Copper-Catalyzed Multicomponent Reactions toward Synthesis of 1,2,3-Triazoles

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Thesis Title	Copper-catalyzed multicomponent reactions toward synthesis of 1,2,3-triazoles
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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 การสังเคราะห์อนุพันธ์ 1,2,3-triazoles ผ่านปฏิกิริยาแบบ multi-component โดยมีคอปเปอร์เป็นตัวเร่งปฏิกิริยา

ผู้เขียน นายอับดุลฮากีม หะยีบือราเฮง

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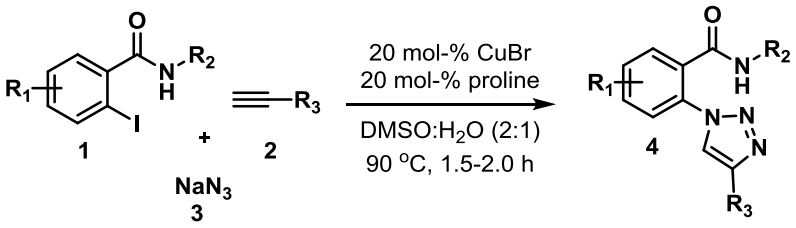

ปัจจุบันการสังเคราะห์สารโดยการใช้ปฏิกิริยาแบบ multicomponnent (MCRs) ได้ถูกนำมาประยุกต์ใช้ในการสังเคราะห์สารผลิตภัณฑ์ธรรมชาติและยาในเชิงพาณิชย์มากขึ้น เนื่องจากช่วยลดจำนวนหรือขั้นตอนการทำปฏิกิริยาและเป็นมิตรกับสิ่งแวดล้อม ผู้วิจัยได้สังเคราะห์สารอนุพันธ์ 1,2,3-triazoles จากสารตั้งต้น 2-iodobenzamides, sodium azide และ terminal alkynes ผ่านปฏิกิริยาแบบ Cu(I)-catalyzed multicomponent reaction โดยมีกลไกการเกิดปฏิกิริยาคือ Ullmann type coupling (การสร้างพันธะ C(aryl)–N) และ azide–alkyne cycloadditon reaction และสามารถทำได้ในขั้นตอนเดียวภายใต้สภาวะปฏิกิริยาที่ไม่รุนแรงและใช้เวลาอันสั้น ปฏิกิริยาถูกออกแบบเพื่อให้ aryl azide intermediate สามารถเกิดปฏิกิริยากับ terminal alkyne ได้ทันทีโดยไม่ต้องผ่านกระบวนการทำให้สารบริสุทธิ์ นอกจากนี้การทำปฏิกิริยาในสภาวะที่ไม่ใช้เบสเป็นปัจจัยสำคัญที่ช่วยแก้ปัญหาแข่งขันการเกิดปฏิกิริยาระหว่าง azide และ terminal alkyne

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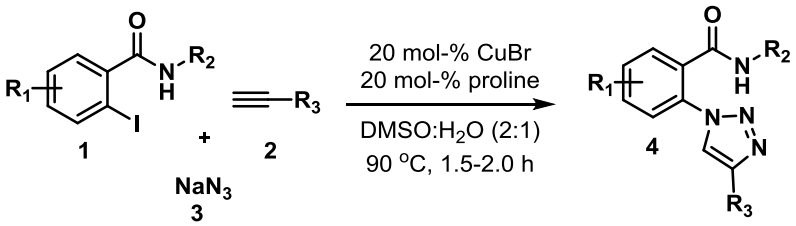
ABSTRACT



In recent years, multicomponent reactions (MCRs) have been applied to the synthesis of natural products and commercial drugs. They can reduce the number of required reaction steps and being an efficient eco-friendly protocol. The synthesis of 2-(1,2,3-triazolyl)benzamide derivatives **4** was accomplished in a one-step process *via* copper-catalyzed reaction from 2-iodobenzamides, NaN_3, and terminal alkynes. The domino process consisted of C(aryl)–N bond formation to generate aryl azide intermediate, followed by an azide–alkyne cycloaddition. The purification of aryl azide intermediate was not necessary in our protocol. In addition, the absence of external base was a solved key in the competitive reaction pathway.

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Abdulhakim hayeebueraheng

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LIST OF ABBREVATIONS AND SYMBOLS

General

ν	=	absorption
Å	=	angstrom (10-10 meters)
aq	=	aqueous
atm	=	atmosphere
br	=	broad
calcd.	=	calculated
cat.	=	catalyst
δ	=	chemical shift relative to TMS
J	=	coupling constant
oC	=	degree Celsius
d	=	doublet
dd	=	doublet of doublets
equiv.	=	equivalent
ESI	=	electrospray ionization
FT-IR	=	Fourier transform Infrared
g	=	gram
Hz	=	hertz
HRMS	=	high-resolution mass spectroscopy
h	=	hour
m/z	=	mass-to-charge ratio
MHz	=	megahertz
µ	=	micro
mg	=	milligram
mL	=	milliliter
mmol	=	millimole
M	=	molar
mol%	=	mole percent

LIST OF ABBREVATIONS AND SYMBOLS (Continued)

m	=	multiplet
NMR	=	nuclear magnetic resonance
Nu	=	nucleophile
ppm	=	part per million
H	=	proton
psi	=	pound per square inch
q	=	quartet
cm-1	=	reciprocal centimeter (wavenumber)
sat.	=	saturated
Temp	=	temperature
TLC	=	thin-layer chromatography
t	=	triplet

Chemicals

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

LIST OF ABBREVATIONS AND SYMBOLS (Continued)

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

LIST OF PUBLICATION

Hayeebueraheng, A.; Kaewmee, B; Rukachaisirikul, V.; Kaeobamrung, J. 2017. Synthesis of 2-(1,2,3-triazolyl)benzamide derivatives by Copper(I)-catalyzed multicomponent reaction. Eur. J. Org. Chem. 6714–6721.

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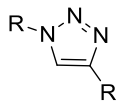
CHAPTER 1
INTRODUCTION

1.1 Overview

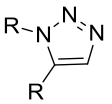
Over the past decade, multicomponent reactions (MCRs) have been received much attention from synthetic chemists because it reduced the number of required reaction steps significantly and provided complex organic molecules from simple starting materials. The creation of molecular diversity and complexity from simple and readily available substrates are one of the major current challenges in organic chemistry.

The important heterocyclic molecules, 1,2,3-triazoles existed in two isomeric forms including 1,4- and 1,5-disubstituted trizoles (**Figure 1**).

Figure 1. Two isomers of 1,2,3-triazole



1,4-disubstituted triazoles

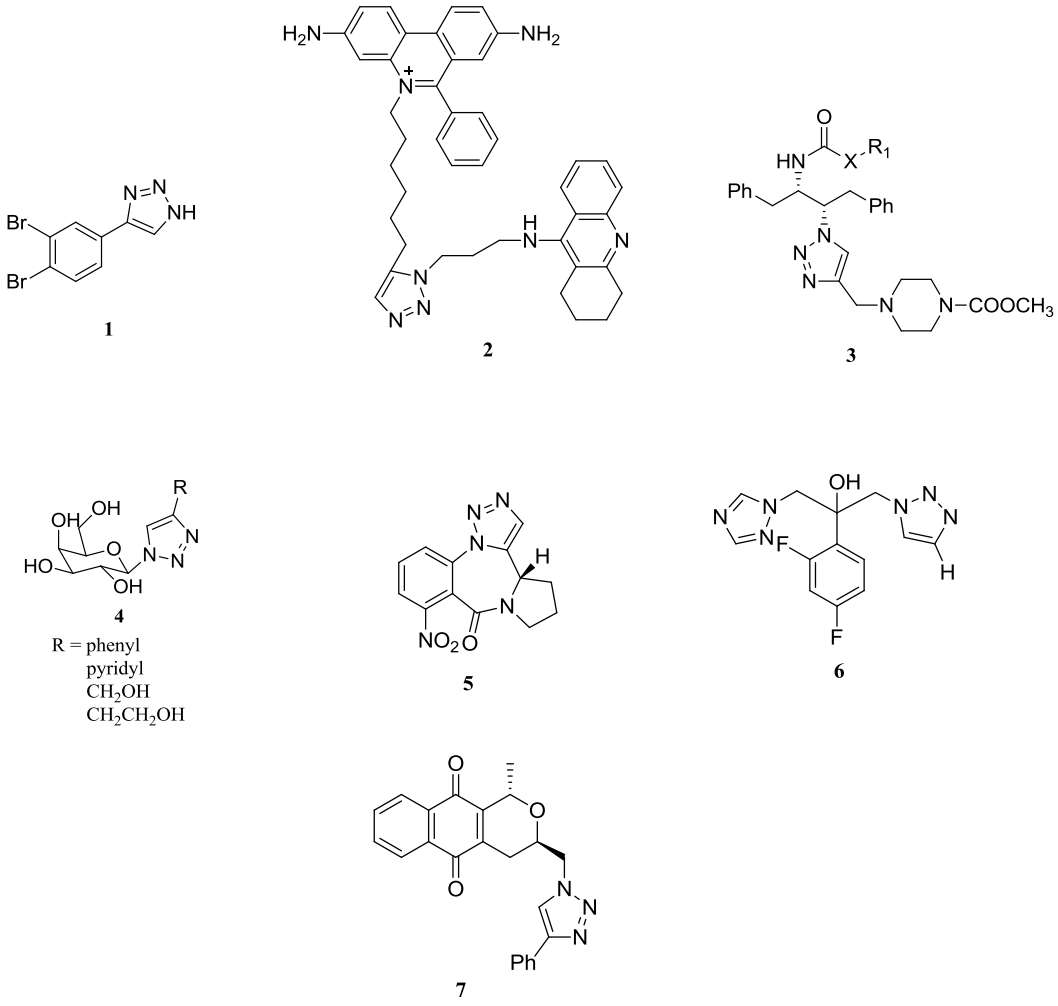


1,5-disubstituted triazoles

1,2,3-Triazoles demonstrated a broad range of biological properties, for example, aryl-1,2,3-triazole **1** showed anti-tumor activity against the enzyme inhibitor of human methionine aminopeptidase type 2 (hmetap2) helping to inhibit the spread of cancer cells (Soltis *et al.*, 2005). Phenanthridinium **2** displayed activity against acetylcholinesterase (AChE) enzyme which resisted a chemical neurotransmitter involving with the treatment of Alzheimer's disease (Senapati *et al.*, 2006). 1,2,3-Triazole **3** illustrated activity against human immunodeficiency virus type1 Protease (HIV-1-Pr) that could inhibit the replication of the HIV virus (Silva *et al.*, 2009). 1,2,3-Triazole-substituted galactose derivatives **4** proved to be Trypanosoma cruzi trans-sialidase (TcTS) inhibitor (Carvalho *et al.*, 2010). Diazapine **5** that could inhibit serine protease showed cytotoxicity against blood coagulation (Mohapatra *et al.*, 2009). Fluconazole **6** potentially showed antifungal activity against *Candida* species having MIC ranging from 3.12 to 6.25 μg/mL (Pore *et al.*, 2006). In addition,

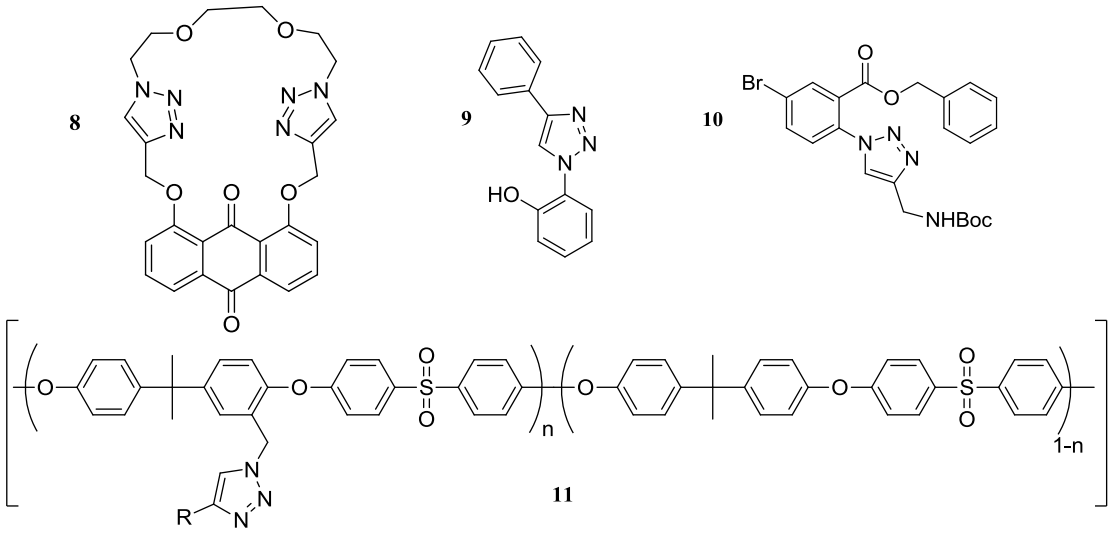
pyranonaphthoquinone **7** showed antibiotic activity. (Rathwell *et al*., 2010) (**Figure 2**).

Figure 2 Examples of bioactive 1,2,3-triazoles



Moreover, 1,2,3-triazoles have been used in material applications (**Figure 3**), such as a bis-triazole macrocycle incorporating anthraquinone **8** as a fluorescent showing excellent selectivity with Al^{3+}(Kim *et al*., 2010) and 1,2,3-triazole **9** a detector of F^- anion showing fluorescence under UV lamp of long wavelength 365 nm (Ghosh *et al*.; 2015). Aryltriazolyl amino acid benzyl ester **10** was applied to form a gelator by using intermolecular forces (Srivastava *et al*., 2013). 1,2,3-Triazoles **11** incorporating into polymer were proton exchange membrane (Sood *et al*., 2016).

Figure 3 Examples of 1,2,3-triazoles in material sciences



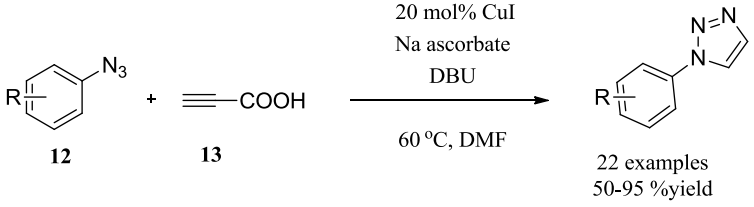
1.2 Literature reviews

1.2.1 The traditional method for the synthesis of 1,2,3-triazoles

Due to the vast advantages of 1,2,3-triazole compounds mentioned above not only in pharmaceutical but also in material sciences, several scientists created novel methodologies to access 1,2,3-triazoles. The traditionally well-known synthesis was the CuAAC (copper-catalyzed azide-alkyne cycloaddition) which was one of the best click reactions to date (Himo *et al*., 2004.).

In 2011, Xu and co-workers reportep;d the CuAAc for 1,2,3-traizoles. The aryl azide **12** and alkyne **13** were utilized as starting materials in the presence of CuI as a catalyst, sodium ascorbate as a reducing agent and DBU as a base at 60 ^{o}C. 1,2,3-Triazoles were achieved in good yields (50-95 %) (**Scheme 1**) (Xu *et al*., 2011.).

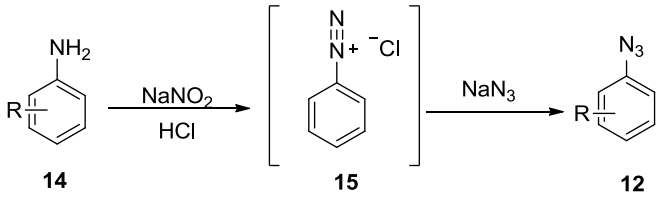
Scheme 1. Click chemistry via copper-catalyzed reaction



This reaction was considered as one of efficient tandem catalysis protocols to give 1,2,3-traizoles. However, aryl azide derivatives were rarely found for

commercially available and not stable. The preparation of fresh azides was required. The synthesis of aryl azides **14** could be prepared by anilines **12** reacting with $NaNO_2$ to give diazonium salt **13** which was further reacted with NaN_3 (**Scheme 2**) (Zimmermann *et al.*, 2005)**.**

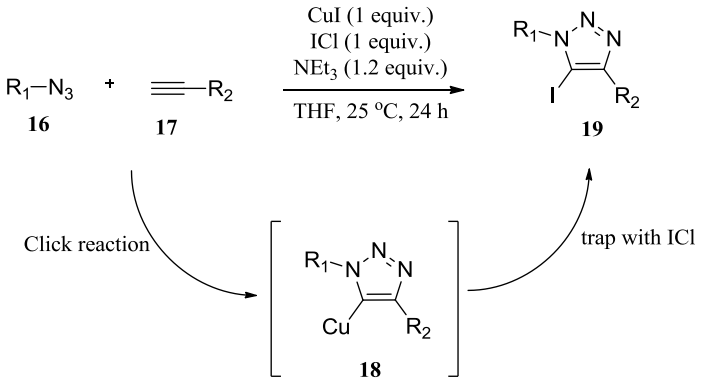
Scheme 2. Preparation of aryl azides



1.2.2. Selected click reactions with a variety of catalysts

In 2005, Wu and co-workers exhibited 5-cuprated 1,2,3-triazoles (18) to be key intermediates in azide-alkyne click reaction with terminal alkynes, then trapped with electrophile to deliver 1,4,5-trisubstituted products. The stoichiometric quantity of copper(I) salts was used together with the stoichiometric amount of adequately reactive electrophiles. The intermediates **18** could be interrupted to afford C–5-functionalized 1,2,3-triazoles **19**. This reaction was developed by using ICl as trapping reagent (**Scheme 3**) (Wu *et al.*, 2005).

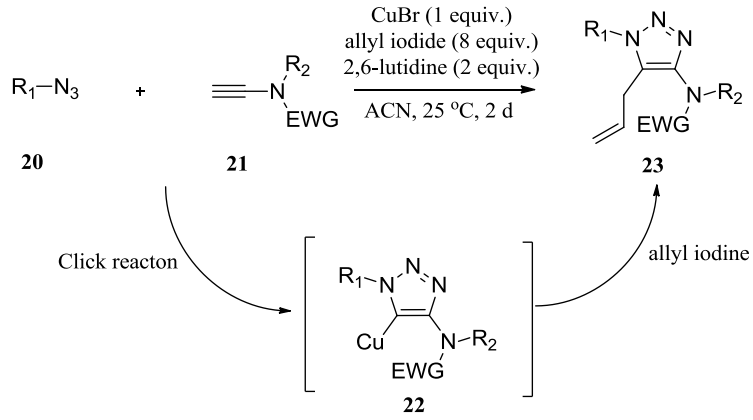
Scheme 3. Synthesis of 1,4,5-trisubstituted-1,2,3-triazole via One-Pot Reaction



In 2007, Zhang and co-workers demonstrated the synthesis of 1,4,5-trisubstituted-1,2,3-triazoles as a precursor of ring-closing diene or enyne metathesis reactions via copper-mediated [3+2] cycloaddition with ynamides. The reaction

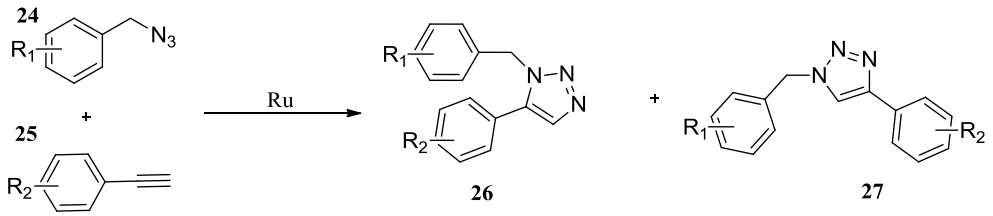
occurred through the intermediate **22** and directly underwent coupling with allyl iodide to yield 1,2,3-triazoles **23** in 26-78 % (**Scheme 4**) (Zhang *et al*., 2007).

Scheme 4. Synthesis of triazole-templated ring-closing metathesis



In 2005, Zhang and co-workers discovered the synthesis of 1,2,3-triazoles via ruthenium-catalyzed cycloaddition of azides **24** and terminal alkynes **25**. The main point of this task was to control the regioselectivity between 1,5-(**26**)and 1,4-(**27**) trisubstituted triazoles (**Scheme 5**) (Zhang *et al*., 2005).

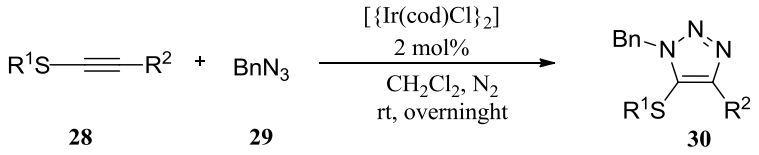
Scheme 5. Ruthenium-catalyzed cycloaddition of alkynes and organic azides



$Ru(OAc)_2(PPh_3)_2$	-	100%
$CpRuCl(PPh_3)_2$	85%	15%
$Cp^*RuCl(PPh_3)_2$	100%	-
Cp*RuCl(NDB)	100%	-

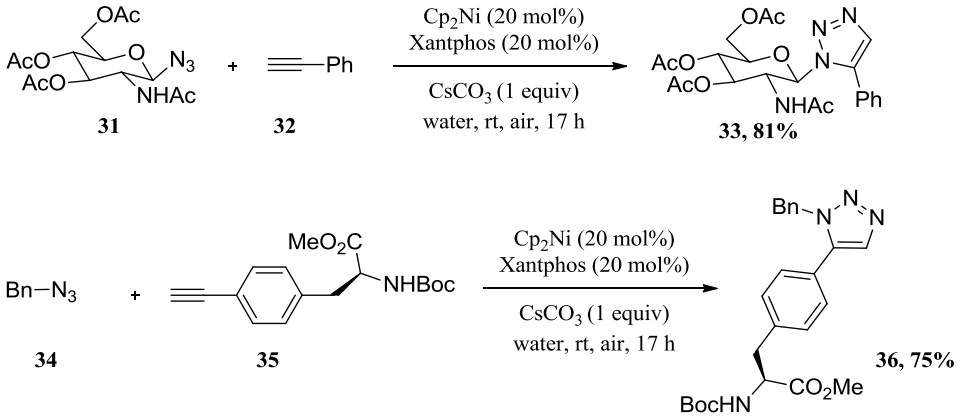
In 2014, Ding and co-workers presented an iridium-catalyzed azide–alkyne cycloaddition reaction of electron-rich internal alkynes **28**. They used $[\{Ir(cod)Cl\}_2]$ as a magnificent catalyst to synthesize the desired 5-thio-1,2,3-triazoles **30** not only in substantially quantitative yield but also with absolute regioselectivity. In addition this reaction occurred under mild conditions (**Scheme 6**) (Ding *et al*., 2014).

Scheme 6. Iridium-catalyzed reaction of Internal thioalkynes



In 2017, Kim and co-workers represented the synthesis of the 1,5-disubstituted 1,2,3-triazoles from common reagents by using an azide−alkyne cycloaddition. The highlight of this methodology was the synthetic utility of nickel-catalyzed pathway through the functionalization of carbohydrates and amino acids (**Scheme 7**). The nickel-catalyzed reaction could occur in water at room temperature (Kim *et al*., 2017).

Scheme 7. Nickel-catalyzed azide−alkyne cycloaddition

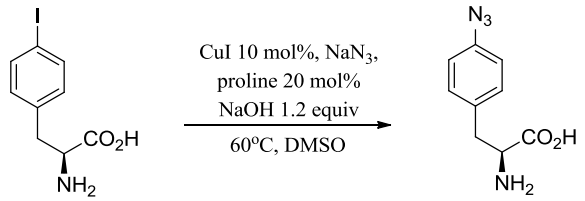


According to the information from literature reviews, the azide-alkyne click reactions were able to be accomplished with a variety of catalysts such as Cu, Ru, Ir, and Ni. The Cu-catalyzed reaction has been considered as one of the best choices because copper-catalyzed can undergo both Ullmann-type coupling and azide-alkyne cycloaddtion under mild condition. In addition, copper is available catalyst, low cost and low toxicity.

1.2.3 Selected developments of azides and aryl halide couplings

In 2004**,** Zhu and co-workers reported the synthesis of aryl azide via proline-promoted Cu(I)-catalyzed coupling reactions from L-phenylalanine **37** and sodium azide Cu(I) was used as a catalyst. This reaction provided aryl azide **38** in high yield (91%) (**Scheme 8**) (Zhu *et al*., 2004).

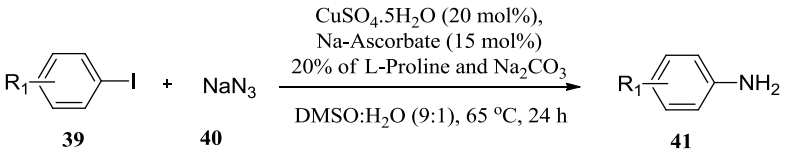
Scheme 8. Synthesis of aryl azides *via* proline-promoted Cu(I)-catalyzed reactions



37 **38**

In 2010, Goriya and Ramana accomplished the synthesis of aniline derivatives via copper-catalyzed aryl iodine and NaN_3 coupling. They found that aryl azide intermediates underwent reduction to yield the corresponding aniline derivatives **41** in 65-70% (**Scheme 9**) (Goriya *et al*., 2010).

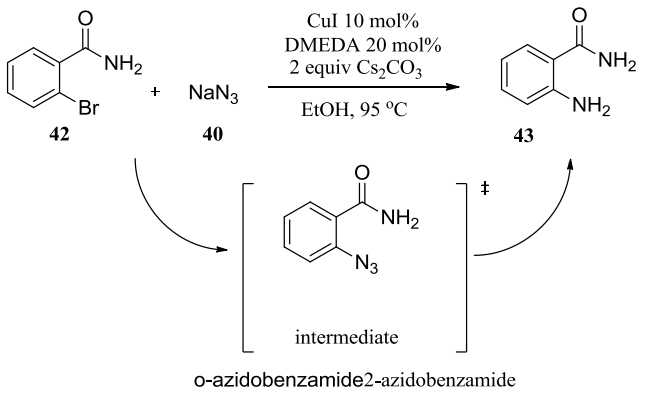
Scheme 9. Synthesis of benzyl amines



39 **40** **41**

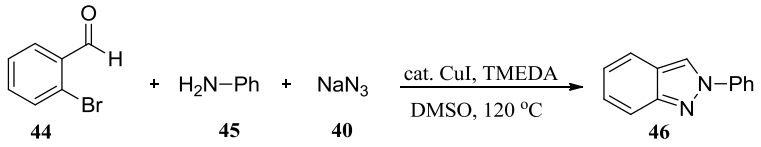
In 2010, Zhao and co-workers synthesized fifteen *o*-amino benzamide derivatives (**43**) in 43-95% yields. They utilized the copper-catalyzed aryl-azide coupling by using *o*-halobenzamide **42** and NaN_3. This reaction occurred through *o*-azidobenzamide intermediate, which was then reduced to *o*-amino benzamide (**43**) (**Scheme 10**) (Zhao *et al*., 2010).

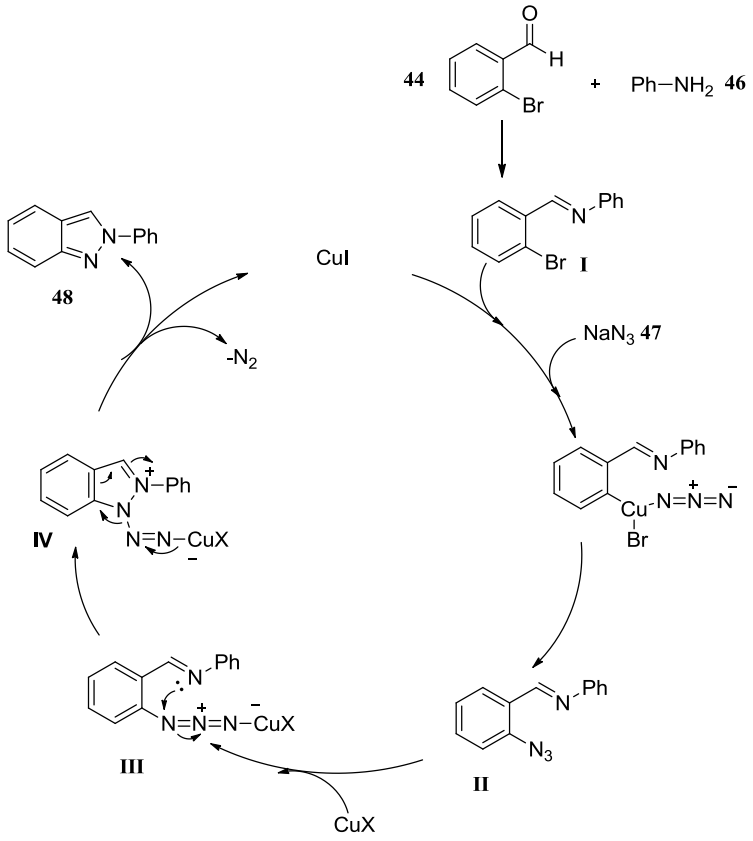
Scheme 10. Copper-catalyzed direct amination



In 2011, Kumar and co-workers demonstrated a multicomponent reaction of 2*H*-indazoles synthesis. The products were obtained in 30-96% yields. They proposed that the imine **I** was initially formed from the condensation of aldehyde **44** and aniline (**45**). Next, imine **I** underwent Ullmann-type coupling with NaN_3 to form aryl azide intermediate **II** followed by cyclization and elimination to provide the desired 2*H*-indazoles **46**. (**Scheme 11**) (Kumar *et al.*, 2011).

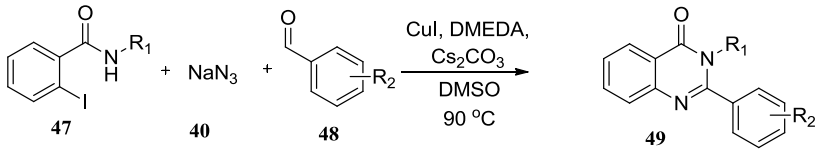
Scheme 11. Copper-catalyzed one-pot three-component synthesis of 2*H*-Indazole

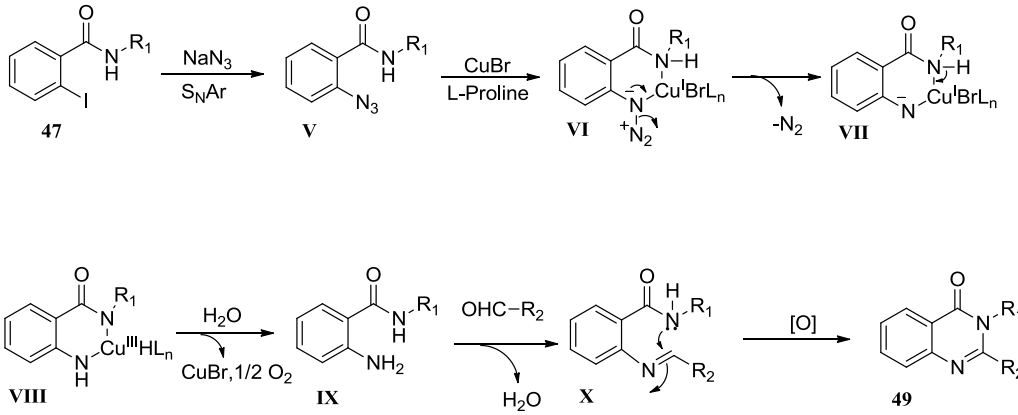




In 2016, Li and co-workers showed a multicomponent reaction to synthesize quinazolinones from simple 2-iodobenzamides **47**, sodium azide (**40**) and benzaldehydes **48**. The sequences of the reaction consisted of five key steps. The first was the copper-catalyzed aryl halide-azide coupling to generate 2-azidobenzamide **V**. Secondly, **V** underwent reduction to give 2-aminobenzamide **IX** in the presence of copper. The third was the formation of imine **X** from **IX** and aldehyde. Then, intramolecular cyclization occurred to give dihydroquinazolinones, followed by an oxidation to accomplish target quinazolinone **49**. (**Scheme 12**) (Li *et al*., 2016).

Scheme 12. Copper-catalyzed three component reaction to construct quinazolinones

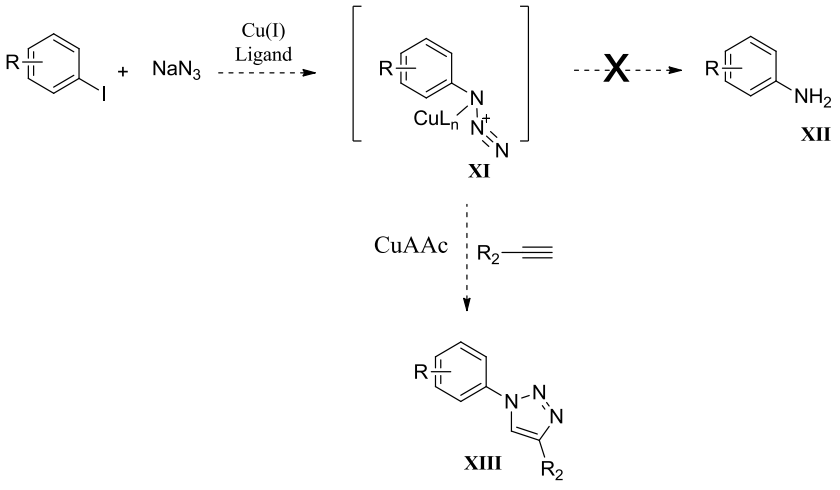




Based on the reports showing above, the coupling reaction between aryl halides and sodium azide under copper catalysis mostly gave aryl amine except Xu's work giving aryl azide. This indicated that aryl azides were not stable and immediately underwent reduction yielding a corresponding aryl amine.

Therefore, it was a challenging task to force azide intermediate **XI** to proceed CuAAc rather than the azide reduction (**Scheme 13**).

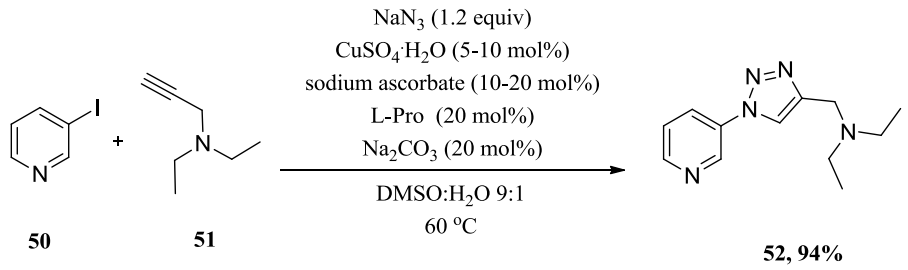
Scheme 13. The pathway to furnish 1,2,3-traizole compounds



Remarkably, there are some research groups could accomplish 1,2,3-triazole synthesis via copper-catalyzed multicomponent reaction using the coupling of aryl halide and NaN_3 as their key step.

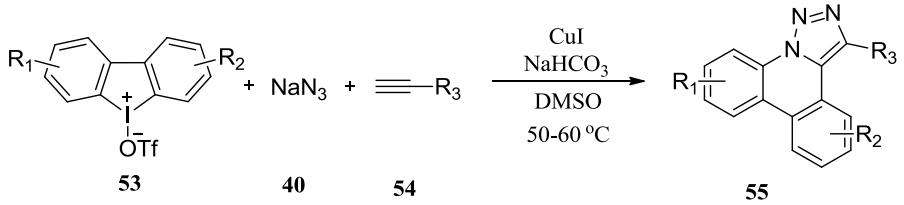
In 2004**,** Feldman and co-workers reported the synthesis of 1,4-disubstituted 1,2,3-triazole **52** directly from a variety of aryl halides **50,** alkyne **51** and sodium azide by using a multicomponent reaction. Therefore, an isolation of the azide intermediates was not required in this reaction (**Scheme 14**) (Feldman *et al*., 2004).

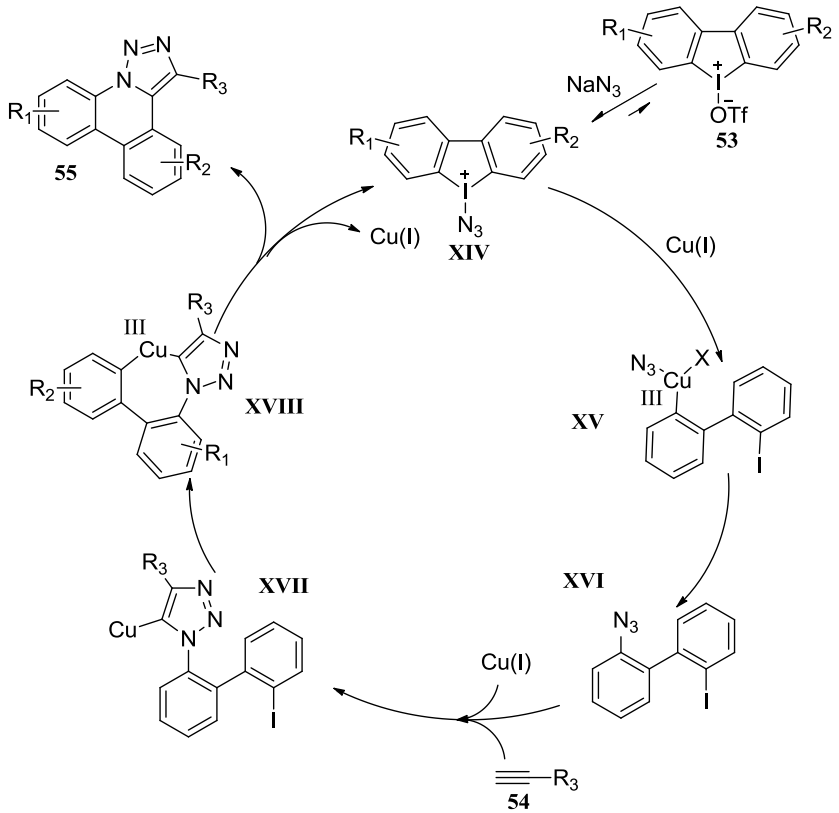
Scheme 14. One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles



In 2014, Liu and co-workers displayed a three-component cascade reaction of triazolophenanthridine synthesis. diaryliodonium **53**, NaN_3, and terminal alkynes **54** were utilized to construct the desired product **59**. The possible mechanism was proposed in **Scheme 15**. First, the triflate anion of **56** was interchanged with azide of **40**, followed by Ullmann-type coupling catalyzed by CuI to afford **XVI**. Intermediate **XVI** reacted with alkynes **51** to give intermediate **XVII** via a CuAAC reaction. Finally, triazolophenanthridines **55** were generated from a C-C bond formation of **XVII** through complex **XVIII** (Liu *et al*., 2014).

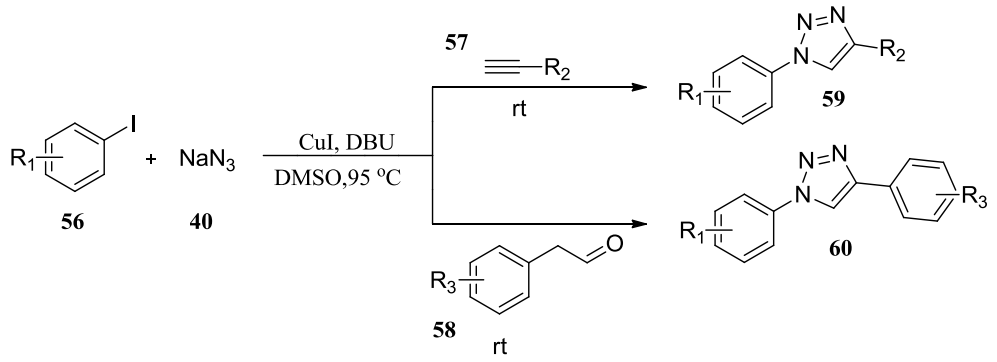
Scheme 15. Mild Cu(I)-catalyzed cascade reaction of triazolophenanthridines





In 2016, 1,4-disubstituted-1,2,3-triazoles were prepared by Jiang and co-workers with a short period of time by using a two-step reaction process in one pot fashion. The aryl azides were generated from aryl halides **56** and NaN_3 **40** at first step, and then aryl azides reacted with terminal alkynes **57** or phenylacetaldehyde derivatives **58** to yield the desired products in 70-94% (**Scheme 16**) (Jiang *et al*., 2014).

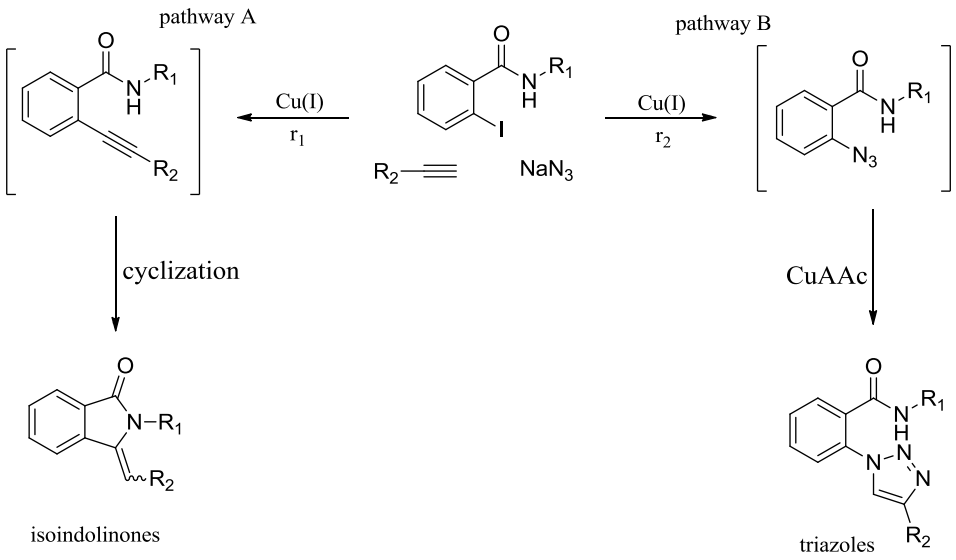
Scheme 16. Cu-catalyzed one-pot protocol for synthesis of 1,2,3-triazoles



Although methodologies of 1,2,3-triazole synthesis have been reported consistently, most of them required two step processes (forming aryl-azide and cycloaddition) and long period of time. Therefore, the synthesis of 1,2,3-triazole via multicomponent reaction in one step process and short period of time still remained as a challenge task.

We alternatively anticipated that the reaction of 2-iodobenzamides, NaN_3 and terminal alkynes could potentially undergo domino process to give 1,2,3-triazoles in one-step process. However, our multicomponent-designed reaction faced a competitive reaction, in which 2-iodobenzamide and terminal alkyne could form isoindolinone (**Scheme 17**, pathway A). We tried to develop a copper-catalyzed MCR in which the 2-iodobenzamides first undergo a reaction with NaN_3 to form the aryl azide intermediates. In the presence of terminal alkynes, a subsequent CuAAC reaction would take place to give the 1,4-disubstituted 1,2,3-triazoles (**Scheme 17**, pathway B).

Scheme 17. Possible reaction pathways of copper-catalyzed MCR



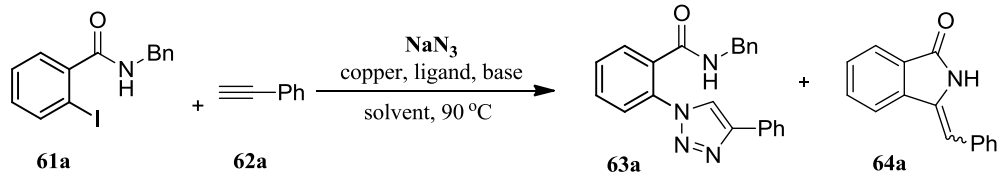
1.3 Objectives

1. To achieve the common method of 1,2,3-triazole and its derivatives via copper-catalyzed multicomponent reactions of terminal alkyne, sodium azide and 2-iodo benzamide.
2. To understand the copper-catalyzed multicomponent reactions and the reaction mechanism.

CHAPTER 2
RESULTS AND DISCUSSION

To test our hypothesis, we started our Cu(I)-catalyzed multicomponent reaction by taking *N*-benzyl-2-iodobenzamide **61a**, sodium azide, and phenylacetylene **62a** as our reaction model. The optimization of the reaction included catalyst, ligands, bases and solvents.

Table 1 Optimization of reaction conditions[a]



Entry	Cu	Ligand	Base	Solvent	Yield (%)*b*
1	CuBr	DMEDA	Cs_2CO_3	DMSO	Trace [c]
2	CuBr	1,10-phenanthroline	Cs_2CO_3	DMSO	Trace [c]
3	CuBr	1,2-diaminocyclohexane	Cs_2CO_3	DMSO	35 (52)
4	CuBr	L-proline	Cs_2CO_3	DMSO	44 (39)
5	CuBr	2,2′-bipyridine	Cs_2CO_3	DMSO	Trace [c]
6	CuBr	picolinic acid	Cs_2CO_3	DMSO	Trace [c]
7	CuBr	-	Cs_2CO_3	DMSO	Trace [c]
8	CuBr	L-proline	K_3PO_4	DMSO	32 (38)
9	CuBr	L-proline	K_2CO_3	DMSO	43 (31)
10	CuBr	L-proline	$NaHCO_3$	DMSO	66 (22)
11	CuBr	L-proline	-	DMSO	66 (12)
12	CuI	L-proline	-	DMSO	61 (14)
13	Cu_2O	L-proline	-	DMSO	53 (9)
14	$Cu(OAc)_2$	L-proline	-	DMSO	49 (10)
15	CuBr	L-proline	-	DMF	57 (9)
16	CuBr	L-proline	-	CAN	39 (15)
17	CuBr	L-proline	-	DMSO/H_2O (2:1)	73 (8)

Table 1 (continued)

Entry	Cu	Ligand	Base	Solvent	Yield (%)
18	**CuBr**	**L-proline**	**-**	**DMSO/H_2O (2:1, 0.4 M)**	**82 (5)**
19	CuBr	L-proline	-	DMSO/H_2O (2:1, 1.0 M)	70 (trace *c*)
20	CuBr	L-proline	-	DMSO/H_2O (1:1, 1.0 M)	63 (trace *c*)

[a] Reaction conditions: **61a** (0.4 mmol), **62a** (0.6 mmol), **NaN_3** (0.6 mmol), catalyst (20 mol%), ligand (20 mol%), solvent (0.2 M) at 90 ^oC for 2 h in sealed tube.
[b] Isolated yield.
[c] Trace amount of product observed from the 1H NMR spectrum of the crude reaction mixture.

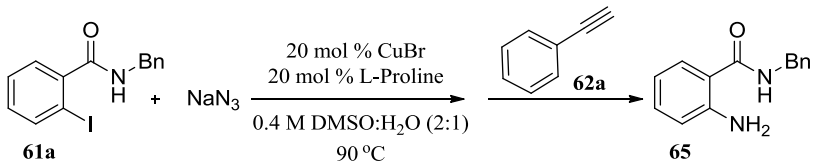
We started to explore a common ligands, such as *N*,*N*′-dimethylethylene-diamine (DMEDA), 1,10-phenanthroline, 1,2-diaminocyclohexane, L-proline, 2,2′-bipyridine, picolinic acid and the absence of ligand in the reaction (Table 1, entries 1–7). Satisfactorily, the product was obtained in 35% yield when 1,2-diamino-cyclohexane was used. By-product, isoindolinone, was also found in this reaction (entry 3). Changing ligand to L-proline slightly increased the yield of product to 44% with 39% of byproduct (entry 4).

Isoindolinone **64a** was undesired product in our reaction. Therefore, we tried to minimize the amount of isoindolinenone **64a**. We assumed that isoindolinonone occurred from competitive reaction (pathway A) (**Scheme 17**). If we could decrease the rate(r_1) of isoindolinone formation, the yield of triazole **63a** would be improved. We thought that base was an important factor in forming of Cu-alkyne complex, key intermediate for pathway A. Consequently, a various bases, such as K_3PO_4, K_2CO_3 and $NaHCO_3$, were explored (entries 8-10). The yield of triazole **63a** and isoindoline **64a** were obtained in 32% and 38% from K_3PO_4, respectively (Table 1, entry 8). Changing base to K_2CO_3, the yield of reaction was similar to that of K_3PO_4 in which **63a** and **64a** were obtained in 43% and 31%, respectively (Table 1, entry 9). When we used weak base, $NaHCO_3$, the yield of triazole was dramatically improved to 66% and the yield of by-product **64a** was also decreased to 22% (Table 1, entry 10). Significantly, with no base condition the yield of desired product **63a** still remained 66% while the yield of isoindolinone was diminished to 12% yield (Table 1, entry

11). These results suggested that with no base the rate of the formation of Cu-alkyne complex was decreased. We continued our investigation with the absence of base. Next, a variety of copper salts was applied to the reaction. The cases of CuI, Cu_2O and $Cu(OAc)_2$ gave product **63a** in moderate yields (61, 53 and 49%, respectively) (Table 1, entries 12–14). In order to improve the yield of product, we proposed that the other factor that increased the yield of triazole was a solubility of starting material. Therefore, commons polar solvents were investigated (entries 15 and 16). Unfortunately, both DMF and ACN gave product in moderate yields (57 and 39% respectively). The attempt to increase the rate of azidation by increasing solubility of NaN_3 was crucially successful. The product yield was increased to 73% when H_2O was mixed to the solvent (entry 17). High concentration also affected the reaction. To our delight, high yield (82%) was obtained when the concentration of the reaction was increased to 0.4 M (entry 18). Note that the higher concentration of reaction mixture would be problem with solubility of substrate. Lower yields were obtained (entries 19 and 20).

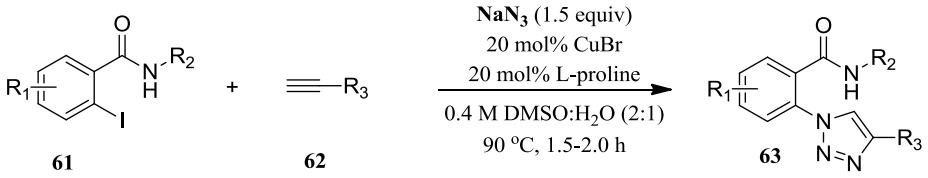
Interestingly, when we tried to solve the problem of isoindolinones **64a** by using a two-step process reaction in one pot. The reaction afforded aniline by-product **65** instead of 1,2,3-triazole **63a**. This result suggested that azidobenzamide could be reduced rapidly under copper catalysis condition, and one-step process was necessary for our multicomponent reaction (**Scheme 18**).

Scheme 18. Two-step process reaction in one-pot manner



With the optimal reaction conditions in hand, we next studied the scope of substrates for an exploration of the reaction efficiency (**Table 2**).

Table2 The synthesis of 2-(1,2,3-triazolyl)benzamide derivatives from 2-iodobenzamides **61**, terminal alkynes **62** and sodium azide[a]



61 **62** **63**

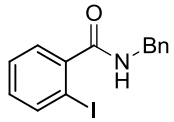
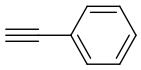
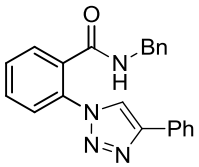
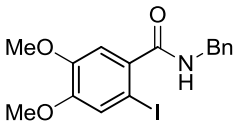
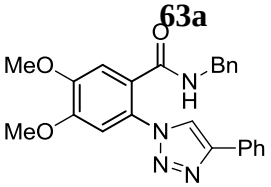
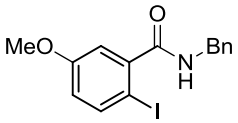
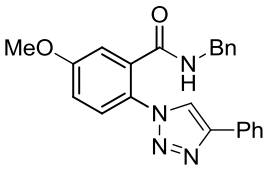
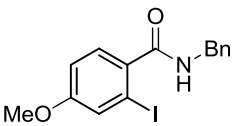
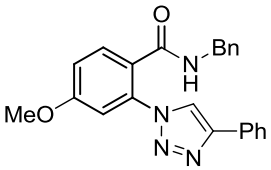
Entry	2-Iodobenzamide	Terminal alkynes	1,2,3-Triazole	Yield (%)*b*
1	 **61a**	 **62a**	 **63a**	82%
2	 **61b**	**62a**	 **63b**	60%
3	 **61c**	**62a**	 **63c**	90%
4	 **61d**	**62a**	 **63d**	93%[c]

Table 2 (continued)

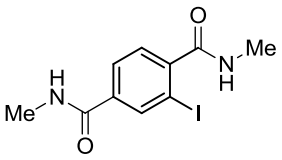
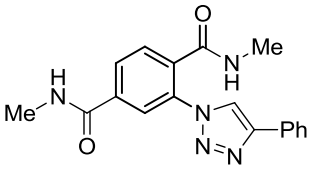
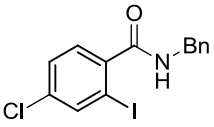
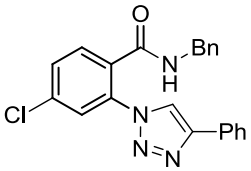
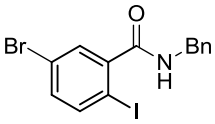
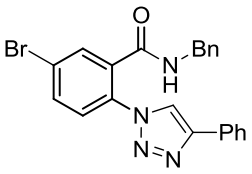
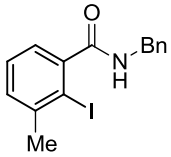
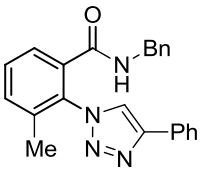
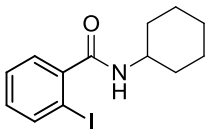
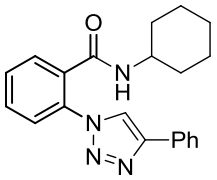
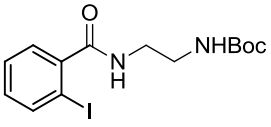
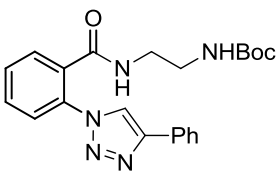
Entry	2-Iodobenzamide	Terminal alkynes	1,2,3-Triazole	Yield (%)*b*
5	 **61e**	**62a**	 **63e**	92%
6	 **61f**	**62a**	 **63f**	70%
7	 **61g**	**62a**	 **63g**	73%
8	 **61h**	**62a**	 **63h**	71%
9	 **61i**	**62a**	 **63i**	90%
10	 **61j**	**62a**	 **63j**	96%

Table 2 (continued)

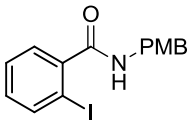
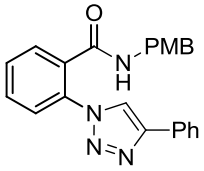
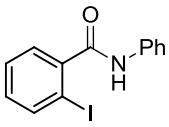
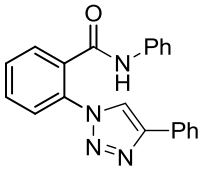
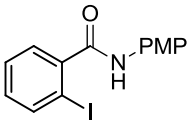
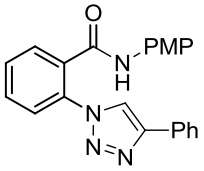
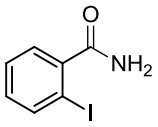
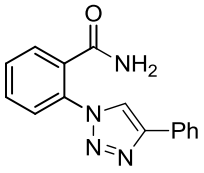
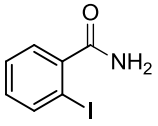
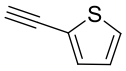
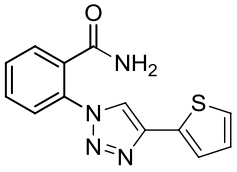
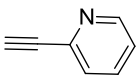
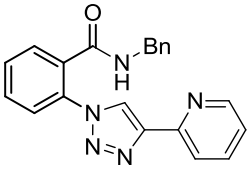
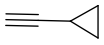
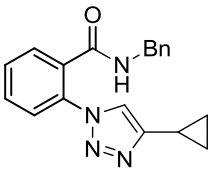
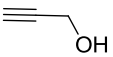
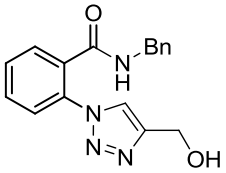
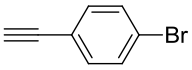
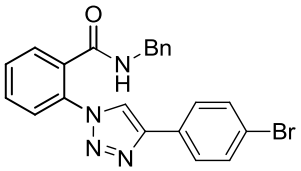
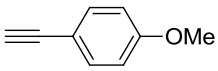
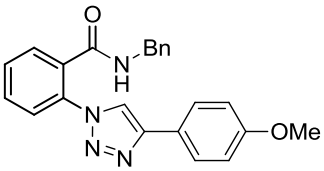
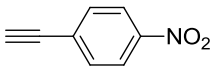
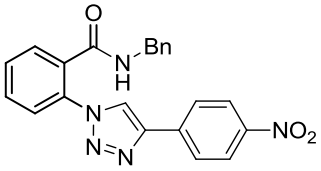
Entry	2-Iodobenzamide	Terminal alkynes	1,2,3-Triazole	Yield (%)[b]
11	 **61k**	**62a**	 **63k**	81%
12	 **61l**	**62a**	 **63l**	68%
13	 **61m**	**62a**	 **63m**	80%
14	 **61n**	**62a**	 **63n**	90%
15	 **61n**	 **62b**	 **63o**	96%
16	**61a**	 **62c**	 **63p**	93%

Table 2 (continued)

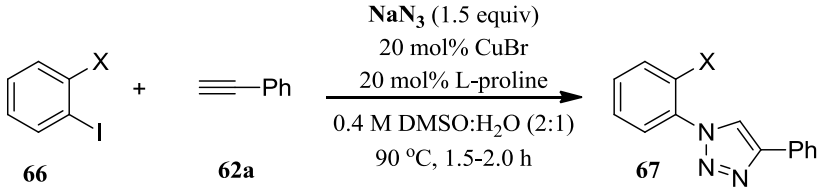
Entry	2-Iodobenzamide	Terminal alkynes	1,2,3-Triazole	Yield (%)[b]
17	**61a**	 **62d**	 **63q**	71%
18	**61a**	 **62e**	 **63r**	67%
19	**61a**	 **62f**	 **63s**	72%
20	**61a**	 **62g**	 **63t**	82%
21	**61a**	 **62h**	 **63u**	95%

[a] Reaction conditions : **61** (0.4 mmol), **62** (0.6 mmol).
[b] Isolated yield.

First, we considered a various substituents on aromatic ring of 2-iodobenzamide. We found that both electron-donating groups (entries 2–4) and electron-withdrawing group (entry 5) could give the corresponding triazoles in the reaction. However, 2-iodobenzamide with dimethoxy substituents afforded **63b** in a moderate yield, 60% (entry 2). On the contrary, with mono substituent of methoxy the high yields of products were obtained (entries 3 and 4). Amide functionality was a representative of electron-withdrawing group provided the product **63e** in excellent 92% yield (entry 5). Halogen substituents of 2-iodobenzamide were also suitable to our reaction. Relatively good yields were obtained from **61d** and **61g** in 70% and 73%, respectively (entries 6 and 7). Having methyl substituent next to the iodine slightly affected the yield of reaction. The product was obtained in 71% (entry 8). A variety of substituents on amide nitrogen was also included in our substrate scope study. The alkyl substituents gave excellent yields of the product (entries 9 and 10). The yields of corresponding triazoles were slightly decreased when N-aryl substituted 2-iodobenzamides were used (entries 11–13). We assumed that the resonance effect from aromatic ring on nitrogen atom significantly affected to the Lewis basicity of the amide, resulting in less directing group ability. 2-Iodobenzamide with free amide also provided high yield of the product 90% (entry 14). Furthermore, we explored a variety of terminal alkynes in the reaction. A broad range of terminal alkynes was applicable to the reaction. The yields of corresponding triazoles were obtained relatively high (entries 15–21). Thiophene and pyridine-substituted acetylenes gave high yield of triazoles (96% and 93%, respectively) (entries 15 and 16). Alkyl-substituted acetylenes also provided good yield of products (entries 17 and 18). Significantly, propagyl alcohol was suitable to the reaction giving triazole in 67% (entry 18). Wide ranges of substituents of phenylacetylenes were also applicable to the reaction. The yields of product were obtained in high yields (entries 19–21).

After we found the directing ability of amide nitrogen played a role in the reaction, we turned our interest to a variety of directing groups of phenyl iodide (**Table 3**).

Table 3. 1,2,3-Triazole formation by using other directing groups[a]



66 **62a** **67**

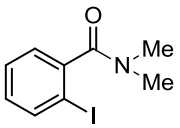
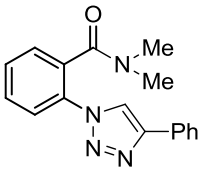
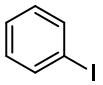
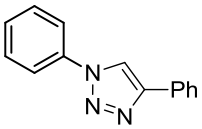
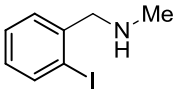
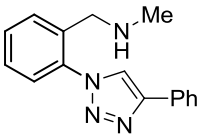
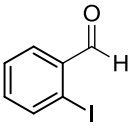
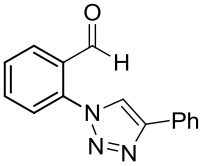
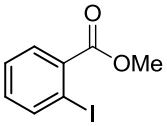
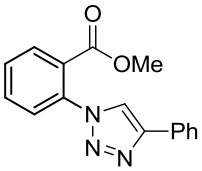
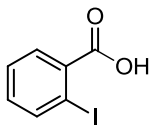
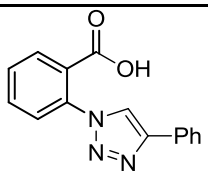
Entry	The functional groups *ortho* to the iodine atom	1,2,3-Triazole	Yield (%)*b*
1	 **66a**	 **67a**	NR[c]
2	 **66b**	 **67b**	28%
3	 **66c**	 **67c**	95%
4	 **66d**	 **67d**	63%
5	 **66e**	 **67e**	87%

Table 3 (continued)

Entry	The functional groups *ortho* to the iodine atom	1,2,3-Triazole	Yield (%)*b*
6			47%
	66f	**67f**	

[a] **Reaction conditions. : 66 (0.4 mmol), 62a (0.6 mmol).**
[b] **Isolated yield.**
[c] **No reaction.**

To test the effect of the directing group, we used the tertiary amide **66a** in the reaction. The product **67a** was not observed (entry 1). We only observed the starting materials from the ^{1}H NMR spectrum of the crude reaction mixture. The less coordination ability and steric hindrance of the tertiary amide were the main reason of the failed reaction. Without any directing group, the reaction of iodobenzene provided **67b** in low 28% yield (entry 2). Triazole **67c** was obtained in excellent 95% yield from an aryl amide **67c** having a secondary amine as the directing group (entry 3). Other directing groups, such as aldehyde and ester, provided moderate to good yields of the products (entries 4 and 5). However, with free acid functionality the yield of product was reduced to 47% (entry 6).

CHAPTER 3
CONCLUSION

We accomplished the synthesis of 1,4-disubstituted 1,2,3-triazole derivatives *via* copper-catalyzed multicomponent reaction from 2-iodobenzamides, sodium azide and terminal alkynes under mild reaction conditions in a short period of time. The multicomponent reaction processes represented the efficient method to construct 2-(1,2,3-triazolyl)benzamides and the isolation of the aryl azide intermediates were not required. In addition, we could minimize the competitive reaction (coupling of terminal alkyne and 2-iodobenzamide) by using non-external base condition. We also found that the solubility of NaN_3 played a huge role in our reaction leading to the high yield of the products.

CHAPTER 4
EXPERIMENTAL

4.1 General Information

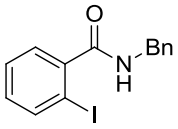
Solvents for extraction and column chromatography were distilled at their boiling point ranges prior to use. Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} (Merck) and were visualized by fluorescence quenching under UV light. Column chromatography was performed on SilicaFlash®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

4.2 Preparation of Starting Materials

General Procedure A – Synthesis of 2-Iodobenzamide

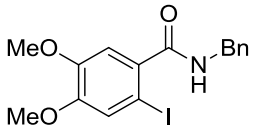
Prepared according to literature procedure (Kitching *et al*., 2012). A flame-dried round bottom flask was charged with 1.0 equiv of 2- iodobenzoic acid in CH_2Cl_2 (0.3 M) and DMF (2 drops), followed by the addition of 1.25 equiv of oxalyl chloride at 0 ºC. The reaction mixture was allowed to stir at room temperature for 4 h. After that, the mixture was evaporated to dryness. The prepared acid chloride was dissolved in CH_2Cl_2 (0.3 M). The solution of amine (1.5 equiv) and triethylamine (3.0 equiv) was added at 0 ºC. The reaction mixture was allowed to stir at room temperature for 15 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over

anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to afford the title compound.



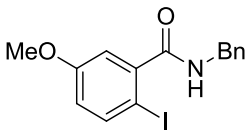
***N*-Benzyl-2-iodobenzamide (61a).**

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-iodo-4,5-dimethoxybenzamide (61b).**

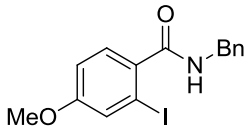
Prepared according to the general procedure A. Yield 96% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.24 (m, 5H), 7.19 (s, 1H), 7.01 (s, 1H), 6.25 (brs, 1H), 4.62 (d, *J* = 5.7 Hz, 2H), 3.86 (s, 3H) 3.85 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 150.5, 149.2, 137.6, 134.1, 128.7, 128.2, 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*-benzyl-2-iodo-5-methoxybenzamide(61c)**

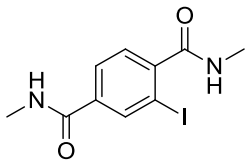
Prepared according to the general procedure A. Yield 94% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 4.3 Hz, 1H), 7.42–7.30 (m, 5H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.69 (dd, *J* = 1.5, 4.4 Hz, 1H), 6.03 (brs, 1H), 4.65 (d, *J* = 2.8 2H), 3.79 (s, 3H);

^{13}C NMR (75 MHz, DMSO-d_6) δ 169.0, 159.6, 144.1, 140.5, 139.5, 128.7, 127.9, 127.3, 117.4, 114.7, 82.3, 56.0, 43.0; IR (thin film) ν 3855, 3736, 2958, 2862, 2343, 1698, 1522, 1053 cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{15}H_{14}INO_2$ 389.9967, found 390.0021.



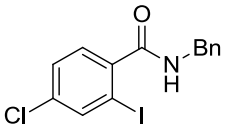
***N*-benzyl-2-iodo-4-methoxybenzamide (61d)**

Prepared according to the general procedure A. Yield 94% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 7H), 6.78 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.55 – 6.44 (m, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 168.9, 160.5, 137.9, 134.0, 129.3, 128.6, 128.1, 127.5, 125.3, 113.8, 93.1, 55.6, 44.1. ATR-IR 3280 (w), 1634 (s), 1592 (s), 1537 (m), 1480 (m), 1286 (m), 1228 (s), 1021 (s), 697 (m). These data matched to the literature values (Yao *et al.*, 2013).



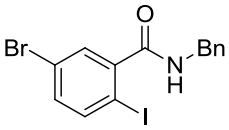
2-iodo-*N*^{1},*N*^{4}-dimethylterephthalamide (61e)

Prepared according to the general procedure A. Yield 98% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21(s, 1H), 7.73-7.70 (m, 1H), 7.41–7.38 (m, 1H), 6.29 (brs, 1H), 5.92 (brs, 1H), 3.05–3.01 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.4, 165.0, 145.8, 137.9, 136.5, 128.2, 127.2, 94.0, 26.8, 26.5; IR (thin film) ν 3850, 3736, 3275, 2963, 2343, 1648, 1542cm^{-1} . HRMS (ESI) $[M+Na]^+$ calcd. For $C_{10}H_{11}IN_2O_2$ 340.9763, found 340.9762.



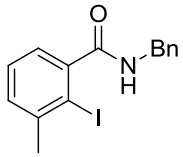
N-benzyl-4-chloro-2-iodobenzamide (61f)

Prepared according to the general procedure A. Yield 89% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.03 (m, 1H), 7.86 (s, 1H), 7.48 (dd, 8.4, 2.0 Hz, 1H), 7.38-7.32 (m, 5H), 6.08 (bs, 1H), 4.63 (s, 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): 3264, 2924, 2853, 1644, 1541, 1386, 1125, 1060 cm^{-1}. These data matched to the literature values (Balkrishna *et al*., 2013)



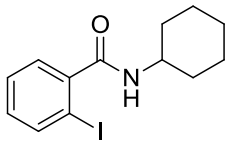
***N*-Benzyl-5-bromo-2-iodobenzamide (61g)**

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}; These data matched to the literature values (Songsichan *et al*., 2014)



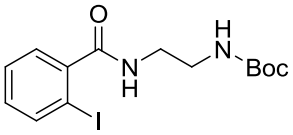
***N*-benzyl-2-iodo-3-methylbenzamide (61h)**

Prepared according to the general procedure A. Yield 92% 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 (Songsichan *et al*., 2014).



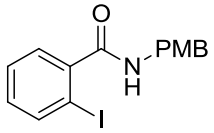
_N_-cyclohexyl-2-iodobenzamide (61i)

2% NaOH (4.4 ml) was added to a solution of an amine (1.0 mmol) in DCM (2 mL). The mixture was cooled to 0 ^{o}C and o-iodobenzoic acid chloride (1.1 mmol) dissolved in DCM (3 ml) was added dropwise. The reaction mixture was stirred in room temperature for 20h and the product was extracted with DCM. Combined organic layers were washed with saturated $NaHCO_3$ and dried over magnesium sulphate. The solvent was removed under reduced pressure and the product was obtained yield 92% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68 (dt, J = 3.5, 13.3 Hz, 1H), 1.42-1.50 (m, 2H), 1.20-1.35 (m, 3H), 1.79 (dt, J = 4.2, 14.0 Hz, 2H), 2.07-2.15 (m, 2H), 4.00-4.08 (m, 1H), 5.65 (s, 1H), 7.11 (ddd, J = 2.1, 7.0, 8.4 Hz, 1H), 7.38-7.44 (m, 2H), 7.88 (dd, J=0.7, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 26.5x2, 33.9x2, 49.9, 93.4 , 129.1, 129.2, 131.9, 140.7, 143.6, 169.5; IR 3286, 2853, 1730, 1636, 1537, 1168, 1015 cm^{-1}. These data matched to the literature values (Agata *et al*., 2014).



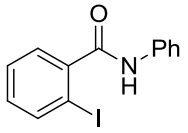
***tert*-butyl 2-(2-iodobenzamido)ethylcarbamate (61j)**

Prepared according to the general procedure A. Yield 89% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 7.9 Hz, 1H), 7.41-7.29 (m, 2H), 7.13–7.02 (m, 1H), 6.59 (brs, 1H), 5.11 (brs, 1H), 3.55 (q, J = 5.6 Hz, 2H), 3.39 (q, J = 5.6 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 156.8, 142.0, 139.8, 131.1, 128.1, 128.0, 92.5, 79.8, 40.9, 40.1, 28.4; IR (thin film) ν 3318, 2976, 2930, 1693, 1640, 1253, 1015, 751 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{14}H_{19}IN_2O_3$ 413.0338, found 413.0338.



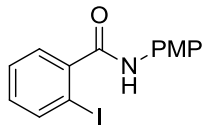
2-iodo-*N*-(4-methoxybenzyl)benzamide (61k)

Prepared according to the general procedure A. Yield 91% as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.86 (t, *J* = 6.0 Hz, 1H), 7.88 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.44 (ddd, *J* = 8.0, 7.6, 1.2 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.17 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 3.74 (s, 3H); 13C NMR (75 MHz, DMSO-d_6) δ 168.83, 158.24, 142.98, 139.14, 131.09, 130.76, 128.74, 128.05, 128.02, 113.66, 93.53, 55.07, 41.96; IR (thin film): ν 3441, 1656, 1545, 1514, 1027, 824, 762 cm^{-1}. These data matched to the literature values (Iqbal *et al*., 2015).



2-iodo-*N*-phenylbenzamide (61l)

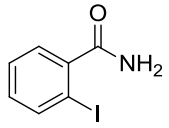
Prepared according to the general procedure A. Yield 93% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 1H), 7.73 (brs, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.46 (dd, J = 7.5, 1.5 Hz, 1H), 7.40- 7.33 (m, 2H), 7.19-7.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 142.1, 140.1, 137.7, 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 (Songsichan *et al*., 2014)



2-iodo-*N*-(4-methoxyphenyl)benzamide (61m)

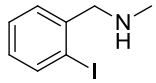
Prepared according to the general procedure A. Yield 94% as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.82 (s, 3H), 6.92 (d, *J* = 8.8, 2H), 7.15 (td, *J* = 7.6, 1.6 Hz, 1H), 7.30–7.38 (br, 1H), 7.43 (td, J = 7.2, 0.8 Hz, 1H), 7.50–7.60 (m, 3H), 7.91 (dd, J = 8.0, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 55.5, 92.4, 114.3, 121.9, 128.3,

128.5, 130.5, 131.4, 140.0, 142.2, 156.9, 167.1; IR (thin film) ν 3306, 1651, 1510, 1412, 1229 cm^{-1}. These data matched to the literature values (Miyura *et al*., 2012).



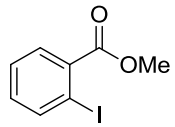
2-iodobenzamide (61n)

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 ºC. The reaction mixture was allowed to stir at room temperature for 4 h. After that, the mixture was evaporated to dryness. The prepared acid chloride was dissolved in CH_2Cl_2 (0.3 M). NH_4OH (28-30%, 1.5 equiv) was added dropwise at 0 ºC. The reaction mixture was allowed to stir at room temperature for 2 h. The precipitate was filtered and washed with water to give **66n** as white solid. ^1H 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-*d6*) 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 (Songsichan *et al*., 2014).



1-(2-iodophenyl)-*N*-methylmethanamine (66c).

2-Iodobenzaldehyde (494 mg, 2 mmol) was dissolved in MeOH (4 mL) and methylamine (0.35 mL, 4 mmol, 2 equiv, 40% wt. soln in H_2O). The yellow solution was stirred for 1 h at rt then $NaBH_4$ (76 mg, 2 mmol, 1 equiv) was added. The reaction was stirred for 1 h at rt. Then 50 mL of H_2O was added and extracted in EtOAc (3 x 50 mL) then dried over Na_2SO_4, filtered, and concentrated to give **81c** as yellow oil. ^1H NMR (300 MHz, $CDCl_3$) 7.80 - 6.95 (m, 4H,), 3.70 (s, 2H,) 2.45 (s, 3H,), 1.95 (br.s, lH,); These data matched to the literature values (Phelippea, *et al*., 1988).

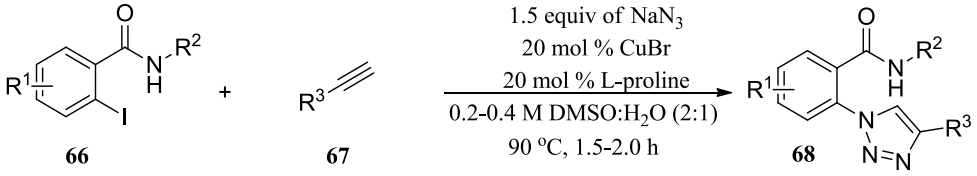


methyl 2-iodobenzoate (66e)

2- Haloarylcarboxylic acid (12 mmol) was dissolved in 60 mL of methanol. To the stirred reaction mixture 7.7 mL (12 eq) of concentrated sulfuric acid were then added dropwise. The reaction mixture was stirred at reflux until no more starting product was detected by TLC analysis. The reaction mixture was then cooled to rt and concentrated under reduced pressure. The residue was diluted with EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ (30 × 3 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed at reduced pressure to provode **71e** as Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.9 Hz, 1H,), 7.80 (d, *J* = 7.4 Hz, 1H,), 7.40 (t, J = 7.5 Hz, 1H,), 7.15 (t, *J* = 7.4 Hz, 1H,), 3.93 (s, 3H,). These data matched to the literature values (Gianni, *et al*., 1988).

4.3 Synthesis of 2-(1,2,3-triazole)benzamide derivatives

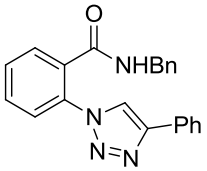
General Procedure for Copper-Catalyzed Multicomponent Reaction for Synthesis of 2-(1,2,3-Triazole)Benzamide Derivatives



66 **67** **68**

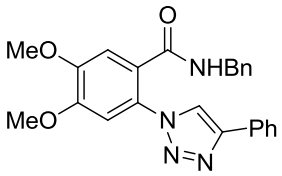
The reaction of *N*-benzyl-2-iodobenzamide (**61a**) and phenylacetylene (**62a**) is representative. A dried flask was charged with 2-iodobenzamide (**61a**) (0.5 mmol), commercially available phenylacetylene (0.6 mmol), sodium azide (0.75 mmol), CuBr 20 mol%, and L-proline 20 mol% in DMSO:H_2O (2:1) (1.25 mL). The reaction mixture was allowed to stir at 90 ^{o}C for 2 h. After completion of reaction, the reaction mixture was cooled to room temperature. Quenched with saturated NH_4Cl, extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford crude residue. Purification by column

chromatography (4:1 EtOAc:Hexane) to provide **63a** in 145.3 mg (82 % yield) as a light yellow solid.



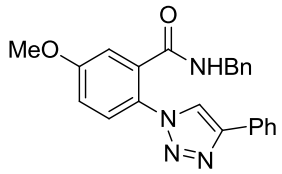
***N*-benzyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63a)**

Prepared according to general procedure from *N*-benzyl-2-iodobenzamide (**61a**) and phenylacetylene (**62a**). Yield 145.1 mg (82%) as light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.93 (t, J = 5.8 Hz, 1H), 8.79 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.59–7.52 (m, 4H), 7.37 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 7.1 Hz, 1H), 7.11–7.06 (m, 5H), 4.23 (d, J = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.6, 146.9, 139.4, 134.6, 133.5, 131.2, 130.9, 130.1, 129.4, 129.3, 128.6 (128.64), 128.6 (128.56), 127.2, 126.1, 125.8, 123.2, 42.9; IR (thin film) ν 3409, 2940, 2838, 1654, 1644, 1414, 1022 cm^{-1}. HRMS (ESI) [M+H]$^{+}$ calcd. for $C_{22}H_{18}N_4O$ 355.1559, found 355.1558.



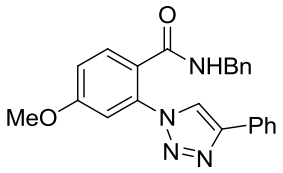
***N*-benzyl-4,5-dimethoxy-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63b)**

Prepared according to general procedure from *N*-benzyl-2-iodo-4,5-dimethoxybenzamide (**61b**) and phenylacetylene (**62a**). Yield 124.3 mg (60%) as light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.84 (t, J = 5.8 Hz, 1H), 8.68 (s, 1H), 7.87 (d, J = 7.4 Hz, 2H), 7.48 (t, J = 7.4 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.22–7.18 (m, 6H), 4.30 (d, J = 5.8 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.3, 150.3, 149.3, 146.6, 139.3, 130.8, 129.4, 128.6 (128.64), 128.6 (128.55), 128.0, 127.5, 127.2, 125.7, 125.5, 123.5, 111.7, 110.1, 56.6, 56.5, 43.0; IR (thin film) ν 3775, 3033, 2892, 2746, 1588, 1039, 956 cm^{-1}. HRMS (ESI) [M+H]$^{+}$ calcd. for $C_{24}H_{22}N_4O_3$ 415.1770, found 415.1770.



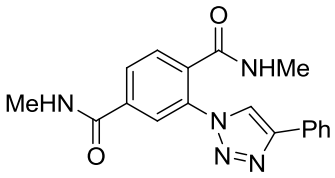
***N*-benzyl-5-methoxy-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63c)**

Prepared according to general procedure from *N*-benzyl-2-iodo-5-methoxybenzamide (**61c**) and phenylacetylene (**62a**). Yield 172.8 mg (90%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.01 (t, *J* = 5.8 Hz, 1H), 8.73 (s, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.26–7.18 (m, 6H), 4.33 (d, *J* = 5.8 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.2, 160.0, 146.6, 139.3, 134.8, 131.0, 129.4, 128.6, 128.5, 127.9, 127.7, 127.5, 127.2, 125.7, 123.5, 116.1, 114.4, 56.4, 42.9; IR (thin film) ν 3775, 3072, 2758, 1588, 1179, 1039, 957 cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{23}H_{20}N_4O_2$ 407.1484, found 407.1484.



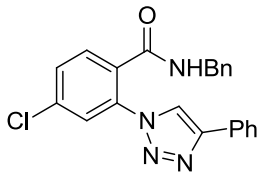
***N*-benzyl-4-methoxy-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63d)**

Prepared according to general procedure from N-benzyl-2-iodo-4-methoxybenzamide (**61d**) and phenylacetylene (**62a**). 178.8 mg (93%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (*s*, 1H), 7.88 (*dd*, *J* = 4.4, 0.8 Hz, 2H), 7.77 (*d*, *J* = 4.4 Hz, 1H), 7.53–7.40 (*m*, 3H), 7.31 (*s*, 1H), 7.18–7.01 (*m*, 5H), 7.18–7.08 (*m*, 6H), 6.20 (*brs*, 1H), 4.42 (*d*, *J* = 3Hz, 2H), 3.93 (*s*, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 161.4, 148.2, 137.2, 135.2, 130.9, 129.9, 128.9, 128.6, 128.5, 127.8, 127.5, 125.9, 124.8, 122.1, 115.9, 111.7, 55.9, 44.3; IR (thin film) ν 3288, 1638, 1612, 1277, 1165, 1031 cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{23}H_{20}N_4O_2$ 407.1484, found 407.1484.



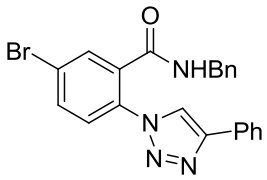
***N*[1],*N*[4]-dibenzyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)terephthalamide (68e)**

Prepared according to general procedure from *N*[1],*N*[4]-dibenzyl-2-iodoterephthalamide (**61e**) and phenylacetylene (**62a**). Yield 163.3 mg (92%) as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.92 (s, 1H) 8.71 (q, *J* = 4.4 Hz, 1H), 8.50 (q, *J* = 4.4 Hz, 1H), 8.10 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 2.81 (d, *J* = 4.4 Hz, 3H), 2.64 (d, *J* = 4.4 Hz, 3H) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.5, 165.2, 147.0, 136.8, 135.4, 134.5, 130.7, 129.6, 129.5, 128.7, 128.5, 125.8, 124.5, 123.0, 26.8, 26.5; IR (thin film) ν 3776, 3073, 2884, 2746, 1588, 1169, 957 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. $C_{18}H_{17}N_5O_2$ 336.1460, found 336.1460.



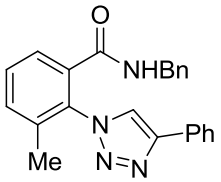
***N*-benzyl-4-chloro-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63f)**

Prepared according to general procedure from *N*-benzyl-4-chloro-2-iodobenzamide (**61f**) and phenylacetylene (**62a**). Yield 136.1 mg (70%) as light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.08 (t, *J* = 5.8 Hz, 1H), 8.81 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.75-7.67 (m, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.27–7.17 (m, 5H), 4.32 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.0,147.1, 139.0, 135.5, 135.3, 132.0, 131.0, 130.5, 130.0, 128.8, 128.7, 127.6, 127.3, 125.8, 123.1, 43.0; IR (thin film) ν 3778, 3694, 3068, 2883, 1587, 1118, 951 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{22}H_{17}ClN_4O$ 389.1169, found 389.1169.



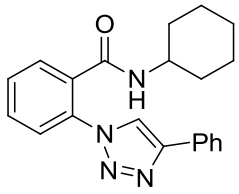
***N*-benzyl-5-bromo-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63g)**

Prepared according to general procedure from *N*-benzyl-5-bromo-2-iodobenzamide (**61g**) and phenylacetylene (**62a**). Yield 158.1 mg (73%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.14 (t, J = 5.8 Hz, 1H), 8.75 (s, 1H), 7.92–7.85 (m, 4H), 7.65 (d, J = 8.5 Hz, 2H), 7.48 (t, J = 7.4 Hz, 2H), 7.21–7.17 (m, 4H), 4.32 (d, J = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.3, 147.1, 138.9, 134.9, 134.1, 133.7, 131.9, 130.4, 129.5, 128.8, 128.7, 128.1, 127.6, 127.3, 125.8, 123.0, 122.9, 43.1; IR (thin film) ν 3790, 3090, 2879, 1599, 1128, 956 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{22}H_{17}BrN_4O$ 433.0664, found 433.0664.



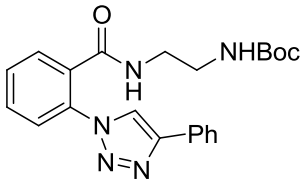
***N*-benzyl-3-methyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63h)**

Prepared according to general procedure from *N*-benzyl-2-iodo-3-methylbenzamide (**61h**) and phenylacetylene (**62a**). Yield 130.7 mg (71%) as light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.86 (d, J = 7.1 Hz, 2H), 7.60 (dd, J = 7.4, 1.4 Hz, 4H), 7.54–7.36 (m, 4H), 7.12–7.08 (m, 3H), 7.03–7.00 (m, 2H), 4.29 (d, J = 5.8 Hz, 2H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 166.1, 148.1, 137.1, 136.5, 135.0, 133.0, 132.8, 130.6, 129.9, 128.9, 128.6, 128.5, 127.7, 126.9, 125.9, 122.7, 44.2, 17.4; IR (thin film) ν 3776, 3697, 2884, 1588, 1169, 957 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{22}H_{17}BrN_4O$ 433.0664, found 433.0664.



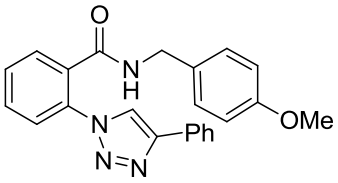
***N*-cyclohexyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63i)**

Prepared according to general procedure from *N*-cyclohexyl-2-iodobenzamide (**61i**) and phenylacetylene (**62a**). Yield 155.9 mg (90%) as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 2H), 7.71–7.68 (m, 1H), 7.58–7.35(m, 3H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 3.77–3.74 (m, 1H), 1.75–1.72 (m, 2H), 1.58–1.49 (m, 3H), 1.31–1.19 (m, 2H), 1.09–0.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 148.1, 133.8, 133.4, 130.8, 130.1, 130.0, 129.3, 128.9, 128.5, 126.2, 125.9, 122.1, 48.9, 32.4, 25.3, 24.6; IR (thin film) ν 3776, 3697, 3073, 2888, 1588, 1162, 956 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{21}H_{22}N_4O$ 347.1872, found 347.1872.



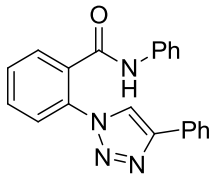
***tert*-butyl 2-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamido)ethylcarbamate (63j)**

Prepared according to general procedure from *tert*-butyl 2-(2-iodobenzamido)-ethylcarbamate (**61j**) and phenylacetylene (**62a**). Yield 195.6 mg (96%) as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.55 (t, *J* = 5.3 Hz, 1H), 7.94 (d, *J* = 7.7 Hz, 2H), 7.70–7.62 (m, 4H), 7.49 (t, *J* = 7.7 Hz, 2H), 6.81 (t, *J* = 5.3 Hz, 1H), 3.36 (brs, 2H), 3.18–3.12 (m, 2H), 3.04–3.01 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.6, 156.1, 146.9, 134.6, 133.3, 131.2, 130.9, 129.9, 129.4, 128.5, 125.9, 125.8, 123.1, 78.2, 28.8; IR (thin film) ν 3776, 3158, 2840, 1598, 1111, 964 cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{22}H_{25}N_5O_2$ 430.1855, found 430.1855.



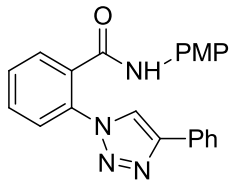
***N*-(4-methoxybenzyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63k)**

Prepared according to general procedure from 2-iodo-*N*-(4-methoxybenzyl)benzamide (**61k**) and phenylacetylene (**62a**). Yield 148.0 mg (77%) as pale solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.84 (d, *J* = 7.3 Hz, 2H), 7.76–7.74 (m, 1H), 7.61–7.56 (m, 3H), 7.50–7.39 (m, 3H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 6.34–6.31 (m , 1H), 4.34 (d, *J* = 6.3 Hz, 2H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 159.0, 148.1, 133.9, 132.9, 131.1, 130.1, 130.0, 129.3, 129.1, 128.9, 128.5, 126.3, 125.9, 122.0, 114.0, 55.1, 43.7; IR (thin film) ν 3775, 3073, 2888, 1588, 1162, 1040, 956 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. For $C_{23}H_{20}N_4O_2$ 385.1665, found 385.1664.



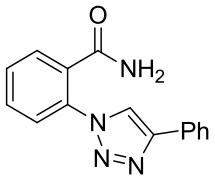
***N*-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63l)**

Prepared according to general procedure from 2-iodo-*N*-phenylbenzamide (**61l**) and phenylacetylene (**62a**). Yield 115.7 mg (68%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88–9.85 (m, 1H), 8.29–8.28 (m, 1H), 7.82–7.78 (m, 2H), 7.73–7.71(m, 1H), 7.62–7.53 (m, 4H), 7.42–7.37 (m, 3H), 7.27–7.22 (m 2H), 7.08–7.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 138.2, 134.2, 133.0, 130.7, 130.1, 129.5, 129.1, 128.7, 125.7, 125.4, 124.3, 121.6, 120.3; IR (thin film) ν 3776, 3639, 3074, 2884, 1588, 1118, 964 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. For $C_{21}H_{16}N_4O$ 341.1402, found 341.1402.



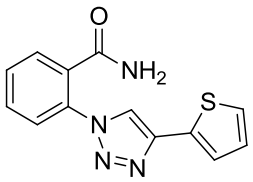
***N*-(4-methoxyphenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63m)**

Prepared according to general procedure from 2-iodo-*N*-(4-methoxyphenyl)-benzamide (**61m**) and phenylacetylene (**62a**). Yield 148.2 mg (80%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.95 (brs, 1H), 7.89–7.82 (m, 3H), 7.62−7.68 (m, 2H), 7.46−7.38 (m, 3H), 7.34 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 3.78 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 156.7, 148.2, 133.9, 132.8, 131.2, 130.5, 129.9, 129.4, 128.9, 128.5, 125.9, 122.3, 121.9, 114.0, 55.4; IR (thin film) ν 3736, 2343, 1648, 1603, 1509, 1234, 1032 cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd. For $C_{22}H_{18}N_4O_2$ 393.1327, found 393.1327.



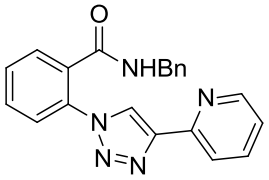
2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzamide (63n)

Prepared according to general procedure from 2-iodobenzamide (**61n**) and phenylacetylene (**62a**). Yield 118.9 mg (90%) as light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 7.1 Hz, 2H), 7.36 (t, *J* = 8.2 Hz, 1H), 6.19 (brs, 1H), 5.96 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 148.2, 134.0, 132.0, 131.5, 129.8, 129.4, 129.0, 128.6, 126.3, 125.9, 122.0; IR (thin film) ν 3775, 3663, 3073, 2884, 1588, 1161, 956 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{12}N_4O$ 265.1089, found 265.1089.



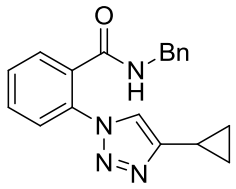
2-(4-(thiophen-2-yl)-1H-1,2,3-triazol-1-yl)benzamide (63o)

Prepared according to general procedure from 2-iodobenzamide (**61n**) and commercially available 2-ethynylthiophene (**62b**). Yield 129.7 mg (96%) as brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1H), 7.95 (brs, 1H), 7.70–7.64 (m, 4H), 7.58 (d, J = 4.7 Hz, 1H), 7.53 (d, J = 3.5 Hz, 1H), 7.49 (brs, 1H), 7.17 (t, J = 4.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.3, 142.2, 134.3, 133.8, 133.1, 131.1, 130.2, 129.2, 128.4, 126.2, 124.9, 122.5; IR (thin film) ν 3775, 3696, 3072, 2892, 2746, 1588, 956 cm^{-1}. HRMS (ESI) [M+Na]$^{+}$ calcd. for $C_{13}H_{10}N_4OS$ 393.0473, found 393.0472.



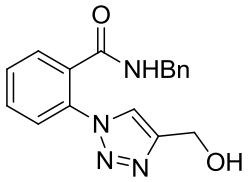
***N*-benzyl-2-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)benzamide (63p)**

Prepared according to general procedure from *N*-benzyl-2-iodobenzamide (**61a**) and commercially available 2-ethynylpyridine (**62c**). Yield 165.2 mg (93%) as brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.01 (t, J = 5.8 Hz, 1H), 8.78 (s, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.92 (t, J = 7.6 Hz, 1H), 7.69–7.65 (m, 4H), 7.36 (t, J = 5.1 Hz, 1H), 7.15–7.11 (m, 4H), 4.30 (d, J = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.6, 150.2, 150.1, 147.8, 139.3, 137.8, 134.4, 133.5, 131.2, 130.3, 129.3, 128.6, 127.6, 127.2, 126.3, 124.9, 123.7, 120.2, 42.9; IR (thin film) ν 3775, 3697, 3052, 2884, 2760, 1588, 956 cm^{-1}. HRMS (ESI) [M+Na]$^{+}$ calcd. for $C_{21}H_{17}N_5O$ 378.1331, found 378.1332.



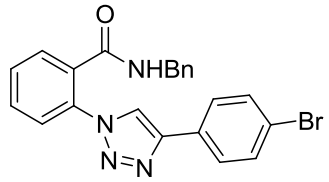
***N*-benzyl-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)benzamide(63q)**

Prepared according to general procedure from *N*-benzyl-2-iodobenzamide (**61a**) and commercially available 2-ethynylpyridine (**62d**). Yield 113.0 mg (71%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.70 (m, 1H), 7.56–7.53 (m, 2H), 7.55 (s, 1H), 7.46–7.43 (m, 1H), 7.33–7.22 (m, 3H), 7.12 (d, *J* = 3.4Hz 2H), 6.32 (brs, *J* = 5.1 Hz, 1H), 4.40 (d, *J* = 2.1 Hz 2H), 1.99–1.90 (m, 1H) 1.02–0.95 (m, 2H) 0.91–0.84 (m, 2H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 166.3, 150.7, 137.2, 134.1, 132.7, 131.0, 129.9, 129.3, 128.7, 127.8, 127.6, 126.3, 122.2, 44.2, 8.0, 6.6,; IR (thin film) ν 3724 2966 2866 2360 1665 1522 1053 1031cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd. For $C_{19}H_{18}N_4O$ 341.1378, found 341.1377.



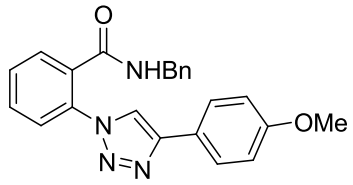
***N*-benzyl-2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)benzamide (63r)**

Prepared according to general procedure from *N*-benzyl-2-iodobenzamide (**61a**) and commercially available prop-2-yn-1-ol (**62e**). Yield 103.3 mg (67%) as light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 8.93 (t, *J* = 5.6 Hz, 1H), 8.07-8.04 (m, 1H), 7.62–7.57 (m, 4H), 5.24 (t, *J* = 5.6 Hz, 1H), 4.59 (d, *J* = 4.7 Hz, 2H), 4.34 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 166.7, 148.6, 139.2, 134.6, 133.3, 130.8, 129.5, 129.1, 128.5, 127.7, 127.1, 125.7, 124.0, 55.5, 43.1; IR (thin film) ν 3775, 3663, 3073, 2883, 1588, 1161, 956 cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{17}H_{16}N_4O_2$ 331.1171, found 331.1172.



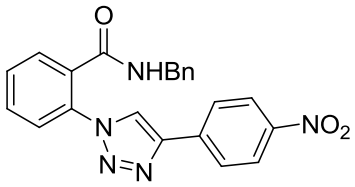
***N*-benzyl-2-(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)benzamide (63s)**

Prepared according to general procedure from *N*-benzyl-2-iodobenzamide (**61a**) and commercially available 1-bromo-4-ethynylbenzene (**62f**). Yield 155.9 mg (72%) as light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.06 (t, J = 5.8 Hz, 1H), 8.90 (s, 1H), 7.87 (d, J = 9.0 Hz, 2H), 7.72–7.19 (m, 5H), 4.34 (d, J = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.5, 145.8, 139.4, 134.5, 133.5, 132.4, 131.2, 130.2, 130.1, 129.4, 128.6, 127.7, 127.6, 127.2, 126.2, 121.5, 42.9; IR (thin film) ν 3774, 3696, 3073, 2883, 1588, 1159, 956 cm^{-1}. HRMS (ESI) [M+Na]$^{+}$ calcd. for $C_{22}H_{17}BrN_4O_2$ 433.0483, found 433.0483.



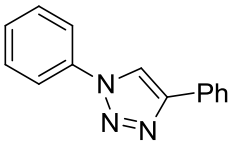
2-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzamide (63t)

Prepared according to general procedure from *N*-benzyl-2-iodobenzamide (**61a**) and commercially available 1-ethynyl-4-methoxybenzene (**62g**). Yield 157.6 mg (82%) as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.04 (t, J = 5.9 Hz, 1H), 8.71 (s, 1H), 7.83 (d, J = 8.6 Hz, 2H), 7.69–7.65 (m, 4H), 7.23–7.18 (m, 4H), 7.05 (d, J = 8.6 Hz, 2H), 4.35 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 159.6, 146.8, 139.4, 134.7, 133.5, 131.1, 130.0, 129.3, 128.7, 127.6, 127.2, 126.0, 123.4, 122.2, 114.8, 55.7. 42.9; IR (thin film) ν 3780, 3696, 3073, 2879, 1586, 1162, 956 cm^{-1}. HRMS (ESI) [M+Na]$^{+}$ calcd. for $C_{23}H_{20}N_4O_2$ 407.1481, found 407.1481.



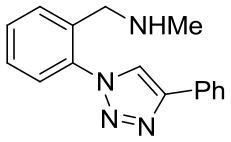
***N*-benzyl-2-(4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl)benzamide (63u)**

Prepared according to general procedure from *N*-benzyl-2-iodobenzamide (**61a**) and commercially available 1-ethynyl-4-nitrobenzene (**62h**). Yield 189.7 mg (95%) as light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.13 (s, 1H), 9.08 (t, J = 5.9 Hz, 1H), 8.37 (d, J = 8.7 Hz, 2H), 8.29 (d, J = 8.7 Hz, 2H), 7.72–7.70 (m, 4H), 7.26–7.17 (m, 4H), 4.34 (d, J = 5.9 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.4, 147.2, 144.9, 139.4, 137.3, 134.4, 133.5, 131.3, 130.4, 129.4, 128.6, 127.6, 127.2, 126.6, 126.3, 125.4, 124.9, 42.9; IR (thin film) ν 3784, 3696, 3072, 2884, 1586, 1039, 956 cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{22}H_{17}N_5O_3$ 422.1229, found 422.1226.



1,4-diphenyl-1*H*-1,2,3-triazole (67b)

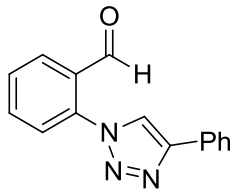
Prepared according to general procedure from commercially available iodobenzene (**66b**). and phenylacetylene (**62a**). Yield 61.9 mg (28%) as light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.81 (d, J = 7.8 Hz, 2H), 7.57 (t, J = 7.5 Hz, 2H), 7.48 (t, J = 7.8 Hz), 7.39 (t, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.8, 129.0, 128.8, 128.5, 125.9, 120.6, 117.6; IR (thin film) ν 3776, 3639, 3072, 2880, 1586, 1039, 956 cm^{-1}. These data matched to the literature values (Barral *et al.*, 2007).



***N*-methyl-1-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)methanamine (67c)**

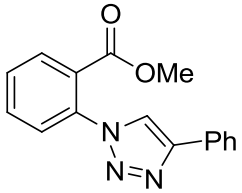
Prepared according to general procedure from 1-(2-iodophenyl)-*N*-methyl-methanamine (**66c**) and phenylacetylene (**62a**). Yield 126.6 mg (95 %) as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.91 (d, J = 7.8, 2H), 7.66 (d, J =

7.2 Hz, 1H), 7.54−7.43 (m, 5H), 7.38 (d, *J* = 7.2 Hz), 5.01 (brs, 2H), 3.69 (brs, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 136.4, 132.9, 131.9, 130.1, 129.9, 129.0, 128.9, 128.7, 128.5, 125.8, 125.4, 121.7, 50.9, 35.1; IR (thin film) ν 1498, 1228, 1033, 989, 763, 689 cm^{-1}. HRMS (ESI) $[M+H]^+$ calcd. for $C_{16}H_{16}N_4$ 265.1453, found 265.1453.



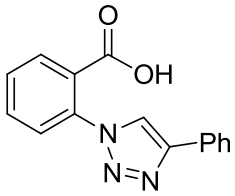
2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzaldehyde (67d)

Prepared according to general procedure from 2-iodobenzaldehyde (**66d**) and phenylacetylene (**62a**). Yield 78.5 mg (63%) as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.21(s, 1H), 8.13 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 2H), 7.79 (td, *J* = 7.7, 1.4 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.5, 134.7, 130.4, 130.1, 129.5, 129.0, 128.8, 125.9, 125.3, 121.6; IR (thin film) ν 3776, 3700, 3072, 2888, 1586, 1039, 957 cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{15}H_{11}N_3O$ 272.0800, found 272.0800.



methyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzoate (67e)

Prepared according to general procedure from methyl 2-iodobenzoate (**66e**)and phenylacetylene (**62a**). Yield 121.5 mg (87%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.02 (dd, *J* = 7.5, 1.5, 1H), 7.92 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.70–7.59 (m, 2H), 7.55 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 147.6, 136.1, 132.8, 131.3, 130.3, 129.9, 128.9, 128.4, 127.6, 126.6, 126.1, 125.9, 121.4, 52.7; IR (thin film) ν 3560, 3134, 2949, 1731, 1489, 1294, 1268, 1125 cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd. for $C_{16}H_{13}N_3O_2$ 302.0905, found 302.0905.



2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzoic acid (67f)

Prepared according to general procedure from 2-iodobenzoic (**66f**) acid and phenylacetylene (**62a**). Yield 62.3 mg (47%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (brs, 1H). 9.00 (s, 1H), 7.94 (m, 3H), 7.78 (m, 1H), 7.70 (t, J = 3.6 Hz 2H), 7.48 (t, J = 3.8 Hz, 2H), 7.37 (m, Hz, 1H), ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.0, 146.8, 136.0, 133.0, 131.0, 130.9, 130.5, 129.5, 129.1, 128.5, 127.8, 125.4, 123.5. These data matched to the literature values (Moses *et al*., 2007).

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APPENDIX

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Full Paper

Multicomponent Reactions

Synthesis of 2-(1,2,3-Triazolyl)benzamide Derivatives by a Copper(I)-Catalyzed Multicomponent Reaction

Abdulhakim Hayeebueraheng,[a] Benyapa Kaewmee,[a] Vatcharin Rukachaisirikul,[a] and Juthanat Kaeobamrung*[a]

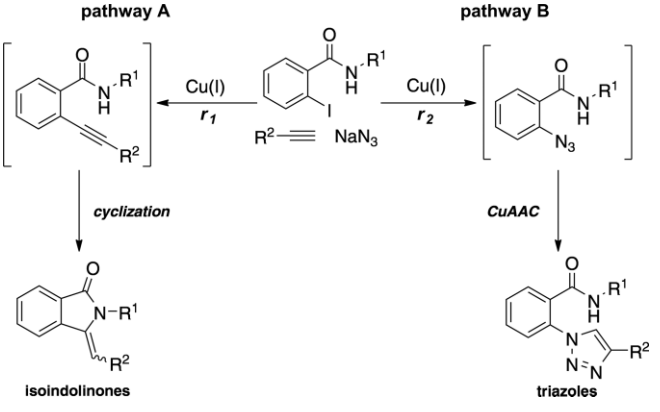
Abstract: The copper-catalyzed multicomponent reaction of 2-iodobenzamides, NaN_3, and terminal alkynes for the synthesis of 2-(1,2,3-triazolyl)benzamide derivatives was achieved in a one-step process over a short period of time under mild conditions. The transformation involved a C(aryl)–N bond formation process followed by an azide–alkyne cycloadditon reaction. The absence of external base was crucial for the preferred reaction pathway to occur.

Introduction

Multicomponent reactions (MCRs) have received much attention from synthetic chemists because of their potential to provide access to diverse and complex organic molecules from simple starting materials in a single step. With an adequate reaction plan, high levels of efficiency can be obtained without the need to isolate and purify reaction intermediates. Moreover, unstable reactive intermediates can also be incorporated into the design of MCRs.[1]

1,4-Disubstituted 1,2,3-triazoles are important heterocyclic molecules. They have a broad range of biological properties[2] as well as unique qualities with applications in chemical and materials science.[3] Because of their wide assortment of uses, methods to synthesize these molecules are continuously being developed, especially after the classical copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction was independently introduced by Sharpless and Meldal.[4] Only a few examples, however, of copper-catalyzed multicomponent reactions for the synthesis of 1,4-disubstituted 1,2,3-triazoles have been reported. These have particularly involved reactions between aryl halides, NaN_3, and alkynes because of the instability of aryl azides. However, an elegant Cu-catalyzed MCR was introduced by the Huang and Wen groups in 2014.[5] They utilized a diaryliodonium species, NaN_3, and terminal alkynes to construct triazolophenanthridine core structures under mild reaction conditions. Fokin and co-workers reported the synthesis of 1,4-disubstituted 1,2,3-triazoles by using copper-catalyzed one-pot reactions of aryl iodides, NaN_3, and terminal alkynes.[6] In their case, pure products were obtained by filtration after the reaction was stirred overnight. Recently, the Jiang and Zhang groups prepared 1,4-disubstituted 1,2,3-triazoles within a short reaction time by using a two-step reaction process that was carried out in one pot.[7] Their protocol relied on the combination of CuI and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to catalyze the reaction of aryl iodides, NaN_3, and terminal alkynes.

The copper-catalyzed MCR of aryl iodides, NaN_3, and terminal alkynes to synthesize 1,4-disubstituted 1,2,3-triazoles in one step over a short reaction time still remains a challenging task. We envision that 2-iodobenzamides would be a good alternative to the aryl iodide in a copper-catalyzed MCR with NaN_3 and terminal alkynes. 2-Iodobenzamides have often been used in copper-catalyzed coupling reactions with various partners. In these transformations, the secondary amide moiety functions as a directing group that coordinates to the copper catalyst and allows the coupling to occur smoothly and rapidly.[8] Significantly, 2-iodobenzamides are also known to efficiently undergo reactions with terminal alkynes through a copper-catalyzed domino process to form the corresponding isoindolinones[9] (Scheme 1, pathway A). We wish to develop a copper-catalyzed MCR in which the 2-iodobenzamides first undergo a reaction with NaN_3 to form the aryl azide intermediates. In the presence of terminal alkynes, a subsequent CuAAC reaction then pro-



Scheme 1. Possible reaction pathways of copper-catalyzed MCR.

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vides the 1,4-disubstituted 1,2,3-triazoles (Scheme 1, pathway B). Herein, we demonstrate the copper-catalyzed multicomponent domino reaction of 2-iodobenzamides, NaN_3, and terminal alkynes for the simple preparation of 2-(1,2,3-triazolyl)benzamides under mild reaction conditions.

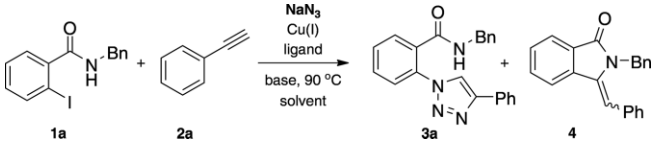
Results and Discussion

We began our investigation by selecting the reaction of *N*-benzyl-2-iodobenzamide, NaN_3, and phenylacetylene as our model and proceeded to optimize the conditions for the triazole formation. A variety of common ligands, such as *N*,*N*′-dimethylethylenediamine (DMEDA), 1,10-phenanthroline, 1,2-diaminocyclohexane, L-proline, 2,2′-bipyridine, and picolinic acid were examined in the reaction. The transformation was also conducted without a ligand (Table 1, Entries 1–7). We found that the reaction that employed the 1,2-diaminocyclohexane and L-proline ligands gave the desired triazole product in 35 and 44 %, respectively. Both reactions, however, also gave the isoindolinone side product in 52 and 39 %, respectively (Table 1, Entries 3 and 4). L-proline was chosen as a ligand for future reactions.

Next, we tried to decrease the likelihood of isoindolinone byproduct formation. Thus, we examined the two different reaction pathways that are involved in the preparation of the desired triazole **3a** and the undesired isoindolinone **4** (Scheme 1, pathways A and B).[10] We realized that there are two factors to consider to increase the yield of **3a**. First, the rate (r_1) of isoindolinone formation had to decrease, and second, the rate (r_2) of azidation needed to increase. With this in mind, we proposed that the rate of formation of the Cu^I-acetylene complex could decrease by using a weak base, thereby decreasing r_1. Consequently, a variety of weak bases, such as K_3PO_4, K_2CO_3, and $NaHCO_3$ were added to the reaction. The transformation was also carried out without a base. The addition of K_3PO_4 gave **3a** and **4** in 32 and 38 % yield, respectively (Table 1, Entry 8). Similar results were realized in the presence of K_2CO_3, and **3a** and **4** were obtained in 43 and 31 %, respectively (Table 1, Entry 9). Delightfully, the yield of **3a** dramatically increased when $NaHCO_3$ was used, and the reaction gave 66 % of **3a** and 22 % of **4** (Table 1, Entry 10). Surprisingly, the reaction occurred smoothly in the absence of base to give the same 66 % yield of **3a**, and a diminished 12 % yield of **4** (Table 1, Entry 11). This result suggests that without the base, the likelihood of the isoindolinone pathway greatly decreases, and the azidation pathway predominates.

The copper salt was also one of our variables for the screening process. CuI, Cu_2O, and $Cu(OAc)_2$ were individually subjected to the reaction conditions and provided the triazole in 61, 53 and 49 % yield, respectively (Table 1, Entries 12–14). Other polar solvents were also subjected to our optimization process. *N*,*N*-dimethylformamide (DMF) afforded a moderate 57 % yield of the triazole (Table 1, Entry 15). A low 39 % yield of the triazole was observed when the reaction was conducted in MeCN (Table 1, Entry 16).

Table 1. Optimization reactions of triazole formation.[a].



1a 2a 3a 4

Entry	Cu salt	Ligand	Base	Solvent	Yield [%][b]
1	CuBr	DMEDA	Cs_2CO_3	DMSO	trace[c]
2	CuBr	1,10-phenanthroline	Cs_2CO_3	DMSO	trace
3	CuBr	1,2-diaminocyclohexane	Cs_2CO_3	DMSO	35 (52)
4	CuBr	L-proline	Cs_2CO_3	DMSO	44 (39)
5	CuBr	2,2′-bipyridine	Cs_2CO_3	DMSO	trace
6	CuBr	picolinic acid	Cs_2CO_3	DMSO	trace
7	CuBr	–	Cs_2CO_3	DMSO	trace
8	CuBr	L-proline	K_3PO_4	DMSO	32 (38)
9	CuBr	L-proline	K_2CO_3	DMSO	43 (31)
10	CuBr	L-proline	$NaHCO_3$	DMSO	66 (22)
11	CuBr	L-proline	–	DMSO	66 (12)
12	CuI	L-proline	–	DMSO	61 (14)
13	Cu_2O	L-proline	–	DMSO	53 (9)
14	$Cu(OAc)_2$	L-proline	–	DMSO	49 (10)
15	CuBr	L-proline	–	DMF	57 (9)
16	CuBr	L-proline	–	MeCN	39 (15)
17	CuBr	L-proline	–	DMSO/H_2O (2:1)	73 (8)
18	CuBr	L-proline	–	DMSO/H_2O (2:1, 0.4 M)	82 (5)
19	CuBr	L-proline	–	DMSO/H_2O (2:1, 1.0 M)	70 (trace)
20	CuBr	L-proline	–	DMSO/H_2O (1:1, 1.0 M)	63 (trace)

[a] Reagents and conditions: **1a** (0.5 mmol), Cu salt (20 mol-%), sodium azide (1.5 equiv.), and **2a** (1.5 equiv.) in solvent (0.2 M) for 1.5 h under air in a sealed tube. [b] Isolated yield of the triazole is reported. The isolated yield of the isoindolinone is found in parentheses. [c] Determined by integration values in ^1H NMR spectrum of the crude reaction mixture.

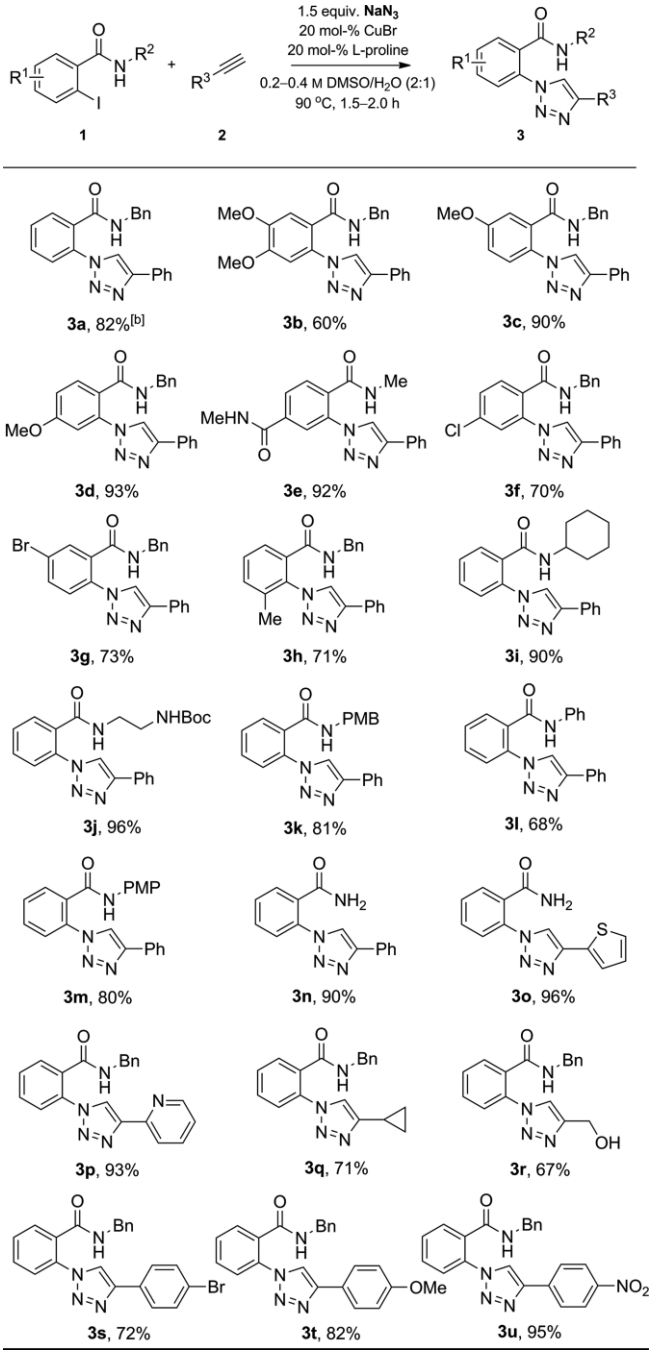
We then tried to increase the rate of the azidation reaction by increasing the solubility of NaN_3 (Scheme 1) and found that the triazole yield significantly increased to 73 % by using a dimethyl sulfoxide (DMSO)/H_2O mixture (2:1) as the solvent (Table 1, Entry 17). A slight increase in the yield to 82 % was observed when we increased the concentration of reaction to 0.4 M (Table 1, Entry 18). However, a 1.0 M concentration of the reaction mixture resulted in a diminished yield of 70 % (Table 1, Entry 19). Attempts to increase product yield by increasing the concentration of the reaction mixture and changing the solvent mixture to 1:1 DMSO/H_2O failed, as this led to the triazole in 63 % yield (Table 1, Entry 20). These results suggest that solubility is crucial to the outcome of our reaction. It is worth noting that 20 mol-% of CuBr was required to give the best product yield and avoid the formation of an aniline byproduct (Table 1).

After establishing the optimal reaction conditions, we then explored the scope of the 2-iodobenzamides and terminal alkynes in the synthesis of the 2-(1,2,3-triazolyl)benzamide derivatives (Table 2). We found 2-iodobenzamides that contain electron-donating groups as well as those that have electron-withdrawing groups were applicable in this reaction. However, the reaction of the benzamide that has two methoxy substituents gave **3b** in only a moderate yield of 60 %. Substrates with one methoxy substituent afforded different results. For example, the reaction of 2-iodo-5-methoxybenzamide gave **3c** in an excellent 90 % yield. Likewise, triazole **3d** was obtained in 93 % yield by starting from 2-iodo-4-methoxybenzamide. These results suggest that the electron density of the 2-iodobenzamides has somewhat of an effect on the reaction. Having an additional amide functionality on the benzamide ring provided **3e** in a high 92 % yield. 2-Iodobenzamides that contain a second halogen atom such as chlorine and bromine were also compatible under the reaction conditions and yielded triazoles **3f** and **3g** in 70 and 73 % yield, respectively. The steric environment surrounding the iodine atom also affected the reaction, as 2-iodo-3-methylbenzamide provided **3h** in a moderate 71 % yield. Substrates with other substituents on the amide nitrogen atom were also subjected to our studies. The reactions of those 2-iodobenzamides that contain *N*-alkyl groups afforded good to excellent yields of the corresponding triazoles (i.e., **3a**, **3i**, **3j**, and **3k**). However, the yield of the product (i.e., **3l**) significantly dropped to 68 % when an *N*-phenyl benzamide was used as the starting material. In contrast, increasing the electron density by introducing a methoxy group as in *N*-(4-methoxyphenyl)benzamide yielded **3m** 80 % yield. On the basis of these results, the Lewis basicity of the amide nitrogen atom must serve a role in the reaction. In addition, 2-iodobenzamide with an unsubstituted nitrogen atom provided an excellent 90 % yield of triazole **3n**.

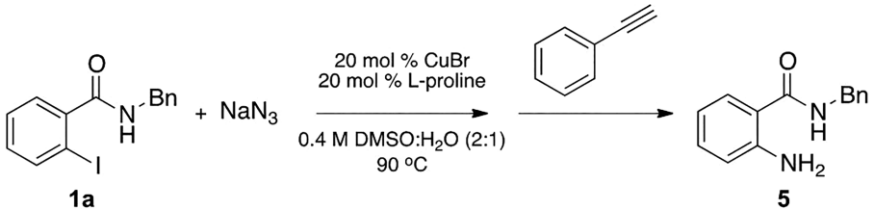
A variety of terminal alkynes, including those that contain either an aryl or alkyl group, could also be used in our multicomponent reaction. Notably, heterocyclic-containing acetylenes (i.e., 2-thiophene and 2-pyridine moieties) provided **3o** and **3p** in excellent yields of 96 and 93 %, respectively. Triazole **3q** was obtained in a good 71 % yield by starting from ethynylcyclopropane as one of the substrates. Satisfactorily, the reaction of an unprotected alcohol gave the desired triazole **3r** in a good yield of 67 %. High to excellent yields of triazoles **3s**, **3t**, and **3u** were obtained by starting from acetylenes that contain bromo, methoxy, and nitro substituents. In short, a broad range of substituted phenylacetylenes were suitable in our reaction.

Interestingly, we found that the desired triazole was not obtained when the reaction was carried out by a two-step proce-

Table 2. The synthesis of 2-(1,2,3-triazolyl)benzamide derivatives (Boc = *tert*-butoxycarbonyl, PMB = *para*-methoxybenzyl, PMP = *para*-methoxyphenyl).[a]



[a] Reagents and conditions: **1** (0.5 mmol) and **2** (1.5 equiv.) under air in a sealed tube. [b] Isolated yields are reported.



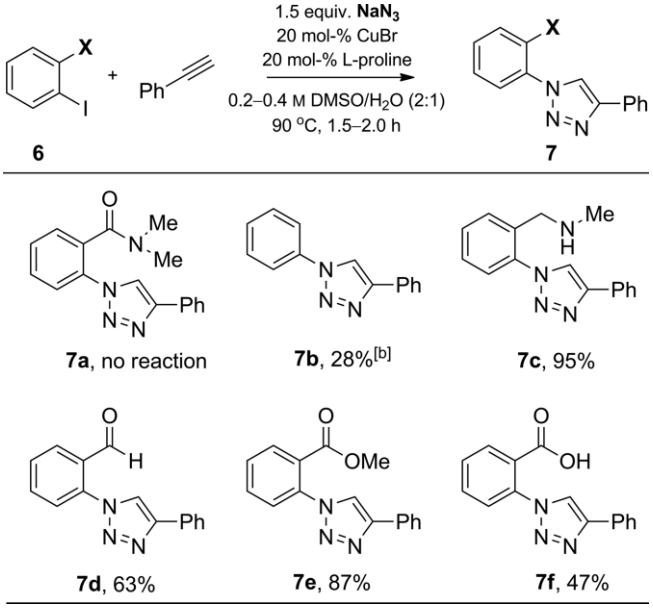
Scheme 2. Two-step process reaction in one-pot manner.

dure using a one-pot protocol. The addition of phenylacetylene only after the 2-iodobenzamide was completely consumed (progress monitoring by thin layer chromatography) did not proceed as expected. This result suggests that the generated aryl azide decomposed into its corresponding amine in the presence of copper under the reaction conditions prior to undergoing the CuAAC reaction with phenylacetylene (Scheme 2).

The generation of aniline from NaN_3 and aryl halide derivatives in the presence of copper salts has been reported by several research groups. For example, Li, Chen, and co-workers used this phenomenon to synthesize quinazolinones[11] from 2-iodobenzamide, NaN_3, and aldehydes. Singh and co-workers utilized the in situ generated 2-aminobenzaldehydes, from 2-bromobenzaldehydes and NaN_3, in a condensation reaction to prepare the corresponding quinolines in a multicomponent manner.[12] Our findings emphasize one of the great features of multicomponent reactions, that is, the utilization of an unstable intermediate.

Next, we explored other functional groups *ortho* to the iodine atom (Table 3). Although we did not exhaustively explore all functionalities, we found that the amide directing group significantly affected our copper-catalyzed multicomponent reaction. We first modified the 2-iodobenzamide from secondary amide into a tertiary amide. In this case, the expected product **7a** was not observed, and no reaction occurred. We only observed the amide starting material in the ^{1}H NMR spectrum of the crude reaction mixture. Presumably, the weaker coordination ability and steric hindrance of the tertiary amide hindered our reaction. Without any directing group, the reaction of iodobenzene provided triazole **7b** in a low yield of 28 %. An excellent 95 % yield of **7c** was obtained by having a secondary amine as the directing group. The aldehyde functionality also influenced the transformation. The reaction of 2-iodobenzaldehye gave **7d** in a moderate 63 % yield. Fortunately, the ester group led to a high yield of 87 % for the corresponding triazole **7e**. These results are significant and suggest that the strength of the Lewis base had a crucial impact on the multicomponent reaction. In contrast, having an acid functionality diminished the yield of **7f** to 47 %.

Table 3. 1,2,3-Triazole formation by using other directing groups.[a]



[a] Reagents and conditions: **6** (0.5 mmol) and phenylacetylene (1.5 equiv.) under air in a sealed tube. [b] Isolated yields are reported.

Conclusions

In summary, we have demonstrated a simple and efficient protocol to synthesize 2-(1,2,3-triazolyl)benzamides under mild reaction conditions over a short period of time. Our multicomponent catalytic reaction offers a strategy for the preparation of triazoles by using semistable aryl azides in a one-pot click reaction, which eliminates the need to purify the intermediary aryl azides. The solubility of sodium azide and the absence of an external base tremendously shift the reaction paradigm towards the formation of the desired triazoles by increasing the rate of the copper-catalyzed azide coupling relative to that of the terminal alkyne coupling. Furthermore, the concentration of our reaction and the Cu catalyst loading favored the click reaction over the generation of an aromatic amine side product from the in situ generated azides.

Experimental Section

General Methods: Commercially available reagents and solvents for reactions [analytical reagent (AR) grade] were used without purification from the commercial source. Solvents for extraction and column chromatography were distilled prior to use. Thin layer chromatography was performed on silica gel 60 GF_{254} (Merck), and the developed plates were visualized by fluorescence quenching under UV light. Column chromatography was performed on SiliaFlash® G60 (70–230 mesh). The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectroscopic data were recorded with a 300 MHz Bruker FTNMR Ultra Shield spectrometer, and tetramethylsilane was used as the internal

standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ = 0.00 ppm), and coupling constants are reported in units of hertz. Splitting patterns of the signals are reported as follows: br. (broad), s (singlet), d (doublet), t (triplet), and m (multiplet). High resolution mass spectrometry (HRMS) data were recorded in the ESI mode with a TOF mass spectrometer. Infrared spectra were recorded with a Perkin–Elmer Spectrum GX FTIR system, and the bands are reported in cm^{-1}.

General Procedure for the Synthesis of 2-Iodobenzamides 1: The 2-iodobenzamides were prepared according to a literature procedure.[13] A flame-dried round-bottomed flask was charged with 2-iodobenzoic acid (1.0 equiv.) in CH_2Cl_2 (0.3 M) and DMF (2 drops) followed by the addition of oxalyl chloride (1.25 equiv.) at 0 °C. The resulting mixture was stirred at room temperature for 4 h, and then the mixture was evaporated to dryness. The prepared acid chloride was dissolved in CH_2Cl_2 (0.3 M), and a solution of benzylamine (1.5 equiv.) and triethylamine (3.0 equiv.) was added at 0 °C. The mixture was stirred at room temperature for 15 h, and the reaction was quenched with saturated NH_4Cl. The mixture was extracted with CH_2Cl_2. The organic extract was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography.

General Procedure for the Synthesis of 2-(1,2,3-Triazolyl)-benzamide Derivatives: A dried flask was charged with 2-iodobenzamide **1a** (0.5 mmol), commercially available phenylacetylene (0.75 mmol), sodium azide (0.75 mmol), CuBr (20 mol-%), and L-proline (20 mol-%) in DMSO/H_2O (1.7:0.8 mL). The reaction mixture was stirred at 90 °C for 2 h. Upon completion of reaction, the mixture was cooled to room temperature, and the reaction was quenched with saturated NH_4Cl. The resulting mixture was extracted with EtOAc, and the organic layer was washed with brine, dried with anhydrous Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to afford crude residue, which was purified by column chromatography over silica gel (ethyl acetate/hexanes) to give the desired product.

***N*-Benzyl-2-iodo-5-methoxybenzamide (1c):** Employing the general procedure for the synthesis of 2-iodobenzamides afforded **1c** (75 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 4.4 Hz, 1 H), 7.42–7.30 (m, 5 H), 7.00 (d, J = 1.5 Hz, 1 H), 6.69 (dd, J = 1.5, 4.4 Hz, 1 H), 6.03 (br. s, 1 H), 4.65 (d, J = 2.8 Hz, 2 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 169.0, 159.6, 144.1, 140.5, 139.5, 128.7, 127.9, 127.3, 117.4, 114.7, 82.3, 56.0, 43.0 ppm. IR (thin film): $\tilde{\nu}$ = 3855, 3736, 2958, 2862, 2343, 1698, 1522, 1053 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{14}INaNO_2$ [M + Na]$^+$ 389.9967; found 390.0021.

2-Iodo-*N*1,*N*4-dimethylterephthalamide (1e): Employing the general procedure for the synthesis of 2-iodobenzamides afforded **1e** (85 % yield). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.58 (d, J = 3.0 Hz, 1 H), 8.34 (d, J = 3.0 Hz, 1 H), 8.26 (s, 1 H), 7.83 (d, J = 9.0 Hz), 7.36 (d, J = 9.0 Hz), 2.76–2.73 (m, 6 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 169.4, 165.0, 145.8, 137.9, 136.5, 128.2, 127.2, 94.0, 26.8, 26.5 ppm. IR (thin film): $\tilde{\nu}$ = 3850, 3736, 3275, 2963, 2343, 1648, 1542 cm^{-1}. HRMS (ESI): calcd. For $C_{10}H_{11}INaN_2O_2$ [M + Na]$^+$ 340.9763; found 340.9762.

***tert*-Butyl-2-(2-iodobenzamido)ethylcarbamate (1j):** Employing the general procedure for the synthesis of 2-iodobenzamides afforded **1j** (88 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 7.9 Hz, 1 H), 7.37–7.27 (m, 2 H), 7.10–7.05 (m, 1 H), 6.59 (br. s, 1 H), 5.11 (br. s, 1 H), 3.58–3.52 (m, 2 H), 3.41–3.38 (m, 2 H), 1.42 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 156.8, 142.0, 139.8, 131.1, 128.1, 128.0, 92.5, 79.8, 40.9, 40.1, 28.4 ppm. IR (thin film): $\tilde{\nu}$ = 3318, 2976, 2930, 1693, 1640, 1253, 1015, 751 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{19}INaN_2O_3$ [M + Na]$^+$ 413.0338; found 413.0338.

***N*-Benzyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3a):** Employing the general procedure and starting from *N*-benzyl-2-iodobenzamide[13] (**1a**) and phenylacetylene (**2a**) afforded **3a** (145.3 mg, 82 % yield) as a light yellow solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.93 (t, J = 5.8 Hz, 1 H), 8.70 (s, 1 H), 7.79 (d, J = 8.0 Hz, 2 H), 7.59–7.52 (m, 4 H), 7.37 (t, J = 7.5 Hz, 2 H), 7.26 (t, J = 7.1 Hz, 1 H), 7.11–7.06 (m, 5 H), 4.23 (d, J = 5.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.6, 146.9, 139.4, 134.6, 133.5, 131.2, 130.9, 130.1, 129.4, 129.3, 128.6 (128.64), 128.6 (128.56), 127.2, 126.1, 125.8, 123.2, 42.9 ppm. IR (thin film): $\tilde{\nu}$ = 3409, 2940, 2838, 1654, 1644, 1414, 1022 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{19}N_4O$ [M + H]$^+$ 355.1559; found 355.1558.

***N*-Benzyl-4,5-dimethoxy-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3b):** Employing the general procedure and starting from *N*-benzyl-2-iodo-4,5-dimethoxybenzamide[8c] (**1b**) and phenylacetylene (**2a**). afforded **3b** (124.3 mg, 60 % yield) as a light yellow solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.82 (t, J = 5.7 Hz, 1 H), 8.74 (s, 1 H), 7.89 (d, J = 7.7 Hz, 2 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.39–7.34 (m, 1 H), 7.25–7.20 (m, 7 H), 4.31 (d, J = 5.7 Hz, 2 H), 3.90 (s, 3 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.3, 150.3, 149.3, 146.6, 139.3, 130.8, 129.4, 128.6 (128.64), 128.6 (128.55), 128.0, 127.5, 127.2, 125.7, 125.5, 123.5, 111.7, 110.1, 56.6, 56.5, 43.0 ppm. IR (thin film): $\tilde{\nu}$ = 3775, 3033, 2892, 2746, 1588, 1039, 956 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{23}N_4O_3$ [M + H]$^+$ 415.1770; found 415.1770.

***N*-Benzyl-5-methoxy-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3c):** Employing the general procedure and starting from *N*-benzyl-2-iodo-5-methoxybenzamide (**1c**) and phenylacetylene (**2a**) afforded **3c** (172.9 mg, 90 % yield) as a white solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.01 (t, J = 5.8 Hz, 1 H), 8.73 (s, 1 H), 7.89 (d, J = 8.6 Hz, 2 H), 7.61 (d, J = 8.6 Hz, 1 H), 7.49 (t, J = 7.3 Hz, 2 H), 7.37 (t, J = 7.3 Hz, 1 H), 7.26–7.18 (m, 7 H), 4.33 (d, J = 5.8 Hz, 2 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.2, 160.0, 146.6, 139.3, 134.8, 131.0, 129.4, 128.6, 128.5, 127.9, 127.7, 127.5, 127.2, 125.7, 123.5, 116.1, 114.4, 56.4, 42.9 ppm. IR (thin film): $\tilde{\nu}$ = 3775, 3072, 2758, 1588, 1179, 1039, 957 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{20}NaN_4O_2$ [M + Na]$^+$ 407.1484; found 407.1484.

***N*-Benzyl-4-methoxy-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3d):** Employing the general procedure and starting from *N*-benzyl-2-iodo-4-methoxybenzamide[14] (**1d**) and phenylacetylene (**2a**) afforded **3d** (178.8 mg, 93 % yield) as a white solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.90 (t, J = 5.7 Hz, 1 H), 8.82 (s, 1 H), 7.89 (d, J = 7.5 Hz, 2 H), 7.63 (d, J = 8.5 Hz, 1 H), 7.49 (t, J = 7.5 Hz, 2 H), 7.40–7.35 (m, 1 H), 7.26–7.22 (m, 7 H), 4.31 (d, J = 5.7 Hz, 2 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 161.4, 148.2, 137.2, 135.2, 130.9, 129.9, 128.9, 128.6, 128.5, 127.8, 127.5, 125.9, 124.8, 122.1, 115.9, 111.7, 55.9, 44.3 ppm. IR (thin film): $\tilde{\nu}$ = 3288, 1638, 1612, 1277, 1165, 1031 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{20}NaN_4O_2$ [M + Na]$^+$ 407.1484; found 407.1485.

***N*1,*N*4-Dimethyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)terephthalamide (3e):** Employing the general procedure and starting from 2-iodo-*N*1,*N*4-dimethylterephthalamide (**1e**) and phenylacetylene (**2a**) afforded **3e** (154.3 mg, 92 % yield) as a yellow solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.95 (s, 1 H), 8.71 (d, J = 4.4 Hz, 1 H), 8.51 (d, J = 4.4 Hz, 1 H), 8.11–8.04 (m, 2 H), 7.94 (d, J = 7.7 Hz, 2 H), 7.73 (d, J = 7.9 Hz, 1 H), 7.50 (t, J = 7.7 Hz, 2 H), 7.40–7.36 (m, 1 H), 2.82 (d, J = 4.4 Hz, 3 H), 2.65 (d, J = 4.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.5, 165.2, 147.0, 136.8, 135.4, 134.5, 130.7, 129.6, 129.5, 128.7, 128.5, 125.8, 124.5, 123.0, 26.8, 26.5 ppm. IR (thin film): $\tilde{\nu}$ = 3776, 3073, 2884, 2746, 1588, 1169, 957 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{18}N_5O_2$ [M + H]$^+$ 336.1460; found 336.1460.

***N*-Benzyl-4-chloro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3f):** Employing the general procedure and starting from *N*-benzyl-4-chloro-2-iodobenzamide[8c] (**1f**) and phenylacetylene (**2a**) afforded **3f** (136.1 mg, 70 % yield) as a light yellow solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.08 (t, *J* = 5.8 Hz, 1 H), 8.91 (s, 1 H), 7.91–7.88 (m, 3 H), 7.77–7.69 (m, 2 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.41–7.36 (m, 1 H), 7.22–7.18 (m, 5 H), 4.33 (d, *J* = 5.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.0, 147.1, 139.0, 135.5, 135.3, 132.0, 131.0, 130.5, 130.0, 128.8, 128.7, 127.6, 127.3, 125.8, 123.1, 43.0 ppm. IR (thin film): $\tilde{\nu}$ = 3778, 3694, 3068, 2883, 1587, 1118, 951 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}ClN_4O$ [M + H]$^+$ 389.1169; found 389.1169.

***N*-Benzyl-5-bromo-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3g):** Employing the general procedure and starting from *N*-benzyl-5-bromo-2-iodobenzamide[8c] (**1g**) and phenylacetylene (**2a**) afforded **3g** (158.1 mg, 73 % yield) as a white solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.15 (t, *J* = 5.8 Hz, 1 H), 8.84 (s, 1 H), 7.95–7.88 (m, 4 H), 7.68 (d, *J* = 8.4 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.40–7.35 (m, 1 H), 7.22–7.18 (m, 5 H), 4.33 (d, *J* = 5.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 165.3, 147.1, 138.9, 134.9, 134.1, 133.7, 131.9, 130.4, 129.5, 128.8, 128.7, 128.1, 127.6, 127.3, 125.8, 123.0, 122.9, 43.1 ppm. IR (thin film): $\tilde{\nu}$ = 3790, 3090, 2879, 1599, 1128, 956 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}BrN_4O$ [M + H]$^+$ 433.0664; found 433.0664.

***N*-Benzyl-3-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3h):** Employing the general procedure and starting from *N*-benzyl-2-iodo-3-methylbenzamide[8c] (**1h**) and phenylacetylene (**2a**) afforded **3h** (130.8 mg, 71 % yield) as a light yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.96 (s, 1 H), 7.89–7.86 (m, 2 H), 7.62–7.60 (m, 1 H), 7.53–7.45 (m, 4 H), 7.42–7.37 (m, 1 H), 7.15–7.10 (m, 3 H), 7.04–7.00 (m, 2 H), 6.26 (br. s, 1 H), 4.29 (d, *J* = 5.8 Hz, 2 H), 2.10 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 166.1, 148.1, 137.1, 136.5, 135.0, 133.0, 132.8, 130.6, 129.9, 128.9, 128.6, 128.5, 127.7, 126.9, 125.9, 122.7, 44.2, 17.4 ppm. IR (thin film): $\tilde{\nu}$ = 3776, 3697, 2884, 1588, 1169, 957 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{20}NaN_4O$ [M + Na]$^+$ 391.1535; found 391.1535.

***N*-Cyclohexyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3i):** Employing the general procedure and starting from *N*-cyclohexyl-2-iodobenzamide[15] (**1i**) and phenylacetylene (**2a**) afforded **3i** (155.9 mg, 90 % yield) as a yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.13 (s, 1 H), 7.85 (d, *J* = 7.7 Hz, 2 H), 7.70–7.68 (m, 1 H), 7.58–7.53 (m, 3 H), 7.47–7.42 (m, 2 H), 7.39–7.34 (m, 1 H), 5.97 (d, *J* = 7.6 Hz, 1 H), 3.77–3.74 (m, 1 H), 1.75–1.71 (m, 2 H), 1.58–1.48 (m, 2 H), 1.31–1.19 (m, 3 H), 1.09–0.91 (m, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 165.4, 148.1, 133.8, 133.4, 130.8, 130.1, 130.0, 129.3, 128.9, 128.5, 126.2, 125.9, 122.1, 48.9, 32.4, 25.3, 24.6 ppm. IR (thin film): $\tilde{\nu}$ = 3776, 3697, 3073, 2888, 1588, 1162, 956 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{23}N_4O$ [M + H]$^+$ 347.1872; found 347.1872.

***tert*-Butyl-2-[2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)benzamido]ethylcarbamate (3j):** Employing the general procedure and starting from *tert*-butyl 2-(2-iodobenzamido)ethylcarbamate (**1j**) and phenylacetylene (**2a**) afforded **3j** (195.6 mg, 96 % yield) as a yellow solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.87 (s, 1 H), 8.52 (br. s, 1 H), 7.92 (d, *J* = 7.6 Hz, 2 H), 7.67–7.64 (m, 4 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.38–7.33 (m, 1 H), 6.78 (br. s, 1 H), 3.13–3.09 (m, 2 H), 3.00–2.98 (m, 2 H), 1.35 (s, 9 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.6, 156.1, 146.9, 134.6, 133.3, 131.2, 130.9, 129.9, 129.4, 128.5, 125.9, 125.8, 123.1, 78.2, 28.8 ppm. IR (thin film): $\tilde{\nu}$ = 3776, 3158, 2840, 1598, 1111, 964 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{25}NaN_5O_3$ [M + Na]$^+$ 430.1855; found 430.2070.

***N*-(4-Methoxybenzyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3k):** Employing the general procedure and starting from 2-iodo-*N*-(4-methoxybenzyl)benzamide[16] (**1k**) and phenylacetylene (**2a**). afforded **3k** (155.7 mg, 81 % yield) as a pale solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.94 (t, *J* = 5.7 Hz, 1 H), 8.77 (s, 1 H), 7.88 (d, *J* = 7.6 Hz, 2 H), 7.68–7.65 (m, 4 H), 7.48 (t, *J* = 7.4 Hz, 2 H), 7.39–7.36 (m, 1 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 4.24 (d, *J* = 5.7 Hz, 2 H), 3.65 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 166.1, 159.0, 148.1, 133.9, 132.9, 131.1, 130.1, 130.0, 129.3, 129.1, 128.9, 128.5, 126.3, 125.9, 122.0, 114.0, 55.1, 43.7 ppm. IR (thin film): $\tilde{\nu}$ = 3775, 3073, 2888, 1588, 1162, 1040, 956 cm^{-1}. HRMS (ESI): calcd. For $C_{23}H_{21}N_4O_2$ [M + H]$^+$ 385.1665; found 385.1664.

***N*-Phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3l):** Employing the general procedure and starting from 2-iodo-*N*-phenylbenzamide[8c] (**1l**) and phenylacetylene (**2a**) afforded **3l** (115.7 mg, 68 % yield) as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.20 (br. s, 1 H), 8.13 (s, 1 H), 7.85–7.78 (m, 3 H), 7.61–7.58 (m, 2 H), 7.55–7.50 (m, 1 H), 7.44–7.34 (m, 5 H), 7.27–7.22 (m, 2 H), 7.10–7.05 (m, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 164.9, 138.2, 134.2, 133.0, 130.7, 130.1, 129.5, 129.1, 128.7, 125.7, 125.4, 124.3, 121.6, 120.3 ppm. IR (thin film): $\tilde{\nu}$ = 3776, 3639, 3074, 2884, 1588, 1118, 964 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{17}N_4O$ [M + H]$^+$ 341.1402; found 341.1402.

***N*-(4-Methoxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3m):** Employing the general procedure and starting from 2-iodo-*N*-(4-methoxyphenyl)benzamide[17] (**1m**) and phenylacetylene (**2a**). afforded **3m** (148.2 mg, 80 % yield) as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.16 (s, 1 H), 7.93–7.83 (m, 4 H), 7.67–7.57 (m, 3 H), 7.48–7.43 (m, 2 H), 7.40–7.30 (m, 3 H), 6.81 (d, *J* = 9.0 Hz, 2 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 164.4, 156.7, 148.2, 133.9, 132.8, 131.2, 130.5, 129.9, 129.4, 128.9, 128.5, 125.9, 122.3, 121.9, 114.0, 55.4 ppm. IR (thin film): $\tilde{\nu}$ = 3736, 2343, 1648, 1603, 1509, 1234, 1032 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}NaN_4O_2$ [M + Na]$^+$ 393.1327; found 393.1425.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)benzamide (3n): Employing the general procedure and starting from 2-iodobenzamide[8c] (**1n**) and phenylacetylene (**2a**) afforded **3n** (118.9 mg, 90 % yield) as a light yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.14 (s, 1 H), 7.90–7.88 (m, 2 H), 7.82–7.79 (m, 1 H), 7.65–7.60 (m, 2 H), 7.57–7.54 (m, 1 H), 7.48–7.43 (m, 2 H), 7.40–7.35 (m, 1 H), 6.00 (br. s, 1 H), 5.69 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.4, 148.2, 134.0, 132.0, 131.5, 129.8, 129.4, 129.0, 128.6, 126.3, 125.9, 122.0 ppm. IR (thin film): $\tilde{\nu}$ = 3775, 3663, 3073, 2884, 1588, 1161, 956 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{13}N_4O$ [M + H]$^+$ 265.1089; found 265.1089.

2-[4-(Thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl]benzamide (3o): Employing the general procedure and starting from 2-iodobenzamide (**1n**) and commercially available 2-ethynylthiophene afforded **3n** (129.7 mg, 96 % yield) as a brown solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.75 (s, 1 H), 7.92 (br. s, 1 H), 7.67–7.65 (m, 4 H), 7.56 (d, *J* = 5.0 Hz, 1 H), 7.49 (d, *J* = 3.5 Hz, 1 H), 7.46 (br. s, 1 H), 7.16–7.14 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 168.3, 142.2, 134.3, 133.8, 133.1, 131.1, 130.2, 129.2, 128.4, 126.2, 124.9, 122.5 ppm. IR (thin film): $\tilde{\nu}$ = 3775, 3696, 3072, 2892, 2746, 1588, 956 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{10}NaN_4OS$ [M + Na]$^+$ 293.0473; found 293.0472.

***N*-Benzyl-2-[4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]benzamide (3p):** Employing the general procedure and starting from *N*-benzyl-2-iodobenzamide (**1a**) and commercially available 2-ethynylpyridine afforded **3p** (165.2 mg, 93 % yield) as a brown solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.03 (t, *J* = 5.8 Hz, 1 H), 8.82 (s, 1 H), 8.64 (d, *J* = 4.1 Hz, 1 H), 8.12 (d, *J* = 7.8 Hz, 1 H), 7.95 (t, *J* = 7.5 Hz, 1 H),

7.73–7.67 (m, 4 H), 7.40 (t, *J* = 5.1 Hz, 1 H), 7.18–7.15 (m, 5 H), 4.33 (d, *J* = 5.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.6, 150.2, 150.1, 147.8, 139.3, 137.8, 134.4, 133.5, 131.2, 130.3, 129.3, 128.6, 127.6, 127.2, 126.3, 124.9, 123.7, 120.2, 42.9 ppm. IR (thin film): $\tilde{\nu}$ = 3775, 3697, 3052, 2884, 2760, 1588, 956 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{17}NaN_5O$ [M + Na]$^+$ 378.1331; found 378.1332.

***N*-Benzyl-2-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)benzamide (3q):** Employing the general procedure and starting from *N*-benzyl-2-iodobenzamide (**1a**) and commercially available 2-ethynylpyridine afforded **3q** (113.0 mg, 71 % yield) as a white solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.96 (t, *J* = 5.7 Hz, 1 H), 8.01 (s, 1 H), 7.64–7.55 (m, 4 H), 7.33–7.20 (m, 5 H), 4.32 (d, *J* = 5.7 Hz, 2 H), 2.01–1.92 (m, 1 H), 0.97–0.91 (m, 2 H), 0.78–0.73 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 166.3, 150.7, 137.2, 134.1, 132.7, 131.0, 129.9, 129.3, 128.7, 127.8, 127.6, 126.3, 122.2, 44.2, 8.0, 6.6 ppm. IR (thin film): $\tilde{\nu}$ = 3724 2966 2866 2360 1665 1522 1053 1031 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{18}NaN_4O$ [M + Na]$^+$ 341.1378; found 341.1377.

***N*-Benzyl-2-[4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]benzamide (3r):** Employing the general procedure and starting from *N*-benzyl-2-iodobenzamide (**1a**) and commercially available prop-2-yn-1-ol. afforded **3r** (103.3 mg, 67 % yield) as light yellow solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.90 (t, *J* = 5.8 Hz, 1 H), 8.17 (s, 1 H), 7.68–7.59 (m, 4 H), 7.33–7.28 (m, 2 H), 7.25–7.21 (m, 3 H), 5.32 (t, *J* = 5.6 Hz, 1 H), 4.57 (d, *J* = 5.5 Hz, 2 H), 4.33 (d, *J* = 5.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$ + [D$_6$]DMSO): δ = 166.7, 148.6, 139.2, 134.6, 133.3, 130.8, 129.5, 129.1, 128.5, 127.7, 127.1, 125.7, 124.0, 55.5, 43.1 ppm. IR (thin film): $\tilde{\nu}$ = 3775, 3663, 3073, 2883, 1588, 1161, 956 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{16}NaN_4O_2$ [M + Na]$^+$ 331.1171; found 331.1172.

***N*-Benzyl-2-[4-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl]benzamide (3s):** Employing the general procedure and starting from *N*-benzyl-2-iodobenzamide (**1a**) and commercially available 1-bromo-4-ethynylbenzene afforded **3s** (155.9 mg, 72 % yield) as a light yellow solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.06 (t, *J* = 5.8 Hz, 1 H), 8.90 (s, 1 H), 7.87 (d, *J* = 9.0 Hz, 2 H), 7.72–7.65 (m, 6 H), 7.27–7.19 (m, 5 H), 4.34 (d, *J* = 5.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.5, 145.8, 139.4, 134.5, 133.5, 132.4, 131.2, 130.2, 130.1, 129.4, 128.6, 127.7, 127.6, 127.2, 126.2, 121.5, 42.9 ppm. IR (thin film): $\tilde{\nu}$ = 3774, 3696, 3073, 2883, 1588, 1159, 956 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{17}BrNaN_4O$ [M + Na]$^+$ 455.0483; found 455.0484.

2-[4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]benzamide (3t): Employing the general procedure and starting from *N*-benzyl-2-iodobenzamide (**1a**) and commercially available 1-ethynyl-4-methoxybenzene afforded **3t** (157.6 mg, 82 % yield) as a yellow solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.02 (t, *J* = 5.8 Hz, 1 H), 8.69 (s, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.67–7.63 (m, 4 H), 7.20–7.17 (m, 5 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 4.32 (d, *J* = 5.8 Hz, 2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.7, 159.6, 146.8, 139.4, 134.7, 133.5, 131.1, 130.0, 129.3, 128.7, 127.6, 127.2, 126.0, 123.4, 122.2, 114.8, 55.7. 42.9 ppm. IR (thin film): $\tilde{\nu}$ = 3780, 3696, 3073, 2879, 1586, 1162, 956 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{20}NaN_4O_2$ [M + Na]$^+$ 407.1484; found 407.1484.

***N*-Benzyl-2-[4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl]benzamide (3u):** Employing the general procedure and starting from *N*-benzyl-2-iodobenzamide (**1a**) and commercially available 1-ethynyl-4-nitrobenzene. afforded **3u** (189.7 mg, 95 % yield) as a light yellow solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.13 (s, 1 H), 9.08 (t, *J* = 5.8 Hz, 1 H), 8.37 (d, *J* = 8.7 Hz, 2 H), 8.18 (d, *J* = 8.7 Hz, 2 H), 7.72–7.70 (m, 4 H), 7.26–7.17 (m, 5 H), 4.34 (d, *J* = 5.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.4, 147.2, 144.9, 139.4, 137.3, 134.4, 133.5, 131.3, 130.4, 129.4, 128.6, 127.6, 127.2, 126.6, 126.3, 125.4, 124.9, 42.9 ppm. IR (thin film): $\tilde{\nu}$ = 3784, 3696, 3072, 2884, 1586, 1039, 956 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{17}NaN_5O_3$ [M + Na]$^+$ 422.1229; found 422.1276.

1,4-Diphenyl-1*H*-1,2,3-triazole (7b): Employing the general procedure and starting from commercially available iodobenzene and phenylacetylene (**2a**) afforded **7b** (31.0 mg, 28 % yield) as a light yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.22 (s, 1 H), 7.93 (d, *J* = 7.5 Hz, 2 H), 7.81 (d, *J* = 7.8 Hz, 2 H), 7.57 (t, *J* = 7.5 Hz, 2 H), 7.48 (t, *J* = 7.8 Hz, 4 H), 7.39 (t, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 129.8, 129.0, 128.8, 128.5, 125.9, 120.6, 117.6 ppm. Other data were identical to the those in the literature.[18]

***N*-Methyl-1-[2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl]methanamine (7c):** Employing the general procedure and starting from 1-(2-iodophenyl)–*N*-methylmethanamine[19] and phenylacetylene afforded **7c** (125.6 mg, 95 % yield) as a yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.32 (s, 1 H), 7.92 (d, *J* = 7.3 Hz, 2 H), 7.59 (d, *J* = 7.2 Hz, 1 H), 7.54–7.52 (m, 2 H), 7.51–7.47 (m, 4 H), 7.40–7.35 (m, 1 H), 3.61 (s, 2 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 147.9, 136.4, 132.9, 131.9, 130.1, 129.9, 129.0, 128.9, 128.7, 128.5, 125.8, 125.4, 121.7, 50.9, 35.1 ppm. IR (thin film): $\tilde{\nu}$ = 1498, 1228, 1033, 989, 763, 689 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{17}N_4$ [M + H]$^+$ 265.1453; found 265.1453.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)benzaldehyde (7d): Employing the general procedure and starting from 2-iodobenzaldehyde and phenylacetylene afforded **7d** (78.5 mg, 63 % yield) as a yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.99 (s, 1 H), 8.20 (s, 1 H), 8.13 (dd, *J* = 6.2, 1.5 Hz, 1 H), 7.94–7.91 (m, 2 H), 7.83–7.77 (m, 1 H), 7.71–7.66 (m, 1 H), 7.61–7.58 (m, 1 H), 7.51–7.48 (m, 2 H), 7.46–7.42 (m, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 188.5, 134.7, 130.1, 129.6, 129.1, 128.8, 125.4, 121.5 ppm. IR (thin film): $\tilde{\nu}$ = 3776, 3700, 3072, 2888, 1586, 1039, 957 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{11}NaN_3O$ [M + Na]$^+$ 272.0800; found 272.0800.

Methyl 2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)benzoate (7e): Employing the general procedure and starting from methyl 2-iodobenzoate and phenylacetylene afforded **7e** (121.5 mg, 87 % yield) as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.06 (s, 1 H), 8.02 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.92 (dd, *J* = 8.4, 1.2 Hz, 2 H), 7.70–7.59 (m, 2 H), 7.55 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.46 (t, *J* = 7.2 Hz, 2 H), 7.38 (d, *J* = 7.5 Hz, 1 H), 3.72 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 165.8, 147.6, 136.1, 132.8, 131.3, 130.3, 129.9, 128.9, 128.4, 127.6, 126.6, 126.1, 125.9, 121.4, 52.7 ppm. IR (thin film): $\tilde{\nu}$ = 3560, 3134, 2949, 1731, 1489, 1294, 1268, 1125 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{13}NaN_3O_2$ [M + Na]$^+$ 302.0905; found 302.0905.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)benzoic Acid (7f): Employing the general procedure and starting from 2-iodobenzoic acid and phenylacetylene afforded **7f** (62.3 mg, 47 % yield) as a white solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.31 (br. s, 1 H), 9.00 (s, 1 H), 7.94 (m, 3 H), 7.78 (m, 1 H), 7.70 (t, *J* = 3.8 Hz, 2 H), 7.48 (t, *J* = 3.8 Hz, 2 H), 7.37 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 167.0, 146.8, 136.0, 133.0, 131.0, 130.9, 130.5, 129.5, 129.1, 128.5, 127.8, 125.4, 123.5 ppm. Other data were identical to those in the literature.[18]

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^{1}H and ^{13}C NMR Spectra

Figure 4 The ^{1}H (300 MHz) in $CDCl_3$and ^{13}CNMR (75 MHz) in DMSO-d_6 spectra of compound **61c**

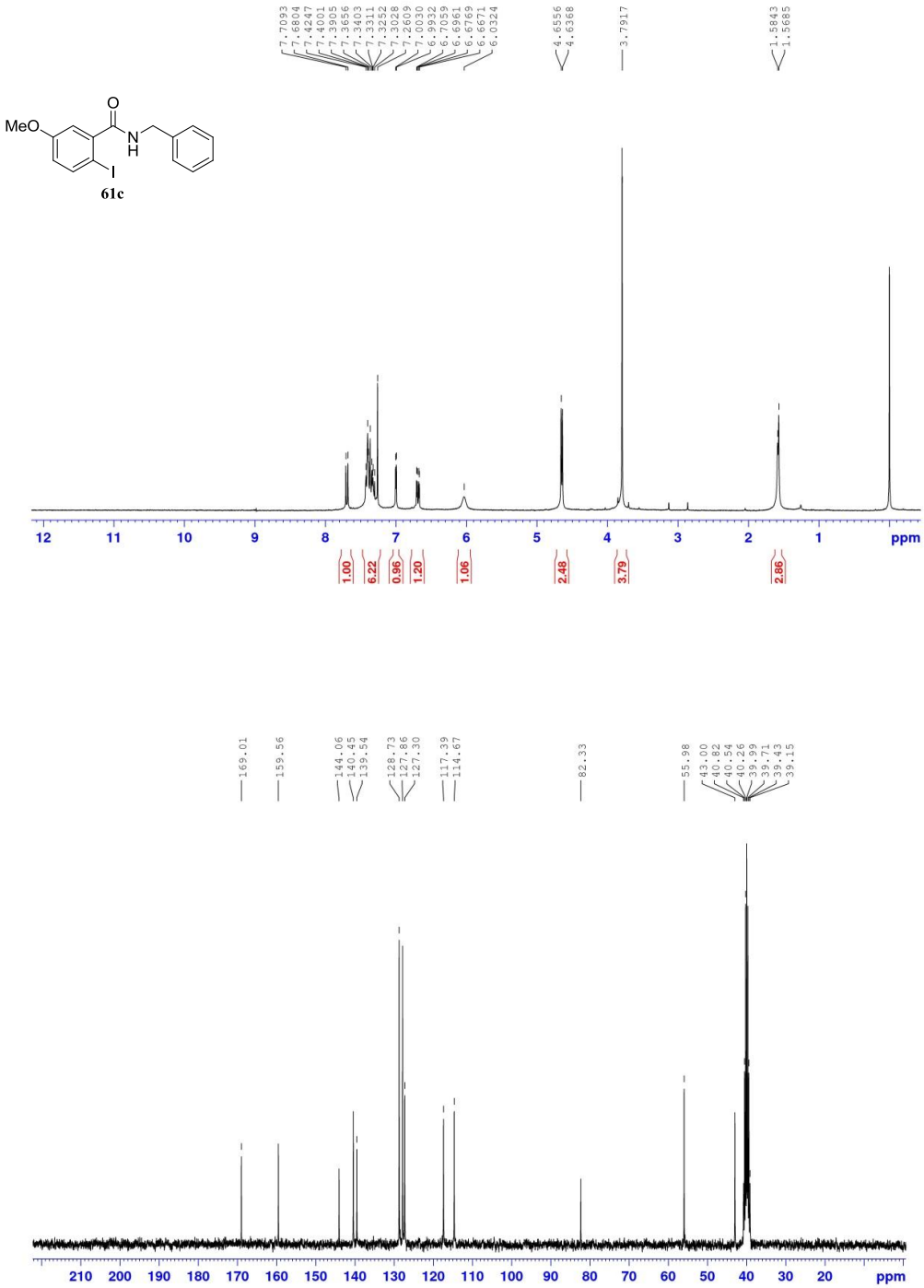


Figure 5 The ^{1}H (300 MHz) in $CDCl_3$ and ^{13}CNMR (75 MHz) in DMSO-$d_6$spectra of compound **61e**

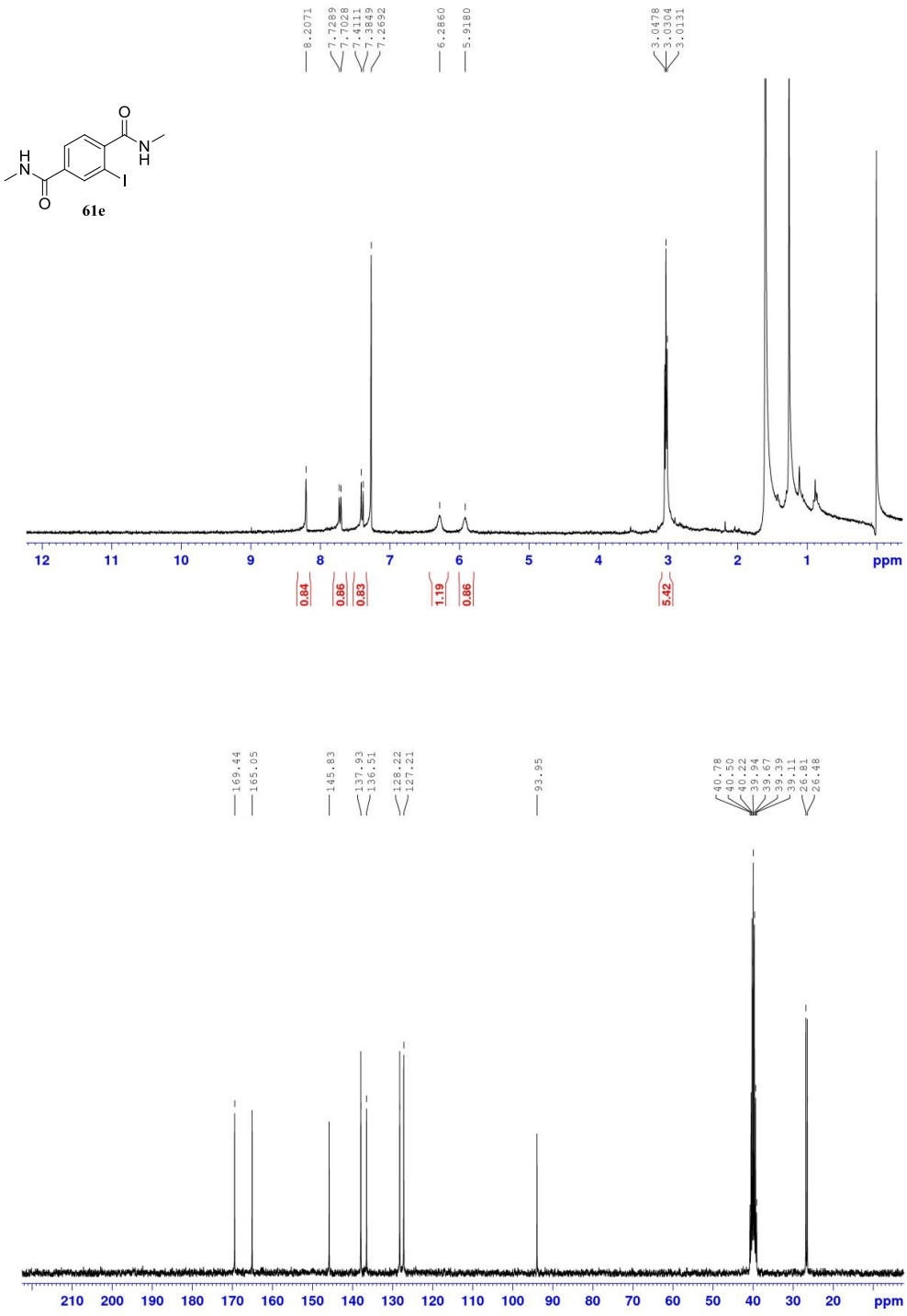


Figure 6 The ^{1}H (300 MHz) in $CDCl_3$and ^{13}CNMR (75 MHz) in DMSO-d_6 spectra of compound **61j**

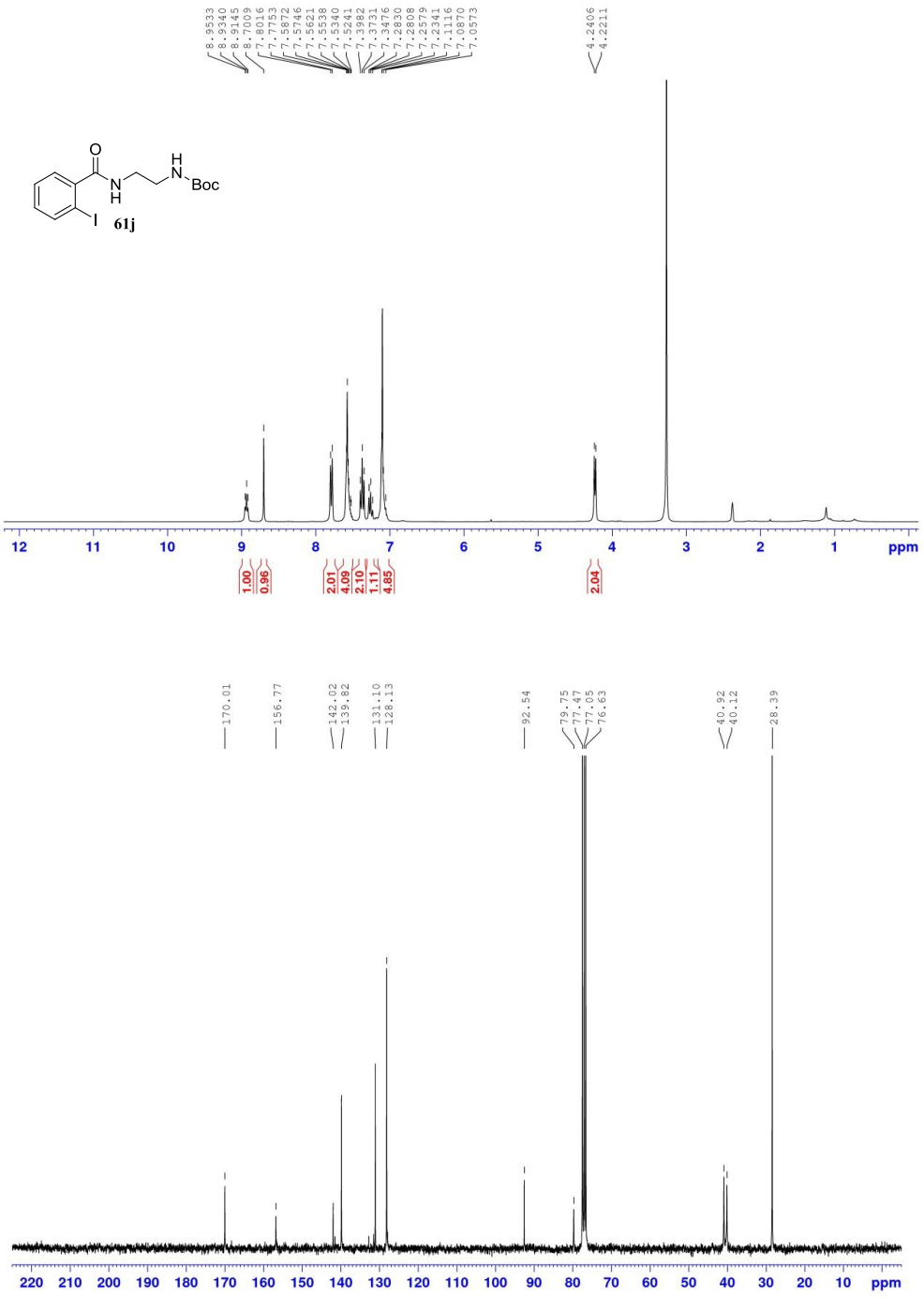


Figure 7 The ^{1}H (300 MHz) in $CDCl_3$and ^{13}CNMR (75 MHz) in DMSO-d_6 spectra of compound **63a**

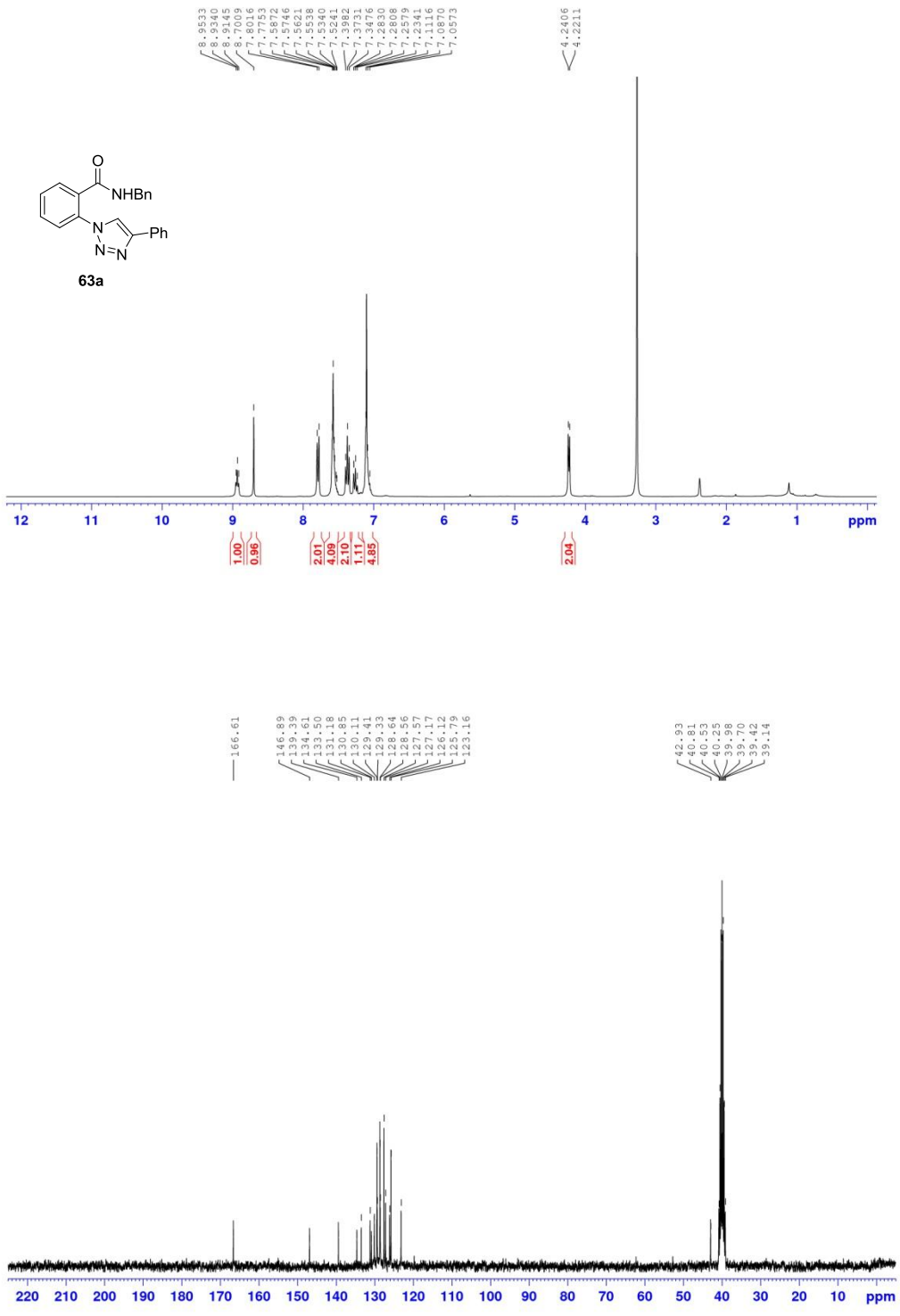


Figure 8 The ^{1}H (300 MHz) in $CDCl_3$and ^{13}CNMR (75 MHz) in DMSO-d_6 spectra of compound **63b**

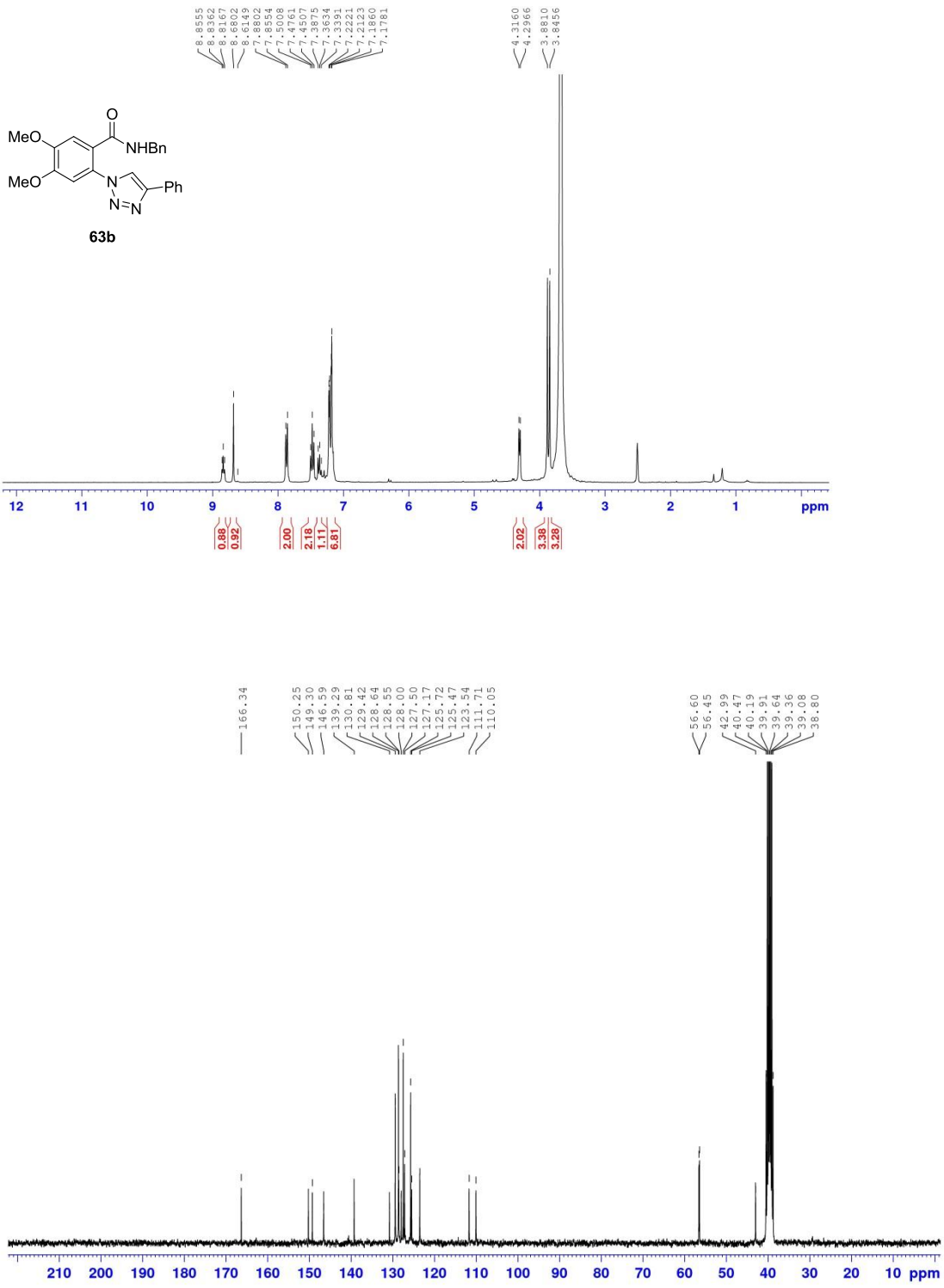


Figure 9 The ^{1}H (300 MHz) in DMOS-d_6 and ^{13}CNMR (75 MHz) in DMSO-d$_6$ spectra of compound **63c**

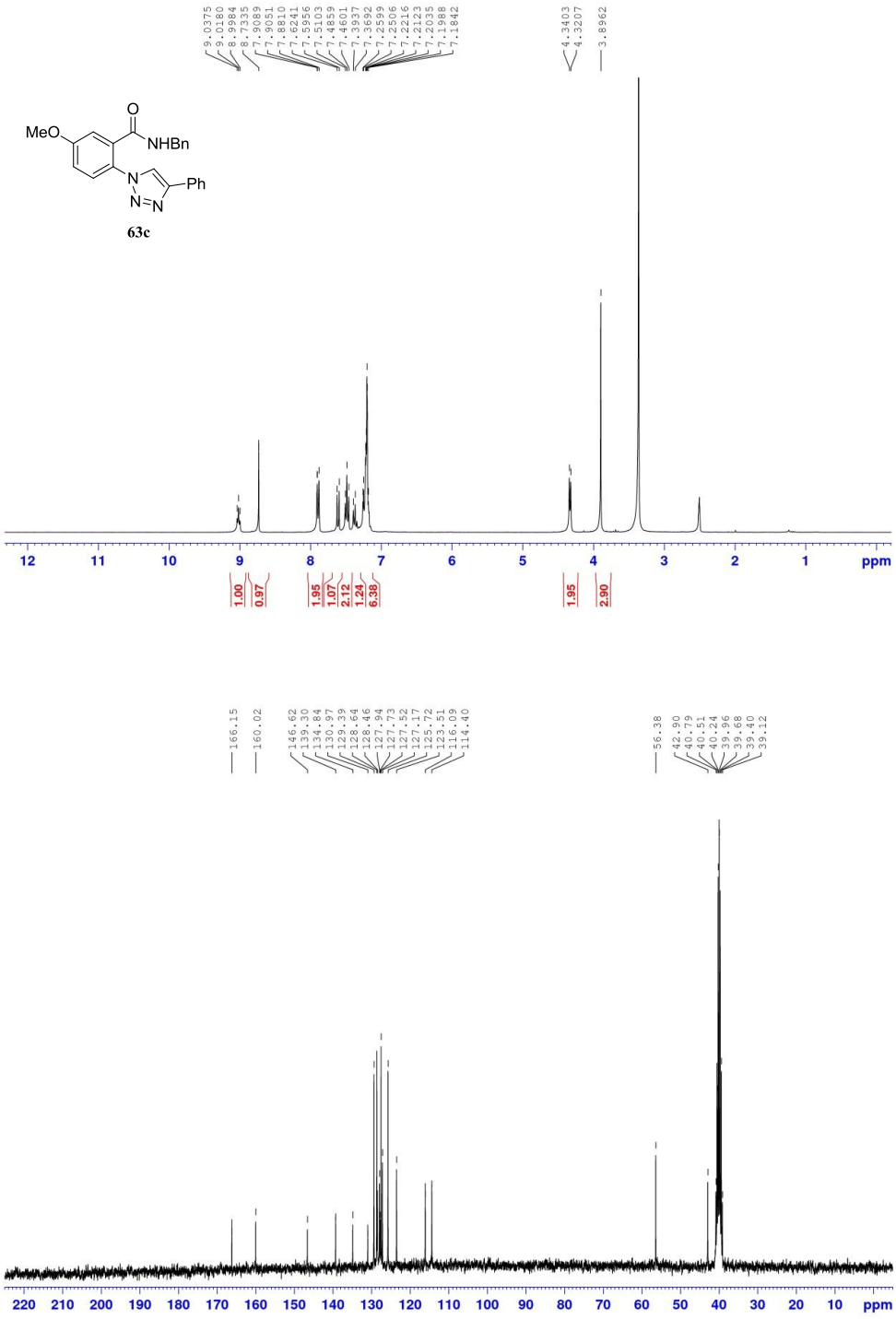


Figure 10 The ^{1}H (300 MHz) in DMSO and $^{13}CNMR$ (75 MHz) in $CDCl_3$ spectra of compound **63d**

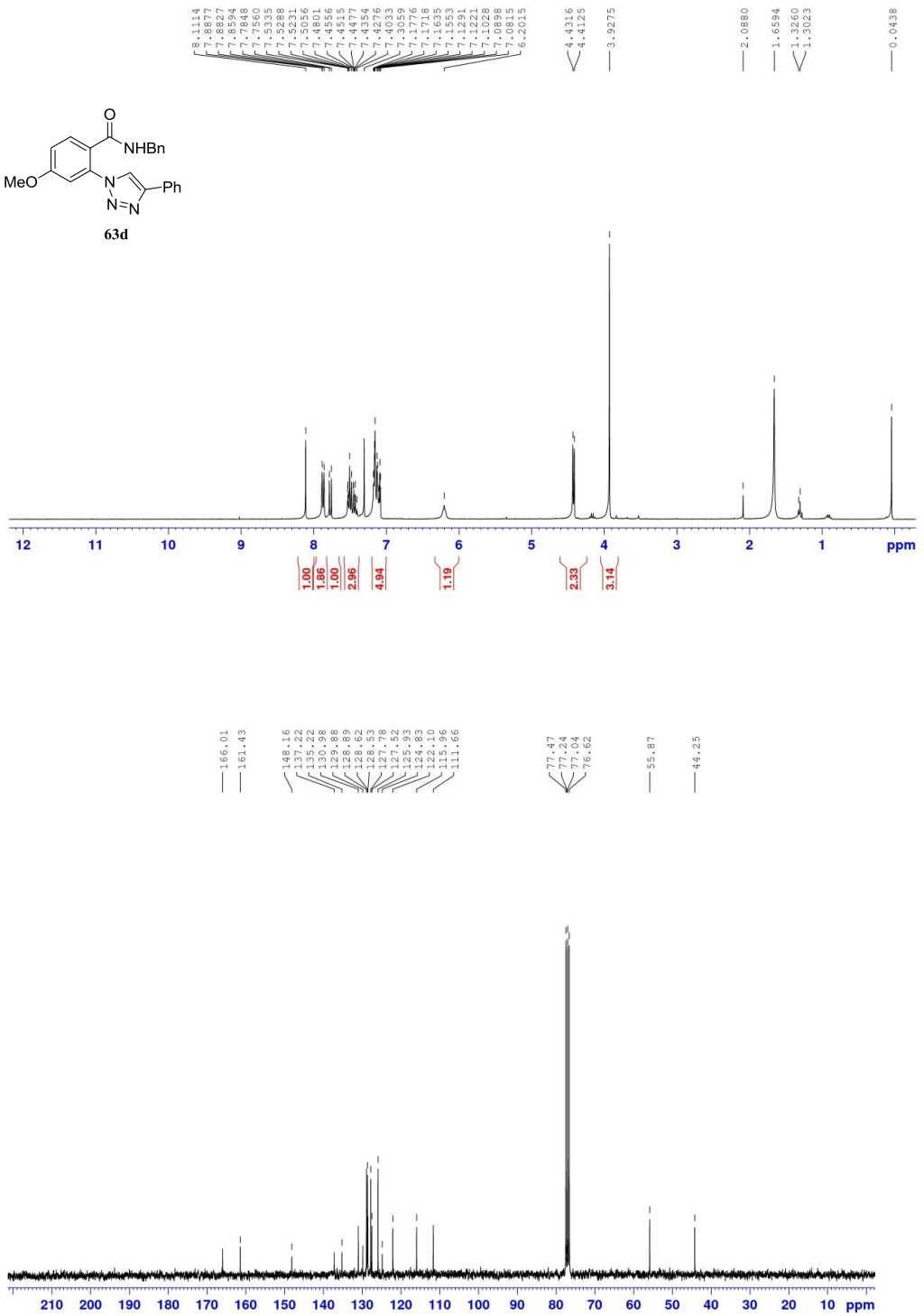


Figure 11 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63e** in DMSO-d_6

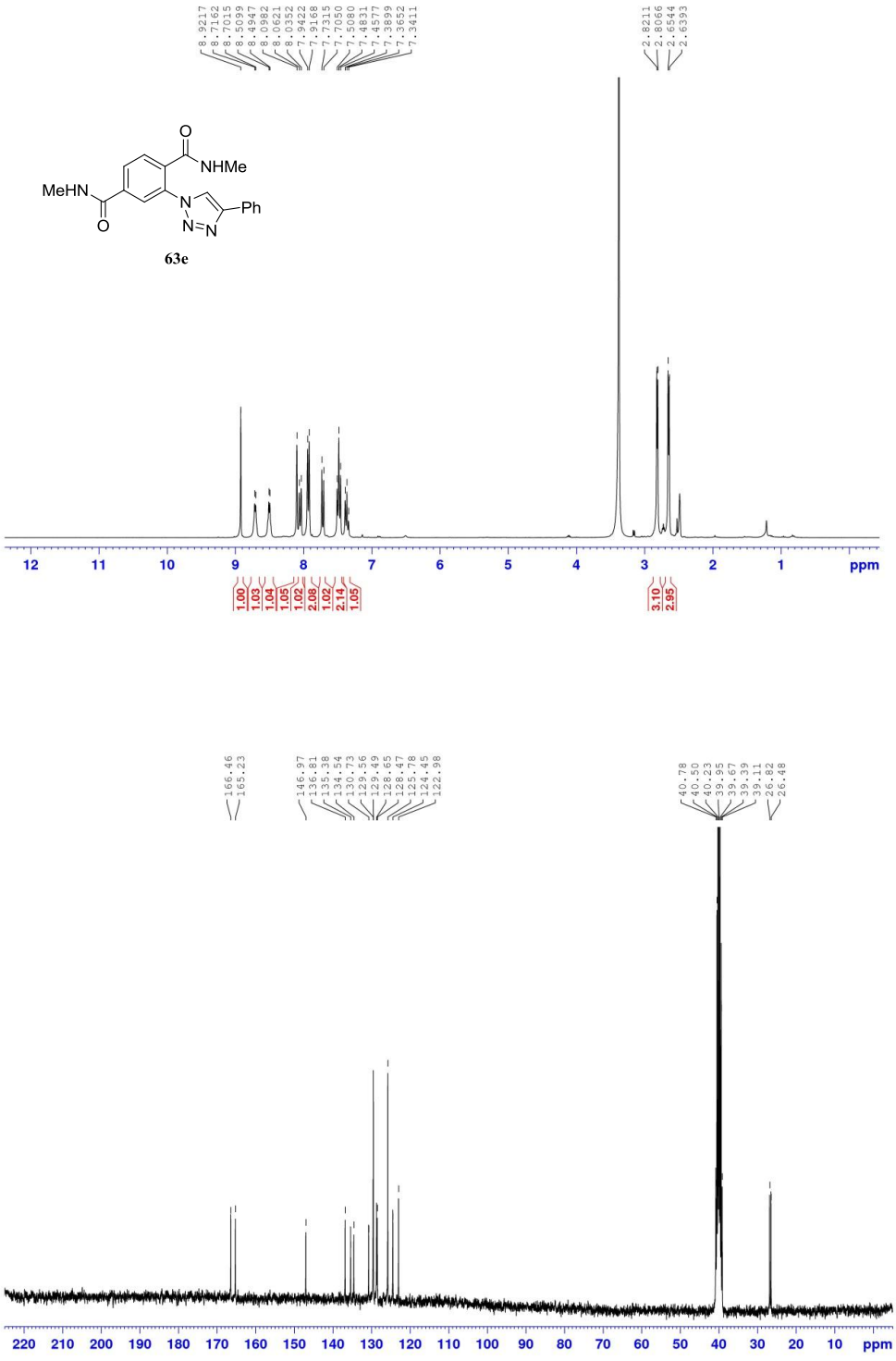


Figure 12 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63f** in DMSO-d_6

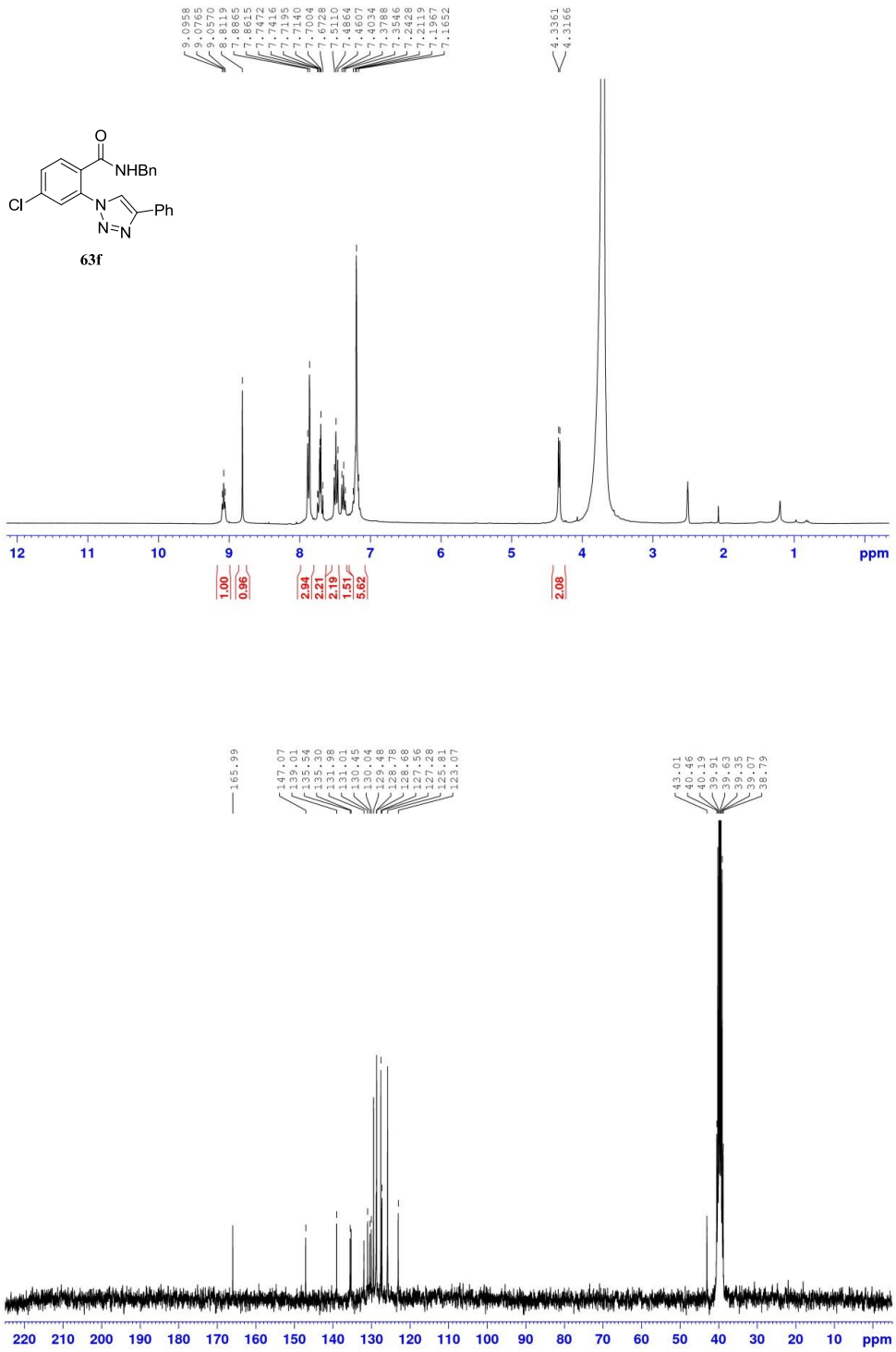


Figure 13 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63g** in DMSO-d_6

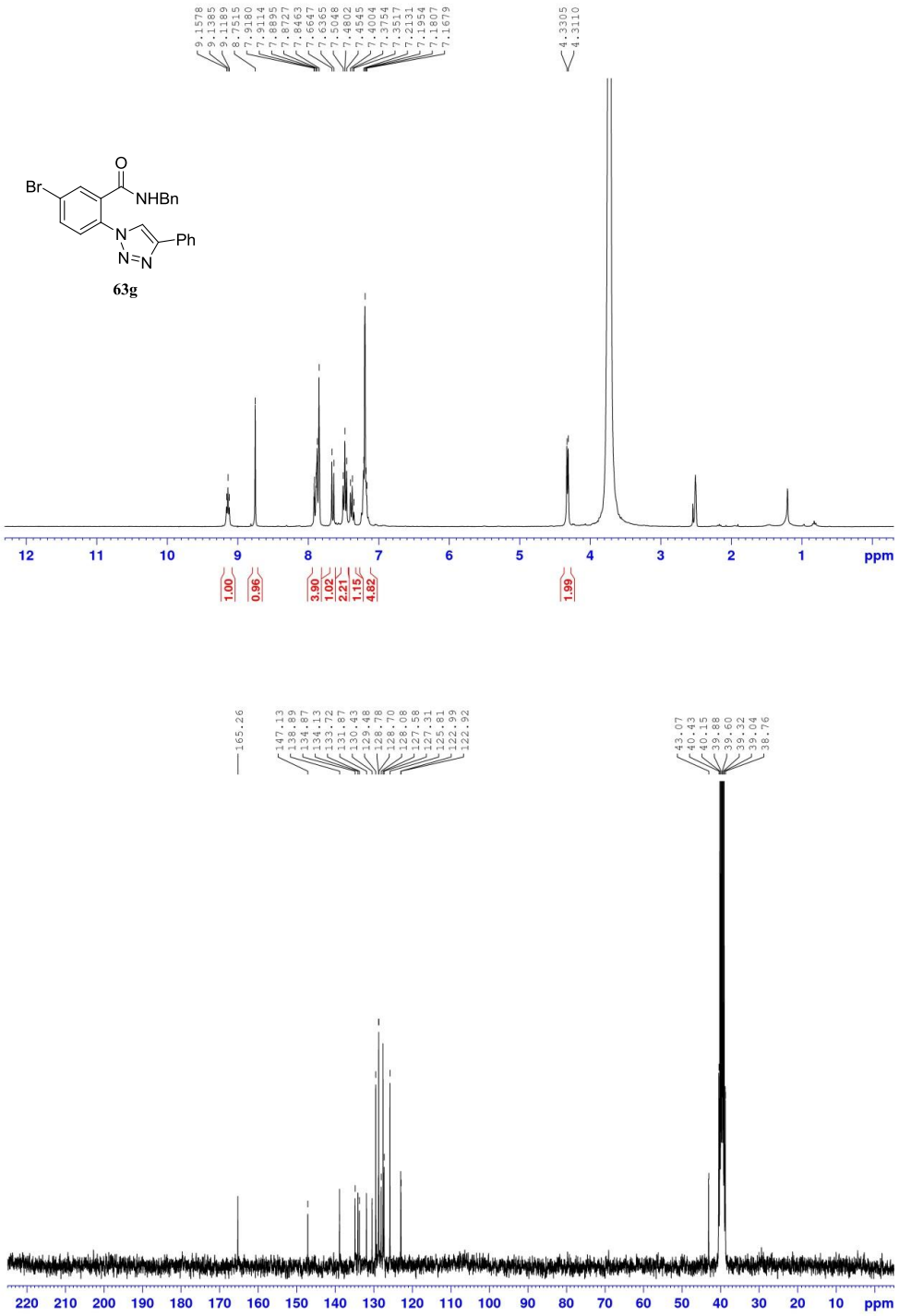


Figure 14 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63h** in $CDCl_3$

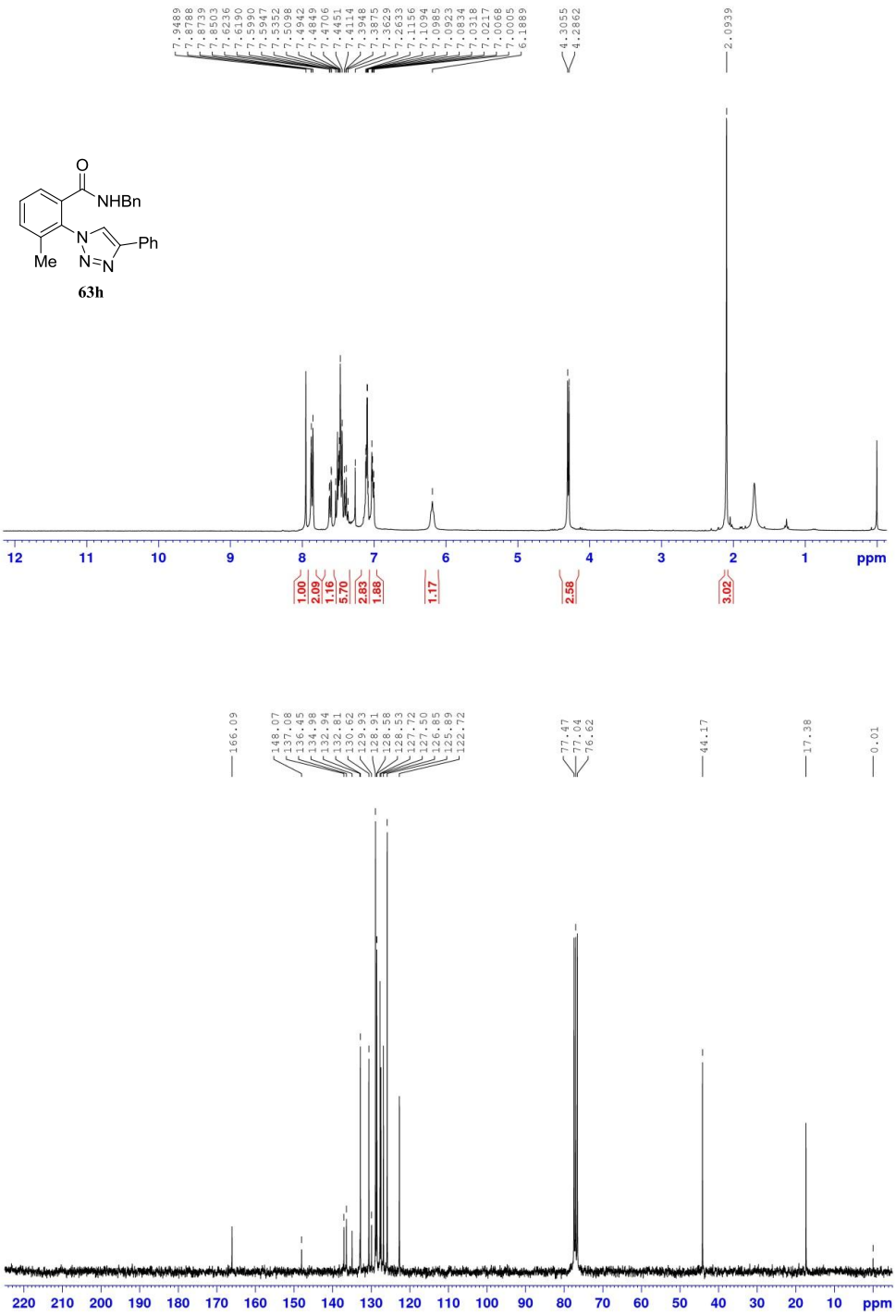


Figure 15 The ^{1}H (300 MHz) and $^{13}CNMR$ (75 MHz) spectra of compound **63i** in $CDCl_3$

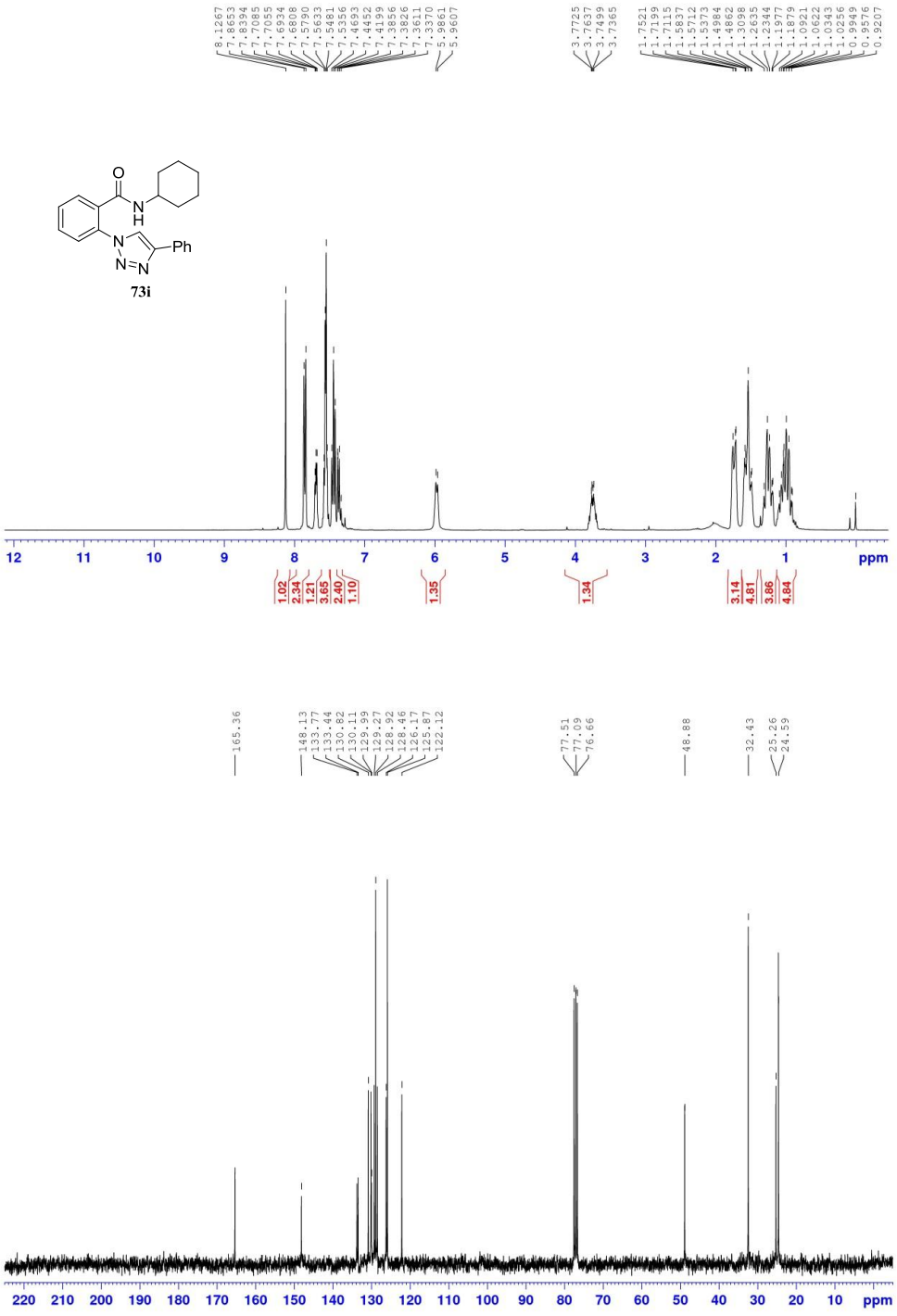


Figure 16 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63j** in DMSO-d_6

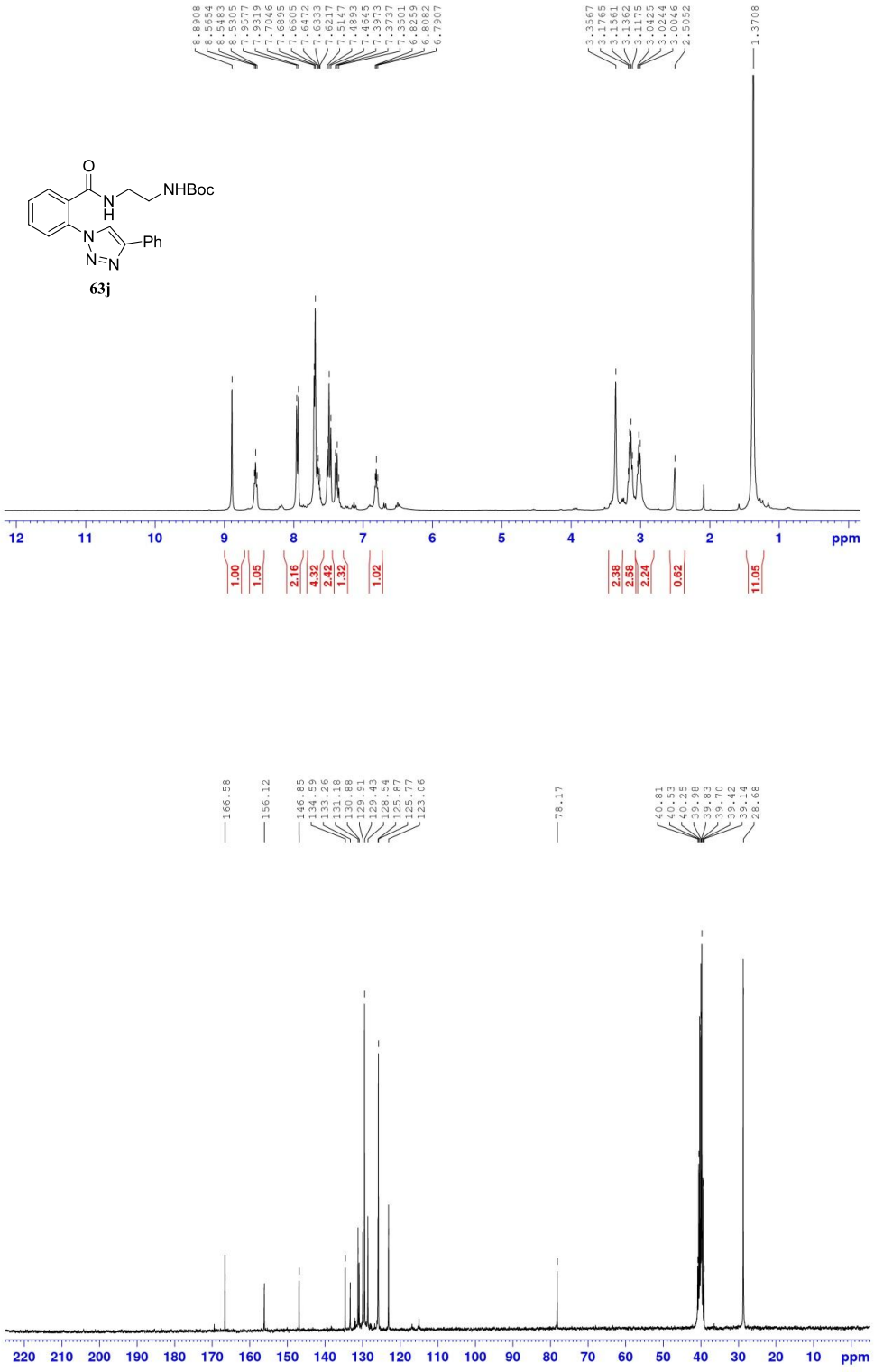


Figure 17 The ^{1}H (300 MHz) in DMSO and $^{13}CNMR$ (75 MHz) in $CDCl_3$ spectra of compound **63k**

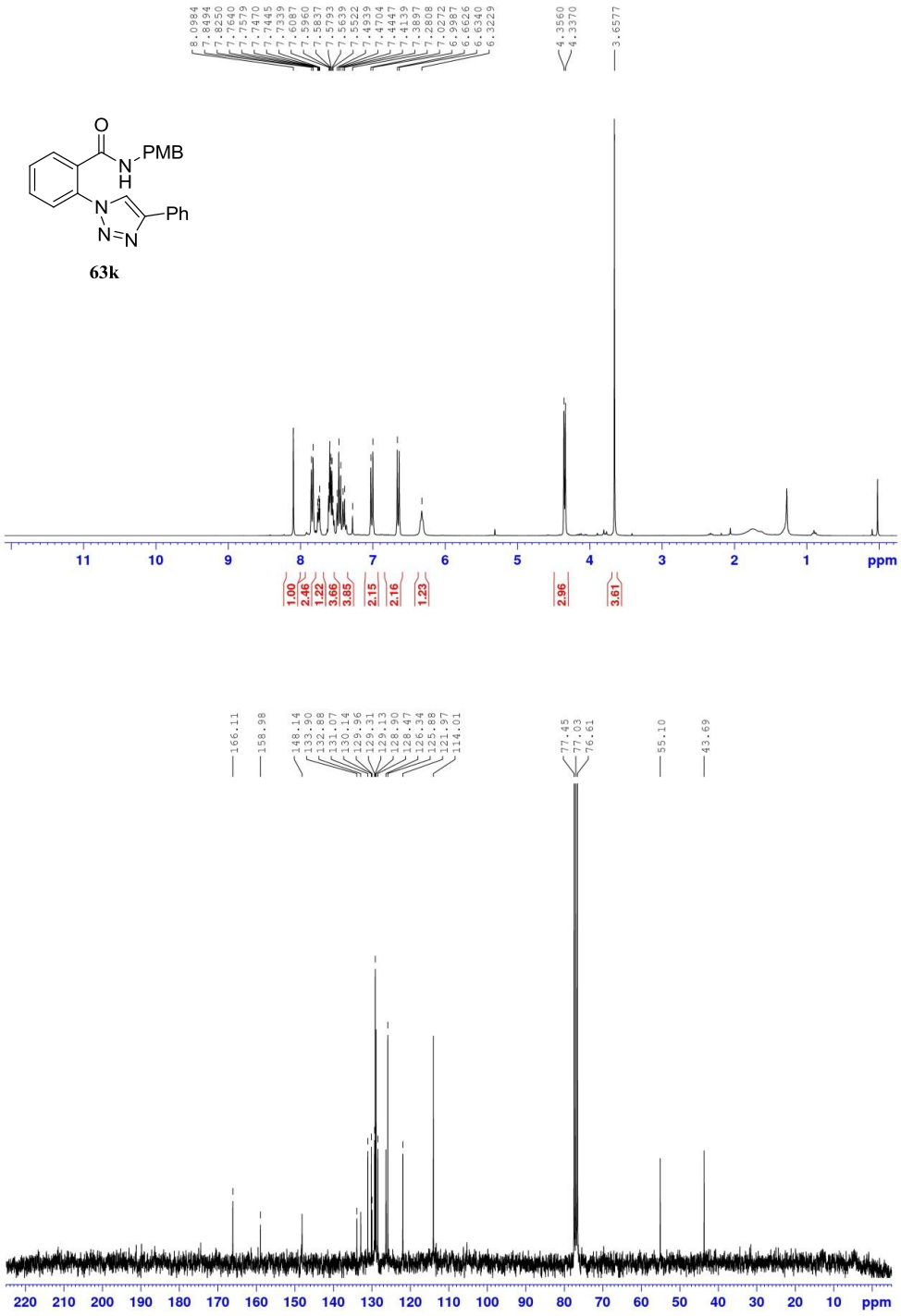
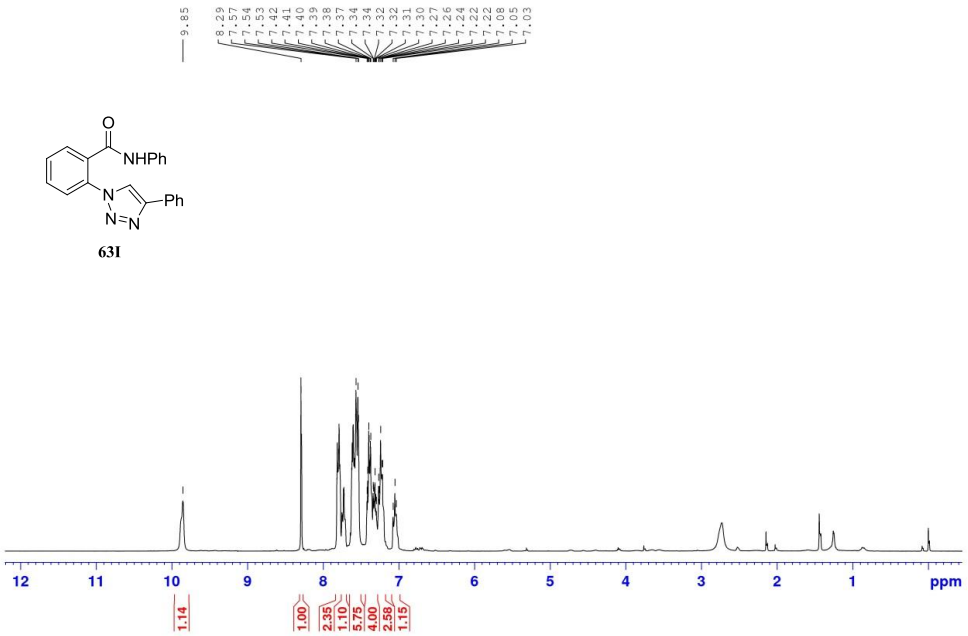


Figure 18 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63l** in $CDCl_3$



1

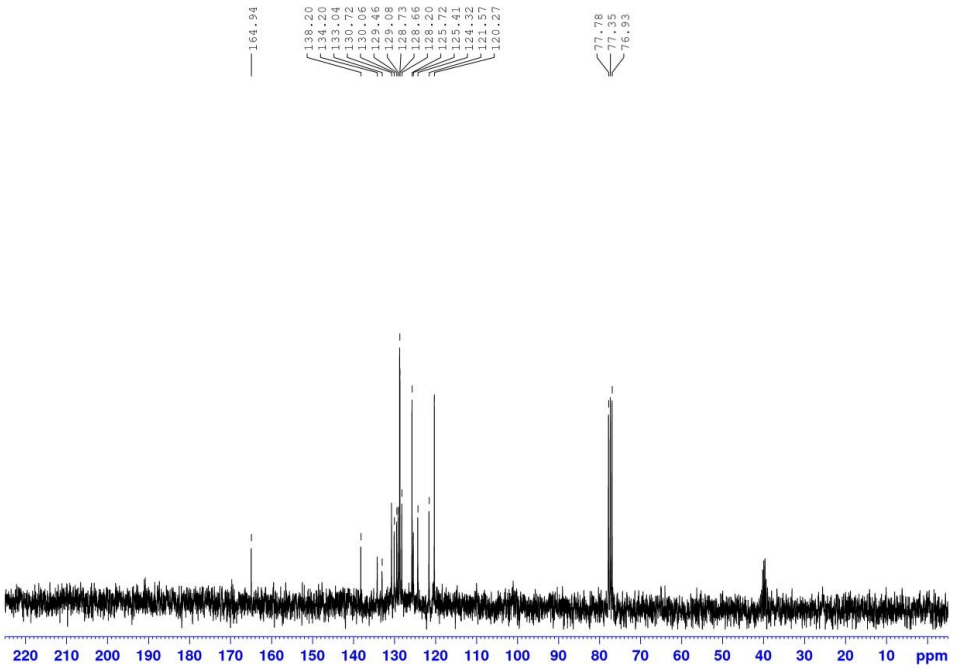


Figure 19 The ^{1}H (300 MHz) and $^{13}CNMR$ (75 MHz) spectra of compound **63m** in $CDCl_3$

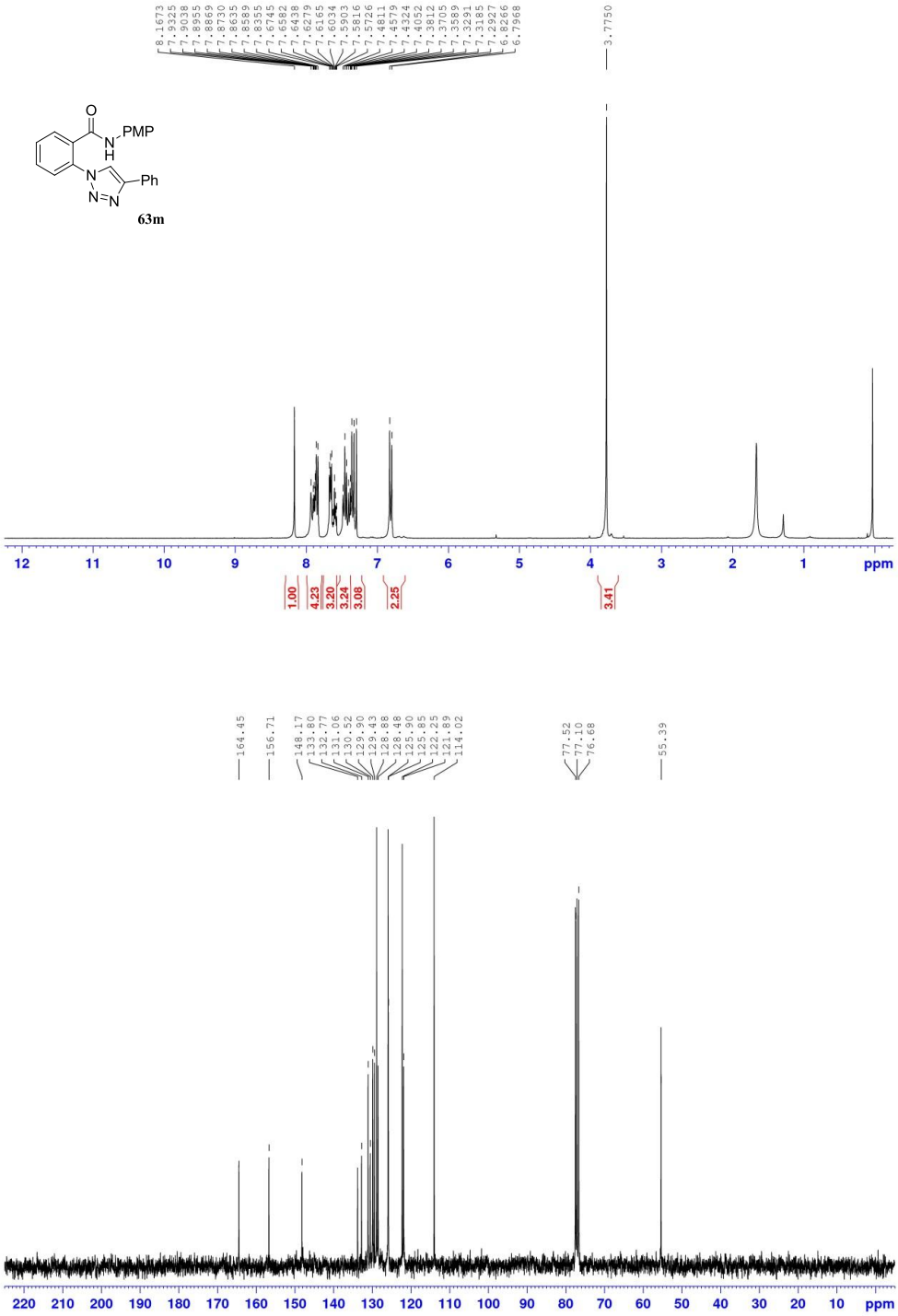


Figure 20 The ^{1}H (300 MHz) and $^{13}CNMR$ (75 MHz) spectra of compound **63n** in $CDCl_3$

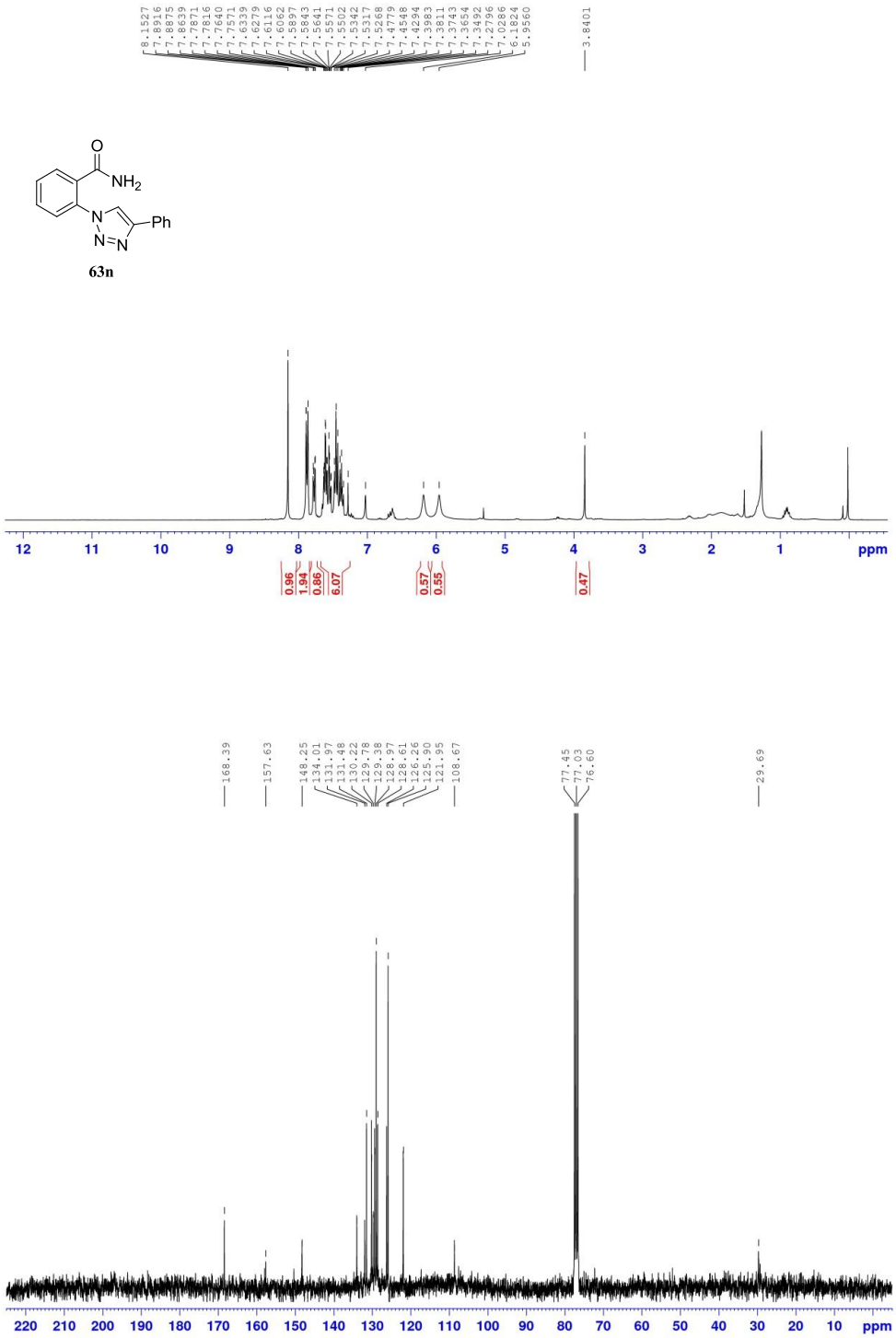


Figure 21 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63o** in DMSO-d_6

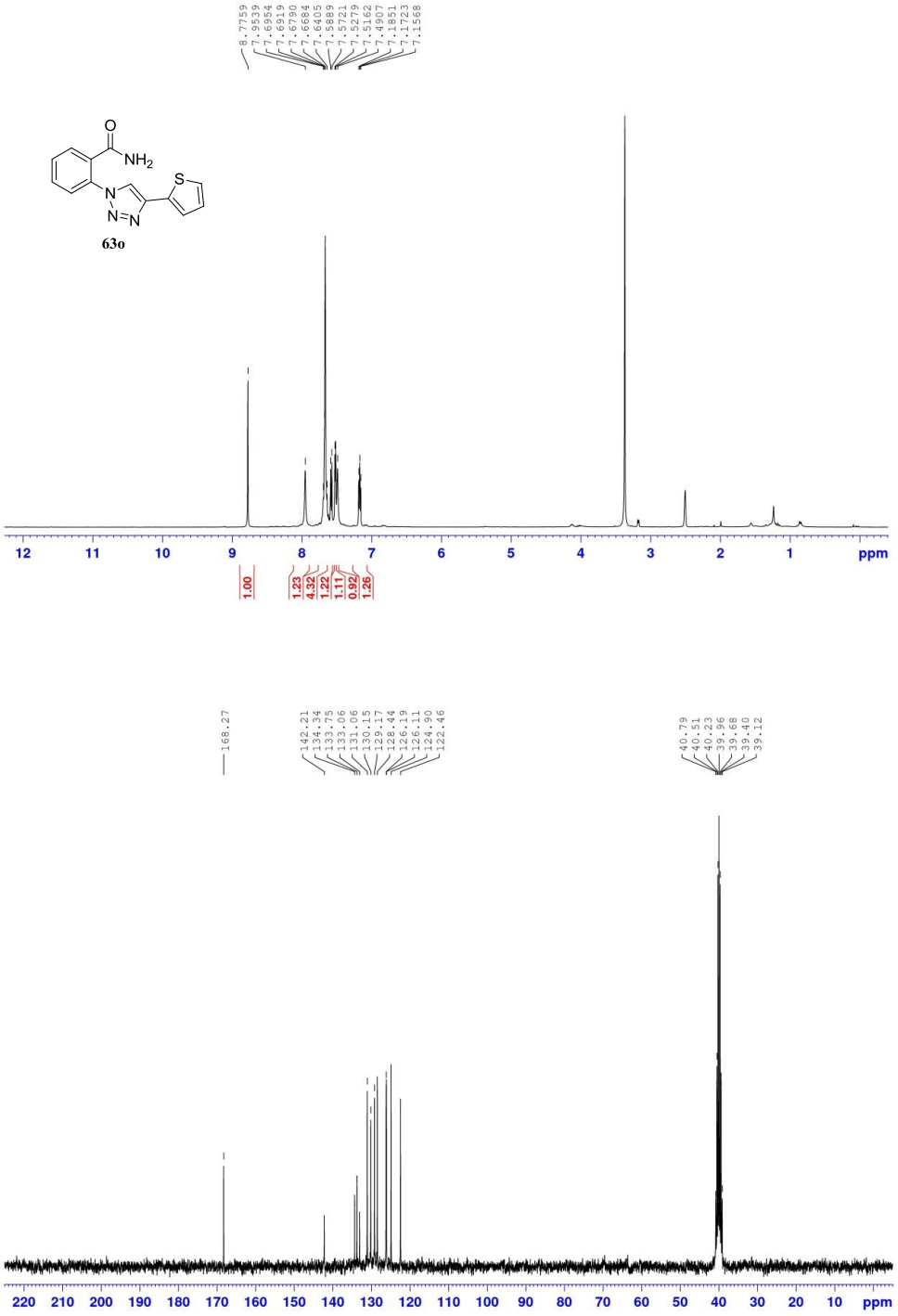


Figure 22 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63p** in DMSO-d_6

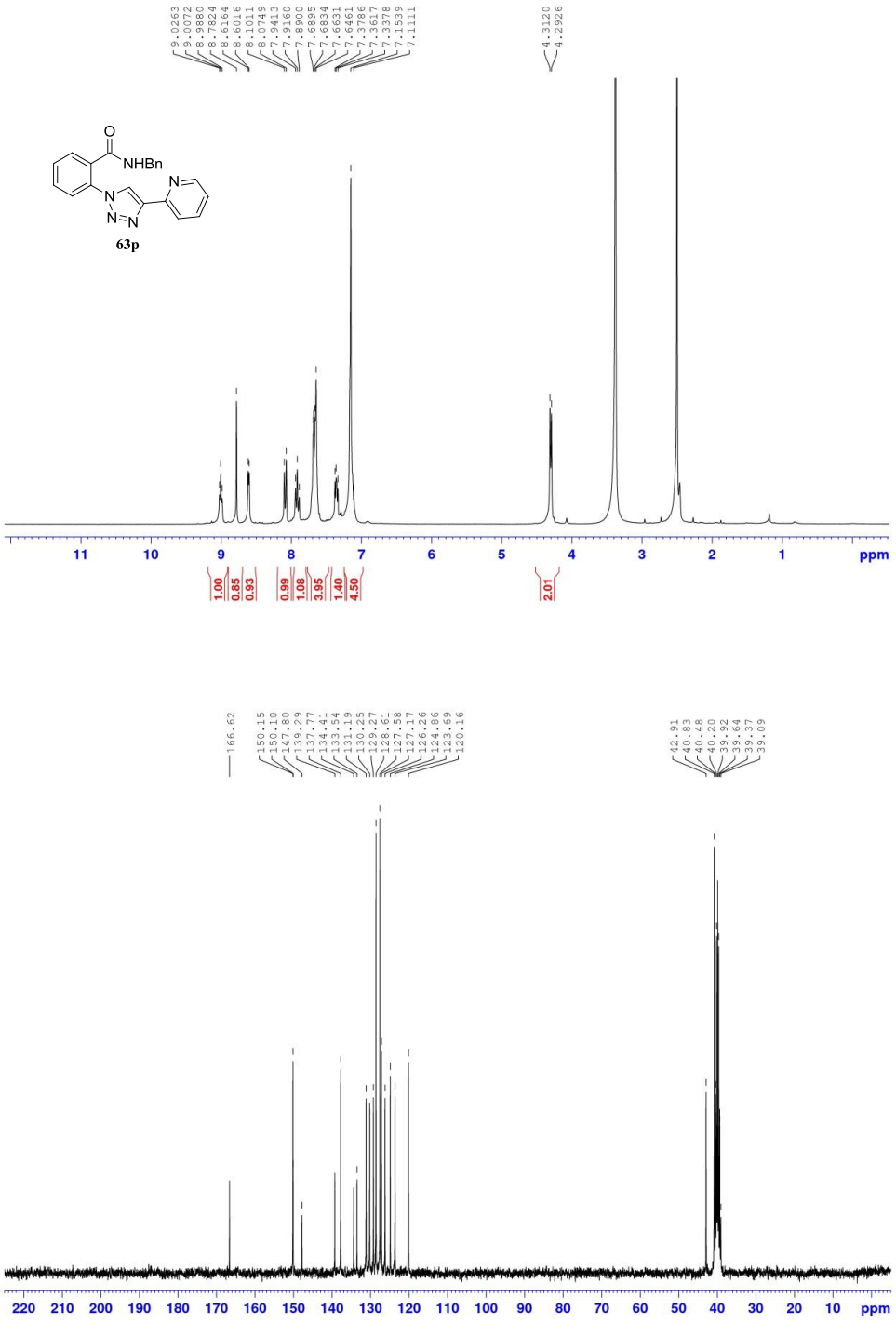


Figure 23 The ^{1}H (300 MHz) in DMSOand $^{13}CNMR$ (75 MHz) in $CDCl_3$ spectra of compound **63q**

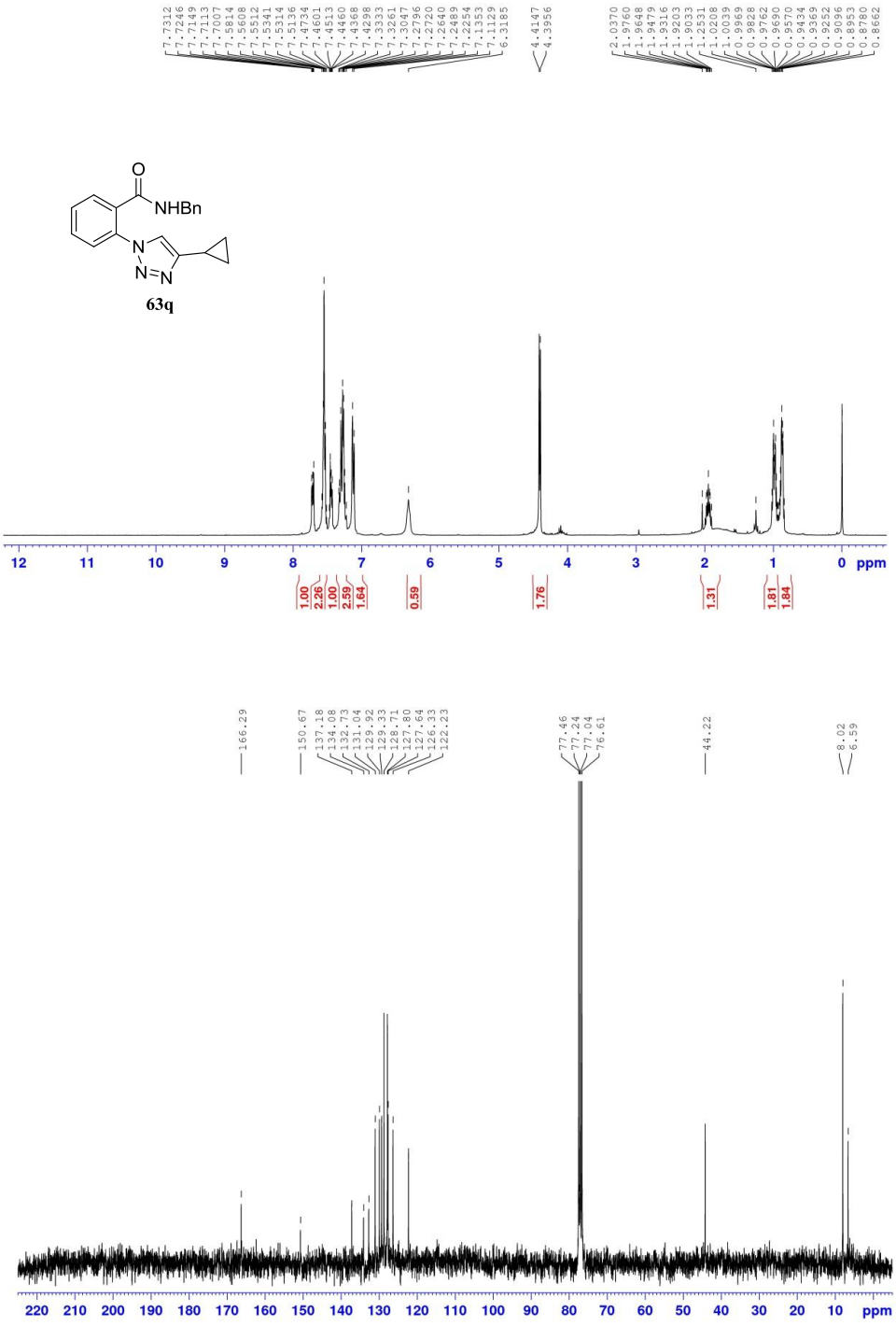


Figure 24 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63r** in DMSO-d_6

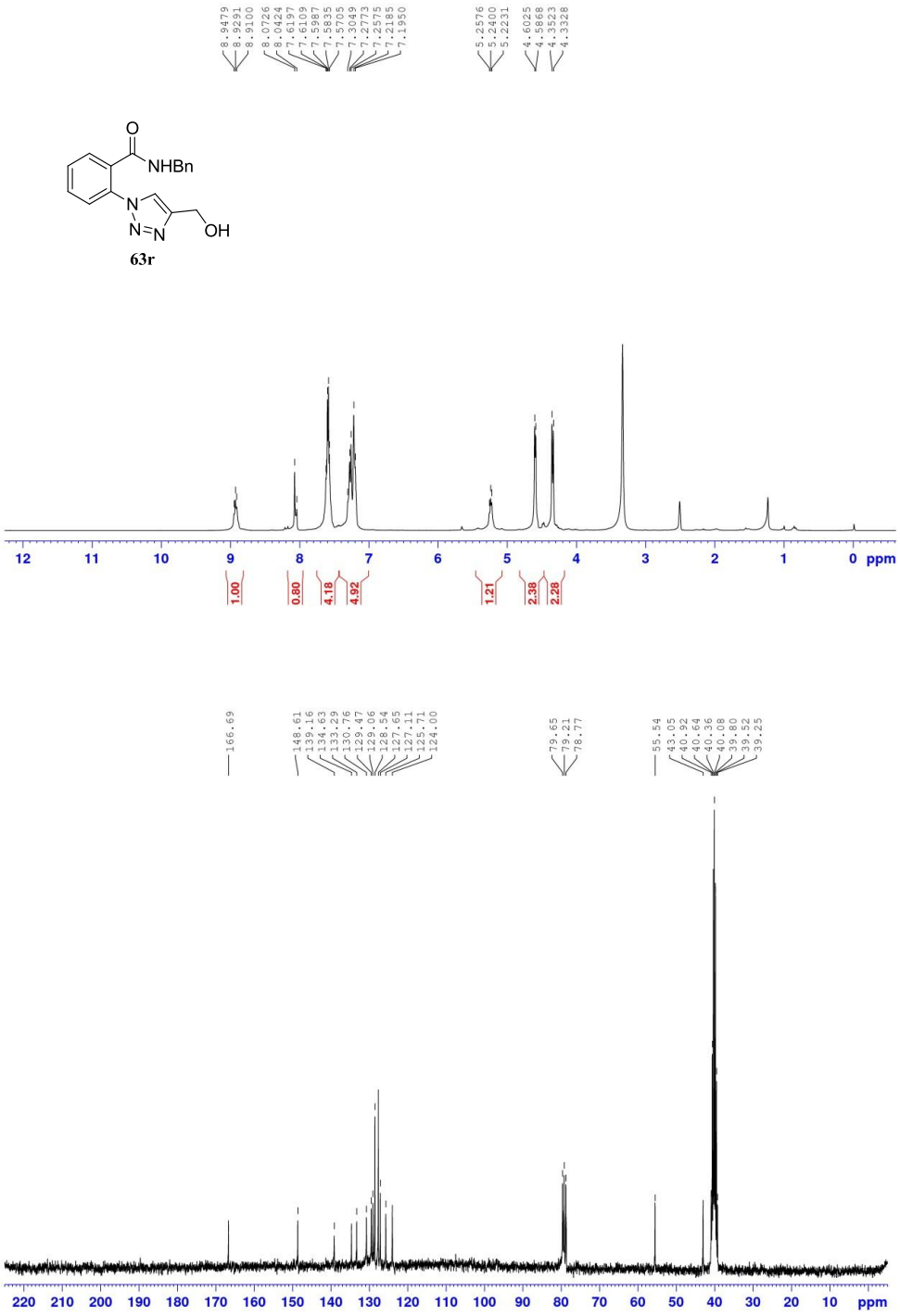


Figure 25 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63s** in DMSO-d_6

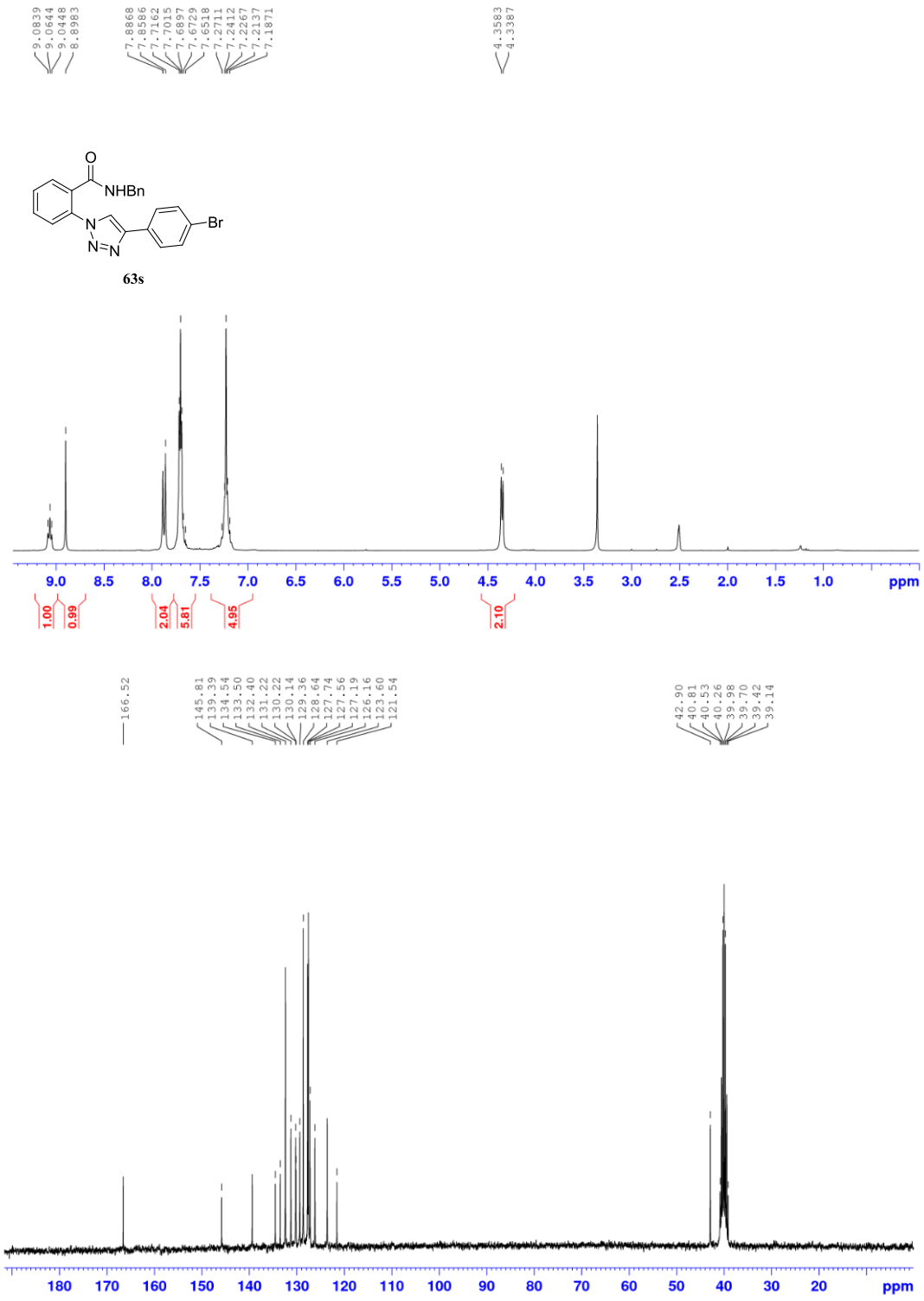


Figure 26 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63t** in DMSO-d_6

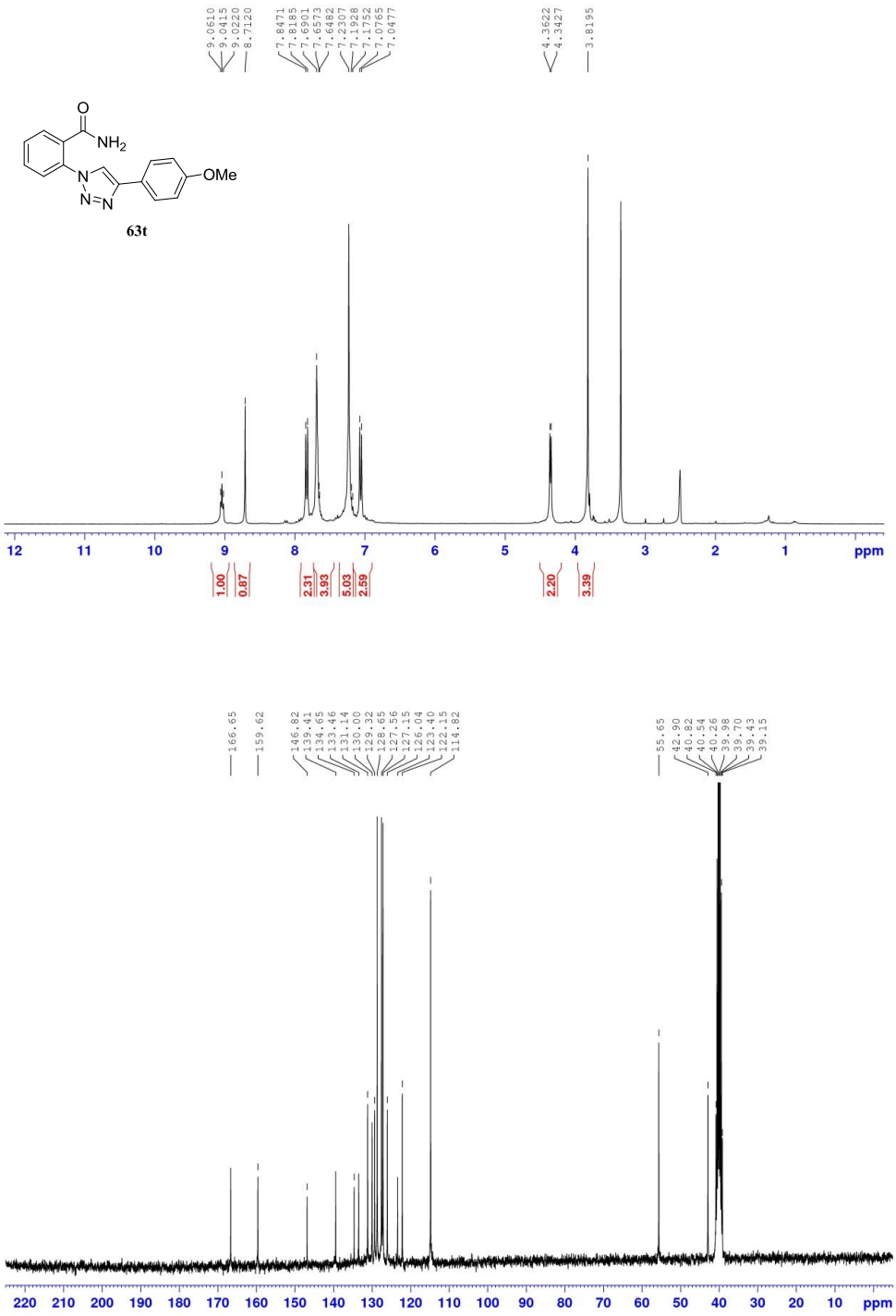


Figure 27 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **63u** in DMSO-d_6

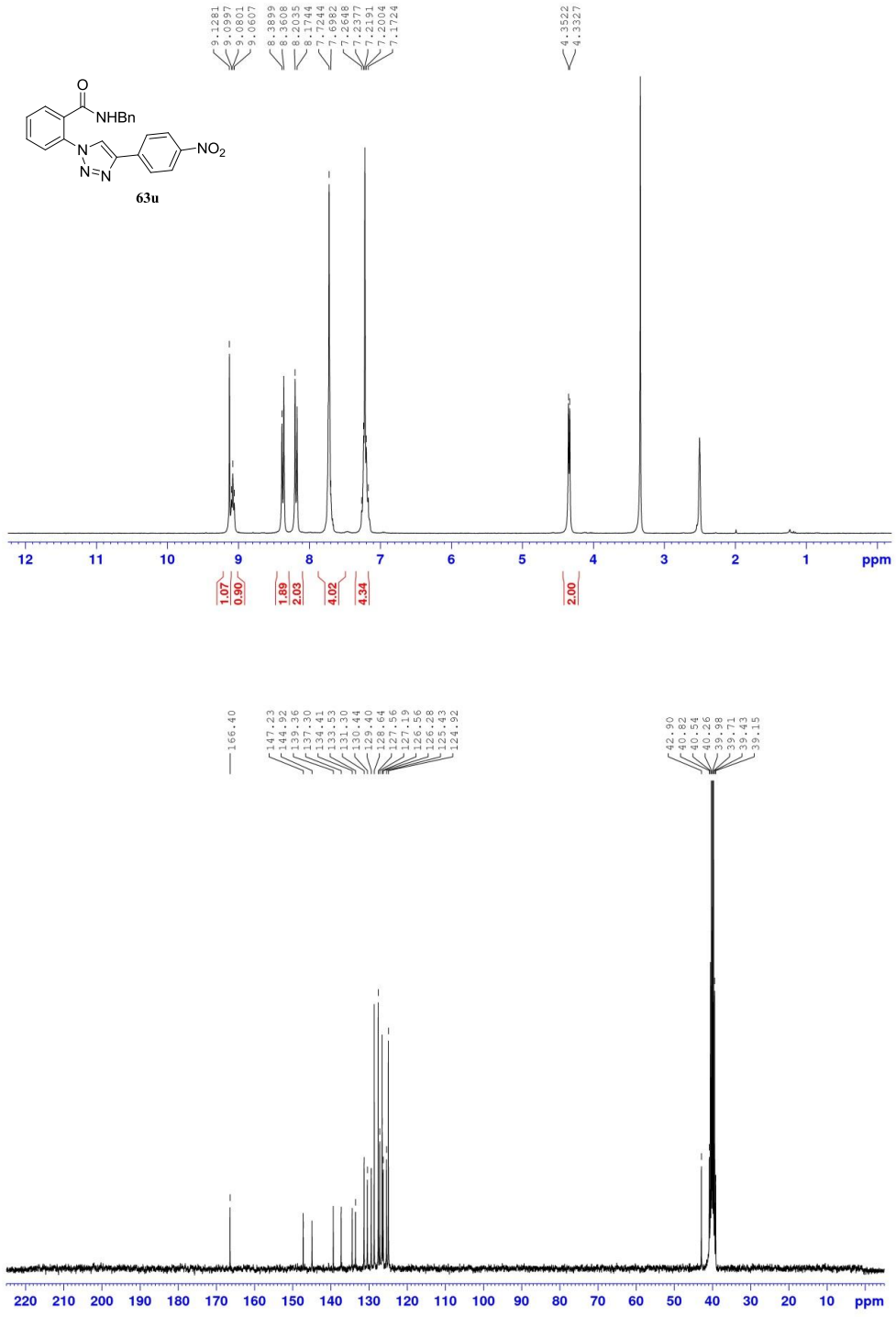


Figure 28 The ^{1}H (300 MHz) and $^{13}CNMR$ (75 MHz) spectra of compound **67c** in $CDCl_3$

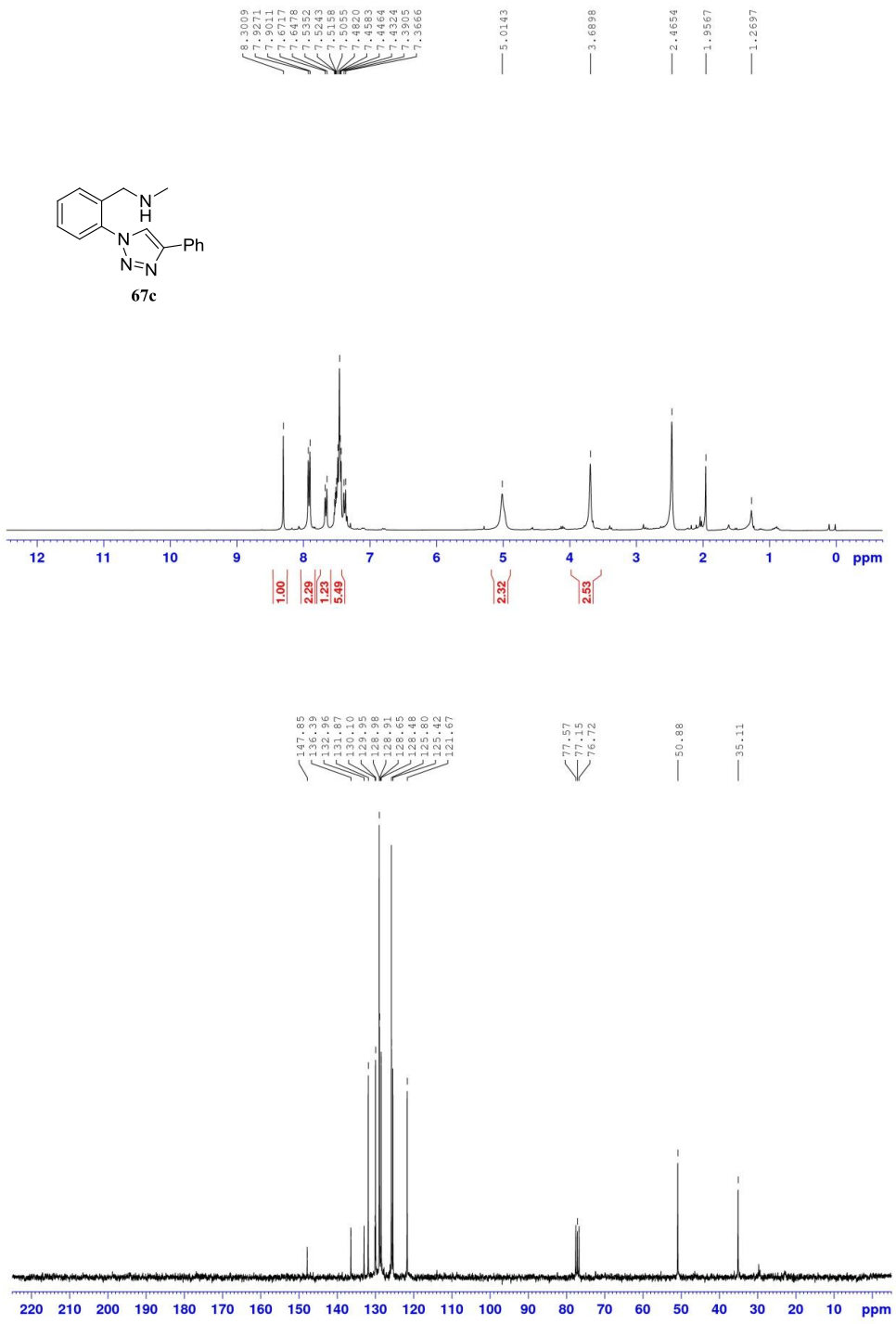


Figure 29 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **67d** in $CDCl_3$

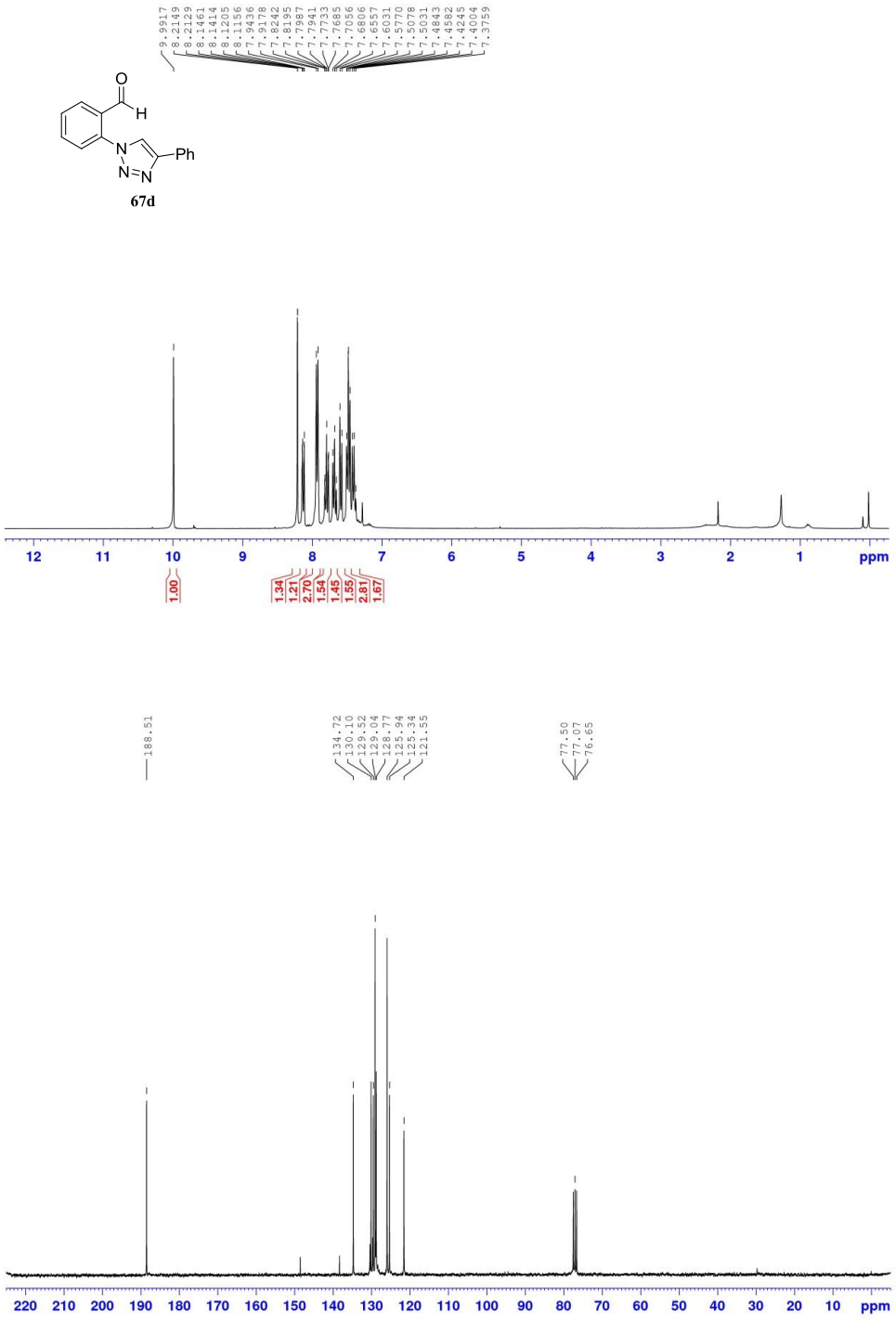
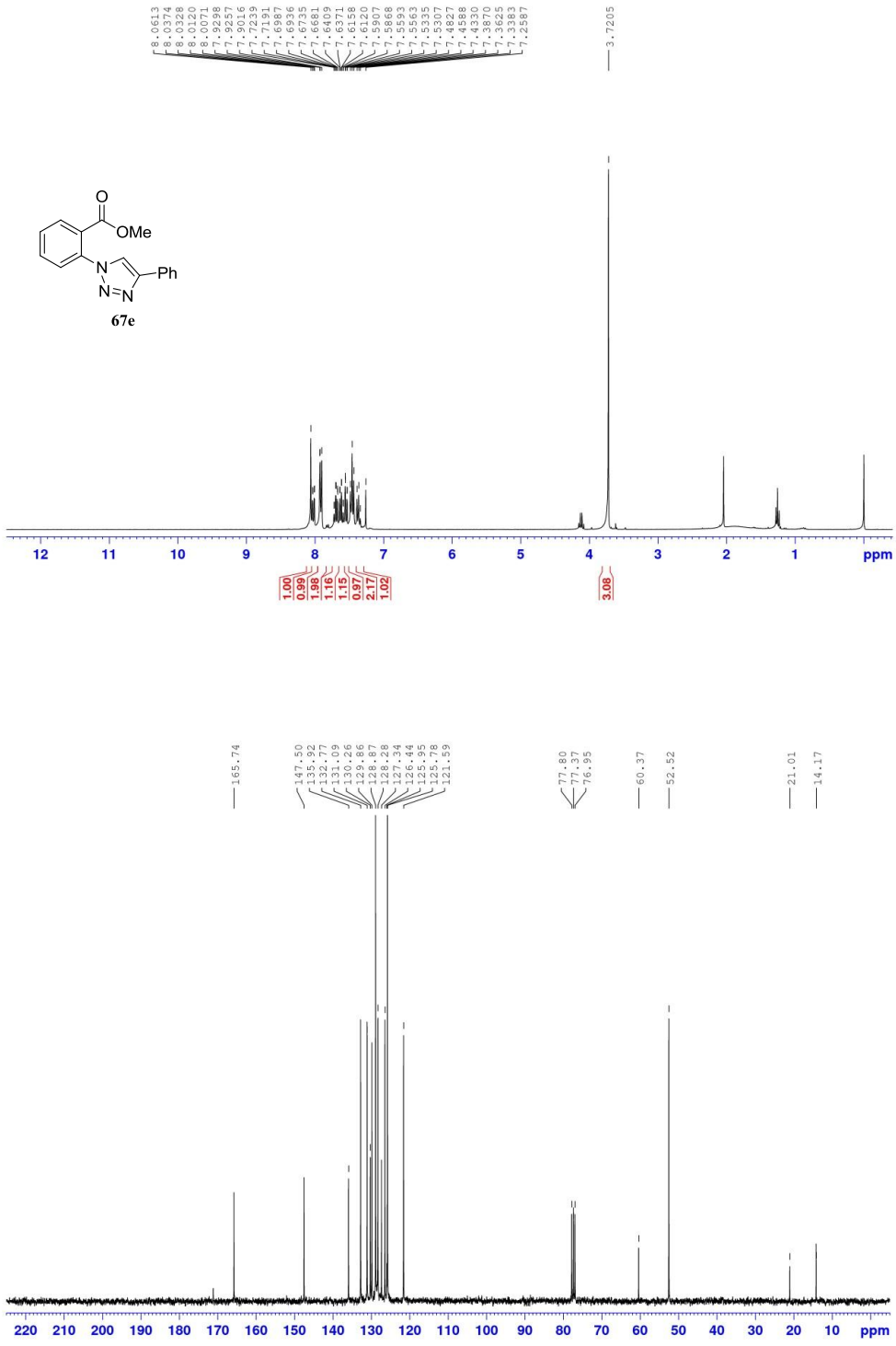


Figure 29 The ^{1}H (300 MHz) and ^{13}CNMR (75 MHz) spectra of compound **67e** in $CDCl_3$



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List of Publication

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