. Synthesis 48 (2016) 1253–1268;
(g) N.M. Moreira, J.R.N. dos Santos, A.G. Corrêa, Eur. J. Org. Chem. 2022; e202200369: 1–29.
[10] (a) T. Onaka, Tetrahedron Lett. 12 (1971) 4387–4390;
(b) M. Mori, H. Kobayashi, M. Kimura, Y. Ban, Heterocycles 23 (1985) 2803–2806;
(c) E.S. Lee, J.-G. Park, Y. Jahng, Tetrahedron Lett. 44 (2003) 1883–1886;
(d) A. Kamal, K.V. Ramana, M.V.J. Rao, Org. Chem. 2001; 66: 997–1001.
[11] B. Ojo, B.K. Chowdhury, Synth. Commun. 42 (2012) 1002–1009.
[12] (a) M.H. Larraufie, C. Courillon, C. Ollivier, E. Lacôte, M. Malacria, L. Fensterbank, J. Am. Chem. Soc. 132 (2010) 4381–4387;
(b) G. Xu, C. Tong, S. Cui, L. Dai, Org. Biomol. Chem. 16 (2018) 5899–5906;
(c) H. Baguia, C. Deldaele, E. Romero, B. Michelet, G. Evano, Synthesis 50 (2018) 3022–3030;
(d) C.L. Sutherell, S.V. Ley, Synthesis 49 (2017) 135–144.
[13] S.B. Mhaske, N. Argade, P, J. Org. Chem. 66 (2001) 9038–9040.
[14] J. Garcia-Ramirez, L. Miranda, Synthesis 523 (2021) 1471–1477.
[15] T. Songsichan, J. Promsuk, V. Rukachaisirikul, J. Kaeobamrung, Org. Bimol. Chem. 12 (2014) 4571–4575.
[16] Y. Nishiyama, M. Hirose, W. Kitagaito, N. Sonoda, Tetrahedron Lett. 43 (2002) 1855–1858.
[17] M.C. Laufersweiler, Y. Wang, D.L. Soper, M.K. Suchanek, A.N. Fancher, W. Lu, R. L. Wang, K.A. Oppong, C.D. Ellis, M.W. Baize, S.V. O'Neil, J.A. Wos, T. Demuth Jr., P, Bioorg. Med. Chem. Lett. 15 (2005) 4322–4326.
[18] W.C. Gao, S. Jiang, R.-L. Wang, C. Zhang, Chem. Commun. 49 (2013) 4890–4892.
[19] M. Sharon, A. Parker, C. Rizzo, J. *Synth. Commun.* 25 (1995) 2781–2789.
[20] N.D. Kimpe, R. Verhé, L.D. Buyck, N. Schamp, J. Org. Chem. 43 (1978) 2933–2935.

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

Figure 10 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **134a** in $CDCl_3$

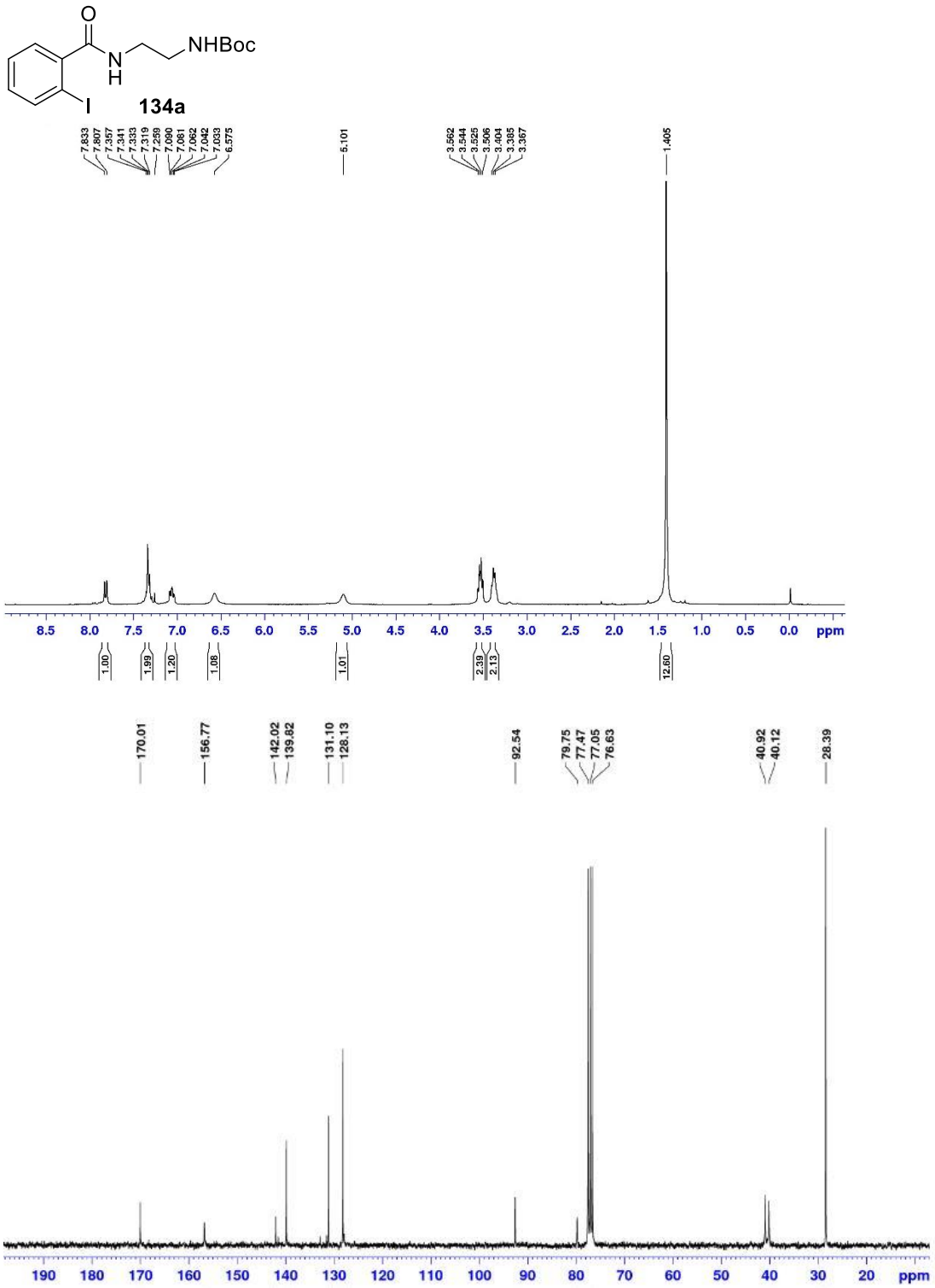


Figure 11 The ^{1}H (300 MHz) spectra in $CDCl_3$ and ^{13}C NMR (75 MHz) spectra in DMSO-d_6 of compound **134b**

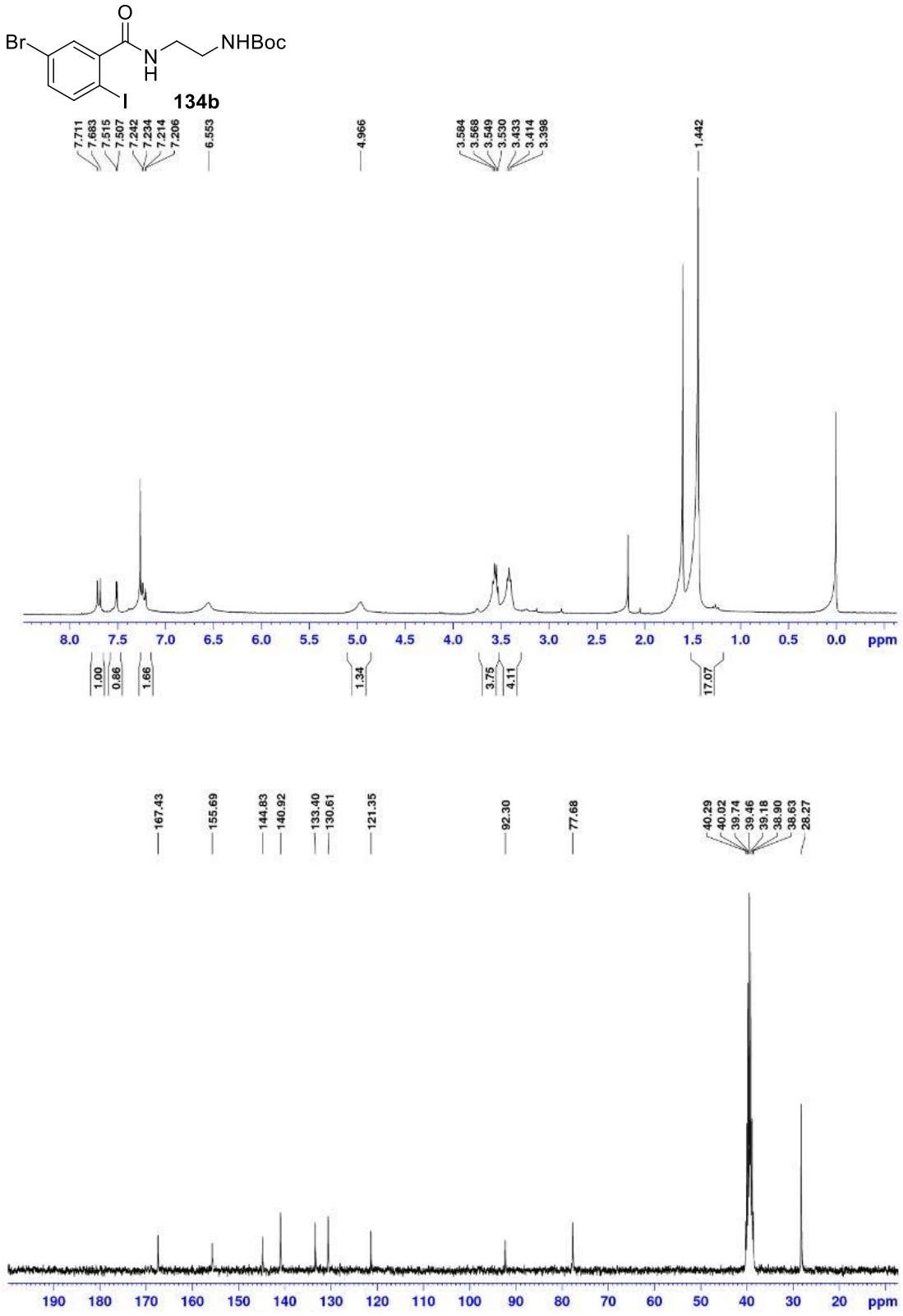


Figure 12 The ^{1}H (300 MHz) spectra in $CDCl_3$ and ^{13}C NMR (75 MHz) spectra in DMSO-d_6 of compound **134C**

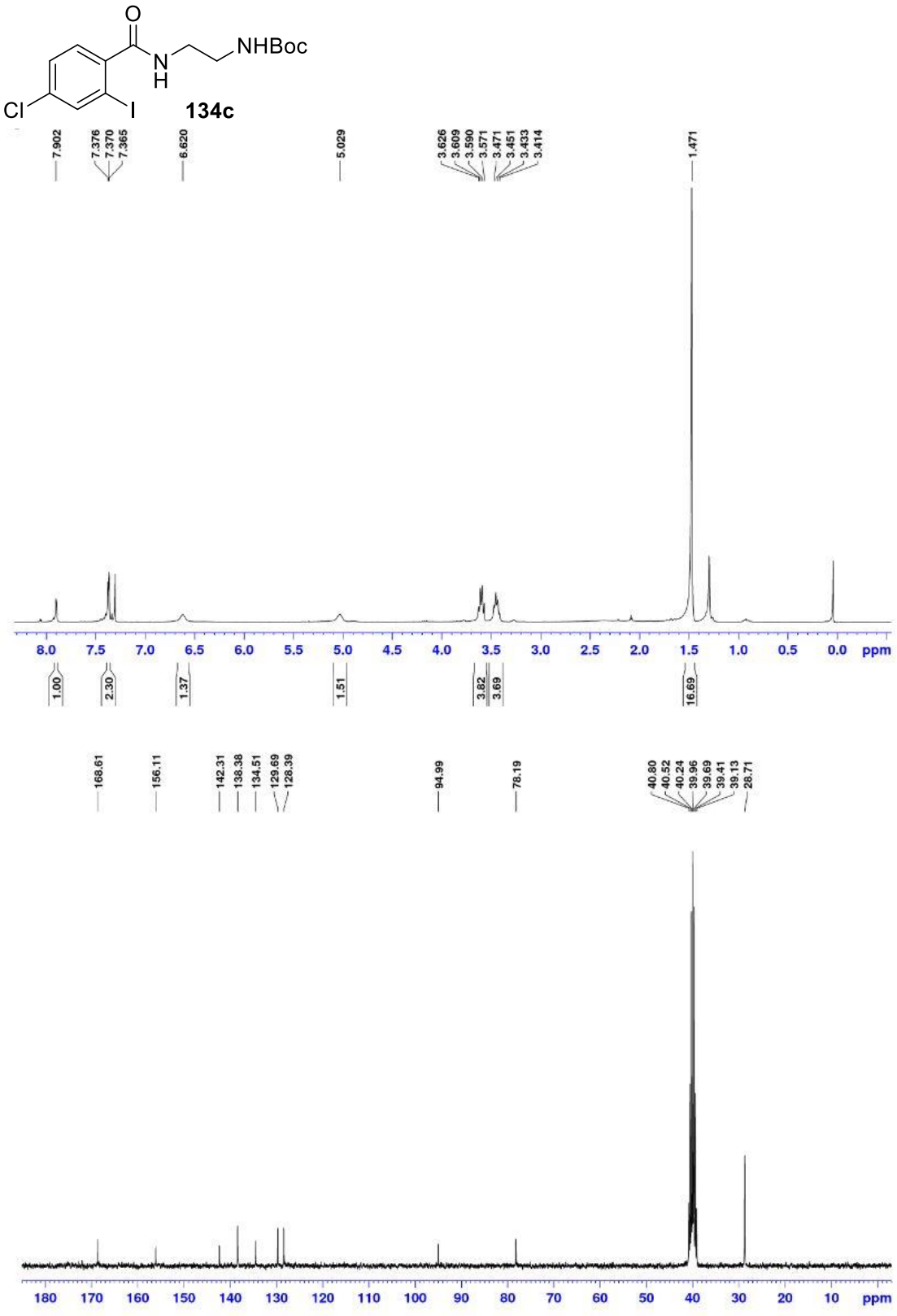


Figure 13 The ^{1}H (300 MHz) spectra in $CDCl_3$ and ^{13}C NMR (75 MHz) spectra in DMSO-d_6 of compound **134d**

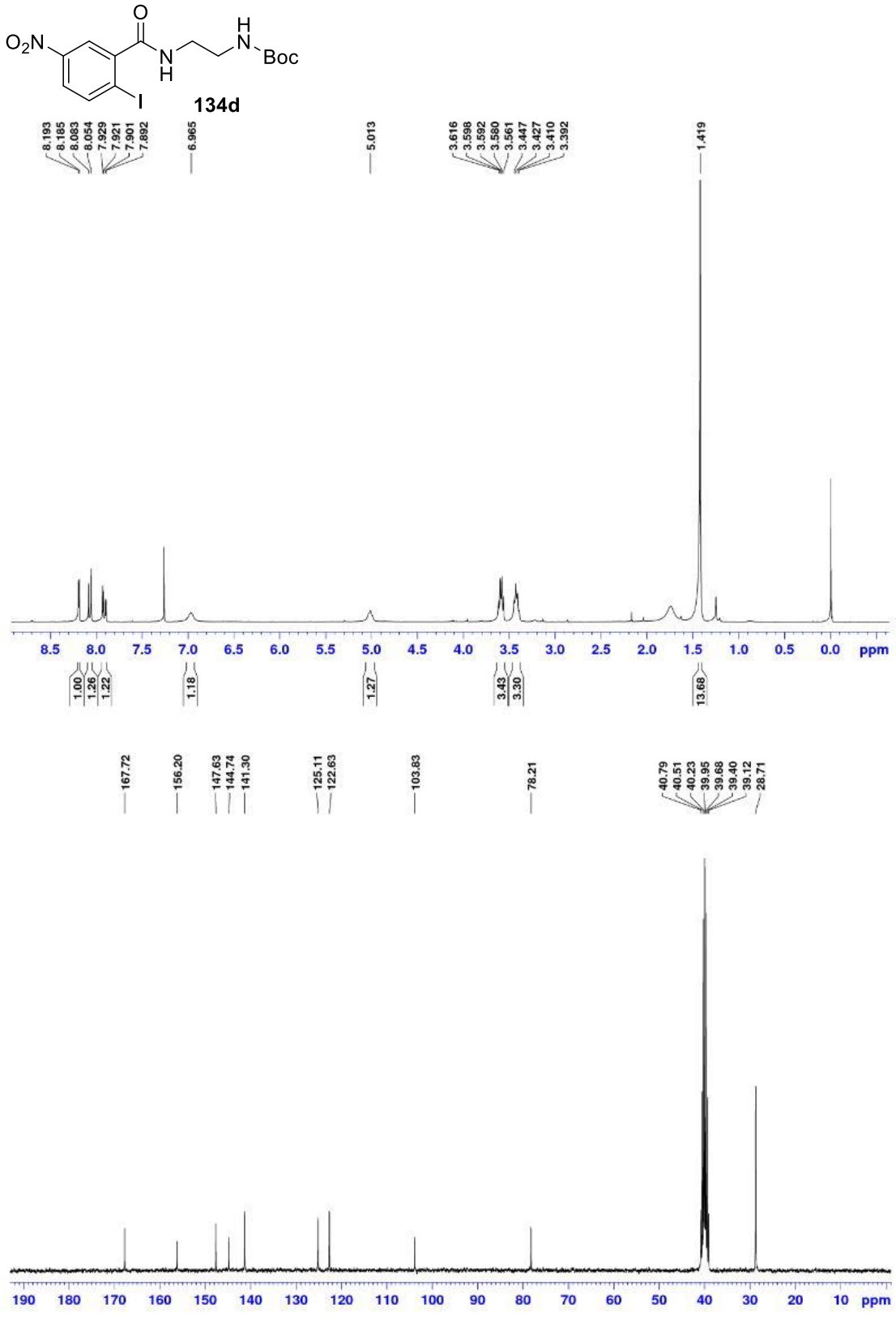


Figure 14 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **134e** in DMSO-d_6

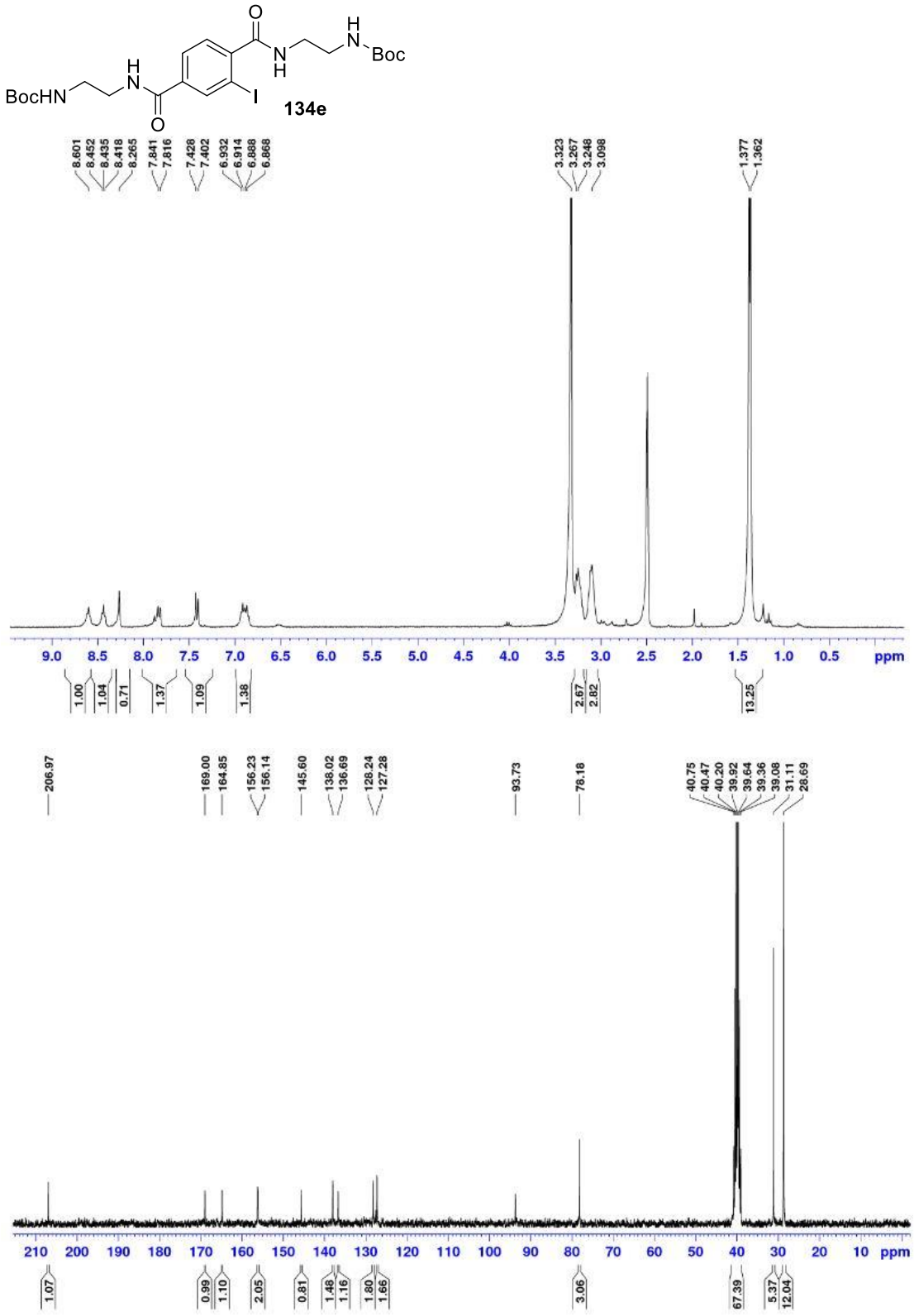


Figure 15 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **134f** in $CDCl_3$

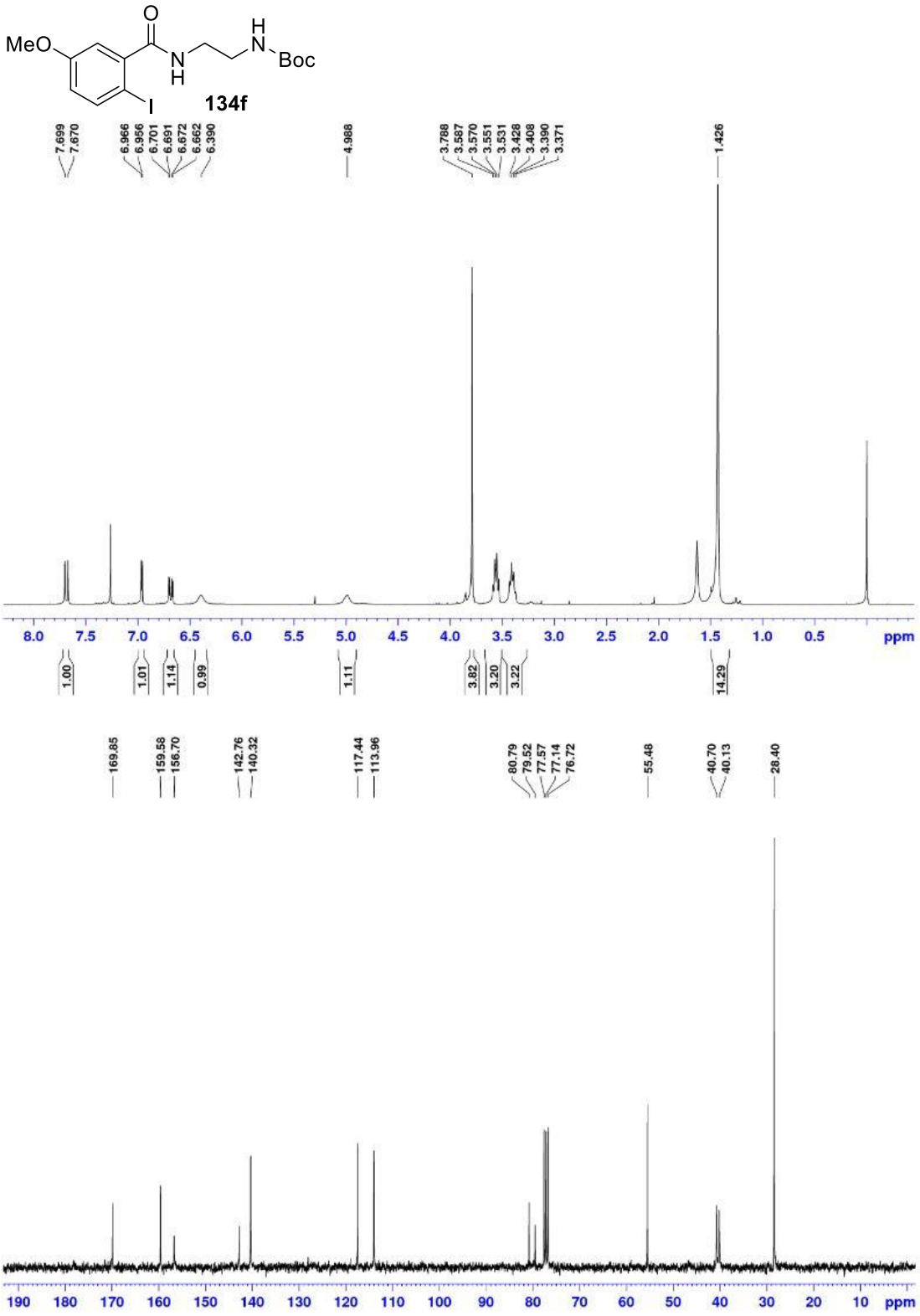


Figure 16 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **134g** in $CDCl_3$

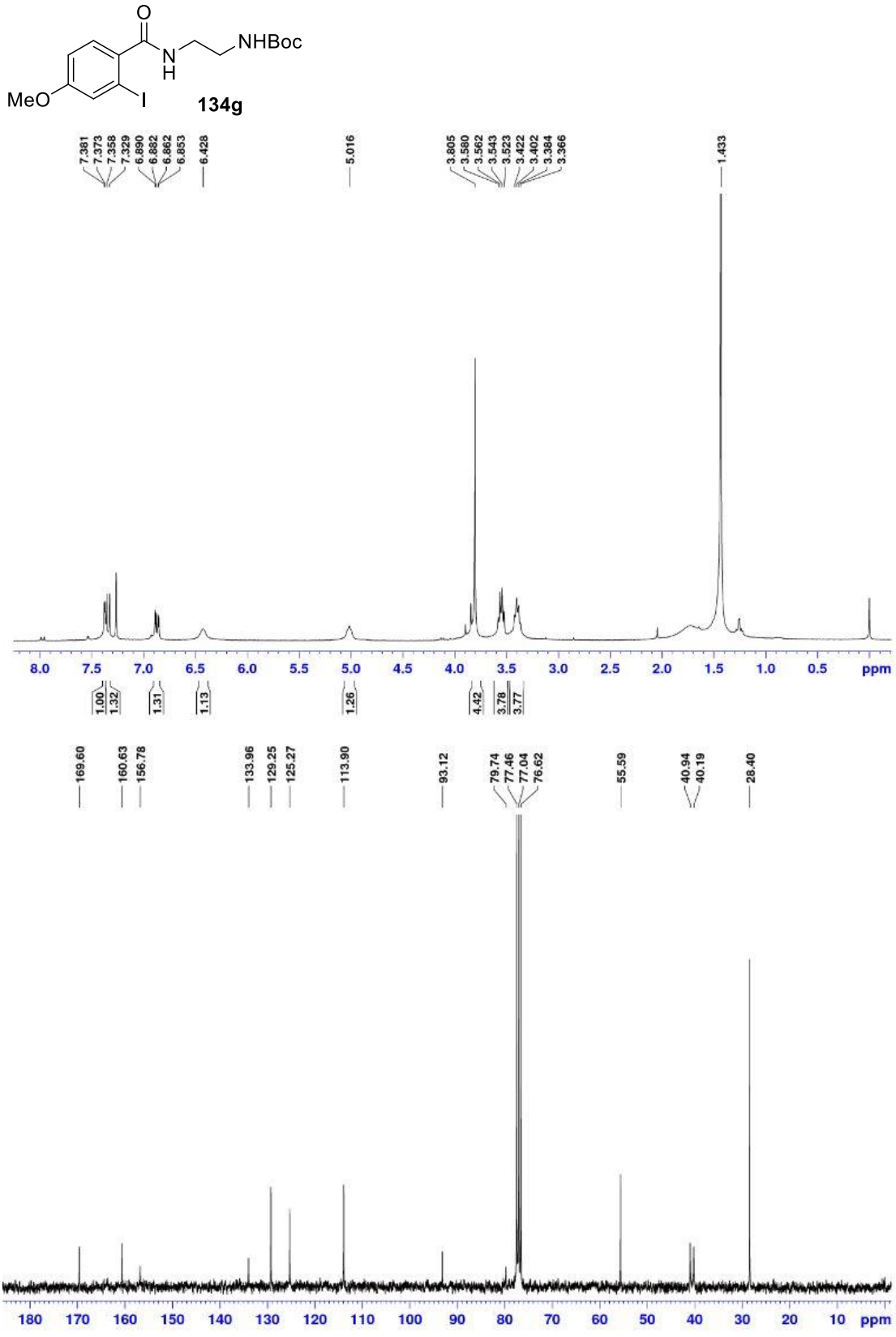


Figure 17 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **134h** in $CDCl_3$

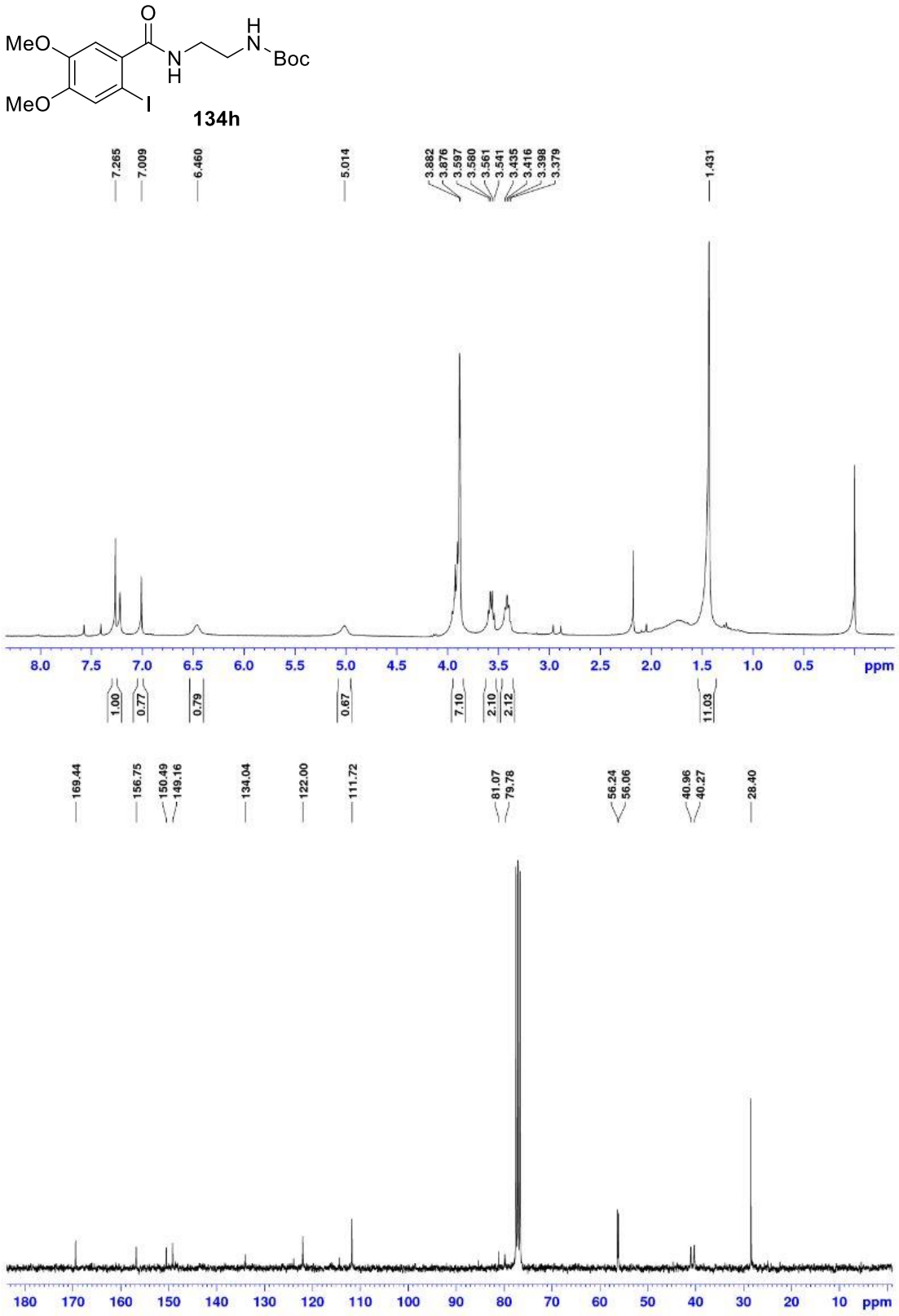


Figure 18 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **135a** in $CDCl_3$

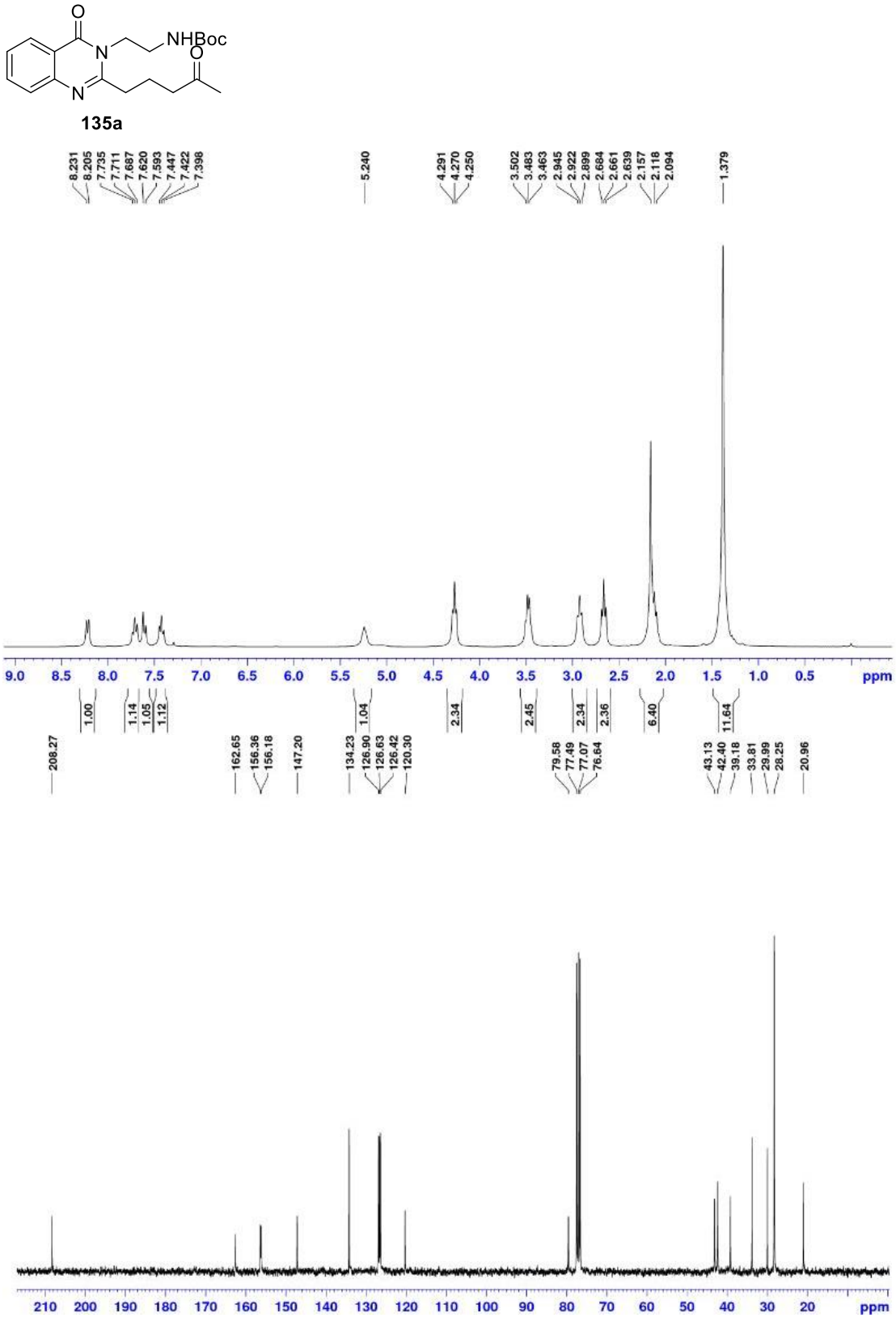


Figure 19 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **135b** in $CDCl_3$

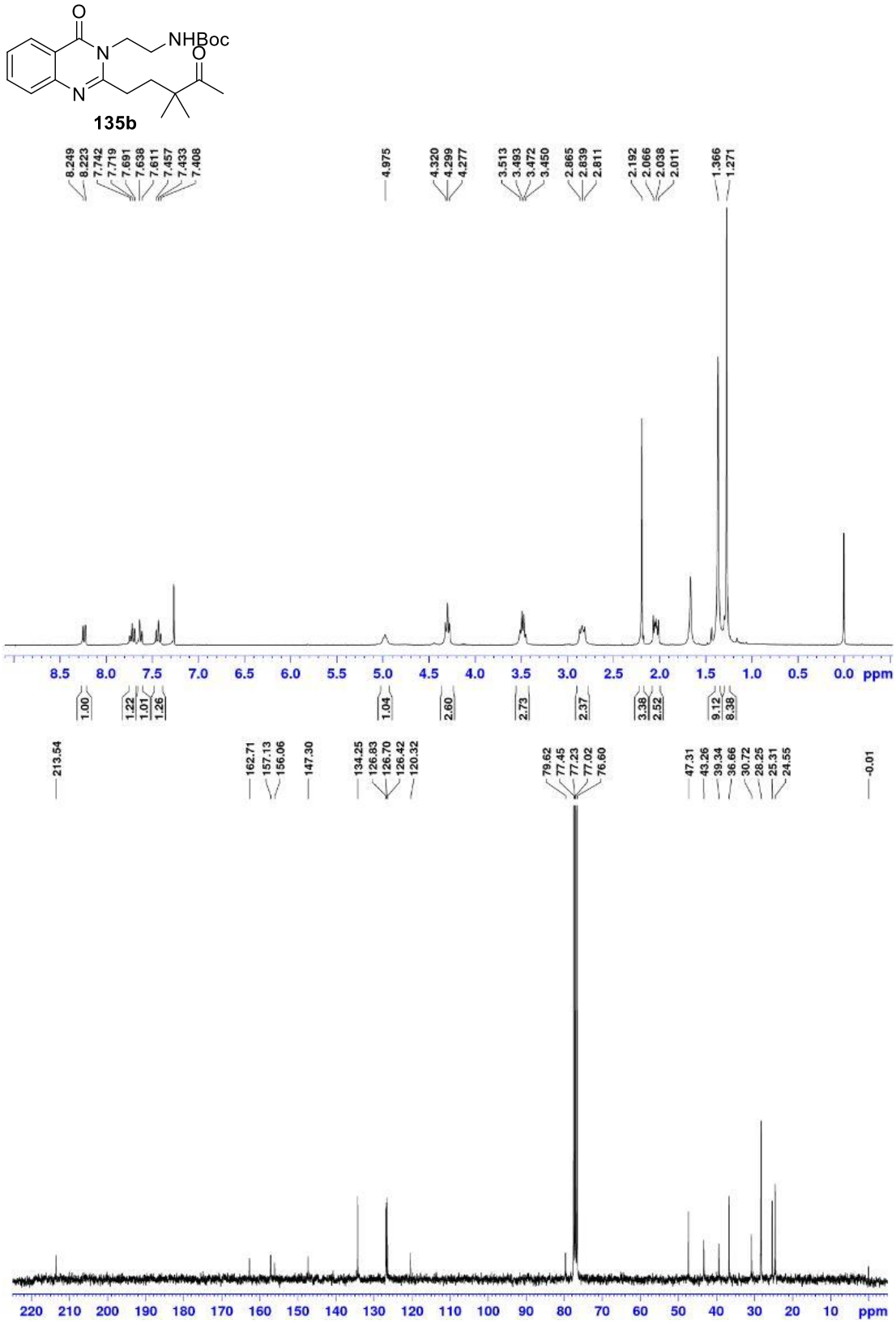


Figure 20 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **135d** in DMSO-d_6

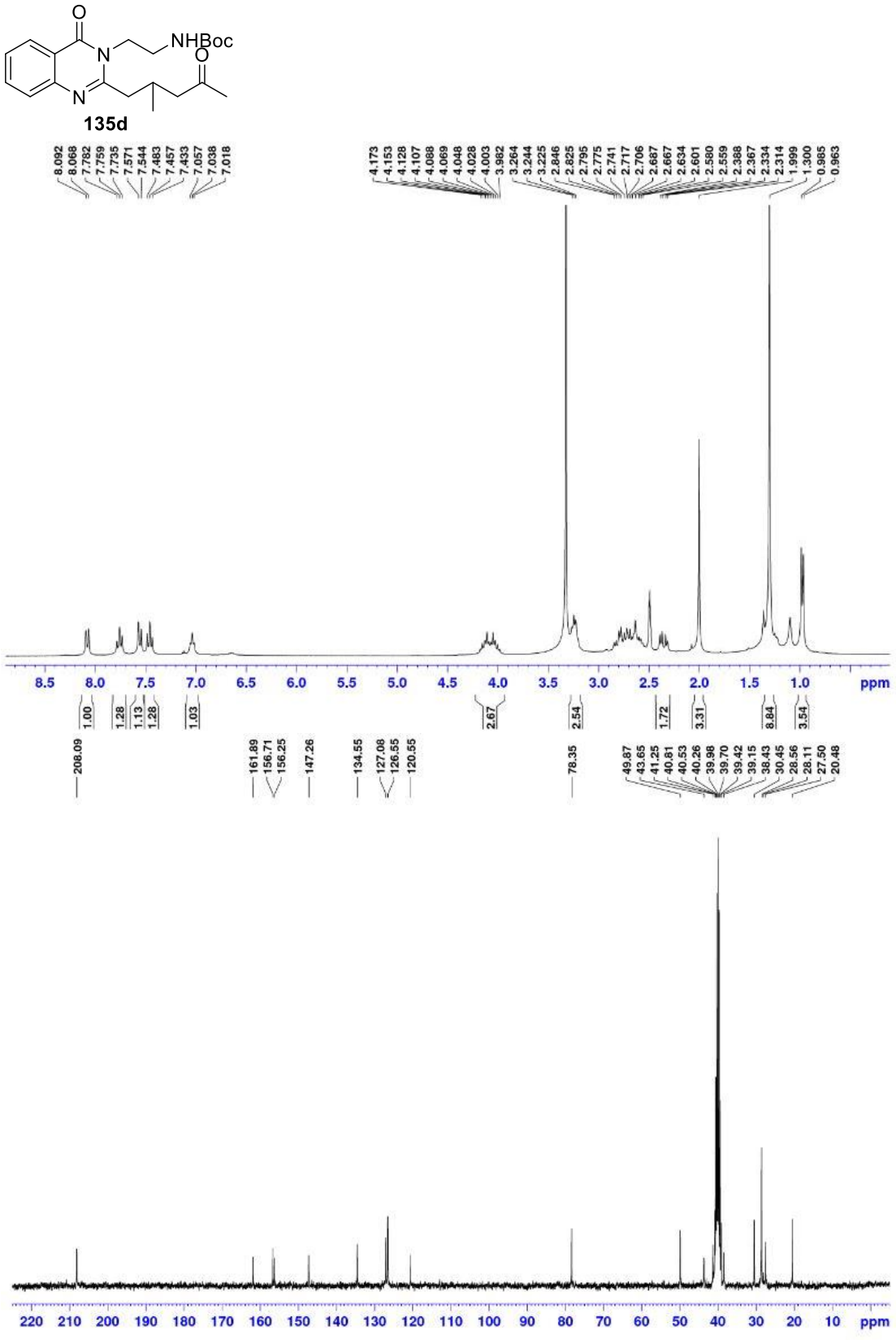


Figure 21 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **135e** in $CDCl_3$

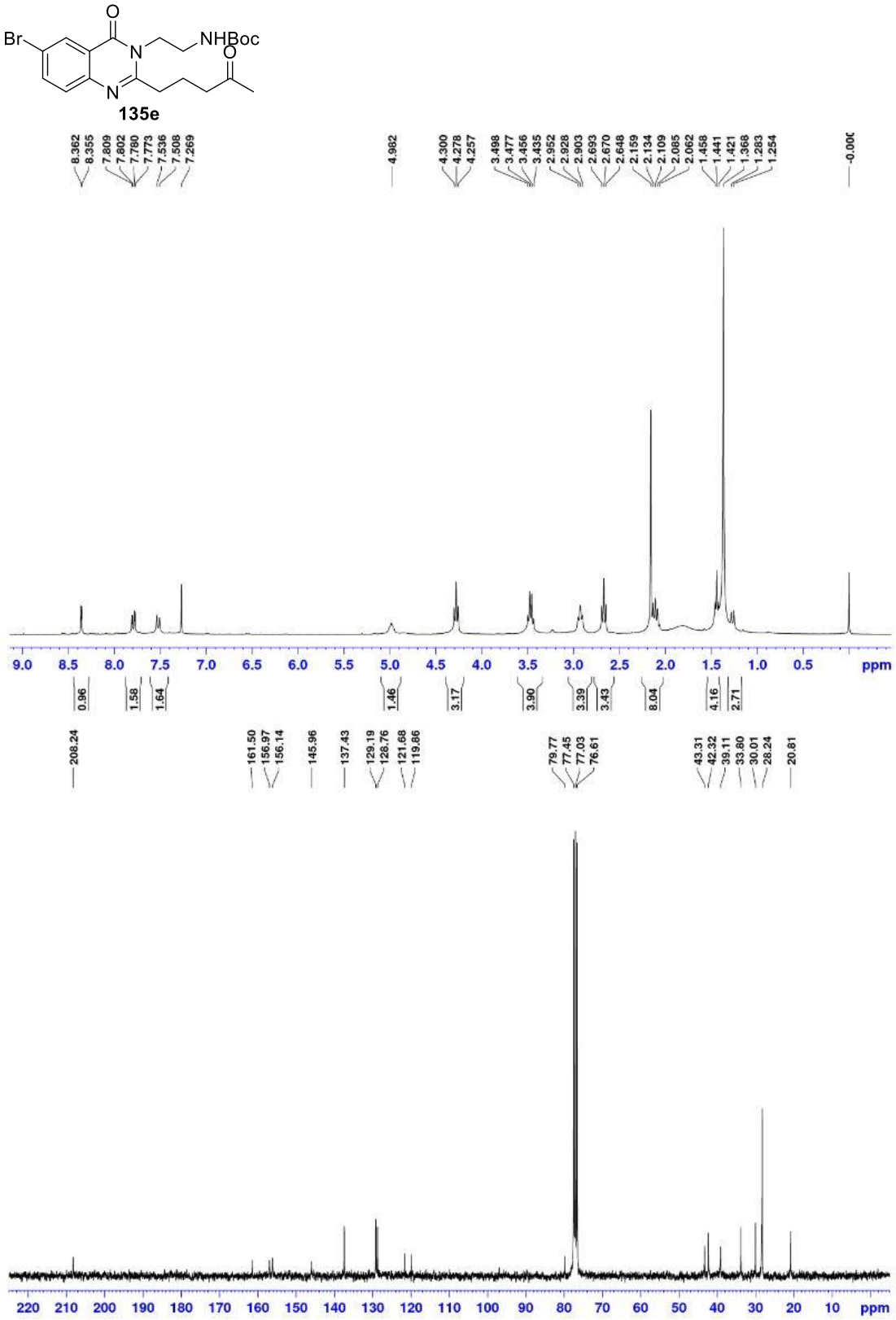


Figure 22 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **135f** in $CDCl_3$

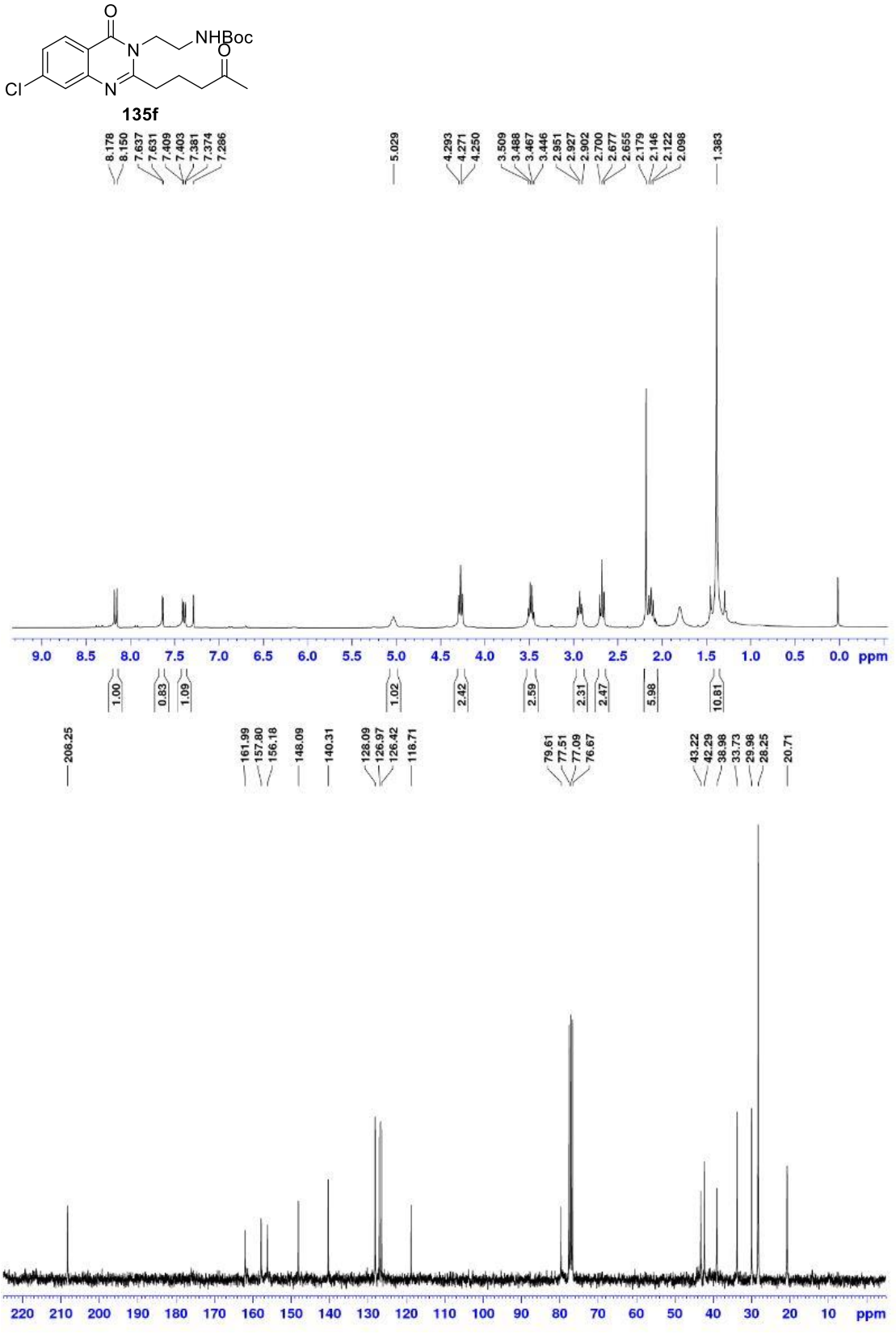


Figure 23 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **135g** in $CDCl_3$

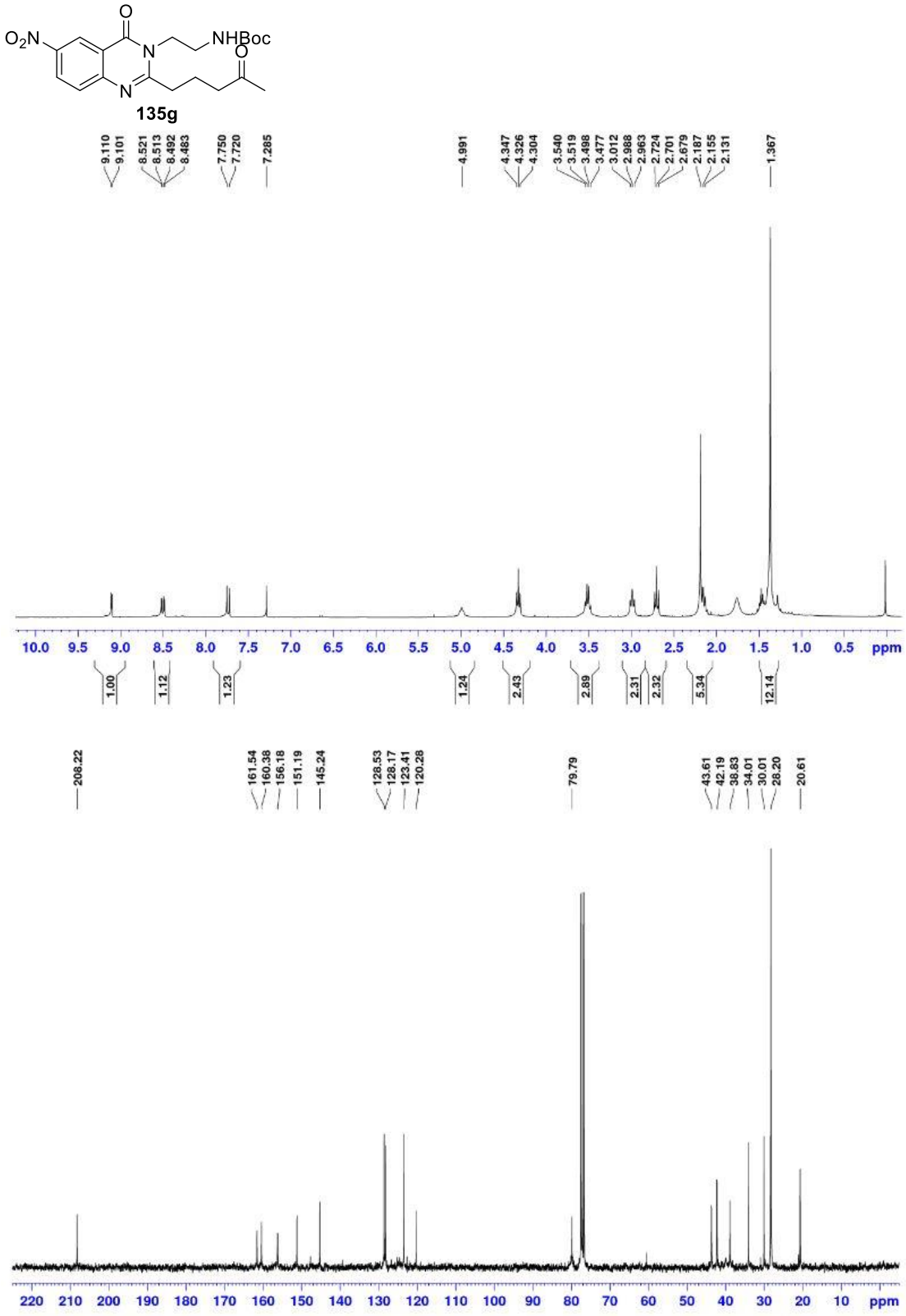


Figure 24 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **135h** in $CDCl_3$

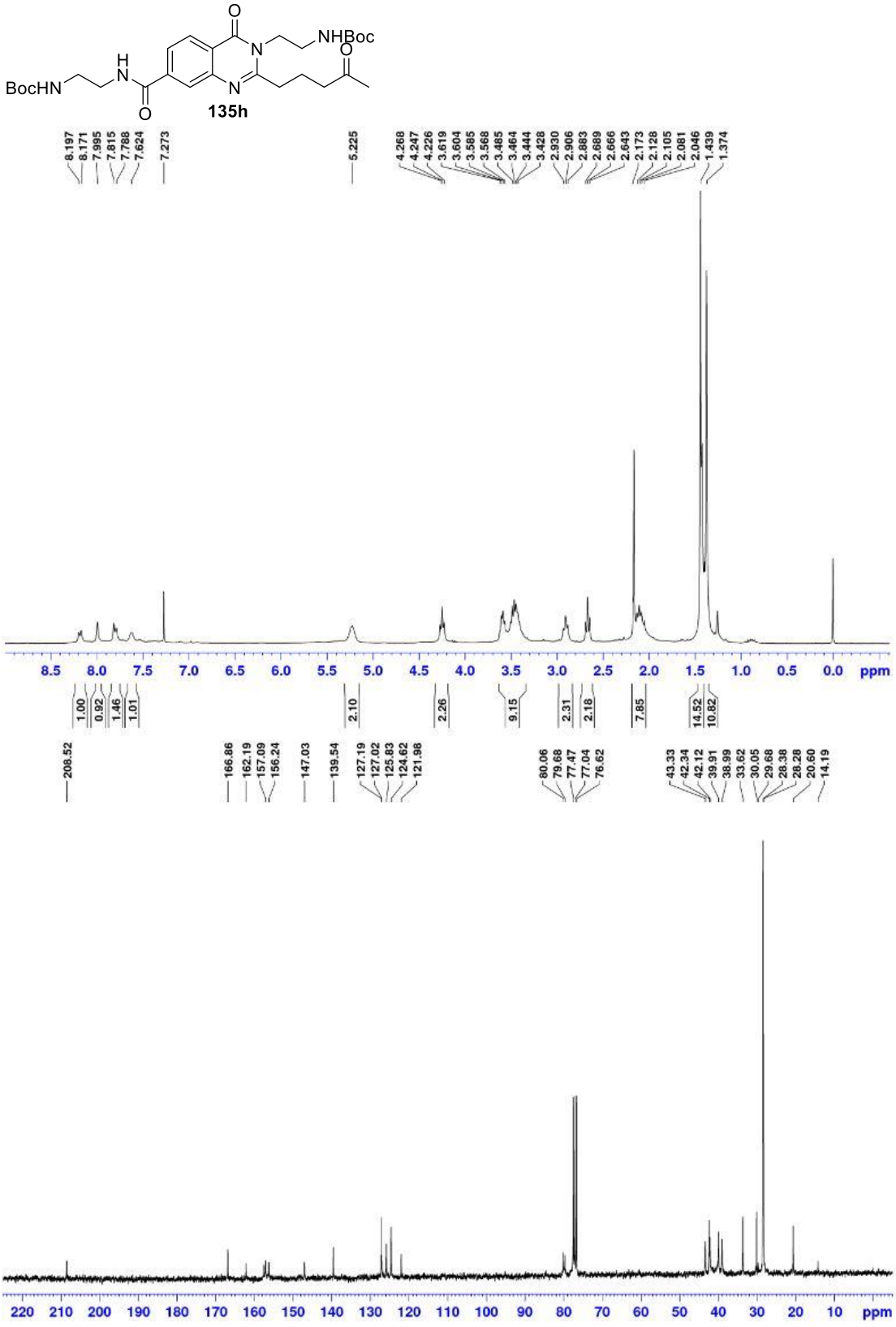


Figure 25 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **135i** in $CDCl_3$

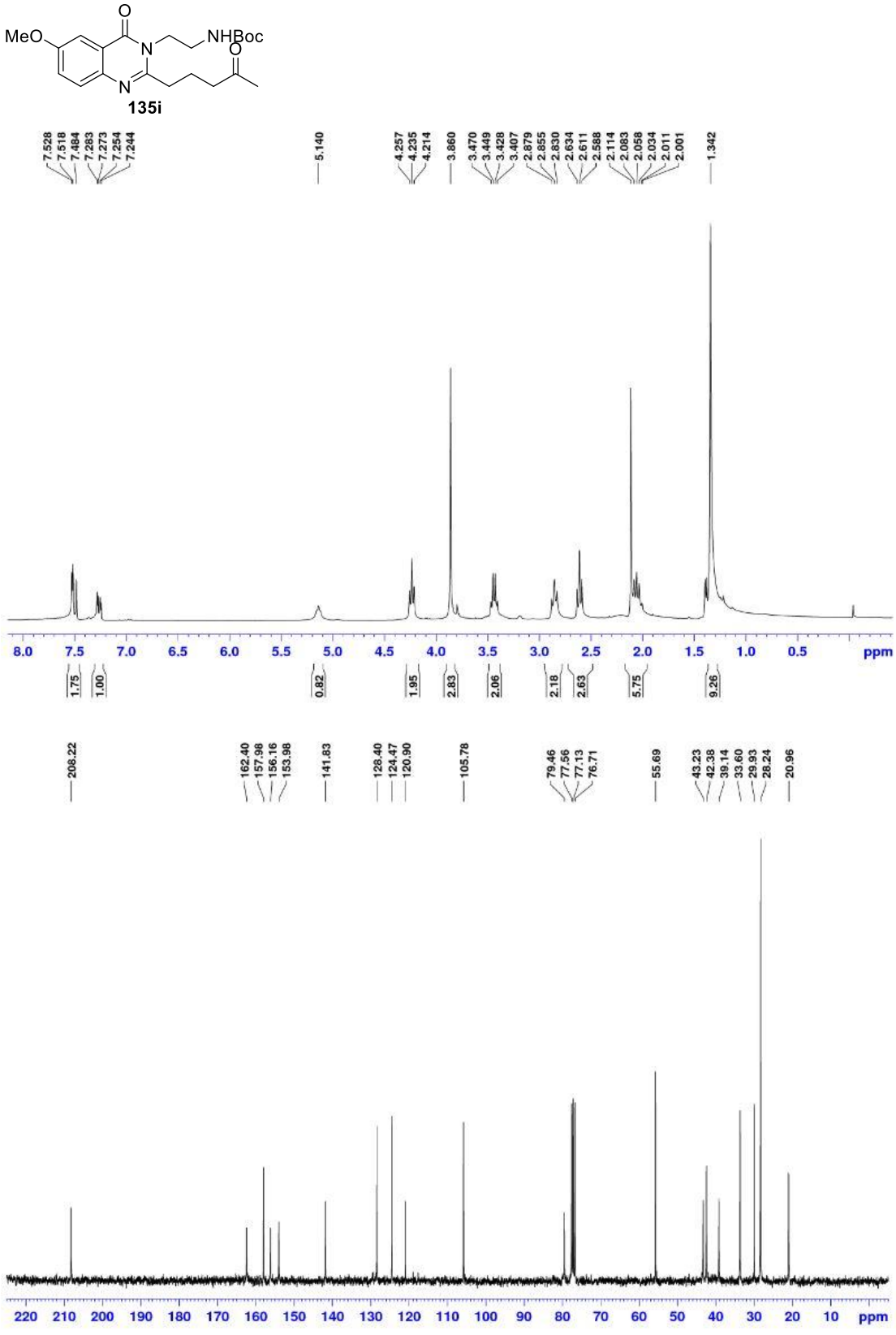


Figure 26 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **135j** in $CDCl_3$

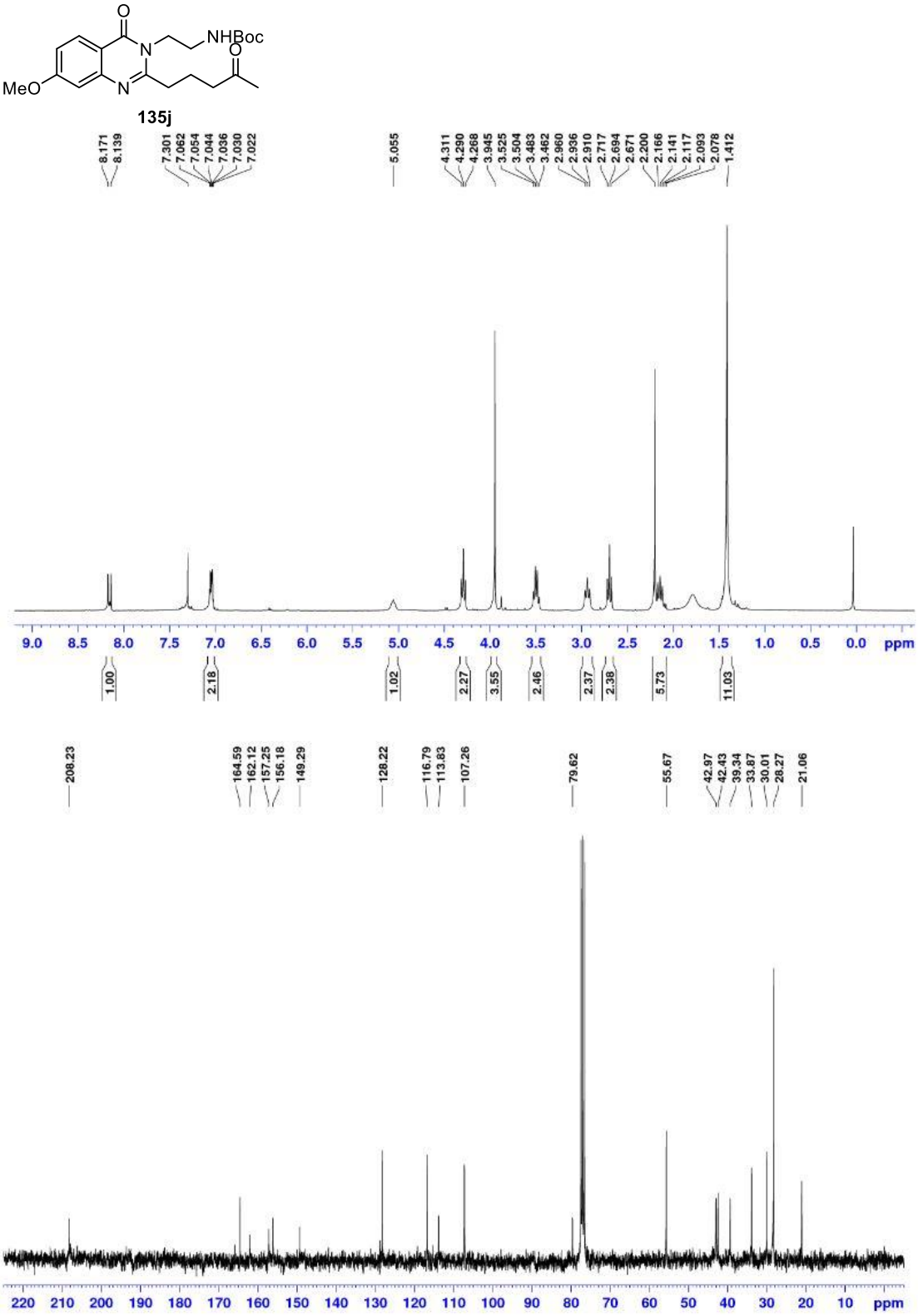


Figure 27 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **137k** in $CDCl_3$

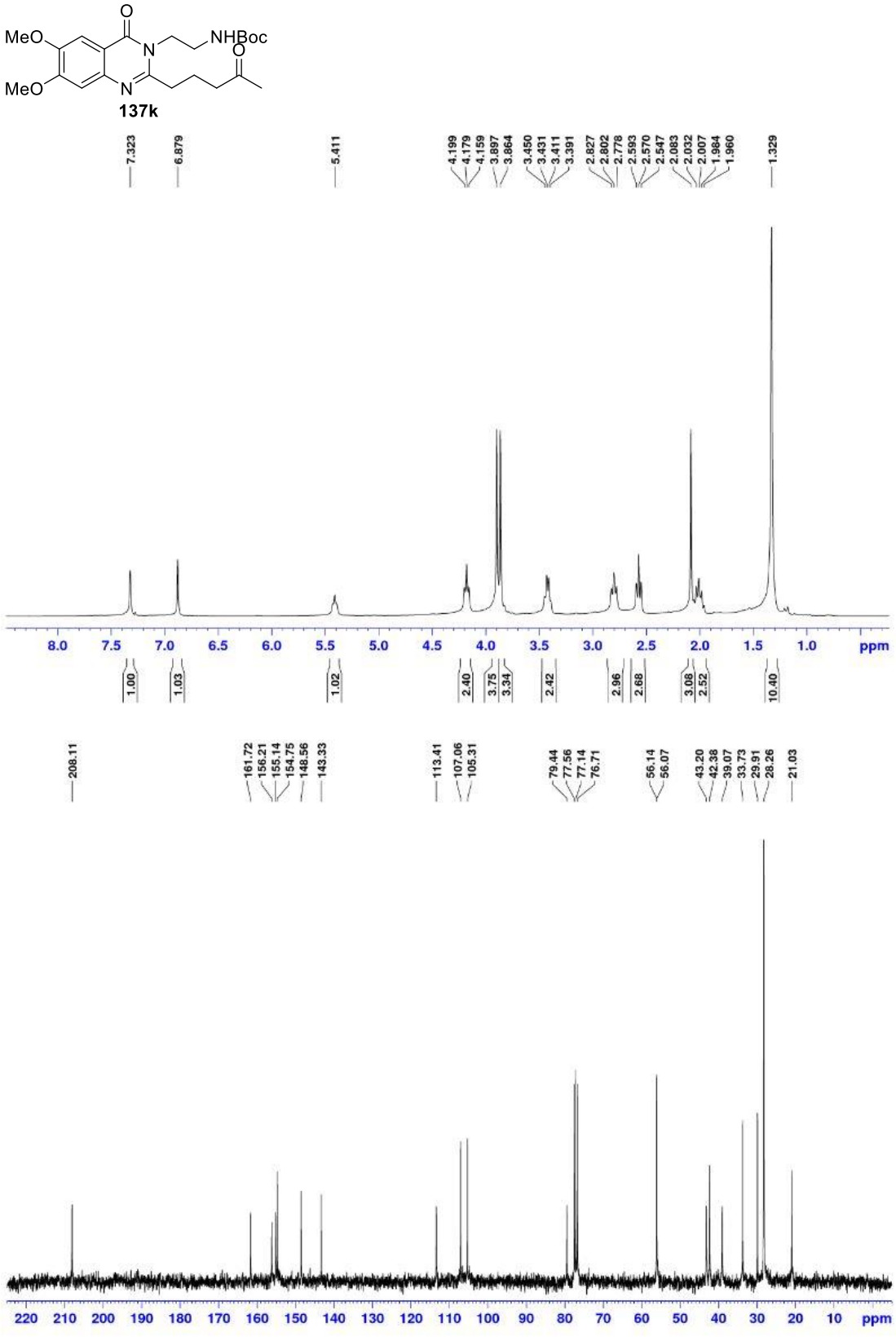


Figure 28 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **135l** in $CDCl_3$

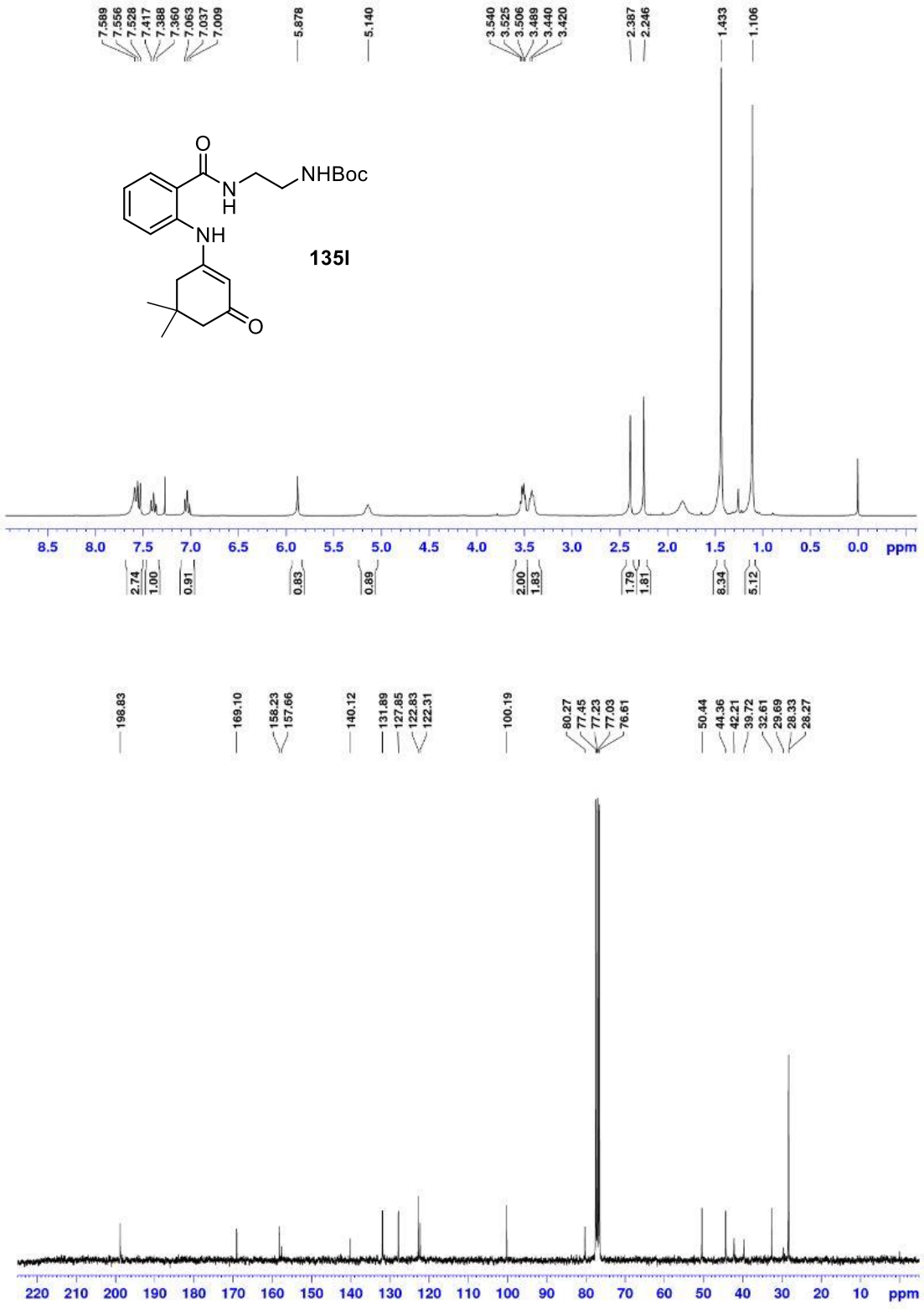


Figure 29 The ^{1}H (300 MHz) in $CDCl_3$ and ^{13}C NMR (75 MHz) in $CDCl_3$ + CD_3OD (2 drops) spectra of compound **148a**

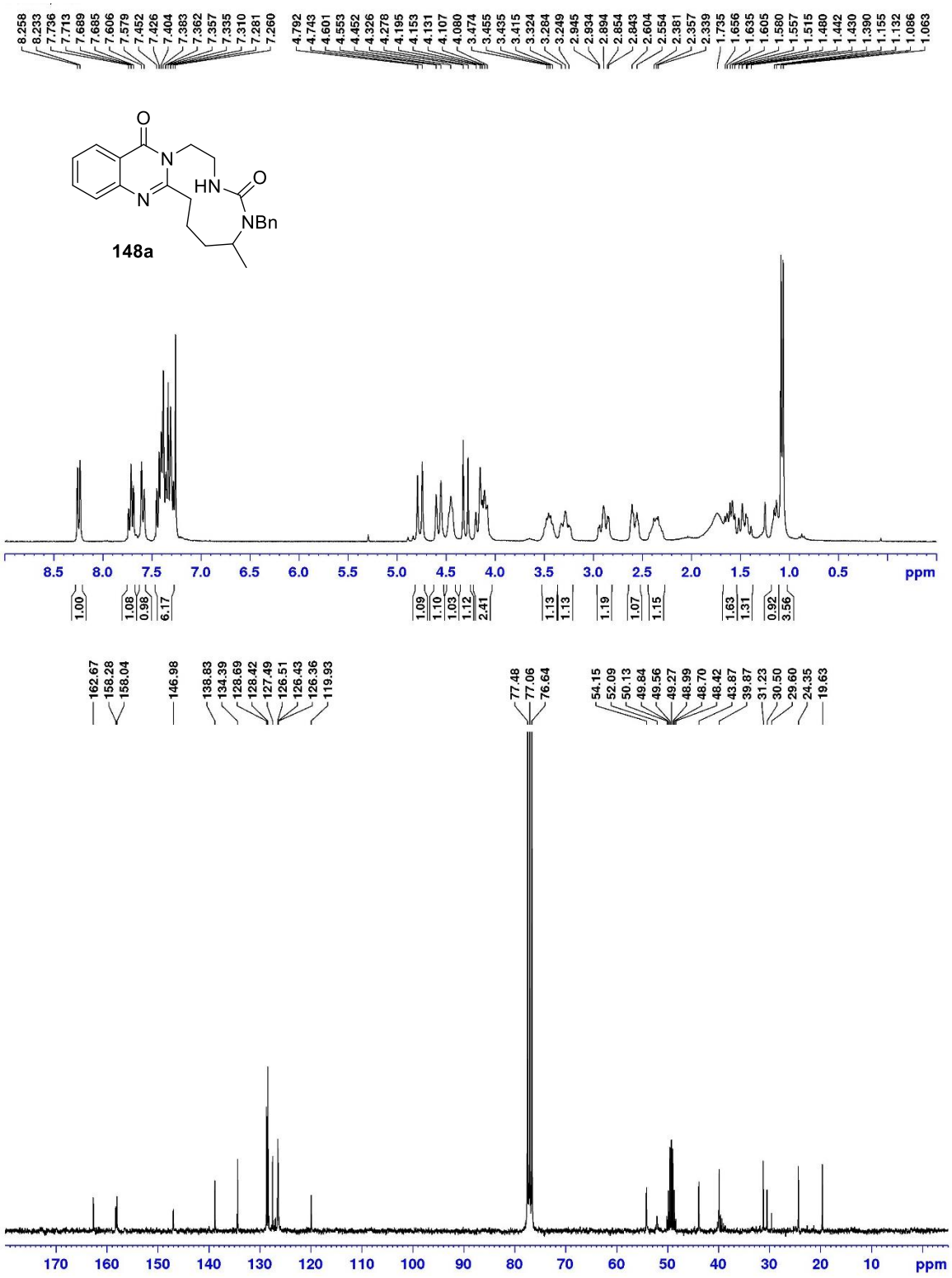


Figure 30 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **148b** in $CDCl_3$

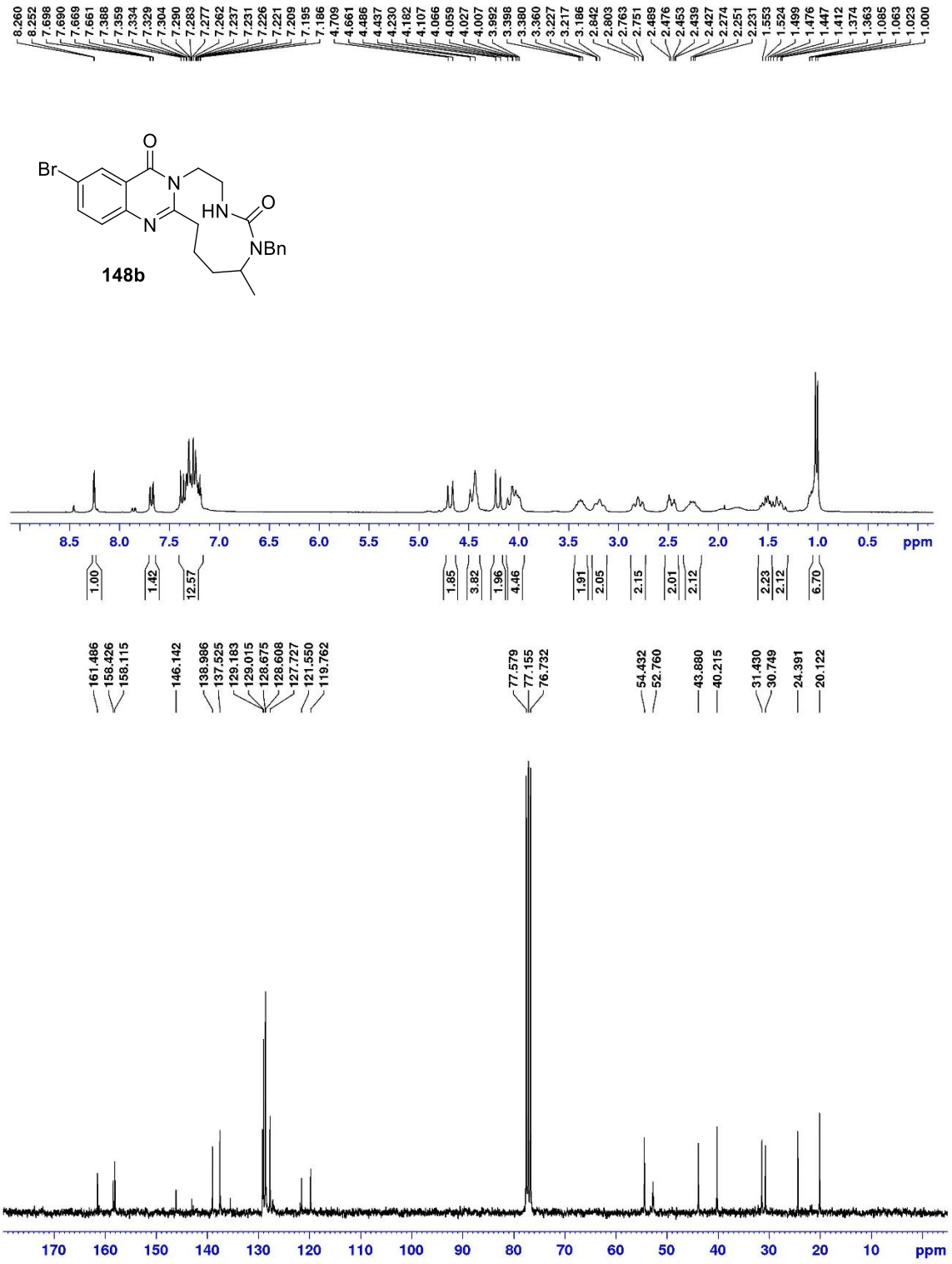


Figure 31 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **148c** in $CDCl_3$

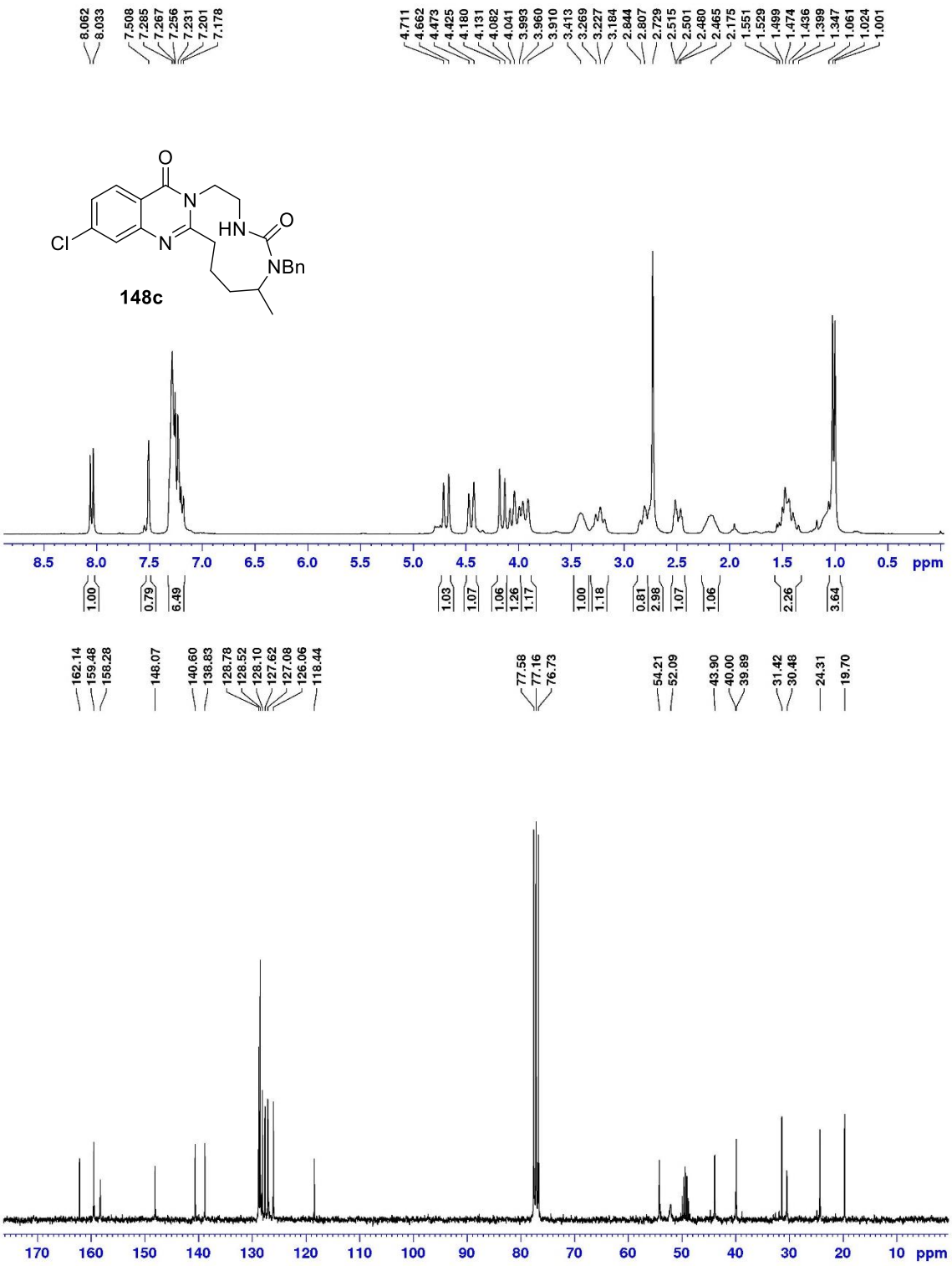


Figure 32 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **148d** in $CDCl_3$

Figure 33 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **148e** in $CDCl_3$

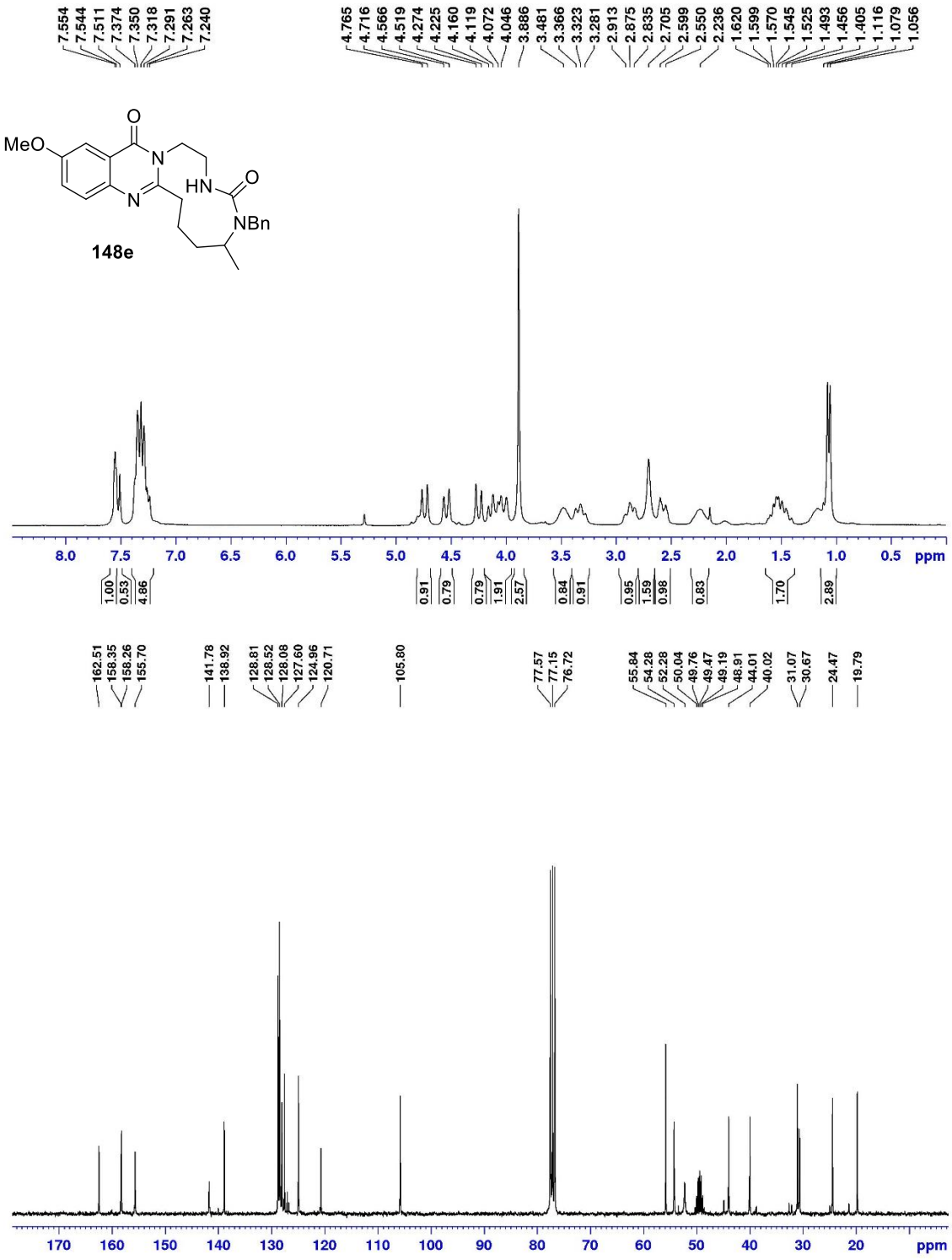


Figure 34 The ^{1}H (300 MHz) spectra in $CDCl_3$ and ^{13}C NMR (75 MHz) spectra in DMSO-d_6 of compound **148f**

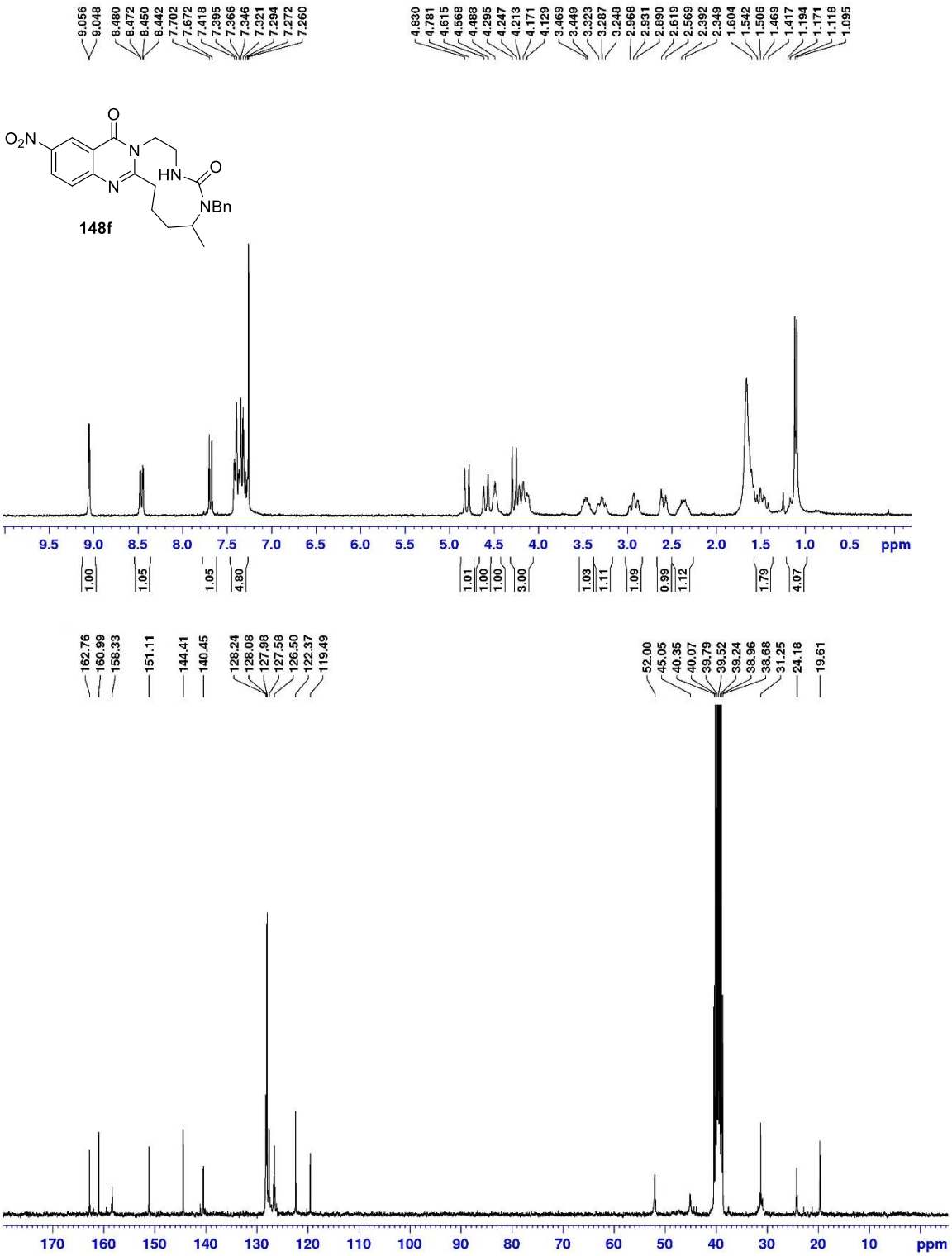


Figure 35 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **141a** in $CDCl_3$

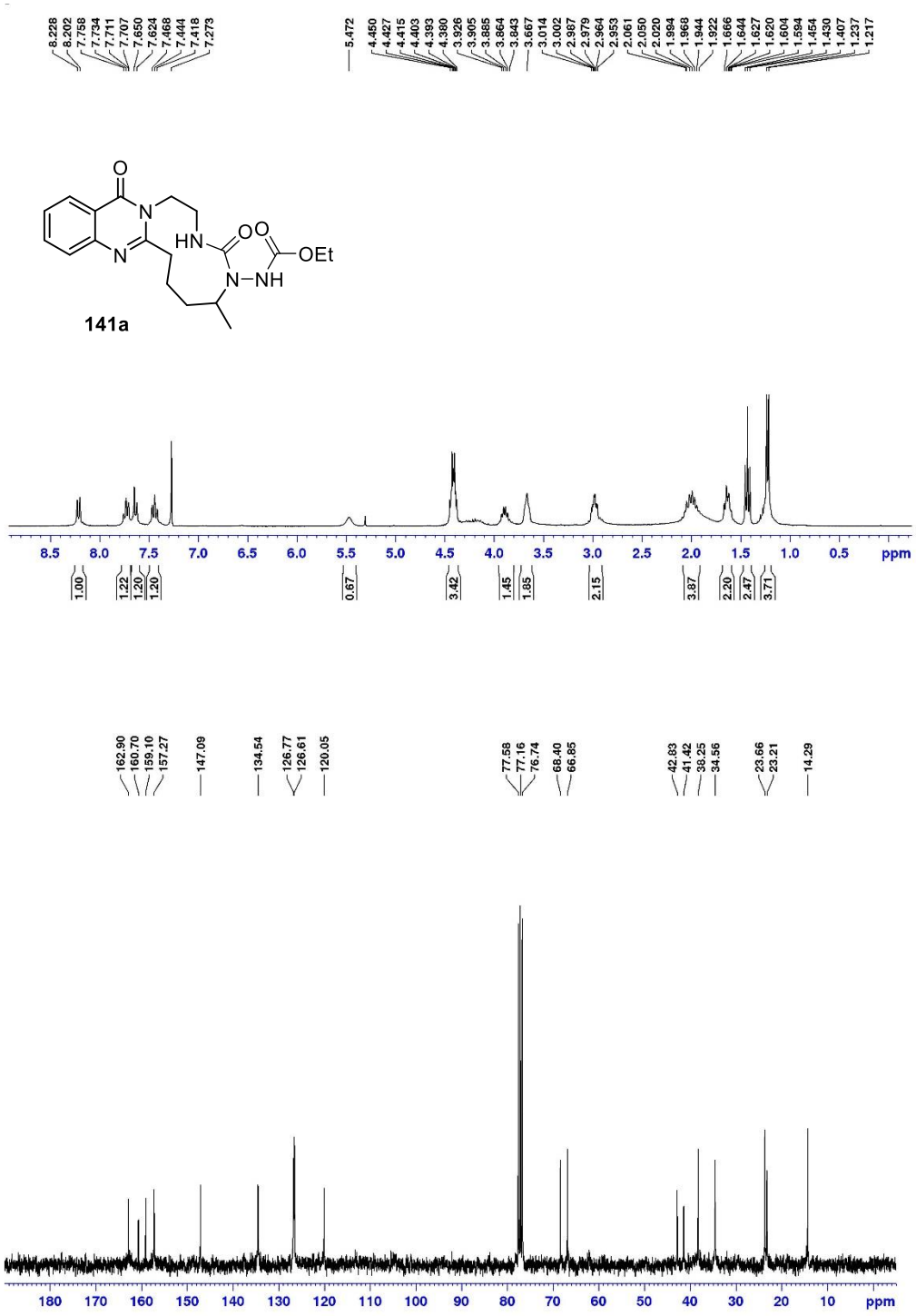


Figure 36 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **145a** in DMSO-d_6

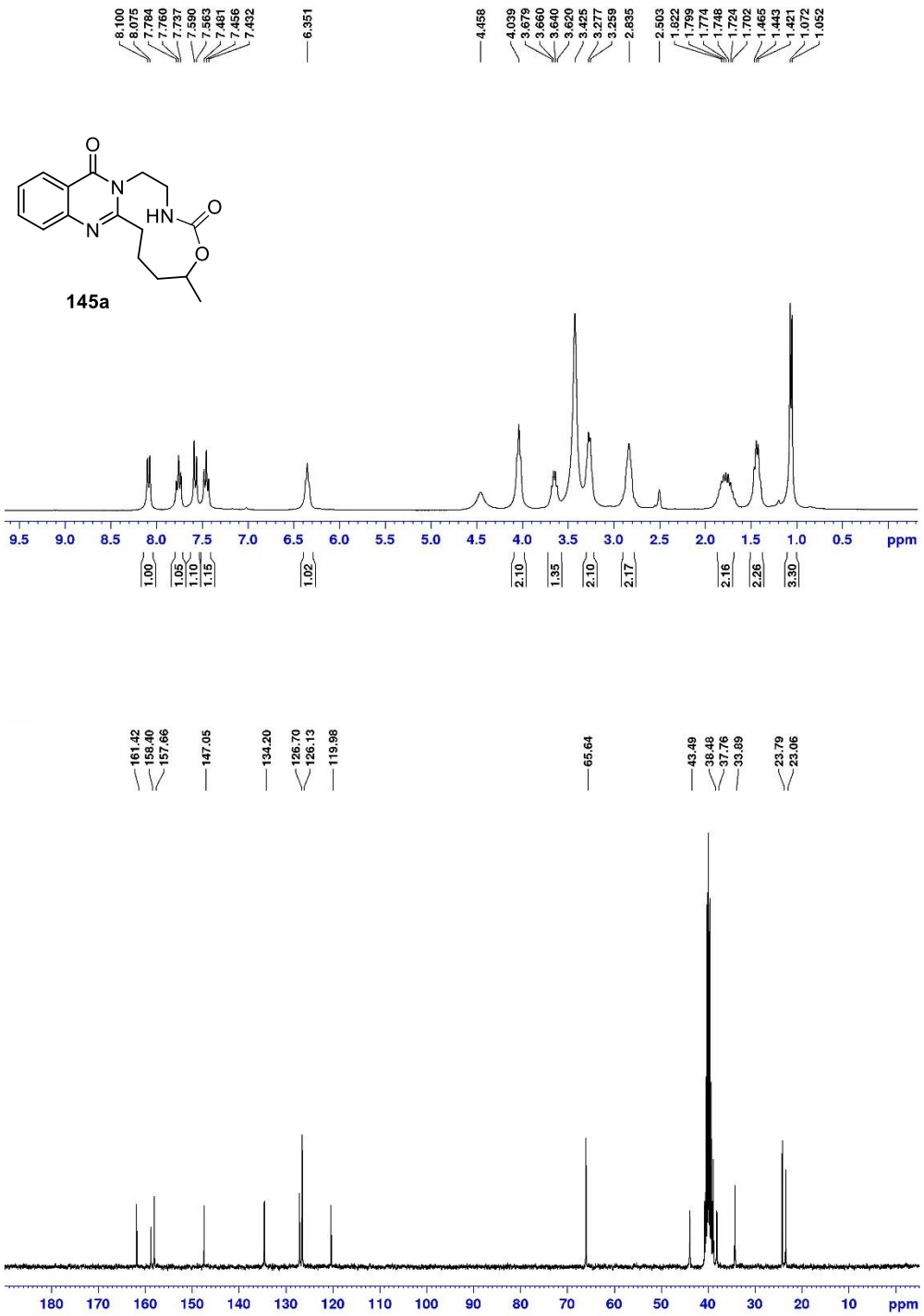
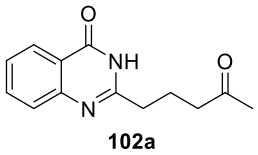


Figure 37 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **102a** in $CDCl_3$



102a

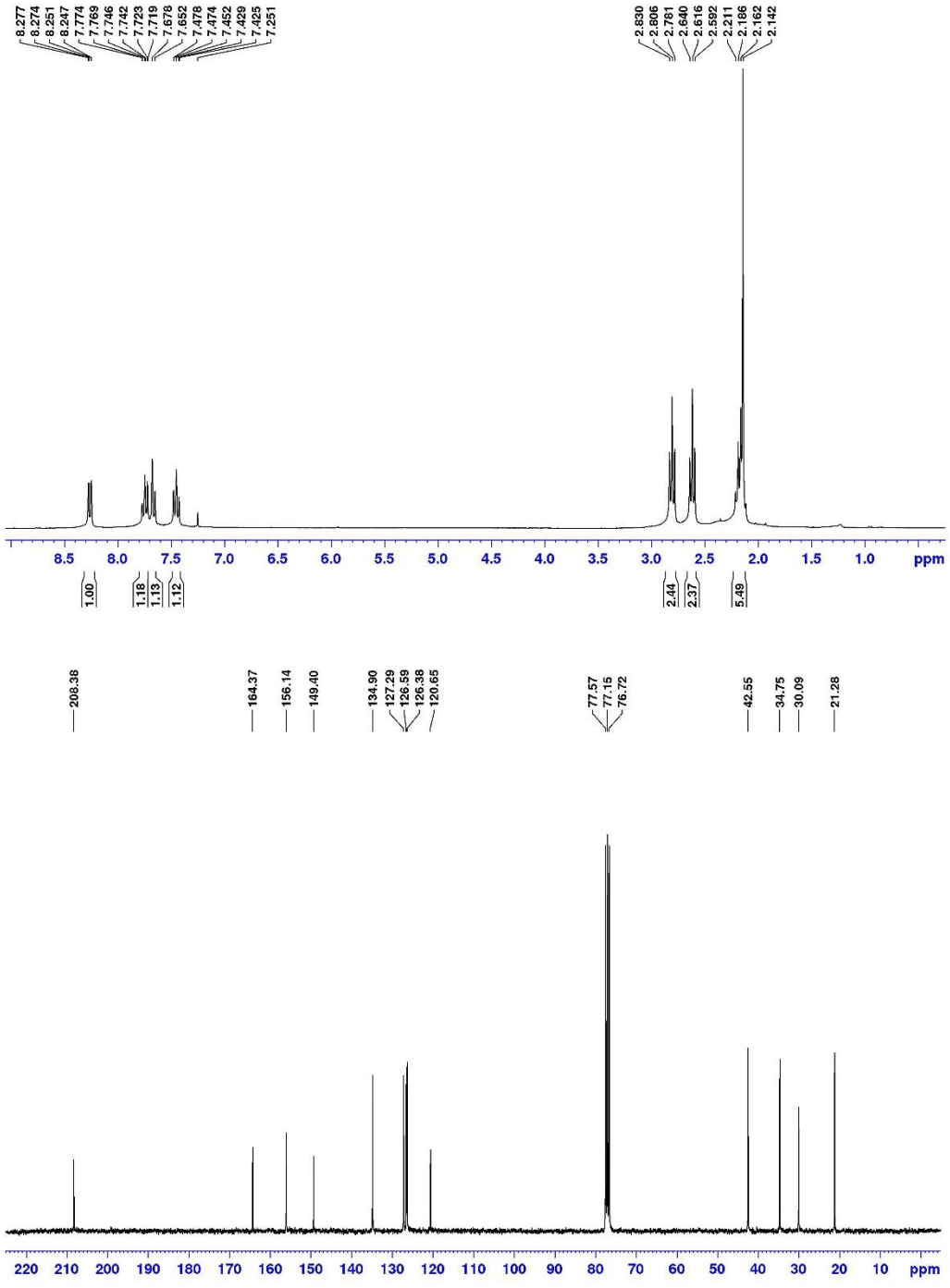


Figure 38 The ^{1}H (300 MHz) in $CDCl_3$ and ^{13}C NMR (75 MHz) spectra of compound **102b** in DMSO-d_6

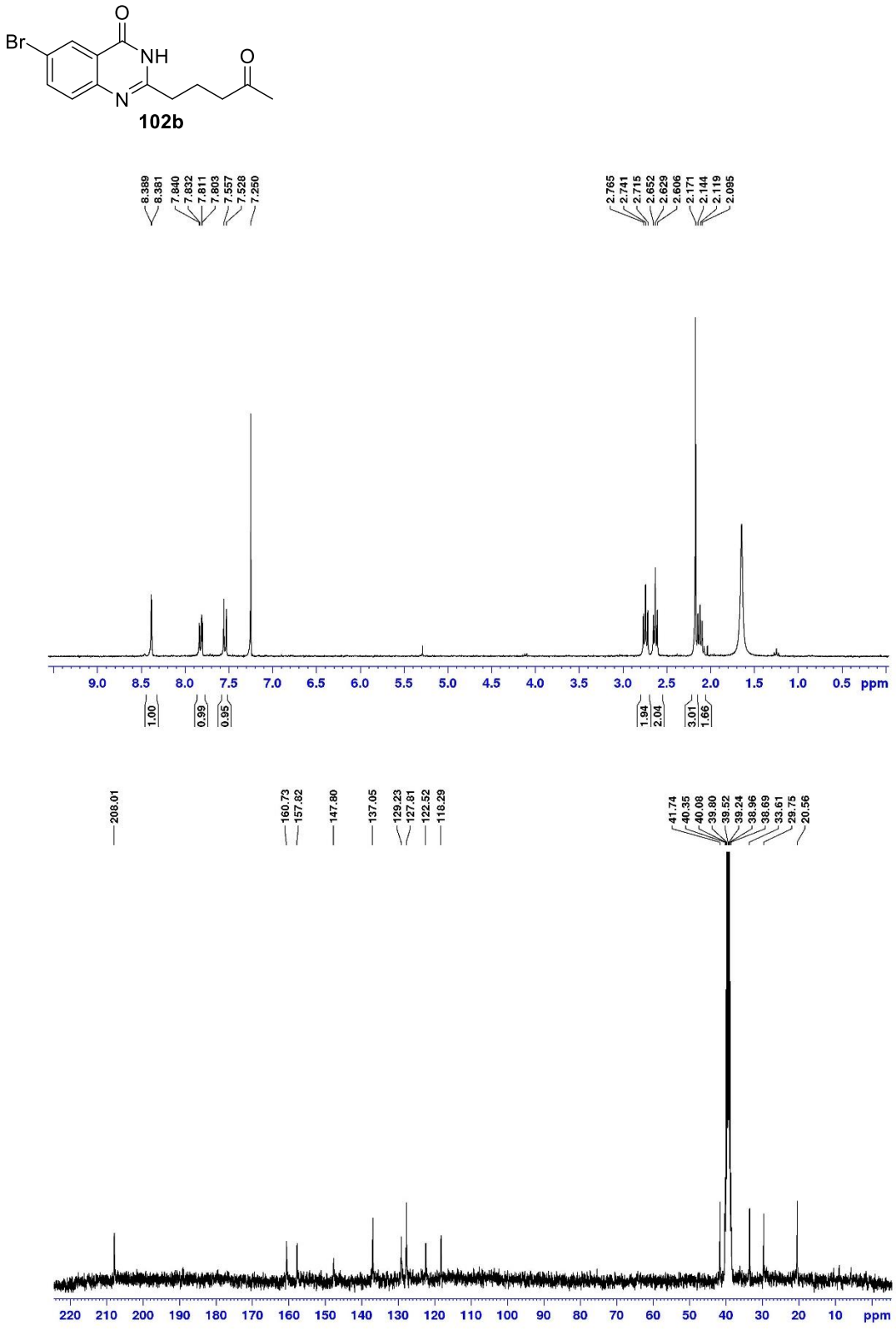
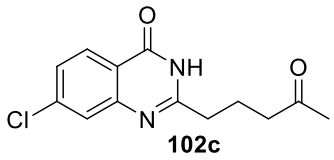


Figure 39 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **102c** in $CDCl_3$



102c

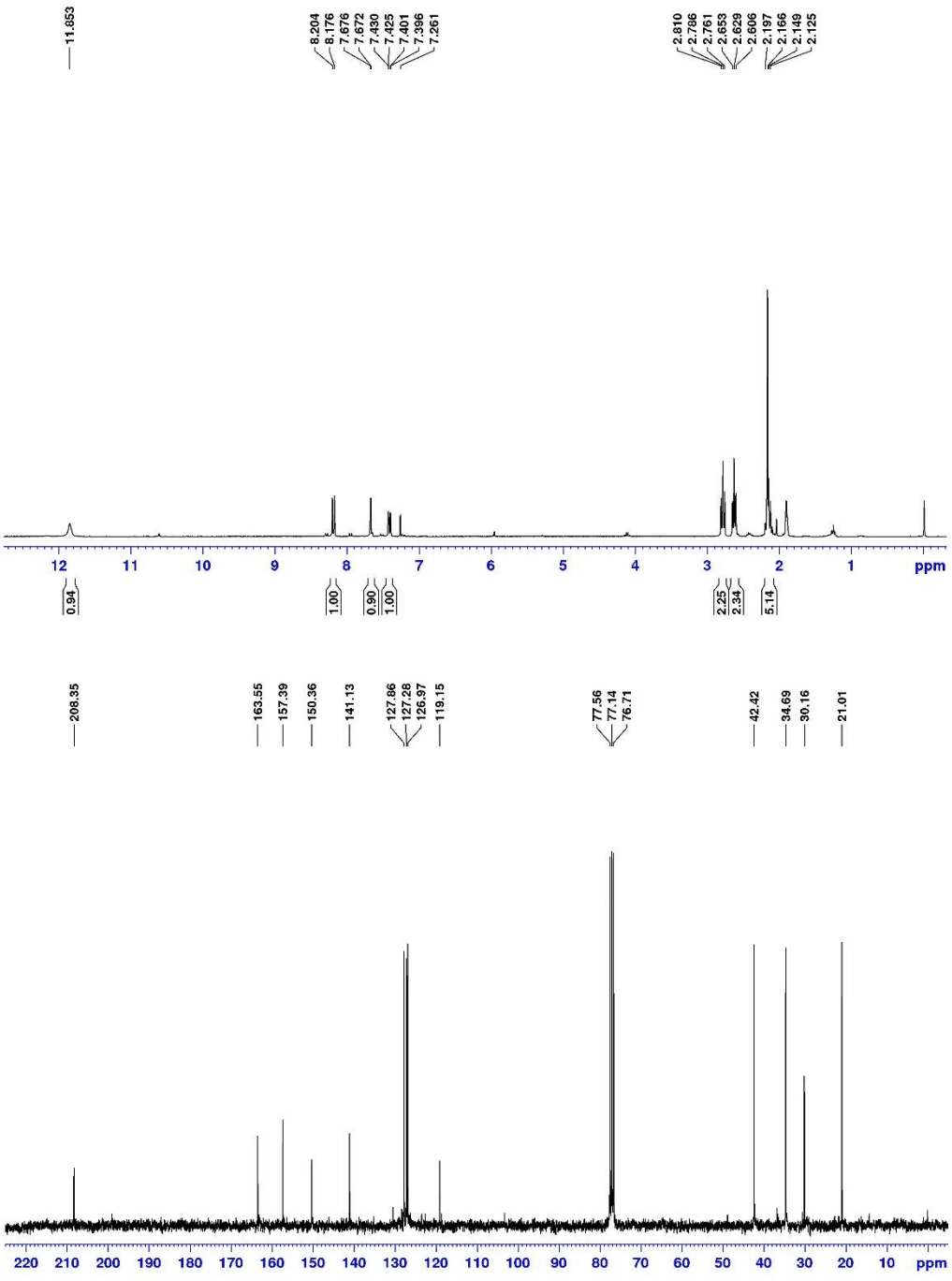


Figure 40 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **102d** in $CDCl_3$

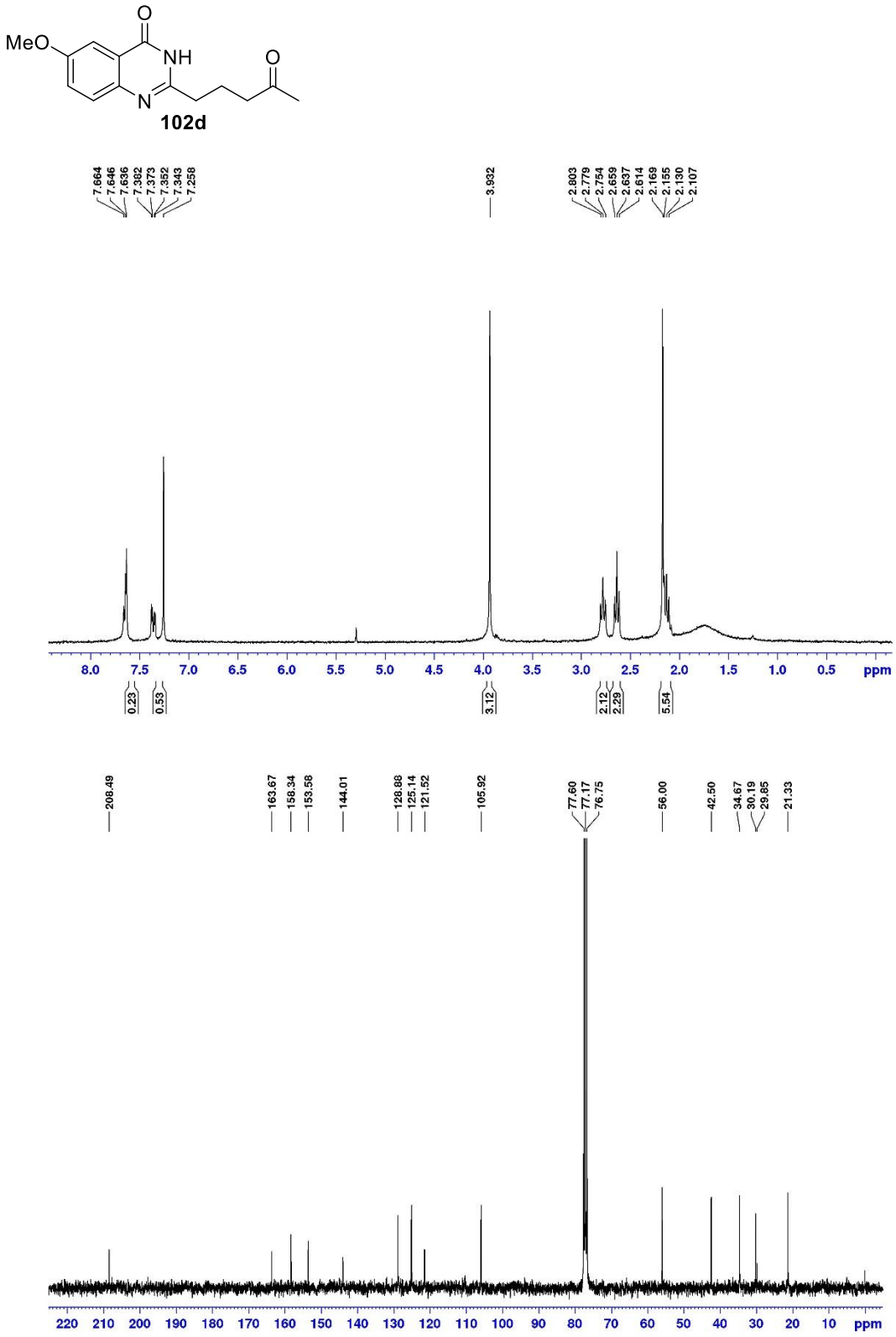


Figure 41 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **102e** in $CDCl_3$

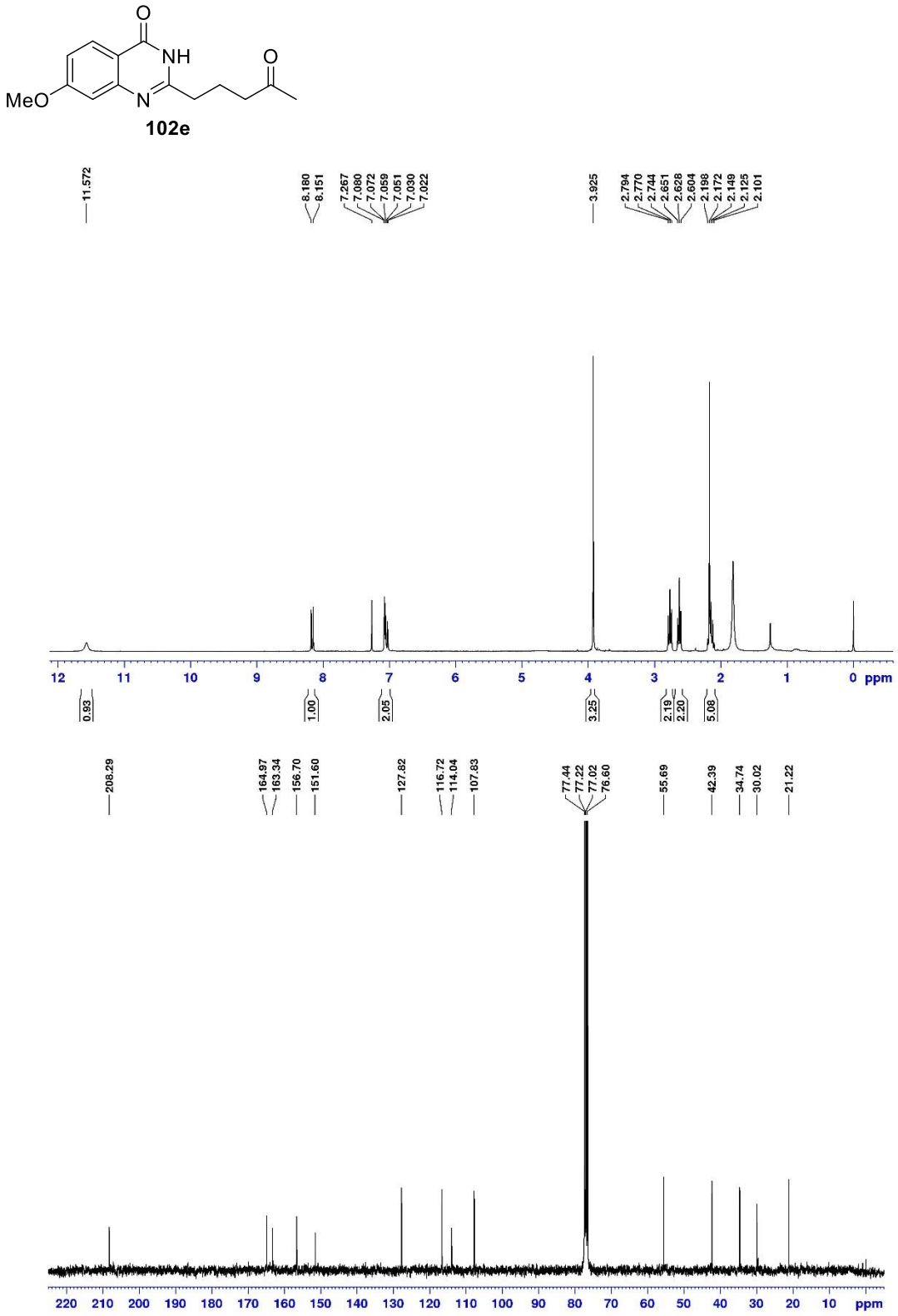


Figure 42 The ^{1}H (300 MHz) in $CDCl_3$ and ^{13}C NMR (75 MHz) spectra of compound **102f** in DMSO-d_6

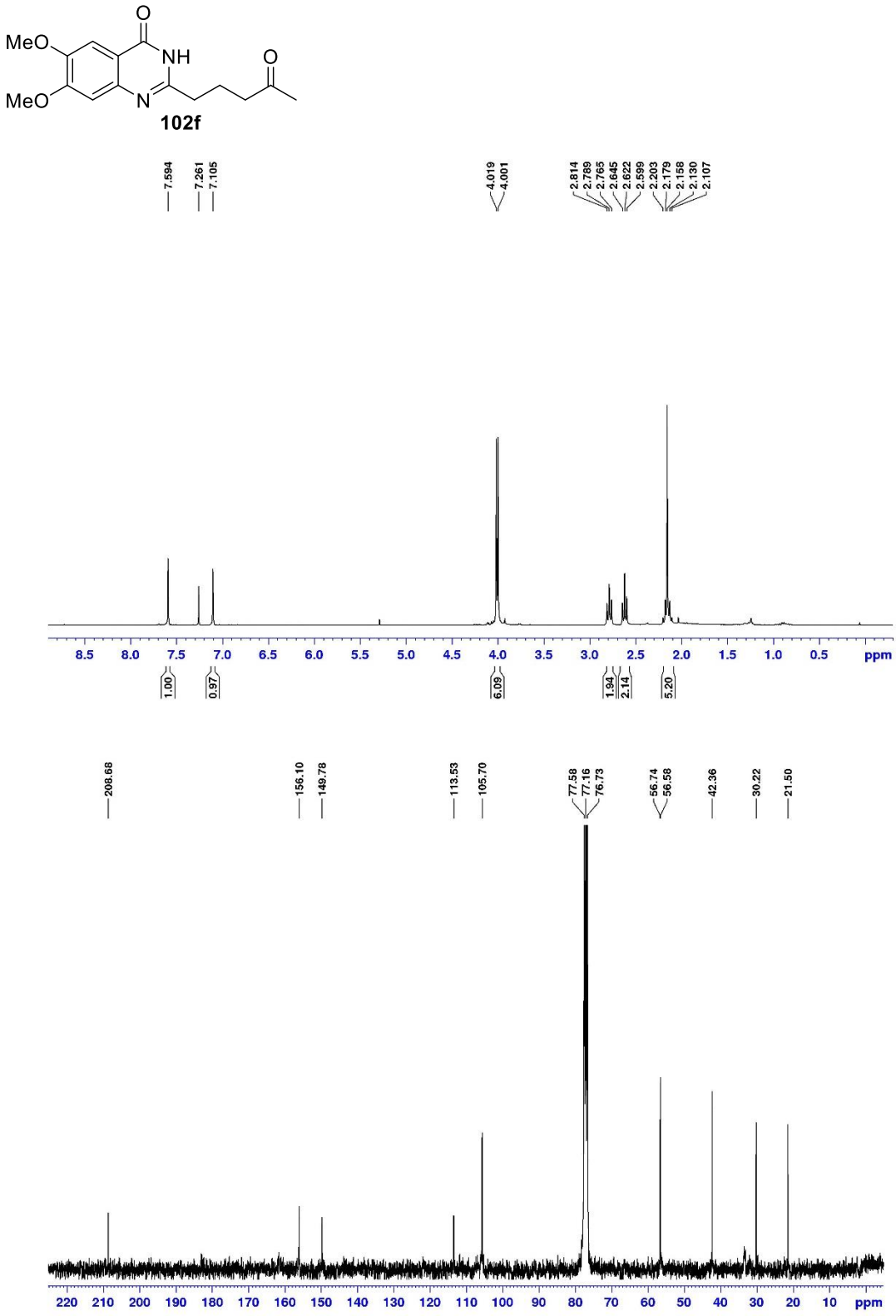


Figure 43 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **102h** in $CDCl_3$

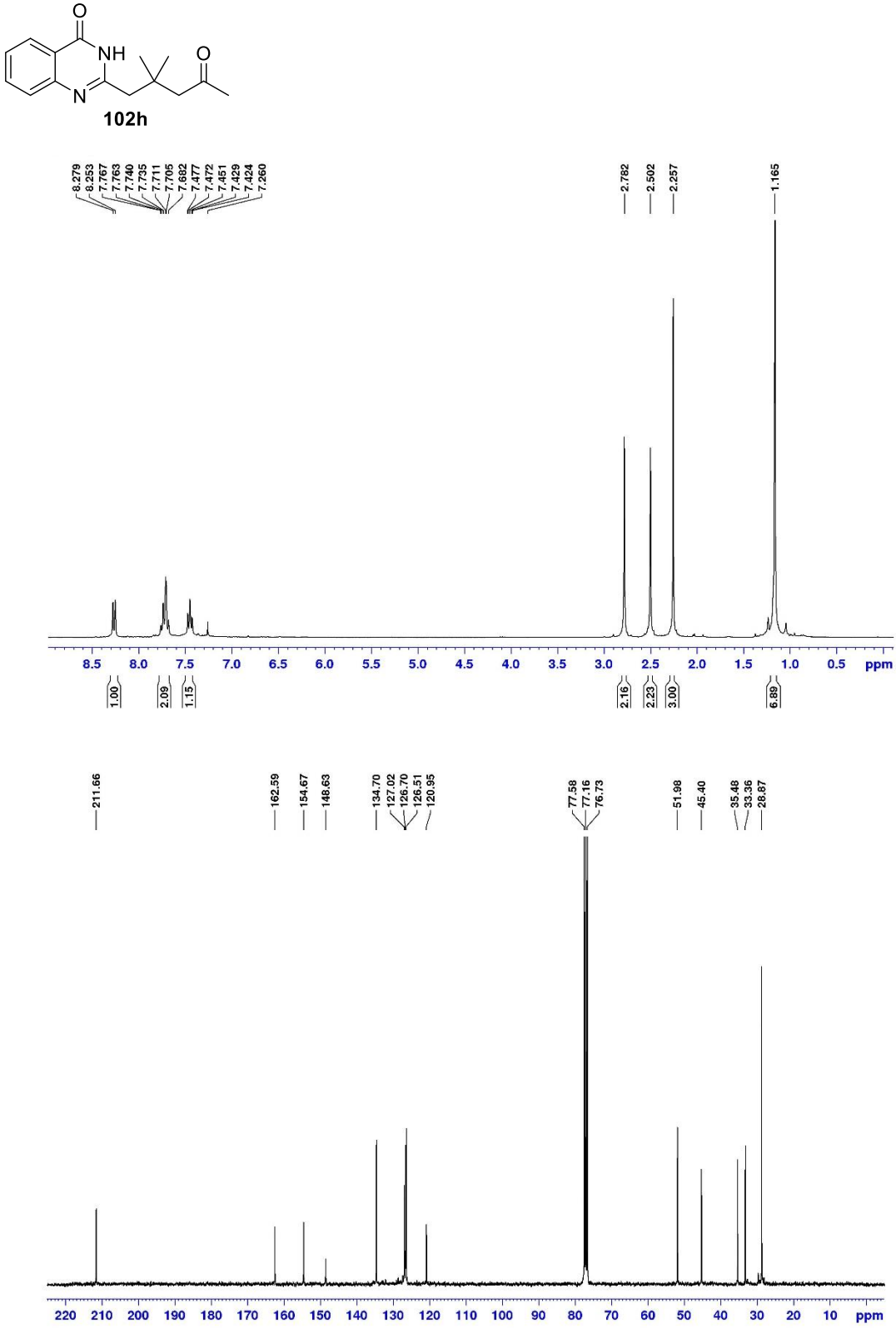
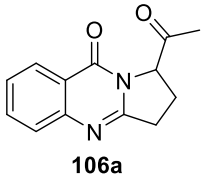
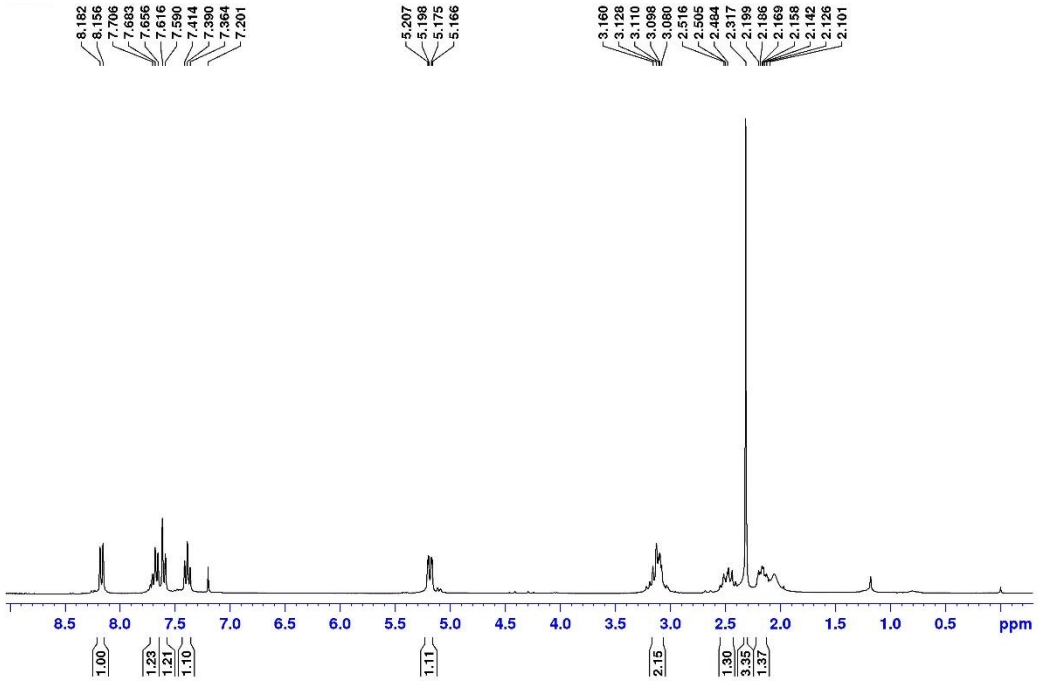


Figure 44 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **106a** in $CDCl_3$



106a



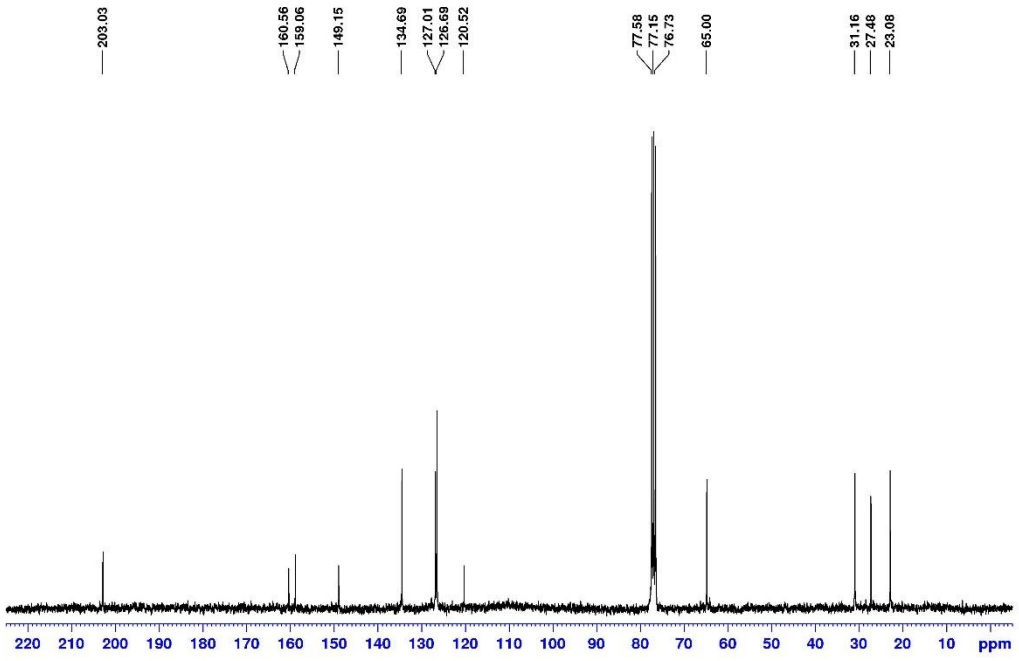


Figure 45 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **106b** in $CDCl_3$

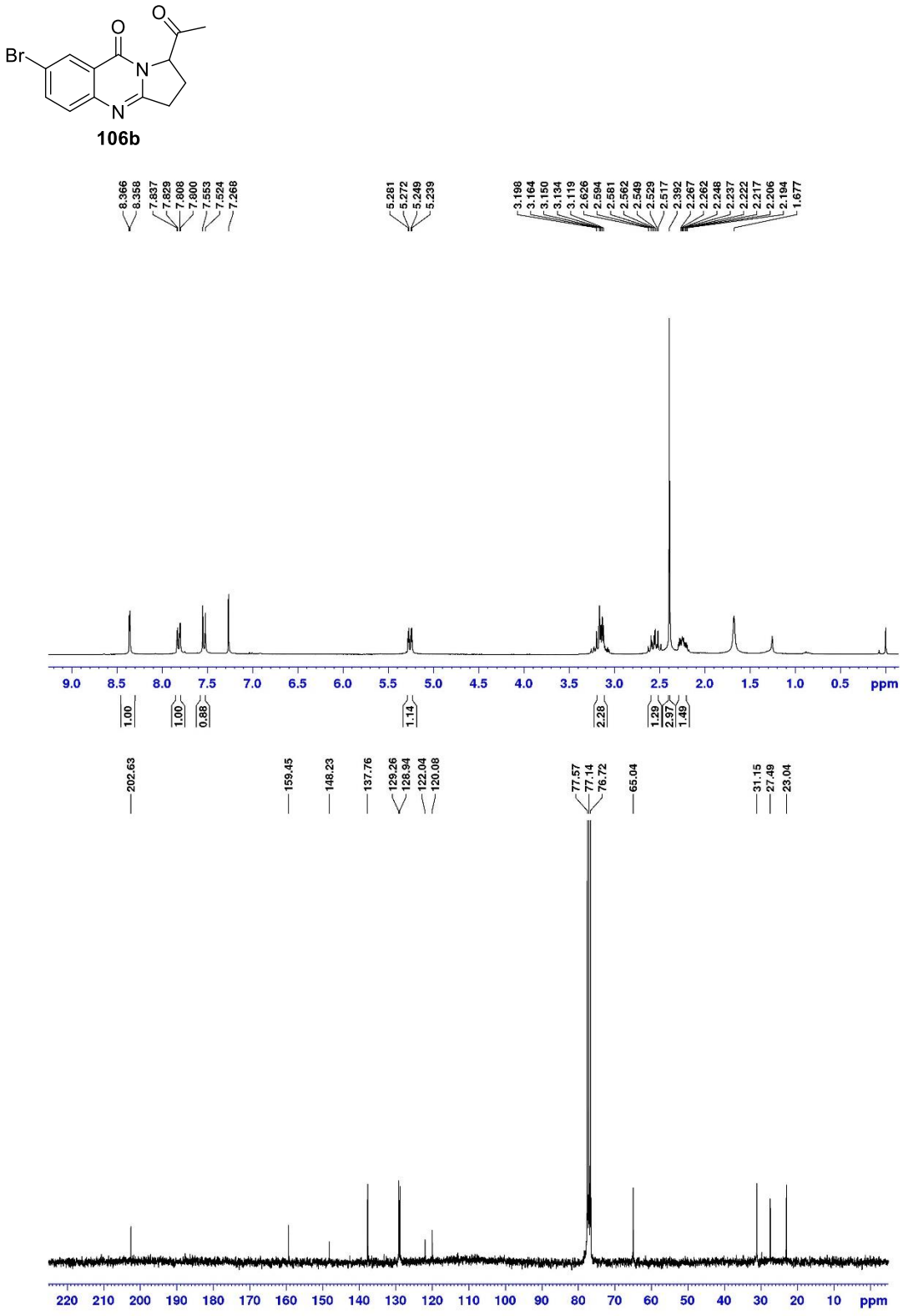


Figure 46 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **106c** in $CDCl_3$

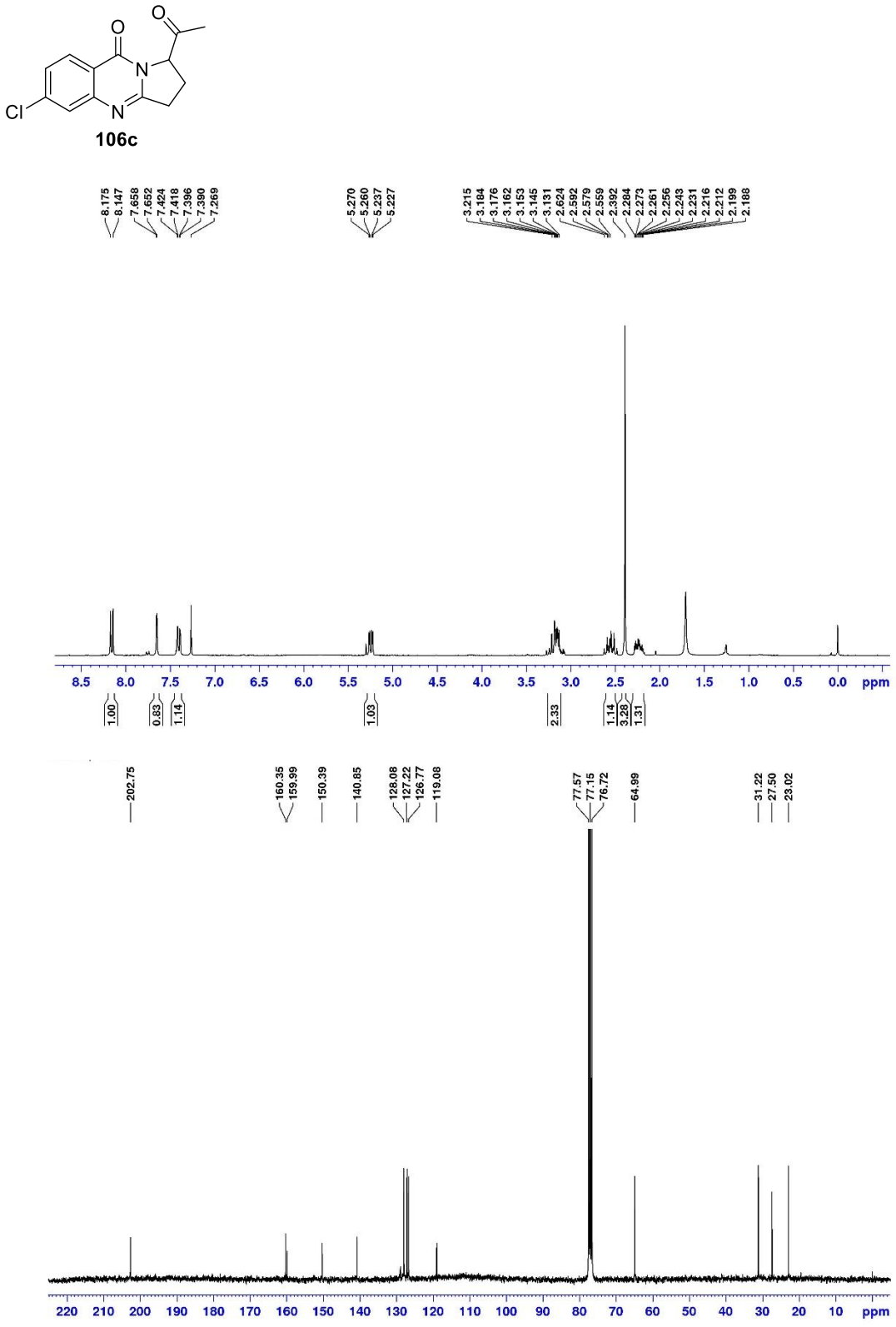


Figure 47 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **106d** in $CDCl_3$

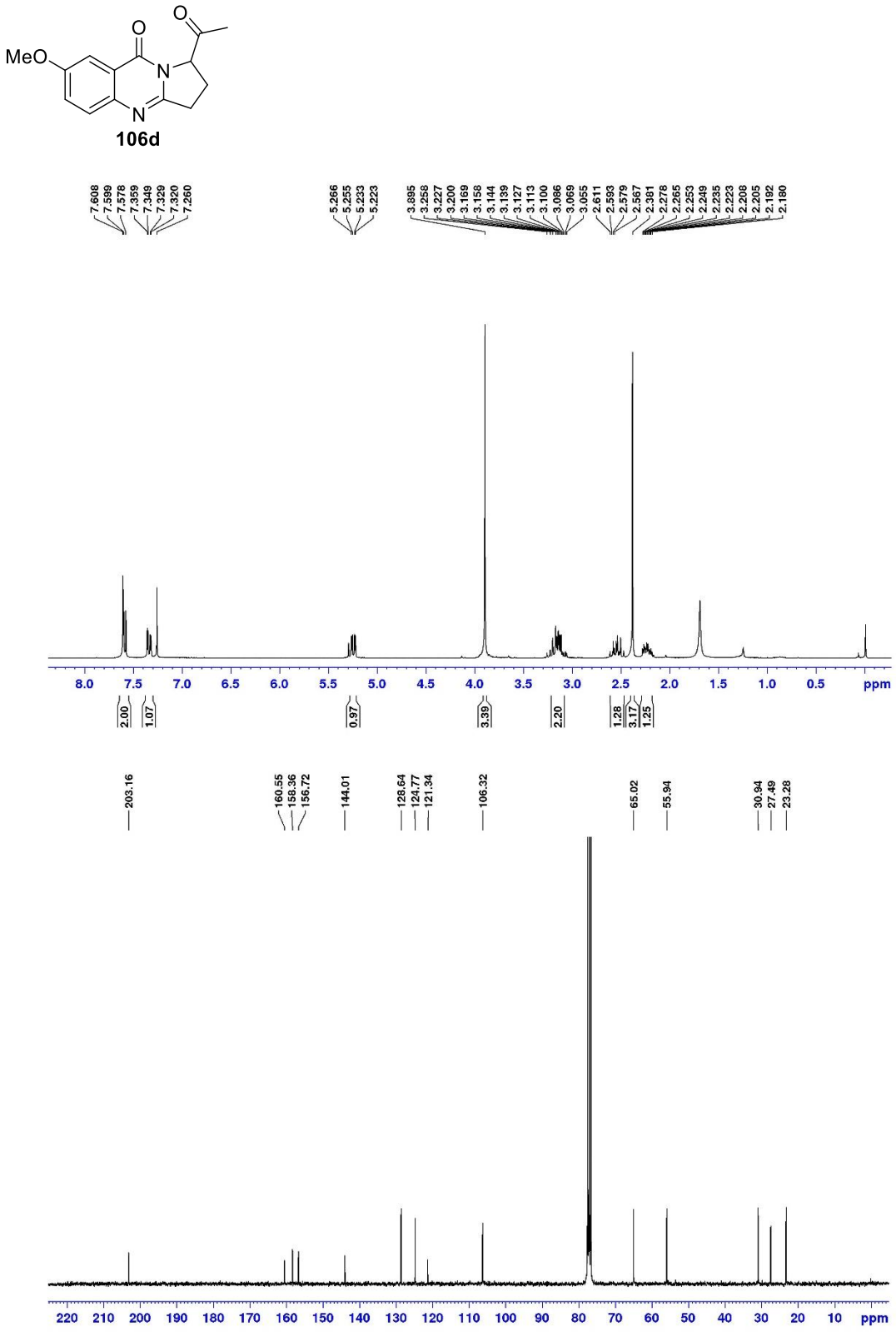
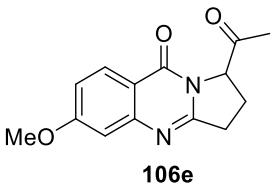


Figure 48 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **106e** in $CDCl_3$



106e

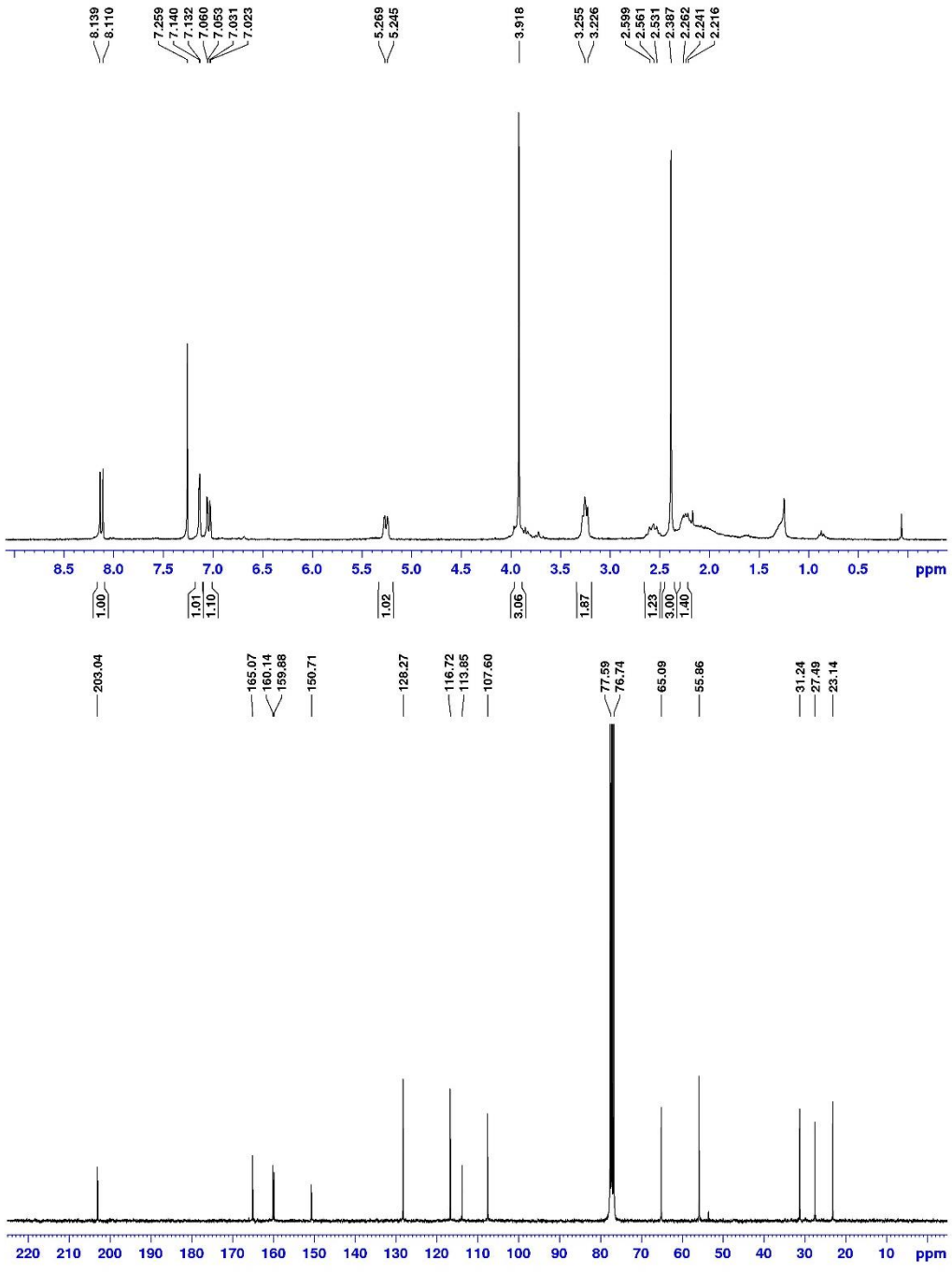
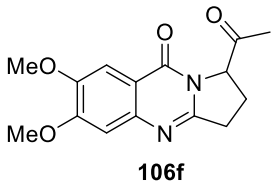


Figure 49 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **106f** in $CDCl_3$



106f

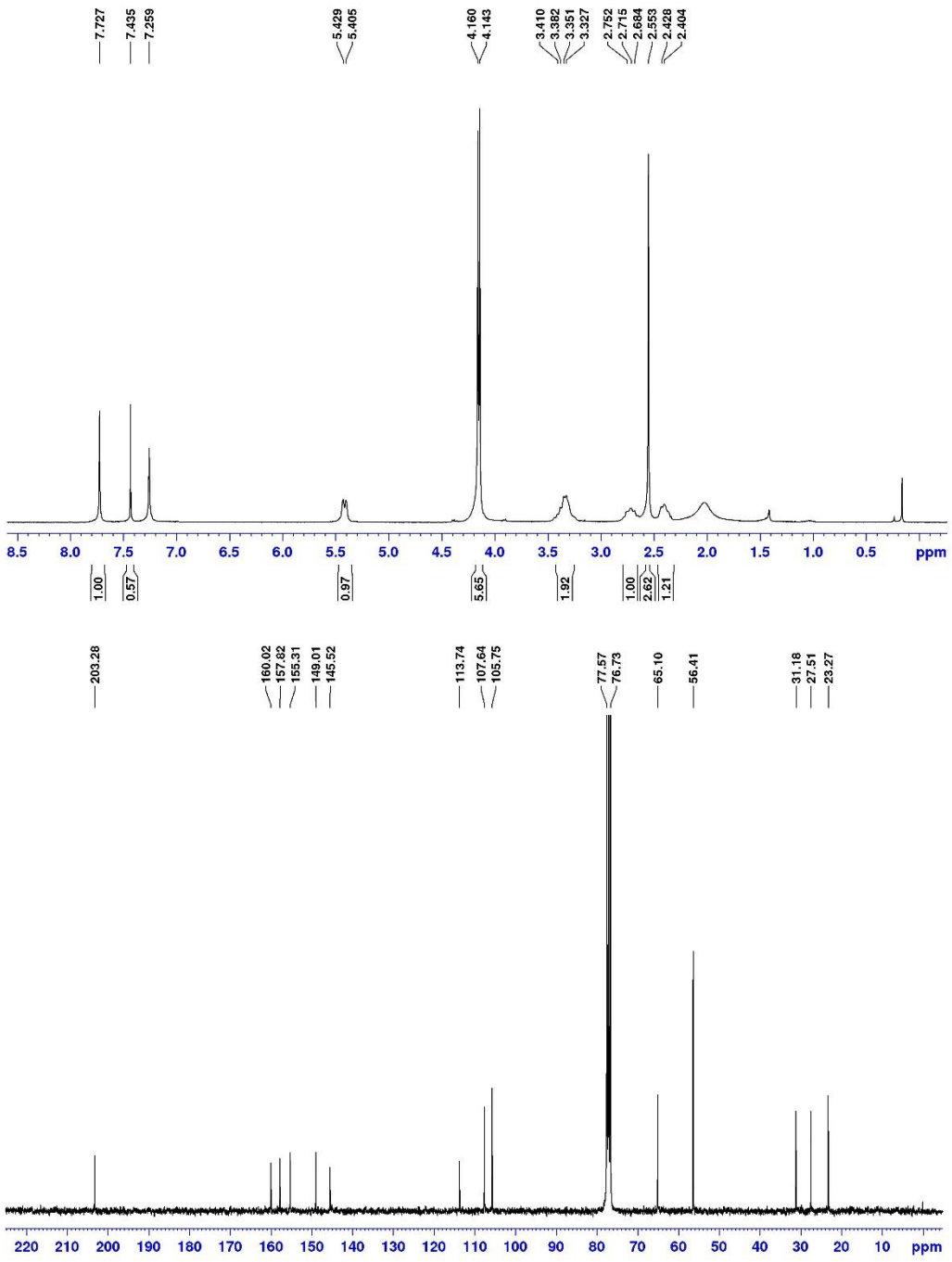
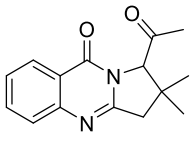


Figure 50 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **106h** in $CDCl_3$



106h

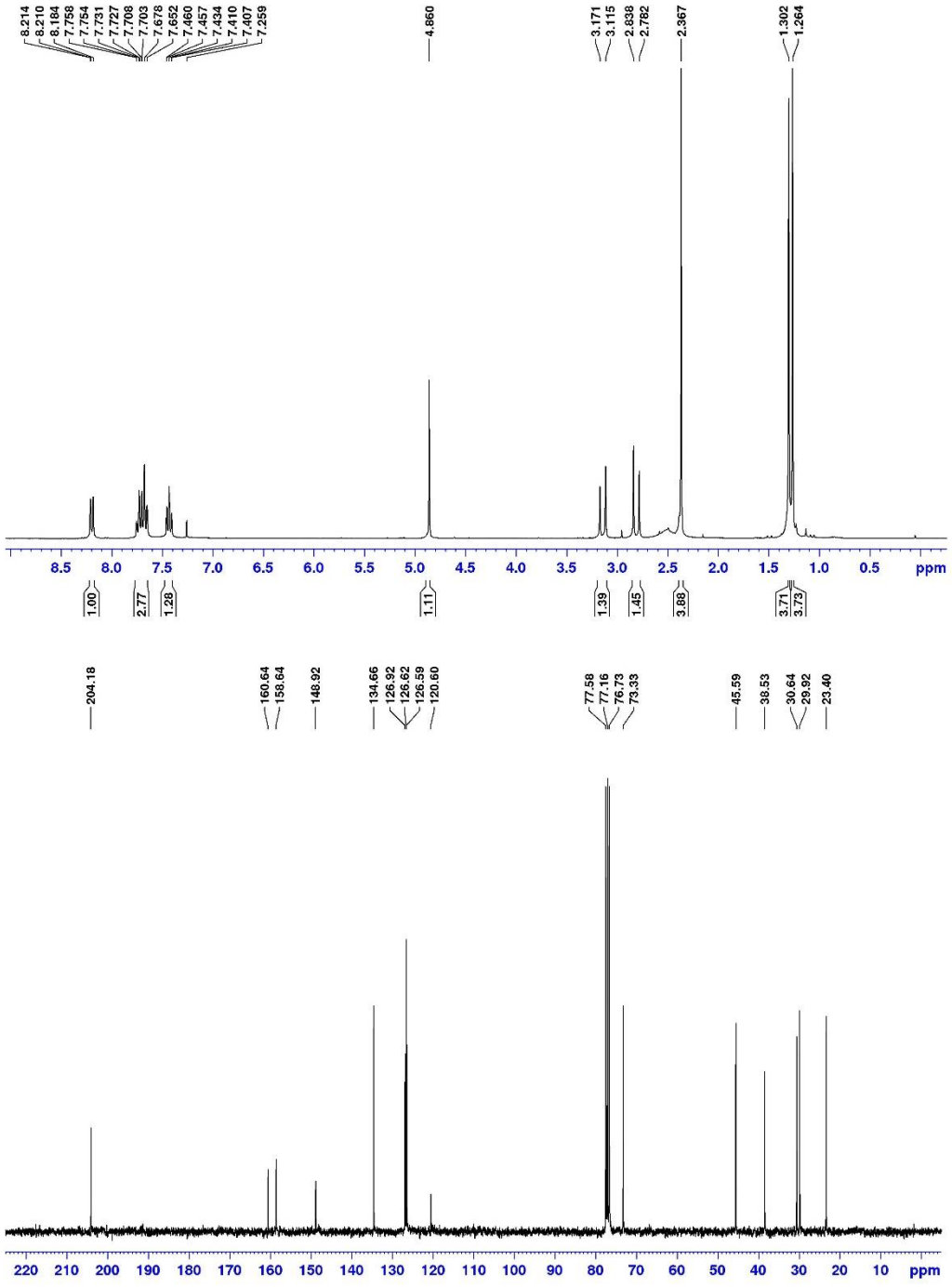
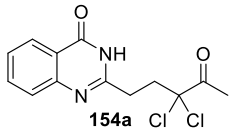
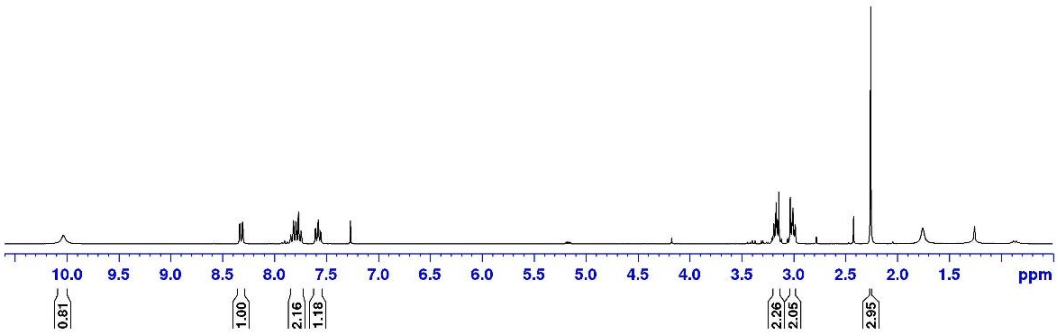


Figure 51 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **154a** in $CDCl_3$





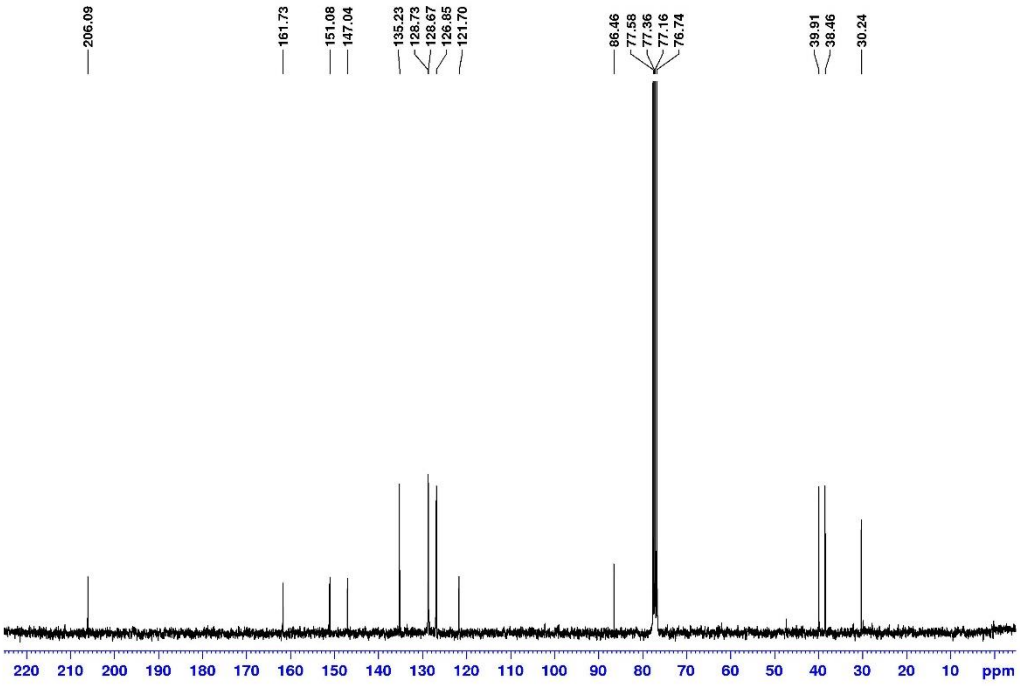


Figure 52 The ^{1}H (300 MHz) in $CDCl_3$ and ^{13}C NMR (75 MHz) spectra of compound **155a** in $CDCl_3$

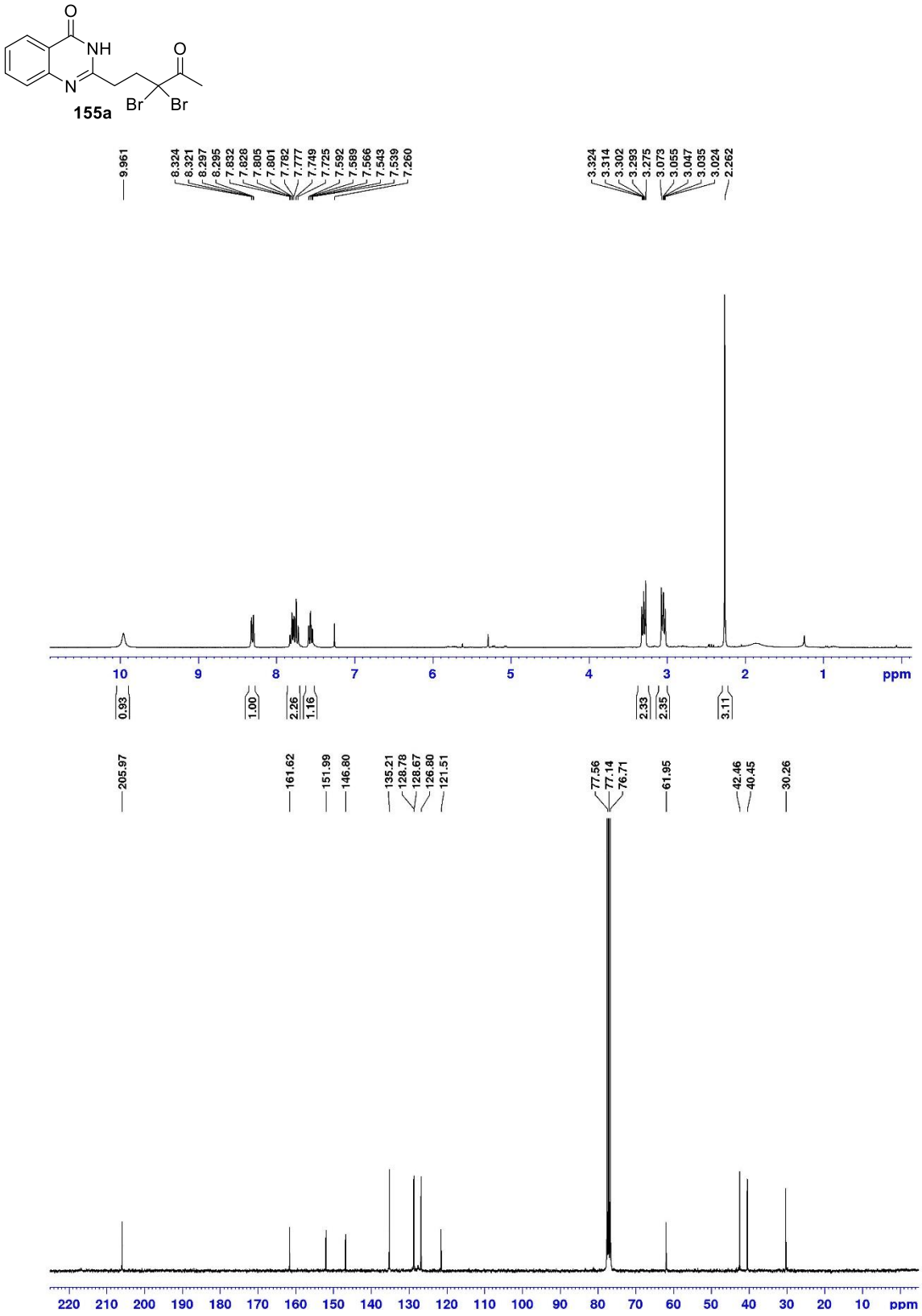


Figure 53 The ^{1}H (300 MHz) in $CDCl_3$ and ^{13}C NMR (75 MHz) spectra of compound **153a** in DMSO-d_6

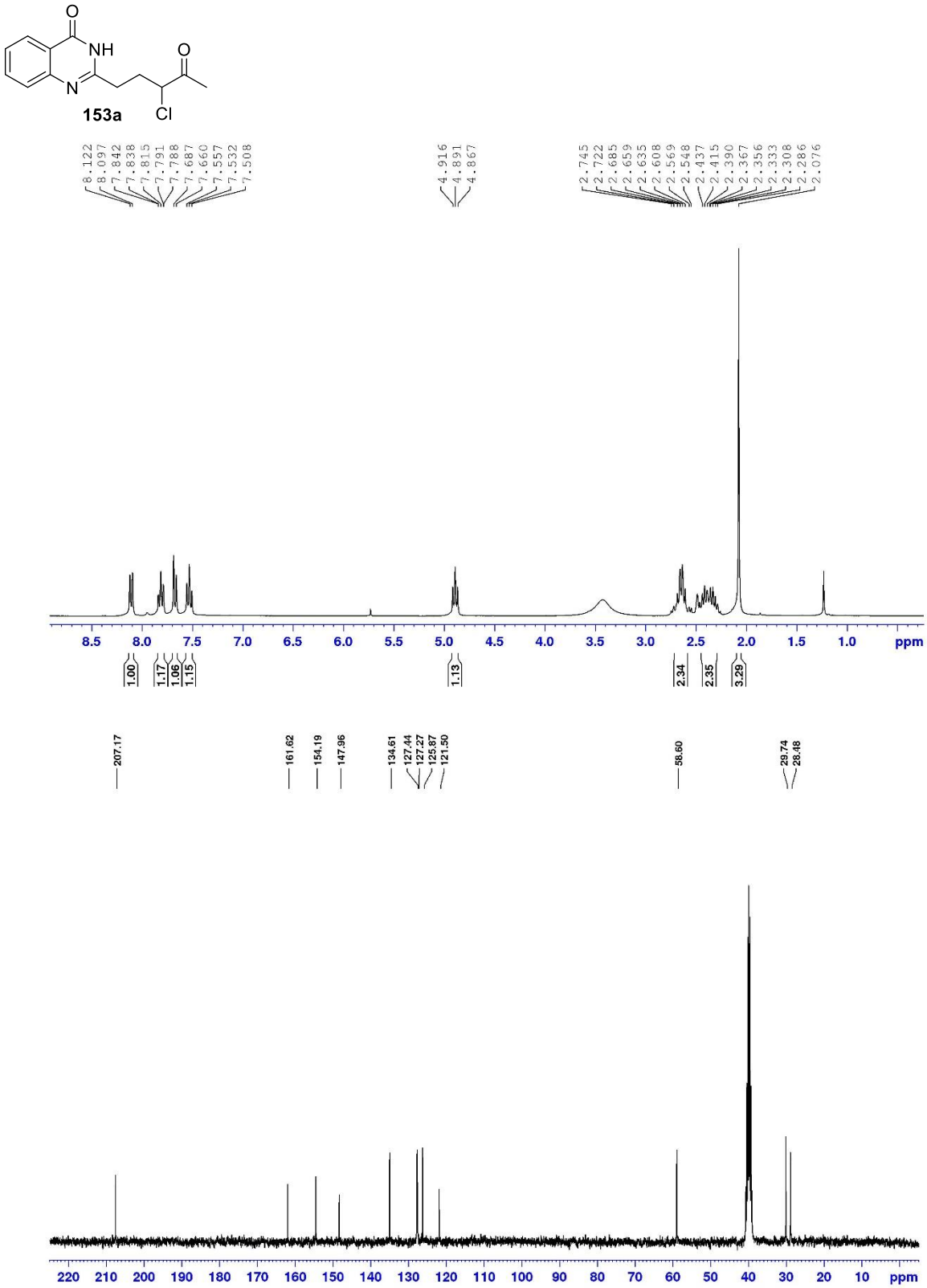


Figure 54 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **156a** in $CDCl_3$

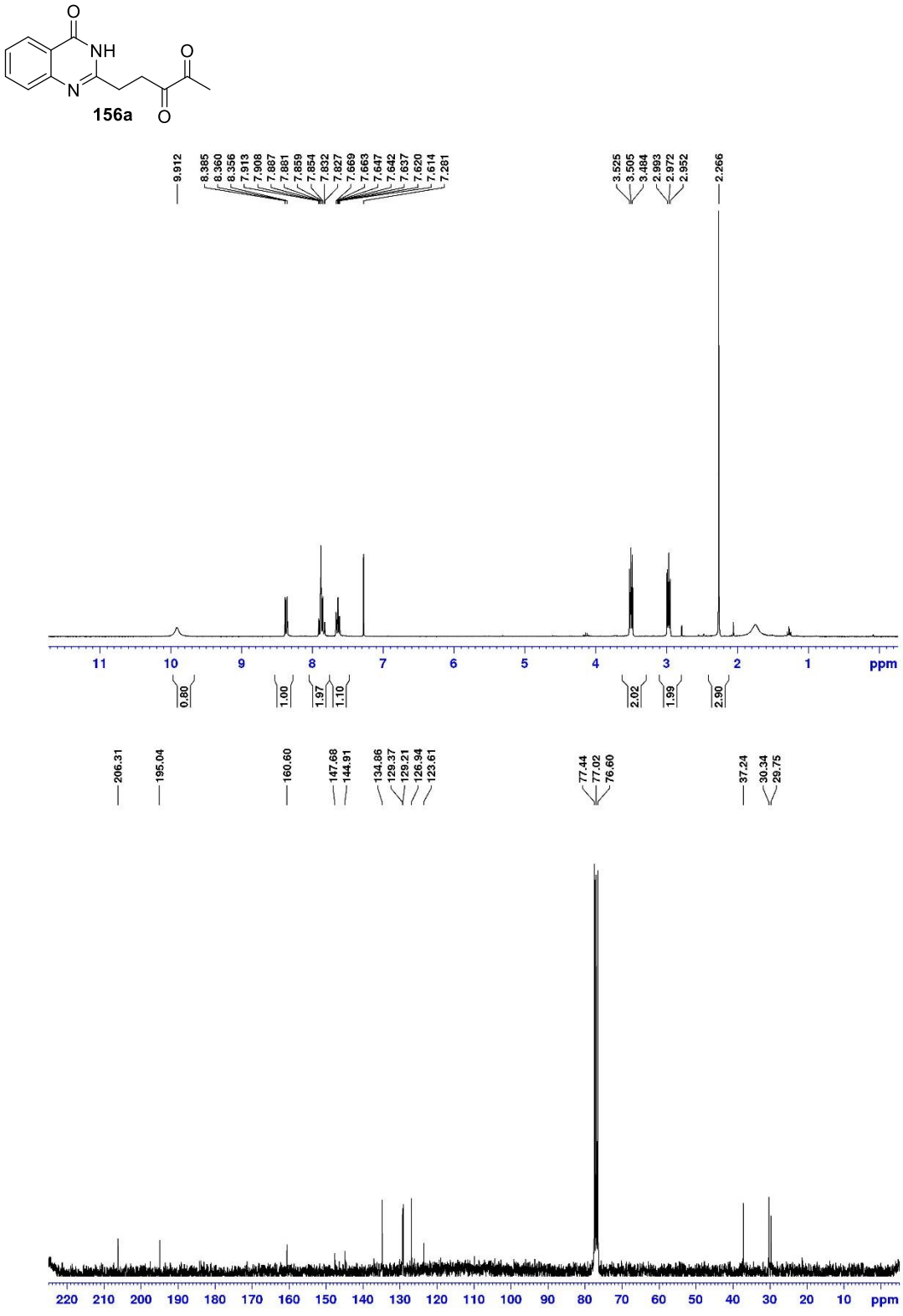
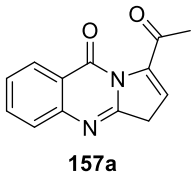


Figure 55 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **157a** in $CDCl_3$



157a

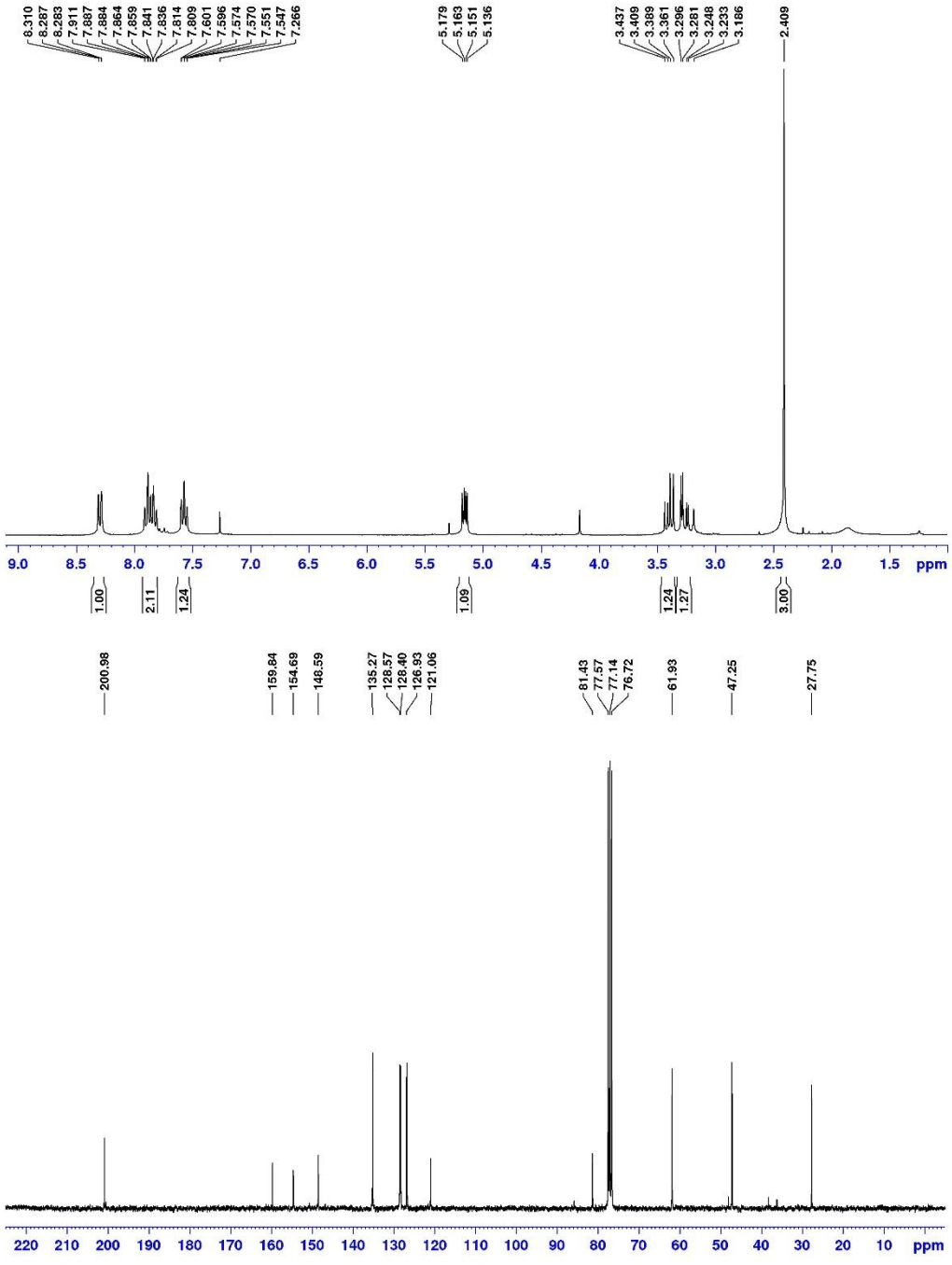


Figure 56 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **157b** in $CDCl_3$

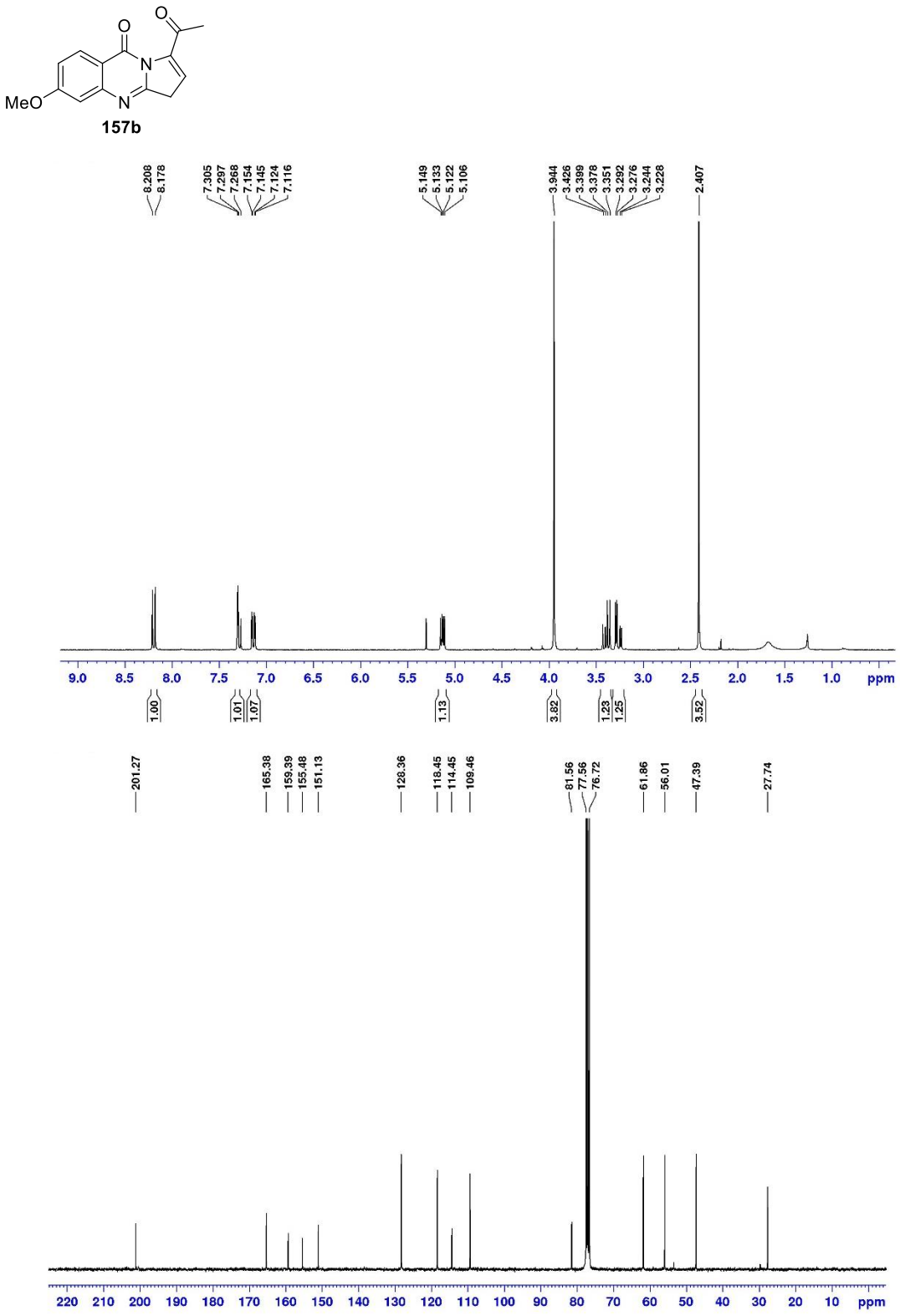


Figure 57 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **157c** in $CDCl_3$

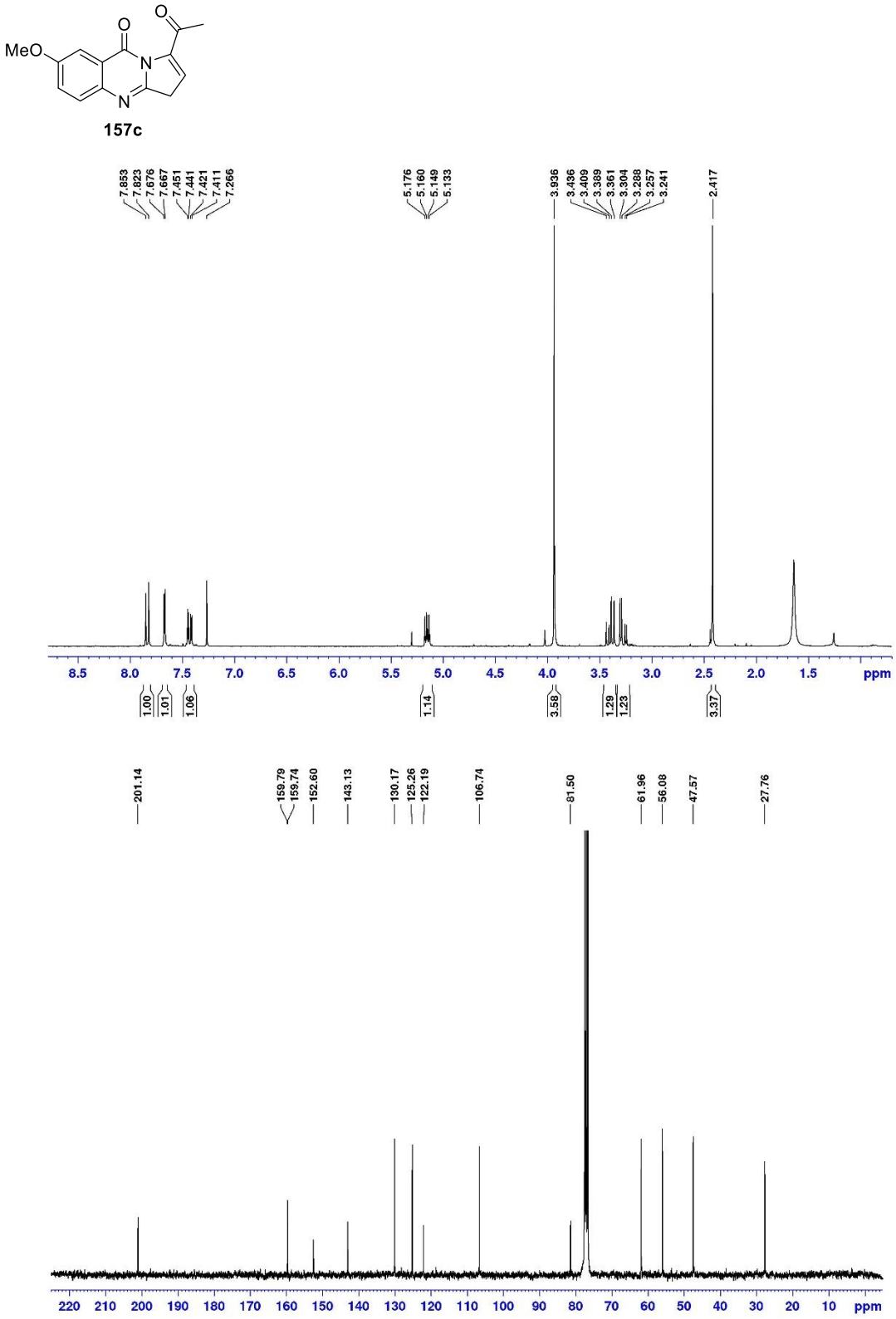


Figure 58 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **157d** in $CDCl_3$

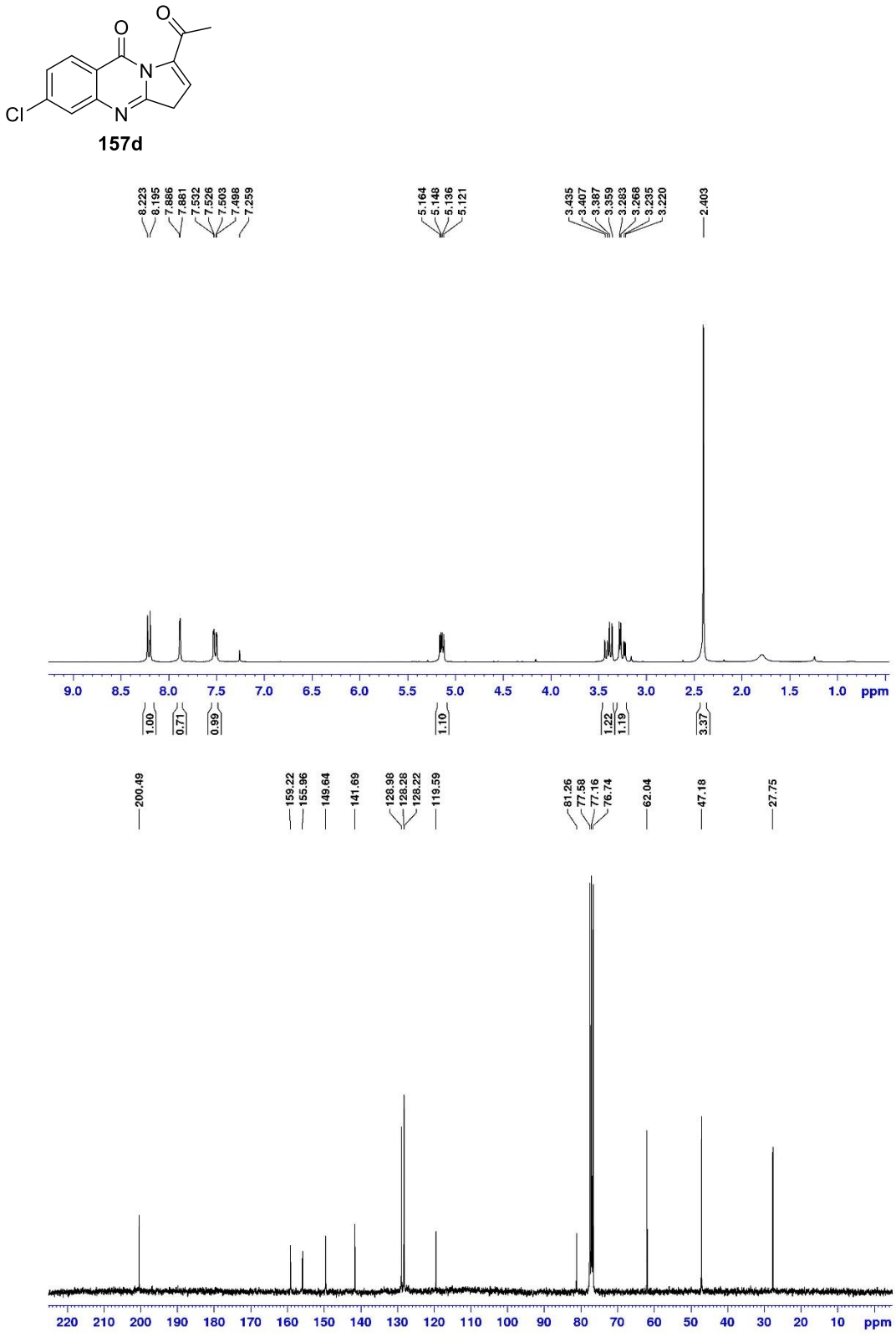
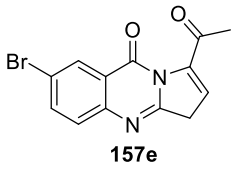
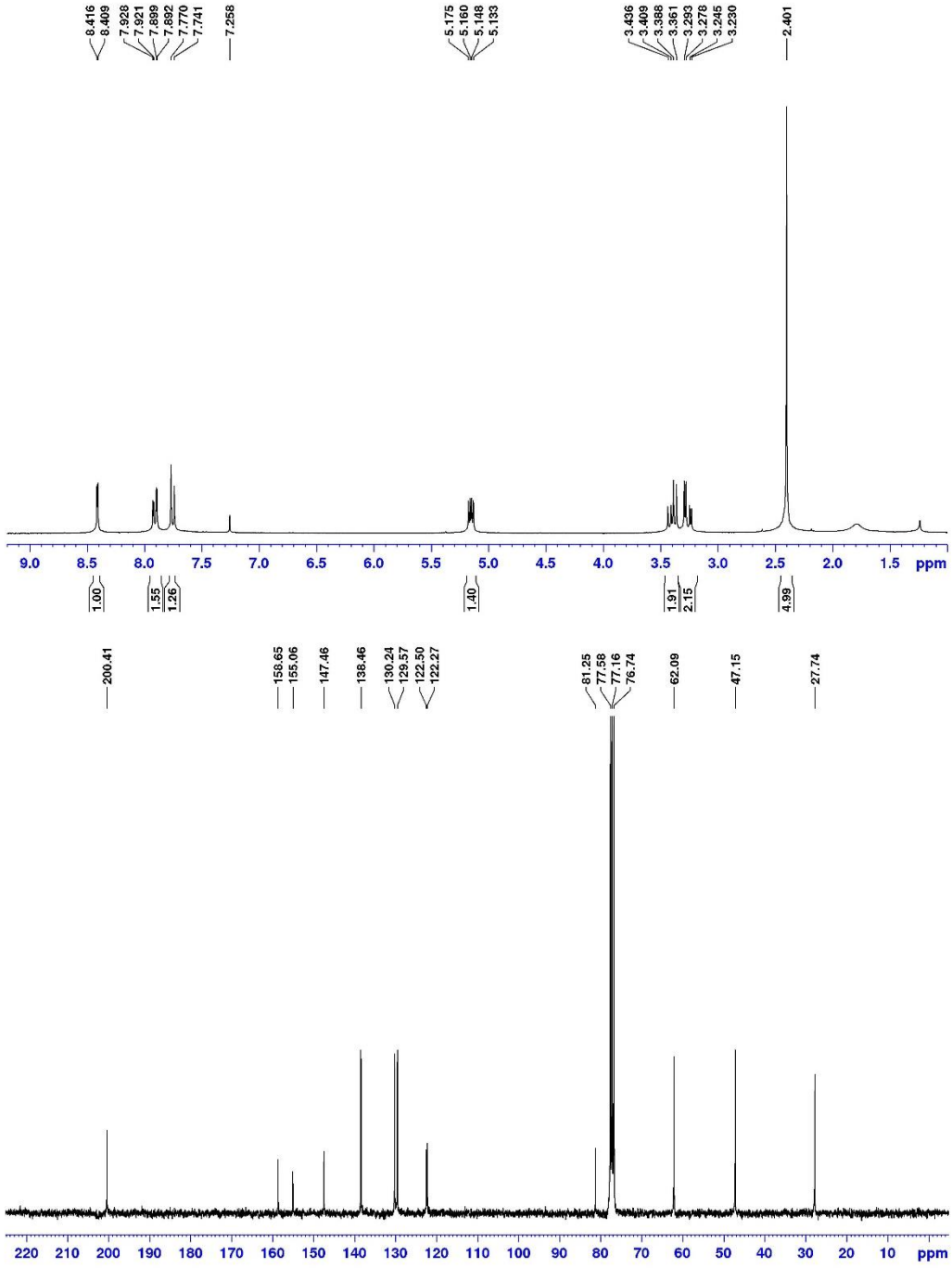


Figure 59 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **157e** in $CDCl_3$



157e



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Scholarship Award during Enrolment

The Science Achievement Scholarship of Thailand (SAST)

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.

Saebang, Y.; Kaeobamrung, J.; Rukachaisirikul, V. 2022. Synthesis of Eleven-Membered Cyclic Urea Fused Quinazolinones. Synlett. 33(14), 1371–1376.

Saebang, Y.; Rukachaisirikul, V.; Kaeobamrung, J. 2023. Synthesis of acetyl deoxyvasicinone analogues from 2-(4-oxopentyl)quinazolin-4(3*H*)-ones *via* linear cyclizations. Tetrahedron Lett. 120, 154484.