DMAP-Catalyzed Domino Reactions of α-Chloroaldoxime O-methanesulfonates and 2-Aminobenzoic acid for the Synthesis of Quinazolinediones

Watcharadet Kaewman

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Science in Chemistry (International Program)

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Thesis Title	DMAP-Catalyzed Domino Reactions of α-Chloroaldoxime *O*-methanesulfonates and 2-Aminobenzoic acid for the Synthesis of Quinazolinediones
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Major Program	Chemistry (International Program)

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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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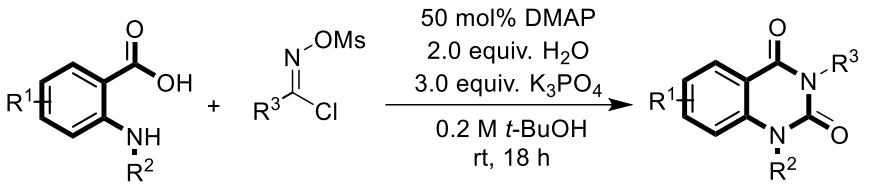
Candidate

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

……...…..Signature
(Mr. Watcharadet Kaewman)
Candidate

ชื่อวิทยานิพนธ์	การสังเคราะห์ควินาโซลีนไดโอนด้วยปฏิกิริยาระหว่างสารตั้งต้น α-Chloroaldoxime *O*-methanesulfonates และ 2-Aminobenzoic acids โดยใช้ DMAP เป็นตัวเร่งปฏิกิริยา
ผู้เขียน	นายวัชรเดช แก้วมั่น
สาขาวิชา	เคมี (หลักสูตรนานาชาติ)
ปีการศึกษา	2566

บทคัดย่อ



2-aminobenzoic acids

quinazolinediones
(0-90% yields)

R^1 = OMe, Me, NO_2,CO_2H
R^2 = benzyl, acyl, carbamate, urea, *para* - methoxybenzyl
R^3 = phenyl, alkyl

ควินาโซลีนไดโอนเป็นสารประกอบทางธรรมชาติที่มีไนโตรเจนเป็นองค์ประกอบ สารกลุ่มนี้มีฤทธิ์ทางชีวภาพหลากหลาย โครงสร้างหลักของควินาโซลีนไดโอนประกอบด้วยวงอะโรมาติกต่อเข้ากับส่วนของยูเรีย ในงานวิจัยนี้ สารประกอบกลุ่มนี้สามารถสังเคราะห์ได้จากสารตั้งต้น α-chloroaldoxime *O*-methanesulfonates และ 2-aminobenzoic acids โดยใช้ DMAP เป็นตัวเร่งปฏิกิริยา กลไกหลักของปฏิกิริยานี้ประกอบด้วยการเพิ่มของนิวคลีโอไฟล์ การจัดเรียงตัวแบบ Tiemann การปิดวงภายในโมเลกุลเพื่อสร้างพันธะ C–O และการจัดเรียงตัวของ *O*-acylisourea เป็นที่น่าสนใจว่าสารประกอบควินาโซลีนไดโอนสามารถสังเคราะห์ขึ้นได้ภายใต้สภาวะที่ไม่รุนแรง จากการวิจัยพบอีกว่า ผลทางอิเล็กทรอนิกส์ของสารตั้งต้นทั้งสองชนิด มีผลอย่างมีนัยสำคัญกับประสิทธิภาพในการเกิดผลิตภัณฑ์ควินาโซลีนไดโอน มากไปกว่านั้น วิธีการสังเคราะห์นี้สามารถเป็นอีกทางเลือกหนึ่งที่นักวิจัยเคมีอินทรีย์สังเคราะห์สามารถนำไปใช้ในการสังเคราะห์สารโมเลกุลต้นแบบเพื่อนำไปใช้ในการสังเคราะห์สารที่มีฤทธิ์ทางชีวภาพต่อไป

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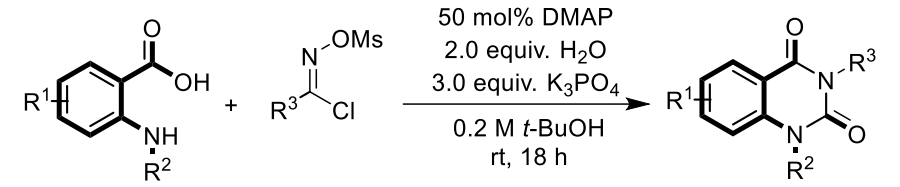
Academic Year	2023

ABSTRACT



R^1 = OMe, Me, NO_2,CO_2H
R^2 = benzyl, acyl, carbamate, urea, *para* - methoxybenzyl
R^3 = phenyl, alkyl

Quinazolinediones are one of the most important *N*-containing natural products with a wide range of biological activities. The structural features of quinazolinedione include a phenyl ring fused with urea moiety. Various quinazolinediones were achieved from 2-aminobenzoic acids and α-chloroaldoxime *O*-methanesulfonates *via* DMAP-catalyzed domino reactions under mild reaction conditions. The reaction pathways plausibly involved nucleophilic addition, Tiemann rearrangement, an intramolecular C–O formation followed by *O*-acylisourea rearrangement. The electronic effect on the nitrogen of 2-aminobenzoic acids and the electrophilicity of α-chloroaldoxime *O*-methanesulfonates both significantly played an important role to the reaction efficiency. Moreover, our methodology could be applied to alternatively achieve a building block for biologically active quinazolinedione.

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Watcharadet Kaewman

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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
Bn	=	benzyl
$CDCl_3$	=	deuterochloroform
$CHCl_3$	=	chloroform
CH_2Cl_2	=	dichloromethane
CH_3CN	=	acetonitrile
Cs_2CO_3	=	cesium carbonate
DABCO	=	1,4-diazabicyclo[2.2.2]octane
DMA	=	dimethylacetamide
DMEDA	=	*N*,*N*′-dimethylethylenediamine

LIST OF ABBREVATIONS AND SYMBOLS (Continued)

DMSO	=	dimethylsulfoxide
DMSO-d_6	=	dimethyl sulfoxide-d_6
DIPEA	=	*N*,*N*-diisopropylethylamine
DMAP	=	*N*,*N*-dimethylaminopyridine
Et	=	ethyl
EtOAc	=	ethyl acetate
EtOH	=	ethanol
Me	=	methyl
MsCl	=	methanesulfonyl chloride
MeOH	=	methanol
Na_2SO_4	=	sodium sulfate
NH_4Cl	=	ammonium chloride
NMP	=	*N*-methyl-2-pyrrolidone
NCS	=	*N*-chlorosuccinamide
$NH_2OH \cdot HCl$	=	hydroxylammonium chloride
Ph	=	phenyl
K_2CO_3	=	potassium carbonate
K_3PO_4	=	potassium phosphate
Tf	=	triflyl
THF	=	tetrahydrofuran
TMS	=	tetramethylsilane

LIST OF PUBLICATION

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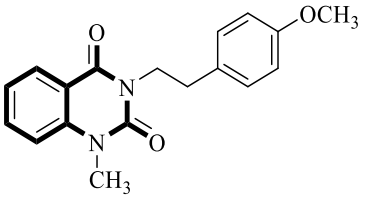
CHAPTER 1

INTRODUCTION

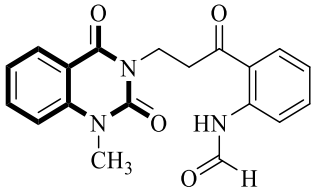
1.1.1 Introduction

Quinazolinediones are one of the important classes of *N*-containing heterocycles. The notable structural features of these compounds consist of benzene ring and 2-pyrimidinone. Quinazolinediones are found in alkaloid natural products and widely used in medicinal chemistry. For example, 1-methyl-3-[2'-(4'-methoxyphenyl)ethyl]-(*1H,3H*)-quinazoline-2,4-dione (**1**) isolated from seed husks of *Zanthoxylum arborescens* species showed antihypertensive activity (Rivero *et al*., 2004). *N*-(2-(3-(1-Methyl-2,4-dioxo-1,4-dihydroquinazolin-3(*2H*)-yl)propanoyl)phenyl)formamide (**2**) isolated from the fruits of *Evodia officinalis*, represented moderate cytotoxicity against HeLa and HT1080 cell lines (Jin *et al*., 2008). 3-Amino-7-((*R*)-3-((*S*)-1-aminoethyl)pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methylquinazoline-2,4(*1H,3H*)-dione (**3**) and (*S*)-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-3-hydroxyquinazoline-2,4(*1H,3H*)-dione (**4**) displayed antibacterial activity (Ellsworth *et al*., 2006). Furthermore, *N*-substituted methylquinazolinedione-2,4(*1H,3H*)-dione derivatives, such as 3-(3-((2-hydroxy-5-nitrophenyl)amino)propanoyl)-1-methylquinazoline-2,4(*1H,3H*)-dione (**5**) and 3-(3-((4-aminophenyl)amino)propanoyl)-1-methylquinazoline-2,4(*1H,3H*)-dione (**6**) had been used in the application of medical treatment as an antioxidant and they also exhibited anticonvulsant activity (Prashanth *et al*., 2013). 3-Ethyl-1-(3-nitrophenyl)quinazoline-2,4(*1H,3H*)-dione (**7**) is a promising agent for treatment of asthma (Dal *et al*., 2000). 3-(3-(*1H*-Imidazol-1-yl)propyl)-7-methoxy-6-(oxazol-5-yl)quinazoline-2,4(*1H,3H*)-dione (**8**) was considered as potential immune-suppressive and anti-inflammatory agent (Buckley *et al*., 2005) (**Figure 1**).

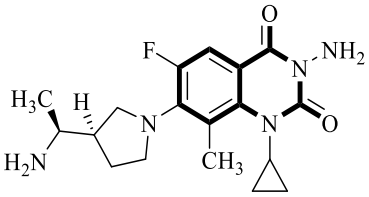
Figure 1 Examples of bioactive quinazolinediones



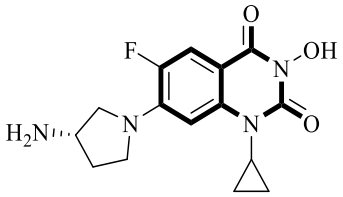
3-(4-methoxyphenethyl)-1-methylquinazoline
-2,4(1*H*,3*H*)-dione (**1**)



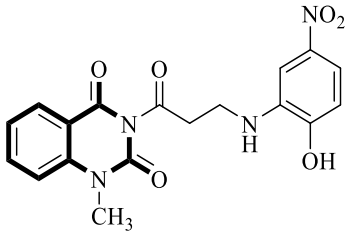
N-(2-(3-(1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)
propanoyl)phenyl)formamide (**2**)



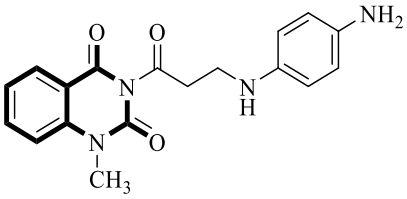
3-amino-7-((*R*)-3-((*S*)-1-aminoethyl)pyrrolidin-1-yl)-1-
cyclopropyl-6-fluoro-8-methylquinazoline
-2,4(1*H*,3*H*)-dione (**3**)



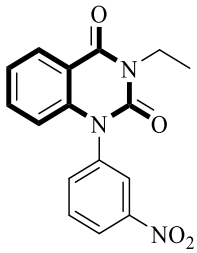
(*S*)-7-(3-aminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-
3-hydroxyquinazoline-2,4(1*H*,3*H*)-dione (**4**)



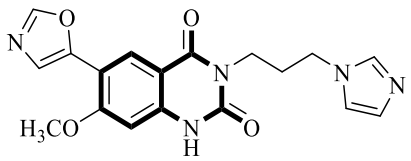
3-(3-((2-hydroxy-5-nitrophenyl)amino)propanoyl)
-1-methylquinazoline-2,4(1*H*,3*H*)-dione (**5**)



3-(3-((4-aminophenyl)amino)propanoyl)
-1-methylquinazoline-2,4(1*H*,3*H*)-dione (**6**)



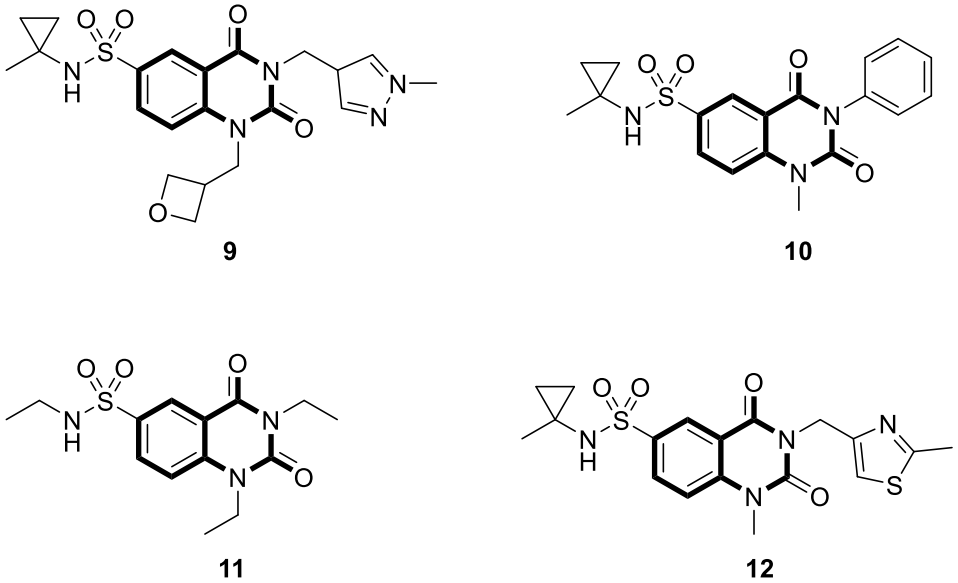
3-ethyl-1-(3-nitrophenyl)quinazoline
-2,4(1*H*,3*H*)-dione (**7**)



3-(3-(1*H*-imidazol-1-yl)propyl)-7-methoxy-6-(oxazol-5-yl)
quinazoline-2,4(1*H*,3*H*)-dione (**8**)

In addition, quinazolinedione derivatives are potentially useful to prevent the DNA derogation. DNA damage repairing enzymes are promising targets in the development of new therapeutic agents for a wide range of cancers and other diseases. The enzyme poly(ADP-ribose)glycohydrolase (PARG) played a pivotal role in the regulation of DNA repairing mechanisms. However, the lack of potent drug-like inhibitors for use in cellular and *in vivo* models has limited the investigation of its potential as novel therapeutic target. Novel quinazolinedione sulfonamides are alternative cell-active small inhibitors of the DNA damage repairing enzyme poly(ADP-ribose)glycohydrolase (PARG). As the hydrogen bonding network observed around the sulfonamide appeared to be a key pharmacophore. All aryl sulfonamides bearing a variety of aliphatic amines were installed for suitable drug-like properties. Nitrogens of cyclic urea moiety were considered as a crucial moiety for interaction with protein binding site (Waszkowycz *et al*., 2018) (**Figure 2**).

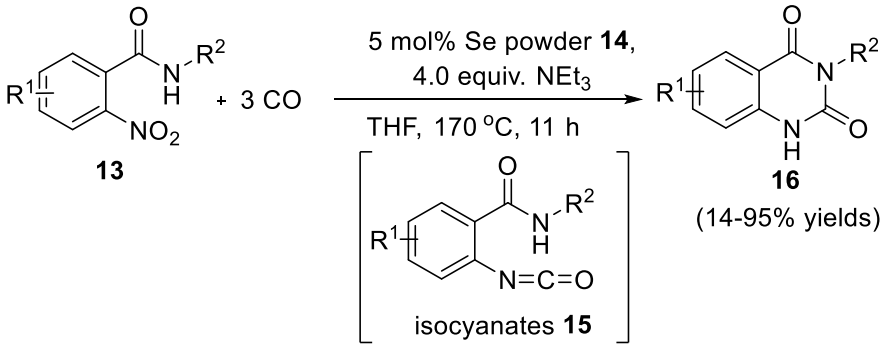
Figure 2 Examples of cell-active small inhibitors of the DNA damage repairing enzyme poly(ADP-ribose)glycohydrolase (PARG)



Due to interesting biological activities of quinazolinediones, methodologies both metal and non-metal catalyzed reactions have been consistently developed. Selected examples of quinazolinedione formation developments were listed below.

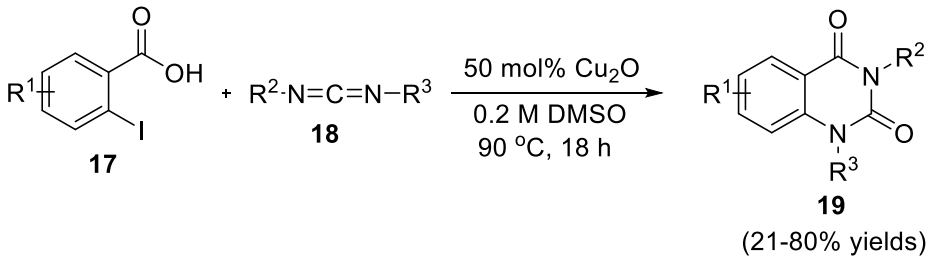
In 2010, Wu and Yu utilized selenium powder as a catalyst to synthesize *1H*-quinazoline-2,4-diones. Selenium powder **14** was used as a catalyst for carbonylation of *o*-nitrobenzamides **13** with carbon monoxide. The proposed reactive intermediate in their synthesis was isocyanates **15**. Intramolecular cyclization of isocyanates **15** provided the desired products **16** in 14-95% yields (**Scheme 1**) (Wu *et al*., 2010).

Scheme 1 Transition metal catalyzed reaction to synthesize *1H*-quinazoline-2,4-diones



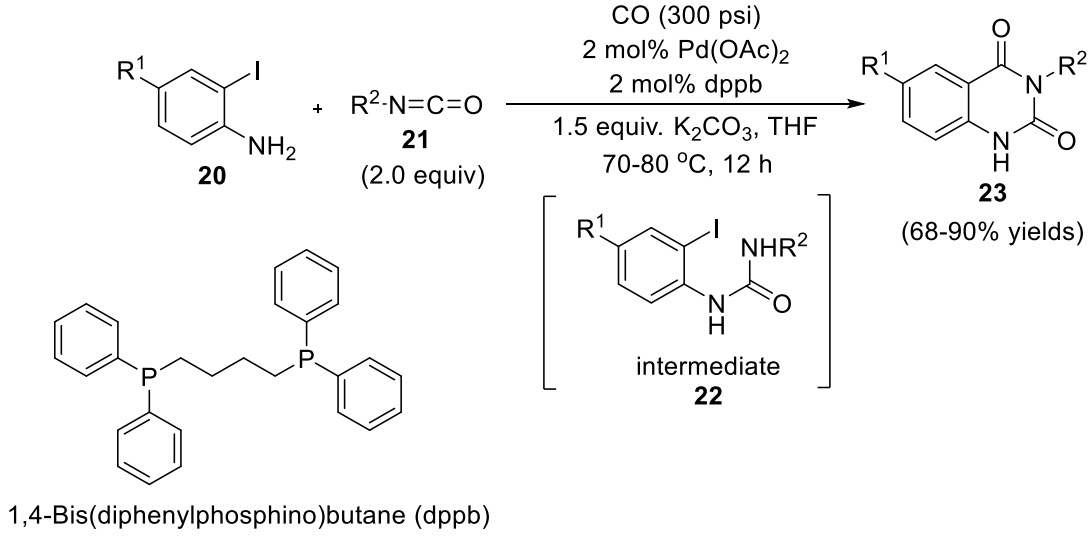
In 2018, Duangjan and co-workers reported the synthesis of quinazoline-2,4-dione derivatives *via* copper-catalyzed domino reaction under mild conditions and simple preparation. 2-Iodobenzoic acids **17** and carbodiimides **18** were used as starting materials in the presence of 50 mol% copper(I) oxide. The quinazolinediones **19** were achieved in 21-80% yields. However, high catalyst loading of copper(I)oxide was required (**Scheme 2**) (Duangjan *et al*., 2018).

Scheme 2 Synthesis of quinazoline-2,4-dione derivatives *via* copper-catalyzed domino reaction



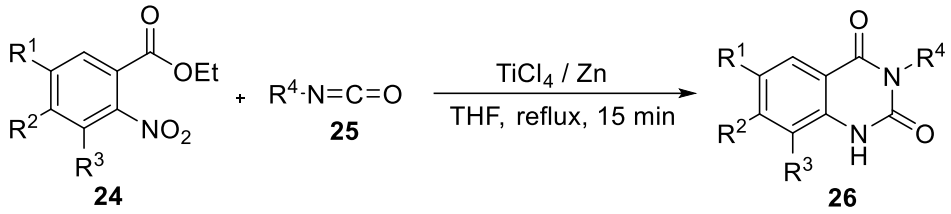
In 2000, Larksarp and Alper used palladium (II) as a catalyst to synthesize quinazolinedione derivatives from *o*-iodoanilines **20** and isocyanates **21** in the presence of CO (300 psi). The reaction mechanism involved the *in situ* generation of ureas **22** followed by palladium-catalyzed carbonylation to provide the desired quinazolinediones **23** in 68-90% yields (**Scheme 3**) (Larksarp *et al*., 2000).

Scheme 3 Palladium-catalyzed cyclocarbonylation of *o*-iodoanilines **20** with isocyanates **21**



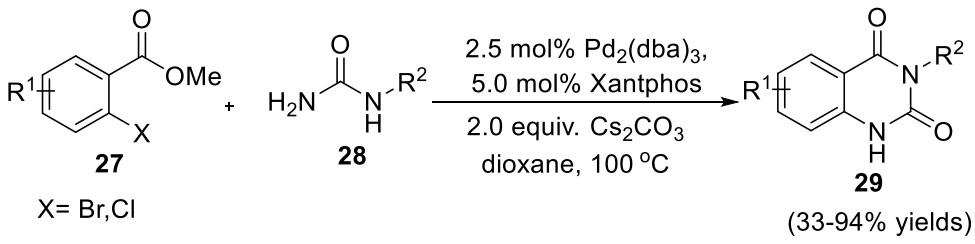
In 2009, Dou and co-workers reported the use of low-valent titanium reagent to synthesize quinazoline-2,4(*1H,3H*)-dione derivatives **26** *via* a reductive cyclization as a key step. The desired products were formed in 75-94% yields from ethyl-2-nitrobenzoates **24** and isocyanates **25** (**Scheme 4**) (Dou *et al*., 2009).

Scheme 4 One-pot synthesis of quinazoline-2,4(*1H,3H*)-diones with the aid of low-valent titanium reagent



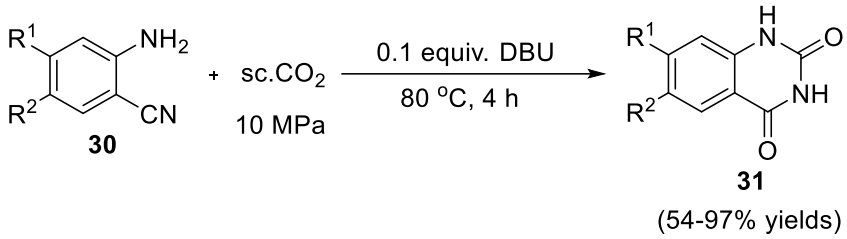
In 2006, Willis and co-workers utilized an application of palladium-catalyzed C–N and C–O bond formation for quinazolinediones synthesis. *o*-Halobenzoates **27** and monoalkyl ureas **28** were used as starting materials. The formation of product involved tandem processes consisting of a regioselective palladium-catalyzed arylation of urea and an intramolecular amidation reaction. The desired products **29** were obtained in 33-94% yields (**Scheme 5**) (Willis *et al*., 2006).

Scheme 5 Palladium-catalyzed arylation and ester amidation of *o*-halobenzoates **27** and monoalkyl ureas **28**



Non-metal catalyzed reaction were vitally alternative methods for preparation of quinazolinediones. In 2004, Mizuno and co-workers successfully developed a new method for the synthesis of 1*H*-quinazoline-2,4-dione derivatives. 2-Aminobenzonitriles **30** and 10 MPa supercritical carbon dioxide (sc. CO_2) were used as starting materials in the presence of DBU (0.1 equiv.) at 80 °C for 4 hours. The desired products **31** were obtained in 54-97% yields (**Scheme 6**) (Mizuno *et al*., 2004).

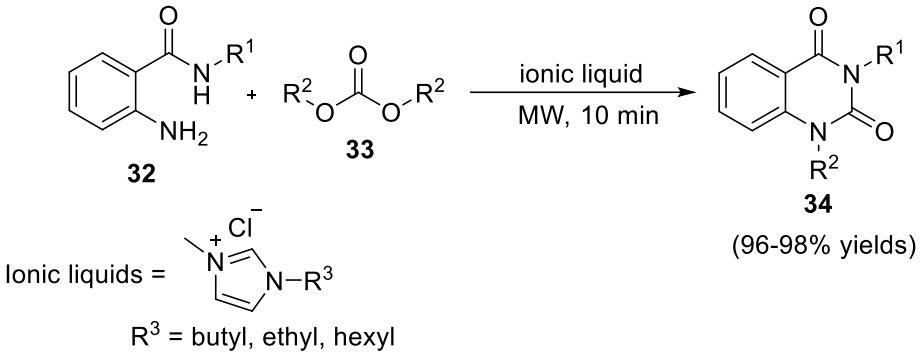
Scheme 6 DBU-catalyzed the synthesis of quinazolinedione derivatives



Since one of the key structural moieties of quinazolinedione is 2-aminobenzoyl, derivatives of 2-aminobenzoic acids or amides are common starting materials to provide corresponding quinazolinediones. Therefore, two common methods are a heterocyclization of 2-aminobenzoic acid derivatives and an installation of carbonyl fragment on aromatic amine functionality of 2-aminobenzamides.

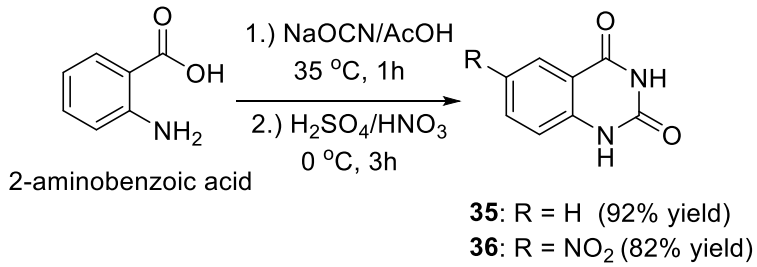
In 2012, Guerrero and co-workers achieved the synthesis of 1-alkylquinazoline-2,4-diones **34** from *o*-aminobenzamides **32** by applying microwave irradiation at 130 °C in the presence of ionic liquids. Dialkyl carbonates **33** was used as both carbonylating and alkylating agents (**Scheme 7**) (Leticia Guerrero *et al*., 2012).

Scheme 7 Reaction of *o*-aminobenzamides **32** with dialkyl carbonates **33** and ionic liquids



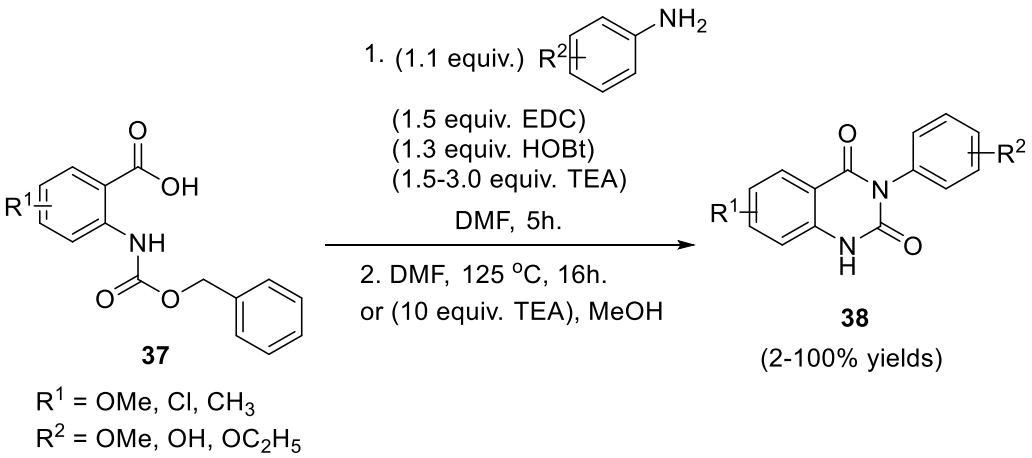
In 1943, Lange and co-workers reported the synthesis of nitro-substituted quinazolinedione **36**. Their method began with the reaction of 2-aminobenzoic acid and sodium cyanate in the presence of acetic acid to completely produce a quinazolinedione **35** in 92% yield. Then, **35** was subjected to nitration reaction using mixture of nitric acid and sulfuric acid to provide a nitro-substituted quinazolinedione **36** in 82% yield (**Scheme 8**) (Gheidari *et al*., 2022).

Scheme 8 Synthesis of quinazolinedione **35** using 2-aminobenzoic acid and sodium cyanate



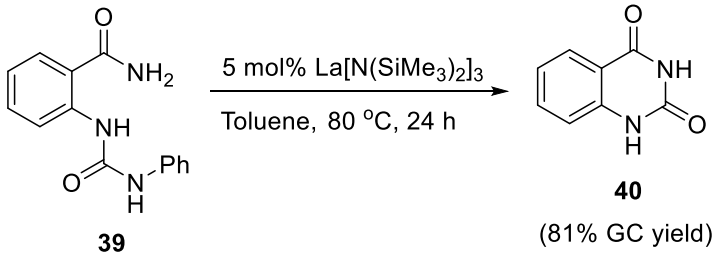
In 2017, Choo and co-workers reported the synthesis of quinazolinediones **38**. The method started with the reaction between functionalized 2-aminobenzoic acids **37** and aniline derivatives followed by cyclization to provide the corresponding products **38** in 2-100% yields (**Scheme 9**) (Choo *et al*., 2002).

Scheme 9 Quinazolinediones synthesis from functionalized 2-aminobenzoic acid **37**



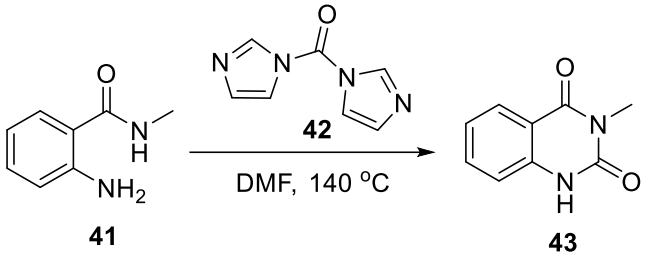
In 2014, Jing and co-workers described a preparation of quinazolinedione **40** from 2-(3-phenylureido)benzamide **39** in the presence of lanthanide catalyst at 80 °C resulting in formation of quinazolinedione **40** in 81% GC yield (**Scheme 10**) (Jing *et al*., 2014).

Scheme 10 Cyclization of 2-(3-phenylureido)benzamide **39** for the construction of quinazolinedione **40**



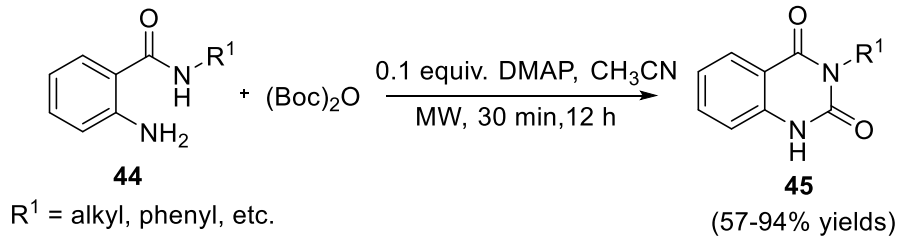
In 2018, Waszkowycz and co-workers achieved the production of quinazolinedione **43** from the reaction of 2-amino-*N*-methylbenzamide **41** and carbonyldiimidazole **42** in DMF at 140 °C. High yield of quinazolinedione **43** was obtained (**Scheme 11**) (Waszkowycz *et al*., 2018).

Scheme 11 Reaction of 2-amino-*N*-methylbenzamide **41** and carbonyldiimidazole **42** for the synthesis of quinazolinedione **43**



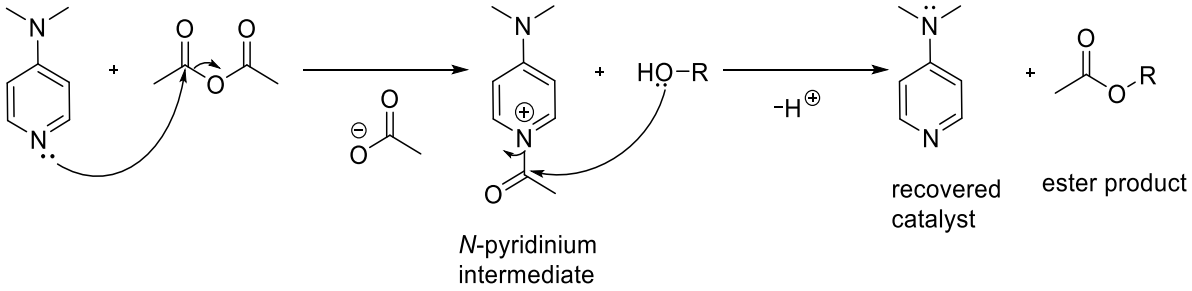
In 2020, Chen and co-workers accomplished a synthesis of quinazolinediones **45** under microwave irradiation in one-pot fashion. The products were obtained in 57-94% yields using 2-aminobenzamides **44** and di-*tert*-butyl dicarbonate ($(Boc)_2O$) as starting materials in the presence of 10 mol% of DMAP (**Scheme 12**) (Chen *et al*., 2020).

Scheme 12 DMAP-catalyzed one-pot synthesis of quinazoline-2,4-diones from 2-aminobenzamides **44** and di-*tert*-butyl dicarbonate ($(Boc)_2O$)



4-Dimethylaminopyridine (DMAP) is one of common organocatalytic reagents that has been widely used to catalyze nucleophilic substitution reactions (Xu *et al*., 2005). Generally, DMAP acts as a nucleophilic catalyst to increase electrophilicity of electrophile starting materials, favoring a fast addition and elimination process *via* the *N*-pyridinium intermediate. The intermediate reacts rapidly with nucleophile to form the desired product (**Scheme 13**).

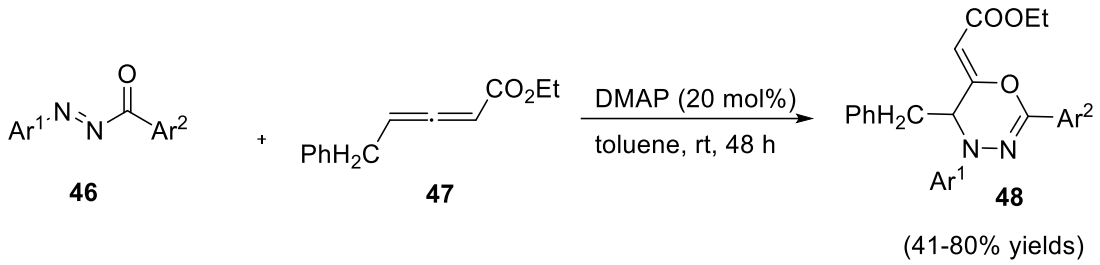
Scheme 13 General chemical reactivity of DMAP



Over the last decade, 4-dimethylaminopyridine (DMAP) has been used to catalyzed various organic reactions. Selected examples of nucleophilic DMAP-catalyzed reactions were listed below.

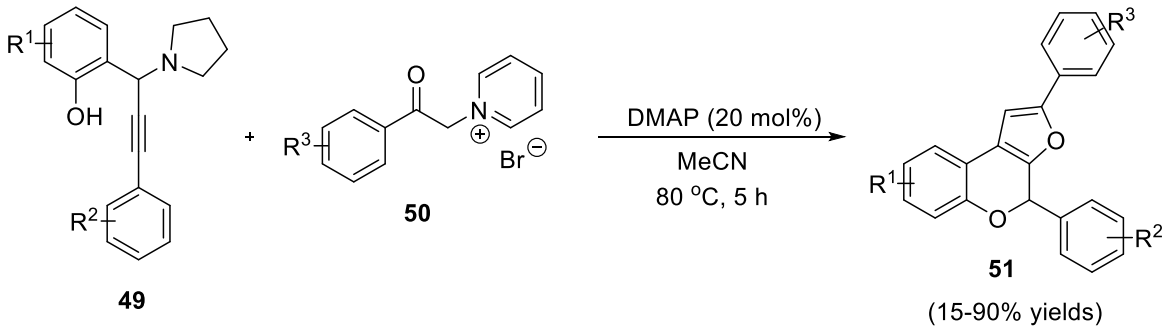
In 2015, an efficient DMAP-catalyzed [2 + 4] cycloaddition of *N*-acyldiazenes **46** and allenoates **47** was reported by Zhang and co-workers. The reaction involved embedding three heteroatoms into a six-membered ring. The corresponding products 1,3,4-oxadiazine derivatives **48** were obtained in 41-80% yields (**Scheme 14**) (Zhang *et al*., 2015).

Scheme 14 DMAP-catalyzed [2 + 4] cycloadditions of *N*-acyldiazenes **46** with allenoates **47**



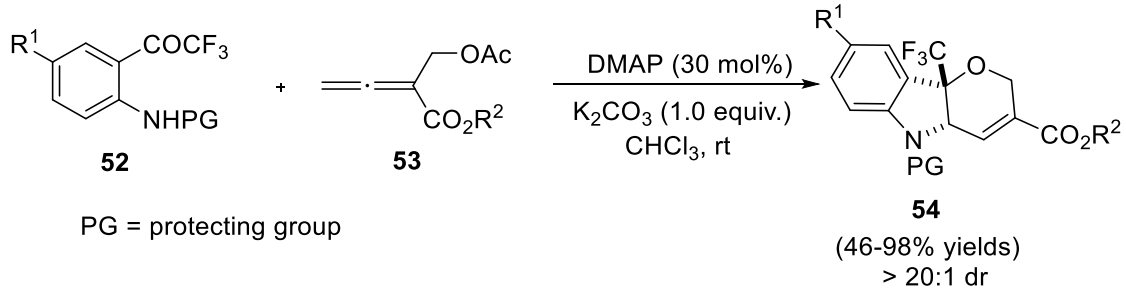
In 2020, He and co-workers found that furan-fused chromenes **51** could be synthesized from propargylamines **49** and *N*-phenacylpyridinium bromides **50** *via* a tandem annulation reaction in the presence of 20 mol% DMAP as a basic catalyst. A variety of polyarylated chromenes were formed in 15-90% yields (**Scheme 15**) (He *et al*., 2020).

Scheme 15 A tandem DMAP-catalyzed reaction of propargylamines **49** and *N*-phenacylpyridinium bromides **50** for the synthesis of furan-fused chromenes **51**



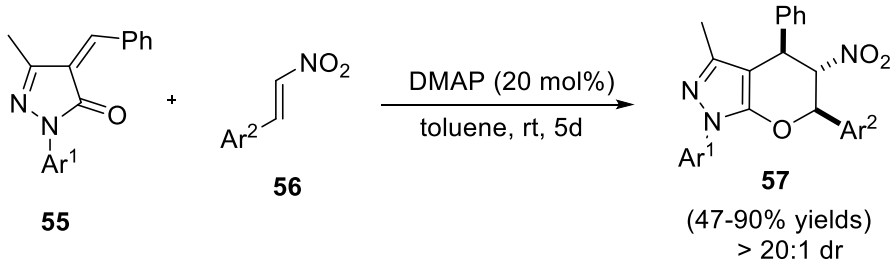
In 2020, a [4+1]/[3+3] domino annulation reaction of *o*-aminotrifluoroacetophenone derivatives **52** and *β′*-acetoxy allenoates **53** enabled by DMAP was reported by Zhu and co-workers. A variety of carbon trifluoride-containing tetrahydropyrano[3,2-b]indoles **54** were obtained in 46-98% yields under basic conditions. The products were found as a single diastereomer (**Scheme 16**) (Zhu *et al*., 2020).

Scheme 16 The construction of carbon trifluoride-containing tetrahydropyrano[3,2-b] indoles **54** through DMAP-catalyzed [4+1]/[3+3]domino annulation



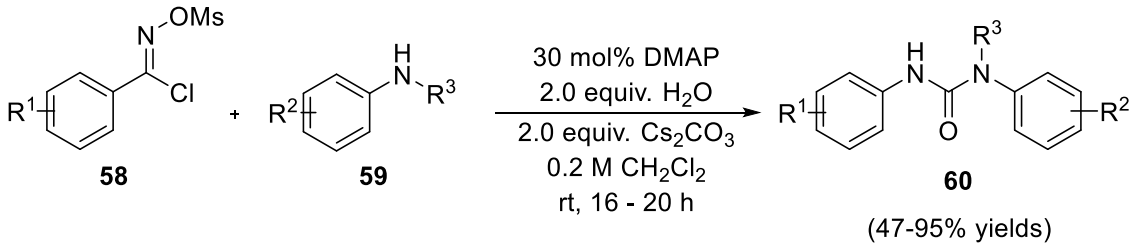
In 2021, a new methodology for the synthesis of tetrahydropyrano[2,3-c]pyrazoles **57** was introduced by Bania and co-workers. A key transformation involved Rauhut-Currier cyclization reaction between alkylidene pyrazolones **55** and nitro-olefins **56** in the presence of catalytic DMAP. The trisubstituted tetrahydropyrano[2,3-c]pyrazoles **57** were obtained in 47-90% yields with excellent diastereoselectivities (**Scheme 17**) (Bania *et al*., 2021).

Scheme 17 DMAP-catalyzed domino Rauhut-Currier cyclization reaction for the synthesis of tetrahydropyrano[2,3-c]pyrazoles **57**



In 2015, Kaeobamrung and co-workers reported the one-pot synthesis of trisubstituted ureas from α-chloroaldoxime *O*-methanesulfonates **58** and secondary amines **59** to give trisubstituted ureas **60** in 47-95% yields. The urea products were smoothly achieved in the presence of catalytic DMAP (**Scheme 18**) (Kaeobamrung *et al*., 2015).

Scheme 18 One-pot synthesis of trisubstituted ureas from α-chloroaldoxime *O*-methanesulfonates **58** and secondary amines **59**

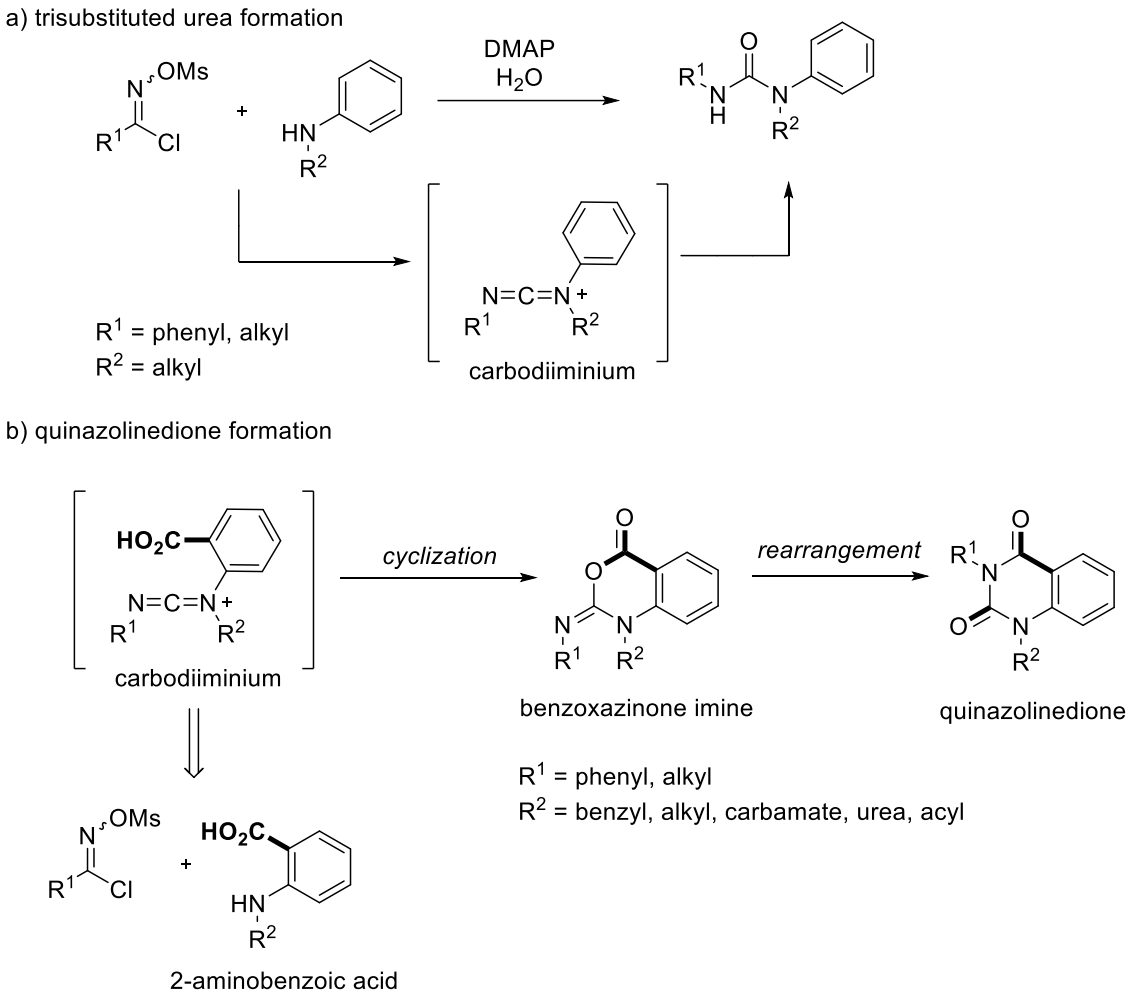


Based on our knowledge, although many methodologies have been developed consistently for the preparation of quinazolinediones, the methods derived directly from acid functionality are not as common as other derivatives. Therefore, alternative direct methodologies in preparation of quinazolinediones from common 2-aminobenzoic acids under mild reaction conditions and simple preparation without metals

or toxic reagents remain a challenge. Additionally, we have been interested in the chemistry of α-chloroaldoxime *O*-methanesulfonates inspired by Yamamoto's findings (Yamamoto *et a*l., 2009). The compounds can be stored at ambient temperature for a long time.

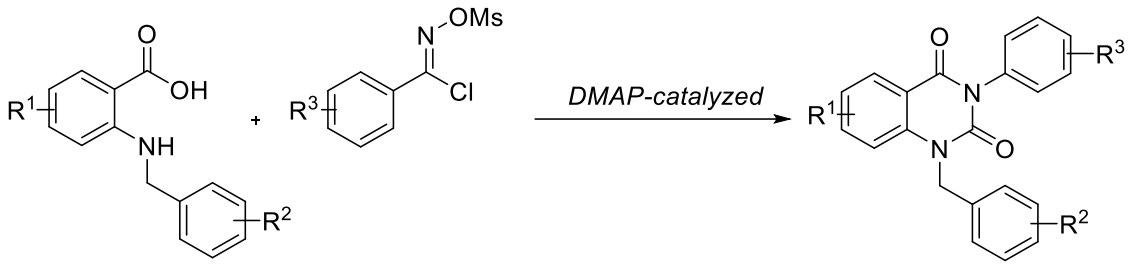
As mentioned above, the α-chloroaldoxime *O*-methanesulfonates and amines could provide urea products. The reaction proceeded through possibly carbodiiminium intermediate (**Scheme 19a**) (Kaeobamrung *et al*., 2015). We envisioned that a carboxylic acid at an *ortho* position of the carbodiiminium intermediate could undergo intramolecular C–O bond formation to form benzoxazinone imine, followed by a rearrangement to give target quinazolinedione (**Scheme 19, b**).

Scheme 19 Urea and quinazolinedione formations



Due to high value of quinazolinediones and good reaction property of α-chloroaldoxime *O*-methanesulfonates. Herein, we introduced an alternative reaction to synthesize quinazolinediones from α-chloroaldoxime *O*-methanesulfonates and 2-(benzylamino) benzoic acids in the presence of DMAP as a catalyst under mild reaction conditions (**Scheme 20**).

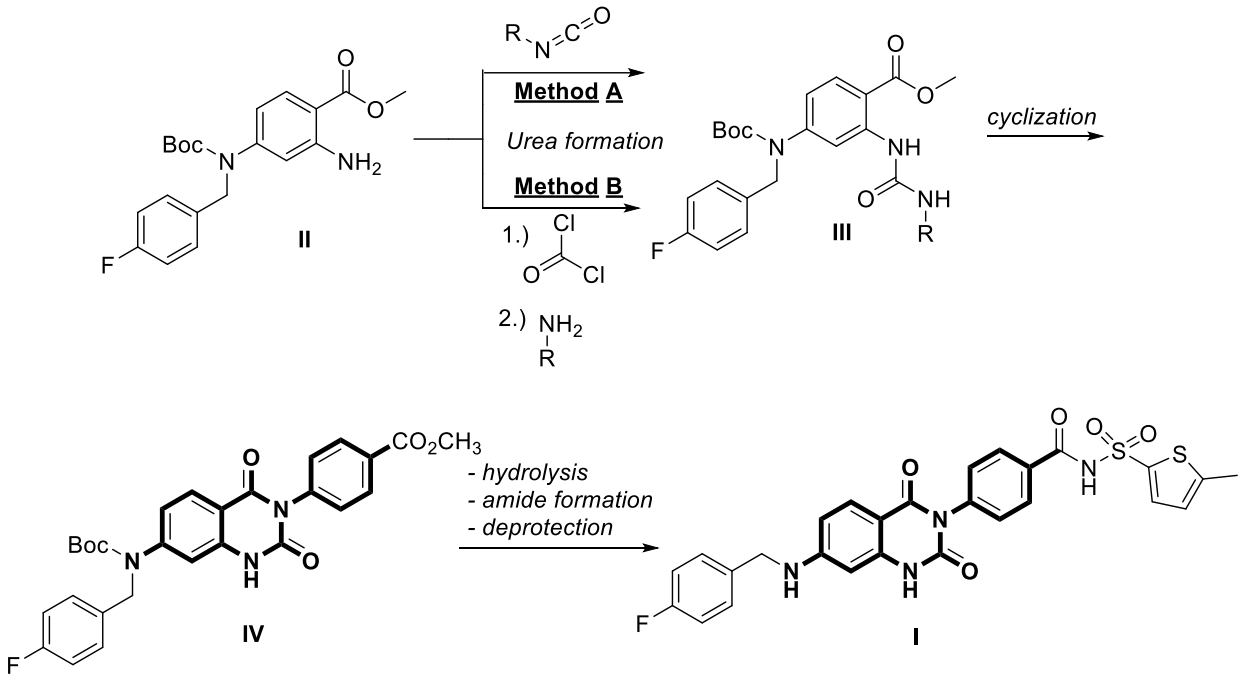
Scheme 20 The DMAP-catalyzed reactions between α-chloroaldoxime *O*-methanesulfonates and 2-(benzylamino)benzoic acids



Interestingly, we found that Scarborough and co-workers (Scarborough *et al*., 2005) reported their quinazolinedione analogues showing an inhibition of aggregation of ADP platelet (ADP: adenosine 5'diphosphate), particularly in a treatment of thrombosis and thrombosis related conditions or disorder (**Scheme 21**). One of their best compounds was 4-(7-((4-fluorobenzyl)amino)-2,4-dioxo-1,2-dihydroquinazolin-3(4*H*)-11yl)-*N*-((5-methylthiophen-2-yl)sulfonyl)benzamide (**I**) showing IC_{50} < 10 μM toward PRP assay (PRP: Platelet-rich plasma).

To synthesize **I** based on Scarborough's report, starting with two-step procedures (urea formation and cyclization) from a 2-aminobenzoate **II** to give urea **III**. Then, intramolecular cyclization of **III** gave quinazolinedione **IV** followed by hydrolysis, amide formation with a proper amine and deprotection to obtain the target **I**. In the urea formation process, it was heavily depended on two methods. The first was the reaction of **II** with corresponding isocyanates (**Method A**) On the other hand, the second method was the reaction of **II** with phosgene and corresponding amines (**Method B**) (**Scheme 21**).

Scheme 21 Scarborough's method for the synthesis of quinazolinedione **I**



The drawbacks of Scarborough's finding were the limited availability of isocyanates and toxic reagent such as phosgene in method **B**. Therefore, we provided our methodology as one of alternative methods to furnish synthetically useful building block for further synthesis of compound **I**.

1.1.2 Objective

To find a novel method to achieve quinazolinedione and derivatives under mild reaction conditions.

To apply our methodology to synthesize a building block.

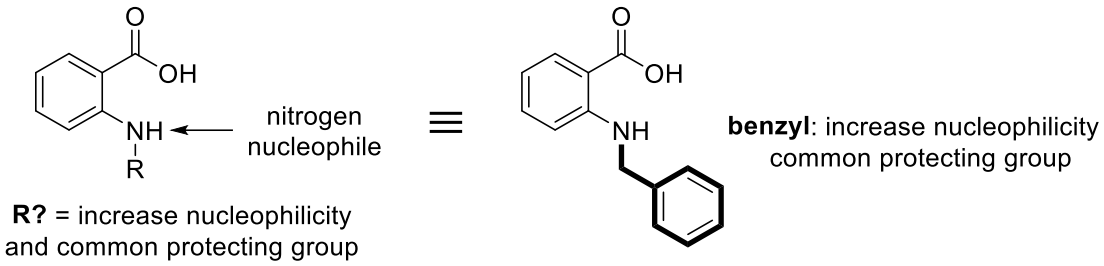
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Results and Discussion

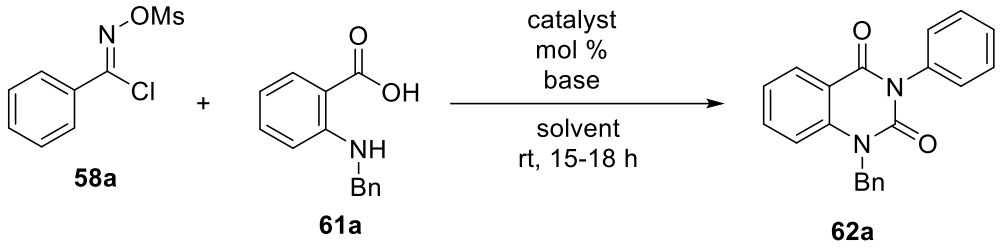
Based on Kaeobamrung's report (Kaeobamrung *et al*., 2015), the nucleophilicity of nitrogen nucleophile was crucial in which the aromatic amine gave low to moderate yields of corresponding products. On the other hand, amines with alkyl substituents gave corresponding product in high yields. The nitrogen of the 2-aminobenzoic acids shows weak nucleophilicity due to the presence of acid functionality (electron-withdrawing group) at *ortho* position. In order to increase the nucleophilicity of the nitrogen of 2-aminobenzoic acid, we consider to put an electron-donating substituent on the nitrogen which can increase the nucleophilicity of the nitrogen. A benzyl group is common nitrogen substituent and also can increase the nitrogen nucleophilicity due to inductive effect (**Figure 3**). Therefore, 2-(benzylamino)benzoic acids were our substrates of choices for exploration of quinazolinedione formation.

Figure 3 A 2-aminobenzoic acid design



Our study toward DMAP-catalyzed reactions for the synthesis of quinazolinediones started with a reaction optimization. A variety of catalysts, bases and solvents were screened. The reaction of α-chloroaldoxime *O*-methanesulfonate (**58a**) and 2-(benzylamino)benzoic acid (**61a**) was selected as a model study (**Table 1**).

Table 1 Optimization of reaction conditions for synthesis of quinazolinediones[a]



58a 61a 62a

Entry	Catalyst	Mol% Cat.	Base	Solvent	Yield (%)[b]
1	DMAP	30	Cs_2CO_3	CH_2Cl_2	42
2	DABCO	30	Cs_2CO_3	CH_2Cl_2	NP[c]
3	Imidazole	30	Cs_2CO_3	CH_2Cl_2	NP
4	DMAP	30	Cs_2CO_3	EtOAc	Trace[d]
5	DMAP	30	Cs_2CO_3	MeCN	Trace
6	DMAP	30	Cs_2CO_3	MeOH	NP
7	DMAP	30	Cs_2CO_3	EtOH	NP
8	DMAP	30	Cs_2CO_3	*t*-BuOH	40
9	DMAP	20	Cs_2CO_3	*t*-BuOH	35
10	DMAP	50	Cs_2CO_3	*t*-BuOH	63
11	DMAP	60	Cs_2CO_3	*t*-BuOH	67
12	DMAP	50	K_2CO_3	*t*-BuOH	60
13	DMAP	50	K_3PO_4	*t*-BuOH	74
14	DMAP	50	NEt_3	*t*-BuOH	12
15	DMAP	50	*i*-Pr_2NEt	*t*-BuOH	10
16[e]	DMAP	50	K_3PO_4	*t*-BuOH	72
17[f]	DMAP	50	K_3PO_4	*t*-BuOH	38

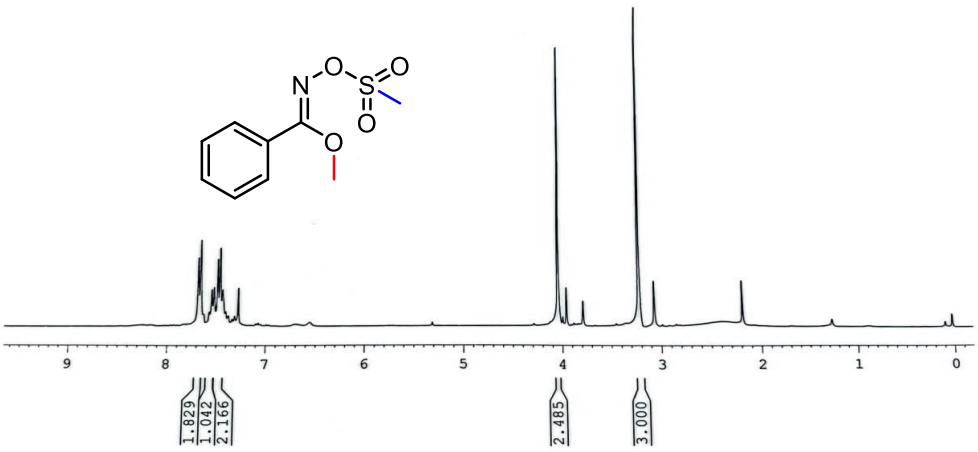
[a] Reaction conditions : All reactions were performed with 1.0 mmol of **61a**, 1.2 equiv. of **58a**, 3.0 equiv. of base and 2.0 equiv. of H_2O in 5.0 mL of solvent in a round bottom flask. [b] Isolated yield. [c] No product. [d] The ^{1}H NMR spectrum of the crude reaction mixture. [e] The reaction was performed at 60 ºC. [f] The reaction was performed without adding H_2O.

Initially, we used the reaction conditions from our previous work which was a trisubstituted urea formation from secondary aromatic amines (Kaeobamrung *et al*., 2020). Fortunately, the reaction gave 42% of quinazolinedione product (entry 1). Reaction using DABCO or imidazole as a catalyst could not provide product (entries 2 and 3). Next, other solvents were subjected to the exploration of conditions. Choices of solvent were selected based on recommended green solvents (Byrne *et al*., 2016). The reaction using ethylacetate (EtOAc) or acetonitrile (MeCN) as a solvent gave trace amount of the product observed from the ^{1}H NMR spectrum of the reaction mixture crudes (entries 4 and 5). Nucleophilic solvents, such as methanol (MeOH) and ethanol (EtOH) were not suitable to the reaction resulting in no products (entries 6 and 7). We observed the remaining **61a** and by-product from the ^{1}H NMR spectrum of the crude reaction mixtures from both reactions. The by-products were formed possibly from the nucleophilic substitution of alcohol and α-chloroaldoxime *O*-methanesulfonate (Figure 4). On the contrary, less-nucleophilic bulky alcohol, such as *t*-BuOH provided 40% yield of product (entry 8) Noteworthy, the product yield of quinazolinedione from *t*-BuOH was comparable to that of CH_2Cl_2 (entry 1). Significantly, *t*-BuOH was considered more environmentally friendly solvent than CH_2Cl_2. Therefore, *t*-BuOH was chosen as a solvent for further optimization. Next, we turned our attention to the amount of DMAP. We found that decreasing the amount of DMAP led to decreasing yields of the product. The reaction using 20 mol% of DMAP gave 35% yield of quinazolinedione (entry 9). The yield of the product was increased to 63% when 50 mol% of DMAP was used (entry 10). A slightly increased yield was obtained with 60 mol% of DMAP (entry 11). The results suggested that the reaction required high amount of catalyst loading in order to

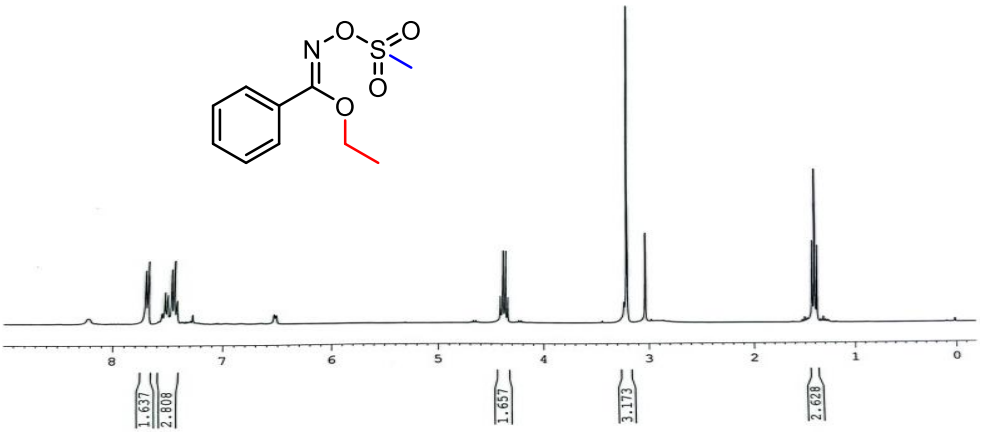
provide the highest yield of product and drive the reaction to complete consumption of **61a**. Other common weaker bases, such as K_2CO_3 and K_3PO_4 were applicable for the reaction giving product in 60% or 74% yields, respectively (entries 12 and 13). Common organic bases, such as triethylamine (TEA) or diisopropyl ethylamine (DIPEA) were used in our reaction. Disappointingly, we observed the remaining both starting materials resulting in low yields of the product, 12% and 10%, respectively (entries 14 and 15). Elevating the reaction temperature did not afford greater product yield. The reaction at 60 ^oC gave product yield in 72% (entry 16). Significantly, low yields of the product were observed without adding H_2O. The reaction gave 38% yield of product (entry 17). In conclusion, the optimal condition was the use of 50 mol% DMAP as a catalyst, K_3PO_4 as a base in *t*-BuOH.

Figure 4 Proposed structure of adducts

a)

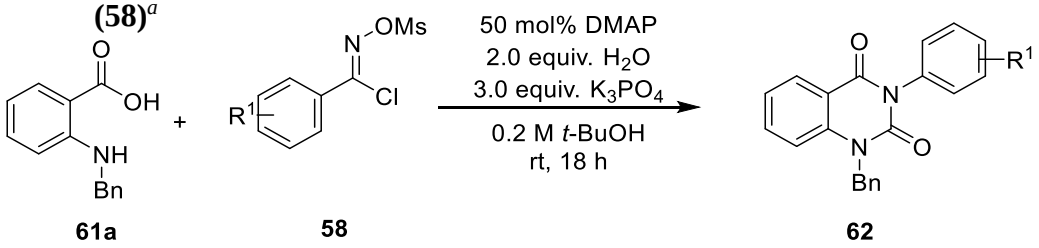


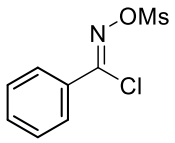
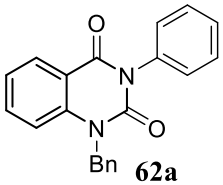
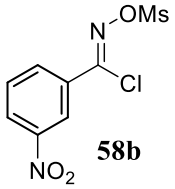
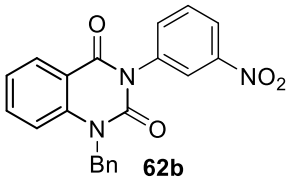
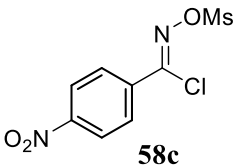
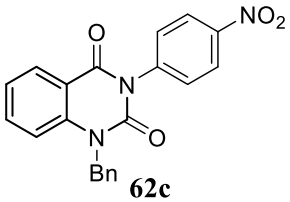
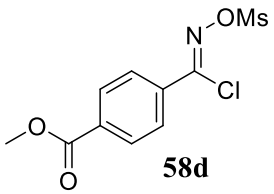
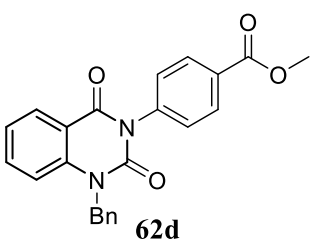
b)

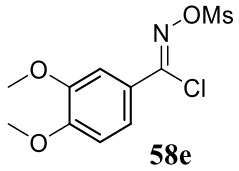
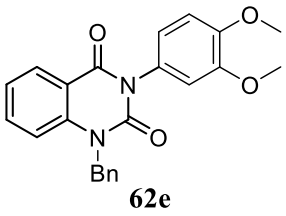
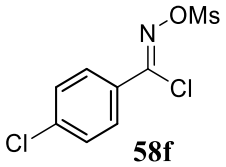
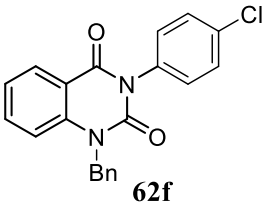
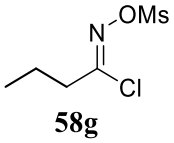
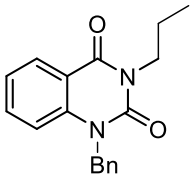


After having the optimal reaction condition, we next turned our focus on an efficiency of the reaction by exploring various starting materials (**Table 2**).

Table 2 The screening of substituents on α-chloroaldoxime *O*-methanesulfonates **(58)**[a]



Entry	Chloroaldoximes	Quinazolinediones	Yield (%)[b]
1	 **58a**	 **62a**	74
2	 **58b**	 **62b**	82
3	 **58c**	 **62c**	90
4	 **58d**	 **62d**	83

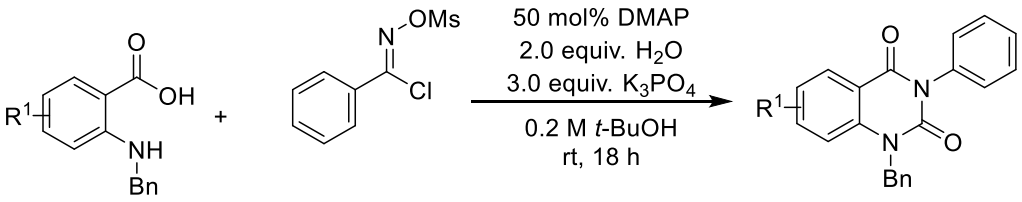
Entry	Chloroaldoximes	Quinazolinediones	Yield (%)[b]
3	 **58e**	 **62e**	0 (50[c])
4	 **58f**	 **62f**	72
5	 **58g**	 **62g**	41

[a] Reaction conditions : All reactions were performed with 1.0 mmol of **61a**, 1.2 equiv. of **58** in 5.0 mL of *t*-BuOH in a round bottom flask.

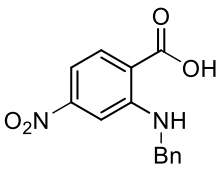
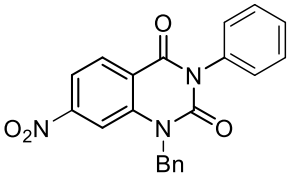
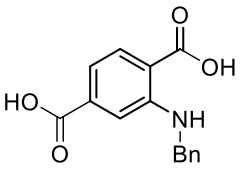
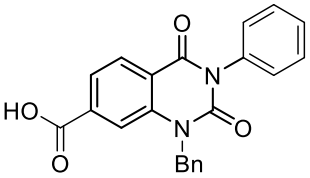
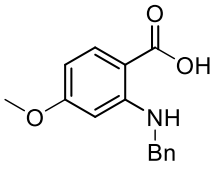
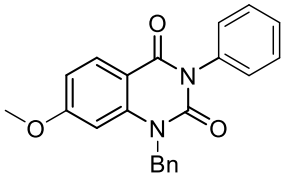
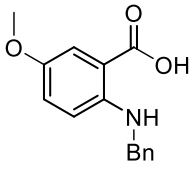
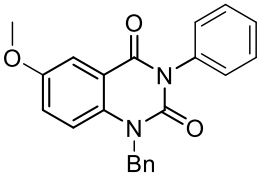
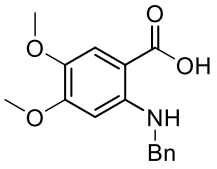
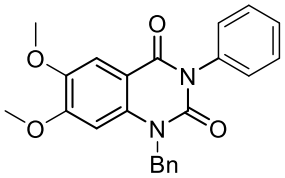
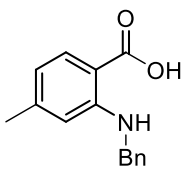
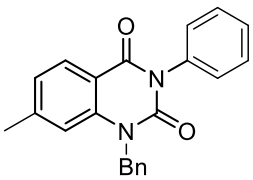
We started with exploring a variety of α-chloroaldoxime *O*-methanesulfonates (**Table 2**). Without any substituents, the reaction of *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**58a**) provided a corresponding quinazolinedione in 74% yield (entry 1). The higher yields of products were obtained from the reaction of α-chloroaldoxime *O*-methanesulfonates bearing electron-withdrawing groups (entry 2-4). Both 3-nitro and 4-nitro substituted α-chloroaldoxime *O*-methanesulfonates provided corresponding products in 82% and 90% yields, respectively (entries 2 and 3). High yield of product was observed from the reaction of methyl 4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate giving product in 83% yield (entry 4). The electron-donating group such as 3,4-dimethoxy-*N*-((methylsulfonyl)oxy)benzimidoyl chloride gave no yield of product. Interestingly, switching to stronger base, *t*-BuOK, the reaction gave the product in 50% yield (entry 5). An α-chloroaldoxime *O*-methanesulfonate bearing 4-chlorosubstituted benzene ring gave 72% yield of quinazolinedione (entry 6). Unfortunately, an alkyl-substituted α-chloroaldoxime *O*-methanesulfonate gave low yield of product. A *N*-((methylsulfonyl)oxy)butyrimidoyl chloride gave 41% yield of product (entry 7). Based on all results, the electrophilicity of the α-chloroaldoxime *O*-methanesulfonates was vital for the reaction. High electrophilic α-chloroaldoxime *O*-methanesulfonates gave significantly high yield of the quinazolinedione products.

We next explored a variety of substituents on the benzene ring of 2-aminobenzoic acids using **58a**.

Table 3 The synthesis of quinazolinediones screening of substituents on benzoic acid from **61** and α-chloroaldoxime *O*-methanesulfonate **58a**[a]



61 **58a** **62**

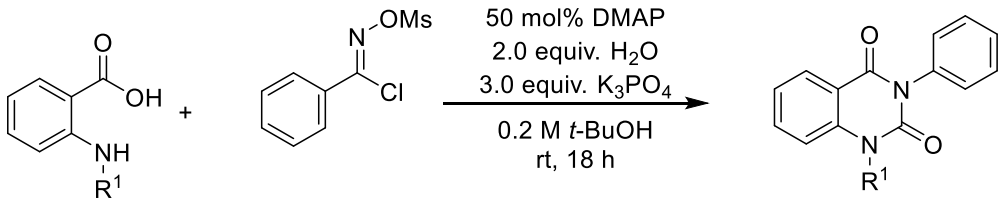
Entry	2-(Benzylamino) benzoic acids	Quinazolinediones	Yield (%)[b]
1	 **61b**	 **62h**	50
2	 **61c**	 **62i**	54
3	 **61d**	 **62j**	79
4	 **61e**	 **62k**	80
5	 **61f**	 **62l**	85
6	 **61g**	 **62m**	80

[a] Reaction conditions : All reactions were performed with 1.0 mmol of **61**, 1.2 equiv. of **58a** in 5.0 mL of *t*-BuOH in a round bottom flask.
[b] Isolated yield.

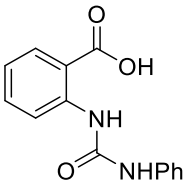
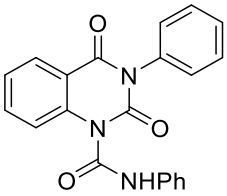
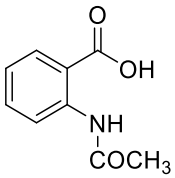
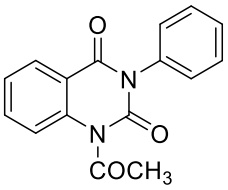
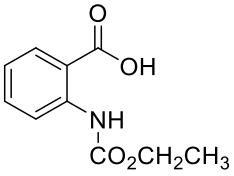
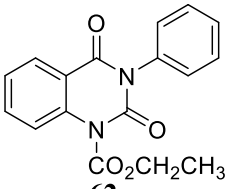
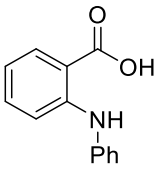
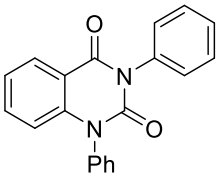
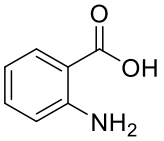
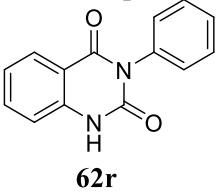
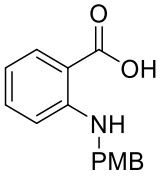
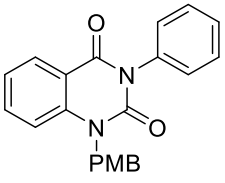
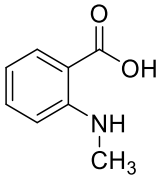
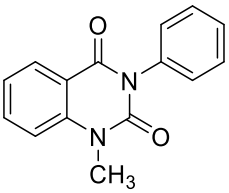
The reaction of 2-(benzylamino)benzoic acids bearing electron-withdrawing substituents, for examples, 4-nitro and 4-carboxyl substituents gave corresponding quinazolinediones in moderate yields 50% and 54%, respectively (entries 1 and 2). On the other hand, 2-(benzylamino)benzoic acids bearing electron-donating substituents provided corresponding products in higher yields (entry 3-6). The 4-methoxy and 5-methoxy-2-(benzylamino)benzoic acids gave yields of products in 79% and 80%, respectively (entries 3 and 4). Greater yield was obtained from 4,5-dimethoxy-2-(benzylamino)benzoic acids giving product in 85% yield (entry 5). Lastly, 4-methyl-2-(benzylamino)benzoic acids provided quinazolinedione in 80% yield (entry 6). Based on results, the electronic effect of 2-(benzylamino)benzoic acids played a crucial role in the reaction. We believed that the electron-rich benzene ring increased the nucleophilicity of nitrogen allowing the reaction to perform smoothly.

In order to understand the electronic property of nitrogen on the 2-(benzylamino)benzoic acids, we continued to explore the substituents on the nitrogen of 2-aminobenzoic acids.

Table 4 The synthesis of quinazolinediones from 2-aminobenzoic acid derivatives **61** and α-chloroaldoxime *O*-methanesulfonate **58a**[a]



61 **58a** **62**

Entry	2-(Benzylamino) benzoic acids	Quinazolinediones	Yield (%)[b]
1	 **61h**	 **62n**	0
2	 **61i**	 **62o**	0
3	 **61j**	 **62p**	0
4	 **61k**	 **62q**	0
5	 **61l**	 **62r**	50
6	 **61m**	 **62s**	74
7	 **61n**	 **62t**	82

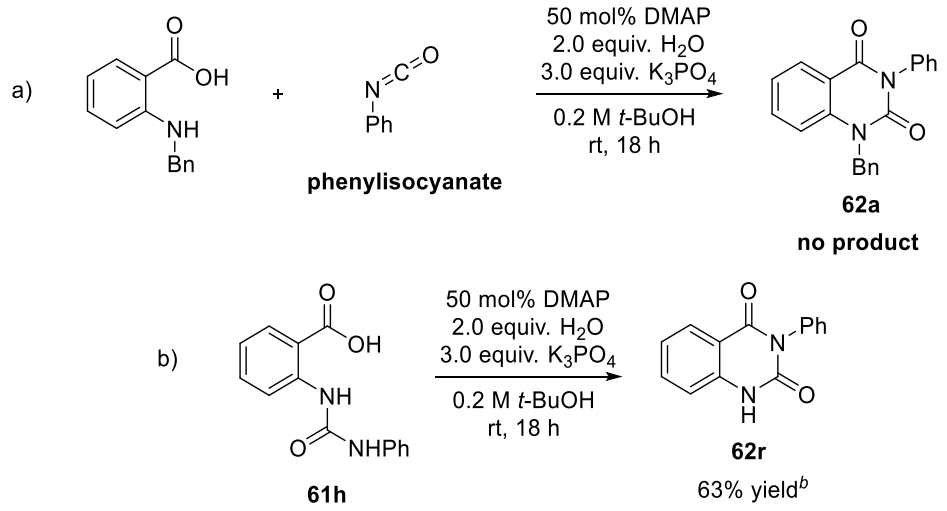
[a] Reaction conditions : All reactions were performed with 1.0 mmol of **61**, 1.2 equiv. of **58a** in 5.0 mL of *t*-BuOH in a round bottom flask. [b] Isolated yield.

None of products were found from the reactions of 2-aminobenzoic acid derivatives containing urea, acetyl, carbamate or phenyl as nitrogen substituents (entry 1-4). Moderate yield was obtained from 2-aminobenzoic acid having free nitrogen giving a corresponding quinazolinedione in 50% (entry 5). Comparable that of yield with the yield of *N*-benzyl quinazolinedione product (Table 1, entry B), we found that benzyl substituent on the nitrogen of 2-aminobenzoic acid obviously affected the reaction efficiency. High yields of quinazolinediones were obtained from alkyl substituted nitrogen. Both 2-(para-methoxyphenylamino) and 2-(methylamino) benzoic acids gave corresponding quinazolinediones in 74% and 82%, respectively (entries 6 and 7). Clearly, the results also suggested that the electronic properties of nitrogen greatly affected the reaction outcome (**Table 4**). Remarkably, although the reaction of 2-(3-phenylureido)benzoic acid (**61h**) gave 0% of the corresponding quinazolinedione, we isolated quinazolinedione **62r**. Therefore, we hypothesized that the urea adduct possibly one of key intermediates of this reaction.

In order to propose mechanism of the reaction, we did two control experiments (**Scheme 22**). We excluded out of the *in situ* formation of isocyanate from α-chloroaldoxime *O*-methanesulfonate by subjecting the phenylisocyanate to the reaction. The result showed that no product **62a** was observed (**Scheme 22a**). Noteworthy, we also observed the same result from our previous work on the synthesis of imidazolin-2-one from the reaction of amines and α-chloroaldoxime *O*-methanesulfonate in which the isocyanate was not an intermediate (Kaeobamrung *et al*., 2020). Since we could isolate **62r** instead of **62n** (**Table 4**), the result enlightened us a clue of a reaction intermediate. Therefore, we did the second control experiment by applying **61h**, presumably a possible intermediate, to the reaction. Informatively, **62r** was obtained in 63% yield (**Scheme 22b**) showing that the urea adduct could undergo cyclization under the reaction condition. Based on the result and better yield

in the presence of H_2O, the urea adduct could highly be an intermediate for the reaction.

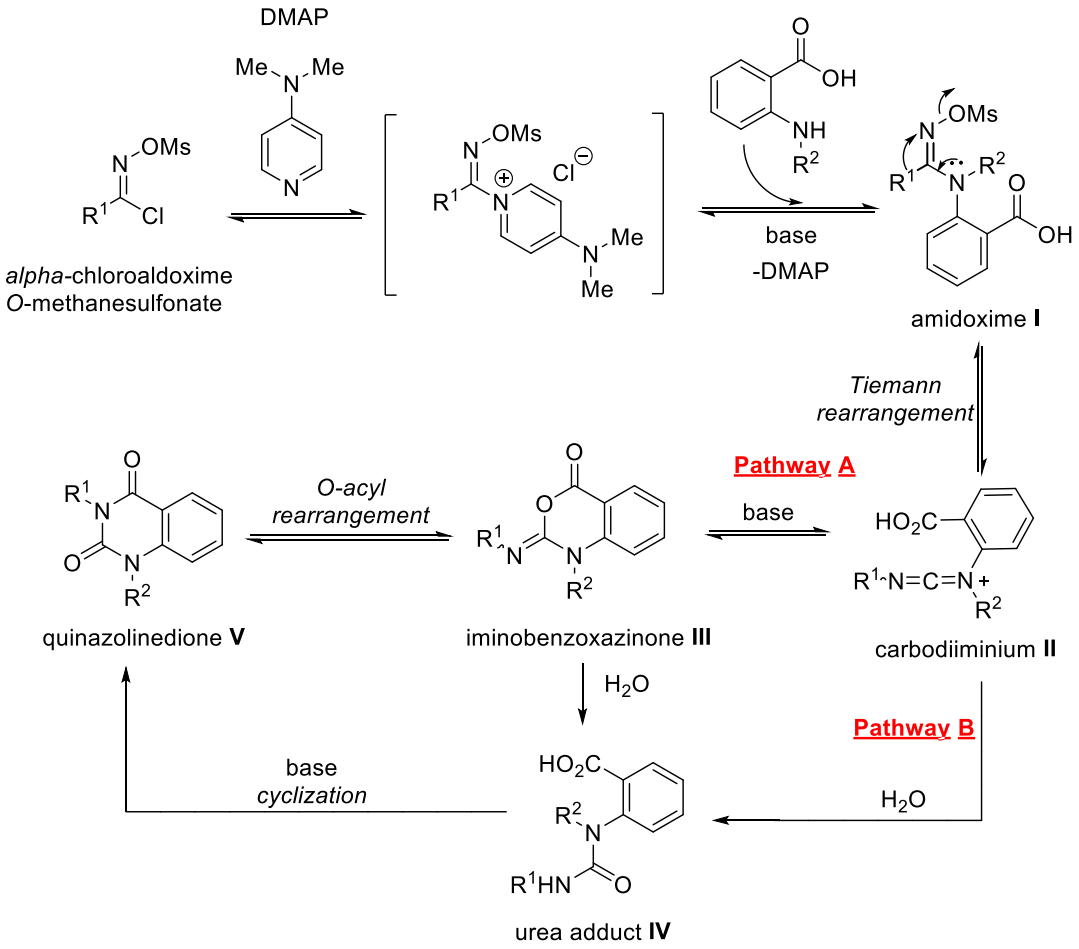
Scheme 22 Control experiments



Then, we proposed the mechanism of the quinazolinedione formation involved DMAP-catalyzed substitution reaction of 2-aminobenzoic acid and α-chloroaldoxime *O*-methanesulfonate to generate amidoxime **I** followed by Tiemann rearrangement to give carbodiiminium intermediate **II**. Although the control experiment suggested the pathway involving the formation of urea adduct, we could not rule out the possibility of a formation of iminobenzoxazinone **III**. The iminobenzoxazinone intermediates were known to undergo a rearrangement to provide a corresponding quinazolinedione (Kaeobamrung *et al*., 2015). Additionally, Beutner and co-workers could divergently synthesize quinazolinediones and iminobenzoxazinones. Their finding confirmed the existence of the **III** and **V** (Beutner *et al*., 2017). Consequently, we proposed two possible pathways. The first pathway, the carbodiiminium **II** underwent intramolecular C–O bond formation to form the iminobenzoxazinone **III**. The intermediate **III** could rearrange from *O*−acyl to *N*−acyl to give the product quinazolinedione **V** (**Scheme 23**, **pathway A**). Alternatively, the ring opening of the iminobenzoxazinone **III** could take place in the

presence of H_2O to give a urea adduct **IV**. On the other hand, the carbodiiminium **II** and H_2O could form a corresponding urea adduct **IV** followed by amide cyclization in the presence of base to provide the product quinazolinedione **V** (**Scheme 23**, **pathway B**).

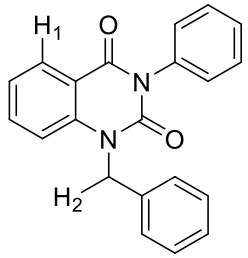
Scheme 23 The proposed mechanism of DMAP-catalyzed synthesis of quinazolinediones



In order to characterize our synthetic quinazolinedione, we used ^{1}H, ^{13}C NMR experiments. Due to the nearly chemical shift of aromatic protons, we picked two obvious protons to identify. We found that ^{1}H NMR spectra of our corresponding product matched to the literature values (Nakagawa *et al*., 2008) (**Scheme 24a**). Although the ^{13}C NMR reference of quinazolinedione is not the exact structure comparing with our synthetic quinazolinedione, the result showed that we got the 2-pyrimidinone moiety of quinazolinedione due to the similar value of carbonyl chemical shift. Notably, since quinazolinedione structure is quite similar to the iminobenzoxazinone intermediate, we assumed that we possibly got an intermediate before *O*-acyl rearrangement. Clearly, two identified carbons chemical shift of iminobenzoxazinone intermediate based on Beutner's report are not matched with desired quinazolinedione. Therefore, I got our target quinazolinedione from our reaction condition (**Scheme 24b**).

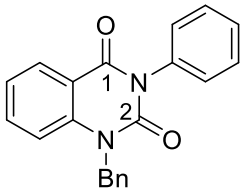
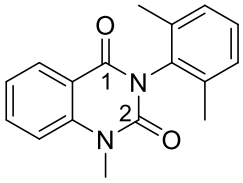
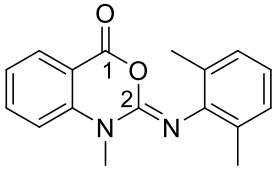
Table 5 Characterizations

a)



H	Synthetic compound (300 MHz, $CDCl_3$)	Reference (400 MHz, $CDCl_3$)
H_1	δ = 8.21 ppm (d, 7.8 Hz)	δ = 8.27 ppm (d, 7.8 Hz, 1H)
H_2	δ = 5.32 ppm (s, 2H)	δ = 5.41 ppm (s, 2H)

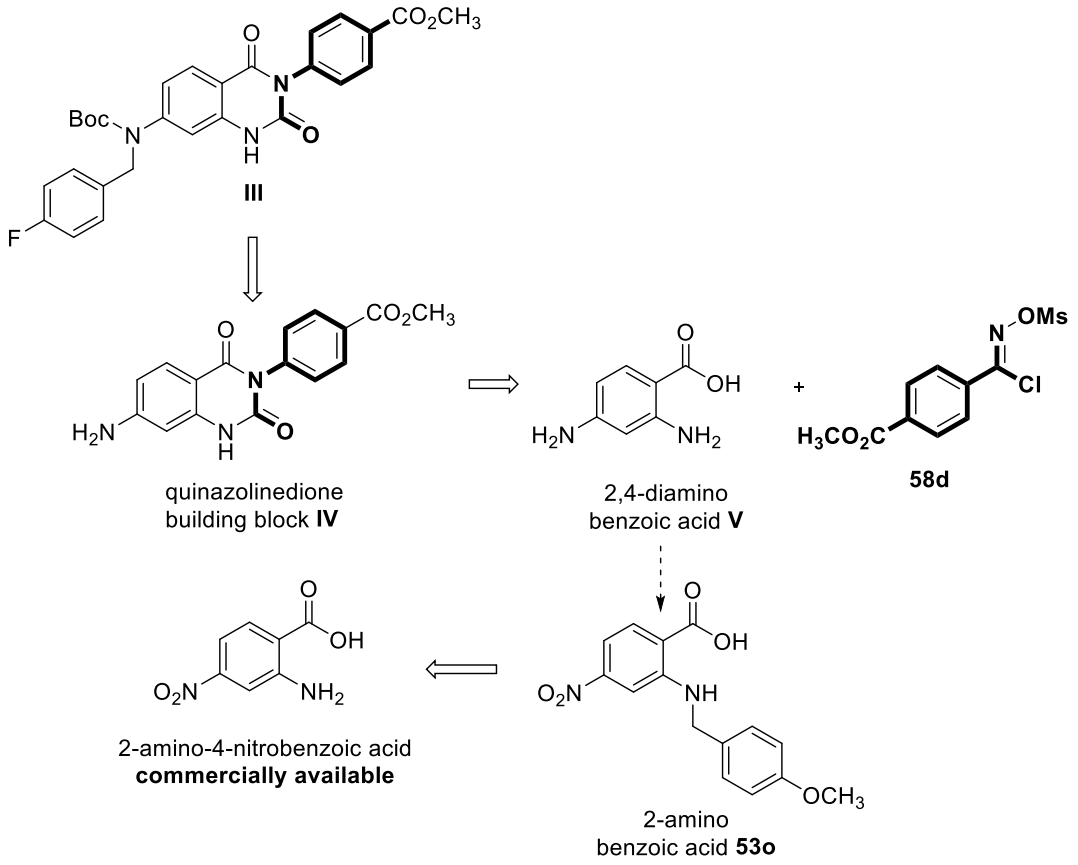
b)

C	 synthetic quinazolinedione	 Beutner's quinazolinedione	 iminobenzazinone
	75 MHz in $CDCl_3$	100 MHz in $CDCl_3$	
1	δ = 161.9 ppm	δ = 160.5 ppm	δ = 157.7 ppm
2	δ = 151.6 ppm	δ = 149.4 ppm	δ = 140.9 ppm

Owing to the findings from Scarborough and co-workers, the compound **III** was their synthetic building block. In order to apply our methodology to synthesize our building block. We provided plausible retrosynthetic analysis of **III**. Firstly, compound **III** could be synthesized from quinazolinedione **IV**. To accomplish compound **IV**, **V** and **58d** were used as starting materials. In our work, we picked the quinazolinedione **IV** as our building block target. The *N*-aryl moiety of **IV** could be derived from α-chloroaldoxime *O*-methanesulfonates **58d**. Notably, the **58d** was highly suitable for the reaction due to electron withdrawing substituents. The other reaction partner would be an equivalent of 2,4-diaminobenzoic acid **V**. Nonetheless, having two free amino groups might cause a problem of regioselectivity and undesired reactions. According to the exploration the substituents on the nitrogen of 2-aminobenzoic acids (**Table 4**, **Entry 6**), the 2-(para-methoxyphenylamino) benzoic acids gave quinazolinedione in good yield. Therefore, we selected *N*-(4-methoxybenzyl)-4-nitro-2-aminobenzoic acid (**53o**). The 2-aminobenzoic acid **53o**

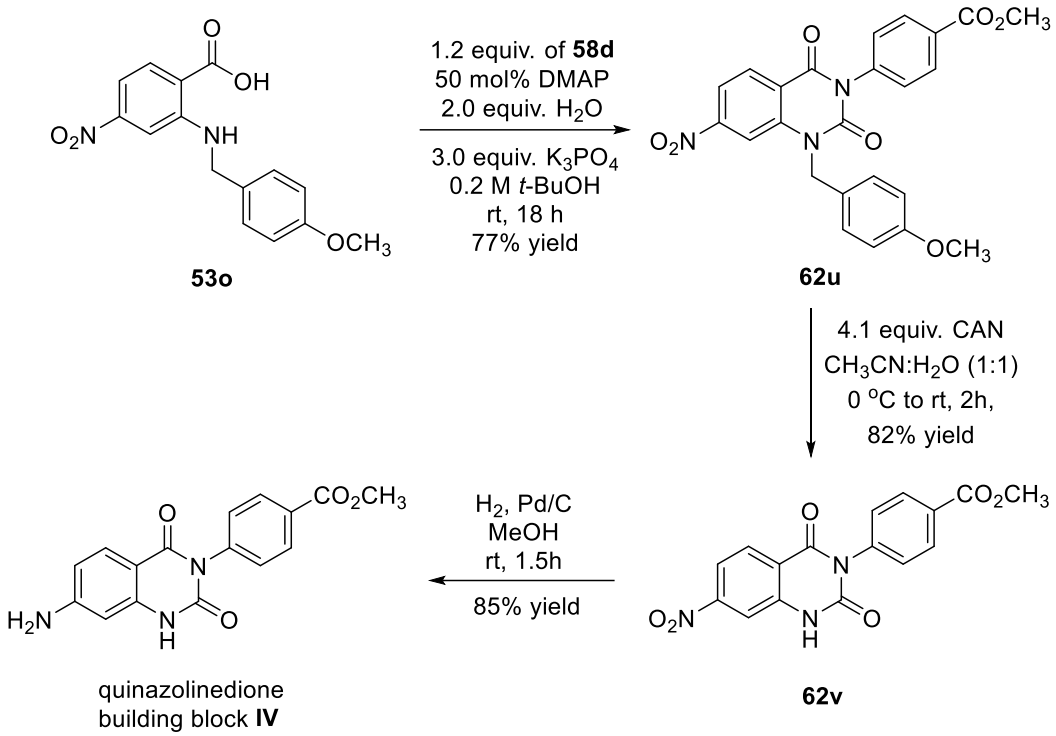
could be readily prepared from commercially available 2-amino-4-nitrobenzoic acid *via* reductive amination.

Scheme 24 Synthetic plan for quinazolinedione building block **IV**



We began our synthesis of building block **IV** with the reaction of *N*-(4-methoxybenzyl)-4-nitro-2-aminobenzoic acid (**53o**) and **58d** under the optimal conditions (**Scheme 25**). The corresponding quinazolinedione **62u** was isolated in 77% yield. Unfortunately, we failed to accomplish a deprotection of 4-methoxybenzyl group in the same time as reduction of nitro group using hydrogenation reaction. However, we could obtain the building block **IV** from two step procedures. Firstly, we could deprotect the 4-methoxybenzyl to provide a desired quinazolinedione **62v** in 82% yield in the presence of ceric ammonium nitrate (CAN) (Magnus *et al*., 2003). Lastly, we obtained the quinazolinedione building block **IV** in 85% yield from a reduction of nitro group *via* hydrogenation catalyzed by Pd/C in methanol.

Scheme 25 The preparation of quinazolinedione building block



CHAPTER 3

CONCLUSION

3.1 Conclusion

We have illustrated the facile synthesis of quinazolinedione derivatives *via* DMAP-catalyzed domino reactions of α-chloroaldoxime *O*-methanesulfonates and 2-(benzylamino)benzoic acids under environmentally friendly conditions and simple preparation. We found that electron-rich nitrogen of 2-(benzylamino)benzoic acids was crucial resulting in good yields of products. Based on the nucleophilicity of nitrogen of 2-(benzylamino)benzoic acids, we found that the appropriate substituents of nitrogen are alkyl groups. Another key factor of the reaction was high electrophilicity of α-chloroaldoxime *O*-methanesulfonates resulting in good yields of quinazolinedione products. As mentioned, the α-chloroaldoxime *O*-methanesulfonates bearing electron-withdrawing substituents were good for increasing the reaction potential. We believed that the chemical transformation involved the formation of carbodiiminium intermediate, followed by two possible pathways. The first was intramolecular cyclization to form iminobenzoxazinone followed by rearrangement to give the product. Secondly, the carbodiiminium reacted with H_2O to form an urea adduct. Then, an intramolecular amidocyclization took place to give corresponding quinazolinedione. Although high catalyst loading was required in order to drive the reaction to completion, this reaction protocol provided an alternative access to a variety of quinazolinediones and also enriched the chemistry of α-chloroaldoxime *O*-methanesulfonates. In addition, we successfully introduced an application of this method to provide quinazolinedione building block for further investigations of biological activities.

CHAPTER 4

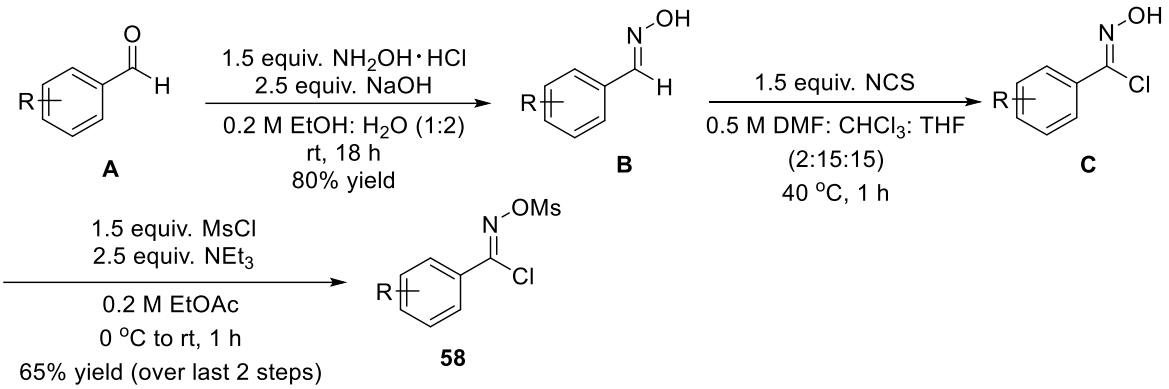
EXPERIMENTAL

4.1 General Information

THF was dried over 4 Å molecular sieves. Solvents for extraction and column chromatography were distilled at their boiling point ranges prior to use. Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} (Merck) and were visualized by fluorescence quenching under UV light. Column chromatography was performed on SilicaFlash® G60 (70-230 Mesh). ^{1}H NMR (300 MHz or 500 MHz) and ^{13}C NMR (75 MHz or 126 MHz) were recorded on a 300 MHz or 500 MHz Bruker FTNMR Ultra Shield spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ 0.00) and coupling constants are reported as Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra (IR) were measured on a Perkin Elmer Spectrum GX FT-IR system and recorded on wavenumber (cm^{-1}).

4.1.2 Preparation of Starting Materials

General Procedure A: Synthesis of α-chloroaldoxime *O*-methanesulfonates 58



Step 1: Benzaldoxime derivatives B

Benzaldoxime derivatives B. Prepared according to literature procedure (Senadi *et al*., 2017). A dried round bottom flask was added with benzaldehyde derivatives (1.0 equiv., 10 mmol) in EtOH:H_2O (0.2 M, [1:2 ratio]), then a solution of sodium hydroxide (NaOH) (2.5 equiv.) in H_2O was added, followed by the addition of a solution of hydroxyammonium chloride ($NH_2OH \cdot HCl$) (1.5 equiv.) in H_2O. A reaction mixture was stirred at room temperature for 18 hours. Then EtOH in the reaction mixture was removed under reduced pressure. After that, the mixture was quenched with 4M HCl and extracted with ethyl acetate. The organic layer was washed brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to provide **B**.

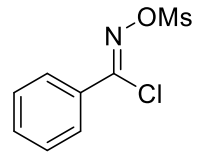
Step 2: *N*-(methylsulfonyloxy)benzimidoyl chloride derivatives C

***N*-(Methylsulfonyloxy)benzimidoyl chloride derivatives C.** Prepared according to literature procedure (Yamamoto *et al*., 2009). A dried round bottom flask was added with benzaldoxime derivatives (1.0 equiv.) in the mixture of 0.5 M of DMF, THF and $CHCl_3$ (2:15:15 ratio), followed by the portion addition of *N*-chlorosuccinamide (NCS) (1.5 equiv.). After the addition was completed, the temperature of reaction was increased to 40 ^oC. After an hour, the reaction was

quenched with water and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc. The resulting solution was cooled to 0 ^oC. After completion of addition, the mixture was allowed to warm to room temperature, stirred for an hour, and followed by filtration. The filtrate was washed with water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (6:1, hexane:EtOAc) to afford *N*-(methylsulfonyloxy) benzimidoyl chloride derivatives **C**.

Step 3: α-chloroaldoxime *O*-methanesulfonate derivatives 58

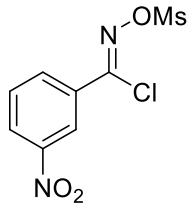
α-Chloroaldoxime *O*-methanesulfonate derivatives 58. Prepared according to literature procedure (Yamamoto *et al*., 2009). The *N*-(methylsulfonyloxy)benzimidoyl chloride derivatives **C** was added EtOAc, and the resulting solution was cooled to 0 °C. TEA (2.5 equiv.) was added to the solution, and the mixture was stirred at the same temperature for 10 min to give a white slurry. MsCl (1.5 equiv.) was added slowly over 10 min to the mixture. the mixture was warmed to room temperature. The mixture was stirred at room temperature for 1 h, the product was purified by column chromatography (10–60% EtOAc/hexane). The filtrate was washed with H_2O (×2), dried over Na_2SO_4, and concentrated under reduced pressure.



58a
$C_8H_8ClNO_3S$
M.W. = 233.6720 g/mol

***N*-(Methylsulfonyloxy)benzimidoyl chloride (58a).** Prepared according to the procedure A yielding **58a** in 1.87 g (80 %, 2 steps) as a white solid product. ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.61–7.56 (m, 1H), 7.51–7.46 (m, 2H),

3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 132.7, 130.4, 128.8, 128.1, 37.0. These data matched to the literature values (Yamamoto *et al*., 2009).

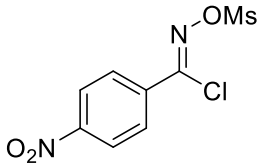


58b

$C_8H_7ClN_2O_5S$

M.W. = 278.6696 g/mol

***N*-(Methylsulfonyloxy)-3-nitrobenzimidoyl chloride (58b).** Prepared according to the procedure A yielding **58b** in 1.39 g (50 %, 2 steps) as a light yellow solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (t, *J* = 1.8 Hz, 1H), 8.43 (d, *J* = 8.0, 1.5 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 8.0 Hz, 1H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 146.8, 133.6, 132.3, 130.3, 127.1, 123.2, 37.3. These data matched to the literature values (Yamamoto *et al*., 2009).

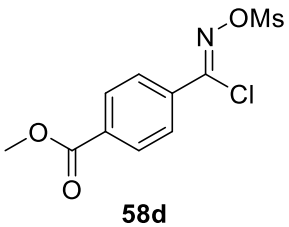


58c

$C_8H_7ClN_2O_5S$

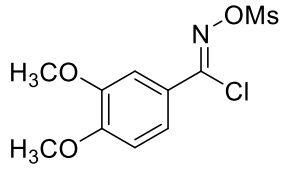
M.W. = 278.6696 g/mol

***N*-(Methylsulfonyloxy)-4-nitrobenzimidoyl chloride (58c).** Prepared according to the procedure A yielding **58c** in 1.67 g (60 %, 2 steps) as a white solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.7 Hz, 2H), 8.16 (d, *J* = 8.7 Hz, 2H), 3.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 146.8, 136.0, 129.2, 123.9, 37.02. These data matched to the literature values (Kaeobamrung *et al*., 2015).



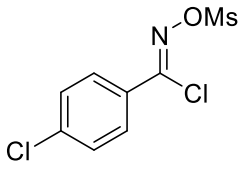
58d
$C_{10}H_{10}ClNO_5S$
M.W. = 291.7081 g/mol

Methyl-*N*-(4-chloro(methylsulfonyloxy)benzimidoyl chloride (58d). Prepared according to the procedure A yielding **58d** in 1.46 g (50 %, 2 steps) as a white solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.7 Hz, 2H), 8.01 (d, *J* = 8.7 Hz, 2H), 3.97 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 148.1, 134.2, 133.7, 129.9, 128.1, 52.6, 37.1. These data matched to the literature values (Kaeobamrung *et al*., 2015).



58e
$C_{10}H_{12}ClNO_5S$
M.W. = 293.0125 g/mol

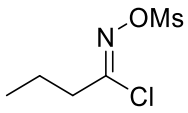
3,4-Dimethoxy-*N*-((methylsulfonyl)oxy)benzimidoyl chloride (58e). Prepared according to the procedure A yielding **58e** in 2.00 g (68 %, 2 steps) as a white solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 6H). These data matched to the literature values (Kaeobamrung *et al*., 2020).



58f
$C_8H_7Cl_2NO_3S$
M.W. = 266.9524 g/mol

4-Chloro-*N*-((methylsulfonyl)oxy)benzimidoyl chloride (58f). Prepared according to the procedure A yielding **58f** in 1.87 g (70 %, 2 steps) as a white solid product. ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 139.2, 129.3, 129.2, 37.1. These data matched to the literature values (Kaeobamrung *et al*., 2015).



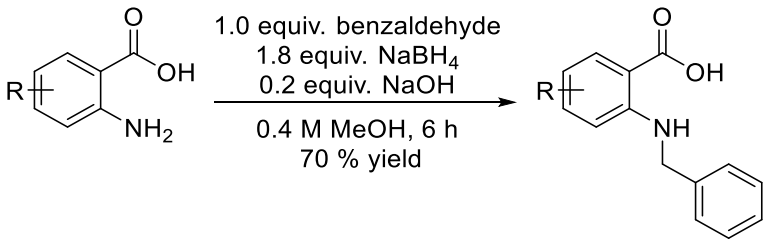
58g

$C_5H_{10}ClNO_3S$

M.W. = 199.6558 g/mol

***N*-(Methylsulfonyloxy)butyrimidoyl chloride (58g).** Prepared according to the procedure A yielding **58g** in 1.30 g (65 %, 2 steps) as a colorless liquid product. ^1H NMR (300 MHz, $CDCl_3$) δ 3.16 (s, 3H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.69–1.77 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 38.6, 36.7, 19.5, 12.9. These data matched to the literature values (Yamamoto *et al*., 2009).

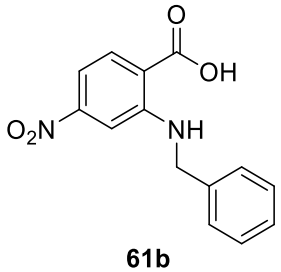
General Procedure B: Synthesis of 2-(benzylamino)benzoic acids 61.



61

2-(benzylamino)benzoic acids 61. A dried round bottom flask was added 2-aminobenzoic acid derivatives (2.0 mmol) in MeOH (5.00 mL) and then benzaldehyde (2.0 mmol) was added. The reaction mixture was stirred 30 minutes at room temperature. After that, added $NaBH_4$ (1.8 equiv.) and NaOH (0.2 equiv.) in H_2O (1.00 mL) to the reaction mixture. Stirred the resulting solution for 6 hours. After the reaction completed, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (50 mL). filtered the organic layer and dried over anhydrous Na_2SO_4 and then removed the solvent under reduced pressure. The residue was purified by column chromatography (20–60% EtOAc/hexane) to afford **61** as brown solid product in 318.16 mg (70 %). ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (br, s, 1H), 7.98 (dd, *J* = 7.8,

1.2 Hz, 1H), 7.26–7.35 (m, 6H), 6.18 (dd, *J* = 8.3, 8.3 Hz, 2H), 4.48 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 151.6, 138.7, 135.6, 132.6, 128.7, 127.2, 126.9, 115.1, 111.9, 109.0, 46.9. These data matched to the literature values (Liu *et al*., 2007).

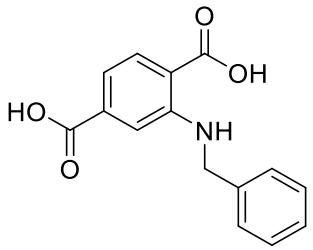


61b

$C_{14}H_{12}N_2O_4$

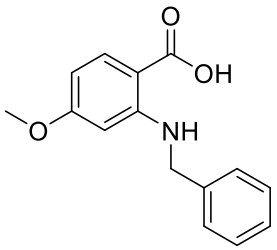
M.W. = 272.2600 g/mol

4-Nitro-2-[(phenylmethyl)amino]benzoic acid (61b). Prepared according to the literature procedure. 4-nitro-2-aminobenzoic acid (20 mmol), the benzaldehyde (40 mmol) and 2 drops conc. HCl were stirred for 15 minutes in 30 ml acetonitrile. The acetonitrile and excess aldehyde were evaporated under reduced pressure to give the crude imine, which redissolved in 30 ml acetonitrile then the portion-wise of $NaBH_4$ (40 mmol) was added over 5 minutes. The reaction is then left to stir for 30 minutes. The acetonitrile was then evaporated under reduced pressure to give the sodium salt of the product. Water was added to the resulting solid followed by concentrated HCl until the product precipitates. The product was collected by filtration with suction in 5.23 g (96 %) as an orange solid product. ^{1}H NMR (300 MHz, DMSO) δ 8.26 (s, 1H), 8.13 (dd, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 2.1 Hz, 1H), 7.36 (m, 6H), 4.45 (s, 2H) (Nonnenmacher *et al*., 1997); ^{13}C NMR (75 MHz, DMSO) δ 168.5, 151.2, 150.7, 138.2, 133.2, 128.5, 127.0, 126.9, 115.5, 108.1, 105.6, 46.1. These data matched to the literature values Heppell *et al*., 2013).



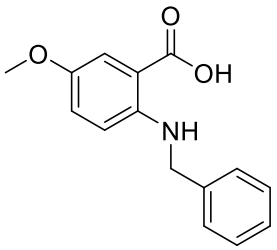
61c
$C_{15}H_{13}NO_4$
M.W. = 271.2720 g/mol

2-(Benzylamino)terephthalic acid (61c). Prepared according to the procedure B yielding **61c** in 396.06 mg (73 %) as a green solid product. ^{1}H NMR (500 MHz, D_2O, NaOD) δ 7.64 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.0 Hz, 2H), 7.27(dd, *J* = 15.0, 7.0 Hz, 2H), 7.19 (t, *J* = 15.0 Hz, 1H), 7.13(s, 1H), 4.35 (s, 2H); ^{13}C NMR (126 MHz, D_2O, NaOD) δ 175.57, 175.53, 148.59, 139.65, 139.42, 131.11, 128.74, 127.38, 127.13, 122.27, 116.57, 113.16, 46.89. These data matched to the literature values (Chatz-Giachia *et al*., 2022).



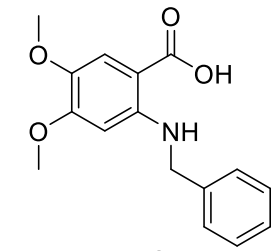
61d
$C_{15}H_{15}NO_3$
M.W. = 257.2890 g/mol

4-Methoxy-*N*-benzylanthranilic acid (61d). Prepared according to the procedure B yielding **61d** in 360.20 mg (70 %) as a white solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.94 (dd, *J* = 8.9, 1.4 Hz, 1H), 7.40–7.27 (m, 5H), 6.21 (dt, *J* = 8.9, 1.9 Hz, 1H), 6.06 (d, *J* = 2.3 Hz, 1H), 4.47 (s, 2H), 3.73 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 165.6, 153.6, 138.7, 134.7, 128.8, 127.3, 127.1, 102.8, 95.7, 55.2, 47.1. These data matched to the literature values (Thi *et al*., 2022).



61e
$C_{15}H_{15}NO_3$
M.W. = 257.2890 g/mol

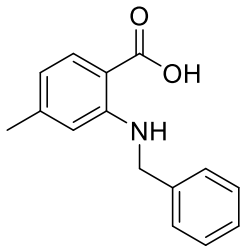
5-Methoxy-*N*-benzylanthranilic acid (61e). Prepared according to the literature. Heat a mixture of benzylamine (17.6 mmol), 2-halobenzoic acid (8.8 mmol), K_2CO_3 (1.21 g, 8.8 mmol), Cu_2O (38 mg, 0.4 mmol) to 110 °C for 24 h. Cool the reaction to room temperature and remove the solvent under reduced pressure. Pour the residue into H_2O (30 mL), treat with charcoal and filter the mixture through celite. Acidify the filtrate (pH 5) with dilute HCl and dissolve in aq Na_2CO_3 (5%, 100 mL), Filter the solution through celite and subject to precipitation. Purify by chromatography (EtOAc:hexane, 30%). The reaction was completely produced **61e** yielding in 1.47 g (65 %) as a yellow solid product. ^{1}H NMR (300 MHz, CD_3OD) δ 7.48 (d, *J* = 3.2 Hz, 1H), 7.36–7.40 (m, 4H), 7.33 (m, 1H), 7.09 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.73 (d, *J* = 9.3 Hz, 1H), 4.51 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 169.7, 148.9, 145.7, 139.7, 128.5, 127.0, 126.9, 122.5, 114.6, 113.2, 110.4, 55.4, 46.3. These data matched to the literature values (Liu *et al*., 2007).



61f
$C_{16}H_{17}NO_4$
M.W. = 287.1158 g/mol

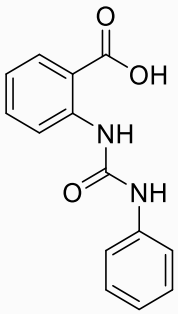
4,5-Methoxy-*N*-benzylanthranilic acid (61f). Prepared according to the literature procedure. The 2-amino-4,5-dimethoxybenzoic acid (2.0 mmol) and benzaldehyde (2.0 mmol) in MeOH (5 mL) were stirred for 30 min at room temperature. $NaBH_4$ (3.5

mmol) and NaOH (0.4 mmol) in H_2O (1 mL) were added to the reaction mixture and the resulting solution was stirred for 6 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with water (20 mL). The organic layer was filtered and dried over Na_2SO_4 and the solvent was removed to provide **61f** in 562.75 mg (98 %) as a pale brown solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.34–7.42 (m, 4H), 7.29–7.32 (m, 1H), 6.1 (s, 1H), 4.50 (s, 1H), 3.84 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 156.0, 149.0, 139.6, 138.9, 128.7, 127.2, 126.9, 113.9, 99.9, 95.0, 56.3, 55.6, 47.4. These data matched to the literature values (Laha *et al*., 2015).



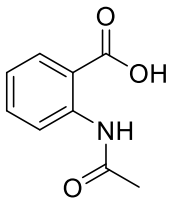
61g
$C_{15}H_{15}NO_2$
M.W. = 241.0899 g/mol

2-(Benzylamino)-4-methylbenzoic acid (61g). Prepared according to the procedure B yielding **61g** in 351.99 mg (73 %) as a solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.41–7.32 (m, 5H), 6.52 (s, 1H), 6.49 (d, *J* = 7.2 Hz, 1H), 4.52 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 151.5, 146.7, 138.7, 132.6, 128.7, 127.1, 116.9, 112.2, 106.8, 47.0, 22.3. IR (thin film) ν 3375, 2861, 2567, 1657, 1573, 1235, 794, 767, 735. These data matched to the literature values (David *et al*., 2000).



61h
$C_{14}H_{12}N_2O_3$
M.W. = 256.0848 g/mol

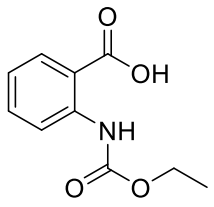
***N,N*-(2-Carboxyl phenyl)phenyl urea (61h).** Prepared according to the literature procedure. A mixture of anthranilic acid (6.85 g, 50 mmol) and phenyl isocyanate (5.6 mL, 4.96 g, 42 mmol) were reacted in dry THF (50 mL) under reflux for 3 h. After cooling to room temperature, aqueous NH_4Cl (10 %, 200 mL) was added and the resulting precipitate was filtered off and washed with water (70 mL). The product was recrystallized from a water-ethanol mixture (1:3), 150 mL and dried under vacuum to give **61h** in 9.35 g (73 %) as a solid product. ^{1}H NMR (300 MHz, DMSO) δ 10.35 (s, 1H), 9.75 (s, 1H), 8.34 (d, *J* = 5.6 Hz, 1H), 8.20–7.90 (m, 9H); ^{13}C NMR (75 MHz, DMSO) δ 169.87, 152.77, 142.68, 140.17, 134.15, 131.43, 129.15, 122.58, 121.3, 120.32, 119.26, 115.99. These data matched to the literature values (Okpareke *et al*., 2019).



61i
$C_9H_9NO_3$
M.W. = 179.0582 g/mol

2-Acetamidobenzoic acid (61i). Prepared according to the literature procedure. To a solution of anthranilic acid (1.1 mmol, 151 mg) in anhydrous THF (4 mL) was added 1.0 mmol of the acetic anhydride at room temperature. After cooling the solution using ice-water bath, 1.5 mmol of triethylamine was added dropwise and reaction was stirred

at room temperature for additional 4–12 h. The mixture was poured into a 20–30 mL cold solution of 1.0 M HCl, and precipitates were collected by filtration to give a white solid product in 137.87 mg (70 %). ^{1}H NMR (500 MHz, DMSO) δ 11.05 (s, 1H), 8.38–8.55 (m, 1H), 7.96 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.56 (d, *J* = 1.3 Hz, 1H), 6.99–7.26 (m, 1H), 2.12 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 169.9, 168.9, 141.3, 134.4, 131.5, 123.0, 120.4, 116.9, 25.4. These data matched to the literature values (Emenike *et al*., 2013).

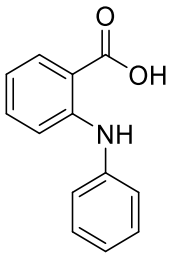


61j

$C_{10}H_{11}NO_4$

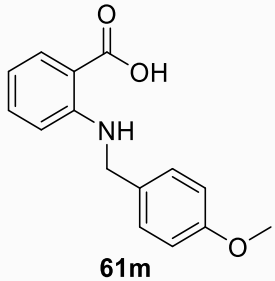
M.W. = 209.0688 g/mol

2-((Ethoxycarbonyl)amino)benzoic acid (61j). To a solution of anthranilic acid (1.37 g) in aqueous sodium carbonate (10.6 ml, 0.53 g) was added a solution of ethyl chloroformate (0.96 ml) in ethanol (20 ml) dropwise with stirring at room temperature when the product separated out immediately. After keeping overnight, the mixture was diluted with water, filtered under suction, washed with water and crystallized from ethanol yielding **61j** in 1.78 g (85 %) as a solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (br, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.13 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.59 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.07 (dd, *J* = 8.1, 0.6 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); IR (thin film) ν 3265, 2685, 2595, 1715, 1700, 1635, 1560, 1490, 1430, 1385, 1 300, 1230, 1200, 1 145, 1050, 760, 745 cm^{-1}. These data matched to the literature values (Gakhar *et al*., 1983).



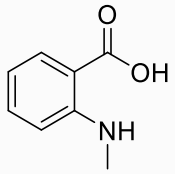
61k
$C_{13}H_{11}NO_2$
M.W. = 213.0790 g/mol

***N*-Phenyl-2-aminobenzoic acid (61k).** Prepared according to the literature procedure. A two-necked round bottom flask was charged with copper acetate 5 % wt (with respect to iodobenzoic acid), iodobenzoic acid (1 mmol), anilines (2 mmol), sodium acetate (1.2 mmol) and water (15 ml). The mixture was refluxed for 1–6 h in an oil bath under vigorous magnetic stirring until the TLC shows the disappearance of starting material. The reaction mixture was cooled to room temperature, acidified with dil HCl to pH 2 and stirred for overnight. The crystals/solids were filtered, washed with dil HCl followed by water, provided **61k** in 202.43 mg (95 %) as a greenish-cream solid. ^{1}H NMR (300 MHz, DMSO) δ 13.01 (s, 1H), 9.60 (s, 1H), 7.90–6.76 (m, 9H); ^{13}C NMR (75 MHz, DMSO) δ 170.0, 146.3, 142.1, 140.6, 135.4, 131.9, 130.2, 129.3, 121.7, 119.9, 118.9, 117.2, 113.6. These data matched to the literature values (Girisha *et al*., 2006).



61m
$C_{14}H_{12}N_2O_3$
M.W. = 256.0848 g/mol

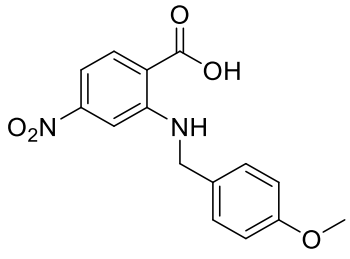
2-((4-Methoxybenzyl)amino)benzoic acid (61m). Prepared according to the literature procedure. Charge a 10 mL sealed tube equipped with a Teflon valve with a magnetic stir bar, CuI (5 mol%), ligand (6 mol%), KOH (3.0 mmol) and solid aryl iodides (1.0 mmol). Evacuate the tube and backfill with nitrogen (repeat the procedure three times). Add H_2O (1.5 mL), 1.0 mmol aryl iodides, 1.5 mmol amines by syringe under a counter flow of nitrogen. Seal the tube quickly and allow the reaction mixture to stir under nitrogen at room temperature for 18 h. Extract the mixture by diethyl ether (3×10 mL) and dry the combine extracts by anhydrous sodium sulfate. Filter and remove the solvent under vacuum. Purify the residue by column chromatography on silica gel with an eluent of hexane and ethyl acetate yielding **61m** in 220.23 mg (86 %) as a white solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.33–7.27 (m, 3H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.54 (t, *J* = 7.2 Hz, 1H), 4.36 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 151.1, 134.8, 132.1, 131.5, 128.9, 114.9, 114.4, 112.1, 111.5, 55.5, 45.9. These data matched to the literature values (Wang *et al*., 2017).



61n
$C_8H_9NO_2$
M.W. = 151.0633 g/mol

2-(Methylamino)benzoic acid (61n). Prepared according to the literature procedure. Add anthranilic acid (10.0 g) to a solution of sodium carbonate (4.0 g, 37.9 mmol) in water (70 mL), followed by dropwise addition of methyl iodide (5.5 mL, 87.5 mmol) with stirring at room temperature. Then, reflux the mixture at 110 °C for 4 hours. Cool the mixture to room temperature. Add water (300 mL) to the solution. Separating the organic layer. Extract the aqueous layer with EtOAc (3×150 mL). Dry the combined organic layer over anhydrous Na_2SO_4. Filter the dried organic solution. Concentrate the dried organic solution under reduced pressure. Purify the residue by column chromatography on silica gel (hexane:EtOAc = 5:2) to give **61n** in 6.94 g (63 %) as a

white solid product. ^{1}H NMR (300 MHz, DMSO) δ 7.77 (dd, *J* = 12.0, 4.0 Hz, 1H), 7.40–7.35 (m, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.55 (t, *J* = 8.0 Hz, 9H), 2.83 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 169.90, 151.68, 134.47, 131.55, 113.92, 110.67, 109.88, 29.16. These data matched to the literature values (Huang *et al*., 2020).

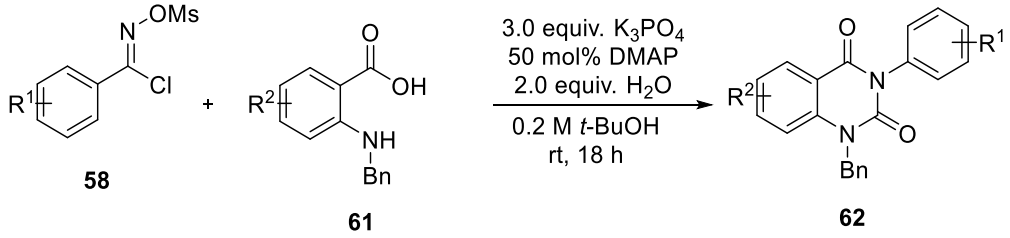


53o
$C_{15}H_{14}N_2O_5$
M.W. = 302.2860 g/mol

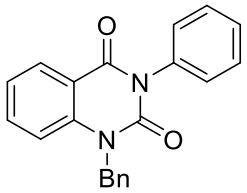
2-((4-Methoxybenzyl)amino)-4-nitrobenzoic acid (53o). Prepared according to procedure. The 2-amino-4-nitrobenzoic acid (2.0 mmol) and benzaldehyde (2.0 mmol) in MeOH (5 mL) were stirred for 30 min at room temperature. $NaBH_4$ (3.5 mmol) and NaOH (0.4 mmol) in H_2O (1 mL) were added to the reaction mixture, and the resulting solution was stirred for 6 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with water (20 mL). The organic layer was filtered and dried over Na_2SO_4 and the solvent was removed to provide **53o** in 338.56 mg (56 %) as a pale brown solid product. ^{1}H NMR (300 MHz, DMSO) δ 8.01 (d, *J* = 8.7 Hz, 1H), 7.41 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 3H), 6.92 (d, *J* = 8.4 Hz, 2H), 4.46 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 169.2, 158.9, 151.6, 151.2, 133.8, 130.5, 128.9, 128.4, 115.9, 114.5, 113.9, 108.6, 106.2, 55.5, 45.9; IR (thin film) ν 2964, 1706, 1658, 1371, 1230, 751, 746, 735, 705 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{15}H_{14}N_2O_5$ 303.0975, Found 303.0976.

4.1.3 Synthesis of Quinazolinedione Derivatives

General Procedure C: Synthesis of Quinazolinedione Derivatives 62



The reaction of α-chloroaldoxime *O*-methanesulfonates **58** and 2-(benzylamino)benzoic acids **61** is representative: A round bottom flask was added with 2-(benzylamino)benzoic acids **61** (1.0 equiv, 1 mmol) as a solid, α-chloroaldoxime *O*-methanesulfonate**s 58** (1.2 equiv.), K_3PO_4 (3.0 equiv.), DMAP (50 mol%), in *t*-BuOH. Then H_2O (2.0 equiv.) was added to a reaction mixture. The reaction mixture was allowed to stir at room temperature for 15–18 hours. After completion of reaction, the brown orange reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layers were dried over sat. NaCl (brine), and anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (10–50% hexane:EtOAc) to provide **62** as a white solid (74% yield).



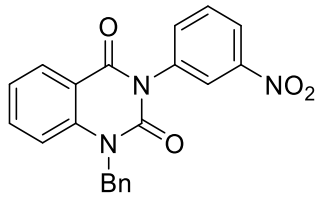
62a

$C_{21}H_{16}N_2O_2$

M.W. = 328.1212 g/mol

1-Benzyl-3-phenylquinazoline-2,4(*1H,3H*)-dione (62a). Prepared according to general procedure C yielding **62a** in 242.81 mg (74 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.8 Hz, 1H), 7.65–7.47 (m, 4H), 7.42–7.24 (m, 9H), 5.44 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 151.6, 140.3, 135.6, 129.4, 129.0, 128.8, 128.5, 127.8, 127.1, 123.5, 115.9, 114.9, 47.6; IR (thin film) ν 1704, 1656, 1349, 1317,

1330, 760, 702, 691, 672 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{16}N_2O_2Na$ 351.1104; Found 351.1105.

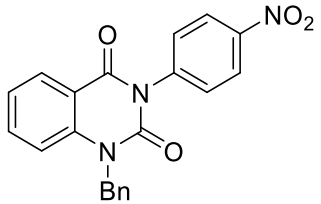


62b

$C_{21}H_{15}N_3O_4$

M.W. = 373.1063 g/mol

1-Benzyl-3-(3-nitrophenyl)quinazoline-2,4(*1H*,*3H*)-dione (62b). Prepared according to general procedure C yielding **62b** in 335.80 mg (90 %) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (m, 1H), 8.19 (m, 2H), 7.71 (m, 1H), 7.60 (m, 3H), 7.32–7.16 (m, 6H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 151.1, 148.8, 140.2, 136.5, 135.9, 135.3, 130.1, 129.4, 129.1, 128.0, 126.7, 124.5, 123.7, 124.7, 115.8, 114.9, 47.7; IR (thin film) ν 1710, 1651, 1401, 1348, 1282, 799, 762, 708, 687 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{15}N_3O_4Na$ 396.0960; Found 396.0954.



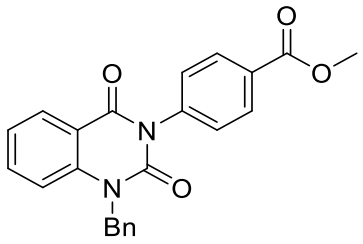
62c

$C_{21}H_{15}N_3O_4$

M.W. = 373.1063 g/mol

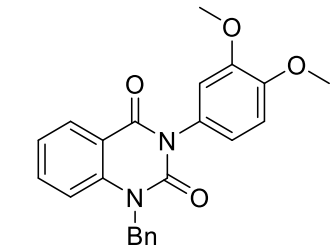
1-Benzyl-3-(4-nitrophenyl)quinazoline-2,4(*1H*,*3H*)-dione (62c). Prepared according to general procedure C yielding **62c** in 305.95 mg (82 %) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.7 Hz, 2H), 8.20 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.59 (t, *J* = 1.8 Hz, 1H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.33–7.16 (m, 7H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 150.9, 147.7, 141.2, 140.2, 136.0, 135.2, 130.1, 129.4, 129.1, 128.0, 126.7, 126.4, 124.6, 123.7, 115.8, 114.9, 113.4, 47.6; IR (thin film) ν 1704 1663

1344 1310 1478 860 752 699 688 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{16}N_3O_4$ 374.1135; Found 374.1136.



62d
$C_{23}H_{18}N_2O_4$
M.W. = 386.1267 g/mol

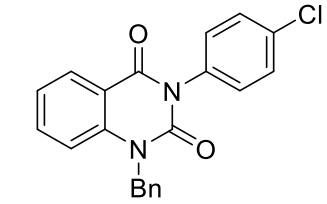
Methyl-4-(1-benzyl-2,4-dioxo-1,4-dihydroquinazolin-3(*2H*)-yl) benzoate (62d). Prepared according to general procedure C yielding **62d** in 308.90 mg (80 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.8 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 2H), 7.62 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.38–7.23 (m, 7H), 5.42 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 161.6, 151.2, 140.2, 139.7, 135.6, 135.5, 130.7, 130.5, 129.4, 129.0, 128.8, 127.8, 126.7,123.4, 116.0, 114.7, 77.5, 52.3, 47.5; IR (thin film) ν 3032, 1722, 1706, 1660, 1602, 1327, 1274, 759, 727 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{18}N_2O_4Na$ 409.1164; Found 409.1158.



62e
$C_{23}H_{20}N_2O_4$
M.W. = 388.1423 g/mol

1-Benzyl-3-(3,4-dimethoxyphenyl)quinazoline-2,4(*1H,3H*)-dione (62e). Prepared according to general procedure C yielding **62e** in 194.07 mg (50 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.2 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.37–7.21 (m, 8H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.93 (s, 1H), 6.84 (s, 1H), 5.43 (s, 2H), 3.93 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 151.8, 149.6, 149.3, 140.3, 135.7, 135.4, 129.4, 129.0, 128.3, 127.8, 126.8, 123.2, 120.6, 116.1, 114.6, 111.6, 111.5, 56.0, 47.6;

IR (thin film) ν 2943, 2831, 1666, 1448, 1114, 1021, 628 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{21}N_2O_4$ 389.1501; Found 389.1496.

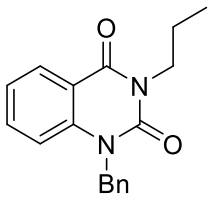


62f

$C_{21}H_{15}ClN_2O_2$

M.W. = 362.0822 g/mol

1-Benzyl-3-(4-chlorophenyl)quinazoline-2,4(*1H*,*3H*)-dione (62f). Prepared according to general procedure C yielding **62f** in 260.70 mg (72 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.53 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.40 (dd, *J* = 6.9, 1.8 Hz, 2H), 7.29–7.11 (m, 9H), 5.31 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 151.4, 140.2, 135.6, 135.5, 134.7, 134.0, 129.9, 129.7, 129.4, 129.0, 127.8, 126.7, 123.4, 116.0, 114.7, 47.6; IR (thin film) ν 1711, 1663, 1331, 1319, 1090, 1019, 827, 759, 720 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{15}N_2O_2ClNa$ 385.0720; Found 385.0713.

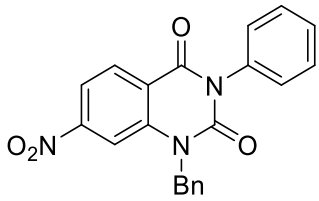


62g

$C_{18}H_{18}N_2O_2$

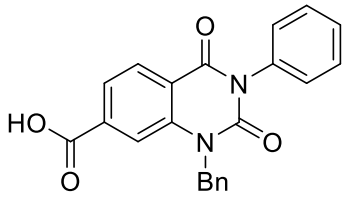
M.W. = 294.1368 g/mol

1-Benzyl-3-propylquinazoline-2,4(*1H*,*3H*)-dione (62g). Prepared according to general procedure C yielding **62g** in 117.65 mg (40 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.55 (dt, *J* = 8.7, 1.5 Hz, 1H), 7.38–7.20 (m, 6H), 7.13 (d, *J* = 8.7 Hz, 1H), 5.40 (s, 2H), 4.14 (t, *J* = 7.5 Hz, 2H), 1.80 (sex, *J* = 7.5 Hz, 2H), 1.02 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 151.4, 139.9, 135.8, 134.9, 129.2, 128.3, 127.5, 126.5, 123.0, 115.8, 114.1, 47.3, 43.6, 21.6, 11.2. IR (thin film) ν 2966, 2933, 2875, 1694, 1651, 1364, 1345, 1262, 763 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{19}N_2O_2$ 295.1447; found 295.1442.



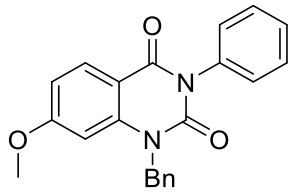
62h
$C_{21}H_{15}N_3O_4$
M.W. = 373.1063 g/mol

1-Benzyl-7-nitro-3-phenylquinazoline-2,4(*1H,3H*)-dione (62h). Prepared according to general procedure C yielding **62h** in 186.55 mg (50 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.7 Hz, 1H), 8.17 (s, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.60–7.33 (m, 11H), 5.46 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 151.9, 151.2, 140.9, 134.9, 134.5, 131.3, 129.6, 129.4, 129.3, 128.4, 128.2, 127.1, 124.3, 121.2, 120.3, 117.3, 110.2, 48.1. IR (thin film) ν 1717, 1674, 1462, 1294, 1230, 751, 746, 735, 705 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{16}N_3O_4$ 374.1141; Found 374.1136.



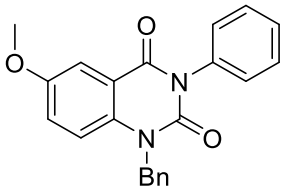
62i
$C_{22}H_{16}N_2O_4$
M.W. = 372.1110 g/mol

1-Benzyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinazoline-7-carboxylic acid (62i). Prepared according to general procedure C yielding **62i** in 200.94 mg (54 %) as a white solid.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.1 Hz, 1H), 8.03 (s, 1H), 7.90 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.57–7.26 (m, 10H), 5.44 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 161.4, 151.5, 140.3, 136.2, 135.4, 129.9, 129.6, 129.2, 129.1, 128.5, 128.1, 127.3, 124.2, 121.5, 120.6, 119.5, 116.5, 47.8. IR (thin film) ν 3476, 1706, 1658, 1288, 1266, 887, 767, 737, 699 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{16}N_2O_4Na$ 395.1002, found 395.1001.



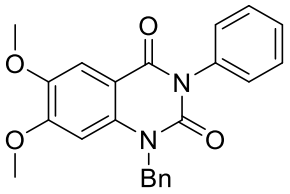
62j
$C_{22}H_{18}N_2O_3$
M.W. = 358.1317 g/mol

1-Benzyl-7-methoxy-3-phenylquinazoline-2,4(*1H*,*3H*)-dione (62j). Prepared according to general procedure C yielding **62j** in 282.92 mg (79 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.7 Hz, 1H), 7.57–6.81 (m, 10H), 6.79 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.56 (d, *J* = 2.1 Hz, 1H), 5.37 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 161.5, 151.9, 142.0, 135.8, 131.3, 129.4, 129.0, 128.7, 128.5, 127.8, 126.8, 109.9, 109.4, 99.7, 55.7, 47.7; IR (thin film) ν 3060, 2927, 1701, 1658, 1376, 1333, 817, 777, 751 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{18}N_2O_3Na$ 381.1215; Found 381.1211.



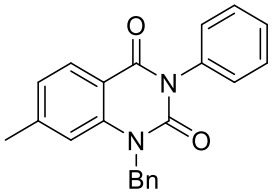
62k
$C_{22}H_{18}N_2O_3$
M.W. = 358.1317 g/mol

1-Benzyl-6-methoxy-3-phenylquinazoline-2,4(*1H*,*3H*)-dione (62k). Prepared according to general procedure C yielding **62k** in 286.51 mg (80 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 2.7 Hz, 1H), 7.57–7.43 (m, 3H), 7.38–7.12 (m, 9H), 5.38 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 155.7, 151.4, 135.9, 135.8, 134.5, 129.5, 129.1, 128.9, 128.5, 127.9, 126.8, 124.4, 117.0, 116.4, 110.4, 56.0, 47.7. IR (thin film) ν 3060, 2927, 1701, 1658, 1376, 1333, 817, 777, 751 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{18}N_2O_3Na$ 381.1215; Found 381.1209.



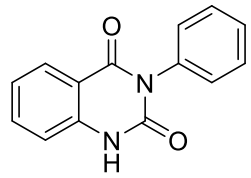
62l
$C_{23}H_{20}N_2O_4$
M.W. = 388.1423 g/mol

1-Benzyl-6,7-dimethoxy-3-phenylquinazoline-2,4(*1H,3H*)-dione (62l). Prepared according to general procedure C yielding **62l** in 329.92 mg (85 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.56–7.32 (m, 10H), 6.63 (s, 1H), 5.39 (s, 2H), 3.90 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 155.3, 152.0, 145.8, 136.1, 136.0, 129.5, 129.2, 128.8, 128.6, 128.0, 126.8, 109.3, 108.6, 98.0, 56.4, 48.0. IR (thin film) ν 2934, 1700, 1654, 1455, 1336, 1258, 707, 770, 746 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{21}N_2O_4$ 389.1501; Found 389.1495.



62m
$C_{22}H_{18}N_2O_2$
M.W. = 342.1368 g/mol

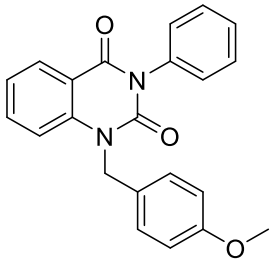
1-Benzyl-7-methyl-3-phenylquinazoline-2,4(*1H,3H*)-dione (62m). Prepared according to general procedure C yielding **62m** in 273.71 mg (80 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.1 Hz, 1H), 7.55 (dd, *J* = 8.7, 7.2 Hz, 2H), 7.50 (d, *J* = 1.2 Hz, 1H), 7.39–7.11 (m, 7H), 7.06 (m, 2H), 5.42 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 151.8, 146.8, 140.4, 135.9, 135.7, 129.5, 129.4, 129.1, 128.9, 128.8, 128.5, 128.0, 127.8, 126.8, 125.0, 124.6, 114.8, 113.8, 47.5, 22.5. IR (thin film) ν 1713, 1659, 1360, 1318, 773, 753, 724, 698, 642, 608 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{19}N_2O_2$ 343.1447; Found 343.1443.



62r

$C_{14}H_{10}N_2O_2$
M.W. = 238.0742 g/mol

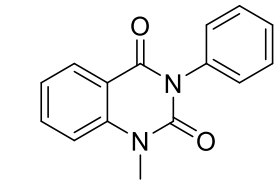
3-Phenylquinazoline-2,4(*1H*,*3H*)-dione (62r) Prepared according to general procedure C yielding **62r** in 176.17 mg (74 %) as a white solid. ^{1}H NMR (500 MHz, DMSO) δ 11.54 (brs, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.0 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (126 MHz, DMSO) δ 162.3, 150.3, 139.9, 135.8, 135.3, 129.2, 128.9, 128.2, 127.7, 122.6, 115.3, 114.4 These data matched to the literature values (Huang *et al*., 2020).



62s

$C_{22}H_{18}N_2O_3$
M.W. = 358.1317 g/mol

1-(4-Methoxybenzyl)-3-phenylquinazoline-2,4(*1H*,*3H*)-dione(62s). Prepared according to general procedure C yielding **62s** in 286.51 mg (80 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.65–7.23 (m, 10H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.35 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 159.2, 151.6, 140.3, 135.6, 135.4, 129.5, 129.4, 129.0, 128.8, 128.4, 128.3, 127.7, 123.4, 123.2, 120.2, 116.1, 114.6, 114.4, 55.3, 47.0; IR (thin film) ν 2964, 1706, 1658, 1371, 1332, 1030, 764, 754, 737 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{18}N_2O_3Na$ 381.1215; Found 381.1211.

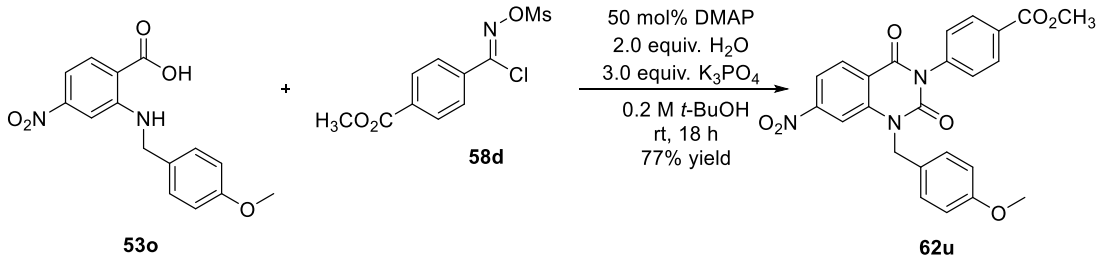


62t
$C_{15}H_{12}N_2O_2$
M.W. = 252.0899 g/mol

1-Methyl-3-phenylquinazoline-2,4(*1H*,*3H*)-dione (62t). Prepared according to general procedure C yielding **62t** in 206.71 mg (82 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.77 (dt, *J* = 9.0, 1.5 Hz, 1H), 7.55–7.33 (m, 3H), 7.28 (d, *J* = 6.9 Hz, 4H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 151.2, 140.8, 135.5, 129.5, 129.3, 128.8, 128.4, 123.2, 115.9, 113.8, 30.9 These data matched to the literature values (Beutner *et al*., 2017).

4.1.4 Synthesis of quinazolinedione building block (IV)

Methyl 4-(1-(4-methoxybenzyl)-7-nitro-2,4-dioxo-1,4-dihydroquinazolin-3(*2H*)-yl)benzoate (62u)

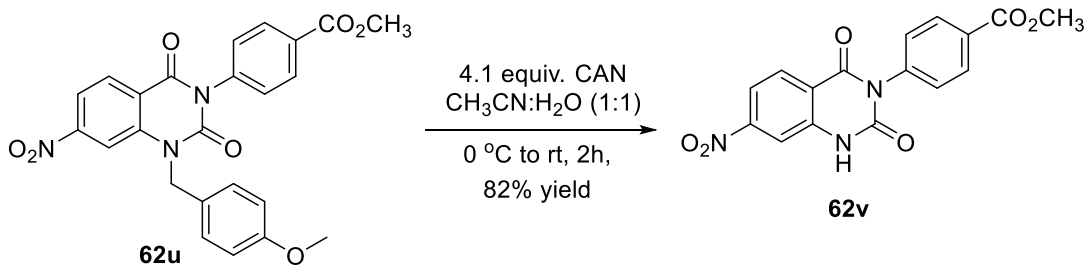


53o **58d** **62u**

Prepared according to general procedure from methyl-*N*-(4-chloro(methylsulfonyloxy)benzimidoyl chloride (**58d**) and 2-((4-methoxybenzyl)amino)-4-nitrobenzoic acid (**53o**) yielding **62u** in 355.06 mg (77 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 2H), 8.15 (s, 1H), 7.97 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.31 (s, 2H), 3.89 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 160.3, 159.8, 152.2, 150.9, 141.0, 139.0, 131.4, 131.1,

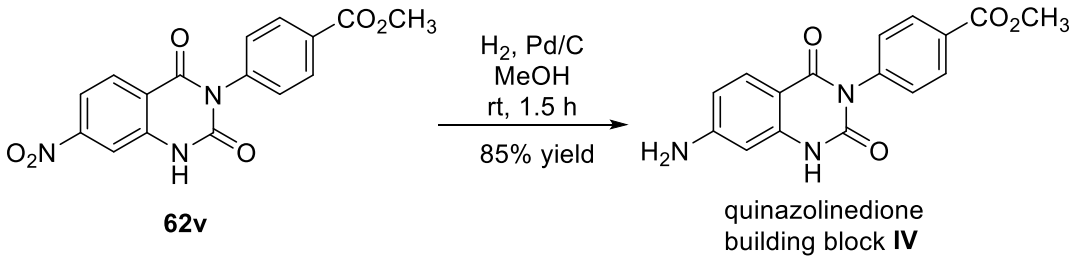
128.8, 128.7, 126.4, 120.2, 117.5, 114.9, 110.5, 55.5, 52.6, 47.8; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{19}N_3O_7Na$ 484.1121; Found 484.1112.

Methyl 4-(7-amino-2,4-dioxo-1,4-dihydroquinazolin-3(*2H*)-yl)benzoate (62v)



Prepared according to a modified literature procedure (Magnus *et al*., 2003). To a dried round bottom flask equipped with **62u** (1.0 mmol) in acetonitrile and water with the ratio of 1:1 (10.0 mL). Ceric ammonium nitrate (4.0 mmol) was added at 0 ^oC. Then, the mixture was stirred at ambient temperature until the reaction was completed. monitored by thin layer chromatography (TLC) with 1:1 ratio of EtOAc:hexane as a mobile phase. The reaction was quenched with water followed by extraction with EtOAc. A combined organic solution was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (2:1 hexane:EtOAc) to provide **62v** in 279.67 mg (82 %) as a white solid. ^1H NMR (300 MHz, DMSO) δ 12.01 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 2H), 8.01−7.96 (m, 3H), 7.54 (d, *J* = 8.1 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 166.2, 161.5, 151.8, 1.050.2, 140.9, 140.1, 130.2, 130.1, 130.0, 119.4, 116.9, 110.9, 52.8, IR (thin film) ν 1720, 1671, 1350, 1273, 877, 824, 765, 731, 699 cm^{-1}, HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{11}N_3O_6Na$ 364.0546; Found 364.0541.

Methyl 4-(7-amino-2,4-dioxo-1,4-dihydroquinazolin-3(*2H*)-yl)benzoate (IV)



To a stirred solution of **62v** (1.0 mmol) in MeOH (2.0 mL), a palladium on carbon (0.05 mmol) was added under hydrogen atmosphere at ambient temperature. The reaction was monitored by TLC with 1:6 ratio of EtOAc:hexane as a mobile phase. After completion of reaction, the reaction mixture was filtered. The filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (1:1 CH_2Cl_2:EtOAc) to provide the quinazolinedione building block (**IV**) in 264.43 mg (85 %) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ 11.21 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 6.41 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.30 (s, 1H), 6.24 (d, *J* = 2.1 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 166.3, 161.9, 155.7, 150.9, 142.2, 141.0, 130.4, 129.9, 129.5, 111.0, 102.9, 96.3, 52.7, IR (thin film) ν 3452, 3358, 2920, 2850, 1706, 1681, 1280, 854, 770 cm^{-1}, HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{13}N_3O_4Na$ 334.0804; Found 334.0795.

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APPENDIX

Review Report

FILESTAGE
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GENERAL INFORMATION

Project name
0220-L

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23/05/2023, 13:15
By Manuel van Gemmeren

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REVIEW SUMMARY Review Step 1 Version 1

APPROVED BY

- **WH5TzIV6**
  24/05/2023, 11:09
- **NXEuUZVn**
  25/05/2023, 22:53
- **e0CoKff0**
  25/05/2023, 09:50

REQUESTED CHANGES BY

- **7ZknxKnz**
  24/05/2023, 15:22
- **yVLBRz/G**
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- **ghuWol1K**
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- **NKbgPe9+**
  24/05/2023, 08:50
- **/ewCO6q3**
  24/05/2023, 23:09
- **YDJ6tcPS**
  26/05/2023, 06:13

AWAITING REVIEW DECISION

None

General Comments

NKbgPe9+
24/05/2023, 08:50

This paper is well written, the method is of interest and the supporting is clear. I recommend for publication in Synlett after adressing the few questions from reviewers

WH5TzIV6
24/05/2023, 10:48

Agree. This transformation described here is well designed and studied. However, as a letter paper, there are too many schemes in this paper. Scheme 2, Scheme 3 and Table 2 are suggested to merge into one single Scheme as there are not so many substrates in each part. Additionally the retrosynthetic analysis in Scheme 7 and the synthetic route in Scheme 8 describe the same thing. The retrosynthetic analysis could be deleted as this is a methodology paper rather than total synthesis paper. Schemes 6-8 are recommended to merged into one single scheme.

7ZknxKnz
24/05/2023, 15:20

Agree, I recommend for publication after the authors addressing the issues and tidying up the manuscript.

ghuWoI1K
25/05/2023, 06:34

Agree. Accept after addressing other reviews' comments and polishing the manuscript.

e0CoKff0
25/05/2023, 09:03

Agree, I recommend the publication after minor revision based on the comments of reviewers. The language needs polishing.

DMAP-catalyzed domino reactions of α-chloroaldoxime O-methanesulfonates and 2-aminobenzoic acids for the synthesis of quinazolinediones

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Abstract:	Quinazolinedione derivatives were obtained from 2-aminobenzoic acids and bench-stable α-chloroaldoxime O-methanesulfonates via DMAP-catalyzed domino reactions under mild reaction conditions in one-pot fashion. Chemical transformations involved nucleophilic substitution, Tiemann rearrangement and cyclic urea formation. The strength of nitrogen nucleophile of 2-aminobenzoic acids and the high level of carbon electrophile of α-chloroaldoxime O-methanesulfonates were crucial for the reaction outcome. An application to synthesize a quinazolinedione building block was introduced.

DMAP-catalyzed domino reactions of *α*-chloroaldoxime *O*-methanesulfonates and 2-aminobenzoic acids for the synthesis of quinazolinediones

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Abstract

Quinazolinedione derivatives were obtained from 2-aminobenzoic acids and bench-stable *α*-chloroaldoxime *O*-methanesulfonates *via* DMAP-catalyzed domino reactions under mild reaction conditions in one-pot fashion. Chemical transformations involved nucleophilic substitution, Tiemann rearrangement and cyclic urea formation. The strength of nitrogen nucleophile of 2-aminobenzoic acids and the high level of carbon electrophile of *α*-chloroaldoxime *O*-methanesulfonates were crucial for the reaction outcome. An application to synthesize a quinazolinedione building block was introduced.

Key words

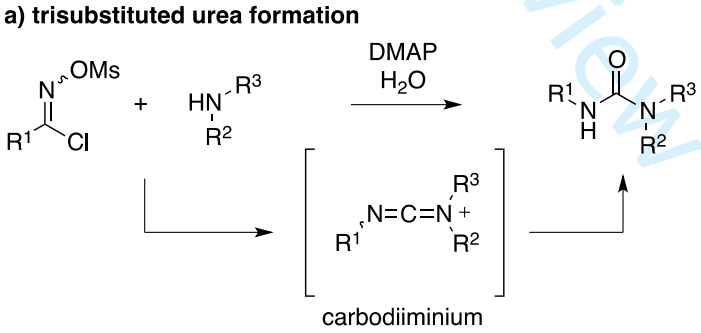
Quinazolinediones, Cylic ureas, Organocatalysis, intramolecular C−N amide bond formation, Tiemann rearrangement

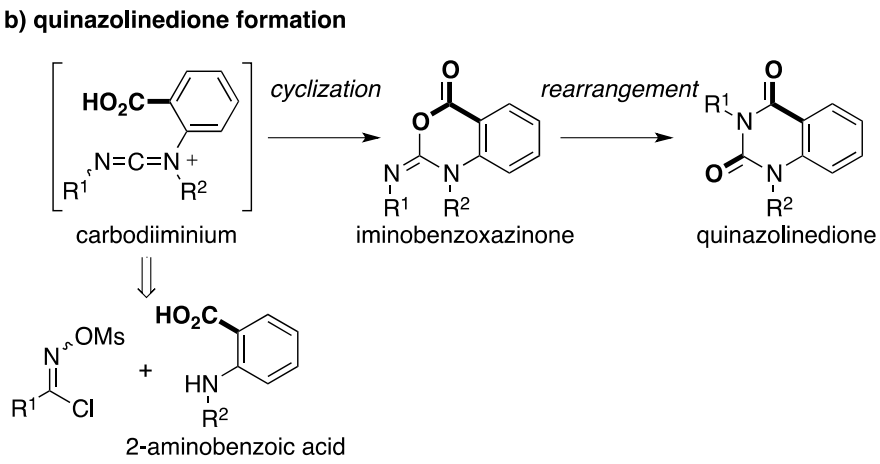
Introduction

Quinazolinediones are one of the most important nitrogen-containing heterocyclic compounds due to their common occurrence in natural products.[1] Furthermore, quinazolinedione motif are also found in medicinal chemistry with a wide range of biological activities, such as anticarcinoma,[2] antihypertensive,[3] antimicrobial,[4] antimalarial[5] and antidiabetic.[6] Therefore, a number of methodologies have been developed from both metal and non-metal catalysis.[7] A key structural motif of quinazolinedione is a cyclic acyl urea moiety. Two common used processes for producing quinazolinedione are a heterocyclization of 2-aminobenzoic acid derivatives[8] and an introduction of 2-position carbonyl to 2-aminobenzamide derivatives.[9] Generally, the use of 2-aminobenzoic acids for direct heterocyclization giving a corresponding quinazolinedione core structure was accomplished with isocyanates or urea derived from carbonyl sources and corresponding amines. Scalable reaction or high yield of

products was obtained. However, high temperature was required. Additionally, commercially available isocyanates are limited. Therefore, environmentally friendly alternative methodologies for construction of cyclic acyl urea core have remained to be explored.

Alternatively, we have been interested in the chemistry of *α*-chloroaldoxime *O*-methanesulfonates inspired by Yamamoto findings.[10] Not only chemical reactivity is interesting but also the compound is found to be bench-stable and stored at ambient temperature without any precautions. Based on our knowledge, two reaction pathways of *α*-chloroaldoxime *O*-methanesulfonates were introduced. Firstly, they could provide the imine moiety *via* intramolecular substitution reaction.[10a] Secondly, they could undergo Tiemann rearrangement to provide versatile carbodiimide intermediates.[10b] The carbodiimide intermediate could be converted to urea in the presence of H_2O. We took this chemistry to successfully achieve trisubstituted ureas from both secondary aliphatic and aromatic amines (Scheme 1, **a**).[11] Plausibly, the reaction proceeds via a carbodiiminium intermediate. We envisioned that having carboxylic acid at an *ortho* position of the carbodiiminium intermediate could undergo intramolecular C–O bond formation to form iminobenzoxazinone, followed by a rearrangement[12] of O−acyl to N−acyl to give a corresponding quinazolinedione (Scheme 1, **b**). The carboxyl carbodiiminium intermediate could be directly accomplished from the reaction of 2-aminobenzoic acid and *α*-chloroaldoxime *O*-methanesulfonate. Herein, we introduced an alternative direct synthesis of quinazolinediones from *α*-chloroaldoxime *O*-methanesulfonates and 2-aminobenzoic acids *via* domino reactions catalyzed by 4-dimethylaminopyridine (DMAP).



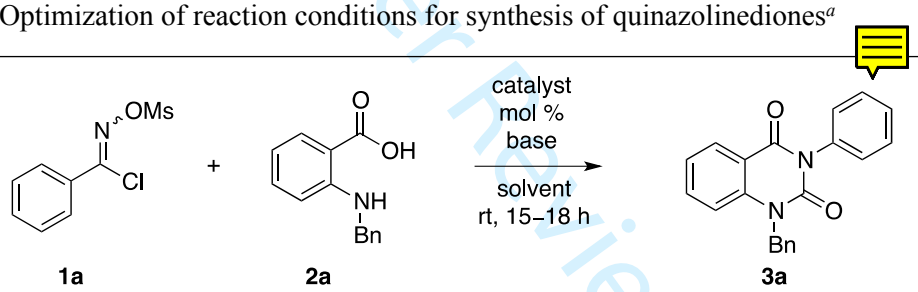


Scheme 1 Urea and quinazolinedione formations

Results and Discussion

We began our exploration by optimization of the reaction. The reaction of *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and 2-(benzylamino)benzoic acid (**2a**) was selected as a model (Table 1).

Table 1 Optimization of reaction conditions for synthesis of quinazolinediones[a]



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

Entry	Mol% Catalyst	Base	Solvent	Yield[b] (%)
1	30% DMAP	Cs_2CO_3	CH_2Cl_2	42
2	30% DABCO	Cs_2CO_3	CH_2Cl_2	NP[c]
3	30% Imidazole	Cs_2CO_3	CH_2Cl_2	NP
4	30% DMAP	Cs_2CO_3	EtOAc	Trace[d]
5	30% DMAP	Cs_2CO_3	ACN	Trace
6	30% DMAP	Cs_2CO_3	MeOH	NP
7	30% DMAP	Cs_2CO_3	EtOH	NP
8	30% DMAP	Cs_2CO_3	*t*-BuOH	40
9	20% DMAP	Cs_2CO_3	*t*-BuOH	35

10	50% DMAP	Cs_2CO_3	*t*-BuOH	63
11	60% DMAP	Cs_2CO_3	*t*-BuOH	67
12	50% DMAP	K_2CO_3	*t*-BuOH	60
13	50% DMAP	K_3PO_4	*t*-BuOH	74
14	50% DMAP	NEt_3	*t*-BuOH	12
15	50% DMAP	*i*-Pr_2NEt_3	*t*-BuOH	10
16[e]	50% DMAP	K_3PO_4	*t*-BuOH	72
17[f]	50% DMAP	K_3PO_4	*t*-BuOH	38

[a]Reaction condition: All reactions were performed with 1.0 mmol of **2a**, 1.2 equiv. of **1a**, 3.0 equiv. of base and 2.0 equiv. of H_2O in 5.0 mL of solvent in round bottom flask. [b]Isolated yield. [c]No product. [d]The ^1H NMR of the crude reaction mixture. [e]The reaction was performed at 60 °C. [f]The reaction was performed without adding H_2O.

Initially, we took the condition from our previous trisubsituted urea formation from secondary aromatic amines.[11] Luckily, a moderate yield of the product, 42% was obtained (entry 1). Other nucleophilic catalysts, such as DABCO or imidazole could not provide the quinazolinedione (entries 2 and 3). Next, other solvents were subjected to the exploration of condition. We selected recommended-green solvents[13] for the reactions. The reaction using EtOAc or ACN as a solvent gave trace amount of the product based on a ^1H NMR of the crude reaction mixture (entries 4 and 5). Nucleophilic alcohols, such as MeOH or EtOH, were not applicable for the reaction resulting in no product (entries 6 and 7). We only observed the remaining **2a** from the ^1H NMR of the crude reaction mixtures. On the contrary, non-nucleophilic alcohol, such as *t*-BuOH provided 40% yield of product (entry 8). The result was comparable to the result of the reaction in CH_2Cl_2. Moreover, *t*-BuOH was considered more environmental friendly than CH_2Cl_2. Therefore, *t*-BuOH was selected as a solvent for further optimization of the reaction. Next, we considered the amount of DMAP loading. We found that decreasing the amount of DMAP resulted in decreasing yields of the products (entry 9). The yield of product was increased to 63% when 50 mol% of DMAP was used (entry 10). A comparable yield was obtained with 60 mol% of DMAP. The result suggested that the reaction required high amount of catalyst loading in order to provide the highest yield of product. Other weak-common bases, such as K_2CO_3 or K_3PO_4, were applicable for the reaction giving product yield in 60% or 74%, respectively (entries 12 and 13). Common organic bases, such as triethylamine (TEA) or diisopropyl ethylamine (DIPEA) were not

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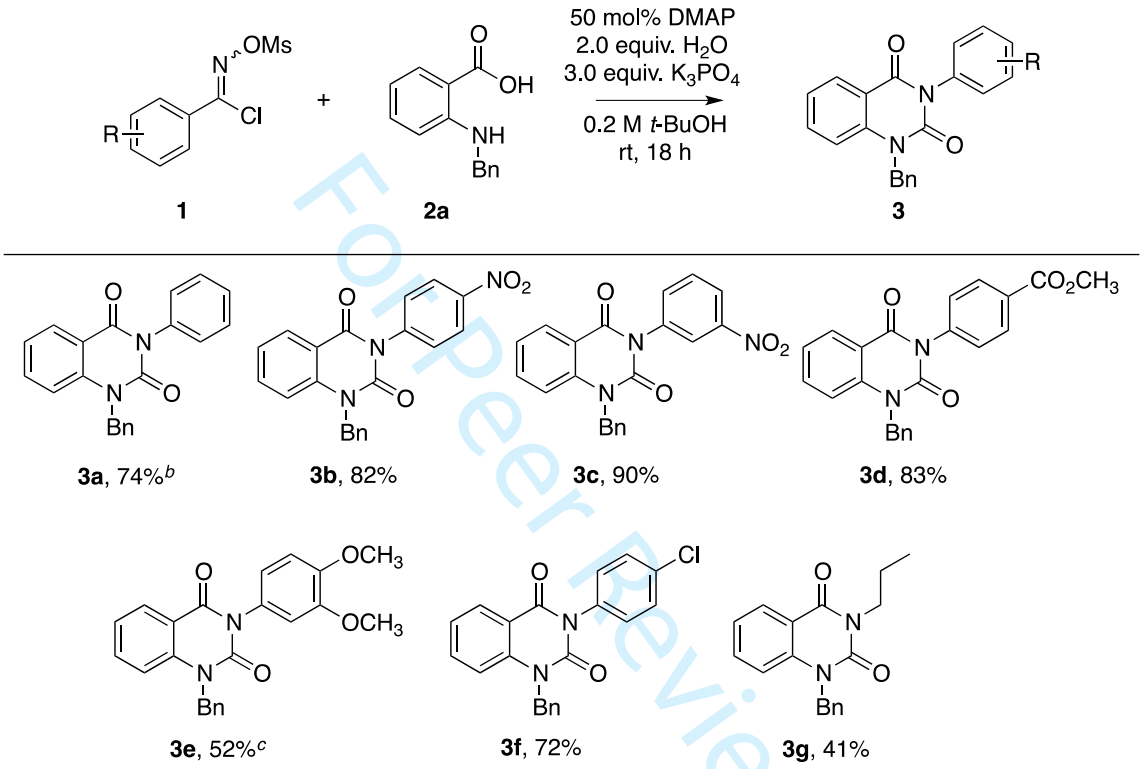
suitable for the reaction. We observed the remaining both starting materials resulting in low yields of the product, 12% and 10%, respectively (entries 14 and 15). Elevation of the reaction temperature did not afford greater product yield. The reaction at 60 °C gave product yield in 72% (entry 16). Significantly, without adding H_2O low yields of the product were observed. The reaction gave 38% yield (entry 17). In conclusion, the optimal condition was the use of 50 mol% DMAP as a catalyst, K_3PO_4 as a base in *t*-BuOH.

Scheme 2 Quinazolinediones from *α*-chloroaldoxime *O*-methanesulfonates[a]

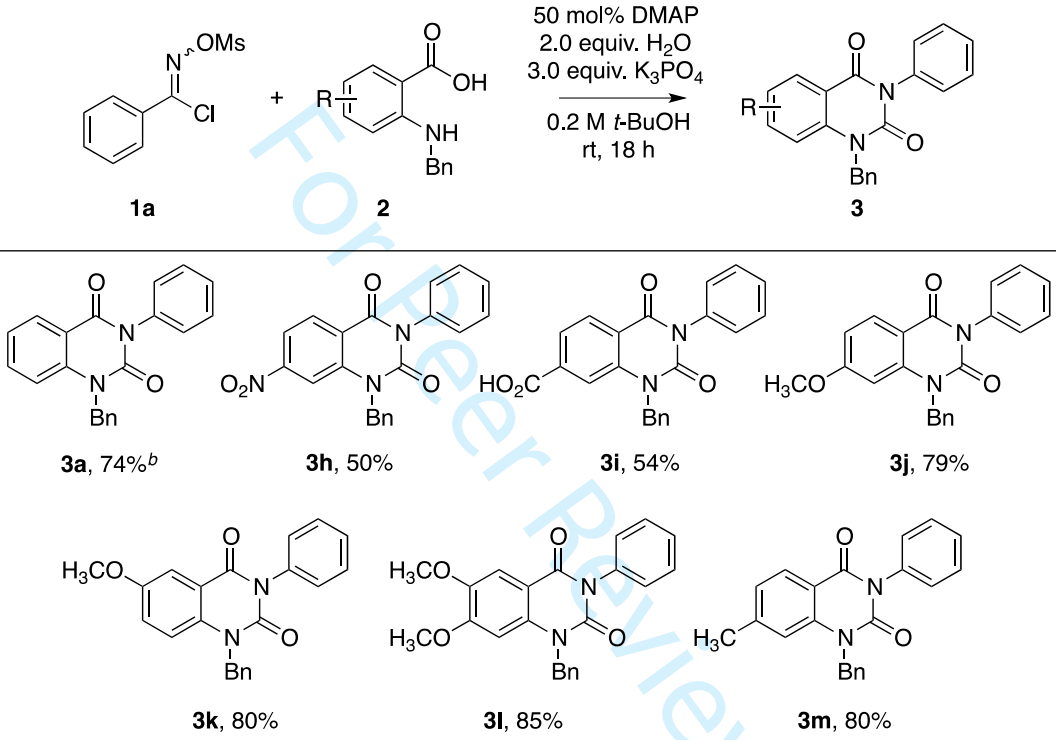


[a]Reaction condition: All reactions were performed with 1.0 mmol of **2a**, 1.2 equiv. of **1** in 5.0 mL of *t*-BuOH in round bottom flask. [b]Isolated yield. [c]*t*-BuOK was used as base.

After having the optimal reaction condition, we explored the scope of substrates. We started out with exploring a variety of *α*-chloroaldoxime *O*-methanesulfonates (Scheme 2). Without any substituent, the reaction of *N*-((methylsulfonyl)oxy) benzimidoyl chloride provided good yield of the product, 74% (**3a**). Great yields of corresponding products were obtained from the reaction of *α*-chloroaldoxime *O*-methanesulfonates bearing electron-withdrawing group (**3b–c**). Both 4-nitro and 3-nitro substituted *α*-chloroaldoxime *O*-methanesulfonates provided corresponding products in 82% and 90%, respectively (**3b** and **3c**). Comparable high yield of product was observed from the reaction of methyl 4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate giving product in 83% (**3d**). Having electron-donating group a 3,4-dimethoxy-*N*-((methylsulfonyl)oxy) benzimidoyl chloride

provided no reaction. However, changing to strong base, such as *t*-Bu gave the product in moderate yield, 52% (**3e**). A *α*-chloroaldoxime *O*-methanesulfonate bearing chloro-substituted benzene ring gave good yield, 72%, of the quinazolinedione product (**3f**). An alkyl-substituted *α*-chloroaldoxime *O*-methanesulfonate was also compatible to the reaction. A *N*-((methylsulfonyl)oxy) butyrimidoyl chloride gave 41% yield of the product (**3g**). Based on the results, the electrophilicity of the *α*-chloroaldoxime *O*-methanesulfonates was crucial giving significantly high yield of the quinazolinedione products.

Scheme 3 Quinazolinediones from a variety of *N*-benzyl-2-aminobenzoic acids[a]



[a]Reaction condition: All reactions were performed with 1.0 mmol of **2**, 1.2 equiv. of **1a** in 5.0 mL of *t*-BuOH in round bottom flask. [b]Isolated yield.

We then turned our focus on a variety of *N*-benzyl 2-aminobenzoic acids (Scheme 3). Moderate yields were obtained from the reaction of *N*-benzyl 2-aminobenzoic acids having electron-withdrawing group substituents. The reactions of *N*-benzyl 2-aminobenzoic acids having 4-nitro or 4-carboxyl substituent gave the corresponding product in 50% or 54%, respectively (**3h** and **3i**). On the other hand, high yields of the products were observed when *N*-benzyl 2-aminobenzoic acids having electron-donating group substituents were used. Both 4-methoxy- and 5-methoxy-2-(*N*-benzyl)aminobenzoic acids provided the corresponding product in 79% and 80%, respectively (**3j** and **3k**). Moreover, *N*-benzyl 2-aminobenzoic acid having 4,5-dimethoxy substituent gave better yield of the product in 85% (**3l**). Based on the results, the electronic effect of the benzene ring of 2-aminobenzoic acid played a crucial role

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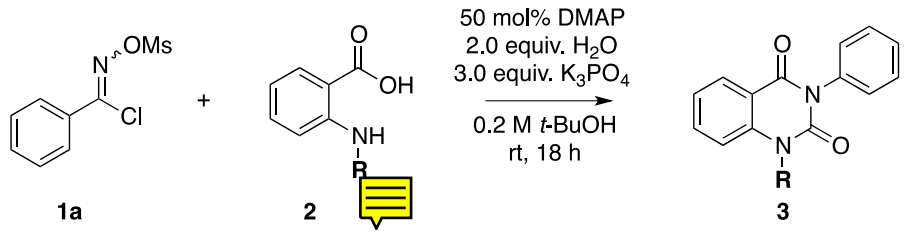
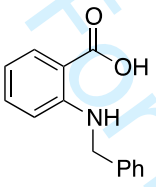
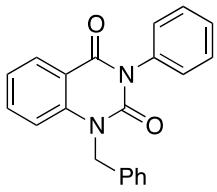
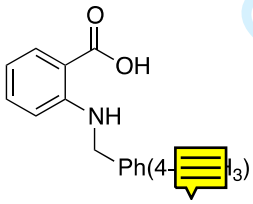
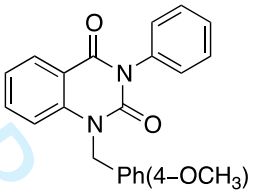
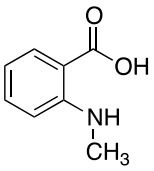
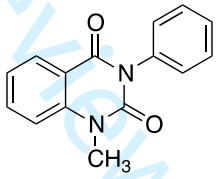
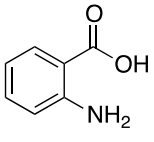
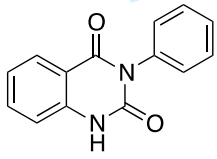
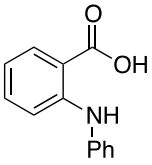
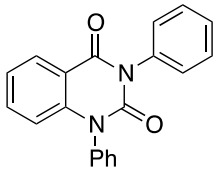
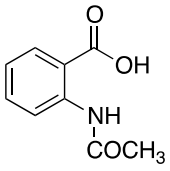
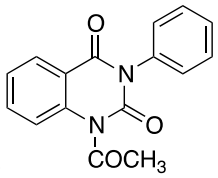
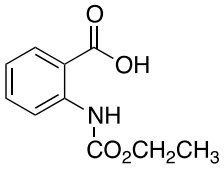
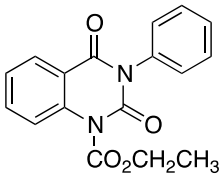
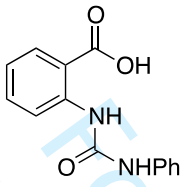
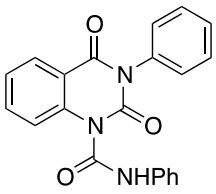
in the reaction. We believed that the electron-rich benzene ring increased the nucleophilicity of nitrogen resulting in high yields of corresponding products. The 2-(benzylamino)-4-methylbenzoic acid also gave high yield of the corresponding product, 80% (**3m**).

Table 2 Quinazolinediones from other substituents of nitrogen of 2-amino benzoic acid[a]



Entry	2	3	Yield[b]
1	 **2a**	 **3a**	74
2	 **2h**	 **3n**	74
3	 **2i**	 **3o**	82
4	 **2j**	 **3p**	50
5	 **2k**	 **3q**	0

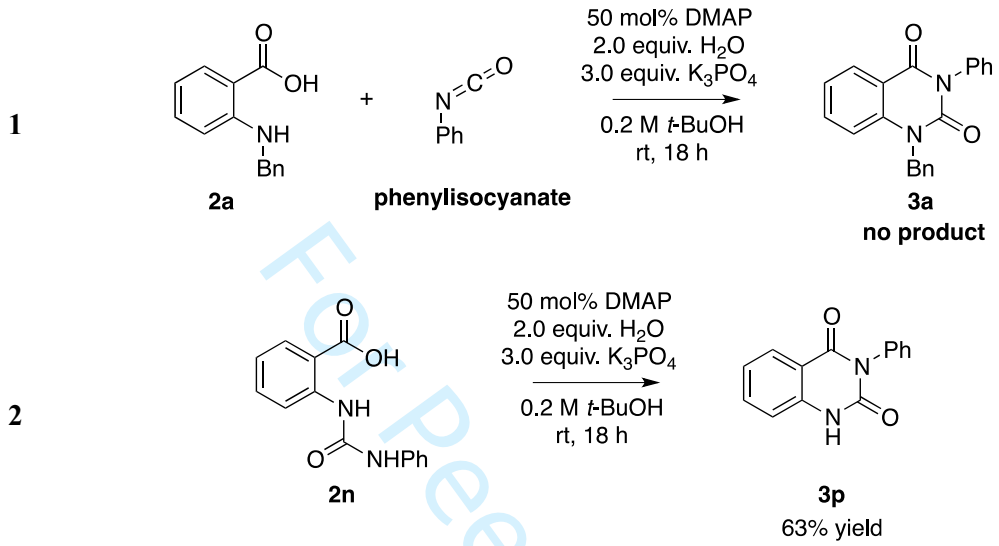
6	 **2l**	 **3r**	0
7	 **2m**	 **3s**	0
8	 **2n**	 **3t**	0

[a]Reaction condition: All reactions were performed with 1.0 mmol of **2**, 1.2 equiv. of **1a** in 5.0 mL of *t*-BuOH in round bottom flask. [b]Isolated yield.

The electronic effect of the benzene ring was crucial due to the nucleophilicity of the nitrogen. Then, we explored a variety of nitrogen substituents of 2-aminobenzoic acids (Table 2). Comparable yields of the benzyl or *para*-methoxybenzyl substituted 2-amino benzoic acid were observed. Both gave products in 74% yields (entries 1 and 2). A slightly increased yield was obtained from a *N*-methyl substituent presumably due to less steric hindrance of methyl substituent providing the product in 82% (entry 3). The product yield was dramatically diminished down to 50% when 2-aminobenzoic acid **2j** was used (entry 4). Moreover, 2-aminobenzoic acids having electron delocalization substituents, such as phenyl, acetyl, carbamate and urea gave no yield of the corresponding products (entries 5–7). The results also suggested that nucleophilic nitrogen of 2-aminobenzoic acids was important. Interestingly, although the reaction of 2-(3-phenylureido)benzoic acid (**2n**) did not gave an expected product **3t**, instead 3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**3p**) was obtained (entry 8). The result enlightened us a clue of the chemical transformation in which a possible intermediate of the reaction was the urea adduct.

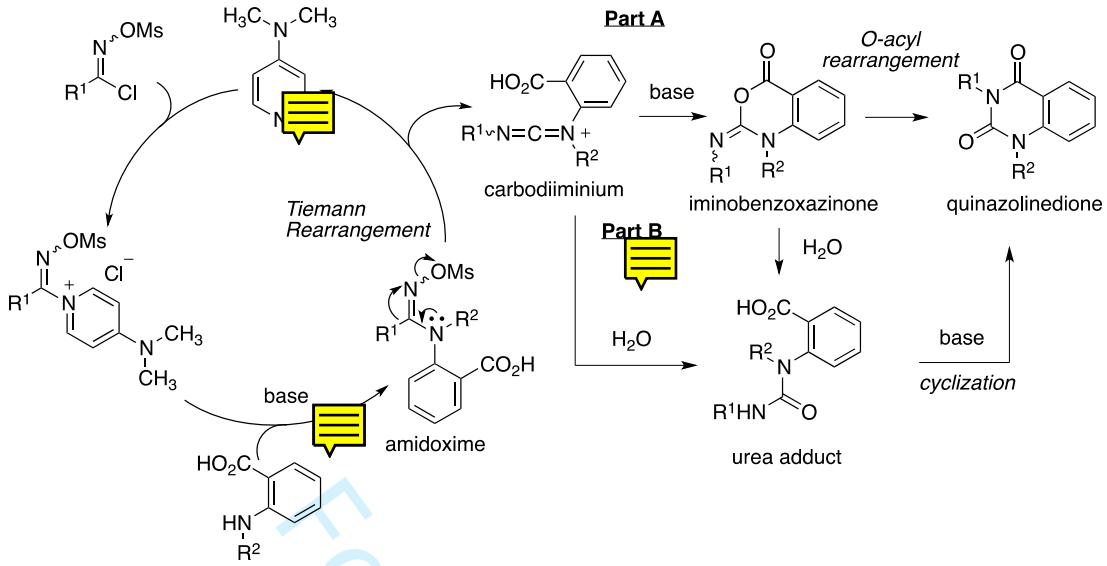
In order to propose mechanism of the reaction, we did two control experiments (Scheme 4). We excluded out of the *in situ* formation of isocyanate from *α*-chloroaldoxime *O*-methanesulfonate due to no formation of **3a** from the reaction of phenylisocyanate and **2a** (Scheme 4, 1). Noteworthy, we also observed the same result from our previous work on the

synthesis of imidazolin-2-one.[14] Since we observed and isolated **3p** from **2n** (Table 2, entry 8), we did the second control experiment by applying **2n**, presumably a possible intermediate, to the reaction condition. Nicely, **3p** was obtained in 63% yield (Scheme 4, 2) showing that the urea adduct could undergo cyclization under the reaction condition. Based on the result and better yield in the presence of H_2O, the urea adduct could highly be an intermediate for the reaction.



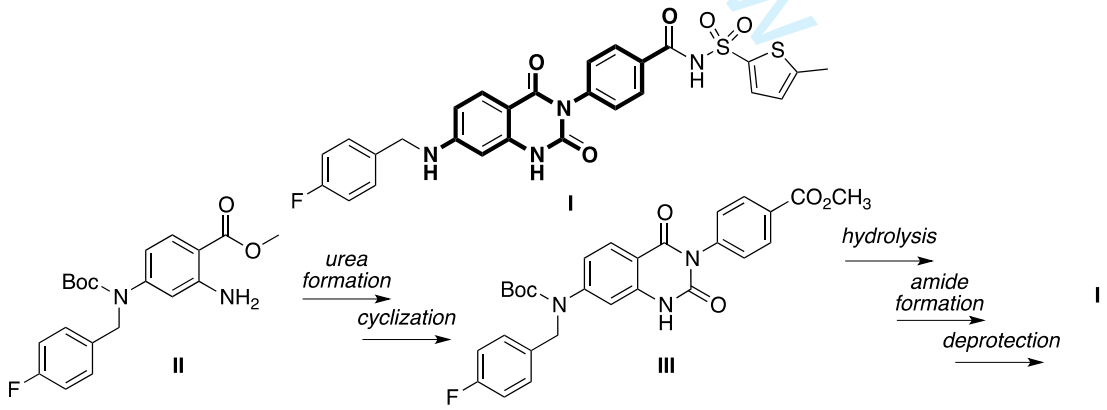
Scheme 4 Control experiments

Therefore, the possible mechanism of the quinazolinedione formation was postulated *via* DMAP-catalyzed substitution reaction of 2-aminobenzoic acid and *α*-chloroaldoxime *O*-methanesulfonate to generate amidoxime followed by Tiemann rearrangement to give carbodiiminium intermediate.[15] Although the control experiment suggested the pathway involving the formation of urea adduct, we could not rule out the possibility of a formation of iminobenzoxazinone intermediate. The iminobenzoxazinone intermediates were known to undergo rearrangement to provide a corresponding quinazolinediones. Additionally, Beutner and co-workers could divergently synthesized quinazolinediones and iminobenzoxazinones.[12b] Their finding confirmed the exist of the intermediate. Consequently, we proposed two possible pathways. Firstly, the carbodiiminium underwent intramolecular C–O bond formation to form the iminobenzoxazinone intermediate. The intermediate could rearrange from O−acyl to N−acyl to give the product quinazolinedione directly. Alternatively, the iminobenzoxazinone intermediate could undergo ring opening in the presence of H_2O to give the urea adduct (Scheme 5, pathway A). On the other hand, the carbodiiminium and H_2O could form a corresponding urea adduct, followed by intramolecular amide cyclization in the presence of base to provide the product (Scheme 5, pathway B).



Scheme 5 Possible mechanism

This methodology was highly suitable to synthesize quinazolinediones having electron-withdrawing group substituted aryl ring on nitrogen at the second position. Interestingly, we found that Scarborough and co-workers reported their quinazolinedione analogues showing an inhibition of aggregation of ADP-platelet (ADP: adenosine 5'-diphosphate), particularly in a treatment of thrombosis and thrombosis related conditions or disorder (Scheme 6).[16] One of their best compounds was 4-(7-((4-fluorobenzyl)amino)-2,4-dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)-*N*-((5-methylthiophen-2-yl)sulfonyl)benzamide (I) showing IC_{50} < 10 μM toward PRP assay (PRP: Platelet-rich plasma).



Scheme 6 Quinazolinedione derivative from Scarborough finding.

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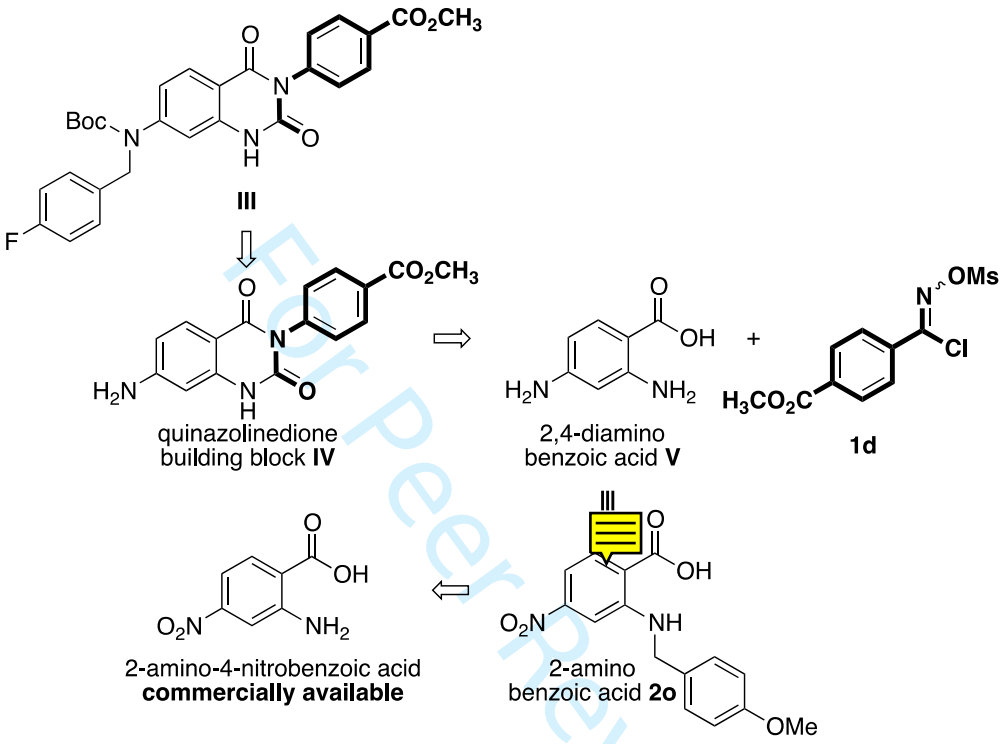
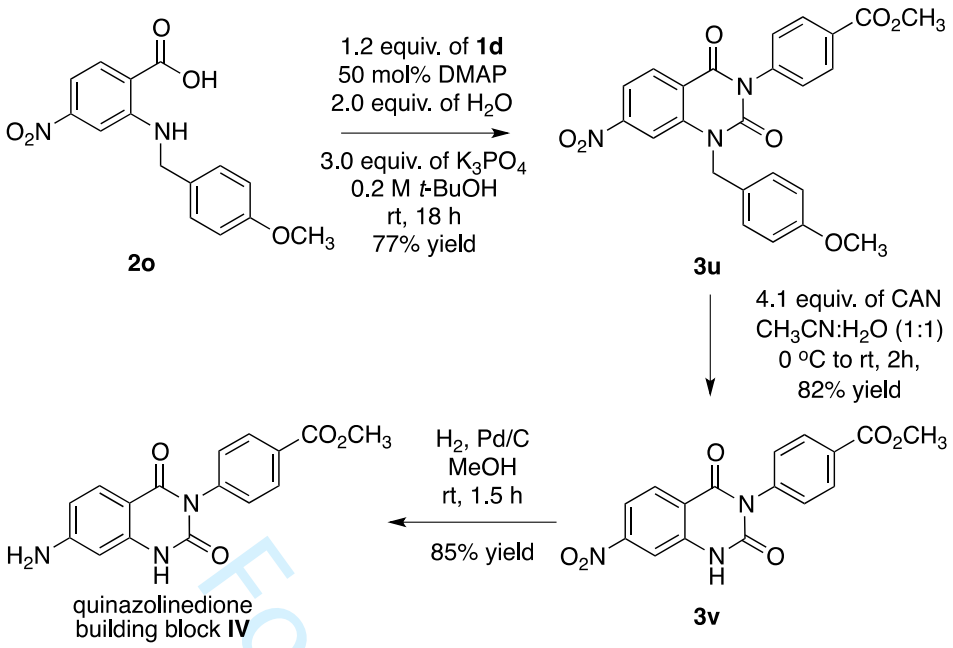
The preparation in Scarborough's report started with two-step procedures (urea formation and cyclization) from a 2-aminobenzoate **II** to give quinazolinedione **III**. Then **III** underwent hydrolysis and amide formation with a proper amine followed by Boc deprotection to obtain the product **I**. The urea formation was heavily depended on two methods. The first was the reaction of **II** with corresponding isocyanates. On the other hand, the second method was the reaction of **II** with phosgene and corresponding amines.



Scheme 7 Synthesis plan for quinazolinedione building block

Based on the Scarborough finding, we envisioned that we could apply our methodology to provide synthetically useful building block for their compounds as an alternative method due to limitation of isocyanate availability and toxic reagent, such as phosgene (Scheme 7). Consideration of their intermediate **III**, we found that the *N*-aryl ester moiety could be derived from a favored electron-withdrawing substituted *α*-chloroaldoxime *O*-methanesulfonate **1d**. The other reaction partner would be an equivalent of 2,4-diaminobenzoic acid **V**. Having two free amino groups might be problematic due to regioselectivity and undesired reactions. Therefore, we selected *N*-(4-methoxybenzyl)-4-nitro-2-aminobenzoic acid (**VI**) as a reaction partner.



Scheme 8 The preparation of quinazolinedione building block

Good yield, 77%, of a corresponding quinazolinedione was obtained from *N*-(4-methoxybenzyl)-4-nitro-2-aminobenzoic acid and **1d** under the optimal reaction condition (Scheme 8). The attempts for deprotection of 4-methoxybenzyl in the same time as reduction of nitro group were failed. However, deprotection of 4-methoxybenzyl was achieved in the presence of CAN[17] to provide a desired quinazolinedione **3v** in 82% yield. Lastly, we obtained the quinazolinedione building block **IV** in 85% yield from a reduction of nitro *via* hydrogenation in the presence of Pd/C in methanol.

Conclusion

We have herein demonstrated the facile synthesis of quinazolinedione derivatives *via* DMAP-catalyzed domino reactions of *α*-chloroaldoxime *O*-methanesulfonates and 2-(benzylamino)benzoic acids under mild condition and simple preparation. We found that the nucleophilicity of nitrogen of 2-(benzylamino)benzoic acids was crucial resulting in good yields of products from 2-(benzylamino)benzoic acids bearing electron-donating substituents on benzene ring. Although substituents of nitrogen were limited to alkyl groups, common benzyl or *p*-methoxy benzyl substituents are applicable to the reaction. Another key factor of the reaction was the electrophilicity of *α*-chloroaldoxime *O*-methanesulfonates resulting in good yields with electron-withdrawing substituents, and moderate yield from aliphatic *α*-chloroaldoxime *O*-methanesulfonates. We highly believed that the chemical transformation involved the formation of carbodiiminium intermediate, followed by two possible pathways.

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The first was intramolecular cyclization to form iminobenzoxazione followed by rearrangement to give the product. On the other hand, the carbodiiminium reacted with H_2O to form urea adduct. Then, intramolecular amidocyclization took place to give the product. Although high catalyst loading was required in order to drive the reaction to completion, this reaction protocol provided an alternative access to a variety of quinazolinediones and also enriched the chemistry of *α*-chloroaldoxime *O*-methanesulfonates. In addition, we introduced an application of this method to provide quinazolinedione building block for further investigations of biological activities.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at …

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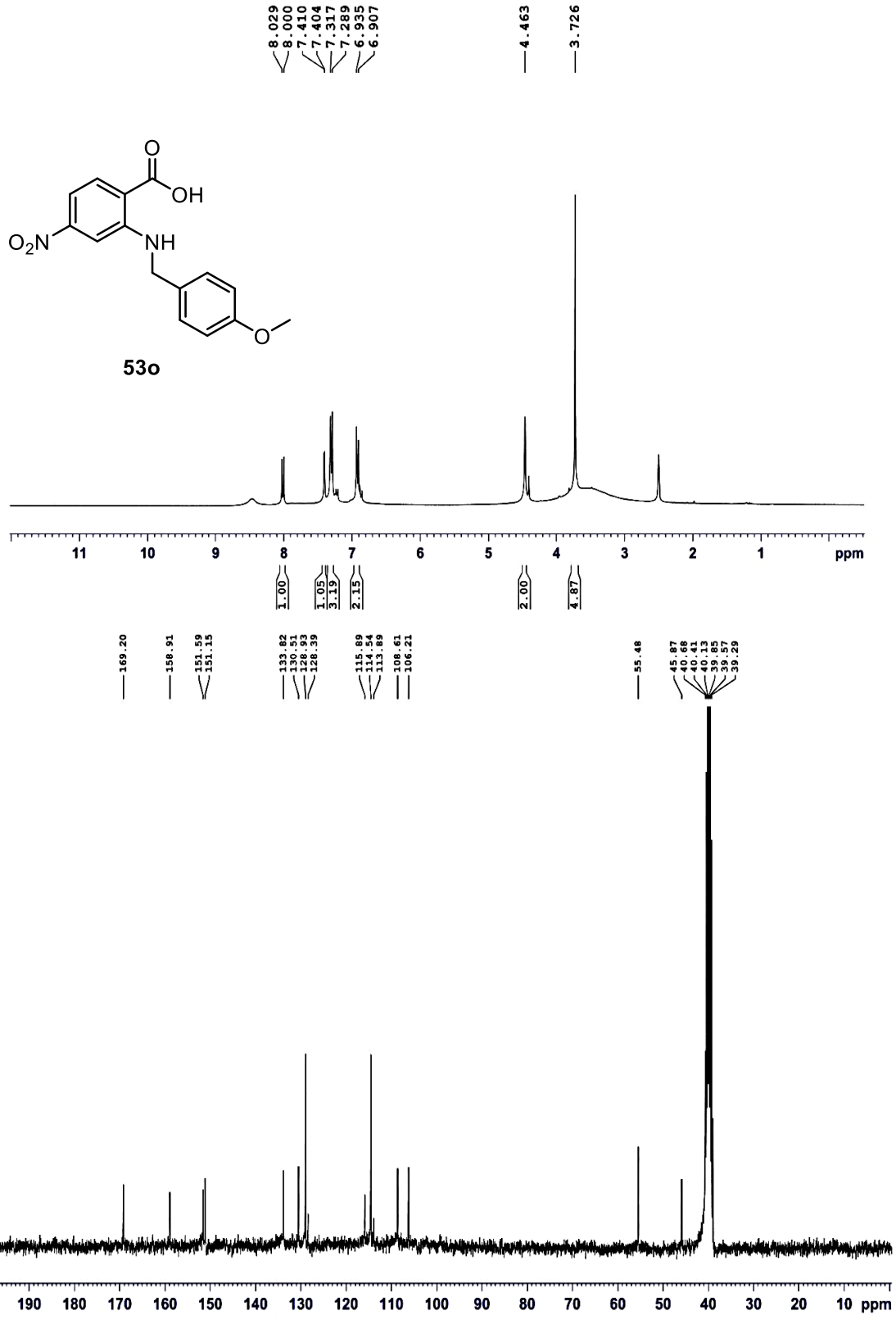
^{1}H and ^{13}C NMR Spectra of New Compound of Starting Material

Figure 5 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **53o** in DMSO- d_6



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

Figure 6 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62a** in $CDCl_3$

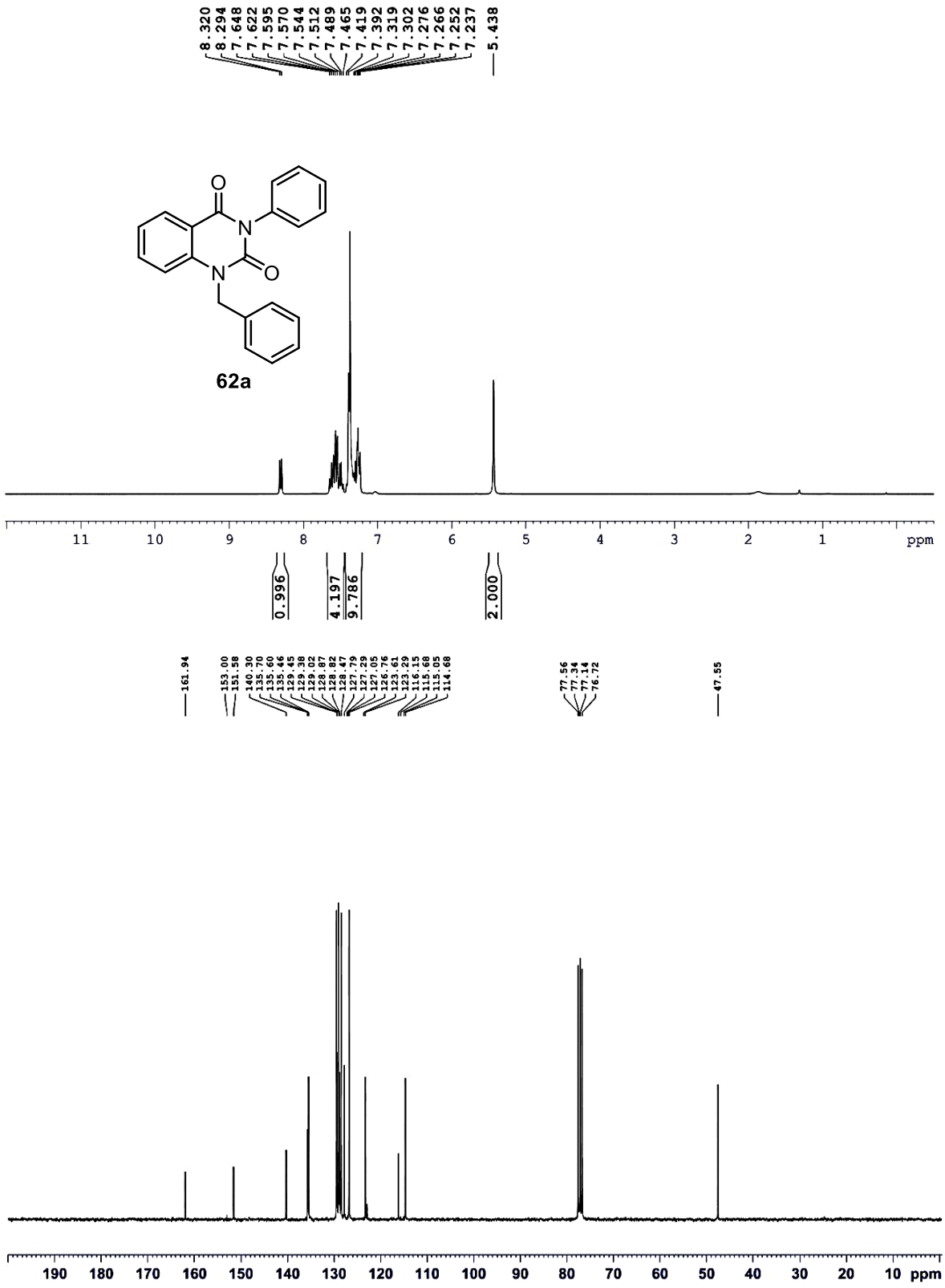


Figure 7 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62b** in $CDCl_3$

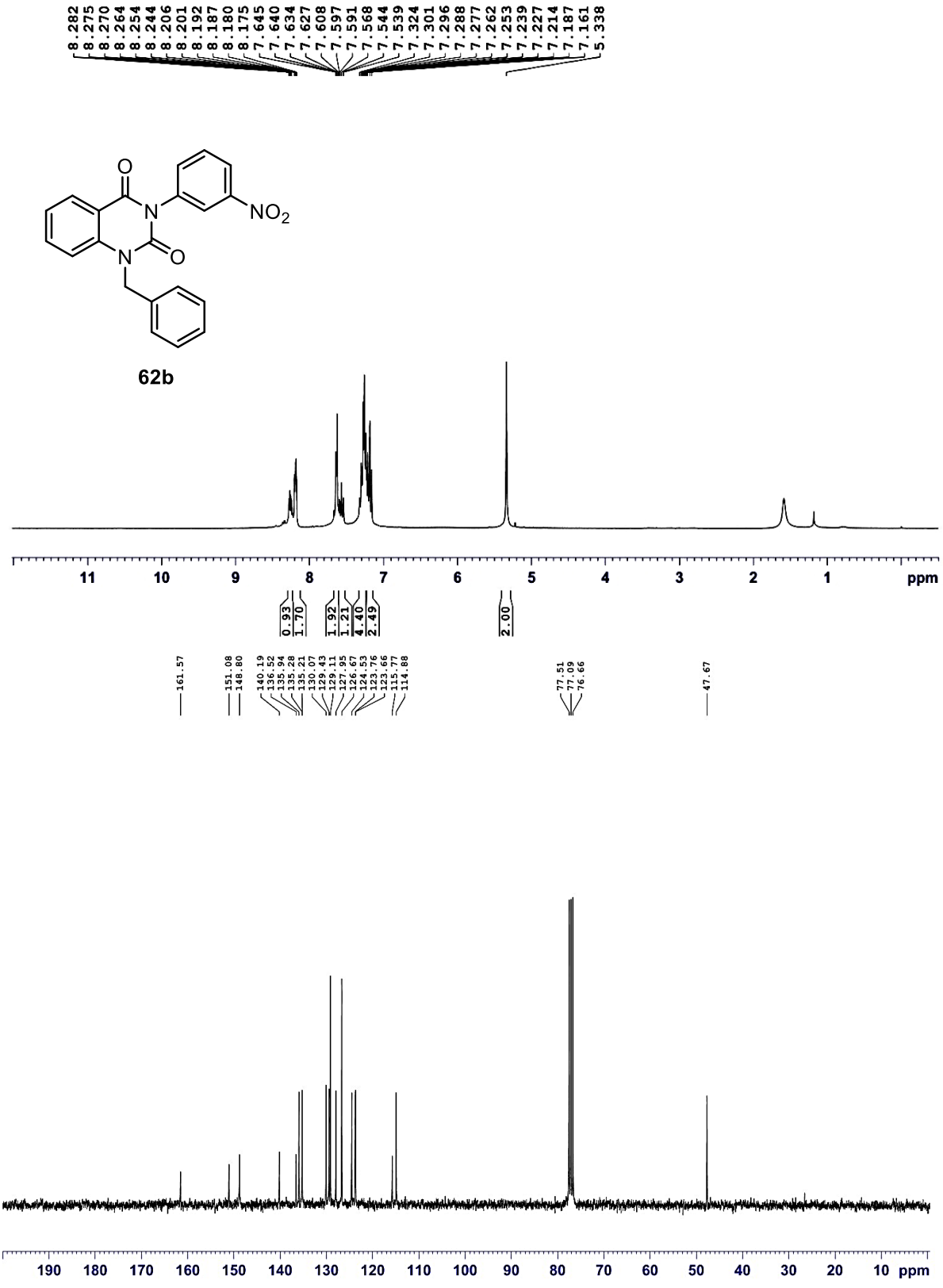


Figure 8 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62c** in $CDCl_3$

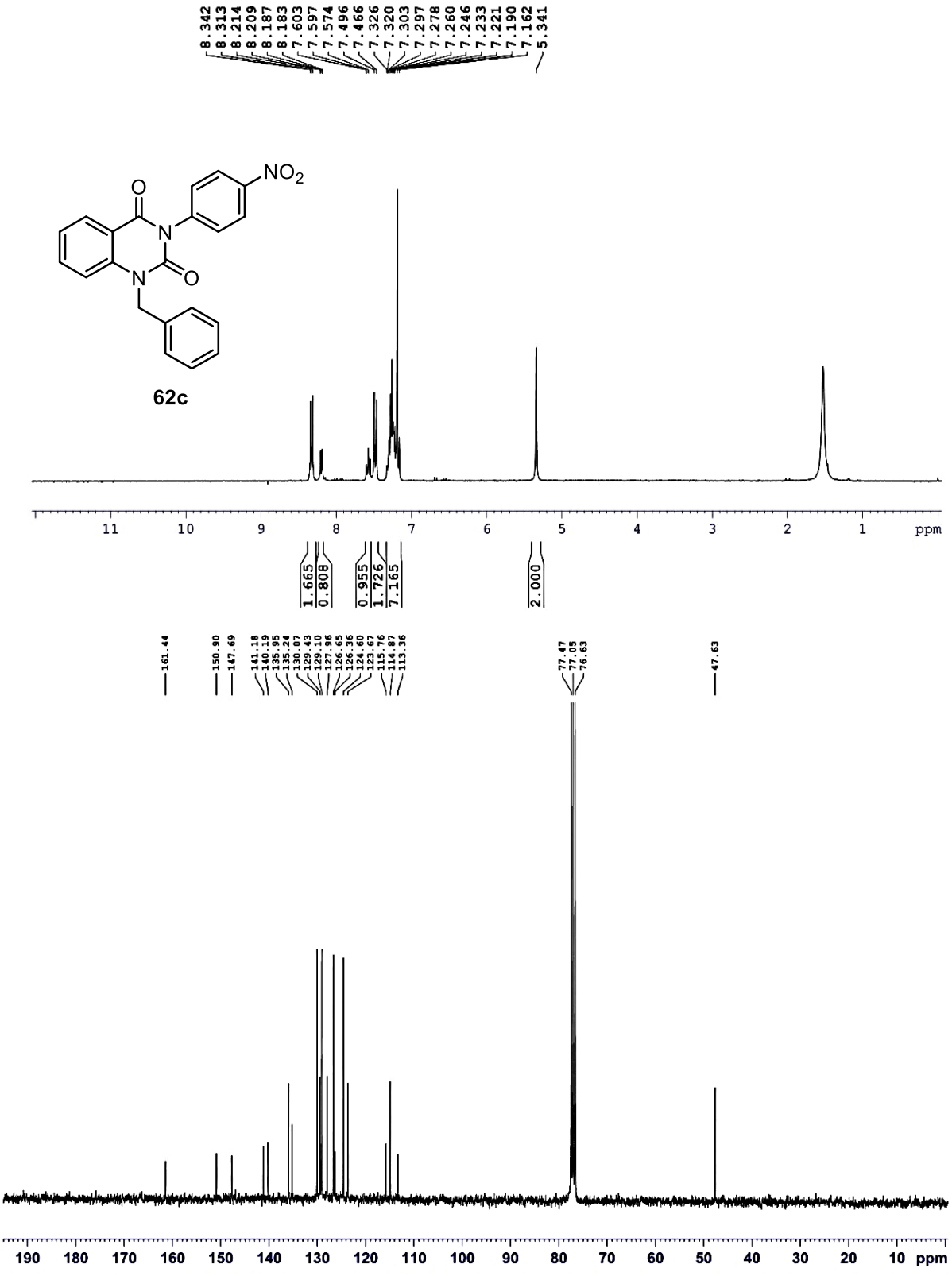


Figure 9 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62d** in $CDCl_3$

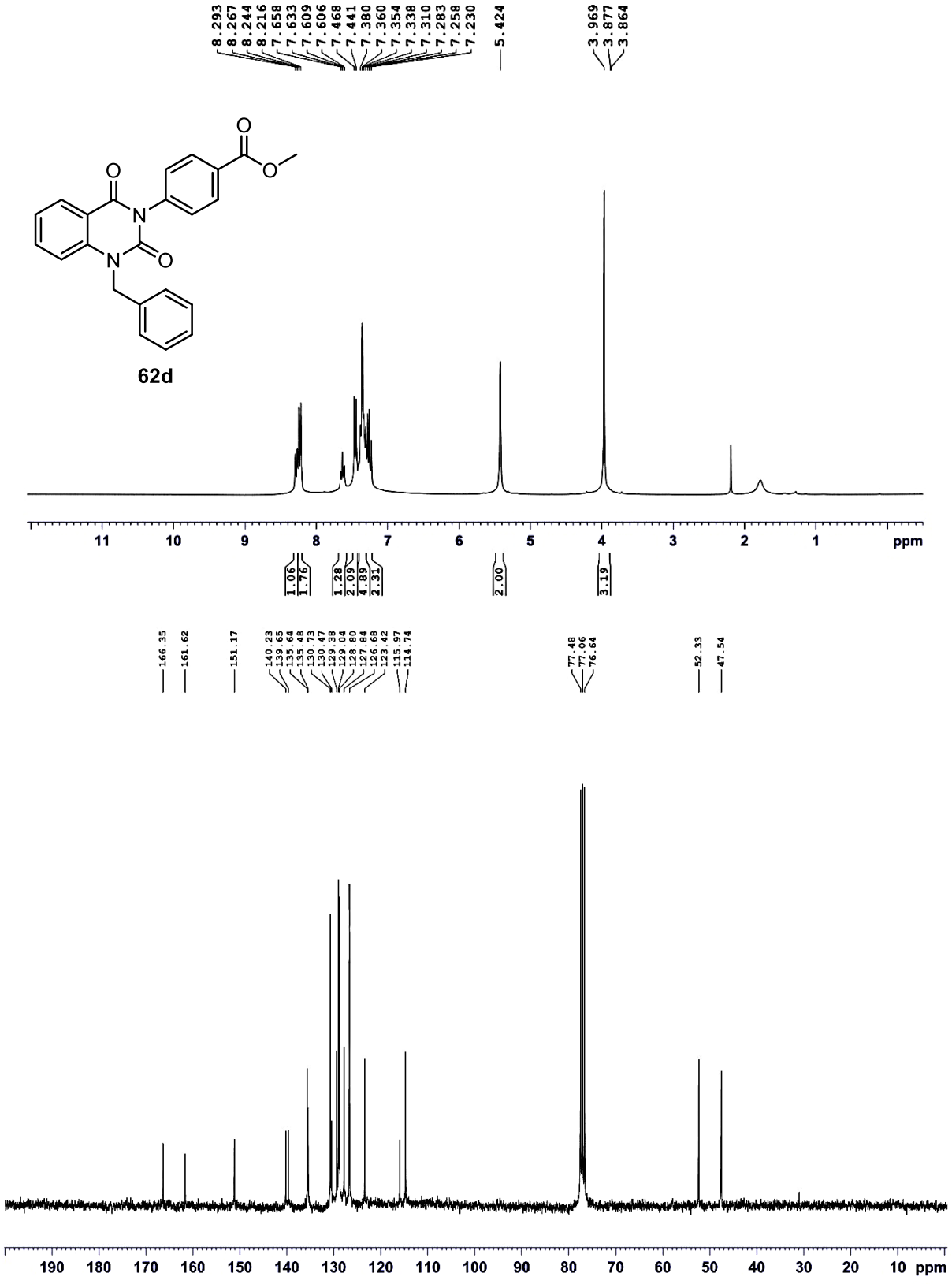


Figure 10 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62e** in $CDCl_3$

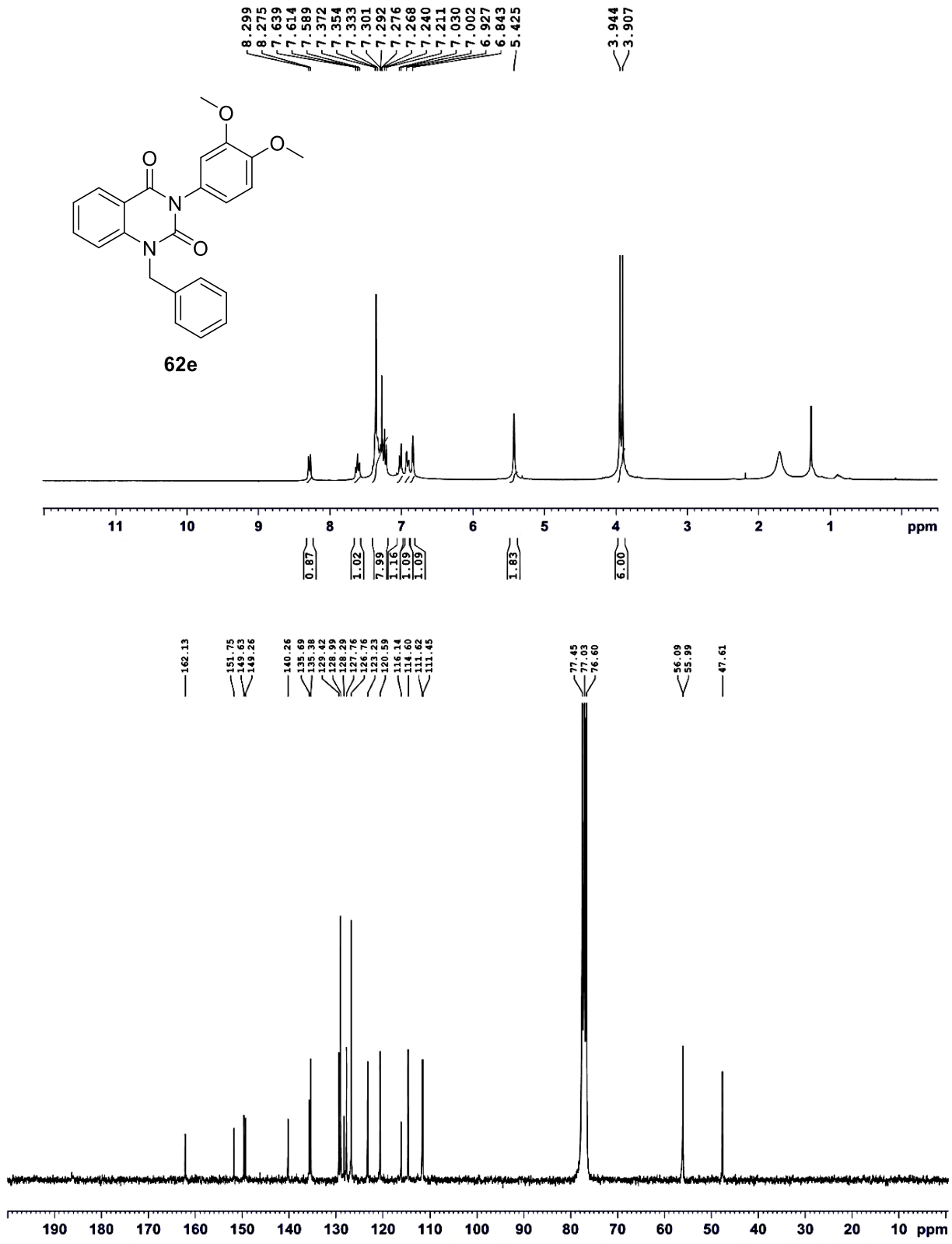


Figure 11 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62f** in $CDCl_3$

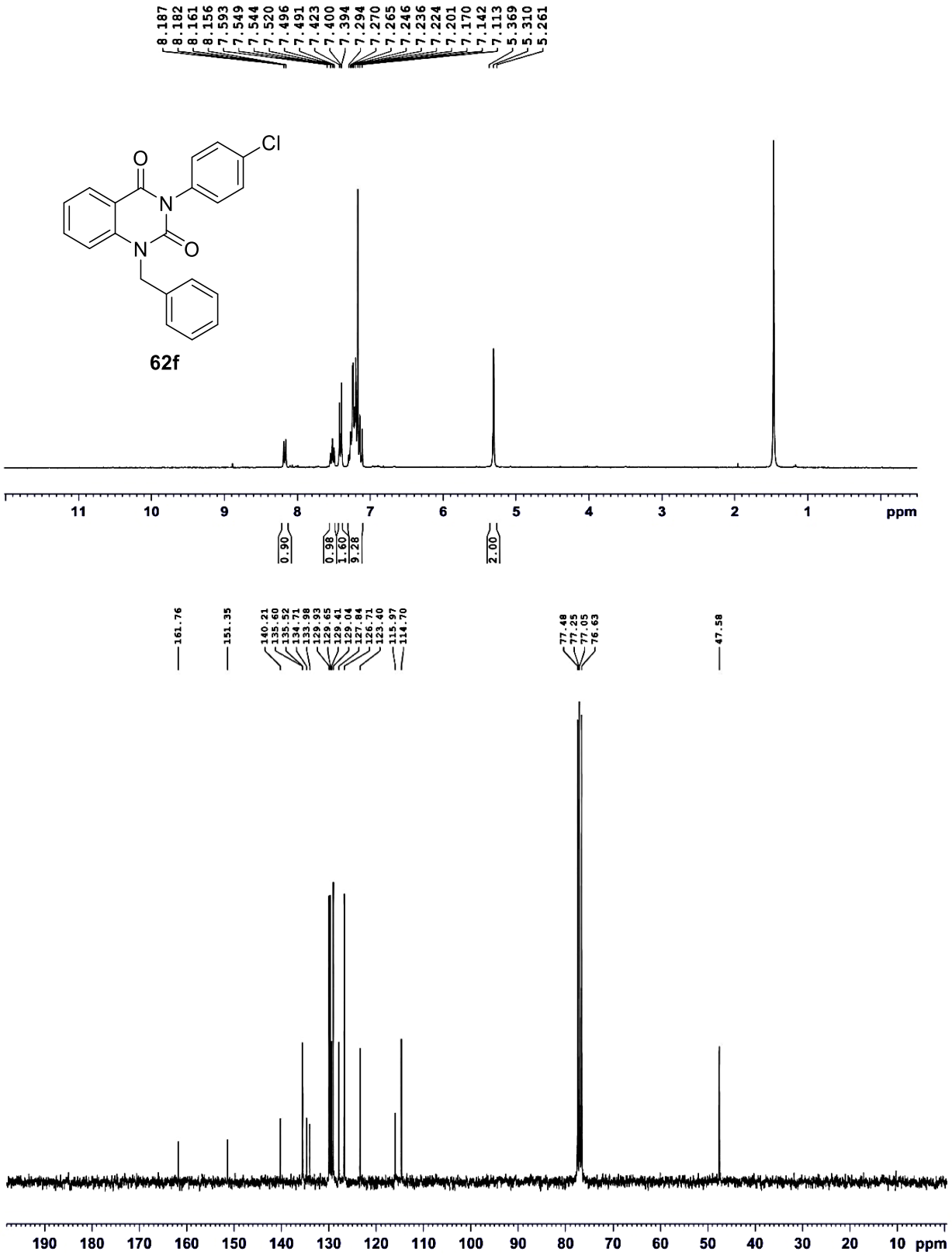


Figure 12 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62g** in $CDCl_3$

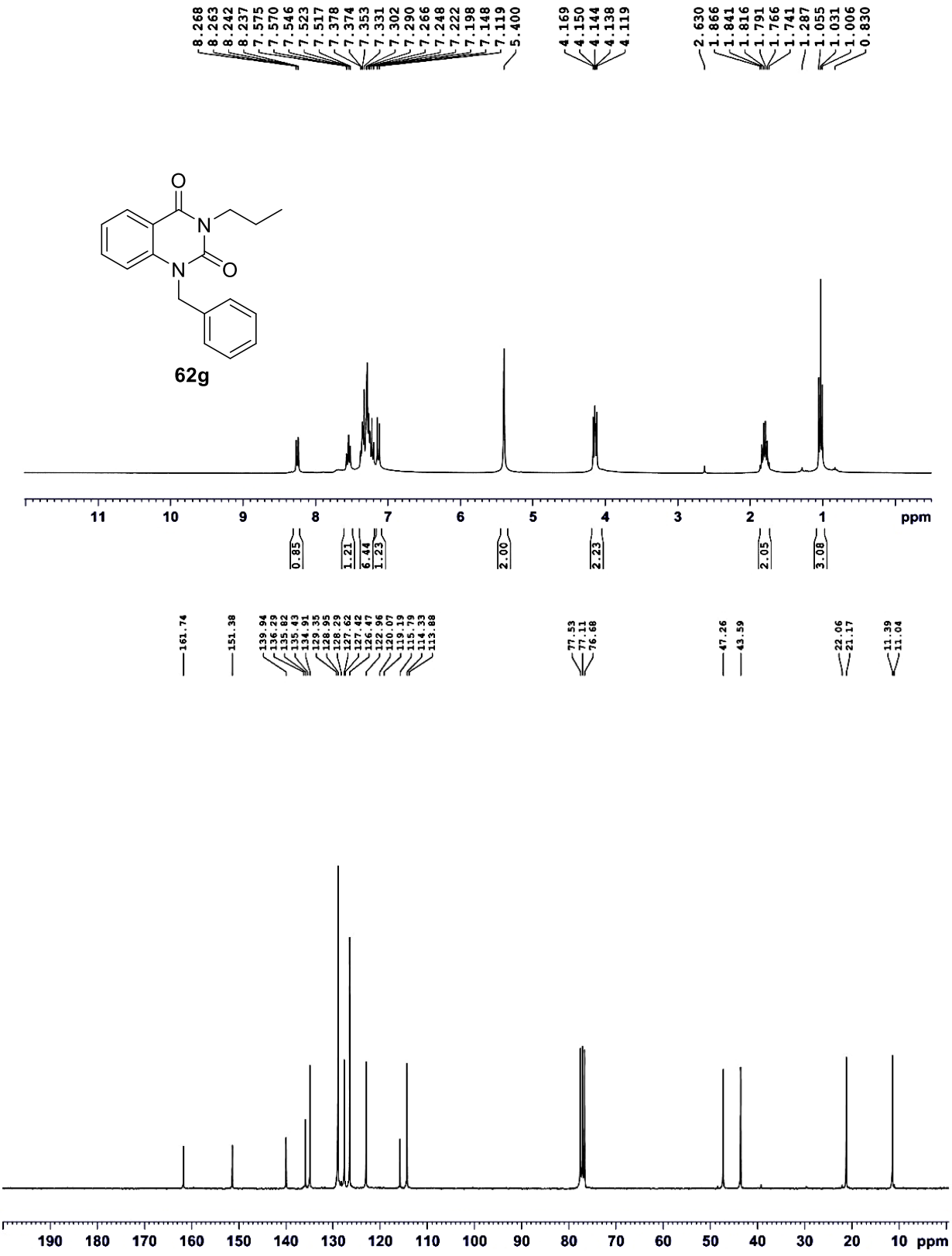


Figure 13 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62h** in $CDCl_3$

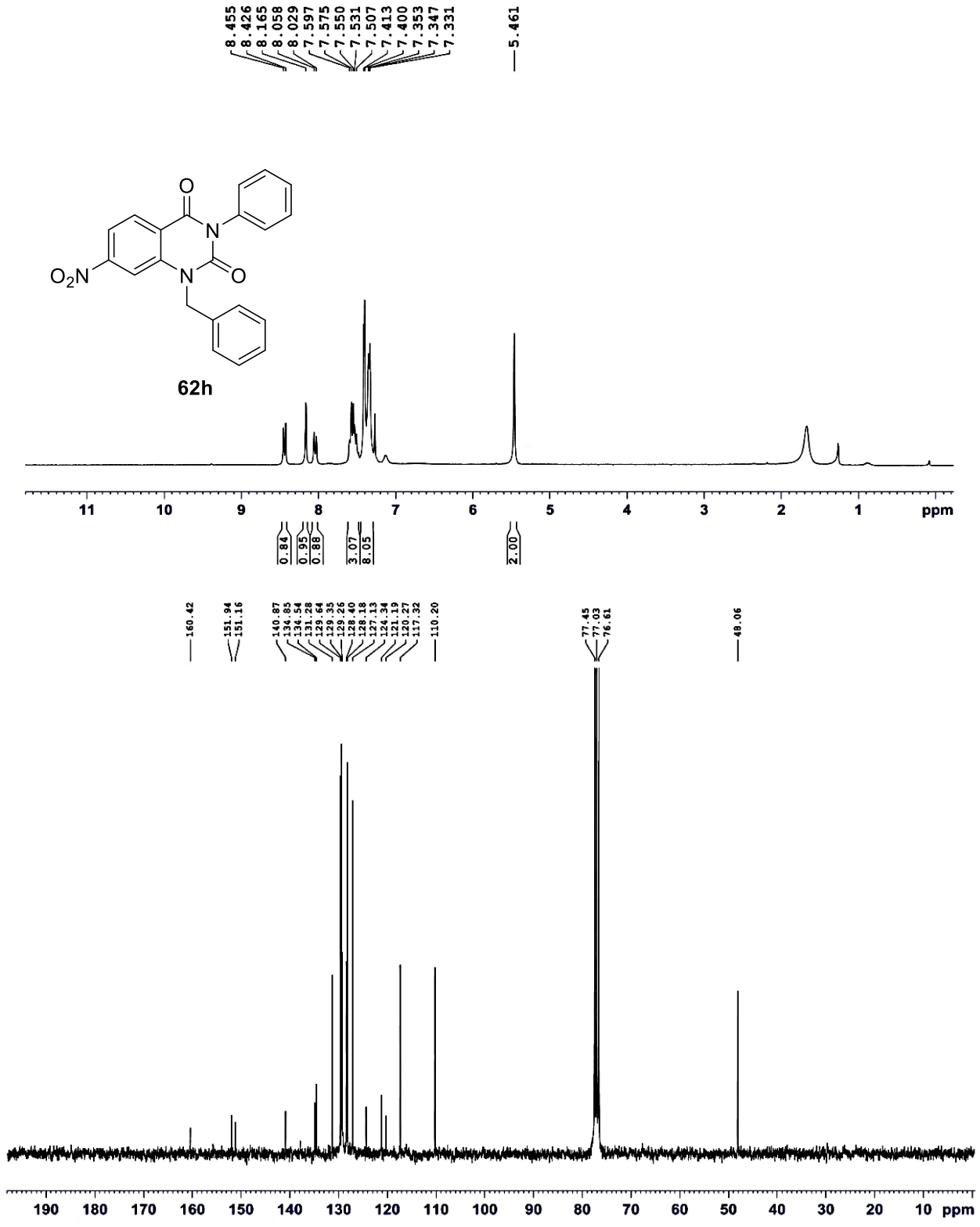


Figure 14 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62i** in $CDCl_3$

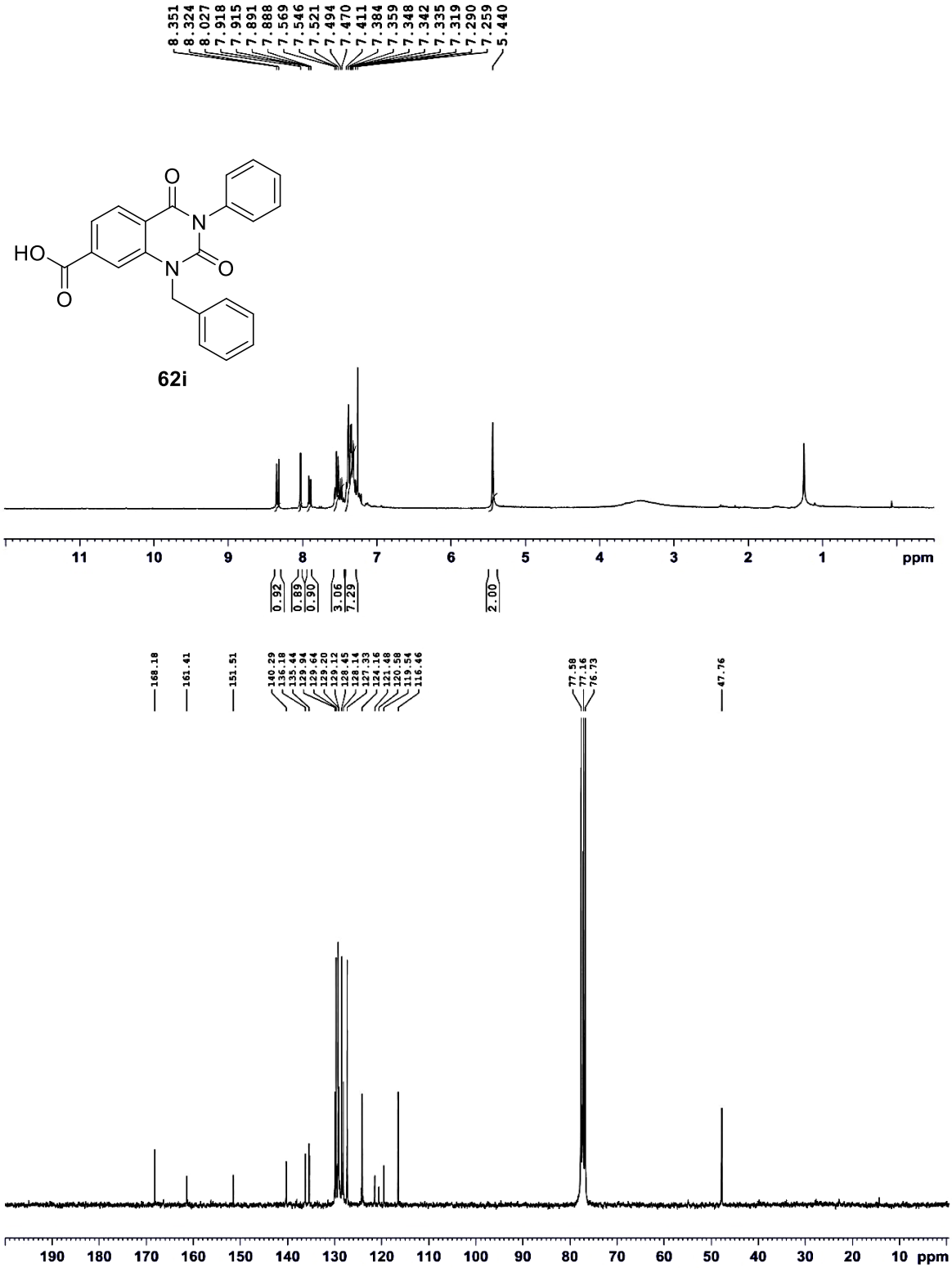


Figure 15 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62j** in $CDCl_3$

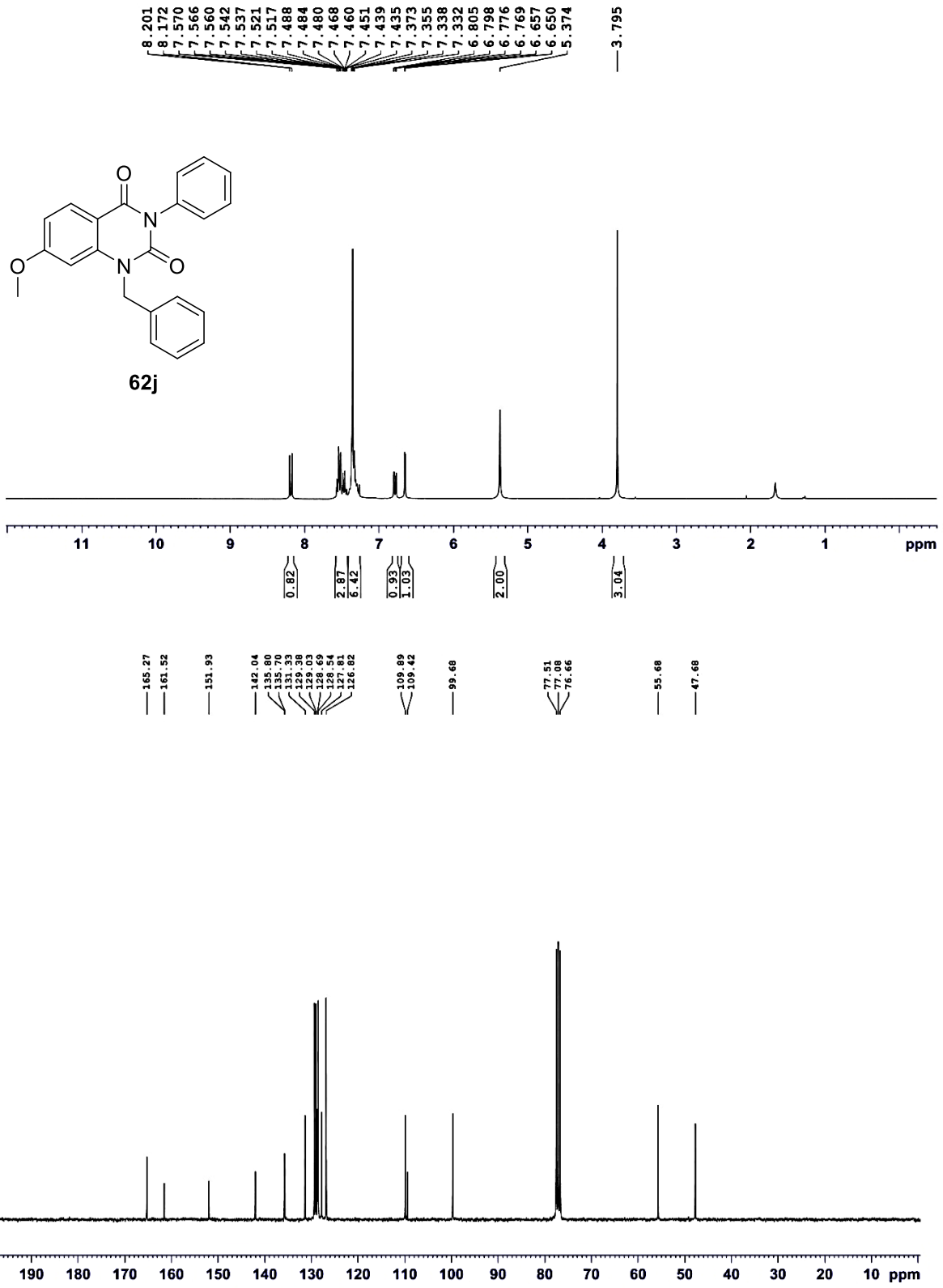


Figure 16 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62k** in $CDCl_3$

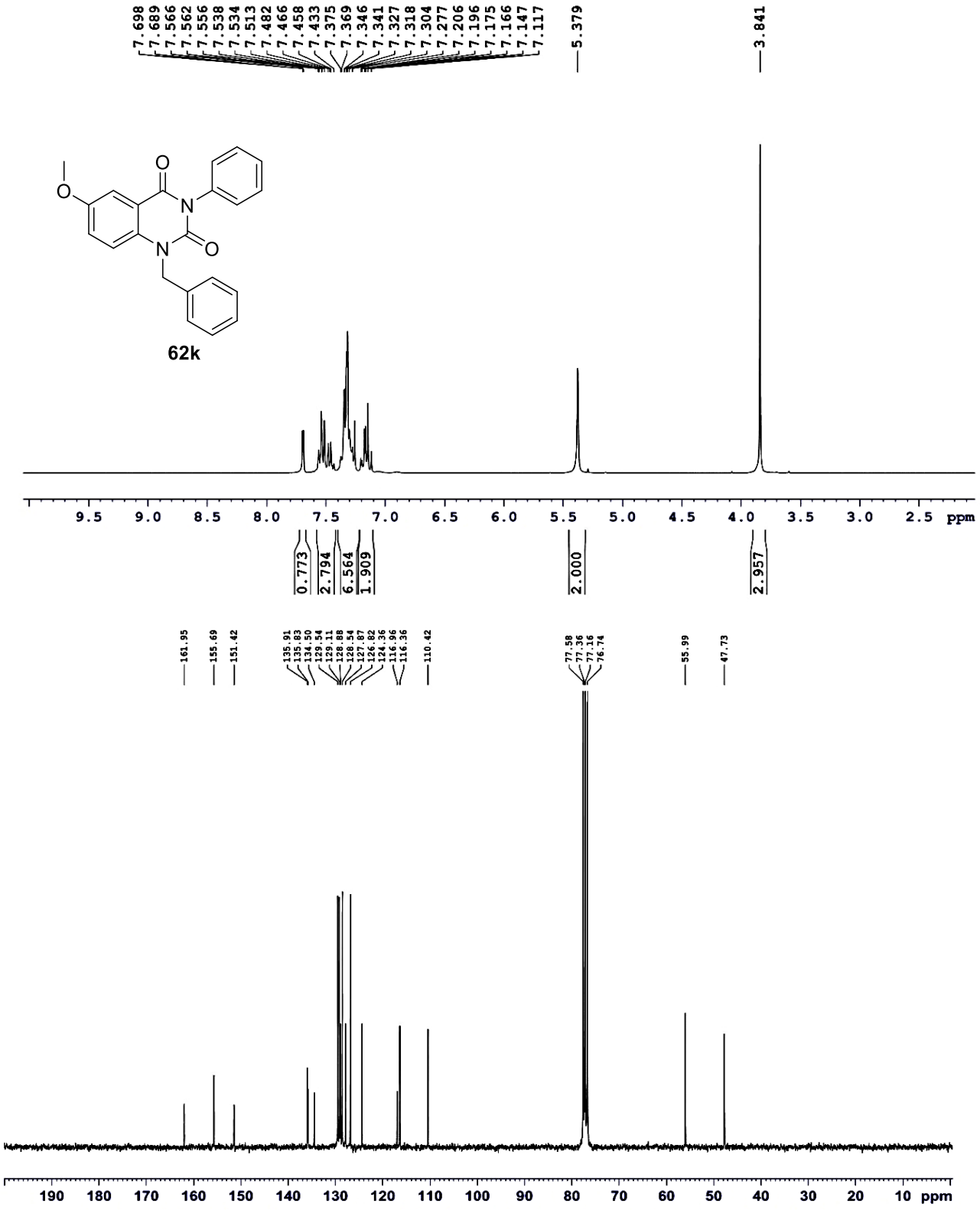


Figure 17 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62l** in $CDCl_3$

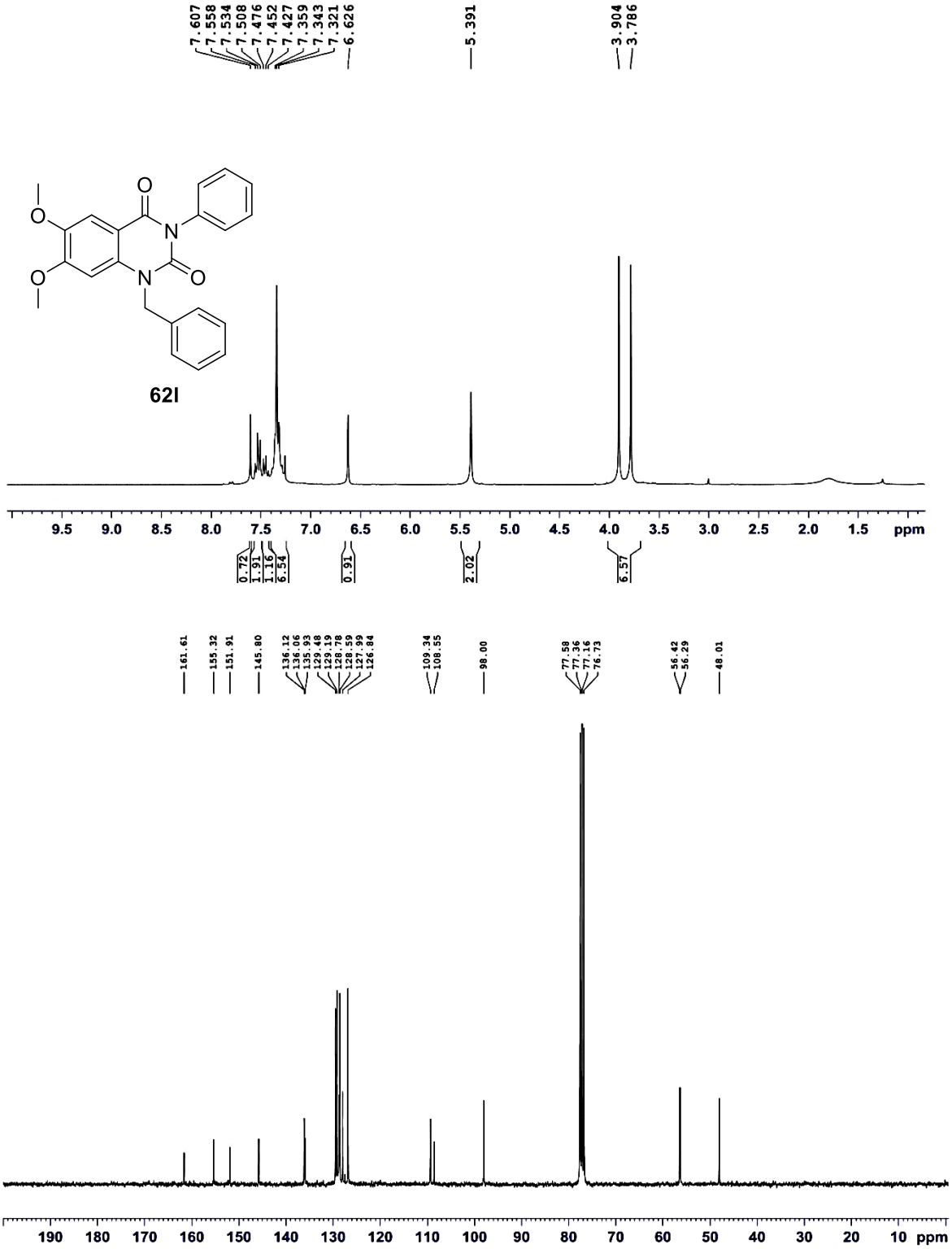


Figure 18 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62m** in $CDCl_3$

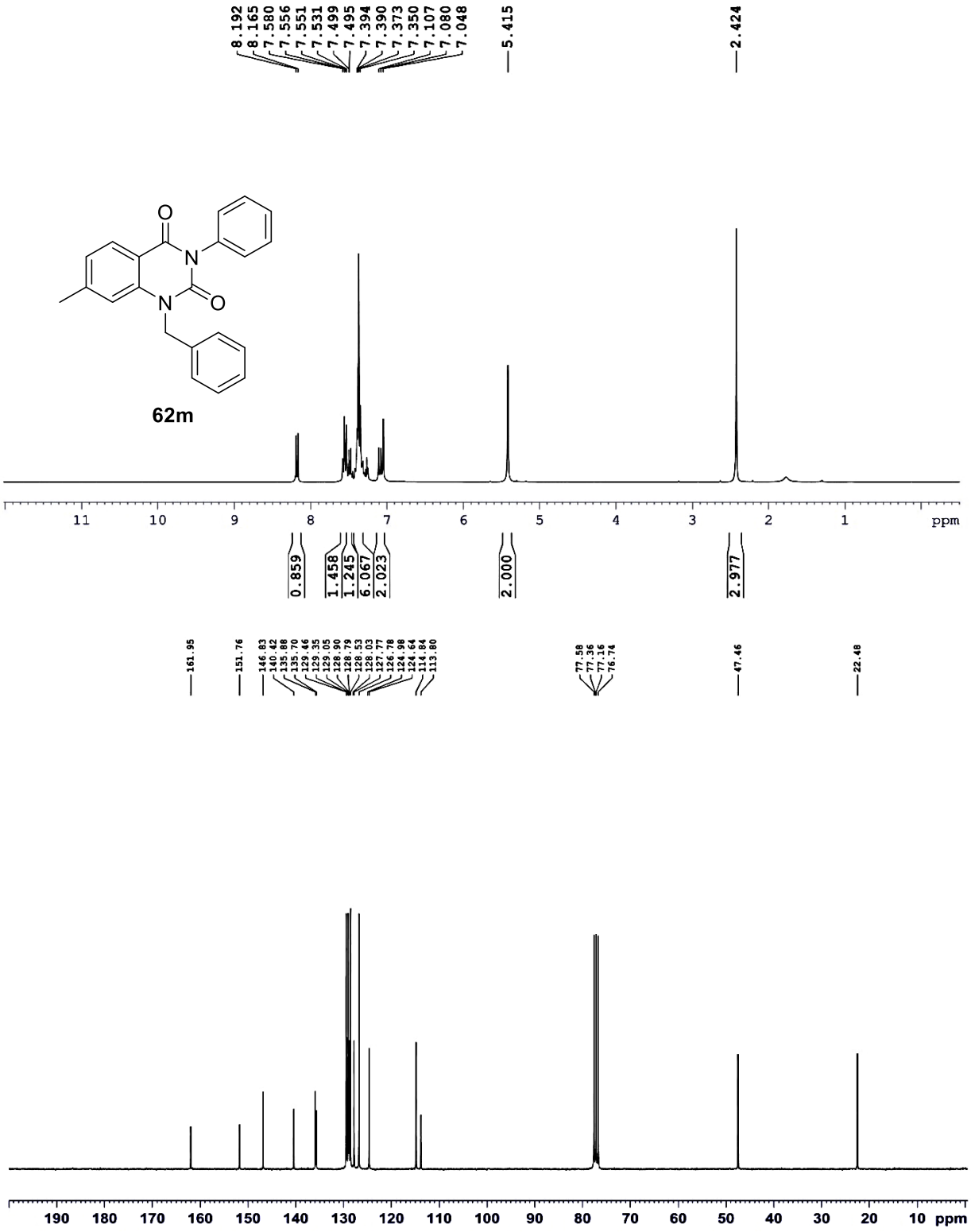


Figure 19 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62s** in $CDCl_3$

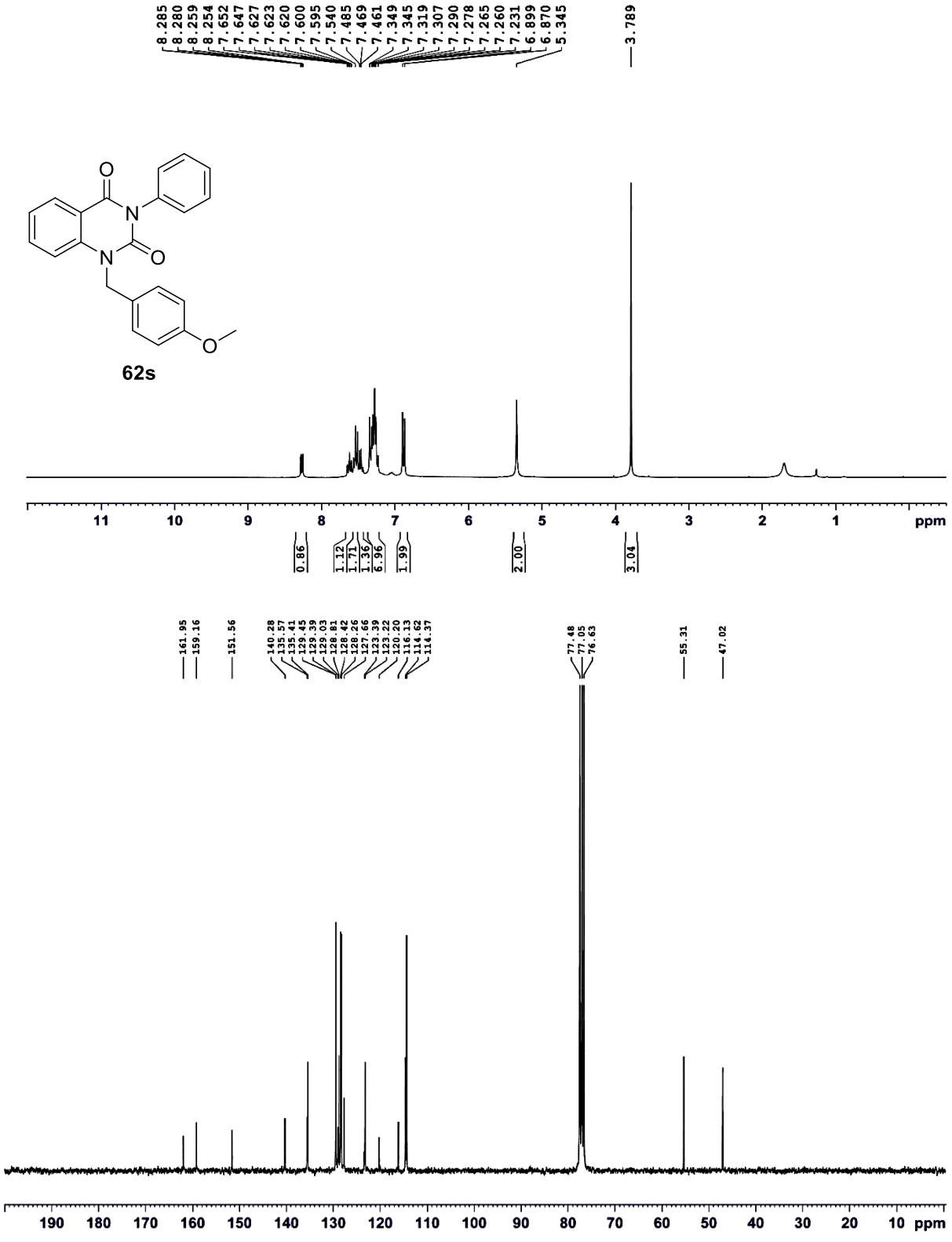


Figure 20 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62u** in $CDCl_3$

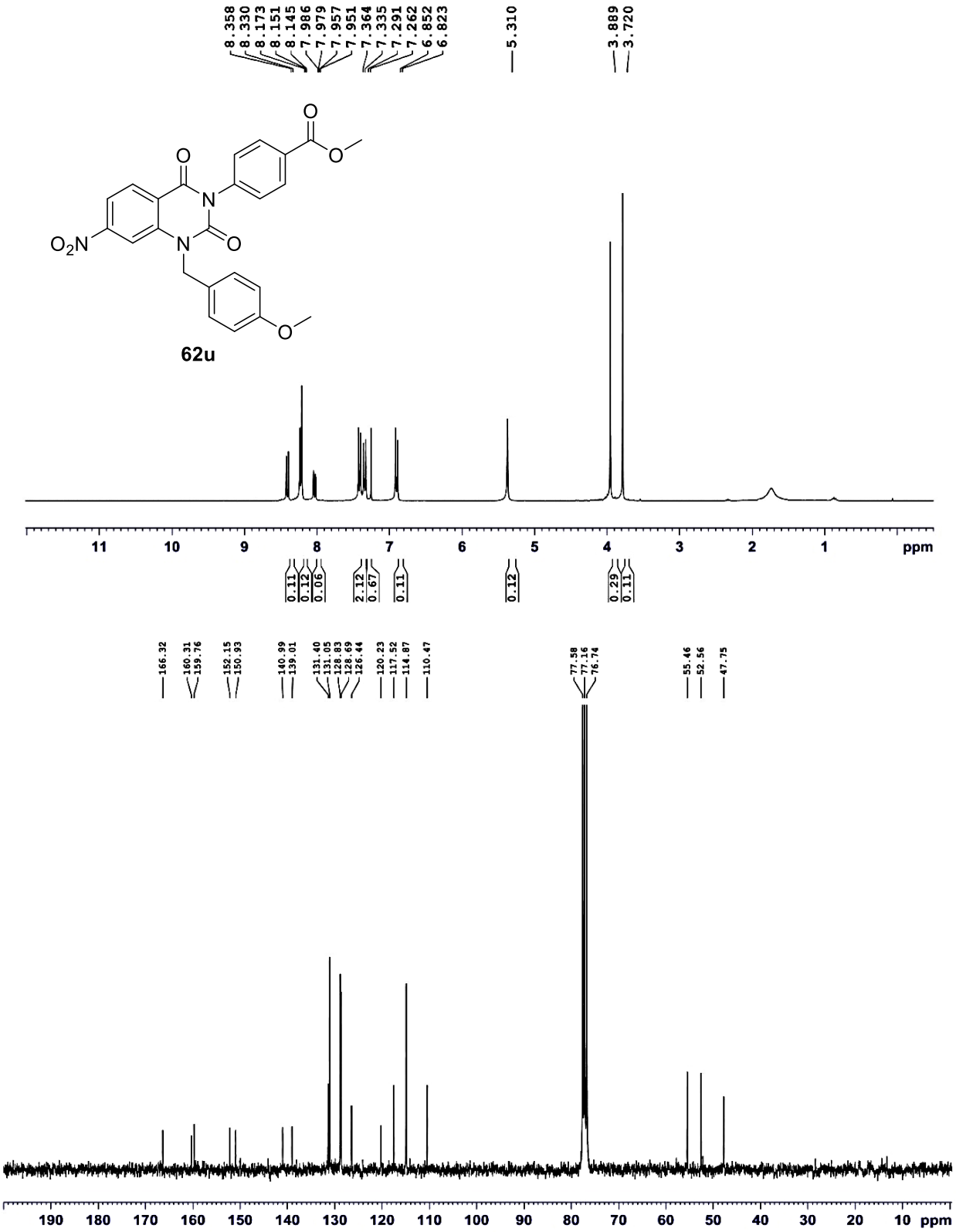


Figure 21 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **62v** in DMSO- d_6

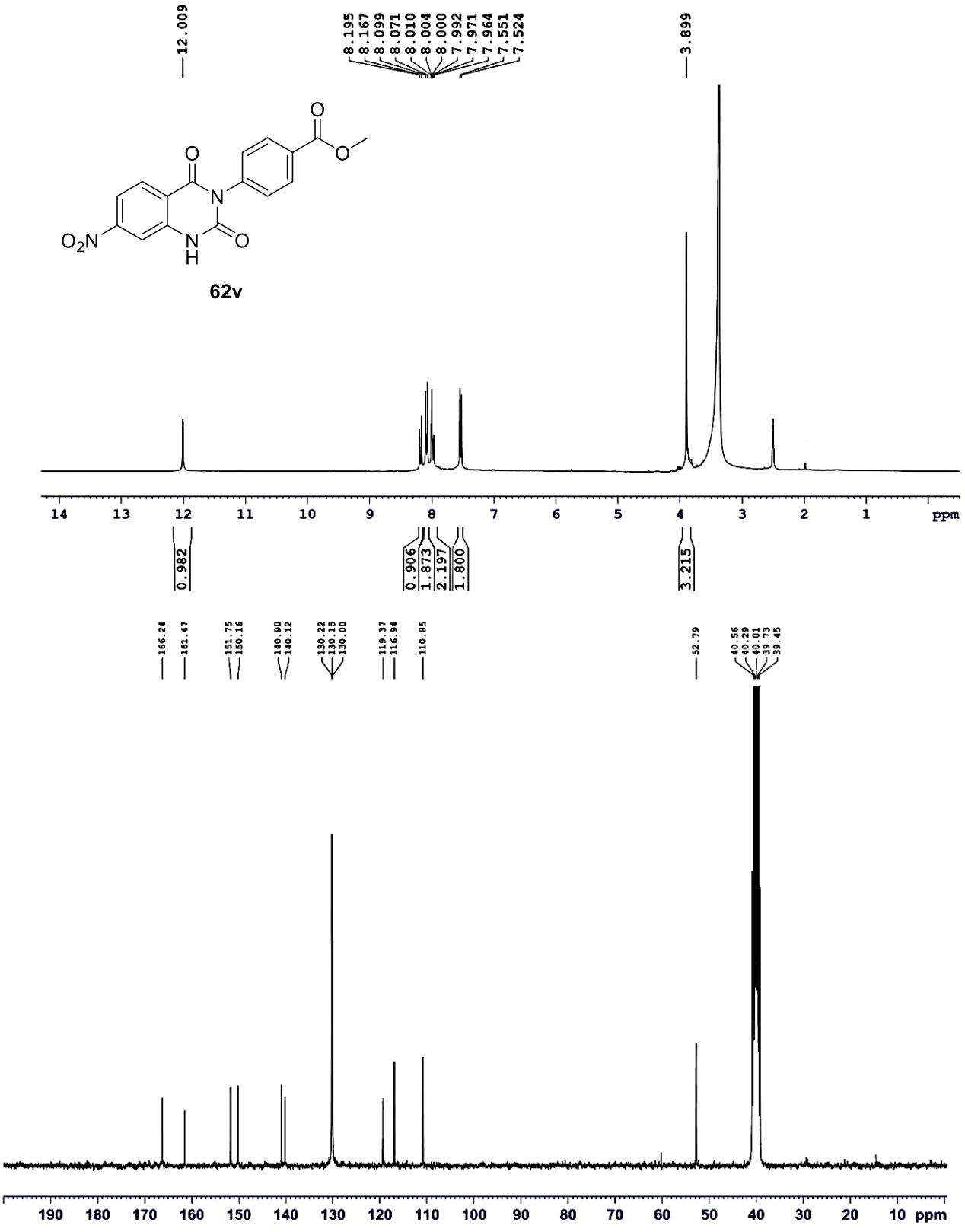
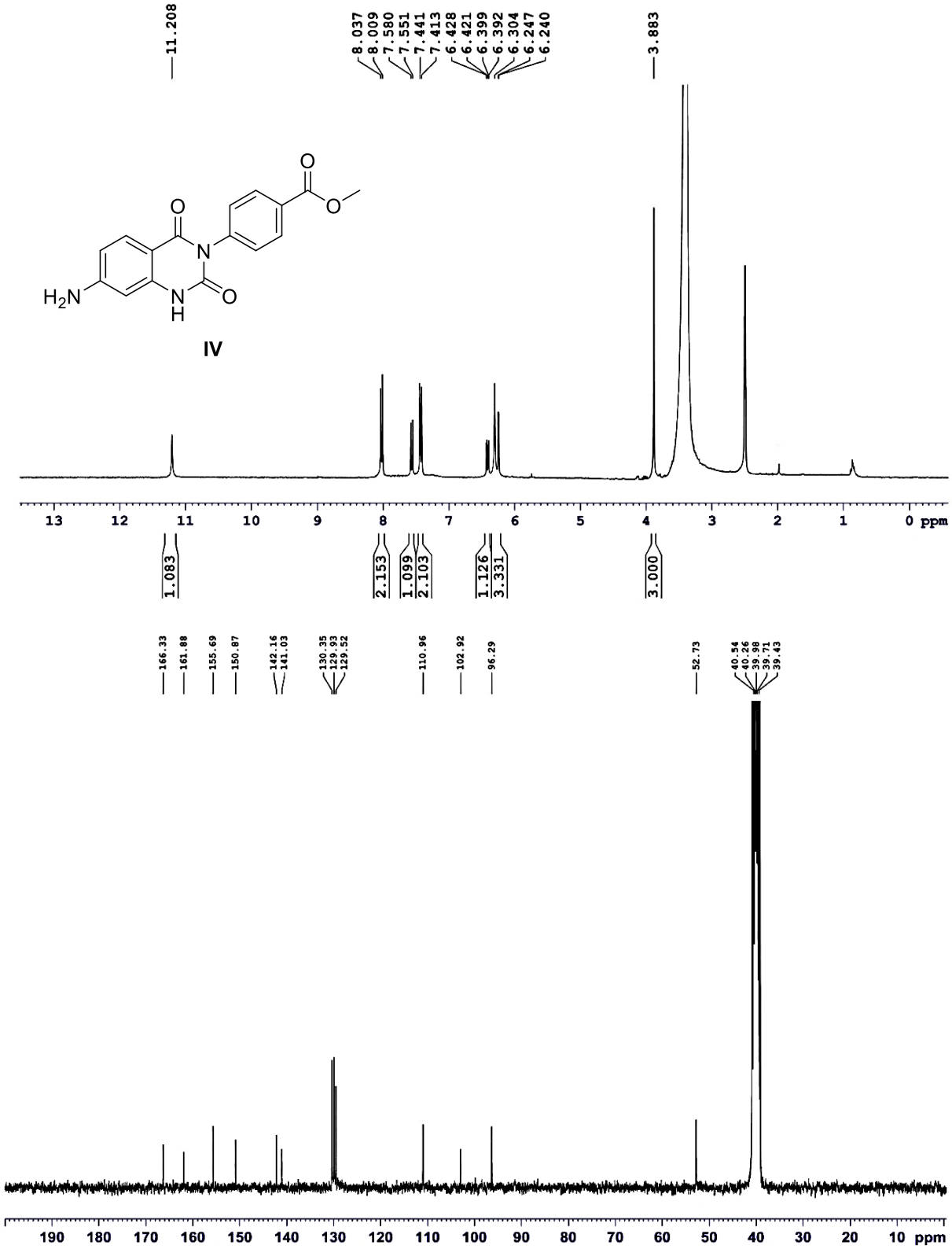


Figure 22 The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra of compound **IV** in DMSO- d_6



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List of Publication

Kaewman, W.; Kaeobamrung, J. 2023. DMAP-catalyzed domino reactions of α-chloroaldoxime *O*-methanesulfonates and 2-aminobenzoic acids for the synthesis of quinazolinediones. SYNLETT. DOI: 10.1055/a-2107-5653.