Synthesis of Cyclic Ureas: Quinazolinediones and Imidazolidinones from Copper and DMAP-Catalyzed Reactions

Chanikan Duangjan

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Organic Chemistry
Prince of Songkla University
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Major Program	Organic Chemistry

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Dean of Graduate School

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

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……..Signature

(Miss Chanikan Duangjan)
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

(Miss Chanikan Duangjan)
Candidate

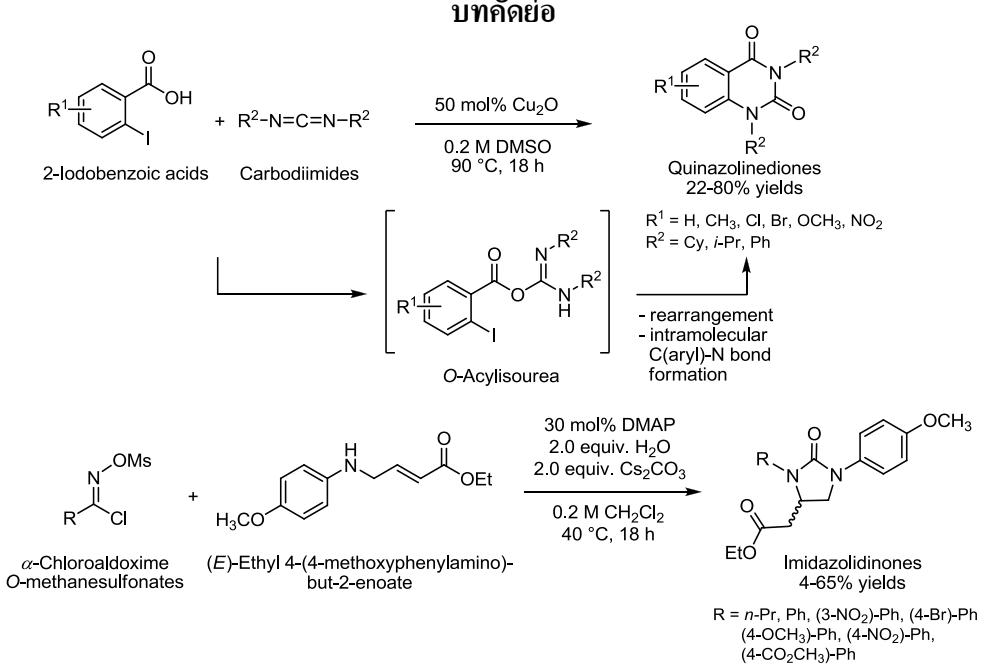
ชื่อวิทยานิพนธ์ การสังเคราะห์ควินาโซลีนไดโอนและอิมิดาโซลิดิโนน ซึ่งเป็นอนุพันธ์ไซคลิกยูเรียด้วยปฏิกิริยาที่ใช้คอปเปอร์ และ DMAP เป็นตัวเร่งปฏิกิริยา

ผู้เขียน นางสาวชนิกาญจน์ ดวงจันทร์

สาขาวิชา เคมีอินทรีย์

ปีการศึกษา 2561

บทคัดย่อ



ควินาโซลีนไดโอน และอิมิดาโซลิดิโนน เป็นผลิตภัณฑ์ธรรมชาติที่มียูเรียเป็นองค์ประกอบแสดงฤทธิ์ทางชีวภาพที่น่าสนใจ ซึ่งควินาโซลีนไดโอนเป็นสารประกอบไซคลิกยูเรียชนิดวงหกเหลี่ยม สามารถสังเคราะห์ได้จากปฏิกิริยาที่เกิดแบบหลายขั้นตอน โดยใช้คอปเปอร์เป็นตัวเร่งปฏิกิริยา โดยใช้สารตั้งต้นเป็น 2-iodobenzoic acids และ carbodiimides กลไกการเกิดปฏิกิริยาเกี่ยวข้องกับ การจัดเรียงตัวใหม่ของ O-acylisourea และ intramolecular C(aryl)–N bond formation ตามลำดับ ซึ่งผลอิเล็กทรอนิกส์บน วงอะโรมาติกของ benzoic acid และหมู่แทนที่บนไนโตรเจนของ carbodiimides มีผลต่อร้อยละผลิตภัณฑ์ของอนุพันธ์ควินาโซลีนไดโอน ซึ่งสามารถสังเคราะห์ได้ 22-80% ส่วนอิมิดาโซลิดิโนน เป็นสารประกอบไซคลิกยูเรียชนิดวงห้าเหลี่ยม สามารถสังเคราะห์ได้จากปฏิกิริยาที่ใช้ N,N-dimethylpyridin-4-amine (DMAP) เป็นตัวเร่งปฏิกิริยา ภายใต้สภาวะที่ไม่รุนแรง โดยสารตั้งต้นเป็น α-chloroaldoxime O-methanesulfonates และ (E)-ethyl 4-(4-methoxyphenyl-amino)but-2-enoate กลไกเกิดปฏิกิริยาประกอบด้วย การจัดเรียงตัวใหม่แบบ Tiemann และ ตามด้วย intramolecular Michael addition ซึ่งสามารถสังเคราะห์อนุพันธ์อิมิดาโซลิดิโนนได้ 4-65%

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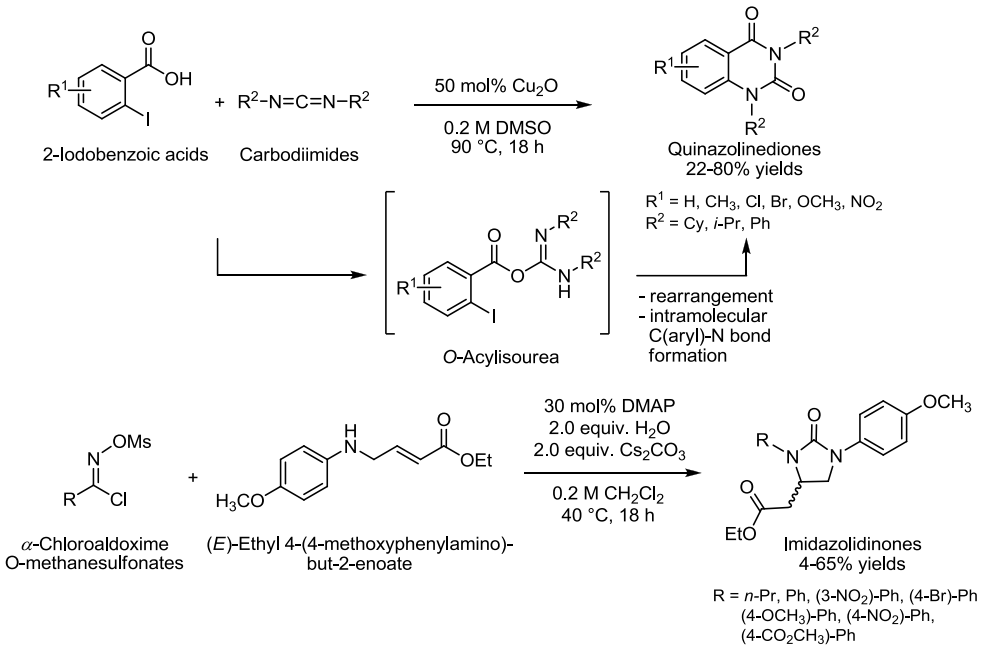
Abstract



Quinazolinediones and imidazolidinones consisting of urea moiety displayed a wide range of biological activities. Quinazolinediones, hexacyclic urea, were synthesized from 2-iodobenzoic acids and carbodiimides *via* copper-catalyzed domino reactions. The domino processes include rearrangement of *O*-acylisourea and intramolecular C(aryl)–N bond formation. The electronic effect on aromatic ring of benzoic acid affected the product yields. A variety of quinazolinedione derivatives were synthesized in 22-80% yields. Imidazolidinones, pentacyclic urea, were synthesized from *α*-chloroaldoxime *O*-methanesulfonates and (*E*)-ethyl 4-(4-methoxyphenylamino)but-2-enoate *via* *N*,*N*-dimethylpyridin-4-amine (DMAP)-catalyzed reaction under mild conditions. The mechanism consisted of Tiemann rearrangement and intramolecular Michael addition to provide corresponding imidazolidinones in 4-65% yields.

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I would like to express my sincere gratitude to all people who generously help me for my graduate study success. First of all, I would like to thank my advisor, Asst. Prof. Dr. Juthanat Kaeobamrung for his excellent suggestions, expert guidance, and motivation encouraging me to achieve my educational goals.

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Chanikan Duangjan

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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
Ar	=	aryl
AcOH	=	acrtic acid
$CDCl_3$	=	deuterochloroform
$CHCl_3$	=	chloroform
CH_2Cl_2	=	dichloromethane
CH_3CN	=	acetonitrile
m-CPBA	=	*m*-chloroperoxybenzoic acid
Cs_2CO_3	=	cesium carbonate
Cy	=	cyclohexyl
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene

LIST OF ABBREVATIONS AND SYMBOLS (Continued)

DCC	=	*N*,*N*-dicyclohexylcarbodiimide
DIPEA	=	*N*,*N*-diisopropylethylamine
DMEDA	=	*N*,*N*′-dimethylethylenediamine
DMF	=	dimethylformamide
DMSO	=	dimethylsulfoxide
DMSO-d_6	=	dimethyl sulfoxide-d_6
Et	=	ethyl
EtOAc	=	ethyl acetate
EtOH	=	ethanol
H_2SO_4	=	sulfuric acid
HCl	=	hydrochloric acid
K_2CO_3	=	potassium carbonate
K_3PO_4	=	potassium phosphate
Me	=	methyl
MsCl	=	methanesulfonyl chloride
MeOH	=	methanol
Na_2CO_3	=	sodium carbonate
NaOH	=	sodium hydroxide
$NaOCH_3$	=	sodium methoxide
Na_2SO_4	=	sodium sulfate
NCS	=	*N*-chlorosuccinimide
NEt_3	=	triethylamine
NH_2OH•HCl	=	hydroxylammonium chloride
NH_4Cl	=	ammonium chloride
Ph	=	phenyl
$PhCH_3$	=	toluene
PMP	=	*p*-methoxyphenyl

LIST OF ABBREVATIONS AND SYMBOLS (Continued)

THF	=	tetrahydrofuran
TMG	=	trimethylguanidine
TMS	=	tetramethylsilane

LIST OF PUBLICATION

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CHAPTER 1

Synthesis of 2,4-Quinazolinedione Derivatives *via* Copper-Catalyzed Domino Reactions

1.1INTRODUCTION

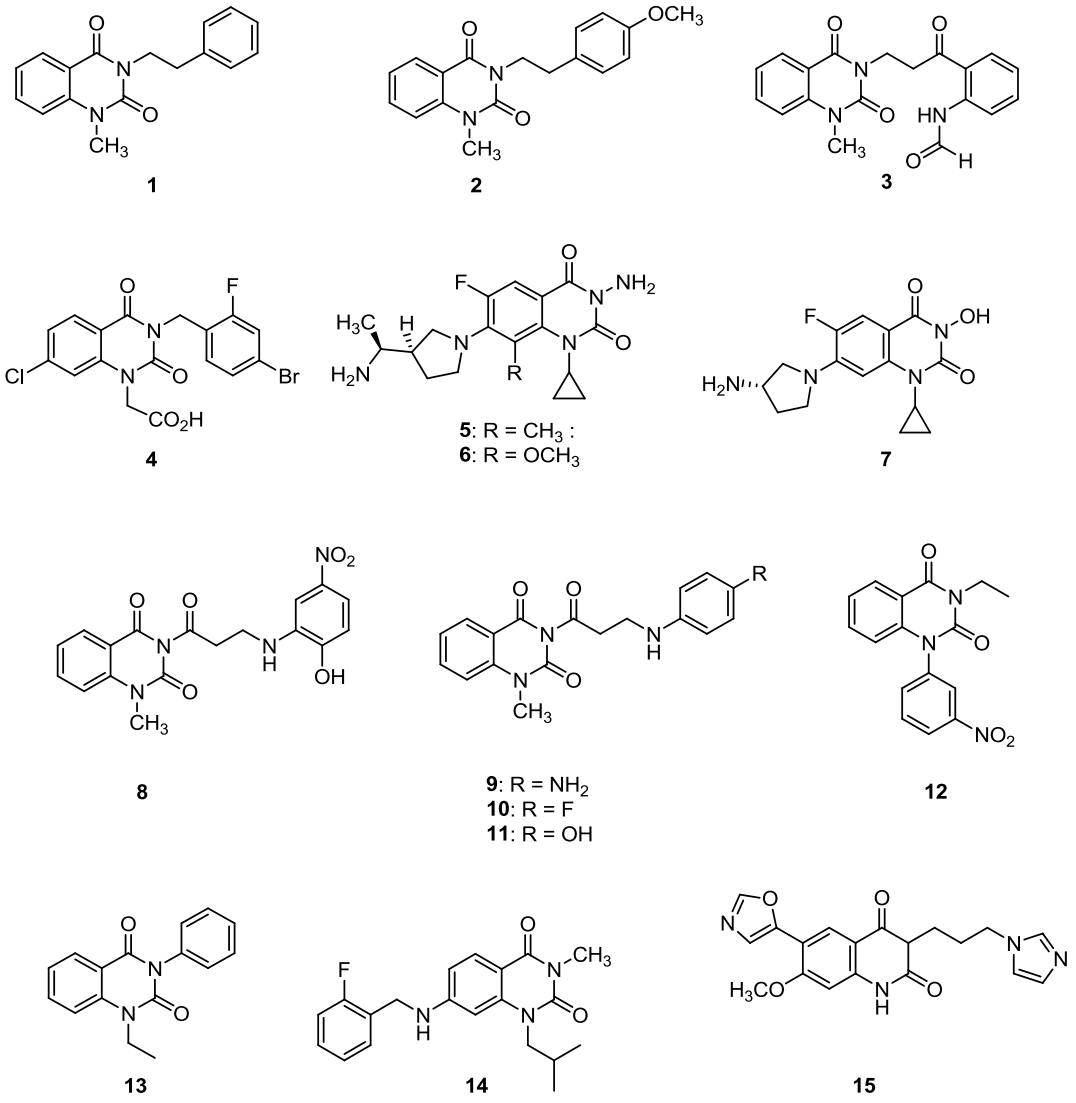
1.1.1 Introduction

N-containing heterocyclic compounds are one of the most important targets for organic chemists because of their applications in agrochemicals, pharmaceuticals, and special materials. Among known heterocycles, quinazolinediones have an interesting organic framework containing urea moiety in molecules. Their derivatives have shown attractive biological activities including several drugs. Moreover, related structures have been applied in therapy (Li *et al*., 2014).

Quinazolinediones are one of the important classes of N-containing heterocycles. They are found in alkaloid natural products, and commonly used in medicinal chemistry because of their pharmacological properties, such as antimicrobial, anticonvulsant, anti-inflamatory, and antidepressant activities (Li *et al*., 2009). 1-Methyl-3-(2'-phenylethyl)-1*H*,3*H*-quinazoline-2,4-diones (**1**) and 1-methyl-3-[2'-(4'-methoxyphenyl)ethyl]-1*H*,3*H*-quinazoline-2,4-diones (**2**), isolated from seed husks of Mexican *Zanthoxylum* species, showed antihypertensive activity (Rivero *et al*., 2004). Wuchuyuamide IV (**3**), isolated from the fruits of *Evodia officinalis,* showed the cytotoxicity against Hela and HT1080 cell lines (Jin *et al*., 2008). The quinazoline-2,4-dione **4** exhibited antidiabetic activity (Willis *et al*., 2006). In addition, 3-aminoquinazolinediones **5**, **6** and 3-hydroxy- quinazolinediones **7** displayed antibacterial activity (Ellsworth *et al*., 2006). Furthermore, *N*-substituted methylquinazolinedione-2,4-diones derivatives, such as methylquinazolinedione-2,4-diones **8**, **9**, **10**, and **11** have 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(1*H*,3*H*)-dione (**12**) exhibited as a promising

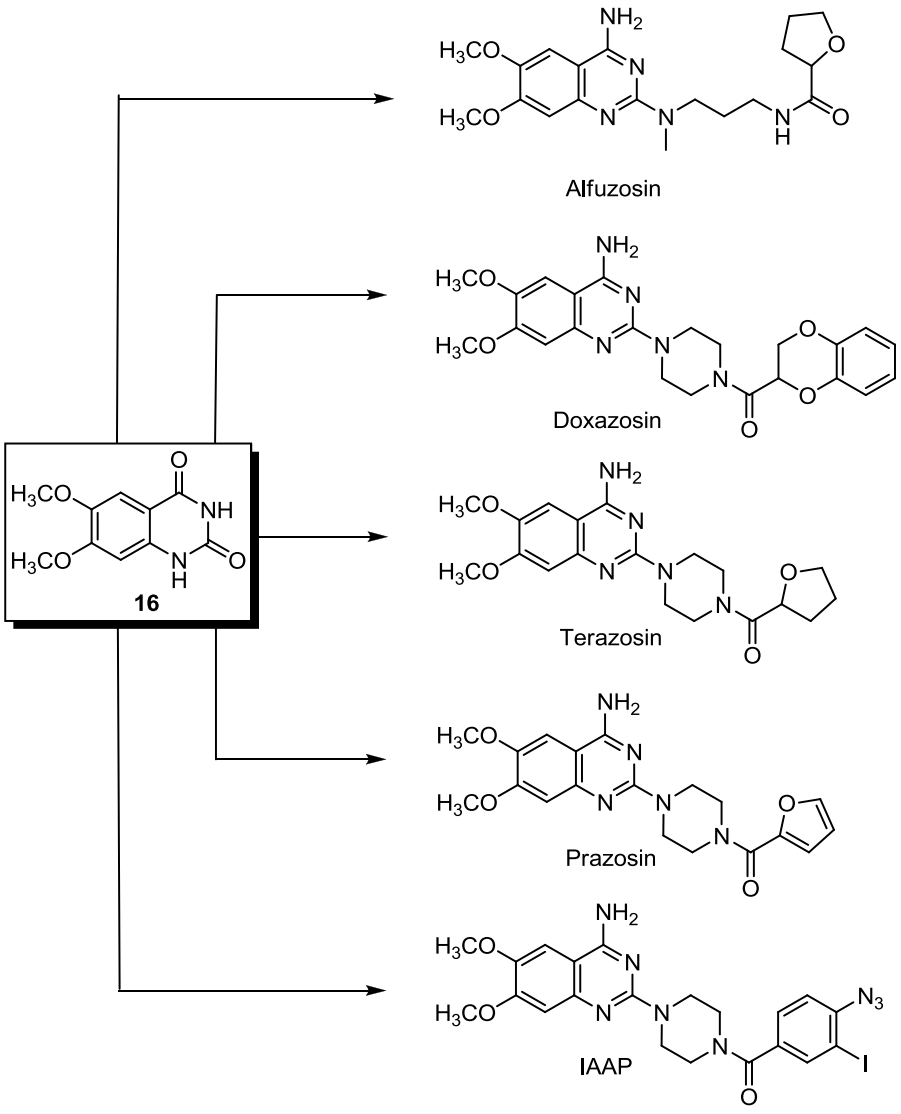
agent for the treatment of asthma (Piaz and Giovannoni, 2000). 1-Ethyl-3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**13**) showed progesterone receptor agonistic activity. Quinazolinedione **14** was a potential target for medical intervention in diseases such as systemic lupus erythematosus (Buckley *et al*., 2005). In addition, quinazoline-2,4-dione **15** was considered as potential immuno-suppressive and anti-inflammatory agent in nuclear factor of activated T-cells-1-regulated β-galactosidase expression (Michne *et al*., 1995) (**Figure 1**).

Figure 1 Examples of quinazolinedione derivatives



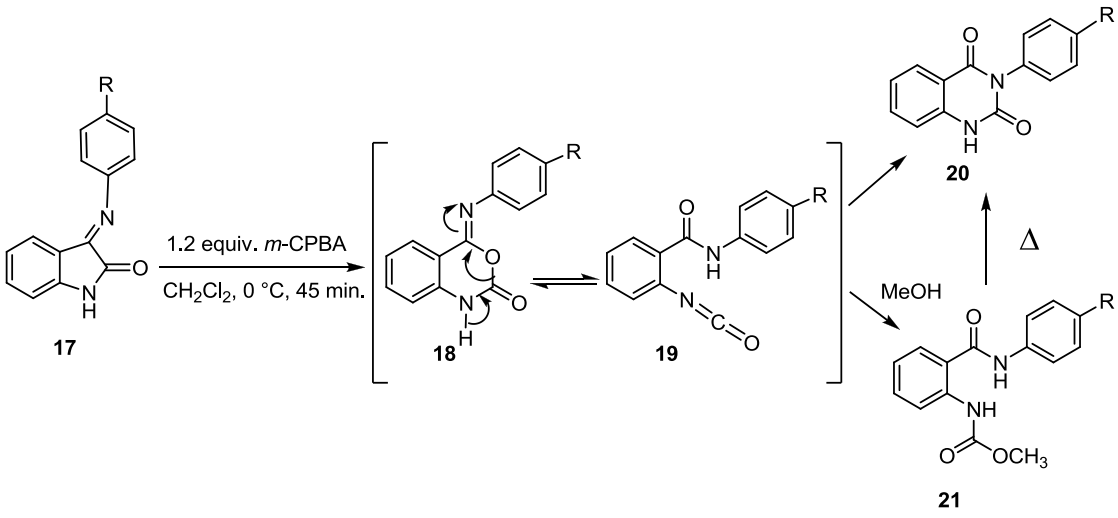
Moreover, quinazolinediones were used as a key intermediate for production of medicine. For instance, 6,7-dimethoxyquinazoline-2,4(1*H*,3*H*)-dione (**16**) was transformed to α1-adrenergic blocker drugs such as alfuzosin, prazosin, terazosin, doxazosin, and IAAP. These drugs were useful for antihypertensive activity (**Figure 2**) (Jiarong *et al*., 2009). Consequently, over the last decade many researchers became interested in the synthesis of quinazolinedione derivatives.

Figure 2 6,7-Dimethoxyquinazoline-2,4(1*H*,3*H*)-dione is a key intermediate of alfuzosin, prazosin, terazosin, doxazosin, and IAAP preparations



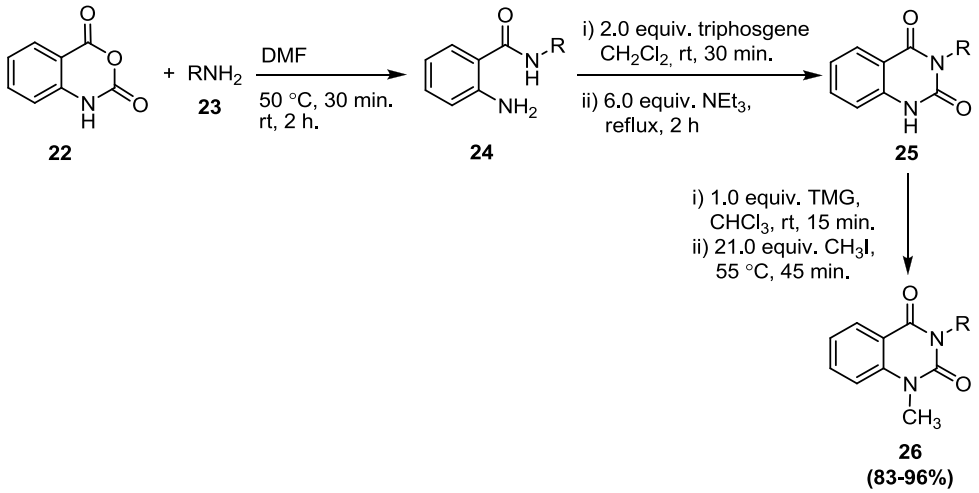
In 2000, Azizian and co-workers reported 2,4-quinazolinediones synthesis from rearrangement of 4-amino-(1*H*,4*H*)-3,1-benzoxazine-2-ones (**17**) *via* an isocyanate carboxamide intermediates **19**. The target products **20** were synthesized from imine **17** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane at 0 ºC *via* Baeyer-Villiger oxidation followed by the rearrangement of **18**. The desired products were obtained from recrystallization of the crude mixture with methanol, affording carbamates **21**. Then the carbamates **21** were heated at their melting points, resulting in ring closure to provide quinazolinediones **20** in 80-93% yields (**Scheme 1**) (Azizian *et al.*, 2000).

Scheme 1 The 2,4-quinazolinediones synthesis *via* an isocyanates carboxamide intermediate



In 2004, Rivero and co-workers synthesized quinazoline-2,4-dione derivatives **26**, which were known to exhibit potential anti-hypertensive property. They accomplished the synthesis of these compounds in 3 steps. The quinazoline-2,4-dione backbone was constructed from isatoic anhydride **22** and amines **23** to give the corresponding 2-aminobenzamides **24**. Subsequently, they used triphosgene as carbonylating reagent to form the amides **25** followed by methylation to give products in good yields (**Scheme 2**) (Rivero *et al*., 2004).

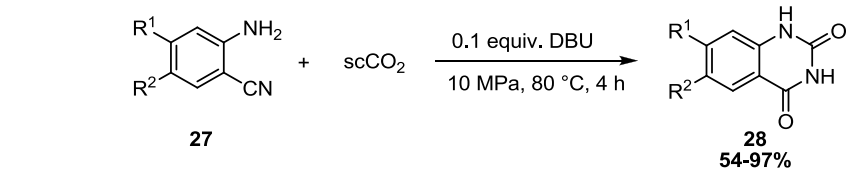
Scheme 2 Rivero's synthesis of 2,4-quinazolinediones

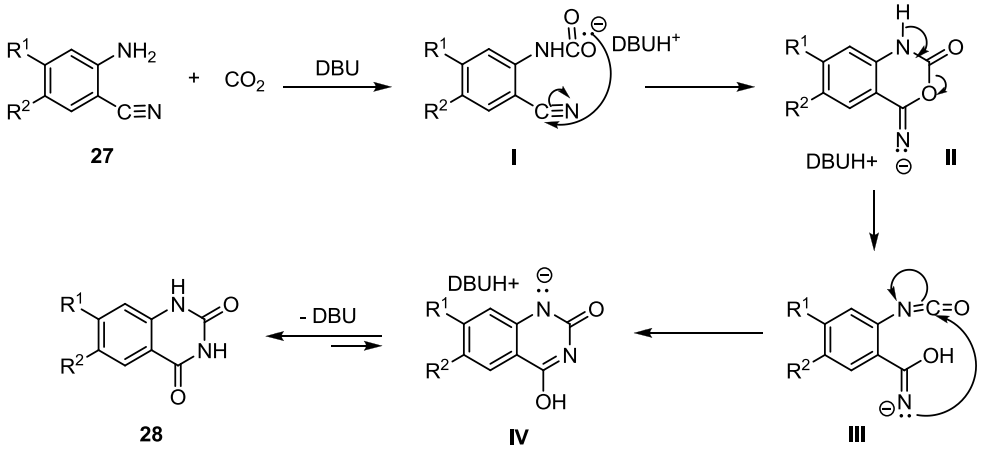


Mizuno and co-workers achieved the development of a new method for the synthesis of 1*H*-quinazoline-2,4-dione derivatives. They used 2-aminobenzonitriles **27** as starting materials reacting with supercritical carbon dioxide in a catalytic amount of DBU (0.1equiv.) at 80 ºC for 4 hours to afford the desired products **28** in 54-97% yields (**Scheme 3**).

The plausible pathway for the formation of **28** from **27** and carbon dioxide assisted by catalytic amount of DBU was demonstrated in scheme 3. The carbonylation of **27** with CO_2 formed a carbamate salt **I** in the presence of catalytic DBU. Then, nucleophilic cyclization of **I** to provide **II** followed by rearrangement of **II** to form isocyanate intermediate **III**. Then, cyclization of **III** gave **IV**. Finally, the isomerization of **IV** gave more stable products **28** (**Scheme 3**) (Mizono *et al.*, 2004).

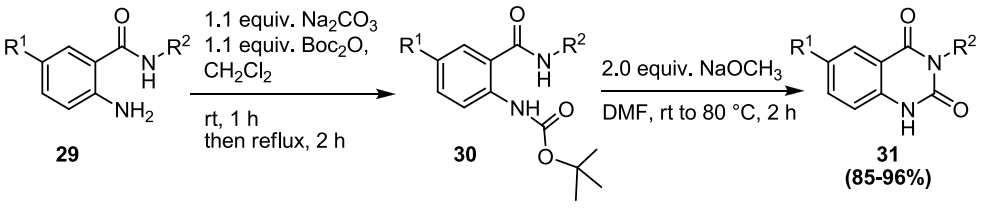
Scheme 3 Mizono's method of quinazolinedione derivatives synthesis





Li reported the simple synthesis of quinazoline-2,4-dione derivatives in 2 steps. He achieved the quinazolinediones **31** in excellent yields *via* carbonylation of substituted anthranilamides **29** with Boc anhydride as a carbonylation reagent. The reaction involved the generation of Boc-protected anthranilamides **30** followed by cyclization in the presence of the sodium methoxide as a base (**Scheme 4**) (Li, 2009).

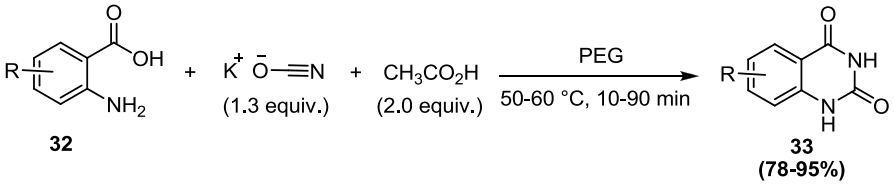
Scheme 4 The 2,4-quinazolinediones synthesis by using Boc strategy



In 2012, a new approach for the synthesis of 2,4-quinazolinediones in one-pot manner was discovered by Kolkeshvandi and Nikpoure. Their reaction involved cyclization reaction of anthranilic acids **32** with potassium cyanate (KOCN) and

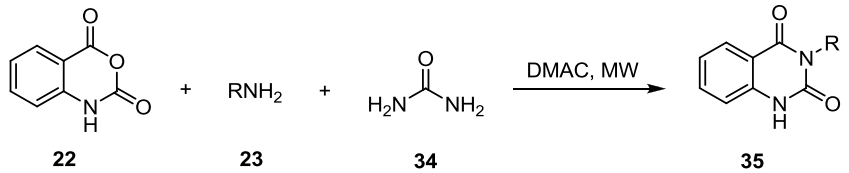
acetic acid. Simply, the reaction was heated in polyethylenegylcol (PEG) to provide products **33** in high yields, in short reaction times (10-90 min.) without the use of any catalyst (**Scheme 5**) (Sharafi-Kolkeshvandi *et al*., 2012).

Scheme 5 A new approach for one-pot synthesis of 2,4-quinazolinediones by Kolkeshvandi and Nikpoure



Recently, microwave irradiation was selected as a synthetically useful method to accurate the organic reactions. In 2003, Azizian and co-workers attempted to synthesize quinazolinediones **35** under microwave irradiation. The quinazolinediones derivatives **35** were obtained in excellent yields from condensation of isotoic anhydride **22**, with primary amines **23** (1.2 equiv.) and urea **34** (1.0 equiv.) in *N*,*N*-dimethylacetamide (DMAC). This reaction was conducted in open vessels under microwave irradiation, and completed in several minutes (**Scheme 6**) (Azizian *et al*, 2003).

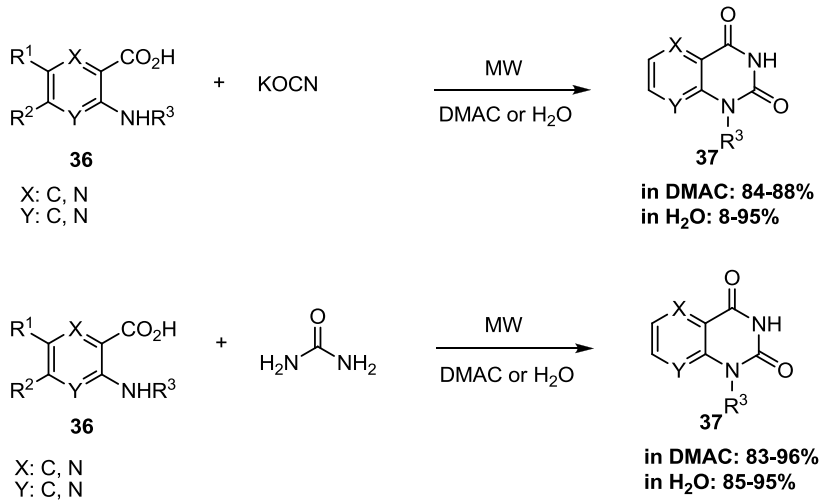
Scheme 6 The synthesis of 2,4-(1*H*,3*H*)-quinazolinediones under microwave irradiation



Nikpour and Paibast were also interested in the synthesis of quinazolinedione derivatives under microwave irradiation in one-pot fashion. They reported the condensation of anthranilic acid derivatives **36** with KOCN in the absence of any

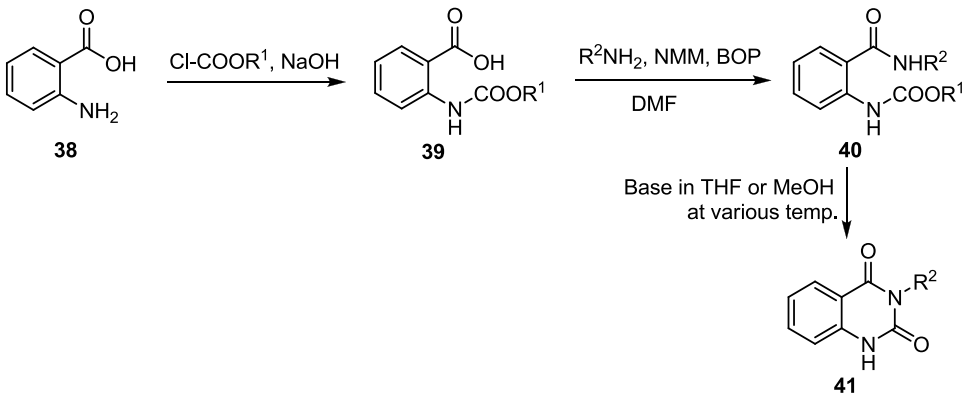
catalyst to obtain corresponding quinazolinediones **37**. Interestingly, they found that when the reaction was carried out in water, the urea was more reactive than KOCN (**Scheme 7**) (Nikpour *et al.*, 2005).

Scheme 7 The 2,4-(1*H*,3*H*)-quinazolinediones synthesis from anthranilic acid **36** and KOCN or urea under microwave irradiation



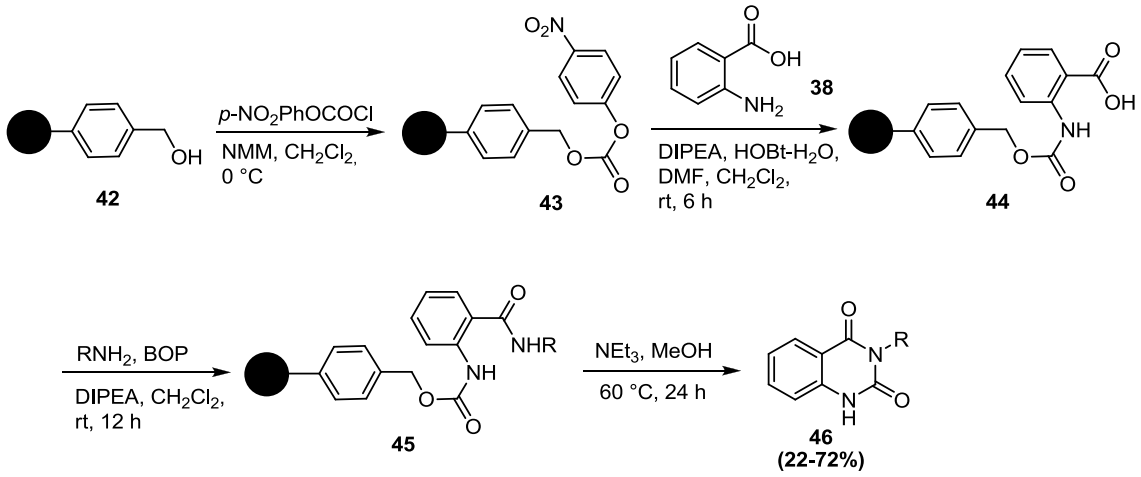
In 1996, Gouilleux and co-workers adapted Gadekar's method for the quinazolinediones derivatives synthesis. They began the synthesis with anthranilic acid (**38**), which was converted to *N*-urethane derivatives **39** using alkylchloroformate in 1 M NaOH. Then, coupling of the *N*-urethanes **39** with primary amines provided an intermediates **40** followed by cyclization to complete the products **41** in high yields (**Scheme 8**).

Scheme 8 The synthesis of quinazoline-2,4-diones **41** *via* urethane protected anthranilamides **40**



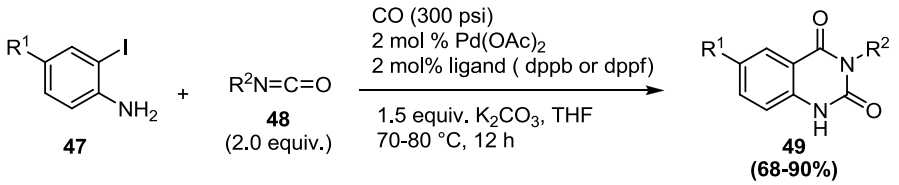
Interestingly, they applied solid phase synthesis to their quinazolinedione formation. The reaction started with hydroxymethyl polystyrene resin **42**, which was easily converted to its *N*-urethane **43** by using *N*-methylmorpholine (NMM) and *p*-nitrophenylchloroformate. Then, coupling of urethane **43** with anthranilic acid **38** (5.0 equiv.) in the presence of HOBt (3.0 equiv.) and *N*,*N*-diisopropylethylamine (DIPEA) (6.0 equiv.) in a mixture of DMF:CH_2Cl_2 (1:2 ratio) as a solvent afforded resin compound **44**. The amino molecules (or C-terminal protected amino acid derivatives) reacted with **44** to provide amide **45**. Treatment of the resin intermediate **45** with NEt_3 (10.0 equiv.) in methanol at 60 ºC for 24 hours gave desired products **46** in 22-72% yields (**Scheme 9**) (Gouilleux *et al*., 1996).

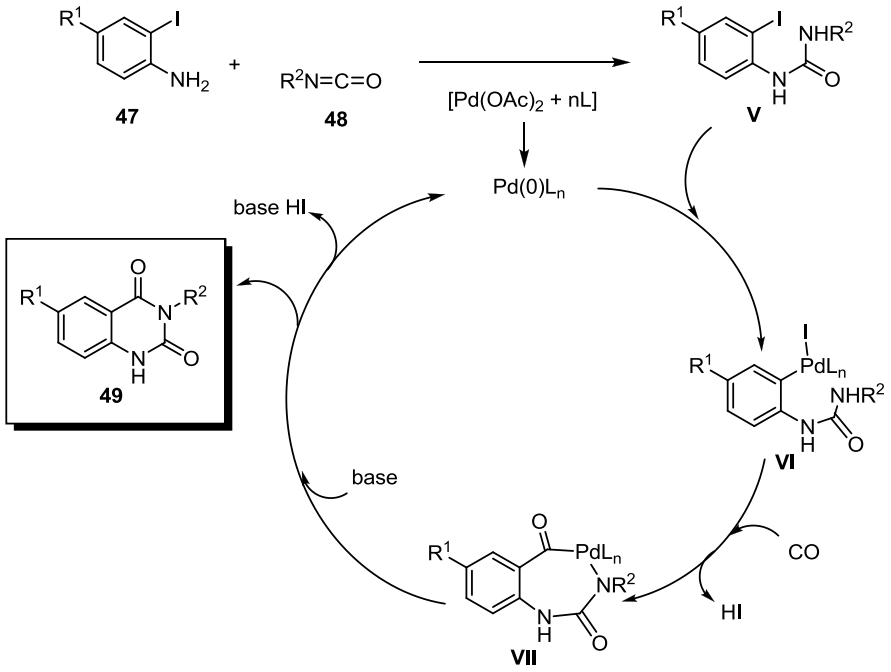
Scheme 9 The solid phase synthesis of quinazoline-2,4-diones



In 2000, Larksarp and Alper used palladium as a catalyst to synthesize quinazolinedione derivatives from aniline **47** and isocyanate **48** in the presence of CO. The reaction mechanism involved the in *situ* generation of urea **V** followed by palladium-catalyzed carbonylation to provide desired quinazolinediones **49** (**Scheme 10**) (Larksarp *et al*., 2000).

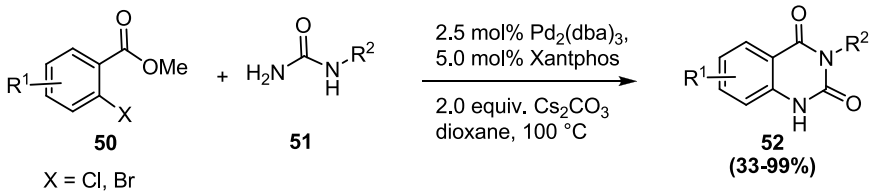
Scheme 10 Palladium-catalyzed cyclocarbonylation of *o*-iodoanilines with isocyanates





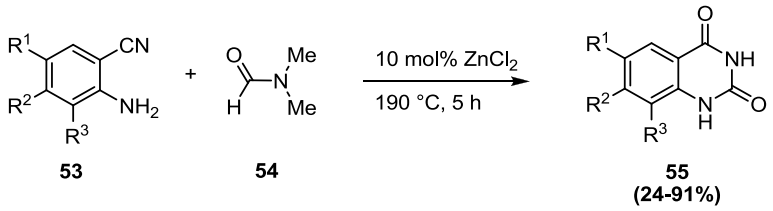
In 2006, Willis and co-workers were interested in the application of palladium-catalyzed C−N and C−O bond formation in sequence process for heterocycle synthesis. They used *o*-halobenzoates **50** and monoalkylureas **51** to construct 3-alkyl quinazolinediones **52.** The formation of product involved tandem regioselective palladium-catalyzed arylation of urea followed by and intramolecular amidation reaction in one step to provide desired products **52** in 33-99% yields (**Scheme 11**) (Willis *et al.*, 2006).

Scheme 11 Palladium-catalyzed arylation-ester amidation of *o*-halobenzoates **50** and monoalkyl ureas **51**



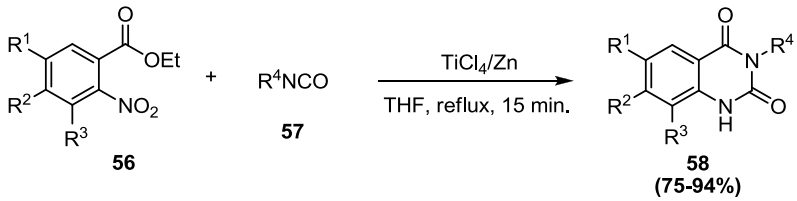
Moreover, quinazoline-2,4-diones were synthesized from several metal-catalyzed reactions, such as zinc, titanium, and selenium. In 2009, Jiarong and co-workers discovered the preparation of quinazoline-2,4-diones *via* Zn-catalyzed domino reactions. The domino process involved a condensation of aromatic *o*-aminonitriles **53** and *N*,*N*-dimethylformamide (**54**) in the presence of $ZnCl_2$ in sealed reactor to produce the corresponding products **55** in 24-91% yields at high temperature (**Scheme 12**) (Jiarong *et al*., 2009).

Scheme 12 The condensation of aromatic *o*-aminonitriles **53** and *N*,*N*-dimethylformamide (**54**)



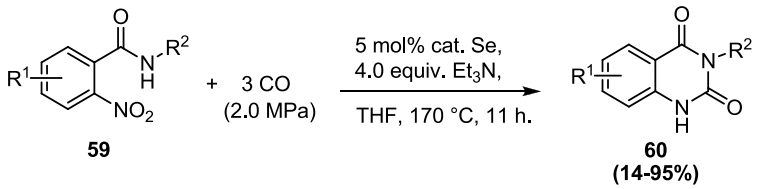
In 2009, Dou and co-workers reported the use of low-valent titanium reagent ($TiCl_4$/Zn) to synthesize quinazoline-2,4(1*H*,3*H*)-dione derivatives *via* the novel reductive cyclization from substituted ethyl-2-nitrobenzoates **56** and isocyanates **57** (**Scheme 13**) (Dou *et al*., 2009).

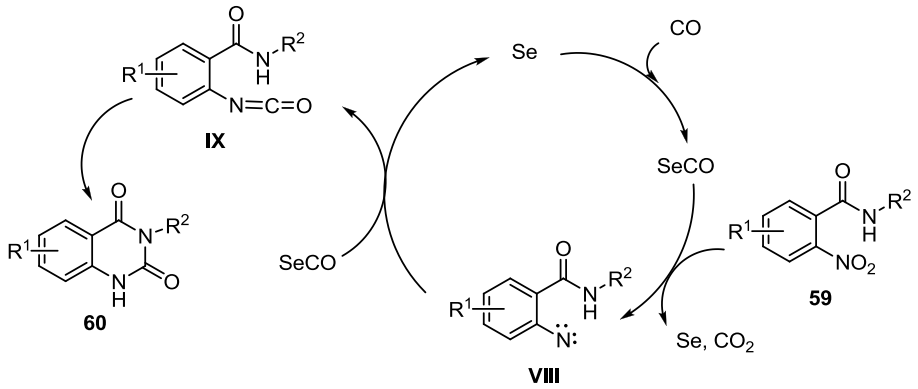
Scheme 13 One-pot synthesis of quinazoline-2,4(1*H*,3*H*)-diones with the aid of law-valent titanium reagent



In 2010, Wu and Yu were interested in applying transition metal catalyzed reaction to synthesize of 1*H*-quinazoline-2,4-diones. They used selenium as a catalyst for carbonylation of *o*-nitrobenzamides **59** with carbon monoxide. The reaction began with the generation of carbonyl selenide from selenium and CO. Then, reduction of **59** by carbonyl selenide occurred to give nitrene **VIII**, subsequently reacting with another molecule of carbonyl selenide to form isocyanates **IX**. The last transformation was intramolecular cyclization of **IX** to give desired products **60** in 14-95% yields (**Scheme 14**) (Wu *et al.*, 2010).

Scheme 14 The selenium-catalyzed carbonylation of *o*-nitrobenzamides **59**

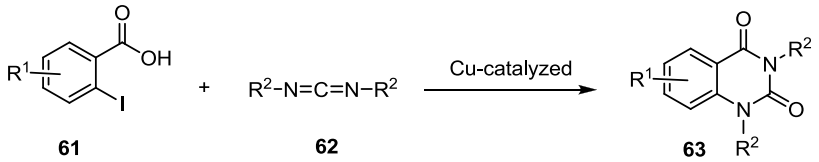




Based on searched literatures mentioned above, most of starting materials for quinazolinedione syntheses were *N*-substituted aryl derivatives, and some of these procedures had drawbacks, such as involving multistep reactions, long reaction time, the use of toxic reagents, and harsh reaction conditions. We are therefore in finding a new reaction by applying a different *o*-substituted starting material for construction of a new C−N bond.

Domino reactions have been one of the most powerful procedures for the synthesis of complex organic molecules from simple substrates in a single reaction preparation (Tietze *et al*., 2004). Copper-catalyzed domino reactions were widely used in the construction of carbon-heteroatom and carbon-carbon bonds in the organic synthesis due to their high reactivity, low toxicity, and easy handling. In conclusion, we herein present an alternative method in the synthesis of quinazoline-2,4-diones **63** *via* copper-catalyzed domino reactions from 2-iodobenzoic acids **61** and carbodiimides **62** (**Scheme 15**).

Scheme 15 The copper-catalyzed domino reaction from 2-iodobenzoic acid **61** and carbodiimides **62**



61 **62** **63**

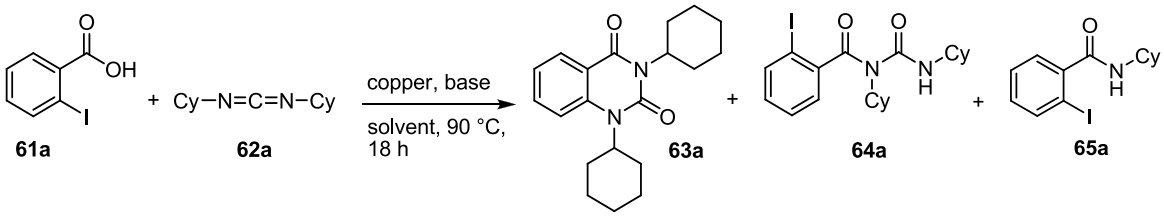
1.1.2 Objective

To find a new procedure for the synthesis of quinazoline-2,4-diones *via* copper catalyzed domino reaction under mild condition in one step.

1.2 RESULTS AND DISCUSSION

Our study toward Cu(l)-catalyzed domino reactions for the synthesis of quinazolinediones started with optimization reaction consisting of equivalent of **62a**, catalysts, bases and solvents. The reaction of 2-iodobenzoic acid (**61a**) and *N*,*N*'-carbodiimides **62a** were selected as a model starting material study (**Table 1**).

Table 1 Optimization of reaction conditions of 2-iodobenzoic acid **61a** and carbodiimides **62a**[a]



Entry	Equiv. of 62a	mol%: Cu	Base	Solvent	Yield (%[b] of 63a)
1	1.1	10: Cu_2O	K_2CO_3	DMSO	31
2	1.1	10: CuI	K_2CO_3	DMSO	21
3	1.1	10: CuBr	K_2CO_3	DMSO	Trace[c]
4	1.1	10: $Cu(OAc)_2$	K_2CO_3	DMSO	Trace[c]
5	1.1	10: Cu_2O	K_2CO_3	CH_3CN	27
6	1.1	10: Cu_2O	K_2CO_3	DMF	22
7	1.1	10: Cu_2O	K_2CO_3	Toluene	0
8	1.5	10: Cu_2O	K_2CO_3	DMSO	35
9	2.0	10: Cu_2O	K_2CO_3	DMSO	38
10	3.0	10: Cu_2O	K_2CO_3	DMSO	36
11	2.0	10: Cu_2O	K_3PO_4	DMSO	21
12	2.0	10: Cu_2O	Cs_2CO_3	DMSO	Trace[c]
13	2.0	10: Cu_2O	*t*-BuOK	DMSO	Trace[c]
14	2.0	10: Cu_2O	NEt_3	DMSO	47

Table 1 Optimization of reaction conditions of 2-iodobenzoic acid **61a** and carbodiimides **62a**[a] (continued)

Entry	Equiv. of 62a	mol%: Cu	Base	Solvent	Yield (%[b] of 63a)
15	2.0	30: Cu_2O	NEt_3	DMSO	64
16	2.0	50: Cu_2O	NEt_3	DMSO	64
17	2.0	-	-	DMSO	0
18	2.0	-	NEt_3	DMSO	0
19	**2.0**	**50: Cu_2O**	**-**	**DMSO**	**75**
20	2.0	30: Cu_2O	-	DMSO	63
21	2.0	20: Cu_2O	-	DMSO	50
22	2.0	10: Cu_2O	-	DMSO	37

[a] Reaction conditions: **62a** (0.50 mmol), base (1.5 equiv.), solvent (0.2 M) at 90 ºC for 18 h in sealed tube.

[b] Isolated yield.

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

An initial study began with screening of a variety of copper catalysts (entries 1-4). The reaction with Cu_2O gave the yield of quinazolinediones **63a** in 31% (entry 1). Then changing copper catalyst to CuI and CuBr, the yield was decreased to 21% and trace amount, respectively (entries 2-3). Furthermore, copper(II) was also tested in this reaction. However, with copper acetate ($Cu(OAc)_2$) the reaction gave the desired product in trace amount (entry 4). From these results, the Cu_2O was the most reactive and suitable copper catalyst for the reaction.

Next, we examined a variety of solvents. Polar solvents provided the desired product although the yields were low. Acetonitrile and dimethylsulfoxide gave 27% and 22%, respectively (entries 5 and 6). On the other hand, toluene, non-polar solvent, gave 0% yield of product (entry 7).

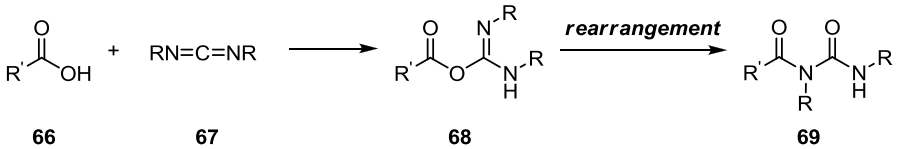
Next, we moved our variable to equivalent of *N*,*N*'-carbodiimides **62a**. Interestingly, increasing amounts of carbodiimides gave better yields of a desired quinazolinediones. When equivalent of carbodiimides was 1.5, the quinazolinediones was obtained in 35% yield (entry 8). With 2.0 equivalents, the product yield was improved to 38% (entry 9). However, with 3.0 equivalents of **62a**, the yield of product was not increased (entry 10). Therefore, a suitable equivalent of carbodiimides in this reaction was 2.0 equivalents.

Next, various bases were investigated. The reaction using K_3PO_4 as a base gave product in 21% (entry 11). Attempts changing base to Cs_2CO_3 and *t*-BuOK were failed. Both gave trace amount of the desired product (entries 12 and 13). Different result was found when using an organic base, triethylamine, resulting in moderate yield of product, 47%, (entry 14).

We tried to improve the yield of product by increasing amount of Cu_2O. With 30 mol% or 50 mol% of Cu_2O, the yield was increased to 64% (entries 15 and 16). Based on these results, the amount of copper catalyst was crucial.

In addition, we found that reaction provided the *N*-acylurea **64a** in the absence of copper catalyst and base (entry 17). Our result was similar to the report from Khorana in 1953 (Khorana *et al.*, 1953). They showed that the carboxylic acid **66** could smoothly react with carbodiimides **67** to generate *O*-acylurea **68**, and then rearrangement took place to provide *N*-acylurea **69** without any catalyst (**Scheme 16**).

Scheme 16 The *N*-acylurea **69** was constructed from carboxylic acid **66** and carbodiimides **67**

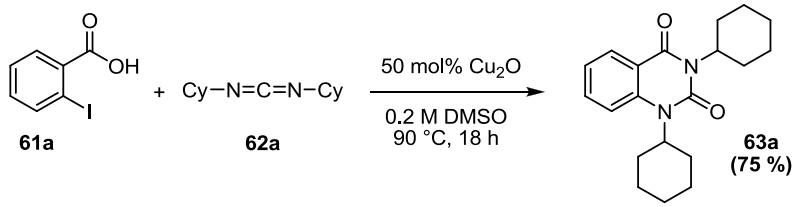


The desired quinazolinedione was not obtained from the reaction without copper (entry 18). Instead, *N*-acylurea **64a** and an amide by-product **65a** were obtained. The result suggested that base caused an elimination of **64a** to obtain the

amide by-product. Based on the result, we applied the condition without external base. Significantly, the yield of product was dramatically increased to 75% in the presence of 50 mol% of copper (entry 19). Trying to low catalyst loading to 30 mol%, 20 mol%, and 10 mol% decreased the yield down to 63%, 50%, 37%, respectively (entries 20-22). These results suggested that the high amount of copper loading was crucial.

Base on the above results, we conclude that the suitable conditions of the reaction were 2.0 equivalents of *N*,*N*'-carbodiimides , 50 mol% of Cu_2O as a catalyst, in DMSO as a solvent at 90 ºC for 18 hours (**Scheme 17**).

Scheme 17 The optimal conditions for the synthesis of quinazolinediones



With the optimal condition in hand**,** we next studied an efficiency of the reaction by exploring various starting materials. Firstly, we focused on the study of 2-iodobenzoic acid derivatives **61** which have electron donating group, electron withdrawing group, and halogen group substituent on aromatic ring (**Figure 3**). The results of the reaction with different substituents on aromatic ring of **61** were shown in **Table 2**.

Figure 3 The various starting materials of 2-iodobenzoic acid

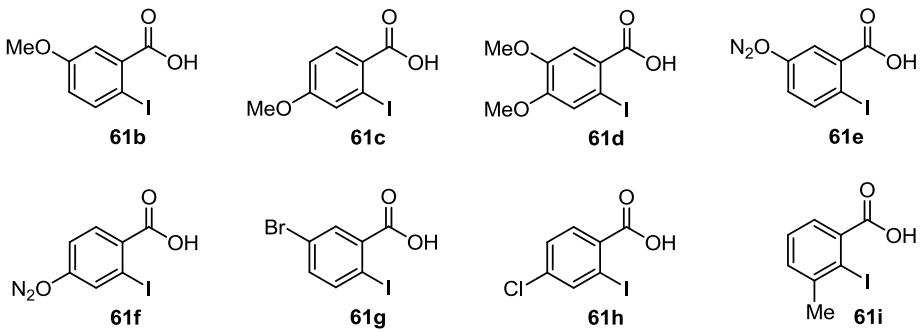
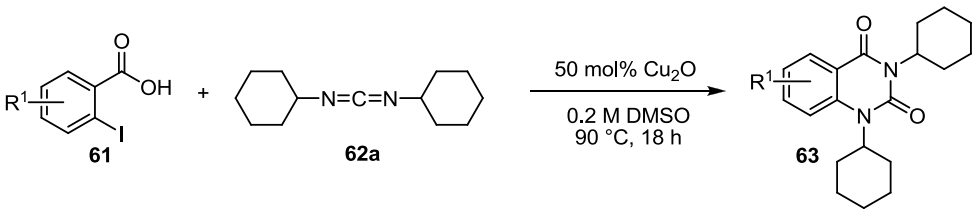


Table 2 The synthesis of quinazolinediones from 2-iodobenzoic acids **61** and carbodiimides **62a**[a]



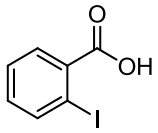
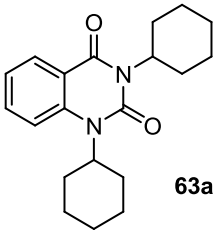
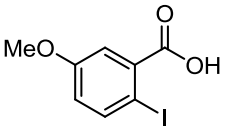
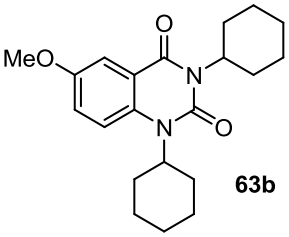
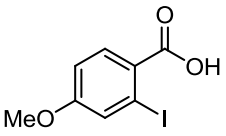
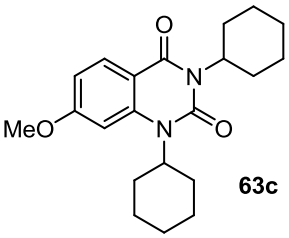
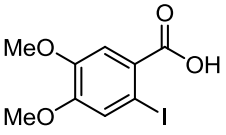
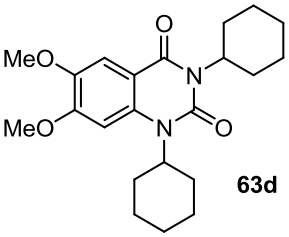
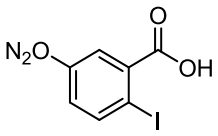
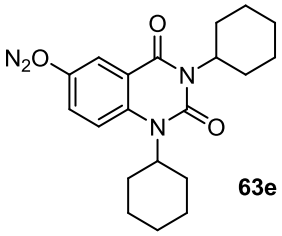
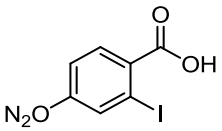
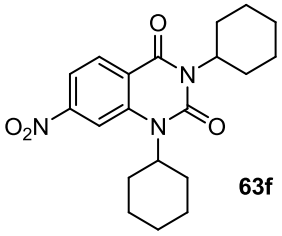
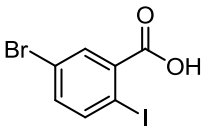
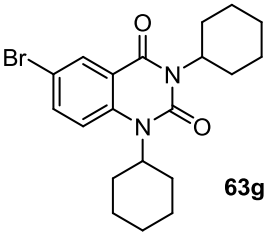
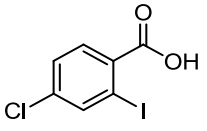
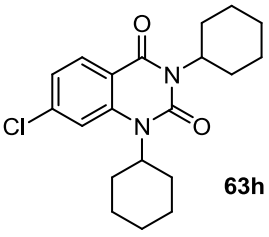
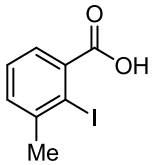
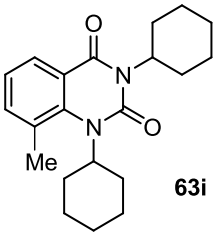
Entry	2-Iodobenzoic acid	Quinazolinediones	Yield (%)[b]
1	 **61a**	 **63a**	75
2	 **61b**	 **63b**	67
3	 **61c**	 **63c**	77
4	 **61d**	 **63d**	58

Table 2 The synthesis of quinazolinediones from 2-iodobenzoic acids **61** and carbodiimides **62a**[a] (continued)

Entry	2-Iodobenzoic acid	Quinazolinediones	Yield (%)[b]
5	 **61e**	 **63e**	22
6	 **61f**	 **63f**	7
7	 **61g**	 **63g**	74
8	 **61h**	 **63h**	67
9	 **61i**	 **63i**	80

[a] Reaction conditions: **61** (0.5 mmol), **62a** (1.0 mmol).
[b] Isolated yield.

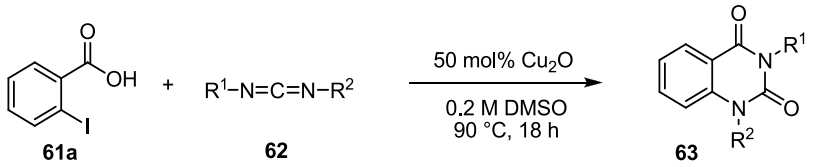
The reaction with 2-iodobenzoic acid (**61a**) without a substituent group as shown in table 2, provided the desired product, 1,3-dicyclohexylquinazoline-2,4(1*H*,3*H*)-dione (**63a**), in 75% yield (entry 1.). Then the reaction of 2-iodobenzoic acid derivatives containing electron donating substituent provide the corresponding quinazolinediones in good yields, for examples, 2-iodo-5-methoxybenzoic acid (**61b**) and 2-iodo-4-methoxybenzoic acid (**61c**) which provided quinazolinediones **63b** and **63c** in 67% and 77% yields, respectively (entries 2 and 3).

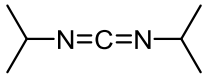
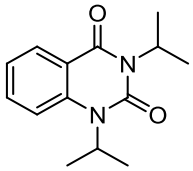
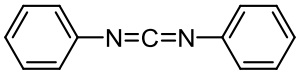
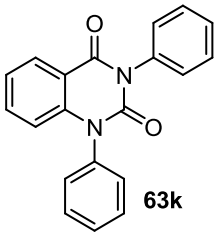
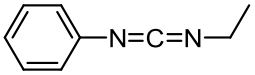
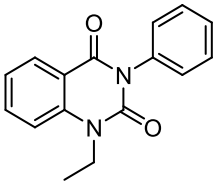
Different result was found when 2-iodobenzoic acid with two methoxyl substituents, 4,5-dimethoxy-2-iodobenzoic acid (**61d**), also gave moderate yield, 58% yield (entry 4). On the other hand, 2-iodobenzoic acid containing the electron withdrawing group provided low yield of the desired product. Both 2-iodo-5-nitrobenzoic acid (**61e**) and 2-iodo-4-nitrobenzoic acid (**61f**) gave quinazolinediones **63e** and **63f** in 22% and 7% yields, respectively (entries 5 and 6). We observed the corresponding *N*-acylurea as major products from both benzoic acids. Based on the results, the benzoic acid bearing the electron withdrawing group preferably underwent to non-catalyzed reaction.

The benzoic acids with halogen substituent on benzene ring were suitable to the reaction. The 5-bromo-2-iodobenzoic acid (**61g**) provided the corresponding quinazolinedione **63g** in a good yield, 74% yield (entry 7). Similar result was obtained when 4-chloro-2-iodobenzoic acid (**61h**) was used giving the corresponding product **63h** in 67% yield (entry 8). Moreover, benzene ring containing methyl group next to iodine provided product **61i** in high yield (entry 9).

Next, we focused on the scope of carbodiimides **62** including symmetric carbodiimides with alkyl or aryl substituent and asymmetric carbodiimides (**Table 3**).

Table 3 The synthesis of quinazolinediones from 2-iodobenzoic acid **61a** and carbodiimides **62**[a]

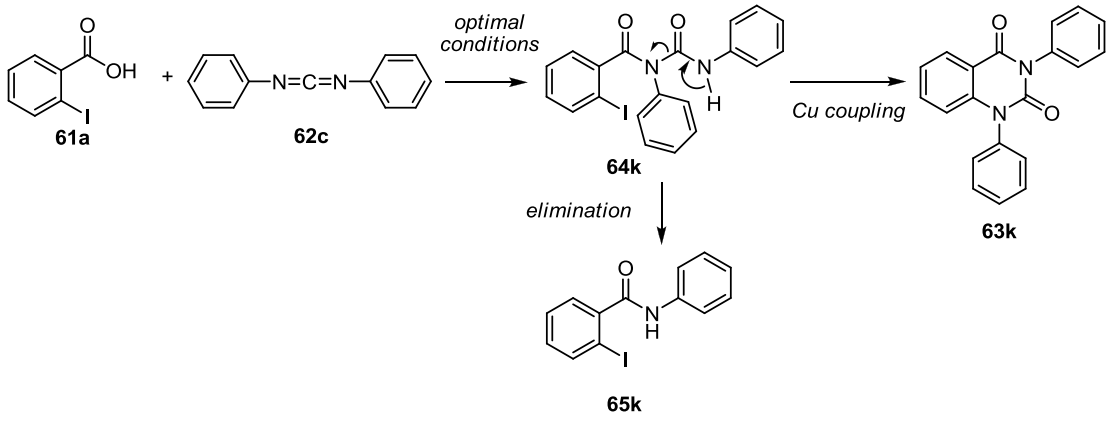


Entry	Carbodiimide	Quinazolinediones	Yield (%)[b]
1	 **62b**	 **63j**	65
2	 **62c**	 **63k**	30
3	 **62d**	 **63l**	22

[a] Reaction conditions: **61a** (0.5 mmol), **62** (1.0 mmol).
[b] Isolated yield

Symmetrical alkyl carbodiimides, (*N*,*N*'-methanediylidenedipropan-2-amine; (**62b**)) provided the quinazolinediones **63j** in high yield at 65% yield (entry 1). On the contrary, diarylsubstituted carbodiimides, *N*,*N*'-methanediylidenedianiline (**62c** gave **63k** in low) yield, 30% (entry 2). A major product of this reaction was the amide by-product. We proposed that amide by-product **65k** was obtained from the elimination of *N*-acylurea **64k** (**Scheme 18**).

Scheme 18 The elimination of *N*-acylurea generated amide by-product



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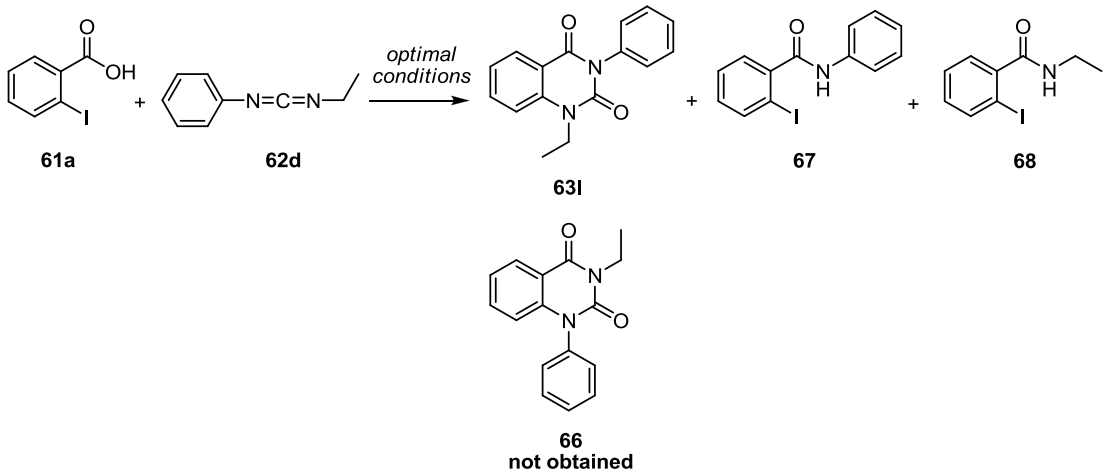
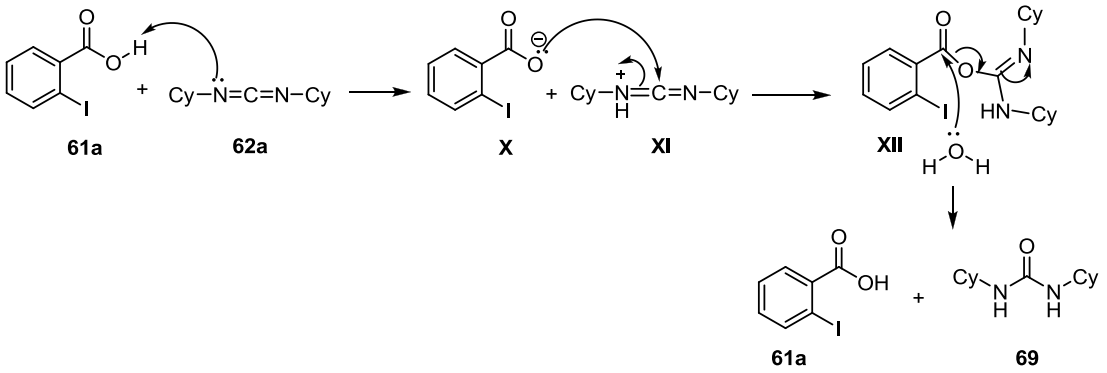
Moreover, with asymmetric carbodiimides, *N*-((ethylimino)methylene)-aniline, (**62d**), the reaction afforded only 1-ethyl-3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**63l**) in low yield, 22 % (entry 3). We did not obtain another regioisomer, 3-ethyl-1-phenylquinazoline-2,4(1*H*,3*H*)-dione (**66**). The amide by-product **67** was found to be a major product. In addition, 2-iodo-*N*-phenylbenzamide (**68**) was also obtained from this reaction. Based on the result, aryl-substituted carbodiimides were not applicable to the reaction giving low yield of corresponding quinazolinediones. Amide by-product always was found as major products resulted from elimination presumably due to acidicity of amide proton (**Scheme 19**).

Scheme 19 The result of benzoic acid **61a** and carbodiimides **62d** under optimal conditions



Next, we focused on a possible reaction mechanism. Since we did observe 1,3-dicyclohexylurea **69** from the ^{1}H NMR spectrum of the crude reaction mixture. We proposed that urea **69** was possibly obtained from the moisture in the solvent (**Scheme 20**).

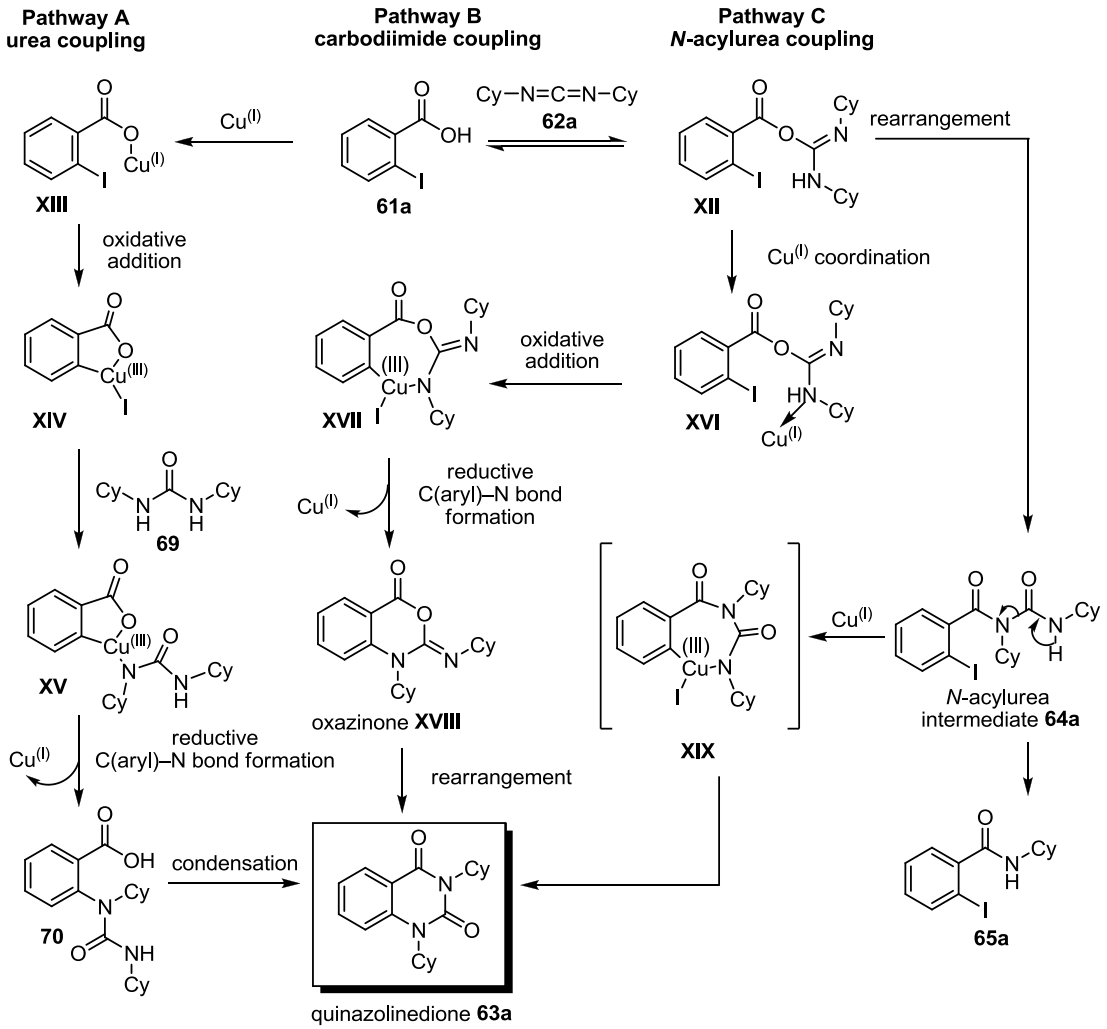
Scheme 20 The possible pathway of the generation of **69**



We expected the first possibility of the mechanism involving a coupling reaction of 2-iodobenzoic acid **61a** and the urea **69**, generated *in situ* from carbodiimides **62a** with moisture in the reaction. Then benzoic acid intermediate **70** underwent condensation to form the desired product (**Scheme 21**, **Pathway A**).

The second plausible pathway to obtain the desired product was a coupling of 2-iodobenzoic acid (**61a**) and carbodiimides **62a** to provide intermediate **XII** followed by intramolecular copper coupling to form C(aryl)−N bond giving an intermediate oxazinone **XVIII**. The last transformation was the rearrangement of **XVIII** to generate the desired quinazolinedione **63a** (**Scheme 21**, **Pathway B**).

Scheme 21 Possible reaction mechanisms

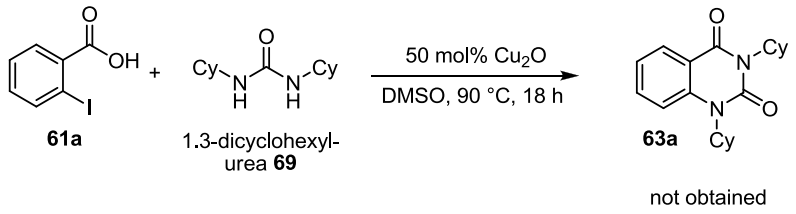


Our last proposed possible reaction pathway involved the intramolecular copper coupling of *N*-acyl urea intermediate **64a** to form the desired product. The reasons were that **64a** could be isolated, and we also proved that the generation of **64a** was a non-catalyzed reaction. Moreover, **64a** could undergo an elimination to give amide by-product **65a** considering as a competitive reaction.

We tried to prove those plausible pathways of the reaction mechanism from our control experiments. Initially, we focused on condensation of benzoic acid **70** (**Pathway A**). We designed the experiment by subjecting 2-iodobenzoic acid **61a** and 1,3-dicyclohexylurea **69** to optimal conditions. The desired product **63a** was not obtained. We observed the remaining starting materials from the ^{1}H NMR spectrum of the crude reaction mixture (**Scheme 22**).

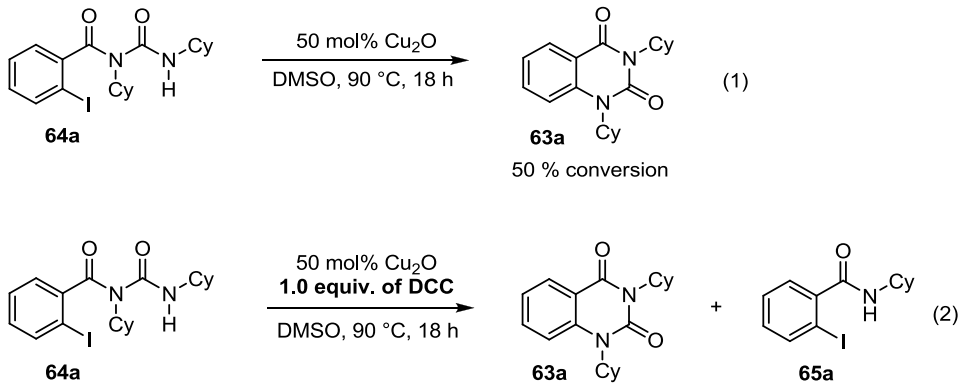
Based on this control experiment, we could conclude that the generation of product was not from pathway A.

Scheme 22 The first control experiments



Next, we focused on the pathway C involving the *N*-acylurea intermediate **64a** under optimal conditions. The result showed the intermediate **64a**. The *N*-acyl urea **64a** was subjected to the optimal conditions. The result of reaction showed that formed with 1:1 ratio of the product **63a** and *N*-acyl urea **64a** (**Scheme 23**, eq. (1)). The result showed that **64a** could be converted to product **63a**. Since our optimal conditions required two equivalents of DCC, we added one equivalent of DCC to the reaction (**Scheme 23,** eq. (2)). The **64a** was completely consumed providing product **63a** and by-product amide **65a** in 3:1 ratio. The result displayed that the excess DCC could act as a based to eliminate the *N*-acylurea **64a** to give the amide byproduct. Based on these results, the quinazolinedione **63a** could be synthesized through *N*-acylurea intermediate which was shown in the pathway C.

Scheme 23 The control experiments

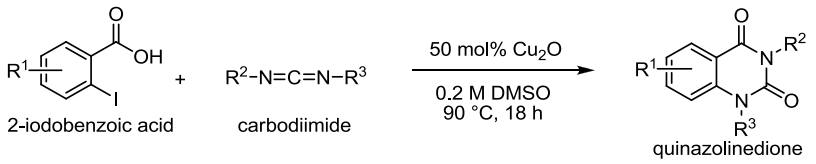


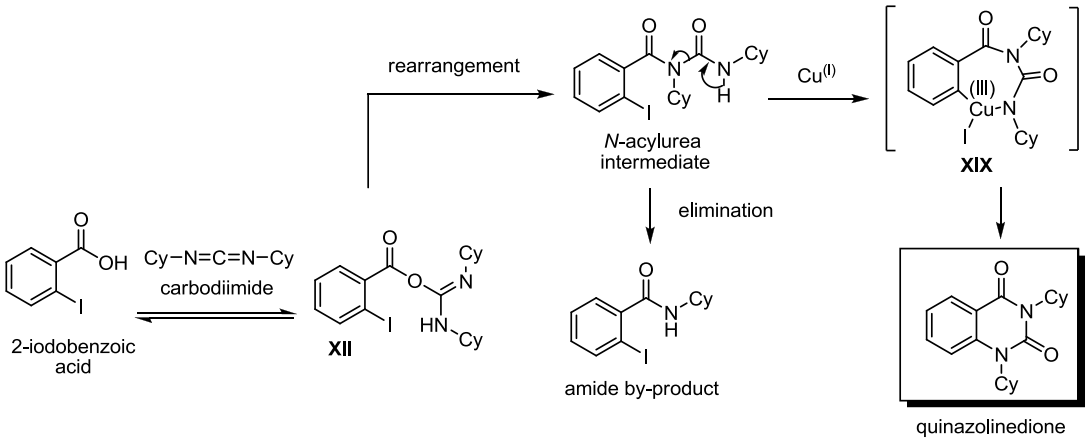
Next, attempts to investigate pathway B by finding an oxazinone intermediate *via* ^{1}H NMR spectrum of the crude reaction mixture were failed. Although we could

not rule out the pathway B, based on the results from the control experiments we believed that the desired product was highly obtained from *N*-acylurea intermediate (**Scheme 21**, **Pathway C**).

1.3 CONCLUSION

We achieved to synthesize quinazolinedione derivatives *via* copper-catalyzed domino reaction from 2-iodobenzoic acids and carbodiimides under simple conditions in one-pot manner. The domino procedures consisted of intramolecular C(aryl)−N formation and rearrangement. The non-catalyzed pathway was the generation of the *N*-acylurea. We also found that in the presence of base, *N*-acylurea intermediate could undergo elimination to give amide by-product. Furthermore, a variety of 2-iodobenzoic acids with electron-donating group provided good yields whereas electron-withdrawing substituent gave low yield. Moreover, the category of carbodiimides was also explored. The good yields of products were obtained from dialkyl symmetric substituent. On the other hand, the reactions provided the low yield of product in diaryl symmetric or asymmetric substituents carbodiimides. In addition, although we could not clarify the mechanism, based on control experiments we suggested that the quinazolinediones were obtained from *N*-acylurea intermediates.





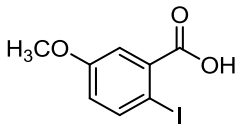
1.4 EXPERIMENTAL

1.4.1 General Information

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

1.4.2 Preparation of Starting Materials

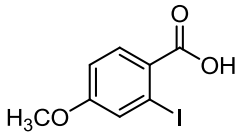
1.4.2.1 Synthesis of 2-Iodobenzoic Acids



61b
$C_8H_7IO_3$
M.W. = 278.0439 g/mol

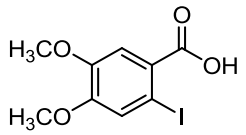
2-iodo-5-methoxybenzoic acid (61b). Prepared according to literature procedure (Uyanik *et al.*, 2009). A solution of 2-amino-5-methoxybenzoic acid (835.8 mg, 5.0 mmol) in water (10.0 mL) and conc. H_2SO_4 (5.0 mL) was stirred at 0 ˚C. The solution was white-yellow. Then a solution of sodium nitrite (414.0 mg, 6.0 mmol) in water (5.0 mL) was added slowly. The reaction mixture changed to orange brown and was allowed to stir at 0 ˚C for 1 hour, followed by a slow addition of potassium iodide

(2,490.0 mg, 15.0 mmol) in water (7.5 mL). The reaction became dark brown and stirred at 90 ˚C for 2 hours. After that, the mixture was quenched with sat. NH_4Cl and extracted with EtOAc. The iodine in organic extracted layer was moved by sat. $Na_2S_2O_3$. The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to obtain a violet-orange solid. The residue was purified by column chromatography (4:1, hexanes:EtOAc) to obtain a desired product as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.7 Hz, 1H), 7.55 (d, *J* = 3.0 Hz, 1H), 6.80 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 159.6, 142.5, 113.9, 120.5, 117.3, 83.1, 55.6. Other data were identical to the literature values (Nguyen *et al.*, 2007).



61c
$C_8H_7IO_3$
M.W. = 278.0439 g/mol

2-iodo-4-methoxybenzoic acid (61c). Prepared according to literature procedure (Uyanik *et al.*, 2009). A solution of 2-amino-4-methoxybenzoic acid (501.5 mg, 3.0 mmol) in conc. HCl (4.0 mL) was stirred at 0 ˚C. Then a solution of sodium nitrite (310.5 mg, 4.5 mmol) in water (1.0 mL) was added. The reaction mixture became orange yellow. After that a solution of potassium iodide (996.0 mg, 6.0 mmol) in water (2.4 mL) was added slowly. The reaction mixture was stirred at 0 ˚C for 30 minutes. The reaction mixture changed to dark brown and was stirred at room temperature, and heated at 90 ˚C for 2 hours. The reaction was completed then cooled at room temperature. The mixture was diluted with water and extracted with EtOAc. The organic extracted layers were washed with sat. $Na_2S_2O_3$ and brine. The resulting extract was dried over anhydrous Na_2SO_4, filtered and concentrated to afford orange solid. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.82 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 1.9 Hz, 1H), 7.08 (dd, *J* = 8.7, 1.9 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 166.9, 161.4, 132.1, 127.2, 126.2, 113.7, 96.0, 55.7. Other data were identical to the literature values (Nguyen *et al.*, 2007).



61d
$C_9H_9IO_4$
M.W. = 308.0698 g/mol

2-iodo-4,5-dimethoxybenzoic acid (61d):

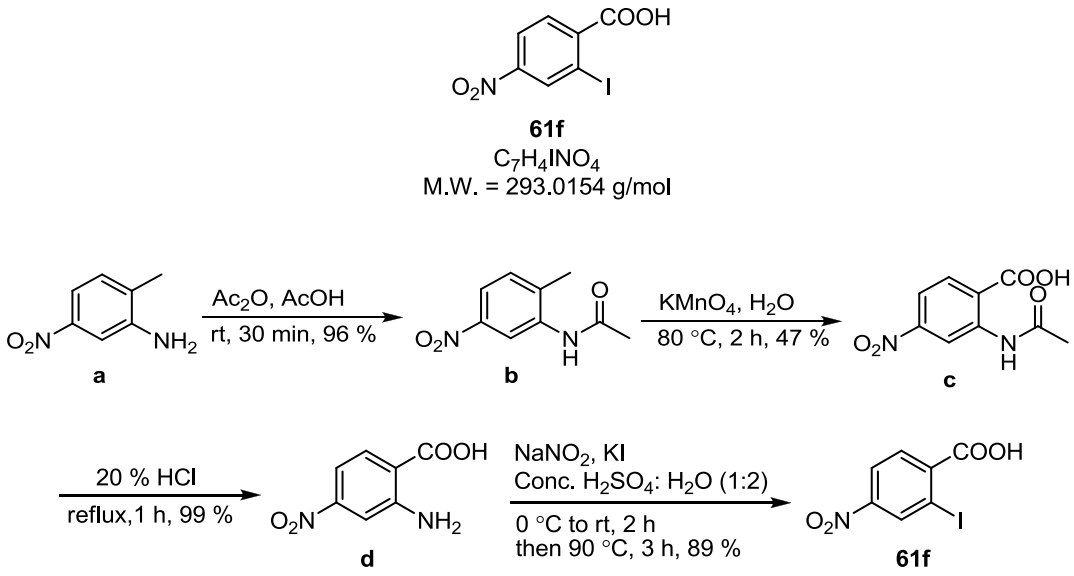
Step 1: Preparation of 2-iodo-4,5-dimethoxybenzaldehyde.

2-Iodo-4,5-dimethoxybenzaldehyde. Prepared according to literature procedure (Hathaway *et al*., 2007). A solution of 3,4-dimethoxybenzaldehyde (369.0 mg, 2.2 mmol) in MeOH (13.0 mL) was added silver nitrate (377.0 mg, 2.2 mmol) and iodine (650.0 mg, 2.6 mmol). The reaction was stirred at room temperature for overnight under argon. The yellow participate of silver iodide was filtered off and washed with methanol. The filtrate was evaporated and diluted with EtOAc, then washed with sat. $Na_2S_2O_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (4:1 hexanes:EtOAc) to afford a yellow solid (660.0 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 154.4, 149.7, 128.3, 121.7, 111.0, 92.7, 56.5, 56.0. Other data were identical to the literature values (McGill *et al*., 2007).

Step 2: Preparation of 2-iodo-4,5-dimethoxybenzoic acid (**61d**).

2-iodo-4,5-dimethoxybenzoic acid (61d). Prepared according to literature procedure (Su *et al*., 2008). A solution of 2-iodo-4,5-dimethoxybenzaldehyde (584.0 mg, 2.0 mmol) in *t*-BuOH (12.0 mL) was added 2-methyl-2-butene (2.0 mL, 20.0 mmol). Then added the mixture solution of $NaHPO_4$ (1,440.0 mg, 12.0 mmol) and sodium chlorite (542.6 mg, 6.0 mmol) in water (6.0 mL). The yellow white reaction mixture was stirred at 0 ˚C to room temperature for overnight. The mixture was quenched with 1M HCl, then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to provide **61d** as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.44 (s, 1H), 3.94 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 152.7, 148.8, 124.5, 124.4, 114.8, 85.5, 56.4, 56.1. Other data were identical to the literature values (Llangovan *et al*., 2016).

General Procedure for the Synthesis of 2-iodo-4-nitrobenzoic acid (61f).



Step 1: Preparation of *N*-(2-methyl-5-nitrophenyl)acetamide (**b**).

Prepared according to literature procedure (Al-Rawi *et al*., 2014). To a solution of 2-methyl-5-nitroaniline (**a**) (1,521.5 mg, 10.0 mmol) in acetic acid (12.0 mL) was added slowly the acetic anhydride (3.8 mL, 40.0 mmol) at room temperature for 30 minutes. The acetic acid was removed under vacuum at 50 ˚C to afford a white solid of *N*-(2-methyl-5-nitrophenyl)acetamide (**b**) in 1,873 mg (96% yield).

Step 2: Preparation of 2-acetamido-4-nitrobenzoic acid (**c**).

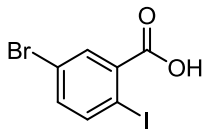
Prepared according to literature procedure (Al-Rawi *et al*., 2014). To a solution of acetamide **b** (1,941.8 mg, 10.0 mmol) in water (33.0 mL) refluxed at 80 ˚C. Then KMnO4 (8,691.6 mg, 55.0 mmol) was added in eight portions. The mixture was dark brown and then stirred at the same temperature for 2 hours. After that the mixture was cooled at room temperature. The black solid of MnO_2 was filtered with suction funnel. The orange eluted liquid was cooled in ice bath and was acidic with 4M HCl. The orange liquid became yellow solid and filtered with suction funnel to provide a yellow solid of 2-acetamido-4-nitrobenzoic acid (**c**) in 1,058.8 mg (47% yield).

Step 3: Preparation of 2-amino-4-nitrobenzoic acid (**d**).

Prepared according to literature procedure (Heppell *et al*., 2014). To a solution of 2-acetamido-4-nitrobenzoic acid (**c**) (1,000 mg, 4.46 mmol) in 20% v/v HCl (15.0 mL) was refluxed at 120 ˚C for 1 hour. The reaction mixture changed orange yellow to orange. After that the mixture was cooled at room temperature, then cooled at 0 ˚C, and followed by addition of a solution of NaOH to neutralize the reaction mixture. The reaction mixture was crystallized with ethyl ether and filtered through the suction funnel to provide red orange solid in 810.9 mg (99 % yield).

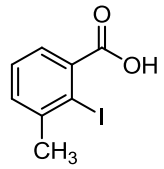
Step 4: Preparation of 2-iodo-4-nitrobenzoic acid (**61f**).

Prepared according to literature procedure (Uyanik *et al*., 2009). To a solution of 2-amino-4-nitrobenzoic acid (**d**) (445.3 mg, 2.5 mmol) in conc. H_2SO_4 (2.5 mL) stirred at 0 ˚C for 15 minutes. Then a solution of sodium nitrite (431.2 mg, 6.25 mmol) in water (3.5 mL) was added to appear a yellow orange mixture. The reaction mixture was cooled at 0 ˚C to room temperature for 2 hours. After that a solution of potassium iodide (1,245.0 mg, 7.5 mmol) in water (2.5 mL) was added to provide black mixture. The mixture was cooled at room temperature and heat at 90 ˚C for 1 hour. A completion of reaction cooled the mixture to room temperature. After that, the mixture was quenched with sat. NH_4Cl, extracted with EtOAc and washed sat. $Na_2S_2O_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated with vacuum that to obtain yellow-orange solid in 649.9 mg (89 % yield). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.64 (d, *J* = 2.1 Hz, 1H), 8.28 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 167.6, 148.1, 143.4, 134.3, 130.1, 123.1, 93.5. Other data were identical to the literature values (Cui *et al*., 2011).



61g
$C_7H_4BrIO_2$
M.W. = 326.9139

5-bromo-2-iodobenzoic acid (61g). Prepared according to literature procedure (Valois-Escamilla *et al*., 2011). A solution of 2-iodobenzoic acid (1,240.0 mg, 5.0 mmol) in Conc. H_2SO_4 (10.0 mL) was heated at 60 ˚C for 20 minutes. The solution was yellow orange. Then *N*-bromosuccinimide (1,668.0 mg, 6.0 mmol) was added in three portions each during 15 minutes. The mixture was brown and allowed to stir for 2 hours. After the reaction was completed, filtered and wash with cold water. A white solid was obtained. The aqueous eluted was extracted with EtOAc, the organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated that to obtain white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 2.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.33 (dd, *J* = 8.4, 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 143.2, 136.6, 134.9, 134.7, 122.4, 92.7. Other data were identical to the literature values (Valois-Escamilla *et al*, 2011).

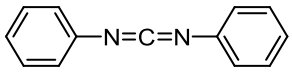


61i
$C_8H_7IO_2$
M.W. = 262.0445 g/mol

2-iodo-3-methylbenzoic acid (61i): Prepared according to literature procedure (Moorthy *et al*., 2011). A solution of 2-amino-3-methylbenzoic acid (453.5 mg, 3.0 mmol) in conc. H_2SO_4 (1.70 mL) and water (3.4 mL) was stirred at 0 ˚C for 15 minutes, then added slowly a solution of sodium nitrite (271.0 mg, 3.90 mmol) in water (1 mL) to afford orange yellow mixture. The reaction mixture was maintained at 0 ˚C for 1.5 hours, then added slowly a solution of potassium iodide (2,490 mg, 14.99 mmol) in water (3.0 mL) to appear brown mixture. The mixture was stirred at room temperature for overnight, then diluted with H_2O and extracted with EtOAc. The extracted mixture was washed with sat. $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (7:3 hexanes:EtOAc) to afford 2-iodo-3-methylbenzoic acid (**61i**) as orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2,

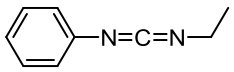
143.9, 136.2, 132.9, 128.4, 127.8, 100.7, 30.1. Other data were identical to the literature values (Imbos *et al*., 2002).

1.4.2.2 Synthesis of Carbodiimides



62c
$C_{13}H_{10}N_2$
M.W. = 194.2319 g/mol

***N,N'*-methanediylidenedianiline (62c):** Prepared according to literature procedure (Chaudhari *et al*., 2010). To round bottom flask was added IBX (560.0 mg, 2.0 mmol) in CH_2Cl_2 (9.0 mL) at 0 ˚C followed by addition of triethylamine (506 µL, 4.0 mmol). A 1,3-diphenylthiourea (456.0 mg, 2.0 mmol) was added to the mixture. The reaction mixture was maintained at 0 ˚C for 30 minutes to provide a light yellow mixture, then filtered the white solid with cotton and concentrated with vacuum. The crude mixture was diluted with hexanes and then sucked up a hexanes layer. The hexanes layer dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (100% hexanes) to provide coloress oil in 100 mg (25% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (m, 6H), 7.19-7.17 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 136.2, 129.2, 125.2, 124.0. Other data were identical to the literature values (Akamanchi *et al*., 2010).



62d
$C_9H_{10}N_2$
M.W. = 146.1891 g/mol

***N*-((ethylimino)methylene)aniline (62d):**

Step 1: Preparation of 1-ethyl-3-phenylurea.

Prepared according to literature procedure (Houlden *et al*., 2008). To stir a solution of ethylamine (676.0 µL, 12 mmol) in CH_2Cl_2 (44.0 mL) at 0 ˚C for 10 minutes was added slowly phenylisocyanate (1,100 µL, 10.11 mmol). The reaction mixture was stirred at 0 ˚C to room temperature for 16 hours to provide coloress mixture, washed

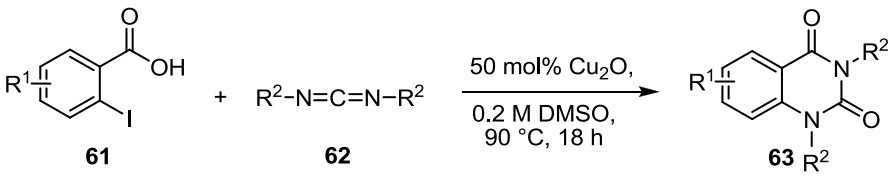
with 2M HCl 2 times, then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The white solid of 1-ethyl-3-phenylurea was obtained in 1,620 mg (98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 4.2 Hz, 3H), 7.10-7.02 (m, 1H), 6.91 (s, 1H), 5.16 (brs, 1H), 3.26 (q, *J* = 7.2 Hz, 2H), 1.71 (brs, 1H), 1.12 (t, *J* = 7.2 Hz, 3H). Other data were identical to the literature values (Lee *et al*., 2004).

Step 2: Preparation of *N*-((ethylimino)methylene)aniline (**62d**).

Prepared according to literature procedure (Yu *et al*., 2008). To round bottom flask was added a solution of 1-ethyl-3-phenylurea (821.0 mg, 5.0 mmol) in CH_2Cl_2 (40 mL), then added PPh_3 (2,885.1 mg, 11.0 mmol) and NEt_3 (2,810.8 µL, 20.0 mmol), followed by a solution of CBr_4 (3,647.9 mg, 11.0 mmol) in CH_2Cl_2 (12.5 mL) was added slowly to provide light yellow mixture. The reaction mixture was stirred at 0 ˚C to room temperature for 16 hours and concentrated with vacuum. The crude mixture was purified by column chromatography (4:1 hexanes:EtOAc) to afford *N*-((ethylimino)methylene)aniline (**62d**) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.22 (m, 2H), 7.12-7.04 (m, 3H), 3.44 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 136.6, 129.4, 124.7, 123.5, 41.8, 17.0. Other data were identical to the literature values (Katritzky *et al*., 1990).

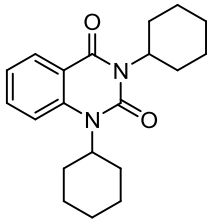
1.4.3 Synthesis of 2,4-Quinazolinedione Derivatives

General Procedure A: Synthesis of Quinazolinedione Derivatives



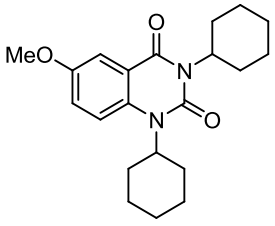
The reaction of 2-iodobenzoic acids (**61a**) and *N*,*N*′-methanediylidenedicyclohexanamines (**62a**) is representative: A round bottom flask was added with 2-

iodobenzoic acids (**61a**) (0.50 mmol), *N,N'*-methanediylidenedicyclohexanamine (**62a**) (1.0 mmol), Cu_2O (0.25 mmol), in DMSO (2.5 mL). The reaction mixture was allowed to stir at 90 ^oC for 18 hours. After completion of reaction, the dark-brown reaction mixture was cooled to room temperature, quenched with 1M HCl, extracted with EtOAc, and DMSO was moved by distilled water. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (4:1 hexanes:EtOAc) to provide **63a** as a white solid (122.4 mg, 75% yield).



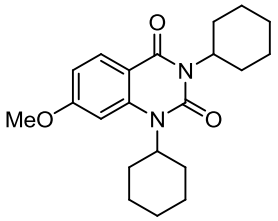
63a
$C_{20}H_{26}N_2O_2$
M.W. = 326.4326 g/mol

1,3-dicyclohexylquinazoline-2,4(1*H*,3*H*)-dione (**63a**). Prepared according to general procedure A from 2-iodobenzoic acid (**61a**) and *N,N'*-methanediylidenedicyclo-hexanamine (**62a**). Yield 122.4 mg (75 %) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.60 (td, *J* = 8.5, 1.5 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 4.89 (m, 1H), 4.42 (brs, 1H), 2.50-2.45 (m, 4H), 1.96-1.65 (m, 8H), 1.46-1.25 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 150.4, 140.5, 134.2, 129.2, 122.3, 116.8, 113.9, 58.1, 54.8, 29.1, 28.8, 26.6, 26.5, 25.4, 25.3; IR (thin film) ν 2931, 2855, 1703, 1659, 1608, 1481, 1375, 1309, 759 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. for $C_{20}H_{26}N_2O_2$ 349.1892, found 349.1893.



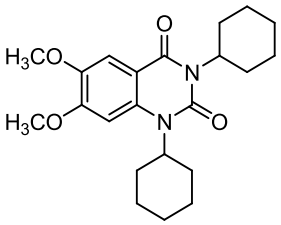
63b
$C_{21}H_{28}N_2O_3$
M.W. = 356.4586 g/mol

1,3-dicyclohexyl-6-methoxyquinazoline-2,4(1*H*,3*H*)-dione (**63b**). Prepared according to general procedure A from 2-iodo-5-methoxybenzoic acid (**61b**) and *N*,*N*′-methanediylidenedicyclohexanamine (**62a**). The residue was purified by column chromatography (5:1 hexanes:EtOAc) to give **63b** as a light yellow solid (119.4 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 3.0 Hz, 1H), 7.29 (s, 1H), 7.18 (dd, *J* = 9.2, 3.0 Hz, 1H), 4.87 (m, 1H), 4.40 (brs, 1H), 3.84 (s, 3H), 2.53-2.41 (m, 4H), 1.93-1.64 (m, 10H), 1.46-1.22 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 154.8, 150.3, 134.6, 123.2, 117.5, 115.7, 109.9, 58.1, 55.8, 55.0, 29.2, 28.8, 26.6, 26.5, 25.4, 25.3; IR (thin film) ν 2932, 2854, 1698, 1657, 1503, 1474, 1367, 1311, 1262, 754 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. for $C_{21}H_{28}N_2O_3$ 379.1998, found 379.1997.



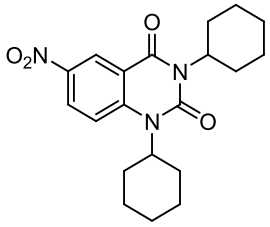
63c
$C_{21}H_{28}N_2O_3$
M.W. = 356.4586 g/mol

1,3-dicyclohexyl-7-methoxyquinazoline-2,4(1*H*,3*H*)-dione (**63c**). Prepared according to general procedure A from 2-iodo-4-methoxybenzoic acid (**61c**) and *N*,*N*′-methanediylidenedicyclohexanamine (**62a**). The residue was purified by column chromatography (4:1 hexanes:EtOAc) to provide **63c** as a white solid (137.3 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.5 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.89 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.81 (s, 4H), 3.52 (m, 1H), 2.05-1.67 (m, 9H), 1.34-1.02 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 160.0, 153.1, 135.2, 127.1, 124.5, 113.6, 92.7, 57.7, 55.4, 49.3, 32.1, 30.5, 26.0, 25.2, 25.0, 24.4; IR (thin film) ν 2931, 2855, 1698, 1648, 1592, 1515, 1228, 1024, 755 cm-1; HRMS (ESI) *m/z*: [M+H]+ calcd. for $C_{21}H_{28}N_2O_3$ 357.2178, found 357.2177.



63d
$C_{22}H_{30}N_2O_4$
M.W. = 386.4846 g/mol

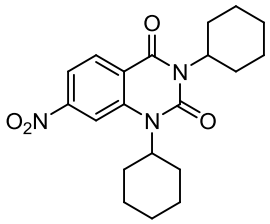
1,3-dicyclohexyl-6,7-dimethoxyquinazoline-2,4(1*H*,3*H*)-dione (**63d**). Prepared according to general procedure A from 2-iodo-4,5-dimethoxybenzoic acid (**61d**) and *N*,*N*′-methanediylidenedicyclohexanamine (**62a**). The residue was purified by column chromatography (3:1:1 hexanes:EtOAc:acetone) to provide **63d** as a white solid **(**112.1 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 6.79 (s, 1H), 4.89 (m, 1H), 4.45 (m, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 2.54-2.41 (m, 4H), 1.97-1.65 (m, 10H), 1.50-1.20 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 154.3, 150.9, 145.1, 135.9, 109.3, 97.4, 56.2, 54.9, 29.4, 28.9, 26.6, 26.5, 25.5, 25.4; IR (thin film) υ 2932, 2856, 1704, 1660, 1608, 1481, 1455, 1374, 1310, 1218, 759 cm-1; HRMS (ESI) *m/z*: [M+H]+ calcd. For $C_{22}H_{30}N_2O_4$ 387.2284, found 387.2285.



63e
$C_{20}H_{25}N_3O_4$
M.W. = 371.4302 g/mol

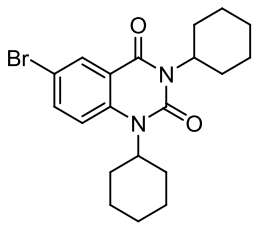
1, 3-dicyclohexyl-6-nitroquinazoline-2, 4(1*H*, 3*H*)-dione (**63e**). Prepared according to general procedure A from 2-iodo-5-nitrobenzoic acid (**61e**) and *N*,*N*′-methanediylidenedicyclohexanamine (**62a**). The residue was purified by column chromatography (10:1 hexanes:EtOAc) to provide **63e** as a white solid (40.8 mg, 22%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (d, *J* = 2.7 Hz, 1H), 8.42 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.45 (d, *J* = 9.3 Hz, 1H), 4.87 (m, 1H), 4.48 (brs, 1H), 2.54-2.39 (m, 4H), 1.99-1.67 (m, 8H), 1.51-1.20 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 150.0, 144.7, 142.3, 128.8, 125.7, 116.9, 145.0, 59.2, 55.6, 29.2, 28.7, 26.5, 26.3, 25.3, 25.2;

IR (thin film) ν 2932, 2855, 1670, 1612, 1510, 1327, 745 cm-1; HRMS (ESI) *m/z*: [M+H]+ calcd. for $C_{20}H_{25}N_3O_4$ 372.1923, found 372.1925.



63f
$C_{20}H_{25}N_3O_4$
M.W. = 371.4302 g/mol

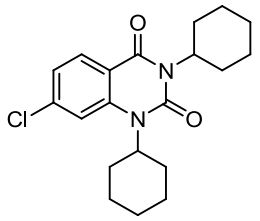
1,3-dicyclohexyl-7-nitroquinazoline-2,4(1*H*,3*H*)-dione (**63f**). Prepared according to general procedure A from 2-iodo-4-nitrobenzoic acid (**61f**) and *N*,*N*′-methanediylidenedicyclohexanamine (**62a**). The residue was purified by column chromatography (9:1 hexanes:EtOAc) to provide **63f** as a white solid (12.9 mg, 7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.6 Hz, 1H), 8.23 (s, 1H), 7.98 (dd, *J* = 8.6, 1.7 Hz, 1H), 4.92-4.81 (m, 1H), 4.49 (brs, 1H), 2.54-2.38 (m, 4H), 1.99-1.63 (m, 10H), 1.55-1.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 151.3, 150.1, 140.9, 130.9, 120.8, 116.3, 109.7, 58.8, 55.6, 29.1, 28.7, 26.4, 26.3, 25.2, 25.1; IR (thin film) ν 2933, 2857, 1713, 1667, 1621, 1595, 1538, 1456, 1348, 1214, 835 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. For $C_{20}H_{25}N_3O_4$ 394.1743, found 394.1740.



63g
$C_{20}H_{25}BrN_2O_2$
M.W. = 405.3287 g/mol

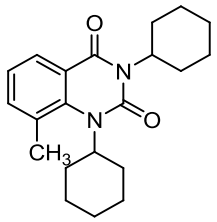
6-bromo-1, 3-dicyclohexylquinazoline-2, 4(1*H*, 3*H*)-dione (**63g**). Prepared according to general procedure A from 5-bromo-2-iodobenzoic acid (**61g**) and *N*,*N*′-methanediylidenedicyclohexanamine (**62a**). The residue was purified by column chromatography (10:1 hexanes:EtOAc) to provide **63g** as a white solid (149.9 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.5 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.5

Hz, 1H), 7.22 (d, *J* = 9.0 Hz, 1H), 4.91-4.80 (m, 1H), 4.34 (brs, 1H), 2.50-2.39 (m, 4H), 1.96-1.65 (m, 9H), 1.44-1.25 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 150.2, 139.4, 136.9, 131.6, 118.4, 115.9, 115.1, 58.4, 55.2, 29.1, 28.8, 26.5, 26.4, 25.3, 25.2; IR (thin film) ν 2933, 2855, 1704, 1659, 1600, 1486, 1455, 895, 750 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. For $C_{20}H_{25}N_2O_2Br$ 427.0997, found 427.0996.



63h
$C_{20}H_{25}ClN_2O_2$
M.W. = 360.8777 g/mol

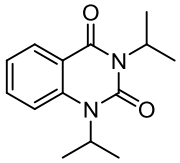
7-chloro-1,3-dicyclohexylquinazoline-2,4(1*H*,3*H*)-dione (**63h**). Prepared according to general procedure A from 4-chloro-2-iodobenzoic acid (**61h**) and *N*,*N*′-methanediylidenedicyclohexanamine (**62a**). The residue was purified by column chromatography (5:1 hexanes:EtOAc) to provide **63h** as a white solid (120.8 mg, 67 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.30 (s, 1H), 7.16 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.86 (m, 1H), 4.30 (brs, 1H), 2.50-2.38 (m, 4H), 1.96-1.64 (m, 10H), 1.50-1.20 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 150.3, 141.3, 140.6, 130.7, 122.8, 115.2 114.1, 58.5, 55.0, 29.1, 28.8, 26.5, 26.4, 25.3, 25.2; IR (thin film) υ 2933, 2856, 1707, 1662, 1603, 1456, 1362, 1345, 1299, 1216, 756 cm-1; HRMS (ESI) *m/z*: [M+H]+ calcd. For $C_{20}H_{25}N_2O_2Cl$ 361.1683, found 361.1685.



63i
$C_{21}H_{28}N_2O_2$
M.W. = 340.4592 g/mol

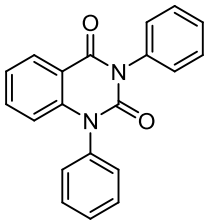
1,3-dicyclohexyl-8-methylquinazoline-2,4(1*H*,3*H*)-dione (**63i**). Prepared according to general procedure A from 2-iodo-3-methylbenzoic acid (**61i**) and *N*,*N*′-methanediylidenedicyclohexanamine (**62a**). The residue was purified by column

chromatography (10:1 hexanes:EtOAc) to provide **63i** as a white solid (136.2 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 4.72-4.62 (m, 1H), 3.63-3.53 (m, 1H), 2.50-2.38 (m, 7H), 1.88-1.85 (m, 6H), 1.69-1.66 (m, 4H), 1.46-1.29 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 152.8, 143.1, 138.0, 126.4, 126.1, 123.4, 120.3, 65.4, 55.0, 30.7, 28.9, 26.8, 26.4, 25.4, 25.2, 20.8; IR (thin film) υ 3019, 2932, 2855, 1704, 1667, 1592, 1486, 1412, 1367, 1340, 1294, 1198, 1096, 896 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. For $C_{21}H_{28}N_2O_2$ 363.2048, found 363.2048.



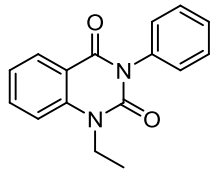
63j
$C_{14}H_{18}N_2O_2$
M.W. = 246.3049 g/mol

1,3-diisopropylquinazoline-2,4(1*H*,3*H*)-dione (**63j**). Prepared according to general procedure A from 2-iodobenzoic acid (**61a**) and *N,N'*-methanediylidenedipropan-2-amine (**62b**). The residue was purified by column chromatography (2:1 hexanes:EtOAc) to provide **63j** as a white solid (73.8 mg, 60 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.60 (td, *J* = 7.9, 1.5 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 5.31 (m, 1H), 5.05 (brs, 1H), 1.62 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 150.3, 140.0, 134.2, 129.2, 122.3, 116.7, 114.0, 48.5, 46.4, 19.8, 19.5 cm-1; IR (thin film) υ 2969, 2935, 1705, 1661, 1610, 1483, 1368, 1313, 1231, 762 cm-1; HRMS (ESI) *m/z*: [M+H]+ calcd. For $C_{14}H_{18}N_2O_2$ 247.1447, found 247.1448.



63k
$C_{20}H_{14}N_2O_2$
M.W. = 314.3374 g/mol

1,3-diphenylquinazoline-2,4(1*H*,3*H*)-dione (**63k**). Prepared according to general procedure A from 2-iodobenzoic acid (**61a**) and *N,N'*-methanediylidenedianiline (**62c**). The residue was purified by silica column chromatography (5:1 hexanes:EtOAc) to provide **63k** as a white solid (37.7 mg, 24 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.8 Hz, 1H), 7.67-7.25 (m, 12H), 6.64 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 150.8, 141.8, 136.3, 135.2, 135.0, 130.3, 129.4, 129.3, 129.1, 129.0, 128.7, 128.5, 123.4, 120.8, 115.6 cm-1; IR (thin film) υ 3267, 3065, 2927, 2857, 1716, 1674, 1608, 1494, 1476, 1382, 1318, 1235, 1207, 1152, 1024, 755, 693 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. For $C_{20}H_{14}N_2O_2$ 337.0953, found 337.0954.

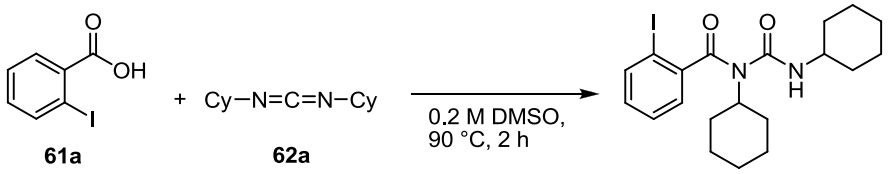


63l
$C_{16}H_{14}N_2O_2$
M.W. = 266.2946 g/mol

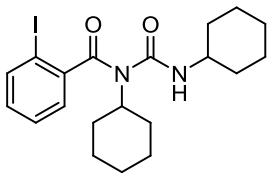
1-ethyl-3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**63l**). Prepared according to general procedure A from 2-iodobenzoic acid (**61a**) and *N*-((ethylimino)methylene)aniline (**62d**). The residue was purified by column chromatography (4:1 hexanes:EtOAc) and then 1:1, 1:2 Hexanes:CH_2Cl_2 to provide **63l** as a white solid (35.9 mg, 27 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 6.7, 1.2 Hz, 1H), 7.74-7.68 (m, 1H), 7.55-7.43 (m, 4H), 7.41-7.27 (m, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 150.5, 139.8, 135.5, 135.3, 129.4, 129.2, 128.5, 128.3, 122.8, 116.0, 113.5, 38.8, 12.4; IR (thin film) υ 1704, 1682, 1654, 1605, 1479, 1396, 1296, 762 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. For $C_{16}H_{14}N_2O_2$ 289.0953, found 289.0951.

1.4.4 Synthesis of *N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-2-iodobenzamide (64a)

General Procedure B: Synthesis of *N*-cyclohexyl-*N*-(cyclohexylcarbamoyl) -2-iodobenzamide (64a).



The reaction of 2-iodobenzoic acids (**61a**) and *N*,*N*′-methanediylidenedicyclohexanamines (**62a**) is representative: A round bottom flask was added with 2-iodobenzoic acids (**61a**) (0.50 mmol) and *N*,*N*′-methanediylidenedicyclohexanamine (**62a**) (1.0 mmol) in DMSO (2.5 mL). The reaction mixture was allowed to stir at 90 ^{o}C for 2 hours. After completion of reaction, the colorless reaction mixture was cooled to room temperature, quenched with 1M HCl, extracted with EtOAc, and DMSO was moved by distilled water. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (4:1 hexanes:EtOAc) to provide **64a** as a white solid (80% yield).



64a
$C_{20}H_{27}IN_2O_2$
M.W. = 454.3451 g/mol

***N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-2-iodobenzamide** (**64a**). Prepared according to general procedure B from 2-iodobenzoic acid (**61a**) and *N*,*N*′-methanediylidenedicyclohexanamine (**62b**). White solid was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 3.83 (brs, 1H), 3.51 (brs, 1H), 2.03-1.59 (m, 10H), 1.33-1.02 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 153.2, 143.0, 139.2, 130.6,

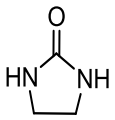
128.3, 126.6, 92.6, 57.9, 49.7, 32.3, 30.8, 26.3, 25.5, 25.3, 24.7; IR (thin film) ν 2931, 2855, 1698, 1684, 1522, 1226, 1153, 1051, 756 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. for $C_{20}H_{27}IN_2O_2$ 477.1015, found 477.1014.

CHAPTER 2

Synthesis of Imidazolidinones from *α*-Chloroaldoxime *O*-Methanesulfonates and Secondary Amine

2.1 INTRODUCTION

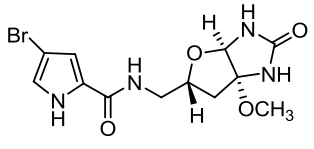
2.1.1 Introduction



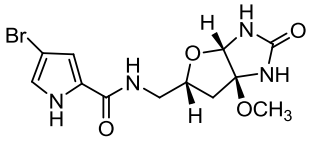
Imidazolidinone **71**

Imidazolidinone **71** is an interesting heterocyclic compound consisting of urea moiety in the structure. It is an important building block that is found in many natural products. Examples of natural products containing imidazolidinone moiety are shown in **Figure 4**. Slagenin B (**72**) and C (**73**) were extracted from the Okinawan marine sponge *Agelas nakamurai* and exhibited against marine leukemia L1210 cell *in vitro* with IC_{50} values of 7.5 and 7.0 µg/mL, respectively (Tsuda *et al*., 1999). Moreover, agelastatin A (**74**), isolated by Pietra and co-worker in 1994 from the deep water marine sponge *Agelas dendromorpha*, inhibited cancer cell proliferation in human bladder, skin, colon and breast carcinomas (Hama *et al*., 2009). In addition, Spironaamidine (**75**) was isolated from the marine sponge *Leucetta microraphis* and showed antimicrobial activity against *Bacillus cereus* (Nagasawa *et al*., 2011).

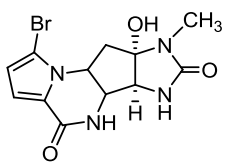
Figure 4 Examples of natural imidazolidinones



Slagenin B (**72**)

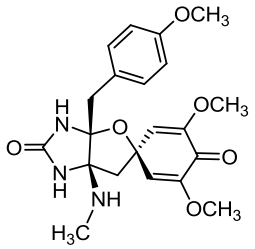


Slagenin C (**73**)



Agelastatin A (**74**)

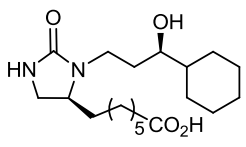
Figure 4 Examples of natural imidazolidinones (continued)



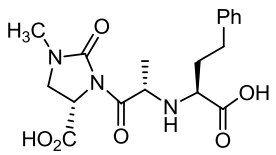
Spironaamidine (**75**)

Furthermore, many synthetic imidazolidinones were found in biologically active drugs. They exhibited a variety of medicinal properties. Some of them were shown in **Figure 5**. Imidazolidin-2-one **76** was a potent inhibitor of human platelet aggregation (Barraclough *et al.*, 1991). Imidapril (**77**) was used in a treatment of cardiovascular diseases (Hosoya *et al.*, 2002). 4,4-Disubstituted-2-imidazolidinone **78** exhibited potent neurokinin 1 (NK_1) which was applied in a treatment of emesis (Reichard *et al.*, 2003). (*S*)-1-(1-(4-Aminobenzoyl)indolin-6-ylsulfonyl)-4-phenyl-imidazolidin-2-one (**79**) displayed anticancer activity against human colorectal adenocarcinoma cell lines (Lee *et al.*, 2014). In addition, imidazolidinone **80** showed high activity against enterovirus E71 (Chang *et al.*, 2005). Compounds **81** and **83** were reactive against promastigote and amastigote of *Leishmania mexicana*. Moreover, these compounds and their analogues, such as **82** and **84**, showed activity of antileishmanial (Robert *et al.*, 2003).

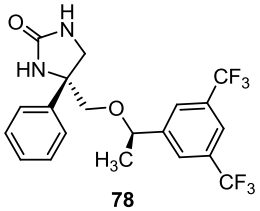
Figure 5 Examples of synthetic imidazolidinones



76

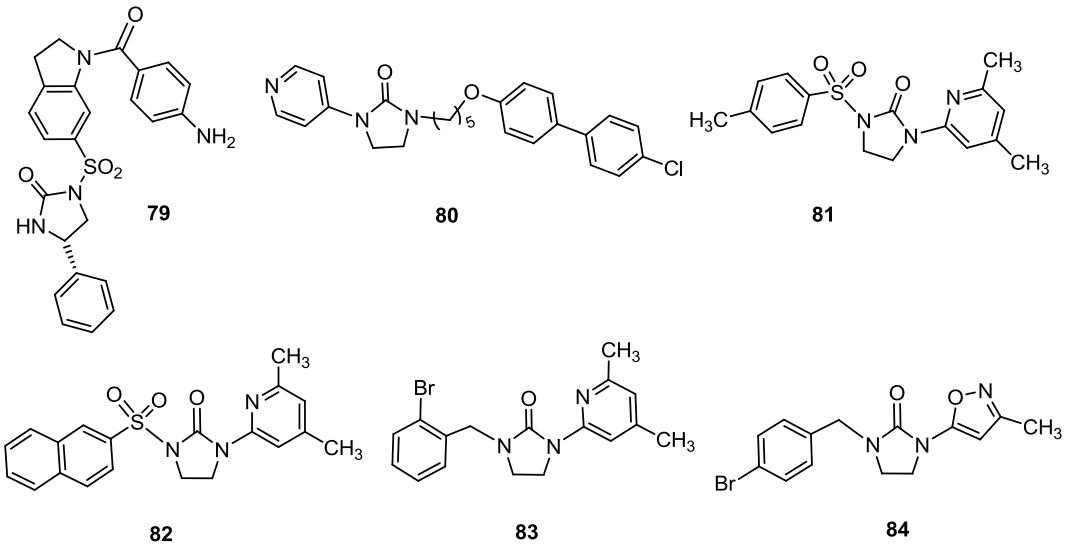


Imidapril (**77**)



78

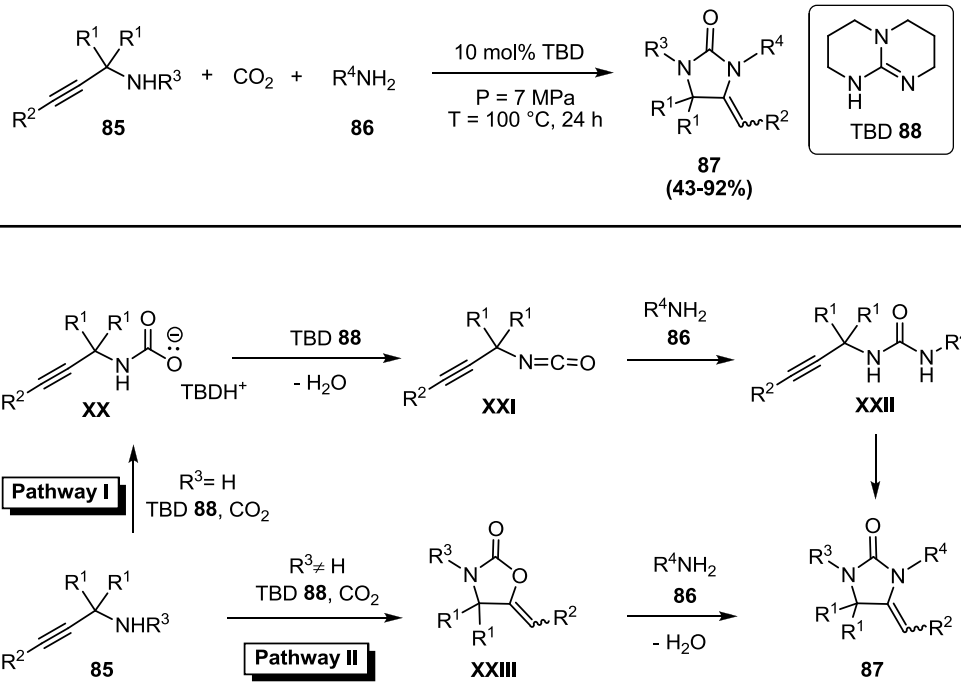
Figure 5 Examples of synthetic imidazolidinones (continued)



Because of their biological activities, many research groups were interested in the development of the imidazolidinone synthesis. In 2017, Marchegiani and co-worker reported one-pot synthesis of the imidazolidinone derivatives. 5-Methyleneimidazolidin-2-ones **87** were prepared from propargylamines **85**, primary amines **86**, and carbon dioxide (CO_2) with bicyclic guanidines **88** as a catalyst under solvent-free and mild conditions (**Scheme 24**) (Marchegiani *et al.*, 2017).

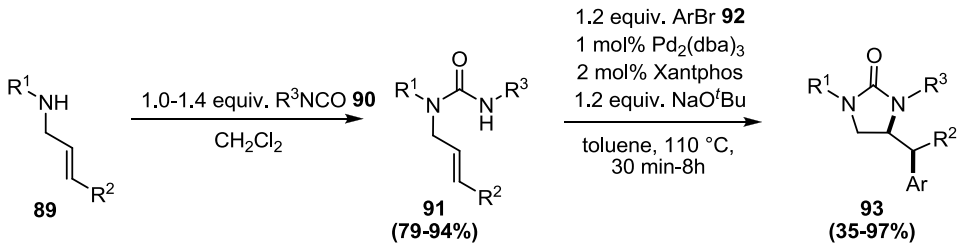
The possible formation pathway was proposed in two pathways. Firstly, the primary propargylamines **85** reacted with CO_2 to provide the carbamate intermediate **XX** which underwent in *situ* dehydration to give isocyanates **XXI**. Then, the excess of primary amines **86** reacted with the isocyanates **XXI** to provide acyclic urea **XXII**, followed by cyclization to afford target products **87**. The second pathway involved the formation of oxazolidinone **XXIII** from secondary propargylamines **85**, and CO_2 to give the desired product **87.** After that the oxazolidinone **XXIII** reacted with access primary amine **86**.

Scheme 24 The synthesis of 5-methyleneimidazolidin-2-ones derivatives **87**



Some research groups prepared the substituted imidazolidin-2-one derivatives by using metal catalysis. In 2006, Fritz and co-workers reported the synthesis of imidazolidin-2-ones **93** *via* Pd-catalyzed carboamination in two steps. They started the synthesis from *N*-allylamines **89**. Addition of the amines **89** to isocyanates **90** provided *N*-allylureas **91**. Then *N*-ayllyureas **91** were converted to corresponding products **93** *via* Pd-catalyzed cascade coupling with allyl bromide **92** (**Scheme 25**) (Fritz *et al*., 2006).

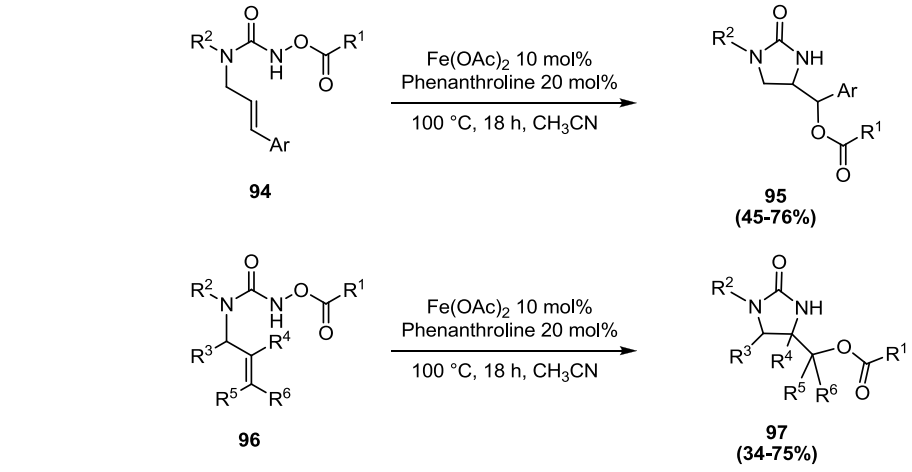
Scheme 25 The synthesis of imidazolidin-2-ones **93** *via* Pd-catalyzed carboamination of *N*-allyureas **89**

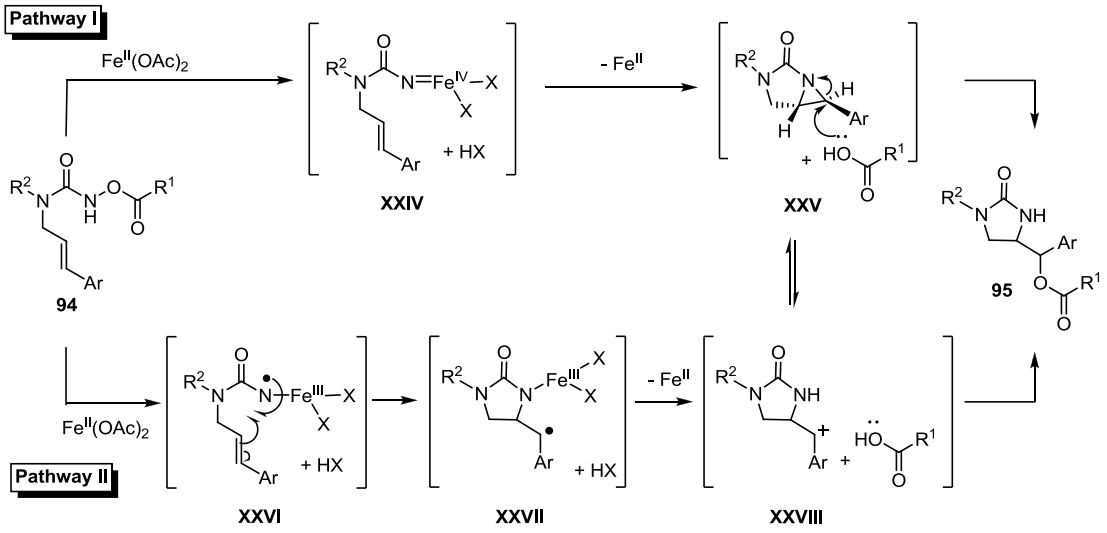


In addition, the synthesis of imidazolidinone derivatives **95** and **97** were prepared from allylbenzoyloxy ureas **94** and **96** *via* iron-catalyzed intramolecular amino-oxygenation that was reported by Prestat and co-worker in 2018 (**Scheme 26**) (Manick *et al.*, 2018). The imidazolidiones **95** could be obtained from two plausible mechanisms.

The first pathway involved the generation of singlet nitrene iron (IV) species **XXIV** followed by the formation of aziridine intermediate **XXV**. The intermediate **XXV** underwent S_N2 type ring opening to give desired product. The second pathway involved the formation of triplet nitrene iron (III) species **XXVI**, followed by a generation of short-lived carboradical species **XXVII**. The intermediate **XXVII** underwent oxidation to provide carbocationic intermediate **XXVIII** followed by an addition of nucleophile to give the desired imidazolidinone.

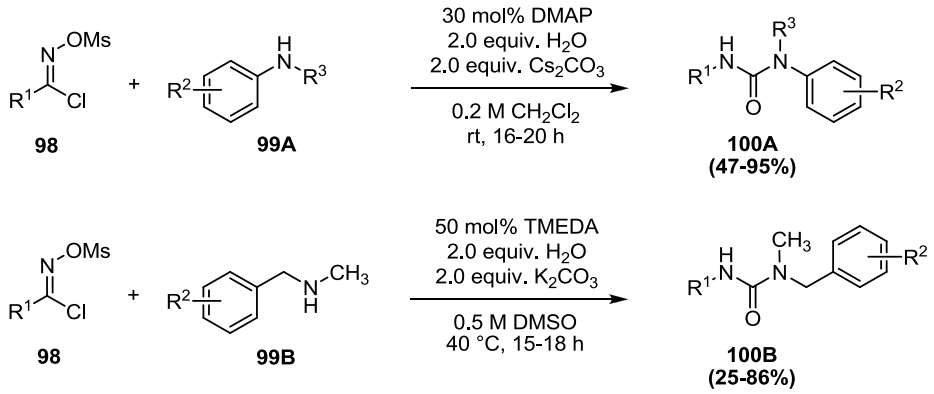
Scheme 26 The preparation of imidazolidinone derivatives **95** and **97** from allylbenzoyloxy urea derivatives **94** and **96** *via* iron-catalyzed intramolecular amino-oxygenation





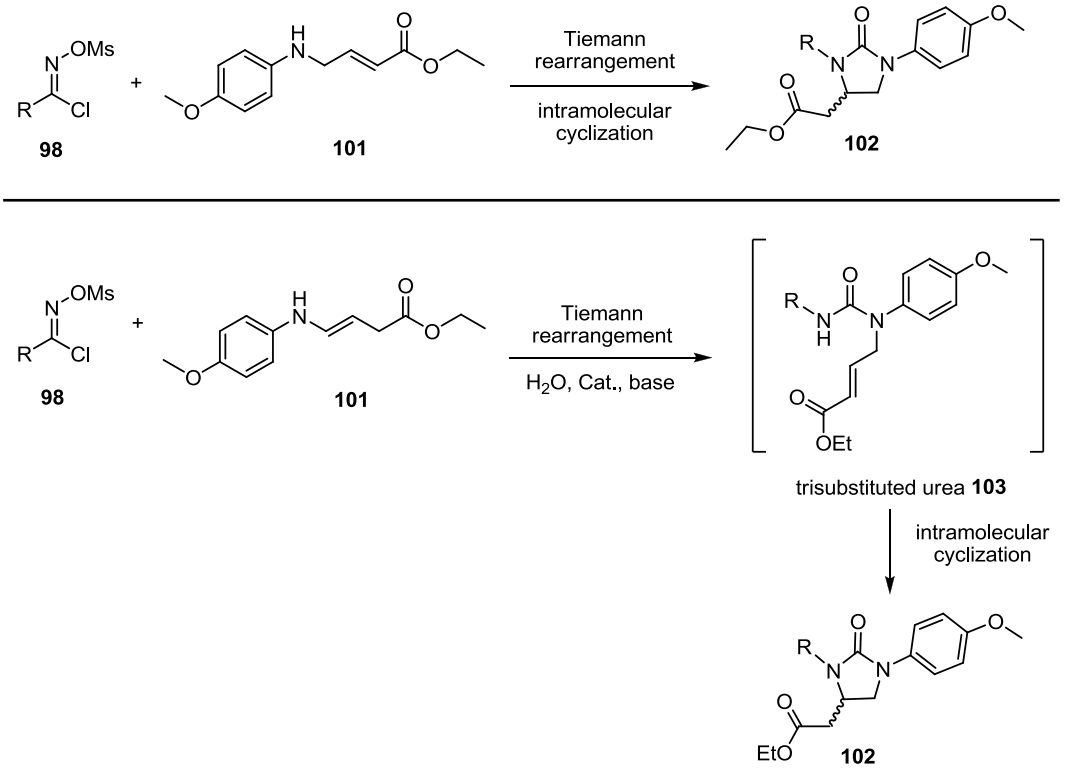
From literature reviews, we found that many reactions were catalyzed with metal catalysts. Some methods were hard to handle and the cost of catalysts was expensive so we were interested in development of a new method to synthesize imidazolidinones. Recently, our research group reported the synthesis of trisubstituent ureas **100** from *α*-chloroaldoxime *O*-methanesulfonates **98** and secondary amines **99** *via* Tiemann rearrangement (**Scheme 27**) (Kaeobamrung *et al*., 2013).

Scheme 27 The trisubstituent ureas synthesis *via* Tiemann rearrangement



Interestingly, the structure of products consists of the urea moiety in the structure. This method could be further applied to accomplish an imidazolidinone. We designed the coupling partner of *α*-chloroaldoxime *O*-methanesulfonate **98** in which a secondary amine **99** should have a suitable electrophile moiety that can form cyclic urea after the formation of trisubstituted urea. A secondary amine **101** bearing *α*,*β*-unsaturated ester moiety would be a potential coupling partner of *α*-chloroaldoxime *O*-methanesulfonate**s 98** for the synthesis of imidazolidinone **102**. We planed that *O*-methanesulfonates **98** reacted with the secondary amine **101** and water to generate trisubstituted urea intermediates **103** *via* Tiemann rearrangement. Then intramolecular cyclization of the intermediates **103** provided corresponding imidazolidinones **102** (**Scheme 28**).

Scheme 28 Synthesis plan of imidazolidinone derivatives *via* Tiemann rearrangement follow by intramolecular cyclization



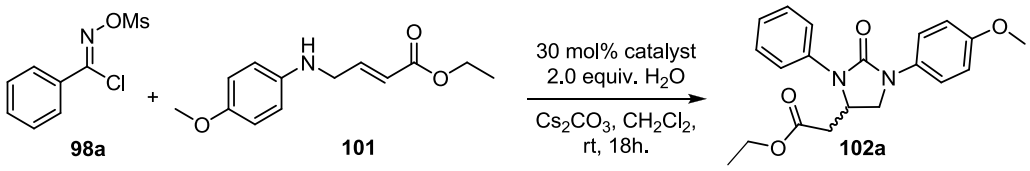
2.1.2 Objective

To accomplish the synthesis of imidazolidinones from *α*-chloroaldoxime *O*-methanesulfonates and secondary amines *via* Tiemann rearrangement and intramolecular cyclization.

2.2 RESULTS AND DISCUSSION

We started investigation for the synthesis of imidazolidinones **102a** with optimization of the reaction by using *O*-methanesulfonates **98a** and unsaturated aromatic amine **101** as model substrates. The optimization reaction involved catalyst, bases, solvents and temperatures. (**Table 4**).

Table 4 The screening of catalysts[a]



Entry	Catalysts	%Yield of 102a[b]
1	**DMAP**	**48**
2	DABCO	trace*c*
3	Imidazole	0[c]
4	-	0[c]

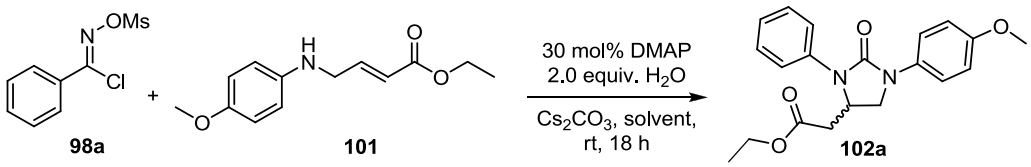
[a] Reaction conditions: all reactions were performed with 0.2 mmol of **98a**, 1.2 equiv. of **101**, 2.0 equiv. of H_2O, 2.0 equiv. of base and 1.00 mL of solvent, for 18 h.

[b] Isolated yield, [c] From ^{1}H NMR spectrum of the crude reaction mixture.

Initially, a variety of common organic catalysts were explored. The 30 mol% of DMAP was loaded in the reaction to give the target product in 48% yield (**Table 4**, entry 1). Other common nucleophilic catalysts such as DABCO and imidazole were tested. The reaction with DABCO provided trace amount of the desired product (**Table 4**, entry 2). Moreover, we did not obtain the imidazolidinone when imidazole was used as a catalyst in the reaction. Instead, we observed a remaining starting materials from a ^{1}H NMR spectrum of the crude reaction mixture (**Table 4**, entry 3). The results showed that DMAP was the most reactive catalyst and suitable for the

reaction. The control experiment with no catalyst was tested. Without a catalyst, the reaction gave 0% yield of the product (**Table 4**, entry 4).

Table 5 The study of solvent effect[a]



Entry	Solvent	% Yield of 102a[b]
1	**CH_2Cl_2**	**48**
2	THF	38
3	CH3CN	10
4	DMSO	0[c]
5	*t*-BuOH	38
6	toluene	30

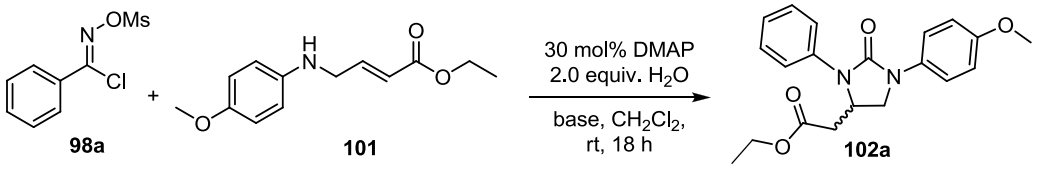
[a] Reaction conditions: all reactions were performed with 0.2 mmol of **98a**, 1.2 equiv. of **101**, 2.0 equiv. of H_2O, 2.0 equiv. of base and 1.00 mL of solvent, for 18 h.

[b] Isolated yield., [c] From ^{1}H NMR spectrum of the crude reaction mixture.

Next, we explored the effect of solvent in the reaction. Firstly, we started with polar aprotic solvent such as CH_2Cl_2, THF, CH_3CN, and DMSO. Both CH_2Cl_2 and THF provided the desired product in moderated yields, 48% and 38%, respectively (**Table 5**, entries 1 and 2). On the other hand, CH_3CN and DMSO, high polarity solvents, provided the low and no yield of product, respectively (**Table 5**, entries 3 and 4). Interestingly, moderate yield of product was obtained when *t*-BuOH was used (**Table 5**, entry 5). In addition, with toluene as a non polar solvent, the desired product was obtained in 30% yield (**Table 5**, entry 6). From these results, highly polar solvents were not suitable for the reaction except for *t*-BuOH. We hypothesized that

the solubility of substrates was a crucial key of the reaction. Therefore, the optimal solvent for the reaction was CH_2Cl_2.

Table 6 The screening of bases[a]



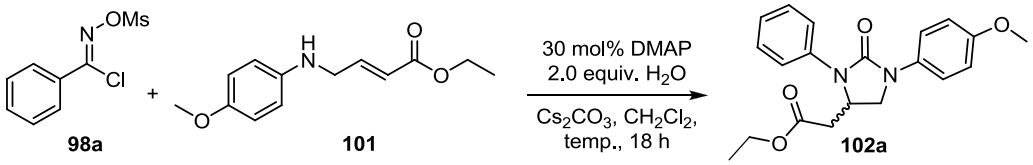
Entry	Base	%Yield of 102a[b]
1	**Cs_2CO_3**	**48**
2	K_2CO_3	46
3	K_3PO_4	36
4	*t*-BuOK	Trace[c]
5	NEt_3	Trace[c]
6	-	0*c*

[a] Reaction conditions: all reactions were performed with 0.2 mmol of **98a**, 1.2 equiv. of **101**, 2.0 equiv. of H_2O, 2.0 equiv. of base and 1.00 mL of solvent, for 18 h.

[b] Isolated yield., [c] From ^{1}H NMR spectrum of the crude reaction mixture.

Next, we moved to focus on a variety of bases. Cs_2CO_3 provided the corresponding product in 48% yield (**Table 6**, entry 1)**.** K_2CO_3 and K_3PO_4 were also explored in the optimization. The yields decreased to 46 % and 36%, respectively (**Table 6**, entries 2 and 3). Changing base to *t*-BuOK provided trace amount of target product (**Table 6**, entry 4). NEt_3 was not suitable to the reaction giving trace amount of imidazolidinone (**Table 6**, entry 5). Lastly, the absence of base gave no a product. The remaining starting materials were observed from ^{1}H NMR spectrum of the crude reaction mixture (**Table 6**, entry 6). From above experiments, the optimal base was Cs_2CO_3.

Table 7 The study of temperature and solvents[a]



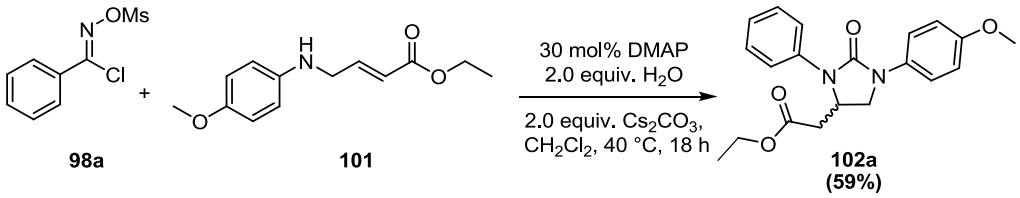
Entry	Solvent	Temp.	%Yield of 102a[b]
1	CH_2Cl_2	rt	48
2	**CH_2Cl_2**	**40 °C**	**59**
3	THF	40 °C	36
4	*t*-BuOH	40 °C	43

[a] Reaction conditions: all reactions were performed with 0.2 mmol of **98a**, 1.2 equiv. of **101**, 2.0 equiv. of H_2O, 2.0 equiv. of base and 1.00 mL of solvent, for 18 h.

[b] Isolated yield., [c] From ^1H NMR spectrum of the crude reaction mixture.

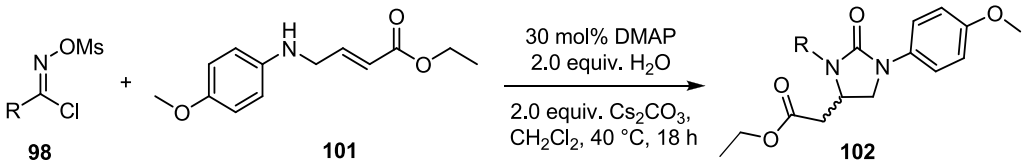
We also interested in the effect of temperature. We tested the reaction based on the optimal solvent, CH_2Cl_2, in which at room temperature the yield of product was obtained in 48% (**Table 7**, entry 1). Then, increasing temperature to 40 °C the yield was increased to 59% (**Table 7**, entry 2). At 40 °C, THF and *t*-BuOH were also gave moderate yield of product (**Table 7**, entries 3 and 4). Based on the results of optimization, we summarized that the suitable conditions were 1.2 equivalents of amine **101**, 30 mol% of DMAP as a catalyst, 2.0 equivalents of H_2O, 2.0 equivalents of Cs_2CO_3, in CH_2Cl_2 at 40 °C for 18 hours (**Scheme 29**).

Scheme 29 The optimal conditions for the imidazolidinones synthesis



With the optimal conditions in hand, we next investigated the scope of substrates for imidazolidinone synthesis. We focused on a variety of *α*-chloroaldoxime *O*-methanesulfonates **98**.

Table 8 The formation of imidazolidinones **102** from chloroaldoxime derivatives **98** and secondary amine **101**[a]



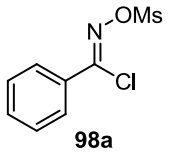
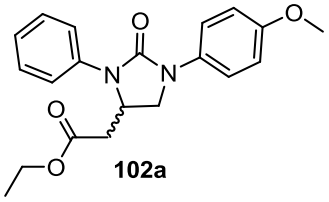
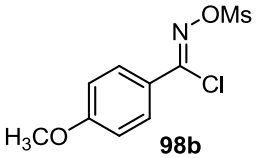
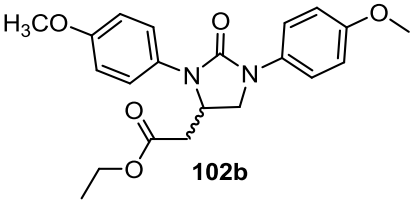
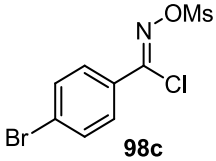
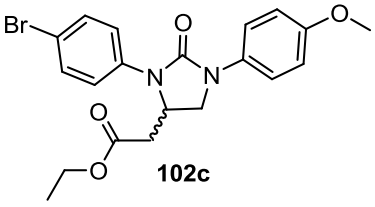
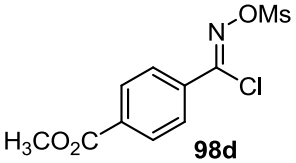
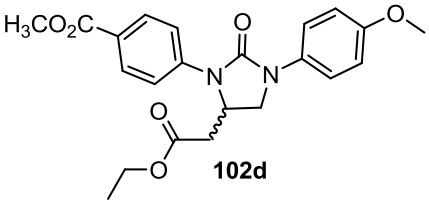
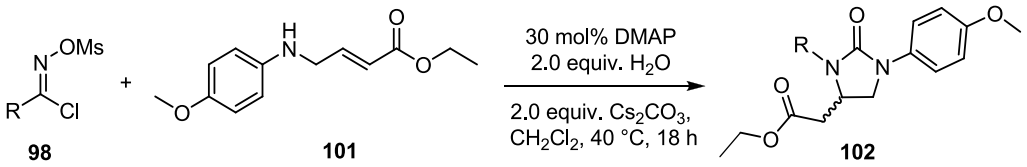
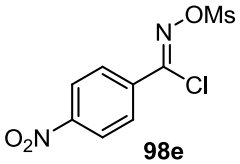
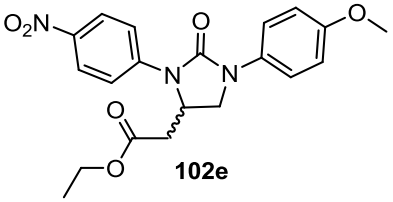
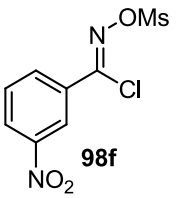
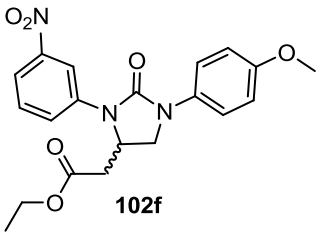
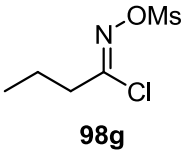
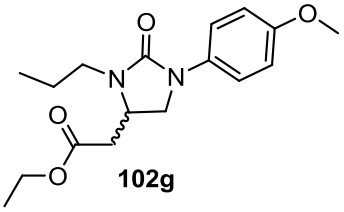
Entry	Chloroaldoxime	Imidazolidinone	Yield (%)[b]
1	 **98a**	 **102a**	59
2	 **98b**	 **102b**	31
3	 **98c**	 **102c**	42
4	 **98d**	 **102d**	65

Table 8 The formation of imidazolidinones **102** from chloroaldoxime derivatives **98** and secondary amine **101**[a] (continued)



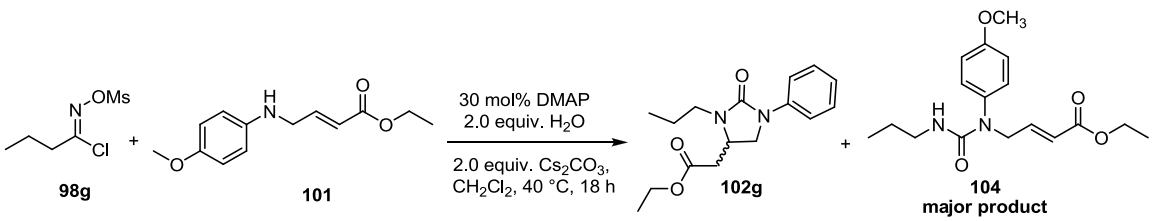
Entry	Chloroaldoxime	Imidazolidinone	Yield (%)[b]
5			58
6			50
7			4

[a] Reaction conditions: **98** (0.8 mmol), **101** (0.96 mmol).
[b] Isolated yield.

Firstly, unsubstituent *α*-chloroaldoxime *O*-methanesulfonates **98a** gave moderate yield of corresponding imidazolidinone with (*E*)-ethyl 4-(4-methoxyphenylamino)but-2-enoate (**101**) (**Table 8**, entry 1). The aryl group bearing electron-donating substituent such as methoxy group provided low yield of product **102b** in 31% (**Table 8**, entry 2). Furthermore, the target product **102c** was obtained in moderate yield when bromo-substituted chloroaldoxime **98c** was used (**Table 8**, entry

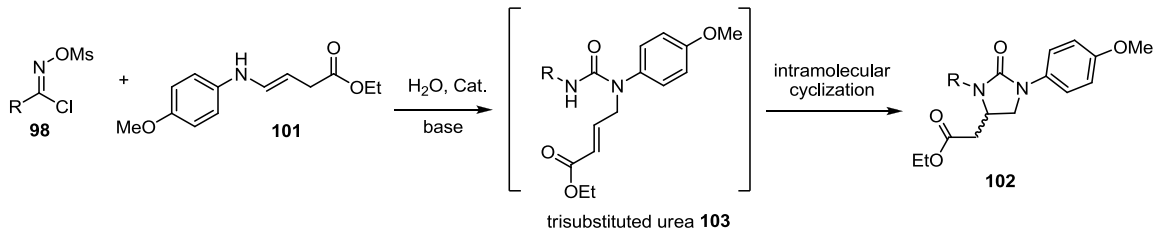
3). Ester-substituted chloroaldoxime **98d** provided good yield of the product (**Table 8**, entry 4). Nitro-substituted chloroaldoximes were applicable to the reaction. The 4- and 3-nitro substituted chloroaldoximes **98e**, **98f** gave the corresponding products in 58% and 50% yield, respectively (**Table 8**, entries 5 and 6). Based on these results, electron density on aromatic ring of chloroaldoxime **98** played an important role for the formation of target product. Interestingly, chloroaldoxime containing alkyl group such as *N*-(methylsulfonyloxy)-butyrimidoyl chloride **98g** provided the imidazolidinone **102g** in the very low yield (**Table 8**, entry 7). A major product was trisubstituted urea **104** (**Scheme 30**).

Scheme 30 The synthesis of imidazolidinone **102g** under optimal conditions



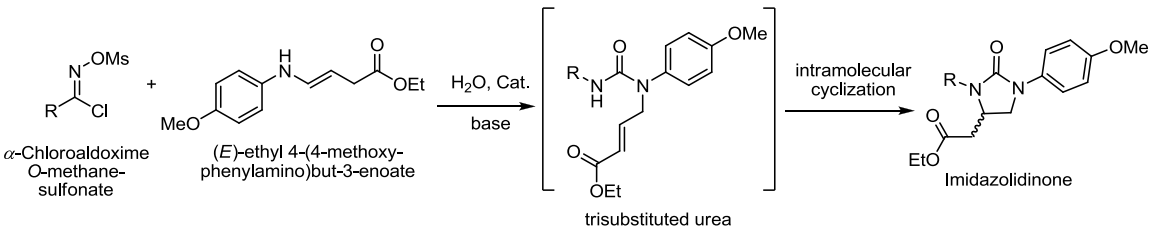
Next, we turn our interest to the plausible mechanism of the imidazolidinone synthesis. From the results of optimal conditions and substrate scope study, we suggested that the desired product was synthesized through trisubstituted urea intermediate **103** based on the results obtained by our research group (Kaeobamrung *et at.*, 2013), then followed by an intramolecular cyclization *via* Michael addition of the urea intermediate **103** (**Scheme 31**).

Scheme 31 The possible pathway of the imidazolidinone formation



2.3 CONCLUSION

We completed the synthesis of imidazolidinone derivatives from *α*-chloroaldoxime *O*-methanesulfonate and secondary aryl amine under mild conditions and simple method in one pot fashion. The substrate scopes study showed the variety of *O*-methanesulfonate with different type of substituted group on aromatic ring such as electron donating group which provided the imidazolidinone in a low yield, and the moderate yield of desired product with halogen group. In contrast, the *O*-methanesulfonates with electron withdrawing groups on aromatic ring afforded good yields of products. Unfortunately, *α*-chloroaldoxime *O*-methanesulfonate with alkyl substitutent gave a very low yield of target product. The formation of imidazolidinones involved the generation of trisubstituted urea intermediates, and subsequent intramolecular cyclization.



2.4 EXPERIMENTAL

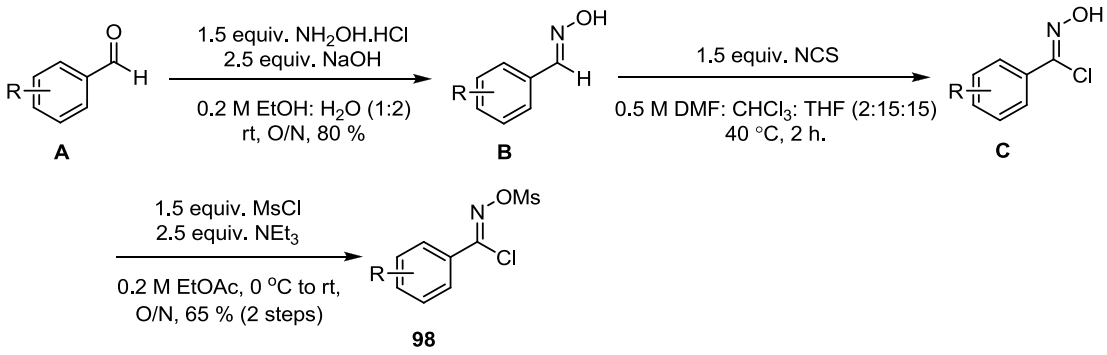
2.4.1 General Information

Dichloromethane (CH_2Cl_2) was used for reaction from commercial AR grade solvent. 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). ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a 300 MHz Bruker FTNMR Ultra Shield spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ 0.00) and coupling constant are reported as Hertz (Hz). Splitting paterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared spectra (IR) were measured on a Perkin Elmer Spectrum GX FT-IR system and recorded on wave number (cm^{-1}).

2.4.2 Preparation of Starting Materials

2.4.2.1 Synthesis of α-Chloroaldoxime-*O*-Methanesulfonates

General Procedure A: Synthesis of α-Chloroaldoxime-*O*-Methanesulfonates 98



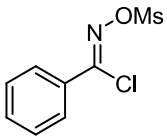
Step 1: **Benzaldoxime derivatives B.**

Benzaldoxime derivatives B. Prepared according to literature procedure (Slagbrand *et al*., 2017). A dried round bottom flask was added with benzaldehye derivatives (1.0 equiv.) 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•HCl) (1.5 equiv.) in H_2O. A reaction mixture was stirred at room temperature for overnight. 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**.

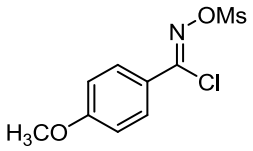
***N*-(methylsulfonyloxy)benzimidoyl chloride derivatives C**.

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 wash 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 before the slow addition of 2.5 equiv of triethylamine. The reaction mixture was stirred for 10 min. Then, 1.5 equiv of chloromethanesulfonate was added dropwise at 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, hexanes:EtOAc) to afford *N*-(methylsulfonyloxy)-benzimidoyl chloride derivatives **98**.



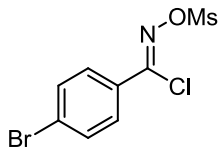
98a
$C_8H_8ClNO_3S$
M.W. = 233.6720 g/mol

***N*-(methylsulfonyloxy)benzimidoyl chloride** (**98a**). Prepared according to the procedure A. Yield 80 % (2 steps) as a white solid product. ^{1}H 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. Other data were identical to the literature values (Yamamoto *et al.*, 2009).



98b
$C_9H_{10}ClNO_4S$
M.W. = 263.6980 g/mol

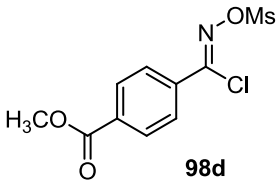
4-Methoxy-*N*-(methylsulfonyloxy)benzimidoyl chloride (**98b**). Prepared according to the procedure A. Yield 48 % (2 steps) as a white solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 148.8, 129.9, 122.5, 114.2, 55.6, 36.9; IR (thin film) ν 3422, 1607, 1510, 1372, 1261, 1148, 820, 522 cm-1; HRMS (ESI) [M+Na]+ calcd. for $C_9H_{10}ClNO_4S$ 285.9917, found 285.9917.



98c
$C_8H_7BrClNO_3S$
M.W. = 312.5681 g/mol

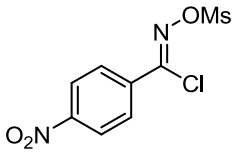
4-bromo-*N*-(methylsulfonyloxy)benzimidoyl chloride (**98c**). Prepared according to the procedure A. Yield 60 % (2 steps) as a yellow solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 3.28 (s, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 148.2, 132.2, 129.5, 129.4, 127.8, 37.2. Other data were identical to the literature values (Yamamoto *et al.*, 2009).



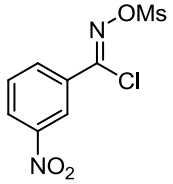
98d
$C_{10}H_{10}ClNO_5S$
M.W. = 291.7081 g/mol

Methyl 4-(chloro(methylsulfonyloxyimino)methyl)benzoate (**98d**). Prepared according to the procedure A. Yield 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. Other data were identical to the literature values (Kaeobamrung *et al*., 2015).



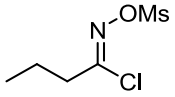
98e
$C_8H_7ClN_2O_5S$
M.W. = 278.6696 g/mol

***N*-(Methylsulfonyloxy)-4-nitrobenzimidoyl chloride** (**98e**). Prepared according to the procedure A. Yield 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, 37.2. Other data were identical to the literature values (Kaeobamrung *et al*., 2015).



98f
$C_8H_7ClN_2O_5S$
M.W. = 278.6696 g/mol

***N*-(methylsulfonyloxy)-3-nitrobenzimidoyl chloride** (**98f**). Prepared according to the procedure A. Yield 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. Other data were identical to the literature values (Yamamoto *et al.*, 2009).

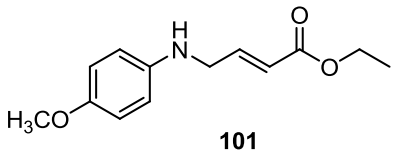


98g
$C_5H_{10}ClNO_3S$
M.W. = 199.6558 g/mol

***N*-((Methylsulfonyl)oxy)butyrimidoyl chloride** (**98g**)**.** Prepared according to the procedure A. Yield 65 % (2 steps) as a colorless liquid product. ^{1}H 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. Other data were identical to the literature values (Yamamoto *et al.*, 2009).

2.4.2.2 Synthesis of Ethyl 4-(4-methoxyphenylamino)but-2-enoate

General Procedure B: Synthesis of ethyl 4-(4-methoxyphenylamino)but-2-enoate (**101**)



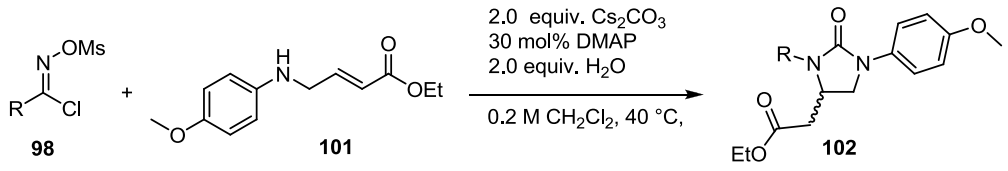
101
$C_{13}H_{17}NO_3$
M.W. = 235.2790 g/mol

ethyl 4-(4-methoxyphenylamino)but-2-enoate (**101**). A dried round bottom flask was added ethyl 4-bromocrotonate (2.75 mL, 20.0 mmol) in CH_2Cl_2 (8.00 mL) and then *p*-anisidine (4,926 mg, 40.0 mmol) was added. The reaction mixture was stirred at 0 ºC to room temperature for overnight. After the reaction completed, the mixture was quenched with H_2O then extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated with vacuum. The residue was purified by column chromatography hexanes:EtOAc (9:1)

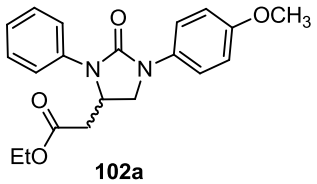
to afford **2** as yellow liquid (3058.0 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (dt, *J* = 15.7, 4.7 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 6.04 (dt, *J* = 15.7, 1.8 Hz, 1H), 4.18 (q, *J* = 7.14 Hz, 2H), 3.91 (dd, *J* = 4.7, 1.8 Hz, 2H), 3.75 (s, 3H). 1.28 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 152.6, 146.0, 141.6, 121.9, 115.1, 114.3, 60.5, 55.9, 45.8, 14.3. (thin film) ν 3395, 2834, 1714, 1659, 1514, 1369, 1179, 1038, 967, 821 cm-1; HRMS (ESI) *m/z*: [M+H]+ calcd. for $C_{13}H_{17}NO_3$ 236.1287, found 236.1283

2.4.3 Synthesis of Imidazolidinone Derivatives

General Procedure B: Synthesis of Quinazolinedione Derivatives 102



The reaction of *N*-(methylsulfonyloxy)benzimidoyl chloride **98** and ethyl 4-(4-methoxyphenylamino)but-2-enoate **101** is representative: A round bottom flask was added with ethyl 4-(4-methoxyphenylamino)but-2-enoate **101** (0.96 mmol) as a yellow liquid, *N*-(methylsulfonyloxy)benzimidoyl chloride **98** (0.80 mmol), Cs_2CO_3 (1.60 mmol), DMAP (0.24 mmol), in CH_2Cl_2 (4.00 mL). Then H_2O (1.60 mmol) was added to a reaction mixture. The reaction mixture was allowed to stir at 40 ^{o}C for 15-18 hours. After completion of reaction, the brown orange reaction mixture was cooled to room temperature, 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 (6:1, hexanes:EtOAc) to provide **102** as a light yellow solid (167.3 mg, 59% yield).

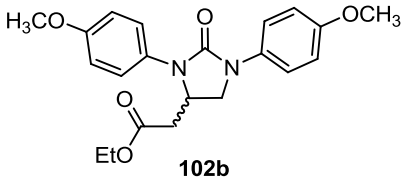


102a

$C_{20}H_{22}N_2O_4$

M.W. = 354.3997 g/mol

Ethyl 2-(1-(4-methoxyphenyl)-2-oxo-3-phenylimidazolidin-4-yl)acetate (**102a**). Prepared according to general procedure B from *N*-(methylsulfonyloxy)benzimidoyl chloride **98a** and ethyl 4-(4-methoxyphenylamino)but-2-enoate **101**. Yield 167.3 mg (59 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.9 Hz, 4H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.78-4.69 (m, 1H), 4.20 (t, *J* = 9.1 Hz, 1H), 4.13 (q, *J* = 7.14 Hz, 2H), 3.79 (s, 3H), 3.67 (dd, *J* = 9.4, 4.9 Hz, 1H), 2.88 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.56 (dd, *J* = 16.4, 9.8 Hz, 1H), 1.24 (t, *J* = 7.14 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 155.8, 155.2, 137.9, 133.2, 129.2, 124.7, 122.0, 120.1, 114.3, 61.2, 55.6, 49.9, 48.9, 37.7, 14.2; IR (thin film) ν 2926, 2853, 1716, 1702, 1504, 1418, 1282, 1246, 1180, 1156, 1030, 826, 751 cm-1; HRMS (ESI) *m/z*: [M+H]+ calcd. for $C_{20}H_{22}N_2O_4$ 377.1472, 377.1470.



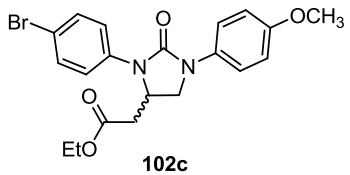
102b

$C_{21}H_{24}N_2O_5$

M.W. = 384.4257 g/mol

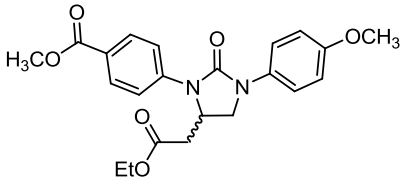
Ethyl 2-(1,3-bis(4-methoxyphenyl)-2-oxoimidazolidin-4-yl)acetate (**102b**). Prepared according to general procedure B from 4-Methoxy-*N*-(methylsulfonyloxy)-benzimidoyl chloride **98b** and ethyl 4-(4-methoxyphenylamino)but-2-enoate **101**. Yield 95.3 mg (31 %) as a light brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 6.89 (t, *J* = 8.2 Hz, 4H), 4.63-4.54 (m, 1H), 4.15 (t, *J* = 9.1 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.64 (dd, *J* = 9.1, 5.5 Hz, 1H), 2.78 (dd, *J* = 16.3, 3.3 Hz, 1H), 2.52 (dd, *J* = 16.3, 9.5 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 157.2, 155.7, 155.5, 133.4, 130.6, 125.0, 119.7, 114.4, 114.1, 61.0, 55.5, 50.7, 48.9, 37.8, 14.1; IR (thin

film) ν 2936, 2835, 1702, 1509, 1430, 1411, 1245, 1180, 1031, 828 cm-1; HRMS (ESI) *m/z*: [M+H]+ calcd. for $C_{21}H_{24}N_2O_5$ 385.1758, found 385.1759.



102c
$C_{20}H_{21}BrN_2O_4$
M.W. = 433.2957 g/mol

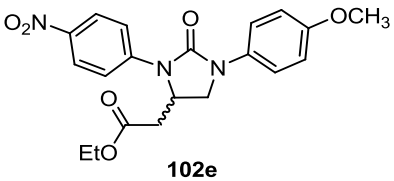
Ethyl 2-(3-(4-bromophenyl)-1-(4-methoxyphenyl)-2-oxoimidazolidin-4-yl)acetate (**102c**). Prepared according to general procedure B from 4-bromo-*N*-(methylsulfonyl-oxy)benzimidoyl chloride (**98c**) and ethyl 4-(4-methoxyphenyl-amino)but-2-enoate **101**. Yield 145.6 mg (42 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.37 (m, 6H), 6.89 (d, *J* = 9.1 Hz, 2H), 4.73-4.64 (m, 1H), 4.17 (t, *J* = 9.1 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.66 (dd, *J* = 9.4, 4.5 Hz, 1H), 2.83 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.55 (dd, *J* = 16.4, 9.7 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.9, 154.8, 137.1, 132.8, 132.1, 123.0, 120.2, 117.2, 114.2, 61.2, 55.6, 49.6, 48.7, 37.4, 14.2; IR (thin film) ν 2980, 2831, 1709, 1515, 1492, 1414, 1376, 1286, 1247, 1181, 1033, 827 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. for $C_{20}H_{21}N_2O_4Br$ 455.0577, found 455.0575.



102d
$C_{22}H_{24}N_2O_6$
M.W. = 412.4358 g/mol

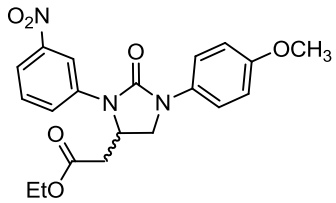
Methyl 4-(5-(2-ethoxy-2-oxoethyl)-3-(4-methoxyphenyl)-2-oxoimidazolidin-1-yl) benzoate (**102d**). Prepared according to general procedure B from Methyl-4-(chloro(methylsulfonyloxyimino)methyl)benzoate (**98d**) and ethyl 4-(4-methoxy-phenylamino)but-2-enoate **101**. Yield 214.5 mg (65 %) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.9 Hz, 2H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.46 (d, *J* = 9.1 Hz, 2H), 6.91 (d, *J* = 9.1 Hz, 2H), 4.85-4.76 (m, 1H), 4.21 (t, *J* = 9.1 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.69 (dd, *J* = 9.5, 3.7 Hz,

1H), 2.91 (dd, *J* = 16.4, 2.8 Hz, 1H), 2.61 (dd, *J* = 16.4, 10.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 166.8, 156.2, 154.5, 142.4, 132.7, 130.9, 125.0, 120.6, 119.2, 114.4, 61.4, 55.6, 52.1, 49.3, 48.8, 37.2, 14.2; IR (thin film) ν 3432, 2980, 1716, 1606, 1511, 1431, 1409, 1376, 1275, 1249, 1183, 1110, 1032, 828 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. for $C_{22}H_{24}N_2O_6$ 435.1527, found 435.1525.



102e
$C_{20}H_{21}N_3O_6$
M.W. = 399.3972 g/mol

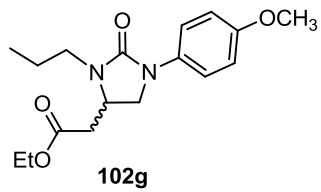
Ethyl 2-(1-(4-methoxyphenyl)-3-(4-nitrophenyl)-2-oxoimidazolidin-4-yl)acetate (**102e**). Prepared according to general procedure B from *N*-((Methylsulfonyl)oxy)-4-nitrobenzimidoyl chloride (**98e**) and ethyl 4-(4-methoxyphenylamino)but-2-enoate **101**. Yield 185.3 mg (58 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.3 Hz, 2H), 7.76 (d, *J* = 9.3 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 4.87-4.79 (m, 1H), 4.24 (t, *J* = 9.1 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.72 (dd, *J* = 9.5, 3.2 Hz, 1H), 2.91 (dd, *J* = 16.4, 2.7 Hz, 1H), 2.67 (dd, *J* = 16.4, 9.9 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 156.5, 154.0, 144.3, 142.7, 132.3, 125.1, 120.8, 118.6, 114.4, 61.5, 55.6, 49.3, 48.7, 37.0, 14.2; IR (thin film) ν 3434, 2982, 2835, 1716, 1597, 1516, 1506, 1430, 1409, 1376, 1285, 1249, 1032, 847, 830 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. for $C_{20}H_{21}N_3O_6$ 422.1323, found 422.1323.



102f
$C_{20}H_{21}BrN_3O_6$
M.W. = 399.3972 g/mol

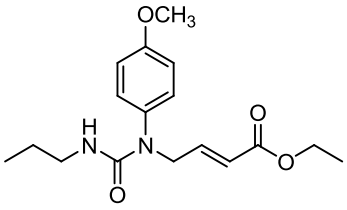
Ethyl 2-(1-(4-methoxyphenyl)-3-(3-nitrophenyl)-2-oxoimidazolidin-4-yl)acetate (**102f**). Prepared according to general procedure B from *N*-(methylsulfonyloxy)-3-

nitrobenzimidoyl chloride (**98f**) and ethyl 4-(4-methoxyphenylamino)but-2-enoate **101**. Yield 159.7 mg (50 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.9 (t, *J* = 6.7 Hz, 2H), 7.53 (t, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 4.86-4.77 (m, 1H), 4.24 (t, *J* = 9.1 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.74 (dd, *J* = 9.5, 4.1 Hz, 1H), 2.88 (dd, *J* = 16.4, 2.9 Hz, 1H), 2.64 (dd, *J* = 16.4, 9.5 Hz, 1H), 1.25 (t, *J* = 7.11 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 156.2, 154.5, 148.8, 139.4, 132.4, 129.9, 126.3, 120.5, 118.5, 115.0, 114.0, 61.4, 55.6, 49.4, 48.8, 37.2, 14.2; IR (thin film) ν 3095, 2983, 2836, 1714, 1615, 1582, 1516, 1349, 1248, 1035, 829, 738 cm-1; HRMS (ESI) *m/z*: [M+Na]+ calcd. for $C_{20}H_{21}N_3O_6$ 422.1323, found 422.1321.



102g
$C_{17}H_{24}N_2O_6$
M.W. = 320.3835 g/mol

Ethyl 2-(1-(4-methoxyphenyl)-2-oxo-3-propylimidazolidin-4-yl)acetate (**102g**). Prepared according to general procedure B from *N*-((Methylsulfonyl)oxy)-butyrimidoyl chloride (**98g**) and ethyl 4-(4-methoxyphenylamino)but-2-enoate **101**. Yield 12.0 mg (4 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 9.1 Hz, 2H), 6.87 (d, *J* = 9.1 Hz, 2H), 4.17 (q, *J* = 7.11 Hz, 2H), 4.09-3.98 (m, 2H), 3.78 (s, 3H), 3.53-3.42 (m, 2H), 3.03-2.94 (m, 1H), 2.81 (dd, *J* = 16.0, 3.8 Hz, 1H), 2.50 (dd, *J* = 16.0, 8.7 Hz, 1H), 1.59-1.49 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 157.6, 155.3, 133.9, 119.4, 114.3, 61.2, 55.7, 49.3, 49.1, 43.4, 38.0, 21.1, 14.3, 11.4; IR (thin film) ν 2964, 2934, 1731, 1704, 1515, 1484, 1377, 1245, 1180, 1125, 1034, 829, 800, 152 cm-1; HRMS (ESI) *m/z*: [M+H]+ calcd. for $C_{17}H_{24}N_2O_4$ 321.1809, found 321.1809.



104

$C_{17}H_{24}N_2O_6$

M.W. = 320.3835 g/mol

(*E*)-ethyl 4-(1-(4-methoxyphenyl)-3-propylureido)but-2-enoate (**104**). Prepared according to general procedure B from *N*-((Methylsulfonyl)oxy)butyrimidoyl chloride (**98g**) and ethyl 4-(4-methoxyphenylamino)but-2-enoate **101**. Yield 75.0 mg (39 %) as a light brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.87 (d, *J* = 15.7 Hz, 1H), 4.38 (dd, *J* = 5.6, 1.3 Hz, 3H), 4.31 (t, *J* = 5.6 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.12 (dd, *J* = 13.4, 6.6 Hz, 2H), 1.48-1.36 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 159.1, 157.2, 144.6, 134.1, 129.7, 122.5, 115.3, 60.4, 55.5, 50.7, 42.5, 23.4, 14.3, 11.3; IR (thin film) ν 3442, 3407, 2963, 2936, 2057, 1718, 1655, 1581, 1509, 1466, 1368, 1249, 1182, 1106, 1037, 980, 935, 839 cm-1; HRMS (ESI) *m/z*: [M+H]+ calcd. for $C_{17}H_{24}N_2O_4$ 321.1809, found 321.1811.

REFERENCES

Azizian, J.; Mehrdad, M.; Jadidi, K.; Sarrafi, Y. 2000. Rearrangement of 4-imino-(1*H*, 4*H*)-3,1-benzoxazine-2-ones to 2,4-quinazolinediones via an isocyanate carboxamide intermediate. Tetrahedron Lett. 41, 5265−5268.

Azizian, J.; Mohammadi, A. A.; Karimi, A. R. 2003. A Efficient One-pot Procedure for Preparation of 2,4 (1*H*, 3*H*)-Quinazolinediones and 2-Thioxoquinazolinone Derivatives under Microwave Irradiation. Synth. Commun. 33, 415−420.

Barraclough, P.; Jackson, W. P.; Harris, C. J. 1991. Imidazolidin-2-one Prostaglandin Analogues. Arch. Pharm. 324, 473−477.

Buckley, G. M.; Davies, N.; Dyke, H. J.; Gilbert, P. J.; Hannah, D. R.; Haughan, A. F.; Hunt, C. A.; Pitt, W. R.; Profit, R. H.; Ray, N. C.; Richard, M. D.; Sharpe, A.; Taylor, A. J.; Whitworth, J. M.; Williams, S. C. 2005. Quinazolinethiones and quinazolinediones, novel inhibitors of inosine monophosphate dehydrogenase: synthesis and initial structure activity relationships. Bioorg. Med. Chem. Lett. 15, 751−754.

Chang, Chih-Shiang.; Lin, Ying-Ting.; Shih, Shin-Ru.; Lee, Chung-Chi.; Lee, Yen-Chun.; Tai, Chia-Liang.; Tseng, Sung-Nien.; Chern, Jyh-Haur. 2005. Design, Synthesis, and Antipicornavirus Activity of 1-[5-(4-Arylphenoxy)alkyl]-3-pyridin-4-ylimidazolidin-2-one Derivatives. J. Med. Chem. 48, 3522−3535.

Chaudhari, S. P.; Dangate, P. S.; Akamanchi, K. G. 2010. *o*-Iodoxybenzoic Acid Mediated Oxidative Desulfurization of 1,3-Disubstituted Thioureas to Carbodiimides. Synlett. 20, 3065−3067.

Cui, Li-Qian.; Dong, Zhi-Lei.; Liu, K.; Zhang, C. 2011. Design, Synthesis, Structure, and Dehydrogenation Reactivity of a Water-Soluble *o*-Iodoxybenzoic Acid Derivative Bearing a Trimethylammonium Group. Org. Lett. 13, 6488–6491.

Duo, Guo-Lan.; Wan, Man-Man.; Huang, Zhi-Bin.; Shi, Da-Qing. 2009. One-Pot Synthesis of Quinazoline-2,4 (1*H*, 3*H*)-diones and 2-Thioxoquinazolinones with the Aid of Law-Valent Titanium Reagent. J. Heterocyclic Chem. 46, 645−649.

Ellsworth, E. L.; Tran, T. P.; Showalter, H. D. H.; Sanchez, J. P.; Watson, B. M.; Stier, M. A.; Domagala, J. M.; Gracheck, S. J.; Joannides, E. T.; Shapiro, M. A.; Dunham, S. A.; Hanna, D. L.; Huband, M. D.; Gage, J. W.; Bronstein, J. C.; Liu, J. Y.; Nguyen, D. Q.; Singh, R. 2006. 3-Aminoquinazolinediones as a New Class of Antibacterial Agents Demonstrating Excellent Antibacterial Activity Against Wild-Type and Multidrug Resistant Organisms. J. Med. Chem. 49, 6435−6438.

Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. 2006. A New Synthesis of Imidazolidin-2-ones via Pd-Catalyzed Carboamination of *N*-Allylureas. Org. Lett. 8, 2531−2534.

Gabbutt, C. D.; Heron, B. M.; Instone, A. C. 2006. The synthesis and electronic absorption spectra of 3-phenyl-3(4-pyrrolidino-2-substitutedphenyl)-3*H*-naphtho[2,1-*b*]pyrans: further exploration of the *ortho* substituent effect. Tetrahedron 62, 737−745.

Gordeev, M. F.; Hui, H. C.; Gordon, E. M.; Patel, D. V. 1997. A General and Efficient Solid Phase Synthesis of Quinazoline-2,4-diones. Tetrahedron Lett. 38, 1729−1732.

Gouilleux, L.; Fehrentz, Jean-Alain.; Winternitz, F.; Martinez, J. 1996. Solid Phase Synthesis of Chiral 3-Substituted Quinazoline-2,4-diones. Tetrahedron Lett. 37, 7031−7034.

Hama, N.; Matsuda, T.; Sato, T.; Chida, N.; 2009. Total Synthesis of (−)-Agelastatin A: The Application of a Sequential Sigmatropic Rearrangement. Org. Lett. 11, 2687−2690.

Hathaway, B. A.; White, K. L.; McGill, M. E. 2007. Comparison of Iodination of Methoxylated Benzaldehydes and Related Compounds using Iodine/Silver Nitrate and Iodine/Periodic Acid. Synth. Commun. 37, 3855−3860.

Heppell, J.; Al-Rawi, Jasim. 2014. Functionalization of Quinazolin-4-ones Part 1: Synthesis of Novel 7-Substituted-2-thioxo Quinazolin-4-ones from 4-Substituted-2-Aminobenzoic Acids and $PPh_3(SCN)_2$. J. Heterocyclic Chem. 51, 162−174.

Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gangé, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. 2008. Distinct Reactivity of $Pd(OTs)_2$: The Intermolecular Pd(II)-Catalyzed 1,2-Carboamination of Dienes. J. Am. Chem. 130, 10066−10067.

Hosoya, K.; Ishimitsu, T. 2002. Protection of the Cardiovascular System by Imidapril, a Versatile Angiotensin-Converting Enzyme Inhibitor. Cardiovasc. Drug. Rev. 20, 93−110.

Imbos, R.; Minnaard, A. J.; Feringa, B. L. 2002. A Highly Enantioselective Intramolecular Heck Reaction with a Monodentate Ligand. J. Am. Chem. Soc. 124, 184−185.

Jiarong, L.; Xian, C.; Daxin, S.; Shuling, M.; Qing, L.; Qi, Z.; Jianhong, T. 2009. A New and Facile Synthesis of Quinazoline-2,4(1*H*,3*H*)-diones. Org. Lett. 11, 1193−1196.

Jin, Hui-Zi.; Du, Jing-Ling.; Zhang, Wei-Dong.; Yan, Shi-Kai.; Chen, Hai-Sheng.; Lee, Jeong-Hyung.; Lee, Jung-Joong. 2008. A new quinazolinedione alkaloid from the fruits of *Evodia officinalis*. Fitoterapia 79, 317–318.

Kaeobamrung, J.; Lanui, A.; Mahawong, S.; Duangmak, W.; Rukachaisirikul, V. 2015. One-pot Synthesis of Trisubstituted Ureas from α-Chloroaldoxime *O*-Methanesulfonates and Secondary Amines. RSC Adv. 5, 58587−58594.

Katritzky, A. R.; Jiang, J.; Urogdi, L. 1990. 1-(Triphenylphosphoroylidene-aminomethyl)benzotriazole (BETMIP) a Novel +CH2N= Synthetic Equivalent: Its Application to the Synthesis of Carbodiimides, Imines, Isothiocyanates, Aziridines, and Secondary Amines. Synthesis. 7, 565−567.

Khorana, H. G. 1953. The Chemistry of Carbodiimides. Chem. Rev. 53, 145−166.

Larksarp, C.; Alper, H. 2000. Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Heterocumulenes: Regioselective Preparation of 4(3*H*)-Quinazolinone Derivatives. J. Org. Chem. 65, 2773−2777.

Lee, Ki-Cheul.; Venkateswararao, E.; Sharma, V. K.; Jung, Sang-Hun.; 2014. Investigation of amino acid conjugates of (S)-1-[1-(4-aminobenzoyl)-2,3-dihydro-1*H*-indol-6-sulfonyl]-4-phenyl-imidazolidin-2-one (DW2282) as water soluble anticancer prodrugs. Eur. J. Med. Chem. 80, 439−446.

Lee, Sang-Hyeup.; Matsushita, H.; Koch, G.; Zimmermann, J.; Clapham, B.; Janda, K. D. 2004. Smart Cleavage Reactions: the Synthesis of an Array of Ureas from Polymer-Bound Carbamates. J. Comb. Chem. 6, 822−827.

Li, H.; Li, W.; Spannenberg, A.; Baumann, W.; Neumann, H.; Beller, M.; Wu, Xiao-Feng. 2014. A Novel Domino Synthesis of Quinazolinediones by Palladium-Catalyzed Double Carbonylation. Chem. Eur. J. 20, 8541–8544.

Li, X. Q. 2009. The simple synthesis of quinazoline-2,4-dione derivatives using Boc strategy. Chin. Chem. Lett. 20, 1201−1203.

Liu, Y.; Wan, Jie-Ping. 2011. Tandem reactions initiated by copper-catalyzed cross-coupling: A new strategy towards heterocycle synthesis. Org. Biomol. Chem. 9, 6873−6894.

Llangovan, A,; Sakthivel, P.; Sakthivel, P. 2016. Green and Practical Transition Metal-Free One-Pot Conversion of Substituted Benzoic Acids to Anilines Using Tosyl Azide. Org. Chem. Front. 3, 1680−1685.

Lü. P.; Huang, K.; Xie, L.; Xu, X. 2011. Palladium-Catalyzed Tandem Reaction to Construct Benzo[c]phenanthridine: Application to the Total Synthesis of Benzo[c]phenanthridine alkaloids. Org. Biomol. Chem. 9, 3133−3135.

Marchegiani, M.; Nodari, M.; Tansini, F.; Massera, C.; Mancuso, R.; Gabriele, B.; Costa, M.; Ca, N. D. 2017. Urea derivatives from carbon dioxide and amines by guanidine catalysis: Easy access to imidazolidin-2-ones under solvent-free conditions. J. CO_2 Util. 21, 553−561.

Manick, Anne-Doriane.; Aubert, S.; Yalcouye, B.; Prangé, T.; Berhal, F.; Prestat, G. 2018. Access to Functionalized Imidazolidin-2-one Derivatives by Iron-Catalyzed Oxyamination of Alkenes. Chem. Eur. J. 24, 1−9.

Mason, C. K.; McFarlane, S.; Johnston, P. G.; Crowe, P.; Erwin, P. J.; Domostoj, M. M.; Campbell, F. C.; Manaviazar, S.; Hale, K. J.; El-Tanani, M. 2008. Agelastatin A: a novel inhibitor of osteopontin-mediated adhesion, invasion, and colony formation. Mol. Cancer. Ther. 7, 548−558.

Michne, W. F.; Schroeder, J. D.; Guiles, J. W.; Treasurywala, A. M.; Weigelt, C. A.; Stansberry, M. F.; Avoy, E. Mc.; Shah, C. R.; Baine, Y.; Sawutz, D. G.; Miller, P. B.; Stankunas, B. M.; Reid, J.; Bump, E.; Schlegel, D. 1995. Novel Inhibitors of the Nuclear Factor of Activated T Cells (NFAT)-Mediated Transcription of β-Galactosidase: Potential Immunosupressive and Anti-inflammatory Agents. J. Med. Chem. 38, 2557−2569.

Mizuno, T.; Iwai, T.; Ishino, Y. 2004. The Simple Solvent-Free Synthesis of 1*H*-Quinazoline-2,4-diones using Supercritical Carbon dioxide and Catalytic Amount of Base. Tetrahedron Lett. 45, 7073−7075.

Monnier, F.; Taillefer, M. 2009. Catalytic C−C, C−N, and C−O Ullmann-Type Coupling Reactions. Angew. Chem. Int. Ed. 48, 6954−6971.

Moorthy, J. N.; Senapati, K.; Parida, K. N.; Jhulki, S.; Sooraj, K.; Nair, N. N. 2011. Twist Does a Twist to the Reactivity: Stoichiometric and Catalytic Oxidations with Twisted Tetramethyl-IBX. J. Org. Chem. 76, 9593−9601.

Nagasawa, Y.; Kato, H.; Rotinsulu, H.; Mangindaan, R. E. P.; de Voogd, N. J.; Tsukamoto, S. 2011. Spironaamidine, a new spiroquinone-containing alkaloid from the marine sponge *Leucetta microraphis*. Tetrahedron Lett. 52, 5342−5344.

Nguyen, Thi-Huu.; Chau, N. T. T.; Castanet, Anne-Sophie.; Nguyen, K. P. P.; Mortier, J. 2007. First General, Direct, and Regioselective Synthesis of Substituted Methoxybenzoic Acids by ortho Metalation. J. Org. Chem. 72, 3419−3429.

Nikpour, F.; Paibast, T. 2005. A Green, Facile, and One-pot Synthesis of 2,4-(1*H*, 3*H*)-Quinazolinediones under Microwave Irradiations. Chem. Lett. 34, 1438−1439.

Piaz, V. D.; Giovannoni, M. P. 2000. Phosphodiesterase 4 inhibitors, structurally unrelated to rolipram, as promising agents for the treatment of asthma and other pathologies. Eur. J. Med. Chem. 35, 463−480.

Prashanth, M. K.; Madaiah, M.; Revanasiddappa, H. D.; Veeresh, B. 2013. Synthesis, anticonvulsant, antioxidant and binding interaction of novel *N*-substituted methylquinazoline-2,4(1H,3H)-dione derivatives to bovine serum albumin:

A structure–activity relationship study. Spectrochim. Acta. A Mol. Biomol. Spectrosc. 110, 324−332.

Reichard, G. A.; Stengone, C.; Paliwal, S.; Mergelsberg, I.; Majmundar, S.; Wang, C.; Tiberi, R.; McPhail, A. T.; Piwinski, J. J.; Shih, Neng-Yang. 2003. Asymmetric Synthesis of 4,4-Disubstituted-2-Imidazoli-dinones: Potent NK1 Antagonists. Org. Lett. 5, 4249−4251.

Rivero, I. A.; Espinoza, K.; Somanathan, R. 2004. Syntheses of Quinazoline-2,4-dione Alkaloids and Analogues from Mexican *Zanthoxylum* Species. Molecules 9, 609−616.

Robert, Jean-Michel, H.; Sabourin, C.; Alvarez, N.; Robert-Piessard, S.; Baut, G. L.; Pape, P. L. 2003. Synthesis and antileishmanil activity of new imidazolidin-2-one derivatives. Eur. J. Med. Chem. 38, 711−718.

Sharafi-Kolkeshvandi, M.; Nikpour, F. 2012. A facile and convenient approach for the one-pot synthesis of 2,4(1*H*,3*H*)-quinazolinediones. Chin. Chem. Lett. 23, 431−433.

Slagbrand, T.; Kervefors, G.; Tinnis, F.; Adolfsson, H. 2017. An Efficient One–pot Procedure for the Direct Preparation of 4,5-Dihydroisoxazoles from Amides. Adv. Synth. Catal. 359, 1990−1995.

Sociali, G.; Galeno, L.; Parenti, M. D.; Grozio, A.; Bauer, I.; Passalacqua, M.; Boero, S.; Donadini, A.; Millo, E.; Bellotti, M.; Sturla, L.; Damonte, P.; Paddu, A.; Ferroni, C.; Varchi, G.; Franceschi, C.; Ballestrero, A.; Poggi, A.; Bruzzone, S.; Nencioni, A.; Rio, A. D. 2015. Quinazolinedione SIRT6 inhibitors sensitize cancer cells to chemotherapeutics. Eur. J. Med. Chem. 102, 530−539.

Su, X.; Surry, D. S.; Spandl, R. J.; Spring, D. R. 2008. Total Synthesis of Sanguiin H-5. Org. Lett. 10, 2593−2596.

Tietze L. F.; Rackelmann, N. 2004. Domino reactions in the synthesis of heterocyclic natural products and analogs. Pure. Appl. Chem. 76, 2004, 1967−1983.

Tsuda, M.; Uemoto, H.; Kobayashi, J. 1999. Slagenins A-C, Novel Bromopyrrole Alkaloids from Marine Sponge *Agelas nakamurai*. Tetrahedron Lett. 40, 5709−5712.

Uyanik, M.; Akakura, M.; Ishihara, K. 2009. 2-Iodoxybenzenesulfonic Acid as an Extremely Active Catalyst for the Selective Oxidation of Alcohols to Aldehydes, Ketones, Carboxylic Acids, and Enones with Oxone. J. Am. Chem. Soc. 131, 251−262.

Valois-Escamilla, I.; Alvarez-Hernandez, A.; Rangel-Ramos, L. F.; Suárez-Castillo, O. R.; Ayala-Mata, F.; Zepeda-Vallejo, G. 2011. Synthesis of 6-bromo-2-arylindoles using 2-iodobenzoic acid as precursor. Tetrahedron Lett. 52, 3726−3728.

Willis, M. C.; Snell, R. H.; Fletcher, A. J.; Woodward, R. L. 2006. Tandem Palladium-Catalyzed Urea Arylation−Intramolecular Ester Amidation: Regioselective Synthesis of 3-Alkylated 2,4-Quinazolinediones. Org. Lett. 8, 5089−5091.

Wu, X.; Yu, Z.; 2010. Metal and phosgene-free synthesis of 1*H*-quinazoline-2,4-diones by selenium-catalyzed carbonylation of *o*-nitrobenzamides. Tetrahedron Lett. 51, 1500−1503.

Yamamoto, Y.; Mizuno, H.; Tsuritani, T.; Mase, T. 2009. Synthesis of α-Chloro-aldoxime *O*-methanesulfonates and Their Use in the Synthesis of Functionalized Benzimidazoles. J. Org. Chem. 74, 1394−1396.

Yu, R. T.; Rovis, T. 2008. Asymmetric Synthesis of Bicyclic Amidines via Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition of Carbodiimides. J. Am. Chem. Soc. 130, 3262−3263.

APPENDIX

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Copper-catalyzed domino reaction of carbodiimides and benzoic acid derivatives for the synthesis of quinazolinediones

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ABSTRACT

Quinazolinediones were obtained from 2-iodobenzoic acids and carbodiimide derivatives under mild reaction conditions *via* a copper-catalyzed domino reaction. The absence of an external base was essential to avoid the generation of amide by-products. Both alkyl- and aryl-substituted carbodiimides gave the corresponding quinazolinediones. However, the use of aryl-substituted carbodiimides resulted in low yields due to an undesired elimination process.

Introduction

Copper-catalyzed domino reactions are a useful method to synthesize organic molecules [1]. In addition, the domino concept allows access to complex molecules from simple starting materials. As part of our interest in the synthesis of *N*-containing heterocycles, we have focused on the search for simple and interesting organic molecules which are potentially suitable for domino processes. Interestingly, carbodiimides could be used to obtain heterocycles *via* domino processes due to their properties, including the electrophilicity of the middle carbon and the presence of a nitrogen donor for C-N bond formation.

Carbodiimides have been widely used for amide bond formation. Nakajima and Ikada extensively studied the reaction mechanism for the formation of amides from carbodiimides and carboxylic acids [2]. A key intermediate in this reaction is an *O*–acylisourea adduct; the amide products are formed *via* nucleophilic substitution of the *O*-acylisoureas with amines, and urea is generated as a by-product. Recently, Zhao and co-workers utilized carbodiimides and ethyl-2-aminobenzoates to synthesize quinazolinones [3]. Likewise, Xi and co-workers also used the reaction of carbodiimides with 2-haloanilines to synthesize 2-aminobenzimidazoles [4]. Alternatively, based on the reaction of carbodiimides and benzoic acids, we envisioned that *O*-acylisoureas could be utilized to obtain quinazolinediones *via* a domino process involving rearrangement to form *N*-acylureas, followed by intramolecular copper-catalyzed C-N bond formation (Scheme 1).

Quinazolinediones are important *N*-containing heterocyclic compounds which possess a wide range of biological activities, such as anti-inflammatory, antihypertensive, anticancer, antitumor, and antibacterial properties [5]. Therefore, methodologies for quinazolinedione synthesis have been developed *via* both metal and non-metal catalysis [6]. Herein, we report a straightforward protocol to obtain quinazolinediones *via* a copper-catalyzed domino process under mild reaction conditions.

Results and discussion

We began our investigation by optimizing the model reaction of commercially available 2-iodobenzoic acid and *N,N'*-dicyclohexylcarbodiimide (DCC) (Table 1). Firstly, we explored a variety of copper salts, such as Cu_2O, CuI, CuBr and $Cu(OAc)_2$ (Entries 1–4). We found that Cu_2O and CuI provided quinazolinedione **3a** in 31% and 21% yield, respectively, whereas CuBr and $Cu(OAc)_2$ were not reactive. Next, various solvents, such as CH_3CN, DMF and toluene were investigated, resulting in 27%, 22% and 0% yield, respectively (Entries 5–7).

Increasing the amount of carbodiimide slightly increased the product yield (Entries 8–10). However, we found that with three equivalents of carbodiimide the yield was decreased to 26% (Entry 10). Common bases, such as K_3PO_4, Cs_2CO_3, NEt_3 and ^tBuOK, were also investigated (Entries 11–14). Unfortunately, none provided good yields, while NEt_3 gave a moderate 47% yield (Entry 13).

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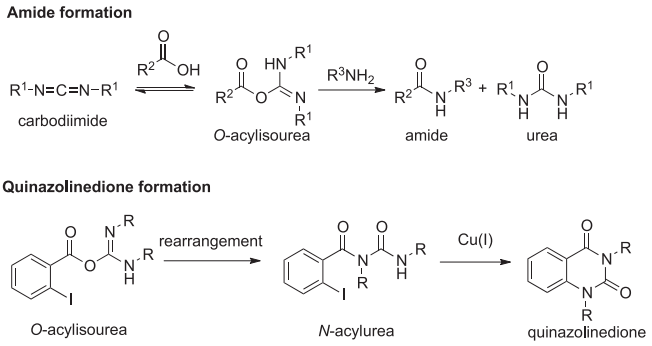
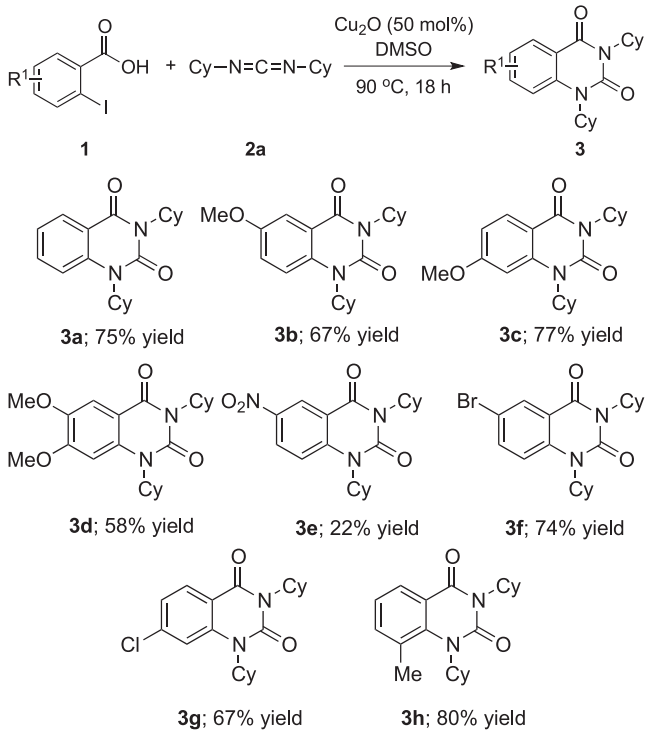


Scheme 1. Amide and quinazolinedione formation from carbodiimides.

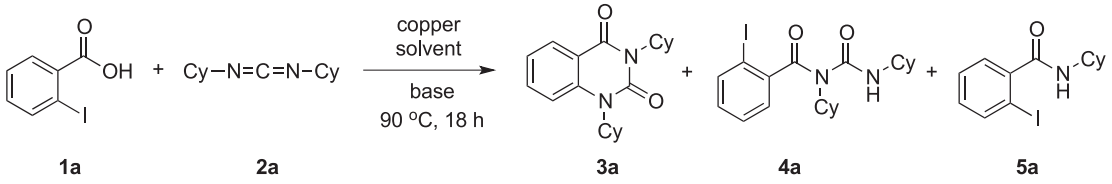
We found that *N*-acylurea **4a** was exclusively obtained in the absence of a copper catalyst and base (Entry 15). This finding was in agreement with the report from Nakajima and co-workers who showed that benzoic acid reacted with carbodiimides to generate *N*-acylureas without any catalyst [2]. Based on this result, the formation of **4a** was a non-catalyzed reaction pathway. Therefore, in order to improve the product yield we hypothesized that increasing the amount of Cu_2O would enhance the rate of quinazolinedione formation. We then investigated the amount of Cu_2O (Entries 16 and 17). Significantly, the yield was improved to 64% using 30 mol% or 50 mol% of Cu_2O. Additionally, according to a report from Kishikawa and co-workers, **4a** could undergo elimination to give amide **5a** in the presence of base [7]. Crucially, in the absence of an external base the yield of quinazolinedione **3a** was increased to 75% (Entry 18). Non-external base conditions were found to be an important factor to determine the reaction pathway

Table 2
Formation of quinazolinediones from 2 to iodobenzoic acid derivatives.[a]



[a] Reagents and conditions: **1a**–**h** (0.5 mmol), **2a** (1.0 mmol).

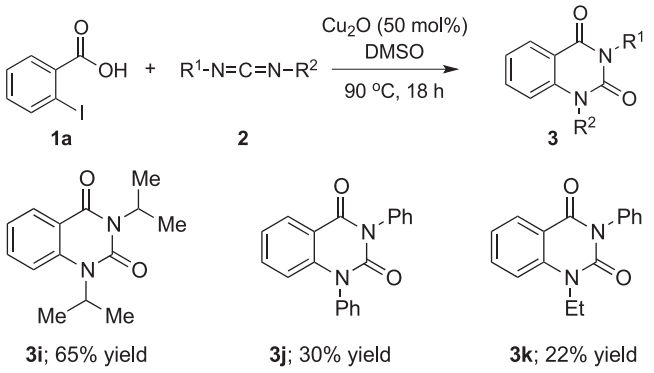
Table 1
Optimization of the reaction conditions.[a]



Entry	**2a** (equiv.)	Cu (mol%)	Base	Solvent	Yield **3a** (%)[b]
1	1.1	Cu_2O (10)	K_2CO_3	DMSO	31
2	1.1	CuI (10)	K_2CO_3	DMSO	21
3	1.1	CuBr (10)	K_2CO_3	DMSO	trace
4	1.1	$Cu(OAc)_2$ (10)	K_2CO_3	DMSO	trace
5	1.1	Cu_2O (10)	K_2CO_3	CH_3CN	27
6	1.1	Cu_2O (10)	K_2CO_3	DMF	22
7	1.1	Cu_2O (10)	K_2CO_3	toluene	0
8	1.5	Cu_2O (10)	K_2CO_3	DMSO	35
9	2.0	Cu_2O (10)	K_2CO_3	DMSO	38
10	3.0	Cu_2O (10)	K_2CO_3	DMSO	26
11	2.0	Cu_2O (10)	K_3PO_4	DMSO	21
12	2.0	Cu_2O (10)	Cs_2CO_3	DMSO	trace
13	2.0	Cu_2O (10)	NEt_3	DMSO	47
14	2.0	Cu_2O (10)	^tBuOK	DMSO	trace
15	2.0	–	–	DMSO	0
16	2.0	Cu_2O (30)	NEt_3	DMSO	64
17	2.0	Cu_2O (50)	NEt_3	DMSO	64
18	2.0	Cu_2O (50)	–	DMSO	75
19	2.0	Cu_2O (10)	–	DMSO	37

[a] Reagents and conditions: **1a** (0.5 mmol), base (1.5 equiv.).
[b] Isolated yield.

Table 3
Formation of quinazolinediones from a variety of carbodiimides.[a]



[a]Reagents and conditions: **1a** (0.5 mmol), **2** (1.0 mmol).

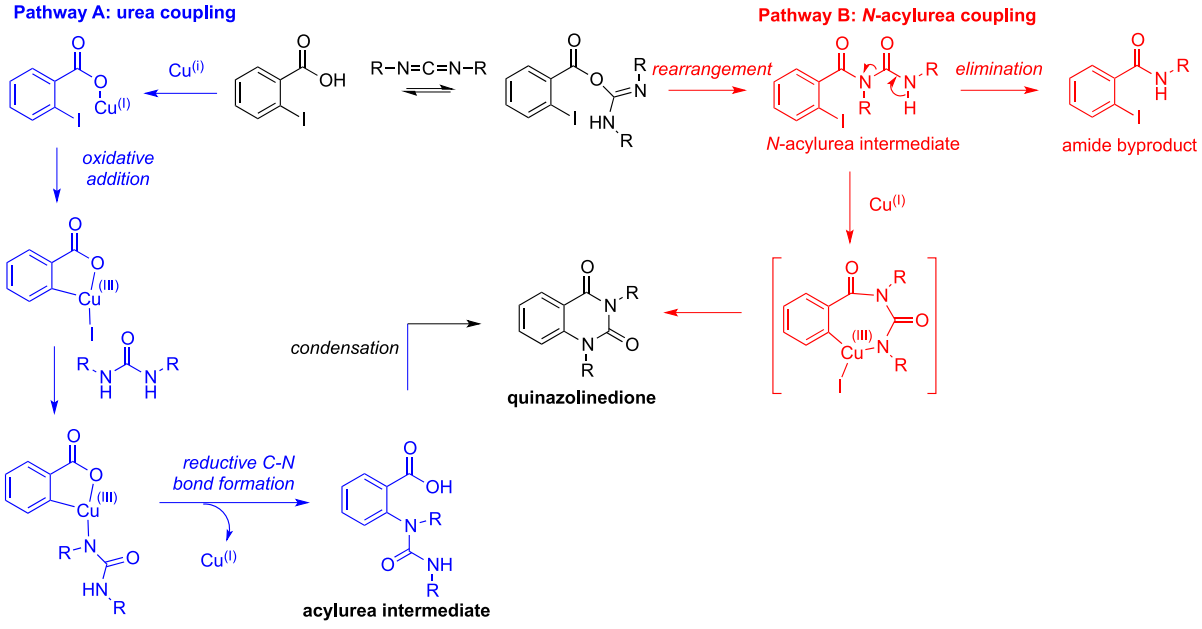
[8]. Unfortunately, lowering the amount of Cu_2O to 10 mol% under non-external base conditions gave low yields of the desired quinazolinedione (Entry 19). Attempts to improve the product yield using cooperating ligands with Cu_2O (10 mol%) resulted in low product yields with high amounts of the amide by-product.

With the optimal reaction conditions in hand (Table 1, entry 18), we further explored the substrate scope using a variety of 2-iodobenzoic acid derivatives (Table 2).

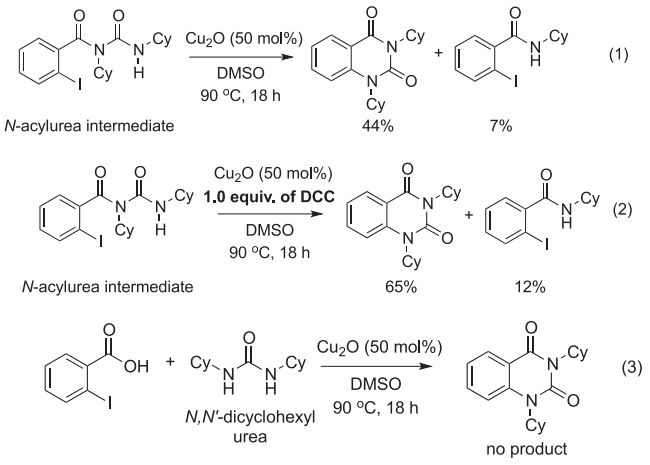
The reaction of 2-iodobenzoic acid derivatives bearing electron-donating substituents provided the corresponding quinazolinediones in good yields. Both 2-iodo-5-methoxy- and 2-iodo-4-methoxybenzoic acids gave quinazolinediones **3b** and **3c** in 67% and 77% yield, respectively, while 2-iodobenzoic acid with two methoxy groups provided quinazolinedione **3d** in 58% yield. However, the reaction of 2-iodo-5-nitrobenzoic acid gave quinazolinedione **3e** in only 22% yield. We observed the formation of the corresponding *N*-acylurea as a major by-product. Based on these results, we believe that benzoic acids bearing electron-withdrawing groups preferably undergo the non-catalyzed reaction pathway. Halogen substituents were also applicable to the reaction of 5-bromo-2-iodobenzoic acid which gave quinazolinedione **3f** in 74% yield. Likewise, 4-chloro-2-iodobenzoic acid gave the corresponding quinazolinedione **3g** in 67% yield. Interestingly, the presence of a methyl substituent next to the iodine did not hinder the reaction and provided **3h** in 80% yield.

Next, we examined the scope of the carbodiimides. Three types of carbodiimide were selected: dialkyl (*N*,*N*'-methanediylidenebis(propan-2-amine); **2b**), diaryl (*N*,*N*'-methanediylidenedianiline; **2c**) and an asymmetric carbodiimide (*N*-((ethylimino)methylene)aniline; **2d**) (Table 3). The *N*,*N*'-methanediylidenebis(propan-2-amine) **2b** gave quinazolinedione **3i** in 65% yield. In contrast, **2c** gave low yields of the desired quinazolinedione **3j**. The major product of this reaction was the corresponding amide by-product which was isolated in 58% yield. This result suggested that carbodiimides with diaryl substituents undergo *N*-acylurea formation faster than the copper-catalyzed reaction. Then, elimination of the *N*-acylurea occurs to yield the amide by-product. A similar result was found when the asymmetric carbodiimide was subjected to the reaction, resulting in a low yield of the corresponding 1-ethyl-3-phenylquinazoline-2,4(1*H*,3*H*)-dione **3k**. We did not obtain the other regioisomer, 3-ethyl-1-phenylquinazoline-2,4-(1*H*,3*H*)-dione. Instead, both *N*-ethyl and *N*-phenyl benzamides were obtained, which suggested that the *N*-ethyl-2-iodo-*N*-(phenylcarbamoyl)benzamide intermediate underwent elimination to generate the *N*-ethyl amide by-product faster than that of *N*-(ethylcarbamoyl)-2-iodo-*N*-phenylbenzamide, possibly due to the more acidic proton of the phenylcarbamoyl moiety.

Next, we turned our interest to investigating the reaction mechanism. Since we observed 1,3-dicyclohexylurea formation, we first postulated the mechanism involving a coupling reaction of 2-iodobenzoic acid and the urea generated *in situ* from the reaction of the carbodiimide and moisture in DMSO. Then, an acylurea intermediate undergoes condensation to form the desired product (Scheme 2, pathway A). Secondly, based on our results as well as the reports from Nakajima [2] and Kishikawa [7] related to the role of carbodiimides in amide formation, we postulated that quinazolinediones could be obtained from the copper-catalyzed intramolecular C-N bond formation of an *N*-acylurea intermediate



Scheme 2. Possible reaction mechanisms.



Scheme 3. Control experiments.

generated from the non-catalyzed reaction of the acid-carbodiimide (Scheme 2, pathway B). The competitive reaction of this pathway was the elimination of an *N*-acylurea intermediate resulting in generation of the amide by-product. Importantly, Perkins and co-workers recently reported the formation of quinazolinediones from *N*-acylureas *via* a copper-catalyzed coupling reaction [9]; these findings supported our second mechanistic postulation.

According to our postulated possible reaction mechanisms, we performed several control experiments (Scheme 3). Due to generation of the amide by-product, we first focused on the pathway involving the *N*-acylurea. The reaction of the *N*-acylurea intermediate under the optimal reaction conditions gave quinazolinedione **3a** and amide **5a** in 44% and 7% yield, respectively, with the *N*-acylurea remaining (Scheme 3, eq. 1). Since the reaction was not complete, and the optimal reaction conditions required 2.0 equivalents of the carbodiimide, another equivalent of *N,N'*-dicyclohexylcarbodiimide was added to the reaction (Scheme 3, eq. 2). The desired product **3a** was obtained in 65% yield and amide **5a** was obtained in 12% yield. This result showed that the excess carbodiimide possibly acted as a base to trigger elimination of the *N*-acylurea intermediate resulting in generation of the amide by-product. Moreover, the yield of **3a** from the second control experiment was similar to the yield using the optimal reaction conditions. Based on these results and the report [9] from Perkins, the quinazolinediones could possibly be synthesized *via* an *N*-acylurea intermediate.

To examine the possibility of pathway A, *N,N'*-dicyclohexylurea and 2-iodobenzoic acid were subjected to the reaction, however, the desired quinazolinedione was not observed (Scheme 3, eq. 3). Based on this result, we propose that quinazolinediones are not generated from the urea.

Conclusion

The synthesis of quinazolinediones from 2-iodobenzoic acids and carbodiimides *via* a copper-catalyzed domino reaction is reported. The non-catalyzed pathway, leading to *N*-acylureas, crucially impacted the product yields, resulting in the requirement of high copper loading. Non-external base conditions were required in order to minimize the amount of amide by-product resulting from elimination of the *N*-acylurea intermediate. A variety of 2-iodobenzoic acids were applicable, although those with electron-withdrawing substituents provided low yields. Although the exact mechanism could not be determined, based on control experiments we believe that the quinazolinediones are obtained from *N*-acylurea intermediates. Further mechanistic studies are ongoing.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.08.028.

References

[1] a) Q. Liao, X. Yang, C. Xi, J. Org. Chem. 79 (2014) 8507–8515;
c) Y. Liu, J.-P. Wan, Org. Biomol. Chem. 9 (2011) 6873–6894;
d) S.D. Surry, S.L. Buchwald, Chem. Sci. 1 (2010) 13–31;
e) F. Monnier, M. Taillefer, Angew. Chem. Int. Ed. 48 (2009) 6954–6971;
f) D. Ma, Q. Cai, Acc. Chem. Res. 41 (2008) 1450–1460;
g) I.P. Beletskaya, A.V. Cheprakov, Coord. Chem. Rev. 248 (2004) 2337–2364.
[2] N. Nakajima, Y. Ikada, Bioconjugate Chem. 6 (1995) 123–130.
[3] C. Lu, C. Gong, B. Zhao, L. Hu, Y. Yao, J. Org. Chem. 83 (2018) 1154–1159.
[4] F. Wang, S. Cai, Q. Liao, C. Xi, J. Org. Chem. 76 (2011) 3174–3180.
[5] a) S.B. Mhaske, N.P. Argade, Tetrahedron 62 (2006) 9787–9862;
b) V. Murugan, M. Kulkarni, R.M. Anand, E.P. Kumar, B. Suresh, V.M. Reddy, Asian J. Chem. 18 (2006) 900–906;
c) V. Alagarsamy, S.V. Raja, K. Dhanabal, Bioorg. Med. Chem. 15 (2007) 235–241;
d) J.A. Lowe III, R.L. Archer, D.S. Chapin, J.B. Cheng, D. Helwag, J.L. Johnson, B.K. Koe, L.A. Lebel, P.F. Moore, J.A. Nielsen, J. Med. Chem. 34 (1991) 624–628;
e) G.M. Buckley, N. Davies, H.J. Dyke, P.J. Gilbert, D.R. Hannah, A.F. Haughan, C. A. Hunt, W.R. Pitt, R.H. Profit, N.C. Ray, M.D. Richard, A. Sharpe, A.J. Taylor, J.M. Whitworth, S.C. Williams, Bioorg. Med. Chem. Lett. 15 (2005) 751–754.
[6] a) M.C. Willis, R.H. Snell, A.J. Fletcher, R.L. Woodward, Org. Lett. 8 (2006) 5089–5091;
b) G.L. Beutner, Y. Hsiao, T. Razler, E.M. Simmons, W. Wertjes, Org. Lett. 19 (2017) 1052–1055;
c) P. Xu, F. Wang, T.-Q. Wei, L. Yin, S.-Y. Wang, S.-J. Ji, Org. Lett. 19 (2017) 4484–4487;
d) H. Li, W. Li, A. Spannenberg, W. Baumann, H. Neumann, M. Beller, X.-F. Wu, Chem. Eur. J. 20 (2014) 8541–8544;
e) S. Makino, N. Suzuki, E. Nakanishi, T. Tsuji, Synlett 3 (2001) 333–336;
f) S.-L. Wang, K. Yang, C.-S. Yao, X.-S. Wang, Synth. Commun. 42 (2012) 341–349;
g) D.S. Matharu, D.P. Flaherty, D.S. Simpson, C.E. Schroeder, D. Chung, D. Yan, J. W. Noah, C.B. Jonsson, E.L. White, J. Aube, R.K. Plemper, W.E. Severson, J.E. Golden, J. Med. Chem. 57 (2014) 10314–10328;
h) M. Sharafi-Kolkeshvandi, F. Nikpour, Chin. Chem. Lett. 23 (2012) 431–433;
i) J. Azizian, M. Mehrdad, K. Jadidi, Y. Sarrafi, Tetrahedron Lett. 41 (2000) 5265–5268.
[7] K. Kishikawa, H. Eida, S. Kohmoto, M. Yamamoto, K. Yamada, Synthesis (1994) 173–175.
[8] a) Selective developments, see: A. Hayeebueraheng, B. Kaewmee, V. Rukachaisirikul, J. Kaeobamrung J. Eur. J. Org. Chem. (2017) 6714–6721;
b) J. Kaeobamrung, J. Mahatthananchai, P. Zheng, W.J. Bode, J. Am. Chem. Soc. 132 (2010) 8810–8812.
[9] E. Durham, D. Perkins, J.S. Scott, J. Wang, S. Watson, Synlett 27 (2016) 965–968.

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

Figure 6 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63a**.

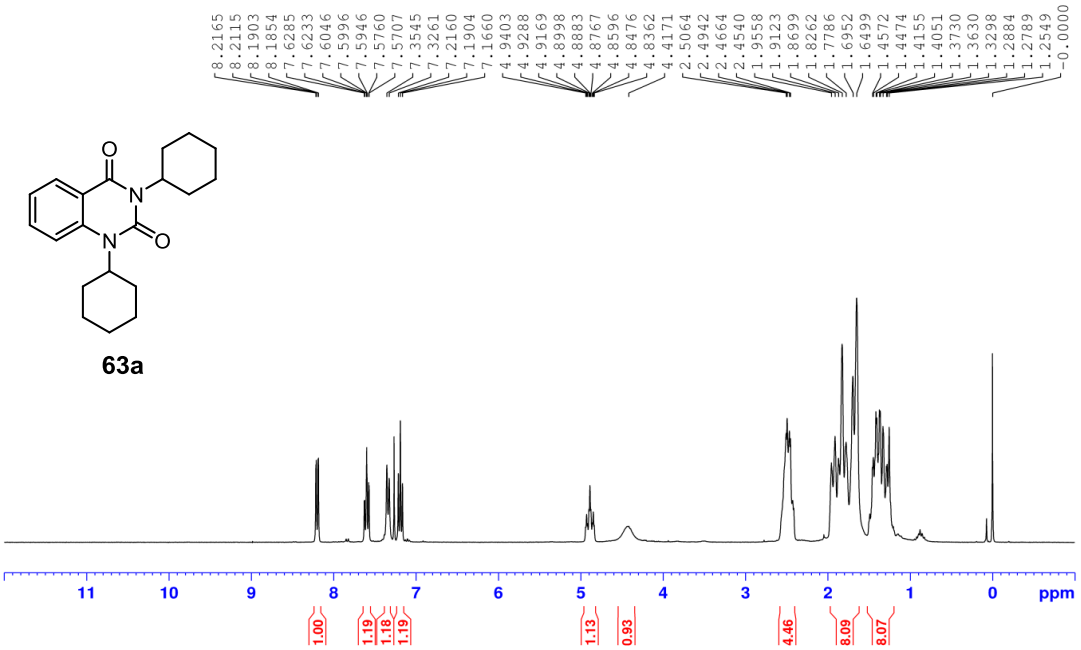


Figure 7 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **63a**.

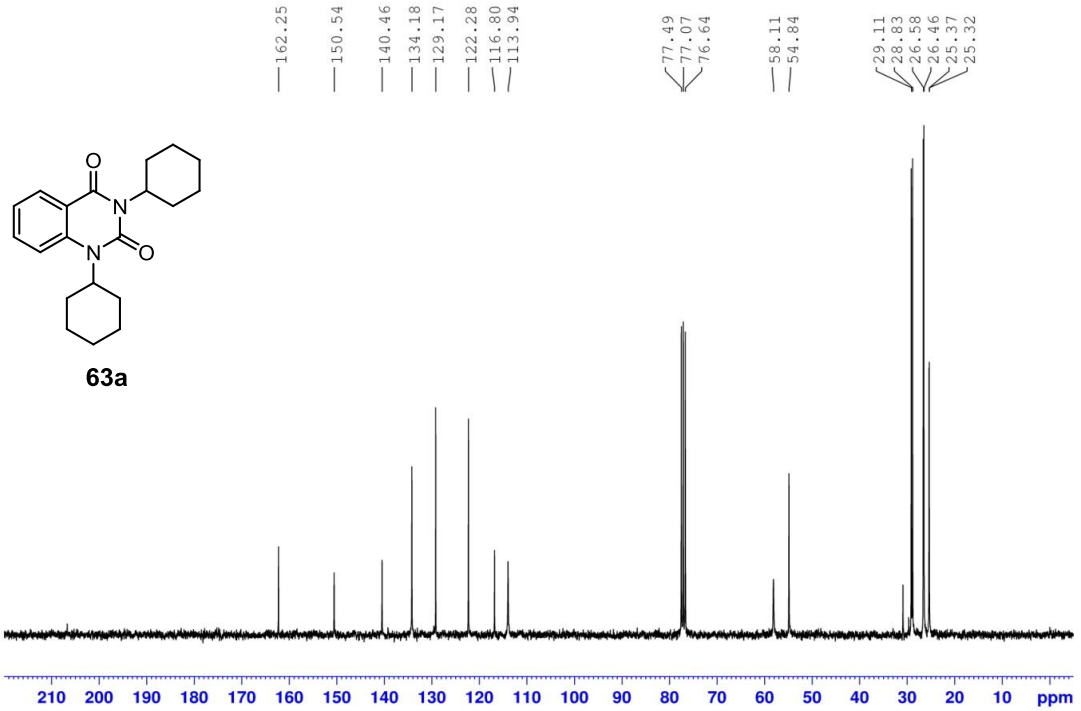


Figure 8 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63b**.

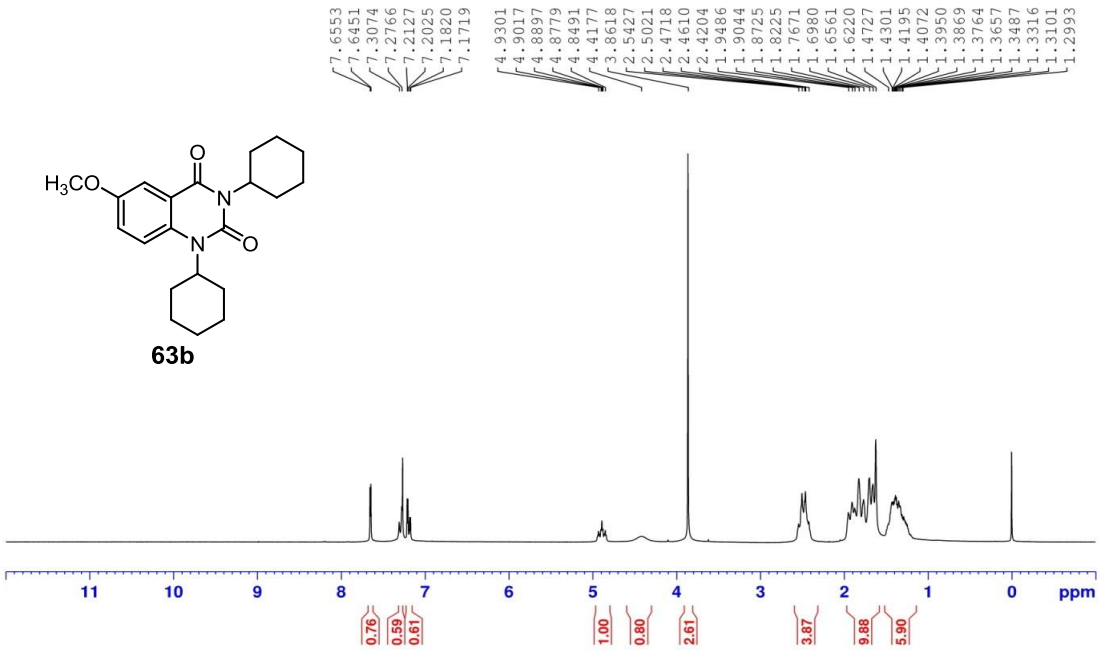


Figure 9 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **63b**.

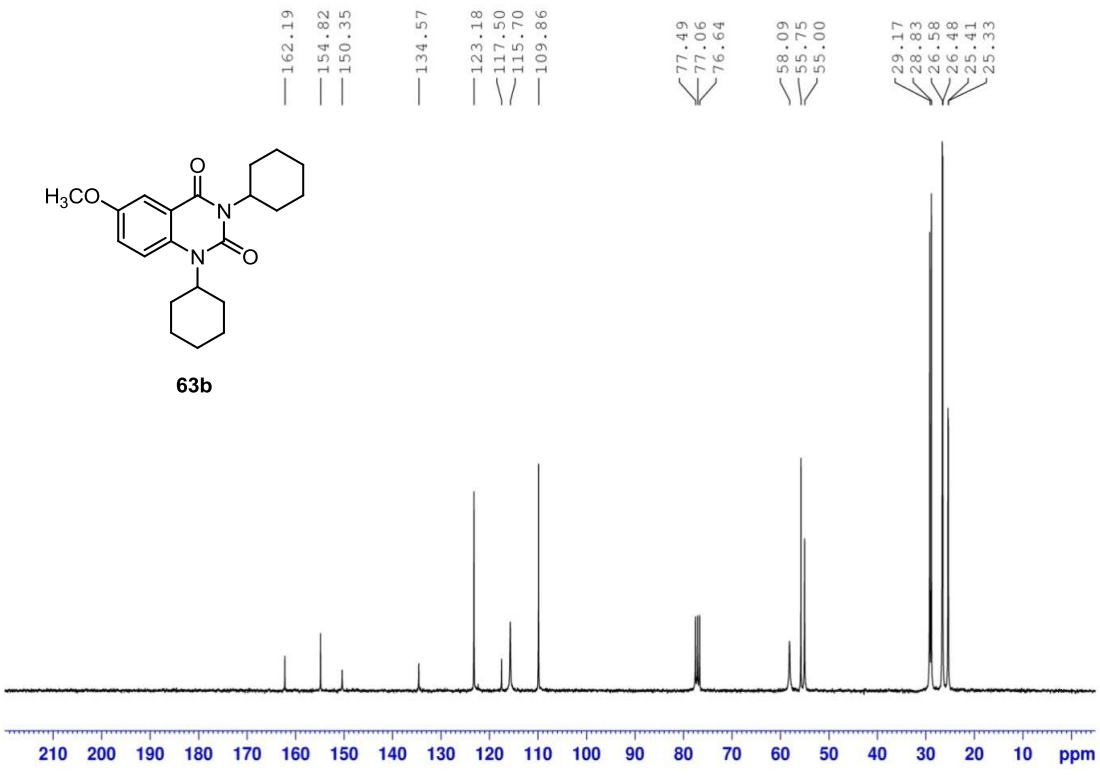


Figure 10 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63c**.

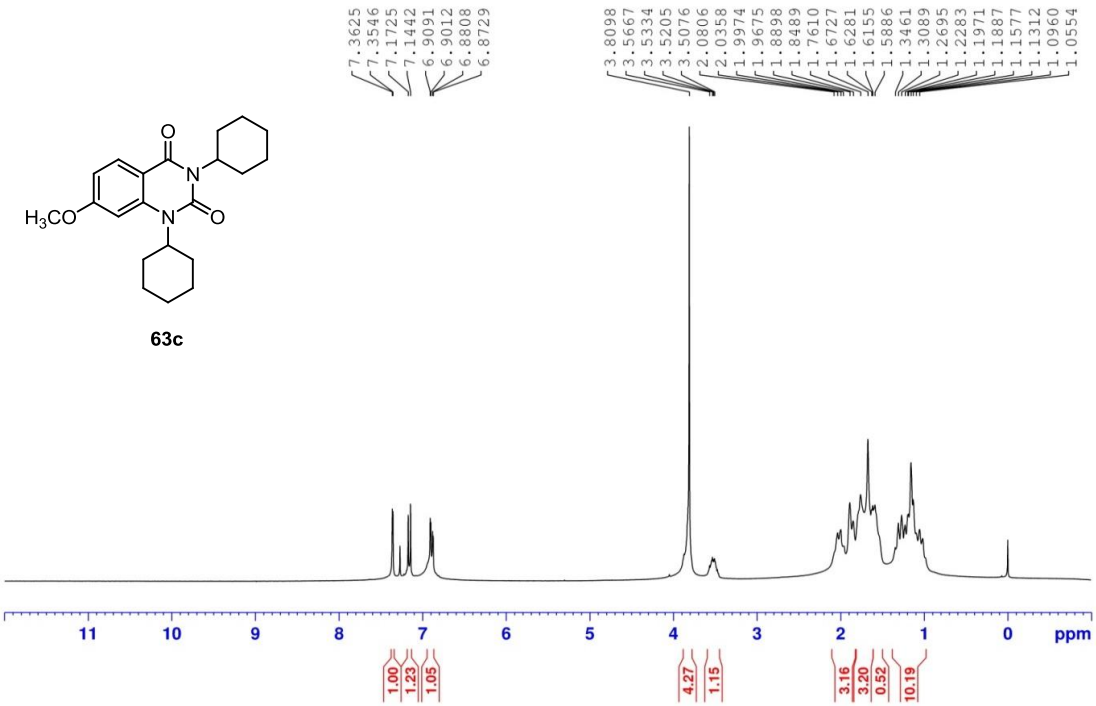


Figure 11 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **63c**.

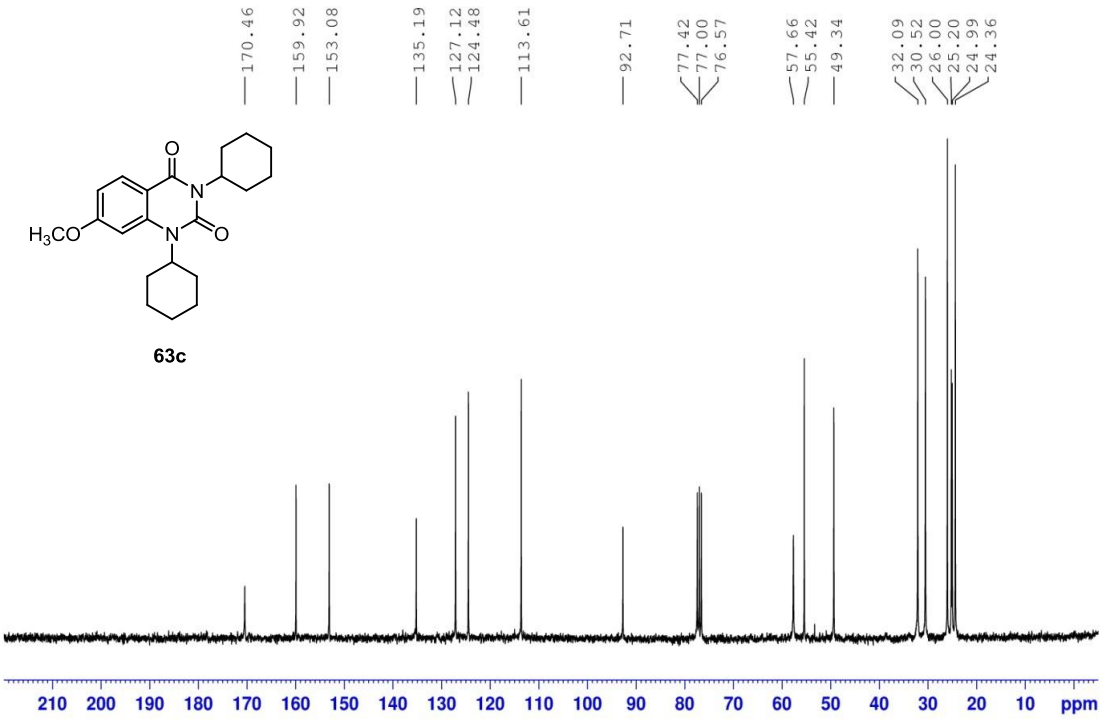


Figure 12 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63d**.

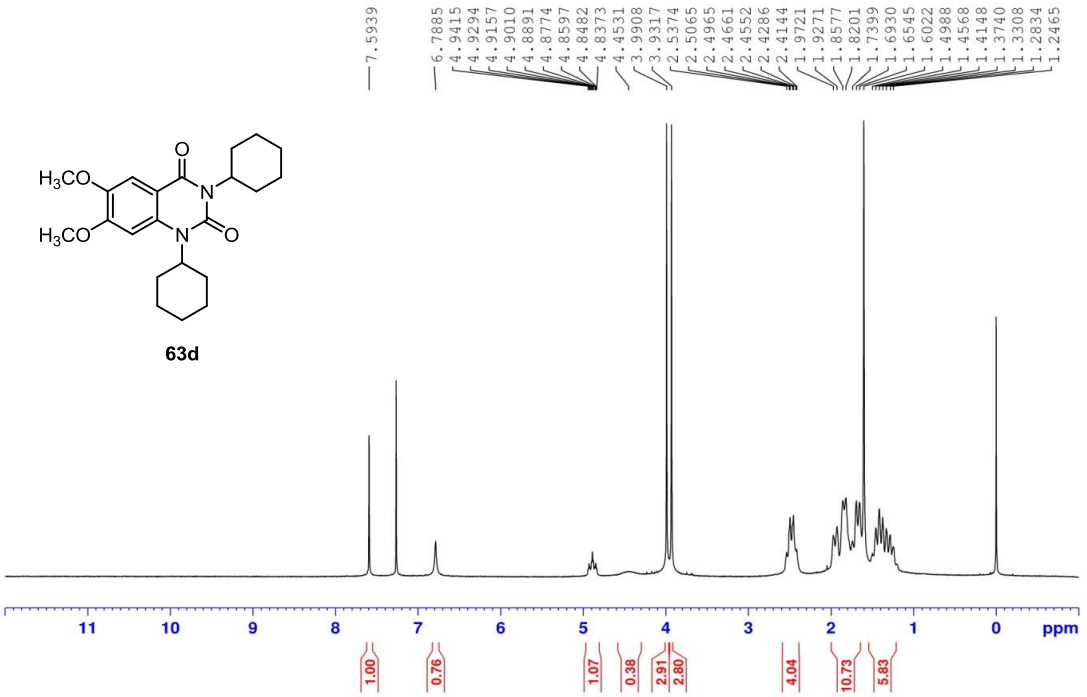


Figure 13 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **63d**.

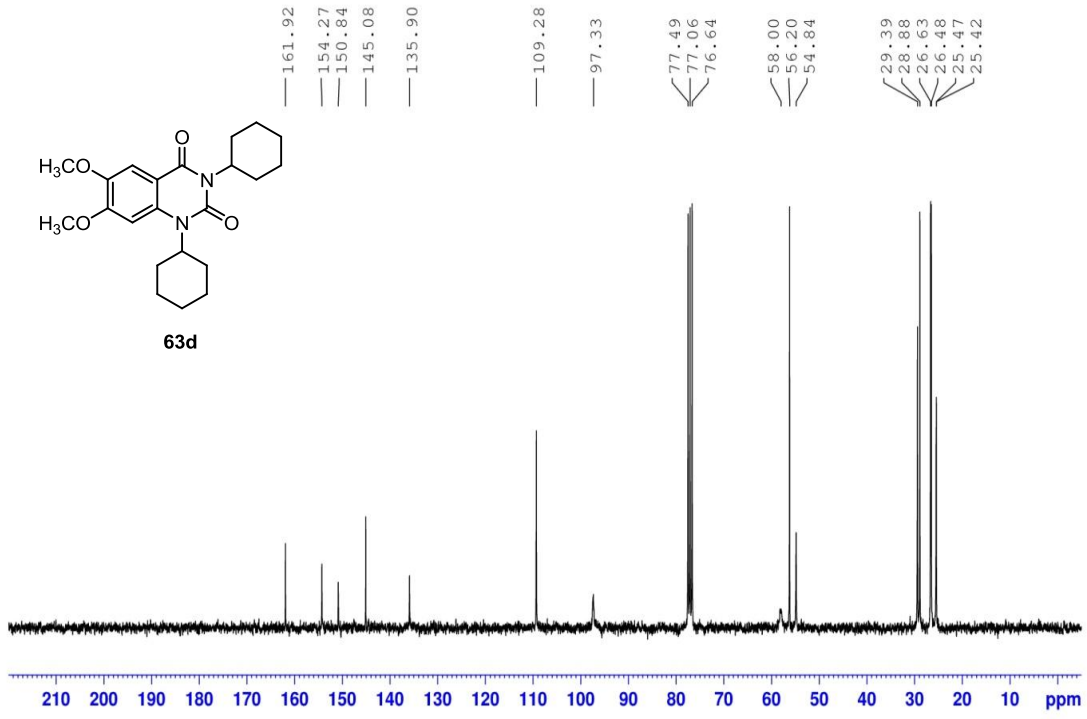


Figure 14 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63e**.

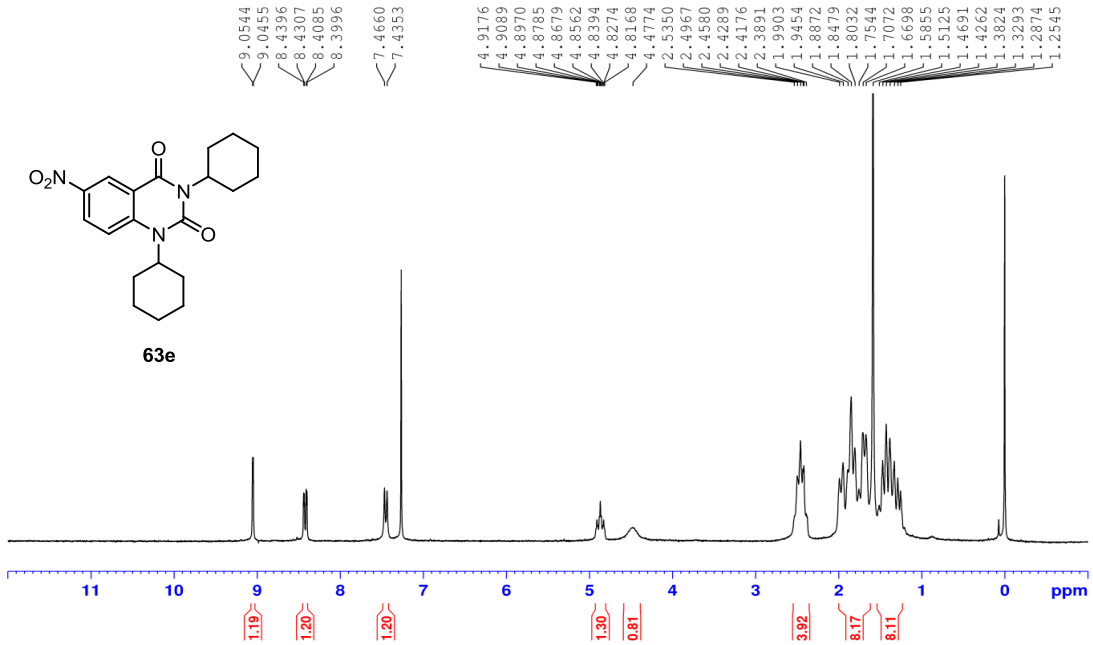


Figure 15 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **63e**.

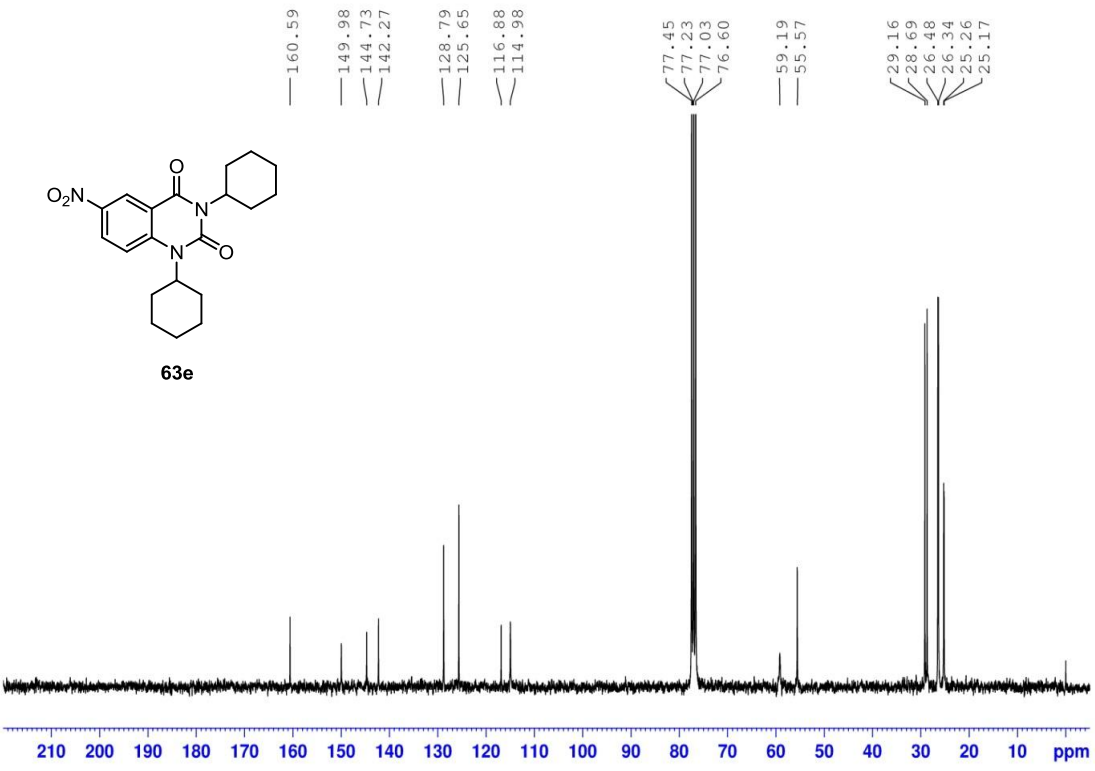


Figure 16 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63f**.

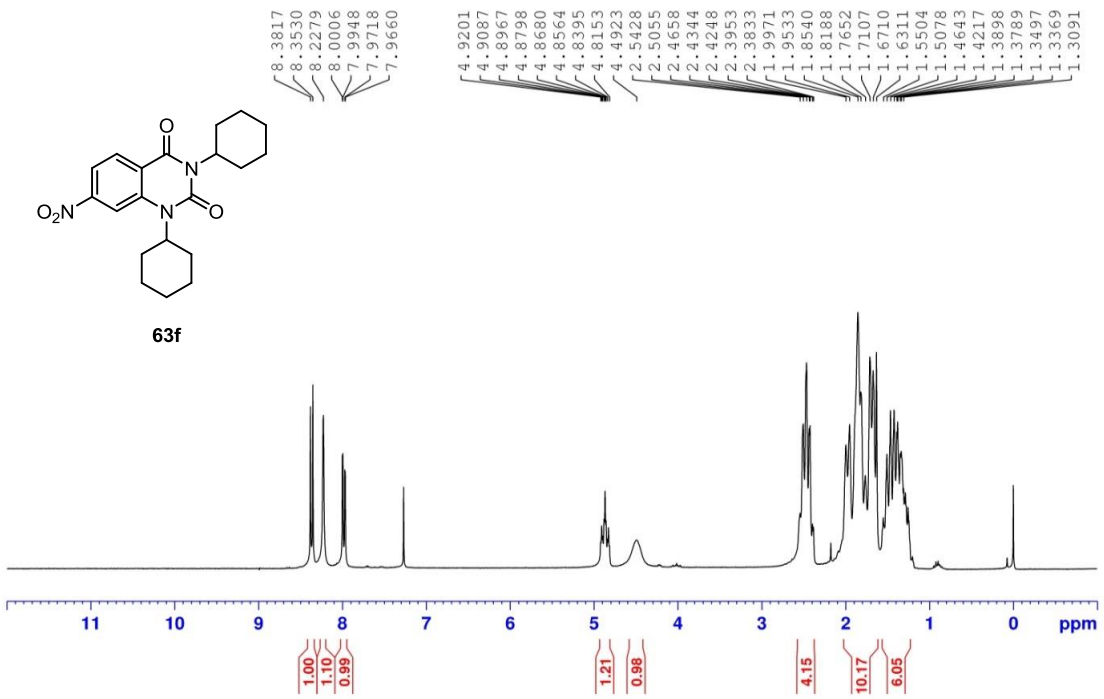


Figure 17 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **63f**.

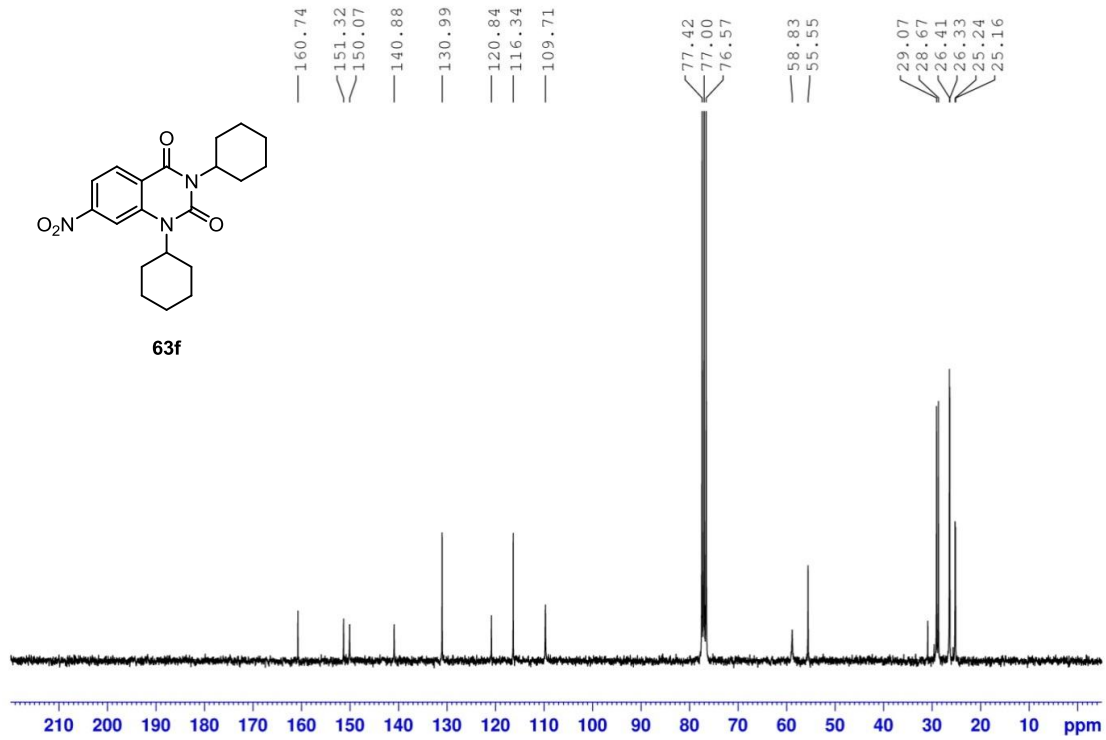


Figure 18 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63g**.

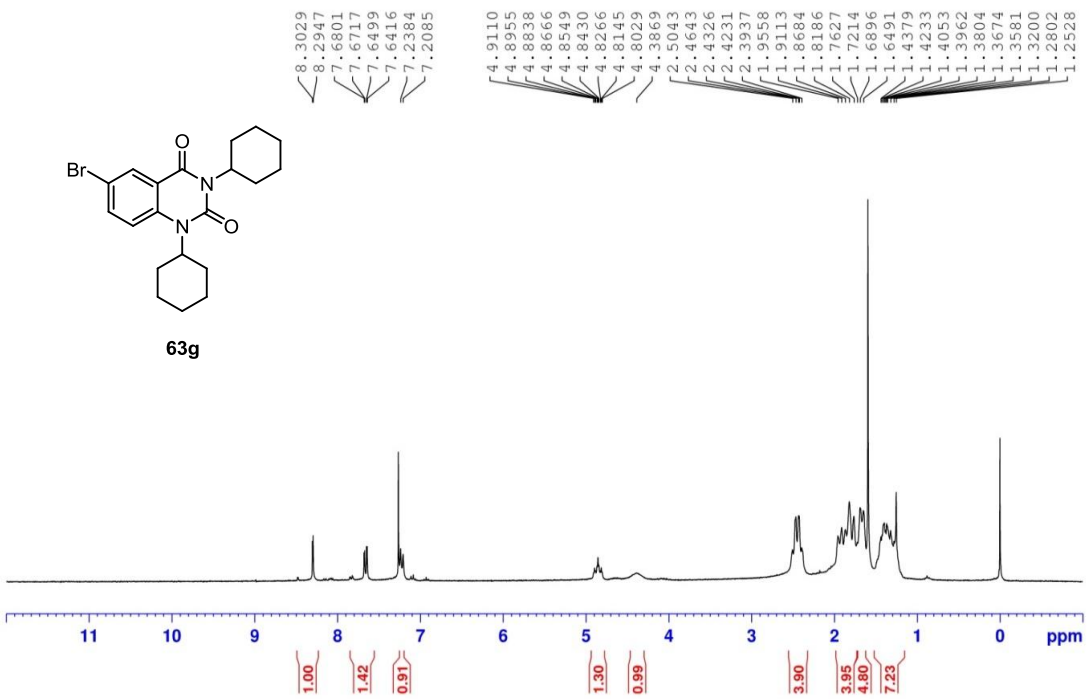


Figure 19 The ^{13}C NMR spectrum (300 MHz, $CDCl_3$) of compound **63g**.

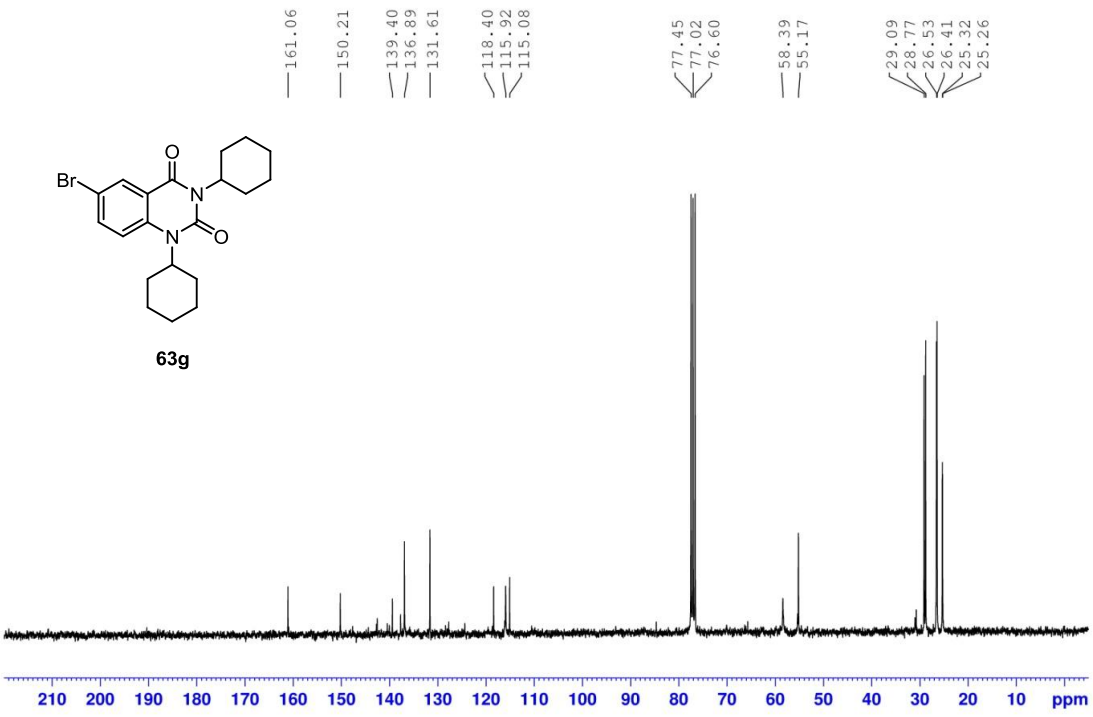


Figure 20 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63h**.

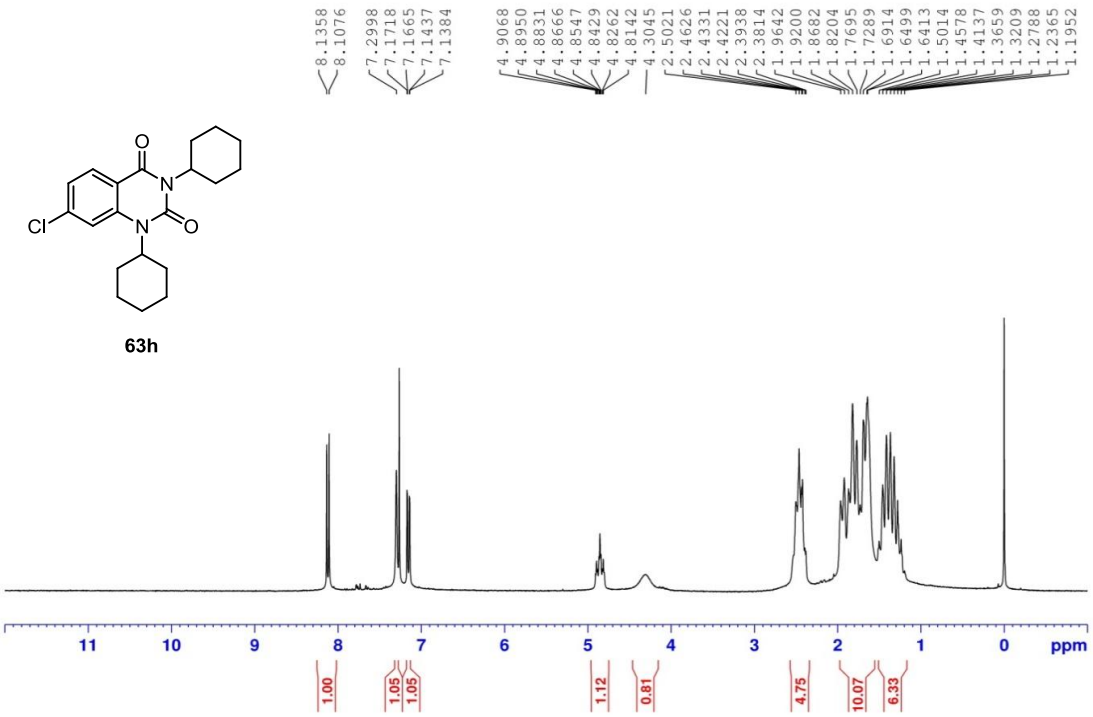


Figure 21 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **63h**.

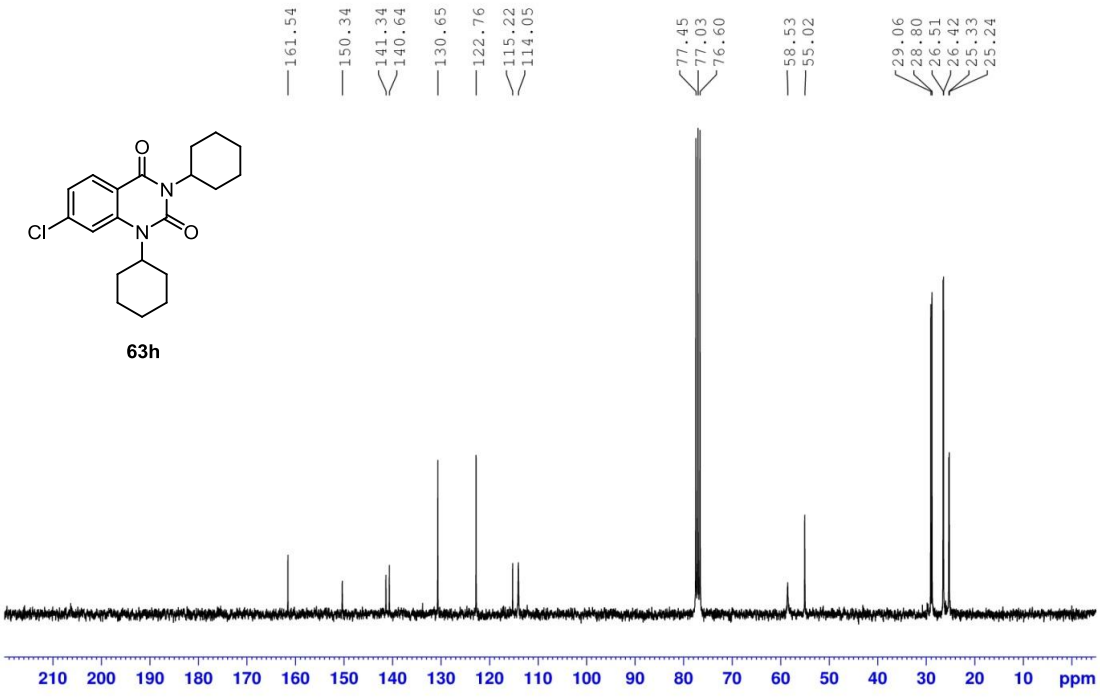


Figure 22 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63i**.

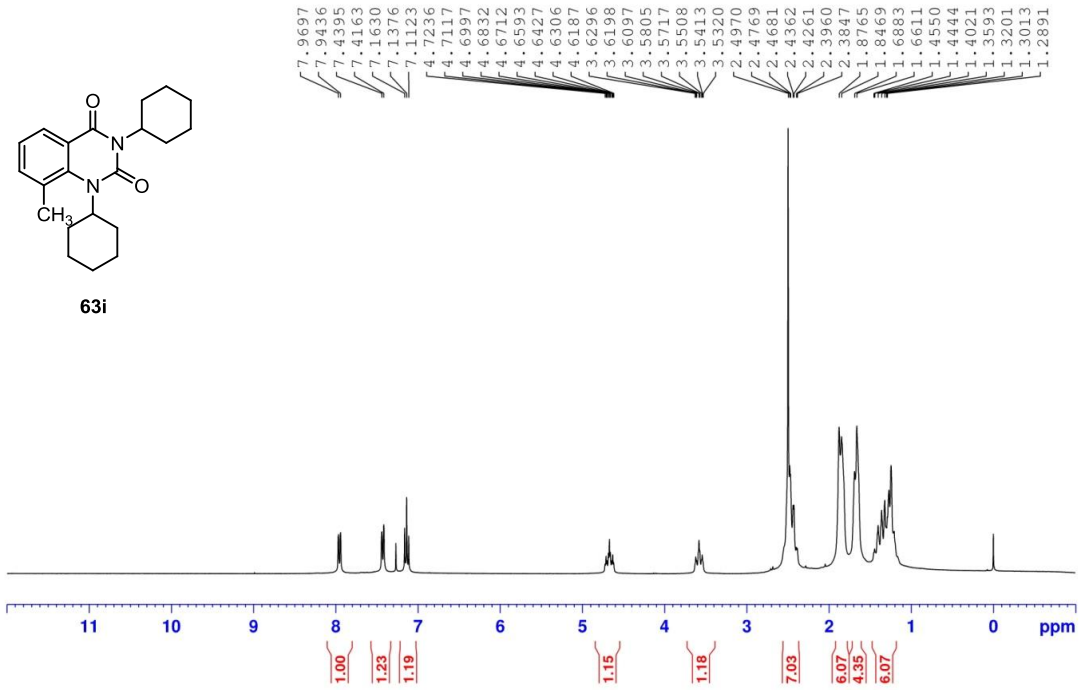


Figure 23 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **63i**.

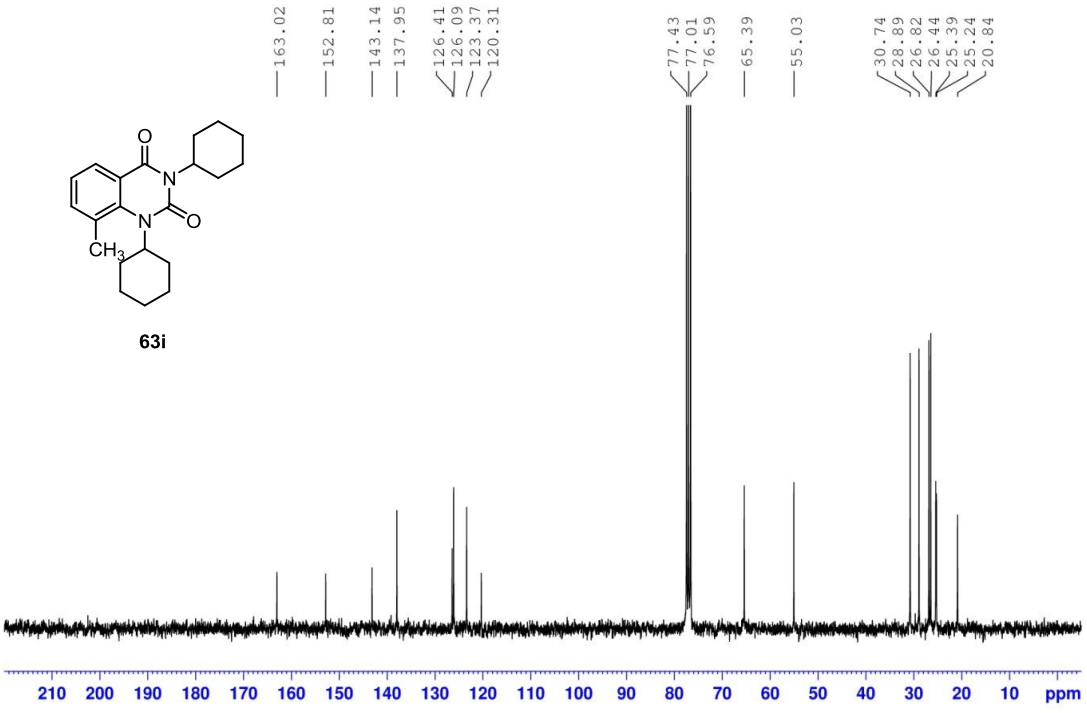


Figure 24 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63j**.

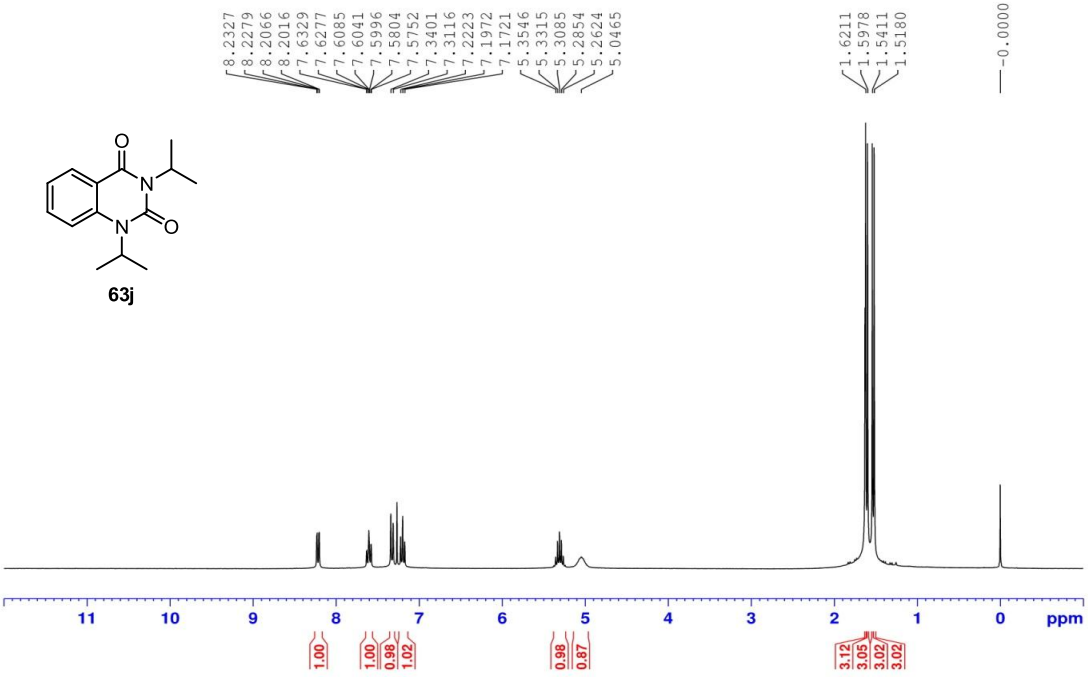


Figure 25 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **63j**.

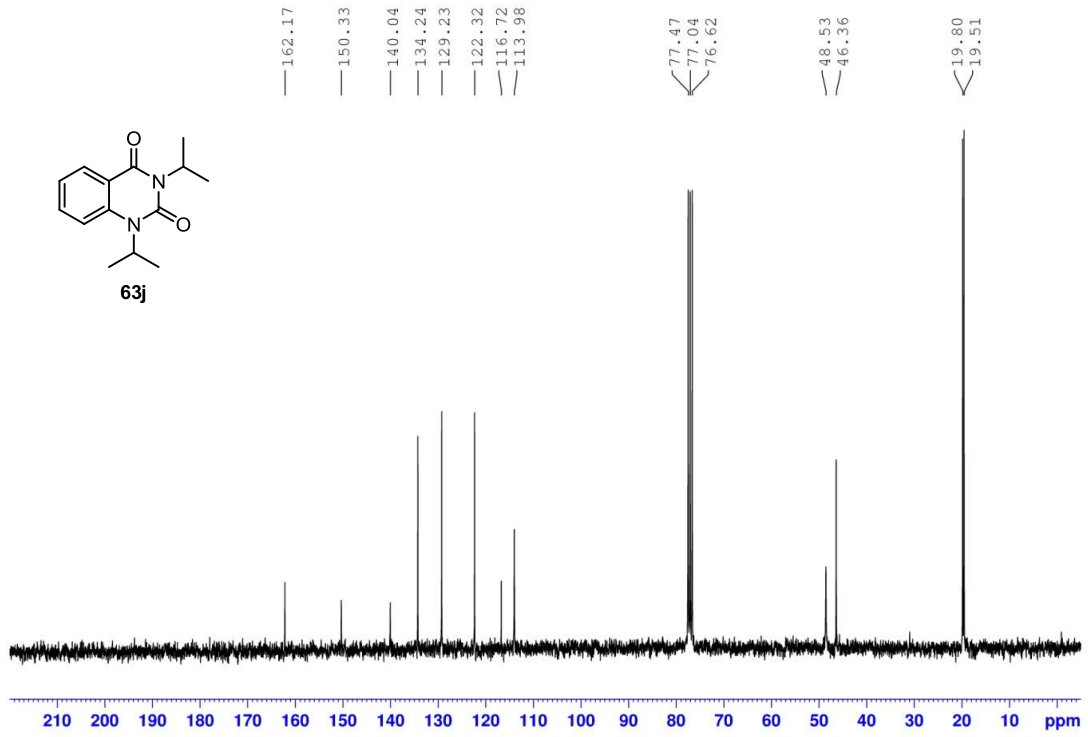


Figure 26 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63k**.

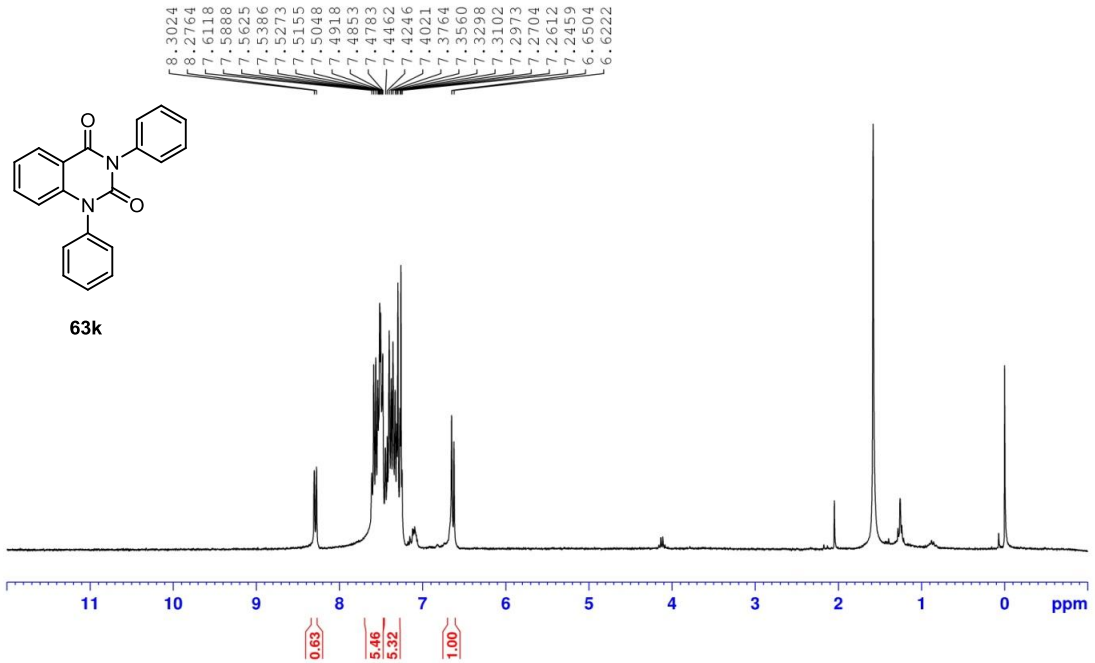


Figure 27 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **63k**.

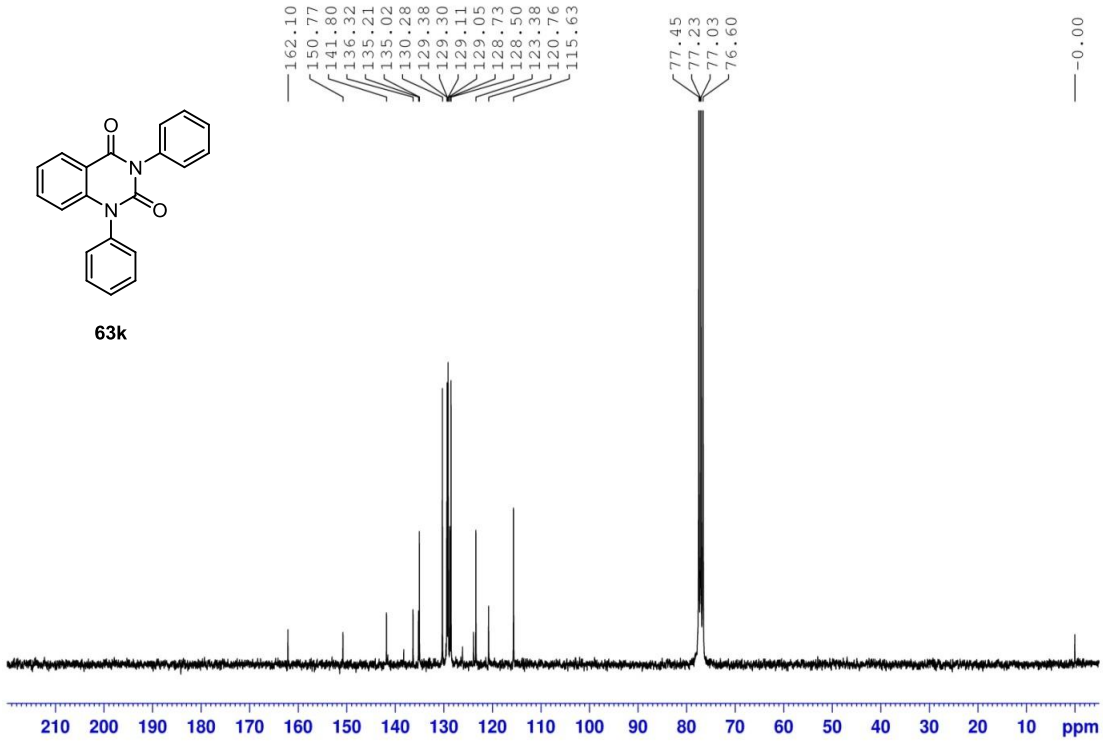


Figure 28 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **63l**.

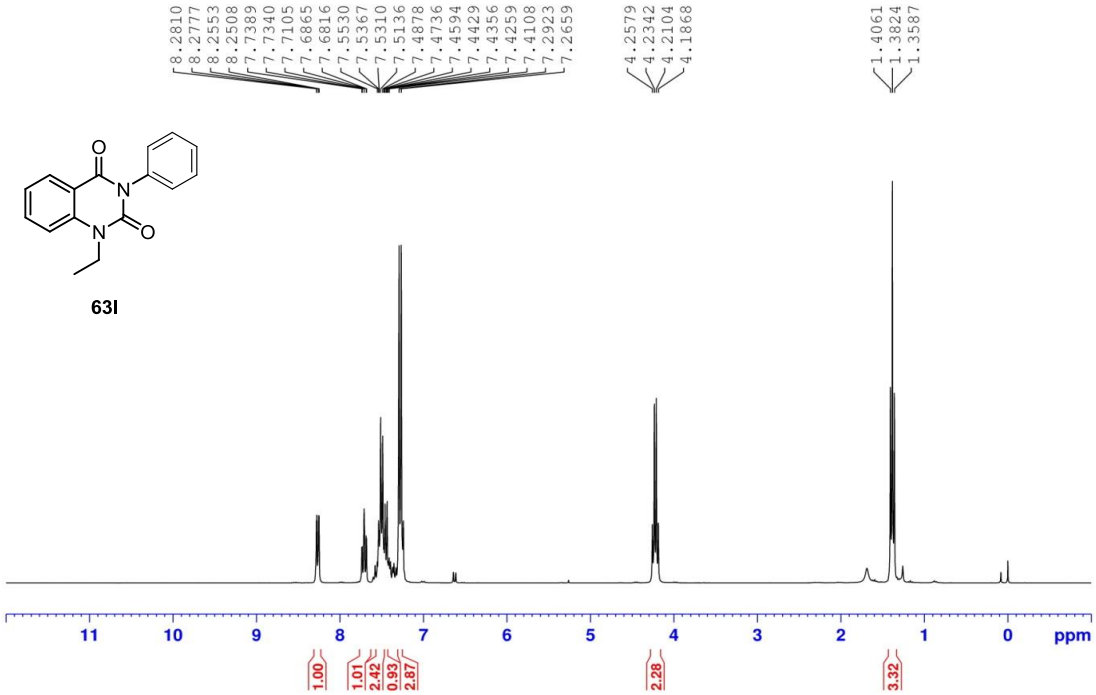


Figure 29 The ^{13}C NMR spectrum (300 MHz, $CDCl_3$) of compound **63l**.

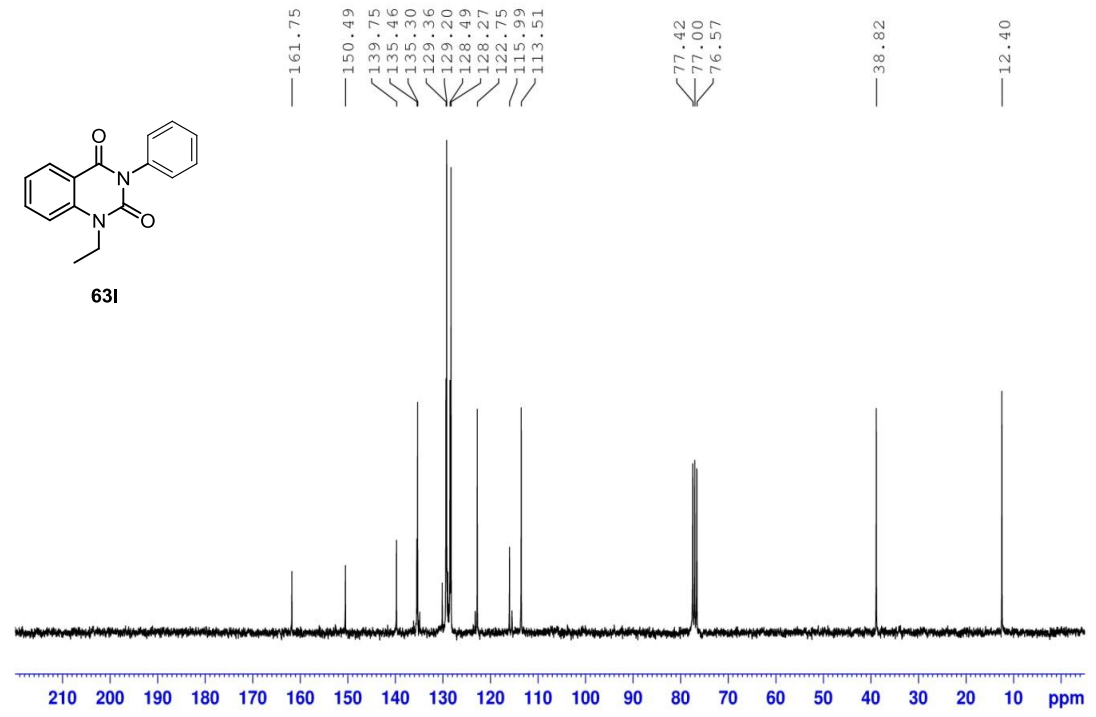


Figure 30 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **64a**.

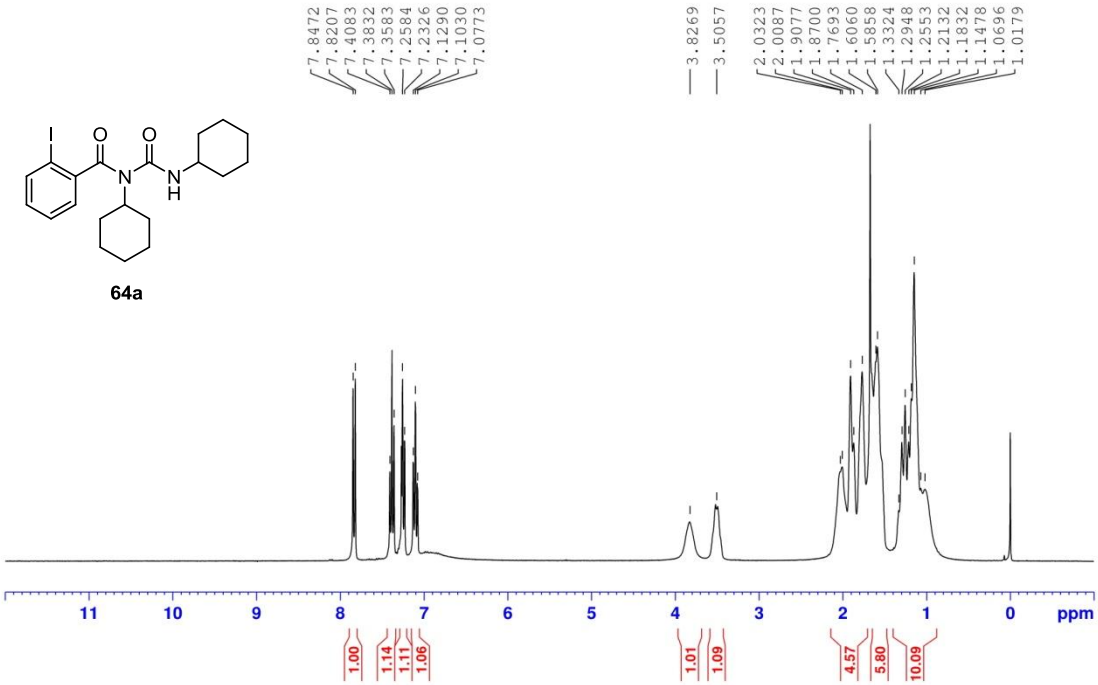
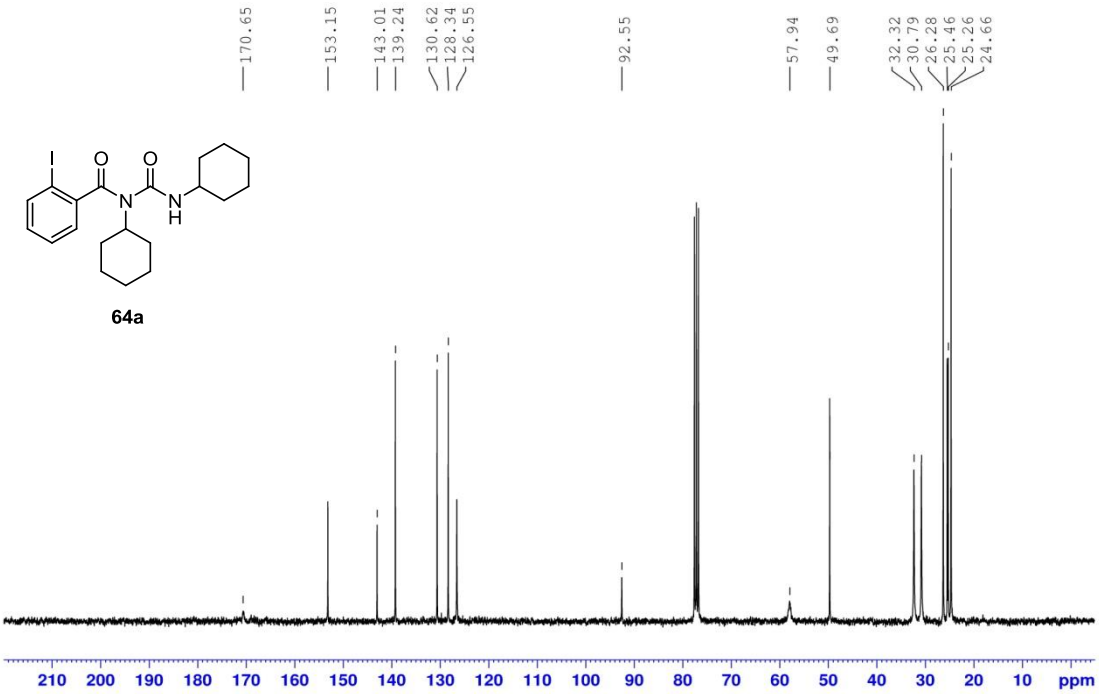


Figure 31 The ^{13}C NMR spectrum (300 MHz, $CDCl_3$) of compound **64a**.



^{1}H NMR and ^{13}C NMR Spectra of New Starting Material for Imidazolidinones Synthesis.

Figure 32 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **101.**

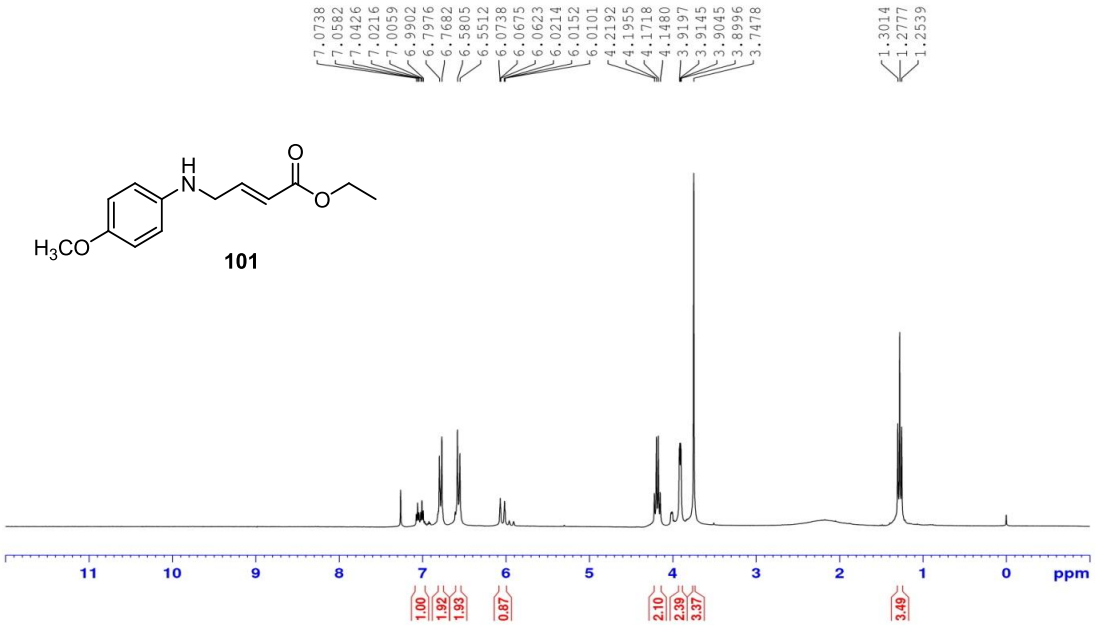
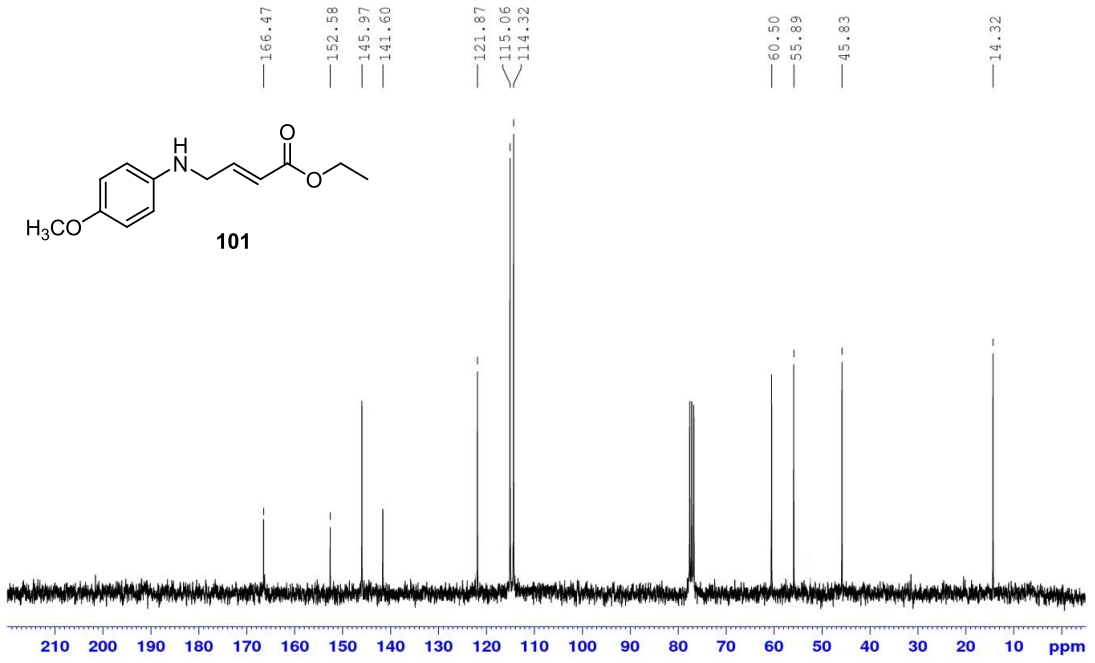


Figure 33 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **101.**



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

Figure 34 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **102a**.

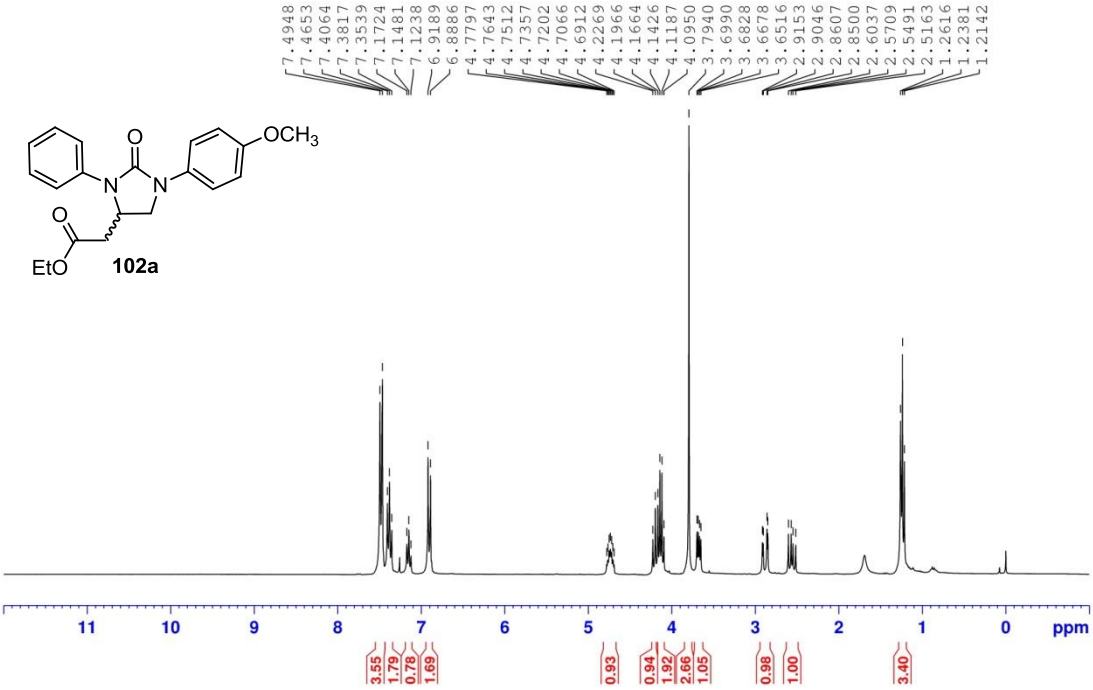


Figure 35 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **102a**.

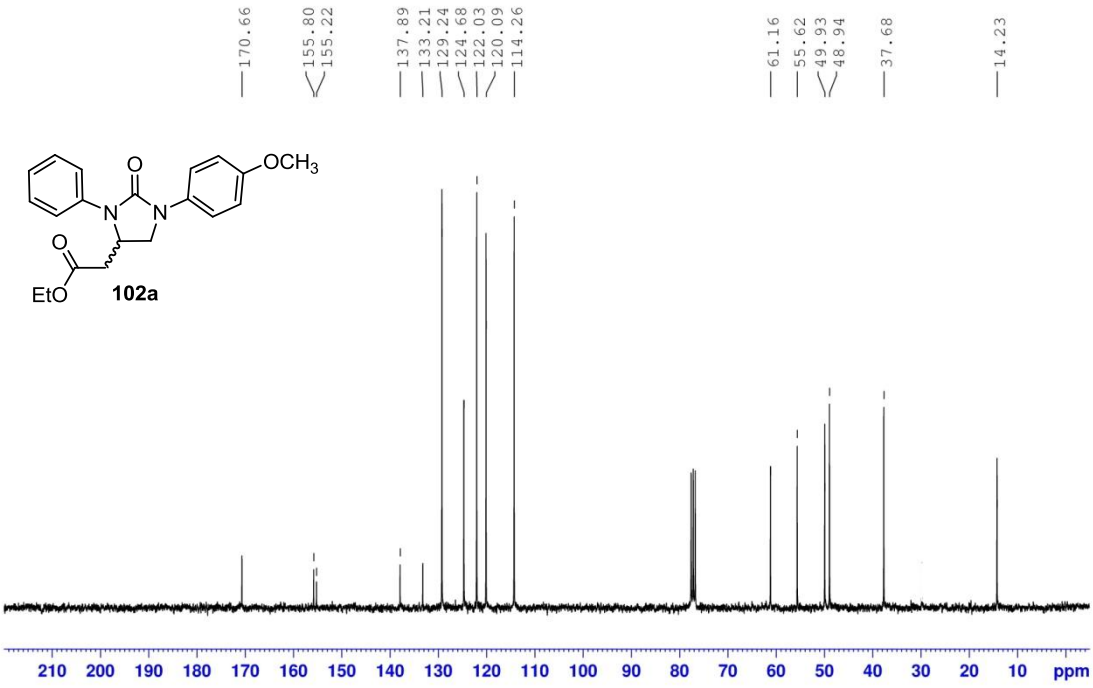


Figure 36 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **102b**.

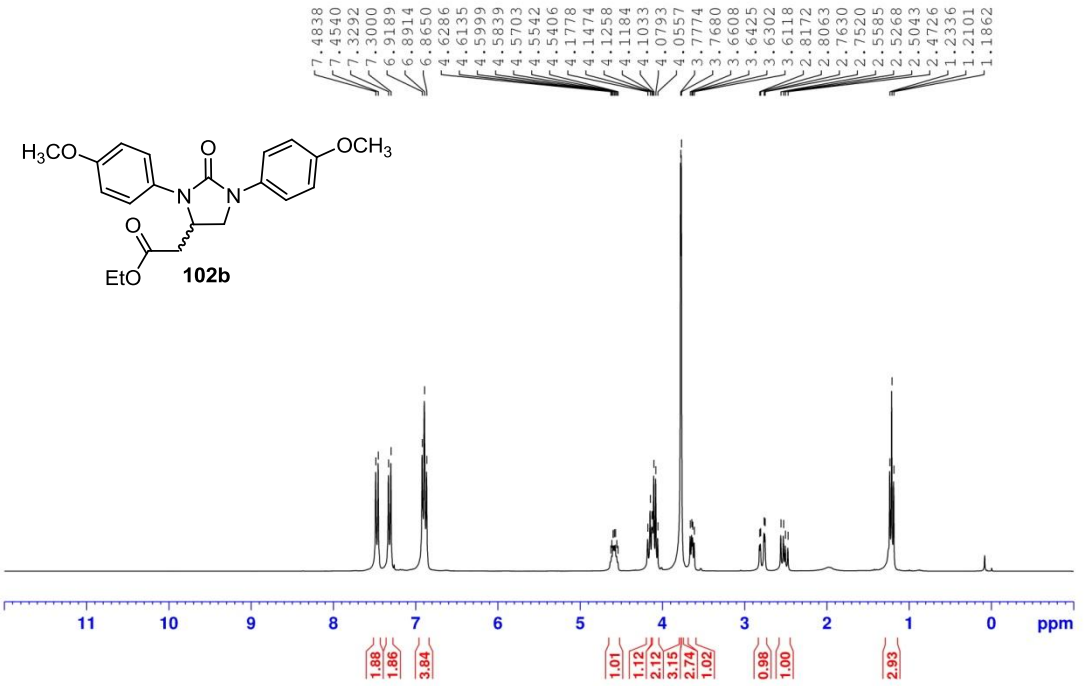


Figure 37 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **102b**.

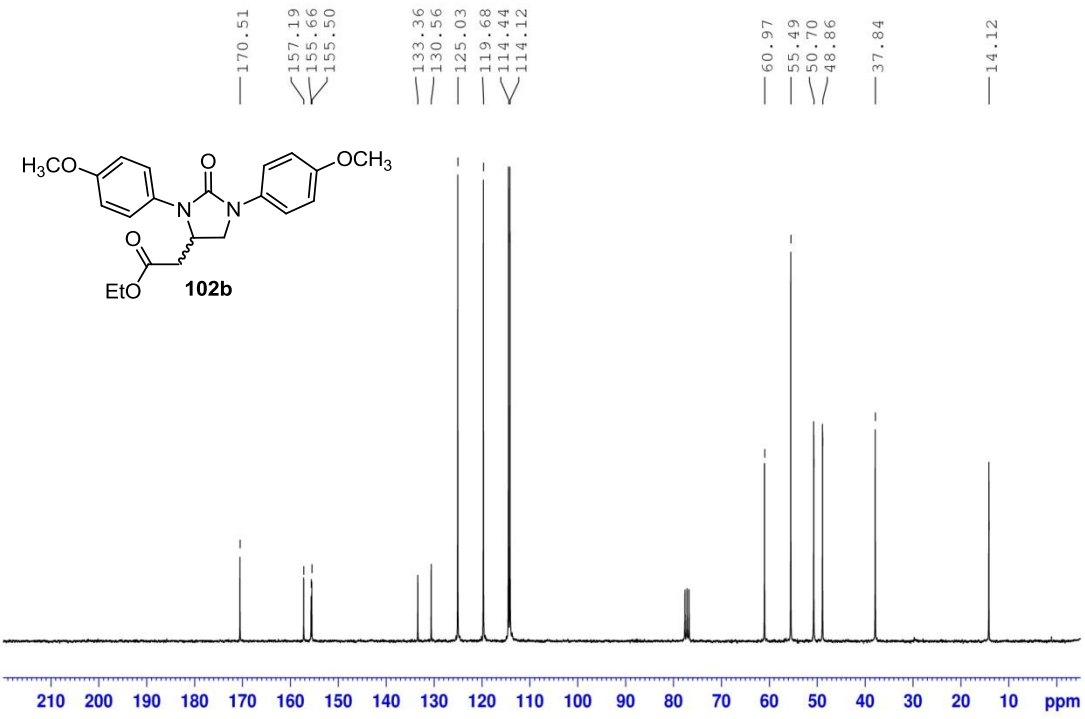


Figure 38 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **102c**.

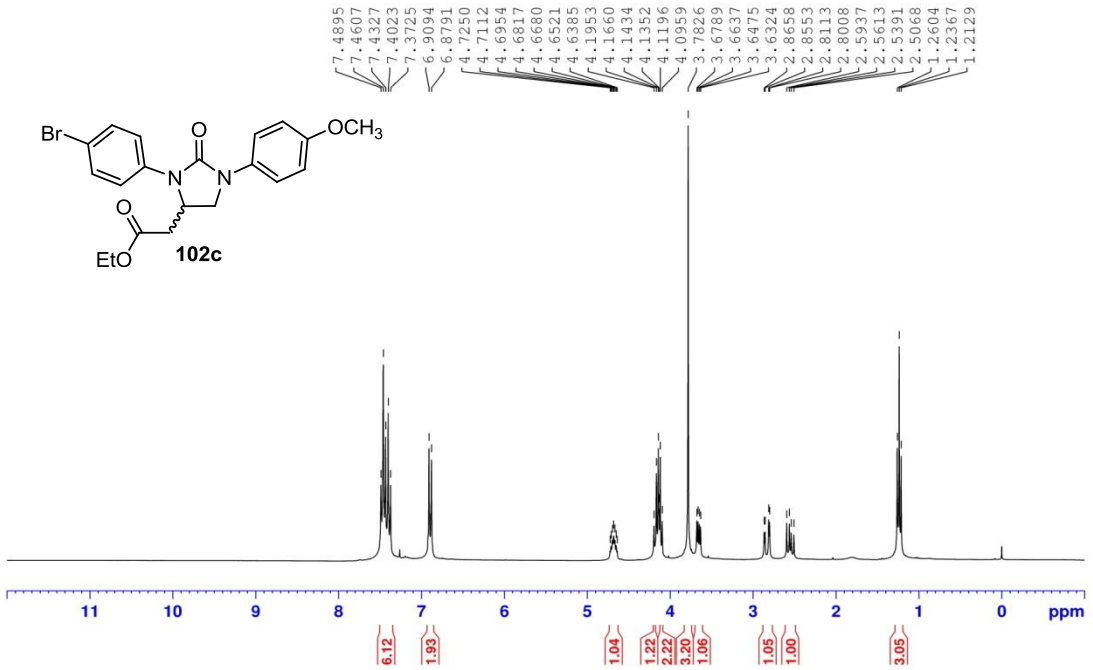


Figure 39 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **102c**.

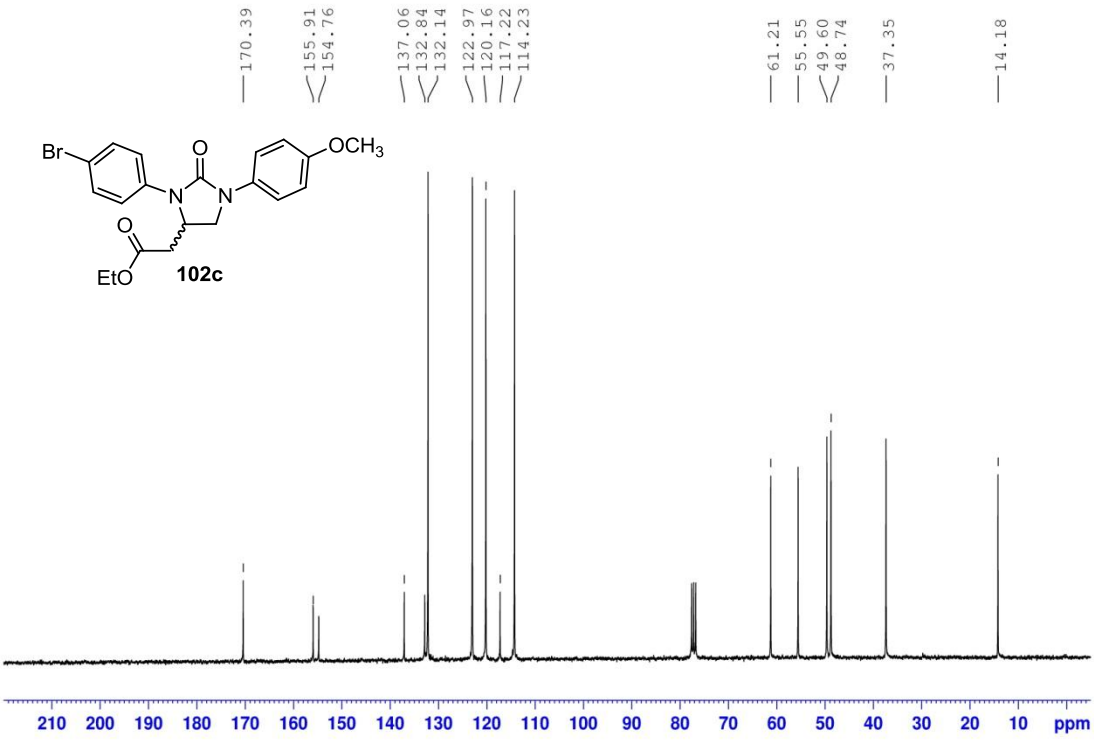


Figure 40 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **102d**.

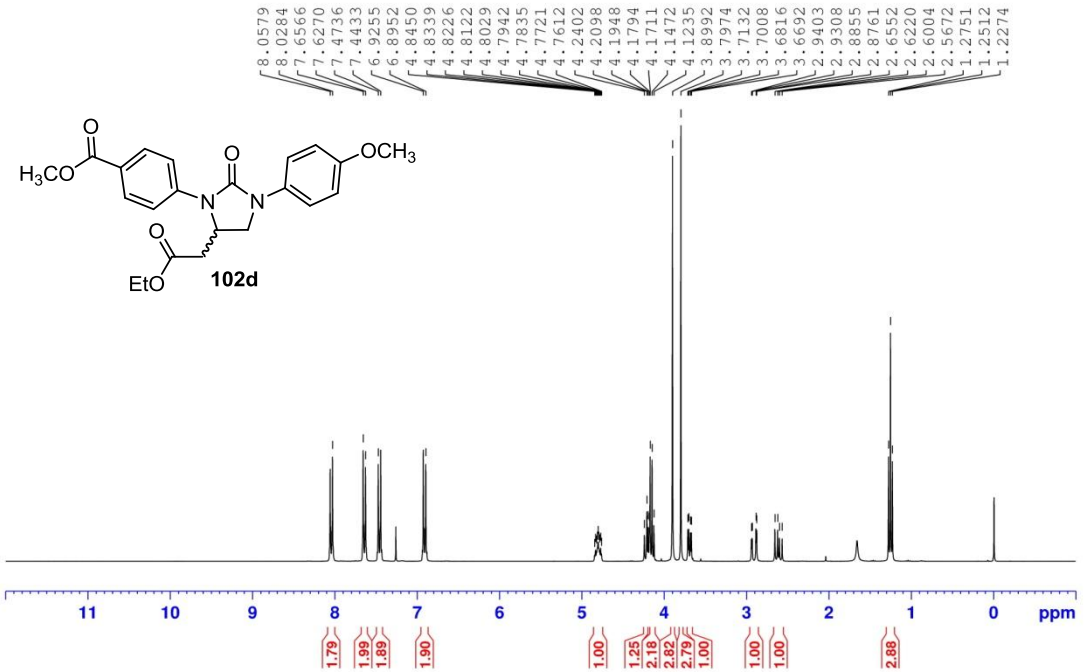


Figure 41 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **102d**.

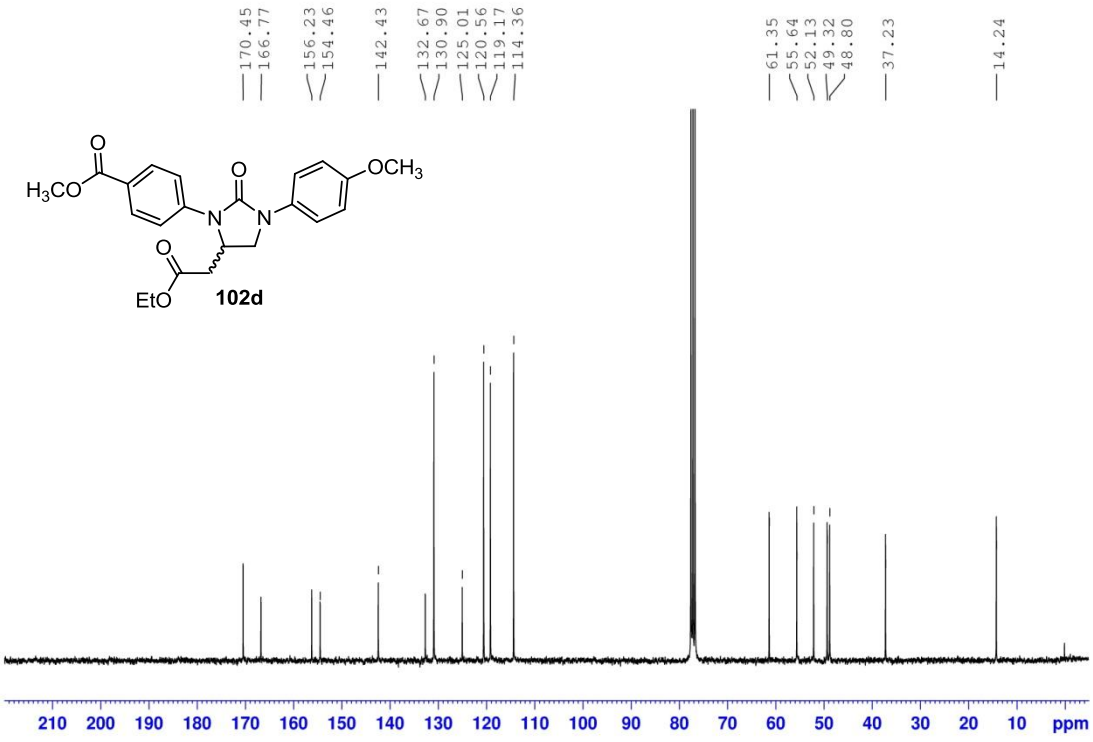


Figure 42 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **102e**.

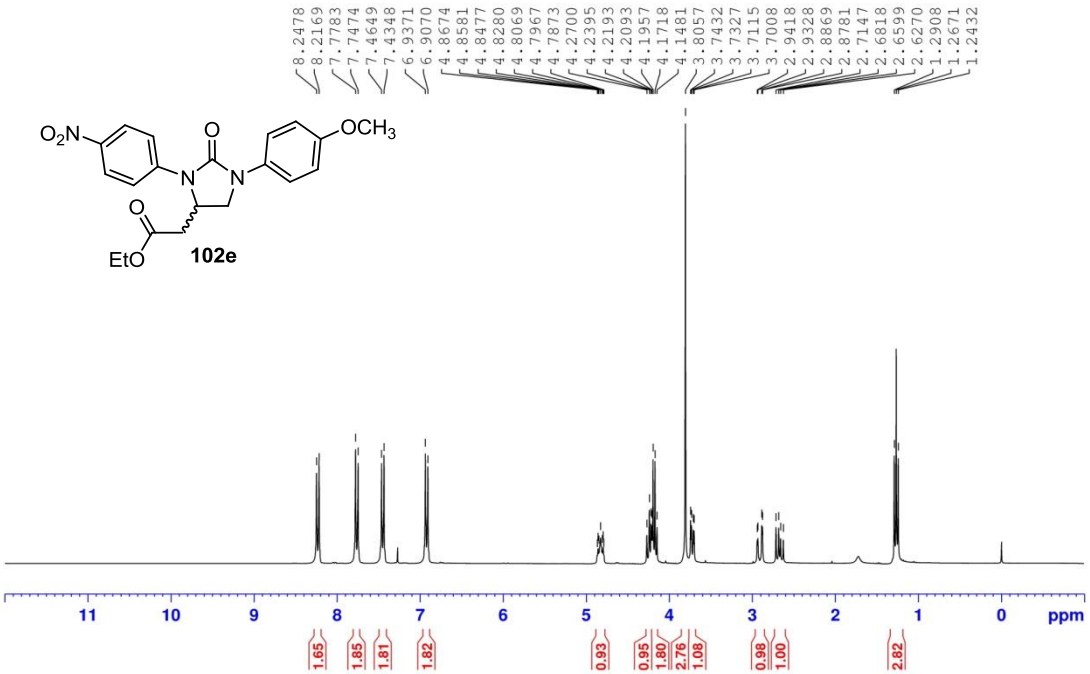


Figure 43 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **102e**.

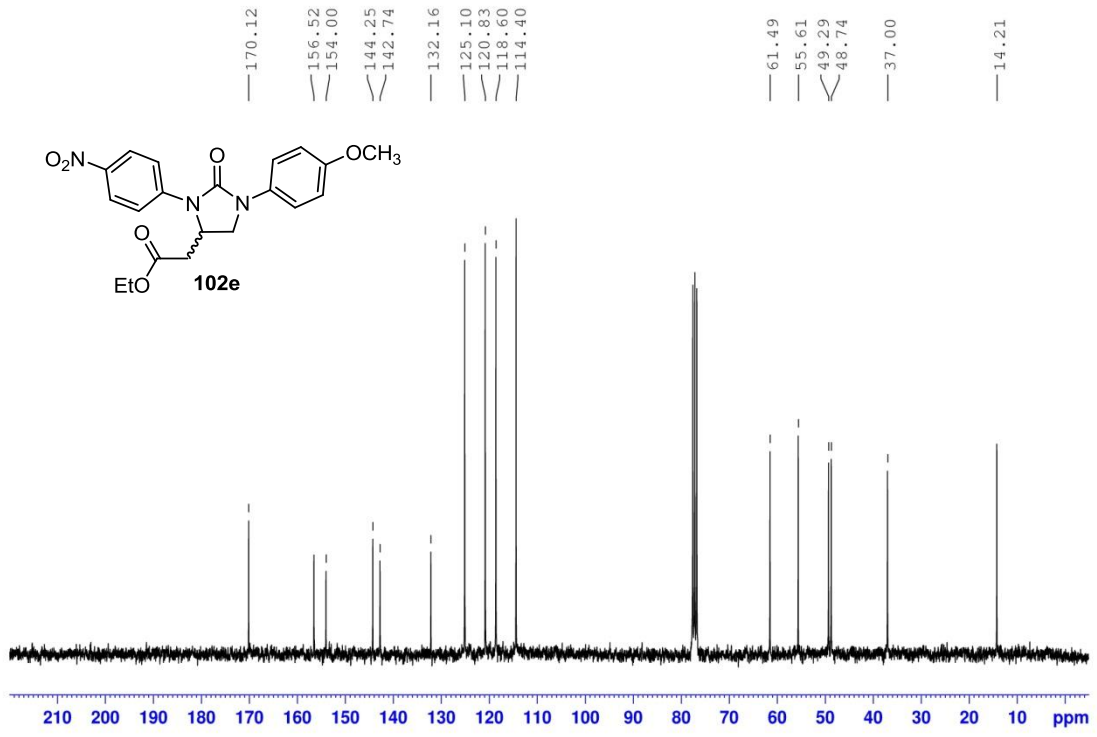


Figure 44 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **102f**.

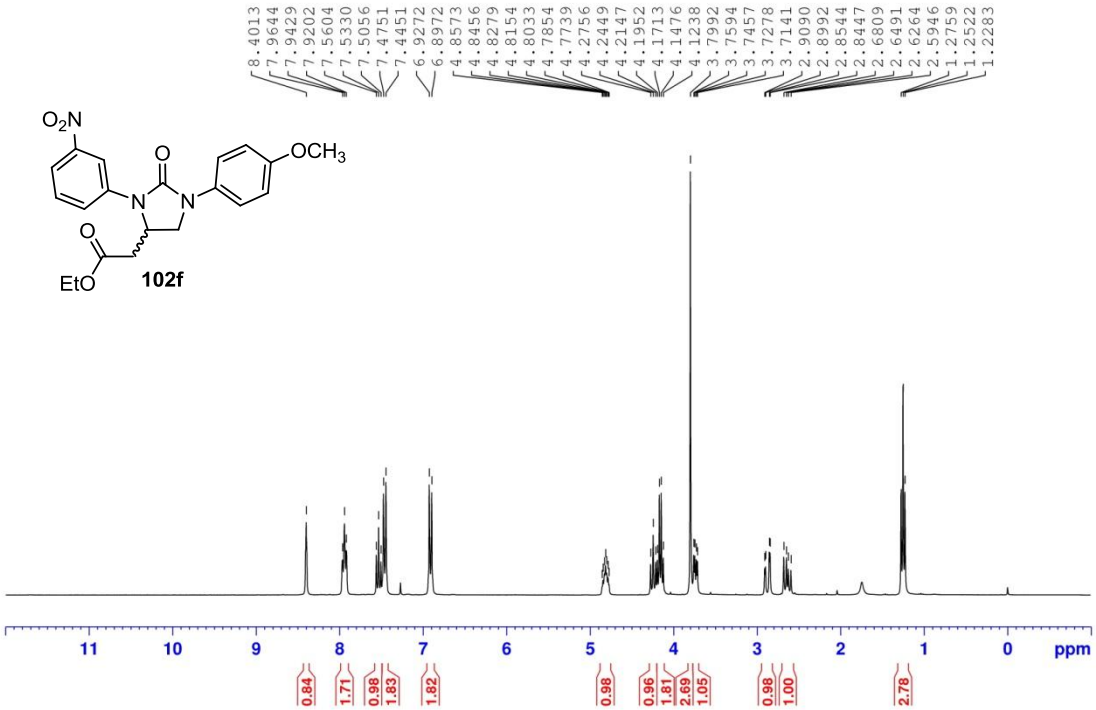


Figure 45 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **102f**.

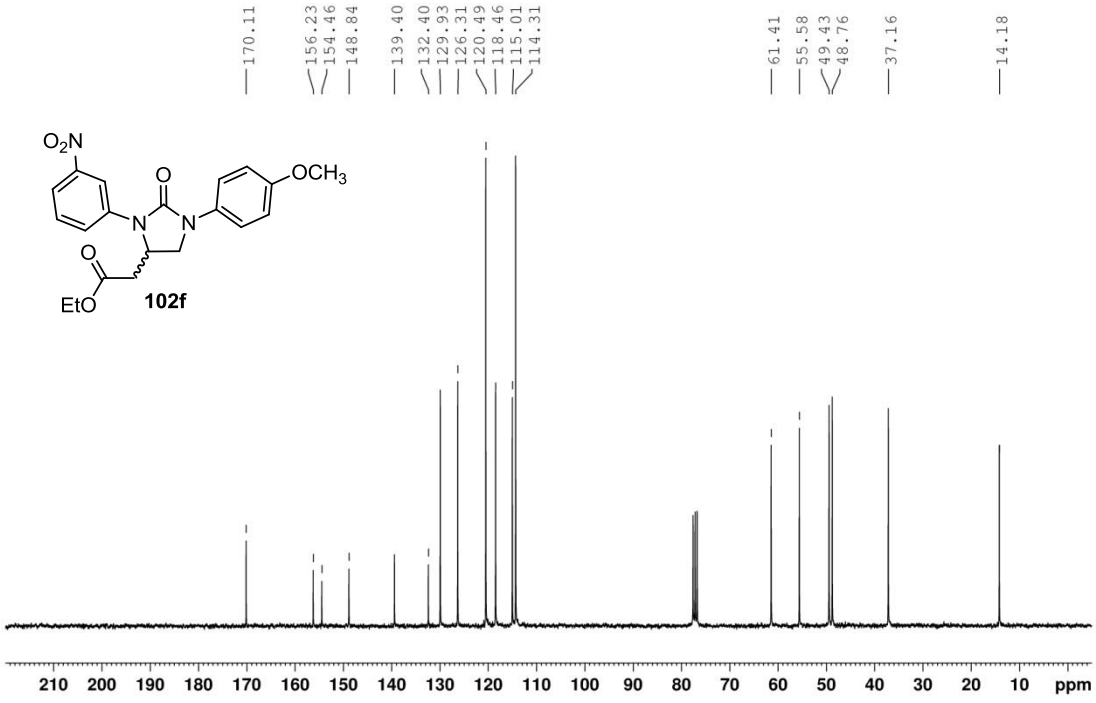


Figure 46 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **102g**.

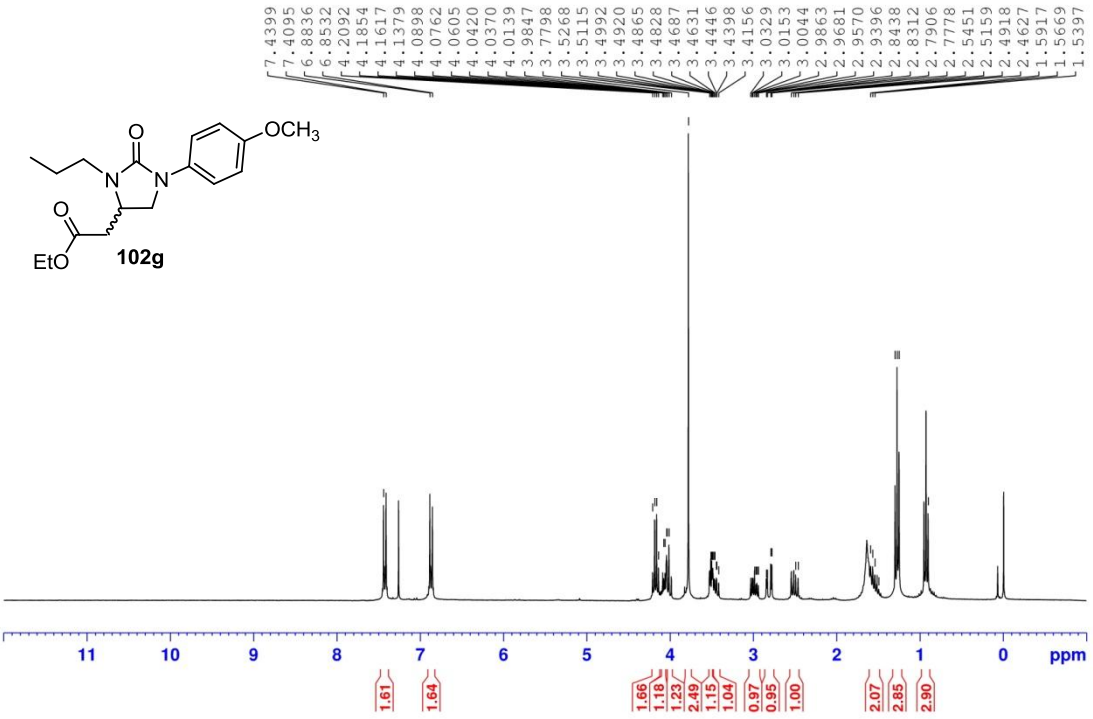


Figure 47 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **102g**.

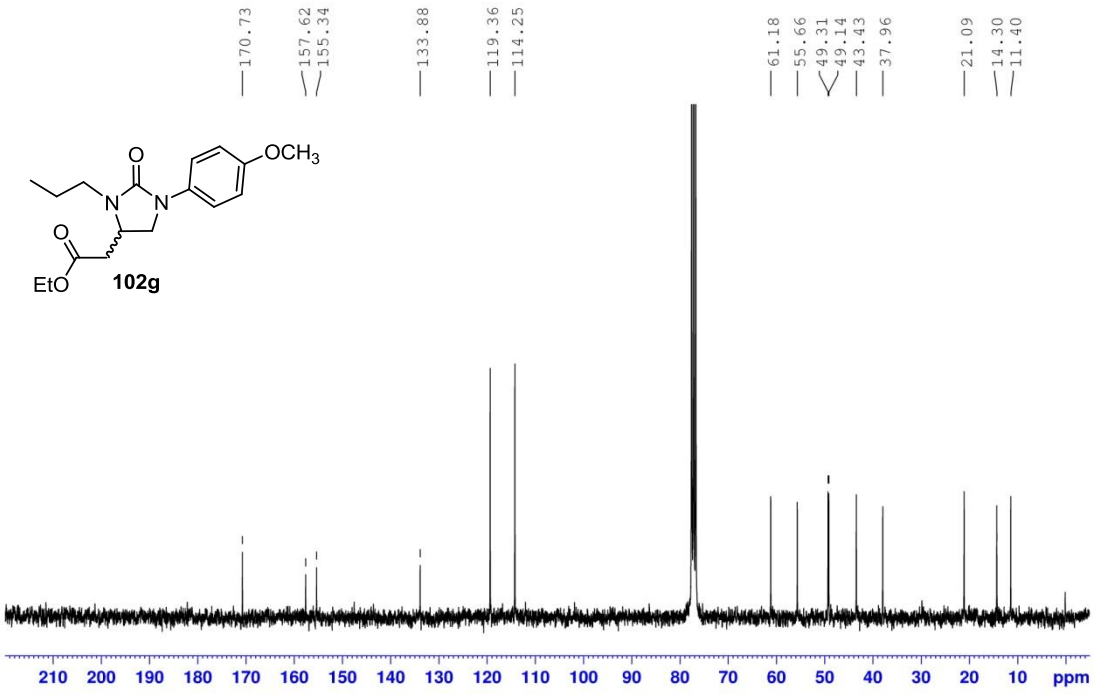


Figure 48 The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **104**.

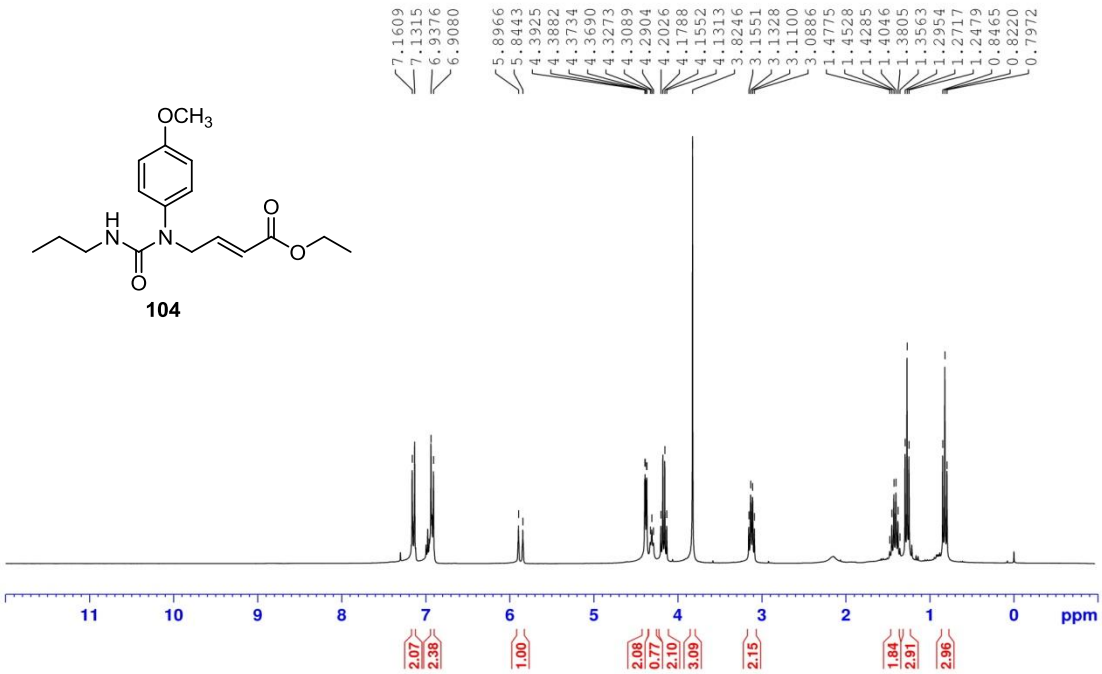
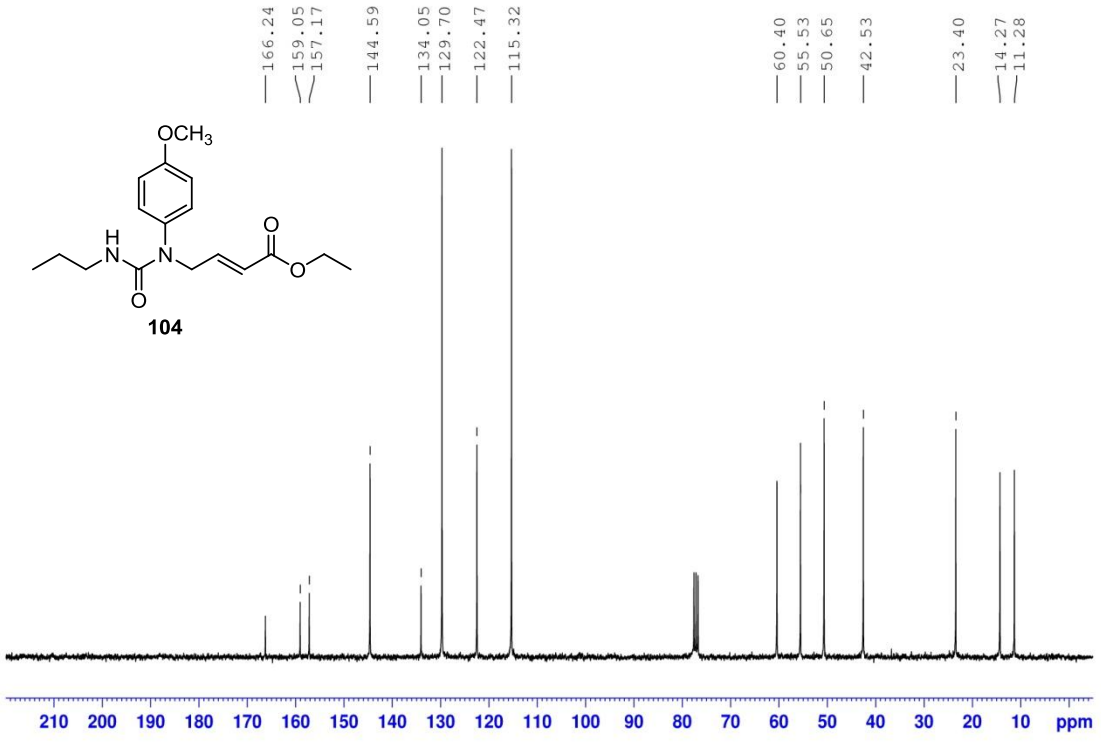


Figure 49 The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **104**.



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List of Publications

Duangjan, C.; Rukachaisirikul, V.; Saithong. S.; Kaeobamrung, J. 2018, Copper-catalyzed domino reaction of carbodiimides and benzoic acid derivatives for the synthesis of quinazolinediones.Tetrahedron Lett. 59, 3537−3540.