SYNTHETIC STUDIES OF NITROGEN CONTAINING BIOACTIVE ORGANIC COMPOUNDS AND THEIR ANALOGUES

A Thesis submitted to Goa University for the Award of the Degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

By

Mr. HARI K. KADAM

GOA UNIVERSITY

Taleigao Plateau, Goa

2014

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Research Guide

PROF. SANTOSH G. TILVE

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GOA UNIVERSITY

Taleigao Plateau, Goa

2014

DEPARTMENT OF CHEMISTRY

CERTIFICATE

This is to certify that the thesis entitled, "**SYNTHETIC STUDIES OF NITROGEN CONTAINING BIOACTIVE ORGANIC COMPOUNDS AND THEIR ANALOGUES**" submitted by Mr. **HARI K. KADAM**, is a record of research work carried out by the candidate during the period of study under my supervision and that it has not previously formed the basis for the award of any degree or diploma or other similar titles.

Goa University
June 2014

Prof. Santosh G. Tilve
Research Guide and Head
Department of Chemistry
Goa University

DECLARATION

I hereby declared that the work embodied in the thesis entitled "**SYNTHETIC STUDIES OF NITROGEN CONTAINING BIOACTIVE ORGANIC COMPOUNDS AND THEIR ANALOGUES**" is the result of investigations carried out by me under the guidance of **PROF. SANTOSH G. TILVE** at Department of Chemistry, Goa University and that it has not previously formed the basis for the award of any degree or diploma or other similar titles.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Goa University
June 2014

Mr. Hari K. Kadam
Ph.D. Student
Department of Chemistry
Goa University

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Finally with silent words I thank God for the energy, health and life so far and in future.

....**Hari K. Kadam**

DEDICATED TO

MY PARENTS

TABLE OF CONTENT

GENERAL REMARKS

- ✓ The compound numbers, figure numbers, scheme numbers and reference numbers given in each chapter refer to that particular chapter only.
- ✓ Commercial reagents were used without further purification.
- ✓ Solvents were distilled prior to use and dried if necessary using standard procedures.
- ✓ Petroleum ether refers to the hydrocarbon fraction collected in the boiling range 60 - 80 °C.
- ✓ Microwave reactions were carried out using Milestone Start-Synth microwave instrument.
- ✓ Thin layer chromatography (TLC) were carried out on Silica gel 60 F254 aluminium plates purchased from Merck and were developed in iodine or UV chamber.
- ✓ GC analyses were done on Nucon 5765 Gas chromatograph instrument with HP-5 column, N_2 as carrier gas and FI detector.
- ✓ Chromatographic purification was conducted by column chromatography using silica gel (60-120 mesh size) or by flash chromatography using silica gel (230-400 mesh size) on Combiflash Companion instrument.
- ✓ All melting points and boiling points were recorded using Thiele's tube and are uncorrected.
- ✓ IR spectra were recorded on Shimadzu FT-IR spectrophotometer.
- ✓ ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AVANCE 400 MHz instrument and the multiplicities of carbon signals were obtained from DEPT experiment.
- ✓ High resolution mass spectra (HRMS) were recorded on MicroMass ES-QTOF mass spectrometer. LCMS were recorded on Agilent Technologies instrument and GCMS on a Varian GC/MS instrument.
- ✓ CHNS analyses were performed on Elementar CHNS analyser instrument.

ABBREVIATIONS

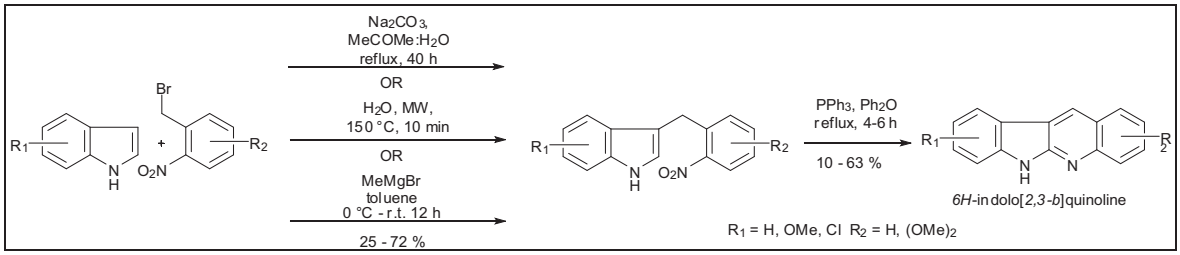
General Abbreviations		*Compound Abbreviations*		*Spectroscopic Abbreviations*	
g	Gram/s	Ac	Acetyl	IR	Infrared
mg	Milligram/s	Ac_2O	Acetic anhydride	υ_{max}	Frequency maximum
mmol	Millimole	Ts	*p*-Toluene sulfonyl	cm^{-1}	Frequency in wavenumber
mL	Milliliter	Ar	Aryl	UV	Ultra violet
m.p.	Melting point	Boc	tert-Butyl carbonyl	MHz	Megahertz
b.p.	Boiling point	Bn	Benzyl	Hz	Hertz
dil.	Dilute	Bz	Benzoyl	*J*	Coupling constant
lit.	Literature	t-Bu	tert-Butyl	br s	Broad singlet
d	Day/s	TFA	Trifluoro acetic acid	ppm	Parts per million
h	Hour/s	TFAA	Trifluoro acetic anhydride	$CDCl_3$	Deuterated chloroform
min	Minute/s	AcOH	Acetic acid	s	Singlet
sec	Second/s	MeOH	Methanol	d	Doublet
Z	Zussamen (together)	EtOH	Ethanol	t	Triplet
E	Eentegegen (opposite)	*m*-CPBA	*m*-Chloroperbenzoic acid	q	Quartet
R	Rectus	*p*-TsOH	*p*-Toluene sulfonic acid	m	Multiplet
S	Sinister	DMSO	Dimethyl sulfoxide	dd	Doublet of doublet
Fig.	Figure	DMF	N,N-Dimethylformamide	δ	Chemical shift in ppm
conc.	Concentrated	THF	Tetrahydrofuran	*m/z*	Mass to charge ratio
glac.	Glacial	Et	Ethyl	M^+	Molecular ion
sat.	Saturated	Me	Methyl	$CDCl_3$	Deuterated chloroform
aq.	Aqueous	LDA	Lithium diisopropylamide	DMSO-d_6	Deuterated dimethyl sulfoxide
anhyd.	Anhydrous	Py	Pyridine		
°C	Degree Celcius	TBHP	tert-Butyl hydroperoxide	HRMS	High Resolution Mass Spectrum
hυ	Irradiation	EtOAc	Ethyl acetate		
%	Percentage	n-BuLi	n-Butyl lithium	DEPT	Distortionless Enhancement by Polarization Transfer
r.t.	Room temperature	t-BuOK	Potassium tertiary butoxide		
Expt.	Experiment	PMB	*p*-Methoxybenzyl		
Temp.	Temperature	Ph	Phenyl	NMR	Nuclear magnetic resonance
MW	Microwave	MOM	Methoxymethyl ether		
o	Ortho	Ms	Methane sulfonyl		
m	Meta	TMS	Trimethylsilyl		
p	Para	TMSCN	Cyanotrimethyl silane		
MS	Molecular sieves	PPA	Polyphosphoric acid		
cat.	Catalytic	CAN	Cerric ammonium nitrate		
atm.	Atmospheric	NBS	N-Bromosuccinimide		
et al.	Et alia (and others)	DMP	Dess-Martin periodinane		
psi	Pounds per square inch	Boc_2O	tert-Butyl dicarbonate		
		Pet. ether	Petroleum ether		
TLC	Thin layer chromatography	TsCl	Tosyl chloride		
		AIBN	Azobisisobutyronitrile		
		DMAP	*4*-Dimethyl amino pyridine		
		HMPA	Hexamethylphosphoramide		
		DIAD	Diisopropyl azodicaboxylate		
		DCC	Dicyclohexyl cabodiimide		
		TBAF	Tetrabutylammonium fluoride		
		TBAF	Tetrabutyl ammonium fluoride		
		LAH	Lithium aluminium hydride		
		DIBALH	Diisobutyl aluminium hydride		
		DDQ	*2,3*-Dichloro-*5,6*-dicyanobenzoquinone		
		Pd/C	Palladium on activated charcoal		
		i-PrOH	Iso-propanol		

ABSTRACT OF THESIS

TITLE: **SYNTHETIC STUDIES OF NITROGEN CONTAINING BIOACTIVE ORGANIC COMPOUNDS AND THEIR ANALOGUES**

Nitrogen containing organic compounds are widely studied in chemistry because of their applications in diverse biological fields like pharmaceutical drugs, agro-chemicals, cosmetics, nutrients, etc. and frequent natural occurrences. The thesis is divided into four chapters.

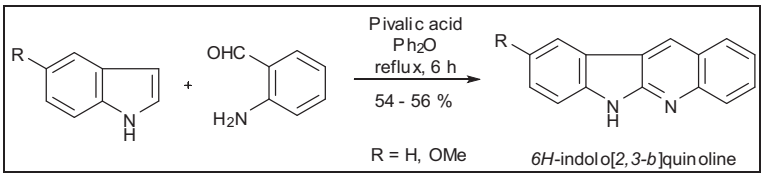
The ***First*** chapter presents a concise two step method for the synthesis of *6H*-indolo[*2,3-b*]quinoline employing indole C-3 alkylation followed by tandem reductive cyclisation – oxidation reaction (Scheme 1). Alkylation of indole was studied by three different routes to achieve maximum yield including the use of microwave irradiation to accelerate the alkylation selectively at C-3 position of indole. Several substituted indoloquinolines were prepared with substituent on both the rings i.e. indole as well as quinoline ring of indoloquinoline.



Scheme 1

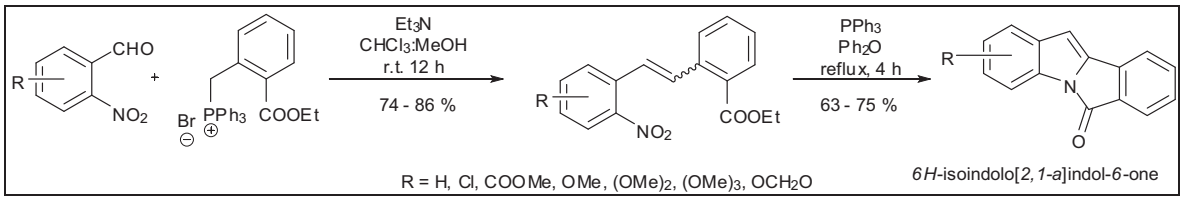
This chapter also describes a pivalic acid assisted one-pot synthesis of indoloquinoline using indole and *o*-aminobenzaldehyde as starting materials. This approach exploits a tandem alkylation - dehydration - cyclisation - aromatisation sequence (Scheme 2). The methodology was optimized to achieve the maximum yield and applied to prepare an analogue of indoloquinoline. A probable mechanism for the tandem one-pot process is also presented.

These two methods constitute the formal synthesis of alkaloid neocryptolepine.



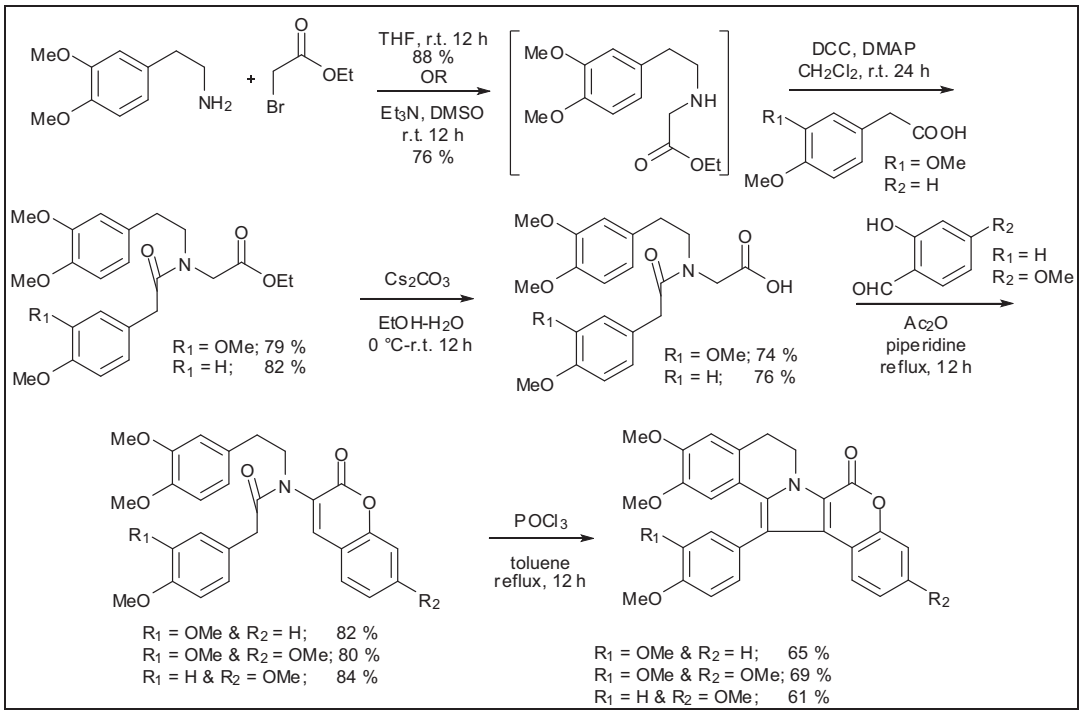
Scheme 2

The ***Second*** chapter deals with our efforts in developing a simple and efficient two step route to *6H*-isoindolo[*2,1-a*]indol-*6*-ones starting from *o*-nitrobenzaldehydes. Here we employed Wittig reaction to prepare stilbenes with required functionalities and then subjected these to tandem reductive cyclisation – lactamisation reaction to finally give isoindoloindolones (Scheme 3). A series of isoindoloindolones incorporating various electron withdrawing as well as electron donating substituent on indole nucleus have been prepared.



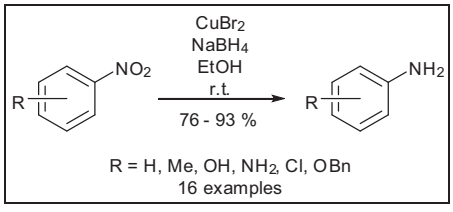
Scheme 3

The ***Third*** chapter describes with our efforts to devise a novel, simple and efficient method for the synthesis of lamellarin skeleton. Several different approaches were studied for the synthesis of lamellarin scaffold. Finally the lamellarin scaffold was successfully synthesised using a multi step route involving Perkin reaction followed by a tandem Bischler-Napieralski reaction – Michael reaction – oxidation sequence (Scheme 4). This chapter also describes our efforts towards synthesis of the ningalin A skeleton.



Scheme 4

The ***Fourth*** chapter presents a comprehensive review of green methods available in literature for reduction of nitroarenes. This chapter also describes our protocol for nitro-reduction using $CuBr_2$ as a procatalyst and sodium borohydride as reducing agent which involves *in situ* generation of active Cu nanoparticles and use them simultaneously for reduction of nitroarenes (Scheme 5).



Scheme 5

PUBLICATIONS

Publications in International & National Journals:

1. MoO_2Cl_2: Versatile Catalyst for Organic Reactions, **Hari K. Kadam**, *Synlett* (spotlight), **2014**, *25*, 1793.
2. An alternate synthesis of *6H*-Indolo[*2,3-b*]quinoline via one-pot Alkylation-Dehydration Cyclisation-Aromatization approach, **Hari K. Kadam** and Santosh G. Tilve, *J. Heterocyclic Chem.* **2014**, accepted.
3. Intramolecular Diels-Alder reaction as a key step in tandem or sequential processes: A versatile tool for the synthesis of fused and bridged bicyclic or polycyclic compounds, (Review) Prakash T. Parvatkar, **Hari K. Kadam** and Santosh G. Tilve, *Tetrahedron*, **2014**, *70*, 2857.
4. Synthesis of *6H*-Isoindolo[*2,1-a*]indol-*6*-ones through Wittig Reaction and Tandem Reductive Cyclization–Lactamization, **Hari K. Kadam** and Santosh G. Tilve, *Eur. J. Org. Chem.* **2013**, 4280.
5. Graphite catalyzed green synthesis of quinoxalines, **Hari K. Kadam**, Salman Khan, Rupesh A. Kunkalkar and Santosh G. Tilve, *Tetrahedron Lett*. **2013**, *54*, 1003.
6. Copper(*II*) bromide as a procatalyst for in situ preparation of active Cu nanoparticles for reduction of nitroarenes, **Hari K. Kadam** and Santosh G. Tilve, *RSC Advances*, **2012**, *2*, 6057.
7. A concise synthesis of *6H*-indolo[*2,3-b*]quinolines: Formal synthesis of neocryptolepine (cryptotackieine), **Hari K. Kadam**, Prakash T. Parvatkar and Santosh G. Tilve, *Synthesis*, **2012**, *44*, 1339.
8. Synthesis of *2,2'*-Biindole: Formal Synthesis of Arcyriaflavin-A and Staurosporinone (K-252c), P. T. Parvatkar, **H. K. Kadam**, P. S. Parameswaran and S. G. Tilve, *Asian J. Chem*. **2012**, *24*, 2213.
9. Synthesis and Anti-microbial studies of (*E*)-*4*-Oxoalk-*2*-enoic acids, Reshma Kurangi, **Hari Kadam**, Santosh Tilve and Savita Kerkar, *J. Chem. Pharm. Res*. **2010**, *2*, 83.
10. Convergent synthetic route for Lamellarin scaffold, **Hari K. Kadam** and Santosh G. Tilve, *Manuscript communicated for publication*.
11. Advancement in green methodologies for reduction of nitroarenes, (Review) **Hari K. Kadam** and Santosh G. Tilve, *Manuscript communicated for publication*.

Conferences Attended & Poster Presentation:

1. Presented poster entitled "Synthesis and antimicrobial studies of (*E*)-Oxoalkenoic Acids" at RSC-West India Section Ph.D. Students Symposium in Goa University, Goa (3rd - 4th September 2010).
2. Presented poster entitled "Concise Synthetic Approach Towards Indoloquinolines" at National Conference on Recent Trends in Organic Synthesis in Bharathidasan University, Tamilnadu (24th -26th February 2011).
3. Participated in the two days symposium entitled "Chemistry in Human Well-being: Emerging Opportunities and Challenges" in Goa University, Goa (4th – 5th March 2011).
4. Participated in the J-NOST Conference for Research Scholars in IISER-Mohali, Punjab (15th - 18th December 2011).
5. Participated in the 3-day conference on Chemical (Industrial) Disaster Management (CIDM): Chemical, Pharmaceutical and hydrocarbon Industry in Cidade De Goa, Goa (16th -18th April 2013).
6. Presented poster entitled "Exploring Reductive Cyclisation for synthesis of *6H*-indolo[*2,3 b*]quinolines and *6H*-isoindolo[*2,1-a*]indol-*6*-ones" at J-NOST Conference for Research Scholars in IISER-Bhopal, Madhya Pradesh (4th – 6th December 2013).

Chapter 1

Synthetic Studies of *6H*-Indolo[*2,3-b*]quinolines

1.1: Introduction

Indoloquinoline alkaloids are well known for their natural occurrence and diverse biological activities.[1] *6H*-Indolo[*2,3-b*]quinoline **1**, also known as quinindoline or norcryptotackeine was isolated from leaves of *Justicia betonica*[2] along with *5H*-indolo[*2,3-b*]quinolin-*11(6H)*-one **2** (Figure 1). Quinindoline **1** is a recognised precursor of well known alkaloid *5*-methyl-*5H*-indolo[*2,3-b*]quinoline **3** named as Neocryptolepine or Cryptotakeine isolated from roots of West African plant *Cryptolepis sanguinolenta*.[3]

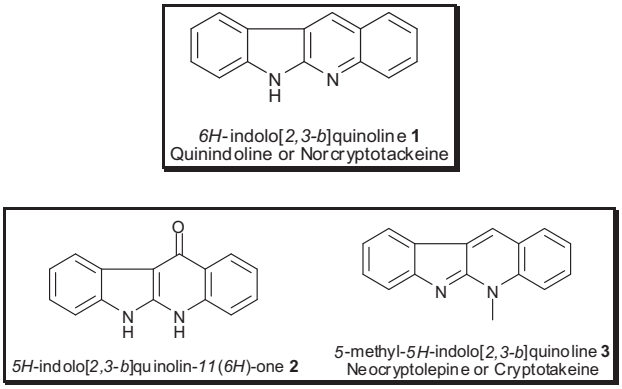


Figure 1: Naturally occurring indolo[*2,3-b*]quinolines.

Other naturally occurring appended indole and quinoline skeletons isolated from *C. sanguinolenta* [4] are *5*-methyl-*5H*-indolo[*3,2-b*]quinoline **4**, *5*-methyl-*5H*-indolo[*3,2-c*]quinoline **5**, and *5*-methyl-*5H*-indolo[*3,2-b*]quinolin-*11(10H)*-one **6** (Figure 2). *5*-Methyl-*5H*-indolo[*3,2-b*]quinoline **4** named as cryptolepine was initially isolated from *C. triangularis.*[1] *5*-Methyl-*5H*-indolo[*3,2-c*]quinoline **5** named as isocryptolepine or cryptosanguinolentine was simultaneously and independently isolated by two groups from same source *C. sanguinolenta*. [1,4]

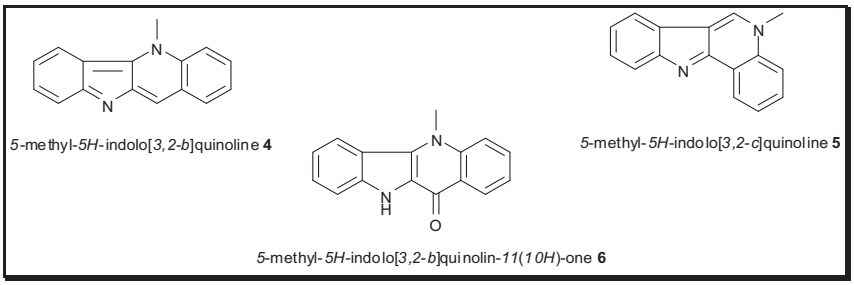


Figure 2: Other naturally occurring inqoloquinolines.

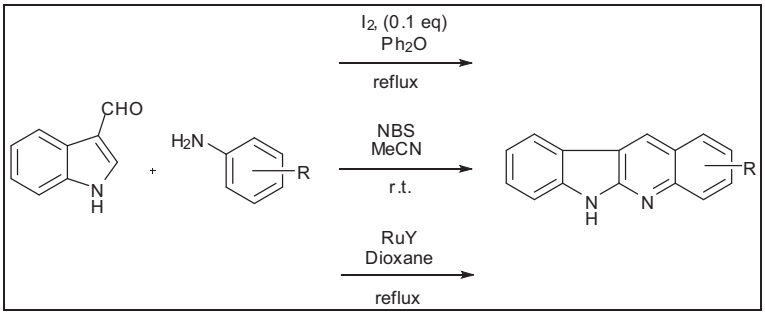
Decoction of *C. sanguinolenta* was used in the past for the treatment of infectious diseases, fever and malaria. This made the isolated alkaloids a subject of intense biological screening and these invariably proved to be medicinally important compounds.[5] Neocryptolepine **3** and cryptolepine **4** exhibited *in vitro* and *in vivo* antiplasmodial activity against chloroquine-resistant *Plasmodium*

falciparum.[5a] Neocryptolepine **3** showed antibacterial activity against gram positive bacteria and also inhibited the growth of the yeast *Candida albicans*.[5b] Many methyl derivatives of neocryptolepine **3** displayed antibacterial activity, antimycotic activity, *in vitro* cytotoxic activity, *in vivo* antitumor properties and DNA topoisomerase II inhibition property.[5c-f] Many synthetic derivatives of neocryptolepine **3** and cryptolepine **4** displayed *in vitro* inhibition of β-haematin formation[5g-h] in cell-free systems indicating a potential mechanism for their antiplasmodial activity. Substituted neocryptolepine derivatives also exhibited antitrypanosomal activity.[5i] Antiproliferative study on human hepatocellular carcinoma HepG2 and Human breast carcinoma MCF-7 cells revealed methyl substituted *6H*-indolo[*2,3-b*]quinolines to be most active.[5j] Aminosubstituted neocryptolepine derivatives exhibited antischistosomicidal activity.[5k]

1.2: Literature synthetic methods

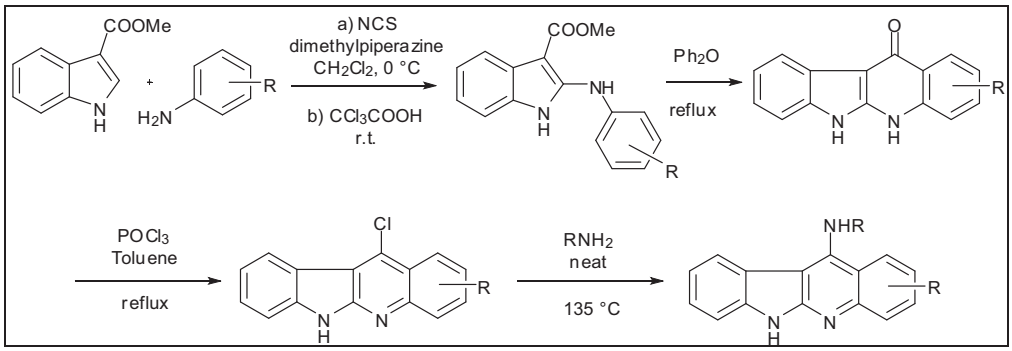
Immense potential biological applications have motivated many synthetic chemists to develop methodologies for its preparations through diverse approaches.[6] Recent examples are depicted here.

Our group had developed a one-pot synthesis of indoloquinoline (Scheme 1) by reaction of indole-3-carboxaldehyde and aryl amines in presence of iodine as a catalyst in refluxing diphenylether.[7a] This process involves iodine catalysed sequential imination, nucleophilic addition and annulations reactions. Thereafter Vaghei and Malaekehpoor[7b] reported NBS as catalyst instead of iodine for this reaction at room temperature and synthesized various substituted indoloquinolines. A recyclable heterogenous Ru catalyst is also reported by Khorshidi A. and Tabatabaeian K.[7c] for this reaction.



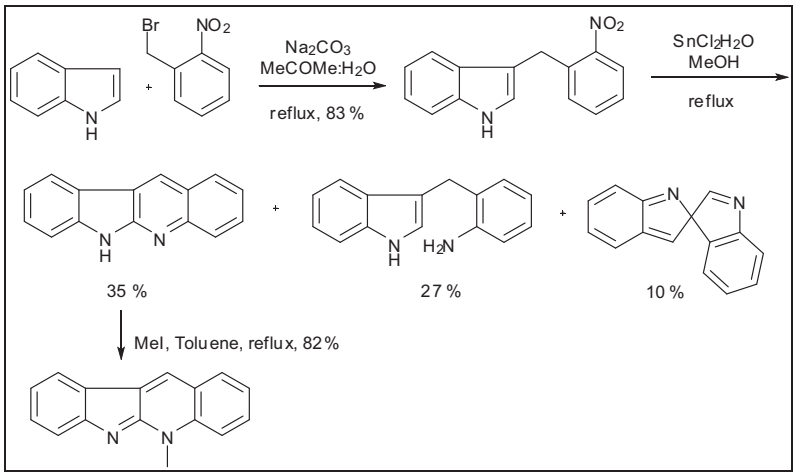
Scheme 1

Sayed *et al*.[8] has developed a route using anilines and methyl indole-3-carboxylate (Scheme 2). They were condensed to methyl indole-2-phenylamino-3-carboxylate by using NCS and dimethylpiperazine followed by treatment with trichloroacetic acid. This anilinocarboxylate was then cyclised to indoloquinolone and chlorinated by $POCl_3$ to get 11-chloronorcyptotackeine. Further heating with amine gave 11-aminonorcryptotackiene.

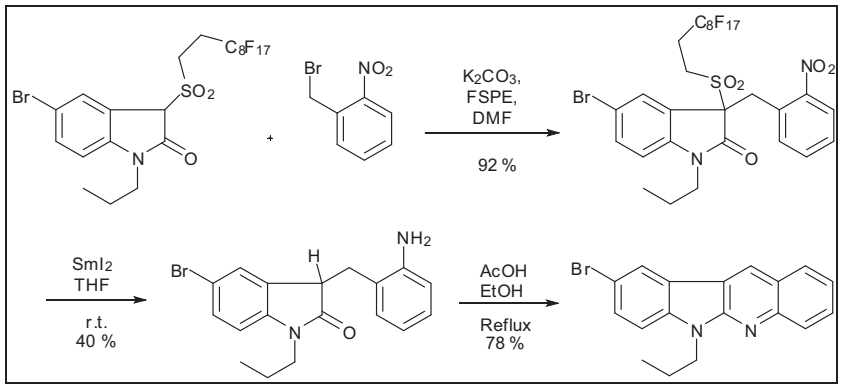


Scheme 2

Stannous chloride mediated intramolecular cyclisation of *o*-nitrobenzylindole was explored by Sharma and Kundu[9] to prepare indoloquinoline (Scheme 3). The precursor was obtained by C-3 benzylation of indole. Uncyclised reduction product and spiro-compound was also obtained along with the desired indoloquinoline.



Scheme 3

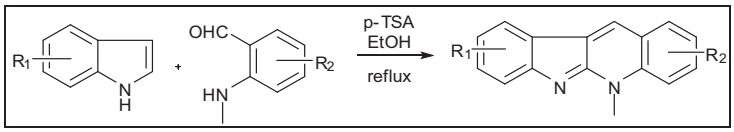


Scheme 4

Procter's group[10] developed a samarium iodide mediated linker cleavage and nitro reduction technique for synthesis of indoloquinoline (Scheme 4). Alkylation of fluorous-tagged oxindole with o-nitrobenzyl bromide and purification with fluorous solid-phase extraction (FSPE) technique

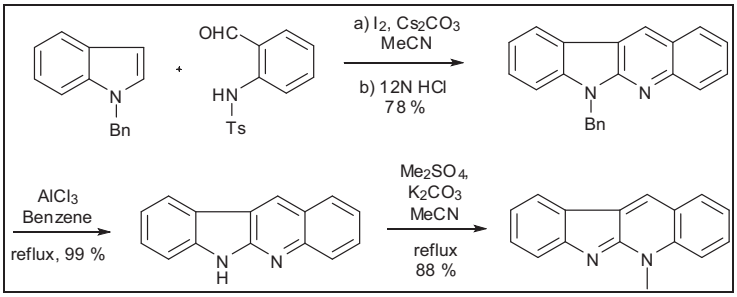
followed by treatment with SmI_2 resulted in sequential removal of the fluorous tag and reduction of aryl nitro group to give anilino-substituted oxindole. Further acid mediated cyclization gave indoloquinoline.

Seidel's group[11] explored a divergent reaction of indole with N-methyl-*2*-aminobenzaldehyde using *p*-TSA to get directly neocryptolepine (Scheme 5).



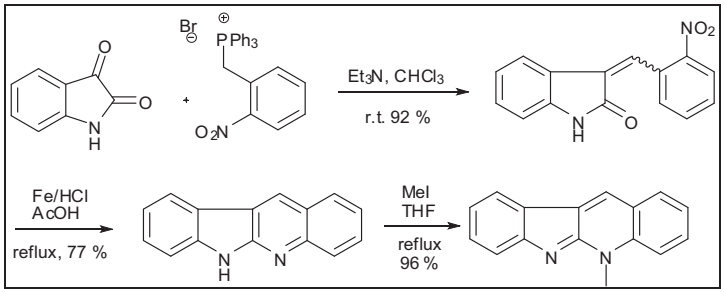
Scheme 5

Similarly Liang's group[12] exploited a metal free iodine mediated selective difunctionalization of indoles by Friedel-Craft alkylation with *2*-tosylaminobenzaldehyde to give benzylindoloquinoline (Scheme 6). This was then debenzylated to indoloquinoline by $AlCl_3$.



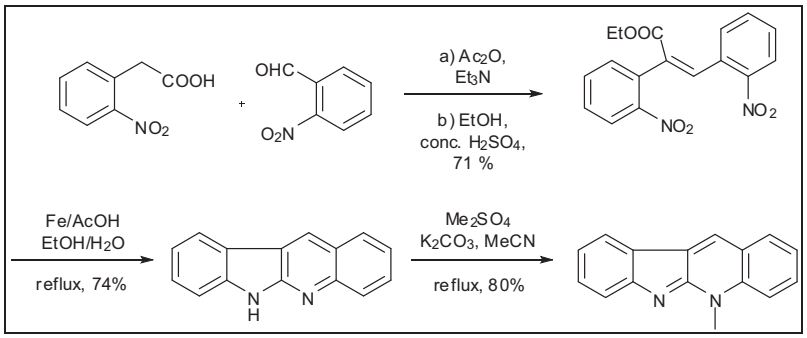
Scheme 6

Our group[13] had also developed a two step synthesis from isatin using Wittig reaction followed by Bechamp reduction (Scheme 7).



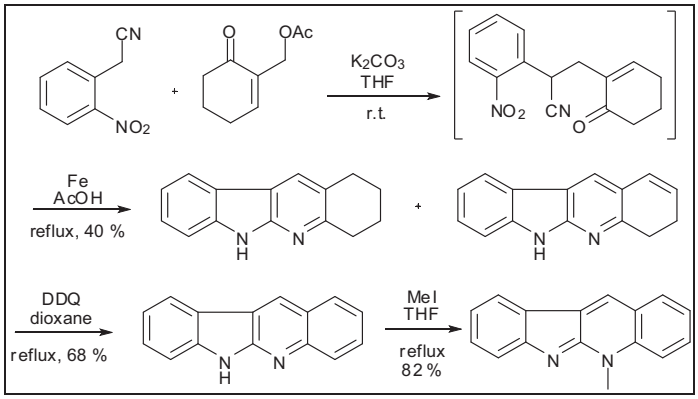
Scheme 7

A synthetic route involving Perkin reaction and tandem double reduction-double cyclisation reaction was demonstrated by our group[14] for the synthesis of indoloquinoline (Scheme 8). *o*-Nitrophenylacetic acid and *o*-nitrobenzaldehyde were used as starting materials for Perkin reaction and the obtained dinitrocompound was subsequently subjected to tandem reduction – cyclisation process. The indoloquinoline obtained was then converted to neocryptolepine by regio-selective methylation at the quinoline nitrogen.



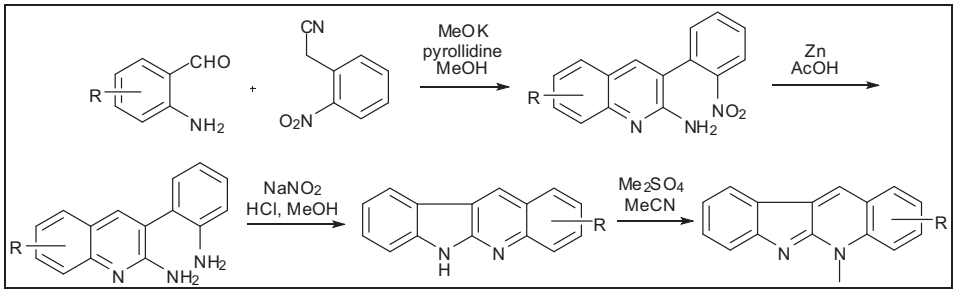
Scheme 8

Basavaiah and Reddy[15] developed a facile synthesis of indoloquinoline from the Baylis-Hillman acetates in 3 steps (Scheme 9). The sequence involves initial mono alkylation of *2*-nitroaryl-acetonitrile with the acetate, Bechamp reduction and cyclisation followed by oxidation with DDQ.



Scheme 9

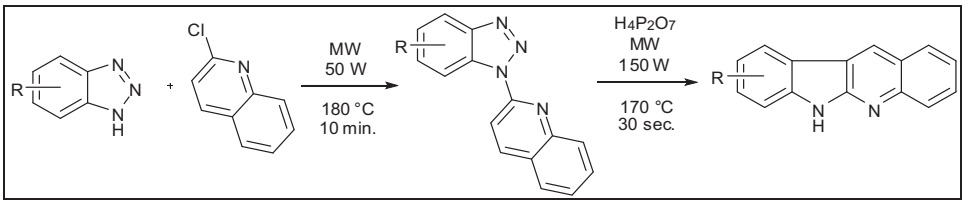
Kurth and co-workers[16] developed a 3-step protocol for indoloquinolines (Scheme 10). The reaction of *2*-aminobenzaldehyde and *2*-nitrobenzylcyanide afforded *2*-amino-*3*-(*2*-nitroaryl)quinoline which was reduced using Zn in acetic acid to corresponding *3*-(*2*-aminophenyl)quinolin-*2*-amines. Cyclisation of this under acidic conditions in presence of sodium nitrite afforded indoloquinoline.



Scheme 10

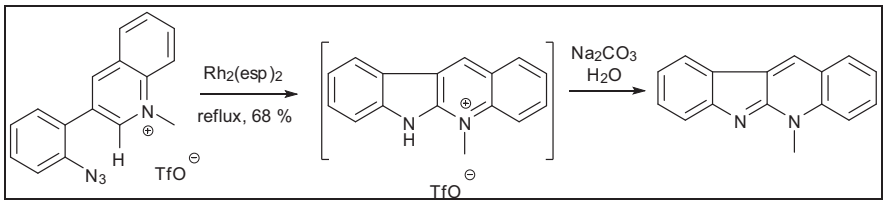
Vaquero and co-workers[17] reported synthesis of indoloquinoline through a modified Graebe-Ullman reaction under microwave irradiation (Scheme 11). Quinolinylbenzotriazole were obtained

from benzotriazole and *2*-chloroquinoline by microwave reaction and further converted to indoloquinoline.



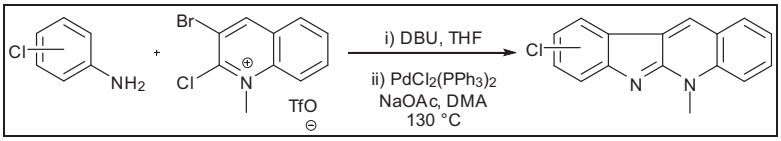
Scheme 11

Pumphrey *et al*.[18] demonstrated a Rh catalysed C-H bond amination strategy for synthesis of neocryptolepine using aryl azide (Scheme 12).



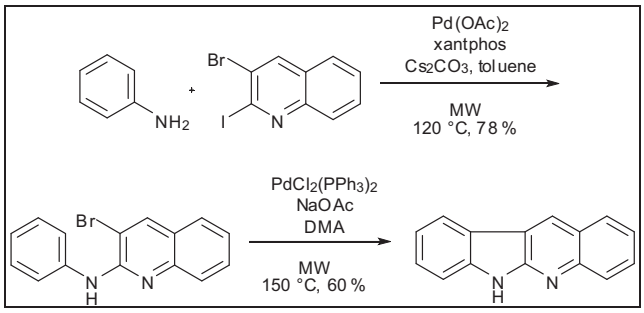
Scheme 12

Maes's group[19] synthesised chloroneocryptolepine starting from quinolinium triflates and chloroanilines *via* a one pot condensation and Pd catalysed intramolecular direct arylation strategy (Scheme 13).



Scheme 13

Indoloquinoline was synthesised by Boganyi and Kaman[20] using two consecutive Pd-catalysed reaction involving regioselective Buchwald-Hartwig amination on bromo-iodo-quinoline and aniline followed by intramolecular Heck reaction under microwave irradiation (Scheme 14).



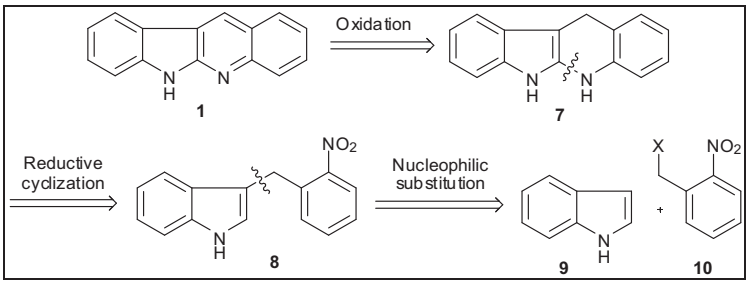
Scheme 14

1.3: Results and Discussion

This section is divided into two parts. Part A describes a reductive cyclisation approach and part B describes a one pot annulation approach.

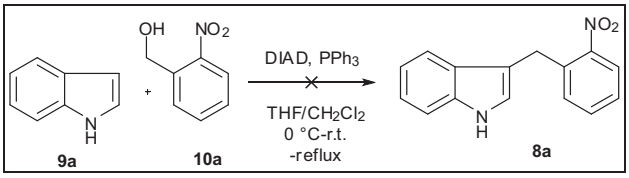
1.3.A: Part A: Reductive cyclisation approach

Our retro-synthetic route to *6H*-indoloquinoline is described in scheme 15. We thought that indoloquinoline **1** can be obtained by aromatization or oxidation of dihydroindoloquinoline **7**, which could be achieved by reductive cyclization of *o*-nitrobenzylindole. This compound in turn could be prepared by C-alkylation of indole.



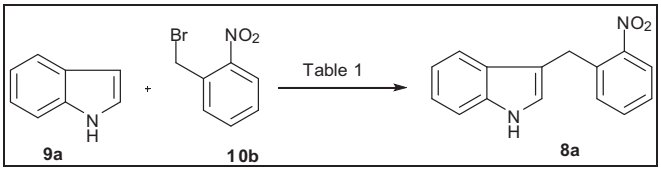
Scheme 15

To begin with we used commercially available indole and *o*-nitrobenzyl alcohol and subjected it to Mitsunobu reaction condition[21] with an intention to get compound **8a** (Scheme 16). But these attempts failed to yield us the required product.



Scheme 16

We then moved towards using *o*-nitrobenzyl bromide (commercially available) for C-3 benzylation of indole (Scheme 17).

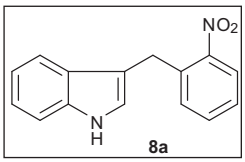


Scheme 17

Following a reported procedure,[22] using Na_2CO_3 as base in refluxing acetone:water mixture for 40 h gave us the required *3*-(*o*-nitrobenzyl)indole **8a** in 65 % yield along with *o*-nitrobenzyl alcohol as hydrolysed product in 10 % yield. The structures of these two compounds were confirmed by

comparing their physical properties and spectral data with literature.[9,22] This reaction being very slow took 40 h for completion and required 5 equiv. of indole (Method A).

^{1}H NMR data of *3*-(*2*-Nitrobenzyl)-*1H*-indole **(8a)**[9,22]



8a

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (s, 2H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.87 (s, 1H), 7.12-7.14 (m, 2H), 7.19-7.24 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 8.05 (br s, 1H) ppm.

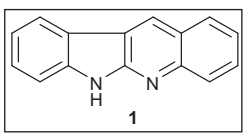
Recently alkylation of indole was reported in water by microwave irradiation.[23] Thus we thought of employing the same to increase the yield of this product (Table 1). Using microwave condition, (Method B) this reaction was complete in just 10 minutes and product **8a** was obtained in 68 % yield. Although there was no much improvement in the yield of product but the microwave irradiation drastically reduced the duration of reaction. Further in order to increase the nucleophilicity of C-3 position of indole we used MeMgBr as base (Method C) and product **8a** was obtained under this Grignard base condition[24] in 72 % yield.

Table 1: Indole alkylation (Scheme 17)

Method	Reaction Condition	% Isolated yield (**8a**)
A	Na_2CO_3, acetone:water (4:1), reflux, 40 h	65
B	MW, 200 W, water, 150 °C, 10 min	68
C	MeMgBr, toluene, -5 °C – r.t. 12 h	72

After having sufficient quantity of this compound in hand we then moved towards our next step of reductive cyclisation. Initially we used Cadogan's protocol[25] using triethylphosphite for the reductive cyclisation. Here we obtained a complex mixture of products. Then we used PPh_3 at high temperature[26] to carry out this reaction. Chromatographic separation leads us a yellow solid. The absence of NO_2 stretching frequency peaks in the IR spectrum of product were indication of the success of reductive cyclisation. The PMR spectrum showed a singlet at δ 9.0 which is a characteristic of *6H*-indolo[*2,3-b*]quinoline system.

NMR data of *6H*-Indolo[*2,3-b*]quinoline **(1a)** [7,9,13,14]

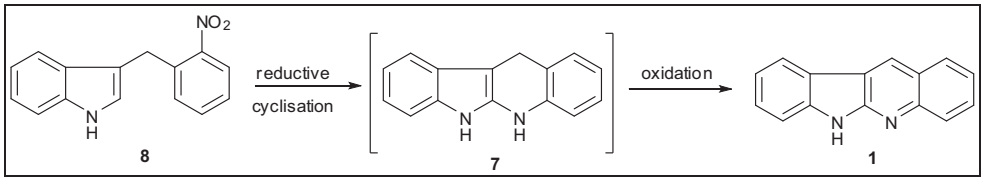


1

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27 (t, *J* = 7.4 Hz, 1 H), 7.46- 7.55 (m, 3 H), 7.72 (t, *J* = 7.6 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 1 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 8.26 (d, *J* = 8.0 Hz, 1 H), 9.06 (s, 1 H), 11.71 (s, 1 H) ppm.

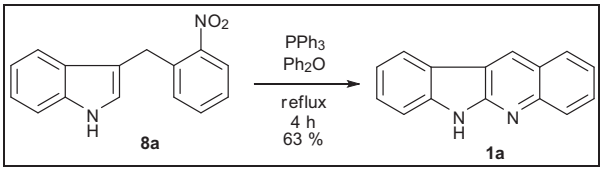
^{13}C NMR (100 MHz, DMSO-d_6): δ 110.9 (CH), 117.8 (Cq), 119.6 (CH), 120.2 (Cq), 121.8 (CH), 122.7 (CH), 123.6 (Cq), 126.9 (CH), 127.5 (CH), 128.2 (CH), 128.6 (CH), 128.7 (CH), 141.4 (Cq), 146.3 (Cq), 152.8 (Cq) ppm.

The PMR and CMR spectra of this product obtained were matching with the literature data.[9,14] Hence it was confirmed that this reaction using PPh_3 at high temperature directly gave us the final product in 63 % yield by tandem reductive cyclisation-oxidation reaction (Scheme 18).



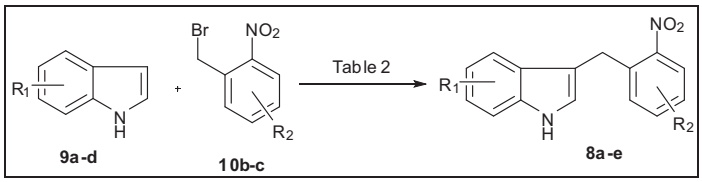
Scheme 18

In an attempt to increase the yield of this reaction, we tried a recently developed method employing $MoO_2Cl_2(dmf)_2$[27] catalyst along with PPh_3 for such reaction without success. We remained satisfied with the 63 % yield of product obtained by tandem reductive cyclisation-oxidation reaction using PPh_3 in refluxing diphenylether (Scheme 19) though the possibility of some product decomposition at high temperature could not be ruled out.



Scheme 19

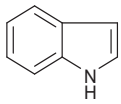
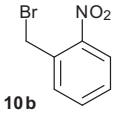
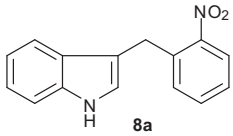
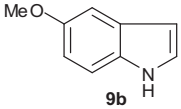
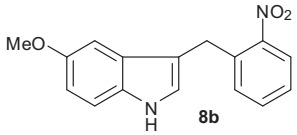
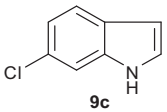
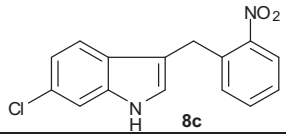
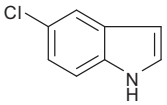
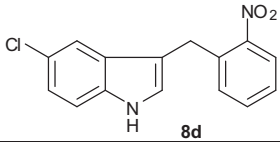
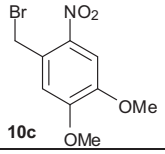
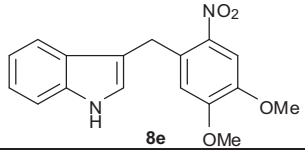
On successfully achieving the goal as visualised in the retro-synthetic scheme for developing a concise route for synthesis of indoloquinoline, we then extended this procedure to prepare a series of substituted indoloquinolines. Keeping this in mind we used various commercially available substituted indoles and substituted *o*-nitrobenzyl bromides (Scheme 20). We used all 3 methods A, B, and C as described in Table 1 for preparing substituted *o*-nitrobenzylindoles. 5-Methoxyindole **9b** (Entry 2) and 6-chloroindole **9c** (Entry 3) gave us consistently good yields of corresponding products **8b-8c**.



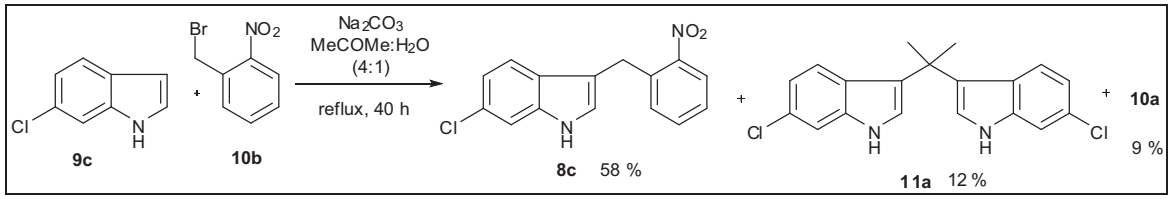
Scheme 20

The *5*-chloroindole **9d** (Entry 4) and dimethoxy-*o*-nitrobenzylbromide **10c** (Entry 5) gave us poor yields in all three methods. Some side-products were obtained in method A by reaction with solvent and by N-alkylation in method C as shown in Scheme 21-23.

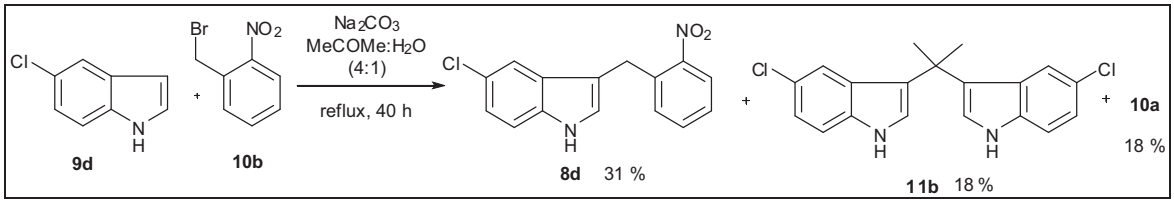
Table 2: Substrate study (Scheme 20).

Entry	Indole **9a-d**	benzyl bromides **10b-c**	Product **8a-e**	% Yield[a] [b] Method		
				A	B	C
1	 **9a**	 **10b**	 **8a**	65	68	72
2	 **9b**	**10b**	 **8b**	60	61	68
3	 **9c**	**10b**	 **8c**	58	56	65
4	 **9d**	**10b**	 **8d**	31	43	29
5	**9a**	 **10c**	 **8e**	28	35	25

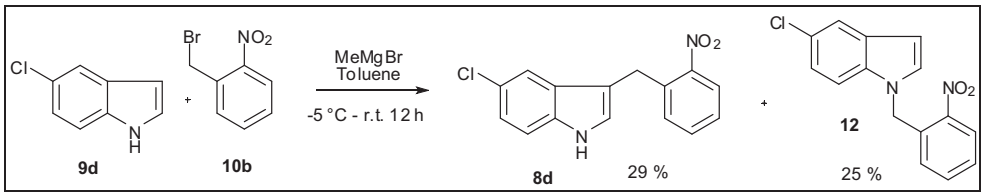
[a] Isolated yield after column chromatography.
[b] Method A: Na_2CO_3, acetone:water (4:1), reflux, 40 h; Method B: MW, 200 W, water, 150 °C, 10 min. Method C: MeMgBr, toluene, -5 °C – r.t., 12 h.



Scheme 21

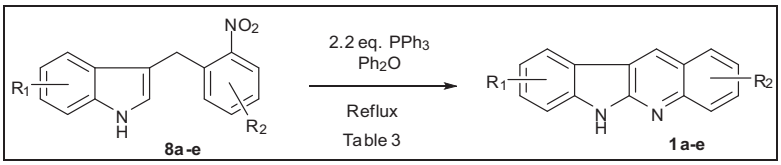


Scheme 22



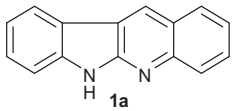
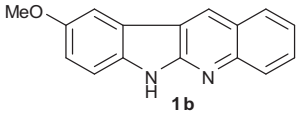
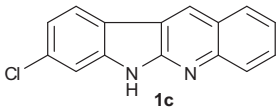
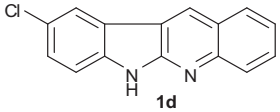
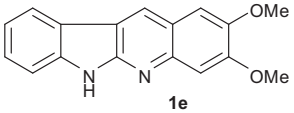
Scheme 23

Having the derivatives **8a-8e** in hand, they were further subjected to reductive cyclisation using PPh_3 in diphenylether (Scheme 24). *9*-Methoxy and *8*-chloroindoloquinolines **1b** & **1c** were obtained in good yields (Table 3). However, tarry material was obtained along with *9*-chloroindoloquinoline **1d** during tandem reductive cyclisation – oxidation reaction of **8d**. *2,3*-Dimethoxyindoloquinoline **1e** was also obtained in poor yield.



Scheme 24

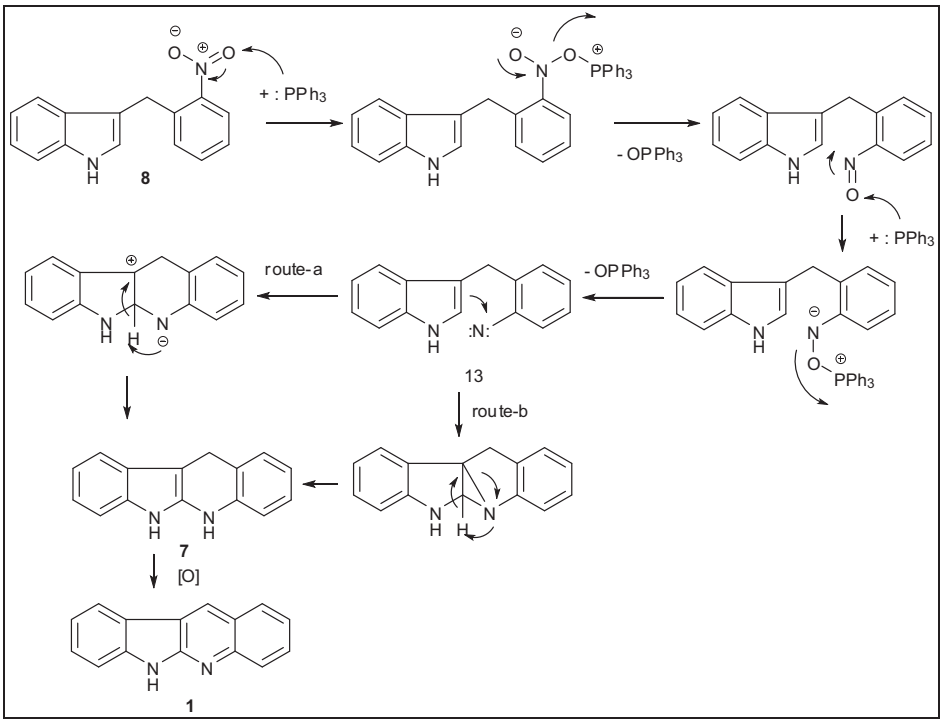
Table 3: Substrate study on Tandem reductive cyclization – oxidation reaction (Scheme 20).

Entry	Product **1a-g**	% Yield[a]	Overall % yield[b]
1	 **1a**	63	45.4
2	 **1b**	60	40.8
3	 **1c**	55	35.7
4	 **1d**	10	4.3
5	 **1e**	19	7.0

[a] Isolated yield after column chromatography. [b] Calculated over 2 steps.

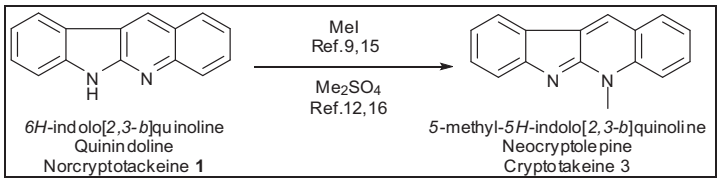
A probable mechanism for the tandem reductive cyclisation – oxidation reaction is depicted in scheme 25. The formation of reactive nitrene intermediate **13** from nitro compound **8** using 2 equiv. of PPh_3 is well known in literature.[25,28] The nitrene intermediate **13** undergoes either sp^2 C-H bond insertion via route-a or aziridine formation via route-b to give the dihydroindoloquinoline **7**.

This being susceptible to air oxidation under the high temperature reaction conditions directly gives the aromatised final product as indoloquinoline **1**.



Scheme 25

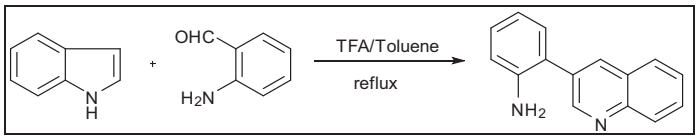
The transformation of natural product indoloquinoline **1** to neocryptolepine **3** is well known in literature using MeI or Me_2SO_4 as methylating agents (Scheme 26). Thus this synthesis formulates a formal synthesis of another natural alkaloid neocryptolepine **3**.



Scheme 26

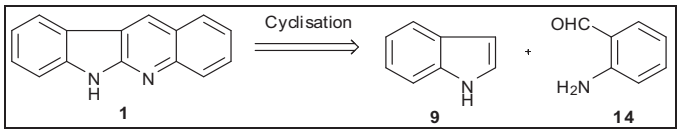
1.3.B: Part B: One pot approach

In literature[11,12] as described earlier N-methyl-*o*-amino-benzaldehyde (Scheme 5) and N-tosyl-*o*-aminobenzaldehyde (Scheme 6) are reported as substrates for the synthesis of indolo[*2,3-b*]quinoline system in an one-pot manner. However direct use of unsubstituted *o*-aminobenzaldehyde is lacking perhaps may be because of its tendency for dimerisation, agglomeration and polymerisation. Strong acid like TFA is known to give *3*-(*2*-amino-phenyl)quinolines (Scheme 27) with indole and *o*-aminobenzaldehyde.[11]



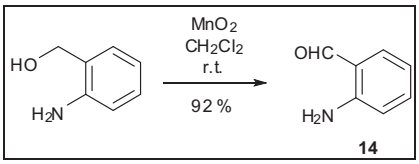
Scheme 27

We thought that directly using *o*-aminobenzaldehyde **14** can give us *6H*-indolo[*2,3-b*]quinoline **1** by proper manipulation of reaction conditions, (Scheme 28) and its N-alkylation can give neocryptolepine **3** and its analogues. Further as indole being not protected additional step of removal of the protecting group from nitrogen may not be required.



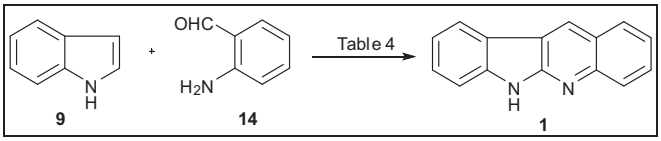
Scheme 28

o-Aminobenzaldehyde **14** was freshly prepared in 92 % by MnO_2 oxidation of commercially available o-aminobenzyl alcohol (Scheme 29) and immediately used for further reaction.



Scheme 29

Initially we tried the reaction (Scheme 30, Table 4) using *p*-TSA and I_2 condition reported for N-methylindole but this reaction with indole gave a complex mixture of products. We then tried reaction using indole **4** and freshly prepared *o*-aminobenzaldehyde **14** and heated this mixture in solvent (Table 4, Entry 3) at high temperature, we were delighted to observe direct formation of final product **1** after reflux for 6 h but on purification product **1** was isolated in albeit 11 % yield.



Scheme 30

Then we investigated this reaction by employing various reagents that we anticipated were responsible for oxidation. We tried MnO_2, Pd/C, and DDQ in refluxing dioxane but were unsuccessful to get any product formation (Table 4), these oxidising agents in refluxing Ph_2O led to decomposition of *o*-aminobenzaldehyde.

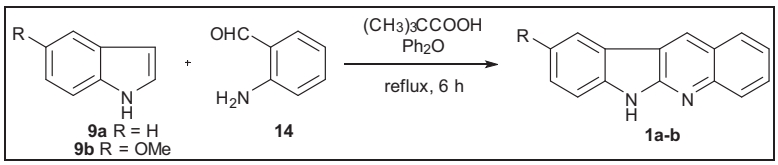
Table 4: Various catalysts and reagents tried for the one-pot reaction (Scheme 30).

Entry	Reaction condition	% Yield[a]
1	p-TSA, Ph_2O, reflux, 4 h	Complex mixture
2	I_2, Dioxane, reflux, 24 h	Complex mixture
3	Ph_2O, reflux, 6 h	11
4	MnO_2, Dioxane, reflux, 24 h	No reaction
5	Pd/C, Dioxane, reflux, 24 h	No reaction
6	DDQ, Dioxane, reflux, 24 h	No reaction
7	PivOH (10 %), Ph_2O, reflux, 6 h	56
8	PivOH, reflux, 6 h	Complex mixture

[a] Isolated yield.

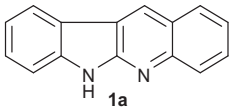
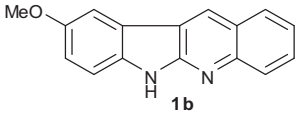
Pivalic acid being a non-nucleophilic weak acid binds reversible to the amino group and activates the carbonyl thereby increasing the electrophilicity of aldehyde **14**. We tried it for this reaction (Entry 7) and obtained product **1** in good yield. Reaction tried using pivalic acid itself as solvent did not furnish us product formation and instead gave a complex mixture. This one pot reaction using pivalic acid although average yielding was very simple and efficient.

We then extended this methodology (Scheme 31) for synthesising a derivative using *5*-methoxyindole **9b** and obtained the corresponding product **1b** in 54 % yield (Table 5).



Scheme 31

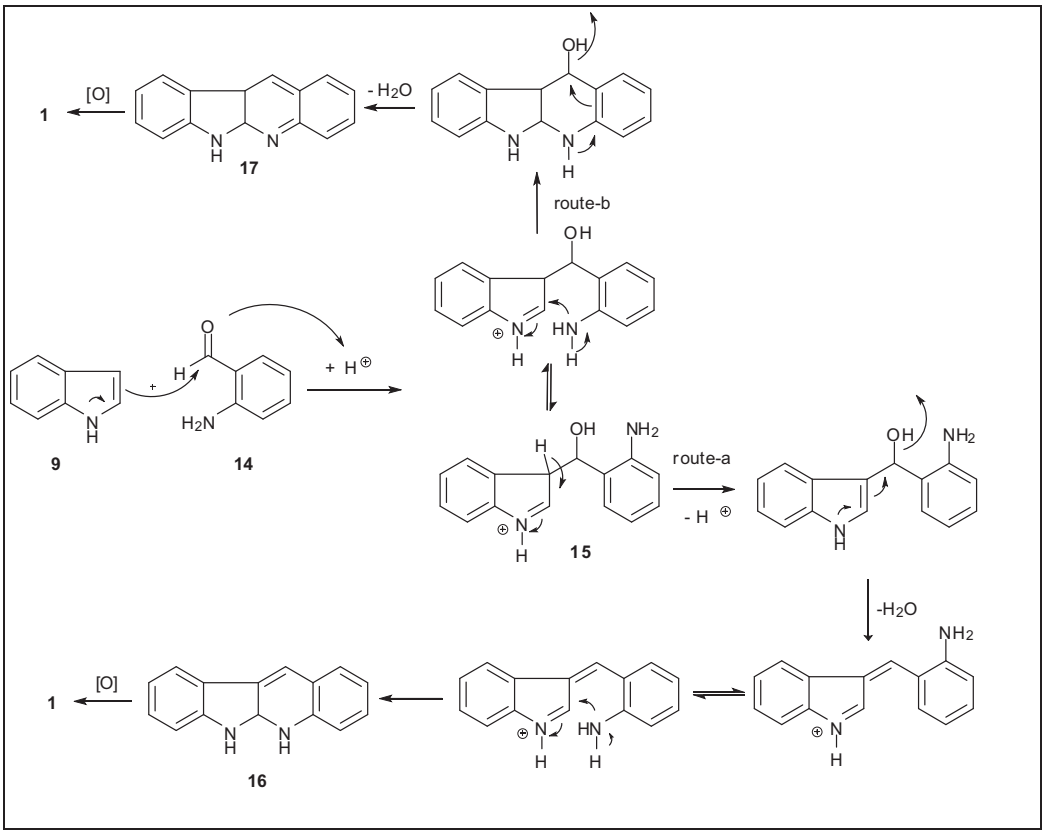
Table 5: Scope of reaction (Scheme 31).

Entry	Indoloquinoline **1a-b**	% Isolated yield[a]
1	 **1a**	56
2	 **1b**	54

[a] **9** (1 mmol), **14** (1.5 mmol), pivalic acid (1 mL), Ph_2O (10 mL) reflux, 6 h.

Based on the product formation and reaction conditions employed, a probable mechanism is postulated (Scheme 32) via two possible routes. Here alkylation of indole **9** with *o*-aminobenzaldehyde **14** gives addition intermediate **15.** This following route-a undergoes deprotonation, dehydration and cyclisation to give dihydroindoloquinoline **16** that aromatises to the final product indoloquinoline **1**. Alternatively the addition intermediate **15** following route-b,

underogoes cyclisation and dehydration to give isomeric dihydroindoloquinoline **17** that subsequently oxidises to give final product indoloquinoline **1**.



Scheme 32

1.4: Conclusion

6H-Indolo[*2,3-b*]quinoline is successfully synthesised using a concise two-step route employing indole C-3 alkylation and tandem reductive cyclisation-oxidation reaction.

A series of indoloquinolines is prepared with substituents on both sides indoles as well as quinoline rings of indoloquinolines to prove the versatility of this method and make available the substrates for biological applications.

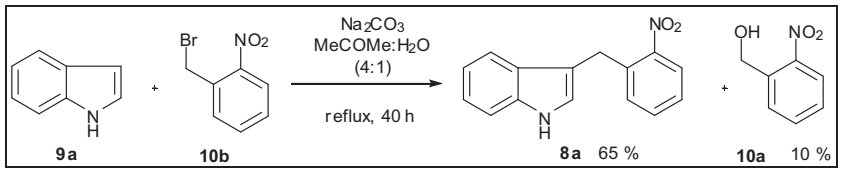
Microwave irradiation is employed to significantly reduce the reaction time and prevent any side-product formation during alkylation of indole.

6H-Indolo[*2,3-b*]quinoline is also successfully synthesised using a pivalic acid assisted one-pot alkylation-cyclisation-dehydration-aromatization approach with indole and *o*-aminobenzaldehyde.

Synthesis of *6H*-indolo[*2,3-b*]quinoline constitute the formal synthesis of alkaloid neocryptolepine.

1.5: Experimental

1.5.1: *3*-(*2*-Nitrobenzyl)-*1H*-indole (8a)



Method A: *2*-Nitrobenzyl bromide **10b** (0.43 g, 2 mmol), indole **9a** (0.94 g, 8 mmol) and Na_2CO_3 (0.42 g, 4 mmol) were mixed in acetone:water (4:1, 10 mL) and stirred at 80 °C for 40 h. Water (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhyd. Na_2SO_4, concentrated under vacuum and purified by flash chromatography (EtOAc:hexanes, 1:5). The product **8a** was obtained in 65 % (0.33 g) yield. Further elution with EtOAc:hexanes (1:3) gave *o*-nitrobenzyl alcohol **10a** in 10 % (0.03 g) yield.

***3*-(*2*-Nitrobenzyl)-*1H*-indole (8a)**

Light brown oil.[9,22]

R_f: 0.53 (EtOAc:hexanes, 1:5)

IR (neat): ν_{max} 3416, 3057, 2926, 1605, 1528, 1452, 1350 cm^{-1}.

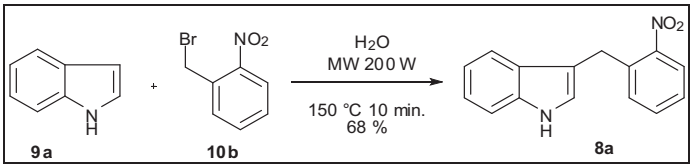
***o*-Nitrobenzyl alcohol (10a)**

Pale yellow solid, m.p. 68-70 °C [lit. m.p.: 69-72 °C][29]

R_f: 0.58 (EtOAc:hexanes, 1:4)

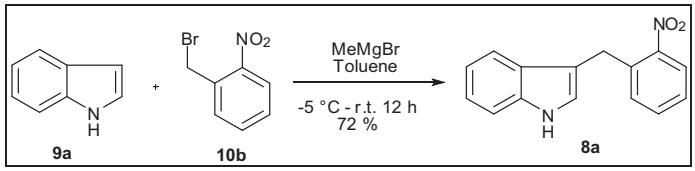
^1H NMR (400 MHz, $CDCl_3$): δ 2.53 (t, *J* = 6.4 Hz, 1 H), 4.98 (d, *J* = 6.4 Hz, 2 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H) ppm.

1.5.2: *3*-(*2*-Nitrobenzyl)-*1H*-indole (8a)



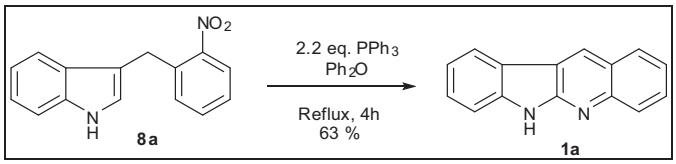
Method B: *2*-Nitrobenzyl bromide **10b** (0.43 g, 2 mmol) and indole **9a** (0.28 g, 2.4 mmol) were mixed in H_2O (10 mL) and reacted in MW reactor at 150 °C (200 W) for 10 min. Saturated aq. K_2CO_3 (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhyd. Na_2SO_4, concentrated under vacuum and purified by flash chromatography (EtOAc:hexanes, 1:5). The product **8a** was obtained in 68 % (0.34 g) yield.

1.5.3: *3*-(*2*-Nitrobenzyl)-*1H*-indole (8a)



Method C: Indole **9a** (0.23 g, 2 mmol) was dissolved in dry toluene (10 mL) and cooled to -5 °C. To this MeMgBr (3M in Et_2O) (0.7 mL, 2.1 mmol) was added and stirred at -5 °C to r.t. for 1 h. The solution was again cooled to -5 °C and *2*-nitrobenzyl bromide **10b** (0.43 g, 2 mmol) in dry toluene (2 mL) was added and mixture was stirred at r.t. for 24 h. Water (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhyd. Na_2SO_4, concentrated under vacuum and purified by flash chromatography (EtOAc:hexanes, 1:5). The product **8a** was obtained in 72 % (0.36 g) yield.

1.5.4: *6H*-Indolo[*2,3-b*]quinoline (1a)



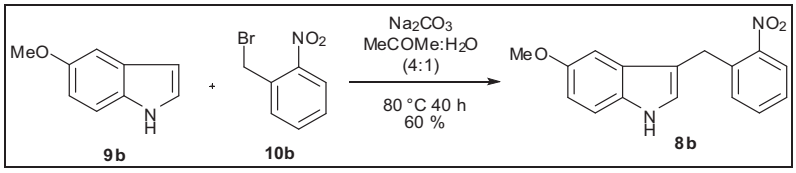
3-(*o*-Nitrobenzyl)indole **8a** (0.25 g, 1 mmol) and PPh_3 (0.58 g, 2.2 mmol) were refluxed in Ph_2O (10 mL) for 4 h. After cooling, the mixture was chromatographed (silica gel), Ph_2O was removed by elution with hexanes and further elution with EtOAc:hexanes (1:5) afforded the product **1a** in 63 % (0.14 g) yield.

Yellow solid, m.p. >300 °C [Lit. m.p.: 342-346 °C][7,9,13,14]

R_f: 0.39 (EtOAc:hexanes, 1:3)

IR (KBr): ν_{max} 3143, 3055, 1612, 1580 cm^{-1}.

1.5.5: *5*-Methoxy-*3*-(*2*-nitrobenzyl)-*1H*-indole (8b)



Method A: Following the similar procedure as described in section 1.5.1 with *5*-methoxyindole **9b** (1.18 g, 8 mmol) gave the product **8b** in 60 % (0.33 g) yield.

Light brown oil.

R_f: 0.37 (EtOAc:hexanes, 1:5)

IR (neat): ν_{max} 3415, 2960, 1581, 1521, 1485, 1350 cm^{-1}.

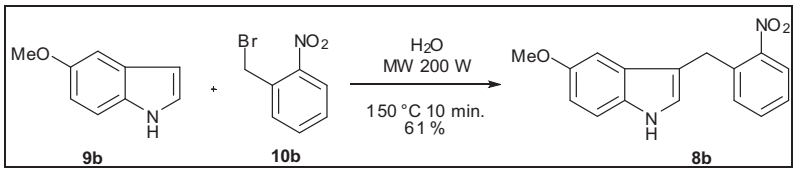
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3 H), 4.43 (s, 2 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 6.90 (s, 1 H), 6.97 (s, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 7.34-7.39 (m, 2 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 8.03 (br s, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.36 (CH_2), 55.90 (CH_3), 100.72 (CH), 112.00 (CH), 112.31 (CH), 112.64 (Cq), 123.91 (CH), 124.60 (CH), 127.09 (CH), 127.68 (Cq), 131.48 (Cq), 131.75 (CH), 132.88 (CH), 136.07 (Cq), 149.40 (Cq), 154.07 (Cq) ppm.

GC-MS (*m/z*): [M^+] 282.

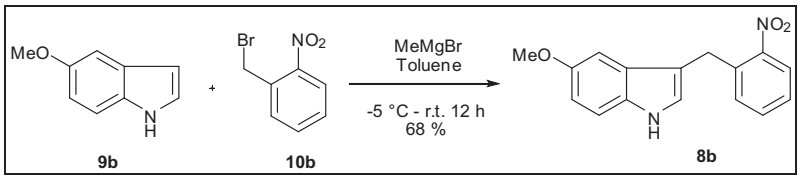
HRMS (*m/z*): calculated for $C_{16}H_{14}N_2O_3Na$ [M + Na]$^+$: 305.0902; found: 305.0902.

1.5.6: *5*-Methoxy-*3*-(*2*-nitrobenzyl)-*1H*-indole (8b)



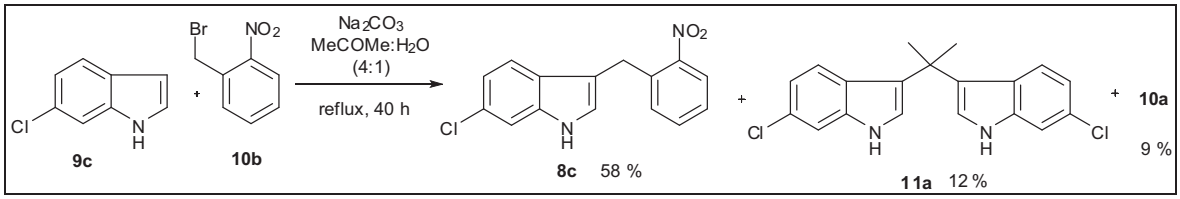
Method B: Following the similar procedure as described in experiment 1.5.2 with *5*-methoxyindole **9b** (0.29 g, 2 mmol) gave the product **8b** in 61 % (0.34 g) yield.

1.5.7: *5*-Methoxy-*3*-(*2*-nitrobenzyl)-*1H*-indole (8b)



Method C: Following the similar procedure as described in experiment 1.5.3 with *5*-methoxyindole **9b** (0.29 g, 2 mmol) gave the product **8b** in 68 % (0.38 g) yield.

1.5.8: *6*-Chloro-*3*-(*2*-nitrobenzyl)-*1H*-indole (8c)



Method A: Following the similar procedure as described in experiment 1.5.1 with *6*-chloroindole **9c** (1.21 g, 8 mmol) gave the product **8c** was obtained in 58 % (0.33 g) yield. The side-product **11a** was obtained in 12 % (0.082 g) yield and alcohol **10a** in 9 % (0.027 g) yield.

***6*-Chloro-*3*-(*2*-nitrobenzyl)-*1H*-indole (8c)**

Orange solid, m.p.: 112-114 °C

R_f: 0.47 (EtOAc:hexanes, 1:5)

IR (KBr): ν_{max} 3355, 2980, 1562, 1511, 1465, 1346 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 4.43 (s, 2 H), 6.99 (s, 1 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 7.35-7.39 (m, 4 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 8.11 (br s, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.40 (CH_2), 111.23 (CH), 113.10 (Cq), 119.74 (CH), 120.33 (CH), 123.79 (CH), 124.75 (CH), 125.83 (Cq), 127.31 (CH), 128.12 (Cq), 131.75 (CH), 133.02 (CH), 135.77 (Cq), 136.67 (Cq), 149.29 (Cq) ppm.

HRMS (*m/z*): calculated for $C_{15}H_{11}N_2O_2ClNa$ $[M + Na]^+$: 309.0407; found: 309.0406.

3,3'-(Propane-2,2-diyl)bis(6-chloro-1H-indole) (11a)

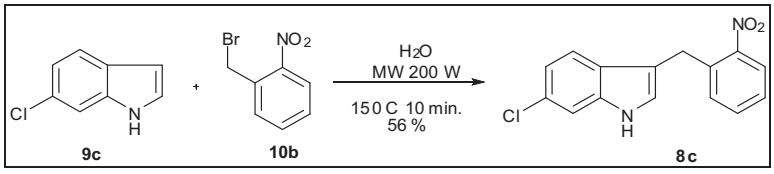
Brown gummy mass.

R_f: 0.53 (EtOAc:hexanes, 1:6)

^1H NMR (400 MHz, DMSO-d_6): δ 1.76 (s, 6 H), 6.67 (d, *J* = 8.4 Hz, 2 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 7.31 (s, 2 H), 7.34 (s, 2 H), 10.9 (s, 2 H) ppm.

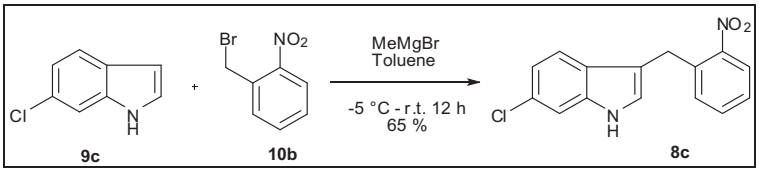
^{13}C NMR (100 MHz, DMSO-d_6): δ 30.46 (CH_3), 34.30 (Cq), 111.33 (CH), 118.39 (CH), 121.54 (CH), 122.41 (CH), 124.24 (Cq), 125.05 (Cq), 125.69 (Cq), 137.82 (Cq) ppm.

1.5.9: *6*-Chloro-*3*-(*2*-nitrobenzyl)-*1H*-indole (8c)



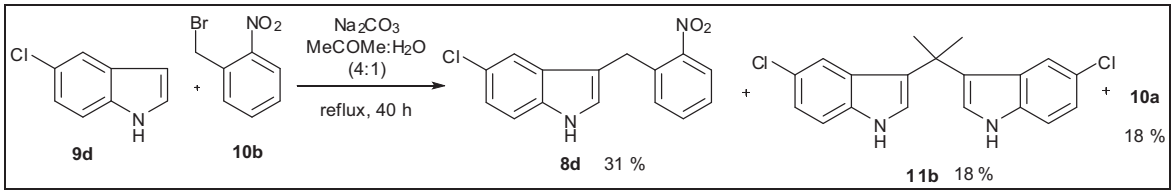
Method B: Following the similar procedure as described in experiment 1.5.2 with *6*-chloroindole **9c** (0.30 g, 2 mmol) gave the product **8c** in 56 % (0.32 g) yield.

1.5.10: *6*-Chloro-*3*-(*2*-nitrobenzyl)-*1H*-indole (8c)



Method C: Following the similar procedure as described in experiment 1.5.3 with *6*-chloroindole **9c** (0.30 g, 2 mmol) gave the product **8c** in 65 % (0.37 g) yield.

1.5.11: *5*-Chloro-*3*-(*2*-nitrobenzyl)-*1H*-indole (8d)



Method A: Following the similar procedure as described in experiment 1.5.1 with *5*-chloroindole **9d** (1.21 g, 8 mmol) gave the product **8d** in 31 % (0.176 g) yield. The side-product **11b** was obtained in 18 % (0.123 g) yield and alcohol **10a** in 18 % (0.054 g) yield.

Brown oil.

R_f: 0.49 (EtOAc:hexanes, 1:5)

IR (KBr): ν_{max} 3355, 2980, 1562, 1511, 1465, 1346 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 4.41 (s, 2 H), 7.00 (s, 1 H), 7.14 (d, *J* = 8.8 Hz, 1 H), 7.27 (d, *J* = 8.4 Hz, 1 H), 7.36-7.39 (m, 2 H), 7.43 (s, 1 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 8.18 (br s, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.41 (CH_2), 112.34 (CH), 112.70 (Cq), 118.33 (CH), 122.55 (CH), 124.52 (CH), 124.81 (CH), 125.34 (Cq), 127.35 (CH), 128.34 (Cq), 131.73 (CH), 133.08 (CH), 134.66 (Cq), 135.66 (Cq), 149.25 (Cq) ppm.

HRMS (*m/z*): calculated for $C_{15}H_{11}N_2O_2ClNa$ $[M+Na]^+$: 309.0407; found: 309.0408.

3,3'-(Propane-2,2-diyl)bis(5-chloro-1H-indole) (11b)

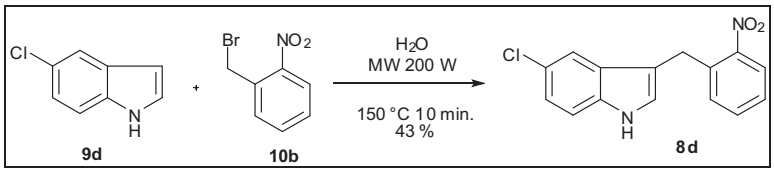
Brown gummy mass.

R_f: 0.50 (EtOAc:hexanes, 1:6)

^1H NMR (400 MHz, $CDCl_3$): δ 1.88 (s, 6 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 7.15 (s, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.31 (s, 2 H), 8.00 (s, 2 H) ppm.

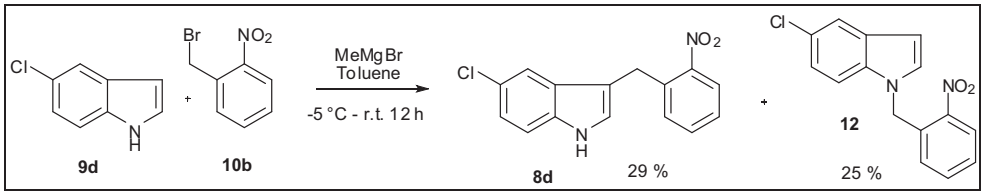
^{13}C NMR (100 MHz, $CDCl_3$): δ 29.80 (CH_3), 34.52 (Cq), 112.18 (CH), 120.25 (CH), 121.75 (CH), 121.87 (CH), 124.31 (Cq), 124.74 (Cq), 127.20 (Cq), 135.47 (Cq) ppm.

1.5.12: *5*-Chloro-*3*-(*2*-nitrobenzyl)-*1H*-indole (8d)



Method B: Following the similar procedure as described in experiment 1.5.2 with *5*-chloroindole **9d** (0.30 g, 2 mmol) gave the product **8d** in 43 % (0.246 g) yield.

1.5.13: *5*-Chloro-*3*-(*2*-nitrobenzyl)-*1H*-indole (8d)



Method C: Following the similar procedure as described in experiment 1.5.3 with *5*-chloroindole **9d** (0.30 g, 2 mmol) gave the product **8d** in 29 % (0.166 g) yield. The by-product **12** was obtained in 25 % (0.142 g) yield.

***5*-Chloro-*1*-(*2*-nitrobenzyl)-*1H*-indole (12)**

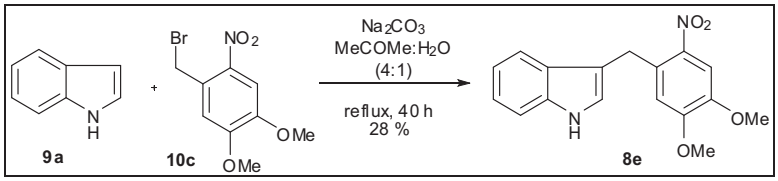
Pale yellow oil.

R_f: 0.50, (EtOAc:hexanes, 1:8)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (s, 2 H), 7.48-7.55 (m, 3 H), 7.61-7.64 (m, 1 H), 7.66-7.72 (m, 2 H), 8.11-8.18 (m, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 63.38 (CH_2), 125.15 (CH), 128.58 (3X CH), 128.82 (CH), 128.90 (CH), 129.55 (Cq), 129.79 (2X CH), 132.40 (Cq), 133.44 (CH), 133.85(CH), 165.96 (Cq) ppm.

1.5.14: *3-(4,5*-Dimethoxy-*2*-nitrobenzyl)-*1H*-indole (8e)



Method A: Following the similar procedure as described in experiment 1.5.1 with *4,5*-dimethoxybenzyl bromide **10c** (0.55 g, 2 mmol) gave the product **8e** in 28 % (0.175 g) yield.

Brown oil.

R_f: 0.43, (EtOAc:hexanes, 2:5)

IR (KBr): ν_{max} 3387, 2941, 1581, 1518, 1462, 1327 cm^{-1}.

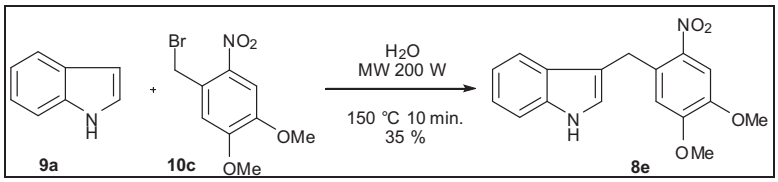
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3 H), 3.95 (s, 3 H), 4.50 (s, 2H), 6.82 (s, 2 H), 7.01 (s, 2 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 7.20 (t, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.65 (s, 1 H), 8.09 (br s, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 29.06 (CH_2), 56.19 (CH_3), 56.32 (CH_3), 108.19 (CH), 111.27 (CH), 113.27 (CH), 113.43 (Cq), 118.88 (CH), 119.61 (CH), 122.22 (CH), 122.91 (CH), 127.26 (Cq), 131.64 (Cq), 136.33 (Cq), 141.12 (Cq), 147.09 (Cq), 152.90 (Cq) ppm.

GCMS (*m/z*): $[M]^+$ 312.

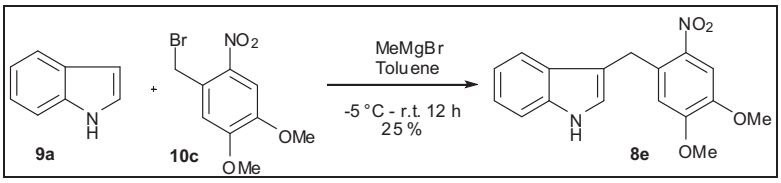
HRMS m/z: $[M+Na]^+$ calculated for $C_{17}H_{16}N_2O_4Na$: 335.1008; found: 335.1006.

1.5.15: *3-(4,5*-Dimethoxy-*2*-nitrobenzyl)-*1H*-indole (8e)



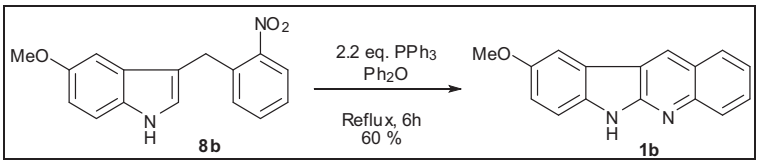
Method B: Following the similar procedure as described in experiment 1.5.2 with *4,5*-dimethoxybenzyl bromide **10c** (0.55 g, 2 mmol) gave the product **8e** in 35 % (0.218 g) yield.

1.5.16: *3-(4,5*-Dimethoxy-*2*-nitrobenzyl)-*1H*-indole (8e)



Method C: Following the similar procedure as described in experiment 1.5.3 with *4,5*-dimethoxybenzyl bromide **10c** (0.55 g, 2 mmol) gave the product **8e** in 25 % (0.156 g) yield.

1.5.17: *9*-Methoxy-*6H*-indolo[*2,3-b*]quinoline (1b)



Following the similar procedure as described in experiment 1.5.4 with *5*-methoxy-*3*-(*2*-nitrobenzyl)-*1H*-indole **8b** (0.28 g, 1 mmol) for 6 h gave the corresponding indoloquinoline **1b** in 60 % (0.14 g) yield.

Light green solid. m.p.: 284-286 °C.

R_f: 0.49, (EtOAc:hexanes, 1:3)

IR (KBr): ν_{max} 3144, 3073, 1613, 1579 cm^{-1}.

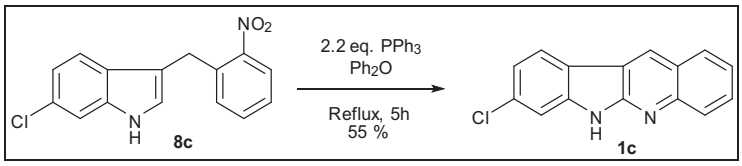
^1H NMR (400 MHz, DMSO-d_6): δ 3.87 (s 3 H), 7.16 (d, *J* = 8.8 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.46 (t, *J* = 8.4 Hz, 1 H), 7.71 (t, *J* = 8.0 Hz, 1 H), 7.88 (s 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 9.04 (s, 1 H), 11.51 (s, 1 H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ 56.12 (CH_3), 105.85 (CH), 112.12 (CH), 117.05 (CH), 118.58 (Cq), 121.23 (Cq), 123.01 (CH), 123.86 (Cq), 127.39 (CH), 128.16 (CH), 129.14 (2X CH), 136.31 (Cq), 146.81 (Cq), 153.74 (Cq), 154.07 (Cq) ppm.

LCMS (*m/z*): $[M+H]^+$ 249.

HRMS (*m/z*): calculated for $C_{16}H_{12}N_2ONa$ $[M+Na]^+$: 271.0864; found: 271.0847.

1.5.18: *8*-Chloro-*6H*-indolo[*2,3-b*]quinoline (1c)



Following the similar procedure as described in experiment 1.5.4 with *6*-chloro-*3*-(*2*-nitrobenzyl)-*1H*-indole **8c** (0.29 g, 1 mmol) for 5 h gave the corresponding indoloquinoline **1c** in 55 % (0.14 g) yield.

Light brown solid, m.p.: 296 - 298 °C.

R_f: 0.55, (EtOAc:hexanes, 1:3)

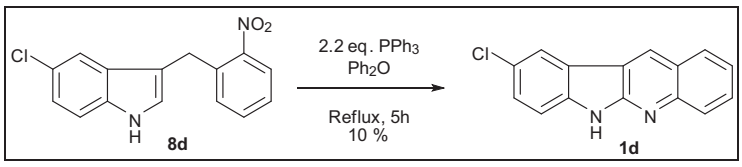
IR (KBr): ν_{max} 3145, 3056, 1640, 1613 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 7.29 (d, *J* = 8.4 Hz, 1 H), 7.50- 7.52 (m, 2 H), 7.74 (t, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 8.11 (d, *J* = 8.4 Hz, 1 H), 8.27 (d, *J* = 8.4 Hz, 1 H), 9.07 (s, 1 H), 11.86 (s, 1 H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ 111.18 (CH), 117.59 (Cq), 119.69 (Cq), 120.31 (CH), 123.62 (CH), 123.75 (CH), 124.27 (Cq), 127.46 (CH), 128.62 (CH), 129.21 (CH), 129.56 (CH), 132.95 (Cq), 142.67 (Cq), 146.76 (Cq), 153.40 (Cq) ppm.

HRMS (*m/z*): calculated for $C_{15}H_{10}N_2Cl$ $[M+H]^+$: 253.0533; found: 253.0531.

1.5.19: *9*-Chloro-*6H*-indolo[*2,3-b*]quinoline (1d)



Following the similar procedure as described in experiment 1.5.4 with *5*-chloro-*3*-(*2*-nitrobenzyl)-*1H*-indole **8d** (0.29 g, 1 mmol) for 5 h gave the corresponding indoloquinoline **1d** in 10 % (0.025 g) yield.

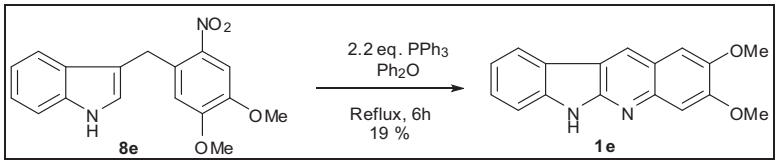
Brown solid, m.p.: >300 °C (decomposition).[8]

R_f: 0.56, (EtOAc:hexanes, 1:3)

^1H NMR (400 MHz, DMSO-d_6): δ 7.48-7.56 (m, 1 H), 7.74 (t, *J* = 6.8 Hz, 1 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 8.38 (s, 1 H), 9.12 (s, 1 H), 11.85 (s, 1 H) ppm.

LCMS (*m/z*): $[M+H]^+$ 253, $[M-H]^+$ 251.

1.5.20: *2,3*-Dimethoxy-*6H*-indolo[*2,3-b*]quinoline (1e)



Following the similar procedure as described in experiment 1.5.4 with *5*-methoxy-*3*-(*2*-nitrobenzyl)-*1H*-indole **8e** (0.31 g, 1 mmol) for 6 h gave the corresponding indoloquinoline **1e** in 19 % (0.053 g) yield.

Light green solid,[30] m.p.: 200-202 °C.

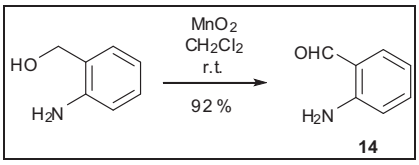
R_f: 0.35, (EtOAc:hexanes, 1:3)

IR (KBr): ν_{max} 3144, 3073, 1613, 1579 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 3.92 (s, 3 H), 3.94 (s, 3 H), 7.19-7.23 (m, 1 H), 7.35 (s, 1 H), 7.45-7.46 (m, 3 H), 8.15 (d, *J* = 7.6 Hz, 1 H), 8.83 (s, 1 H), 11.51 (s, 1 H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ 55.50 (CH_3), 55.52 (CH_3), 106.22 (CH), 106.48 (CH), 110.70 (CH), 115.43 (Cq), 118.55 (Cq), 119.21 (CH), 120.45 (Cq), 121.07 (CH), 125.87 (CH), 127.14 (CH), 140.53 (Cq), 143.27 (Cq), 146.86 (Cq), 151.76 (Cq), 151.90 (Cq) ppm.

1.5.21: *o*-Aminobenzaldehyde (14)



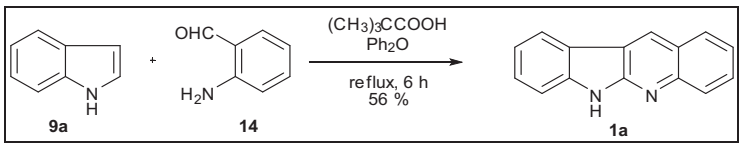
o-Aminobenzyl alcohol (0.615 g, 5 mmol) and MnO_2 (2.0 g) were stirred in CH_2Cl_2 at r.t. for 12 h. Filteration and removal of the solvent under vacuum gave product **14** in 92 % (0.557 g) yield.

Orange oil.[31]

R_f: 0.50, (EtOAc:hexanes, 1:20)

^1H NMR (400 MHz, DMSO-d_6): δ 6.05 (br s, 2 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 6.66 (t, *J* = 7.6 Hz, 1 H), 7.23 (t, *J* = 7.2 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 9.78 (s, 1 H) ppm.

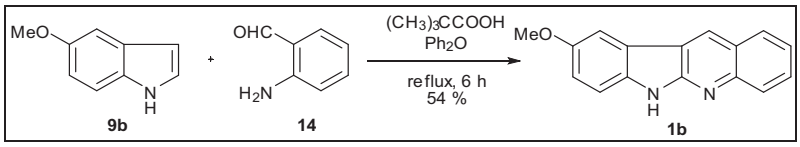
1.5.22: *6H*-Indolo[*2,3-b*]quinoline (1a)



Indole **9a** (0.117 g, 1 mmol), freshly prepared *o*-aminobenzaldehyde **14** (0.182 g, 1.5 mmol) and pivalic acid (1 mL) were refluxed in Ph_2O (10 mL) for 6 h. After cooling, the mixture was

chromatographed (silica gel), Ph_2O was removed eluting with hexanes, and further elution with EtOAc/hexanes (1:3) afforded the product **1a** in 56 % (0.122 g) yield.

1.5.23: *9*-Methoxy-*6H*-indolo[*2,3-b*]quinoline (1b)



Following the similar procedure as described in experiment 1.5.22 with *5*-methoxyindole **9b** (0.147 g, 1 mmol) and freshly prepared *o*-aminobenzaldehyde **14** (0.182 g, 1.5 mmol) for 6 h gave the corresponding indoloquinoline **1b** in 54 % (0.134 g) yield.

1.6: References

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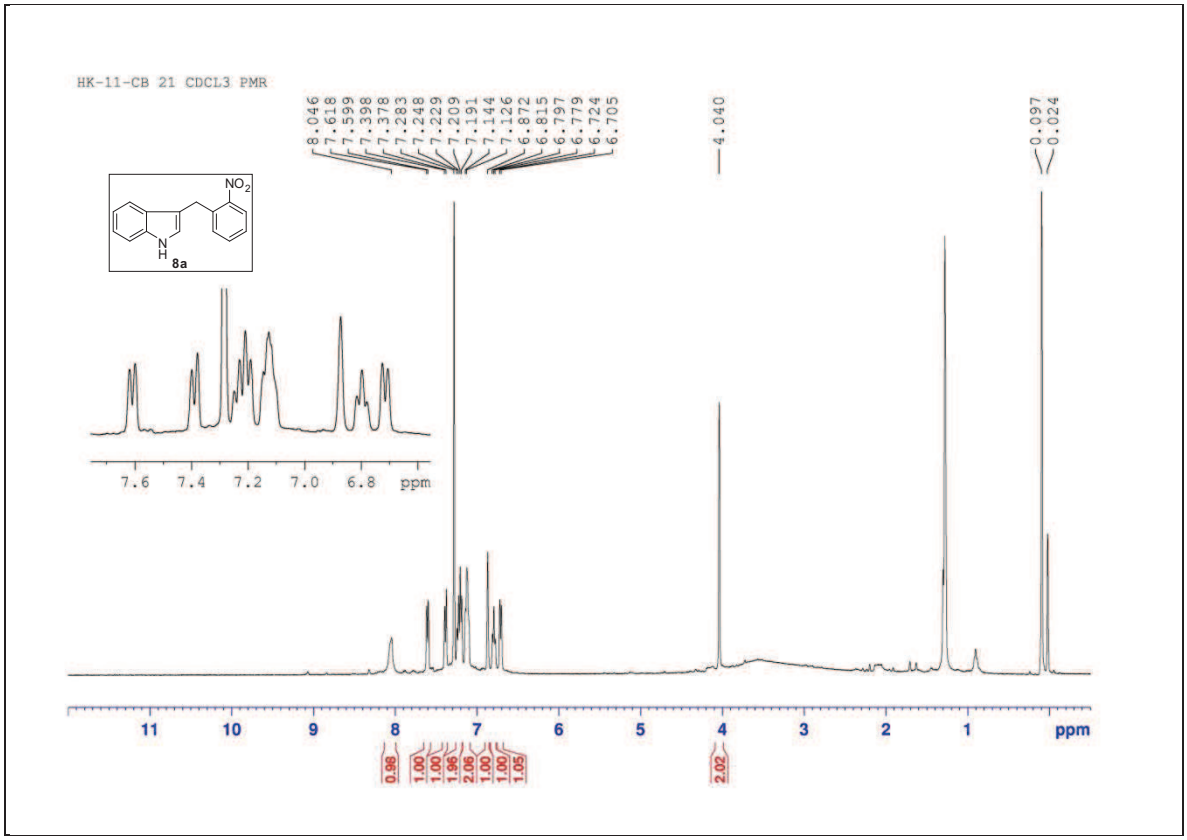
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7.599
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7.209
7.191
7.144
7.126
6.872
6.815
6.797
6.779
6.724
6.705
4.040
0.097
0.024
NO2
N
H
8a
7.6 7.4 7.2 7.0 6.8 ppm
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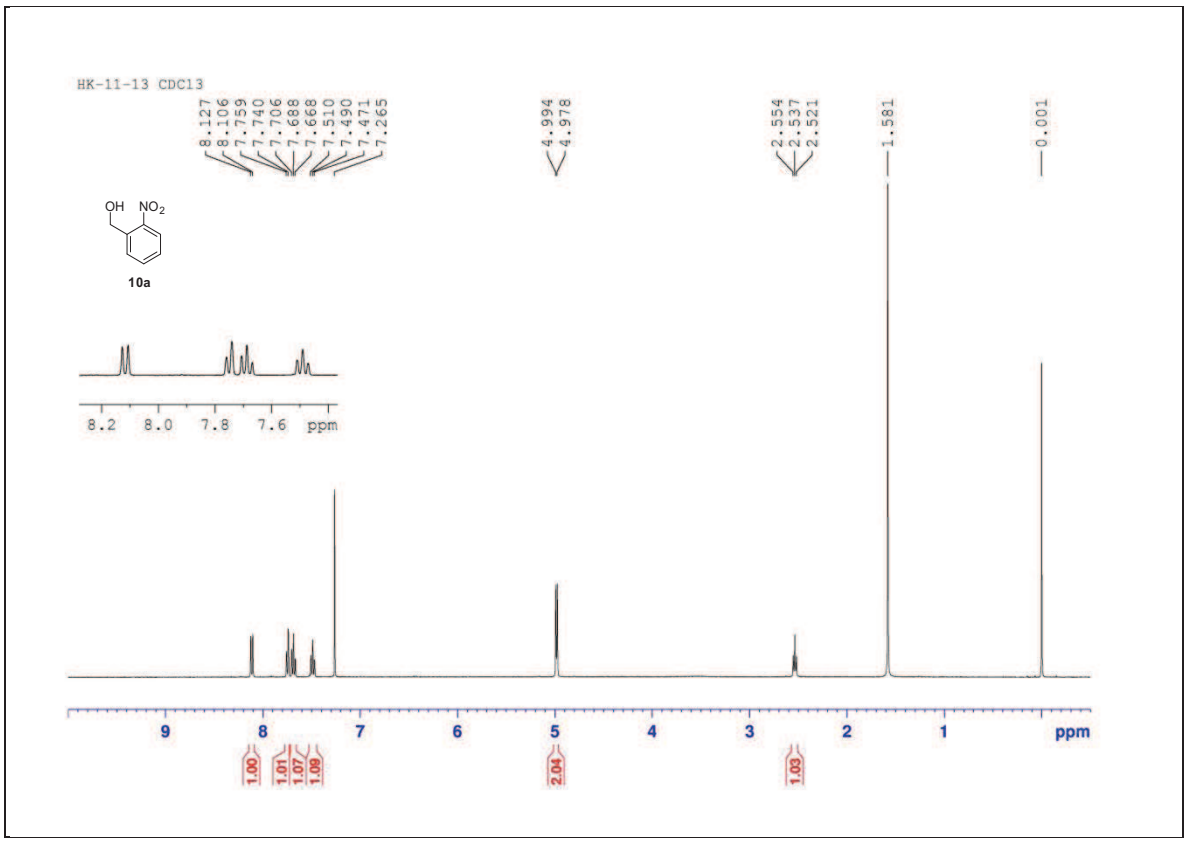
2.02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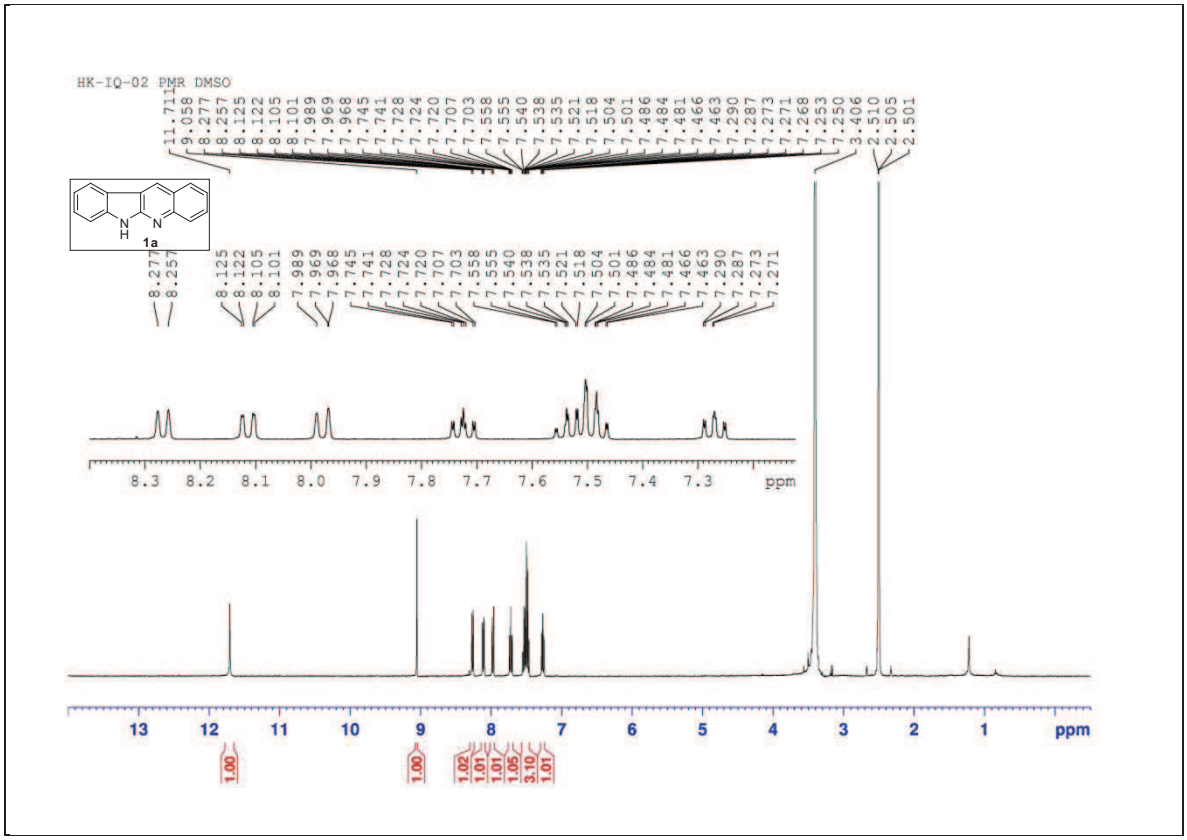
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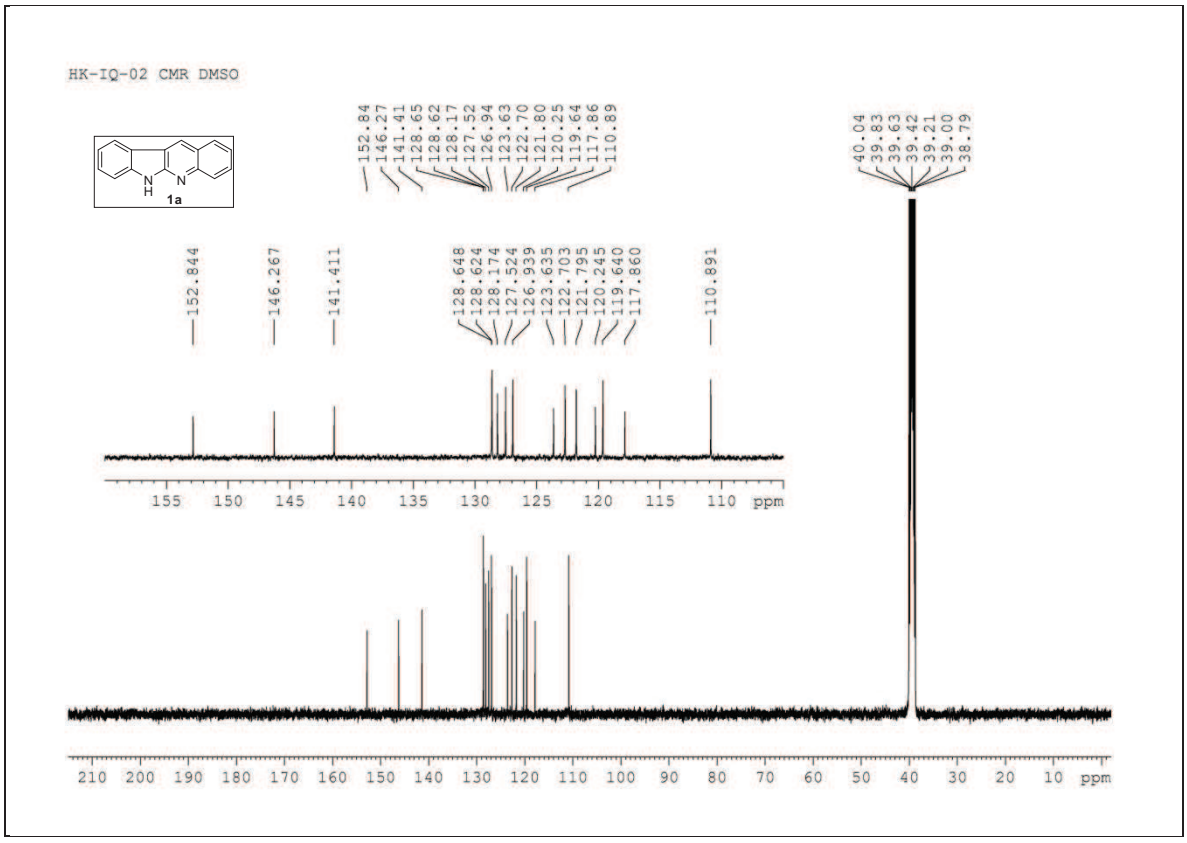
ppm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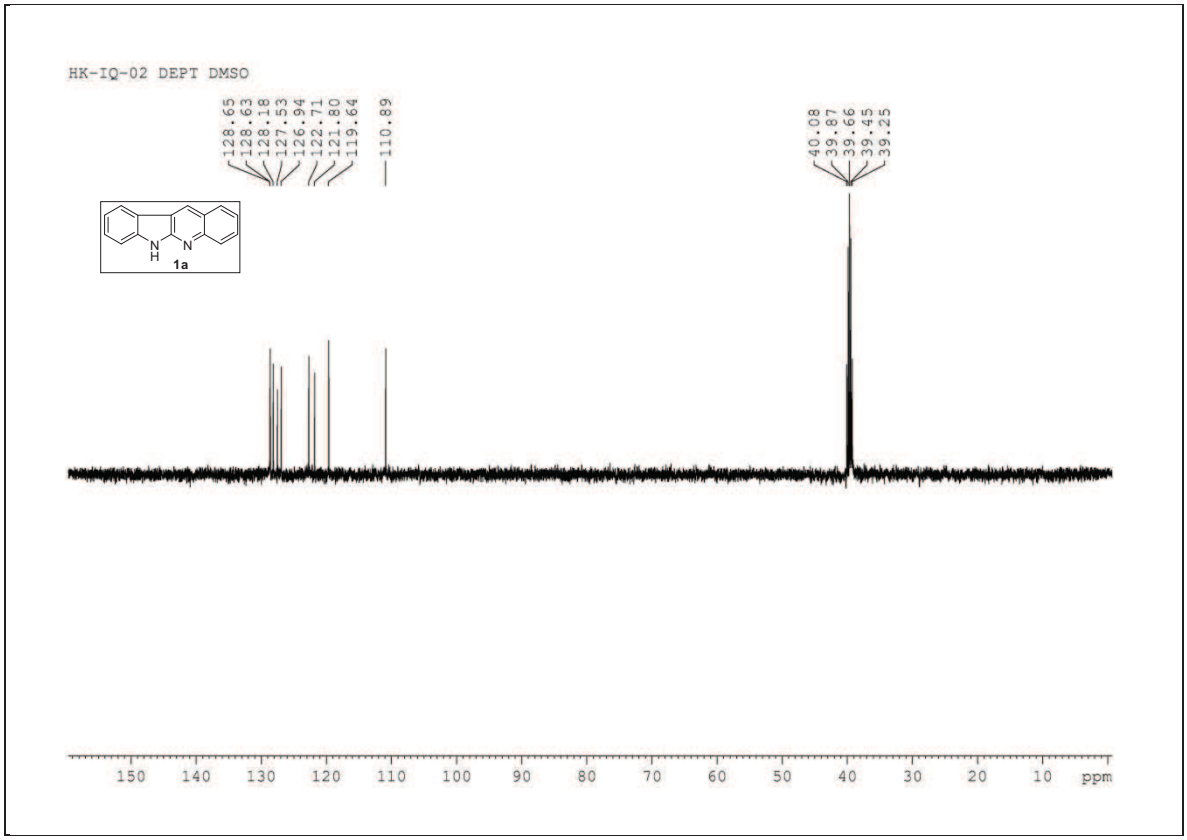
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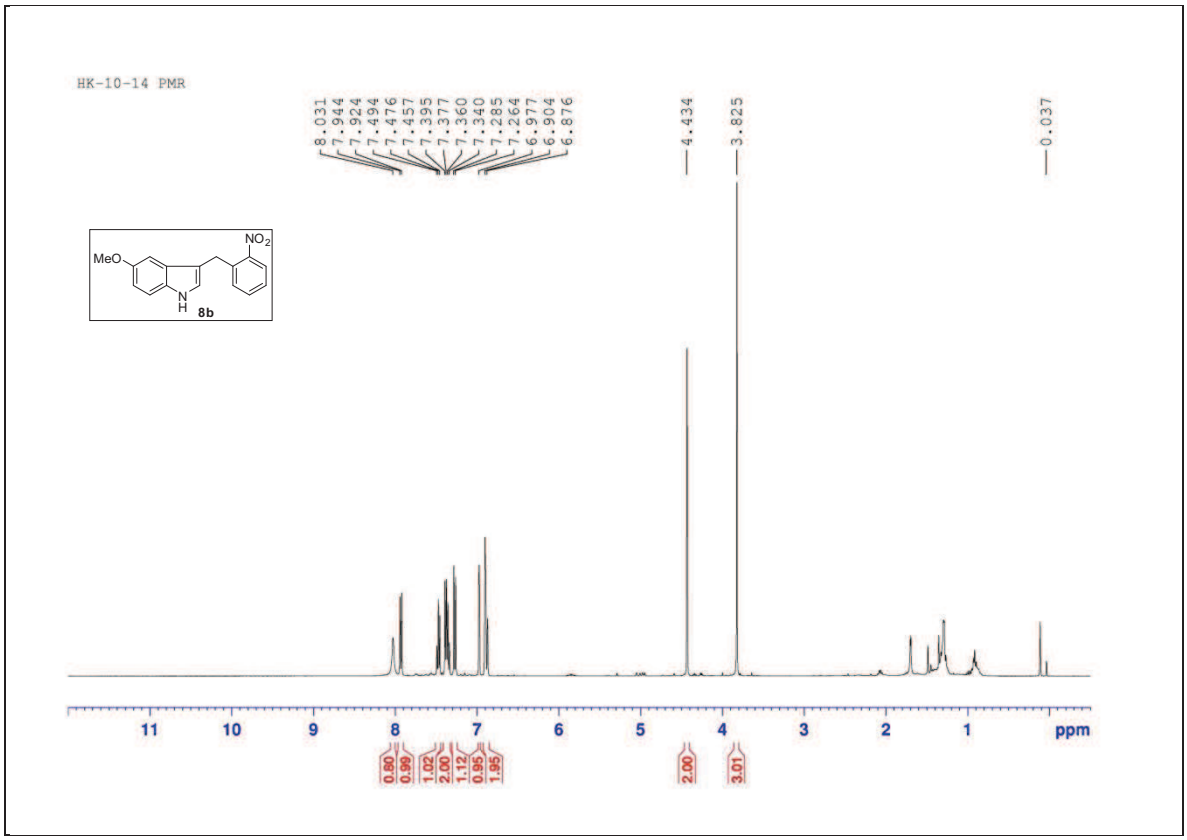
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NO2
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10
9
8
7
6
5
4
3
2
1
ppm
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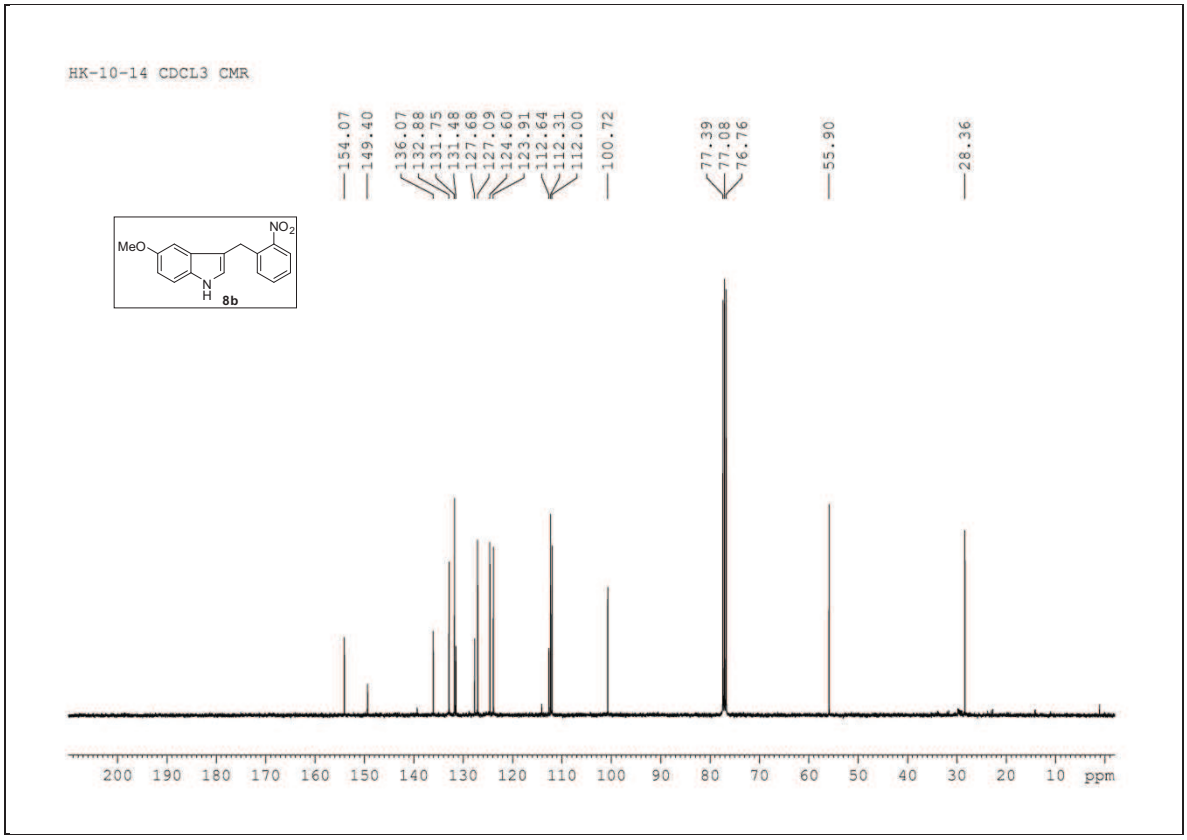
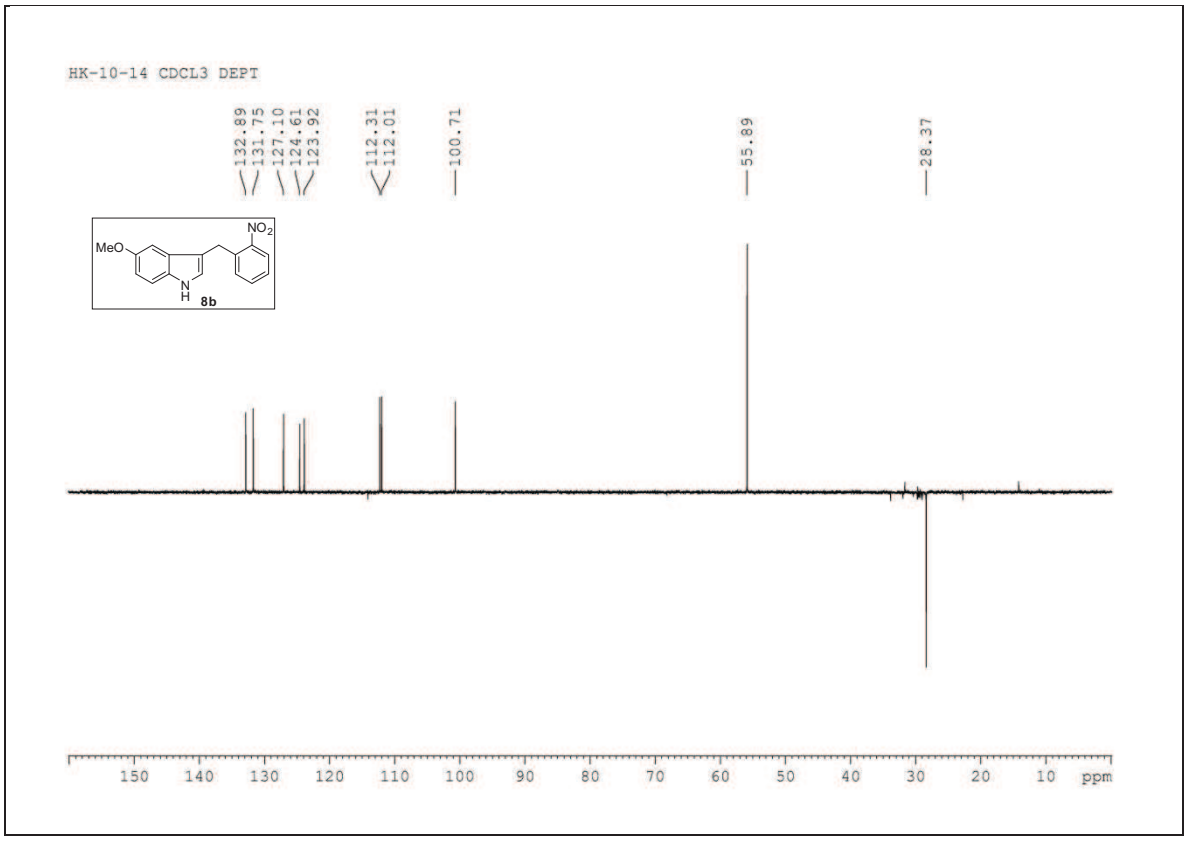
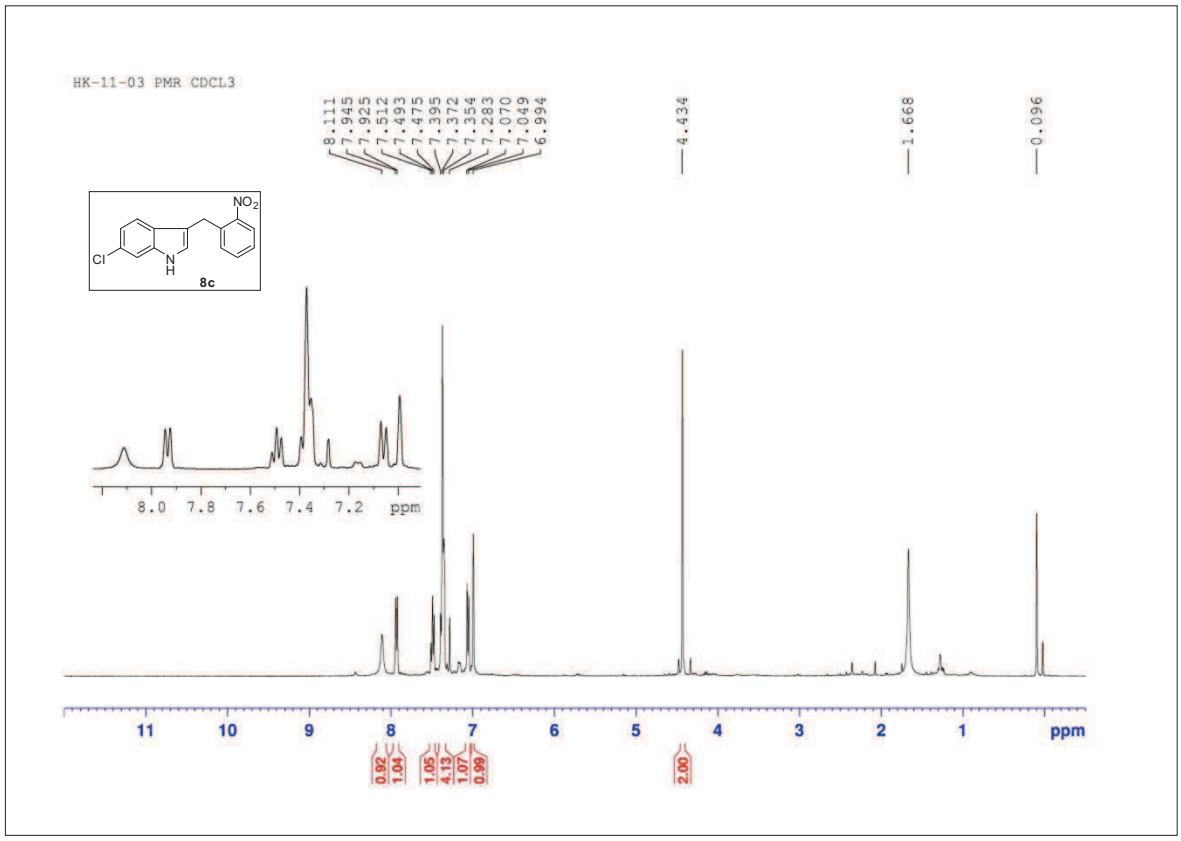
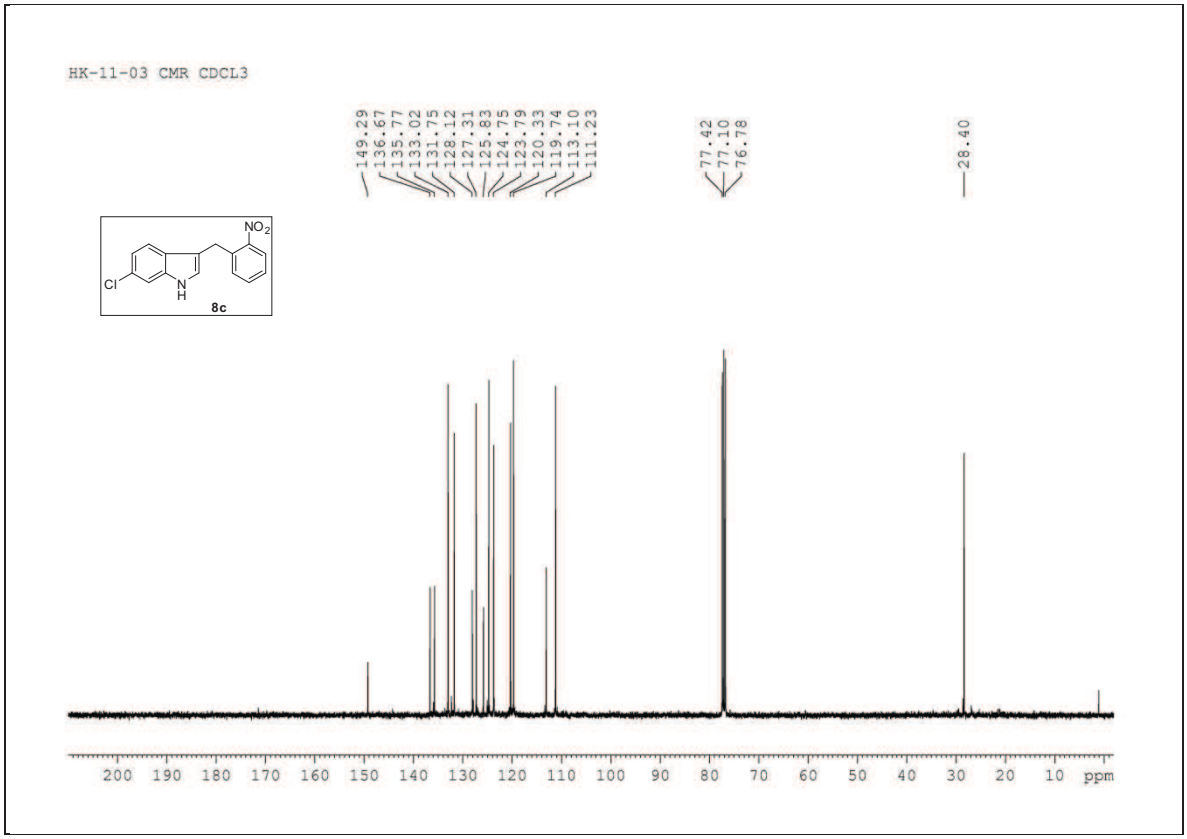
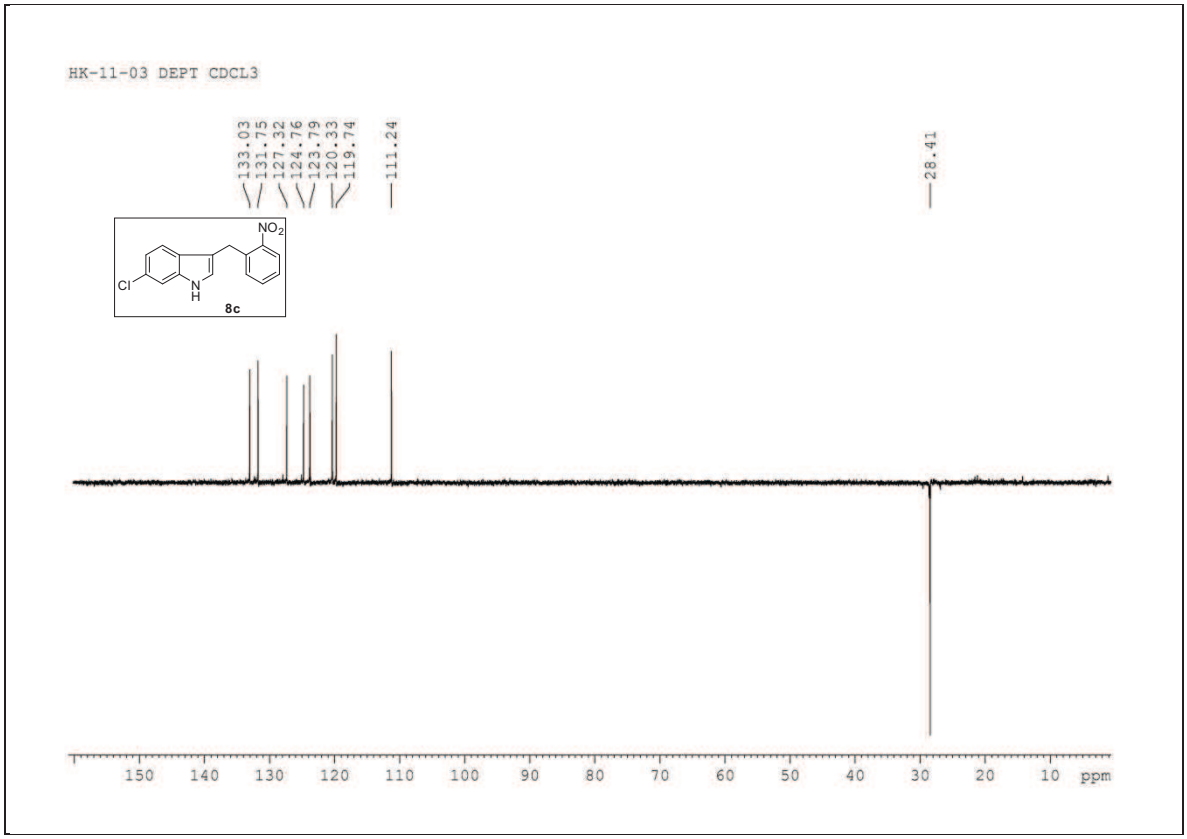
0.99
1.02
2.00
1.12
0.95
1.95
2.00
3.01

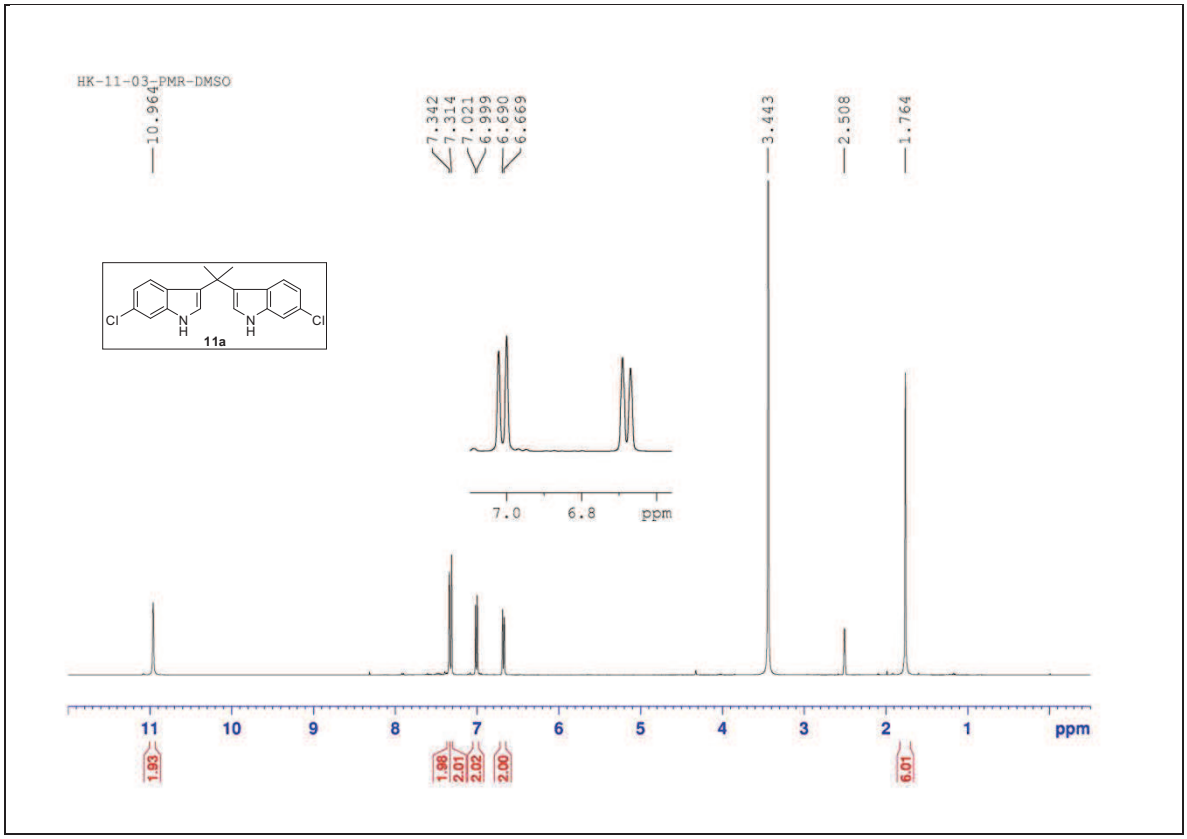

HK-10-14 CDCL3 CMR
154.07
149.40
136.07
132.88
131.75
131.48
127.68
127.09
124.60
123.91
112.64
112.31
112.00
100.72
77.39
77.08
76.76
55.90
28.36
MeO
NO2
N
H
8b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

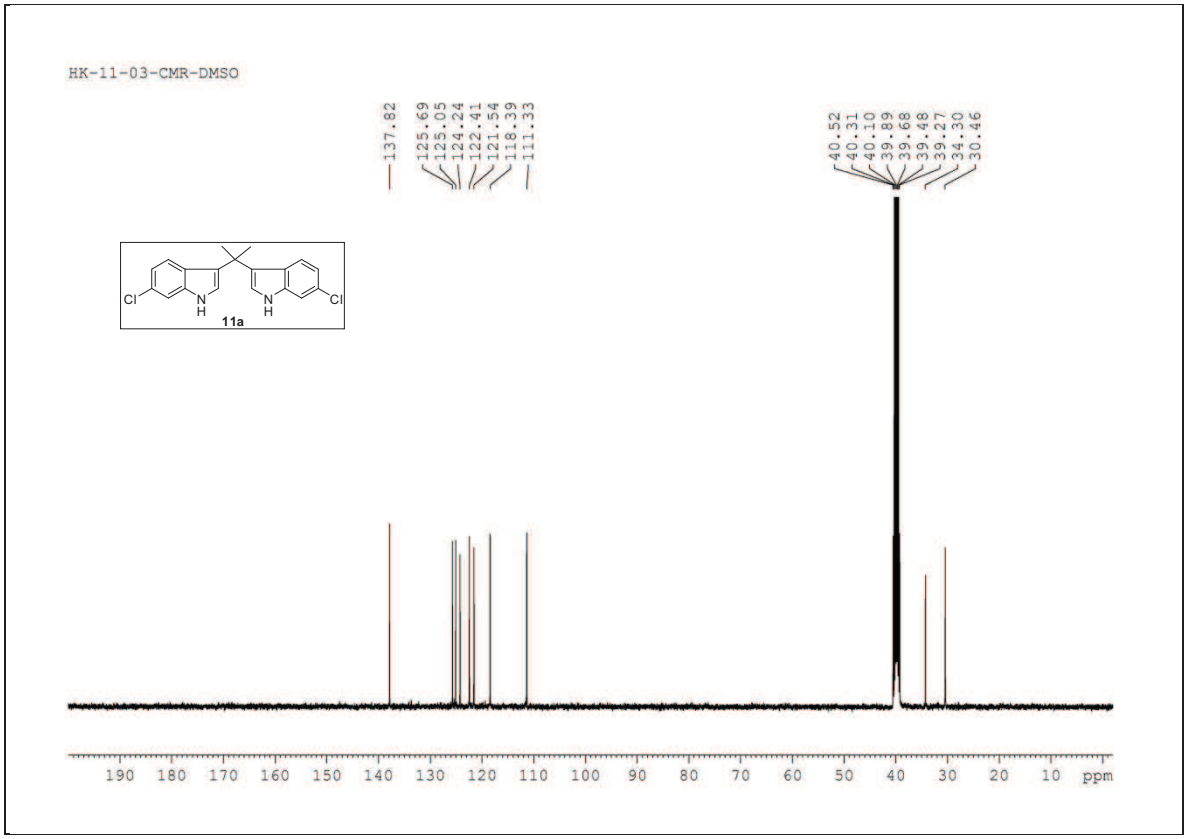

HK-10-14 CDCL3 DEPT
132.89
131.75
127.10
124.61
123.92
112.31
112.01
100.71
55.89
28.37
MeO
NO2
N
H
8b
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

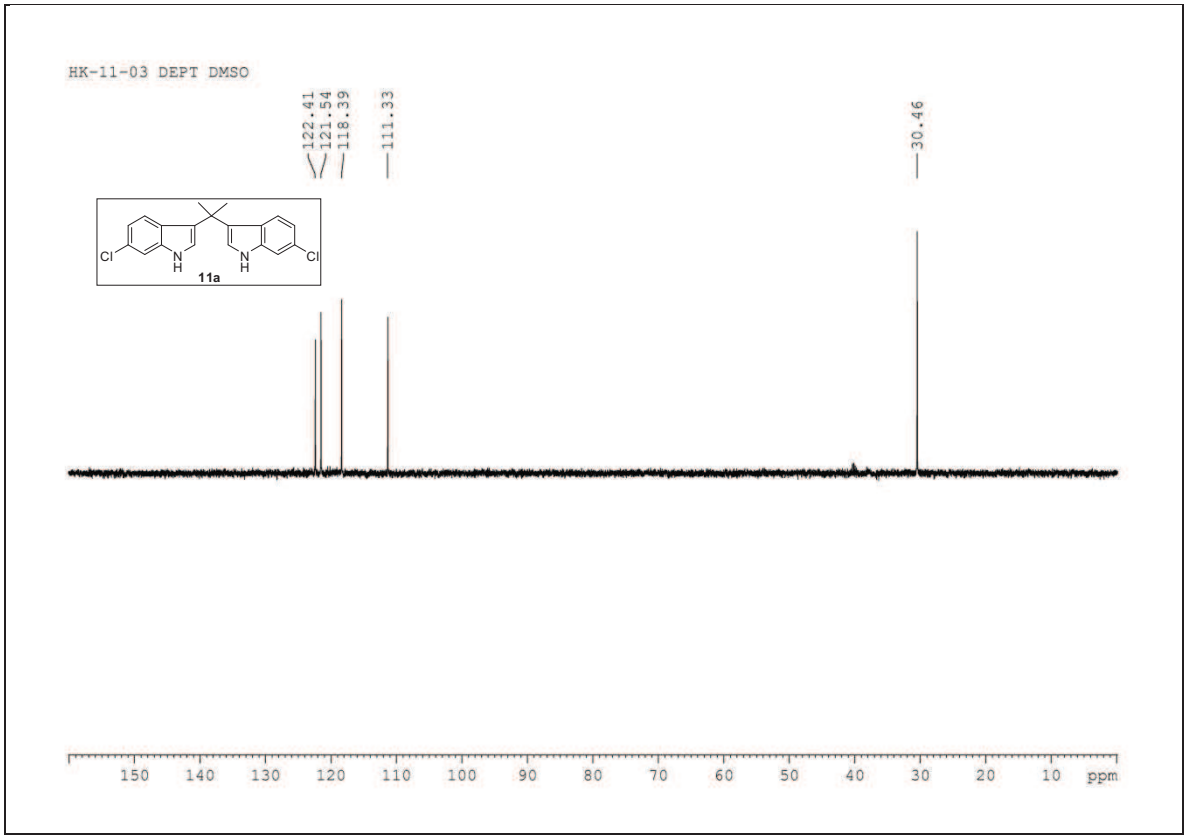

HK-11-03 PMR CDCL3
8.111
7.945
7.925
7.512
7.493
7.475
7.395
7.372
7.354
7.283
7.070
7.049
6.994
4.434
1.668
0.096
NO2
Cl
N
H
8c
8.0 7.8 7.6 7.4 7.2 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
0.92
1.04
1.05
4.13
1.07
0.99
2.00

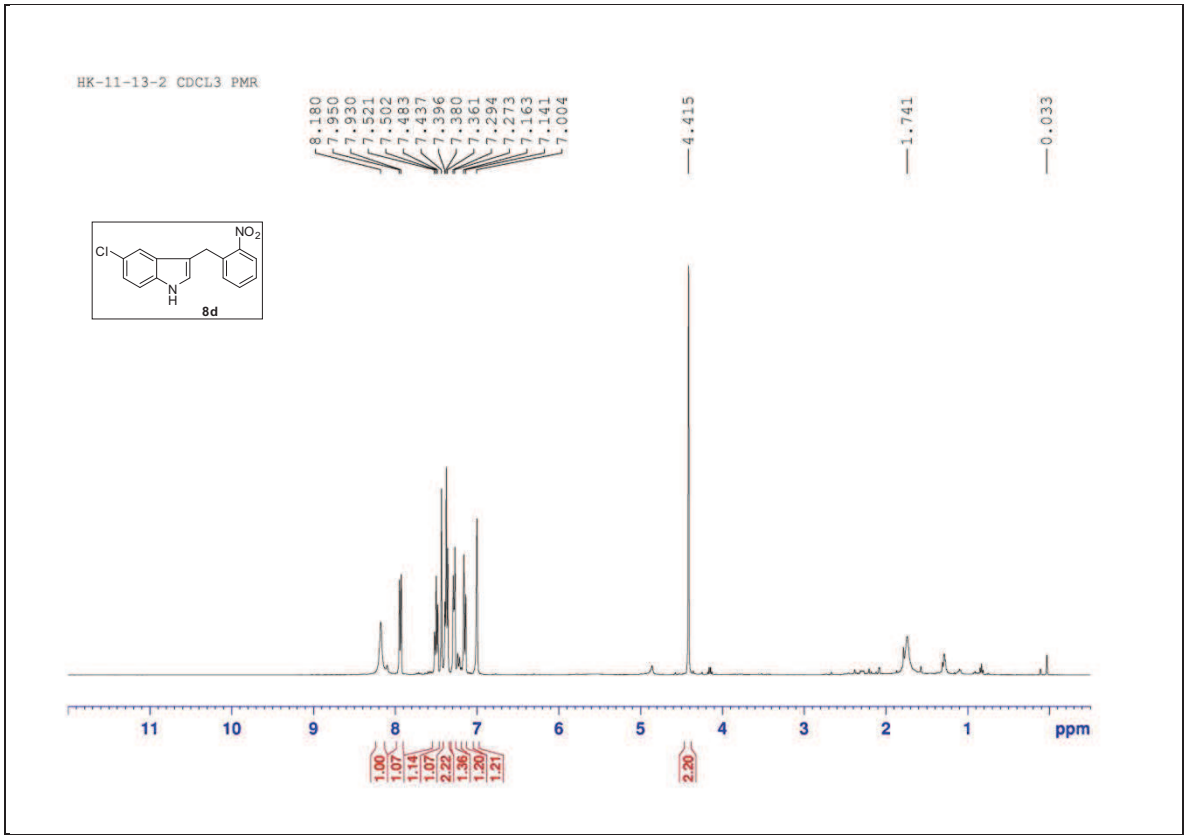

HK-11-03 CMR CDCL3
149.29
136.67
135.77
133.02
131.75
128.12
127.31
125.83
124.75
123.79
120.33
119.74
113.10
111.23
77.42
77.10
76.78
28.40
NO2
Cl
N
H
8c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

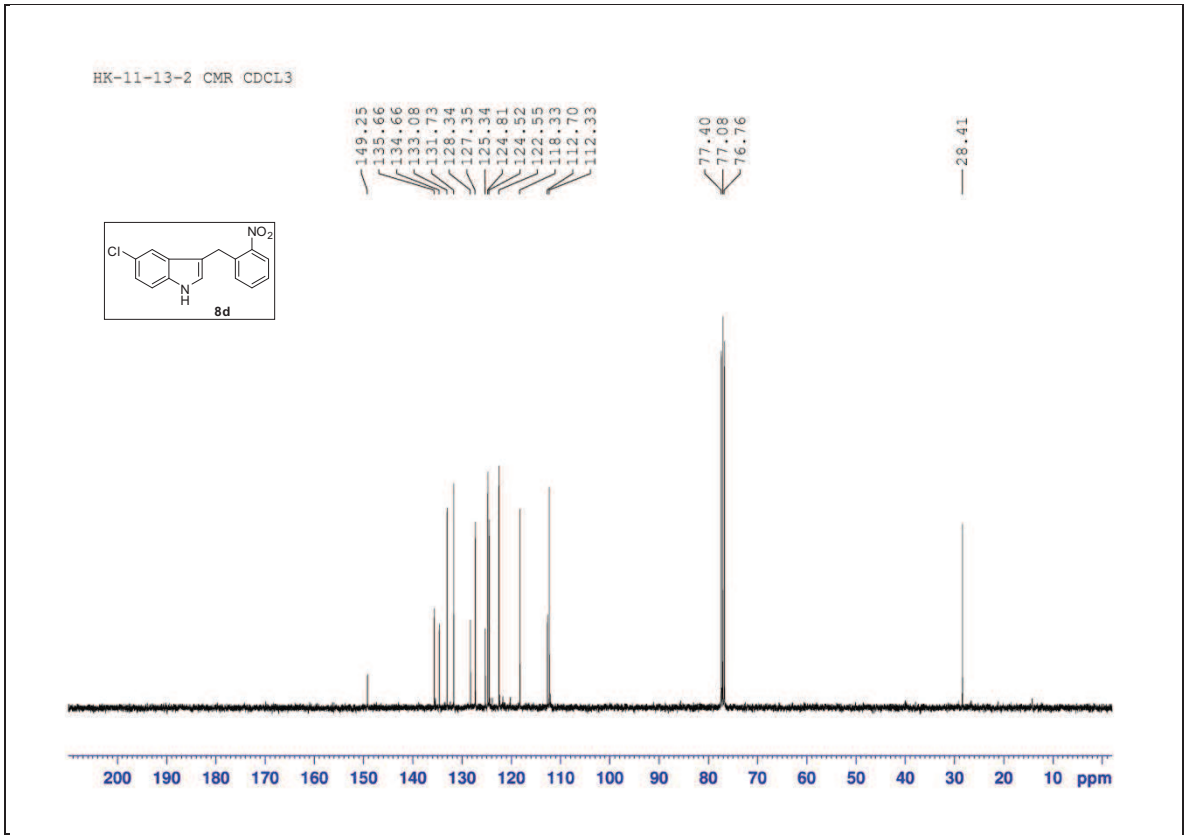

HK-11-03 DEPT CDCL3
133.03
131.75
127.32
124.76
123.79
120.33
119.74
111.24
28.41
NO2
Cl
N
H
8c
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

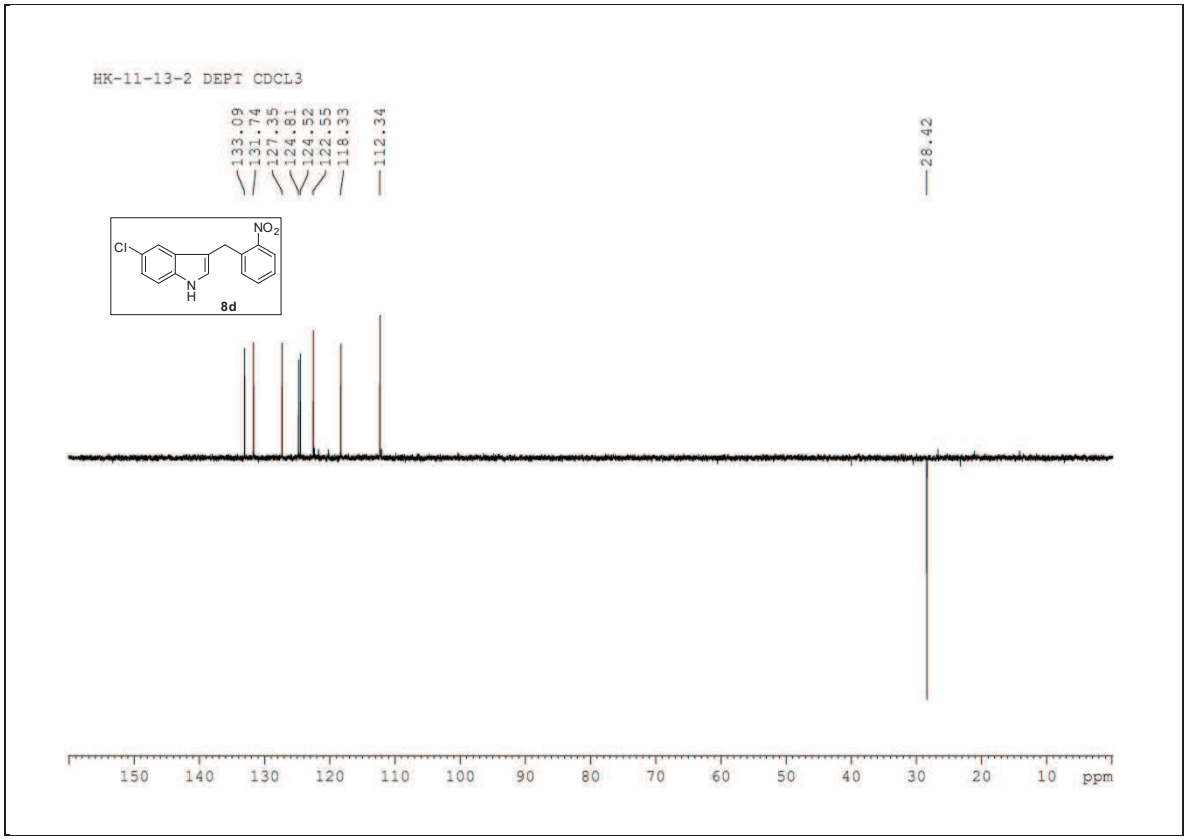

HK-11-03-PMR-DMSO
10.964
7.342
7.314
7.021
6.999
6.690
6.669
3.443
2.508
1.764
Cl
N
H
N
H
Cl
11a
7.0
6.8
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.93
1.98
2.01
2.02
2.00
6.01

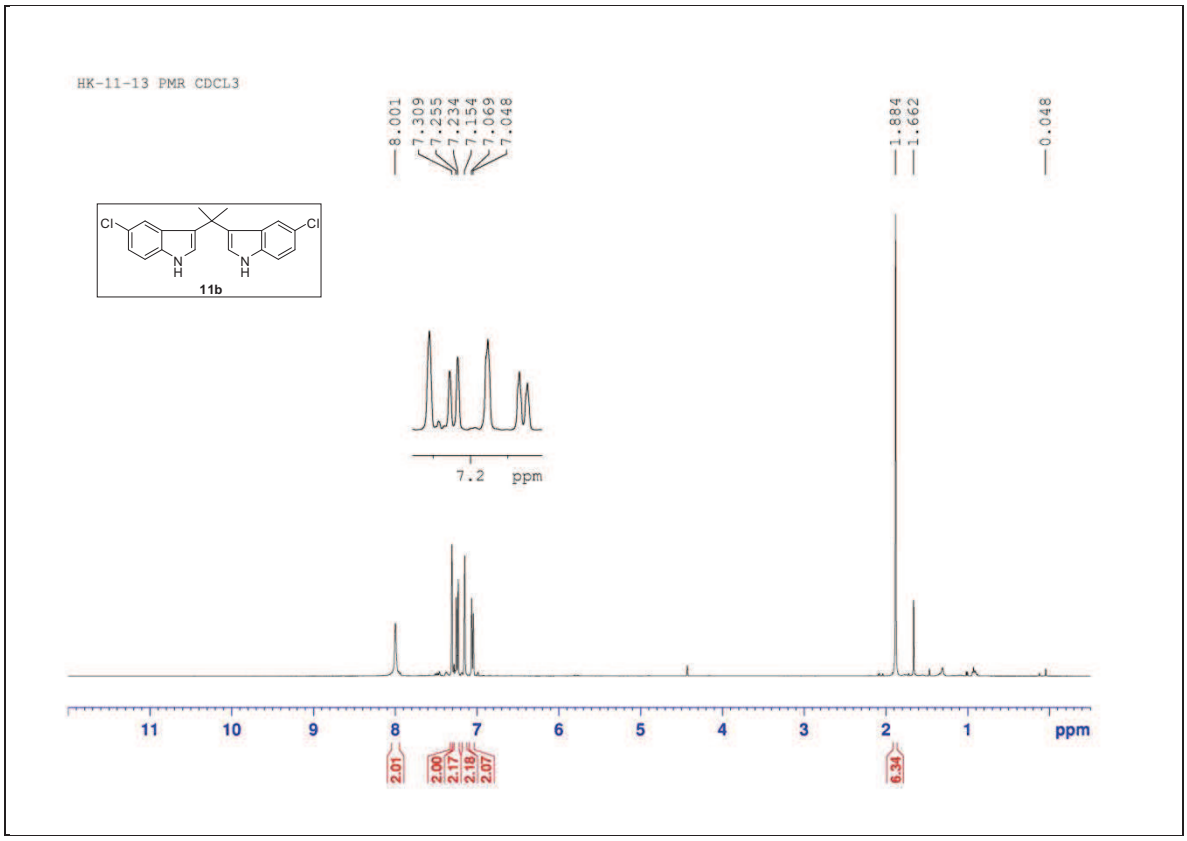

HK-11-03-CMR-DMSO
137.82
125.69
125.05
124.24
122.41
121.54
118.39
111.33
40.52
40.31
40.10
39.89
39.68
39.48
39.27
34.30
30.46
Cl
N
H
N
H
Cl
11a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

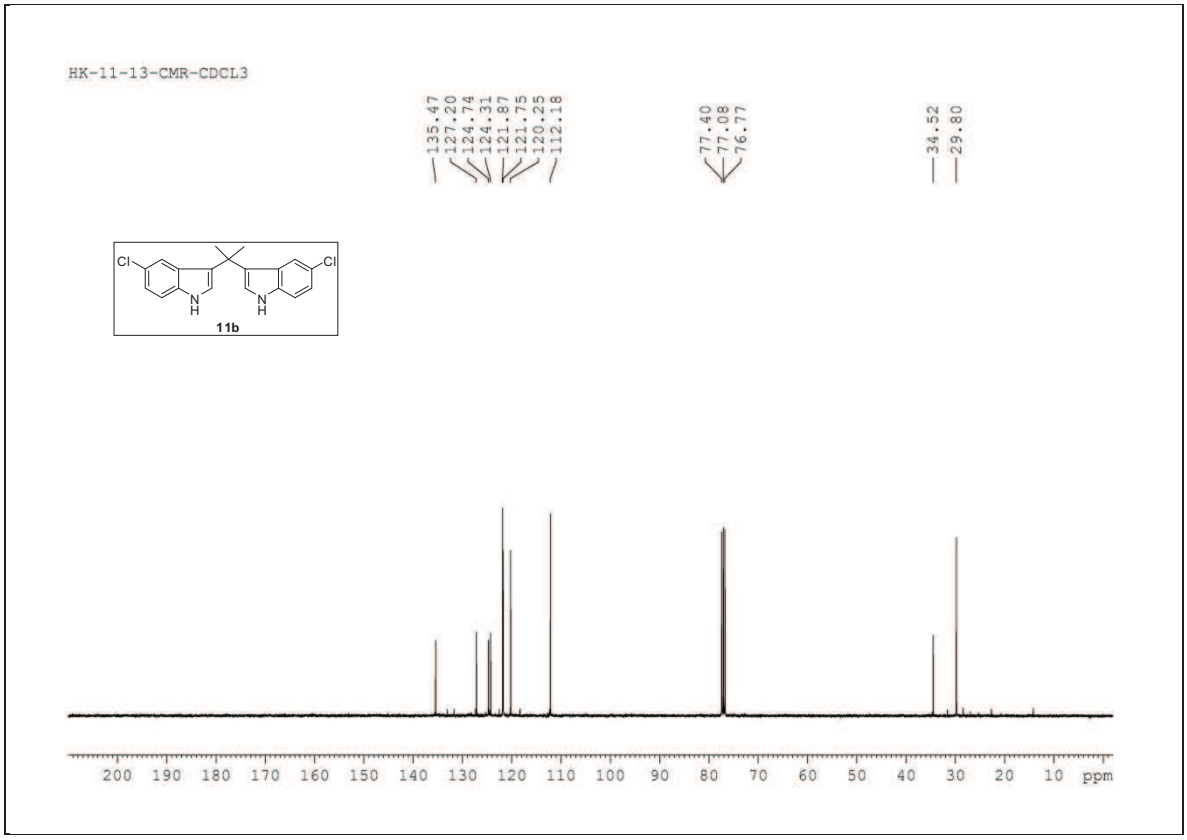

HK-11-03 DEPT DMSO
122.41
121.54
118.39
111.33
30.46
Cl
N
H
N
H
Cl
11a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

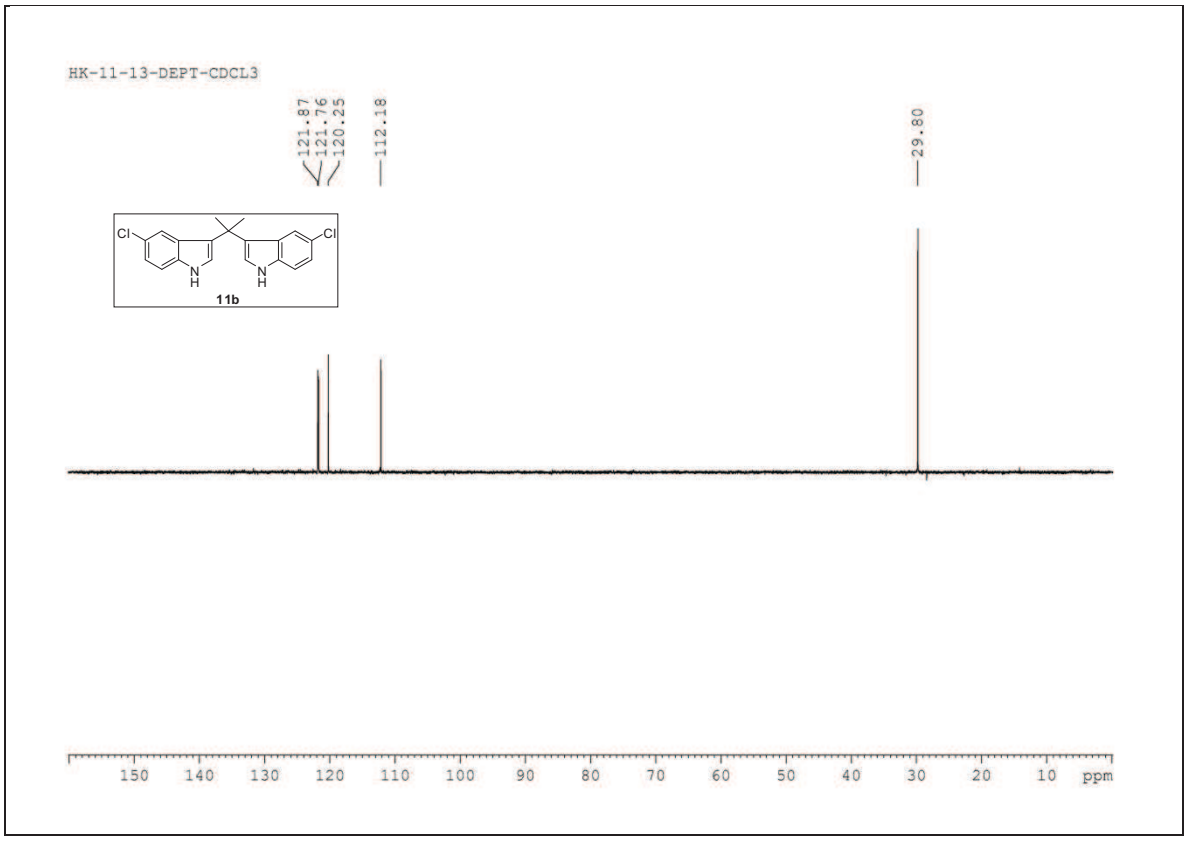

HK-11-13-2 CDCL3 PMR
8.180
7.950
7.930
7.521
7.502
7.483
7.437
7.396
7.380
7.361
7.294
7.273
7.163
7.141
7.004
4.415
1.741
0.033
Cl
NO2
N
H
8d
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.07
1.14
1.07
2.22
1.36
1.20
1.21
2.20

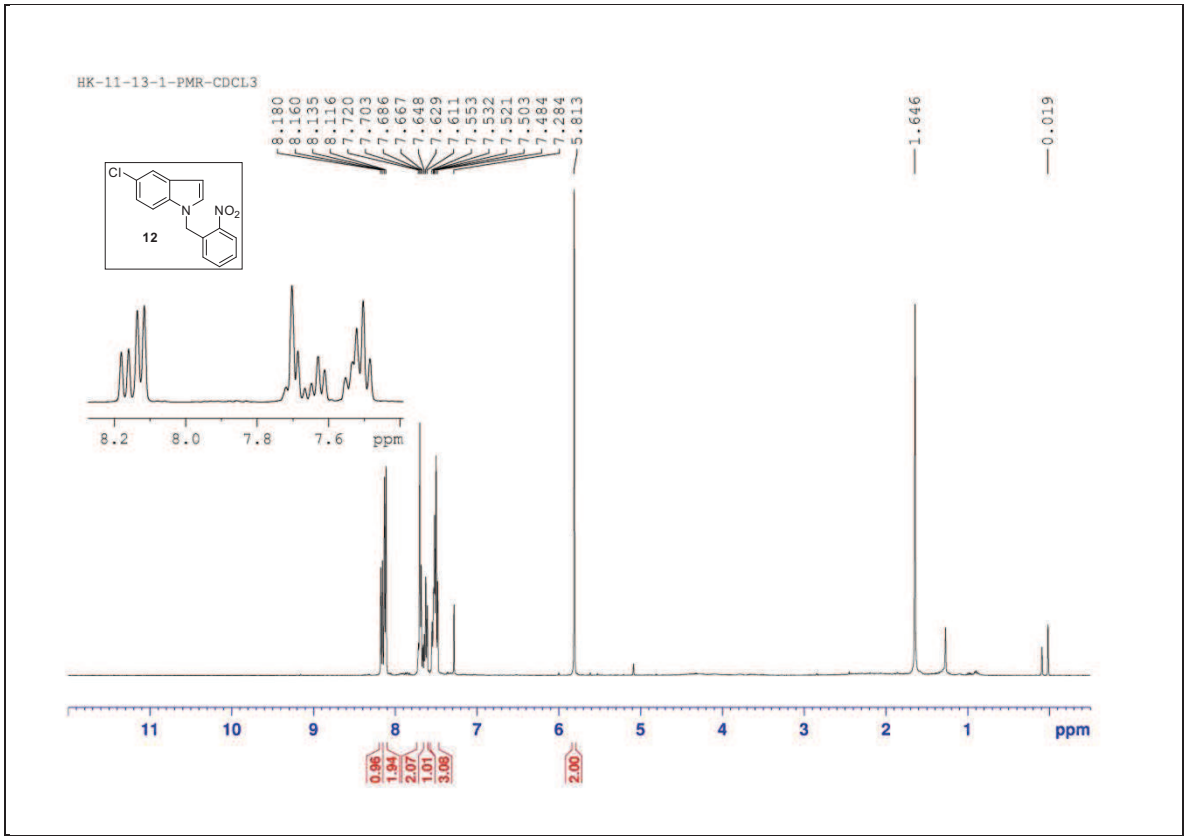

HK-11-13-2 CMR CDCL3
149.25
135.66
134.66
133.08
131.73
128.34
127.35
125.34
124.81
124.52
122.55
118.33
112.70
112.33
77.40
77.08
76.76
28.41
Cl
NO2
N
H
8d
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

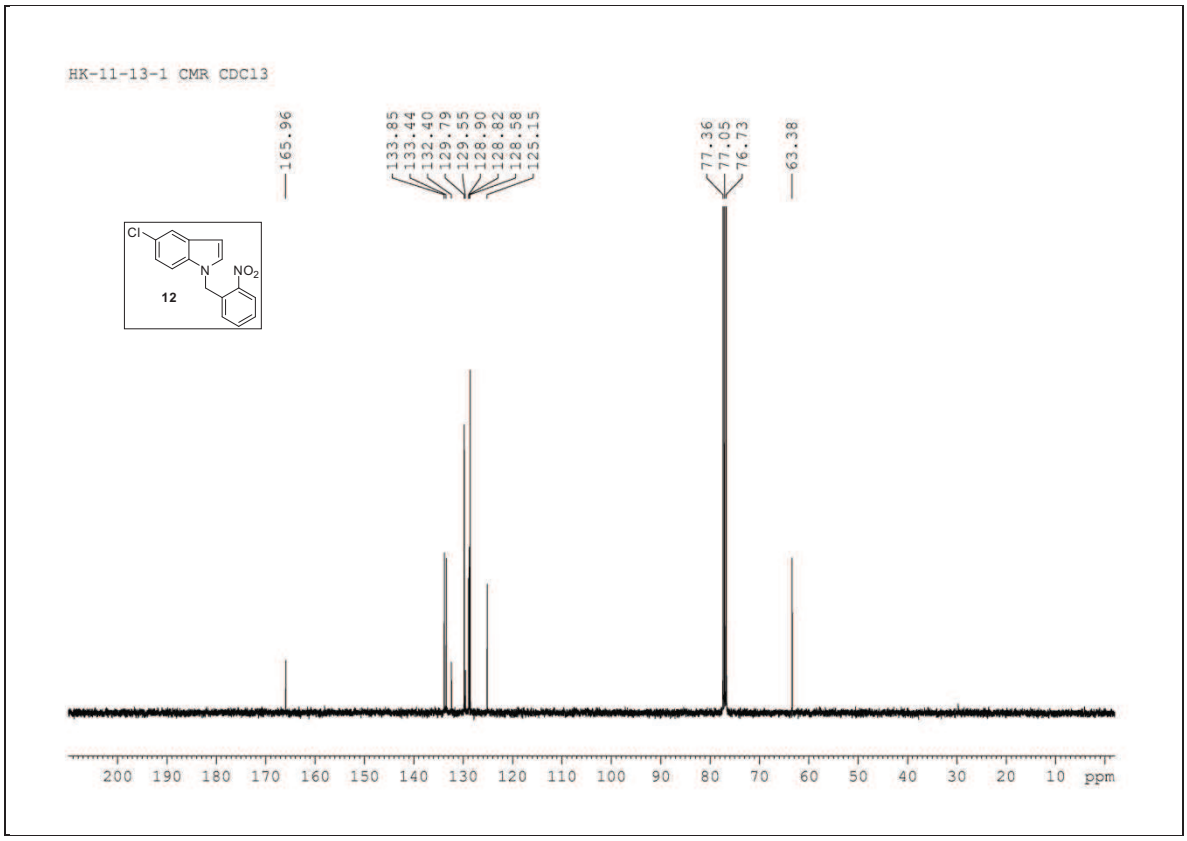

HK-11-13-2 DEPT CDCL3
133.09
131.74
127.35
124.81
124.52
122.55
118.33
112.34
28.42
Cl
NO2
N
H
8d
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

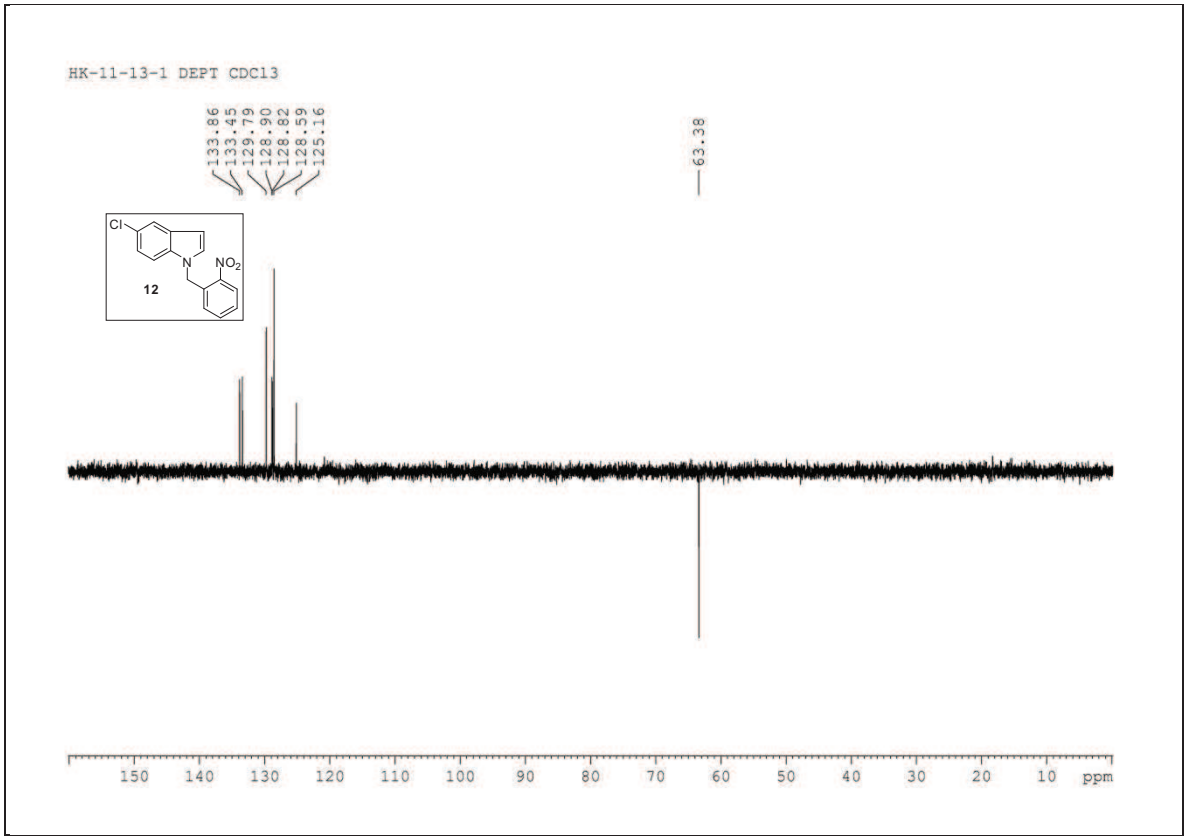

HK-11-13 PMR CDCL3
8.001
7.309
7.255
7.234
7.154
7.069
7.048
1.884
1.662
0.048
Cl
Cl
N
H
N
H
11b
7.2
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
2.01
2.00
2.17
2.18
2.07
6.34

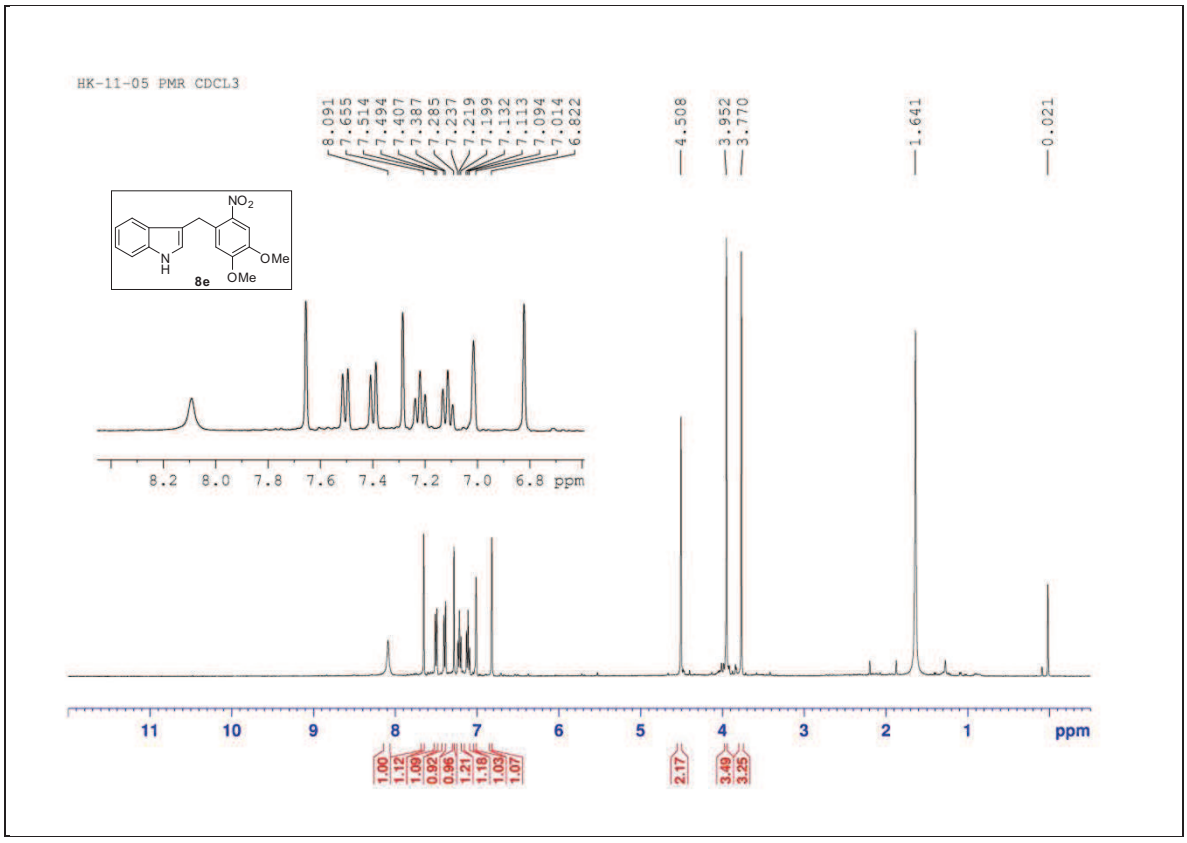

HK-11-13-CMR-CDCL3
135.47
127.20
124.74
124.31
121.87
121.75
120.25
112.18
77.40
77.08
76.77
34.52
29.80
Cl
Cl
N
H
N
H
11b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

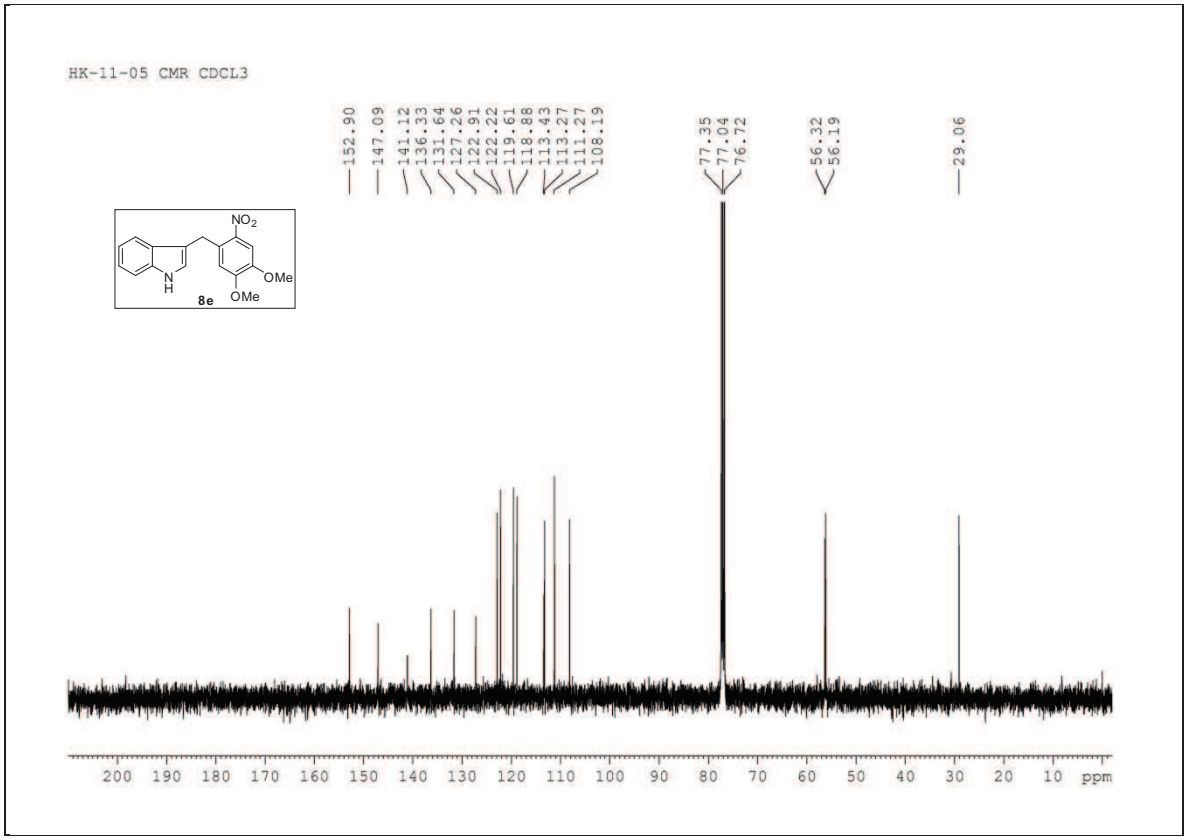

HK-11-13-DEPT-CDCL3
121.87
121.76
120.25
112.18
29.80
Cl
Cl
N
H
N
H
11b
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

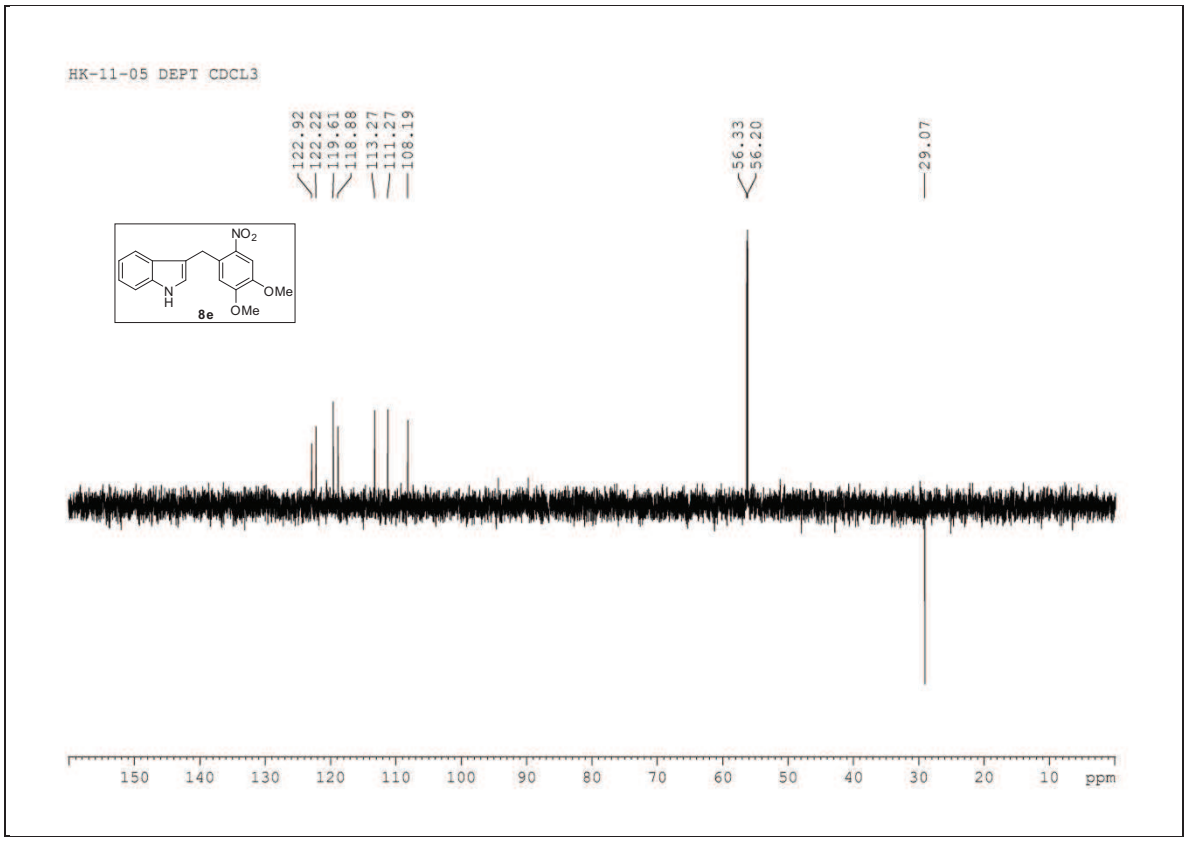

HK-11-13-1-PMR-CDCL3
8.180
8.160
8.135
8.116
7.720
7.703
7.686
7.667
7.648
7.629
7.611
7.553
7.532
7.521
7.503
7.484
7.284
5.813
1.646
0.019
Cl
N
NO2
12
8.2
8.0
7.8
7.6
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
0.96
1.94
2.07
1.01
3.06
2.00

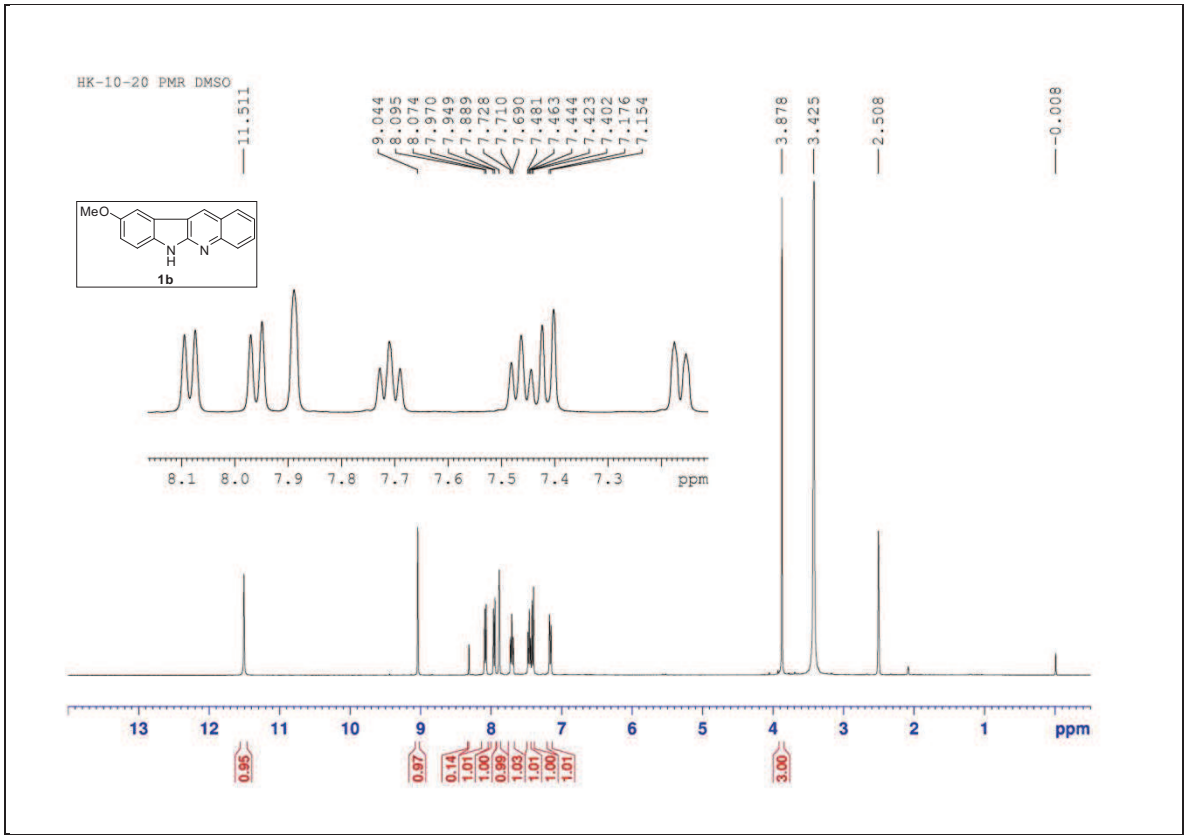

HK-11-13-1 CMR CDCl3
165.96
133.85
133.44
132.40
129.79
129.55
128.90
128.82
128.58
125.15
77.36
77.05
76.73
63.38
Cl
N
NO2
12
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

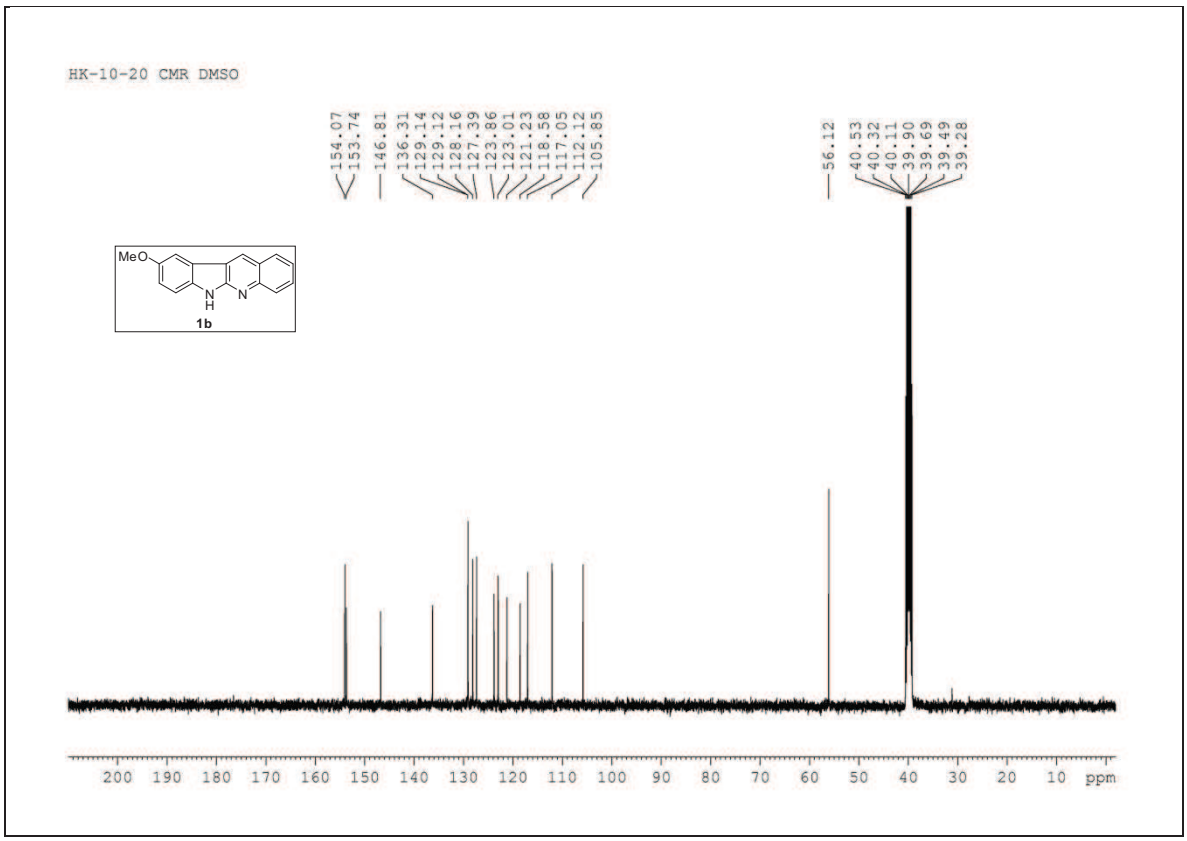

HK-11-13-1 DEPT CDCl3
133.86
133.45
129.79
128.90
128.82
128.59
125.16
63.38
Cl
N
NO2
12
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

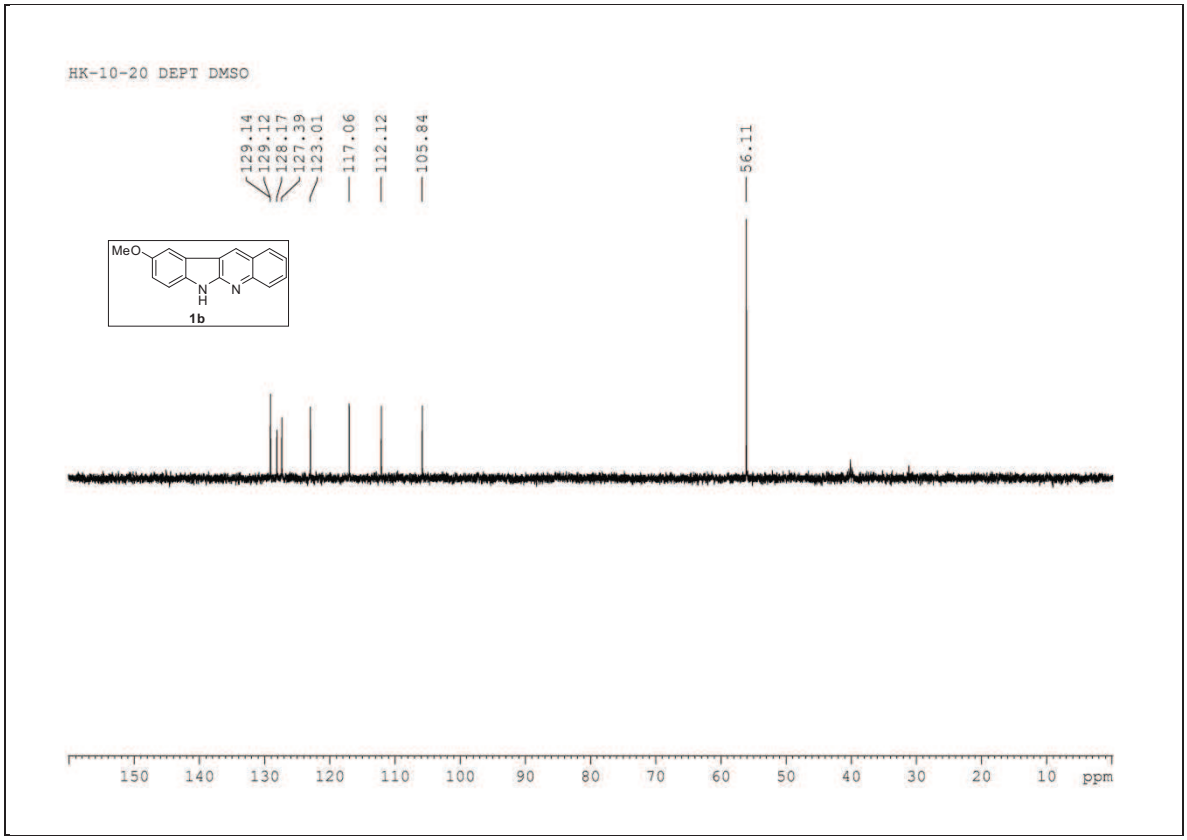

HK-11-05 PMR CDCL3
8.091
7.655
7.514
7.494
7.407
7.387
7.285
7.237
7.219
7.199
7.132
7.113
7.094
7.014
6.822
4.508
3.952
3.770
1.641
0.021
NO2
N
H
OMe
OMe
8e
8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.12
1.09
0.92
0.96
1.21
1.18
1.03
1.07
2.17
3.49
3.25

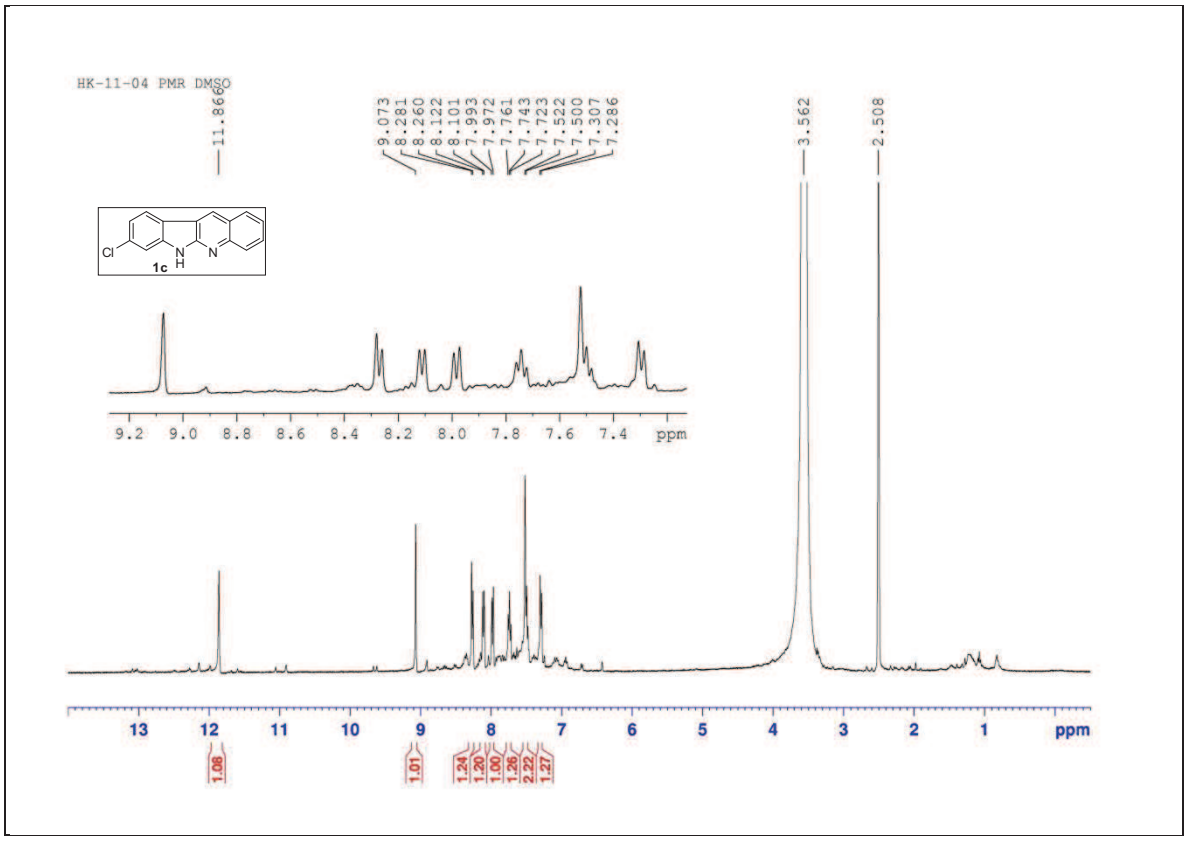

HK-11-05 CMR CDCL3
152.90
147.09
141.12
136.33
131.64
127.26
122.91
122.22
119.61
118.88
113.43
113.27
111.27
108.19
77.35
77.04
76.72
56.32
56.19
29.06
NO2
OMe
OMe
N
H
8e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

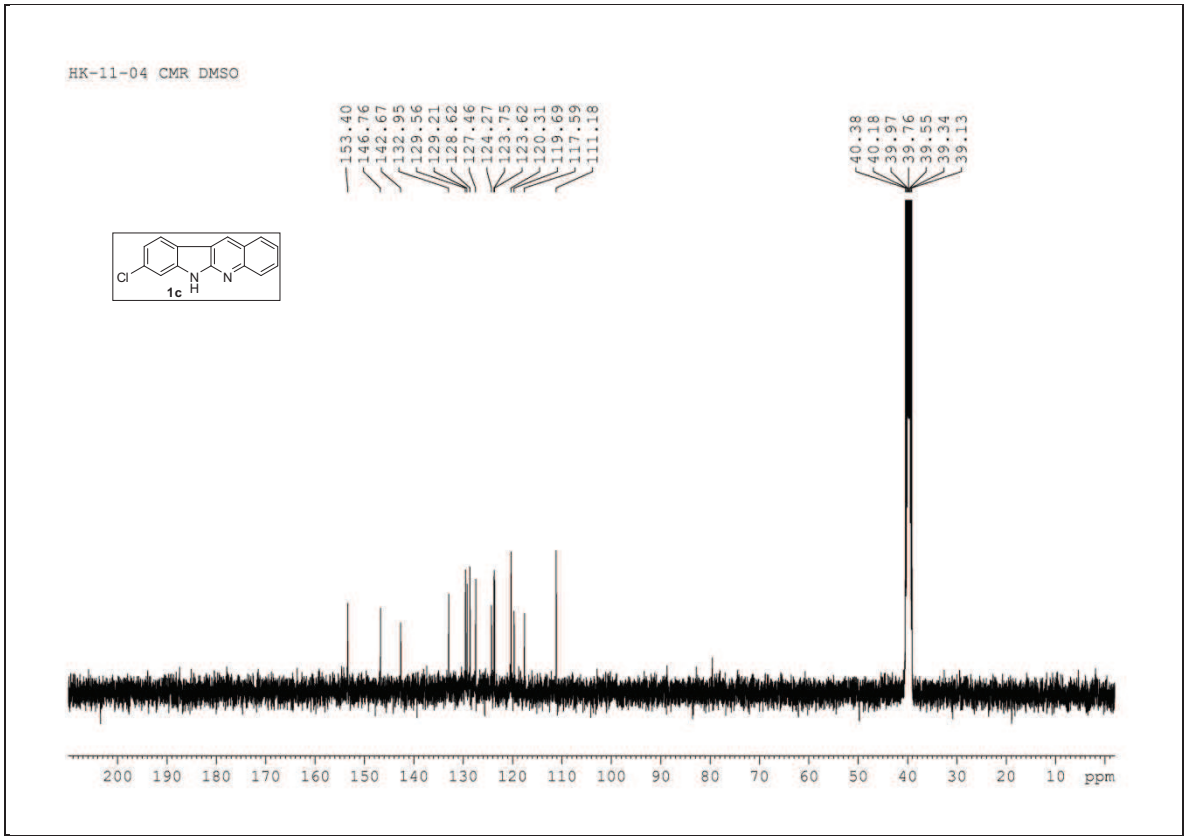

HK-11-05 DEPT CDCL3
122.92
122.22
119.61
118.88
113.27
111.27
108.19
56.33
56.20
29.07
NO2
OMe
OMe
N
H
8e
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

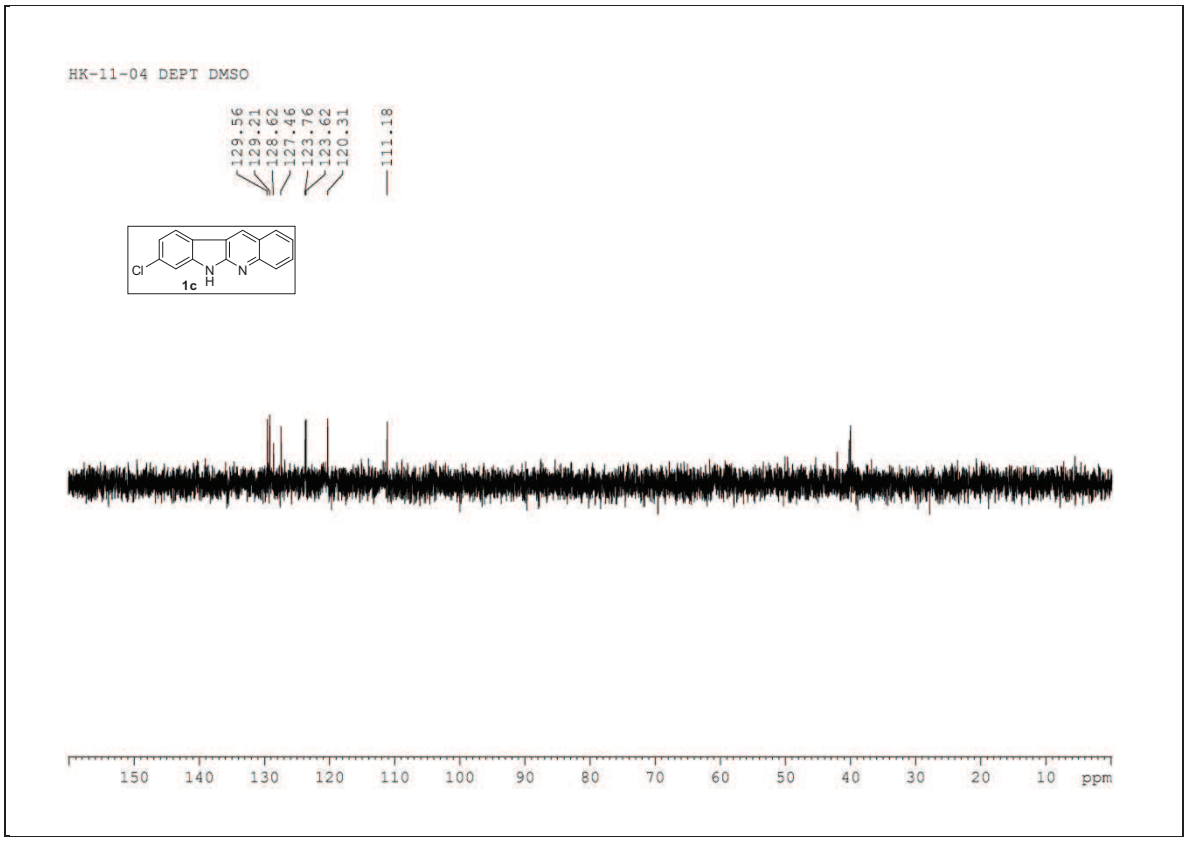

HK-10-20 PMR DMSO
11.511
9.044
8.095
8.074
7.970
7.949
7.889
7.728
7.710
7.690
7.481
7.463
7.444
7.423
7.402
7.176
7.154
3.878
3.425
2.508
0.008
MeO
N
H
1b
8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.95
0.97
0.14
1.01
1.00
0.99
1.03
1.01
1.00
1.01
3.00

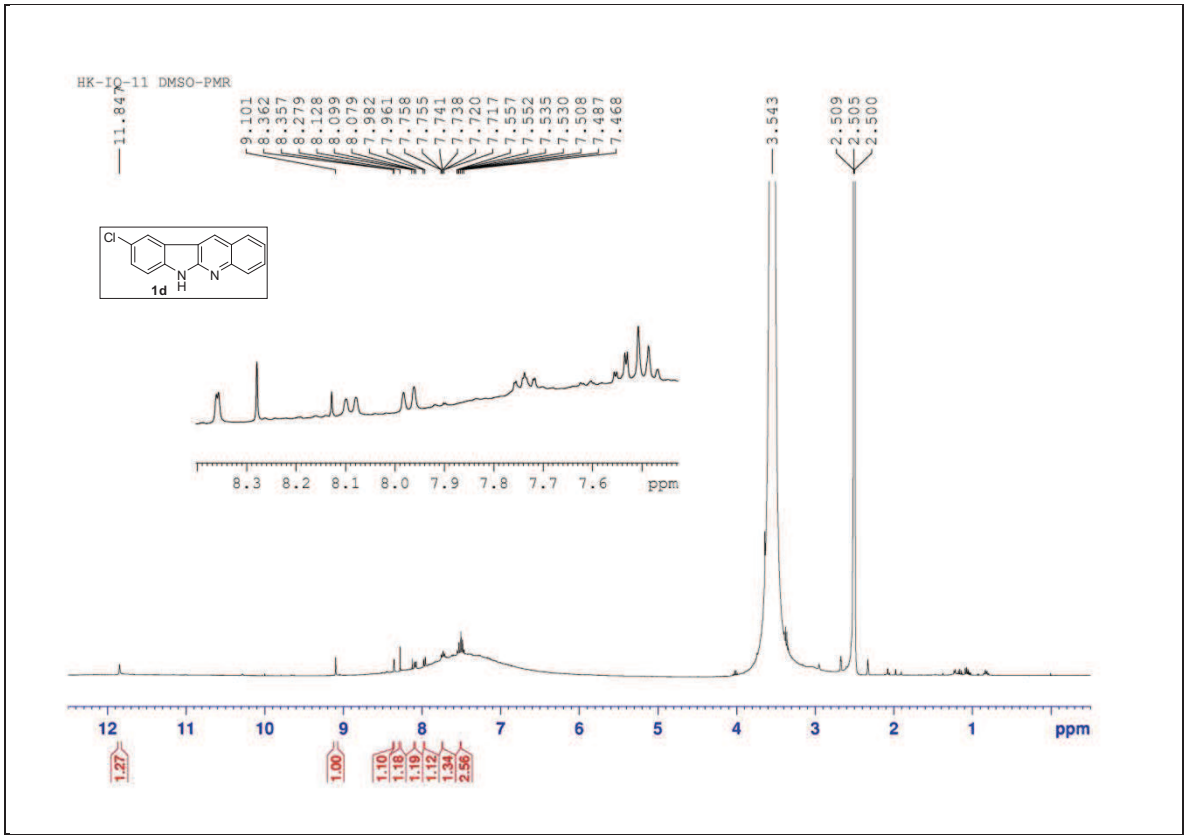

HK-10-20 CMR DMSO
154.07
153.74
146.81
136.31
129.14
129.12
128.16
127.39
123.86
123.01
121.23
118.58
117.05
112.12
105.85
56.12
40.53
40.32
40.11
39.90
39.69
39.49
39.28
MeO
N
H
1b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

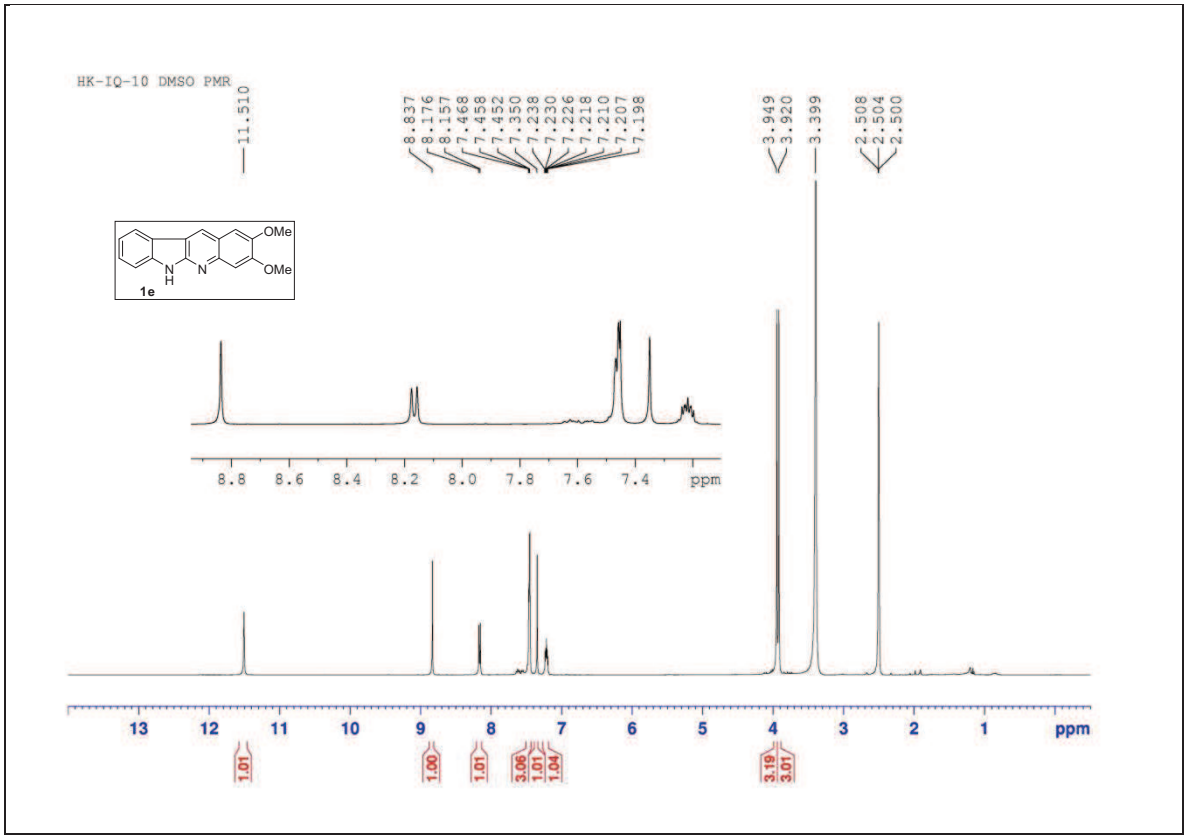

HK-10-20 DEPT DMSO
129.14
129.12
128.17
127.39
123.01
117.06
112.12
105.84
56.11
MeO
N
H
N
1b
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

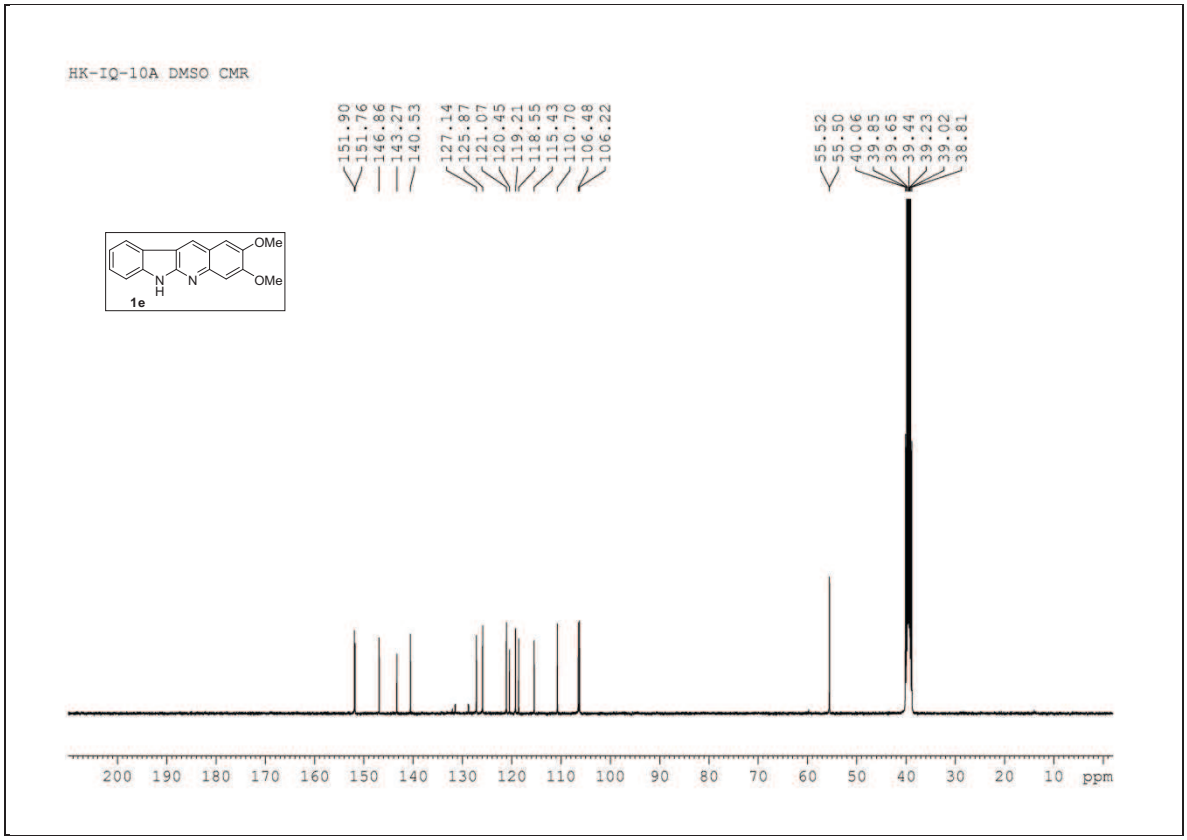

HK-11-04 PMR DMSO
11.866
9.073
8.281
8.260
8.122
8.101
7.993
7.972
7.761
7.743
7.723
7.522
7.500
7.307
7.286
3.562
2.508
Cl
N
H
N
1c
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.08
1.01
1.24
1.20
1.00
1.26
2.22
1.27

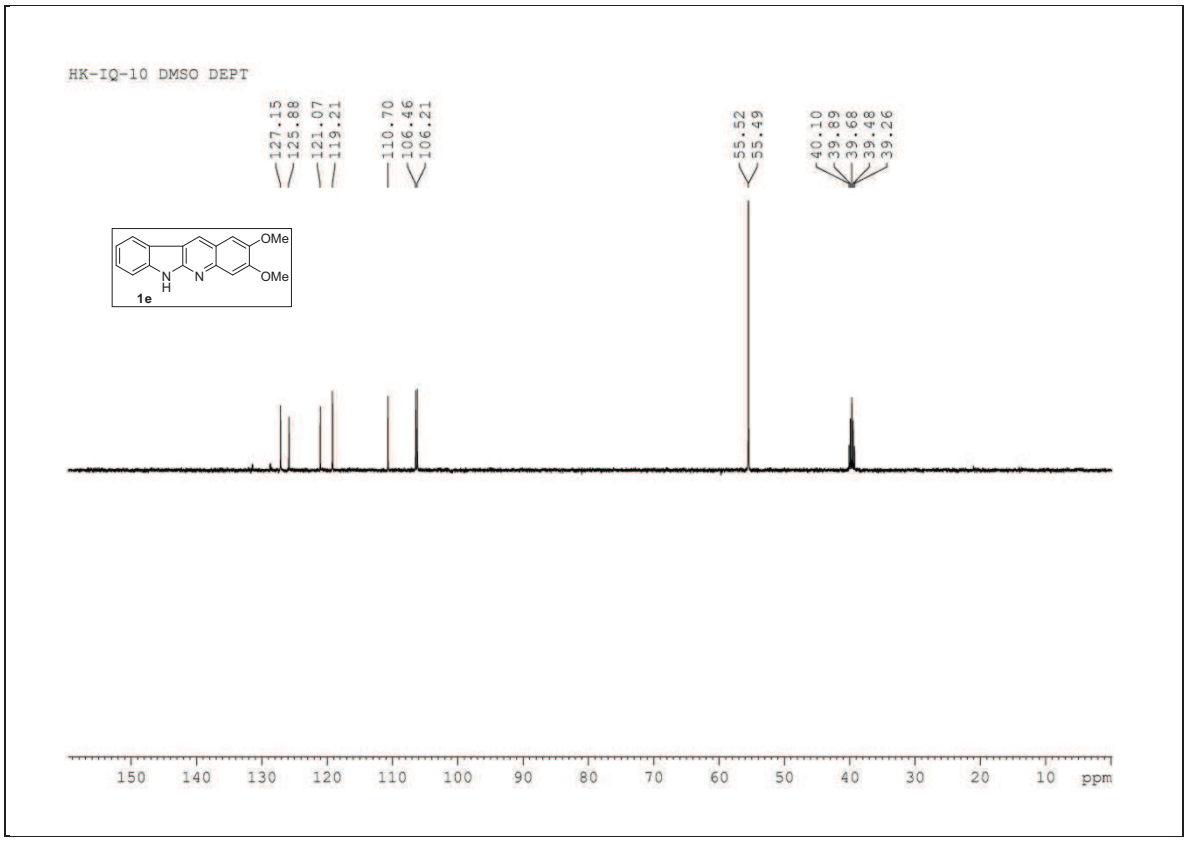

HK-11-04 CMR DMSO
153.40
146.76
142.67
132.95
129.56
129.21
128.62
127.46
124.27
123.75
123.62
120.31
119.69
117.59
111.18
40.38
40.18
39.97
39.76
39.55
39.34
39.13
Cl
N
H
N
1c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

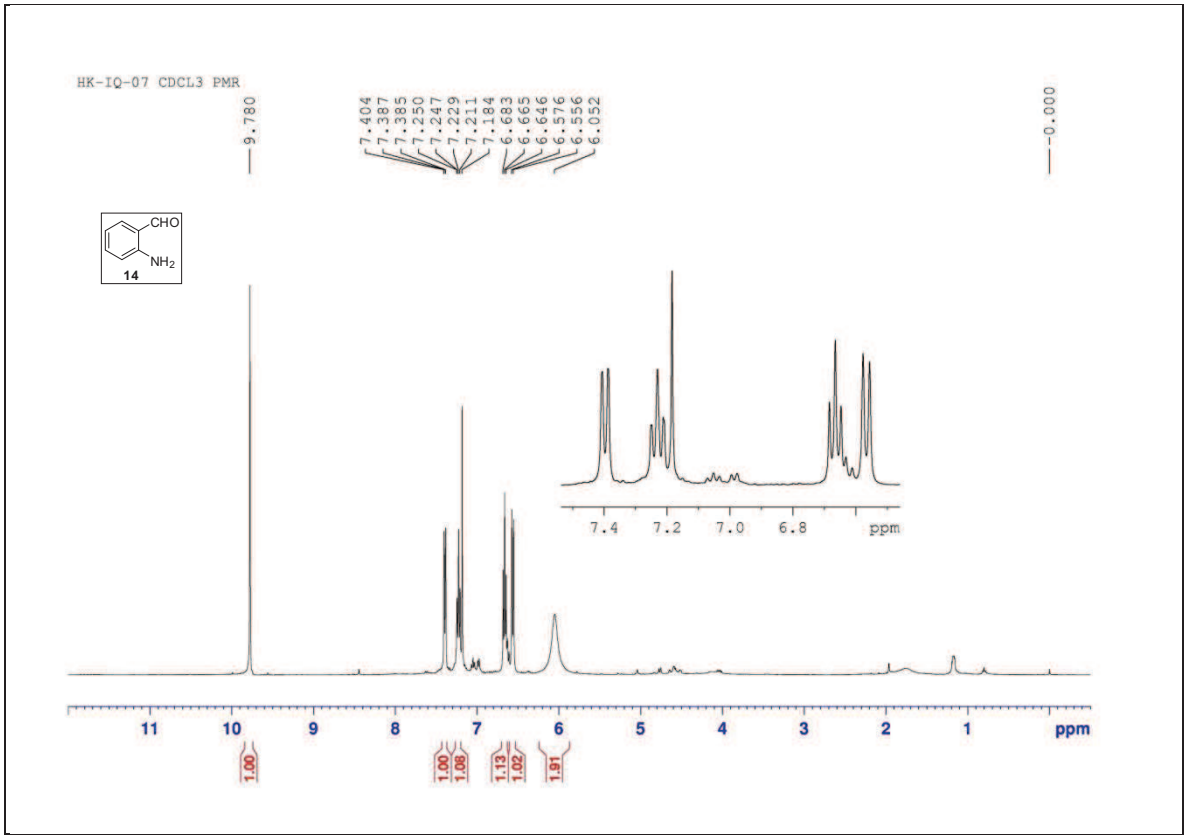

HK-11-04 DEPT DMSO
129.56
129.21
128.62
127.46
123.76
123.62
120.31
111.18
Cl
N
H
N
1c
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HK-IQ-11 DMSO-PMR
11.847
9.101
8.362
8.357
8.279
8.128
8.099
8.079
7.982
7.961
7.758
7.755
7.741
7.738
7.720
7.717
7.557
7.552
7.535
7.530
7.508
7.487
7.468
3.543
2.509
2.505
2.500
Cl
N
H
N
1d
8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 ppm
12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.27
1.00
1.10
1.18
1.19
1.12
1.34
2.56


HK-IQ-10 DMSO PMR
11.510
8.837
8.176
8.157
7.468
7.458
7.452
7.350
7.238
7.230
7.226
7.218
7.210
7.207
7.198
3.949
3.920
3.399
2.508
2.504
2.500
OMe
OMe
N
H
N
1e
8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.01
1.00
1.01
3.06
1.01
1.04
3.19
3.01


HK-IQ-10A DMSO CMR
151.90
151.76
146.86
143.27
140.53
127.14
125.87
121.07
120.45
119.21
118.55
115.43
110.70
106.48
106.22
55.52
55.50
40.06
39.85
39.65
39.44
39.23
39.02
38.81
OMe
OMe
N
H
N
1e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HK-IQ-10 DMSO DEPT
127.15
125.88
121.07
119.21
110.70
106.46
106.21
55.52
55.49
40.10
39.89
39.68
39.48
39.26
OMe
OMe
N
H
N
1e
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HK-IQ-07 CDCL3 PMR
9.780
7.404
7.387
7.385
7.250
7.247
7.229
7.211
7.184
6.683
6.665
6.646
6.576
6.556
6.052
-0.000
CHO
NH2
14
7.4
7.2
7.0
6.8
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.00
1.08
1.13
1.02
1.91

Chapter 2

Synthetic Studies of *6H*-Isoindolo[*2,1-a*]indol-*6*-ones

2.1: Introduction

Indole based organic compounds are usually encountered in bioactive substrates. *6H*-Isoindolo[*2,1-a*]indol-*6*-one **1** is a common and predominant candidate of such type. Structurally it is a tetracyclic system having an indole ring fused to isoindoline moiety with tethered nitrogen (Figure 1).

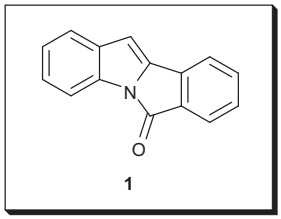


Figure 1: *6H*-Isoindolo[*2,1-a*]indol-*6*-one

Although this heterocyclic structural motif is yet to be revealed in any natural product. It has already received its position of major importance as a bioactive compound.[1] Some of its derivatives are well known for their specific bioactivity profiles. Isoindoloindolone derivatives are reported as potent ligands of MT_3.[2] The third melatonin binding site, MT_3 is an enzyme, quinine reductase-2 and not a usual seven transmembrane domains receptor. *2*-Hydroxy-*8,9*-dimethoxy-*6H*-isoindolo[*2,1-a*]indol-*6*-one **2a** have subnanomolar affinity for melatonin binding site MT_3.

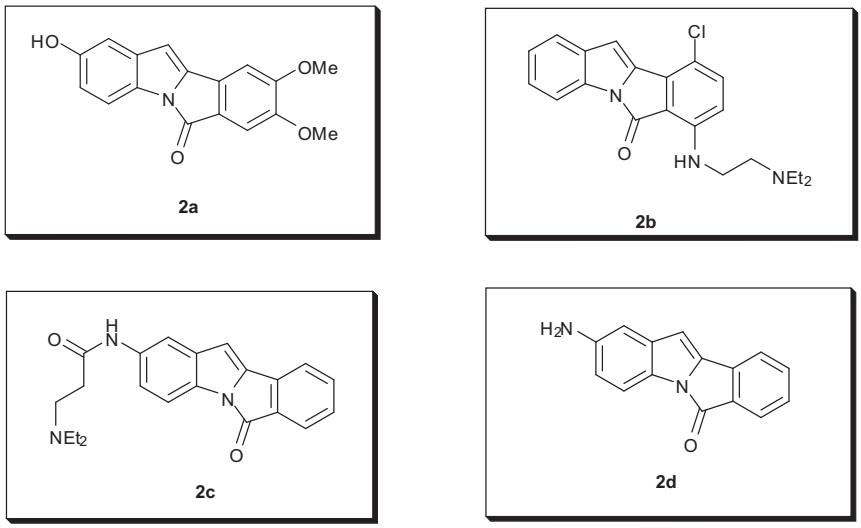


Figure 2: Biologically important Isoindoloindolones

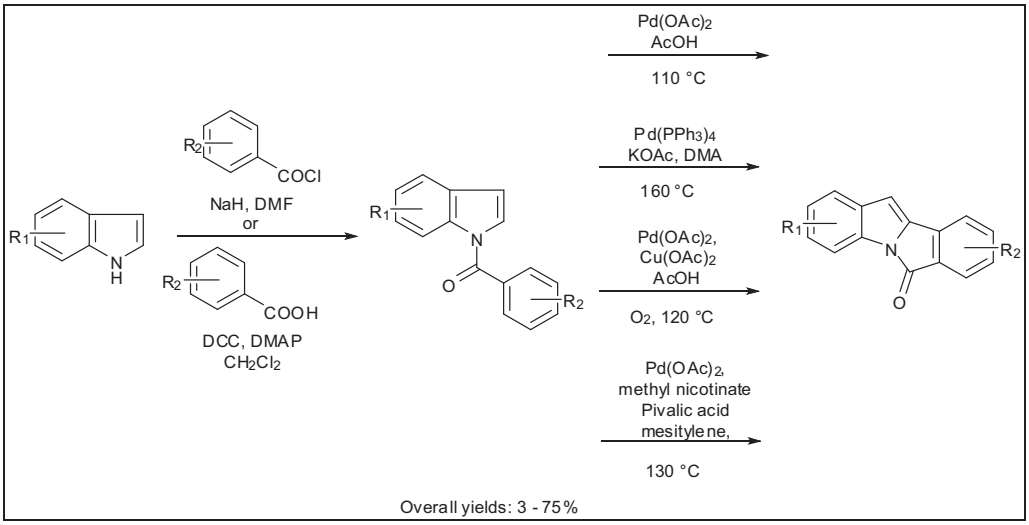
10-Chloro-*7*-(*2*-(diethylamino)-ethylamino)-*6H*-isoindolo[*2,1-a*]indol-*6*-one **2b**, *3*-(diethylamino)-N-(*6*-oxo-*6H*-isoindolo[*2,1-a*]indol-*2*-yl)propanamide **2c**, and *2*-amino-*6H*-isoindolo[*2,1-a*]indol-*6*-one **2d** shows DNA binding ability and non-specific interference with the topoisomerase-I catalytic cycle (Figure 2). Compound **2b** also displays antiproliferative effect against HT-29 and L1210 cell lines. Compounds **2c** and **2d** exhibits inhibitory potency for topoisomerase-II comparable to that of etoposide.[3] The NorA protein is a multidrug resistant efflux in bacterium

Staphylococcus aureas. This has resulted in resistance towards numerous structurally dissimilar antibiotics such as norfloxacin, ethidium bromide, berberine, etc. *6H*-Isoindolo[*2,1-a*]indol-*6*-one **1** is used as precursor for the synthesis of *2*-aryl-*5*-nitro-indoles as NorA efflux pump inhibitors.[4] *6H*-Isoindolo[*2,1-a*]indol-*6*-one **1** also exhibit charge transfer fluorescence with high quantum yields in non polar solvents.[5]

2.2: Literature review

Syntheses of Isoindoloindolones were developed by various research groups all over the world for decades due to their diverse applications. Some of these efficient and remarkable achievements are discussed below.

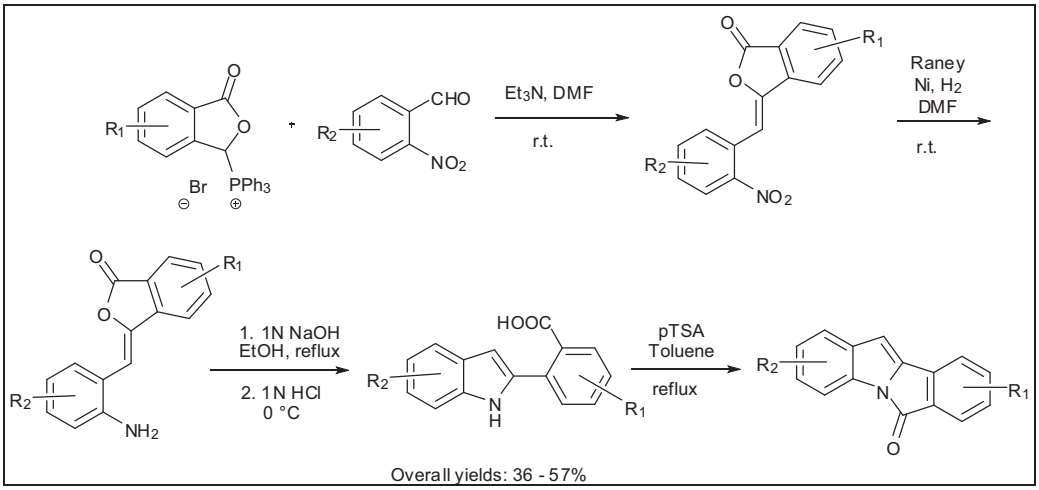
Palladium acetate promoted intramolecular-dehydrogenative cyclisation of *1*-benzoylindole is a short and simple method for the synthesis of isoindoloindolones (Scheme 1) as developed and explored by Toshio Itahara since 1979.[6a-d] *1*-Benzoylindole was prepared in 64 % yield by reaction of NaH and indole in DMF followed by addition of Benzoyl chloride.[6a]



Scheme 1

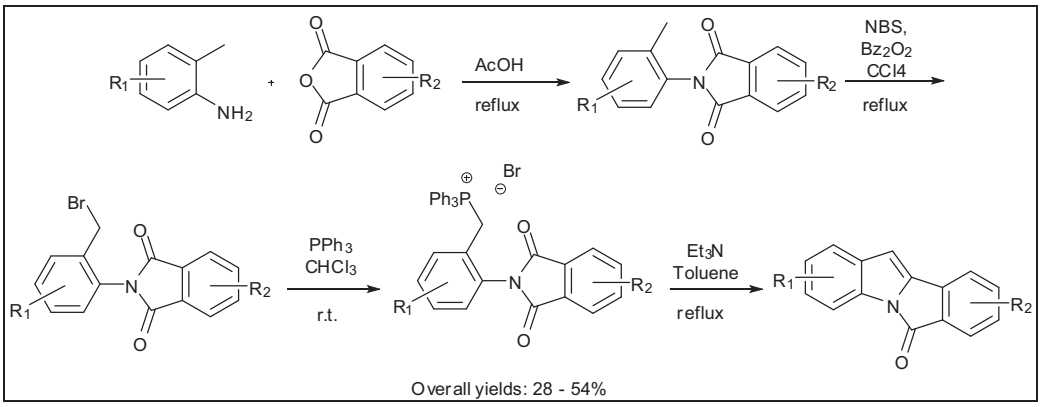
Similarly this method was further explored by many research groups. Bremner and his group[4a] used DCC coupling of indole and benzoic acid for preparing *1*-benzoylindoles and then reacted with Palladium acetate in refluxing acetic acid to give isoindoloindolone in 47 % yield. Dinnell *et al*.[1b] used $Pd(PPh_3)_4$ as catalyst and KOAc as base in refluxing DMA for the synthesis of isoindoloindolones. B. DeBoef and co-workers[6e] used $Cu(OAc)_2$ along with $Pd(OAc)_2$ in refluxing acetic acid in O_2 atmosphere for intramolecular aerobic oxidative coupling of 1-benzoylindoles to give isoindoloindolones. S. R. Kandukuri and M. Oestreich[6f] used methyl nicotinate as ligand for $Pd(OAc)_2$ in mesitylene and pivalic acid in O_2 atmosphere for aerobic dehydrogenative double C-H coupling in 1-benzoylindoles to give isoindoloindolones.

Boutin and co-workers[2] have developed a sequence involving Wittig olefination of *o*-nitrobenzaldehyde and reduction of nitroarene to aniline by Raney Ni followed by base hydrolysis of lactone and cyclisation to prepare isoindoloindolone (Scheme 2).

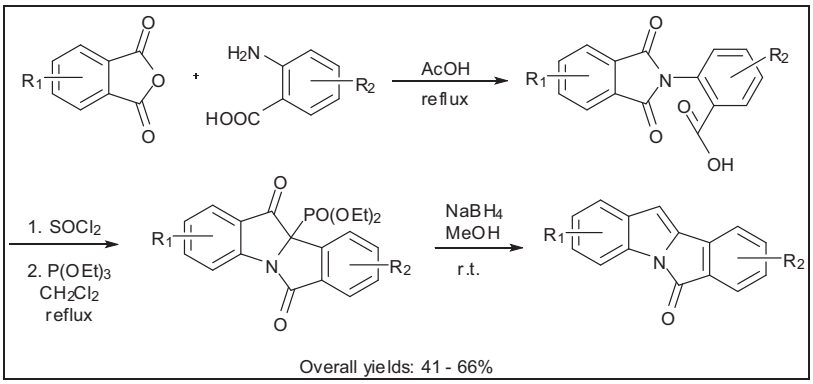


Scheme 2

Intramolecular Wittig reaction is employed as a key step by Monneret and his group[3] to synthesize isoindoloindolones (Scheme 3). The Wittig salt was prepared by benzylic bromination of N-(*o*-tolyl)-phthalimides followed by reaction with PPh_3.



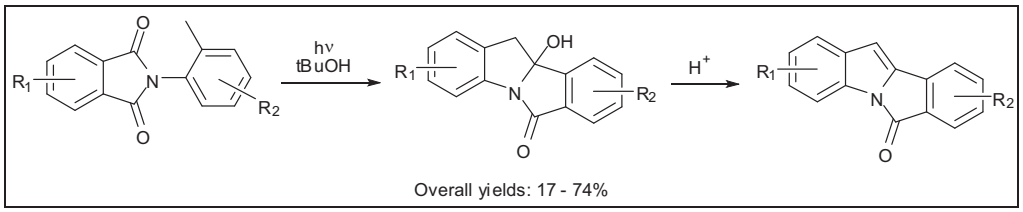
Scheme 3



Scheme 4

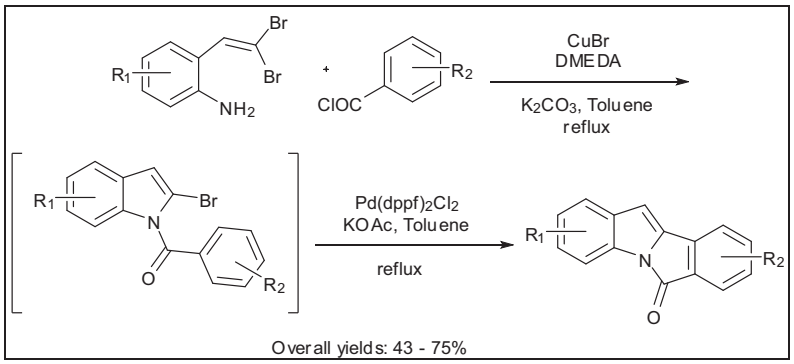
Griffiths and his group[7] developed a route to isoindoloindolones using *o*-(N-phthaloyl)benzoic acids (Scheme 4). Process involves formation of acid chlorides followed by reaction with triethylphosphite to give tetracyclic-β-keto phosphonates that on reaction with $NaBH_4$ gave required isoindoloindolones in good overall yields.

UV irradiation of N-(*o*-tolyl)phthalimides followed by dehydration with acid as reported by Kanaoka and co-workers[8a-c] (Scheme 5) resulted in photochemical cyclisation[8d] to isoindoloindolones.

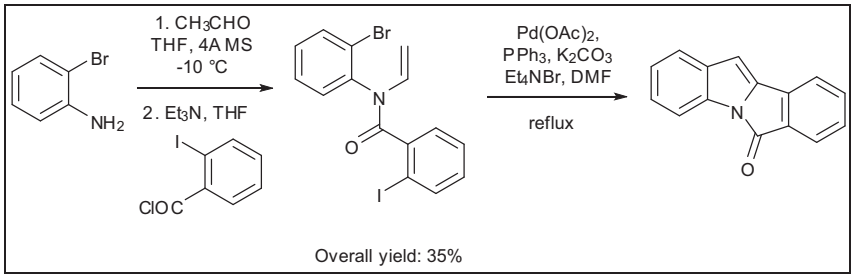


Scheme 5

Bao's group[9] reported synthesis of isoindoloindolones through a one-pot sequential Cu catalysed C-N coupling and Pd catalysed C-H activation reaction (Scheme 6). This two-step one-pot synthesis uses *o*-gem-dibromovinylanilines as a starting material.



Scheme 6

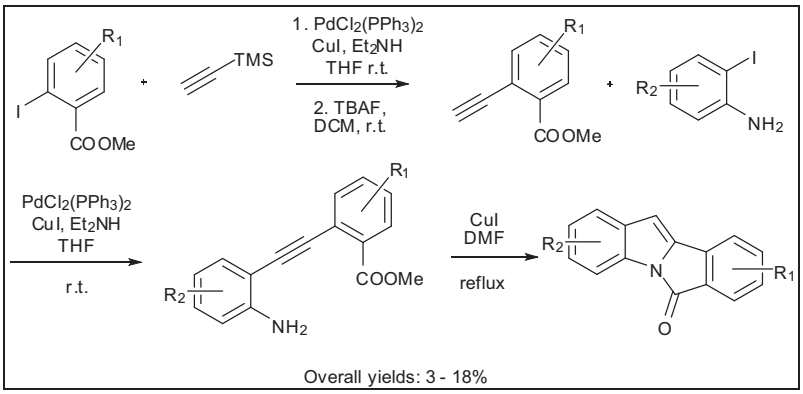


Scheme 7

Cyclisation of dihalo-*N*-vinylbenzamides to isoindoloindolone by tandem Heck reaction is demonstrated by Dominguez's group[10] in 81 % yield (Scheme 7). The required dihalo-*N*-

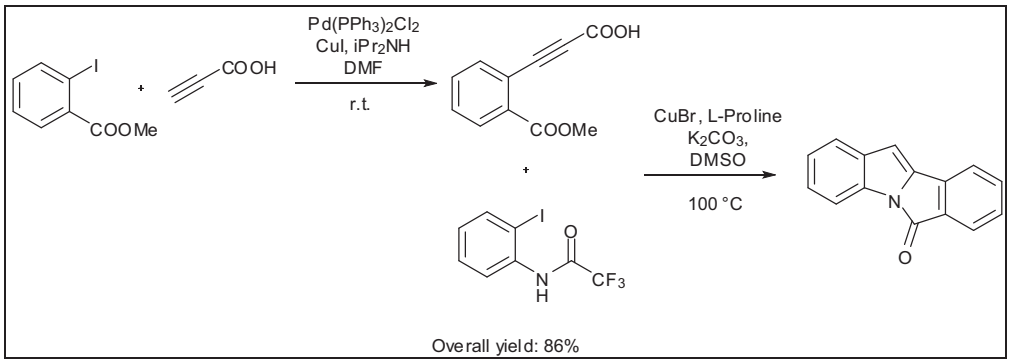
vinylbenzamide was obtained by condensation of *o*-bromoarylamine with acetaldehyde followed by benzoylation with *o*-iodobenzoyl chloride.

Estevez's group[11] reported a copper mediated intramolecular cyclisation of methyl-*2*-(*2*-amino-phenylethynyl)benzoates to isoindoloindolones (Scheme 8). The required precursor was prepared by double Sonogashira coupling reactions initially between trimethylsilylacetylene and methyl-*o*-iodobenzoate then subsequently with *o*-iodoaniline.

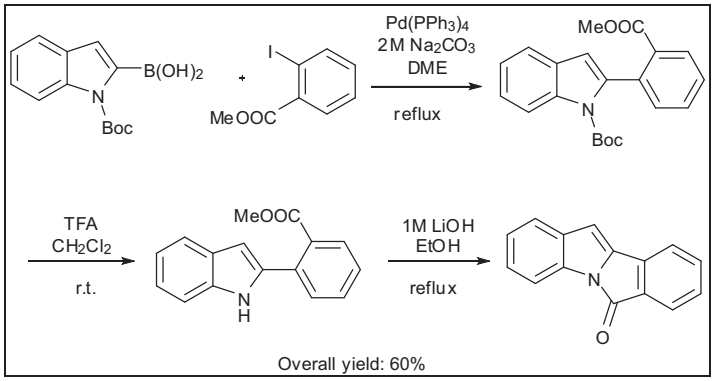


Scheme 8

T. Ponpandian and S. Muthusubramanian[12] achieved isoindoloindolone using copper catalysed domino sp-sp^2 decarboxylative cross coupling reaction of arylpropiolic acids with *o*-iodotriflouroacetanilide and subsequent cyclisation (Scheme 9).



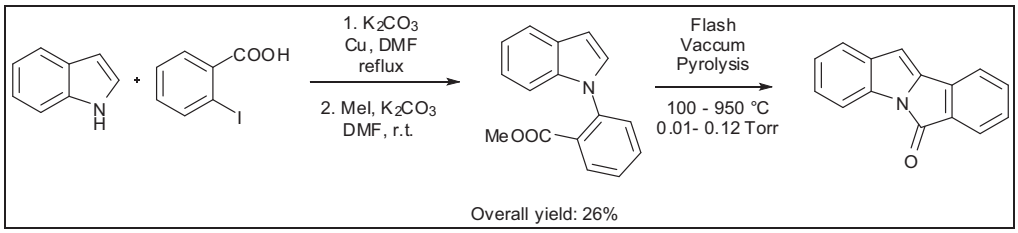
Scheme 9



Scheme 10

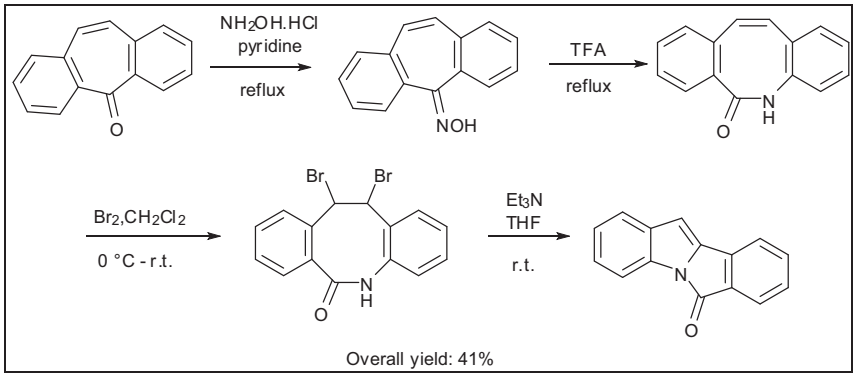
Hibino and co-workers[13] prepared isoindoloindolone by employing Suzuki–Miyaura reaction of methyl-*o*-iodobenzoate and N-Boc-indole-boronic acid followed by deprotection and base mediated cyclisation to isoindoloindolones (Scheme 10).

Flash vaccum pyrolysis of methyl-*2*-(indol-*1*-yl)-benzoate to isoindoindolone is developed by McNab *et. al*.[14] (Scheme 11). Here high temperature cascade reaction involving sigmatropic shift-elimination-cyclisation provided isoindoloindolones. Methyl-*2*-(indol-*1*-yl)-benzoate was prepared by C-N coupling of indole and o-iodobenzoic acid followed by esterification.



Scheme 11

A metal free synthesis of isoindoloindolones is reported by B. Wang's group[15] using dibenzocyclo-hepten-*5*-one as starting material (Scheme 12). This method involves Beckmann rearrangement of dibenzocycloheptен-*5*-one oxime using TFA followed by bromination and intramolecular cyclisation of dibromodibenzoazocin-*6*-one to isoindoloindolone.

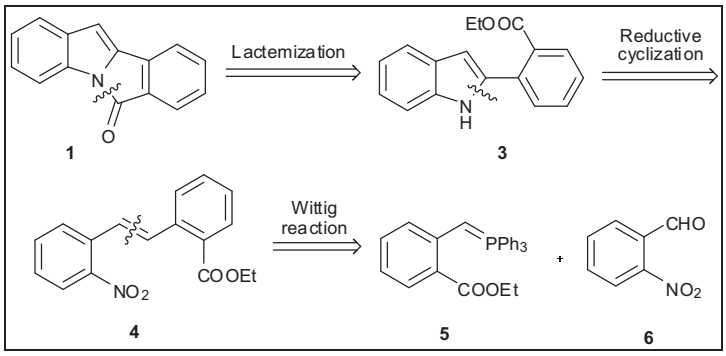


Scheme 12

2.3: Results and Discussion

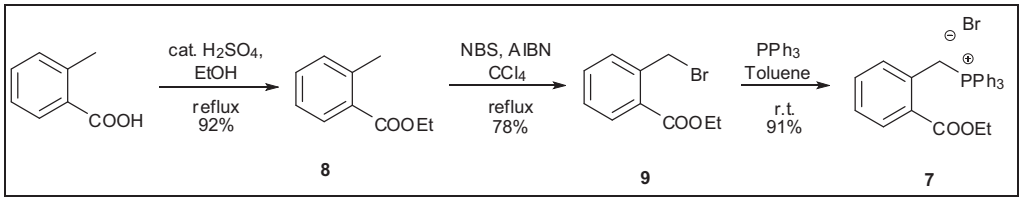
Evaluating the reported synthesis revealed that a simple and high yielding procedure to synthesize isoindoloindolone is still needed. We proposed the retro-synthesis as depicted in Scheme 13.

We thought of achieving isoindoloindolone **1** from ethyl *2*-(*1H*-indol-*2*-yl)benzoate **3** by lactamization which in turn could be obtained from ethyl *2*-(*2*-nitrostyryl)benzoate **4** via reductive cyclization. This could be obtained by Wittig reaction of phosphorane **5** and *o*-nitrobenzaldehyde **6**.



Scheme 13

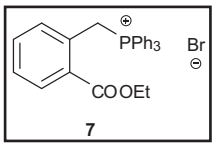
Following this strategy we began our synthesis with preparation of Wittig salt **7** from cheaply available *o*-toluic acid as a starting material (Scheme 14).



Scheme 14

o-Toluic acid was esterified by Fischer esterification using ethanol and cat. H_2SO_4 to give compound **8** as an oily liquid. The spectral details were complying with those reported in literature[16a] for ethyl *o*-toluate **8**. It was then subjected to benzylic bromination[16b] using NBS and cat. AIBN in refluxing CCl_4. The bromo compound **9** formed was as such reacted without any purification with triphenyl phosphine in toluene[16c] at r.t. and product **7** was obtained as white solid with 65 % overall yield in 3 steps.

Spectral data of ethyl (*2*-(ethoxycarbonyl)benzyl)triphenylphosphonium bromide **7:**



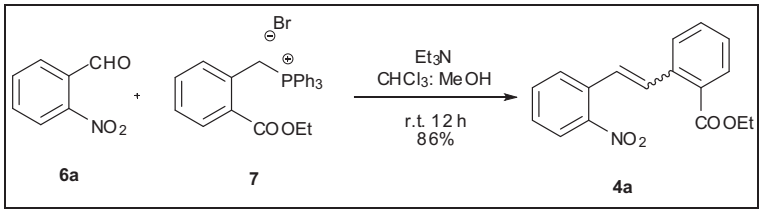
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, *J* = 7.2 Hz, 3 H), 3.92 (q, *J* = 7.2 Hz, 2 H), 5.89 (d, *J* = 14.8 Hz, 2 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.60–7.63 (m, 12 H), 7.63–7.79 (m, 4 H), 7.89 (d, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.03 (CH_3), 28.78 (d, *J* = 47.0 Hz, CH_2), 61.02 (CH_2), 117.44 (Cq) 118.30 (Cq) 128.73 (CH), 128.77 (CH), 129.42 (Cq) 129.47 (Cq) 129.95 (CH), 130.07 (CH), 130.51 (Cq) 130.60 (Cq) 131.47 (CH), 131.50 (CH), 133.61 (CH), 133.64 (CH), 133.71 (CH), 133.77 (CH), 134.42 (CH), 134.52 (CH), 134.84 (CH), 134.87 (CH), 166.12 (Cq) ppm.

LCMS (m/z): $[M\text{-}Br]^+$ 425.0, $[M\text{-}C_2H_4Br]^+$ 396.9.

Based on these spectral details and mode of formation, structure **7** was assigned to this Wittig salt and further confirmed based on its mass spectra.

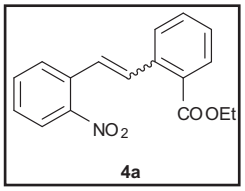
The ylide **5** being moderately unstable was prepared *in situ* from the phosphonium salt **7** by slow addition of triethylamine to it in presence of *o*-nitrobenzaldehyde **6a** to give the required Wittig product **4a** as a pale yellow solid in 86 % yield (Scheme 15).



Scheme 15

The Infrared spectrum of compound **4a** showed peaks at 1344, 1522 and 1712 cm^{-1} corresponding to nitro and ester functionalities respectively indicating the formation of desired product via Wittig reaction. The structure was further confirmed to be ethyl *2*-(*2*-nitrostyryl)benzoate **4a** based on the its ^{1}H and ^{13}C NMR spectra and their correlation to the reported values.[17] The PMR spectra suggested it to be a mixture of *cis-trans* isomers.

Spectral data of ethyl *2*-(*2*-nitrostyryl)benzoate **4a:**

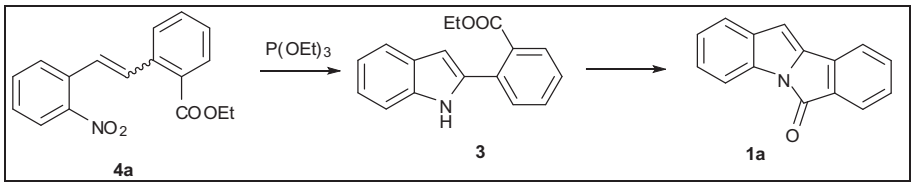


IR (KBr): ν_{max} 1344, 1522, 1712, 2990, 3080 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.2 Hz, 3 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 6.85–6.95 (m, 3 H), 7.11–7.20 (m, 5 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.34 (CH_3), 61.16 (CH_2), 124.49 (CH), 126.16 (CH), 127.39 (CH), 127.81 (CH), 129.69 (Cq), 130.52 (CH), 131.40 (CH), 131.87 (CH), 132.79 (CH), 132.85 (CH), 132.91 (CH), 133.31 (Cq), 138.34 (Cq), 148.34 (Cq), 166.94 (Cq) ppm.

The next step in the synthesis was reductive cyclization to get ethyl *2*-(*1H*-indol-*2*-yl)benzoate **3** which then could be converted to isoindoloindolone **1a**. For this step (Scheme 16) we used a known method[18] of reductive cyclization employing refluxing triethyl phosphite for 30 min. which yielded us a florescent yellow solid in 56 % yield (Table 1 entry 1).



Scheme 16

The difference in retention factor between the product and starting material on TLC (hexanes-$CHCl_3$; 1:1) was very less but the disappearance of nitro functionality peaks in the IR spectrum of product indicated the success of reductive cyclisation reaction. Absence of N-H stretching peak in

IR spectra expected due to reductive cyclisation and disappearance of peak due ester functionality was an indication of further cyclization product. The no. of protons and carbons accounted from the NMR spectra revealed the formation of *6H*-isoindolo[*2,1-a*]indol-*6*-one **1a**.

McNab's group[14] assigned the NMR values for this structure as shown in figure 3 by performing COSY, NOESY and HSQC experiments. Our data was in agreement with these literature values[6a,8d,9,14a,15] and the proposed structure was further confirmed to be *6H*-isoindolo[*2,1-a*]indol-*6*-one **1a** based on its elemental analysis. Elemental analysis: $C_{15}H_9NO$ (219.24): calculated % C 82.18, H 4.14, N 6.39; found % C 82.39, H 4.34, N 6.73.

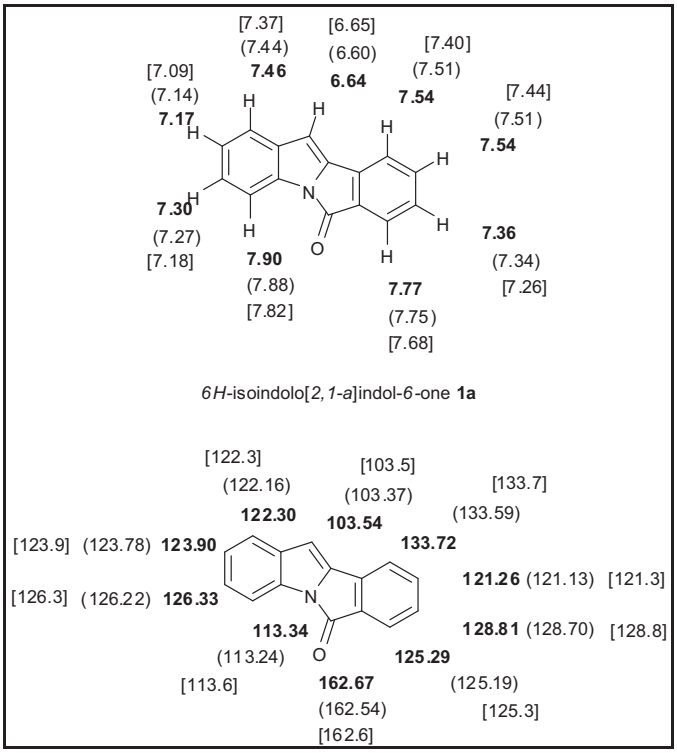
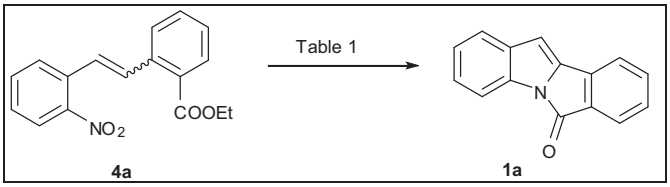


Figure 3: NMR data comparison with literature; Bold- our data; ( )- ref. 14a; [ ]- ref. 15.

In this experiment, tandem reductive cyclization – lactamization reaction took place in one pot.

The yield for this reaction being moderate, we then tried the $MoO_2Cl_2(dmf)_2$ catalyst[19] along with PPh_3 for reductive cyclization but no encouraging results were obtained as the yield was just 51 % (Table 1, entry 2).



Scheme 17

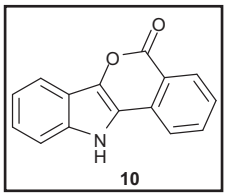
Table 1: Tandem Reductive cyclization – Lactamization reaction (Scheme 17).

Entry	Reaction Condition	% Yield[a]
1	$P(OEt)_3$, Reflux, 30 min	56
2	$MoO_2Cl_2dmf_2$ (10 mol %), PPh_3, Toluene, Reflux, 12 h	51
3	PPh_3, Ph_2O, Reflux, 4 h	75[b]

[a] Isolated yield after column chromatography.
[b] Consistent yield at 10 mmol scale.

Good yields were achieved only with PPh_3 at high temperature[20] for 4 h giving the desired product **1a** in 75 % yield (Table 1, entry 3). This reaction was performed at 10 mmol scale (2 g) and was completed within same reaction time with consistent yield. In some instances, isochromeno[*4,3-b*]indol-*5(11H)*-one **10** as indicated by its spectral data[21] was formed as by-product in 6-8 % yield. Formation of this product was not consistent as experiments conducted to check its reproducibility were unsuccessful and instead gave a tarry material.

Spectral data of Isochromeno[*4,3-b*]indol-*5(11H)*-one **10:**



10

IR (KBr): ν_{max} 1608, 1716, 3205 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ 7.17 (t, *J* = 8.0 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.60 (t, *J* = 8.0 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 7.97 (t, *J* = 8.0 Hz, 1 H), 8.06 (d, *J* = 7.2 Hz, 1 H), 8.27 (d, *J* = 8.0 Hz, 1 H), 12.03 (s, 1H, NH) ppm.

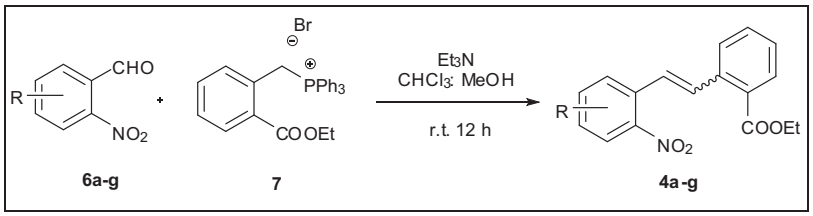
^{13}C NMR (100 MHz, DMSO): δ 112.32 (CH), 115.77 (Cq), 116.96 (Cq), 117.08 (CH), 118.87 (Cq), 120.03 (CH), 120.70 (CH), 124.40 (CH), 127.48 (CH), 130.45 (Cq), 130.93 (CH), 133.58 (Cq), 135.10 (Cq), 135.48 (CH), 161.46 (Cq) ppm.

LCMS (m/z): $[M-H]^+$ 234.

The structure was further confirmed to be isochromeno[*4,3-b*]indol-*5(11H)*-one **10** based on its HRMS value.

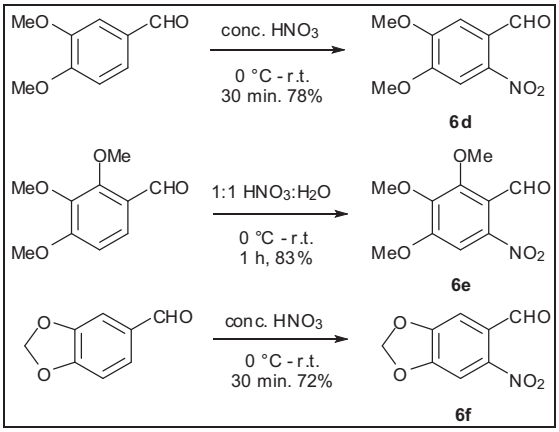
HRMS (*m/z)*: calculated for $C_{15}H_8NO_2$ $[M-H]^+$ 234.0622; found 234.0607.

After successfully synthesizing the *6H*-isoindolo[*2,1-a*]indol-*6*-one **1a,** we thought of extending the method for preparing a series of substituted isoindoloindolones in order to investigate the effect of substituent on the reaction yields and make available a library of isoindoloindolones for biological study. Substrates with electron withdrawing groups like Cl and COOMe were commercially available as *5*-chloro-*2*-nitrobenzaldehyde **6b** and methyl *3*-formyl-*4*-nitrobenzoate **6c,** hence subjected to Wittig reaction (Scheme 18) to prepare ethyl *2-(5*-chloro-*2*-nitrostyryl)benzoate **4b** and methyl *3-(2*-(ethoxycarbonyl)styryl)-*4*-nitrobenzoate **4c** in 77 % and 79 % yields respectively (Table 2, entry 2, 3).



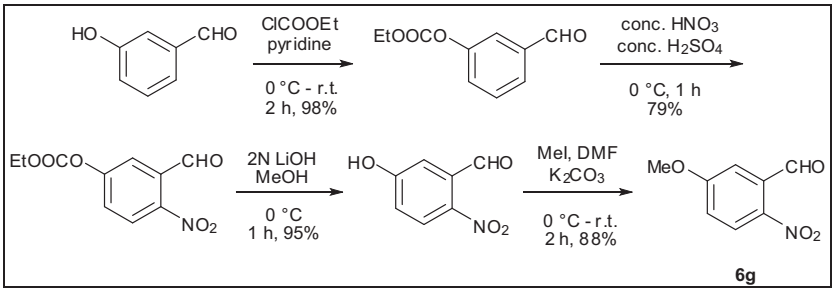
Scheme 18

Electron donating groups like dimethoxy, trimethoxy and methylenedioxy were explored by preparing required aldehydes **6d-f** from commercially available substrates using literature methods[22] of nitration as described in scheme 19.



Scheme 19

5-Methoxy-*2*-nitrobenzaldehyde **6g** was prepared from 5-hydroxy-2-nitrobenzaldehyde by a 4-step route[23] (Scheme 20) with 64 % overall yield.

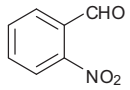
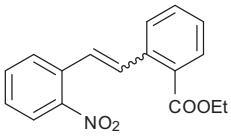
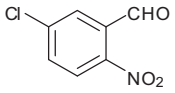
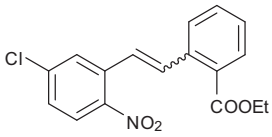
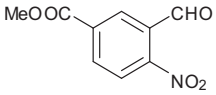
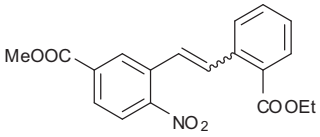
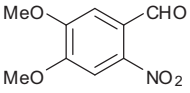
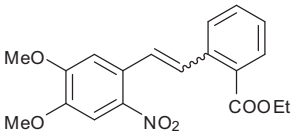
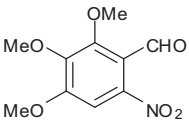
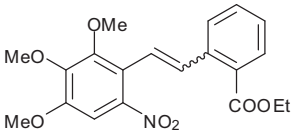
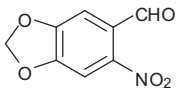
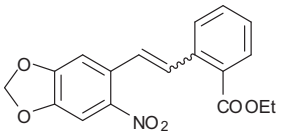
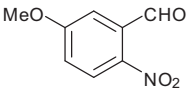
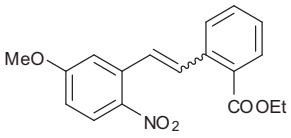


Scheme 20

The structures of these synthesized *o*-nitrobenzaldehydes **6d-f** were confirmed by comparing their physical constant and spectral data with the reported values.[22,23]

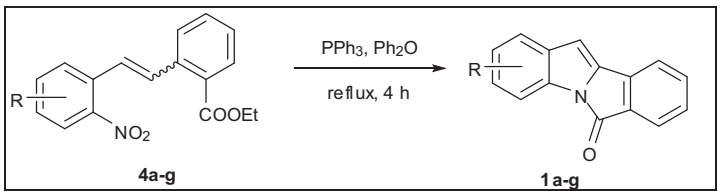
These substituted *o*-nitrobenzaldehydes **6d-g** were then subjected to Wittig reaction according to Scheme 18 and corresponding substituted ethyl *2*-(*2*-nitrostyryl)benzoate **4d-g** were formed in 78, 74, 80 and 83 % yields respectively (Table 2, entry 4-7).

Table 2: Substrate study with Wittig reaction (Scheme 18).

Entry	Reactant **6a-g**	Product **4a-g**	% Yield[a]
1	 **6a**	 **4a**	86
2	 **6b**	 **4b**	77
3	 **6c**	 **4c**	85
4	 **6d**	 **4d**	78
5	 **6e**	 **4e**	74
6	 **6f**	 **4f**	80
7	 **6g**	 **4g**	83

[a] Isolated yield after column chromatography.

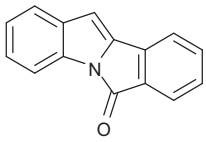
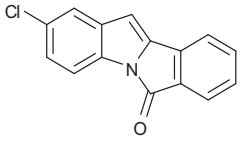
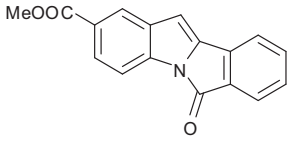
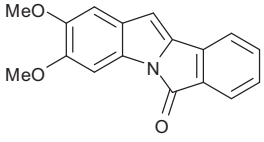
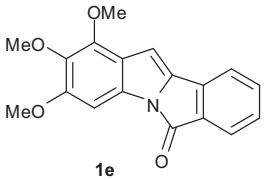
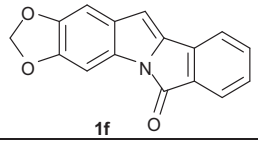
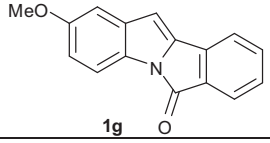
All these derivatives **4b-g** were characterised based on their spectral details and confirmed by their mass spectra.



Scheme 21

These derivatives **4b-g** were then subjected to tandem reductive cyclisation – lactamization reaction using 2 equiv. PPh_3 in refluxing diphenylether for 4 h (Scheme 21). The corresponding isoindoloindolones **1b-g** were obtained in good yields (Table 3).

Table 3: Substrate study on Tandem reductive cyclization - lactamization reaction (Scheme 20).

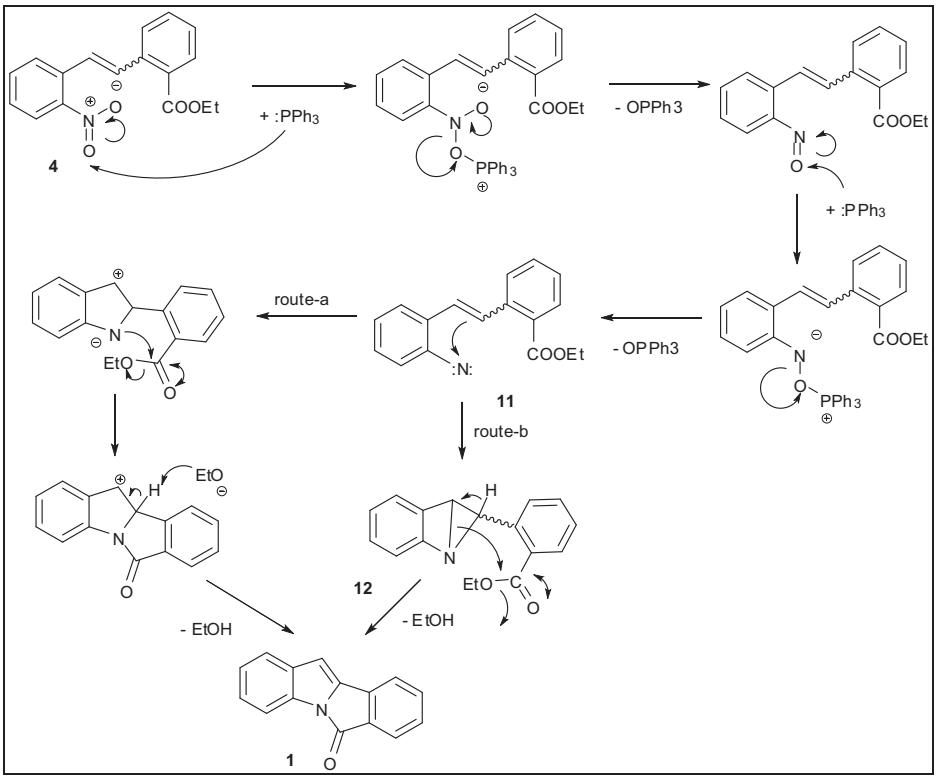
Entry	Product **1a-g**	% Yield[a]	Overall % yield[b]
1	 **1a**	75	64.5
2	 **1b**	70	54.0
3	 **1c**	75	59.2
4	 **1d**	72	56.2
5	 **1e**	63	46.6
6	 **1f**	73	58.4
7	 **1g**	68	56.4

[a] Isolated yield after column chromatography. [b] Calculated over 2 steps.

The structures of all these derivatives **1b-g** were predicted based on spectral details and further confirmed by their mass spectra. Attempts were made to isolate any traces of substituted derivatives of compound **10** from the corresponding reaction mixture without success.

A probable mechanism for the tandem reductive cyclisation – lactamization process is given in scheme 22. This mechanism involves reduction of nitro group to reactive nitrene intermediate using

2 equivalents of triphenylphosphine and elimination of triphenylphosphine oxide. The reactive nitrene intermediate **11** then forms the indole core (route-a) by sp^2 C-H bond insertion or forms an aziridine intermediate **12** (route-b). In both ways intramolecular cyclisation with elimination of ethanol gives the required isoindoloindolone **1**.



Scheme 22

All the synthesised derivatives of isoindoloindolones **1a-g** were tested for antimicrobial activity on various gram positive and gram negative bacteria and fungi in Marine Biotechnology Department of this University using disc diffusion assay.

Microbial cultures tested for bioassay of the compounds:

Bacteria	**Fungi**
Salmonella typhimurium	*Trichoderma* sp.
Escherichia coli	*Rhizopus* sp.
Proteus vulgaris	*Mucor* sp.
Staphylococcus aureus	*Penicillium* sp.
Bacillus subtilis	*Aspergilus niger*
Methicillin Resistant *Staphylococcus aureus* (MRSA)	*Aspergillus fumigatus*

The synthesised derivatives did not show any growth inhibition on these tested micro-organisms indicating their inability to act as antibacterial or antifungal agents.

2.4: Conclusion

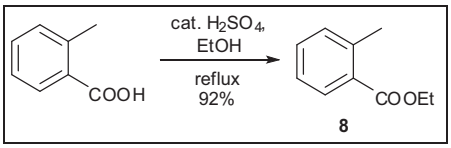
6H-Isoindolo[*2,1-a*]indol-*6*-one, a tetracyclic indole fused unnatural bioactive heterocyclic system is prepared through Wittig reaction and tandem reductive cyclization – lactamization approach.

The flexibility of this method is demonstrated by synthesizing series of isoindoloindolone core with electron donating groups like methoxy, dimethoxy, trimethoxy, and methylenedioxy as well as electron withdrawing groups like chloro and carbomethoxy.

The overall yields in this methodology were comparable with the other efficient syntheses known in literature.

2.5: Experimental

2.5.1: Ethyl *o*-toluate 8



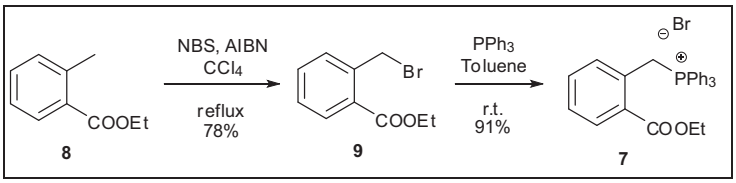
o-Toluic acid (5 g, 36 mmol) was dissolved in absolute EtOH (25 mL) and conc. H_2SO_4 (0.2 mL) was added. This solution was refluxed at 80 °C for 8 h. Solvent was removed under vacuum and Et_2O (50 mL) was added. The organic layer was washed with saturated aq. $NaHCO_3$ (10 mL X 5) and finally with brine (10 mL), dried over anhyd. Na_2SO_4 and concentrated under vacuum to give pure product **8** in 92 % (5.55 g) yield.

Colourless oil.[16a]

R_f: 0.67, (EtOAc:hexanes, 1:20)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, *J* = 7.2 Hz, 3 H), 2.59 (s, 3 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 7.22–7.25 (m, 2 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H) ppm.

2.5.2: (*2*-(Ethoxycarbonyl)benzyl)triphenylphosphonium bromide 7

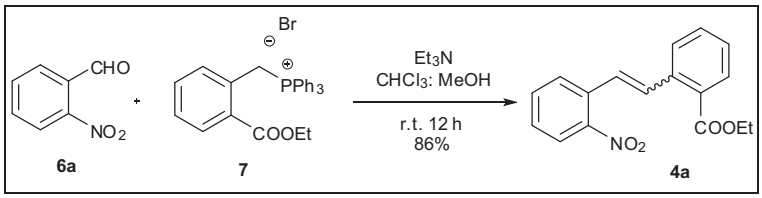


Ethyl *o*-toluate **8** (5 g, 30.48 mmol) was mixed with NBS (6.04 g, 33.5 mmol) and AIBN (0.25 g, 1.5 mmol) in CCl_4 (20 mL). This solution was refluxed at 85 °C for 7 h and filtered hot under vacuum. The filtrate was dried under vacuum, Et_2O was added to it and passed through small silica bed and washed with Et_2O. Finally solvent was removed under vacuum and corresponding benzyl bromide was obtained as a pale yellow liquid in 78 % (5.77 g) yield. *(Caution: lacrymatic and skin irritant)* This was immediately used for next reaction by adding dry toluene (20 mL). To this, triphenylphosphine (7.86 g, 30 mmol) dissolved separately in dry toluene (10 mL) was added with vigorous stirring. This stirring was continued for 24 h until solid product separated out as a white solid. Dry Et_2O (20 X 3 mL) was added thrice and decanted. Product **7** was obtained in 91 % (10.91 g) yield. *The product was sufficiently stable in dry & air-tight container.*

White solid, m.p.: 210-211 °C.

R_f: 0.32, ($CHCl_3$:MeOH, 10:1)

2.5.3: Ethyl *2-(2*-nitrostyryl)benzoates (4a)

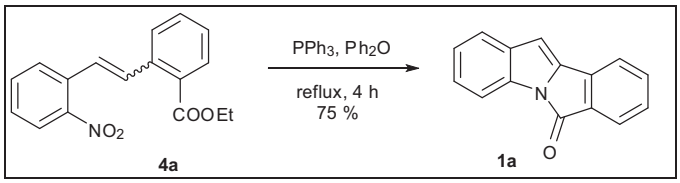


o-Nitrobenzaldehyde **6a** (0.30 g, 2 mmol) and (*2*-(ethoxycarbonyl)-benzyl)-triphenylphosphonium-bromide **7** (1.51 g, 3 mmol) were dissolved in $CHCl_3$:MeOH (4:1, 20 mL) and stirred at r.t. To this, Et_3N (0.56 mL, 4 mmol) was added slowly with stirring and mixture was stirred at r.t. for 12 h. Solvent was removed under vacuum and water (20 mL) was added, mixture was extracted in EtOAc (15 X 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (CH_2Cl_2:hexanes, 2:1). The Wittig product **4a** was obtained in 86 % (0.51 g) yield.

Pale-yellow solid,[17] m.p.: 87–88 °C.

R_f: 0.50 (CH_2Cl_2:hexanes, 3:2)

2.5.4: *6H*-Isoindolo[*2,1-a*]indol-*6*-ones (1a)



Ethyl *2*-(*2*-nitrostyryl)benzoate **4a** (0.3 g, 1 mmol) and triphenylphosphine (0.57 g, 2.2 mmol) was refluxed in dry Ph_2O for 4 h. After cooling, mixture was chromatographed on silica and diphenylether was removed by eluting with hexanes, further elution with EtOAc:hexanes (1:10) afforded isoindoloindolone **1a** in 75 % (0.16 g) yield.

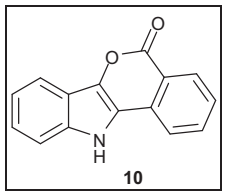
Yellow solid, m.p.: 153–154 °C. [lit. m.p.: 153-154 °C][6a,8d,9,14a,15]

R_f: 0.52 (CH_2Cl_2:hexanes, 3:2)

IR (KBr): ν_{max} 1444, 1725, 3057 cm^{-1}.

2.5.5: Isochromeno[*4,3-b*]indol-*5(11H)*-one 10:

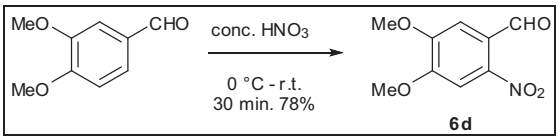
Following the similar procedure as described in section 2.5.4, further elution of column with EtOAc:hexanes (1:3) gave compound **10** in 8 % (0.018 g) yield.



Light Brown solid, m.p.: >300 °C. [Lit. m.p.: 304-305 °C][21]

R_f: 0.45 (CH_2Cl_2:EtOAc, 3:1)

2.5.6: *4,5*-Dimethoxy-*2*-nitrobenzaldehyde (*6*-Nitroveratraldehyde) 6d:

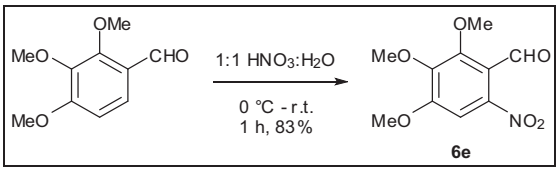


Conc. HNO_3 (10 mL) was cooled to 0 °C and veratraldehyde (1 g, 6 mmol) was added in small portions with stirring. This mixture was vigorously stirred from 0 °C to r.t. for 30 min. and poured in crushed ice (100 mL). Solid formed was filtered under vacuum and washed with EtOH:H_2O (1:3, 50 mL). The product **6d** was obtained in 78 % (0.98 g) yield.

Yellow solid, m.p.: 130 – 132 °C. [Lit. m.p.: 132 - 133 °C][22a]

R_f: 0.49 (CH_2Cl_2:hexanes, 3:1)

2.5.7: *2,3,4*-Trimethoxy-*6*-nitrobenzaldehyde 6e:



HNO_3:H_2O (1:1, 20 mL) was cooled to 0 °C and *2,3,4*-trimethoxybenzaldehyde (1 g, 5.10 mmol) was added in small portions with stirring. This mixture was vigorously stirred from 0 °C to r.t. for 1 h and poured in crushed ice (100 mL). Solid formed was filtered under vacuum and washed with EtOH:H_2O (1:3, 50 mL). The product **6e** was obtained in 83 % (1.02 g) yield.

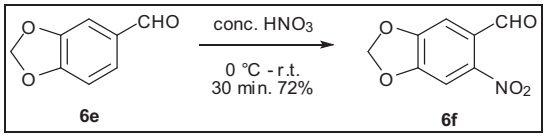
Yellow solid, m.p.: 82 – 84 °C. [lit. m.p.: 82 - 83 °C][22b]

R_f: 0.40 (CH_2Cl_2:hexanes, 3:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98-3.99 (m, 9 H), 7.32 (s, 1 H), 10.26 (s, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 56.70 (CH_3), 61.29 (CH_3), 62.83 (CH_3), 103.58 (CH), 120.71 (Cq), 143.34 (Cq), 146.63 (Cq), 153.24 (Cq), 155.79 (Cq), 186.98 (Cq) ppm.

2.5.8: *6*-Nitrobenzo*[1,3]*dioxole-*5*-carbaldehyde *(6*-Nitropiperonal*)* 6f:



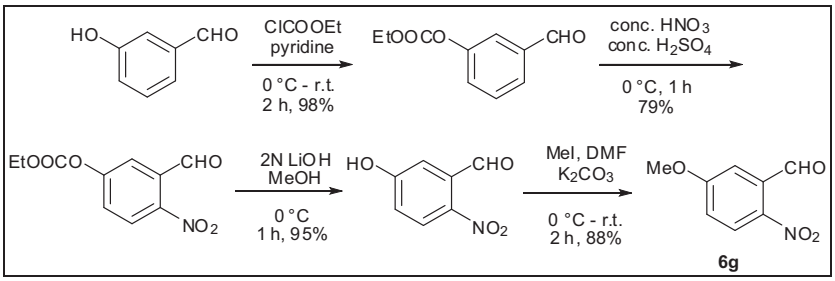
Following the similar procedure as described in section 2.5.6 with piperonal (1 g, 6.66 mmol) gave the product **6f** in 72 % (0.94 g) yield.

Pale yellow solid, m.p.: 92 - 94 °C. [lit. m.p.: 93 - 94 °C][22c]

R_f: 0.53 (CH_2Cl_2:hexanes, 3:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (s, 2 H), 7.28 (s, 1 H), 7.47 (s, 1 H), 10.24 (s, 1 H) ppm.

2.5.9: *5*-Methoxy-*2*-nitrobenzaldehyde 6g*:*



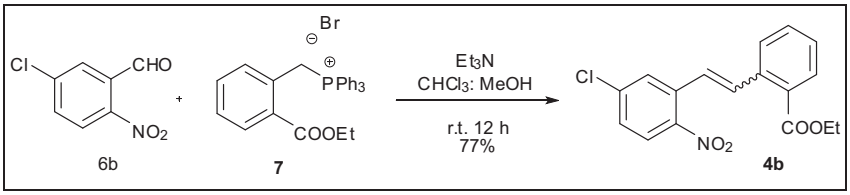
3-Hydroxybenzaldehyde (1 g, 8.2 mmol) was added to pyridine (5 mL) at 0 °C and stirred for 5 min. To this solution, ethyl chloroformate (1.2 mL, 12.5 mmol) was added and stirred from 0 °C to r.t. After 2 h, it was poured in ice cold 2N HCl (30 mL) and extracted in Et_2O (15 X 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum. Product was isolated as colourless oil in 98 % (1.56 g) yield. This compound was as such added to conc.H_2SO_4 (10 mL) at 0 °C and stirred. Conc.HNO_3 (1 mL) in conc.H_2SO_4 (5 mL) was slowly added to it maintaining the temperature at 0 °C. After stirring at 0 °C for 1 h, it was poured in crushed ice (100 mL) and extracted in $CHCl_3$ (15 X 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum. Product was obtained as viscous oil in 79 % (1.51 g) yield. Successively MeOH was added to it and cooled to 0 °C. 2N LiOH (10 mL) was then added slowly and stirred maintaining the temperature of 0 °C for 1 h. This mixture was then poured in ice cold 2N HCl (20 mL), acidified and extracted in $CHCl_3$ (15 X 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under vacuum. Product was isolated in 95 % (1 g) yield as a yellow solid, m.p.: 166-168 °C [Lit. m.p.: 167-168 °C].[23a] This was then mixed with DMF (5 mL), K_2CO_3 (1.18 g, 8.9 mmol), cooled to 0 °C and MeI (0.34 mL, 6.6 mmol) was added to it dropwise. The mixture was stirred from 0 °C to r.t. for 2 h and then poured in ice cold water (100 mL) and extracted in diethylether (15 X 3 mL). The combined organic layers were washed with 1N HCl (20 mL), saturated aq. $NaHCO_3$ (20 mL), brine and dried over anhyd. Na_2SO_4 and concentrated under vacuum. The product **6g** was obtained in 88 % (0.95 g) yield.

Pale yellow gummy mass.[23]

R_f: 0.59 (CH_2Cl_2:hexanes, 3:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3 H), 7.08 (dd, J = 9.2 & 2.8 Hz, 1 H), 7.26 (d, J = 2.8 Hz, 1 H), 8.09 (d, J = 8.8 Hz, 1 H), 10.42 (s, 1 H) ppm.

2.5.10: Ethyl *2-(5*-chloro-*2*-nitrostyryl)benzoate 4b*:*



Following the similar procedure as described in section 2.5.3 with *5*-chloro-*2*-nitrobenzaldehyde **6b** (0.37 g, 2 mmol) gave the Wittig product **4b** in 77 % (0.51 g) yield.

Pale-yellow solid, m.p.: 68–69 °C.

R_f: 0.43 (CH_2Cl_2:hexanes, 2:1)

IR (KBr): ν_{max} 1344, 1520, 1711, 2982, 3063 cm^{-1}.

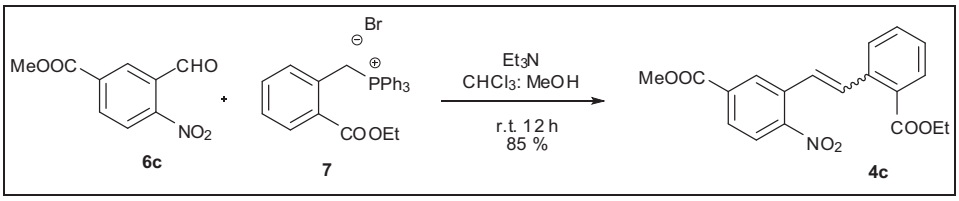
^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.2 Hz, 3 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 6.82–6.91 (m, 3 H), 7.17–7.26 (m, 4 H), 7.90–7.95 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.31 (CH_3), 61.23 (CH_2), 124.92 (CH), 126.01 (CH), 127.79 (CH), 127.92 (CH), 129.68 (Cq), 130.72 (CH), 131.11 (CH), 132.03 (CH), 132.47 (CH), 133.91 (CH), 135.13 (Cq), 137.67 (Cq), 139.08 (Cq), 146.57 (Cq), 166.77 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{17}H_{14}ClNO_4Na$ $[M+Na]^+$ 354.0509; found 354.0509.

Elemental analysis: $C_{17}H_{14}ClNO_4$ (331.75): calculated % C 61.55, H 4.25, N 4.22; found % C 61.73, H 4.17, N 4.36.

2.5.11: Methyl *3-(2-(*ethoxycarbonyl)styryl*)-4*-nitrobenzoate 4c*:*



Following the similar procedure as described in experiment 2.5.3 with *3*-formyl-*4*-nitrobenzoate **6c** (0.41 g, 2 mmol) gave the Wittig product **4c** in 85 % (0.60 g) yield.

Pale yellow solid, m.p.: 71-72 °C.

R_f: 0.35 (CH_2Cl_2:hexanes, 2:1)

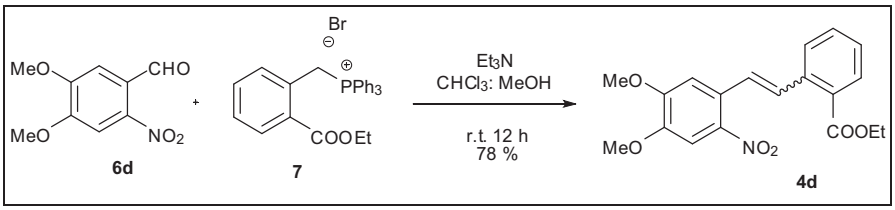
IR (KBr): ν_{max} 1344, 1522, 1712, 1724, 2990, 3080 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.2 Hz, 3 H), 3.72 (s, 3 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 6.82–6.85 (m, 2 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 8.0 Hz, 1 H), 7.28 (d, *J* = 12.0 Hz, 1 H), 7.61 (s, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.91–7.94 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.27 (CH_3), 52.55 (CH_3), 61.15 (CH_2), 124.41 (CH), 124.59 (CH), 127.65 (CH), 128.65 (CH), 129.71 (Cq), 130.70 (CH), 130.93 (CH), 131.95 (CH), 133.10 (Cq), 133.45 (Cq), 134.02 (CH), 134.32 (CH), 137.78 (Cq), 150.86 (Cq), 164.85 (Cq), 166.92 (Cq) ppm.

LCMS (m/z): $[M+Na]^+$ 377.9.

2.5.12: Ethyl *2-(4,5*-dimethoxy-*2*-nitrostyryl)benzoate 4d*:*



Following the similar procedure as described in experiment 2.5.3 with 4,5-dimethoxy-2-nitrobenzaldehyde **6d** (0.42 g, 2 mmol) gave the Wittig product **4d** in 78 % (0.56 g) yield.

Yellow solid, m.p.: 56–57 °C.

R_f: 0.58 (CH_2Cl_2:hexanes, 3:1)

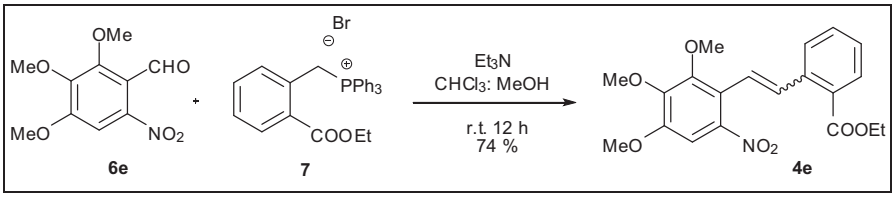
IR (KBr): ν_{max} 1345, 1530, 1709, 2990, 3075 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.2 Hz, 3 H), 3.32 (s, 3 H), 3.84 (s, 3 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 6.31 (s, 1 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 7.01 (d, *J* = 12.0 Hz, 1 H), 7.14–7.19 (m, 3 H), 7.57 (s, 1 H), 7.88 (d, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.29 (CH3), 54.87 (CH3), 55.21 (CH3), 60.16 (CH2), 106.30 (CH), 113.18 (CH), 126.25 (CH), 126.36 (CH), 127.11 (Cq), 128.80 (Cq), 129.17 (CH), 130.43 (CH), 130.79 (CH), 130.93 (CH), 137.71 (Cq), 139.46 (Cq), 146.72 (Cq), 151.40 (Cq), 166.08 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{19}H_{19}NO_6Na$ $[M+Na]^+$ 380.1110; found 380.1111.

2.5.13: Ethyl *2*-(*2,3,4*-trimethoxy-*6*-nitrostyryl)benzoate 4e:



Following the similar procedure as described in experiment 2.5.3 with *2,3,4*-trimethoxy-*6*-nitrobenzaldehyde **6e** (0.48 g, 2 mmol) gave the Wittig product **4e** in 74 % (0.57 g) yield.

Yellow solid, m.p.: 45–46 °C.

R_f: 0.45 (CH_2Cl_2:hexanes, 3:1)

IR (KBr): ν_{max} 1344, 1527, 1710, 2950, 3060 cm^{-1}.

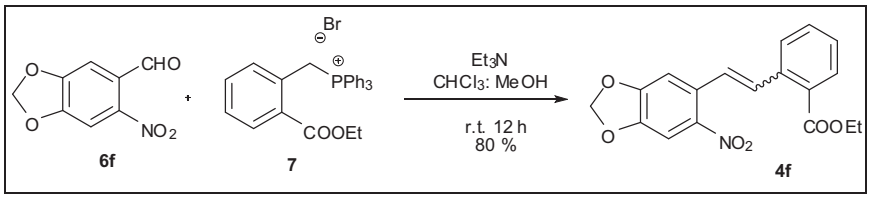
^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 3 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 3.90 (s, 3 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 6.93 (d, *J* = 16.0 Hz, 1 H), 7.20 (s, 1 H), 7.28 (t, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.84 (s, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.31 (CH3), 56.36 (CH3), 61.05 (CH2), 61.16 (CH3), 61.22 (CH3), 104.08 (CH), 121.21 (Cq), 121.50 (CH), 127.38 (CH), 127.60 (CH), 129.24 (Cq), 130.43 (CH), 132.15 (CH), 133.81 (CH), 139.11 (Cq), 144.51 (Cq), 146.85 (Cq), 151.99 (Cq), 152.46 (Cq), 167.23 (Cq) ppm.

LCMS (m/z): $[M+H]^+$ 388.

HRMS (*m/z)*: calculated for $C_{20}H_{21}NO_7Na$ $[M+Na]^+$ 410.1216; found 410.1215.

2.5.14: Ethyl *2*-(*2*-(*6*-nitrobenzo*[1,3]*dioxol-*5*-yl)vinyl)benzoate 4f:



Following the similar procedure as described in experiment 2.5.3 with *6*-nitrobenzo*[1,3]*dioxole-*5*-carbaldehyde **6f** (0.39 g, 2 mmol) gave the Wittig product **4f** in 80 % (0.55 g) yield.

Yellow solid, m.p.: 123–124 °C.

R_f: 0.55 (CH_2Cl_2:hexanes, 3:1)

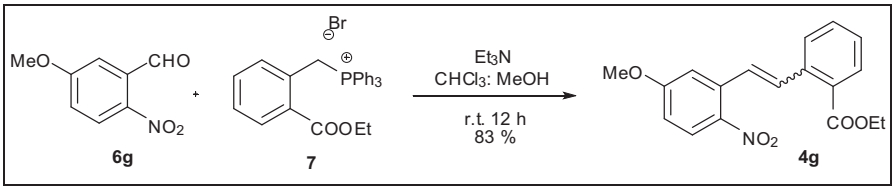
IR (KBr): ν_{max} 1321, 1518, 1712, 2982, 3125 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.2 Hz, 3 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 5.92 (s, 2 H), 6.31 (s, 1 H), 6.84–6.91 (m, 2 H), 7.10 (d, *J* = 12.4 Hz, 1 H), 7.10–7.16 (m, 2 H), 7.51 (s, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.31 (CH3), 61.16 (CH2), 102.80 (CH2), 105.16 (CH), 111.19 (CH), 126.98 (CH), 127.42 (CH), 129.62 (Cq), 130.53 (CH), 130.68 (Cq), 131.35 (CH), 131.78 (CH), 131.99 (CH), 138.29 (Cq), 142.26 (Cq), 147.05 (Cq), 151.47 (Cq), 166.97 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{18}H_{15}NO_6Na$ $[M+Na]^+$ 364.0797; found 364.0806.

2.5.15: Ethyl *2*-(*5*-methoxy-*2*-nitrostyryl)benzoate 4g:



Following the similar procedure as described in experiment 2.5.3 was followed with *5*-methoxy-*2*-nitrobenzaldehyde **6g** (0.36 g, 2 mmol) gave the Wittig product **4g** in 83 % (0.54 g) yield.

Pale yellow oil.

R_f: 0.63 (CH_2Cl_2:hexanes, 3:1)

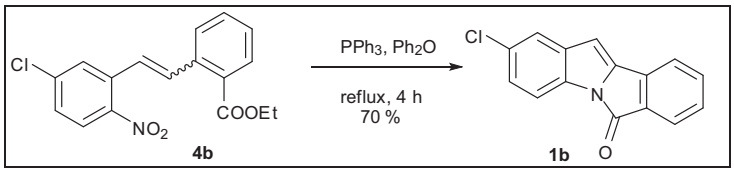
IR (neat): ν_{max} 1335, 1525, 1711, 2982, 3062 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3 H), 3.36 (s, 3 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 6.33 (s, 1 H), 6.62 (d, *J* = 9.2 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 6.90 (d, *J* = 12.0 Hz, 1 H), 7.09–7.15 (m, 3 H), 7.83 (d, *J* = 7.6 Hz, 1 H), 7.94 (d, *J* = 9.2 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.28 (CH_3), 55.52 (CH_3), 61.12 (CH_2), 113.80 (CH), 116.69 (CH), 127.10 (CH), 127.28 (CH), 127.33 (Cq), 129.74 (Cq), 130.31 (CH), 131.24 (CH), 131.89 (CH), 132.24 (CH), 136.08 (CH), 138.27 (Cq), 141.20 (Cq), 162.66 (Cq), 166.91 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{18}H_{17}NO_5Na$ $[M+Na]^+$ 350.1004; found 350.1004.

2.5.16: *2*-Chloro-*6H*-isoindolo*[2,1-a]*indol-*6*-one 1b:



Following the similar procedure as described in experiment 2.5.4 with ethyl *2*-(*5*-chloro-*2*-nitrostyryl)benzoate **4b** (0.33 g, 1 mmol) gave the isoindoloindolone **1b** in 70 % (0.18 g) yield.

Yellow solid, m.p.: 160–162 °C.

R_f: 0.49 (CH_2Cl_2:hexanes, 2:1)

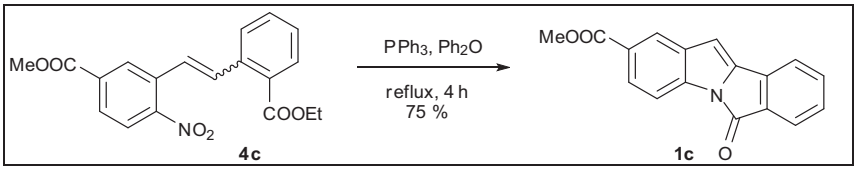
IR (KBr): ν_{max} 1440, 1728, 3059 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 6.48 (s, 1 H), 7.15 (d, *J* = 7.6 Hz, 1 H), 7.28–7.31 (m, 1 H), 7.34 (s, 1 H), 7.45–7.46 (m, 2 H), 7.68–7.73 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 102.56 (CH), 114.05 (CH), 121.50 (CH), 121.96 (CH), 125.47 (CH), 126.31 (CH), 129.24 (CH), 129.36 (Cq), 131.87 (Cq), 133.64 (Cq), 133.96 (CH), 134.36 (Cq), 135.70 (Cq), 140.08 (Cq), 162.44 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{15}H_8ClNOH$ $[M+H]^+$ 254.0373; found 254.0370.

2.5.17: Methyl *6*-oxo-*6H*-isoindolo*[2,1-a]*indole-*2*-carboxylate 1c:



Following the similar procedure as described in experiment 2.5.4 with methyl *3*-(*2*-(ethoxycarbonyl)styryl)-*4*-nitrobenzoate **4c** (0.36 g, 1 mmol) gave the isoindoloindolone **1c** in 75 % (0.21 g) yield.

Yellow solid, m.p.: 212-213 °C.

R_f: 0.43 (CH_2Cl_2:hexanes, 2:1)

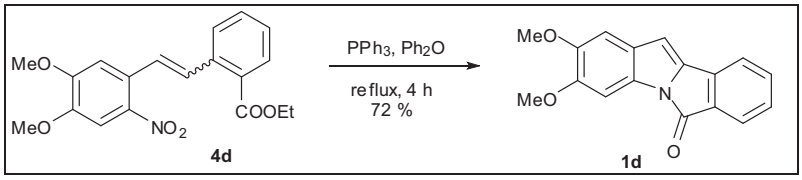
IR (KBr): ν_{max} 1610, 1716, 1736, 3105 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3 H), 6.60 (s, 1 H), 7.29–7.32 (m, 1 H), 7.47–7.48 (m, 2 H), 7.70 (d, *J*= 8.0 Hz, 1 H), 7.82 (d, *J*= 8.0 Hz, 1 H), 7.91 (dd, *J* = 8.0 & 1.6 Hz, 1 H), 8.10 (s, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 52.16 (CH_3), 103.50 (CH), 112.82 (CH), 121.62 (CH), 124.31 (CH), 125.60 (CH), 125.80 (Cq), 127.90 (CH), 129.28 (CH), 133.50 (Cq), 134.14 (CH), 134.37 (Cq), 134.48 (Cq), 136.13 (Cq), 139.85 (Cq), 162.55 (Cq), 167.08 (Cq) ppm.

LCMS (m/z): $[M+H]^+$ 277.9; $[M+Na]^+$ 299.9.

2.5.18: *2,3*-Dimethoxy-*6H*-isoindolo*[2,1-a]*indol-*6*-one 1d:



Following the similar procedure as described in experiment 2.5.4 with ethyl *2*-(*4,5*-dimethoxy-*2*-nitrostyryl)benzoate **4d** (0.36 g, 1 mmol) gave the isoindoloindolone **1d** in 72 % (0.20 g) yield.

Light-brown solid,[9] m.p.: 168–169 °C.

R_f: 0.61 (CH_2Cl_2:hexanes, 3:1)

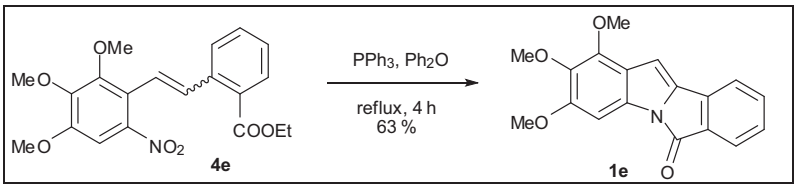
IR (KBr): ν_{max} 1445, 1724, 3055 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3 H), 3.89 (s, 3 H), 6.39 (s, 1 H), 6.82 (s, 1 H), 7.19–7.20 (m, 1 H), 7.32–7.38 (m, 3 H), 7.61 (d, *J* = 7.2 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 55.23 (CH_3), 55.33 (CH_3), 96.01 (CH), 102.71 (CH), 103.29 (CH), 119.49 (CH), 124.19 (CH), 125.75 (Cq), 127.02 (CH), 127.20 (Cq), 132.47 (Cq), 132.66 (CH), 134.10 (Cq), 136.56 (Cq), 145.83 (Cq), 148.36 (Cq), 161.73 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{17}H_{13}NO_3Na$ $[M+Na]^+$ 302.0793; found 302.0792.

2.5.19: *1,2,3*-Trimethoxy-*6H*-isoindolo*[2,1-a]*indol-*6*-one 1e:



Following the similar procedure as described in experiment 2.5.4 with ethyl *2*-(*2,3,4*-trimethoxy-*6*-nitrostyryl)benzoate **4e** (0.39 g, 1 mmol) gave the isoindoloindolone **1e** in 63 % (0.20 g) yield.

Brown solid, m.p.: 156–158 °C.

R_f: 0.49 (CH_2Cl_2:hexanes, 3:1)

IR (KBr): ν_{max} 1437, 1724, 3061 cm^{-1}.

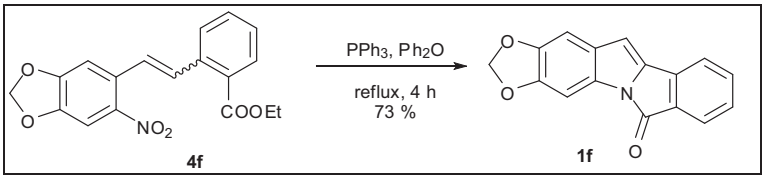
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3 H), 3.85 (s, 3 H), 3.98 (s, 3 H), 6.55 (s, 1 H), 7.09 (s, 1 H), 7.17–7.19 (m, 1 H), 7.33–7.37 (m, 2 H), 7.61 (d, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 56.48 (CH_3), 61.13 (CH_3), 61.34 (CH_3), 92.76 (CH), 101.45 (CH), 120.53 (Cq), 120.60 (CH), 125.25 (CH), 128.10 (CH), 130.46 (Cq), 133.40 (Cq), 133.71 (CH), 134.83 (Cq), 136.58 (Cq), 138.26 (Cq), 147.20 (Cq), 154.09 (Cq), 162.75 (Cq) ppm.

LCMS (m/z): $[M+H]^+$ 309.9.

HRMS (*m/z)*: calculated for $C_{18}H_{15}NO_4Na$ $[M+Na]^+$ 332.0899; found 332.0895.

2.5.20: *6H-[1,3]*Dioxolo*[4,5-f]*isoindolo*[2,1-a]*indol-*6*-one 1f:



Following the similar procedure as described in experiment 2.5.4 with ethyl *2*-(*2-(6*-nitrobenzo*[1,3]*dioxol-*5*-yl)vinyl)benzoate **4f** (0.34 g, 1 mmol) gave the isoindoloindolone **1f** in 73 % (0.19 g) yield.

Orange solid, m.p.: 201–202 °C.

R_f: 0.59 (CH_2Cl_2:hexanes, 3:1)

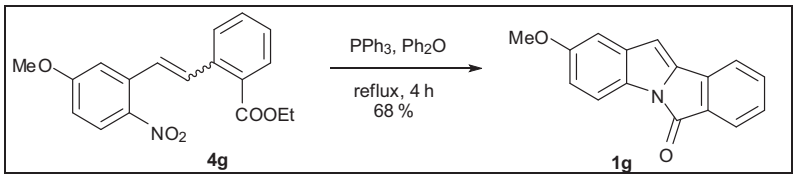
IR (KBr): ν_{max} 1468, 1724, 3057 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 5.91 (s, 2 H), 6.38 (s, 1 H), 6.75 (s, 1 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 7.31 (s, 1 H), 7.34 (d, *J* = 7.6 Hz, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.63 (d, *J* = 7.6 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 95.36 (CH), 101.36 (CH_2), 101.54 (CH), 103.88 (CH), 120.51 (CH), 125.28 (CH), 128.10 (CH), 128.23 (Cq), 128.80 (Cq), 133.35 (Cq), 133.77 (CH), 135.14 (Cq), 137.79 (Cq), 145.11 (Cq), 147.42 (Cq), 162.66 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{16}H_9NO_3Na$ $[M+Na]^+$ 286.0480; found 286.0480.

2.5.21: *2*-Methoxy-*6H*-isoindolo*[2,1-a]*indol-*6*-one 1g:



Following the similar procedure as described in experiment 2.5.4 with ethyl *2*-(*5*-methoxy-*2*-nitrostyryl)benzoate **4g** (0.33 g, 1 mmol) gave the isoindoloindolone **1g** in 68 % (0.17 g) yield.

Yellow solid,[3b] m.p.: 160–161 °C.

R_f: 0.65 (CH_2Cl_2:hexanes, 3:1)

IR (neat): ν_{max} 1440, 1724, 3057 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 3 H), 6.37 (s, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.79 (s, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.32–7.37 (m, 2 H), 7.58–7.63 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 55.69 (CH_3), 103.40 (CH), 105.86 (CH), 113.77 (CH), 113.94 (CH), 121.07 (CH), 125.09 (CH), 128.21 (Cq), 128.71 (CH), 133.50 (CH), 133.9 (Cq), 134.59 (Cq), 135.49 (Cq), 139.66 (Cq), 156.69 (Cq), 162.30 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{16}H_{11}NO_2Na$ $[M+Na]^+$ 272.0687; found 272.0687.

Elemental analysis: $C_{16}H_{11}NO_2$ (249.27): calculated % C 77.10, H 4.45, N 5.62; found % C 77.40, H 4.40, N 5.99.

2.6: References

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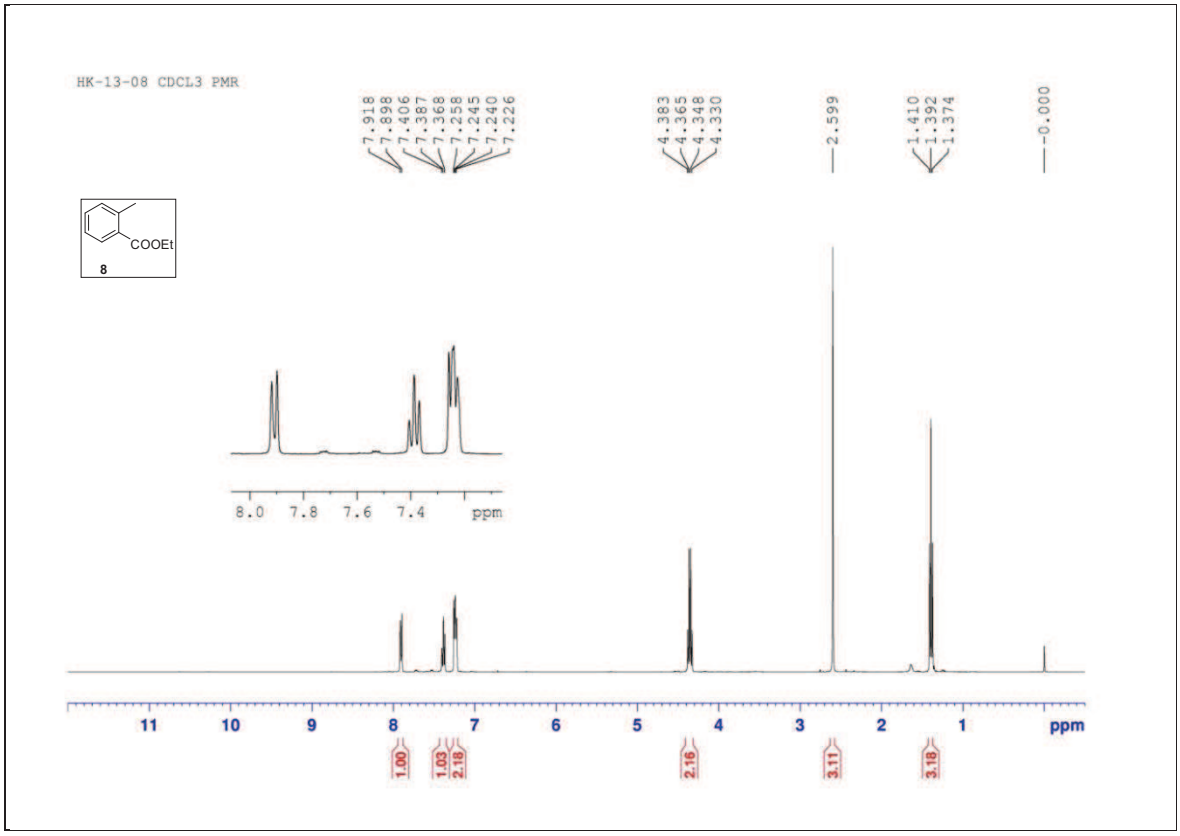
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7.406
7.387
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7.240
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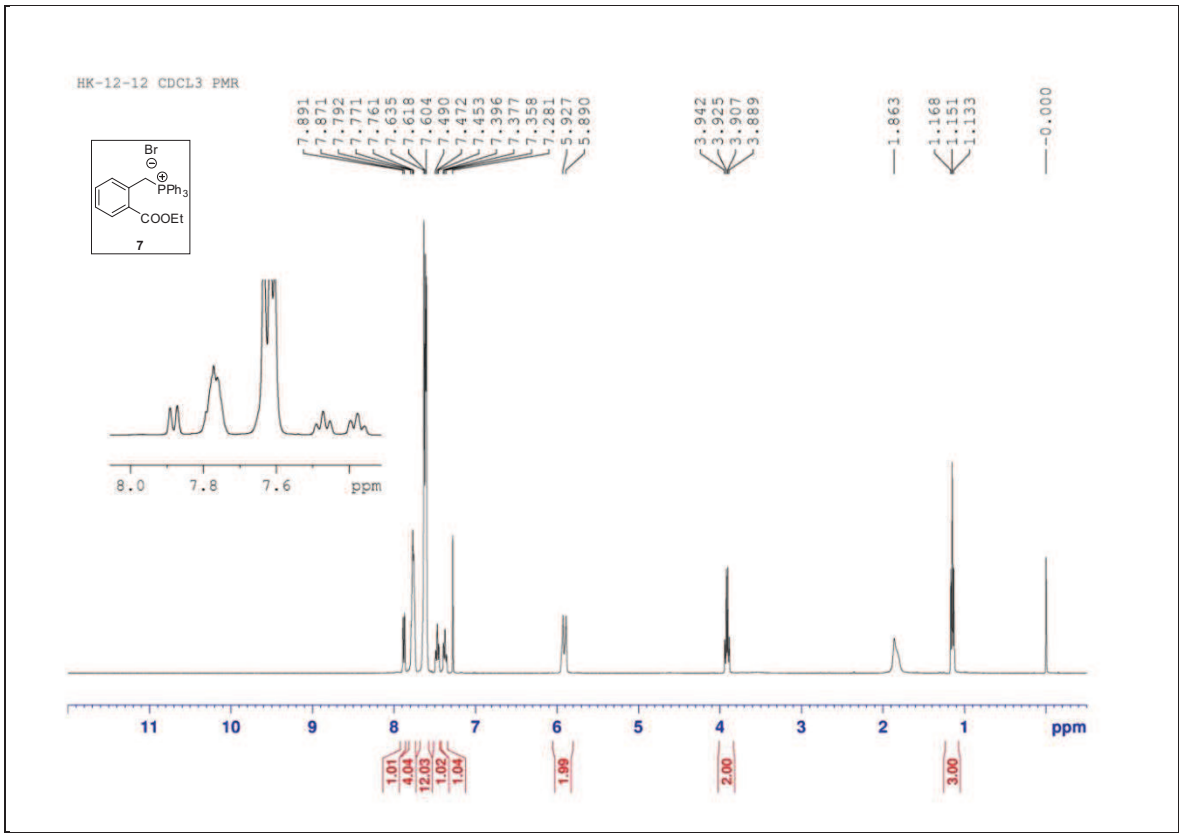
4.383
4.365
4.348
4.330
2.599
1.410
1.392
1.374
0.000
COOEt
8
8.0
7.8
7.6
7.4
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.03
2.18
2.16
3.11
3.18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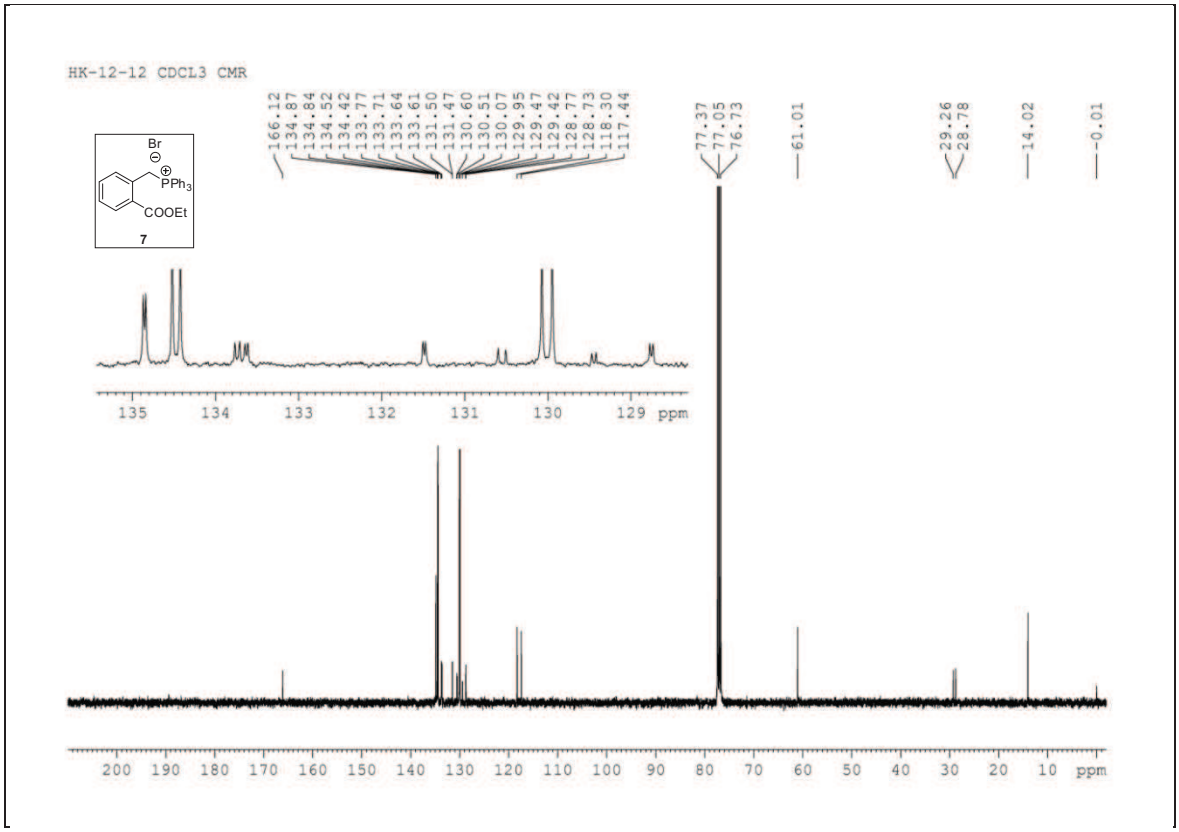
7.792
7.771
7.761
7.635
7.618
7.604
7.490
7.472
7.453
7.396
7.377
7.358
7.281
5.927
5.890
3.942
3.925
3.907
3.889
1.863
1.168
1.151
1.133
0.000
Br
PPh3
COOEt
7
8.0
7.8
7.6
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.01
4.04
12.03
1.02
1.04
1.99
2.00
3.00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134.52
134.42
133.77
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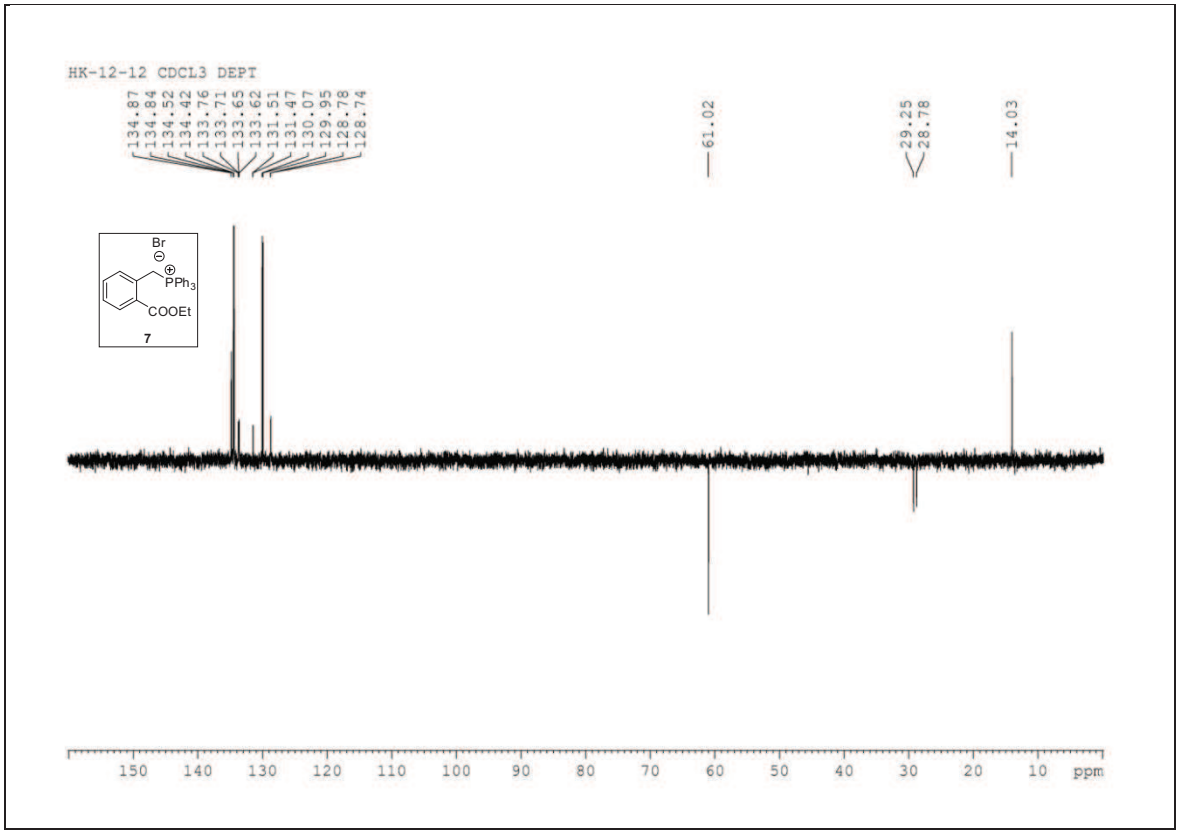
133.64
133.61
131.50
131.47
130.60
130.51
130.07
129.95
129.47
129.42
128.77
128.73
118.30
117.44
77.37
77.05
76.73
61.01
29.26
28.78
14.02
0.01
Br
PPh3
COOEt
7
135 134 133 132 131 130 129 ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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133.71
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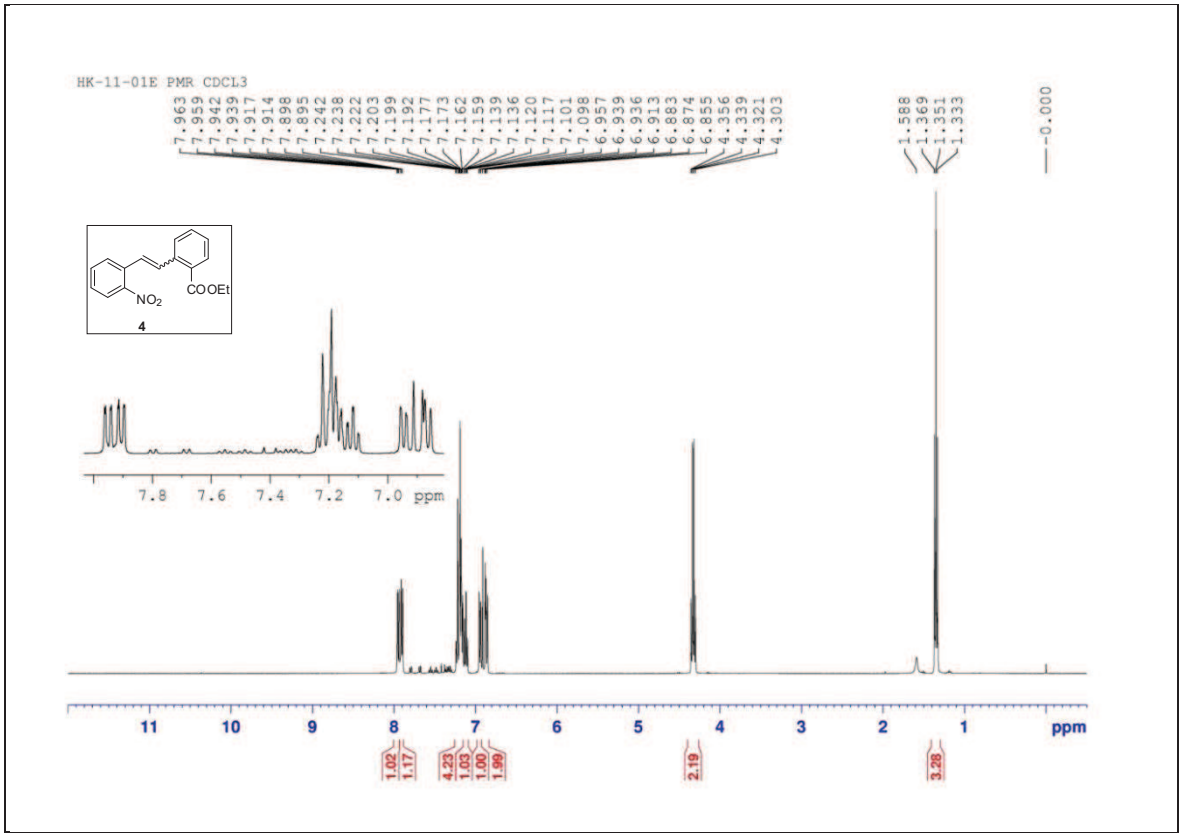
133.62
131.51
131.47
130.07
129.95
128.78
128.74
61.02
29.25
28.78
14.03
Br
PPh3
COOEt
7
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.242
7.238
7.222
7.203
7.199
7.192
7.177
7.173
7.162
7.159
7.139
7.136
7.120
7.117
7.101
7.098
6.957
6.939
6.936
6.913
6.883
6.874
6.855
4.356
4.339
4.321
4.303
1.588
1.369
1.351
1.333
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COOEt
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7.8
7.6
7.4
7.2
7.0 ppm
11
10
9
8
7
6
5
4
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2
1
ppm
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4.23
1.03
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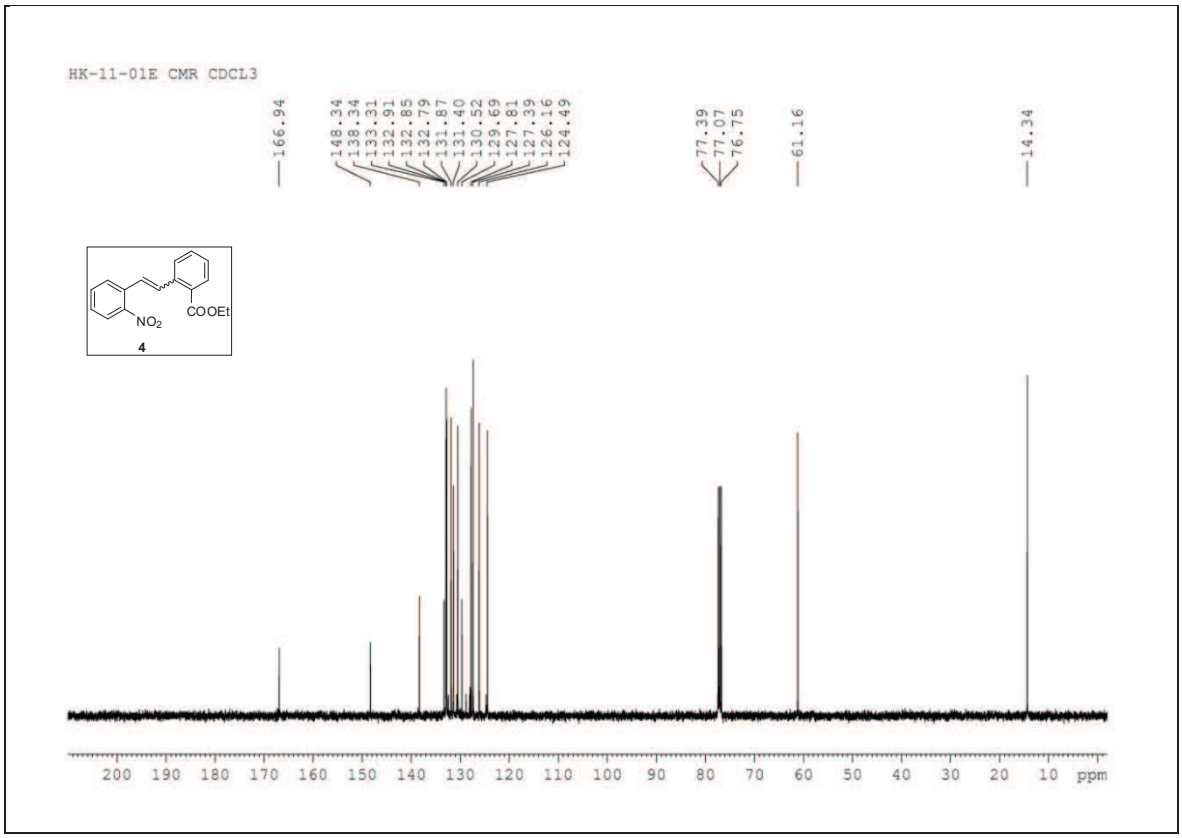
1.99
2.19
3.28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138.34
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132.79
131.87
131.40
130.52
129.69
127.81
127.39
126.16
124.49
77.39
77.07
76.75
61.16
14.34
NO2
COOEt
4
200
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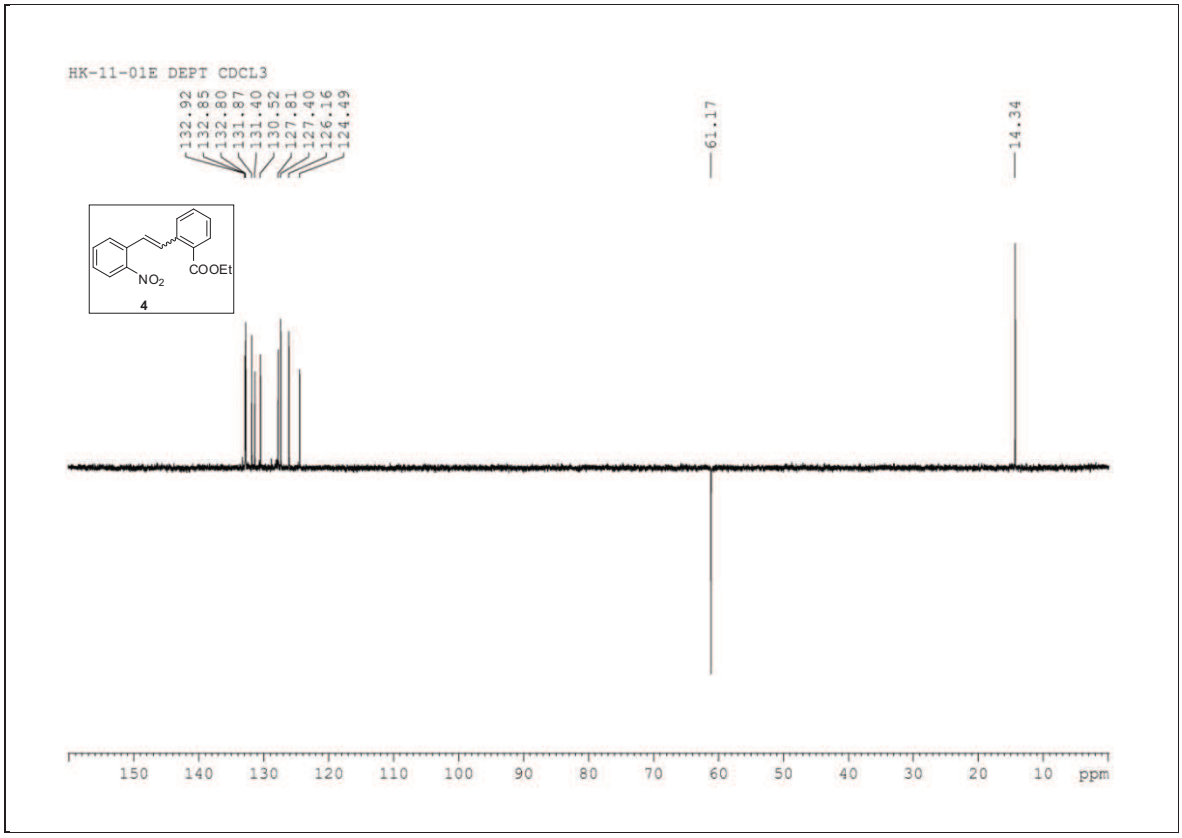
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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127.40
126.16
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61.17
14.34
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COOEt
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120
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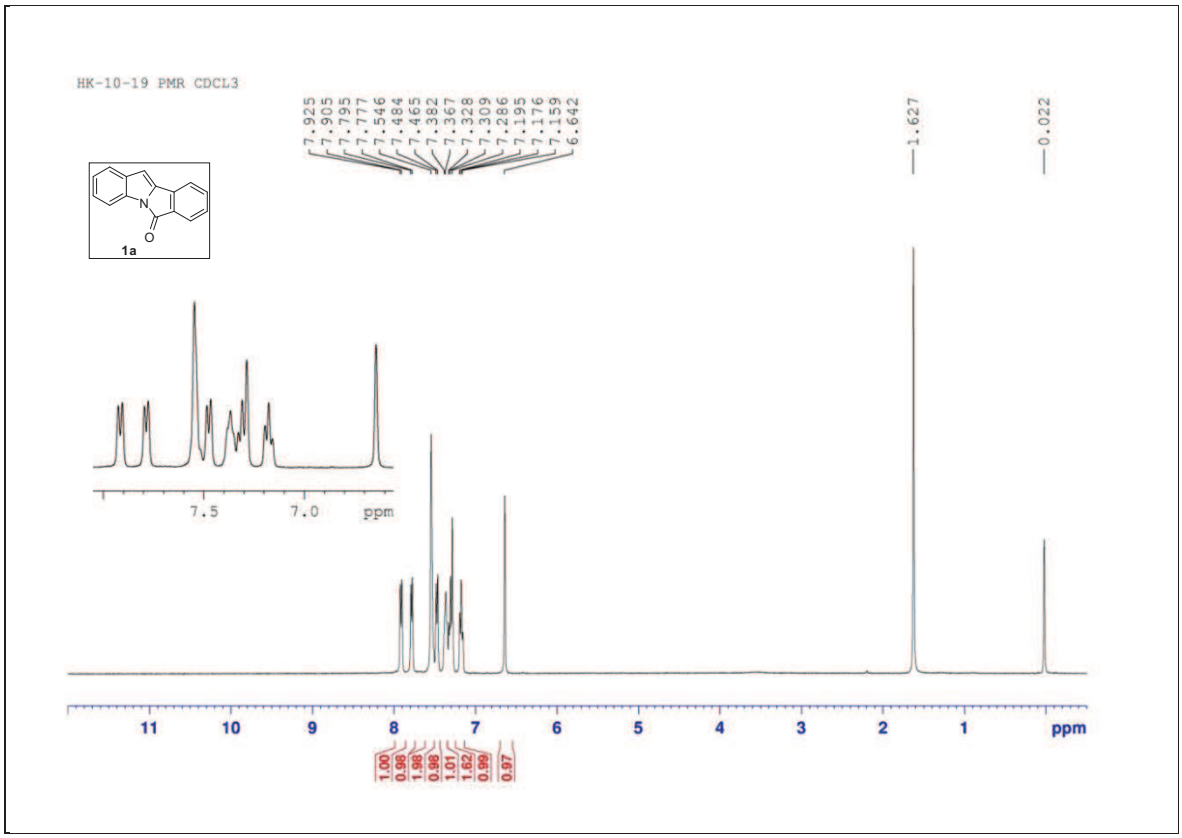
40
30
20
10
ppm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7.309
7.286
7.195
7.176
7.159
6.642
1.627
0.022
1a
7.5
7.0
ppm
11
10
9
8
7
6
5
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2
1
ppm
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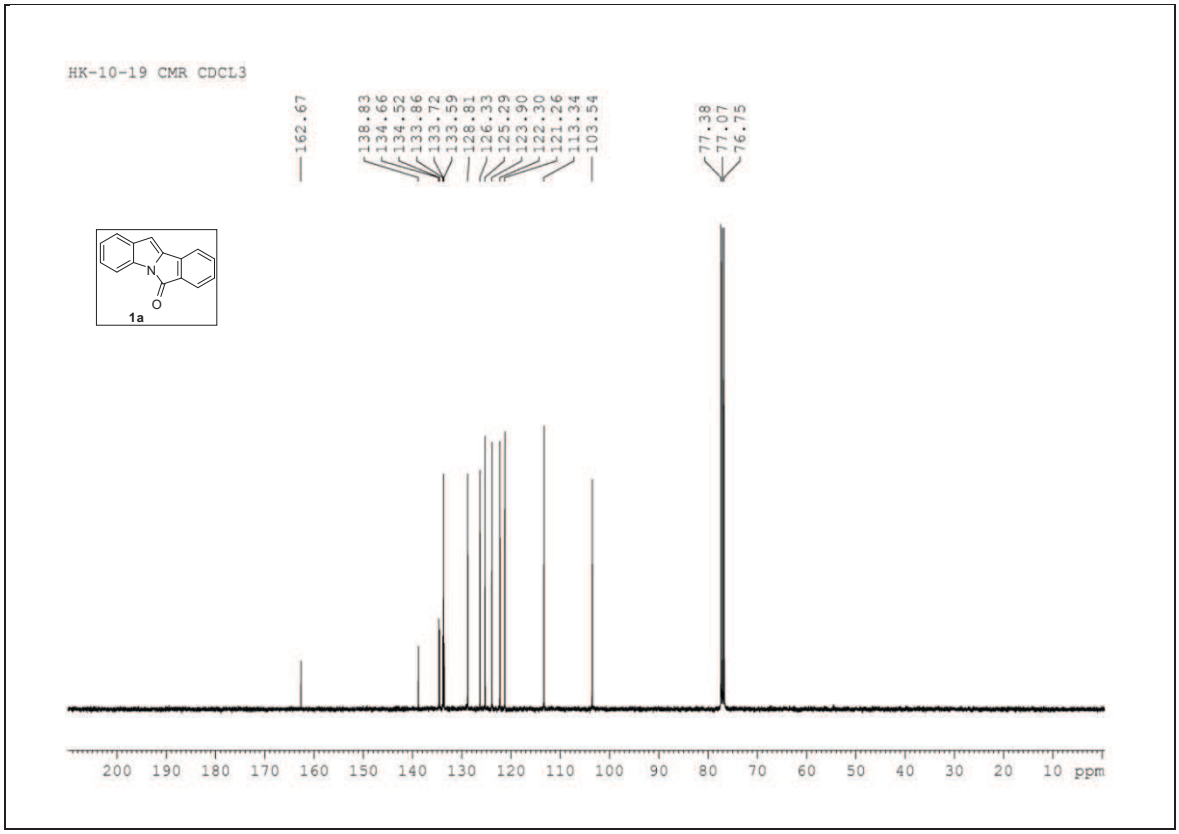
0.97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123.90
122.30
121.26
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103.54
77.38
77.07
76.75
1a
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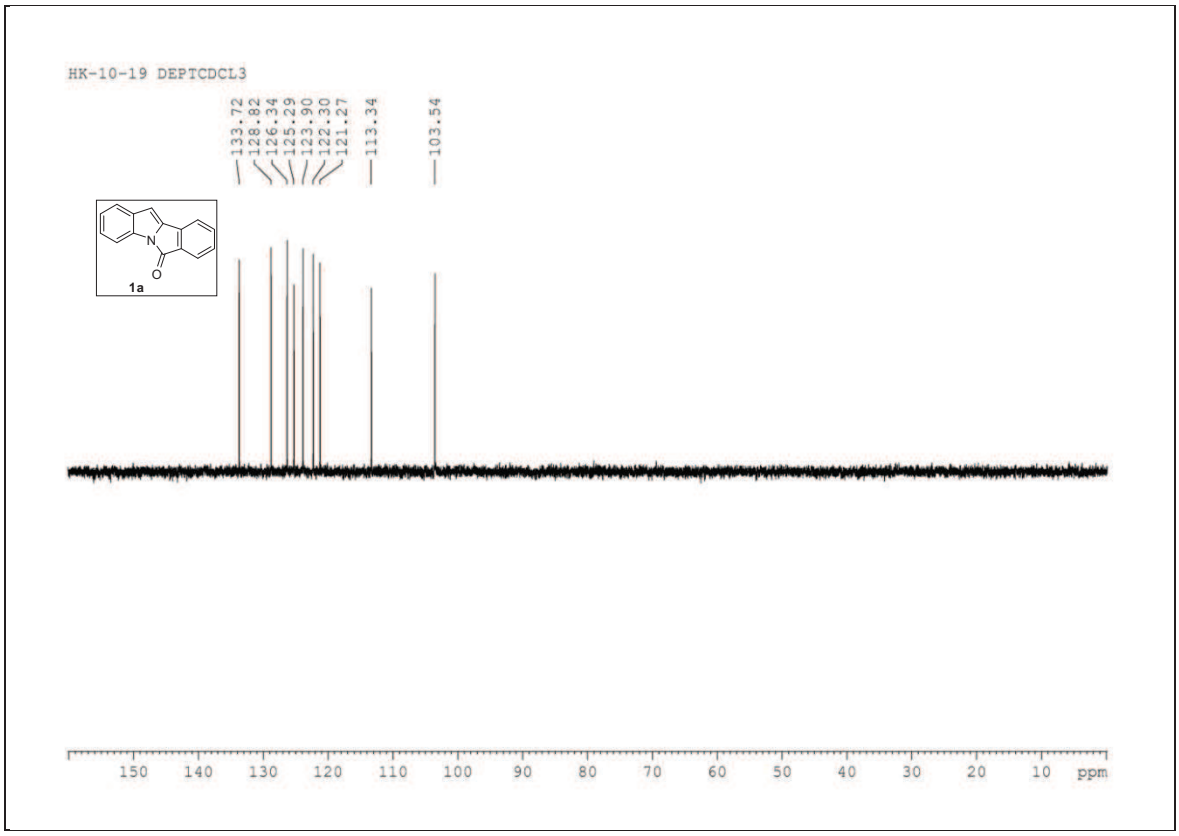
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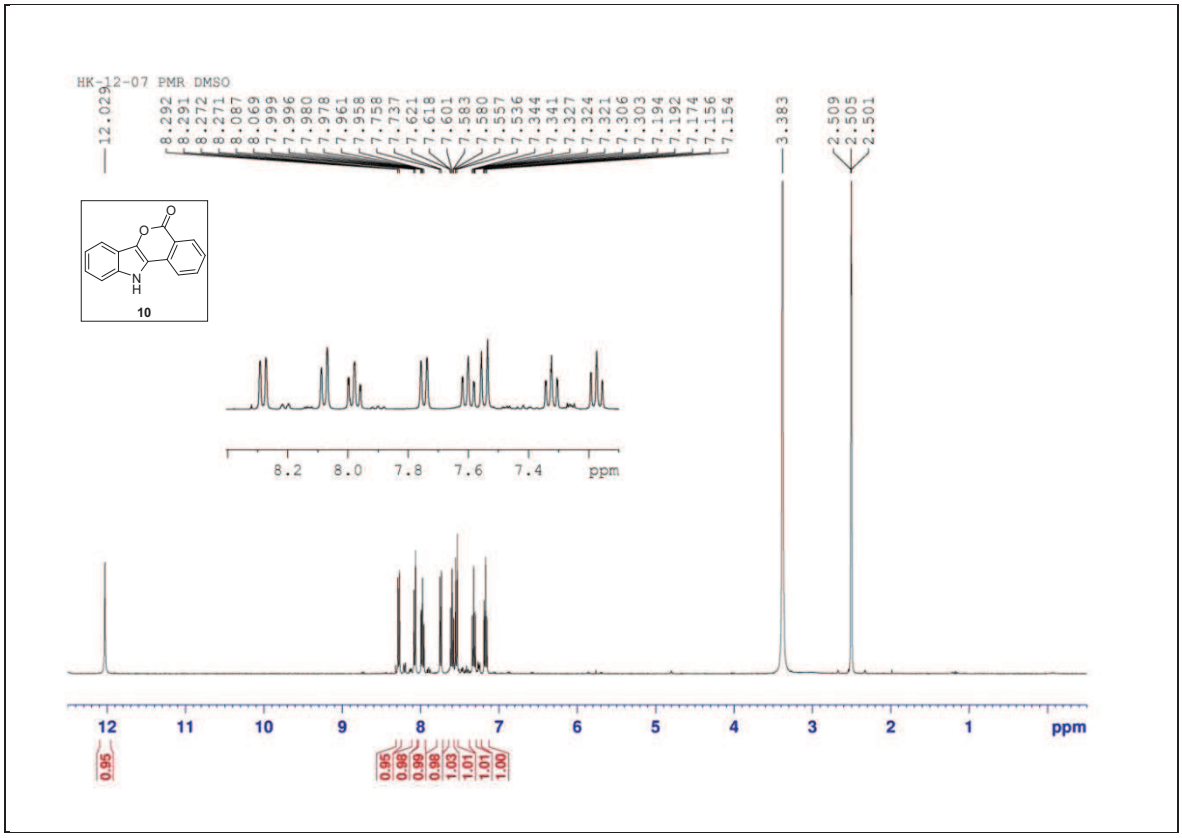
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8.271
8.087
8.069
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7.996
7.980
7.978
7.961
7.958
7.758
7.737
7.621
7.618
7.601
7.583
7.580
7.557
7.536
7.344
7.341
7.327
7.324
7.321
7.306
7.303
7.194
7.192
7.174
7.156
7.154
3.383
2.509
2.505
2.501
10
8.2
8.0
7.8
7.6
7.4
ppm
12
11
10
9
8
7
6
5
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ppm
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0.98
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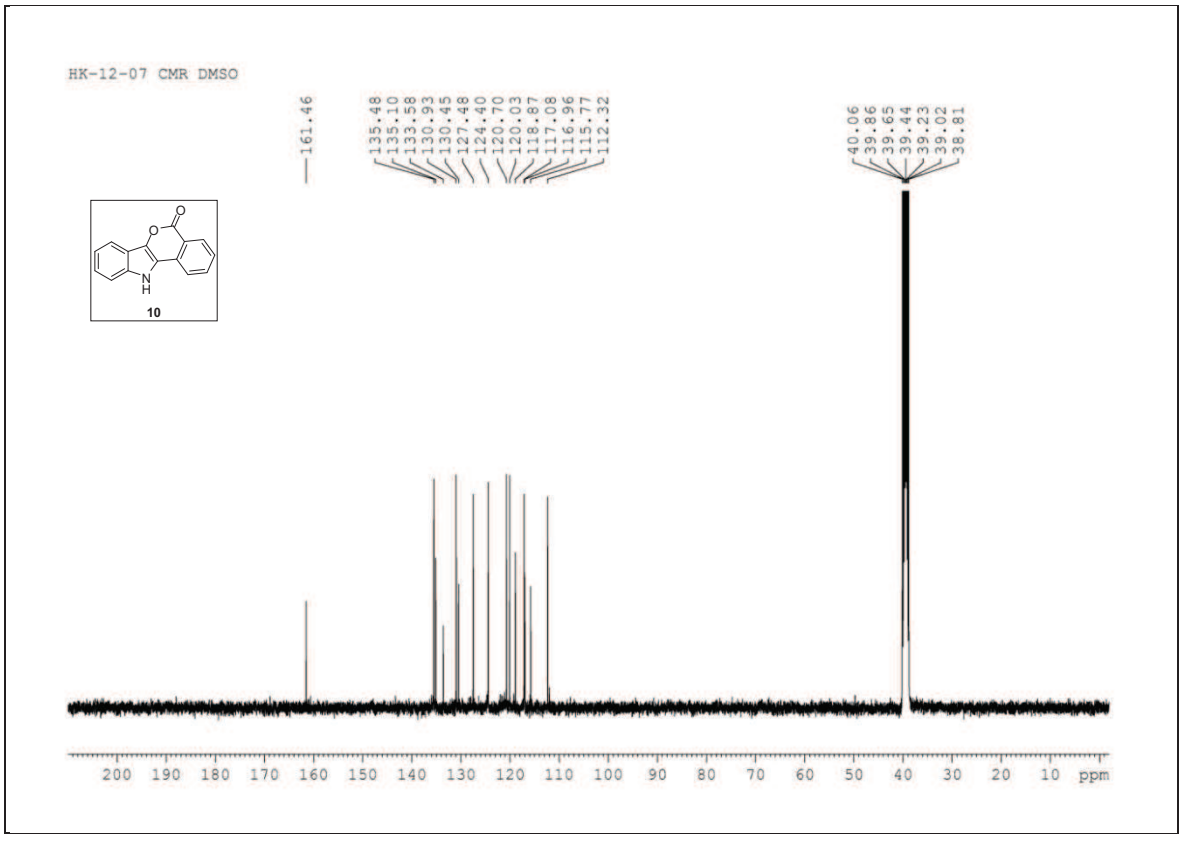
1.01
1.01
1.00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118.87
117.08
116.96
115.77
112.32
40.06
39.86
39.65
39.44
39.23
39.02
38.81
10
200
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150
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120
110
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70
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30
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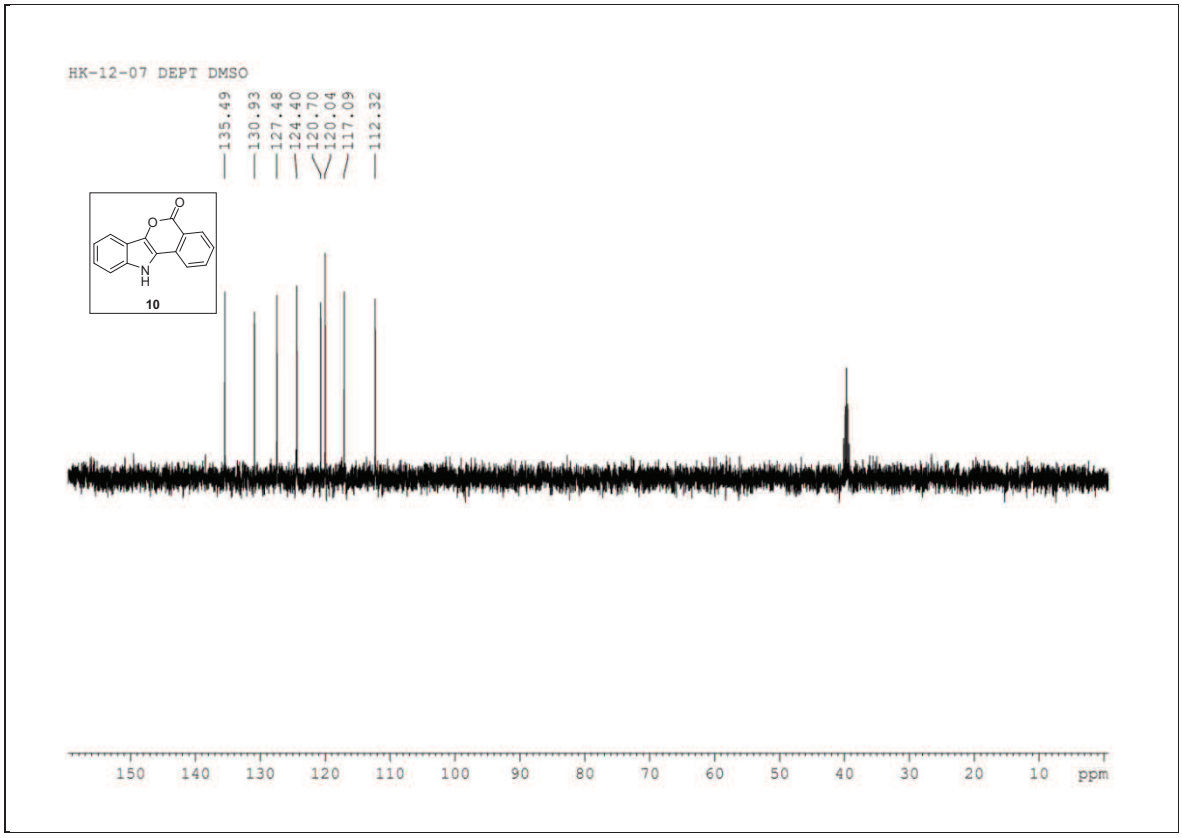
10
ppm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112.32
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O
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150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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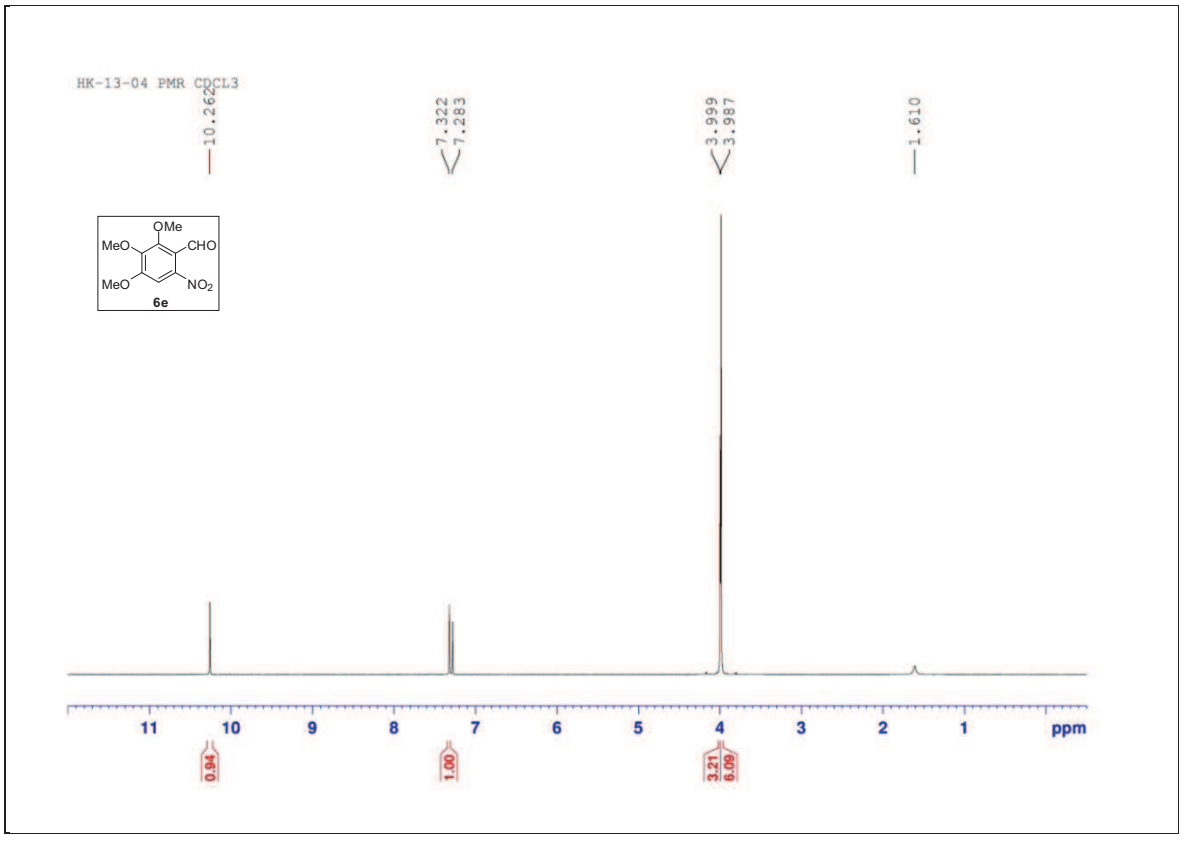
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3.999
3.987
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OMe
MeO
CHO
MeO
NO2
6e
11
10
9
8
7
6
5
4
3
2
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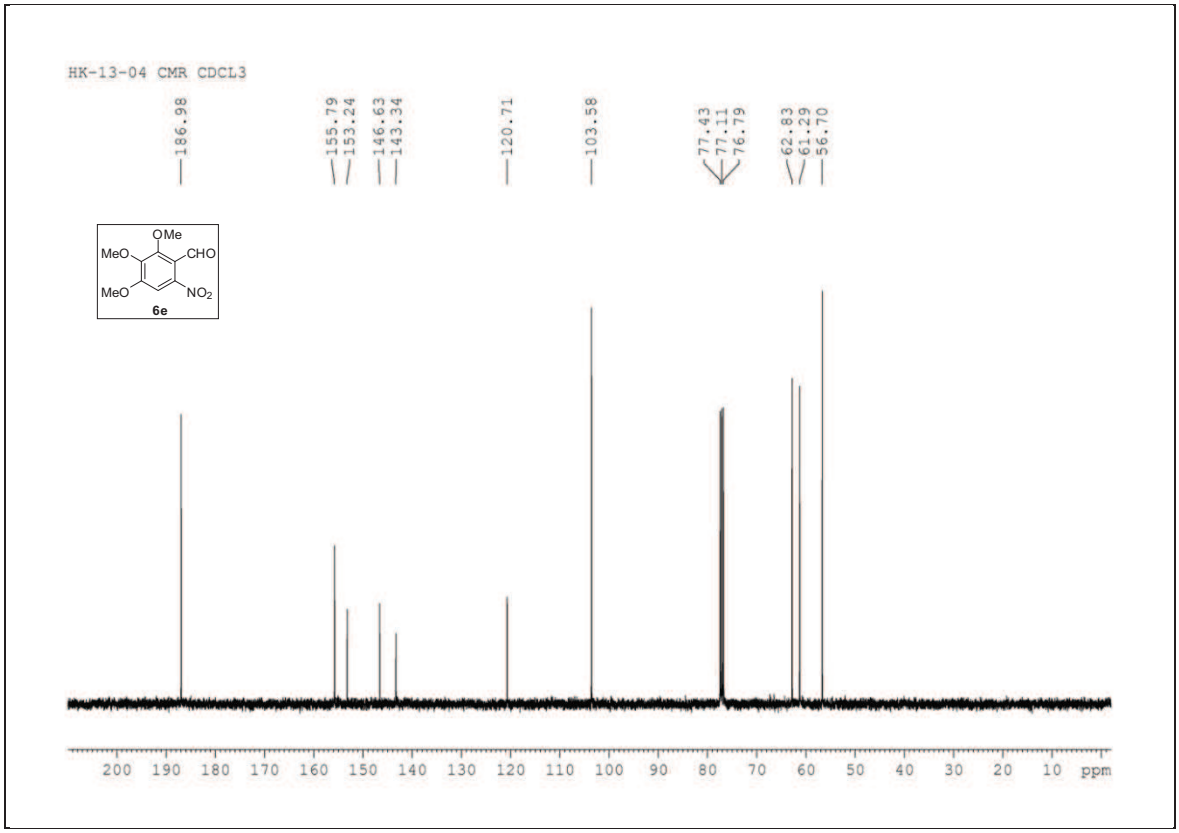
ppm
0.94
1.00
3.21
6.09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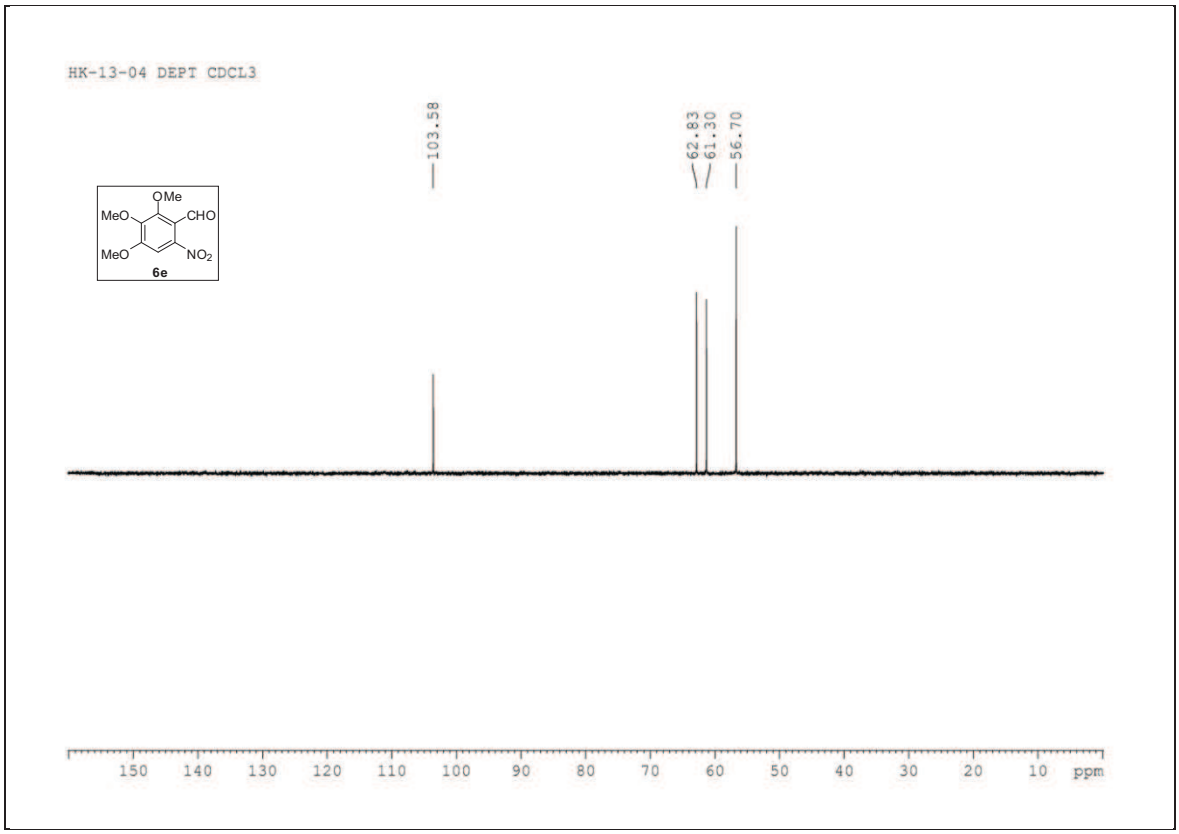
155.79
153.24
146.63
143.34
120.71
103.58
77.43
77.11
76.79
62.83
61.29
56.70
OMe
MeO
CHO
MeO
NO2
6e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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6e
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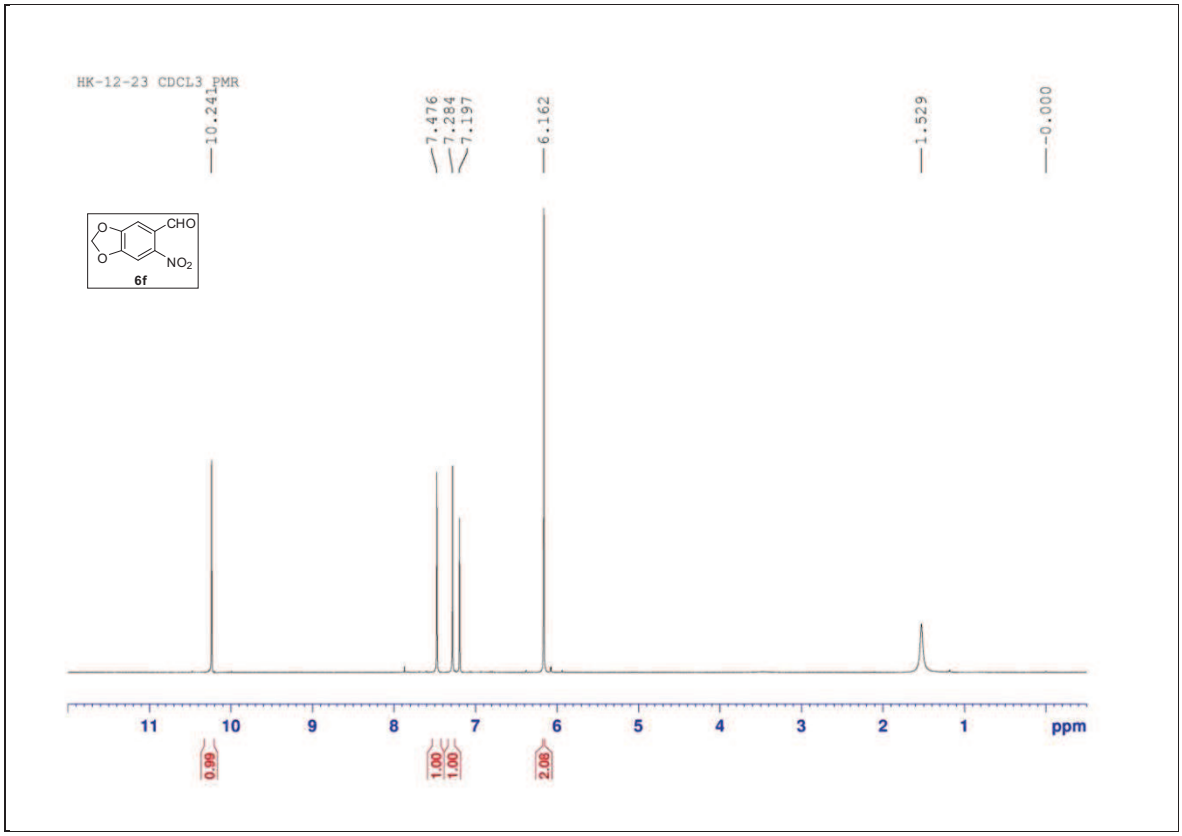
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CHO
NO2
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7
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ppm
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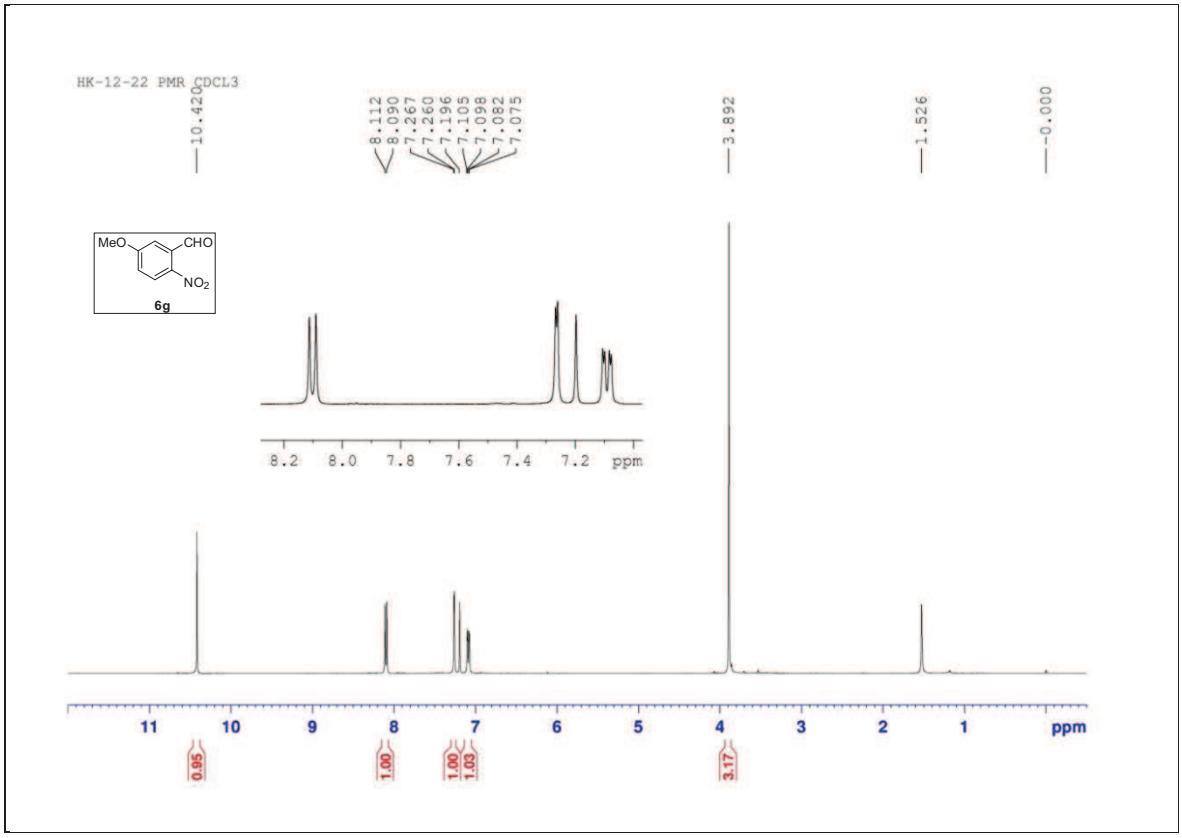
2.08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7.098
7.082
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3.892
1.526
-0.000
MeO
CHO
NO2
6g
8.2
8.0
7.8
7.6
7.4
7.2
ppm
11
10
9
8
7
6
5
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3
2
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ppm
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1.00
1.03
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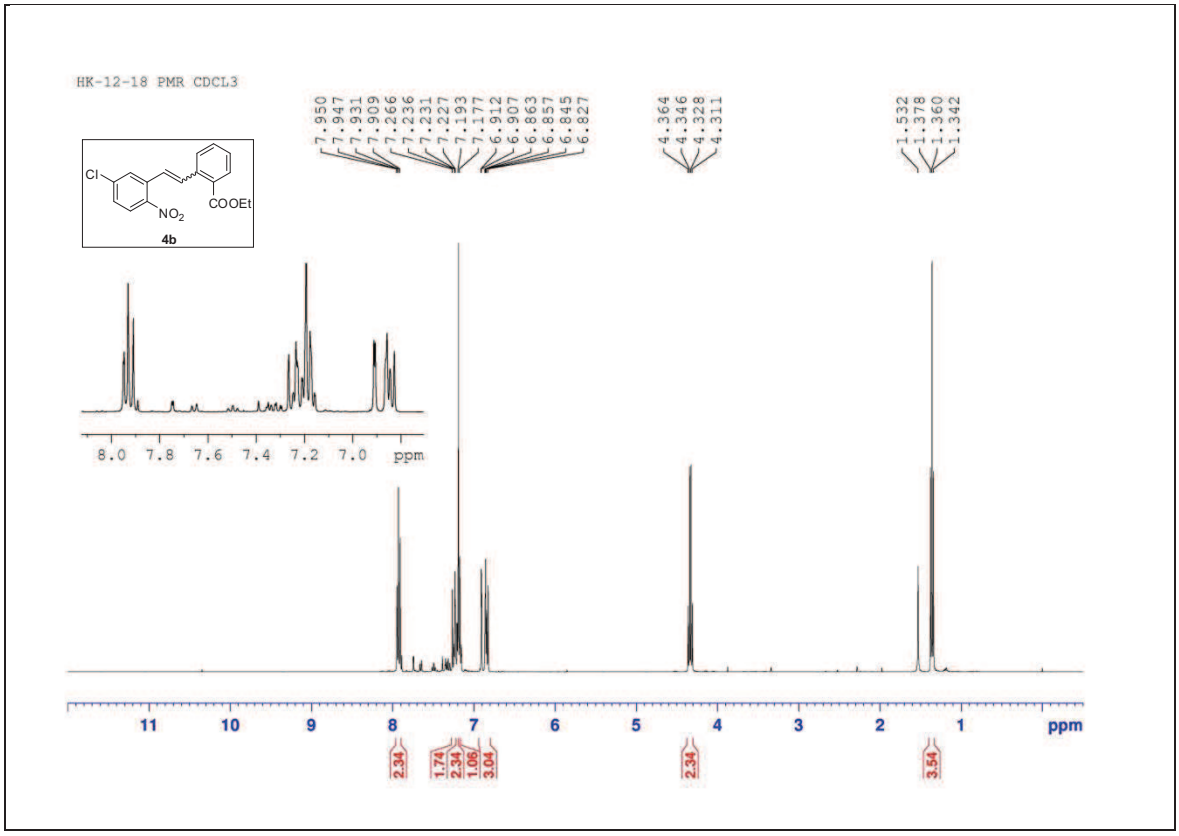
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7.266
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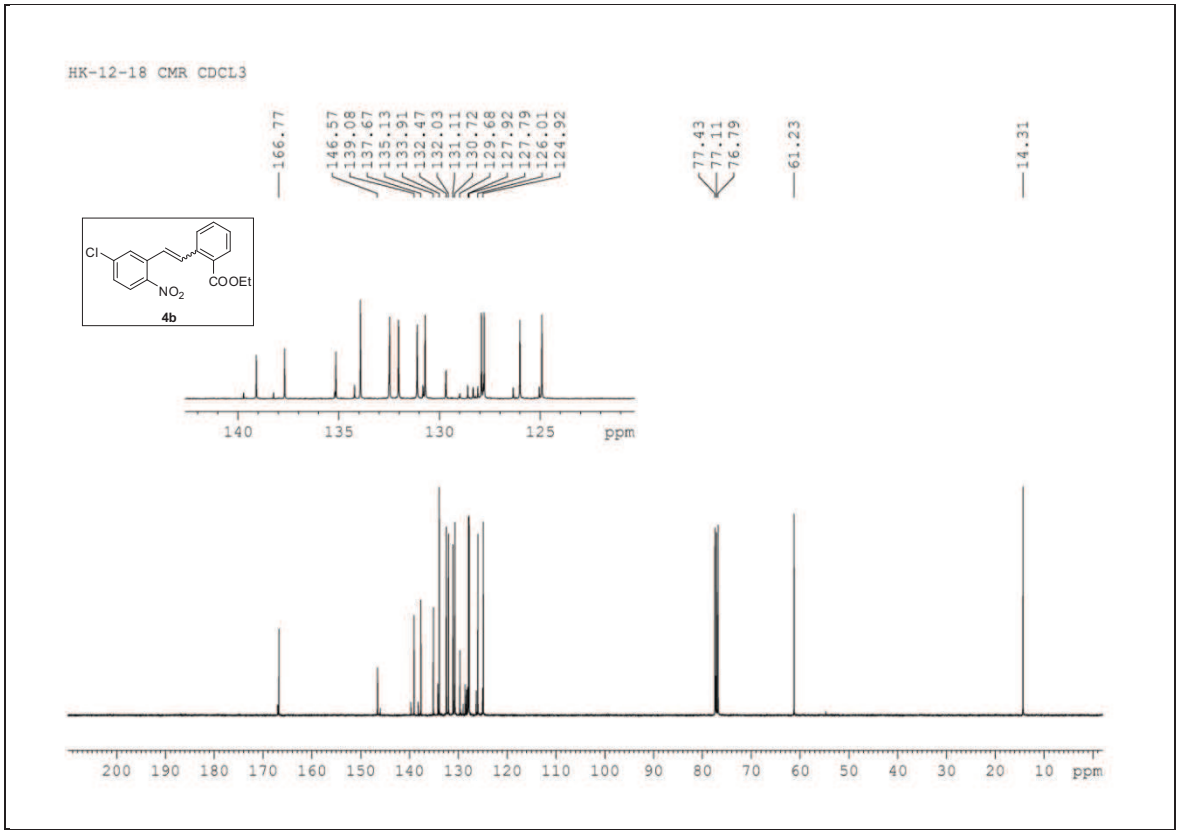
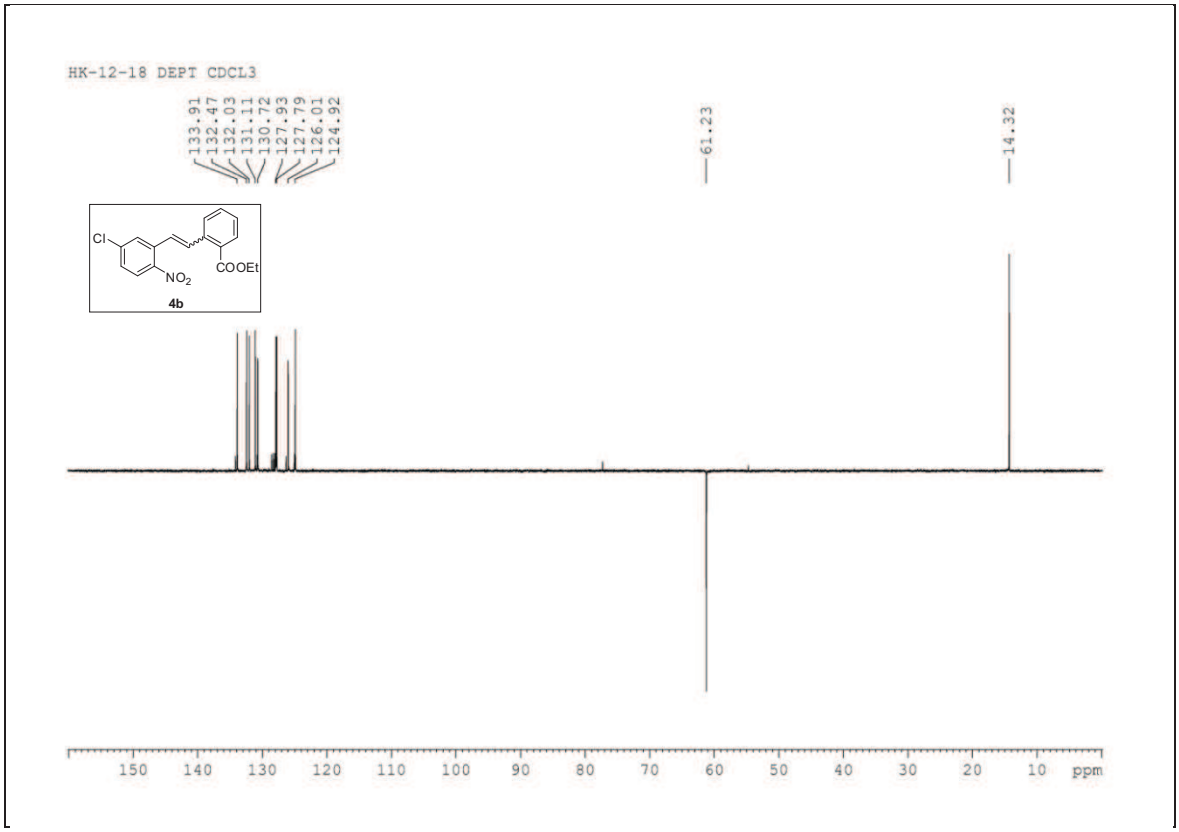
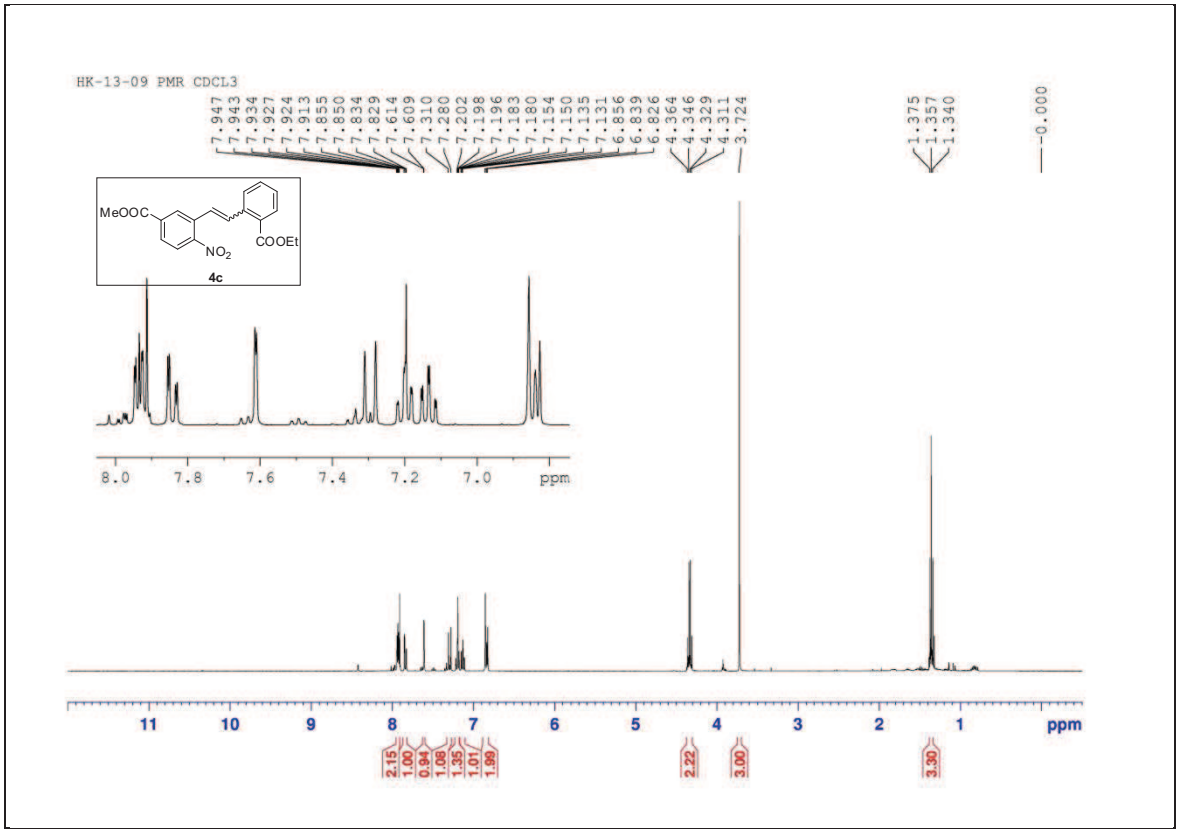
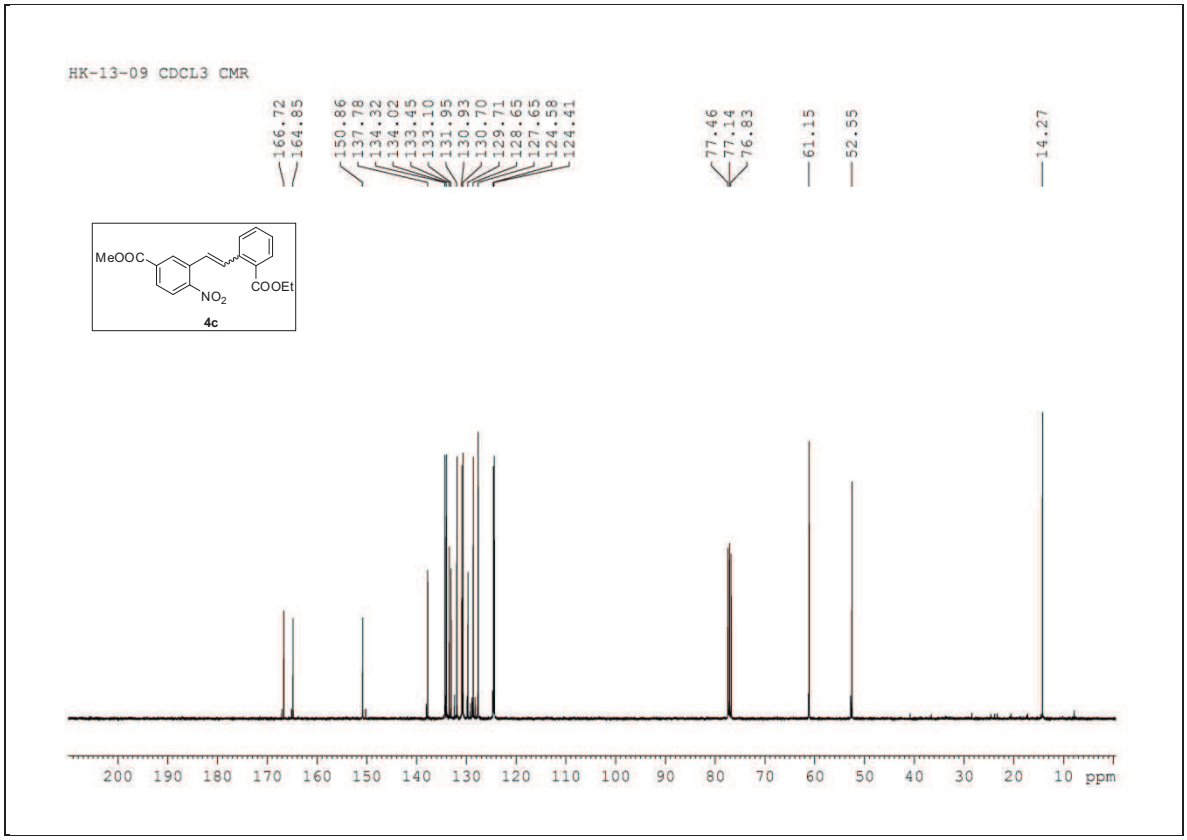
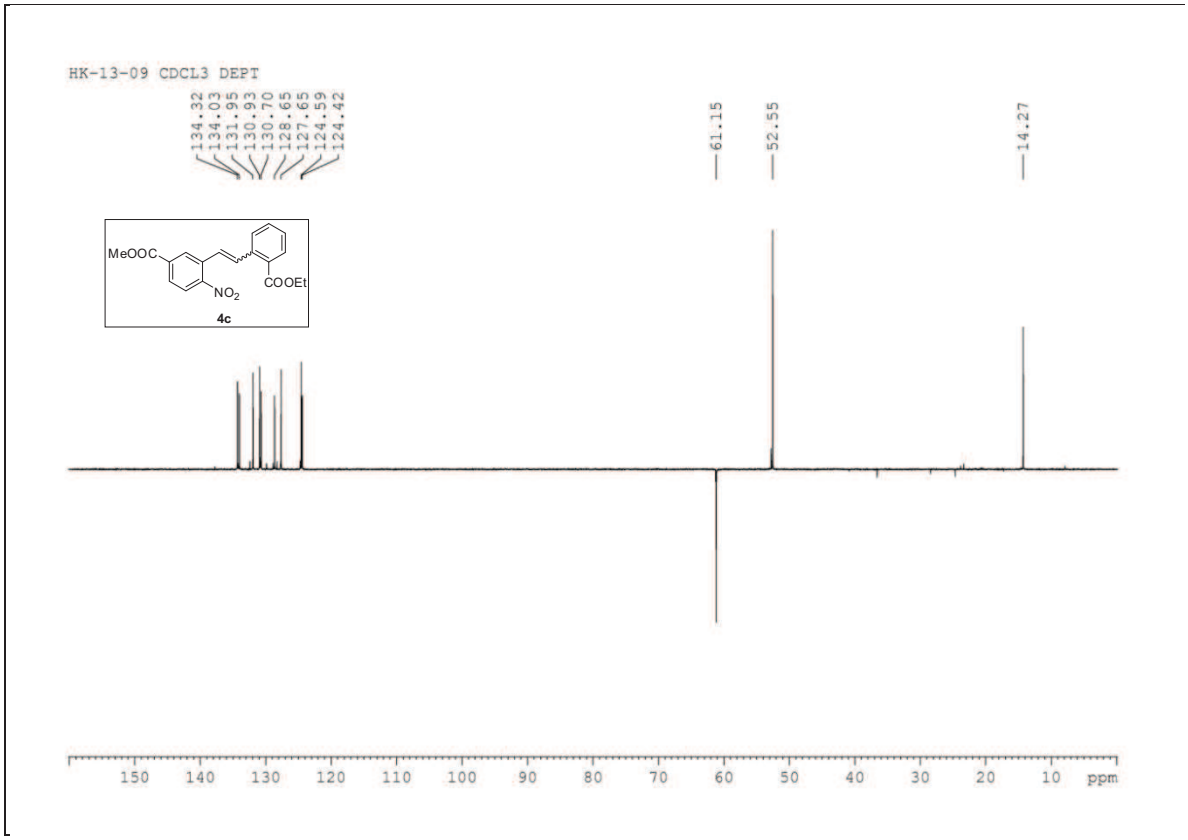
7.231
7.227
7.193
7.177
6.912
6.907
6.863
6.857
6.845
6.827
4.364
4.346
4.328
4.311
1.532
1.378
1.360
1.342
Cl
NO2
COOEt
4b
8.0 7.8 7.6 7.4 7.2 7.0 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
2.34
1.74
2.34
1.06
3.04
2.34
3.54

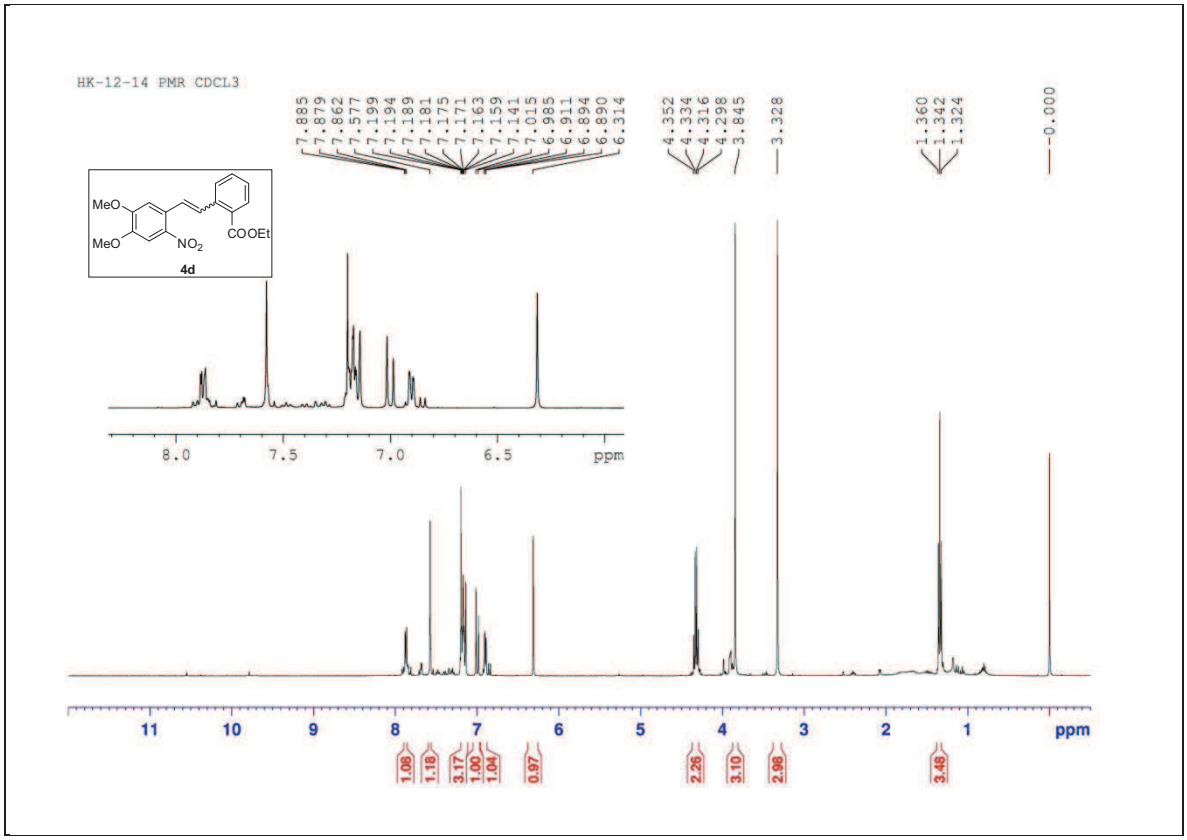

HK-12-18 CMR CDCL3
166.77
146.57
139.08
137.67
135.13
133.91
132.47
132.03
131.11
130.72
129.68
127.92
127.79
126.01
124.92
77.43
77.11
76.79
61.23
14.31
Cl
NO2
COOEt
4b
140 135 130 125 ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

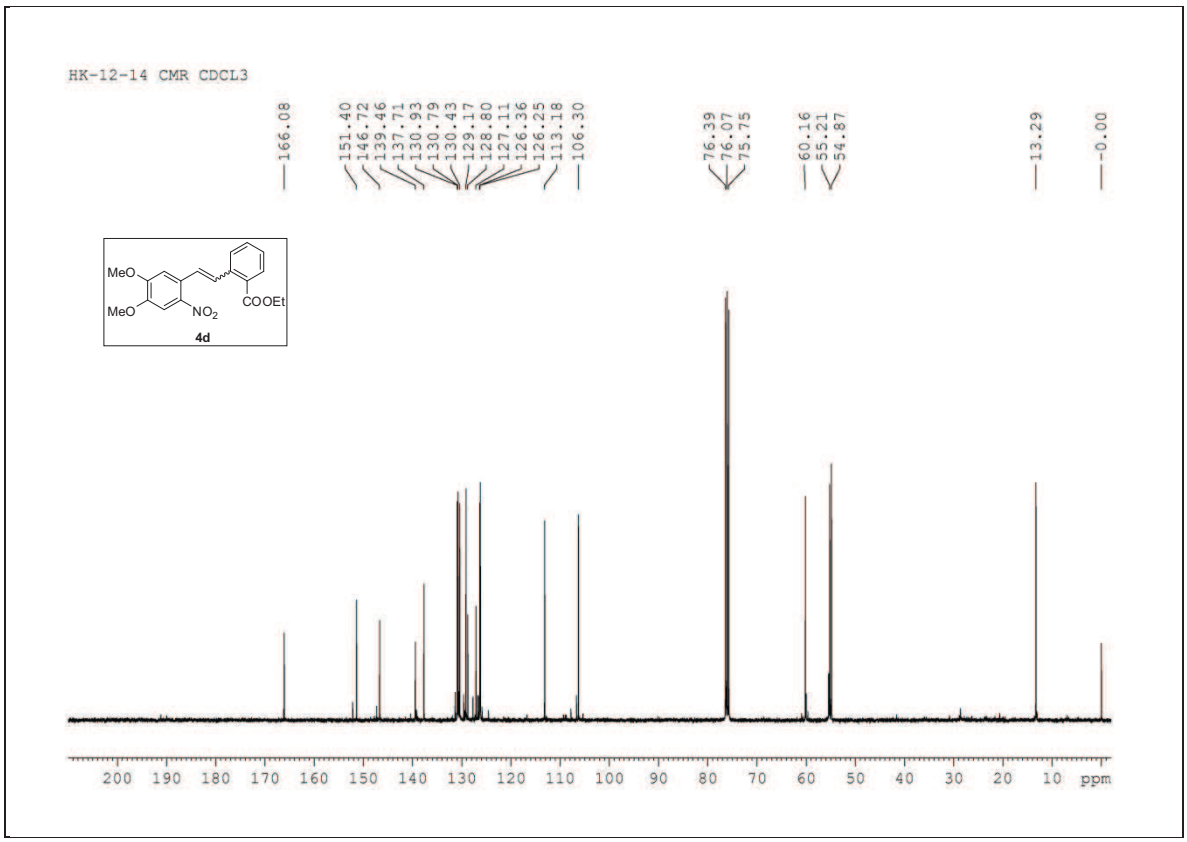

HK-12-18 DEPT CDCL3
133.91
132.47
132.03
131.11
130.72
127.93
127.79
126.01
124.92
61.23
14.32
Cl
NO2
COOEt
4b
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

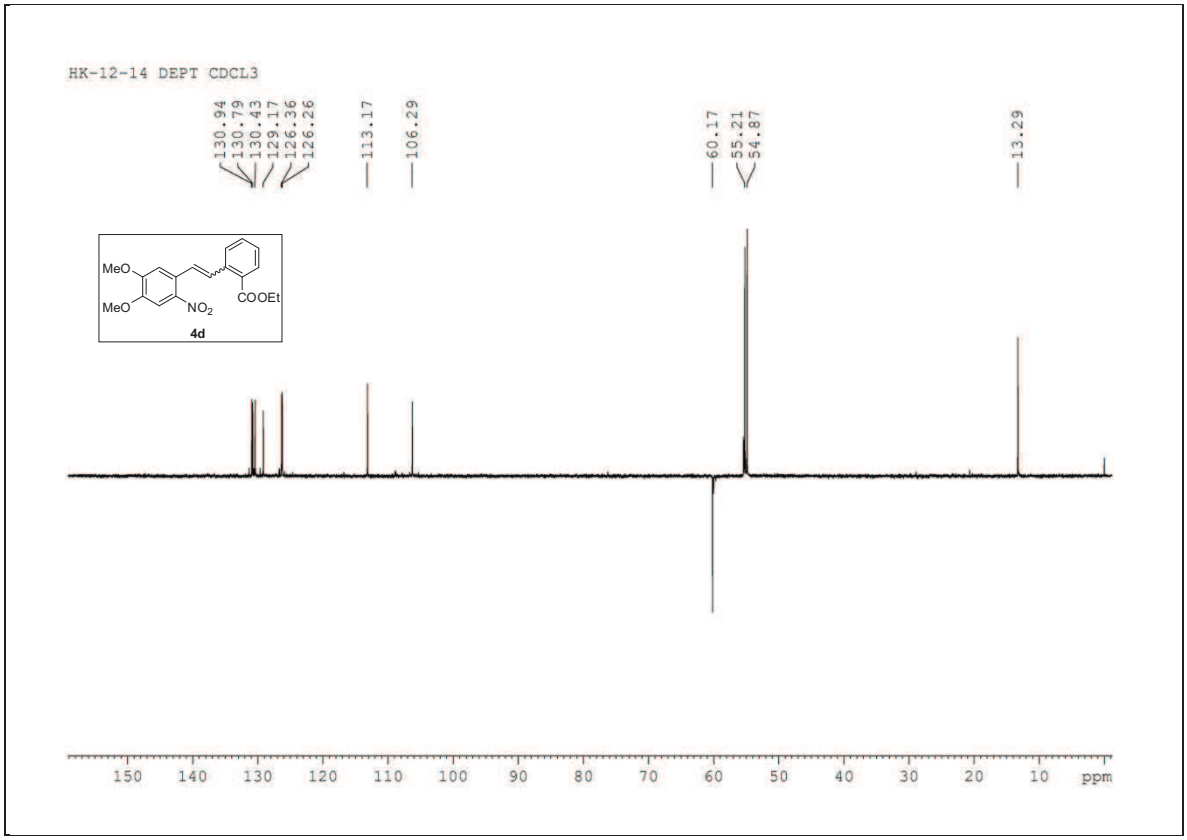

HK-13-09 PMR CDCL3
7.947
7.943
7.934
7.927
7.924
7.913
7.855
7.850
7.834
7.829
7.614
7.609
7.310
7.280
7.202
7.198
7.196
7.183
7.180
7.154
7.150
7.135
7.131
6.856
6.839
6.826
4.364
4.346
4.329
4.311
3.724
1.375
1.357
1.340
0.000
MeOOC
NO2
COOEt
4c
8.0
7.8
7.6
7.4
7.2
7.0
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
2.15
1.00
0.94
1.08
1.35
1.01
1.99
2.22
3.00
3.30

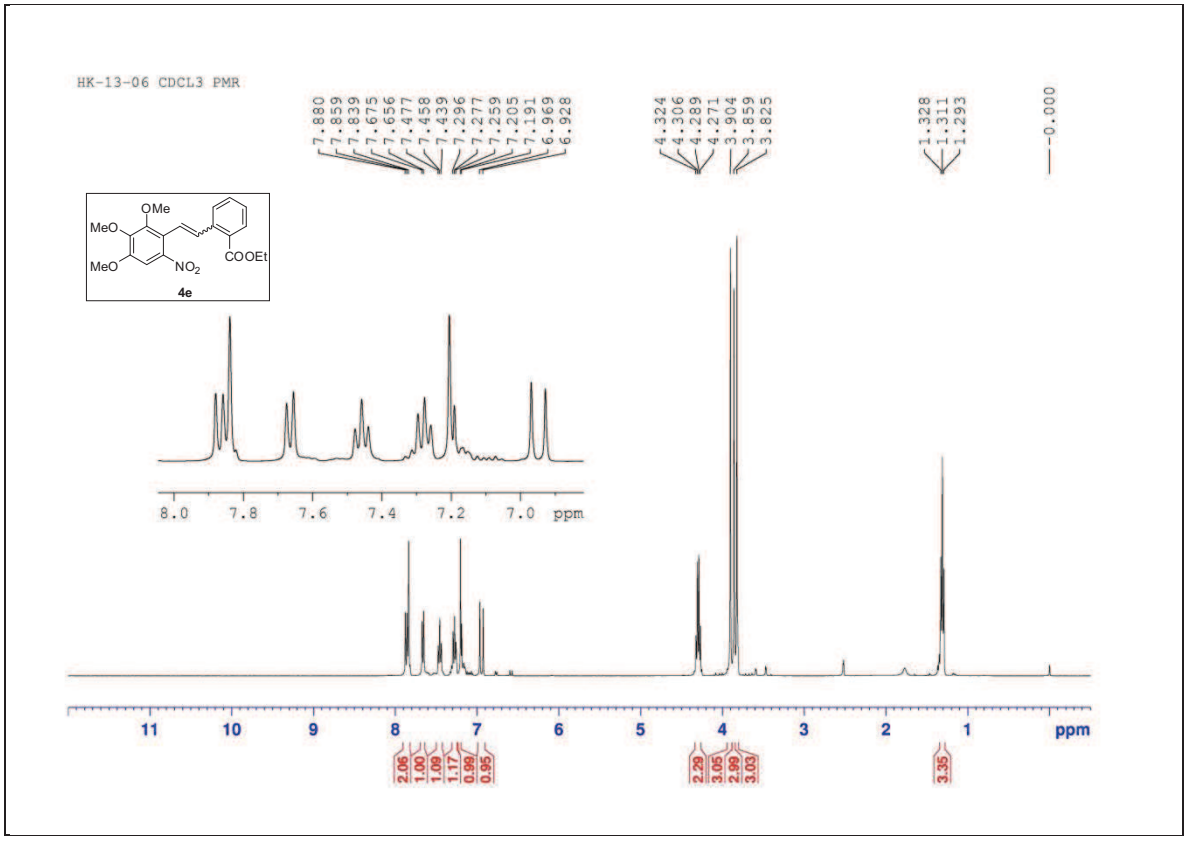

HK-13-09 CDCL3 CMR
166.72
164.85
150.86
137.78
134.32
134.02
133.45
133.10
131.95
130.93
130.70
129.71
128.65
127.65
124.58
124.41
77.46
77.14
76.83
61.15
52.55
14.27
MeOOC
NO2
COOEt
4c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

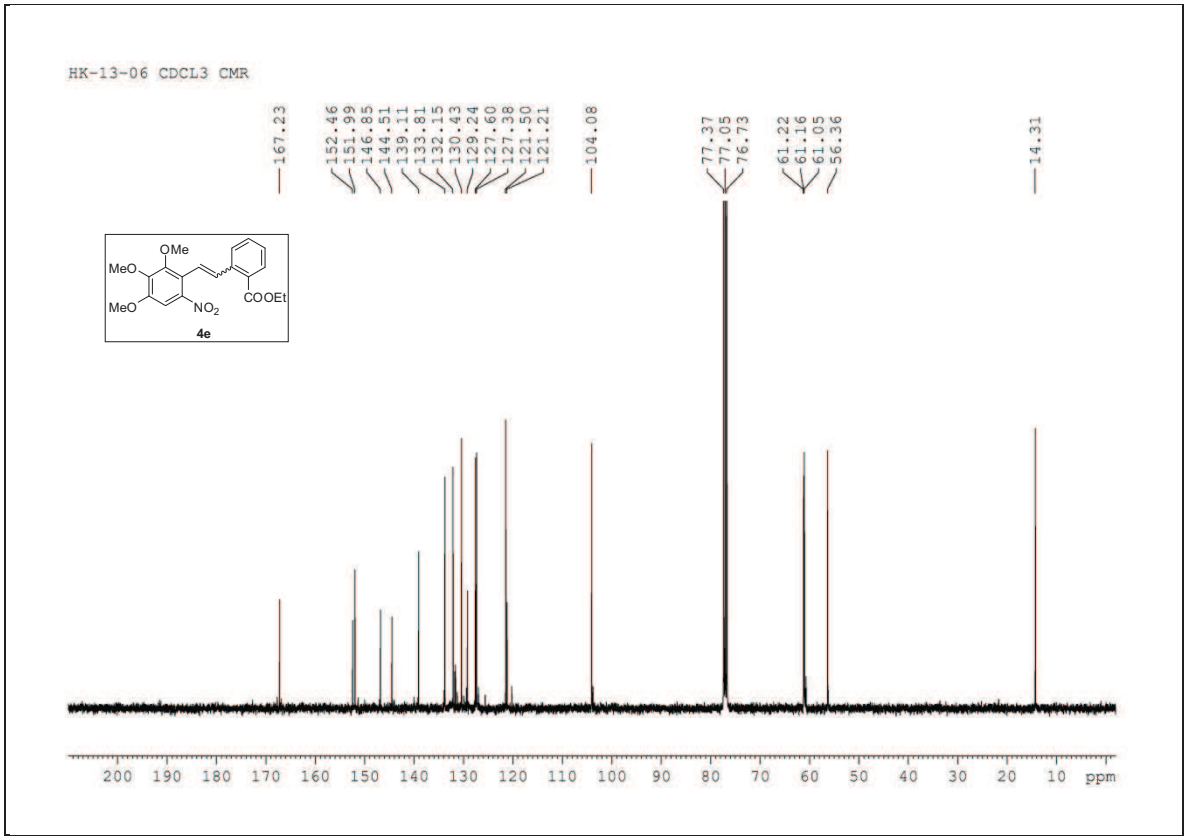

HK-13-09 CDCL3 DEPT
134.32
134.03
131.95
130.93
130.70
128.65
127.65
124.59
124.42
61.15
52.55
14.27
MeOOC
NO2
COOEt
4c
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

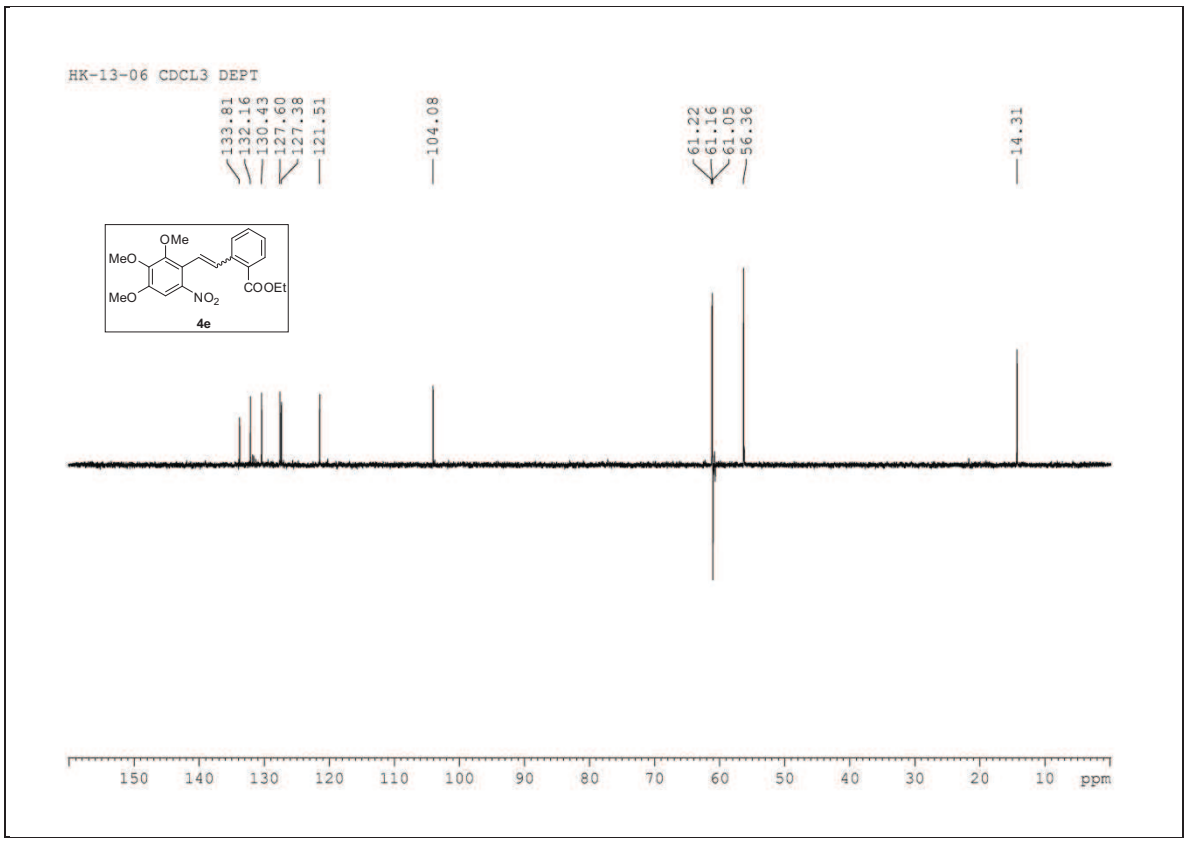

HK-12-14 PMR CDCL3
7.885
7.879
7.862
7.577
7.199
7.194
7.189
7.181
7.175
7.171
7.163
7.159
7.141
7.015
6.985
6.911
6.894
6.890
6.314
4.352
4.334
4.316
4.298
3.845
3.328
1.360
1.342
1.324
0.000
MeO
MeO
NO2
COOEt
4d
8.0
7.5
7.0
6.5
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.08
1.18
3.17
1.00
1.04
0.97
2.26
3.10
2.98
3.48

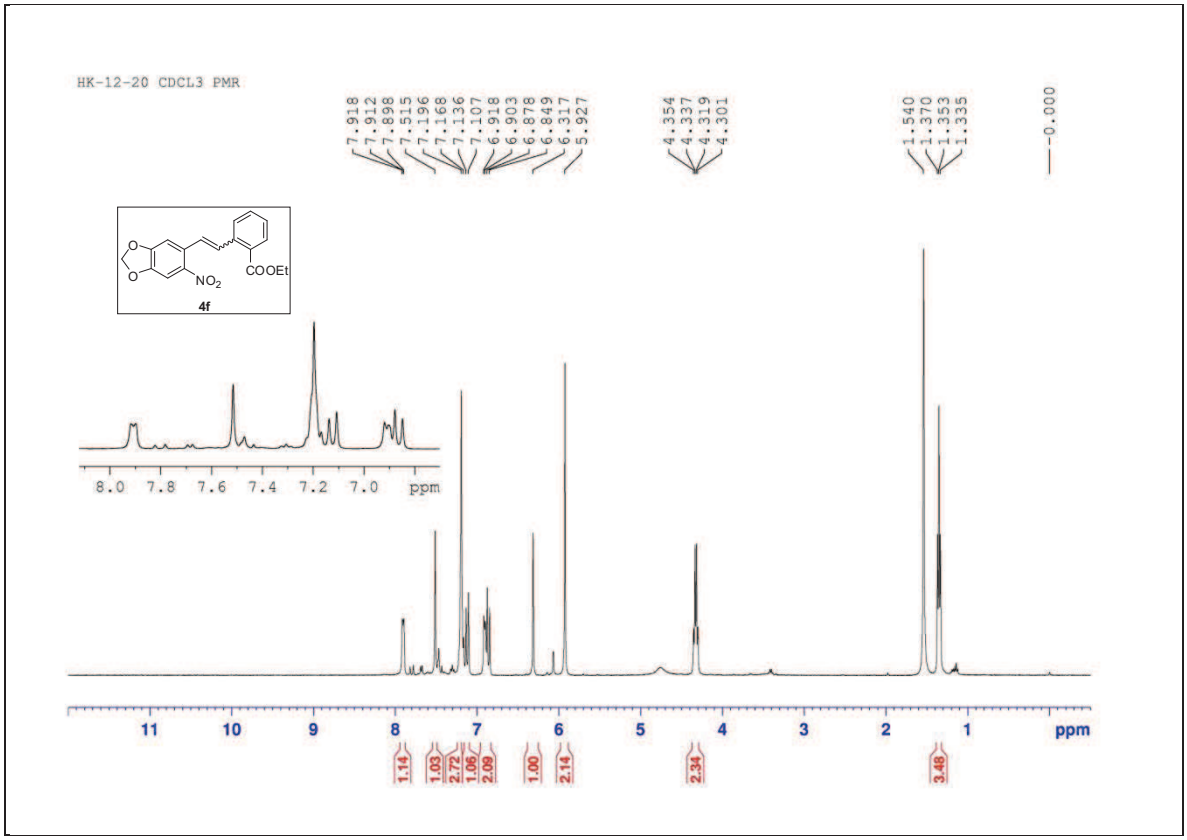

HK-12-14 CMR CDCL3
166.08
151.40
146.72
139.46
137.71
130.93
130.79
130.43
129.17
128.80
127.11
126.36
126.25
113.18
106.30
76.39
76.07
75.75
60.16
55.21
54.87
13.29
0.00
MeO
MeO
NO2
COOEt
4d
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

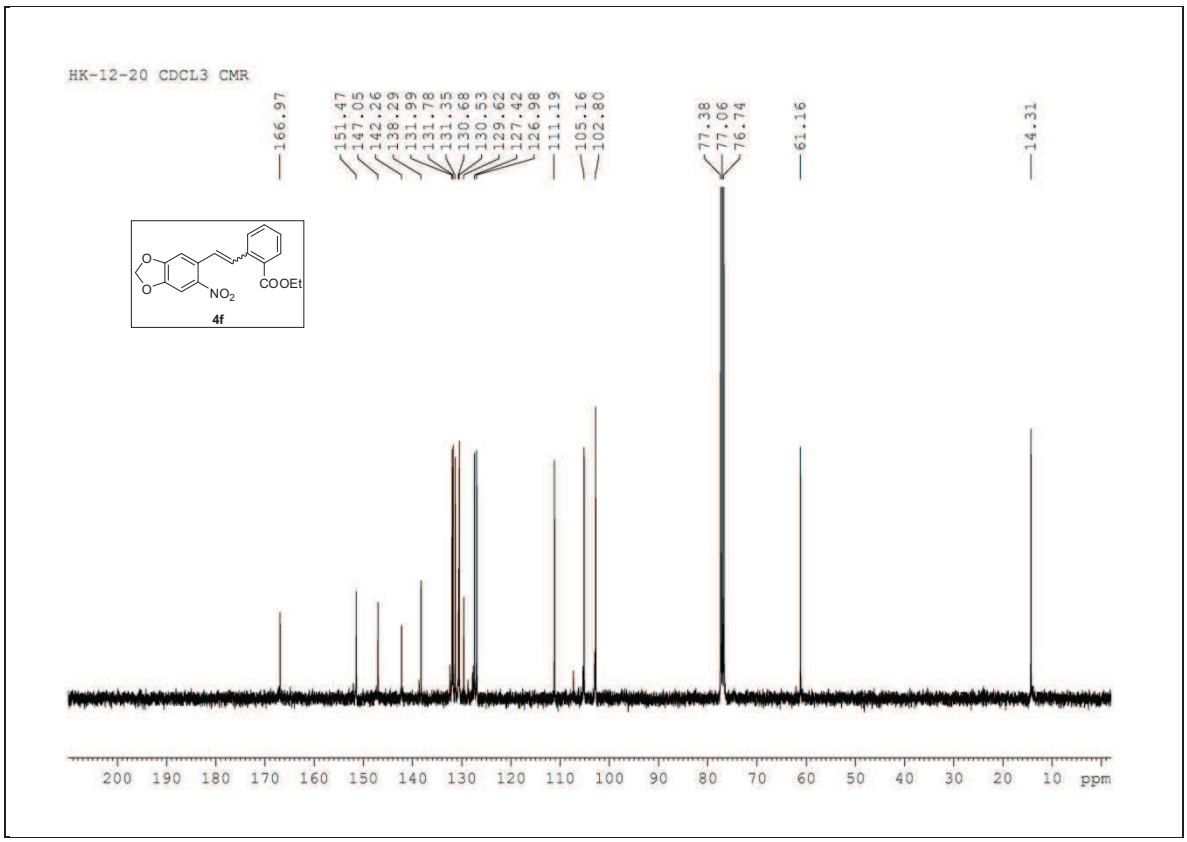

HK-12-14 DEPT CDCL3
130.94
130.79
130.43
129.17
126.36
126.26
113.17
106.29
60.17
55.21
54.87
13.29
MeO
MeO
NO2
COOEt
4d
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

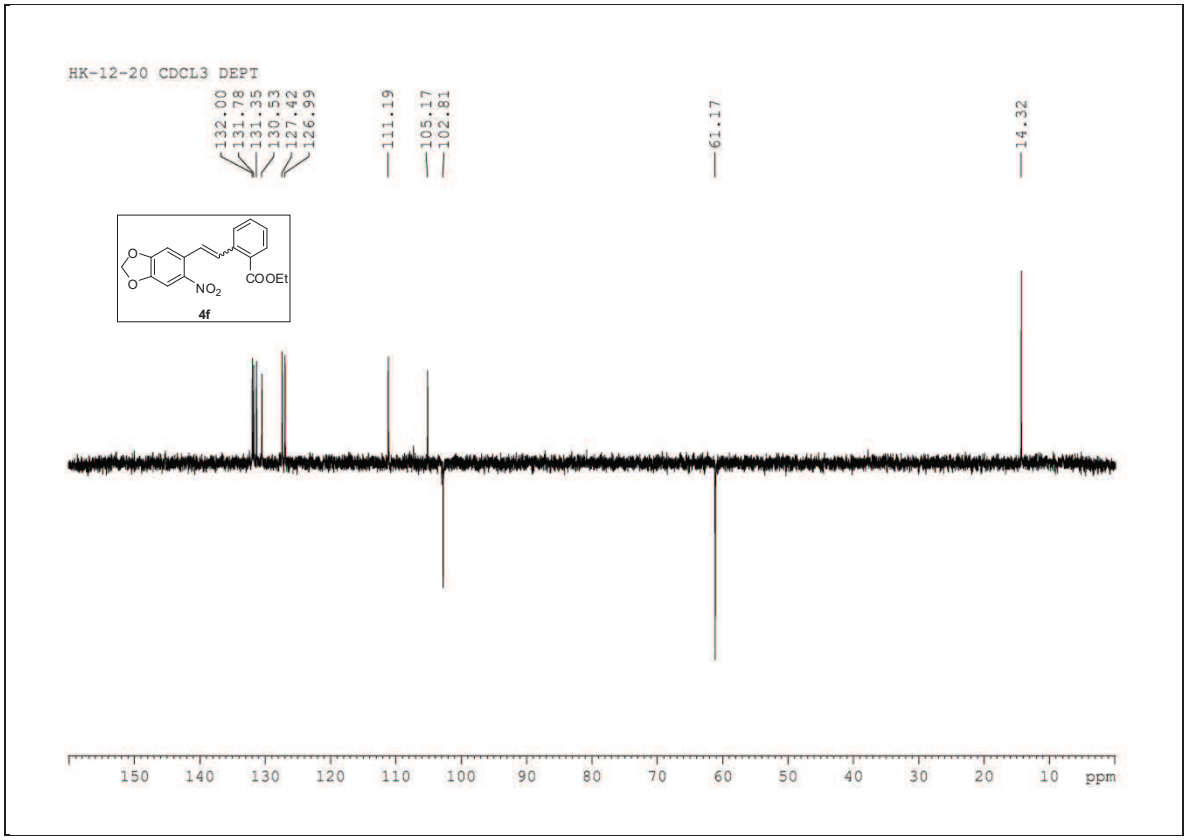

HK-13-06 CDCL3 PMR
7.880
7.859
7.839
7.675
7.656
7.477
7.458
7.439
7.296
7.277
7.259
7.205
7.191
6.969
6.928
4.324
4.306
4.289
4.271
3.904
3.859
3.825
1.328
1.311
1.293
0.000
OMe
MeO
MeO
NO2
COOEt
4e
8.0
7.8
7.6
7.4
7.2
7.0
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
2.06
1.00
1.09
1.17
0.99
0.95
2.29
3.05
2.99
3.03
3.35

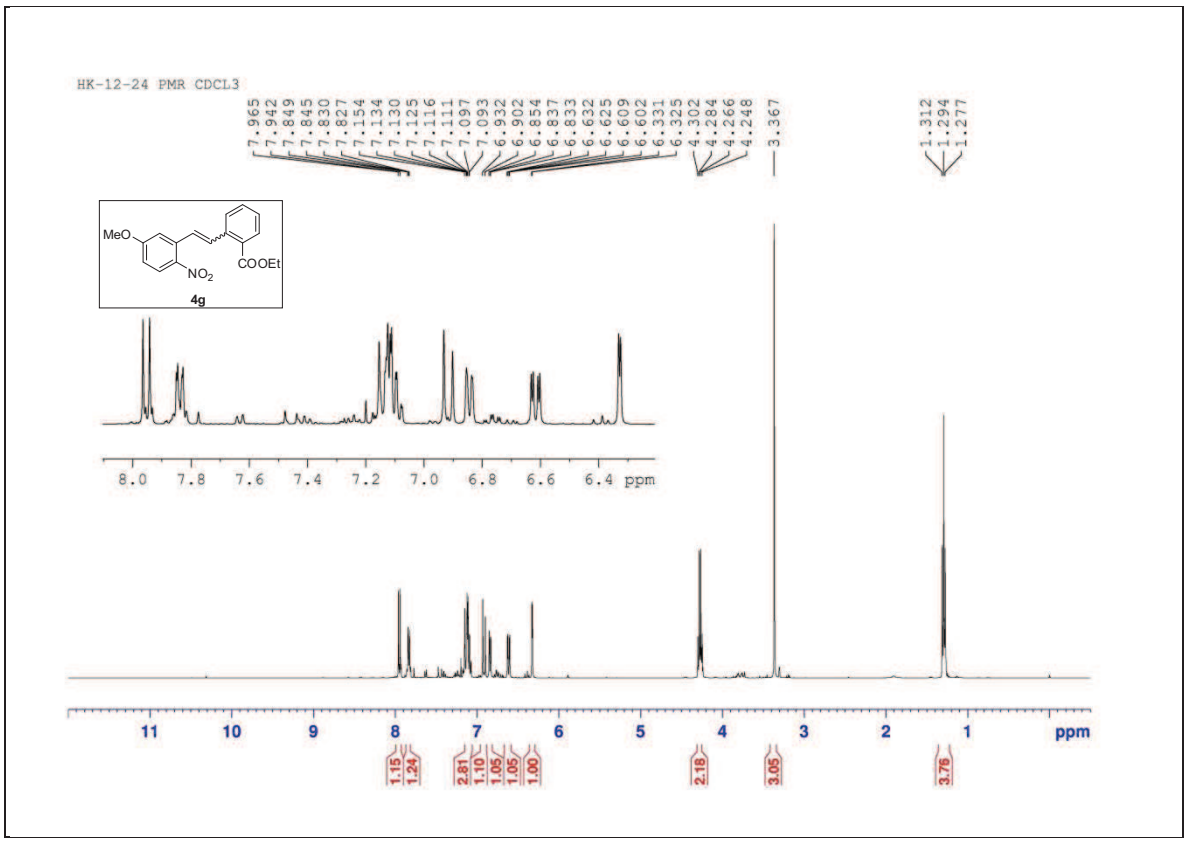

HK-13-06 CDCL3 CMR
167.23
152.46
151.99
146.85
144.51
139.11
133.81
132.15
130.43
129.24
127.60
127.38
121.50
121.21
104.08
77.37
77.05
76.73
61.22
61.16
61.05
56.36
14.31
OMe
MeO
MeO
NO2
COOEt
4e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

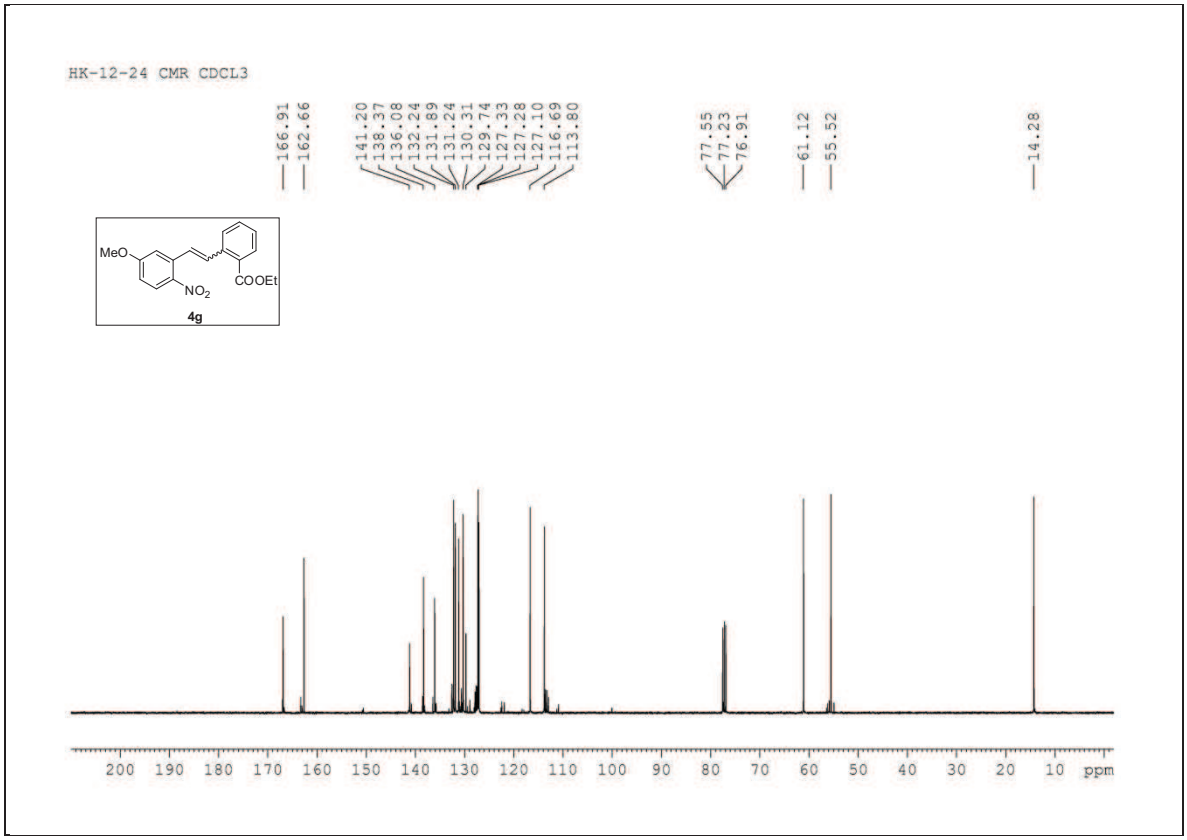

HK-13-06 CDCL3 DEPT
133.81
132.16
130.43
127.60
127.38
121.51
104.08
61.22
61.16
61.05
56.36
14.31
OMe
MeO
MeO
NO2
COOEt
4e
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

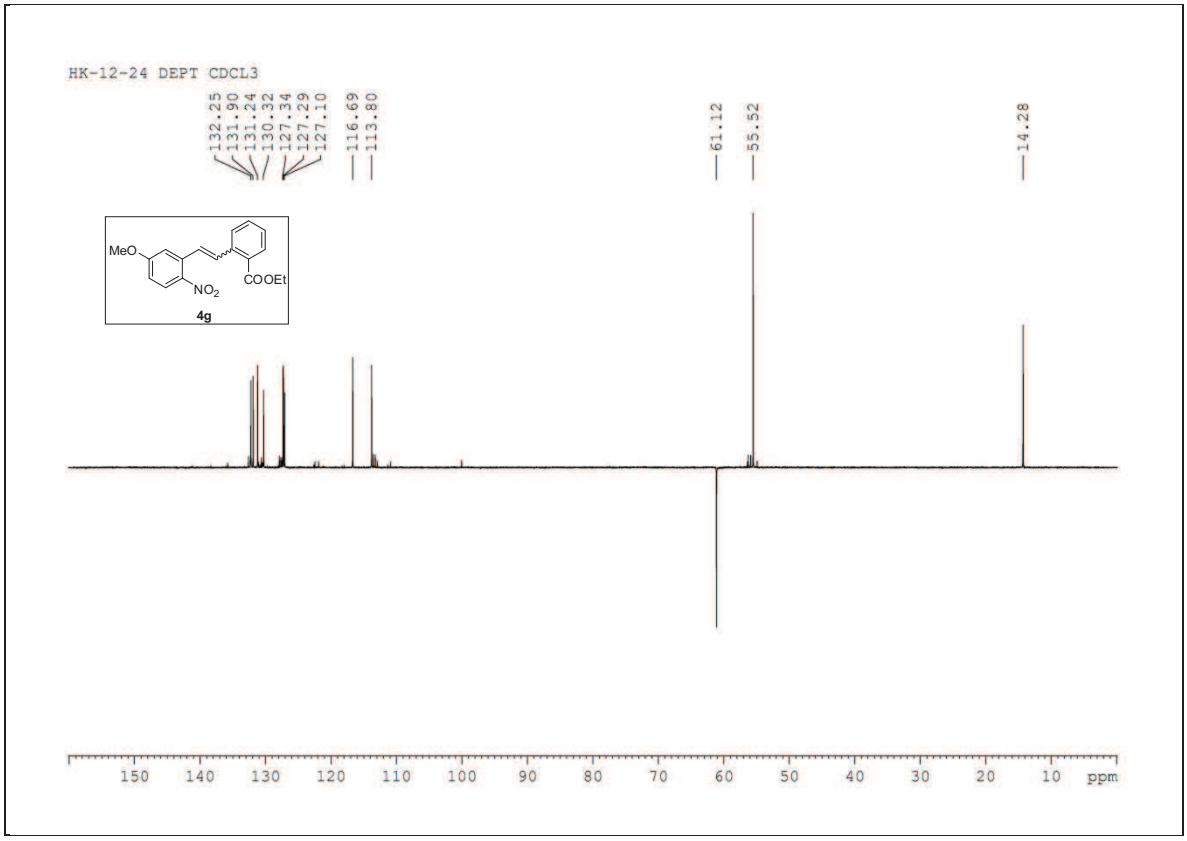

HK-12-20 CDCL3 PMR
7.918
7.912
7.898
7.515
7.196
7.168
7.136
7.107
6.918
6.903
6.878
6.849
6.317
5.927
4.354
4.337
4.319
4.301
1.540
1.370
1.353
1.335
0.000
COOEt
NO2
4f
8.0 7.8 7.6 7.4 7.2 7.0 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.14
1.03
2.72
1.06
2.09
1.00
2.14
2.34
3.48

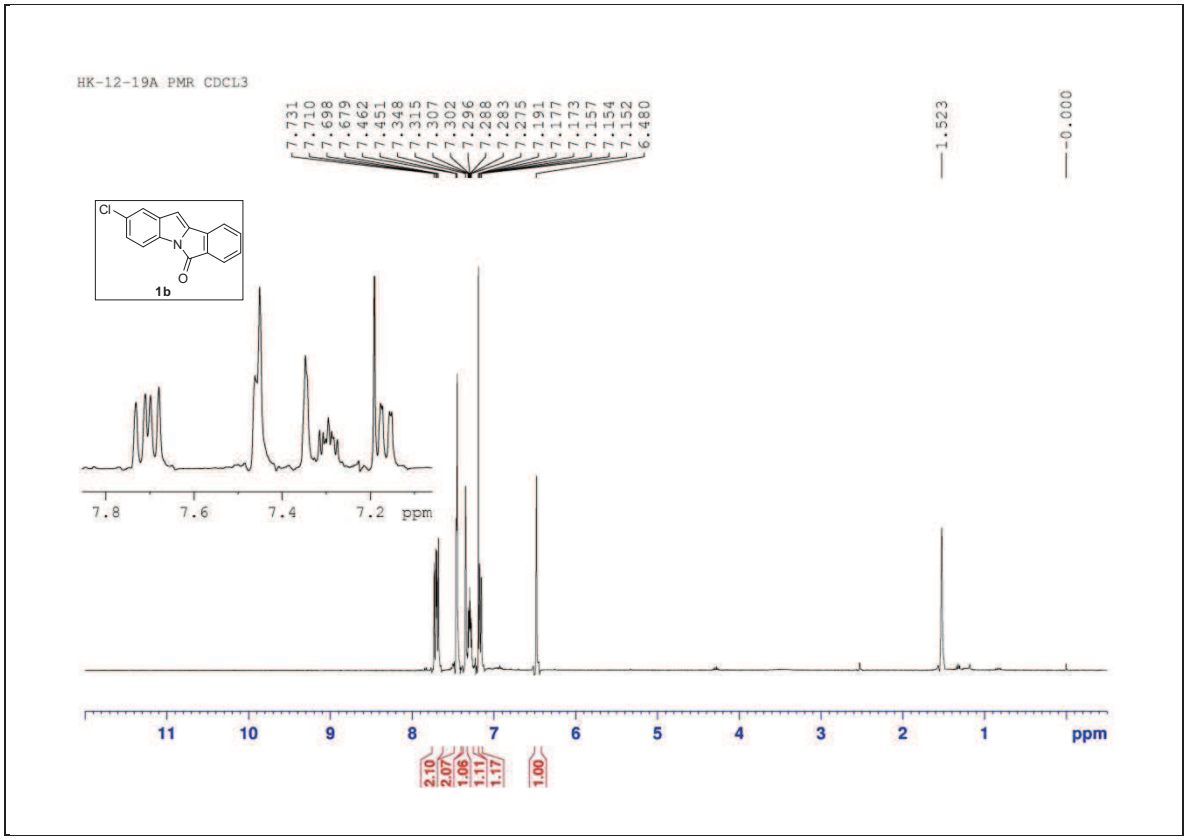

HK-12-20 CDCL3 CMR
166.97
151.47
147.05
142.26
138.29
131.99
131.78
131.35
130.68
130.53
129.62
127.42
126.98
111.19
105.16
102.80
77.38
77.06
76.74
61.16
14.31
COOEt
NO2
4f
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

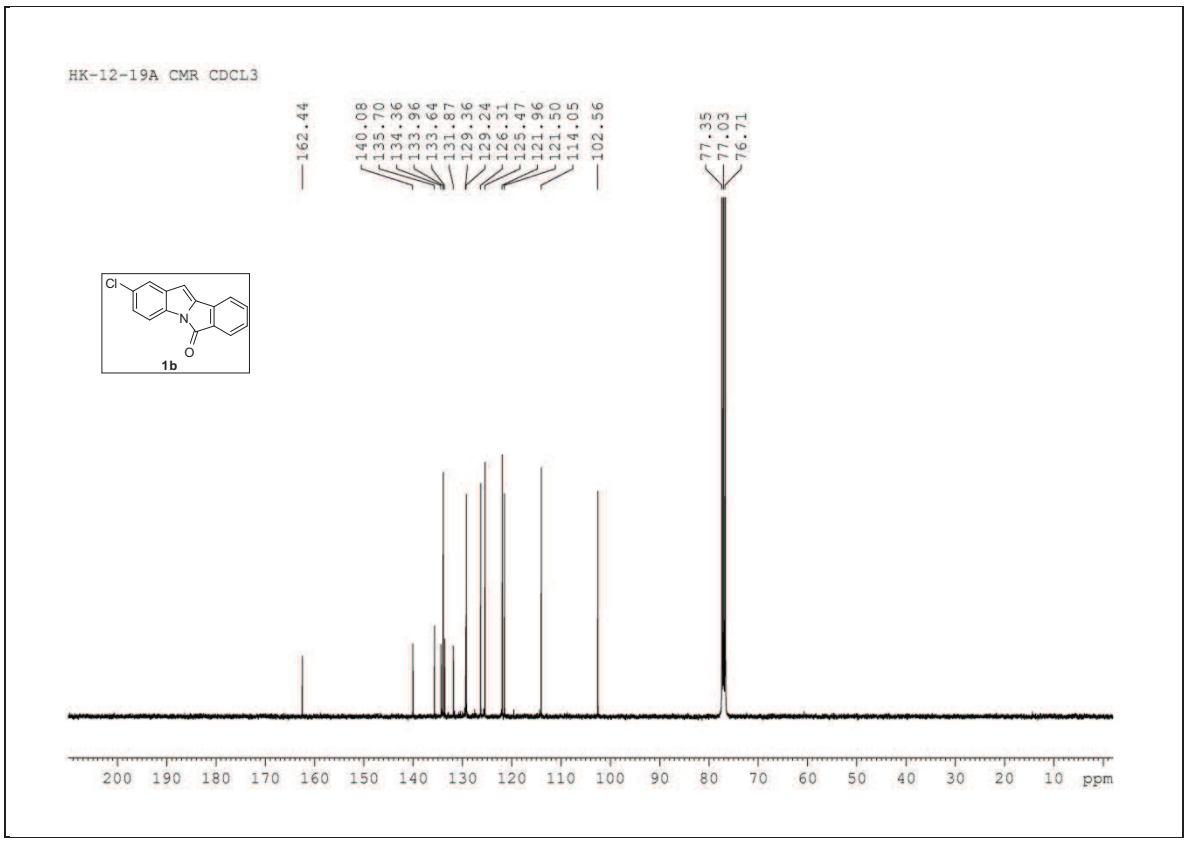

HK-12-20 CDCL3 DEPT
132.00
131.78
131.35
130.53
127.42
126.99
111.19
105.17
102.81
61.17
14.32
O
O
NO2
COOEt
4f
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

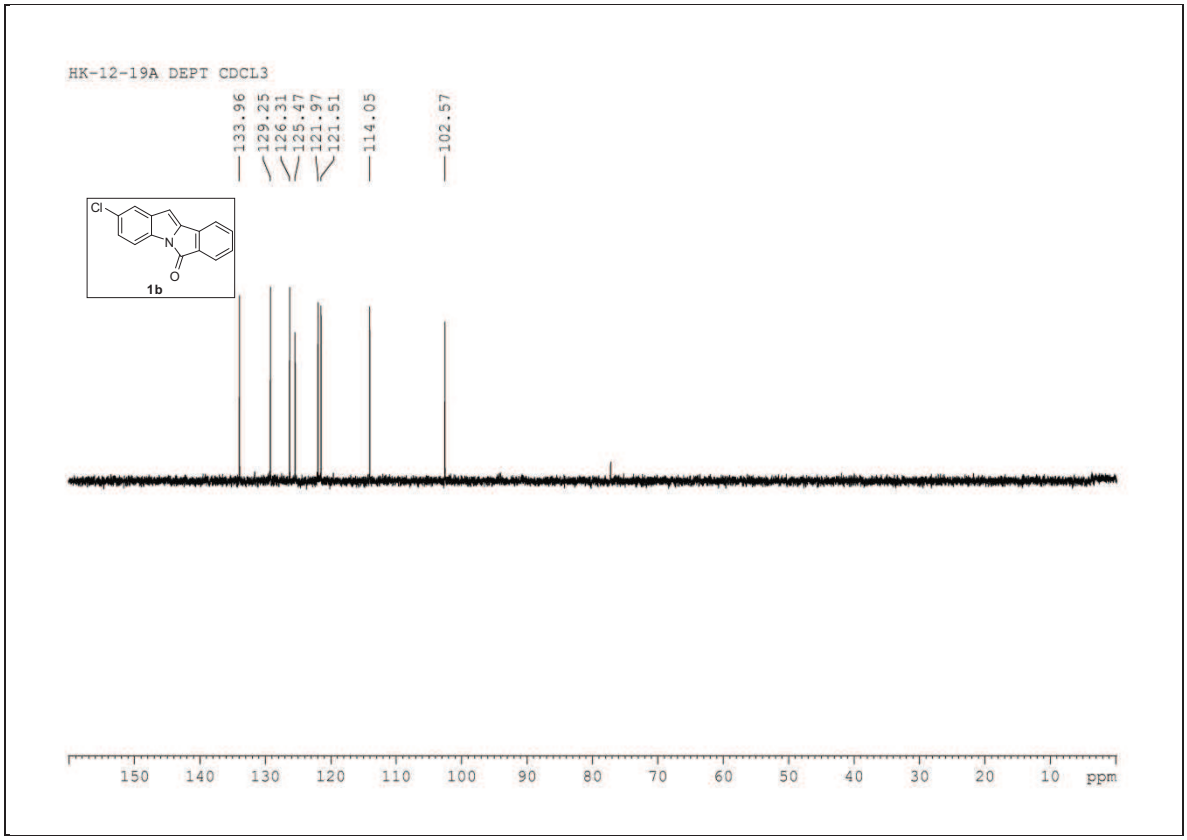

HK-12-24 PMR CDCL3
7.965
7.942
7.849
7.845
7.830
7.827
7.154
7.134
7.130
7.125
7.116
7.111
7.097
7.093
6.932
6.902
6.854
6.837
6.833
6.632
6.625
6.609
6.602
6.331
6.325
4.302
4.284
4.266
4.248
3.367
1.312
1.294
1.277
MeO
NO2
COOEt
4g
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.15
1.24
2.81
1.10
1.05
1.05
1.00
2.18
3.05
3.76

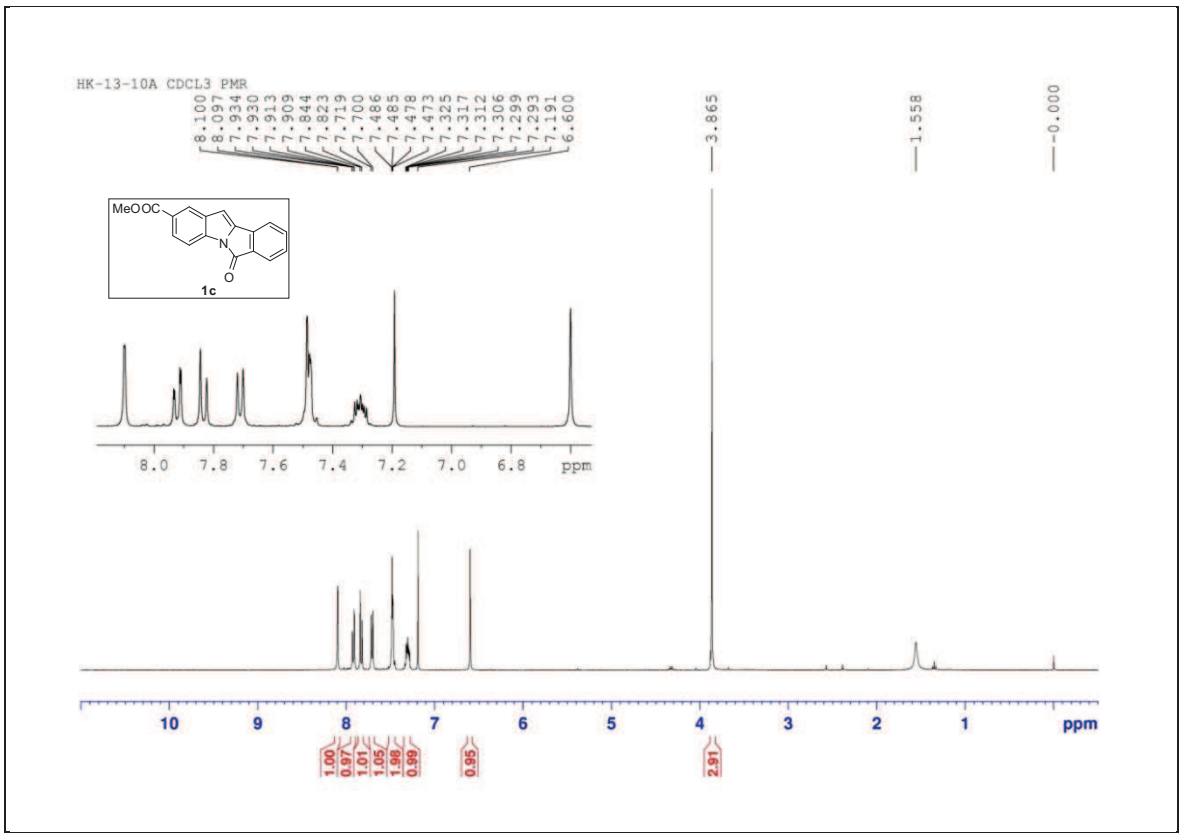

HK-12-24 CMR CDCL3
166.91
162.66
141.20
138.37
136.08
132.24
131.89
131.24
130.31
129.74
127.33
127.28
127.10
116.69
113.80
77.55
77.23
76.91
61.12
55.52
14.28
MeO
NO2
COOEt
4g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

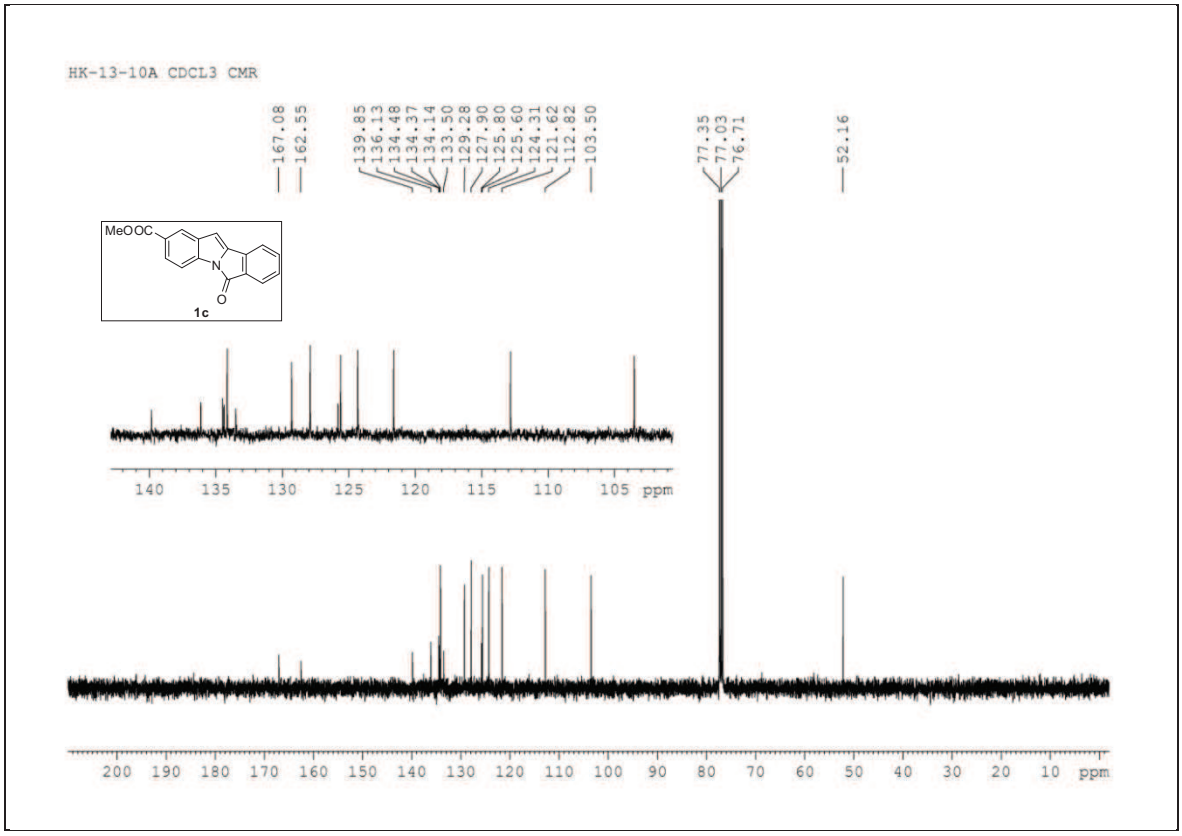

HK-12-24 DEPT CDCL3
132.25
131.90
131.24
130.32
127.34
127.29
127.10
116.69
113.80
61.12
55.52
14.28
MeO
NO2
COOEt
4g
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

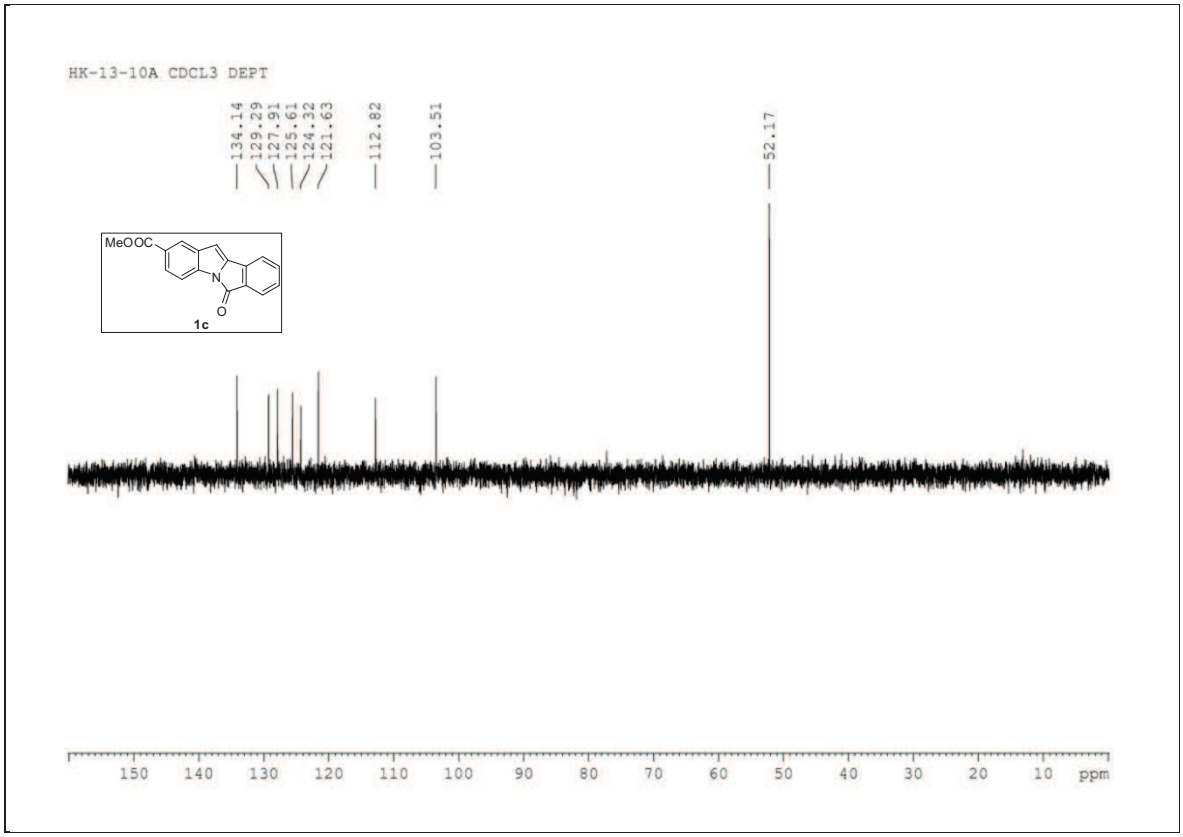

HK-12-19A PMR CDCL3
7.731
7.710
7.698
7.679
7.462
7.451
7.348
7.315
7.307
7.302
7.296
7.288
7.283
7.275
7.191
7.177
7.173
7.157
7.154
7.152
6.480
1.523
0.000
Cl
N
O
1b
7.8
7.6
7.4
7.2
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
2.10
2.07
1.06
1.11
1.17
1.00

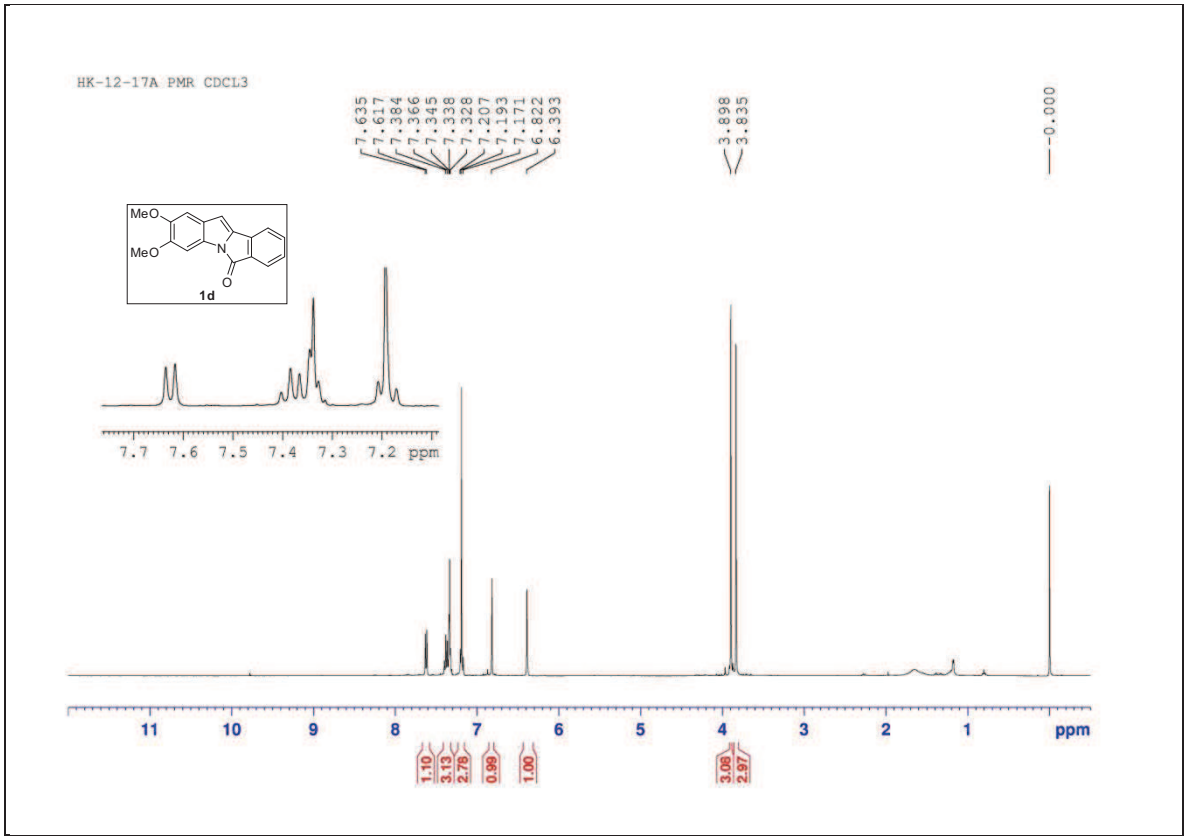

HK-12-19A CMR CDCL3
162.44
140.08
135.70
134.36
133.96
133.64
131.87
129.36
129.24
126.31
125.47
121.96
121.50
114.05
102.56
77.35
77.03
76.71
Cl
N
O
1b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

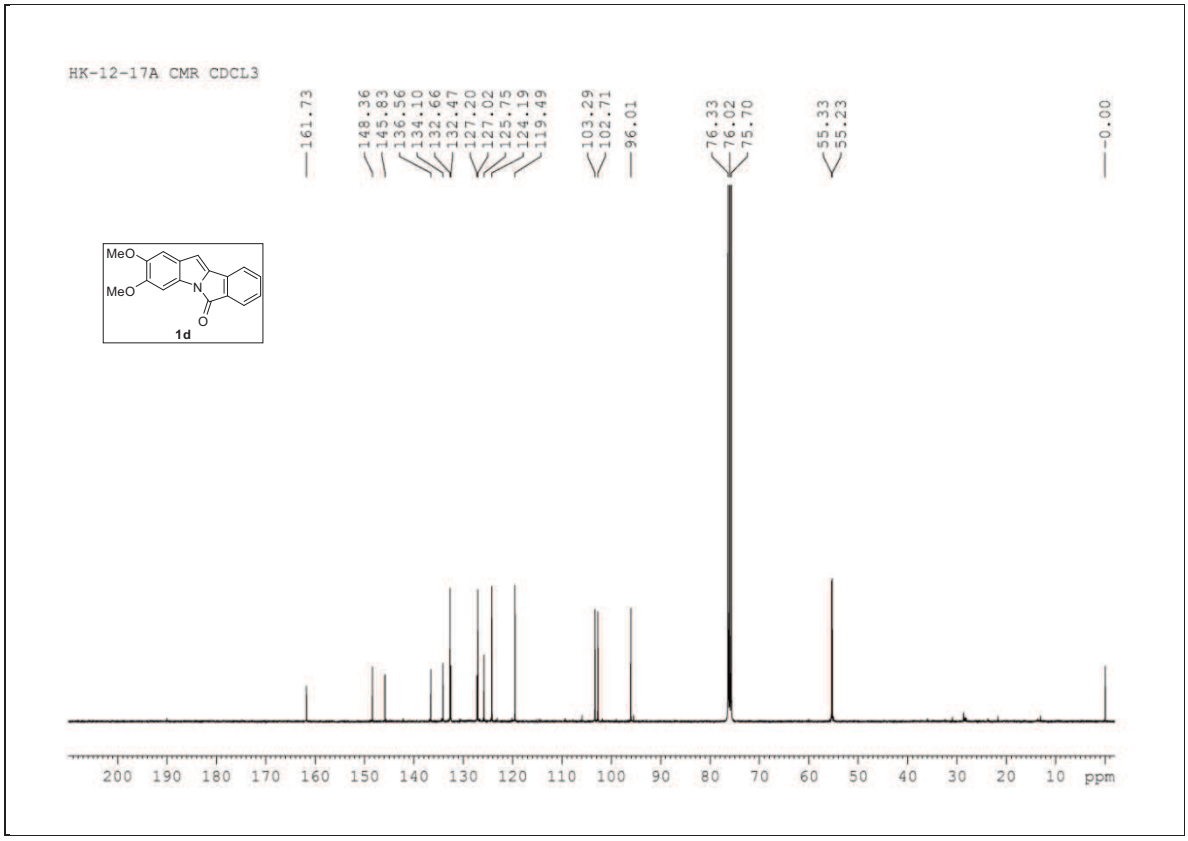

HK-12-19A DEPT CDCL3
133.96
129.25
126.31
125.47
121.97
121.51
114.05
102.57
Cl
N
O
1b
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

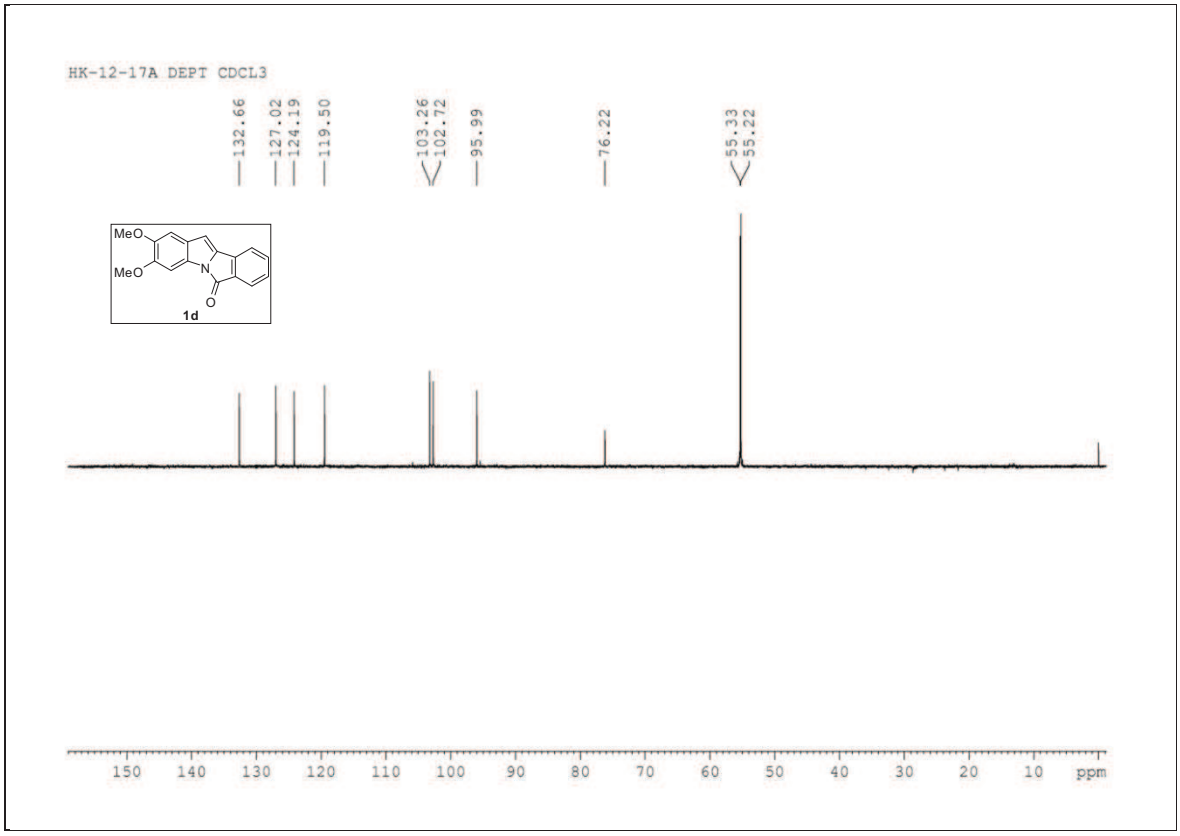

HK-13-10A CDCL3 PMR
8.100
8.097
7.934
7.930
7.913
7.909
7.844
7.823
7.719
7.700
7.486
7.485
7.478
7.473
7.325
7.317
7.312
7.306
7.299
7.293
7.191
6.600
3.865
1.558
0.000
MeOOC
N
O
1c
8.0 7.8 7.6 7.4 7.2 7.0 6.8 ppm
10 9 8 7 6 5 4 3 2 1 ppm
1.00
0.97
1.01
1.05
1.98
0.99
0.95
2.91

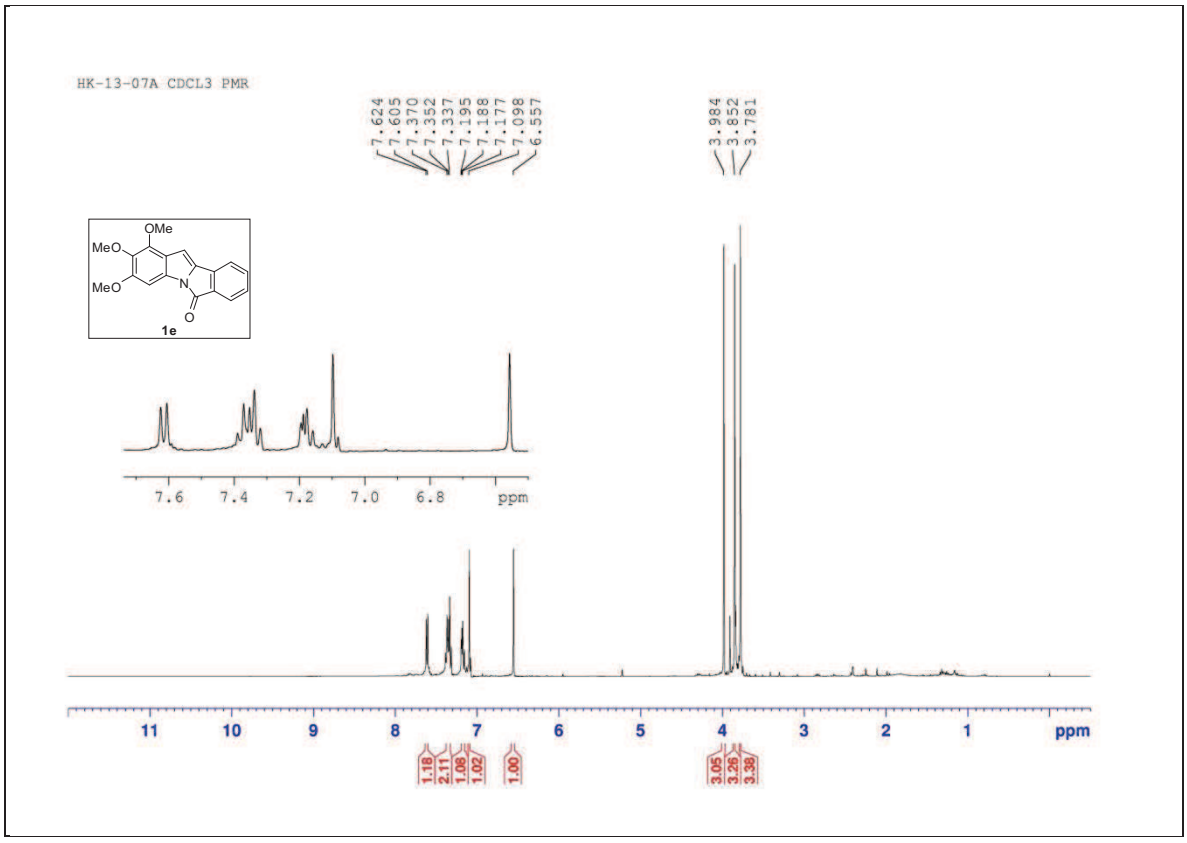

HK-13-10A CDCL3 CMR
167.08
162.55
139.85
136.13
134.48
134.37
134.14
133.50
129.28
127.90
125.80
125.60
124.31
121.62
112.82
103.50
77.35
77.03
76.71
52.16
MeOOC
N
O
1c
140 135 130 125 120 115 110 105 ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HK-13-10A CDCL3 DEPT
134.14
129.29
127.91
125.61
124.32
121.63
112.82
103.51
52.17
MeOOC
N
O
1c
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HK-12-17A PMR CDCL3
7.635
7.617
7.384
7.366
7.345
7.338
7.328
7.207
7.193
7.171
6.822
6.393
3.898
3.835
0.000
MeO
MeO
O
1d
7.7 7.6 7.5 7.4 7.3 7.2 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.10
3.13
2.78
0.99
1.00
3.06
2.97


HK-12-17A CMR CDCL3
161.73
148.36
145.83
136.56
134.10
132.66
132.47
127.20
127.02
125.75
124.19
119.49
103.29
102.71
96.01
76.33
76.02
75.70
55.33
55.23
0.00
MeO
MeO
O
1d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HK-12-17A DEPT CDCL3
132.66
127.02
124.19
119.50
103.26
102.72
95.99
76.22
55.33
55.22
MeO
MeO
N
O
1d
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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3.852
3.781
OMe
MeO
MeO
N
O
1e
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7.4
7.2
7.0
6.8
ppm
11
10
9
8
7
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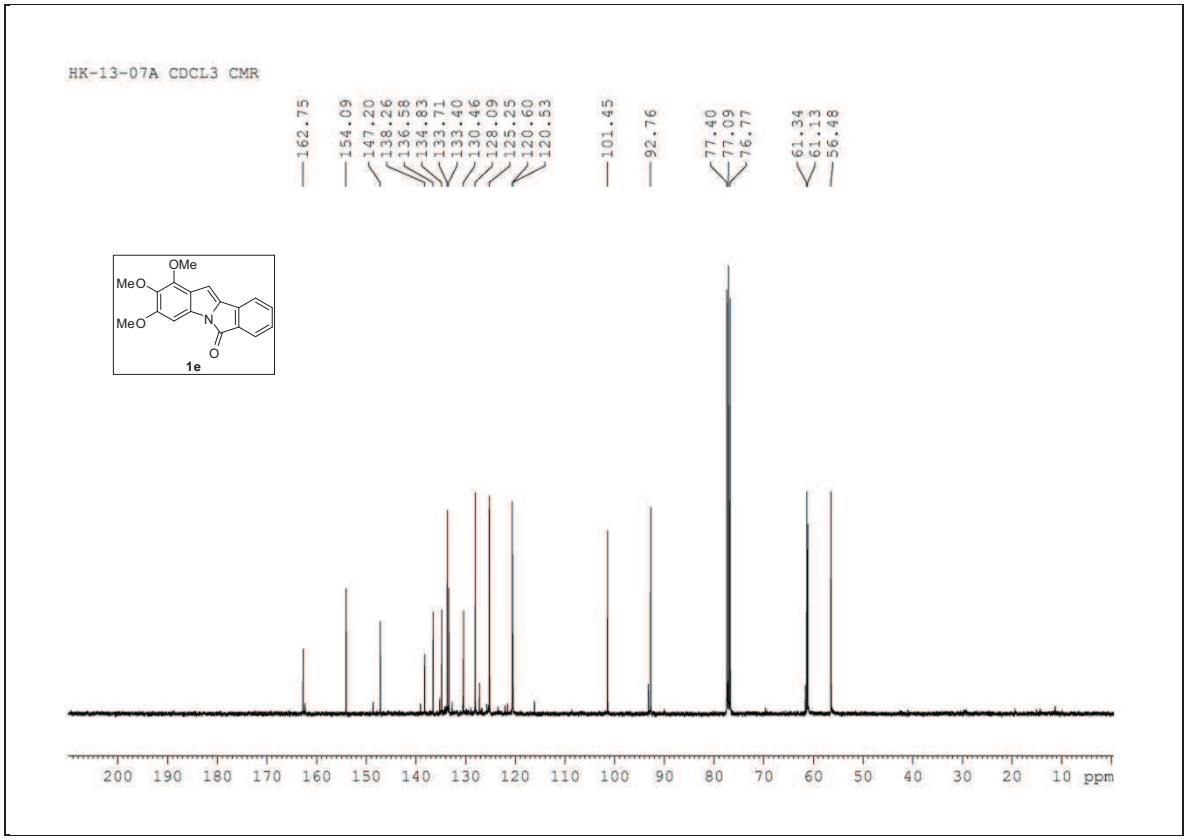
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120.53
101.45
92.76
77.40
77.09
76.77
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O
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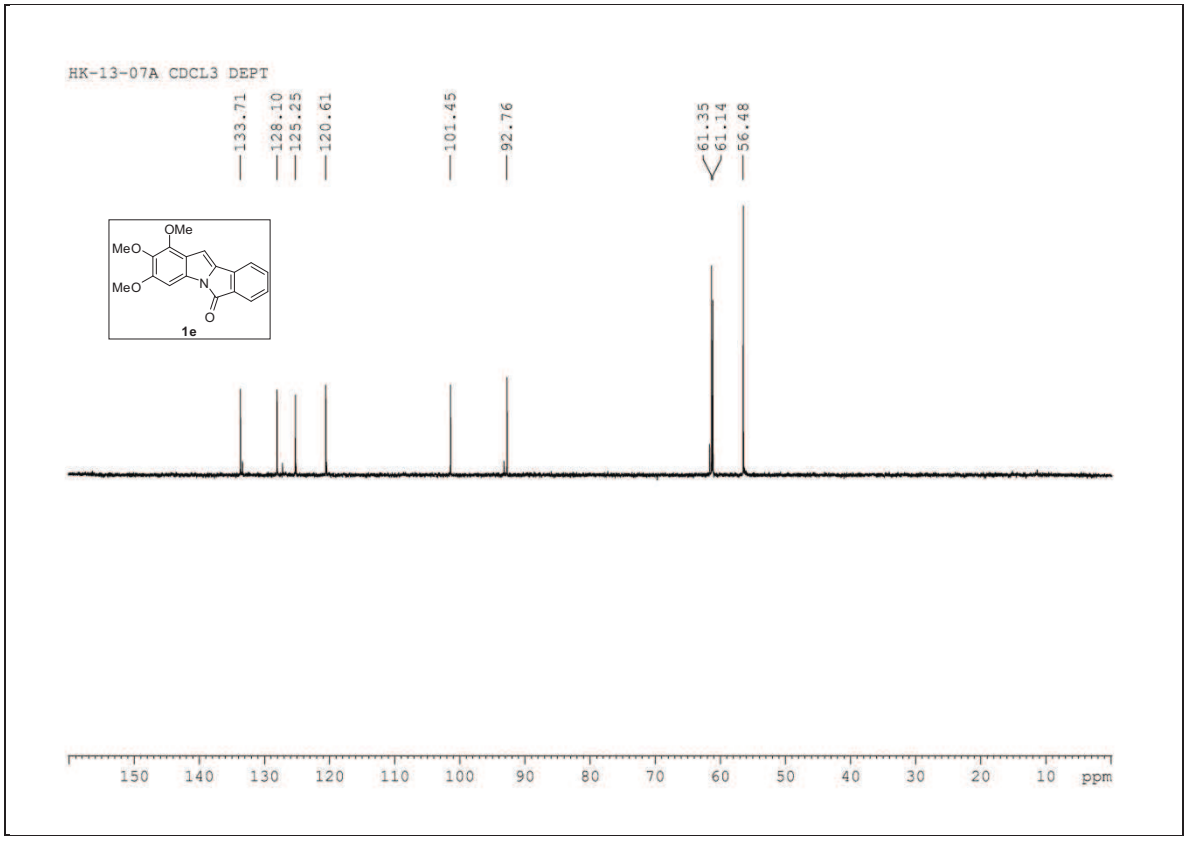
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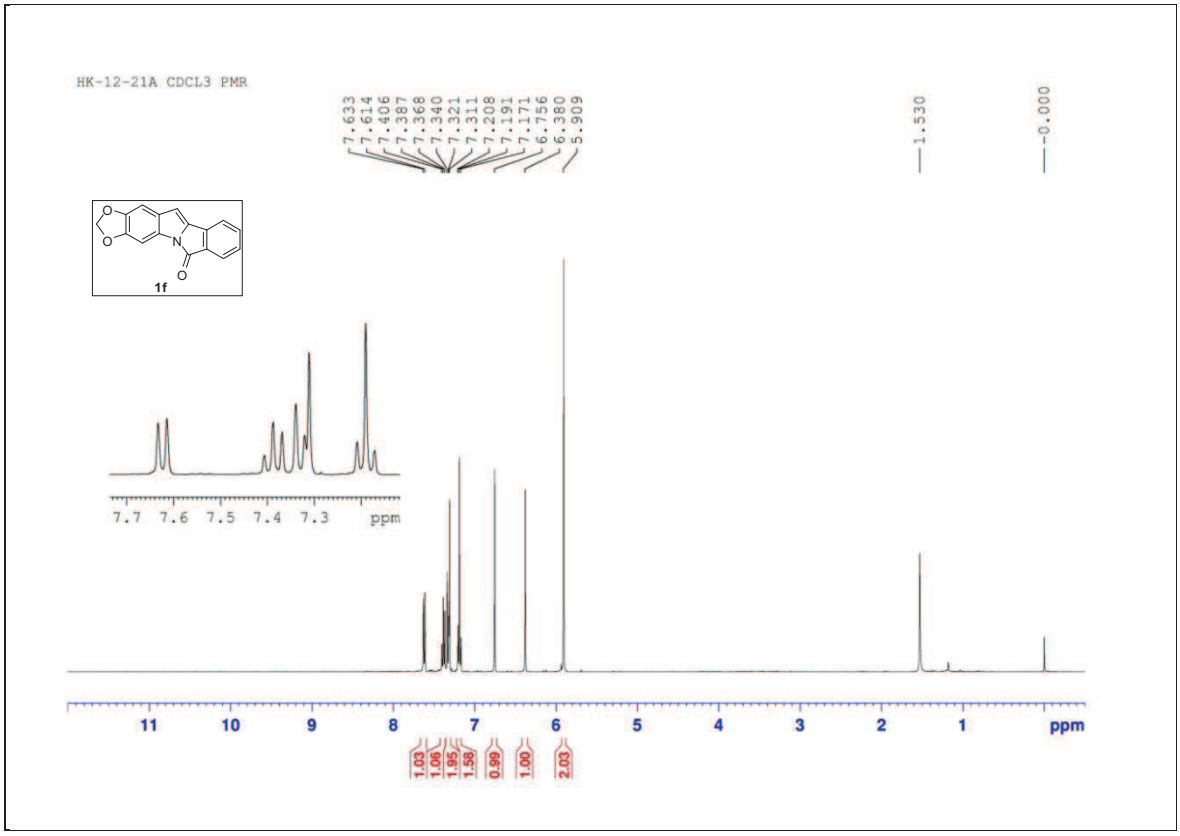
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7.191
7.171
6.756
6.380
5.909
1.530
0.000
1f
7.7 7.6 7.5 7.4 7.3 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
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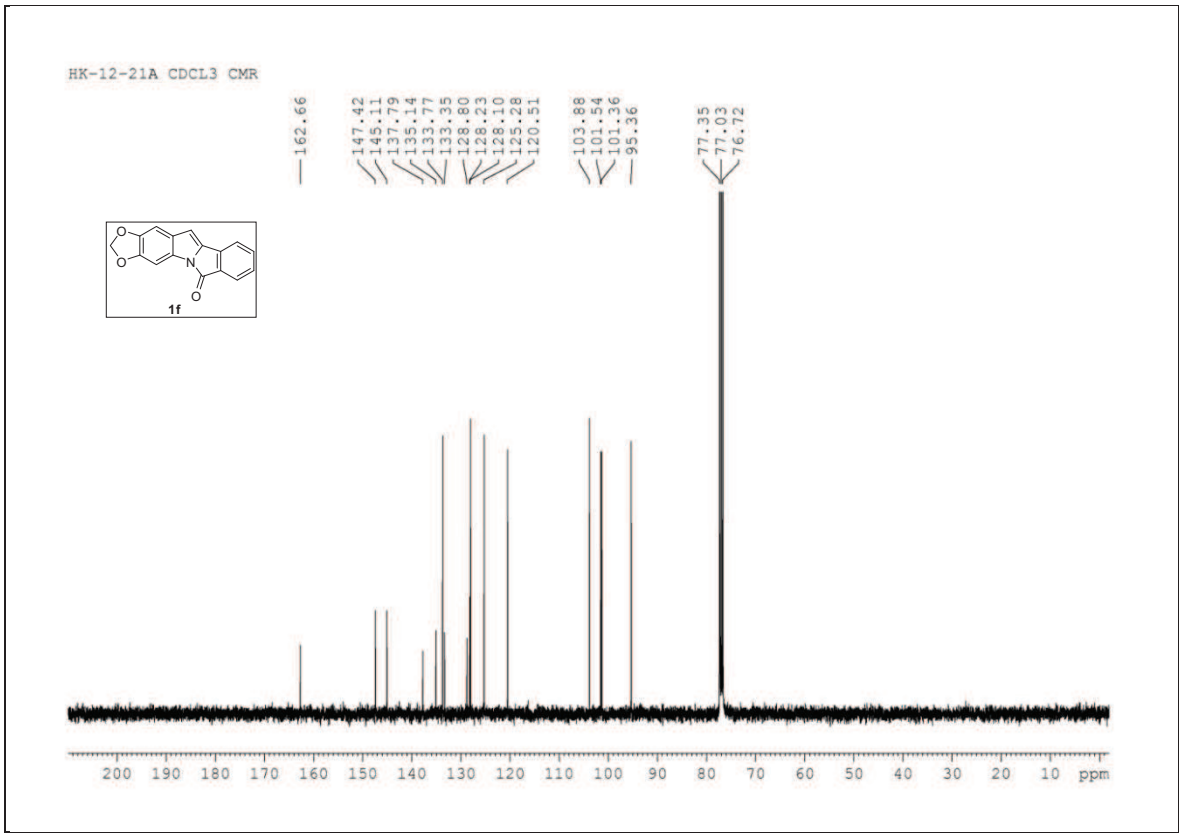
1.06
1.95
1.58
0.99
1.00
2.03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125.28
120.51
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101.36
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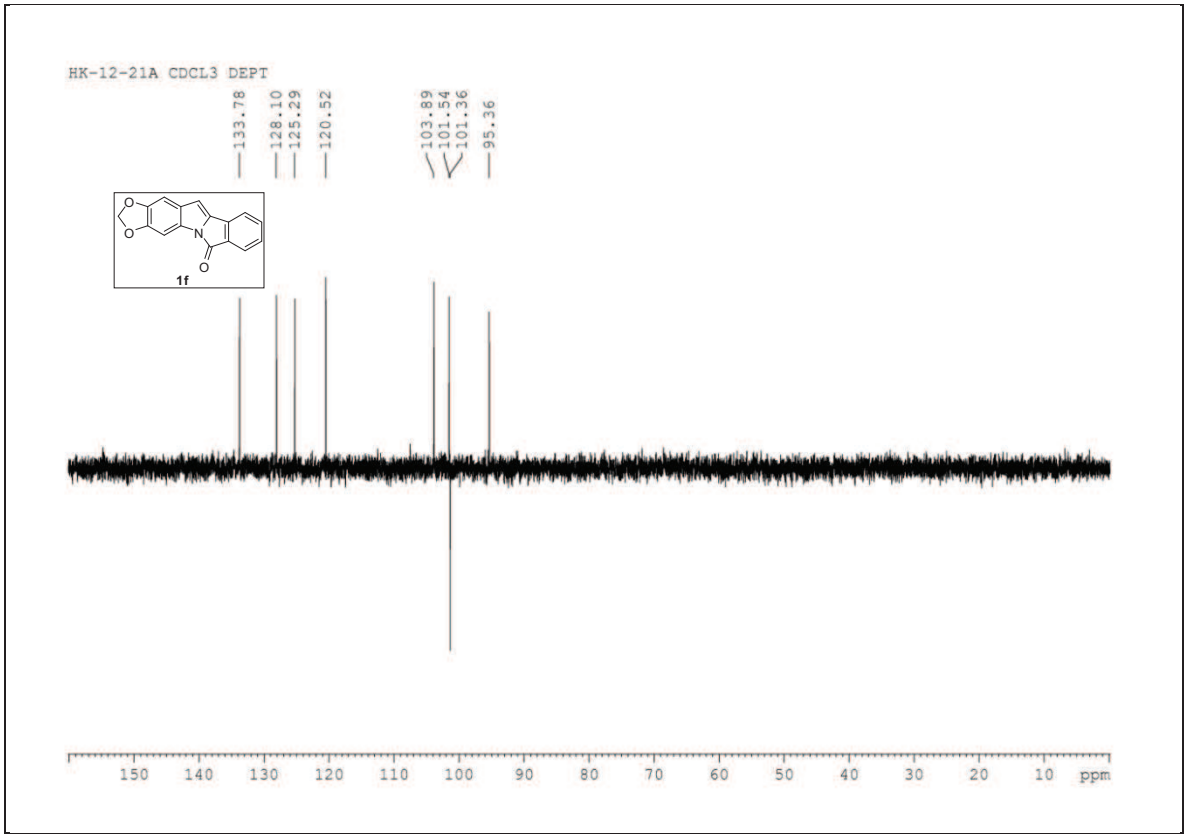
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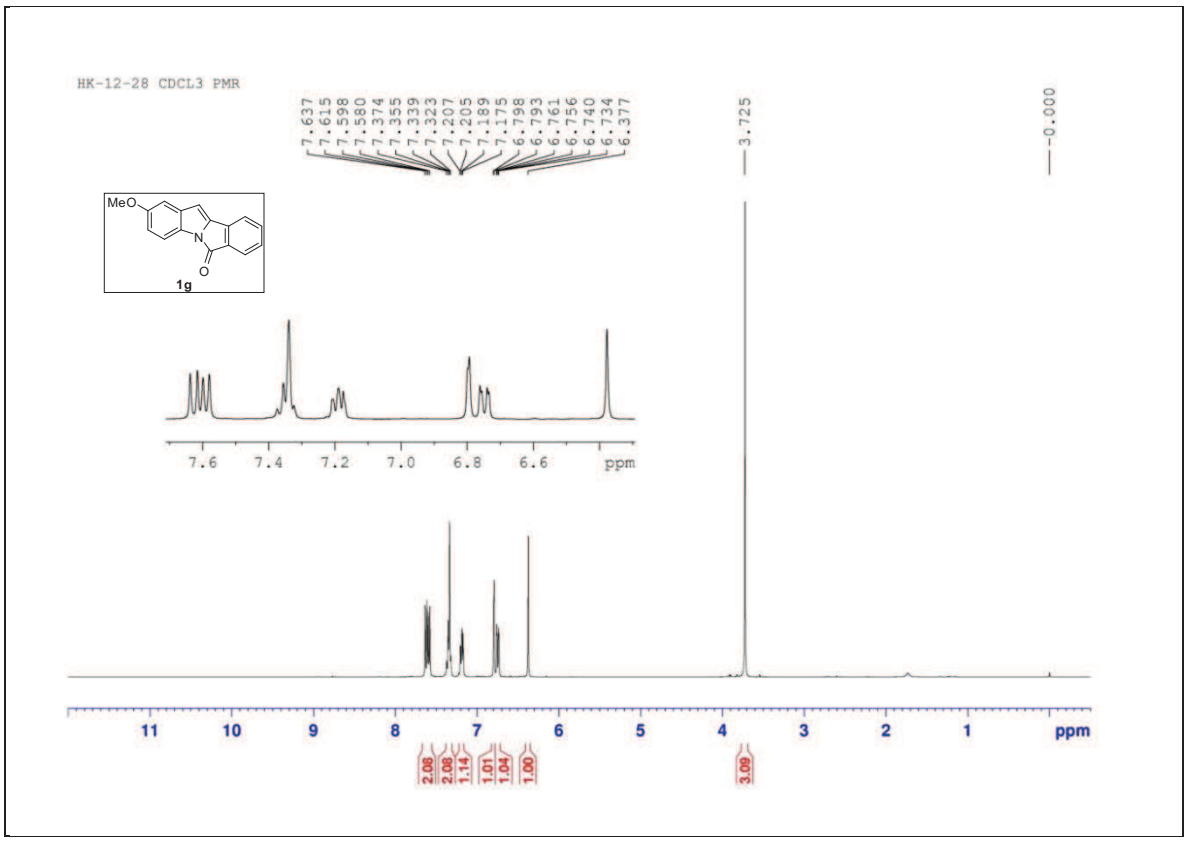
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7.175
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6.793
6.761
6.756
6.740
6.734
6.377
3.725
-0.000
MeO
1g
7.6 7.4 7.2 7.0 6.8 6.6 ppm
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2.08
2.08
1.14
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1.00
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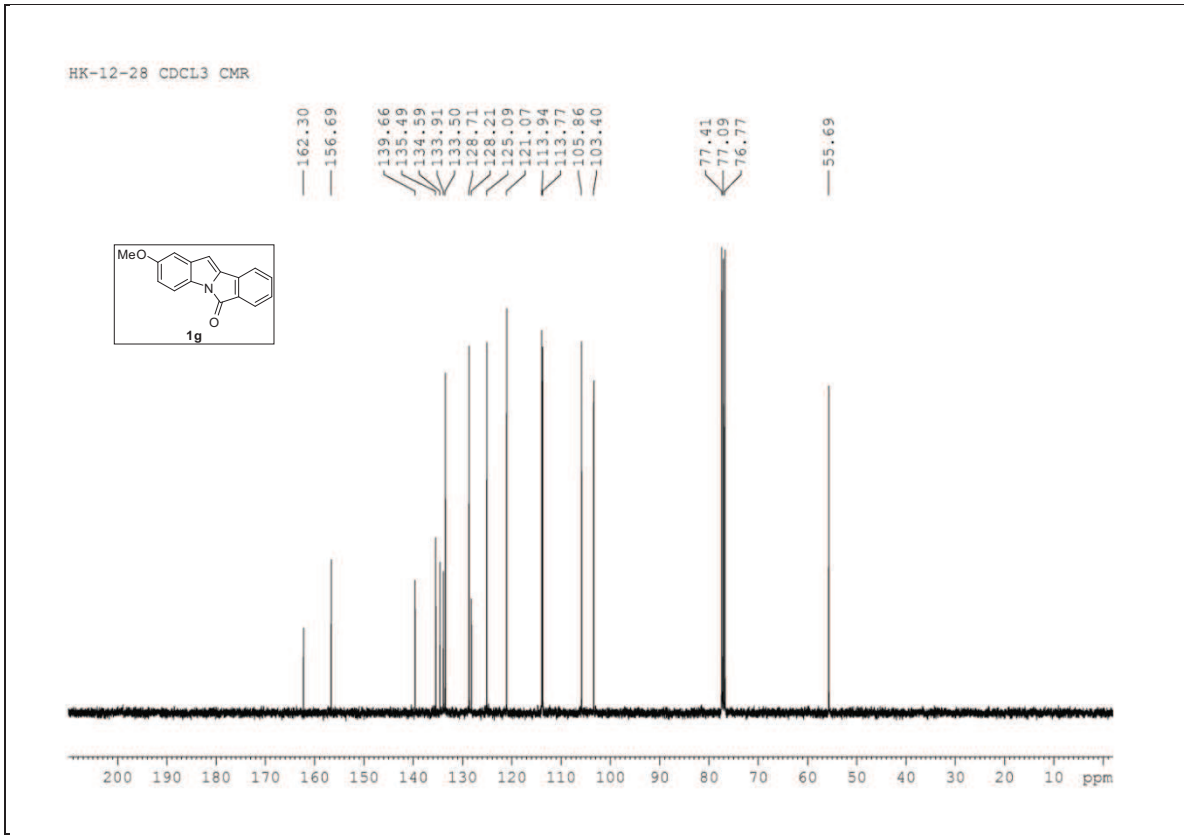
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128.21
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121.07
113.94
113.77
105.86
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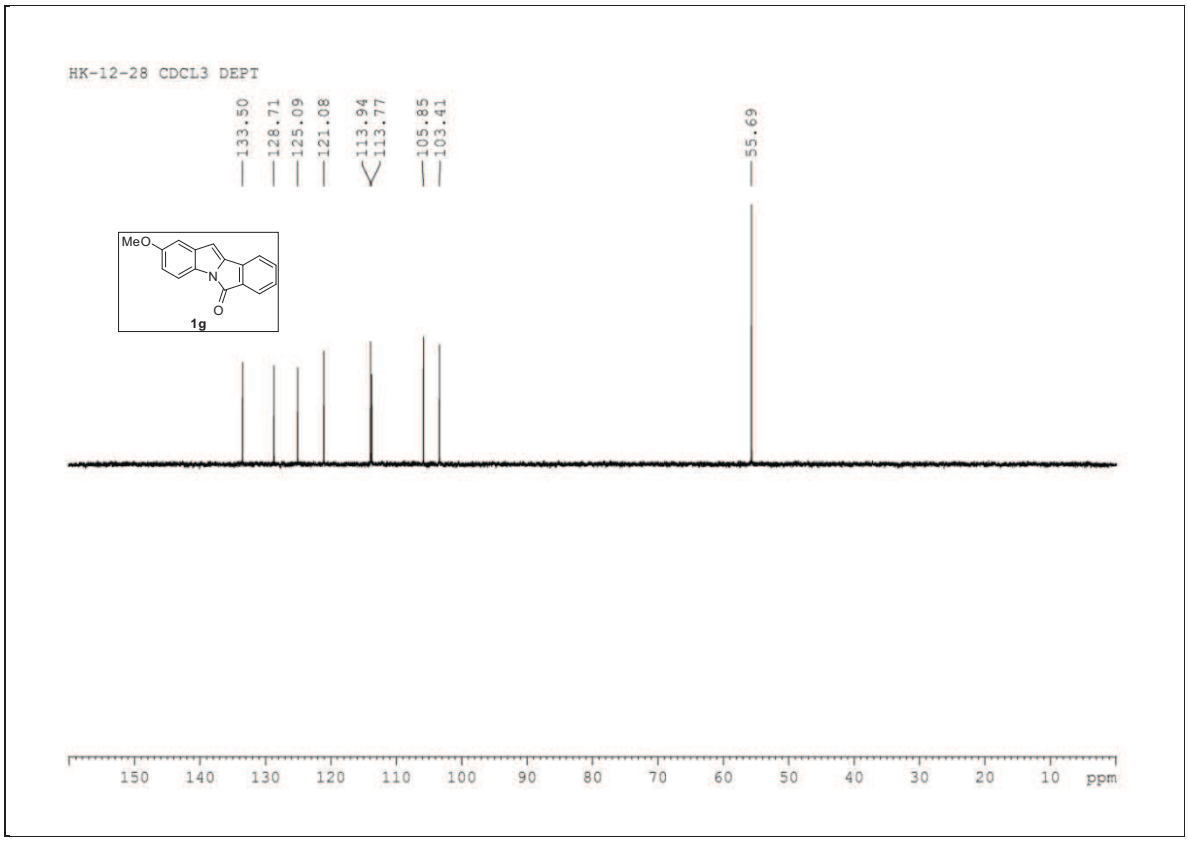
76.77
55.69
MeO
N
O
1g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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1g
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Chapter 3

Synthetic studies towards Lamellarin and Ningalin A scaffolds

Part A: Synthetic studies towards Lamellarin scaffolds

3.A.1: Introduction

Lamellarins are a group of marine natural product with polyaromatic pyrrole-*2*-carboxylate moiety as a common skeleton.[1] Many of these contain the same pentacyclic isoquinolinopyrrole-*2*-lactone core only differing with substituents present on each ring. Accordingly these are classified into two categories possessing either dihydroisoquinoline or isoquinoline subunit (Figure 1, Table 1).

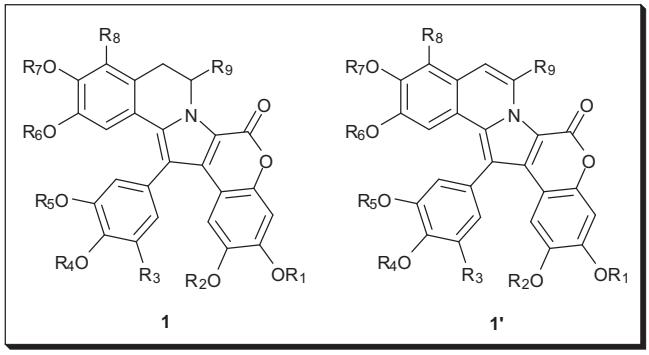


Figure 1: Lamellarin Family

Table 1: substituents on the lamellarin core.

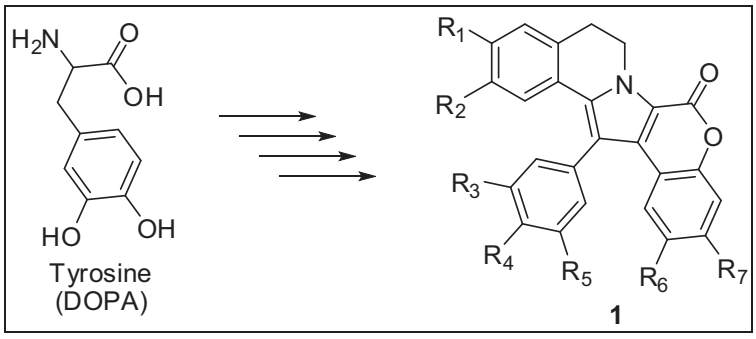
1	**1'**	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
Lamellarin A	-	H	Me	H	H	Me	Me	Me	OMe	OH
Lamellarin C	Lamellarin B	H	Me	H	H	Me	Me	Me	OMe	H
Lamellarin χ	Lamellarin D	H	Me	H	H	Me	Me	H	H	H
Lamellarin E	Lamellarin X	H	Me	H	Me	H	Me	Me	OH	H
Lamellarin F	Lamellarin ϵ	H	Me	H	Me	Me	Me	Me	OH	H
Lamellarin G	-	Me	H	H	Me	H	Me	H	H	H
-	Lamellarin H	H	H	H	H	H	H	H	H	H
Lamellarin I	Lamellarin ζ	H	Me	H	Me	Me	Me	Me	OMe	H
Lamellarin J	-	H	Me	H	Me	Me	Me	H	H	H
Lamellarin K	Lamellarin M	H	Me	H	H	Me	Me	Me	OH	H
Lamellarin L	Lamellarin N	H	Me	H	Me	H	Me	H	H	H
Lamellarin S	-	H	H	H	H	H	Me	H	H	H
Lamellarin T	Lamellarin W	H	Me	H	Me	H	Me	Me	OMe	H
Lamellarin U	Lamellarin α	H	Me	H	Me	H	Me	Me	H	H
Lamellarin V	-	H	Me	H	Me	H	Me	Me	OMe	OH
Lamellarin Y	-	H	Me	H	Me	H	H	Me	H	H
Lamellarin Z	-	Me	H	H	H	H	Me	H	H	H
Lamellarin β	-	H	H	H	Me	H	H	H	H	H
Lamellarin γ	-	H	Me	OMe	-	Me	Me	Me	OH	H
-	Lamellarin ϕ	H	Me	H	H	Me	H	Me	OMe	H
-	Lamellarin η	H	Me	H	Me	Me	Me	Me	H	H

Early 1980's period has seen an extensive research with regard to the isolations of marine natural products.[2] Most of the lamellarins were isolated during this period and till date more than 70

different lamellarins and related naturally occurring pyrrole-derived alkaloids have been reported particularly from marine sources with few instances of terrestrial sources.[3] Lamellarins were named accordingly following the order of their isolations.

Four Lamellarins alkaloids were first isolated by Faulkner and co-workers[3a] in 1985 from the Palauan marine prosobranch mollusc *lamellaria sp*. and hence named lamellarin A-D. Later in 1988,[3b] four more members lamellarin E-H were isolated from the didemnid ascidian *Didemnum chartaceum* collected from Seychelles. Lamellarin I-M and triacetate of lamellarin N were isolated from a Great Barrier Reef colonial ascidian *Didemnum sp*.[3c] in 1993. Lamellarin O and P were isolated in 1994 from a southern Australian marine sponge *Dendrilla cactos* by Capon et. al.[3d] Subsequently in 1995 lamellarins Q and R were also isolated by same group from a geographically distinct re-collection of *D. cactos* harvested from the coast of New South Wales.[3e] Lamellarin S was isolated in 1996 from an Austrialian tunicate *Didemnum sp*.[3f] collected near Duras, New South Wales. Further in 1997 lamellarin T-X were isolated from an unidentified ascidian[3g] obtained from the Trivandrum coast of India along with sulphate of lamellarin Y. Lamellarin Z was isolated from a Great Barrier Reef ascidian *Didemnum chartaceum* Sluiter[3h] in 1999. Lamellarin β was obtained from a purple unidentified encrusting marine ascidian *Didemnum sp*.[3i] collected in the Indian Ocean in 2002. Lamellarins α, γ and ϵ were isolated from the Indian red colonial ascidian *Didemnum obscurum* collected from the Indian Tiruchandur coast[3j] in 2004. Same group in 2005 isolated lamellarins η, ϕ and χ from same source[3k] collected from same place but in different season simultaneously lamellarin ζ was isolated in 2005.[3l]

Although not much research has been carried out with regard to the biogenesis,[1] but since the lamellarins are structurally similar to tyrosine (DOPA), it is more probable to be the biogenetic precursor of lamellarins (Scheme 1).



Scheme 1

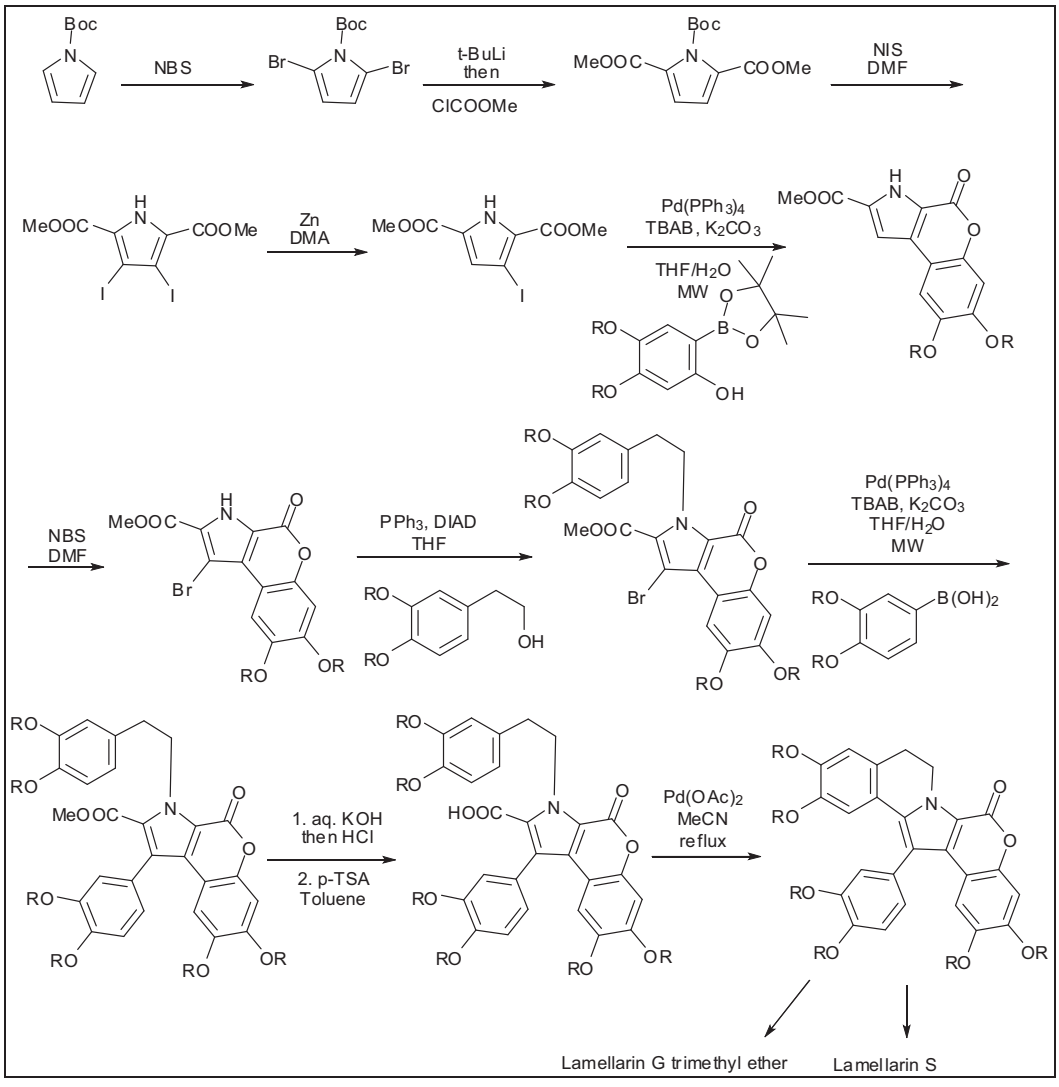
The lamellarins and related pyrrole-derived alkaloids have shown a diverse range of bioactivities[4] such as cytotoxicity and antitumor activity, reversal of multidrug resistance (MDR), HIV-1 integrase inhibition, antibiotic activity, human aldose reductase (h-ALR2) inhibition, cell division inhibition, immunomodulation, antioxidant activity, and feeding deterrence, making these

compounds a particularly important subject for research and have also provoked a great deal of interest in regard to their synthesis.

3.A.2: Literature review

Ample biological applications have made Lamellarin family, a subject of extensive research in chemistry. Various groups over the globe have accomplished syntheses of lamellarins using diverse chemistry.[5] Several reviews with regard to their isolations, syntheses and biological properties are available in the literature.[6] Some of the admirable synthetic approaches are discussed below.

Many syntheses are reported[7] by using cross-coupling reactions between aryl compounds and halogenated pyrroles. M.G. Banwell's group have developed a method for synthesis of Lamellarins G and S.[8] (Scheme 2) They started with the commercially available N-Boc pyrrole and treated it with 2 eq. NBS and the resultant dibromo pyrrole was reacted with 2 eq. t-BuLi and excess methyl chloroformate to give the pyrrole diester.

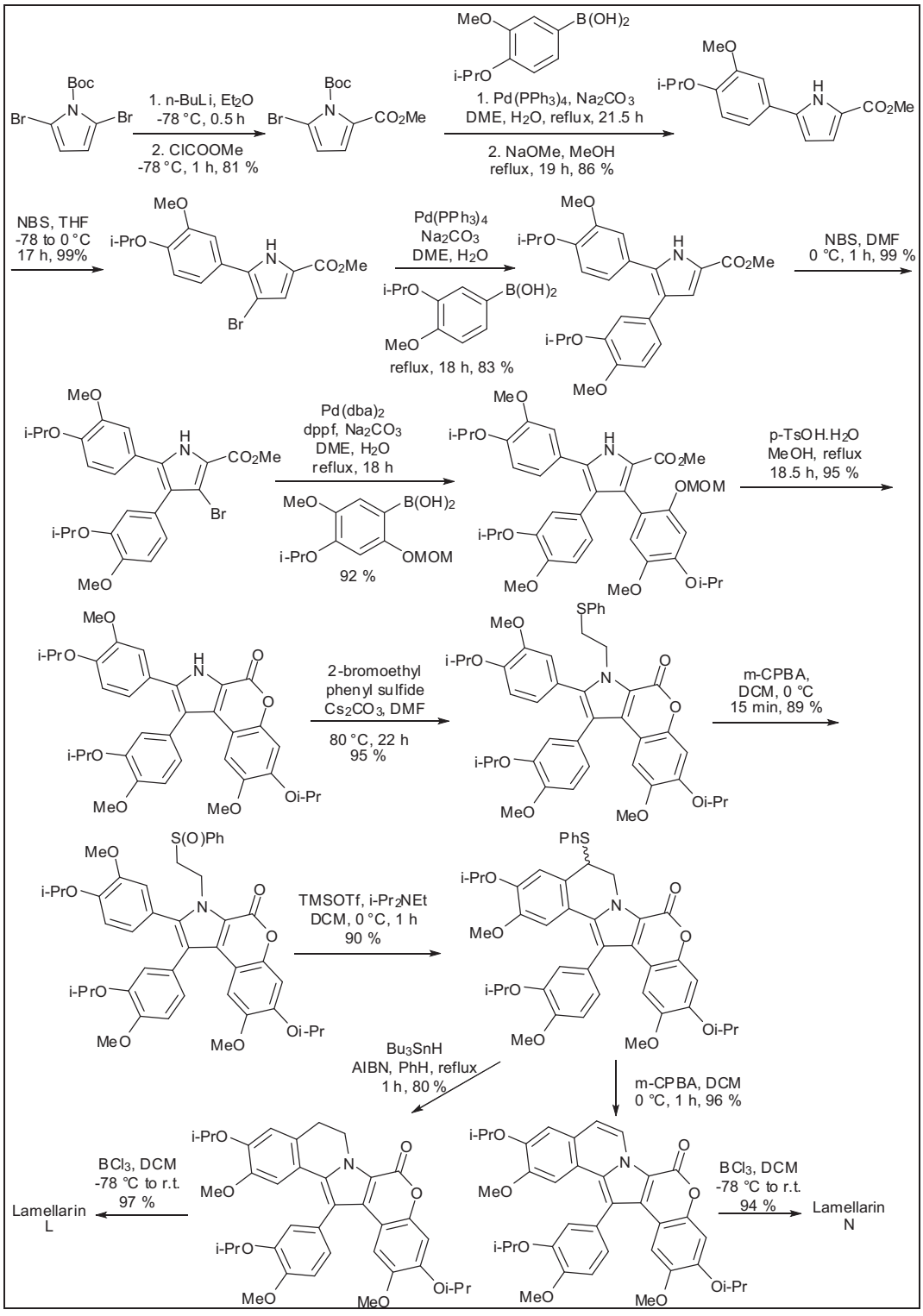


Scheme 2

This was deprotected by heating in DMF and diiodinated by using NIS to give symmetrical diiodo pyrrole diester. Mono-deiodination of this using 1eq. Zn in DMA gave mono-iodo pyrrole diester. Suzuki-Miyaura reaction of this iodo-pyrrole diester with phenolic boronate ester gave pyrrolo-coumarin. This was selectively mono-brominated on pyrrole ring using NBS and subsequently N-alkylated by Mitsunobu reaction with phenethyl alcohol. This bromide on again Suzuki-Miyaura reaction with aryl boronic acid gave the required arylated pyrrole. This pyrrolo-coumarin ester was subjected to saponification using KOH which led to hydrolysis of both ester as well as coumarin, thus treated with cat. pTsOH and molecular sieves in refluxing toluene to reassemble the coumarin ring. Further decarboxylative Heck reaction of this using $Pd(OAc)_2$ gave the Lamellarin derivatives.

M. Iwao's group have published many routes and exploited them to prepare various natural and non-natural lamellarin derivatives to study their biological properties.[9]

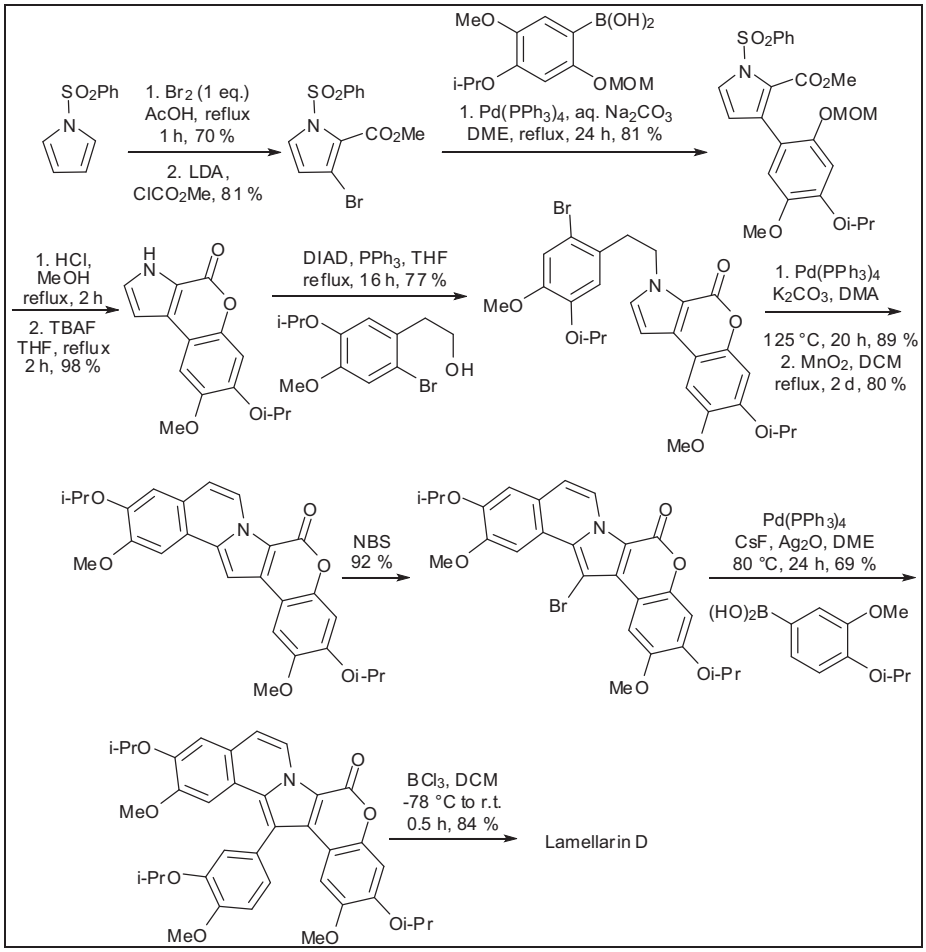
Regioselective arylation of pyrrole core through Suzuki-Miyaura cross-coupling reactions to give lamellarin structure is established by M. Iwao's group (Scheme 3).[10] They started with readily available dibromo-N-Boc-pyrrole and mono-carboxylated by Br-Li exchange followed by treatment with methyl chloroformate. This monobromo-pyrrole ester was subjected to Pd catalysed Suzuki-Miyaura cross-coupling reaction with aryl boronic acid followed by treatment with NaOMe to get the arylated and deprotected pyrrole ester. Subsequent reaction with NBS selectively gave the *4*-bromopyrrole ester due to meta-directing ester group. Another cross coupling reaction with substituted aryl boronic acid gave diarylated pyrrole ester. This pyrrole compound was again brominated using NBS and arylated with substituted *o*-OMOM aryl boronic acid to get the triarylated pyrrole ester. This was treated with *p*-TsOH in refluxing MeOH to get the pyrrolo-coumarin compound. This was alkylated with *2*-bromoethyl phenyl sulphide and oxidation with m-CPBA afforded the sulfoxide. Further Pummerer cyclisation with TMSOTf/Hunig's base condition gave the isoquinoline sulphide. This on radical desulfurization with Bu_3SnH/AIBN followed by deprotection gave the lamellarin N, whereas oxidation of sulphide followed by elimination of phenyl sulsulfinyl group and deprotection gave the lamellarin L.



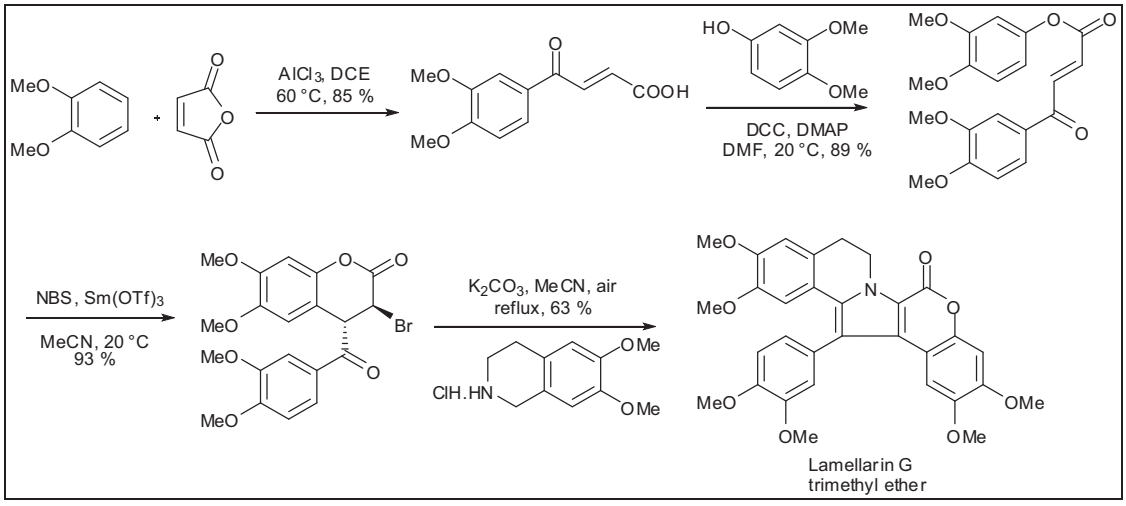
Scheme 3

Another report by M. Iwao's group (Scheme 4) is well recognised.[11] This approach started with N-phenylsulfonyl pyrrole. This on bromination followed by directed lithiation and reaction with methyl chloroformate gave *3*-bromo-N-phenylsulfonyl-pyrrole-*2*-ester. This on Suzuki-Miyaura coupling with aryl boronic acid gave arylted pyrrole ester. This was further cyclised and deprotected to pyrrolo-coumarin which on Mitsunobu reaction with bromo-substituted phenylethyl

alcohol followed by intramolecular Heck reaction MnO_2 oxidation gave isoquinolino-pyrrolo-coumarin. Bromination of this followed by another cross-coupling reaction and deprotection gave the Lamellarin D.



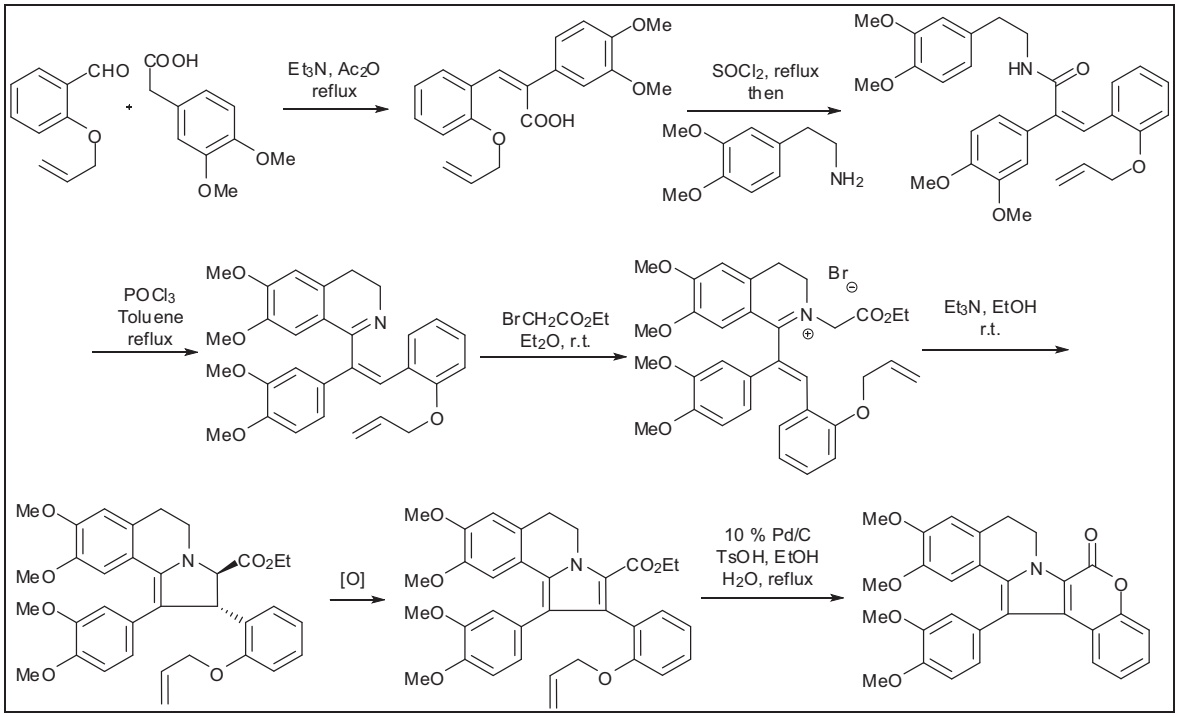
Scheme 4



Scheme 5

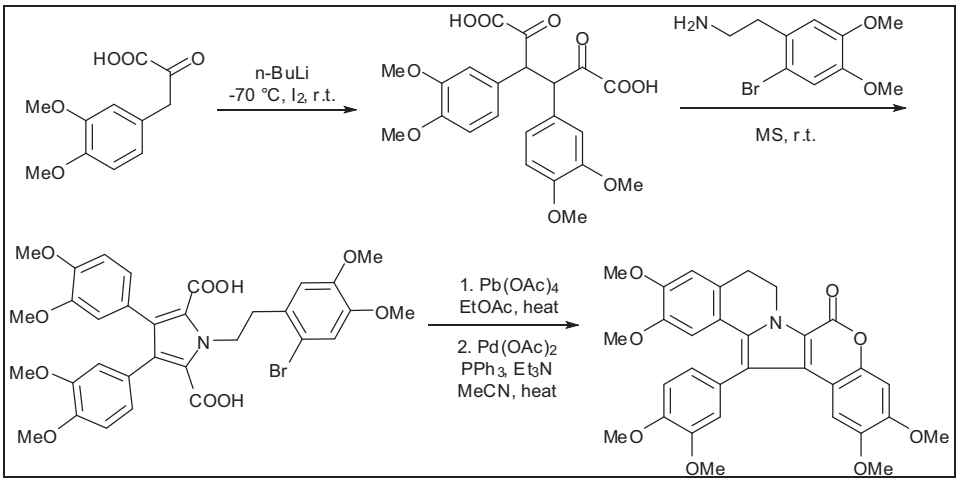
J. S. Yadav et.al reported a synthesis of Lamellarin G trimethy ether (Scheme 5) by using Friedel-Crafts acylation, esterification, haloarylation and oxidative cyclisation.[12] They started with veratrole and maleic anhydride to give arylbutenoic acid under Friedel-Crafts acylation conditions. This acid on esterification with dimethoxyphenol gave the corresponding phenyl ester. This on intramolecular haloarylation using NBS and $Sm(OTf)_3$ gave the *3*-bromo-*4*-aryldihydrocoumarin. This on reaction with dimethoxytetrahydroisoquinoline using K_2CO_3 in refluxing MeCN under aerobic condition directly gave the Lamellarin G trimethyl ether.

M. Nyerges and L. Toke developed a route (Scheme 6) to lamellarin skeleton with 1,5-electrocyclisation as a key step.[13] Homoveratric acid and O-allyl salicyaldehyde on Perkin reaction gave corresponding stilbenic acid. This on conversion to acid chloride and reaction with homoveratryl amine gave the triaryl amide. This under Bischler-Napieralski condition gave corresponding dihydroisoquinoline which on reaction with ethyl bromoacetate gave the quaternary ammonium bromide salt. This salt on reaction with triethylamine underwent *1,5*-electrocyclisation via azomethine ylide intermediate and subsequent air oxidation to give isoquinolino-pyrrole ester. Removal of allyl protection by 10 % Pd/C and TsOH in refluxing $EtOH/H_2O$ directly gave the cyclised product with Lamellarin skeleton.



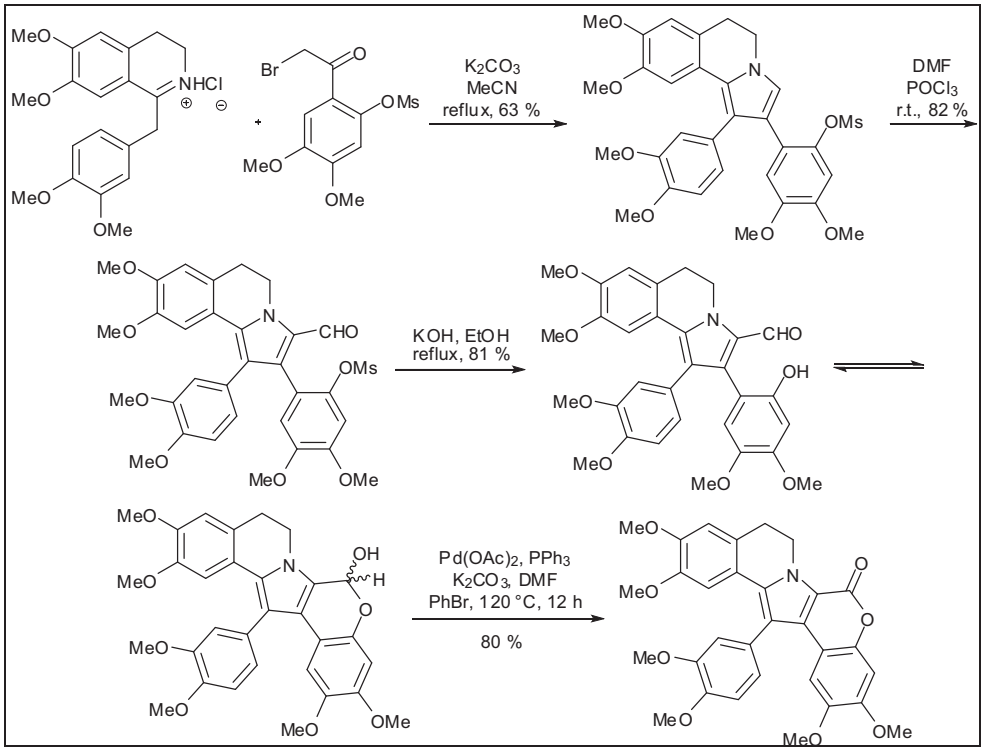
Scheme 6

W. Steglich's group accomplished a biomimetic approach (Scheme 7) for synthesis of lamellarin G trimethyl ether.[14] They started with homoveratric acid and subjected it to homocoupling product as symmetrical bis-ketoacid. This on condensation with homoveratryl amine gave the functionalised tetrasubstituted pyrrole. This penta-substituted pyrrole was then lactonised with $Pb(OAc)_4$ and intramolecular decarboxylative cross-coupling reaction gave the Lamellarin G trimethyl ether.



Scheme 7

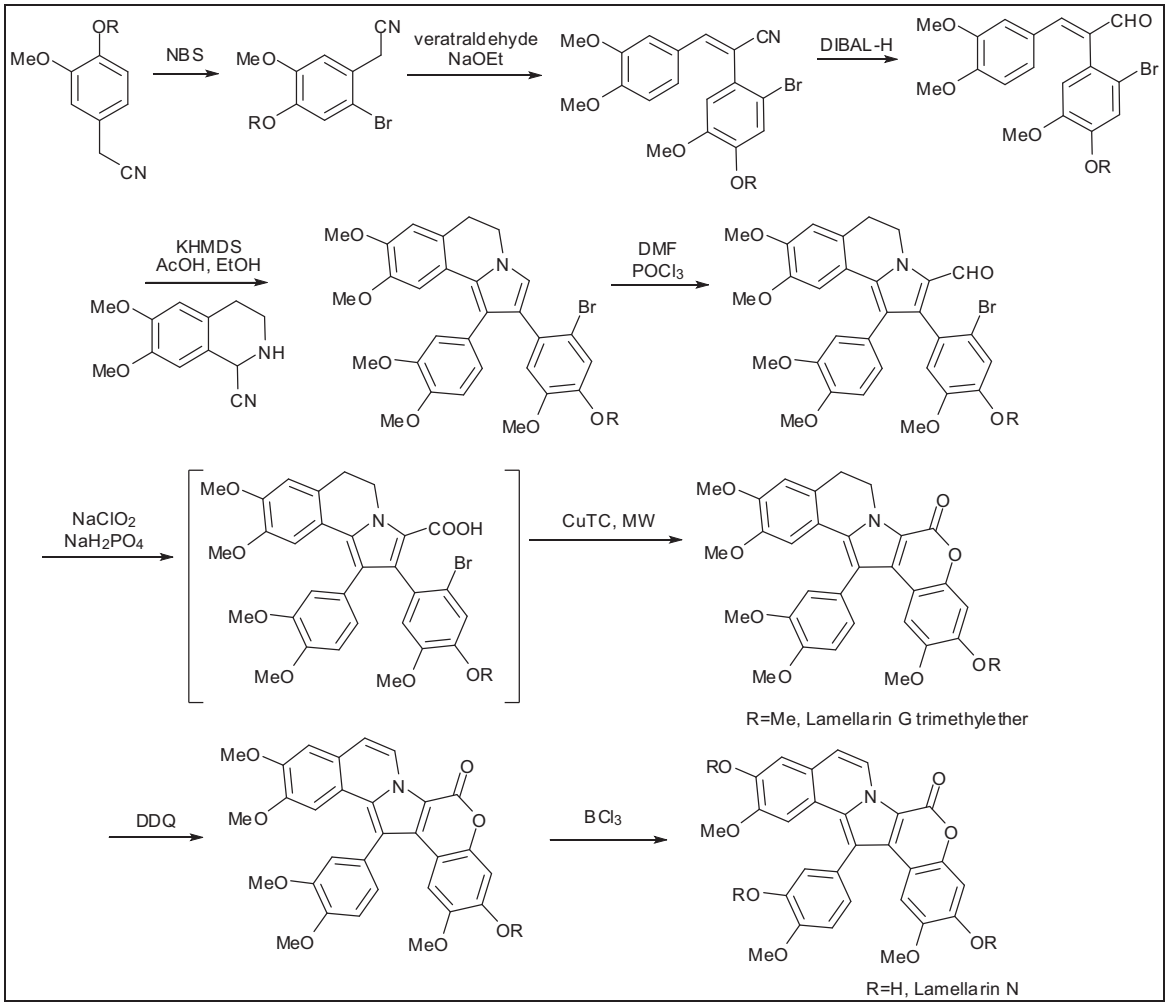
S. Ruchirawat's group have been instrumental in developing many route for synthesis of various lamellarin derivatives. One of the proficient approaches (Scheme 8) among these is described below.[15] Condensation of dihydroisoquinoline with substituted mesyl protected bromo-acetophenone under basic condition gave the isoquinolino-pyrrole derivative. This pyrrole was formylated using DMF/$POCl_3$ reagents. The deprotection followed by oxidative lactonization gave the Lamellarin G trimethyl ether.



Scheme 8

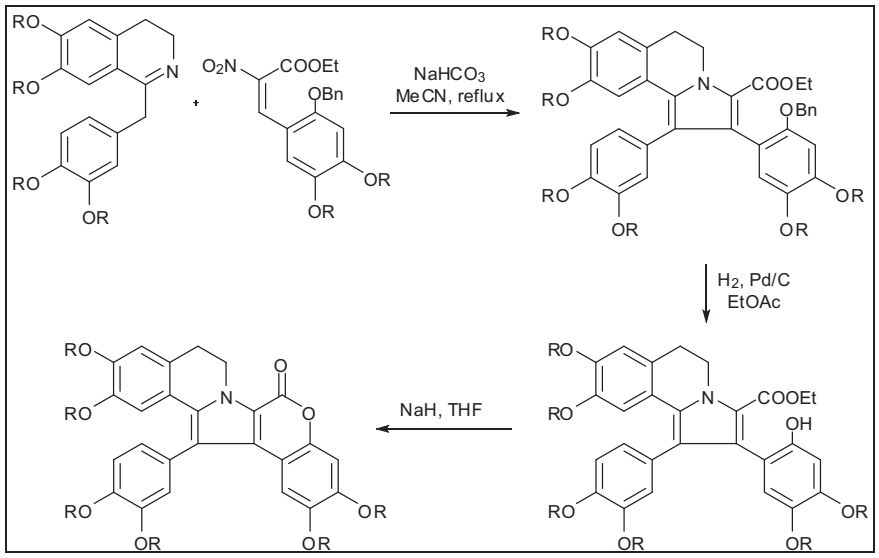
T. Opatz's group reported an efficient synthesis (Scheme 9) of lamellarins.[16] They started with commercially available phenyl-acetonitrile. This on quantitative bromination on aromatic ring

using NBS followed by Knoevenagel condensation with veratraldehyde gave cyanostilbene. The reduction of cyano group with DIBAL-H gave the corresponding aldehyde. Further base mediated reaction of this with cyanoisoquinoline prepared from homoveratrylamine followed by acid mediated dehydration and dehydrocyanation gave the isoquinolino-pyrrole frame work. This on Vilsmeier formylation followed by Pinnick oxidation gave the pyrrole acid which was unstable and immediately treated with copper(*I*)-thiophene-*2*-carboxylate under MW condition to give lamellarin G trimethyl ether. Also oxidation followed by deprotection of the pyrrolo-coumarin gave lamellarin N.



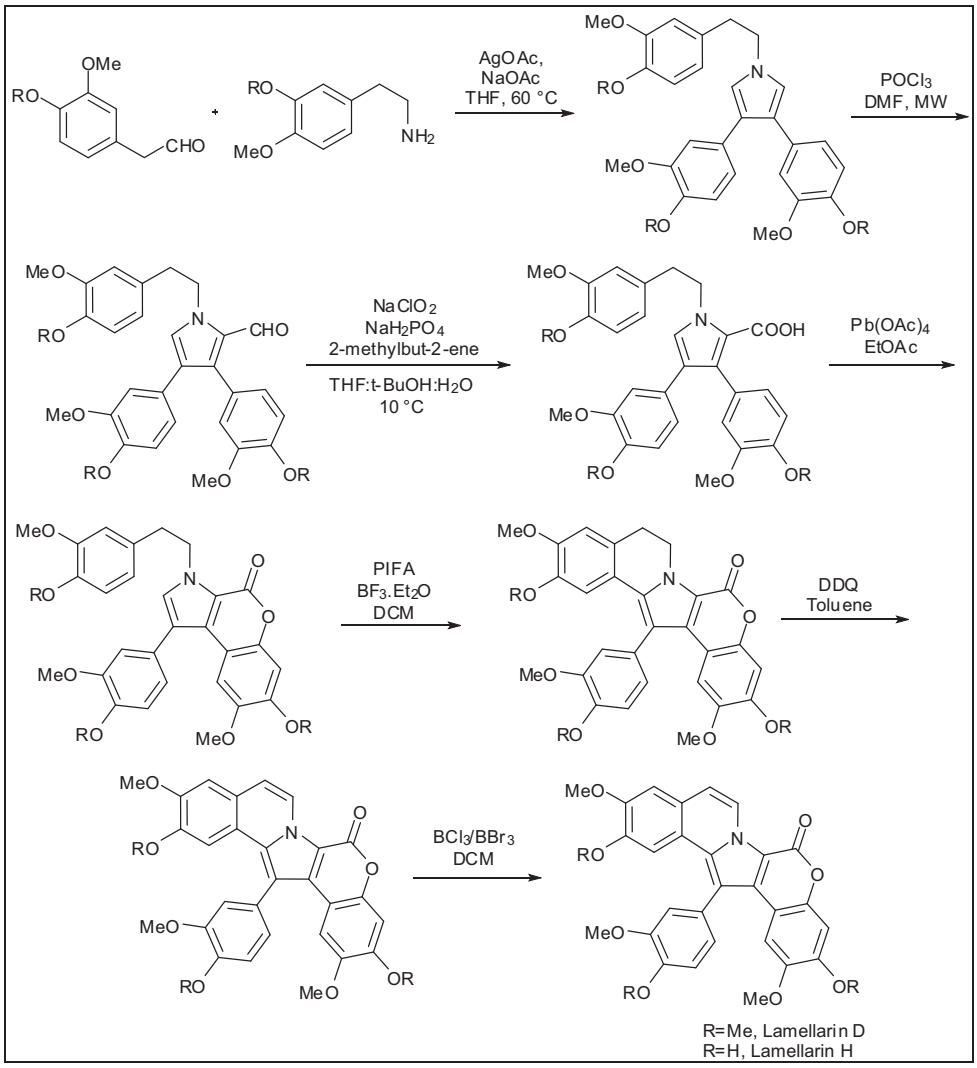
Scheme 9

S. Ruchirawat and co-workers[17] developed a Michael addition/ring-closure reaction (Scheme 10) of dihydroisoquinoline with ethoxycarbonyl-nitrostyrenes to prepare Lamellarin K and L. Initially the reaction of dihydroisoquinoline with benzylated nitrostyrenes gave the pyrrole ring. This on debenzylation and finally lactonisation gave the lamellarin K and L.



Scheme 10

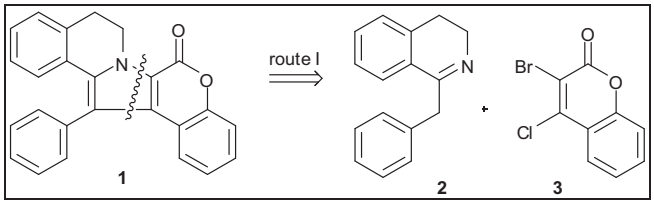
Y. Jia's group[18] reported the total synthesis (Scheme 11) of lamellarins D and H in a biomimetic manner. The key steps in this method were AgOAc mediated oxidative coupling reaction to construct the pyrrole core, $Pb(OAc)_4$ induced oxidative cyclisation to form the lactone and Kita's oxidation reaction to form the pyrrole-arene C-C bond. The substituted phenylacetaldehyde and phenethylamine were used as starting material for AgOAc mediated oxidative coupling reaction using NaOAc to give the required pyrrole. Further Vilsmeier-Haack formylation of pyrrole using $POCl_3$/DMF under MW condition gave the *2*-formylpyrrole. This was oxidised by Lindgren oxidation using $NaClO_2$, NaH_2PO_4 to corresponding acid and further reaction with $Pb(OAc)_4$ in refluxing EtOAc gave the pyrrolocoumarin framework. This was subjected to Kita's oxidation using PIFA/BF_3.Et_2O to give the lamellarin skeleton. Lamellarin D and H were obtained by DDQ oxidation and deprotection using BCl_3 and BBr_3 respectively.



Scheme 11

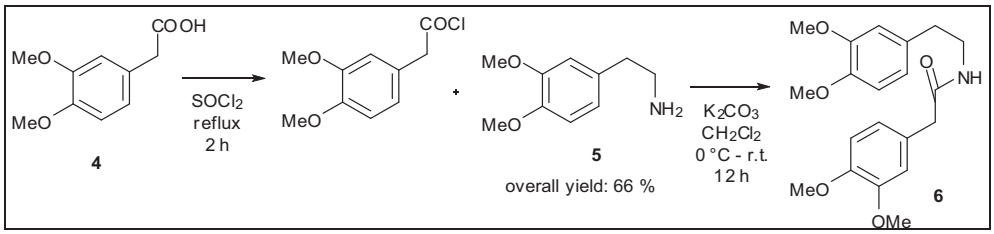
3.A.3: Results and Discussion

As evident from the enormous literature work[8-18] using Suzuki, Heck, Stille coupling to build the lamellarin scaffold **1**, most of these approaches use brominated pyrrole core for cross coupling reactions. We thought of synthesising this structural motif by a different approach using coumarin core and building the pyrrole latter (Scheme 12).



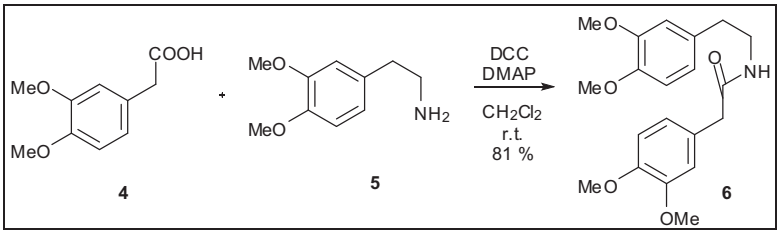
Scheme 12

We envisaged that lamellarin scaffold **1** could be obtained by intramolecular Buchwald-Hartwig reaction preceding a Michael reaction of dihydroisoquinoline **2** and *3*-bromo-*4*-chlorocoumarin **3**.



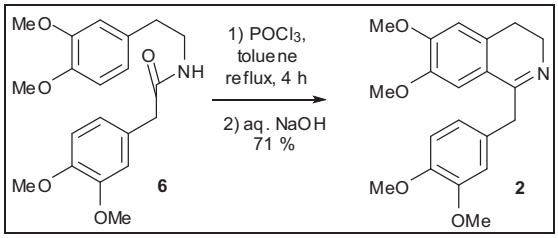
Scheme 13

Following this plan, we started with commercially available homoveratric acid **4**, converted it to acid chloride with $SOCl_2$ and reacted with homoveratryl amine **5** to give sec. amide **6** (Scheme 13). The product was obtained as white amorphous solid in 66 % yield. The m.p. and spectral details were in accordance with the literature values.[19]



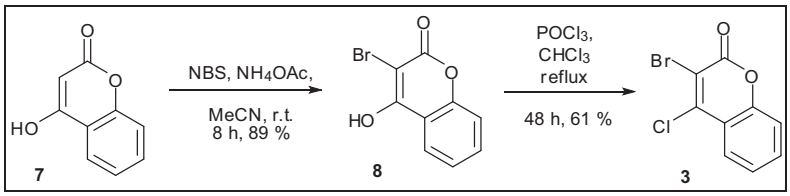
Scheme 14

The same product **6** was obtained in 81 % yield by DCC coupling of commercially available homoveratric acid **4** and homovertryl amine **5** at r.t. (Scheme 14) The dihydroisoquinoline **2** was prepared from amide **6** (Scheme 15) by Bischler-Napieralski (B-N) reaction[20] using $POCl_3$.



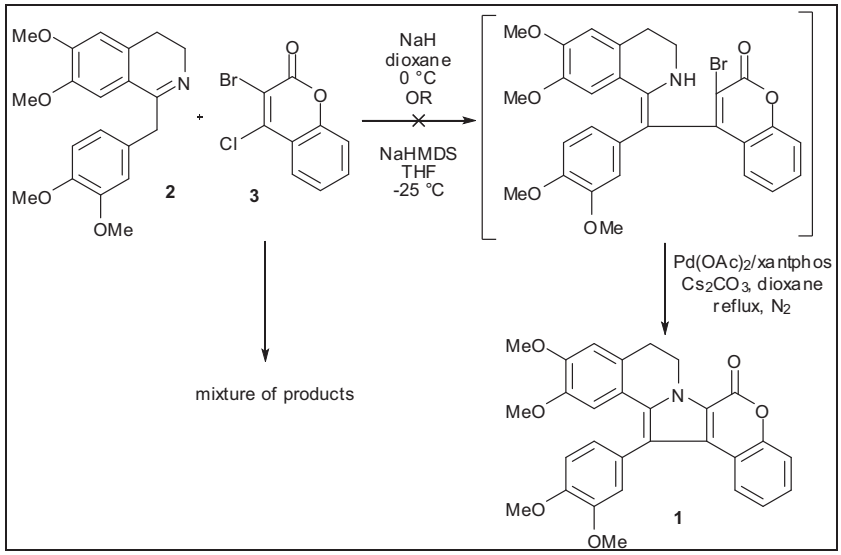
Scheme 15

Further to prepare *3*-bromo-*4*-chlorocoumarin **3**; *3*-bromo-*4*-hydroxycoumarin **8** was first prepared from *4*-hydroxycoumarin **7** using NBS and ammonium acetate as catalyst in MeCN at r.t. (Scheme 16). This product **8** was obtained as off white solid in 89 % yield. The M.P. and spectral details were in accordance with the literature values.[21] *3*-Bromo-*4*-hydroxycoumarin **8** was then converted to *3*-bromo-*4*-chlorocoumarin **3** by $POCl_3$ in refluxing $CHCl_3$. The product **3** was isolated as pale yellow solid in 61 % yield.

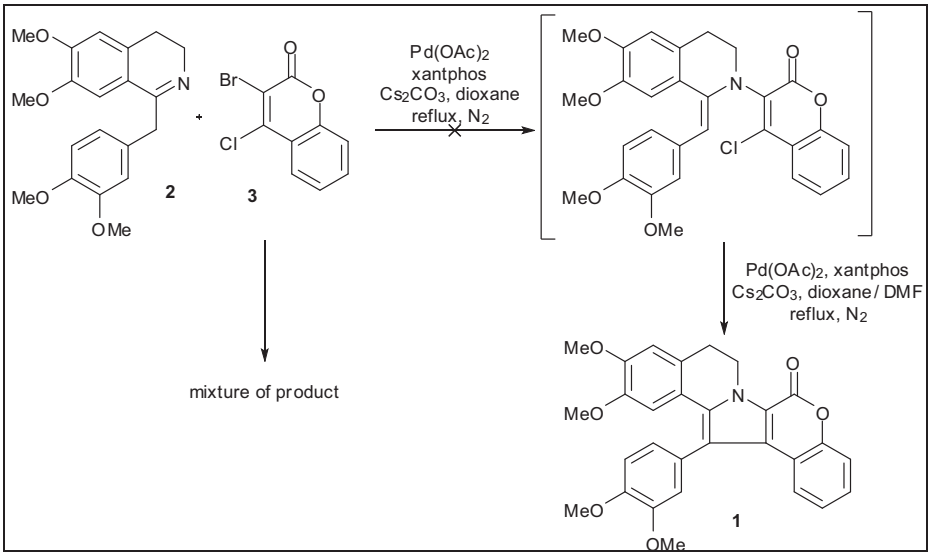


Scheme 16

The freshly prepared dihydroisoquinoline **2** was treated with NaH in dioxane and reacted with *3*-bromo-*4*-chlorocoumarin **3** for Michael reaction and immediately reacted under Buchwald-Hartwig coupling condition[22] using $PdOAc_2$/xantphos as catalyst with Cs_2CO_3 as base in refluxing dioxane expecting lamellarin skeleton **1** (Scheme 17). This attempt yielded us an inseparable mixture of products.



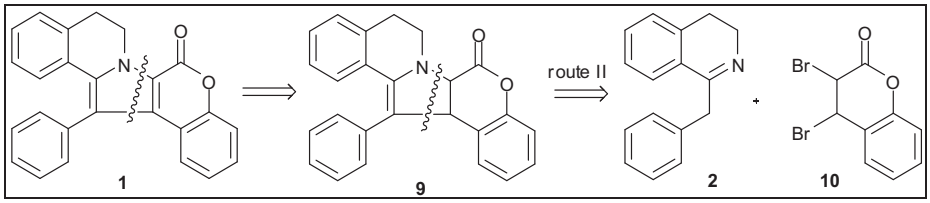
Scheme 17



Scheme 18

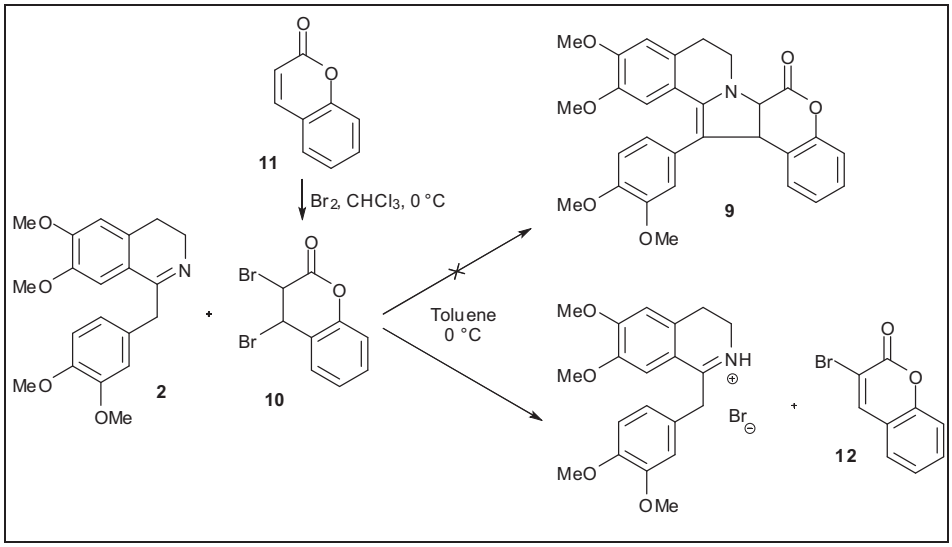
We then subjected these dihydroisoquinoline **2** and 3-bromo-chloro-coumarin **3** to double cross coupling reaction (Scheme 18) involving C-N coupling followed by C-C coupling to directly give lamellarin scaffold **1**. This attempt also gave us a complex mixture of products.

Failure of this strategy prompted us to devise a plan involving use of dihydroisoquinoline **2** and dibromocoumarin **10** to give dihydrolamellarin **9** which on dehydrogenation could give us lamellarin scaffold **1** as depicted in scheme 19.



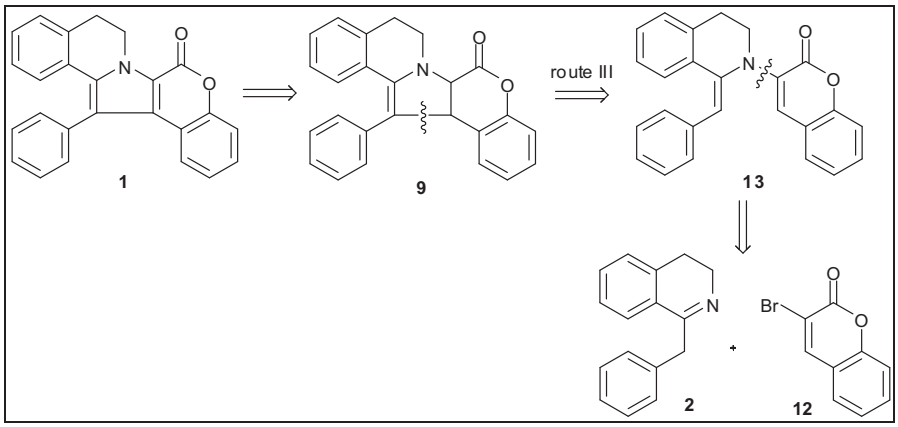
Scheme 19

Coumarin **11** was brominated with Br_2 in $CHCl_3$ at 0 °C to give dibromocoumarin[23] **10** (Scheme 20) and immediately reacted with dihydroisoquinoline **2** as nucleophile to give dihydrolamellarin **9**, but instead dihyisoquinoline **2** acted as base and gave *3*-bromocoumarin **12** with corresponding dihydroisoquinoline salt.



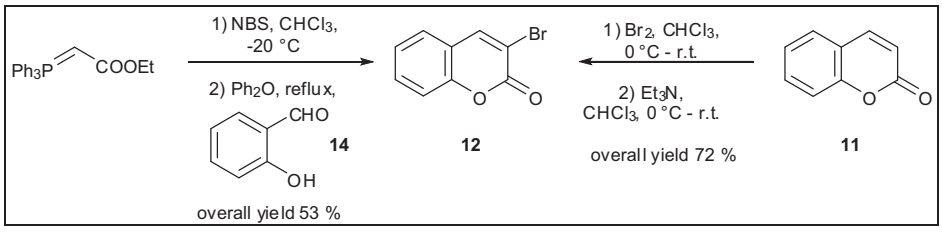
Scheme 20

We than modified our strategy (Scheme 21) and planned to use dihydroisoquinoline **2** for Buchwald-Hartwig coupling reaction. We foresee that the intermediate **9** could be obtained by Michael reaction from isoquinolinocoumarine intermediate **13** which in turn could be obtained by B-H amination of dihydroisoquinoline **2** and 3-bromocoumarin **12**.



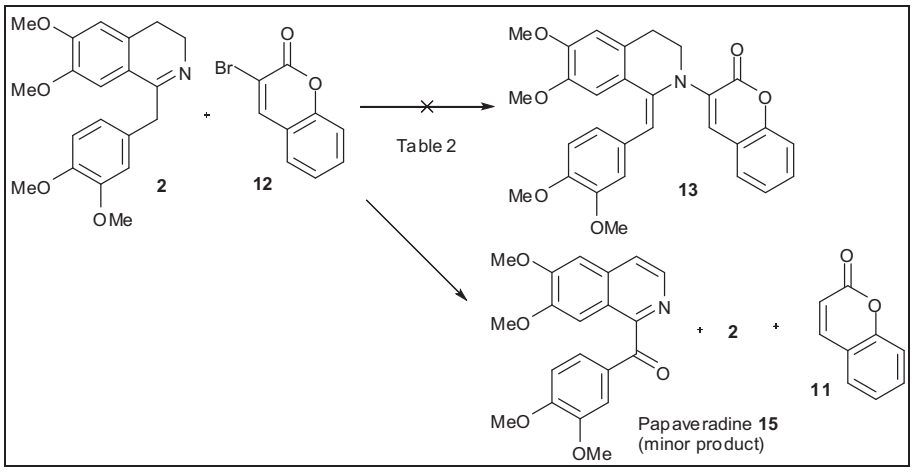
Scheme 21

3-bromocoumarin **12** was prepared by a reported method[24] using carboethoxy-methylene-triphenylphosphorane, salicyaldehyde **14** and NBS in 68 % yield (Scheme 22). Alternatively to simplify the procedure, *3*-bromocoumarin **12** was prepared in large scale (5 g) from coumarin **11** by bromination with Br_2 in $CHCl_3$ at 0 °C followed by dehydrohalogenation using triethylamine as base at 0 °C. The product was obtained as off white solid in 72 % yield. The m.p. and spectral details were in accordance with the literature values.[25]



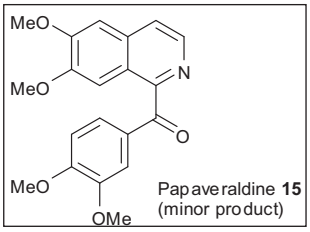
Scheme 22

3-bromocoumarin **12** and dihydroisoquinoline **2** were reacted in presence of $Pd(OAc)_2$/Xantphos as catalyst system[22] and Cs_2CO_3 as base in refluxing toluene or dioxane. This reaction (Scheme 23) failed and gave debrominated coumarin **11** and unreacted dihydroisoquinoline **2** along with minor amount of alkaloid papaveraldine[26] **15** as oxidised product.



Scheme 23

Papaveraldine **15:**



Light brown solid, m.p.: 204-206 °C. [lit.: 206-207 °C][26]

IR (KBr): ν_{max} 3329, 2965, 2835, 1713, 1674, 1535, 1269, 1028 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 3.83 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.97 (s, 3H), 6.76 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.57 (d, *J* = 5.2 Hz, 1H), 7.62 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 1H) ppm.

^{13}C NMR (100MHz, $CDCl_3$): δ 54.99 (CH_3), 55.06 (CH_3), 55.11 (2X CH_3), 103.03 (CH), 103.84 (CH), 108.92 (CH), 110.82 (CH), 120.30 (CH), 121.80 (Cq), 125.96 (CH), 128.85 (Cq), 132.98 (Cq), 138.93 (CH), 148.02 (Cq), 150.02 (Cq), 152.22 (Cq), 152.70 (Cq), 152.84 (Cq), 192.98 (Cq) ppm.

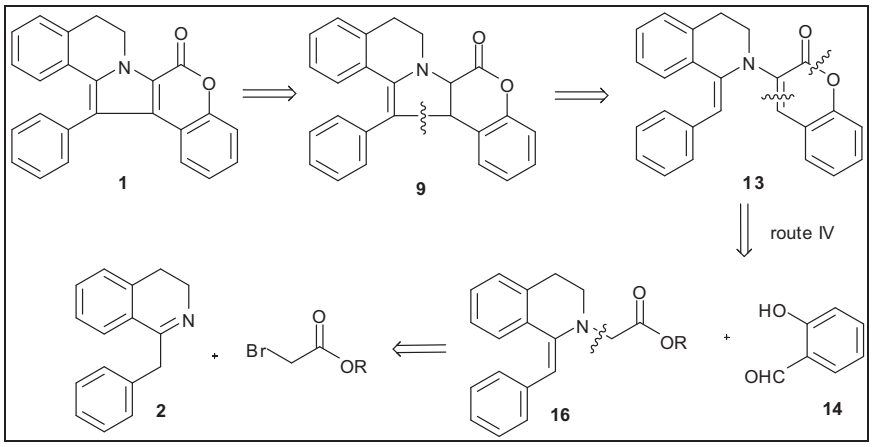
LCMS (*m/z*): $[M+H]^+$ 354.1.

The various other coupling conditions were tried (Table 2) but similar results were obtained with papaveradine **15** as minor product.

Table 2: Various conditions tried with Scheme 23.

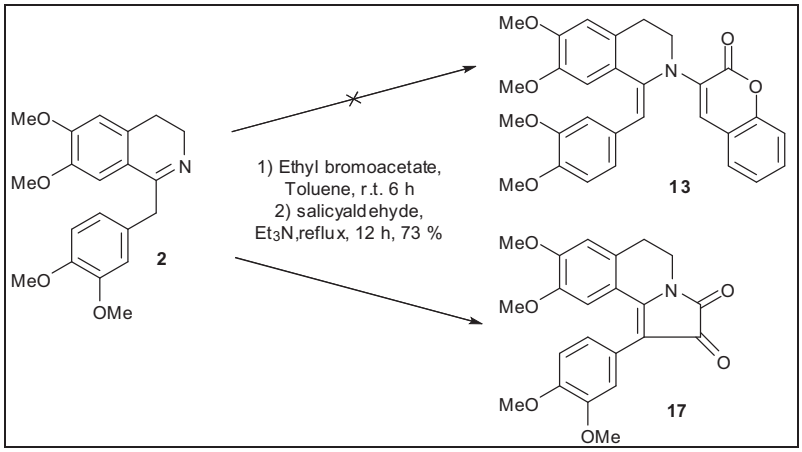
Entry	Reaction Condition
1	$Pd(OAc)_2$/xantphos, Cs_2CO_3, Tolene/Dioxane, reflux, Ar, 8 h
2	CuI, Cs_2CO_3, Toluene, reflux, Ar, 12 h
3	$Cu(OTf)_2$, Cs_2CO_3, Dioxane, reflux, Ar, 8 h
4	$Pd_2(dba)_3$/xantphos, Cs_2CO_3, Toluene, reflux, Ar, 8 h

In our continued efforts to synthesise lamellarin scaffold **1**, we adopted another plan; lamellarin scaffold **1** could be obtained from intermediate **13** (Scheme 24) which could be obtained from amine **16** and salicyaldehyde **14**. This amine **16** can be derived from dihydroisoquinoline **2** and ethyl bromoacetate.



Scheme 24

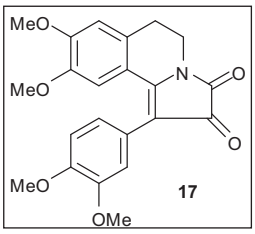
The reaction of ethyl bromoacetate and dihydroisoquinoline **2** at r.t. gave salt, which on treatment with piperidine as base and reaction with salicyaldehyde in refluxing toluene could give us the product **13** but instead gave an insoluble solid compound which could not be analysed further due to its insolubility in common solvents or acidic or basic solution. Amending the base to DBU again gave us similar pale yellow insoluble matter which could not be characterised.



Scheme 25

Further changing the base to TEA gave a Wine red solid along with unreacted salicylaldehyde. The spectral details were suggestive of isoquinoline fused oxopyrrolone structure **17** for the wine red solid which was further confirmed based on its mass spectra. (Scheme 25) This by-product was obtained in 73 % yield.

1-(*3,4*-dimethoxyphenyl)-*8,9*-dimethoxy-*5,6*-dihydropyrrolo[*2,1-a*]isoquinoline-*2,3*-dione **17:**



Wine red solid, m.p.: 176-178 °C

IR (KBr): ν_{max} 3021, 1728, 1705, 1624, 1445 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.06 (t, *J* = 6.0 Hz, 2H), 3.25 (s, 3H), 3.68 (s, 3H), 3.70 (t, *J* = 6.4 Hz, 2H), 3.77 (s, 3H), 3.86 (s, 3H), 6.83 (t, *J* = 8.4 Hz, 1H), 6.85 (s, 1H), 6.92 (s, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 7.09 (s, 1H) ppm.

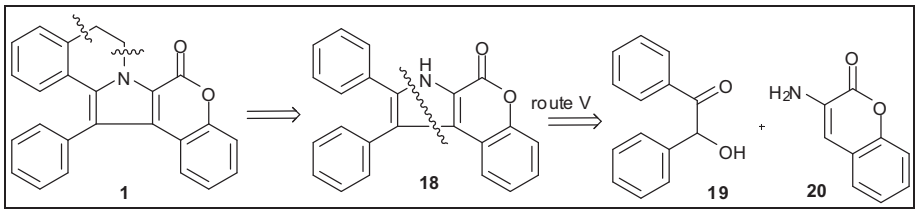
^{13}C NMR (100 MHz, DMSO-d_6): δ 27.55 (CH_2), 35.90 (CH_2), 54.62 (CH_3), 55.53 (CH_3), 55.61 (CH_3), 55.94 (CH_3), 107.24 (Cq), 111.45 (CH), 112.02 (CH), 112.16 (CH), 113.49 (CH), 115.97 (Cq), 122.56 (CH), 122.94 (Cq), 133.84 (Cq), 146.98 (Cq), 148.37 (Cq), 148.82 (Cq), 153.14 (Cq), 157.05 (Cq), 158.00 (Cq), 182.85 (Cq) ppm.

LCMS (*m/z*): $[M+H]^+$ 395.9.

HRMS (*m/z)*: calculated for $C_{22}H_{21}NO_6Na$ $[M+Na]^+$ 418.1267; found 418.1289.

Other bases like pyridine, piperidine or K_2CO_3 gave the same product **17** in similar yields even with excess of salicyaldehyde.

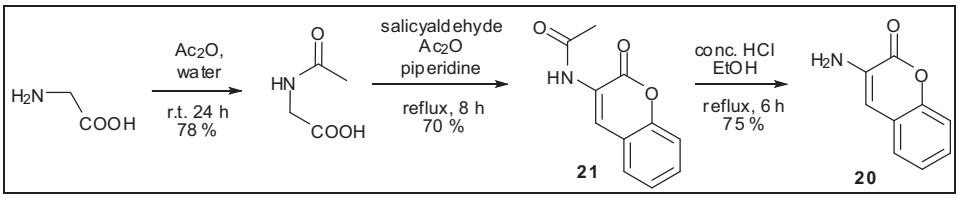
All this unsuccessful attempts for the synthesis of lamellarin scaffold **1** prompted us to try the synthesis of pyrrollocoumarin **18** by using another strategy as described below in scheme 26.



Scheme 26

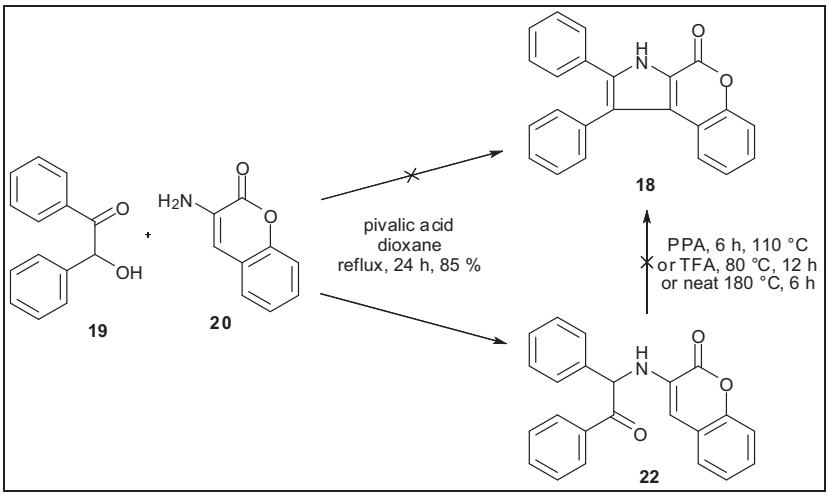
We envisage that benzoin and 3-aminocoumarin **20** would undergo dehydrative condensation to give directly pyrrollocoumarin **18**.

Preparation of *3*-aminocoumarin **20** was carried out following a reported procedure[27] (Scheme 27) with glycine, acetic anhydride and salicyaldehyde. The product was obtained as golden solid in 41 % overall yield. The m.p. and spectral details were in accordance with the literature data.[28]



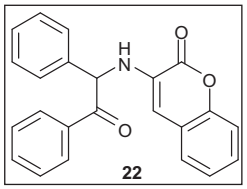
Scheme 27

To follow the plan, *3*-aminocoumarin **20** and benzoin **19** were reacted in refluxing dioxane and pivalic acid to give directly pyrrollocoumarin **18** (Scheme 28). To our surprise the reaction stopped at intermediate step and uncyclised product **22** was obtained as pale yellow solid in 85 % yield. The spectral data unambiguously suggested the proposed structure.



Scheme 28

Spectral data of *3*-(*2*-oxo-*1,2*-diphenylethylamino)-*2H*-chromen-*2*-one **22:**



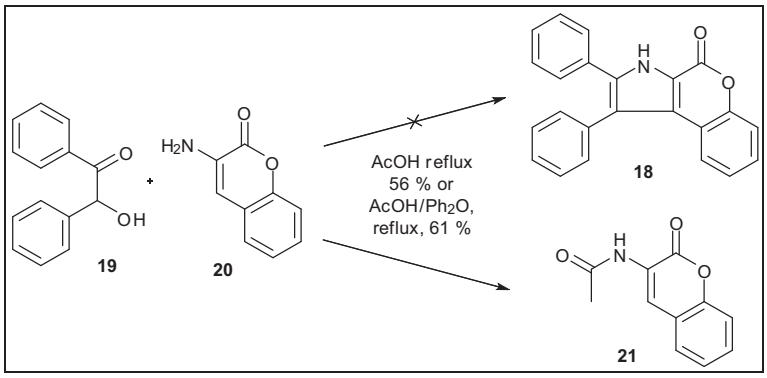
IR (KBr): ν_{max} 3393, 3061, 2893, 1693, 1681, 1630, 1597, 1449 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 5.89 (s, 1H), 6.19 (s, 1H), 7.06 (d, *J* = 7.2 Hz, 1H) 7.12 - 7.18 (m, 4H), 7.25 (t, *J* = 7.2 Hz, 2H) 7.27 7.36 - 7.41 (m, 4H), 7.47 (t, *J* = 7.6 Hz, 1H) 7.94 (d, *J* = 7.6 Hz, 2H) ppm.

^{13}C NMR & DEPT (100MHz, $CDCl_3$): δ 62.10 (CH), 106.52 (CH), 116.07 (CH), 121.25 (Cq), 124.52 (CH), 125.14 (CH), 126.05 (CH), 128.16 (CH), 128.69 (CH), 128.80 (CH), 128.95 (CH), 129.33 (CH), 131.07 (Cq), 133.81 (CH), 134.50 (Cq), 135.90 (Cq), 148.09 (Cq), 159.28 (Cq), 194.67 (Cq) ppm.

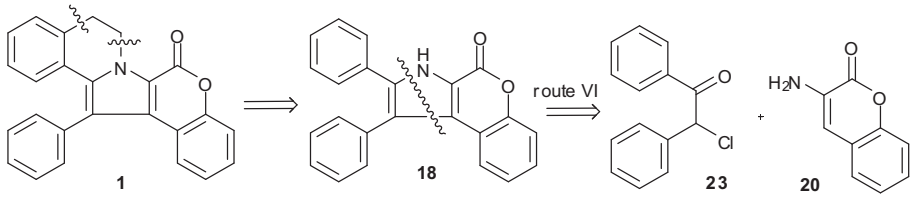
HRMS (*m/z)*: calculated for $C_{23}H_{17}NO_3Na$ $[M+Na]^+$ 378.1106; found 378.1103.

Attempts made separately using PPA, TFA, or neat heating did not give us expected pyrrollocoumarin **18** and the reactant **22** was recovered. Heating the mixture of benzoin and aminocoumarin **20** in acetic acid or acetic acid in diphenylether (Scheme 29) did not give us the expected product instead gave 3-acetamidocoumarin **21**.



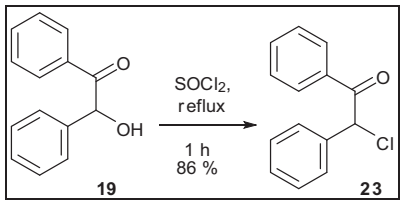
Scheme 29

We thought of using a good leaving group like Cl instead to OH in benzoin for this transformation as shown in scheme 30.



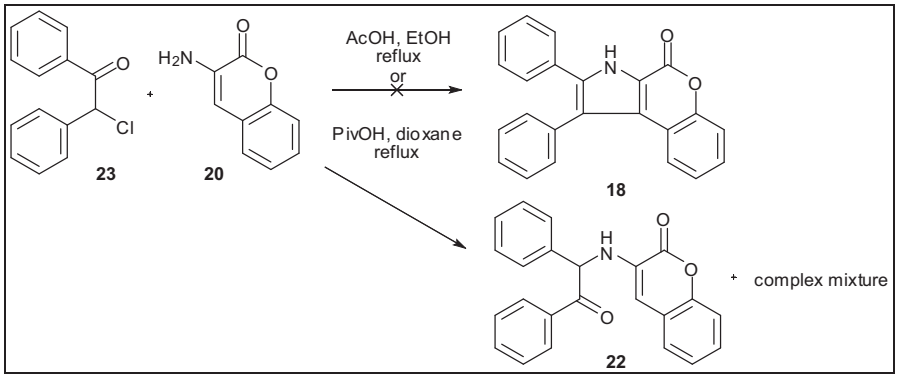
Scheme 30

Chlorobenzoin **23** was prepared from benzoin **19** in 86 % yield by refluxing with $SOCl_2$ for 1 h.[29] (Scheme 31)



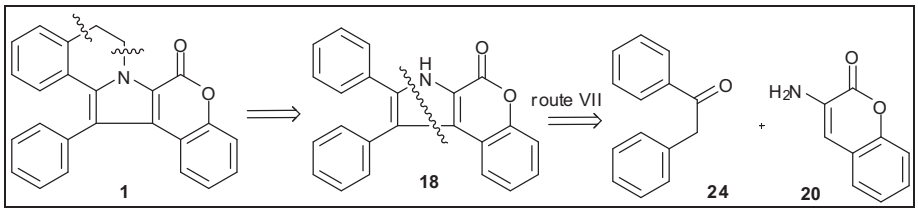
Scheme 31

3-Aminocoumarin **20** and chlorobenzoin **23** was reacted in refluxing dioxane or EtOH with pivalic or acetic acid. This attempt also gave us uncyclised product **22** along with a complex mixture of other products (Scheme 32).



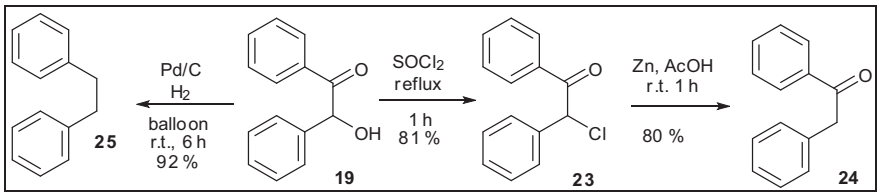
Scheme 32

These failures giving uncylised intermediate **22** suggested that probably the eletrophilic nature of cyclising position is hampering the desired pathway, thus involving a nucleophilic substrate deoxybenzoin **24** for cyclisation by slightly modifying the strategy as described in scheme 33 could directly give us the required pyrrollocoumarin **18**.



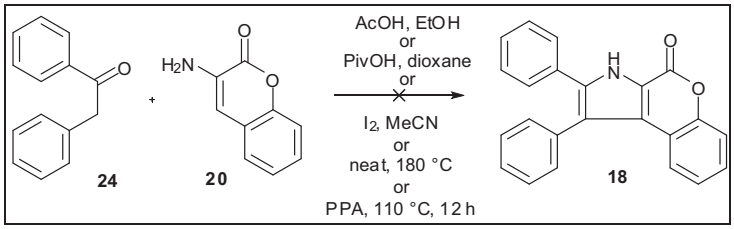
Scheme 33

We used hydrogenation method (Scheme 34) to prepare deoxybenzoin **24** from benzoin **19** in balloon using Pd/C but instead obtained dihydrostilbene **25** as exclusive product. The m.p. and spectral details were in accordance with the literature data.[30] Alternatively, chlorobenzoin **23** was dechlorinated using Zn in acetic acid to give deoxybenzoin **24** as pale yellow solid in 80 % yield. The spectroscopic data unambiguously matched with the literature data.[31]



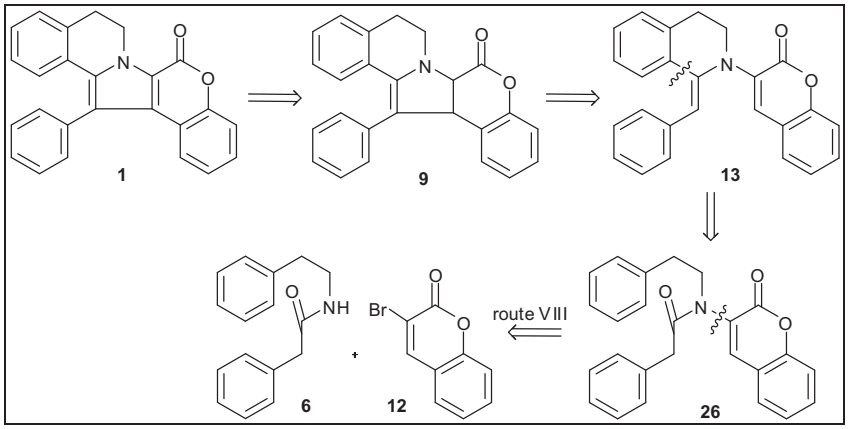
Scheme 34

Further 3-aminocoumarin **20** was reacted with deoxybenzoin **24** in cat. AcOH in EtOH but showed only reactants and no product formation (Scheme 35). We then tried Iodine in MeCN for this reaction but did not get any encouraging results and instead gave an inseperable mixture of products. Also neat heating of these two components did not give any us any product.



Scheme 35

We then planned another route as presented in scheme 36. The lamellarin scaffold **1** could be obtained by dehydrogenation of intermediate **9**. This could be obtained by Michael reaction of intermediate **13** which could be built from tert. amide **26** by Bischler-Napieralski reaction.[32] (Scheme 36)

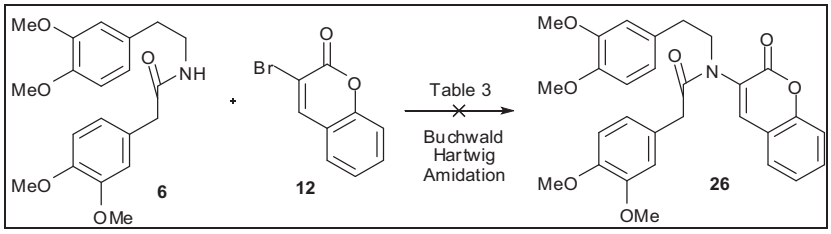


Scheme 36

In recent studies, Buchwald-Hartwig reaction has been an important tool for amination or amidation reaction using aryl halides. We envisaged that Buchwald-Hartwig reaction of *3*-bromocoumarin **12** and sec. amide **6** could give us this tert. amide **26**.

Both these substrates **12** and **6** were reacted together in Buchwald-Hartwig amidation conditions[22,33] using $Pd(OAc)_2$/xantphos catalyst along with Cs_2CO_3 as base in refluxing dioxane.

(Scheme 37, Table 3) This reaction unfortunately did not yield any product and reactant amide **6** was recovered back along with debrominated coumarin **11**. Various other conditions[34] using catalysts such as $Pd(OAc)_2$, $Pd_2(dba)_3$ and CuI, ligands like PPh_3, xantphos, X-Phos, S-Phos, *1,10*-phenanthroline and *1,2*-diaminocyclohexane were tried for this coupling reaction by changing catalyst, base and solvent as mentioned in table 3, but could not succeed in any of these attempts.



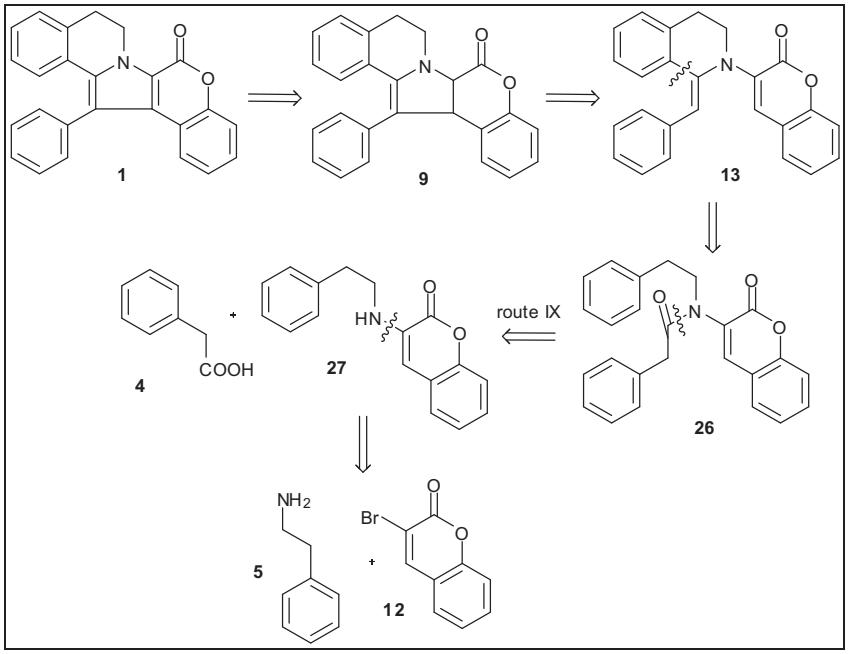
Scheme 37

Table 3: Buchwald Hartwig coupling reaction (Scheme 37).

Entry	Catalyst (mol%)	Ligand (mol%)	Base (1.5 eq)	Solvent	Reaction Condition
1)	$Pd(OAc)_2$ (10)	PPh_3 (20)	Cs_2CO_3	Dioxane	Reflux, 30 h, N_2
2)	$Pd(OAc)_2$ (10)	Xantphos (10)	Cs_2CO_3	Dioxane	Reflux, 30 h, N_2
3)	$Pd(OAc)_2$ (10)	Xantphos (10)	TEA	Toluene	Reflux, 24 h, N_2
4)	$Pd(OAc)_2$ (10)	Xantphos (10)	KOtBu	Toluene	Reflux, 30 h, N_2
5)	$Pd(OAc)_2$ (10)	Xantphos (10)	NaH	Dioxane	Reflux, 12 h, N_2
6)	$Pd(OAc)_2$ (10)	Xantphos (10)	NaOAc	Dioxane	Reflux, 48 h, N_2
7)	$Pd(OAc)_2$ (10)	X-phos (20)	Cs_2CO_3	Dioxane	Reflux, 36 h, N_2
8)	$Pd(OAc)_2$ (10)	S-phos (20)	Cs_2CO_3	Dioxane	Reflux, 48 h, N_2
9)	$Pd_2(dba)_3$ (10)	Xantphos (20)	Cs_2CO_3	Toluene	Reflux, 6 h, Ar
10)	$Pd(OAc)_2$ (10)	Xantphos (10)	NaOAc	DMA	MW
11)	CuI (10)	1,10-phenanthroline	Cs_2CO_3	DMF	Reflux, 12 h, N_2
12)	CuI (10)	1,2diaminocyclohexan	Cs_2CO_3	Dioxane	Reflux, 12 h, Ar

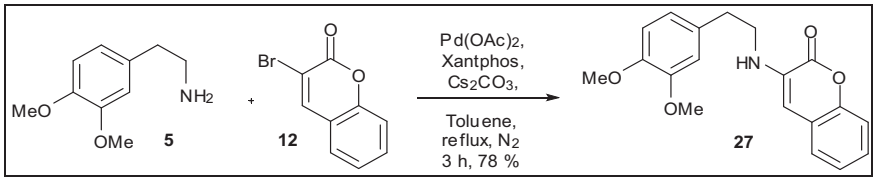
With all these attempts we could conclude that coupling reaction of 3-bromocoumarin **12** could not be accomplished with sec. amide **6** and this was in agreement with the observations of Alami *et al*.[22] for cyclic sec. amide. We than changed our strategy and planned to prepare the required tert. amide intermediate **26** by an alternate path.

As per the plan, intermediate amide **26** could be prepared by using homoveratric acid **4** and sec. amine **27** which inturn could be prepared by Buchwald Hartwig amination reaction between 3-bromocoumarin **12** and homoveratryl amine **5** (Scheme 38).



Scheme 38

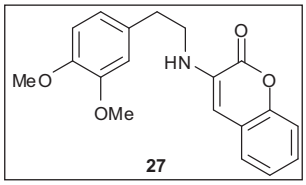
Following this strategy, *3*-bromocoumarin **12** and homoveratryl amine **5** were reacted under Buchwald-Hartwig amination reaction condition[22] using $PdOAc_2$/xantphos as catalyst and Cs_2CO_3 as base in refluxing toluene to give the required sec. amine **27** as pale yellow solid in 78 % yield (Scheme 39).



Scheme 39

The PMR spectra of this product showed triplets for 2H at δ 2.92 and 3.38 ppm suggesting homoveratryl part of product, along with singlet at δ 6.34 ppm for 1H of coumarin part. The structure was confirmed to be as predicted based on its spectral details and mass spectra.

Spectral data of *3*-(*3,4*-dimethoxyphenethylamino)-*2H*-chromen-*2*-one **27:**



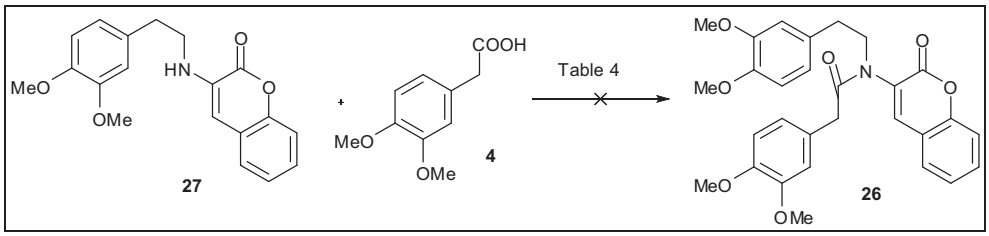
IR (KBr): ν_{max} 3364, 2957, 1713, 1622, 1504, 1364, 1165, 1024 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 2.92 (t, *J* = 7.2 Hz, 2H), 3.40 (t, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 3.89 (s, 3H), 4.94 (br s, 1H), 6.34 (s, 1H), 6.75 (s, 1H), 6.78 – 6.84 (m, 2H), 7.19 – 7.26 (m, 3H), 7.30 (d, *J* = 7.2 Hz, 1H)

ppm.

^{13}C NMR (100MHz, $CDCl_3$): δ 34.42 (CH_2), 44.64 (CH_2), 55.92 (CH_3), 55.95 (CH_3), 104.90 (CH), 111.48 (CH), 111.86 (CH), 116.06 (CH), 120.63 (CH), 121.72 (Cq), 124.65 (CH), 124.96 (CH), 125.69 (CH), 131.10 (Cq), 132.88 (Cq), 147.84 (Cq), 147.87 (Cq), 149.12 (Cq), 159.54 (Cq), ppm.
LCMS (*m/z*): $[M+H]^+$ 326.07.
HRMS (*m/z)*: calculated for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$ 348.1212; found 348.1213.

This sec. amine **27** was reacted with homoveratric acid **4** (Scheme 40, Table 4) to give the required tert. amide **26**.



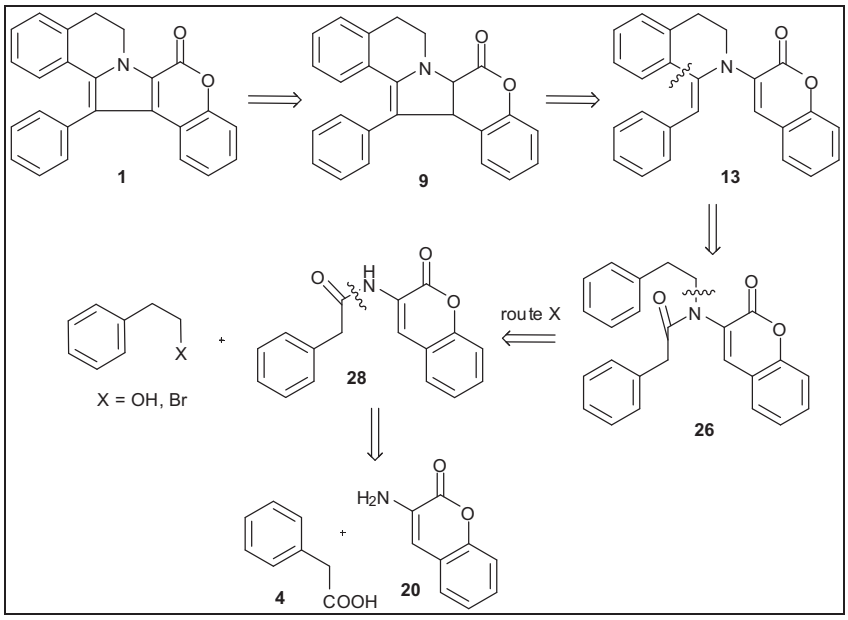
Scheme 40

This reaction although simple did not provide us any product using usual procedure of DCC coupling reaction[35] for amide preparation and reactants were recovered back. Other similar reagent (Table 4) such as EDCl/HOBt was tried but failed to give the required product. Alternatively, sec. amine **27** was reacted with *in situ* prepared homoveratroyl chloride in presence of triethylamine, but failed here to react. This low reactive of sec. amine **27** was attributed to the delocalisation of N lone pairs onto the neighbouring coumarin ring. We tried to enhance the reactivity by adding LDA and then reacting with acid chloride/ethyl ester but these attempts also failed to give us any product.

Table 4: Various conditions tried in scheme 40.

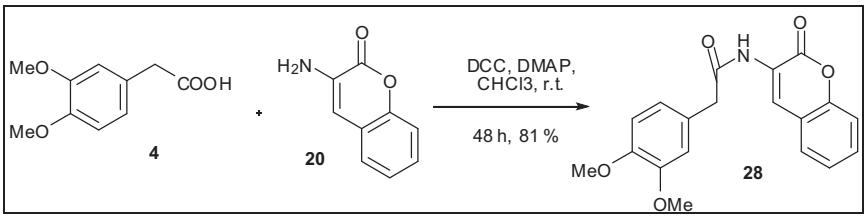
Entry	Reaction Condition	Observation
1	DCC, DMAP, DCM	no reaction, reactant recovered
2	EDCl, TEA, HOBt, DCM	no reaction, reactant recovered
3	a) $SOCl_2$; b) TEA $CHCl_3$	no reaction, reactant recovered
4	$POCl_3$, pyridine, 80 °C	Reactant decomposed
4	neat, 180 °C	no reaction, reactant recovered
5	PPA, 110 °C, 24 h	no reaction
6	a) LDA, THF, -78 °C; b) homoveratroyl chloride/ ethyl homoveratroate	complex mixture including reactants

We then planned to prepare the amide **26** by alkylation of sec. amide **28** (Scheme 41). This amide **28** could be obtained from homoveratric acid **4** and 3-aminocoumarin **20**.



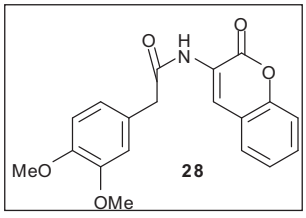
Scheme 41

3-Aminocoumarin **20** was reacted with homoveratric acid **4** in presence of DCC to give the required product **28** as pale yellow amorphous solid in 81 % yield (Scheme 42). The structure of this product **28** was assigned based on its unambiguous NMR data.



Scheme 42

Spectral data of *2*-(*3,4*-dimethoxyphenyl)-N-(*2*-oxo-*2H*-chromen-*3*-yl)acetamide **28:**



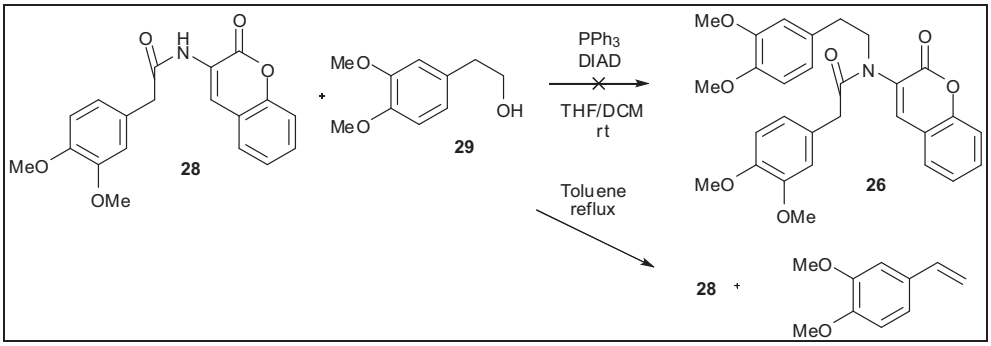
IR (KBr): ν_{max} 3329, 2965, 2835, 1713, 1674, 1535, 1269, 1028 cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ 3.74 (s, 2H), 3.91 (s, 3H), 3.92 (s, 3H), 6.86 (s, 1H), 6.91 (s, 2H), 7.28 - 7.33 (m, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 8.19 (br s, 1H), 8.69 (s, 1H) ppm.

^{13}C NMR (100MHz, $CDCl_3$): δ 44.50 (CH_2), 55.93 (CH_3), 55.97 (CH_3), 111.70 (CH), 112.24 (CH), 116.36 (CH), 119.76 (Cq), 121.61 (CH), 123.29 (CH), 123.89 (Cq), 125.16 (CH), 125.94 (Cq), 127.81 (CH), 129.71 (CH), 148.71 (Cq), 149.51 (Cq), 149.96 (Cq), 158.59 (Cq), 170.56 (Cq) ppm.

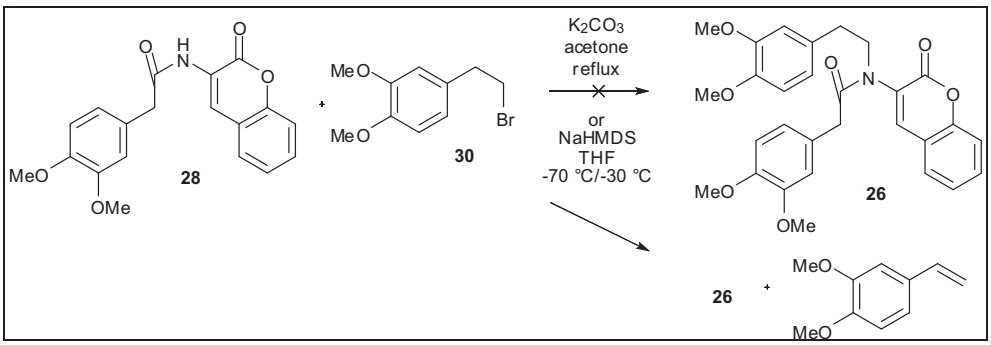
HRMS (*m/z)*: calculated for $C_{19}H_{17}NO_5Na$ $[M+Na]^+$ 362.1004; found 362.1001.

We subjected this amide **28** for alkylation with homoveratryl alcohol **29** under Mitsunobu reaction[36] conditions (Scheme 43) but were unsuccessful with mild condition and reflux condition gave dehydrobrominated product as dimethoxystyrene.[37]



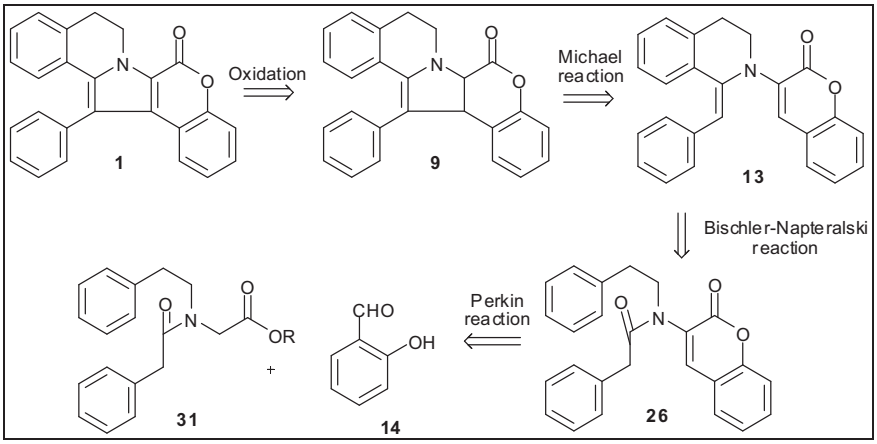
Scheme 43

Alkylation with homoveratryl bromide **30** gave same results (Scheme 44). The nucleophilicity of the amide **28** was enhanced with equiv. amount of NaHMDS and reacted with bromide **30** but instead the sodium salt of amide **28** acted as base and gave dimethoxystyrene.



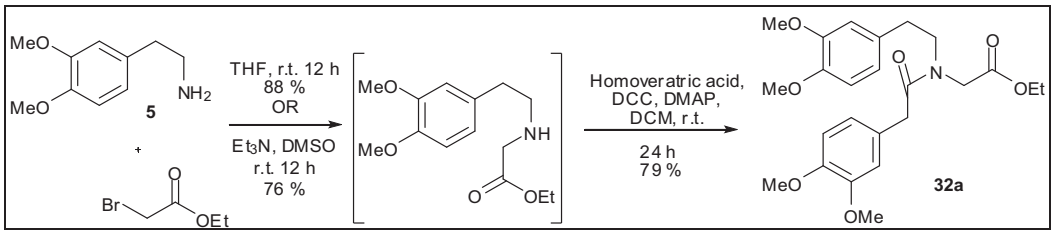
Scheme 44

With all these unfruitful attempts, preparation of the required tert. amide **26** was undertaken by Perkin reaction with salicyaldehyde **14** (Scheme 45) and amide-acid **31** which inturn could be obtained by hydrolysing amide-ester **32**. The amide-ester **32** could be prepared from homoveratric acid **4a** and sec. amine obtained from homoveratryl amine **5** and ethyl bromoacetate.



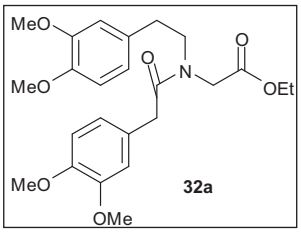
Scheme 45

We followed a reported procedure[38,5e] using homoveratryl amine **5** and ethyl bromoacetate at r.t. to give sec. amine (Scheme 46) which was as such reacted with homoveratric acid **4a** in presence of DCC to give the amide-ester **32a** as pale yellow oil in 79 % yield. The spectral data explicitly suggested the proposed structure.



Scheme 46

Spectral data of ethyl *2*-(N-(*3,4*-dimethoxyphenethyl)-*2*-(*3,4*-dimethoxyphenyl)acetamido)acetate **32a:**



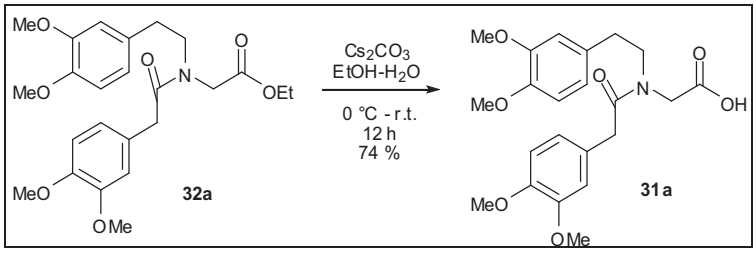
IR (neat): ν_{max} 2936, 2835, 1746, 1643, 1589, 1261 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7.2 Hz, 3 H), 2.61 (t, *J* = 7.2 Hz, 2 H), 3.43 (s, 3 H), 3.48-3.50 (m, 2 H), 3.77-3.79 (m, 12 H), 3.97 (s, 2 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 6.53-6.57 (m, 1 H), 6.61-6.63 (m, 1 H), 6.65-6.69 (m, 1 H), 6.71-6.74 (m, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.12 (CH_3), 34.55 (CH_2), 39.88 (CH_2), 47.92 (CH_2), 51.23 (CH_2), 55.73 (CH3), 55.80 (CH3), 55.83 (CH3), 55.87 (CH3), 61.10 (CH2), 111.15 (CH), 111.36 (CH), 111.81 (CH), 111.86 (CH), 120.65 (2X CH), 120.74 (CH), 127.22 (Cq), 130.54 (Cq), 147.80 (Cq), 149.00 (2X Cq), 169.22 (Cq), 171.77 (Cq) ppm.

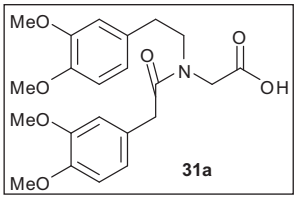
LCMS (*m/z*): $[M+H]^+$ 446.

The amide-ester **32a** was then hydrolysed with Cs_2CO_3/EtOH-H_2O mixture (Scheme 47) and the required acid **31a** was obtained as pale yellow oil in 74 % yield. LiOH in MeOH at r.t. gave the amide-acid **31a** in 21 % yield. This product obtained in very low yield was possibly due to the complete hydrolysis. The expected structural changes were positively reflected in the spectral details of the compound.



Scheme 47

Spectral data of *2*-(N-(*3,4*-dimethoxyphenethyl)-*2*-(*3,4*-dimethoxyphenyl)acetamido)acetic acid **31a:**



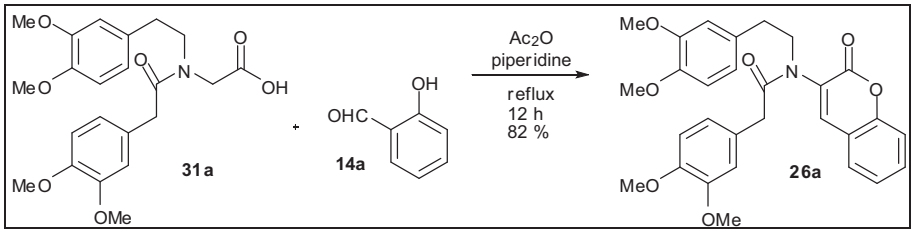
IR (neat): ν_{max} 3205, 3017, 2935, 1732, 1662, 1608, 1514, 1458, 1261, 1155 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 2.60 (t, *J* = 6.8 Hz, 2H), 3.42 (s, 2H), 3.48 (t, *J* = 7.2 Hz, 2H), 3.75 – 3.78 (m, 12H), 4.00 (s, 2H), 5.77 (br s, 1H), 6.52 – 6.73 (m, 6H) ppm.

^{13}C NMR & DEPT (100MHz, $CDCl_3$): δ 34.50 (CH_2), 39.85 (CH_2), 48.42 (CH_2), 51.60 (CH_2), 55.85 (CH_3), 55.88 (CH_3), 55.91 (CH_3), 55.94 (CH_3), 111.24 (CH), 111.48 (CH), 111.76 (CH), 111.97 (CH), 120.76 (2X CH), 126.82 (Cq), 130.27 (Cq), 147.94 (2X Cq), 149.12 (2X Cq), 172.56 (Cq), 172.84 (Cq) ppm.

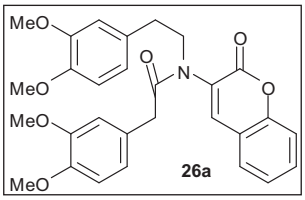
HRMS (*m/z)*: calculated for $C_{22}H_{27}NO_7Na$ $[M+Na]^+$ 440.1685; found 440.1681.

This acid **31a** was reacted with salicylaldehyde **14a** under Perkin reaction[39] condition using acetic anhydride and catalytic piperidine. (Scheme 48) After workup and flash purification in $CHCl_3$: MeOH (1:0.1), an analytically pure product was obtained in 82 % yield. The PMR spectra revealed protons indicating the formation of amide-coumarin **26a** and structure was further confirmed by agreeable CMR, DEPT and mass spectra.



Scheme 48

Spectral data of N-(*3,4*-dimethoxyphenethyl)-*2*-(*3,4*-dimethoxyphenyl)-N-(*2*-oxo-*2H*-chromen-*3*-yl)-acetamide **26a:**



IR (neat): ν_{max} 3017, 2935, 1710, 1662, 1608, 1514, 1458, 1261, 1155 cm^{-1}.

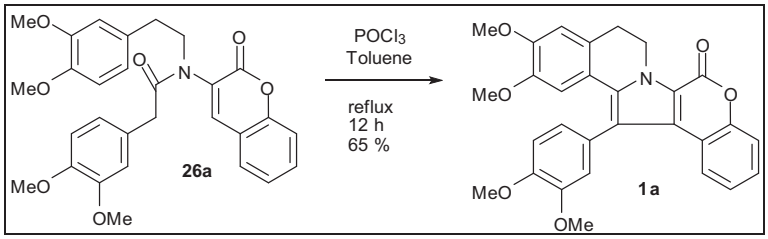
^1H NMR (400 MHz, $CDCl_3$): δ 2.75-2.85 (m, 2 H), 3.35-3.50 (m, 2 H), 3.59 (s, 2 H), 3.69 (s, 3 H), 3.72 (s, 6 H), 3.74 (s, 3 H), 6.49 (buried m, 2 H), 6.56-6.63 (m, 4 H), 6.69 (buried m, 1 H), 7.14 (d, *J* = 7.2 Hz, 1 H), 7.21 (t, *J* = 8.0 Hz, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR & DEPT (100MHz, $CDCl_3$): δ 33.69 (CH_2), 41.58 (CH_2), 49.45 (CH_2), 55.65 (CH_3), 55.83 (CH_3), 55.86 (CH_3), 55.88 (CH_3), 111.15 (CH), 111.19 (CH), 112.02 (CH), 112.16 (CH), 116.68 (CH), 118.30 (Cq), 120.95 (2X CH), 124.99 (CH), 127.28 (Cq), 128.17 (CH), 128.43 (Cq),

131.10 (Cq), 132.41 (CH), 141.74 (CH), 147.59 (Cq), 147.90 (Cq), 148.93 (Cq), 153.07 (Cq), 158.84 (Cq), 171.13 (Cq) ppm.

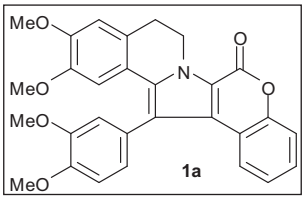
HRMS (*m/z)*: calculated for $C_{29}H_{29}NO_7Na$ $[M+Na]^+$: 526.1842; found 526.1844.

On achieving the long desired tertiary amide **26a**, it was reacted with $POCl_3$ in refluxing toluene expecting Bischler-Napieralski (B-N) reaction. After completion of reaction, the product was extracted with basic workup. (Scheme 49) Further purification and characterisation with PMR spectroscopy revealed 9 aromatic protons, two neighbouring methylene protons and four methoxy substituents. This data was identical with the reported data[40] for lamellarin scaffold **1a**. The CMR and DEPT also implied the lamellarin scaffold and further confirmation was obtained by agreement with HRMS values. This step followed a tandem Bischler-Napieralski reaction – Michael reaction – oxidation sequence.



Scheme 49

Spectral data of Lamellarin **1a:**



IR (KBr): ν_{max} 3025, 1700, 1525, 1480, 1430, 1345 cm^{-1}.

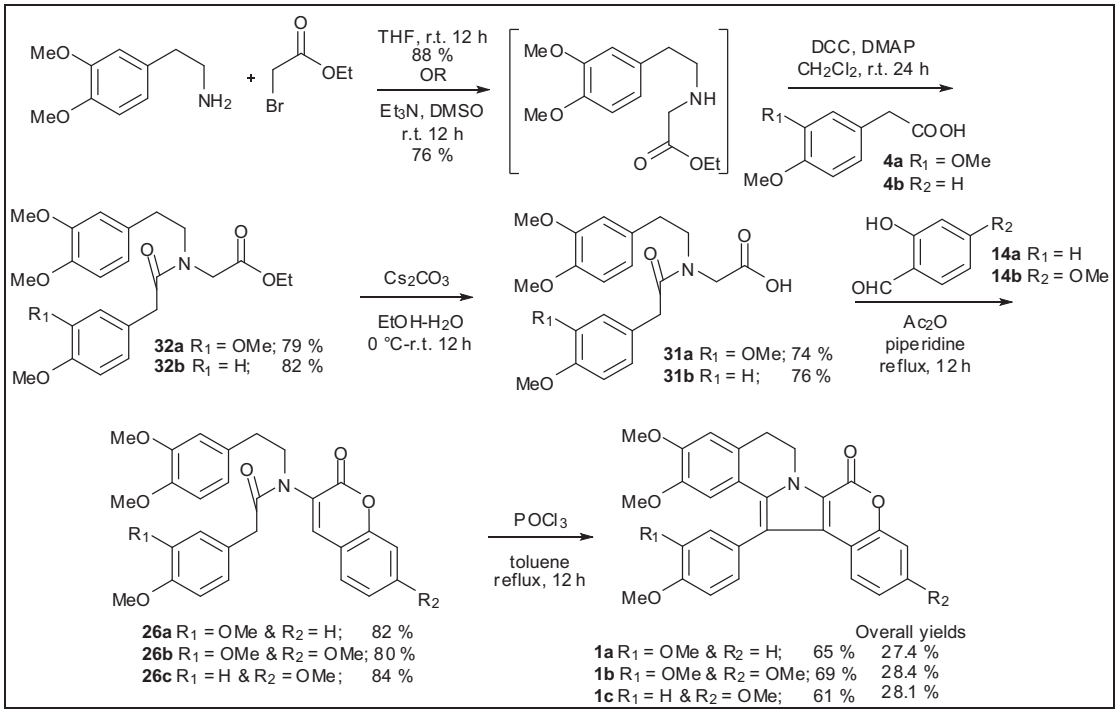
^1H NMR (400 MHz, $CDCl_3$): δ 3.05 (t, *J* = 6.8 Hz, 2 H), 3.29 (s, 3 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 3.91 (s, 3 H), 4.72-4.77 (m, 2 H), 6.57 (s, 1 H), 6.68 (s, 1 H), 6.93-6.95 (m, 2 H), 7.00 (s, 2 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H) ppm.

^{13}C NMR & DEPT (100MHz, $CDCl_3$): δ 27.67 (CH_2), 41.48 (CH_2), 54.17 (CH_3), 54.90 (CH_3), 55.07 (CH_3), 107.66 (CH), 109.91 (CH), 110.94 (CH), 112.68 (CH), 113.45 (Cq), 114.80 (Cq), 116.12 (CH), 117.28 (Cq), 118.97 (Cq), 122.26 (CH), 122.36 (CH), 122.76 (CH), 125.59 (Cq), 126.34 (CH), 126.51 (Cq), 126.79 (Cq), 135.10 (Cq), 146.43 (Cq), 147.88 (Cq), 147.95 (Cq), 148.77 (Cq), 150.25 (Cq), 154.28 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{29}H_{25}NO_6Na$ $[M+Na]^+$ 506.1580; found 506.1580.

As the methoxy substituents on isoquinoline ring were necessary for the Bischler-Napieralski reaction, this method was further explored to change substituents on aryl as well as coumarin ring of the Lamellarin scaffold (Scheme 50).

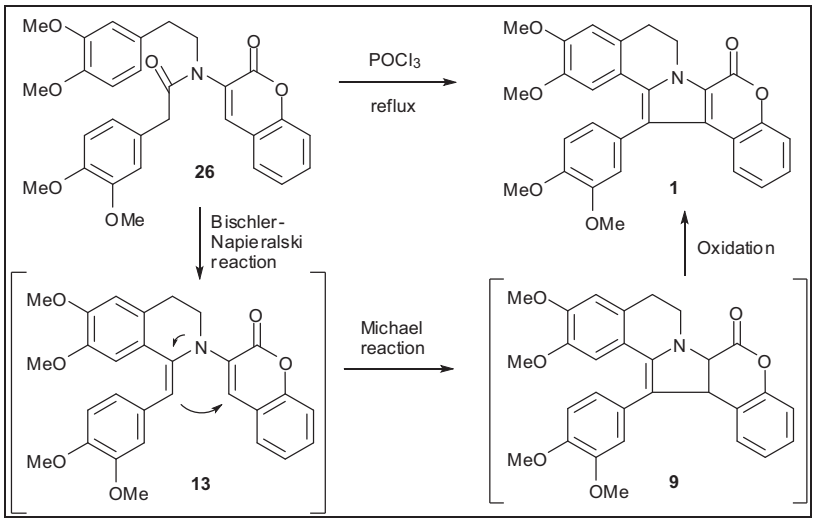
4-Methoxy-salicyalaldehyde **14b** in Perkin reaction gave the corresponding product **26b** in good yield which was further subjected to tandem Bischler-Napieralski reaction – Michael reaction – oxidation sequence and corresponding lamellarin derivative **1b** with methoxy substituent on coumarin ring was obtained in good yield.



Scheme 50

Substituents on aryl ring were changed by using *4*-methoxyphenylacetic acid **4b** for DCC coupling to give amide-ester **32b** which was hydrolysed to amide-acid **31b** and further subjected to Perkin reaction to give amide-coumarin **26c** followed by tandem reaction sequence to finally give lamellarin derivative **1c**.

On successfully preparing the lamellarin derivatives with Perkin reaction and tandem Bischler-Napieralski reaction – Michael reaction – oxidation sequence as key steps, a probable mechanism for the tandem process is described in scheme 51.



Scheme 51: Probable mechanism for the tandem process.

3.A.4: Conclusion

Lamellarin scaffold was successfully synthesised by a metal free route involving Perkin reaction and tandem Bischler-Napieralski reaction – Michael reaction – oxidation sequence.

Derivatives of lamellarin scaffold were synthesised by changing substituents on aryl as well as coumarin ring in good overall yields using this route.

Various one-pot C-N coupling reactions, condensation, cyclisation approaches were studied to develop concise route towards lamellarin scaffold. Interesting side products such as papaveraldine alkaloid and novel isoquinoline fused oxopyrrolone compounds were obtained in some cases.

Buchwald-Hartwig coupling reaction was studied extensively to prepare lamellarin scaffold.

Part B: Synthetic studies towards Ningalin A scaffold

3.B.1: Introduction

Ningalin A is a marine natural product isolated from ascidians of the genus *Didemnum* collected in western Australia near Ningaloo reef.[41] (Figure 2) Biogenetically it is believed to be derived from condensation of *3,4*-dihydroxyphenylalanine (DOPA). (Scheme 52) Ningalin A exhibit cytotoxic activity and multidrug resistance reversal (MDR) activity.

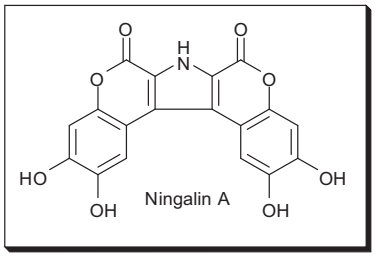
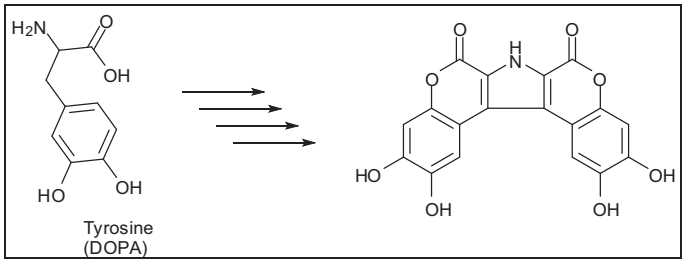


Figure 2: Ningalin A

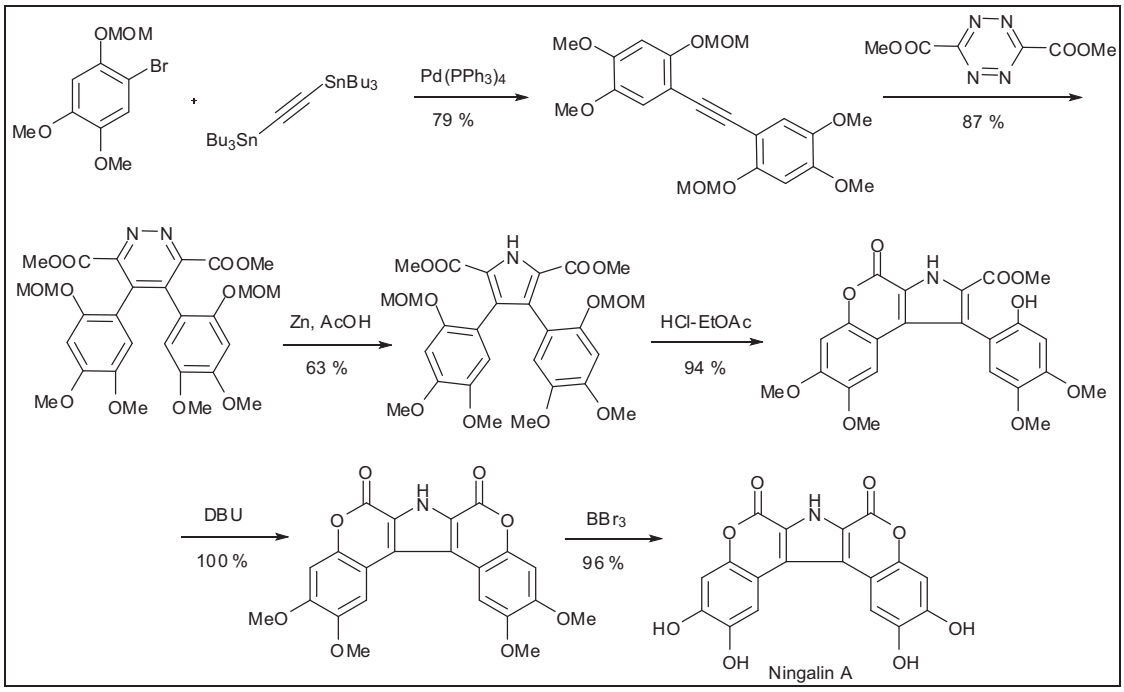


Scheme 52: Biogenetic Pathway

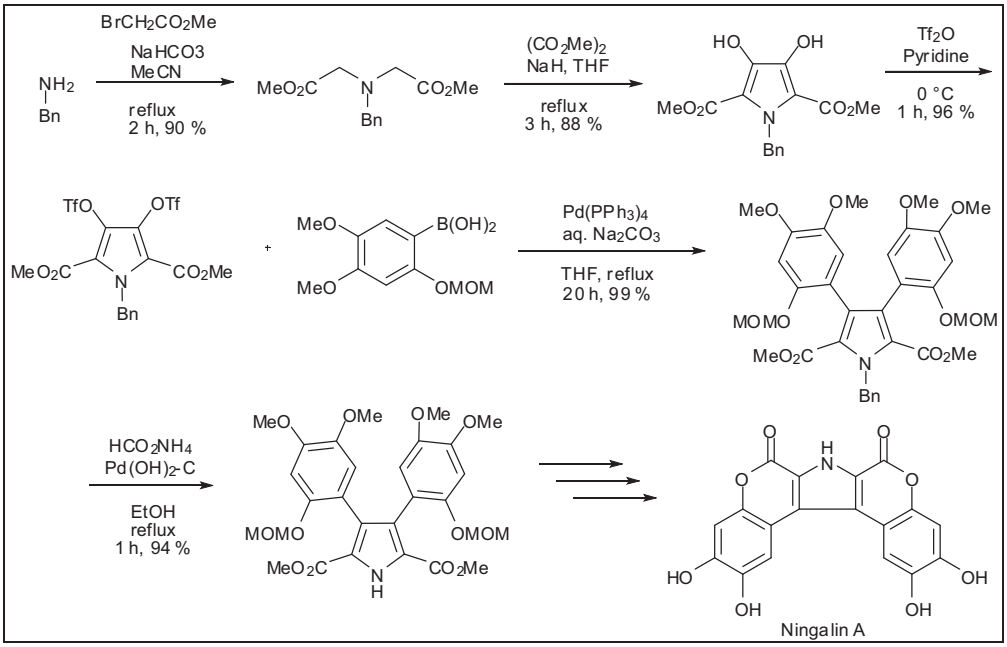
3.B.2: Literature review

This simple looking Ningalin A having symmetrical structure has so far only one synthetic route for its total synthesis and a formal synthesis.[42] This has been attributed to the steric congestion in its structure and the restricted rotational barriers of the two ortho aryl rings.

The first total synthesis of Ningalin A was reported by Boger's group[43] (Scheme 53). Their approach began with a double Stille coupling of substituted bromobenzene with bis(tributylstannyl)acetylene using $Pd(PPh_3)_4$ to give symmetrical diphenylacetylene. The Diels-Alder reaction of this electron-rich acetylene with electron-deficient carbomethoxytetrazine gave the desired 1,2-diazine. The reductive ring contraction of pyridazine to pyrrole was obtained by treatment with Zn in AcOH. Further deprotection of MOM group and SiO_2 column purification directly gave the pyrrole-monolactone. The second coumarin ring was formed by DBU to give tetramethyl ningalin A. The natural product, Ningalin A was obtained by exhaustive demethylation using BBr_3.



Scheme 53



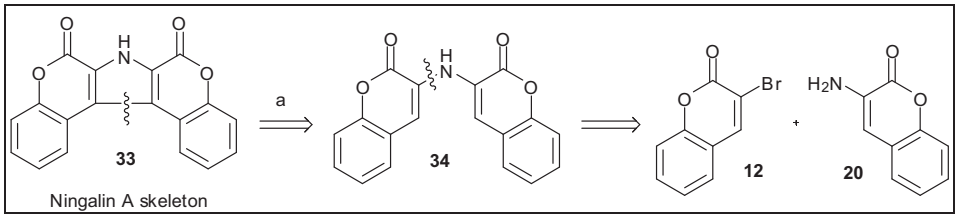
Scheme 54

M. Iwao's group[44] reported a general route for the synthesis of N-unsustituted 3,4-diarylpyrrole-2,5-dicarboxylate (Scheme 54) and applied it to disclose a formal synthesis of Ningalin A by preparing an intermediate compound of the above Scheme 1. Benzylamine was alkylated with methyl bromoacetate to N-benzyliminodiacetate. This on reaction with dimethyloxalate under Hinsberg condition using NaH as base gave dihydroxypyrrole. Further triflation with Tf_2O in pyridine gave bistriflate. Pd-catalysed cross-coupling reaction of this bis-triflate with arylboronic acid gave the arylated N-benzylpyrrole diester. Finally debenzylation using Pearlman's catalyst

($Pd(OH)_2$-C) and ammonium formate gave the required 3,4-diphenylpyrrole. This constituted a formal synthesis of Ningalin A.

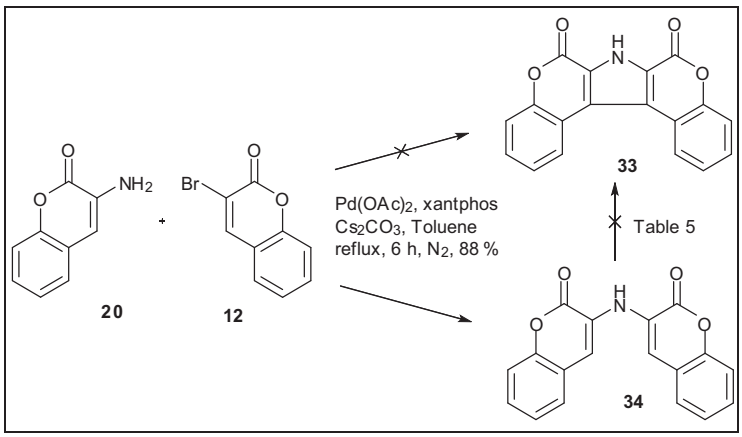
3.B.3: Results and Discussion

The Ningalin A having pyrrolo-coumarin structure is partly similar to the lamellarin skeleton. Thus we predicted the ningalin A skeleton **33** could be formed by a sequential Buchwald-Hartwig coupling reaction followed by an intramolecular dehydrogenative coupling reaction (Scheme 55).



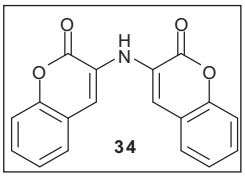
Scheme 55

Following this plan, 3-bromocoumarin **12** and 3-aminocoumarin **20** were subjected to Buchwald-Hartwig amination reaction using $Pd(OAc)_2$/xantphos as catalyst and Cs_2CO_3 as base (Scheme 56). The reaction showed complete consumption of 3-bromocoumarin **12** within 6 h and product was obtained as light brown solid. The NMR spectra of the product revealed an uncyclised symmetrical structure **34**. This was further confirmed by its HRMS value.



Scheme 56

Spectral data of *3,3'*-azanediylbis(*2H*-chromen-*2*-one) **34:**



IR (KBr): ν_{max} 3329, 3084, 3042, 1726, 1630, 1535, 1458, 1358, 1217, 1095 cm^{-1}.

^1H NMR (400MHz, DMSO-d_6,): δ 7.38 - 7.46 (m, 6H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.86 (s, 2H), 7.99 (s, 1H) ppm.

^{13}C NMR (400MHz, DMSO-d_6): δ 115.67 (CH), 116.37 (CH), 120.67 (Cq), 125.61 (CH), 126.37 (Cq), 127.51 (CH), 129.01 (CH), 149.00 (Cq), 159.13 (Cq) ppm.

LCMS (*m/z*): $[M-H]^+$ 304.

HRMS (*m/z)*: calculated for $C_{18}H_{11}NO_4Na$ $[M+H]^+$: 328.0586; found 328.0585

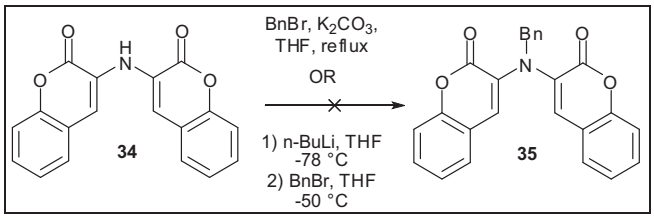
The Buchwald-Hartwig condition gave an uncyclised symmetrical biscoumaryl amine **34** and no cyclisation under this condition was observed even after prolonged heating. Various attempts were made by varying the conditions, reagents, catalysts, base, solvents, etc. (Table 5) But all the tried conditions failed to yield us desired product **33**.[45-60]

Table 5: Various conditions tried in scheme 56.

Entry	Reaction Condition	Observation
1	$Pd(OAc)_2$, Xantphos, Cs_2CO_3, dioxane, reflux, 24 h	65 % dicoumarylamine
2	$Pd(Oac)_2$, Xantphos, Cs_2CO_3, toluene, reflux, 24 h	80 % dicoumarylamine
3	$Pd(OAc)_2$, K_2CO_3, PivOH, reflux, 18 h	No reaction, 86 % reactant recovered
4	$Pd(OAc)_2$, $Cu(OAc)_2$, dioxane, reflux, 24 h	No reaction
5	$Pd(OAc)_2$, $Cu(OAc)_2$, DMF, 100 ºC, 12 h	Reactant decomposed 15 % reactant recovered
6	$Pd(OAc)_2$, $Cu(OAc)_2$, DMF, MW, 100 ºC, 70 min	No reaction
7	$Pd(OAc)_2$, $Cu(Oac)_2$, PivOH, reflux 18 h	No reaction, reactant recovered
8	$Pd(OAc)_2$, TFA, reflux, O_2, 24 h	No reaction
9	$PdCl_2$, $CuCl_2$, DMF, O_2, 100 ºC, 40 h	No reaction
10	$Pd(OAc)_2$, $PhI(OAc)_2$, toluene, reflux, 48 h	No reaction
11	$Pd(OAc)_2$, MnO_2, dioxane, reflux, 24 h	No reaction
12	Pd/C, xylene, reflux, 24 h, air	No reaction
13	AgOAc, NaOAc, dioxane, reflux, 60 h	No reaction
14	$Cu(OTf)_2$, DMF, 100 ºC, 24 h	No reaction
15	NBS, dioxane, reflux, 24 h	No reaction, 45 % reactant recovered
16	i) Br_2, $CHCl_3$, -30 ºC-r.t.; ii) Cs_2CO_3, iii) $Pd(OAc)_2$/xantphos, dioxane reflux, 12 h	No reaction
17	$FeCl_3$, THF, reflux, 24 h	No reaction
18	K-OtBu, DMF, reflux	No reaction
19	SmI_2, THF/dioxane, reflux, 24 h	No reaction,

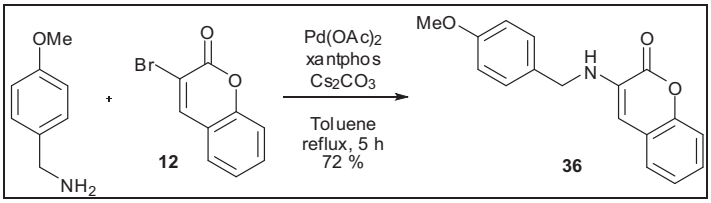
20	Mg/I_2, dioxane, reflux, 48 h	No reaction
21	I_2, aq. TBHP, DMF	No reaction
22	I_2, TBHP, decane, r.t. 6 h	Reactant decomposed
23	I_2, MeCN, reflux, 48 h	No reaction
24	IBX, THF-DMSO, 90 ºC, sealed tube, 48 h,	Reactant decomposed
25	DDQ, dioxane, reflux, 24 h	No reaction
26	CAN, EtOH, reflux, 24 h	No reaction

Speculating the interference of NH in this cyclisation, attempts were made to protect N with benzyl group. Benzylation with K_2CO_3 and benzyl bromide did not proceed, hence tried with *n*-BuLi but this reaction too failed as the reactant **34** was decomposed (Scheme 57).



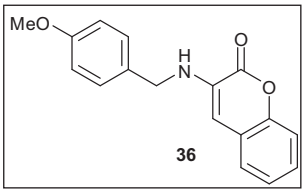
Scheme 57

Alternatively to prepare N-protected biscoumaryl amine, we first reacted *3*-bromocoumarin **12** and *4*-methoxybenzyl amine to give corresponding C-N cross coupling product **36** as yellow oil in 72 % yield (Scheme 58).



Scheme 58

Spectral data of *3*-(*4*-methoxybenzylamino)-*2H*-chromen-*2*-one **36:**



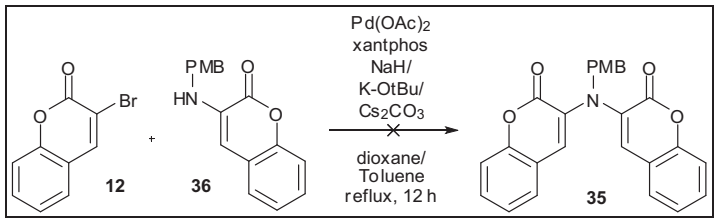
IR (KBr): ν_{max} 3387, 2934, 2849, 1726, 1657, 1597, 1512, 1450, 1258, 1034 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 3.73 (s, 3H), 4.52 (d, *J* = 5.2 Hz, 2H), 6.81 – 6.84 (m, 3H), 7.21 – 7.25 (m, 3H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 7.58 (d, *J* = 7.2 Hz, 2H) ppm.

^{13}C NMR (400MHz, $CDCl_3$): δ 42.93 (CH_2), 55.34 (CH_3), 110.59 (CH), 111.71 (CH), 114.21 (CH), 122.75 (CH), 123.71 (CH), 126.90 (CH), 127.62 (Cq), 129.43 (CH), 129.81 (Cq), 148.63 (Cq), 154.72 (Cq), 158.70 (Cq), 159.23 (Cq) ppm.

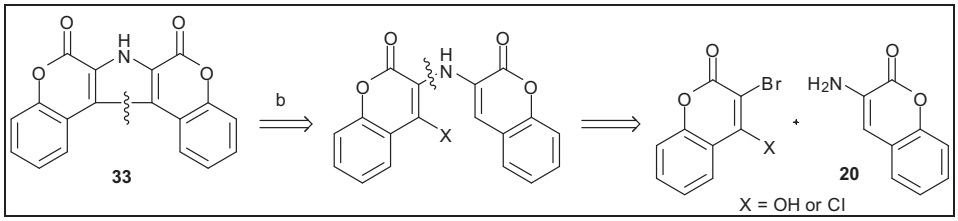
HRMS (*m/z)*: calculated for $C_{17}H_{15}NO_3Na$ $[M+Na]^+$ 304.0950; found 304.0958.

We then tried second Buchwald-Hartwig coupling reaction using *3*-bromocoumarin **12** and N-PMB protected aminocoumarin **36** under same conditions, but this attempt did not yield us any product and debrominated coumarin was recovered (Scheme 59).



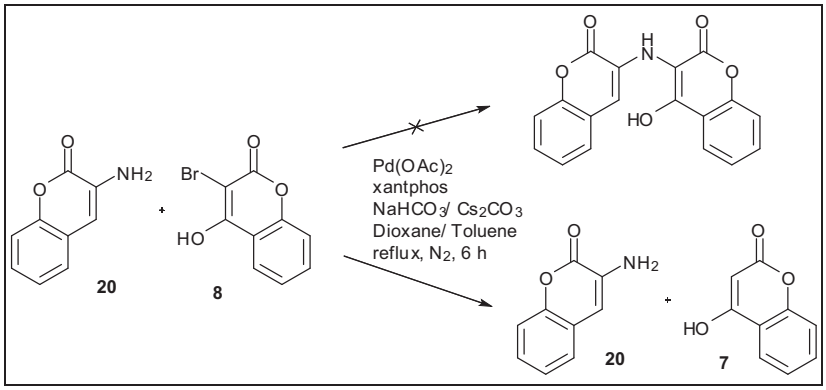
Scheme 59

Further a different approach was planned using 3-bromo-4-hydroxycoumarin **8** for Buchwald-Hartwig reaction followed by dehydration as depicted in retro-synthetic scheme given below (Scheme 60).



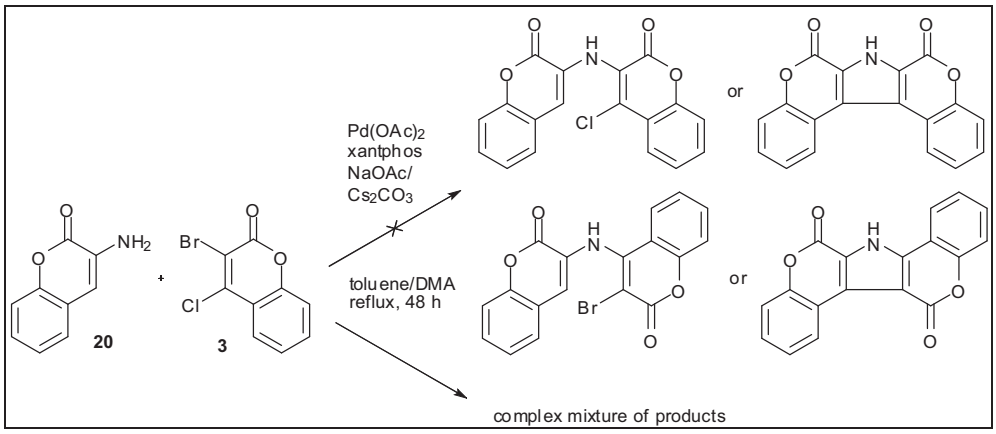
Scheme 60

3-Bromo-*4*-hydroxycoumarin **8** and *3*-aminocoumarin **20** were reacted under Buchwald-Hartwig coupling condition using Cs_2CO_3 as base (Scheme 61). This reaction gave *4*-hydroxycoumarin **7** as debrominated product along with unreacted *3*-aminocoumarin **20**. Using mild base such as $NaHCO_3$ did not solve the problem of debromination.



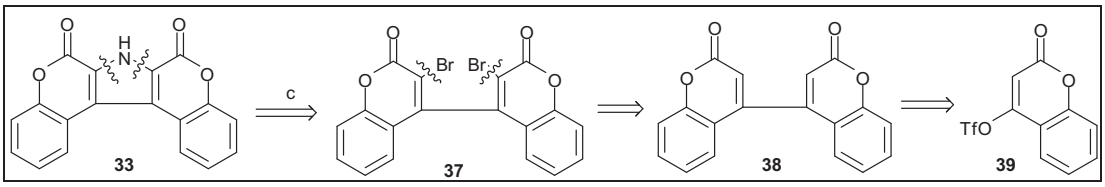
Scheme 61

Alternatively, *3*-bromo-*4*-chlorocoumarin could be used for a sequential Buchwald-Hartwig coupling reaction followed by Heck reaction strategy. The previously prepared *3*-bromo-*4*-chlorocoumarin **3** was reacted with *3*-aminocoumarin **20** under the same Buchwald-Hartwig amination reaction[22] using $Pd(OAc)_2$/xantphos catalyst system with CS_2CO_3 as base (Scheme 62). This reaction in principle could give us many products as coupling reaction as well as Michael reaction was feasible. After 2 hours of reaction under N_2, the coumarin reactant was completely consumed and TLC showed formation of many products. On continuing the reaction with excess amount of $Pd(OAc)_2$ did not give us any improvement and the reaction mixture persisted as it was.



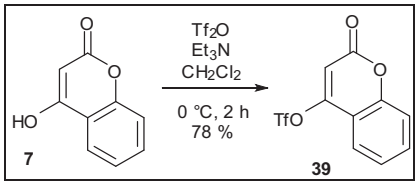
Scheme 62

As the attempts to construct pyrrole ring in ningalin A skeleton **33** via connecting C-4 positions of coumarin were unsuccessful, we then visualised a route to form the pyrrole via introduction of N in the C-3 positions of bis-coumarin **38** which could be obtained by homocoupling of *4*-OTf-coumarin **39** (Scheme 63).



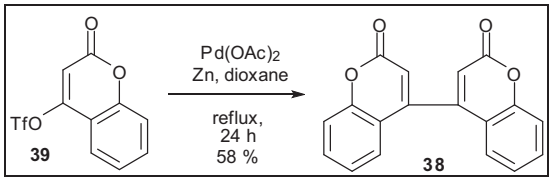
Scheme 63

The *4*-hydrocoumarin **7** was converted to corresponding *O*-triflate following reported procedure[61] with triflic anhydride in triethylamine (Scheme 64). The product **39** was obtained as colourless viscous oil in 78 % yield.



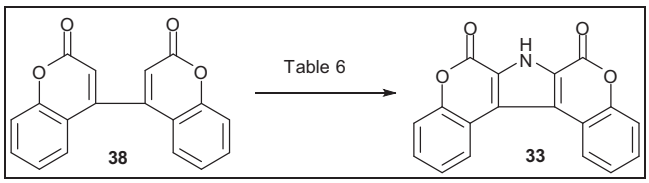
Scheme 64

4-OTf-coumarin **39** was treated with $Pd(OAc)_2$ and Zinc in refluxing dioxane and the expected bis-coumarin[62] **38** was obtained as colourless solid in 58 % (Scheme 65).



Scheme 65

The bis-coumarin **38** was reacted with 2.2 equiv. of bromine in $CHCl_3$ at 0 °C for 1 h and immediately reacted with aq. NH_3 followed by $Pd(OAc)_2$/ xantphos catalyst system in aq. NH_3, but this reaction gave charred reaction mixture (Scheme 66, Table 6). Bromination was again tried using NBS, but this did not yield any change in bis-coumarin reactant at r.t. and heating the bis-coumarin **38** with NBS gave a complex mixture of products. The reaction with Br_2 was repeated with *p*-methoxybenzyl amine along with Cs_2CO_3 as base. But this reaction also gave a complex mixture of products.



Scheme 66

Table 6: Attempts with scheme 66.

Entry	Bromination	Amination	Observation
1	Br_2, $CHCl_3$ 0 °C	$Pd(OAc)_2$, PPh_3, aq. NH_3	Reactant decomposed
2	NBS, $CHCl_3$, r.t.	$Pd(OAc)_2$, PPh_3, aq. NH_3	No reaction
3	NBS, Dioxane, reflux	-	Complex mixture of products
4	Br_2, $CHCl_3$ 0 °C	$Pd(OAc)_2$, PPh_3, PMB-amine	Reactant decomposed

All the unsuccessful attempts at the final stages of constructing pyrrole ring revealed the problems of structural constraints and restricted free rotation of the coumarin rings.

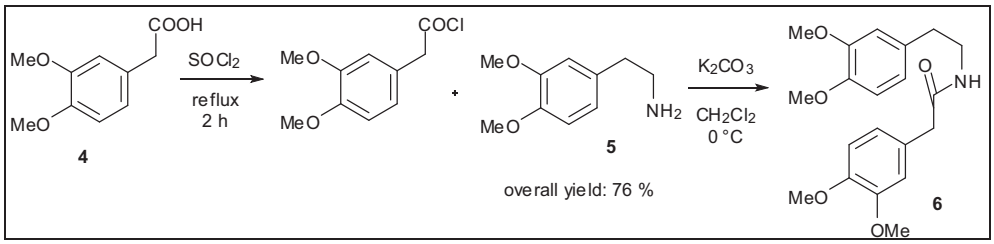
3.B.4: Conclusion

Synthesis of Ningalin A scaffold was attempted by various routes. Construction of pyrrole ring of required scaffold was unsuccessful. However, Buchwald-Hartwig amination reaction was successfully employed to prepare the part components of the Ningalin A scaffold.

3.5: Experimental Section

3.5.1: *N*-(*3,4*-Dimethoxyphenethyl)-*2*-(*3,4*-dimethoxyphenyl)acetamide 6

a) $SOCl_2$ method:



Homoveratric acid **4** (5 g, 25.5 mmol) was added to freshly distilled thionyl chloride (15 mL) and refluxed at 100 °C for 3 h. Excess thionyl chloride was removed from reaction mixture by distillation and dry $CHCl_3$ (10 mL) was added. This solution of acid chloride was added dropwise with stirring to an ice cold solution of homoveratryl amine **5** (4.16 g, 23.0 mmol) and K_2CO_3 (5.53 g 40 mmol) in dry $CHCl_3$ (20 mL). This mixture was stirred for 12 h from 0 °C to r.t. Solvent was removed under vacuum and distilled water (50 mL) was added. The solid thus obtained was filtered and washed with water (20 mL X 3) and dried under vacuum. Analytically pure product **6** was obtained as white amorphous solid in 76 % (6.28 g) yield.

White amorphous solid, m.p.: 124-125 °C. [lit.: m.p.: 124-125 °C][19]

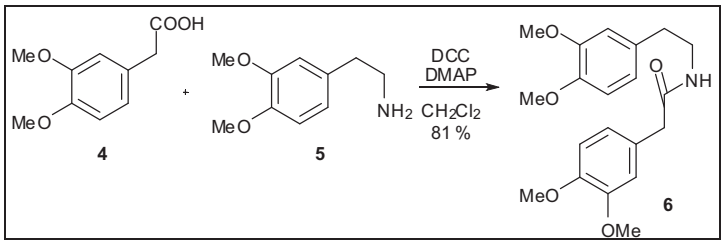
R_f: 0.48 (CH_2Cl_2:MeOH, 1:0.01)

IR (KBr): ν_{max} 3325, 2960, 1641, 1589, 1517, 1028 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 2.7 (t, J=6 Hz, 2H), 3.45 (m, 4H), 3.87 (m, 12H), 5.42 (br s, 1H), 6.52 (d, J=8 Hz, 1H), 6.63 (s, 1H), 6.74 (m, 2H), 6.82 (m, 2H) ppm.

^{13}C NMR & DEPT (100MHz, $CDCl_3$): δ 34.9 (CH_2), 40.7 (CH_2), 43.4 (CH_2), 55.8 (3x CH_3), 111.0 (CH), 111.4 (CH), 111.6 (CH), 112.3 (CH), 120.5 (CH), 121.6 (CH), 127.1 (Cq), 131.0 (Cq), 147.6 (Cq), 148.2 (Cq), 148.9 (Cq), 149.2 (Cq), 171.3 (Cq) ppm.

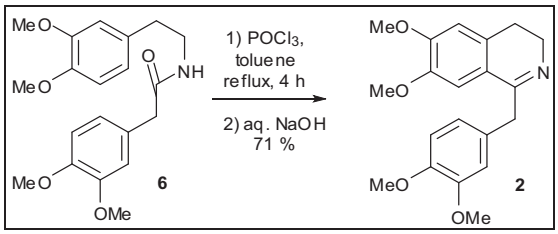
b) DCC coupling method:



Homoveratric acid **4** (5 g, 25.5 mmol), homoveratryl amine **5** (4.62 g, 25.5 mmol) and DMAP (0.05 g) were added in dry CH_2Cl_2 (25 mL) and cooled to 0 °C. To this mixture, DCC (6.19 g, 30 mmol) was added and stirred from 0 °C to r.t. for 24 h. Water (1 mL) and dioxane (2 mL) was

added to this and stirred for 2 h. Solvent was removed under vacuum, CH_2Cl_2 (25 mL) was added, cooled to 0 °C and filtered. The filtrate was again cooled to 0 °C and filtered. The solvent was removed under vacuum and product **6** was obtained as white solid in 81 % (7.41 g) yield.

3.5.2: *1*-(*3,4*-Dimethoxybenzyl)-*6,7*-dimethoxy-*3,4*-dihydroisoquinoline 2



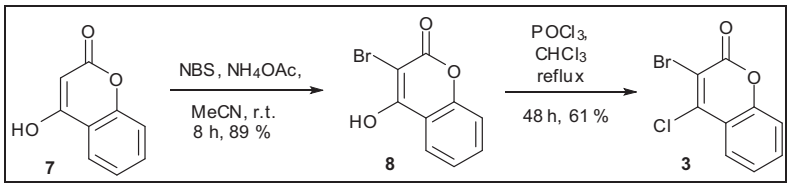
Amide **6** (7.18 g, 20 mmol) was dissolved in dry toluene (10 mL) and freshly distilled $POCl_3$ (5 mL) was added slowly and refluxed for 4 h. The reaction mixture was then poured in ice and basified by cooled aq. NaOH solution (10 N) until pH 14. Product **2** was then extracted in CH_2Cl_2 (20 mL X 2), dried by passing through anhy. Na_2SO_4 and concentrated under vacuum to give 71 % (4.84 g) yield.

Viscous oil.[20]

R_f: 0.39 (CH_2Cl_2:MeOH, 1:0.02)

^{1}H NMR (400MHz, $CDCl_3$): δ 2.96 (t, *J* = 8.0 Hz, 2H), 3.76 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.86 – 3.88 (m, 2H), 3.91 (s, 3H), 4.36 (s, 2H), 6.70 – 6.72 (m, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.95 (s, 1H), 7.25 (s, 1H) ppm.

3.5.3: *3*-Bromo-*4*-chlorocoumarin 3



4-Hydroxycoumarin **7** (3.24 g, 20 mmol), NBS (4.45 g, 25 mmol) and NH_4OAc (0.15 g, 2 mmol) were mixed in dry MeCN (20 mL) and stirred at r.t. for 8 h. Solvent was then removed under vacuum and water (25 mL) was added and product **8** was filtered and dried under vacuum to give 89 % (4.27 g) yield.

3-Bromo-*4*-hydroxycoumarin 8

Colourless solid, m.p.: 190-192 °C. [lit.: m.p.: 192-194 °C][21]

R_f: 0.37 (CH_2Cl_2:MeOH, 1:0.01)

IR (KBr): ν_{max} 3200, 1701, 1610, 1553, 1207, 1196, 995 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 (br s, 2H), 7.66 (br s, 1H), 7.94 (br s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ 88.84 (Cq), 115.97 (Cq), 116.36 (CH), 123.42 (CH), 124.34 (CH), 132.74 (CH), 151.61 (Cq), 158.60 (Cq), 162.52 (Cq) ppm.

3-Bromo-4-hydroxycoumarin **8** (3.60 g, 15 mmol) was mixed in $CHCl_3$ (20 mL) and $POCl_3$ (5 mL) was slowly added and refluxed for 48 h. This solution was then poured in ice and organic layer was separated, dried by passing through anhy. Na_2SO_4 and concentrated under vacuum. Flash chromatography purification (CH_2Cl_2) gave pure product **3** in 61 % (2.36 g) yield.

***3*-Bromo-*4*-chlorocoumarin 3**

Pale yellow solid, m.p.: 160-162 °C. [lit.: m.p.: 162 °C][62]

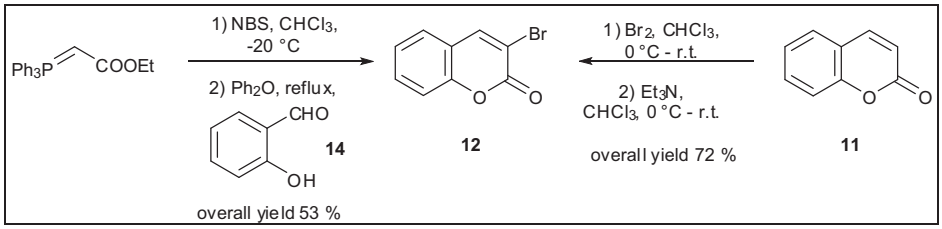
R_f: 0.49 (CH_2Cl_2:hexanes, 1:2)

IR (KBr): ν_{max} 3086, 1724, 1605, 1593, 1545, 1479, 1448, 1298 cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.28 - 7.34 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H) ppm.

^{13}C NMR & DEPT (100MHz, $CDCl_3$): δ 113.08 (Cq), 116.88 (CH), 118.21 (Cq), 125.42 (CH), 125.97 (CH), 133.22 (CH), 148.85 (Cq), 151.24 (Cq), 156.05 (Cq) ppm.

3.5.4: *3*-Bromo-*2H*-chromen-*2*-one 12



(Carbethoxymethylene)triphenylphosphorane (0.35 g, 1.0 mmol) was dissolved in dry $CHCl_3$ (20 mL) and cooled to -20 °C. NBS (0.23 g, 1.3 mmol) was added to this solution and stirred for 1 h, Further solvent was removed under vaccum and salicyaldehyde **14** (0.14 g, 1.1 mmol) and dry Ph_2O was added and mixture was refluxed for 6 h. Column purification (CH_2Cl_2:hexanes, 1:1) gave the product **12** in 53 % yield (0.12 g).

Off white solid, m.p.: 106-108 °C. [lit.: m.p.: 108-110 °C][24]

R_f: 0.47 (CH_2Cl_2:hexanes, 1:1)

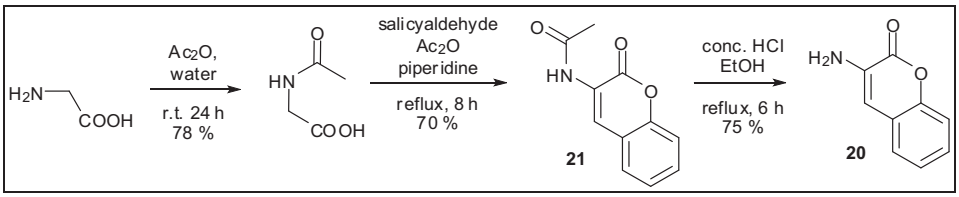
IR (KBr): ν_{max} 3051, 1728, 1606, 1276, 1246, 956 cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.32 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 8.12 (s, 1H) ppm.

Coumarin **11** (5 g, 34 mmol) was dissolved in dry $CHCl_3$ (20 mL) and cooled to 0 °C and bromine (2.1 mL, 41 mmol) was added dropwise with stirring. This mixture was stirred for 1 h from 0 °C to

r.t. and again cooled to 0 °C. a solution of Et_3N (8.5 mL, 60 mmol) in dry $CHCl_3$ (10 mL) was added dropwise maintaining 0 °C during the addition and then stirred for 12 h from 0 °C to r.t. water (50 mL) was added and product was extracted in $CHCl_3$. Further column purification (EtOAc/hexanes, 1:10) gave the product **12** in 72 % yield (5.53 g).

3.5.5: *3*-Amino-*2H*-chromen-*2*-one 20



Acetic anhydride (19 mL, 200 mmol) was added to a solution of glycine (5.0 g, 67 mmol) in water (75 ml). The reaction mixture was stirred for 20 min at room temperature, and cooled in a refrigerator overnight. Acetylglycine separated as crystals was filtered, washed with cold water and dried at 100 °C. Product was obtained in 78 % (6.09 g) yield as white crystalline solid; m.p.: 206-208 °C [lit.: m.p.: 206-207 °C][27]

A mixture of acetylglycine (5.0 g, 43 mmol), salicylaldehyde (12.2 g, 100 mmol) and piperidine (1 drop) was heated in acetic anhydride (5.6 mL, 60 mmol) at 130-140 °C for 6 h. The reaction mixture was cooled, diluted with water (10 mL) and further refluxed for 30 min. The gummy mass thus obtained after removal of water under vacuum was repeatedly washed with ether (10 mL X 3) to remove adhering traces of piperidine and acetylglycine. The crude product when recrystallized from EtOH furnished the product **21** in 70 % (6.07) yield.

***N*-(*2*-Oxo-*2H*-chromen-*3*-yl)acetamide 21**

Orange solid, m.p.: 200-202 °C. [lit.: m.p.: 200-203 °C][27]

R_f: 0.68 (CH_2Cl_2)

IR (KBr): ν_{max} 3329, 3078, 3041, 1707, 1678, 1605, 766 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 2.25 (s, 3H), 7.28 – 7.33 (m, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 8.10 (br s, 1H), 8.68 (s, 1H) ppm.

^{13}C NMR (100MHz, $CDCl_3$): δ 24.74 (CH_3), 116.36 (CH), 119.83 (Cq), 123.29 (CH), 123.97 (Cq), 125.19 (CH), 127.82 (CH), 129.66 (CH), 149.88 (Cq), 158.79 (Cq), 169.40 (Cq) ppm.

3-acetylaminocoumarin **21** (5 g, 24.6 mmol) in hot ethanol (25 mL) with conc. HCl (5 mL) was refluxed for 2 h. The reaction mixture was cooled diluted with water (25 mL), neutralized with Sat. aq. sodium bicarbonate (100 mL) and kept overnight in fridge. The product thus separated was filtered. Further purification by recrystallization from EtOH gave the product **20** in 75 % (2.97 g) yield.

***3*-Amino-*2H*-chromen-*2*-one 20**

Golden solid, m.p.: 136-138 °C. [lit.: m.p.: 135-139 °C][27,28]

R_f: 0.39 (CH_2Cl_2)

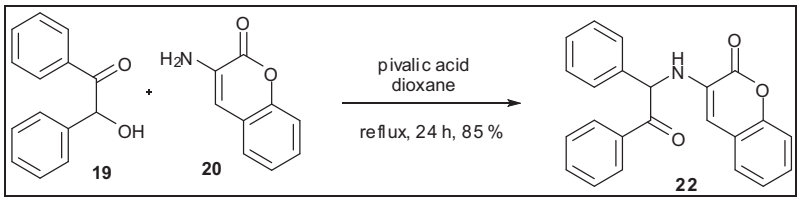
IR (KBr): ν_{max} 3427, 3327, 3065, 1709, 1640, 1589, 1456, 1333, 1173 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 4.26 (br s, 2H), 6.71 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.31 (m, 3H) ppm.

^{13}C NMR (100MHz, $CDCl_3$): δ 110.90 (CH), 116.17 (CH), 121.17 (Cq), 124.63 (CH), 125.08 (CH), 126.64 (CH), 131.98 (Cq), 149.04 (Cq), 159.44 (Cq) ppm.

Elemental analysis: $C_9H_7NO_2$: calculated % C, 67.07; H, 4.38; N, 8.69; found % C 67.19, H 4.46, N 8.08.

3.5.6: *3*-(*2*-Oxo-*1,2*-diphenylethylamino)-*2H*-chromen-*2*-one 22

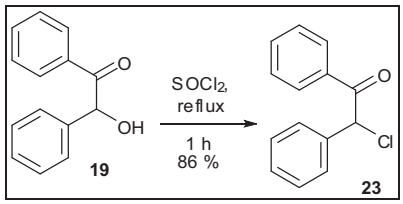


Benzoin **19** (1.06 g, 5.0 mmol) and 3-aminocoumarin **20** (0.8 g, 5 mmol) were dissolved in dry dioxane (10 mL) and pivalic acid (1 mL) and refluxed for 24 h. Solvent was removed under vacuum and sat. aq. Na_2CO_3 solution (10 mL) was added and product was extracted in $CHCl_3$, dried by passing through anhy. Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography using CH_2Cl_2. The product **22** was obtained in 85 % (1.51 g) yield.

Pale yellow solid, m.p.: 196-198 °C.

R_f: 0.41 (CH_2Cl_2:EtOAc, 3:1)

3.5.7: *2*-Chloro-*1,2*-diphenylethanone 23



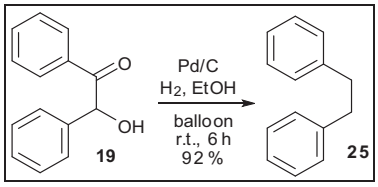
Benzoin **19** (2.12 g, 10 mmol) was mixed in freshly distilled $SOCl_2$ (3 mL) and refluxed for 1 h. Excess $SOCl_2$ was removed by vacuum distillation and $CHCl_3$ was added. Organic layer was washed with water, dried over anhy. Na_2SO_4 and concentrated under vacuum to give product **23** in 86 % (1.98 g) yield.

Pale yellow solid, m.p.: 56-58 °C. [lit.: m.p.: 58-60 °C][29]

R_f: 0.51 (CH_2Cl_2:hexanes, 1:1)

IR (KBr): ν_{max} 3063, 2955, 2868, 1693, 1674, 1595, 1448, 1211 cm^{-1}.

3.5.8: Dihydrostilbene 25



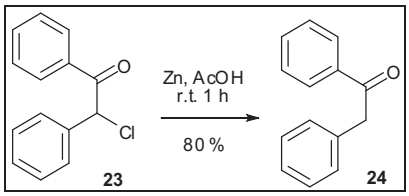
Benzoin **19** (2.12 g, 10 mmol) and Pd/C (5 %, 0.1 g) were mixed in EtOH (10 mL) and stirred at r.t. under H_2 (balloon pressure) for 6 h. The suspension was then filtered and solvent was removed under vacuum to give product **25** in 92 % (1.67 g) yield.

Pale yellow solid, m.p.: 46-48 °C. [lit.: m.p.: 45-47 °C][30]

R_f: 0.56 (CH_2Cl_2:hexanes, 1:10)

IR (KBr): ν_{max} 3024, 2918, 1944, 1873, 1807, 1751, 1599, 1491, 1450, 1026 cm^{-1}.

3.5.9: *1,2*-Diphenylethanone 24



Benzoin chloride **23** (1.15 g, 5 mmol) was mixed in AcOH (10 mL) and activated Zn powder (1.30 g, 20 mmol) was added and stirred at r.t. for 1 h. This suspension was then poured in ice. Product was extracted in $CHCl_3$, washed with water, dried by passing through anhy. Na_2SO_4 and concentrated under vacuum to give product **24** as colourless solid in 80 % (0.78 g) yield.

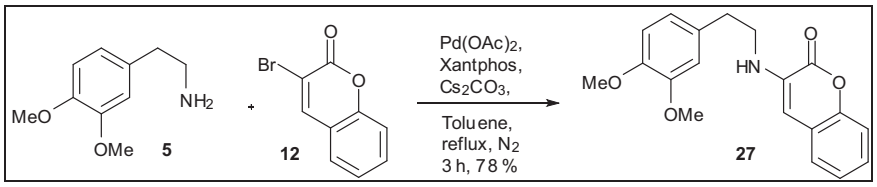
Colourless solid, m.p.: 48-50 °C. [lit.: m.p.: 50-52 °C][31]

R_f: 0.50 (CH_2Cl_2)

IR (KBr): ν_{max} 3059, 3026, 1691, 1680, 1597, 1495, 1447 cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ 4.32 (s, 2H), 7.28 - 7.30 (m, 3H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 2H) ppm.

3.5.10: *3*-(*3,4*-Dimethoxyphenethylamino)-*2H*-chromen-*2*-one 27

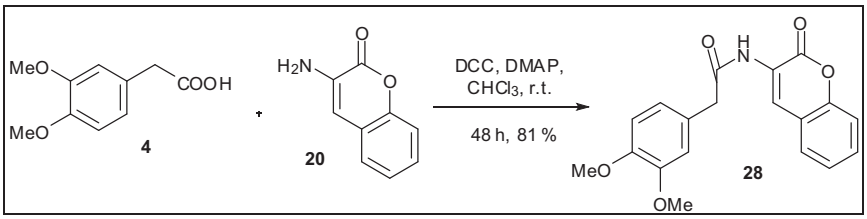


Homoveratryl amine **5** (2.17 g, 12 mmol), 3-bromocoumarin **12** (2.24 g, 10 mmol), $Pd(OAc)_2$ (0.22 g, 1 mmol), xantphos (0.58 g, 1 mmol), and Cs_2CO_3 (4.89 g, 15 mmol) were added to a sealed tube and dry toluene (5 mL) was added. This mixture was flushed with N_2 gas and heated at 120 °C with stirring for 3 h. CH_2Cl_2 (10 mL) was then added and suspension was filtered through ordinary filter paper and solvent was removed under vacuum. The crude product was purified by flash chromatography (CH_2Cl_2). The product **27** was obtained in 78 % (2.54 g) yield.

Pale yellow solid, m.p.: 55-56 °C.

R_f: 0.43 (CH_2Cl_2:hexanes, 4:1)

3.5.11: *2*-(*3,4*-Dimethoxyphenyl)-*N*-(*2*-oxo-*2H*-chromen-*3*-yl)acetamide 28

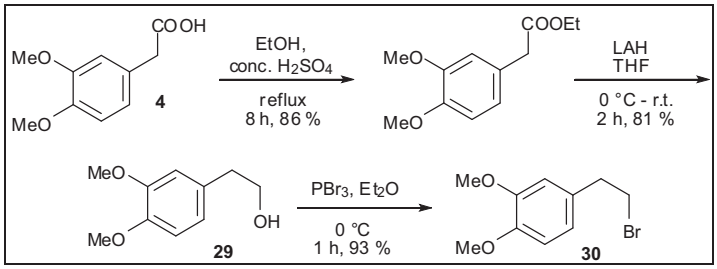


Homoveratric acid **4** (2.35 g, 12 mmol), 3-aminocoumarin **20** (1.61 g, 10 mmol) and DMAP (0.05 g) were dissolved in dry $CHCl_3$ (25 mL) and cooled to 0 °C. DCC (3.10 g, 15 mmol) was added and mixture was stirred at r.t. under dry condition for 48 h. Further solvent was removed under vacuum and CH_2Cl_2 was added and cooled to 0 °C. Filtration and removal of solvent gave the crude product which on purification by flash chromatography (CH_2Cl_2:EtOAc, 4:1) gave the product **28** in 81 % (2.75 g) yield.

Pale yellow amorphous solid, m.p.: 95-97 °C.

R_f: 0.49 (CH_2Cl_2)

3.5.12: *4*-(*2*-Bromoethyl)-*1,2*-dimethoxybenzene 30



Homoveratric acid **4** (3.92 g, 20 mmol) was dissolved in absolute EtOH (20 mL) with conc. H_2SO_4 (1 drop) and refluxed for 8 h. Solvent was then removed under vacuum and Et_2O (50 mL) was added. Organic layer was washed with aqueous sat. $NaHCO_3$ (10 mL X 3) brine and dried over Na_2SO_4. Removal of solvent under vacuum gave the analytically pure ester as colourless oil[63a] in 86 % (3.85 g) yield. This ethyl ester was as such mixed in dry THF (10 mL) and cooled to 0 °C. LAH (0.76 g, 20 mmol) was added cautiously and stirred at 0 °C – r.t. for 2 h. The reaction was quenched in aq. saturated NH_4Cl (20 mL). Product was extracted in Et_2O (20 mL X 2), washed with brine and dried over Na_2SO_4. Removal of solvent under vacuum gave the analytically pure alcohol **29** in 81 % (2.54 g) yield.

***2*-(*3,4*-Dimethoxyphenyl)ethanol 29**

Colourless oil.[63b]

R_f: 0.43 (EtOAc:hexanes, 2:3)

IR (neat): ν_{max} 3477, 2936, 2835, 1516, 1261, 1028 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 2.71 (t, *J* = 6.4 Hz, 2H), 3.72 (t, *J* = 6.4 Hz, 2H), 3.75 (s, 3H), 3.77 (s, 3H), 6.65 – 6.67 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 1H) ppm.

Homoveratryl alcohol **29** (1.82 g, 10 mmol) was mixed in dry Et_2O (20 mL) and cooled to 0 °C. PBr_3 (0.95 mL, 10 mmol) was added dropwise and stirred at 0 °C for 1 h. Water (10 mL) was added and product was extracted in Et_2O (20 mL X 2). Organic layer was dried over Na_2SO_4 and solvent was removed under vacuum to give analytically pure product **30** in 93 % (2.27 g) yield.

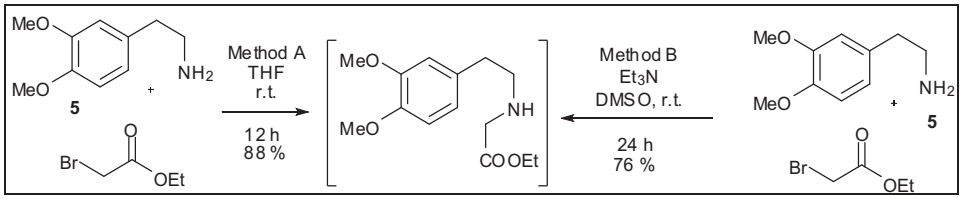
***4*-(*2*-Bromoethyl)-*1,2*-dimethoxybenzene 30**

Pale yellow oil.[63c]

R_f: 0.49 (CH_2Cl_2:hexanes, 1:10)

^1H NMR (400MHz, $CDCl_3$): δ 3.03 (t, *J* = 5.6 Hz, 2H), 3.47 (t, *J* = 8.0 Hz, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 6.65 – 6.70 (m, 2H), 6.74 (d, *J* = 8.0 Hz, 1H) ppm.

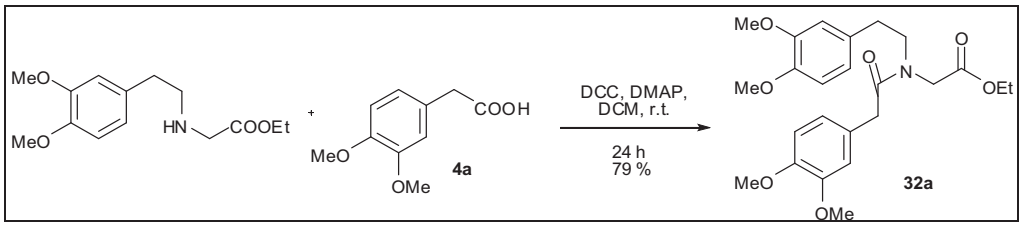
3.5.13: Ethyl *2*-(*N*-(*3,4*-dimethoxyphenethyl)-*2*-(*3,4*-dimethoxyphenyl)acetamido)acetate 32a



Method A: Homoveratryl amine **5** (3.62 g, 20 mmol) was mixed in dry THF and Ethyl bromoacetate (1.67 g, 10 mmol) was added and stirred at r.t. for 12 h. Solvent was removed under vacuum, water was added and product was extracted in Et_2O. Organic layer was washed with brine

and dried over Na_2SO_4. Solvent was removed under vacuum and product obtained in 88 % (2.35 g) yield was as such used for next reaction.

Method B: Homoveratryl amine **5** (2.71 g, 15 mmol) and Et_3N (2.9 mL, 20 mmol) were mixed in DMSO (10 mL) and Ethyl bromoacetate (2.50 g, 15 mmol) was added and stirred at r.t. for 12 h. Water was added and product was extracted in Et_2O (20 mL X 3). Organic layer was washed with water, brine and dried over Na_2SO_4. Solvent was removed under vacuum and product obtained in 76 % (3.04 g) yield was as such used for next reaction.

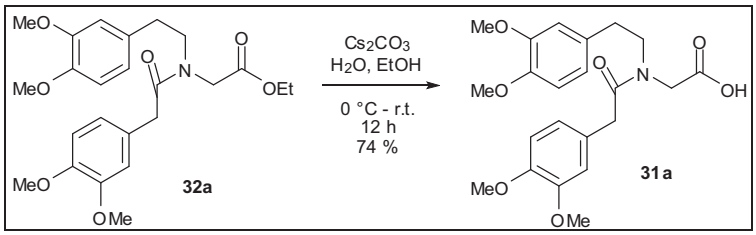


Secondary amine (2.67 g, 10 mmol), Homoveratric acid **4a** (2.35 g, 12 mmol) and DMAP (0.05 g) were dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C. DCC (3.10 g, 15 mmol) was added and stirred at 0 °C - r.t. for 24 h. Suspension was cooled to 0 °C and filtered. This was repeated thrice and organic layer was washed with water, brine and dried over Na_2SO_4. Solvent was removed under vacuum and crude product was purified by flash chromatography (CH_2Cl_2) to give pure product **32a** in 79 % (3.52 g) yield.

Viscous oil.

R_f: 0.36 (CH_2Cl_2)

3.5.14: *2*-(*N*-(*3,4*-Dimethoxyphenethyl)-*2*-(*3,4*-dimethoxyphenyl)acetamido)acetic acid 31a

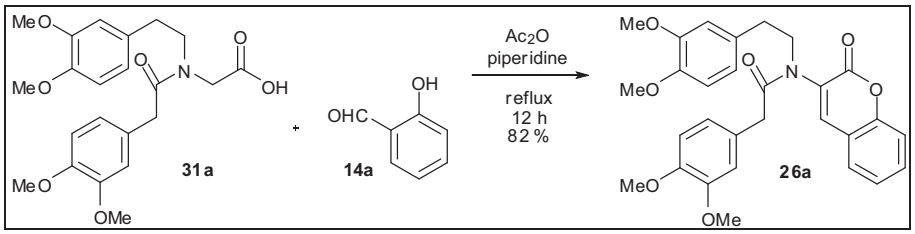


Ester **32a** (2.22 g, 5.00 mmol) was mixed in EtOH (5 mL), water (2 mL) and cooled to 0 °C. Cs_2CO_3 (1.63 g, 5.00 mmol) was added and mixture was stirred at 0 °C – r.t. for 12 h. Solvent was removed under vacuum, aqueous saturated Na_2CO_3 solution (20 mL) and Et_2O (10 mL) was added. Product was extracted in basic aqueous solution and washed with Et_2O (20 mL X 2). On acidifying the basic aqueous solution with 1N HCl till pH 1, product was extracted in CH_2Cl_2, washed with water, brine and dried over Na_2SO_4. Solvent was removed under vacuum to give analytically pure product **31a** in 74 % (1.54 g) yield.

Light brown oil.

R_f: 0.31 (CH_2Cl_2:EtOAc, 1:2)

3.5.15: *N*-(*3,4*-Dimethoxyphenethyl)-*2*-(*3,4*-dimethoxyphenyl)-*N*-(*2*-oxo-*2H*-chromen-*3*-yl)-acetamide 26a

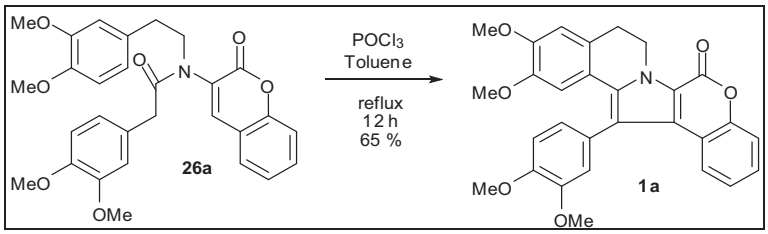


Acid **31a** (0.42 g, 1.00 mmol) and salicyaldehyde **14a** (0.24 g, 2.00 mmol) were mixed in freshly distilled Ac_2O (10 mL). To this solution, piperidine (1 drop) was added and mixture was refluxed for 12 h. Solvent was removed under vacuum and crude oil was washed with petroleum ether (10 mL X 2). Mixture was purified by flash chromatography (CH_2Cl_2: MeOH, 100:1) and product **26a** was obtained in 82 % (0.41 g) yield.

Light brown oil.

R_f: 0.36 (CH_2Cl_2:MeOH, 100:1)

3.5.8: Lamellarin 1

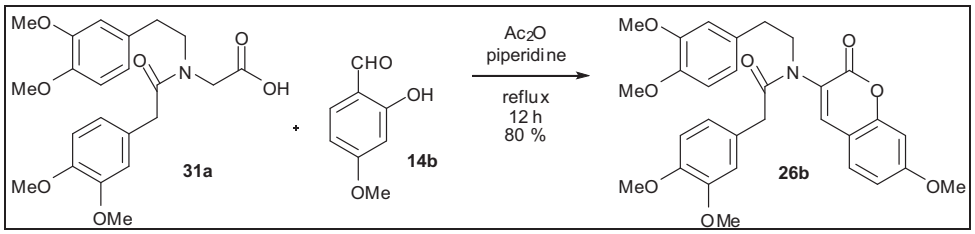


Amide coumarin **26a** (0.25 g, 0.5 mmol) was mixed in dry toluene (10 mL) and freshly distilled $POCl_3$ (3 mL) was added and mixture was refluxed for 12 h. Solution was then poured in ice (150 mL) and cautiously basified with Na_2CO_3 till pH 10. Crude product was extracted in $CHCl_3$, washed with water, brine and dried over Na_2SO_4. Solvent was removed under vacuum and mixture was purified by flash chromatography (CH_2Cl_2: MeOH, 100:1) and product **1a** was obtained in 65 % (0.16 g) yield.

Brown solid, m.p.: 242-244 °C. [lit.: m.p.: 244-245 °C][5k]

R_f: 0.49 (CH_2Cl_2:MeOH, 100:1) fluorescent spot

3.5.17: *N*-(*3,4*-Dimethoxyphenethyl)-*2*-(*3,4*-dimethoxyphenyl)-*N*-(*7*-methoxy-*2*-oxo-*2H*-chromen-*3*-yl)acetamide 26b



Following the similar procedure as described in experiment 3.5.15 with acid **31a** (0.42 g, 1 mmol) and *4*-methoxy salicyaldehyde **14b** (0.30 g, 2 mmol) gave the corresponding product **26b** in 80 % (0.43 g) yield.

Light brown oil.

R_f: 0.46 (CH_2Cl_2:MeOH, 100:2)

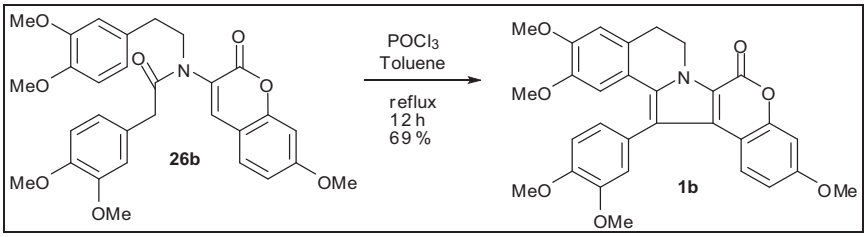
IR (neat): ν_{max} 3020, 2932, 1708, 1664, 1604, 1518, 1460, 1258, 1151 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 2.28-2.94 (m, 2 H), 3.36-3.55 (m, 2 H), 3.68-3.69 (m, 2 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 6.60-6.64 (m, 3 H), 6.69-6.75 (m, 3 H), 6.78-6.84 (m, 4 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 33.55 (CH_2), 42.67 (CH_2), 47.43 (CH_2), 55.49 (CH_3), 55.75 (CH_3), 55.77 (CH_3), 55.80 (CH_3), 55.88 (CH_3), 100.62 (CH), 108.65 (CH), 109.19 (CH), 111.13 (Cq), 111.18 (Cq), 111.19 (Cq), 111.29 (CH), 111.67 (CH), 112.05 (Cq), 112.08 (Cq), 112.14 (Cq), 112.22 (CH), 119.87 (Cq), 120.95 (CH), 128.69 (CH), 133.85 (CH), 142.22 (CH), 147.81 (Cq), 148.85 (Cq), 149.24 (Cq), 161.26 (Cq), 169.33 (Cq) ppm.

LCMS (*m/z*): $[M+H]^+$ 534.

3.5.18: Lamellarin 1b



Following the similar procedure as described in experiment 3.5.16 with amide coumarin **26b** (0.26 g, 0.5 mmol) gave the corresponding product **1b** in 69 % (0.17 g) yield.

Brown solid, m.p.: 248-250 °C.

R_f: 0.53 (CH_2Cl_2:MeOH, 100:2) fluorescent spot

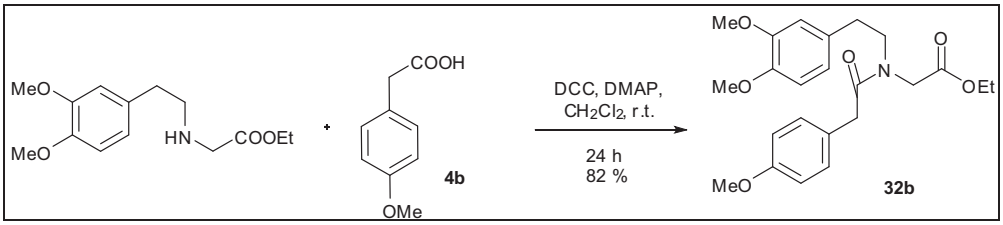
IR (KBr): ν_{max} 3021, 1706, 1531, 1480, 1427, 1250 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.04 (t, *J* = 6.8 Hz, 2 H), 3.28 (s, 3 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 3.91 (s, 3 H), 4.69-4.74 (m, 2 H), 6.55 (d, *J* = 8.8 Hz, 1 H), 6.57 (s, 1 H), 6.68 (s, 1 H), 6.83 (s, 1 H), 6.92 (s, 1 H), 6.98 (s, 1 H), 7.03 (d, *J* = 8.8 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.67 (CH_2), 42.37 (CH_2), 55.17 (CH_3), 55.48 (CH_3), 55.90 (CH_3), 56.07 (2X CH_3), 101.49 (CH), 108.67 (Cq), 110.93 (CH), 111.41 (Cq), 111.44 (CH), 111.94 (CH), 113.30 (Cq), 113.76 (CH), 115.09 (Cq), 120.01 (Cq), 123.32 (CH), 124.07 (CH), 126.62 (Cq), 127.86 (Cq), 128.09 (Cq), 136.18 (Cq), 147.39 (Cq), 148.83 (Cq), 148.91 (Cq), 149.74 (Cq), 152.53 (Cq), 155.41 (Cq), 159.16 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{30}H_{27}NO_7Na$ $[M+Na]^+$ 536.1685; found 536.1687.

3.5.19: Ethyl *2*-(*N*-(*3,4*-dimethoxyphenethyl)-*2*-(*4*-methoxyphenyl)acetamido)acetate 32b



Following the similar procedure as described in experiment 3.5.13 with sec. amine (2.67, 10 mmol) and *4*-methoxyphenylaceticacid **4b** (2.0 g, 12 mmol) gave the corresponding product **32b** in 82 % (3.40 g) yield.

Viscous oil.

R_f: 0.69 (CH_2Cl_2)

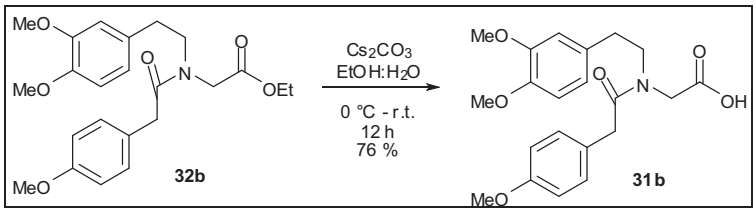
IR (neat): ν_{max} 2936, 2835, 1746, 1643, 1589, 1261 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (t, *J* = 7.2 Hz, 2 H), 3.51 (s, 3 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.04 (s, 2 H), 4.14-4.22 (m, 2 H), 6.60-6.63 (m, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.84-6.88 (m, 3 H), 7.12 (d, *J* = 8.4 Hz, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.16 (CH_3), 33.86 (CH_2), 34.67 (CH_2), 39.50 (CH_2), 48.06 (CH_2), 55.27 (CH_2), 55.93 (CH_3), 55.95 (CH_3), 61.21 (CH_2), 111.93 (CH), 114.09 (2X CH), 120.76 (CH), 126.77 (Cq), 129.75 (2X CH), 130.53 (Cq), 132.17 (CH), 147.91 (Cq), 149.11 (Cq), 158.47 (Cq), 169.36 (Cq), 171.91 (Cq) ppm.

LCMS (*m/z*): $[M+H]^+$ 416.

3.5.20: *2*-(*N*-(*3,4*-Dimethoxyphenethyl)-*2*-(*4*-methoxyphenyl)acetamido)acetic acid 31b



Following the similar procedure as described in experiment 3.5.14 with ester **32b** (2.07 g, 5 mmol) gave the corresponding acid **31b** in 76 % (1.47 g) yield.

Colourless oil.

R_f: 0.41 (CH_2Cl_2:EtOAc, 1:2)

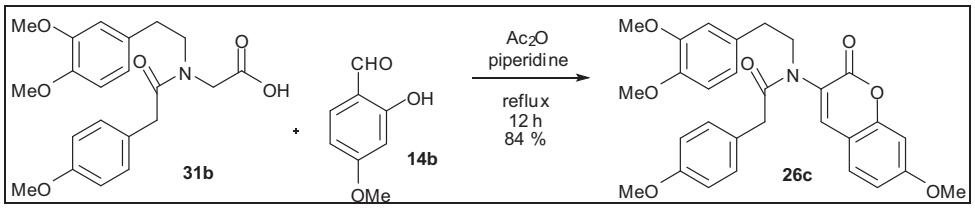
IR (neat): ν_{max} 3200, 3007, 2935, 1731, 1666, 1606, 1518, 1462, 1263, 1151 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 2.66 (t, *J* = 7.2 Hz, 2 H), 3.50 (s, 2 H), 3.54-3.57 (m, 2 H), 3.74 (s, 3 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 4.07 (s, 2 H), 6.59-6.66 (m, 2 H), 6.78 (s, 1 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 8.48 (br s, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 34.47 (CH_2), 39.28 (CH_2), 48.37 (CH_2), 51.59 (CH_2), 55.24 (CH_3), 55.92 (CH_3), 55.94 (CH_3), 111.50 (CH), 111.98 (CH), 114.12 (2X CH), 120.78 (CH), 126.36 (Cq), 129.80 (2X CH), 130.32 (Cq), 147.90 (Cq), 149.09 (Cq), 158.51 (Cq), 172.52 (Cq), 173.03 (Cq) ppm.

HRMS (*m/z)*: calculated for $C_{21}H_{25}NO_6Na$ $[M+Na]^+$ 410.1580; found 410.1578.

3.5.21: *N*-(*3,4*-Dimethoxyphenethyl)-*N*-(*7*-methoxy-*2*-oxo-*2H*-chromen-*3*-yl)-*2*-(*4*-methoxyphenyl)acetamide 26c



Following the similar procedure as described in experiment 3.5.15 with acid **31b** (0.39 g, 1 mmol) and *4*-methoxy salicyaldehyde **14b** (0.30 g, 2 mmol) gave the corresponding product **26c** in 84 % (0.42 g) yield.

Viscous oil.

R_f: 0.53 (CH_2Cl_2:MeOH, 100:2)

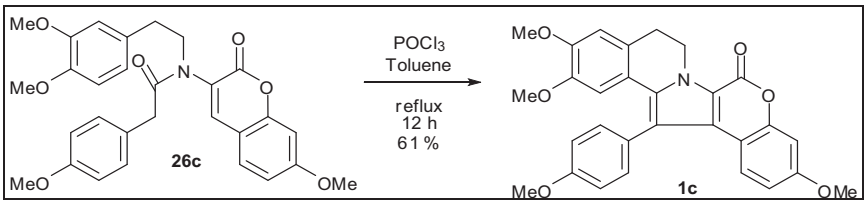
IR (neat): ν_{max} 3026, 2938, 1706, 1665, 1602, 1516, 1456, 1254, 1148 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 2.79-2.95 (m, 2 H), 3.36-3.39 (m, 2 H), 3.52-3.56 (m, 2 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 3.88 (s, 3 H), 6.67-6.75 (m, 4 H), 6.83-6.88 (m, 3 H), 6.95 (d, *J* = 8.8 Hz, 2 H) 7.12-7.14 (m, 1 H), 7.20 (d, *J* = 8.8 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 33.64 (CH_2), 42.55 (CH_2), 47.45 (CH_2), 55.22 (CH_3), 55.82 (CH_3), 55.87 (CH_3), 55.92 (CH_3), 100.67 (CH), 111.19 (CH), 111.48 (Cq), 112.17 (CH) 113.28 (Cq), 113.54 (Cq), 113.90 (2X CH) 114.05 (Cq), 114.30 (Cq), 120.95 (CH), 129.20 (CH) 129.81 (Cq), 129.96 (2X CH), 130.36 (CH) 132.01 (Cq), 142.06 (CH), 148.89 (Cq), 155.04 (Cq) 158.44 (Cq), 169.04 (Cq) ppm.

LCMS (*m/z*): $[M+H]^+$ 504.

3.5.22: Lamellarin 1c



Following the similar procedure as described in experiment 3.5.16 with amide-coumarin **26c** (0.25 g, 0.5 mmol) gave the corresponding product **1c** in 61 % (0.15 g) yield.

Brown solid, m.p.: 234-236 °C.

R_f: 0.61 (CH_2Cl_2:MeOH, 100:2) fluorescent spot

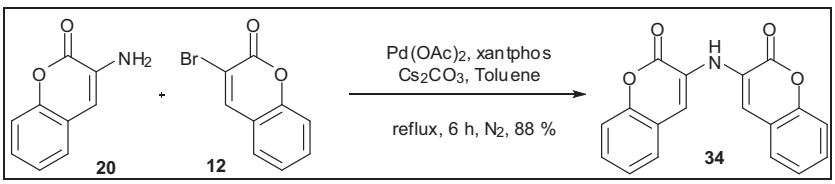
IR (KBr): ν_{max} 3022, 1702, 1528, 1480, 1339, 1244 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (t, *J* = 6.8 Hz, 2 H), 3.34 (s, 3 H), 3.80 (s, 3 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 4.77-4.80 (m, 2 H), 6.57 (s, 1 H), 6.59 (d, *J* = 8.8 Hz, 1 H), 6.74 (s, 1 H), 6.90 (s, 1 H), 7.07-7.11 (m, 1 H), 7.39 (d, *J* = 8.8 Hz, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.73 (CH_2), 42.39 (CH_2), 55.10 (CH_3), 55.46 (CH_3), 55.50 (CH_3), 55.91 (CH_3), 101.51 (CH), 108.70 (CH), 110.92 (CH), 111.41 (CH), 111.59 (Cq), 113.38 (Cq), 111.63 (Cq), 114.85 (2X CH), 120.10 (Cq), 124.02 (CH), 126.63 (Cq), 127.58 (Cq), 128.13 (Cq), 132.24 (2X CH), 136.29 (Cq), 147.36 (Cq), 148.85 (Cq), 152.56 (Cq), 155.48 (Cq), 159.14 (Cq), 159.48 (Cq) ppm.

LRMS (*m/z)*: calculated for $C_{29}H_{25}NO_6$ $[M]^+$ 483.2; found 483.2.

3.5.23: *3,3′*-Azanediylbis(*2H*-chromen-*2*-one) 34



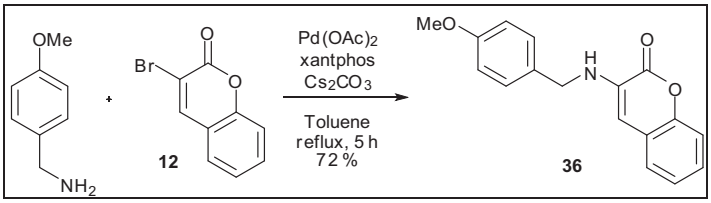
3-aminocoumarin **20** (0.88 g, 5.5 mmol), *3*-bromocoumarin **12** (1.12 g, 5.00 mmol), $Pd(OAc)_2$ (0.11 g, 0.50 mmol), xantphos (0.29 g, 0.50 mmol), and Cs_2CO_3 (2.44 g, 7.50 mmol) were mixed with dry toluene (10 mL) in a sealed tube. Mixture was flushed with N_2 gas and stirred at 120 °C

for 6 h. $CHCl_3$ was added and filtered. Solvent was removed under vacuum and crude product was purified with flash chromatography (CH_2Cl_2:MeOH, 100:1) to give pure product **34** in 88 % (1.34 g) yield.

Light brown solid, m.p.: 234-236 °C.

R_f: 0.46 (CH_2Cl_2:EtOAc, 1:1)

3.5.24: *3*-(*4*-Methoxybenzylamino)-*2H*-chromen-*2*-one 36

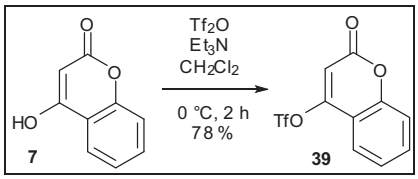


Following the similar procedure as described in experiment 3.5.10 with *4*-methoxybenzylamine (0.16 g, 1.20 mmol), *3*-bromocoumarin **12** (0.22 g, 1.00 mmol), $Pd(OAc)_2$ (0.02 g, 0.10 mmol), xantphos (0.06 g, 0.10 mmol) and Cs_2CO_3 (0.49 g, 1.50 mmol), product **36** was obtained in 72 % (0.20 g) yield.

Viscous oil.

R_f: 0.41 (CH_2Cl_2)

3.5.25: *2*-Oxo-*2H*-chromen-*4*-yl trifluoromethanesulfonate 39



4-hydroxycoumarin **7** (0.65 g, 4.00 mmol) and Et_3N (0.87 mL, 6.00 mmol) were mixed in dry CH_2Cl_2 and cooled to 0 °C. To this solution Tf_2O (0.84 mL, 5.00 mmol) was added dropwise and stirred at 0 °C for 2 h. water was added and product was extracted in CH_2Cl_2, washed with brine and dried over Na_2SO_4. Solvent was removed under vacuum and crude product was purified by flash chromatography (CH_2Cl_2) to give pure product **39** in 78 % (0.92 g).

Pale yellow solid, m.p.: 60 - 62 °C. [lit.: m.p.: 59 - 60 °C][61]

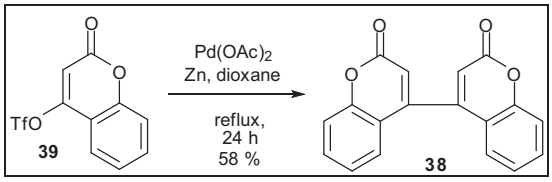
R_f: 0.49 (CH_2Cl_2:hexanes, 1:3)

IR (KBr): ν_{max} 3094, 1755, 1741, 1634, 1607, 1435, 1371, 1221, 1136, 1047 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 6.52 (br s, 1H), 7.44 (br s, 2H), 7.72 (br s, 2H) ppm.

^{13}C NMR (100MHz, $CDCl_3$): δ 105.91 (CH), 113.90 (Cq), 116.87 (Cq), 117.39 (CH), 122.53 (CH), 125.24 (CH), 134.19 (CH), 153.45 (Cq), 157.18 (Cq), 159.57 (Cq) ppm.

3.5.26: *2H,2'H-4,4'*-Bichromene-*2,2'*-dione 38



4-OTfcoumarin **39** (0.59 g, 2.00 mmol), $Pd(OAc)_2$ (0.05 g, 0.20 mmol) and Zn (0.52 g, 8.00 mmol) were mixed with dry dioxane (10 mL) in a sealed tube. Mixture was flushed with N_2 gas and stirred at 120 °C for 24 h. $CHCl_3$ was added and filtered. Solvent was removed under vacuum and crude product was purified with flash chromatography (CH_2Cl_2:hexanes, 1:1) to give pure product **38** in 58 % (0.33 g) yield.

Pale yellow solid, m.p.: 210-212 °C. [lit.: m.p.: 215 - 216 °C][64]

R_f: 0.54 (CH_2Cl_2:hexanes, 1:3)

IR (KBr): ν_{max} 3063, 2964, 1722, 1605, 1562, 1448, 1360, 1186 cm^{-1}.

^1H NMR (400MHz, $CDCl_3$): δ 6.42 (s, 2H), 7.14 – 7.16 (m, 4H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.52 - 7.57 (m, 2H) ppm.

^{13}C NMR (100MHz, $CDCl_3$): δ 116.32 (CH), 117.55 (Cq), 117.65 (CH), 124.92 (CH), 126.28 (CH), 133.08 (CH), 149.17 (Cq), 153.84 (Cq), 159.51 (Cq) ppm.

3.6: References

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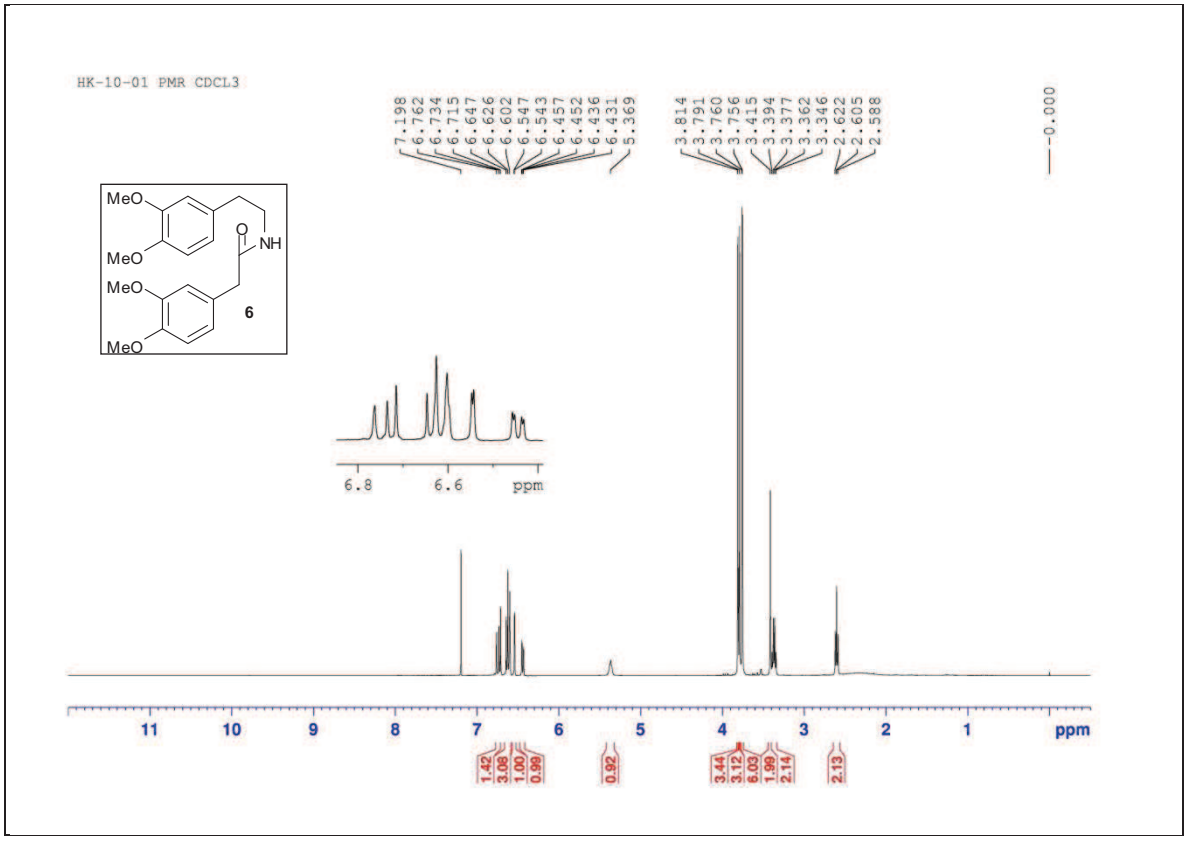
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7
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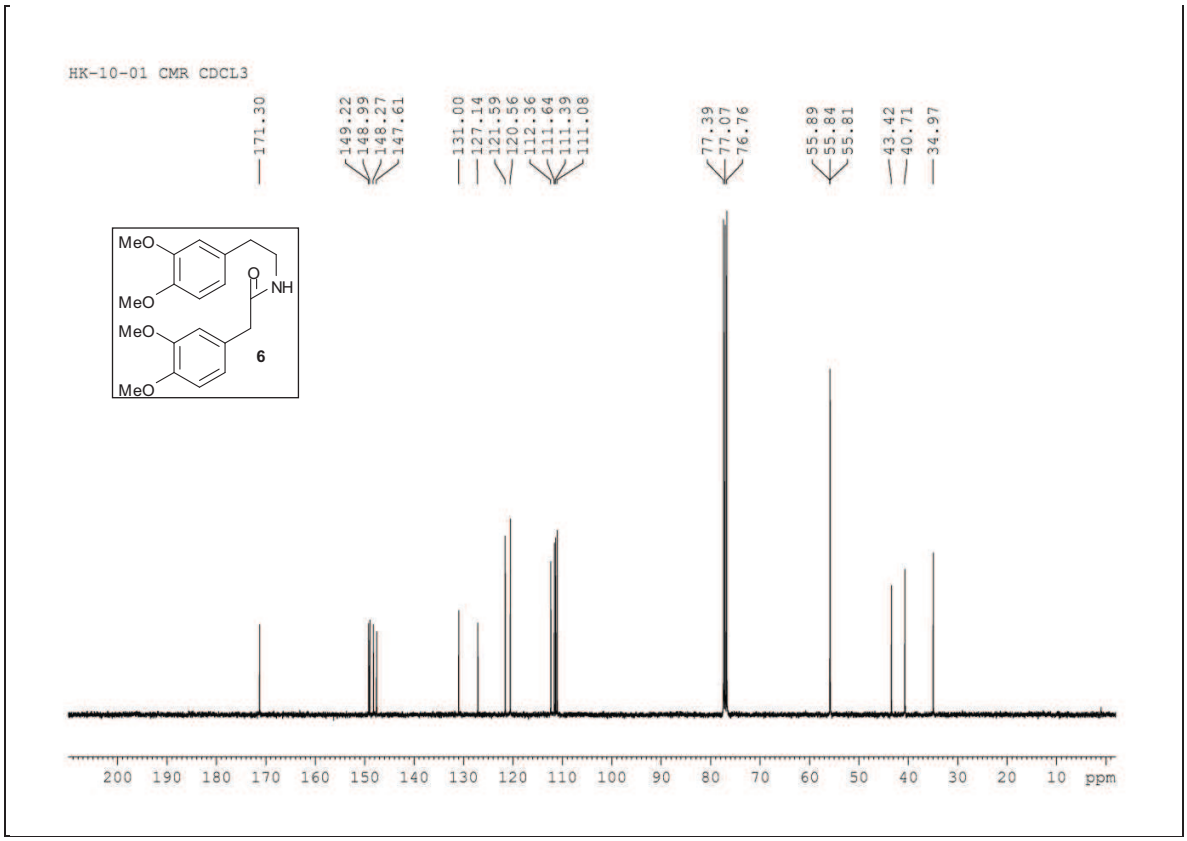
2
1
ppm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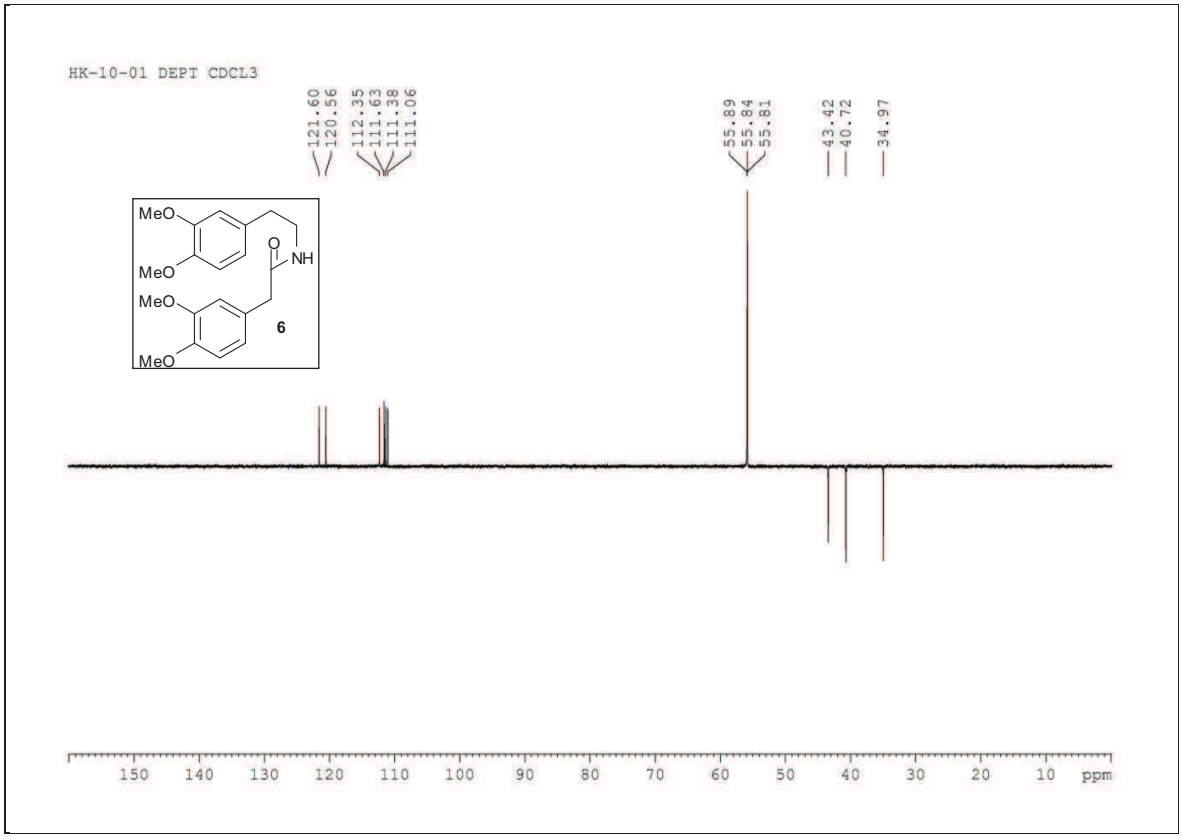
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40.72
34.97
MeO
MeO
MeO
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150
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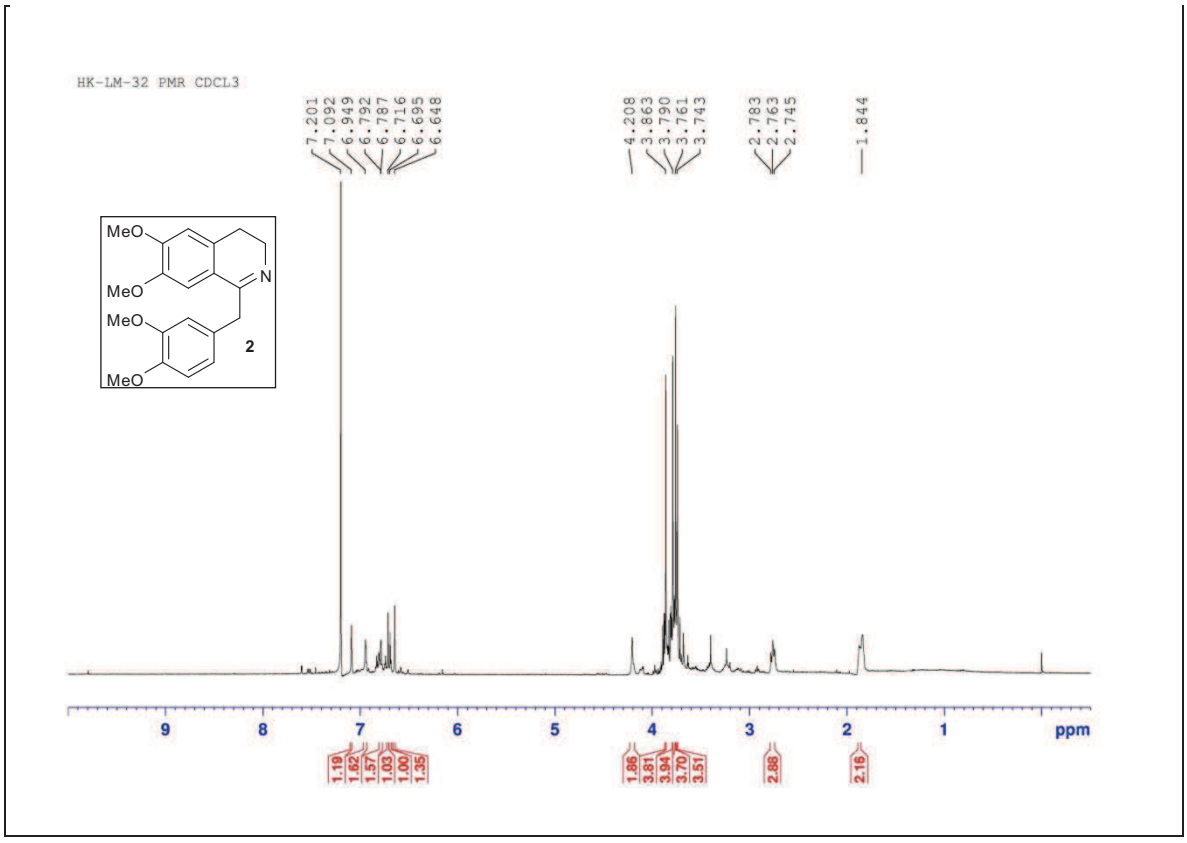
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6.695
6.648
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3.863
3.790
3.761
3.743
2.783
2.763
2.745
1.844
MeO
MeO
MeO
MeO
N
2
9
8
7
6
5
4
3
2
1
ppm
1.19
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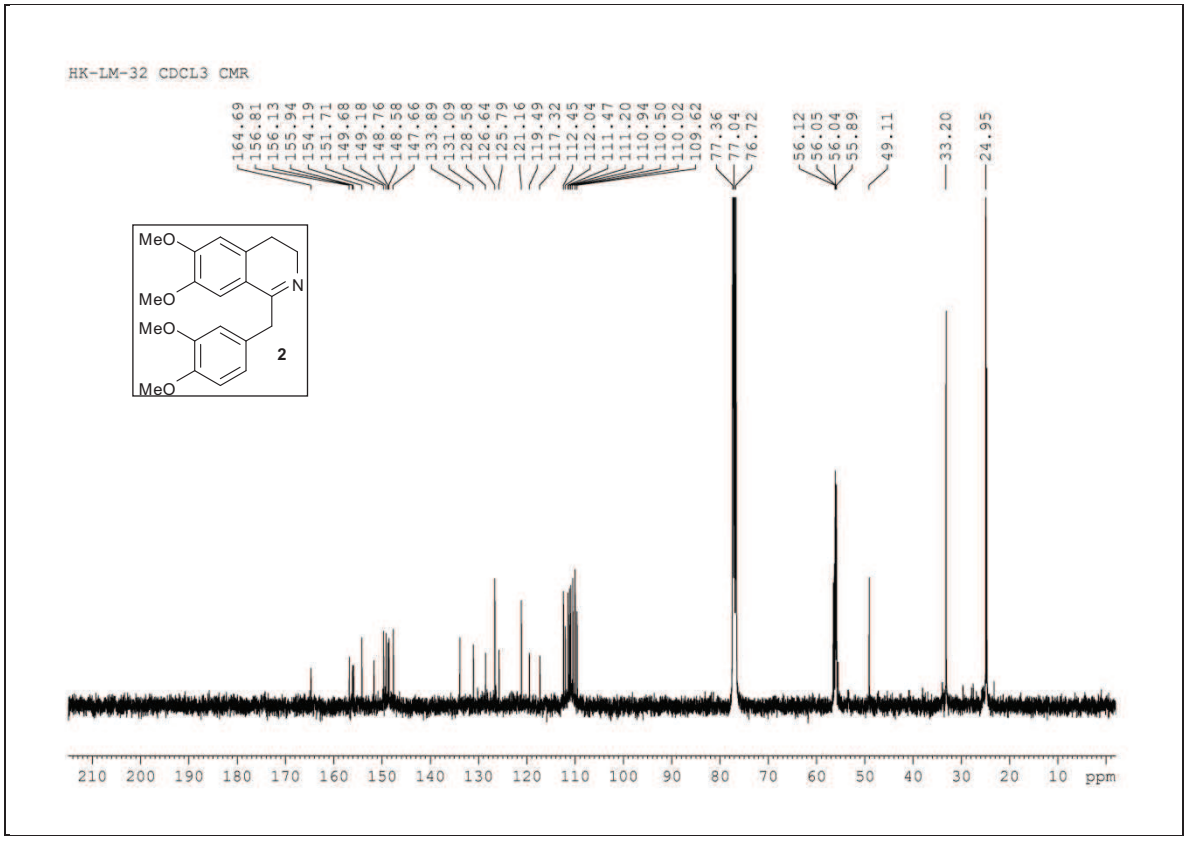
2.16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147.66
133.89
131.09
128.58
126.64
125.79
121.16
119.49
117.32
112.45
112.04
111.47
111.20
110.94
110.50
110.02
109.62
77.36
77.04
76.72
56.12
56.05
56.04
55.89
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MeO
MeO
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N
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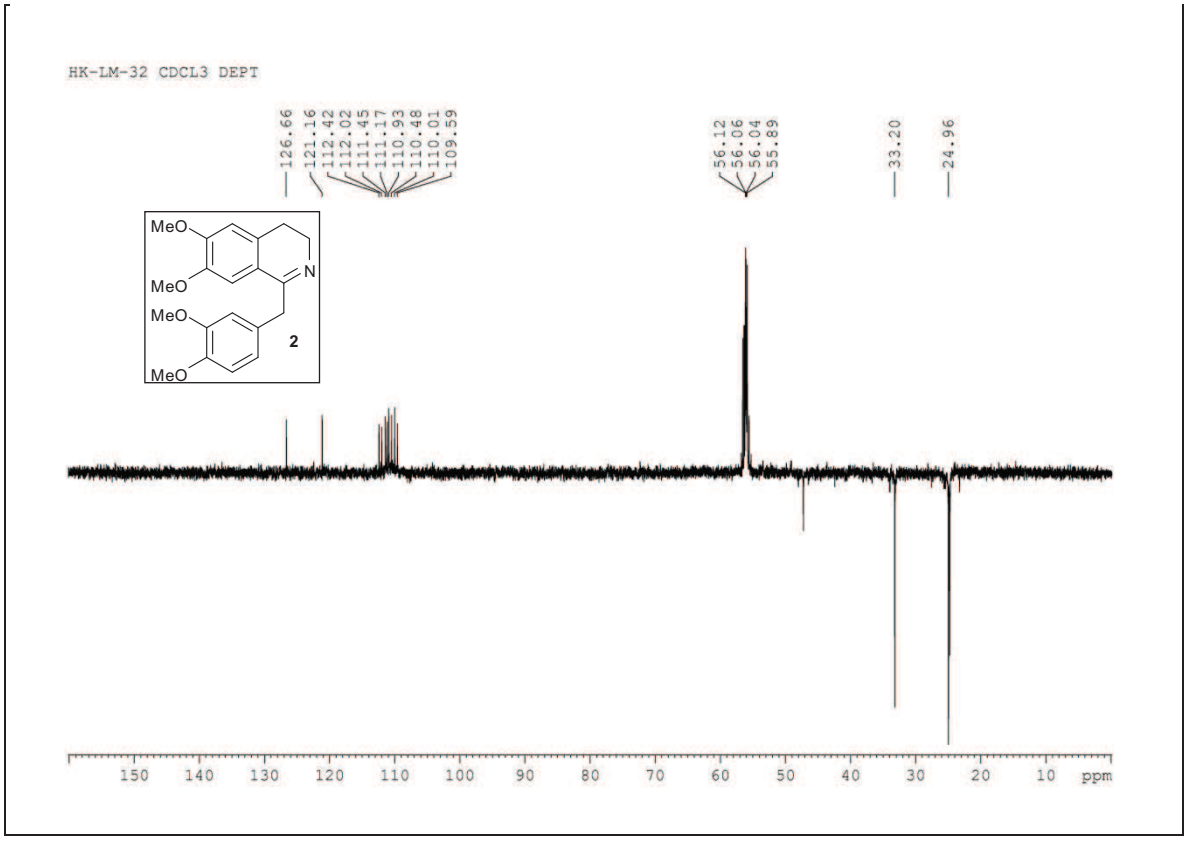
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56.12
56.06
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MeO
MeO
N
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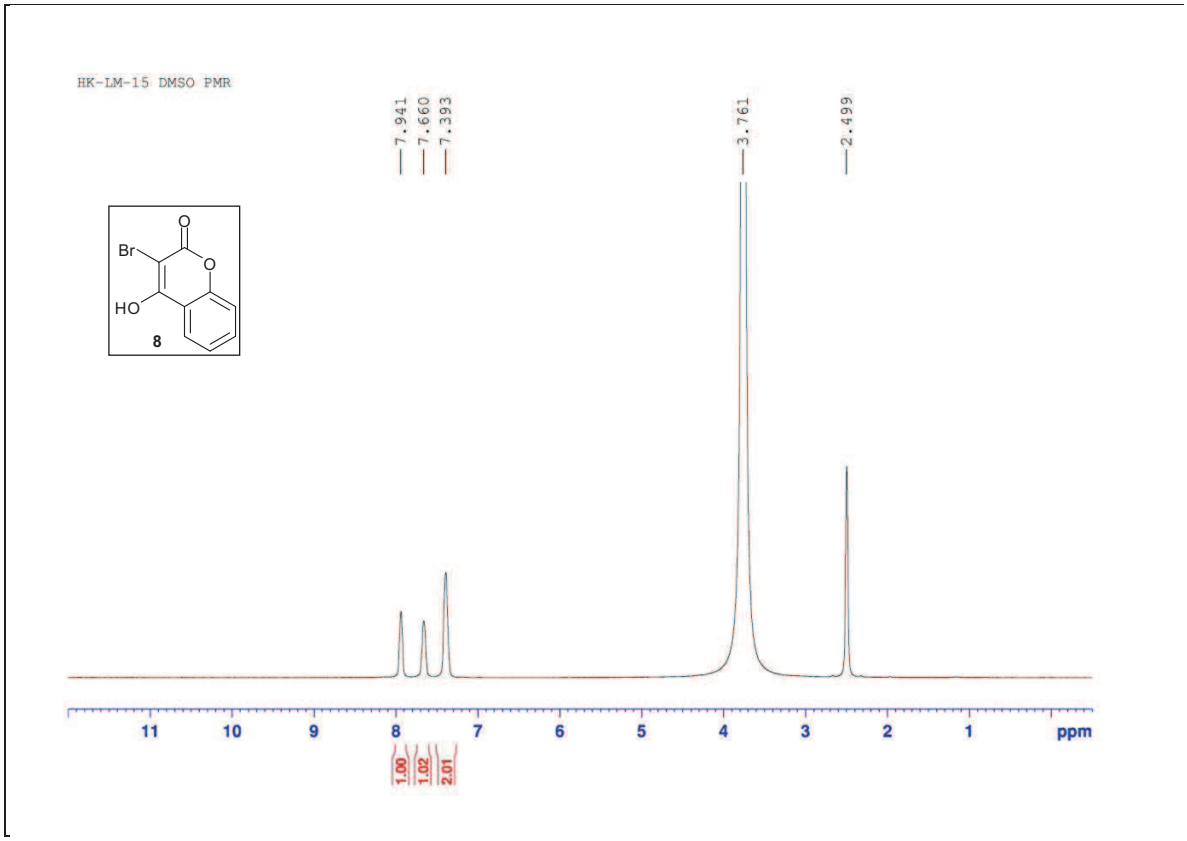
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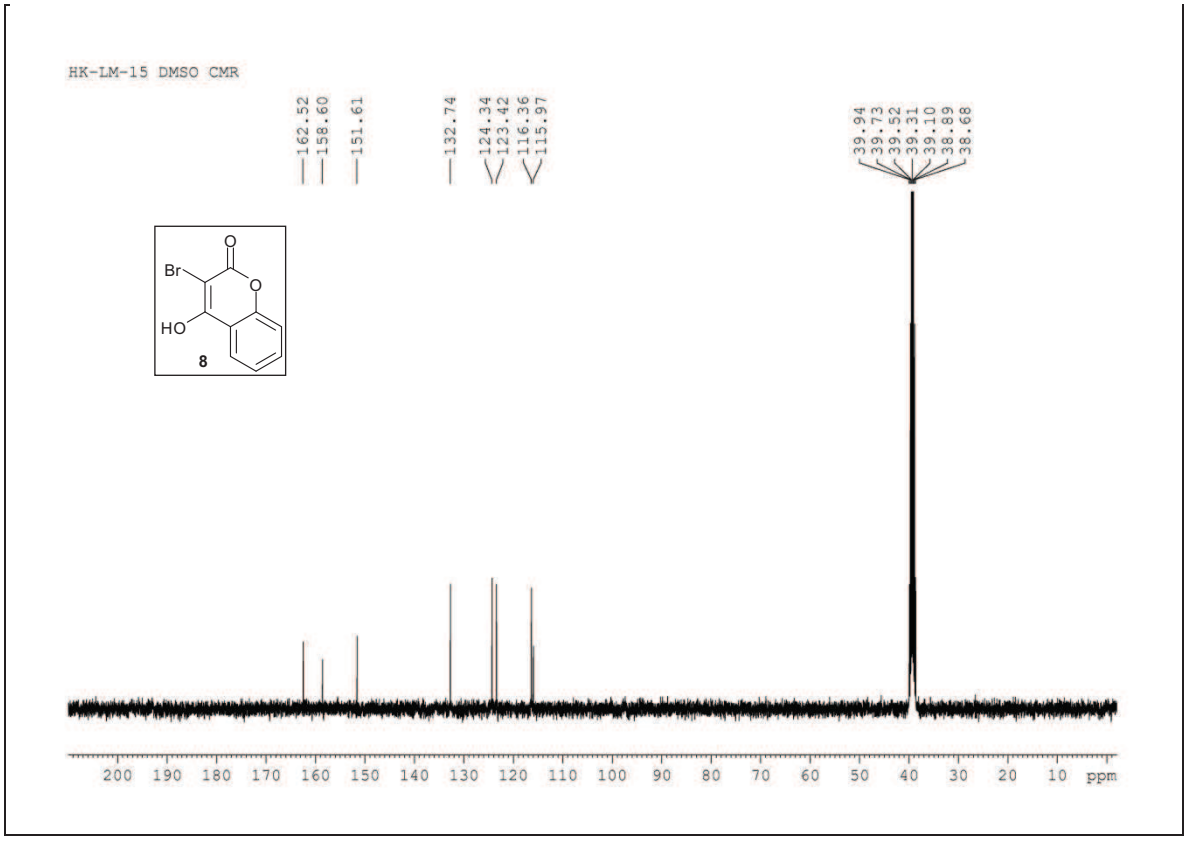
2.01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123.42
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115.97
39.94
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39.52
39.31
39.10
38.89
38.68
Br
O
O
HO
8
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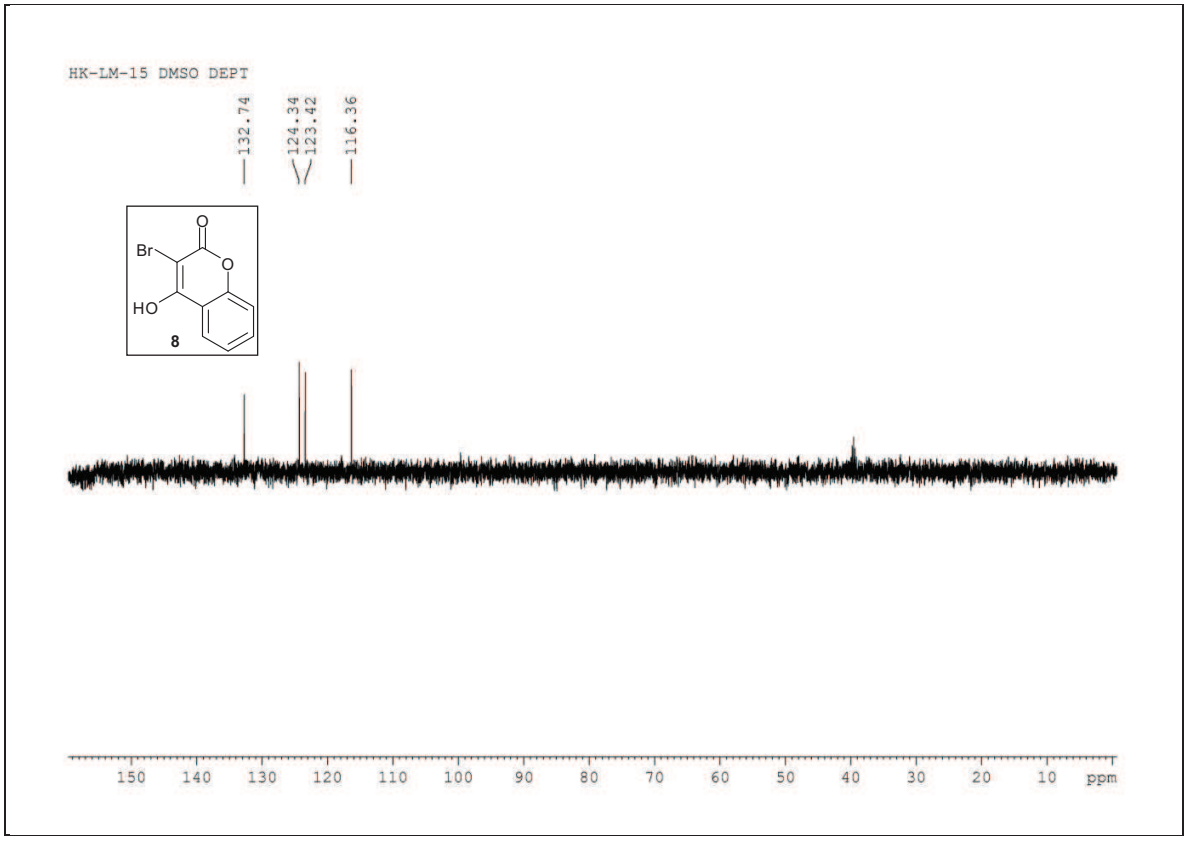
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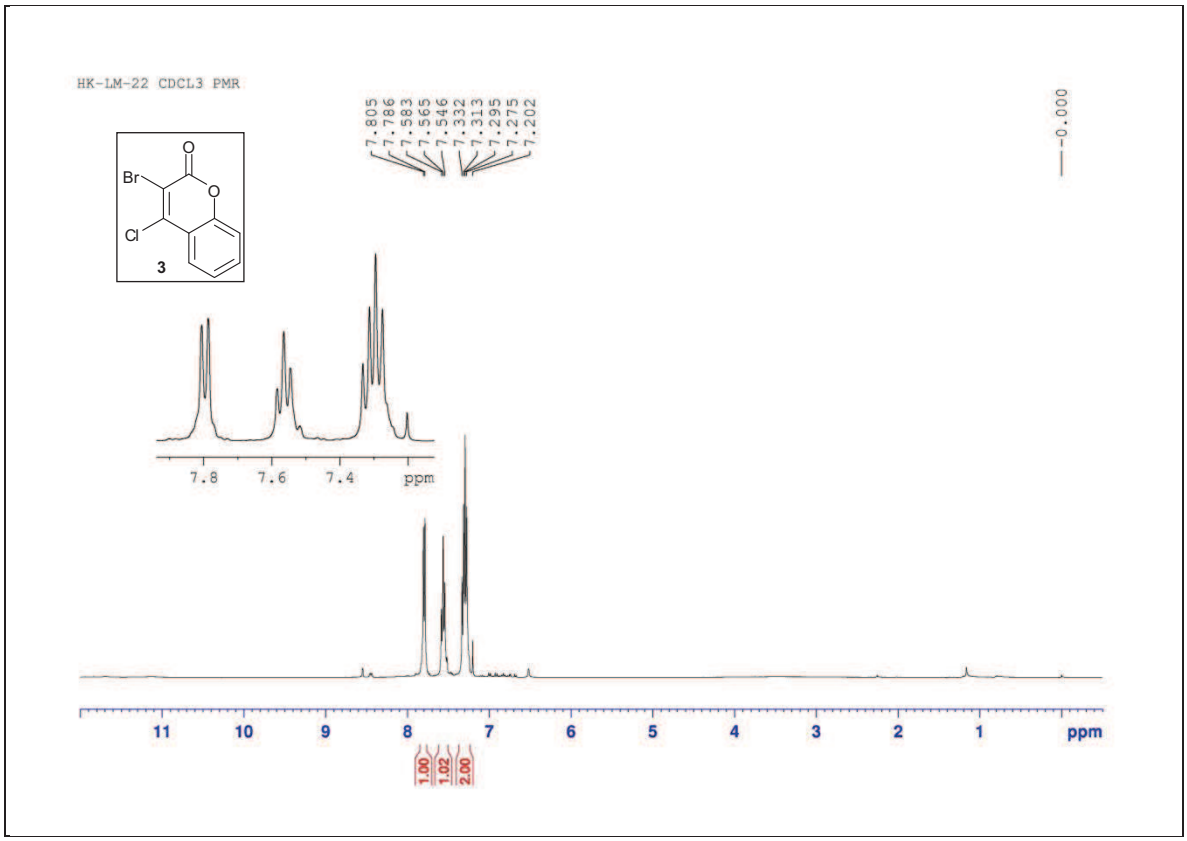
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Br
Cl
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O
3
7.8
7.6
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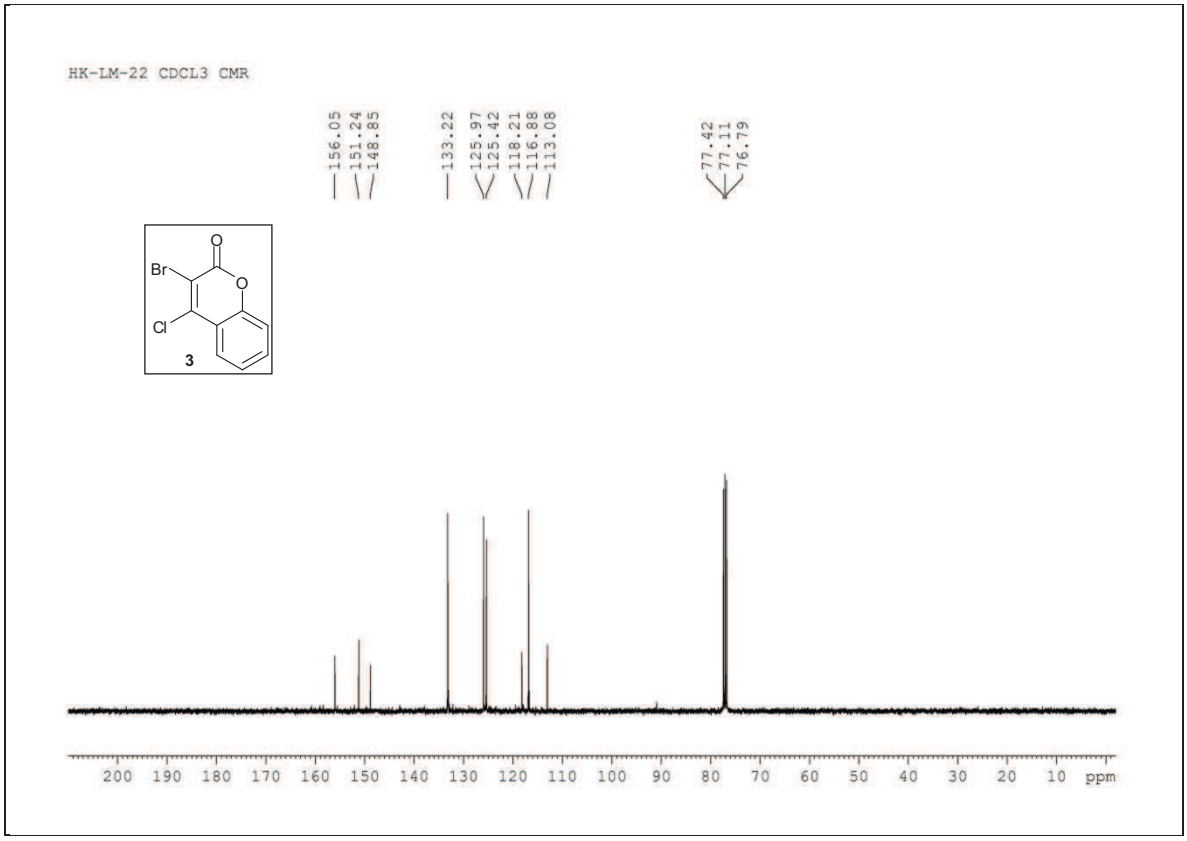
2.00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O
3
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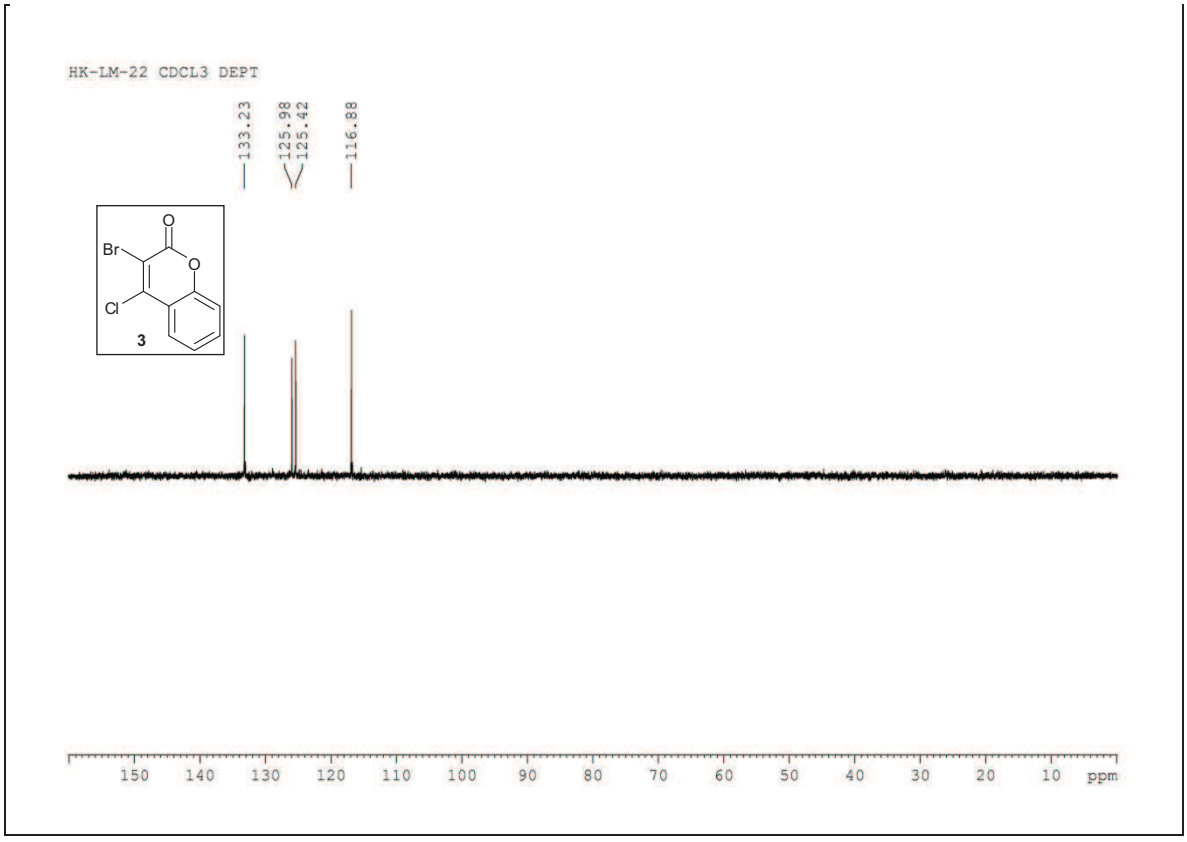
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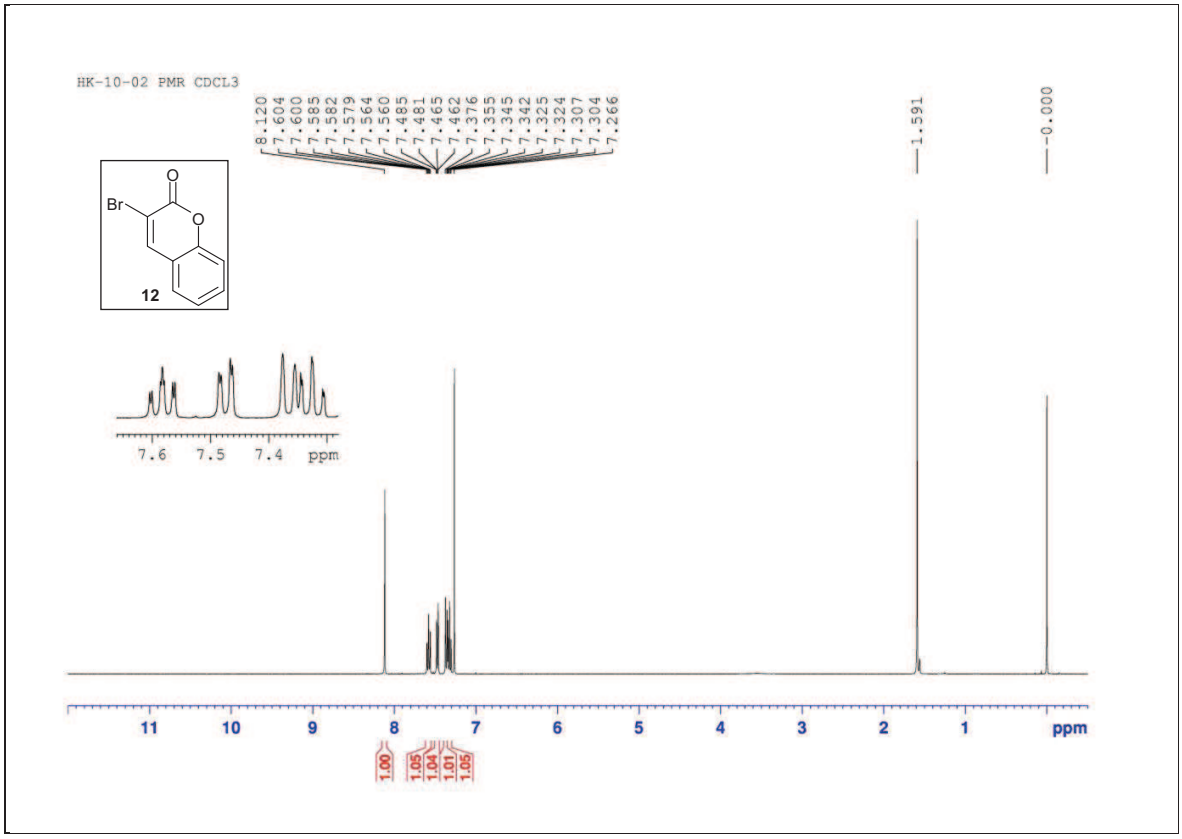
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7.481
7.465
7.462
7.376
7.355
7.345
7.342
7.325
7.324
7.307
7.304
7.266
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7.5
7.4
ppm
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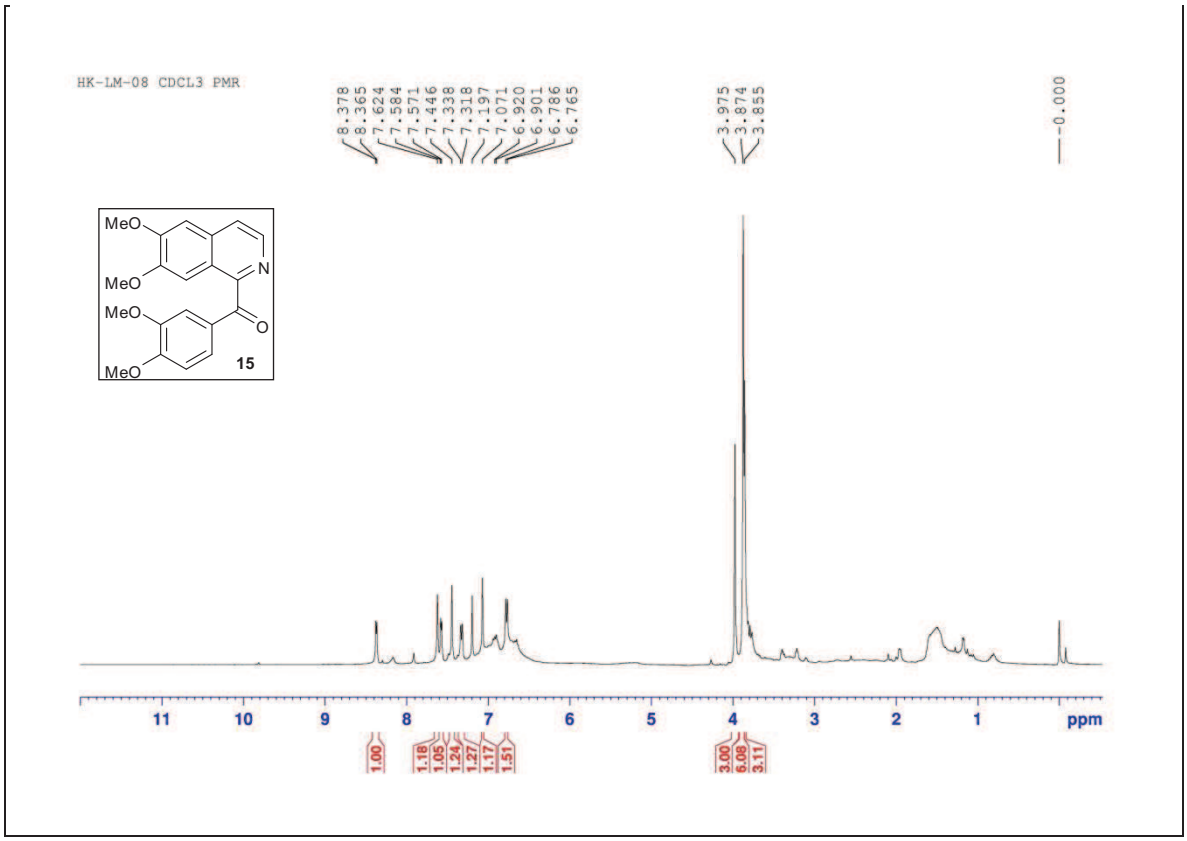
1.01
1.05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6.901
6.786
6.765
3.975
3.874
3.855
0.000
MeO
MeO
MeO
MeO
N
O
15
11
10
9
8
7
6
5
4
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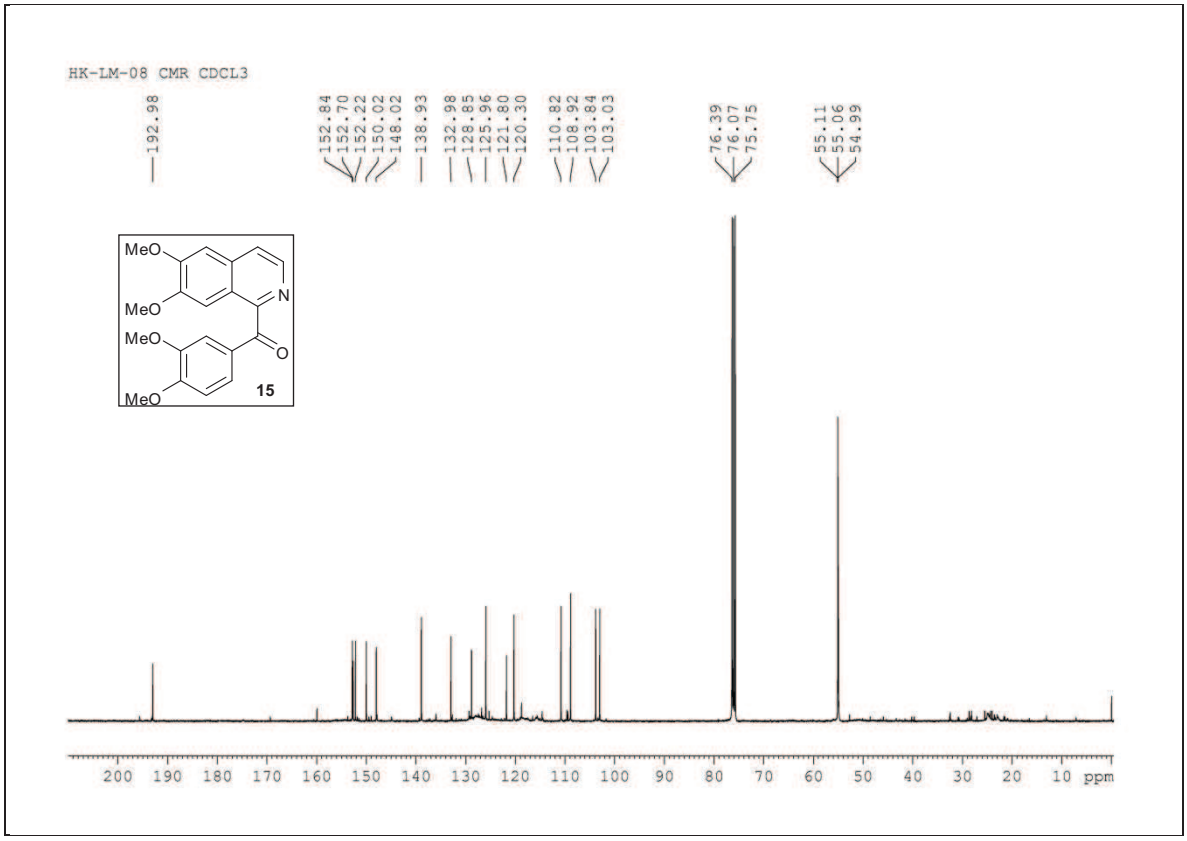
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103.03
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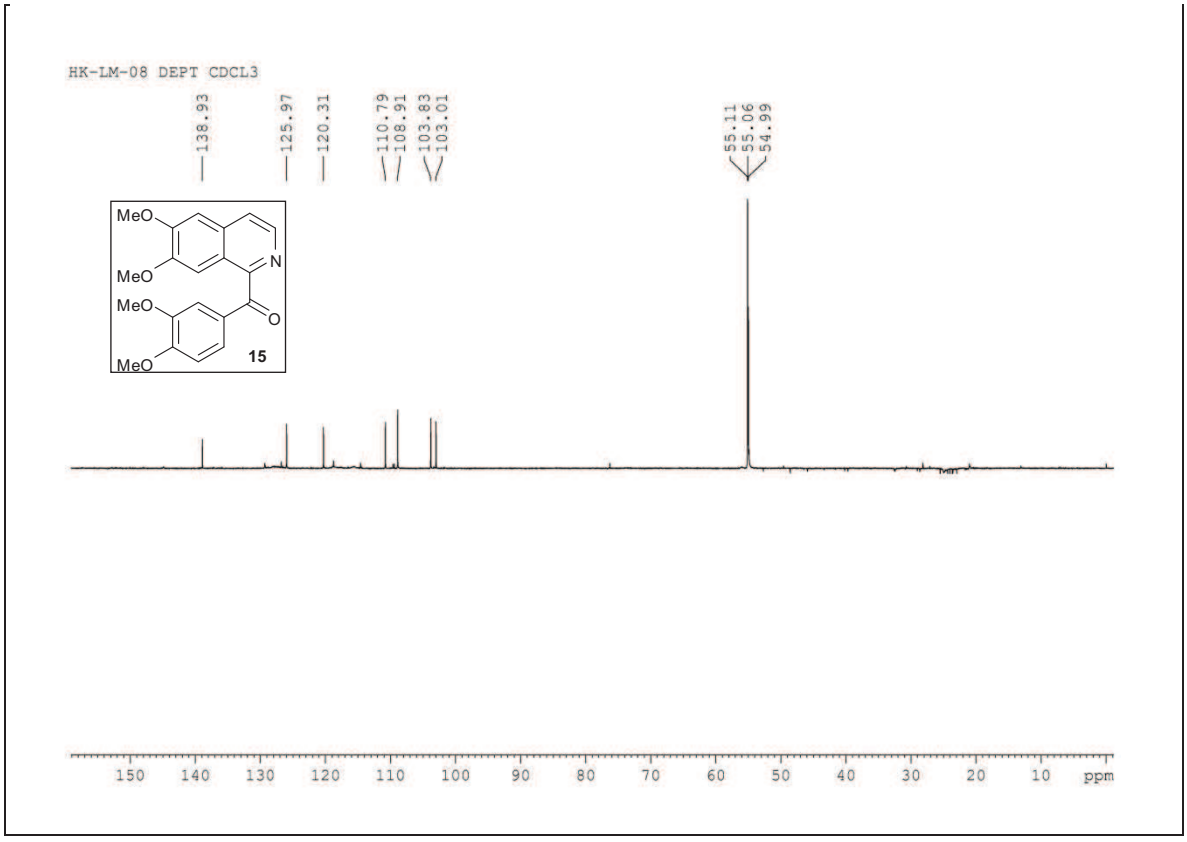
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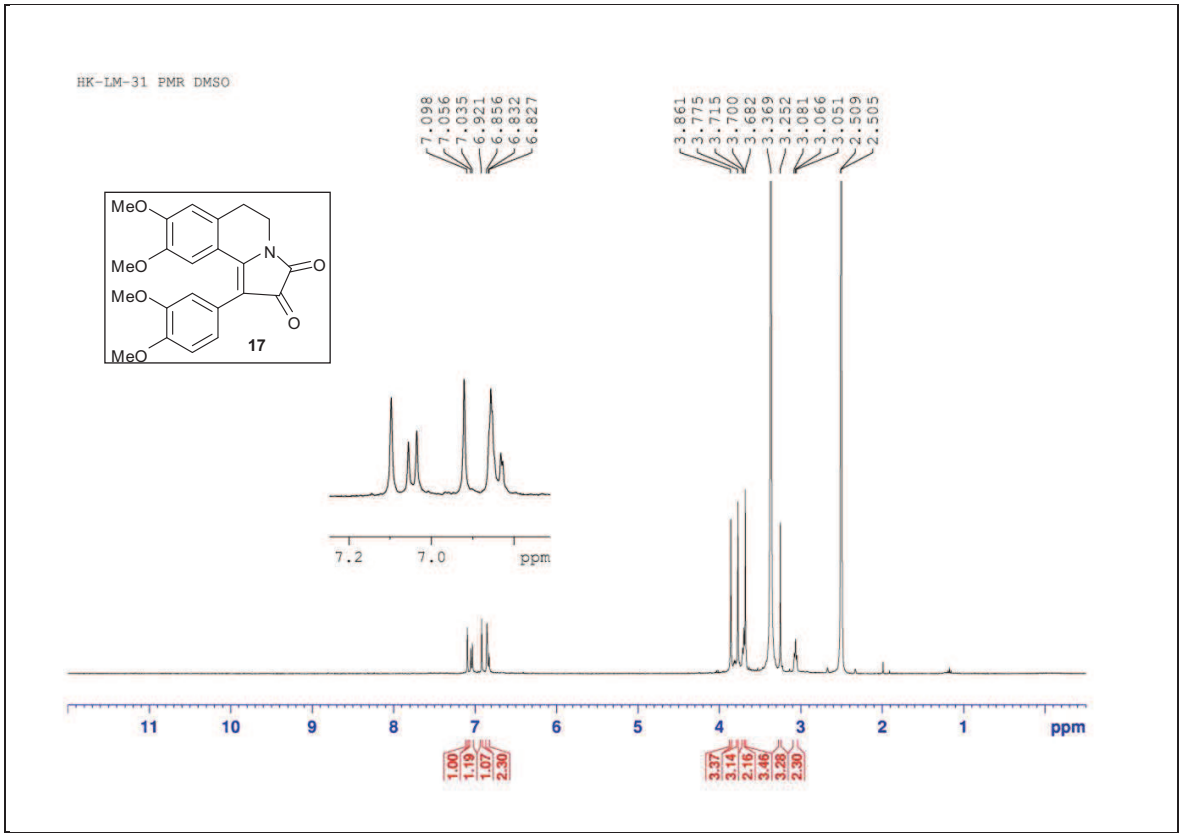
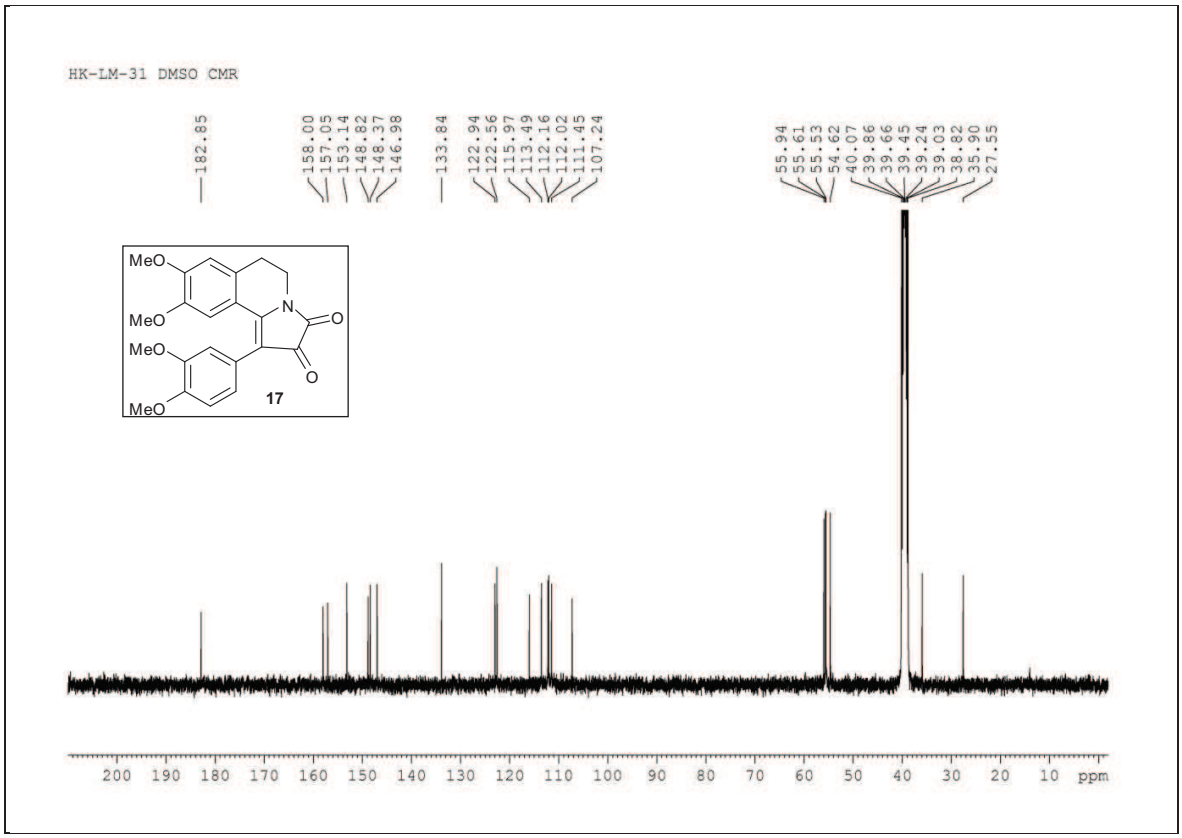
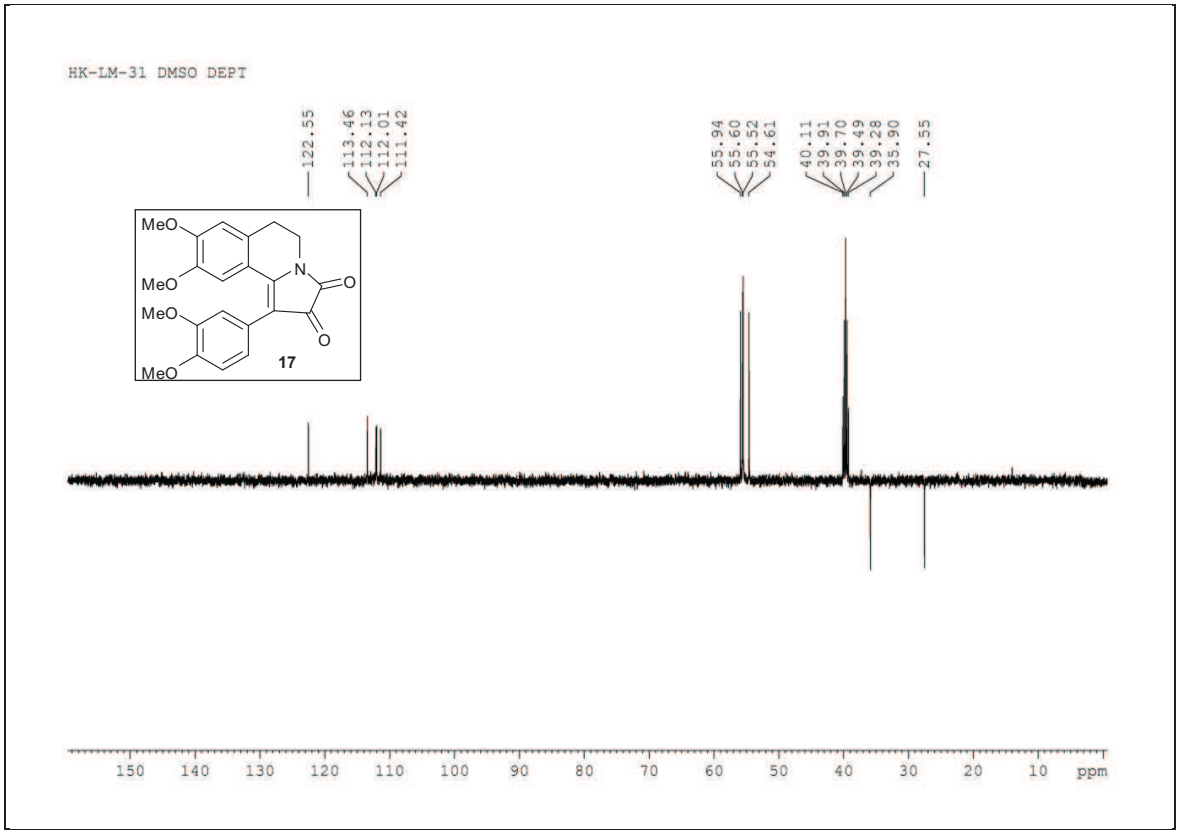
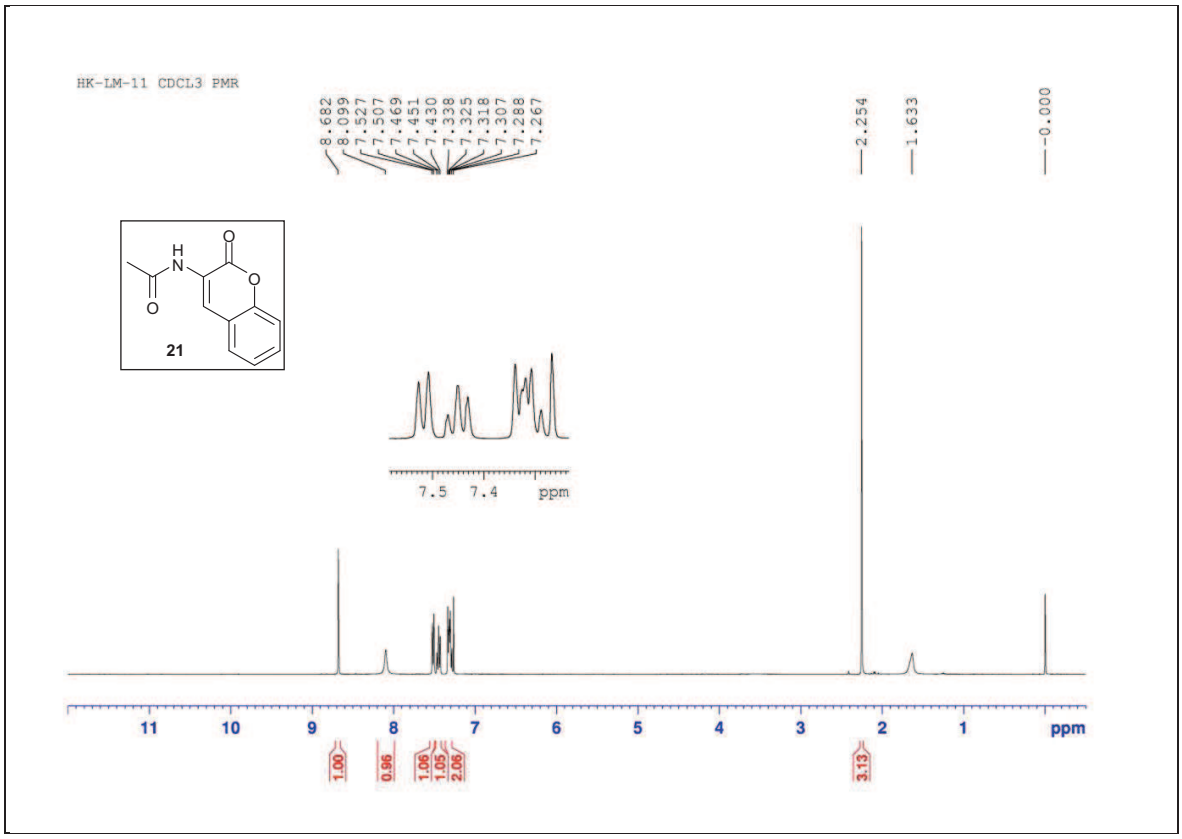
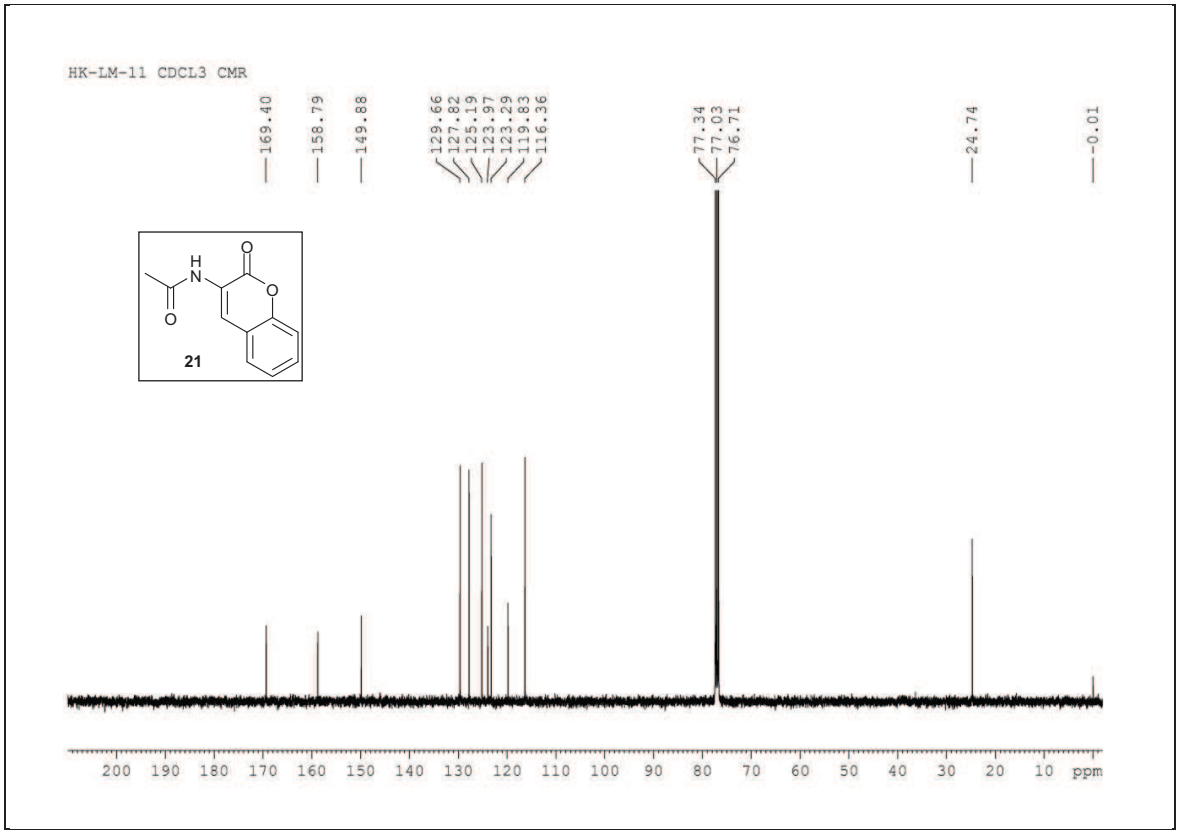
MeO
MeO
MeO
MeO
N
O
15
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

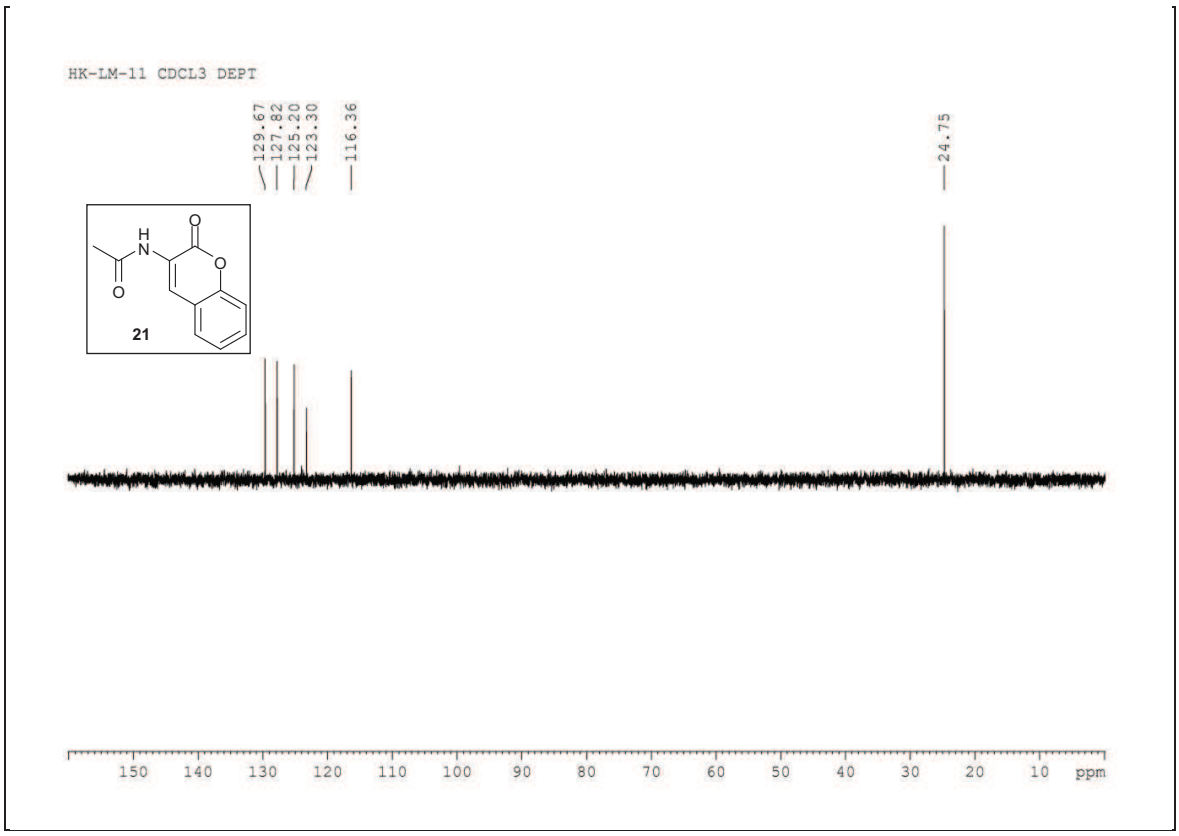

HK-LM-31 PMR DMSO
7.098
7.056
7.035
6.921
6.856
6.832
6.827
3.861
3.775
3.715
3.700
3.682
3.369
3.252
3.081
3.066
3.051
2.509
2.505
MeO
MeO
MeO
MeO
N
O
O
17
7.2
7.0
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.19
1.07
2.30
3.37
3.14
2.16
3.46
3.28
2.30

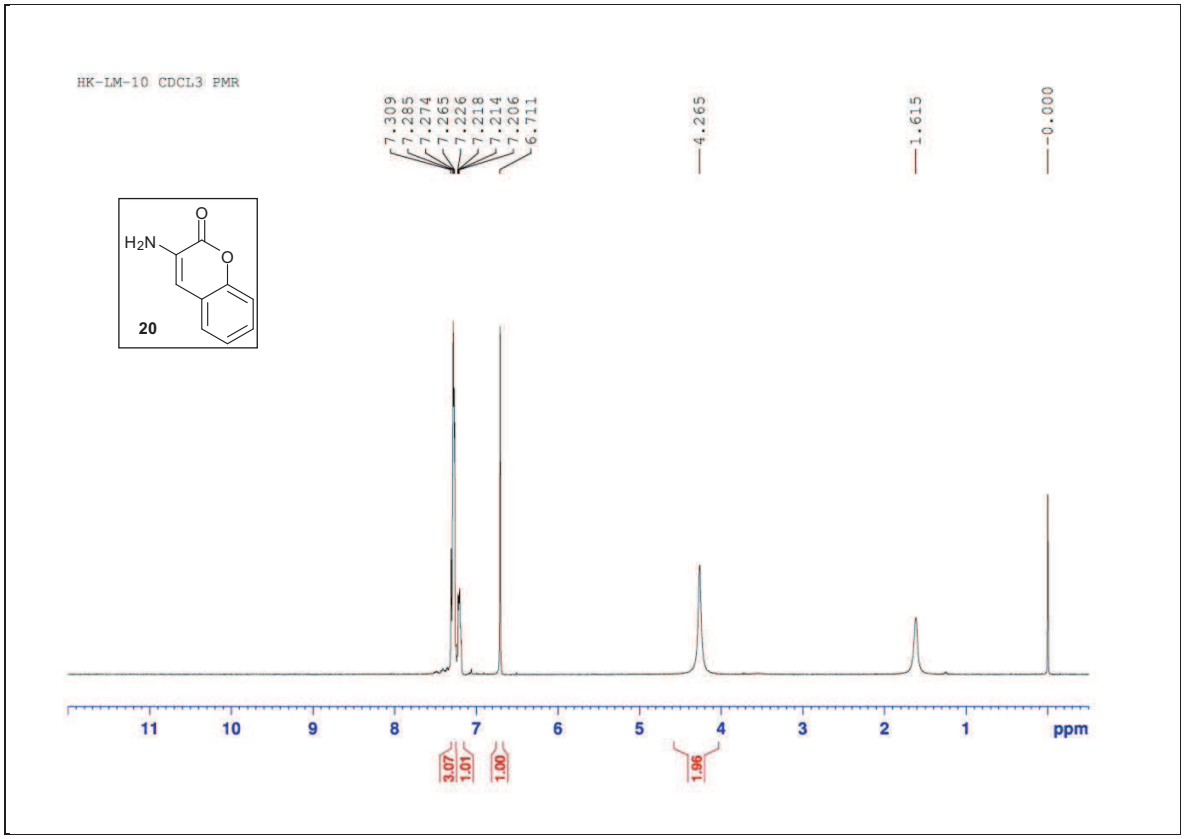

HK-LM-31 DMSO CMR
182.85
158.00
157.05
153.14
148.82
148.37
146.98
133.84
122.94
122.56
115.97
113.49
112.16
112.02
111.45
107.24
55.94
55.61
55.53
54.62
40.07
39.86
39.66
39.45
39.24
39.03
38.82
35.90
27.55
MeO
MeO
MeO
MeO
N
O
O
17
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

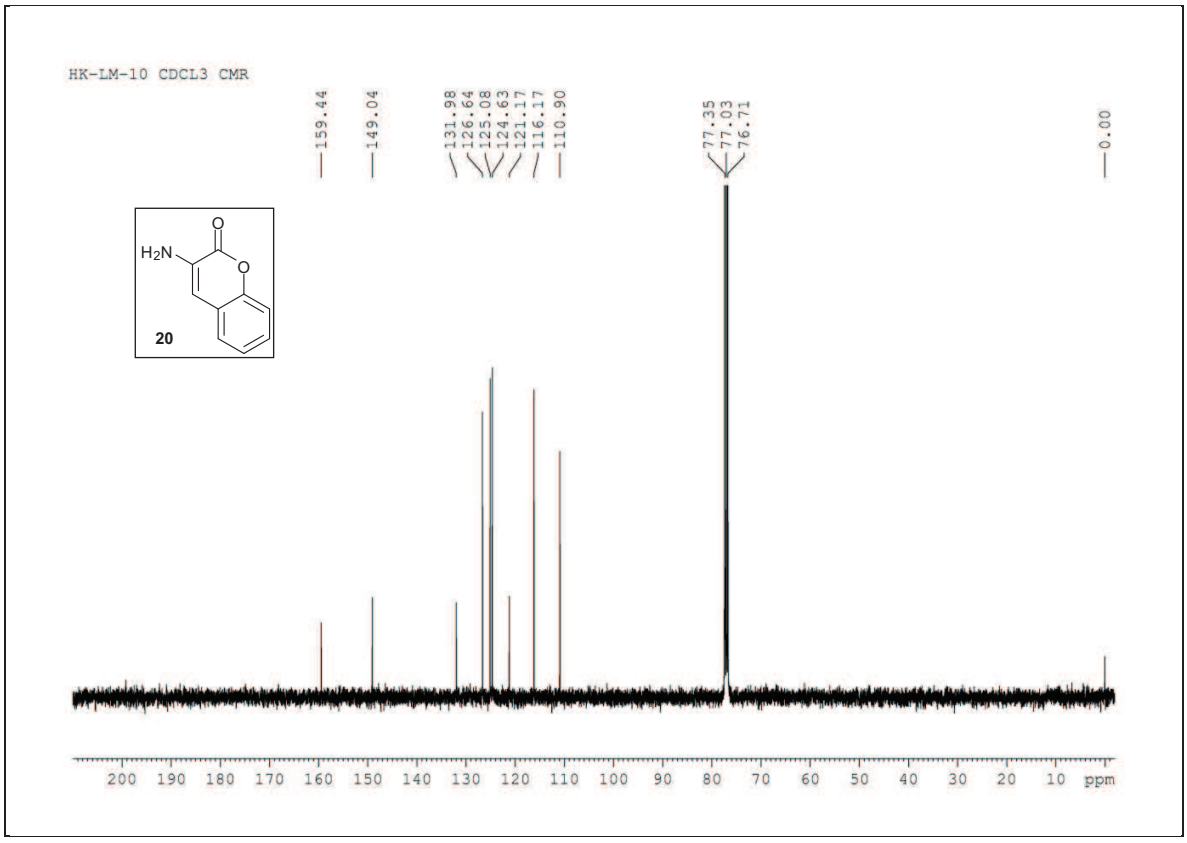

HK-LM-31 DMSO DEPT
122.55
113.46
112.13
112.01
111.42
55.94
55.60
55.52
54.61
40.11
39.91
39.70
39.49
39.28
35.90
27.55
MeO
MeO
MeO
MeO
N
O
O
17
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

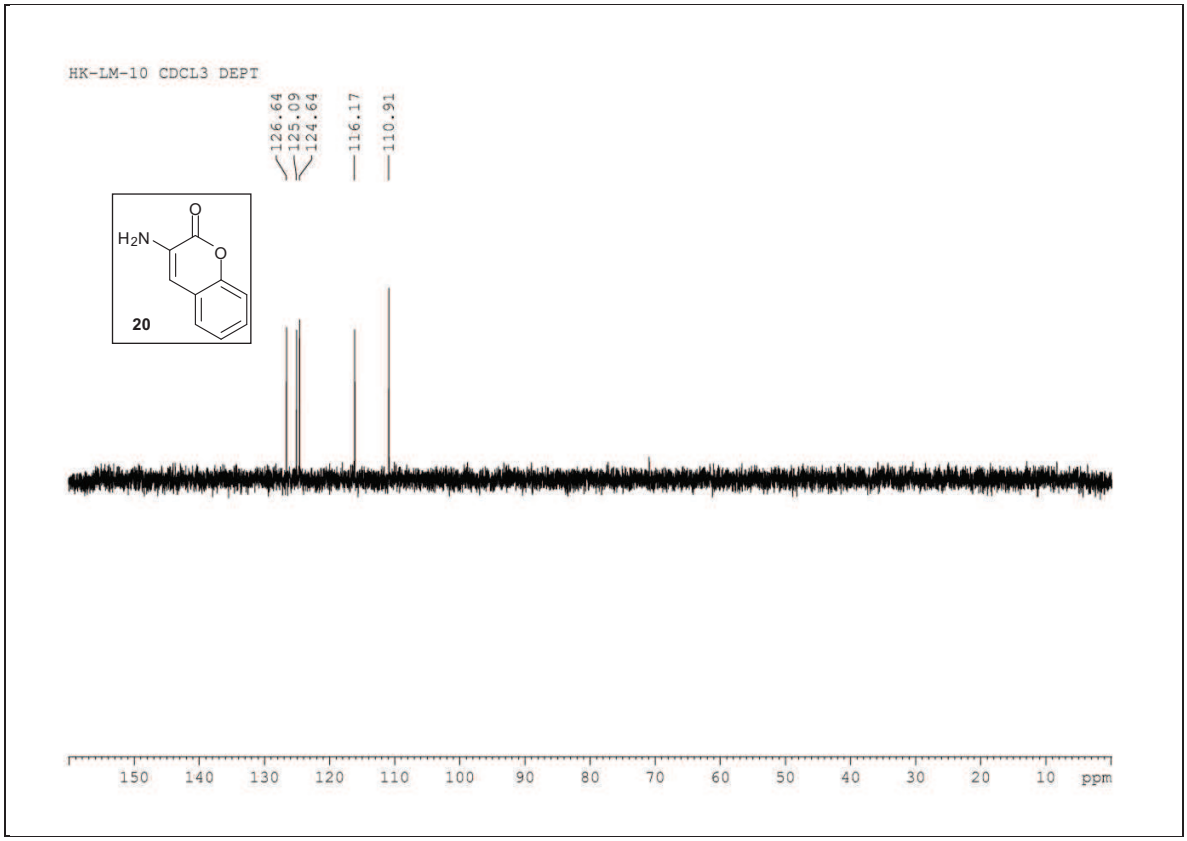

HK-LM-11 CDCL3 PMR
8.682
8.099
7.527
7.507
7.469
7.451
7.430
7.338
7.325
7.318
7.307
7.288
7.267
2.254
1.633
0.000
H
N
O
O
O
21
7.5 7.4 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
0.96
1.06
1.05
2.06
3.13

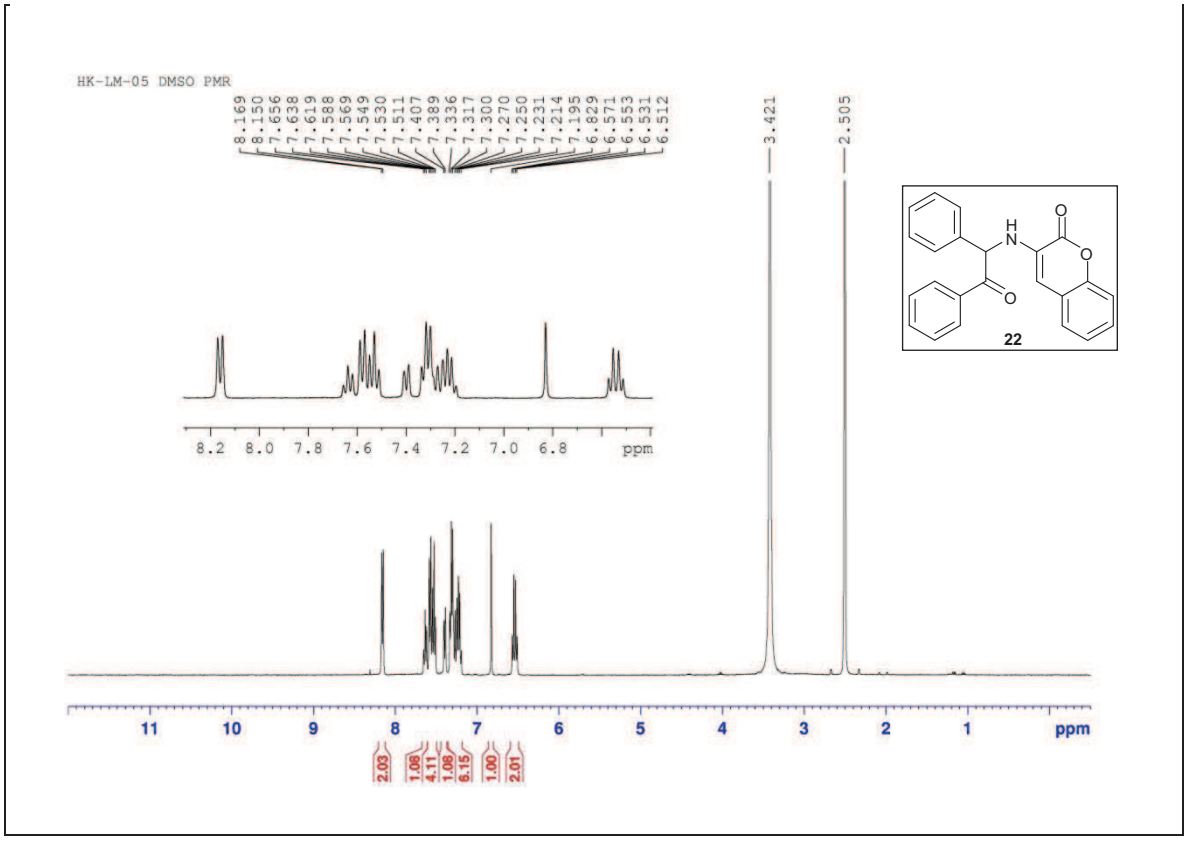

HK-LM-11 CDCL3 CMR
169.40
158.79
149.88
129.66
127.82
125.19
123.97
123.29
119.83
116.36
77.34
77.03
76.71
24.74
-0.01
21
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

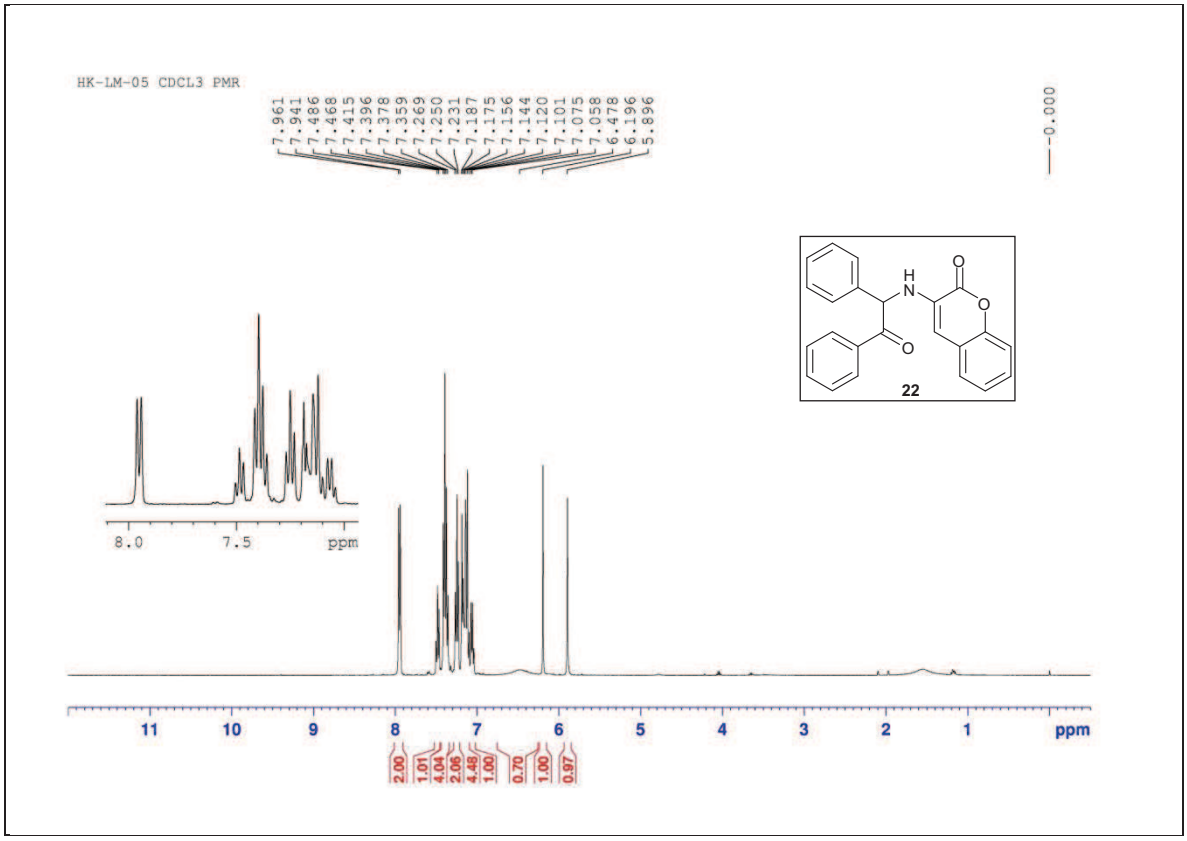

HK-LM-11 CDCL3 DEPT
129.67
127.82
125.20
123.30
116.36
24.75
21
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

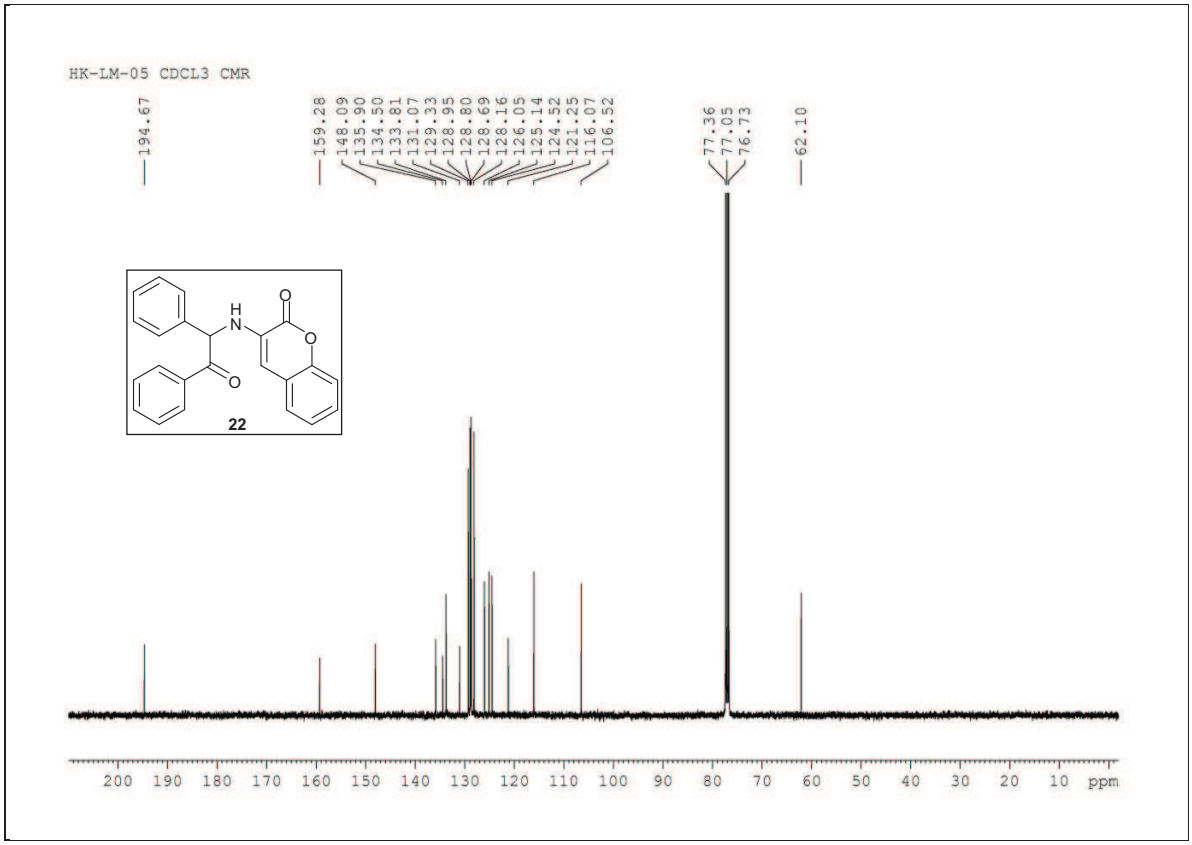

HK-LM-10 CDCL3 PMR
7.309
7.285
7.274
7.265
7.226
7.218
7.214
7.206
6.711
4.265
1.615
0.000
H2N
O
O
20
11
10
9
8
7
6
5
4
3
2
1
ppm
3.07
1.01
1.00
1.96

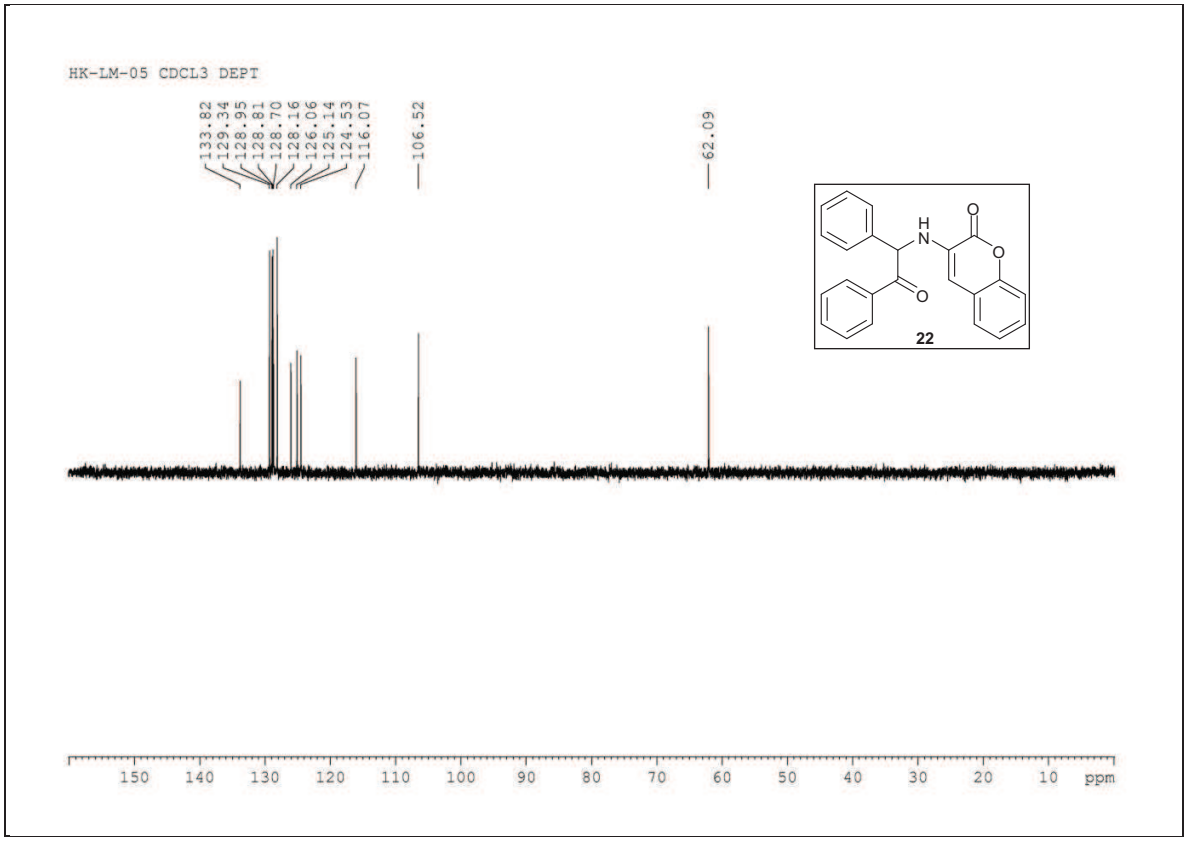

HK-LM-10 CDCL3 CMR
159.44
149.04
131.98
126.64
125.08
124.63
121.17
116.17
110.90
77.35
77.03
76.71
0.00
H2N
O
O
20
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

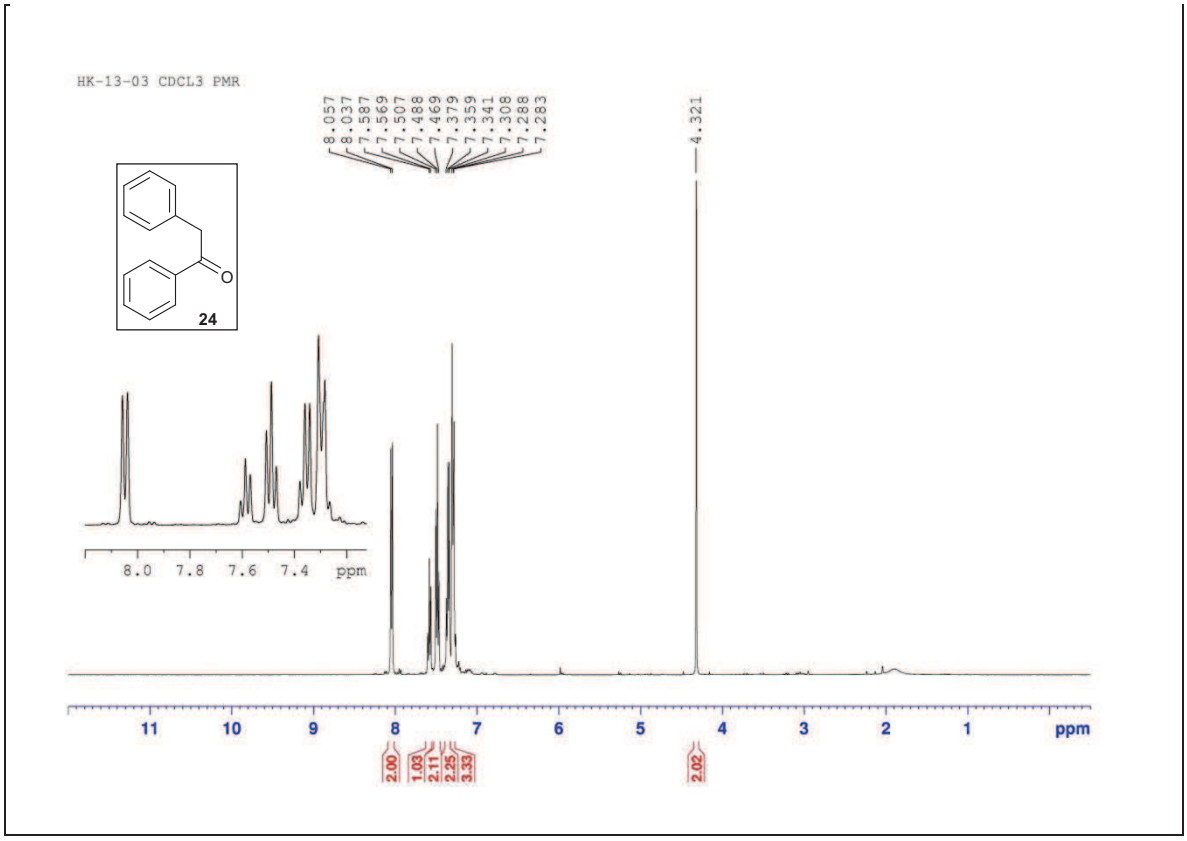

HK-LM-10 CDCL3 DEPT
126.64
125.09
124.64
116.17
110.91
H2N
O
O
20
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

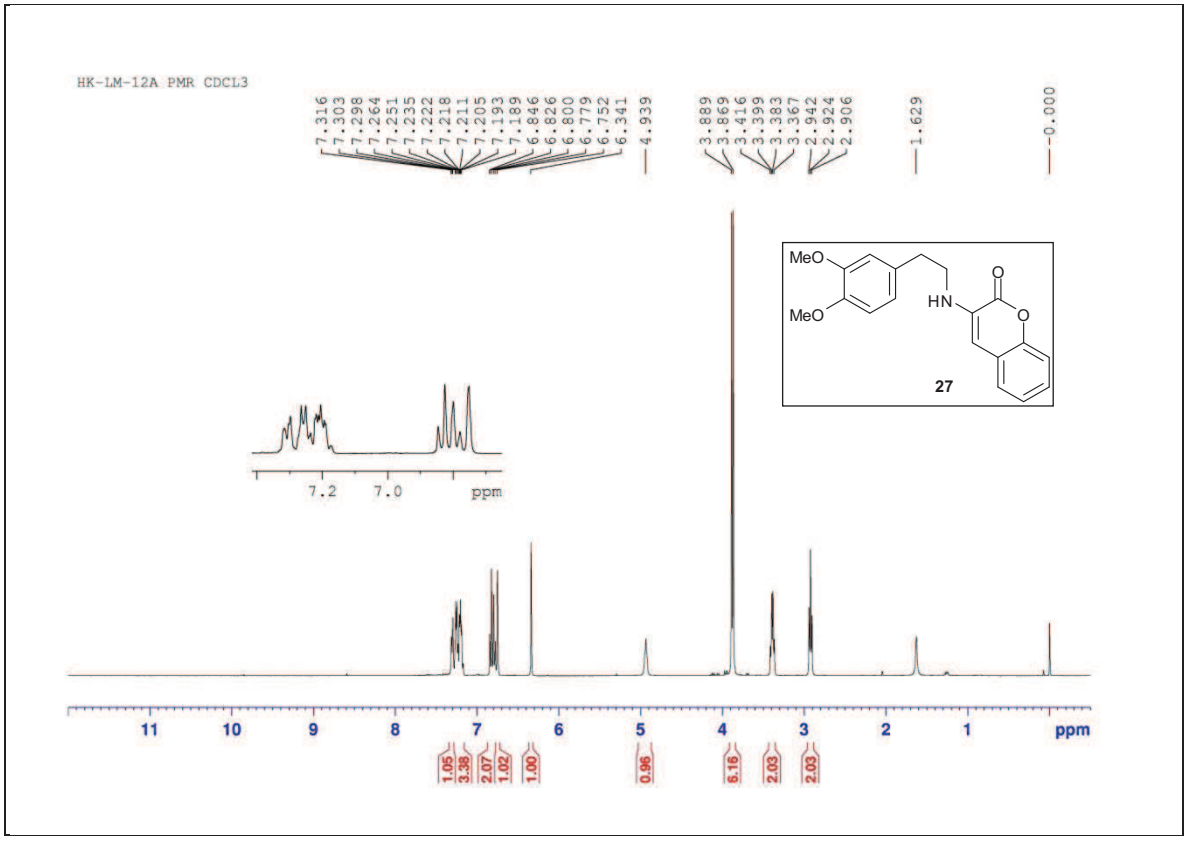

HK-LM-05 DMSO PMR
8.169
8.150
7.656
7.638
7.619
7.588
7.569
7.549
7.530
7.511
7.407
7.389
7.336
7.317
7.300
7.270
7.250
7.231
7.214
7.195
6.829
6.571
6.553
6.531
6.512
3.421
2.505
H
N
O
O
O
22
8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
2.03
1.06
4.11
1.08
6.15
1.00
2.01

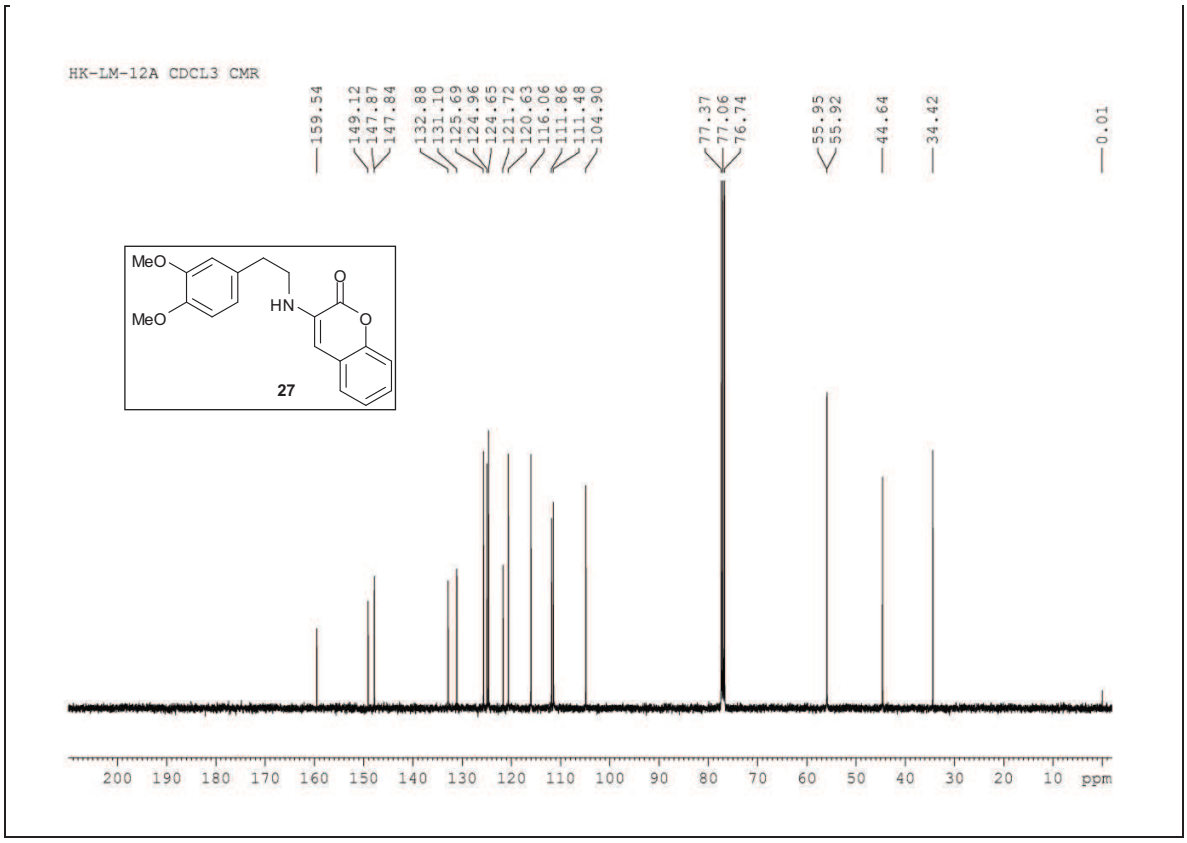

HK-LM-05 CDCL3 PMR
7.961
7.941
7.486
7.468
7.415
7.396
7.378
7.359
7.269
7.250
7.231
7.187
7.175
7.156
7.144
7.120
7.101
7.075
7.058
6.478
6.196
5.896
-0.000
22
8.0
7.5
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
2.00
1.01
4.04
2.06
4.48
1.00
0.70
1.00
0.97

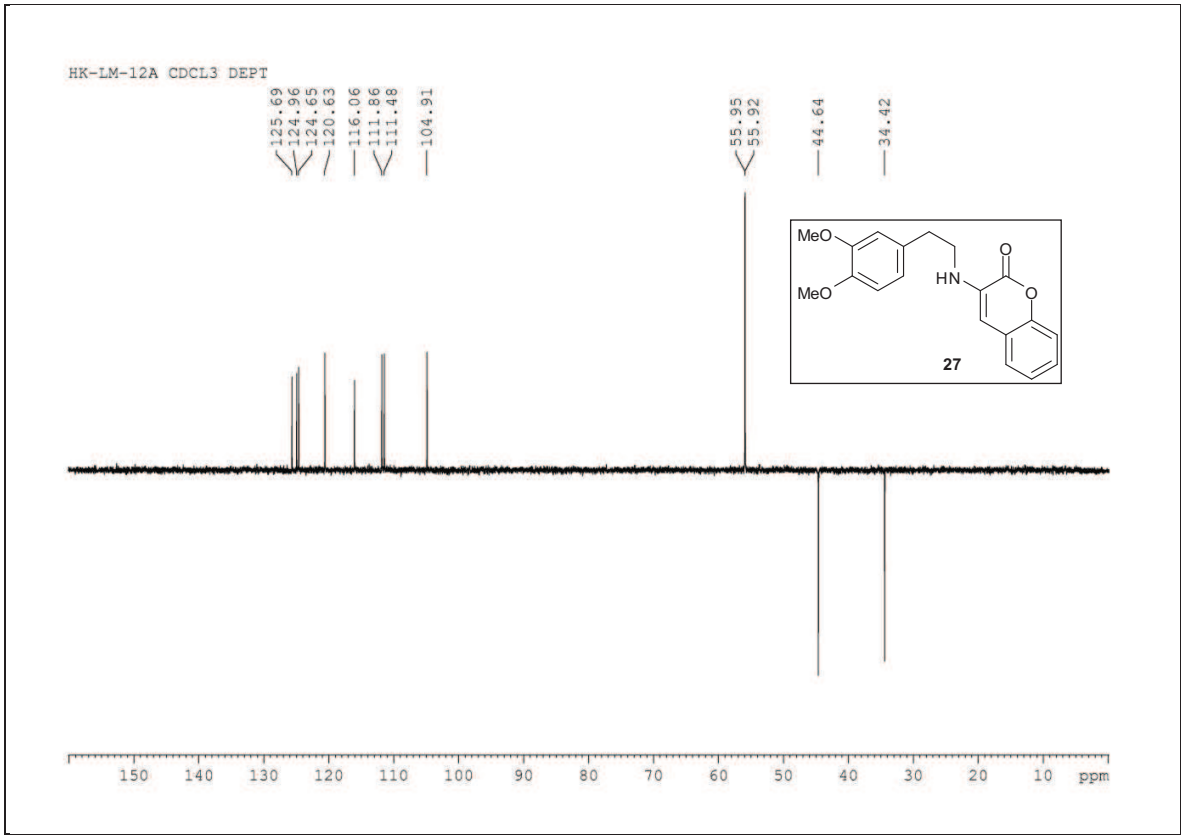

HK-LM-05 CDCL3 CMR
194.67
159.28
148.09
135.90
134.50
133.81
131.07
129.33
128.95
128.80
128.69
128.16
126.05
125.14
124.52
121.25
116.07
106.52
77.36
77.05
76.73
62.10
22
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

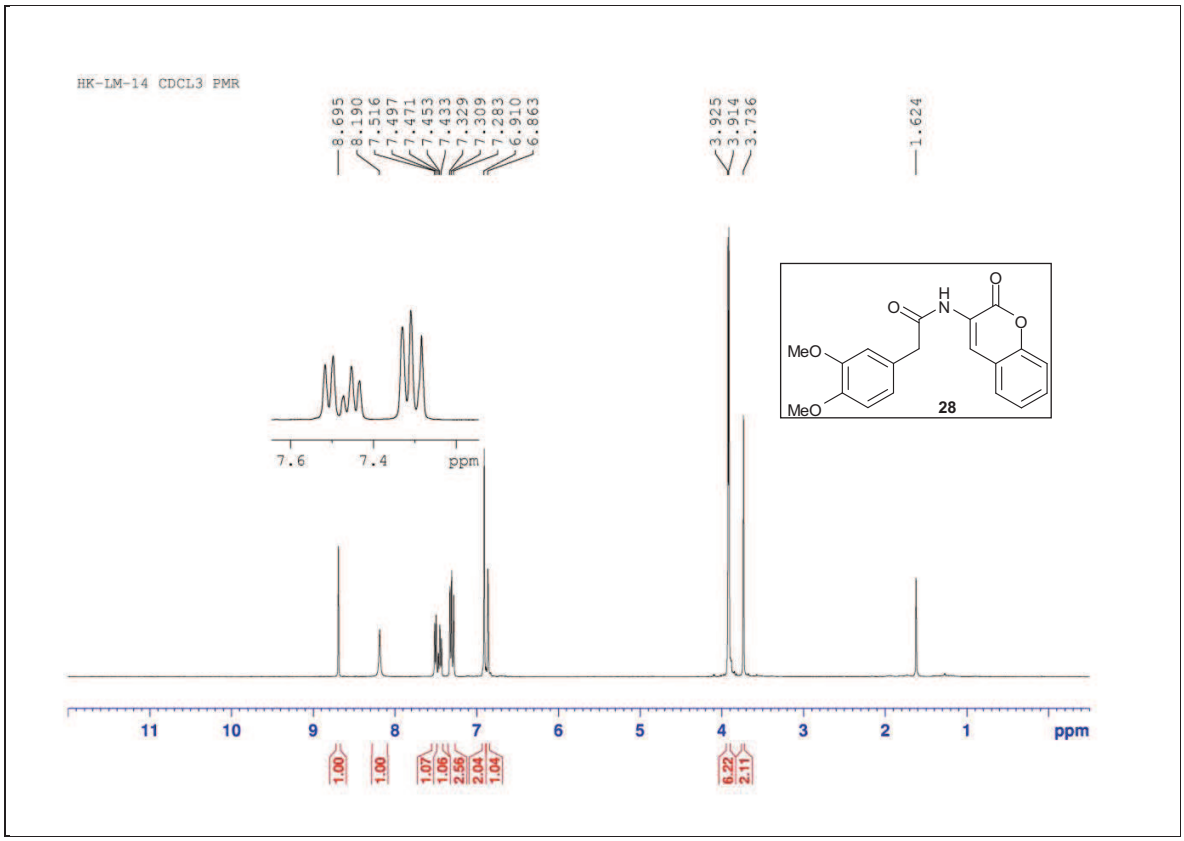

HK-LM-05 CDCL3 DEPT
133.82
129.34
128.95
128.81
128.70
128.16
126.06
125.14
124.53
116.07
106.52
62.09
H
N
O
O
O
22
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

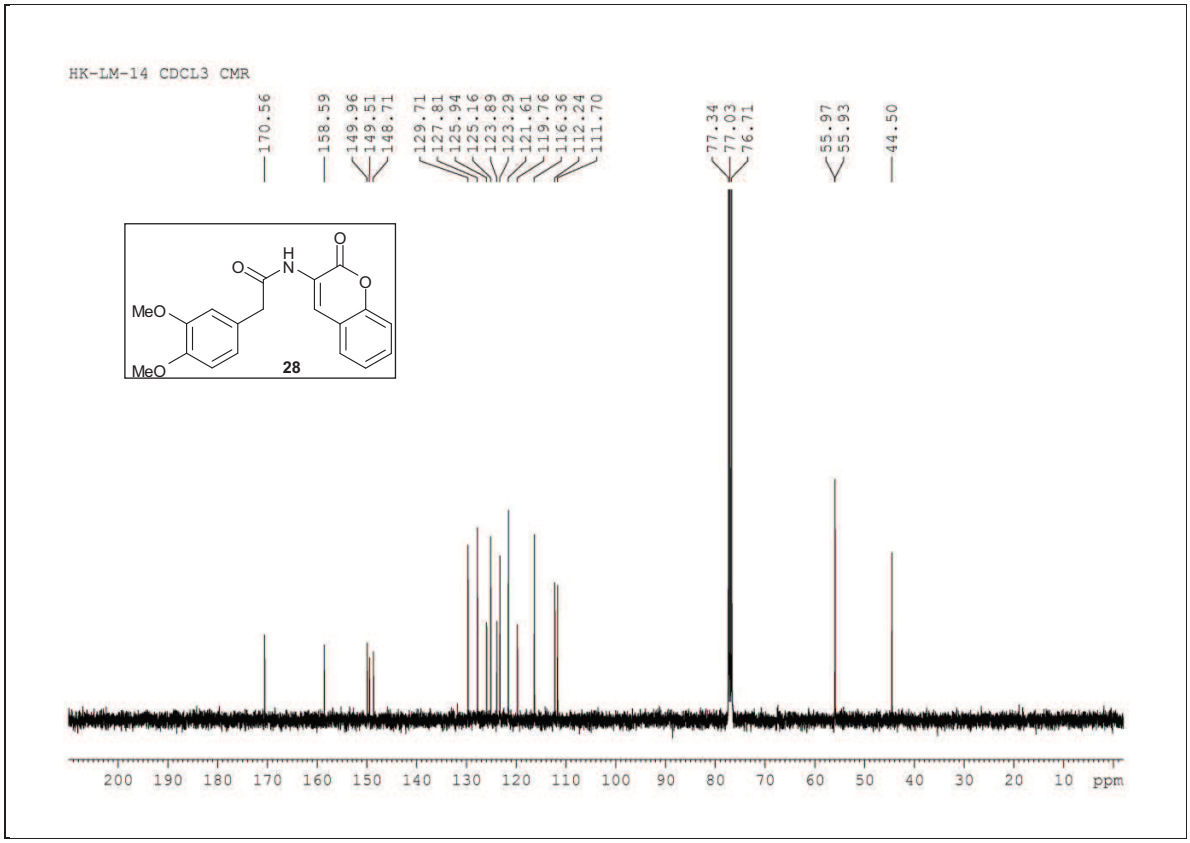

HK-13-03 CDCL3 PMR
8.057
8.037
7.587
7.569
7.507
7.488
7.469
7.379
7.359
7.341
7.308
7.288
7.283
4.321
O
24
8.0 7.8 7.6 7.4 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
2.00
1.03
2.11
2.25
3.33
2.02

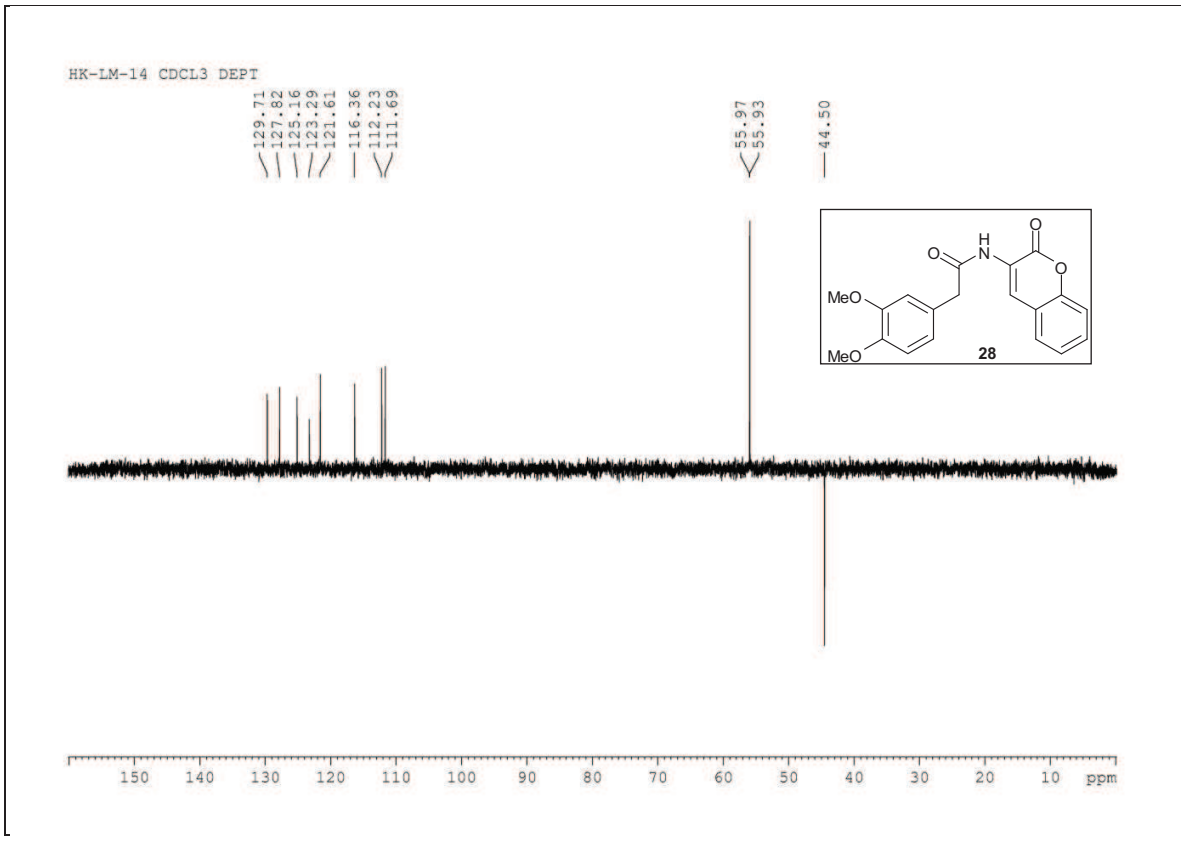

HK-LM-12A PMR CDCL3
7.316
7.303
7.298
7.264
7.251
7.235
7.222
7.218
7.211
7.205
7.193
7.189
6.846
6.826
6.800
6.779
6.752
6.341
4.939
3.889
3.869
3.416
3.399
3.383
3.367
2.942
2.924
2.906
1.629
0.000
MeO
MeO
HN
O
O
27
7.2
7.0
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.05
3.38
2.07
1.02
1.00
0.96
6.16
2.03
2.03

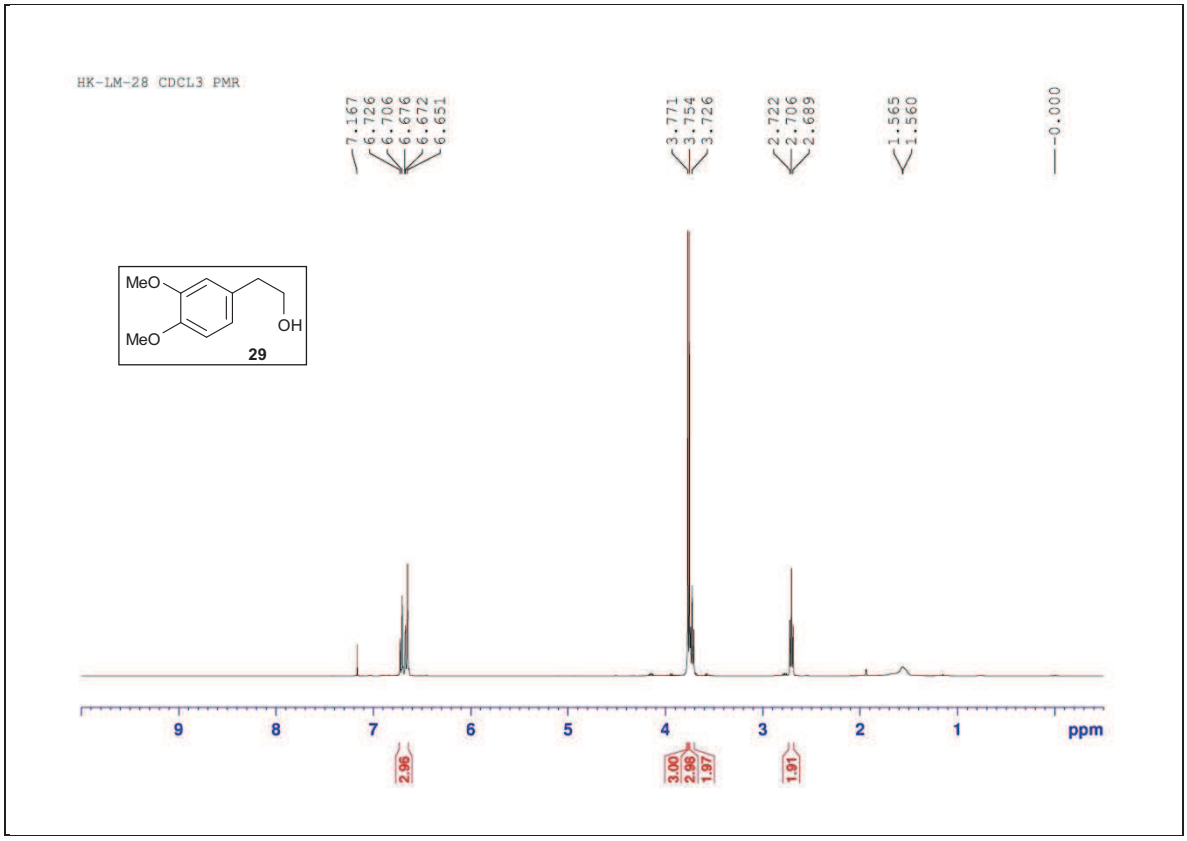

HK-LM-12A CDCL3 CMR
159.54
149.12
147.87
147.84
132.88
131.10
125.69
124.96
124.65
121.72
120.63
116.06
111.86
111.48
104.90
77.37
77.06
76.74
55.95
55.92
44.64
34.42
0.01
MeO
MeO
HN
O
O
27
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

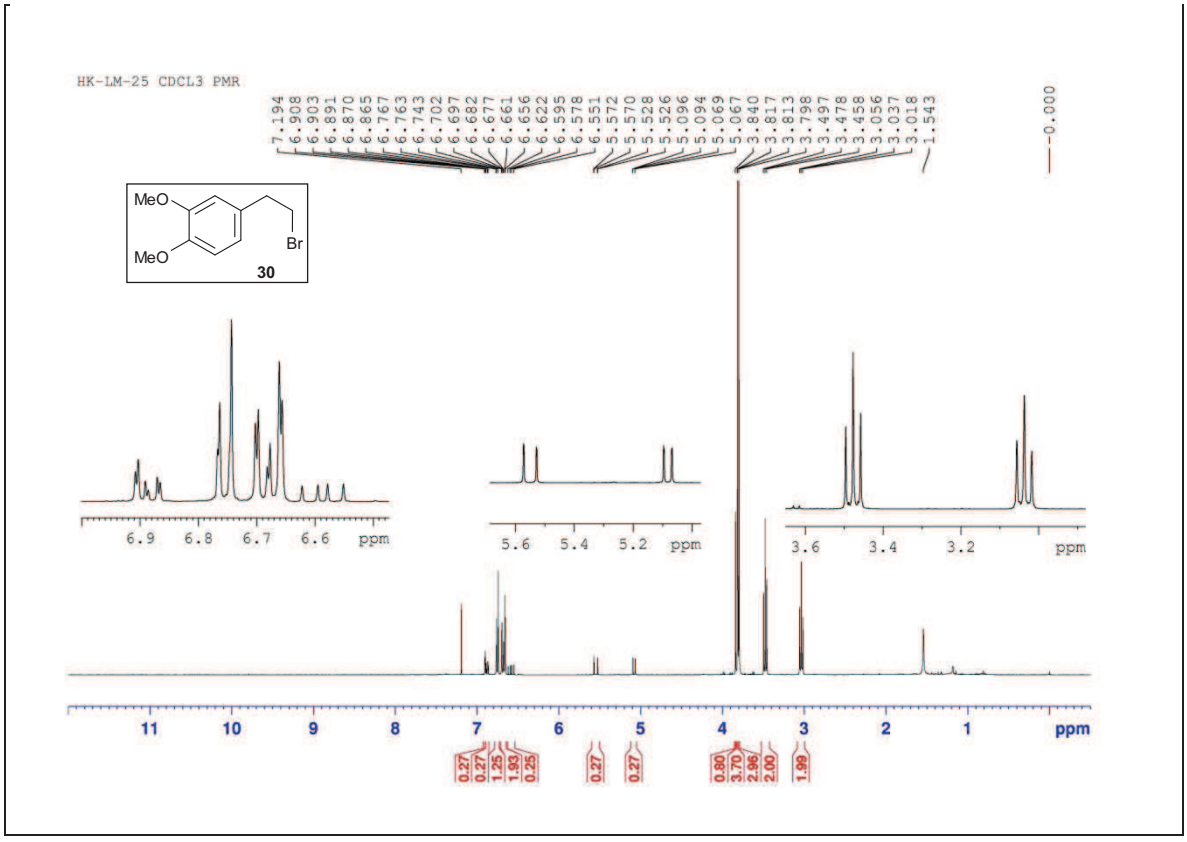

HK-LM-12A CDCL3 DEPT
125.69
124.96
124.65
120.63
116.06
111.86
111.48
104.91
55.95
55.92
44.64
34.42
MeO
MeO
HN
O
O
27
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

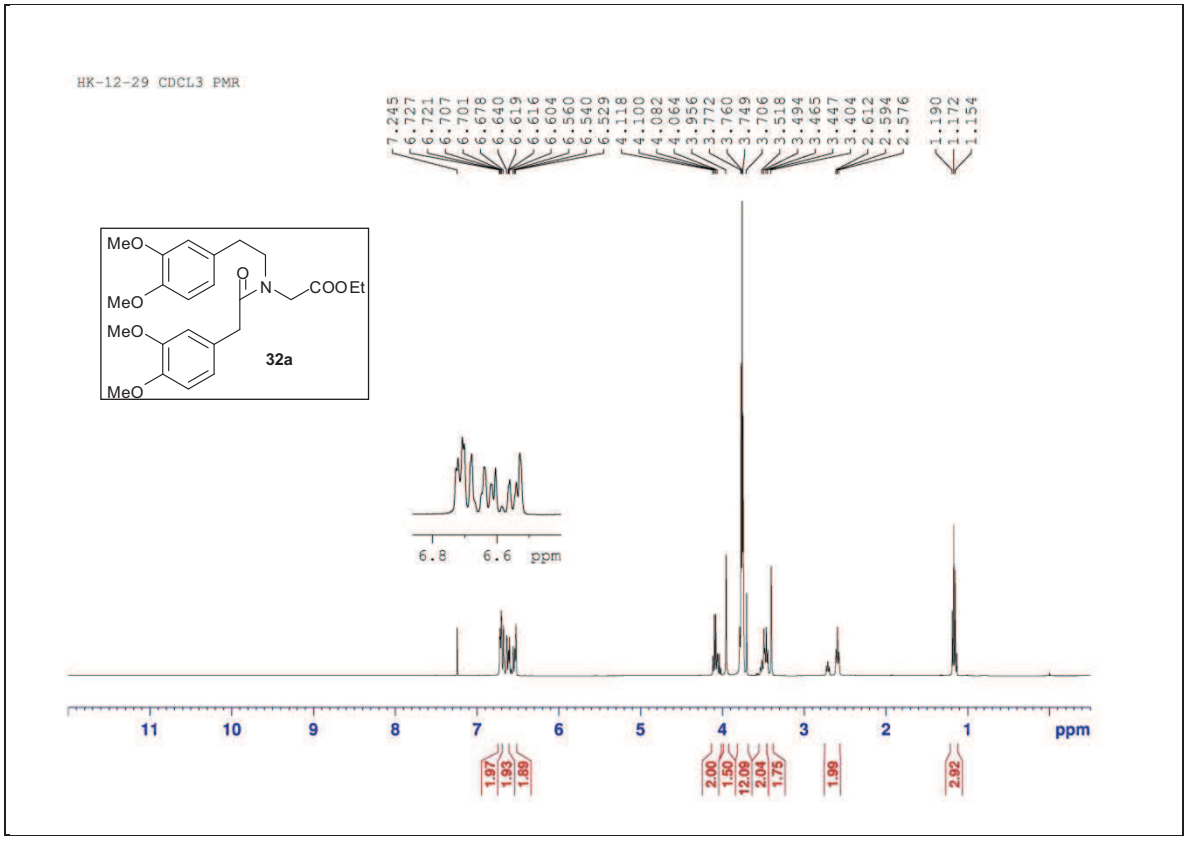

HK-LM-14 CDCL3 PMR
8.695
8.190
7.516
7.497
7.471
7.453
7.433
7.329
7.309
7.283
6.910
6.863
3.925
3.914
3.736
1.624
7.6
7.4
ppm
MeO
MeO
H
N
O
O
O
28
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.00
1.07
1.06
2.56
2.04
1.04
6.22
2.11

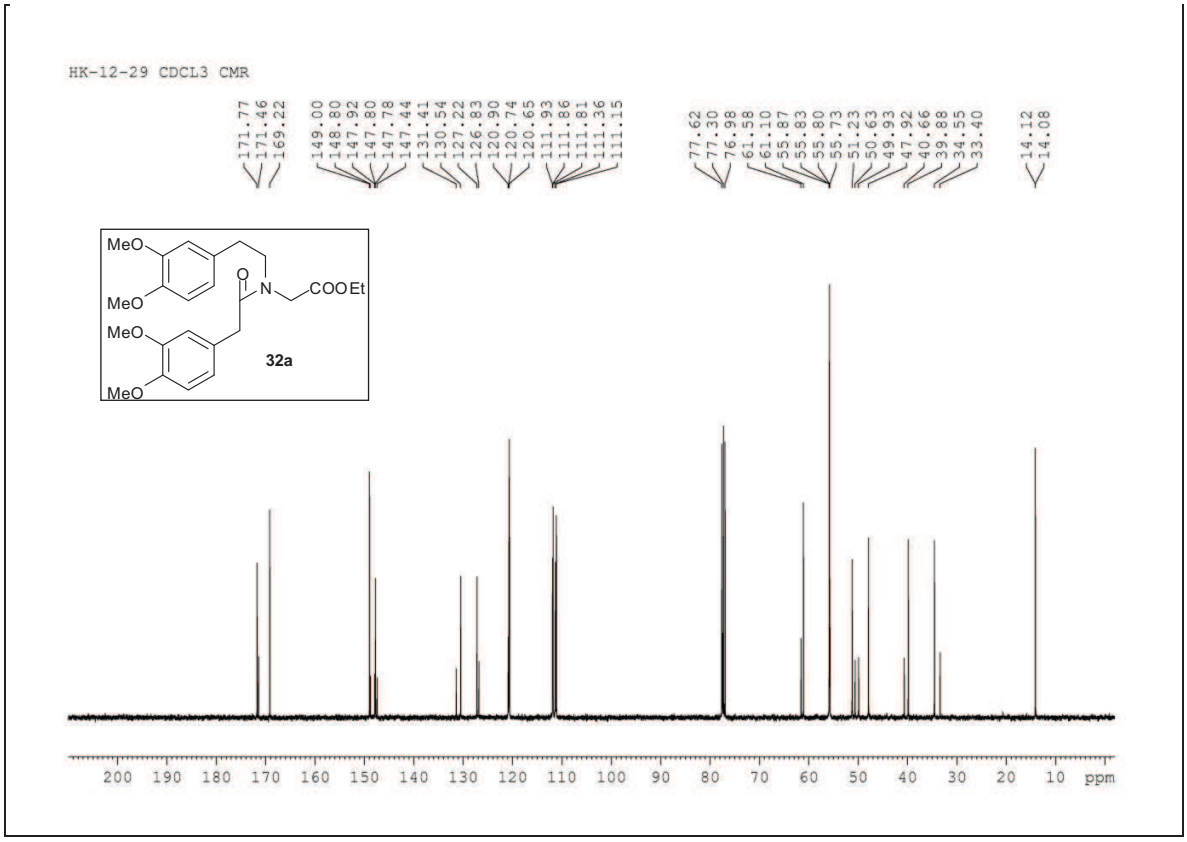

HK-LM-14 CDCL3 CMR
170.56
158.59
149.96
149.51
148.71
129.71
127.81
125.94
125.16
123.89
123.29
121.61
119.76
116.36
112.24
111.70
77.34
77.03
76.71
55.97
55.93
44.50
MeO
MeO
28
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

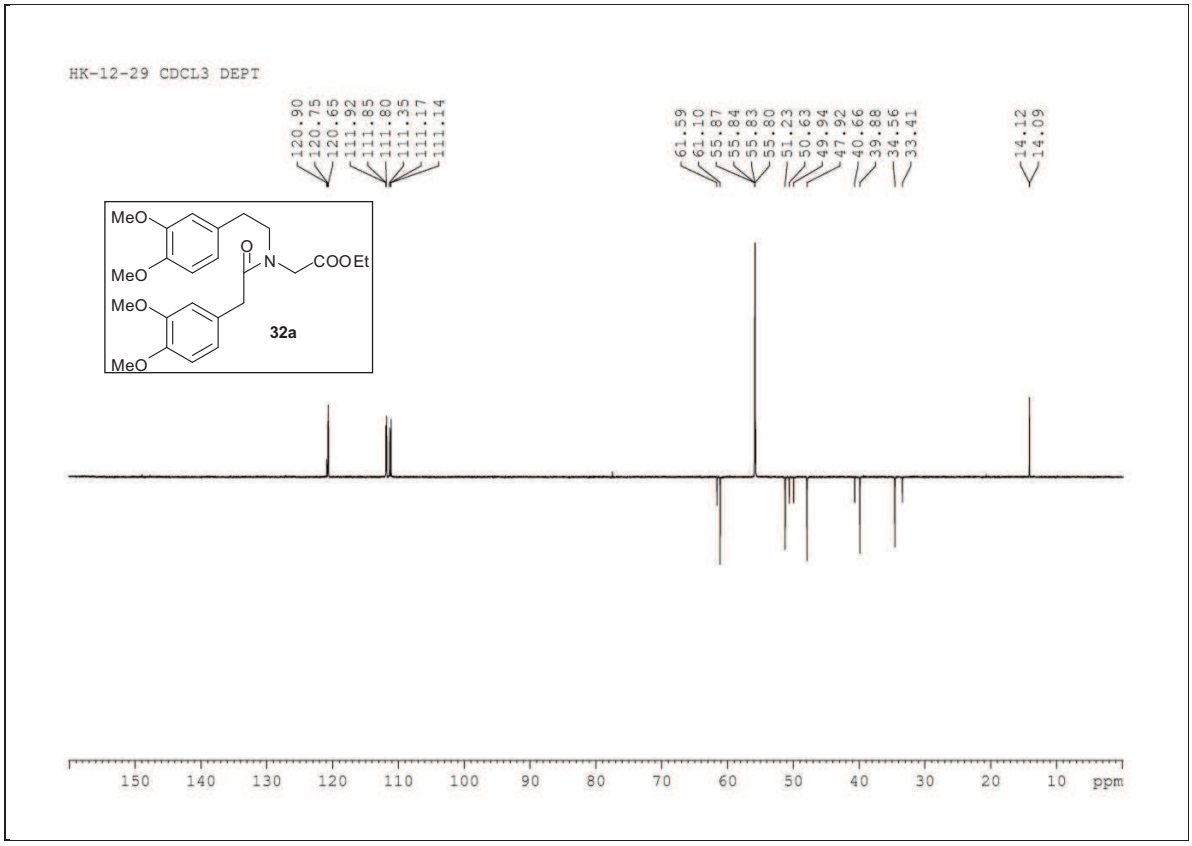

HK-LM-14 CDCL3 DEPT
129.71
127.82
125.16
123.29
121.61
116.36
112.23
111.69
55.97
55.93
44.50
MeO
MeO
28
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

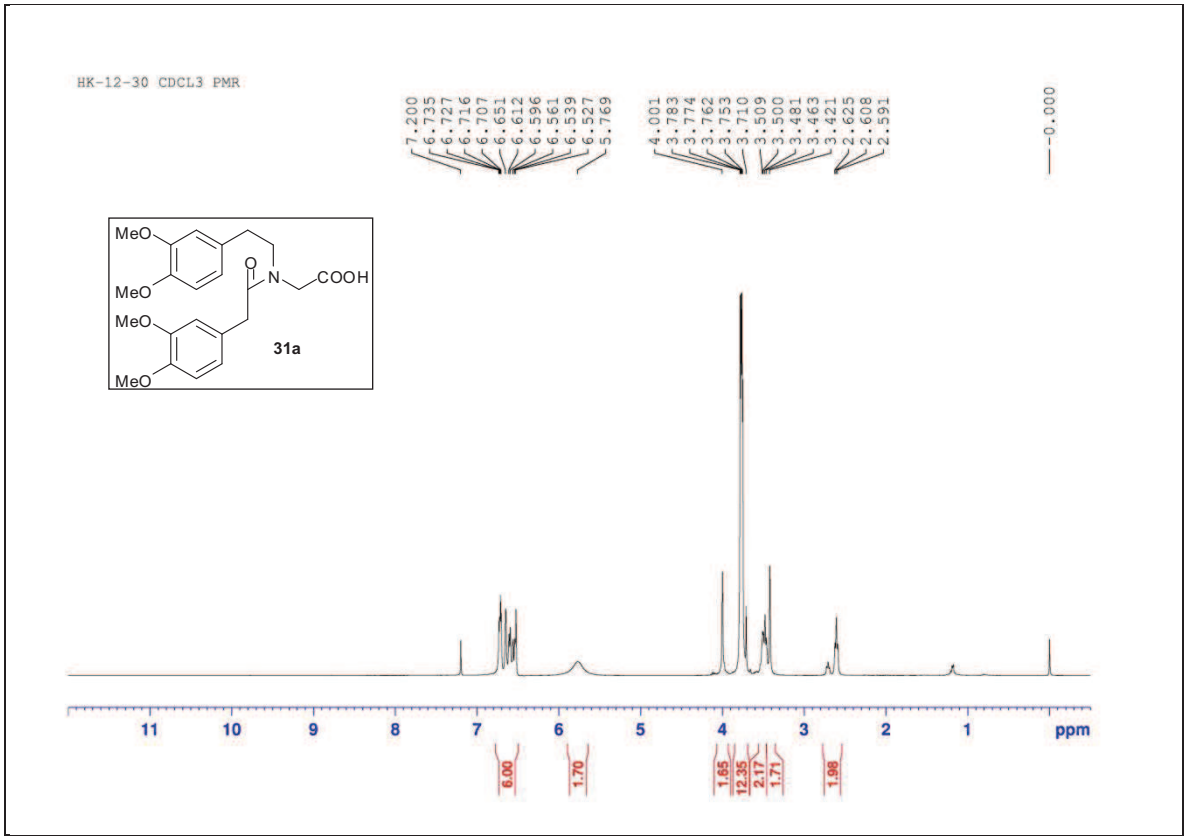

HK-LM-28 CDCL3 PMR
7.167
6.726
6.706
6.676
6.672
6.651
3.771
3.754
3.726
2.722
2.706
2.689
1.565
1.560
-0.000
MeO
MeO
OH
29
9
8
7
6
5
4
3
2
1
ppm
2.96
3.00
2.98
1.97
1.91

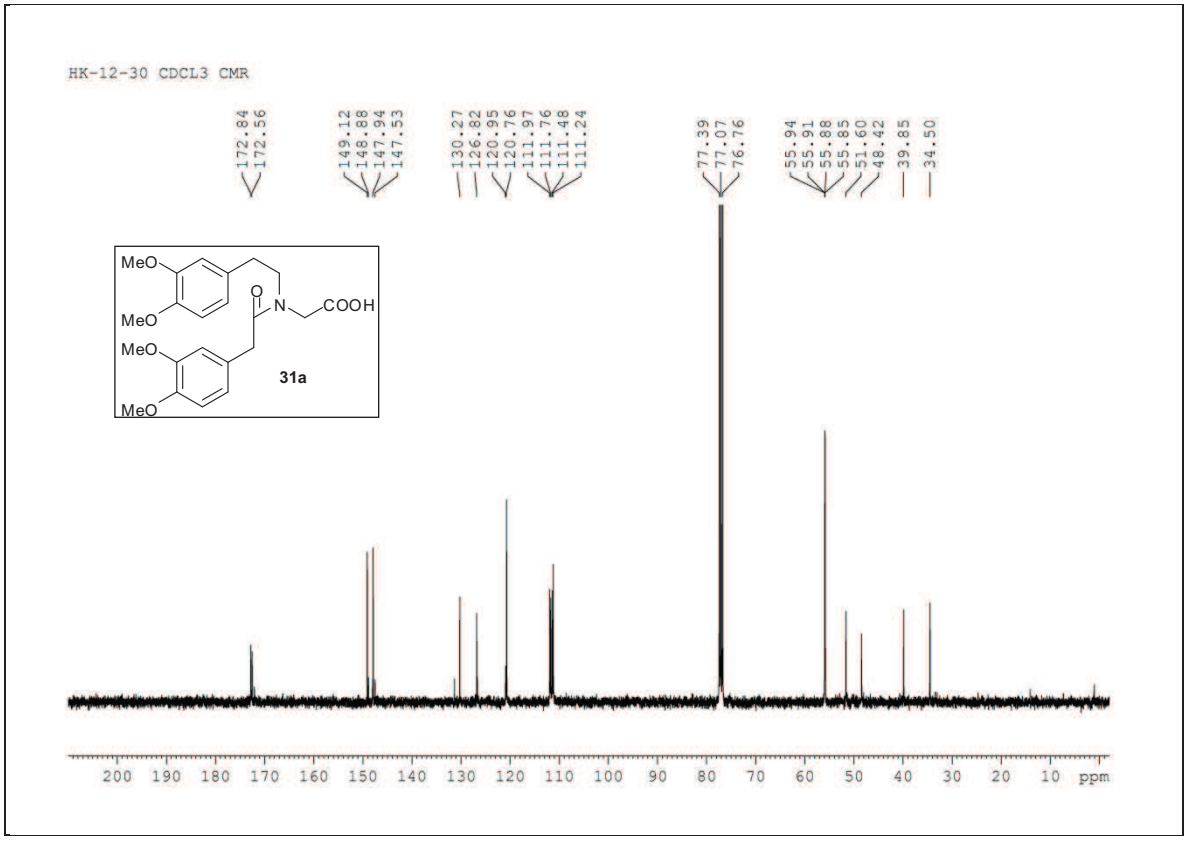

HK-LM-25 CDCL3 PMR
7.194
6.908
6.903
6.891
6.870
6.865
6.767
6.763
6.743
6.702
6.697
6.682
6.677
6.661
6.656
6.622
6.595
6.578
6.551
5.572
5.570
5.528
5.526
5.096
5.094
5.069
5.067
3.840
3.817
3.813
3.798
3.497
3.478
3.458
3.056
3.037
3.018
1.543
-0.000
MeO
MeO
Br
30
6.9
6.8
6.7
6.6
ppm
5.6
5.4
5.2
ppm
3.6
3.4
3.2
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
0.27
0.27
1.25
1.93
0.25
0.27
0.27
0.80
3.70
2.96
2.00
1.99

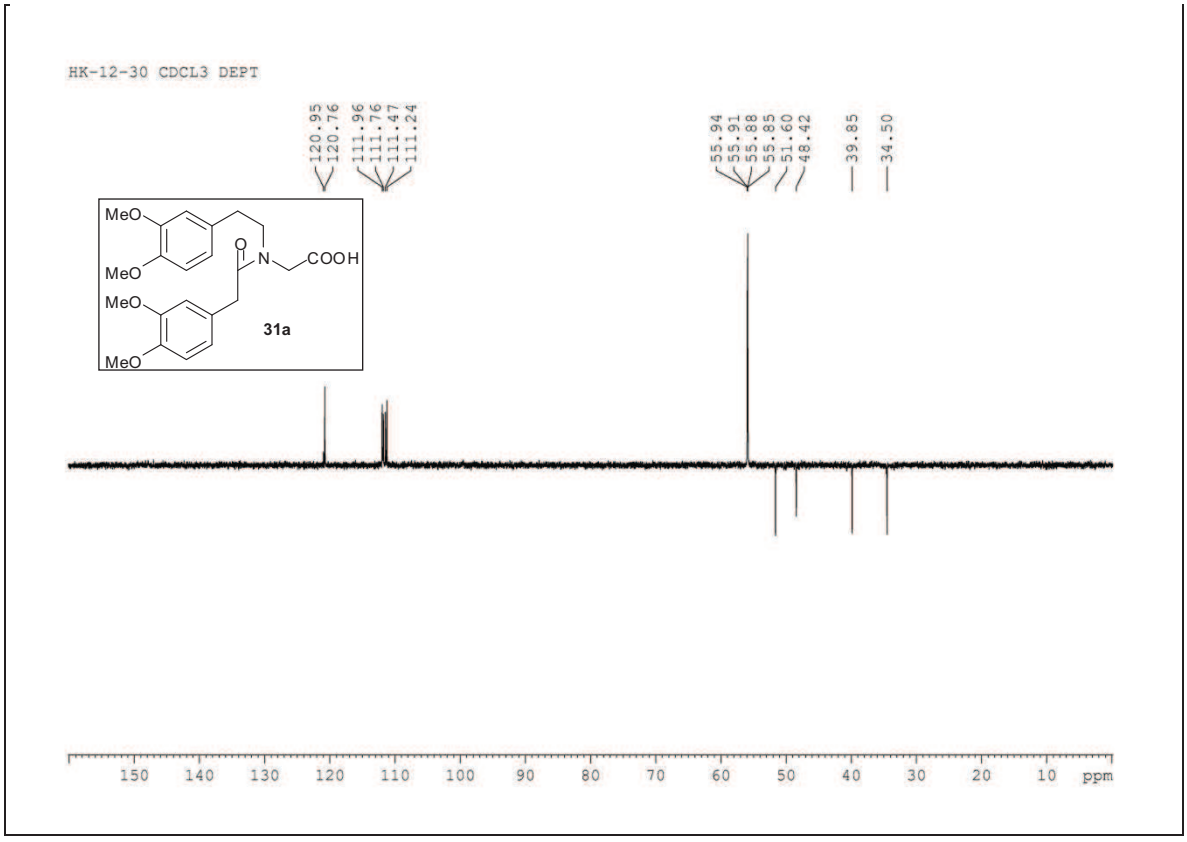

HK-12-29 CDCL3 PMR
7.245
6.727
6.721
6.707
6.701
6.678
6.640
6.619
6.616
6.604
6.560
6.540
6.529
4.118
4.100
4.082
4.064
3.956
3.772
3.760
3.749
3.706
3.518
3.494
3.465
3.447
3.404
2.612
2.594
2.576
1.190
1.172
1.154
MeO
MeO
MeO
MeO
O
N
COOEt
32a
6.8
6.6
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.97
1.93
1.89
2.00
1.50
12.08
2.04
1.75
1.99
2.92

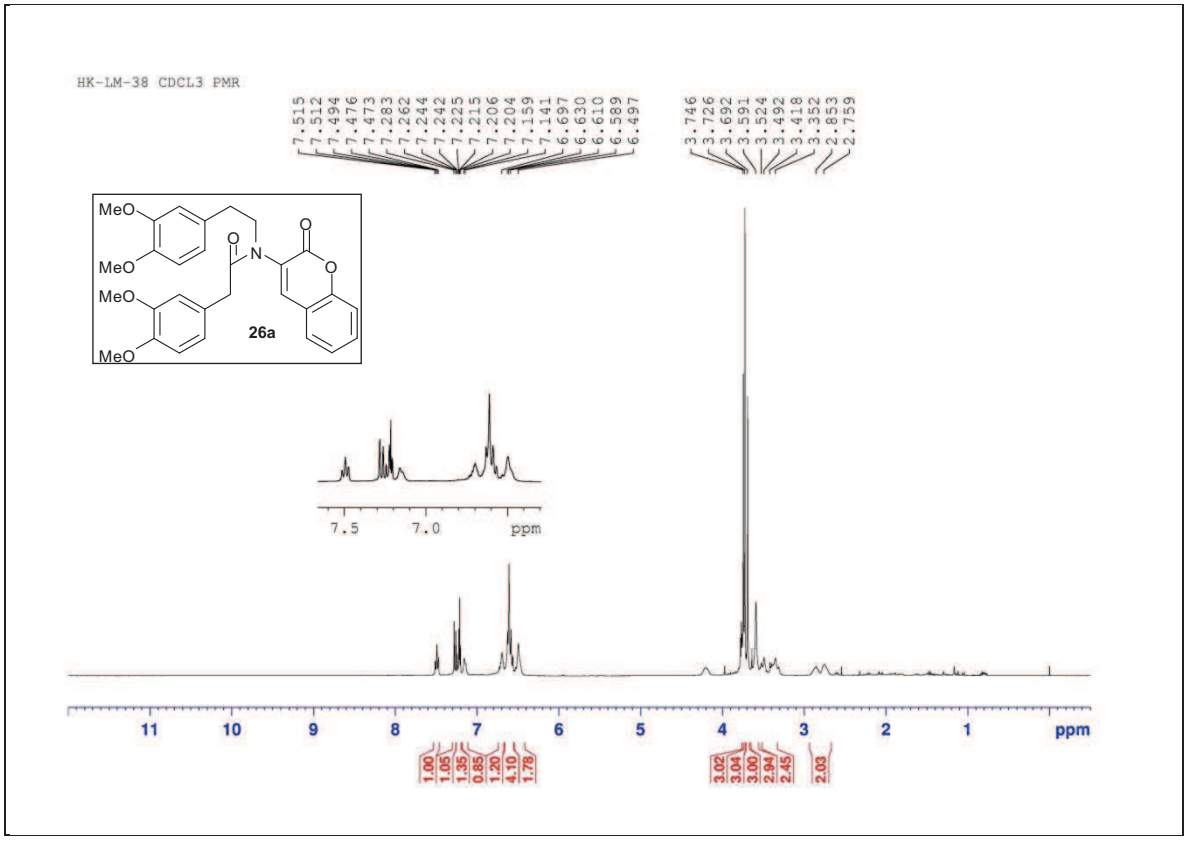

HK-12-29 CDCL3 CMR
171.77
171.46
169.22
149.00
148.80
147.92
147.80
147.78
147.44
131.41
130.54
127.22
126.83
120.90
120.74
120.65
111.93
111.86
111.81
111.36
111.15
77.62
77.30
76.98
61.58
61.10
55.87
55.83
55.80
55.73
51.23
50.63
49.93
47.92
40.66
39.88
34.55
33.40
14.12
14.08
MeO
MeO
MeO
MeO
O
N
COOEt
32a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

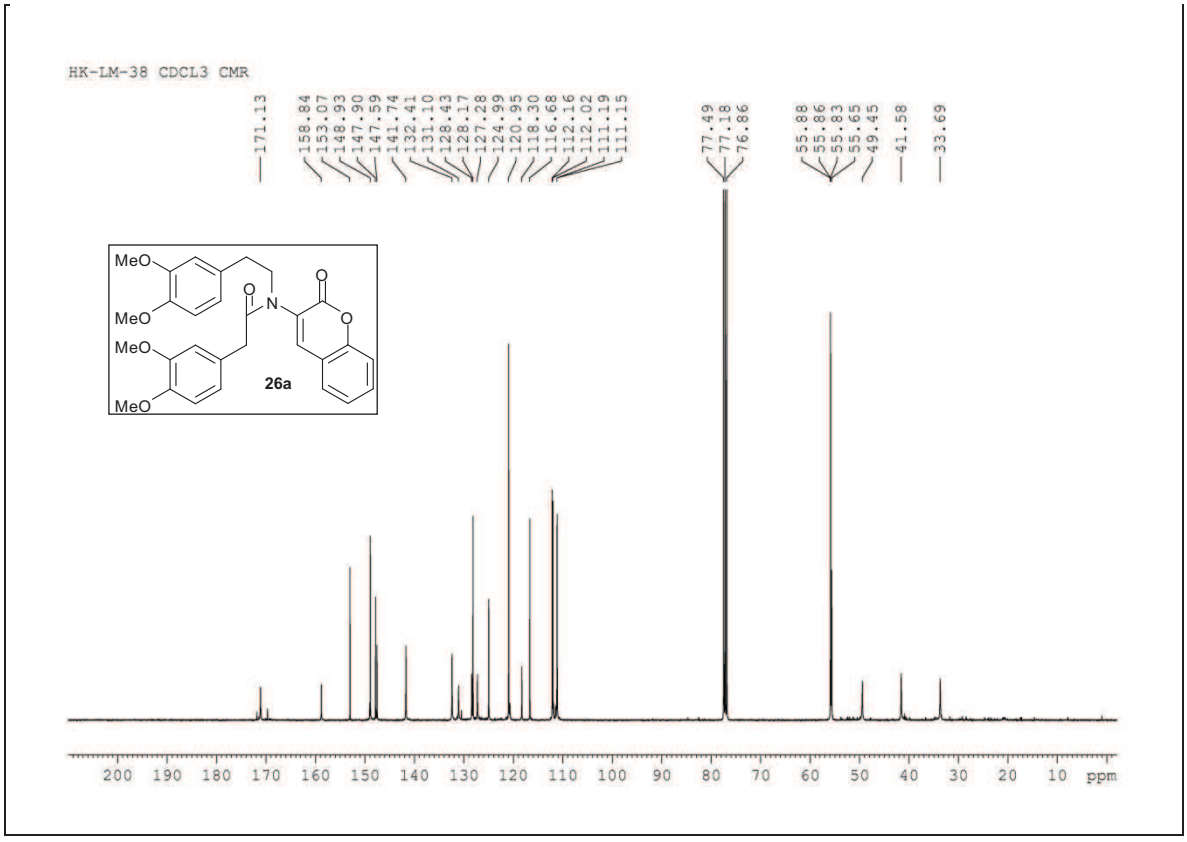

HK-12-29 CDCL3 DEPT
120.90
120.75
120.65
111.92
111.85
111.80
111.35
111.17
111.14
61.59
61.10
55.87
55.84
55.83
55.80
51.23
50.63
49.94
47.92
40.66
39.88
34.56
33.41
14.12
14.09
MeO
MeO
MeO
MeO
O
N
COOEt
32a
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

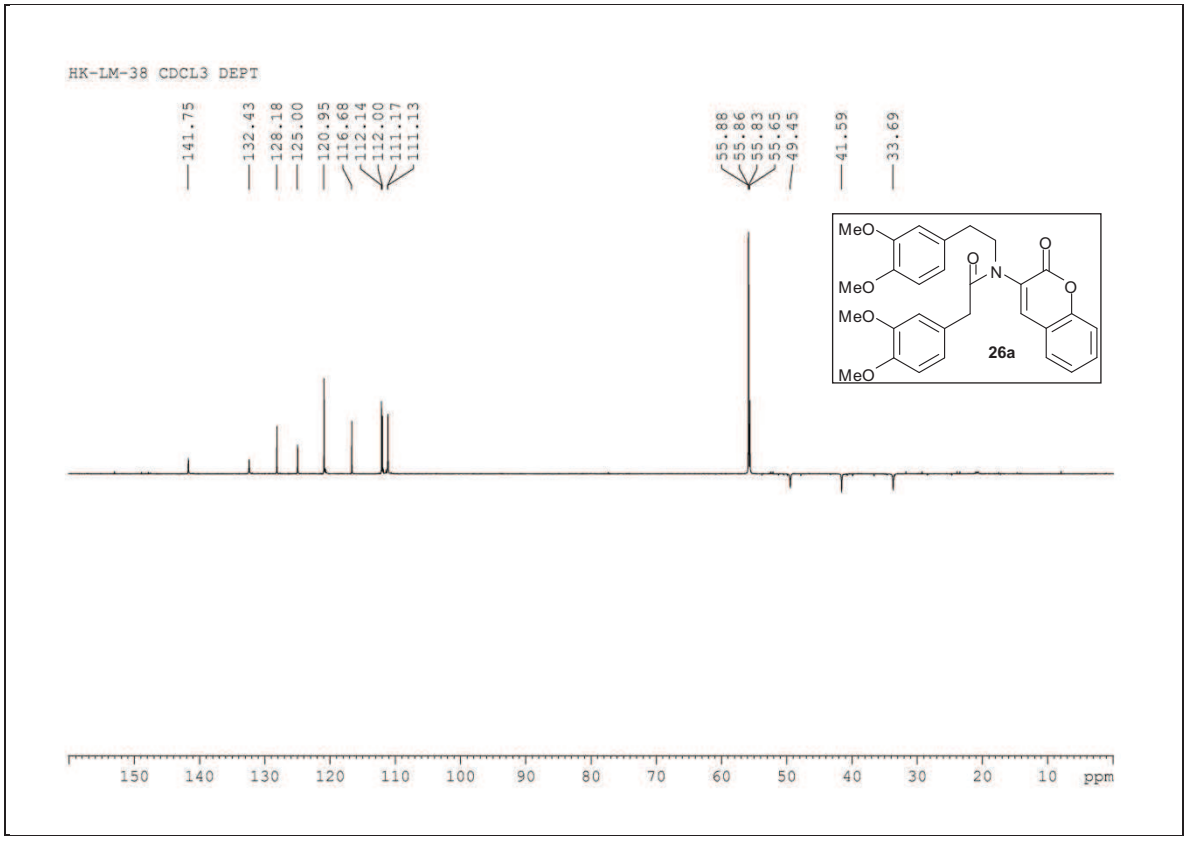

HK-12-30 CDCL3 PMR
7.200
6.735
6.727
6.716
6.707
6.651
6.612
6.596
6.561
6.539
6.527
5.769
4.001
3.783
3.774
3.762
3.753
3.710
3.509
3.500
3.481
3.463
3.421
2.625
2.608
2.591
-0.000
MeO
MeO
MeO
MeO
O
N
COOH
31a
11
10
9
8
7
6
5
4
3
2
1
ppm
6.00
1.70
1.65
12.35
2.17
1.71
1.98

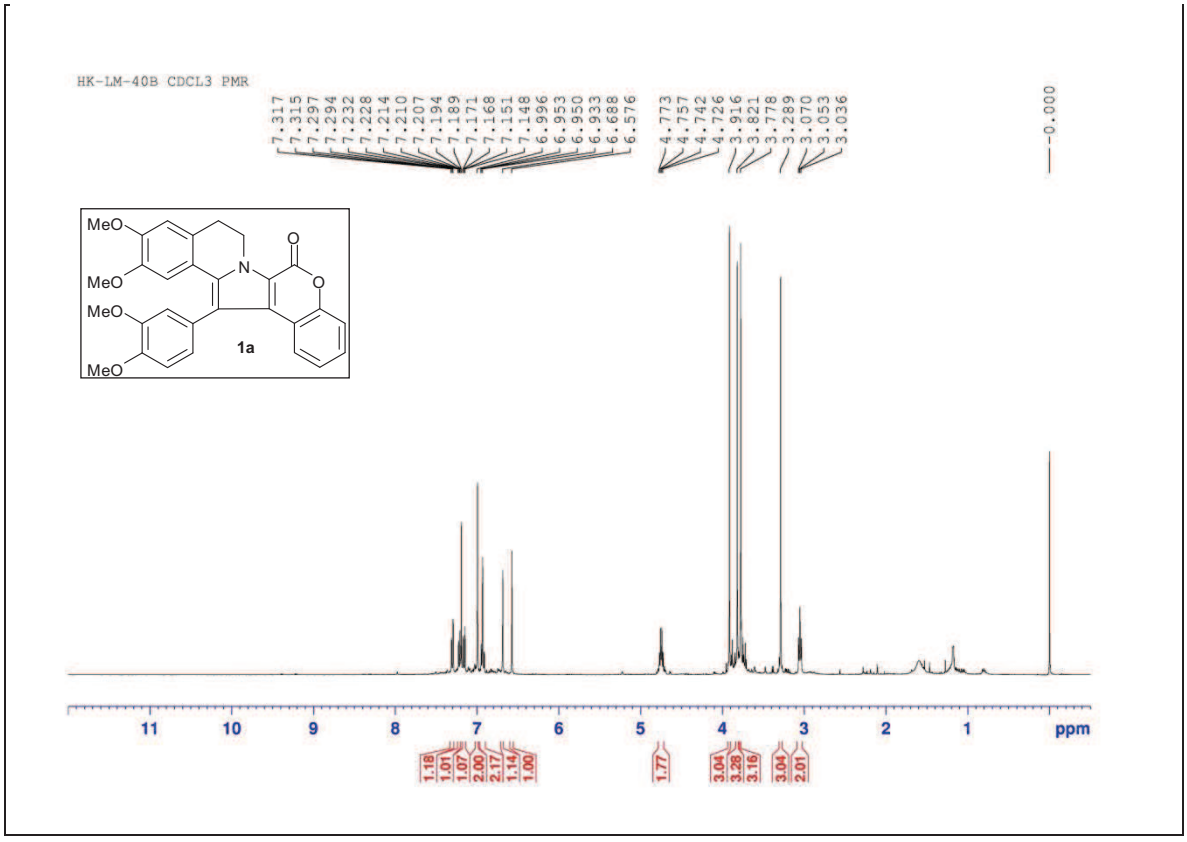

HK-12-30 CDCL3 CMR
172.84
172.56
149.12
148.88
147.94
147.53
130.27
126.82
120.95
120.76
111.97
111.76
111.48
111.24
77.39
77.07
76.76
55.94
55.91
55.88
55.85
51.60
48.42
39.85
34.50
MeO
MeO
MeO
MeO
O
N
COOH
31a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

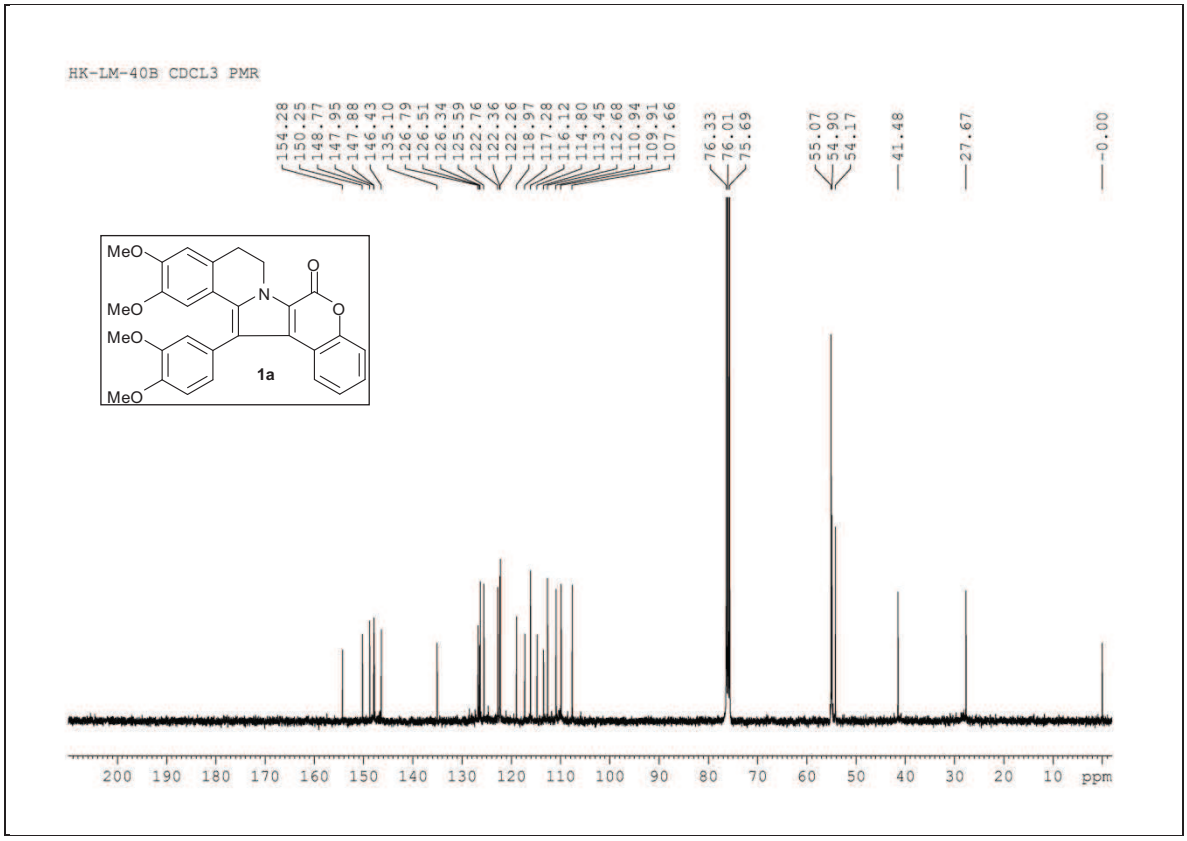

HK-12-30 CDCL3 DEPT
120.95
120.76
111.96
111.76
111.47
111.24
55.94
55.91
55.88
55.85
51.60
48.42
39.85
34.50
MeO
MeO
MeO
MeO
O
N
COOH
31a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

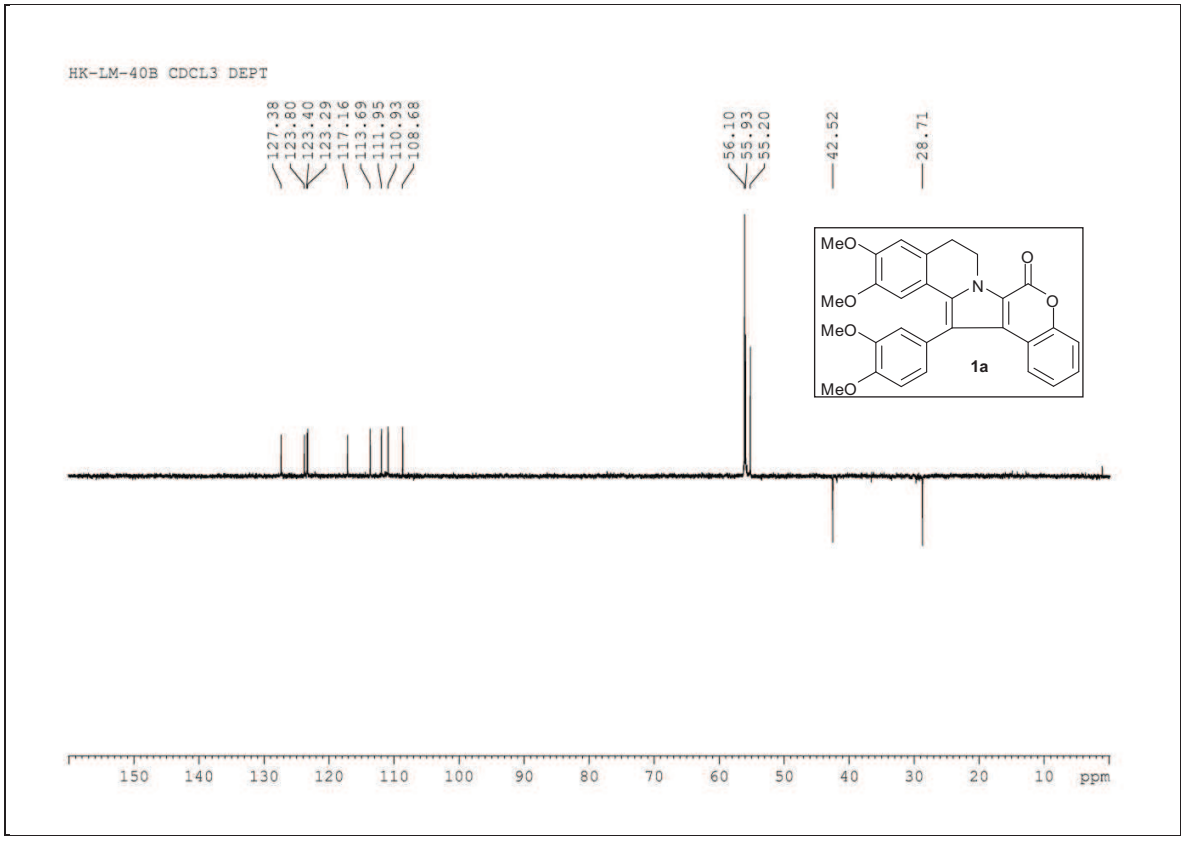

HK-LM-38 CDCL3 PMR
7.515
7.512
7.494
7.476
7.473
7.283
7.262
7.244
7.242
7.225
7.215
7.206
7.204
7.159
7.141
6.697
6.630
6.610
6.589
6.497
3.746
3.726
3.692
3.591
3.524
3.492
3.418
3.352
2.853
2.759
MeO
MeO
MeO
MeO
O
N
O
O
26a
7.5
7.0
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.05
1.35
0.85
1.20
4.10
1.78
3.02
3.04
3.00
2.94
2.45
2.03

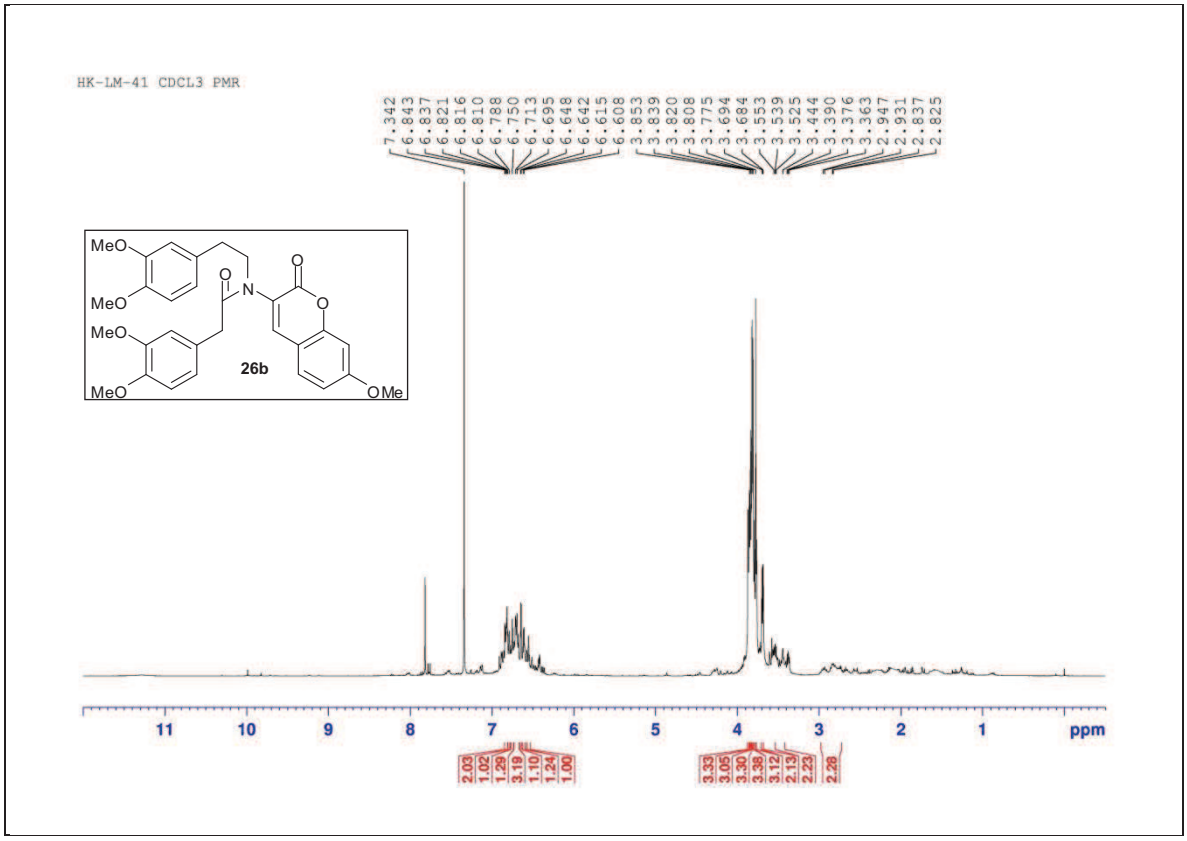

HK-LM-38 CDCL3 CMR
171.13
158.84
153.07
148.93
147.90
147.59
141.74
132.41
131.10
128.43
128.17
127.28
124.99
120.95
118.30
116.68
112.16
112.02
111.19
111.15
77.49
77.18
76.86
55.88
55.86
55.83
55.65
49.45
41.58
33.69
MeO
MeO
MeO
MeO
O
N
O
O
26a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

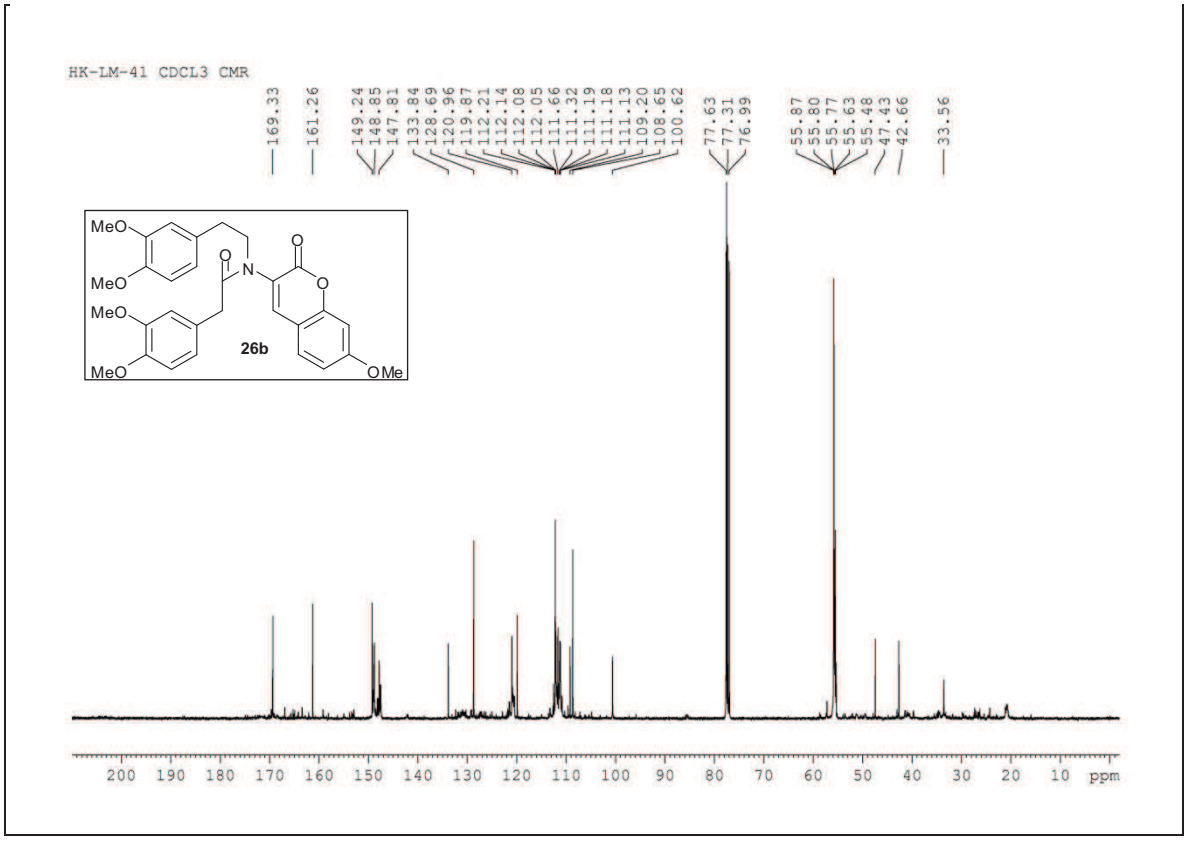

HK-LM-38 CDCL3 DEPT
141.75
132.43
128.18
125.00
120.95
116.68
112.14
112.00
111.17
111.13
55.88
55.86
55.83
55.65
49.45
41.59
33.69
MeO
MeO
MeO
MeO
O
N
O
O
26a
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

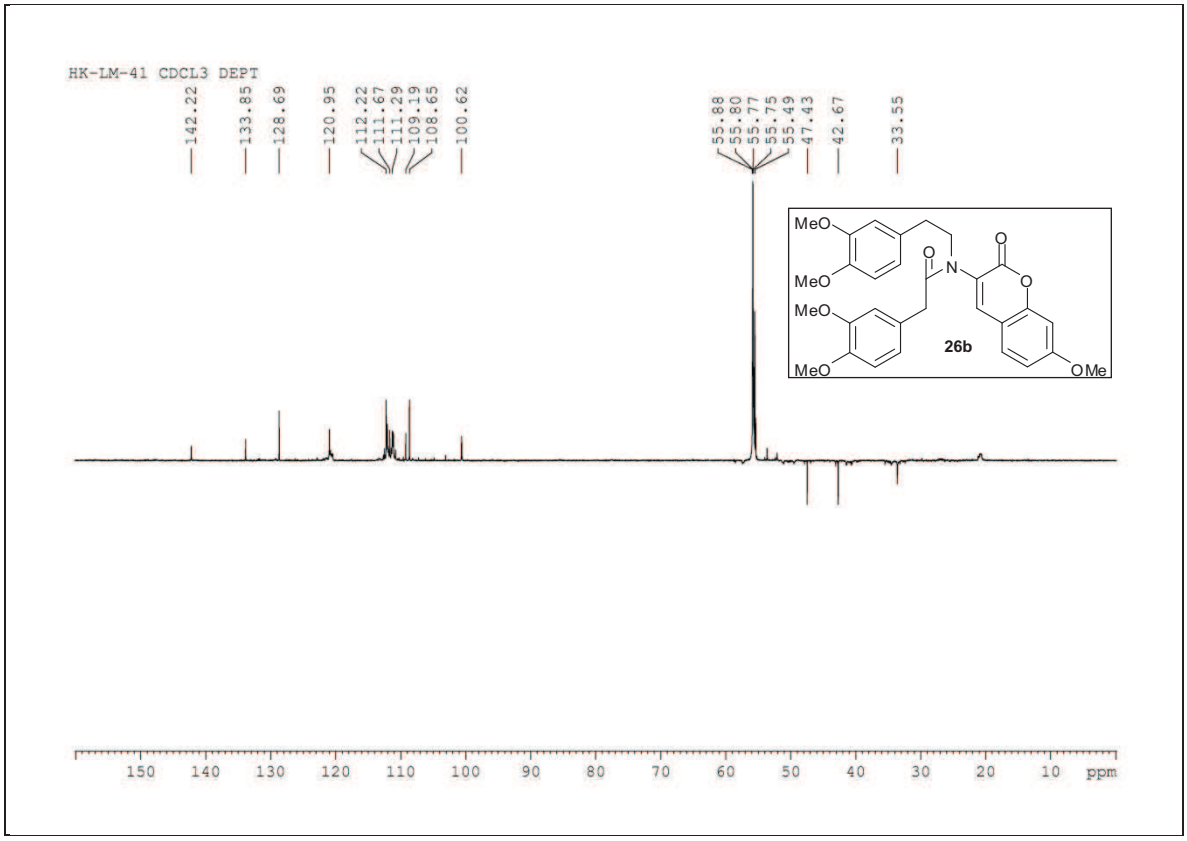

HK-LM-40B CDCL3 PMR
7.317
7.315
7.297
7.294
7.232
7.228
7.214
7.210
7.207
7.194
7.189
7.171
7.168
7.151
7.148
6.996
6.953
6.950
6.933
6.688
6.576
4.773
4.757
4.742
4.726
3.916
3.821
3.778
3.289
3.070
3.053
3.036
0.000
MeO
MeO
MeO
MeO
N
O
O
1a
11
10
9
8
7
6
5
4
3
2
1
ppm
1.18
1.01
1.07
2.00
2.17
1.14
1.00
1.77
3.04
3.28
3.16
3.04
2.01

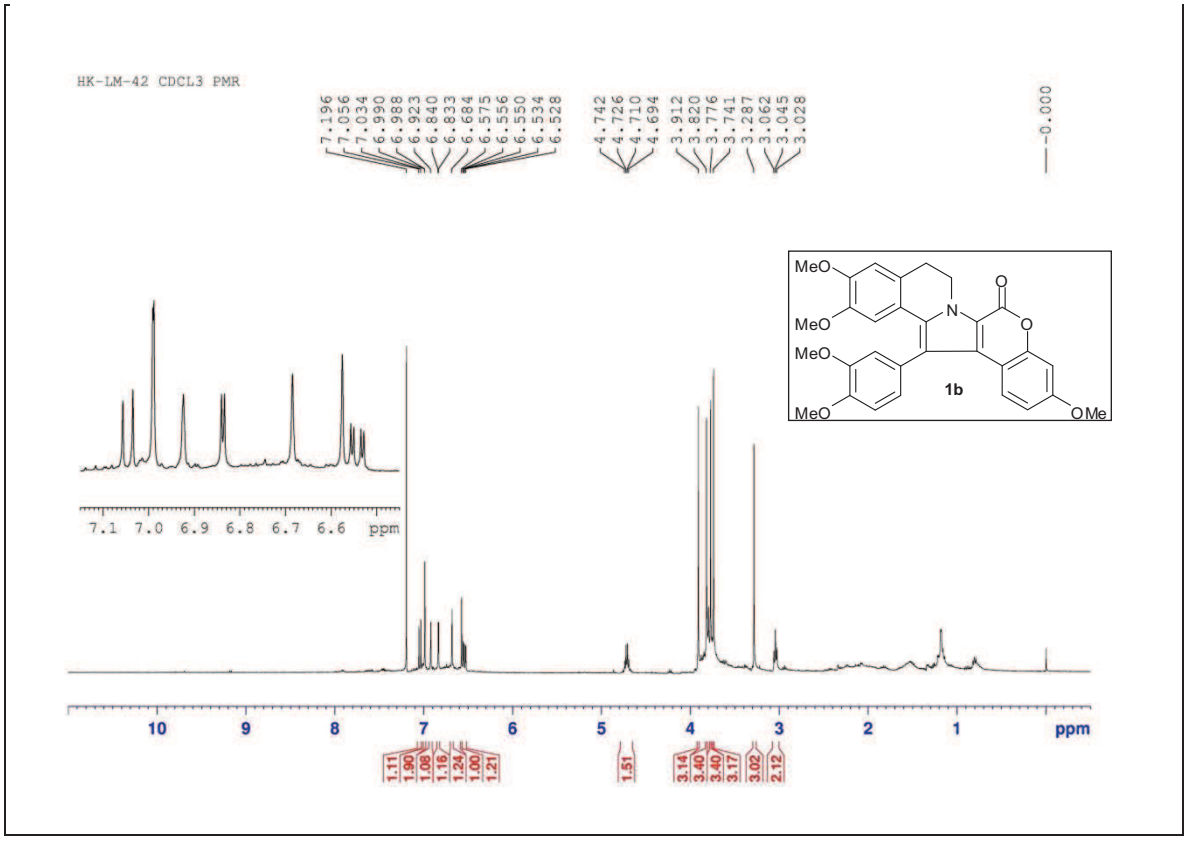

HK-LM-40B CDCL3 PMR
154.28
150.25
148.77
147.95
147.88
146.43
135.10
126.79
126.51
126.34
125.59
122.76
122.36
122.26
118.97
117.28
116.12
114.80
113.45
112.68
110.94
109.91
107.66
76.33
76.01
75.69
55.07
54.90
54.17
41.48
27.67
0.00
MeO
MeO
MeO
MeO
N
O
O
1a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

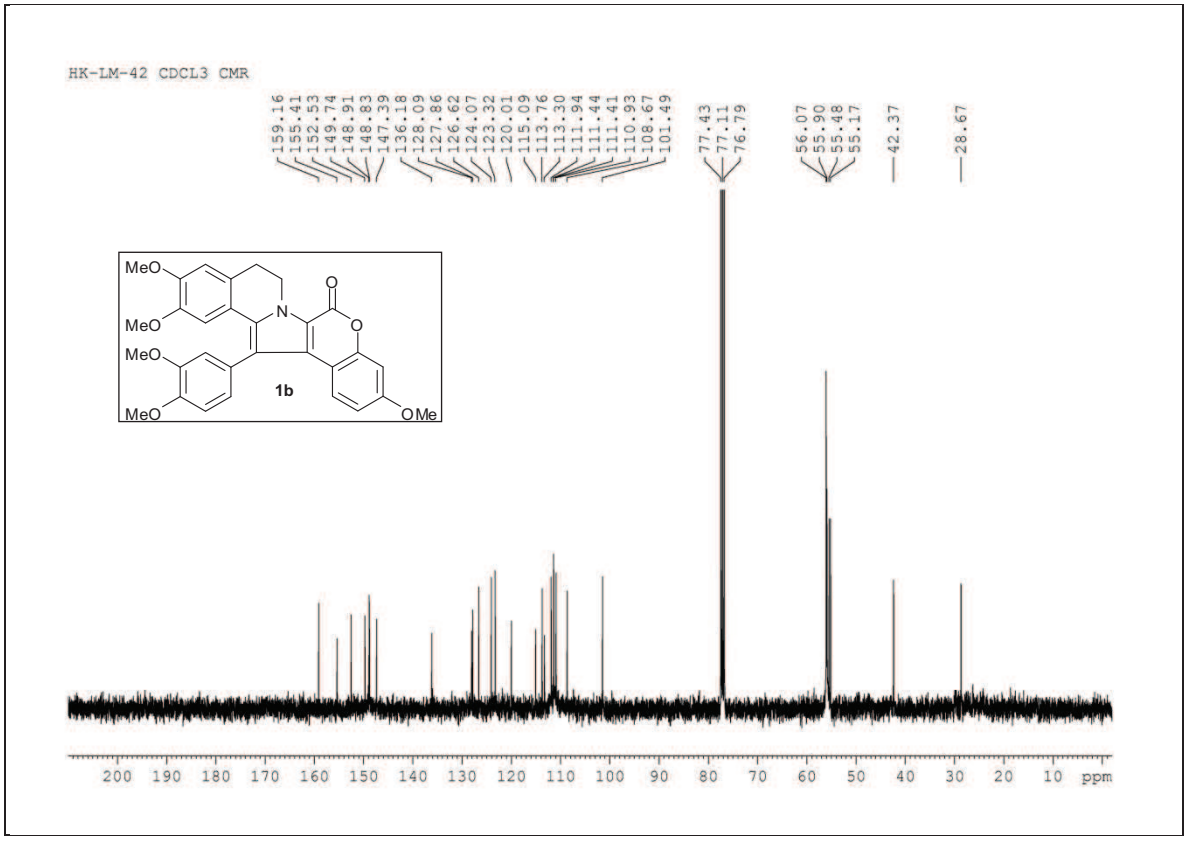

HK-LM-40B CDCL3 DEPT
127.38
123.80
123.40
123.29
117.16
113.69
111.95
110.93
108.68
56.10
55.93
55.20
42.52
28.71
MeO
MeO
MeO
MeO
N
O
O
1a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

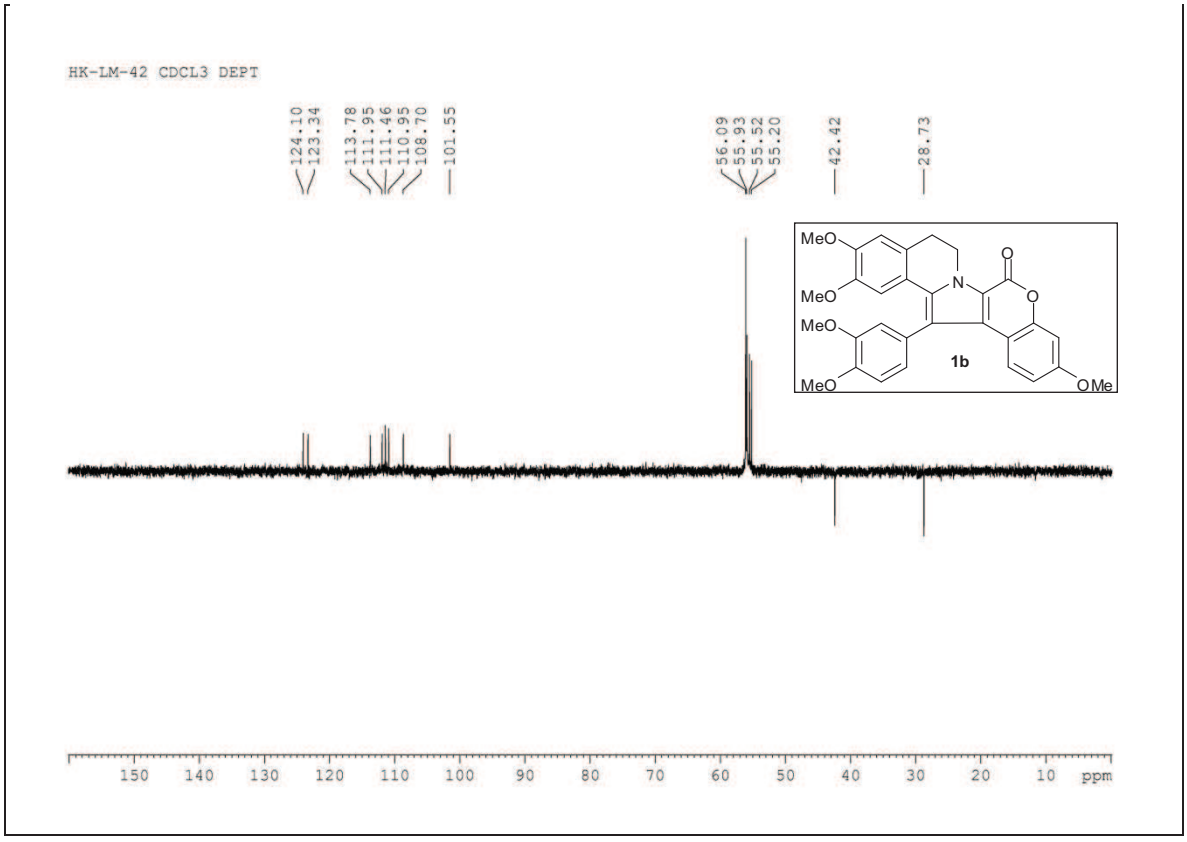

HK-LM-41 CDCL3 PMR
7.342
6.843
6.837
6.821
6.816
6.810
6.788
6.750
6.713
6.695
6.648
6.642
6.615
6.608
3.853
3.839
3.820
3.808
3.775
3.694
3.684
3.553
3.539
3.525
3.444
3.390
3.376
3.363
2.947
2.931
2.837
2.825
MeO
MeO
MeO
MeO
O
N
O
O
26b
OMe
11
10
9
8
7
6
5
4
3
2
1
ppm
2.03
1.02
1.29
3.19
1.10
1.24
1.00
3.33
3.05
3.30
3.38
3.12
2.13
2.23
2.28

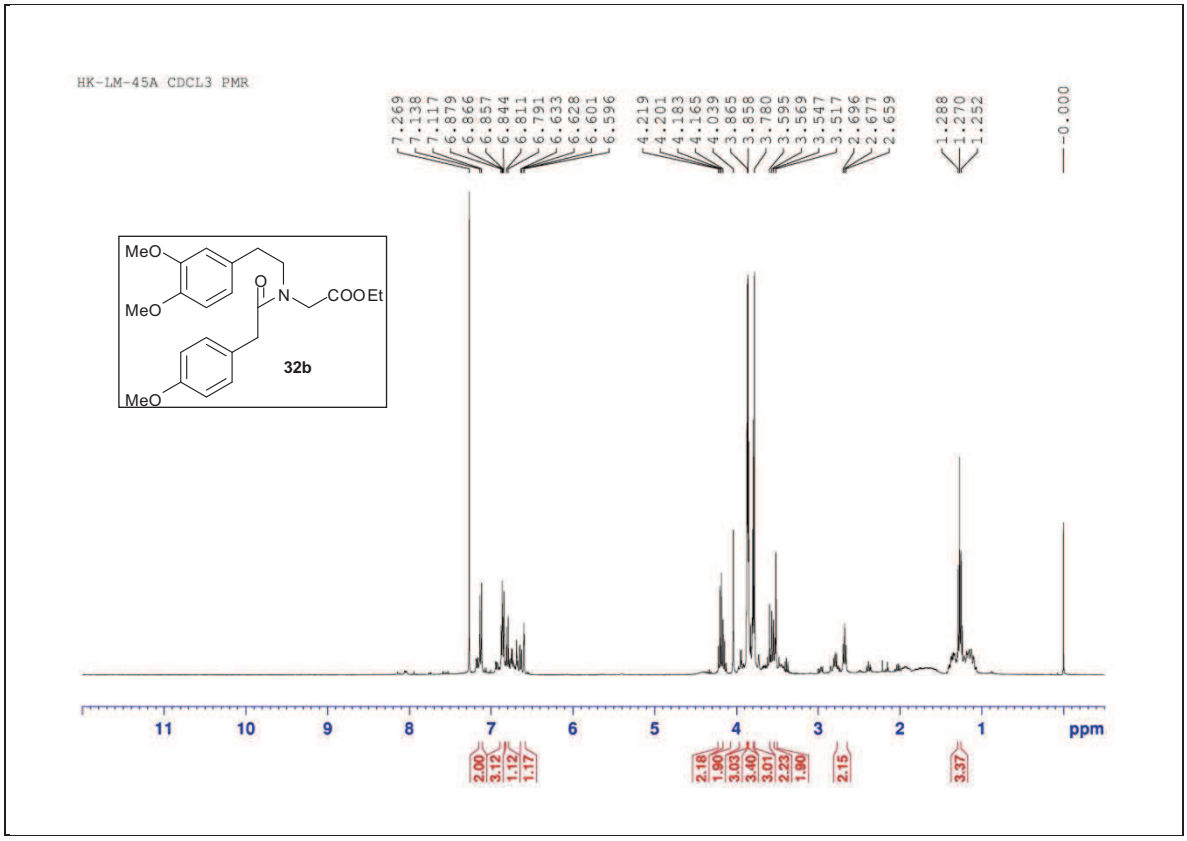

HK-LM-41 CDCL3 CMR
169.33
161.26
149.24
148.85
147.81
133.84
128.69
120.96
119.87
112.21
112.14
112.08
112.05
111.66
111.32
111.19
111.18
111.13
109.20
108.65
100.62
77.63
77.31
76.99
55.87
55.80
55.77
55.63
55.48
47.43
42.66
33.56
MeO
MeO
MeO
MeO
O
N
O
O
26b
OMe
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

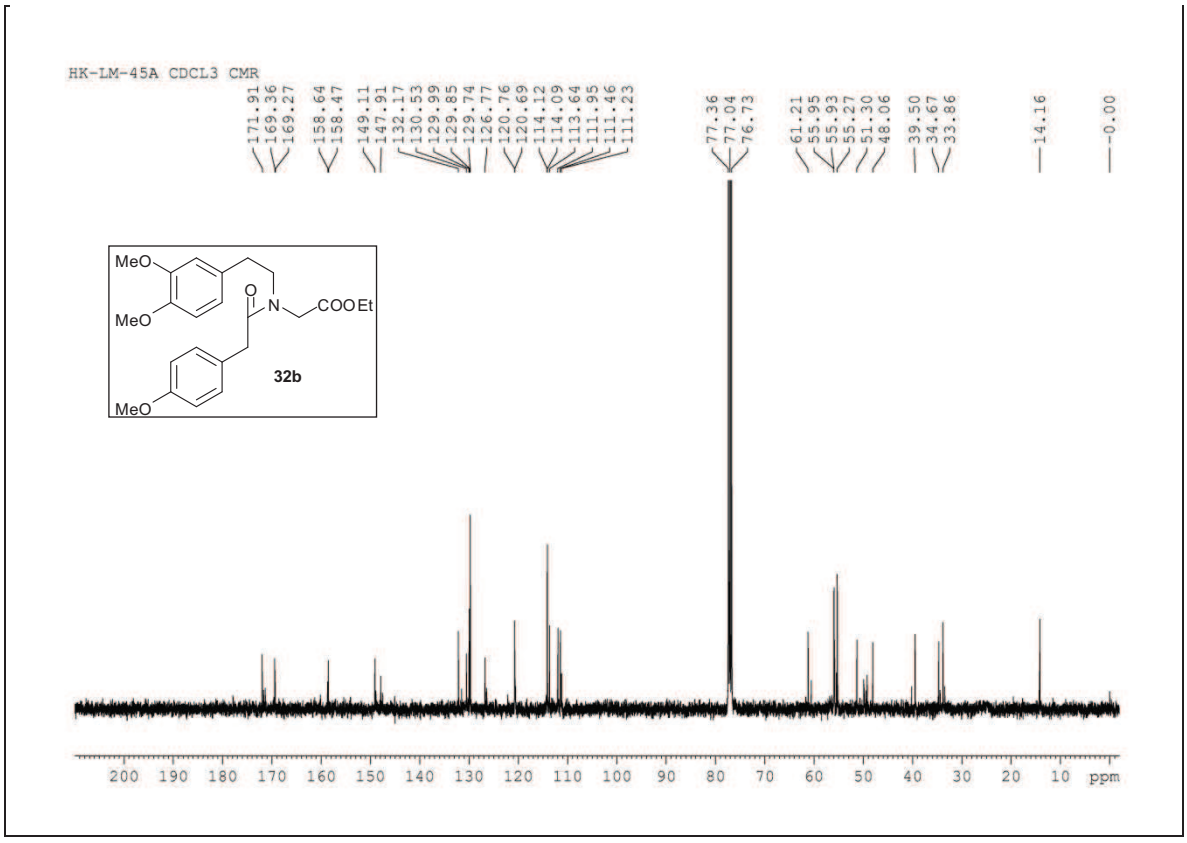

HK-LM-41 CDCL3 DEPT
142.22
133.85
128.69
120.95
112.22
111.67
111.29
109.19
108.65
100.62
55.88
55.80
55.77
55.75
55.49
47.43
42.67
33.55
MeO
MeO
MeO
MeO
O
N
O
O
26b
OMe
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

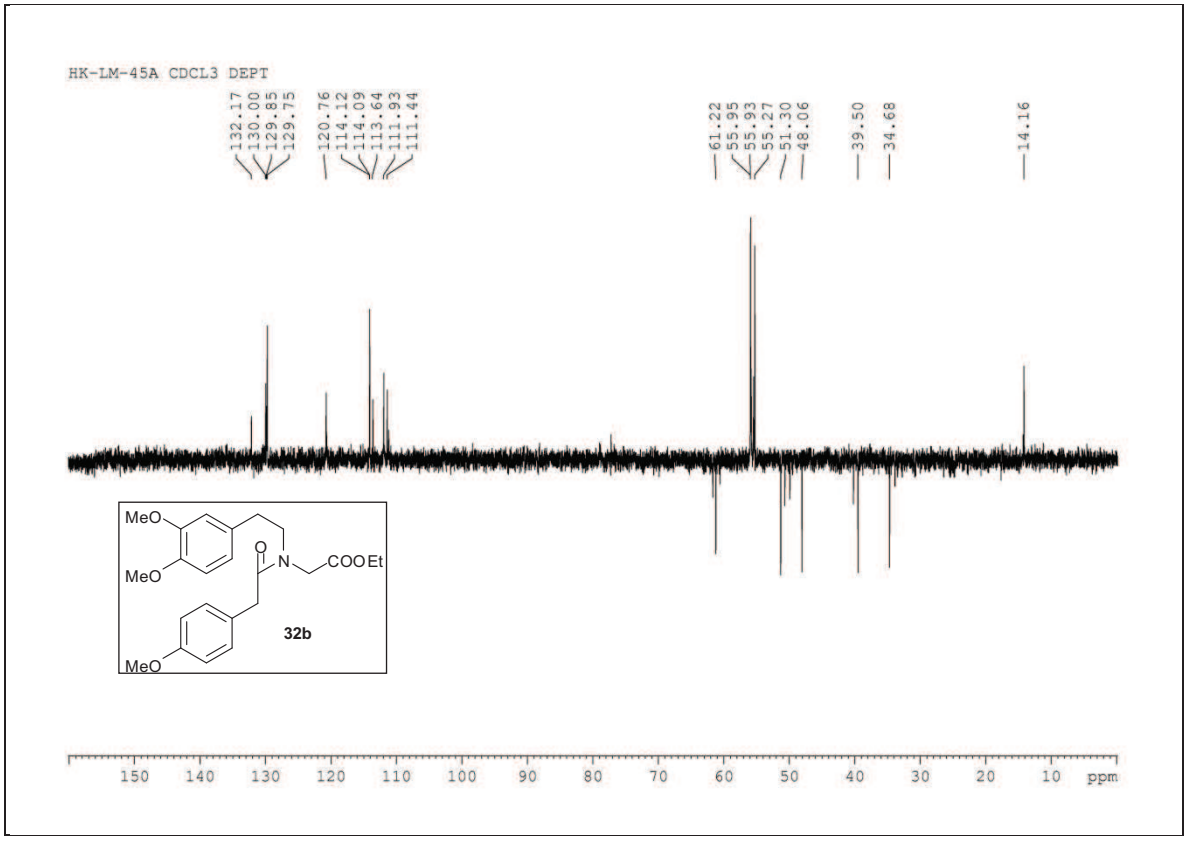

HK-LM-42 CDCL3 PMR
7.196
7.056
7.034
6.990
6.988
6.923
6.840
6.833
6.684
6.575
6.556
6.550
6.534
6.528
4.742
4.726
4.710
4.694
3.912
3.820
3.776
3.741
3.287
3.062
3.045
3.028
0.000
MeO
MeO
MeO
MeO
N
O
O
1b
OMe
7.1 7.0 6.9 6.8 6.7 6.6 ppm
10 9 8 7 6 5 4 3 2 1 ppm
1.11
1.90
1.08
1.16
1.24
1.00
1.21
1.51
3.14
3.40
3.40
3.17
3.02
2.12

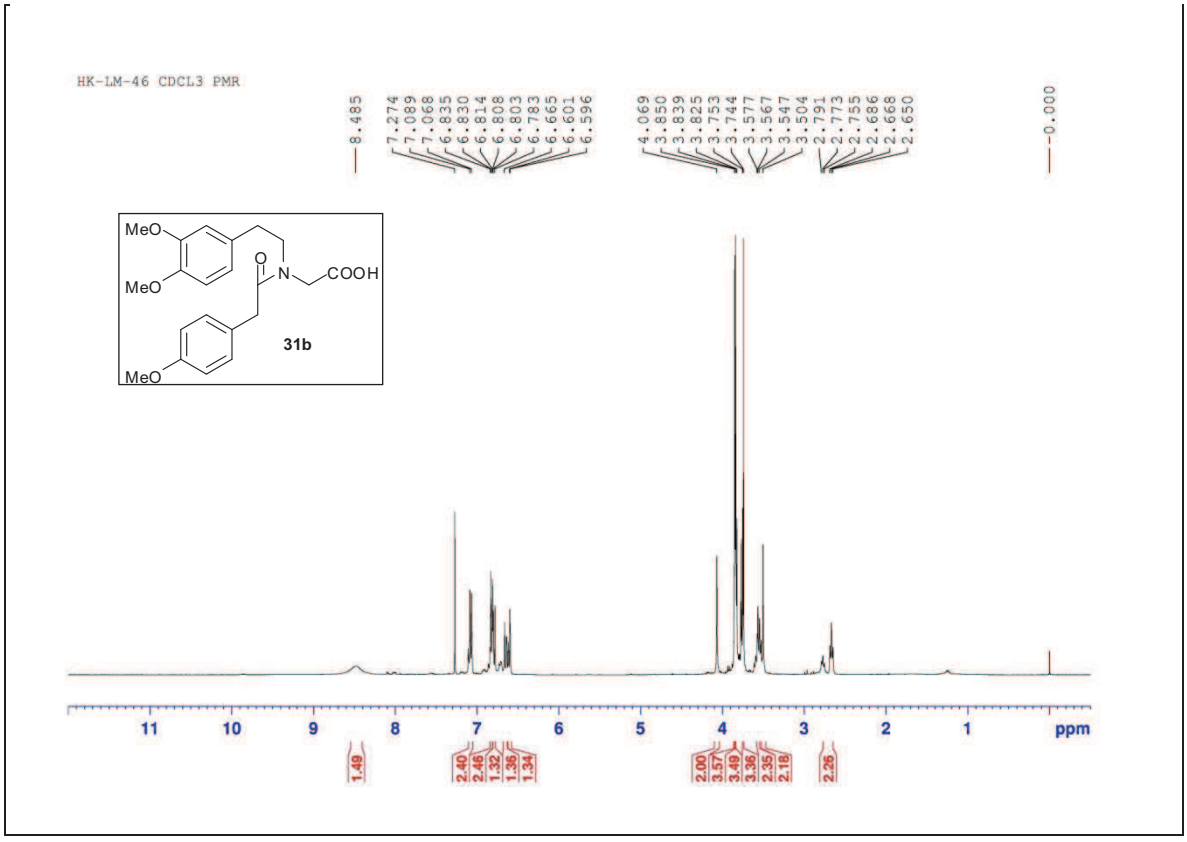

HK-LM-42 CDCL3 CMR
159.16
155.41
152.53
149.74
148.91
148.83
147.39
136.18
128.09
127.86
126.62
124.07
123.32
120.01
115.09
113.76
113.30
111.94
111.44
111.41
110.93
108.67
101.49
77.43
77.11
76.79
56.07
55.90
55.48
55.17
42.37
28.67
MeO
MeO
MeO
MeO
N
O
O
1b
OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HK-LM-42 CDCL3 DEPT
124.10
123.34
113.78
111.95
111.46
110.95
108.70
101.55
56.09
55.93
55.52
55.20
42.42
28.73
MeO
MeO
MeO
MeO
N
O
O
1b
OMe
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HK-LM-45A CDCL3 PMR
MeO
MeO
MeO
N
O
COOEt
32b
ppm


HK-LM-45A CDCL3 CMR
MeO
MeO
MeO
N
O
COOEt
32b
ppm


HK-LM-45A CDCL3 DEPT
132.17
130.00
129.85
129.75
120.76
114.12
114.09
113.64
111.93
111.44
61.22
55.95
55.93
55.27
51.30
48.06
39.50
34.68
14.16
MeO
MeO
MeO
O
N
COOEt
32b
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


HK-LM-46 CDCL3 PMR
8.485
7.274
7.089
7.068
6.835
6.830
6.814
6.808
6.803
6.783
6.665
6.601
6.596
4.069
3.850
3.839
3.825
3.753
3.744
3.577
3.567
3.547
3.504
2.791
2.773
2.755
2.686
2.668
2.650
0.000
MeO
MeO
MeO
O
N
COOH
31b
11
10
9
8
7
6
5
4
3
2
1
ppm
1.49
2.40
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1.36
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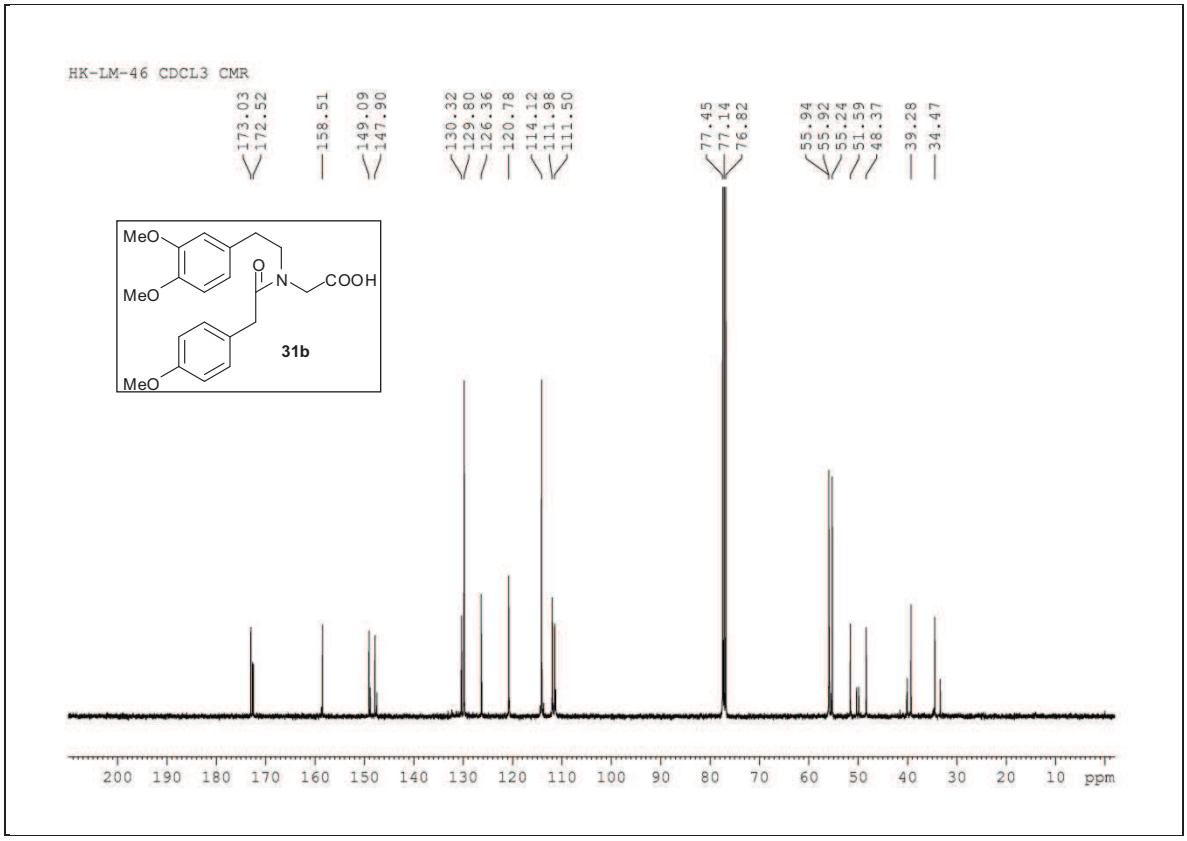
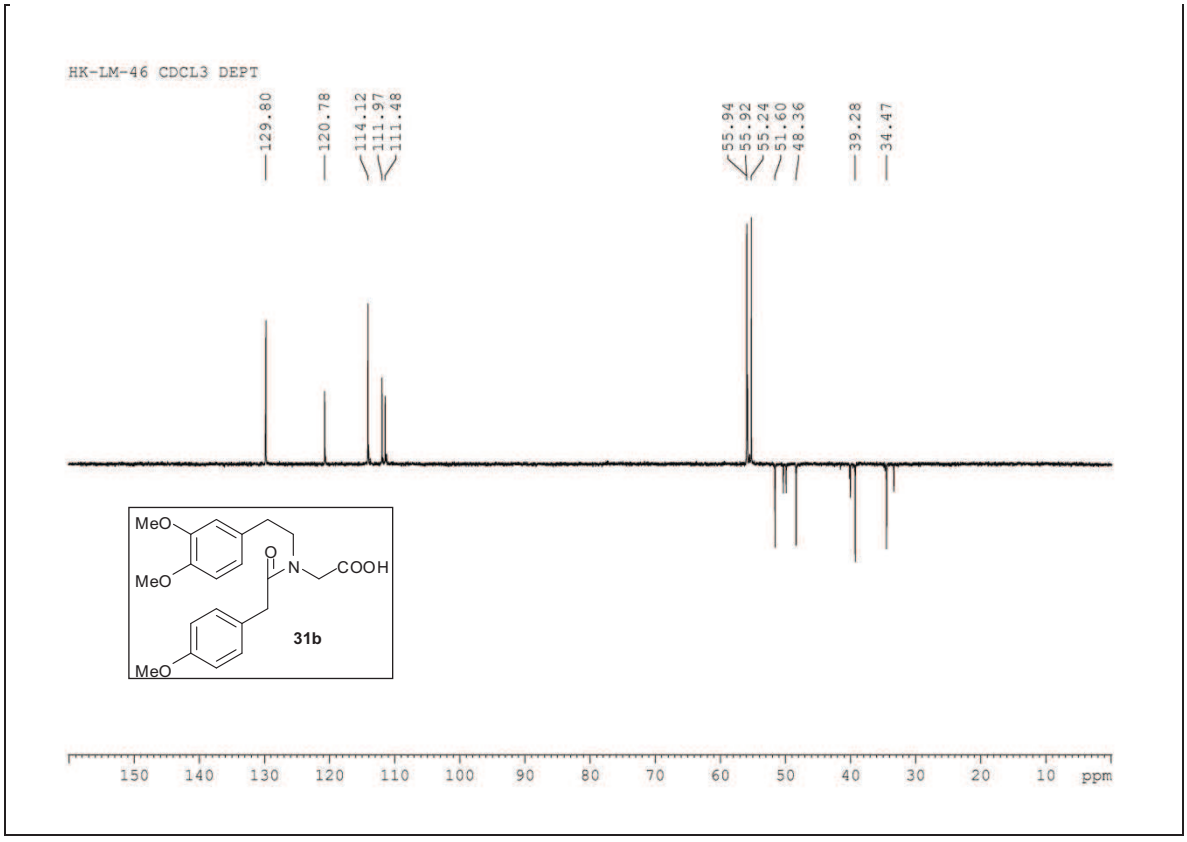
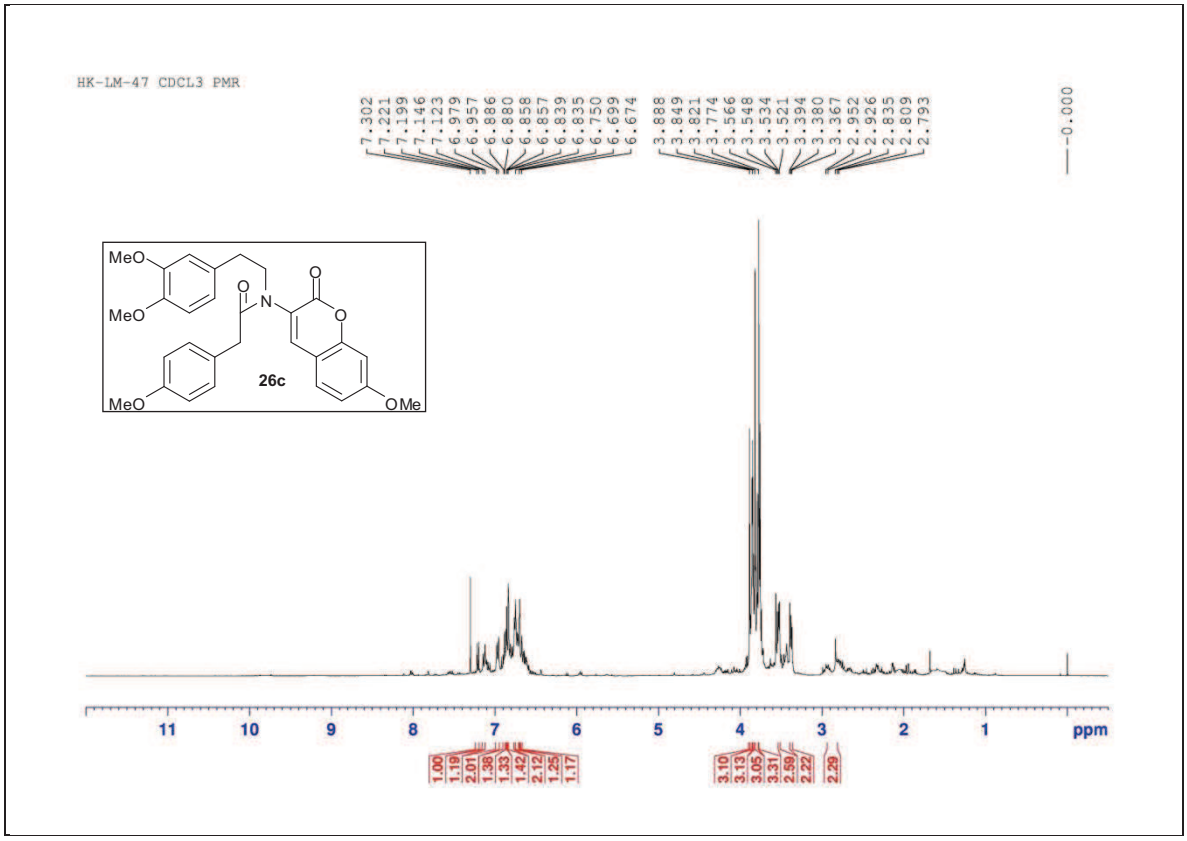
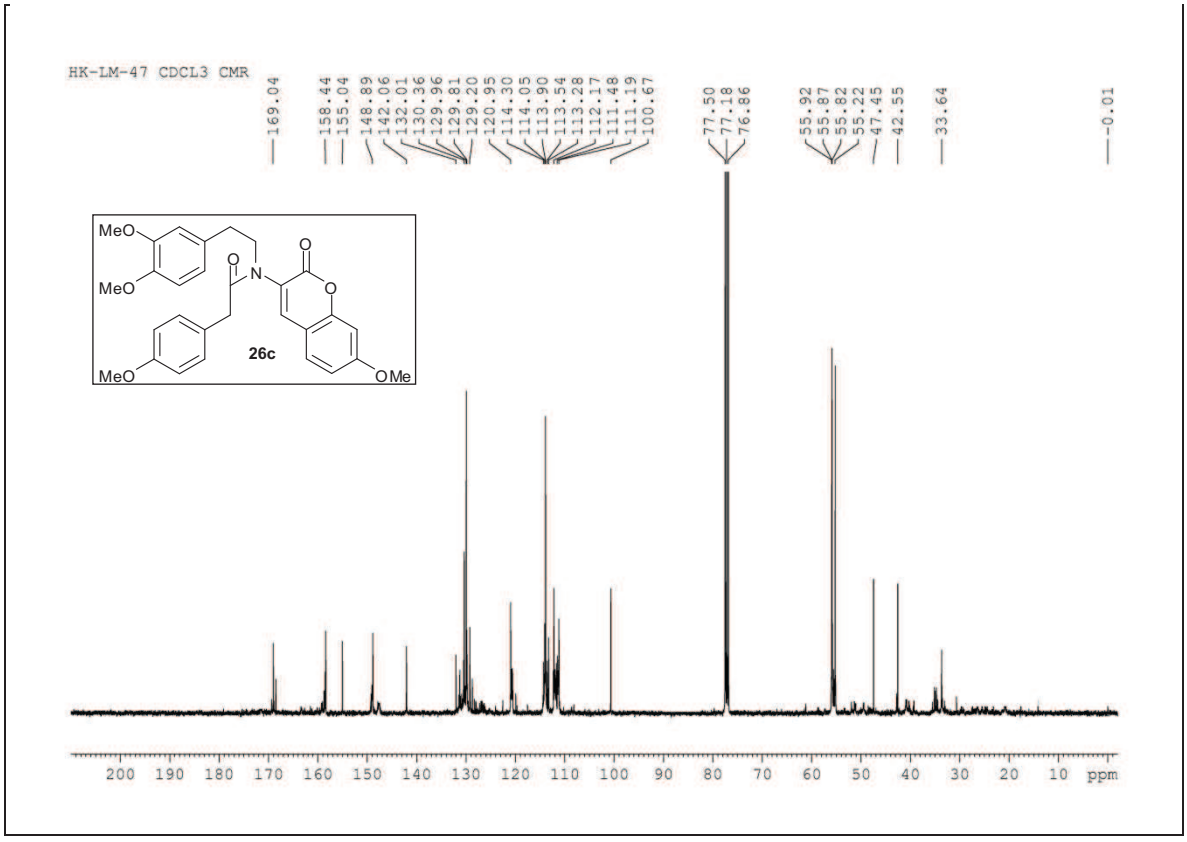
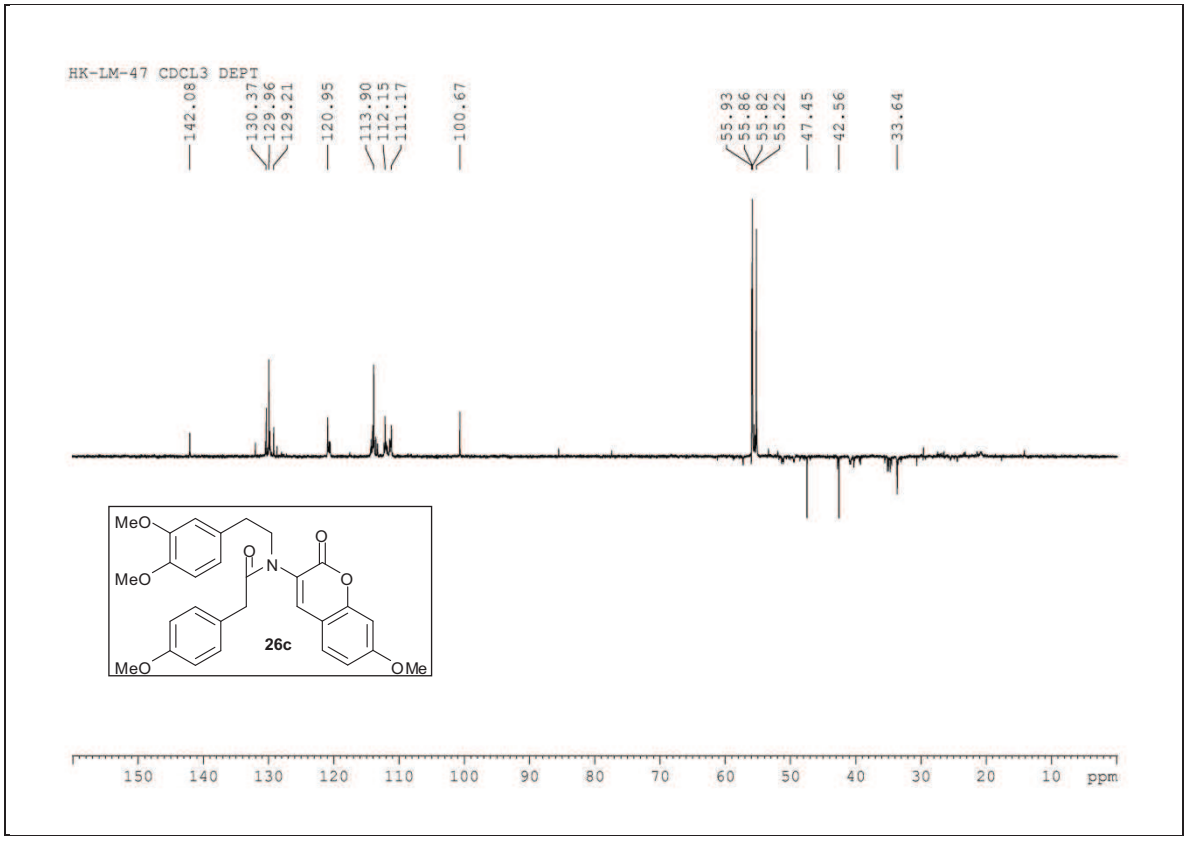
3.57
3.49
3.36
2.35
2.18
2.26

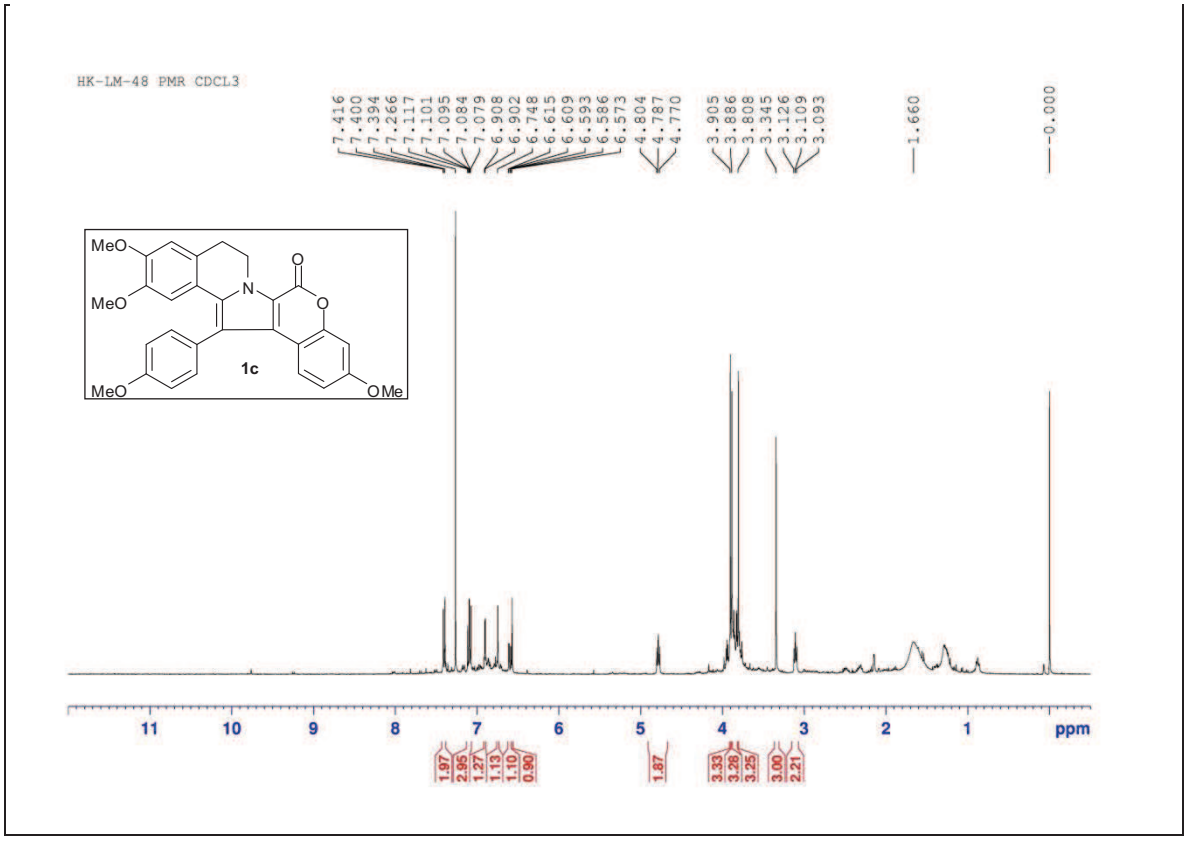

HK-LM-46 CDCL3 CMR
173.03
172.52
158.51
149.09
147.90
130.32
129.80
126.36
120.78
114.12
111.98
111.50
77.45
77.14
76.82
55.94
55.92
55.24
51.59
48.37
39.28
34.47
MeO
MeO
MeO
O
N
COOH
31b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HK-LM-46 CDCL3 DEPT
129.80
120.78
114.12
111.97
111.48
55.94
55.92
55.24
51.60
48.36
39.28
34.47
MeO
MeO
MeO
O
N
COOH
31b
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


HK-LM-47 CDCL3 PMR
7.302
7.221
7.199
7.146
7.123
6.979
6.957
6.886
6.880
6.858
6.857
6.839
6.835
6.750
6.699
6.674
3.888
3.849
3.821
3.774
3.566
3.548
3.534
3.521
3.394
3.380
3.367
2.952
2.926
2.835
2.809
2.793
-0.000
MeO
MeO
MeO
OMe
26c
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.19
2.01
1.38
1.33
1.42
2.12
1.25
1.17
3.10
3.13
3.05
3.31
2.89
2.22
2.29


HK-LM-47 CDCL3 CMR
169.04
158.44
155.04
148.89
142.06
132.01
130.36
129.96
129.81
129.20
120.95
114.30
114.05
113.90
113.54
113.28
112.17
111.48
111.19
100.67
77.50
77.18
76.86
55.92
55.87
55.82
55.22
47.45
42.55
33.64
-0.01
MeO
MeO
MeO
OMe
26c
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


HK-LM-47 CDCL3 DEPT
142.08
130.37
129.96
129.21
120.95
113.90
112.15
111.17
100.67
55.93
55.86
55.82
55.22
47.45
42.56
33.64
MeO
MeO
MeO
OMe
26c
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


HK-LM-48 PMR CDCL3
7.416
7.400
7.394
7.266
7.117
7.101
7.095
7.084
7.079
6.908
6.902
6.748
6.615
6.609
6.593
6.586
6.573
4.804
4.787
4.770
3.905
3.886
3.808
3.345
3.126
3.109
3.093
1.660
0.000
MeO
MeO
MeO
OMe
1c
11
10
9
8
7
6
5
4
3
2
1
ppm
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1.13
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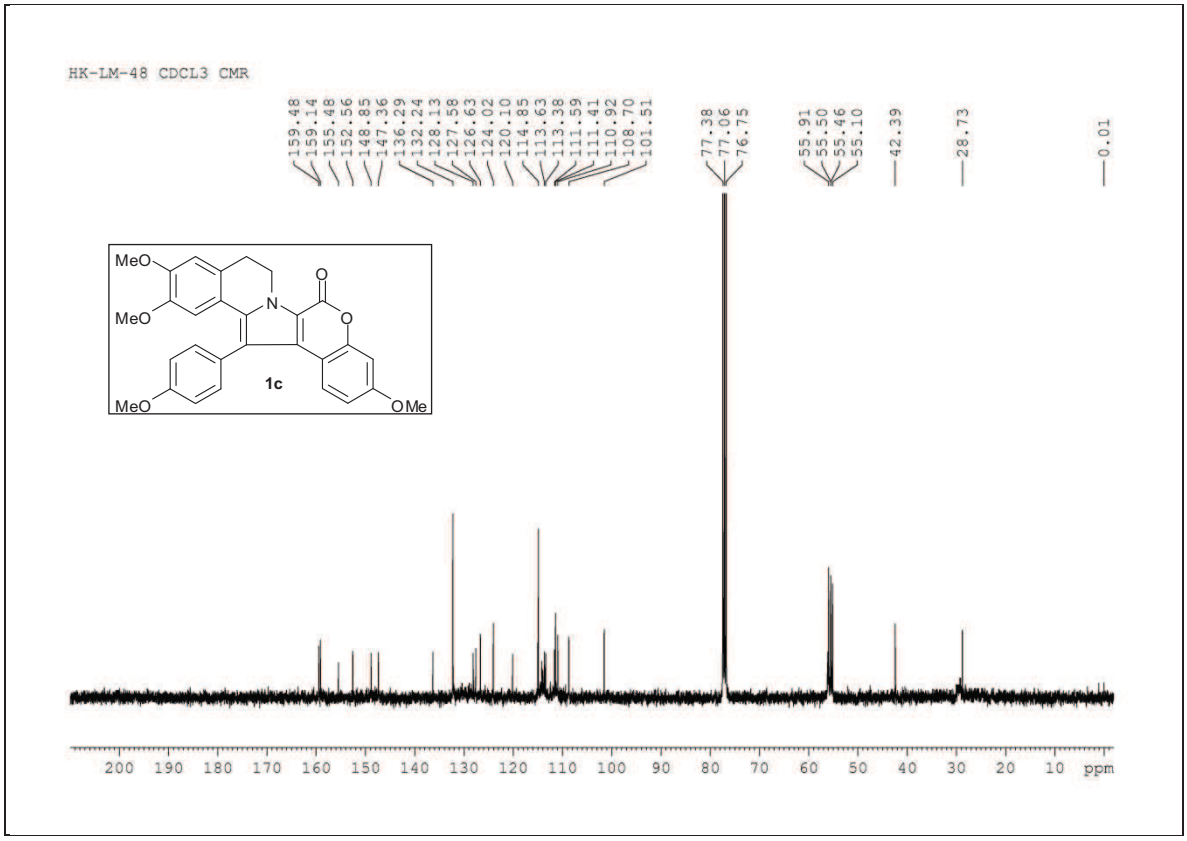
0.90
1.87
3.33
3.28
3.25
3.00
2.21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124.02
120.10
114.85
113.63
113.38
111.59
111.41
110.92
108.70
101.51
77.38
77.06
76.75
55.91
55.50
55.46
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MeO
MeO
MeO
OMe
1c
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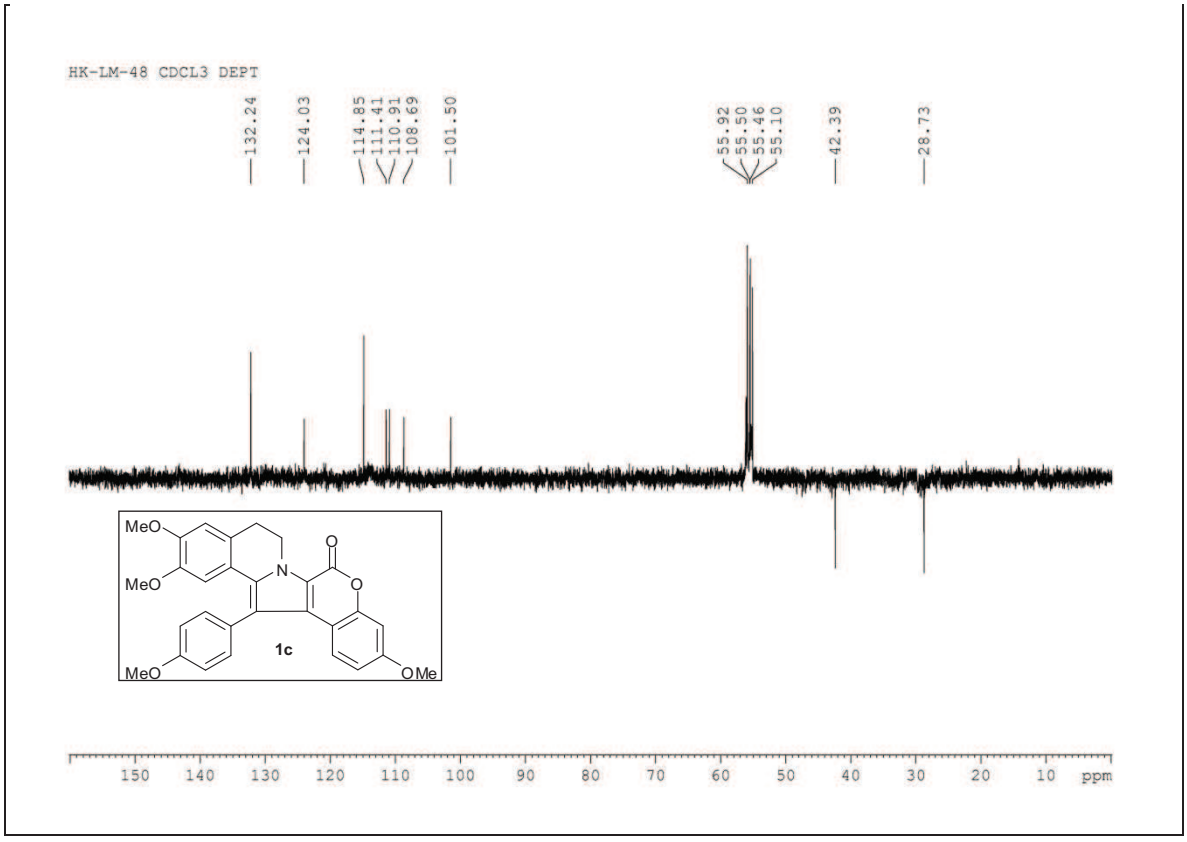
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42.39
28.73
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MeO
MeO
OMe
1c
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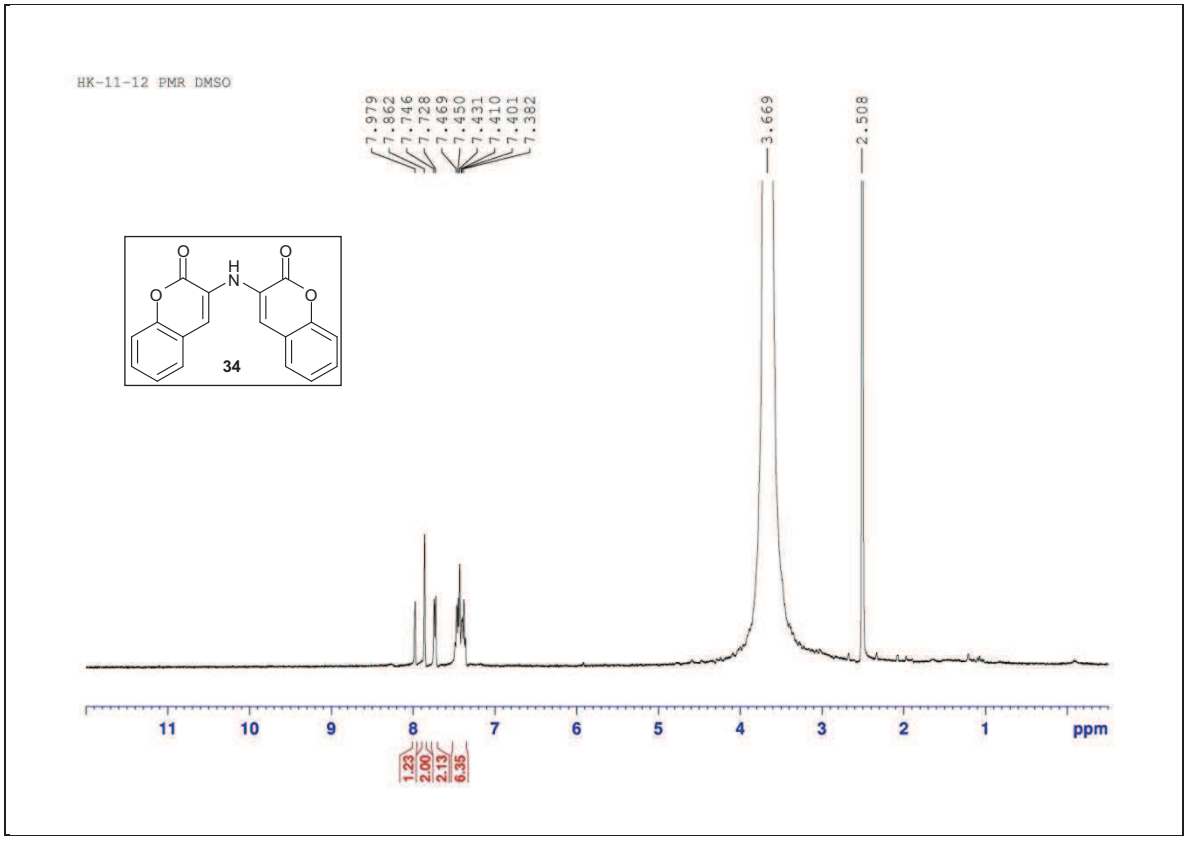
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7.401
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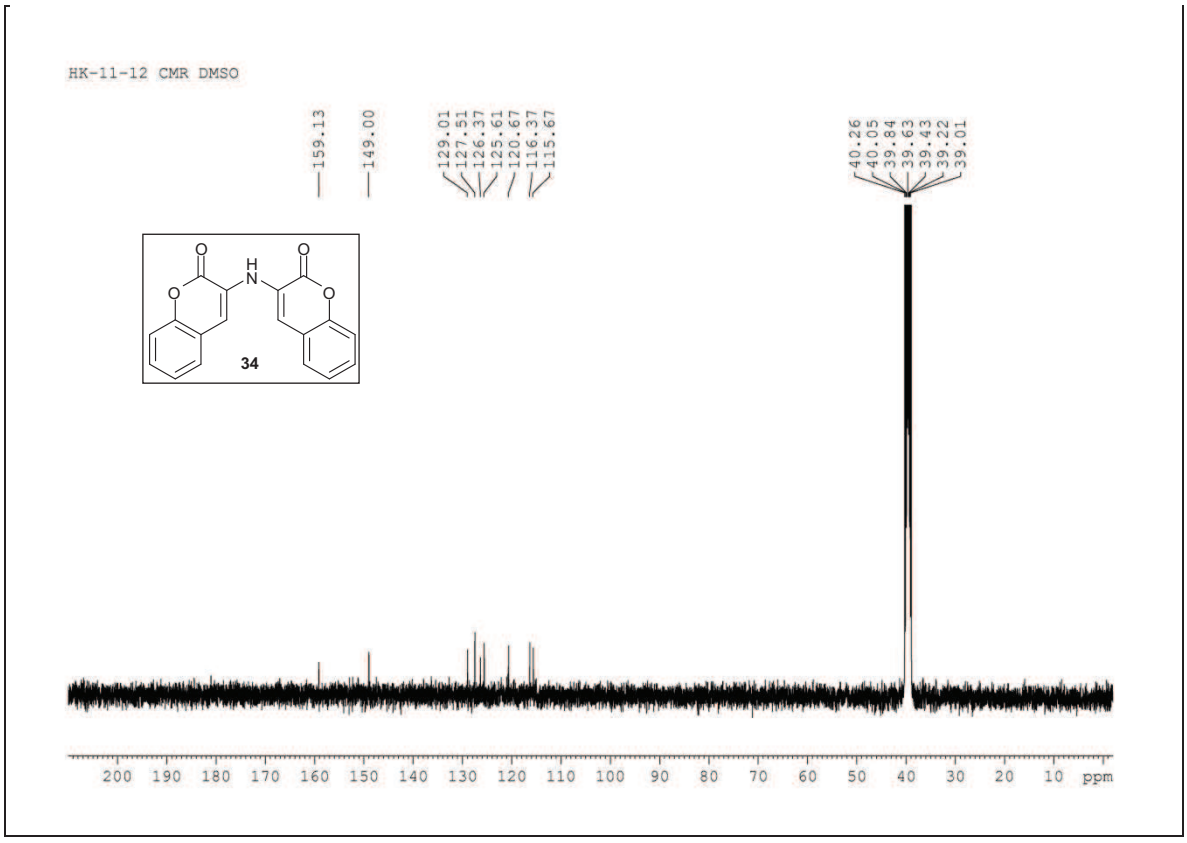
2
1
ppm
1.23
2.00
2.13
6.35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40.05
39.84
39.63
39.43
39.22
39.01
34
200
190
180
170
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150
140
130
120
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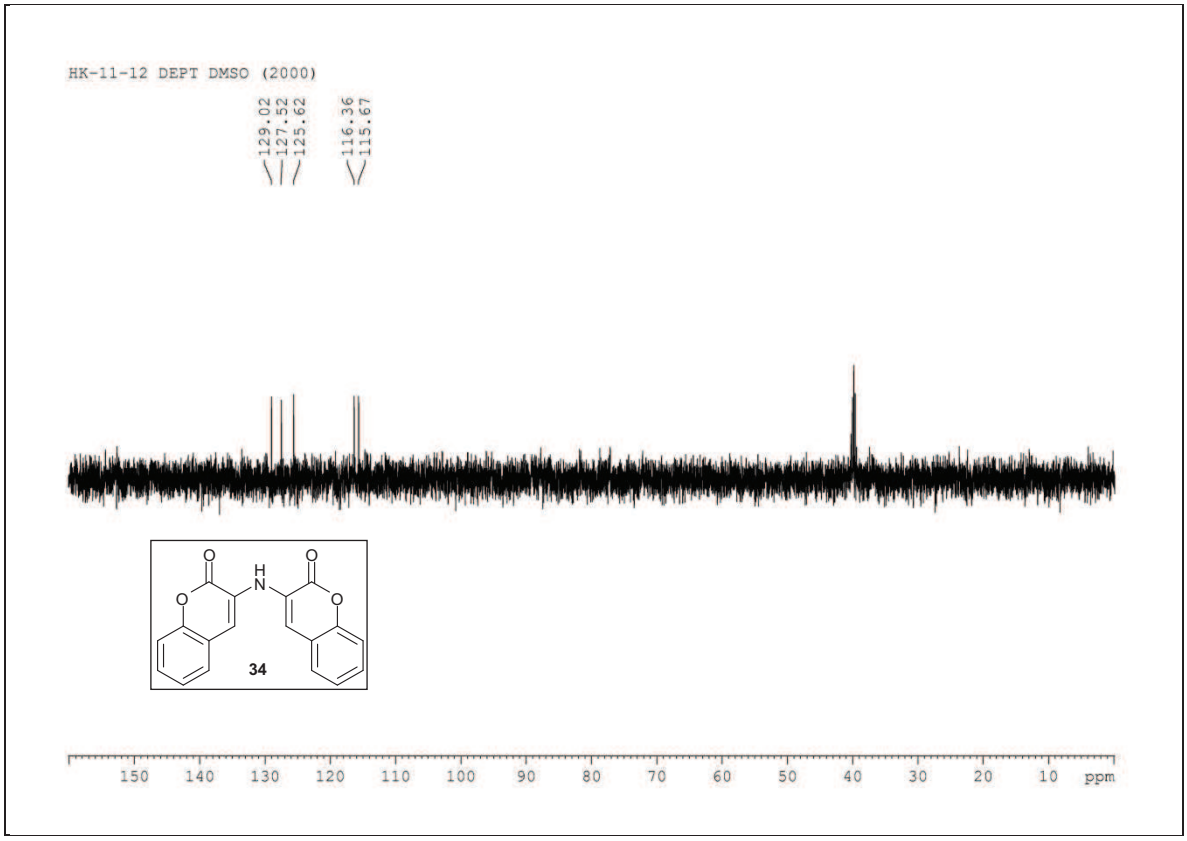
100
90
80
70
60
50
40
30
20
10
ppm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115.67
34
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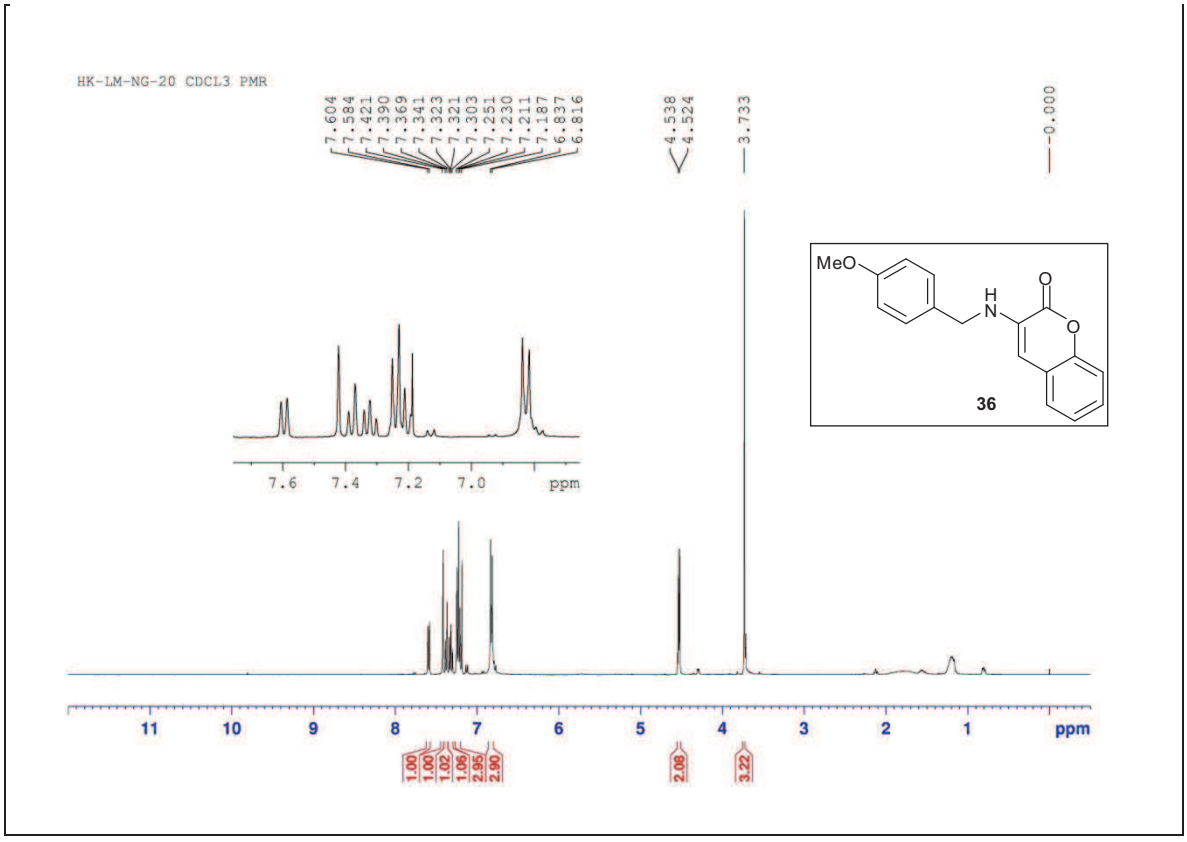
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7.584
7.421
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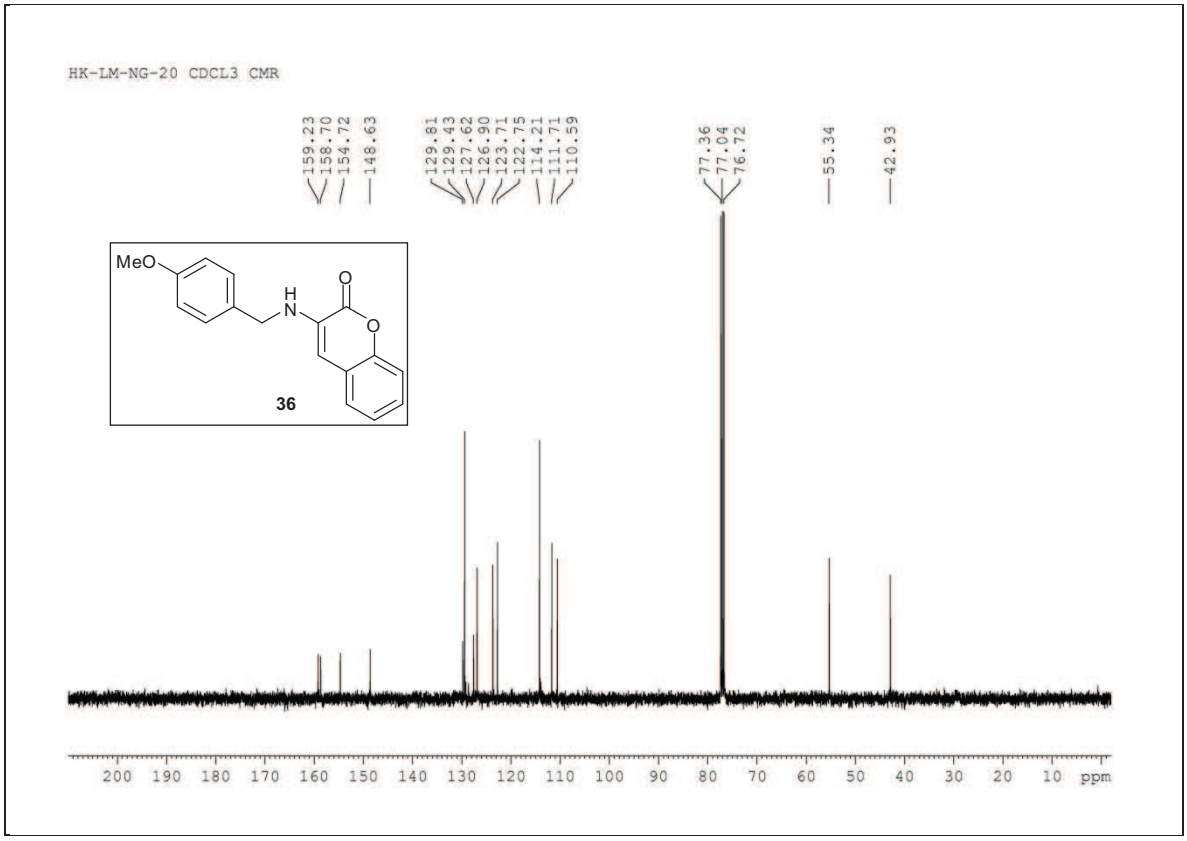
7.341
7.323
7.321
7.303
7.251
7.230
7.211
7.187
6.837
6.816
4.538
4.524
3.733
0.000
MeO
36
7.6 7.4 7.2 7.0 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.00
1.02
1.05
2.95
2.90
2.06
3.22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129.81
129.43
127.62
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122.75
114.21
111.71
110.59
77.36
77.04
76.72
55.34
42.93
MeO
H
N
O
O
36
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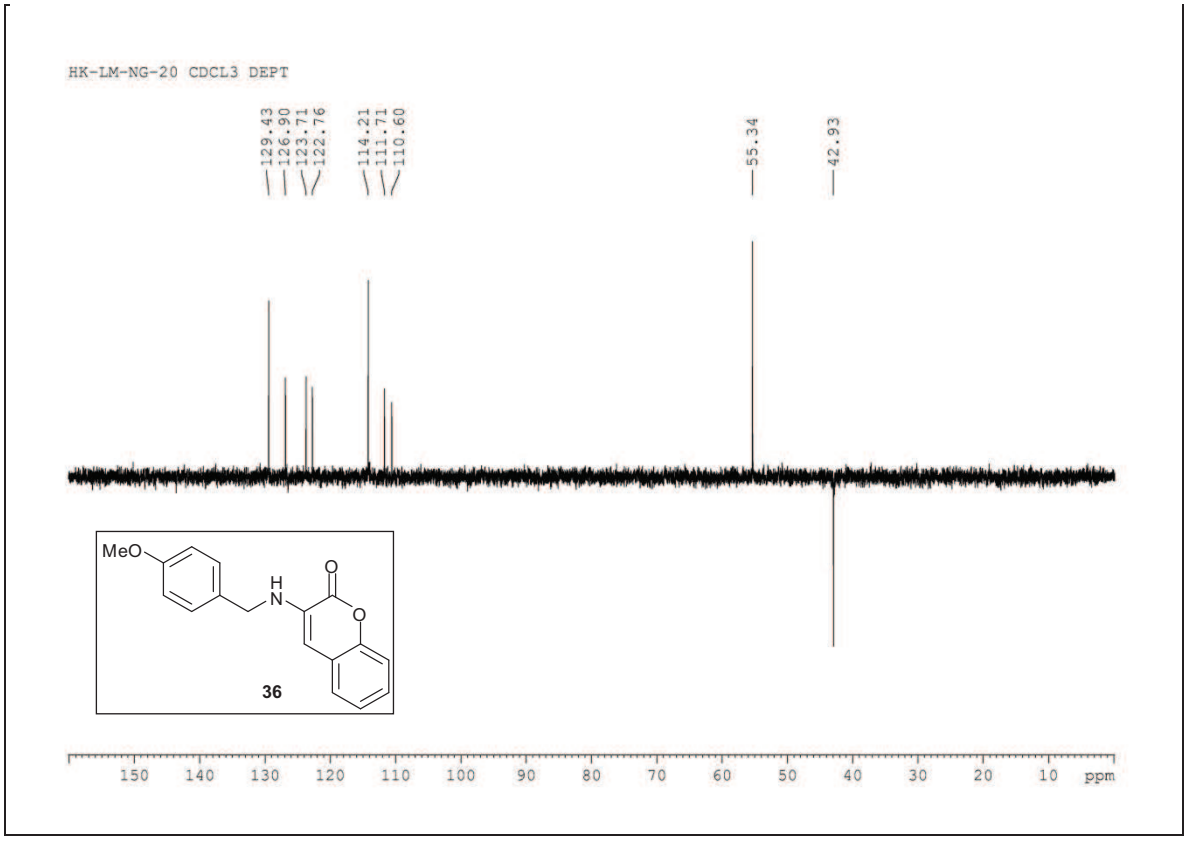
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36
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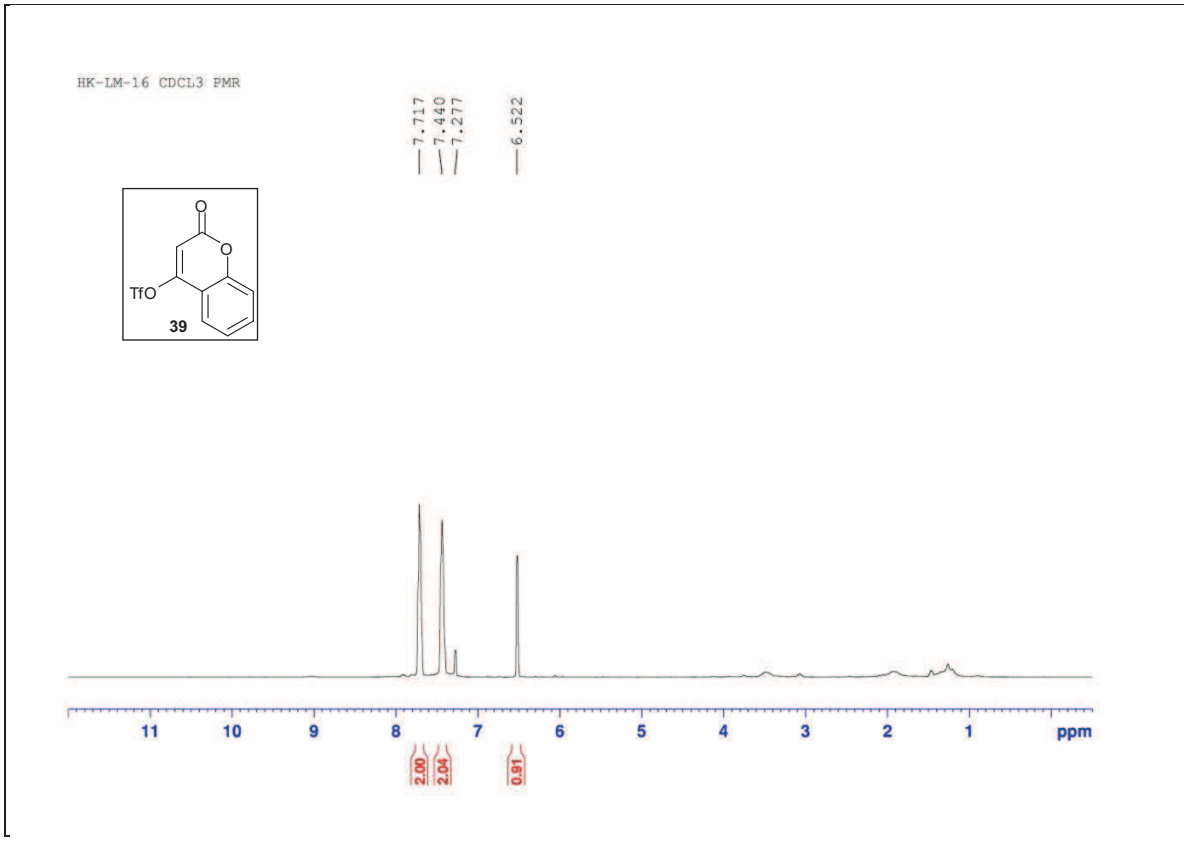
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7.440
7.277
6.522
TfO
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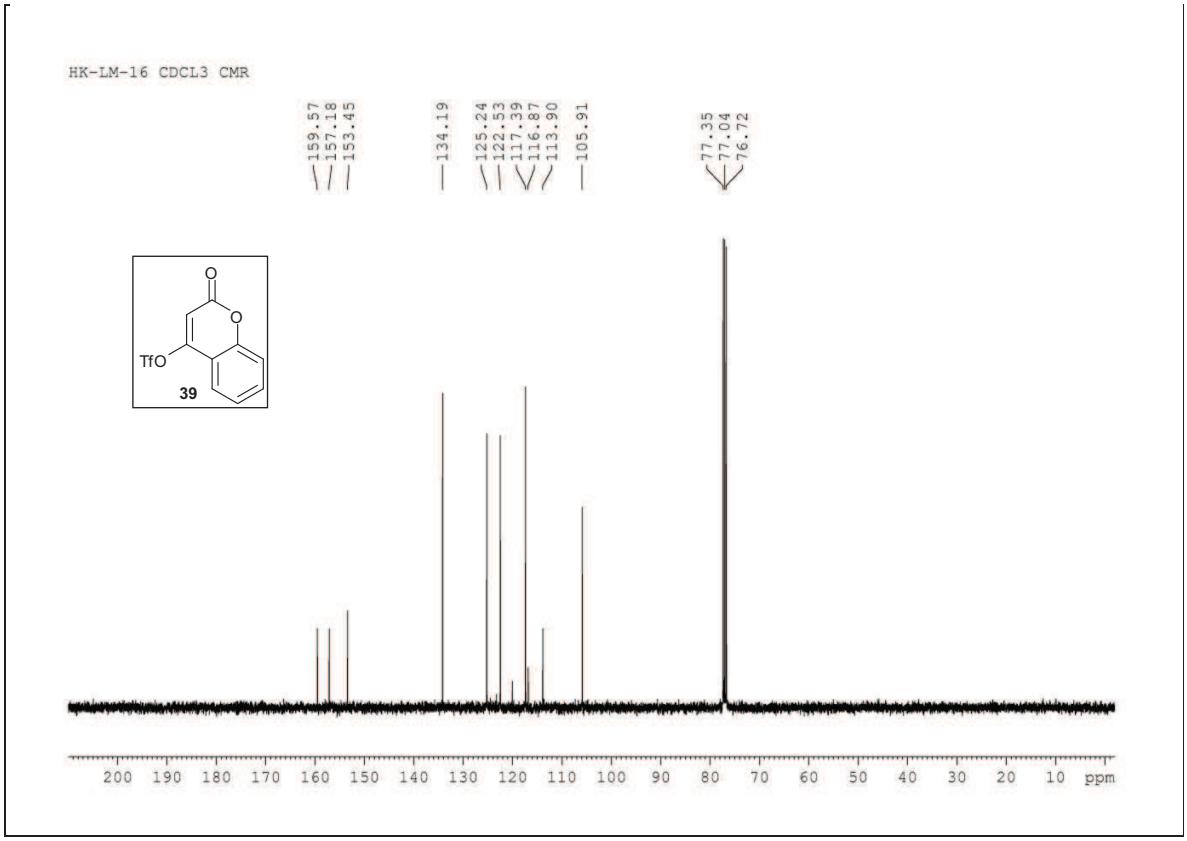
11
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.04
0.91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77.04
76.72
TfO
39
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90
80
70
60
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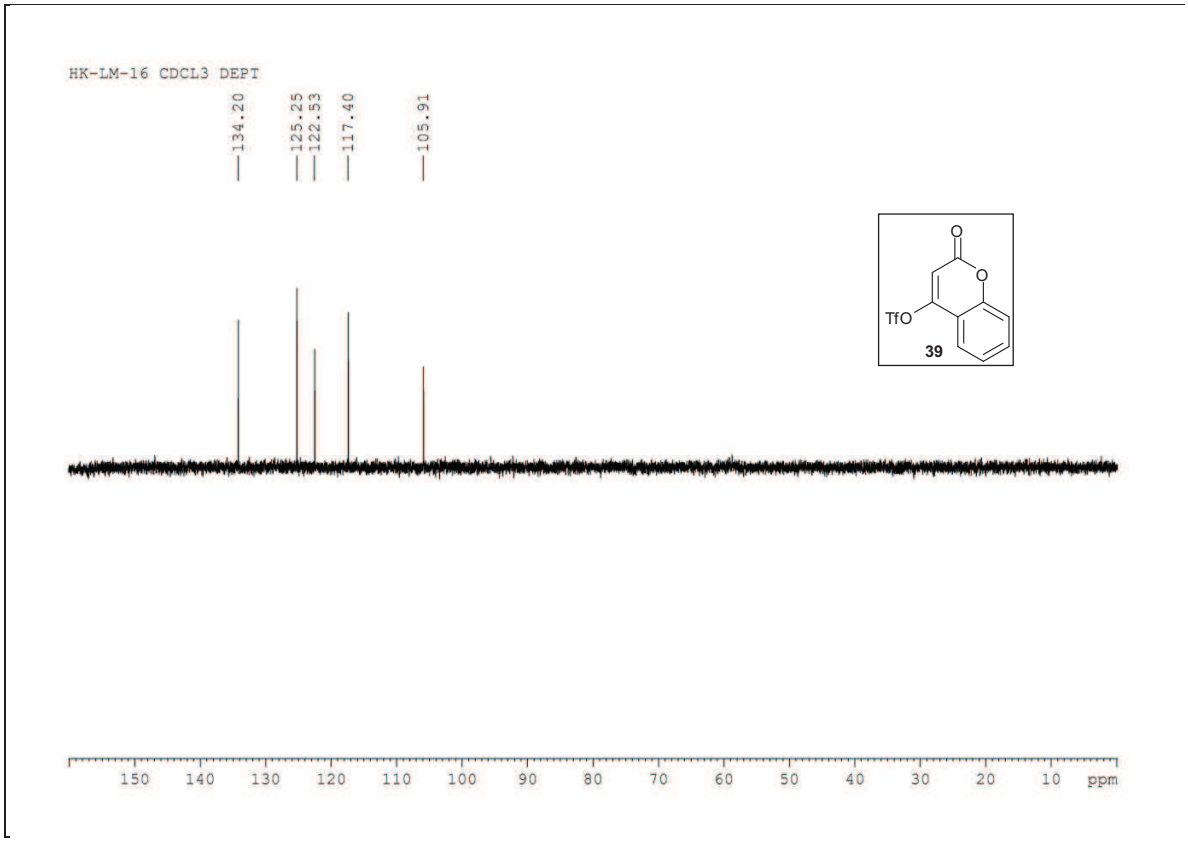
40
30
20
10
ppm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105.91
TfO
39
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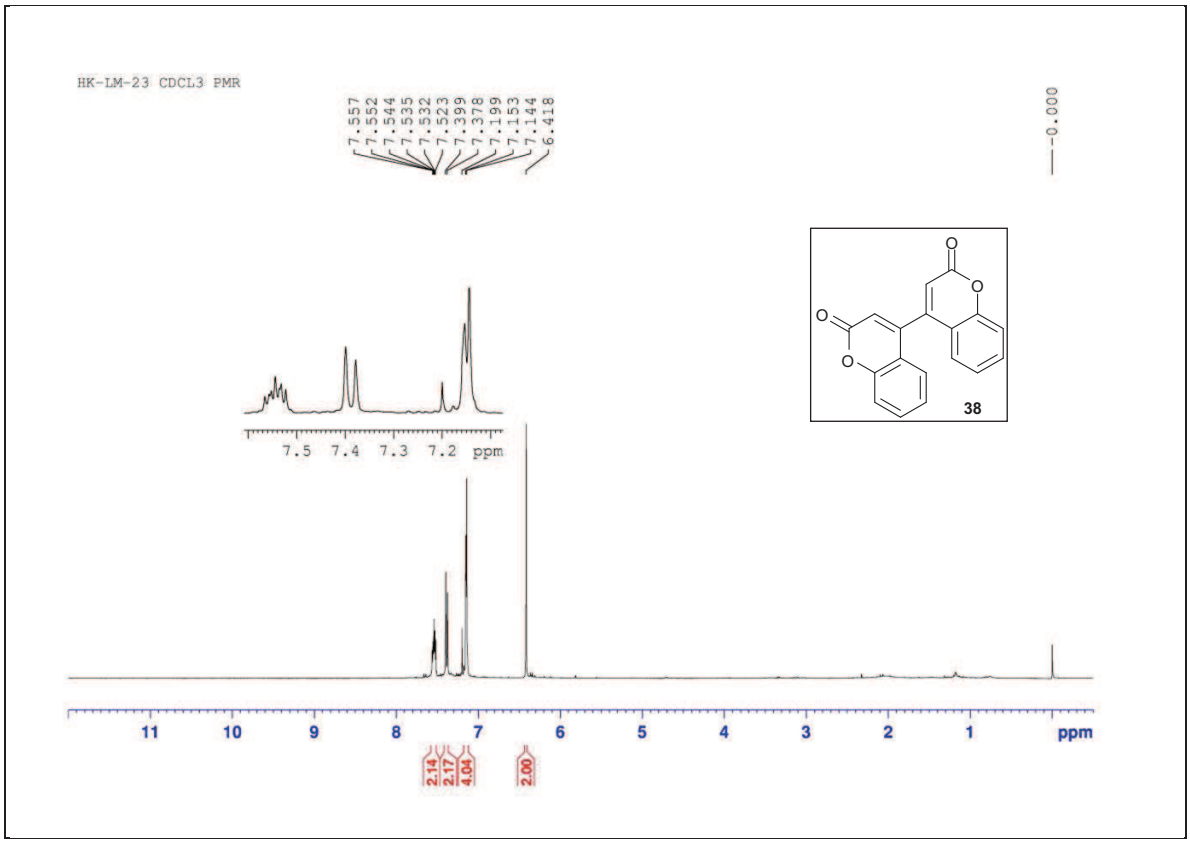
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7.532
7.523
7.399
7.378
7.199
7.153
7.144
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0.000
38
7.5 7.4 7.3 7.2 ppm
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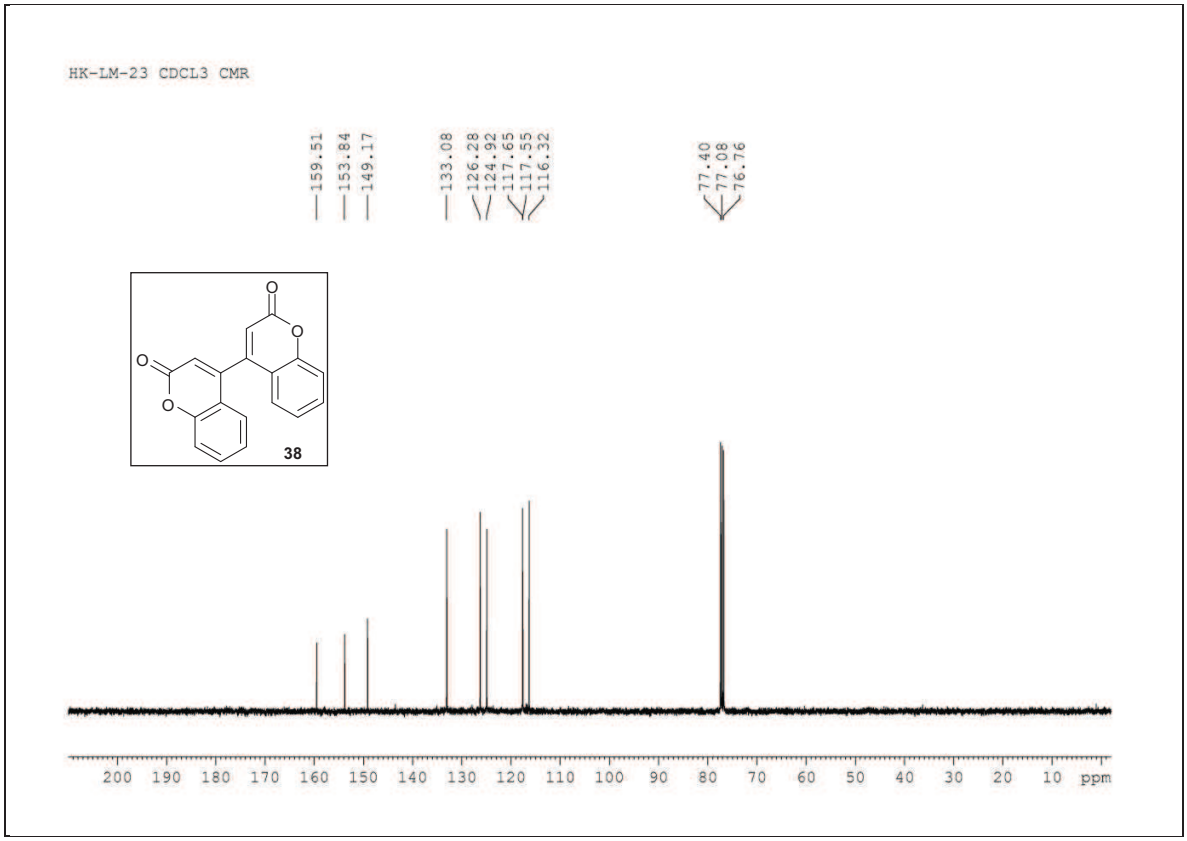
2.14
2.17
4.04
2.00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133.08
126.28
124.92
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117.55
116.32
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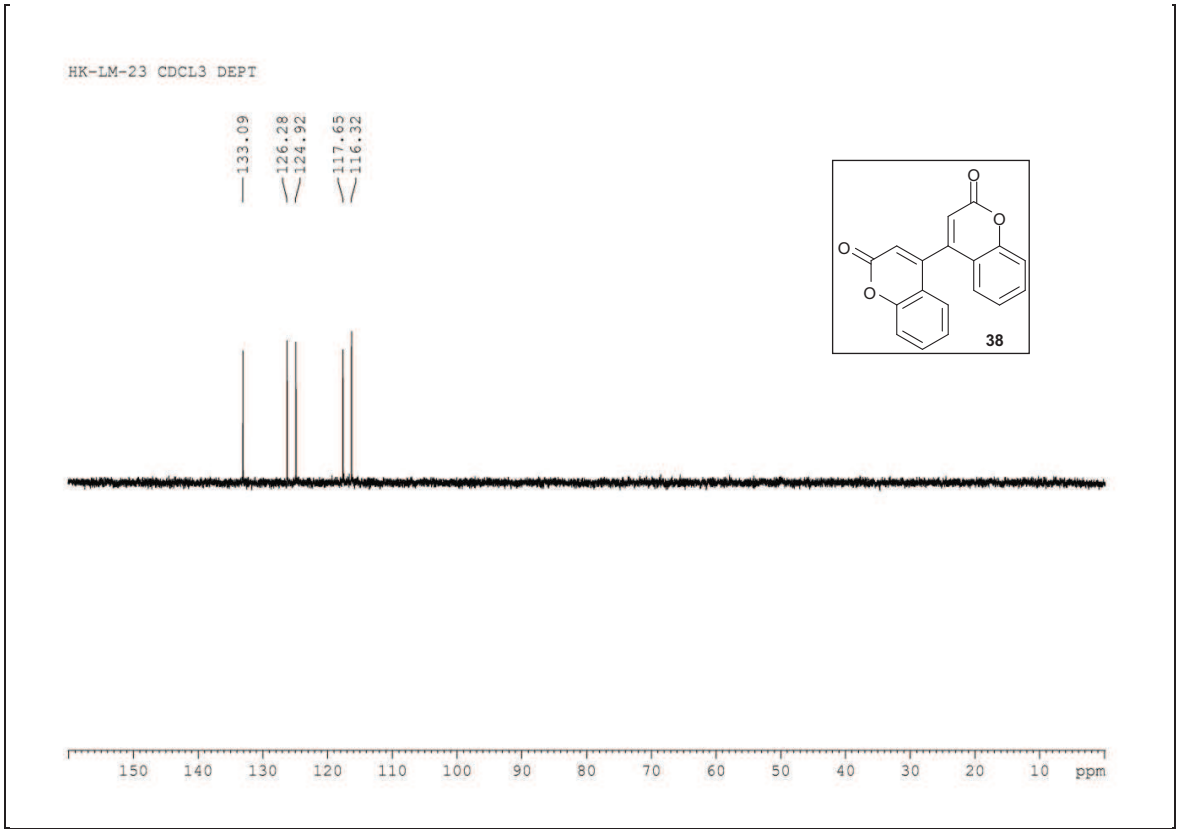

HK-LM-23 CDCL3 DEPT
133.09
126.28
124.92
117.65
116.32
38
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Chapter 4

Reduction of nitroarenes to anilines using sodium borohydride and catalytic Copper (*II*) bromide

4.1: Introduction

Aromatic amines are important intermediates in synthesis of several nitrogen containing biologically active compounds, agrochemicals, dyes, polymers, etc.[1] They are the precursor for many synthetically important intermediates like amides, imines, azo compounds, isocyanates and diazonium salts which could be converted to various other functional groups.[2] Anilines also form substructures of many pharmaceutical compounds (Figure 1). Paracetamol[3] **1a**, a widely used analgesic and antipyretic is an acetyl derivative of *p*-aminophenol. Bicalutamide[4] **1b** is a non-steroidal antiandrogen administered orally for the treatment of prostate cancer and hirsutism. This drug has a *p*-cyano-*m*-trifluoroaniline component in its structure. Nilutamide[5] **1c** having a *p*-nitro-*m*-trifluoromethylaniline core in its chemical structure is an antiandrogen used in treatment of advanced stage prostate cancer. Erlotinib[6] **1d** having an *m*-acetylenyl aniline and quinazoline component is a reversible tyrosine kinase inhibitor being used in treatment of non-small cell lung cancer and pancreatic cancer. Linezolid[7] **1e**, a synthetic antibiotic for multi drug resistant gram positive bacteria has *m*-fluoro-*p*-morpholinoaniline component. Fosamprenavir[8] **1f**, an anti-HIV drug and pro-drug of Amprenavir has a *p*-sulfonamidoaniline branch in its structure.

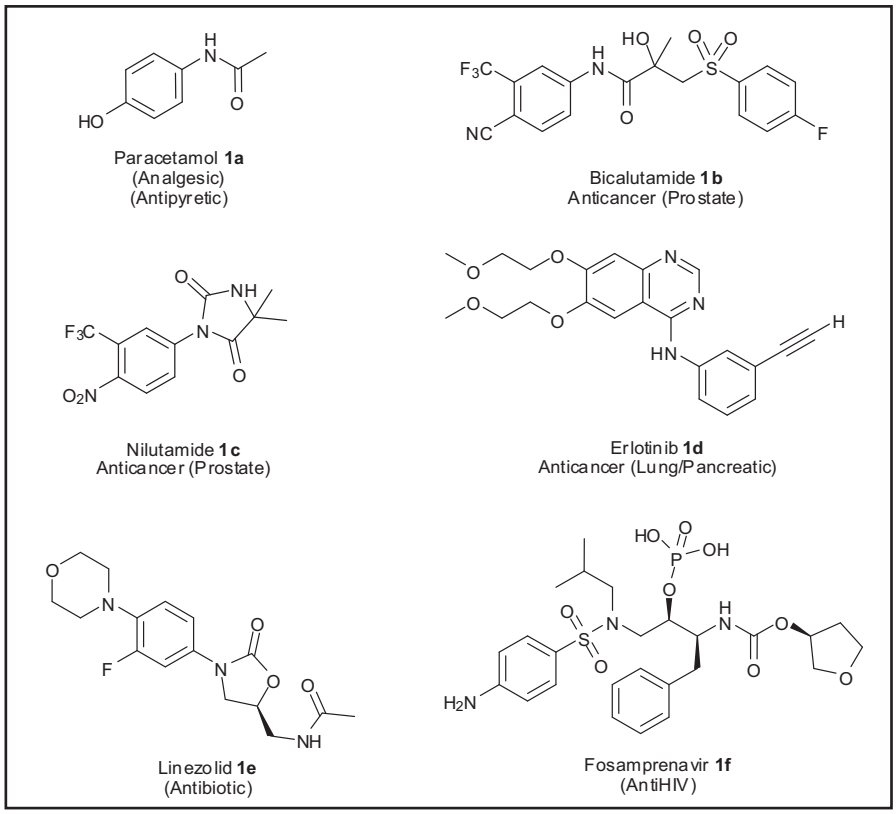
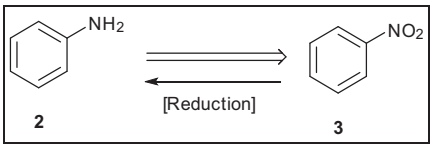


Figure 1: Medicinal compounds with arylamine core structure.

Reduction of nitroarenes to aromatic amines is a most common, simple and efficient approach for their synthesis (Scheme 1).



Scheme 1

Traditional methods like Bechamp reduction[9] involve use of excess transitional metals with strong acid. Some use catalytic but costly noble metals.[1,10] Most of these methods either generate a lot of metallic waste during work-up or lack in selective reduction in presence of other functionalities. Over decades this topic has been a subject of extensive studies for improving the efficiency, selectivity of the reduction process and developing a simple and green procedure for this transformation. Hence, this is a reaction of choice for many research groups working in the field of metal based catalysis.[11-15] Several elegant methods are developed in this course.

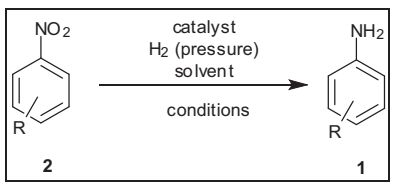
4.2: Literature review

4.2.A: Green methodologies for reduction of nitroarenes

The discussion is classified with respect to the use of reducing agents; such as molecular H_2, hydrides, hydrazine hydrate, silyl hydrides, transfer hydrogenation, metal/organic reductants, light mediated electron transfer and biotic conditions as benign, clean, non-hazardous and non-polluting sources for reduction of nitroarenes.

1. Hydrogen gas
2. Insitu hydrogen generation using sodium borohydride.
3. Silyl hydrides
4. Hydrazine hydrate
5. Transfer hydrogenation
6. Direct metal
7. Non classical green reagents
8. Light mediated photo catalysts
9. Biotic reduction of nitroarenes

Hydrogen gas



Scheme 3

Table 1: Reduction of nitroarenes using hydrogen gas.

Entry	Reagents	H_2 (pressure)	Solvent, conditions	Ref.
1	Fe_3O_4-NH_2-Pd	1 atm	EtOH, r.t.	16
2	Pd/Fe_3O_4	1 atm	EtOH/THF, r.t.	17
3	Polyurea entrapped Pd nanoclusters	1 atm	n-Hexanes, r.t.	18
4	Pd-B-mesoporous molecular sieve	2 MPa	scCO_2, 50 °C	19
5	Colloidal gum acacia – Pt nanoparticles	1 atm	water, r.t.	20
6	Pt/carbon nano tubes	1 atm	EtOH, r.t.	21
7	Pt - multiwalled carbon nanotubes	4 MPa	aniline, 60 °C	22
8	Pt-ionic liquid	1 MPa	90 °C	23
9	Pt- polysiloxane gel	10 atm	EtOAc, r.t. – 50 °C	24
10	Pt/SiO_2	1 bar	IPA, r.t.	25
11	Pt-Au-TiO_2	1 MPa	EtOH, 50 °C	26
12	Au-organic-inorganic hybrid SiO_2	4 MPa	EtOH, 100-140 °C	27
13	Au-ZrO_2	1 MPa	EtOH, 150 °C	28
14	Au-TiO_2	9 bar	toluene, 100 °C	29
15	Au-TiO_2/ Au-Fe_2O_3	9-25 bar	toluene, 110 °C	30
16	Ag-CeO_2	6 atm	dodecane, 110 °C	31
17	Colloidal Ni-carboxymethyl cellulose	40 bar	H_2O-MeOH, r.t.	32
18	Ni-TiO_2	4 MPa	H_2O-CO_2, 35 °C	33
19	Ni-SiO_2	2-3 MPa	EtOH, 110 °C	34
20	Ru - reduced graphine oxide	2 MPa	EtOH-H_2O, 110 °C	35
21	Mixed Ln-succinate-sulfate	0.5 MPa	toluene, 90 °C	36

Amine functionalized magnetic Fe_3O_4 nanoparticles supporting 1.6 mol% Pd is developed as catalyst for reduction of aromatic nitro compounds to anilines using H_2 gas in ethanol at r.t.[16] Here magnetic separation helped in efficient recovery of the catalyst. Halogens or hydroxyl group bearing nitrobenzenes were selectively reduced to corresponding anilines with 92-99 % yield. This reduction system could also reduce the double bonds in stilbene, cinnamyl alcohol and methyl cinnamate. Heck reaction was performed in excellent yield using this catalyst. Similarly, Pd supported on magnetic Fe_3O_4 and Pd(0) immobilized with polyethyleneimmine on Fe_3O_4 nanoparticles are developed for hydrogenation of nitroarenes to anilines.[17] Former was also used for Suzuki reaction and latter can also be used for reduction of double and triple bonds and Suzuki-Miyaura reaction. The stability and efficient magnetic recovery of catalyst in turn helped in enhancing the reusability of this catalyst.

Palladium nanoclusters entrapped in polyurea have been prepared and shown to exhibit dual catalytic activity for reduction of nitro compounds and dehalogenation of aromatic chlorides in atmospheric hydrogen with 100 % yield for reduction of nitro compounds at room temperature and >99 % yield for dehalogenation of aromatic chlorides under refluxing methanol conditions.[18] This immobilizing method was particularly effective and eliminated the need of special chelating groups. Supercritical CO_2 is used as solvent along with Pd nanoparticles supported on B-MCM-41 as catalyst and H_2 gas for hydrogenation of nitroaromatics.[19] This system could also reduce a nitrile group and a phenol to cyclohexanone.

Hydrogenation of nitroarenes is catalysed by gum acacia supported Pt colloids with 0.24 mol % catalyst loading in water at r.t. using H_2 at 1 atm.[20] This catalytic condition was inert to halogens, aldehydes and ketones with selective reduction of nitro group in 68 to 95 % yield.

Pt supported on carbon nanotubes is demonstrated as catalyst for selective hydrogenation of *m*- and *o*- chloro nitrobenzene to corresponding chloroanilines.[21] Introduction of Fe in Pt supported carbon nanotubes increased the efficiency of catalyst. Aniline as solvent with ultrafine Pt deposited on carbon nanotubes are reported for hydrogenation of nitrobenzene and nitrosobenzene to aniline.[22]

Ionic-liquid-like copolymer stabilized Pt nano catalysts are used for selective hydrogenation of aromatic chloro nitro compounds to chloroanilines using H_2 gas.[23] Polysiloxane gels containing Pt species, [Pt]@SiC_6 and [Pt]@SiC_6-TAA, act as recyclable heterogeneous catalysts for reduction of various nitro compounds to their corresponding amines with other functional groups remaining intact.[24]

Substituted nitroaromatics were selectively hydrogenated to the corresponding N-aryl hydroxylamines in excellent yields (up to 99 %) using supported platinum catalysts such as Pt/SiO_2 under a hydrogen atmosphere (1 bar) at room temperature.[25] This reduction was carried out in IPA with DMSO and n-$BuNH_2$ as additives.

Adding a small amount of Pt entities (0.01–0.03 wt%) onto the Au surface of a Au/TiO_2 catalyst is an efficient approach to improve the catalytic activity of Au for the hydrogenation of *p*-chloronitrobenzene, where the C–Cl bond in the *p*-CNB molecule remained intact. Excess amounts of Pt (>0.03 wt%) and high reaction temperatures causes the occurrence of the undesired catalytic hydrodechlorination reaction of *p*-CNB.[26]

Highly dispersed gold nanoparticles supported on organic–inorganic hybrid silica exhibited good catalytic activity and stability for liquid phase catalytic hydrogenation of aromatic nitro compounds with H_2.[27] Similarly hydrogenation of chloronitrobenzene to chloroaniline is reported over Au/ZrO_2 catalyst with H_2 gas in ethanol,[28] and Au on TiO_2 is used as a hydrogenation catalyst to prepare azo

compounds directly from nitroaromatics through a two-step (hydrogenation followed by aerobic oxidation), one-pot, one-catalyst reaction.[29]

Nitroarenes containing double bonds, carbonyl, nitrile or amide groups have been hydrogenated on supported gold nanoparticles (Au/TiO_2 and Au/Fe_2O_3), using a batch reactor under H_2 pressure.[30]

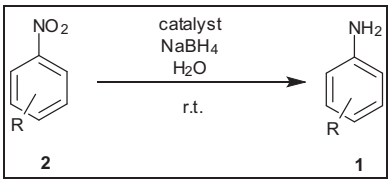
$Ag@CeO_2$ core shell nano composite is used as catalyst for reduction of nitro compounds to anilines by H_2 gas.[31] This catalyst helped to achieve complete selectivity towards nitro reduction in presence of double bond with > 95 % yield. This system could also reduce epoxide to alkenes.

A biopolymer-inorganic catalyst system involving colloidal Ni and carboxymethylcellulose is reported for reduction of nitroaromatics using H_2 gas at r.t. in MeOH-water mixture.[32] 79-96 % yields of various aniline products were obtained with substrate:catalyst ratio of 100 and 40 bar H_2 gas. Reduction was achieved in presence of ester, OH and NH_2 on aromatic ring. This system was also useful for reduction of ketone to 2° alcohol. Low pressure CO_2-water system with Ni is applied for reduction of nitrobenzene to aniline. Ni was supported on Al_2O_3 for this reduction.[33] Under similar conditions, chloronitrobenzene was reduced to chloroaniline with Ni/TiO_2 in low pressure CO_2 (3MPa) – water system. Ni/SiO_2 catalyst is used for reduction of nitroarenes to anilines using H_2 gas.[34] While ketones, aldehydes, chloro, amides were found to be unaffected during reduction with this system.

A reduced graphene oxide (RGO) supported-ruthenium (Ru) catalyst was prepared where Ru nanoparticles were in an electron-deficient state due to the electron transfer between the nanoparticles and the RGO sheets and applied for the selective hydrogenation of *p*-chloronitrobenzene (*p*-CNB) to *p*-chloroaniline (*p*-CAN), exhibiting a turnover frequency (TOF) of 1800 h^{-1} and a selectivity of 99.6 % at complete conversion of *p*-CNB.[35]

Mixed lanthanide succinate–sulfate isostructural 3D polymeric metal–organic frameworks monoclinic space group showed high chemoselectivity towards reduction of the nitro group.[36]

***Insitu* hydrogen generation using $NaBH_4$**



Scheme 4

Table 2: Reduction of nitroarenes using sodium borohydride.

Entry	catalyst	Ref.
1	Pd-poly-(*3,4*)-ethylenedioxy-thiophene matrix	37
2	Solid supported Pd,[a]	38
3	Au-Fe_3O_4 nanocatalyst	39
4	Au-Nano Active MgO Plus	40
5	Au nanorods, KBH_4	41
6	Au-epigallocatechin-*3*-gallate-collagen fiber	42
7	Au-resorcinarene nanoparticles	43
8	Au-alumina/membrane	44
9	Au-double hydrophilic block copolymer	45
10	Au-graphene hydrogel	46
11	Au-TiO_2,[b]	47
12	Ag-Au-Fe_3O_4-carbon composite	48
13	Ag-halloysite nanotubes	49
14	Ag quantum clusters	50
15	Ag-graphite-poly-(amidoamine)-dendrimer	51
16	Hollow Ag nanospheres	52
17	(Pt/Au) nanoparticles	53
18	$CuBr_2$,[c]	54
19	Cu/MIL-101(Cr) nanocomposites	55
20	Co-Co_2B,[d]	56

[a] MeOH-H_2O, r.t.-50 °C; [b] NH_3BH_3, EtOH; [c] EtOH, [d] MeOH

Synthesis of Pd incorporated poly-(*3,4*)ethylenedioxythiophene (PEDOT) matrix in aqueous medium was achieved and its catalytic activity was demonstrated using a model reaction, i.e., reduction of 4-nitrophenol to *4*-aminophenol.[37]

Solid supported Pd(0) catalyzed highly chemoselective reduction of nitroarenes to the corresponding anilines was accomplished under a mild condition. This catalyst showed high compatibility with various reducing agents like $NaBH_4$, Et_3SiH, and $NH_2NH_2.H_2O$ and a large number of reducible functional groups such as sulfonamide, amides, carboxylic acid, ester, alcohol, halide, hetero cycle, nitrile, alkene, carbonyl, O-benzyl, and N-benzyl were tolerated.[38]

Dumbbell- and flower-like Au-Fe_3O_4 heterostructures have been fabricated by thermal decomposition of the iron oleate complex in the presence of Au nanoparticles (NPs) using different sizes of Au NPs as the seeds and employed as magnetically recyclable catalysis of *p*-nitrophenol

and 2,4-dinitrophenol reduction.[39] Nanocrystalline Magnesium oxide supported gold nanoparticles are used as recyclable heterogeneous catalyst for reduction of nitroarenes to anilines using sodium borohydride in double distilled water at room temperature.[40] This reduction system could tolerate varied substitution of aromatic ring like F, Cl, Br, I, OCH_3, COOMe, vinyl, CN, OH and NH_2.

Uniform-sized gold nanorods have been prepared via a three-step seed-mediated growth method using a long-chain ionic liquid (IL), C_{12}mimBr, as a capping agent and exhibited excellent catalytic efficiency for the reduction of nitro compounds.[41] Size-controlled gold nanoparticles (AuNPs) supported on collagen fiber (CF) at room temperature were prepared. Epigallocatechin-3-gallate (EGCG), a typical plant polyphenol, was grafted onto CF surface to serve as reducing/stabilizing agent, so that the AuNPs were generated on CF surface without introduction of extra chemical reagents or physical treatments. Stabilized AuNPs were found to be active heterogeneous catalysts for the reduction of 4-nitrophenol to 4-aminophenol in aqueous phase.[42]

Resorcinarene-functionalized gold nanoparticles (AuNPs) were prepared in aqueous solution in the presence of amphiphilic tetramethoxyresorcinarene tetraaminoamide. The catalytic activity of the obtained AuNPs in the reduction of aromatic nitro compounds was investigated.[43] Layer-by-layer deposition of polyelectrolyte/Au nanoparticle films in porous alumina, track-etched polycarbonate and nylon substrates gave catalytic membranes that showed high catalytic activity in the reduction of nitroaromatic compounds with sodium borohydride.[44]

Water-dispersible gold nanoparticles (Au NPs) using a double hydrophilic block copolymer (DHBC), poly(ethylene oxide)-block-poly(acrylic acid) (PEO-b-PAA) as a template were prepared and found to be highly effective in catalyzing the reduction of a series of nitroarenes.[45] Similarly catalytic reduction of 4-nitrophenol by sodium borohydride was achieved in the presence of Pt/Au nanoparticles embedded in spherical polyelectrolyte brushes, which consist of a polystyrene core onto which a dense layer of cationic polyelectrolyte brushes are grafted. The average size of these nanoparticles was approx. 2 nm.[46]

A cylindrical piece of Au/graphene hydrogel, 1.08 cm in diameter and 1.28 cm in height, has been synthesized through the self-assembly of Au/graphene sheets under hydrothermal conditions. The hydrogel, containing 2.26 wt% Au, 6.94 wt% graphene, and 90.8 wt% water, exhibited excellent catalytic performance towards the reduction of 4-nitrophenol (4-NP) to 4-aminophenol (4-AP). The high catalytic activity arises from the synergistic effect of graphene: (1) the high adsorption ability of graphene towards 4-NP, providing a high concentration of 4-NP near to the Au nanoparticles on graphene; and (2) electron transfer from graphene to Au nanoparticles, facilitating the uptake of electrons by 4-NP molecules.[47]

Quantitative reduction of nitroarenes into anilines and nitroalkanes into alkylhydroxylamines by the ammonia- borane complex was achieved using gold nanoparticles supported on titania catalyst, even at a ppm loading level.[48]

The heterostructure Ag−Au bimetallic nanocrystals supported on Fe_3O_4@carbon composite microspheres were synthesized by facile and controllable approach, wherein the Ag nanocrystals attached on the Fe_3O_4@carbon microspheres were prepared first and served as reductant for the galvanic replacement reaction with the Au precursor ($HAuCl_4$). They could give high yields for reduction of nitroaromatic compounds with various substituents, irrespective of the linked electron-donating or electron-withdrawing groups.[49]

The silver nanoparticles supported halloysite nanotubes (Ag/HNTs), with Ag content of about 11%, were used for the catalyzed reduction of 4-nitrophenol (4-NP) with $NaBH_4$ in alkaline aqueous solutions.[50] Quantum clusters (QCs) of silver such as $Ag_7(H_2MSA)_7$, $Ag_8(H_2MSA)_8$ (H_2MSA, mercaptosuccinic acid) were synthesized by the interfacial etching of Ag nanoparticle precursors and were loaded on metal oxide supports to prepare active catalysts such as Al_2O_3@$Ag_{7,8}$, SiO_2@$Ag_{7,8}$, TiO_2@$Ag_{7,8}$, and Fe_2O_3@$Ag_{7,8}$. These catalysts showed enhanced catalytic activity for the reduction of several nitro compounds.[51]

Hyperbranched polyamidoamine (PAMAM) dendrimer were grafted on the graphite surface and silver nanoparticles (AgNPs) were synthesized within the graphite grafted PAMAM dendrimer templates and applied as nanocatalysts in the reduction of nitro aromatics. The efficiency of this system has been demonstrated through the reduction of halonitroarenes without dehalogenation in the halo-substituted nitro benzenes and selective reduction of nitro groups in the presence of imine functionalities under mild condition.[52]

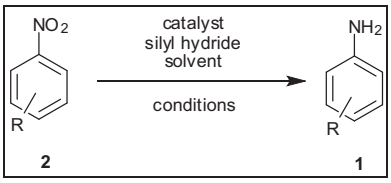
Hollow silver nanospheres colloids were prepared by a simple reaction of silver nitrate ($AgNO_3$), sodium hydroxide (NaOH) and hydroxylammonium hydrosulfate ($(NH_2OH)_2{\cdot}H_2SO_4$) in the presence of gelatin. Superior catalytic performance was observed in 4-nitrophenol (4-NP) and 4-nitroaniline (4-NA) reduction in the presence of freshly prepared ice cold aqueous solution of sodium borohydride ($NaBH_4$) at room temperature.[53]

Copper(II) bromide as a procatalyst for the in situ preparation of active Cu nanoparticles for the efficient reduction of nitroarenes using sodium borohydride is described.[54]

Cu nanoparticles (NPs) loaded on a MIL-101 (Cr) metal–organic framework showed enhanced catalytic activity for the reduction of aromatic nitro compounds.[55]

Magnetically recoverable and recyclable Co–Co_2B nanocomposites are described for the catalytic and chemoselective reduction of nitroarenes using two different hydrogen sources, sodium borohydride and hydrazine hydrate.[56]

Silyl Hydrides



Scheme 5

Table 3: Reduction of nitroarenes using silyl reagents.

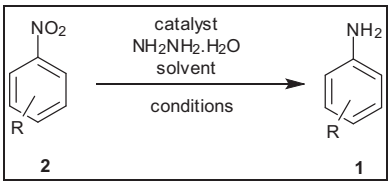
Entry	catalyst	Silyl reagent	Solvent/conditions	Ref.
1	$FeBr_2$, PPh_3,	$PhSiH_3$	toluene, 110 °C	57
2	$Fe(acac)_3$	tetramethyldisiloxane	THF, 60 °C	58
3	Au-Fe_3O_4,	tetramethyldisiloxane	EtOH, r.t.	59
4	$ReOCl_3(PPh_3)_2$	$PhMe_2SiH$	toluene, 110 °C	60

Iron-based catalytic system consisting of $FeBr_2$–Ph_3P has been discovered for the reduction of nitroarenes with organosilanes. The procedure is general and the selectivity of the catalyst has been demonstrated applying challenging substrates with C=O, C≡N, C=C, and OH groups.[57]

An efficient reduction of the nitro group with a catalytic amount of $Fe(acac)_3$ and TMDS in THF at 60 °C affording the corresponding amine is described. Similarly the system *1,1,3,3*-tetramethyldisiloxane (TMDS)/$Fe(acac)_3$ is used for nitroreduction and amines were isolated as hydrochloride salts with good to excellent yields.[58]

Magnetically separable gold-nanoparticle catalyst was prepared, and it showed excellent activity for chemoselective reduction of nitroarenes with hydrosilanes.[59] Alternatively, the reduction of aromatic nitro compounds to the corresponding amines with silanes catalyzed by high valent oxo-rhenium complexes is reported. The catalytic systems $PhMe_2SiH/ReIO_2(PPh_3)_2$ (5 mol %) and $PhMe_2SiH/ReOCl_3(PPh_3)_2$ (5 mol %) reduced efficiently a series of aromatic nitro compounds in the presence of a wide range of functional groups such as ester, halo, amide, sulfone, lactone, and benzyl. This methodology also allowed the regioselective reduction of dinitrobenzenes to the corresponding nitroanilines and the reduction of an aromatic nitro group in presence of an aliphatic nitro group.[60]

Hydrazine hydrate



Scheme 6

Table 4: Reduction of nitroarenes using hydrazine.

Entry	catalyst	Solvent/conditions	Ref.
1	PEG-35k-Pd nanoparticles	90 °C	61
2	Pd-C nanospheres	EtOH:H_2O, 80 °C	62
3	$Fe(acac)_3$	MW, 150 °C	63
4	Graphene-Fe_3O_4	70 °C	64
5	Fe_3O_4 nanoparticles	EtOH, 80 °C	65
6	Iron oxide hydroxide, polymer supported NH_2NH_2	iPrOH, 80 °C	66
7	FeSO4 –Fe phthalocyanine	EtOH:H_2O, 120 °C	67
8	Rh-Fe_3O_4	EtOH, 80 °C	68
9	Hollow Rh nanocomposite	EtOH, 80 °C	69
10	Rh-porous ionic copolymer	EtOH, 60 °C	70
11	Zn-phthalocyanine	PEG-400, 100 °C	71
12	Zn or Mg, Hydrazine glyoxalate	r.t.	72
13	Co-Co_2B	MeOH, r.t.	56
14	Multiwalled carbon nanotubes	EtOH, 100 °C	73
15	(Bu_4N)[Ni(toluene-*3,4*-dithioalate)$_2$]	THF, reflux	74
16	MoS_2	toluene, 60-80 °C	75
17	Carbon/Graphite	iPrOH, reflux	76

Polymeric PEG-35K-Pd nanoparticles are used for reduction of nitro compounds to amines with hydrazine hydrate as a reducing agent at 90 °C.[61] This reduction method was inert to halogens giving haloanilines in quantitative yield.

Palladium nanoparticles immobilized on carbon nanospheres are reported to catalyse reduction of nitroaromatic compounds with 1.36 % Pd using hydrazine hydrate in ethanol-water mixture. These nano catalysts extend a sustainable support in renewable catalysis. It is applied to selectively reduce nitro group in presence of vinyl, CHO, OH, NH_2, and the low Pd loading of 1.36 % also

helped to retain halogen in the products. Similarly Pd/C is also studied for selective reduction using hydrazine hydrate under reflux or MW conditions.[62]

In situ generated iron oxide nanocrystals are used for reduction of nitroarenes using MW irradiation.[63] This method using hydrazine hydrate as reducing agent yielded anilines in quantitative yields without affecting halogens, esters, amides or CN.

Graphene-Fe_3O_4 nanocomposite (G-Fe_3O_4) and superparamagnetic graphene-Fe_3O_4 nanocomposite (G- Fe_3O_4) were synthesized by a chemical co-precipitation method which was used as an efficient catalyst for the reduction of nitroarenes with hydrazine hydrate.[64]

Readily available and magnetically separable Fe_3O_4 nanoparticles were utilized for recyclable and efficient nitroarene reduction.[65]

Iron oxide hydroxide catalyst is used for reduction of nitroarenes to anilines with polymer supported hydrazine hydrate in refluxing isopropanol.[66] Anilines were obtained in 93 to 99 % yields without affecting Cl, OH, NH_2, and esters.

Iron pthalocyanine and iron sulfate catalyzed reduction of nitroarenes to anilines is reported with hydrazine hydrate as hydrogen source in mixture of water and ethanol.[67] This method was applied on gram scale to substrate with substituents like acid, nitrile, sulfonamide, hydroxyl, O-benzyl, N-benzyl, lactones, etc. 4-chloro-2-nitrophenol was selectively reduced to corresponding aniline without affecting other functionalities. Also other heterocyclic nitro- compounds like nitro-isoquinoline, nitro-indole, nitro-thioindole, etc. were successfully reduced to corresponding amines.

Rh– Fe_3O_4 heterodimer nanocrystals were prepared by controlled one-pot thermolysis. The nanocrystals exhibited excellent activities for the selective reduction of nitroarenes and alkenes.[68,69] A highly active and selective Rh/highly porous ionic copolymer (PICP) nanocatalyst for the reduction of nitroarenes into corresponding anilines with hydrazine monohydrate under mild conditions is also reported.[70]

Zn Pc is used as catalyst (1 mol%) for reduction of aromatic nitro compounds to anilines using $N_2H_2.H_2O$ as reducing agent and PEG-400 as solvent.[71] This catalyst is also useful for reduction of ketones to alcohols. Various functional groups like acid, ester, amide, sulfonamide, cyano, and halogens were unreactive in this nitro reduction. Aromatic nitro compounds were selectively and rapidly reduced at r.t. to corresponding amines in good yields by employing hydrazine glyoxalate in presence of Zn or Mg powder.[72]

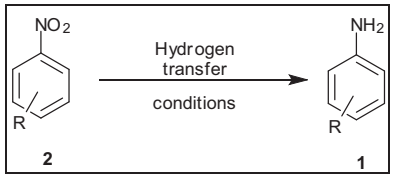
Magnetically recoverable and recyclable Co–Co_2B nanocomposites described earlier for the catalytic and chemoselective reduction of nitroarenes using sodium borohydride have also been demonstrated for reduction of nitro group using hydrazine hydrate.[56]

Multiwalled carbon nanotubes were functionalized with small organic molecules containing specific ketonic carbonyl groups through noncovalent van der Waals and π–π interactions and utilized as metal free catalysts for reduction of nitroarenes Multi-walled carbon nanotubes were.[73]

Transfer hydrogenation of aromatic nitro compounds by hydrazine to the corresponding anilines is catalysed by (Bu_4N)[Ni(toluene-*3,4*-dithioalate)$_2$] in refluxing THF.[74]

Commercial MoS_2 was found to be a highly selective catalyst for the reduction of nitrobenzenes to the corresponding anilines with hydrazine under mild conditions.[75] Reduction of nitroaromatics to anilines by hydrazine is also studied using carbon or graphite as catalysts.[76]

Transfer Hydrogenation



Scheme 7

Table 5: Reduction of nitroarenes by transfer hydrogenation.

Entry	reagents	Solvent/conditions	Ref.
1	HCOOH	HTP water, 300 °C	77
2	CeY zeolite, HCOOH or $HCOONH_4$	MW, 140 °C	78
3	$Mo_3S_4H_3(dmpe)_3BPh_4$, HCOOH, Et_3N,	THF, 70 °C	79
4	Ni-Fe_3O_4, KOH, glycerol	80 °C	80
5	Polymer-bound palladium, K_3PO_4, cyclohexanol	DMF, 110 °C	81
6	$LaFeO_3$, KOH, iPrOH	MW	82
7	Ru-acid activated montmorillonite clay or Ag-mesoporous poly-triallylamine, NaOH, iPrOH	80 °C	83
8	Au-TiO_2, CO (5 atm)	EtOH-H_2O, r.t.	84
9	Ru-MgF_2, CO (2 MPa)	EtOH-H_2O, 175 °C	85

Continuous hydrogenation of nitrobenzene to aniline is developed in High Temperature-Pressurized Water (HTPW) using H_2 generated by thermal decomposition of HCOOH.[77] This reaction is carried out in absence of any added catalyst and can be conveniently performed on laboratory scale.

CeY Zeolite and formic acid under MW gave good yields of reduction products within 10 min. Aliphatic nitro compounds even with ester functionality were reduced to corresponding amines, while aldehyde, acid, amides, CN, Cl, Br, were retained in corresponding anilines.[78]

Cubane-type $[Mo_3S_4X_3(dmpe)_3]^+$ clusters have been developed as catalysts (X=H) or precatalysts (X=Cl) for the reduction of functionalized nitroarenes using formates as a reducing agent.[79]

Heterogeneous Fe_3O_4-Ni MNPs catalyst is demonstrated for hydrogen-transfer reactions by using the environmentally friendly solvent glycerol as a hydrogen donor.[80]

Polymer-bound palladium catalyst was prepared as PdO nanoparticles bound on the surface of polystyrene beads. This catalytic system showed good activities in the reduction of nitro arenes and the hydrodehalogenation of aryl halides with 10 mol% PdO and K_3PO_4 (1.5 equiv.) in DMF/cyclohexanol at 110 °C.[81]

Transfer hydrogenation of nitroaromatic to anilines in isopropylalcohol using KOH and Ru nanoparticles stabilized on Montmorrilonite clay as catalyst is achieved. Catalyst was selective towards nitro reduction to corresponding anilines without affecting F, Cl, Br or CN. Perovskite-type $LaFeO_3$ nanoparticles were readily synthesized via thermal decomposition of the $La[Fe(CN)_6]\cdot 5H_2O$ complex. This nanosized perovskite-type oxide with an average particle size of 35 nm and a specific surface area 38.5 m^2/g was used as a reusable heterogeneous catalyst for selective reduction of aromatic nitro compounds into their corresponding amines by using propan-*2*-ol as the hydrogen donor under microwave irradiation.[82,83] Ag-mesoporous poly-triallyl amine catalyst is reported under similar conditions.[83b]

Ru and Ir catalysts, which are not particularly selective under the conditions of conventional hydrogenation carried out with molecular hydrogen, when used in the Aqueous-Phase Reforming/Hydrogenation (APR/Hyd) process, become >99.9 % selective for hydrogenation of o-chloronitrobenzene to *o*-chloraniline.[84,85]

Direct metal

Scheme 8

Table 6: Reduction of nitroarenes using metal.

Entry	Metal reagent	solvent	Ref.
1	Fe nm powder,	H_2O, 210 °C	86
2	Fe nanoparticles, 3 eq.,	H_2O, r.t.	87
3	FeS, NH_4Cl	MeOH, H_2O, reflux	88
4	Te,	H_2O, 275 °C	89
5	Zn, NH_4Cl,	H_2O, 80 °C	90
6	Zn, CO_2, (8 MPa),	H_2O, 80 °C	91
7	Zn, CO_2, 0.1 MPa	H_2O, r.t.	92
8	Zn, CO_2, 0.1 MPa	H_2O, ultrasound	93
9	$RuCl_2(PPh_3)_3$, KOH, Zn	H_2O, dioxane, 40 °C	94
10	Zn, SiO_2-PEG	H_2O, r.t. - reflux	95
11	Sm, AcOH	[BMIM][BF_4], r.t.	96
12	Mn, $CuCl_2$	THF, H_2O, r.t.	97
13	$NbCl_5$/In	THF, r.t.	98

Nanosized activated metallic iron powder is used as reducing agent for reduction of nitroarenes to anilines in water at 210 °C (near critical water).[86] This method unlike Bichamp reduction, avoids use of strong acidic conditions and could sustain substituents like OMe, COMe, COOEt, F, Cl, Br, and I. This method could also reduce nitronaphthalene to naphthylamine but not aliphatic nitro compounds and nitrostyrenes. Similarly highly selective reduction of nitroarenes has been achieved using iron metal nanoparticles in water at room temperature. During the reaction a change in shape of Fe nanoparticles was observed.[87]

Reduction is achieved in refluxing MeOH-water mixture using FeS and ammonium chloride.[88] Sensitive substituents like chloro, ester, N-benzyl were unreactive in this reduction and corresponding anilines were obtained in 56 to 81 % yields. Te metal is used as reducing agent for preparation of anilines from nitro aromatics in neat critical water at 275 °C.[89]

Chemoselective reduction of nitroarenes to anilines is reported using Zn and NH_4Cl in water at 80 C.[90a] The functionalities like ester, amide and halogens were unaffected and sterically hindered 2,6 dinitrobenzene was also reduced to corresponding anilines in 95 % yield. Similarly zinc powder in aqueous solutions of chelating ethers is also used. The donor ether acts as a ligand and also serves as a co-solvent with water being the proton source.[90b] With Zn-H_2O-CO_2 system, water acted as direct hydrogen donor in super critical CO_2 as solvent.[91] This method gave excellent yields of reduction product in presence of F, Cl, Br, I, acid and ketone functional groups.

Controlled reduction of nitroarenes to N-phenylhydroxylamine was achieved using Zn in CO_2/H_2O system. 88 % yield of N-phenyl hydroxylamine was obtained when 3 eq. of Zn was used in 0.1MPa CO_2 at 25 °C for 1.5 h.[92] Using this stiochiometric conditions, dinitrobenzene was selectively reduced to *m*-nitro-N-phenylhydroxylamine in 99 % yield. Similarly Zinc in CO_2-water mixture with application of ultrasound gave excellent yields in just 60 min. Other reducible functional groups like CN, keto, Cl, Br were not affected in these methods.[93,94]

Reduction of nitro compounds to anilines is achieved in water using zinc powder and silica gel supported PEG.[95] The products were isolated in 68-92 % yield by mere acid base purification with retention of other substituents like NH_2, COOH, and also sensitive functionalities like CHO, Cl, CH_2Br.

Sm and AcOH in ionic liquid is used at r.t. for nitro-reduction.[96] In this system halogen, CHO, COOH, CN, NHTos groups were unaffected and corresponding anilines were obtained in 83 to 98 % yields.

Reduction of aromatic nitro compounds to anilines is reported in THF-water mixture at r.t. using Mn as reducing agent and $CuCl_2$ as catalyst.[97] Nitro group was selectively reduced to NH_2 in presence of OH, NH_2, Cl, COOH, ester and CN with 75-88 % yield. The products were isolated in pure form by mere acid- base treatment. Similarly $NbCl_5$/In system mediates an efficient and mild reduction of aromatic nitro compounds to the corresponding amines.[98]

Non classical green reagents

Scheme 9

Table 7: Reduction of nitroarenes by non-classical reagents.

Entry	reagents	Solvent/conditions	Ref.
1	D-glucose, KOH,	H_2O:DMSO, 110 °C	99
2	Pd/C, 1,4-cyclohexadiene,	MeOH, MW, 120 °C	100
3	Pinacol, $MoO_2Cl_2(dmf)_2$	toluene, MW, 150 °C	101
4	(*2*-Pyridyl)phenyl methanol	toluene, 110 °C	102
5	10 % Pd/C, NaH_2PO_2	H_2O, 50 °C	103
6	5 % Pd/C, H_3PO_2, NaH_2PO_3	ultrasound	104
7	H_3PO_2, H_3PO_3, NaI, aq. HBr,	AcOH, 115 °C	105

D-glucose, abundantly available carbohydrate is reported as a source of hydrogen for reduction of nitroarenes in catalyst free aqueous system. D-glucose/KOH system in water: DMSO mixture is employed for this reduction of nitro arenes at 110 °C.[99] Substituents like C≡N, CHO, C=C, C=N and halogens on nitroarenes were tolerated. Even dinitroarenes was found to selectively reduce to mononitroanilines in excellent yields.

Commonly available Pd/C or Pt/C catalyst is extremely effective with 1,4-cyclohexadiene as the hydrogen transfer source. For substrates containing potentially labile aromatic halogens, Pt/C is effective and results in little or no dehalogenation. In general, the reactions were complete within 5 min at 120 °C under microwave heating conditions.[100]

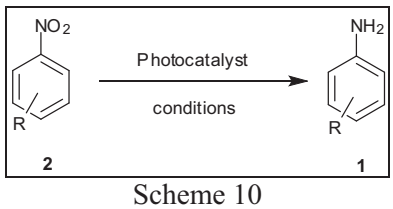
Pinacol is used as reducing agent in presence of $MoO_2Cl_2(dmf)_2$ as catalyst for reduction of nitro aromatics to anilines.[101] This reduction system was compatible with most halogens, amide, ester and ketones. Good yields were obtained under MW condition and acetone and water are the only by-products in this reduction. This system could also be used for deoxygenation of sulphoxides.

(*2*-Pyridyl)phenyl methanol is used as hydrogen donor for reduction of aromatic nitro compounds to arylamines. These were subsequently subjected to conjugate addition through aza-Michael reaction in one pot manner.[102]

Sodium hypophosphite is used as hydrogen source in water for reduction of nitro compounds. This process was catalysed by Pd/C (10 mol%) with along with Na_2CO_3 as base.[103] Aromatic as well as aliphatic nitro compounds were reduced to amines at 50 °C in more than 99 % yield. Sodium hypophosphite is also used for dehalogenation, debenzylation and double bond hydrogenation. Similarly mixture of phosphinic acid and sodium hypophosphite with Pd/C is used as heterogenous catalyst in water: 2-methylTHF system.[104] Here aliphatic nitro group was selectively reduced in presence of indole or coumarin. Nitro arenes were reduced to corresponding anilines in presence of CN, ester, keto and halogen groups.

A novel iodide-catalyzed reduction method using hypophosphorous and/or phosphorus acids was developed to reduce both diaryl ketones and nitroarenes chemoselectively in the presence of chloro and bromo substituents in high yield. This efficient and practical method has been successfully applied to a large scale production of a potential anticancer agent, Lonafarnib.[105]

Light mediated photo catalysts



Scheme 10

Table 8: Reduction of nitroarenes.

Entry	reagents	Solvent/conditions	Ref.
1	TiO_2, Hg arc(>300 nm), HCOOH,	H_2O-MeCN, r.t.	106
2	TiO_2, TEOA, 530 nm	MeCN, r.t.	107
3	TiO_2, oxalic acid, HCl, UV	H_2O, r.t.	108
4	CdS nanosphere / reduced graphene oxide, 420 nm, $HCOONH_4$	H_2O, r.t.	109
5	CdS, nanowires, reduced grapheme oxide, <420 nm	H_2O, r.t.	110
6	$HCOONH_4$, Pd@CeO_2, <420 nm	H_2O, r.t.	111
7	$PbBiO_2Br$, 440 nm, TEOA	MeCN, r.t.	112

TiO_2 is used as photocatalyst under UV irradiation for reduction of nitrobenzene to aniline using oxalic acid as reducing agent and hole scavenger.[106] Vinyl, halogens, acid and ketones were unreactive in this reduction. Ru dye sensitized TiO_2 is also reported as catalyst in presence of green light for this reduction.[107] Here, triethanolamine (TEOA) is used as reducing agent thus method was compatible to aldehyde, ketone, ester, cyano and halogen.

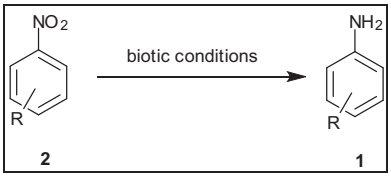
Photocatalytic reduction in aqueous suspensions of titanium(*IV*) oxide (TiO_2) in the presence of hole scavengers under various conditions was examined. *m*-Nitrobenzenesulfonic acid was almost quantitatively converted into *m*-aminobenzenesulfonic acid in the presence of formic acid as a hole scavenger under deaerated conditions with high efficiency (>99 %).[108a] Similarly, nitroaromatic compounds can be photocatalytically reduced into the corresponding amines using TiO_2 as a photocatalyst in the UV/TiO_2/holes scavenger and Vis/TiO_2/dye-sensitized systems. In the UV/TiO_2/holes scavenger system, reaction substrate alcohols such as methanol could be used as the hole scavengers, and in the Vis/TiO_2/dye-sensitized system, substrate alcohols could be oxidized to the corresponding aldehydes with high selectivity.[108b]

Self-assembly of uniform CdS nanospheres/ graphene (CdS NSPs/GR) hybrid nanocomposites is observed via electrostatic interaction of positively charged CdS nanospheres (CdS NSPs) with negatively charged graphene oxide (GO), followed by GO reduction via a hydrothermal treatment. These nanocomposites exhibited high visible light photocatalytic performance and excellent reusability toward selective reduction of aromatic nitro organics to corresponding amino organics in water.[109] Similarly, the CdS nanowires-reduced graphene oxide nanocomposites (CdS NWs-RGO NCs) were synthesized by same process. Furthermore, the presence of RGO also improves the adsorption capacity of CdS NWs- RGO NCs toward aromatic nitro organics.[110]

Pd nanoparticle cores encapsulated within CeO_2 hollow shells are used for thermocatalytic and photocatalytic reduction of aromatic nitro compounds to anilines in water at room temp.[111] Thermocatalytic method uses $NaBH_4$ as reducing agent whereas photocatalytic method uses ammonium oxalate as reducing agent and visible light irradiation. This catalyst showed good selectivity for nitro reduction in presence of Cl and Br.

$PbBiO_2Cl$ and $PbBiO_2Br$ were used as catalyst for reduction of nitrobenzene derivatives using TEOA in blue light.[112] Catalysts were selective for nitro reductionin presence of CN, CHO, keto but could reduce pyridine aldehyde.

Biotic reduction of nitroarenes



Scheme 11

Table 9: Reduction of nitroarenes.

Entry	Natural sources	conditions	Ref.
1	*Escherichia coli reductases*	pH 7 buffer, 30 °C	113
2	Plant cells from *Lens culinaris* seeds	H_2O, 30 °C	114
3	Plant cells from Grapes *(Vitis vinifera* L.)	H_2O, 25 °C	115
4	Cattle tick *Boophilus microplus*, Spider *Nephila plumipes*	*in vivo*	116
5	Microbial consortium,	H_2, pH 6.5-6.8, 30 °C	117
6	Biocatalysed cathode	Glucose, 25 °C	118
7	FMN-dependent nitro-reductase	Glucose	119
8	BaNTR1, BmGDH NADP	Glucose, 0.1 M sodium phosphate buffer, 30 °C	120

Escherichia coli is able to reduce azo compounds such as methyl red (MR) and nitro compounds such as 7-nitrocoumarin-3-carboxylic acid (7NCCA). In depth study revealed enzyme AzoR to reduce both MR and 7NCCA, whereas enzymes NfsA and NfsB could only reduce the nitro compound.[113] Similarly, a series of aliphatic and aromatic aldehydes and ketones, as well as some nitrocompounds were reduced using whole plant cells from *Lens culinaris* seeds.[114]

Plant cells from a grape (*Vitis vinifera* L.) reduced aromatic nitro compounds under mild conditions to the corresponding hydroxylamines.[115]

Two species of Arachnida *Boophilis Microplus* (a cattle tick) and *Nephila Plumipes* (a Sydney spider) metabolized ^{14}C nitrobenzene to aniline *in vivo*. These species could also metabolise N,N-dimethylamino-azobenzene to anilines.[116] This was the first and only report of observing reduction of nitrobenzene to aniline in living organisms.

Conversion of nitrobenzene to aniline, a less toxic end product that can easily be mineralized is carried out in a continuous-flow anaerobic bioreactor using H_2 gas and a microbial consortium.[117] The reduction is sensitive to both pH and temperature. Optimum reduction was obtained in pH 6.5-6.8 and at 30 °C.

A fed-batch bioelectrochemical system with microbially catalyzed cathode could transform nitrobenzene to aniline within 24 h when a voltage of 0.5 V was applied in the presence of glucose.[118]

Due to the chemical versatility of the flavin cofactor, FMN-dependent ene-reductases and nitroreductases can catalyze or mediate a diverse spectrum of chemical reactions. Nitroreductases have evolved as natural remediation tools in contaminated environments with a major role in the reduction of toxic nitro-aromatics.[119]

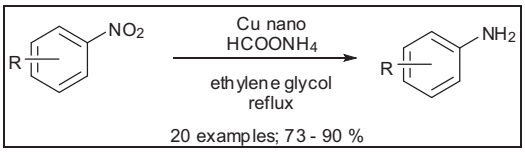
Bacterial nitroreductase BaNTR1 is recently identified and used as biocatalyst for controllable reduction of nitroarenes with electron withdrawing groups like NO_2, CN, amide, acid and ester to corresponding N-aryl hydroxylamines.[120]

4.2.B: Biorelevent metals in reduction of nitroarenes

Use of bio-relevant metals in reduction of nitrobenzenes is known for long period.[9,13] Particularly, copper salts and copper nanoparticles are known for reduction of nitroarenes since 1979[121] and for past several years there have been extensive research to develop these aspects. Since then various Cu salts such as sulphates, acetates, acetylacetonates, phthalocyanines, etc. are reported for nitro reduction. Studies are even carried by changing the reducing agents varying from $NaBH_4$, ammonium formate, hydrazine hydrate, formic acid, etc. Various forms of Cu nanoparticles are prepared and studied for this reduction like Cu nanorods, nanospheres, nanosheets, etc. Here are some of the highlights of methods using Cu, Fe and Co as catalysts for reduction of nitroarenes.

Copper for nitro reduction

B. Ranu and co-workers[122a] developed a chemoselective reduction of nitro compounds to amines using 3 eq. of Cu nanoparticles with 5 eq. of ammonium formate in ethylene glycol at 120 °C (Scheme 12). Under similar conditions and 0.5 eq. of Cu nanoparticles, azides[122b] were also selectively reduced to amines.

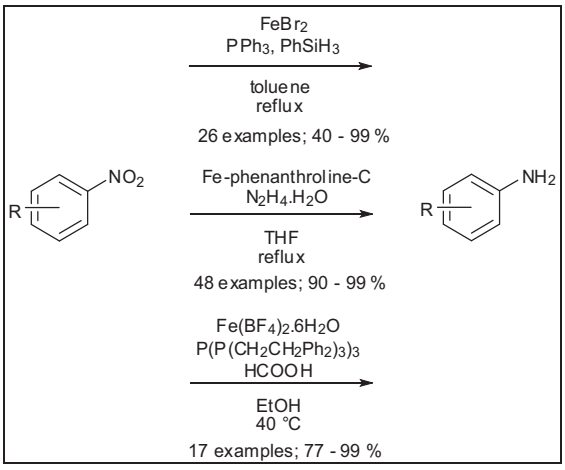


Scheme 12

N. Pradhan *et.al*.[123] reported coinage metal nanoparticles such as Au, Ag and Cu with aq. $NaBH_4$ for reduction of nitrophenols and nitroanilines. B. Singh's group[124] used copper(*II*) and cobalt(*II*) phthalocyanines for chemoselective reduction of nitro group in presence of aldehydes, keto, halides, nitriles, etc. A. Bhaumik and co-workers[125,126] prepared Cu nanorods and nanospheres and studied their activity for reduction of nitrophenol and nitroisophthalic acid using aq. $NaBH_4$. K. Hanaya *et.al*.[121] investigated various transition metal acetylacetonates such as Cu(II), Co(II), Ni(II), Fe(II) and reported Copper(II)acetylacetonate as a effective catalyst for reduction of aromatic nitro compounds with $NaBH_4$ to corresponding amines. Study by J. Drouin's group[127] revealed that the reduction of nitrobenzene with sodium borohydride and copper sulfate in ethanol as reported by S. Yoo's group[128] could not be reproduced, whereas sodium borohydride-Copper(II) acetate in ethanol gave satisfactorily yields of anilines. B. M. Reddy and co-workers[129] prepared monometallic CuO-Ceria-Silica mixed oxide and bimetallic CuO-CoO and CuO-NiO-Ceria-Silica mixed oxide for selective reduction of *o*-chloronitrobenzene to corresponding chloroanilines.

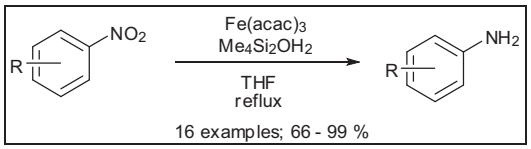
Iron for nitro reduction

M. Beller's group[57,130] explored a $FeBr_2/PPh_3$ catalytic system with phenylsilanes as reducing agents for nitro reduction. (Scheme 13) This group further prepared a catalyst using $Fe(OAc)_2$,1,10-phenanthroline and vulcan XC72R carbon powder and employed this Iron catalyst with hydrazine hydrate in refluxing THF for selective reduction of nitroarenes. They also reported a $Fe(BF_4)_2.H_2O$ catalyst with phosphine ligand for this reduction using formic acid as reducing agent.



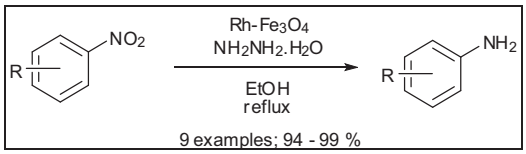
Scheme 13

M. Lemaire and co-workers[58] used iron(*III*)acetylacetonate (10 mol%) as catalyst and *1,1,3,3*-tetramethyldisiloxane (TMDS) as reducing agent for reduction of nitro groups. (Scheme 14)



Scheme 14

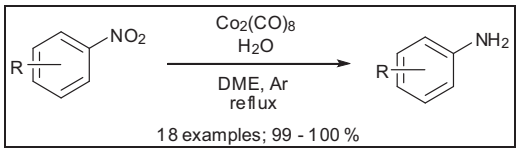
B. M. Kim, T. Hyeon and co-workers[68] synthesised Rh-Fe_3O_4 nanocrystals and used this magnetically separable heterodimer catalyst for selective reduction of nitroarenes and alkenes. (Scheme 15)



Scheme 15

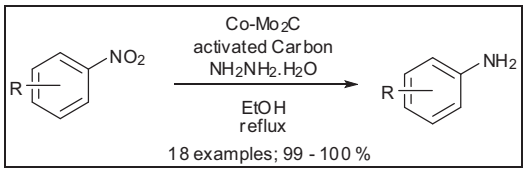
Cobalt for nitro reduction

Use of Cobalt for nitro reduction has been relatively rare. Recent examples in this regard are discussed here. Co_2CO_8 is used as a reducing agent with water for selective reduction of nitro group in refluxing dimethoxyethane.[131] (Scheme 16)



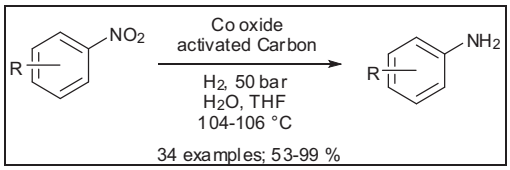
Scheme 16

Z. Zhao et.al[132] synthesised Co modified Mo Carbide catalyst on activated carbon and exploited them as efficient catalyst for chemo selective reduction of aromatic nitro compounds to aryl amines (Scheme 17).



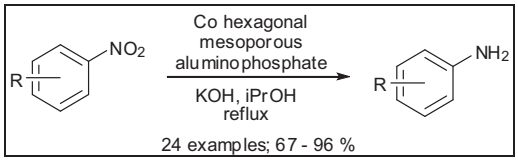
Scheme 17

Heterogeneous Co oxide catalyst[133] was prepared by M. Beller's group by immobilization and pyrolysis on activated carbon and subsequently used them for reduction of nitroarenes to anilines (Scheme 18).



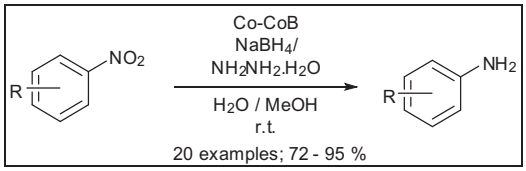
Scheme 18

Co substituted hexagonal mesoporous aluminophosphate molecular sieves were prepared by P. Selvam's group[134] and used as heterogenous catalysts for transfer hydrogenation of aromatic nitro and carbonyl compounds using isopropanol (Scheme 19).



Scheme 19

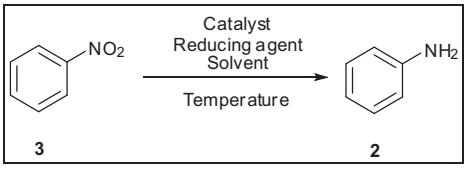
Recently our group have also reported magnetically recoverable Co-Co_2B nanocomposites[56] for the chemoselective reduction of aromatic nitro compounds to anilines using sodium borohydride and also with hydrazine hydrate as reducing agents (Scheme 20).



Scheme 20

4.3: Results and Discussions

In our group biorelevant metal such as Co was found to be effective catalyst for reduction of aromatic nitro compounds. With an intention of using other biorelevant metals such as copper for reduction of nitroarenes, (Scheme 21) we tested various bench top available Cu catalysts as shown in table 10.



Scheme 21

To begin with, a previously known $CuSO_4$ (entry 2) catalyst gave moderate yield of aniline with some unreacted nitrobenzene. $Cu(OAc)_2$ (entry 3) and $CuCl_2$ (entry 4) also gave low yield of product with nitrobenzene remaining unreacted. We then tried $CuBr_2$ (entry 5), CuBr (entry 6) and

CuI (entry 7) for reduction wherein CuBr and CuI showed no encouraging results but $CuBr_2$ gave complete conversion of nitrobenzene to aniline in 5 h with 90 % isolated yield after work-up. Furthermore we also tested a simple iron salt (entry 8), $FeCl_3$ for this reduction but it did not facilitate the reaction and only 5 % product was isolated. $CuBr_2$ was long ago in 1988[135] reported for bromination of aromatic hydrocarbons using 5 equiv. But our 10 mol% catalyst loading did not provide us any brominated by-product.

Table 10: Catalyst screening.[a]

Entry	Catalyst	% Aniline[b]	% Nitrobenzene[b]
1	-	0	100
2	$CuSO_4.5H_2O$	75	10
3	$Cu(OAc)_2.H_2O$	12	46
4	$CuCl_22H_2O$	22	60
5	$CuBr_2$	90	0
6	CuBr	36	51
7	CuI	41	20
8	$FeCl_3$	5	70

[a] Catalyst (10 mol%), $NaBH_4$ (3-5 equiv.), EtOH (10 mL), r.t. 5 h [b] Isolated Yield.

On discovering the catalytic effect of Cu(II) bromide, we moved to investigate the effect of solvent on this reaction. (Table 11) Switching onto the green solvent i.e. water gave low yield of aniline and also some unreacted nitrobenzene even with excess reducing agent, probably due to loss of H_2 by rapid decomposition of $NaBH_4$.[136] Changing to polar aprotic solvent like THF gave average yield with incomplete reaction.

Realising the support of ethanol in this reduction, we studied other alcohols to note any change in reaction progress. Reduction was very slow in other branched and long chain alcohols and was incomplete even after 24 h due to insolubility of $NaBH_4$ and inefficient release of H_2 into the reaction medium. The study showed ethanol and methanol to be the best solvents for this catalytic system. Methanol was avoided for further applications due to its toxicity to living organisms and environment.

Table 11: Solvent selection.[a]

Entry	Solvent	Time (h)	% Aniline[b]	% Nitrobenzene[b]
1	Water	5	50	15
2	Ethanol	5	90	0
3	Tetrahydrofuran	5	30	45
4	Isopropanol	24	41	50
5	n-Butanol	24	10	72
6	t-Butanol	24	15	64
7	Methanol	5	91	0

[a] $CuBr_2$ (10 mol%), $NaBH_4$ (3-5 equiv.), Solvent (10 mL), r.t. [b] Isolated Yield.

Amount of catalyst being a crucial factor for such type of reactions, we studied different catalyst loading ratios and also the effect of temperature. The mole percent of $CuBr_2$ and reaction temperature were then optimized by varying the catalyst amount and temperature (Table 12) Lowering the catalyst loading to 5 mol % rendered incomplete reaction even after 12 h and increasing the catalyst amount or the temperature did not improve the yield of reduction product..

This experiments concluded that 10 mol% of $CuBr_2$ gave the maximum yield (90%) at room temperature. It was expected that the reduction would take place more rapidly at higher temperature but rapid decomposition of sodium borohydride at higher temperature might be responsible for the observed poor results.

Table 12: Optimization of $CuBr_2$ concentration and reaction condition.[a]

Entry	Mole %	Temp. °C	Time h	% Aniline[b]	% Nitrobenzene[b]
1	5	28	12	35	52
2	10	28	5	91	0
3	20	28	5	90	0
7	10	60	5	21	36

[a] $CuBr_2$ (5, 10, 20 mol%), $NaBH_4$ (3-5 equiv.), EtOH (10 mL), r.t.- 60 °C [b] Isolated Yield.

In order to compare this work with earlier reports,[122-129] we investigated the role of other reducing agents as described in table 4. The inefficiency of H_2 gas in this reduction revealed that the concentration of H_2 gas in solvent was important for this reduction. Cu nanoparticles along with ammonium formate are known[122a] for nitro reduction under reflux condition. But our results (Table 13) showed that other reducing agents i.e. H_2 gas, hydrazine hydrate, sodium formate and ammonium formate were not helpful for this nitro-reduction process. This suggested that they were unable to reduce $CuBr_2$ to Cu (0) at room temperature unlike $NaBH_4$.[136]

Table 13: Effect of other reducing agents. [a]

Entry	[H]	Temp. °C	Time h	% Aniline[b]	% Nitrobenzene[b]
1	$NaBH_4$	28	5	90	0
2	H_2	28	24	0	100
3	$NH_2NH_2.H_2O$	28	24	0	> 95
4	$HCOONH_4$	100	12	< 5	> 90
5	HCOONa	100	12	< 5	> 95

[a] $CuBr_2$ (5, 10, 20 mol%), $NaBH_4$ (3-5 equiv.), EtOH (10 mL), r.t.- 60 °C [b] Isolated Yield.

After optimizing the method for nitro reduction using $CuBr_2$ (10 mol%) and $NaBH_4$ (3 eq.) in ethanol, it was necessary to examine the fate of catalyst after reaction. The report by G. N. Glavee and co-workers[137] disclosed that Cu salts in presence of $NaBH_4$ are reduced to Cu nanoparticles. Thus, we subjected the recovered catalyst for structural analysis like XRD, SEM, EDX and TEM.

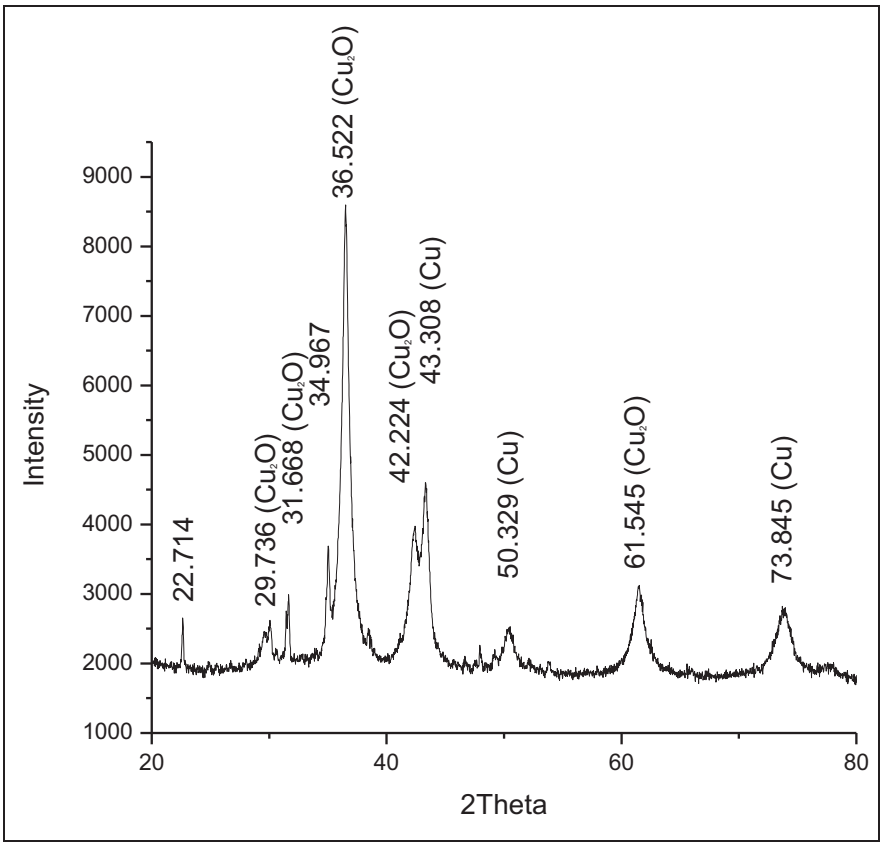


Figure 2: XRD of recovered Cu catalyst after reaction.

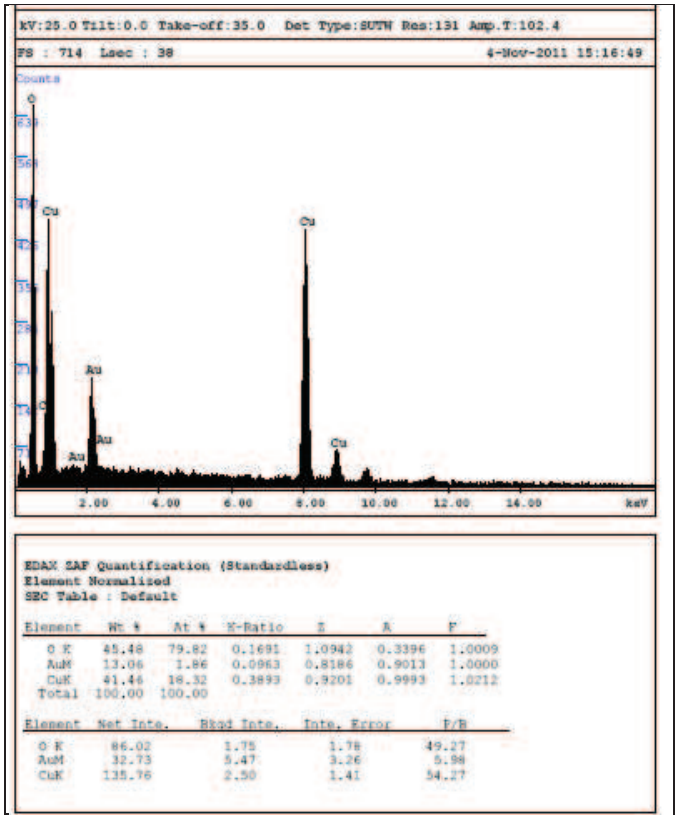


Figure 3: EDX of recovered Cu catalyst after reaction.

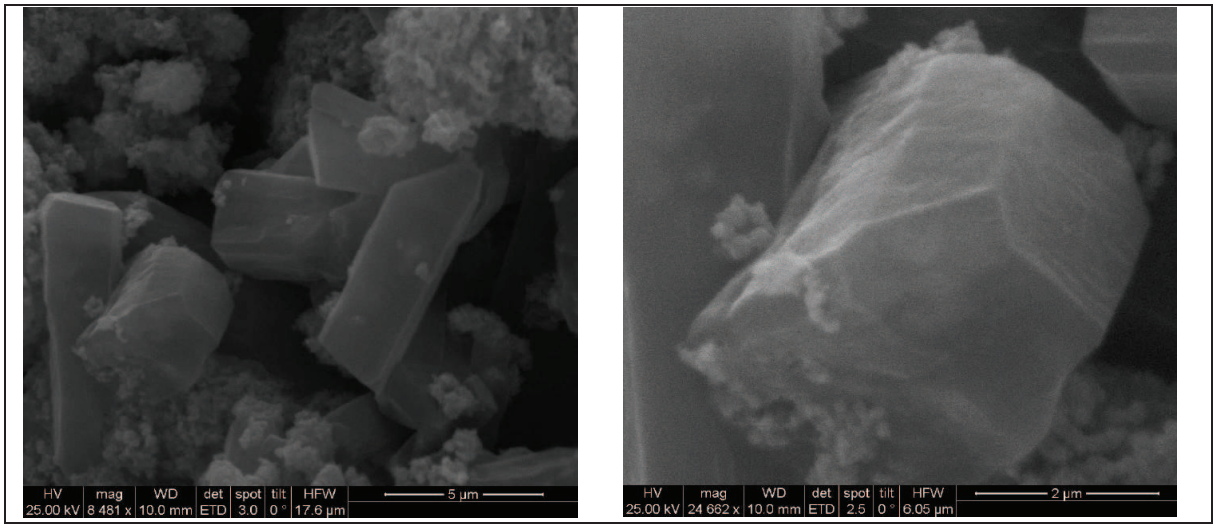


Figure 4: SEM images of recovered Cu catalyst.

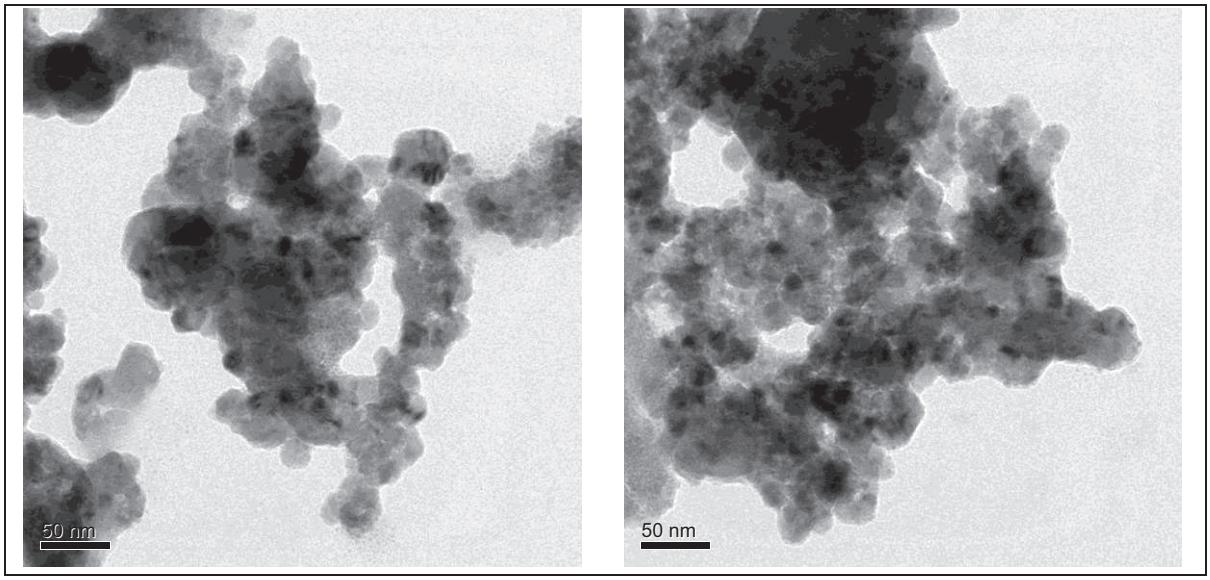


Figure 5: TEM images of recovered Cu catalyst.

Powder X-Ray Diffraction (Figure 2) revealed that Cu(0) is formed in the reaction medium by $NaBH_4$. The Cu_2O and CuO peaks were seen in XRD and also EDX showed the presence of oxygen. (Figure 3) This may be due to the surface oxidation of active copper nanoparticles by air. This data was in accordance with the reported observations.[136-138] The XRD indicating that the *in situ* formed Cu nanoparticles that catalysed the nitro reduction were stabilised by aniline formed in reaction medium.

SEM (Figure 4) and TEM images showed presence of uniform nanopartices along with some micron sized material possibly the oxides of Cu. The formation of Cu nanoparticles in the range 40–50 nm was confirmed by TEM (Figure 5) images of the recovered catalyst. Also, in the SEM images, micron-sized cubes of Cu_2O were observed.

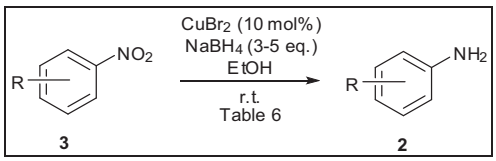
Commercially available Cu nanoparticles were used in reduction and were found to catalyse the reaction to some extent (Table 14). To further confirm any role of Cu oxides during the reduction, the reaction was attempted using Cu_2O and CuO. In the case of CuO there was no reduction observed whereas Cu_2O resulted in deposition of Cu metal on the surface of reaction flask, indicating that the reaction is probably catalysed by Cu metal formed by reduction of Cu_2O.

Table 14: Possible Cu intermediates.[a]

Entry	[Cu]	% Aniline[b]	% Nitrobenzene[b]
1	Cu nano	34	40
2	Cu_2O	68	18
3	CuO[c]	0	100

[a] Catalyst (10 mol%), $NaBH_4$ (3-5 equiv.), EtOH (10 mL), r.t. [b] Isolated Yield. [c] CuO (1 eq.)

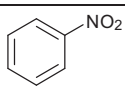
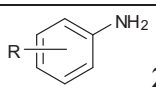
To study the generality and selectivity of this system, various nitroarenes were subjected to reduction (Scheme 22, Table 15). Along with nitrobenzene (Entry 1), *p*-,*m*-,*o*-nitrotoluenes (Entry 2, 3, 4) were readily reduced to *p*-,*m*-,*o*-toluidines. As expected *o*-nitrobenzaldehyde (Entry 5) rapidly gave *o*-aminobenzyl alcohol as the sole product. The acid group (Entry 6, 11) was intact and gave the respective aminobenzoic acids after long reaction times. Halogens like chloro and iodo (Entry 7, 17) were retained in the products displaying a selectivity that is usually not observed when noble metals are used.[10]

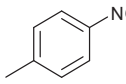
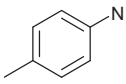
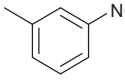
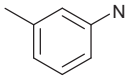
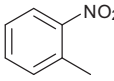
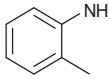
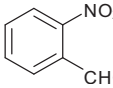
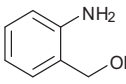
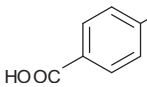
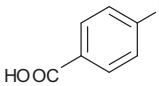
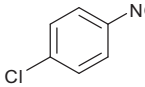
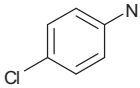
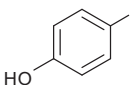
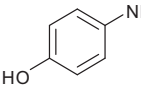
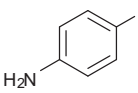
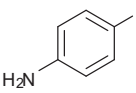
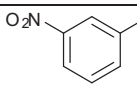
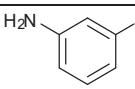
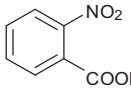
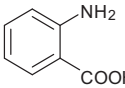
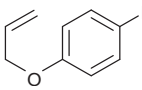
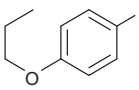
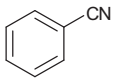
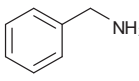
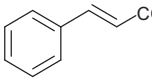
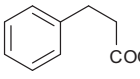
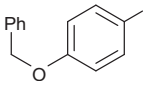
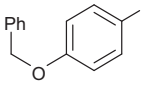
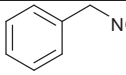
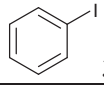


Scheme 22

Functionalities like hydroxyl and amino groups (Entry 8, 9) had not affected the reduction in this catalytic system. *m*-Dinitrobenzene (Entry 10) was completely reduced to *m*-aminoaniline with 5 eq. of sodium borohydride and *m*-nitroaniline was not observed during the course of reaction on TLC. The allylic double bond (Entry 12) was found to reduce completely, but this system very well retained the O-benzyl protection during nitro reduction (Entry 15) unlike catalytic hydrogenation.[1] Functional group CN (Entry 13) was completely reduced giving benzyl amine. Ethylcinnamate **3n** was reduced to dihydroethylcinnamate **2n** (Entry 14) indicating that conjugated double bonds are also reduced in this system. This methodology was more efficient than an earlier report which used excess of metal salt.[139] Aliphatic nitro group (Entry 16) was unaffected in this catalytic system.

Table 15: Substrate study (Scheme 22).[a]

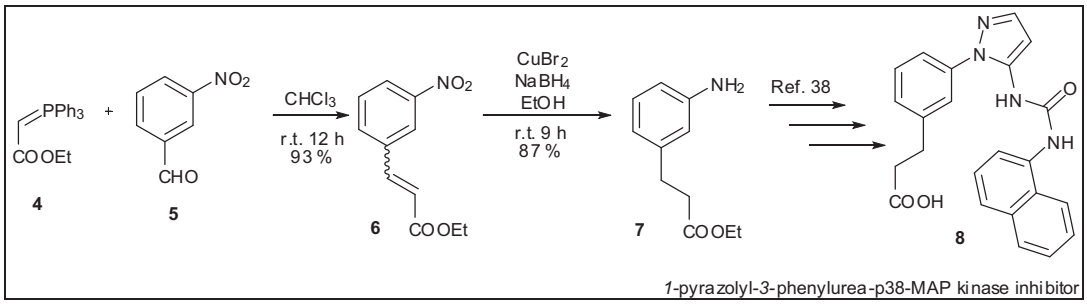
Entry	Reactant **3**	Product **2**	Time	% Yield[b]
1	 **3a**	 **2a**	5	90

2	 **3b**	 **2b**	5	93
3	 **3c**	 **2c**	5	92
4	 **3d**	 **2d**	5	90
5	 **3e**	 **2e**	3	85
6	 **3f**	 **2f**	8	78
7	 **3g**	 **2g**	4	82
8	 **3h**	 **2h**	3.5	88
9	 **3i**	 **2i**	14	84
10	 **3j**	 **2j**	12	85
11	 **3k**	 **2k**	10	86
12	 **3l**	 **2l**	12	89
13	 **3m**	 **2m**	10	88
14	 **3n**	 **2n**	9	91
15	 **3o**	 **2o**	12	82
16	 **3p**	-	12	n.r.
17	 **3q**	-	12	n.r.

[a] $CuBr_2$ (10 mol%), $NaBH_4$ (3-5 equiv.), EtOH (10 mL), r.t. [b] Isolated Yield. n.r.: no reaction.

To study the utility of this method in synthesis of biologically important compounds, we prepared ethyl 3-nitrocinnamate **6** by Wittig reaction[140] and subjected it to reduction reaction. Here the nitro group and the unsaturated double bond were reduced simultaneously to give directly the Ethyl *3*-(*3*'-aminophenyl)propanoate **7** in 87% yield (Scheme 23), thus saving the number of steps in a multistep synthesis. This is the building block of *1*-pyrazolyl-*3*-phenylurea-p38-MAP kinase

inhibitors **8** which are effective for the treatment of inflammation and hyperproliferative diseases.[141]



Scheme 23

Table 16: Scalability.[a]

Entry	Moles of reactant	% Yield[b]
1	0.1	90
2	1	90
3	5	90
4	10	92
5	100	92

[a] $CuBr_2$ (10 mol%), $NaBH_4$ (3-5 equiv.), EtOH (10 mL), r.t. [b] Isolated Yield.

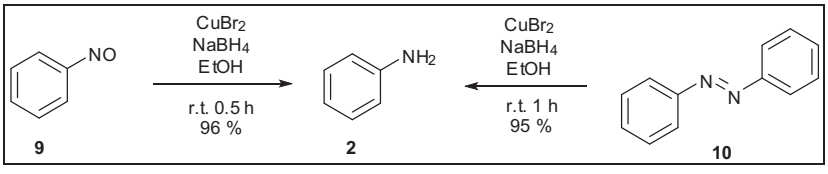
A scalability study of the reduction of nitrobenzene revealed that reproducible isolated yields were obtained at both 0.1 mmol and 100 mmol scale (90 and 92% respectively). (Table 16) This highlighted the usefulness of this catalyst for industrial applications.

Table 17: Reusability.[a]

Entry	cycle	Time h	% Yield[b]
1	0	5	90
2	1	5	91
3	2	6	89
4	3	6	89
5	4	7	81

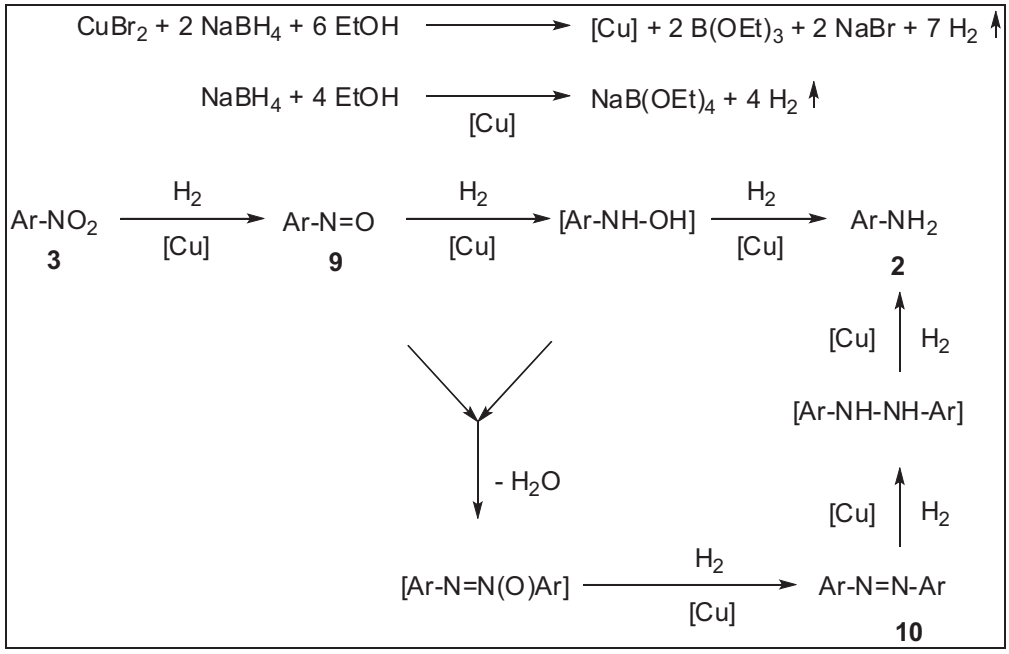
[a] $CuBr_2$ (10 mol%), $NaBH_4$ (3-5 equiv.), EtOH (10 mL), r.t. [b] Isolated Yield.

The recovered catalyst was again used for 4 consecutive cycles (Table 17) of reduction with nitrobenzene and yields were found to be consistent up to 3 catalytic cycles with increasing duration of reaction, this was expected as Cu nanoparticles tend to oxidise on exposure to air and moisture.



Scheme 24

To understand the mechanism of the reduction process in this method, some of the known intermediates like nitrosobenzene and azobenzene (Scheme 24) were subjected to this reduction protocol and were found to reduce completely to aniline as the only product within 0.5 and 1 h respectively. The mechanism (Scheme 25) for the reduction of nitroarenes probably follows both reduction pathways[10b,122] via directly from hydroxyl amine and via azobenzene intermediates.



Scheme 25

The reduction probably takes place on the active surface of Cu nanoparticles by the liberated hydrogen formed by decomposition of sodium borohydride on Cu nanoparticles. The proposed mechanism is further supported by reduction of nitrobenzene using hydrogen gas (60 psi at r.t.) and employing excess active copper (> 1 equiv.) prepared separately from $CuBr_2$ and sodium borohydride.

GC analyses were done to study the reaction kinetics. It was observed that the initially exotherm obtained drives the reaction to the maximum extent and the product is formed in major amount at the 1st hour of reaction. Graph of reaction progress v/s time (Figure 6) shows an exponential curve, indicating it to be the 1st order reaction.

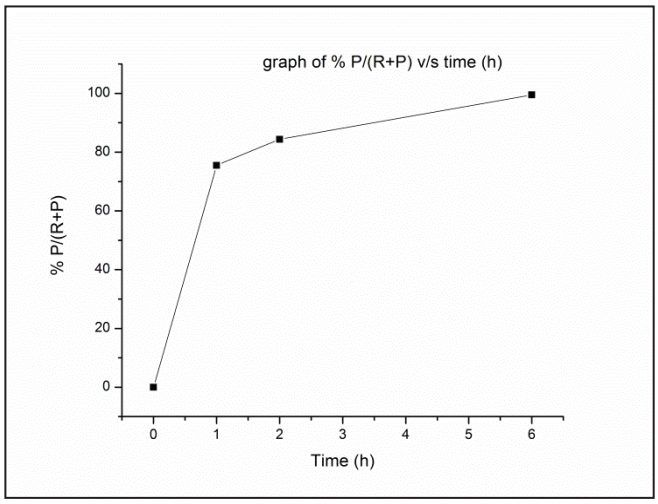


Figure 6: Graph of Product/(Reactant+Product) % v/s Time (h)

4.4: Conclusion

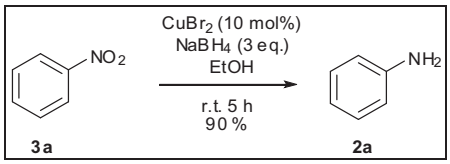
We have developed a one-pot protocol for *in situ* generation of Cu nanopartcles using $CuBr_2$ as a procatalyst and sodium borohydride as reducing agent and use them simultaneously for reduction of nitroarenes.

Functionalities like phenoxy, iodo, aliphatic nitro and acids were well tolerated in this reduction system.

This methodology have been successfully utilised for improving the synthesis of MAP-kinase inhibitor.

4.5: Experimental

4.5.1: Reduction of nitrobenzene to aniline (2a)



Nitrobenzene **3a** (0.615 g, 5 mmol) and $CuBr_2$ (0.112g, 0.5 mmol) was dissolved in ethanol (25 mL) and stirred for 2 min and $NaBH_4$ (0.567 g, 15 mmol) was added slowly (exotherm observed) and stirred at room temperature for 5 h. Reaction was monitored using GC. On completion, the reaction was filtered and solvent was removed under vacuum. The crude residue was then partitioned between brine (10 mL) and ethylacetate (3 X 15 mL) and the combined organic layers were dried over anhyd. Na_2SO_4 which was filtered off and the solvent was removed under vacuum to yield aniline **2a** as the pure product in 90 % (0.419 g) yield.

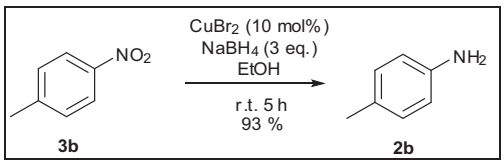
Yellow oil.[142]

R_f: 0.48 (Ethylacetate:hexanes, 1:20)

IR (KBr): ν_{max} 3429, 3354, 3034, 1620, 1600, 1498, 1276, 1174, 752, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 3.39 (br s, 2 H), 6.71 (d, J = 8.0 Hz, 2 H), 6.79 (t, J = 7.6 Hz, 1 H), 7.19 (t, J = 7.6 Hz, 2 H) ppm.

4.5.2: *p*-Toluidine (2b)



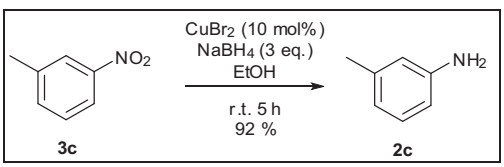
Following the similar procedure as described in experiment 4.5.1 with *p*-nitrotoluene **3b** (0.686 g, 5 mmol) and $NaBH_4$ (0.567 g, 15 mmol) gave the *p*-toluidine **2b** in 93 % (0.498 g) yield.

Yellow oil.[143]

R_f: 0.45 (Ethylacetate:hexanes, 1:20)

IR (KBr): ν_{max} 3429, 3352, 3010, 1622, 1516, 1269, 813, 756 cm^{-1}.

4.5.3: *m*-Toluidine (2c)



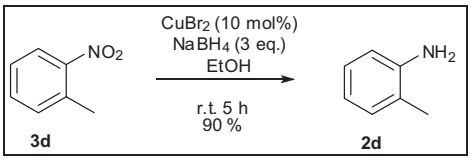
Following the similar procedure as described in experiment 4.5.1 with *m*-nitrotoluene **3c** (0.686 g, 0.59 mL, 5 mmol) and $NaBH_4$ (0.567 g, 15 mmol) gave the *m*-toluidine **2c** in 92 % (0.493 g) yield.

Yellow oil.[144]

R_f: 0.46 (Ethylacetate:hexanes, 1:20)

IR (KBr): ν_{max} 3431, 3352, 3032, 1622, 1591, 1492, 1292, 1170, 775, 690 cm^{-1}.

4.5.4: *o*-Toluidine (2d)



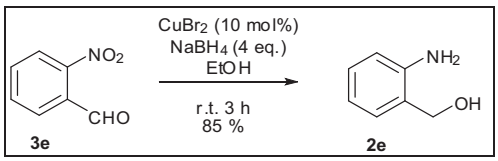
Following the similar procedure as described in experiment 4.5.1 with *o*-nitrotoluene **3d** (0.686 g, 0.59 mL, 5 mmol) and $NaBH_4$ (0.567 g, 15 mmol) gave the *o*-toluidine **2d** in 90 % (0.482 g) yield.

Yellow oil.[145]

R_f: 0.50 (Ethylacetate:hexanes, 1:20)

IR (KBr): ν_{max} 3454, 3369, 3018, 1622, 1496, 1467, 1301, 1271, 752 cm^{-1}.

4.5.5: *o*-Aminobenzyl alcohol (2e)



Following the similar procedure as described in experiment 4.5.1 with *o*-nitrobenzaldehyde **3e** (0.756 g, 5 mmol) and $NaBH_4$ (0.757 g, 20 mmol) for 3 h gave the *o*-aminobenzyl alcohol **2e** was obtained in 85 % (0.523 g) yield.

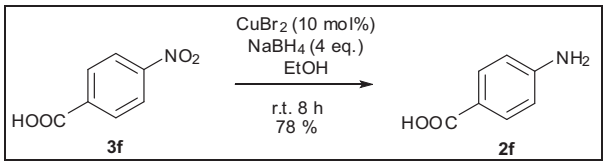
Pale yellow solid, m.p.: 80 °C. [Lit. m.p.: 81-83 °C][146]

R_f: 0.44 (CH_2Cl_2:MeOH, 20:1)

IR (KBr): ν_{max} 3388, 3151, 1629, 1502, 1460, 1350, 1269, 1004, 748 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 3.27 (br s, 2 H), 4.65 (d, J = 6.8 Hz, 2 H), 6.69–6.74 (m, 2 H), 7.06 (d, J = 7.2 Hz, 1 H), 7.14 (t, J = 7.6 Hz, 1 H) ppm.

4.5.6: *p*-Aminobenzoic acid (2f)



Following the similar procedure as described in experiment 4.5.1 with *p*-nitrobenzoic acid **3f** (0.836 g, 5 mmol) and $NaBH_4$ (0.757 g, 20 mmol) for 8 h gave the *p*-aminobenzoic acid **2f** in 78 % (0.535 g) yield.

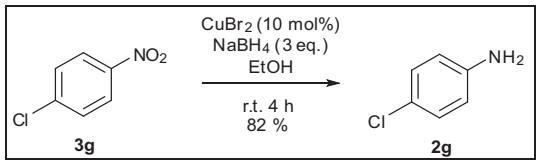
Light pink solid, m.p.: 185 °C. [Lit. m.p.: 187-189 °C][147]

R_f: 0.48 (CH_2Cl_2:MeOH, 20:1)

IR (KBr): ν_{max} 3460, 3363, 2987, 1672, 1600, 1421, 1311, 1290, 1174, 842, 771 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 1.60 (br s, 2 H), 4.15 (br s, 1 H), 6.65 (d, *J* = 8.4 Hz, 2 H), 7.90 (d, *J* = 8.4 Hz, 2 H) ppm.

4.5.7: ***p*-Chloroaniline (2g)**



Following the similar procedure as described in experiment 4.5.1 with *p*-chloronitrobenzene **3g** (0.836 g, 5 mmol) and $NaBH_4$ (0.567 g, 15 mmol) for 4 h gave the *p*-chloroaniline **2f** in 82 % (0.523 g) yield.

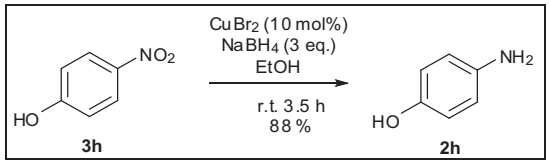
Pale yellow oil.[148]

R_f: 0.51 (CH_2Cl_2:hexanes, 1:2)

IR (KBr): ν_{max} 3473, 3383, 3196, 3057, 1612, 1489, 1288, 1182, 1091, 1004, 827, 640 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (br s, 2 H), 6.62 (d, *J* = 8.4 Hz, 2 H), 7.11 (d, *J* = 8.8 Hz, 2 H) ppm.

4.5.8: *p*-Aminophenol (2h)



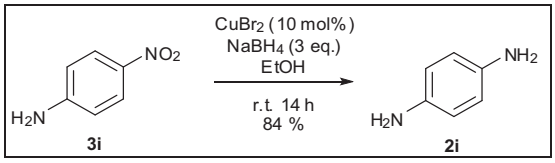
Following the similar procedure as described in experiment 4.5.1 with *p*-Nitrophenol **3h** (0.696 g, 5 mmol) and $NaBH_4$ (0.567 g, 15 mmol) for 3.5 h gave the *p*-aminophenol **2h** in 88 % (0.480 g) yield.

Brown solid, m.p.: 182 °C. [Lit. m.p.: 185-189 °C][149]

R_f: 0.50 (CH_2Cl_2:MeOH, 100:1)

^1H NMR (400 MHz, $CDCl_3$): δ 3.41 (br s, 2 H), 4.34 (br s, 1 H), 6.59 (d, *J* = 8.4 Hz, 2 H), 6.66 (d, *J* = 8.4 Hz, 2 H) ppm.

4.5.9: *p*-Phenylenediamine (2i)



Following the similar procedure as described in experiment 4.5.1 with *p*-nitroaniline **3i** (0.691 g, 5 mmol) and $NaBH_4$ (0.567 g, 15 mmol) for 14 h gave the *p*-phenylenediamine **2i** in 84 % (0.454 g) yield.

Light brown solid, m.p.: 140 °C. [Lit. m.p.: 138-143 °C][150]

R_f: 0.41 (CH_2Cl_2:MeOH, 50:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.33 (br s, 4 H), 6.57 (br s, 4 H) ppm.

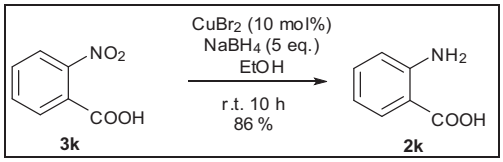
4.5.10: *m*-Phenylenediamine (2j)

Following the similar procedure as described in experiment 4.5.1 with *m*-dinitrobenzene **3j** (0.841 g, 5 mmol) and $NaBH_4$ (0.945 g, 25 mmol) for 12 h gave the *m*-phenylenediamine **2j** in 85 % (0.460 g) yield.

Light brown solid, m.p.: 60 °C. [Lit. m.p.: 64-66 °C][151]

R_f: 0.46 (CH_2Cl_2:MeOH, 50:1)

4.5.11: Anthranilic acid (2k)



Following the similar procedure as described in experiment 4.5.1 with *o*-nitrobenzoic acid **3k** (0.836 g, 5 mmol) and $NaBH_4$ (0.945 g, 25 mmol) for 10 h gave the anthranilic acid **2k** in 86 % (0.590 g) yield.

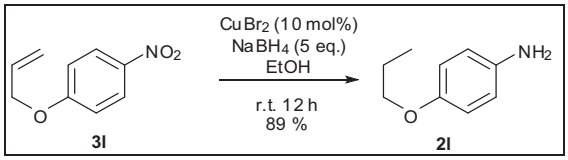
Light brown solid, m.p.: 142 °C. [Lit. m.p.: 144-148 °C][152]

R_f: 0.41 (CH_2Cl_2:MeOH, 50:1)

IR (KBr): ν_{max} 3471, 3373, 3059, 1672, 1562, 1487, 1415, 1300, 1244, 916, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66 -6.68 (m, 2 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.92 (d, *J* = 8.0 Hz, 1 H) ppm.

4.5.12: *p*-Propyloxyaniline (2l)



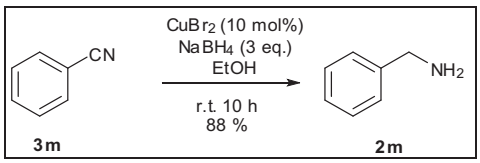
Following the similar procedure as described in experiment 4.5.1 with *p*-allyloxynitrobenzene **3l** (0.896 g, 5 mmol) and $NaBH_4$ (0.945 g, 25 mmol) for 12 h gave the *p*-propyloxyaniline **2l** in 89 % (0.673 g) yield.

Pale yellow oil.[122]

R_f: 0.46 (CH_2Cl_2:hexanes, 1:2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.2 Hz, 3 H), 1.78 (sext, *J* = 7.2 Hz, 2 H), 3.37 (br s, 2 H), 3,86 (t, *J* = 6.4 Hz, 2 H), 6.65 (d, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 8.0 Hz, 2 H) ppm.

4.5.13: Benzyl amine (2m)



Following the similar procedure as described in experiment 4.5.1 with cyanobenzene **3m** (0.516 g, 5 mmol) and $NaBH_4$ (0. 567 g, 15 mmol) for 10 h gave the benzyl amine **2m** in 88 % (0.471 g) yield.

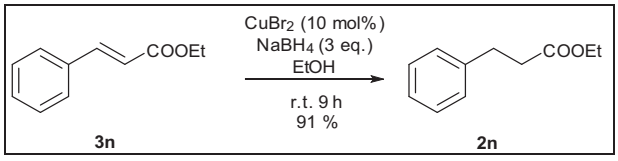
Pale yellow oil.[153]

R_f: 0.41 (CH_2Cl_2:hexanes, 1:1)

IR (KBr): ν_{max} 3363, 3061, 1643, 1452, 752, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (br s, 2 H), 3.87 (s, 2 H), 7.30-7-36 (m, 5 H) ppm.

4.5.14: Ethyl dihydrocinnamate (2n)



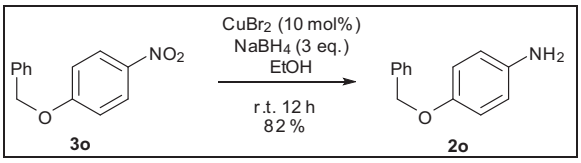
Following the similar procedure as described in experiment 4.5.1 with ethyl cinnamate **3n** (0.881 g, 5 mmol) and $NaBH_4$ (0. 567 g, 15 mmol) for 9 h gave the ethyl dihydrocinnamate **2n** in 91 % (0.810 g) yield.

Colourless oil.[154]

R_f: 0.52 (CH_2Cl_2:hexanes, 1:10)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 3 H), 2.60 (t, *J* = 8.0 Hz, 2 H), 2.94 (t, *J* = 8.0 Hz, 2 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 7.17-7.20 (m, 3 H), 7.25–7.29 (m, 2 H) ppm.

4.5.15: *p*-Benzyloxyaniline (2o)



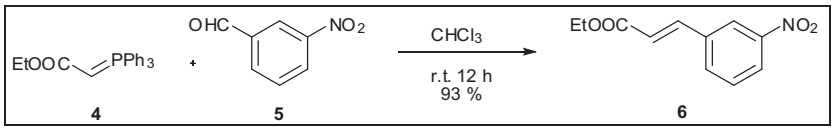
Following the similar procedure as described in experiment 4.5.1 with *p*-benzyloxynitrobenzene **3o** (1.145 g, 5 mmol) and $NaBH_4$ (0. 567 g, 15 mmol) for 12 h gave the *p*-benzyloxyaniline **2o** in 82 % (0.816 g) yield.

Pale yellow oil.[68,122]

R_f: 0.35 (CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (br s, 2 H), 5.02 (s, 2 H), 6.66 (d, *J* = 7.6 Hz, 2 H), 6.84 (d, *J* = 7.6 Hz, 2 H), 7.32-7.46 (m, 5 H) ppm.

4.5.16: Ethyl *3*-(*3*-nitrophenyl)acrylate (6)



m-Nitrobenzaldehyde **5** (1.510 g, 10 mmol) and carboethoxymethylenephosphorane **4** (4.177 g, 12 mmol) mixed in dry $CHCl_3$ (20 mL) and stirred for 12 h at r.t. After completion of reaction (TLC: 10 % Ethylacetate/hexanes), solvent was removed under vacuum and mixture was purified by Flash chromatography (Ethylacetate:hexanes, 1:20). Ethyl 3-(3-nitrophenyl)acrylate **6** was obtained in 95 % (2.056 g) yield.

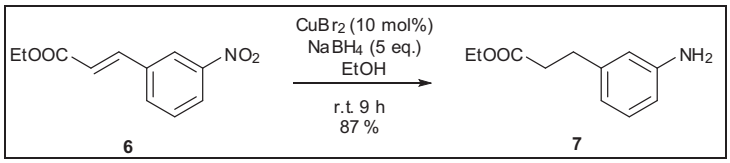
Pale yellow solid, m.p.: 70-72 °C. [Lit. m.p.: 71-72 °C].[155]

R_f: 0.53 (CH_2Cl_2:hexanes, 1:10)

IR (KBr): ν_{max} 1344, 1522, 1712, 2990, 3080 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 16.0 Hz, 1 H), 7.76 (d, *J* = 5.6 Hz, 1 H), 8.16 (t, *J* = 8.0 Hz, 1 H), 8.31 (s, 1 H) ppm.

4.5.17: Ethyl *3*-(*3*-aminophenyl)propanoate (7)



Following the similar procedure as described in experiment 4.5.1 with ethyl 3-(3-nitrophenyl)acrylate **6** (1.106 g, 5 mmol) and $NaBH_4$ (0. 945 g, 25 mmol) for 9 h gave the ethyl 3-(3-aminophenyl)propanoate **7** in 87 % (0.840 g) yield.

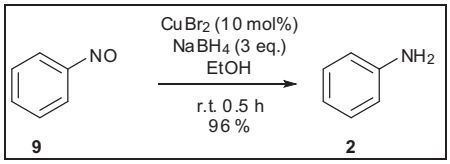
Pale yellow oil.[156]

R_f: 0.54 (CH_2Cl_2)

IR (KBr): ν_{max} 3458, 3371, 2980, 1728, 1620, 1255, 1166, 781, 696 cm^{-1}.

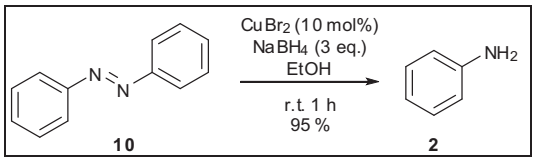
^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.2 Hz, 3 H), 2.59 (t, *J* = 7.2 Hz, 2 H), 2.85 (t, *J* = 8.0 Hz, 2 H), 3.41 (br s, 2 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 6.51–6.54 (m, 2 H), 6.59 (d, *J* = 7.2 Hz, 1 H), 7.07 (t, *J* = 7.6 Hz, 1 H) ppm.

4.5.18: Reduction of nitrosobenzene (9) to aniline (2)



Following the similar procedure as described in experiment 4.5.1 with nitrosobenzene **9** (0.536 g, 5 mmol) and $NaBH_4$ (0. 567 g, 15 mmol) for 0.5 h gave the aniline **2** in 96 % (0.447 g) yield.

4.5.19: Reduction of azobenzene (10) to aniline (2)



Following the similar procedure as described in experiment 4.5.1 with azobenzene **10** (0.911 g, 5 mmol) and $NaBH_4$ (0. 567 g, 15 mmol) for 1 h gave the aniline **2** in 95 % (0.442 g) yield.

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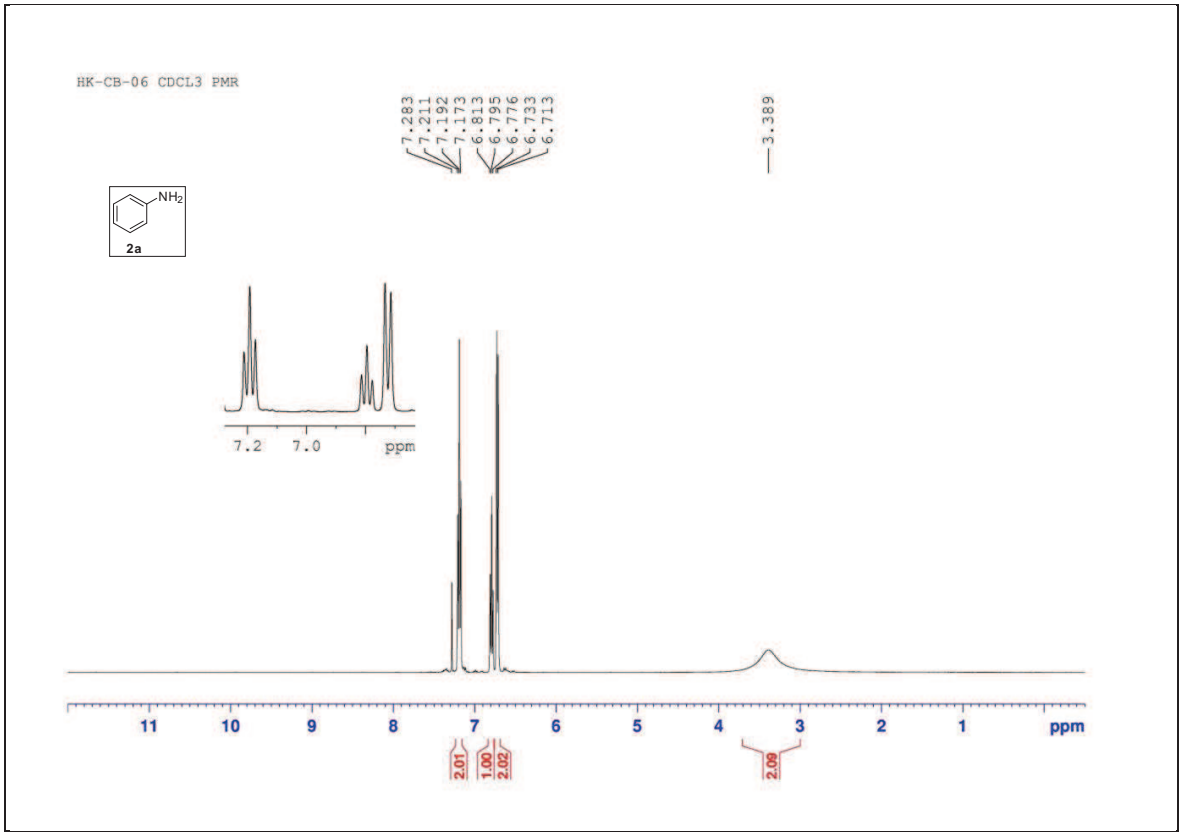
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ppm
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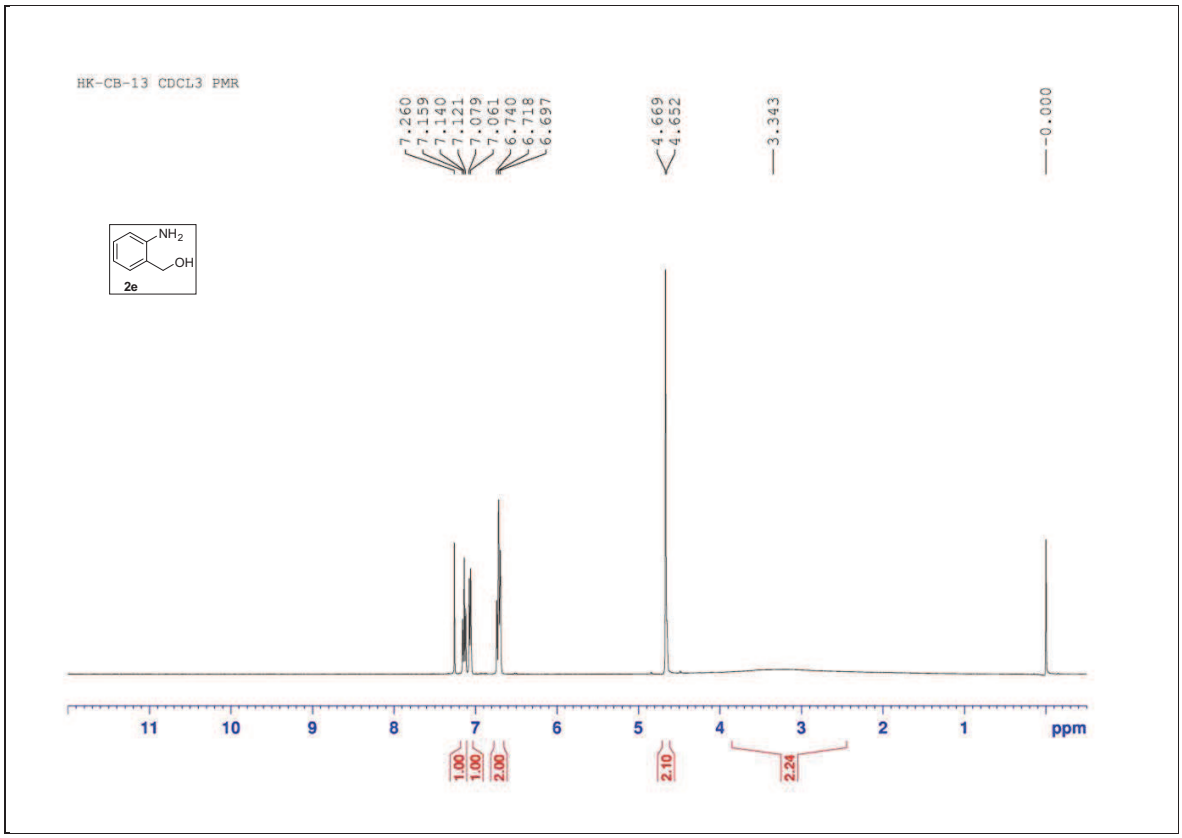
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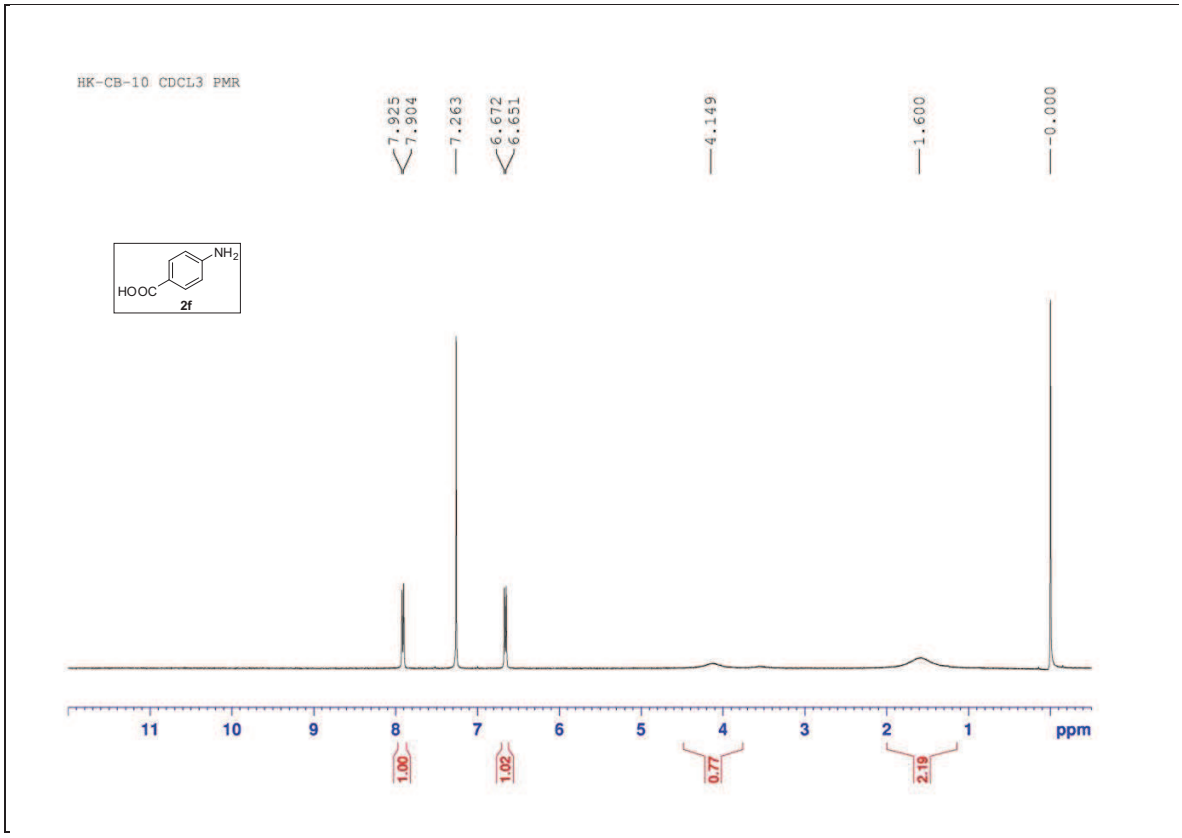
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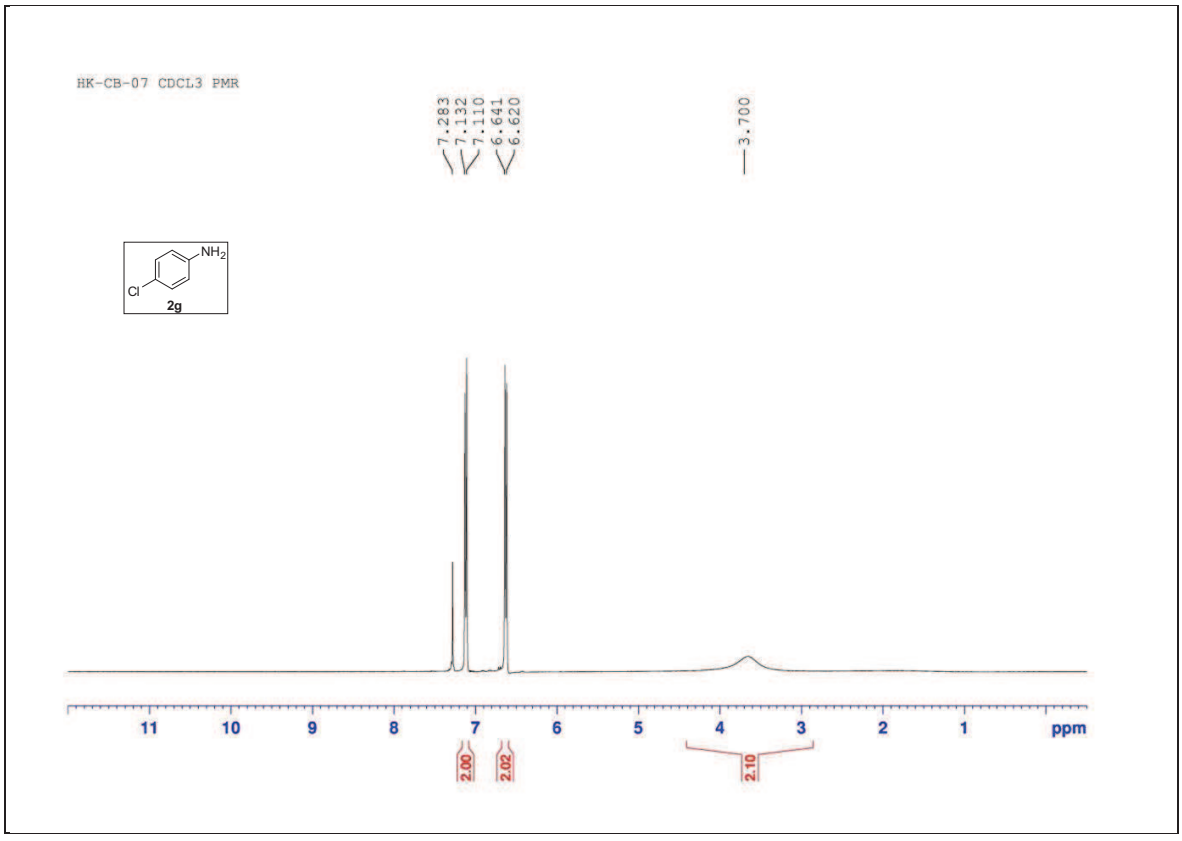
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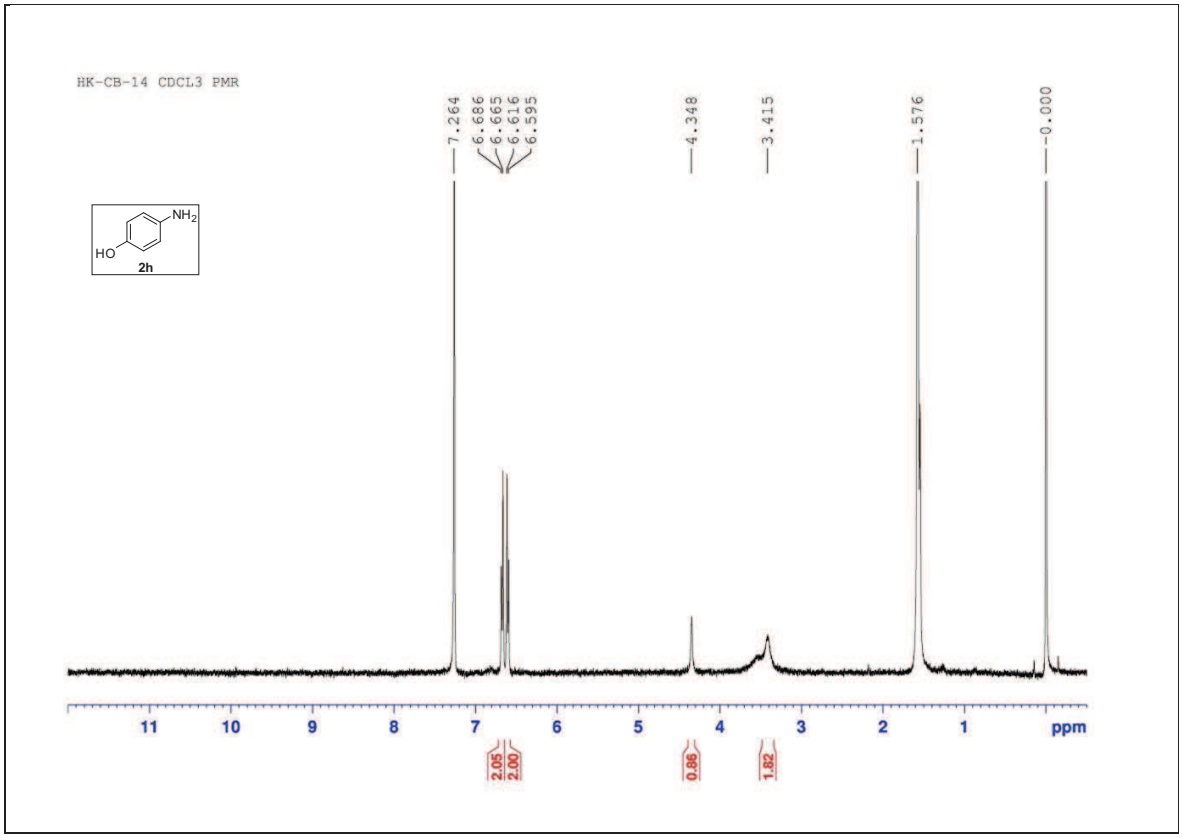
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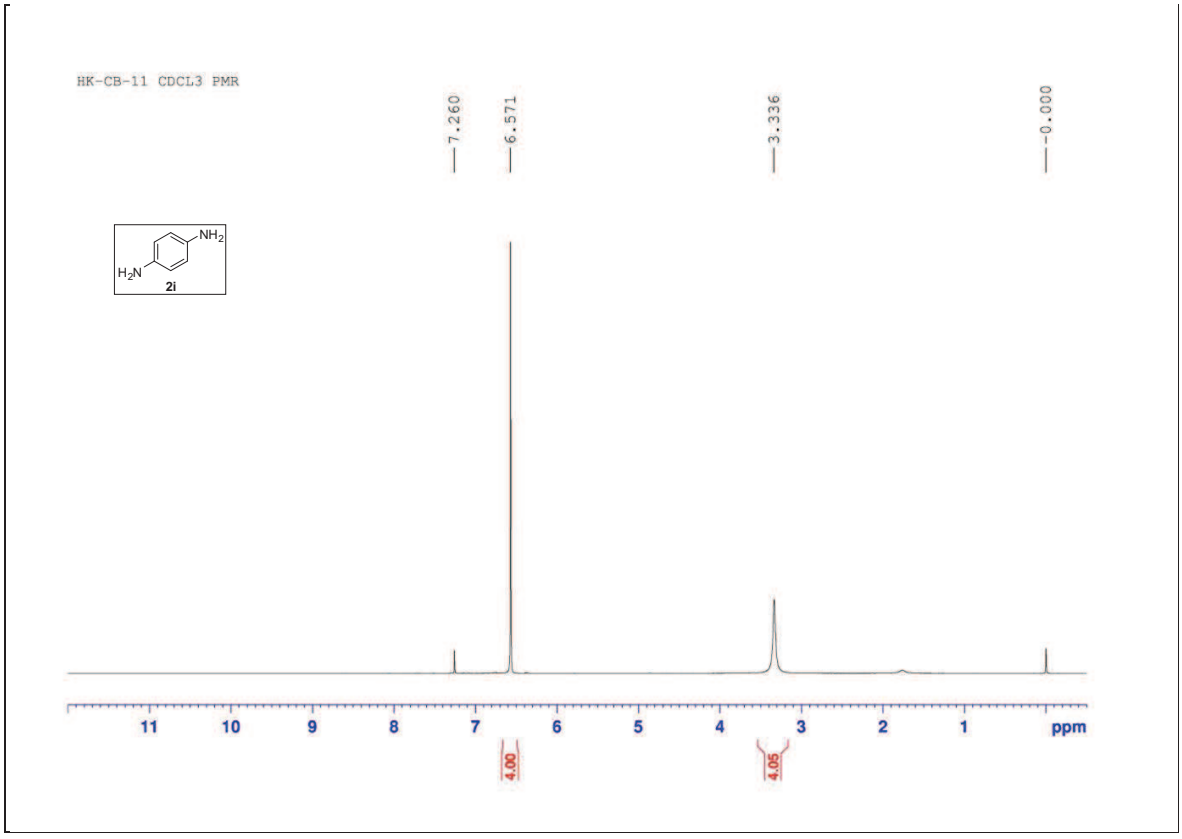
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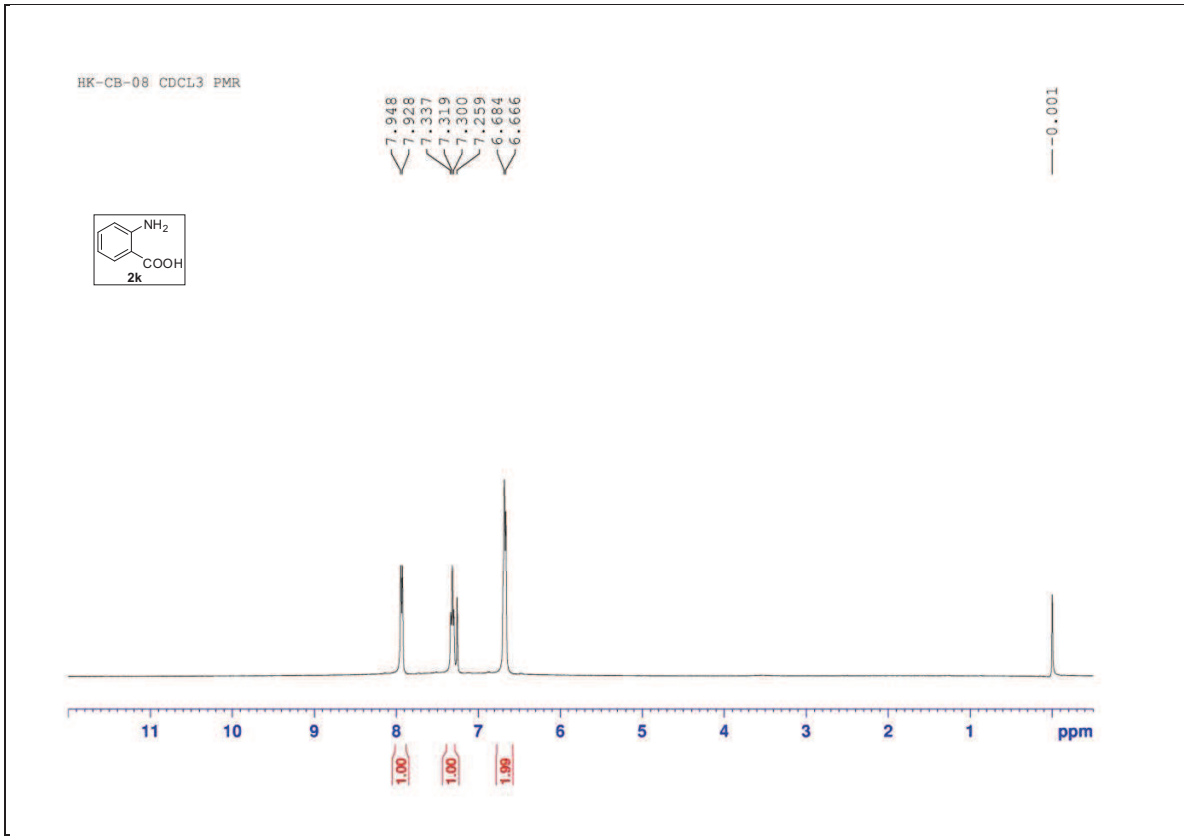
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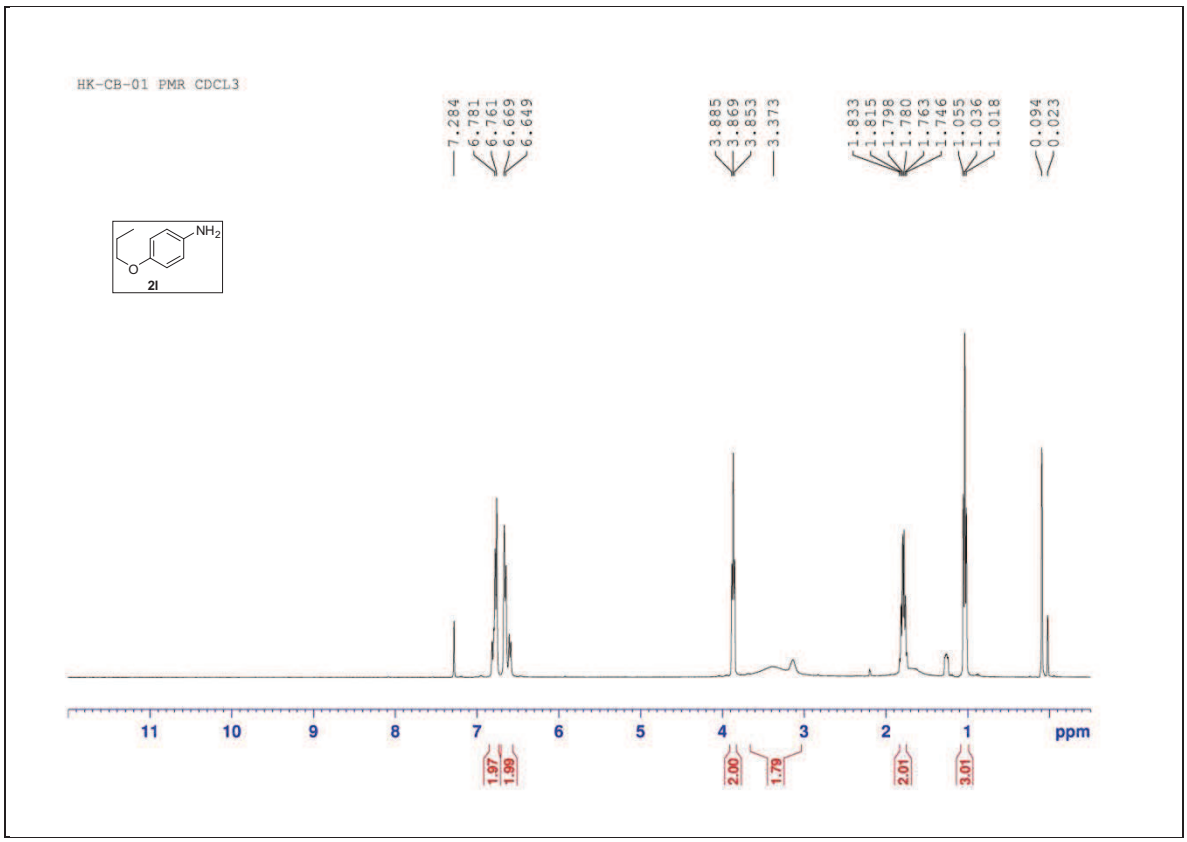
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1.815
1.798
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1.763
1.746
1.055
1.036
1.018
0.094
0.023
NH2
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2l
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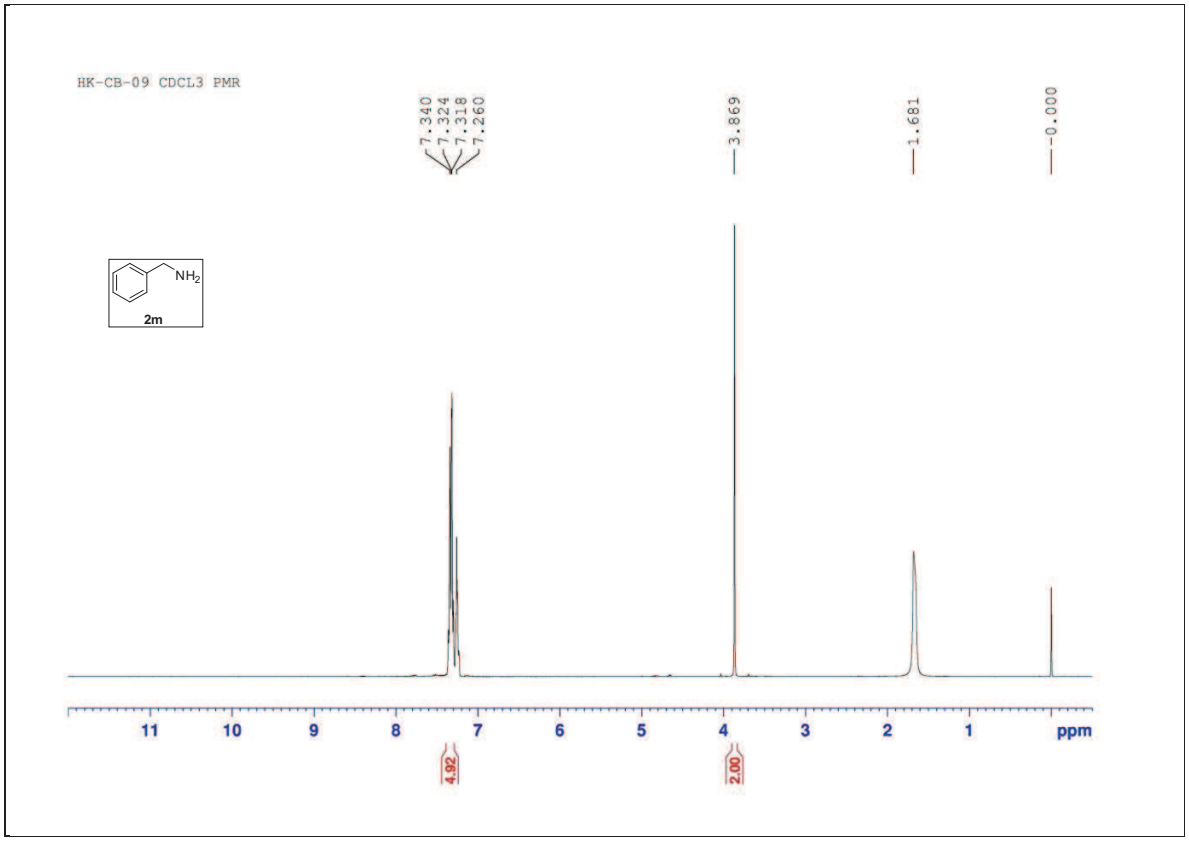
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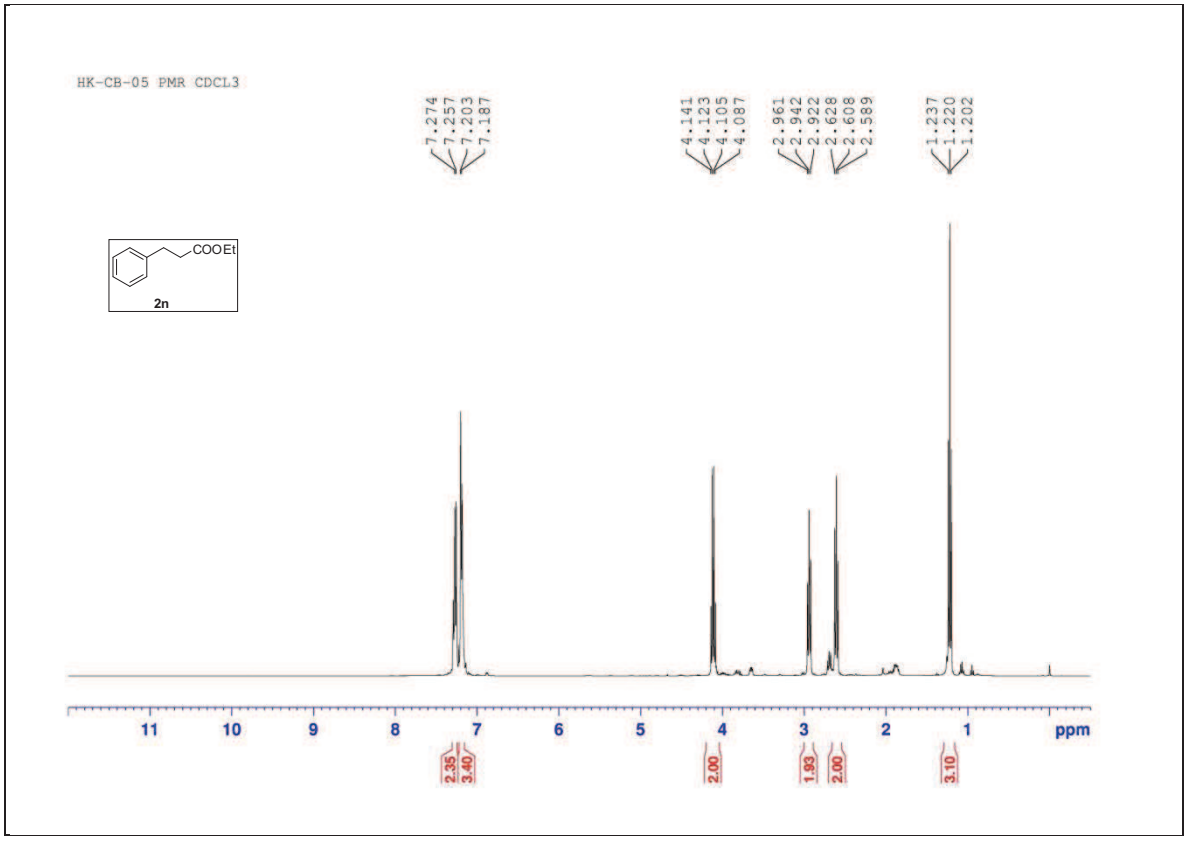
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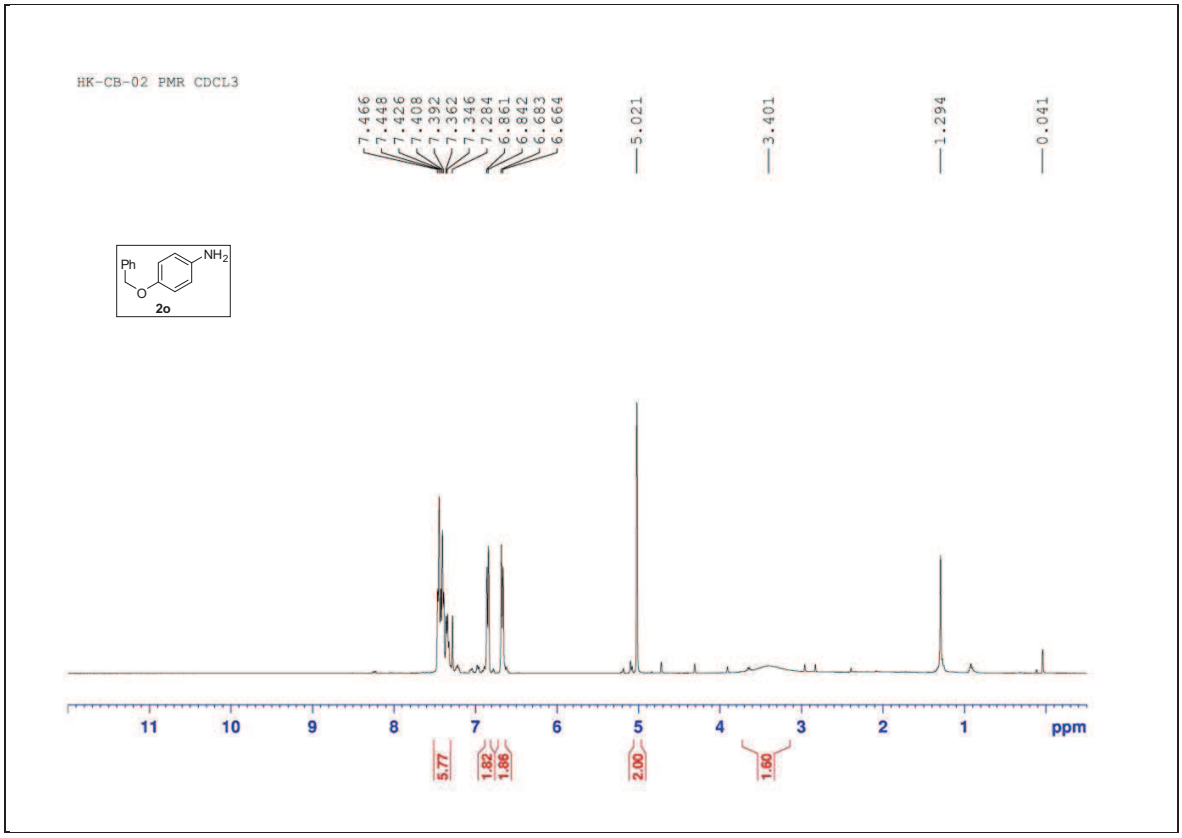
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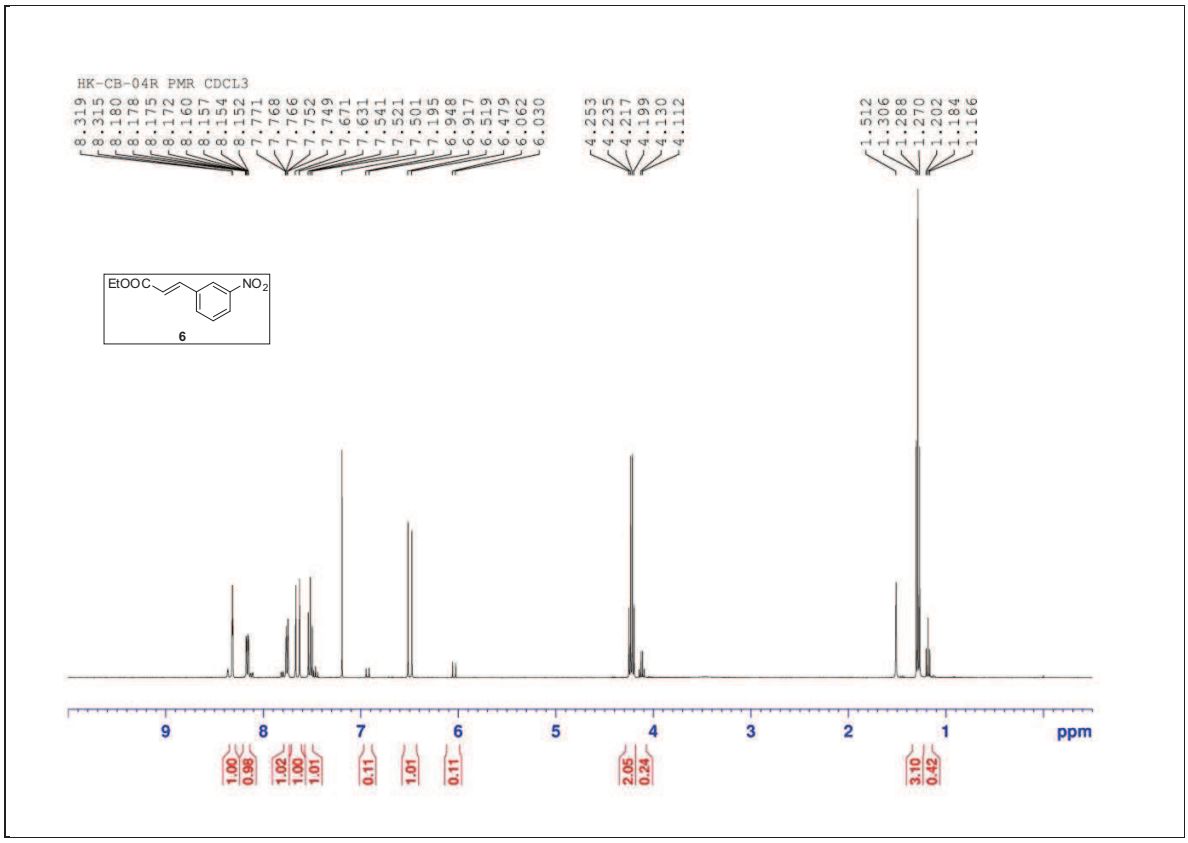
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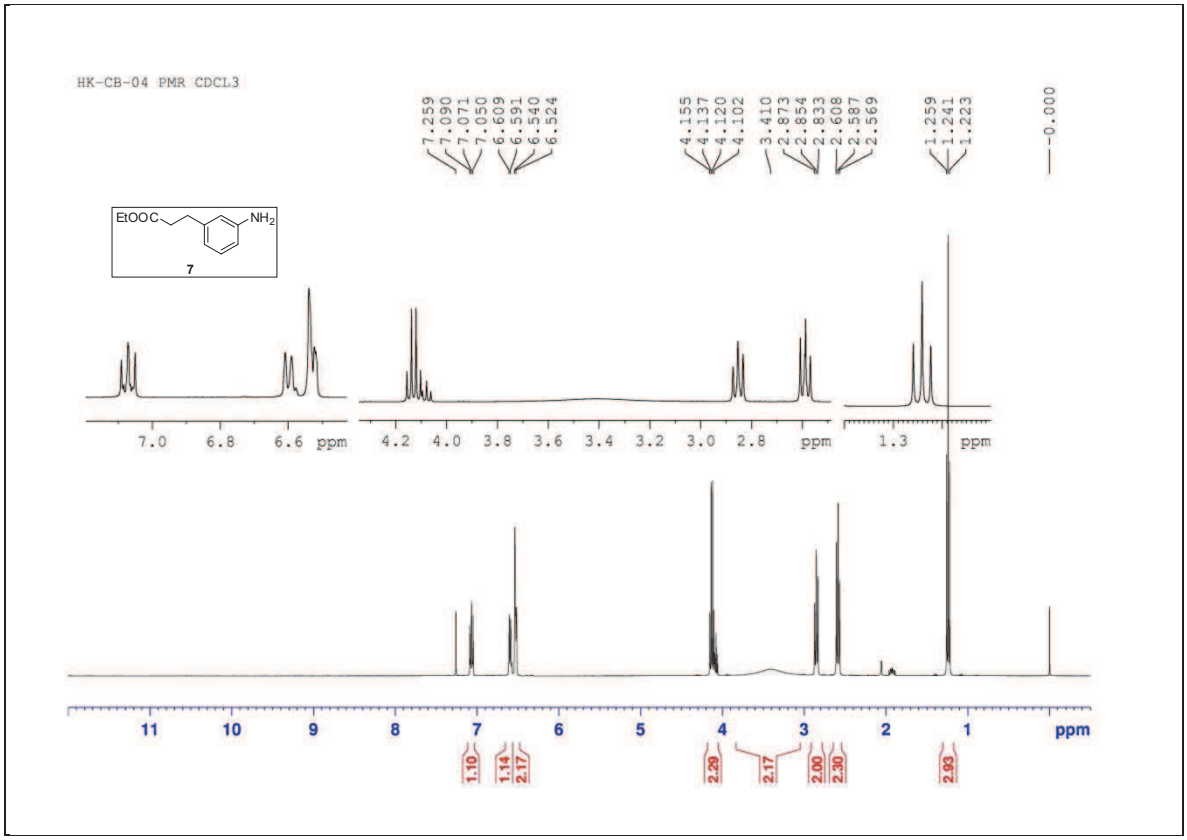
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