# Cu(I)-Catalyzed Synthesis of Quinazolinone Derivatives

Teerawat Songsichan



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

Master of Science in Organic Chemistry

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| **Thesis Title** | Cu(I)-Catalyzed Synthesis of Quinazolinone Derivatives |
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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.

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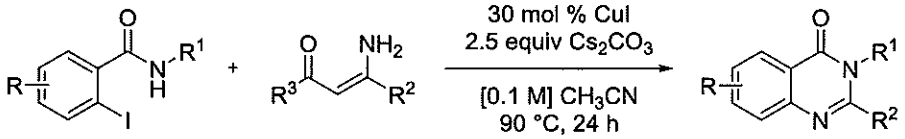
| **ชื่อวิทยานิพนธ์** | การสังเคราะห์อนุพันธ์ควินาโซลิโนนโดยใช้คอปเปอร์(I) เป็นตัวเร่งปฏิกิริยา |
| **ผู้เขียน** | นายธีรวัฒน์ สงสีจันทร์ |
| **สาขาวิชา** | เคมีอินทรีย์ |
| **ปีการศึกษา** | 2557 |

## บทคัดย่อ




ควินาโซลิโนนเป็นโครงสร้างหลักของสารผลิตภัณฑ์ธรรมชาติ ที่แสดงฤทธิ์ทางชีวภาพหลากหลาย อนุพันธ์ควินาโซลิโนนถูกสังเคราะห์ได้ 20—78% โดยวิธีการใหม่ที่ง่ายและไม่รุนแรง โดยมีคอปเปอร์(I) เป็นตัวเร่งปฏิกิริยา และใช้ 2-iodobenzamides และ *Z*-enaminones เป็นสารตั้งต้น และไม่ใช้ลิแกนด์อื่น ความเกะกะของสารตั้งต้นทั้งสองและความเป็นนิวคลีโอไฟล์ของอะตอมไนโตรเจนของสาร 2-iodobenzamides มีผลต่อปฏิกิริยา ปฏิกิริยาเกิดผ่าน Ullmann-type coupling reaction, intramolecular Michael addition และ retro-Mannich reaction ตามลำดับ โดยการตรวจพบสารตัวกลาง *N*-arylation จากปฏิกิริยาระหว่าง *N*-benzyl 2-iodobenzamide กับ *E*-enaminone สนับสนุนลำดับการเกิดปฏิกิริยา จากการนำสารผลิตภัณฑ์ทั้งหมดที่สังเคราะห์ได้ไปทดสอบฤทธิ์ยับยั้งเชื้อจุลินทรีย์ เชื้อวัณโรคและเชื้อมาลาเรีย ตลอดจนความเป็นพิษต่อเซลล์มะเร็ง พบว่าบางสารแสดงฤทธิ์ยับยั้งเชื้อราและเชื้อวัณโรค นอกจากนี้ยังแสดงความป็นพิษต่อเซลล์มะเร็งช่องปากและเซลล์มะเร็งเต้านม

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| **Major Program** | Organic Chemistry |
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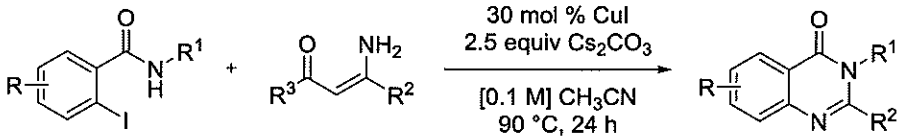
# ABSTRACT


Quinazolinone is a key core structure of natural products which show a wide range of biological activities. A variety of quinazolinone derivatives were synthesized in 20–78% yields by the new, simple and mild Cu(I)-catalyzed domino reaction using 2-iodobenzamides and *Z*-enaminones as the starting materials without the assistance of external ligand. The steric hindrance of both substrates and the nucleophilicities of nitrogen atom of 2-iodobenzamides affected the reaction. The domino reactions underwent sequential Ullmann-type coupling reaction, intramolecular Michael addition, and retro-Mannich reaction. The detection of stable *N*-arylation intermediate from the reaction of *N*-benzyl 2-iodobenzamide with *E*-enaminone supported the sequence of domino process. All synthesized products were evaluated for their antimicrobial, antimycobacterial, antimalarial and cytotoxic activities. Some of them displayed antifungal, antimycobacterial and cytotoxic (against KB and MCF-7) activities.

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I wish to express my deepest gratitude and sincere appreciation to my advisor, Dr. Juthanat Kaeobamrung, for his valuable instruction, expert guidance and excellent suggestion. I would also like to express my appreciation to him for correction of my thesis. I would also like to thank Prof. Dr. Vatcharin Rukachaisirikul, co-advisor, for her helpful suggestion and partial support.

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Finally, I thank the members of laboratory, my family and friends for their love and encouragement. I also thank them all for their kindness and valuable advice. Everything will be always kept in my mind.

Teerawat Songsichan

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# LIST OF ABBREVIATIONS AND SYMBOLS

## General

| | | |
|---|---|---|
| ν | = | absorption frequencies |
| Å | = | angstrom ($10^{-10}$ meters) |
| aq | = | aqueous |
| atm | = | atmosphere |
| br | = | broad |
| calcd. | = | calculated |
| cat. | = | catalyst |
| δ | = | chemical shift relative to TMS |
| *J* | = | coupling constant |
| °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 ABBREVIATIONS AND SYMBOLS (Continued)

| | | |
|---|---|---|
| m | = | multiplet |
| NMR | = | nuclear magnetic resonance |
| Nu | = | nucleophile |
| *p-* | = | *para-* |
| ppm | = | part per million |
| H | = | proton |
| psi | = | pound per square inch |
| $cm^{-1}$ | = | reciprocal centimeter (wavenumber) |
| rt | = | room temperature |
| sat. | = | saturated |
| s | = | singlet |
| Temp | = | temperature |
| *t-* | = | *tert-* |
| TLC | = | thin-layer chromatography |
| t | = | triplet |
| td | = | triplet of doublets |
| UV | = | ultraviolet |

## Chemical

| | | |
|---|---|---|
| Ac | = | acetyl |
| AcOH | = | acetic acid |
| Ar | = | aryl |
| Bn | = | benzyl |
| cata*C*Xium®A | = | di(1-adamantyl)-*n*-butylphosphine ($BuPAd_2$) |
| $CDCl_3$ | = | deuterochloroform |
| dba | = | dibenzalacetone |
| DBU | = | 1,8-Diazabicyclo[5.4.0]undec-7-ene |

# LIST OF ABBREVIATIONS AND SYMBOLS (Continued)

| | | |
|---|---|---|
| DIPEA | = | *N*,*N*-diisopropylethylamine |
| DMF | = | *N*,*N*-dimethylformamide |
| DMSO | = | dimethyl sulfoxide |
| DMSO-$d_6$ | = | deuterated dimethyl sulfoxide |
| dppf | = | 1,1′-bis(diphenylphosphino)ferrocene |
| DPPP | = | 1,3-bis(diphenylphosphino)propane |
| Et | = | ethyl |
| EtOH | = | ethanol |
| EtOAc | = | ethyl acetate |
| HBTU | = | *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl) uronium hexafluorophosphate |
| HMDS | = | hexamethyldisilazane or bis(trimethylsilyl)amine |
| MeOH | = | methanol |
| NMP | = | *N*-methyl-2-pyrrolidone |
| Pd | = | palladium |
| Ph | = | phenyl |
| $PhCH_3$ | = | toluene |
| $PPh_3$ | = | triphenylphosphine |
| TBHP | = | *tert*-butyl hydroperoxide |
| THF | = | tetrahydrofuran |
| TMS | = | tetramethylsilane |
| TPPMS | = | sodium (diphenylphosphino)benzene-3-sulfonate |
| UHP | = | urea hydroperoxide |

# LIST OF PUBLICATION

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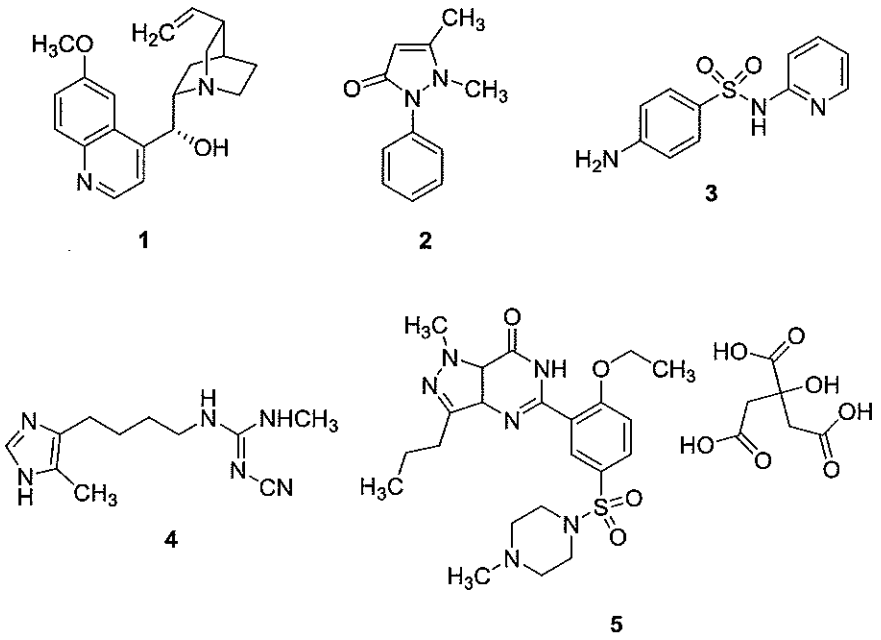
# CHAPTER 1

# INTRODUCTION

## 1.1 Introduction

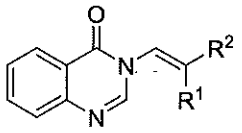
Heterocyclic compounds are cyclic molecules containing at least one heteroatom (nitrogen, oxygen, sulfur, etc.) in a ring. Heterocyclic compounds are important due to their common occurrences in natural products and synthetic drugs which display significant biological activities. Examples of them are shown in **Figure 1**. In the 16$^{th}$ century, quinine (**1**) was used as the antimalarial drug though the structure was not known at that time. Antipyrine (**2**), fever reducing drug, was the first synthetic drug. In 1938, sulfapyridine (**3**) was known as the first effective antibiotic drug. In 1970s, Tagamet® (**4**), the first multi-million pound drug, was used as the anti-ulcer drug. Viagra® (**5**) has been used for treatment of male impotence since 1997 (Clayden *et al.*, 2001).

**Figure 1** Examples of heterocyclic drugs

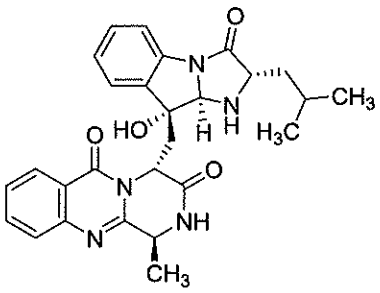


Quinazolin-4(3*H*)-one (quinazolinone) is one of the common core structures of fused N-containing heterocyclic compounds found in natural products, synthetic drugs and drug candidates. Quinazolinones exhibit a variety of biological activities. Based on structure search from SciFinder Scholar Database, there are more than 300,000 compounds of quinazolinone substructures and about 40,000 compounds of them were known to be biologically active (Li *et al.*, 2013). Examples of natural quinazolinones were shown in **Figure 2**. (*E*)- and (*Z*)-bogorins (**6-7**) from *Glycosmis cf. chlorosperma*, as well as (–)-fumiquinazolines I and H (**8-9**) from *Acremonium* sp. displayed antifungal activity. Isaindigotone (**10**) from *Isatis indigotica* and *Isatis tinctoria* exhibited antioxidant activity. In addition, luotonins A and B (**11-12**) from the aerial parts of *Peganum nigellastrum*, 1-methoxy-7,8-dehydrorutaecarpine (**13**) from *Zanthoxylum integrifolium*, and fumiquinazolines A-G (**14-20**) from *Aspergillus fumigatus* displayed cytotoxic activity toward many cancer cell lines. Besides, luotonin F (**21**) from *P. nigellastrum* demonstrated a potent antitumor activity. Moreover, 2-methoxyrutaecarpine (**22**) and 2-methoxy-13-methylrutaecarpine (**23**) from *Araliopsis tabouensis*, and febrifugine (**24**) from an Asian plant, *Dichroa febrifuga*, showed an antimalarial activity. 1-Methoxyrutaecarpine (**25**), another natural rutaecarpine isolated from *Zanthoxylum integrifolium*, was indicated as an anti-platelet aggregation agent. Tryptoquivaline analogs, 27-*epi*-tryptoquivaline (**26**) and 27-*epi*-nortryptoquivaline (**27**) from *Corynascus setous*, are the epimers of the previously known quinazolinone alkaloids which were isolated from *Aspergillus clavatus* and displayed tremorgenic activity. Vasicinone derivatives, quinazolinones fused with a pyrrole ring system, were isolated from *Adhatoda vasica*. Deoxyvasicinone (**28**) possessed antimicrobial, anti-inflammatory and antidepressant activities. On the other hand, (–)-vasicinone (**29**) showed antitumor, bronchodilating, hypotensive, anthelmintic and anti-anaphylactic activities (Mhaske *et al.*, 2006).

**Figure 2** Examples of natural quinazolinones



**6**: $R^1$ = H, $R^2$ = Ph
**7**: $R^1$ = Ph, $R^2$ = H



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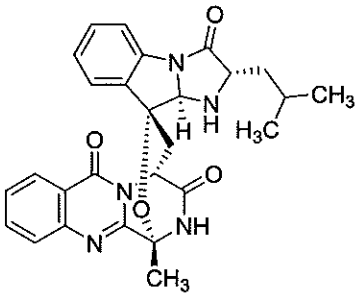

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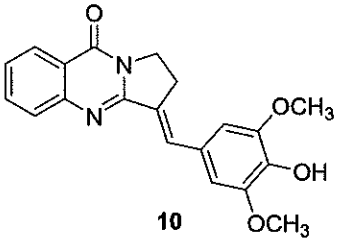

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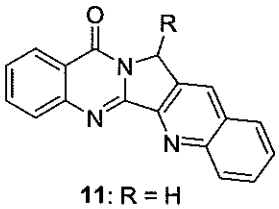
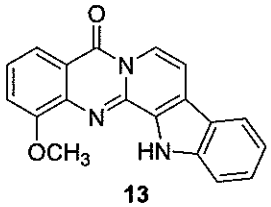


**11**: R = H
**12**: R = OH



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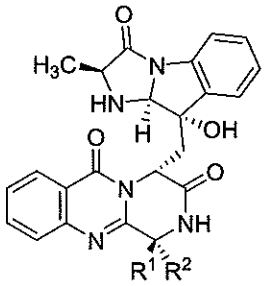
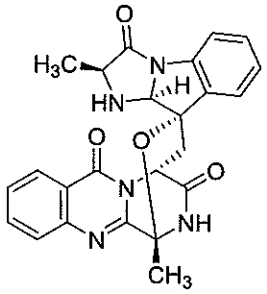


**14**: $R^1$ = $CH_3$, $R^2$ = H
**15**: $R^1$ = H, $R^2$ = $CH_3$
**18**: $R^1$ = $CH_3$, $R^2$ = $OCH_3$



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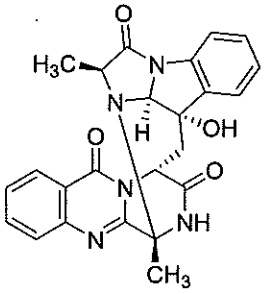

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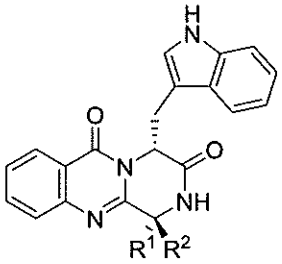
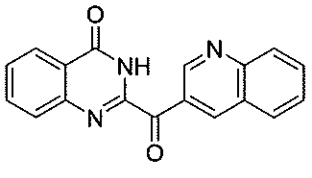


**19**: $R^1$ = H, $R^2$ = $CH_3$
**20**: $R^1$ = $CH_3$, $R^2$ = H



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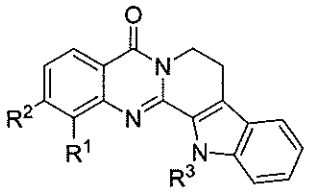
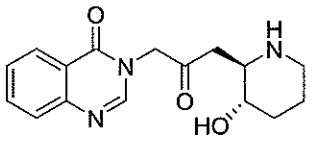
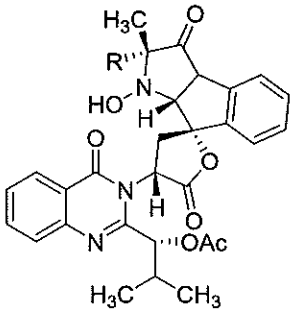


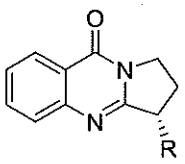
**22**: $R^1$ = H, $R^2$ = $OCH_3$, $R^3$ = H
**23**: $R^1$ = H, $R^2$ = $OCH_3$, $R^3$ = $CH_3$
**25**: $R^1$ = $OCH_3$, $R^2$ = H, $R^3$ = H



**24**



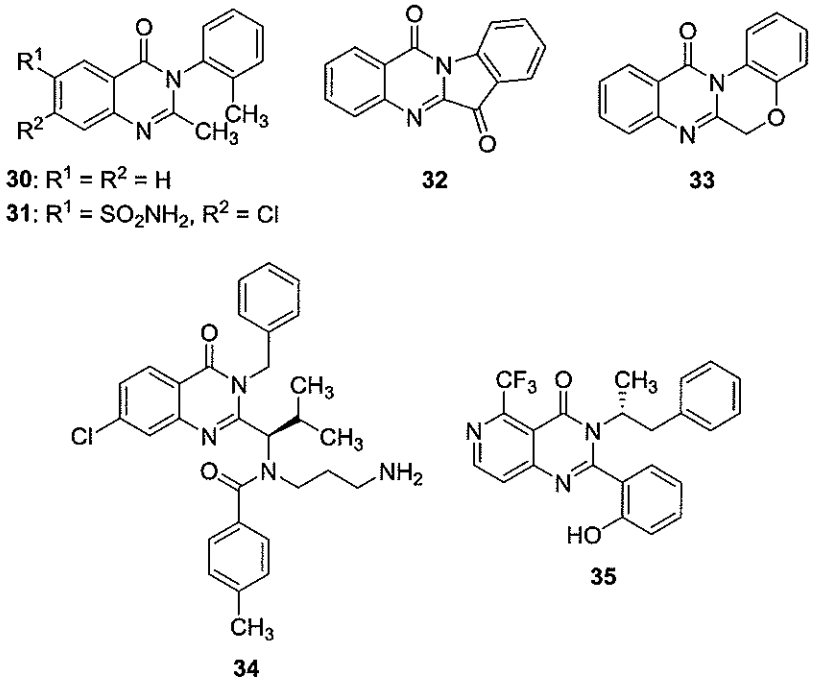
**26**: R = $CH_3$
**27**: R = H



**28**: R = H
**29**: R = OH

Furthermore, many synthetic quinazolinones are now known to have a wide range of biological and medicinal properties. Some of them were shown in **Figure 3**. Methaqualone (**30**), synthesized for the first time in 1951, is clinically used as sedative-hypnotic medication. Metolazone (**31**), developed in the 1970s, is a diuretic drug used for treatment of high blood pressure and fluid accumulation. Tryptanthrin (**32**) is used as an antibiotic drug. Quinazolino[2,3-*c*][1,4]benzoxazin-12(6*H*)-one (**33**) is an antifertility agent (Mhaske *et al.*, 2006). Ispinesib (**34**) is now in clinical trial as the potential anticancer agent (Holland *et al.*, 2013). (*R*)-2-(2-hydroxyphenyl)-3-(1-phenylpropan-2-yl)-5-(trifluoromethyl)pyrido[4,3-*d*]pyrimidin-4(3H)-one (**35**) is an orally active calcium-sensing receptor (CaR) targeted for treatment of osteoporosis (Li *et al.*, 2013).

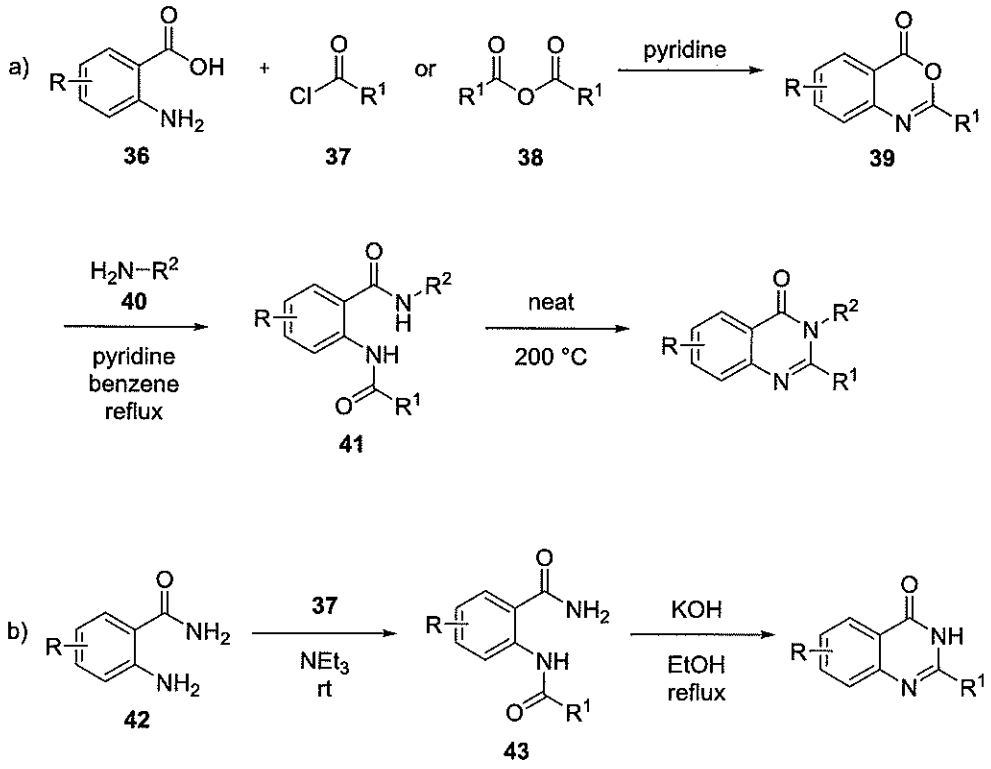
**Figure 3** Examples of synthetic quinazolinones




Because of their biological activities, a number of methodologies have been developed toward the quinazolinone synthesis. From the SciFinder Scholar Database, synthetic organic chemists have reported the synthesis of quinazolinones since 1869. Traditional procedures for preparation of quinazolinones were shown in **Scheme 1**. Condensation of benzoxazinones (**39**), the intermediates from cyclization of

substituted anthranilic acids (**36**) with acyl chlorides (**37**) or acid anhydrides (**38**), with several amines (**40**) under high temperature yielded quinazolinone derivatives (**Scheme 1a**) (Shcherbakova *et al.*, 2005). Moreover, quinazolinones were obtained from the dehydrative cyclization of diamide intermediates (**43**) which were prepared from the reactions of anthranilamides (**42**) and acyl chlorides (**37**) (**Scheme 1b**) (Mhaske *et al.*, 2004).

**Scheme 1** Traditional procedures for synthesis of quinazolinones




However, these traditional procedures generally suffer from multistep reactions, low overall yields, harsh reaction conditions, tedious workup and costly syntheses. Because of these problems, several groups have applied transition metal-catalyzed reactions to develop new methods for the quinazolinone synthesis including the use of palladium (Pd), iron (Fe) and copper (Cu) as catalysts.

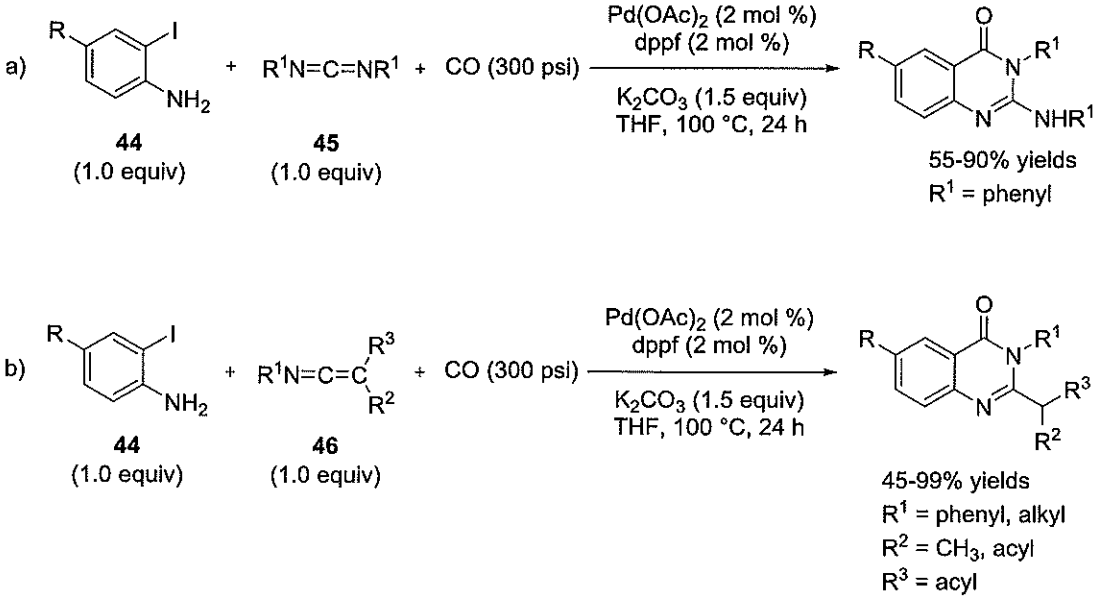
Since 2000, Alper research group has reported novel methods for the synthesis of quinazolinones by the palladium-catalyzed reactions. In 2000, Larksarp and Alper reported the palladium-catalyzed cyclocarbonylation reaction of 2-iodoanilines (**44**)

with carbodiimides (**45**) or ketenimines (**46**) and carbon monoxide (CO) for the synthesis of 2-aminoquinazolinones (**Scheme 2a**) and 2-alkylquinazolinones (**Scheme 2b**), respectively. They used $Pd(OAc)_2$ as a catalyst and 1,1′-bis(diphenylphosphino)-ferrocene (dppf) as a ligand. Products were obtained in moderate to excellent yields (45–99%) (Larksarp *et al.*, 2000).

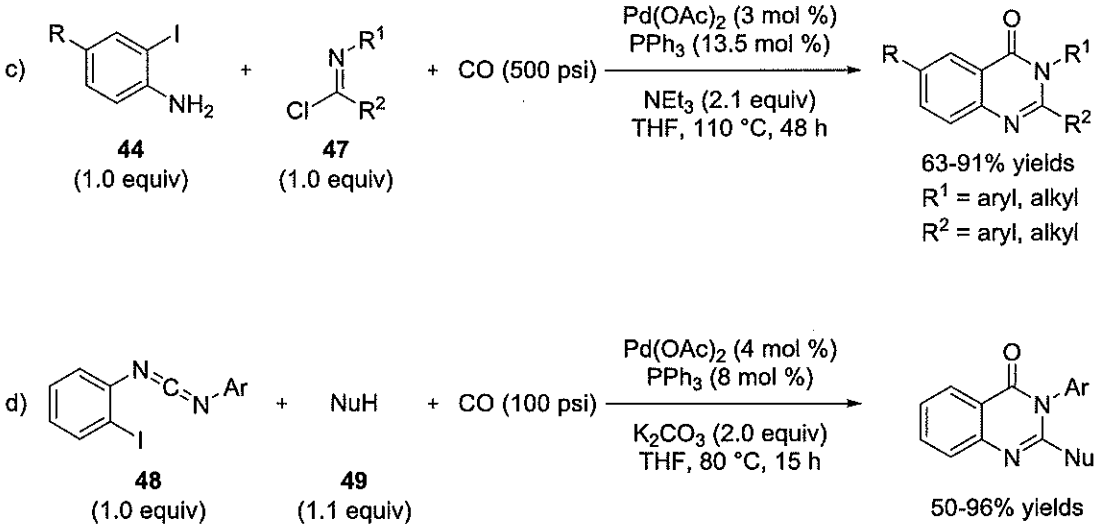
In 2008, Zheng and Alper could prepare 2,3-disubstituted quinazolinone derivatives in 63–91% yields by the palladium-catalyzed cyclocarbonylation reaction of 2-iodoanilines (**44**) with imidoyl chlorides (**47**) and gaseous CO. $Pd(OAc)_2$ was used as a catalyst and triphenylphosphine ($PPh_3$) was used as a ligand for this transformation (**Scheme 2c**) (Zheng *et al.*, 2008).

In addition, in 2010, Alper group also reported a new method for the synthesis of 2-heteroquinazolinones by a tandem palladium-catalyzed addition/cyclo-carbonylation of 2-iodoarylcarbodiimides (**48**) under mild conditions. A wide range of 2,3-disubstituted quinazolinones were obtained in good to excellent yields (50–96%) (**Scheme 2d**) (Zeng *et al.*, 2010).

**Scheme 2** The palladium-catalyzed reactions for the synthesis of quinazolinones reported by the Alper group

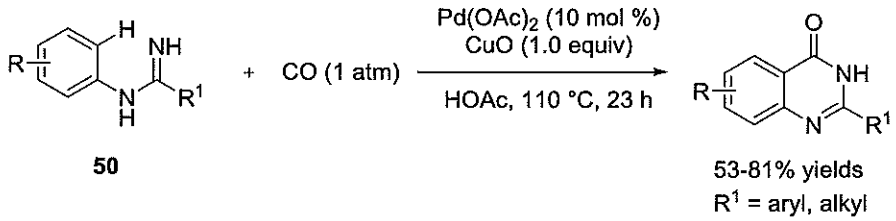


**Scheme 2** (continued)




Moreover, other groups also reported palladium-catalyzed reactions for the synthesis of quinazolinone derivatives. In 2011, the Zhu group reported an example of an intramolecular reaction for the quinazolinone synthesis. The reaction involved Pd(II)-catalyzed intramolecular C($sp^2$)–H carboxamidation of *N*-arylamidines (**50**) in the presence of $Pd(OAc)_2$ as a catalyst, copper(II) oxide (CuO) as an oxidant under CO atmosphere. The *N*-arylamidine starting materials (**50**) were readily derived from the condensation of anilines and nitriles. The 2-substituted quinazolinones were obtained in moderate to good yields (53–81%) (**Scheme 3**) (Ma *et al.*, 2011).

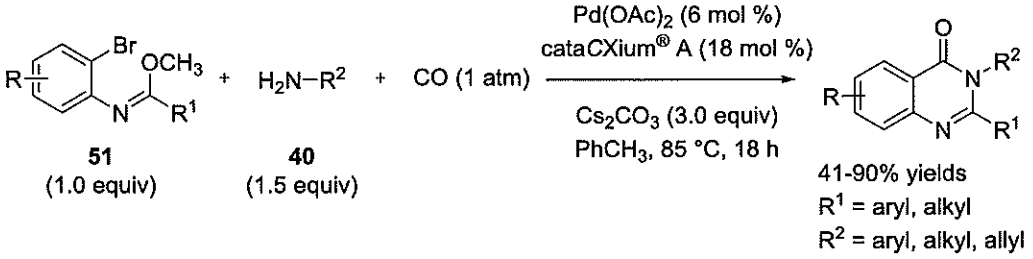
**Scheme 3** The palladium-catalyzed intramolecular C($sp^2$)–H carboxamidation of *N*-arylamidines (**50**)




In 2012, the Willis group reported the palladium-catalyzed synthesis of *N*-heterocycles. They showed that benzimidazoles and quinazolinones were prepared from the common precursor. The structural diversities of 2,3-disubstituted

quinazolinones were obtained in moderate to excellent yields by the palladium-catalyzed aminocarbonylation reaction of *N*-(2-bromophenyl)imidates (**51**) with a variety of *N*-nucleophiles (**40**) (**Scheme 4**) (Sadig *et al.*, 2012).

**Scheme 4** The palladium-catalyzed aminocarbonylation reaction of *N*-(2-bromophenyl)imidates (**51**) with *N*-nucleophiles (**40**)




**51** (1.0 equiv)

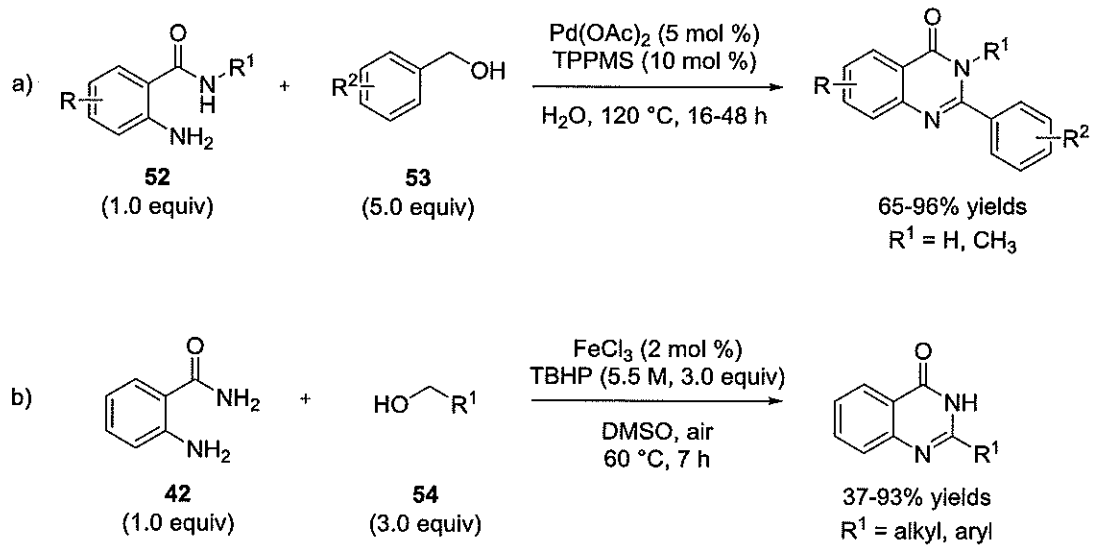
**40** (1.5 equiv)

41-90% yields
$R^1$ = aryl, alkyl
$R^2$ = aryl, alkyl, allyl

Hikawa, Yokoyama and co-workers introduced a novel method for the synthesis of 2-phenyl substituted quinazolinones by a Pd(II)-catalyzed benzylic C–H amidation of 2-aminobenzamides (**52**) with benzyl alcohols (**53**) in water. They used $Pd(OAc)_2$ as a catalyst, sodium (diphenylphosphino)benzene-3-sulfonate (TPPMS) as a ligand. This process required water as the solvent and it might play a role in the generation of active species of palladium by activation of the hydroxyl group of benzyl alcohols and in the last dehydrogenation step to accomplish the quinazolinone products (**Scheme 5a**) (Hikawa *et al.*, 2012).

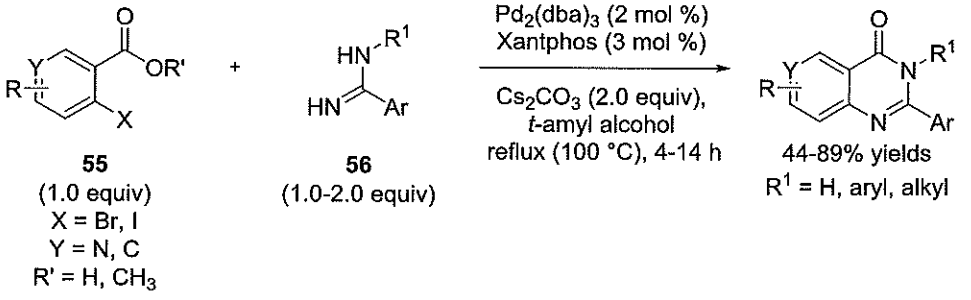
Additionally, Jian-Xin Li group developed the synthesis of *N*-heterocycles *via* an iron-catalyzed oxidative reaction from not only benzyl alcohols but also other primary alcohols. N-containing heterocycles including quinazolinone, quinazoline and 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide derivatives, were prepared under similar conditions. 2-Substituted quinazolinones were isolated in low to excellent yields (37–93%). The inexpensive and nontoxic $FeCl_3$ was used for the oxidation of primary alcohols (**54**) to the corresponding aldehydes which were condensed with 2-aminobenzamide (**42**) yielding 2-substituted quinazolinones *via* further oxidation (**Scheme 5b**) (Zhao *et al.*, 2014).

**Scheme 5** a) The Pd(II)-catalyzed benzylic C–H amidation of 2-aminobenzamides (**52**) with benzyl alcohols (**53**) in water; b) The iron-catalyzed oxidative synthesis of quinazolinones from primary alcohols (**54**)



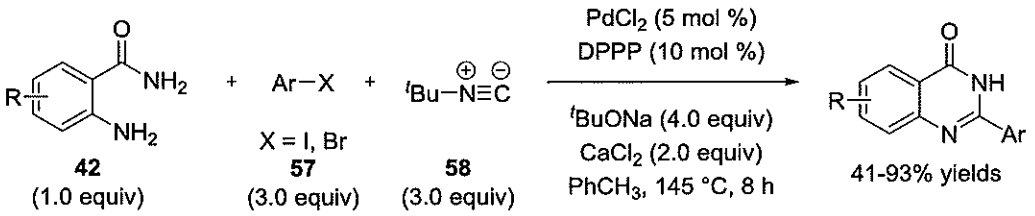

Recently, in 2013, Li and co-workers demonstrated an alternative route for the synthesis of 2,3-disubstituted quinazolinone derivatives by palladium-catalyzed *N*-arylation of 2-bromo or 2-iodobenzoate esters (**55**) with amidines (**56**). The quinazolinone products were obtained in 44-89% yields by reacting both substrates catalyzed with $Pd_2(dba)_3$ and Xantphos (**Scheme 6**). In addition, they could prepare pyrido[4,3-*d*]pyrimidin-4-(3*H*)-one (**35**) from the reaction of 2-trifluoromethyl-4-iodo-nicotinic acid and (*R*)-2-methoxy-*N*-(1-phenylpropan-2-yl)benzimidamide, followed by cyclization (amidation) with *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) and subsequent demethylation using $PhBCl_2$ (Li *et al.*, 2013).

**Scheme 6** The Pd(II)-catalyzed *N*-arylation of 2-halobenzoate (**55**) with amidines (**56**)



In 2014, Zhu, Ji and co-workers demonstrated a new palladium-catalyzed three-component reaction for the synthesis of quinazolinones from anthranilamides (**42**) and aryl halides (**57**) with isocyanide insertion in one-pot fashion. This method constructed 2-substituted quinazolinones in moderate to excellent yields (41–93%). The reactions were performed in the presence of $PdCl_2$ as a catalyst, 1,3-bis(diphenylphosphino)propane (DPPP) as a ligand and $CaCl_2$ as a drying agent. *tert*-Butyl isocyanide (**58**) was used as a versatile C1 building block in palladium-catalyzed insertion into carbon–halogen bonds, avoiding the use of toxic CO under high pressure conditions (**Scheme 7**) (Jiang *et al.*, 2014).

**Scheme 7** The palladium-catalyzed three-component reaction for the synthesis of quinazolinone derivatives reported by the Zhu group




Moreover, the group of Wu has recently published methodologies for the synthesis of quinazolinones by the palladium-catalyzed reactions. In 2013, various 2-aryl quinazolinones were prepared in moderate to excellent yields by the palladium-catalyzed carbonylative reactions of readily available 2-aminobenzamides (**59**) and aryl bromides (**57**, X = Br). $Pd(OAc)_2$ was used as a catalyst and di(1-adamantyl)-*n*-butylphosphine ($BuPAd_2$ or cata*C*Xium® A) was used as a ligand. The use of 10 bar of CO was required in the reaction conditions (**Scheme 8a**) (Wu *et al.*, 2013).

An alternative route was achieved in 2014, interestingly, $Mo(CO)_6$ (**62**) was used as a CO source instead of directly using gaseous CO. The 3-substituted quinazolinones were obtained in moderate to excellent yields from 2-bromoformanilides (**60**) and organo nitros (**61**) *via* a palladium-catalyzed carbonylative reaction. Various aromatic and aliphatic nitro derivatives were suitable substrates for this transformation. In this system, $Mo(CO)_6$ played not only the role of

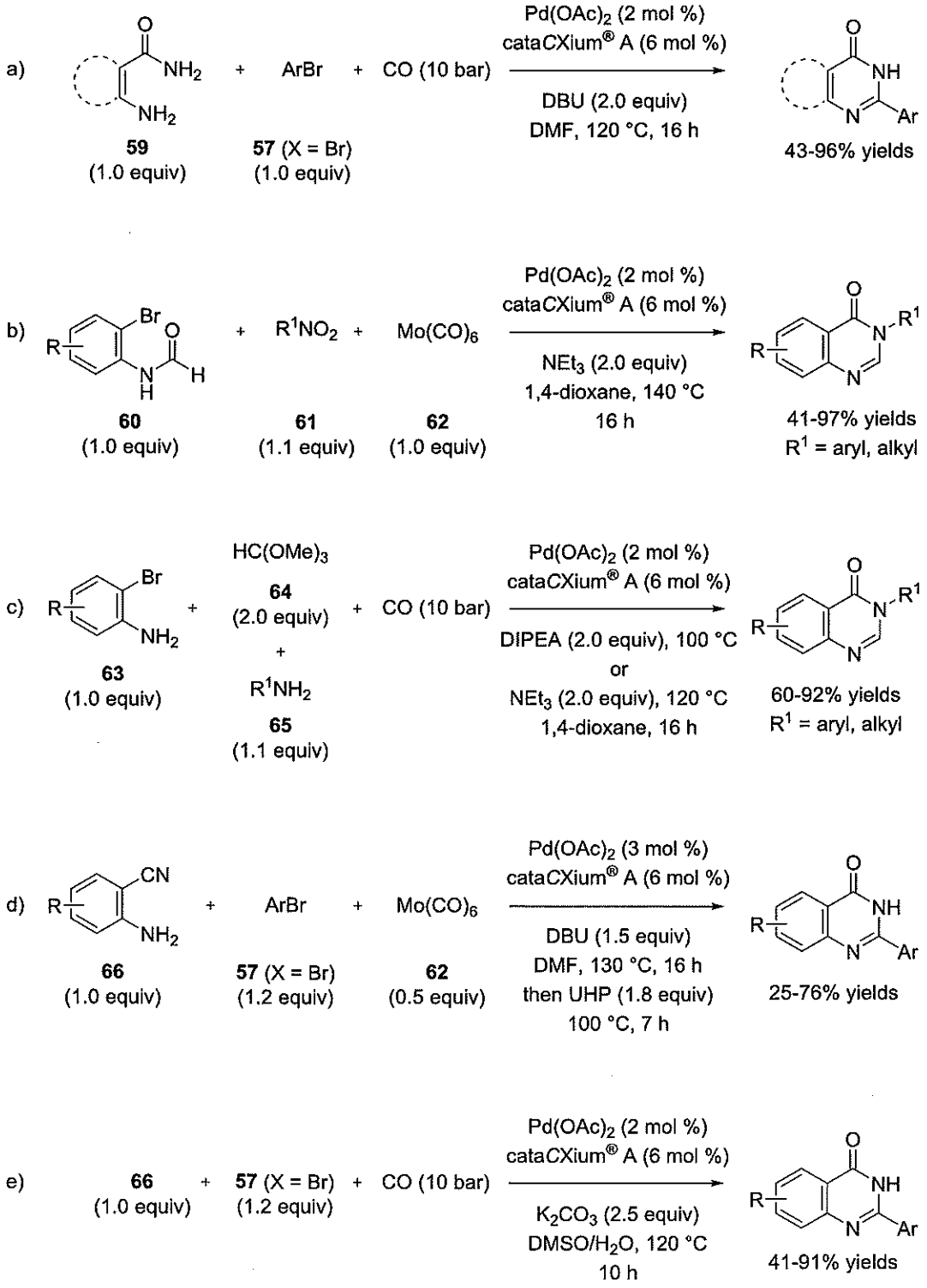
CO source but also as a reducing agent of nitro compounds and cyclization promoter (**Scheme 8b**) (He *et al.*, 2014a).

Another route for preparation of 3-substituted quinazolinones *via* multicomponent reaction including 2-bromoanilines (**63**), trimethyl orthoformate (**64**), amines (**65**) and CO(g) was reported. The reactions were performed in the presence of $Pd(OAc)_2$ and cata*C*Xium® A, using *N*,*N*-diisopropylethylamine (DIPEA) as a base for reactions of anilines or $NEt_3$ for reactions of alkyl amines (**Scheme 8c**) (He *et al.*, 2014b).

A procedure for the palladium-catalyzed carbonylative synthesis of *N*-(2-cyanoaryl)benzamides from 2-aminobenzonitriles (**66**) and aryl bromides (**57**, X = Br) has been developed. Because the limitation of commercially available 2-aminobenzamides, the use of 2-aminobenzonitriles which could be applied as the substrates *via in situ* hydration of nitrile group was performed. In this procedure, $Mo(CO)_6$ was applied as a CO source and urea hydroperoxide (UHP) was used as an oxidizing agent of nitrile to amide. A wide range of *N*-(2-cyanoaryl)benzamides were obtained in low to excellent yields. The reaction was performed in the presence of $Pd(OAc)_2$ as a catalyst and cata*C*Xium® A as a ligand under the assistance of DBU as the base, which additionally played the part of a promoter to release CO from $Mo(CO)_6$. Subsequently, UHP mediated-cyclization yielded the corresponding quinazolinones in low to good yields (**Scheme 8d**) (Wu *et al.*, 2014).

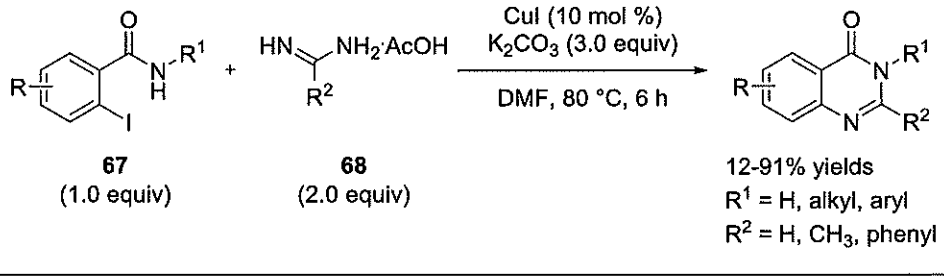
Later, the one-pot synthesis of quinazolinones from 2-aminobenzonitriles (**66**) and aryl bromides (**57**, X = Br) through a palladium-catalyzed carbonylation reaction has been developed, using 10 bar of CO(g) instead of $Mo(CO)_6$. In the presence of water and base ($K_2CO_3$), *N*-(2-cyanophenyl)benzamides, the intermediates, obtained from the palladium-catalyzed aminocarbonylation of aryl bromides, were hydrolyzed into the corresponding *N*-(2-carbamoylphenyl)benzamides which underwent intramolecular condensation to give quinazolinone products. Various 2-aryl quinazolinones were obtained in moderate to excellent yields (**Scheme 8e**) (Li *et al.*, 2014).

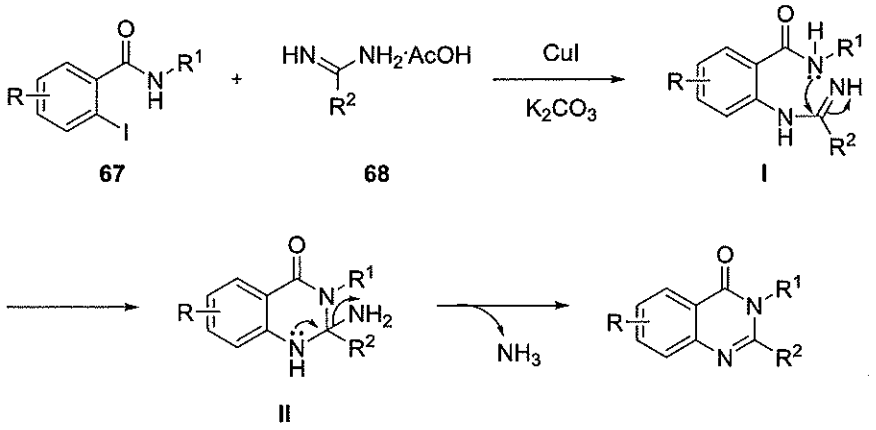
**Scheme 8** The palladium-catalyzed reactions for the synthesis of quinazolinones reported by Xiao-Feng Wu group



Furthermore, the copper-catalyzed Ullmann type coupling reaction has been a powerful strategy to construct quinazolinone derivatives. In 2008, Ding group discovered that the one-pot ligand-free CuI-catalyzed Ullmann *N*-arylation of 2-iodobenzamides (**67**) with amidine acetates (**68**) could afford 3-substituted and 2,3-disubstituted quinazolinone derivatives in 12–91% yields. The proposed mechanism of this reaction was outlined in **Scheme 9**. The CuI-catalyzed Ullmann type coupling reaction of 2-iodobenzamide with amidine acetate provides the intermediate **I**, followed by the condensative cyclization and the elimination of ammonia ($NH_3$) to yield the desired quinazolinone product (Zhou *et al.*, 2008).

**Scheme 9** The CuI-catalyzed Ullmann *N*-arylation of 2-iodobenzamides (**67**) with amidine acetates (**68**)

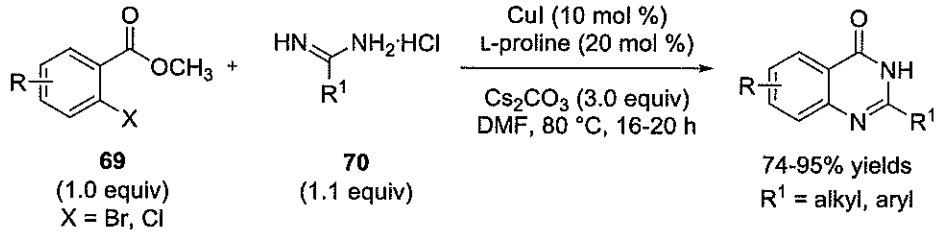


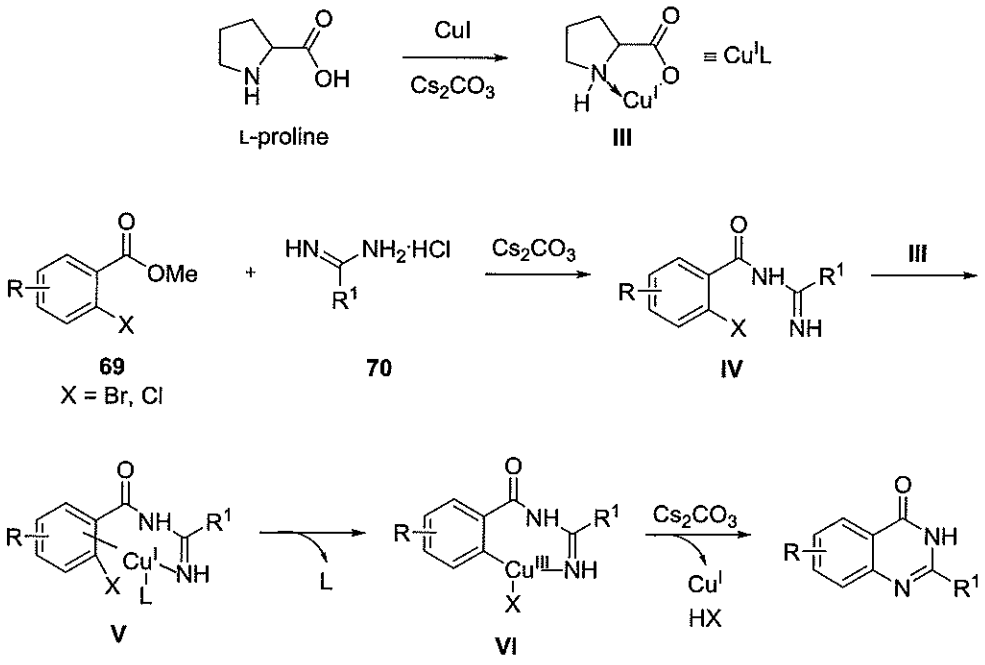




The Fu group was interested in the copper-catalyzed reaction for the synthesis of *N*-heterocycles including quinazolinone derivatives. In 2008, they developed a general and efficient copper-catalyzed reaction for the synthesis of quinazolinones. The target products were obtained in good to excellent yields by reactions of methyl 2-halobenzoates (**69**) with amidine hydrochlorides (**70**). CuI was used as a catalyst

and L-proline as a ligand. A plausible mechanism of the quinazolinone formation was proposed in **Scheme 10**. First, coordination of CuI and L-proline in the presence of $Cs_2CO_3$ forms **III**. In basic conditions, the substitution reaction of methyl 2-halobenzoate with amidine hydrochloride gives **IV**. The complexation of **III** and **IV** provides intermediate **V**, followed by oxidative addition to give intermediate **VI**, and subsequent reductive elimination of **VI** yields the target product (Huang *et al.*, 2008).

**Scheme 10** The copper-catalyzed *N*-arylation of methyl 2-halobenzoates (**69**) with amidine hydrochlorides (**70**)

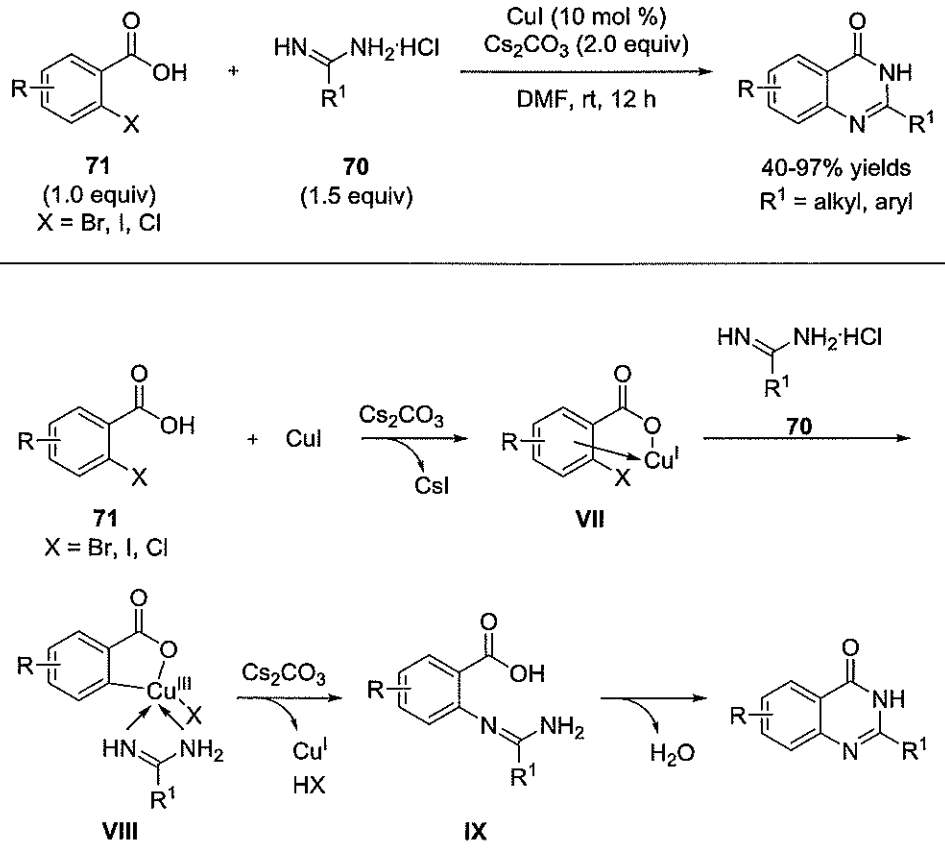



In 2009, the Fu group reported a simple, practical and efficient strategy for the synthesis of quinazolinones by the copper-catalyzed reaction without ligands or additives. Quinazolinone products were prepared in moderate to excellent yields by the coupling reactions of commercially available 2-halobenzoic acids (**71**) with

amidines (**70**) or guanidines at room temperature (**Scheme 11**). It was shown that the reactions proceeded well without the addition of a ligand or an additive at room temperature. Reactions of nonactive 2-chlorobenzoic acid or guanidines worked well when the reaction temperature was increased to 80 °C. The proposed mechanism starts from coordination of CuI and 2-halobenzoic acid to generate **VII** in the presence of $Cs_2CO_3$. Oxidative addition of **VII** and complexation of copper with amidine or guanidine gives **VIII**, which undergoes reductive elimination to provide *N*-arylation product **IX**. Condensation of the carboxyl and amino groups of **IX** affords the quinazolinone product and releases water molecule (Liu *et al.*, 2009).

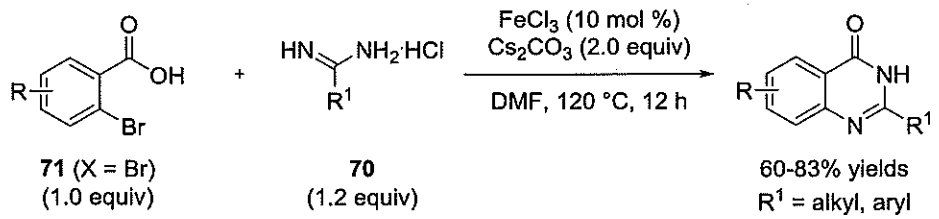
**Scheme 11** The CuI-catalyzed synthesis of quinazolinones from 2-halobenzoic acids (**71**) with amidines (**70**)




Moreover, the Fu group also published the iron-catalyzed cascade synthesis of quinazolinones using both 2-bromobenzoic acids (**71**, X = Br) with amidine hydrochlorides (**70**) as starting materials. The inexpensive and environmentally

friendly $FeCl_3$ was used as a catalyst. Ligand or additive was not required for this transformation. Although the reactions were performed at 120 °C, this iron-catalyzed *N*-arylation in the absence of ligand was the first example of construction of *N*-heterocycles (**Scheme 12**) (Yang *et al.*, 2009).

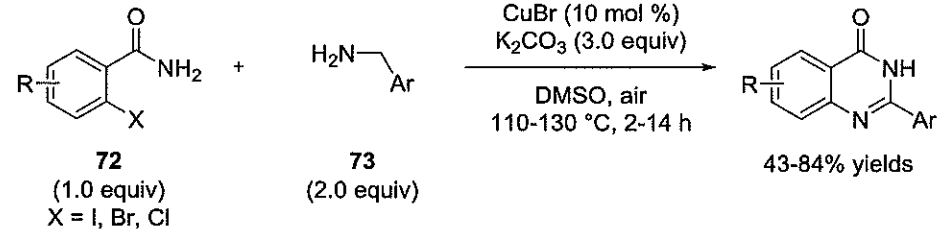
**Scheme 12** The iron-catalyzed *N*-arylation of 2-bromobenzoic acids (**71**) with amidine hydrochlorides (**70**)

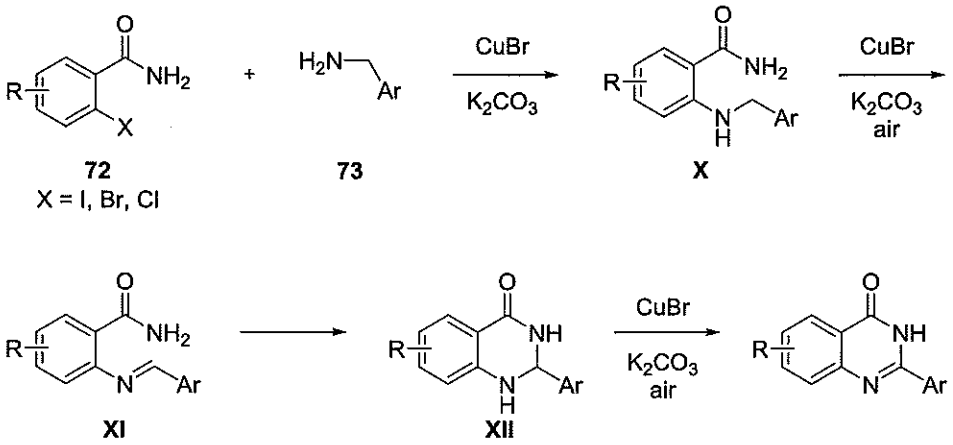



**71** (X = Br) (1.0 equiv) + **70** (1.2 equiv) → 60-83% yields, $R^1$ = alkyl, aryl

Later, in 2011, the Fu group demonstrated the first example of constructing 2-aryl quinazolinones by economically sequential reactions, Ullmann-type *N*-arylation and aerobic oxidative C–H amidation. Substituted 2-halobenzamides (**72**) and (aryl)methanamines (**73**) were used as starting materials, CuBr as a catalyst without addition of any ligand or additive, and air as the oxidant in this protocol. The corresponding quinazolinone products were obtained in moderate to good yields (43–84%) (**Scheme 13**). The domino reactions involve the CuBr-catalyzed *N*-arylation to provide the *N*-arylation product **X**, which undergoes CuBr-catalyzed aerobic oxidation to give the imine intermediate **XI**. The intramolecular nucleophilic addition of amide to imine of **XI** occurs to generate **XII**, followed by further aerobic oxidation to afford the target product (Xu *et al.*, 2011a).

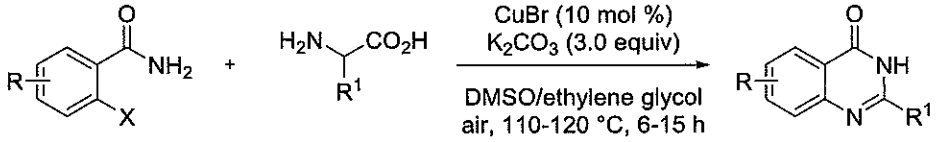
**Scheme 13** The CuBr-catalyzed aerobic oxidative domino synthesis of quinazolinone derivatives from 2-halobenzamides (**72**) and (aryl)methanamines (**73**)




In the same year, the Fu group also reported an alternative route for the synthesis of 2-substituted quinazolinone derivatives by the CuBr-catalyzed domino reactions of substituted 2-halobenzamides (**72**) and α-amino acids (**74**) under aerobic conditions. α-Amino acids were used as the nitrogen-containing motif instead of (aryl)methanamines (**73**). The quinazolinones were obtained in moderate to good yields (40–72%) (**Scheme 14**). The domino process can be achieved from two possible pathways. For pathway A, the transformation starts from copper-catalyzed Ullmann-type coupling, aerobic oxidation, C–H amidation, and decarboxylation, sequentially. For pathway B, it begins with copper-catalyzed Ullmann-type coupling, decarboxylation, C–H amidation, and aerobic oxidation process (Xu *et al.*, 2011b).

**Scheme 14** The synthesis of quinazolinones from 2-halobenzamides (**72**) and α-amino acids (**74**) by the CuBr-catalyzed domino reactions




**72** (1.0 equiv) X = I, Br, Cl

**74** (2.0 equiv)

40-72% yields
$R^1$ = H, alkyl, aryl

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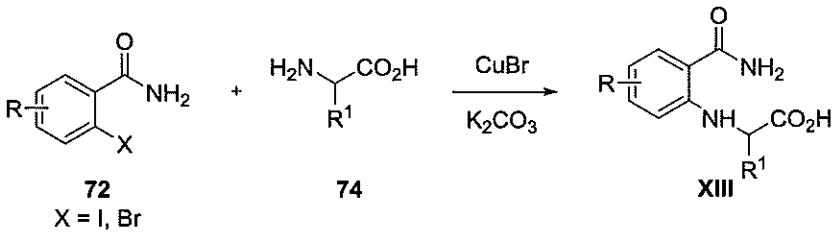
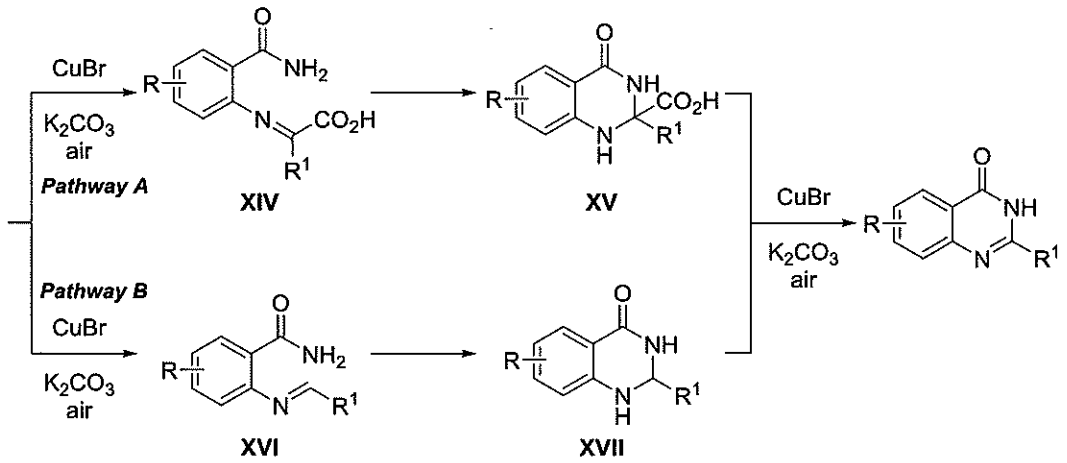



**72** X = I, Br

**74**

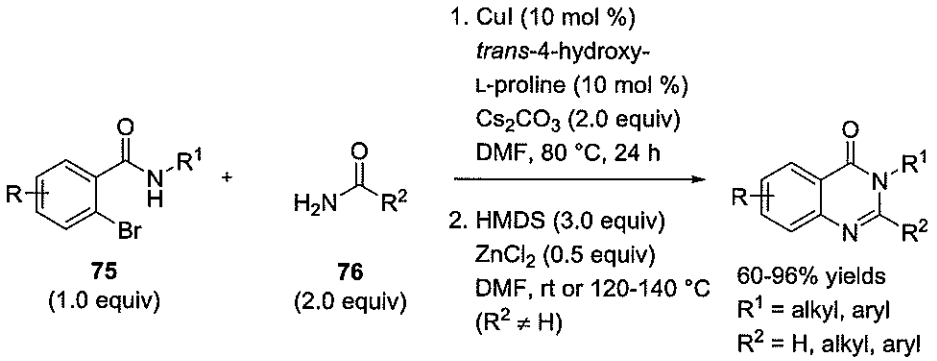
**XIII**

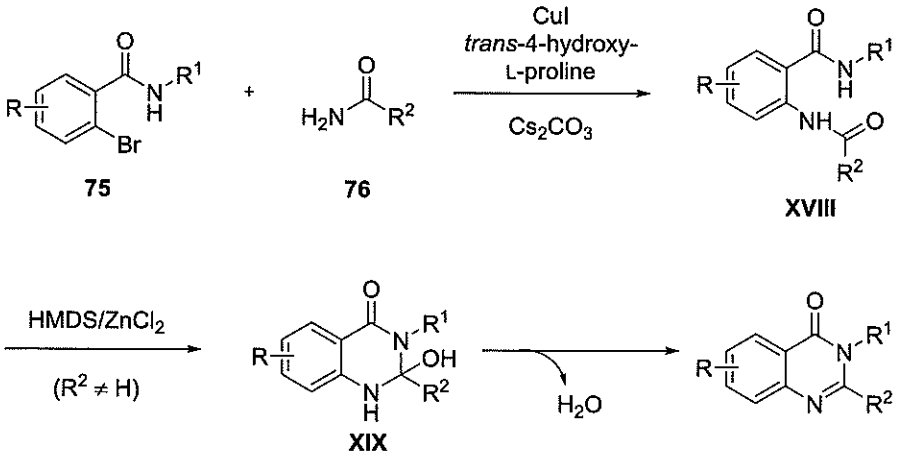



**XIV** **XV** **XVI** **XVII**

In addition, other research groups were also interested in the copper-catalyzed reactions for the synthesis of quinazolinones. In 2012, Ma and co-workers reported a simple route for the synthesis of 3-substituted and 2,3-disubstituted quinazolinones. The CuI-catalyzed coupling reactions of *N*-substituted 2-bromobenzamides (**75**) with formamide (**76**, $R^2$ = H) furnished 3-substituted quinazolinones directly. On the other hand, the HMDS/$ZnCl_2$ mediated condensative cyclization was required as the second step for the synthesis of 2,3-disubstituted quinazolinones from the reactions of amide substrates (**76**, $R^2 \neq$ H). A variety of products were obtained in good to excellent yields *via* domino reactions including copper-catalyzed *N*-arylation, intramolecular nucleophilic addition and dehydration, sequentially (**Scheme 15**) (Xu *et al.*, 2012).

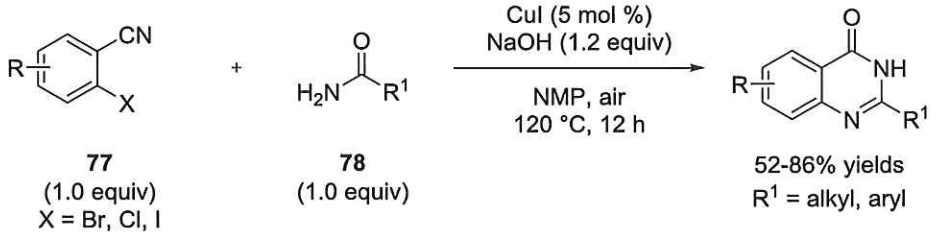
**Scheme 15** The CuI-catalyzed synthesis of quinazolinones from *N*-substituted 2-bromobenzamides (**75**) with amides (**76**)

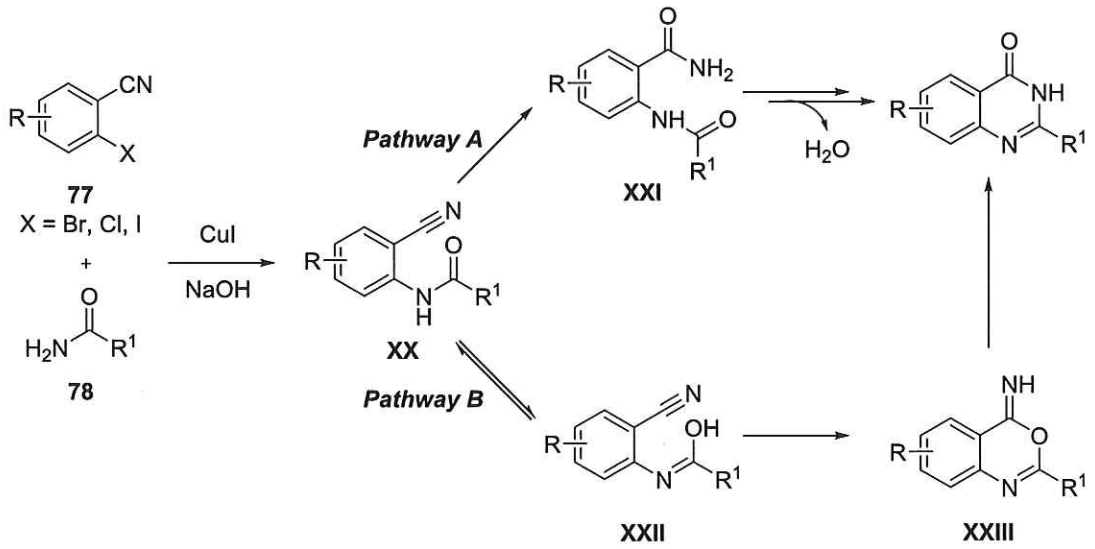



Recently, Shi reported a practical copper-catalyzed domino reactions for quinazolinone synthesis from commercially available 2-halobenzonitriles (**77**) and amides (**78**). 3-Substituted quinazolinones were obtained in 52–86% yields under the optimal conditions. A plausible mechanism for the domino reactions is shown in **Scheme 16**. The CuI-catalyzed *N*-arylation of 2-halobenzonitrile and amide first provides *N*-(2-cyanoaryl)amide **XX** which can undergo two possible pathways. For pathway A, hydration of the cyano group takes place to give diamide intermediate **XXI**, followed by intramolecular condensative cyclization and dehydration to afford the product. For pathway B, the enolization of **XX**, followed by intramolecular Pinner reaction provides benzoxazine intermediate **XXIII** and product is obtained after subsequent rearrangement (Chai *et al.*, 2014).

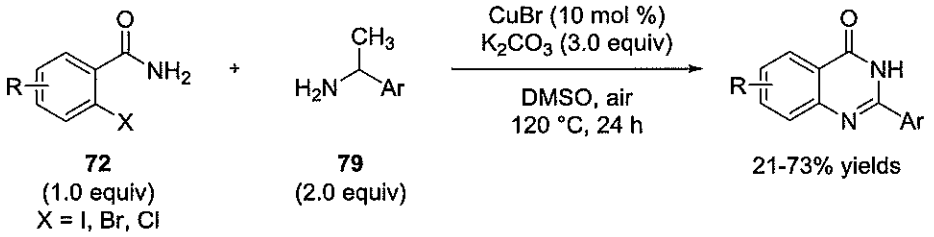
**Scheme 16** The copper-catalyzed domino reactions for quinazolinone synthesis from 2-halobenzonitriles (**77**) and amides (**78**)

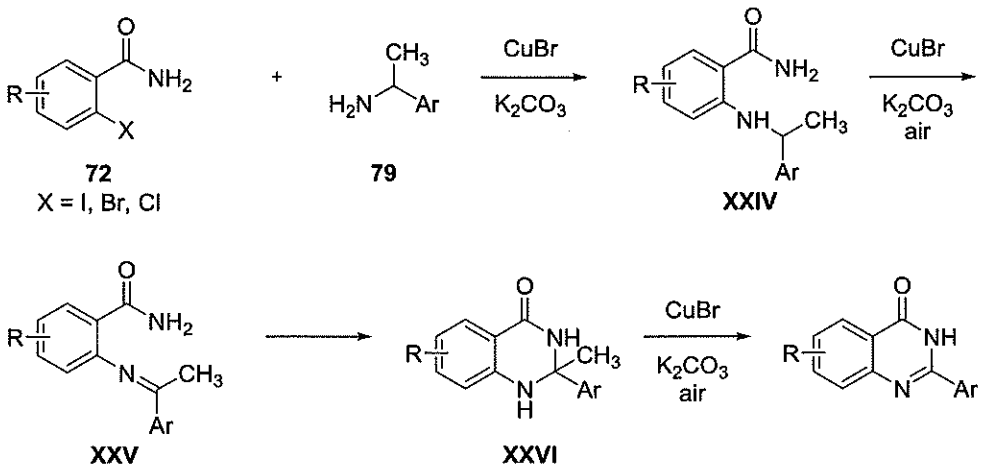



A copper-catalyzed domino reactions involving intramolecular C–C bond cleavage for the synthesis of 2-aryl quinazolinones was reported by the Tang group in 2014. 2-Halobenzamides (**72**) and α-methyl arylmethanamines (**79**) were used as starting materials. Domino reactions were performed under the optimized conditions; CuBr as a catalyst, $K_2CO_3$ as a base and air as an accelerant. 2-Aryl quinazolinone products were obtained in low to good yields. The domino reactions involve Ullmann-type coupling reaction, oxidation, intramolecular nucleophilic addition and C–C bond cleavage (**Scheme 17**) (Wang *et al.*, 2014).

**Scheme 17** CuBr-catalyzed domino synthesis of quinazolinones from 2-halobenzamides (**72**) and α-methyl arylmethanamines (**79**)




From literature reviews, we found that the reactions catalyzed with palladium were harsher than the copper-catalyzed reactions. The use of toxic gaseous CO as the versatile C1 building block under high pressure conditions is risky and hard to handle. Besides the harsher conditions, the costs of palladium catalysts are more expensive than those of copper. We decided to enrich the chemistry of copper-catalyzed domino reactions by the study of quinazolinone synthesis using copper as a catalyst.

## 1.2 Objectives

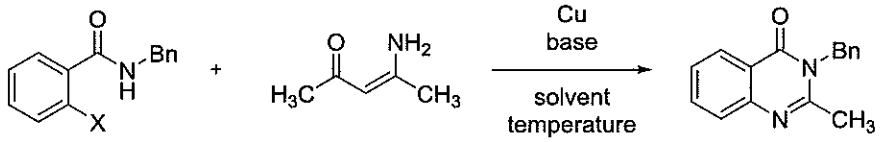
1. To accomplish a new, simple, fast and convenient method to synthesize quinazolinone derivatives.
2. To understand the reaction mechanisms of copper-catalyzed reactions.
3. To evaluate the biological activities of synthesized quinazolinone derivatives.

# CHAPTER 2

## RESULTS AND DISCUSSION

As part of our studies toward novel methodologies in constructing N-containing heterocyclic molecules, we found that the copper-catalyzed reaction of *N*-substituted 2-iodobenzamides and enaminones could undergo domino process to accomplish the quinazolinone derivatives. For our initial studies, the optimization of the reaction conditions including catalysts, bases, solvents, and reaction temperatures, was investigated (**Table 1**). *N*-benzyl 2-iodobenzamide (**80a**) and (*Z*)-4-aminopent-3-en-2-one (**81a**) were chosen as the model substrates.

**Table 1** Optimization of reaction conditions for the copper-catalyzed domino reaction of *N*-benzyl 2-halobenzamides with *Z*-enaminone **81a** to form quinazolinone **82a**[a]




**81a** **82a**

| Entry | X | Catalyst | Base | Solvent | Temp (° C) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | I | CuI | $K_2CO_3$ | $CH_3CN$ | 60 | 0 |
| 2 | I | CuI | $Cs_2CO_3$ | DMSO | 60 | 0 |
| 3 | I | CuI | $Cs_2CO_3$ | $CH_3CN$ | 60 | 14 |
| **4** | **I** | **CuI** | **$Cs_2CO_3$** | **$CH_3CN$** | **90** | **78** |
| 5 | Br | CuI | $Cs_2CO_3$ | $CH_3CN$ | 90 | 45 |
| 6 | I | CuI | $Cs_2CO_3$ | DMSO | 90 | 49 |
| 7 | I | CuI | $Cs_2CO_3$ | DMF | 90 | 56 |
| 8 | I | CuCl | $Cs_2CO_3$ | $CH_3CN$ | 90 | 62 |
| 9 | I | CuBr | $Cs_2CO_3$ | $CH_3CN$ | 90 | 50 |

**Table 1** (continued)

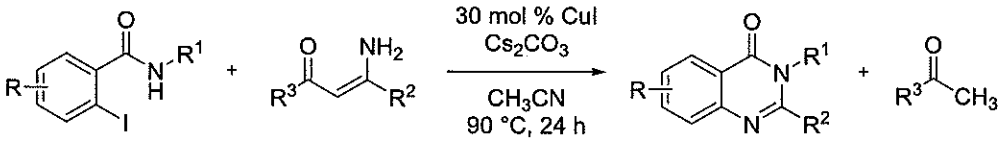
| Entry | X | Catalyst | Base | Solvent | Temp (° C) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 10 | I | $Cu(OAc)_2$ | $Cs_2CO_3$ | $CH_3CN$ | 90 | 46 |
| 11 | I | CuI + L-proline[c] | $Cs_2CO_3$ | $CH_3CN$ | 90 | 51 |

[a]Reaction conditions: all reactions were performed with 0.3 mmol of amides, 2.0 equiv of **81a**, 30 mol % of Cu catalyst, 2.5 equiv of base, 3.0 mL of solvent, for 24 h. [b]Isolated yield. [c]30 mol % of L-proline was added.

Firstly, the use of CuI as a catalyst, $K_2CO_3$ as a base and $CH_3CN$ as a solvent at 60 °C led to no reaction (entry 1). We then changed the base to $Cs_2CO_3$ and the reaction was performed in DMSO, no product was observed (entry 2). When we changed the solvent back to $CH_3CN$, the corresponding quinazolinone product **82a** was isolated in 14% yield (entry 3). Next, it was found that the limiting starting material **80a** was completely consumed and the product was obtained in 78% yield when the reaction temperature was raised to 90 °C and 30 mol % of CuI was used (entry 4). In addition, we found that *N*-benzyl 2-iodobenzamide (**80a**) was the better substrate than *N*-benzyl 2-bromobenzamide (entries 4–5). Other solvents, DMSO and DMF, were subjected in optimization studies, and $CH_3CN$ gave the best result (entries 4, 6–7). Copper sources, CuCl, CuBr and $Cu(OAc)_2$, were also investigated, and CuI provided the highest yield (entries 4, 8–10). Note that, when L-proline was added as a ligand, the reaction gave lower yield (entries 4 and 11). Ethylenediamine and 1,10-phenanthroline were also used as the ligands, but the reaction without external ligands still gave the best result. Based on these results, we believed that *Z*-enaminone **81a** played the role of substrate and the ligand for this transformation. Note that, 2.0 equivalents of **81a** were crucial to drive the reaction to completion. Based on these results, we concluded that the use of 1.0 equiv of 2-iodobenzamides and 2.0 equiv of *Z*-enaminones as the substrates, 30 mol % of CuI as the catalyst, 2.5 equiv of $Cs_2CO_3$ as the base and $CH_3CN$ as the solvent at 90 °C for 24 hours was the optimal conditions for this transformation.

The scope of substrates for the CuI-catalyzed domino synthesis of quinazolinone derivatives from 2-iodobenzamides (**80**) and *Z*-enaminones (**81**) was investigated under the identified conditions (**Table 2**).

**Table 2** Substrate scope for the CuI-catalyzed synthesis of quinazolinones from 2-iodobenzamides (**80**) and *Z*-enaminones (**81**)[a]




**80** + **81** → **82** + $R^3COCH_3$

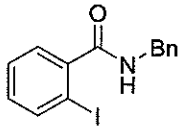
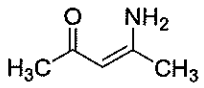
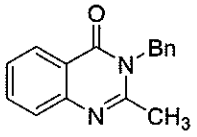
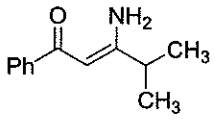
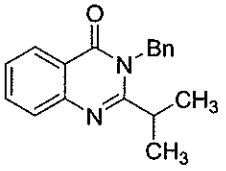
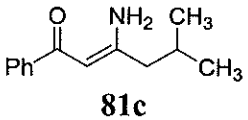
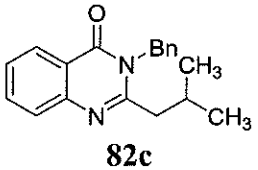
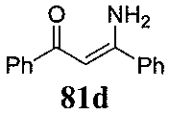
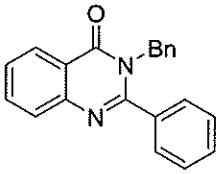
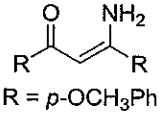
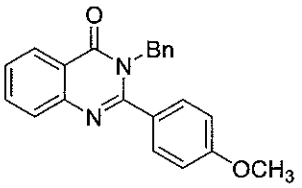
| Entry | 2-Iodobenzamide | Enaminone | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  **80a** |  **81a** |  **82a** | 78 |
| 2 | **80a** |  **81b** |  **82b** | 30 |
| 3 | **80a** |  **81c** |  **82c** | 35 |
| 4 | **80a** |  **81d** |  **82d** | 71 |
| 5 | **80a** |  R = *p*-$OCH_3$Ph **81e** |  **82e** | 50 |

**Table 2** (continued)

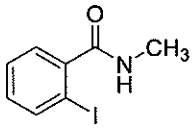
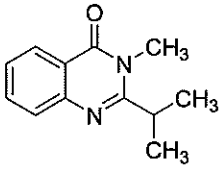
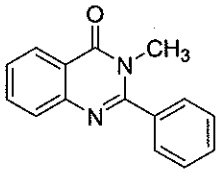
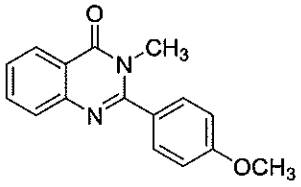
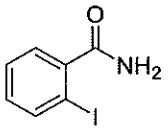
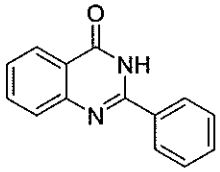
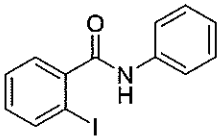
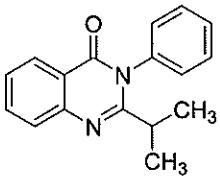
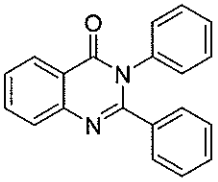
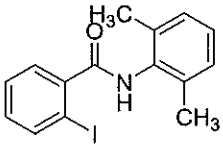
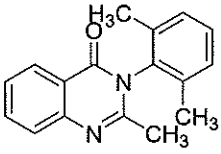
| Entry | 2-Iodobenzamide | Enaminone | Product | Yield[b] (%) |
|---|---|---|---|---|
| 6 |  **80b** | **81b** |  **82f** | 25 |
| 7 | **80b** | **81d** |  **82g** | 70 |
| 8 | **80b** | **81e** |  **82h** | 65 |
| 9 |  **80c** | **81d** |  **82i** | 48 |
| 10 |  **80d** | **81b** |  **82j** | 34 |
| 11 | **80d** | **81d** |  **82k** | 30 |
| 12 |  **80e** | **81a** |  **82l** | 53 |

**Table 2** (continued)

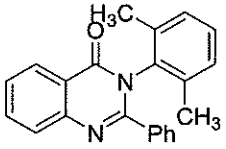
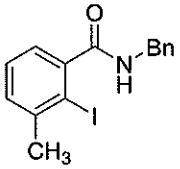
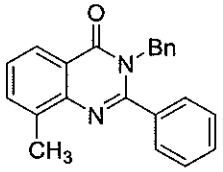
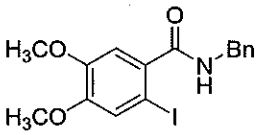
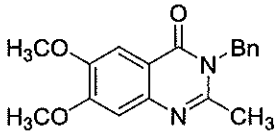
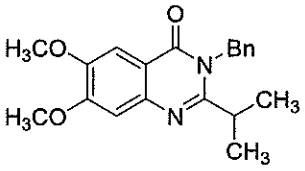
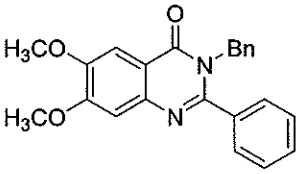
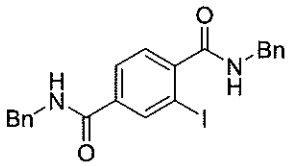
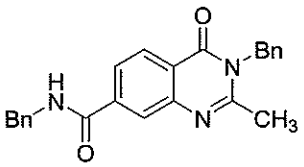
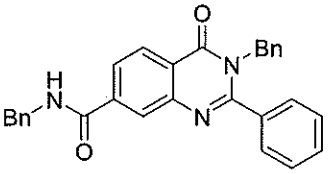
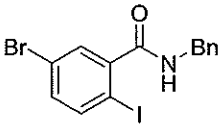
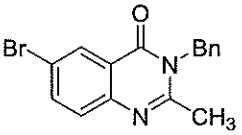
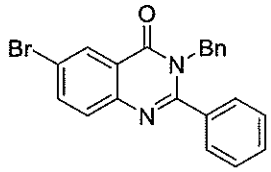
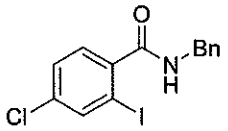
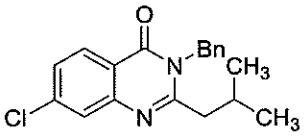
| Entry | 2-Iodobenzamide | Enaminone | Product | Yield[b] (%) |
|---|---|---|---|---|
| 13 | **80e** | **81d** |  **82m** | 35 |
| 14 |  **80f** | **81d** |  **82n** | 34 |
| 15 |  **80g** | **81a** |  **82o** | 38 |
| 16 | **80g** | **81b** |  **82p** | 35 |
| 17 | **80g** | **81d** |  **82q** | 73 |
| 18[c] |  **80h** | **81a** |  **82r** | 29 |
| 19[c] | **80h** | **81d** |  **82s** | 41 |
| 20 |  **80i** | **81a** |  **82t** | 20 |

**Table 2** (continued)

| Entry | 2-Iodobenzamide | Enaminone | Product | Yield[b] (%) |
|---|---|---|---|---|
| 21 | **80i** | **81d** |  **82u** | 45 |
| 22 |  **80j** | **81c** |  **82v** | 54 |

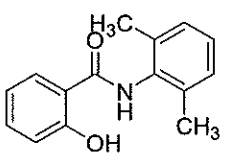
[a]Reaction conditions: all reactions were performed with 0.5 mmol of amides, 2.0 equiv of *Z*-enaminones, 30 mol % of CuI, 2.5 equiv of $Cs_2CO_3$, 5.0 mL of $CH_3CN$. [b]Isolated yield. [c]DMF was used as solvent instead of $CH_3CN$.

The results showed that a wide range of both substrates were applicable to this methodology and diverse 2,3-disubstituted quinazolinones were obtained in low to good yields. The reactions of **80a** with various *Z*-enaminones showed that the product yields decreased when the size of substituents on *Z*-enaminones increased (entries 1–3), indicating that the steric hindrance of *Z*-enaminones had an impact on the reaction. The reactions of **80a** with phenyl substituted *Z*-enaminones (**81d** and **81e**) were converted to the corresponding quinazolinones in moderate to good yields (entries 4 and 5). The reaction of *N*-methyl 2-iodobenzamide (**80b**) with *Z*-enaminone **81a** failed to give the quinazolinone product and a lot of unidentified byproducts were formed. As we expected, **82f** was isolated in low yield due to steric hindrance of *Z*-enaminone **81b** (entry 6). On the other hand, 2-phenyl substituted quinazolinones **82g** and **82h** were obtained in good yields (entries 7 and 8). The reaction of 2-iodobenzamide (**80c**) and **81d** gave 2-phenylquinazolinone (**82i**) in 48% yield (entry 9). The reactions of *N*-phenyl 2-iodobenzamide (**80d**) and *N*-(2,6-dimethylphenyl)-2-iodobenzamide (**80e**) yielded the corresponding quinazolinones in low to moderate yields (entries 10–13). These results suggested that nucleophilicities of amide nitrogen atoms affected the reaction. In addition, the steric hindrance of *N*-substituents of amide substrates had a minor impact on the reaction (entries 11 and

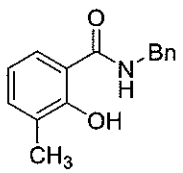
13). Furthermore, the steric hindrance at the 3-position of aromatic ring of 2-iodobenzamide substrate had an influence on the yield observed from the reaction of *N*-benzyl-2-iodo-3-methylbenzamide (**80f**) (entry 14). The 2-iodobenzamides with either electron-donating (**80g**) or electron-withdrawing (**80h**) substituents on the aromatic ring generated corresponding quinazolinones in low yields when these compounds were reacted with alkyl substituted *Z*-enaminones, **81a** and **81b**, (entries 15–16 and 18). On the other hand, the quinazolinones were produced in moderate to good yields when **81d**, phenyl substituted *Z*-enaminone, was used (entries 17 and 19). These results also confirmed that the steric of *Z*-enaminones affecting our domino reactions. Moreover, the reactions of *N*-benzyl-5-bromo-2-iodobenzamide (**80i**) with two *Z*-enaminones, **81a** and **81d**, gave the Br-substituted products (**82t** and **82u**) in low to moderate yields (entries 20 and 21), indicating that the **80i** was fairly tolerant in this system. Lastly, a Cl-substituted quinazolinone (**82v**), a precursor of the synthesis of Ispinesib (Holland *et al.*, 2013), was generated in 54% yield (entry 22).

In addition, three major byproducts were formed in many reactions (**Figure 4**). For example, the steric hindrance of amide substrates caused the formation of hydroxygenated byproducts. *N*-(2,6-dimethylphenyl)-2-hydroxybenzamide (**83**) was obtained in 24% and 20% from the reactions of **80e** with **81a** and **81d**, respectively. *N*-Benzyl-2-hydroxy-3-methylbenzamide (**84**) was isolated from the reaction of **80f** in 22%. Furthermore, the replacement of iodine atom by hydrogen atom was observed as a byproduct, *N*-benzyl-3,4-dimethoxybenzamide (**85**), in the reaction of amide **80g** with **81a** and **81d** in 27% and 5%, respectively. The other isolable byproducts were biaryl compounds (**86**). They could be generated in the copper-catalyzed reaction *via* the classical Ullmann reaction (Fanta, 1974).

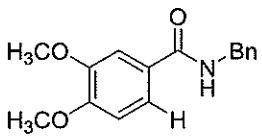
**Figure 4** Examples of byproducts formed in some reactions



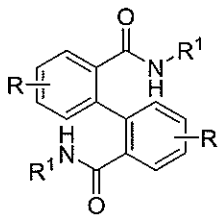

**83**




**84**



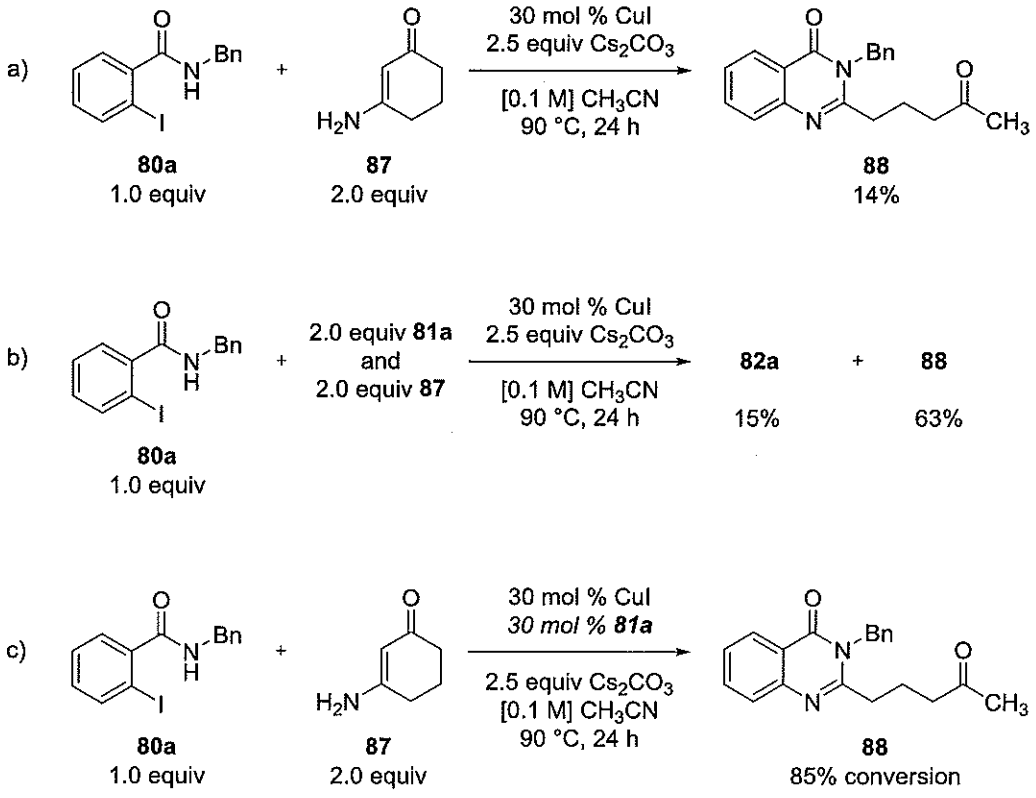

**85**




**86**

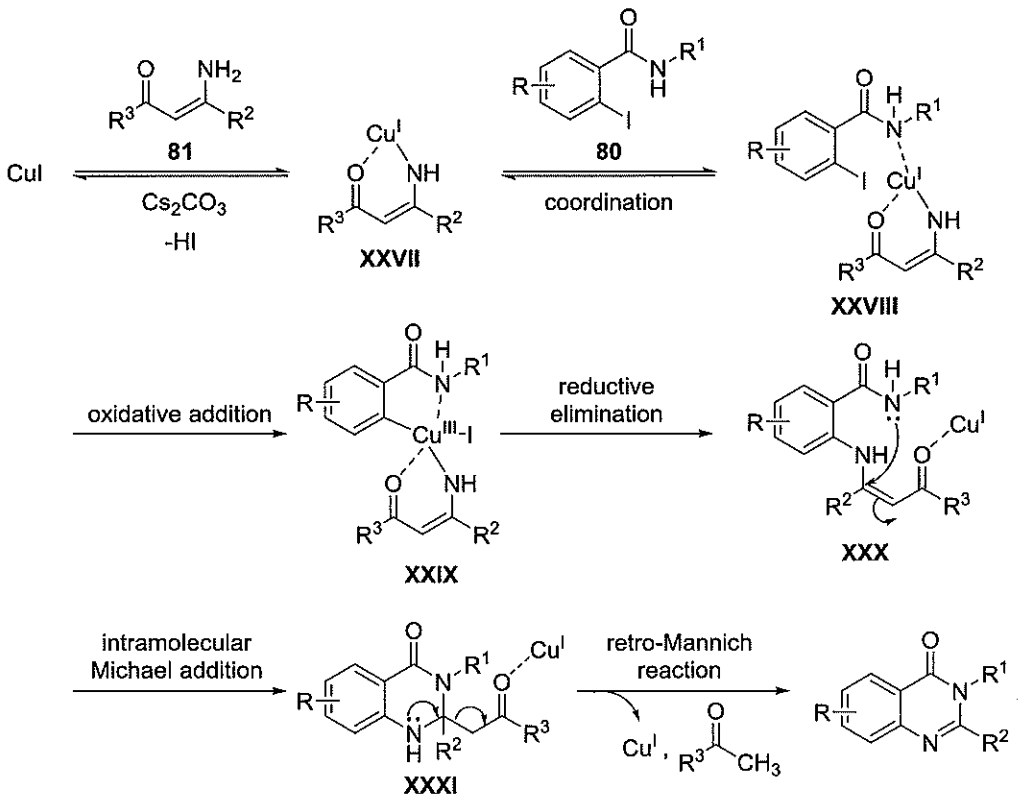
We then turned our interest to *E*-enaminone in order to expand the substrate scope and enrich this work. Surprisingly, when we tried to use 3-aminocyclohex-2-en-1-one (**87**), the representative of *E*-enaminone, the corresponding quinazolinone (**88**) was isolated in low yield (**Scheme 18a**). Based on this result, we assumed that the geometry of enaminones gave different reactivity in our domino reactions. In order to prove our hypothesis, the mixture of *Z*- and *E*-enaminones (**81a** and **87**) was reacted with **80a** under the standard conditions. Surprisingly, the quinazolinone **88**, product derived from *E*-enaminone **87**, was obtained as a major product (**Scheme 18b**), indicating that the *E*-enaminone exhibited better reactivity than *Z*-enaminone. We assumed that *E*-enaminone lacks the intramolecular H-bonding, it acted as the nucleophile better than *Z*-enaminone. Moreover, we found that the reaction of *E*-enaminone required the assistance of *Z*-enaminone as the ligand. To demonstrate the requirement of ligand, 30 mol % of *Z*-enaminone **81a** was added as a ligand to the reaction of **80a** and **87**, affording the quinazolinone **88** in 85% conversion observed from the $^1$H NMR spectrum of the crude reaction mixture (**Scheme 18c**).

**Scheme 18** The study of the reactivity of *E*-enaminone in this process



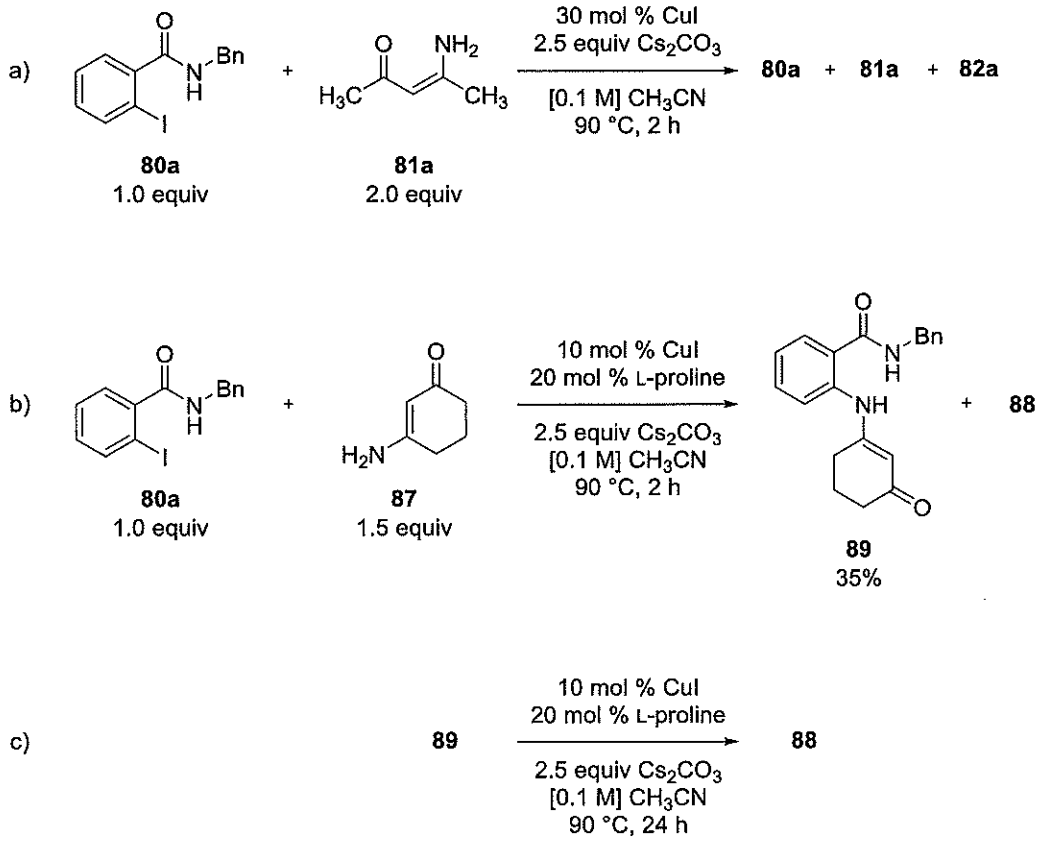
The proposed mechanism for the CuI-catalyzed domino synthesis of quinazolinone derivatives from 2-iodobenzamides (**80**) and *Z*-enaminones (**81**) is outlined in **Scheme 19**. Initially, the association of CuI and *Z*-enaminone generates the active Cu(I) complex **XXVII** (Liu *et al.*, 2013) which then coordinates with 2-iodobenzamide to give the intermediate **XXVIII**. The oxidative addition of Cu(I) to C–I bond produces Cu(III) complex **XXIX**, followed by the reductive elimination to provide the *N*-arylation intermediate **XXX**, accelerating by *ortho*-substituent effect (Cai *et al.*, 2006). Subsequently, the intramolecular Michael addition takes place to form the dihydroquinazolinone intermediate **XXXI**, in which the retro-Mannich reaction occurs to expel a ketone molecule and yield the quinazolinone product. The Cu(I) may also act as a Lewis acid activator in the last two steps. The 4′-methoxyacetophenone was isolated from all reactions of *Z*-enaminone **81e**, insisting the liberation of ketone molecules. The last two steps were proposed according to the condensation reaction of 2-aminobenzamides with 1,3-diketones (Maloshitskaya *et al.*, 2005 and Lu *et al.*, 2013).

**Scheme 19** The proposed mechanism for the CuI-catalyzed domino reactions



To prove the proposed mechanism, attempts to detect the intermediates showed in the mechanism were applied. First, the reaction of **80a** and *Z*-enaminone **81a** was performed according to the general procedure but the reaction time was reduced to 2 hours. Unfortunately, none of the expected intermediates was detected. From the $^1$H NMR spectrum of the crude mixture, the starting material **80a** and product **82a** in the ratio of 1:1 was observed together with the remaining *Z*-enaminone **81a** (**Scheme 20a**). Fortunately, the *N*-arylation intermediate **89** was obtained in 35% after stopping the reaction of **80a** and *E*-enaminone **87** under the further optimized reaction conditions in 2 hours (**Scheme 20b**). Then, intermediate **89** was exposed to the same conditions and fully converted to the product **88** (**Scheme 20c**). These results illustrated that the copper-catalyzed Ullmann-type coupling was the first transformation of the domino process, supporting our proposed mechanism.

**Scheme 20** Mechanism investigation experiments



All synthesized products were tested for biological activities including antimicrobial (toward *Staphylococcus aureus* ATCC25923, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* ATCC27853, *Escherichia coli* ATCC25922, *Candida albicans* NCPF3153, flucytosine-resistant *Cryptococcus neoformans* ATCC90113 and *Microsporum gypseum* clinical isolate), antimycobacterial (against *Mycobacterium tuberculosis*, $H_{37}Ra$ strain), antimalarial (toward *Plasmodium falciparum*, K1 strain) and cytotoxicities against oral human cavity cancer cells (KB), breast cancer cells (MCF-7) and noncancerous Vero cells (**Table 3**).

**Table 3** Antifungal, antimycobacterial and cytotoxic activities for the synthesized products

| **Compound** | **Antifungal** (MIC, µg/mL) | **Antimycobacterial** (MIC, µg/mL) | **Cytotoxicity** ($IC_{50}$, µg/mL) | | |
|---|---|---|---|---|---|
| | *M. gypseum* | *M. tuberculosis* | KB | MCF-7 | Vero |
| **82a** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82b** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82c** | >200 | Inactive | Inactive | Inactive | 17.58 |
| **82d** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82e** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82f** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82g** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82h** | 64 | Inactive | Inactive | Inactive | Inactive |
| **82i** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82j** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82k** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82l** | 32 | Inactive | Inactive | Inactive | 22.67 |
| **82m** | >200 | Inactive | 30.63 | Inactive | 17.09 |
| **82n** | 128 | 50.00 | Inactive | Inactive | 17.35 |
| **82o** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82p** | >200 | Inactive | Inactive | 36.78 | 24.68 |

**Table 3** (continued)

| Compound | Antifungal (MIC, μg/mL) | Antimycobacterial (MIC, μg/mL) | Cytotoxicity ($IC_{50}$, μg/mL) | | |
|---|---|---|---|---|---|
| | *M. gypseum* | *M. tuberculosis* | KB | MCF-7 | Vero |
| **82q** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82r** | >200 | Inactive | - | - | Inactive |
| **82s** | >200 | Inactive | - | - | Inactive |
| **82t** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82u** | >200 | Inactive | Inactive | Inactive | Inactive |
| **82v** | >200 | 50.00 | Inactive | Inactive | 18.64 |
| **88** | >200 | Inactive | 19.43 | Inactive | Inactive |
| Micronazole | 0.5 | - | - | - | - |
| Rifampicin | - | 0.025 | - | - | - |
| Streptomycin | - | 1.25 | - | - | - |
| Isoniazid | - | 0.0469 | - | - | - |
| Ofloxacin | - | 0.781 | - | - | - |
| Ethambutol | - | 0.938 | - | - | - |
| Ellipticine | - | - | 2.10 | - | 1.27 |
| Doxorubicin | - | - | 1.11 | 14.29 | - |
| Tamoxifen | - | - | - | 7.60 | - |

- = not evaluated.

All compounds showed no antimalarial activity against *P. falciparum*. For antimicrobial activities, compounds **82h**, **82l** and **82n** displayed antifungal activity against *M. gypseum* with MIC values of 32–128 μg/mL. In addition, compounds **82n** and **82v** exhibited mild antimycobacterial activity with the same MIC value of 50.00 μg/mL. For cytotoxic activities, compounds **82m** and **88** displayed weak activity against KB cell lines with the $IC_{50}$ values of 30.63 and 19.43 μg/mL, respectively. Compound **82p** demonstrated weak activity toward MCF-7 cell lines with the $IC_{50}$ value of 36.78 μg/mL. However, these active compounds, except **88**, showed stronger cytotoxicity to Vero cells.

# CHAPTER 3

# CONCLUSION

A wide range of 2,3-disubstituted quinazolinone derivatives were synthesized by a new, simple, fast and mild CuI-catalyzed domino reaction in low to good yields. The readily prepared *N*-substituted 2-iodobenzamides and enaminones were used as the starting materials. *Z*-enaminones played not only the role of substrates but also the ligands for the transformation. The steric hindrance on *Z*-enaminones and on the aromatic ring of 2-iodobenzamide substrate together with the nucleophilicities of nitrogens of 2-iodobenzamide substrates had significant impacts on the product yields. The domino process proceeded *via* an Ullmann-type coupling reaction, an intramolecular Michael addition, and a retro-Mannich reaction, sequentially. Quinazolinone products were evaluated for biological activities. Some of them showed antifungal, antimycobacterial and cytotoxic (against KB and MCF-7) activities.

# CHAPTER 4

# EXPERIMENTAL

## 4.1 General Information

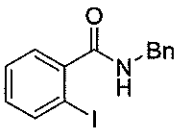
$CH_3CN$ was dried over 4 Å molecular sieves. Solvents for extraction and column chromatography were distilled at their boiling point ranges prior to use. Thin-layer chromatography (TLC) was performed on silica gel 60 $GF_{254}$ (Merck) and were visualized by fluorescence quenching under UV light. Column chromatography was performed on SiliaFlash® 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 ($\delta$ 0.00) and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra (IR) were measured on a Perkin Elmer Spectrum GX FT-IR system and recorded on wavenumber ($cm^{-1}$). Mass spectra were obtained from a liquid chromatograph-mass spectrometer (2090, LCT, Waters, Micromass).

## 4.2 Preparation of Starting Materials

### 4.2.1 General Procedure A - Synthesis of 2-Iodobenzamides

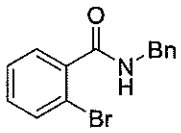
Prepared according to literature procedure (Kitching *et al.*, 2012). A flame-dried round bottom flask was charged with 1.0 equiv of 2-iodobenzoic acid derivative in $CH_2Cl_2$ (0.3 M) and DMF (2 drops), followed by the addition of 1.25 equiv of oxalyl chloride at 0 °C. The reaction mixture was allowed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

was dissolved in $CH_2Cl_2$ (0.3 M). The solution of amine (1.5 equiv) and triethylamine (3.0 equiv) was added at 0 °C. The reaction mixture was allowed to stir at room temperature for 15 hours. The reaction mixture was quenched with sat. $NH_4Cl$ and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by column chromatography to afford the title compounds.



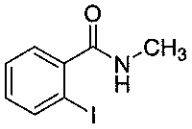

**_N_-Benzyl-2-iodobenzamide (80a).**

Prepared according to the general procedure A. Yield 99% as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, $J$ = 7.8 Hz, 1H), 7.40-7.25 (m, 7H), 7.10-7.04 (m, 1H), 6.15 (brs, 1H), 4.61 (d, $J$ = 5.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.0, 141.9, 139.7, 137.4, 131.0, 128.6, 128.1, 128.0, 127.6, 92.3, 44.1; IR (thin film) ν 3256, 3030, 1646, 1522, 771, 744, 697 cm$^{-1}$. These data matched to the literature values (Kitching *et al.*, 2012).



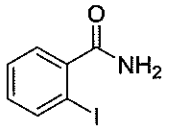

**_N_-Benzyl-2-bromobenzamide.**

Prepared according to the general procedure A. Yield 93% as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.49 (td, $J$ = 8.1, 1.2 Hz, 2H), 7.34-7.16 (m, 7H), 6.22 (brs, 1H), 4.58 (d, $J$ = 5.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.6, 137.7, 133.3, 131.2, 129.5, 128.7, 128.0, 127.6, 127.5, 119.4, 44.1; IR (thin film) ν 3256, 3030, 1646, 1522, 771, 744, 697 cm$^{-1}$. These data matched to the literature values (Thansandote *et al.*, 2009).



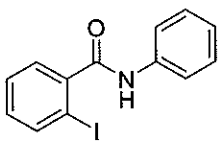
**2-Iodo-*N*-methylbenzamide (80b).**

Prepared according to the general procedure A. Yield 90% as a white solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, $J$ = 8.1 Hz, 1H), 7.40-7.33 (m, 2H), 7.14-7.06 (m, 1H), 5.81 (brs, 1H), 3.02 (d, $J$ = 4.8 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.2, 142.4, 139.8, 131.1, 128.3, 128.2, 92.6, 26.8; IR (thin film) ν 3288, 1629, 1542, 1312, 764 $cm^{-1}$. These data matched to the literature values (Kundu *et al.*, 2000).



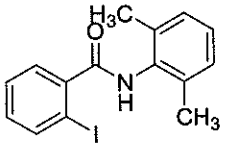
**2-Iodobenzamide (80c).**

A flame-dried round bottom flask was charged with 1.0 equiv of 2-iodobenzoic acid in $CH_2Cl_2$ (0.3 M) and DMF (2 drops), followed by the addition of 1.25 equiv of oxalyl chloride at 0 °C. The reaction mixture was allowed to stir at room temperature for 4 hours. After that, the mixture was evaporated to dryness. The prepared acid chloride was dissolved in $CH_2Cl_2$ (0.3 M). $NH_4OH$ (28-30%, 1.5 equiv) was added dropwise at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 hours. The precipitate was filtered and washed with water to give **80c** in 95% as a white solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, $J$ = 7.8 Hz, 1H), 7.50 (d, $J$ = 7.8 Hz, 1H), 7.41 (t, $J$ = 7.8 Hz, 1H), 7.14 (td, $J$ = 7.8, 1.5 Hz, 1H), 5.88 (brs, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 170.8, 142.9, 139.2, 129.0, 128.0, 127.8, 93.0; IR (thin film) ν 3349, 3174, 1651, 1622, 1399, 1127, 770, 739 $cm^{-1}$. These data matched to the literature values (Jithunsa *et al.*, 2011).



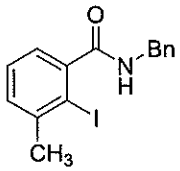
**2-Iodo-*N*-phenylbenzamide (80d).**

Prepared according to the general procedure A. Yield 94% as a white solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, $J$ = 8.1 Hz, 1H), 7.73 (brs, 1H), 7.62 (d, $J$ = 7.8 Hz, 2H), 7.46 (dd, $J$ = 7.5, 1.5 Hz, 1H), 7.40-7.33 (m, 2H), 7.19-7.08 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.4, 142.1, 140.1, 137.7, 131.5, 129.2, 128.6, 128.4, 125.0, 120.3, 92.5; IR (thin film) ν 3256, 3056, 1654, 1600, 1542, 1440, 1324, 755, 692 cm$^{-1}$. These data matched to the literature values (Jithunsa *et al.*, 2011).



**2-Iodo-*N*-(2,6-dimethylphenyl)benzamide (80e).**

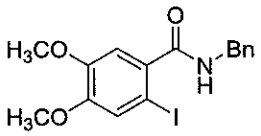
Prepared according to the general procedure A. Yield 93% as a white solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, $J$ = 8.1 Hz, 1H), 7.52 (dd, $J$ = 7.5, 1.5 Hz, 1H), 7.40 (t, $J$ = 7.5 Hz, 1H), 7.18-7.07 (m, 4H), 2.35 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.5, 142.2, 140.3, 135.7, 133.1, 131.4, 128.4, 128.2, 127.7, 92.4, 19.0; IR (thin film) ν 3235, 2918, 1653, 1522, 772, 749 cm$^{-1}$. These data matched to the literature values (Pan *et al.*, 2013).



***N*-Benzyl-2-iodo-3-methylbenzamide (80f).**

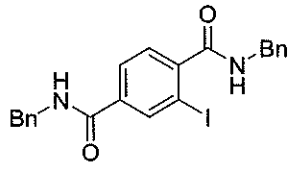
Prepared according to the general procedure A. Yield 97% as a white solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.36-7.12 (m, 7H), 7.03-6.99 (m, 1H), 6.38 (brs, 1H), 4.51 (d, $J$ = 6.0 Hz, 2H), 2.42 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.3, 143.7, 142.8, 137.8, 130.4, 128.7, 128.1, 128.0, 127.6, 125.1, 99.4, 44.0, 29.2; IR (thin film) ν 3273, 3031,

1646, 1523, 1313, 1012, 776, 720, 698 $cm^{-1}$. These data matched to the literature values (Balkrishna *et al.*, 2010).



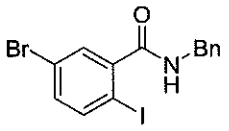
**_N_-Benzyl-2-iodo-4,5-dimethoxybenzamide (80g).**

Prepared according to the general procedure A. Yield 96% as a white solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.47-7.24 (m, 5H), 7.19 (s, 1H), 7.01 (s, 1H), 6.26 (brs, 1H), 4.62 (d, $J$ = 5.7 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 168.7, 150.5, 149.2, 137.6, 134.1, 128.7, 128.2, 127.7, 122.0, 112.0, 80.9, 56.2, 56.1, 44.4; IR (thin film) ν 3285, 3028, 2932, 1638, 1593, 1498, 1255, 1210, 1027, 862, 772, 699 $cm^{-1}$. These data matched to the literature values (Yao *et al.*, 2005).



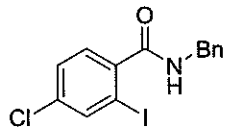
**_N_$^1$,_N_$^4$-Dibenzyl-2-iodoterephthalamide (80h).**

Prepared according to the general procedure A but 2.5 equiv of oxalyl chloride, 3.0 equiv of benzylamine and 6.0 equiv of triethylamine were used. Yield 90% as a white solid. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 9.22 (t, $J$ = 5.4 Hz, 1H), 9.00 (t, $J$ = 5.4 Hz, 1H), 8.38 (s, 1H), 7.95 (d, $J$ = 7.8 Hz, 1H), 7.46 (d, $J$ = 7.8 Hz, 1H), 7.43-7.24 (m, 10H), 4.49 (d, $J$ = 5.4 Hz, 1H), 4.47 (d, $J$ = 5.4 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 169.0, 164.7, 145.7, 139.7, 139.4, 138.1, 136.4, 128.81, 128.77, 128.4, 127.8, 127.7, 127.5, 127.4, 127.3, 93.9, 43.2, 43.0; IR (thin film) ν 3265, 3059, 3033, 1637, 1540, 1314, 698 $cm^{-1}$.



***N*-Benzyl-5-bromo-2-iodobenzamide (80i).**

Prepared according to the general procedure A. Yield 92% as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, $J$ = 8.4 Hz, 1H), 7.49 (d, $J$ = 2.4 Hz, 1H), 7.37-7.29 (m, 5H), 7.20 (dd, $J$ = 8.4, 2.4 Hz, 1H), 6.21 (brs, 1H), 4.59 (d, $J$ = 5.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.6, 143.5, 141.1, 137.1, 134.1, 131.1, 128.7, 128.0, 127.7, 122.4, 90.3, 44.2; IR (thin film) ν 3276, 3011, 1646, 1541, 1086, 1016, 977, 772, 700 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{11}BrINO$ 437.8966, found 437.8966.

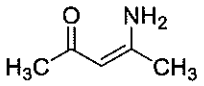


***N*-Benzyl-4-chloro-2-iodobenzamide (80j).**

Prepared according to the general procedure A. Yield 86% as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, $J$ = 1.5 Hz, 1H), 7.43-7.29 (m, 7H), 6.24 (brs, 1H), 4.63 (d, $J$ = 5.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.1, 140.2, 139.2, 137.2, 136.0, 128.8, 128.6, 128.3, 128.0, 127.6, 92.5, 44.1; IR (thin film) ν 3266, 3030, 1637, 1541, 827, 773, 742 cm$^{-1}$. These data matched to the literature values (Balkrishna *et al.*, 2010).

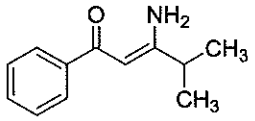
### 4.2.2 General Procedure B - Synthesis of Enaminones

To an oven-dried round bottom flask was added 1.0 equiv of 1,3-diketone compound, 5.0 equiv of $NH_4OAc$ and EtOH (0.5 M). The reaction mixture was heated to reflux for overnight. After cooling to room temperature, EtOH was removed. $H_2O$ was added and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated. The crude product was purified by column chromatography to afford the title compound.



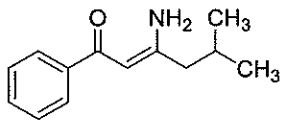
**(*Z*)-4-Aminopent-3-en-2-one (81a).**

To a round bottom flask with a suspension of acetylacetone (10.0 mmol) and $SiO_2$ (20 mg) in $H_2O$ (10 ml) was added $NH_4OH$ (28-30%, 1.32 mL) dropwise. After stirring overnight at room temperature, the mixture was extracted with $CH_2Cl_2$. The organic extracts were dried over anhydrous $Na_2SO_4$, filtered and concentrated to dryness to give the title compound as a yellow oil in 84% which was used without further purification. $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.59 (brs, 1H), 5.73 (brs, 1H), 4.92 (s, 1H), 1.92 (s, 3H), 1.82 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 196.1, 162.4, 95.2, 28.9, 21.8; IR (thin film) ν 3348, 3184, 1615, 1538, 1416, 1294 $cm^{-1}$. These data matched to the literature values (Dash *et al.*, 2009).



**(*Z*)-3-Amino-4-methyl-1-phenylpent-2-en-1-one (81b).**

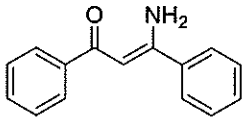
Prepared according to the general procedure B from 4-methyl-1-phenylpentane-1,3-dione (Singh *et al.*, 2010 and Bartlett *et al.*, 2011). Yield 65% as yellow crystals. $^1H$ NMR (300 MHz, $CDCl_3$) δ 10.37 (brs, 1H), 7.87 (dd, $J$ = 7.2, 1.5 Hz, 2H), 7.46-7.36 (m, 3H), 5.76 (s, 1H), 5.50 (brs, 1H), 2.44 (septet, $J$ = 6.9 Hz, 1H), 1.22 (d, $J$ = 6.9 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 190.0, 172.8, 140.6, 130.7, 128.2, 127.1, 89.4, 35.3, 21.2; IR (thin film) ν 3350, 3170, 2968, 1603, 1528, 1280, 755, 695 $cm^{-1}$. These data matched to the literature values (Sugiura *et al.*, 2009).



**(*Z*)-3-Amino-5-methyl-1-phenylhex-2-en-1-one (81c).**

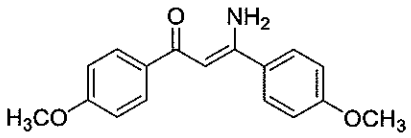
Prepared according to the general procedure B from 5-methyl-1-phenylhexane-1,3-dione (Singh *et al.*, 2010 and Bartlett *et al.*, 2011). Yield 47% as yellow crystals. $^1H$ NMR (300 MHz, $CDCl_3$) δ 10.31 (brs, 1H), 7.91 (dd, $J$ = 7.8, 2.4 Hz, 2H), 7.48-7.39 (m, 3H), 5.84 (brs, 1H), 5.72 (s, 1H), 2.11 (d, $J$ = 7.2 Hz, 2H), 2.00-1.93 (m, 1H), 0.97

(d, $J$ = 6.3 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.3, 167.0, 140.4, 130.8, 128.2, 127.1, 92.2, 46.2, 28.0, 22.4; IR (thin film) ν 3337, 3168, 2958, 1599, 1526, 1292, 744, 693 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{17}NO$ 204.1388, found 204.1380.



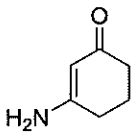

**(*Z*)-3-Amino-1,3-diphenylprop-2-en-1-one (81d).**

Prepared according to the general procedure B from commercially available 1,3-diphenylpropane-1,3-dione. Yield in quantitative as yellow crystals. $^1$H NMR (300 MHz, $CDCl_3$) δ 10.43 (brs, 1H), 7.98-7.93 (m, 2H), 7.70-7.53 (m, 2H), 7.52-7.39 (m, 6H), 6.15 (s, 1H), 5.46 (brs, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.8, 162.8, 140.1, 137.2, 130.8, 130.4, 128.8, 128.0, 127.0, 126.2, 91.5; IR (thin film) ν 3356, 3164, 3060, 1600, 1567, 1526, 1484, 1326, 1225, 772, 740, 694 cm$^{-1}$. These data matched to the literature values (Sugiura *et al.*, 2009).




**(*Z*)-3-Amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (81e).**

Prepared according to the general procedure B from commercially available 1,3-bis(4-methoxyphenyl)propane-1,3-dione. Yield 88% as yellow crystals. $^1$H NMR (300 MHz, $CDCl_3$) δ 10.39 (brs, 1H), 7.94 (d, $J$ = 9.0 Hz, 2H), 7.59 (d, $J$ = 9.0 Hz, 2H), 6.97 (d, $J$ = 9.0 Hz, 2H), 6.93 (d, $J$ = 9.0 Hz, 2H), 6.09 (s, 1H), 5.38 (brs, 1H), 3.86 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 188.8, 162.0, 161.8, 161.5, 133.1, 129.8, 129.0, 127.6, 114.2, 113.3, 90.7, 55.3, 55.2; IR (thin film) ν 3362, 1595, 1490, 1255, 1227, 1172, 1028, 840, 777 cm$^{-1}$. These data matched to the literature values (Yoshii *et al.*, 2013).

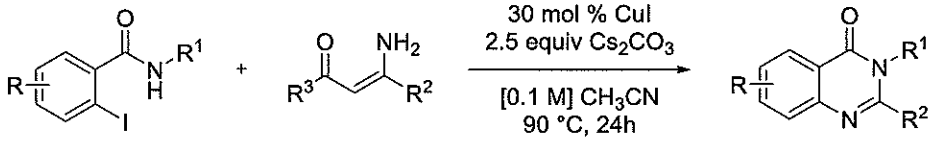


**3-Aminocyclohex-2-enone (87).**

To an oven-dried round bottom flask was added 1.0 equiv of 1,3-cyclohexanedione, 1.0 equiv of $NH_4OAc$ and EtOH (0.5 M). The reaction mixture was heated to reflux for overnight. After cooling to room temperature, EtOH was removed. The crude product was purified by column chromatography (6:1 EtOAc:MeOH) to give the title compound as a pale yellow solid in 90%. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 6.76 (brs, 2H), 4.93 (s, 1H), 2.27-2.22 (m, 2H), 2.04-1.99 (m, 2H), 1.81-1.72 (m, 2H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 195.3, 168.0, 97.9, 36.3, 28.4, 22.0; IR (thin film) ν 3336, 3143, 2940, 1671, 1542, 1259, 1190, 1145 $cm^{-1}$. These data matched to the literature values (Putkonen *et al.*, 2003).

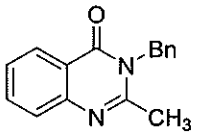
## 4.3 Synthesis of Quinazolinone Derivatives

**General Procedure C: Copper-Catalyzed Domino Reactions for Synthesis of Quinazolinone Derivatives.**



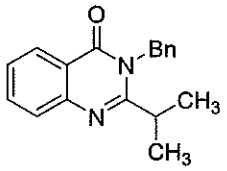

**80** 1.0 equiv + **81** 2.0 equiv → **82**

A 10 mL round bottom flask equipped with a magnetic stirring bar was charged with 2-iodobenzamide derivative (**80**) (0.5 mmol), *Z*-enaminone (**81**) (1.0 mmol), CuI (0.15 mmol) and $Cs_2CO_3$ (1.25 mmol) in $CH_3CN$ (5.0 mL). The reaction mixture was allowed to stir at 90 °C for 24 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by column chromatography to provide quinazolinone product (**82**).



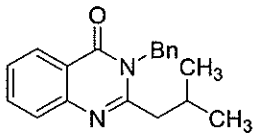
**3-Benzyl-2-methylquinazolin-4(3*H*)-one (82a).**

Prepared according to the general procedure C from *N*-benzyl-2-iodobenzamide (**80a**) and (*Z*)-4-aminopent-3-en-2-one (**81a**). Yield 97.6 mg (78%) as a yellow oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.30 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.73 (td, $J$ = 8.1, 1.5 Hz, 1H), 7.63 (d, $J$ = 8.1 Hz, 1H), 7.45 (td, $J$ = 8.1, 1.5 Hz, 1H), 7.35-7.27 (m, 3H), 7.20-7.17 (m, 2H), 5.38 (s, 2H), 2.53 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.4, 154.7, 147.3, 135.9, 134.4, 129.0, 127.7, 127.1, 126.7, 126.6, 126.5, 120.4, 47.1, 23.4; IR (thin film) ν 3064, 3032, 2960, 1668, 1598, 1389, 1341, 774, 717, 697 cm$^{-1}$. These data matched to the literature values (Kitching *et al.*, 2012).



**3-Benzyl-2-isopropylquinazolin-4(3*H*)-one (82b).**

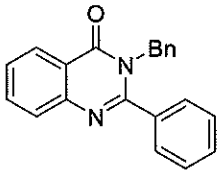
Prepared according to the general procedure C from *N*-benzyl-2-iodobenzamide (**80a**) and (*Z*)-3-amino-4-methyl-1-phenylpent-2-en-1-one (**81b**). Yield 41.8 mg (30%) as a pale yellow solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, $J$ = 7.8 Hz, 1H), 7.75-7.66 (m, 2H), 7.43 (t, $J$ = 7.8 Hz, 1H), 7.33-7.24 (m, 3H), 7.14 (d, $J$ = 7.2 Hz, 2H), 5.46 (s, 2H), 3.09 (septet, $J$ = 6.6 Hz, 1H), 1.26 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.5, 161.6, 147.4, 136.4, 134.0, 128.7, 127.3, 127.0, 126.8, 126.1, 125.9, 120.2, 45.7, 31.9, 21.2; IR (thin film) ν 2969, 1673, 1593, 774, 697 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{18}N_2O$ 279.1497, found 279.1498.



**3-Benzyl-2-isobutylquinazolin-4(3*H*)-one (82c).**

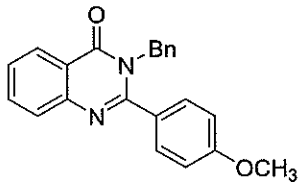
Prepared according to the general procedure C from *N*-benzyl-2-iodobenzamide (**80a**) and (*Z*)-3-amino-5-methyl-1-phenylhex-2-en-1-one (**81c**). Yield 51.2 mg (35%) as a

yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, $J$ = 7.5 Hz, 1H), 7.77-7.66 (m, 2H), 7.46 (t, $J$ = 7.8 Hz, 1H), 7.34-7.23 (m, 3H), 7.16 (d, $J$ = 6.9, 2H), 5.42 (s, 2H), 2.63 (d, $J$ = 6.9 Hz, 2H), 2.37-2.23 (m, 1H), 0.98 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.3, 156.2, 146.9, 135.9, 134.0, 128.5, 127.2, 126.7, 126.1, 126.0, 119.9, 46.1, 43.3, 26.8, 22.1; IR (thin film) ν 2957, 1671, 1595, 1168, 773, 697 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{20}N_2O$ 293.1654, found 293.1655.




**3-Benzyl-2-phenylquinazolin-4(3*H*)-one (82d).**

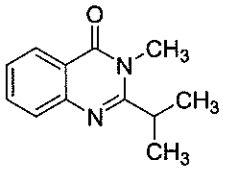
Prepared according to the general procedure C from *N*-benzyl-2-iodobenzamide (**80a**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**81d**). Yield 110.9 mg (71%) as a pale yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, $J$ = 7.5 Hz, 1H), 7.79-7.77 (m, 2H), 7.56-7.33 (m, 6H), 7.22-7.20 (m, 3H), 6.93-6.92 (m, 2H), 5.28 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.5, 156.4, 147.3, 136.6, 135.3, 134.6, 129.9, 128.6, 128.5, 128.0, 127.6, 127.4, 127.2, 127.1, 127.0, 120.9, 48.8; IR (thin film) ν 3063, 1675, 1568, 1375, 1245, 1148, 970, 771, 697 cm$^{-1}$. These data matched to the literature values (Liu *et al.*, 2005).




**3-Benzyl-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one (82e).**

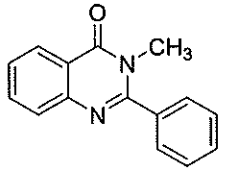
Prepared according to the general procedure C from *N*-benzyl-2-iodobenzamide (**80a**) and (*Z*)-3-amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**81e**). Yield 85.6 mg (50%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, $J$ = 7.8 Hz, 1H), 7.85-7.65 (m, 2H), 7.55-7.40 (m, 1H), 7.30 (d, $J$ = 8.1 Hz, 2H), 7.25-7.15 (m, 3H), 6.97-6.94 (m, 2H), 6.88 (d, $J$ = 8.1 Hz, 2H), 5.28 (s, 2H), 3.79 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.3, 160.6, 156.1, 147.0, 136.5, 134.3, 129.4, 128.3, 127.3, 127.2, 126.8,

126.6, 120.4, 113.7, 55.2, 48.8; IR (thin film) ν 3031, 2959, 1675, 1607, 1250, 1177, 1028, 833, 774 $cm^{-1}$. These data matched to the literature values (Wang *et al.*, 2013).



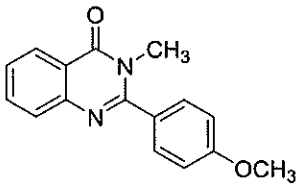
**2-Isopropyl-3-methylquinazolin-4(3*H*)-one (82f).**

Prepared according to the general procedure C from 2-iodo-*N*-methylbenzamide (**80b**) and (*Z*)-3-amino-4-methyl-1-phenylpent-2-en-1-one (**81b**). Yield 25.3 mg (25%) as a yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.25 (d, $J$ = 7.8 Hz, 1H), 7.73-7.64 (m, 2H), 7.42 (t, $J$ = 7.8 Hz, 1H), 3.67 (s, 3H), 3.21 (septet, $J$ = 6.6 Hz, 1H), 1.39 (d, $J$ = 6.6 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 162.8, 161.1, 147.3, 134.0, 127.0, 126.6, 126.2, 120.2, 32.2, 30.1, 20.8; IR (thin film) ν 2970, 1674, 1591, 775, 697 $cm^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{14}N_2O$ 203.1184, found 203.1184.



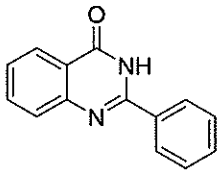
**3-Methyl-2-phenylquinazolin-4(3*H*)-one (82g).**

Prepared according to the general procedure C from 2-iodo-*N*-methylbenzamide (**80b**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**81d**). Yield 82.7 mg (70%) as a pale yellow solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.33 (d, $J$ = 7.5 Hz, 1H), 7.76-7.74 (m, 2H), 7.56-7.47 (m, 6H), 3.50 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 162.7, 156.1, 147.3, 135.4, 134.3, 130.1, 128.9, 128.0, 127.5, 127.0, 126.7, 120.6, 34.2; IR (thin film) ν 3064, 1671, 1564, 1354, 1050, 771, 698 $cm^{-1}$. These data matched to the literature values (Hikawa *et al.*, 2012).



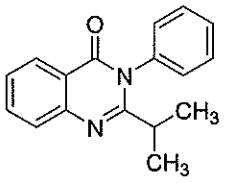
**2-(4-Methoxyphenyl)-3-methylquinazolin-4(3*H*)-one (82h).**

Prepared according to the general procedure C from 2-iodo-*N*-methylbenzamide (**80b**) and (*Z*)-3-amino-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**81e**). Yield 86.5 mg (65%) as a white solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, $J$ = 8.1 Hz, 1H), 7.67-7.65 (m, 2H), 7.49 (d, $J$ = 8.4 Hz, 2H), 7.44-7.39 (m, 1H), 6.98 (d, $J$ = 8.4 Hz, 2H), 3.82 (s, 3H), 3.47 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.6, 160.6, 155.7, 147.0, 133.9, 129.5, 127.4, 127.0, 126.4, 126.3, 120.0, 113.9, 55.2, 34.1; IR (thin film) ν 3004, 2958, 1671, 1607, 1589, 1253, 1176, 1025, 834, 774, 698 cm$^{-1}$. These data matched to the literature values (Deepthi *et al.*, 2000).



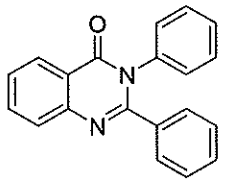
**2-Phenylquinazolin-4(3*H*)-one (82i).**

Prepared according to the general procedure C from 2-iodobenzamide (**80c**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**81d**). Yield 53.3 mg (48%) as a pale yellow solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 11.62 (brs, 1H), 8.35-8.31 (m, 1H), 8.28-8.24 (m, 2H), 7.87-7.77 (m, 2H), 7.60-7.58 (m, 3H), 7.54-7.48 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.1, 151.9, 149.6, 134.9, 132.8, 131.6, 129.0, 128.0, 127.5, 126.8, 126.4, 120.8; IR (thin film) ν 3080, 1668, 1297, 768, 694 cm$^{-1}$. These data matched to the literature values (Wang *et al.*, 2013).



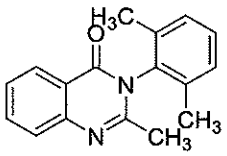
**2-Isopropyl-3-methylquinazolin-4(3*H*)-one (82j).**

Prepared according to the general procedure C from 2-iodo-*N*-phenylbenzamide (**80d**) and (*Z*)-3-amino-4-methyl-1-phenylpent-2-en-1-one (**81b**). Yield 44.9 mg (34%) as a yellow solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, $J$ = 7.5 Hz, 1H), 7.78-7.70 (m, 2H), 7.59-7.41 (m, 4H), 7.26 (d, $J$ = 6.6 Hz, 2H), 2.69 (septet, $J$ = 6.6 Hz, 1H), 1.22 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.7, 161.6, 147.8, 137.5, 134.4, 129.8, 129.1, 128.4, 127.2, 127.0, 126.4, 120.8, 32.4, 21.3; IR (thin film) ν 3064, 2972, 1683, 1588, 773, 697 cm$^{-1}$. These data matched to the literature values (Ozaki *et al.*, 1985).



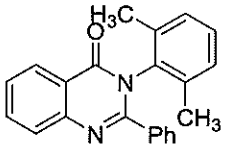
**2,3-Diphenylquinazolin-4(3*H*)-one (82k).**

Prepared according to the general procedure C from 2-iodo-*N*-phenylbenzamide (**80d**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**81d**). Yield 44.8 mg (30%) as a pale yellow solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, $J$ = 8.1 Hz, 1H), 7.84-7.77 (m, 2H), 7.55-7.49 (m, 1H), 7.35-7.14 (m, 10H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.3, 155.3, 147.6, 137.8, 135.5, 134.8, 129.4, 129.2, 129.0, 128.5, 128.0, 127.8, 127.4, 127.3, 121.0; IR (thin film) ν 3064, 1683, 1559, 1340, 1271, 770, 697 cm$^{-1}$. These data matched to the literature values (Liu *et al.*, 2005).



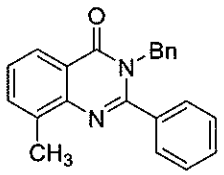
**2-Methyl-3-(2,6-dimethylphenyl)quinazolin-4(3*H*)-one (82l).**

Prepared according to the general procedure C from 2-iodo-*N*-(2,6-dimethylphenyl)-benzamide (**80e**) and (*Z*)-4-aminopent-3-en-2-one (**81a**). Yield 70.0 mg (53%) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, $J$ = 7.8 Hz, 1H), 7.79 (t, $J$ = 8.1 Hz, 1H), 7.70 (d, $J$ = 7.8 Hz, 1H), 7.48 (t, $J$ = 7.5 Hz, 1H), 7.33-7.21 (m, 3H), 2.15 (s, 3H), 2.09 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 161.1, 154.4, 147.8, 136.0, 135.0, 134.6, 129.3, 129.1, 127.2, 126.8, 126.6, 120.7, 23.1, 17.7; IR (thin film) ν 2923, 1683, 1603, 1339, 773, 700 cm$^{-1}$. These data matched to the literature values (Boltze *et al.*, 1963).



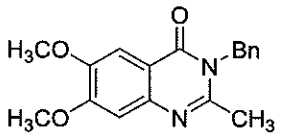
**3-(2,6-Dimethylphenyl)-2-phenylquinazolin-4(3*H*)-one (82m).**

Prepared according to the general procedure C from 2-iodo-*N*-(2,6-dimethylphenyl)-benzamide (**80e**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**81d**). Yield 57.1 mg (35%) as a pale yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, $J$ = 7.8 Hz, 1H), 7.88-7.82 (m, 2H), 7.55 (td, $J$ = 8.1, 1.8 Hz, 1H), 7.35 (d, $J$ = 7.5 Hz, 2H), 7.31-7.11 (m, 4H), 7.03 (d, $J$ = 7.5 Hz, 2H), 2.10 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 161.4, 155.3, 148.0, 136.3, 135.5, 134.8, 129.8, 129.1, 128.6, 128.4, 127.8, 127.7, 127.5, 127.3, 127.2, 120.8, 18.3; IR (thin film) ν 2923, 1685, 1560, 1471, 1330, 1271, 771, 697 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{18}N_2O$ 327.1497, found 327.1486.



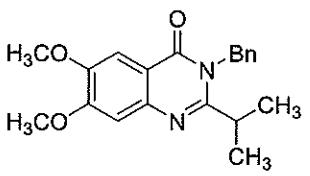
**3-Benzyl-8-methyl-2-phenylquinazolin-4(3*H*)-one (82n).**

Prepared according to the general procedure C from *N*-benzyl-2-iodo-3-methyl-benzamide (**80f**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**81d**). Yield 55.5 mg (34%) as a pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, $J$ = 7.8 Hz, 1H), 7.63 (d, $J$ = 6.9 Hz, 1H), 7.48-7.38 (m, 6H), 7.21-7.19 (m, 3H), 7.00-6.92 (m, 2H), 5.29 (s, 2H), 2.61 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.0, 154.8, 146.0, 136.8, 136.3, 135.8, 135.1, 129.8, 128.5, 128.4, 127.3, 127.0, 126.7, 124.7, 120.8, 48.8, 17.4; IR (thin film) ν 3031, 2924, 1671, 1591, 1455, 1357, 1254, 770, 700 cm$^{-1}$. These data matched to the literature values (Wang *et al.*, 2013).



**3-Benzyl-6,7-dimethoxy-2-methylquinazolin-4(3*H*)-one (82o).**

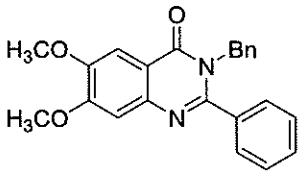
Prepared according to the general procedure C from *N*-benzyl-2-iodo-4,5-dimethoxy-benzamide (**80g**) and (*Z*)-4-aminopent-3-en-2-one (**81a**). Yield 60.0 mg (38%) as yellow crystals. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.38-7.21 (m, 5H), 7.10 (s, 1H), 5.44 (s, 2H), 4.03 (s, 6H), 2.57 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 161.6, 155.1, 153.5, 148.9, 143.3, 135.9, 128.9, 127.7, 126.5, 113.6, 107.0, 106.0, 56.3, 56.2, 47.2, 23.2; IR (thin film) ν 2962, 1662, 1498, 1398, 1245, 1026, 774, 703 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{18}N_2O_3$ 311.1395, found 311.1382.



**3-Benzyl-2-isopropyl-6,7-dimethoxyquinazolin-4(3*H*)-one (82p).**

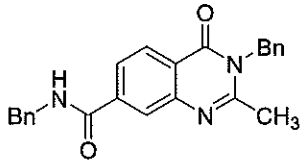
Prepared according to the general procedure C from *N*-benzyl-2-iodo-4,5-dimethoxy-benzamide (**80g**) and (*Z*)-3-amino-4-methyl-1-phenylpent-2-en-1-one (**81b**). Yield

59.2 mg (35%) as a pale yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.33-7.21 (m, 3H), 7.13 (d, $J$ = 7.2 Hz, 2H), 7.08 (s, 1H), 5.45 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.07 (septet, $J$ = 6.6 Hz, 1H), 1.24 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 162.0, 160.6, 155.0, 148.8, 143.8, 136.7, 128.9, 127.5, 126.1, 113.6, 107.5, 106.0, 56.3, 56.2, 45.9, 32.0, 21.4; IR (thin film) ν 2966, 1664, 1498, 1405, 1235, 1007, 866, 735 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{22}N_2O_3$ 339.1708, found 339.1693.




**3-Benzyl-6,7-dimethoxy-2-phenylquinazolin-4(3*H*)-one (82q).**

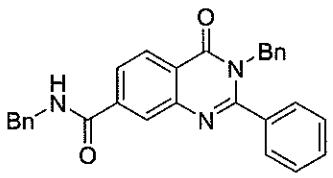
Prepared according to the general procedure C from *N*-benzyl-2-iodo-4,5-dimethoxy-benzamide (**80g**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**81d**). Yield 135.9 mg (73%) as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.49-7.30 (m, 5H), 7.22-7.18 (m, 4H), 6.95-6.91 (m, 2H), 5.28 (s, 2H), 4.02 (s, 3H), 3.98 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 161.8, 155.3, 155.2, 149.4, 143.6, 136.8, 135.4, 129.8, 128.6, 128.5, 128.1, 127.7, 127.0, 114.3, 108.0, 106.0, 56.4, 48.8; IR (thin film) ν 3006, 2962, 1663, 1496, 1246, 1017, 869, 756, 702 cm$^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{20}N_2O_3$ 373.1552, found 373.1555.




***N*,3-Dibenzyl-2-methyl-4-oxo-3,4-dihydroquinazoline-7-carboxamide (82r).**

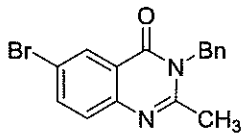
Prepared according to the general procedure C from $N^1$,$N^4$-dibenzyl-2-iodo-terephthalamide (**80h**) and (*Z*)-4-aminopent-3-en-2-one (**81a**) but DMF was used as solvent instead of $CH_3CN$. Yield 55.6 mg (29%) as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, $J$ = 8.1 Hz, 1H), 7.99 (s, 1H), 7.90 (d, $J$ = 8.1 Hz, 1H), 7.38-7.26 (m, 8H), 7.19 (d, $J$ = 7.2 Hz, 2H), 6.72 (brs, 1H), 5.38 (s, 2H), 4.67 (d, $J$ = 5.4 Hz, 2H), 2.56 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.2, 161.7, 156.2, 146.6,

140.3, 137.8, 135.4, 129.2, 129.0, 128.1, 127.9, 126.7, 125.4, 124.7, 122.2, 47.5, 44.5, 23.3; IR (thin film) ν 3279, 3063, 3033, 1647, 1597, 1541, 1304, 748, 696 $cm^{-1}$.



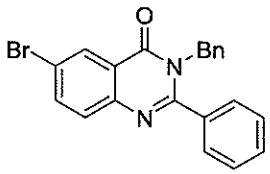
**_N_,3-Dibenzyl-4-oxo-2-phenyl-3,4-dihydroquinazoline-7-carboxamide (82s).**

Prepared according to the general procedure C from $N^1$,$N^4$-dibenzyl-2-iodo-terephthalamide (**80h**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**81d**) but DMF was used as solvent instead of $CH_3CN$. Yield 91.3 mg (41%) as a yellow solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.1 Hz, 1H), 8.05 (s, 1H), 7.90 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.49-7.22 (m, 10H), 7.20-7.18 (m, 3H), 6.91-6.87 (m, 3H), 5.23 (s, 2H), 4.61 (d, *J* = 5.4 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 166.4, 162.0, 157.4, 147.0, 140.3, 137.8, 136.2, 134.8, 130.2, 128.9, 128.70, 128.66, 128.00, 127.95, 127.84, 127.79, 127.7, 127.0, 125.8, 122.6, 49.1, 44.4; IR (thin film) ν 3316, 3063, 3031, 1654, 1561, 1542, 1311, 1237, 753, 697 $cm^{-1}$.



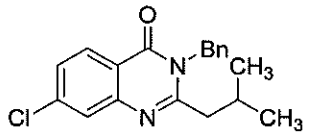
**3-Benzyl-6-bromo-2-methylquinazolin-4(3*H*)-one (82t).**

Prepared according to the general procedure C from *N*-benzyl-5-bromo-2-iodo-benzamide (**80i**) and (*Z*)-4-aminopent-3-en-2-one (**81a**). Yield 32.9 mg (20%) as a pale yellow solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 2.1 Hz, 1H), 7.81 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.37-7.27 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 2H), 5.38 (s, 2H), 2.54 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 161.3, 155.2, 146.1, 137.6, 135.5, 129.6, 129.0, 128.6, 127.9, 126.5, 121.8, 120.0, 47.3, 23.4; IR (thin film) ν 3064, 2926, 1676, 1595, 1467, 1382, 1335, 833, 724 $cm^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{13}BrN_2O$ 329.0289, found 329.0297.




**3-Benzyl-8-methyl-2-phenylquinazolin-4(3*H*)-one (82u).**

Prepared according to the general procedure C from *N*-benzyl-5-bromo-2-iodo-benzamide (**80i**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**81d**). Yield 88.0 mg (45%) as a pale yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, $J$ = 2.1 Hz, 1H), 7.82 (dd, $J$ = 8.7, 2.1 Hz, 1H), 7.61 (d, $J$ = 8.4 Hz, 1H), 7.48-7.32 (m, 5H), 7.21-7.18 (m, 3H), 6.92-6.90 (m, 2H), 5.26 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 161.3, 156.8, 146.1, 137.7, 136.3, 135.0, 130.1, 129.6, 129.4, 128.7, 128.6, 128.0, 127.6, 127.0, 122.2, 120.7, 49.0; IR (thin film) ν 3064, 1681, 1559, 1467, 1232, 833, 772, 700 cm$^{-1}$. These data matched to the literature values (Cabrera-Rivera *et al.*, 2012).

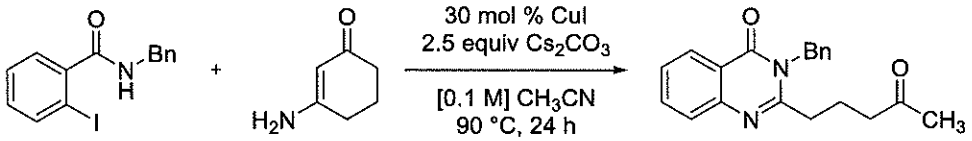



**3-Benzyl-7-chloro-2-isobutylquinazolin-4(3*H*)-one (82v).**

Prepared according to the general procedure C from *N*-benzyl-4-chloro-2-iodo-benzamide (**80j**) and (*Z*)-3-amino-5-methyl-1-phenylhex-2-en-1-one (**81c**). Yield 88.2 mg (54%) as a pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, $J$ = 8.7 Hz, 1H), 7.68 (d, $J$ = 1.8 Hz, 1H), 7.40 (dd, $J$ = 8.7, 1.8 Hz, 1H), 7.35-7.26 (m, 3H), 7.15 (d, $J$ = 6.6 Hz, 2H), 5.39 (s, 2H), 2.61 (d, $J$ = 6.6 Hz, 2H), 2.37-2.23 (m, 1H), 0.97 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 161.9, 157.8, 148.1, 140.4, 135.8, 128.8, 128.4, 127.6, 127.0, 126.5, 126.2, 118.6, 46.4, 43.5, 26.9, 22.3; IR (thin film) ν 2958, 1678, 1593, 1456, 1394, 1332, 1166, 879, 731, 696 cm$^{-1}$. These data matched to the literature values (Liu a *et al.*, 2005).

## 4.4 Experiments to Investigate the Effect of the Geometry of Enaminones

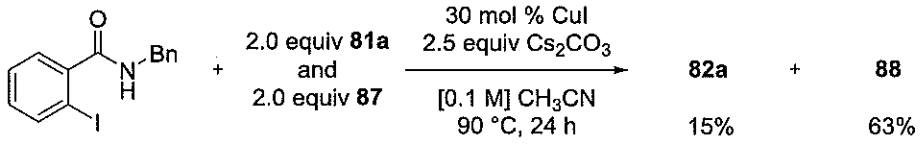
**Scheme 18a:**




**80a** 1.0 equiv + **87** 2.0 equiv → **88** 14%

A 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-benzyl-2-iodobenzamide (**80a**) (0.5 mmol), 3-aminocyclohex-2-enone (**87**) (1.0 mmol), CuI (0.15 mmol) and $Cs_2CO_3$ (1.25 mmol) in $CH_3CN$ (5.0 mL). The reaction mixture was allowed to stir at 90 °C for 24 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with 1M HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by column chromatography (2% $MeOH/CH_2Cl_2$) to provide **88** in 14% yield as a white solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.32 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.75 (td, $J$ = 8.1, 1.5 Hz, 1H), 7.66 (d, $J$ = 8.1 Hz, 1H), 7.47 (td, $J$ = 8.1, 1.5 Hz, 1H), 7.34-7.25 (m, 3H), 7.20 (d, $J$ = 8.1 Hz, 2H), 5.48 (s, 2H), 2.76 (t, $J$ = 7.5 Hz, 2H), 2.57 (t, $J$ = 6.6 Hz, 2H), 2.11-2.02 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 208.2, 162.5, 156.6, 147.2, 136.3, 134.3, 128.9, 127.6, 127.5, 127.2, 127.1, 126.9, 126.6, 126.4, 120.4, 46.2, 42.3, 34.0, 30.0, 20.9; IR (thin film) ν 2952, 1673, 1595, 1454, 1170, 976, 879, 775, 697 $cm^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{20}N_2O_2$ 321.1603, found 321.1603.

**Scheme 18b:**

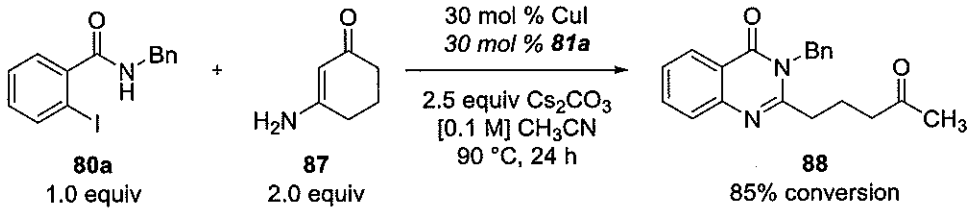



**80a** 1.0 equiv → **82a** 15% + **88** 63%

A sealed tube equipped with a magnetic stirring bar was charged with *N*-benzyl-2-iodobenzamide (**80a**) (0.1 mmol), (*Z*)-4-aminopent-3-en-2-one (**81a**) (0.2 mmol), 3-aminocyclohex-2-enone (**87**) (0.2 mmol), CuI (0.03 mmol) and $Cs_2CO_3$ (0.25 mmol)

in $CH_3CN$ (1.0 mL). The reaction mixture was allowed to stir at 90 °C for 24 hours. After cooling down to room temperature, the reaction mixture was quenched with sat. $NH_4Cl$ and extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated. The $^1H$ NMR spectrum of crude mixture showed 1:4 ratio of **82a** and **88**. The isolated yields were 15% and 63% respectively.

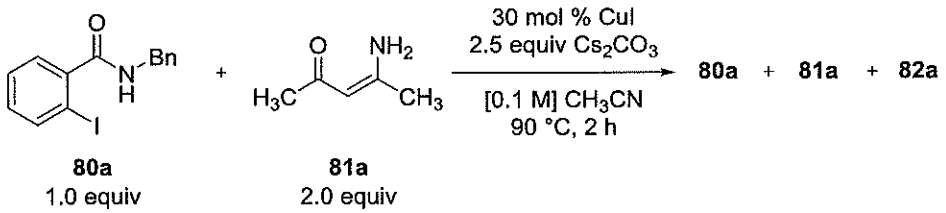
**Scheme 18c**:




A sealed tube equipped with a magnetic stirring bar was charged with *N*-benzyl-2-iodobenzamide (**80a**) (0.1 mmol), (*Z*)-4-aminopent-3-en-2-one (**81a**) (0.03 mmol), 3-aminocyclohex-2-enone (**87**) (0.2 mmol), CuI (0.03 mmol) and $Cs_2CO_3$ (0.25 mmol) in $CH_3CN$ (1.0 mL). The reaction mixture was allowed to stir at 90 °C for 24 hours. After cooling down to room temperature, the reaction mixture was quenched with sat. $NH_4Cl$ and extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated. The $^1H$ NMR spectrum of residue showed 1:6 ratio of **80a** and **88**.

## 4.5 Mechanism Investigation Experiments

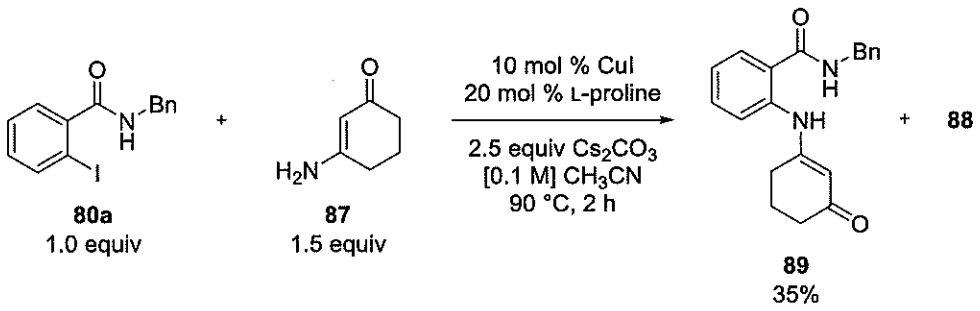
**Scheme 20a**:




The reaction was performed according to the general procedure C from *N*-benzyl-2-iodobenzamide (**80a**) and (*Z*)-4-aminopent-3-en-2-one (**81a**). The reaction time was

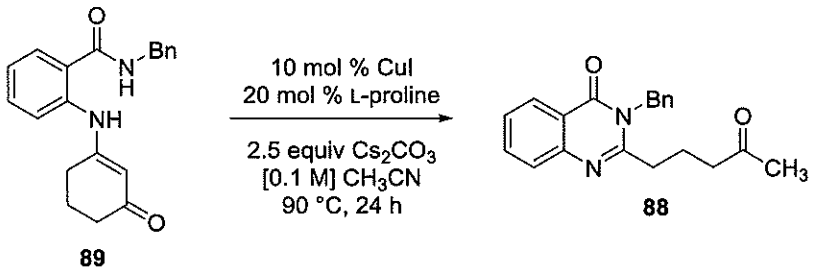
reduced to 2 hours and the reaction mixture was quenched with sat. $NH_4Cl$. The $^1H$ NMR spectrum of crude mixture showed 1:1 ratio of **80a** and **82a** along with the remaining **81a**.

**Scheme 20b**:




A 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-benzyl-2-iodobenzamide (**80a**) (0.5 mmol), 3-aminocyclohex-2-enone (**87**) (0.75 mmol), CuI (0.05 mmol), L-proline (0.1 mmol) and $Cs_2CO_3$ (1.25 mmol) in $CH_3CN$ (5.0 mL). The reaction mixture was allowed to stir at 90 °C for 2 hours. The $^1H$ NMR spectrum of crude mixture showed 1:1 ratio of *N*-benzyl-2-(3-oxocyclohex-1-enylamino)benzamide (**89**) and **88**. The crude mixture was purified by column chromatography (3:1 hexanes:EtOAc) to provide **89** in 56.1 mg (35% yield) as a yellow solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.44 (brs, 1H), 7.51 (dd, $J$ = 7.8, 1.2 Hz, 1H), 7.43 (d, $J$ = 7.8 Hz, 1H), 7.36-7.26 (m, 6H), 7.00 (td, $J$ = 7.8, 1.2 Hz, 1H), 5.72 (s, 1H), 4.56 (d, $J$ = 5.7 Hz, 2H), 2.46 (t, $J$ = 6.0 Hz, 2H), 2.30 (t, $J$ = 6.0 Hz, 2H), 1.99-1.94 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 199.2, 168.6, 160.8, 139.3, 137.8, 131.8, 128.8, 127.9, 127.8, 127.7, 124.0, 123.2, 122.8, 101.0, 43.9, 36.4, 30.4, 21.6; IR (thin film) ν 2925, 1670, 1594, 1302, 1168, 976, 773, 697 $cm^{-1}$; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{20}N_2O_2$ 321.1603, found 321.1603.

**Scheme 20c**:




**89** **88**

A 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-benzyl-2-(3-oxocyclohex-1-enylamino)benzamide (**89**) (0.18 mmol), CuI (0.018 mmol), L-proline (0.036 mmol) and $Cs_2CO_3$ (0.45 mmol) in $CH_3CN$ (2.0 mL). The reaction mixture was allowed to stir at 90 °C for 24 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with sat. $NH_4Cl$ and extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated. The $^1H$ NMR spectrum of residue showed only signals of **88**.

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# APPENDIX

Organic & Biomolecular Chemistry

COMMUNICATION

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# Syntheses of quinazolinones from 2-iodobenzamides and enaminones *via* copper-catalyzed domino reactions†

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**N-Substituted 2-iodobenzamides and enaminones undergo cascade transformations to achieve quinazolinones *via* a copper-catalyzed Ullmann-type coupling, a Michael addition and a retro-Mannich reaction. A unique stereochemical feature of this domino process was that *Z*-enaminones reacted without external ligands, whereas *E*-enaminones required the assistance of ligands.**

Transition metal-catalyzed domino reactions have been one of the most selective tools for synthesizing complex organic molecules.[1] Especially, the copper-catalyzed Ullmann N-arylation[2] has been a powerful strategy for constructing N-containing heterocycles.[3] Quinazolinones are one of the most important N-containing heterocyclic compounds due to their common occurrence in alkaloid natural products.[4] Furthermore, they also show a variety of biological activities.[5] Therefore, a number of methodologies have been developed towards quinazolinone synthesis.[6]

Recently, Fu described a remarkable domino synthesis of quinazolinone derivatives *via* an Ullmann-type coupling followed by aerobic oxidation, starting from 2-halobenzamides and amines.[7] This system provided a powerful synthetic tool to synthesize aromatic-substituted quinazolinones (Fig. 1a). Later, Ma also reported the elegant domino reactions of 2-bromobenzamides and amides catalyzed by Cu(I), to facilitate aryl amidation followed by dehydration.[8] In Ma's system, a variety of substituted quinazolinones were possible. However, cyclization with the use of HMDS/$ZnCl_2$ was required (Fig. 1b). We have undertaken studies aimed specifically at copper-catalyzed domino reactions to produce N-containing heterocyclic compounds under mild and simple reaction conditions. During our studies, we found that N-substituted 2-iodobenzamides and enaminones could undergo domino processes in the presence of CuI to furnish quinazolinone derivatives (Fig. 1c). In our catalytic system, the enaminone serves as a stable surrogate of an unstable imine equivalent, to construct the quinazolinone core structure in one cascade process. We believe that the enaminone could be a synthetically useful coupling partner in Ullmann-type reactions for the synthesis of N-containing heterocyclic molecules. Furthermore, a variety of enaminones have been readily prepared from the condensation reactions of nitrogen sources and 1,3-diketone compounds.[9]

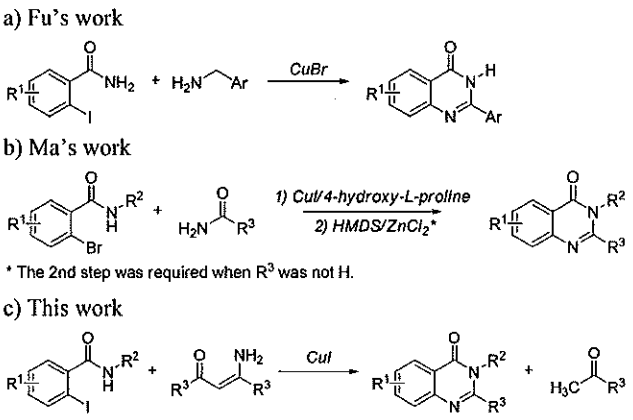


**Fig. 1** Copper-catalyzed domino reactions for quinazolinone synthesis.

To investigate our reaction, we initially began with reaction optimization. *N*-Benzyl-2-iodobenzamide (**1a**), (*Z*)-4-aminopent-3-en-2-one (**2a**), and the use of CuI as the catalyst were selected as the model system (Table 1). The reaction's outcome depended on the nature of the base, and the use of $K_2CO_3$ gave no reaction (entry 1). However, quinazolinone **3** was obtained in 14% yield by changing the base from $K_2CO_3$ to $Cs_2CO_3$ under otherwise identical conditions (entry 2). 2-Iodobenzamide **1a** was completely consumed when the reaction was carried out at 90 °C, and gave the highest yield (entry 3). The effects of the solvent were also investigated, and $CH_3CN$ was chosen as the optimal solvent (entries 3–5). An investigation for finding the optimal source of copper was undertaken (entries 3, 6, 7 and 8), revealing that CuI was the most suitable for this domino transformation. Interestingly, in the presence

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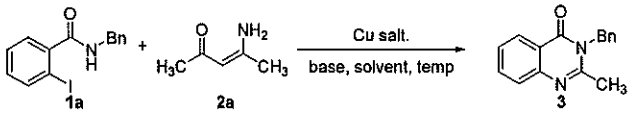
†Electronic supplementary information (ESI) available: Including experimental data and characterization data. See DOI: 10.1039/c4ob00400k

**Table 1** Copper-catalyzed domino reactions of *N*-benzyl 2-iodobenzamide (**1a**) and enaminone (**2a**): optimization of reaction conditions[a]




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

| Entry | Cu salt | Base | Solvent | Temp (°C) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | CuI | $K_2CO_3$ | $CH_3CN$ | 60 | 0 |
| 2 | CuI | $Cs_2CO_3$ | $CH_3CN$ | 60 | 14 |
| 3 | CuI | $Cs_2CO_3$ | $CH_3CN$ | 90 | 78 |
| 4 | CuI | $Cs_2CO_3$ | DMSO | 90 | 49 |
| 5 | CuI | $Cs_2CO_3$ | DMF | 90 | 56 |
| 6 | CuCl | $Cs_2CO_3$ | $CH_3CN$ | 90 | 62 |
| 7 | CuBr | $Cs_2CO_3$ | $CH_3CN$ | 90 | 50 |
| 8 | $Cu(OAc)_2$ | $Cs_2CO_3$ | $CH_3CN$ | 90 | 46 |
| 9 | CuI + (L-proline)[c] | $Cs_2CO_3$ | $CH_3CN$ | 90 | 51 |

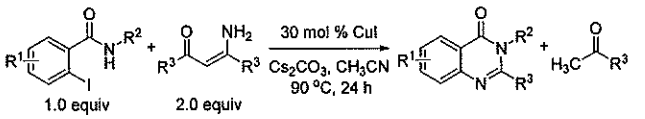
[a] Reaction conditions: all reactions were performed with 0.3 mmol of **1a**, 30 mol% of Cu salt, 2.0 equiv. of **2a**, 2.5 equiv. of base, and 3.0 mL of solvent, for 24 h. [b] Isolated yield. [c] Reaction was performed with 30 mol% of L-proline.

of L-proline as a ligand, the reaction gave a lower yield (entry 9). Based on this result, we believe that **2a** played not only the role of a substrate but also as a ligand for this transformation, corresponding to a recent finding from Liu.[10] Note that, 2.0 equiv. of **2a** were crucial to promoting the highest product yields. The use of 1.0 equiv. of **2a** with 30 mol% L-proline and without L-proline under the optimal conditions gave 31% and 36% yields respectively.

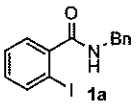
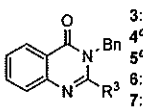
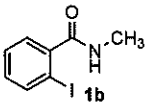
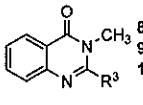
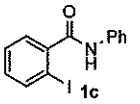
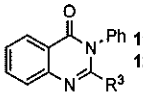
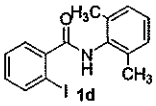
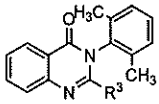
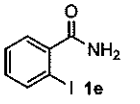
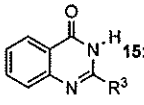
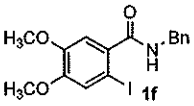
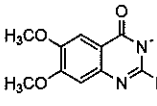
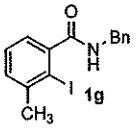
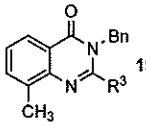
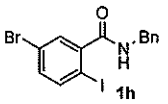
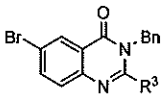
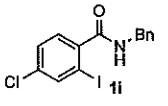
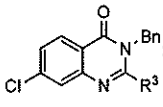
After the optimized conditions had been established, the scope of the substrates in the copper-catalyzed domino reactions was investigated. A variety of N-substituted benzamides and enaminones were applicable for the copper-catalyzed domino reactions (Table 2). As the size of the substituents on the enaminones increased, the yields of corresponding quinazolinones were dramatically diminished (entry 1, compounds **3–5**), demonstrating that steric hindrance, especially the substituents on the enaminones, played a crucial role in determining the product yields.

On the other hand, the enaminones with aryl substituents were efficiently converted to the corresponding quinazolinones (entry 1, compounds **6** and **7**). *N*-Phenyl substituted benzamides (**1c** and **1d**) gave low yields due to their low nucleophilicities for Michael additions. In addition, the comparable yields of **12** and **14** suggested that the steric hindrance of the *N*-phenyl substituted benzamides had a minor impact on the reactions (entries 3 and 4). Moreover, the moderate yield from the reaction of **1e**, a naked amide, and a phenyl-substituted enaminone suggested that the nucleophilicity of the amide nitrogen dictated the product yield (entry 5). *N*-Benzyl-2-iodobenzamide (**1f**), with electron-donating substituents on the aromatic ring, was compatible in the domino reaction (entry 6). However, the reaction of *N*-benzyl-3-methyl-2-iodobenzamide (**1g**) gave a low yield (entry 7). The results indicated that accessibility to the C–I bond was vital. The Br-substituted quinazolinones, derived from *N*-benzyl-5-bromo-2-iodobenzamide

**Table 2** CuI-catalyzed domino syntheses of quinazolinones from 2-iodobenzamides and *Z*-enaminones[a]



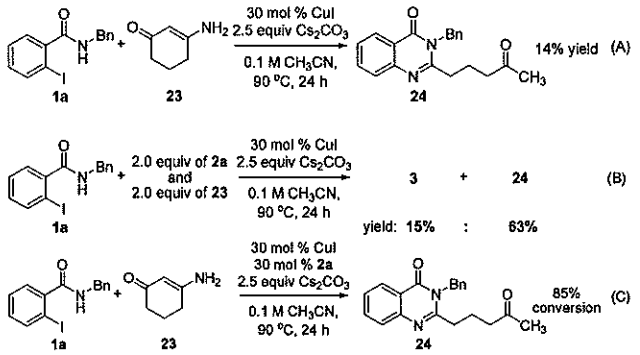

1.0 equiv 2.0 equiv

| Entry | 2-Iodobenzamides | Quinazolinones (% yield)[b] |
|---|---|---|
| 1 |  **1a** |  **3**: $R^3 = CH_3$ (78%); **4**[c]: $R^3 = i$-Pr (30%); **5**[d]: $R^3 = i$-Bu (35%); **6**: $R^3$ = Ph (71%); **7**: $R^3 = p$-$OCH_3$-Ph (50%) |
| 2 |  **1b** |  **8**[c]: $R^3 = i$-Pr (25%); **9**: $R^3$ = Ph (70%); **10**: $R^3 = p$-$OCH_3$-Ph (65%) |
| 3 |  **1c** |  **11**[c]: $R^3 = i$-Pr (34%); **12**: $R^3$ = Ph (30%) |
| 4 |  **1d** |  **13**: $R^3 = CH_3$ (53%); **14**: $R^3$ = Ph (35%) |
| 5 |  **1e** |  **15**: $R^3$ = Ph (48%) |
| 6 |  **1f** |  **16**: $R^3 = CH_3$ (38%); **17**[c]: $R^3 = i$-Pr (35%); **18**: $R^3$ = Ph (73%) |
| 7 |  **1g** |  **19**: $R^3$ = Ph (34%) |
| 8 |  **1h** |  **20**: $R^3 = CH_3$ (20%); **21**: $R^3$ = Ph (45%) |
| 9 |  **1i** |  **22**[d]: $R^3 = i$-Bu (54%) |

[a] Reaction conditions: all reactions were carried out with 0.5 mmol of 2-iodobenzamides, and 2.5 equiv. of $Cs_2CO_3$, in 0.1 M $CH_3CN$. [b] Isolated yield. [c] 3-Amino-4-methyl-1-phenylpent-2-en-1-one was used. [d] 3-Amino-5-methyl-1-phenylhex-2-en-1-one was used.

(**1h**), were isolated in low to moderate yields, showing that **1h** was fairly tolerant of this catalytic system (entry 8). It is noteworthy that the Cl-substituted quinazolinone (**22**), a precursor of the Ispinesib synthesis reported by Holland,[11] was generated smoothly and in a moderate yield (entry 9).

Next, we turned our interest to the effects of the geometries of the enaminones. *E*-Enaminones would serve as better nitrogen nucleophiles than *Z*-enaminones, since they lack intramolecular H-bonding. Surprisingly, when 3-aminocyclohex-2-enone (**23** as the *E*-enaminone representative) was subjected to the reaction conditions, the corresponding quinazolinone was




**Scheme 1** (A) The CuI-catalyzed domino reaction of **1a** and **23**. (B) The comparison reaction between **2a** and **23**. (C) The CuI-catalyzed domino reaction with **2a** as a ligand.

obtained in low yield (Scheme 1, (A)). The results gave us a clue about the geometrically-dependant reactivities of the two types of enaminones.

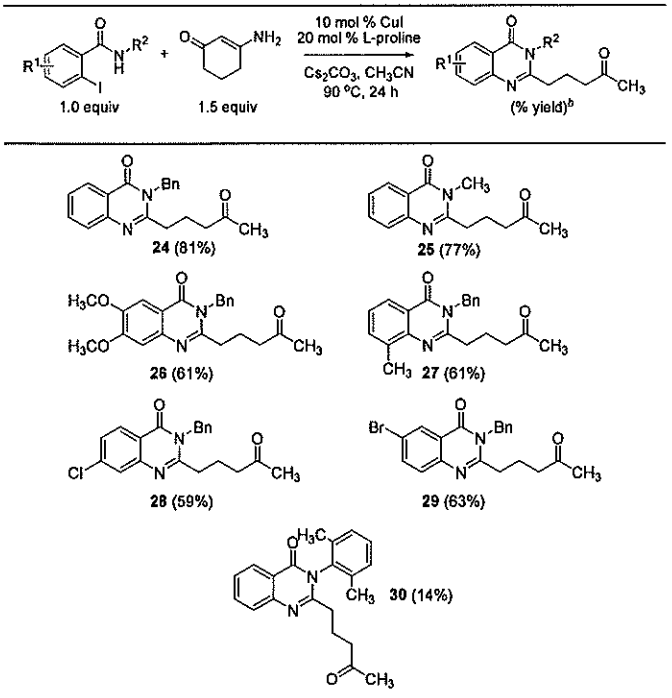
Interestingly, exposure of **1a** with a mixture of enaminones, **2a** and **23** (2.0 equiv. each), under standard conditions, gave quinazolinones **3** and **24** in 15% and 63% yields respectively (Scheme 1, (B)). Based on the results, the *E*-enaminone exhibited a better reactivity than the *Z*-enaminone in the cascade process, demonstrating that the domino reaction of the 2-iodobenzamides and the *E*-enaminones required the assistance of the *Z*-enaminone, in which we believe that **2a** played the role of a ligand. To emphasize the ligand requirement, 30 mol% of **2a** was used as a ligand, resulting in the facile domino transformation of **1a** and **23** to afford **24** with 85% conversion (Scheme 1, (C)).

We were delighted to find that L-proline was a compatible ligand, albeit we have not thoroughly explored a variety of ligands. After further optimization of the reaction of **1a** and **23**, the use of 10 mol% CuI, 20 mol% L-proline, and 2.5 equiv. $Cs_2CO_3$, in 0.1 M $CH_3CN$, with a reaction temperature of 90 °C were identified as the optimal conditions.

As we expected, better nucleophiles allowed us to lower the catalyst loading to 10 mol%, along with the amount of enaminones. Although we have not exhaustively explored the scope for this reaction, we found that **23** could be coupled with a variety of *N*-substituted 2-iodobenzamides with moderate to good yields (Table 3, compounds **24–29**). The results showed that the electronic effects of the aromatic rings of the 2-iodobenzamides had only a minor impact on the reactions. On the other hand, the reaction of **1d** and **23** gave a low yield (Table 3, compound **30**), indicating that steric hindrance and the effect of the aryl substituent greatly affected the reaction. We were pleased to discover that the domino transformation of **23** was possible, as being a surrogate of a hydrocarbon chain, with a ketone functionality, it could be further functionalized.

The possible mechanism of the quinazolinone syntheses from 2-iodobenzamides and enaminones was postulated *via* a domino process, an Ullmann-type coupling, an intramolecular Michael addition, and a retro-Mannich reaction. The last two steps were proposed according to the condensation of anthranilamides and 1,3-diketones.[12] Along with the mechanistic study of copper-catalyzed arylation of nucleophiles,[13] the complexation of ligands and Cu(I) was crucial, allowing the coupling reaction to occur smoothly at a low temperature.[14] Our initial mechanism involves the association of Cu(I) and the *Z*-enaminone to generate the active Cu(I) complex **I**,[10] which undergoes an Ullmann-type coupling to form the N-arylation intermediate, **III**, under relatively mild coupling conditions due to the *ortho*-substitution effect performed by the N-substituent.[15] Subsequently, the intramolecular Michael addition of **III** takes place to form the dihydroquinazolinone intermediate **IV**, followed by the retro-Mannich reaction to produce the quinazolinone and to expel acetone (Scheme 2A).

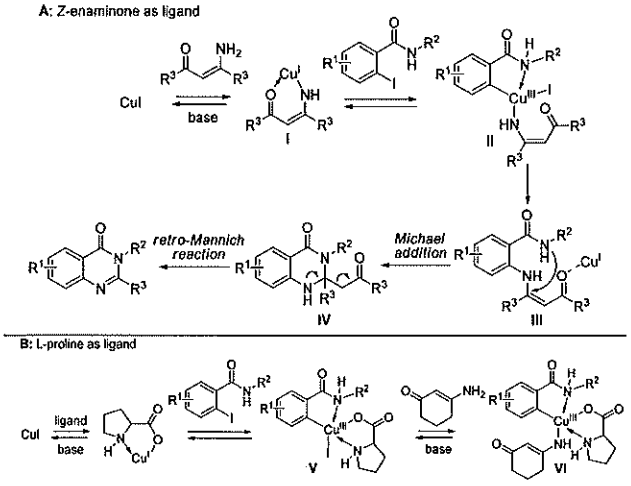
**Table 3** CuI-catalyzed domino syntheses of quinazolinones from 2-iodobenzamides and 3-aminocyclohex-2-enone[a]



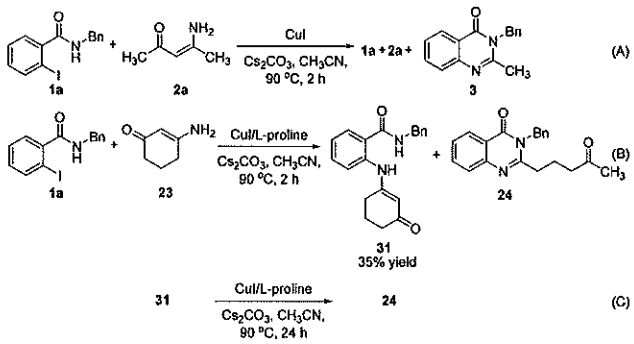

[a] Reaction conditions: all reactions were carried out with 0.5 mmol of 2-iodobenzamides, and 2.5 equiv. of $Cs_2CO_3$, in 0.1 M $CH_3CN$. [b] Isolated yield.

Although the geometries of the enaminones affect the reactions, we believe that both geometries undergo domino processes with the same reaction mechanisms. *Z*-Enaminones are promoted with the possible mechanism shown in Scheme 2A. On the other hand, in the case of *E*-enaminones (Scheme 2B), L-proline plays the role of a ligand in the copper-catalyzed Ullmann-type coupling, as remarkably described by Ma.[16] The *E*-enaminone, **23**, acts as the nitrogen nucleophile to form complex **VI**, and then undergoes reductive elimination to generate the N-arylation intermediate followed by the sequential mechanisms described in Scheme 2A, revealing the pendant ketone functionality.

In order to explore the sequence of the reactions, attempts to detect the intermediates described in the proposed mechan-




Scheme 2 Possible mechanism for the domino syntheses of quinazolinones *via* CuI-catalyzed Ullmann-type coupling.




Scheme 3 Mechanism investigation experiments.

ism were applied. Stopping the reaction of **1a** and **2a** prior to completion revealed a 1 : 1 ratio of **1a** and **3** (Scheme 3, (A)), as identified by the $^1$H NMR spectrum of the crude mixture. None of the expected intermediates were obtained. In contrast, the exposure of **1a** and **23** to the standard reaction conditions for 2 h resulted in a complete consumption of **1a**, and the N-arylation intermediate **31** was isolated in a 35% yield (Scheme 3, (B)). **31** was then smoothly converted to **24** under the standard conditions (Scheme 3, (C)), indicating that the first transformation of the domino process was the copper-catalyzed N-arylation, supporting our proposed mechanism. Although we did not perform a study of the isotope effects, based on our findings, the detection of a stable intermediate, which accumulated after the Ullmann-type coupling, implied that the rate-determining step of the domino reaction of **1a** and **23** was possibly the intramolecular Michael addition.

## Conclusions

We have demonstrated domino syntheses of quinazolinone derivatives *via* a copper-catalyzed Ullmann-type coupling, an intramolecular Michael addition and a retro-Mannich reaction, under mild and simple reaction conditions. The geometry of the double bonds in the enaminones played an important role in the reactions. *Z*-Enaminones could undergo sequential reactions without the addition of any external ligands. On the other hand, *E*-enaminones showed better reactivity, but required the assistance of ligands. Furthermore, the two major contributions to the reaction were the steric hindrance of the enaminones and the nucleophilicities of the amide nitrogens. Although the product yields suffered from steric hindrance, our method provides a variety of quinazolinones from one-pot syntheses using simple enaminones. Further applications of the reaction and a study of the reaction mechanism are ongoing.

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

**Figure 5** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **80h** in DMSO-$d_6$

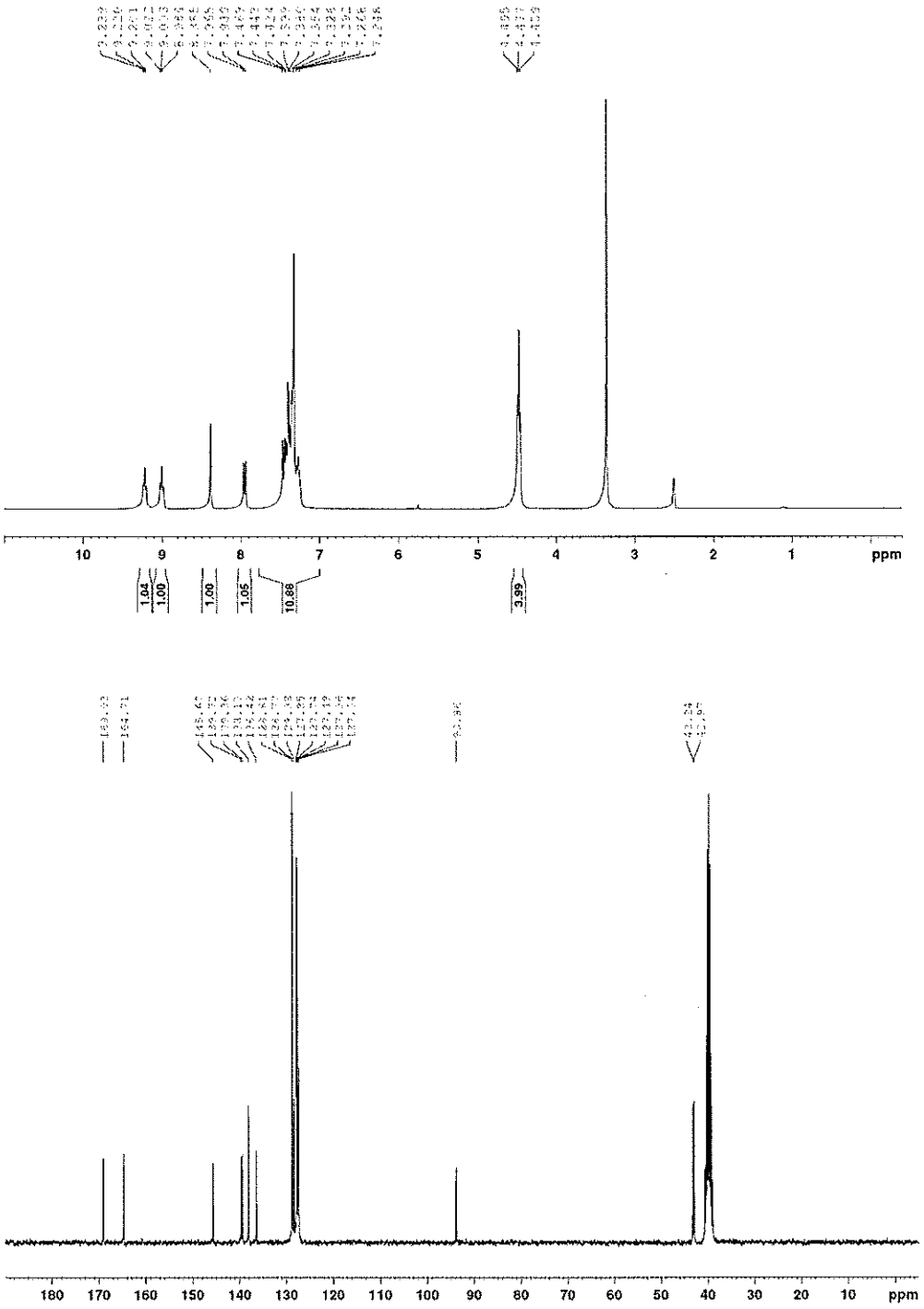


**Figure 6** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **80i** in $CDCl_3$

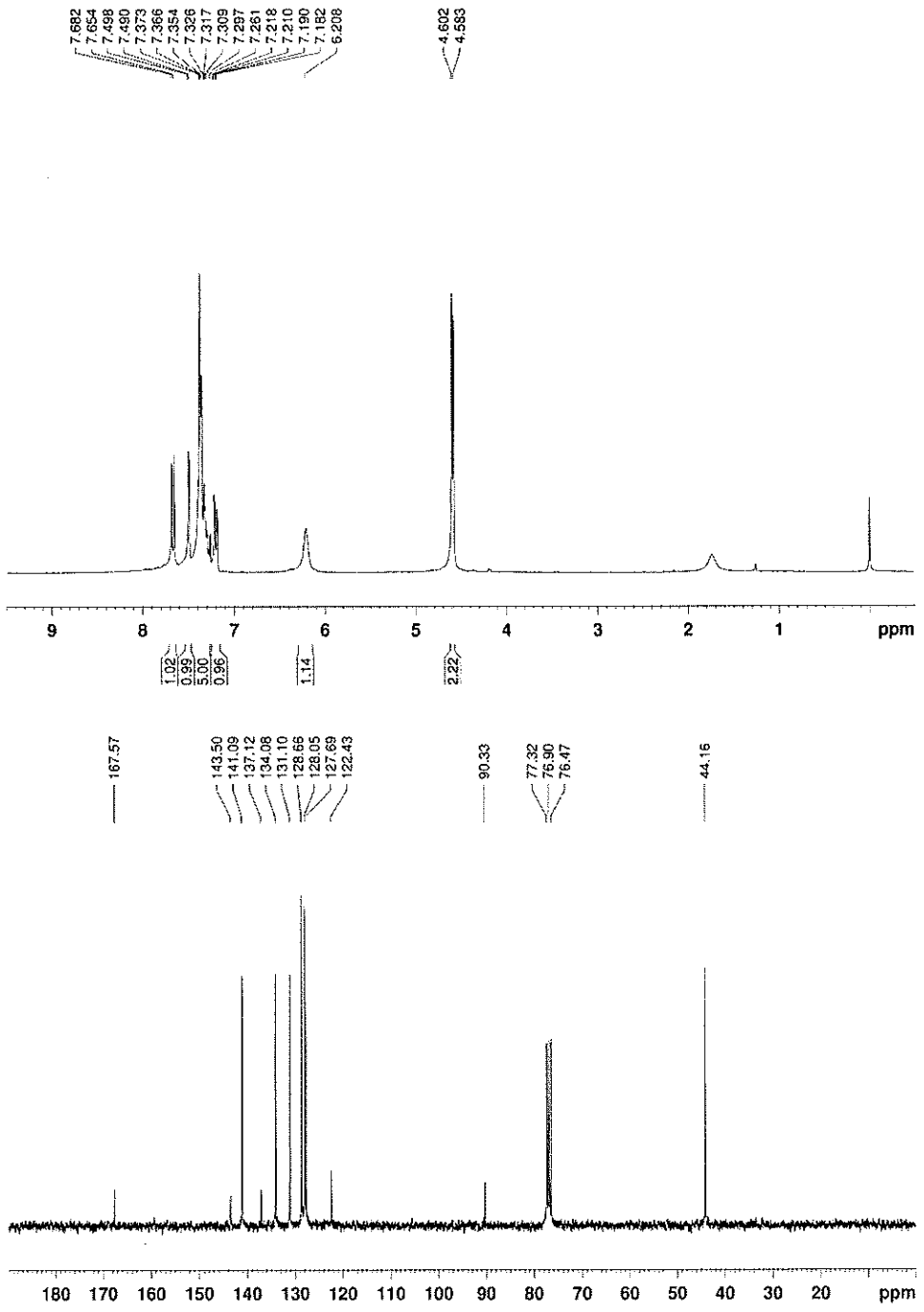


**Figure 7** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **81c** in $CDCl_3$

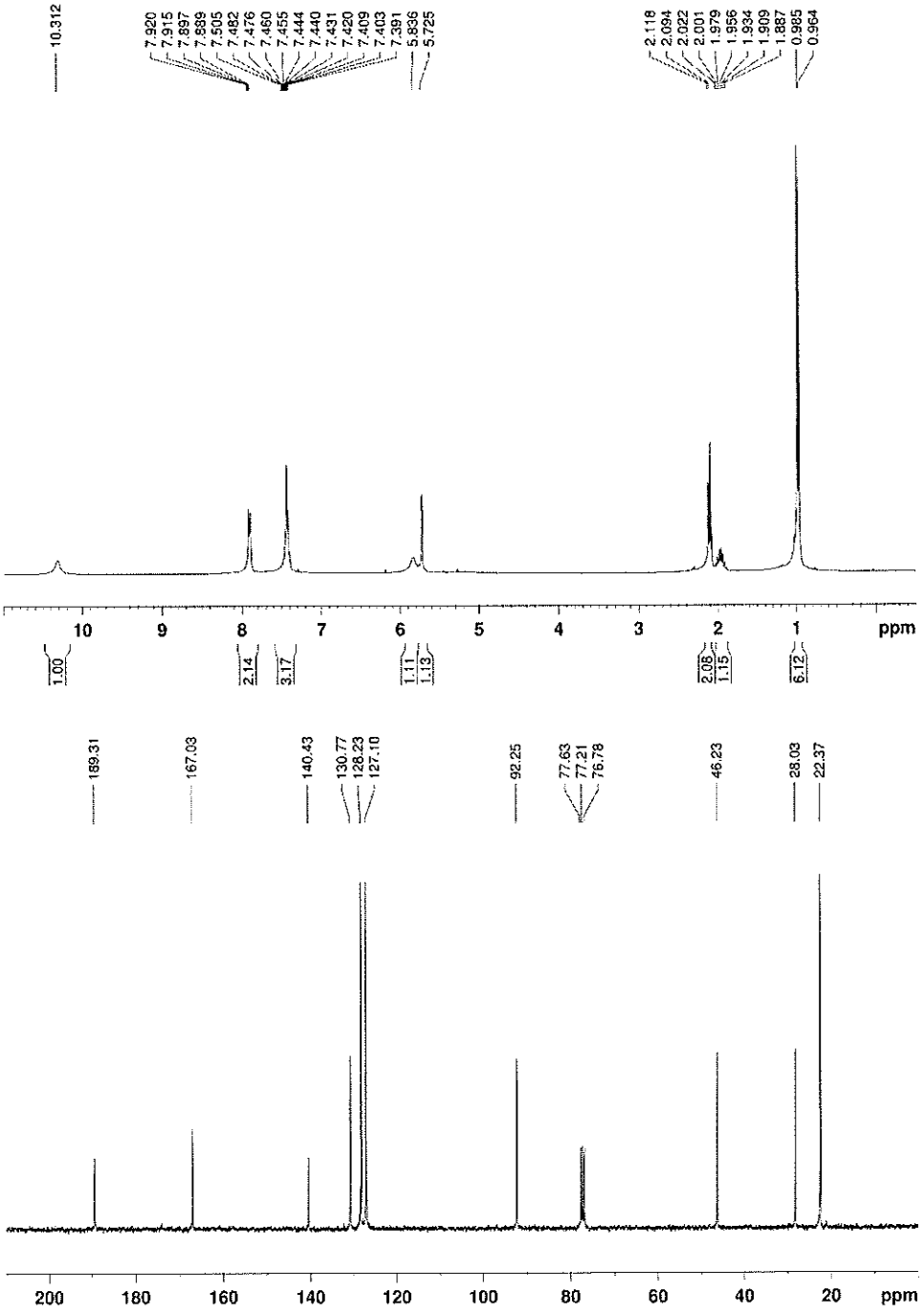


**Figure 8** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **82b** in $CDCl_3$

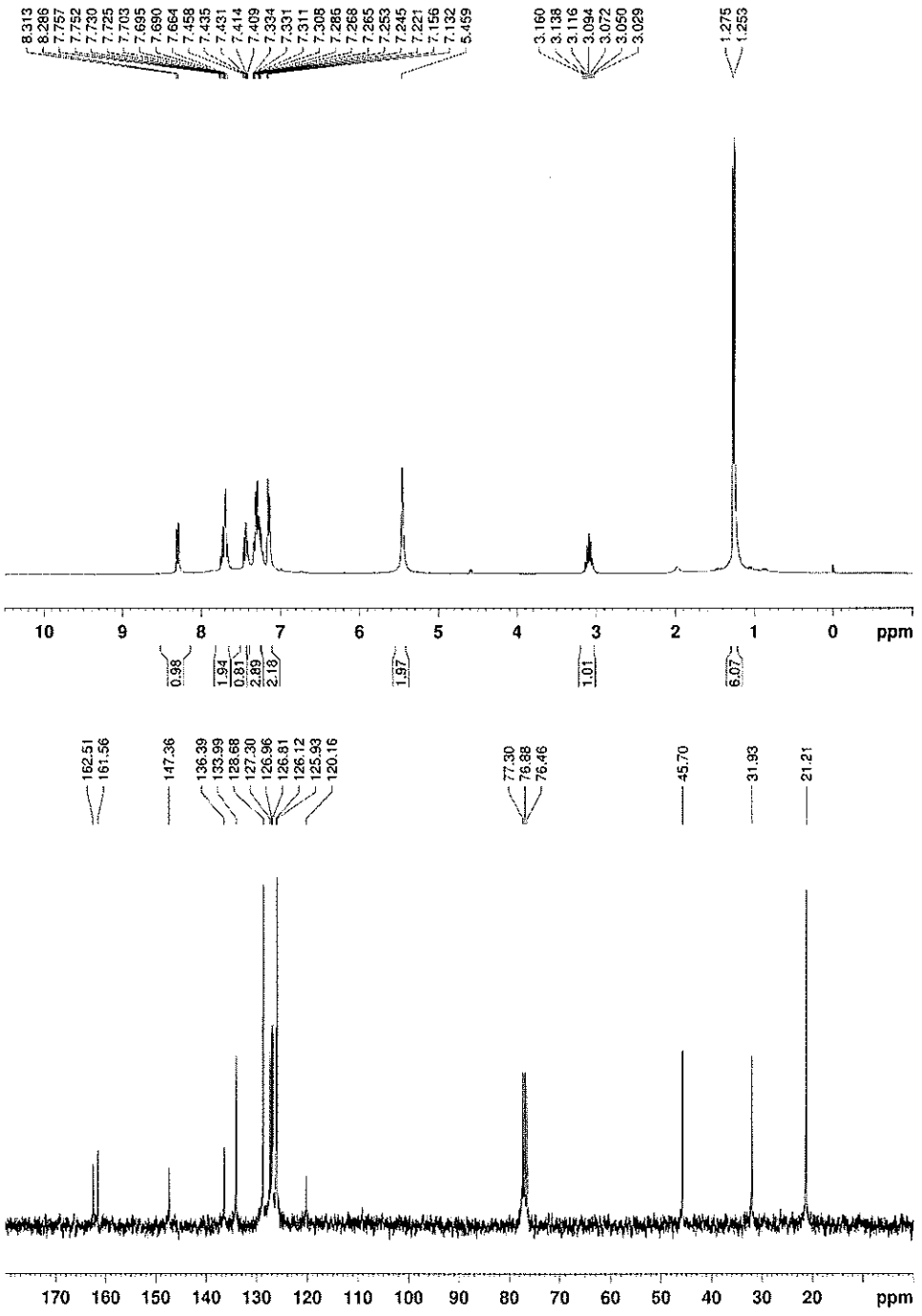


**Figure 9** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **82c** in $CDCl_3$

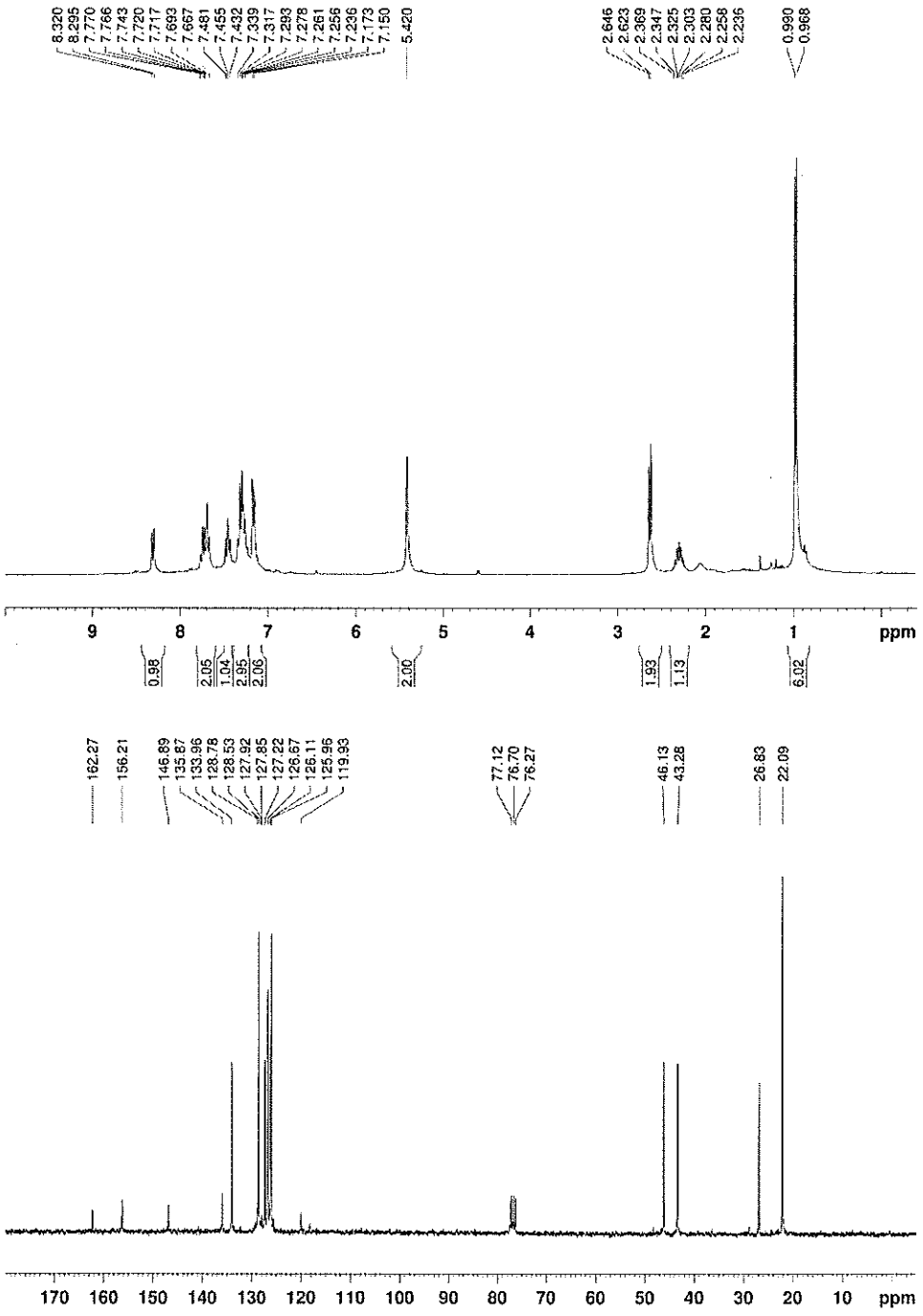


**Figure 10** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **82f** in $CDCl_3$

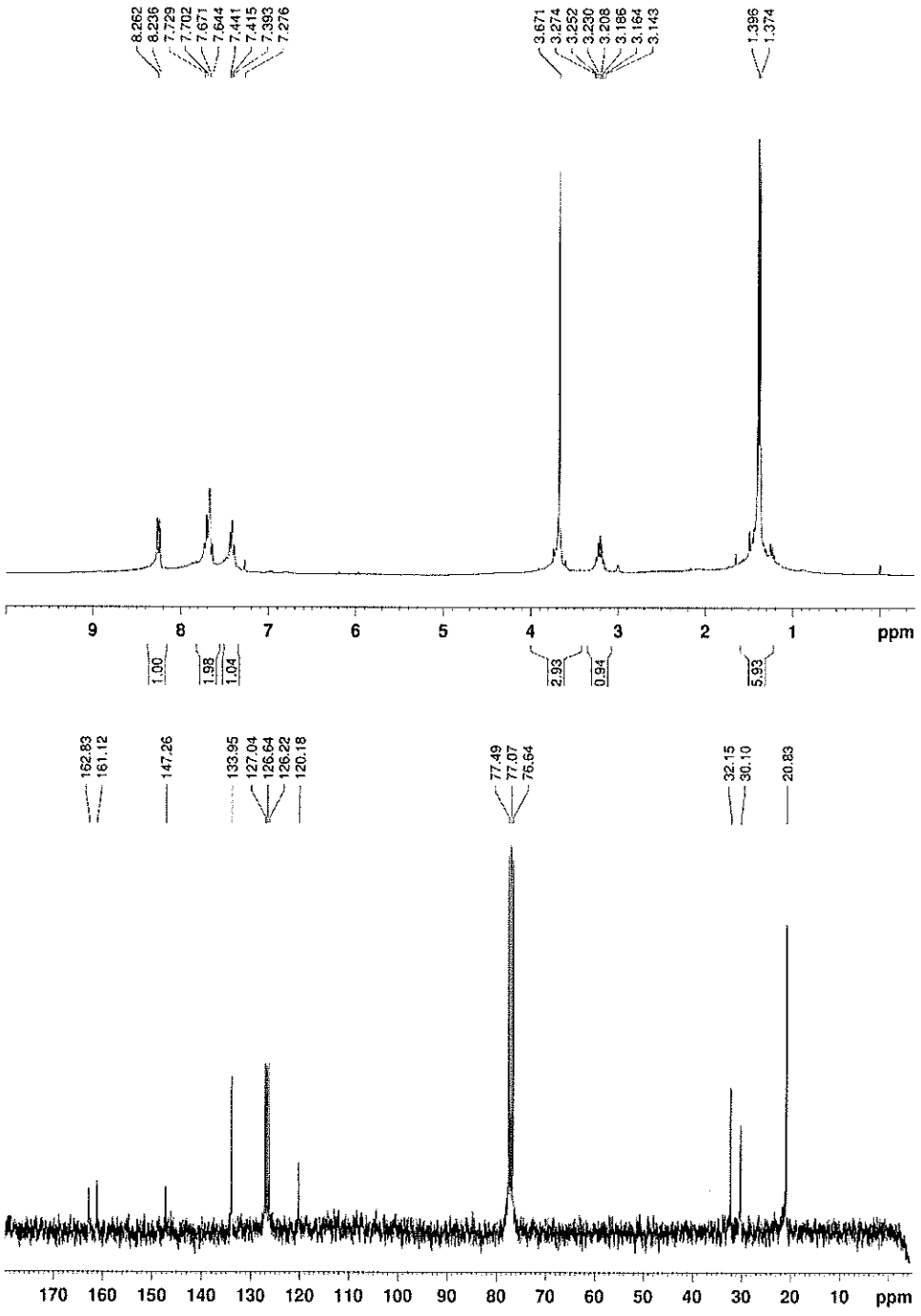


**Figure 11** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **82m** in $CDCl_3$

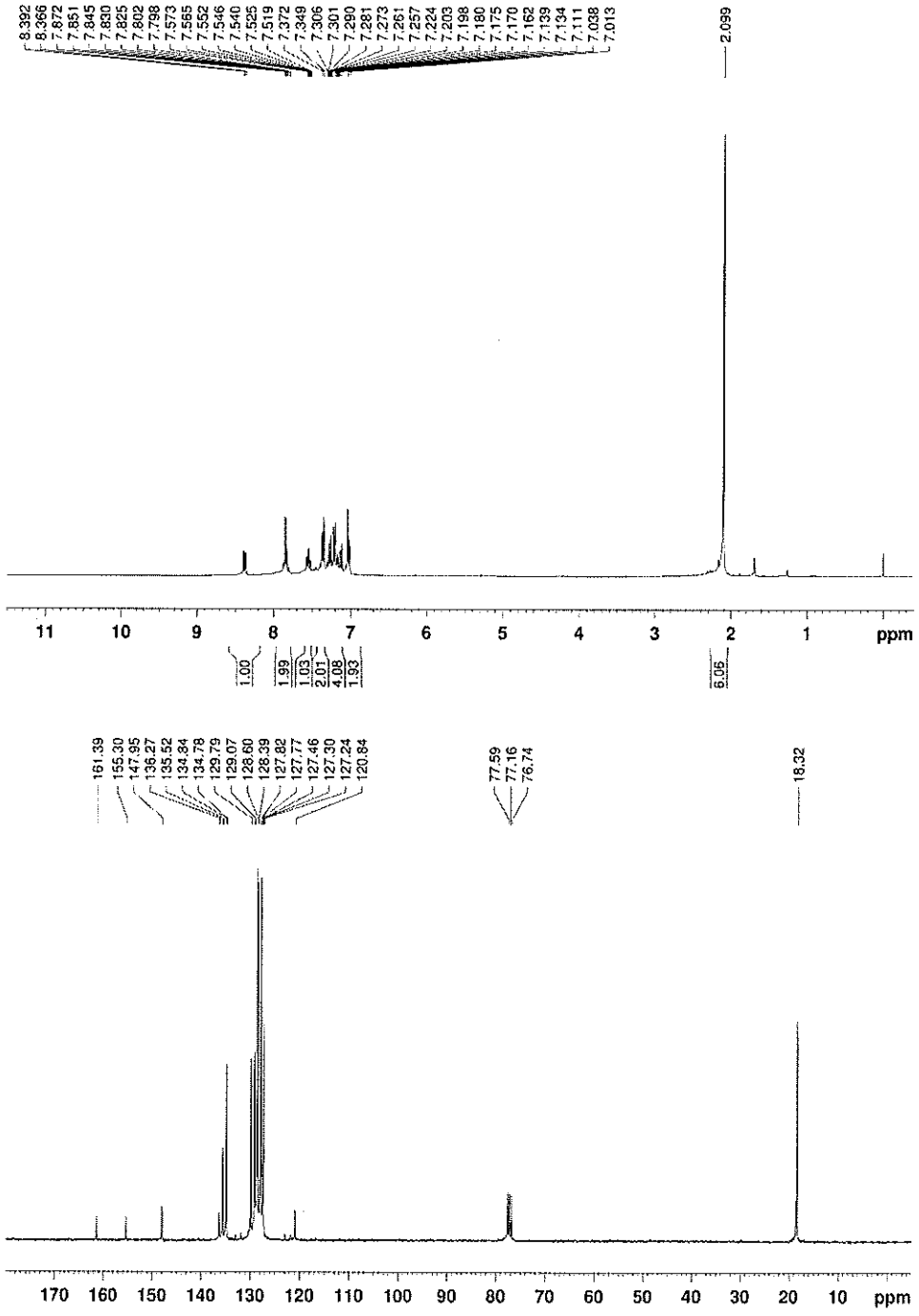


**Figure 12** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **82o** in $CDCl_3$

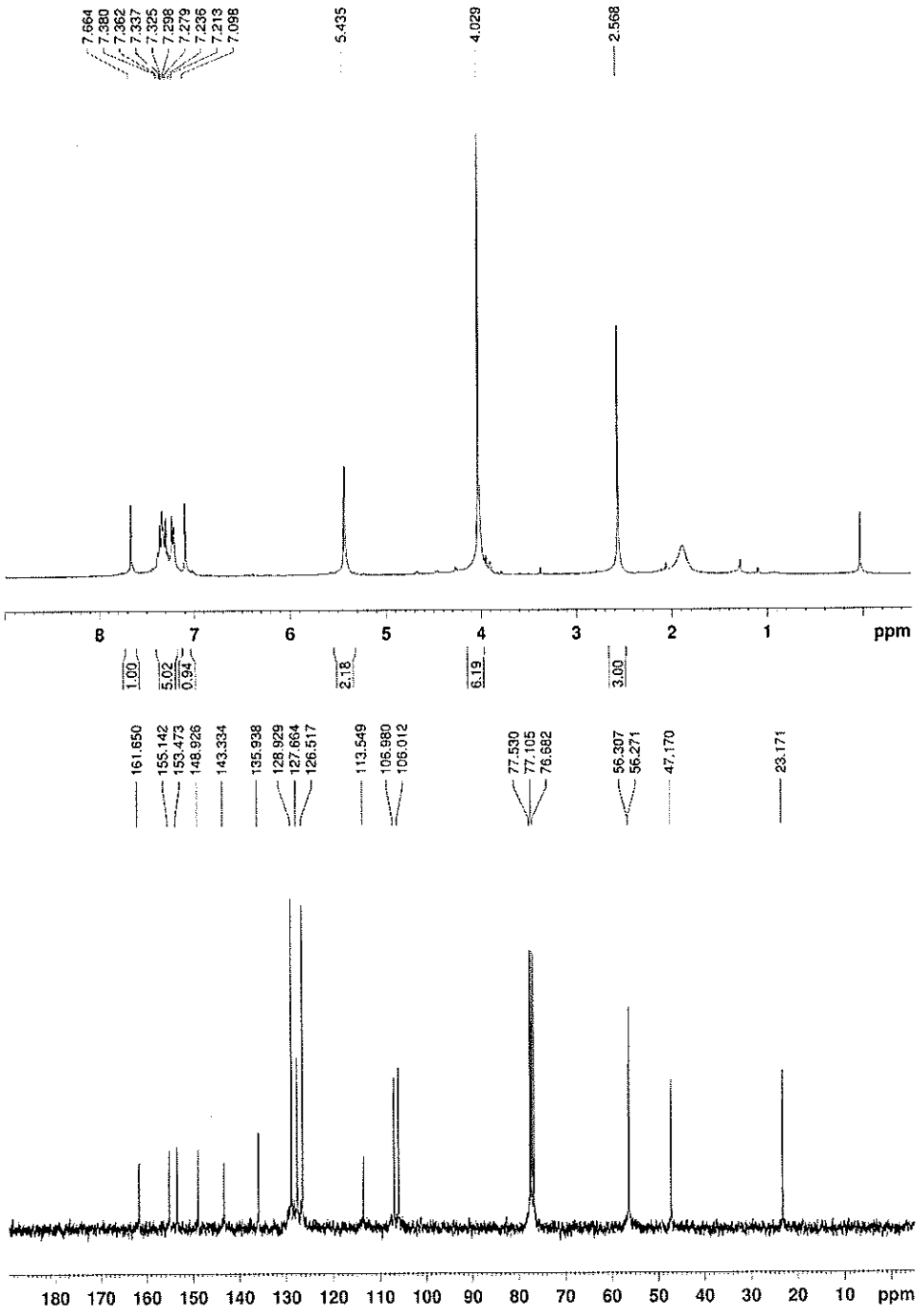


**Figure 13** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **82p** in $CDCl_3$

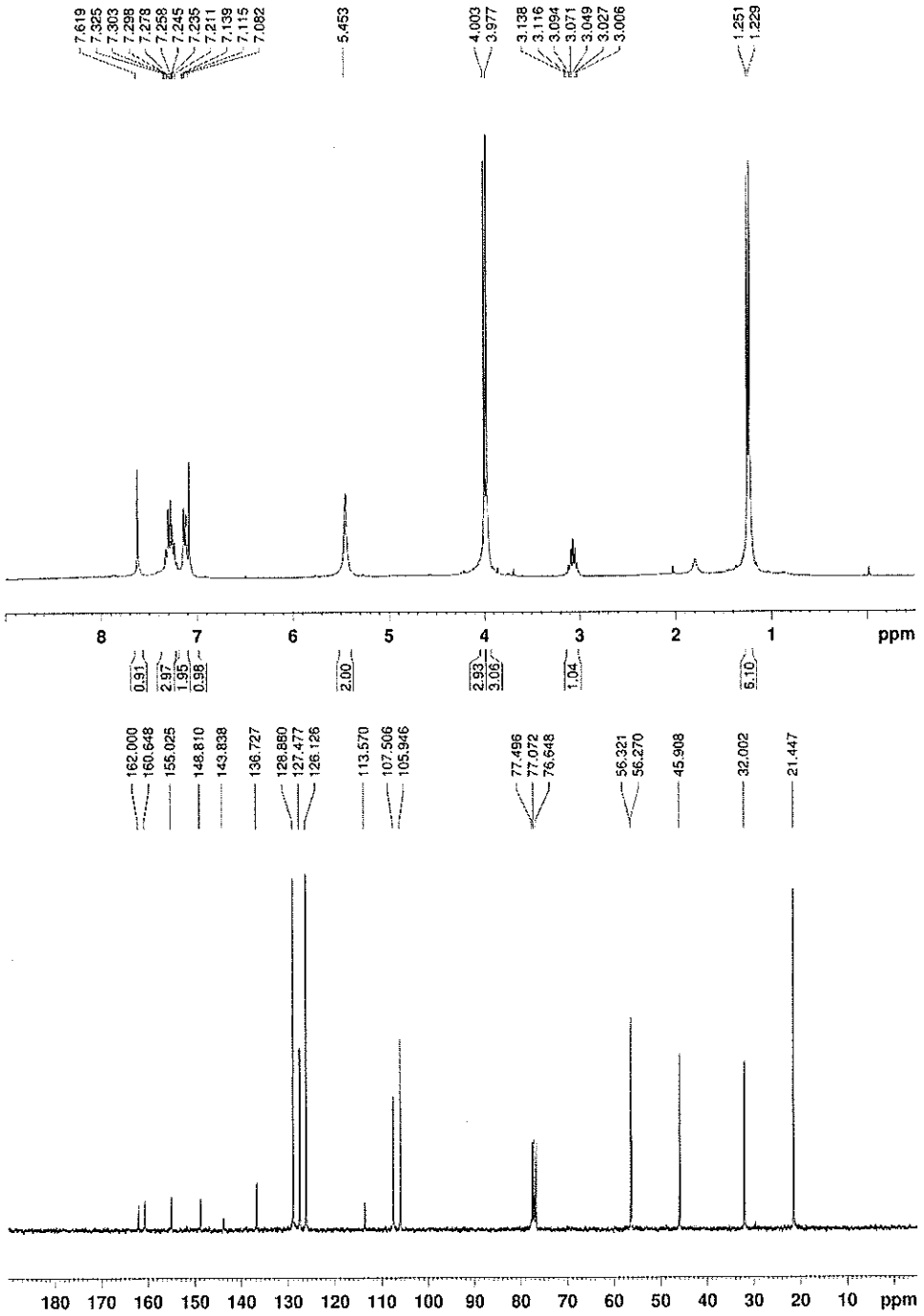


**Figure 14** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **82q** in $CDCl_3$

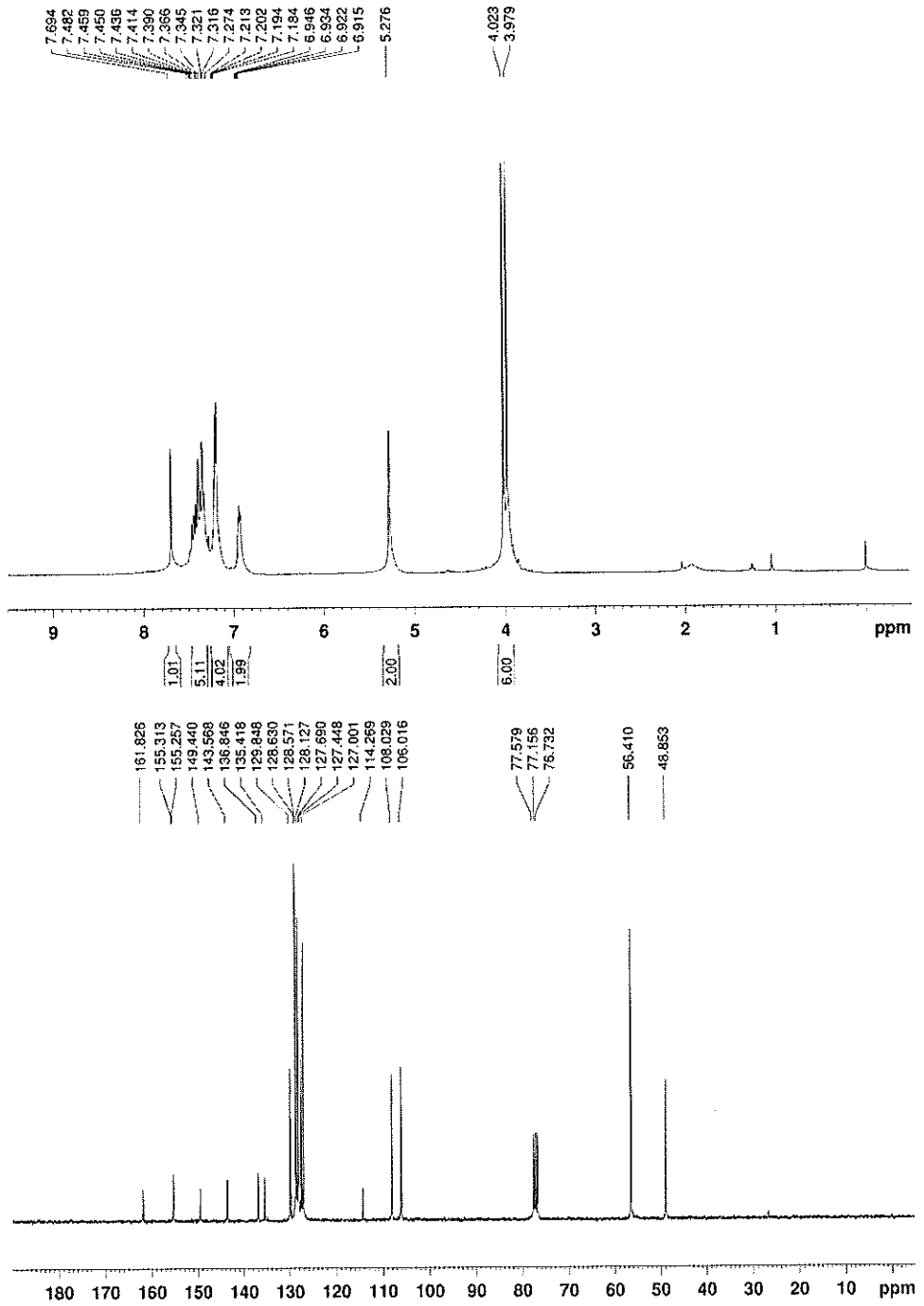


**Figure 15** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **82r** in $CDCl_3$

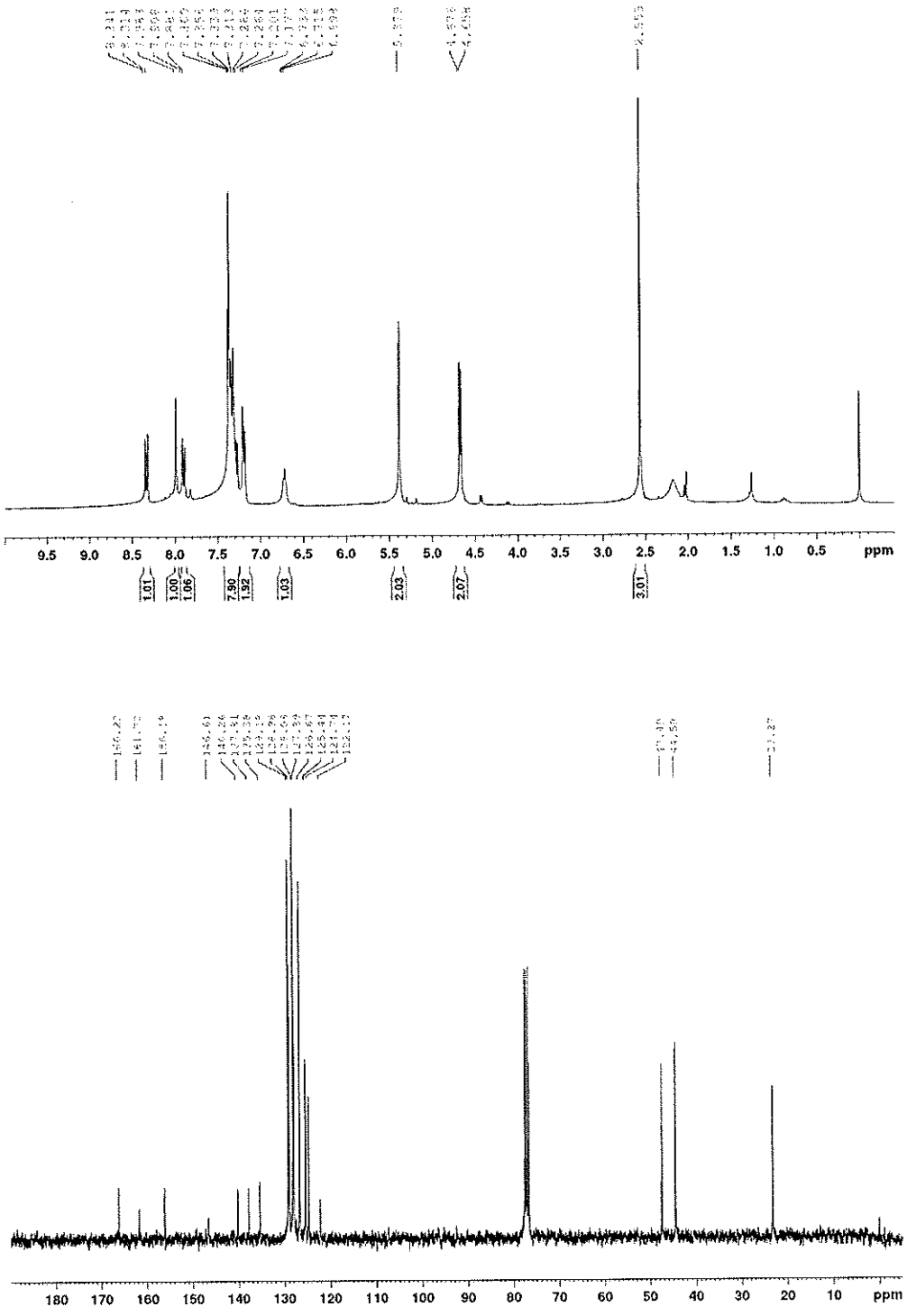


**Figure 16** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **82s** in $CDCl_3$

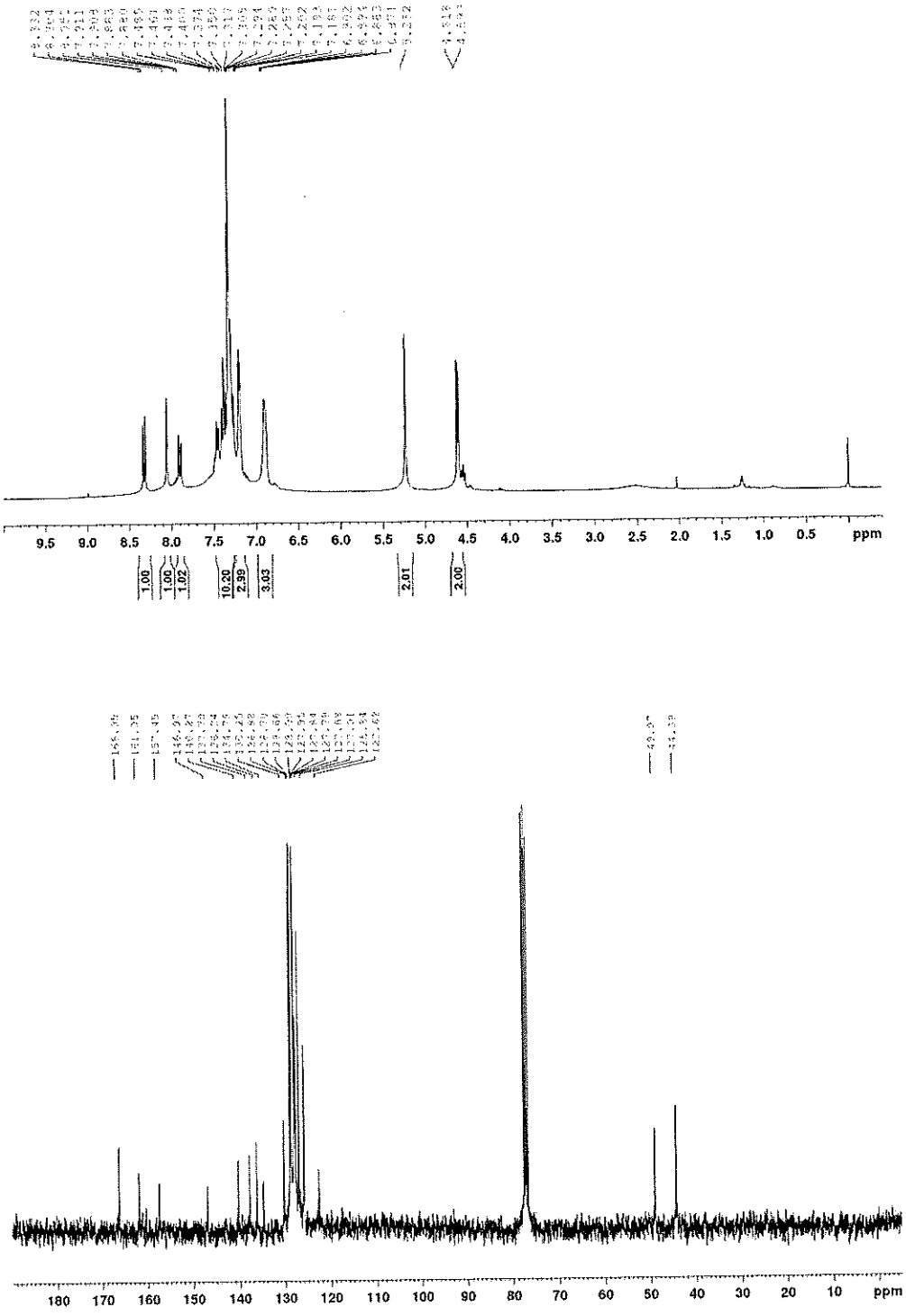


**Figure 17** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **82t** in $CDCl_3$

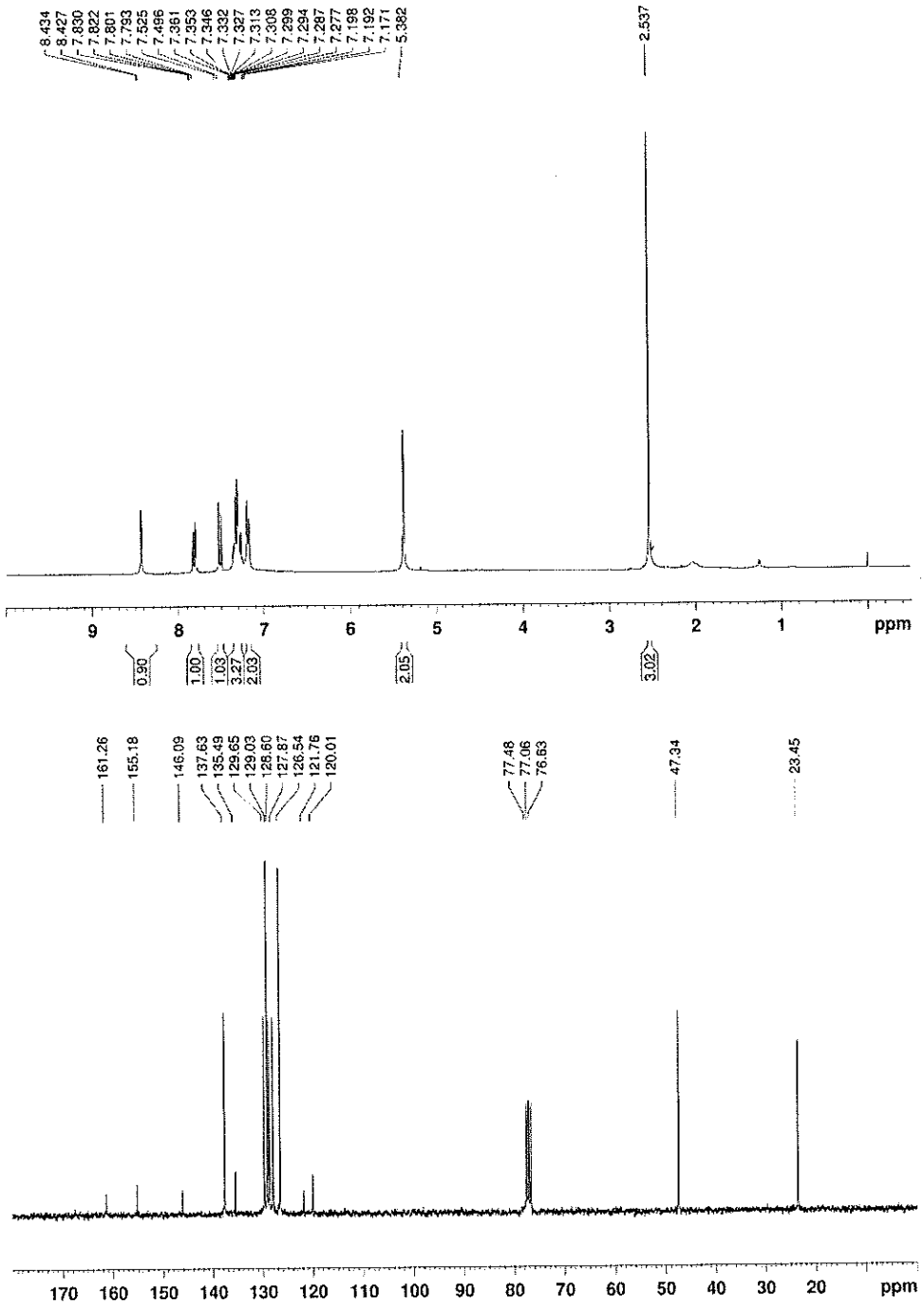


**Figure 18** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **88** in $CDCl_3$

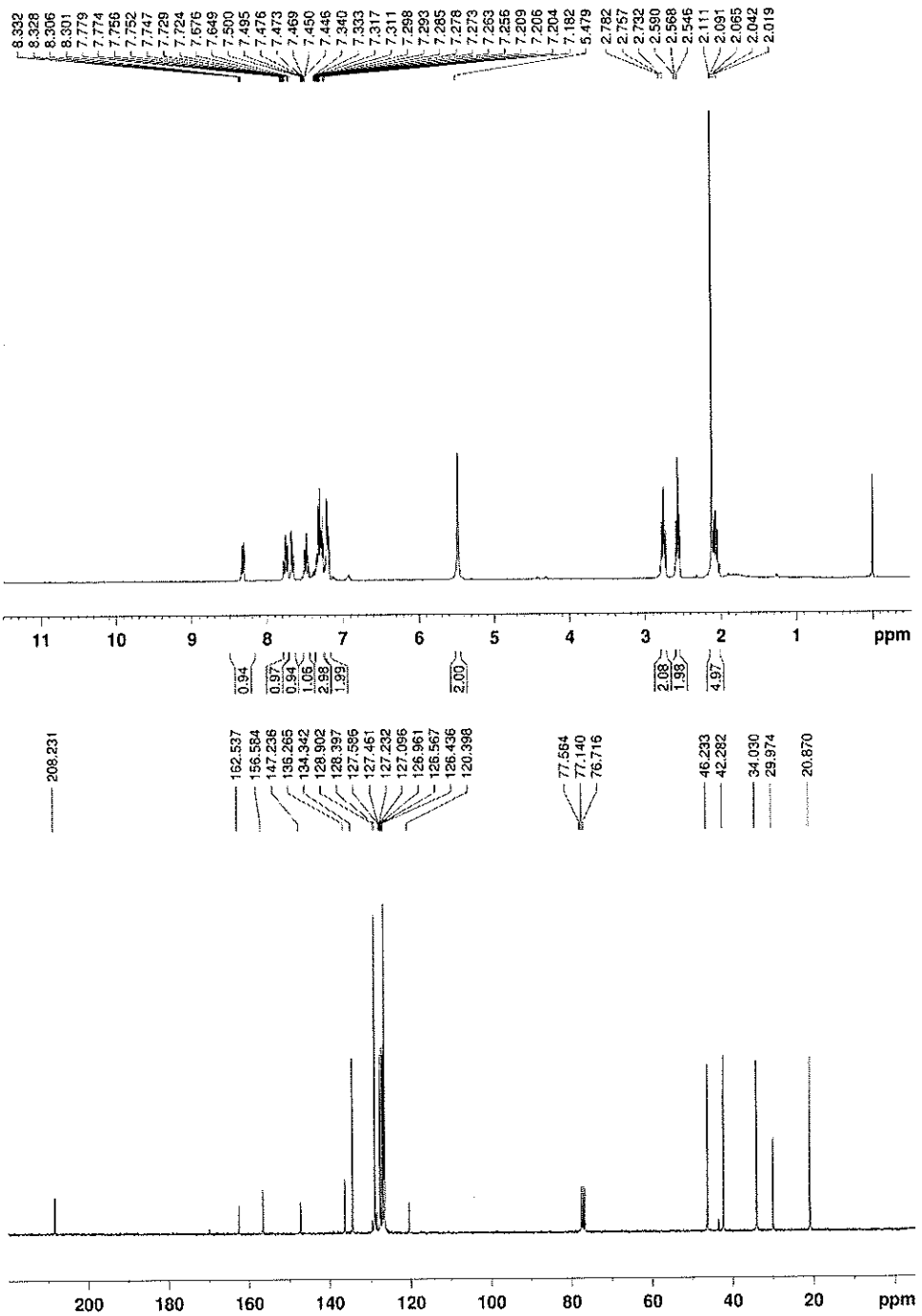
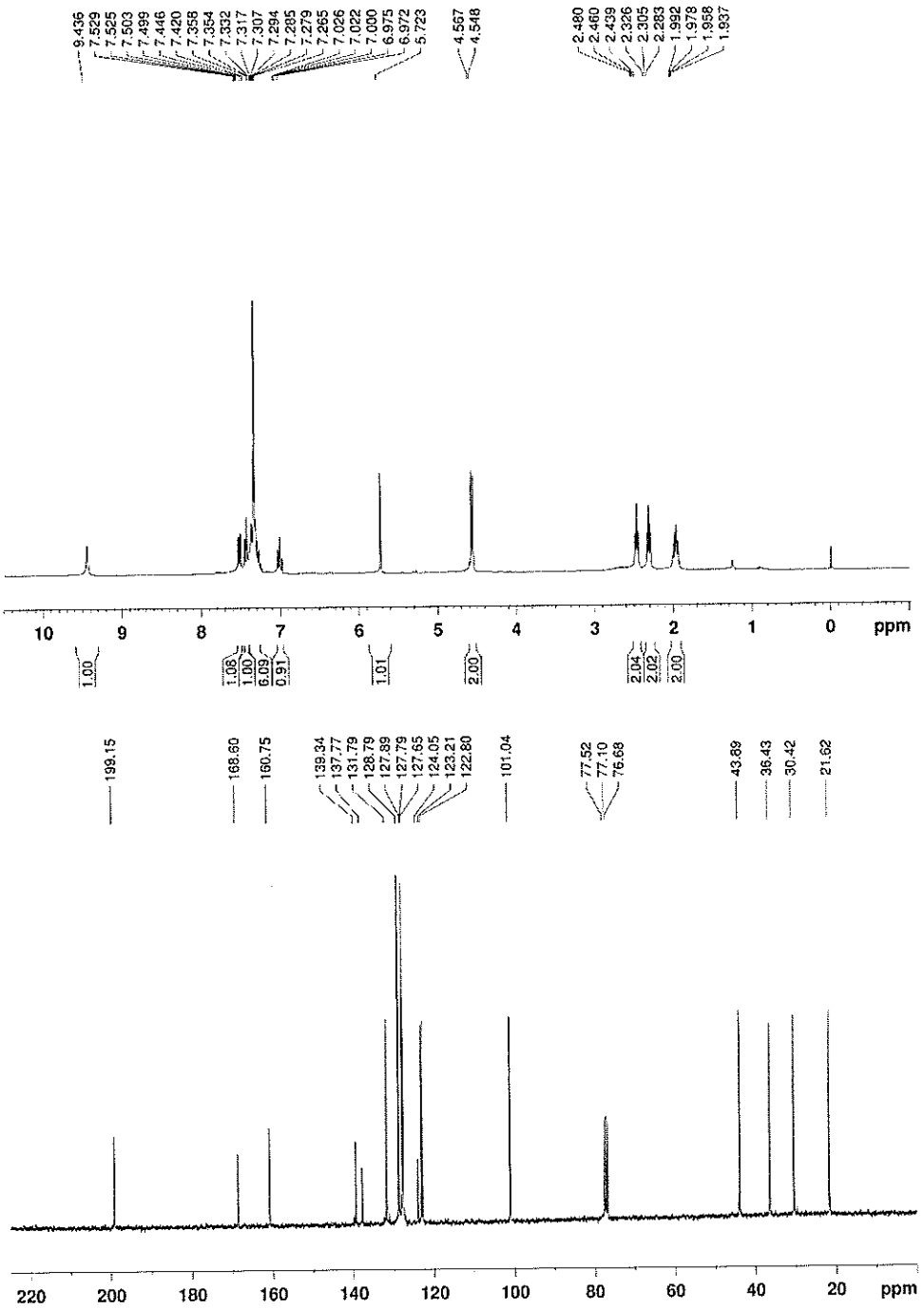


**Figure 19** The $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra of compound **89** in $CDCl_3$



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**List of Publication**

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