Pd(II)-Catalyzed Direct β-Arylation of C(sp^3)-H Bonds of Aliphatic and Alicyclic Carboxamides *Via* One-pot Method

Sruthi Mohan
Reg. No. MS11034

A dissertation submitted for the partial fulfillment of BS-MS dual degree in science

Department of Chemical Sciences,
Indian Institute of Science Education and Research
Mohali, Knowledge City, Sector 81, SAS Nagar,
Manauli P.O., Punjab
April 2016

Certificate of Examination

This is to certify that the dissertation titled "*Pd(II)-Catalyzed Direct β-Arylation of C(sp^3)-H Bonds of Aliphatic and Alicyclic carboxamides Via One-pot Method*" submitted by Ms. Sruthi Mohan (Reg. No. MS11034) for the partial fulfillment of BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

Dr. Sripada S. V. Rama Sastry	Dr. R. Vijaya Anand	Dr. S. Arulananda Babu
Assistant Professor	Associate Professor	Associate Professor
IISER Mohali	IISER Mohali	IISER Mohali (Supervisor)

Dated : April 22, 2016

Declaration

The work presented in this dissertation has been carried out by me under the guidance of **Dr. S. Arulananda Babu** at the Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussion. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Sruthi Mohan
(Candidate)

Dated : April 22, 2016

In my capacity as the supervisor of the candidate's project work, I certify that the above statement by the candidate are true to the best of my knowledge.

Dr. S. Arulananda Babu
(Supervisor)

Acknowledgement

It is my privilege to express my sincere gratitude to my master thesis supervisor, **Dr. S. Arulananda Babu** for his invaluable support, guidance, and supervision throughout the research work. After joining Dr. Arulananda Babu's lab I have learned more synthetic methodology of organic chemistry. I was part of three different project from this lab under his excellent guidance. I am very thankful to him for exposing me to various interesting field of research. Additionally, I would like to express my deep gratitude to him for compiling the project report in this good research work form.

I am extremely thankful to Mr. Ramarao Parella, Mr. Gopalakrishnan and Mr. Nayyar Ahmad Aslam for their initial help in learning the experimental techniques. Their inspiring and invaluable conceptual understanding that has benefited me during the course of the project. I am also thankful to all my other group members, Mr. Rajkumar, Mr. Chennakesava Reddy, Mr. Naveen, Ms. Padmavathi, Mr. Narendra, and Mr. Akshay Sandhu for keeping me motivated and to have maintained a comfortable atmosphere in the lab. I am very thankful to the faculty members in the Department of Chemical Science IISER Mohali for their encouragement and support throughout the journey of my master degree. Also I thank the teaching lab assistants for their help during my course of studies. This research was funded by IISER-Mohali. I thank the NMR, HRMS and X-ray facilities of IISER-Mohali and DST for providing the INSPIRE fellowship.

Personally, I am thankful to all my classmates and friends for their support throughout the MS project. Also I am very much thankful to my family for their love and support.

List of Figures

List of Schemes

List of Tables

NOTATIONS AND ABBREVIATIONS

C-H	Carbon-Hydrogen
DG	Directing group
TLC	Thin layer chromatography
NMR	Nuclear magnetic resonance
δ	Chemical shift in ppm
ppm	Parts per million
EtOAc	Ethyl acetate
MeOH	Methanol
EtOH	Ethanol
IR	Infra-red
s	Singlet
d	Doublet
t	Triplet
m	Multiplet
br s	Broad singlet
dd	Doublet of doublet
dt	Doublet of triplet
td	Triplet of doublet
MP	Melting point
MS	Mass spectrometry
ESI	Electron Spray Ionization

Contents

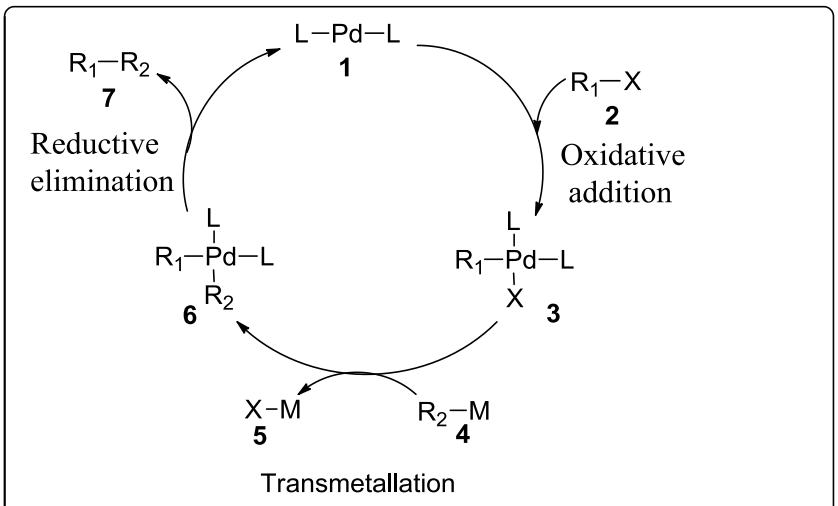
Abstract

A step economical one-pot multicomponent reaction protocol comprising the installation of the bidentate directing group followed by the Pd(II)-catalyzed C-H activation and β-arylation of C(sp^3)-H bonds of carboxamides is reported. Accordingly, the reaction of a mixture of an acid chloride, bidentate ligand (e.g., 8-aminoquinoline), and an aryl iodide in the presence of the $Pd(OAc)_2$ catalyst and Ag_2CO_3 additive directly afforded the corresponding β-C-H -arylated *N*-(quinolin-8-yl) carboxamide derivatives.

Chapter 1

Introduction

The most demanding synthetic method in organic chemistry is the invention and improvement of carbon-carbon bond and carbon-heteroatom bond formation. Transition metal catalyzed synthetic methods, especially cross-coupling reactions[1, 2] have made a great impact on organic chemistry. These methods revolutionized the field of organic chemistry for discovering novel reactions with yield and efficiency. General reaction mechanism (Scheme 1) of cross-coupling reactions starts with the oxidative addition of an electrophile **2** to the metal **1** generates the intermediate **3**. Next, transmetallation of organometallic reagent **4** with **5** gives the intermediate **6**. Last step reductive elimination of intermediate **6** gives the C-C coupled product **7**. Cross-coupling reactions have some limitations such as a) it requires pre-functionalized starting materials, b) use of costly and bulky ligands, c) production of hazardous side products. Therefore, C-C bond and C-X bond formation *via* C-H activation methodology is considered as the most demanding synthetic strategy.



Scheme 1: General Mechanism of Cross-coupling Reactions

Carbon-Hydrogen (C-H) activation is the process of activation of a particular C-H bond using a low valent transition metal in the presence of oxidants or additives[3]. C-H functionalization is the reaction in which activation of C-H bond, cleavage and replacement of C-H bond to C-X bond[4] (X can be carbon, nitrogen, oxygen) (figure 1). Transition metal-catalyzed C-H activation followed by the C-C

coupling reaction is one of the remarkable synthetic transformations in organic synthesis[5].

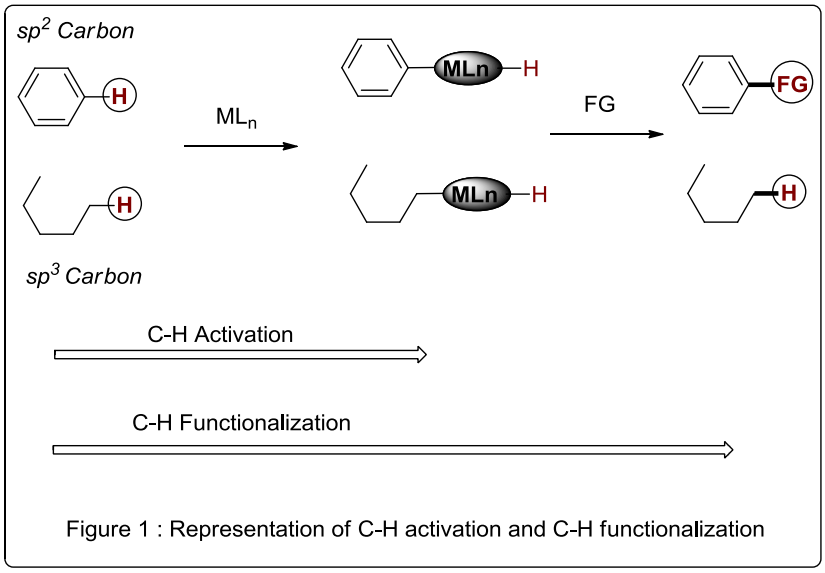
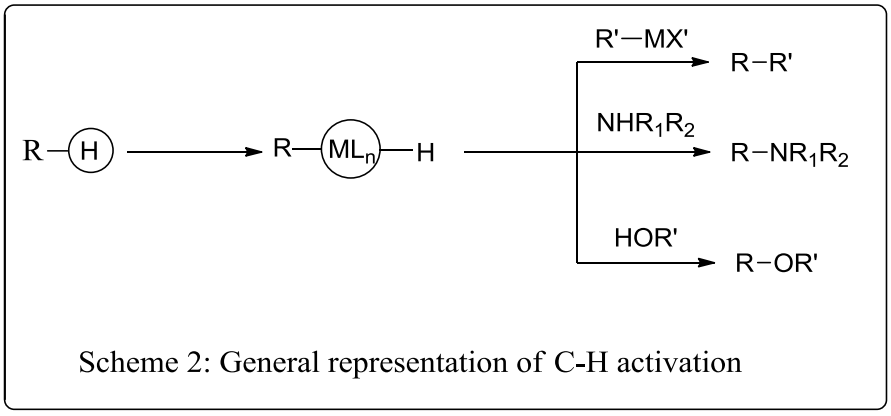


Figure 1 : Representation of C-H activation and C-H functionalization

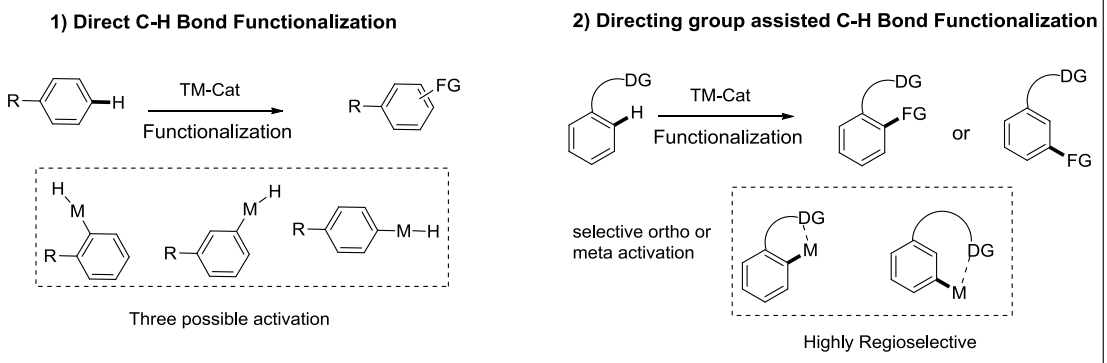
Carbon-Hydrogen bond is ubiquitous, often inert and largely found in organic molecules. C-H bond have high dissociation energy 85-120 Kcal/mol and non-polarizable in nature. Utilization of this C-H bond was a challenging task in earlier times. So C-H activation methodology gained much importance in the field of organic chemistry. C-H activation has been well explored during last decades because of its advantages like a) do not require pre-functionalized starting material and b) do not generate any hazardous by-products. Many complex molecules can be easily synthesized from simple starting material through activating the C-H bond (Scheme 2). C-H activation is the complementary tool for the total synthesis of complex natural products[6].



Scheme 2: General representation of C-H activation

Different Methods of C-H Functionalization

Two different methods of C-H functionalizations are known. a) Direct functionalization of inert C-H bonds and b) directing group assisted C-H functionalization. In first method, there is no regioselectivity, because all the C-H bonds have the equal possibility to undergo C-H activation[7, 8]. But in directing group assisted C-H activation, the metal center will coordinate with the heteroatom thereby activates the proximal C-H bond leaving other C-H unreactive[9]. (Scheme 3)

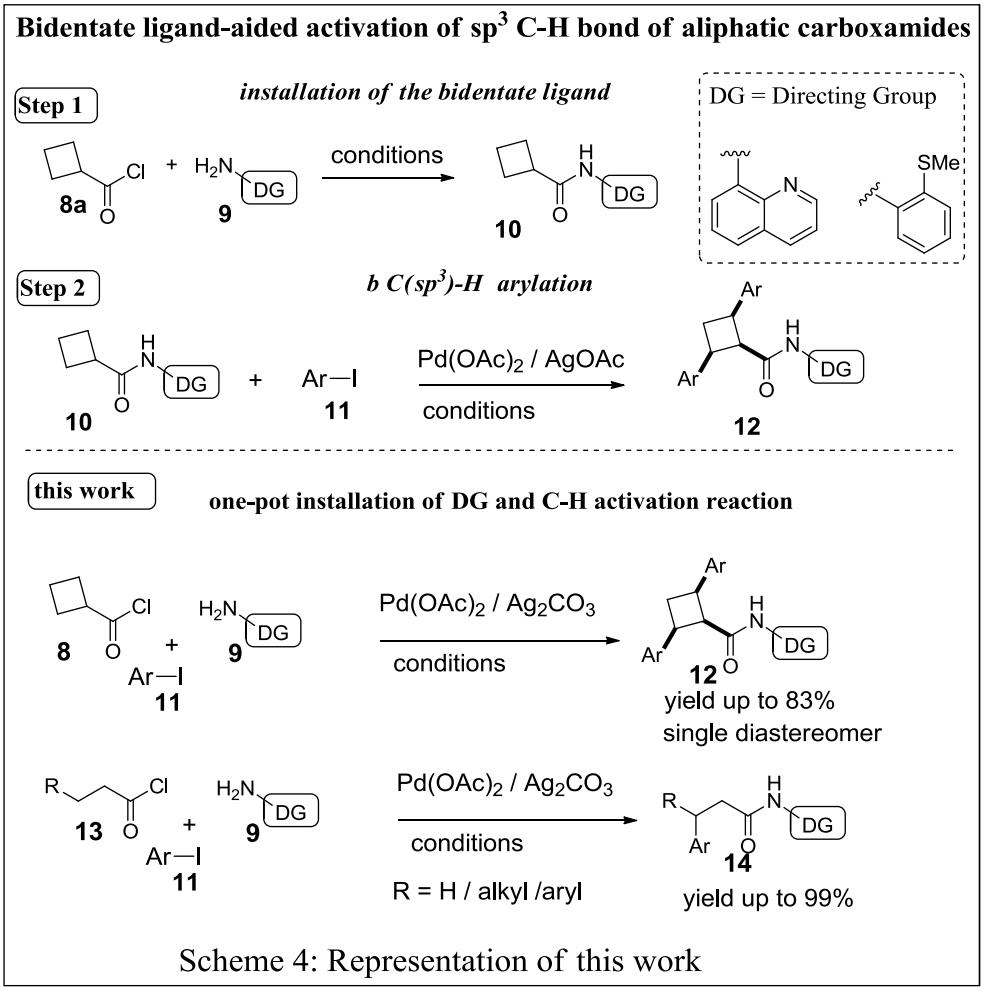


Scheme 3: Representation of both direct C-H bond and directing group assisted C-H bond functionalization

Three classes of directing groups (DG) are reported till now. They are a) non-modifiable DG, b) modifiable or transformable DG and c) reusable DG[9]. Non-modifiable DG cannot be modified in to any other functionality[10]. But modifiable DGs can be transformed in to desired functionality after the completion of reaction[11]. Pre-installed chelating groups in to the starting material can be readily recovered from the C-H functionalized product are termed as reusable DGs. In this project we explored the use of reusable DGs[9].

One of the major challenges in this field is the installation of DGs plays a key role in C-H activation processes. Present emergency is to develop a complementary technology to enhance the efficiency of DG-based C-H activation transformations. In this regard, *Wan et al*. reported a multicomponent reaction method of Pd-catalyzed C-H arylation of sp^2 C-H bonds of aromatic carboxamides[12]. Understanding the importance of the bidentate ligand directed Pd-catalyzed sp^3 C-H functionalization of carboxamides in synthetic organic chemistry, we developed a simple methodology to enhance the efficiency of Pd-catalyzed sp^3 C-H functionalization reactions[13, 14].We report a one-pot multicomponent reaction protocol comprising installation of

bidentate DG, Pd-catalyzed C-H activation and β-arylation of C(sp^3)-H bonds of various aliphatic and alicyclic carboxamides (scheme 4).



Scheme 4: Representation of this work

Cyclobutane is the second smallest, strained four-membered carboxylic ring. It presents as the core unit of many natural products (Figure 2), synthetic compounds and many pharmaceutical agents[15, 16]. Monoarylated and bis-arylated cyclobutane carboxamides exhibit a wide range of biological activities and medicinal properties[17]. This type of compounds can be easily synthesized by one-pot multicomponent reaction methodology of Pd-catalyzed C-H activation of sp^3 bonds of alicyclic carboxamides. Substituted fatty acids can also be easily synthesized *via* Pd-catalyzed C-H activation on sp^3 bonds of aliphatic carboxamides.

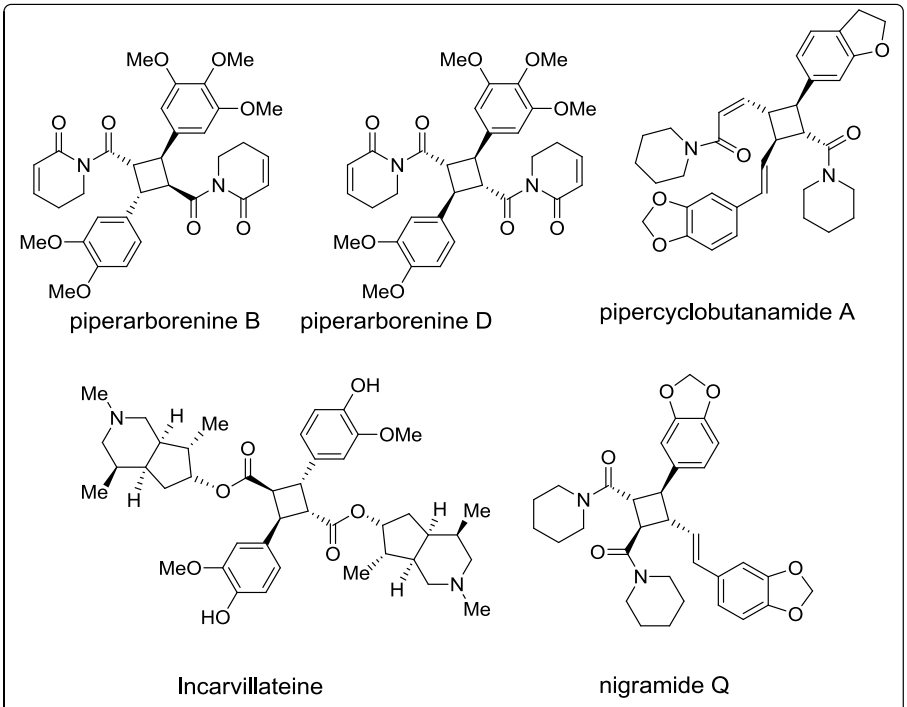


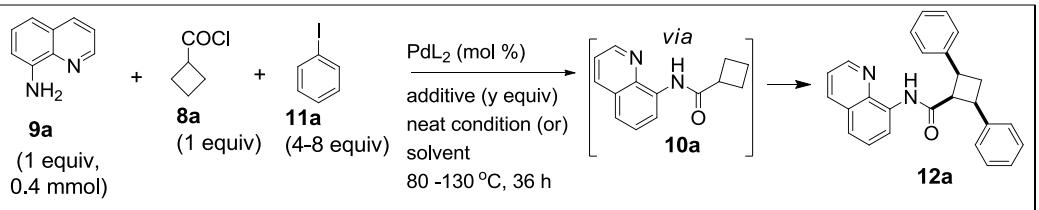
Figure 2: Bis-arylated cyclobutane natural products

Chapter 2

Results and Discussions

We carried out optimization studies to get the best reaction conditions for establishing a one-pot reaction protocol comprising the installation of bidentate ligand and β-arylation on sp^3 C-H on cyclobutane based carboxamides. Multicomponent reaction of a mixture of bidentate ligand 8-aminoquinoline (**9a**), cyclobutanecarbonyl chloride (**8a**) and PhI (**11a**), $Pd(OAc)_2$ catalyst and Ag salt as an additive represents the Table 1. We carried out the reaction of a mixture of 8-aminoquinoline (**9a**), cyclobutanecarbonyl chloride (**8a**) and PhI (**11a,** 4 equiv), $Pd(OAc)_2$ catalyst and AgOAc additive in toluene at 110 ^{O}C, which resulted in the formation of bis-arylated cyclobutane carboxamide in 20% yield (Table 1, entry 1). To the same reaction, instead of toluene solvent *tert*-butanol was added .This reaction also afforded the bis-arylated cyclobutane carboxamide in only 20% yield (Table 1, entry 2). Next, we performed another reaction of a mixture of 8-aminoquinoline (**9a**), cyclobutanecarbonyl chloride (**8a**) and PhI (**11a,** 8 equiv), $Pd(OAc)_2$ catalyst, AgOAc and K_2CO_3 as additive in *o*-xylene at 120 ^{O}C failed to give the product **12a** (Table 1, entry 3). Again, we carried out the same reaction with 4 equiv of PhI, instead of AgOAc additive Ag_2CO_3 was used. Here we observed the formation of bis-arylated product in comparatively good yield ie, 59% (Table 1, entry 4).

After observing the use of Ag_2CO_3 instead of AgOAc improved the yield, next we performed some reactions using Ag_2CO_3 as additive. Multicomponent reaction of a mixture of 8-aminoquinoline (**9a**), cyclobutanecarbonyl chloride (**8a**) and PhI (**11a,** 4 equiv), $Pd(OAc)_2$ catalyst and Ag_2CO_3 additive in *t*-amylOH at 80 ^{O}C also afforded the same bis-arylated product in 68% yield (Table 1, entry 5). The same reaction in *o*-xylene instead of *t*-amylalcohol also resulted in the same product with yield 62%.(Table 1, entry 6). Then tried the same reaction by increasing the equivalent of PhI to 8 equiv in o-xylene solvent and gave the product of 82% yield (Table 1, entry 7). Then we tried one reaction with K_2CO_3 additive instead of Ag_2CO_3, which failed to afford the product **12a** (Table 1, entry 8).



entry	**11a** (equiv)	PdL_2 (mol %)	additive (y equiv)	solvent (mL)	T (°C)	**12a**: yield (%)
1	4	$Pd(OAc)_2$ (10)	AgOAc (2)	toluene	110 °C	20
2	4	$Pd(OAc)_2$ (10)	AgOAc (2)	*t*butanol	80 °C	20
3	8	$Pd(OAc)_2$ (10)	AgOAc (1) + K_2CO_3 (1)	*o*-xylene	130 °C	traces
4	4	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)	toluene	110 °C	59
5	4	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)	*t*amylOH	80 °C	68
6	4	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)	*o*-xylene	130 °C	62
7	8	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)	*o*-xylene	130 °C	82
8	4	$Pd(OAc)_2$ (10)	K_2CO_3 (1)	*o*-xylene	130 °C	NR
9[c]	4	$Pd(OAc)_2$(5)	Ag_2CO_3 (2)	*o*-Xylene	130 °C	54
10[c]	6	$Pd(OAc)_2$(5)	Ag_2CO_3 (2)	*o*-Xylene	130 °C	75
11	8	$Pd(OAc)_2$ (10)	Ag_2CO_3 (1) + Cs_2CO_3 (1)	*o*-xylene	130 °C	28
12	8	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)	neat	100 °C	58
13[b]	6	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)	*t*amylOH	80 °C	66
14[c]	6	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)	*t*amylOH	80 °C	72

Table 1: Optimization of reaction conditions

[a] The reaction period for all the reactions is 36 h. [b] The reaction period is 12 h. [c] The reaction period is 24 h.

Then the reaction of **9a**, **8a**, PhI (**11a**, 4 or 6 equiv) and Ag_2CO_3 additive in the presence of 5 mol% of the $Pd(OAc)_2$ catalyst instead of 10mol% catalyst gave the product **12a** in 54-75% yields (Table 1, entries 9 and 10). In another trial, the mixture of **9a**, **8a** and PhI (**11a,** 8 equiv), $Pd(OAc)_2$ catalyst in the presence of Ag_2CO_3 and Cs_2CO_3 additives gave the product **12a** in only 28% yield (Table 1, entry 11). In similar trial, instead of the mixture of additives we used the Ag_2CO_3 under neat condition resulted in the formation of product **12a** in a improved yield 58% (Table 1, entry 12). The same reaction in *tert*-amylOH instead of *o*-xylene also afforded the product **12a** in 66-72% yield (Table 1, entries 13 and 14).

From these optimization reactions, it is clear that the one-pot Pd-catalyzed C-H arylation reaction of a mixture of 8-aminoquinoline (**9a**), cyclobutanecarbonyl chloride (**8a**) and PhI (**11a,** 8 equiv), $Pd(OAc)_2$ catalyst successfully afforded the product **12a** only in the presence of Ag_2CO_3 additive.

In the conventional reaction condition for the synthesis of bis-arylated cyclobutane carboxamide derivatives AgOAc was used as the additive, which helps to regenerate the $Pd(OAc)_2$ catalyst in the proposed Pd^{II}-Pd^{IV} catalytic cycle. In this multicomponent reaction methodology, AgOAc is not favouring for C-H arylated product **12a** in satisfactory yield**.** But Ag_2CO_3 is promoting the DG installation reaction as well as C-H arylation reaction.

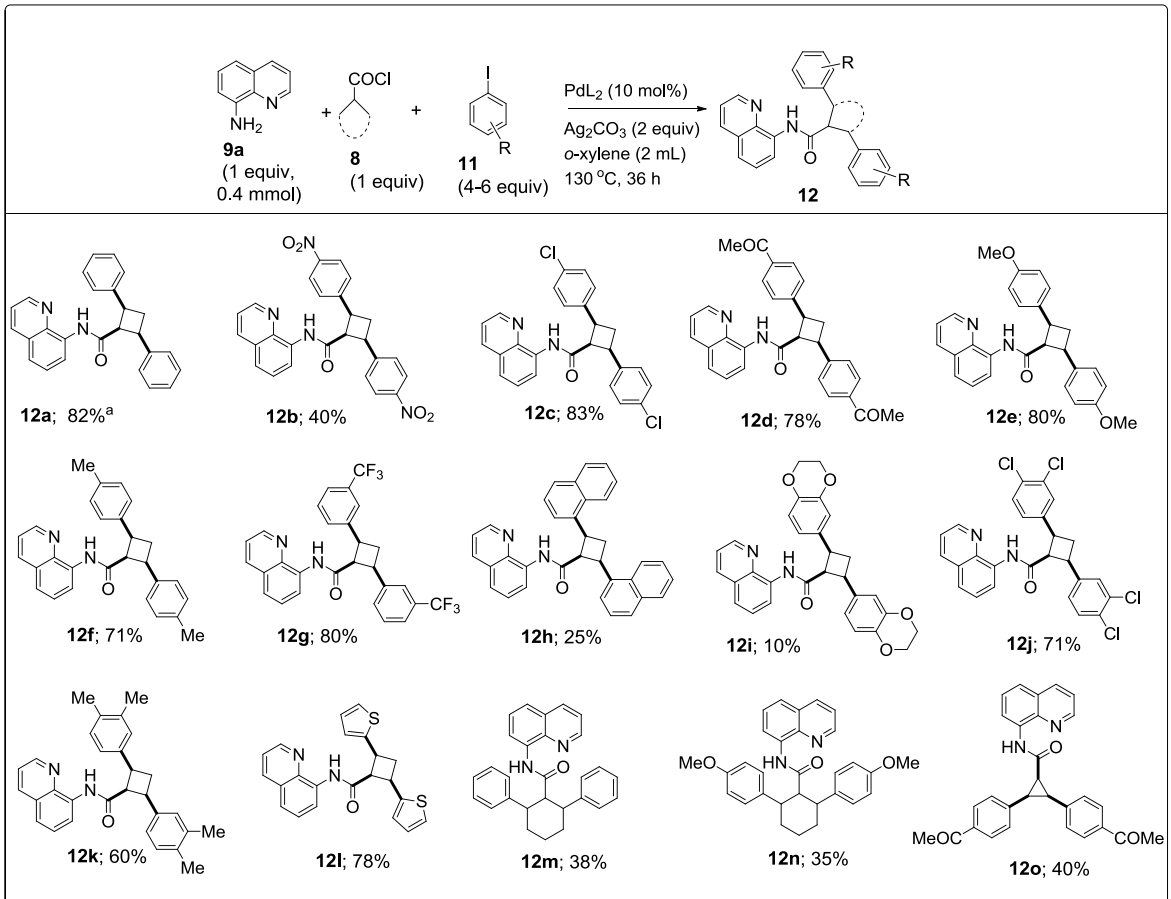


Table 2: Bis-arylated cycloalkane carboxamide derivatives

After the optimization of reaction conditions, we investigated the scope and generality of this multicomponent reaction in one-pot method to synthesize different varieties of bis-arylated cycloalkane carboxamide derivatives. We carried out some reactions of Ag_2CO_3 mediated, Pd-catalyzed C-H activation protocol involving 8-aminoquinoline (**9a**), cyclobutanecarbonyl chloride (**8a**) and a variety of aryl iodides,

which resulted in the formation of bis-arylated cyclobutane carboxamide derivatives **12a-l** (Table 2). We performed certain reactions with aryl iodides containing electron withdrawing and donating groups at the *para* position afforded the product **12b-g** in low to high yields (40-83%, Table 2). Reaction with 1-iodo-4-nitrobenzene gave the product **12b** in low yield (40%, Table 2) may be due to the low reactivity which contains a strong electron-withdrawing group (nitro group) at the *para* position. Same reaction with aryl iodide containing the CF_3 group at meta position gave the product **12g** in 80% yield (Table 2).

Multicomponent reactions with two different aryl iodides like 1-iodonaphthalene and 6-iodo-2,3-dihydrobenzo[*b*][1,4] dioxine gave the corresponding products **12h** (25%) and **12i** (10%) in only low yields. Low yields in these reactions may be due to the low reactivity of the corresponding aryl iodides. Next, we performed Ag_2CO_3 mediated, Pd-catalyzed C-H activation reactions involving 8-aminoquinoline (**9a**), cyclobutanecarbonyl chloride (**8a**) and di-substituted aryl iodides afforded the corresponding products **12j** (71%) and **12k** (60%) (Table 2). C-H arylation protocol using the heteroaryl iodide such as 2-iodothiophene with substrates 8-aminoquinoline (**9a**), cyclobutanecarbonyl chloride (**8a**) furnished the product **12l** in 78% yield (Table 2).

We also investigated the one-pot C-H arylation reactions on different substrates such as cyclohexanecarbonyl chloride and cyclopropanecarbonyl chloride. In the same Pd-catalyzed, Ag_2CO_3 mediated C-H arylation reaction, instead of cyclobutanecarbonyl chloride (**8a**), cyclohexanecarbonyl chloride was used along with 8-aminoquinoline (**9a**) and different aryl iodides like PhI (**11a**) and 4-iodoanisole furnished the products **12m** (38%), **12n** (35%) (Table 2). Traces of by-products are also obtained that we could not isolate in pure form. Low yield in cyclohexane system may be due to the increasing steric crowding and the C-H arylation seems to be sluggish here. We performed the Pd-catalyzed, Ag_2CO_3 mediated C-H arylation reaction in cyclopropane system furnished the product **12o** (40%) (Table 2). This low yield may be because the C-H arylation of cyclopropane reaction seems to be sluggish in nature.

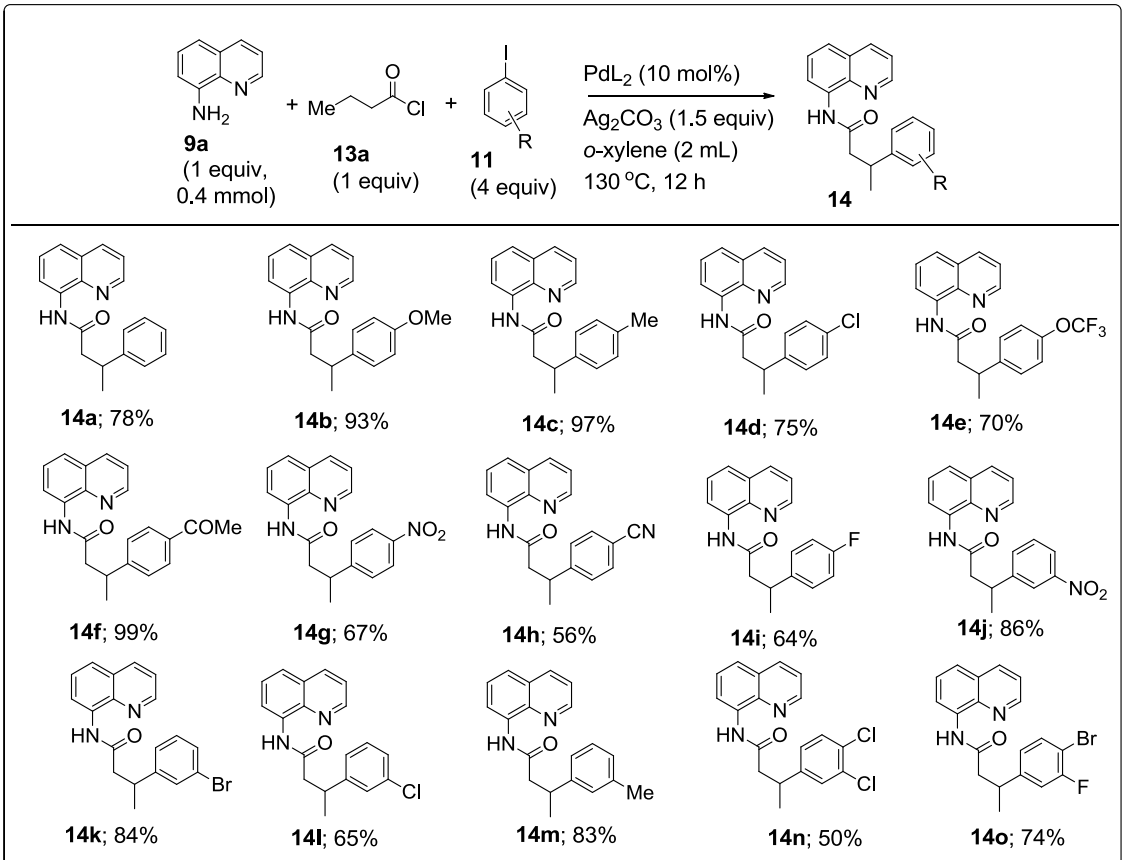


Table:3 Mono arylated butane carboxamide derivatives

Successively, we elaborated the scope and generality of this method by using various aliphatic carbonyl chlorides. First we carried out some reactions of Pd-catalyzed, Ag_2CO_3 mediated C-H arylation protocol involving the butyryl chloride (**13a**), 8-aminoquinoline (**9a**) and aryl iodides containing various substituents at the *meta/para* position or disubstituted aryl iodides, which resulted in the formation of mono-arylated butane carboxamides **14a-o** in good to high yields (50-99%, Table 3). Further we elaborated this reaction methodology to check the substrate scope using different aliphatic carbonyl chlorides. Accordingly, various β-methylene C(sp^3)-H arylated aliphatic carboxamides **14p-u** were obtained in high yields (80-97%, Table 4). We performed the same Pd-catalyzed, Ag_2CO_3 mediated C-H arylation protocol using propionyl chloride gave the corresponding mono arylated (**14v**) and bis arylated propanecarboxamide (**14v'**) derivatives in 17 and 58% yields (Table 4).

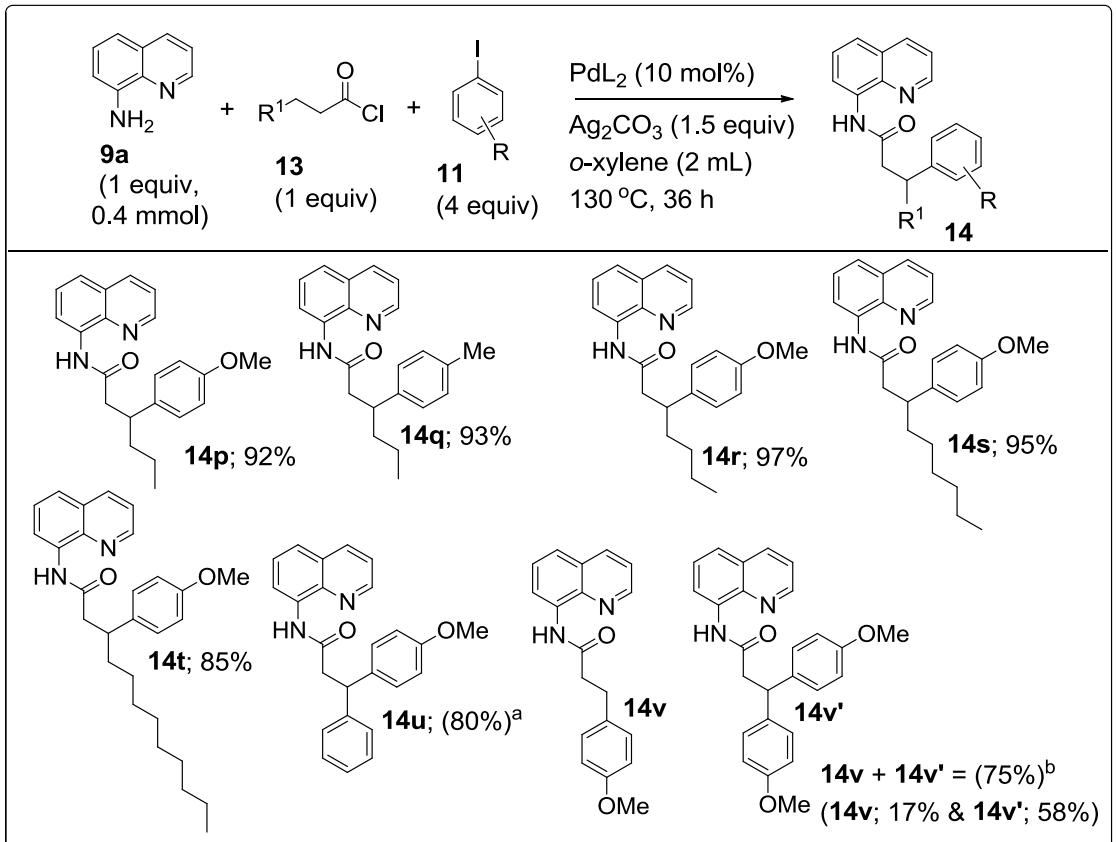


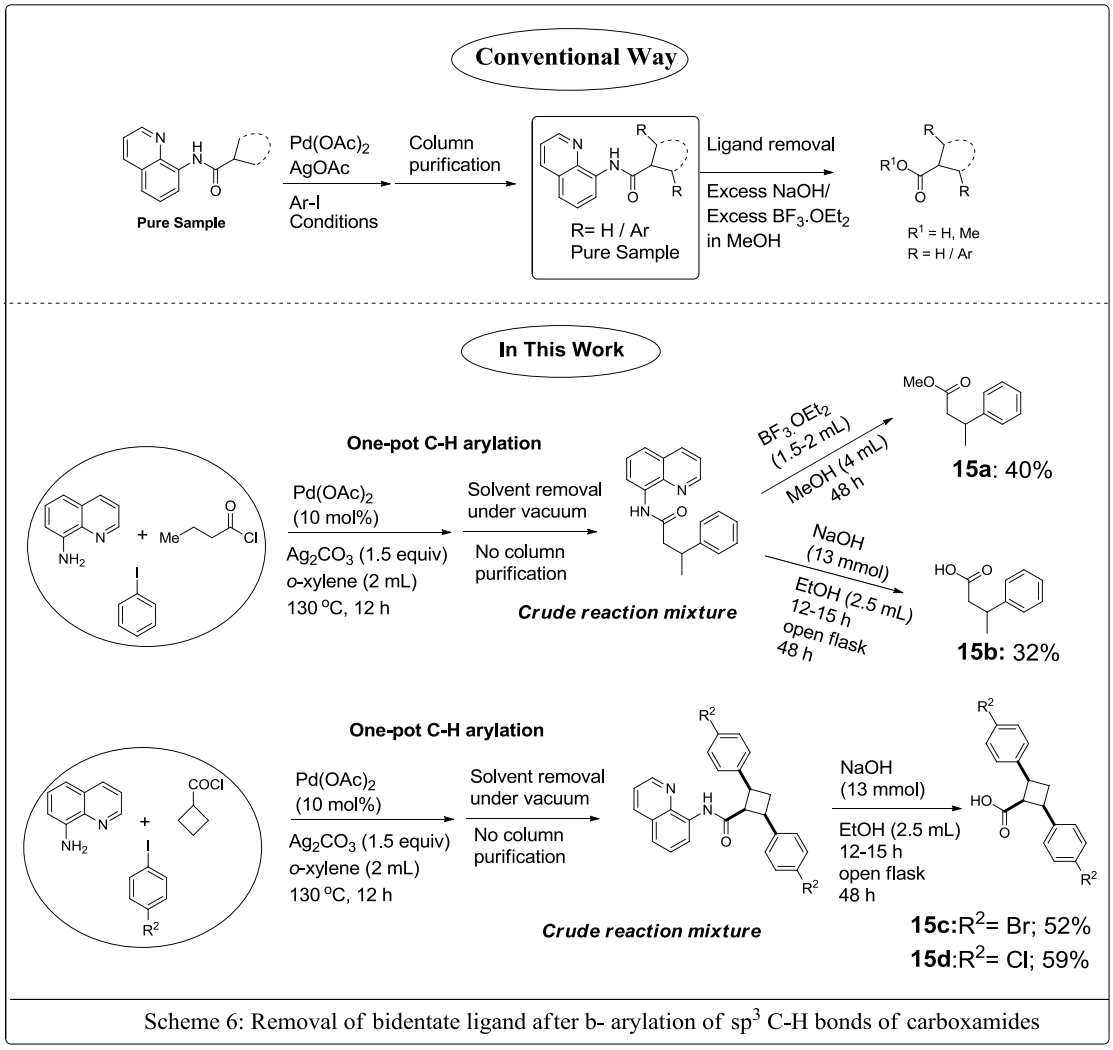
Table 4: Examination of substrate scope

Next we carried out some reactions to find out the feasibility of using other bidentate ligands such as, 2-(methylthio)aniline (**9b**) and N^l,N^l-dimethylethane-1,2-diamine (**9c**) for this one-pot multicomponent reaction protocol comprising installation of bidentate DG followed by Pd-catalyzed C-H activation and arylation of C(sp^3)-H bonds of carboxamides. One-pot Pd-catalyzed, Ag_2CO_3 mediated C-H arylation protocol involving bidentate ligands 2-(methylthio)aniline (**9b**) or N^l,N^l-dimethylethane-1,2-diamine (**9c**), cyclobutanecarbonyl chloride (**8a**) and 4-iodoanisole failed to afford the bis-arylated cyclobutanecarboxamides **12p** and **12q** (Scheme 5). Based on the reactions in Table 1, 2, 3 and 4, the bidentate ligand 8-aminoquinoline (**9a**) found to be the best for accomplishing the one-pot multicomponent reaction protocol comprising installation of bidendate DG followed by Pd-catalyzed C-H activation and arylation of C(sp^3)-H bonds of carboxamides.

We have also used the condition reported by Quin *et al*. Pd-catalyzed, $PhI(OAc)_2$ mediated C-H arylation protocol involving 8-aminoquinoline (**9a**),

cyclobutanecarbonyl chloride (**8a**) and PhI (**11a,** 2.5 equiv) also afforded the product **12a** in 40% yield (Scheme 5).

We noted that the reagents for alkylation and arylation are different in literature reports and the arylation of sp^3 C-H bonds are more easier than alkylation of sp^2 C-H bonds of carboxamides. We tried one alkylation reaction on sp^3 C-H bond using the reported condition involving 8-aminoquinoline (**9a**), cyclobutanecarbonyl chloride (**8a**) and *n*-butyl iodide failed to afford the C-H alkylated cyclobutanecarboxamide **12r** (Scheme 5). But we got the corresponding product **12s (**15-25%) of alkylation reaction in another trial using the condition reported by Daugulis group on propionyl based system. It should be noted that the alkylation condition needs a base, such as K_2CO_3 and the low yield may be due to the side reaction of N-alkylation of bidentate ligand. In order to examine whether the alkylation of C-H bonds will work or not, we tried one reaction involving 8-aminoquinoline (**9a**), benzoyl chloride and *n*-butyl iodide or *n*-heptyl iodide. Notably, this multicomponent-based sp^2 alkylation reactions were successful and the products **12t** (45%) and **12u** (60%) were obtained in satisfactory yield.



Scheme 6: Removal of bidentate ligand after b- arylation of sp^3 C-H bonds of carboxamides

Removal of bidentate DGs from C-H arylated carboxamides has also been successfully achieved. In the conventional method, the starting material C-H arylated carboxamides usually isolates through column chromatography. Here we attempted to avoid the column chromatographic purification step of crude reaction mixture and directly performed the hydrolysis reaction of amide bond from the crude reaction mixture. The NaOH mediated amide hydrolysis or $BF_3.OEt_2$ mediated esterification of the carboxamides resulted in the formation of products **15a** (40%), **15b** (32%), **15c** (52%), and **15d** (59%) in satisfactory yields (Scheme 6).

Chapter 3

Experimental Methods

General. Melting points of compounds are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz spectrometers respectively with TMS as an internal or external standard. IR spectra were recorded as KBr pellets or thin films. Column chromatographic purification of the crude reaction mixtures was performed using silica gel (100-200 mesh). HRMS measurements of compounds reported in this work were obtained from QTOF mass analyzer using electrospray ionization (ESI) technique. Reactions were carried out in dry solvent under nitrogen atmosphere wherever required. Solutions were dried using anhydrous sodium sulfate. Reagents were added to the reaction flask with the help of syringe. Thin layer chromatography (TLC) was performed on silica plates or and components were visualized by observation under iodine vapor. Isolated yields of all the products were reported (yields were not optimized). Characterization of the known compounds was carried out by comparing the data with the literature data.

General Procedure A for the synthesis of carboxamides

8-Aminoquinoline (0.4 mmol) and aryl iodide (4-6 equiv.) were taken in a 10 mL round bottom (RB) flask attached with a condenser under N_2 atmosphere. To this mixture, $Pd(OAc)_2$ catalyst (10 mol%), Ag_2CO_3 additive (1.5-2 equiv.) and cyclobutanecarbonyl chloride (0.4 mmol) were added. Finally, added the solvent o-xylene (2 mL) in to the RB and sealed the condenser with a stopper. The mixture was stirred at 120 ^{O}C for 36 h. After the completion of reaction, the mixture was allowed to cool in room temperature. The solvent was removed at reduced pressure. The residue was subjected to silica gel column chromatography to give pure products by using hexane and ethyl acetate (5:0.25).

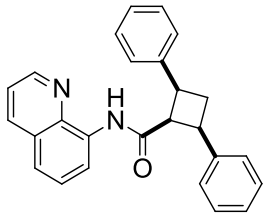
Procedure B: Hydrolysis of amide bond using esterification method.

Procedure A was used to synthesize the carboxamide. After the completion of reaction, removal of solvent was done under reduced pressure and hydrolysis procedure was done on dried crude reaction mixture. Column chromatography purification step is not required. To the dried reaction mixture, MeOH (2 mL) was

added and stirred vigorously under nitrogen atmosphere for 5 min. Finally, $BF_3.OEt_2$ (1 mL) was added in to the reaction mixture and allowed to stir for 24 h at 85 ^{O}C. After the completion of reaction, the mixture is quenched by Triethyl amine and removed the solvent under reduced pressure. The residue was subjected to silica gel column chromatography to give pure products by using hexane and ethyl acetate (5:0.1).

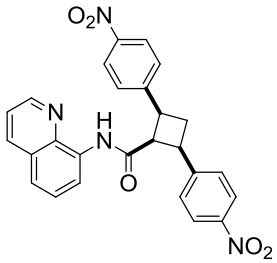
Procedure C: Hydrolysis of amide bond to corresponding acids

Procedure A was used to synthesize the carboxamide. After the completion of reaction, removal of solvent was done under reduced pressure and hydrolysis procedure was done on dried crude reaction mixture. Column chromatography purification step is not required. To the dried reaction mixture, ethanol (3 mL) was added and stirred vigorously under open atmosphere. NaOH (13 mmol) was added to the reaction mixture and was allowed to stir it for 24 h at 85 ^{O}C. After the reaction, transferred the reaction mixture in to a separating funnel and extracted with diethyl ether. Water layer was collected separately and that was basic in nature. Con.HCL was added into the aqueous layer to make it acid nature. Then again extracted with diethyl ether and collected the organic layer separately. The combined organic layers were dried over anhydrous Na_2SO_4. Thus the desired carboxylic acid was successfully obtained after the removal of solvent in high vacuum.

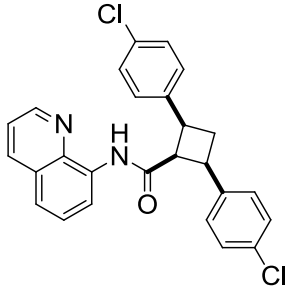


2,4-diphenyl-N-(quinolin-8-yl)cyclobutanecarboxamide (12a): Following the general procedure A described above, **12a** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as brown color solid (77 mg, 82%); R_f 0.40 (15% EtOAc/Hexane); mp 145-147 ^{o}C; IR (DCM): υ_{max} 3342, 1669, 1521, 1484, 993 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 8.75 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 8.31 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 8.06 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.41-7.26 (m, 8H), 7.25-7.22 (m, 4H), 7.12-7.09 (m, 2H), 4.19 (dd, J_1 = 8.4 Hz, J_2 = 3.2 Hz, 1H), 4.14-4.09 (m, 2H), 3.62-3.54 (m, 1H), 2.80-2.77 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 147.8, 140.6, 138.2, 136.2, 134.2, 128.1, 127.7, 127.5, 127.0, 126.1, 121.3, 120.9, 116.4, 54.6, 38.1, 29.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O$: 379.1810; found 379.1824.

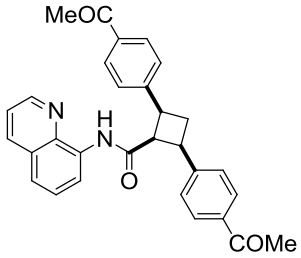


2,4-bis(4-nitrophenyl)-N-(quinolin-8-yl)cyclobutanecarboxamide (12b): Following the general procedure A described above, **12b** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 20 : 80) as brown color solid (46 mg, 40%); R_f 0.40 (30% EtOAc/Hexane); mp 182-184 ^oC; IR (DCM): υ_{max} 3344, 1682, 1596, 1391, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.78-8.76 (m, 1H), 8.21-8.19 (m, 1H), 8.14-8.11 (m, 1H), 8.10-8.07 (m, 4H), 7.49-7.41 (m, 6H), 7.32 (d, *J* = 8.0 Hz, 1H), 4.32 (dd, J_1 = 8.4 Hz, J_2 = 3.2 Hz, 1H), 4.22-4.15 (m, 2H), 3.65-3.56 (m, 1H), 2.90-2.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 148.1, 148.0, 146.5, 138.0, 136.5, 133.3, 127.8, 127.6, 127.2, 123.5, 121.9, 121.7, 116.5, 54.5, 38.7, 30.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}N_4O_5$: 469.1511; found 469.1500.

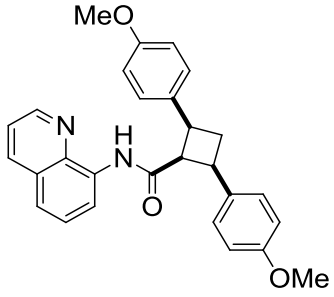


2,4-bis(4-chlorophenyl)-N-(quinolin-8-yl)cyclobutanecarboxamide (12c): Following the general procedure A described above, **12c** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as yellow colour solid (93 mg, 83%); R_f 0.40 (15% EtOAc/Hexane); mp 171-174 ^oC; IR (DCM): υ_{max} 2988, 1698, 1598, 1351, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (s, 1H), 8.75 (d, *J* = 3.6 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.44-7.39 (m, 2H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 4H), 7.19 (d, *J* = 8.0

Hz, 4H), 4.17-4.12 (m, 1H), 4.05-3.99 (m, 2H), 3.47 (q, J = 10.8 Hz, 1H), 2.77-2.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 147.9, 138.9, 138.2, 136.3, 133.9, 131.9, 128.4, 128.2, 127.8, 127.3, 121.5, 121.4, 116.5, 54.4, 38.4, 30.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}Cl_2N_2O$: 447.1030; found 447.1010.

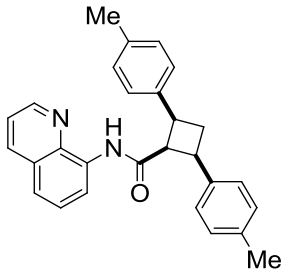


2,4-bis(4-acetylphenyl)-N-(quinolin-8-yl)cyclobutanecarboxamide (12d): Following the general procedure A described above, **12d** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as yellow color solid (89 mg, 78%); R_f 0.1 (30% EtOAc/Hexane); mp181-183 ^oC; IR (DCM): υ_{max} 3345, 1605, 1524, 1391, 793 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.76 (dd, J_1 = 4.4 Hz, J_2 = 1.2 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1 Hz), 8.09 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.81 (d, J = 8.0 Hz, 4H), 7.44-7.37 (m, 6H), 7.31-7.27 (m, 1H), 4.30-4.25 (m, 1H), 4.17-4.10 (m, 2H), 3.63-3.55 (m, 1H), 2.86-2.79 (m, 1H), 2.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 168.3, 148.0, 146.3, 138.1, 136.3, 135.1, 133.8, 128.3, 127.7, 127.2, 127.0, 121.5, 121.4, 116.4, 54.5, 39.0, 29.8, 26.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}N_2O_3$: 463.2021; found 463.2012.

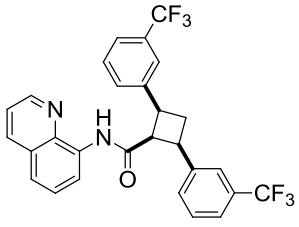


2,4-bis(4-methoxyphenyl)-N-(quinolin-8-yl)cyclobutanecarboxamide (12e): Following the general procedure A described above, **12e** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as yellow colour solid (88 mg, 80%); R_f 0.40 (15% EtOAc/Hexane); mp 146-149 ^oC; IR (DCM): υ_{max} 2936, 1689, 1612, 1519, 825 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49

(s, 1H), 8.73 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 8.37 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 8.06 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.40-7.29 (m, 7H), 6.77 (d, J = 8.4 Hz, 4H), 4.09-4.07 (m, 1H), 4.02-4.00 (m, 2H), 3.70 (s, 6H), 3.53-3.45 (m, 1H), 2.72-2.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 157.9, 147.8, 138.2, 136.1, 134.3, 132.7, 128.2, 127.7, 127.2, 121.3, 120.9, 116.4, 113.5, 55.1, 54.8, 38.5, 30.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_3$: 439.2021; found 439.2019.

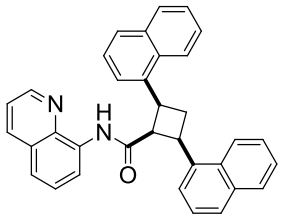


N-(quinolin-8-yl)-2,4-di-p-tolylcyclobutanecarboxamide (12f): Following the general procedure A described above, **12f** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as pale yellow color solid (71 mg, 71%); R_f 0.40 (15% EtOAc/Hexane); mp 156-160 ^oC; IR (DCM): υ_{max} 3359, 1689, 1595, 1484, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (s, 1H), 8.75-8.73 (m, 1H), 8.37 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 8.07 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.41-7.29 (m, 3H), 7.25 (d, J = 8.0 Hz, 4H), 7.03 (d, J = 7.6 Hz, 4H) 4.16-4.11 (m, 1H), 4.07-4.00 (m, 2H), 3.55-3.47 (m, 1H), 2.74-2.68 (m, 1H), 2.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 147.7, 138.2, 137.6, 136.1, 135.4, 134.3, 128.8, 127.7, 127.3, 126.9, 121.3, 120.8, 116.5, 54.6, 38.9, 30.2, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O$: 407.2123; found 407.2117.

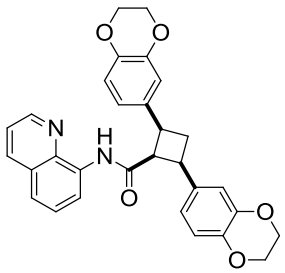


N-(quinolin-8-yl)-2,4-bis(3-(trifluoromethyl)phenyl)cyclobutanecarboxamide (12g): Following the general procedure A described above, **12g** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as brown color solid (101 mg, 80%); R_f 0.40 (15% EtOAc/Hexane); mp 114-116 ^oC; IR (DCM): υ_{max} 3445, 1519, 1321, 1313, 989 cm^-1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56

(s, 1H), 8.75 (d, J = 4.0 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.60-7.53 (m, 4H), 7.43-7.29 (m, 7H), 4.25-4.22 (m, 1H), 4.17-4.10 (m, 2H), 3.58 (dd, J_1 = 22.0 Hz, J_2 = 11.2 Hz, 1H), 2.84 (dd, J_1 = 10.0 Hz, J_2 = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 148.0, 141.3, 138.1, 136.2, 133.7, 130.3 (q, J = 32 Hz) , 128.5, 127.7, 127.1, 126.8 (q, J = 271 Hz), 123.7 (q, J = 4 Hz), 123.1 (q, J = 4 Hz), 121.4, 121.4, 116.4, 54.2, 38.7, 29.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{21}F_6N_2O$: 515.1558; found 515.1536.

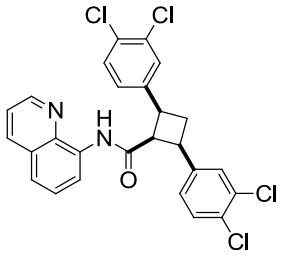


2,4-di(naphthalen-1-yl)-N-(quinolin-8-yl)cyclobutanecarboxamide (12h): Following the general procedure A described above, **12h** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as brown color solid (30 mg, 25%); R_f 0.40 (15% EtOAc/Hexane); mp 225-227 ^{o}C; IR (DCM): υ_{max}): 3351, 1683, 1523, 1485, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (br s, 1H), 8.42 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.23 (d, 2H, J = 8.4 Hz), 7.84 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 7.76 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 7.69 (d, 2H, J = 7.0 Hz), 7.65 (d, 2H, J = 8.0 Hz), 7.58-7.51 (m, 4H), 7.42 (t, 2H, J = 8.0 Hz), 7.33 (t, 2H, J = 7.0 Hz), 7.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.03-6.94 (m, 2H), 4.78-4.72 (m, 3H), 4.11-4.03 (m, 1H), 2.91-2.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 147.3, 137.7, 135.8, 135.7, 133.7, 133.5, 131.8, 128.8, 127.2, 127.0, 126.7, 126.0, 125.4, 125.2, 125.0, 123.5, 120.9, 120.5, 115.8, 56.1, 38.0, 28.1;; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{27}N_2O$: 479.2123; found 479.2115.

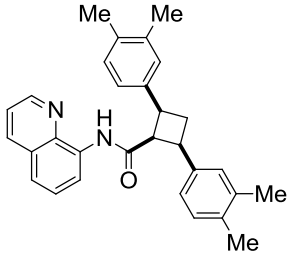


2,4-bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-N-(quinolin-8-yl)cyclobutanecarboxamide (12i): Following the general procedure A described

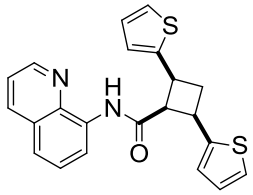
above, **12i** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 5 : 95) as brown semi solid (13 mg, 10%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3333, 2935, 1681, 1510, 1485, 1384, 1162, 1068, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.82 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 8.71 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 8.15-8.13 (m, 1H), 7.57-7.49 (m, 2H), 7.44-7.41 (m, 1H), 6.97-6.85 (m, 6H), 4.28 (s, 8H), 3.77 (dd, J_1 = 18 Hz, J_2 = 9.6 Hz, 2H), 3.31–3.36 (m, 1H), 2.76-2.69 (m, 1H), 2.38-2.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 148.0, 143.5, 142.3, 138.4, 136.5, 136.2, 134.5, 127.8, 127.4, 121.6, 121.5, 120.1, 117.3, 116.5, 115.8, 64.4, 64.4, 57.6, 39.0, 32.5; HRMS (ESI): calcd. for $C_{30}H_{27}N_2O_5$ $[M + H]^+$ 495.1920; found 495.1904.



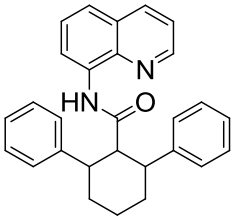
2,4-bis(3,4-dichlorophenyl)-N-(quinolin-8-yl)cyclobutanecarboxamide (12j): Following the general procedure A described above, **12j** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as white color solid (91 mg, 71%); R_f 0.40 (15% EtOAc/Hexane); mp 140-145^oC; IR (DCM): υ_{max} 3341, 1631, 1587, 1332, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 8.77 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 8.31 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 8.13-8.10 (m, 1H), 7.45-7.41 (m, 4H), 7.36 (t, J = 8.0 Hz, 1H), 7.29-7.24 (m, 2H), 7.17-7.14 (m, 2H), 4.12 (dd, J_1 = 8.0 Hz, J_2 = 3.2 Hz, 1H), 4.01-3.95 (m, 2H), 3.41 (dd, J_1 = 22.4 Hz, J_2 = 11.6 Hz, 1H), 2.76-2.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 148.1, 138.2, 136.4, 136.1, 134.0, 134.0, 132.6, 129.7, 128.8, 127.7, 127.0, 126.8, 121.5, 121.3, 116.2, 53.6, 37.4, 27.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{19}Cl_4N_2O$: 515.0251; found 515.0249.



2,4-bis(3,4-dimethylphenyl)-N-(quinolin-8-yl)cyclobutanecarboxamide (12k): Following the general procedure A described above, **12k** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 3 : 97) as pale yellow color solid (64 mg, 60%); R_f 0.40 (15% EtOAc/Hexane); mp 99-102 ^oC; IR (DCM): υ_{max} 3435, 1575, 1365, 1291, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.47 (s, 1H), 8.74 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 8.39-8.37 (m, 1H), 8.08-8.06 (m, 1H), 7.41-7.29 (m, 4H), 7.13-7.08 (m, 4H), 6.97 (d, J = 7.6 Hz, 2H), 4.11 (dd, J_1 = 8.4 Hz, J_2 = 3.2 Hz, 1H), 4.04-3.97 (m, 2H), 3.53-3.44 (m, 1H), 2.72-2.70 (m, 1H), 2.11 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 147.7, 138.3, 138.0, 136.1, 136.0, 134.4, 134.1, 129.3, 128.3, 127.7, 127.2, 124.4, 121.2, 120.7, 116.4, 54.7, 38.9, 30.3, 19.7, 19.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{31}N_2O$: 435.2423; found 435.2419.

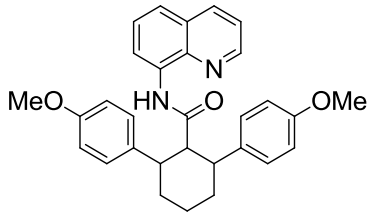


N-(quinolin-8-yl)-2,4-di(thiophen-2-yl)cyclobutanecarboxamide (12l): Following the general procedure A described above, **12l** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 5 : 95) as yellow color solid (76 mg, 78%); R_f 0.30 (15% EtOAc/Hexane); mp 99-102 ^oC; IR (DCM): υ_{max} 3313, 1612, 1554, 1302, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 8.75 (dd, J_1 = 4.4 Hz, J_2 = 1.6 Hz, 1H), 8.55-8.53 (m, 1H), 8.10-8.08 (m, 1H), 7.42-7.39 (m, 3H), 7.09-7.05 (m, 4H), 6.89 (dd, J_1 = 4.8 Hz, J_2 = 3.6 Hz, 2H), 4.22-4.15 (m, 2H), 4.00-4,01 (m,1H), 3.59-3.50 (m, 1H), 2.94-2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 147.9, 143.4, 138.2, 136.2, 134.3, 127.7, 127.3, 126.7, 125.2, 123.9, 121.4, 121.2, 116.6, 55.9, 35.7, 35.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2OS_2$: 391.0938; found 391.0936.

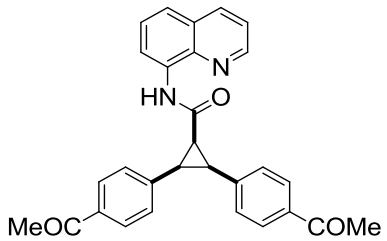


2,6-diphenyl-N-(quinolin-8-yl)cyclohexanecarboxamide (12m): Following the general procedure A described above, **12m** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as white solid (38 mg, 33%);

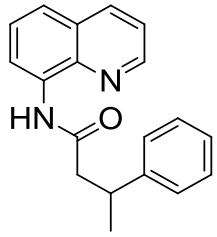
R_f 0.5 (15% EtOAc/Hexane); mp 176-178 ^oC; IR (DCM): υ_{max} 3357, 2929, 2247, 1682, 1520, 1486, 1324, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.54 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 8.45 (dd, J_1 = 4.4 Hz, J_2 = 1.6 Hz, 1H), 7.99 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.44–7.34 (m, 6H), 7.29–7.26 (m, 2H), 7.13 (t, J = 7.6 Hz, 4H), 6.98–6.94 (m, 2H), 3.22–3.18 (m, 3H), 2.87–2.77 (m, 2H), 2.30–2.24 (m, 1H), 1.86–1.82 (m, 2H), 1.70–1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 147.4, 144.1, 1378.0, 135.7, 134.1, 128.2, 127.5, 127.4, 127.0, 126.3, 121.1, 120.9, 115.9, 59.9, 47.9, 26.6, 25.6; HRMS (ESI): calcd. for $C_{28}H_{27}N_2O$ $[M + H]^+$ 407.2123; found 407.2130.



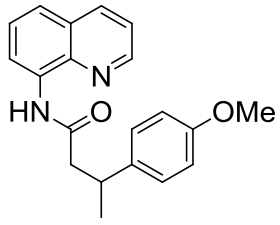
2,6-bis(4-methoxyphenyl)-N-(quinolin-8-yl)cyclohexanecarboxamide (12n): Following the general procedure A described above, **12n** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 8 : 92) as pale yellow semi solid (34 mg, 30%); R_f 0.30 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3054, 2925, 2313, 1716, 1525, 1425, 1265, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.52 (d, J = 7.6 Hz, 1H), 8.48 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 8.02-8.00 (m, 1H), 7.45–7.41 (m, 1H), 7.37-7.35 (m, 1H), 7.31-7.23 (m, 6H), 6.65 (d, J = 8.4 Hz, 4H), 3.54 (s, 6H), 3.16-3.10 (m, 3H), 2.74 (dd, J_1 = 12.8 Hz, J_2 = 4.0 Hz, 2H), 2.25-2.21 (m, 1H), 1.82-1.78 (m, 2H), 1.68-1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 157.9, 147.4, 138.0, 136.4, 135.7, 134.3, 128.4, 127.5, 127.0, 121.1, 120.8, 116.0, 113.6, 57.4, 55.0, 47.0, 26.7, 25.8; HRMS (ESI): calcd. for $C_{30}H_{31}N_2O_3$ $[M + Na]^+$ 467.2335; found 467.2321.



2,3-bis(4-acetylphenyl)-N-(quinolin-8-yl)cyclopropanecarboxamide (12o): Following the general procedure A described above, **12o** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 5 : 95) as yellow solid (44 mg, 40%); R_f 0.40 (15% EtOAc/Hexane); mp 83 - 85 ^oC; IR (DCM): υ_{max} 3346, 3053, 1682, 1525, 1486, 1325, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 8.72–8.70 (m, 1H), 8.61 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 1H), 8.14 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.80 (d, J = 8.4 Hz, 4H), 7.47–7.42 (m, 3H), 7.35 (d, J = 8.4 Hz, 4H), 3.16 (d, J = 9.2 Hz, 2H), 2.91 (t, J = 9.2 Hz, 1H), 2.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 166.2, 148.0, 139.9, 138.1, 136.4, 135.3, 134.3, 131.2, 127.9, 127.6, 127.3, 121.6, 121.5, 116.5, 29.9, 29.4, 26.6; HRMS (ESI): calcd. for $C_{29}H_{25}N_2O_3$ $[M + H]^+$ 449.1865; found 449.1848.

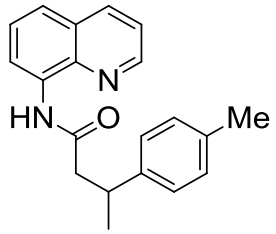


3-phenyl-N-(quinolin-8-yl)butanamide (14a): Following the general procedure A described above, **14a** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as light yellow liquid (57 mg, 78%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3353, 2959, 1680, 1510, 1480, 1322, 1162, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.81-8.79 (m, 2H), 8.16 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.57–7.44 (m, 3H), 7.38-7.22 (m, 5H), 3.53 (dd, J_1 = 14.8 Hz, J_2 = 6.8 Hz, 1H), 2.95-2.90 (m, 1H), 2.80 (dd, J_1 = 14.8 Hz, J_2 = 8.4 Hz, 1H), 1.44 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 148.1, 146.0, 138.3, 136.3, 134.4, 128.6, 127.9, 127.4, 126.9, 126.4, 121.6, 121.5, 116.5, 46.9, 36.9, 21.9; HRMS (ESI): calcd. for $C_{19}H_{19}N_2O$ $[M + H]^+$ 291.1497; found 291.1489.

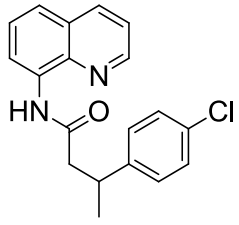


3-(4-methoxyphenyl)-N-(quinolin-8-yl)butanamide (14b): Following the general procedure A described above, **14b** was obtained after purification by silica gel column

chromatography (EtOAc : Hexane = 4 : 96) as pale yellow liquid (67 mg, 93%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3354, 2958, 1680, 1520, 1483, 1242, 1034, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.79 (m, 2H), 8.16 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.56–7.44 (m, 4H), 7.27 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 3.50–3.45 (m, 1H), 2.90–2.74 (m, 2H), 1.41 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 158.1, 148.1, 138.3, 138.0, 136.3, 134.4, 127.9, 127.8, 127.4, 121.6, 121.4, 116.4, 114.0, 55.2, 47.2, 36.1, 22.1; HRMS (ESI): calcd. for $C_{20}H_{21}N_2O_2$ $[M + H]^+$ 321.1603; found 321.1589.

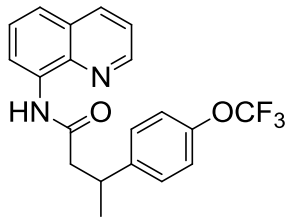


N-(quinolin-8-yl)-3-(p-tolyl)butanamide (14c): Following the general procedure A described above, **14c** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as yellow semi solid (73 mg, 97%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3352, 2958, 1682, 1522, 1484, 1322, 1019, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.81 (d, J = 6.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 1H), 7.57–7.44 (m, 3H), 7.29-7.25 (m, 2H), 7.15 (d, J = 7.6 Hz, 2H), 3.53-3.48 (m, 1H), 2.94-2.88 (m, 1H), 2.82-2.76 (m,1H), 2.33 (s, 3H), 1.43 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 148.1, 143.0, 138.3, 136.3, 135.9, 134.5, 129.3, 127.9, 127.4, 126.7, 121.6, 121.4, 116.5, 47.0, 36.5, 22.0, 21.0; HRMS (ESI): calcd. for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1654; found 305.1642.

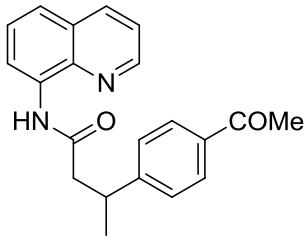


3-(4-chlorophenyl)-N-(quinolin-8-yl)butanamide (14d): Following the general procedure A described above, **14d** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as pale yellow semi solid (61 mg, 75%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3349, 2960, 1681, 1521, 1484, 1322, 1164, 1086, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.79-8.75 (m, 2H),

8.15 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.53–7.44 (m, 3H), 7.28 (s, 4H), 3.53-3.48 (m, 1H), 2.89-2.76 (m, 2H), 1.41 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 148.1, 144.4, 138.2, 136.4, 134.3, 132.0, 128.7, 128.3, 127.9, 127.4, 121.6, 121.6, 116.5, 46.8, 36.3, 21.9; HRMS (ESI): calcd. for $C_{19}H_{18}ClN_2O$ $[M + H]^+$ 325.1105; found 325.1095.

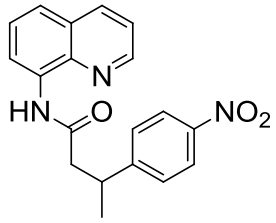


N-(quinolin-8-yl)-3-(4-(trifluoromethoxy)phenyl)butanamide (14e): Following the general procedure A described above, **14e** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as colorless liquid (66 mg, 70%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3339, 2923, 2247, 1716, 1510, 1466, 1242, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.79-8.76 (m, 2H), 8.16 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.54–7.44 (m, 3H), 7.37 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 3.55 (q, J = 7.2 Hz, 1H), 2.91-2.85 (m,1H), 2.83-2.77 (m, 1H), 1.43 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 148.1, 147.7, 147.7, 144.6, 138.2, 136.4, 134.3, 128.2, 127.9, 127.4, 121.6, 121.6, 121.1, 116.4, 46.8, 36.2, 21.8; HRMS (ESI): calcd. for $C_{20}H_{18}F_3N_2O_2$ $[M + H]^+$ 375.1320; found 375.1304.

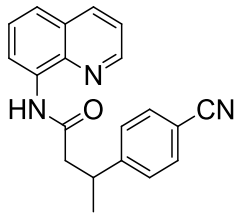


3-(4-acetylphenyl)-N-(quinolin-8-yl)butanamide (14f): Following the general procedure A described above, **14f** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 20 : 80) as brown semi solid (82 mg, 99%); R_f 0.10 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3349, 2964, 1682, 1525, 1486, 1325, 1164, 1014, 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.77-8.74 (m, 2H), 8.15 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.5–7.43 (m, 5H), 3.62–3.56 (m, 1H), 2.92–2.80 (m, 2H), 2.56 (s, 3H), 1.44 (d, J = 7.2 Hz, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 197.9, 169.8, 151.6, 148.1, 138.2, 136.4, 135.5, 134.2, 128.8, 127.9, 127.4, 127.2, 121.6, 121.6, 116.5, 46.3, 36.9, 26.6, 21.7; HRMS (ESI): calcd. for $C_{21}H_{21}N_2O_2$ $[M + H]^+$ 333.1603; found 333.1588.

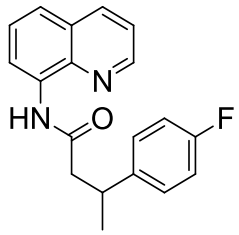


3-(4-nitrophenyl)-N-(quinolin-8-yl)butanamide (14g): Following the general procedure A described above, **14g** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as yellow solid (56 mg, 67%); R_f 0.40 (15% EtOAc/Hexane); mp 98-100 ^oC; IR (DCM): υ_{max} 3354, 2962, 1685, 1520, 1484, 1345, 1035, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.77-8.75 (m, 1H), 8.72 (dd, J_1 = 6.0 Hz, J_2 = 2.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 3H), 7.52–7.44 (m, 5H), 3.65 (dd, J_1 = 14.4 Hz, J_2 = 7.2 Hz, 1H), 2.88 (dd, J_1 = 7.2 Hz, J_2 = 2.8 Hz, 2H), 1.45 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 153.6, 148.2, 146.6, 138.2, 136.4, 134.1, 127.9, 127.9, 127.3, 123.9, 121.7, 121.7, 116.5, 46.1, 36.8, 21.6; HRMS (ESI): calcd. for $C_{19}H_{18}N_3O_3$ $[M + H]^+$ 336.1348; found 336.1335.

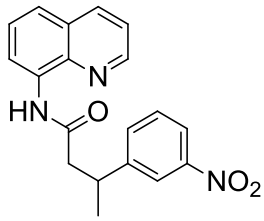


3-(4-cyanophenyl)-N-(quinolin-8-yl)butanamide (14h): Following the general procedure A described above, **14h** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 10 : 90) as brown semi solid (43 mg, 56%); R_f 0.10 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3345, 2965, 2229, 1680, 1521, 1485, 1163, 1016, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.78 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 8.73 (dd, J_1 = 6.0 Hz, J_2 = 2.8 Hz, 1H), 8.16 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.61–7.43 (m, 7H), 3.58 (q, J = 7.2 Hz, 1H), 2.85 (dd, J_1 = 7.2 Hz, J_2 = 5.2 Hz, 2H), 1.43 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 151.5, 148.2, 138.2, 136.4, 134.1, 132.5, 127.9, 127.8, 127.4, 121.7, 119.0, 116.5, 110.3,

46.1, 36.9, 21.5; HRMS (ESI): calcd. for $C_{20}H_{18}N_3O$ $[M + H]^+$ 316.1450; found 316.1440.

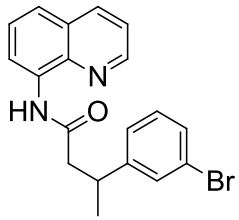


3-(4-fluorophenyl)-N-(quinolin-8-yl)butanamide (14i): Following the general procedure A described above, **14i** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as colourless liquid (46 mg, 64%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3353, 2963, 1680, 1521, 1486, 1325, 1158, 1016, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.79-8.76 (m, 2H), 8.18-815 (m, 1H), 7.56–7.45 (m, 3H), 7.33-7.29 (m, 2H), 7.00 (t, J = 8.8 Hz, 2H), 3.51 (q, J = 7.2 Hz, 1H), 2.86 (q, J = 7.2 Hz, 1H), 2.81-2.76 (m, 1H), 1.42 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 162.7, 160.2, 148.1, 141.5 (d, J = 12.0 Hz), 138.2, 136.4, 134.3, 128.3 (d, J = 31.6 Hz), 127.9, 127.4, 121.6 (d, J = 38.4 Hz), 116.4, 115.4 (d, J = 83.0 Hz), 47.0, 36.2, 22.0; HRMS (ESI): calcd. for $C_{19}H_{18}FN_2O$ $[M + H]^+$ 309.1403; found 309.1388.

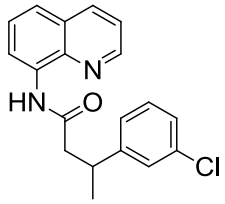


3-(3-nitrophenyl)-N-(quinolin-8-yl)butanamide (14j): Following the general procedure A described above, **14j** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 7 : 93) as brown semi solid (72 mg, 86%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3348, 2965, 1682, 1531, 1486, 1350, 1164, 1031, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.76 (dd, J_1 = 4.0 Hz, J_2 = 1.2 Hz, 1H), 8.72 (dd, J_1 = 6.4 Hz, J_2 = 2.8 Hz, 1H), 8.23 (s, 1H), 8.14 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.04 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.51–7.43 (m, 4H), 3.68–3.63 (m, 1H), 2.95–2.84 (m, 2H), 1.47 (d, J = 6.8 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 148.5, 148.2, 148.0, 138.2, 136.4,

134.1, 133.7, 129.5, 127.9, 127.3, 121.7, 121.6, 121.6, 116.5, 46.2, 36.5, 21.7 ; HRMS (ESI): calcd. for $C_{19}H_{18}N_3O_3$ $[M + H]^+$ 336.1348; found 336.1333.

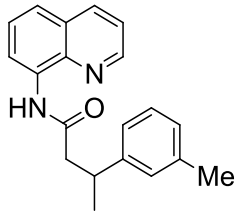


3-(3-bromophenyl)-N-(quinolin-8-yl)butanamide (14k): Following the general procedure A described above, **14k** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as colorless liquid (77 mg, 84%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3339, 2923, 2247, 1716, 1510, 1466, 1242, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.80 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 8.77 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 8.16 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.56–7.45 (m, 4H), 7.33 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 9.2 Hz, 1H), 7.19-7.15 (m, 1H), 3.52-3.47 (m, 1H), 2.89 (dd, J_1 = 14.8 Hz, J_2 = 6.8 Hz, 1H), 2.78 (dd, J_1 = 14.8 Hz, J_2 = 8.0 Hz, 1H), 1.42 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 148.3, 148.1, 138.3, 136.4, 134.3, 130.2 129.9, 129.6, 127.9, 127.4, 127.4, 125.8, 122.7, 121.6, 121.6, 116.5, 46.6, 36.6, 21.7; HRMS (ESI): calcd. for $C_{19}H_{18}BrN_2O$ $[M + Na]^+$ 369.0603; found 369.0590.

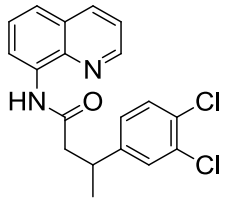


3-(3-chlorophenyl)-N-(quinolin-8-yl)butanamide (14l): Following the general procedure A described above, **14l** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as pale yellow liquid (53 mg, 65%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3339, 2923, 2247, 1716, 1510, 1466, 1242, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.80 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 8.78-8.76 (m, 1H), 8.16 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.56–7.45 (m, 3H), 7.35 (s, 1H), 7.24-7.18 (m, 2H), 3.51 (dd, J_1 = 14.4 Hz, J_2 = 6.8 Hz, 1H), 2.89 (dd, J_1 = 14.8 Hz, J_2 = 6.8 Hz, 1H), 2.79 (dd, J_1 = 14.8 Hz, J_2 = 8.0 Hz, 1H), 1.42 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 148.1, 148.0, 138.2,

136.4, 134.4, 134.3, 129.9, 127.9, 127.4, 127.0, 126.6, 125.3, 121.6, 121.6, 116.5, 46.6, 36.6, 21.7; HRMS (ESI): calcd. for $C_{19}H_{18}ClN_2O$ $[M + H]^+$ 325.1108; found 325.1093.

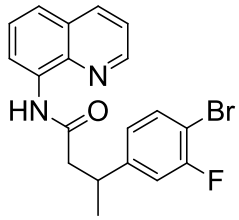


N-(quinolin-8-yl)-3-(m-tolyl)butanamide (14m): Following the general procedure A described above, **14m** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as colorless liquid (63 mg, 83%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3339, 2923, 2247, 1716, 1510, 1466, 1242, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.82-8.79 (m, 2H), 8.16 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.57–7.44 (m, 3H), 7.25-7.16 (m, 3H), 7.04 (d, J = 7.2 Hz, 1H), 3.53-3.47 (m, 1H), 2.95-2.90 (m, 1H), 2.79 (dd, J_1 = 14.4 Hz, J_2 = 8.4 Hz, 1H), 2.36 (s, 3H), 1.44 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 148.1, 146.0, 138.3, 138.2, 136.3, 134.4, 128.5, 127.9, 127.7, 127.4, 127.2, 123.9, 121.6, 121.4, 116.4, 46.9, 36.9, 21.9, 21.5; HRMS (ESI): calcd. for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1654; found 305.1640.

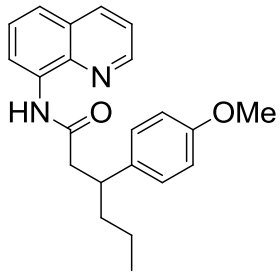


3-(3,4-dichlorophenyl)-N-(quinolin-8-yl)butanamide (14n): Following the general procedure A described above, **14n** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 5 : 95) as pale yellow solid (45 mg, 50%); R_f 0.40 (15% EtOAc/Hexane); mp 85-87 ^oC; IR (DCM): υ_{max} 3412, 2965, 1684, 1526, 1485, 1325, 1122, 1039, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.79 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H), 8.74 (dd, J_1 = 6.8 Hz, J_2 = 2 Hz, 1H), 8.16 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.56–7.44 (m, 4H), 7.35 (d, J = 8.4 Hz, 1H), 7.17 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 3.51–3.46 (m, 1H), 2.88–2.76 (m, 2H), 1.41 (d, J = 6.8 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 148.2, 146.2, 138.2, 136.4, 134.2, 132.5,

130.5, 130.3, 128.9, 127.9, 127.3, 126.6, 121.6, 116.5, 46.5, 36.2, 21.7; HRMS (ESI): calcd. for $C_{19}H_{17}Cl_2N_2O$ $[M + H]^+$ 359.0718; found 359.0706.

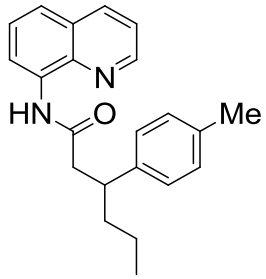


3-(4-bromo-3-fluorophenyl)-N-(quinolin-8-yl)butanamide (14o): Following the general procedure A described above, **14o** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as pale yellow solid (71 mg, 74%); R_f 0.40 (15% EtOAc/Hexane); mp 146-148 ^oC; IR (DCM): υ_{max} 3339, 2923, 2247, 1716, 1510, 1466, 1242, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.79 (dd, J_1 = 4.4 Hz, J_2 = 1.6 Hz, 1H), 8.75-8.73 (m, 1H), 8.18-815 (m, 1H), 7.56–7.43 (m, 4H), 7.13 (dd, J_1 = 9.6 Hz, J_2 = 2.0 Hz, 1H), 7.02 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 3.50 (q, J = 7.2 Hz, 1H), 2.88-2.83 (m, 1H), 2.79 (dd, J_1 = 14.8 Hz, J_2 = 7.6 Hz, 1H), 1.41 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 160.4, 157.9, 148.2, 147.8 (d, J = 25.2 Hz), 138.2, 136.4, 134.2, 133.5, 127.9, 127.4, 124.0 (d, J = 12.4 Hz), 121.7, 116.5, 115.0 (d, J = 87.6 Hz), 106.5 (d, J = 83.6 Hz), 46.4, 36.3, 36.3, 21.7; HRMS (ESI): calcd. for $C_{19}H_{17}BrFN_2O$ $[M + H]^+$ 387.0508; found 387.0495.

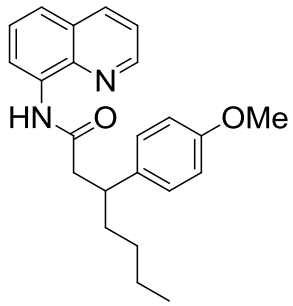


3-(4-methoxyphenyl)-N-(quinolin-8-yl)hexanamide (14p): Following the general procedure A described above, **14p** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 7 : 93) as red solid (92 mg, 92%); R_f 0.40 (15% EtOAc/Hexane); mp 85-87 ^oC; IR (DCM): υ_{max} 3355, 2956, 1683, 1525, 1485, 1325, 1248, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 8.77-8.75 (m, 2H), 8.13 (d, J = 8.0 Hz, 1H), 7.54–7.42 (m, 3H), 7.23 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H), 3.31–3.27 (m, 1H), 2.85–2.82 (m, 2H), 1.79–1.66 (m, 2H), 1.29–

1.22 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 158.1, 148.0, 138.3, 136.3, 136.3, 134.5, 128.5, 127.9, 127.4, 121.5, 121.4, 116.4, 113.9, 55.2, 46.2, 41.6, 38.6, 20.6, 14.0; HRMS (ESI): calcd. for $C_{22}H_{25}N_2O_2$ $[M + H]^+$ 349.1916; found 349.1906.

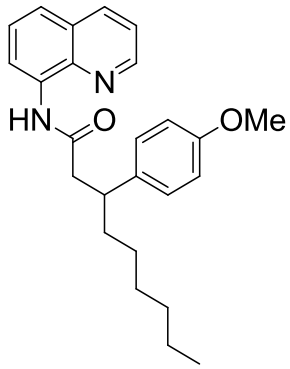


N-(quinolin-8-yl)-3-(p-tolyl)hexanamide (14q): Following the general procedure A described above, **14q** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 5 : 95) as pale yellow semi solid (77 mg, 93%); R_f 0.40 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3356, 2956, 1688, 1525, 1485, 1325, 1160, 1114, 825 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.79–8.77 (m, 2H), 8.14 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.54–7.43 (m, 3H), 7.21 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 3.33–3.30 (m, 1H), 2.86 (d, J = 6.8 Hz, 2H), 2.31 (s, 3H), 1.80–1.68 (m, 2H), 1.29–1.22 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 148.0, 141.3, 138.3, 136.3, 135.8, 134.5, 129.2, 127.9, 127.4, 127.4, 121.5, 121.3, 116.4, 46.0, 42.0, 38.5, 21.1, 20.6, 14.1; HRMS (ESI): calcd. for $C_{22}H_{25}N_2O$ $[M + H]^+$ 333.1967; found 333.1960.

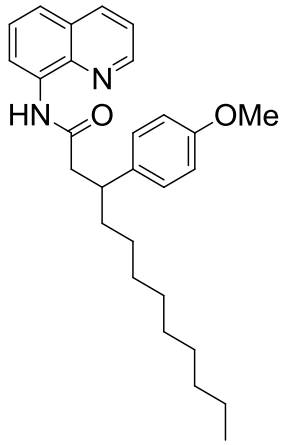


3-(4-methoxyphenyl)-N-(quinolin-8-yl)heptanamide (14r): Following the general procedure A described above, **14r** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 5 : 95) as pale yellow solid (94 mg, 97%); R_f 0.40 (15% EtOAc/Hexane); mp 89-91 ^{o}C; IR (DCM): υ_{max} 3356, 2929, 1682, 1525, 1486, 1325, 1247, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 8.77–8.74

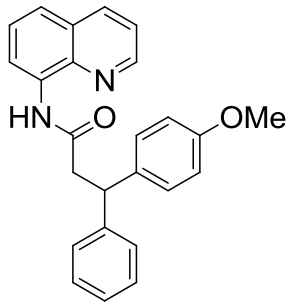
(m, 2H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.54–7.43 (m, 3H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.76 (s, 3H), 3.28–3.24 (m, 1H), 2.85–2.81 (m, 2H), 1.80–1.67 (m, 3H), 1.32–1.17 (m, 5H), 0.90–0.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 158.0, 148.0, 138.3, 136.4, 136.3, 134.4, 128.4, 127.8, 127.4, 121.5, 121.3, 116.4, 113.9, 55.2, 46.2, 41.8, 36.1, 29.7, 22.7, 14.0; HRMS (ESI): calcd. for $C_{23}H_{27}N_2O_2$ $[M + H]^+$ 363.2073; found 363.2082.



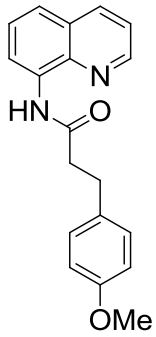
3-(4-methoxyphenyl)-N-(quinolin-8-yl)nonanamide (14s): Following the general procedure A described above, **14s** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 7 : 93) as pale yellow solid (93 mg, 95%); R_f 0.40 (15% EtOAc/Hexane); mp 75-77 ^{o}C; IR (DCM): υ_{max} 3356, 2928, 1683, 1520, 1486, 1325, 1247, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 8.78–8.75 (m, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.54–7.43 (m, 3H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.76 (s, 3H), 3.28–3.25 (m, 1H), 2.85–2.81 (m, 2H), 1.79–1.67 (m, 2H), 1.28–1.22 (m, 8H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 158.0, 148.0, 138.3, 136.4, 136.3, 134.5, 128.4, 127.9, 127.4, 121.5, 121.3, 116.4, 113.9, 55.2, 46.2, 41.9, 36.4, 31.8, 29.3, 27.4, 22.6, 14.1; HRMS (ESI): calcd. for $C_{25}H_{31}N_2O_2$ $[M + H]^+$ 391.2386; found 391.2379.



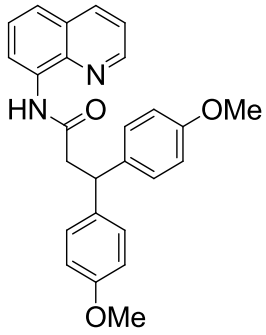
3-(4-methoxyphenyl)-N-(quinolin-8-yl)dodecanamide (14t): Following the general procedure A described above, **14t** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 7 : 93) as pale yellow solid (91 mg, 85%); R_f 0.40 (15% EtOAc/Hexane); mp 56-58 ^oC; IR (DCM): υ_{max} 3356, 2926, 1683, 1520, 1486, 1325, 1248, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 8.77–8.75 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 7.51–7.43 (m, 3H), 7.23 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 3.30–3.25 (m, 1H), 2.85–2.81 (m, 2H), 1.80–1.67 (m, 2H), 1.30–1.22 (m, 15H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 158.0, 148.0, 138.3, 136.4, 136.3, 134.5, 128.4, 127.9, 127.4, 121.5, 121.3, 116.4, 113.9, 55.1, 46.2, 41.9, 36.4, 31.9, 29.6, 29.6, 29.6, 29.3, 27.5, 22.7, 14.2; HRMS (ESI): calcd. for $C_{28}H_{37}N_2O_2$ $[M + H]^+$ 433.2855; found 433.2838.



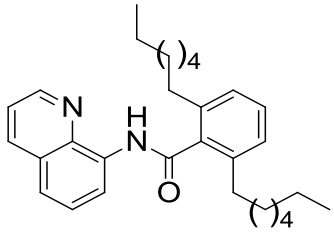
3-(4-methoxyphenyl)-3-phenyl-N-(quinolin-8-yl)propanamide (14u): Following the general procedure A described above, **14u** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 8 : 92) as brown semi solid (76 mg, 80%); R_f 0.20 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3339, 2923, 2247, 1716, 1510, 1466, 1242, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.78-8.75 (m, 2H), 8.12 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.51–7.29 (m, 9H), 7.21 (t, J = 7.2 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 4.79 (t, J = 7.6 Hz, 1H), 3.75 (s, 3H), 3.33 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 158.2, 148.1, 144.2, 138.2, 136.3, 135.9, 134.4, 128.8, 128.7, 127.9, 127.7, 127.4, 126.5, 121.6, 121.5, 116.5, 114.0, 55.2, 46.4, 44.7; HRMS (ESI): calcd. for $C_{25}H_{23}N_2O_2$ $[M + Na]^+$ 383.1760; found 383.1745.



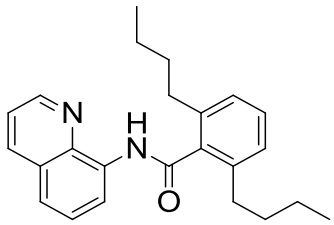
3-(4-methoxyphenyl)-N-(quinolin-8-yl)propanamide (14v): Following the general procedure A described above, **14v** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 4 : 96) as brown semi solid (13 mg, 17%); R_f 0.20 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3339, 2923, 2247, 1716, 1510, 1466, 1242, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.82-8.79 (m, 2H), 8.18 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.56–7.45 (m, 3H), 7.29-7.23 (m, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 3.14-3.10 (m, 2H), 2.90-2.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 158.0, 148.1, 138.3, 136.3, 134.4, 132.8, 129.4, 127.9, 127.4, 121.6, 121.5, 116.5, 114.0, 55.3, 40.1, 30.7; HRMS (ESI): calcd. for $C_{19}H_{19}N_2O_2$ $[M + H]^+$ 307.1447; found 307.1436.



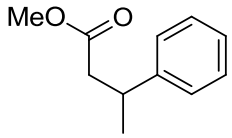
3,3-bis(4-methoxyphenyl)-N-(quinolin-8-yl)propanamide (14v'): Following the general procedure A described above, **14v'** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 8 : 92) as brown semi solid (60 mg, 58%); R_f 0.20 (15% EtOAc/Hexane; IR (DCM): υ_{max} 3339, 2923, 2247, 1716, 1510, 1466, 1242, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 8.78-8.76 (m, 1H), 8.73 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 1H), 8.16-8.14 (m, 1H), 7.51–7.43 (m, 3H), 7.29-7.25 (m, 4H), 6.84 (d, J = 8.4 Hz, 4H), 4.68-4.72 (m, 1H), 3.75 (s, 6H), 3.27 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 158.1, 148.0, 138.2, 136.3, 136.3, 134.4, 128.7, 127.8, 127.4, 121.6, 121.4, 116.5, 114.0, 55.2, 45.6, 44.9; HRMS (ESI): calcd. for $C_{26}H_{25}N_2O_3$ $[M + H]^+$ 413.1865; found 413.1848.



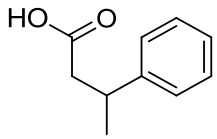
2,6-diheptyl-N-(quinolin-8-yl)benzamide (12t): Following the general procedure A described above, **12t** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 2 : 98) as brown semi solid (62 mg, 45%); R_f 0.8 (15% EtOAc/Hexane); IR (DCM υ_{max} 3348, 2925, 2855, 1677, 1522, 1480, 1325, 1262, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 9.04-9.01 (m, 1H), 8.76-8.74 (m, 1H), 8.21 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.66-7.58 (m, 2H), 7.46 (dd, J_1 = 8.4 Hz, J_2 = 4.4 Hz, 1H) 7.36-7.32 (m, 1H), 7.18 (d, J = 8.0 Hz, 2H), 2.73 (t, J = 8.0 Hz, 4H), 1.73-1.65 (m, 4H), 1.30-1.12 (m, 18H), 0.79-0.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 148.2, 139.5, 138.5, 137.5, 136.3, 134.5, 129.0, 128.0, 127.5, 126.7, 121.8, 121.8, 121.6, 116.7, 33.5, 31.7, 31.6, 29.6, 29.0, 22.6, 14.0; HRMS (ESI): calcd. for $C_{30}H_{41}N_2O$ $[M + H]^+$ 445.3219; found 445.3236.



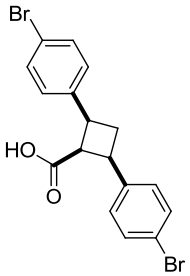
2,6-dibutyl-N-(quinolin-8-yl)benzamide (12u): Following the general procedure A described above, **12u** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 2 : 98) as brown semi solid (49 mg, 55%); R_f 0.8 (15% EtOAc/Hexane); IR (DCM): υ_{max} 3347, 2927, 2858, 1676, 1522, 1482, 1325, 1262, 1126, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 9.01 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 8.75 (dd, J_1 = 4.4 Hz, J_2 = 1.6 Hz, 1H), 8.22-8.20 (m, 1H), 7.67-7.58 (m, 2H), 7.48-7.45 (m, 1H), 7.36-7.32 (m, 1H), 7.18 (d, J = 7.6 Hz, 2H), 2.73 (t, J = 8.0 Hz, 4H), 1.73-1.65 (m, 5H), 1.32 (dd, J_1 = 14.8 Hz, J_2 = 7.6 Hz, 4H), 0.84-0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 148.2, 139.5, 138.5, 137.5, 136.3, 134.5, 128.9, 128.0, 127.5, 126.7, 121.9, 121.7, 116.8, 33.8, 33.2, 22.7, 13.9; HRMS (ESI): calcd. for $C_{24}H_{29}N_2O$ $[M + H]^+$ 316.2280; found 316.2265.



methyl 3-phenylbutanoate (15a): Following the general procedure B described above, **15a** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 1 : 99) as pale yellow liquid (31 mg, 37%); R_f 0.80 (5% EtOAc/Hexane); IR (DCM): υ_{max} 3339, 2923, 2247, 1716, 1510, 1466, 1242, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H), 3.65 (s, 3H), 3.32 (dd, J_1 = 14.8 Hz, J_2 = 7.2 Hz, 1H), 2.66 (dd, J_1 = 15.2 Hz, J_2 = 6.8 Hz, 1H), 2.57 (dd, J_1 = 15.2 Hz, J_2 = 8.4 Hz, 1H, 1.33 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 145.7, 128.5, 126.7, 126.4, 51.5, 42.7, 36.4, 21.8; HRMS (ESI): calcd. for $C_{11}H_{14}NaO_2$ $[M + Na]^+$ 201.0891; found 201.0883.

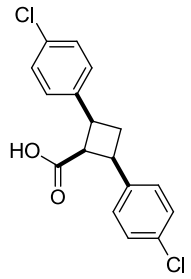


3-phenylbutanoic acid (15b): Following the general procedure C described above, **15b** was obtained (EtOAc : Hexane = 1 : 99) as brown semi solid (16 mg, 32%); IR (DCM): υ_{max} 3339, 2923, 2247, 1716, 1510, 1466, 1242, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H), 3.30 (dd, J_1 = 14.8 Hz, J_2 = 7.2 Hz, 1H), 2.70 (dd, J_1 = 15.2 Hz, J_2 = 6.8 Hz, 1H), 2.61 (dd, J_1 = 15.6 Hz, J_2 = 8.4 Hz, 1H), 1.35 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 145.5, 128.6, 126.7, 126.5, 42.5, 36.2, 21.9; HRMS (ESI): calcd. for $C_{10}H_{11}O_2$ $[M - H]^+$ 163.0759; found 163.0752.



2,4-Bis(4-bromophenyl)cyclobutanecarboxylic acid (15c). Following the general procedure C described above, **15c** was obtained as a brown color solid (crude material was almost pure); 65 mg, 52% yield; mp131-133 ^oC; IR (DCM): υ_{max} 2922, 1698,

1516, 1425, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.4 Hz, 4H), 7.20 (d, J = 8.4 Hz, 4H), 3.76 (dd, J_1 = 18.4 Hz, J_2 = 9.6 Hz, 2H), 3.24 (t, J = 9.6 Hz, 1H), 2.80 (dd, J_1 = 18.8 Hz, J_2 = 8.4 Hz, 1H), 2.26 (dd, J_1 = 20.8 Hz, J_2 = 10.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 141.4, 131.6, 128.4, 120.6, 52.2, 38.8, 32.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{14}Br_2O_2Na$: 430.9258; found 430.9281.



2,4-Bis(4-chlorophenyl)cyclobutanecarboxylic acid (15d). Following the general procedure C described above, **15d** was obtained as a white colour liquid (crude material was almost pure); 83 mg, 59% yield; IR (DCM): υ_{max} 2966, 1565, 1432, 1331, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 8.4 Hz, 4H), 7.25 (d, J = 8.4 Hz, 4H), 3.80 (dd, J_1 = 18.4 Hz, J_2 = 9.6 Hz, 2H), 3.27 (t, J = 9.6 Hz, 1H), 2.82 (dd, J_1 = 18.8 Hz, J_2 = 8.4 Hz, 1H), 2.28 (dd, J_1 = 21.2 Hz, J_2 = 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 140.9, 132.6, 128.7, 128.0, 52.4, 38.8, 32.5; FT-IR (DCM): 2966, 1565, 1432, 1331, 800 cm^{-1}; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{17}H_{13}Cl_2O_2$: 319.0292; found 319.0298.

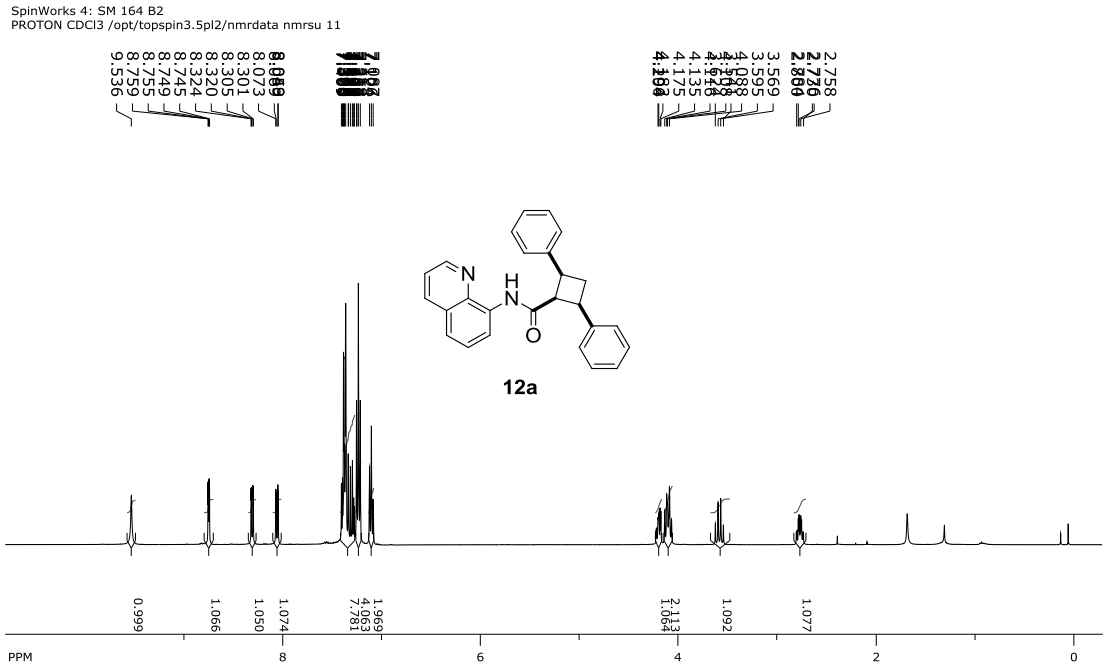
Summary

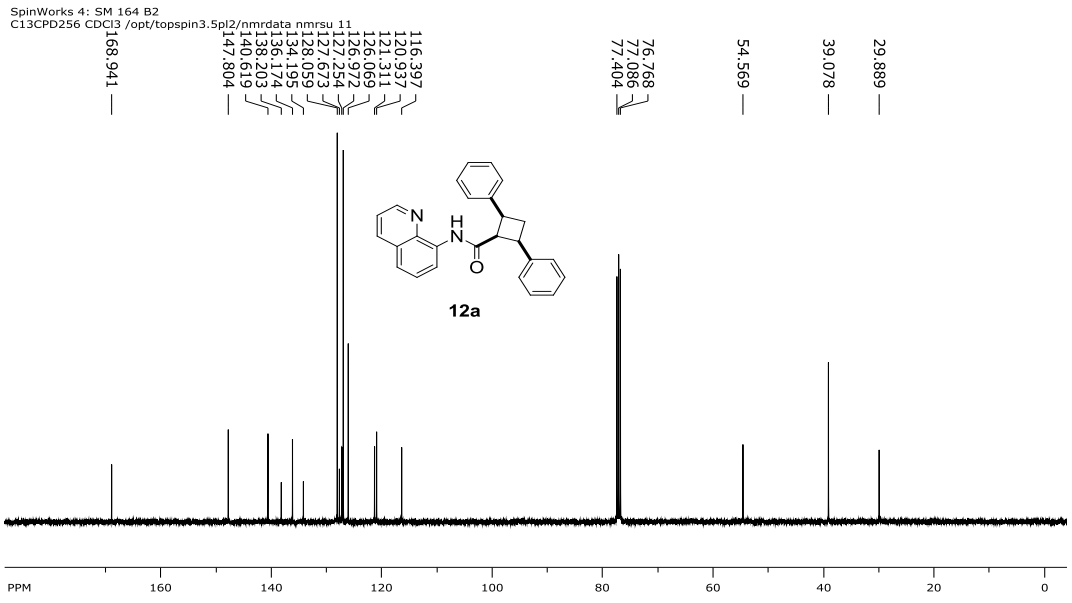
In summary, Pd-catalyzed Ag_2CO_3 mediated one-pot multicomponent reaction method for DG installation, C-H activation and β- arylation of sp^3 C-H bonds of various carboxamide derivatives were successfully achieved. The multicomponent reaction of a mixture of a bidentate ligand, acid chloride and aryl iodide in the presence of $Pd(OAc)_2$ catalyst and Ag_2CO_3 additive directly afforded the corresponding β-arylated N-(quinolin-8-yl)carboxamide derivative. The bidentate ligand 8-aminoquinoline was found to be the best DG to promote the one-pot Pd-catalyzed C-H activation reaction on sp^3 C-H bonds. Various types of acid chlorides and aryl iodides were used to check the efficiency of the reaction. We have explored a step economical and straightforward synthetic methodology via one-pot manner for the synthesis of a variety of β-arylated carboxamide derivatives in moderate to high yields.

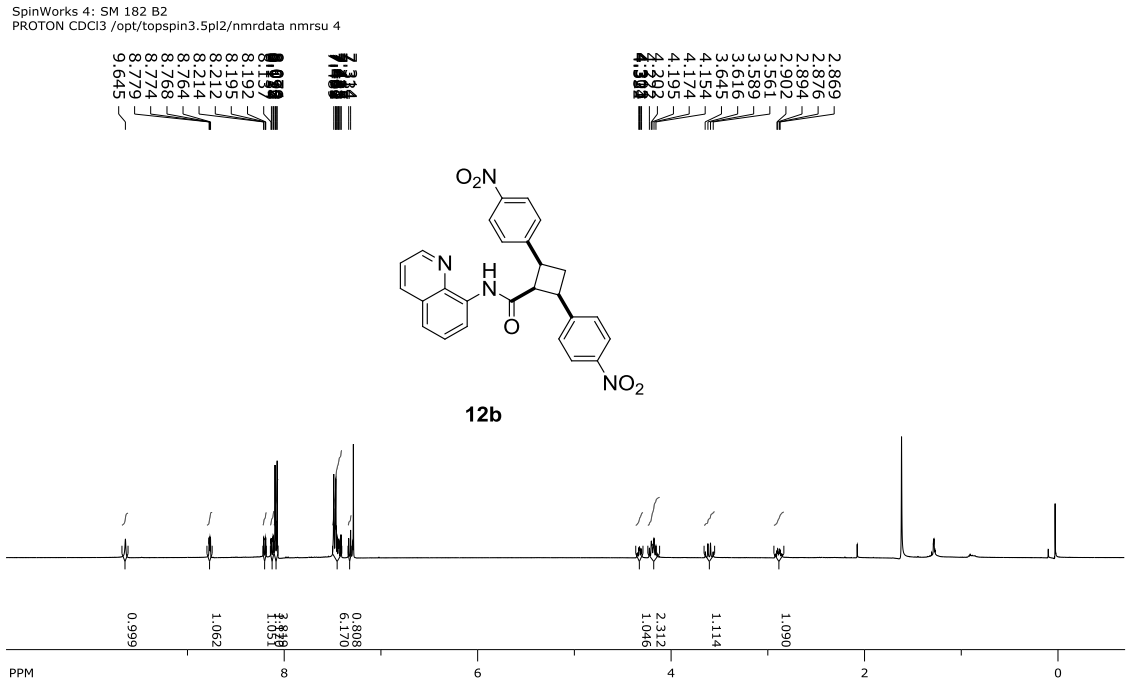
Bibliography

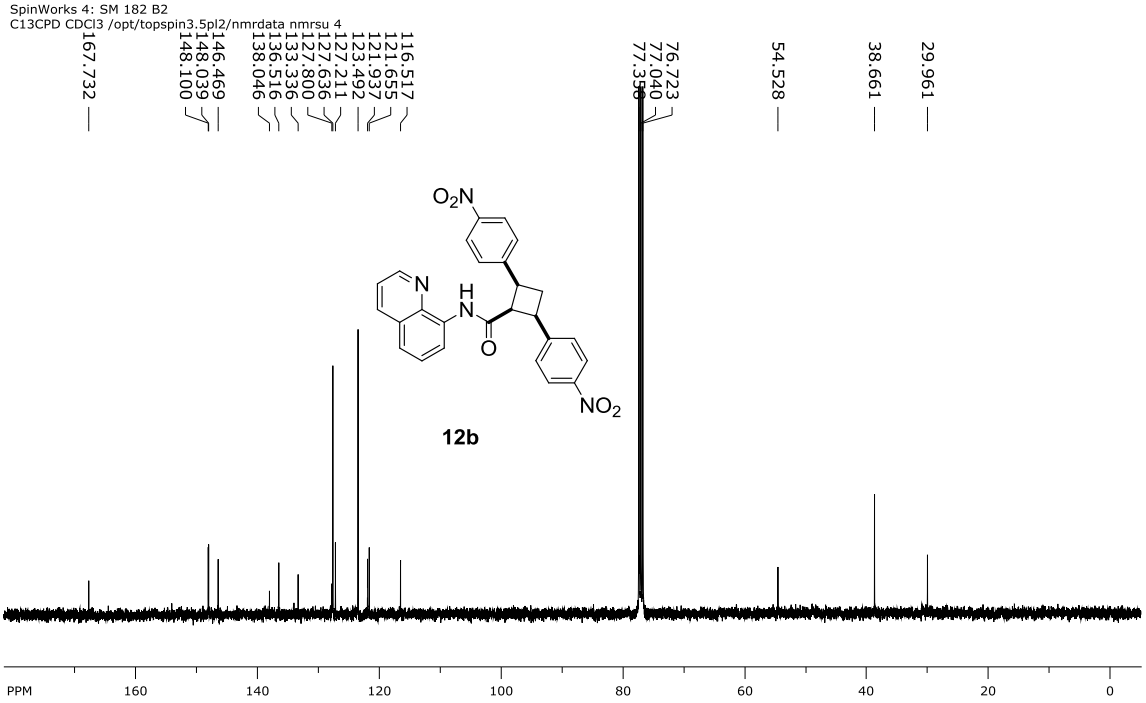
1. Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, 95, 2457.
2. Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, 25, 508.
3. Kuhl, N.; Hopkinson, M. N.; Delord, J. W.; Glorius, F. *Angew. Chem. Int. Ed*. **2012**, 51, 10236.
4. Chen, X.; Engle, K.M.; Wang, D. H.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2009**, 48, 5094.
5. Davies, H. M. L.; Bois, J. D.; Yu. J. Q. *Chem. Soc. Rev*. **2011**, 40, 1855.
6. Chen, D. Y. K.; Youn, S. W. *Chem. Eur. J*. **2012**, 18, 9452.
7. Stuart, D. R.; Fagnnou, K. *Science*. **2007**, 129, 12404.
8. Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, 36, 1173.
9. Shabashov, D.; Daugulis.O. *J. Am. Chem. Soc.* **2010**, 132, 3965.
10. Kalyani, D.; McMurtrey, K.B.; Neufeldt, S.R.; Sanford, M.S. *J. Am. Chem. Soc*, **2011**, 133, 18566.
11. Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, 50, 2450.
12. Liu, Y.; Zhang, Y.; Huang, M.; Wan, J. P. *Rsc. Adv.* **2015**, 5, 46192.
13. Wei, Y.; Tang, H.; Cong, X.; Rao, B.; Zeng, X. *Org. Lett.* **2014**, 16, 2248.
14. Iyanaga, M.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, 79, 11933.
15. Lee-Ruff, E.; Madenova, G. *Chem. Rev*. **2003**, 103, 1449.
16. Bucholtz, K. M.; Gareiss, P. G.; Taje, S. G.; Miller, B. L. *Org. Biomol. Chem.* **2006**, 4, 3973.
17. Parella, R.; Gopalakrishnan, B.; Babu. S. A. *J. Org. Chem*. **2013**, 78, 11911.

Appendix
NMR Spectra of Representative Compounds

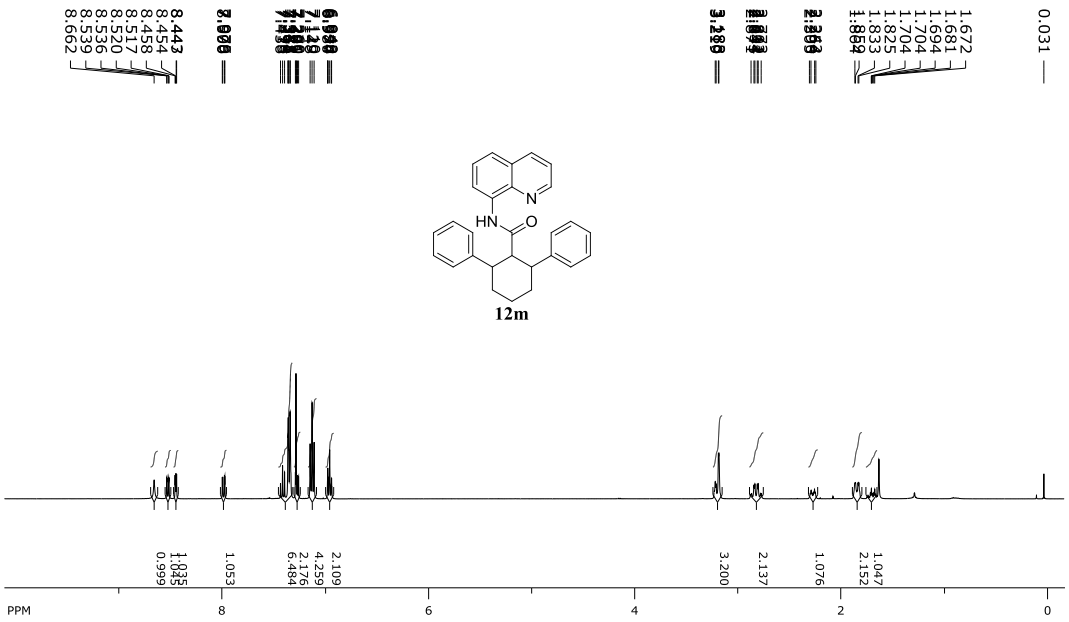




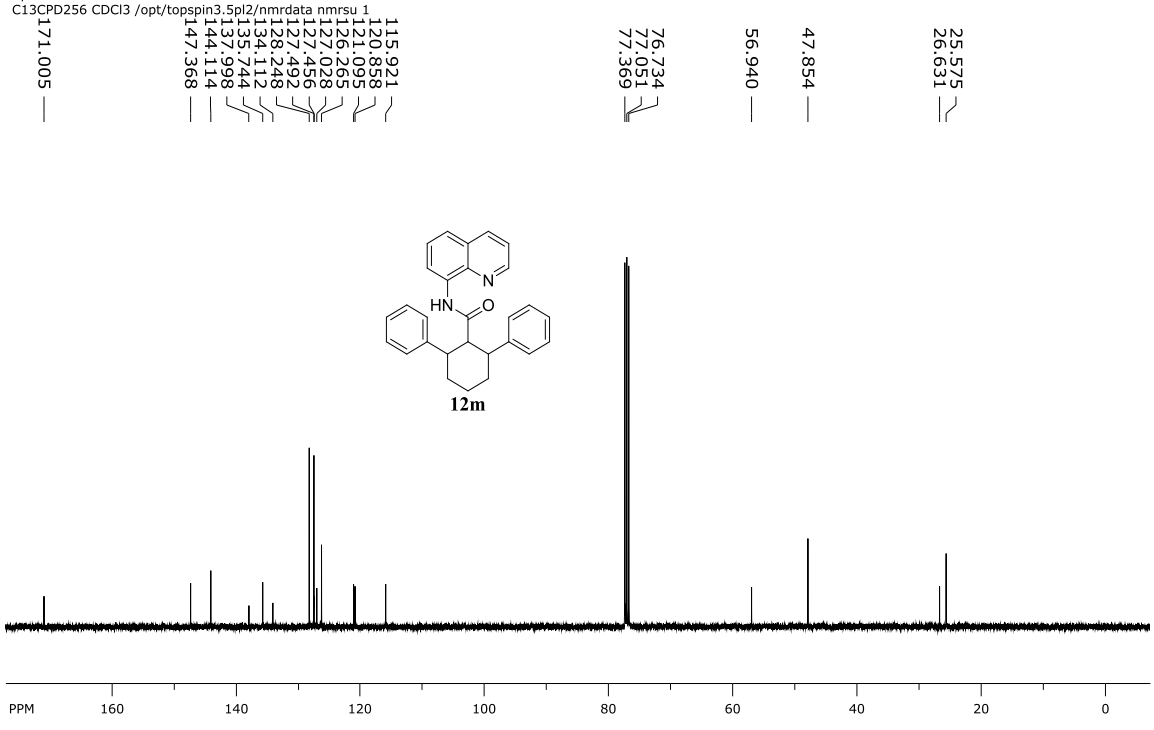

SpinWorks 4: SM 182 B2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 4
9.645
8.779
8.774
8.768
8.764
8.214
8.212
8.195
8.192
4.195
4.174
4.154
3.645
3.616
3.589
3.561
2.902
2.894
2.876
2.869
O2N
N
H
N
O
NO2
12b
0.999
1.062
0.808
6.170
2.312
1.046
1.114
1.090
PPM
8
6
4
2
0

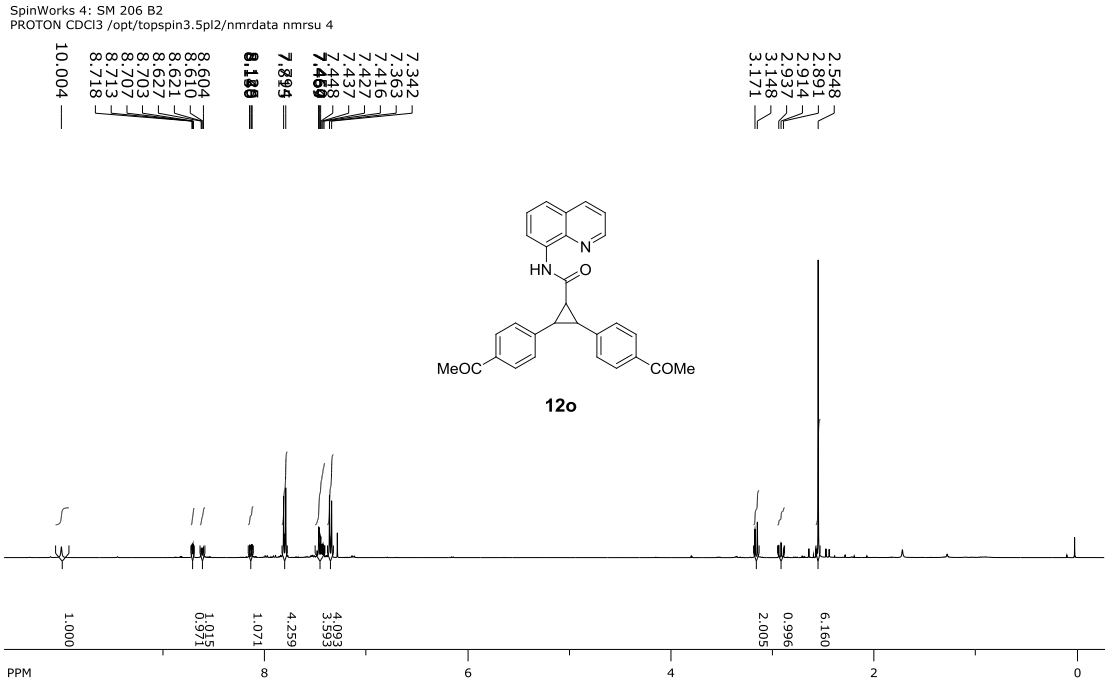

SpinWorks 4: SM 182 B2
C13CPD CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 4
167.732
148.100
148.039
146.469
138.046
136.516
133.336
127.800
127.636
127.211
123.492
121.937
121.655
116.517
77.356
77.040
76.723
54.528
38.661
29.961
O2N
N
H
N
O
NO2
12b
PPM
160
140
120
100
80
60
40
20
0

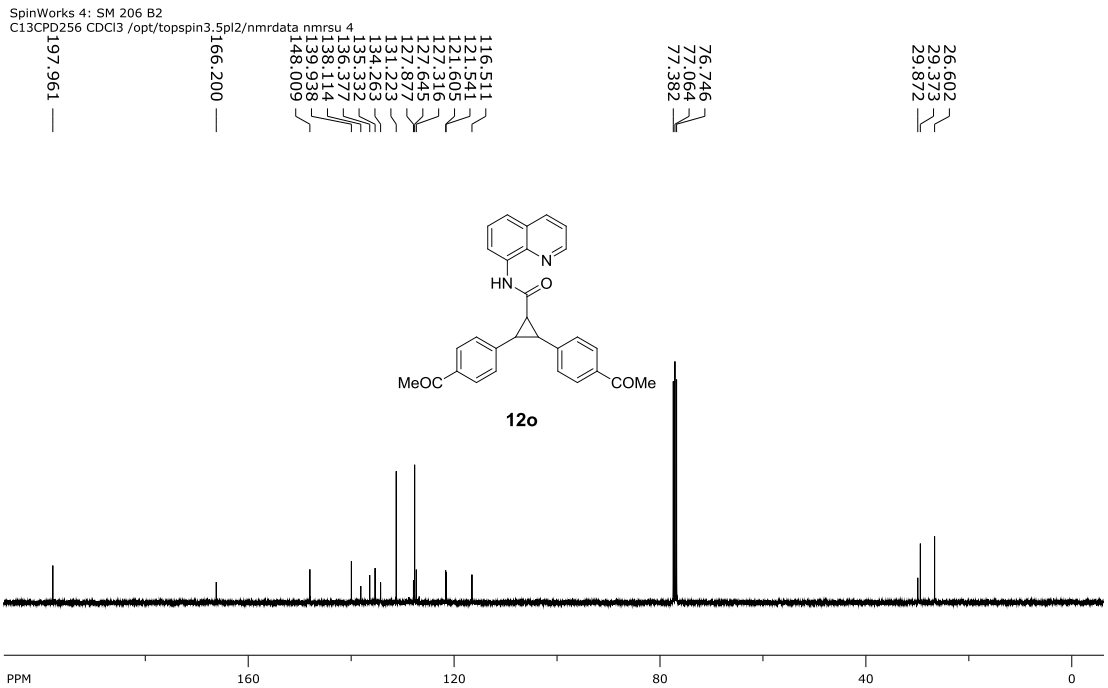
SpinWorks 4: SM 203 A2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 1



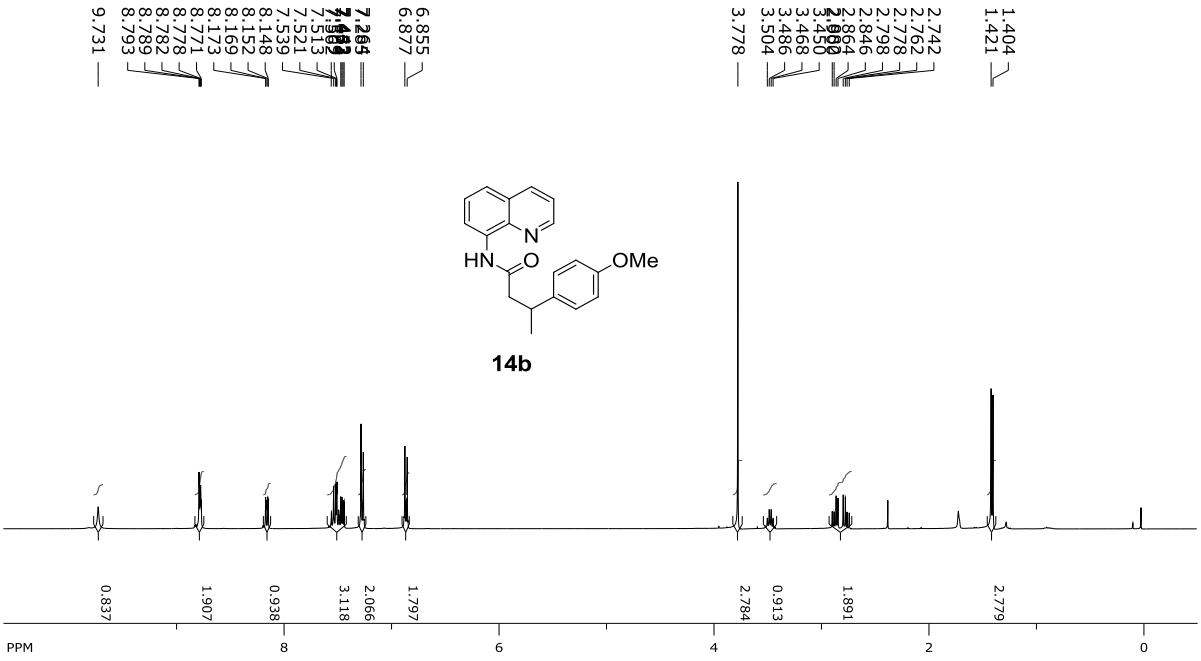
SpinWorks 4: SM 203 A2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 1



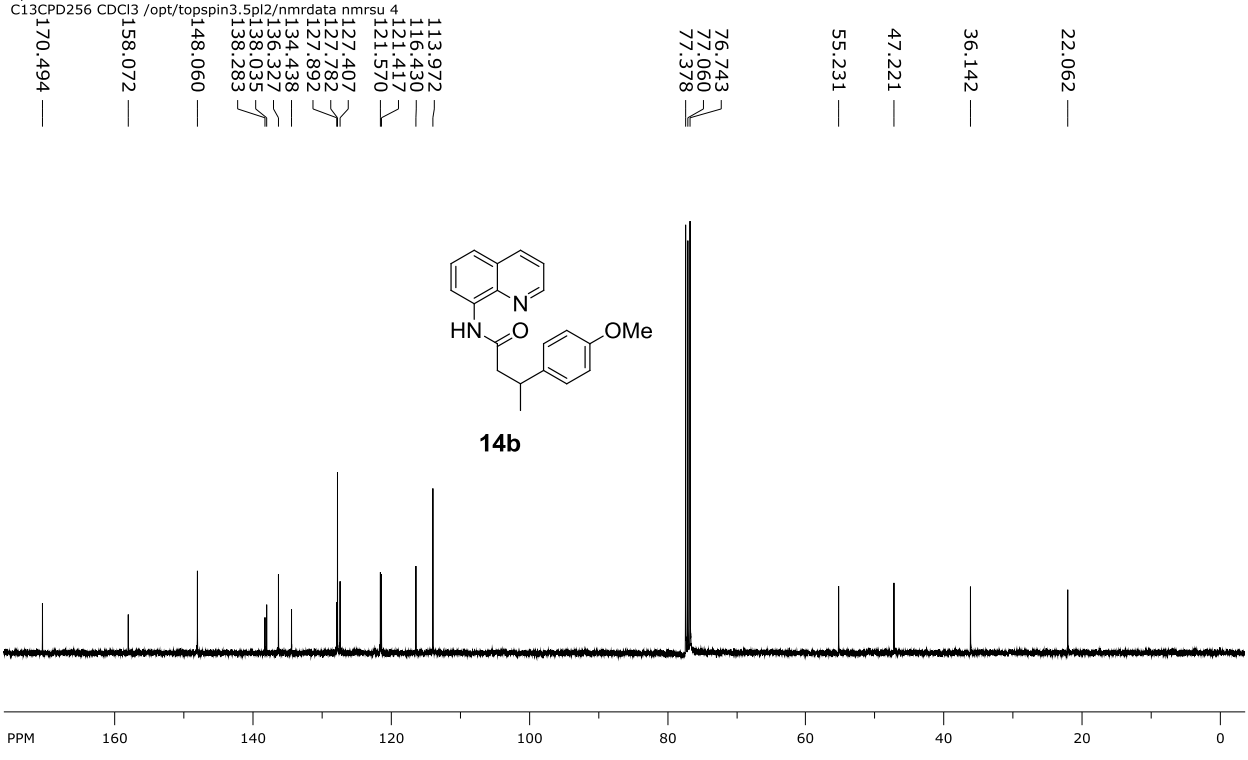

SpinWorks 4: SM 206 B2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 4
10.004
8.718
8.713
8.707
8.703
8.627
8.621
8.610
8.604
7.895
7.448
7.437
7.427
7.416
7.363
7.342
3.171
3.148
2.937
2.914
2.891
2.548
HN
O
N
MeOC
COMe
12o
1.000
1.015
0.971
1.071
4.259
4.093
3.593
2.005
0.996
6.160
PPM
8
6
4
2
0

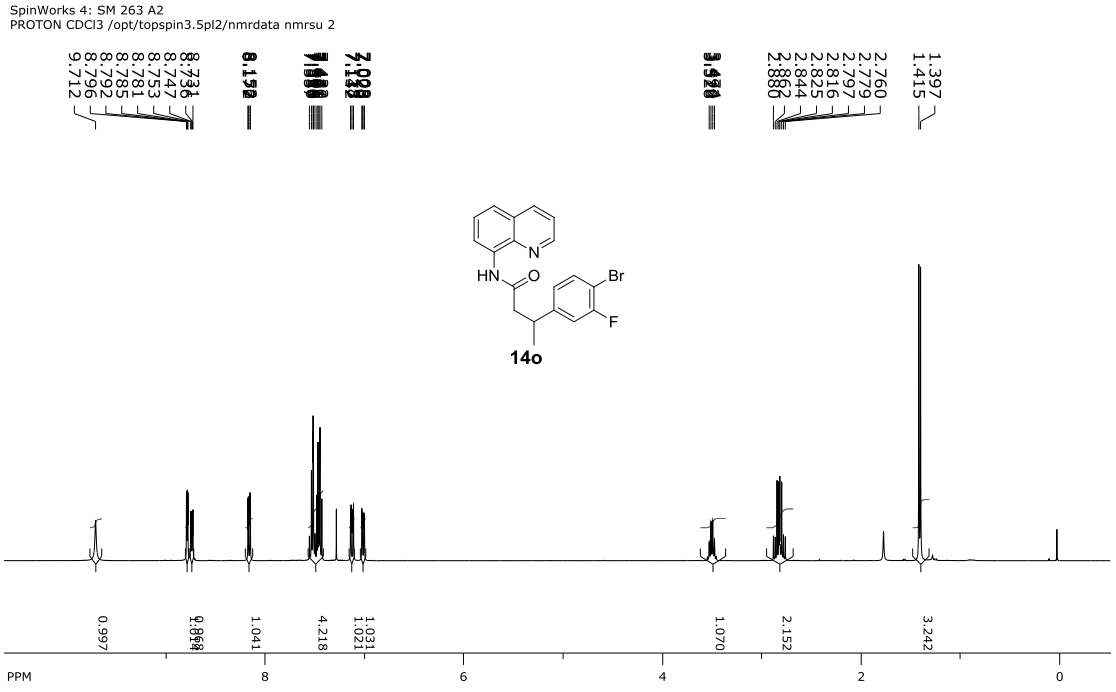

SpinWorks 4: SM 206 B2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 4
197.961
166.200
148.009
139.938
138.114
136.377
135.332
134.263
131.223
127.877
127.645
127.316
121.605
121.541
116.511
77.382
77.064
76.746
29.872
29.373
26.602
HN
O
N
MeOC
COMe
12o
PPM
160
120
80
40
0

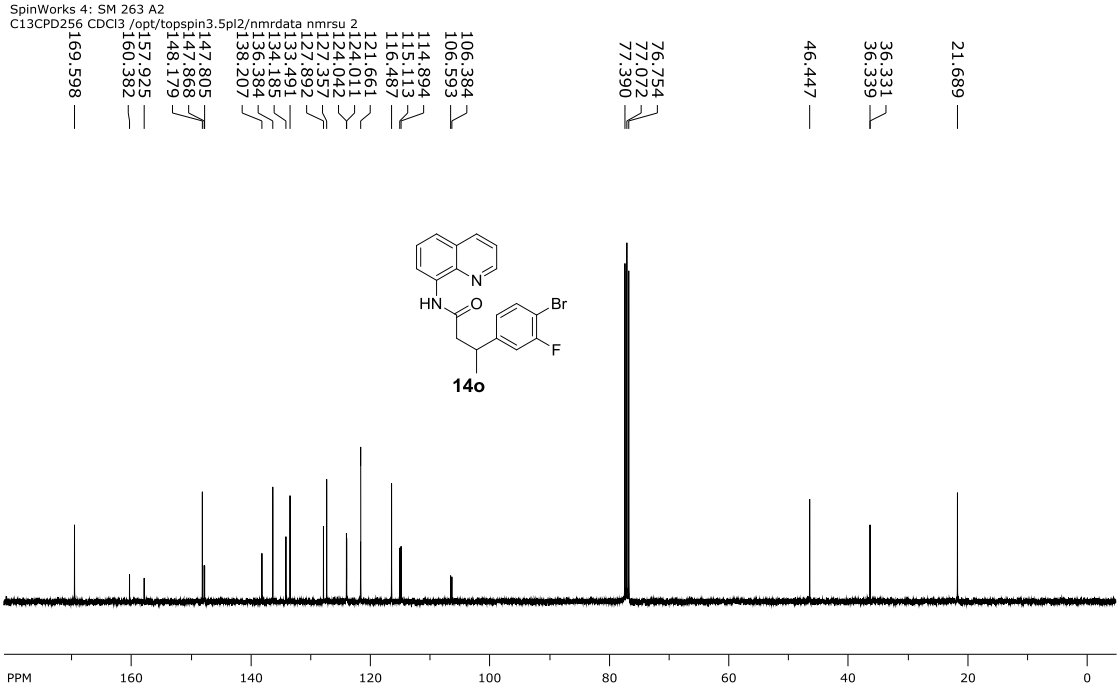
SpinWorks 4: SM-214-A2



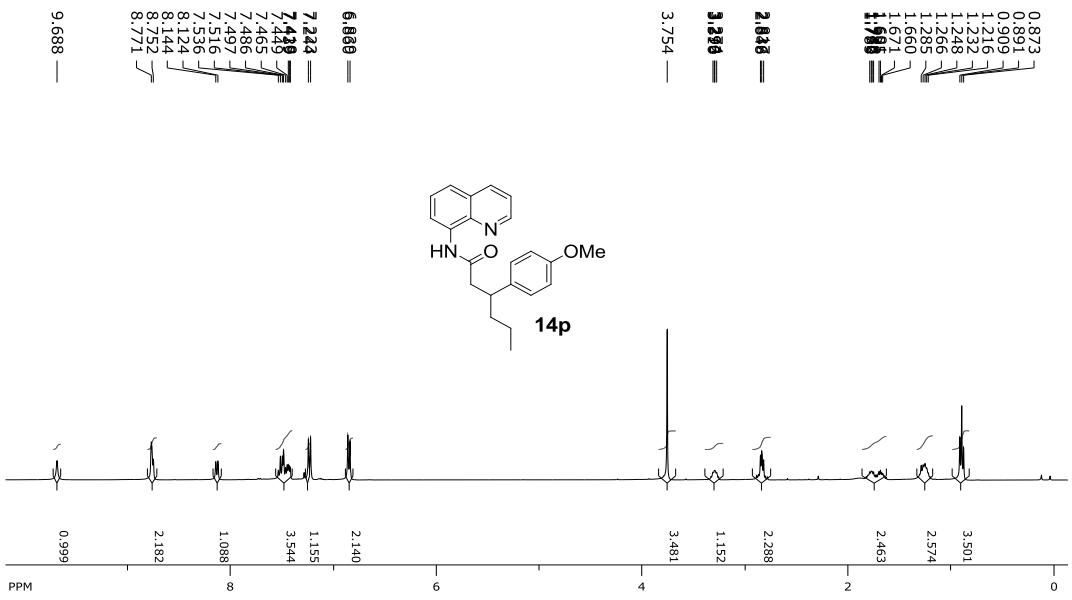
SpinWorks 4: SM 214 A2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 4



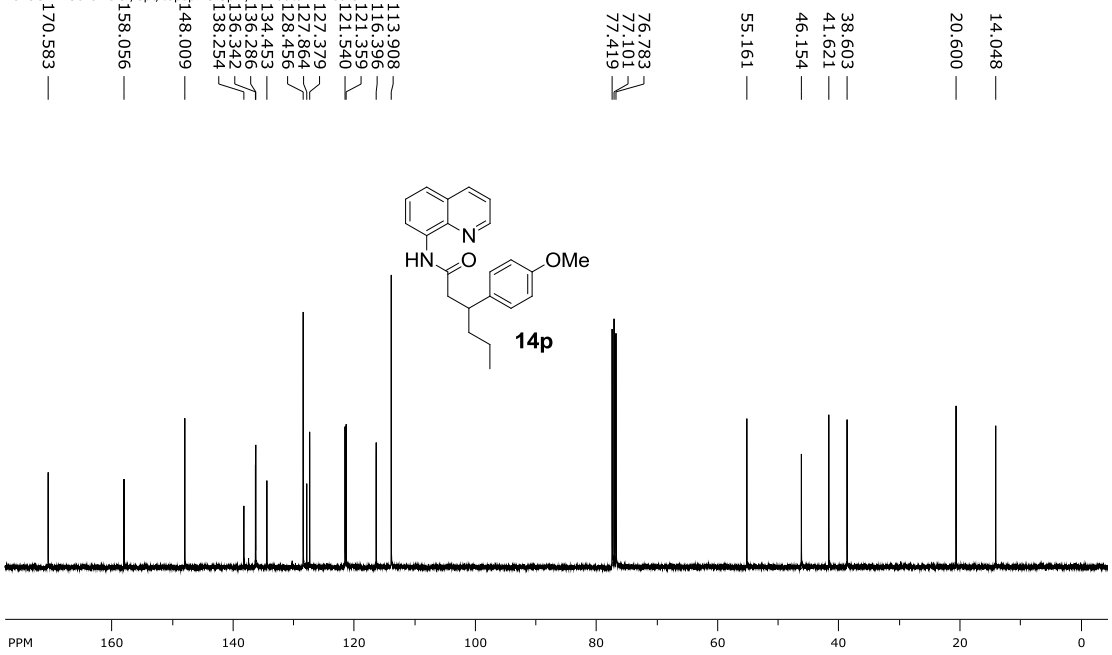

SpinWorks 4: SM 263 A2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 2
9.712
8.796
8.792
8.785
8.781
8.753
8.747
8.736
2.880
2.862
2.844
2.825
2.816
2.797
2.779
2.760
1.415
1.397
HN
O
N
Br
F
14o
0.997
1.041
4.218
1.031
1.021
1.070
2.152
3.242
PPM
8
6
4
2
0


SpinWorks 4: SM 263 A2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 2
169.598
160.382
157.925
148.179
147.868
147.805
138.207
136.384
134.185
133.491
127.892
127.357
124.042
124.011
121.661
116.487
115.113
114.894
106.593
106.384
77.390
77.072
76.754
46.447
36.339
36.331
21.689
HN
O
N
Br
F
14o
PPM
160
140
120
100
80
60
40
20
0

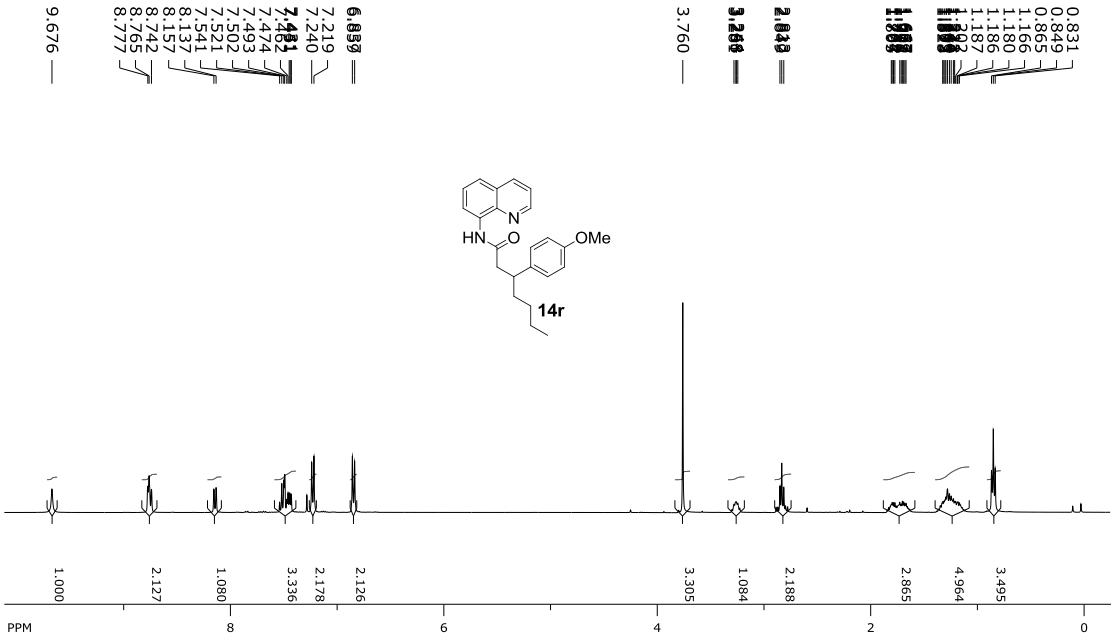
SpinWorks 4: SM-215-A2



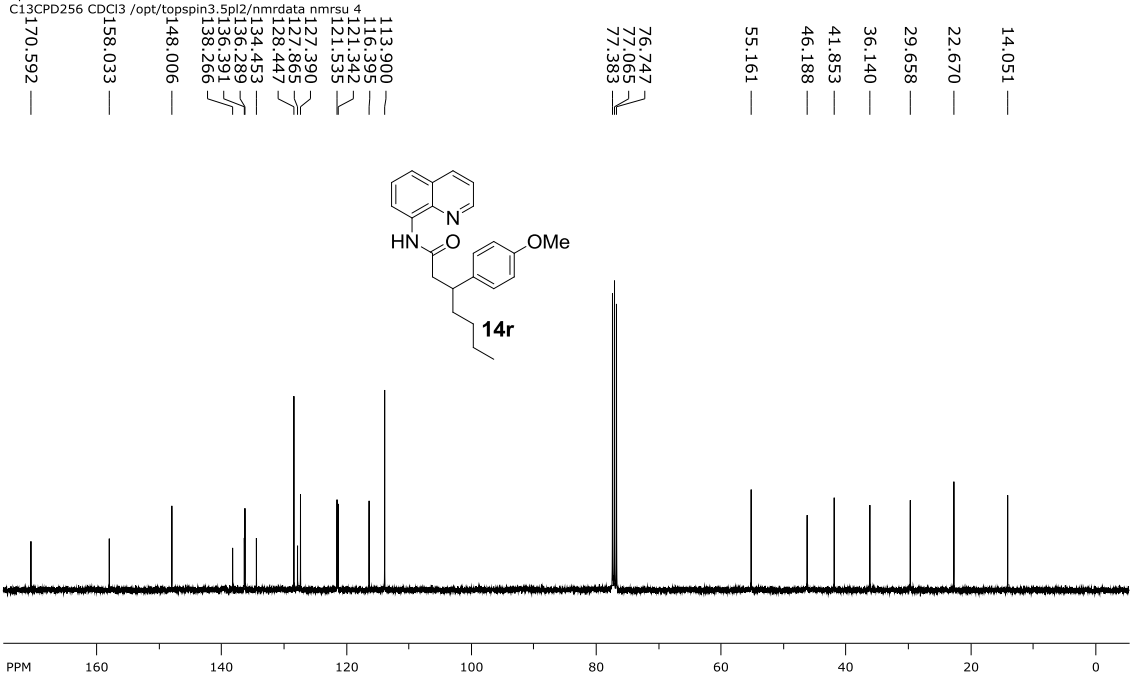
SpinWorks 4: SM 215 A2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 5

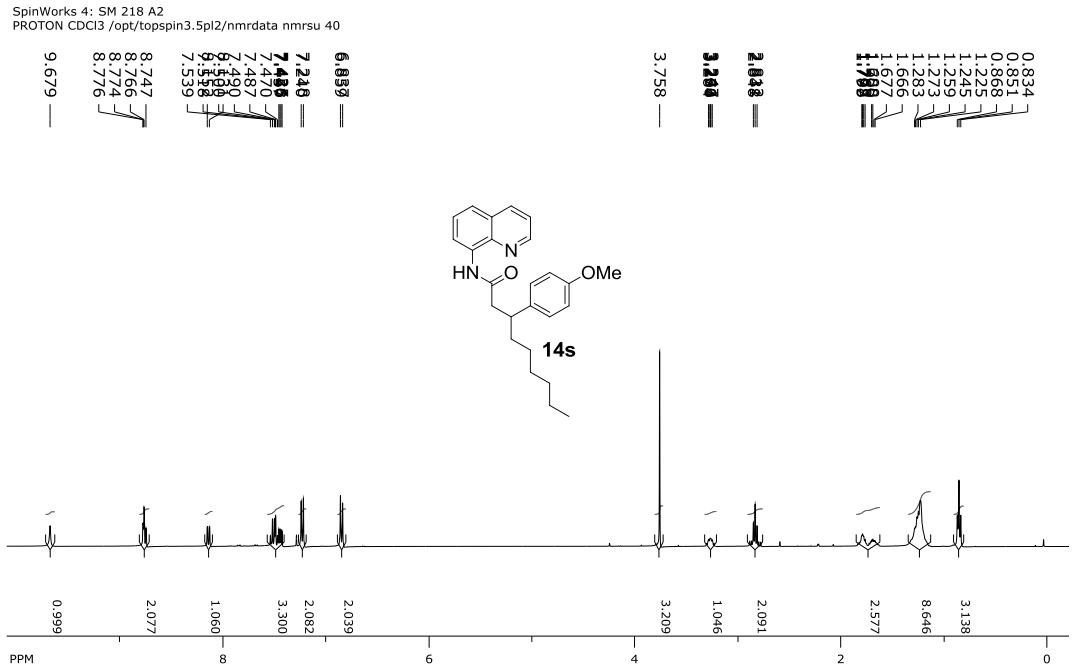


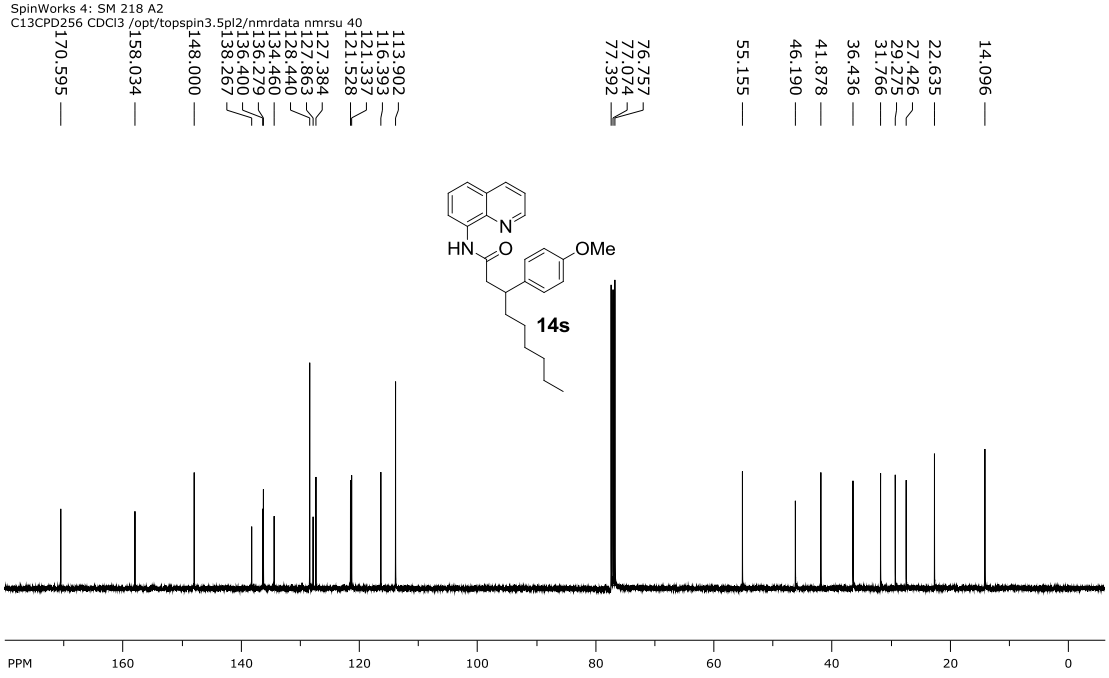
SpinWorks 4: sm 217 a2

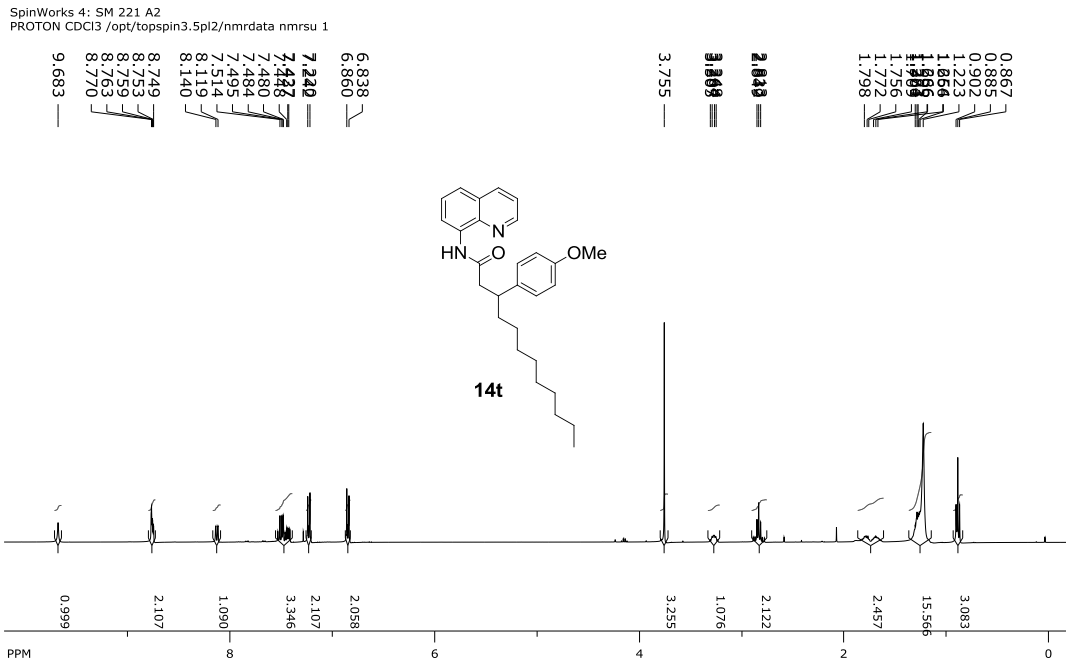


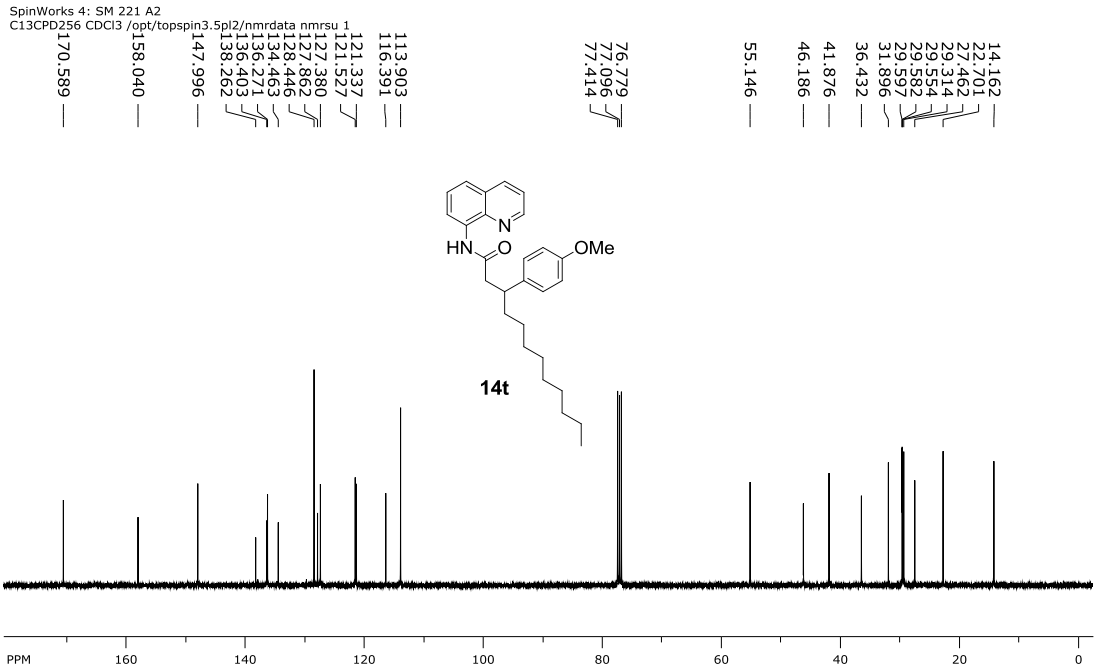
SpinWorks 4: SM 217 A2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 4

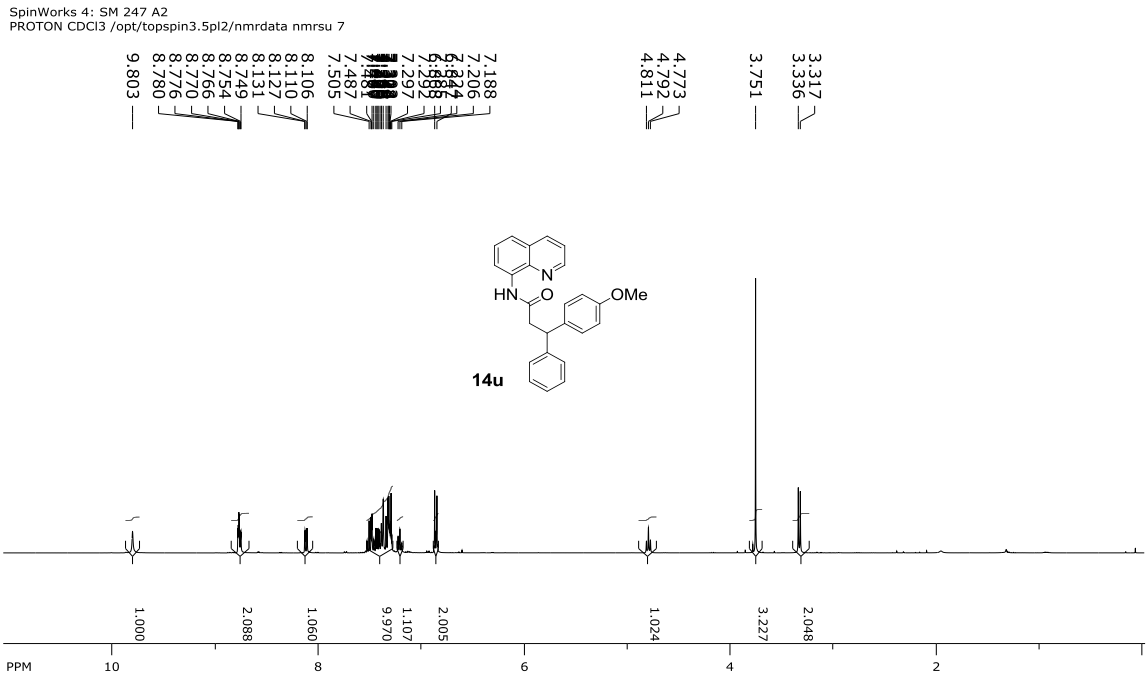


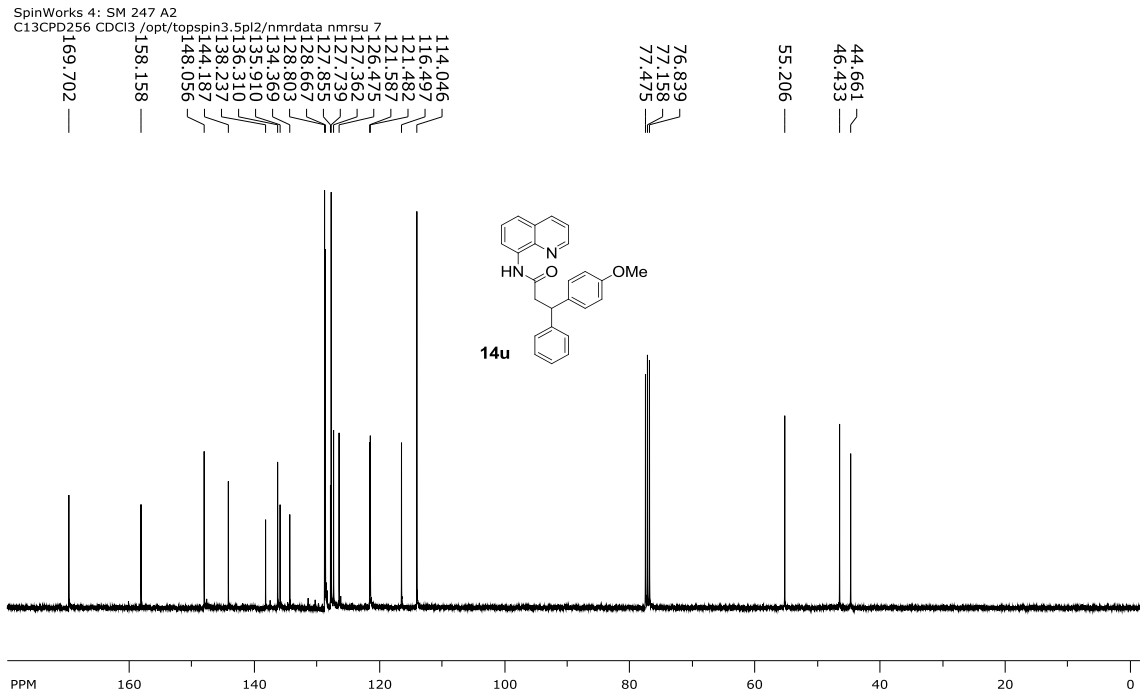

SpinWorks 4: SM 218 A2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 40
9.679
8.776
8.774
8.766
8.747
7.539
7.487
7.240
6.037
3.758
1.677
1.666
1.283
1.273
1.259
1.245
1.225
0.868
0.851
0.834
HN
O
N
OMe
14s
0.999
2.077
1.060
3.300
2.082
2.039
3.209
1.046
2.091
2.577
8.646
3.138
PPM
8
6
4
2
0

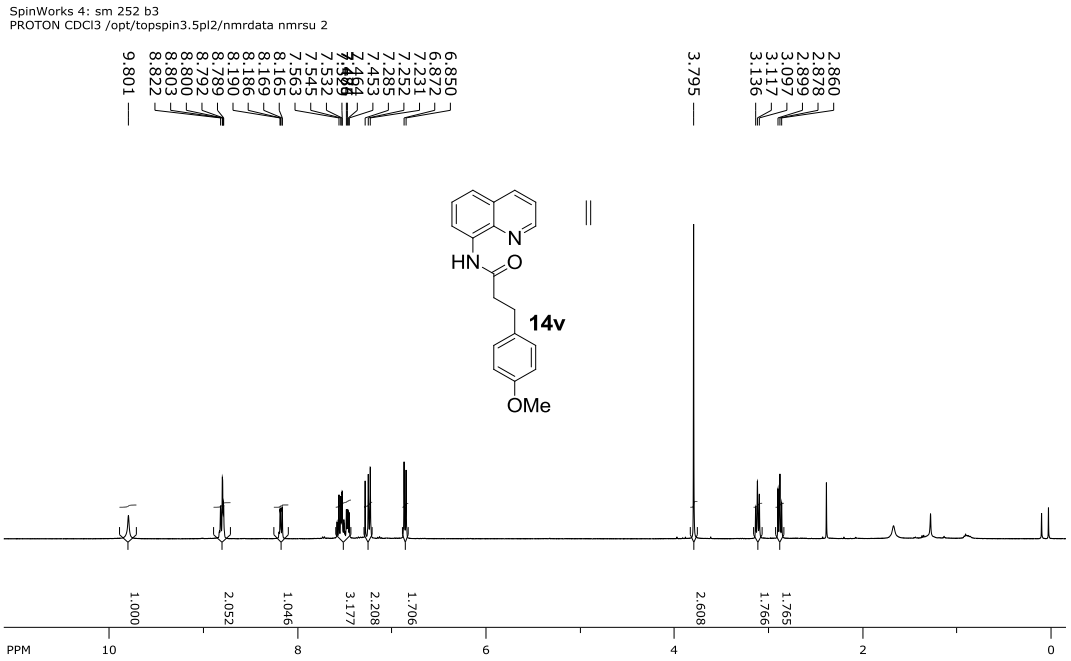

SpinWorks 4: SM 218 A2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 40
170.595
158.034
148.000
138.267
136.400
136.279
134.460
128.440
127.863
127.384
121.528
121.337
116.393
113.902
77.392
77.074
76.757
55.155
46.190
41.878
36.436
31.766
29.275
27.426
22.635
14.096
HN
O
N
OMe
14s
PPM
160
140
120
100
80
60
40
20
0

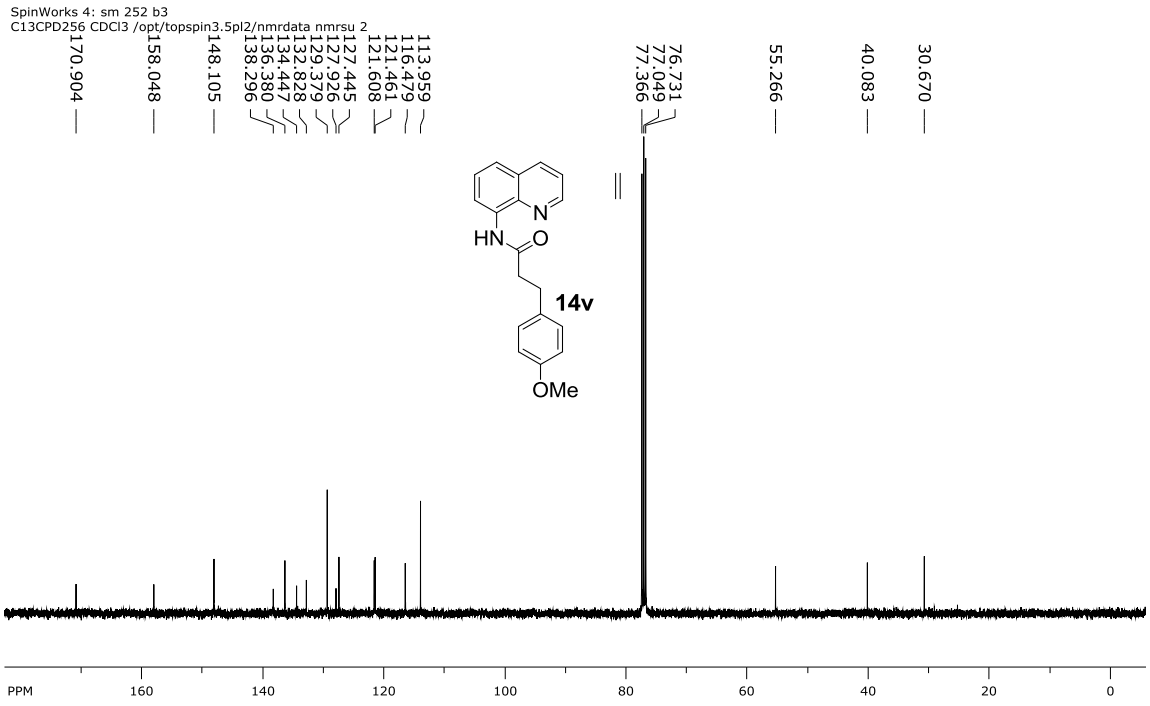

SpinWorks 4: SM 221 A2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 1
9.683
8.770
8.763
8.759
8.753
8.749
8.140
8.119
7.514
7.495
7.484
7.480
6.860
6.838
3.755
1.798
1.772
1.756
1.223
0.902
0.885
0.867
HN
O
OMe
14t
0.999
2.107
1.090
3.346
2.107
2.058
3.255
1.076
2.122
2.457
15.566
3.083
PPM
8
6
4
2
0

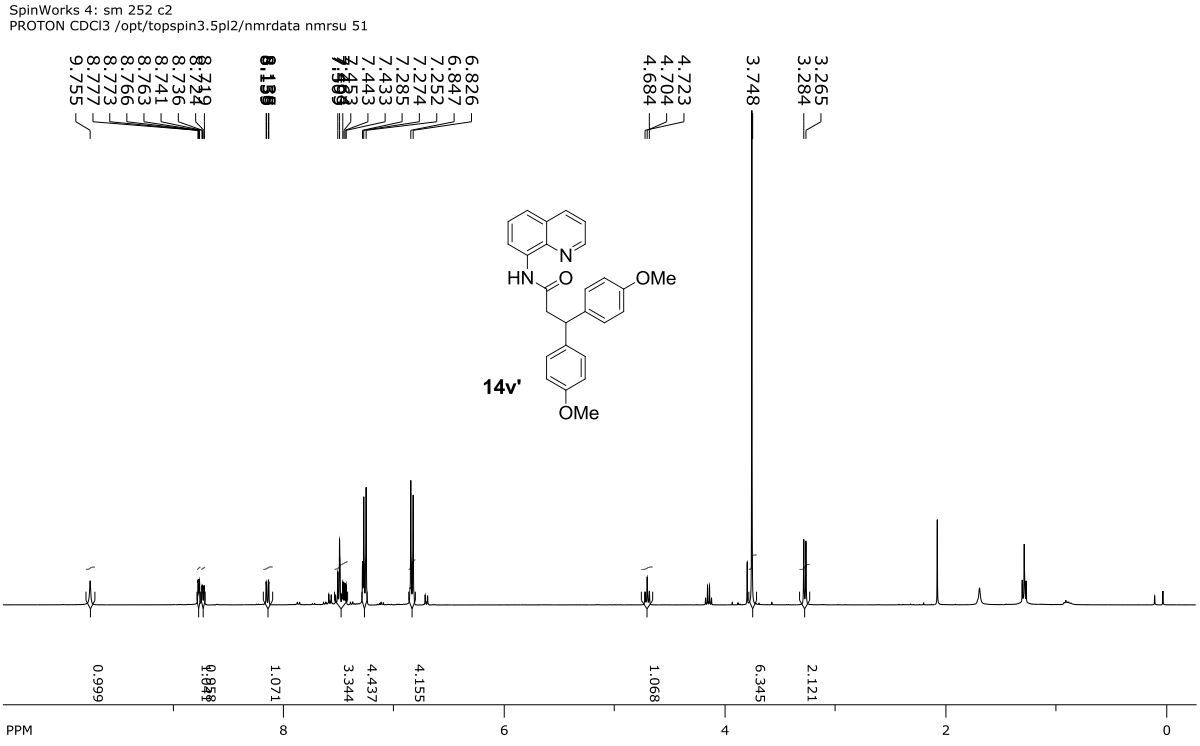

SpinWorks 4: SM 221 A2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 1
170.589
158.040
147.996
138.262
136.403
136.271
134.463
128.446
127.862
127.380
121.527
121.337
116.391
113.903
77.414
77.096
76.779
55.146
46.186
41.876
36.432
31.896
29.597
29.582
29.554
29.314
27.462
22.701
14.162
HN
O
OMe
14t
PPM
160
140
120
100
80
60
40
20
0

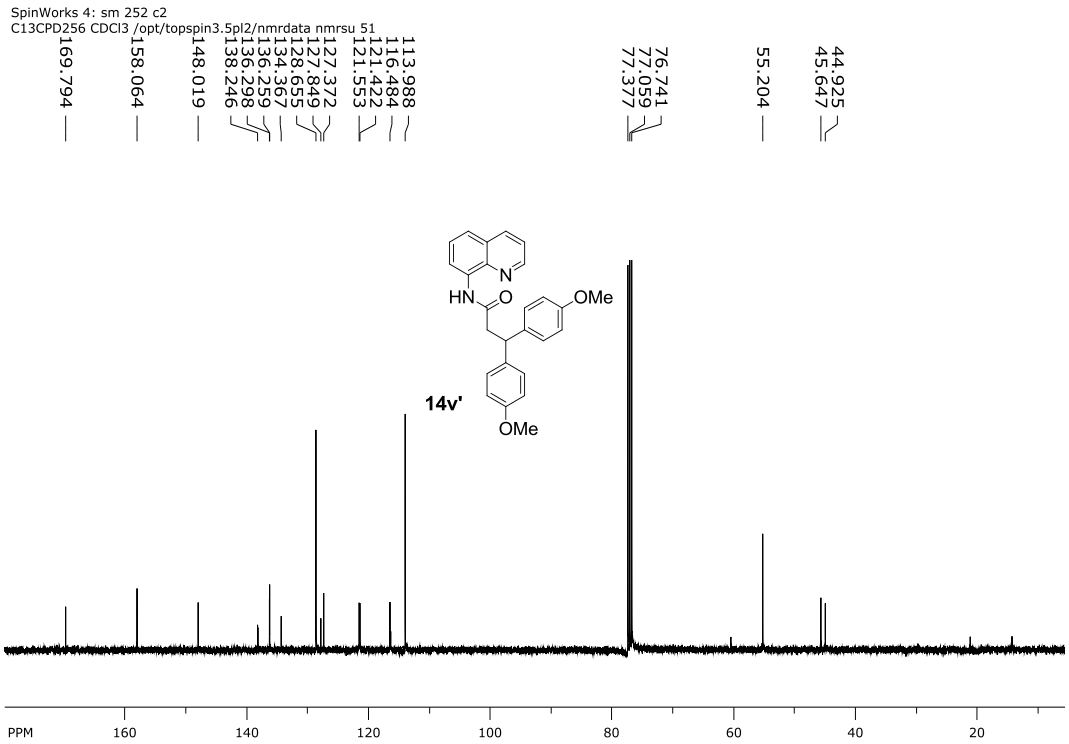

SpinWorks 4: SM 247 A2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 7
9.803
8.780
8.776
8.770
8.766
8.754
8.749
8.131
8.127
8.110
8.106
7.505
7.188
7.206
7.297
4.773
4.792
4.811
3.751
3.317
3.336
HN
O
N
OMe
14u
1.000
2.088
1.060
9.970
1.107
2.005
1.024
3.227
2.048
PPM
10
8
6
4
2

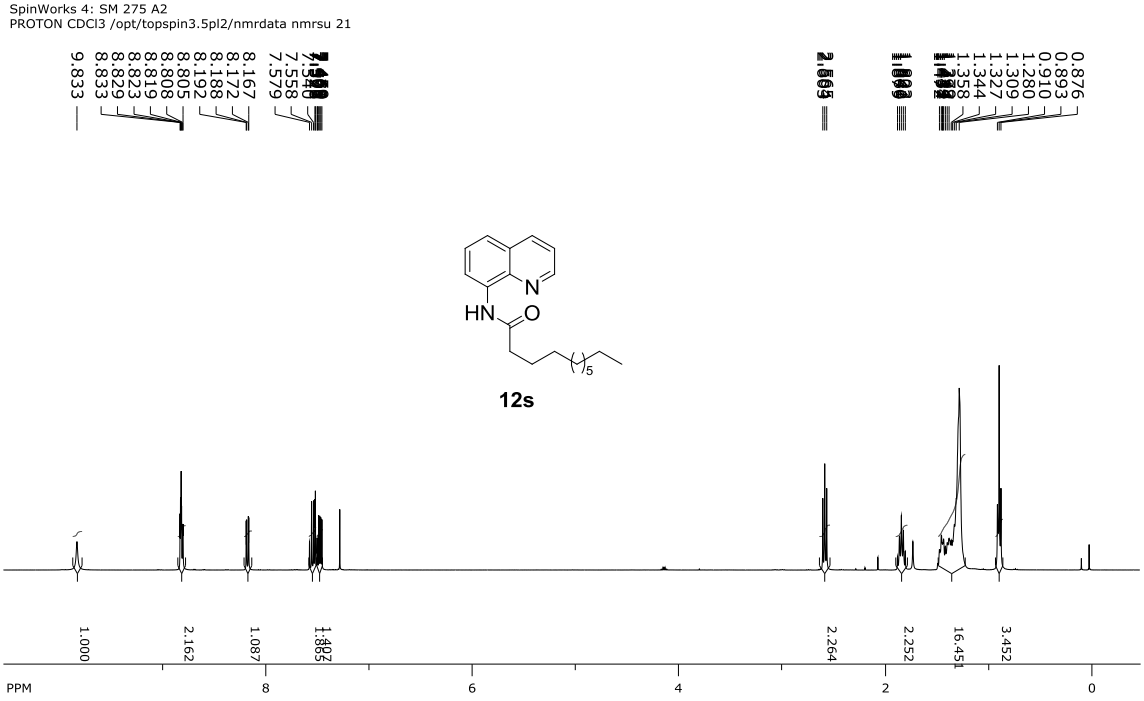

SpinWorks 4: SM 247 A2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 7
169.702
158.158
148.056
144.187
138.237
136.310
135.910
134.369
128.803
128.667
127.855
127.739
127.362
126.475
121.587
121.482
116.497
114.046
77.475
77.158
76.839
55.206
46.433
44.661
HN
O
N
OMe
14u
PPM
160
140
120
100
80
60
40
20
0

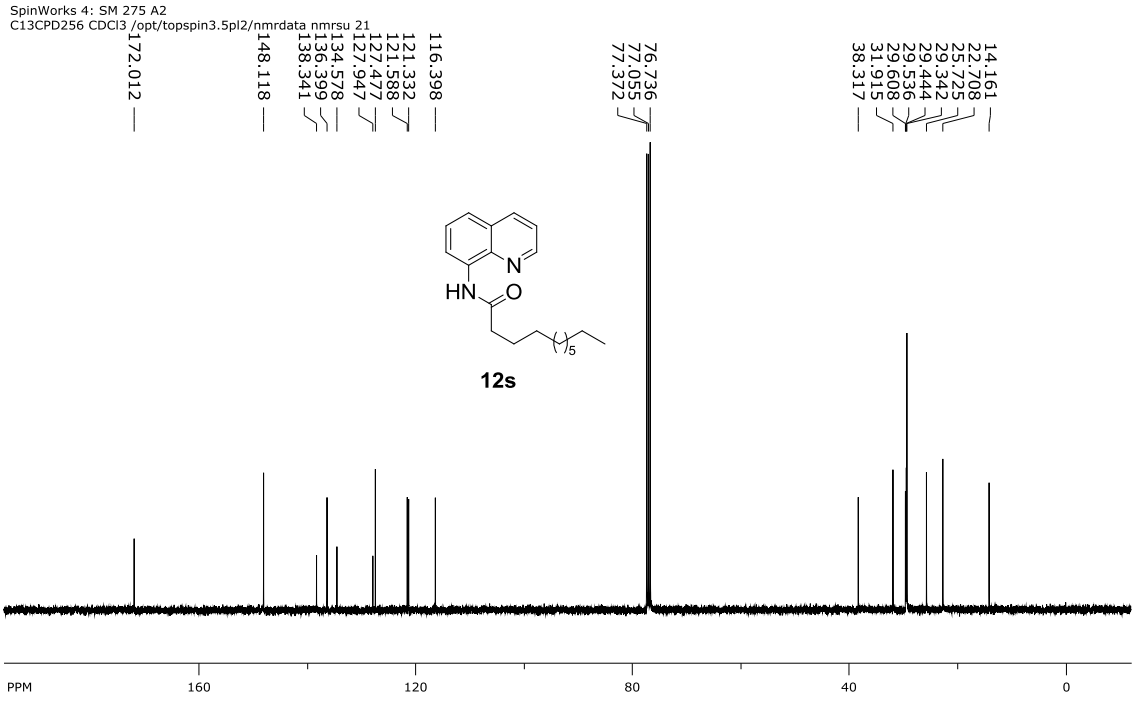

SpinWorks 4: sm 252 b3
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 2
9.801
8.822
8.803
8.800
8.792
8.789
8.190
8.186
8.169
8.165
7.563
7.545
7.532
6.850
6.872
7.231
7.252
7.285
7.453
3.795
3.136
3.117
3.097
2.899
2.878
2.860
HN
O
N
14v
OMe
1.000
2.052
1.046
3.177
2.208
1.706
2.608
1.766
1.765
PPM
10
8
6
4
2
0


SpinWorks 4: sm 252 b3
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 2
170.904
158.048
148.105
138.296
136.380
134.447
132.828
129.379
127.926
127.445
121.608
121.461
116.479
113.959
77.366
77.049
76.731
55.266
40.083
30.670
HN
O
N
14v
OMe
PPM
160
140
120
100
80
60
40
20
0

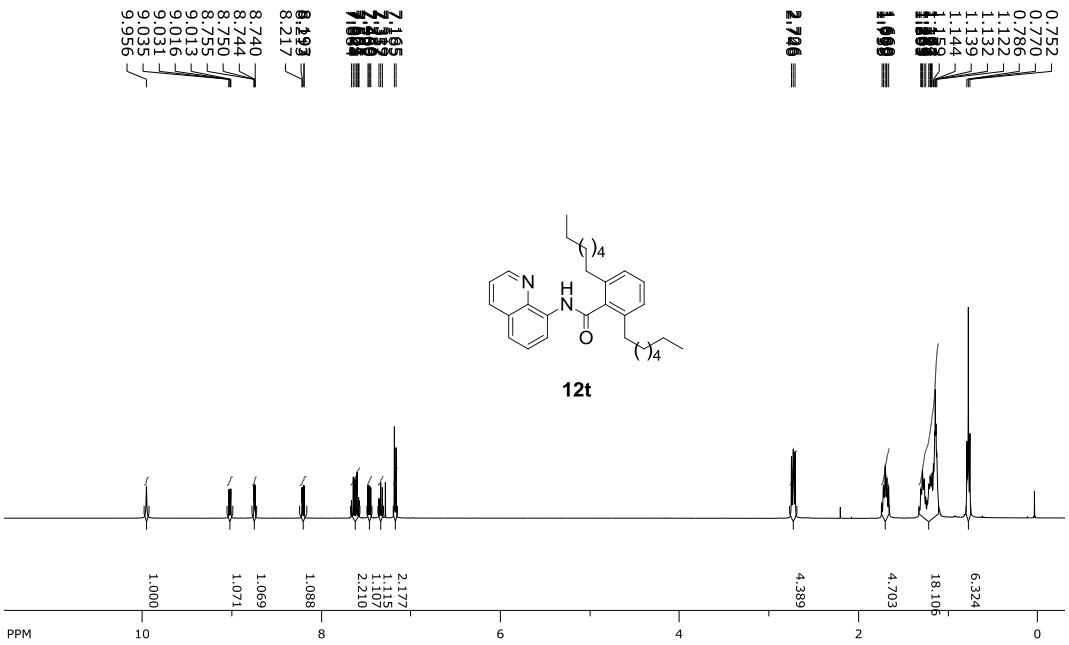

SpinWorks 4: sm 252 c2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 51
9.755
8.777
8.773
8.763
8.766
8.741
8.736
8.724
8.719
6.826
6.847
7.252
7.274
7.285
7.433
7.443
4.684
4.704
4.723
3.748
3.265
3.284
HN
O
N
OMe
OMe
14v'
0.999
1.071
3.344
4.437
4.155
1.068
6.345
2.121
PPM
8
6
4
2
0


SpinWorks 4: sm 252 c2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 51
169.794
158.064
148.019
138.246
136.298
136.259
134.367
128.655
127.849
127.372
121.553
116.484
113.988
77.377
77.059
76.741
55.204
45.647
44.925
HN
O
N
OMe
OMe
14v'
PPM
160
140
120
100
80
60
40
20

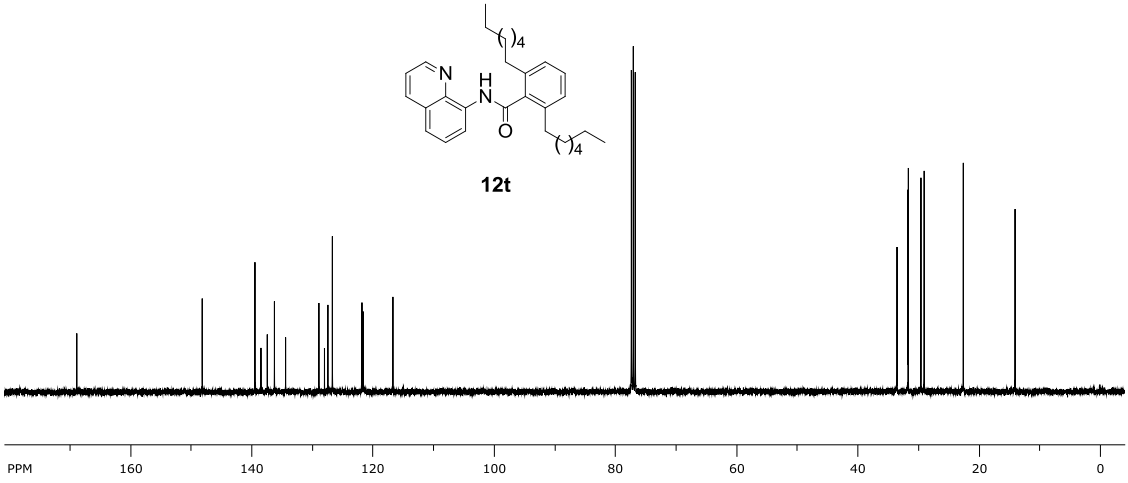

SpinWorks 4: SM 275 A2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 21
9.833
8.833
8.829
8.823
8.819
8.808
8.805
8.192
8.188
8.172
8.167
7.579
7.558
0.876
0.893
0.910
1.280
1.309
1.327
1.344
1.358
HN
O
5
12s
1.000
2.162
1.087
2.264
2.252
16.451
3.452
PPM
8
6
4
2
0

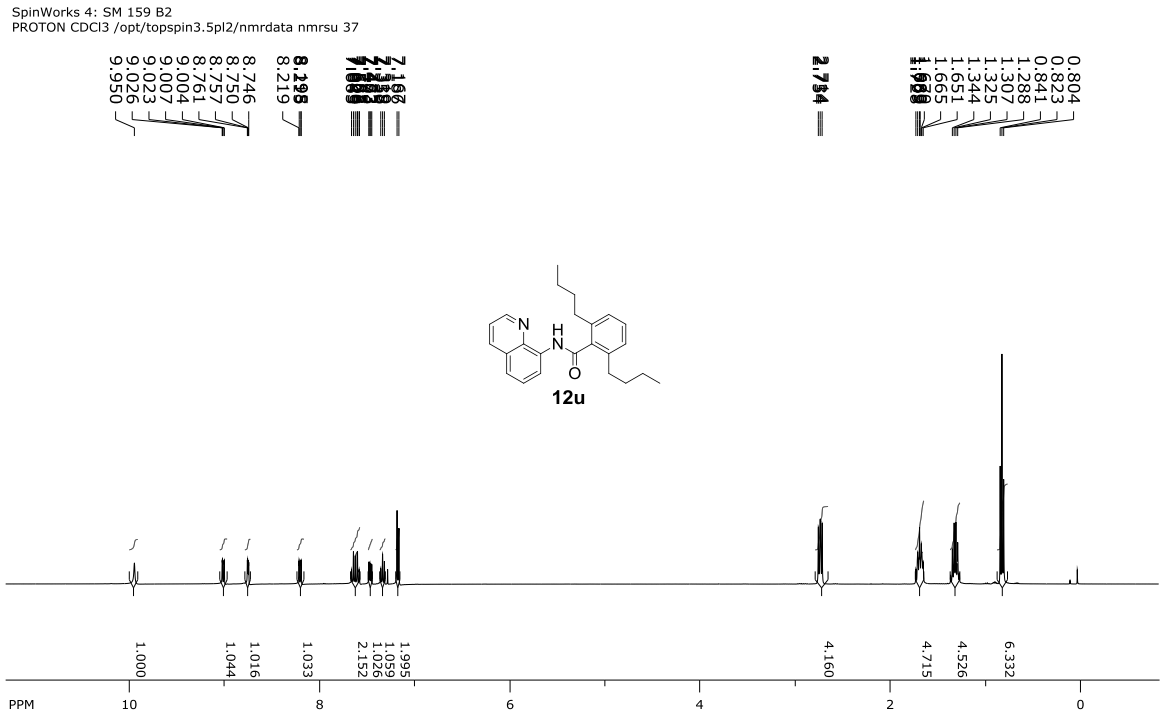

SpinWorks 4: SM 275 A2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 21
172.012
148.118
138.341
136.399
134.578
127.947
127.477
121.588
121.332
116.398
77.372
77.055
76.736
38.317
31.915
29.608
29.536
29.444
29.342
25.725
22.708
14.161
HN
O
5
12s
PPM
160
120
80
40
0

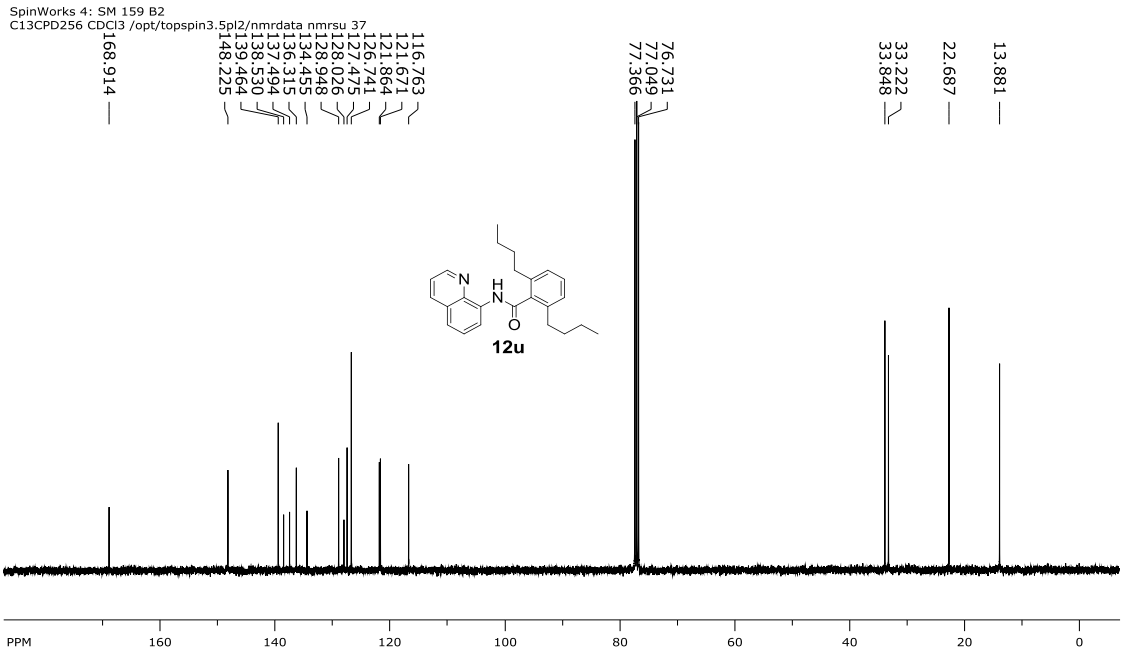
SpinWorks 4: sm 160 b2

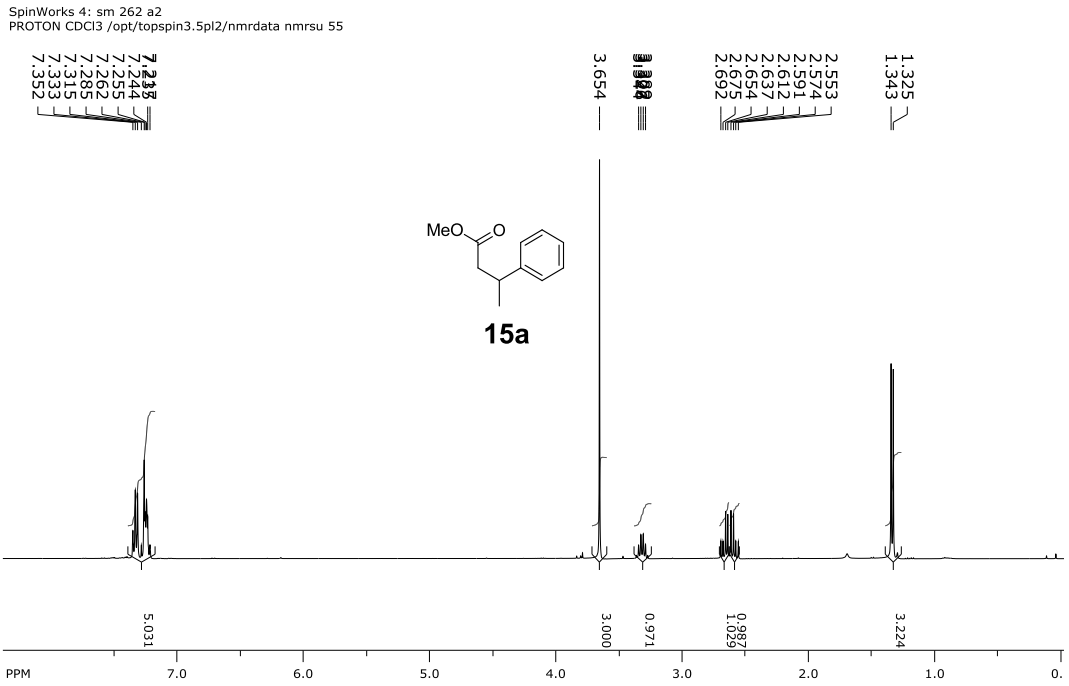


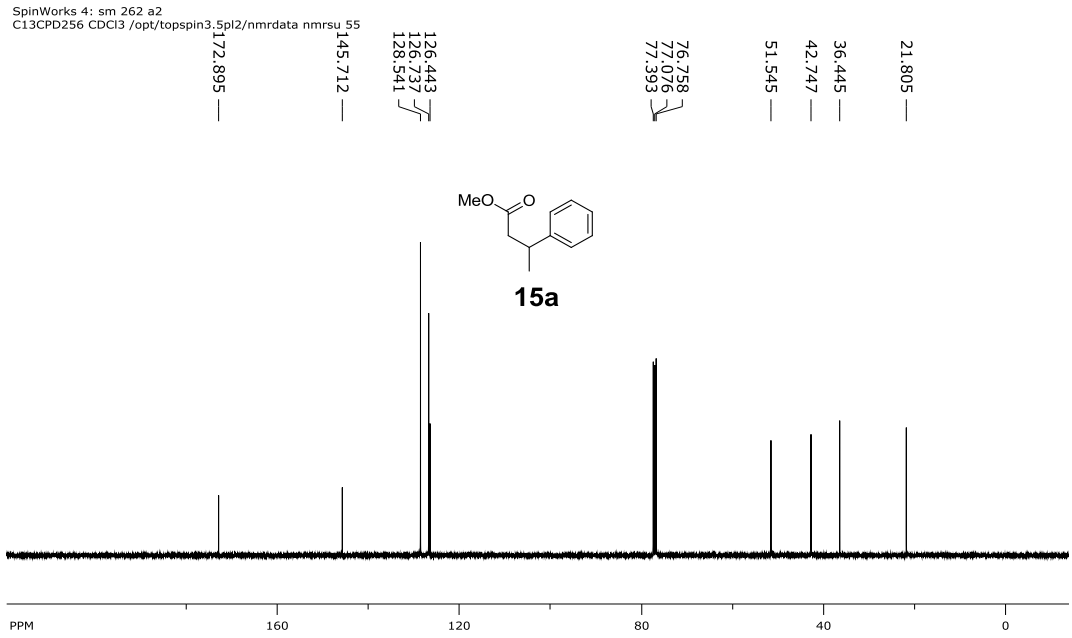
SpinWorks 4: SM 160 B2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 23

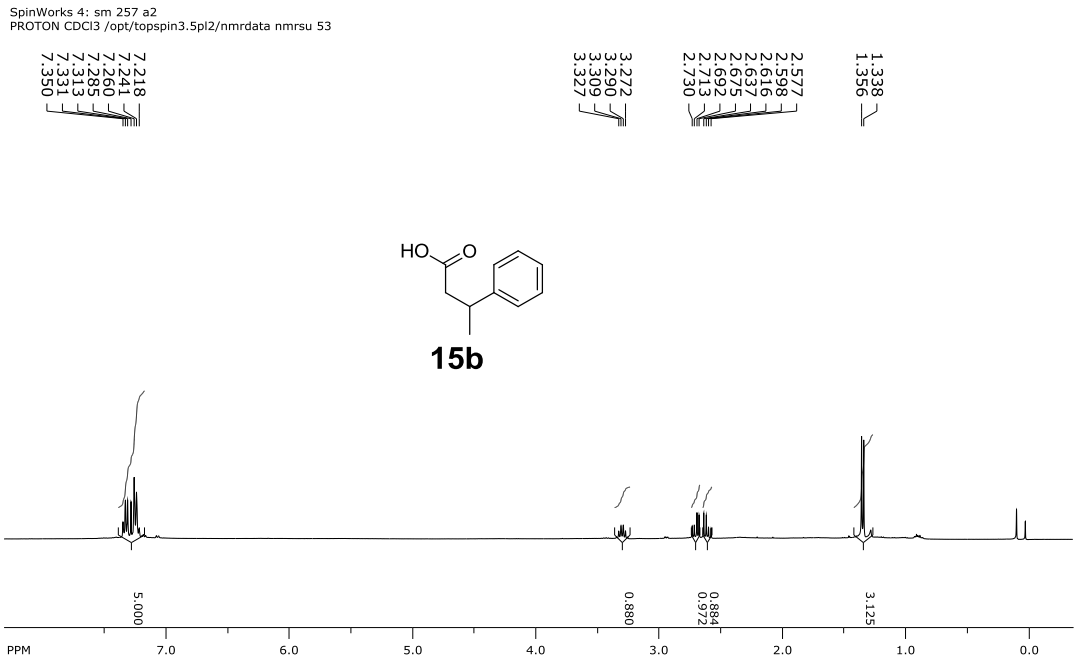


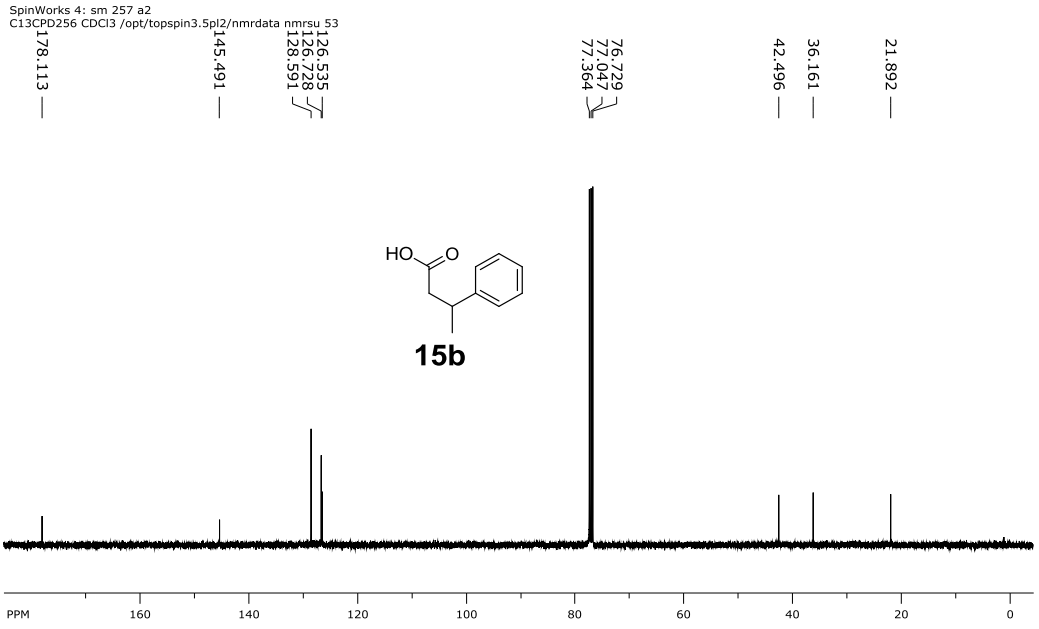

SpinWorks 4: SM 159 B2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 37
9.950
9.026
9.023
9.007
9.004
8.761
8.757
8.750
8.746
8.219
2.714
0.804
0.823
0.841
1.288
1.307
1.325
1.344
1.651
1.665
12u
1.000
1.044
1.016
1.033
2.152
1.026
1.059
1.995
4.160
4.715
4.526
6.332
PPM
10
8
6
4
2
0

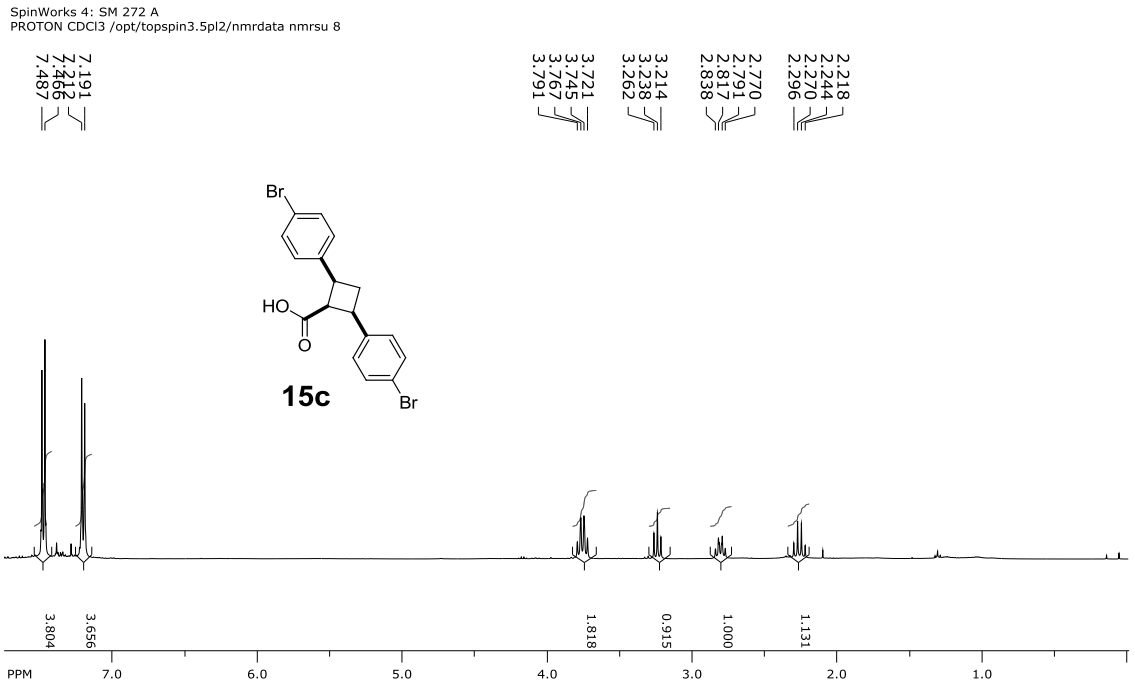

SpinWorks 4: SM 159 B2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 37
168.914
148.225
139.464
138.530
137.494
136.315
134.455
128.948
128.026
127.475
126.741
121.864
121.671
116.763
77.366
77.049
76.731
33.848
33.222
22.687
13.881
12u
PPM
160
140
120
100
80
60
40
20
0

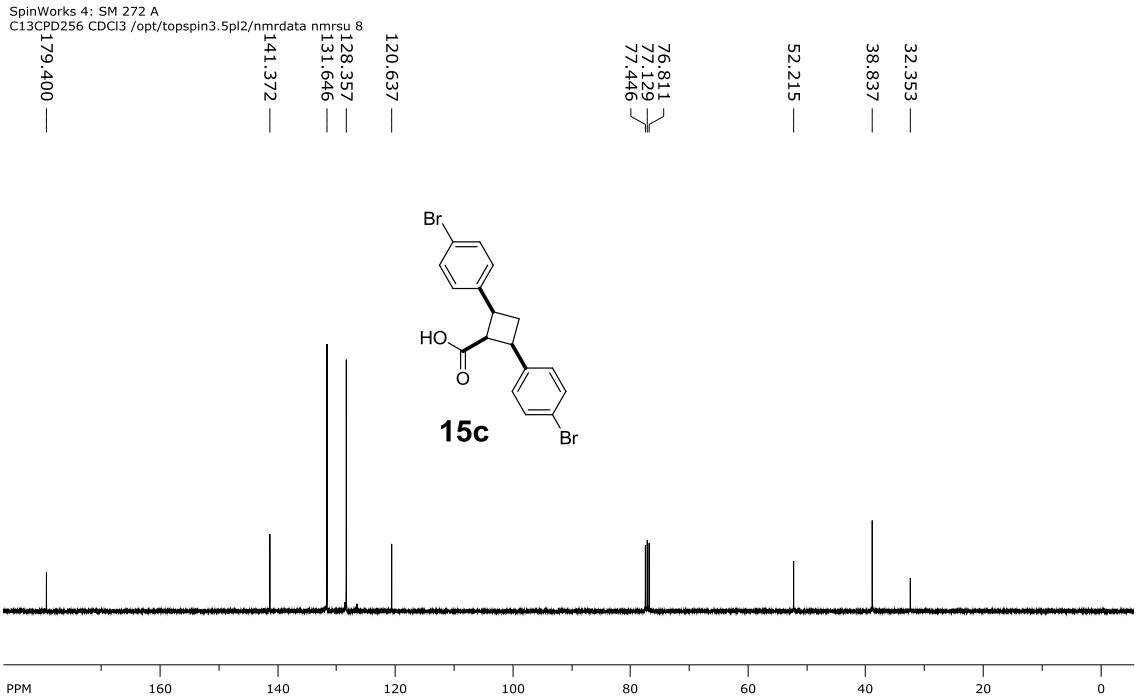

SpinWorks 4: sm 262 a2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 55
7.352
7.333
7.315
7.285
7.262
7.255
7.244
3.654
2.692
2.675
2.654
2.637
2.612
2.591
2.574
2.553
1.343
1.325
MeO
O
15a
5.031
3.000
0.971
0.987
1.029
3.224
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0


SpinWorks 4: sm 262 a2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 55
172.895
145.712
128.541
126.737
126.443
77.393
77.076
76.758
51.545
42.747
36.445
21.805
MeO
O
15a
PPM
160
120
80
40
0


SpinWorks 4: sm 257 a2
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 53
7.350
7.331
7.313
7.285
7.260
7.241
7.218
3.327
3.309
3.290
3.272
2.730
2.713
2.692
2.675
2.637
2.616
2.598
2.577
1.356
1.338
HO
O
15b
5.000
0.880
0.884
0.972
3.125
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


SpinWorks 4: sm 257 a2
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 53
178.113
145.491
128.591
126.728
126.535
77.364
77.047
76.729
42.496
36.161
21.892
HO
O
15b
PPM
160
140
120
100
80
60
40
20
0


SpinWorks 4: SM 272 A
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 8
7.487
7.466
7.212
7.191
3.791
3.767
3.745
3.721
3.262
3.238
3.214
2.838
2.817
2.791
2.770
2.296
2.270
2.244
2.218
Br
HO
O
Br
15c
3.804
3.656
1.818
0.915
1.000
1.131
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0


SpinWorks 4: SM 272 A
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 8
179.400
141.372
131.646
128.357
120.637
77.446
77.129
76.811
52.215
38.837
32.353
Br
HO
O
Br
15c
PPM
160
140
120
100
80
60
40
20
0