“SYNTHETIC STUDIES OF SELECTED BIOACTIVE NITROGEN HETEROCYCLES CONTAINING INDOLE, ISOINDOLINONE AND ACRIDINE MOTIFS”

THESIS

Submitted to

GOA UNIVERSITY

For the award of the degree of

DOCTOR OF PHILOSOPHY
In
CHEMISTRY
By

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Under the Guidance of

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JANUARY 2017

CERTIFICATE

This is to certify that the thesis entitled, “**Synthetic Studies of Selected Bioactive Nitrogen Heterocycles Containing Indole, Isoindolinone and Acridine Motifs**” submitted by Mr. **Prajesh Sitaram Volvoikar**, 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
January 2017

Prof. Santosh G. Tilve
Research Guide
Department of Chemistry
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DECLARATION

I hereby declare that the matter embodied in this thesis entitled, "**Synthetic Studies of Selected Bioactive Nitrogen Heterocycles Containing Indole, Isoindolinone and Acridine Motifs**" is the result of investigation carried out by me, in the Department of Chemistry, Goa University, Goa-India, under the supervision of **Prof. S. G. Tilve** and it has not previously formed basis for any other 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
January 2017

Mr. Prajesh Sitaram Volvoikar
Research Student
Department of Chemistry
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ACKNOWLEDGEMENT

I take this opportunity to express my deep sense of gratitude to all those who directly and indirectly supported me in various respects during the completion of my doctoral thesis.

First and most important, I express my sincere gratitude to my research supervisor, **Prof. S. G. Tilve**, for allowing me to carry out my research work under his valuable guidance, suggestion, innovative ideas, motivation and hard work. I thank him for giving me independence to work in any area of my interest and being the biggest support throughout this journey. Words shall never be enough to describe the role he has played in my life in developing me not only as a researcher but also as a person. I owe all my success to him and will always be indebt to him for what I am today.

I am greatly thankful to my subject expert Prof. V. S. Nadkarni for his valuable suggestions and help during the course of my research work.

I am sincerely grateful to CSIR, New Delhi, for providing me financial assistance which supported me during the course of 5 years.

I express my sincere gratitude to our Vice-chancellor, Prof. V. Sahni, Registrar Prof. Y. V. Reddy and also to our former Vice-chancellor Dr. S. R. Shetye and former Registrar, Prof. V. P Kamat Goa University for allowing me to conduct my research work in this institute and frequent support during all the needy times. I am indeed thankful to Prof. B. R. Srinivasan (Head, Department of Chemistry, Goa University), Prof. A. V. Salker (Dean and Ex-Head of Department), Prof. J. B. Fernandes (Ex-Head of Department and Ex-Dean), Prof. S. P. Kamat (Ex-Head of Department), Prof. J. A. E. Desa (Ex-Dean), providing all the necessary facilities for my research work.

I also wish to thank to the faculty teachers of the department, Dr. V. M. S. Verenkar, Dr. R. N. Shirsat, Dr. S. N. Dhuri, Dr. M. S. Majik, Dr. Gururaja, Dr. P. Morajkar, Mrs. S. Girkar, and Dr. S. Parsekar for their support.

I acknowledge all the non-teaching staff of the Department of Chemistry, Goa University, for their support. I also thank Librarian Dr. Gopakumar and all the staff members of Library, Goa University, for their constant help

I deeply thank Dr. Kamlesh Pai Fondekar, Head T & E Department, Deccan Fine Chemicals Pvt. Ltd., Goa for giving me opportunity to work in his group and for his support.

I express my earnest gratitude to Organic chemistry division of IISc Bangalore and Syngenta Biosciences Pvt. Ltd., Goa for providing me with the HRMS facility.

I am thankful to Dr. P. Parvatkar for the immense initial help in my research work. I also thank Dr. S. Shetgoankar, Dr. A. Vernekar and Dr. Kiran Naik for their valuable help during my literature work.

I was blessed to have seniors like Dr. Chinmay, Dr. Prachi, Dr. Hari, Dr. Sandesh, Dr. Kashinath, Dr. Rohan, Dr. Lactina, Dr. Shrikant, and Dr. Kiran, I thank them for sharing useful knowledge and suggestions. I am very grateful to Dr. Prachi for her consistent support throughout the course of my thesis and words shall not be enough to thank her.

My journey so far was made alot easier and enjoyable with company of Mr. Sagar, Dr. Pradnyesh, Mr. Satu, Dr. Madhavi and Mr. Shambu. I thank them for being there at every stage of my PhD life, providing necessary suggestions, help and constant encouragement. I also wish to thank Ms. Pooja, Mr. Mithil, Mr. Sudesh, Ms. Mira, Mr. Abhijeet, Mr. Diptesh, Mrs. Celia, Mr. Dattaprasad, Mr. Vishal, Mr. Daniel, Ms. Savita, Ms. Rita, Mr. Vishnu, Mr. Pratik, Mr. Chandan, Mr. Rahul and Ms. Prajyoti for their valuable company and help which they generously provided.

I am grateful to my lab mates, Ms. Durga, Ms. Mayuri, Mrs. Pratibha, Mr. Shashank and Mr. Ketan for being kind and helpful.

There is no measure to thank my friends Ms. Sneha, Mr. Mahendra, Mr. Mayuresh and Mr. Sachin who stood beside me in every joy, need, hardship, downfall and bearing me in the time of disappointment.

Most important, my family members without whose support no work was possible. I am greatly indebted to my father Mr. Sitaram and mother Mrs. Sunita for the immense hard work put by her during my education and for making me the person I am today. I also deeply thank my sisters Mrs. Utkarsha, Mrs. Nilima and Mrs. Reshma and my brothers Mr. Subash and Mr. Nilesh for their constant support and encouragement. I feel very fortunate to have advice and support from Mr. Umakant in every stage of my life. Hard times were made simpler with never ending love and patience shown towards me by my nephew and nieces.

Finally I thank all mighty for giving me good health and helping me at every stage of my life.

.... Mr. Prajesh S. Volvoikar

DEDICATED TO

MY BELOVED PARENTS

GENERAL REMARKS

1) The compound numbers, figure numbers, scheme numbers and reference numbers given in each chapter refer to that particular chapter only.

2) All melting points and boiling points were recorded using Thiele's tube and are uncorrected.

3) Commercial reagents were used without further purification.

4) All solvents were distilled prior to use and then dried using standard procedure.

5) Petroleum ether refers to the hydrocarbon fraction collected in the boiling range 60 - 80 °C.

6) All reagents were prepared using literature methods.

7) Chromatographic purification was conducted by column chromatography using silica gel (60 – 120 mesh size) or by flash chromatography using silica gel (200-400 mesh size).

8) Thin layer chromatography (TLC) were carried out on silica gel 60 F254 aluminium plates purchased from Merck.

9) The IR spectra were recorded on Shimadzu FT-IR spectrophotometer.

10) ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Brucker AVANCE 400 instrument and the multiplicities of carbon signals were obtained from DEPT experiment. Chemical shifts are expressed in δ relative to tetramethylsilane (TMS) which is expressed in ppm. Chemical shifts are represented in the round brackets.

11) The high resolution mass spectra (HRMS) were recorded on MicroMass ES- QTOF mass spectrometer.

DEFINITION OF ABBREVIATIONS

1) General Abbreviations

g	Gram/s	*o*	Ortho
mg	Milligram/s	*m*	Meta
mmol	Millimole	*p*	Para
mL	Milliliter	*MS*	Molecular sieves
m.p.	Melting point	*psi*	Pounds per square inch
b.p.	Boiling point	*cat.*	Catalytic
Eq.	Equation/s	*atm.*	Atmospheric
lit.	Literature	*et al*	Et alia (and others)
d	Day/s	*TLC / tlc*	Thin layer chromatography
h	Hour/s	sat.	Saturated
min	Minute/s	Expt.	Experiment
sec	Second/s	*Calcd.*	Calculated
hv	Irradiation	MW / μW	Microwave
%	Percentage	Temp.	Temperature
R	Rectus	anhyd.	Anhydrous
S	Sinister	°C	Degree Celcius
fig.	Figure	RT / rt	Room temperature
conc.	Concentrated	*Z*	Zussamen (together)
dil.	Dilute	*E*	Eentegegen (opposite)
aq.	Aqueous	equiv	Equivalent

2) Compound Abbreviations

Ac	Acetyl	Ph	Phenyl
Ac$_2$O	Acetic anhydride	PMB	*p*-Methoxybenzyl
TBHP	*tert*-Butyl hydroperoxide	PPh$_3$	Triphenylphosphine
Ph	Phenyl	THF	Tetrahydrofuran
Boc	*tert*-Butyl carbonyl	Ms	Methane sulfonyl
Bn	Benzyl	TMS	Trimethylsilyl
Bz	Benzoyl	TMSCN	Cyanotrimethyl silane
t-Bu	*tert*-Butyl	Ts	*p*-Toluene sulfonyl
TFA	Trifluoro acetic acid	Py	Pyridine
TFAA	Trifluoro acetic anhydride	NMO	*N*-Methyl morpholine oxide
Et$_3$N	Triethyl amine	DCM	Dichloromethane
AcOH	Acetic acid	DCE	1,2-Dichloroethane
MeOH	Methanol	PCC	Pyridinium chlorochromate
EtOH	Ethanol	LDA	Lithium diisopropylamide

m-CPBA	*m*-Chloroperbenzoic acid	HOBt	Hydroxybenzotriazole
p-TsOH/ *p*-TSA	*p*-Toluene sulfonic acid	CAN	Cerric ammonium nitrate
DMSO	Dimethyl sulfoxide	TsCl	Tosyl chloride
DMF	*N,N*-Dimethylformamide	DMAP	4-Dimethyl amino pyridine
TBAF	Tetrabutylammonium fluoride	HMPA	Hexamethylphosphoramide
Et	Ethyl	TBSOTf	*t*-Butyldimethylsilyltrifloro-methane sulphonate
Me	Methyl	DCC	Dicyclohexyl cabodiimide
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone	EDCl	1-Ethyl-3-(3dimethylamino-propyl)-carbodiimide
LAH	Lithium aluminium hydride	DBU	1,8-Diazabicyclo-[5.4.0]undec-7-ene
NBS	*N*-Bromosuccinimide	DMP	Dess-Martin periodinane
EtOAc	Ethyl acetate	DIBAL-H	Diisobutyl aluminium hydride
n-BuLi	*n*-Butyl lithium	MOM	Methoxymethyl ether
t-BuLi	*t*-Butyl lithium	Boc_2O	*tert*-Butyl dicarbonate
Pd/C	Palladium on activated charcoal	*i*-PrOH	*Iso*-propanol
Pet ether	Petroleum ether		

3) Spectroscopic Abbreviations

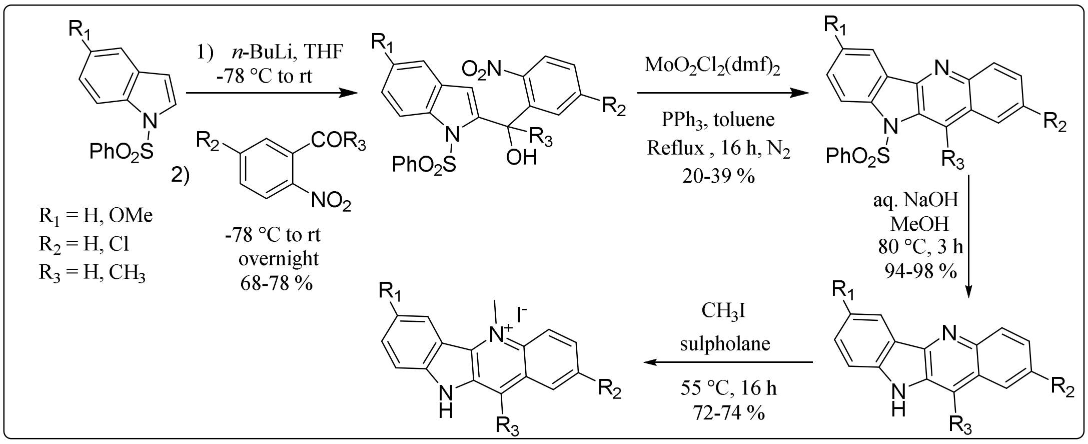
IR	Infrared	s	Singlet
$\tilde{\nu}$	Frequency maximum	d	Doublet
cm^{-1}	Frequency in wavenumber	t	Triplet
UV	Ultra violet	q	Quartet
NMR	Nuclear magnetic resonance	m	Multiplet
$CDCl_3$	Deuterated chloroform	dd	Doublet of doublet
DMSO-d_6	Deuterated dimethyl sulfoxide	td	Triplet of a doublet
DEPT	Distortionless Enhancement by Polarization Transfer	HRMS	High Resolution Mass Spectrum
ppm	Parts per million	M^+	Molecular ion
δ	Delta (Chemical shift in ppm)	*m/z*	Mass to charge ratio
MHz	Megahertz	*J*	Coupling constant
Hz	Hertz	br	Broad

ABSTRACT OF THESIS

TITLE: **SYNTHETIC STUDIES OF SELECTED BIOACTIVE NITROGEN HETEROCYCLES CONTAINING INDOLE, ISOINDOLINONE AND ACRIDINE MOTIFS**

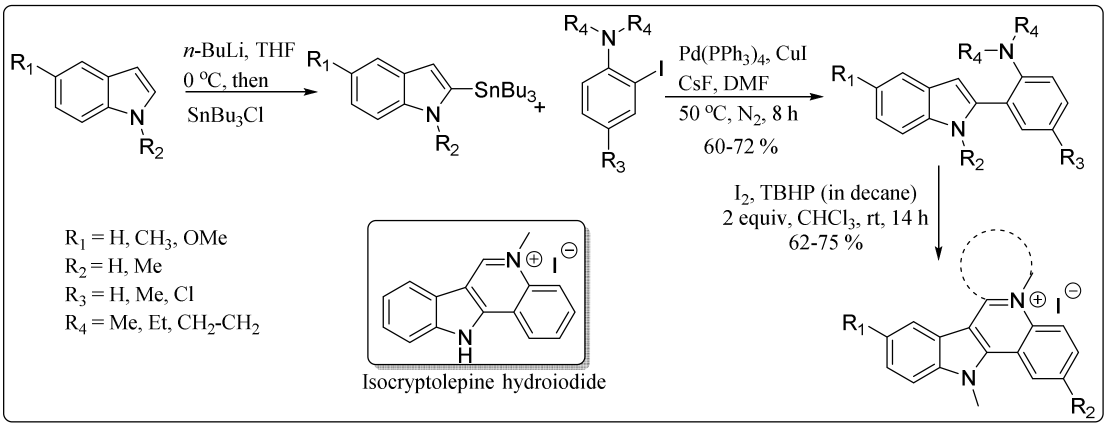
A vast number of drugs in the market contain one or more heterocyclic rings, of which nitrogen heterocycle constitutes a major part. The objective of this thesis was to develop synthetic methods for nitrogen containing hetrocycles which are isolated from natural sources and to build their synthetic analogues. The thesis is divided into five chapters.

The ***First*** chapter describes the synthesis of naturally occurring indoloquinoline alkaloid cryptolepine as its hydroiodide. The synthesis of this compound is achieved in 4 steps starting from *N*-phenylsulfonyl indole and *o*-nitrobenzaldehyde. The key synthetic steps involved are C-C bond formation by directed lithiation of *N*-phenylsulfonyl indole and tandem nitrene mediated reductive cyclization and dehydration to complete the tetracyclic core. Further, deprotection and regioselective methylation afforded cryptolepine hydroiodides (Scheme 1). Optimization of the tandem reductive cyclization dehydration step is also presented.



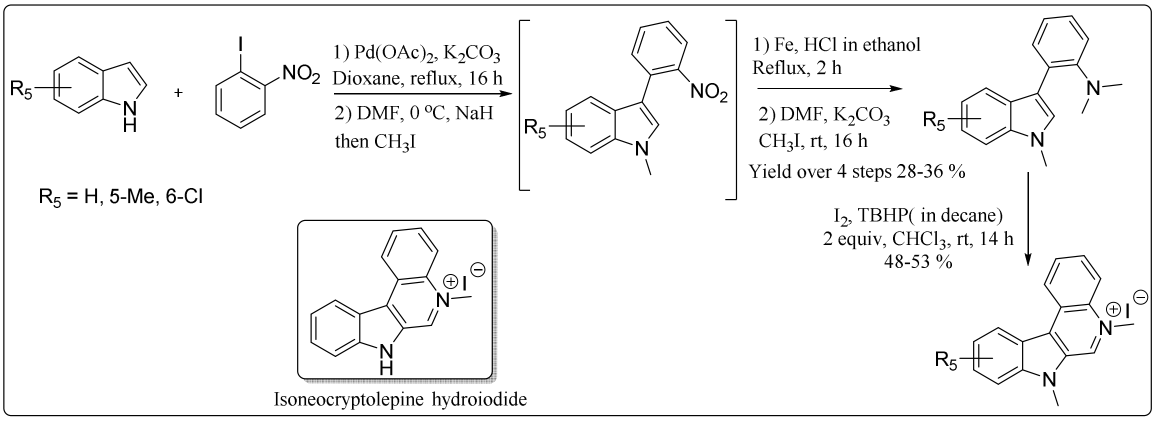
Scheme 1

The ***Second*** chapter describes the intramolecular dehydrogenative coupling (IMDC) approach for synthesis of *N*-alkyl indolo[3,2-*c*]quinoline iodides. The cyclization of 2-phenyl indole derivative followed by aromatization resulted in iodide salts in good yields using an equivalent amount of iodine and 2 equivalents of TBHP. Conditions for IMDC were optimized. The required starting indole derivatives were synthesized using Stille coupling reactions (Scheme 2). Salts obtained were further converted to other derivatives by treating with nucleophiles. The optimized reaction condition for IMDC was applied in preparing naturally occurring isocryptolepine in its hydroiodide form. Controlled reactions were conducted and a plausible hypoiodite mechanism is proposed for the transformation.


n-BuLi, THF
0 °C, then
SnBu3Cl
Pd(PPh3)4, CuI
CsF, DMF
50 °C, N2, 8 h
60-72 %
I2, TBHP (in decane)
2 equiv, CHCl3, rt, 14 h
62-75 %
R1 = H, CH3, OMe
R2 = H, Me
R3 = H, Me, Cl
R4 = Me, Et, CH2-CH2
Isocryptolepine hydroiodide

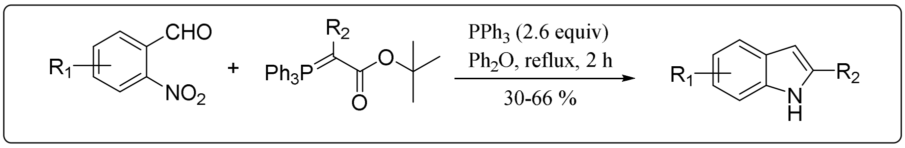
Scheme 2

This chapter also describes the application of standardized dehydrogenative protocol for successful synthesizing of *N*,*N*-dimethylindolo[2,3-*c*]quinoline iodides. The required substrates were prepared by palladium catalyzed C-3 arylation of indole, followed by methylation, reduction and dimethylation (Scheme 3).


1) Pd(OAc)2, K2CO3
Dioxane, reflux, 16 h
2) DMF, 0 °C, NaH
then CH3I
1) Fe, HCl in ethanol
Reflux, 2 h
2) DMF, K2CO3
CH3I, rt, 16 h
Yield over 4 steps 28-36 %
I2, TBHP(in decane)
2 equiv, CHCl3, rt, 14 h
48-53 %
R5 = H, 5-Me, 6-Cl
Isoneocryptolepine hydroiodide

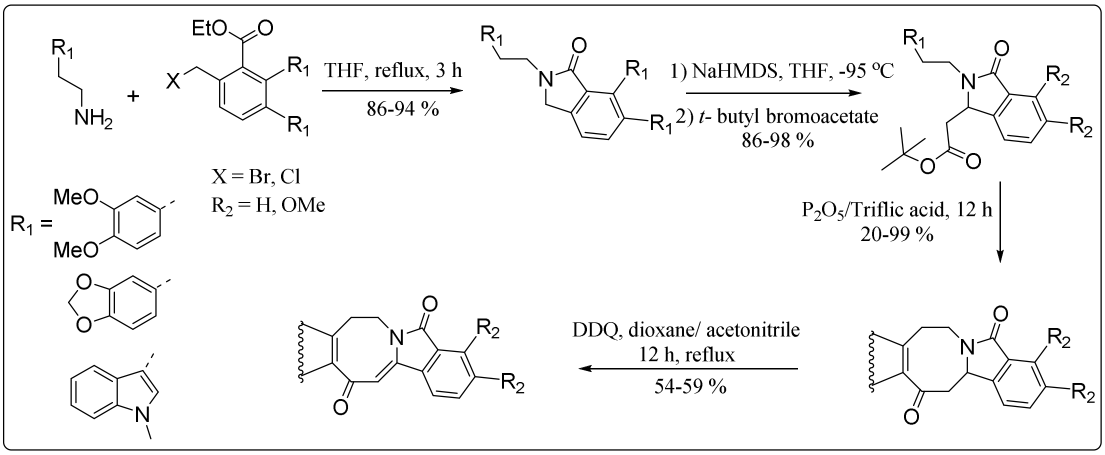
Scheme 3

The ***Third*** chapter describes a new route for synthesis of indoles using Wittig reaction; nitrene mediated reductive cyclization, hydrolysis and decarboxylation in a single step (Scheme 5) is described. The strategy has also been applied to the synthesis of 2-alkyl indoles, which are important starting materials for many potent drugs.


PPh3 (2.6 equiv)
Ph2O, reflux, 2 h
30-66 %

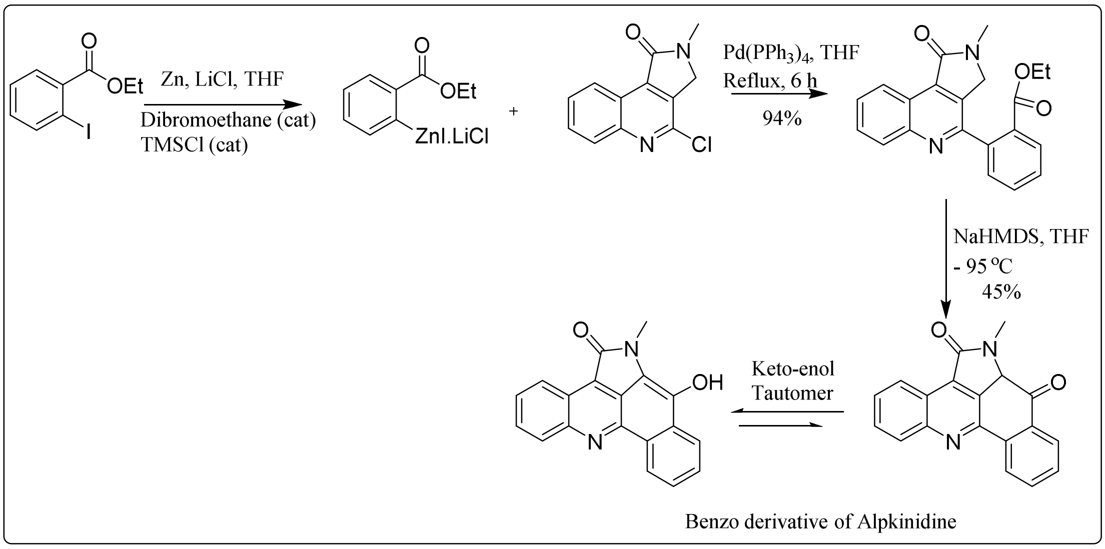
Scheme 4

The ***Fourth*** chapter discusses the successful synthesis of eight membered azocine ring in just three steps starting from easily available substrates. Synthesis involves *N*-alkylation, amidation and then *C*-alkylation by generating anion on isoindolinone motif, followed by a one step Friedel-Craft's cyclization of an ester functionality using Eaton's reagent to result in an eight membered azocine ring (Scheme 5).


THF, reflux, 3 h
86-94 %
1) NaHMDS, THF, -95 ºC
2) t- butyl bromoacetate
86-98 %
P2O5/Triflic acid, 12 h
20-99 %
DDQ, dioxane/ acetonitrile
12 h, reflux
54-59 %
X = Br, Cl
R2 = H, OMe
R1 =
EtO
NH2
MeO
MeO

Scheme 5

The ***Fifth*** chapter describes our efforts towards synthesis of naturally occurring alpkinidine alkaloid. This section describes an efficient route for the synthesis of a benzo analogue of alpkinidine using Negishi coupling and cyclization onto an ester by anion formation on isoindolinone motif (Scheme 6).


OEt
Zn, LiCl, THF
Dibromoethane (cat)
TMSCl (cat)
ZnI.LiCl
Cl
Pd(PPh3)4, THF
Reflux, 6 h
94%
NaHMDS, THF
- 95 ºC
45%
Keto-enol
Tautomer
OH
Benzo derivative of Alpkinidine

Scheme 6

LIST OF PUBLICATIONS

1) Tandem reductive cyclization–dehydration approach for the synthesis of cryptolepine hydroiodide and its analogues, **Volvoikar, P. S**.; Parvatkar, P. T.; Tilve, S. G. *Eur. J. Org. Chem.* **2013,** 2172-2178.
2) Iodine mediated Intramolecular Dehydrogenative Coupling: Synthesis of N-alkylindolo[3,2-*c*] and [2,3-c]quinoline Iodides, **Volvoikar, P. S**.; Tilve, S. G. *Org. Lett.* **2016**, *18*, 892-895.
3) Influence of acid chain length on the properties of TiO_2 prepared by sol-gel method and LC-MS studies of methylene blue photodegradation, Bakre, P. V.; **Volvoikar, P. S**. Vernekar, A. A.; Tilve, S. G. *Journal of Colloid and Interface Science* **2016**, *474*, 58-67.
4) One pot Wittig reaction, reductive cyclisation, hydrolysis and decarboxylation : route to indoles from *o*-nitrobenzaldehydes, **Volvoikar, P. S**.; Tilve, S. G. (Manuscript under preparation).
5) Synthesis of Magallanesine and its analogues having azocine containing ring, **Volvoikar, P. S**.; Tilve, S. G. (Manuscript under preparation).

Conferences attended and poster presentations:

1) Presented poster entitled “Intramolecular Dehydrogenative Cross Coupling for the Synthesis of *N*-methyl Isocryptolepine iodides” at **Transcending Frontiers in Organic Chemistry** in **CSIR-NIIST, Trivandrum** (9th - 11th October 2014).
2) Presented poster entitled “Synthesis of Indoloquinoline alkaloid Cryptolepine and Isocryptolepine using tandem reductive cyclisation and Intramolecular Dehydrogenative coupling” at **10th** Junior**-National Organic Symposium Trust (J-NOST) Conference** for Research Scholars in **IIT-Madras** (4th - 6th December 2014).
3) Presented poster entitled “Synthetic studies of Indoloquinoline alkaloids Cryptolepine and Isocryptolepine” at **New Frontiers in Chemistry-from Fundamentals to Applications** in **BITS Pilani, Goa** (18th - 19th December 2015).
4) Participated in the 3-day conference on **Chemical (Industrial) Disaster Management (CIDM): Chemical, Pharmaceutical and hydrocarbon Industry**: held at Cidade De Goa, Goa (16th - 18th April, 2013).
5) Participated in **8th** Junior**-National Organic Symposium Trust (J-NOST-2012) Conference**, for Research Scholars held at IIT Guwahati (15th - 17th December 2012).

Chapter 1

Synthetic study of Cryptolepine hydroiodides

1.1: Introduction

Cryptolepine **1** is an indoloquinoline alkaloid containing a tetracyclic indolo[3,2-*b*]quinoline ring system. Due to the presence of a basic quinoline nitrogen atom, **1** exists as its corresponding salt form under acidic conditions (Figure 1). [1a]

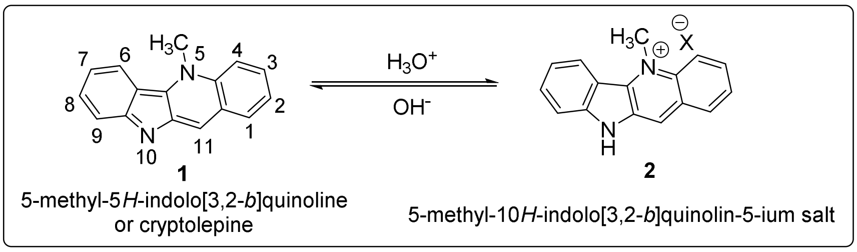

7
6
H_3C
5
4
3
8
2
9
10
11
1
1
5-methyl-5*H*-indolo[3,2-*b*]quinoline
or cryptolepine
H_3O^+
OH^-
H_3C
X
N
H
2
5-methyl-10*H*-indolo[3,2-*b*]quinolin-5-ium salt

Figure 1. Cryptolepine and its corresponding salt.

Cryptolepine **1** was first isolated from terrestrial plant *Cryptolepis triangularis* in the year 1929 [2a] but synthesis of this molecule was reported much earlier in 1906 by Fichter and Boehringer. [3] Later in 1951 it was isolated from the roots of West African shrub *Cryptolepis sanguinolenta* by Gellert *et al.* [2b] which were found to be a rich source of other members of the indoloquinoline family, such as neocryptolepine **3**, isocryptolepine **4** , quindoline **7a** and others (Figure 2). [4] So far 13 alkaloids have been isolated from the roots of this plant. Based on mode of the fusing of indole and quinoline ring, **1** and **3** are mentioned as linear indoloquinolines whereas **4** and **5** are angular fused, of which **5** is not naturally isolated. [5]

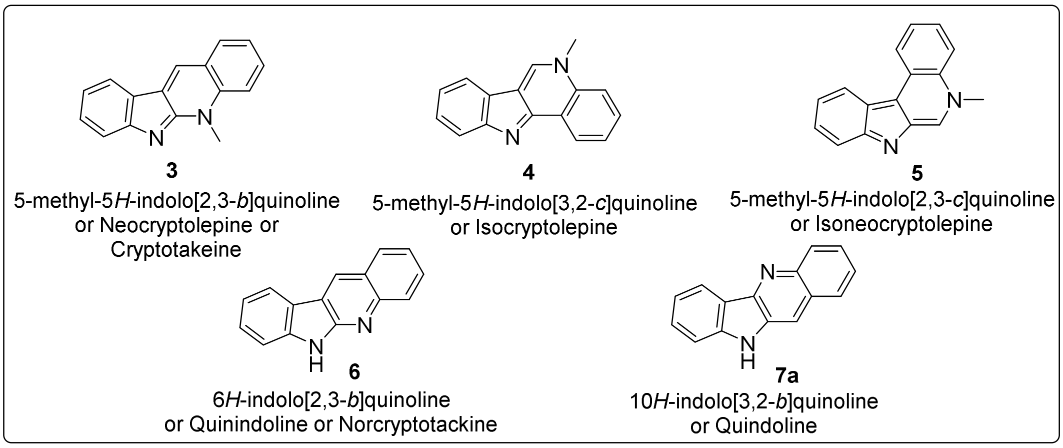

3
5-methyl-5*H*-indolo[2,3-*b*]quinoline
or Neocryptolepine or
Cryptotakeine
4
5-methyl-5*H*-indolo[3,2-*c*]quinoline
or Isocryptolepine
5
5-methyl-5*H*-indolo[2,3-*c*]quinoline
or Isoneocryptolepine
6
6*H*-indolo[2,3-*b*]quinoline
or Quinindoline or Norcryptotackine
7a
10*H*-indolo[3,2-*b*]quinoline
or Quindoline

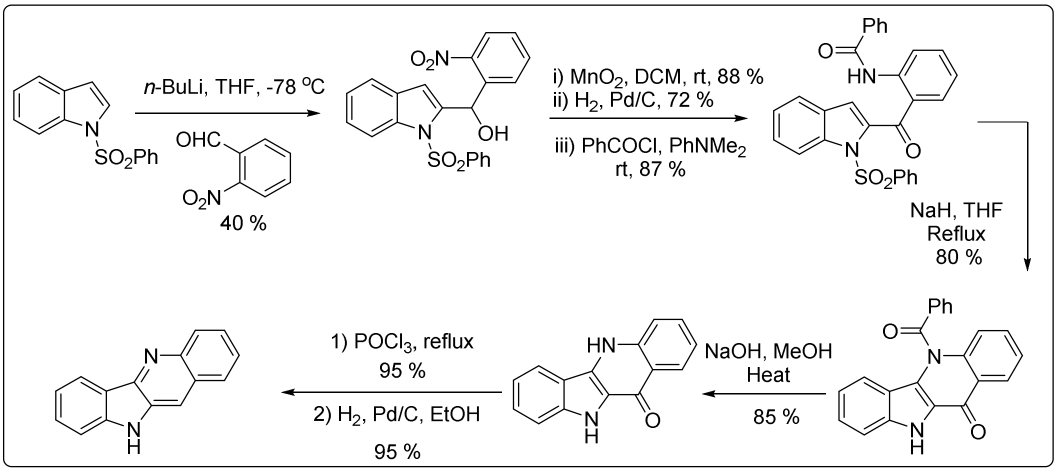
Figure 2. Indoloquinoline Alkaloids.

The medicinal importance of this plant was known to the people in early days and its decoction was used to treat a variety of health disorders like malaria in central and West Africa by Ghanaian healers. [6] Earlier studies revealed neocryptolepine **3** to have similar activity to cryptolepine **1** against malaria [7a-b] but recent studies have revealed the higher activity of the latter against *Plasmodium falciparum* strain which is known to be resistant against chloroquine. [7c] It is also known to inhibit the DNA replication and transcription by acting as intercalating agent and alter the double helical structure of DNA. [8a] X-ray studies along with spectroscopic methods have shown cryptolepine to bind 10 times stronger with B16 melanoma cells than other alkaloids of indoloquinoline series leading to its higher cytotoxicity. [8b-c] Apart from its potency against malaria, **1** and its substituted derivatives are also known to posses's activities such as antibacterial, antifungal, antithrombotic, vasodilation, antihyperglycemic, anticancer and cytotoxic, anti-inflammatory, hypotensive and antipyretic, presynaptic α-adrenoceptor blocking action and anti-muscarinic. [4a-i, 6d, 9a-d]

1.2: Literature Reported Methods

Due to application of cryptolepine in drug studies, various routes for the synthesis of its tetracyclic core have been reported. Many of the synthetic routes start with substituted indole [6d, 10a] and quinoline [5, 11a-f] as the starting materials. Synthetic reports of indoloquinoline alkaloids were compiled by Ablordeppey's group [1a] in the year 2008 and in 2011 by our group.[1b] Some of the recent synthetic reports for synthesis of cryptolepine and quindoline are listed below.

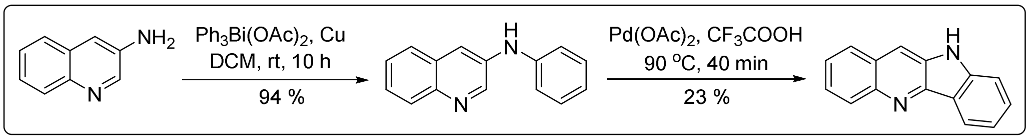
Joule *et al.* [10a] synthesized quindoline from *N*-phenyl sulfonyl indole in eight steps (Scheme 1).



Scheme 1

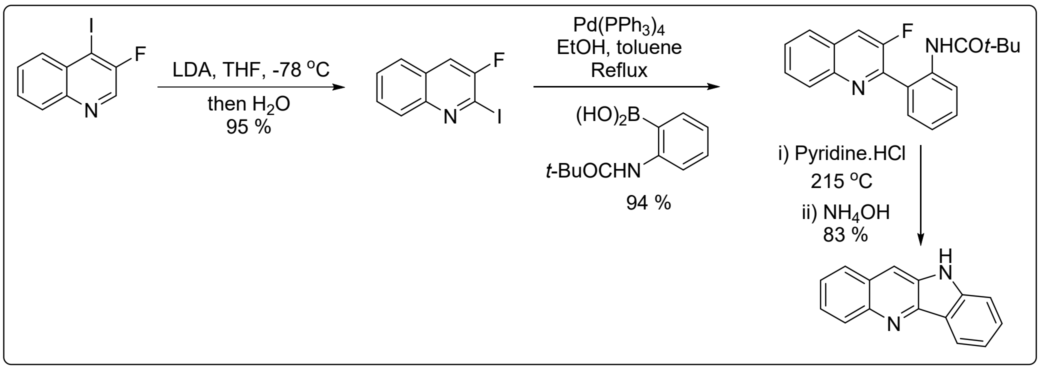
N-phenyl sulfonyl indole was metallated at 2-position followed by reaction with *o*-nitrobenzaldehyde to give a secondary alcohol, which was oxidized to ketone with MnO$_2$. Nitro group was reduced under catalytic hydrogenation followed by benzoylation with benzoyl chloride to give amido ketone. This was then cyclized using intramolecular βnucleophilic substitution and desulphonation to give the tetracycle which on *N*-debenzoylation under basic conditions and further treatment with $POCl_3$, followed by dechlorination under catalytic hydrogenation gave quindoline.

Fan and Ablordeppy [11a] have described a two step synthesis of quindoline. 3-Aminoquinoline on treatment with triphenylbismuth diacetate in the presence of copper underwent *N*-arylation. Further, treating under acidic condition with palladium acetate furnished quindoline *via* oxidative cyclisation in low yield (Scheme 2).


NH2
Ph3Bi(OAc)2, Cu
DCM, rt, 10 h
94 %
H
N
N
Pd(OAc)2, CF3COOH
90 °C, 40 min
23 %
H
N
N
N

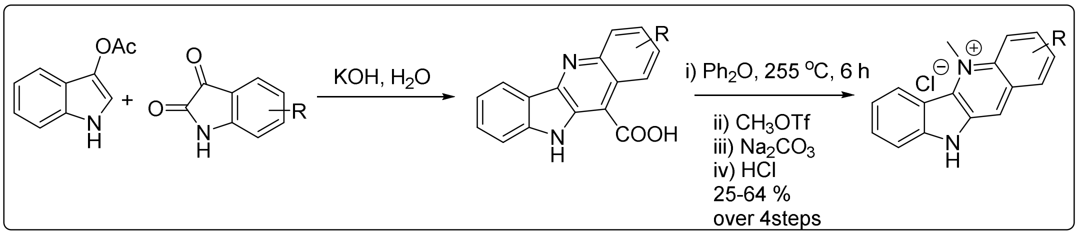
Scheme 2

Arzel *et al*. [11b] synthesized 3-fluoro-2-iodoquinoline *via* halogen dance from 3-fluro-4-iodo-quinoline and carried out Suzuki cross coupling with it to give biaryl derivative which in boiling pyridinium hydrochloride gave quindoline *via* nucleophillic displacement of fluoride atom (Scheme 3).


I
F
N
LDA, THF, -78 °C
then H2O
95 %
F
N
I
Pd(PPh3)4
EtOH, toluene
Reflux
(HO)2B
t-BuOCHN
94 %
F
NHCOt-Bu
N
i) Pyridine.HCl
215 °C
ii) NH4OH
83 %
H
N
N

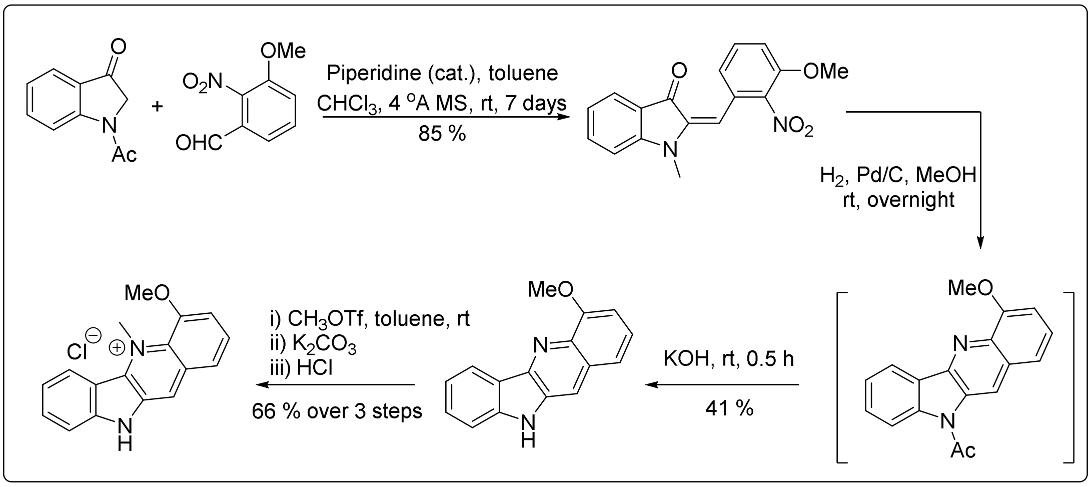
Scheme 3

Quindoline carboxylic acids [6d] were obtained in one step on treatment of indolyl acetates with derivatives of isatin. The acid was then decarboxylated in refluxing diphenyl ether to fetch quindolines which on methylation with methyl triflate afforded corresponding triflate salts. The triflate salt on basification and treatment with hydrochloric acid yielded cryptolepine hydrochlorides (Scheme 4).


OAc
+
N
H
O
O
N
H
R
KOH, H2O
N
R
N
H
COOH
i) Ph2O, 255 °C, 6 h
ii) CH3OTf
iii) Na2CO3
iv) HCl
25-64 %
over 4steps
Cl⊖
N⊕
R
N
H

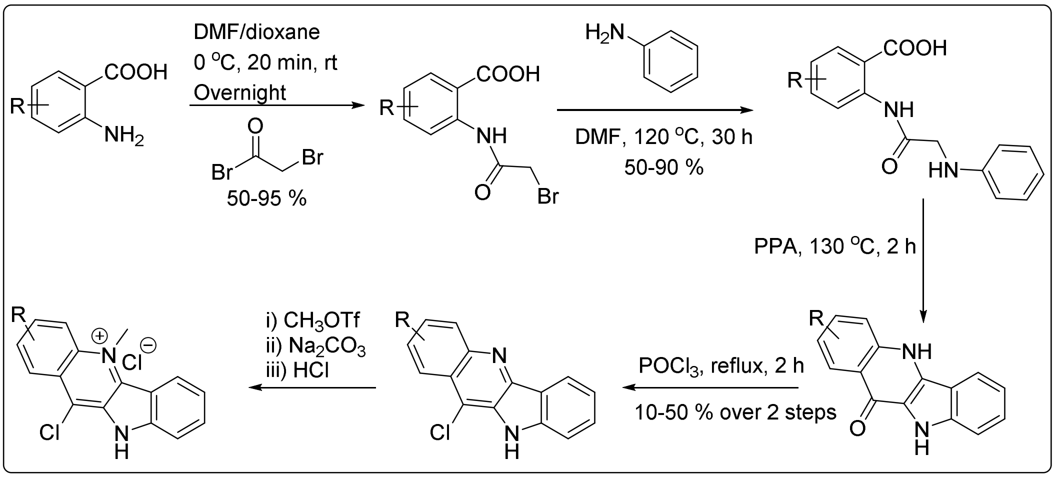
Scheme 4

1-Acetylindolin-3-one and 3-methoxy-2-nitrobenzaldehyde were condensed in the presence of catalytic amount of piperidine to give a mixture of *E*/*Z* isomers, which on hydrogenation and deprotection with alkali afforded 4-methoxyquindoline [6d] (Scheme 5). Methylation with methyl triflate, basification and treatment with hydrochloric acid gave 4-methoxy-cryptolepine hydrochloride salt.


O
N
Ac
+
OMe
O2N
OHC
Piperidine (cat.), toluene
CHCl3, 4 °A MS, rt, 7 days
85 %
O
OMe
NO2
N
H2, Pd/C, MeOH
rt, overnight
MeO
N
N
Ac
KOH, rt, 0.5 h
41 %
MeO
N
N
H
i) CH3OTf, toluene, rt
ii) K2CO3
iii) HCl
66 % over 3 steps
MeO
Cl⊖
⊕N
N
H

Scheme 5

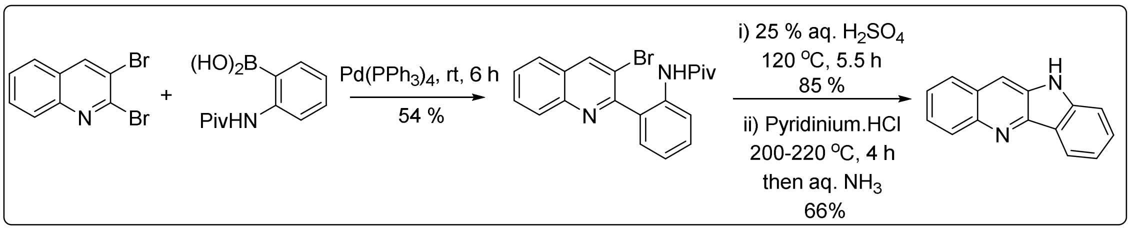
2-(2-(Phenylamino)acetamido)benzoic acids [6d] were obtained by reaction of anthranilic acids with bromoacetyl bromide followed by heating with anilines in DMF (Scheme 6).


R
COOH
NH2
DMF/dioxane
0 °C, 20 min, rt
Overnight
O
Br
Br
50-95 %
R
COOH
NH
O
Br
H2N
DMF, 120 °C, 30 h
50-90 %
R
COOH
NH
O
HN
PPA, 130 °C, 2 h
R
NH
O
N
H
POCl3, reflux, 2 h
10-50 % over 2 steps
R
N
Cl
N
H
i) CH3OTf
ii) Na2CO3
iii) HCl
R
⊕
N
Cl⊖
Cl
N
H

Scheme 6

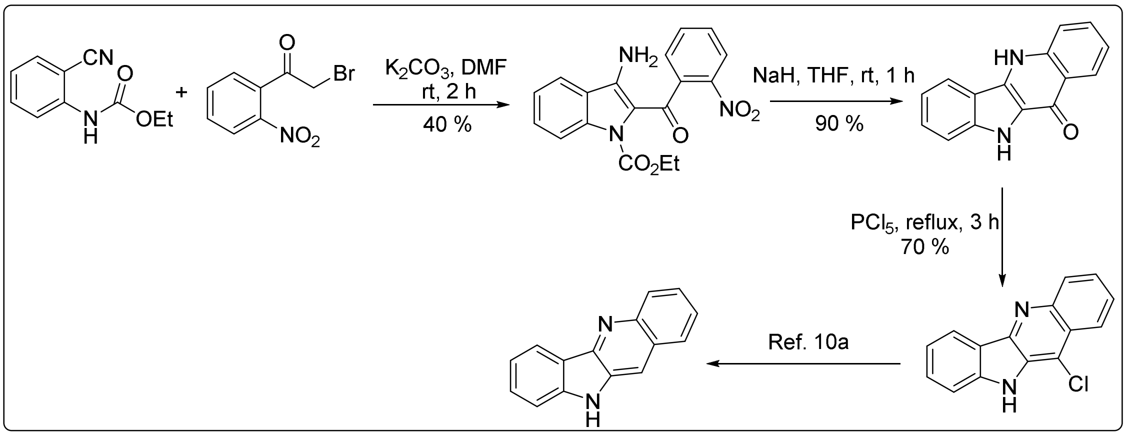
Acid derivatives on heating with PPA resulted in quindolones which on treatment with $POCl_3$ gave 11-chloroquindolines which were then converted to their hydrochloride salts.

Csanyi *et al.* [11c] carried out regioselective Suzuki reaction on 2,3-dibromoquinoline at 2-position to get a biaryl compound which on subjecting to aqueous sulphuric acid gave free amine. This when reacted with pyridinium hydrochloride at 220 ^oC displaced bromo atom to result in quindoline (Scheme 7).


Br
N
Br
+
$(HO)_2B$
PivHN
$Pd(PPh_3)_4$, rt, 6 h
54 %
Br
NHPiv
N
i) 25 % aq. H_2SO_4
120 ^oC, 5.5 h
85 %
ii) Pyridinium.HCl
200-220 ^oC, 4 h
then aq. NH_3
66%
H
N
N

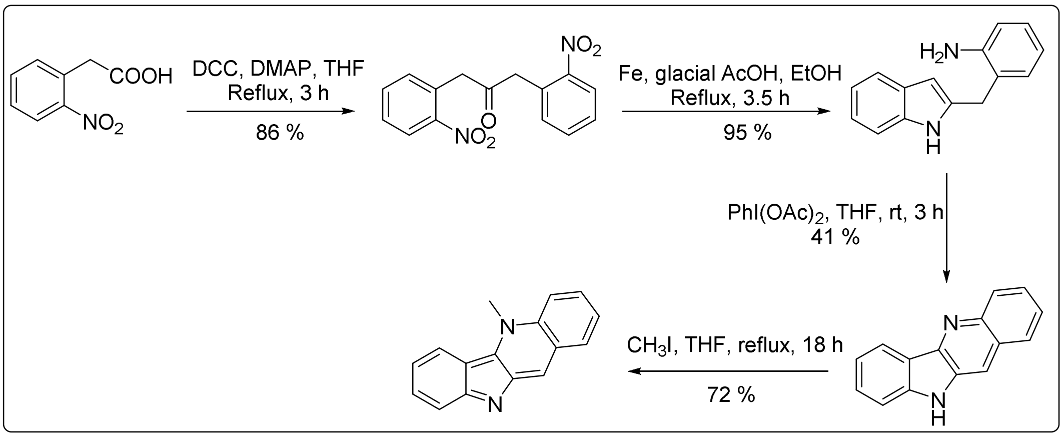
Scheme 7

Radl and co-workers [10c] synthesized quindolone starting from ethyl (2-cyanophenyl)carbamate and 2-bromo-1-(2-nitrophenyl)ethan-1-one in basic medium to give an intermediate which on treatment with alkali hydride underwent nucleophilic denitrocyclisation to fetch quindolones (Scheme 8). Further PCl_5 treatment furnished 11-chlorocryptolepine, which was converted to quindoline using procedures described by Cooper. [10a]


CN
O
N
H
OEt
+
O
Br
NO_2
K_2CO_3, DMF
rt, 2 h
40 %
NH_2
N
CO_2Et
O
NO_2
NaH, THF, rt, 1 h
90 %
HN
N
H
O
PCl_5, reflux, 3 h
70 %
N
N
H
Cl
Ref. 10a
N
N
H

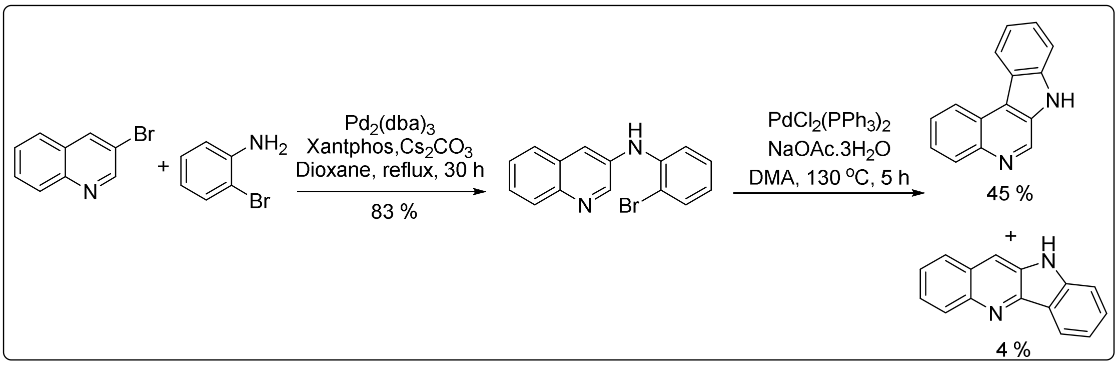
Scheme 8

Ho and co-workers [10d] synthesized cryptolepine in 4 steps, starting with DCC coupling of 2-nitrophenyl acetic acid to yield 1,3-bis(2-nitrophenyl)propan-2-one, which on reduction with Fe in an acidic medium and subsequent oxidative cyclisation with iodobenzene diacetate gave quinolidine which on methylation yielded cryptolepine (Scheme 9).


COOH
NO2
DCC, DMAP, THF
Reflux, 3 h
86 %
NO2
O
NO2
Fe, glacial AcOH, EtOH
Reflux, 3.5 h
95 %
H2N
N
H
PhI(OAc)2, THF, rt, 3 h
41 %
N
N
H
CH3I, THF, reflux, 18 h
72 %
N
N

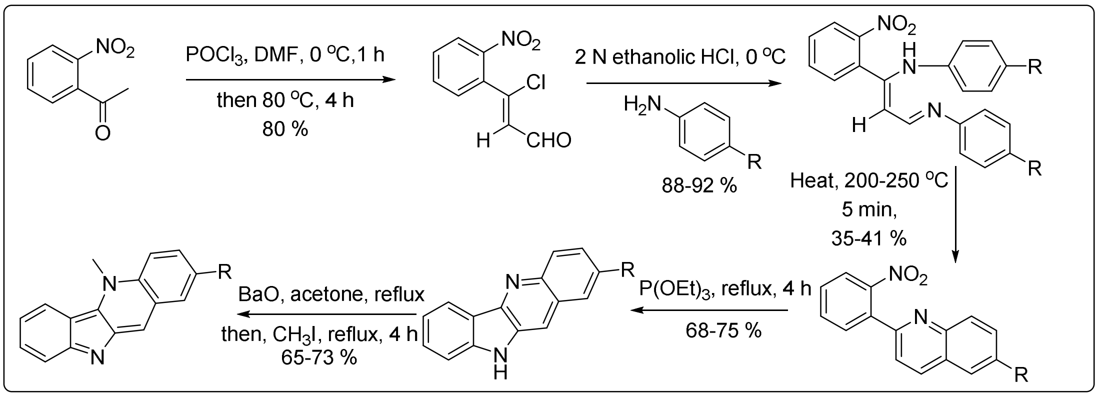
Scheme 9

Maes *et al.* [5] carried out regioselective cross amination between 3-bromoquinoline and *o*-bromoanilne with palladium to give *N*-(2-bromophenyl)quinolin-3-amine in good yield. Further intramolecular palladium catalyzed coupling resulted in 7*H*-indolo[2,3-*c*]quinoline as the major product, which is a synthetically derived indoloquinoline and quindoline in minor amount (Scheme 10).


Br
N
+
NH2
Br
Pd2(dba)3
Xantphos,Cs2CO3
Dioxane, reflux, 30 h
83 %
H
N
N
Br
PdCl2(PPh3)2
NaOAc.3H2O
DMA, 130 °C, 5 h
NH
N
45 %
+
H
N
N
4 %

Scheme 10

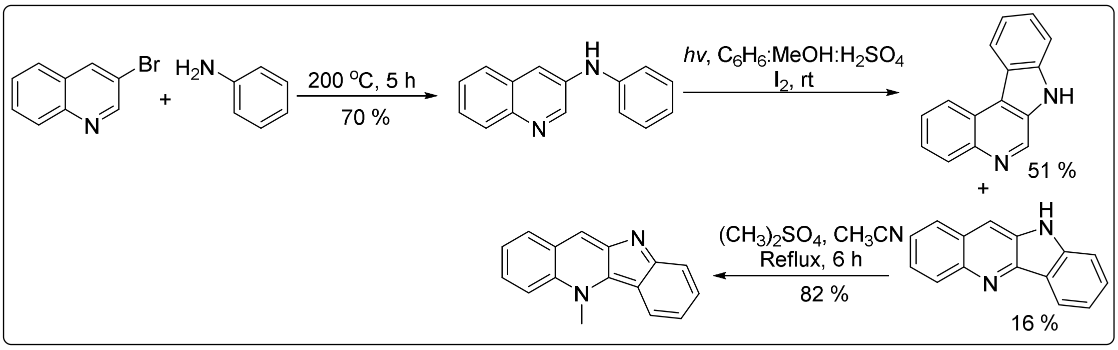
Ray *et al.* [10e] treated 2-nitroacetophenone under Vilsmeier-Haack reaction to give *β*-chlorocinnamaldehyde which in ethanolic HCl reacted with arylamines to give enaminoimine hydrochlorides (Scheme 11).


NO2
O
POCl3, DMF, 0 °C,1 h
then 80 °C, 4 h
80 %
NO2
Cl
H
CHO
2 N ethanolic HCl, 0 °C
H2N
R
88-92 %
NO2
H
N
R
H
N
R
Heat, 200-250 °C
5 min,
35-41 %
NO2
N
R
P(OEt)3, reflux, 4 h
68-75 %
N
R
N
H
BaO, acetone, reflux
then, CH3I, reflux, 4 h
65-73 %
N
R
N

Scheme 11

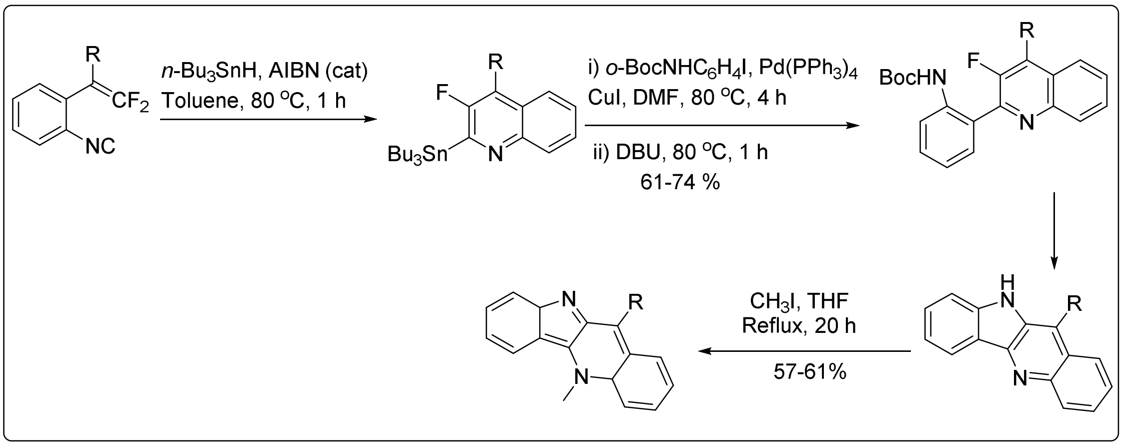
Thermal cyclization gave 2-(2-nitrophenyl) quinolines, followed by reductive cyclization with triethyl phosphite gave quindolines, which on methylation gave 2-substituted cryptolepines.

Mohan *et al*. [11d] heated 3-bromoquinoline with aniline at 200 °C to yield *N*-phenylquinolin-3-amine, which on photocyclization in acidic condition yielded quindoline as a minor product and precursor of isocryptolepine **4**, 11*H*-indolo[3,2-*c*]quinoline as a major product (Scheme 12). Quindoline was further regioselectively methylated with dimethyl sulfate to yield cryptolepine.


Br
H2N
+
200 °C, 5 h
70 %
H
N
N
hv, C6H6:MeOH:H2SO4
I2, rt
NH
51 %
+
H
N
(CH3)2SO4, CH3CN
Reflux, 6 h
82 %
16 %

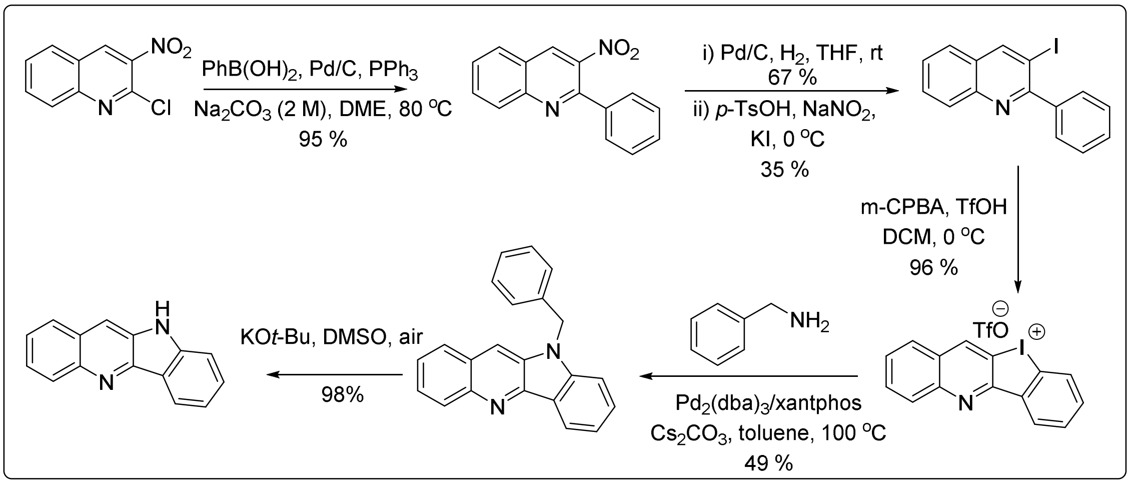
Scheme 12

Mori and Ichikawa [10f] treated *o*-isocyano substituted *β*,*β*-difluorostyrenes with tributyltin hydride in the presence of a radical initiator to obtain 2-stannyl-quinoline derivatives. These were then subjected to Stille coupling with *tert*-butyl (2-iodophenyl) carbamate followed by heating with pyridinium hydrochloride to obtain 11-alkylquindolines which on methylation furnished corresponding cryptolepines (Scheme 13).


R
CF2
NC
n-Bu3SnH, AIBN (cat)
Toluene, 80 °C, 1 h
R
F
Bu3Sn
N
i) o-BocNHC6H4I, Pd(PPh3)4
CuI, DMF, 80 °C, 4 h
ii) DBU, 80 °C, 1 h
61-74 %
R
F
BocHN
N
CH3I, THF
Reflux, 20 h
57-61%
H
N
R
N
N
R
N

Scheme 13

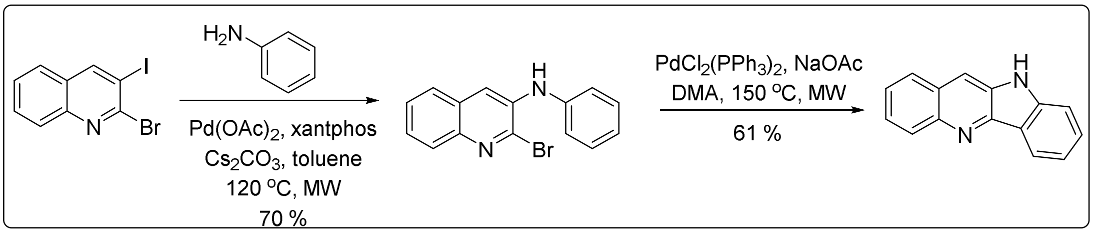
Detert *et al*. [11e] synthesized quindoline starting from 2-chloro-3-nitroquinoline, which on Suzuki coupling with phenyl boronic acid gave 3-nitro-2-phenylquinoline. This on reduction followed by diazotization was converted to 3-iodo-2-phenylquinoline (Scheme 14). Further treatment with *m*-CPBA in the presence of triflic acid yielded benzoquinolinoiodolium salt, which was further subjected to two fold Buchwald-Hartwig amination with benzyl amine. The product obtained on debenzylation in basic medium gave the desired quindoline.



PhB(OH)2, Pd/C, PPh3
Na2CO3 (2 M), DME, 80 °C
95 %
i) Pd/C, H2, THF, rt
67 %
ii) p-TsOH, NaNO2,
KI, 0 °C
35 %
m-CPBA, TfOH
DCM, 0 °C
96 %
Pd2(dba)3/xantphos
Cs2CO3, toluene, 100 °C
49 %
KOt-Bu, DMSO, air
98%

Scheme 14

Kaman *et al.* [11f] started with 2-bromo-3-iodoquinoline which was synthesized from 3-bromoquinoline using a series of steps (Scheme 15). This synthetically obtained dihalo derivative was treated with aniline under regioselective Buchwald-Hartwig amination followed by second palladium catalyzed intramolecular Heck coupling to furnish quindoline.

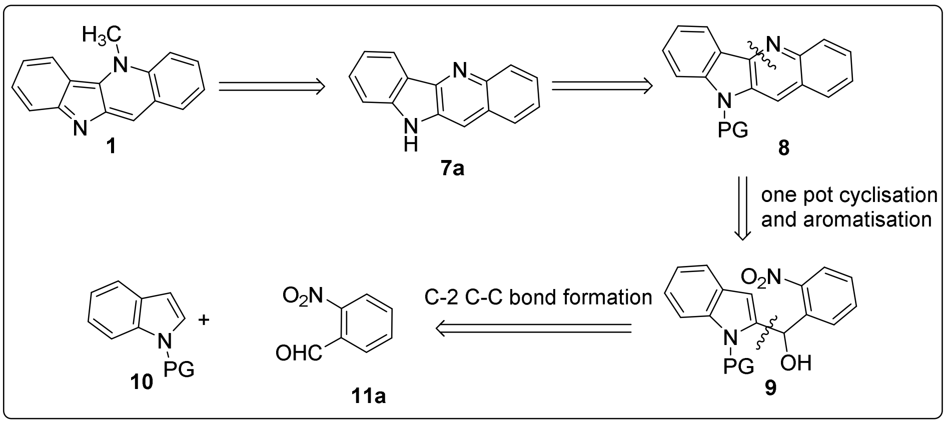


Pd(OAc)2, xantphos
Cs2CO3, toluene
120 °C, MW
70 %
PdCl2(PPh3)2, NaOAc
DMA, 150 °C, MW
61 %

Scheme 15

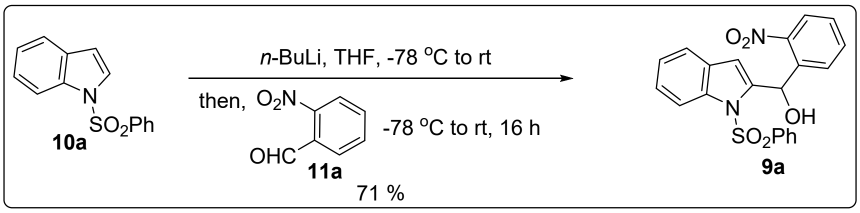
1.3: Results and discussion

Our retrosynthetic pathway to cryptolepine is depicted in scheme 16. It is known that, a regioselective methylation of quinoline nitrogen is possible from quindoline **7a** which in turn could be obtained from deprotection of its derivative **8**. We envisaged that **8** could be obtained in one step from **9** under reductive cyclization condition *via* nitrene followed by aromatization by loss of water. Compound **9** could be synthesized from corresponding *o*-nitrobenzaldehyde and *N*-protected indole.



Scheme 16

For the protection of the indole, sulfonyl group was chosen as it is known to be stable at elevated temperatures and also allows anion formation at the 2-position of indole. Thus, *N*-phenylsulfonyl indole **10a** was treated with *n*-butyl lithium at -78 °C and warmed to room temperature over 2 h (Scheme 17). [10a] The reaction mixture formed a wine-red coloration indicating anion formation, which was reacted with *o*-nitrobenzaldehyde **11a** at -78 °C to room temperature. The work-up and silica gel column purification yielded product **9a** in 71 % yield, which showed bands in its IR spectrum at 3541, 1526, 1363 and 1172 cm^{-1} accounting for –OH, NO_2 and SO_2 groups respectively. The structure of **9a** was further confirmed by spectral data.



Scheme 17

Spectral data of (2-nitrophenyl)(1-(phenylsulfonyl)-1*H*-indol-2-yl)methanol (9a):

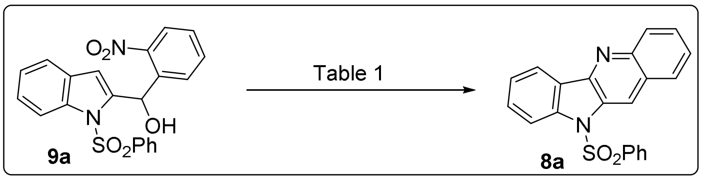
IR (KBr): $\tilde{\nu}$ = 3541, 3065, 1526, 1363, 1172, 723 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.107 (d, J = 8 Hz, 2 H), 8.06 (d, J = 8 Hz, 1 H), 7.97 (d, J = 7.6 Hz, 2 H), 7.78 (t, J = 7.2 Hz, 1 H), 7.62-7.55 (m, 2 H), 7.51 (t, J = 8 Hz, 2 H), 7.38-7.28 (m, 2 H), 7.22 (t, J = 7.6 Hz, 1 H), 7.05 (s, 1 H), 6.04 (s, 1 H), 3.98 (br s, 1 H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 147.4 (C), 142.4 (C), 138.2 (C), 137.1 (C), 136.2 (C), 134.2 (CH), 133.9 (CH), 129.6 (CH), 129.4 (2 × CH), 128.9 (CH), 128.6 (C), 126.8 (2 × CH), 125.3 (CH), 124.7 (CH), 123.9 (CH), 121.4 (CH), 114.5 (CH), 110.5 (CH), 65.1 (CH).

HRMS (ESI): calcd for $C_{21}H_{16}N_2O_5SNa$ [M + Na]$^+$ 431.0678, found 431.0680.

Having obtained the required intermediate **9a**, we then subjected it to our key step proposed in the strategy i.e. tandem reductive cyclization-dehydration reaction with PPh_3 in refluxing diphenyl ether (Table 1 entry 1). The reaction showed complete conversion in 3 h (monitored by TLC), which however on isolation gave only 34 % of cyclized tetracyle **8a** (Scheme 18). IR spectrum showed disappearance of –OH and NO_2 peaks as expected. Further confirmation of the structure was done by spectral study.



Scheme 18

Spectral data of 10-sulfonyl-indolo[3,2-*b*]quinoline (8a):

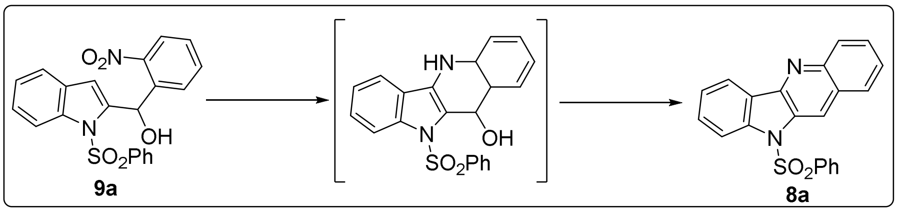
IR (KBr): $\tilde{\nu}$ = 3061, 1614, 1373, 1360, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (s, 1 H), 8.40-8.38 (m, 2 H), 8.27 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 7.79 (d, *J* = 8 Hz, 1 H), 7.72-7.63 (m, 2 H), 7.53-7.46 (m, 2 H), 7.35-7.31 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4 (C), 146.3 (C), 141.5 (C), 137.2 (C), 134.2 (CH), 131.1 (C), 130.9 (CH), 129.3 (2 × CH), 129.0 (CH), 128.9 (CH), 128.5 (CH), 127.1 (C), 126.6 (2 × CH), 126.4 (CH), 125.7 (C), 124.9 (CH), 122.0 (CH), 120.0 (CH), 115.2 (CH).

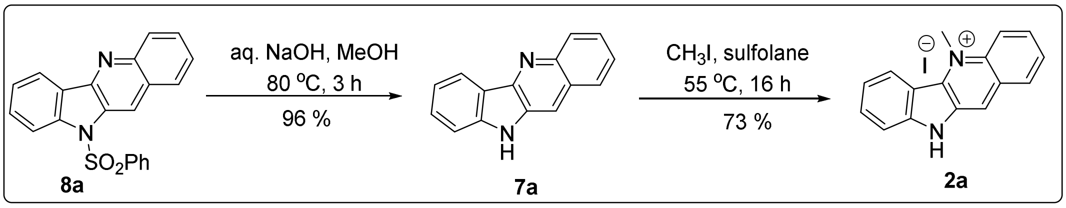
HRMS (ESI): calcd for $C_{21}H_{15}N_2O_2S$ $[M + H]^+$ 359.0854, found 359.0856.

During this step two reactions occurred in one pot, i.e. the cyclization *via* nitrene and dehydration to give **8a** from **9a**.



Scheme 19

Compound **8a** was desulfonated with aqueous sodium hydroxide to obtain quindoline **7a** in excellent yield and the structure was confirmed by comparison with literature reports (Scheme 20). [10d]



Scheme 20

^{1}H NMR of 10*H*-Indolo[3,2-*b*]quinoline (7a): [10d]

^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 11.45 (s, 1H), 8.36 (d, J = 8 Hz, 1H), 8.30 (s, 1 H), 8.19 (d, J = 8.4 Hz, 1 H), 8.12 (d, J = 8 Hz, 1 H), 7.66-7.54 (m, 4 H), 7.29 (t, J = 8 Hz, 1 H).

7a on treatment with methyl iodide gave a mixture of products. Next sulfolane was used as the solvent for regioselective methylation of quinoline nitrogen, during which cryptolepine hydroiodide **2a** was achieved in good 73 % yield (Scheme 20). [11a] The salt **2a** on basification is known to give **1**.

^{1}H NMR of Cryptolepine Hydroiodide (2a): [10d]

^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 12.92 (s, 1 H), 9.32 (s, 1 H), 8.84-8.77 (m, 1 H), 8.60 (d, J = 8 Hz, 1 H), 8.19 (t, J = 8 Hz, 1 H), 7.97 (t, J = 7.6 Hz, 2 H), 7.88 (d, J = 8.4 Hz, 1 H), 7.55 (t, J = 7.6 Hz, 1 H), 5.05 (s, 3 H).

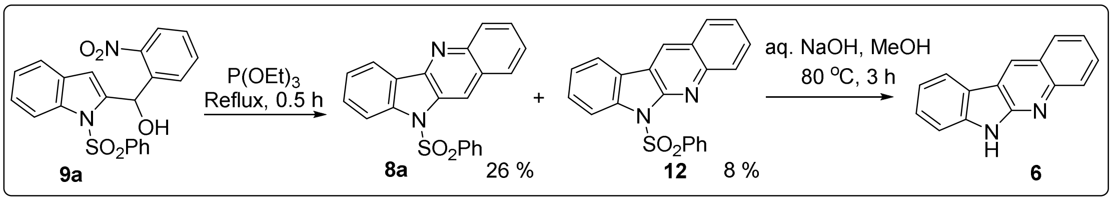
Although the strategy was successful in giving us our desired product **2a**, the yield of the key step was not satisfactory. Low yield of **8a** was attributed to the high temperature used in the domino step. We next focused our efforts on increasing the yield of this step. For this, we tried nitrene formation at lower temperature using $MoO_2Cl_2(dmf)_2$ as a catalyst [14] in refluxing toluene with PPh_3 (Table 1, entry 2).

Table 1: Optimisation of tandem reductive cyclisation.

Entry	Reaction Condition	% Isolated yield of **8a**
1	PPh_3, diphenyl ether, 250-260 °C, N_2, 3 h	34
2	PPh_3, $MoO_2Cl_2(dmf)_2$, toluene, 110 °C, N_2, 16 h	35
3	PBu_3, diphenyl ether, 120 °C, N_2, 3 h	27
4	$P(OEt)_3$, 150-160 °C, N_2, 0.5 h	26

The reaction was found to be slow and took 16 h to complete. However, the product **8a** was obtained only with marginal improvement in the yield. Using more reactive phosphorous reagent like tributyl phosphine gave only 27 % of **8a** as the sole product at a lower temperature as compared to triphenyl phosphine (Table 1, entry 3).

Treatment of **9a** with triethyl phosphite, following the Cadogan's [15] procedures, showed complete conversion in just 0.5 h. However, a formation of another product **12** with the same mass as **8a** in 8 % yield was observed along with the expected **8a** in 26 % yield (Scheme 21). Based on IR and NMR spectra compound **12** was identified to be a regioisomer of **8a** formed due to the high reactivity of $P(OEt)_3$.



Scheme 21

The ^{1}H NMR spectrum of **8a** showed a singlet at 9.0 ppm whereas in **12** singlet appeared at 8.61 ppm. This downfield shift was attributed to the presence of electron withdrawing SO_2Ph group in close vicinity of C-11 proton in case of **8a**.

Spectral data of 10-sulfonyl-indolo[2,3-*b*]quinoline (12):

IR (KBr): $\tilde{\nu}$ = 2964, 1601, 1261, 1174, 768 cm^{-1}.

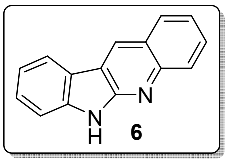
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1 H), 8.53 (d, *J* = 8.4 Hz, 1 H), 8.31-8.26 (m, 3 H), 8.05 (d, *J* = 7.2 Hz, 1 H), 7.97 (d, *J* = 7.2 Hz, 1 H), 7.97 (d, *J* = 7.2 Hz, 1 H), 7.77-7.75 (m, 1 H), 7.65-7.42 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9 (C), 145.4 (C), 138.4 (C), 137.6 (C), 132.9 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.7 (2 × CH), 127.0 (2 × CH), 126.4 (CH), 124.6 (C), 124.3 (CH), 122.9 (CH), 121.8 (C), 120.1 (CH), 118.1 (C), 114.1 (CH).

HRMS (ESI): calcd for $C_{21}H_{14}N_2O_2SNa$ $[M + Na]^+$ 381.0674, found 381.0672.

Compound **12** was further confirmed to be a regioisomer by desulfonation with alkali hydroxide to fetch 6*H*-indolo[2,3-*b*]quinoline **6**, whose spectral data matched with data reported in literature. [16a-g] The resulting compound **6** is a naturally occurring alkaloid isolated from *Justicia betonica* [16h] and also the immediate precursor of naturally occurring neocryptolepine (cryptotackieine) **3**. Regioisomers **7a** and **6** could be differentiated based on PMR spectrum in which the singlet signal of C-11 proton appeared at 8.30 ppm in case of **7a,** whereas singlet of C-5 proton appeared at 9.06 ppm in case of **6** in deuterated DMSO solvent.

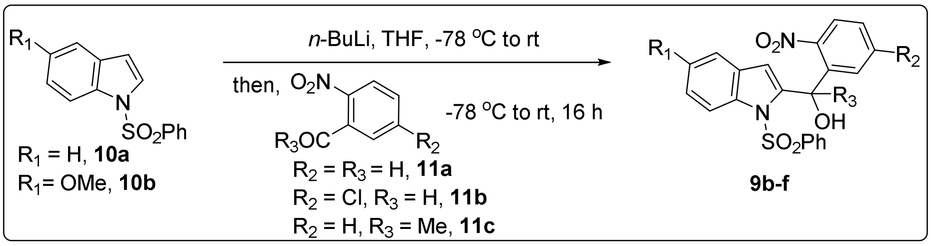
^{1}H NMR of 10*H*-Indolo[2,3-*b*]quinoline (6): [16a-g]

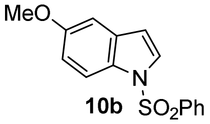
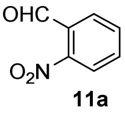
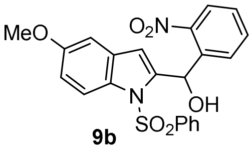
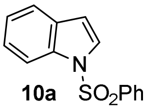
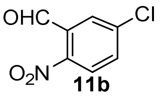
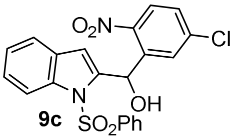
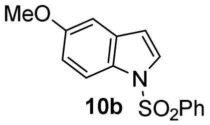
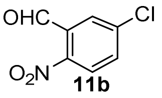
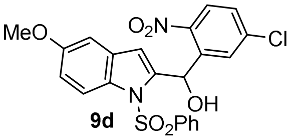

6

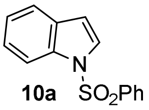
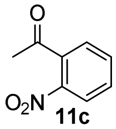
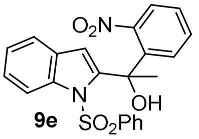
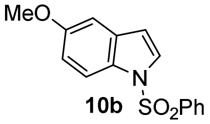
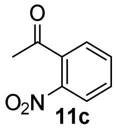
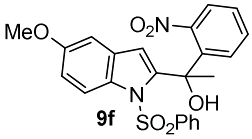
^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 11.71 (s, 1 H), 9.06 (s, 1 H), 8.26 (d, *J* = 7.6 Hz, 1 H), 8.11 (d, *J* = 7.6 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.72 (dt, *J* = 8.4 Hz, 1.2 Hz, 1 H), 7.58-7.46 (m, 3 H), 7.28 (dt, *J* = 8.4 Hz, 1.2 Hz, 1 H).

It is known in the literature [9b-d, 10b] that the presence of substituents like methoxy, halogen or alkyl group on cryptolepine molecule enhances biopotency remarkably. Having successfully synthesized the cryptolepine salt, we thought of applying the same stratergy for the synthesis of various derivatives of this compound. For this purpose, 1-phenylsulfonyl-1*H*-indole **10a** and 5-methoxy-1-(phenylsulfonyl)-1*H*-indole **10b** were subjected to directed metallation and treated with *o*-nitro carbonyl benzenes like 2-nitrobenzaldehyde **11a**, 5-chloro-2-nitrobenzaldehyde **11b** and 2-nitroacetophenone **11c** to give the products **9b-f** in good yields (Table 2).

Table 2: Substrate study for C-2 lithiation.


R1
N
SO2Ph
R1 = H, 10a
R1= OMe, 10b
n-BuLi, THF, -78 °C to rt
then, O2N
R3OC
R2
-78 °C to rt, 16 h
R2 = R3 = H, 11a
R2 = Cl, R3 = H, 11b
R2 = H, R3 = Me, 11c
R1
O2N
R2
R3
OH
N
SO2Ph
9b-f

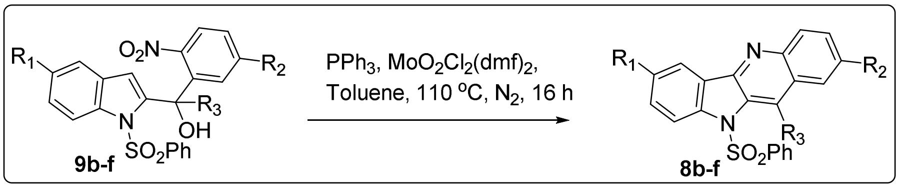
Entry	*N*-phenylsulfonyl indole **10a-b**	2-nitrocarbonyls **11a-c**	Product **9b-f**	% yield **9b-f** ^{a}
1	 **10b**	 **11a**	 **9b**	78
2	 **10a**	 **11b**	 **9c**	68
3	 **10b**	 **11b**	 **9d**	71

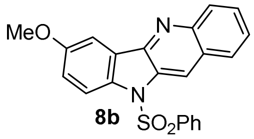
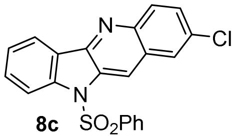
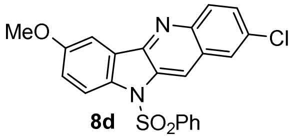
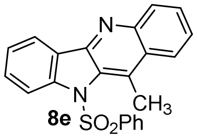
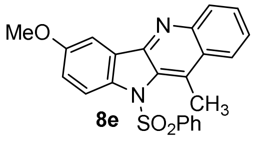
4	 **10a**	 **11c**	 **9e**	71
5	 **10b**	 **11c**	 **9f**	76

[a] isolated yield after column purification based on recovered **10a** and **10b**.

Once all the intermediates **9b-f** were obtained, we subjected them to reductive cyclization using Sanz *et al.*'s method [PPh_3, $MoO_2Cl_2(dmf)_2$] (Table 3).

Table 3: One pot reductive cyclisation-aromatisation of **9b-f** to **8b-f**.

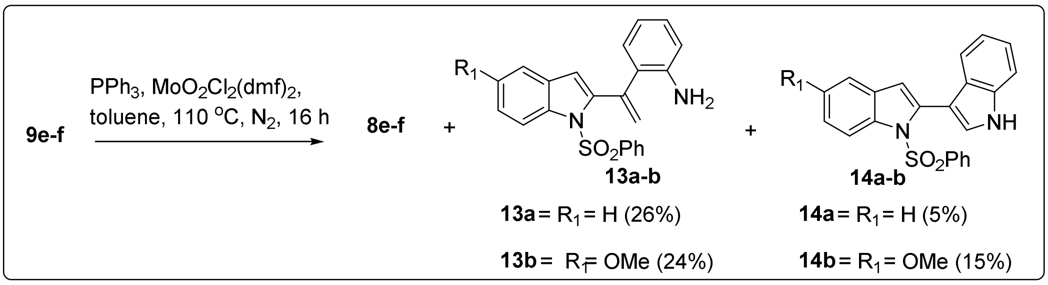


Entry	Starting Material **9b-f**	Product **8b-f**	% yield of **8b-f** [a]
1	**9b**	 **8b**	39
2	**9c**	 **8c**	38
3	**9d**	 **8d**	37
4	**9e**	 **8e**	20 [b]
5	**9f**	 **8e**	20 [b]

[a] isolated yield after column purification.

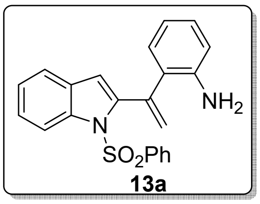
[b] compound **13** and **14** were obtained under reaction condition along with **8e** and **8f**.

It was interesting to discover that **9e** and **9f** which have a presence of tertiary alcohol, under the reaction condition undergo dehydration before cyclization giving amine **13a**/**14a** and **13b**/**14b** as side products respectively (Scheme 22). The IR spectrum of compound **13a** showed two peaks at 3424 and 3348 cm^{-1} indicating the presence of a primary amine group. Compound **14a** showed a broad peak at 3410 cm^{-1} indicating the presence of the secondary amine group. These compounds were further confirmed based on their spectral data.



Scheme 22

Spectral data of 2-{1-[1-(phenylsulfonyl)-1*H*-indol-2-yl]ethenyl}aniline (13a):



13a

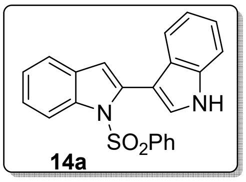
IR (KBr): $\tilde{\nu}$ = 3424, 3348, 2926, 1446, 1171, 722 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.03 (d, J = 8.4 Hz, 1 H), 7.50 (dd, J = 8 Hz, 1.2 Hz, 3 H), 7.45-7.41 (m, 1 H), 7.33-7.23 (m, 3 H), 7.07 (dt, J = 8 Hz, 1.2 Hz, 1 H), 6.76-6.73 (m, 4 H), 6.54 (dt, J = 7.6 Hz, 1.2 Hz, 1 H), 5.82 (m, 2 H), 4.18 (br s, 2 H).

^{13}C NMR (100 MHz, CDCl$_3$): δ144.7 (C), 142.3 (C), 139.3 (C), 138.2 (C), 137.5 (C), 133.4 (CH), 129.7 (C), 129.6 (CH), 128.8 (2 × CH), 128.7 (CH), 126.6 (2 × CH), 125.7 (C), 124.9 (CH), 123.9 (CH), 121.0 (CH), 120.1 (CH$_2$), 118.1 (CH), 116.6 (CH), 115.3 (CH), 113.7 (CH).

HRMS (ESI): calcd for $C_{22}H_{19}N_2O_2S$ [M + H]$^+$ 375.1167, found 375.1169.

Spectral data of 1-(phenylsulfonyl)-1*H*,1'*H*-2,3'-biindole (14a):



14a

IR (KBr): $\tilde{\nu}$ = 3410, 3061, 1447, 1175, 746, 684 cm^{-1}.

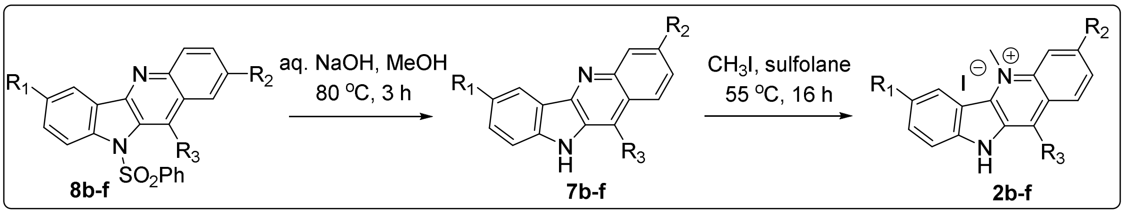
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.49 (br s, 1 H), 8.36 (d, J = 8 Hz, 1 H), 7.52 (d, J = 2.4 Hz, 1 H), 7.47-7.41 (m, 4 H), 7.37-7.21 (m, 5 H), 7.11-6.68 (m, 3 H), 6.68 (s, 1 H).

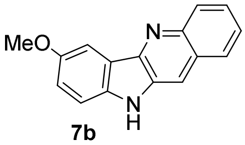
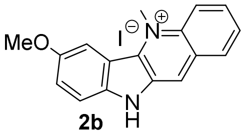
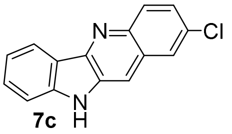
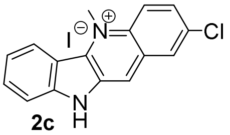
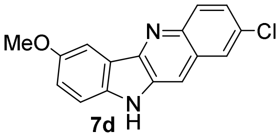
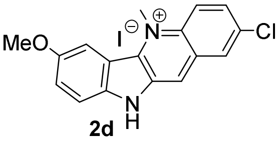
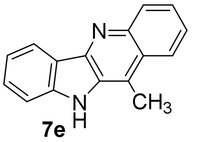
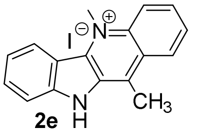
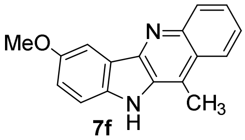
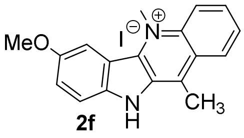
^{13}C NMR (100 MHz, CDCl$_3$): δ 138.0 (C), 137.5 (C), 135.3 (C), 135.1 (C), 133.2 (CH), 130.9 (C), 128.4 (2 × CH), 127.5 (C), 127.1 (CH), 126.7 (2 × CH), 124.3 (CH), 124.2 (CH), 122.5 (CH), 120.6 (CH), 120.3 (CH), 119.4 (CH), 116.6 (CH), 112.6 (CH), 111.3 (CH), 107.3 (C).

HRMS (ESI): calcd for $C_{22}H_{16}N_2O_2SNa$ $[M + Na]^+$ 395.0830, found 395.0829.

Compound **8b-f** were then hydrolyzed with sodium hydroxide to corresponding quindolines **7b-f** which were further regioselectively methylated to 7-methoxycryptolepine hydroiodide **2b**, 2-chlorocryptolepine hydroiodide **2c**, 2-chloro-7-methoxycryptolepine hydroiodide **2d**, 11-methylcryptolepine hydroiodide **2e** and 11-methyl-7-methoxycryptolepine hydroiodide **2f** in good yields.

Table 4: Deprotection **8b-f** and regioselective methylation of **7b-f**.

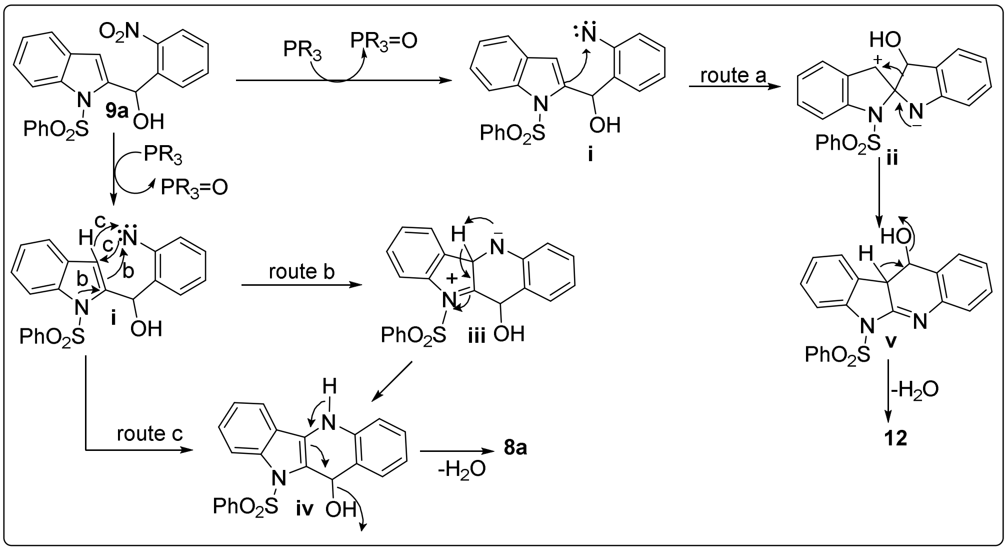


Entry	Starting material	Desulphonated product **7b-f**	% yield of **7b-f** [a]	Hydroiodide salt **2b-f**	% yield of **2b-f** [a]
1	**8b**	 **7b**	96	 **2b**	73
2	**8c**	 **7c**	96	 **2c**	72
3	**8d**	 **7d**	97	 **2d**	74
4	**8e**	 **7e**	95	 **2e**	73
5	**8f**	 **7f**	98	 **2f**	74

[a] isolated yields

Based on the products obtained during the reductive cyclization, the probable route for the formation of **8a** and **12** are proposed (Scheme 23). The nitrene intermediate **i** formed during the reaction may undergo electrophilic substitution [15b,15e] at C-2 position (route a) in case of

$P(OEt)_3$ or at C-3 position (route b) of indole nucleus or may directly undergo C-H insertion [14] (route c) at C-3 to form intermediates **ii**, **iii**, and **iv** respectively. The five–membered spiro intermediate **ii** [15d] then rearranges to form **v**, which on elimination of water molecule leads to *N*-benznesulfonyl-6*H*-indolo[2,3-*b*]quinoline **12**. The intermediate **iii** then gets transformed to **iv** which on dehydration gives *N*-benzenesulfonyl-6*H*-indolo[3,2-*b*]quinoline **8a**.



Scheme 23

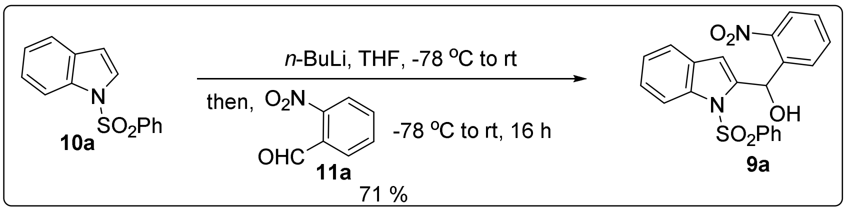
1.4: Conclusion

A useful four step synthesis of cryptolepine hydroiodides is developed using *o*-nitro carbonyl benzenes and *N*-phenyl-sulfonyl indoles. The strategy involves deprotonation of indole derivatives at 2-position and tandem reductive cyclisation dehydration as key steps.

Various derivatives of indoloquinolines are prepared containing substituents like methoxy, chloro and methyl on indole as well as quinoline ring, thus showing the versatility of the protocol which can be applied further for synthesis of various other analogues.

1.5: Experimental

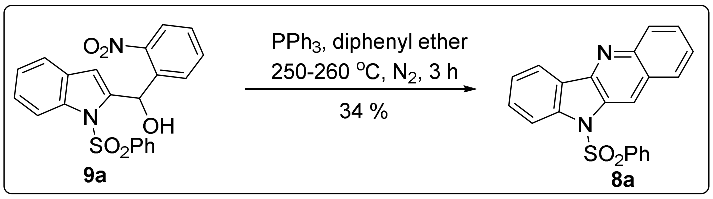
1.5.1: (2-Nitrophenyl)(1-(phenylsulfonyl)-1*H*-indol-2-yl)methanol (9a)



To a magnetically stirred solution of 1-(phenylsulfonyl)-1*H*-indole **10a** (0.898 g, 3.49 mmol) in dry THF (12 mL), under N_2 atmosphere at -78 ^oC was added *n*-BuLi (1.6M in hexane) (2.63 mL, 4.19 mmol) drop wise over a period of 5 min and stirred at this temperature for 30 min. The solution was allowed to warm to room temperature and further stirred for 2 h. The resulting wine red solution was again cooled to -78 ^oC and then a solution of 2-nitro benzaldehyde **11a** (0.580 g, 3.84 mmol) in dry THF (4 mL) was added drop wise over a period of 5 min. The resulting mixture was allowed to warm to room temperature and stirred overnight. The mixture was then poured over 5% NH_4Cl (20 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with water (20 mL), $NaHCO_3$ (20 mL), brine (2 × 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue obtained was flash chromatographed and the unreacted *N*-phenylsulfonyl indole **10a** (0.225 g) was removed using 5 % ethyl acetate in petroleum ether as an eluent. Further elution with 30 % ethyl acetate in petroleum ether afforded **9a** in 71 % (0.759 g) yield (based on recovery of **10a**).

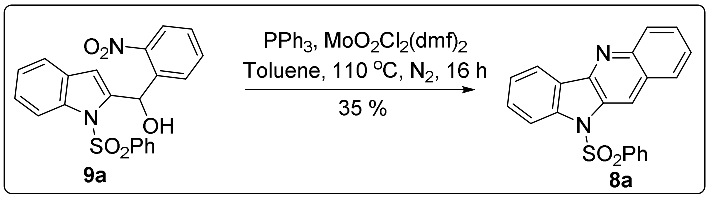
Light yellow solid, m.p. 174-176 ^oC.

1.5.2: 10-Sulfonyl-indolo[3,2-*b*]quinoline (8a)



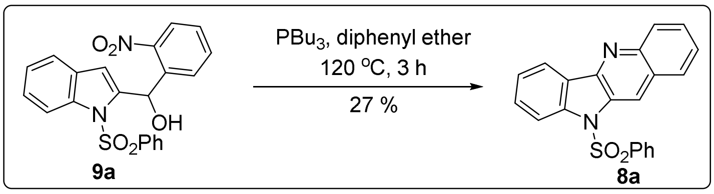
Method A: (2-Nitrophenyl)[1-(phenylsulfonyl)-1*H*-indol-2-yl]methanol **9a** (1.401 g, 3.43 mmol) and triphenyl phosphine (2.968 g, 11.32 mmol) were refluxed in diphenyl ether (18 mL) under N_2 atmosphere for 3 h (monitored by TLC). After cooling, the reaction mixture was chromatographed on silica gel and diphenyl ether was removed using petroleum ether as an eluent. Further elution with 10% ethyl acetate in petroleum ether afforded the 10-phenylsulfonyl-indolo[3,2-*b*]quinoline **8a** in 34 % (0.418 g) yield.
Light yellow solid, m.p. 166-168 ^oC.

1.5.3: 10-Sulfonyl-indolo[3,2-*b*]quinoline (8a)



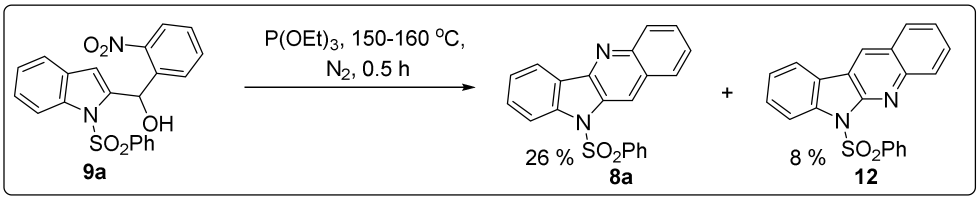
Method B: To a solution of (2-nitrophenyl)[1-(phenylsulfonyl)-1*H*-indol-2-yl]methanol **9a** (0.310 g, 0.76 mmol) and triphenyl phosphine (0.637 g, 2.43 mmol) in toluene (15 mL) was added $MoO_2Cl_2(dmf)_2$ (0.024 g, 0.07mmol) and stirred at 110 °C under N_2 atmosphere for 16 h (monitored by TLC). After cooling, the solvent was removed under reduced pressure and the residue was purified by flash chromatography using petroleum ether as an eluent to remove excess triphenyl phosphine. Further elution with 10% ethyl acetate in petroleum ether afforded the 10-phenylsulfonyl indolo[3,2-*b*]quinoline **8a** in 35 % (0.095 g) yield.

1.5.4: 10-Sulfonyl-indolo[3,2-*b*]quinoline (8a)



Method C: A mixture of (2-nitrophenyl)[1-(phenylsulfonyl)-1*H*-indol-2-yl]methanol **9a** (0.139 g, 0.34 mmol) and tributyl phosphine (0.303 g, 1.5 mmol) was heated at 120 °C in diphenyl ether (8 mL) under N_2 atmosphere for 3 h (monitored by TLC). After cooling, the reaction mixture was chromatographed on silica gel and diphenyl ether was removed using petroleum ether as an eluent. Further elution with 10% ethyl acetate in petroleum ether afforded the 10-sulfonyl-indolo[3,2-*b*]quinoline **8a** in 27 % (0.033 g) yield.

1.5.5: 10-Sulfonyl-indolo[3,2-*b*]quinoline (8a)

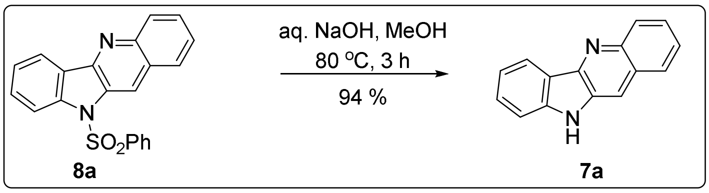


Method D: A solution of (2-nitrophenyl)[1-(phenylsulfonyl)-1*H*-indol-2-yl]methanol **9a** (0.850 g, 2.08 mmol) and triethyl phosphite (15 mL) was heated at 150-160 °C under N_2 atmosphere for 0.5 h (monitored by TLC). Excess of triethyl phosphite was removed under reduced pressure and the residue was purified by flash chromatography using 10% ethyl acetate in petroleum ether to give the 10-phenylsulfonyl indolo[3,2-*b*]quinolines **8a** in 26 % (0.194 g) yield and 10-phenylsulfonyl indolo[2,3-*b*]quinoline **12** in 8 % (0.06 g) yield.

10-Sulfonyl-indolo[2,3-*b*]quinoline (12)

Light yellow solid, m.p. 222-224 °C.

1.5.6: 10*H*-Indolo[3,2-*b*]quinoline (7a)

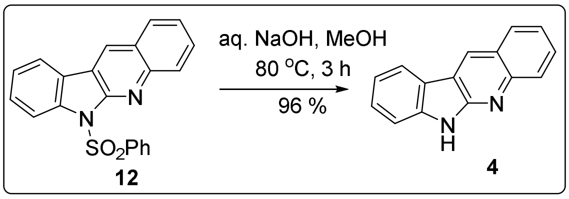


NaOH (2.0M, 10 mL) was added to a stirring solution of 10-phenylsulfonyl indolo[3,2-*b*]quinolines **8a** (0.197 g, 0.55 mmol) in methanol (10 mL). The reaction mixture was refluxed for 3 h (monitored by TLC). Methanol was removed under reduced pressure and the product was extracted using chloroform (3 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give **7a** in 94 % (0.113 g) yield

Yellow solid, m.p. 250-252 °C [lit.[10d] m.p. 252-253 °C].

IR (KBr): $\tilde{\nu}$ = 3161, 3057, 1490, 1338, 737 cm^{-1}.

1.5.7: 10*H*-Indolo[2,3-*b*]quinoline (4)

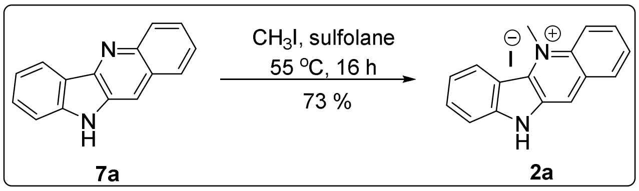


Following the similar protocol described in section 1.5.6 with 10-sulfonyl-indolo[2,3-*b*]quinoline **12** (0.034 g, 0.09 mmol) gave the product 10*H*-Indolo[2,3-*b*]quinoline **6** in 96 % (0.02 g) yield.

Yellow solid, m.p. > 300 °C (lit. [17d] m.p. 342-346 °C).

IR (KBr): $\tilde{\nu}$ = 3160, 3052, 1493, 1338, 736 cm^{-1}.

1.5.8: 5-Methyl-10*H*-indolo[3,2-*b*]quinolin-5-ium iodide or Cryptolepine Hydroiodide (2a)

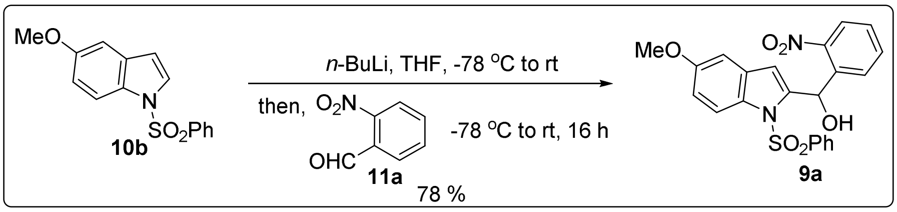


10*H*-Indolo[3,2-*b*]quinoline **7a** (0.039 g, 0.18 mmol), methyl iodide (1 mL) and sulfolane [11a] (2 mL) were taken in a sealed tube and heated at 55 °C for 16 h *i.e.* till the precipitate was formed. The mixture was cooled to room temperature and precipitated further with 1:1 petroleum ether: ethyl acetate, filtered and washed with ethyl acetate and then dried to afford **2a** in 72 % (0.047 g) yield.

Bright yellow solid, m.p. 272-274 °C (lit. [10d] m.p. 273-274 °C).

IR (KBr): $\tilde{\nu}$ = 3080, 1643, 1615, 1256, 758 cm^{-1}.

1.5.9:[5-Methoxy-1-(phenylsulfonyl)-1*H*-indol-2-yl](2-nitrophenyl)methanol (9b)


MeO
N
SO2Ph
10b
n-BuLi, THF, -78 °C to rt
then, O2N
OHC
11a
-78 °C to rt, 16 h
78 %
MeO
O2N
N
OH
SO2Ph
9a

Following the similar protocol described in section 1.5.1 with 5-methoxy-1-(phenylsulfonyl)-1*H*-indole **10b** (0.717 g, 2.5 mmol), *n*-BuLi (1.9 mL, 3.0 mmol) and 2-nitrobenzaldehyde **11a** (0.415 g, 2.75 mmol) gave the product [5-Methoxy-1-(phenylsulfonyl)-1*H*-indol-2-yl](2-nitrophenyl)methanol **9b** in 78 % (0.806 g) yield (0.041 g of **10b** was recovered).

Yellow solid, m.p. 142-144 °C.

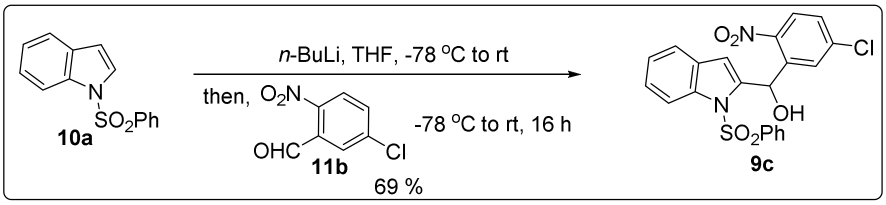
IR (KBr): $\tilde{\nu}$ = 3534, 2934, 1612, 1526, 1366, 1344, 1176, 723 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.09 (d, J = 7.6 Hz, 1 H), 8.04-7.93 (m, 2 H), 7.23 (d, J = 7.2 Hz, 2 H), 7.56 (m, 1 H), 7.60-7.50 (m, 4 H), 6.99 (s, 1 H), 6.93 (d, J = 8.8 Hz, 1 H), 6.81 (s, 1 H), 5.97 (s, 1 H), 4.12 (br s, 1 H), 3.76 (s, 3 H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 156.7 (C), 147.5 (C), 142.9 (C), 138.1(C), 136.1(C), 134.2 (CH), 133.9 (CH), 131.7 (C), 129.6 (CH), 129.5 (CH), 129.4 (2 × CH), 128.9 (CH), 126.7 (2 × CH), 124.7 (CH), 115.4 (CH), 114.2 (CH), 110.7 (CH), 103.6 (CH), 65.2 (CH), 55.6 (CH_3).

HRMS (ESI): calcd for $C_{22}H_{18}N_2O_6SNa$ $[M + Na]^+$ 461.0783, found 461.0782.

1.5.10: (5-Chloro-2-nitrophenyl)[1-(phenylsulfonyl)-1*H*-indol-2-yl]methanol (9c)

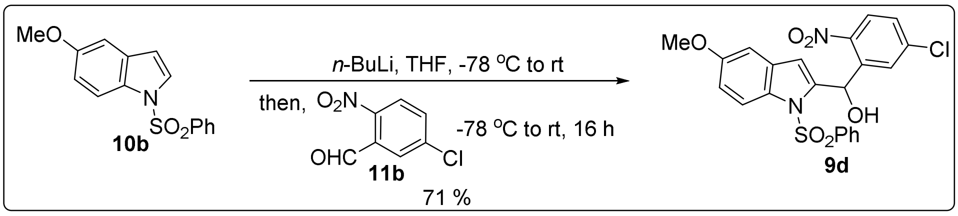

N
SO2Ph
10a
n-BuLi, THF, -78 °C to rt
then, O2N
OHC
Cl
11b
-78 °C to rt, 16 h
69 %
O2N
Cl
N
OH
SO2Ph
9c

Following the similar protocol described in section 1.5.1 with 1-(phenylsulfonyl)-1*H*-indole **10a** (0.514 g, 2.0 mmol), *n*-BuLi (1.51 mL, 2.4 mmol) and 5-chloro-2-nitrobenzaldehyde

11b (0.408 g, 2.2 mmol) gave the product (5-chloro-2-nitrophenyl)[1-(phenylsulfonyl)-1*H*-indol-2-yl]methanol **9c** in 69 % (0.585 g) yield (0.021 g of **10a** was recovered).
Light yellow solid, m.p. 169-170 °C.

IR (KBr): $\tilde{\nu}$ = 3586, 3111, 1607, 1521, 1358, 1145, 744 cm^{-1}.
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.09- 8.05 (m, 3 H), 7.95 (d, J = 7.6 Hz, 2 H), 7.59 (t, J = 7.6 Hz, 1 H), 7.53-7.47 (m, 3 H), 7.37-7.29 (m, 2 H), 7.20 (t, J = 7.6 Hz, 1 H), 7.04 (d, J = 4.4 Hz, 1 H), 6.00 (s, 1 H), 4.14 (d, J = 4.4 Hz, 1 H).
^{13}C NMR (100 MHz, CDCl$_3$): δ 145.5 (C), 141.8 (C), 140.8 (C), 138.3 (C), 138.1 (C), 137.0 (C), 134.3 (CH), 129.8 (CH), 129.5 (2 × CH), 129.1 (CH), 128.4 (C), 126.8 (2 × CH), 126.4 (CH), 125.5 (CH), 124.0 (CH), 121.4 (CH), 114.5 (CH), 110.3 (CH), 64.9 (CH).
HRMS (ESI): calcd for $C_{21}H_{15}ClN_2O_5SNa$ [M + Na]$^+$ 465.0288, found 465.0283.

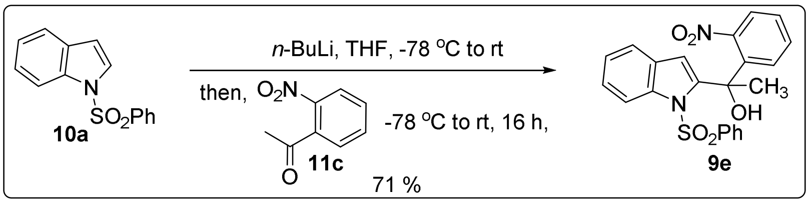
1.5.11: (5-Chloro-2-nitrophenyl)[5-methoxy-1-(phenylsulfonyl)-1*H*-indol-2-yl]methanol (9d)



Following the similar protocol described in section 1.5.1 with 5-methoxy-1-(phenylsulfonyl)-1*H*-indole **10b** (0.430 g, 1.5 mmol), *n*-BuLi (1.13 mL, 1.8 mmol) and 5-chloro-2-nitrobenzaldehyde **11b** (0.306 g, 1.65 mmol) gave the product (5-chloro-2-nitrophenyl)[5-methoxy-1-(phenylsulfonyl)-1*H*-indol-2-yl]methanol **9d** in 71 % (0.432 g) yield (0.060 g of **10b** was recovered).
Yellow solid, m.p. 136-138 °C.

IR (KBr): $\tilde{\nu}$ = 3547, 3103, 1525, 1340, 1157, 721 cm^{-1}.
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.00-7.97 (m, 2 H), 7.90 (d, J = 9.2 Hz, 1 H), 7.85-7.83 (m, 2 H), 7.53 (t, J = 7.6 Hz, 1 H), 7.46-7.40 (m, 3 H), 6.92 (s, 1 H), 6.85 (dd, J = 9.2 Hz, 2.4 Hz, 1 H), 6.73 (d, J = 2.4 Hz, 1 H), 5.87 (s, 1 H), 3.69 (s, 3 H).
^{13}C NMR (100 MHz, CDCl$_3$): δ 156.7 (C), 145.5 (C), 142.3 (C), 140.8 (C), 138.2 (C), 138.1 (C), 134.3 (CH), 131.6 (C), 129.8 (CH), 129.4 (2 × CH), 129.1 (CH), 126.7 (2 × CH), 126.3 (CH), 115.4 (CH), 114.4 (CH), 110.5 (CH), 103.6 (CH), 64.9 (CH), 55.6 (CH$_3$).
HRMS (ESI): calcd for $C_{22}H_{17}ClN_2O_6SNa$ [M + Na]$^+$ 495.0394, found 495.0393

1.5.12: 1-(2-Nitrophenyl)-1-[1-(phenylsulfonyl)-1*H*-indol-2-yl]ethanol (9e)



Following the similar protocol described in section 1.5.1 with 1-(phenylsulfonyl)-1*H*-indole **10a** (0.385 g, 1.5 mmol), *n*-BuLi (1.13 mL, 1.8 mmol) and 2-nitro acetophenone (1-(2-nitrophenyl)ethan-1-one) **11b** (0.272 g, 1.65 mmol) gave the product (1-(2-nitrophenyl)-1-[1-(phenylsulfonyl)-1*H*-indol-2-yl]ethanol **9e** in 71 % (0.396 g) yield (0.046 g of **10a** was recovered).

White solid, m.p. 158-160 °C.

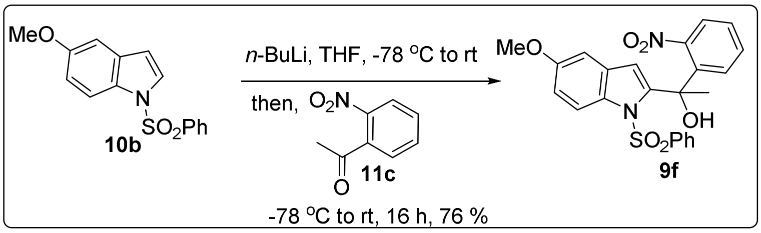
IR (KBr): $\tilde{\nu}$ = 3497, 2993, 1537, 1364, 1346, 1219, 723 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.94 (d, J = 8 Hz, 1 H), 7.58-7.53 (m, 3 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.44-7.21 (m, 7 H), 7.15 (s, 1 H), 6.90 (s, 1 H), 5.46 (s, 1 H), 2.21 (s, 3 H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 148.2 (C), 143.0 (C), 137.3 (C), 137.1 (C), 136.6 (C), 132.8 (CH), 129.3 (CH), 128.1 (2 × CH), 127.3 (CH), 127.1 (C), 126.8 (CH), 125.3 (2 × CH), 124.8 (CH), 123.2 (CH), 122.4 (CH), 120.6 (CH), 114.0 (CH), 112.8 (CH), 72.9 (C), 30.4 (CH$_3$).

HRMS (ESI): calcd for $C_{22}H_{18}N_2O_5SNa$ $[M + Na]^+$ 445.0834, found 445.0836.

1.5.13: [5-Methoxy-1-(phenylsulfonyl)-1*H*-indol-2-yl](2-nitrophenyl)ethanol (9f)



Following the similar protocol described in section 1.5.1 with 5-methoxy-1-(phenylsulfonyl)-1*H*-indole **10b** (0.433 g, 1.5 mmol), *n*-BuLi (1.13 mL, 1.8 mmol) and 2-nitro acetophenone (1-(2-nitrophenyl)ethan-1-one) **11b** (0.272 g, 1.65 mmol) gave the product [5-methoxy-1-(phenylsulfonyl)-1*H*-indol-2-yl](2-nitrophenyl)ethanol **9f** in 76 % (0.485 g) yield (0.025 g of **10b** was recovered).

White solid, m.p. 184-186 °C.

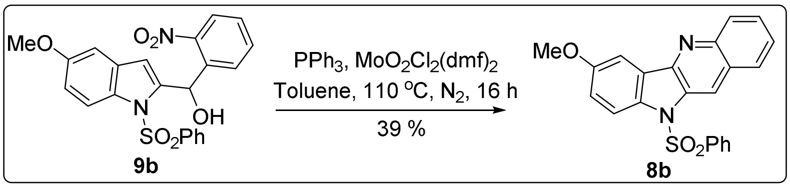
IR (KBr): $\tilde{\nu}$ = 3476, 2988, 1537, 1369, 780 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.77 (d, J = 9.2 Hz, 1 H), 7.46 (d, J = 7.2 Hz, 2 H), 7.38 (t, J = 7.2 Hz, 1 H), 7.33-7.18 (m, 5 H), 7.10 (s, 1 H), 6.88-6.74 (m, 3 H), 5.40 (s, 1 H), 3.73 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 156.8 (C), 149.3 (C), 144.7 (C), 138.4 (C), 138.1 (C), 133.8 (CH), 132.2 (C), 130.4 (CH), 129.2 (C), 129.1 (2 × CH), 128.4 (CH), 127.9 (CH), 126.3 (2 × CH), 123.5 (CH), 116.1 (CH), 114.8 (CH), 114.2 (CH), 103.7 (CH), 73.9 (C), 55.6 (CH$_3$), 31.4 (CH$_3$).

HRMS (ESI): calcd for $C_{23}H_{20}N_2O_6SNa$ $[M + Na]^+$ 475.0940, found 475.0937.

1.5.14: 7 Methoxy-10-phenylsulfonyl-indolo[3,2-*b*]quinoline (8b)


MeO
O$_2$N
N
SO$_2$Ph
OH
9b
PPh$_3$, MoO$_2$Cl$_2$(dmf)$_2$
Toluene, 110 °C, N$_2$, 16 h
39 %
MeO
N
N
SO$_2$Ph
8b

Method B: Following the similar protocol described in section 1.5.3 with [5-methoxy-1-(phenylsulfonyl)-1*H*-indol-2-yl](2-nitrophenyl)methanol **9b** (0.423 g, 0.966 mmol), PPh$_3$ (0.820 g, 3.09 mmol), MoO$_2$Cl$_2$(dmf)$_2$ (0.033 g, 0.096 mmol) gave the product 7 methoxy-10-phenylsulfonyl-indolo[3,2-*b*]quinoline **8b** 39 % (0.150 g) yield.

Light yellow solid, m.p. 180-182 °C.

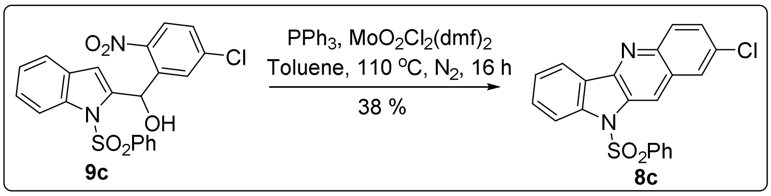
IR (KBr): $\tilde{\nu}$ = 2960, 1614, 1180, 1026, 732 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.91 (s, 1 H), 8.19 (d, J = 8.8 Hz, 2 H), 7.99 (d, J = 8.4 Hz, 1 H), 7.81 (s, 1 H), 7.72-7.68 (m, 3 H), 7.56 (t, J = 7.6 Hz, 1 H), 7.37 (t, J = 7.6 Hz, 1 H), 7.23-7.18 (m, 3 H), 3.88 (s, 3 H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 157.6 (C), 145.9 (C), 144.3 (C), 135.8 (C), 134.8 (C), 133.2 (CH), 130.1 (C), 128.3 (CH), 128.2 (2 × CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 126.0 (C), 125.5 (2 × CH), 120.2 (CH), 119.5 (CH), 115.5 (CH), 103.0 (CH), 55.0 (CH$_3$).

HRMS (ESI): calcd for $C_{22}H_{17}N_2O_3S$ $[M + H]^+$ 389.0960, found 389.0961.

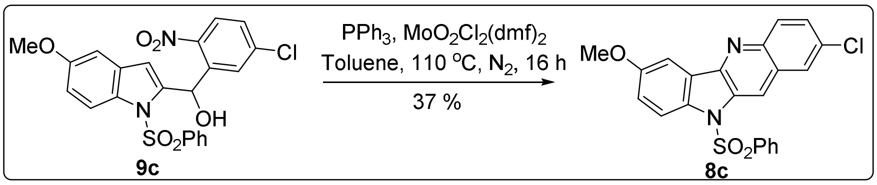
1.5.15: 2-Chloro-10-phenylsulfonyl-indolo[3,2-*b*]quinoline (8c)


O$_2$N
Cl
N
SO$_2$Ph
OH
9c
PPh$_3$, MoO$_2$Cl$_2$(dmf)$_2$
Toluene, 110 °C, N$_2$, 16 h
38 %
N
Cl
N
SO$_2$Ph
8c

Method B: Following the similar protocol described in section 1.5.3 with (5-chloro-2-nitrophenyl)[1-(phenylsulfonyl)-1*H*-indol-2-yl]methanol **9c** (0.434 g, 0.980 mmol), PPh_3 (0.822 g, 3.136 mmol), $MoO_2Cl_2(dmf)_2$ (0.034 g, 0.098 mmol) gave the product 2-Chloro-10-phenylsulfonyl-indolo[3,2-*b*]quinoline **8c** in 38 % (0.146 g) yield.
Light yellow solid, m.p. 222-224 °C.

IR (KBr): $\tilde{\nu}$ = 3063, 1624, 1182, 743 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (s, 1 H), 8.40 (s, 1 H), 8.30 (d, *J* = 8.4 Hz, 1 H), 8.18 (s, 1 H), 7.99 (d, *J* = 1.6 Hz, 1 H), 7.76 (d, *J* = 7.6 Hz, 2 H), 7.67-7.62 (m, 2 H), 7.43 (q, *J* = 7.6 Hz, 2 H), 7.28 (t, *J* = 8.4 Hz, 2 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6 (C), 144.6 (C), 141.5 (C), 137.2 (C), 134.3 (CH), 132.1 (C), 131.5 (C), 131.2 (CH), 130.5 (CH), 129.7 (CH), 129.3 (2 × CH), 127.6 (C), 126.9 (CH), 126.6 (2 × CH), 125.3 (C), 125.0 (CH), 122.0 (CH), 118.8 (CH), 115.2 (CH).
HRMS (ESI): calcd, for $C_{21}H_{14}ClN_2O_2S$ $[M + H]^+$ 393.0465, found 393.0465.

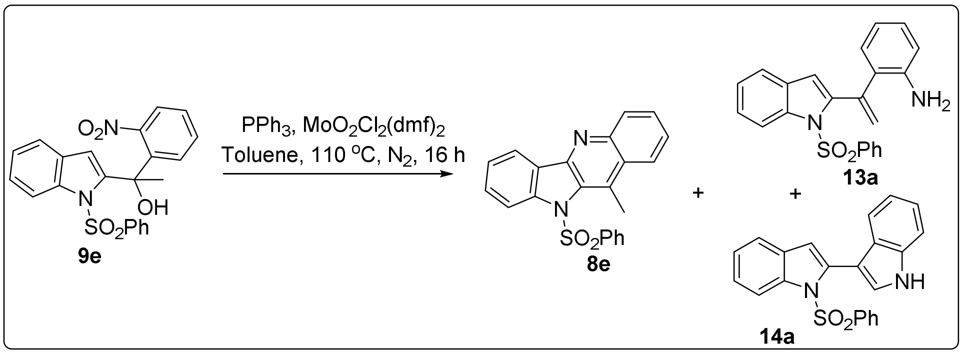
1.5.16: 2-Chloro-7-methoxy-10-phenylsulfonyl-indolo[3,2-*b*]quinoline (8d)



Method B: Following the similar protocol described in section 1.5.3 with (5-chloro-2-nitrophenyl)[5-methoxy-1-(phenylsulfonyl)-1*H*-indol-2-yl]methanol **9d** (0.481 g, 1.02 mmol), PPh_3 (0.854 g, 3.257 mmol), $MoO_2Cl_2(dmf)_2$ (0.035 g, 0.102 mmol) gave the product 2-chloro-7-methoxy-10-phenylsulfonyl-indolo[3,2-*b*]quinoline **8d** in 37 % (0.159 g) yield.
Yellow solid, m.p. 236-238 °C.

IR (KBr): $\tilde{\nu}$ = 2963, 1612, 1184, 1035, 733 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1 H), 8.19 (d, *J* = 8.8 Hz, 1 H), 8.07 (d, *J* = 8.8 Hz, 1 H), 7.96 (d, *J* = 2 Hz, 1 H), 7.70-7.69 (m, 3 H), 7.61 (dd, *J* = 9.2 Hz, 2.4 Hz, 1 H), 7.38 (t, *J* = 7.2 Hz, 1 H), 7.23-7.18 (m, 3 H), 3.88 (s, 3 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5 (C), 146.7 (C), 143.5 (C), 135.9 (C), 134.7 (C), 133.2 (CH), 131.1 (C), 131.0 (C), 129.4 (CH), 128.7 (CH), 128.2 (2 × CH), 126.6 (C), 125.9 (CH), 125.5 (2 × CH), 125.4 (C), 119.2 (CH), 118.2 (CH), 115.4 (CH), 102.6 (CH), 54.9 (CH_3).
HRMS (ESI): calcd for $C_{22}H_{16}ClN_2O_3S$ $[M + H]^+$ 423.0570, found 423.0572.

1.5.17: 11-Methyl-10-phenylsulfonyl-indolo[3,2-*b*]quinoline (8e)


O2N
OH
N
SO2Ph
9e
PPh3, MoO2Cl2(dmf)2
Toluene, 110 °C, N2, 16 h
N
N
SO2Ph
8e
+
+
NH2
N
SO2Ph
13a
N
NH
SO2Ph
14a

Method B: Following the similar protocol described in section 1.5.3 with (1-(2-nitrophenyl)-1-[1-(phenylsulfonyl)-1*H*-indol-2-yl]ethanol **9e** (0.490 g, 1.158 mmol), PPh_3 (0.972 g, 3.70 mmol), $MoO_2Cl_2(dmf)_2$ (0.040 g, 0.116 mmol) gave the product 11-Methyl-10-phenylsulfonyl-indolo[3,2-*b*]quinoline **8e** in 20 % (0.098 g) yield.

11-Methyl-10-phenylsulfonyl-indolo[3,2-*b*]quinoline (8e)

Light yellow solid, m.p. 192-194 °C.

IR (KBr): $\tilde{\nu}$ = 3071, 1447, 1360, 1171, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25-8.15 (m, 4 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.24-7.20 (m, 1 H), 6.99-6.93 (m, 4 H), 3.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ150.9 (C), 146.7 (C), 144.5 (C), 136.3 (C), 134.1 (C) 133.6 (CH), 132.7 (C), 130.4 (CH), 129.5 (CH), 129.3 (C), 129.1 (CH), 128.3 (2 × CH), 127.8 (C), 127.1 (2 × CH), 126.5 (CH), 126.3 (CH), 124.8 (CH), 121.7 (CH), 119.9 (CH), 17.6 (CH_3).

HRMS (ESI): calcd for $C_{22}H_{17}N_2O_2S$ $[M + H]^+$ 373.1011, found 373.1013.

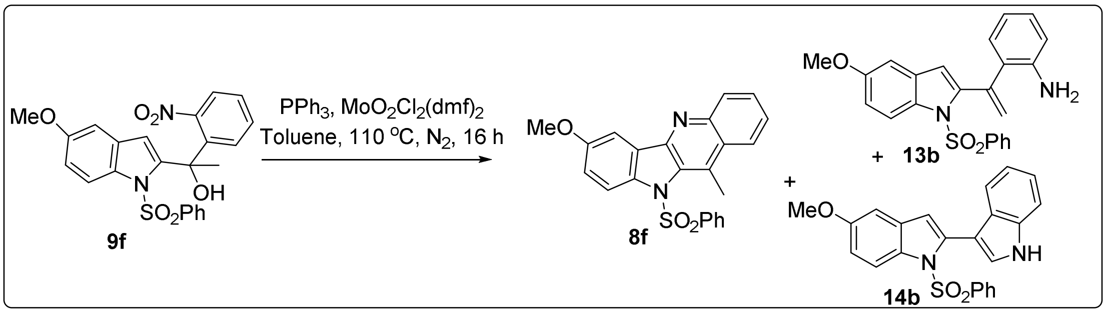
2-{1-[1-(Phenylsulfonyl)-1*H*-indol-2-yl]ethenyl}aniline (13a)

White solid, 26% (0.112 g) yield, m.p. 126-128 °C.

1-(Phenylsulfonyl)-1*H*,1'*H*-2,3'-biindole (14a)

White solid, 5% (0.022 g) yield, m.p. 76-80 °C.

1.5.18: 7-Methoxy-11-methyl-10-phenylsulfonyl-indolo[3,2-*b*]quinoline (8f)


MeO
O2N
OH
N
SO2Ph
9f
PPh3, MoO2Cl2(dmf)2
Toluene, 110 °C, N2, 16 h
MeO
N
N
SO2Ph
8f
MeO
NH2
N
+ 13b
SO2Ph
+
MeO
N
NH
14b
SO2Ph

Method B: Following the similar protocol described in section 1.5.3 with [5-methoxy-1-(phenylsulfonyl)-1*H*-indol-2-yl](2-nitrophenyl)ethanol **9f** (0.428 g, 0.945 mmol), PPh_3 (0.793 g, 3.024 mmol), $MoO_2Cl_2(dmf)_2$ (0.032 g, 0.094 mmol) gave the product 7-Methoxy-11-methyl-10-phenylsulfonyl-indolo[3,2-*b*]quinoline **8f** in 20 % (0.076 g) yield.

7-Methoxy-11-methyl-10-phenylsulfonyl-indolo[3,2-*b*]quinoline (8f)

Light yellow solid, m.p. 210-212 °C.

IR (KBr): $\tilde{\nu}$ = 2963, 1483, 1261, 1022, 797 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.16 (dd, *J* = 8.4 Hz, 0.8 Hz, 1 H), 8.07-8.03 (m, 2 H), 7.68 (dt, *J* = 8.4 Hz, 1.2 Hz, 1 H), 7.58 (dt, *J* = 8 Hz, 1.2 Hz, 1 H), 7.39 (d, *J* = 2.4 Hz, 1 H), 7.21-7.16 (m, 1 H), 7.07 (dd, *J* = 9.2 Hz, 2.4 Hz, 1 H), 6.96-6.91 (m, 4 H), 3.80 (s, 3 H), 3.11 (s, 3 H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 157.6 (C), 150.0 (C), 145.6 (C), 137.1 (C), 135.4 (C), 132.8 (C), 132.5 (CH), 132.4 (C), 129.4 (C), 128.3 (CH), 128.1 (CH), 127.2 (2 × CH), 126.8 (C), 126.1 (2 × CH), 125.2 (CH), 123.8 (CH), 120.0 (CH), 118.1 (CH), 102.5 (CH), 54.8 (CH_3), 16.5 (CH_3).

HRMS (ESI): calcd for $C_{23}H_{18}N_2O_3SNa$ $[M + Na]^+$ 425.0936, found 425.0933.

2-{1-[5-Methoxy-1-(phenylsulfonyl)-1*H*-indol-2-yl]ethenyl}aniline (13b)

White solid, 24 % (0.096 g) yield, m.p. 180-182 °C.

IR (KBr): $\tilde{\nu}$ = 3441, 3364, 2936, 1618, 1209, 754 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.85 (d, *J* = 8.8 Hz, 1 H), 7.43 (d, *J* = 7.6 Hz, 2 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.19 (t, *J* = 8.8 Hz, 2 H), 6.97 (dt *J* = 8 Hz, 0.8 Hz, 1 H), 6.86-6.82 (m, 2 H), 6.69-6.66 (m, 2 H), 6.59 (s, 1 H), 6.48 (t, *J* = 7.6 Hz, 1 H), 5.73 (d, *J* = 8 Hz, 2 H), 4.22 (br s, 1 H), 3.72 (s, 3 H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 155.8 (C), 143.6 (C), 142.1 (C), 138.4 (C), 136.9 (C), 132.3 (CH), 131.1 (C), 129.8 (C), 128.5 (CH), 127.7 (2 × CH), 127.6 (CH), 125.5 (2 × CH), 124.7 (C), 118.9 (CH_2), 117.1 (CH), 115.5 (CH), 115.4 (CH), 113.2 (CH), 112.7 (CH), 102.3 (CH), 54.6 (CH_3).

HRMS (ESI): calcd for $C_{23}H_{20}N_2O_3SNa$ $[M + Na]^+$ 427.1092, found 427.1094.

5-Methoxy-1-(phenylsulfonyl)-1*H*,1'*H*-2,3'-biindole (14b)

White solid, 15 % (0.06 g) yield, m.p. 74-76 °C.

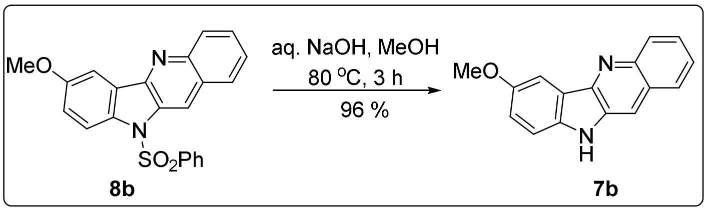
IR (KBr): $\tilde{\nu}$ = 3422, 2928, 1605, 1460, 1209, 1029, 725 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): *δ* 8.50 (s, 1 H), 8.16 (d, *J* = 8.8 Hz, 1 H), 7.41-7.32 (m, 3 H), 7.23-7.12 (m, 4 H), 7.04-6.97 (m, 3 H), 6.87-6.82 (m, 2 H), 6.53 (s, 1 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, CDCl$_3$): *δ* 157.0 (C) , 137.1 (C), 136.3 (C), 135.4 (C), 133.2 (CH), 132.5 (C), 132.3 (C), 128.4 (2 × CH), 127.2 (C), 127.1 (CH), 126.7 (2 × CH), 122.4 (CH), 120.6 (CH), 119.4 (CH), 117.7 (CH), 112.8 (CH), 112.7 (CH), 111.5 (CH), 107.4 (C), 102.8 (CH), 55.6 (CH$_3$).

HRMS (ESI): calcd for $C_{23}H_{18}N_2O_3SNa$ [M + Na]$^+$ 425.0936, found 425.0934.

1.5.19: 7-Methoxy-10*H*-indolo[3,2-*b*]quinoline (7b)



Following the similar protocol described in section 1.5.6 with 7-methoxy-10-phenysulfonyl-indolo[3,2-*b*]quinoline **8b** (0.119 g, 0.307 mmol) gave the product 7-methoxy-10*H*-indolo[3,2-*b*]quinoline **7b** in 96 % (0.073 g) yield.

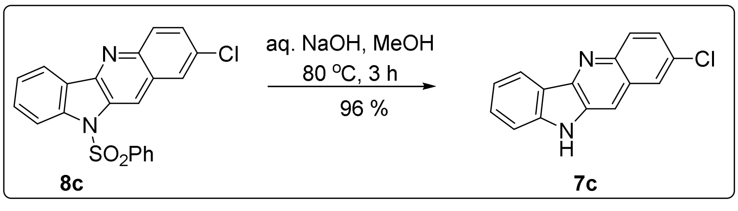
Yellow solid, m.p. 226-228 °C (lit.[17 b] m.p. 228-230 °C),

IR (KBr): $\tilde{\nu}$ = 3161, 3045, 1624, 1022, 810 cm^{-1}.

^{1}H NMR (400 MHz, [D$_6$]DMSO): *δ* 11.39 (s, 1 H), 8.38 (s, 1 H), 8.25 (d, *J* = 8.4 Hz, 1 H), 8.18 (d, *J* = 8 Hz, 1 H), 7.92 (d, *J* = 2 Hz, 1 H), 7.72 (t, *J* = 7.6 Hz, 1 H), 7.64-7.57 (m, 2 H), 7.34 (dd, *J* = 8.8 Hz, 2.4 Hz, 1 H), 3.97 (s, 3 H).

^{13}C NMR (100 MHz, [D$_6$]DMSO): *δ* 153.4 (C), 144.9 (C), 142.5 (C), 138.9 (C), 133.1 (C), 128.0 (CH), 127.6 (CH), 126.6 (C), 126.3 (CH), 124.9 (CH), 120.7 (C), 119.6 (CH), 113.8 (CH), 112.6 (CH), 103.2 (CH), 55.6 (CH$_3$).

1.5.20: 2-Chloro-10*H*-indolo[3,2-*b*]quinoline (7c)



Following the similar protocol described in section 1.5.6 with 2-chloro-10-phenylsulfonyl-indolo[3,2-*b*]quinoline **8c** (0.100 g, 0.255 mmol) gave the product 2-Chloro-10*H*-indolo[3,2-*b*]quinoline **7c** in 96 % (0.062 g) yield.

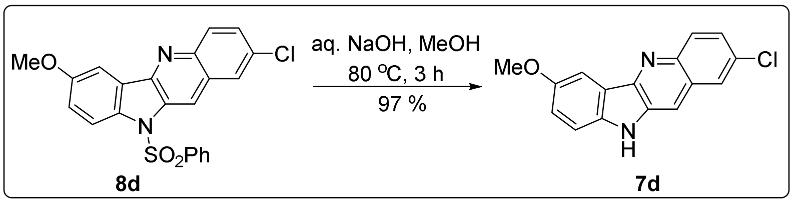
Light yellow solid, m.p. 242-244 °C (lit. [17a] m.p. 244 °C).

IR (KBr): $\tilde{\nu}$ = 3408, 2962, 1612, 1262, 824 cm^{-1}.

^{1}H NMR (400MHz [D$_6$]DMSO): δ 11.57 (s, 1 H), 8.35 (d, J = 8 Hz, 1 H), 8.29 (s, 1 H), 8.25 (d, J = 2.4 Hz, 1 H), 8.20 (d, J = 9.2 Hz, 1 H), 7.67-7.57 (m, 3 H), 7.30 (t, J = 8 Hz, 1 H).

^{13}C NMR (100 MHz, [D$_6$]DMSO): δ 146.2 (C), 144.2 (C), 141.6 (C), 132.8 (C), 130.7 (CH), 130.1 (CH), 129.1 (C), 127.4 (C), 126.4 (CH), 125.9 (CH), 121.5 (CH), 120.7 (C), 119.6 (CH), 112.3 (CH), 111.6 (CH).

1.5.21: 2-Chloro-7-methoxy-10*H*-indolo[3,2-*b*]quinoline (7d)



Following the similar protocol described in section 1.5.6 with 2-chloro-7-methoxy-10-phenylsulfonyl-indolo[3,2-*b*]quinoline **8d** (0.104 g, 0.247 mmol) gave the product 2-Chloro-7-methoxy-10*H*-indolo[3,2-*b*]quinoline **7d** in 97 % (0.068 g) yield.
Yellow solid, m.p. 240-242 °C.

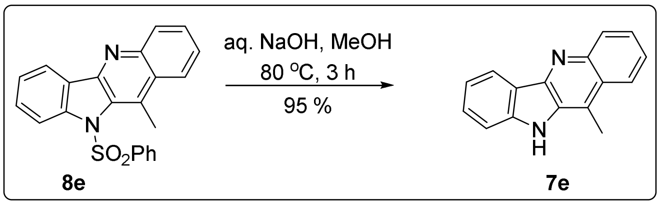
IR (KBr): $\tilde{\nu}$ = 3180, 2962, 1604, 1261, 1161, 721 cm^{-1}.

^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 11.45 (s, 1 H), 8.34 (s, 1 H), 8.30 (d, J = 2.4 Hz, 1 H), 8.25 (d, J = 9.2 Hz, 1 H), 7.90 (d, J = 2.4 Hz, 1 H), 7.70 (dd, J = 9.2 Hz, 2.4 Hz, 1 H), 7.59 (d, J = 8.8 Hz, 1 H), 7.35 (dd, J = 8.8 Hz, 2.4 Hz, 1 H), 3.97 (s, 3 H).

^{13}C NMR (100 MHz, [D$_6$]DMSO): δ 153.5 (C), 146.0 (C), 141.3 (C), 138.9 (C), 133.4 (C), 130.6 (CH), 129.0 (C), 127.3 (C), 126.3 (CH), 125.9 (CH), 120.9 (C), 119.6 (CH), 112.6 (CH), 112.3 (CH), 103.2 (CH), 55.6 (CH$_3$).

HRMS (ESI): calcd for $C_{16}H_{12}ClN_2O$ [M + H]$^+$ 283.0638, found 283.0645.

1.5.22: 11-Methyl-10*H*-indolo[3,2-*b*]quinoline (7e)



Following the similar protocol described in section 1.5.6 with 11-methyl-10-phenylsulfonyl-indolo[3,2-*b*]quinoline **8e** (0.051 g, 0.135 mmol) gave the product 11-Methyl-10*H*-indolo[3,2-*b*]quinoline **7e** in 95 % (0.03 g) yield.

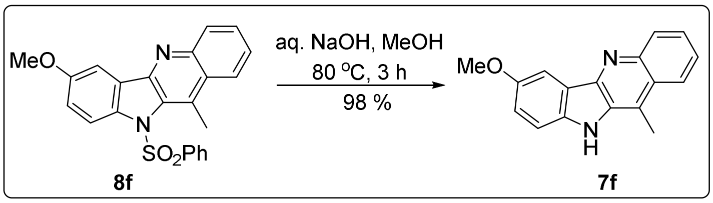
Yellow solid, m.p. 262-264 °C (lit.[17c] m.p. >260 °C).

IR (KBr): $\tilde{\nu}$ = 3177, 2924, 1612, 1261, 1018, 743 cm^{-1}.

^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 11.46 (s, 1 H), 8.39 (d, *J* = 8 Hz, 1 H), 8.26 (t, *J* = 9.6 Hz, 2 H), 7.34-7.62 (m, 4 H), 7.33 (dt, *J* = 7.6 Hz, 1.2 Hz, 1 H), 2.97 (s, 3 H).

^{13}C NMR (100 MHz, [D$_6$]DMSO): δ 144.8 (C), 143.9 (2 × C), 143.5 (C), 131.8 (C), 129.5 (CH), 129.3 (CH), 125.9 (C), 125.8 (CH), 124.6 (CH), 123.3 (CH), 121.4 (CH), 121.3 (C), 119.2 (CH), 111.4 (CH), 12.4 (CH$_3$).

1.5.23: 7-Methoxy-11-methyl-10*H*-indolo[3,2-*b*]quinoline (7f)



Following the similar protocol described in section 1.5.6 with 7-Methoxy-11-methyl-10-phenylsulfonyl-indolo[3,2-*b*]quinoline **8f** (0.06 g, 0.147 mmol) gave the product 7-Methoxy-11-methyl-10*H*-indolo[3,2-*b*]quinoline **7f** in 98 % (0.038 g) yield.

Yellow solid, m.p. 216-218 °C.

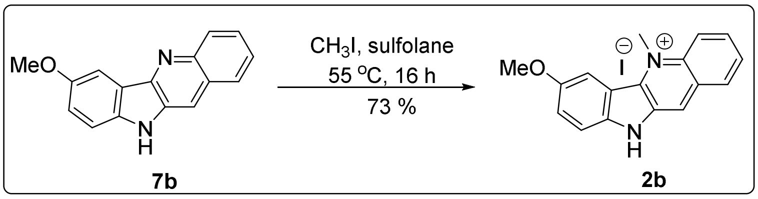
IR (KBr): $\tilde{\nu}$ = 3441, 2926, 1625, 1493, 1225, 748 cm^{-1}.

^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 11.23 (s, 1 H), 8.24 (t, *J* = 8.8 Hz, 2 H), 7.88 (d, *J* = 2.4 Hz, 1 H), 7.70 (t, *J* = 7.2 Hz, 1 H), 7.63 (t, *J* = 7.2 Hz, 1 H), 7.56 (d, *J* = 8.8 Hz, 1 H), 7.31 (dd, *J* = 8.8 Hz, 2.4 Hz, 1 H), 3.96 (s, 3 H), 2.95 (s, 3 H).

^{13}C NMR (100 MHz, [D$_6$]DMSO): δ 153.3 (C), 144.6 (C), 143.3 (C), 138.7 (C), 132.5 (C), 129.2 (CH), 125.8 (C), 125.7 (CH), 124.5 (CH), 123.3 (C), 121.6 (C), 121.3 (CH), 119.1 (CH), 112.4 (CH), 103.2 (CH), 55.6 (CH$_3$), 12.4 (CH$_3$).

HRMS (ESI): calcd for $C_{17}H_{15}N_2O$ $[M + H]^+$ 263.1184, found 263.1183.

1.5.24: 7-Methoxycryptolepine Hydroiodide (2b)



Following the similar protocol described in section 1.5.8 with 7-methoxy-10*H*-indolo[3,2-*b*]quinoline **7b** (0.03 g, 0.122 mmol) gave the product **7-**methoxycryptolepine hydroiodide **2b** in 73 % (0.035 g) yield.

Bright red solid, m.p. 268-272 °C.

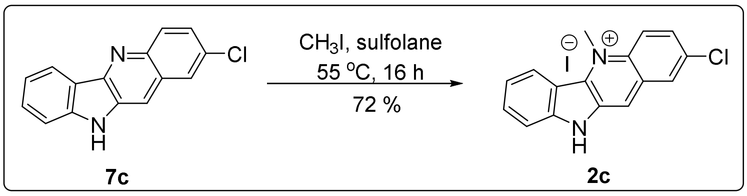
IR (KBr): $\tilde{\nu}$ = 3065, 2927, 1618, 1230, 763 cm^{-1}.

^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 12.78 (s, 1 H), 9.28 (s, 1 H), 8.77 (d, J = 8.4 Hz, 1 H), 8.56 (d, J = 8 Hz, 1 H), 8.18-8.11 (m, 2 H), 7.93 (t, J = 7.2 Hz, 1 H), 7.81 (d, J = 9.2 Hz, 1 H), 7.64 (d, J = 8.4 Hz, 1 H), 5.04 (s, 3 H), 3.99 (s, 3 H).

^{13}C NMR (100 MHz, [D$_6$]DMSO): δ 154.1 (C), 141.2 (C), 137.4 (C), 135.3 (C), 133.7 (C), 132.4 (CH), 129.8 (CH), 126.8 (CH), 125.9 (C), 125.0 (CH), 124.9 (CH), 117.8(CH), 114.3 (CH), 113.7 (C), 106.4 (CH), 56.1 (CH$_3$), 52.8 (CH$_3$).

HRMS (ESI): calcd for $C_{17}H_{15}N_20^+$ 263.1184, found 263.1182.

1.5.25: 2-Chlorocryptolepine Hydroiodide (2c)



Following the similar protocol described in section 1.5.8 with 2-Chloro-10*H*-indolo[3,2-*b*]quinoline **7c** (0.02 g, 0.079 mmol) gave the product 2-chlorocryptolepine hydroiodide **2c** in 72 % (0.023 g) yield.

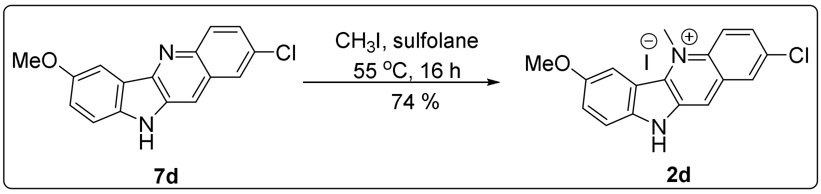
Bright yellow solid, m. p. 284-286 °C (lit. [17a] m.p. 287-289 °C).

IR (KBr): $\tilde{\nu}$ = 3068, 2924, 1608, 1256, 750 cm^{-1}.

^{1}H NMR (400MHz, [D$_6$]DMSO): δ 12.99 (s, 1 H), 9.23 (s, 1 H), 8.84 (d, J = 9.6 Hz, 2 H), 8.76 (d, J = 2.4 Hz, 1 H), 8.20 (dd, J = 9.2 Hz, 1.6 Hz, 1 H), 7.99 (t, J = 7.6 Hz, 1 H), 7.88 (d, J = 8.4 Hz, 1 H), 7.55 (t, J = 7.6 Hz, 1 H), 5.05 (s, 3 H).

^{13}C NMR (100 MHz, [D$_6$]DMSO): δ 146.1 (C), 138.7 (C), 134.4 (C), 134.0 (C), 133.9 (CH), 132.1 (CH), 131.5 (C), 128.0 (CH), 127.0 (C), 126.5 (CH), 123.5 (CH), 121.6 (CH), 120.3 (CH), 113.8 (C), 113.3 (CH), 52.8 (CH$_3$).

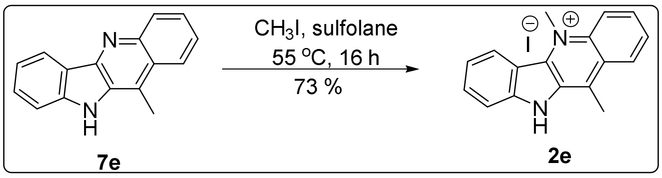
1.5.26: 2-Chloro-7-methoxycryptolepine Hydroiodide (2d)



Following the similar protocol described in section 1.5.8 with 2-Chloro-7-methoxy-10*H*-indolo[3,2-*b*]quinoline **7d** (0.03 g, 0.105 mmol) gave the product 2-chloro-7-methoxycryptolepine hydroiodide **2d** in 74 % (0.033 g) yield.
Bright red solid, m.p. 280-284 °C.

IR (KBr): $\tilde{\nu}$ = 3069, 2949, 1618, 1234, 825 cm^{-1}.
^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 12.86 (s, 1 H), 9.19 (s, 1 H), 8.82 (d, *J* = 9.6 Hz, 1 H), 8.72 (d, *J* = 2.4 Hz, 1 H), 8.17 (dd, *J* = 9.6 Hz, 2.4, 1 H), 8.11 (d, *J* = 2.4 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.66 (dd, *J* = 9.6 Hz, 2.4 Hz, 1 H), 5.04 (s, 3 H), 3.99 (s, 3 H).
^{13}C NMR (100 MHz, [D$_6$]DMSO): δ 154.3 (C), 141.6 (C), 137.9 (C), 134.4 (C), 133.9 (C), 132.0 (CH), 131.3 (C), 127.9 (CH), 126.7 (C), 125.4 (CH), 123.8 (CH), 120.3 (CH), 114.3 (CH), 113.7 (C), 106.5 (CH), 56.2 (CH$_3$), 52.8 (CH$_3$).
HRMS (ESI): calcd for $C_{17}H_{14}ClN_2O^+$ 297.0795, found 297.0792.

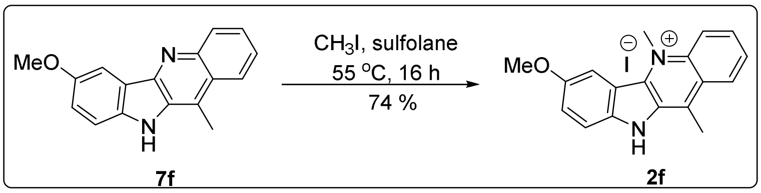
1.5.27: 11-Methylcryptolepine Hydroiodide (2e)



Following the similar protocol described in section 1.5.8 with 11-Methyl-10*H*-indolo[3,2-*b*]quinoline **7e** (0.013 g, 0.057 mmol) gave the product 11-methylcryptolepine hydroiodide **2e** in 73 % (0.016 g) yield.
Bright yellow solid, m.p. 274-276 °C.

IR (KBr): $\tilde{\nu}$ = 3180, 1636, 1508, 1240, 754 cm^{-1}.
^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 12.87 (s, 1 H), 8.80-8.74 (m, 2 H), 8.65 (d, *J* = 8 Hz, 1 H), 8.18 (t, *J* = 7.6 Hz, 1 H), 8.00-7.91 (m, 2 H), 7.85 (d, *J* = 8.4 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 4.96 (s, 3 H), 3.20 (s, 3 H).
^{13}C NMR (100 MHz, [D$_6$]DMSO): δ 145.2 (C), 136.4 (C), 135.8(C), 135.1 (C), 133.6 (CH), 132.7 (C), 132.1 (CH), 126.8 (CH), 126.1 (CH), 125.9 (CH), 125.2 (CH), 121.3 (CH), 118.1 (CH), 114.1 (C), 113.0 (CH), 39.89 (CH$_3$), 14.22 (CH$_3$).
HRMS (ESI): calcd for $C_{17}H_{15}N_2^+$ 247.1235, found 247.1235.

1.5.28: 11-Methyl-7-methoxycryptolepine Hydroiodide (2f)



Following the similar protocol described in section 1.5.8 with 7-methoxy-11-methyl-10*H*-indolo[3,2-*b*]quinoline **7f** (0.01 g, 0.036 mmol) gave the product 11-methyl-7-methoxycryptolepine hydroiodide **2f** in 74 % (0.011 g) yield.

Bright orange solid, m.p. 270-274 °C.

IR (KBr): $\tilde{\nu}$ = 3104, 2839, 1613, 1500, 1233, 770 cm^{-1}.

^{1}H NMR (400 MHz, [D$_6$]DMSO): δ 12.68 (s, 1 H), 8.69 (d, *J* = 9.2 Hz, 1 H), 8.41 (d, *J* = 9.6 Hz, 1 H), 8.09 (dt, *J* = 7.6 Hz, 2 Hz, 1 H), 8.03 (d, *J* = 2 Hz, 1 H), 7.91-7.88 (m, 2 H), 7.73 (d, *J* = 9.2 Hz, 1 H), 7.56 (dd, *J* = 9.6 Hz, 2.4 Hz, 1 H), 4.94 (s, 3 H), 3.93 (s, 3 H), 3.15 (s, 3 H).

^{13}C NMR (100 MHz, [D$_6$]DMSO): δ 154.1 (C), 140.8 (C), 136.0 (C), 135.2 (C), 133.2 (C), 132.1 (CH), 126.6 (CH), 125.9 (CH), 125.0 (C), 124.7 (CH), 118.1 (CH), 114.2 (CH), 114.1 (C), 106.4 (CH), 103.1 (C), 56.09 (CH_3), 39.75 (CH_3), 14.2 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{17}N_2O^+$ 277.134, found 277.1342.

1.6: References

1. (a) Eyunni, V. K.; Kumar, S.; Etukala, J. R.; Ablordeppey, S. Y. *Mini-Reviews in Medicinal Chemistry* **2008**, *8*, 538. (b) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Curr. Org. Chem.* **2011**, *15*, 1036.
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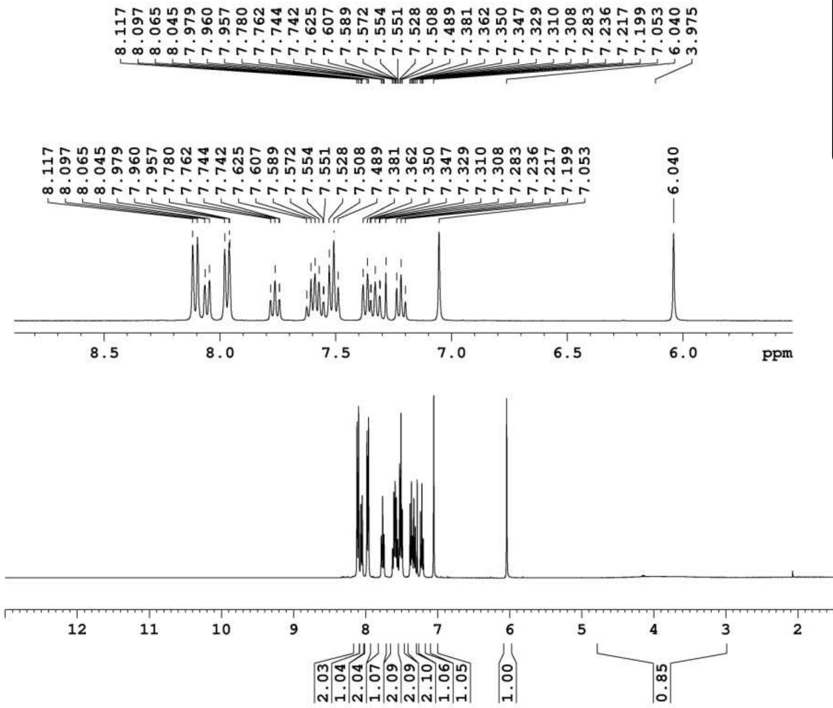
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7.551
7.528
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7.489
7.381
7.362
7.350
7.347
7.329
7.310
7.308
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7.199
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6.040
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7.0
6.5
6.0
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9
8
7
6
5
4
3
2
1
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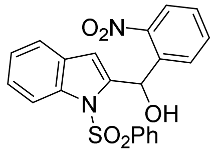
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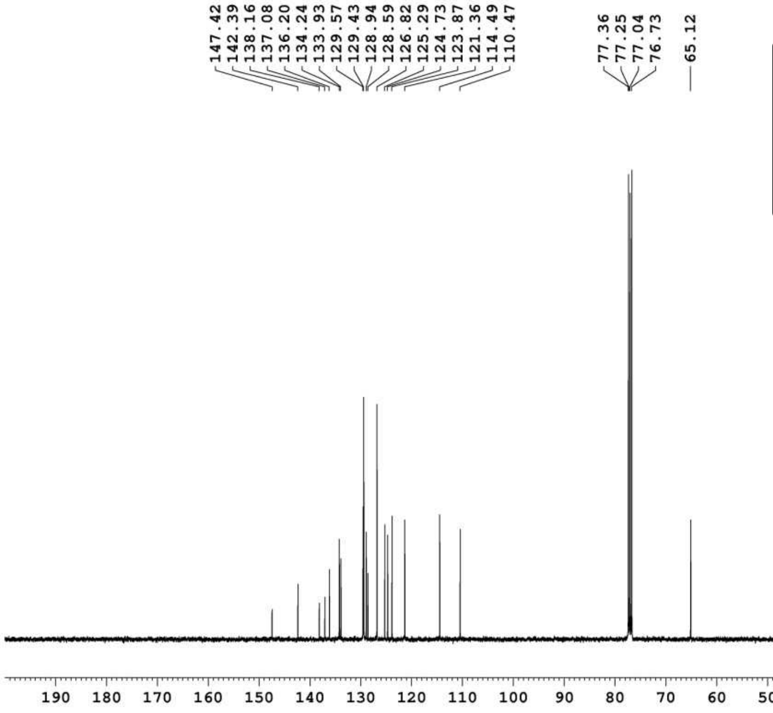
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123.87
121.36
114.49
110.47
77.36
77.25
77.04
76.73
65.12
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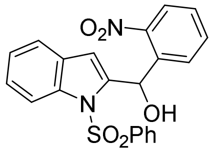
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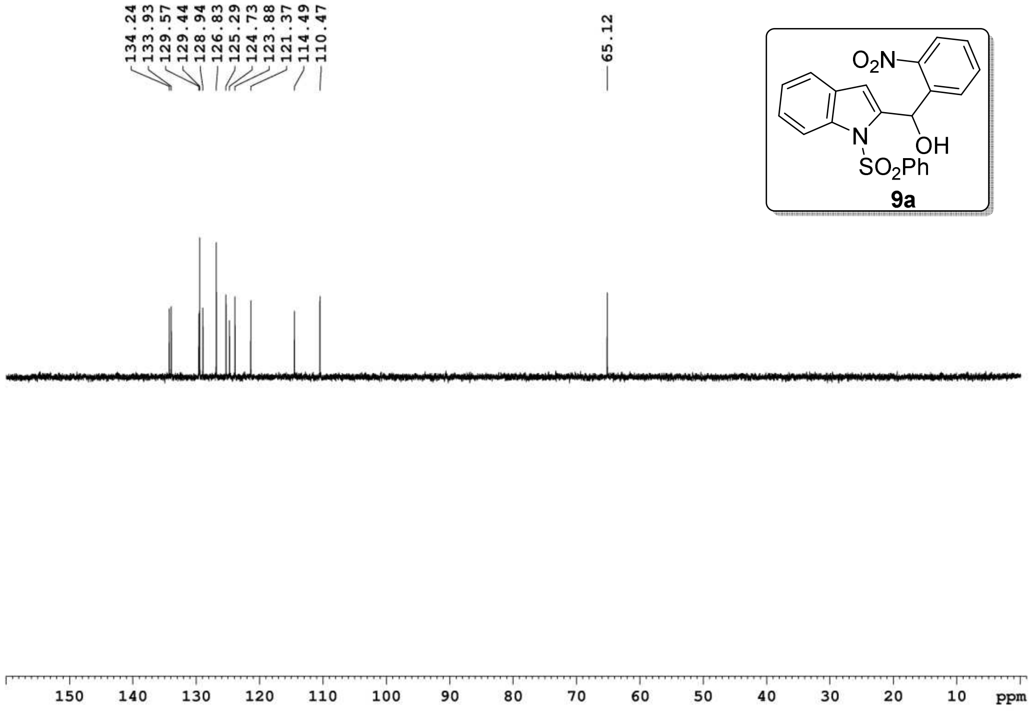
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65.12
O$_2$N
N
OH
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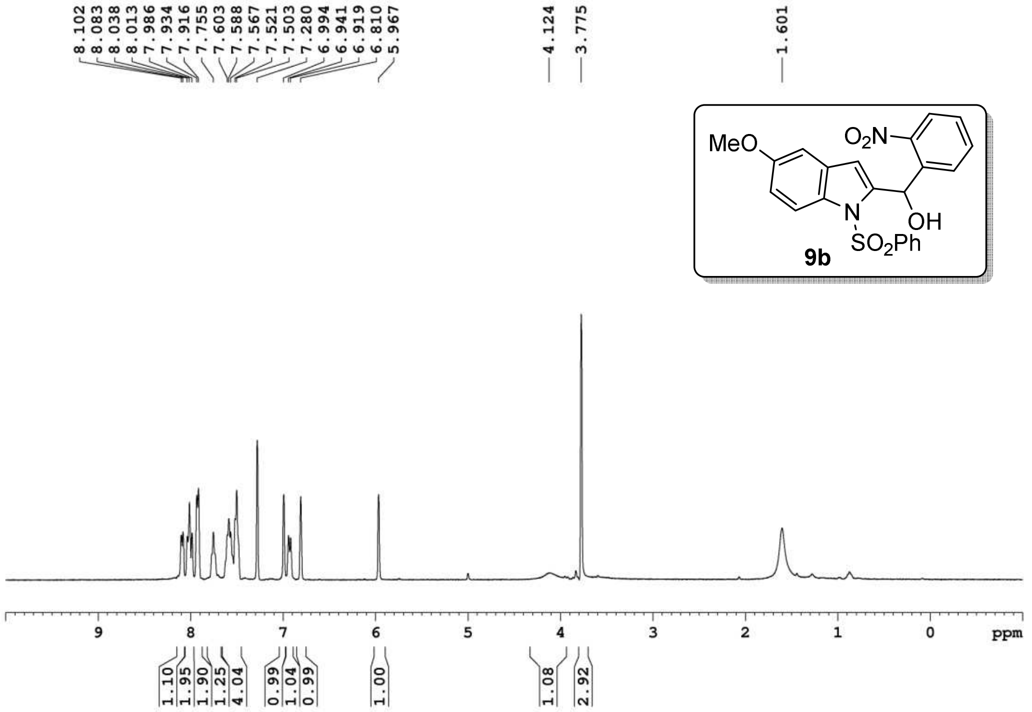
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O$_2$N
N
OH
SO$_2$Ph
9b
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7
6
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4
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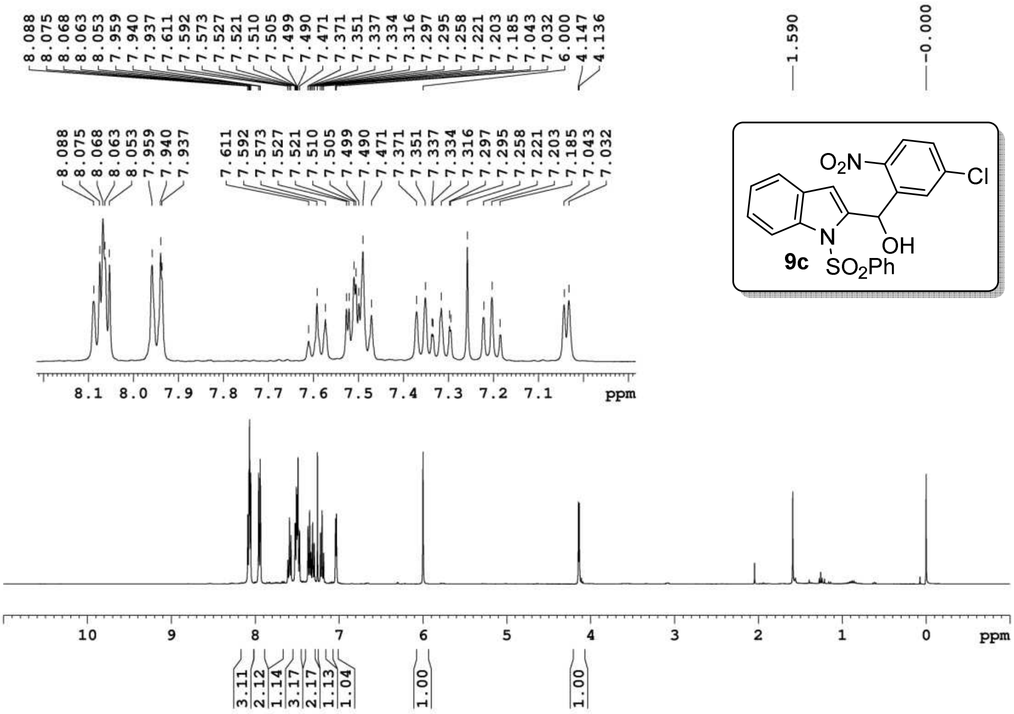
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Cl
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SO2Ph
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ppm
10
9
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7
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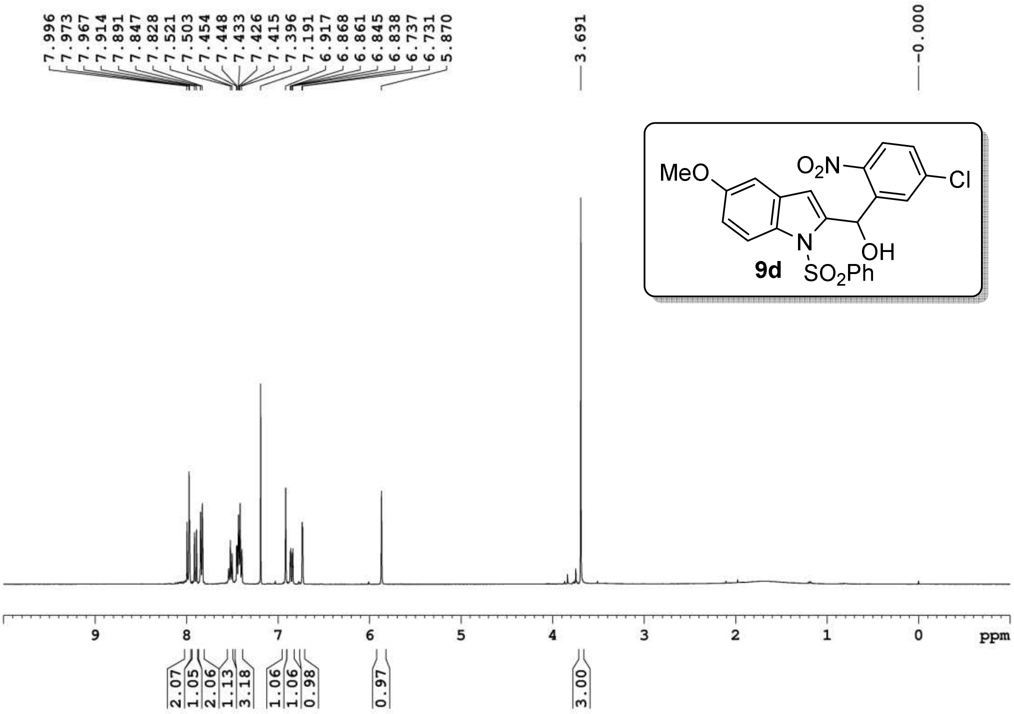
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N
OH
9d
SO2Ph
9
8
7
6
5
4
3
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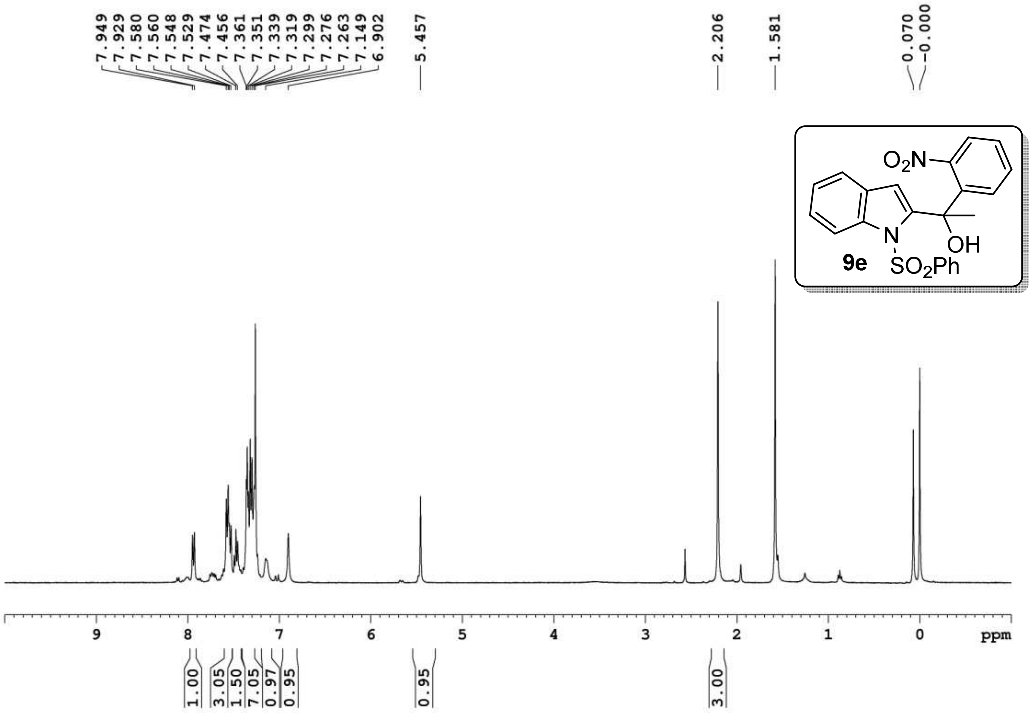
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OH
9e
SO_2Ph
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8
7
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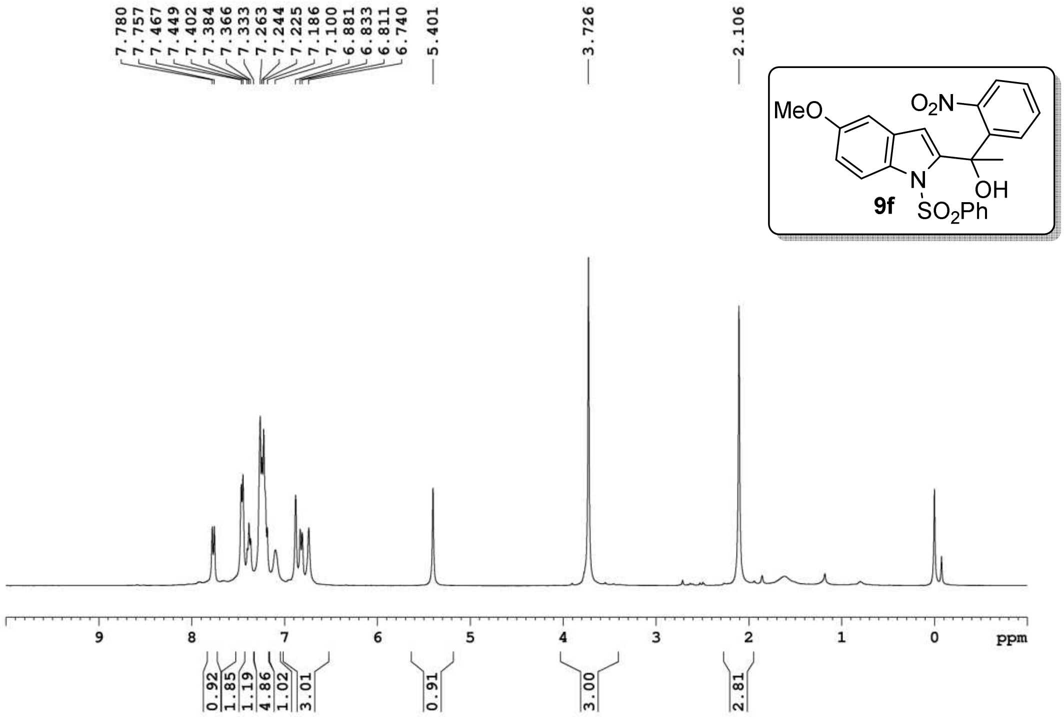
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6.833
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6.740
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O_2N
N
OH
9f
SO_2Ph
9
8
7
6
5
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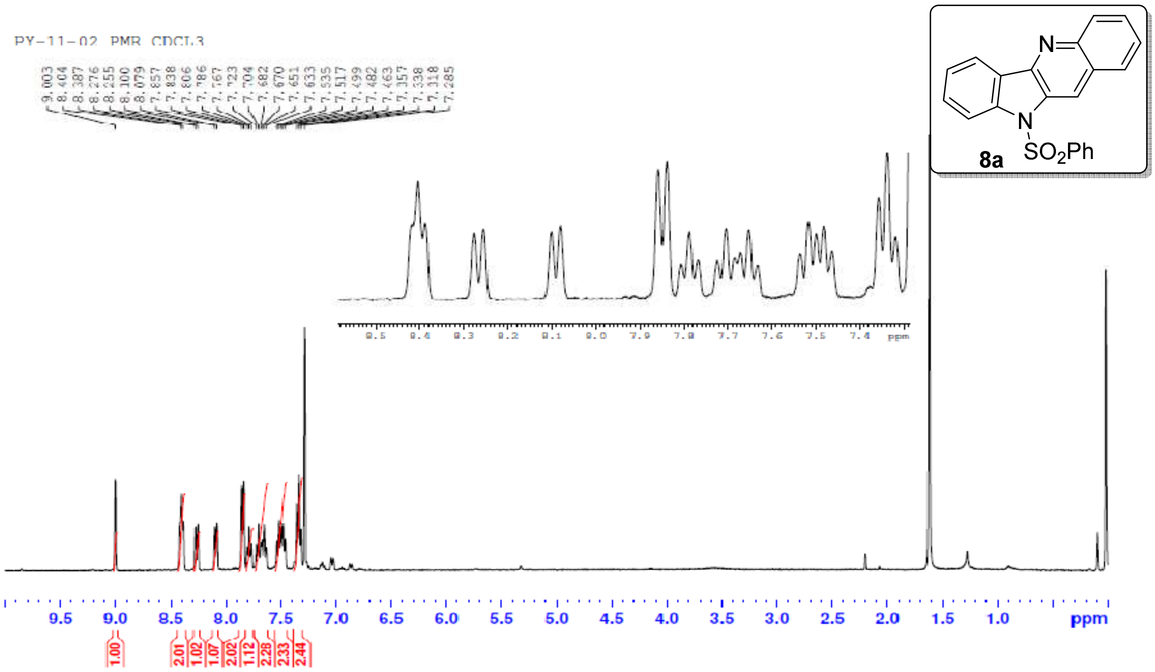
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7.633
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7.463
7.357
7.338
7.318
7.285
8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 ppm
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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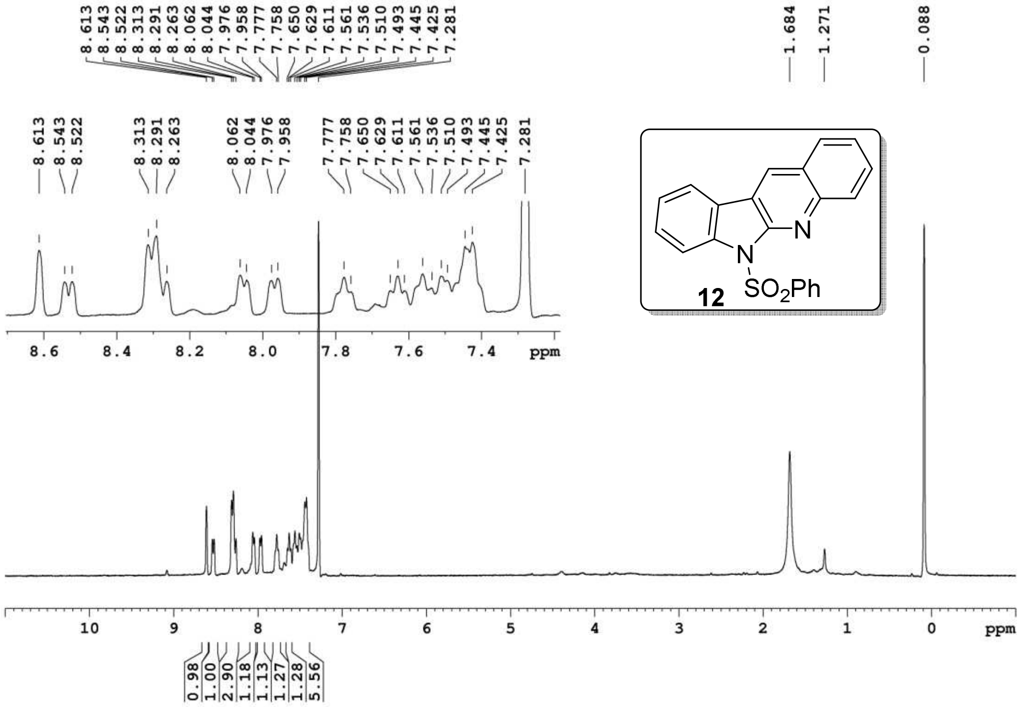
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7.629
7.611
7.561
7.536
7.510
7.493
7.445
7.425
7.281
1.684
1.271
0.088
8.6 8.4 8.2 8.0 7.8 7.6 7.4 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
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SO2Ph
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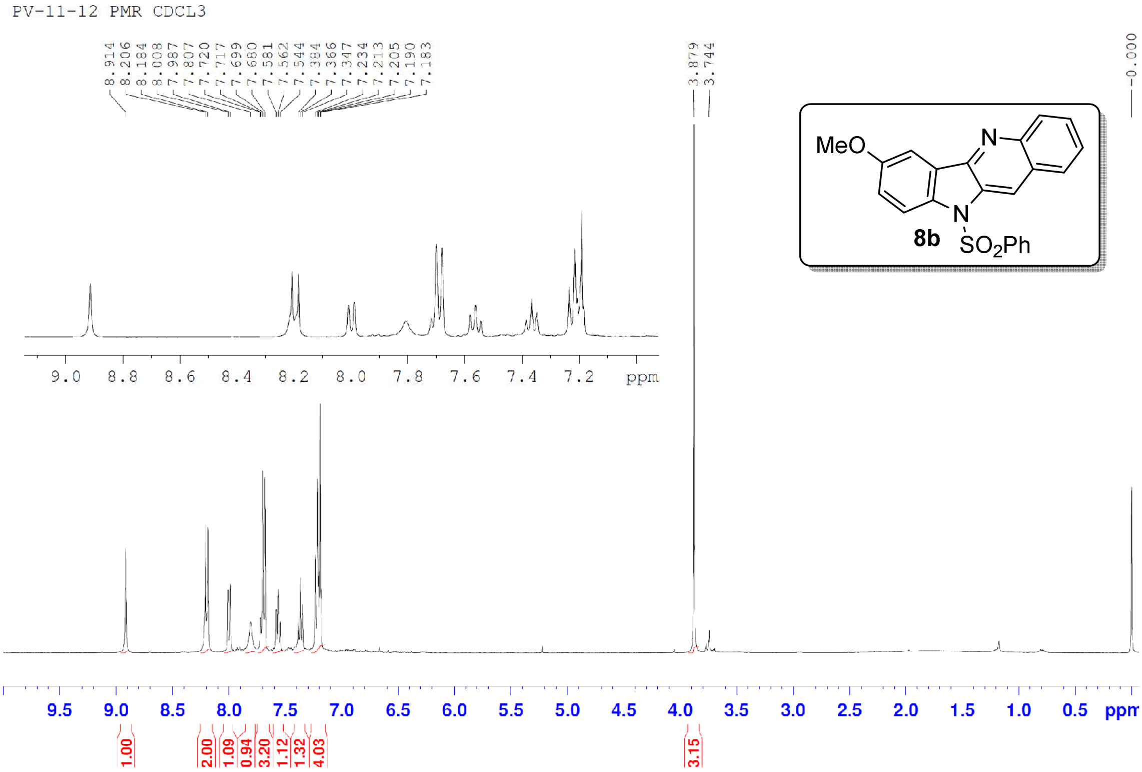
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7.213
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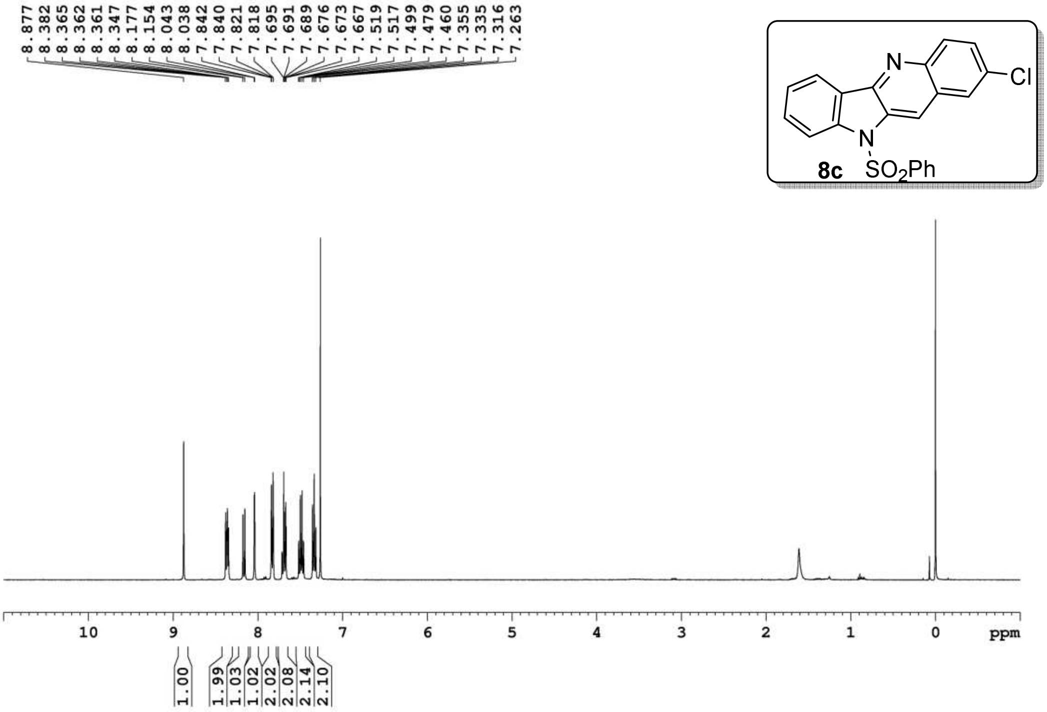
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7.460
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7.335
7.316
7.263
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2.08
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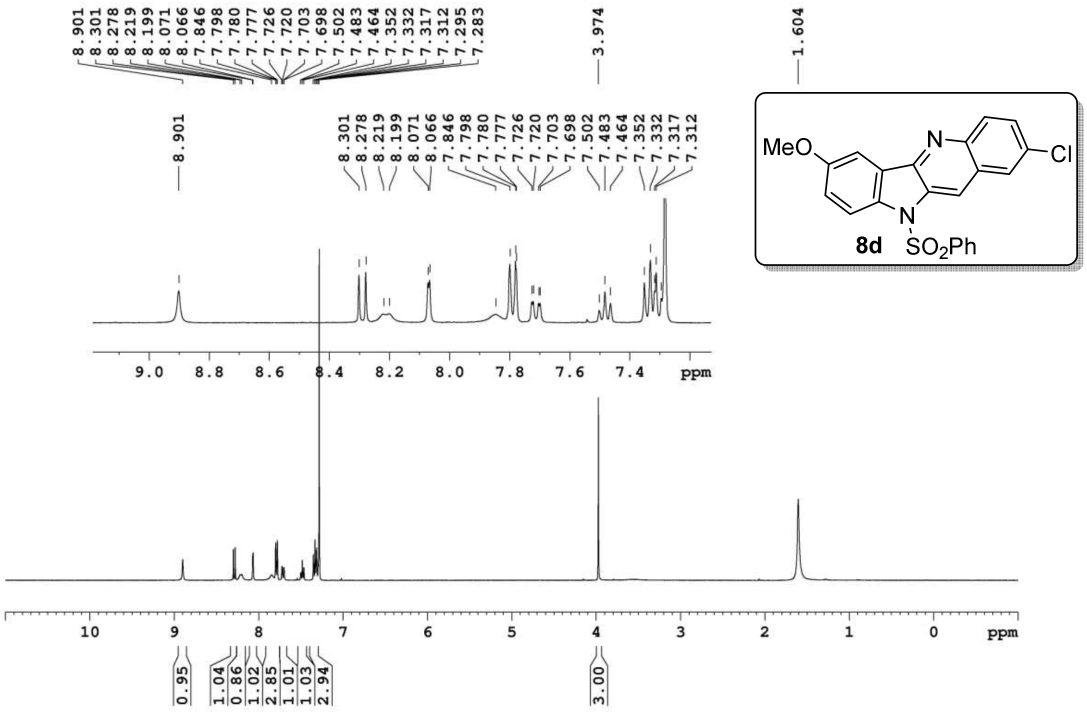
2.10
ppm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7.464
7.352
7.332
7.317
7.312
7.295
7.283
3.974
1.604
MeO
N
Cl
N
SO2Ph
9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
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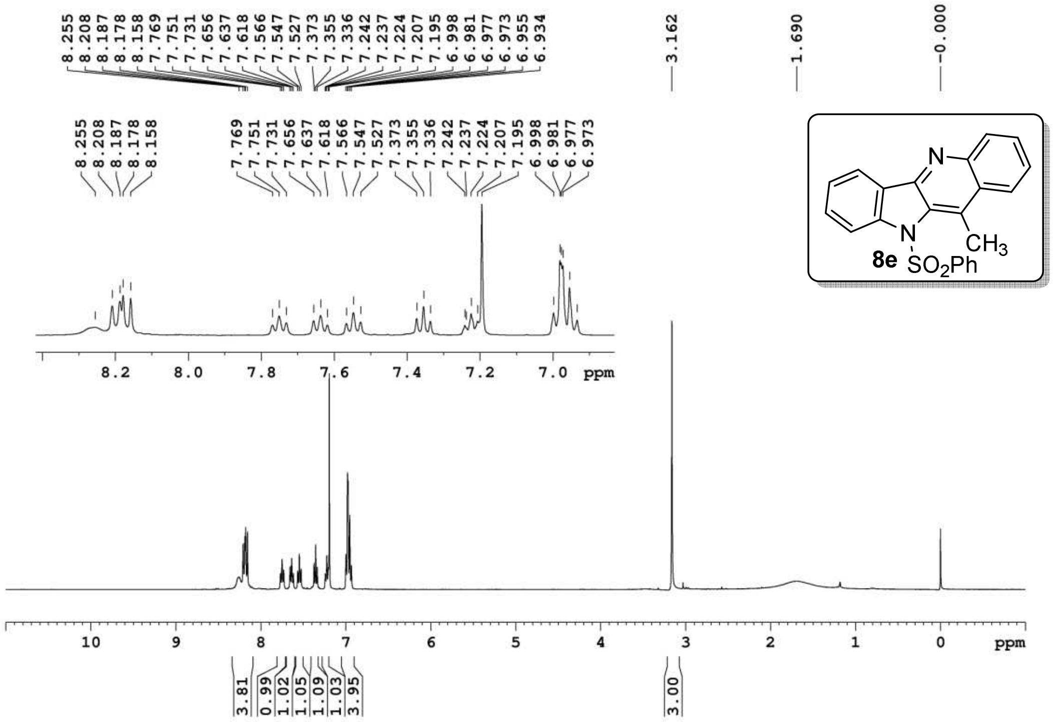
2.85
1.01
1.03
2.94
3.00

8d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7.373
7.355
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7.237
7.224
7.207
7.195
6.998
6.981
6.977
6.973
6.955
6.934
3.162
1.690
0.000
N
N
CH3
SO2Ph
8.2 8.0 7.8 7.6 7.4 7.2 7.0 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
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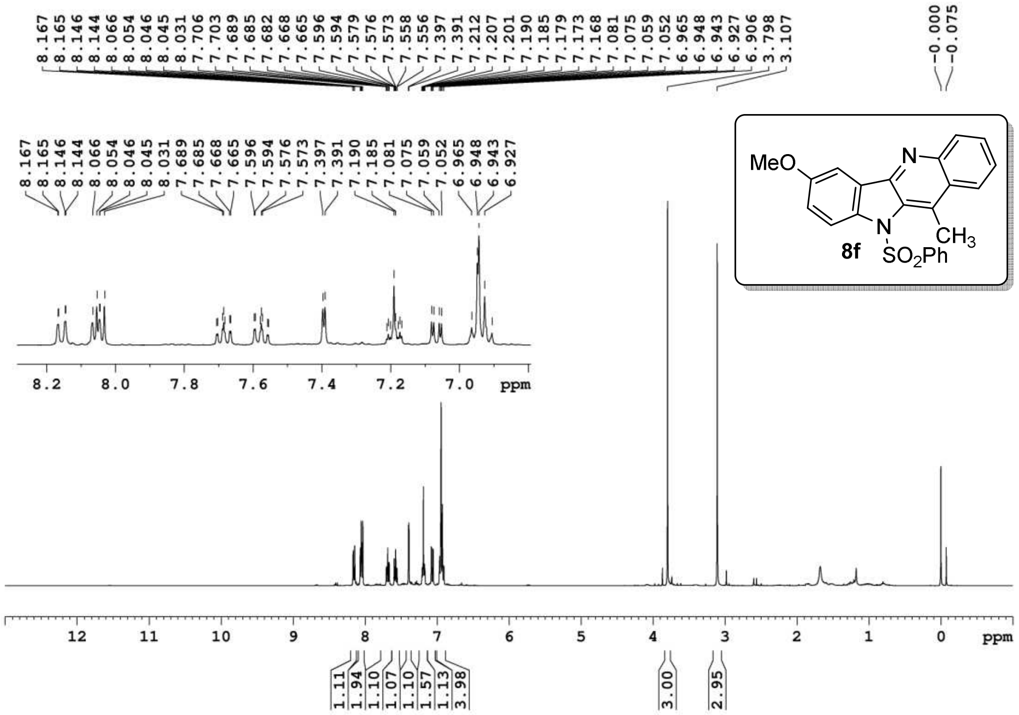
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7.556
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7.207
7.201
7.190
7.185
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7.173
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7.052
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7.6
7.4
7.2
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ppm
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N
CH3
SO2Ph
8f
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11
10
9
8
7
6
5
4
3
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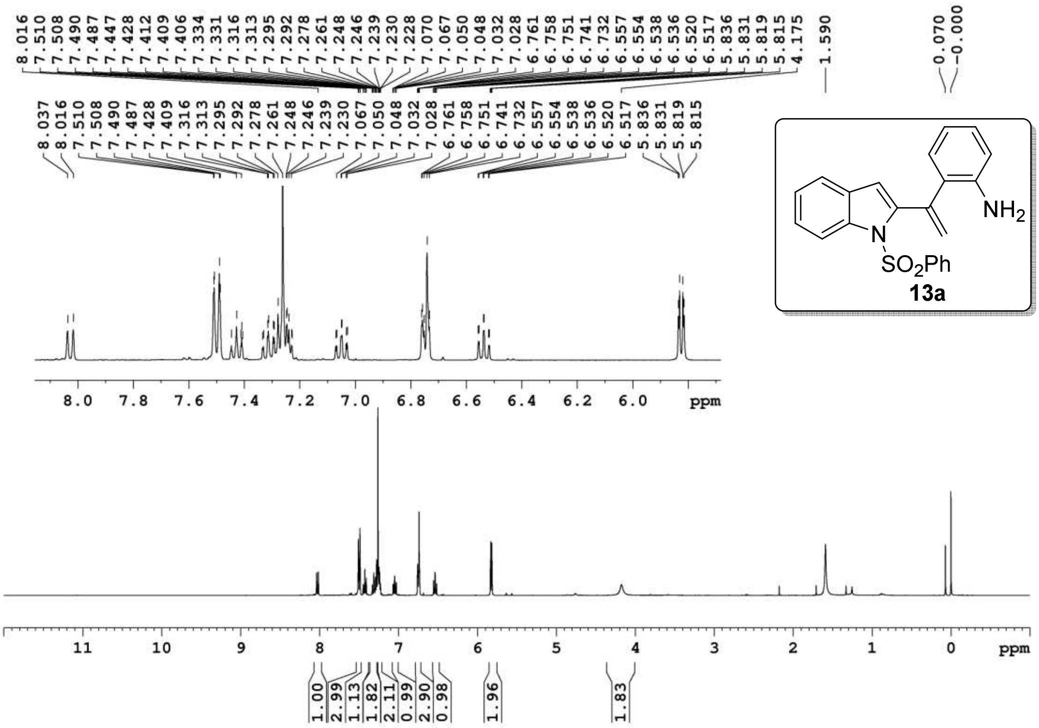
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7.313
7.295
7.292
7.278
7.261
7.248
7.246
7.239
7.230
7.228
7.070
7.067
7.050
7.048
7.032
7.028
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6.758
6.751
6.741
6.732
6.557
6.554
6.538
6.536
6.520
6.517
5.836
5.831
5.819
5.815
4.175
1.590
0.070
-0.000
8.037
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
ppm
N
NH2
SO2Ph
13a
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10
9
8
7
6
5
4
3
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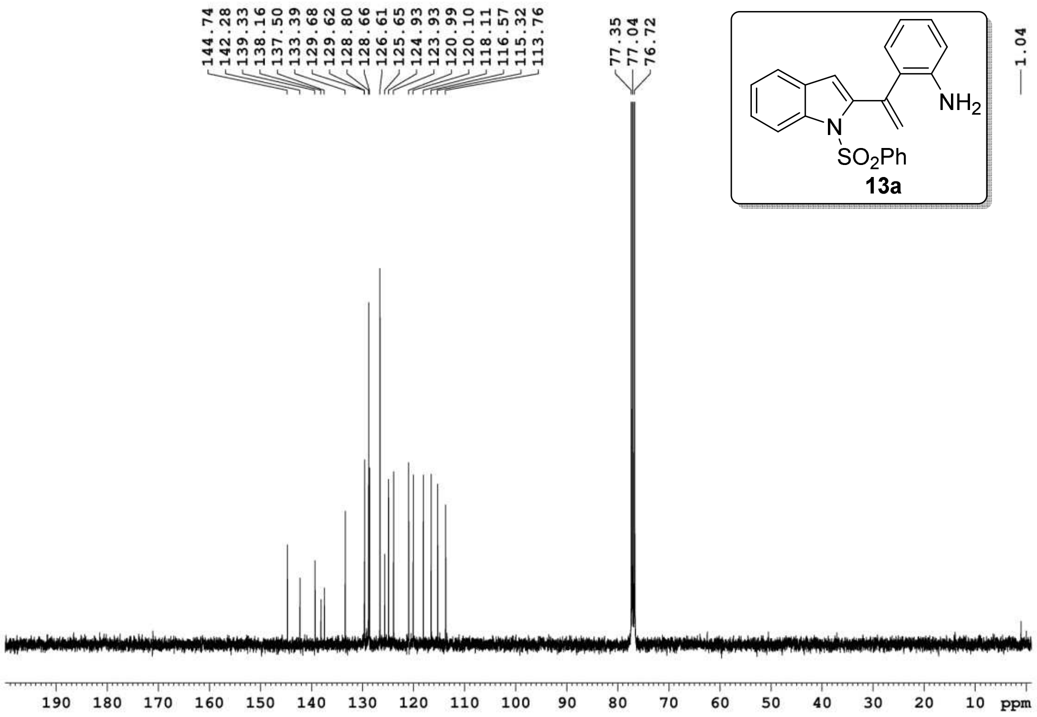
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124.93
123.93
120.99
120.10
118.11
116.57
115.32
113.76
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76.72
1.04
N
NH2
SO2Ph
13a
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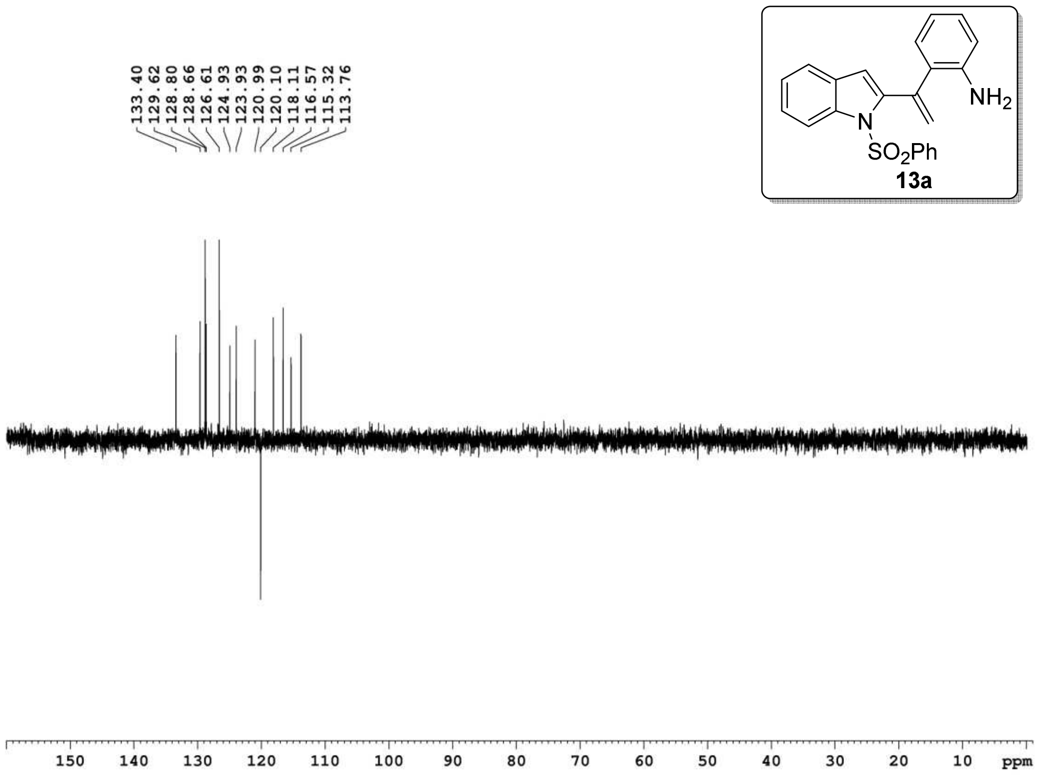
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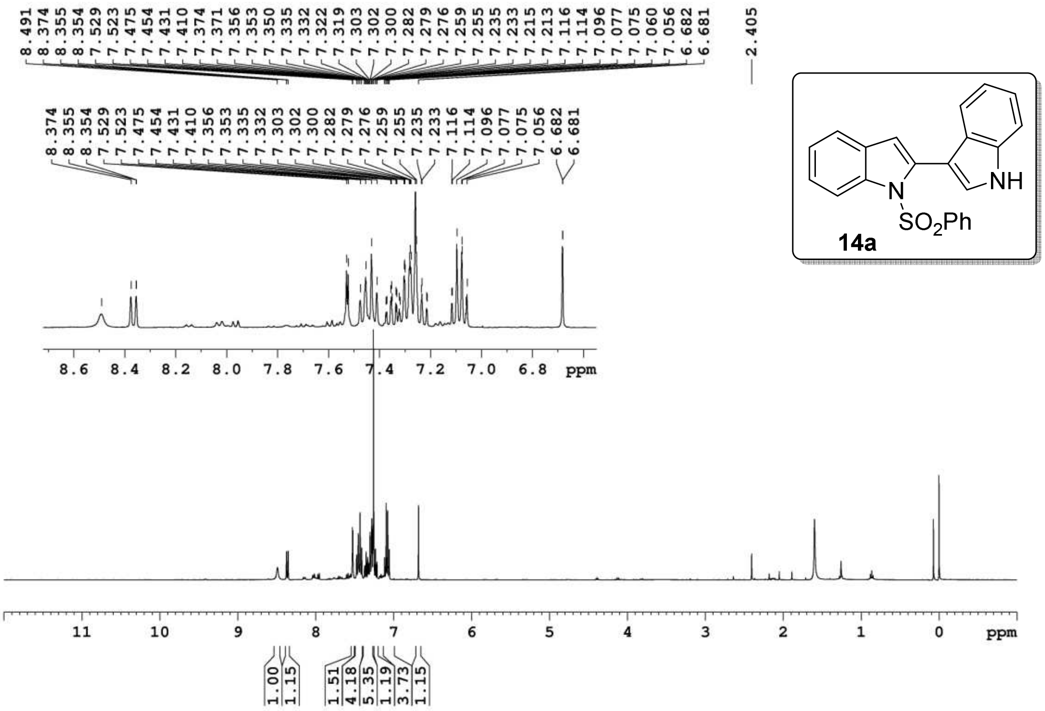
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7.353
7.350
7.335
7.332
7.322
7.319
7.303
7.302
7.300
7.282
7.279
7.276
7.259
7.255
7.235
7.233
7.215
7.213
7.116
7.114
7.096
7.077
7.075
7.060
7.056
6.682
6.681
2.405
8.374
8.355
8.354
7.529
7.523
7.475
7.454
7.431
7.410
7.356
7.353
7.335
7.332
7.303
7.302
7.300
7.282
7.279
7.276
7.259
7.255
7.235
7.233
7.116
7.114
7.096
7.077
7.075
7.056
6.682
6.681
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8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
ppm
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10
9
8
7
6
5
4
3
2
1
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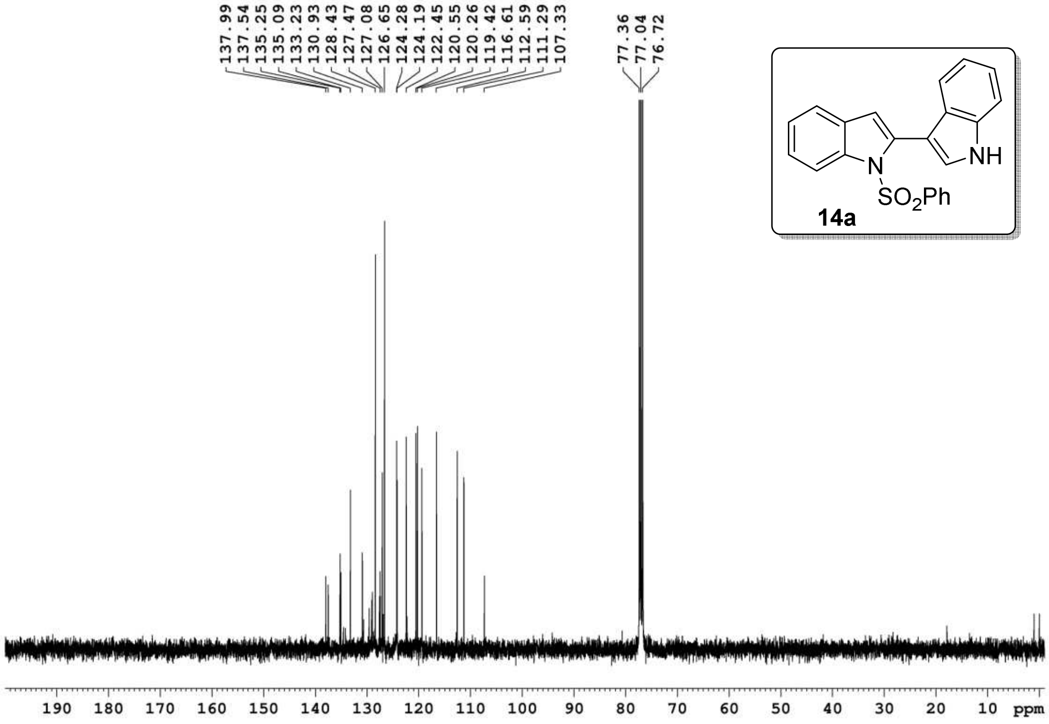
N
NH
SO2Ph
14a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127.47
127.08
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122.45
120.55
120.26
119.42
116.61
112.59
111.29
107.33
77.36
77.04
76.72
190
180
170
160
150
140
130
120
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100
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10
ppm
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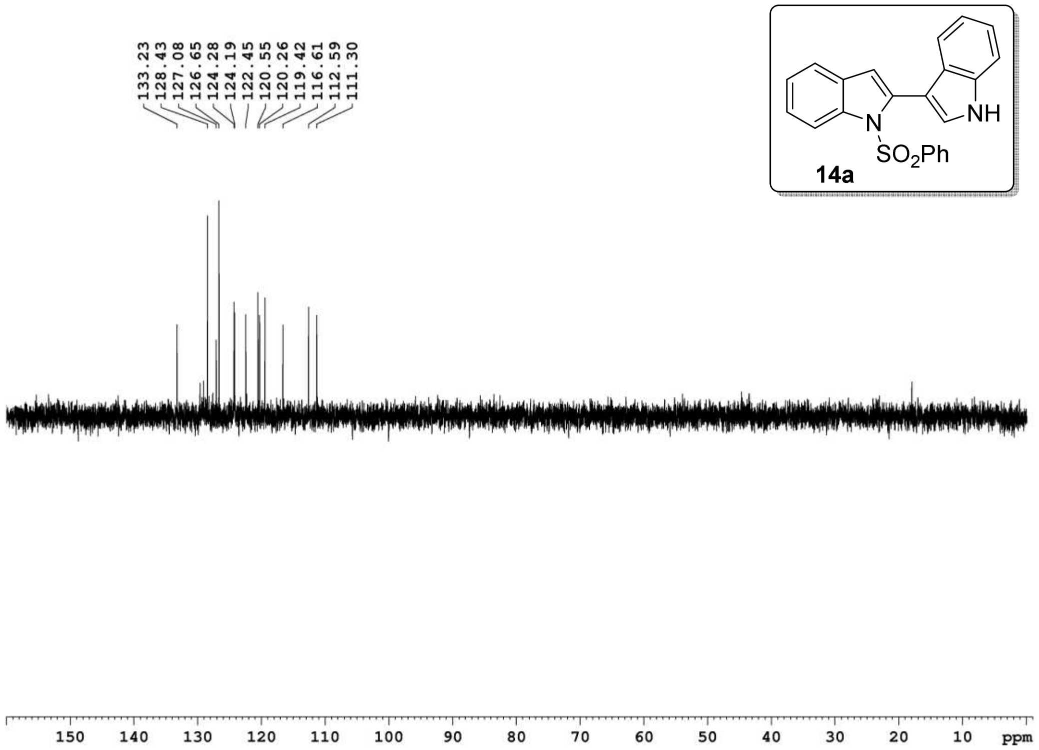
NH
SO2Ph
14a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120.55
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111.30
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SO2Ph
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150
140
130
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110
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90
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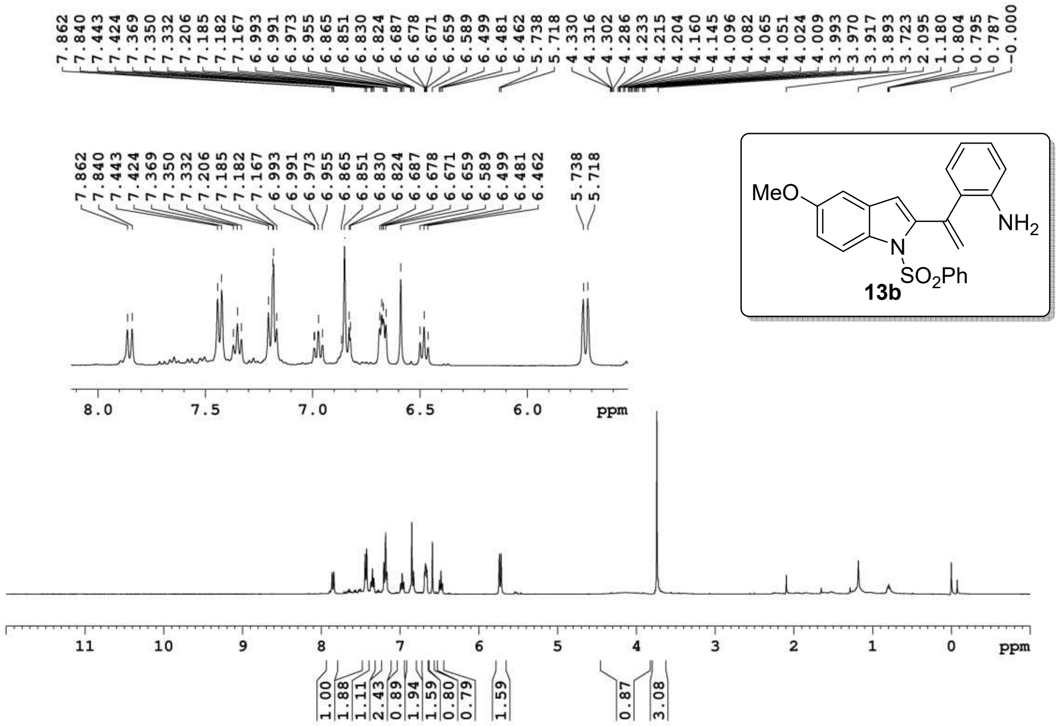
70
60
50
40
30
20
10
ppm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6.991
6.973
6.955
6.865
6.851
6.830
6.824
6.687
6.678
6.671
6.659
6.589
6.499
6.481
6.462
5.738
5.718
4.330
4.316
4.302
4.286
4.233
4.215
4.204
4.160
4.145
4.096
4.082
4.065
4.051
4.024
4.009
3.993
3.970
3.917
3.893
3.723
2.095
1.180
0.804
0.795
0.787
-0.000
MeO
NH2
N
SO2Ph
13b
8.0
7.5
7.0
6.5
6.0
ppm
11
10
9
8
7
6
5
4
3
2
1
0
ppm
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2.43
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1.59
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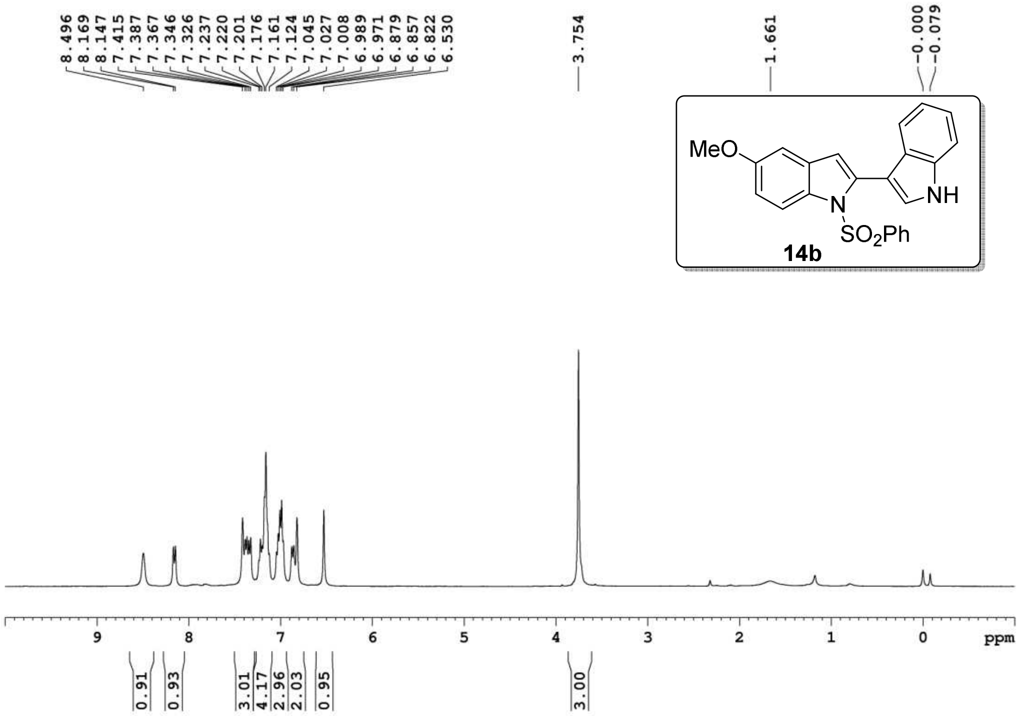
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7.161
7.124
7.045
7.027
7.008
6.989
6.971
6.879
6.857
6.822
6.530
3.754
1.661
-0.000
-0.079
MeO
N
SO2Ph
NH
14b
9
8
7
6
5
4
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1
0
ppm
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0.93
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4.17
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2.03
0.95
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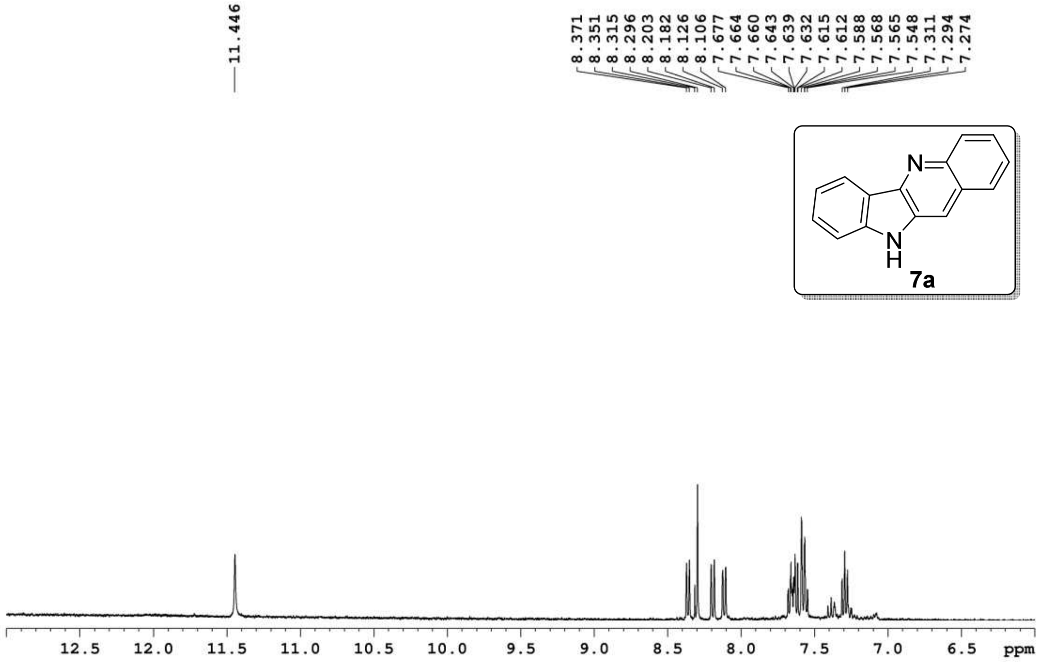
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7.632
7.615
7.612
7.588
7.568
7.565
7.548
7.311
7.294
7.274
N
N
H
7a
12.5
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10.5
10.0
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9.0
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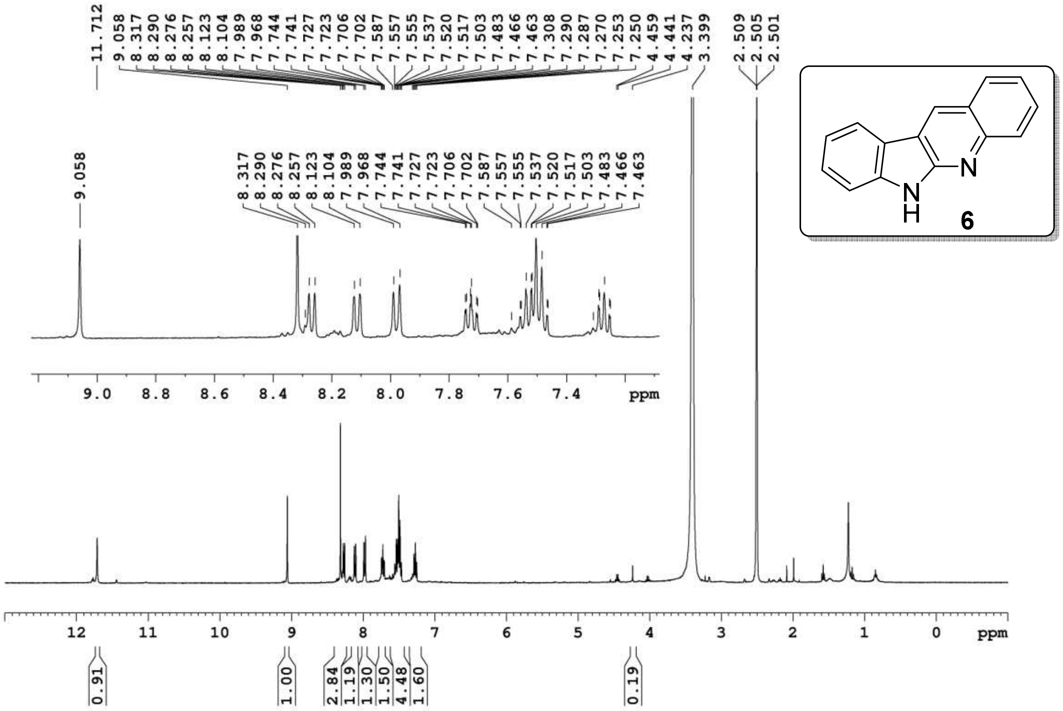
8.0
7.5
7.0
6.5
ppm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4.459 4.441 4.237 3.399
2.509 2.505 2.501
9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 ppm
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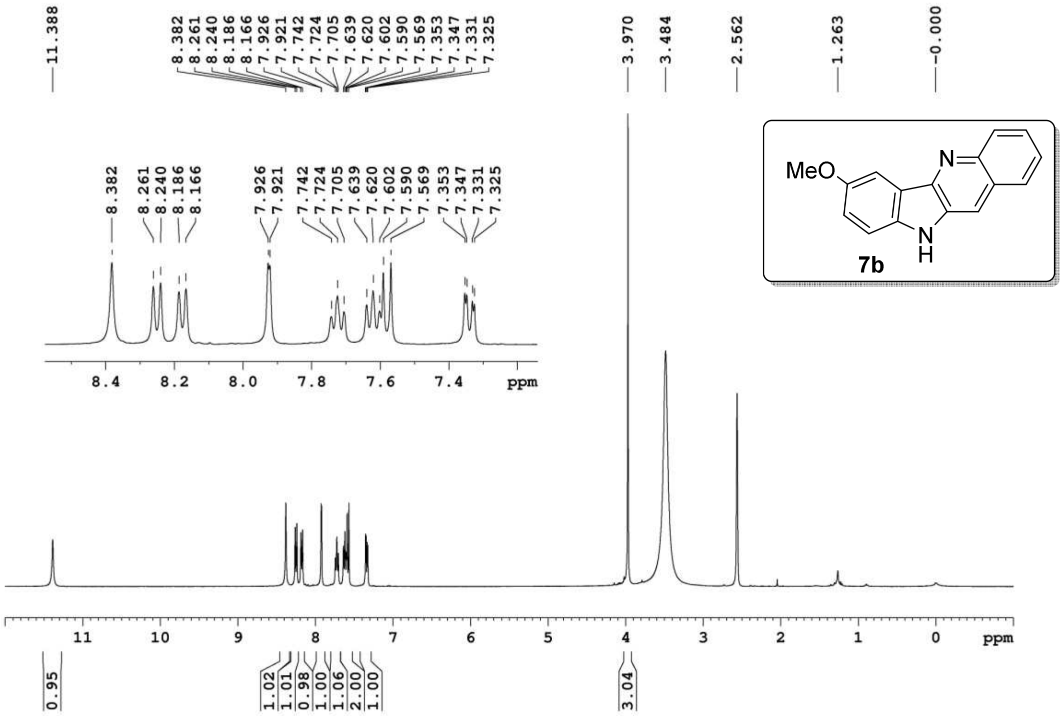
N
H
N
6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3.970
3.484
2.562
1.263
0.000
8.4 8.2 8.0 7.8 7.6 7.4 ppm
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.95
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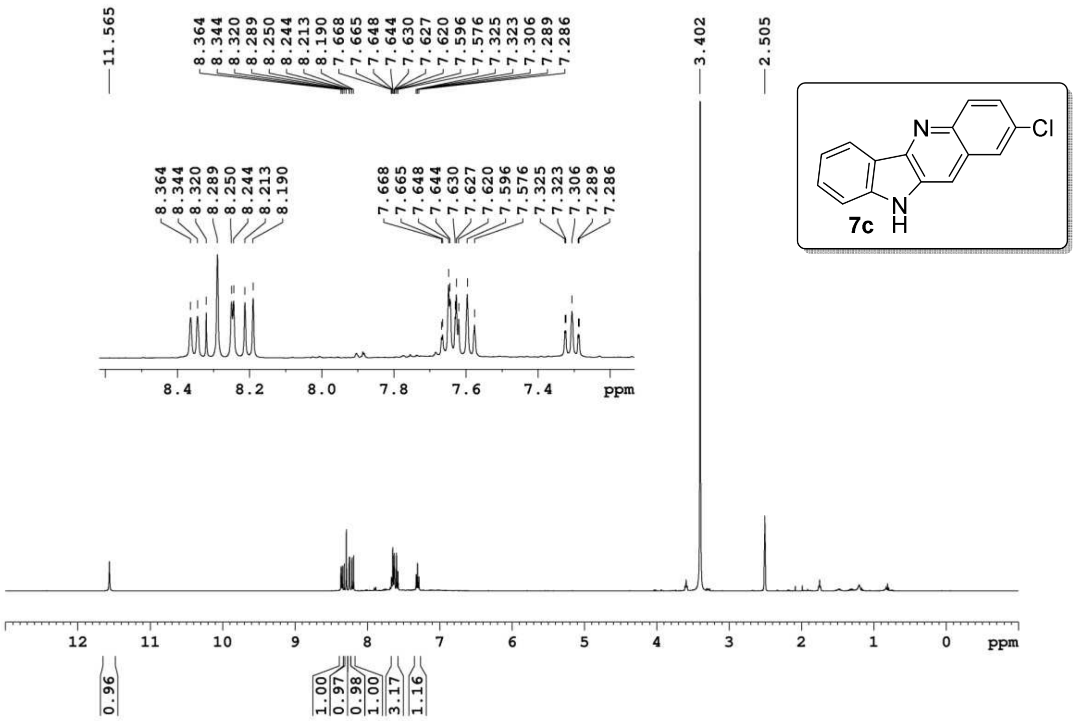
MeO
N
N
H
7b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7.644
7.630
7.627
7.620
7.596
7.576
7.325
7.323
7.306
7.289
7.286
3.402
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N
H
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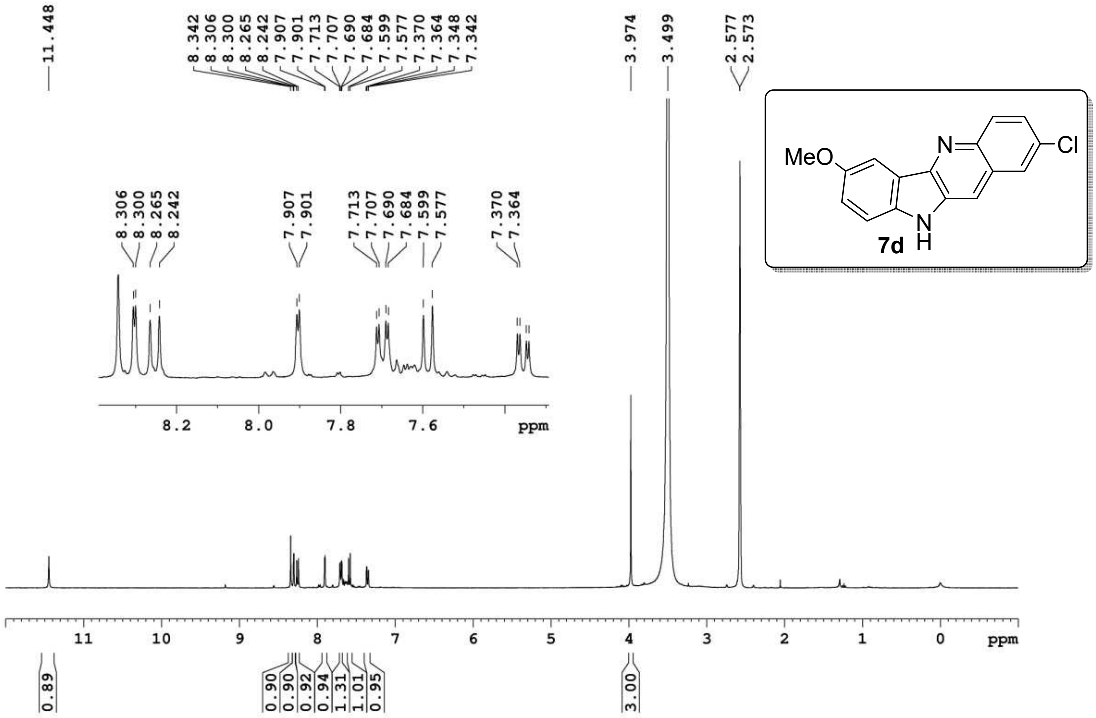
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7.348
7.342
3.974
3.499
2.577
2.573
MeO
N
Cl
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H
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ppm
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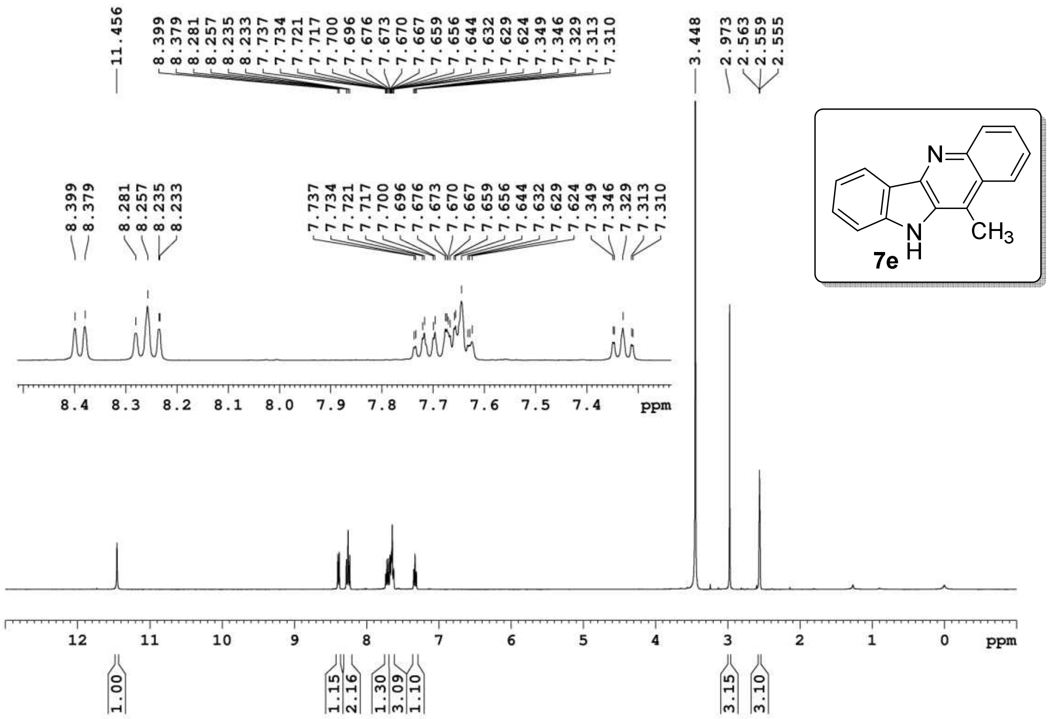
1.01
0.95
3.00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7.667
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7.313
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3.448
2.973
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2.559
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N
CH3
N H
7e
ppm
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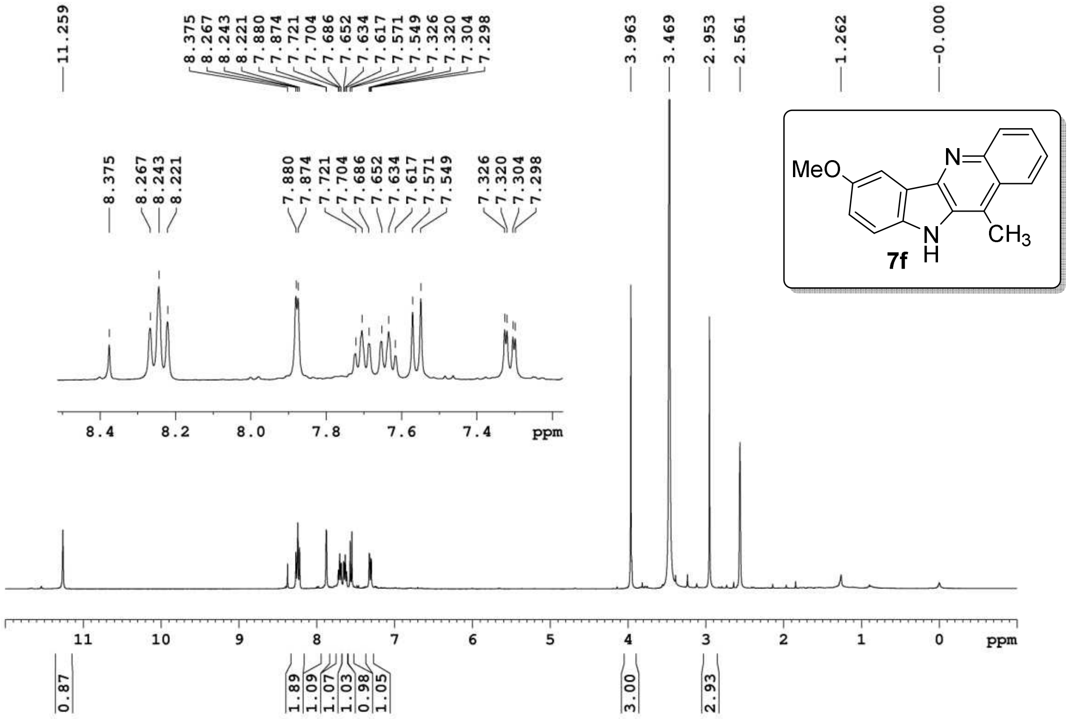
3.10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7.320
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3.469
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-0.000
MeO
N
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N H
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ppm
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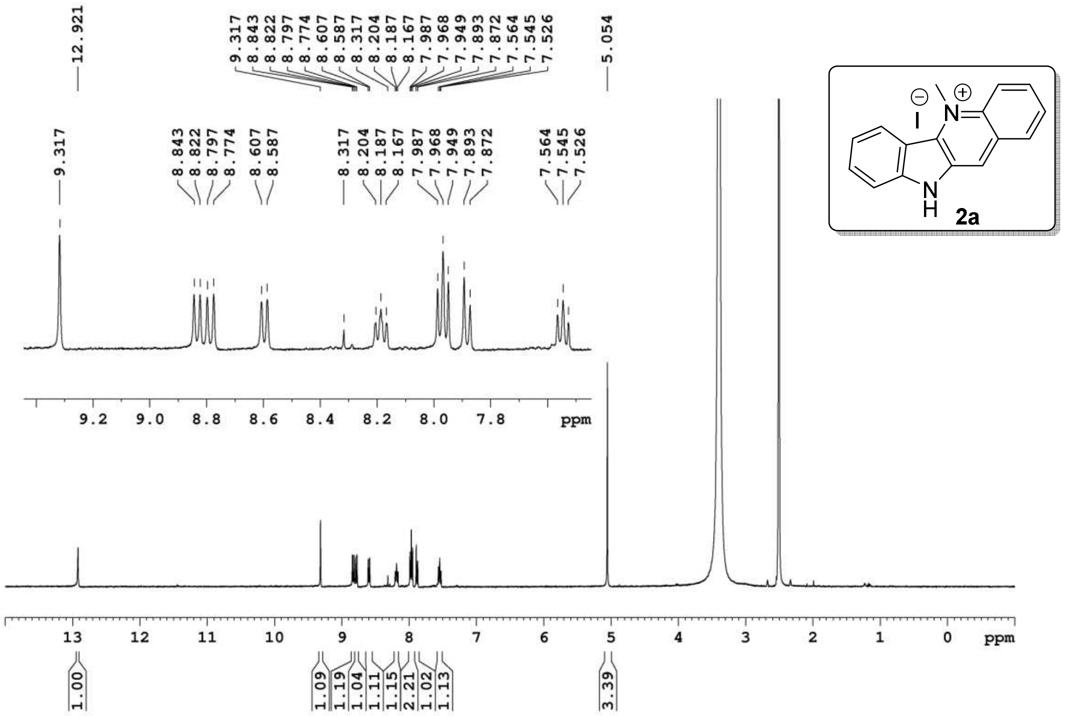
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7.987
7.968
7.949
7.893
7.872
7.564
7.545
7.526
5.054
9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
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1.19
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1.11
1.15
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1.02
1.13
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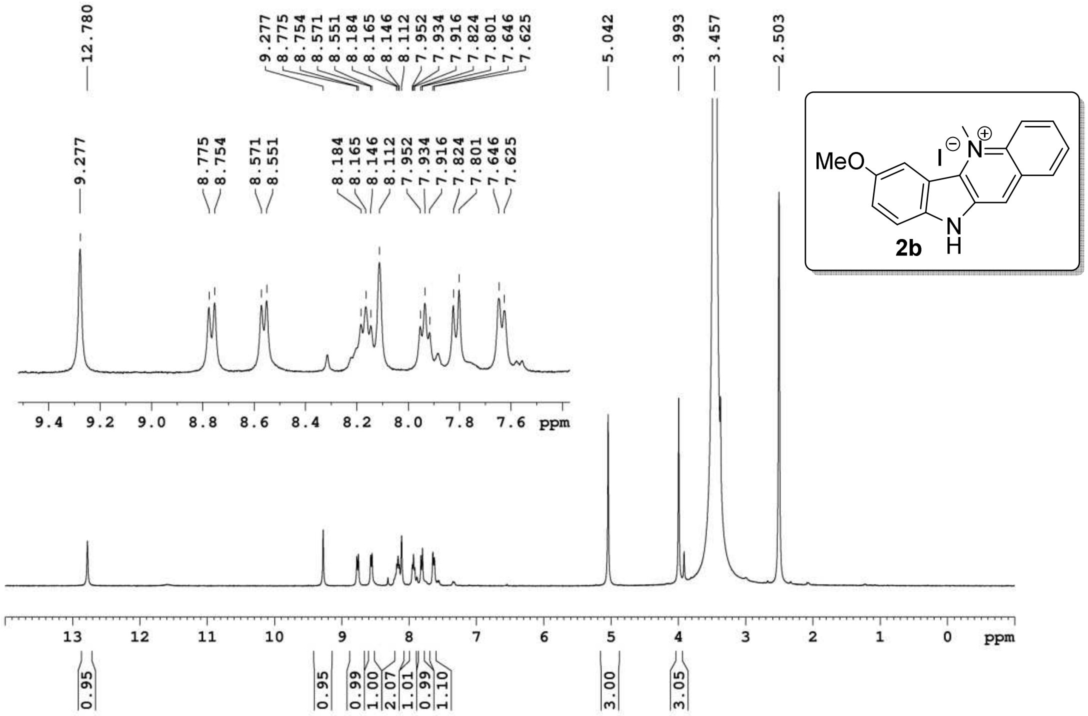
I
N
N
H
2a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7.916
7.824
7.801
7.646
7.625
5.042
3.993
3.457
2.503
9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.95
0.95
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1.01
0.99
1.10
3.00
3.05
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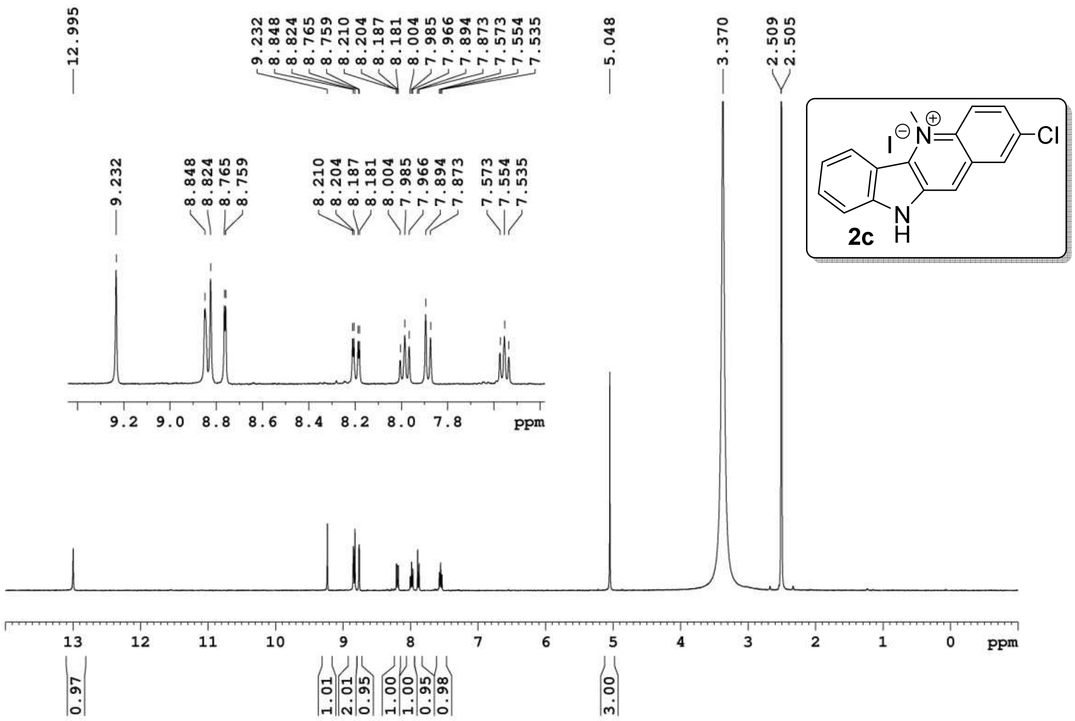
N
H
2b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7.894
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7.573
7.554
7.535
5.048
3.370
2.509
2.505
9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.97
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2.01
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1.00
1.00
0.95
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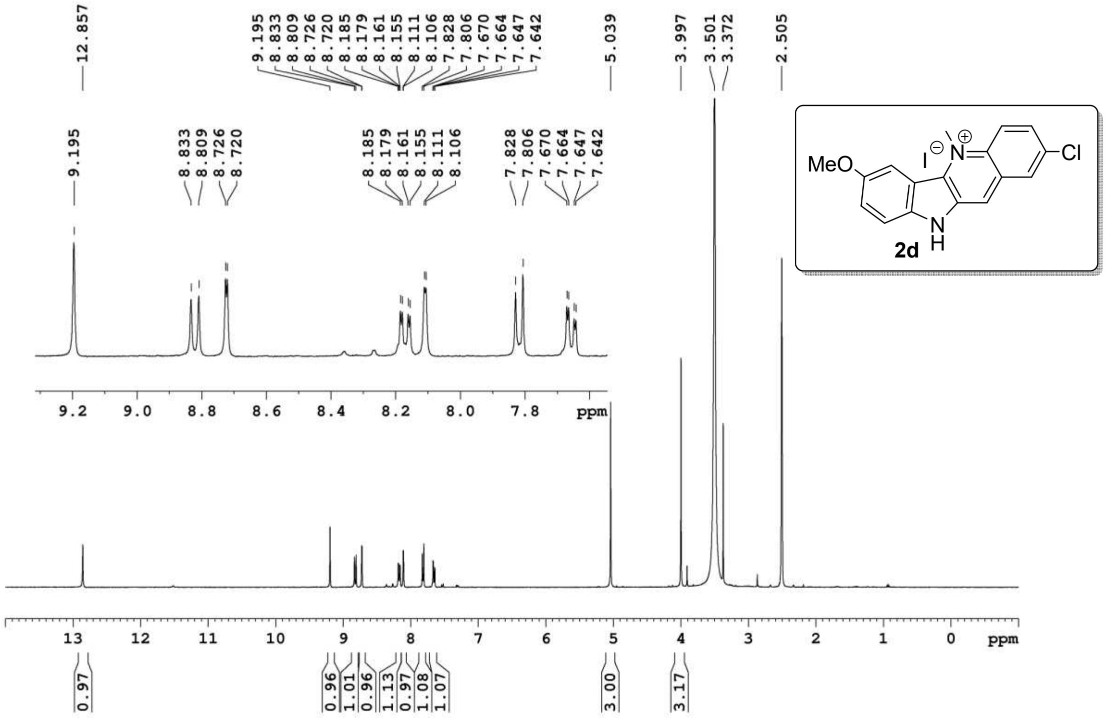
3.00
I
N
Cl
N
H
2c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8.155
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7.828
7.806
7.670
7.664
7.647
7.642
5.039
3.997
3.501
3.372
2.505
9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.97
0.96
1.01
0.96
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0.97
1.08
1.07
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I
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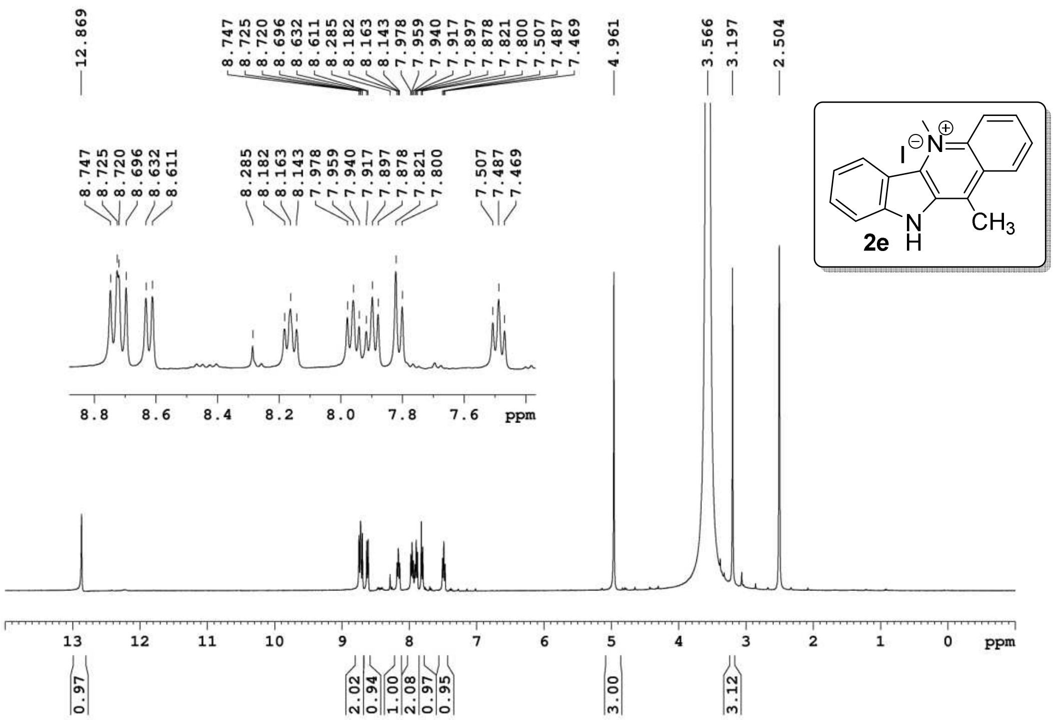
2d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3.566
3.197
2.504
8.8 8.6 8.4 8.2 8.0 7.8 7.6 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
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3.00
3.12
I
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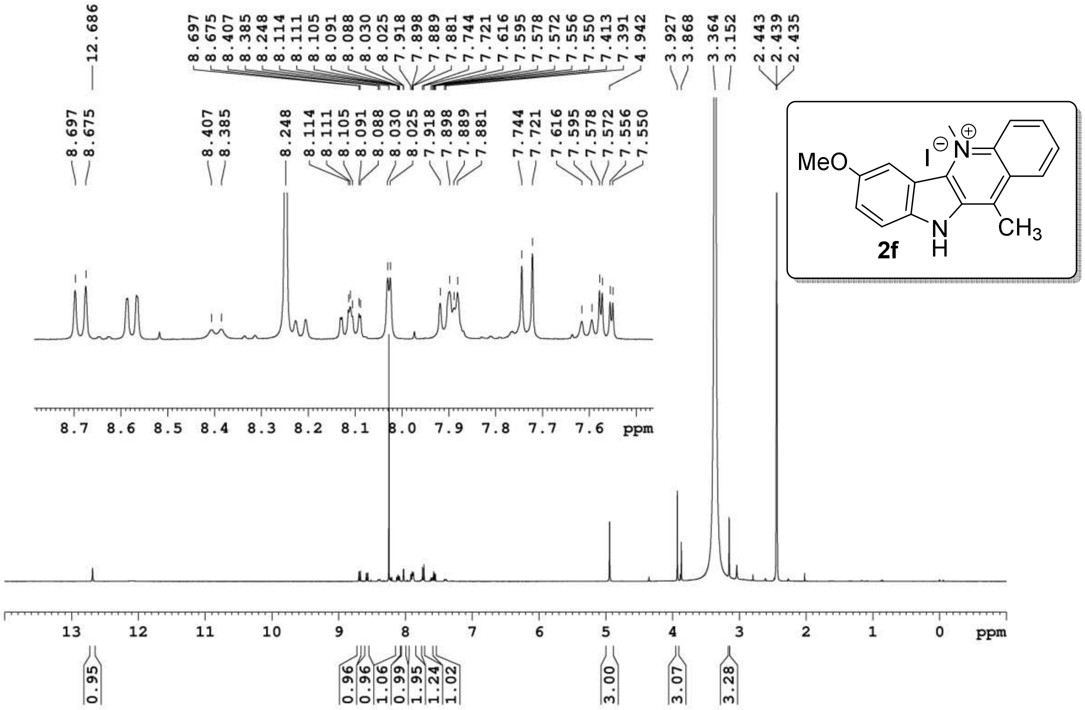
CH3
2e
N
H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3.927 3.868
3.364 3.152
2.443 2.439 2.435
8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.95
0.96 0.96 1.06 0.99 1.95 1.24 1.02
3.00
3.07
3.28
MeO
I
N
CH3
2f
N
H

Chapter 2

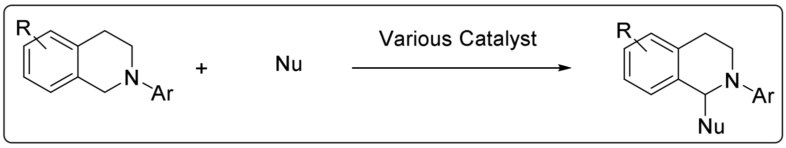
Synthesis of *N*-alkylindolo[3,2-*c*] and [2,3-*c*]quinoline Iodides using Iodine mediated Intramolecular Dehydrogenative Coupling (IMDC)

2.1: Introduction

Construction of C-C bond in an efficient, green and sustainable manner has always been an interesting and challenging task for organic chemists. Over the last few decades, for the construction of C-C bond prefunctionalization of substrate was essential.[1] However, in recent years chemists have achieved the direct formation of C-C bond without substrate prefunctionalization. This allows the synthesis of target molecules in least number of steps.[2] This coupling strategy often comes with the advantages of lower cost and lesser by-products. Cross dehydrogenative coupling (CDC) is one such method which allows direct bond formation and has gained tremendous importance in recent years. However, this C-C bond formation process does not involve the release of H_2 gas as a byproduct and hence the use of sacrificial oxidant becomes an inevitable component.[2c]

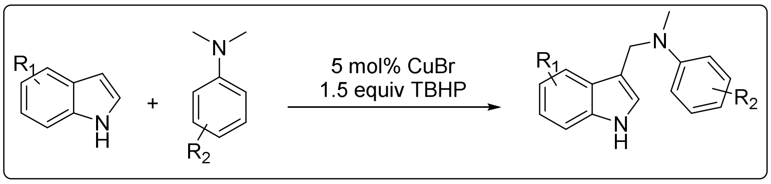
Pioneering studies in the oxidative C-H functionalization of amines have been done by the Murahashi's [3a-d] group and Li's [3e-i] group. Various nucleophiles are added on C-H bond adjacent to amines, ethers, activated ethers, and C-H bonds of alkanes.[4] However, inspite of extensive work in this field, the use of CDC reactions for synthesis of tetracycles leading to synthesis of natural compounds and their scaffolds is less explored and is a challenging task.[2a] A few among the vast explored examples of CDC [4] reaction reported are presented below.

Oxidative functionalization of benzylic C-H in tetrahydroisoquinolines has been well studied with various catalysts. Chao-Jun Li *et al*.[3f] developed CDC with indole as nucleophile using CuBr as a catalyst. Since then various groups have used oxidants like DDQ,[4e, 5a-b] TEMPO,[5c] iodobenzene diactate,[5d] iodine,[5e-f] or transition metals [3c, 3e-i, 4f, 5, 6] or recently photocatalyst such as eosin-Y [7a] or Iridium complexes [7b-f] or just acidic medium. [7g] Even enantioselective synthesis [7h] using oxidative C-H activation is achieved. Thus, this allows a vast scope to produce functionalized tetrahydroisoquinoline derivatives (Scheme 1).



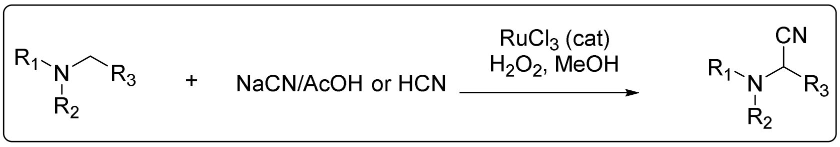
Scheme 1

Huang and co-workers [4m] carried out CDC reaction between indoles and *N*,*N*-dimethyl anilines to afford C-3 alkylated indoles using a catalytic amount of CuBr and oxidant like TBHP (in decane).


R1
N
H
+
N
R2
5 mol% CuBr
1.5 equiv TBHP
R1
N
N
H
R2

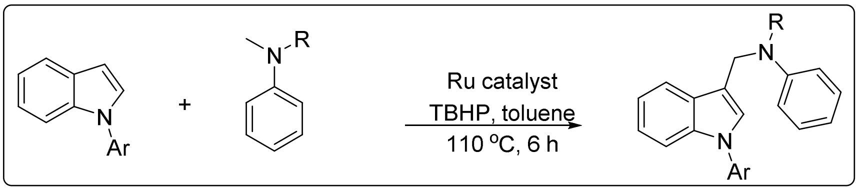
Scheme 2

Murahashi *et al.*[3a] functionalized the sp3 C-H bond adjacent to nitrogen with cyanide using ruthenium catalyst in the presence of hydrogen peroxide or molecular oxygen as oxidants.


R1
N
R3
R2
+
NaCN/AcOH or HCN
RuCl3 (cat)
H2O2, MeOH
CN
R1
N
R3
R2

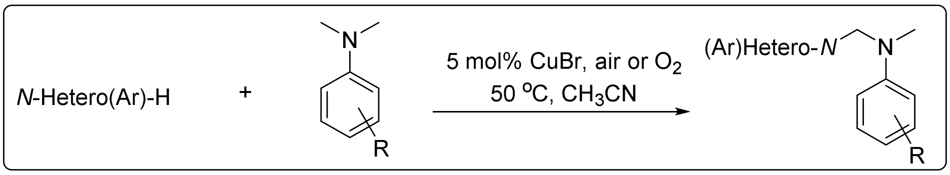
Scheme 3

Che *et al.* [4r] developed an oxidative coupling using TBHP between *tert*- amine and indoles to result in the C-3 alkylation of indole in the presence of ruthenium catalyst.


N
Ar
+
N
R
Ru catalyst
TBHP, toluene
110 °C, 6 h
R
N
N
Ar

Scheme 4

Zhang and co-workers [4s] developed a mild method for the cross coupling reaction between *N*,*N*-dimethylanilines and heteroarenes such as indole, imidazoles, indolizines and anilines using Cu catalyst in the presence of air or molecular oxygen.


N-Hetero(Ar)-H
+
N
R
5 mol% CuBr, air or O2
50 °C, CH3CN
(Ar)Hetero-N
N
R

Scheme 5

Section A: Synthesis of *N*-alkylindolo[3,2-*c*]quinoline Iodides

2. A. 1: Introduction

Isocryptolepine is a naturally occurring terrestrial alkaloid isolated from the roots of the plant *cryptolepis sanguinolenta.* [8a] For ages this plant was used as a traditional medicine source in West and Central Africa and the roots of this plant has been a source of several isomeric indoloquinoline alkaloids having interesting biological properties, moreover showing excellent antimalarial activities. [8b] Isocryptolepine **1** and its synthetic analogue isocryptolepine hydroiodide **2** show promising DNA binding activity accounting for anticancer and cytotoxic properties. [8c, d] *N*-Methyl-isocryptolepine salt **3** is a synthetically prepared derivative showing excellent antiplasmodial activity in the nanomolar range on L6 cells. [8e] Compound **1-3** comprises of indolo[3,2-*c*]quinoline fused system and display a wide range of biological activities. Hence various methods for their synthesis have been reported in recent years and the same is reviewed by Ablordeppey's group [9a] in year 2008 and by our group [9a] in the year 2011.

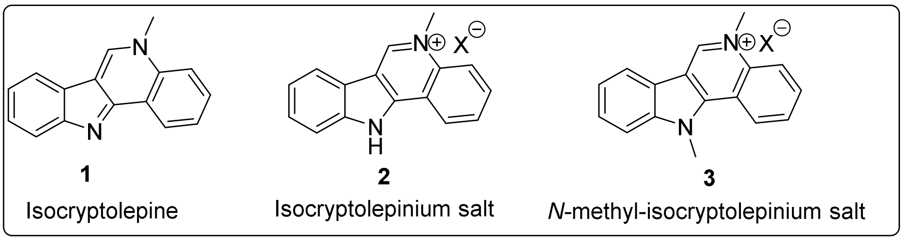
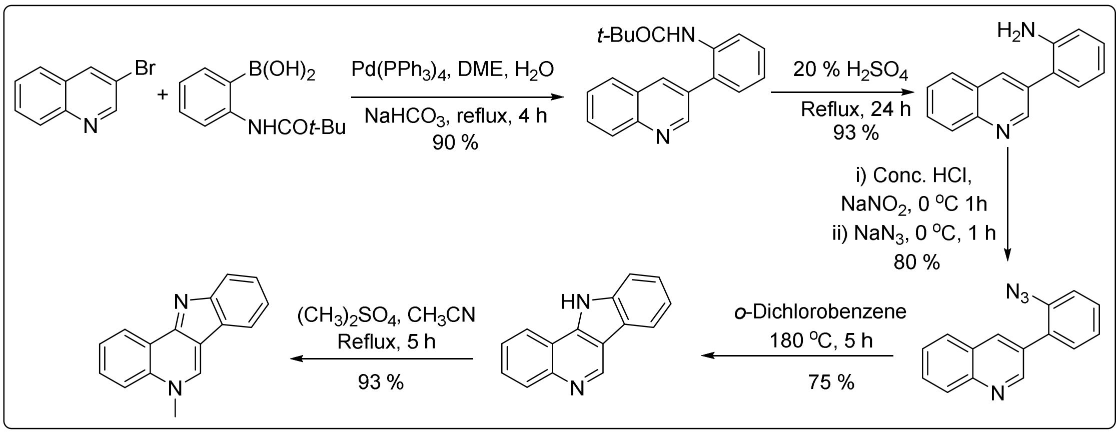

1
Isocryptolepine
2
Isocryptolepinium salt
3
N-methyl-isocryptolepinium salt

Figure 1: Isocryptolepine and its iodide salts

2. A. 2: Literature Reported Methods

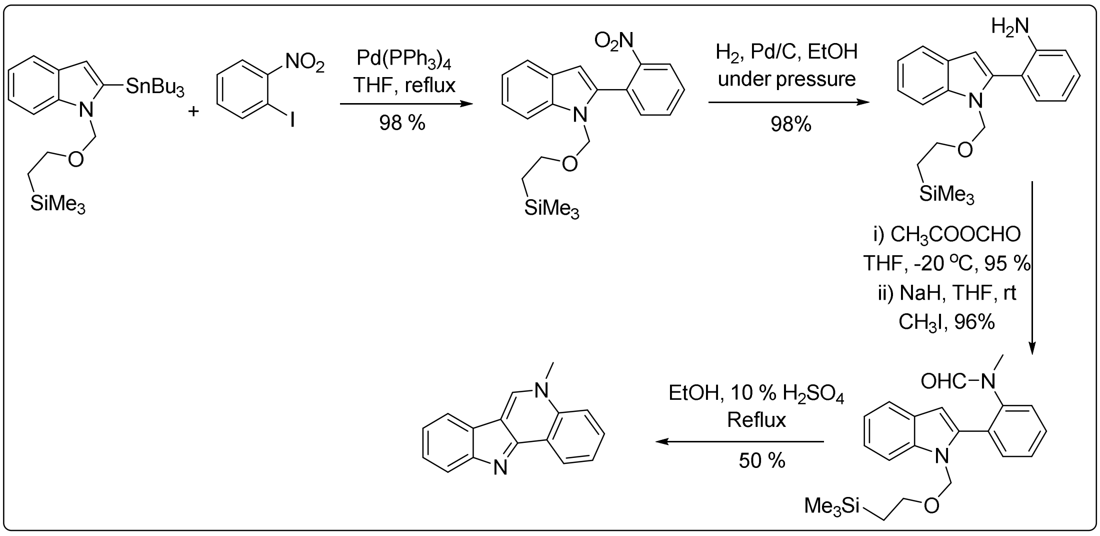
Timari *et al.* [10a] coupled 3-bromoquinoline under Suzuki conditions to give a biaryl amide intermediate which on hydrolysis under acidic condition gave amine (Scheme 6).


Pd(PPh3)4, DME, H2O
NaHCO3, reflux, 4 h
90 %
20 % H2SO4
Reflux, 24 h
93 %
i) Conc. HCl, NaNO2, 0 °C 1h
ii) NaN3, 0 °C, 1 h
80 %
o-Dichlorobenzene
180 °C, 5 h
75 %
(CH3)2SO4, CH3CN
Reflux, 5 h
93 %

Scheme 6

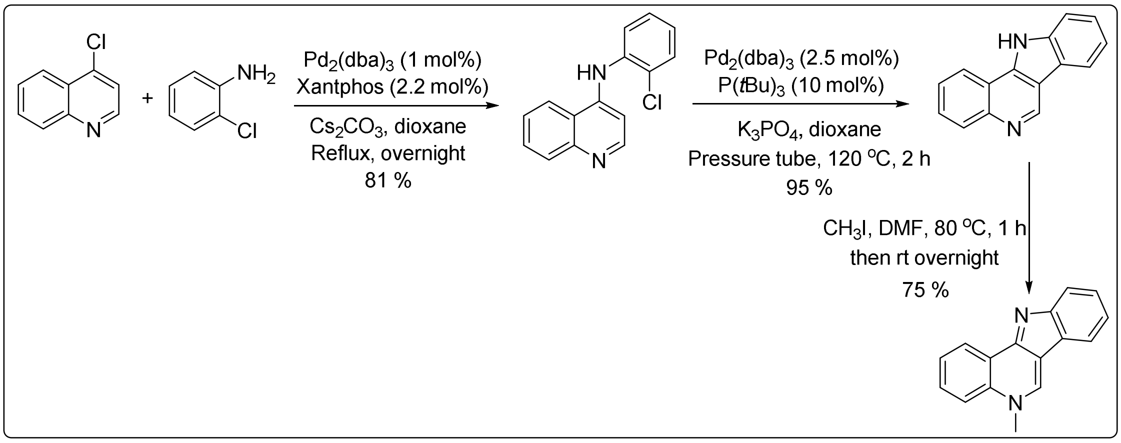
Further diazotisation and treatment with sodium azide afforded azide derivative, which under thermal condition underwent cyclisation to give 11*H*-indolo[3,2-*c*]quinoline core. This upon regioselective methylation gave naturally occurring isocryptolepine.

Murray *et al.* [10b] treated *N*-protected 2-stannyl indole under Stille conditions with 2-iodonitrobenzene to give substituted 2-aryl indole. Reduction of aromatic nitro functionality to amine followed by *N*-formylation and *N*-methylation gave the intermediate which under acid reflux in alcohol gave isocryptolepine (Scheme 7).


SnBu$_3$
N
O
SiMe$_3$
+
NO$_2$
I
Pd(PPh$_3$)$_4$
THF, reflux
98 %
O$_2$N
H$_2$, Pd/C, EtOH
under pressure
98%
H$_2$N
i) CH$_3$COOCHO
THF, -20 ^oC, 95 %
ii) NaH, THF, rt
CH$_3$I, 96%
OHC–N
Me$_3$Si
EtOH, 10 % H$_2$SO$_4$
Reflux
50 %

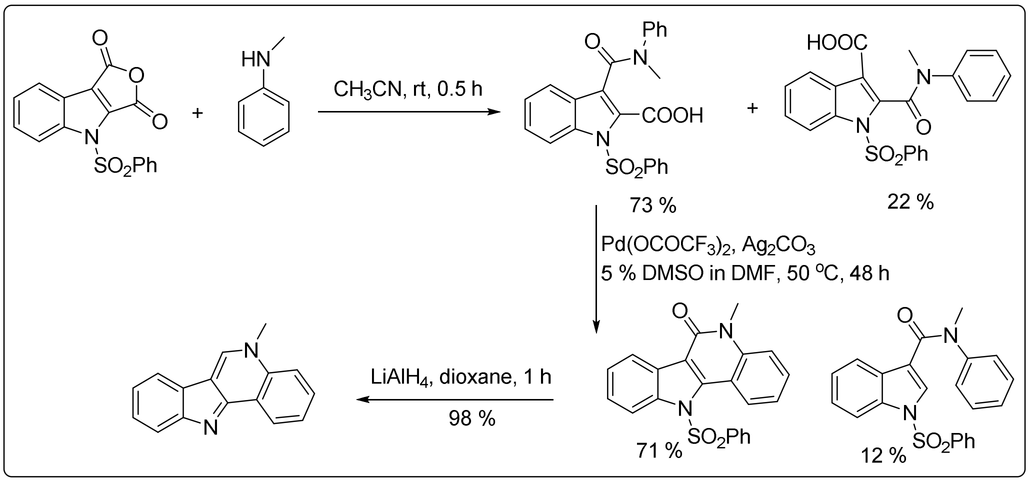
Scheme 7

Jonckers *et al.* [10c] carried out a selective Buchwald-Hartwig reaction between 2-chloroaniline and 4-chloroquinoline with palladium catalyst followed by intramolecular Heck reaction to give the tetracyclic core which upon methylation gave isocryptolepine (Scheme 8).


Cl
N
+
NH$_2$
Cl
Pd$_2$(dba)$_3$ (1 mol%)
Xantphos (2.2 mol%)
Cs$_2$CO$_3$, dioxane
Reflux, overnight
81 %
HN
Pd$_2$(dba)$_3$ (2.5 mol%)
P(*t*Bu)$_3$ (10 mol%)
K$_3$PO$_4$, dioxane
Pressure tube, 120 ^oC, 2 h
95 %
HN
CH$_3$I, DMF, 80 ^oC, 1 h
then rt overnight
75 %

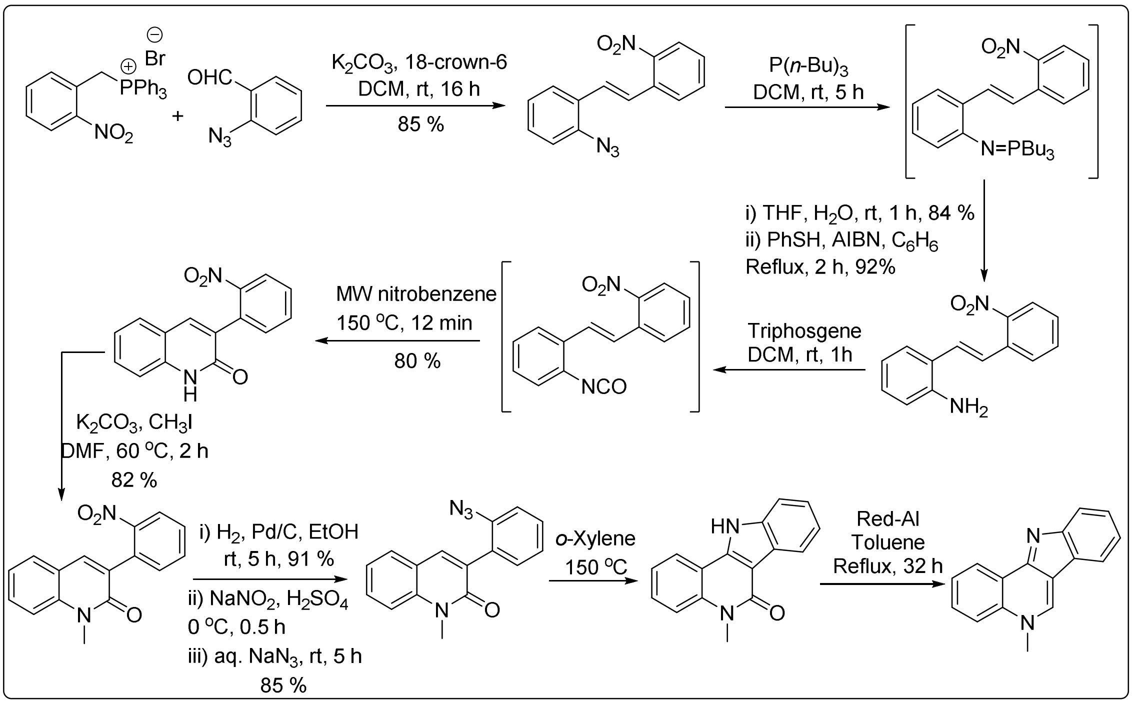
Scheme 8

Miki *et al*.[10d] followed Myers method [10e] and reacted anhydride with *N*-methylaniline to give both possible amides (Scheme 9). Treatment of major acid under decarboxylative Heck cyclisation with palladium[II]triflate and silver carbonate gave the desired cyclized product along with a minor uncyclized decarboxylated compound. Major cyclized compound on reduction with LAH underwent desulfonation to give isocryptolepine.


CH_3CN, rt, 0.5 h
73 %
22 %
$Pd(OCOCF_3)_2$, Ag_2CO_3
5 % DMSO in DMF, 50 °C, 48 h
$LiAlH_4$, dioxane, 1 h
98 %
71 %
12 %
SO_2Ph
COOH
HOOC
Ph

Scheme 9

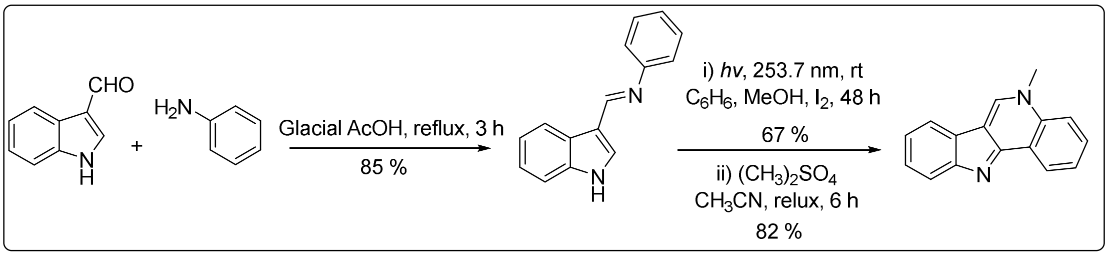
Fresneda and Molina [10f] carried out Wittig reaction between 2-azidobenzaldehyde and phosphonium bromide under basic medium to get *E/Z* alkene (Scheme 10). The alkene mixture was then converted into iminophosphorane which on hydrolysis followed by isomerization of alkene gave *E*-stilbene derivative.


K_2CO_3, 18-crown-6
DCM, rt, 16 h
85 %
$P(n\text{-}Bu)_3$
DCM, rt, 5 h
N=PBu_3
i) THF, H_2O, rt, 1 h, 84 %
ii) PhSH, AIBN, C_6H_6
Reflux, 2 h, 92%
Triphosgene
DCM, rt, 1h
MW nitrobenzene
150 °C, 12 min
80 %
NCO
NH_2
K_2CO_3, CH_3I
DMF, 60 °C, 2 h
82 %
i) H_2, Pd/C, EtOH
rt, 5 h, 91 %
ii) $NaNO_2$, H_2SO_4
0 °C, 0.5 h
iii) aq. NaN_3, rt, 5 h
85 %
o-Xylene
150 °C
Red-Al
Toluene
Reflux, 32 h

Scheme 10

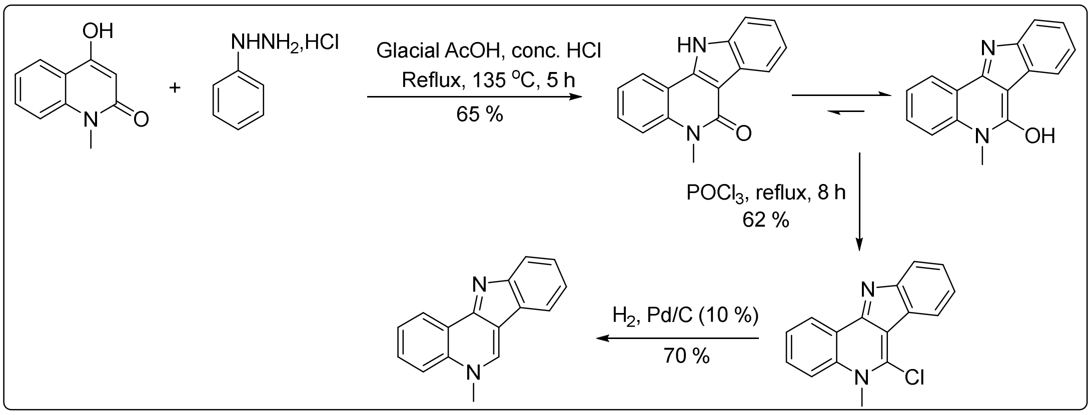
This was reacted with phosgene to obtain an isocyanate, which on microwave heating in nitrobenzene furnished the 3-substituted quinolin-2-one. Further conversion of the nitrophenyl quinolinone to the corresponding azido compound followed by nitrene mediated cyclization afforded isocryptolepine.

Ila and co-workers [10g] condensed 3-formylindole with aniline under acidic conditions to give Schiff's base which under photochemical cyclization in the presence of iodine underwent *E* to *Z* isomerization followed by ring closure and oxidation to yield 11*H*-indolo[3,2-*c*]quinoline which was then methylated (Scheme 11).


CHO
N
H
+
H2N
Glacial AcOH, reflux, 3 h
85 %
N
N
H
i) hv, 253.7 nm, rt
C6H6, MeOH, I2, 48 h
67 %
ii) (CH3)2SO4
CH3CN, relux, 6 h
82 %
N
N

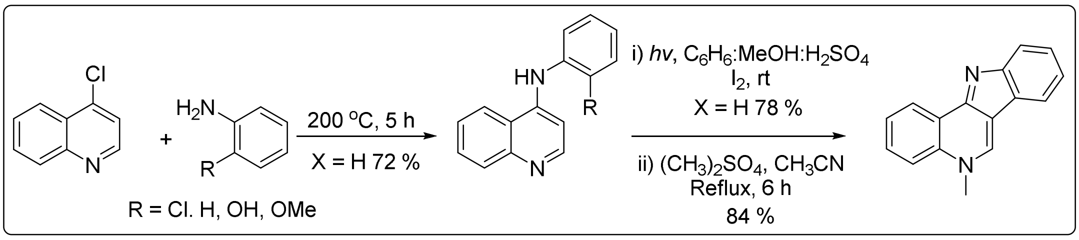
Scheme 11

Dhanabal *et al.* [10j] achieved synthesis of isocryptolepine using Fischer indole cyclization from 4-hydroxy-1-methyl-1*H*-quinolin-2-one and phenylhydrazine hydrochloride to give the indoloquinolinone which after treatment with $POCl_3$ and followed by hydrogenolysis gave the target molecule (Scheme 12).


OH
N
O
+
NHNH2,HCl
Glacial AcOH, conc. HCl
Reflux, 135 °C, 5 h
65 %
HN
N
O
N
N
OH
POCl3, reflux, 8 h
62 %
N
N
Cl
H2, Pd/C (10 %)
70 %
N
N

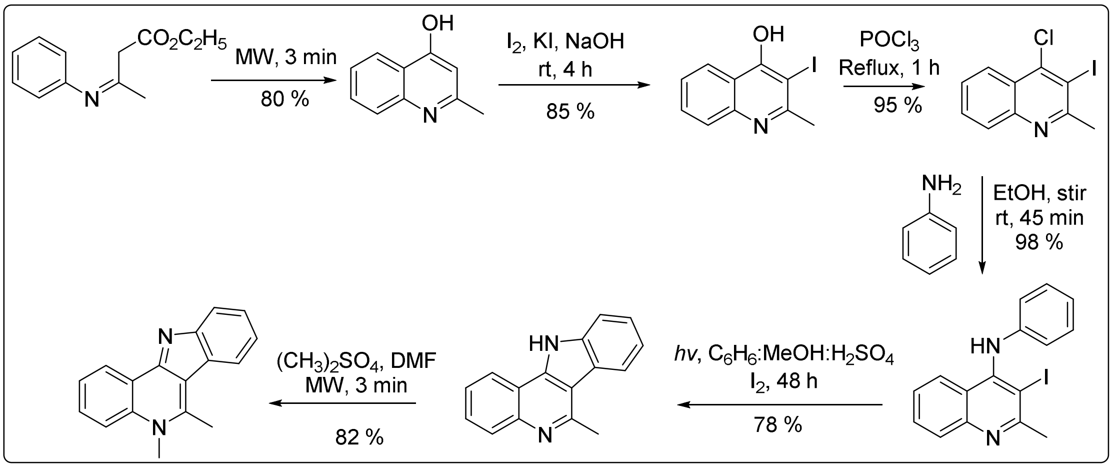
Scheme 12

Mohan and co-workers [10h] treated 4-chloroquinoline and anilines to give *N*-phenylquinolin-4-amine *via* nucleophillic substitution reaction which was photo-cyclized and methylated to give isocryptolepine (Scheme 13).



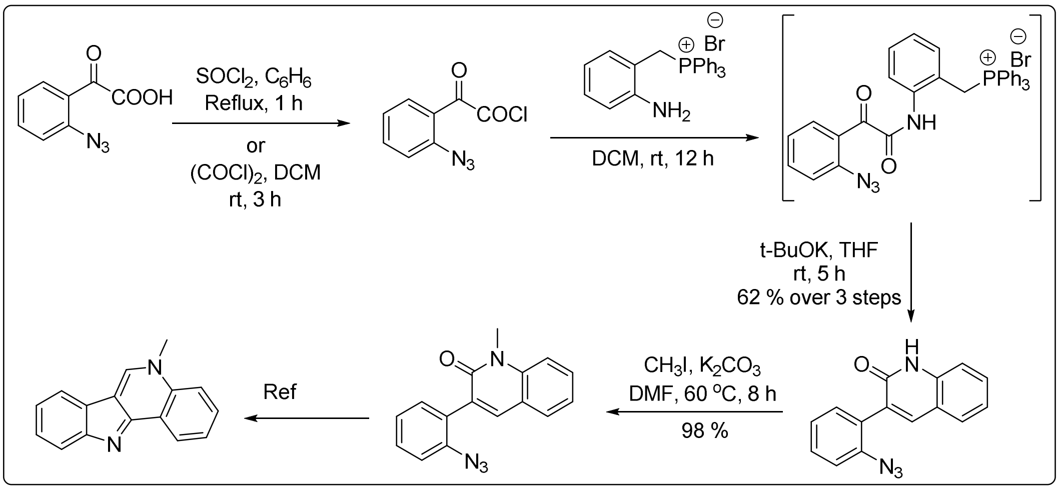
Scheme 13

Pitchai *et al.* [10i] have described a synthesis of methyl derivative of isocryptolepine. *β*-Anilinocrotonate on microwave irradiation gave 4-hydroxy-2-methyl quinoline which on iodination and then treatment with $POCl_3$ gave 4-chloro-3-iodo-2-methylquinoline. Nucleophillic displacement of the chloro group with aniline followed by photocyclization and *N*-methylation gave substituted methyl isocryptolepine (Scheme 14).



Scheme 14

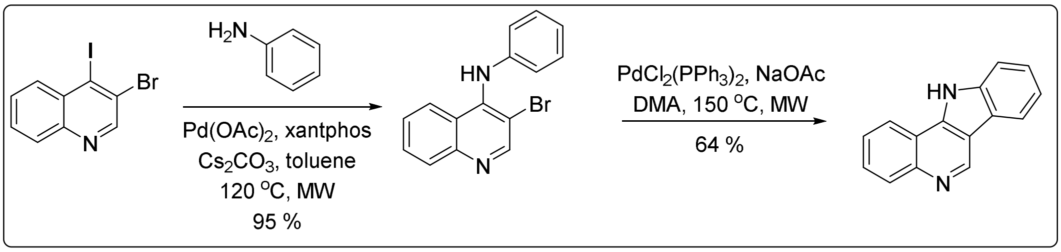
Kraus *et al.*[10k] converted 2-(2-azidophenyl)-2-oxoacetic acid to its corresponding acid chloride and carried out amidation with (2-aminobenzyl)triphenylphosphonium bromide.



Scheme 15

The intermediate was then treated with base to carryout intramolecular Wittig reaction to give 3-(2-azidophenyl)quinolin-2(1*H*)-one (Scheme 15). Methylation followed by the reductive cyclization under thermal conditions, according to the method described in Scheme 10 resulted in isocryptolepine.

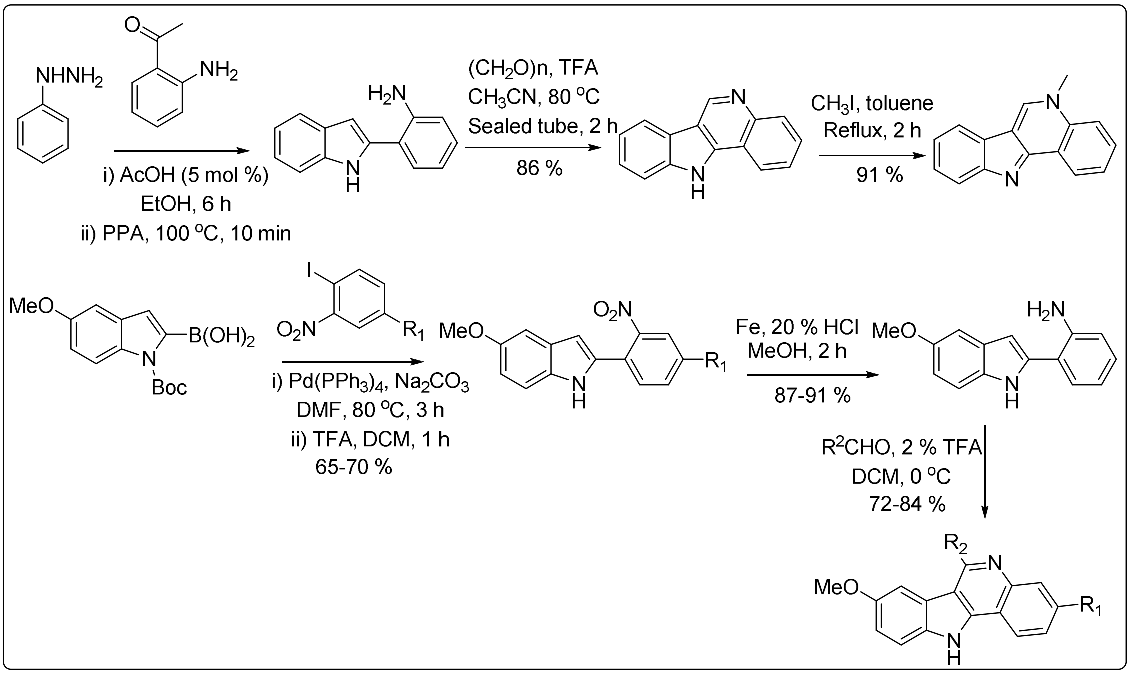
Boganyi and Kaman [10l] synthesised 11*H*-indolo[3,2-*c*]quinoline *via* consecutive palladium coupling reactions. First a regioselective Buchwald-Hartwig amination between 3-bromo-4-iodoquinoline and aniline followed by intramolecular Heck coupling furnished the desired compound (Scheme 16).



I
Br
N
H2N
Pd(OAc)2, xantphos
Cs2CO3, toluene
120 °C, MW
95 %
HN
Br
N
PdCl2(PPh3)2, NaOAc
DMA, 150 °C, MW
64 %
HN
N

Scheme 16

Kunduand co-workers [10m] developed a synthesis of isocryptolepine and substituted isocryptolepines *via* modified Pictet-Spengler cyclization reaction. The intermediate 2-(1*H*-indol-2-yl) aniline was synthesized using Fischer indole cyclization followed by Pictet-Spengler cyclization to give 11*H*-indolo[3,2-*c*]quinoline. Regioselective methylation gave isocryptolepine (Scheme 17).

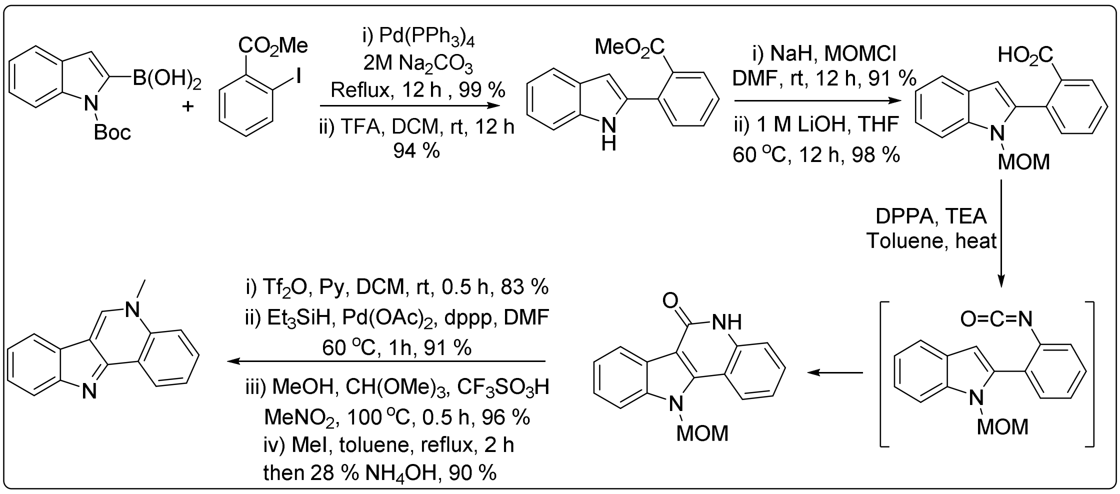


NHNH2
O
NH2
i) AcOH (5 mol %)
EtOH, 6 h
ii) PPA, 100 °C, 10 min
H2N
N
H
(CH2O)n, TFA
CH3CN, 80 °C
Sealed tube, 2 h
86 %
N
N
H
CH3I, toluene
Reflux, 2 h
91 %
N
N
MeO
B(OH)2
N
Boc
I
O2N
R1
i) Pd(PPh3)4, Na2CO3
DMF, 80 °C, 3 h
ii) TFA, DCM, 1 h
65-70 %
MeO
O2N
R1
N
H
Fe, 20 % HCl
MeOH, 2 h
87-91 %
MeO
H2N
N
H
R2CHO, 2 % TFA
DCM, 0 °C
72-84 %
R2
N
MeO
R1
N
H

Scheme 17

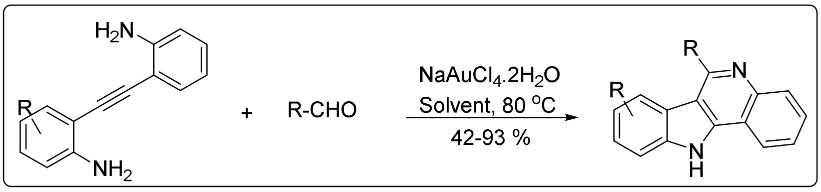
For substituted isocryptolepine the key intermediate was synthesized from 2-(5-methoxy-1*H*-indol-2-yl)aniline which was obtained from the Suzuki coupling reaction between (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid and 4-substituted 1-iodo-2-nitrobenzene followed by reduction of the nitro group to amine (Scheme 17). The amine on Pictet-Spengler cyclization reaction with a variety of benzaldehydes gave substituted isocryptolepines.

Hibino and co-workers [10n] carried out Suzuki coupling between (1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid and methyl 2-iodobenzoate, followed by protection of the N-H group and hydrolysis to give 2-(1-(methoxymethyl)-1*H*-indol-2-yl)benzoic acid (Scheme 18). This on treatment with diphenylphosphoryl azide gave the isocyanate intermediate which underwent Curtius rearrangement and electrocyclic cyclization to give tetracyclic lactum. Further sequential four steps furnished isocryptolepine.


B(OH)2
N
Boc
+
CO2Me
I
i) Pd(PPh3)4
2M Na2CO3
Reflux, 12 h , 99 %
ii) TFA, DCM, rt, 12 h
94 %
MeO2C
N
H
i) NaH, MOMCl
DMF, rt, 12 h, 91 %
ii) 1 M LiOH, THF
60 °C, 12 h, 98 %
HO2C
N
MOM
DPPA, TEA
Toluene, heat
O=C=N
N
MOM
O
NH
N
MOM
i) Tf2O, Py, DCM, rt, 0.5 h, 83 %
ii) Et3SiH, Pd(OAc)2, dppp, DMF
60 °C, 1h, 91 %
iii) MeOH, CH(OMe)3, CF3SO3H
MeNO2, 100 °C, 0.5 h, 96 %
iv) MeI, toluene, reflux, 2 h
then 28 % NH4OH, 90 %
N
N

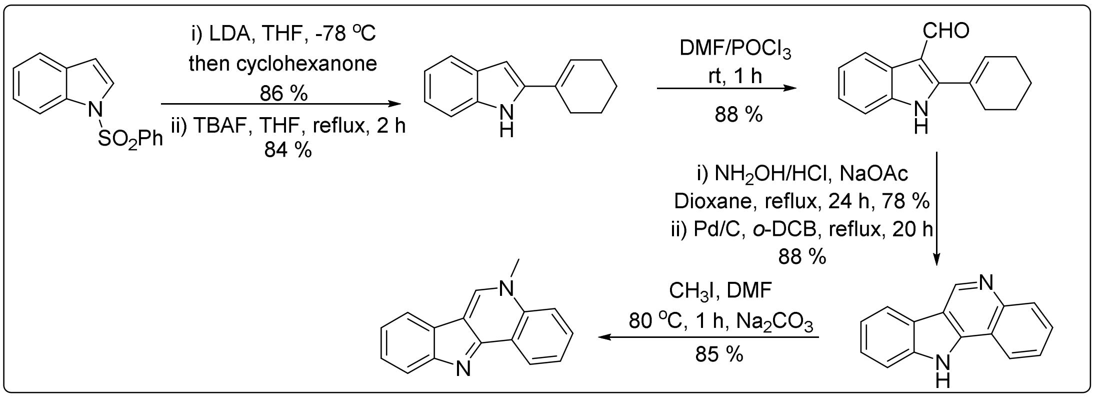
Scheme 18

Arcadi and co-workers [10o] described a regioselective gold catalyzed one-pot reaction between 2-[(2-aminophenyl)ethynyl]phenylamines and aldehydes to give 6-substituted-11*H*-indolo[3,2-*c*]quinoline and its derivatives under mild and neutral conditions (Scheme 19).


H2N
R
NH2
+
R-CHO
NaAuCl4.2H2O
Solvent, 80 °C
42-93 %
R
R
N
N
H

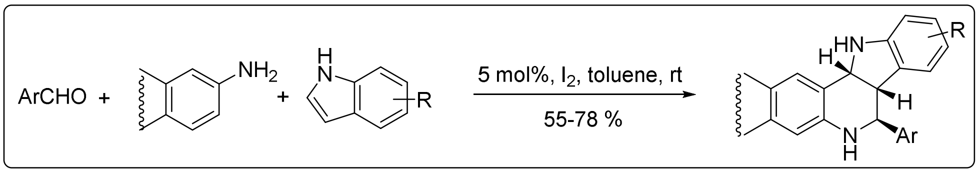
Scheme 19

Hingane and Kusurkar[10p] metallated 1-(phenylsulfonyl)-1*H*-indole at 2-position of indole ring and treated with cyclohexanone. The *tert*-alcohol obtained was then deprotected and dehydrated to give 2-(cyclohex-1-en-1-yl)-1H-indole. Vilsmeier-Haack formylation and oximation with hydroxylamine hydrochloride in refluxing dioxane gave tetracycle *via* electrocyclisation. Dehydrogenative aromatisation and methylation gave isocryptolepine (Scheme 20).


i) LDA, THF, -78 °C
then cyclohexanone
86 %
ii) TBAF, THF, reflux, 2 h
84 %
SO2Ph
DMF/POCl3
rt, 1 h
88 %
CHO
i) NH2OH/HCl, NaOAc
Dioxane, reflux, 24 h, 78 %
ii) Pd/C, o-DCB, reflux, 20 h
88 %
CH3I, DMF
80 °C, 1 h, Na2CO3
85 %

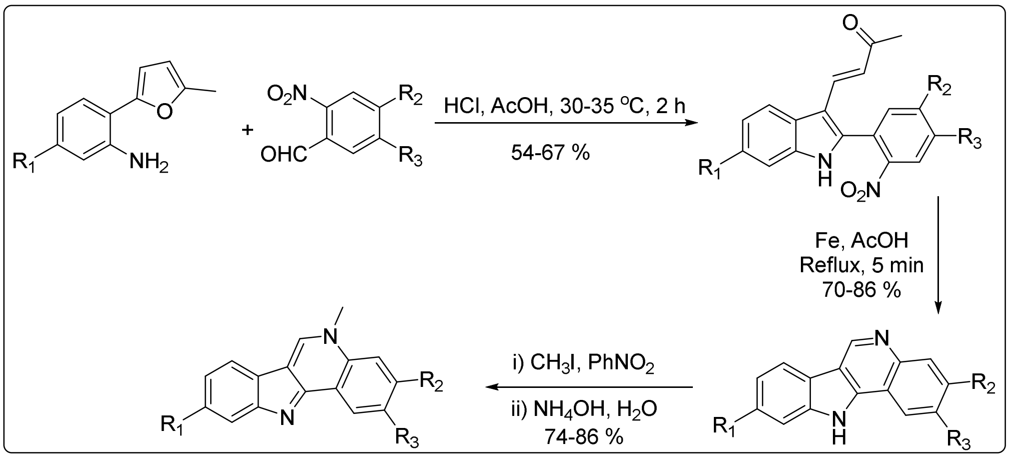
Scheme 20

Wang *et al.* [10q] described an iodine mediated three component Povarov reaction between an aldehyde, aromatic amine and indole to give indolo[3,2-*c*]quinoline core in high selectivity. This Povarov reaction was then applied to prepare a variety of compounds having indolo[3,2-*c*]quinoline system (Scheme 21).


ArCHO +
NH2
+
R
5 mol%, I2, toluene, rt
55-78 %
HN
R
H
H
Ar

Scheme 21

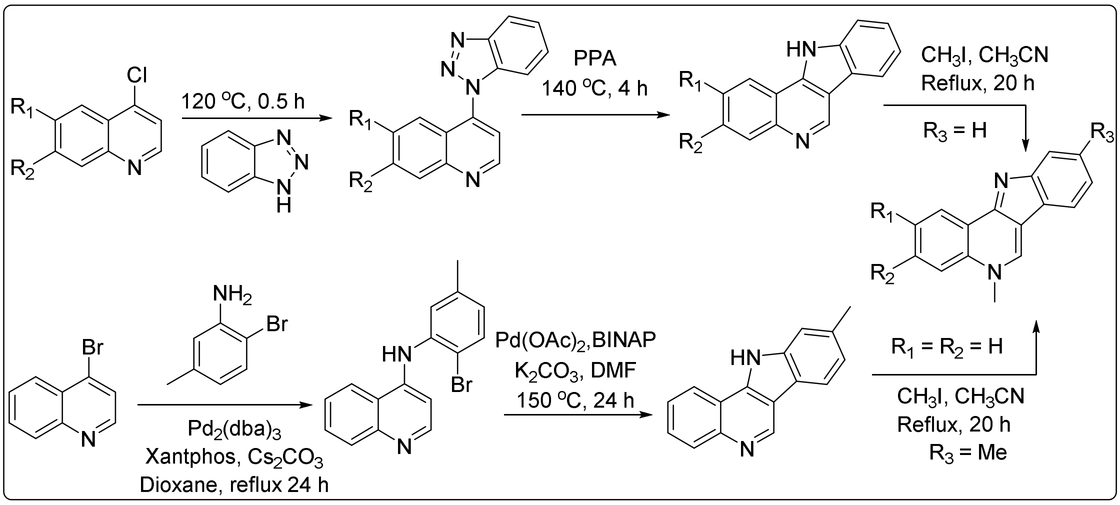
Butin and co-workers [10r] synthesized isocryptolepine and its derivatives from 2-furylanilines obtained from furfural by a series of transformations (Scheme 22).


R1
NH2
O
+
O2N
OHC
R2
R3
HCl, AcOH, 30-35 °C, 2 h
54-67 %
O2N
Fe, AcOH
Reflux, 5 min
70-86 %
i) CH3I, PhNO2
ii) NH4OH, H2O
74-86 %

Scheme 22

2-Furylanilines on treatment with 2-nitrobenzaldehydes under acidic condition gave 2-(2-nitrophenyl)indoles which on reduction with Fe/HCl underwent reductive cyclization to give indolo-[3,2-*c*]-quinoline core. Methylation of this gave isocryptolepines.

Murray and co-workers [10s] synthesized and analyzed the activity of isocryptolepine and its derivative, using a procedure described by Molina and co-workers. [10t]

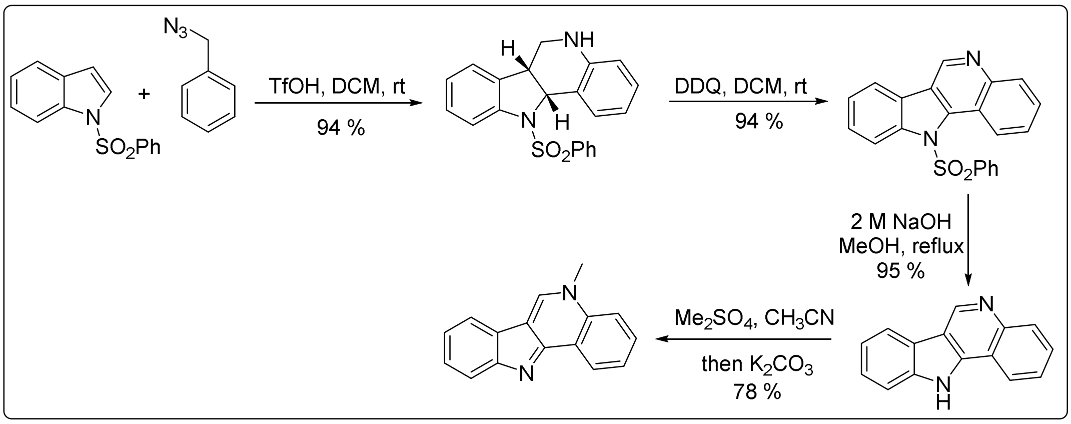


120 °C, 0.5 h
PPA
140 °C, 4 h
CH3I, CH3CN
Reflux, 20 h
R3 = H
Pd2(dba)3
Xantphos, Cs2CO3
Dioxane, reflux 24 h
Pd(OAc)2,BINAP
K2CO3, DMF
150 °C, 24 h
R1 = R2 = H
CH3I, CH3CN
Reflux, 20 h
R3 = Me

Scheme 23

Adduct obtained on nucleophillic displacement of chloro group of 4-chloroquinolines with benzotriazole was heated with polyphosphoric acid to give indolo[3,2-*c*]quinolines which on methylation gave isocryptolepines (Scheme 23). 9-Methylisocryptolepine was synthesized by modifying Jonckers *et al.*’s [10u] method.

Tummatorn *et al.* [10v] trapped the iminium ion generated from arylmethyl azide formed by Aube-Schmidt’s rearrangement under acidic conditions with various nucleophiles (Scheme 24).

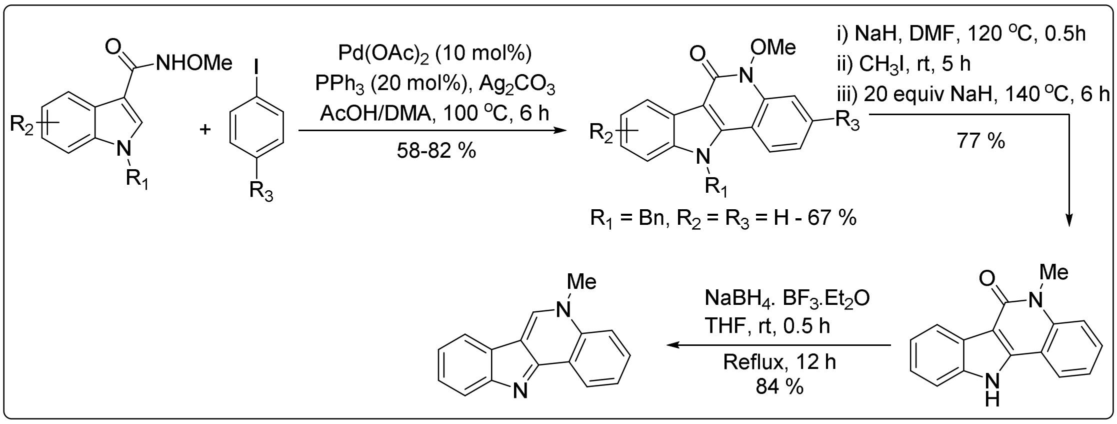


TfOH, DCM, rt
94 %
DDQ, DCM, rt
94 %
2 M NaOH
MeOH, reflux
95 %
Me2SO4, CH3CN
then K2CO3
78 %

Scheme 24

This was followed by a cycloaddition reaction to give polycyclic heteroaromatic compounds. Isocryptolepine was synthesized by employing this method from 1-(phenylsulfonyl)-1*H*-indole and (azidomethyl)benzene. 11-(Phenylsulfonyl)-6,6a,11,11a-tetrahydro-5*H*-indolo[3,2-*c*]quinoline thus obtained was aromatized with DDQ and then base mediated desulfonation followed by methylation gave isocryptolepine.

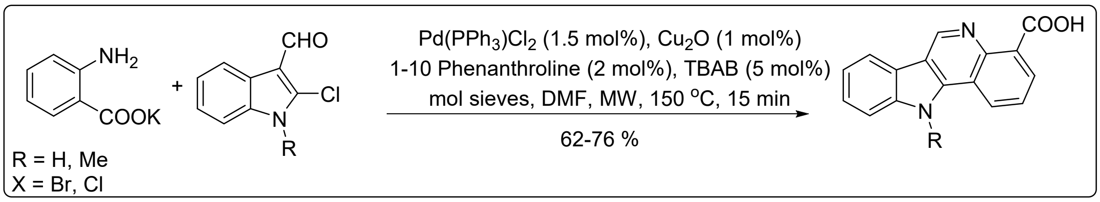
Yao and co-workers [10w] constructed the indoloquinoline framework by Pd-catalyzed tandem C-C and C-N bond formation (Scheme 25).


Pd(OAc)2 (10 mol%)
PPh3 (20 mol%), Ag2CO3
AcOH/DMA, 100 °C, 6 h
58-82 %
i) NaH, DMF, 120 °C, 0.5h
ii) CH3I, rt, 5 h
iii) 20 equiv NaH, 140 °C, 6 h
77 %
R1 = Bn, R2 = R3 = H - 67 %
NaBH4. BF3.Et2O
THF, rt, 0.5 h
Reflux, 12 h
84 %

Scheme 25

Treating 1-benzyl-*N*-methoxy-1*H*-indole-3-carboxamide with iodobenzene under optimized condition provided 11-benzyl-5-methoxy-5,11-dihydro-6*H*-indolo[3,2-*c*]quinolin-6-one. This on removal of methoxy group, methylation, debenzylation and reduction gave isocryptolepine.

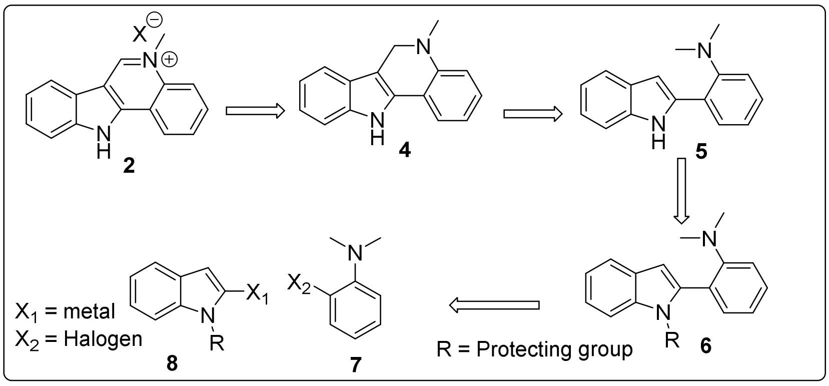
Batra and co-workers [10x] described a Pd/Cu catalyzed two component cyclization reaction to give substituted phenanthridines and pyrazolo[4,3-*c*]quinolines. The same method was applied for synthesis of isocryptolepine skeleton from potassium 2-aminobenzoate and 2-halo-1*H*-indole-3-carbaldehyde or 2-halo-1-methyl-1*H*-indole-3-carbaldehyde to give corresponding 11*H*-indolo[3,2-*c*]quinoline-4-carboxylic acid or 11-methyl-11*H*-indolo[3,2-*c*]quinoline-4-carboxylic acid (Scheme 26).


Pd(PPh3)Cl2 (1.5 mol%), Cu2O (1 mol%)
1-10 Phenanthroline (2 mol%), TBAB (5 mol%)
mol sieves, DMF, MW, 150 °C, 15 min
62-76 %
R = H, Me
X = Br, Cl

Scheme 25

2. A. 3: Results and Discussion

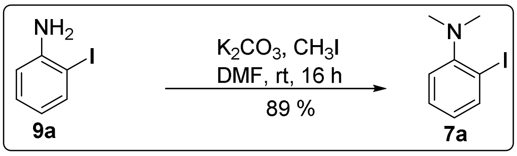
Although various methods for synthesis of 11*H*-indolo[3,2-*c*]quinolines are available, none of the methods involve direct synthesis using activation of sp3 bond adjacent to aromatic nitrogen. We envisaged an activation of sp3 bond adjacent to the nitrogen atom to synthesize the isocryptolepine framework. Retrosynthetic pathway for this is shown in Scheme 27.



Scheme 27

We thought isocryptolepine salt **2** to be an oxidized product of the intermediate **4** which in turn could be obtained from the intramolecular dehydrogenative coupling of intermediate **5**. This key intermediate **5** could be obtained from corresponding *N*-protected indole derivative **6** which we intended to synthesize by coupling reaction between 2-halo-*N*,*N*-dimethylaniline **7** and *N*-protected-2-metallated indole **8**.

Following our retrosynthetic pathway we prepared the required 2-iodo-*N*,*N*-dimethylaniline **7a** according to the procedure described by Larock and co-workers [11a] from 2-iodoaniline **9a** and its ^{1}H NMR chemical shift values were found in accordance with the reported values (Scheme 28).

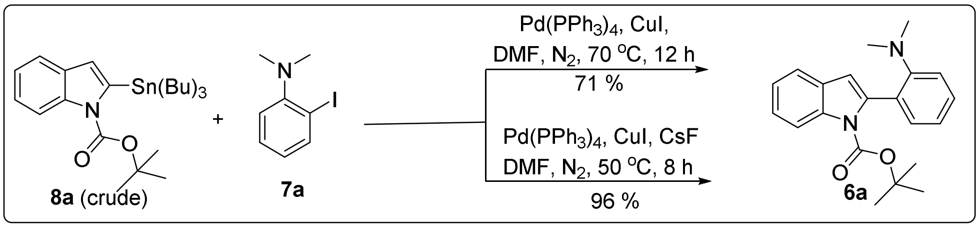


Scheme 28

^{1}H NMR of 2-iodo-*N*,*N*-dimethylaniline (7a) : [11a]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 2.82 (s, 6H).

Next, *N*-boc indole **10a** was treated with *n*-BuLi at -78 °C followed by reacting with tributyl tin chloride (Scheme 29) to get *t*-butyl 2-(tributylstannyl)-1*H*-indole-1-carboxylate[11b] **8a**. Reaction of **8a** under Stille conditions with **7a**, in the presence of $Pd(PPh_3)_4$ and CuI at 70 °C for 12 h afforded *t*-butyl-2-(2-(dimethylamino)phenyl)-1*H*-indole-1-carboxylate **6a** in 71 % yield. The coupling was confirmed from ^1H NMR of the product which showed peak at 1.23 (s, 9H) and 2.43 (s, 6H) ppm. The yield of the reaction was further increased to 96 %, when Stille coupling was carried out using reaction conditions established by Baldwin and co-workers [11c] which makes use of CsF, as a source of fluoride ion.



Scheme 29

Spectral data of *tert*-butyl 2-(2-(dimethylamino)phenyl)-1*H*-indole-1-carboxylate (6a):

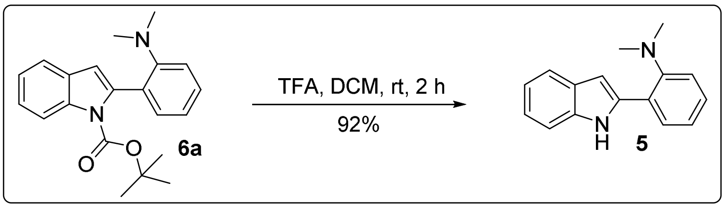
IR (KBr): $\tilde{\nu}$ =2962, 2870, 1710, 1479, 1320, 1150 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (dd, J = 8.0 Hz, J = 0.8 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.23-7.19 (m, 3H), 7.14 (dt, J = 7.6 Hz, J = 0.8 Hz, 1H), 6.92-6.87 (m, 2H), 6.49 (d, J = 0.4 Hz, 1H), 2.43 (s, 6H), 1.23 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6 (C), 150.1 (C), 139.7 (C), 137.0 (C), 130.8 (CH), 129.4 (C), 128.9 (CH), 127.5 (C), 123.9 (CH), 122.4 (CH), 121.0 (CH), 120.4 (CH), 117.0 (CH), 114.8 (CH), 108.8 (CH), 82.7 (C), 42.8 (2 X CH_2), 27.7 (3 X CH_3).

HRMS (ESI): calcd for $C_{21}H_{24}N_2O_2H$ $[M+H]^+$ 337.1916, found 337.1917.

Compound **6a** was then deprotected using TFA in DCM to give the key intermediate 2-(1*H*-indol-2-yl)-*N*,*N*-dimethylaniline **5** (Scheme 30). Compound **5** showed a strong N-H stretch in the region 3331 cm^{-1} and was further confirmed by spectral analysis.



Scheme 30

Spectral data of 2-(1*H*-indol-2-yl)-*N*,*N*-dimethylaniline (5):

IR (KBr): $\tilde{\nu}$ =3331, 3051, 2864, 1923, 1571, 1469, 1452, 1303, 1105, 939, 794 cm^{-1}.

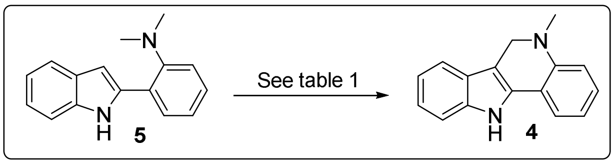
^{1}H NMR (400 MHz, CDCl$_3$): δ 10.78 (s, 1H), 7.75 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.41 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.29-7.21 (m, 3H), 7.19-7.07 (m, 3H), 6.82 (q, J = 0.8 Hz, 1H), 2.70 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 150.6 (C), 137.8 (C), 136.2 (C), 129.4 (CH), 128.3, 126.1 (C), 124.1 (CH), 121.8 (CH), 120.2 (CH), 119.7 (CH), 119.6 (CH), 110.9 (CH), 99.7 (CH), 44.6 (CH$_3$).

HRMS (ESI): calcd for $C_{16}H_{16}N_2H$ [M+H]$^+$ 237.1392, found 237.1392.

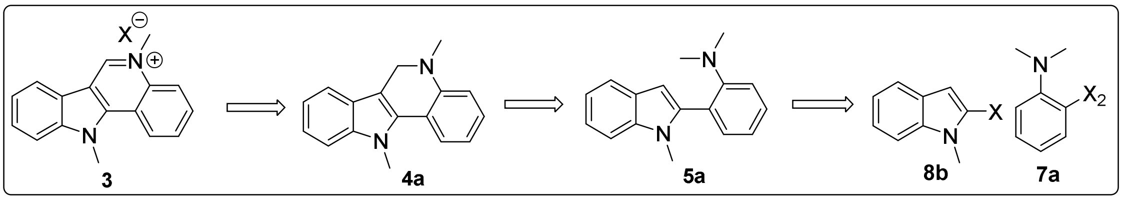
Once a sufficient amount of this compound was in hand, we next focused our efforts on the key step of the strategy. For cyclization through C-H activation *via* oxidative dehydrogenative coupling, intermediate **5** was treated under some of the reaction conditions reported in literature for functionalization of amines to obtain 5-methyl-6,11-dihydro-5*H*-indolo[3,2-*c*]quinoline **4**. However, both metal free (Table 1, entry1,2) and metal mediated (Table 1, entry 3-5) reactions gave undesirable mixture of compounds.

Table 1: IMDC for conversion of **5** to **4**.



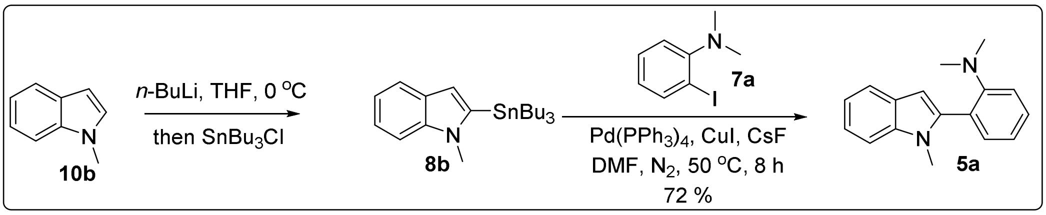
Entry	Reaction condition	Results obtained
1	DCM, BTI, NaN$_3$, rt, 2 h[4t]	A mixture of compounds
2	K-*t*-butoxide (3equiv) toluene, heat 3 h[2f]	A mixture of compounds
3	RuCl$_3$, Acetic acid, MeOH, O$_2$, 60 °C[3a]	A mixture of compounds
4	FeCl$_3$.6H$_2$O, toluene, open air, TBHP,0 °C, 3h[4u]	Black mass obtained
5	CuBr, TBHP, neat rt, 1h[4m]	A mixture of compounds

Assuming that the mixture of products may be due to the free N-H group in intermediate **5**, we next thought of an alternate pathway in which *N*-methylated intermediate **5a** was to be employed. The proposed pathway is depicted in scheme 31.



Scheme 31

We synthesized the intermediate **5a** in a similar manner as intermediate **5** was prepared. *N*-Methyl indole **10b**, was treated with *n*-BuLi at 0 ^{o}C and then with tributyl tin chloride to give 1-methyl-2-(tributylstannyl)-1*H*-indole **8b** after aqueous work-up. **8b** and **7a** were then reacted under modified Stille conditions to give desired product *N,N*-dimethyl-2-(1-methyl-1*H*-indol-2-yl)aniline **5a** in 72 % yield (Scheme 32). The coupling was confirmed based on ^{1}H NMR of the product which showed peaks at 2.47 (s, 6H) and 3.47 (s, 3H) ppm, accounting for units from both the startings and further confirmed by spectral data mentioned below.



Scheme 32

Spectral data of *N,N*-dimethyl-2-(1-methyl-1*H*-indol-2-yl)aniline (5a):

IR (KBr): $\tilde{\nu}$ =2937, 2835, 1928, 1886, 1462, 1323, 1136, 947, 744 cm^{-1}.

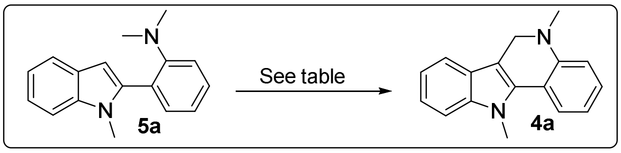
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.55 (d, J = 7.6 Hz, 1H), 7.29-7.23 (m, 3H), 7.14 (dt, J = 8.8 Hz, 1.2Hz, 1H), 7.04 (dt, J = 8.0 Hz, 1.2 Hz, 1H), 6.95-6.41 (m, 2H), 6.41 (s, 1H), 3.47 (s, 3H), 2.47 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 152.1 (C), 141.8 (C), 137.6 (C), 133.4 (CH), 129.5 (CH), 128.4 (C), 121.1 (CH), 120.7 (CH), 120.3 (CH), 119.4 (CH), 117.2 (CH), 109.4 (CH), 100.9 (CH), 42.3 (2 X CH$_3$), 30.7 (CH$_3$).

HRMS (ESI): calcd for $C_{17}H_{18}N_2H$ [M +H]$^{+}$ 251.1548, found 251.1545.

Treating **5a** under the same catalytic condition, however again resulted in a complex mixture of products (Table 2). When oxidant like TBHP in decane in presence of a metal catalyst like CuBr or RuCl$_3$ was employed the result was same as in previous experiments. To prevent the oxidation of indole ring we added pivalic acid[12a-c] but still no success was observed. Attempts to carry out the reaction under metal free conditions also did not give the expected product. Starting **5a** did not undergo any change with CuBr in the presence of oxygen as oxidant. Addition of DDQ[4e, 5a-b] to **5a** in toluene gave a black tarry mass.

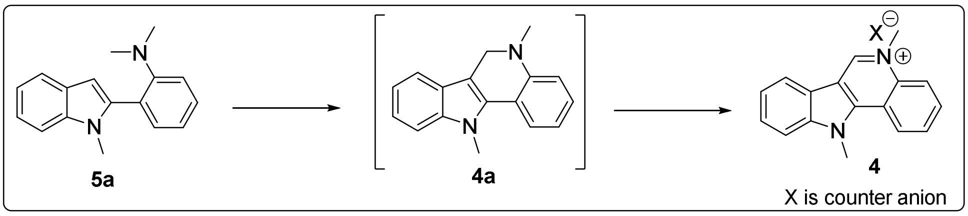
Table 2: Screening IMDC for conversion of **5a** to **4a**.



Entry	Reaction condition[a]	Results
1	TBHP in decane, CuBr, rt, 1 h	Mixture of compounds obtained
2	TBHP in decane, $RuCl_3$, rt, 1 h	Mixture of compounds obtained
3	$RuCl_3$, TBHP in decane, Pivalic acid, rt, 3h	Mixture of compounds obtained
4	KI, TBHP, Pivalic acid, DMSO, 55 °C, 2 h	Mixture of compounds obtained
5	TBHP in decane Toluene, Bu_4NI, KI, 60 °C, 3 h	Mixture of compounds obtained
6	CuBr, O_2 balloon, CH_3CN, 55 °C, 24 h	Starting material recovered
7	DDQ, Dioxane, rt, 5 min	Black tarry mass obtained

[a] 2 equiv of oxidant TBHP (in decane) or DDQ used.

Hence we thought the mixture obtained may be not due to oxidation of indole ring, but might be due to compound **4a**, which might be undergoing further oxidation to give the quaternised product (Scheme 33). To overcome this problem we thought of preparing the iodide salts of these compounds, since iodide derivatives are reported in CDC reactions. Thus, intermediate **5a** was treated with 1 equiv of the halide source along with 2 equiv of the oxidant.



Scheme 33

Screening for the optimum condition did not provide much success with NaI and KI or even when pivalic acid was used as additive (Table 3, entry 1-3). Next, when the iodide source was changed to *N*-iodosuccinimide (NIS) and iodine in chloroform, in the presence of TBHP gave a yellow solid after aging reaction mixture for 14 h at room temperature. ^{1}H NMR spectrum showed a peak at 10.26 (s, 1H) and two singlet peaks merging together accounting for 6H at 4.58-4.55 ppm. By comparing with reported data [8e] compound **3a** was confirmed to be 5,11-dimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide. The yield of the product was found to be 36 % and 70 % with NIS and I_2 respectively in $CHCl_3$. Changing the halide source to tetrabutyl ammonium iodide (TBAI) at room temperature did not show any much change in starting.

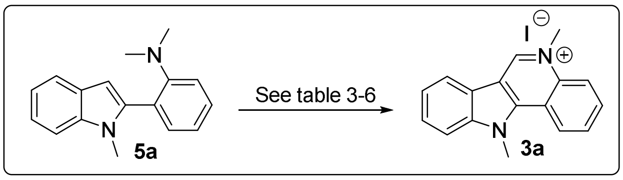


Table 3: Screening of iodide source.

Entry	**Reaction condition**[a]	**Results**
1	KI, TBHP, $CHCl_3$, rt, 3 h	Mixture of compounds obtained
2	NaI, TBHP, $CHCl_3$, rt, 14 h	Mixture of compounds obtained
3	KI, TBHP, $CHCl_3$, Pivalic acid, rt, 3 h	Mixture of compounds obtained
4	NIS, TBHP, $CHCl_3$, rt, 14 h	Isolated 36 % of **3a**
5	**I_2, TBHP, $CHCl_3$, rt, 14 h**	**Isolated 70 % of 3a**
6	TBAI, TBHP, $CHCl_3$, rt, 14 h	No reaction

[a] 2 equiv of TBHP (in decane) used.

Spectral data of 5,11-dimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3a):

IR (KBr): $\tilde{\nu}$ =2970, 1894, 1637, 1604, 1504, 1375, 1257, 750 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 10.26 (s, 1H), 9.13 (d, J = 8 Hz, 1H), 8.51 (d, J = 8.8 Hz, 1H), 8.42 (d, J = 7.2 Hz, 1H), 8.21 (t, J = 8.0 Hz, 1H), 8.13-8.07 (m, 2H), 7.80 (t, J = 8.4 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 4.58-4.55 (m, 6H).

^{13}C NMR (100 MHz, DMSO-d6): δ 143.2 (CH), 142.2 (C), 141.8 (C), 136.5 (C), 132.1 (CH), 128.3 (CH), 128.2 (CH), 125.2 (CH), 123.8 (CH), 121.0 (C), 120.5 (CH), 119.6 (CH), 117.1 (C), 113.6 (C), 111.9 (CH), 44.7 (CH_3), 34.3 (CH_3).

HRMS (ESI): calcd for $C_{17}H_{15}N_2$ $[M]^+$ 247.1235, found 247.1235.

Since molecular iodine gave better results, it was used for further studies. Next step was to investigate the effect of oxidant on reaction product. Changing the oxidant from TBHP in decane to aq. TBHP reaction had to be conducted at higher temperature and in acetonitrile as in chloroform reaction appeared biphasic. However, yields were on the lower side. The same was observed with H_2O_2 as an oxidant (Table 4, entry 1, 2). Conducting reaction in molecular oxygen or air didn't give any product.

Table 4: Screening of oxidant.

Entry	Reaction condition	Results
1 [a]	I_2, TBHP (aq), CH_3CN, 60°C, 10 h	Isolated 45 % of **3a**
2 [a]	I_2, H_2O_2 (30%) (aq), CH_3CN, 60°C, 10 h	Isolated 40 % of **3a**
3	I_2, O_2, $CHCl_3$, 80°C, 16 h	No reaction
4	I_2, air, $CHCl_3$, 80°C, 16 h	No reaction

[a] 2 equiv of oxidant used.

We then screened the optimum solvent for the IMDC reaction (Table 5). Using an excess of TBHP (in decane) without any solvent gave **3a** in 24 % yield while protic solvent like ethanol gave a yield of product in 46 % yield but at 60 °C (table 5, entry 1 & 2). Non protic solvents like ethyl acetate, acetonitrile, acetone and toluene gave the desired product in 62, 67, 62 and 48 % yield respectively, but reaction had to be conducted at higher temperature (table 5, entry 3-6). Chlorinated solvents like dichloromethane and chloroform gave **3a** in 67 and 70 % yield respectively at room temperature.

Table 5: Screening of solvent.

Entry	Reaction condition[a]	% yield of 3a [b]
1	I_2, TBHP (excess), rt, 14 h	24
2	I_2, TBHP, EtOH, 60°C, 10 h	46
3	I_2, TBHP, EtOAc, 60°C, 10 h	62
4	I_2, TBHP, CH_3CN, 60°C, 10 h	67
5	I_2, TBHP, acetone, 60°C, 10 h	62
6	I_2, TBHP, toluene, 60°C, 10 h	48
7	I_2, TBHP, CH_2Cl_2, rt, 14 h	67
8	**I_2, TBHP, $CHCl_3$, rt, 14 h**	**70**

[a] 2 equiv of TBHP (in decane) used.

[b] Isolated yield.

Having optimized the halide source (1 equiv), oxidant and solvent, we then studied the effect of iodine concentration on the reaction. In the absence of iodine no change in starting was seen even at 60 °C (Table 6). On varying the amount of iodine from 0.5, 1, and 1.1 equiv the yield was seen to increase from 16, 70, to 74 % respectively (table 6, entry 2-4). Further increase in iodine concentration to 1.2, 1.5 and 2 did not have any better outcome on the product yield (table 6, entry 5-7).

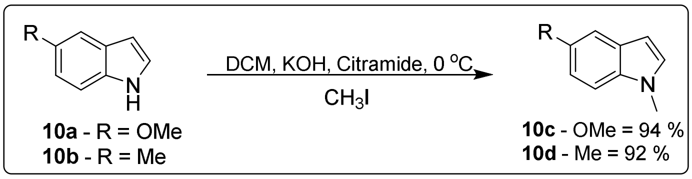
Table 6: Optimisation of I_2 concentration.

Entry	Reaction condition[a]	% yield of 3a [b]
1	TBHP, $CHCl_3$, 60°C, 10 h	No reaction
2	I_2(0.5 equiv), TBHP, $CHCl_3$, rt, 14 h	16
3	I_2(1.0 equiv), TBHP, $CHCl_3$, rt, 14 h	70
4	**I_2(1.1 equiv), TBHP, $CHCl_3$, rt, 14 h**	**74**
5	I_2(1.2 equiv), TBHP, $CHCl_3$, rt, 14 h	73
6	I_2(1.5 equiv), TBHP, $CHCl_3$, rt, 14 h	72
7	I_2(2 equiv), TBHP, $CHCl_3$, rt, 14 h	74

[a] 2 equiv of TBHP (in decane) used.

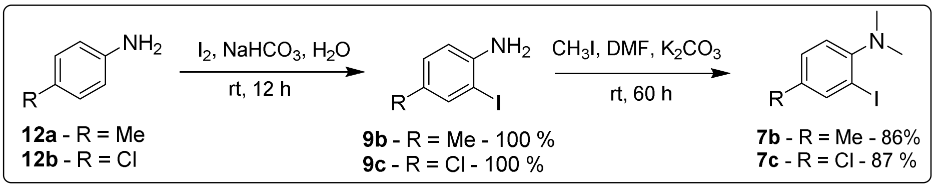
[b] Isolated yield.

Having established the optimum conditions [I_2 (1.1 equiv), TBHP (2.0 equiv), $CHCl_3$, rt; entry 20] for this transformation, we then examined the scope of the reaction with different substituents on the indole ring. Hence methoxy and methyl indole were *N*-methylated with methyl iodide and used for further studies (Scheme 34).


R
N
H
10a - R = OMe
10b - R = Me
DCM, KOH, Citramide, 0 °C
CH3I
R
N
10c - OMe = 94 %
10d - Me = 92 %

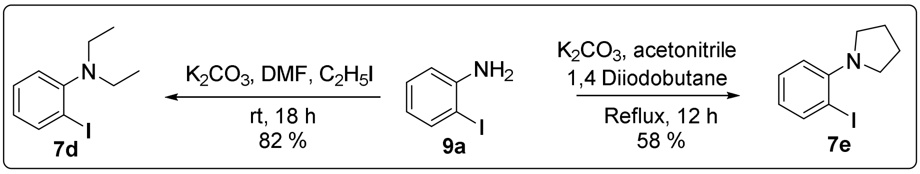
Scheme 34

We then carried out iodination of *para* substituted anilines with molecular iodine in basic medium, [11d] followed by dimethylation with methyl iodide in the presence of K_2CO_3 to get *p*-substituted 2-iodo-*N*,*N*-dimethylanilines **7b** [11e] and **7c** [11e] (Scheme 35).


NH2
R
12a - R = Me
12b - R = Cl
I2, NaHCO3, H2O
rt, 12 h
NH2
R
I
9b - R = Me - 100 %
9c - R = Cl - 100 %
CH3I, DMF, K2CO3
rt, 60 h
N
R
I
7b - R = Me - 86%
7c - R = Cl - 87 %

Scheme 35

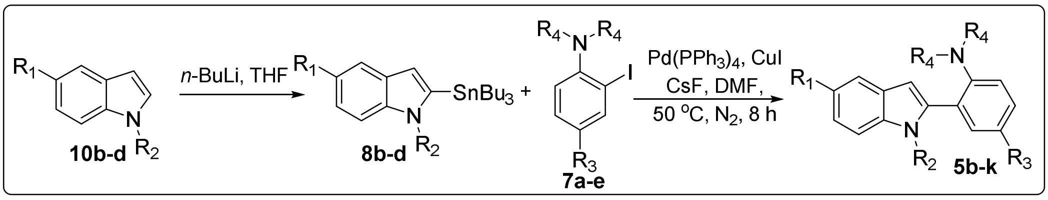
2-Iodo-*N*,*N*-diethylaniline [11f] was synthesized from 2-iodoaniline by dialkylation with ethyl iodide (Scheme 36). Similarly pyrrolidine [11f] was introduced by treating 2-iodoaniline with 1,4-diiodobutane. Attempts to prepare piperidine [11f] substituent failed to give the desired product on treatment of 2-iodoaniline with 1,5-diiodopentane.

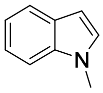
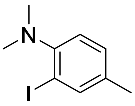
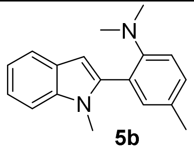
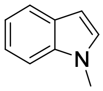
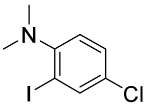
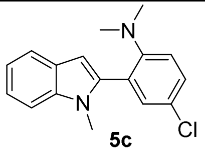
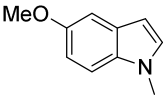
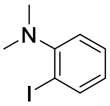
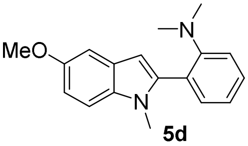
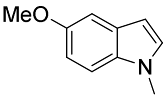
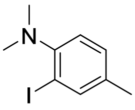
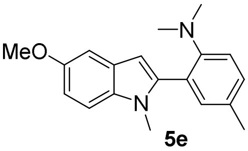
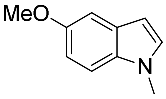
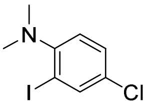
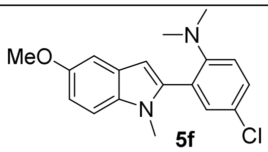

N
I
7d
K₂CO₃, DMF, C₂H₅I
rt, 18 h
82 %
NH₂
I
9a
K₂CO₃, acetonitrile
1,4 Diiodobutane
Reflux, 12 h
58 %
N
I
7e

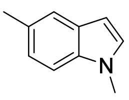
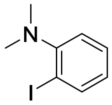
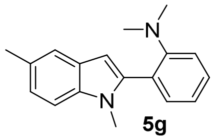
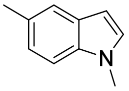
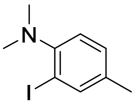
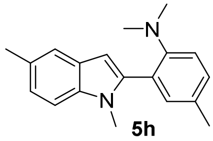
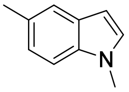
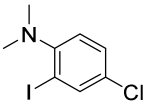
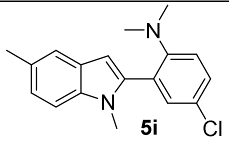
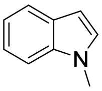
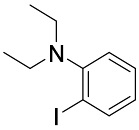
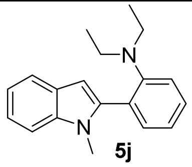
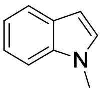
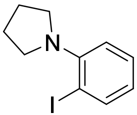
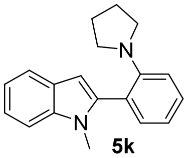
Scheme 36

We then treated the starting **10b**, **10c** and **10d** with *n*-BuLi and subjected the anion formed with tributyl tin chloride. The crude stannyl product **8b-d** obtained on aqueous workup was reacted under a Stille coupling condition with **7a-e** to give intermediates **5b-k** in 61- 69 % yield which is summarized in table 7.

Table 7: Preparation for *N*,*N*-dialkyl-2-(1-methyl-1*H*-indol-2-yl)aniline **5b-k**.


R1
N
R2
10b-d
n-BuLi, THF
R1
SnBu3 +
N
R2
8b-d
R4
N
R4
I
R3
7a-e
Pd(PPh3)4, CuI
CsF, DMF,
50 °C, N2, 8 h
R4
R4–N
R1
N
R2
5b-k
R3

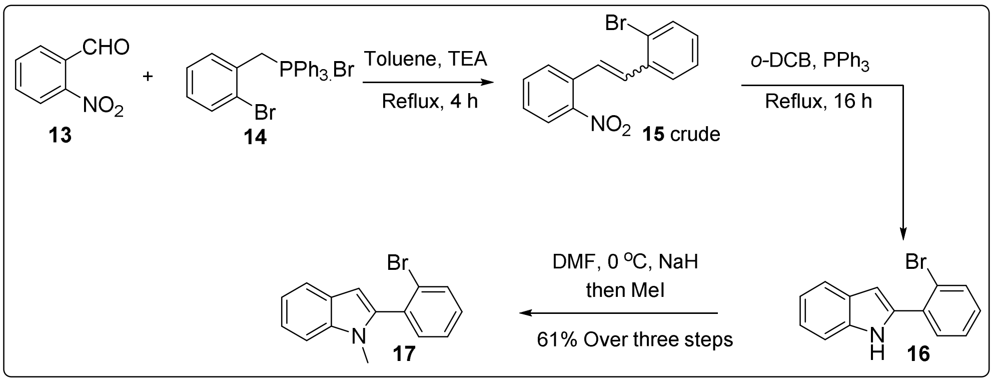
Entry	*N*-methyl indoles 10b-d	*N*,*N*-dialkyl-2-iodoanilines 7a-e	Product 5b-k	% yield 5b-k [a]
1	 **10b**	 **7b**	 **5b**	68
2	 **10b**	 **7c**	 **5c**	69
3	 **10c**	 **7a**	 **5d**	61
4	 **10c**	 **7b**	 **5e**	63
5	 **10c**	 **7c**	 **5f**	64

6	 **10d**	 **7a**	 **5g**	66
7	 **10d**	 **7b**	 **5h**	63
8	 **10d**	 **7c**	 **5i**	60
9	 **10b**	 **7d**	 **5j**	65
10	 **10b**	 **7e**	 **5k**	67

[a] isolated yields.

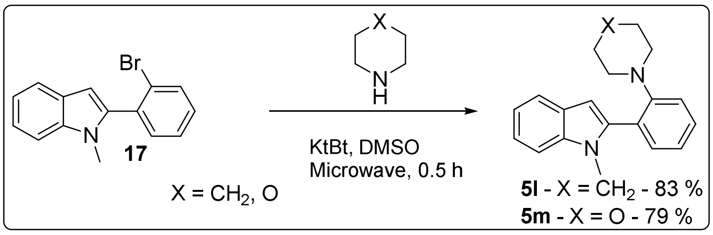
Synthesis of 2-(2-bromophenyl)-1-methyl-1*H*-indole (17)

Since attempts to synthesize piperidine system failed, an alternative route was chosen for synthesis of **5l** (Scheme 37). Wittig reaction between *o*-nitrobenzaldehyde **13** and Wittig salt **14** under basic condition gave alkene **15** as *E/Z* mixture, which on heating in *o*-dichlorobenzene with triphenyl phosphine underwent reductive cyclisation to give indole derivative **16** which was methylated to get intermediate **17** in 61 % overall yields.


CHO
NO2
13
+
PPh3.Br
Br
14
Toluene, TEA
Reflux, 4 h
Br
NO2
15 crude
o-DCB, PPh3
Reflux, 16 h
Br
N
H
16
DMF, 0 oC, NaH
then MeI
61% Over three steps
Br
N
17

Scheme 37

Intermediate **17** was treated with piperidine and morpholine under microwave conditions in the presence of potassium *t*-butoxide in DMSO [11g] to get intermediate **5l** and **5m** in 83 and 79 % yield respectively (Scheme 38).

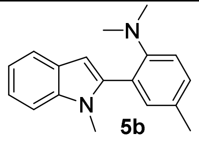
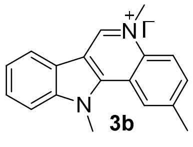
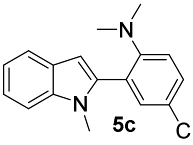
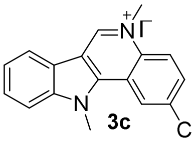


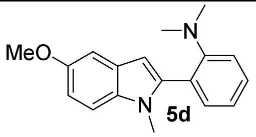
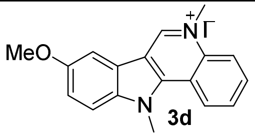
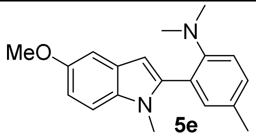
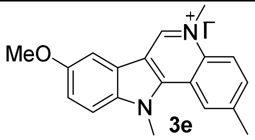
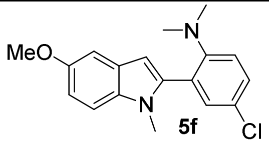
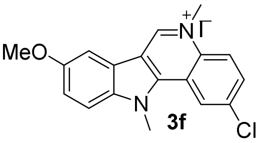
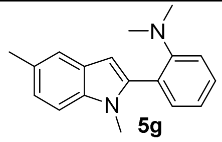
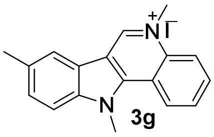
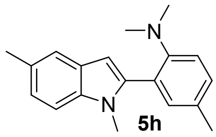
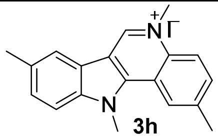
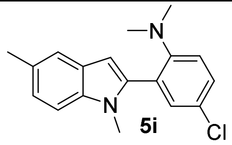
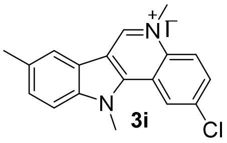
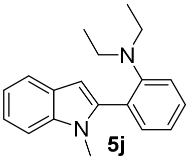
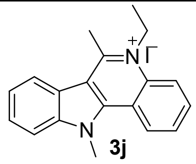
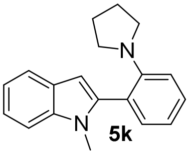
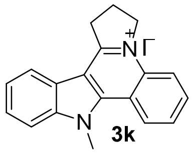
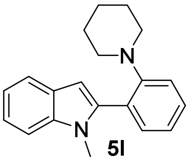
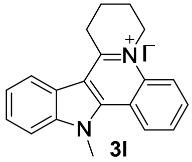
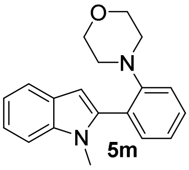
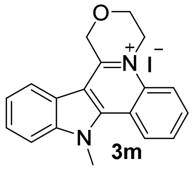
Scheme 38

Scope of IMDC for synthesis of *N*-alkylindolo[3,2-*c*]quinoline Iodides

Once required substrate **5b-m** was synthesized we subjected them to our optimised IMDC reaction. Methoxy and methyl substituent on indole **5d-5i** gave good yields of **3d-i**, indicating a negligible effect of electron-donating groups at the 5-position of indole. Similarly presence of a substituent at the *para* position of aniline ring did not have any pronounced effect on yields of the product. When *N*,*N*-dimethyl group was replaced with *N*,*N*-diethyl **5j**, pyrrolidine **5k**, or piperidine **5l** it gave **3j** and pentacyclic hetrocycles **3k** and **3l**, respectively. Morpholine substituted derivative **5m** failed to give cyclized product **3m**, hence reactions were conducted at elevated temperature where only trace amount of compound was identified by HRMS which showed peak at m/z 289.1344 accounting for $C_{19}H_{17}N_2O$ $[M]^+$ [calcd at 289.1341]. It was also observed that, when nucleophilicity of the indole ring was reduced by placing an electron-withdrawing group such as *tert*-butoxycarbonyl on the nitrogen, no reaction was observed in 24 h and a complex mixture was obtained at higher temperature.

Table 8: Scope of IMDC for synthesis of indole[3,2,*c*]quinoline ring system **3b-m**.

Entry	Starting **5b-m**	Product **3b-m**	% Yield of **3b-m** [a]
1	 **5b**	 **3b**	75
2	 **5c**	 **3c**	72

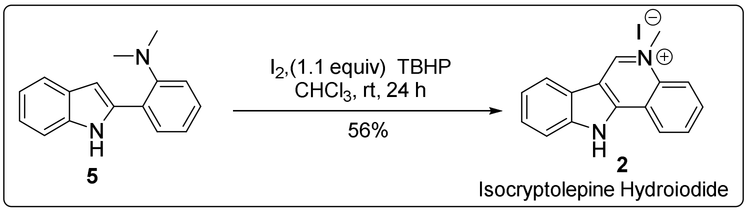
3	 5d	 3d	70
4	 5e	 3e	72
5	 5f	 3f	69
6	 5g	 3g	71
7	 5h	 3h	72
8	 5i	 3i	68
9	 5j	 3j	58
10	 5k	 3k	62
11	 5l	 3l	60
12 [b]	 5m	 3m	trace

[a] isolated yield

[b] reaction was conducted at 50 °C for 48 h.

Synthesis of isocryptolepine hydroiodide (2)

To evaluate the protocol for the synthesis of naturally occurring isocryptolepine **1**, we treated intermediate **5** with the optimized conditions during which to our delight isocryptolepine hydroiodide **2a** was obtained in 56% yield (Scheme 39). This salt **2a** has been reported to give isocryptolepine **1** on basification with NH_4OH. [10n] Interestingly, during this reaction the free NH group of indole did not interfere in the course of the reaction.


5
I2,(1.1 equiv) TBHP
CHCl3, rt, 24 h
56%
2
Isocryptolepine Hydroiodide

Scheme 39

Spectral data of 5-methyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (2): [10p]

IR (KBr): $\tilde{\nu}$ = 2929, 2852, 1732, 1608, 1452, 1352, 1259, 1120, 748 cm^{-1}.

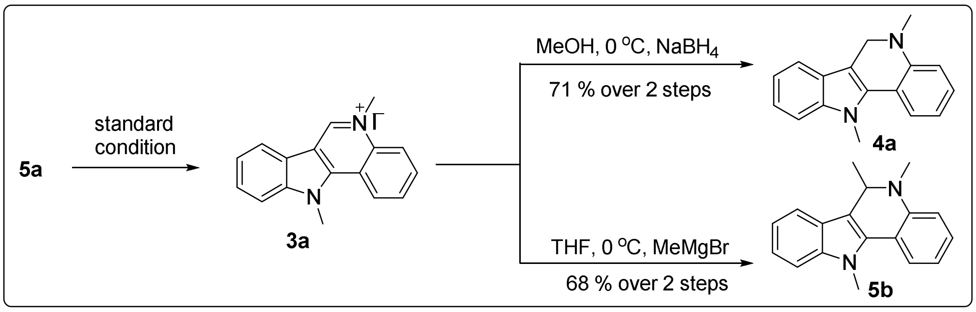
^{1}H NMR (400 MHz, DMSO-d6): δ 14.41 (s, 1H), 10.26 (s, 1H), 8.94 (d, J = 8.8 Hz, 1H), 8.38 (d, J = 7.6 Hz, 1H), 8.19 (t, J = 7.6 Hz, 1H), 8.09 (t, J = 7.6 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 7.6 Hz, 7.58 (t, J = 7.6 Hz, 1H), 4.58 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 144.1 (CH), 143.5 (C), 140.1 (C), 136.1 (C), 132.5 (CH), 128.5 (CH), 128.2 (CH), 124.3 (CH), 123.2 (CH), 121.7 (C), 120.9 (CH), 119.6 (CH), 116.2 (C), 113.4 (C), 113.3 (CH), 44.4 (CH_3).

HRMS (ESI): calcd for $C_{16}H_{13}N_2$ $[M]^+$ 233.1079, found 233.1079.

Derivatisation of salt 3a

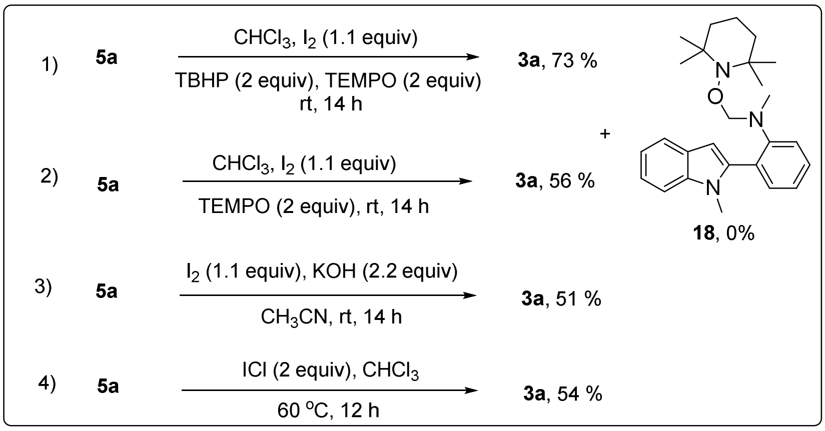
Salts **3a-m** can potentially be further derivatized by treating them with reagents like $NaBH_4$ or Grignard reagent. To verify this we subjected **3a** with sodium borohydride and methyl magnesium bromide in methanol and tetrahydrofuran respectively at 0 °C to get addition product **4a** and **4b** in 71 and 68 % in overall yield respectively (Scheme 40).


5a
standard condition
3a
MeOH, 0 °C, NaBH4
71 % over 2 steps
4a
THF, 0 °C, MeMgBr
68 % over 2 steps
5b

Scheme 40

Mechanistic pathway for conversion of 5a to 3a.

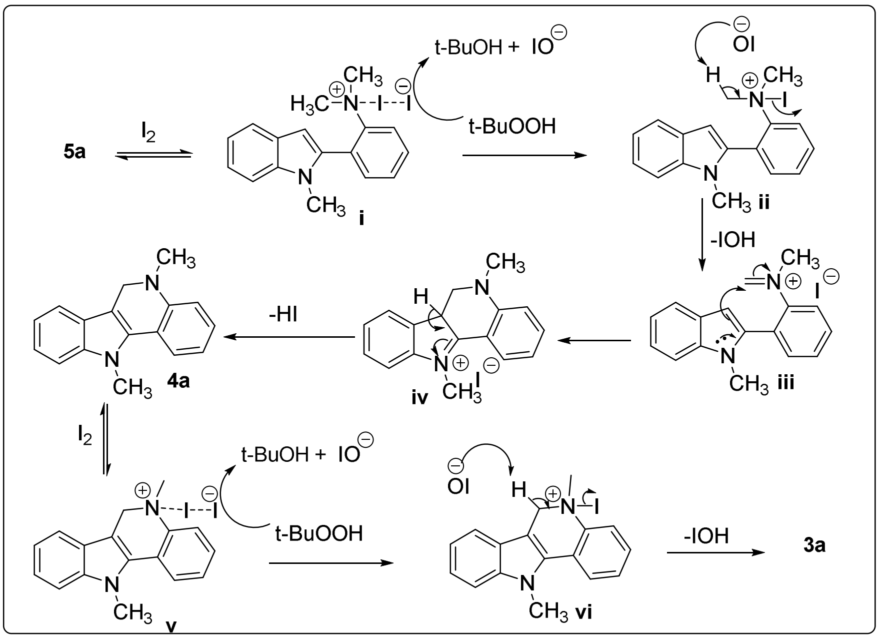
To elucidate the mechanism, reaction was carried out on **5a** in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), a known radical inhibitor during which **3a** was obtained in 73% yield. When TBHP was replaced with TEMPO, **3a** was obtained in 56% yield (Scheme 41).


1) 5a
CHCl3, I2 (1.1 equiv)
TBHP (2 equiv), TEMPO (2 equiv) rt, 14 h
3a, 73 %
2) 5a
CHCl3, I2 (1.1 equiv)
TEMPO (2 equiv), rt, 14 h
3a, 56 %
+
18, 0%
3) 5a
I2 (1.1 equiv), KOH (2.2 equiv)
CH3CN, rt, 14 h
3a, 51 %
4) 5a
ICl (2 equiv), CHCl3
60 °C, 12 h
3a, 54 %

Scheme 41

In both cases, no tempo-bound adduct **18** was observed, indicating that the reaction may not be following a radical pathway. [4m,13a] Compound **5a** on treatment with iodine and KOH gave **3a** in 51% yield, and treatment with 2 equiv of iodine monochloride gave **3a** in 54% yield. This suggests that the reaction may be following a (hypo)iodite-mediated pathway.[13b-d]

A plausible mechanistic pathway for the transformation is depicted in Scheme 42.


5a
I2
i
t-BuOH + IO
t-BuOOH
ii
-IOH
iii
iv
-HI
4a
I2
v
t-BuOH + IO
t-BuOOH
vi
-IOH
3a

Scheme 42

We assume that iodine must have coordinated with **5a** through the tertiary amine moiety, which is then oxidized with TBHP to give *tert*-butyl alcohol and IO^-. The hypoiodite anion, then abstracts the proton from intermediate **ii** to give iminium species **iii**, which then undergoes an intramolecular nucleophilic attack to give **iv**, which loses the molecule of HI to give **4a**. Further oxidation of **4a** *via* a similar hypoiodite intermediate provided **3a**.

2. A. 4: Conclusion

We have developed a mild and efficient method for the activation of an sp3 carbon adjacent to nitrogen with Intramolecular Dehydrogenative Coupling (IMDC) followed by aromatization to obtain hydroiodide salts of indolo[3,2-*c*]quinolines.

This protocol is successfully applied to the synthesis of isocryptolepine hydroiodide which constitute the formal synthesis of naturally occurring isocryptolepine.

The usefulness of *N*,*N*-dialkyindole[3,2,-*c*]quinoline salts as precursors for making analogous compounds was successfully demonstrated by preparing addition adducts with a hydride and Grignard reagent.

Hypoiodite pathway is proposed to rationalize the product formation in the IMDC reaction protocol based on control experiments conducted.

Section B: Synthesis of *N*,*N*-dimethylindolo[2,3-*c*]quinoline Iodides

2. B. 1: Introduction

Isoneocryptolepine **19** constitutes the fourth possible fused system of indole and quinoline comprising of indolo[2,3-c]quinoline framework. **19** is not naturally isolated, but is known to be a potentially important molecule as its other naturally occurring isomers shows interesting biological activities. [8b-d] Its hydroiodide salt **20** and methyl derivative **21** is targeted for their promising biological activities (Figure 2). Compound **20** shows activity like inhibition in β-hematin formation and IC_{50} value is similar to other naturally occurring alkaloids like neocryptolepine and isocryptolepine against *Plasmodium* sps. [8e]

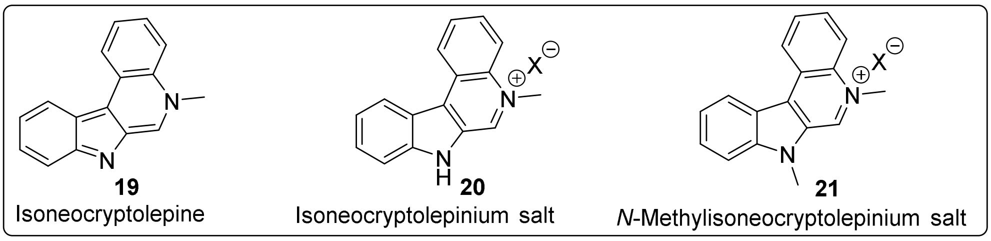
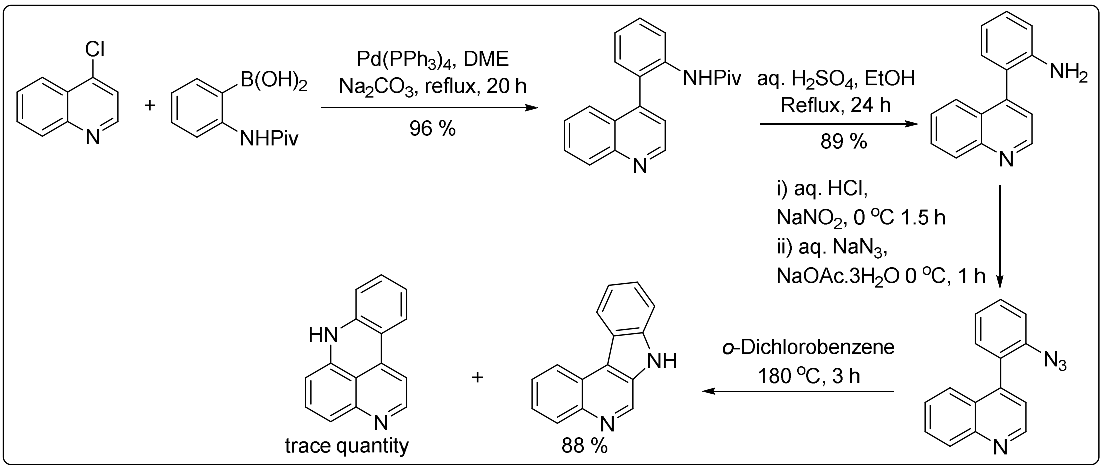

19
Isoneocryptolepine
20
Isoneocryptolepinium salt
21
N-Methylisoneocryptolepinium salt

Figure 2: Isoneocryptolepine and its iodide salts

2. B. 2: Literature Reported Methods

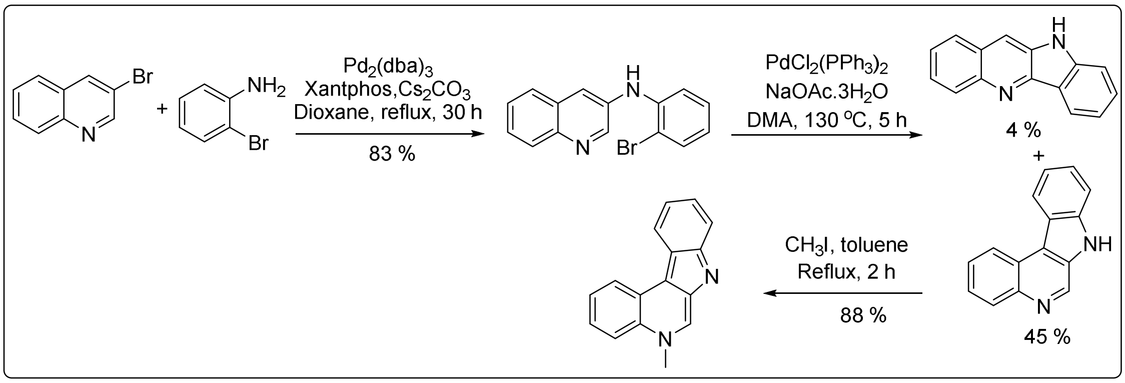
Maes and co-workers [14] designed two routes for the fourth possible fusion of indoloquinoline skeleton. The first, an intramolecular Suzuki coupling reaction between (2-pivalamidophenyl)-boronic acid and 4-chloroquinoline to furnish *N*-(2-(quinolin-4-yl)phenyl)pivalamide (Scheme 34), which on acid hydrolysis, diazotization and then treatment with NaN_3 gave 4-(2-azidophenyl)quinoline.


Cl
N
B(OH)2
NHPiv
Pd(PPh3)4, DME
Na2CO3, reflux, 20 h
96 %
NHPiv
aq. H2SO4, EtOH
Reflux, 24 h
89 %
NH2
i) aq. HCl,
NaNO2, 0 °C 1.5 h
ii) aq. NaN3,
NaOAc.3H2O 0 °C, 1 h
N3
o-Dichlorobenzene
180 °C, 3 h
NH
88 %
HN
trace quantity

Scheme 43

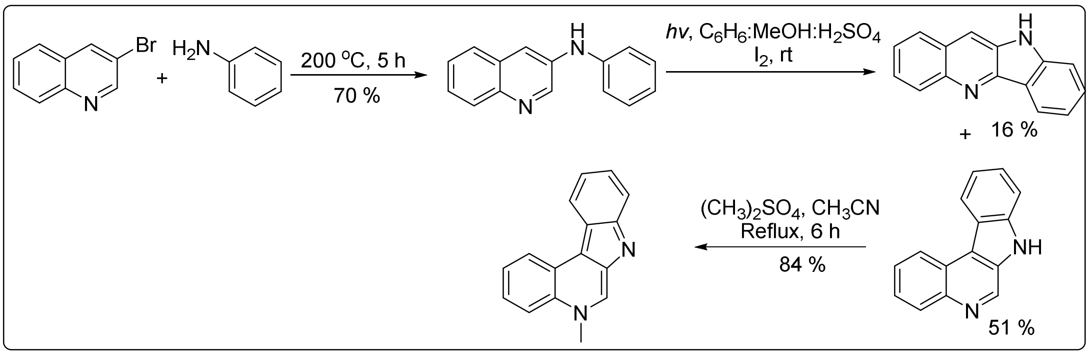
The azide derivative on heating underwent reductive cyclization to the desired 7*H*-indolo[2,3-*c*]quinoline as a major compound and 7*H*-pyrido[2,3,4-*kl*]acridine in trace amounts.

In the second route the author has described, consecutive two palladium catalyzed reactions (Scheme 44). First the regioselective Buchwald-Hartwig amination of 3-bromoquinoline with 2-bromoaniline followed by an intramolecular Heck coupling to give 7*H*-indolo[2,3-*c*]quinoline as a major and 10*H*-indolo[3,2-*b*]quinoline as a minor component. The former on regioselective methylation resulted in 5-methyl-5*H*-indolo[2,3-*c*]quinoline.


Br
NH2
Br
Pd2(dba)3
Xantphos,Cs2CO3
Dioxane, reflux, 30 h
83 %
PdCl2(PPh3)2
NaOAc.3H2O
DMA, 130 °C, 5 h
4 %
45 %
CH3I, toluene
Reflux, 2 h
88 %

Scheme 44

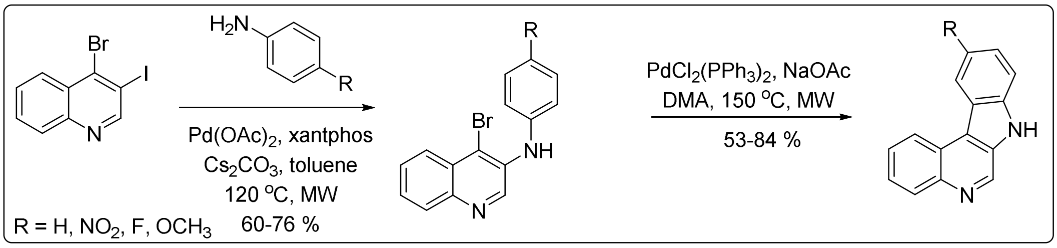
Mohan and co-workers [10h] conducted thermal displacement of 3-bromoquinoline with aniline to give *N*-phenylquinolin-3-amine, which under photochemical cyclization gave both possible cyclizations to give the precursor of cryptolepine in minor amount and 7*H*-indolo[2,3-*c*]quinoline in a major amount. The major compound obtained was further methylated to give isoneocryptolepine (Scheme 45).


Br
H2N
200 °C, 5 h
70 %
hv, C6H6:MeOH:H2SO4
I2, rt
16 %
51 %
(CH3)2SO4, CH3CN
Reflux, 6 h
84 %

Scheme 45

Boganyi and Kaman [10l] have synthesized all the possible fused indoloquinoline ring systems. 7*H*-Indolo[2,3-*c*]quinoline core was synthesized by two palladium catalyzed reactions (Scheme 46). First regioselective Buchwald-Hartwig amination between anilines and 4-

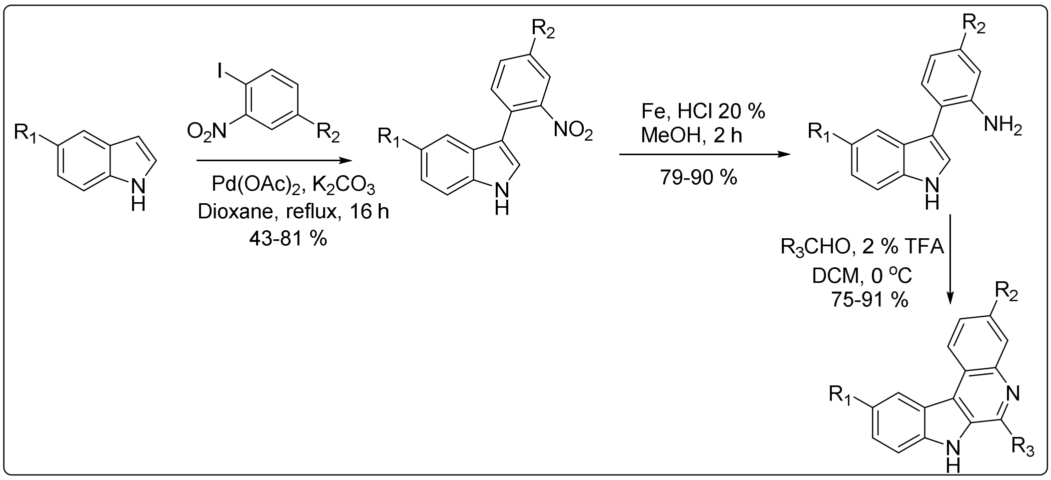
bromo-3-iodoquinoline was performed and this was followed by an intramolecular Heck coupling.



Pd(OAc)$_2$, xantphos
Cs$_2$CO$_3$, toluene
120 °C, MW
60-76 %
R = H, NO$_2$, F, OCH$_3$
PdCl$_2$(PPh$_3$)$_2$, NaOAc
DMA, 150 °C, MW
53-84 %

Scheme 46

Kundu and co-workers [10m] arylated indoles with substituted 2-nitro iodobenzenes at C-3 position using palladium acetate (Scheme 47).



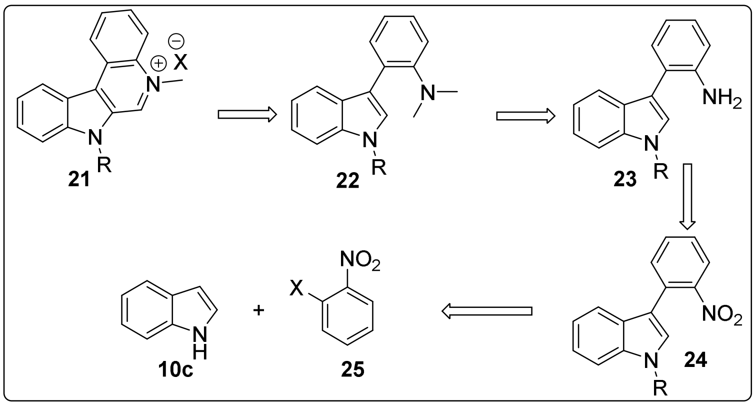
Pd(OAc)$_2$, K$_2$CO$_3$
Dioxane, reflux, 16 h
43-81 %
Fe, HCl 20 %
MeOH, 2 h
79-90 %
R$_3$CHO, 2 % TFA
DCM, 0 °C
75-91 %

Scheme 47

Reduction of nitro to amine functionality using Fe/HCl and then treating with aldehydes in acidic conditions gave Pictet-Spengler cyclization product 7*H*-indolo[2,3-*c*]quinolines.

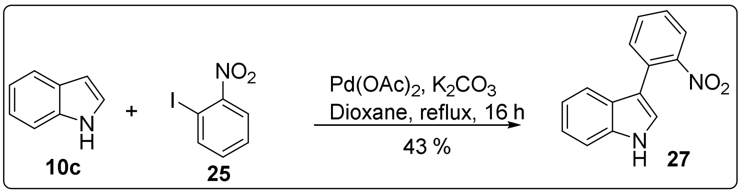
2. B. 3: Results and Discussion

After successful synthesis of the indolo[3,2-*c*]quinoline fused rings using IMDC, we thought to extend the methodology for the synthesis of other possible indolo[2,3-*c*]quinoline fused system. The proposed reterosynthetic pathway is depicted in scheme 48. The final *N*,*N*-dimethyl-indolo[2,3-*c*]quinoline salt **21** could be obtained in one pot from the intermediate **22** using IMDC reaction. Intermediate **22** could easily be prepared from its corresponding amine derivative **23** which in turn could be obtained from the corresponding nitro derivative **24**. Intermediate **24** is reported by C-3 arylation of indole **10c** and 2-halonitrobenzene **25** using palladium coupling reaction.


21
22
23
24
10c
25
R
X
NH2
NO2
N
H

Scheme 48

The required C-3 arylated indole **26** was prepared according to the procedure established by Kundu and co-workers [10m] between indole **10c** and 1-iodo-2-nitrobenzene **25a** using palladium acetate under basic medium in refluxing dioxane (Scheme 49). The ^{1}H NMR spectrum matched with the reported spectrum in literature.

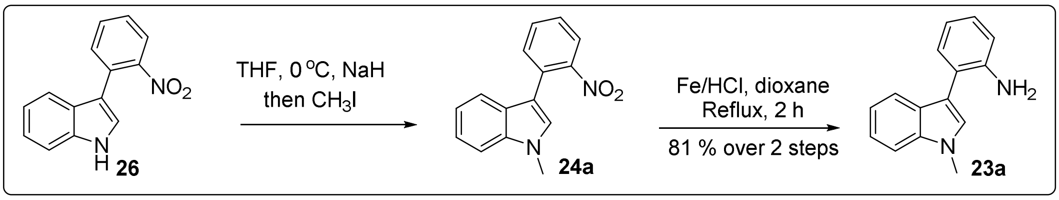

10c
25
27
NO2
Pd(OAc)2, K2CO3
Dioxane, reflux, 16 h
43 %

Scheme 49

^{1}H NMR of 3-(2-nitrophenyl)-1H-indole (27): [10m]

^{1}H NMR (400 MHz, DMSO-d6): δ 11.49 (br s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.76-7.66 (m, 2H), 7.55-7.50 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.02 (t, J = 7.2 Hz, 1H).

Arylated intermediate **26** was alkylated with methyl iodide and was subjected to reduction under Fe/HCl to give amine derivative **23a** (Scheme 50). IR spectrum showed a broad band at 3321 cm^{-1} indicating the presence of amine functionality which was further confirmed from spectral data.


26
24a
23a
NO2
NH2
THF, 0 °C, NaH
then CH3I
Fe/HCl, dioxane
Reflux, 2 h
81 % over 2 steps

Scheme 50

Spectra data of 2-(1-methyl-1*H*-indol-3-yl)aniline (23a):

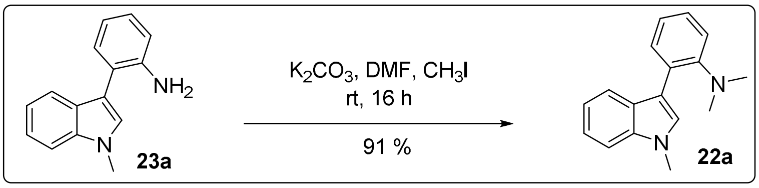
IR (KBr): $\tilde{\nu}$ = 3321, 3020, 2861, 1920, 1467, 1300, 1101, 790 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.48 (d, *J* = 7.6 Hz, 1H), 7.24-7.04 (m, 3H), 7.02-6.98 (m, 3H), 6.74-6.70 (m, 2H), 3.84 (br s, 2H), 3.67 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 144.0 (C), 137.1 (C), 131.2 (CH), 127.7 (CH), 126.9 (CH), 122.0 (CH), 121.0 (CH), 119.6 (CH), 118.8 (CH), 115.8 (CH), 113.1 (C), 109.5 (CH), 32.8 (CH$_3$).

HRMS (ESI): calcd for $C_{15}H_{14}N_2H$ [M +H]$^+$223.1235, found 223.1235.

Amine derivative **23a** was dimethylated using an excess of methyl iodide in the presence of K_2CO_3 in DMF (Scheme 51). Compound **22a** was confirmed based on ^{1}H NMR which showed a singlet at δ 2.52 ppm attributing for 6H and further confirmed from other spectral data.



Scheme 51

Spectra data of *N,N*-Dimethyl-2-(1-methyl-1*H*-indol-3-yl)aniline (22a):

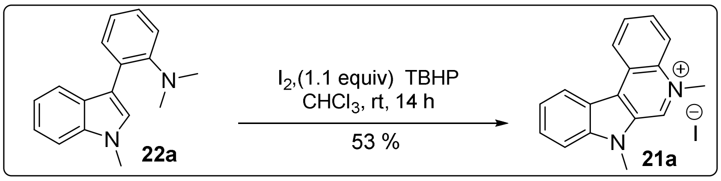
IR (KBr): $\tilde{\nu}$ = 3045, 2937, 2792, 1544, 1487, 1373, 1220, 759 cm^{-1}

^{1}H NMR (400 MHz, MeOD): δ 7.58 (d, *J* = 0.8 Hz, 1H), 7.37-7.33 (m, 3H), 7.21-7.15 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.02 (dt, *J* = 8.0 Hz, *J* = 0.8 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 2.52 (s, 6H).

^{13}C NMR (100 MHz, MeOD): δ 153.1 (C), 138.6 (C), 132.8 (CH), 129.9 (C), 128.6 (CH), 128.1 (C), 128.0 (CH), 122.6 (C), 122.5 (CH), 121.6 (CH), 120.1 (CH), 119.0 (CH), 116.7 (C), 110.2 (CH), 43.6(2 X CH$_3$), 32.9 (CH$_3$).

HRMS (ESI): calcd for $C_{17}H_{18}N_2H$ [M +H]$^+$ 251.1548, found 251.1548.

The key intermediate **22a** was treated with our standardized condition for IMDC with 1.1 equiv of iodine, 2 equiv of TBHP in chloroform for 14 h at room temperature to give a solid material which was washed with 20 % ethyl acetate in petroleum ether to give desired 5,7-dimethyl-7*H*-indolo[2,3-*c*]quinolin-5-ium iodide [14a] **21a** in 53 % yield.



Scheme 52

Spectra data of 5,7-Dimethyl-7*H*-indolo[2,3-*c*]quinolin-5-ium iodide (21a):[14a]

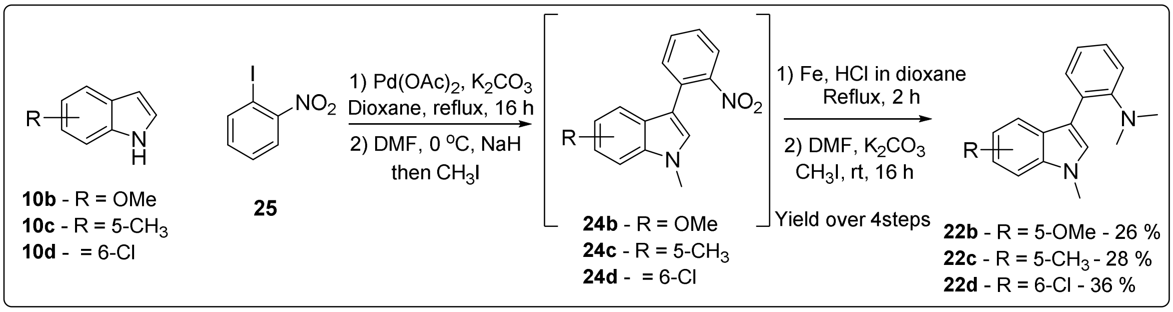
IR (KBr): $\tilde{\nu}$ = 3043, 2945, 1613, 1502, 1469, 1344, 1134, 752 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 10.13 (s, 1H), 9.11-9.09 (m,1H), 8.86 (d, J = 8.0 Hz, 1H), 8.51 (d, J = 9.6 Hz, 1H), 8.09-8.07 (m, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.90 (t, J = 8.0 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 4.71 (s, 3H), 4.17 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 143.7 (C), 136.9 (CH), 132.7 (C), 131.2 (C), 130.7 (C), 129.9 (CH), 129.8 (CH), 125.2 (C), 125.0 (CH), 124.4 (CH), 123.5 (C), 122.6 (CH), 119.6 (CH), 119.3 (C), 111.8 (CH), 45.7 (CH_3), 30.3 (CH_3).

HRMS (ESI): calcd for $C_{17}H_{15}N_2$ $[M]^+$ 247.1235, found 247.1235

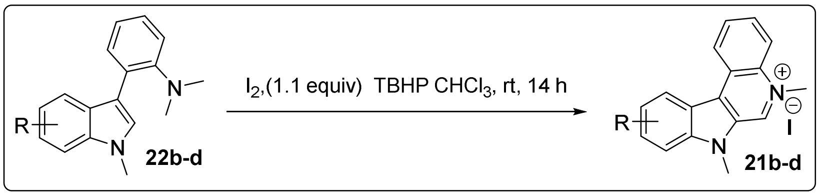
Having successfully synthesized 5,7-dimethyl-7*H*-indolo[2,3-*c*]quinolin-5-ium iodide **21a**, the scope of the reaction was extended to synthesize derivatives of this compound by varying the substituents on indole ring. 5-Methoxy indole **11a**, 5-methyl indole **11b** and 6-chloro indole **11d** were reacted with 1-iodo-2-nitrobenzene along with 10 mol% of palladium acetate and 2 equiv of K_2CO_3 to give arylated products, which were methylated with methyl iodides using NaH as a base to give intermediate **24b-d** (Scheme 53). Nitro derivatives **24b-d** were then reduced with Fe/HCl in refluxing dioxane and were then dimethylated with methyl iodide in the presence of K_2CO_3 in DMF to afford dimethyl intermediates **22b-d**.

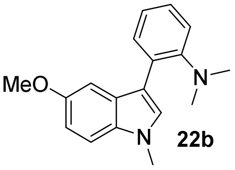
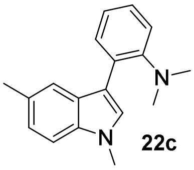
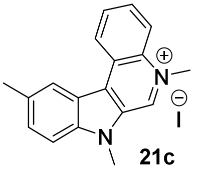
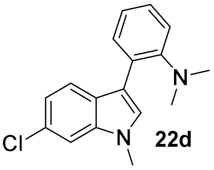
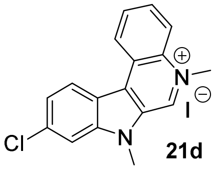

10b - R = OMe
10c - R = 5-CH3
10d - = 6-Cl
25
1) Pd(OAc)2, K2CO3
Dioxane, reflux, 16 h
2) DMF, 0 °C, NaH
then CH3I
24b - R = OMe
24c - R = 5-CH3
24d - = 6-Cl
1) Fe, HCl in dioxane
Reflux, 2 h
2) DMF, K2CO3
CH3I, rt, 16 h
Yield over 4steps
22b - R = 5-OMe - 26 %
22c - R = 5-CH3 - 28 %
22d - R = 6-Cl - 36 %

Scheme 53

The intermediate **22b-d** was then subjected to IMDC protocol. In case of **22b** a mixture of compounds were obtained (Table 9), while compound **22c** and **22d** gave the desired compound **21c** and **21d** in 52 and 48 % yields respectively.

Table 9: Scope of IMDC for synthesis of indole[2,3,*c*]quinolines.

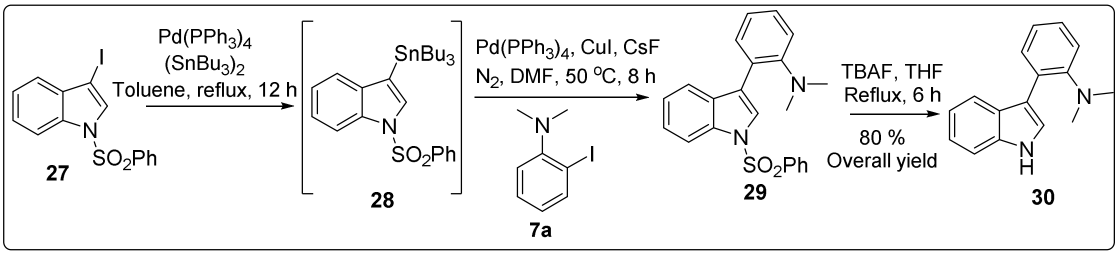

22b-d
I2,(1.1 equiv) TBHP CHCl3, rt, 14 h
21b-d

Entry	Starting **22b-d**	Product **21b-d**	Yield in % of **21b-d** [a]
1	 **22b**	Mixture of Compounds	-
2	 **22c**	 **21c**	52
3	 **22d**	 **21d**	48

[a] isolated yield

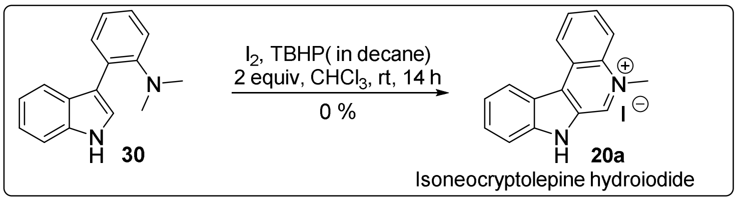
Attempted synthesis of Isoneocryptolepine (20a)

For the synthesis of isoneocryptolepine; 3-iodo-1-(phenylsulfonyl)-1*H*-indole[14b] **27** was treated with bis(tributyltin) in refluxing toluene in the presence of $Pd(PPh_3)_4$ to give stannyl derivative **28** which was directly subjected to Stille coupling with 2-iodo-*N*,*N*-dimethylaniline **7a** to give *N*,*N*-dimethyl-2-(1-(phenylsulfonyl)-1*H*-indol-3-yl)aniline **29**. Desulfonation was done using TBAF in refluxing THF to give 2-(1*H*-indol-3-yl)-*N*,*N*-dimethylaniline **30**.


Pd(PPh3)4
(SnBu3)2
Toluene, reflux, 12 h
27
SO2Ph
SnBu3
28
Pd(PPh3)4, CuI, CsF
N2, DMF, 50 °C, 8 h
7a
29
TBAF, THF
Reflux, 6 h
80 %
Overall yield
30

Scheme 54

Intermediate **30** was then subjected to our standardized condition for IMDC during which we failed to obtain the isoneocryptolepine hydroiodide **20a** as the final product even after many attempts.


I2, TBHP(in decane)
2 equiv, CHCl3, rt, 14 h
0 %
30
20a
Isoneocryptolepine hydroiodide

Scheme 55

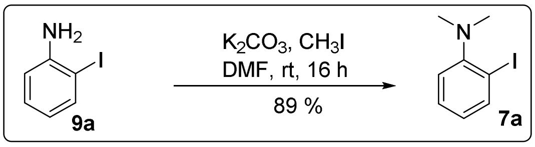
2. B. 4: Conclusion

We successfully applied our IMDC procedure for synthesis 5,7-dimethyl-7*H*-indolo[2,3-*c*]quinolin-5-ium iodides in moderate yields.

Attempts to synthesize isoneocryptolepine hydroiodide failed under optimized conditions from 2-(1*H*-indol-3-yl)-*N*,*N*-dimethylaniline.

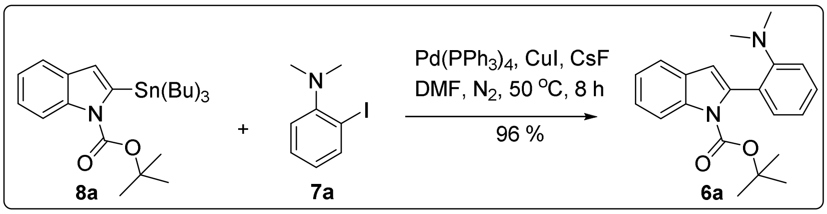
2. 5: Experimental

2.5.1: 2-iodo-*N*,*N*-dimethylaniline (7a)[11a]


K2CO3, CH3I
DMF, rt, 16 h
89 %
9a
7a

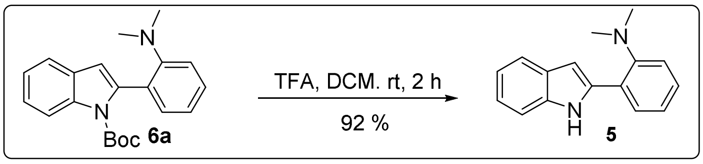
o-Iodoaniline (2.190 g, 10 mmol) was dissolved in 15 mL anhydrous DMF, K_2CO_3 (2.760 g, 20 mmol) and iodomethane (1.31 mL, 21 mmol) were added and the reaction mixture stirred at room temperature for 16 h. Water (20 mL) was added and extracted with diethyl ether (3 X 10 mL). The organic layers were combined, washed with water (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by flash chromatography using petroleum ether:ethyl acetate 19:1, to give the product *N*,*N*-dimethyl 2-iodoaniline [11a] **7a** as a pale yellow oil in 89 % (2.200 g) yield.

2.5.2: *tert*-Butyl 2-(2-(dimethylamino)phenyl)-1*H*-indole-1-carboxylate (6a)


Pd(PPh3)4, CuI, CsF
DMF, N2, 50 °C, 8 h
96 %
8a
7a
6a

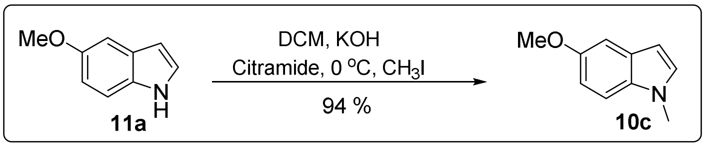
To a solution of *t*-butyl 2-(tributylstannyl)-1*H*-indole-1-carboxylate[11b] **8a**, (crude, 0.506 g, 1 mmol) and 2-iodo-*N*,*N*-dimethylaniline **7a** (0.124 g, 0.5 mmol) in anhydrous DMF (2 mL) was added tetrakistriphenylpalladium(0) (0.029 g, 0.025 mmol), copper(I)iodide (0.010 g, 0.05 mmol) and caesium fluoride (0.151 g, 1 mmol) under argon atmosphere. It was then heated at 50 °C for 8 h. On complete consumption of 2-iodo-*N*,*N*-dimethylaniline (monitored by TLC) the reaction was cooled to room temperature and diluted with 10 mL of water and 10 mL ethyl acetate and stirred for 30 minutes. This was then filtered through a bed of celite and further washed with ethyl acetate (10 mL). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (2 X 10 mL). The combined organic layer was washed with sat. NaCl solution dried over anhydrous $Na_2SO_4$and concentrated under reduced pressure. The crude product obtained was purified by flash chromatography (95:5 petroleum ether: ethyl acetate) to afford title compound **6a** as a viscous liquid in 96 % (0.162 g) yield.

2.6.3: 2-(1*H*-Indol-2-yl)-N,N-dimethylaniline (5)



tert-Butyl-2-(2-(dimethylamino)phenyl)-1*H*-indole-1-carboxylate **6a** (0.135 g, 0.4 mmol)was dissolved in 5 mL DCM and cooled to 0 °C and TFA (0.076 g, 1 mmol) was added. The mixture was allowed to stir at room temperature for 2 h. Reaction mixture was quenched by adding 10 mL sat. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with DCM (5 mL X 2). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the title compound **5** as a white solid (mp. 60-62 °C) in 92 % (0.087 g) yield.

2.5.4: 5-Methoxy-1-methyl-1*H*-indole (10c) [11h]

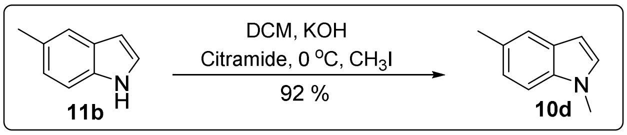


To a stirred solution of 5-methoxy indole (1.460 g, 10 mmol) in 20 mL DCM at 0 °C was added KOH (0.672 g, 12 mmol) and citramide (0.140 g, 10 % w/w). The reaction was aged for 20 min and methyl iodide (1.704 g, 12 mmol) was added drop wise, the mixture was allowed to stir at room temperature for an additional 3 h. Water (20 mL) was added and organic layer was separated, aqueous layer was further extracted with DCM (10 mL X 2).

The combined organic layer was washed with 10 mL of brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to give a crude material which was purified by flash chromatography with petroleum ether: ethyl acetate (9:1) to give 5-methoxy-1-methyl-1*H*-indole [11h] **10c** 94% (1.485 g) yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.25 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 6.8 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H).

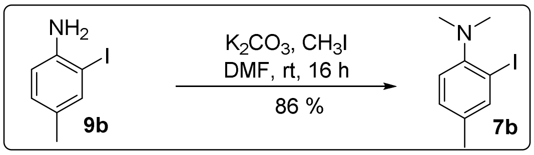
2.5.5: 1,5-Dimethyl-1*H*-indole (10d) [11h]



Following the similar procedure described in section 2.5.4 with 5-methyl indole **11b** (1.312 g, 10 mmol) gave 1,5-dimethyl-1*H*-indole [11h] **10d** 92 % (1.334 g) yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.47 (d, J = 3.6 Hz, 1H), 7.27 (d, J = 7.2 Hz, 1H), 7.12-7.09 (m, 1H), 7.05 (s, 1H), 6.45 (s, 1H), 3.81 (s, 3H), 2.51 (d, J = 5.2 Hz, 3H).

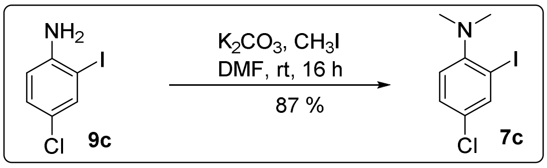
2.5.6: 2-Iodo-*N*,*N*,4-trimethylaniline (7b) [11e]



Following the similar procedure described in section 2.5.1 with 2-iodo-4-methylaniline **9b** (2.330 g, 10 mmol), gave 2-iodo-*N*,*N*,4-trimethylaniline in **7b** 86 % (2.245 g) yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.72 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 2.77 (s, 6H), 2.29 (s, 3H).

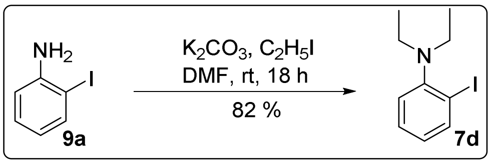
2.5.7: 4-Chloro-2-iodo-*N*,*N*-dimethylaniline (7c) [11e]



Following the similar procedure described in section 2.5.1 with 4-chloro-2-iodoaniline **9c** (2.545 g, 10 mmol), gave 4-chloro-2-iodo-*N*,*N*-dimethylaniline [11e] **7c** in 87 % (2.336 g) yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.83 (d, J = 2.4 Hz, 1H), 7.30-7.27 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 2.75 (s, 3H).

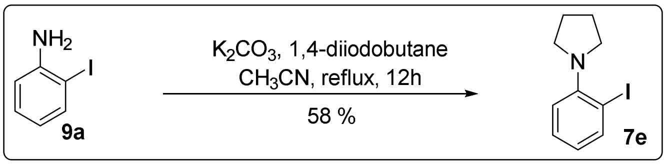
2.5.8: *N,N*-Diethyl-2-iodoaniline (7d) [11f]



Following the similar procedure described in section 2.5.1 with 2-iodoaniline **9a** (0.219 g, 1 mmol), and ethyl iodide (0.088 mL, 1.1 mmol) gave *N*,*N*-diethyl-2-iodoaniline [11f] **7d** in 82 % (0.226 g) yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.86 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 7.31-7.24 (m, 1H), 7.07 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 6.80 (dt, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 3.02 (q, *J* = 7.2 Hz, 4H), 1.00 (t, *J* = 7.2 Hz, 6H).
^{13}C NMR (100 MHz, CDCl$_3$): δ 152.0 (C), 139.8 (CH), 128.6 (CH), 125.8 (C), 124.2 (C), 102.7 (C), 48.2 (CH$_2$), 12.5 (CH$_3$).

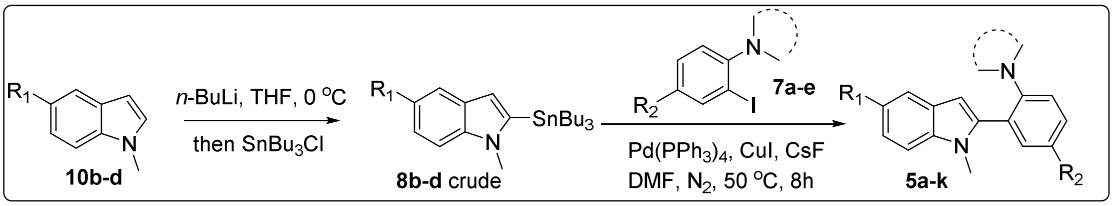
2.5.9: 1-(2-iodophenyl)pyrrolidine (7e) [11f]



o-Iodoaniline **9a** (0.438 g, 2 mmol) was dissolved in anhydrous acetonitrile (10 mL), K$_2$CO$_3$ (0.414 g, 3 mmol) and 1,4-diiodobutane (0.930 g, 3.0 mmol) was added and heated to reflux for 12 h. The solvent was removed under reduced pressure and water (20 mL) was added and the reaction mixture was extracted with diethyl ether (3 X 10 mL). The organic layers were combined and washed with water (10 mL) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using petroleum ether:ethyl acetate 19:1, to give product 1-(2-iodophenyl)pyrrolidine **7e** in 58 % (0.316 g) yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.81 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 7.29-7.20 (m, 1H), 6.94 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 6.65 (dt, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 3.27 (t, *J* = 5.6 Hz, 4H), 1.93 (p, *J* = 3.2 Hz, 4H).
^{13}C NMR (100 MHz, CDCl$_3$): δ 152.1 (C), 141.1 (CH), 128.7 (CH), 123.2 (CH), 118.8 (CH), 91.4 (C), 51.9 (CH$_2$), 24.9 (CH$_2$).

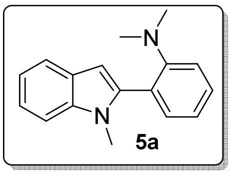
General procedure for synthesis of *N,N*-Dimethyl-2-(1-methyl-1*H*-indol-2-yl)anilines



2.5.10: *N*,*N*-Dimethyl-2-(1-methyl-1*H*-indol-2-yl)aniline (5a)

1-Methyl-1*H*-indole **10b** (0.066 g, 0.5 mmol) was dissolved in dry THF (10 mL) and cooled to 0 °C with an ice bath. A solution of *n*-BuLi (1.6 M in hexane; 0.31 mL, 0.5 mmol) was added and the mixture was stirred at the same temperature for 1h. To this tributyl tin chloride (0.14 mL, 0.5 mmol) in THF (2 mL) was added and the reaction mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was then quenched with sat. NaCl and EtOAc (10 mL) was added and the organic layer was separated. The aqueous layer was further extracted with EtOAc (2 x 10 mL) and the combined organic layers were dried over Na_2SO_4. The organic layer was evaporated in vacuum to give a viscous oil **8b** which was used directly for the next reaction without further purification.

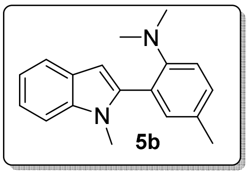
To the above crude stannyl intermediate **8b** and corresponding 2-iodo-*N*,*N*-dimethylaniline **7a** (0.124 g, 0.5 mmol) in anhydrous dimethyformamide (2 mL) was added tetrakistriphenylpalladium(0) (0.030 g, 0.025 mmol), copper(I)iodide (0.010 g, 0.05 mmol) and cesium fluoride (0.151 g, 1 mmol) under argon atmosphere. It was then heated at 50 °C for 8 h. On complete consumption of 2-iodo-*N*,*N*-dimethylaniline (monitored by TLC) reaction was cooled to room temperature and diluted with 10 mL of water and 10 mL ethyl acetate and stirred for 30 minutes. This was then filtered through a bed of celite and further washed with ethyl acetate (10 mL), the organic layer was separated and the aqueous layer was further extracted with ethyl acetate (2 X 10 mL). The combined organic layer was washed with sat. NaCl solution dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by flash chromatography (95:5 petroleum ether: ethyl acetate) to afford title compound **5a** in 72 % (0.090 g) yield.


5a

***N*,*N*-Dimethyl-2-(1-methyl-1*H*-indol-2-yl)aniline (5a):** white crystalline solid, m.p. 86-88 °C.

2.5.11: *N*,*N*,4-Trimethyl-2-(1-methyl-1*H*-indol-2-yl)aniline (5b)

Following procedure described in section 2.5.10 using *N*-methyl indole **10b** (0.066 g) and 2-iodo-*N*,*N*,4-trimethylaniline **7b** (0.131 g) to give **5b** in 68 % (0.090 g) yield.



White crystalline solid, m.p. 92-94 °C.

IR (KBr): $\tilde{\nu}$ =2924, 2852, 1870, 1492, 1456, 1313, 947, 748 cm^{-1}.

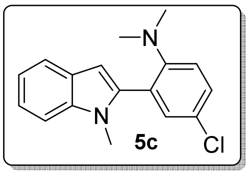
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.56 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.18-7.03 (m, 4H), 6.84 (d, J = 7.6 Hz, 1H), 6.42 (s, 1H), 3.49 (s, 3H), 2.45 (s, 6H), 2.25(s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 149.8 (C), 141.8 (C), 137.5 (C), 133.9 (CH), 130.3 (C), 129.9 (CH), 128.3 (C), 125.1 (C), 120.9 (CH), 120.2 (CH), 119.3 (CH), 117.3 (CH), 109.4 (CH), 100.8 (CH), 42.6 (2 X CH$_3$), 30.7 (CH$_3$), 20.4 (CH$_3$).

HRMS (ESI): calcd for $C_{18}H_{20}N_2H$ [M +H]$^+$ 265.1705, found 265.1701.

2.5.12: 4-Chloro-*N*,*N*-dimethyl-2-(1-methyl-1*H*-indol-2-yl)aniline (5c)

Following procedure described in section 2.5.10 using *N*-methyl indole **10b** (0.066 g) and 4-chloro-2-iodo-*N*,*N*-dimethylaniline **7c** (0.141 g) to give **5c** in 69 % (0.098 g) yield.



White crystalline solid, m.p. 116-118 °C.

IR (KBr): $\tilde{\nu}$ =2940, 2825, 1870, 1845, 1490, 1453, 1312, 946 cm^{-1}.

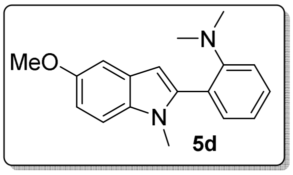
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.57 (td, J = 8.0 Hz, J = 0.8 Hz, 1H), 7.29 (dd, J = 8.0. J = 0.8 Hz, 1H), 7.24-7.15 (m, 2H) 7.06 (dt, J = 8.0 Hz, 0.8Hz, 1H), 6.43 (d, J = 1.2 Hz, 1H), 3.49 (s, 3H), 2.46 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 149.6 (C), 139.2 (C), 136.6 (C), 131.8 (CH), 128.1 (CH), 127.1 (C), 125.1 (C), 124.4 (C), 120.4 (CH), 119.4 (CH), 118.5 (CH), 117.4 (CH), 108.4 (CH), 100.4 (CH), 41.2 (2 X CH$_3$), 29.7 (CH$_3$).

HRMS (ESI): calcd for $C_{17}H_{17}ClN_2H$ [M +H]$^+$ 285.1159, found 285.1156.

2.5.13: 2-(5-Methoxy-1-methyl-1*H*-indol-2-yl)-*N*,*N*-dimethylaniline (5d)

Following procedure described in section 2.5.10 using 5-methoxy-1-methyl-1*H*-indole **10c** (0.081 g) and 2-iodo-*N*,*N*-dimethylaniline **7a** (0.124 g) to give **5d** in 61 % (0.086 g) yield.



White crystalline solid, m.p. 92-94 °C.

IR (KBr): $\tilde{\nu}$ =2942, 2823, 1873, 1848, 1490, 1210, 1138, 835 cm^{-1}.

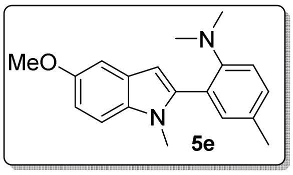
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37-7.31 (m, 2H), 7.25 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 1.6 Hz, 1H), 7.03-6.97 (m, 2H), 6.88 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 6.42 (d, J = 0.8 Hz, 1H), 3.87 (s, 3H), 3.53 (s, 3H), 2.56 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 154.0 (C), 151.9 (C), 142.3 (C), 133.3 (CH), 132.9 (C), 129.4 (CH), 128.5 (C), 124.7 (C), 120.6 (CH), 117.1 (CH), 111.2 (CH), 110.1 (CH), 101.9 (CH), 100.5 (CH), 55.9 (CH$_3$), 42.2 (2 X CH$_3$), 30.8 (CH$_3$).

HRMS (ESI) *m/z* calcd for $C_{18}H_{20}N_2OH$ $[M+H]^+$ 281.1654, found 281.1654.

2.5.14. 2-(5-Methoxy-1-methyl-1*H*-indol-2-yl)-*N*,*N*,4-trimethylaniline (5e)

Following procedure described in section 2.5.10 using 5-methoxy-1-methyl-1*H*-indole **10c** (0.081 g) and 2-iodo-*N*,*N*,-4-trimethylaniline **7b** (0.131 g) to give **5e** in 63 % (0.093 g) yield.


5e

White crystalline solid, m.p. 98-100 °C.

IR (KBr): $\tilde{\nu}$ =2941, 2826, 1874, 1845, 1490, 1253, 1140, 835 cm^{-1}.

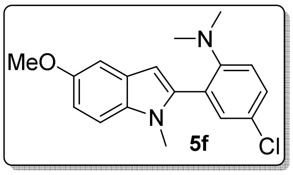
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.20-7.17 (m, 2H), 7.12 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.90 (dd, J = 8.8 Hz, J = 2.8 Hz, 1H), 6.43 (d, J = 8.8 Hz,1H), 3.89 (s, 3H),3.56 (s, 3H), 2.54 (s, 6H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0 (C), 149.7 (C), 142.3 (C), 133.8 (CH), 133.0 (C), 130.2 (C), 129.9 (CH), 128.5 (C), 125.1 (C), 117.3 (CH), 111.1 (CH), 110.1 (CH), 102.0 (CH), 100.4 (CH), 55.9 (CH_3), 42.6 (2 X CH_3), 30.9 (CH_3), 20.4 (CH_3).

HRMS (ESI): calcd for $C_{19}H_{22}N_2OH$ $[M+H]^+$ 295.1810, found 295.1810.

2.5.15: 4-Chloro-2-(5-methoxy-1-methyl-1*H*-indol-2-yl)-*N*,*N*-dimethylaniline (5f)

Following procedure described in section 2.6.9 using 5-methoxy-1-methyl-1*H*-indole**10c** (0.081 g) and 4-chloro-2-iodo-*N*,*N*-dimethylaniline **7c** (0.141 g) to give **5f** in 64 % (0.101 g) yield.


5f

White crystalline solid, m.p. 118-120 °C.

IR (KBr): $\tilde{\nu}$ =2947, 2829, 1870, 1847, 1492, 1450, 1215, 1139, 835 cm^{-1}.

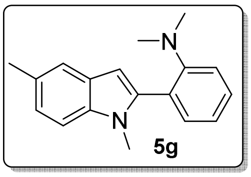
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.16 (m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 6.87-6,81 (m, 2H), 6.35 (d, J = 0.8 Hz, 1H), 3.80 (s, 3H), 3.45 (s, 3H), 2.46(s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ154.2 (C), 150.5 (C), 140.7 (C), 133.0, 132.8 (CH), 129.0 (CH), 128.4 (C), 126.1 (C), 125.3 (C), 118.4 (CH), 111.7 (CH), 110.2 (CH), 102.0 (CH), 101.0 (CH), 55.9 (CH_3), 42.2 (2 X CH_3), 30.9 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{19}ClN_2OH$ $[M+H]^+$ 315.1264, found 315.1262.

2.5.16: 2-(1,5-Dimethyl-1*H*-indol-2-yl)-*N*,*N*-dimethylaniline (5g)

Following procedure described in section 2.5.10 using 1,5-dimethyl-1*H*-indole **10d** (0.073 g) and 2-iodo-*N*,*N*-dimethylaniline **7a** (0.124 g) to give **5d** in 66 % (0.08 g) yield.


5g

White crystalline solid, m.p. 124-126 °C.

IR (KBr): $\tilde{\nu}$ =2914, 2840, 1843, 1479, 1465, 1325, 1150, 940 cm^{-1}.

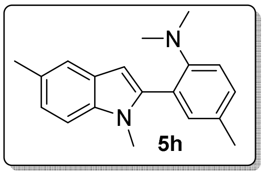
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.42 (s, 1H), 7.37-7.31 (m, 2H), 7.25-7.23 (m, 1H) 7.06-6.96 (m, 3H), 6.41 (s, 1H), 3.53 (s, 3H), 2.55 (s, 6H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 151.9 (C), 141.8 (C), 136.0 (C), 133.3 (CH), 129.3 (CH), 128.5 (2 X C), 124.8 (C), 122.6 (CH), 120.5 (CH), 119.8 (CH), 117.1 (CH), 109.1 (CH), 100.3 (CH), 42.2 (2 X CH$_3$), 30.7 (CH$_3$), 21.4 (CH$_3$).

HRMS (ESI): calcd for $C_{18}H_{20}N_2H[M+H]^+$ 265.1705, found 265.1705.

2.5.17: 2-(1,5-Dimethyl-1*H*-indol-2-yl)-*N*,*N*,4-trimethylaniline (5h)

Following procedure described in section 2.5.10 using 1,5-dimethyl-1*H*-indole **10d** (0.073 g) and 2-iodo-*N*,*N*,4-trimethylaniline **7b** (0.131 g) to give **5h** in 63 % (0.088 g) yield.


5h

White crystalline solid, m.p. 130-132 °C.

IR (KBr): $\tilde{\nu}$ =3012, 2924, 1926, 1610, 1585, 1450, 1361, 1257, 1114, 815 cm^{-1}.

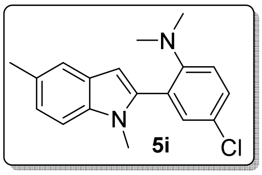
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.41 (t, *J* = 0.8 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.17-7.15 (m, 2H), 7.04 (dd, *J* = 8.8 Hz, *J* = 1.2 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.39 (d, *J* = 0.4, 1H), 3.54 (s, 3H), 2.51 (s, 6H), 2.47 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 148.7 (C), 140.8 (C), 135.0 (C), 132.8 (CH), 129.1 (C), 128.8 (CH), 127.5 (C), 127.4 (C), 124.1 (C), 121.5 (CH), 118.8 (CH), 116.2 (CH), 108.0 (CH), 99.2 (CH), 41.5 (2 X CH$_3$), 29.7 (CH$_3$), 20.4 (CH$_3$), 19.4 (CH$_3$).

HRMS (ESI): calcd for $C_{19}H_{22}N_2H$ [M+H]$^+$ 279.1861, found 279.1860.

2.5.18: 4-Chloro-2-(1,5-dimethyl-1*H*-indol-2-yl)-*N*,*N*-dimethylaniline (5i)

Following procedure described in section 2.5.10 using 1,5-dimethyl-1*H*-indole **10d** (0.073 g) and 4-chloro-2-iodo-*N*,*N*-dimethylaniline **7c** (0.141 g) to give **5i** in 60 % (0.090 g) yield.


5i

White crystalline solid, m.p. 142-144 °C.

IR (KBr): $\tilde{\nu}$ =2914, 2843, 1853, 1479, 1465, 1323, 1153, 943 cm^{-1}.

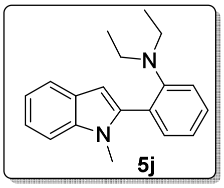
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.44 (d, *J* = 0.8 Hz, 1H),7.44-7.26 (m, 3H), 7.08 (dd, *J* = 8.4, *J* = 0.8 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 0.8 Hz, 1H), 3.55 (s, 3H), 2.46 (s, 6H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 150.5 (C), 140.2 (C), 136.1 (C), 132.8 (CH), 129.0 (CH), 128.7 (C), 128.4 (C), 126.1 (C), 125.3 (C), 123.0 (CH), 120.0 (CH), 118.3 (CH), 109.1 (CH), 100.8 (CH), 42.2 (2 X CH$_3$), 30.7 (CH$_3$), 21.4 (CH$_3$).

HRMS (ESI): calcd for $C_{18}H_{19}ClN_2H$ $[M +H]^+$ 299.1315, found 299.1318.

2.5.19: *N,N*-Diethyl-2-(1-methyl-1*H*-indol-2-yl)aniline (5j)

Following procedure described in section 2.5.10 using *N*-methyl-1*H*-indole **10b** (0.066 g) and *N*,*N*-diethyl-2-iodoaniline **7d** (0.138 g) to give **5j** in 65 % (0.094 g) yield.



Viscous liquid.

IR (KBr): $\tilde{\nu}$ = 3055, 2968, 1539, 1446, 1244, 1176, 781 cm^{-1}.

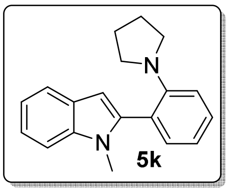
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.63(d, *J* = 8.0 Hz, 1H), 7.36-7.30 (m, 3H), 7.22 (dt, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.12 (dt, *J* = 8.0. Hz, *J* = 1.2 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.01 (dt, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 6.46 (d, *J* = 0.4 Hz, 1H), 3.57 (s, 3H), 2.93(q, *J* = 7.2 Hz, 4H), 0.87 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 150.1 (C), 141.9 (C), 137.4 (C), 133.6 (CH), 128.9 (CH) 128.3 (C), 126.7 (C), 121.0 (CH), 120.9 (CH), 120.1 (CH), 119.9 (CH), 119.3 (CH), 109.3 (CH), 100.8 (CH), 45.2 (2 X CH_2), 31.0 (CH_3), 11.9 (2 X CH_3).

HRMS (ESI): calcd for $C_{19}H_{22}N_2H$ $[M+H]^+$ 279.1861, found 279.1862.

2.5.20: 1-Methyl-2-(2-(pyrrolidin-1-yl)phenyl)-1*H*-indole (5k)

Following procedure described in section 2.5.10 using *N*-methyl-1*H*-indole **10b** (0.066 g) and1-(2-iodophenyl)pyrrolidine **7e** (0.137 g)to give **5k** in 67 % (0.093 g) yield.



Viscous liquid.

IR (KBr): $\tilde{\nu}$ =2962, 2872, 1930, 1886, 1595, 1446, 1336, 1168, 952, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.62 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.35-7.30 (m, 2H), 7.29-7.19(m, 2H), 7.13 (dt, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 6.86-6.79 (m, 2H), 6.49 (d, *J* = 0.8 Hz, 1H), 3.52 (s, 3H), 2.91 (s, 4H), 1.73 (d, *J* = 6.0 Hz, 4H).

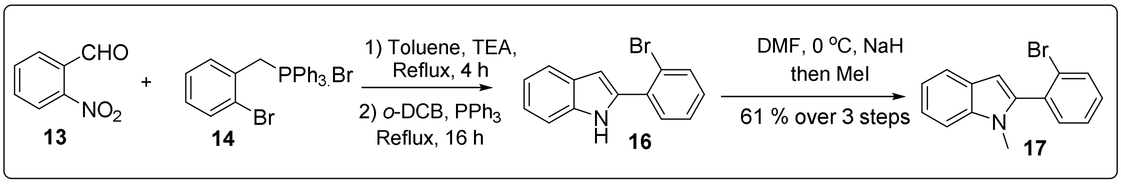
^{13}C NMR (100 MHz, $CDCl_3$): *δ* 148.7 (C), 142.3 (C), 136.6 (C), 133.9 (CH), 129.3 (CH), 128.4 (C), 120.8 (CH), 120.1 (CH), 119.4 (2 X CH), 117.1 (CH), 114.0 (CH), 109.3 (CH), 101.5 (CH), 49.5 (2 X CH_2), 30.2 (CH_2), 25.5 (2 X CH_2).

HRMS (ESI): calcd for $C_{19}H_{20}N_2H$ $[M+H]^+$ 277.1705, found 277.1705.

2.5.21. 2-(2-Bromophenyl)-1-methyl-1*H*-indole (17)

A mixture of *o*-nitrobenzaldehyde **13** (0.605g, 4 mmol) and bromo(2-bromobenzyl)triphenyl-λ^5-phosphane**14** (2.254 g, 4.4 mmol) in a round bottom flask was dissolved in toluene (15 mL) and triethyl amine (0.70 ml, 5 mmol) was added. The reaction mixture was heated at reflux for 4 h and then the crude mixture was evaporated to dryness. The crude mass was dissolved in *o*-DCB (20 mL), and PPh_3 (2.412 g, 9.2 mmol) was added and the mixture was heated at 180 ^oC for 18 h under N_2 atmosphere. The solvent was removed under reduced pressure and crude mass was subjected to column purification. The product was eluted with 15 % ethyl acetate in petroleum ether.

The off-white compound **16** obtained (0.697 g, 2.56 mmol) was dissolved in 10 mL DMF and cooled to 0 ^oC with an ice bath, to this NaH (0.123 g, 3.07 mmol) was added and the reaction mass was stirred at the same temperature for an additional 30 min. Methyl iodide (0.186 mL, 3.0 mmol) was added and the reaction mixture was allowed to stir at room temperature for 6 h. Reaction was then quenched by addition of water (20 mL) and extracted with (3x 10 mL) of diethyl ether. The organic layers were combined and washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile was removed under reduced pressure and crude compound was purified using 10 % ethyl acetate in petroleum ether to give desired compound **17** in 61 % (0.696 g) yield (over 3 steps).



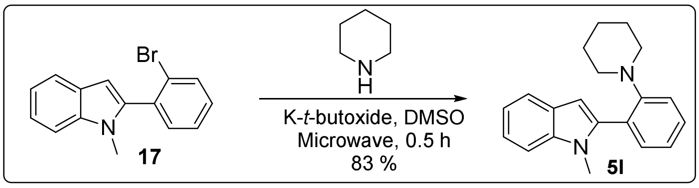
IR (KBr):$\tilde{\nu}$ =2927, 2888, 1538, 1446, 1244, 1176 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.40 (m, 2H), 7.39-7.36 (m, 3H), 7.33-7.24 (m, 2H), 7.15 (dt, J = 8.0 Hz, J = 1.2 Hz, 1H), 6.51 (d, J = 0.8 Hz, 1H), 3.57 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7 (C), 137.3 (C), 134.3 (C), 132.9 (CH), 132.8 (CH), 130.2 (CH), 127.6 (C), 127.2 (CH), 125.2 (C), 121.8 (CH), 120.7 (CH), 119.8 (CH), 109.5 (CH), 102.1 (CH), 30.7 (CH_3).

HRMS (ESI):calcd for $C_{15}H_{12}BrNH$ $[M+H]^+$ 286.0231, found 286.0231.

2.5.22. 1-Methyl-2-(2-(piperidin-1-yl)phenyl)-1*H*-indole (5l)



Compound **17** (0.143 g, 0.5 mmol), potassium-*t*-butoxide (0.112 g, 1 mmol), piperidine (0.1 mL, 1.36 mmol) and DMSO (6 mL) were mixed in Teflon vessel and heated under microwave radiation for 30 min at 170 ^oC. On completion water (10 mL) was added and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile was removed under reduced pressure and crude compound obtained was purified using 20 % ethyl acetate in petroleum ether to give **5l** as oil in 83 % (0.120 g) yield.

Viscous liquid.

IR (KBr): $\tilde{\nu}$ = 3051, 2933, 2805, 1598, 1465, 1442, 1340, 1232, 777 cm^{-1}.

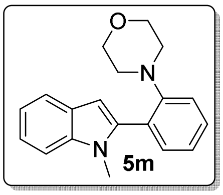
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.55(d, *J* = 7.6 Hz, 1H), 7.29-7.25 (m, 2H), 7.16 (dt, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.07 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 2H), 6.96-6.92 (m, 2H), 6.48 (d, *J* = 0.4 Hz, 1H), 3.68 (s, 3H), 3.16(t, *J* = 4.8 Hz, 4H), 1.69 (s, 4H), 1.54-1.53 (m, 4H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 152.3 (C), 142.4 (C), 138.3 (C), 133.6 (C), 129.1 (CH), 128.1 (C), 121.6 (CH), 120.5 (CH), 120.3 (CH), 119.9 (CH), 117.6 (CH), 116.1 (CH), 109.7 (CH), 101.4 (CH), 50.6 (2 X CH_2), 31.3 (CH_3), 25.9 (2 X CH_2), 24.4 (CH_2).

HRMS (ESI): calcd for $C_{20}H_{22}N_2H$ $[M+H]^+$ 291.1861, found 291.1862.

2.5.23. 4-(2-(1-Methyl-1*H*-indol-2-yl)phenyl)morpholine (5m)

Following procedure described in section 2.5.22 using **17** (0.142 g, 0.5 mmol) and morpholine (0.1 mL, 1.16 mmol) to give 4-(2-(1-methyl-1*H*-indol-2-yl)phenyl)morpholine **5m**i n 79 % (0.116 g) yield.



5m

Viscous liquid.

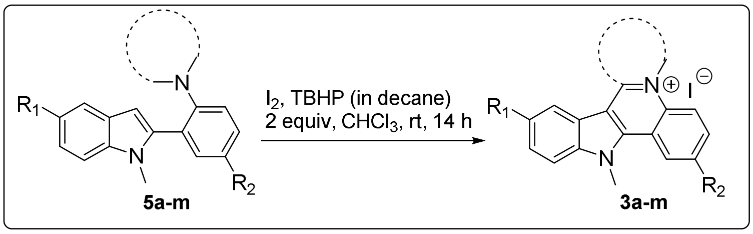
IR (KBr): $\tilde{\nu}$ = 3049, 2930, 2800, 1594, 1460, 1439, 1340, 1231 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.63 (d, *J* =8.0 Hz, 1H), 7.38-7.35 (m, 2H), 7.26-7.22 (m, 1H), 7.15 (dt, *J* =8.0 Hz, *J* =0.8 Hz, 1H), 7.12-7.01 (m, 2H), 7.00-6.94 (m, 1H), 6.55 (d, *J* = 08 Hz, 1H), 3.88 (t, *J* = 4.8 Hz, 1H), 3.74 (s, 3H), 3.21 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 151.3 (C), 141.4 (C), 138.8 (C), 131.6 (C), 129.1 (CH), 123.2 (C), 122.1 (CH), 121.0 (CH), 120.7 (CH), 119.8 (CH), 116.6 (CH), 114.1 (CH), 109.7 (CH), 101.2 (CH), 66.0 (2 X CH_2), 52.6 (2 X CH_2), 31.2 (CH_3).

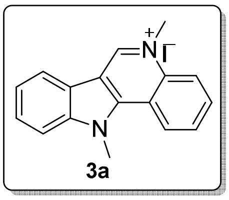
HRMS (ESI): calcd for $C_{19}H_{20}N_2OH$ $[M+H]^+$ 293.1654, found 293.1654.

General procedure for synthesis of Dialkyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide



2.5.24. 5,11-Dimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3a) [8e]

In an oven dried round bottom flask *N*,*N*-dimethyl-2-(1-methyl-1*H*-indol-2-yl)aniline (**5a**, 0.025 g, 0.1 mmol) and iodine (0.028 g, 0.11 mmol) was dissolved in chloroform (1 mL) and TBHP (0.04 mL, 0.2 mmol) was added. The flask was closed with a stopper and stirred at room temperature for 14 h. The reaction mixture was diluted with 20% ethyl acetate in petroleum ether (10 mL). The solid product that separated out was filtered and dried to get the salt **3a** (0.028 g, 75%). The compound was further purified by passing through a short bed of neutral alumina eluting with 9:1 chloroform: methanol.

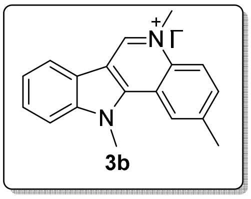


3a

Off-white solid, m.p. decomp. > 310 ^{o}C (lit. [8e] m.p.> 300 ^{o}C).

2.5.25: 2,5,11-Trimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3b)

Following procedure described in section 2.5.24 using **5b** to give **3b** in 75 % (0.030 g) yield Off-white solid, m.p. decomp. > 316 ^{o}C.



3b

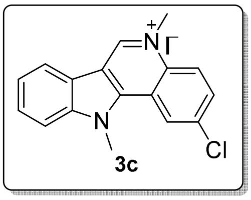
IR (KBr): $\tilde{\nu}$ = 3051, 1938, 1820, 1633, 1602, 1504, 1369, 1253 cm^{-1}.
^{1}H NMR (400 MHz, DMSO-d6): δ 10.18 (s, 1H), 8.87 (s, 1H), 8.41 (t, *J* = 9.6, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 4.58 (s, 3H), 4.55 (s, 3H), 2.73 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 142.5 (CH), 141.9 (C), 138.5 (C), 134.9 (C), 133.7 (CH), 128.1 (CH), 124.0 (CH), 123.7 (CH), 121.0 (C), 120.4 (CH), 119.4 (CH), 117.2 (C), 113.6 (C), 112.0 (CH), 44.7 (CH_3), 34.3 (CH_3), 21.2 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{17}N_2$ $[M]^+$ 261.1392, found 261.1392.

2.6.26: 2-Chloro-5,11-dimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3c)

Following procedure described in section 2.5.24 using **5c** to give **3c** in 72 % (0.030 g) yield.



3c

Off-white solid, m.p. decomp. > 326 ^{o}C.

IR (KBr): $\tilde{\nu}$ = 3037, 1924, 1851, 1602, 1440, 1367, 1253, 1114, 759 cm^{-1}.

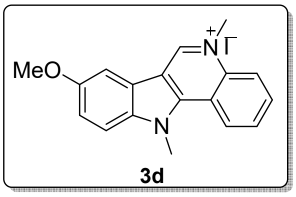
^{1}H NMR (400 MHz, DMSO-d6): δ 10.30 (s, 1H), 9.06 (d, *J* = 2.4 Hz, 1H), 8.57 (d, *J* = 9.6, 1H), 8.44 (d, *J* = 7.6 Hz, 1H), 8.29 (dt, *J* = 9.6 Hz, *J* = 2.0 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.82 (t, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 4.61 (s, 3H), 4.58 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 143.8 (CH), 141.9 (C), 141.2 (C), 135.2 (C), 132.9 (C), 132.1 (CH), 128.5 (CH), 124.1 (CH), 124.0 (CH), 121.9 (CH), 120.9 (C), 120.6 (CH), 118.1 (C), 114.3 (C), 112.2 (CH), 45.0 (CH_3), 34.1 (CH_3).

HRMS (ESI): calcd for $C_{17}H_{14}ClN_2$ $[M]^+$ 281.0846, found 281.0846.

2.5.27: 8-Methoxy-5,11-dimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3d)

Following procedure described in section 2.5.24 using **5d** to give **3d** in 70 % (0.028 g) yield.



3d

Off-white solid, m.p. decomp. > 314 °C.

IR (KBr): $\tilde{\nu}$ =3016, 2966, 1915, 1633, 1610, 1504, 1369, 1273, 829, 758 cm^{-1}.

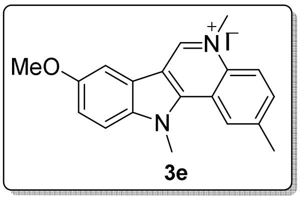
^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 9.09 (d, J = 8 Hz, 1H), 8.50 (d, J = 8.8, 1H), 8.18 (t, J = 8.0, 1H), 8.08-8.04 (m, 2H), 7.99 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 9.2 Hz, 1H), 4.54 (s, 6H), 3.94 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 156.4 (C), 143.5 (C), 141.8 (C), 136.5 (C), 131.9 (CH), 128.9 (CH), 128.1 (CH), 125.1 (CH), 122.0 (C), 119.6 (CH), 117.3 (CH), 117.2 (C), 113.5 (C), 113.1 (CH), 102.7 (CH), 55.8 (CH_3), 44.7 (CH_3), 34.4 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{17}ON_2$ $[M]^+$ 277.1341, found 277.1341

2.5.28: 8-Methoxy-2,5,11-trimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3e)

Following procedure described in section 2.5.24 using **5e** to give **3e** in 72 % (0.030 g) yield. Off-white solid, m.p. decomp. > 326 °C.



3e

IR (KBr): $\tilde{\nu}$ = 2987, 1890, 1637, 1504, 1489, 1367, 1269, 1224, 812 cm^{-1}.

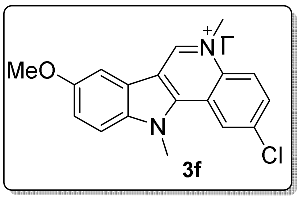
^{1}H NMR (400 MHz, DMSO-d6): δ 10.14(s, 1H), 8.81 (s, 1H), 8.39 (d, J = 9.2, 1H), 8.05-8.01 (m, 2H), 7.95 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 4.53 (s, 3H), 4.51 (s, 3H), 3.93 (s, 3H), 2.71 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 156.3 (C), 142.6 (CH), 141.4 (C), 138.4 (C), 136.4 (C), 134.7 (C), 133.4 (CH), 123.8 (CH), 121.9 (C), 119.4 (CH), 117.3 (C), 117.2 (CH), 113.4 (C), 113.0 (CH), 102.6 (CH), 55.7 (CH_3), 44.6 (CH_3), 34.3 (CH_3), 21.1 (CH_3).

HRMS (ESI): calcd for $C_{19}H_{19}ON_2$ $[M]^+$ 291.1497, found 291.1497.

2.5.29: 2-Chloro-8-methoxy-5,11-dimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3f)

Following procedure described in section 2.5.24 using **5f** to give **3f** in 69 % (0.030 g) yield. Off-white solid, m.p. decomp. > 338 °C.



3f

IR (KBr): $\tilde{\nu}$ = 2983, 1901, 1635, 1504, 1444, 1363, 1253, 1060, 817 cm^{-1}.

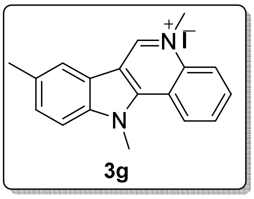
^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (s, 1H), 8.96 (s, 1H), 8.57 (d, *J* = 9.6, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 4.53 (s, 6H), 3.92 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 156.5 (C), 143.7 (CH), 140.6 (C), 136.5 (C), 135.0 (C), 132.7 (C), 131.8 (CH), 123.8 (CH), 121.8 (CH), 121.7 (C), 118.1 (C), 117.7 (CH), 114.0 (C), 113.2 (CH), 102.7 (CH), 55.8 (CH$_3$), 44.9 (CH$_3$), 34.2 (CH$_3$).

HRMS (ESI): calcd for $C_{18}H_{16}OClN_2$ [M]$^+$ 311.0951, found 311.0951.

2.5.30: 5,8,11-Trimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3g)

Following procedure described in section 2.5.24 using **5g** to give **3g** in 71 % (0.028 g) yield



3g

Off-white solid, m.p. decomp. > 320 °C.

IR (KBr): $\tilde{\nu}$ = 3037, 2918, 1905, 1836, 1608, 1504, 1448, 1361, 1253, 1112, 752 cm^{-1}.

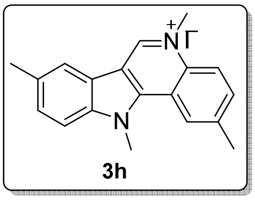
^{1}H NMR (400 MHz, DMSO-d6): δ 10.21 (s, 1H), 9.12 (d, *J* = 8.4 Hz, 1H), 8.51 (d, *J* = 8.8, 1H), 8.23-8.19 (m, 2H), 8.09-8.03 (m, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 4.5 (d *J* = 4.4 Hz, 6H), 2.58 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 143.2 (CH), 142.0 (C), 140.2 (C), 136.5 (C), 133.2 (C), 132.0 (CH), 129.5 (CH), 128.1 (CH), 125.2 (CH), 121.2 (C), 120.0 (CH), 119.6 (CH), 117.1 (C), 113.4 (C), 111.8 (CH), 44.7 (CH$_3$), 34.3 (CH$_3$), 21.1 (CH$_3$).

HRMS (ESI): calcd for $C_{18}H_{17}N_2$ [M]$^+$ 261.1392, found 261.1392.

2.5.31: 2,5,8,11-Tetramethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3h)

Following procedure described in section 2.5.24 using **5h** to give **3h** in 72 % (0.029 g) yield.



3h

Off-white solid, m.p. decomp. > 318 °C.

IR (KBr): $\tilde{\nu}$ = 2926, 2854, 1897, 1726, 1610, 1442, 1357, 1257, 1118, 804 cm^{-1}.

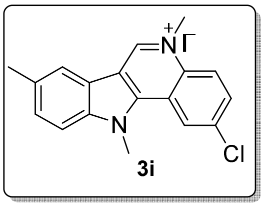
^{1}H NMR (400 MHz, DMSO-d6): δ 10.13 (s, 1H), 8.84 (s, 1H), 8.40 (d, *J* = 9.2, 1H), 8.17 (s, 1H), 8.03 (t, *J* = 8.4 Hz, 2H), 7.60 (dd, *J* = 8.8 Hz, *J* = 1.2 Hz, 1H), 4.54 (d, *J* = 4.0 Hz, 6H), 2.72 (s, 3H), 2.57 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 142.4 (CH), 141.6 (C), 140.2 (C), 138.4 (C), 134.8 (C), 133.6 (CH), 133.1 (C), 129.4 (CH), 123.9 (CH), 121.2 (C), 120.0 (CH), 119.4 (CH), 117.2 (C), 113.4 (C), 111.7 (CH), 44.6 (CH$_3$), 34.3 (CH$_3$), 21.1 (CH$_3$), 21.1 (CH$_3$).

HRMS (ESI): calcd for $C_{19}H_{19}N_2$ $[M]^+$ 275.1548, found 275.1548

2.5.32: 2-Chloro-5,8,11-trimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3i)

Following procedure described in section 2.5.24 using **5i** to give **3i** in 68 % (0.029 g) yield. Off-white solid, m.p. decomp. > 336 °C.



3i

IR (KBr): $\tilde{\nu}$ =3026, 2983, 1892, 1633, 1610, 1504, 1357, 1255, 1128, 819 cm^{-1}.

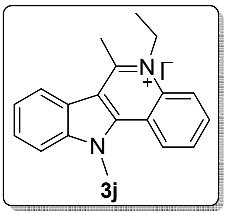
^{1}H NMR (400 MHz, DMSO-d6): δ 10.24 (s, 1H), 9.02 (d, J = 2.4 Hz, 1H), 8.54 (d, J = 9.2 Hz, 1H), 8.26 (dd, J = 9.2 Hz, J = 2.4 Hz, 1H), 8.21(s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.64 (dd, J = 9.2 Hz, J = 1.2 Hz, 1H), 4.57 (d, J = 4.0 Hz, 6H), 2.59 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 143.3 (CH), 140.8 (C), 140.2 (C), 135.0 (C), 133.5 (C), 132.7 (C), 131.9 (CH), 129.8 (CH), 123.8 (CH), 121.7 (CH), 120.9 (C), 120.1 (CH), 117.9 (C), 113.9 (C), 111.9 (CH), 44.8 (CH_3), 34.0 (CH_3), 21.0 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{16}ClN_2$ $[M]^+$ 295.1002, found 295.1002.

2.5.33: 5-Ethyl-6,11-dimethyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (3j)

Following procedure described in section 2.5.24 using **5j** to give **3j** in 58 % (0.023 g) yield.



3j

Pale yellow solid, m.p. decomp. > 306 °C.

IR (KBr): $\tilde{\nu}$ =3 053, 2970, 2929, 1909, 1589, 1321, 1240, 752 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 9.13 (d, J = 8.0 Hz, 1H), 8.63 (d, J = 8.8 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.21-8.14 (m, 2H), 8.03 (t, J = 8.0 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 5.04 (q, J = 7.6 Hz, 2H), 4.55 (s, 3H), 3.51 (s, 3H), 1.60 (t, J = 7.6 Hz, 2H).

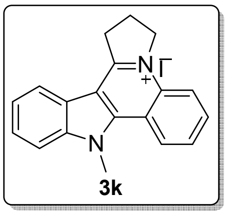
^{13}C NMR (100 MHz, DMSO-d6): δ 154.5 (C), 141.7 (C), 141.5 (C), 136.3 (C), 132.3 (CH), 127.6 (CH), 127.4 (CH), 125.4 (CH), 123.8 (CH), 122.5 (CH), 121.3 (C), 119.4 (C), 116.6 (C), 113.6 (C), 111.9 (CH), 45.5 (CH_2), 34.4 (CH_3), 19.3 (CH_3), 13.7 (CH_3).

HRMS (ESI): calcd for $C_{19}H_{19}N_2$ $[M]^+$ 275.1548, found 275.1549.

2.5.34: 9-Methyl-1,2,3,9-tetrahydroindolo[3,2-*c*]pyrrolo[1,2-*a*]quinolin-4-ium iodide (3k)

Following procedure described in section 2.5.24 using **5k** to give **3k** in 62 % (0.025 g) yield Pale yellow solid, m.p. decomp. > 310 °C.

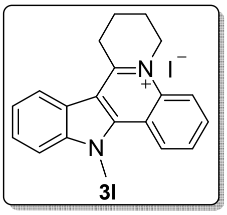
IR (KBr): $\tilde{\nu}$ = 2924, 1953, 1625, 1598, 1504, 1384, 1249, 1166 cm^{-1}.



^{1}H NMR (400 MHz, DMSO-d6): *δ* 9.12 (d, *J* = 8.0 Hz, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.19-8.14 (m, 2H), 8.03 (t, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 5.05 (t, *J* = 3.6 Hz, 2H), 4.58 (s, 3H), 4.16 (t, *J* = 4.0 Hz, 2H), 2.71-2.67 (m, 2H). **^{13}C NMR (100 MHz, DMSO-d6)**: *δ* 156.4 (C), 141.9 (CH), 141.8 (C), 134.7 (C), 131.9 (CH), 127.7 (CH), 125.0 (C), 123.7 (2X CH), 121.4 (CH), 120.9 (C), 119.8 (CH), 116.4 (C), 111.9 (CH), 110.3 (C), 54.7 (CH_2), 34.2 (CH_3), 32.7 (CH_2), 20.0 (CH_2). **HRMS (ESI)**: calcd for $C_{19}H_{17}N_2$ $[M]^+$ 273.1392, found 273.1392.

2.5.35: 10-Methyl-2,3,4,10-tetrahydro-1*H*-indolo[3,2-*c*]pyrido[1,2-*a*]quinolin-5-ium (3l)

Following procedure described in section 2.5.24 using **5l** to give **3l** in 60 % (0.025 g) yield.



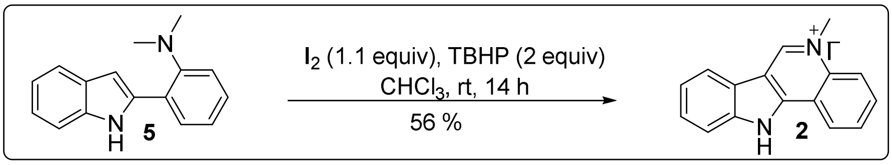
Pale yellow solid, m.p. decomp. > 314 °C.

IR (KBr): $\tilde{\nu}$ = 2956, 2927, 1589, 1446, 1321, 1240, 1166, 752 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): *δ* 9.11 (d, *J* = 8.4 Hz, 1H), 8.60 (d, *J* = 9.2 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 8.20-8.14 (m, 2H), 8.04 (t, *J* = 7.6 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 4.83 (t, *J* = 6.0 Hz, 2H), 4.55 (s, 3H), 3.99 (t, *J* = 6.0 Hz, 2H), 2.29-2.28 (m, 2H), 2.17-2.13 (m, 2H). **^{13}C NMR (100 MHz, DMSO-d6)**: *δ* 155.9 (C), 141.6 (C), 140.7 (C), 137.6 (C), 131.8 (CH), 127.8 (CH), 127.4 (CH), 125.0 (CH), 123.7 (CH), 122.9 (CH), 121.1 (C), 118.9 (CH), 116.4 (C), 112.8 (C), 111.8 (CH), 50.4 (CH_2), 34.4 (CH_3), 29.9 (CH_2), 21.4 (CH_2), 16.9 (CH_2). **HRMS (ESI)**: calcd for $C_{20}H_{19}N_2$ $[M]^+$ 287.1541, found 287.1541.

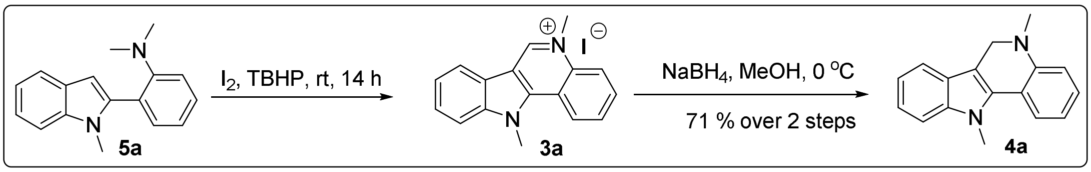
2.5.36: 5-Methyl-11*H*-indolo[3,2-*c*]quinolin-5-ium iodide (2) [10p]

Following procedure described in section 2.5.24 using **5** to give **2** in 56 % (0.020 g) yield



Off-white solid, m.p. 296-298 °C (lit. [10p] m.p. 298-299 °C).

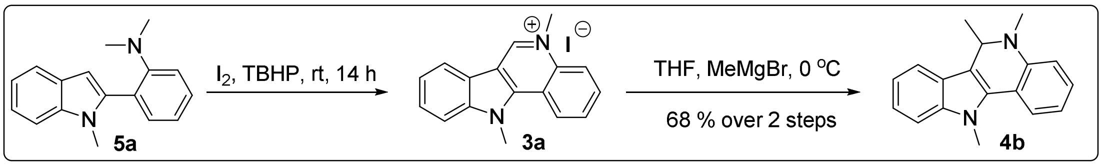
2.5.37: 5,11-Dimethyl-6,11-dihydro-5*H*-indolo[3,2-*c*]quinoline (4a)



Following the similar procedure described in section 2.5.24 but instead of filtering the solvent was decanted. This was followed for three times and the solid compound obtained was suspended in methanol (5 mL) and cooled to 0 °C and $NaBH_4$ (0.002 g, 0.05 mmol) was added and stirred at room temperature for 2 h. Then methanol was removed under reduced pressure and 5 mL water was added and extracted with $CHCl_3$ (3 x 5 mL). The organic layer was combined and dried over anhydrous Na_2SO_4 and concentrated to give pure 5,11-Dimethyl-6,11-dihydro-5*H*-indolo[3,2-*c*]quinoline **4a** in 71 % (0.018 g) yield.
Yellow thick oil.

IR (KBr): $\tilde{\nu}$ = 2924, 1936, 1570, 1388, 1380, 1232, 1093, 765 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.16-7.09 (m, 2H), 7.04 (t, J = 7.2 Hz, 1H), 6.76-6.67 (m, 2H), 4.49 (s, 2H), 3.92 (s, 3H), 2.89 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6 (C), 138.3 (C), 131.2 (C), 127.1 (CH), 123.4 (CH), 121.4 (CH), 120.8 (CH), 118.5 (CH), 117.0 (CH), 116.9 (C), 116.5 (CH), 111.2 (C), 108.2 (CH), 108.0 (C), 48.9 (CH_2), 37.9 (CH_3), 31.6 (CH_3).
HRMS (ESI): calcd for $C_{17}H_{16}N_2H$ $[M+H]^+$ 249.1380, found 249.1380.

2.5.38: 5,6,11-Trimethyl-6,11-dihydro-5*H*-indolo[3,2-*c*]quinoline (4b)

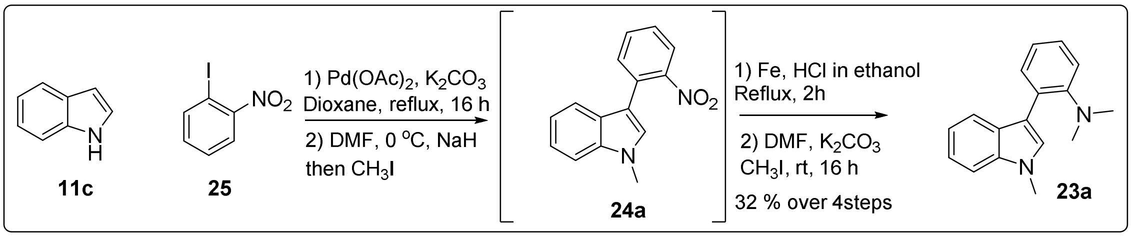


Following the similar procedure described in section 2.5.37 but instead of methanol and $NaBH_4$, 5 mL of THF and methyl magnesium bromide (0.04 mL of 3M solution, 0.11 mmol) was added to give 5,6,11-Trimethyl-6,11-dihydro-5*H*-indolo[3,2-*c*]quinoline in 68 % (0.018 g) yield.
Yellow thick oil.

IR (KBr): $\tilde{\nu}$ = 3051, 2958, 2922, 1926, 1479, 1355, 1273, 1209, 732 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.38 (td, J = 8.0 Hz, 1.2 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.15-7.08 (m, 2H), 7.03 (dt, J = 8.0 Hz, 0.8 Hz, 1H), 6.72 (dt, J = 7.2 Hz, 0.8 Hz, 1H), 6.59 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 4.86 (q, J = 6.4 Hz, 1H), 3.91 (s, 3H), 2.95 (s, 3H), 1.16 (d, J = 6.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6 (C), 138.3 (C), 129.9 (C), 127.1 (CH), 122.9 (C), 121.2(CH), 120.8 (CH), 118.5 (CH), 116.6 (CH), 116.3 (C), 115.8 (CH), 113.3 (C), 111.8 (CH), 108.2 (CH), 54.5 (CH_3), 36.2 (CH_3), 31.6 (CH_3), 16.3 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{18}N_2H$ $[M+H]^+$ 263.1538, found 263.1538.

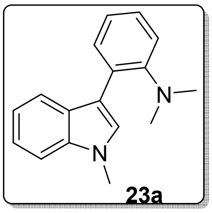
2.5.39: *N,N*-dimethyl-2-(1-methyl-1*H*-indol-3-yl)aniline (23a)



11c
25
1) Pd(OAc)2, K2CO3 Dioxane, reflux, 16 h
2) DMF, 0 °C, NaH then CH3I
24a
1) Fe, HCl in ethanol Reflux, 2h
2) DMF, K2CO3 CH3I, rt, 16 h
32 % over 4steps
23a

Indole **11c** (234 mg, 2 mmol) and *o*-iodonitrobenzene **25** (598 mg, 2.4 mmol) were dissolved in dioxane (10 mL) and degassed with nitrogen. K_2CO_3 (414 mg, 3 mmol) and $Pd(OAc)_2$ (48 mg 0.2 mmol) were added and the reaction mixture was heated at 110 °C for 16 h. After cooling to room temperature, it was filtered through celite, washed with water (20 mL) and ethyl acetate (20 mL). The organic layer was then separated and the aqueous layer was further extracted with ethyl acetate (2 X 20 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (90:10 petroleum ether: ethyl acetate) to obtain 217 mg of the arylated product. This was directly dissolved in anhydrous DMF (5 mL) and cooled to 0 °C and 60% NaH (51.6 mg, 1.3 mmol) was added in one portion and stirred at that temperature for 0.5 h. Methyl iodide (169 mg, 1.2 mmol) was added and stirred at room temperature for 3 h. Reaction mixture is then diluted with water and extracted with ethyl acetate (3 X 10mL). The combined organic layer was dried over anhydrous $Na_2SO_4$and concentrated under reduced pressure to give the crude product **24a**.

The crude compound **24a** was then dissolved in acidic ethanol (1:6 HCl/ethanol, 15 mL) and to this solution Fe powder (335 mg, 6 mmol) was added and heated at 80 °C for 2 h in a nitrogen atmosphere, poured on ice water and the pH was made basic (pH 10) by addition of aqueous K_2CO_3 and filtered through a bed of celite and washed with water (20 mL) and ethyl acetate (20 mL). The organic layer was then separated and the aqueous layer was further extracted with ethyl acetate (2 X 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then treated with DMF (5 mL), K_2CO_3 (276 mg, 2 mmol), CH_3I (282 mg, 2 mmol) and stirred at rt for 16 h. The reaction was then diluted with water (10 mL) and extracted with ethyl acetate (10 mL). The organic layer was then separated and the aqueous layer was further extracted with ethyl acetate (2 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (95:5 petroleum ether: ethyl acetate) to obtain desired trimethylated **23a** in 32 % (0.161 g) yield over 4 steps.

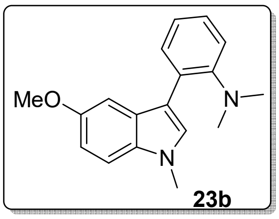


23a

White crystalline solid, m.p. 84-86 ^{o}C.

2.5.40: 2-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-*N*,*N*-dimethylaniline (23b)

Following procedure described in section 2.5.39 using 5-methoxy indole **11a** (0.293 g, 2 mmol) to give **23b** in 26 % (0.146 g) yield over 4 steps.



23b

White crystalline solid, m.p.116-118 ^{o}C.

IR (KBr): $\tilde{\nu}$ = 2940, 2825, 1870, 1850, 1491, 1211, 1139, 835 cm^{-1}.

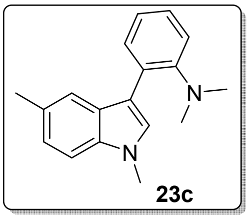
^{1}H NMR (400 MHz, MeOD):δ 7.32 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.21-7.16 (m, 1H), 7.10-7.07 (m, 2H), 6.95 (dt, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 6.83 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.53 (s, 6H).

^{13}C NMR (100 MHz, MeOD): δ 155.2 (C), 153.0 (C), 134.1 (C), 132.6 (CH), 130.1 (C), 129.1 (CH), 128.3 (C), 127.9 (CH), 122.5 (CH), 118.9 (CH), 116.7 (C), 112.7 (CH), 110.8 (CH), 103.8 (CH), 56.2 (CH_3), 43.4 (CH_3), 33.0 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{20}N_2OH$ [M +H]$^{+}$ 281.1648, found 281.1648.

2.5.41: 2-(1,5-Dimethyl-1H-indol-3-yl)-*N*,*N*-dimethylaniline (23c)

Following procedure described in section 2.5.39 using5-methyl indole **11b** (0.262 g, 2 mmol) to give **23c** in 28 % (0.149 g) yield over 4 steps.



23c

White crystalline solid, m.p. 82-84 ^{o}C.

IR (KBr): $\tilde{\nu}$ = 2943, 2829, 2777, 1546, 1487, 1325, 1161, 758 cm^{-1}.

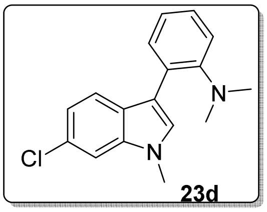
^{1}H NMR (400 MHz, MeOD): δ 7.35-7.32 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.18 (dt, *J* = 8.0, *J* = 1.2 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.02-6.95 (m, 2H), 3.81 (s, 3H), 2.53 (s, 6H), 2.39 (s, 3H).

^{13}C-NMR (100 MHz, MeOD): δ 153.2 (C), 137.1 (C), 132.7 (CH), 130.1 (C), 129.2 (C), 128.7 (CH), 128.4 (C), 127.9 (CH), 124.0 (CH), 122.7 (CH), 121.2 (CH), 118.9 (CH), 116.2 (C), 109.9 (CH), 43.6 (2 X CH_3), 32.8 (CH_3), 21.7 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{20}N_2H$ [M +H]$^{+}$ 265.1698, found 265.1698.

2.5.42: 2-(6-Chloro-1-methyl-1*H*-indol-3-yl)-*N*,*N*-dimethylaniline (23d)

Following procedure described in section 2.5.39 using 5-methyl indole **11d** (0.303 g, 2 mmol) to give **23d** in 36 % (0.204 g) yield over 4 steps.



23d

White crystalline solid, m.p. 108-110 °C.

IR (KBr): $\tilde{\nu}$ = 3059, 2933, 2785, 1543, 1487, 1327, 1217, 754 cm^{-1}.

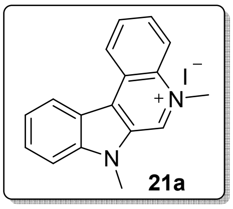
^{1}H NMR (400 MHz, MeOD): δ 7.42 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 1.6 Hz, 1H), 7.21 (s, 1H), 7.19 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.10 (dt, *J* = 7.2 Hz, *J* = 1.6 Hz, 1H), 6.98 (dd, *J* = 8.4 Hz, *J* = 1.2 Hz, 1H), 6.90-6.83 (m, 2H), 3.70 (s, 3H), 2.40 (s, 6H).

^{13}C NMR (100 MHz, MeOD): δ 153.1 (C), 139.0 (C), 132.7 (CH), 129.4 (CH), 129.3 (C), 128.4 (C), 128.3 (CH), 126.6 (C), 123.0 (CH), 122.6 (CH), 120.5 (CH), 119.0 (CH), 117.4 (C), 110.2 (CH), 43.4 (2 X CH_3), 33.0 (CH_3).

HRMS (ESI): calcd for $C_{17}H_{17}ClN_2H$ $[M+H]^+$ 285.1149, found 285.1149.

2.5.43: 5,7-Dimethyl-7*H*-indolo[2,3-*c*]quinolin-5-ium iodide (21a) [14a]

Following procedure described in section 2.5.24 using *N*,*N*-dimethyl-2-(1-methyl-1*H*-indol-3-yl)aniline **23a** (0.025 g, 0.1 mmol) to give **21a** in 53 % (0.019 g) yield.

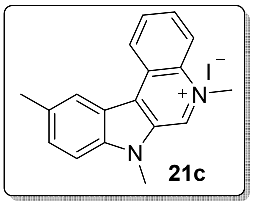


21a

Pale yellow solid, m.p. decomp. > 320 °C.

2.5.44: 5,7,10-Trimethyl-7*H*-indolo[2,3-*c*]quinolin-5-ium (21c)

Following procedure described in section 2.5.24 using 2-(1,5-dimethyl-1*H*-indol-3-yl)-*N*,*N*-dimethylaniline **23c** (0.027 g, 0.1 mmol) to give **21c** in 52 % (0.020 g) yield.



21c

Pale yellow solid, m.p. decomp. > 306 °C.

IR (KBr): $\tilde{\nu}$ = 3039, 2941, 1631, 1544, 1498, 1313, 1236, 759 cm^{-1}.

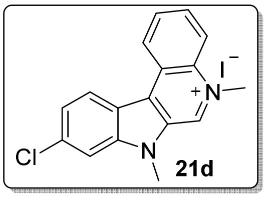
^{1}H NMR (400 MHz, DMSO-d6): δ 10.13 (s, 1H), 9.16 (d, *J* = 7.6 Hz, 1H), 8.72 (s, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.11-8.10 (m, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 4.73 (s, 3H), 4.19 (s, 3H), 2.64 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 142.4 (C), 136.8 (CH), 133.1 (CH), 132.7 (C), 132.1 (C), 130.8 (C), 129.7 (2 X CH), 125.1 (CH), 124.7 (C), 123.5 (C), 123.4 (CH), 119.5 (CH), 111.5 (CH), 45.5 (CH_3), 30.3 (CH_3), 21.0 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{17}N_2$ $[M]^+$ 261.1392, found 261.1392.

2.5.45: 9-Chloro-5,7-dimethyl-7*H*-indolo[2,3-*c*]quinolin-5-ium (21d)

Following procedure described in section 2.5.24 using 2-(6-chloro-1-methyl-1*H*-indol-3-yl)-*N*,*N*-dimethylaniline **23d** (0.029 g, 0.1 mmol) to give **21d** in 48 % (0.020 g) yield.



21d

Pale yellow solid, m.p, decomp. > 318 °C.

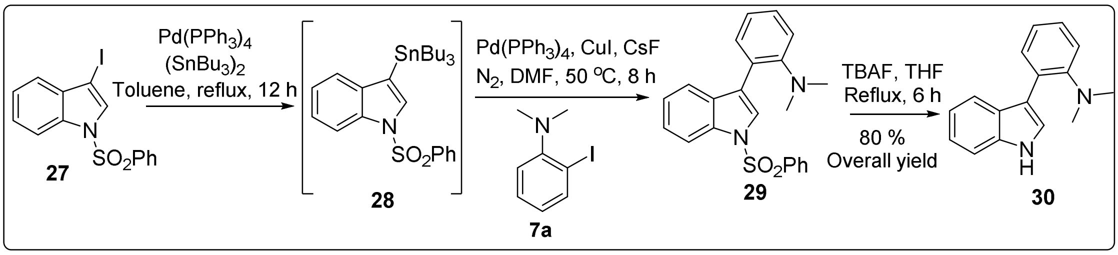
IR (KBr): $\tilde{\nu}$ = 3061, 2933, 1625, 1544, 1492, 1338, 1134, 750 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 10.18 (s, 1H), 9.12-9.10 (m,1H), 8.91 (d, J = 8.8 Hz, 1H), 8.56-8.53 (m, 1H), 8.20 (s, 1H), 8.13-8.10 (m, 2H), 7.60 (d, J = 8.8 Hz, 1H), 4.74 (s, 3H), 4.19 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 144.2 (C), 137.2 (CH), 136.1 (C), 133.0 (C), 131.5 (C), 130.3 (CH), 130.0 (CH), 125.9 (CH), 125.1 (C), 125.0 (CH), 123.3 (C), 123.0 (CH), 119.7 (CH), 118.1 (C), 111.8 (CH), 45.8 (CH_3), 30.5 (CH_3).

HRMS (ESI): calcd for $C_{17}H_{14}ClN_2$ $[M]^+$ 281.0846, found 281.0846.

2.5.46: 2-(1*H*-indol-3-yl)-*N*,*N*-dimethylaniline (30)



3-Iodo-1-(phenylsulfonyl)-1*H*-indole [14b] **27** (0.766 g, 2 mmol) and bis(tributyltin) (1.276 g, 2.2 mmol) was dissolved in toluene (15 mL) and degassed with nitrogen. To this $Pd(PPh_3)_4$ (0.231 g, 0.2 mmol) was added and the mixture was refluxed at 110 °C for 12 h. The crude mixture was purified by column purification and stannyl compound **28** obtained was subjected to Stille condition with 2-iodoaniline **7a** (0.247 g, 1 mmol) according to the procedure described in section 2.5.10, to give *N*,*N*-dimethyl-2-(1-(phenylsulfonyl)-1*H*-indol-3-yl)aniline **29** (0.336 g) which was directly subjected to desulphonation with TBAF (2 mL of 1M solution) in refluxing THF (5 mL) for 6 h. The reaction mixture was concentrated and 10 mL water was added, and extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine 10 mL and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material obtained was purified by column chromatography using 4:1 petroleum ether; ethyl acetate mixture to afford 2-(1*H*-indol-3-yl)-*N*,*N*-dimethylaniline **30**, 80 % (0.188 g) over two steps.

White solid**,** m.p. 58-60 °C.

IR (KBr): $\tilde{\nu}$ =3330, 3054, 1920, 1573, 1470, 1452, 1301, 1100, 937 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 8.12 (br s, 1H), 7.67 (td, *J* = 8 Hz, *J* = 0.4 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.38 (dd, *J* = 7.6Hz, *J* = 2.0 Hz, 1H), 7.32 (td, *J* = 8.0 Hz, *J* = 0.8 Hz, 1H), 7.20-7.12 (m, 2H), 7.07-7.00 (m, 2H), 6.94 (dt, *J* = 7.6Hz, *J* = 2.0Hz, 1H), 2.48 (s, 6H).

^{13}C NMR (100 MHz, DMSO-d6): δ 150.9 (C), 135.1 (C), 130.7 (CH), 127.0 (C), 126.1 (CH), 125.3 (C), 121.8 (CH), 120.9 (CH), 120.3 (CH), 119.8 (CH), 118.6 (CH), 116.7 (CH), 116.0 (C), 109.9 (CH), 42.0 (2 X CH_3).

HRMS (ESI): calcd for $C_{16}H_{16}N_2H$ $[M+H]^+$ 237.1392, found 237.1392.

2.6: References

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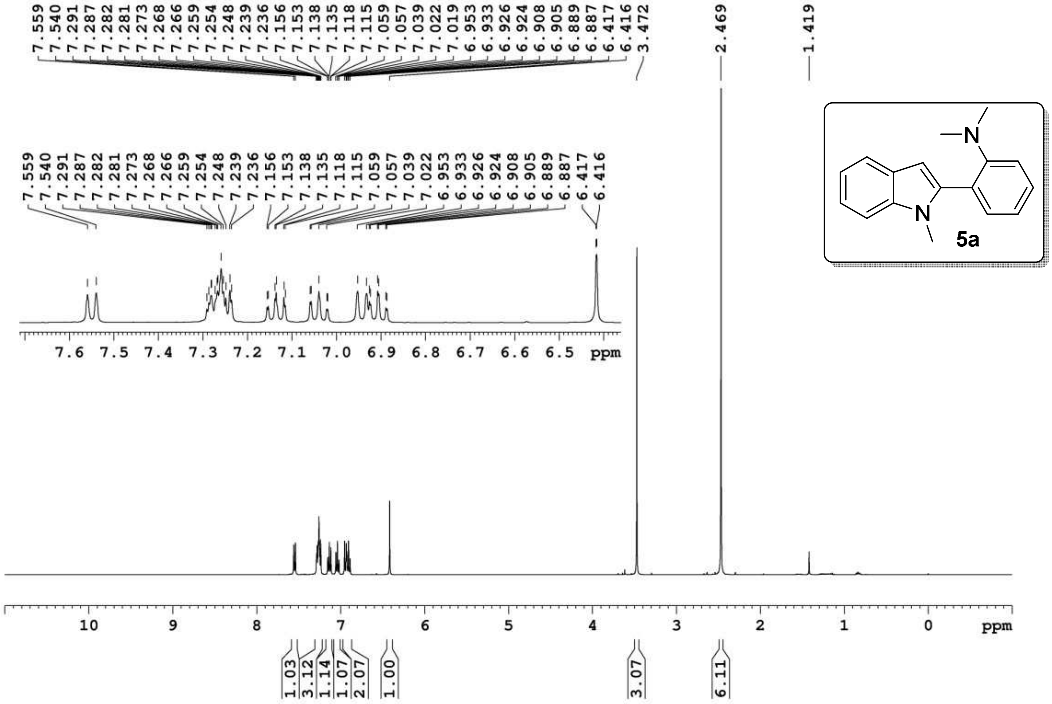
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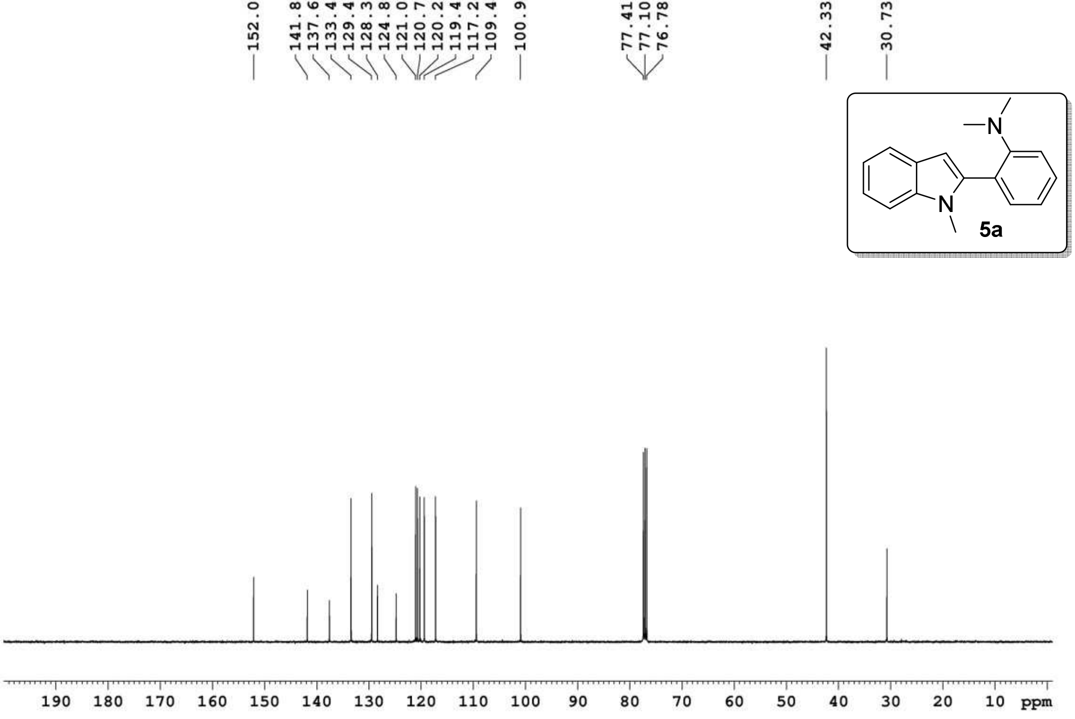
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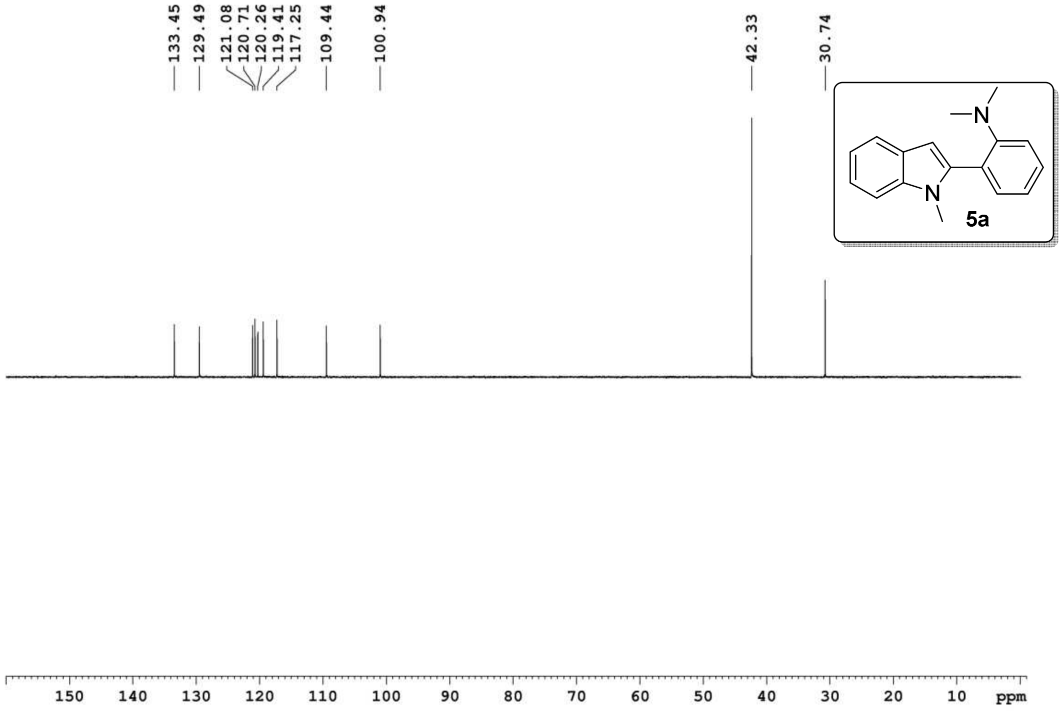

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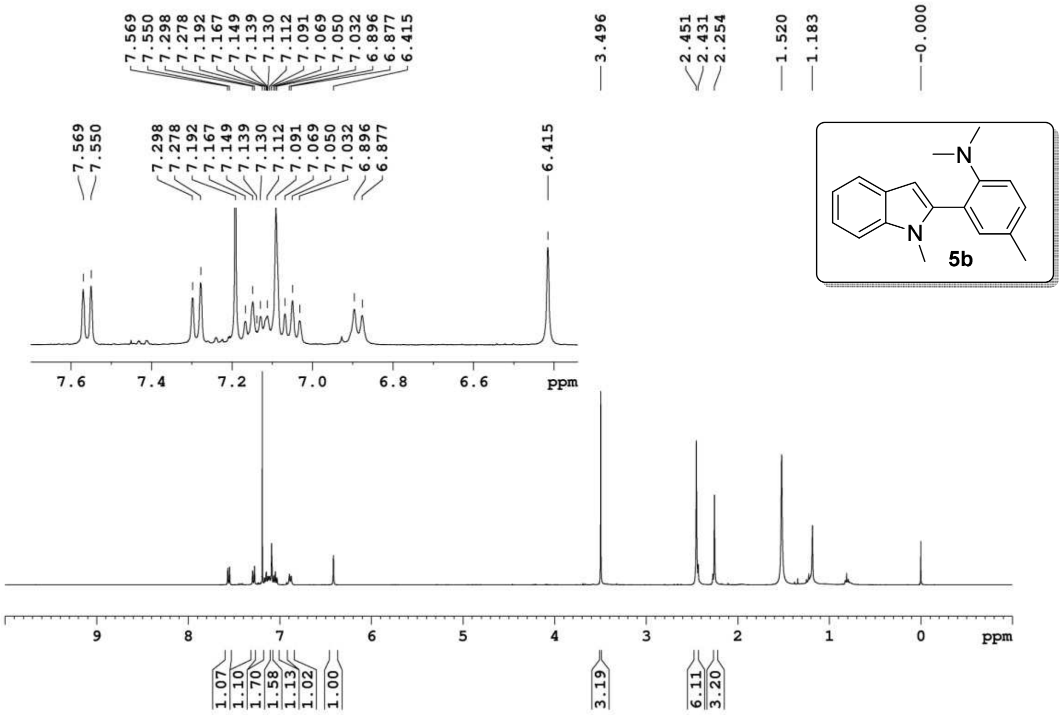

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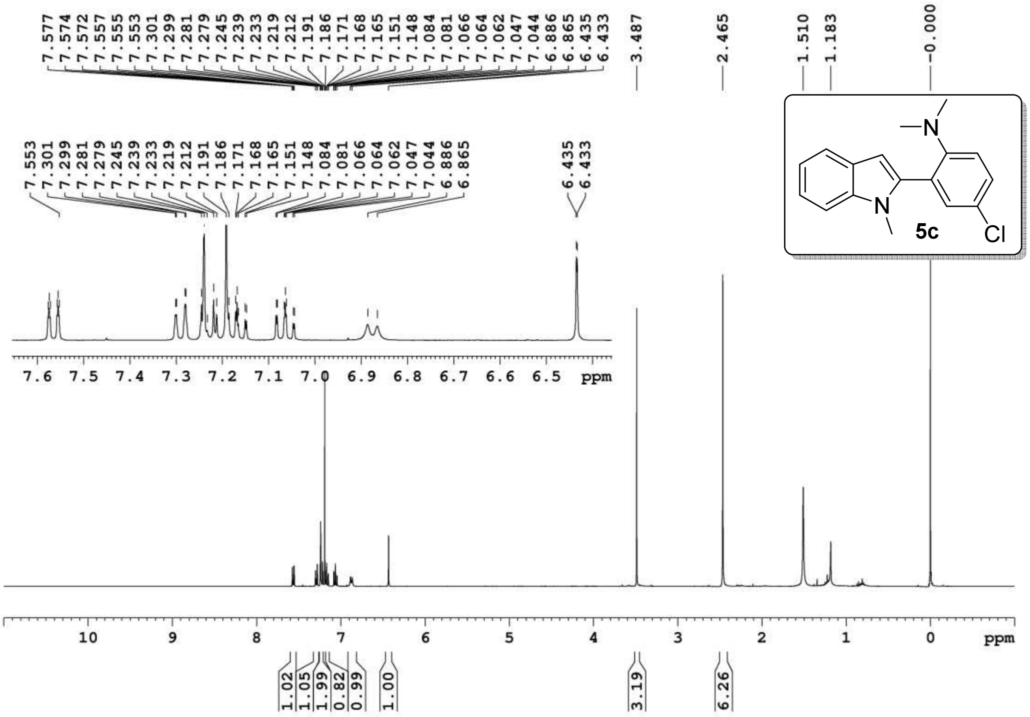
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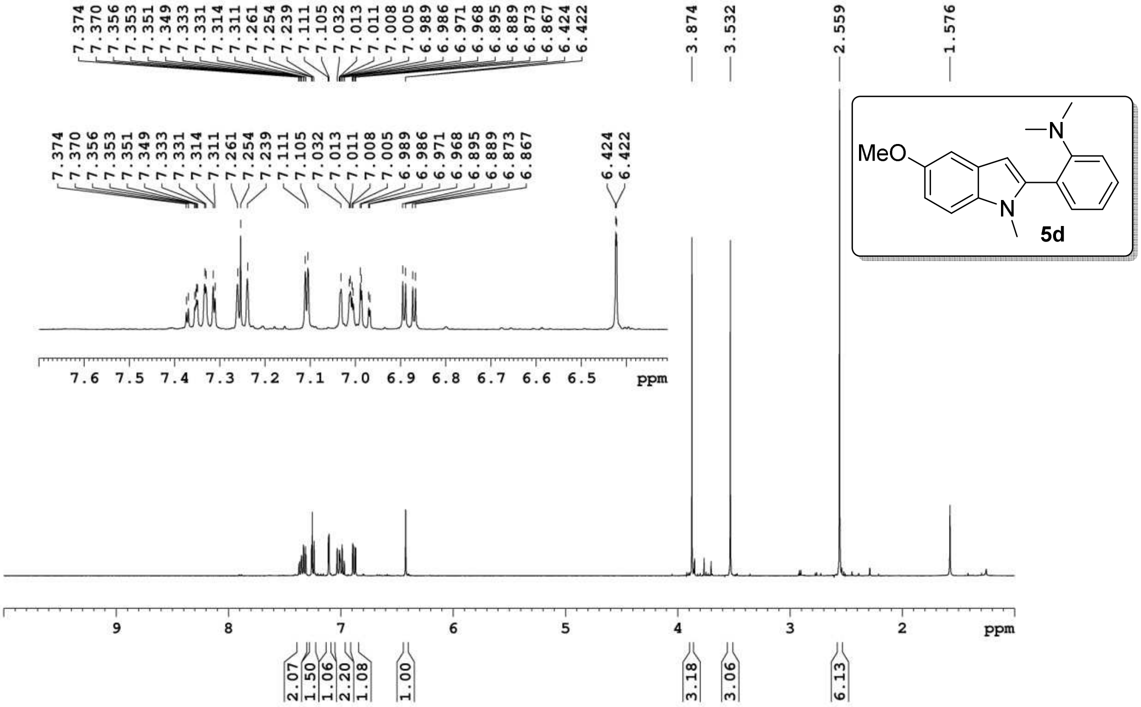
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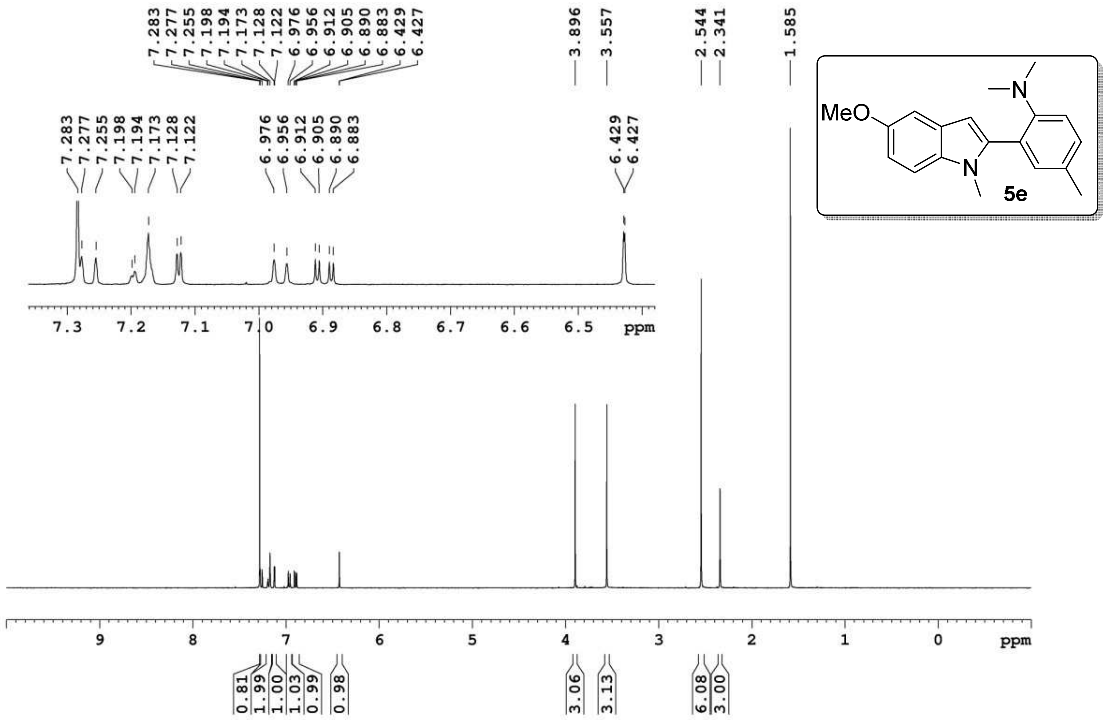
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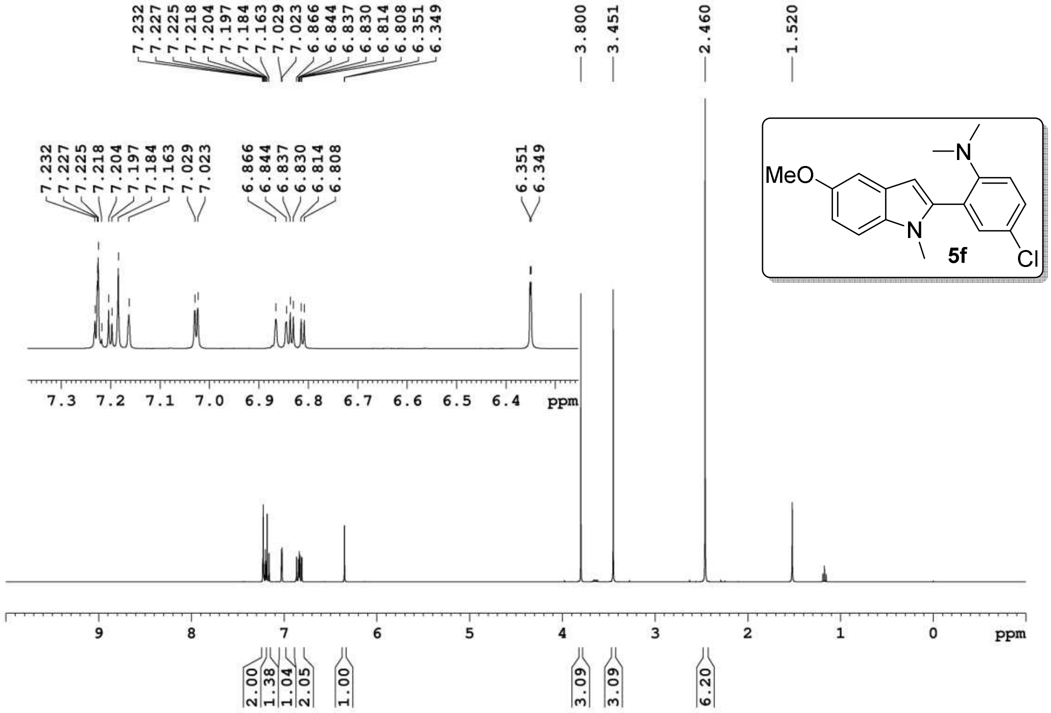
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7.023
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6.844
6.837
6.830
6.814
6.808
6.351
6.349
3.800
3.451
2.460
1.520
7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 ppm
9 8 7 6 5 4 3 2 1 0 ppm
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1.04
2.05
1.00
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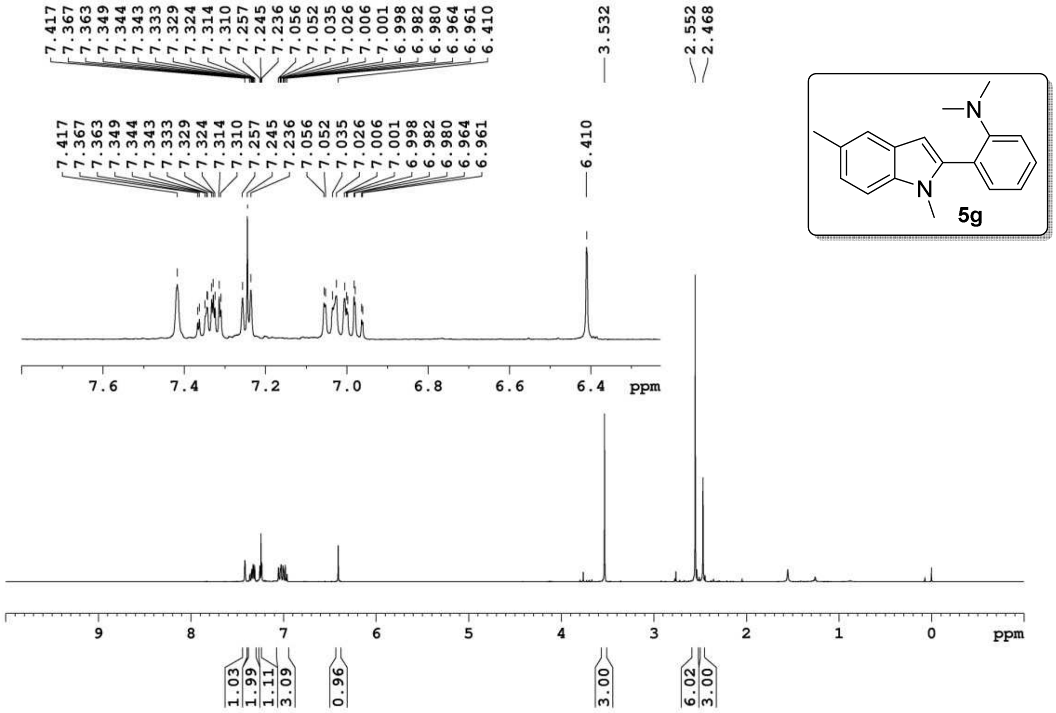
3.09
6.20
MeO
N
N
5f
Cl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7.245
7.236
7.056
7.052
7.035
7.026
7.006
7.001
6.998
6.982
6.980
6.964
6.961
6.410
3.532
2.552
2.468
N
7.6
7.4
7.2
7.0
6.8
6.6
6.4
ppm
9
8
7
6
5
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ppm
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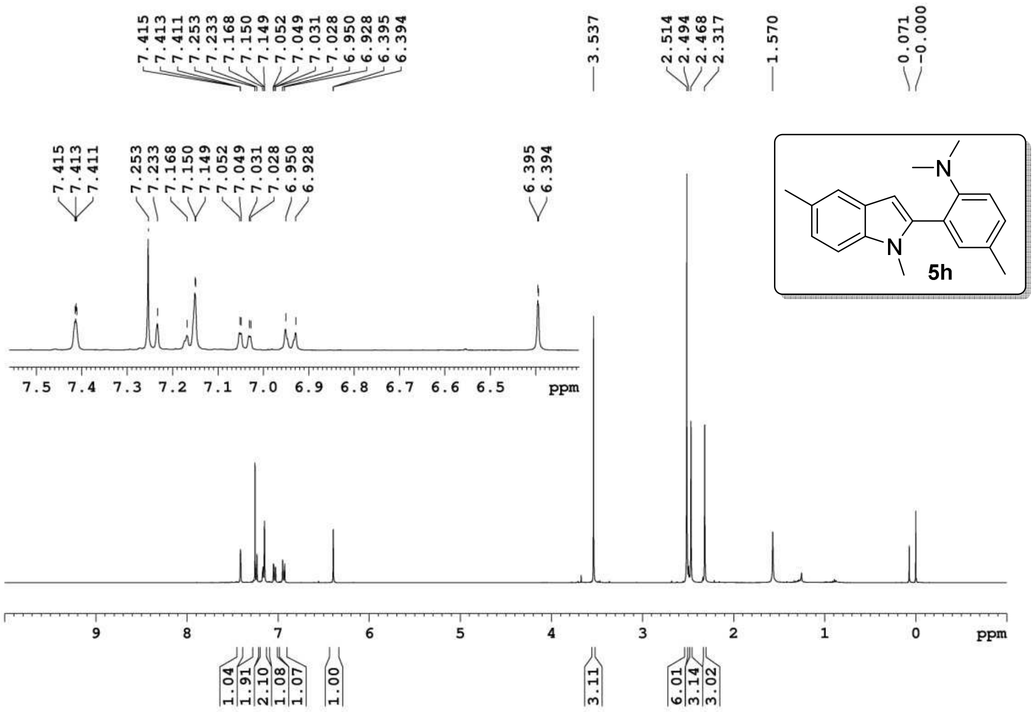
6.02
3.00

5g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7.149
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6.950
6.928
6.395
6.394
3.537
2.514
2.494
2.468
2.317
1.570
0.071
-0.000
N
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
ppm
9
8
7
6
5
4
3
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3.11
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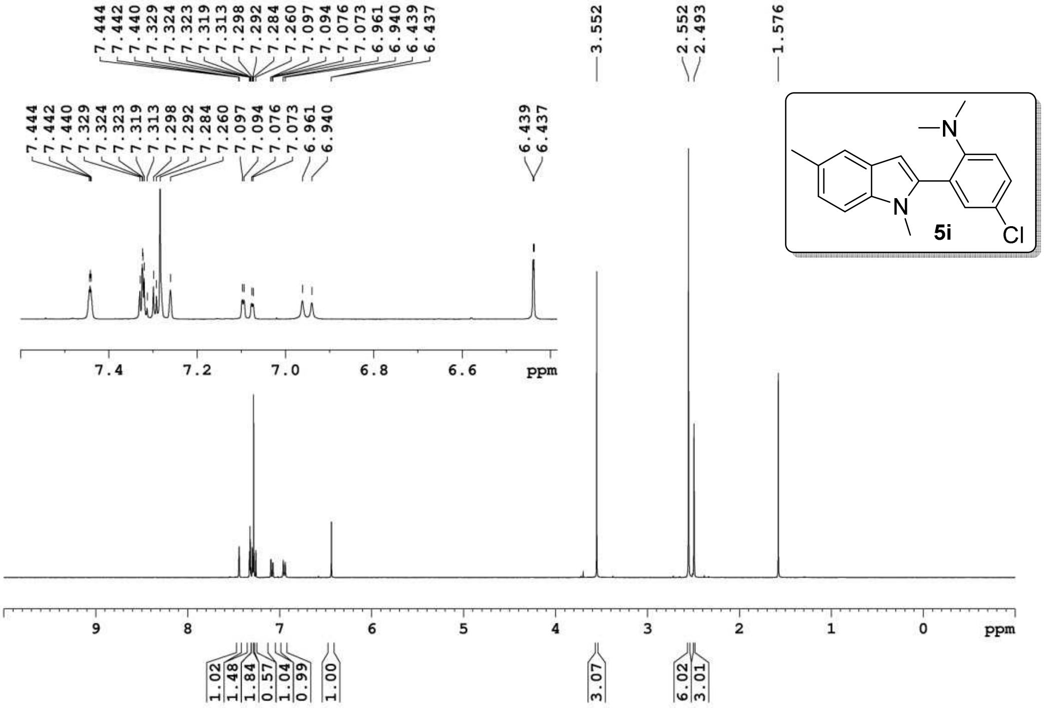
3.14
3.02

5h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7.313
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7.284
7.260
7.097
7.094
7.076
7.073
6.961
6.940
6.439
6.437
3.552
2.552
2.493
1.576
7.4
7.2
7.0
6.8
6.6
ppm
N
N
5i
Cl
9
8
7
6
5
4
3
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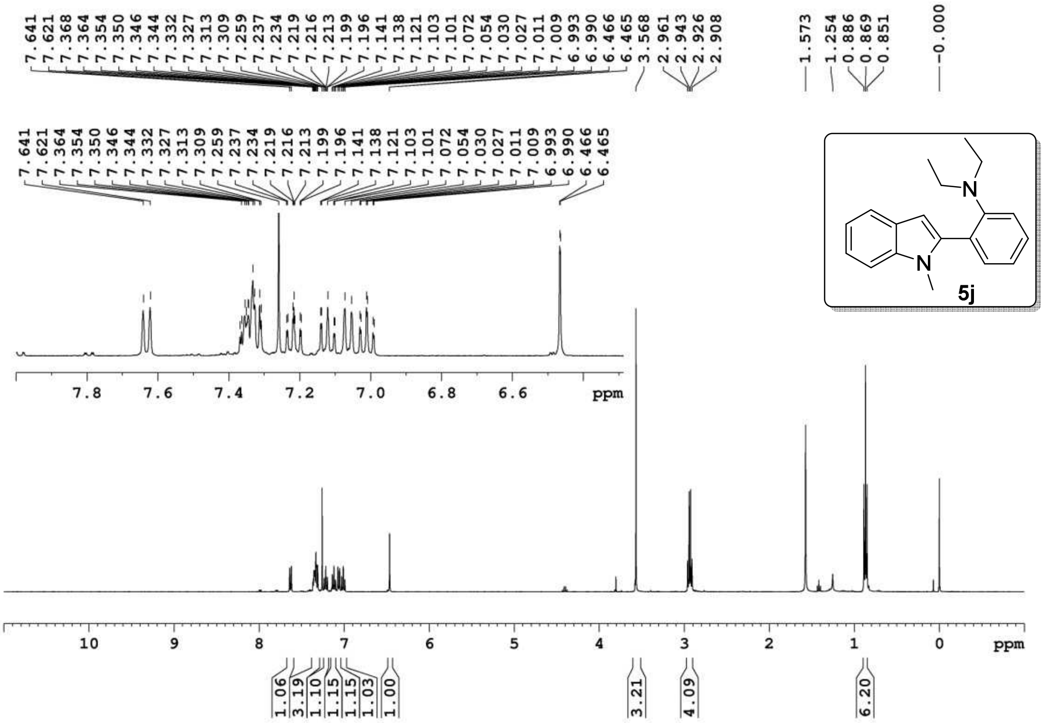
3.01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7.344
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7.309
7.259
7.237
7.234
7.219
7.216
7.213
7.199
7.196
7.141
7.138
7.121
7.103
7.101
7.072
7.054
7.030
7.027
7.011
7.009
6.993
6.990
6.466
6.465
3.568
2.961
2.943
2.926
2.908
1.573
1.254
0.886
0.869
0.851
-0.000
7.8
7.6
7.4
7.2
7.0
6.8
6.6
ppm
N
N
5j
10
9
8
7
6
5
4
3
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1.15
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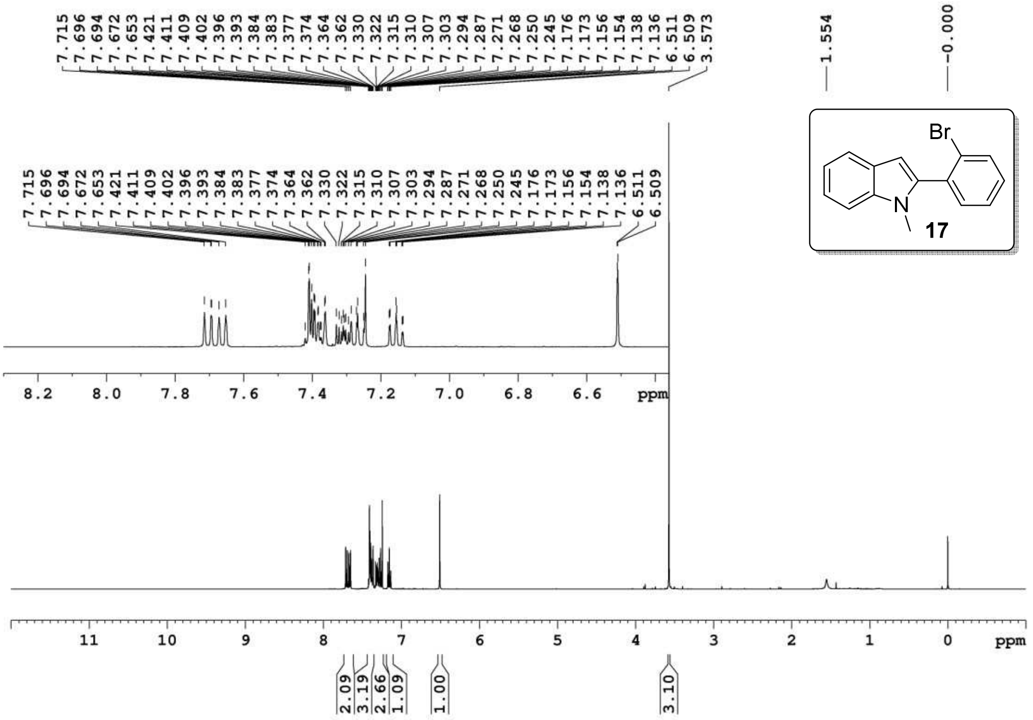
4.09
6.20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7.411
7.409
7.402
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7.393
7.384
7.383
7.377
7.374
7.364
7.362
7.330
7.322
7.315
7.310
7.307
7.303
7.294
7.287
7.271
7.268
7.250
7.245
7.176
7.173
7.156
7.154
7.138
7.136
6.511
6.509
3.573
1.554
-0.000
Br
N
17
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
ppm
11
10
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8
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5
4
3
2
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ppm
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3.19
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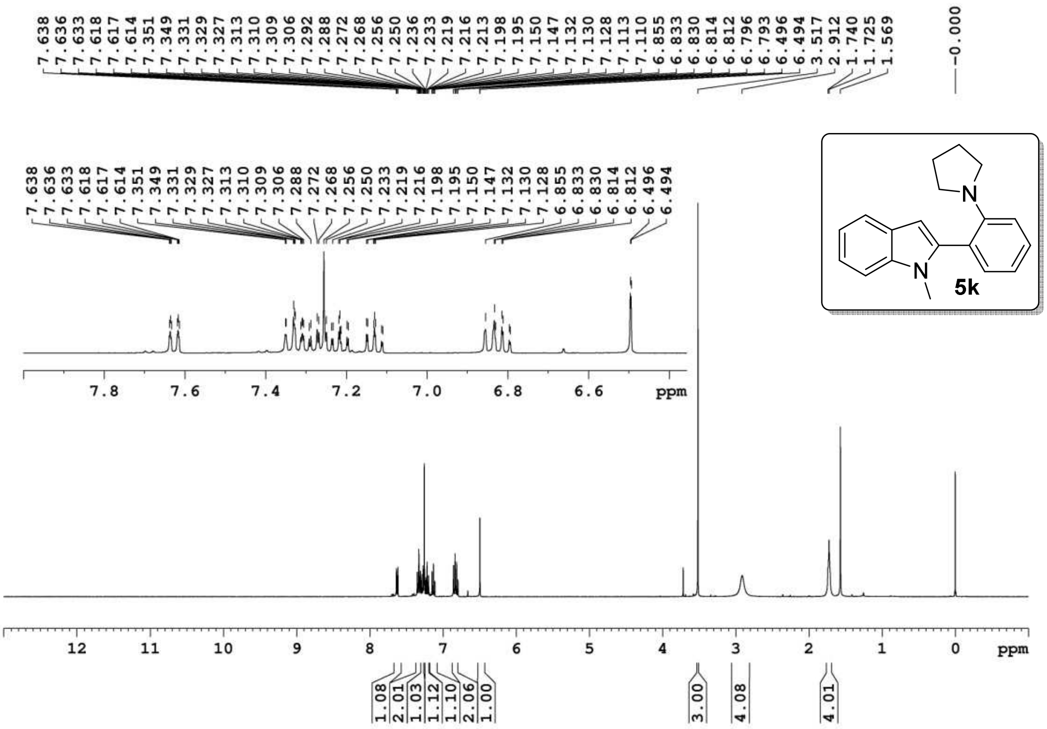
1.09
1.00
3.10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7.633
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7.617
7.614
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7.349
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7.329
7.327
7.313
7.310
7.309
7.306
7.292
7.288
7.272
7.268
7.256
7.250
7.236
7.233
7.219
7.216
7.213
7.198
7.195
7.150
7.147
7.132
7.130
7.128
7.113
7.110
6.855
6.833
6.830
6.814
6.812
6.796
6.793
6.496
6.494
3.517
2.912
1.740
1.725
1.569
-0.000
N
N
5k
7.8
7.6
7.4
7.2
7.0
6.8
6.6
ppm
12
11
10
9
8
7
6
5
4
3
2
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ppm
1.08
2.01
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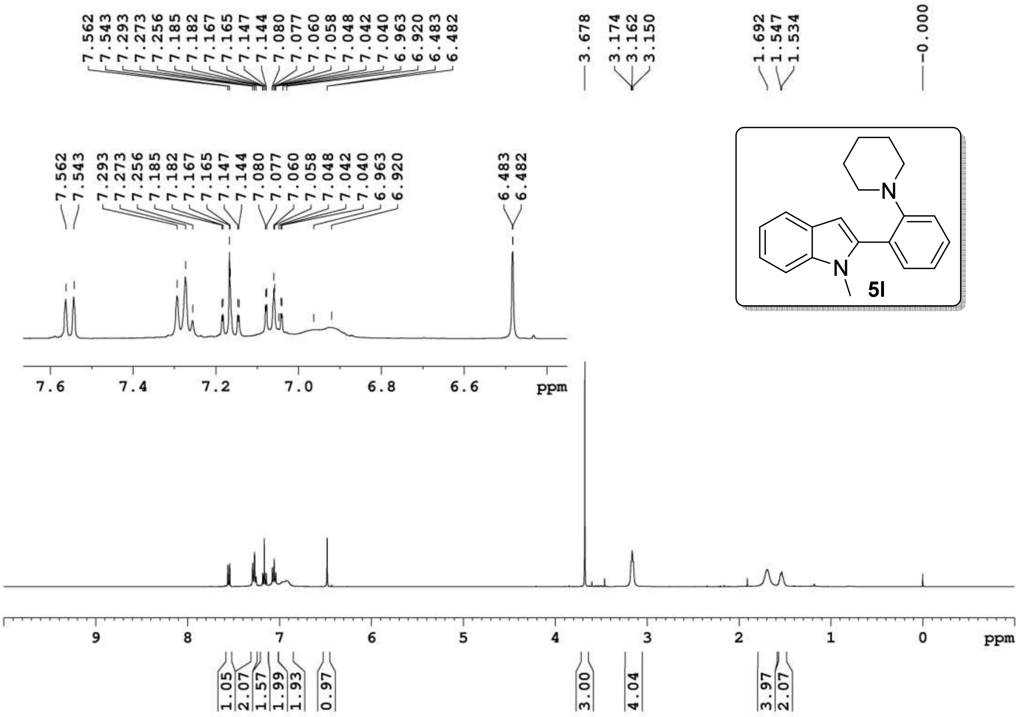
1.12
1.10
2.06
1.00
3.00
4.08
4.01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7.293
7.273
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7.167
7.165
7.147
7.144
7.080
7.077
7.060
7.058
7.048
7.042
7.040
6.963
6.920
6.483
6.482
3.678
3.174
3.162
3.150
1.692
1.547
1.534
-0.000
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5l
ppm
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2.07
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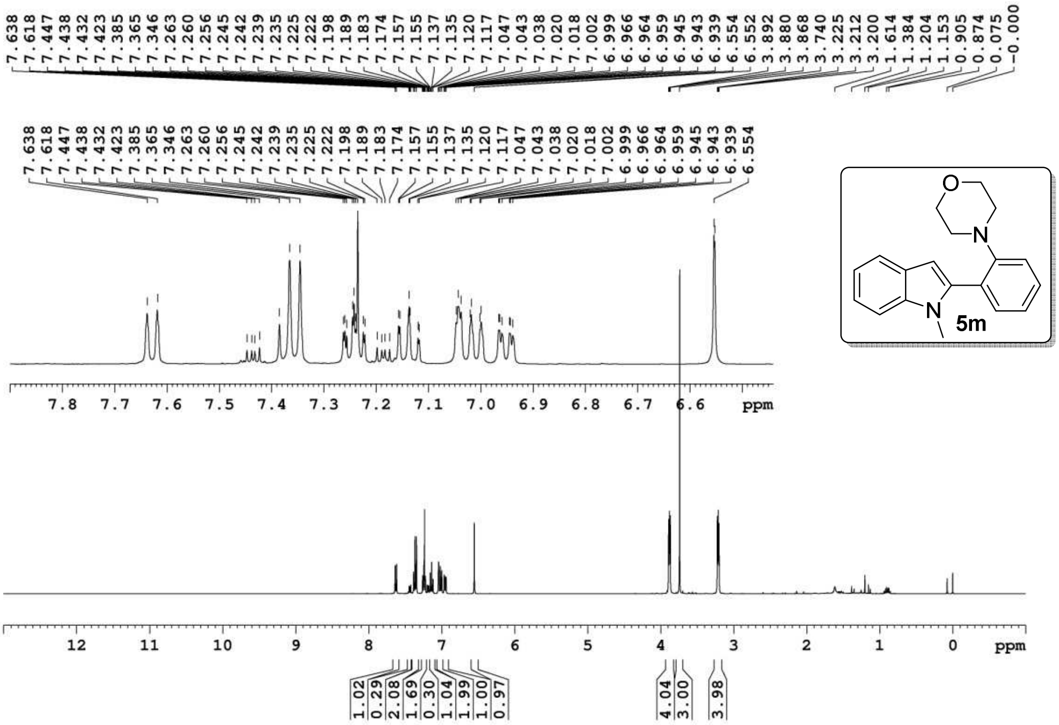
1.99
1.93
0.97
3.00
4.04
3.97
2.07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7.447
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7.432
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7.263
7.260
7.256
7.245
7.242
7.239
7.235
7.225
7.222
7.198
7.189
7.183
7.174
7.157
7.155
7.137
7.135
7.120
7.117
7.047
7.043
7.038
7.020
7.018
7.002
6.999
6.966
6.964
6.959
6.945
6.943
6.939
6.554
6.552
3.892
3.880
3.868
3.740
3.225
3.212
3.200
1.614
1.384
1.204
1.153
0.905
0.874
0.075
-0.000
O
N
N
5m
ppm
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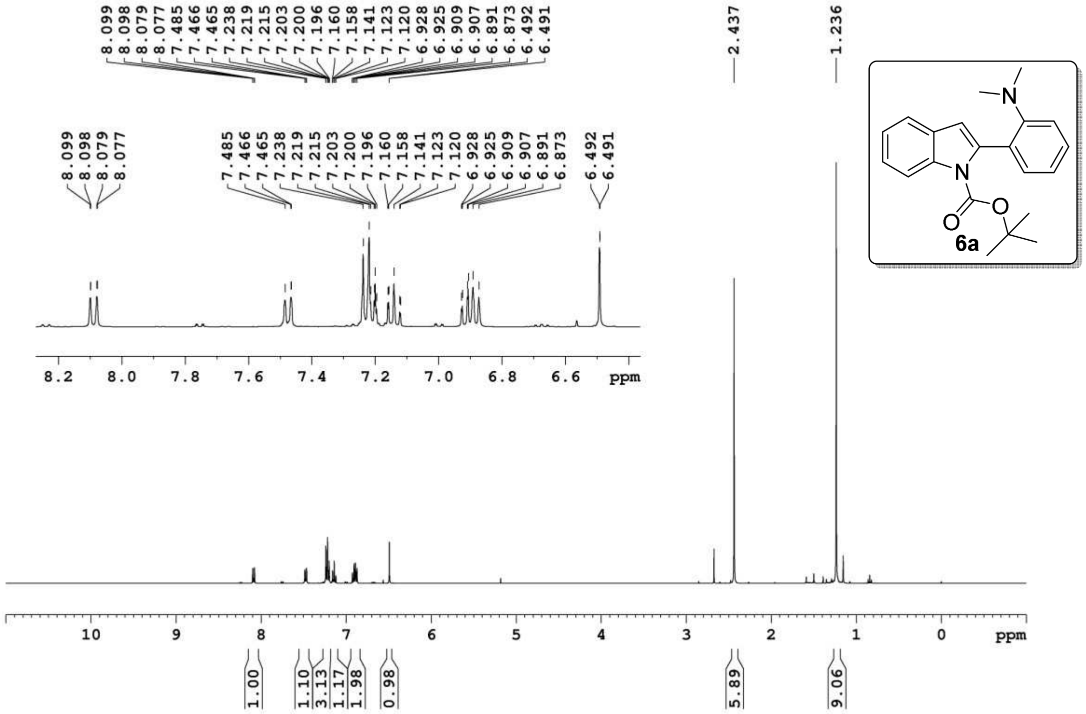
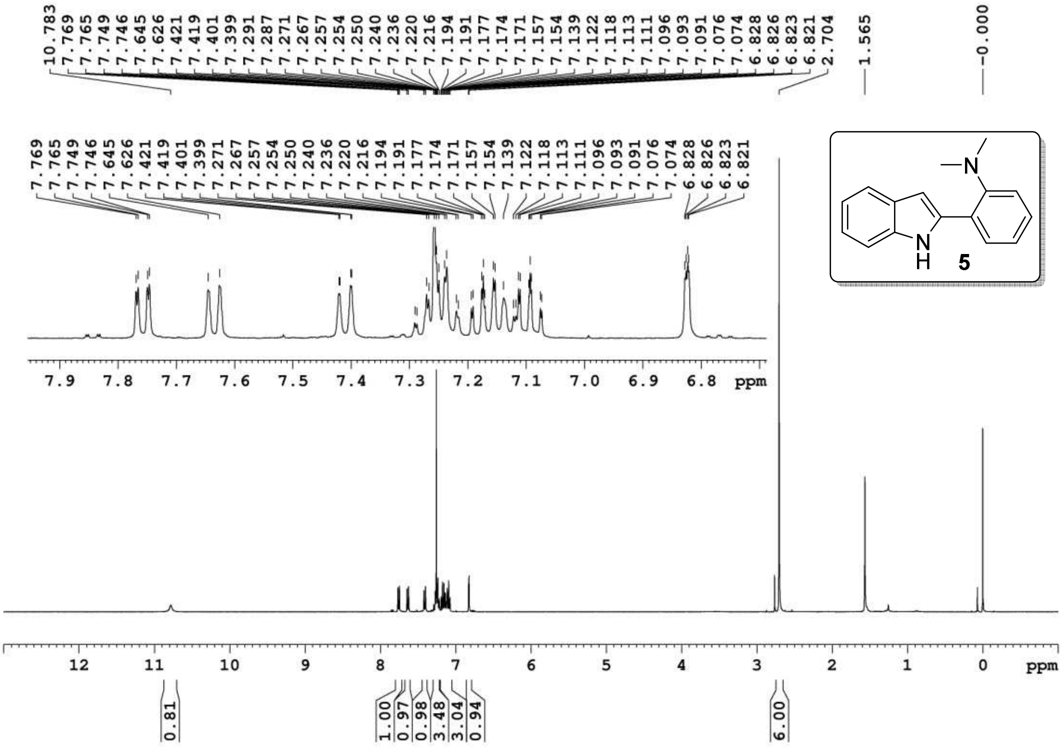
0.29
2.08
1.69
0.30
1.04
1.99
1.00
0.97
4.04
3.00
3.98



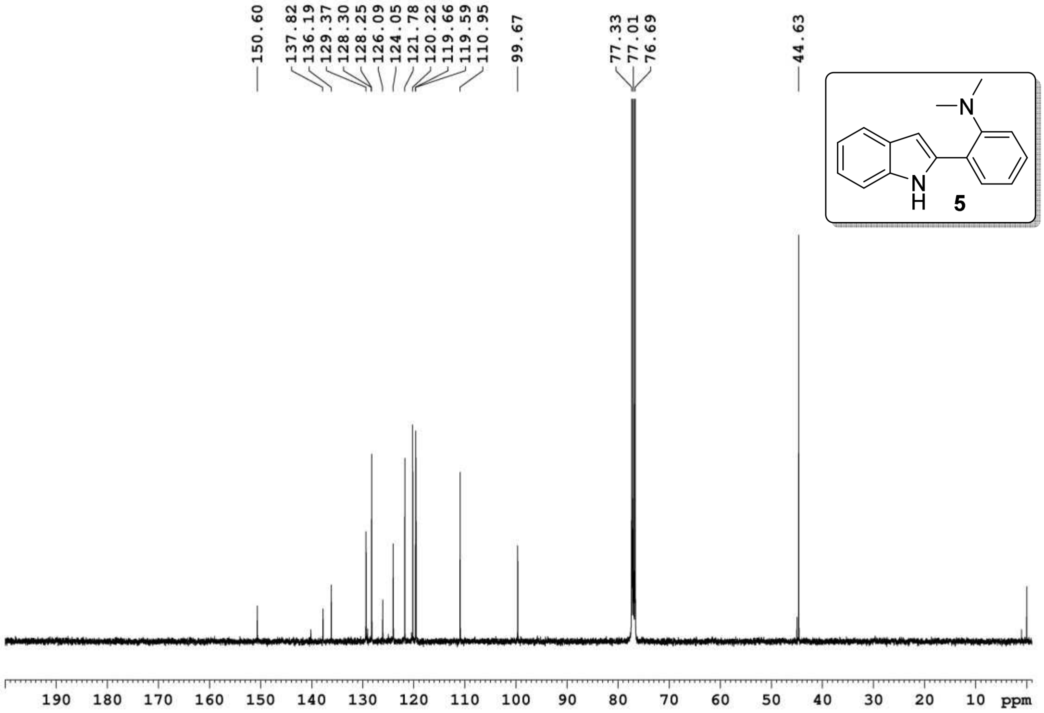
6a

8.099 8.098 8.079 8.077 7.485 7.466 7.465 7.238 7.219 7.215 7.203 7.200 7.196 7.160 7.158 7.141 7.123 7.120 6.928 6.925 6.909 6.907 6.891 6.873 6.492 6.491
2.437
1.236
8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.10 3.13 1.17 1.98 0.98 5.89 9.06
N
O



5

10.783 7.769 7.765 7.749 7.746 7.645 7.626 7.421 7.419 7.401 7.399 7.291 7.287 7.271 7.267 7.257 7.254 7.250 7.240 7.236 7.220 7.216 7.194 7.191 7.177 7.174 7.171 7.157 7.154 7.139 7.122 7.118 7.113 7.111 7.096 7.093 7.091 7.076 7.074 6.828 6.826 6.823 6.821 2.704
1.565
-0.000
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 ppm
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.81 1.00 0.97 0.98 3.48 3.04 0.94 6.00
N
N
H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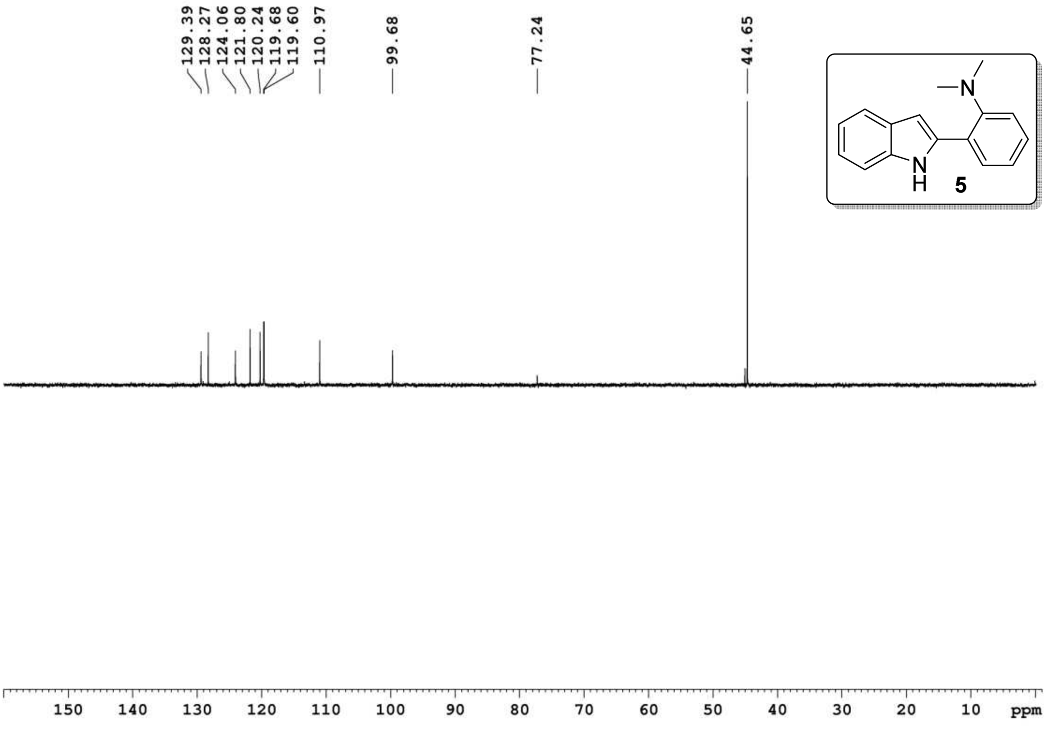
136.19
129.37
128.30
128.25
126.09
124.05
121.78
120.22
119.66
119.59
110.95
99.67
77.33
77.01
76.69
44.63
N
N
H
5
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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120.24
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110.97
99.68
77.24
44.65
N
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H
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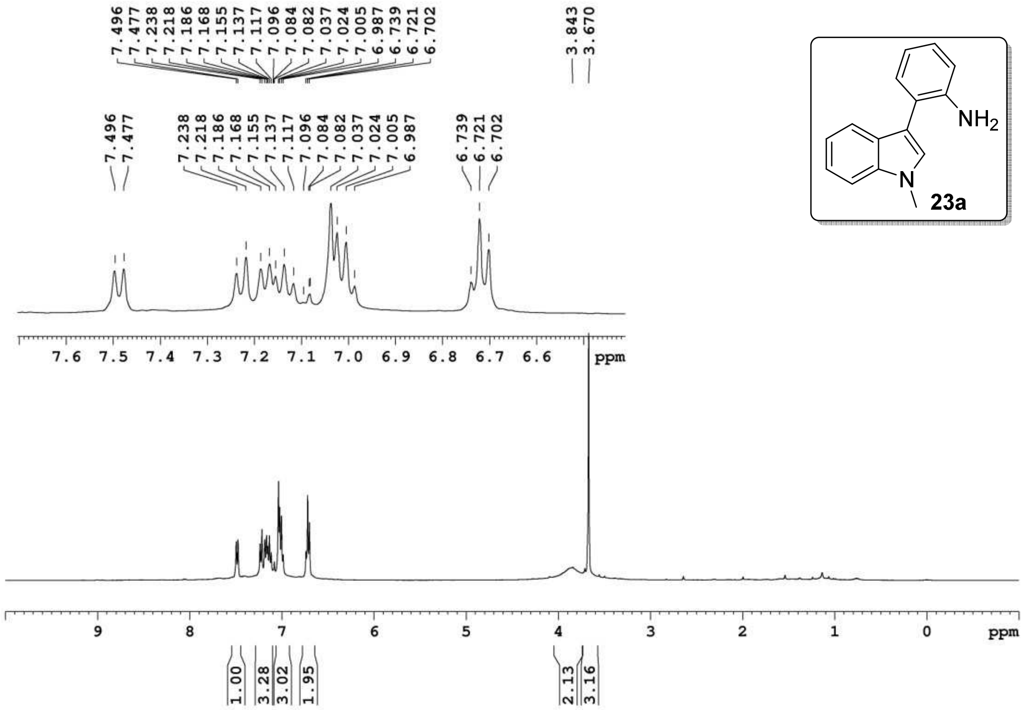
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.137
7.117
7.096
7.084
7.082
7.037
7.024
7.005
6.987
6.739
6.721
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ppm
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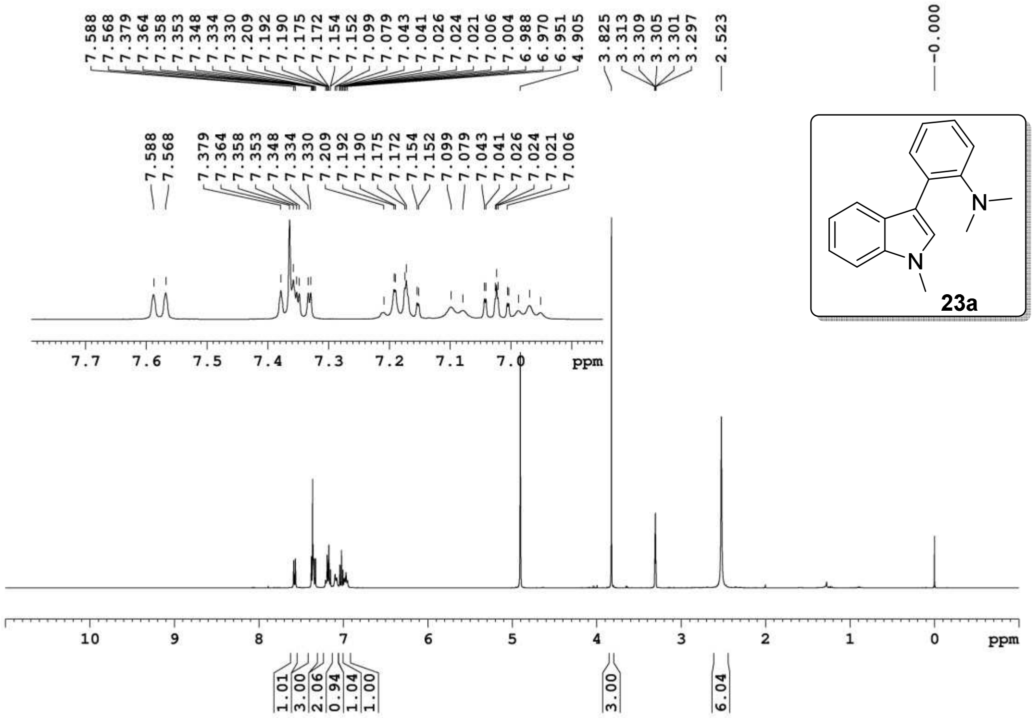
2.13
3.16
NH2
N
23a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7.175
7.172
7.154
7.152
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7.079
7.043
7.041
7.026
7.024
7.021
7.006
7.004
6.988
6.970
6.951
4.905
3.825
3.313
3.309
3.305
3.301
3.297
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1.00
3.00
6.04
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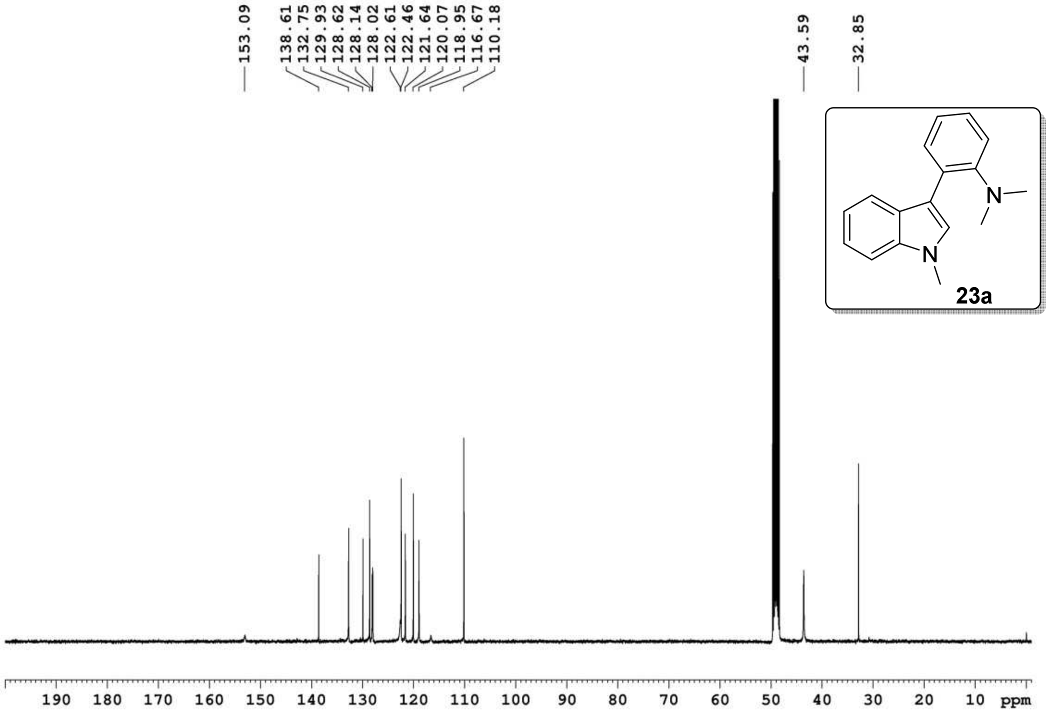
23a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132.75
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128.62
128.14
128.02
122.61
122.46
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118.95
116.67
110.18
43.59
32.85
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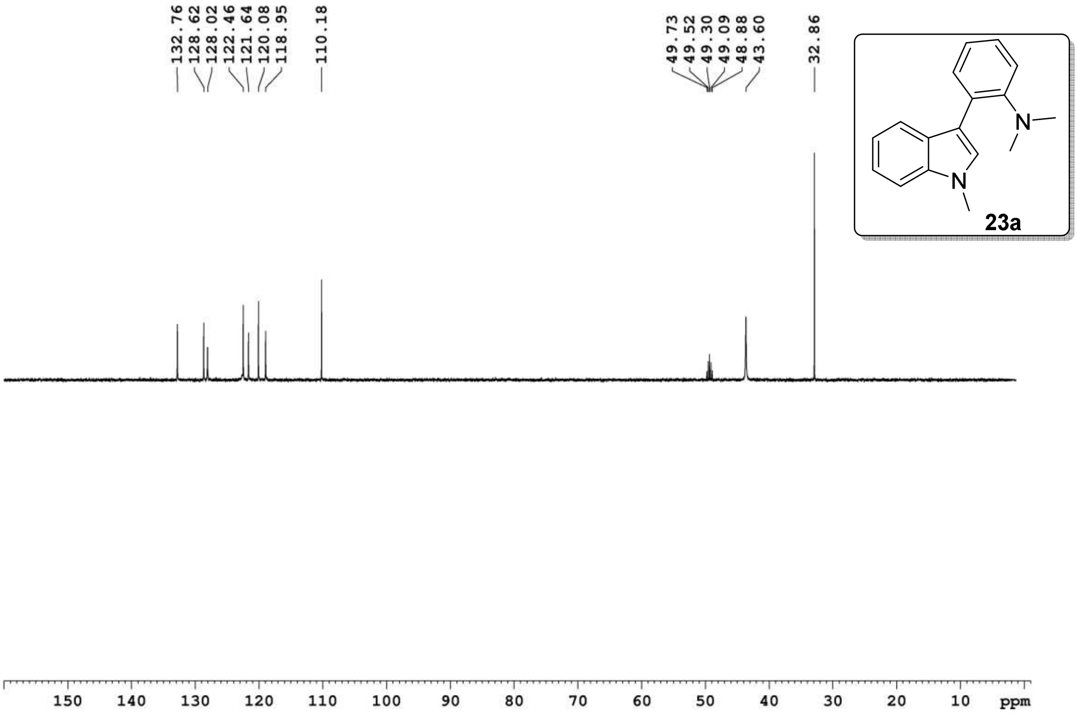
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128.02
122.46
121.64
120.08
118.95
110.18
49.73
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49.30
49.09
48.88
43.60
32.86
23a
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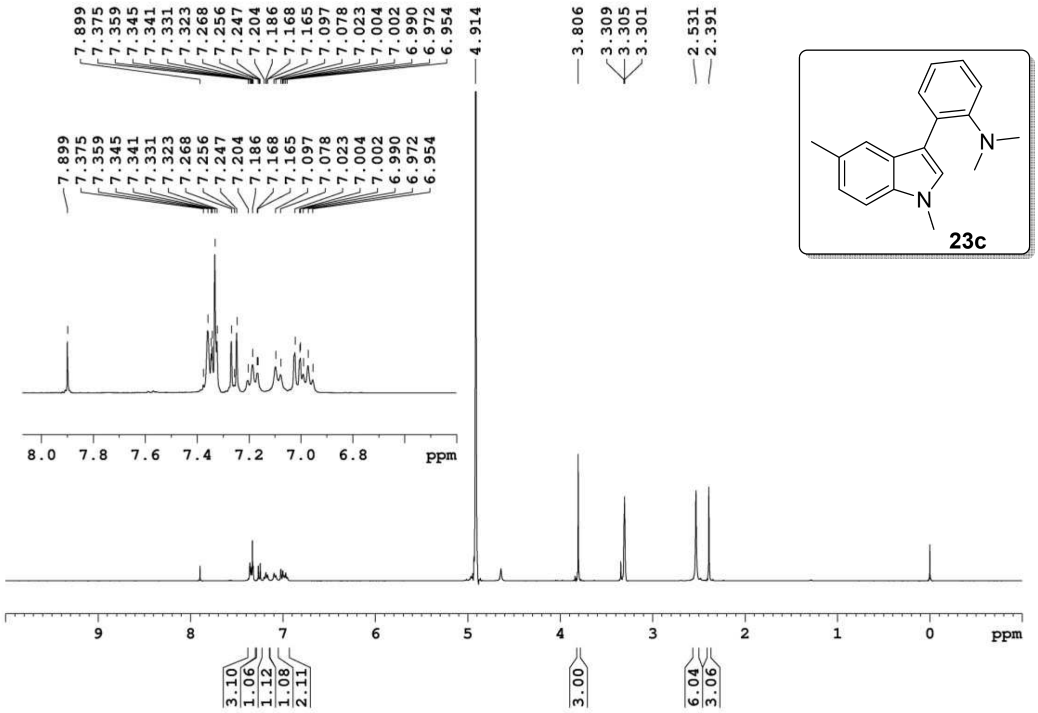
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7.268
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7.247
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7.186
7.168
7.165
7.097
7.078
7.023
7.004
7.002
6.990
6.972
6.954
4.914
3.806
3.309
3.305
3.301
2.531
2.391
8.0 7.8 7.6 7.4 7.2 7.0 6.8 ppm
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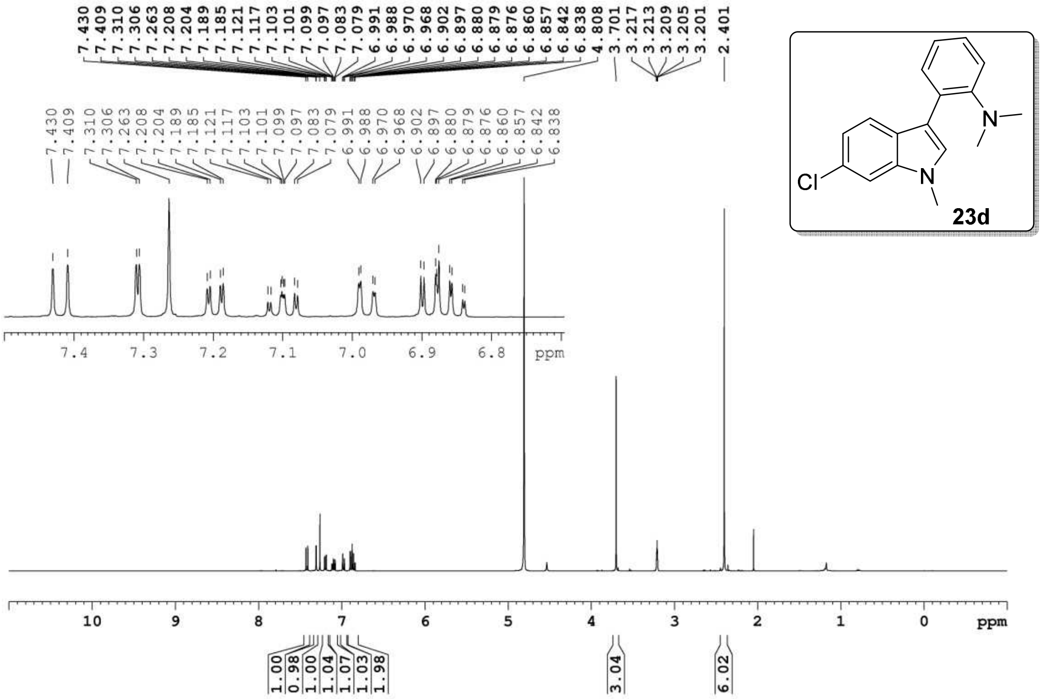
1.06
1.12
1.08
2.11
3.00
6.04
3.06
N
N

23c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7.208
7.204
7.189
7.185
7.121
7.117
7.103
7.101
7.099
7.097
7.083
7.079
6.991
6.988
6.970
6.968
6.902
6.897
6.880
6.879
6.876
6.860
6.857
6.842
6.838
4.808
3.701
3.217
3.213
3.209
3.205
3.201
2.401
7.4 7.3 7.2 7.1 7.0 6.9 6.8 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
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1.00
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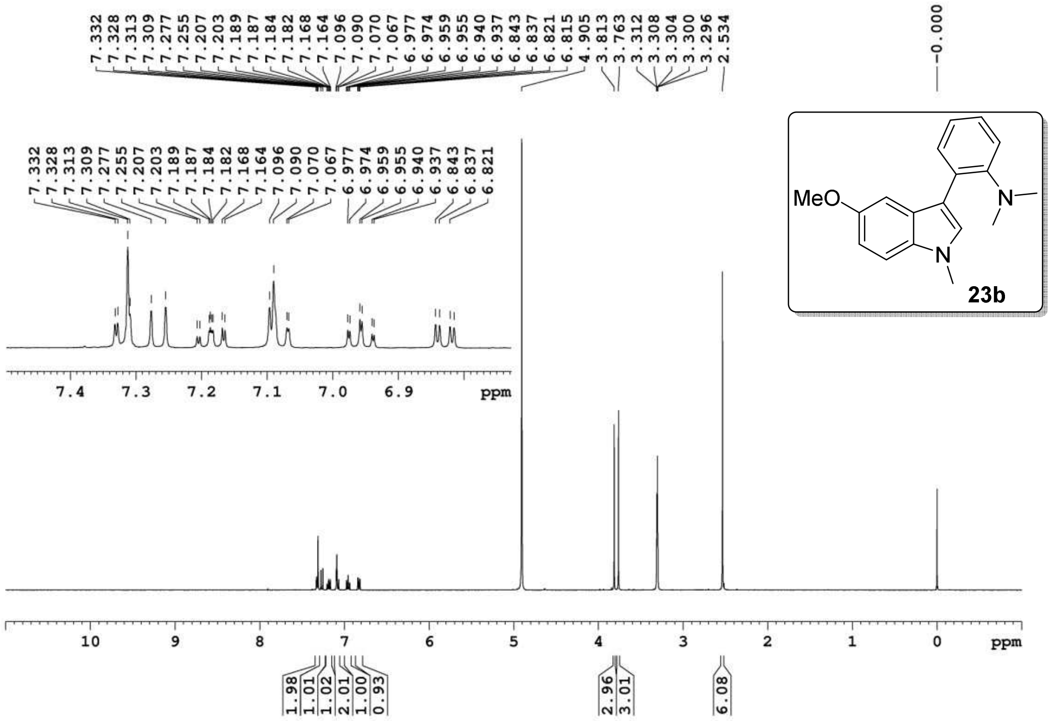
1.03
1.98
3.04
6.02
N
Cl
N

23d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7.164
7.096
7.090
7.070
7.067
6.977
6.974
6.959
6.955
6.940
6.937
6.843
6.837
6.821
6.815
4.905
3.813
3.763
3.312
3.308
3.304
3.300
3.296
2.534
-0.000
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7.3
7.2
7.1
7.0
6.9
ppm
MeO
N
N
23b
10
9
8
7
6
5
4
3
2
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0
ppm
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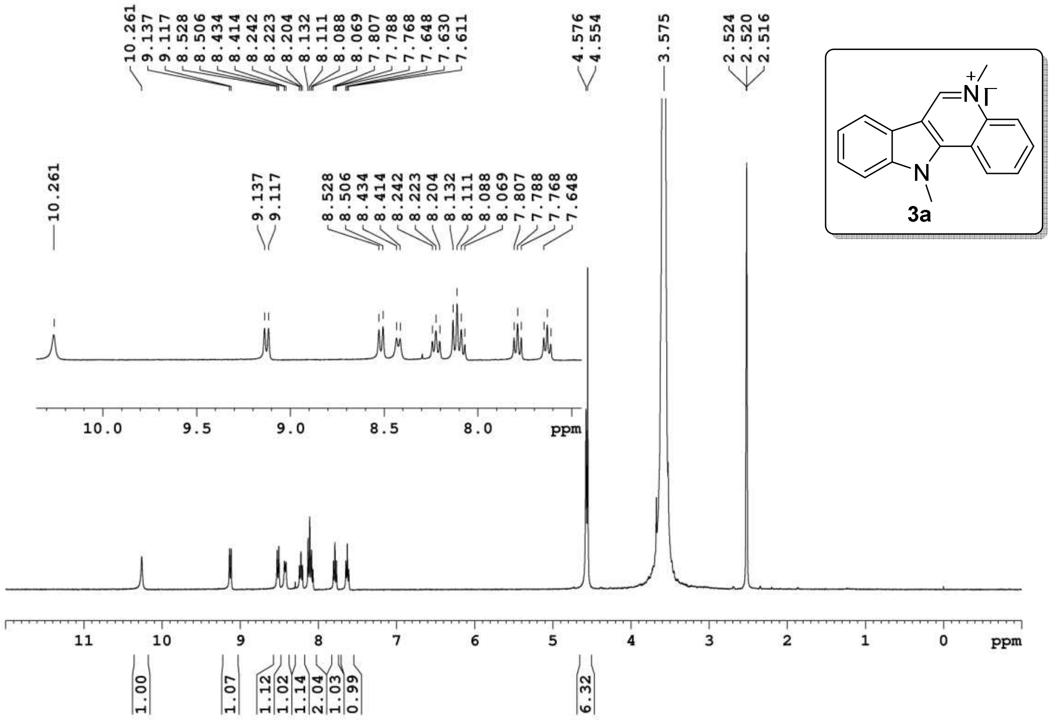
1.01
1.02
2.01
1.00
0.93
2.96
3.01
6.08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8.434
8.414
8.242
8.223
8.204
8.132
8.111
8.088
8.069
7.807
7.788
7.768
7.648
7.630
7.611
4.576
4.554
3.575
2.524
2.520
2.516
N+
I−
N
3a
10.0
9.5
9.0
8.5
8.0
ppm
11
10
9
8
7
6
5
4
3
2
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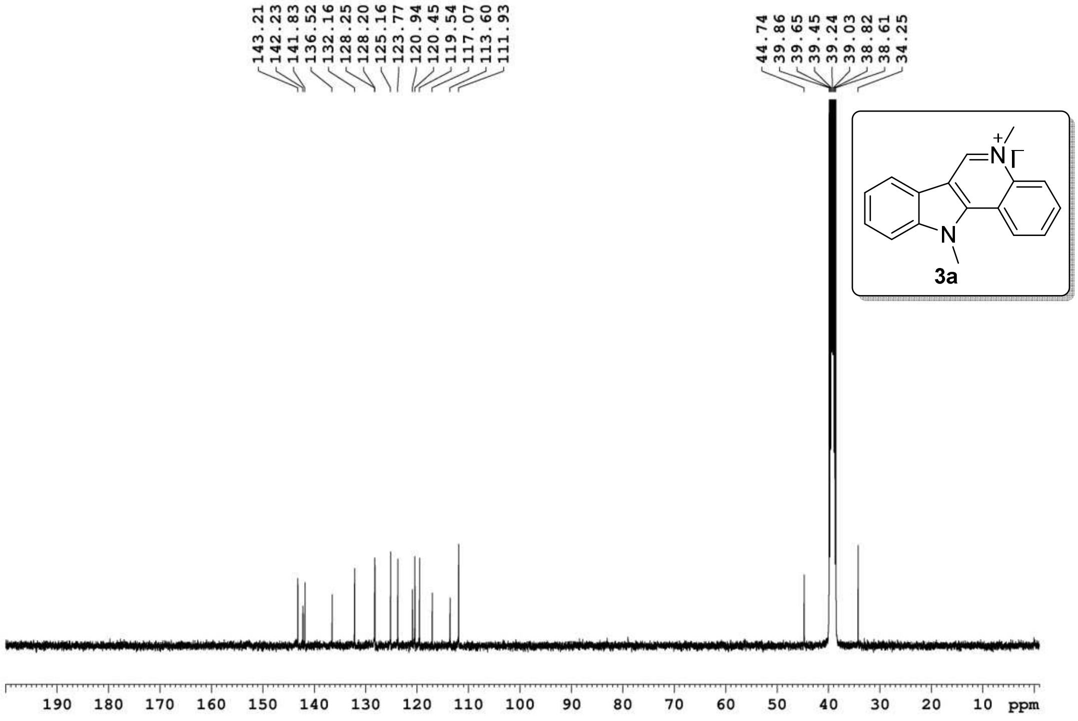
ppm
1.00
1.07
1.12
1.02
1.14
2.04
1.03
0.99
6.32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142.23
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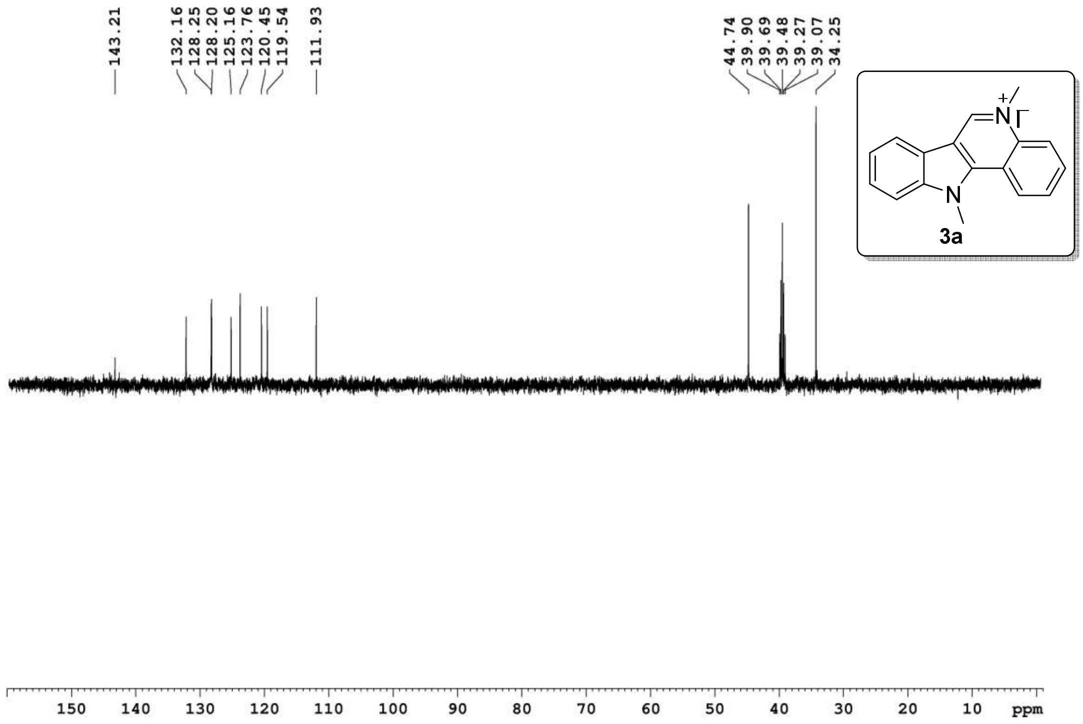
136.52
132.16
128.25
128.20
125.16
123.77
120.94
120.45
119.54
117.07
113.60
111.93
44.74
39.86
39.65
39.45
39.24
39.03
38.82
38.61
34.25
N
N
+
I⁻
3a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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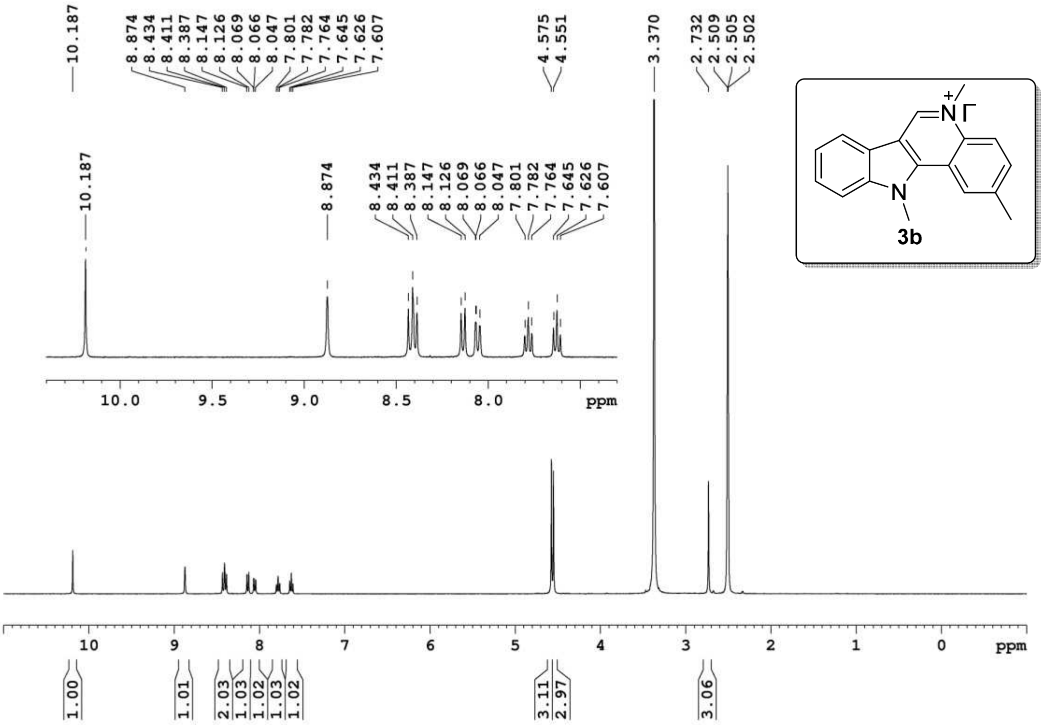
128.20
125.16
123.76
120.45
119.54
111.93
44.74
39.90
39.69
39.48
39.27
39.07
34.25
N
N
+
I⁻
3a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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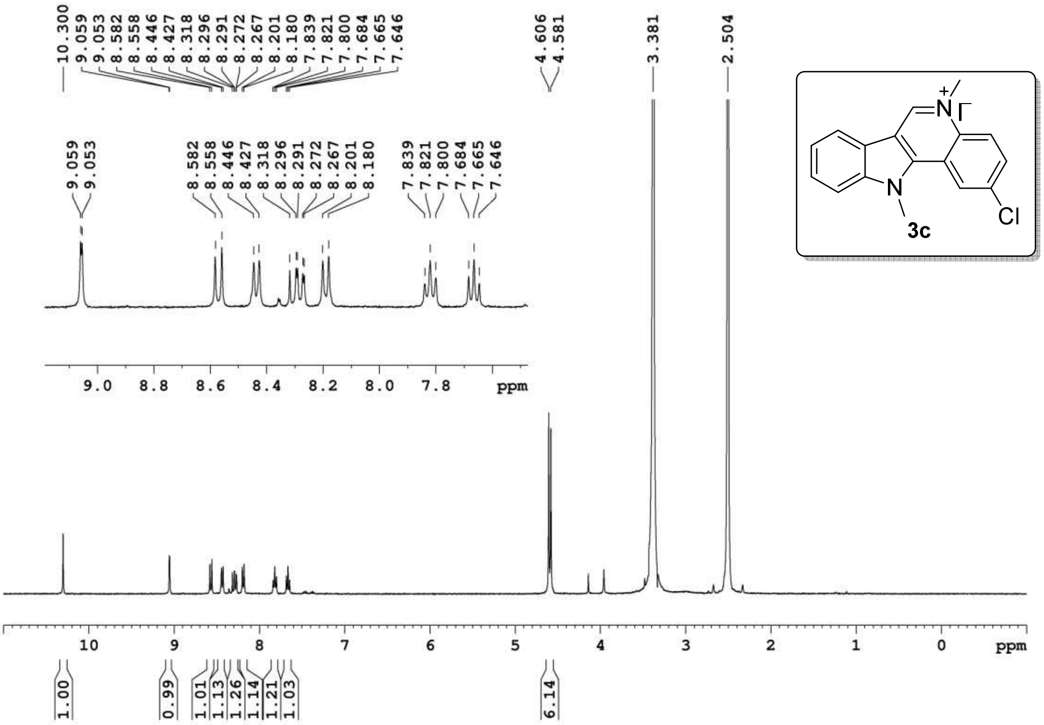
7.764
7.645
7.626
7.607
4.575
4.551
3.370
2.732
2.509
2.505
2.502
10.0
9.5
9.0
8.5
8.0
ppm
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
2.03
1.03
1.02
1.03
1.02
3.11
2.97
3.06
N
+
I⁻
N
3b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9.053
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8.446
8.427
8.318
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8.291
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8.267
8.201
8.180
7.839
7.821
7.800
7.684
7.665
7.646
4.606
4.581
3.381
2.504
9.0
8.8
8.6
8.4
8.2
8.0
7.8
ppm
10
9
8
7
6
5
4
3
2
1
0
ppm
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1.21
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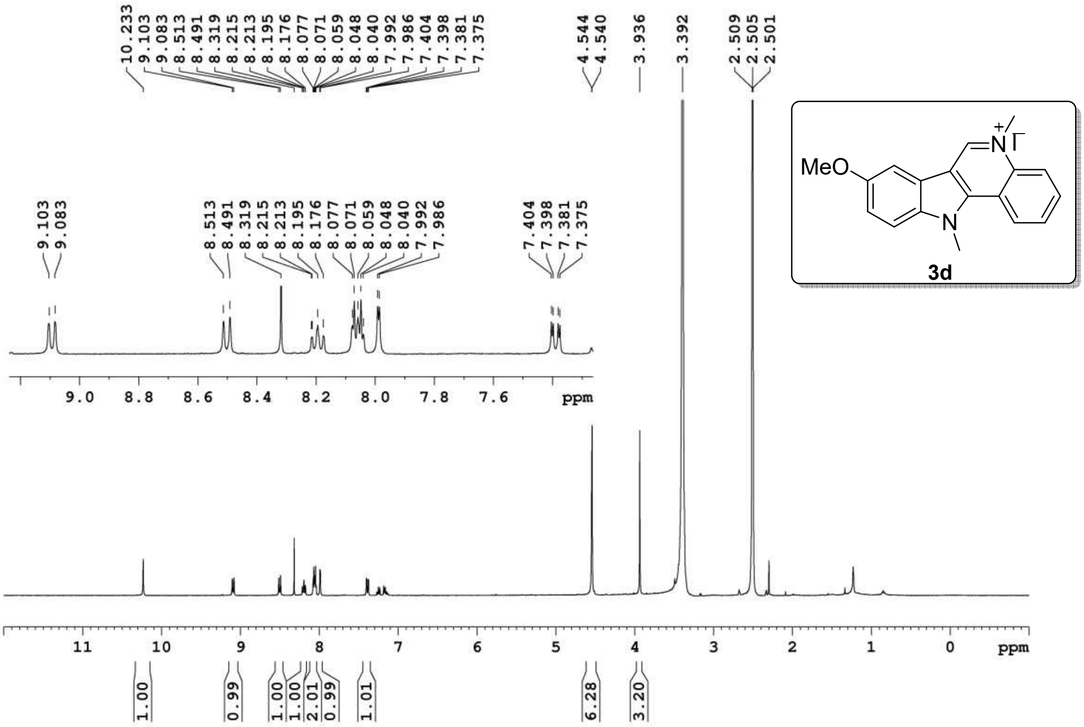
+
I⁻
N
Cl
3c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8.213
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8.059
8.048
8.040
7.992
7.986
7.404
7.398
7.381
7.375
4.544
4.540
3.936
3.392
2.509
2.505
2.501
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1.00
1.00
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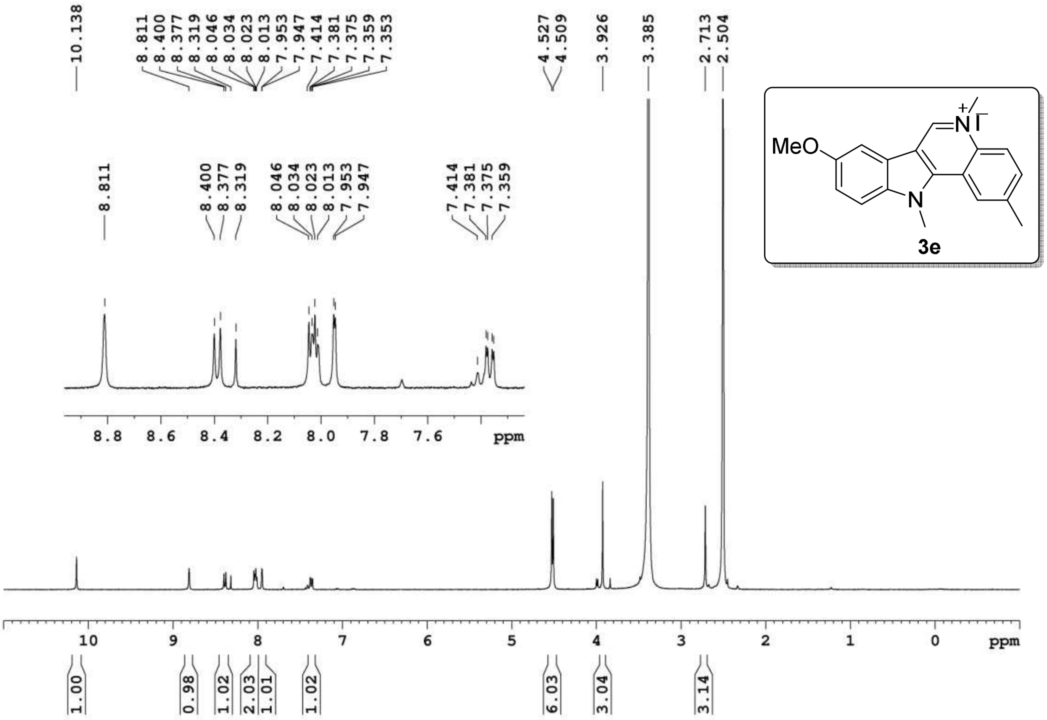
0.99
1.01
6.28
3.20

3d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8.034
8.023
8.013
7.953
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7.414
7.381
7.375
7.359
7.353
4.527
4.509
3.926
3.385
2.713
2.504
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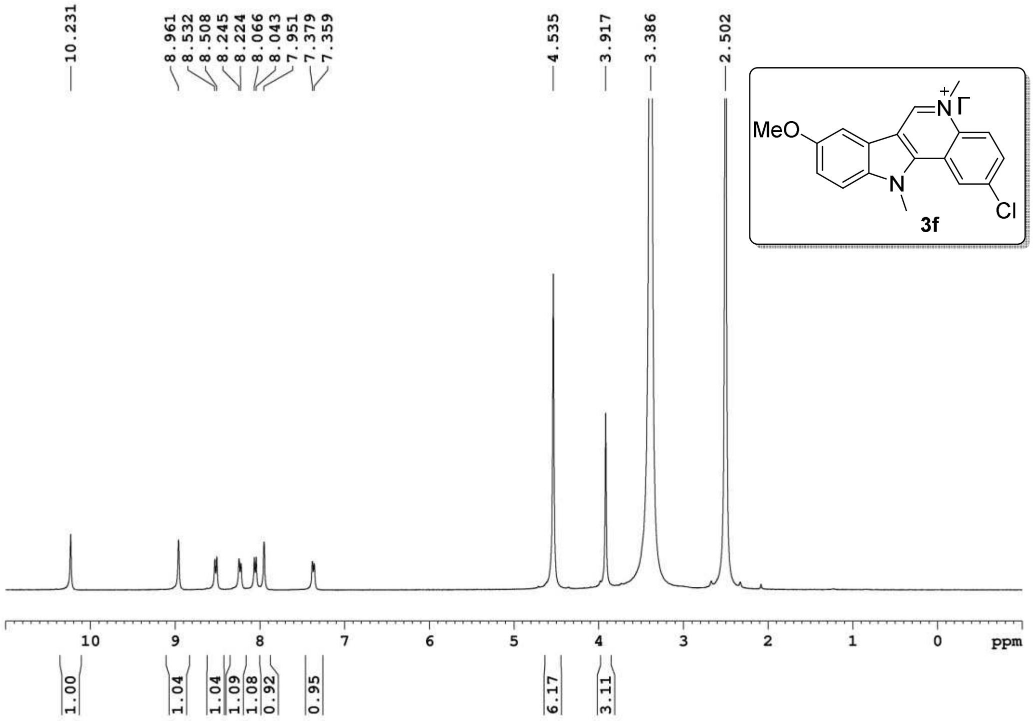
2.03
1.01
1.02
6.03
3.04
3.14

3e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8.043
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7.379
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3.917
3.386
2.502
MeO
N
N
I⁻
Cl
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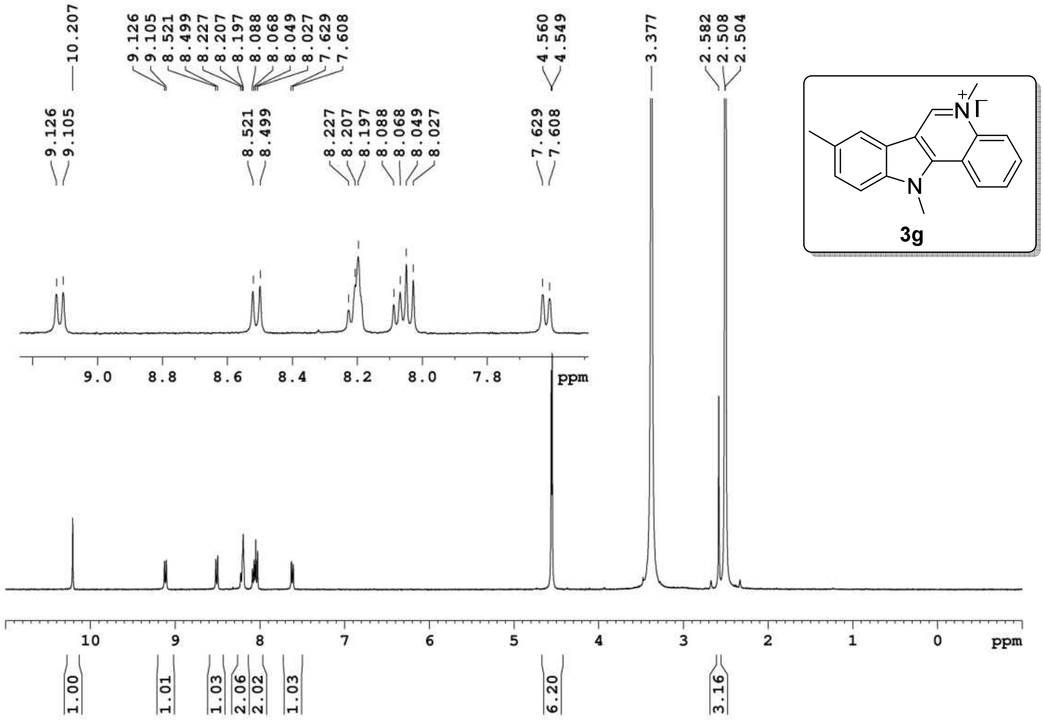
1.04
1.04
1.09
1.08
0.92
0.95
6.17
3.11

3f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7.629
7.608
4.560
4.549
3.377
2.582
2.508
2.504
9.0 8.8 8.6 8.4 8.2 8.0 7.8 ppm
N
N
I⁻
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1.03
6.20
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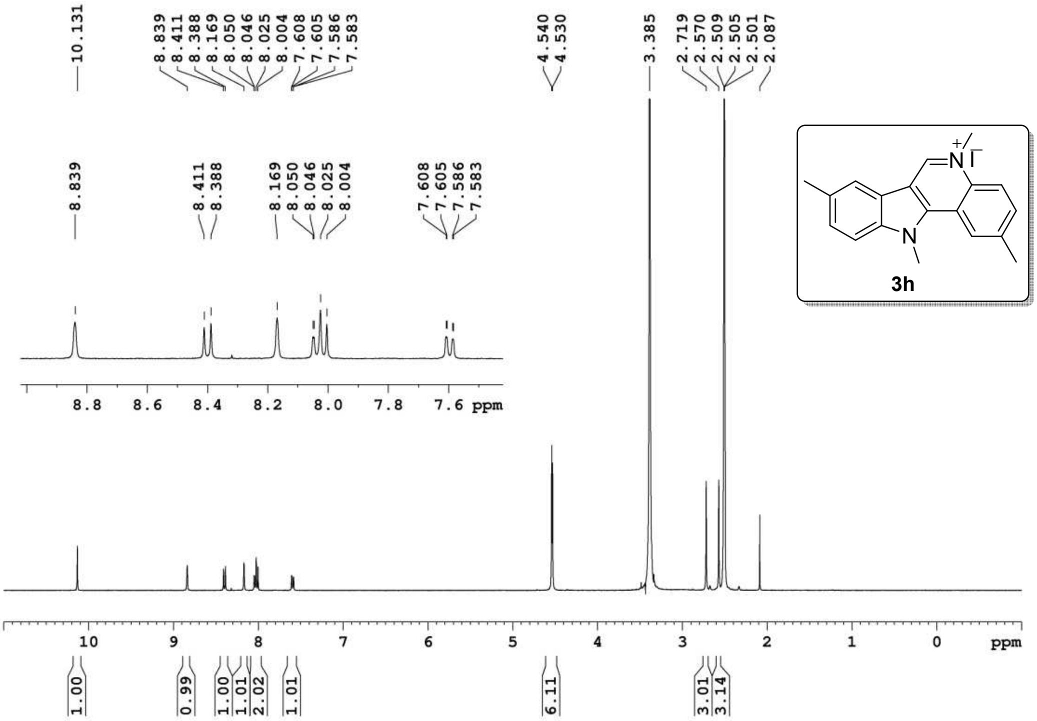
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2.505
2.501
2.087
8.8 8.6 8.4 8.2 8.0 7.8 7.6 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
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1.00
1.01
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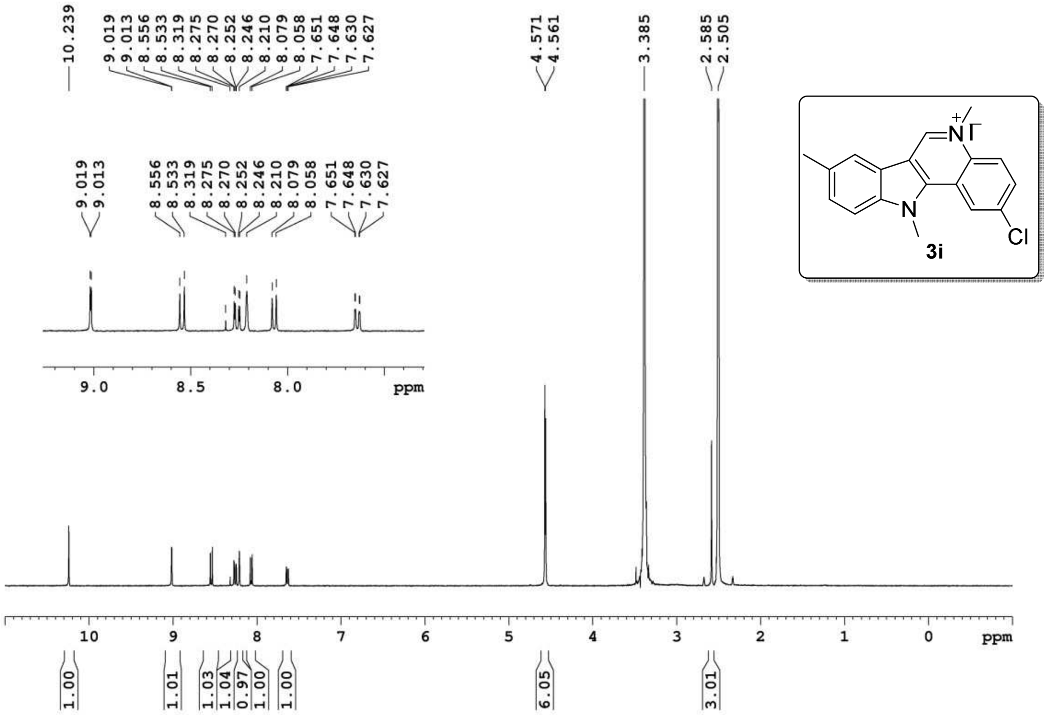
3.01
3.14
N
N
I
3h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8.079
8.058
7.651
7.648
7.630
7.627
4.571
4.561
3.385
2.585
2.505
9.0 8.5 8.0 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
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1.04
0.97
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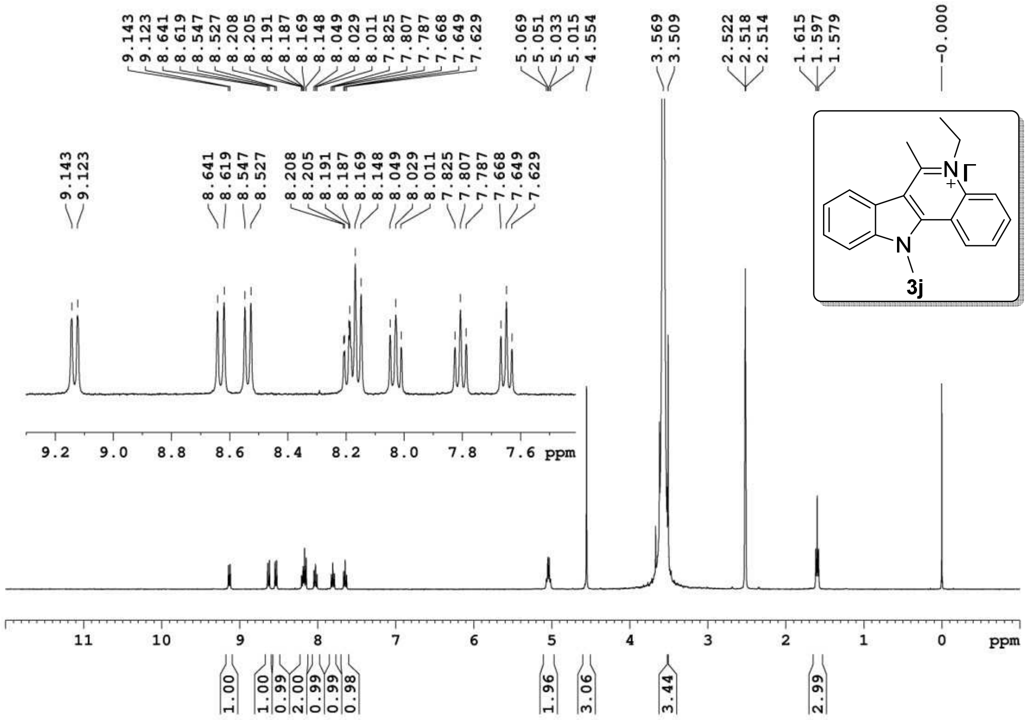
1.00
6.05
3.01
N
N
I
Cl
3i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8.205
8.191
8.187
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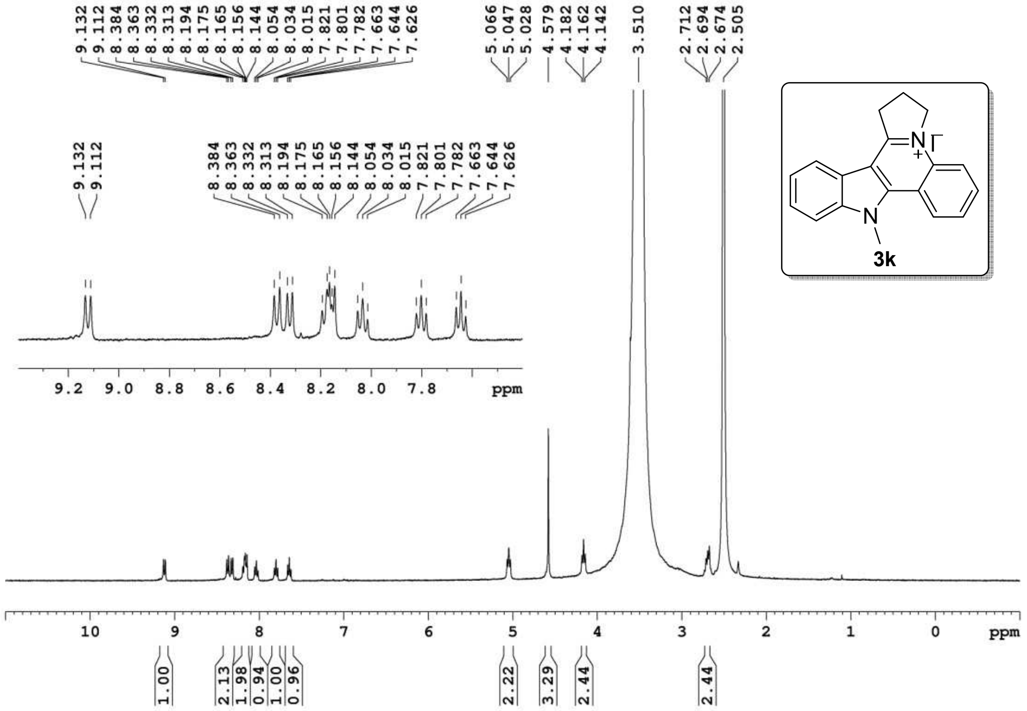
8.049
8.029
8.011
7.825
7.807
7.787
7.668
7.649
7.629
5.069
5.051
5.033
5.015
4.554
3.569
3.509
2.522
2.518
2.514
1.615
1.597
1.579
-0.000
9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 ppm
11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.00
0.99
2.00
0.99
0.99
0.98
1.96
3.06
3.44
2.99
N
+
I⁻
N
3j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8.363
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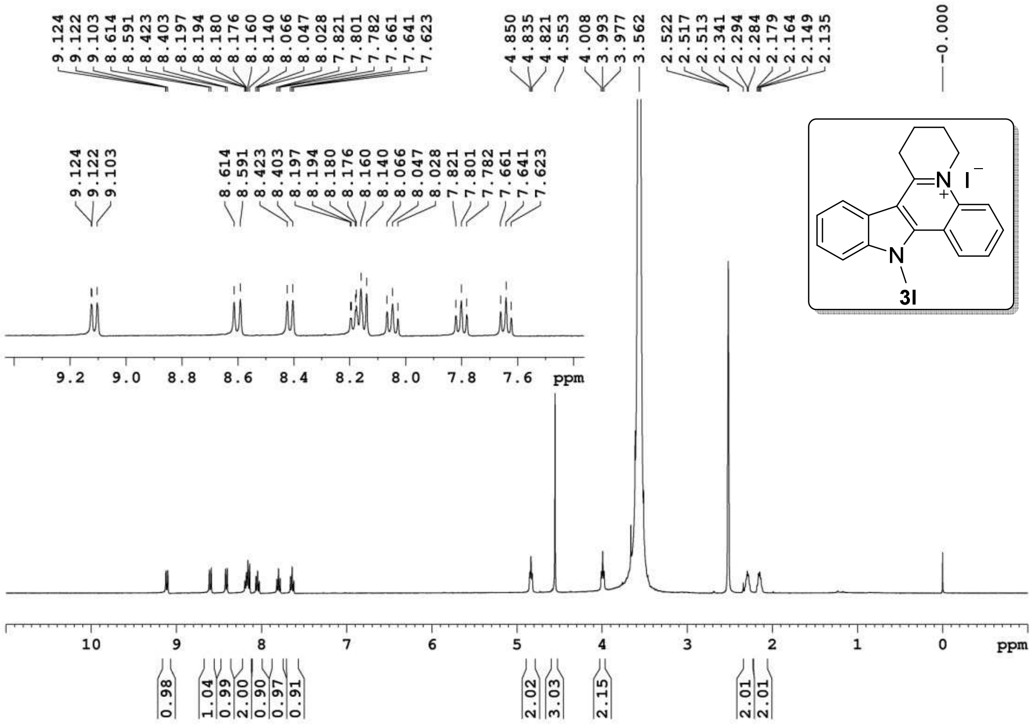
8.194
8.175
8.165
8.156
8.144
8.054
8.034
8.015
7.821
7.801
7.782
7.663
7.644
7.626
5.066
5.047
5.028
4.579
4.182
4.162
4.142
3.510
2.712
2.694
2.674
2.505
9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
2.13
1.98
0.94
1.00
0.96
2.22
3.29
2.44
2.44
N
+
I⁻
N
3k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9.122
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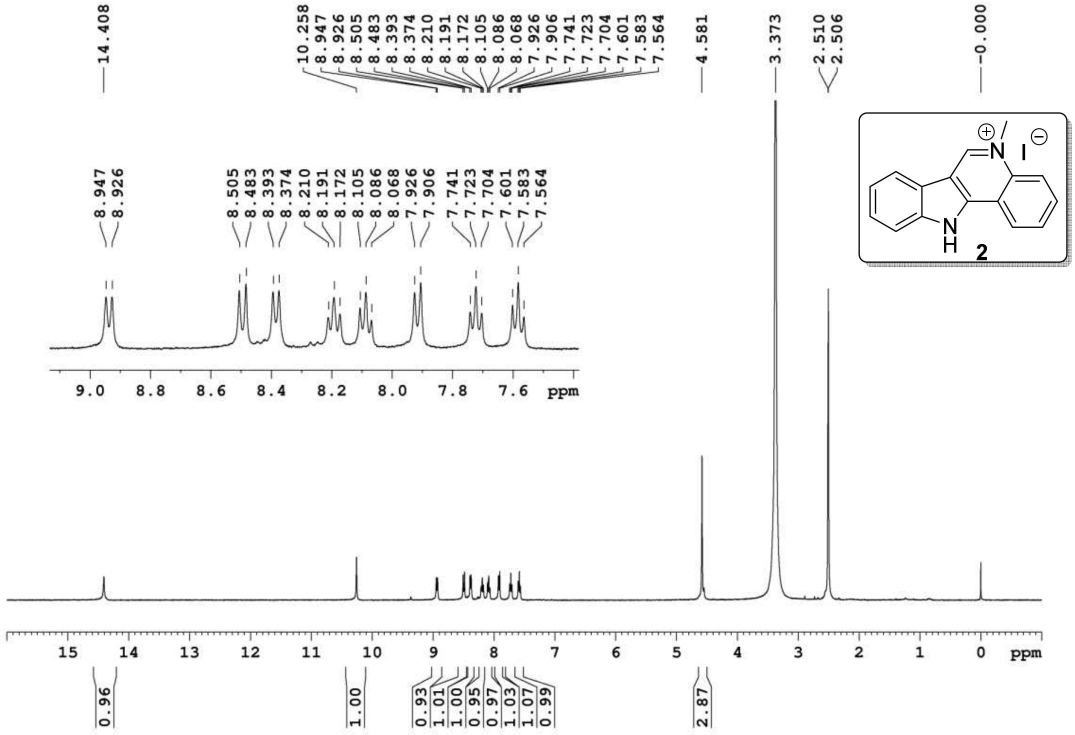
8.591
8.423
8.403
8.197
8.194
8.180
8.176
8.160
8.140
8.066
8.047
8.028
7.821
7.801
7.782
7.661
7.641
7.623
4.850
4.835
4.821
4.553
4.008
3.993
3.977
3.562
2.522
2.517
2.513
2.341
2.294
2.284
2.179
2.164
2.149
2.135
-0.000
9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
0.98
1.04
0.99
2.00
0.90
0.97
0.91
2.02
3.03
2.15
2.01
2.01
N
I⁻
+
N
3l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8.374
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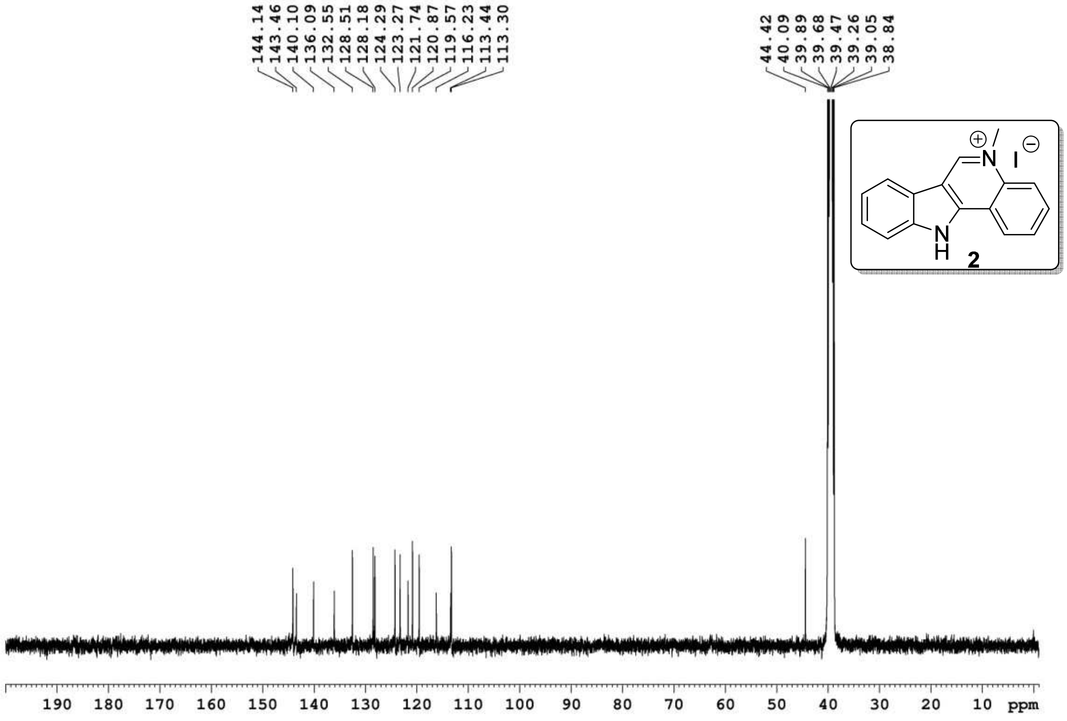
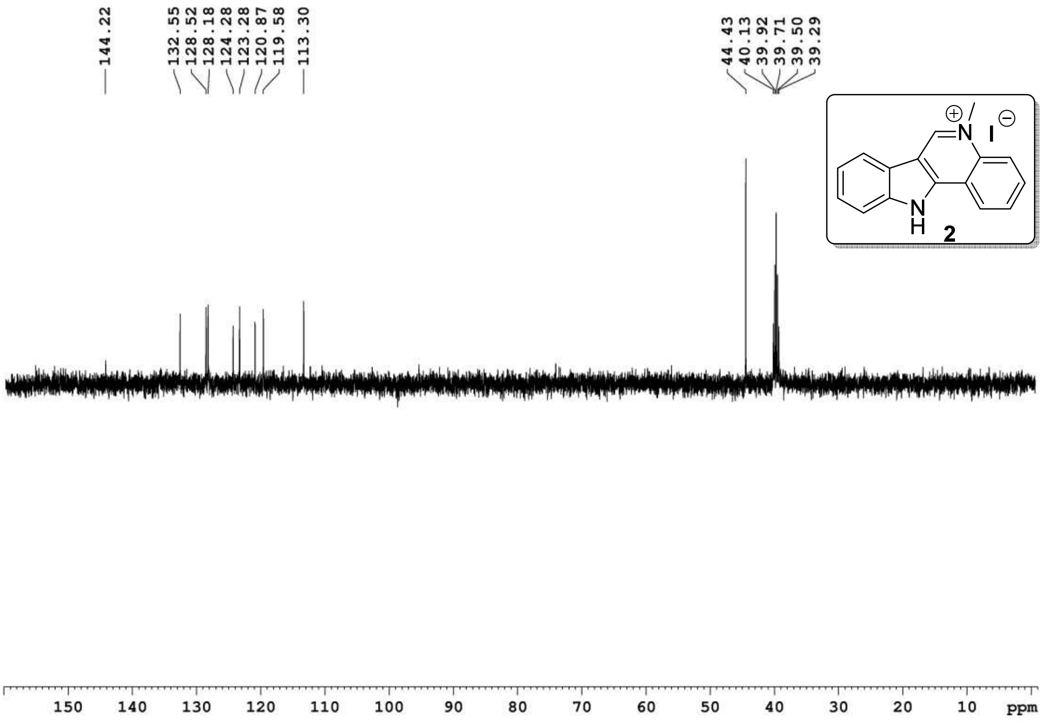
8.191
8.172
8.105
8.086
8.068
7.926
7.906
7.741
7.723
7.704
7.601
7.583
7.564
4.581
3.373
2.510
2.506
-0.000
9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 ppm
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.96
1.00
0.93
1.01
1.00
0.95
0.97
1.03
1.07
0.99
2.87
N
I
N
H
2


144.14
143.46
140.10
136.09
132.55
128.51
128.18
124.29
123.27
121.74
120.87
119.57
116.23
113.44
113.30
44.42
40.09
39.89
39.68
39.47
39.26
39.05
38.84
N
I
N
H
2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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128.18
124.28
123.28
120.87
119.58
113.30
44.43
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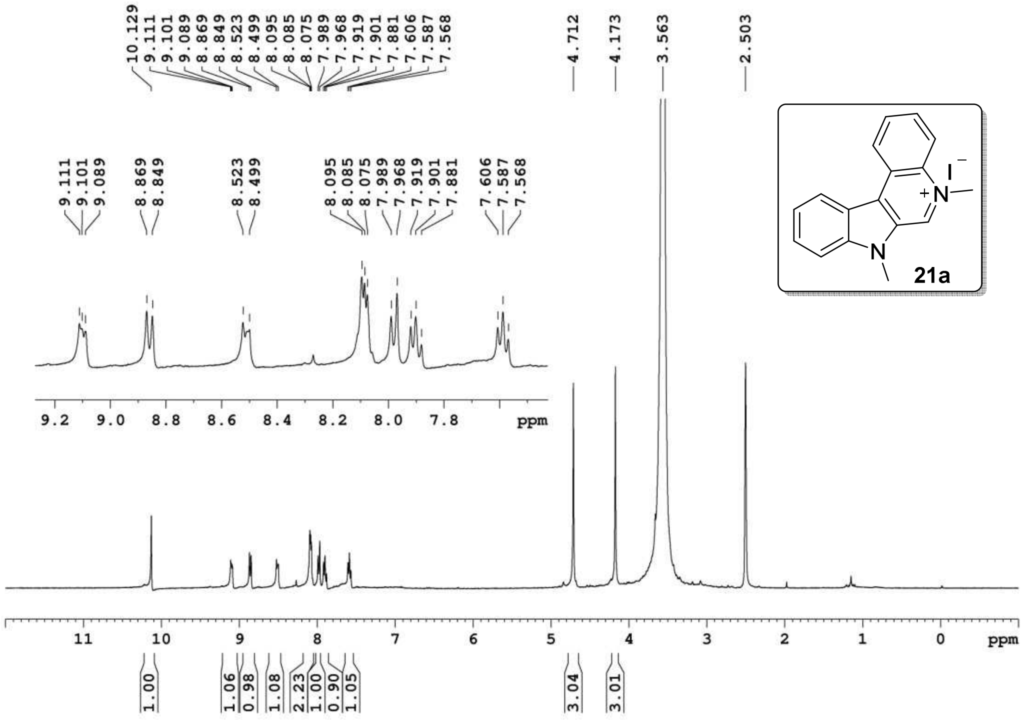
39.92
39.71
39.50
39.29
N
I
N
H
2
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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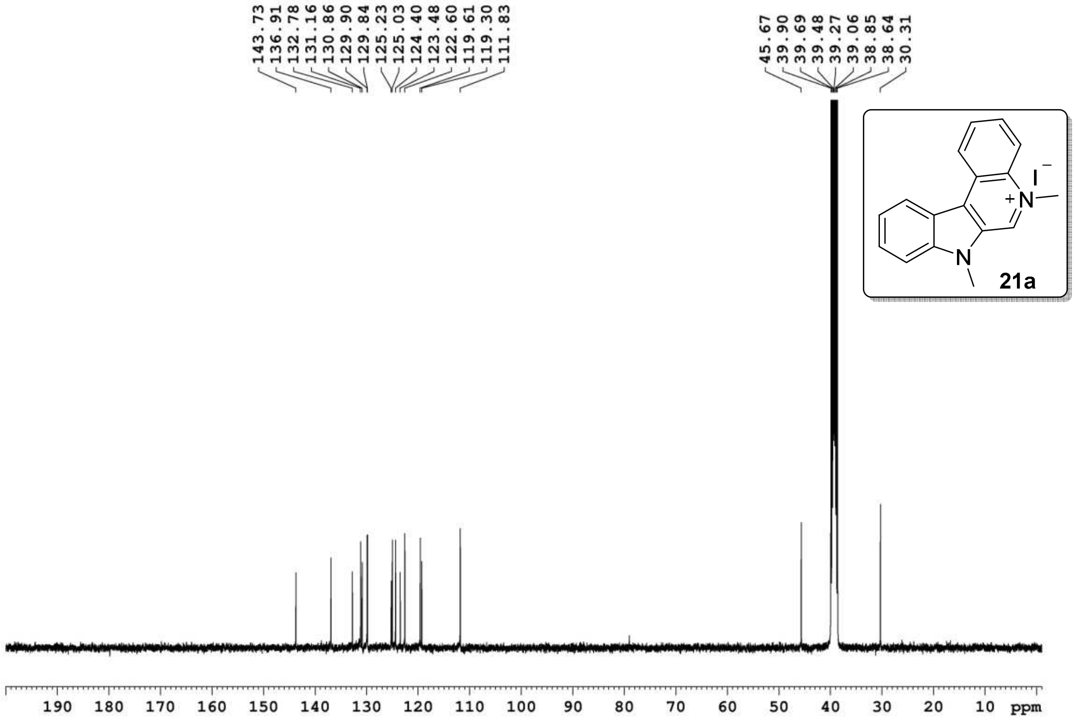
9.101
9.089
8.869
8.849
8.523
8.499
8.095
8.085
8.075
7.989
7.968
7.919
7.901
7.881
7.606
7.587
7.568
4.712
4.173
3.563
2.503
I⁻
+N
N
21a
9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 ppm
11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.06
0.98
1.08
2.23
1.00
0.90
1.05
3.04
3.01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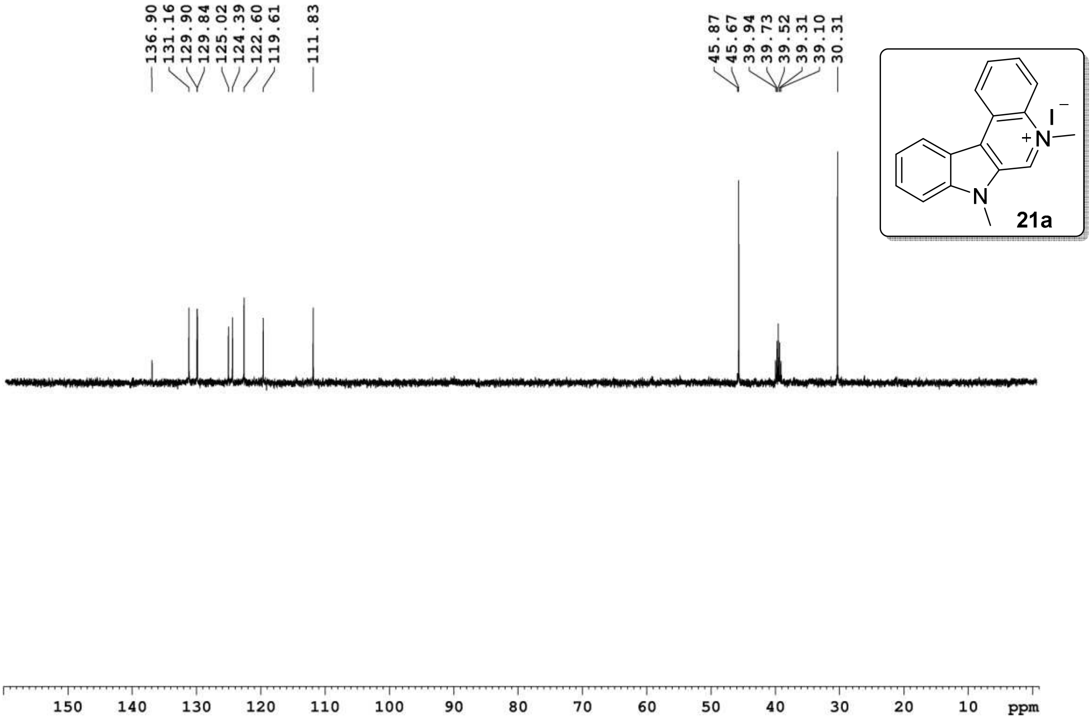
131.16
130.86
129.90
129.84
125.23
125.03
124.40
123.48
122.60
119.61
119.30
111.83
45.67
39.90
39.69
39.48
39.27
39.06
38.85
38.64
30.31
I⁻
+N
N
21a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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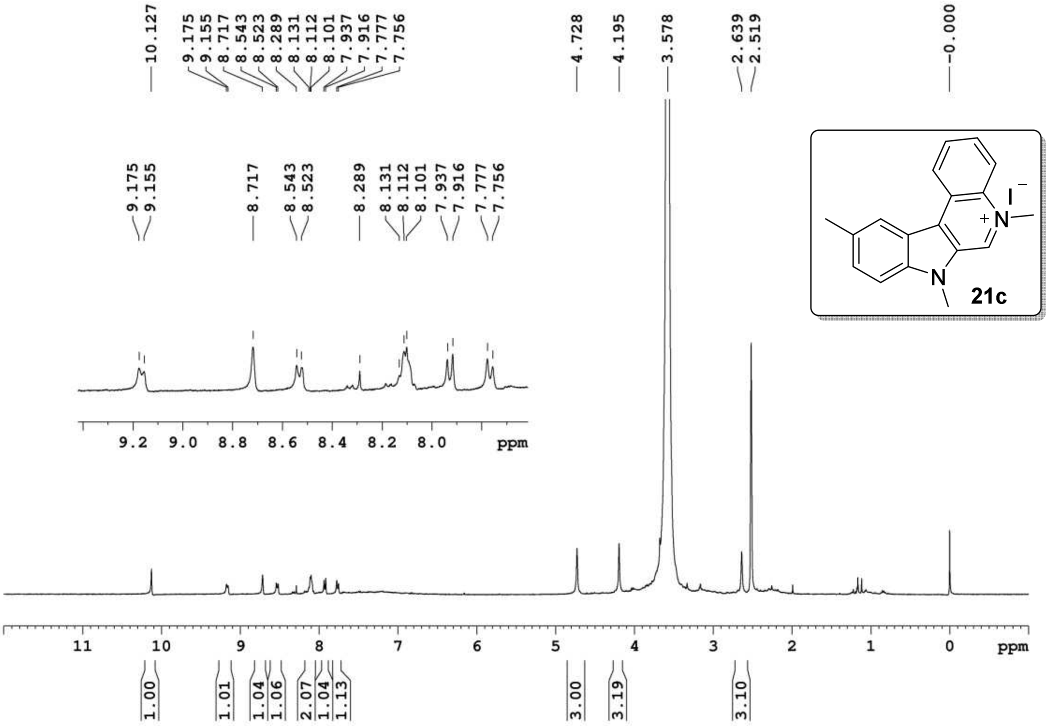
131.16
129.90
129.84
125.02
124.39
122.60
119.61
111.83
45.87
45.67
39.94
39.73
39.52
39.31
39.10
30.31
I⁻
+N
N
21a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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9.155
8.717
8.543
8.523
8.289
8.131
8.112
8.101
7.937
7.916
7.777
7.756
4.728
4.195
3.578
2.639
2.519
-0.000
9.2 9.0 8.8 8.6 8.4 8.2 8.0 ppm
I⁻
+N
N
21c
11 10 9 8 7 6 5 4 3 2 1 0 ppm
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1.01
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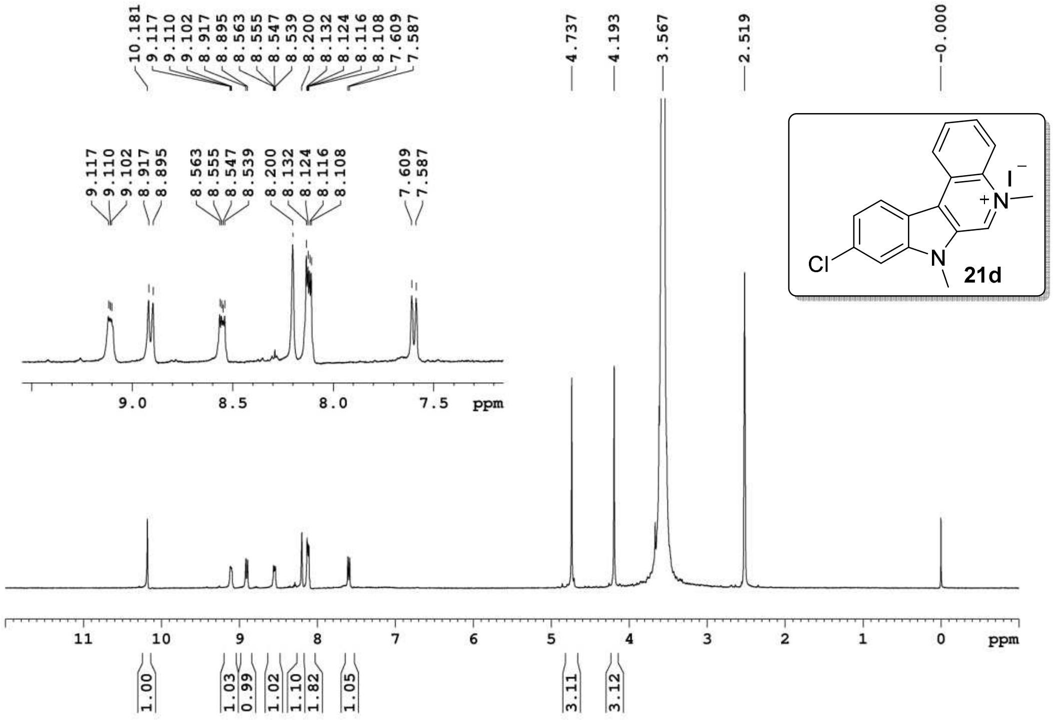
1.13
3.00
3.19
3.10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8.563
8.555
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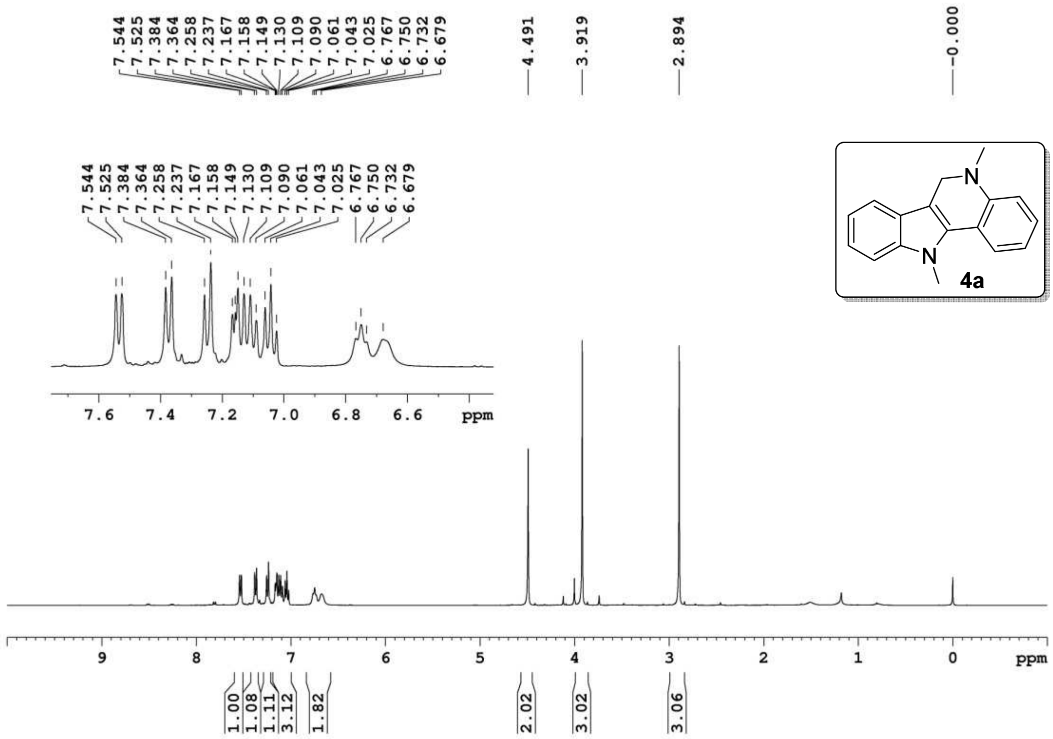
8.539
8.200
8.132
8.124
8.116
8.108
7.609
7.587
4.737
4.193
3.567
2.519
-0.000
9.0
8.5
8.0
7.5
ppm
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.03
0.99
1.02
1.10
1.82
1.05
3.11
3.12
Cl
N
+N
I⁻
21d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7.364
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7.158
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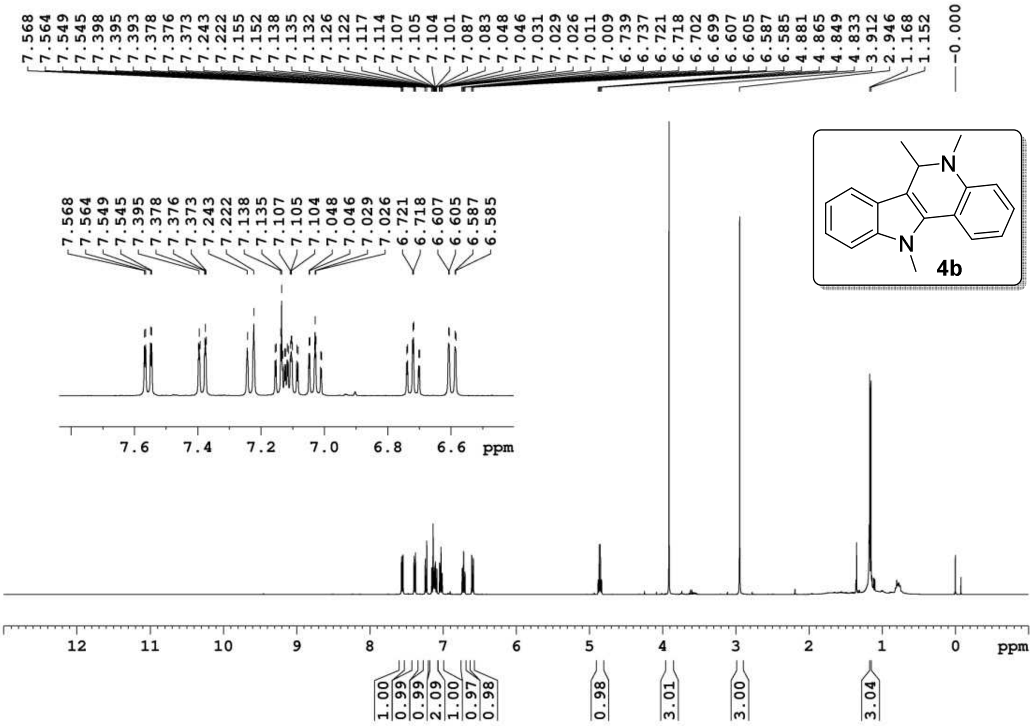
7.130
7.109
7.090
7.061
7.043
7.025
6.767
6.750
6.732
6.679
4.491
3.919
2.894
-0.000
7.6
7.4
7.2
7.0
6.8
6.6
ppm
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.08
1.11
3.12
1.82
2.02
3.02
3.06
N
N
4a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7.393
7.378
7.376
7.373
7.243
7.222
7.155
7.152
7.138
7.135
7.132
7.126
7.122
7.117
7.114
7.107
7.105
7.104
7.101
7.087
7.083
7.048
7.046
7.031
7.029
7.026
7.011
7.009
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6.605
6.587
6.585
4.881
4.865
4.849
4.833
3.912
2.946
1.168
1.152
-0.000
N
N
4b
7.6
7.4
7.2
7.0
6.8
6.6
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.99
0.99
2.09
1.00
0.97
0.98
0.98
3.01
3.00
3.04

Chapter 3

One pot Wittig reaction, reductive cyclization, hydrolysis and decarboxylation: Route to indoles from *o*-nitrobenzaldehydes

3.1: Introduction

The indole nucleus is ubiquitously found in a large number of naturally occurring heterocycles. Moreover, it is an important part of a wide variety of biologically active molecules. Indole containing compounds are found to exhibit antimicrobial, antibacterial, antiinflammatory, antitumor, anticancer etc. properties.[1] Some of these molecules are used as drugs in pharmaceutical industries. It is found that alkyl substituted indoles is present as an active ingredient in many drugs available in the market. For example, some of 2-methyl substituted indoles such as oxypertine **A** is an antipsychotic agent, indomethacin 10 **B** is a nonsteroidal anti-inflammatory agent and paraadoline 12 **C** is an anti-alazaric agent (Fig. 1).[1d]

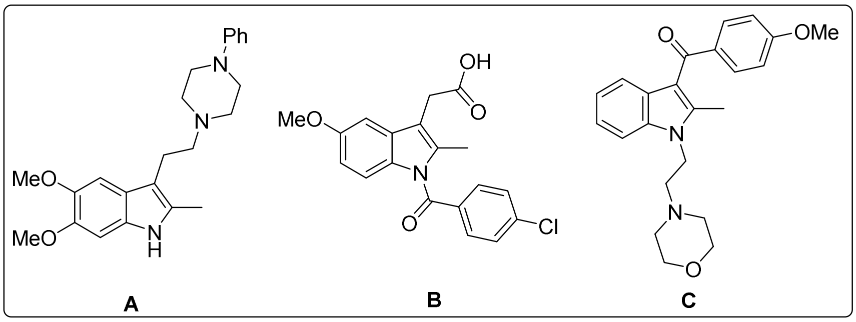


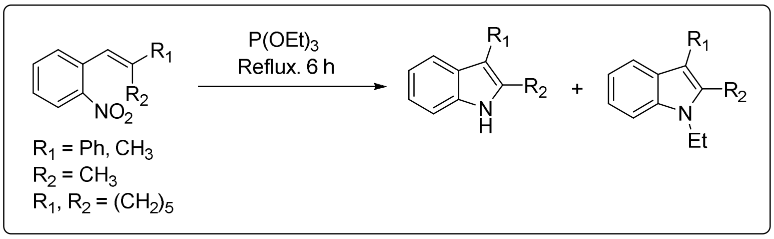
Figure 1: Drugs containing 2-methyl-1*H*-indole

Indole scaffold due to its potential pharmacological activities has remained the target of research for developing methodologies for its synthesis. A large number of methods have been accomplished and the methods are reviewed several times.[2] Over the years, several powerful strategies, including metal catalyzed cross coupling reactions have been developed for this ring system. Moreover, recently C-H functionalization has attracted much interest amongst synthetic organic chemists.[3-4] The C-H insertion could be broadly classified as i) nitrene insertion in C-H bond, ii) carbene insertion in C-H bond, iii) coupling of two sp2 carbon centers, iv) transition metal mediated C-H amination and v) other methods. [2g] This chapter focuses on nitrene type insertion on C-H bond from nitro intermediates.

3.2: Literature Reported Methods

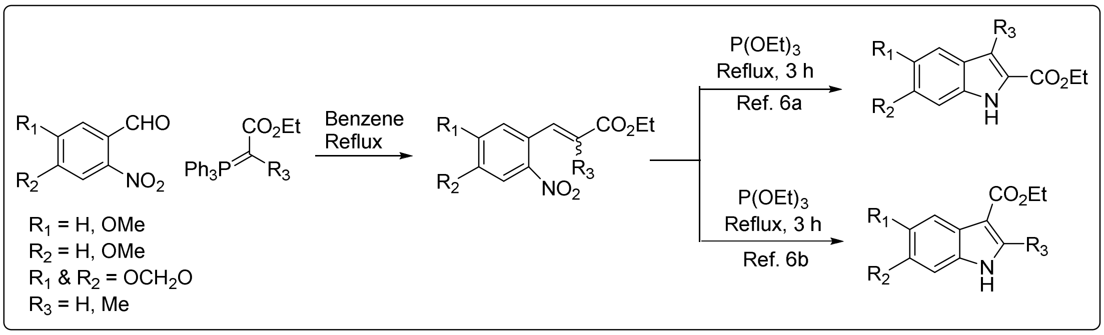
Described below are the reported methods for the synthesis of indole nucleus *via* nitrene intermediates derived from nitrophenyl, *o*-nitro cinnamates or nitro styrene type derivatives.

The C-H insertion through nitrene intermediates was developed by Cadogan, Sundberg and Hessienberger.[5] Cadogan's initial studies in 1965 utilized triethyl phosphite as a reagent for the reductive cyclization leading to indoles along with *N*-ethyl indoles in minor amounts.[5a]


P(OEt)3
Reflux. 6 h
R1
R2
NO2
N
H
Et
R1 = Ph, CH3
R2 = CH3
R1, R2 = (CH2)5

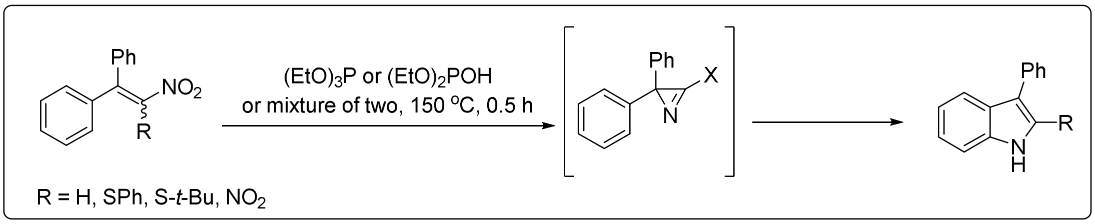
Scheme 1

Mali *et al.* [6a] in the year 1984 showed that the yield to 2-carboethoxy indole could be increased when 5 fold excess of triethyl phosphite was used for reaction. In the same paper the authors synthesized tri-substituted Wittig product which on reductive cyclization gives ethyl 3-methyl-1*H*-indole-2-carboxylates *via* migration of the methyl group (Scheme 2). Later carefully conducted study by the same group in the year 1987 revealed that it is not the methyl but the carboethoxy group that migrates to give ethyl 2-methyl-1*H* -indole-3-carboxylates.[6b]


CHO
NO2
CO2Et
Ph3P
R3
Benzene
Reflux
P(OEt)3
Reflux, 3 h
Ref. 6a
Ref. 6b
R1 = H, OMe
R2 = H, OMe
R1 & R2 = OCH2O
R3 = H, Me

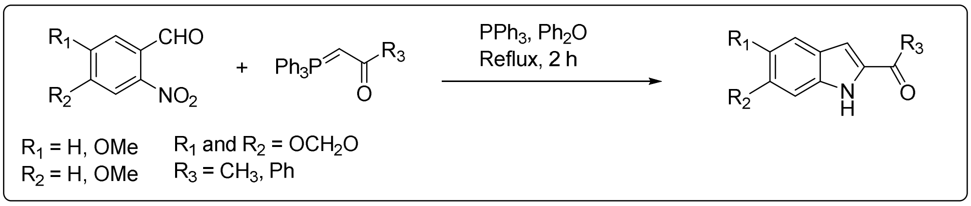
Scheme 2

Russell *et al.* in 1991 created an alternative route using aryl substituted nitro alkenes under reductive cycliszation with phosphites to yield indoles, where in authors presumed an unstable 2*H*-azirine intermediate to be formed which collapses to give indole moiety under the reaction conditions (Scheme 3).[6c]


Ph
NO2
R
(EtO)3P or (EtO)2POH
or mixture of two, 150 °C, 0.5 h
X
N
H
R = H, SPh, S-t-Bu, NO2

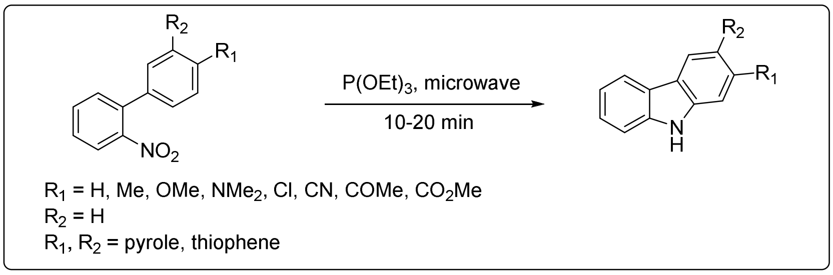
Scheme 3

Our group later in year 2000 first time reported efficient use of triphenyl phosphine in refluxing diphenyl ether for successful synthesis of 2-acyl indoles and 2-benzoylindole. 4-(2-Nitrophenyl)but-3-en-2-one and 2-nitrochalcones were synthesized using Wittig reaction on nitrobenzaldehydes involving stable phosphoranes which were then subjected to reductive cyclization (Scheme 4).[6d] The method has an advantage that the side product of *N*-ethyl derivative obtained using triethyl phosphite was avoided.


R1
CHO
R2
NO2
+
Ph3P
R3
O
PPh3, Ph2O
Reflux, 2 h
N
H
R1 = H, OMe
R2 = H, OMe
R1 and R2 = OCH2O
R3 = CH3, Ph

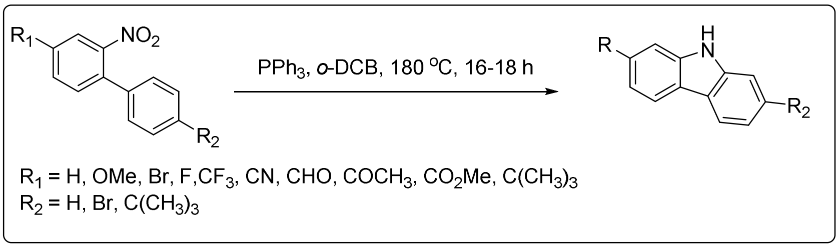
Scheme 4

Dehaen *et al*. in the year 2005 used microwave conditions to get carbazoles from 2-nitro-1,1'-biphenyl under reductive cyclization with triethyl phosphite. [6e] The yields obtained were slightly lower as compared to normal heating reactions, but the time required for reactions was shortened considerably to just 10-20 minutes under microwave irradiation (Scheme 5). The authors synthesized carbazoles with different substituents in one of the benzene rings and also pyrrole and thiophene fused carbazoles.


R2
R1
NO2
P(OEt)3, microwave
10-20 min
N
H
R1 = H, Me, OMe, NMe2, Cl, CN, COMe, CO2Me
R2 = H
R1, R2 = pyrole, thiophene

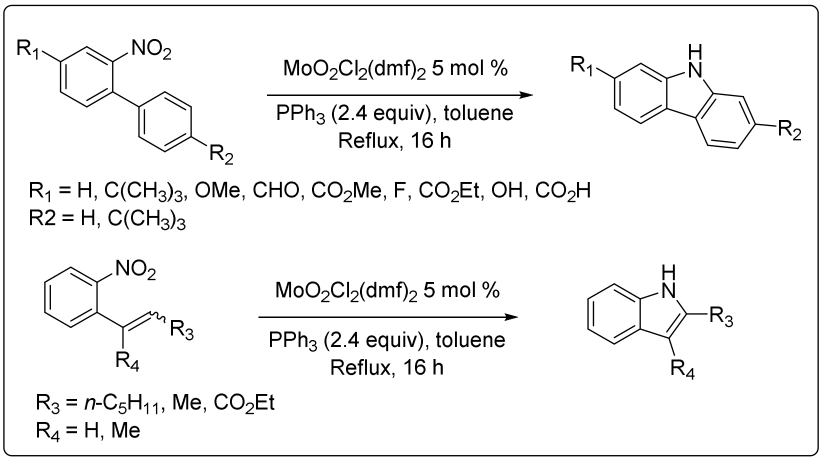
Scheme 5

Later Freeman *et al.* [7a] in 2005 carried out nitrene mediated cyclisation using triphenyl phosphine in refluxing *o*-dichlorobenzene at 180 °C to synthesize carbazoles (Scheme 6). The reaction period was observed to be longer of 16-18 h as compared to the reaction conditions from method reported from our laboratory which took 2-3 h for completion using triphenyl phosphine.


R1
NO2
R2
PPh3, o-DCB, 180 °C, 16-18 h
R
H
N
R2
R1 = H, OMe, Br, F,CF3, CN, CHO, COCH3, CO2Me, C(CH3)3
R2 = H, Br, C(CH3)3

Scheme 6

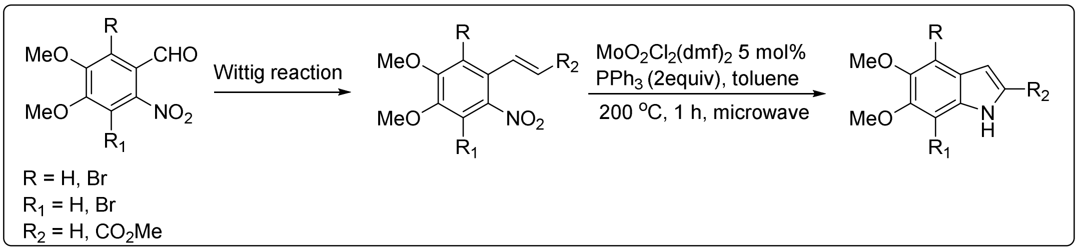
Further decrease in temperature to generate nitrene at lower temperature with triphenyl phosphine was reported by Sanz *et al.* in 2007 which made use of dioxomolybdenium(VI) catalyst [7b] in refluxing toluene. The process was employed to synthesize indoles and carbazoles from corresponding nitro intermediates in relatively good yields. However, this procedure like Freeman's protocol required longer time of 16-18 h for completion (Scheme 7). In the same paper the authors demonstrated the use of polymer bound triphenyl phosphine instead of free triphenyl phosphine for reductive cyclization. The conversion was found almost similar to triphenyl phosphine, but time required for the reaction was longer. The use of polymer bounded phosphine comes with the advantage of easy isolation of product as phosphine oxide stays bound with polymeric support and can be separated by simple filtration.



R_1
NO_2
R_2
$MoO_2Cl_2(dmf)_2$ 5 mol %
PPh_3 (2.4 equiv), toluene
Reflux, 16 h
H
N
$R_1 = H, C(CH_3)_3, OMe, CHO, CO_2Me, F, CO_2Et, OH, CO_2H$
$R2 = H, C(CH_3)_3$
R_3
R_4
$R_3 = n\text{-}C_5H_{11}, Me, CO_2Et$
$R_4 = H, Me$

Scheme 7

Recently in the year 2011 Chai *et al.* [7c] synthesized bromo substituted 5,6-dimethoxyindole from *o*-nitrostilbenes. Nitrostilbenes are in turn obtained from corresponding *o*-nitrobenzaldehydes followed by treating with Sanz's dioxomolybdenium(VI) catalyst using triphenyl phosphine under microwave conditions to give indole derivatives (Scheme 8).

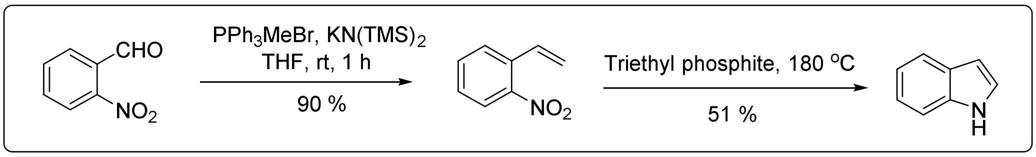


R
MeO
CHO
MeO
NO_2
R_1
Wittig reaction
R_2
$MoO_2Cl_2(dmf)_2$ 5 mol%
PPh_3 (2equiv), toluene
200 °C, 1 h, microwave
N
H
R = H, Br
R_1 = H, Br
$R_2 = H, CO_2Me$

Scheme 8

Nishida *et al.* [7d] carried out Wittig reaction on 2-nitrobenzaldehyde with triphenylmethyl bromide using Potassium bis(trimethylsilyl)amide as the base, to give 2-nitrostyrene in 90 %

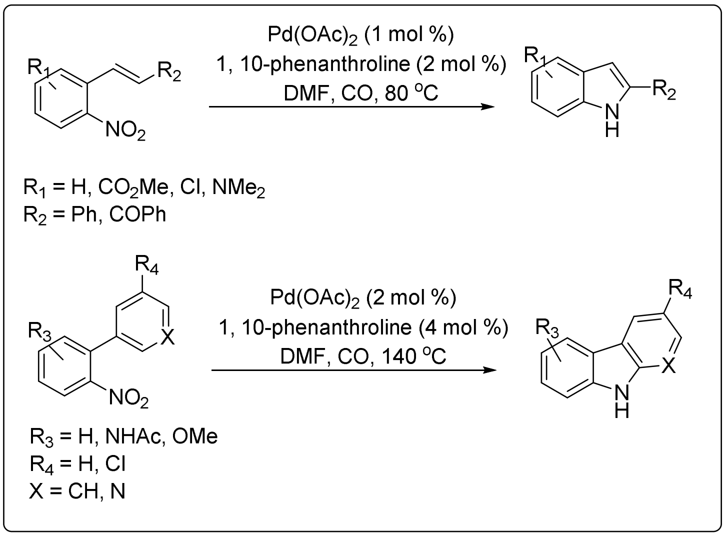
yield. Recently Minguez *et al.* [7e] converted 2-nitrostyrenes to corresponding indoles *via* refluxing in triethyl phosphite. The yield for conversion of 2-nitrostyrene to indole was 51 %. The overall yield over two steps was found to be 46 % with two isolation steps.


CHO
NO2
PPh3MeBr, KN(TMS)2
THF, rt, 1 h
90 %
NO2
Triethyl phosphite, 180 °C
51 %
N
H

Scheme 9

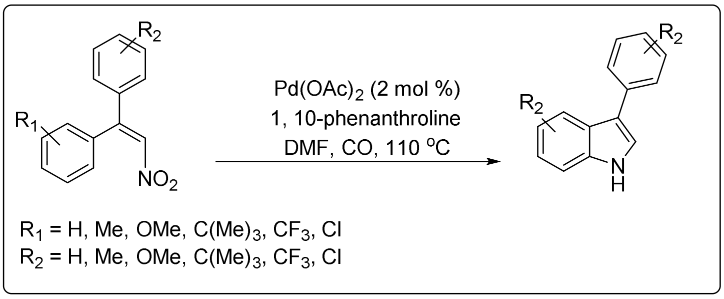
Apart from nitrene insertion by phosphorous reagent, synthesis of indole is achieved using carbon monoxide as reducing agent for cyclisation *via* C-H insertion from nitro intermediates. The advantage of using carbon monoxide as reducing agent over the triphenyl phosphine method is that it avoids the additional step of separating the by-product triphenyl phosphine oxide. However, one needs a special setup to handle carbon monoxide. Two different mechanisms are suggested for this transformation, one *via* nitrene insertion and the other by electrocyclisation. [2g] Here are few selected examples of carbon monoxide used as reducing agent for cyclisation of nitro intermediates to indoles.

Davies *et al.* synthesized indoles and carbazoles ring system from corresponding *o*-nitrostilbeines or *o*-nitrobiphenyls with carbon monoxide as reductant in presence of palladium acetate and suitable ligands like 1,10-phenanthroline [8a-b] (Scheme 10).


R1
R2
NO2
Pd(OAc)2 (1 mol %)
1, 10-phenanthroline (2 mol %)
DMF, CO, 80 °C
R1
R2
N
H
R1 = H, CO2Me, Cl, NMe2
R2 = Ph, COPh
R4
R3
X
NO2
Pd(OAc)2 (2 mol %)
1, 10-phenanthroline (4 mol %)
DMF, CO, 140 °C
R4
R3
X
N
H
R3 = H, NHAc, OMe
R4 = H, Cl
X = CH, N

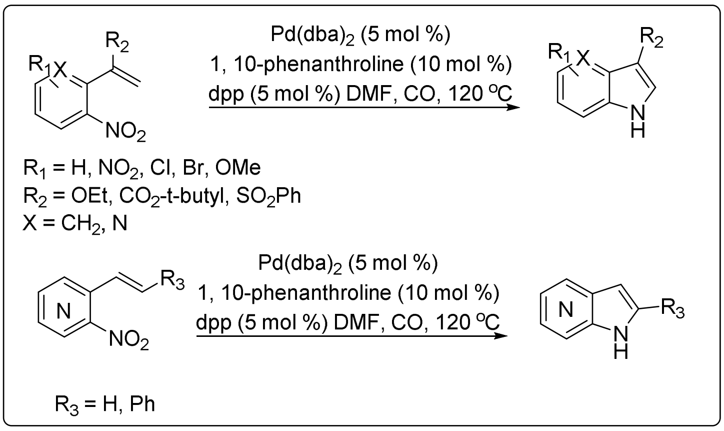
Scheme 10

Dong and co-workers used the same conditions of Davies to cyclize nitroalkenes to give substituted 3-aryl indoles in good yields [8c] (Scheme 11).


Pd(OAc)$_2$ (2 mol %)
1, 10-phenanthroline
DMF, CO, 110 °C
R$_1$
R$_2$
NO$_2$
N
H
R$_1$ = H, Me, OMe, C(Me)$_3$, CF$_3$, Cl
R$_2$ = H, Me, OMe, C(Me)$_3$, CF$_3$, Cl

Scheme 11

Soderberg *et al.* [8d-g] have exploited this reductive cyclization with carbon monoxide to fetch various indole and azaindole derivatives (Scheme 12).


Pd(dba)$_2$ (5 mol %)
1, 10-phenanthroline (10 mol %)
dpp (5 mol %) DMF, CO, 120 °C
R$_1$
R$_2$
X
NO$_2$
N
H
R$_1$ = H, NO$_2$, Cl, Br, OMe
R$_2$ = OEt, CO$_2$-t-butyl, SO$_2$Ph
X = CH$_2$, N
Pd(dba)$_2$ (5 mol %)
1, 10-phenanthroline (10 mol %)
dpp (5 mol %) DMF, CO, 120 °C
R$_3$
N
NO$_2$
R$_3$ = H, Ph

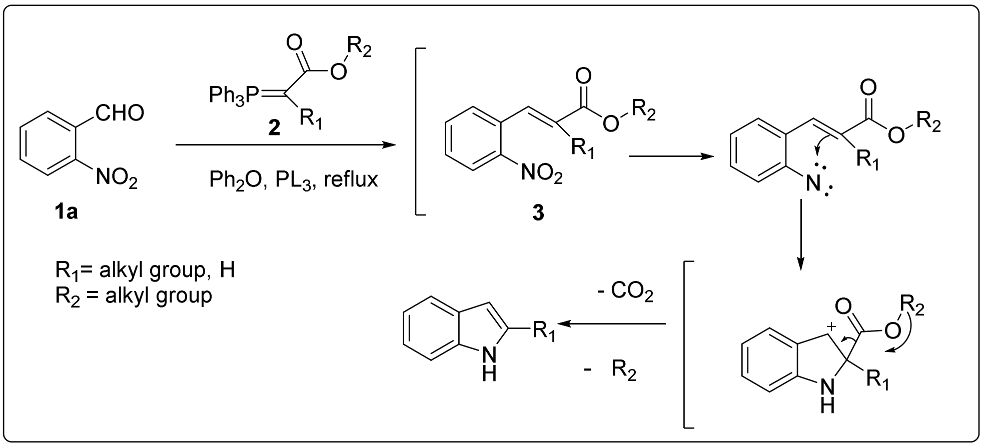
Scheme 12

Continuing our interest in reductive cyclization for the synthesis of nitrogen heterocycles, [9] we report herein a one pot method for the synthesis of 2,3-unsubstituted indoles, and 2-alkyl indoles using stable Wittig reagents.

3.3: Results and discussion

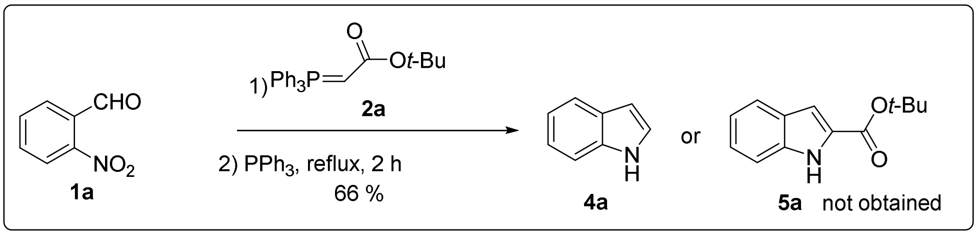
Indoles and 2-substituted indoles can be conveniently prepared by a 2-step synthesis using Cadogan's method wherein first 2-vinyl nitrobenzenes are prepared from 2-nitrobenzaldehydes *via* appropriate unstable Wittig reagent under anhydrous conditions and then reductively cyclized to get the required indoles. However, using triethyl phosphite generates some amount of *N*-ethylated indoles as by-product. Secondly, use of unstabilized phosphonium salts for Wittig reaction normally requires dry reaction conditions with a strong base to generate phosphorane from corresponding salt. In view of these difficulties we were encouraged to develop a more friendly method for the synthesis of indole from reaction condition which does not involve the problem of handling unstable Wittig reagents. It was envisaged that a similar Wittig reaction using an appropriate stable phosphorane followed by removal of the stabilizing group on the newly formed double bond would result in the desired 2-vinyl nitrobenzene with an additional advantage of eliminating the difficulties in handling unstabilized phosphorane. Our visualized synthetic strategy is presented in Scheme 13.

We expected that a stable Wittig reagent like **2** on reaction with *o*-nitrobenzaldehydes would provide the cinnamate ester **3** which during reductive cyclization could undergo hydrolysis and concurrent decarboxylation to provide directly 2-substituted indole in single step.



Scheme 13: Proposed reaction

To test this hypothesis, a mixture of *o*-nitrobenzaldehyde **1a** (1 equiv), phosphorane **2a** (1 equiv) and triphenyl phosphine (2.4 equiv) were refluxed in diphenyl ether for 2 h (Scheme 14). On column purification of the reaction mixture a solid compound was obtained which showed a broad peak at 3401 cm^{-1} accounting for N-H stretch, but no strong peak in the region 1650-1750 cm^{-1} in the IR spectrum indicating absence of any carbonyl unit in the solid. Further, analysis of ^{1}H NMR and ^{13}C NMR spectra confirmed the structure to be indole **4a** and not *tert*-butyl-1*H*-indole-2-carboxylate **5a**.



Scheme 14

Spectral dat of 1*H*-indole (4a):

IR (KBr): $\tilde{\nu}$ = 3401, 3096, 3043, 1496, 1454, 1338, 744 cm^{-1}.

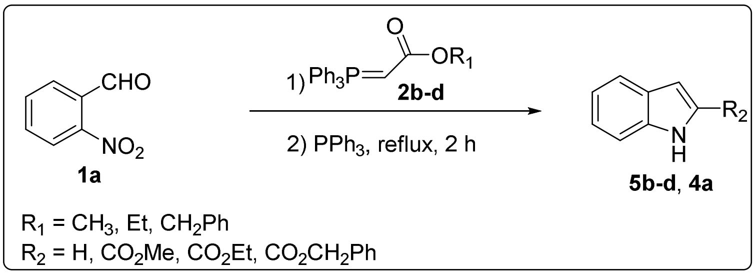
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.07 (brs, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.17-7.10 (m, 1H), 7.05 (t, *J* = 7.6 Hz, 1H) 6.49 (s, 1H).

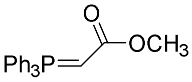
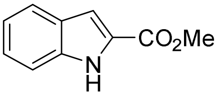
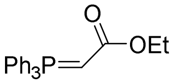
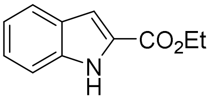
^{13}C NMR (100 MHz, CDCl$_3$): δ 135.8 (C), 127.9 (C), 124.2 (CH), 122.0 (CH), 120.8 (CH), 119.9 (CH), 111.1 (CH), 102.6 (CH).

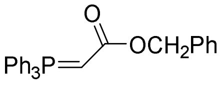
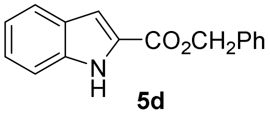
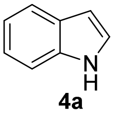
This confirmed that under the reaction conditions, four steps occurred in one pot viz; Wittig reaction between phosphorane **2a** and nitrobenzaldehyde **1a**, followed by nitrene mediated cyclization to form indole core, hydrolysis of the ester and finally decarboxylation to give indole **4a** as the final compound in 66 % yield.

Having obtained compound **4a**, we next investigated whether easily available stable phosphorane **2b-d** could give similar product under these reaction conditions. It was observed that when phosphorane **2b** reacted with **1a,** the product obtained showed a broad peak at 3344 cm^{-1} and 1691 cm^{-1} in IR spectrum accounting for a N-H stretch and carbonyl of ester. Further, the compound was confirmed to be methyl 1*H*-indole-2-carboxylate **5b** based on ^{1}H NMR and ^{13}C NMR spectra (table 1, entry 1). Phosphorane **2c,** reacted similarly to give ethyl 1*H*-indole-2-carboxylate **5c** in 83 % yield (table 1, entry 2). Interestingly, reaction of phosphorane **2d** gave two distinct compounds on isolation. The polar compound showed two strong bands, one broad peak at 3342 cm^{-1} and a sharp peak at 1693 cm^{-1} in its IR spectrum. While, the other less polar compound showed a broad band at 3401 cm^{-1} and no peak corresponding to carbonyl stretch in its IR spectrum. Further on ^{1}H NMR and ^{13}C NMR spectral analysis, these compounds were identified to be benzyl 1*H*-indole-2-carboxylate **5d** and indole **4a** (table 1, entry 3).

Table 1. Treatment of phosphorane **2b-d** with **1a** under one-pot condition.

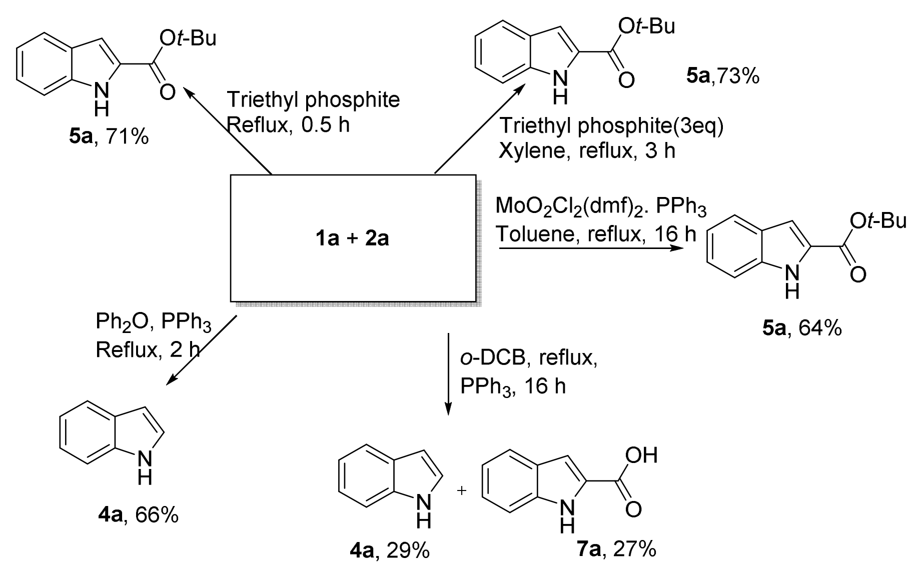


Sr. No.	Phosphorane 2b-d	Product 5b-d, 4a	% Yield 5b-d, 4a [a]
1	 2b	 5b	82
2	 2c	 5c	83

3	 **2d**	 **5d**	34
		 **4a**	29

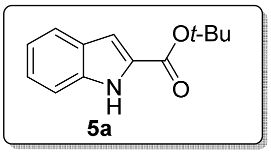
[a] isolated yields

After confirming that only phosphorane **2a** gives the required product **4a** in good yield, reaction was then attempted using different reaction conditions employed in the literature for reductive cyclization of aromatic nitro compounds with phosphorous ligands (Scheme 15). The Cadogan's method in refluxing triethyl phosphite showed complete conversion of starting in just 30 minutes, resulting in ester **5a** in 71% yield. There was a marginal increase seen in the yield of **5a** when reaction with triethyl phosphite was carried out in refluxing xylene, however 3 hours were required for completion of the reaction. Sanz's condition with molybdenum catalyst allowed the reaction to be conducted at a lower temperature, but longer reaction time (16 h) was required and yield of **5a** obtained was also less. Freeman's method of reductive cyclization with triphenyl phosphine in refluxing *o*-dichlorobenzene resulted in a mixture of indole **4a** in 29% yield along with other polar compound **7a**. The IR spectrum of **7a** showed a broad band in the region of 2700-3500 cm^{-1} and carbonyl stretch at 1662 cm^{-1} indicating it to be indole-2-carboxylic acid. Compound **7a** was further confirmed by ^{1}H NMR and ^{13}C NMR spectra.


Ot-Bu
5a, 71%
Triethyl phosphite
Reflux, 0.5 h
Ot-Bu
5a,73%
Triethyl phosphite(3eq)
Xylene, reflux, 3 h
1a + 2a
MoO2Cl2(dmf)2. PPh3
Toluene, reflux, 16 h
Ot-Bu
5a, 64%
Ph2O, PPh3
Reflux, 2 h
4a, 66%
o-DCB, reflux,
PPh3, 16 h
OH
4a, 29%
7a, 27%

Scheme 15. Reductive cyclisation condition.

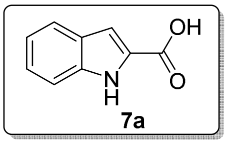
Spectral data of *tert*-butyl 1*H*-indole-2-carboxylate (5a):



5a

IR (KBr): $\tilde{\nu}$ = 3408, 3051, 2947, 1708, 1581, 1245, 1091, 742 cm^{-1}.
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.92 (br s, 1H), 7.60 (d, J = 8.0 Hz, 0.4 Hz, 1H), 7.34 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.23 (dt, J = 8.0 Hz, 0.8 Hz, 1H), 7.08-7.04 (m, 2H).
^{13}C NMR (100 MHz, CDCl$_3$): δ 162.0 (C), 137.1 (C), 129.0 (C), 127.6 (C), 125.1 (CH), 122.5 (CH), 120.6 (CH), 112.1 (CH), 108.3 (CH), 81.9 (C), 28.5 (CH$_3$).

Spectral data of 1*H*-indole-2-carboxylic acid (7a):

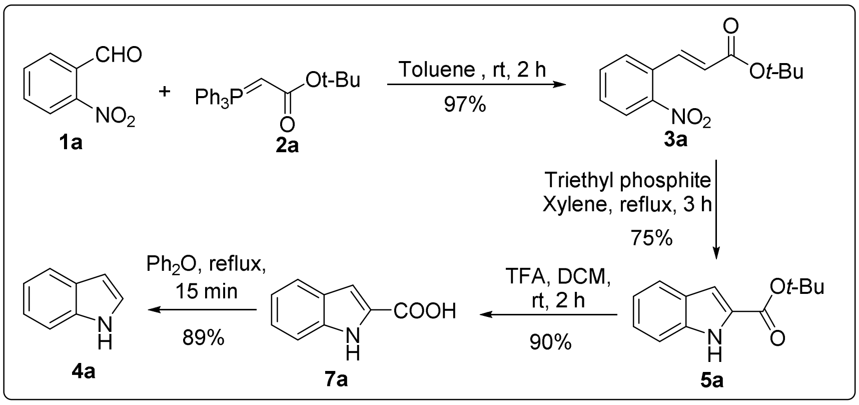


7a

IR (KBr): $\tilde{\nu}$ = 3200, 1662, 1515, 1240, 1193, 738 cm^{-1}.
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.88 (br s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.40-7.28 (m, 3H), 7.10 (dt, J = 8.0 Hz, 1.2 Hz, 1H), 5.50 (br s, 1H).
^{13}C NMR (100 MHz, CDCl$_3$): δ 166.2 (C), 137.3 (C), 127.5 (C), 126.2 (C), 126.1 (CH), 122.9 (CH), 121.1 (CH), 110.8 (CH).

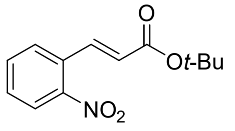
As under only one reaction condition (PPh$_3$, Ph$_2$O, reflux 2 h) indole **4a,** was obtained selectively, it indicated that for getting complete hydrolysis, decarboxylation more than 160 ^{o}C temperatures is needed.

After selecting the phosphorane **2a** as reactant we compared the yield of this one pot protocol with a stepwise reaction sequence with isolation of product at each step (Scheme 16). Cinnamate ester **3a** was thus isolated from the reaction of *o*-nitrobenzaldehyde **1a** and phosphorane **2a** under Wittig reaction in 97% yield. Since the yield of reductive cyclization with triethyl phosphite in xylene gave good (Scheme 14) yield of indole ester **5a**, **3a** was subjected to this reaction condition to get 75% yield of **5a**. Hydrolysis of the ester with TFA gave indole-2-carboxylic acid **7a** in 90 % yield, while decarboxylation furnished indole **4a** in 89% yield.



Scheme 16. Stepwise approach for conversion of **1a** to **4a** with phosphorane **2a**.

Spectral data of *tert*-butyl (*E*)-3-(2-nitrophenyl)acrylate (3a):



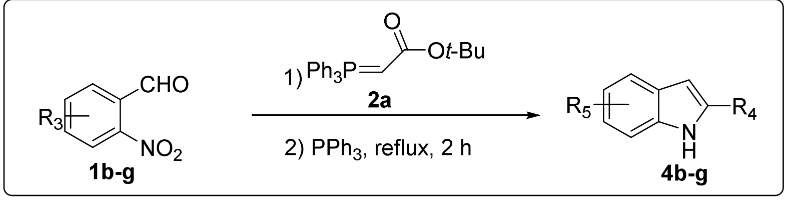
3a

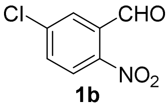
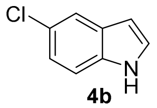
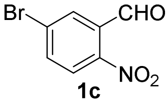
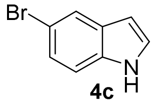
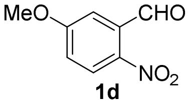
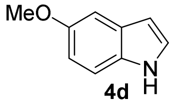
IR (KBr): $\tilde{\nu}$ = 3070, 2981, 1701, 1525, 1342, 1153, 983, 790 cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 7.95 – 7.91 (m, 2H), 7.56 (d, *J* = 3.6 Hz, 2H), 7.47 – 7.43 (m, 1H), 6.22 (d, *J* = 16.0 Hz, 1H), 1.46 (s, 9H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 161.1 (C), 148.3 (C), 138.7 (CH), 133.4 (C), 130.7 (C), 131.1 (CH), 129.1 (CH), 125.3 (CH), 124.9 (CH), 81.2 (C), 28.1 (CH$_3$).

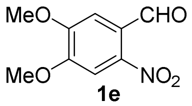
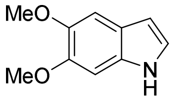
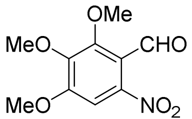
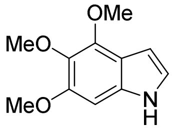
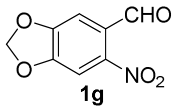
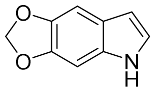
The overall yield of stepwise sequence was found to be 63%, which was lower than the yield obtained during one pot sequence. However, it also involved three chromatographic purification steps. This proved that the one pot protocol was a better method to synthesize indoles compared to the corresponding stepwise synthesis. This was also better than the two step approach of reductive cyclization of *o*-nitro styrene method in scheme 9 where two purification steps are involved.

This method was then explored on a variety of nitro benzaldehydes to obtain the corresponding indoles (See Table 2). Nitrobenzaldehydes with one, two, three methoxy groups and methylenedioxy substituent (**4d-4g**) could be easily converted to its corresponding indole derivatives in moderate yields. This method also furnished important 5-chloro-1*H*-indole **4b** and 5-bromo-1*H*-indole **4c** in 45 and 36% yields respectively.

Table 2. Synthesis of derivatives of 1*H*-indoles in one pot



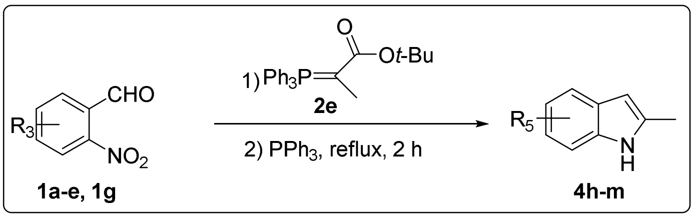
Entry	Starting 1b-g	Product 4b-g	% Yield of 4b-g [a]
1	 **1b**	 **4b**	45
2	 **1c**	 **4c**	41
3	 **1d**	 **4d**	46

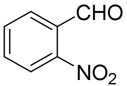
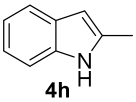
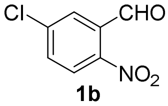
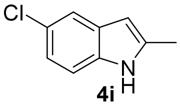
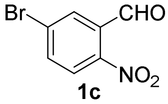
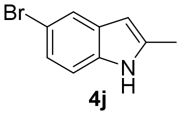
4	 **1e**	 **4e**	47
5	 **1f**	 **4f**	62
6	 **1g**	 **4g**	40

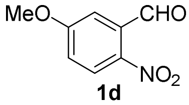
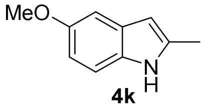
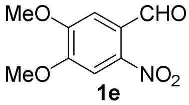
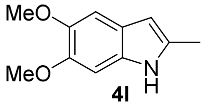
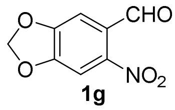
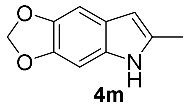
[a] isolated yields.

Phosphorane **2a** was then subjected to alkylation with methyl iodide to give methylated phosphorane **2e**. Carrying out the same reaction on above aldehydes with phosphorane **2e** gave the corresponding 2-methyl-1*H*-indoles derivatives (**4h-4m**) in yields slightly lower than their non alkylated analogues. Lower yields of 2-substituted derivative could be attributed to higher reactivity of 2-alkyl indoles compared to unsubstituted indoles.

Table 3. Synthesis of derivative of 2-methyl-1*H*-indole in one pot

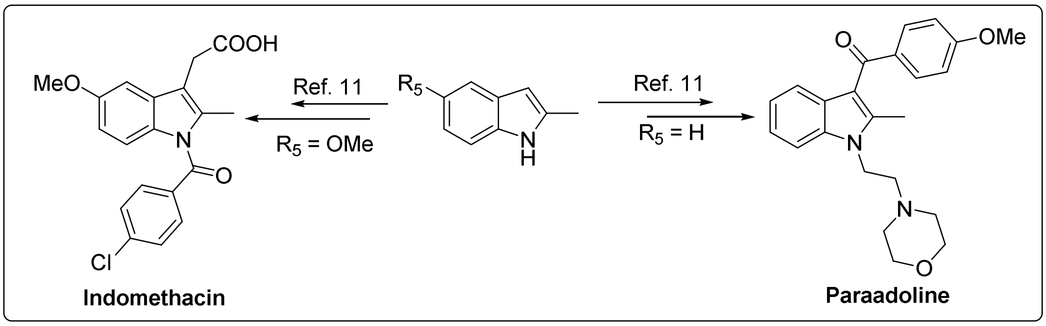


Entry	Starting 1a-g	Product 4h-n	% Yield of 4h-n [a]
1	 **1a**	 **4h**	38
2	 **1b**	 **4i**	42
3	 **1c**	 **4j**	40

4	 **1d**	 **4k**	43
5	 MeO CHO MeO NO_2 **1e**	 **4l**	62
7	 **1g**	 **4m**	31

[a] isolated yields.

These methyl indoles can serve as important intermediates for preparing pharmaceutically active compounds. The synthetic utility of these 2-methyl indoles is known for synthesis of many of pharmaceutically active compounds [11] (Scheme 17). 5-Methoxy-2-methyl-1*H*-indole **4k** is used to synthesize indomethacin which is an antipsychotic agent. Similarly 2-methyl-1*H*-indole **4h** is used in the synthesis of parradoline which is an anti-alazaric agent.


COOH
MeO
N
O
Cl
Indomethacin
Ref. 11
R_5 = OMe
R_5
N
H
Ref. 11
R_5 = H
O
OMe
N
N
O
Paraadoline

Scheme 17. Application to bioactive compounds.

3.4: Conclusion

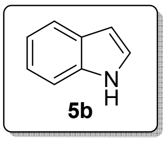
In conclusion, a practical metal free synthesis of various substituted indoles and 2-methyl indoles were achieved in one pot from easily available substituted *o*-nitro benzaldehydes (**1a-g**) and stable phosphorane (**2a, 2e**). Advantages of this protocol are its ease of handling of substrates, short reaction time and no requirements of an inert atmosphere.

3.5: Experimental

General procedure for synthesis of indoles from nitrobenzaldehyde:

A 50 ml round bottom flask containing magnetic stir bar was charged with *o*-nitrobenzaldehydes (2 mmol), phosphorane (2.2 mmol), triphenyl phosphine (4.6 mmol) and diphenyl ether (10 mL) and heated at 260 °C. Reaction progress was monitored by TLC which showed complete conversion in 2-3 h. Reaction vessel was then cooled to room temperature and reaction mass was poured on silica column. The products were isolated by eluting with petroleum ether to 3:1 petroleum ether: ethyl acetate.

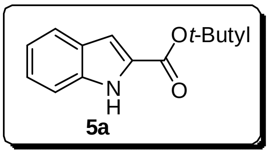
1*H*-indole (4a)



5b

Colorless solid, m. p. 51-52 °C. (lit. [10a] m.p. 51-52°C).

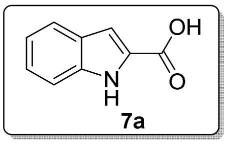
tert-Butyl 1*H*-indole-2-carboxylate (5a)



5a

Off white solid, m. p. 102-103 °C. (lit. [10b-c, i] m.p. 103-105 °C).

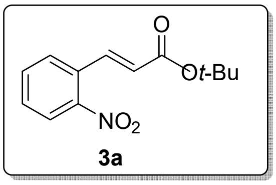
1*H*-Indole-2-carboxylic acid (7a)



7a

White solid, m. p. 204-206 °C. (lit. [10d] m.p. 207-206 °C).

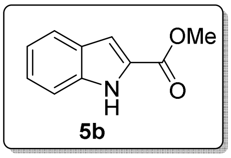
tert-Butyl (*E*)-3-(2-nitrophenyl)acrylate (3a)



3a

Pale yellow solid, m. p. 66-68 °C. (lit. [10e,f-g] m.p. 69-70 °C).

Methyl 1*H*-indole-2-carboxylate (5b)



5b

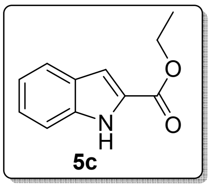
Off white solid, m. p. 142-143 °C. (lit. [10i, 12a-b] m.p. 145-147 °C).

IR (KBr): $\tilde{\nu}$ = 3344, 3035, 2952, 1691, 1524, 1244, 1192, 739 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.99 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.33 (dt, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.26 (d, *J* = 1.2 Hz, 1H), 7.18 (dt, *J* = 8.0 Hz, 0.8 Hz, 1H), 3.98 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 162.8 (C), 137.1 (C), 127.5 (C), 127.1 (C), 125.4 (CH), 122.7 (CH), 120.8 (CH), 112.0 (CH), 108.9 (CH), 52.1 (CH$_3$).

Ethyl 1*H*-indole-2-carboxylate (5c)


5c

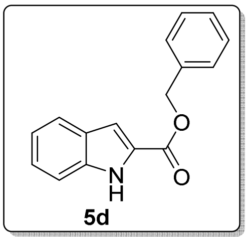
Off white solid, m. p. 120-122 °C. (lit. [10b, 10h-i] m.p. 122-125 °C).

IR (KBr): $\tilde{\nu}$ = 3345, 3038, 2955, 1692, 1520, 1520, 1242, 1191, cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.56 (s, 1H), 7.67 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.42 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.30 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 7.24 (t, J = 0.8 Hz, 1H), 7.13 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 4.42 (q, J = 7.6 Hz, 2H), 1.41 (t, J = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 162.5 (C), 137.2 (C), 127.1 (C), 125.3 (CH), 122.6 (CH), 120.8 (CH), 112.1 (CH), 108.7 (CH), 61.2 (CH$_2$), 14.5 (CH$_3$).

Benzyl 1*H*-indole-2-carboxylate (5d)


5d

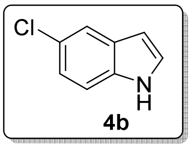
Off white solid, m. p. 133-135 °C. (lit. [10i, 12c] m.p. 135-136 °C).

IR (KBr): $\tilde{\nu}$ = 3342, 3034, 2951, 1693, 1525, 1247, 1197, 736 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.05 (s, 1H), 7.68 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.46 (dd, J = 8.4 Hz, 1.6 Hz, 2H), 7.42-7.24 (m, 6H), 7.15 (dt, J = 8.0 Hz, 1.2 Hz, 1H), 5.39 (s, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 162.1 (C), 137.1 (C), 135.8 (C), 128.7 (CH), 128.5 (CH), 128.3 (CH), 127.5 (C), 127.1 (C), 125.6 (CH), 122.7 (CH), 120.9 (CH), 112.0 (CH), 109.3 (CH), 66.8 (CH$_2$).

5-Chloro-1*H*-indole (4b):


4b

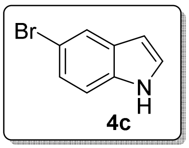
Colorless solid, m. p. 70-72 °C. (lit. [10a, 12d] m.p. 72-73 °C).

IR (KBr): $\tilde{\nu}$ = 3382, 3102, 3030, 1620, 1563, 1450, 1315, 802, 760 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.03 (br s, 1H), 7.51 (d, J = 1.2 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.09 – 7.03 (m, 3H), 6.39 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 131.1 (C), 127.9 (C), 124.5 (C), 124.3 (CH), 121.2 (CH), 119.0 (CH), 111.0 (CH), 101.3 (CH).

5-Bromo-1*H*-indole (4c):


4c

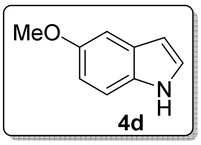
Colorless solid, m. p. 92-94 °C. (lit. [12e] m.p. 90-92 °C).

IR (KBr): $\tilde{\nu}$ = 3384, 3102, 3030, 1621, 1563, 1452, 1312, 800 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.19 (br s, 1H), 7.77 (t, J = 0.8 Hz, 1H), 7.29-7.24 (m, 2H), 7.20 (t, J = 2.4 Hz, 1H), 6.50 (t, J = 2.0 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 134.4 (C), 129.6 (C), 125.4 (CH), 124.9 (CH), 123.2 (CH), 113.0 (C), 112.5 (CH), 102.3 (CH).

5-Methoxy-1*H*-indole (4d):



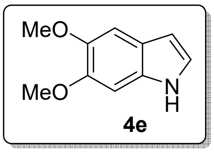
Colorless solid, m. p. 51-52 °C. (lit. [12d] m.p. 53-54 °C).

IR (KBr): $\tilde{\nu}$ = 3352, 3100, 3028, 1625, 1564, 1458, 1310, 798 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.12 (br s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 2.0 Hz, 1H), 7.18 (t, J = 2.8 Hz, 1H), 6.97 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 6.57 (s, 1H), 3.94 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 154.2 (C), 131.1 (C), 128.3 (C), 125.2 (CH), 112.4 (CH), 111.9 (CH), 102.4 (CH), 102.3 (CH) 56.0 (CH$_3$).

5, 6-Dimethoxy-1*H*-indole (4e):



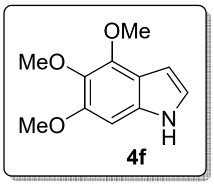
Colorless solid, m. p. 150-152 °C. (lit. [13a] m.p. 155-157 °C).

IR (KBr): $\tilde{\nu}$ = 3348, 3123, 3014, 1621, 1554, 1452, 1308, 792 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.11 (br s, 1H), 7.17 (s, 1H), 6.97 (t, J = 2.0 Hz, 1H), 6.75 (s, 1H), 6.35 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 146.9 (C), 145.0 (C), 130.2 (C), 122.9 (CH), 120.5 (C), 102.3 (CH), 102.2 (CH), 94.5 (CH), 56.3 (CH$_3$), 56.1 (CH$_3$).

4,5,6-Trimethoxy-1*H*-indole (4f):



White solid, m. p. 97-99 °C. (lit. [13b] m.p. 101 °C).

IR (KBr): $\tilde{\nu}$ = 3362, 3124, 3002, 1618, 1550, 1451, 1307, 791 cm^{-1}.

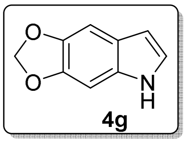
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.64 (br s, 1H), 6.92 (t, J = 2.8 Hz, 1H), 6.48-6.46 (m, 2H), 4.01 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 150.8 (C), 145.6 (C), 135.2 (C), 133.1 (C), 122.7 (CH), 107.2 (C), 99.8(CH), 89.7(CH), 61.6 (CH$_3$), 60.7 (CH$_3$), 56.1(CH$_3$).

5*H*-[1,3]Dioxolo[4,5-*f*]indole (4g):

Colorless solid, m. p. 106-108 °C. (lit. [13c] m.p. 109-110 °C).

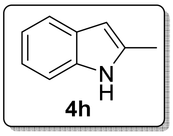
IR (KBr): $\tilde{\nu}$ = 3390, 3024, 2958, 1623, 1552, 1461, 1302, 790 cm^{-1}.


4g

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.95 (br s, 1H), 7.00 (t, J = 2.0 Hz, 1H), 6.94 (s, 1H), 6.77 (s, 1H), 6.35 (d, J = 2.0 Hz, 1H), 5.85 (s, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 144.9 (C), 143.1 (C), 130.7 (C), 122.8 (CH), 121.7 (C), 102.9 (CH), 100.6 (CH$_2$), 99.2 (CH), 91.9 (CH).

2-Methyl-1*H*-indole (4h):


4h

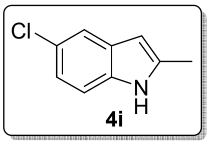
Colorless solid, m. p. 55-57 °C. (lit. [12d,13d] m.p. 56-58 °C).

IR (KBr): $\tilde{\nu}$ = 3510, 3053, 2923, 1623, 1482, 1258, 801, 750 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.72 (d, J = 7.6 Hz, 1H), 7.54 (s, 1H), 7.34 – 7.27 (m, 3H), 6.37 (s, 1H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 132.6 (C), 135.5 (C), 129.2 (CH), 121.1 (CH), 119.8 (2 X CH), 110.7 (CH), 100.3 (CH), 13.7 (CH$_3$).

5-Chloro-2-methyl-1*H*-indole (4i):


4i

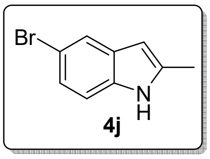
Colorless solid, m. p. 104-106 °C. (lit. [12d, 13d] m.p. 108-111 °C).

IR (KBr): $\tilde{\nu}$ = 3492, 3054, 2910, 1616, 1478, 1253, 804, 743 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.84 (br s, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.93 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.04 (s, 1H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 134.4 (C), 130.2 (C), 129.8 (C), 125.1 (C), 121.0 (CH), 119.0 (CH), 111.2 (CH), 100.0 (CH) 13.7 (CH$_3$).

5-Bromo-2-methyl-1*H*-indole (4j):


4j

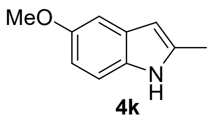
Colorless solid, m. p. 100-102 °C. (lit. [14a-b] m.p. 104-106 °C).

IR (KBr): $\tilde{\nu}$ = 3489, 3056, 2920, 1623, 1472, 1250, 800, 748 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.79 (br s, 1H), 7.55 (d, 2.0, 1H), 7.12-7.06 (m, 2H), 6.06 (s, 1H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 135.6 (C), 131.2 (C), 130.1 (C), 124.6 (CH), 121.2 (CH), 115.0 (CH), 113.2 (C), 101.6 (CH) 13.6 (CH$_3$).

5-Methoxy-2-methyl-1*H*-indole (4k):



4k

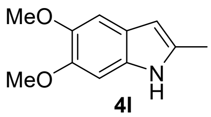
Colorless solid, m. p. 78-80 °C. (lit. [12c-d] m.p. 83-85 °C).

IR (KBr): $\tilde{\nu}$ = 3510, 3082, 2923, 1621, 1470, 1251, 790 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.73 (br s, 1H), 7.06 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 1.2 Hz, 1H), 6.68 (dd, J = 8.8 Hz, 1.2 Hz, 1H), 6.05 (s, 1H), 3.75 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 154.1 (C), 136.0 (C), 131.2 (C), 129.6 (C), 112.4 (CH), 110.9 (CH), 110.7 (CH), 102.0 (CH), 100.3 (CH), 55.9 (CH$_3$), 13.8 (CH$_3$).

5,6-Dimethoxy-2-methyl-1*H*-indole (4l):



4l

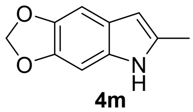
Colorless solid, m. p. 88-90 °C. (lit. [13c] m.p. 90-91 °C).

IR (KBr): $\tilde{\nu}$ = 3515, 3051, 2921, 1621, 1481, 1253, 820, 745 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.79 (s, 1H), 6.88 (s, 1H), 6.58 (s, 1H), 5.98 (s, 1H), 3.77 (s, 3H), 3.70 (s, 1H), 2.24 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 145.9 (C), 144.7 (C), 133.8 (C), 130.3 (C), 121.7 (C), 101.9 (CH), 99.8 (CH), 94.5 (CH), 56.3(CH$_3$), 56.2 (CH$_3$), 13.6 (CH$_3$).

6-Methyl-5*H*-[1,3]dioxolo[4,5-*f*]indole (4m):



4m

Colorless solid, m. p. 123-125 °C. (lit. [14c] m.p. 131-132°C).

IR (KBr): $\tilde{\nu}$ = 3521, 3043, 2912, 1614, 1483, 1251, 821, 760 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.60 (br s, 1H), 7.82 (s, 1H), 6.63 (s, 1H), 5.98 (s, 1H), 5.80 (s, 2H), 2.26 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 143.9 (C), 142.6 (C), 133.8 (C), 130.6 (C), 122.7 (C), 100.5 (CH), 100.4 (CH$_2$), 98.6 (CH), 91.7 (CH), 13.7 (CH$_3$).

3.6: References

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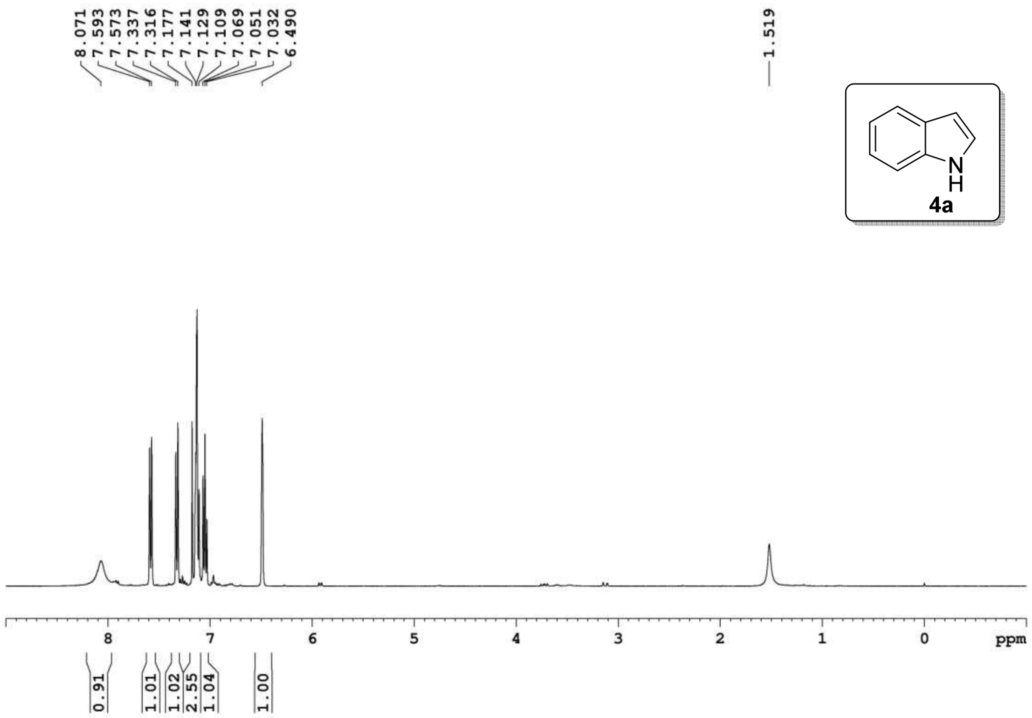
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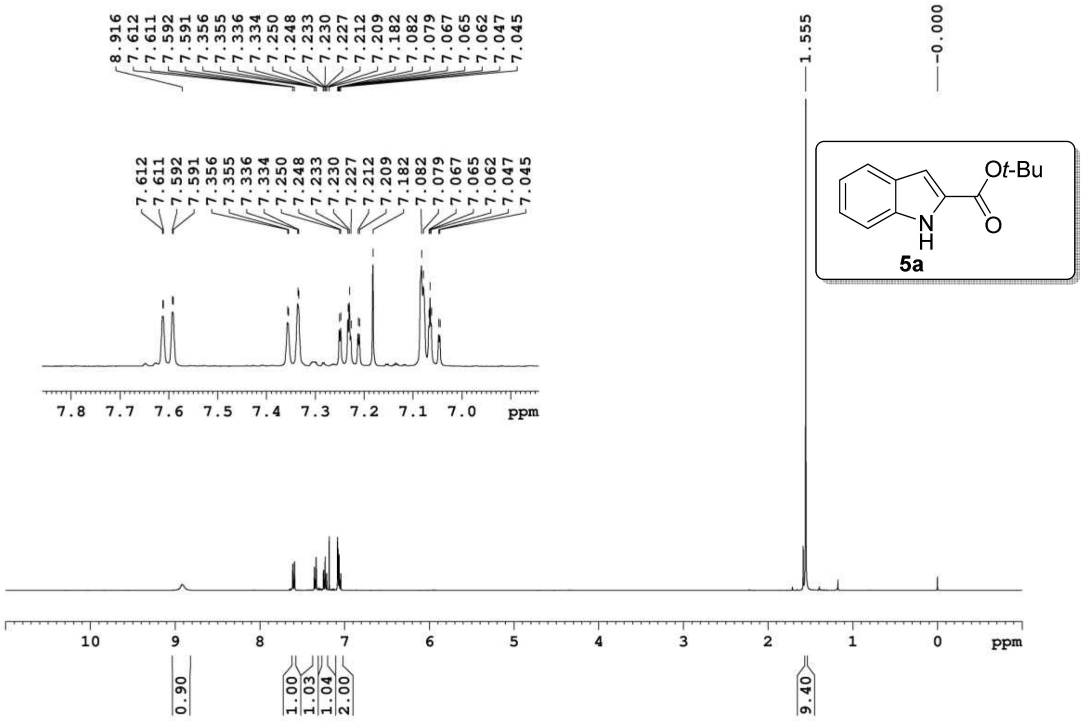
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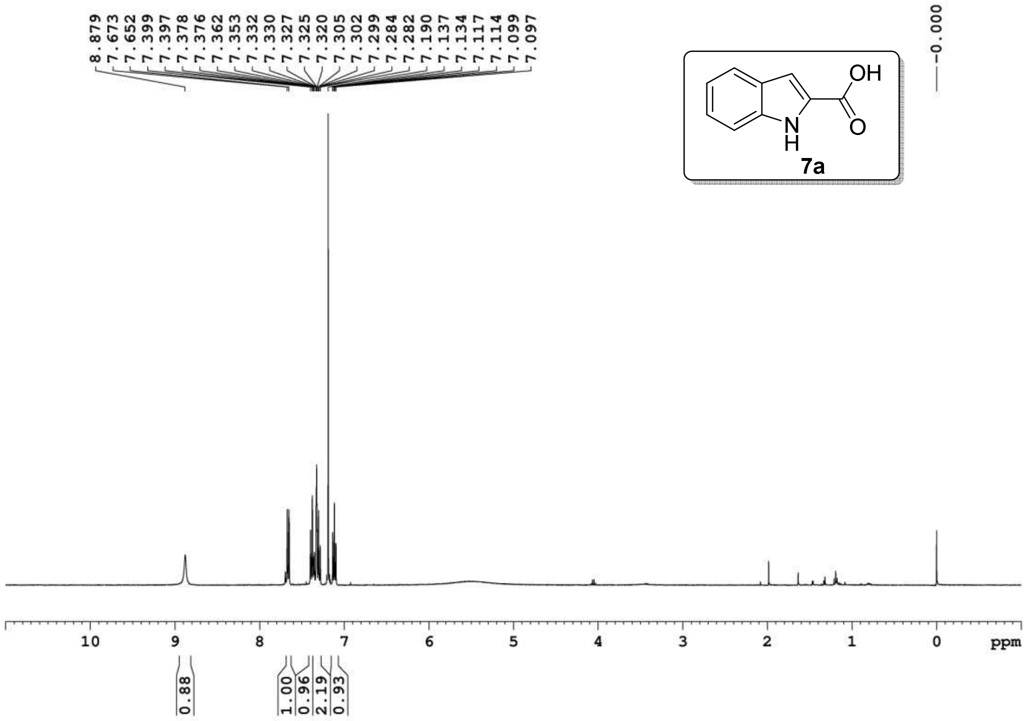
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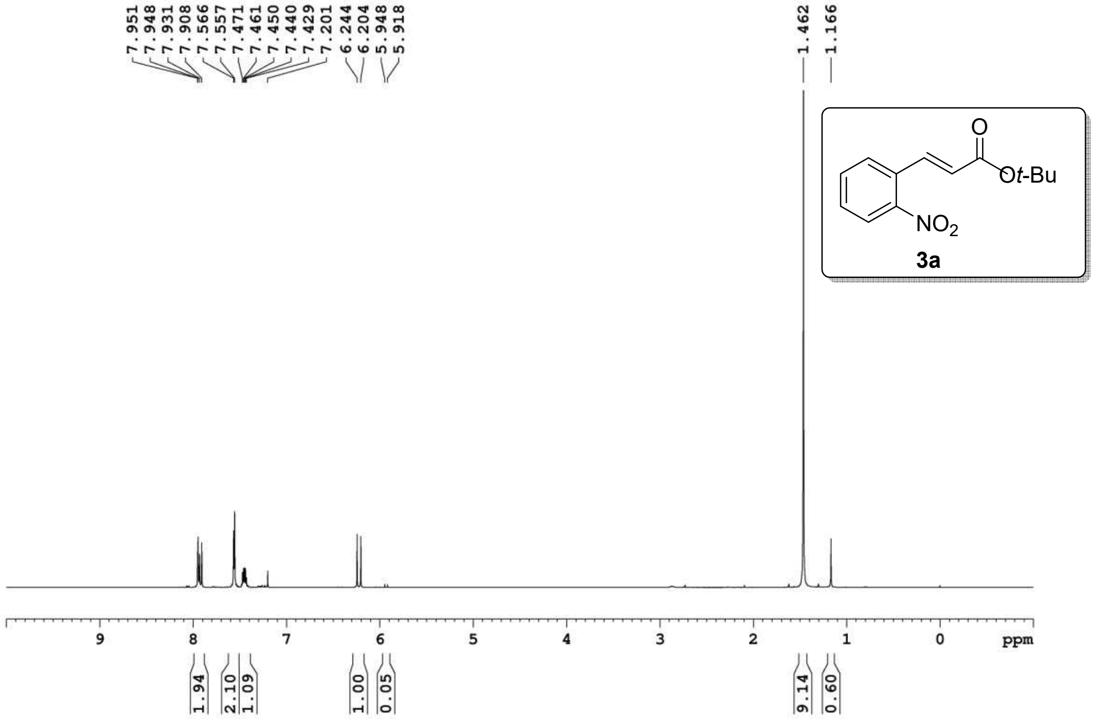
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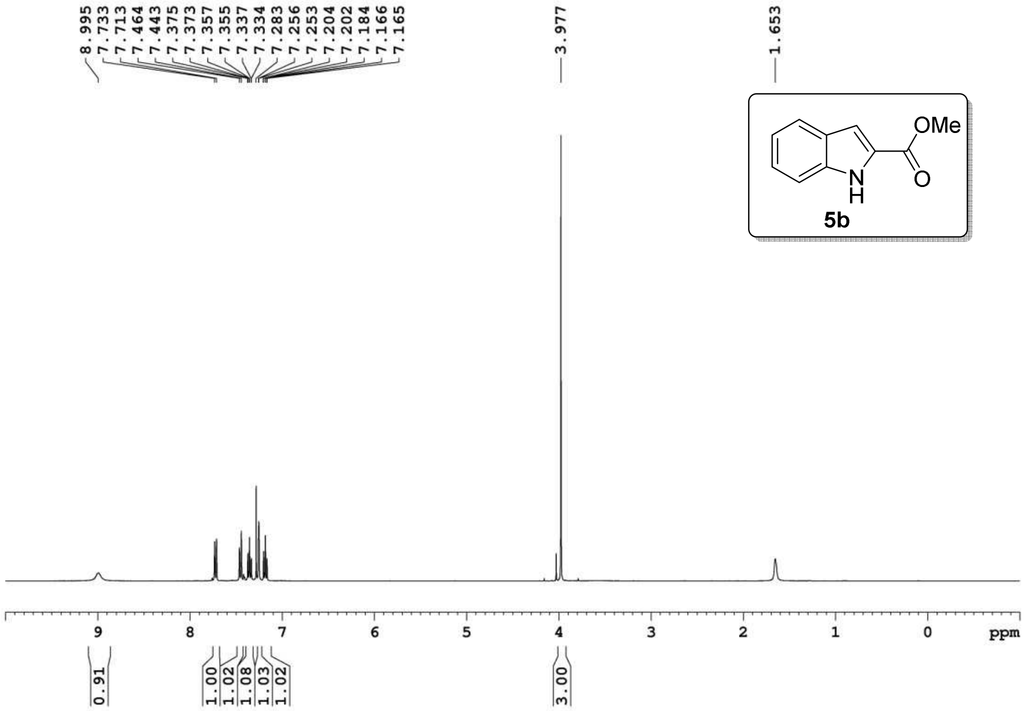
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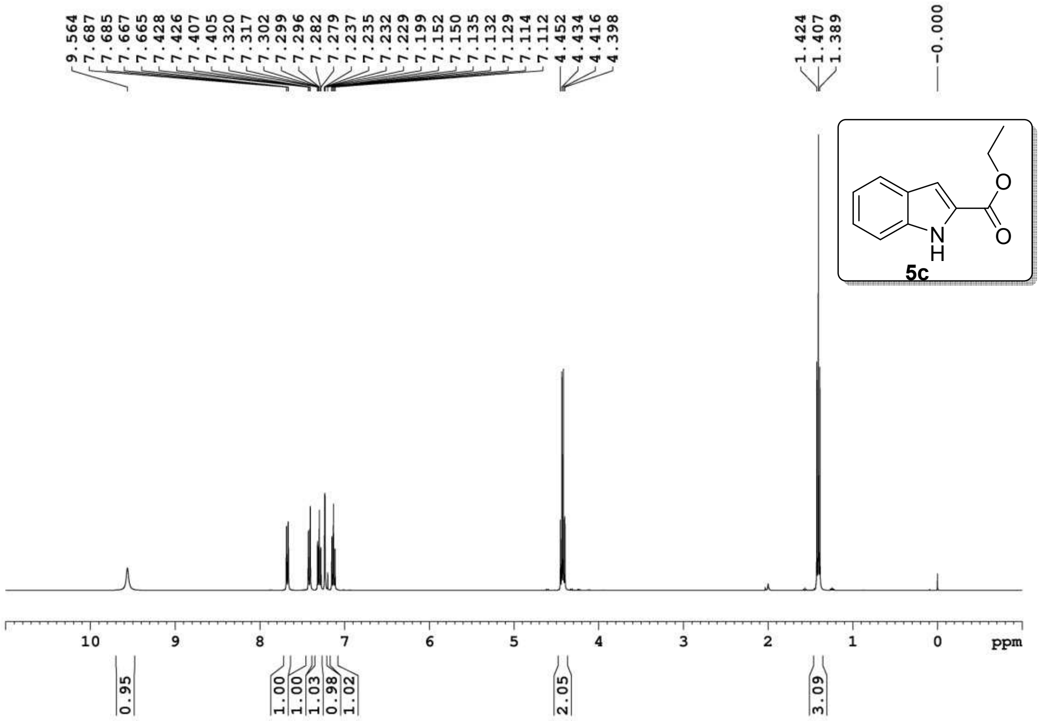
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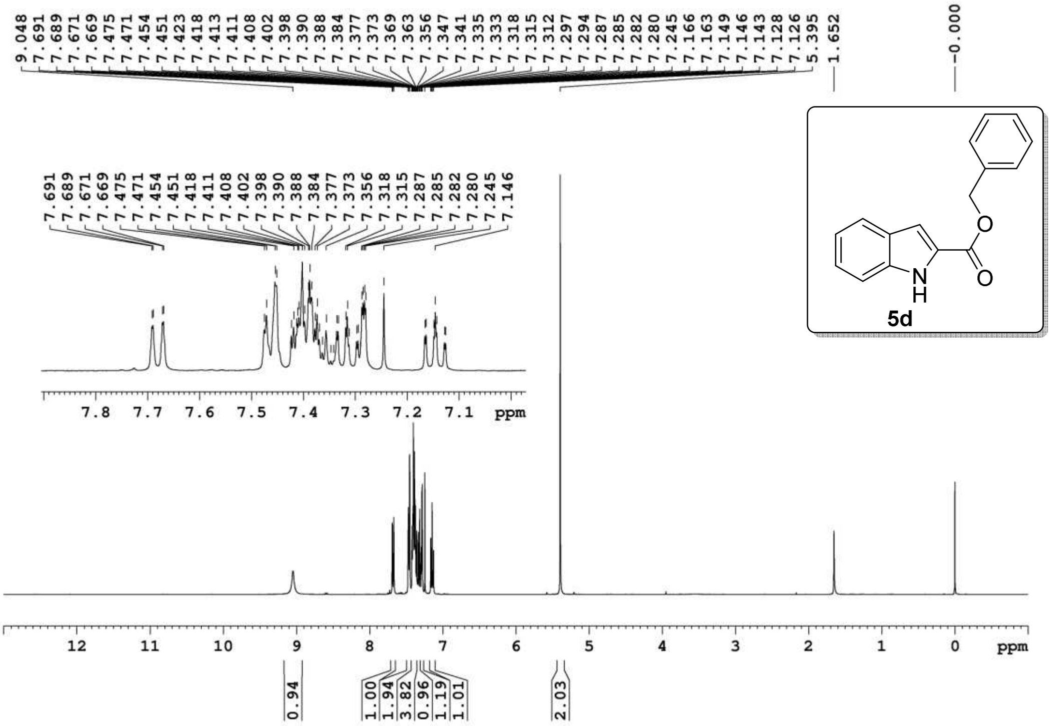
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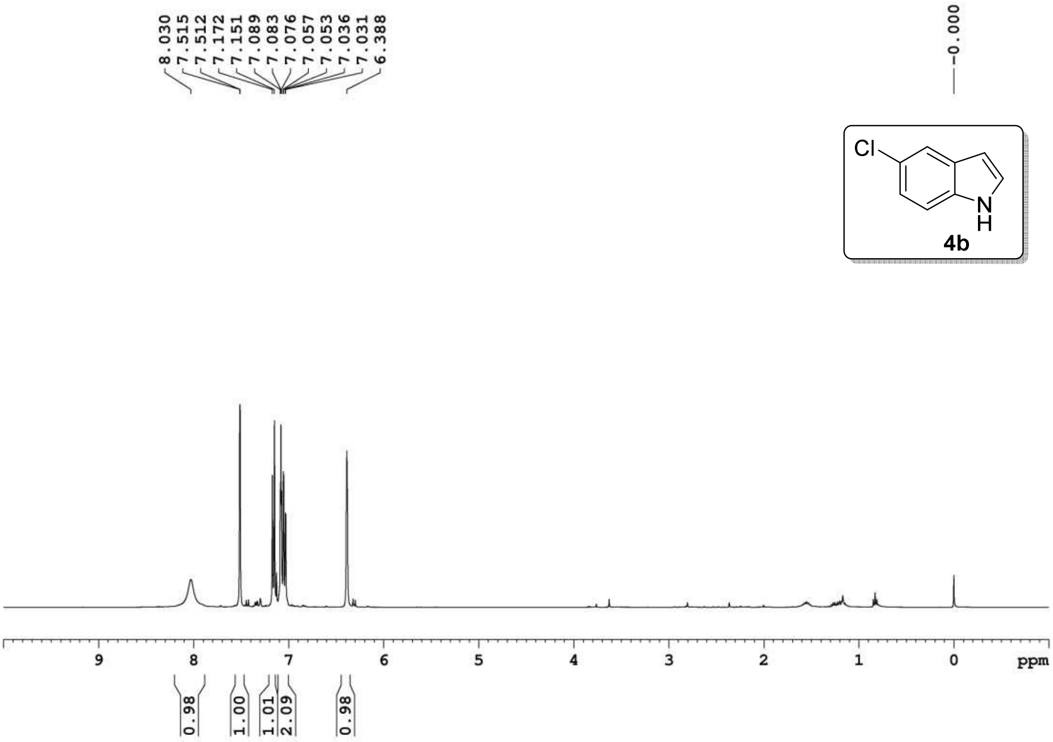
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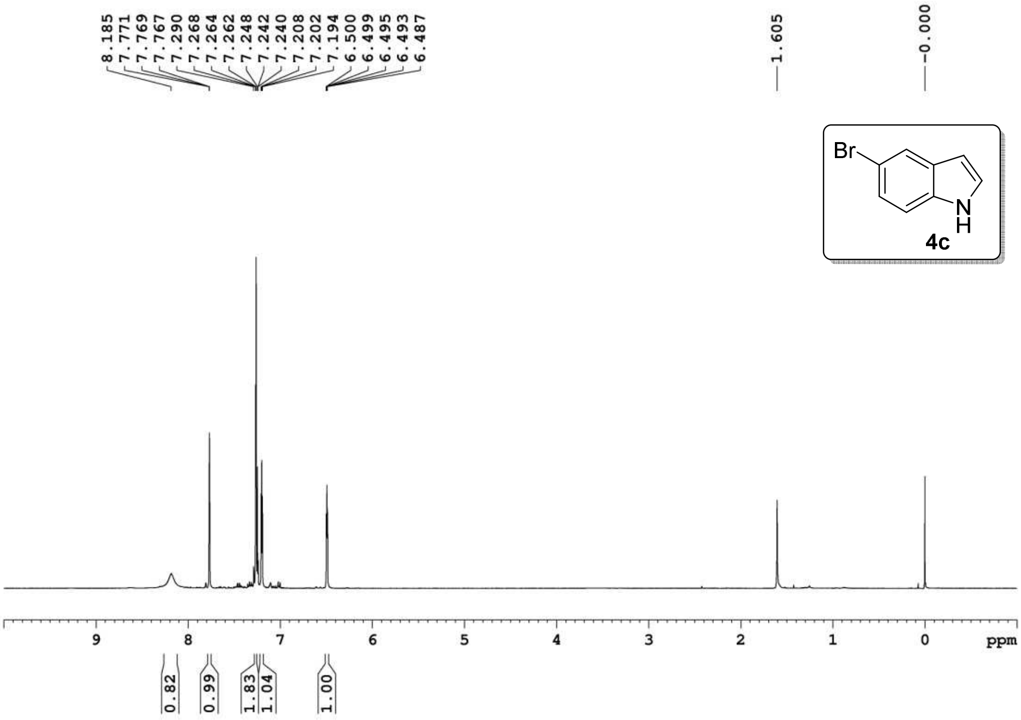
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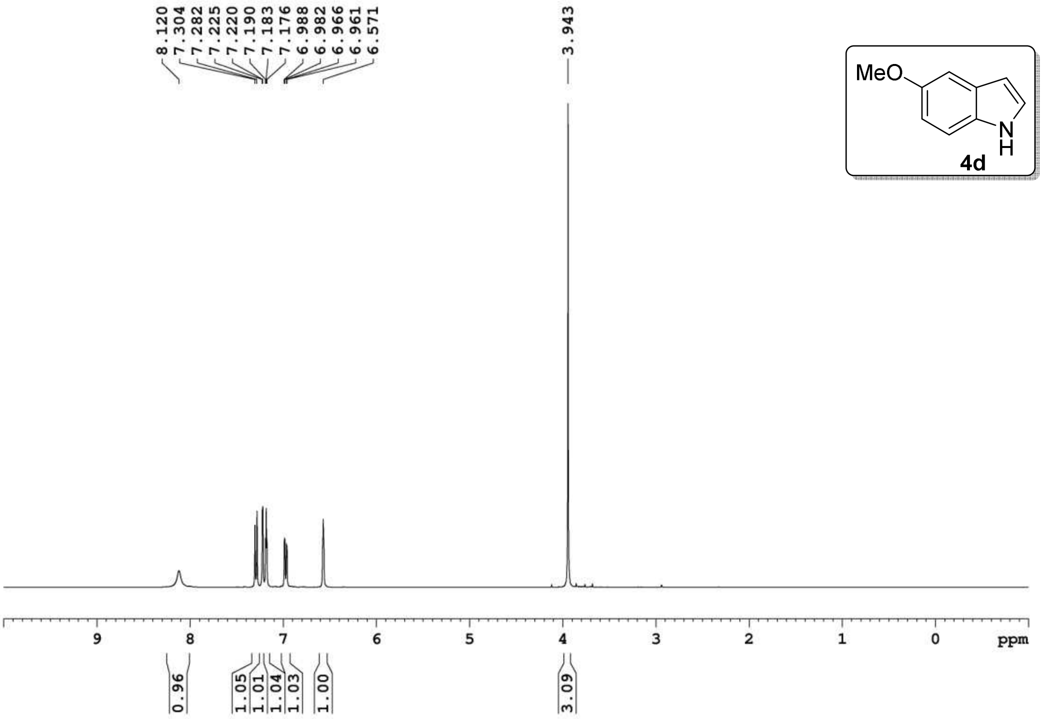
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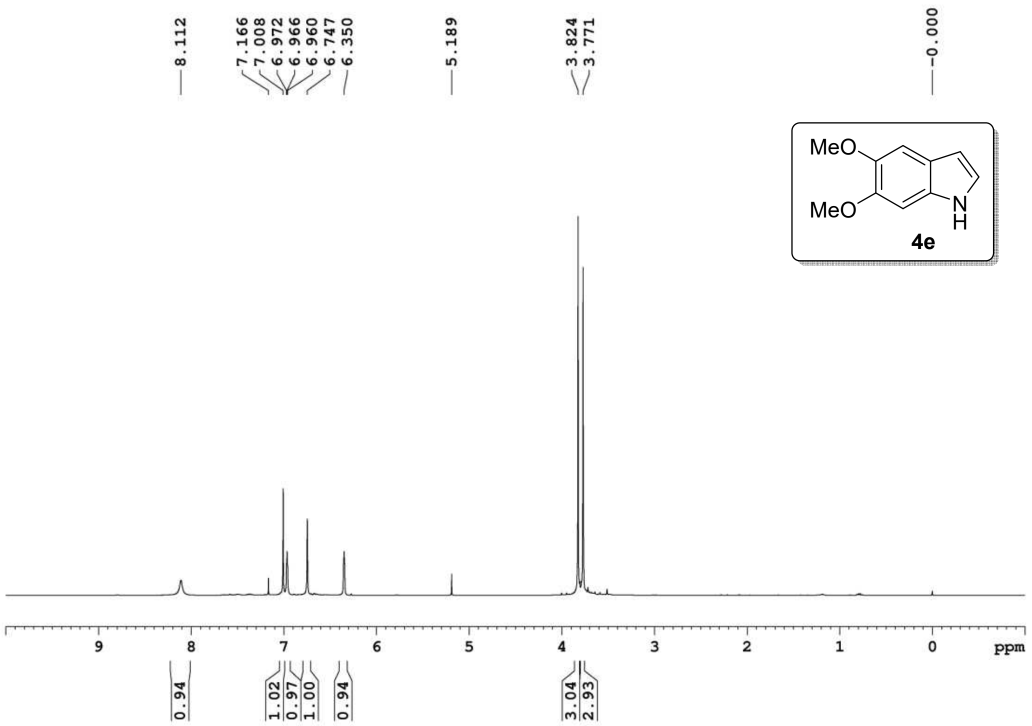
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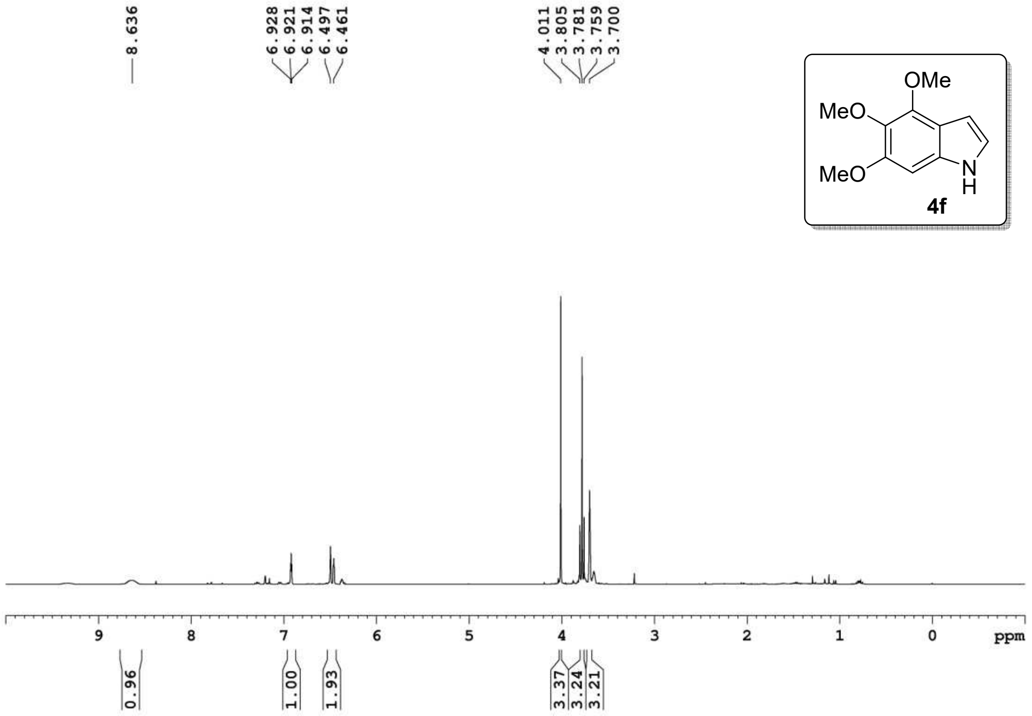
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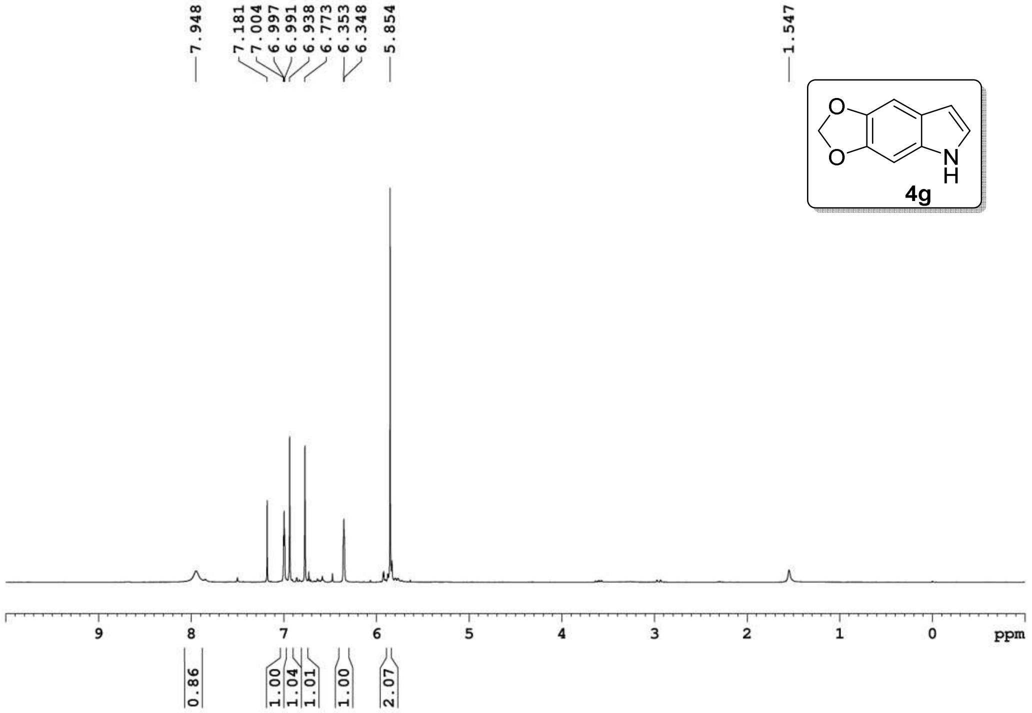
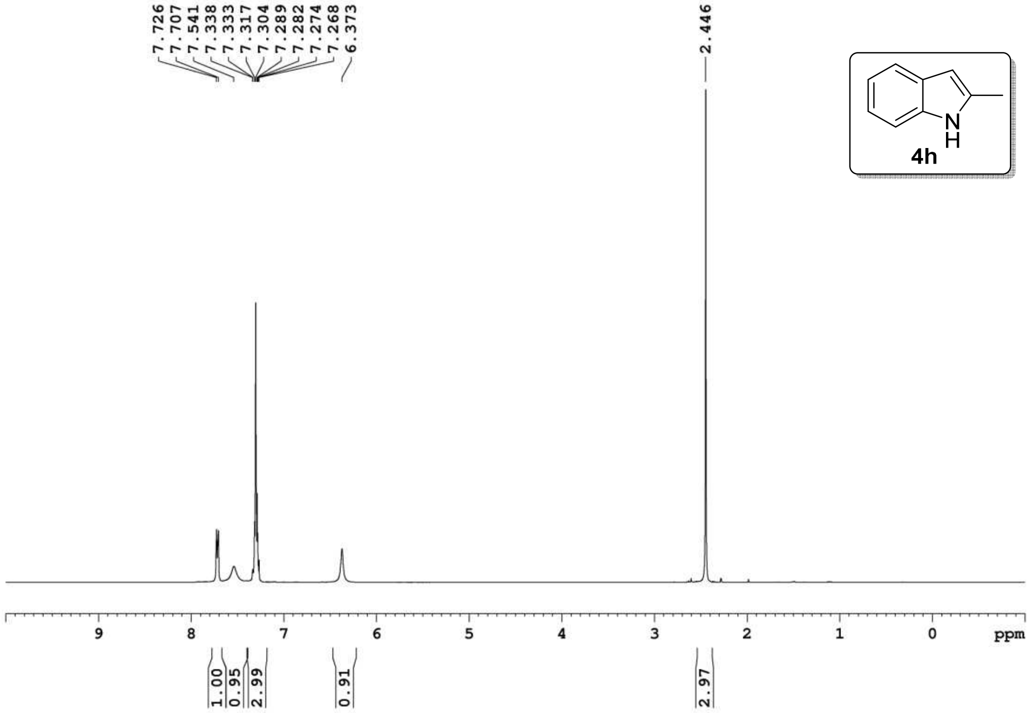
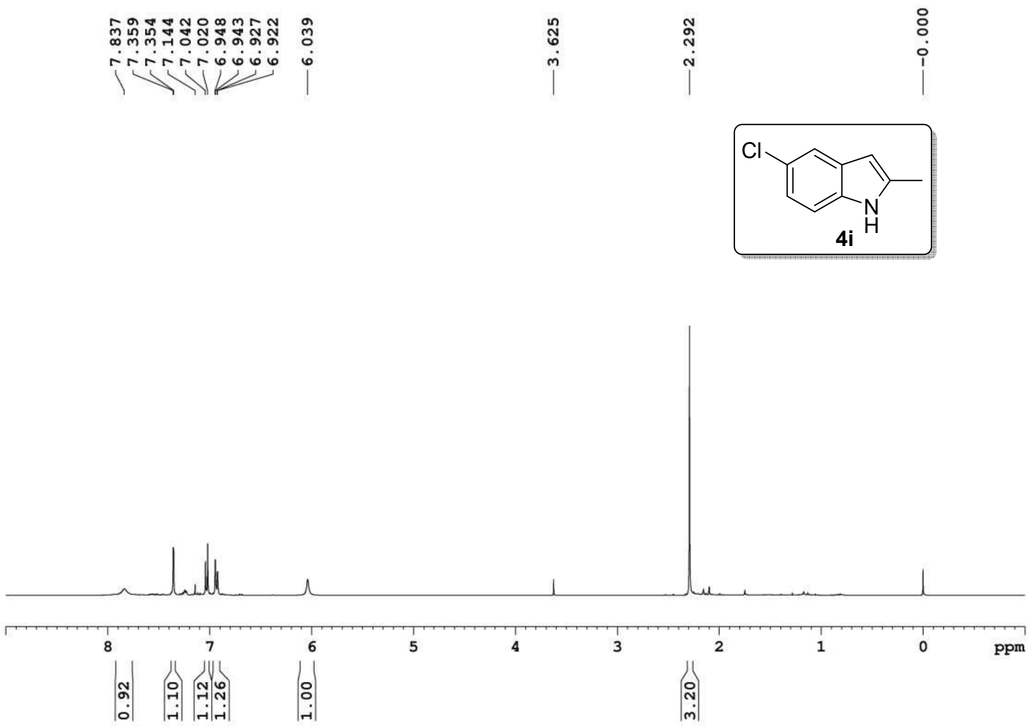
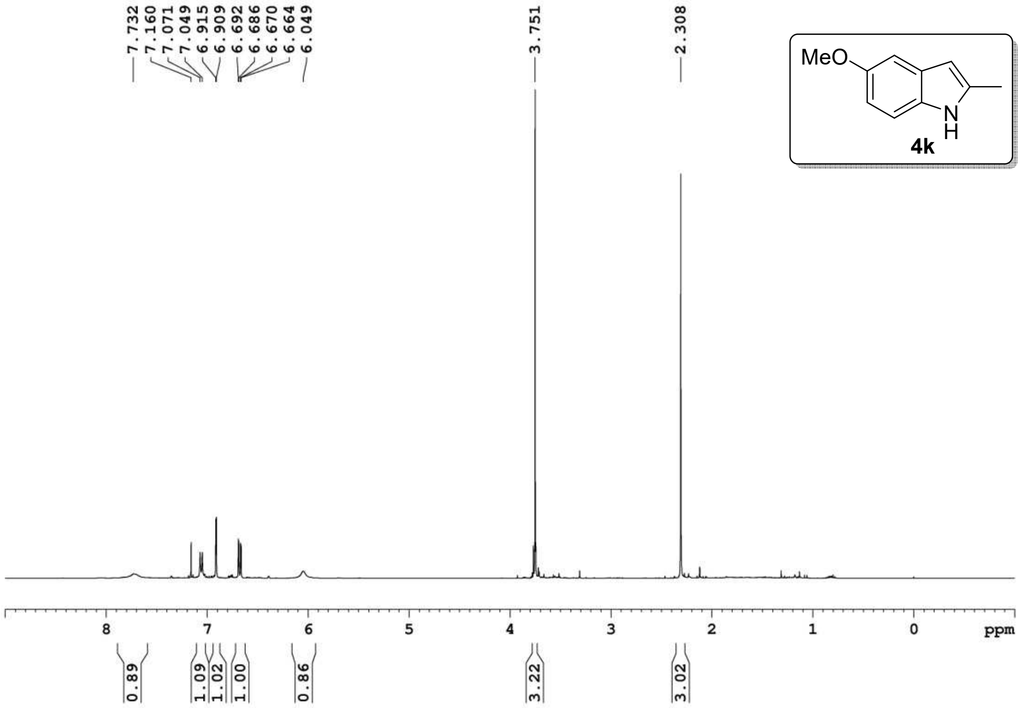
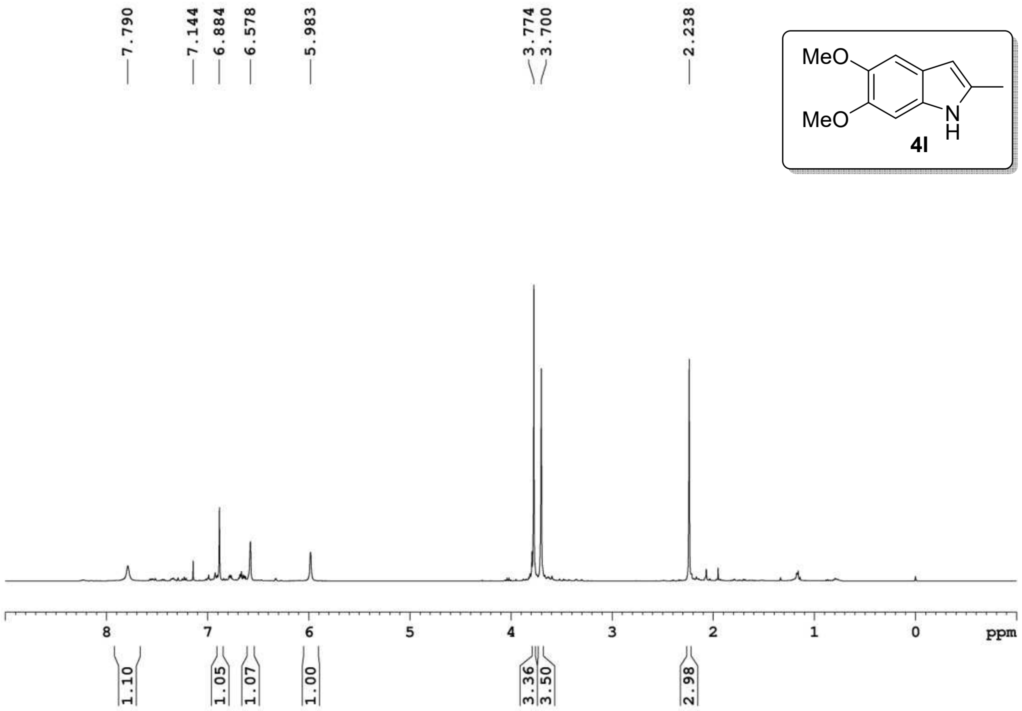
3.24
3.21

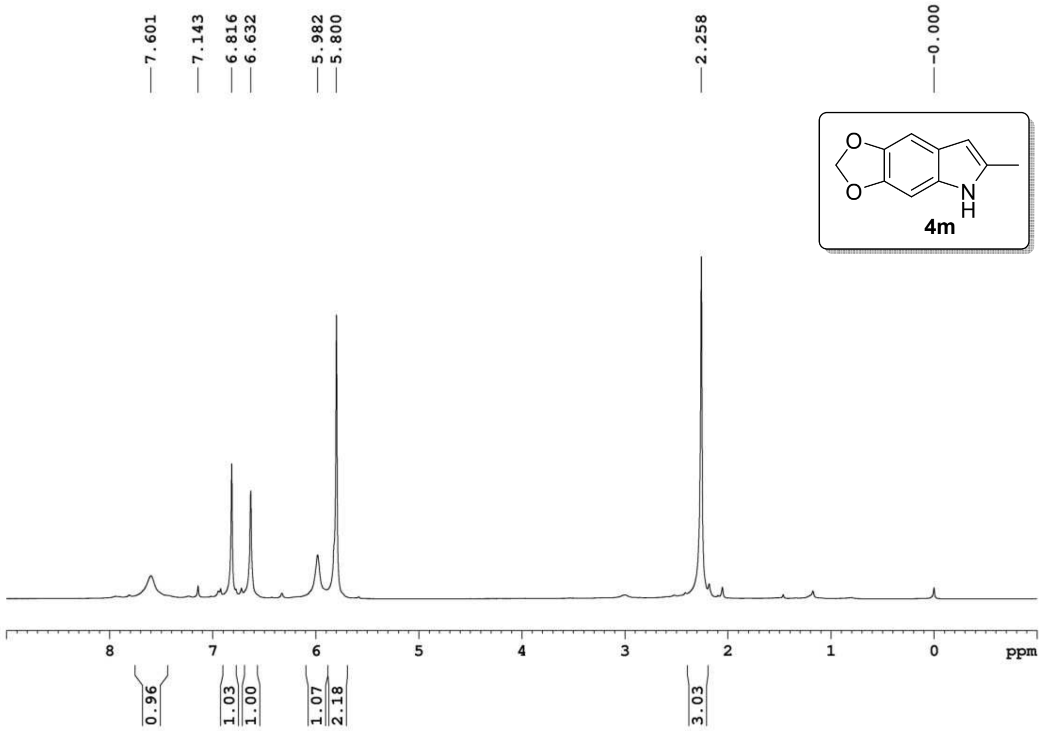

7.948
7.181
7.004
6.997
6.991
6.938
6.773
6.353
6.348
5.854
1.547
O
O
N
H
4g
9
8
7
6
5
4
3
2
1
0
ppm
0.86
1.00
1.04
1.01
1.00
2.07


7.726
7.707
7.541
7.338
7.333
7.317
7.304
7.289
7.282
7.274
7.268
6.373
2.446
N
H
4h
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.95
2.99
0.91
2.97


7.837
7.359
7.354
7.144
7.042
7.020
6.948
6.943
6.927
6.922
6.039
3.625
2.292
-0.000
Cl
N
H
4i
8
7
6
5
4
3
2
1
0
ppm
0.92
1.10
1.12
1.26
1.00
3.20


7.732
7.160
7.071
7.049
6.915
6.909
6.692
6.686
6.670
6.664
6.049
3.751
2.308
MeO
N
H
4k
8
7
6
5
4
3
2
1
0
ppm
0.89
1.09
1.02
1.00
0.86
3.22
3.02


7.790
7.144
6.884
6.578
5.983
3.774
3.700
2.238
MeO
MeO
N
H
4l
8
7
6
5
4
3
2
1
0
ppm
1.10
1.05
1.07
1.00
3.36
3.50
2.98


7.601
7.143
6.816
6.632
5.982
5.800
2.258
-0.000
O
O
N
H
4m
8
7
6
5
4
3
2
1
0
ppm
0.96
1.03
1.00
1.07
2.18
3.03

Chapter 4

Synthesis of Magallanesine and its analogues having azocine ring system.

4.1: Introduction

Nitrogen heterocycles are most abundantly found in nature.[1] Azepine,[2] seven membered ring system containing a nitrogen atom, forms an important class of organic compounds showing interesting conformational structures and a wide range of biological activities. Isoindolobenzapines alkaloids like chilenine **1**, lennoxamine **2** and deoxychilenine **3** (Fig. 1) are isolated from genus *Berberis,*[3] and are known for their potent activities against cancerous cells of lungs, colon, prostrate etc. Another class of nitrogen containing eight membered heterocycles, referred as azocine [4] are also important for their activities like antimalarial, antitissue analogues, antihypertension etc. These compounds are obtained from natural sources as well as from synthetic methods. Magallanesine **4a** is the first isoindolobenzazocine class of alkaloid obtained from *Berberis darwinii*. [5a] Along with the eight membered azocine, and it is also an isoindolinone fused ring system which is known for its potent biological activities. [5b] Benzofuroazocine **5** a synthetically obtained compound with an azocine ring is an important target due to activity in central nervous system.

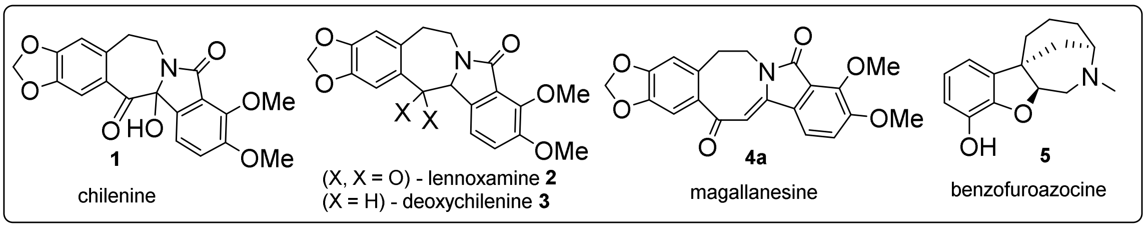
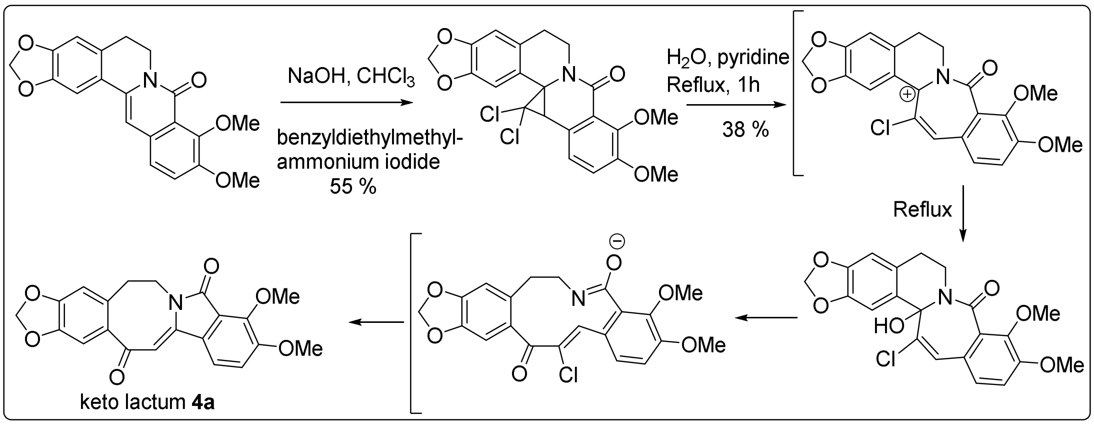


Figure 1: Azepine and azocine ring containing molecules.

Azocine being a medium size ring is often found difficult in synthesizing in its fully functionalized form, and only few reports are available for the synthesis of magallanesine or its azocine containing analogues.

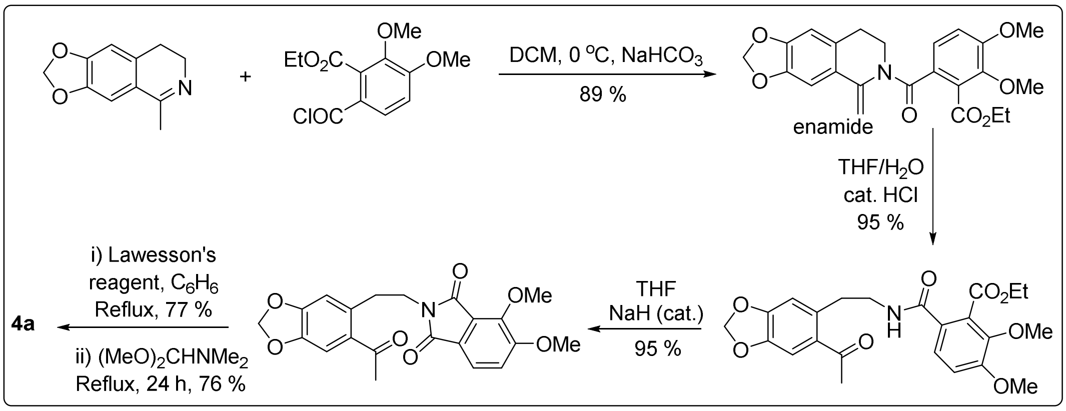
4.2: Literature Reported Methods

Sharma *et al.* [6] achieved the synthesis of magallanesine prior to its isolation from plant *Berberis Darwin.* Oxyberberine on reacting with dichloro carbene resulted in a colorless crystalline adduct. When these adduct was heated with aqueous pyridine it underwent a series of rearrangements giving ring expanded and contracted product which was refered as keto lactum (Scheme 1).


NaOH, $CHCl_3$
benzyldiethylmethyl-ammonium iodide
55 %
H_2O, pyridine
Reflux, 1h
38 %
Reflux
keto lactum 4a

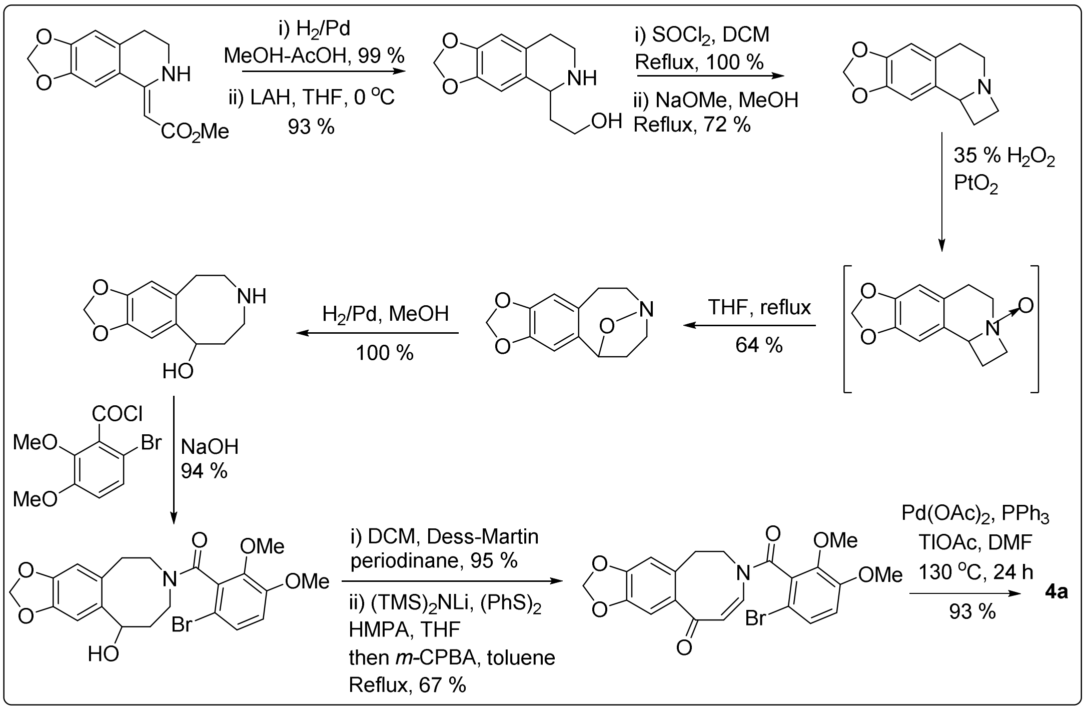
Scheme 1

Danishefsky *et al.* [7] achieved first synthesis of **4a** after its isolation using intramolecular condensation of a methyl ketone with an amide intermediate. Enamide intermediate was synthesized by treating the methyl *β*-hydrastine with an acid chloride derivative in basic medium. Treatment with aq. HCl gave an amide derivative, which on treatment with sodium hydride underwent cyclisation to give imide intermediate, this on treatment with Lawesson's reagent followed by the key reaction with dimethyformamide dimethyl acetal, gave magallanesine as a yellow solid (Scheme 2).


DCM, 0 °C, $NaHCO_3$
89 %
enamide
THF/H_2O
cat. HCl
95 %
THF
NaH (cat.)
95 %
i) Lawesson's reagent, C_6H_6
Reflux, 77 %
ii) $(MeO)_2CHNMe_2$
Reflux, 24 h, 76 %
4a

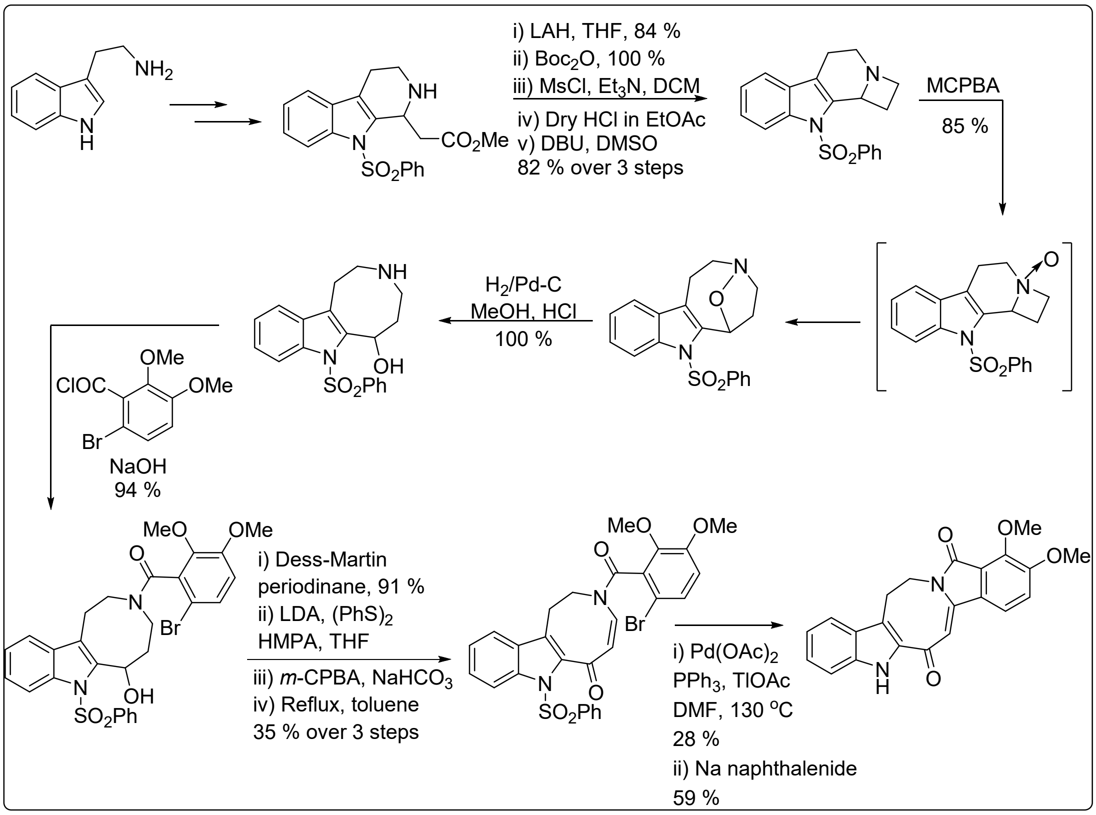
Scheme 2

Kurihara *et al.* [8a-b] synthesized magallanesine by [1,2]-Meisenheimer rearrangement to construct an azocine ring and modified intramolecular Heck cyclisation as key steps (Scheme 3). Hydrogenation and reduction of starting enaminoester gave primary alcohol derivative. Chlorination and intramolecular displacement of chloride gave azetidine, which underwent ring expansion by [1,2]-Meisenheimer rearrangement followed by hydrogenation to result in azocine ring. Amidation and oxidation of secondary alcohol to ketone and dehydrogenation gave the key intermediate for intramolecular Heck coupling. Using TlOAc with $Pd(OAc)_2$ gave the best results for formation of fully functionalized magallanesine.


i) H_2/Pd
MeOH-AcOH, 99 %
ii) LAH, THF, 0 °C
93 %
NH
CO_2Me
OH
i) $SOCl_2$, DCM
Reflux, 100 %
ii) NaOMe, MeOH
Reflux, 72 %
N
35 % H_2O_2
PtO_2
THF, reflux
64 %
H_2/Pd, MeOH
100 %
HO
COCl
MeO
Br
NaOH
94 %
OMe
i) DCM, Dess-Martin
periodinane, 95 %
ii) $(TMS)_2NLi$, $(PhS)_2$
HMPA, THF
then m-CPBA, toluene
Reflux, 67 %
$Pd(OAc)_2$, PPh_3
TlOAc, DMF
130 °C, 24 h
93 %
4a

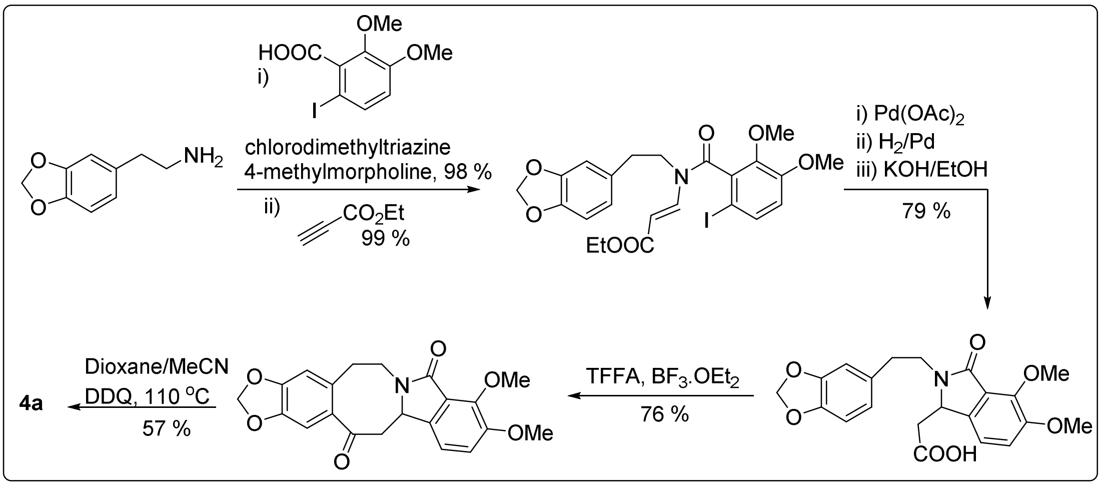
Scheme 3

The same group [8c] later extended the above strategy to synthesize an indole analogue of magallanesine using methyl 2-(9-(phenylsulfonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate which was synthesized from tryptamine (Scheme 4).


NH_2
N
H
NH
CO_2Me
SO_2Ph
i) LAH, THF, 84 %
ii) Boc_2O, 100 %
iii) MsCl, Et_3N, DCM
iv) Dry HCl in EtOAc
v) DBU, DMSO
82 % over 3 steps
MCPBA
85 %
H_2/Pd-C
MeOH, HCl
100 %
OH
ClOC
OMe
Br
NaOH
94 %
MeO
i) Dess-Martin
periodinane, 91 %
ii) LDA, $(PhS)_2$
HMPA, THF
iii) m-CPBA, $NaHCO_3$
iv) Reflux, toluene
35 % over 3 steps
i) $Pd(OAc)_2$
PPh_3, TlOAc
DMF, 130 °C
28 %
ii) Na naphthalenide
59 %

Scheme 4

Recently, Kim *et al.* [9] synthesized **4a** using intramolecular Heck and Friedel-Crafts cyclization reaction (Scheme 5), starting with coupling of 3,4-methylenedioxyphenethylamine with 6-iodo-2,3-dimethoxybenzoic acid followed by Michael reaction with ethyl propiolate to give an adduct ready for Heck cyclization.

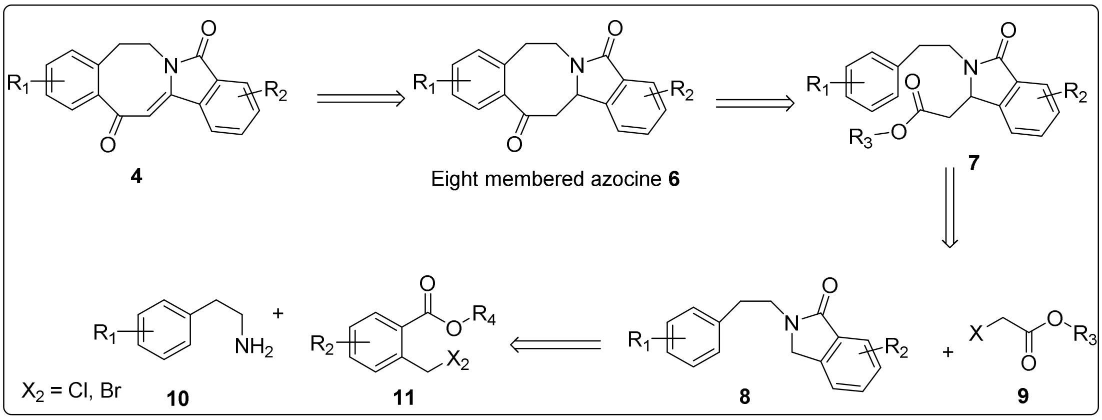

OMe
HOOC
OMe
i)
I
NH2
chlorodimethyltriazine
4-methylmorpholine, 98 %
ii)
CO2Et
99 %
O
OMe
OMe
N
I
EtOOC
i) Pd(OAc)2
ii) H2/Pd
iii) KOH/EtOH
79 %
Dioxane/MeCN
DDQ, 110 °C
57 %
4a
OMe
OMe
TFFA, BF3.OEt2
76 %
COOH

Scheme 5

Successful intramolecular Heck reaction with palladium catalyst followed by hydrogenation and hydrolysis gave the acid intermediate. This acid on heating with trifluoroacetic anhydride in the presence of $BF_3.OEt_2$ underwent formation of eight membered azocine ring, which on dehydrogenation with DDQ gave magallanesine.

4.3: Results and discussion

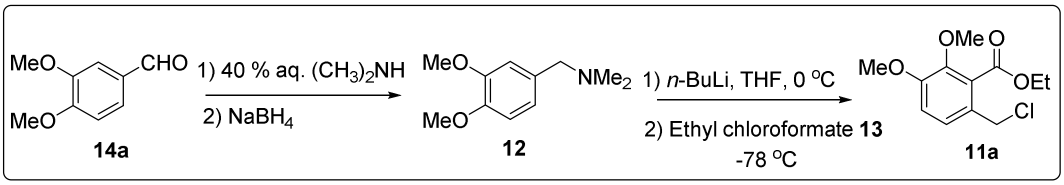
The retrosynthetic pathway envisioned for this molecule is depicted in the below scheme 6. A dehydrogenated azocine derivative **4** could be obtained from its dihydro derivative **6**. We intended to synthesize **6** in one step from its corresponding ester **7**, using Friedel Crafts cyclization.


R1
R2
4
Eight membered azocine 6
R3
7
R1
NH2
+
R2
O
R4
X2
X2 = Cl, Br
10
11
8
X
R3
+
9

Scheme 6

Compound **7** in turn could be obtained by a C-C bond formation by deprotonation of isoindoline derivative **8** followed by alkylation with corresponding alkyl bromoacetates. Isoindoline **8** could be achieved in one pot alkylation-amidation step from compound **10** and **11**.

Ethyl 6-(chloromethyl)-2,3-dimethoxybenzoate **11a** was synthesized according to the procedure established by Rapoport *et al.* [10] by treating 1-(3,4-dimethoxyphenyl)-*N*,*N*-dimethylmethanamine **12** with *n*-BuLi at 0 °C and then reacting the anion formed with ethyl chloroformate **13** at -78 °C to give desired product **11a** by displacement of $N(Me)_2$ group by chloride anion (Scheme 7). The required compound **12** was synthesized from veratraldehyde **14a** by treating with dimethyl amine in water followed by reduction of the imine using $NaBH_4$. [11]

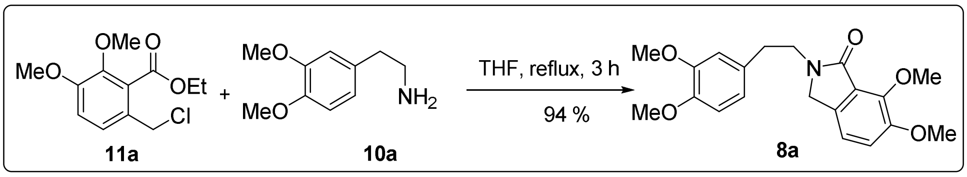

MeO
CHO
MeO
14a
1) 40 % aq. (CH3)2NH
2) NaBH4
MeO
NMe2
MeO
12
1) n-BuLi, THF, 0 °C
2) Ethyl chloroformate 13
-78 °C
OMe O
MeO
OEt
Cl
11a

Scheme 7

^{1}H NMR of ethyl 6-(chloromethyl)-2,3-dimethoxybenzoate (11a): [10]

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.13 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 4.63 (s, 2H), 4.62-4.44 (m, 2H), 3.92-3.91 (m, 6H), 1.43 (t, J = 5.2 Hz, 1H).

On heating **11a** with 2 equiv of commercially available 2-(3,4-dimethoxyphenyl)ethan-1-amine **10a** in THF gave an off white solid on silica gel purification (Scheme 8). The IR spectrum showed absence of broad peak in the region 3300 cm^{-1} for NH_2 group and a strong peak at 1681 cm^{-1} attributing to the amide carbonyl stretch. The product was further confirmed to be 2-(3,4-dimethoxyphenethyl)-6,7-dimethoxyisoindolin-1-one [12] **8a** based on ^{1}H and ^{13}C NMR data.


OMe O
MeO
OEt
Cl
11a
+
MeO
MeO
NH2
10a
THF, reflux, 3 h
94 %
MeO
MeO
N
O
OMe
OMe
8a

Scheme 8

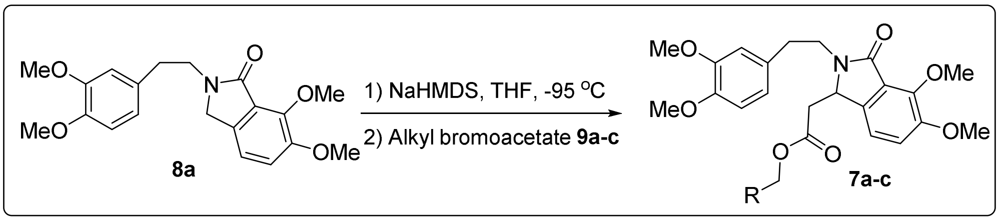
Spectral data of 2-(3,4-dimethoxyphenethyl)-6,7-dimethoxyisoindolin-1-one (8a): [12]

IR (KBr): $\tilde{\nu}$ = 2945, 2833, 1681, 1514, 1492, 1267, 1153, 1031, 821 cm^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.00-6.92 (m, 2H), 6.73-6.67 (m, 3H), 4.02-4.01 (m, 5H), 3.82 (s, 3H), 3.78 (s, 3H), 3.73-3.70 (m, 5H), 2.86 (t, J = 7.6 Hz, 2H).

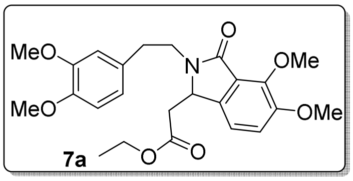
^{13}C-NMR (100 MHz, CDCl$_3$): δ 166.7 (C), 152.3 (C), 148.9 (C), 147.6 (C), 147.2 (C), 134.5 (C), 131.3 (C), 125.1 (C), 120.6 (CH), 117.7 (CH), 116.3 (CH), 111.8 (CH), 111.3 (CH), 62.6 (CH$_3$), 56.8 (CH$_3$), 55.9 (CH$_3$), 55.8 (CH$_3$), 49.8 (CH$_2$), 44.3 (CH$_2$), 34.2 (CH$_2$).

Isoindolinone derivative **8a** was metallated and alkylated to give 3-substituted isoindoline **7a**. [13] Compound **8a** was treated with sodium hexamethylene disilazane (NaHMDS) at -95 °C giving anion which had a deep dark green color. The reaction mixture was then treated with ethyl bromoacetate **9a** and allowed to warm to room temperature (Scheme 9). On isolation and silica gel purification, gave a viscous liquid which in its IR spectrum showed two strong bands at 1728 cm^{-1} and 1694 cm^{-1} attributing for the ester and amide carbonyl stretch respectively. Compound **8a** was further confirmed based on ^{1}H NMR, ^{13}C NMR and HRMS data.



Scheme 9

Spectral data of ethyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate (7a):



IR (KBr): $\tilde{\nu}$ = 2980, 2934, 1728, 1694, 1504, 1493, 1352, 1250, 1150 cm^{-1}.

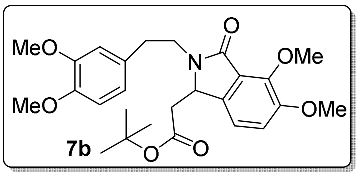
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.00-6.95 (m, 2H), 6.71-6.69 (m, 3H), 4.64 (t, J = 6.0 Hz, 1H), 4.11-4.00 (m, 3H), 3.99 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.26-3.18 (m, 1H), 2.93-2.85 (m, 1H), 2.80-2.75 (m, 1H), 2.67 (dd, J = 16.0 Hz, 5.6 Hz, 1H), 2.51 (dd, J = 16.0 Hz, 6.4 Hz, 1H), 1.51 (t, J = 6.8 Hz, 3H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ 170.6 (C), 166.3 (C), 152.7 (C), 148.9 (C), 147.6 (C), 146.9 (C), 138.0 (C), 131.3 (C), 124.2 (C), 120.6 (CH), 117.5 (CH), 116.3 (CH), 111.9 (CH), 111.3 (CH), 62.4 (CH$_3$), 56.6 (CH$_3$), 55.8 (CH$_3$), 55.7 (CH$_3$), 55.6 (C), 42.4 (CH$_2$), 38.4 (CH$_2$), 34.0 (CH$_2$), 27.8 (CH$_3$), 14.1 (CH$_3$).

HRMS (ESI): calcd for $C_{24}H_{29}NO_7Na$ $[M + Na]^+$ 466.1842, found 466.1841.

Similarly the deep green coloured anion was treated with *t*-butyl bromoacetate **9b** and benzyl bromoacetate **9c** to get **7b** in 90 % and **7c** in 87 % yield respectively as thick viscous oils.

Spectral data of *tert*-butyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate (7b):



7b

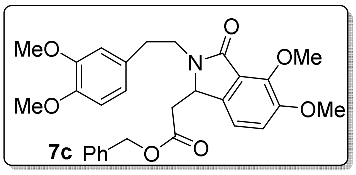
IR (KBr): $\tilde{\nu}$ = 2978, 2935, 1726, 1693, 1504, 1490, 1357, 1249, 1151, 1039 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.00 (s, 2H), 6.71 (d, J = 4.4 Hz, 3H), 4.58 (t, J = 6.0 Hz, 1H), 4.12-4.04 (m, 1H), 4.00 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.26-3.19 (m, 1H), 2.94-2.75 (m, 2H), 2.62 (dd, J = 16.0 Hz, 5.2 Hz, 1H), 2.49 (dd, J = 16.0 Hz, 6.0 Hz, 1H), 1.32 (s, 9H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ 169.6 (C), 166.4 (C), 152.6 (C), 148.9 (C), 147.6 (C), 146.9 (C), 138.1 (C), 131.3 (C), 124.4 (C), 120.7 (CH), 117.5 (CH), 116.2 (CH), 111.9 (CH), 111.3 (CH), 81.6 (C), 62.5 (CH$_3$), 56.7 (CH$_3$), 55.9 (CH$_3$), 55.8 (CH$_3$), 55.7 (C), 42.2 (CH$_2$), 39.1 (CH$_2$), 34.0 (CH$_2$), 27.9 (3 X CH$_3$).

HRMS (ESI): calcd for $C_{26}H_{33}NO_7Na$ [M + Na]$^+$ 494.2155, found 494.2155.

Spectral data of benzyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate (7c):



7c

IR (KBr): $\tilde{\nu}$ = 2990, 2950, 1730, 1695, 1500, 1492, 1350, 1245, 1040 cm^{-1}.

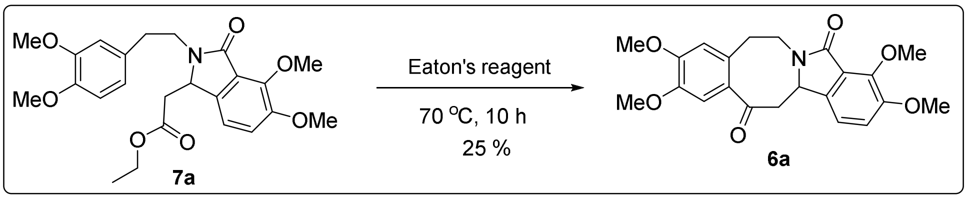
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.39-7.30 (m, 5H), 7.02-6.84 (m, 2H), 6.77-6.75 (m, 3H), 5.17 (s, 2H), 4.37 (t, J = 6.0 Hz, 1H), 4.13-4.07 (m, 4H), 3.89 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.32-3.27 (m, 1H), 2.97-2.79 (m, 3H), 2.62 (dd, J = 16.0 Hz, 6.8 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ 170.4 (C), 166.3 (C), 152.7 (C), 148.9 (C), 147.6 (C), 147.0 (C), 137.9 (C), 135.2 (C), 131.3 (C), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (C), 124.2 (C), 120.7 (CH), 117.6 (C), 117.4 (CH), 116.2 (CH), 111.9 (CH), 111.3 (CH), 66.9 (CH$_2$), 62.5 (CH$_3$), 56.6 (CH$_3$), 55.9 (CH$_3$), 55.8 (CH$_3$), 55.6 (CH), 42.4 (CH$_2$), 38.3 (CH$_2$), 33.9 (CH$_2$).

HRMS (ESI): calcd for $C_{29}H_{31}NO_7Na$ [M + Na]$^+$ 528.1998, found 528.1998.

Baba *et al.* [14] successfully used ester as an acylating agent in Friedel Crafts type cyclization using InBr$_3$ in presence of dimethylchlorosilane. To our knowledge this is the only report where esters are used in acylation. In our first attempt towards intramolecular Friedel Crafts cyclization, ester **7a** was treated polyposphoric acid (PPA) at 110 °C for 16 h, but there was not much change observed in the starting material on TLC. Next **7a** was reacted with 1:10 mixture of P_2O_5/methanesulphonic acid (Eatons reagent), which is known to be advantageous over PPA.[15] At room temperature even after 16 h no change in starting was observed, hence the temperature was raised to 70 °C and reaction aged for 10 h (Scheme 10). On monitoring by TLC it showed complete disappearance of starting material. Silica gel purification afforded a white solid which was expected to be hydrolyzed acid or the desired ketone **6a**. The IR spectrum of the product showed two strong bands at 1728 cm^{-1} and 1695 cm^{-1}, and no broadband in the region 3300-3600 cm^{-1}. The CO stretch was thus attributed to ketone and amide functionality respectively. The compound was further confirmed to be the desired azocine derivative **6a** based on ^1H and ^{13}C NMR and mass analysis. Peak at 195.5 ppm in the CMR spectrum for quaternary carbon confirmed the presence of a ketone.

7a was thought to undergo hydrolysis to acid **14a** first and then cyclized to **6a**.



Scheme 10

Spectral data of 3,4,10,11-tetramethoxy-7,8,14,14a-tetrahydrobenzo[5,6]-azocino[2,1-*a*]isoindole-5,13-dione (6a):

IR (KBr): $\tilde{\nu}$ = 2964, 2914, 1728, 1695, 1462, 1377, 1261, 1095, 1051, 806 cm^{-1}.

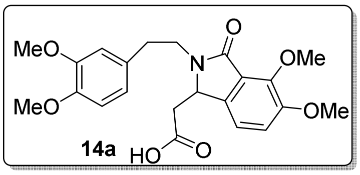
^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 1H), 7.11 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.64 (s, 1H), 4.75 (dd, J = 6.0 Hz, 1.6 Hz, 1H), 4.47-4.39 (m, 1H), 3.91 (dd, J = 14.0 Hz, 6.4 Hz, 1H), 3.86 (s, 3H), 3.78 (d, J = 4.8 Hz, 6H), 3.74-3.66 (m, 4H), 3.37 (dd, J = 14.0 Hz, 5.2 Hz, 1H), 3.17 (dd, J = 14.0 Hz, 2.0 Hz, 1H), 2.96-2.90 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 195.5 (C), 166.0 (C), 153.0 (C), 152.5 (C), 147.7 (C), 146.8 (C), 136.6 (C), 132.8 (C), 130.7 (C), 123.8 (C), 117.5 (CH), 116.3 (CH), 114.0 (CH), 111.9 (CH), 62.3 (CH_3), 57.2 (CH), 56.5 (CH_3), 56.0 (CH_3), 55.8 (CH_3), 46.9 (CH_2), 40.1 (CH_2), 34.7 (CH_2).

HRMS (ESI): calcd for $C_{22}H_{23}NO_6Na$ $[M + Na]^+$ 420.1423, found 420.1423.

Similarly *tert*-butyl derivative **7b** and benzyl derivative **7c** were treated with Eaton’s reagent and to our delight both gave **6a** in 99 % and 51 % respectively after 12 h at room temperature. On quenching the reaction mass of **7b** in Eaton’s reagent after 1 h with water, a polar compound other than **6a** was isolated along with **7b** and **6a**. Its IR spectrum showed a broad peak at 3420 cm^{-1}, and carbonyl peaks at 1695 and 1688 cm^{-1} indicating the presence of amide and acid functionality. Compound **14a** was confirmed to be an acid based on NMR and mass data.

Spectral data of 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetic acid (14a):



14a

IR (KBr): $\tilde{\nu}$ = 3420, 2956, 2920, 1695, 1688, 1460, 1262, 1050 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.04-6.97 (m, 2H), 6.69 (s, 3H), 5.13 (br s, 2H), 4.61 (s, 1H), 4.06-4.01 (m, 4H), 3.97 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.28-3.21 (m, 1H), 2.92-2.73 (m, 3H), 2.55 (dd, *J* = 16.4 Hz, 6.4 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 174.0 (C), 166.8 (C), 152.8 (C), 148.9 (C), 147.6 (C), 146.9 (C), 137.8 (C), 131.2 (C), 124.1 (C), 120.7 (CH), 117.6 (CH), 116.5 (CH), 112.0 (CH), 111.4 (CH), 62.4 (CH$_3$), 56.6 (CH$_3$), 55.9 (CH$_3$), 55.8 (CH$_3$), 55.5 (C), 42.2 (CH$_2$), 37.6 (CH$_2$), 33.9 (CH$_2$) .

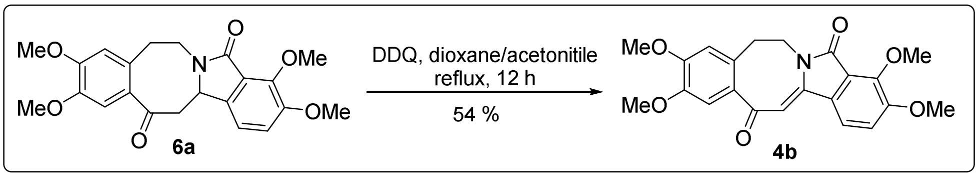
HRMS (ESI): calcd for $C_{22}H_{25}NO_7Na$ [M + Na]$^+$ 438.1529, found 438.1528.

The reaction conditions for ester **7a-c** and results obtained are summarised in table 1.

Table 1: Reaction condition for cyclisation for ester **7a-c**.

Entry	Substrate	Temp. & time	Isolated Yield (%)
1	**7a**	70 °C, 10 h	25
2	**7b**	rt, 12 h	99
3	**7c**	rt, 12 h	51

Compound **6a** was dehydrogenated with DDQ in refluxing mixture of dioxane and acetonitrile according to the procedure reported by Kim *et al.* [9] to give **4b** as a yellow solid in 54 % yield, which was confirmed by spectral analysis (Scheme 11).



Scheme 11

Spectral data of (*Z*)-3,4,10,11-tetramethoxy-7,8-dihydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione (4b):

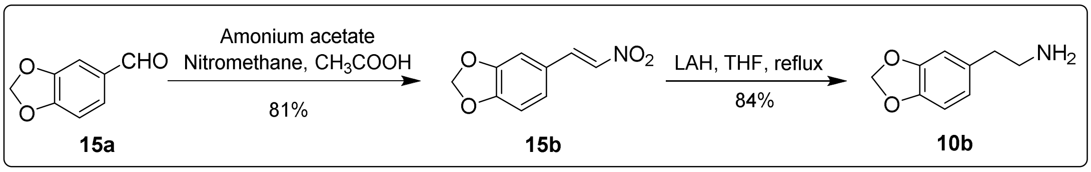
IR (KBr): $\tilde{\nu}$ = 2999, 1701, 1681, 1586, 1504, 1436, 1357, 1289, 1224, 1082 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.57 (s, 1H), 6.22 (s, 1H), 4.05-4.03(m, 5H), 3.86-3.84 (m, 9H), 3.21 (d, J = 5.2 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.5 (C), 165.5 (C), 154.7 (C), 151.7 (C), 147.8 (C), 147.4 (C), 138.8 (C), 133.4 (C), 130.8 (C), 130.7 (C), 119.8 (C), 116.3 (CH), 116.1 (CH), 113.5 (CH), 112.1 (CH), 104.4 (CH), 62.5 (CH_3), 56.6 (CH_3), 56.1 (CH_3), 56.0 (CH_3), 43.0 (CH_2), 33.9 (CH_2).

HRMS (ESI): calcd for $C_{22}H_{21}NO_6H$ $[M + H]^+$ 396.1447, found 396.1447.

Having successfully synthesized the azocine ring containing **4b**, a synthetic derivative of magallanesine, we then undertook the synthesis of magallanesine starting from 2-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-amine [16] **10b,** which was obtained from benzo[*d*][1,3]dioxole-5-carbaldehyde **15a** as shown in scheme 12 below.

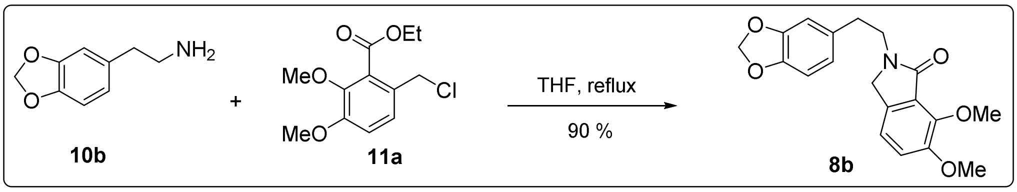


Scheme 12

^{1}H NMR of 2-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-amine (10b):[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73–6.80 (m, 3H), 5.91 (s, 2H), 2.94 (t, J = 6.8, 2H), 2.70 (t, J = 6.8, 2H), 1.40 (br s, 2H).

Compound **10b** on treatment with **11a** in refluxing THF underwent an alkylation followed by amidation in one pot to furnish the lactum **8b**. The structure of **8b** was confirmed by ^{1}H and ^{13}C NMR data.[12] (Scheme 13).



Scheme 13

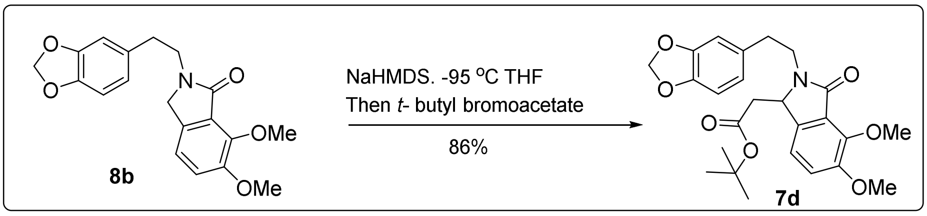
Spectral data of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-6,7-dimethoxyisoindolin-1-one (8b): [12]

IR (KBr): $\tilde{\nu}$ = 2939, 2902, 1683, 1496, 1438, 1271, 1238, 1039, 812 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99-6.92 (m, 2H), 6.64-6.57 (m, 3H), 5.83 (s, 2H), 4.05 (s, 2H), 3.99 (s, 3H), 3.79 (s, 3H), 3.66 (t, J = 7.2 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 152.2 (C), 147.7 (C), 147.1 (C), 146.1 (C), 134.5 (C), 132.6 (C), 125.0 (C), 121.6 (CH), 117.7 (CH), 116.2 (CH), 109.0 (CH), 108.3 (CH), 100.9 (CH_2), 62.5 (CH_3), 56.7 (CH_3), 49.7 (CH_2), 44.3 (CH_2), 34.5 (CH_2).

On treating the isoindoline derivative **8b** with NaHMDS at -95 ^{o}C gave a deep green coloration which was reacted with *t*-butyl bromo acetate **9b** to give **7d** in 84 % yield as a viscous liquid. The structure of **7d** was confirmed by its spectral analysis (Scheme 14).



Scheme 14

Spectral data of *tert*-butyl 2-(2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate (7d):

IR (KBr): $\tilde{\nu}$ = 2978, 2941, 1724, 1689, 1492, 1442, 1280, 1149, 1037 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99-6.97 (m, 2H), 6.66-6.58 (m, 3H), 5.80-5.78 (m, 2H), 4.90 (t, J = 5.6 Hz, 1H), 4.04-3.95 (m, 4H), 3.78-3.76 (m, 3H), 3.21-3.16 (m, 1H), 2.85-2.69 (m, 2H), 1.29-1.27 (m, 9H).

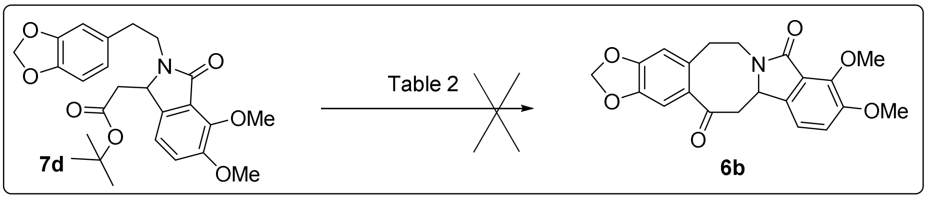
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5 (C), 166.3 (C), 152.5 (C), 147.7 (C), 146.8 (C), 146.1 (C), 138.0 (C), 132.5 (C), 124.3 (C), 121.6 (CH), 117.5 (CH), 116.2 (CH), 109.1 (CH), 108.2 (CH), 100.8 (CH_2), 81.5 (C), 62.4 (CH_3), 56.6 (CH_3), 55.6 (CH), 42.2 (CH_2), 38.9 (CH_2), 34.2 (CH_2), 27.9 (3 X CH_3).

HRMS (ESI): calcd for $C_{25}H_{29}NO_7H$ $[M + H]^+$ 456.2022, found 456.2022.

7d was then subjected to the Eaton's reagent in order to obtain compound **6b** (Table 2). After 2 h at room temperature the reaction turned black in color and its TLC showed no UV active component, instead only a black mass at the base of TLC plate was observed (entry 1). We thought the acidic condition may be decomposing the starting; hence the reaction medium was diluted with dichloromethane, but similar results were obtained (entry 2). No success was achieved even after carrying out the reaction at lower temperature (entry 3). Ester **7d**

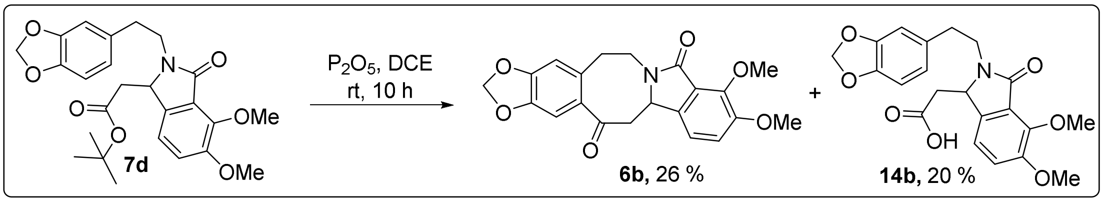
was then hydrolyzed with TFA and treated with Eaton's reagent, however, only decomposition of the starting was seen (entry 4).

Table 2: Attempts to convert **7d** to **6b** using eatons reagent.



Entry	**Reaction condition**	**Results**
1	Eaton reagent, rt, 2 h	Decomposition
2	1:9 (P_2O_5/methanesulphonic acid), DCM, rt, 2 h	Decomposition
3	1:9 (P_2O_5/methanesulphonic acid), DCM, -20 ^oC , 6 h	Decomposition
4	TFA, rt, 2 h, then eaton reagent, 1 h	Decomposition

The decomposition of the starting material was attributed to the presence of methylenedioxy group. Thus the reaction was carried out in the presence of excess of P_2O_5 in dichloroethane during which two major products were obtained on isolation along with some minor impurities. Both these compounds were characterized and confirmed to be the azocine derivative **6d** and hydrolyzed product **14b** (Scheme 15).



Scheme 15

Spectral data of 9,10-dimethoxy-5,6,12b,13-tetrahydro-[1,3]dioxolo[4'',5'':4',5']benzo-[1',2':5,6]azocino[2,1-*a*]isoindole-8,14-dione (6b):

IR (KBr): $\tilde{\nu}$ = 2970, 2920, 1720, 1694, 1460, 1375, 1260, 1050 cm^{-1}.

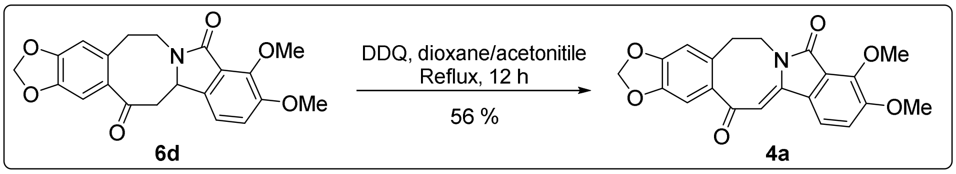
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, J = 8.0 Hz, 1H), 7.04-7.02 (m, 2H), 6.34 (s, 1H), 5.87(dd, J = 12.0 Hz, 1.2 Hz, 2H), 4.75 (s, 1H), 4.45-4.41(m, 1H), 3.88 (d, J = 7.2 Hz, 1H), 3.80 (d, J = 3.6 Hz, 1H), 3.62 (t, J = 4.8 Hz, 1H), 3.56 (d, J = 9.6 Hz, 1H), 3.17 (d, J = 14.6 Hz, 1H), 2.96 (dd, J = 14.0 Hz, 4.4 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ 195.5 (C), 166.07 (C), 152.6 (C), 151.7 (C), 147.2 (C), 146.8 (C), 136.5 (C), 134.6 (C), 132.7 (C), 123.7 (C), 117.5 (CH), 116.4 (CH), 111.3 (CH), 109.1 (CH), 101.8 (CH$_2$), 62.3 (CH$_3$), 57.1 (CH), 56.5 (CH$_3$), 47.1 (CH$_2$), 40.1 (CH$_2$), 34.8 (CH$_2$).
HRMS (ESI): calcd for $C_{21}H_{19}NO_6Na$ [M + Na]$^+$ 404.1110, found 404.1110.

Spectral data of 2-(2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetic acid (14b):

IR (KBr): $\tilde{\nu}$ = 3430, 2952, 2920, 1694, 1690, 1464, 1260, 1055 cm^{-1}.
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.10 (q, *J* = 8.4 Hz, 2H), 6.79-6.67 (m, 3H), 5.90 (q, *J* = 1.6 Hz, 2H), 4.77 (t, *J* = 5.6 Hz, 1H), 4.07 (s, 4H), 3.90 (s, 3H), 3.35-3.28 (m, 1H), 2.96-2.89 (m, 2H), 2.85-2.80 (m, 2H), 2.67 (dd, *J* = 8.4 Hz, 6.4 Hz, 1H).
^{13}C-NMR (100 MHz, CDCl$_3$): δ 174.1 (C), 166.7 (C), 152.6 (C), 147.7 (C), 147.0 (C), 146.2 (C), 137.8 (C), 132.4 (C), 124.0 (C), 121.7 (CH), 117.5 (CH), 116.5 (CH), 109.2 (CH), 108.4 (CH), 100.9 (CH$_2$), 62.5 (CH$_3$), 56.6 (CH$_3$), 55.5 (CH), 42.6 (CH$_2$), 37.8 (CH$_2$), 34.2 (CH$_2$).
HRMS (ESI): calcd for $C_{21}H_{21}NO_7Na$ [M + Na]$^+$ 422.1216, found 422.1216.

Compound **6d** was dehydrogenated using DDQ in dioxane, acetonitrile mixture [9] (Scheme 16). The spectral data were found to be in accordance with literature reported data. [7, 8b, 9]



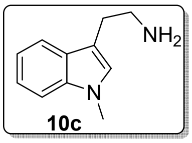
Scheme 16

Spectral data of magallanesine or (*Z*)-9,10-dimethoxy-5,6-dihydro-[1,3]dioxolo[4'',5'':4',5']-benzo[1',2':5,6]azocino[2,1-*a*]isoindole-8,14-dione (4a): [7, 8b, 9]

IR (KBr): $\tilde{\nu}$ = 3007, 2945, 1705, 1690, 1583, 1504, 1276, 1238, 1051, 819 cm^{-1}.
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36 (d, *J* = 8.4 Hz, 1H), 7.16 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.57 (s, 1H), 6.22 (s, 1H), 5.93 (s, 2H), 4.03-4.00 (m, 5H), 3.86 (s, 3H), 3.18 (t, *J* = 5.2 Hz, 2H)
^{13}C NMR (100 MHz, CDCl$_3$): δ 192.3 (C), 165.9 (C), 154.7 (C), 150.5 (C), 147.4 (C), 147.1 (C), 139.1 (C), 134.7 (C), 132.6 (C), 130.9 (C), 119.7 (C), 116.4 (CH), 116.2 (CH), 110.4 (CH), 109.2 (CH), 104.5 (CH), 101.8 (CH$_2$), 62.5 (CH$_3$), 56.6 (CH$_3$), 43.9 (CH$_2$), 33.2 (CH$_2$).
HRMS (ESI): calcd for $C_{21}H_{17}NO_6Na$ [M + Na]$^+$ 402.0954, found 402.0954.

Having successfully synthesized magallanesine **4a** and its dimethoxy derivative **4b**, we extended this strategy for two more analogues. Thus 2-(3,4-dimethoxyphenyl)ethan-1-amine **10a** and 2-(1-methyl-1*H*-indol-3-yl)ethan-1-amine [17] **10c** were condensed with ethyl 2-(bromomethyl)benzoate [18] **11b** to give **8c** and **8d** in 92 and 86 % yield respectively (Table 3).

^{1}H and ^{13}C-NMR of 2-(1-methyl-1H-indol-3-yl)ethan-1-amine (10c): [17]



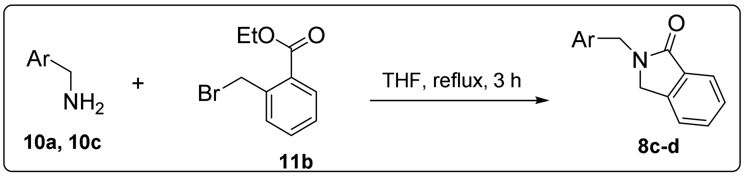
10c

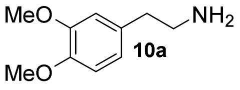
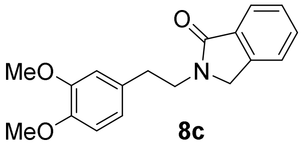
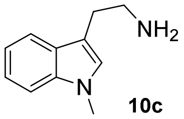
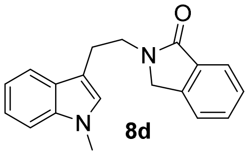
Brown oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.62 (dd, *J* = 7.2 Hz, 0.8 Hz, 1H), 7.33-7.23 (m, 2H), 7.13 (dt, *J* = 6.8 Hz, 08 Hz, 1H), 6.93 (s, 1H), 3.76 (s, 3H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.56 (s, 3H).

^{13}C-NMR (400 MHz, CDCl$_3$): δ 137.2 (C), 127.9 (C), 127.1 (CH), 121.6 (CH), 119.0 (CH), 118.8 (CH), 111.8 (C), 109.3 (CH), 42.2 (CH$_2$), 32.6 (CH$_3$), 28.7 (CH$_2$).

Table 3: One pot alkylation-amidation for synthesis of **8c-d**

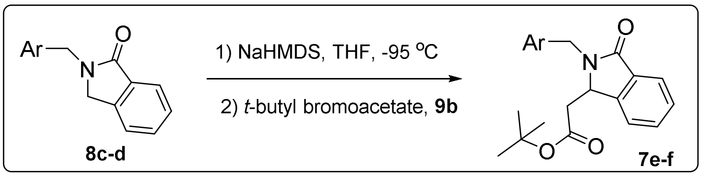


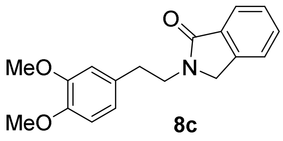
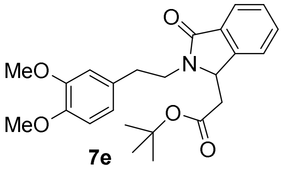
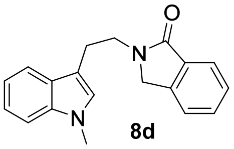
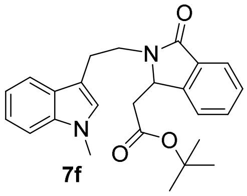
Entry	Starting	Product	% Yield of **8c-d** [a]
1	 **10a**	 **8c**	92
2	 **10c**	 **8d**	86

[a] isolated yield after column purification.

Isoindolinone derivatives **8c** and **8d** were then subjected to anion formation with NaHMDS and alkylation with *t*-butylbromoacetate to achieve alkylated product **7e** and **7f** in 98 and 96 % yield respectively (Table 4).

Table 4: Synthesis of **7e-f**.

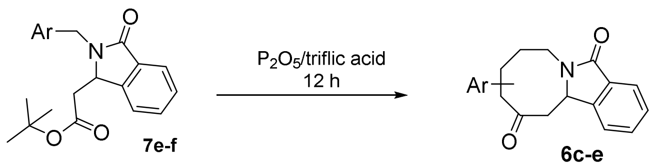


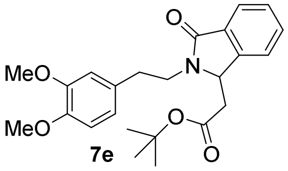
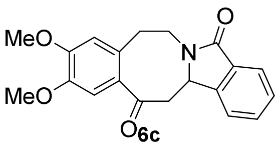
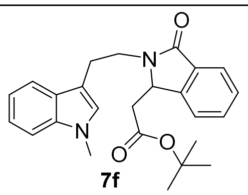
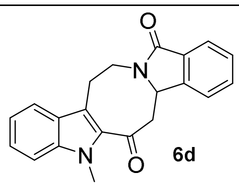
Entry	Starting	Product	% Yield of **7e-f** [a]
1	 **8c**	 **7e**	98
2	 **8d**	 **7f**	96

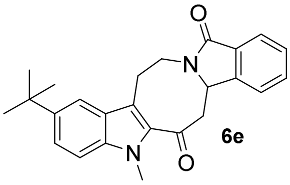
[a] isolated yield after column purification.

Intermediates **7e** and **7f** were subjected to Eaton's reagent to undergo cyclization to form eight membered azocine ring (Table 5). **7e** gave **6c** in 91 % yield as the sole product, whereas **7f** gave two compounds **6d** and **6e** in 30 and 23 % yield respectively. IR spectra of these two compounds were almost similar. But the ^{1}H NMR spectrum of **6e** showed an extra peak at 1.33 ppm accounting for 9 protons. Also a substitution at 5-position of indole ring was observed based on the splitting pattern of the aromatic protons. The compound **6d** was identified to have azocine ring based on the spectral data. The mass spectrum of **6e** showed additional 56 a.m.u ([M + Na]$^+$ 409.1892) as compared to **6d,** which shows [M+Na]$^+$ peak at m/z 353.1266. This suggested the presence of an additional C_4H_9 group which might be coming from *tert*-butanol, which is formed by hydrolysis of the ester.

Table 5: Acylation of **7e-f**



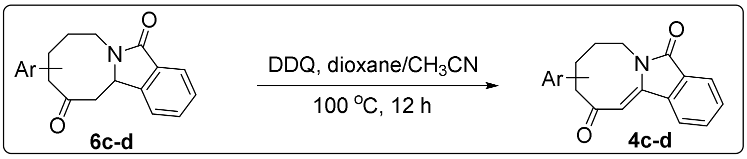
Entry	Starting	Product	% Yield of **6c-e** [a]
1	 **7e**	 **6c**	91
2	 **7f**	 **6d**	30

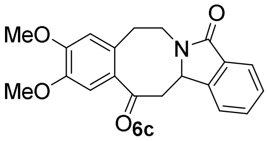
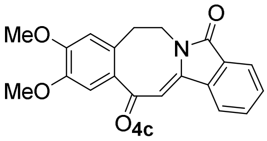
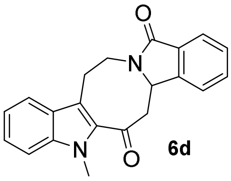
		 **6e**	23

[a] isolated yield after column purification.

Azocine derivative **6c** and **6d** were then subjected to dehydrogenation with DDQ. During this reaction **6c** gave the dehydrogenated product **4c** in 56 % yield (Table 6). However **6d** furnished a mixture of compounds on treating with DDQ (observed on TLC).

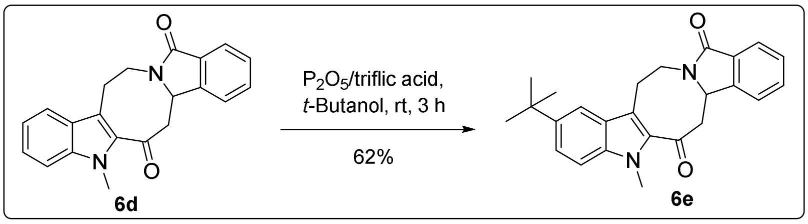
Table 6: Dehydrogenation of **6c-d**



Entry	Starting	Product	% Yield of **4c** [a]
1	 **6c**	 **4c**	56
2	 **6d**	mixtures	-

[a] isolated yield after column purification.

The formation of **6e** was accounted by further reaction of **6d** with *t*-butanol. We conducted a control experiment by treating azocine derivative **6d** with *t*-butanol in Eaton's reagent at room temperature. On isolation 62 % of **6e** was isolated as expected, there by accounting for the formation of **6e** from **7f** during cyclization (Scheme 17).



Scheme 17

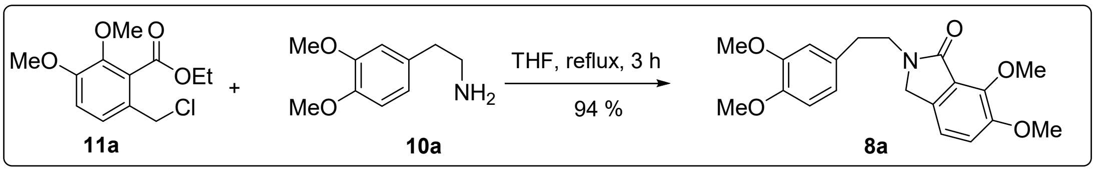
4.4: Conclusion

We have successfully carried out C-C bond formation between isoindolines and alkyl bromoacetates using anion chemistry and one pot Friedel Crafts cyclisation from esters to construct eight membered azocine rings.

The designed synthetic strategy is successfully applied for the synthesis of naturally occurring magallanesine.

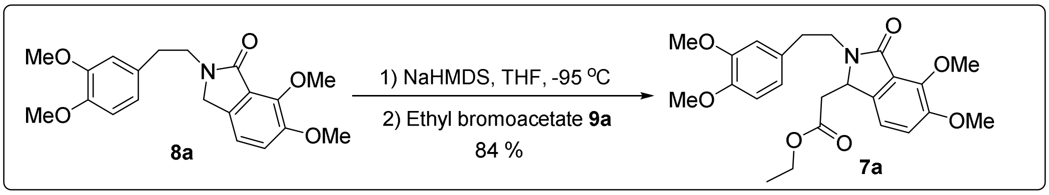
4.5: Experimental

4.5.1: 2-(3,4-dimethoxyphenethyl)-6,7-dimethoxyisoindolin-1-one (8a) [12]



To a magnetically stirred solution of ethyl 6-(chloromethyl)-2,3-dimethoxybenzoate **11a** (1.293 g, 5 mmol) in anhydrous THF (20 mL) was added 2-(3,4-dimethoxyphenyl)ethan-1-amine **10a** (1.82 g, 10 mmol) and refluxed under N_2 atmosphere for 3 h. The resulting mixture was allowed to cool to room temperature and 20 mL water was added and extracted with chloroform (3 x 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and crude product obtained was purified by flash chromatography with 40 % ethyl acetate in petroleum ether to afford 2-(3,4-dimethoxyphenethyl)-6,7-dimethoxyisoindolin-1-one **8a** in 94 % (1.679 g) yield.
Off-white solid, m.p. 116-118 ^{o}C (lit. [12] m.p. 120-120.5 ^{o}C).

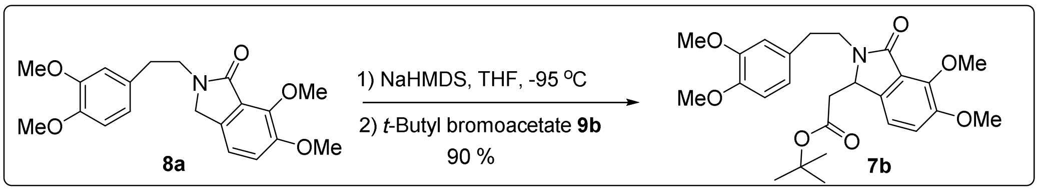
4.5.2: Ethyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate (7a)



To a magnetically stirred solution of 2-(3,4-dimethoxyphenethyl)-6,7-dimethoxyisoindolin-1-one **8a** (0.536 g, 1.5 mmol) in dry THF (10 mL), under N_2 atmosphere at -95 ^{o}C was added NaHMDS (2M in THF) (0.835 mL, 1.65 mmol) in one portion and stirred at this temperature for 1-1.5 h. To the resulting deep green colored solution, ethyl bromoacetate **9a** (0.183 mL, 1.65 mmol) was added at the same temperature. The reaction mixture was then allowed to warm to room temperature and stirred for additional 3 h at rt. This was quenched with 5 % NH_4Cl (10 mL), and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and the residue was flash chromatographed with 30 % ethyl acetate in petroleum ether to afford ethyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate **7a** in 84 % (0.587 g) yield.

Pale yellow liquid.

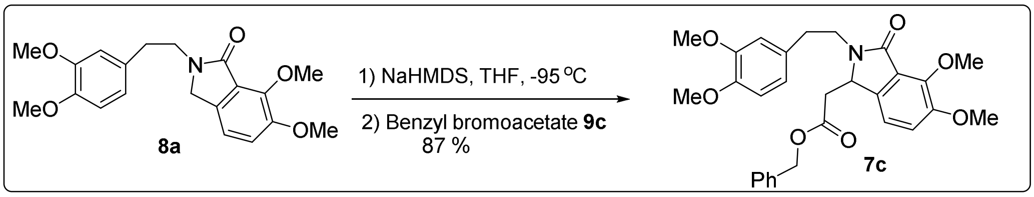
4.5.3: *tert*-Butyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate (7b)



Following the similar procedure described in section 3.5.2 with 2-(3,4-dimethoxyphenethyl)-6,7-dimethoxyisoindolin-1-one **8a** (0.536 g, 1.5 mmol), NaHMDS (0.835 mL, 1.65 mmol) and *tert*-butyl bromoacetate **9b** (0.244 mL, 1.65 mmol) to give *tert*-butyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate **7b** in 90 % (0.636 g) yield.

Pale yellow liquid.

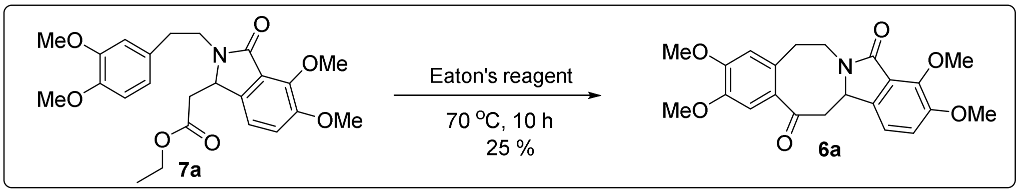
4.5.4: Benzyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate (7c)



Following the similar procedure described in section 3.5.2 with 2-(3,4-dimethoxyphenethyl)-6,7-dimethoxyisoindolin-1-one **8a** (0.536 g, 1.5 mmol), NaHMDS (0.835 mL, 1.65 mmol) and benzyl bromoacetate **9c** (0.261 mL, 1.65 mmol) afforded benzyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate **7c** in 87 % (0.659 g) yield.

Pale yellow liquid.

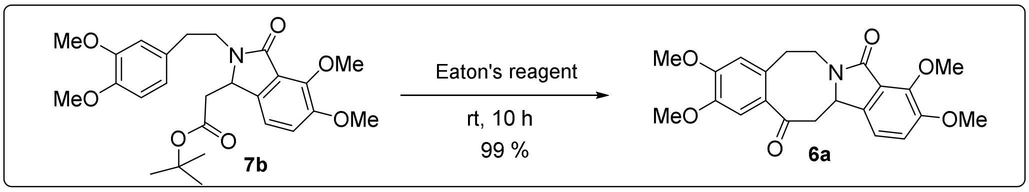
4.5.5: 3,4,10,11-Tetramethoxy-7,8,14,14a-tetrahydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione (6a)


MeO
MeO
OMe
OMe
7a
Eaton's reagent
70 °C, 10 h
25 %
MeO
MeO
OMe
OMe
6a

Ethyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate **7a** (0.443 g, 1 mmol) and Eaton's reagent (4 mL) were heated at 70 °C for 10 h (monitored by TLC). After cooling, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers wereconcentrated under reduced pressure and residue obtained was subjected to flash chromatography with 70 % ethyl acetate in petroleum ether, to afford **6a** in 25 % (0.105 g) yield.

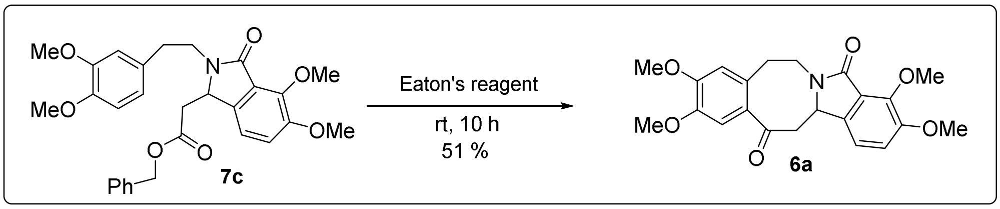
White solid, m.p. 224-226 °C

4.5.6: 3,4,10,11-Tetramethoxy-7,8,14,14a-tetrahydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione (6a)


MeO
MeO
OMe
OMe
7b
Eaton's reagent
rt, 10 h
99 %
MeO
MeO
OMe
OMe
6a

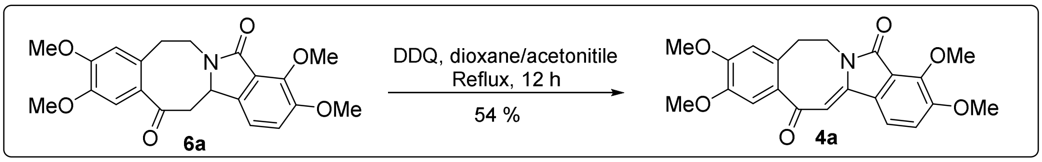
tert-Butyl-2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate **7b** (0.472 g, 1 mmol) and Eaton's reagent (4 mL) were stirred at room temperature for 10 h (monitored by TLC). After cooling, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers wereconcentrated under reduced pressure and residue obtained was purified using flash chromatography with 70 % ethyl acetate in petroleum ether, to afford **6a** in 99 % (0.416 g) yield.

4.5.7: 3,4,10,11-Tetramethoxy-7,8,14,14a-tetrahydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione (6a)


MeO
MeO
OMe
OMe
Ph
7c
Eaton's reagent
rt, 10 h
51 %
MeO
MeO
OMe
OMe
6a

Following the similar protocol described in section 3.5.6 with benzyl 2-(2-(3,4-dimethoxyphenethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate **7c** (0.506 g, 1 mmol) and Eaton's reagent (4 mL) gave product **6a** in 51 % (0.214 g) yield.

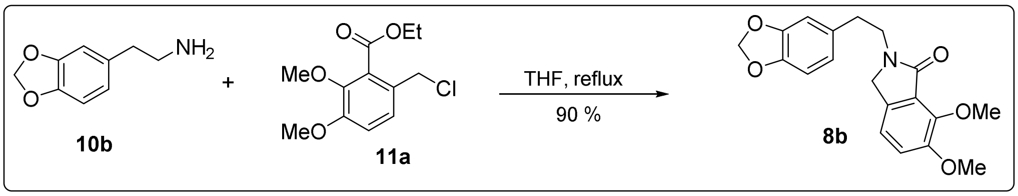
4.5.8: (*Z*)-3,4,10,11-Tetramethoxy-7,8-dihydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione (4a)


MeO
MeO
OMe
OMe
6a
DDQ, dioxane/acetonitile
Reflux, 12 h
54 %
MeO
MeO
OMe
OMe
4a

A magnetically stirred solution of 3,4,10,11-tetramethoxy-7,8,14,14a-tetrahydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione **6a** (0.084 g, 0.2 mmol) and DDQ (0.045 g, 0.2 mmol) in 10 mL of 3:1 mixture of dioxane:acetonitrile was heated at 100 °C for 12 h. The reaction mixture was cooled and concentrated, further purified by flash chromatography using 40 % ethyl acetate in petroleum ether to afford (*Z*)-3,4,10,11-tetramethoxy-7,8-dihydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione **4a** in 54 % (0.045 g) yield.

Yellow solid, m.p. 262-264 °C

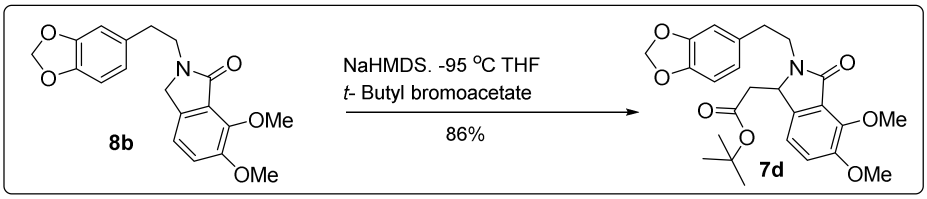
4.5.9: 2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-6,7-dimethoxyisoindolin-1-one (8b) [12]


NH2
10b
+
OEt
MeO
MeO
Cl
11a
THF, reflux
90 %
8b
OMe
OMe

Following the similar protocol described in section 3.5.1 with 2-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-amine **10b** (1.65 g, 10 mmol) and ethyl 6-(chloromethyl)-2,3-dimethoxybenzoate **11a** (1.288 g, 5 mmol), gave the product 2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-6,7-dimethoxyisoindolin-1-one **8b** in 90 % (1.535 g) yield.

Off-white solid, m.p. 96-98 °C (lit. [17d] m.p. 99-100 °C).

4.5.10: *tert*-Butyl 2-(2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate (7d)

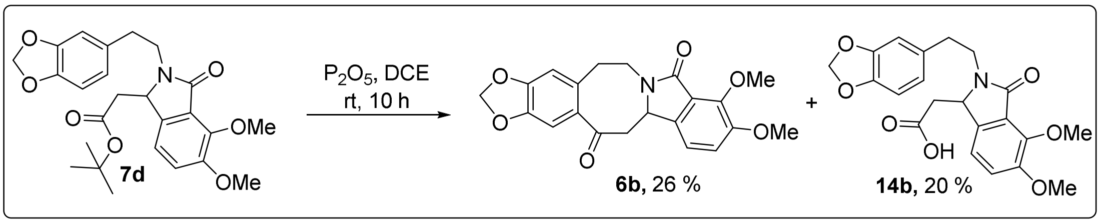

8b
OMe
OMe
NaHMDS. -95 °C THF
t- Butyl bromoacetate
86%
7d
OMe
OMe

Following the similar protocol described in section 3.5.3 with 2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-6,7-dimethoxyisoindolin-1-one **8b** (1.366 g, 4 mmol), NaHMDS (2.20 mL, 4.4 mmol) and *tert*-butyl bromoacetate **9b** (0.650 mL, 4.4 mmol) gave tert-butyl 2-(2-(2-

(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate **7d** in 86 % (1.570 g) yield.

Pale yellow liquid.

4.5.11: 9,10-Dimethoxy-5,6,12b,13-tetrahydro-[1,3]dioxolo[4'',5'':4',5']benzo-[1',2':5,6]azocino[2,1-*a*]isoindole-8,14-dione (6b)



To a magnetically stirred solution of *tert*-butyl 2-(2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetate **7d** (0.183 g, 0.4 mmol) in dichloroethane (5 mL) was added P_2O_5 (0.524 g, 1.84 mmol) and stirred at room temperature for 10 h (monitored by TLC). Reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layers wereconcentrated under reduced pressure and residue obtained was purified using flash chromatography with 70 % ethyl acetate in petroleum ether, to afford **6b** in 26 % (0.042 g) yield and hydrolysed product **14b** in 20 % (0.032 g) yield.

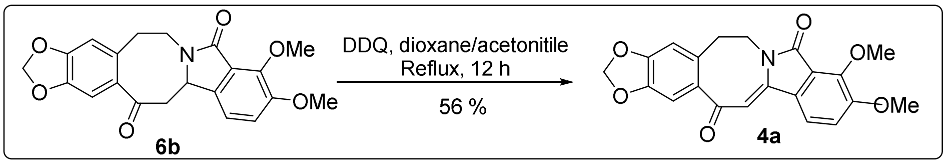
9,10-Dimethoxy-5,6,12b,13-tetrahydro[1,3]dioxolo[4'',5'':4',5']benzo[1',2':5,6]-azocino[2,1-*a*]isoindole-8,14-dione (6b)

White solid, m.p. 216-218 ^oC

2-(2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxy-3-oxoisoindolin-1-yl)acetic acid (14b)

White solid, m.p. 232-234 ^oC

4.5.12:(Z)-9,10-Dimethoxy-5,6-dihydro[1,3]dioxolo[4'',5'':4',5']benzo-[1',2':5,6]azocine-[2,1-*a*]isoindole-8,14-dione (4a) [7, 8b, 9]

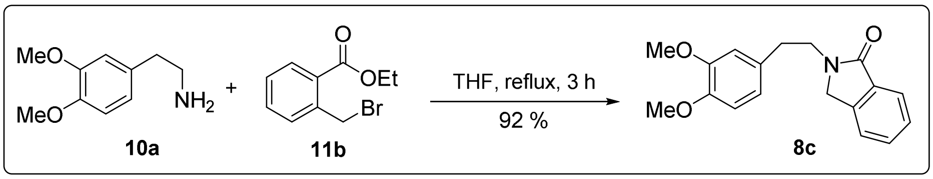


Following the similar protocol described in section 3.5.8 with 9,10-dimethoxy-5,6,12b,13-tetrahydro-[1,3]dioxolo[4",5":4',5']benzo[1',2':5,6]azocino[2,1-*a*]isoindole-8,14-dione **6b** (0.028 g, 0.073 mmol) and DDQ (0.017 g, 0.073 mmol) gave (*Z*)-9,10-dimethoxy-5,6-

dihydro-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':5,6]-azocino[2,1-*a*]isoindole-8,14-dione **4a** 56 % (0.017 g) yield.

Yellow solid, m.p. 252-254 °C (lit.[6] m.p. 255 °C).

4.5. 13: 2-(3,4-Dimethoxyphenethyl)isoindolin-1-one (8c) [12]



Following the similar protocol described in section 3.5.1 with 2-(3,4-dimethoxyphenyl)ethan-1-amine **10a** (0.725 g, 4 mmol) and ethyl 2-(bromomethyl)benzoate **11b** [18] (0.486 g, 2 mmol) furnished 2-(3,4-dimethoxyphenethyl)isoindolin-1-one **8c** 92 % (0.547 g) yield.

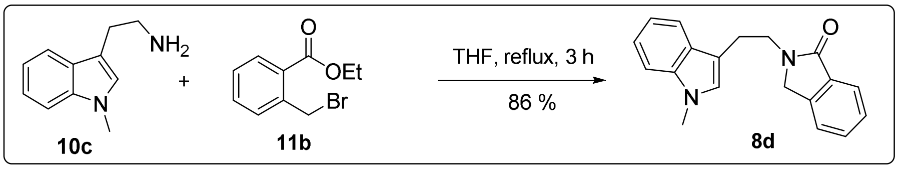
Off white solid, m. p. 97-99 °C (lit.[12] m.p. 98-99 °C).

IR (KBr): $\tilde{\nu}$ = 2999, 2930, 1685, 1591, 1516, 1469, 1232, 1143, 1026, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.2 Hz, 1H), 7.51-7.41 (m, 2H), 7.36 (d, *J* = 7.2 Hz, 1H), 6.77-6.73 (m, 3H), 4.18 (s, 2H), 3.84 (s, 5H), 3.77 (s, 3H), 2.94 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (C), 148.9 (C), 147.6 (C), 141.2 (C), 132.8 (C), 131.3 (C), 131.2 (CH), 128.0 (CH), 123.6 (CH), 122.6 (CH), 120.6 (CH), 111.8 (CH), 111.3 (CH), 55.9 (CH_3), 55.8 (CH_3), 50.8 (CH_2), 44.2 (CH_2), 34.3 (CH_2).

4.5.14: 2-(2-(1-Methyl-1*H*-indol-3-yl)ethyl)isoindolin-1-one (8d)



Following the similar protocol described in section 3.5.1 with 2-(1-methyl-1*H*-indol-3-yl)ethan-1-amine [17] **10c** (0.697 g, 4 mmol) and ethyl 2-(bromomethyl)benzoate [18] **11b** (0.486 g, 2 mmol) gave 2-(2-(1-methyl-1*H*-indol-3-yl)ethyl)isoindolin-1-one **8d** in 86 % (0.499 g) yield.

White solid, m. p. 84-86 °C

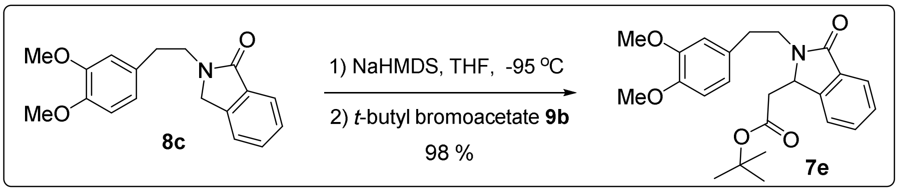
IR (KBr): $\tilde{\nu}$ = 3290, 3070, 2993, 1664, 1597, 1492, 1425, 1236, 1063, 744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.2 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.55-7.46 (m, 2H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.33-7.25 (m, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.96 (s, 1H), 4.32 (s, 2H), 4.00 (t, *J* = 6.8 Hz, 2H), 3.75(s, 3H), 3.18 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (400 MHz, CDCl$_3$): δ 168.6 (C), 141.3 (C), 137.1 (C), 133.0 (C), 131.2 (CH), 128.0 (CH), 126.8 (CH), 123.7 (CH), 122.7 (CH), 121.7 (CH), 118.9 (CH), 118.7 (CH), 111.3 (C), 109.3 (CH), 50.6 (CH$_2$), 43.1 (CH$_2$), 32.7 (CH$_3$), 24.5 (CH$_2$).

HRMS (ESI): calcd for $C_{19}H_{18}N_2ONa$ $[M + Na]^+$ 313.1317, found 313.1317.

4.5.15: *tert*-Butyl-2-(2(3,4-dimethoxyphenethyl)-3-oxoisoindolin-1-yl)acetate (7e)



Following the similar protocol described in section 3.5.3 with 2-(3,4-dimethoxyphenethyl)isoindolin-1-one **8c** (0.446 g, 1.5 mmol), NaHMDS (0.183 mL, 1.65 mmol) and *tert*-butyl bromoacetate **9b** (0.243 mL, 1.65 mmol) afforded *tert*-butyl 2-(2-(3,4-dimethoxyphenethyl)-3-oxoisoindolin-1-yl)acetate **7e** in 98 % (0.605 g) yield.

Light yellow thick oil.

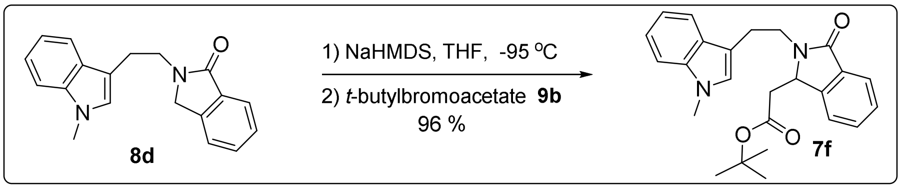
IR (KBr): $\tilde{\nu}$ = 2976, 2935, 1726, 1693, 1514, 1413, 1366, 1263, 1233, 1147 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.72(d, J = 7.6 Hz, 1H), 7.42-7.31 (m, 3H), 6.69-6.65 (m, 3H), 4.62 (t, J = 5.6 Hz, 1H), 4.17-4.10 (m, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.29-3.22 (m, 1H), 2.92-2.85 (m, 1H), 2.80-2.73 (m, 1H), 2.67 (dd, J = 16.0 Hz, 5.2 Hz, 1H), 2.54 (dd, J = 15.6 Hz, 6.0 Hz, 1H), 1.23 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 169.3 (C), 168.2 (C), 148.8 (C), 147.5 (C), 144.7 (C), 132.0 (C), 131.5 (CH), 131.1 (C), 128.3 (CH), 123.3 (CH), 122.4 (CH), 120.6 (CH), 111.8 (CH), 111.2 (CH), 81.4 (C), 56.6 (CH), 55.7 (CH$_3$), 55.6 (CH$_3$), 41.9 (CH$_2$), 38.3 (CH$_2$), 33.9 (CH$_2$), 27.7 (3 X CH$_3$).

HRMS (ESI): calcd for $C_{24}H_{29}NO_5Na$ $[M + Na]^+$ 434.1943, found 434.1943.

4.5.16: *tert*-Butyl 2-(2-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-3-oxoisoindolin-1-yl)acetate (7f)

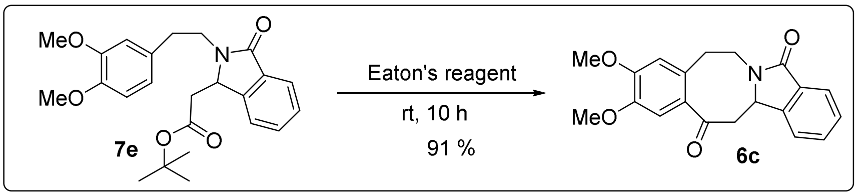


Following the similar protocol described in section 3.5.3 with 2-(2-(1-methyl-1*H*-indol-3-yl)ethyl)isoindolin-1-one **8d** (0.436 g, 1.5 mmol), NaHMDS (0.83 mL, 1.65 mmol) and *tert*-

butyl bromoacetate **9b** (0.243 mL, 1.65 mmol) gave tert-butyl tert-butyl 2-(2-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-3-oxoisoindolin-1-yl)acetate **7f** in 96 % (0.583 g) yield.
Light yellow thick oil.

IR (KBr): $\tilde{\nu}$ = 2976, 2935, 1726, 1680, 1469, 1366, 1151, 1012, 740 cm^{-1}.
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.71(d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.35-7.25 (m, 3H), 7.09-7.25 (m, 2H), 6.95 (t, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.73 (s, 1H), 4.65 (t, *J* = 6.0 Hz, 1H), 4.19-4.15 (m, 1H), 3.46 (s, 3H), 3.36-3.32 (m, 1H), 3.01-2.91 (m, 2H), 2.60 (dd, *J* = 15.6 Hz, 4.8 Hz, 1H), 2.45 (dd, *J* = 16.0 Hz, 7.6 Hz, 1H), 1.16 (s, 9H).
^{13}C-NMR (400 MHz, CDCl$_3$): δ 169.3 (C), 168.3 (C), 144.9 (C), 137.1 (C), 132.3 (C), 131.5 (CH), 128.4 (CH), 127.8 (C), 126.8 (CH), 123.4 (CH), 122.6 (CH), 121.7 (CH), 118.9 (CH), 111.2 (C), 109.3 (CH), 81.4 (C), 56.6 (CH), 40.9 (CH$_2$), 38.2 (CH$_2$), 32.6 (CH$_3$), 27.9 (3 X CH$_3$), 24.4 (CH$_2$).
HRMS (ESI): calcd for $C_{25}H_{28}N_2O_3Na$ [M + Na]$^+$ 427.1998, found 427.1998.

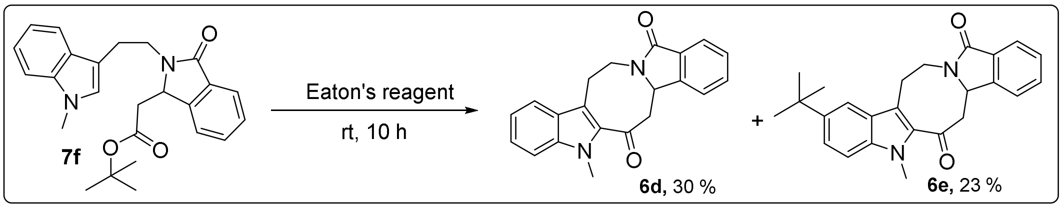
4.5.17: 10,11-Dimethoxy-7,8,14,14a-tetrahydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione (6c)



Following the similar protocol described in section 3.5.6 with tert-butyl 2-(2-(3,4-dimethoxyphenethyl)-3-oxoisoindolin-1-yl)acetate **7e** (0.412 g, 1 mmol), gave 10,11-dimethoxy-7,8,14,14a-tetrahydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione **6c** in 91 % (0.307 g) yield.
White solid, m.p. 228-230 °C

IR (KBr): $\tilde{\nu}$ = 2970, 2910, 1725, 1690, 1463, 1370, 1259, 1088 cm^{-1}.
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.51-7.45 (m, 2H), 7.33 (dt, *J* = 8.0 Hz, 1.2, 1H), 7.15 (s, 1H), 6.64 (s, 1H), 4.84 (d, *J* = 4.8 Hz, 1H), 4.44 (dt, *J* = 13.6 Hz, 5.6 Hz, 1H), 3.96 (dd, *J* = 14.4 Hz, 6.4 Hz, 1H), 3.84 (s, 3H), 3.77-3.68 (m, 4H), 3.43 (dd, *J* = 14.0 Hz, 5.6 Hz, 1H), 3.22 (d, *J* = 14.0 Hz, 1H), 2.93 (dd, *J* = 15.2 Hz, 5.2 Hz, 1H).
^{13}C-NMR (400 MHz, CDCl$_3$): δ 195.2 (C), 168.1 (C), 153.0 (C), 147.7 (C), 143.5 (C), 132.7 (C), 131.9 (CH), 131.5 (C), 130.6 (C), 128.6 (CH), 123.6 (CH), 122.4 (CH), 113.9 (CH), 112.0 (CH), 58.2 (CH), 56.0 (CH$_3$), 55.8 (CH$_3$), 46.3 (CH$_2$), 40.3 (CH$_2$), 34.6 (CH$_2$).
HRMS (ESI): calcd for $C_{20}H_{19}NO_4Na$ [M + Na]$^+$ 360.1212, found 360.1212.

4.5.18: 5-Methyl-7,7a,14,15-tetrahydro-5H-isoindolo[2',1':1,8]azocino[5,4-*b*]indole-6,12-dione (6d)



Following the similar protocol described in section 3.5.6 with *tert*-butyl 2-(2-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-3-oxoisoindolin-1-yl)acetate **7f** (0.404 g, 1 mmol), gave 5-methyl-7,7a,14,15-tetrahydro-5*H*-isoindolo[2',1':1,8]azocino[5,4-*b*]indole-6,12-dione **6d** in 30 % (0.10g) and 2-(*tert*-butyl)-5-methyl-7,7a,14,15-tetrahydro-5*H*-isoindolo[2',1':1,8]-azocino[5,4-*b*]indole-6,12-dione **6e** in 23 % (0.089 g) yield.

5-Methyl-7,7a,14,15-tetrahydro-5H-isoindolo[2',1':1,8]azocino[5,4-*b*]indole-6,12-dione (6d)

Off white solid, m. p. 192-194 ^{o}C

IR (KBr): $\tilde{\nu}$ = 2960, 2908, 1720, 1675, 1420, 1375, 1250, 1108 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.71(d, *J* = 7.6 Hz, 1H), 7.67-7.63 (m, 2H), 7.49-7.45 (m, 1H), 7.38 (dt, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 4.96 (d, *J* = 5.6 Hz, 1H), 4.55-4.50 (m, 1H), 4.11(q, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 3.67-3.65 (m, 2H), 3.56-3.51(m, 1H), 3.30 (d, *J* = 12.4 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ 188.8 (C), 168.7 (C), 143.7 (C), 139.4 (C), 134.1 (C), 131.8 (CH), 131.7 (C), 128.6 (CH), 126.7 (CH), 125.9 (C), 123.8 (CH), 122.5 (CH), 121.2 (C), 120.5 (CH), 120.4 (CH), 110.4 (CH), 58.0 (CH), 46.0 (CH$_2$), 39.8 (CH$_2$), 32.6 (CH$_3$), 24.1 (CH$_2$).

HRMS (ESI): calcd for $C_{21}H_{18}N_2O_2Na$ [M + Na]$^+$ 353.1266, found 353.1266.

2-(*tert*-Butyl)-5-methyl-7,7a,14,15-tetrahydro-5*H*-isoindolo[2',1':1,8]azocino[5,4-*b*]indole-6,12-dione (6e)

Off white solid, m. p. 172-174 ^{o}C

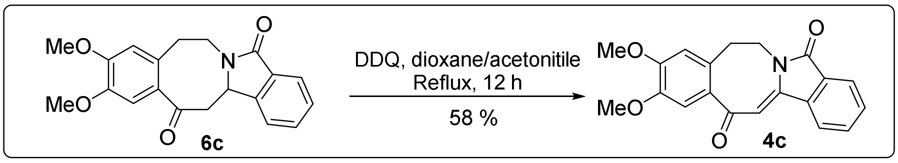
IR (KBr): $\tilde{\nu}$ = 2963, 2904, 1718, 1676, 1633, 1421, 1377, 1242, 1232, 750 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.62 (d, *J* = 7.6 Hz, 1H), 7.57-7.55 (m, 3H), 7.41-7.37 (m, 2H), 7.15 (d, *J* = 8.8 Hz, 1H), 4.87 (d, *J* = 5.6 Hz, 1H), 4.49-4.41 (m, 1H), 4.06-4.00 (m, 1H), 3.67 (s, 3H), 3.63-3.55 (m, 2H), 3.51-3.44 (m, 1H), 3.13 (d, *J* = 13.2 Hz, 1H), 1.33 (s, 9H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ 188.6 (C), 168.8 (C), 143.7 (C), 143.3 (C), 137.9 (C), 134.3 (C), 131.8 (CH), 131.7 (C), 128.6 (CH), 125.8 (CH), 125.5 (C), 123.8 (CH), 122.5 (CH), 121.3 (C), 115.5 (CH), 110.1 (CH), 58.0 (CH), 45.9 (CH_2), 39.8 (CH_2), 34.7 (C), 32.6 (CH_3), 31.7 (3 XCH_3), 24.0 (CH_2).

HRMS (ESI): calcd for $C_{25}H_{26}N_2O_2Na$ $[M + Na]^+$ 409.1892, found 409.1892.

4.5.19: (*Z*)-10,11-Dimethoxy-7,8-dihydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione (4c)



Following the similar protocol described in section 3.5.8 with 10,11-dimethoxy-7,8,14,14a-tetrahydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione **6c** (0.068 g, 0.2 mmol) and DDQ (0.045 g, 0.2 mmol) gave (*Z*)-10,11-dimethoxy-7,8-dihydrobenzo[5,6]azocino[2,1-*a*]isoindole-5,13-dione **4c** 58 % (0.039 g) yield.

Yellow solid, m. p. 248-250 °C

IR (KBr): $\tilde{\nu}$ = 2991, 2956, 1703, 1683, 1580, 1510, 1430, 1355, 1280, 1079 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (td, *J* = 7.2 Hz, 0.8, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.56 (td, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.29 (s, 1H), 6.57 (s, 1H), 6.30 (s, 1H), 4.10-4.07 (m, 2H), 3.86 (d, *J* = 5.6 Hz, 6H), 3.24-3.21 (m, 2H).

^{13}C-NMR (400 MHz, $CDCl_3$): δ 192.8 (C), 167.3 (C), 151.8 (C), 147.8 (C), 138.2 (C), 137.6 (C), 133.6 (C), 132.7 (CH), 130.7 (CH), 130.6 (C), 128.4 (C), 123.9 (CH), 120.4 (CH), 113.6 (CH), 112.3 (CH), 105.8 (CH), 56.1 (CH_3), 56.0 (CH_3), 42.5 (CH_2), 34.4 (CH_2).

HRMS (ESI): calcd for $C_{20}H_{17}NO_4H$ $[M + H]^+$ 336.1236, found 336.1236.

4.6: References

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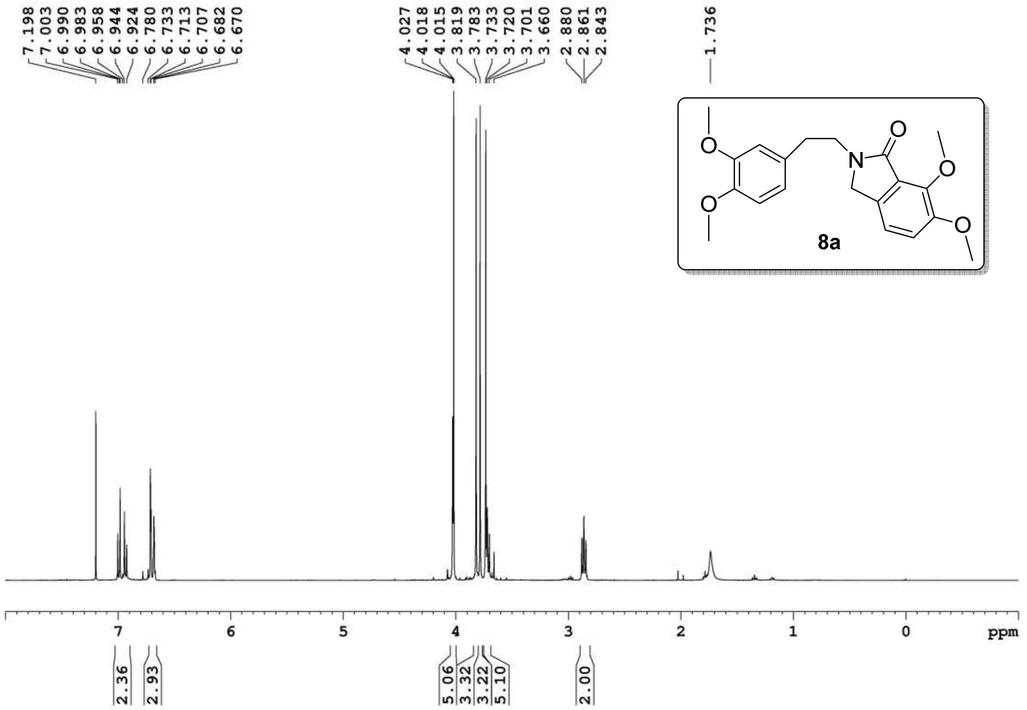
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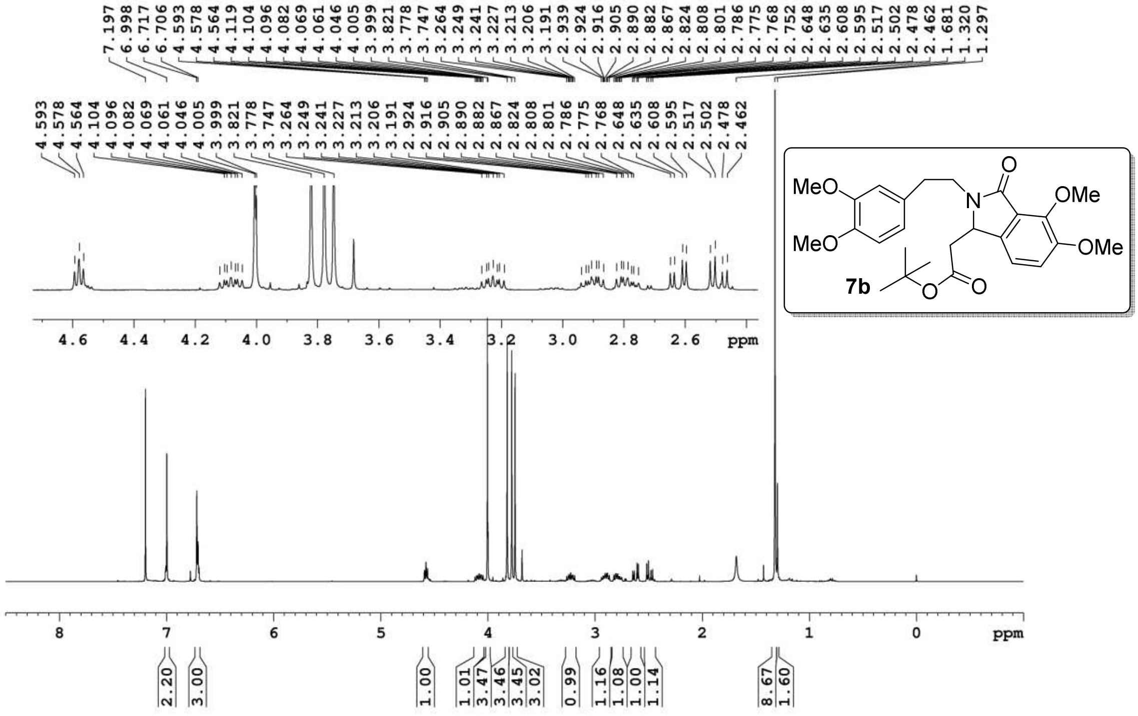
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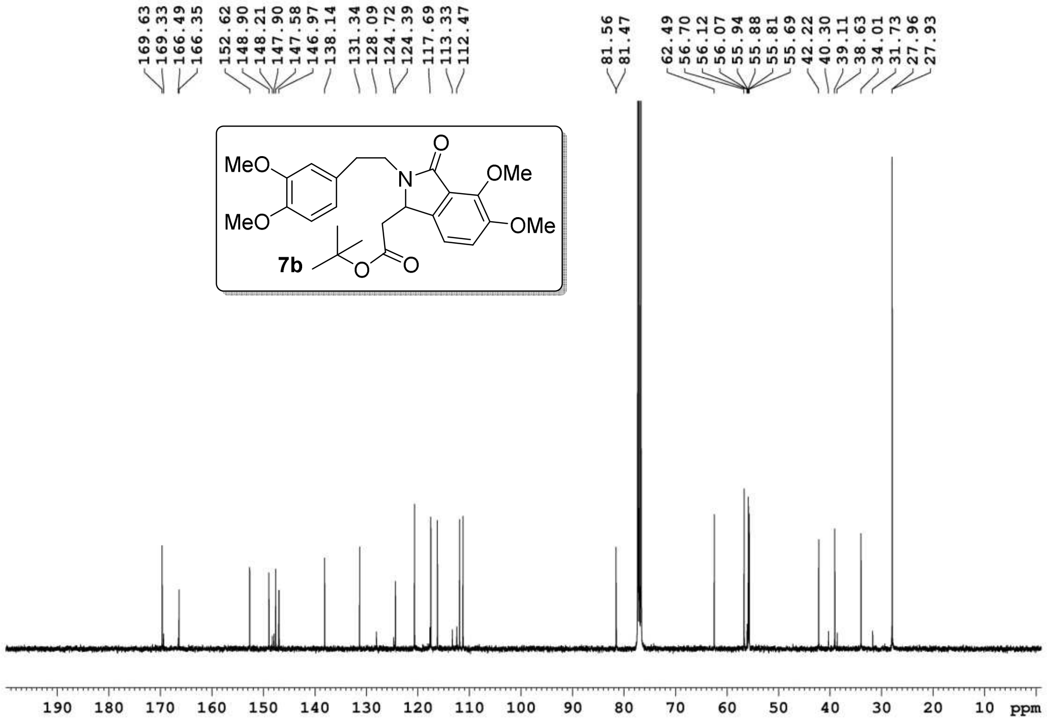
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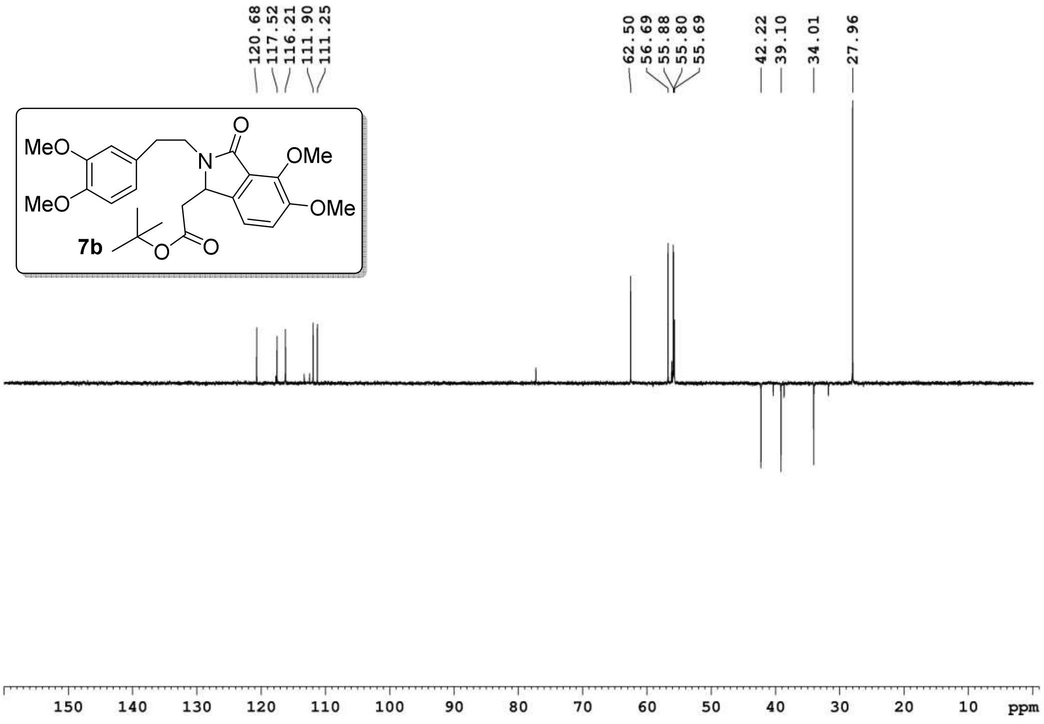
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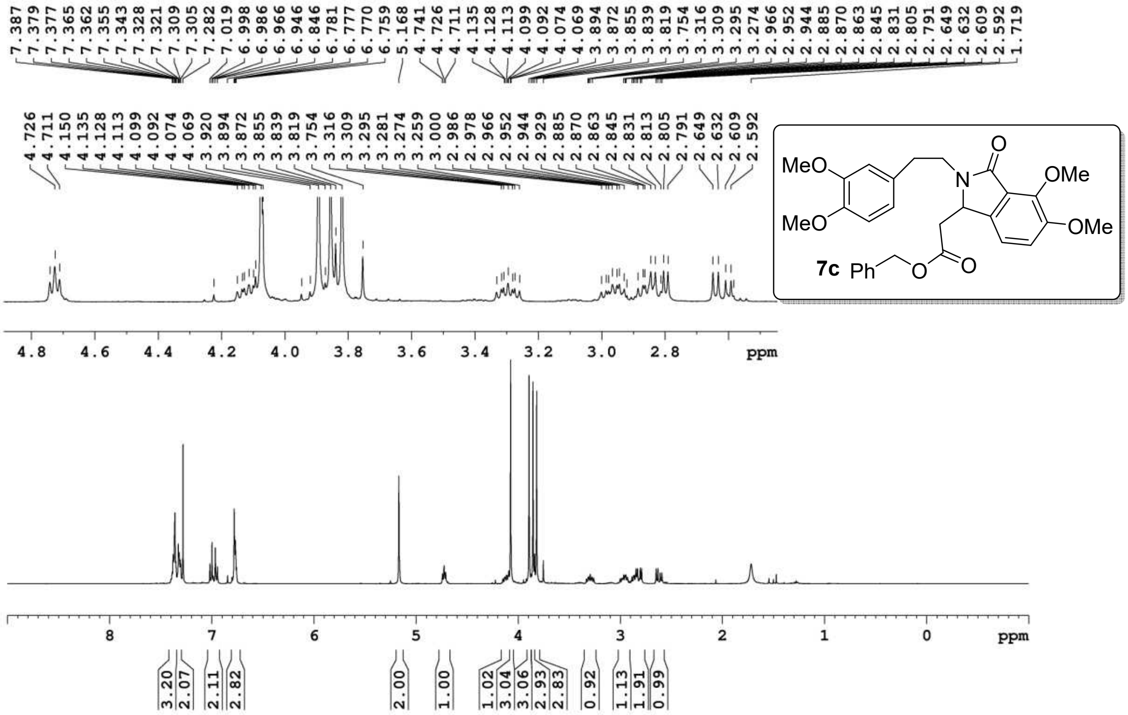
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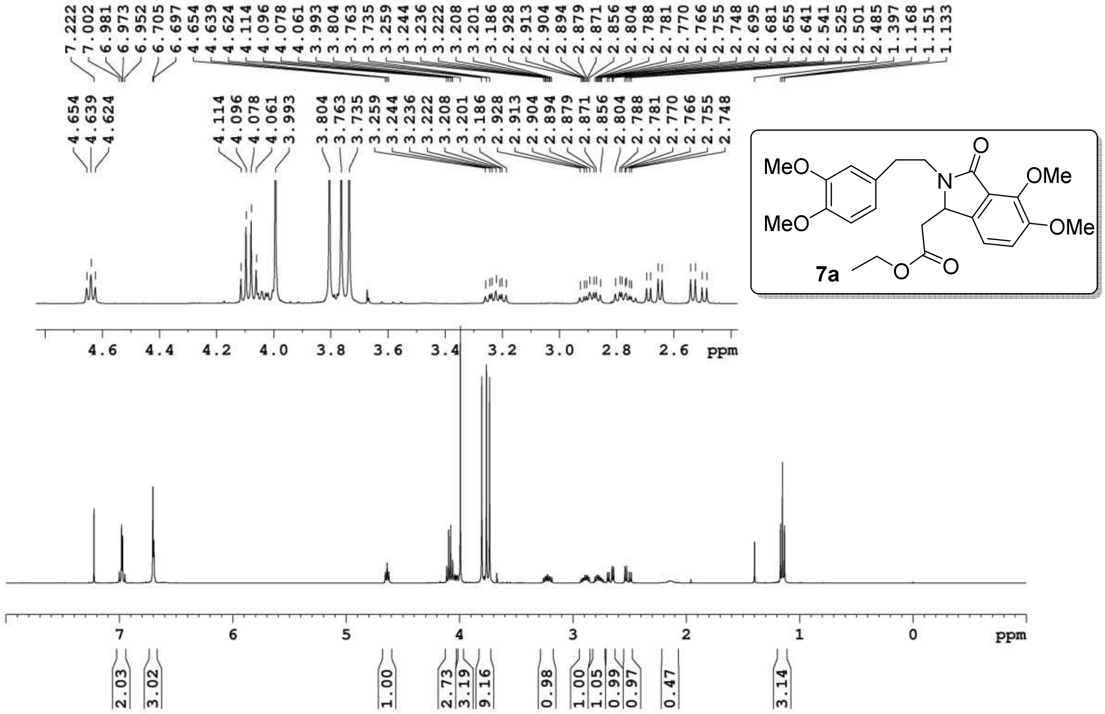
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3.236
3.222
3.208
3.201
3.186
2.928
2.913
2.904
2.894
2.879
2.871
2.856
2.804
2.788
2.781
2.770
2.766
2.755
2.748
2.695
2.681
2.655
2.641
2.541
2.525
2.501
2.485
1.397
1.168
1.151
1.133
4.654
4.639
4.624
4.114
4.096
4.078
4.061
3.993
3.804
3.763
3.735
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3.244
3.236
3.222
3.208
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2.928
2.913
2.904
2.894
2.879
2.871
2.856
2.804
2.788
2.781
2.770
2.766
2.755
2.748
MeO
MeO
N
O
OMe
OMe
7a
O
O
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
ppm
7
6
5
4
3
2
1
0
ppm
2.03
3.02
1.00
2.73
3.19
9.16
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1.00
1.05
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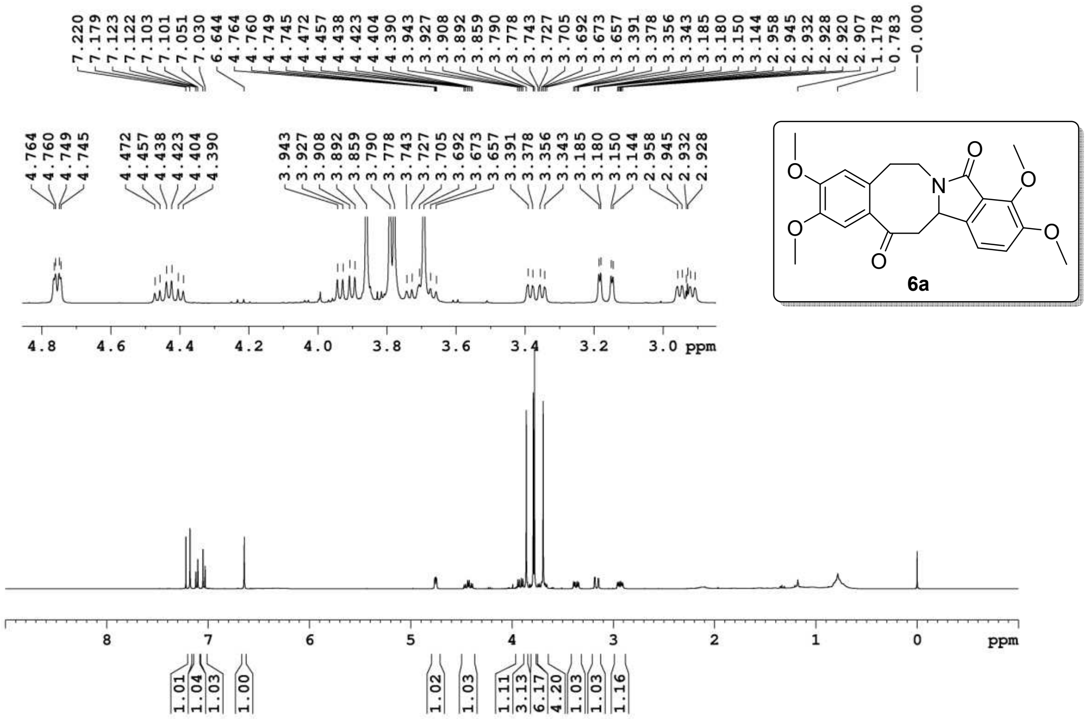
0.97
0.47
3.14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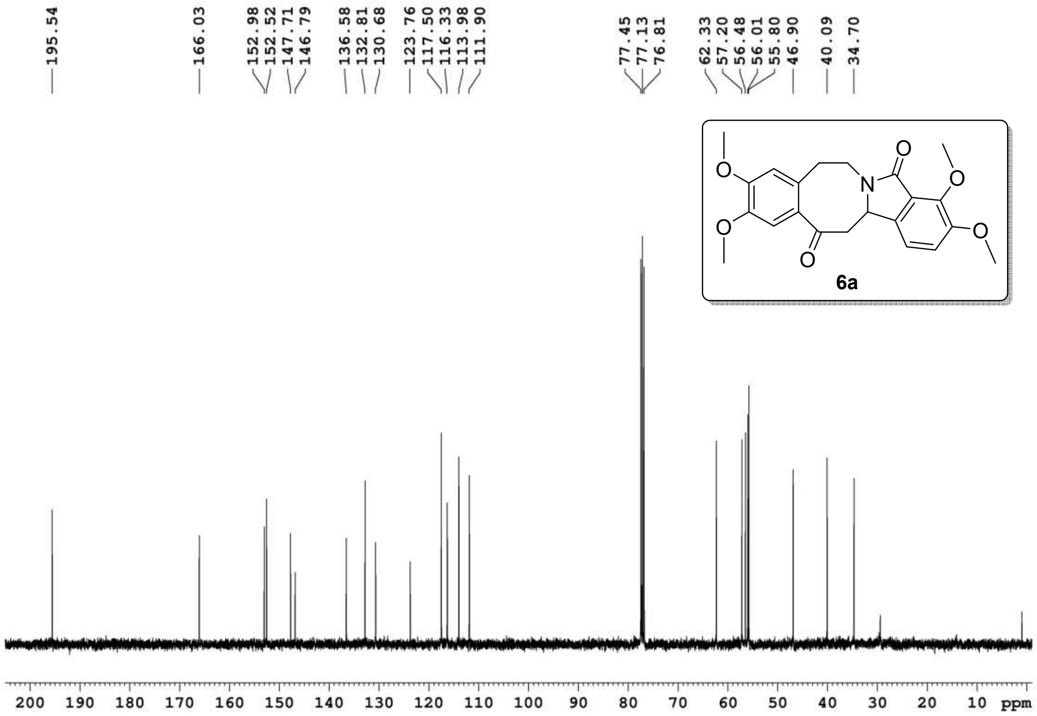
7.179
7.123
7.122
7.103
7.101
7.051
7.030
6.644
4.764
4.760
4.749
4.745
4.472
4.457
4.438
4.423
4.404
4.390
3.943
3.927
3.908
3.892
3.859
3.790
3.778
3.743
3.727
3.705
3.692
3.673
3.657
3.391
3.378
3.356
3.343
3.185
3.180
3.150
3.144
2.958
2.945
2.932
2.928
2.920
2.907
1.178
0.783
-0.000
4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 ppm
8 7 6 5 4 3 2 1 0 ppm
1.01
1.04
1.03
1.00
1.02
1.03
1.11
3.13
6.17
4.20
1.03
1.03
1.16
O
N
6a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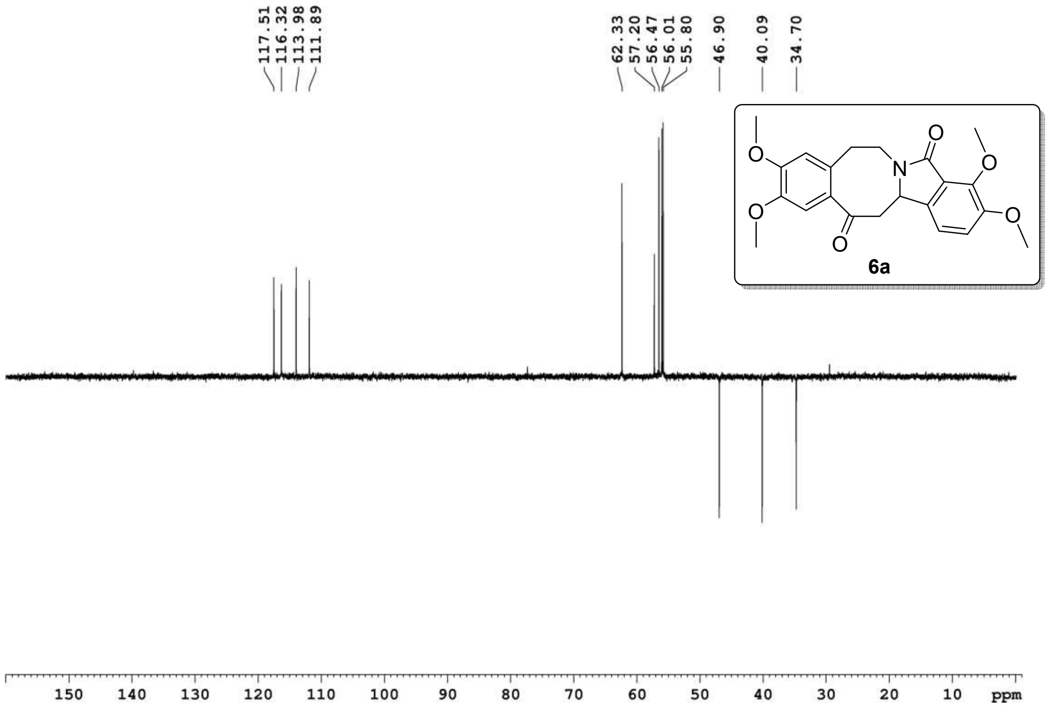
166.03
152.98
152.52
147.71
146.79
136.58
132.81
130.68
123.76
117.50
116.33
113.98
111.90
77.45
77.13
76.81
62.33
57.20
56.48
56.01
55.80
46.90
40.09
34.70
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
O
N
6a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116.32
113.98
111.89
62.33
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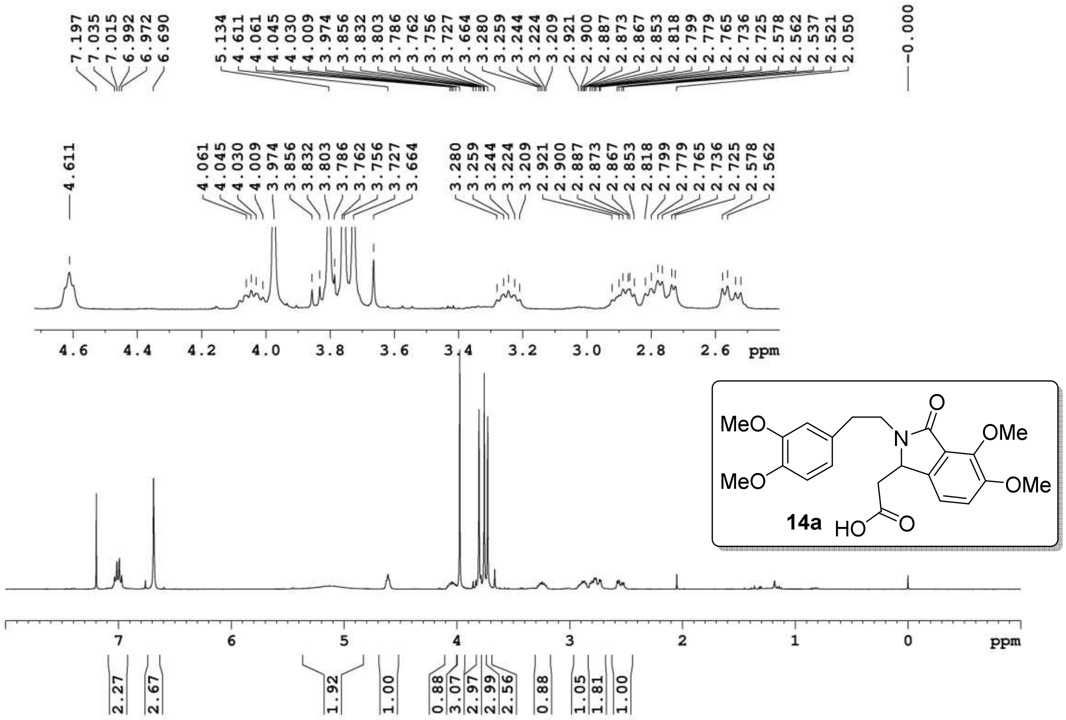
56.47
56.01
55.80
46.90
40.09
34.70
6a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.015
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6.972
6.690
5.134
4.611
4.061
4.045
4.030
4.009
3.974
3.856
3.832
3.803
3.786
3.762
3.756
3.727
3.664
3.280
3.259
3.244
3.224
3.209
2.921
2.900
2.887
2.873
2.867
2.853
2.818
2.799
2.779
2.765
2.736
2.725
2.578
2.562
2.537
2.521
2.050
-0.000
4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 ppm
MeO
MeO
OMe
OMe
N
O
HO
O
14a
7 6 5 4 3 2 1 0 ppm
2.27
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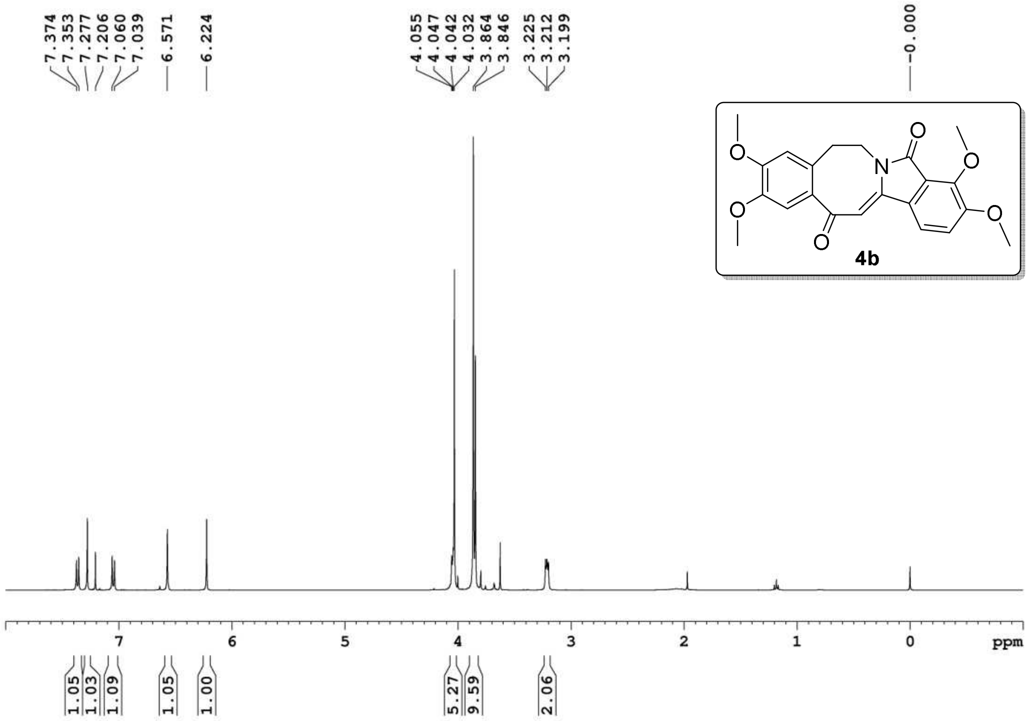
0.88
3.07
2.97
2.99
2.56
0.88
1.05
1.81
1.00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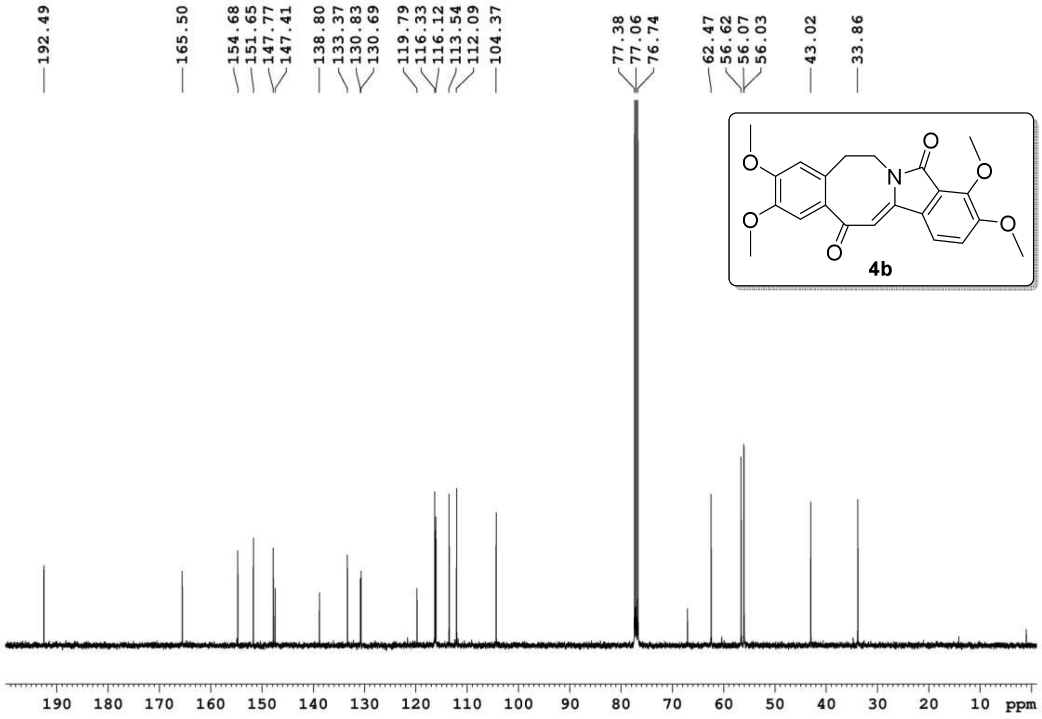
7.277
7.206
7.060
7.039
6.571
6.224
4.055
4.047
4.042
4.032
3.864
3.846
3.225
3.212
3.199
0.000
O
O
N
O
O
O
O
4b
7
6
5
4
3
2
1
0
ppm
1.05
1.03
1.09
1.05
1.00
5.27
9.59
2.06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147.41
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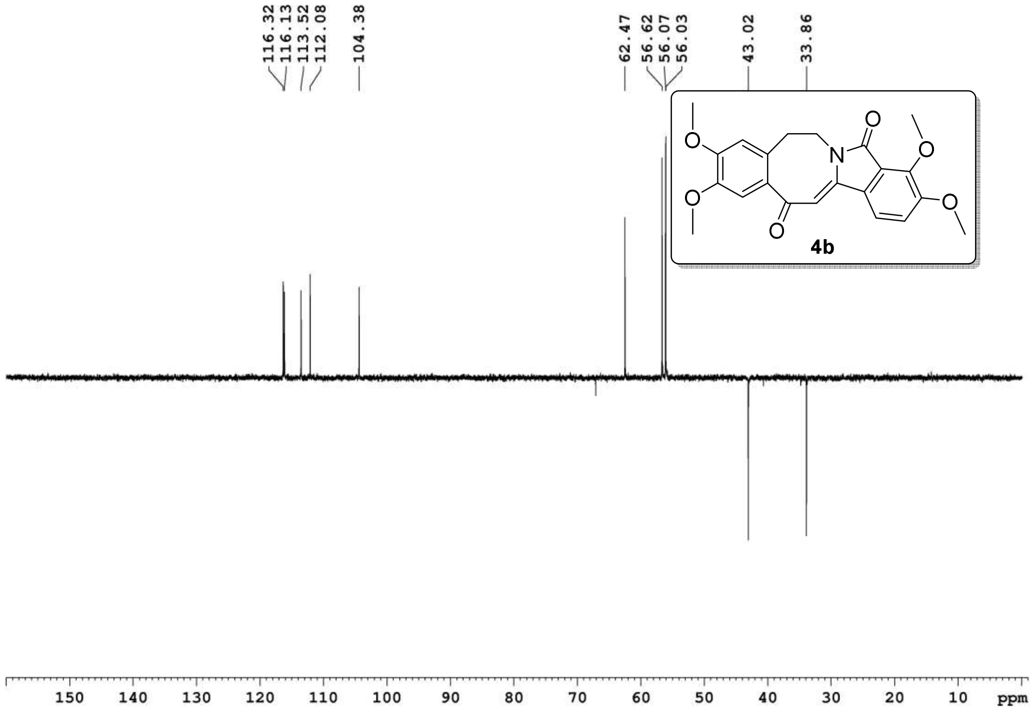
133.37
130.83
130.69
119.79
116.33
116.12
113.54
112.09
104.37
77.38
77.06
76.74
62.47
56.62
56.07
56.03
43.02
33.86
O
O
N
O
O
O
O
4b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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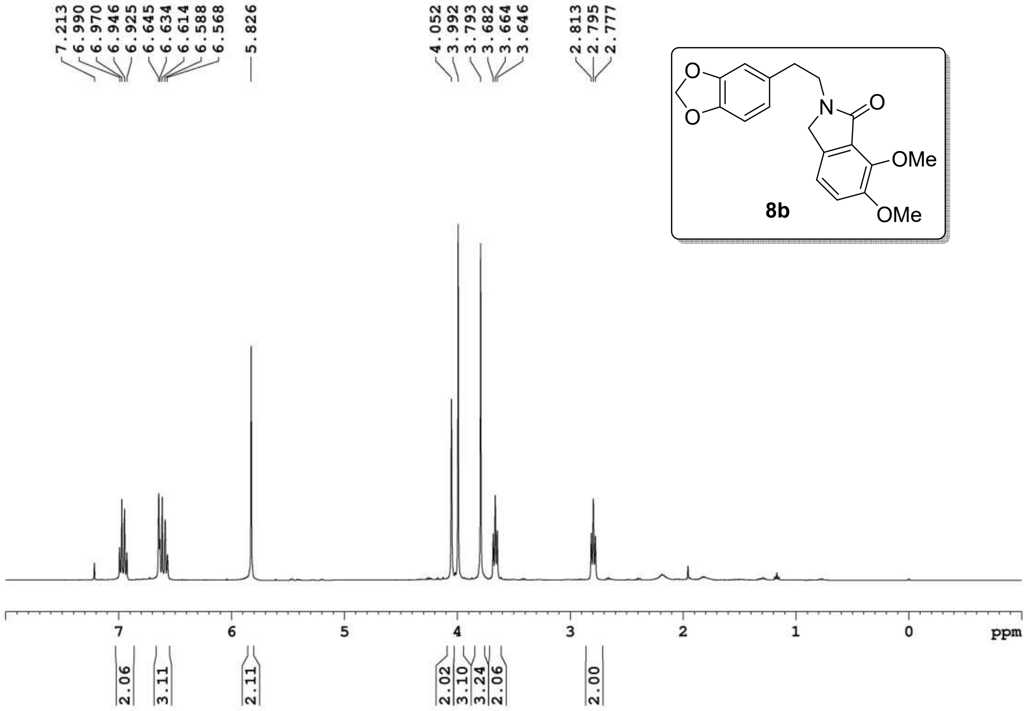
116.13
113.52
112.08
104.38
62.47
56.62
56.07
56.03
43.02
33.86
O
O
O
O
N
O
O
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

4b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6.990
6.970
6.946
6.925
6.645
6.634
6.614
6.588
6.568
5.826
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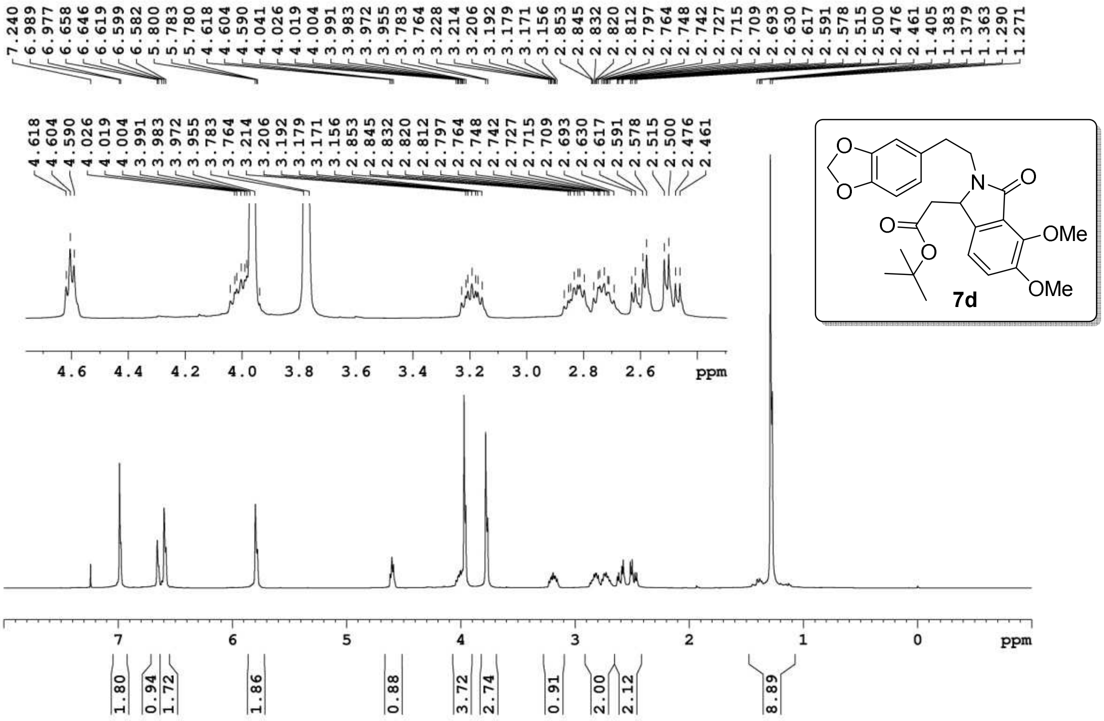
3.992
3.793
3.682
3.664
3.646
2.813
2.795
2.777
O
O
N
O
OMe
OMe
7
6
5
4
3
2
1
0
ppm
2.06
3.11
2.11
2.02
3.10
3.24
2.06
2.00

8b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6.989
6.977
6.658
6.646
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6.599
6.582
5.800
5.783
5.780
4.618
4.604
4.590
4.041
4.026
4.019
4.004
3.991
3.983
3.972
3.955
3.783
3.764
3.228
3.214
3.206
3.192
3.179
3.171
3.156
2.853
2.845
2.832
2.820
2.812
2.797
2.764
2.748
2.742
2.727
2.715
2.709
2.693
2.630
2.617
2.591
2.578
2.515
2.500
2.476
2.461
1.405
1.383
1.379
1.363
1.290
1.271
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
ppm
7
6
5
4
3
2
1
0
ppm
1.80
0.94
1.72
1.86
0.88
3.72
2.74
0.91
2.00
2.12
8.89
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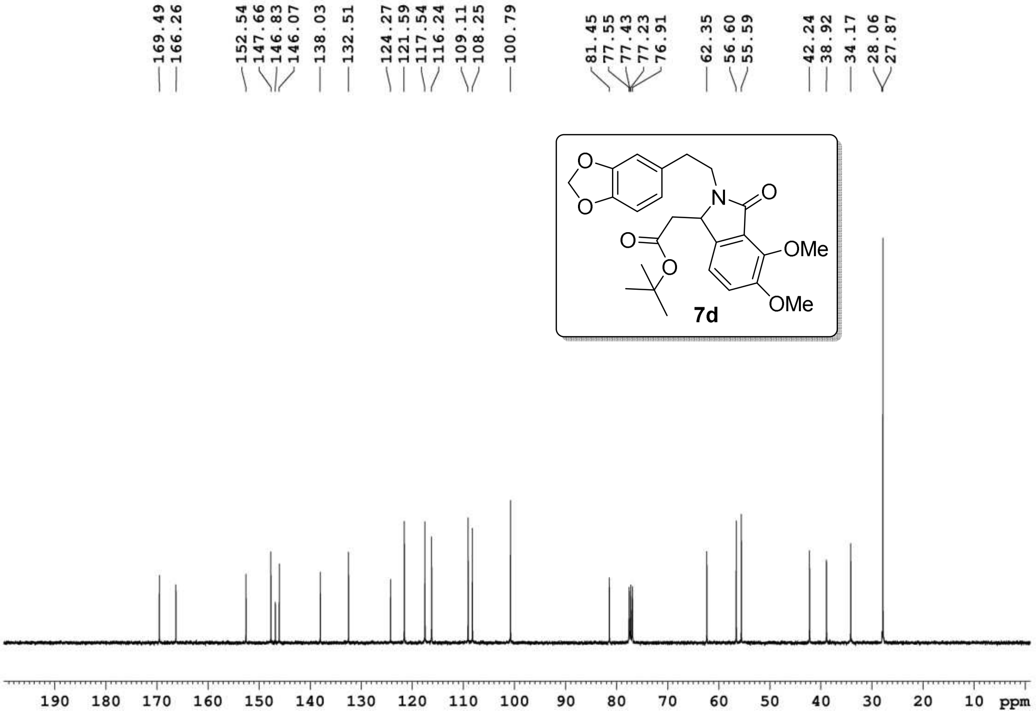
N
O
O
O
OMe
OMe
7d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146.07
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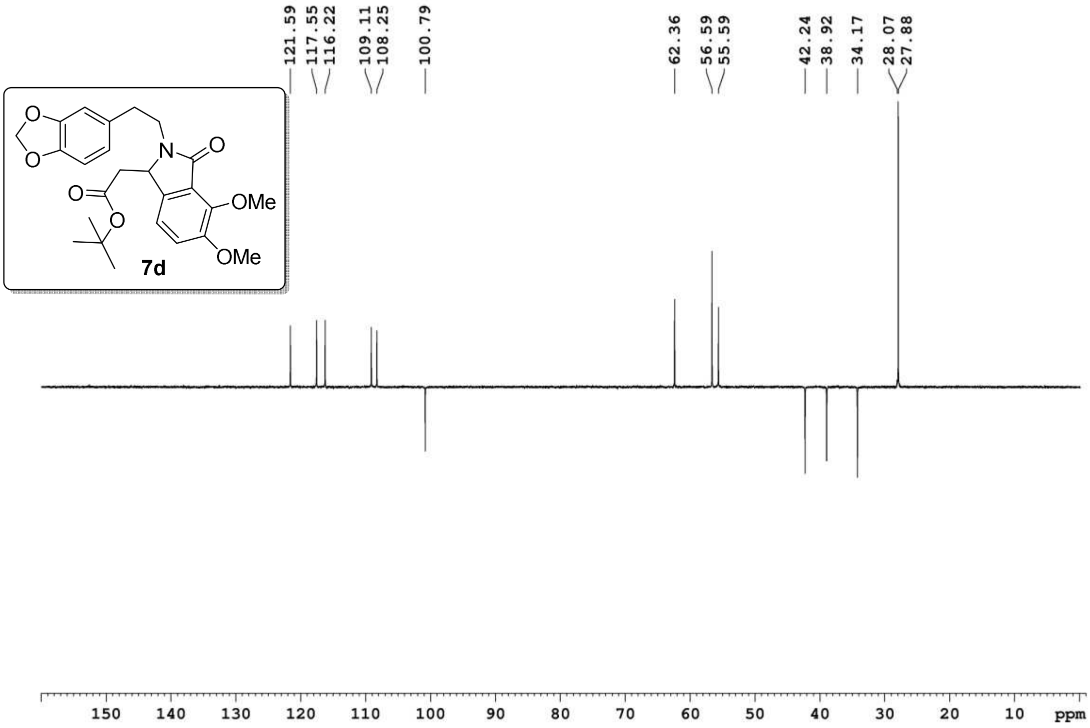
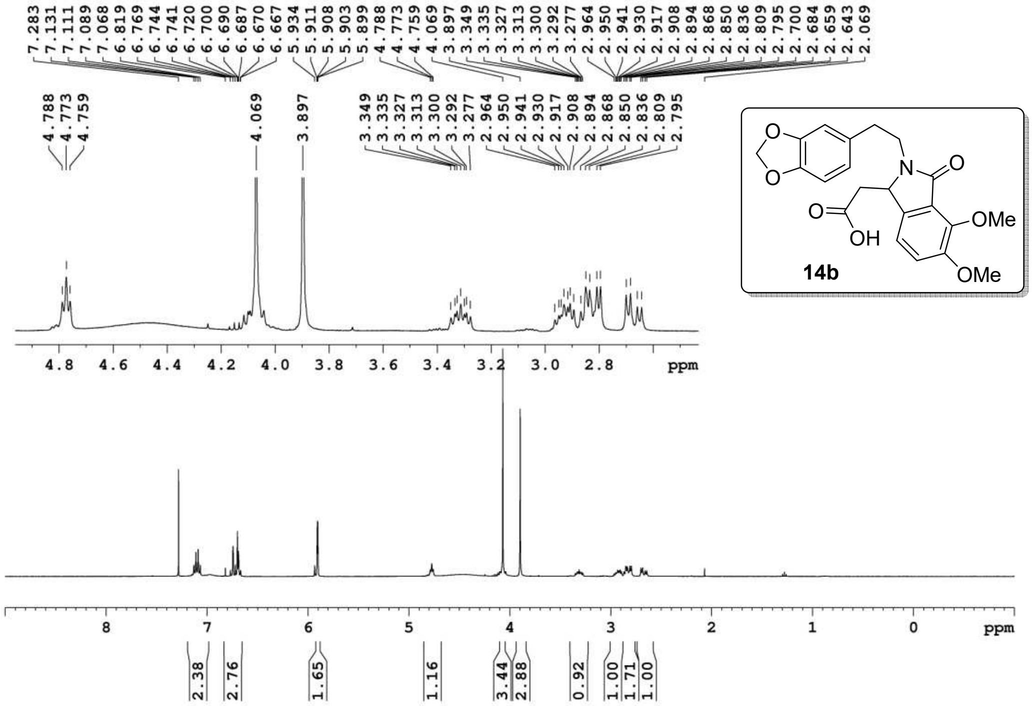
132.51
124.27
121.59
117.54
116.24
109.11
108.25
100.79
81.45
77.55
77.43
77.23
76.91
62.35
56.60
55.59
42.24
38.92
34.17
28.06
27.87
O
O
N
O
O
O
OMe
OMe
7d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


121.59
117.55
116.22
109.11
108.25
100.79
62.36
56.59
55.59
42.24
38.92
34.17
28.07
27.88
O
N
O
OMe
OMe
O
O
O
7d
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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4.788 4.773 4.759
4.069
3.897
3.349 3.335 3.327 3.313 3.300 3.292 3.277 2.964 2.950 2.941 2.930 2.917 2.908 2.894 2.868 2.850 2.836 2.809 2.795
4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 ppm
O
N
O
O
OH
OMe
OMe
14b
8 7 6 5 4 3 2 1 0 ppm
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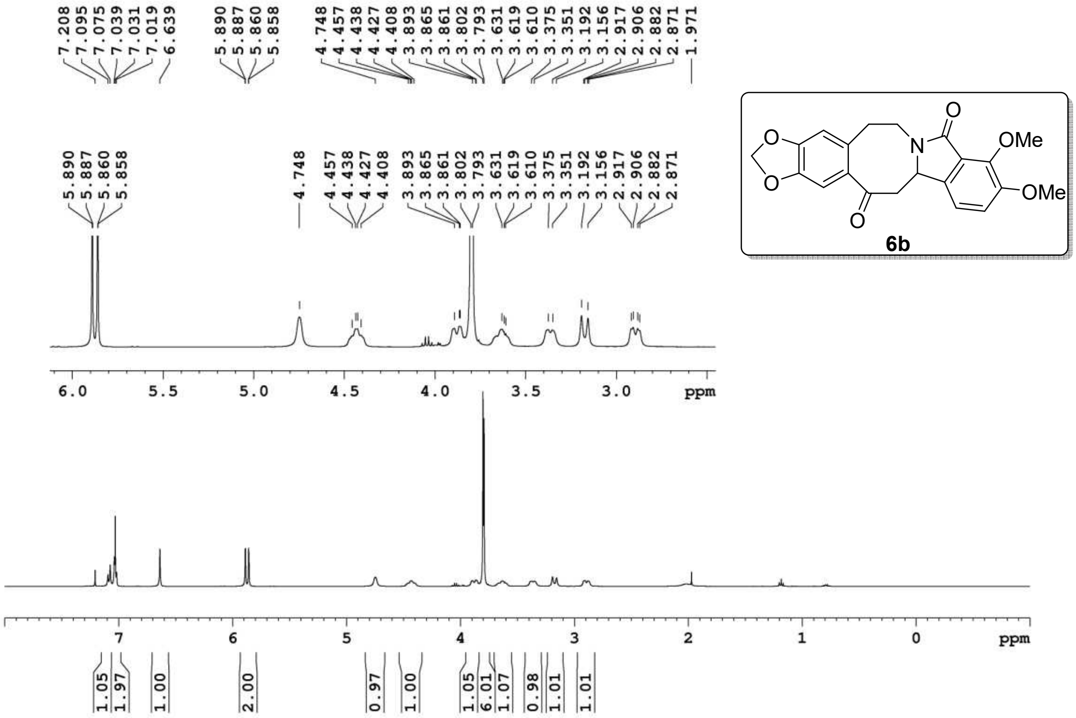
2.76
1.65
1.16
3.44
2.88
0.92
1.00
1.71
1.00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7.019
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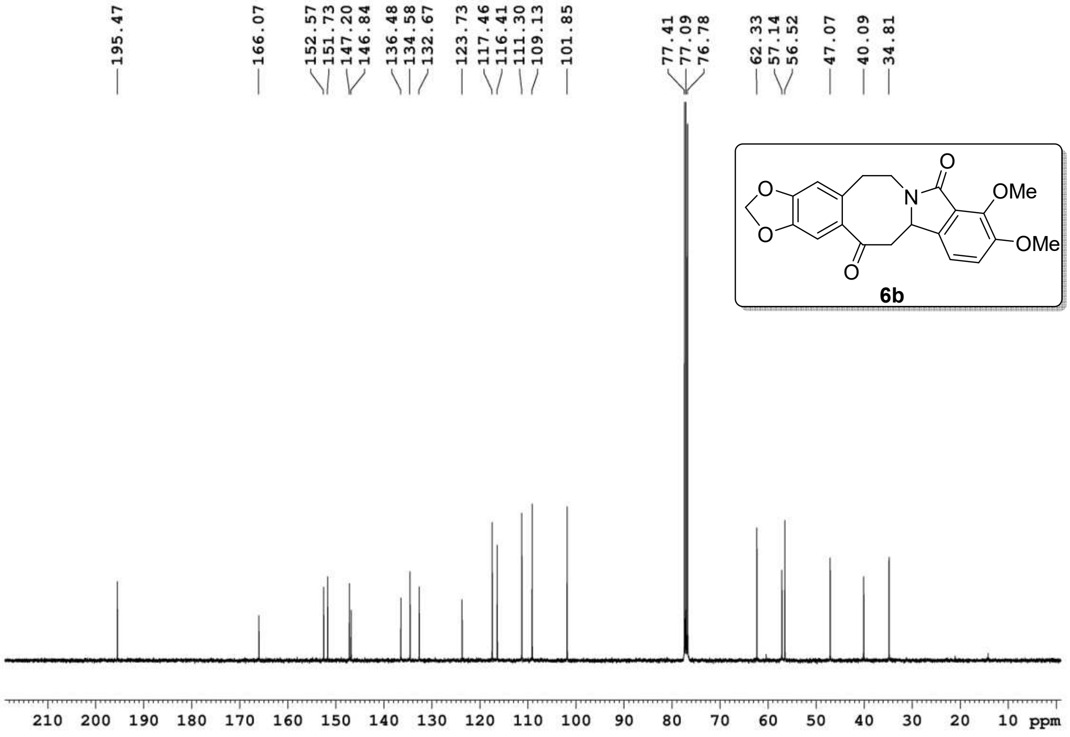
5.860
5.858
4.748
4.457
4.438
4.427
4.408
3.893
3.865
3.861
3.802
3.793
3.631
3.619
3.610
3.375
3.351
3.192
3.156
2.917
2.906
2.882
2.871
1.971
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
7
6
5
4
3
2
1
0
ppm
1.05
1.97
1.00
2.00
0.97
1.00
1.05
6.01
1.07
0.98
1.01
1.01
O
OMe
N
OMe
O
O
O

6b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132.67
123.73
117.46
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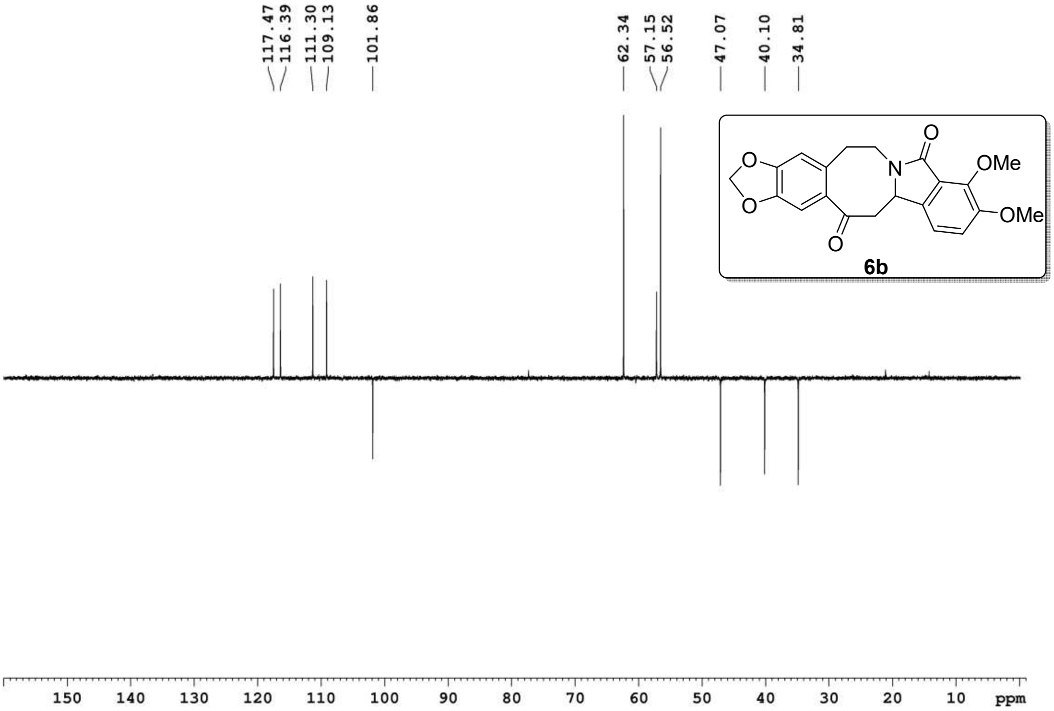
111.30
109.13
101.85
77.41
77.09
76.78
62.33
57.14
56.52
47.07
40.09
34.81
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
O
OMe
N
OMe
O
O
O

6b


6b
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101.86
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57.15
56.52
47.07
40.10
34.81
OMe
OMe
O
N
150
140
130
120
110
100
90
80
70
60
50
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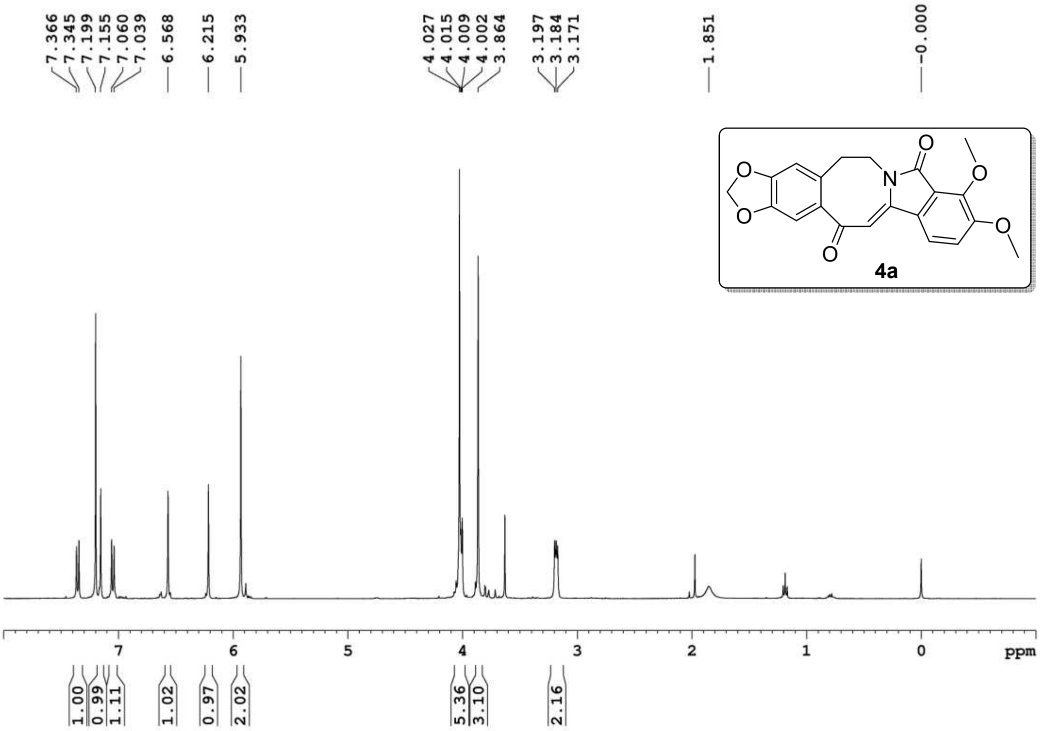
30
20
10
ppm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5.933
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4.009
4.002
3.864
3.197
3.184
3.171
1.851
0.000
O
N
7
6
5
4
3
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ppm
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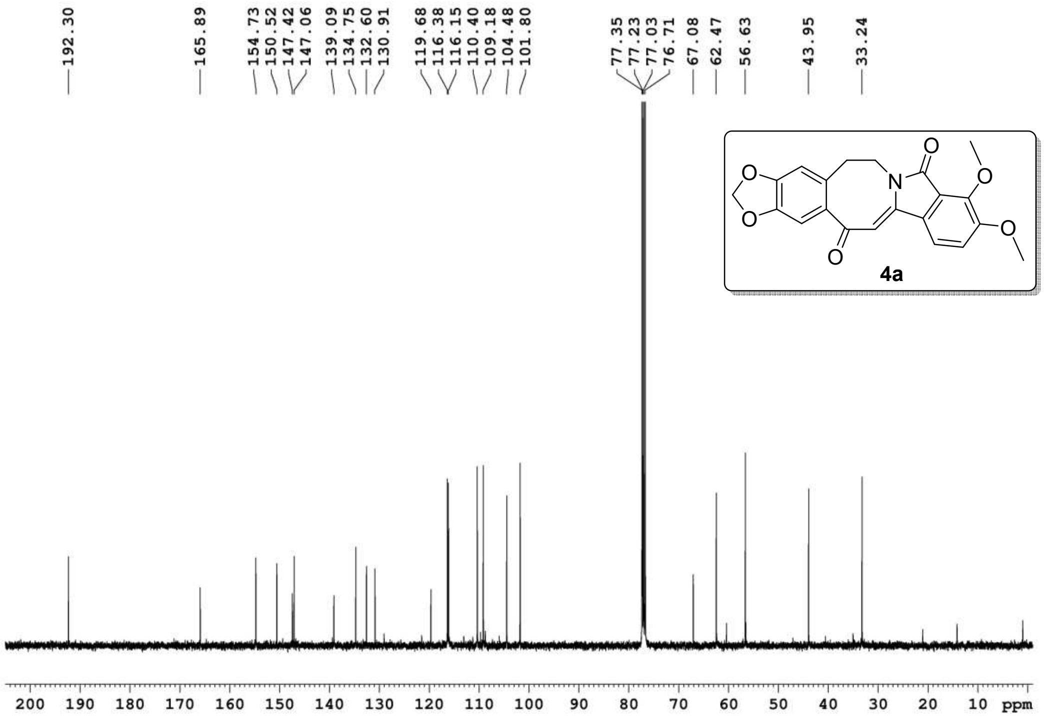
0.99
1.11
1.02
0.97
2.02
5.36
3.10
2.16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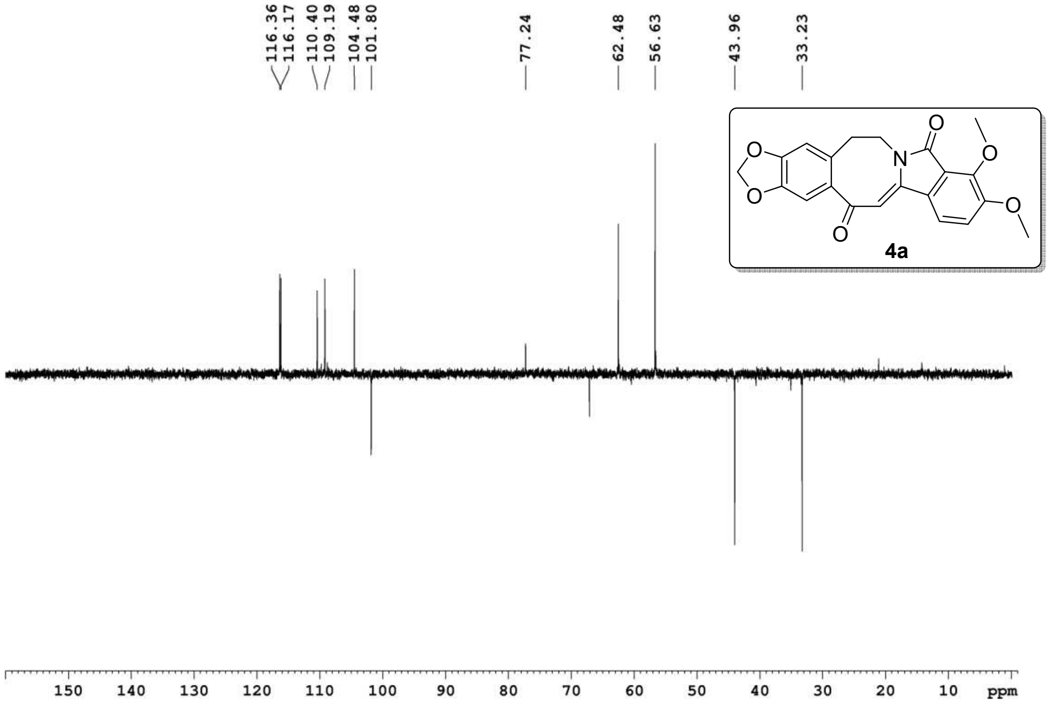
116.15
110.40
109.18
104.48
101.80
77.35
77.23
77.03
76.71
67.08
62.47
56.63
43.95
33.24
O
O
N
O
O
O
O
4a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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101.80
77.24
62.48
56.63
43.96
33.23
O
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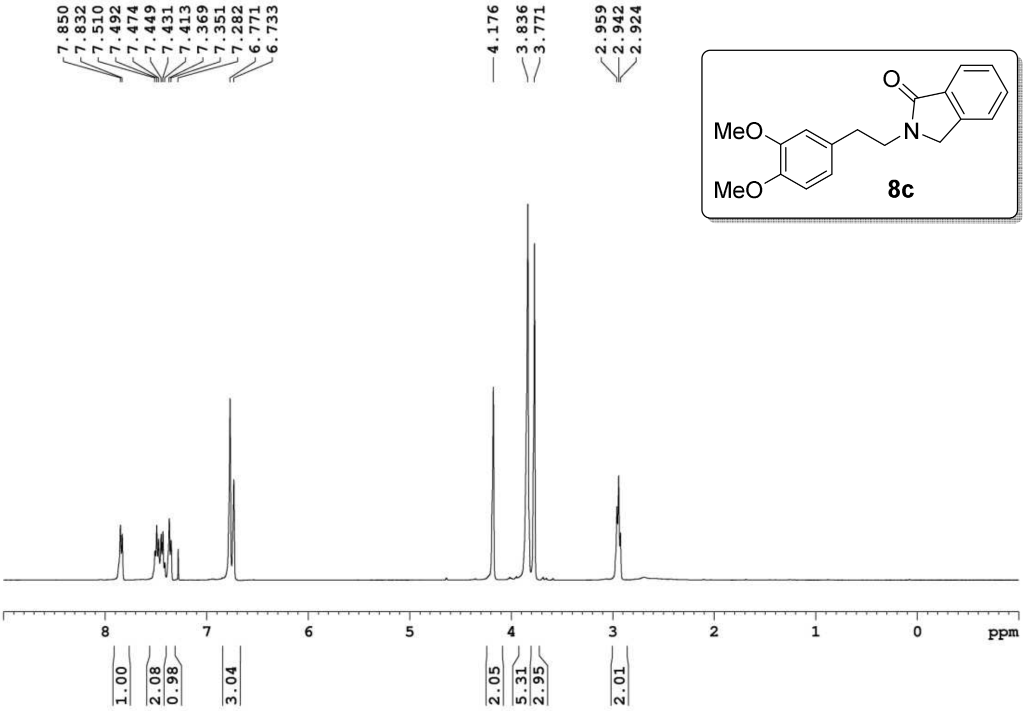
O
O
O
O
4a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.351
7.282
6.771
6.733
4.176
3.836
3.771
2.959
2.942
2.924
MeO
MeO
O
N
8c
8
7
6
5
4
3
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ppm
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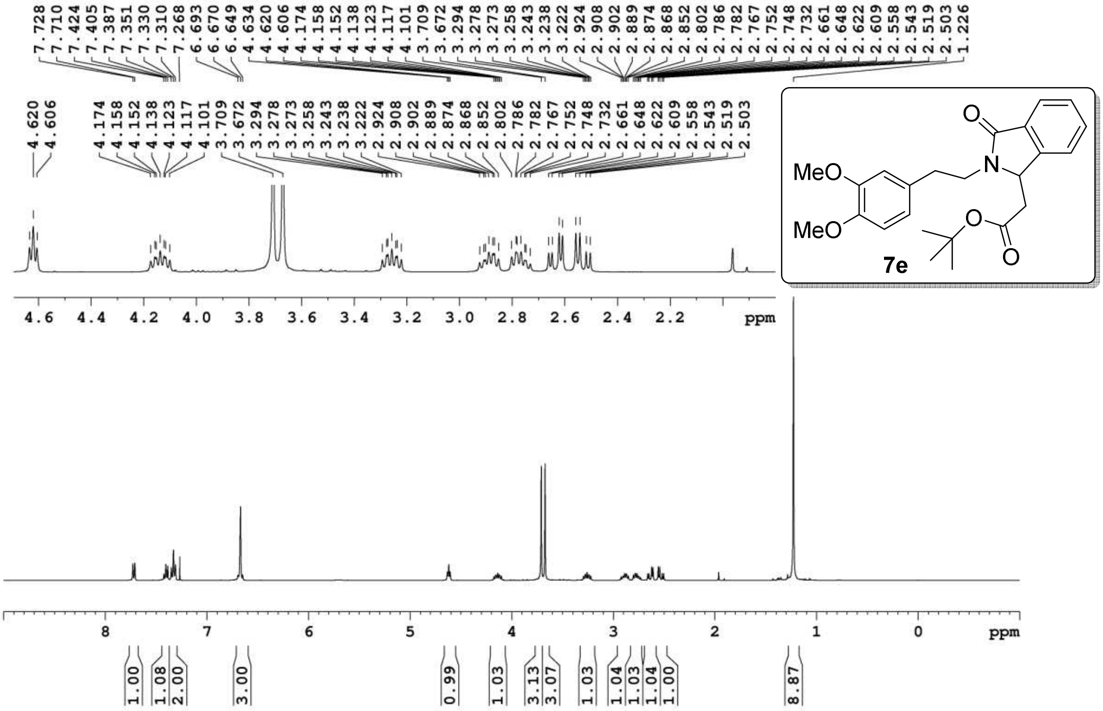
5.31
2.95
2.01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4.634
4.620
4.606
4.174
4.158
4.152
4.138
4.123
4.117
4.101
3.709
3.672
3.294
3.278
3.273
3.258
3.243
3.238
3.222
2.924
2.908
2.902
2.889
2.874
2.868
2.852
2.802
2.786
2.782
2.767
2.752
2.748
2.732
2.661
2.648
2.622
2.609
2.558
2.543
2.519
2.503
1.226
4.620
4.606
4.174
4.158
4.152
4.138
4.123
4.117
4.101
3.709
3.672
3.294
3.278
3.273
3.258
3.243
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3.222
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2.902
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2.852
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2.786
2.782
2.767
2.752
2.748
2.732
2.661
2.648
2.622
2.609
2.558
2.543
2.519
2.503
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
ppm
MeO
MeO
O
N
O
O
7e
8
7
6
5
4
3
2
1
0
ppm
1.00
1.08
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1.04
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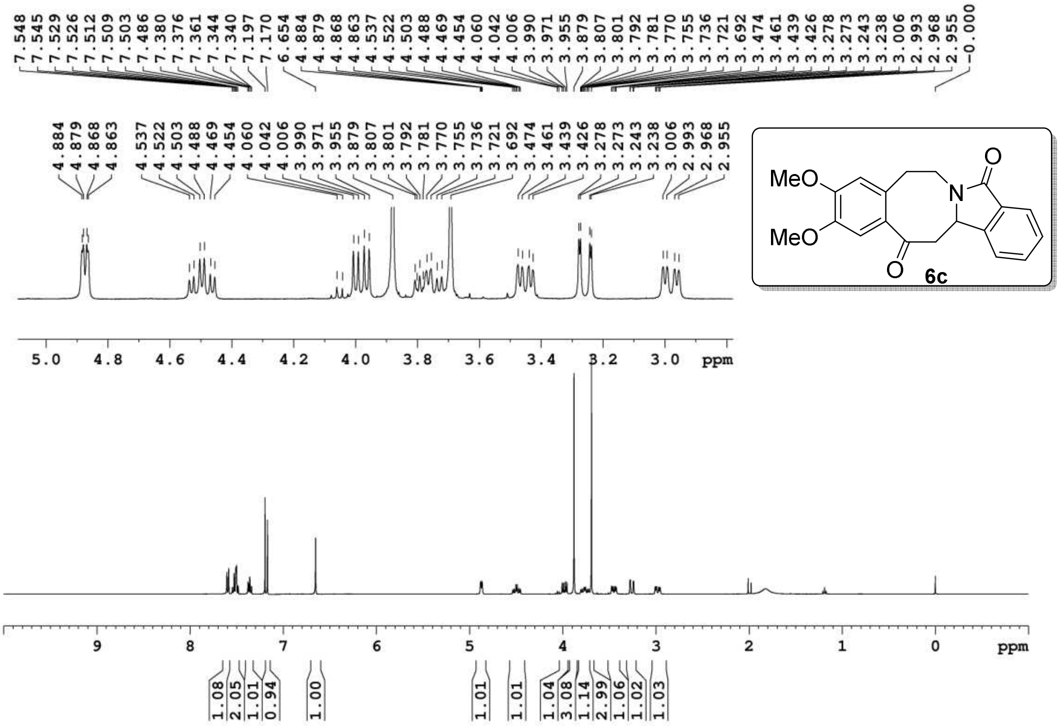
1.04
1.00
8.87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7.486
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7.361
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7.340
7.197
7.170
6.654
4.884
4.879
4.868
4.863
4.537
4.522
4.503
4.488
4.469
4.454
4.060
4.042
4.006
3.990
3.971
3.955
3.879
3.807
3.801
3.792
3.781
3.770
3.755
3.736
3.721
3.692
3.474
3.461
3.439
3.426
3.278
3.273
3.243
3.238
3.006
2.993
2.968
2.955
-0.000
MeO
MeO
N
O
O
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
ppm
9
8
7
6
5
4
3
2
1
0
ppm
1.08
2.05
1.01
0.94
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1.01
1.01
1.04
3.08
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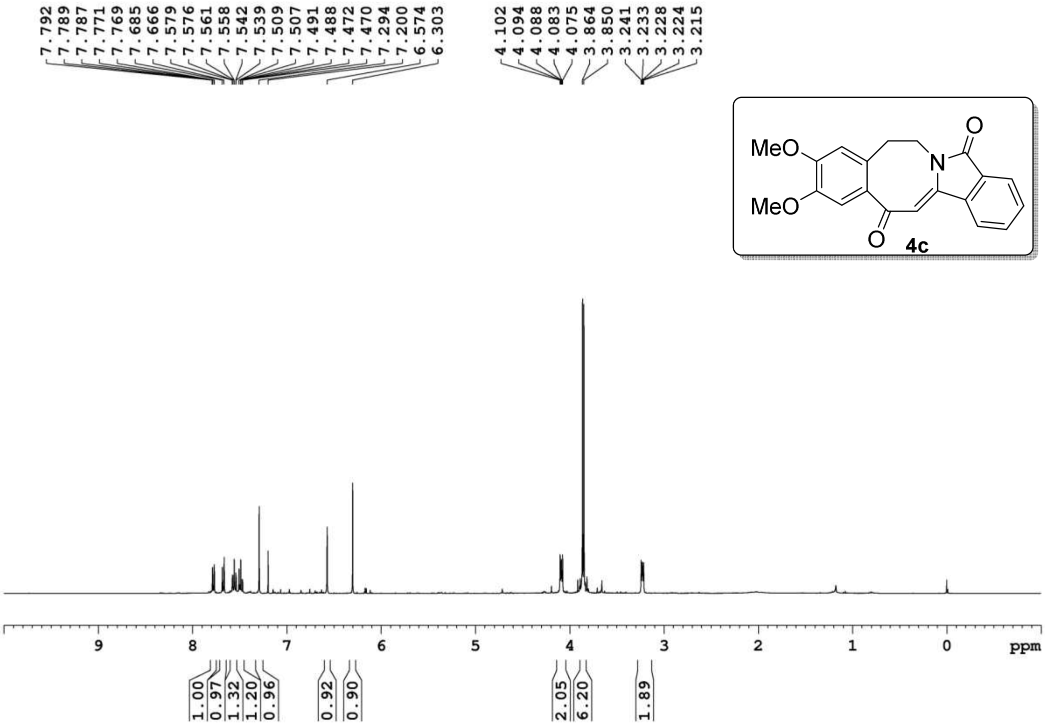
2.99
1.06
1.02
1.03

6c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7.561
7.558
7.542
7.539
7.509
7.507
7.491
7.488
7.472
7.470
7.294
7.200
6.574
6.303
4.102
4.094
4.088
4.083
4.075
3.864
3.850
3.241
3.233
3.228
3.224
3.215
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MeO
N
O
O
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8
7
6
5
4
3
2
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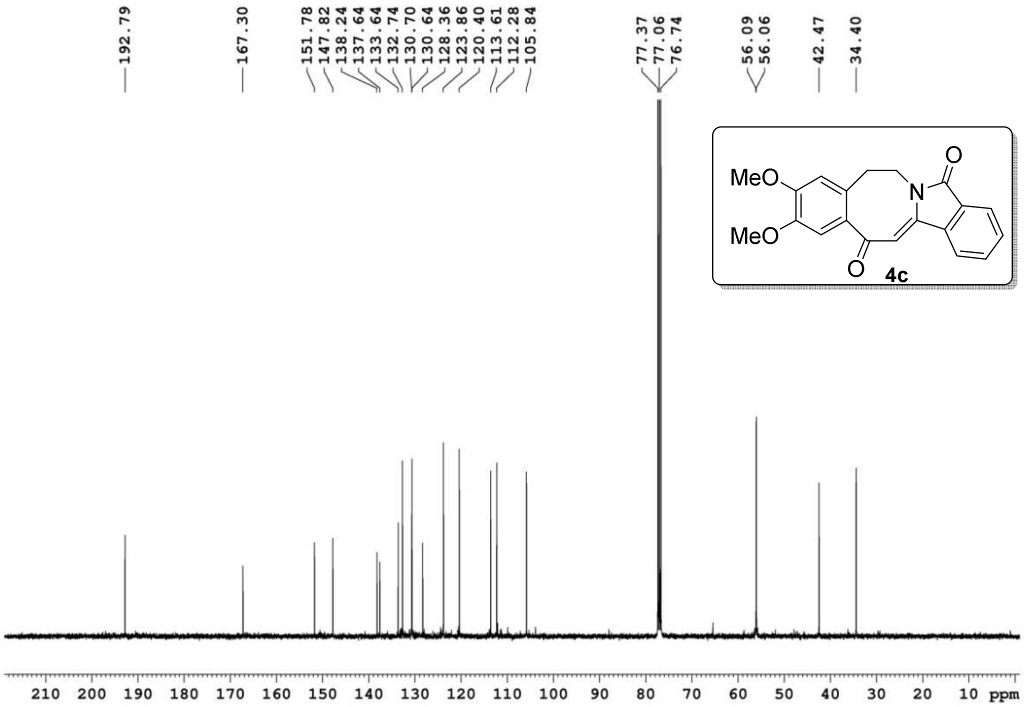
4c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77.06
76.74
56.09
56.06
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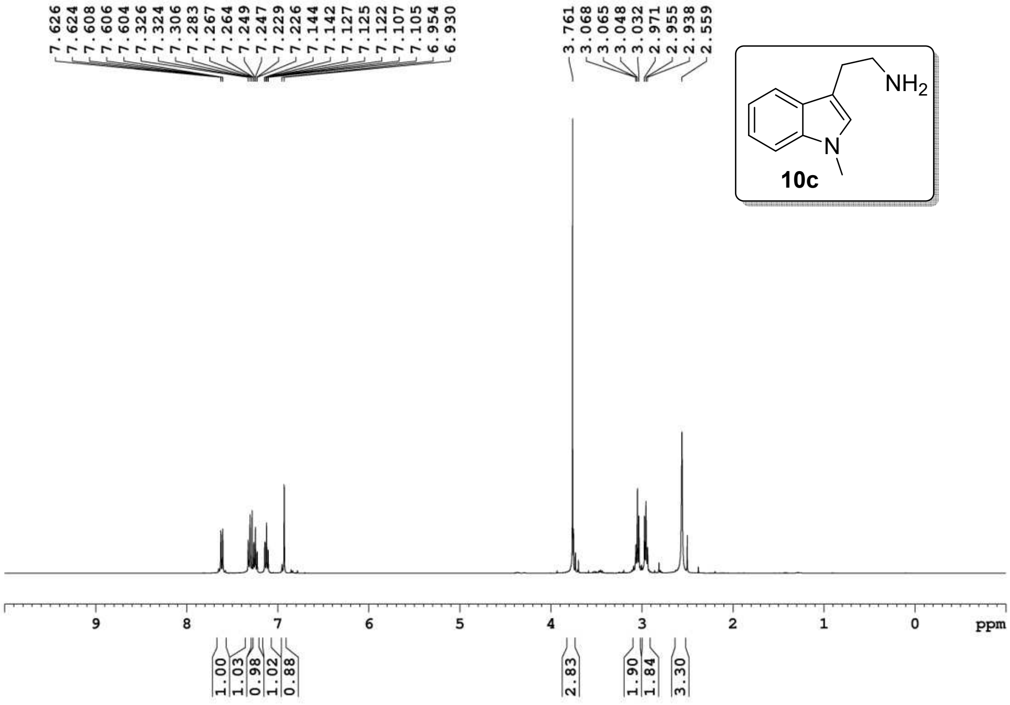
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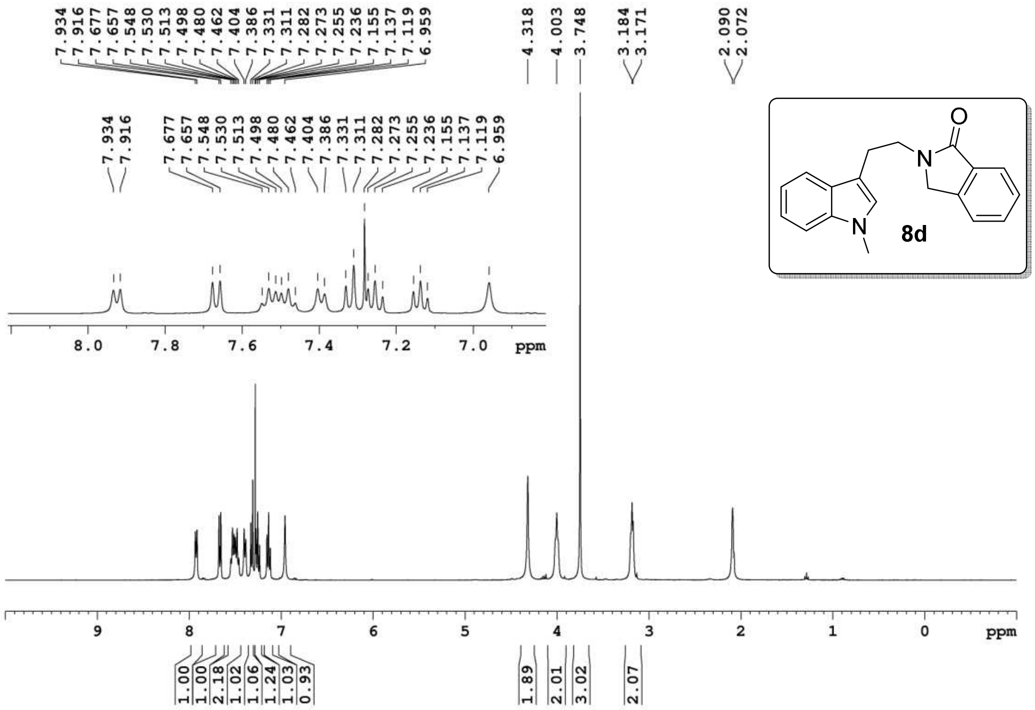
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4.318
4.003
3.748
3.184 3.171
2.090 2.072
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9 8 7 6 5 4 3 2 1 0 ppm
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N
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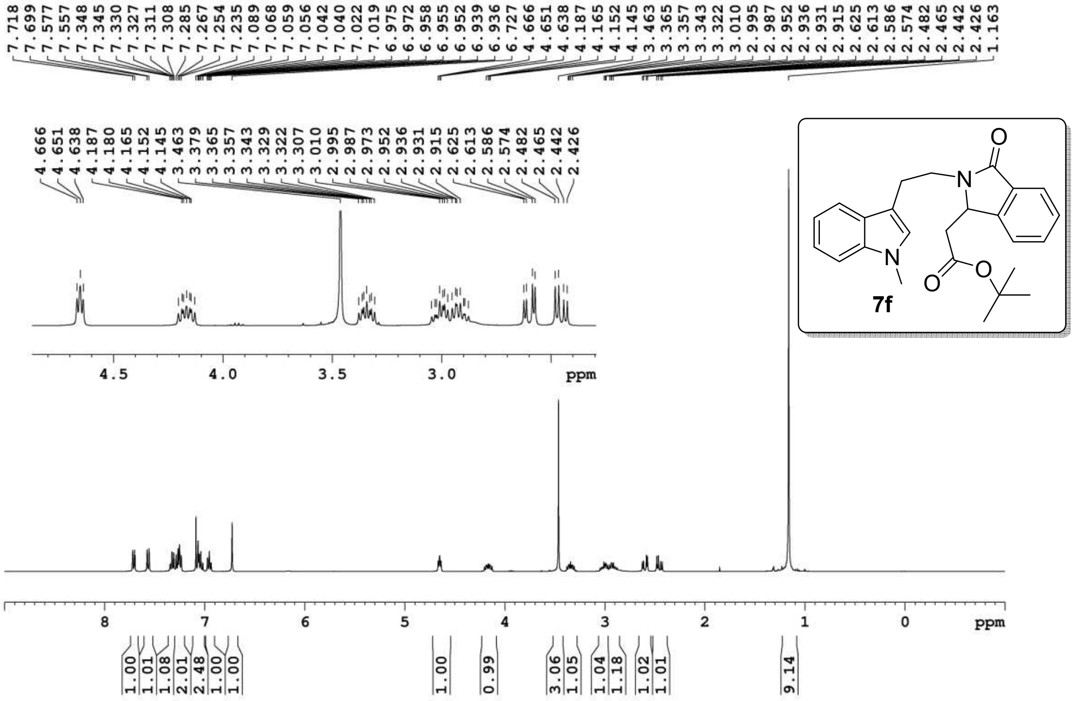
8d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4.666 4.651 4.638 4.187 4.180 4.165 4.152 4.145 3.463 3.379 3.365 3.357 3.343 3.329 3.322 3.307 3.010 2.995 2.987 2.973 2.952 2.936 2.931 2.915 2.625 2.613 2.586 2.574 2.482 2.465 2.442 2.426
4.5 4.0 3.5 3.0 ppm
8 7 6 5 4 3 2 1 0 ppm
1.00 1.01 1.08 2.01 2.48 1.00 1.00
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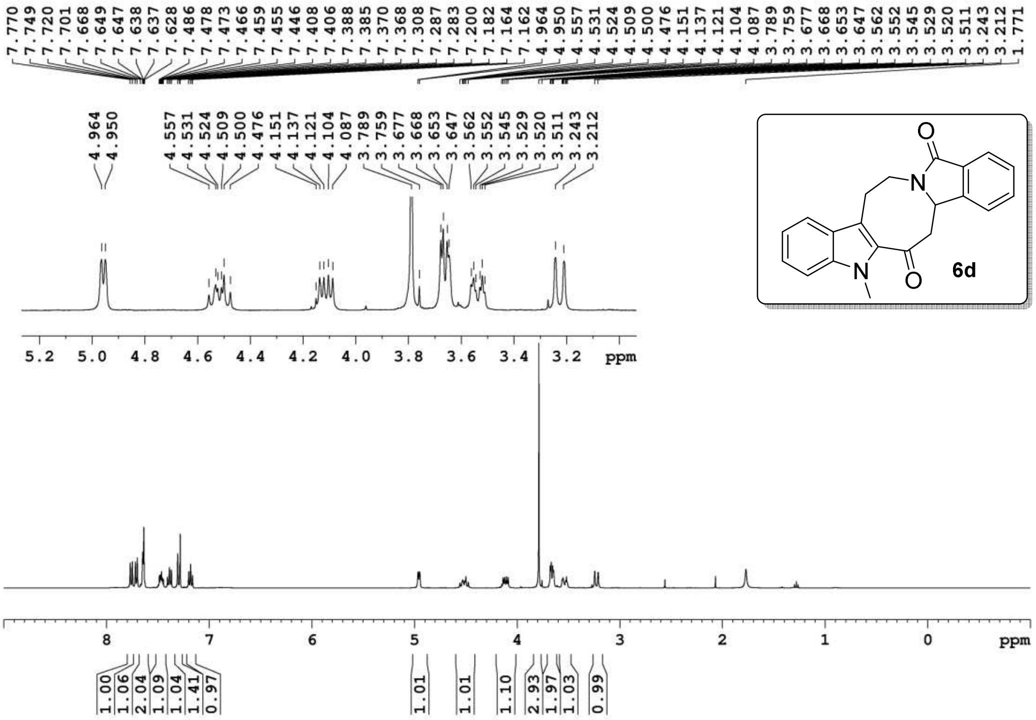
N
N
O
O
7f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4.476
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3.668
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3.647
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3.212
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6d
ppm
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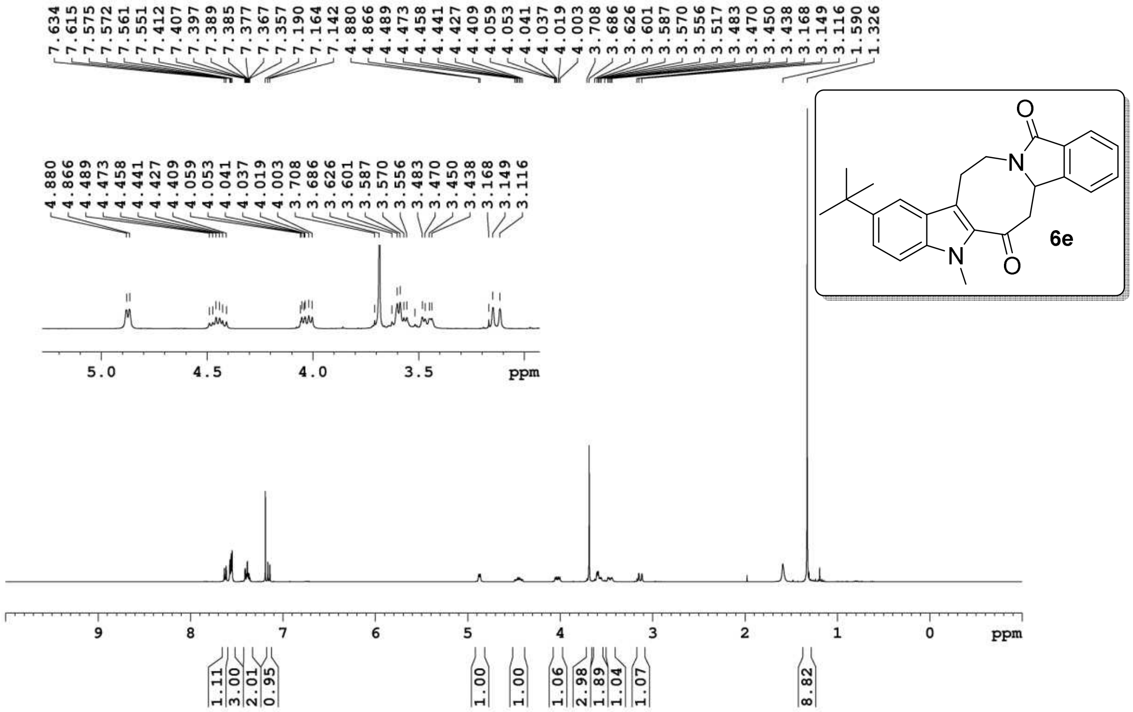
0.99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3.470
3.450
3.438
3.168
3.149
3.116
1.590
1.326
6e
ppm
1.11
3.00
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0.95
1.00
1.00
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2.98
1.89
1.04
1.07
8.82

Chapter 5

Synthetic studies towards Alpkinidine and its benzo analogue

Section A:An approach towards synthesis of Alpkinidine

5. A. 1: Introduction

Alpkinidine is a purple colored pentacyclic marine natural product belonging to pyrroloacridine class of alkaloids isolated from marine sponge *Xestospongia* cf. *carbonaria*.[1a] So far the family of pyrroloacridine consist of only 6 members including alpkinidine. The other members of this family are plakinidine A-E (**2a-2e**) (Figure 1).[1a-f]

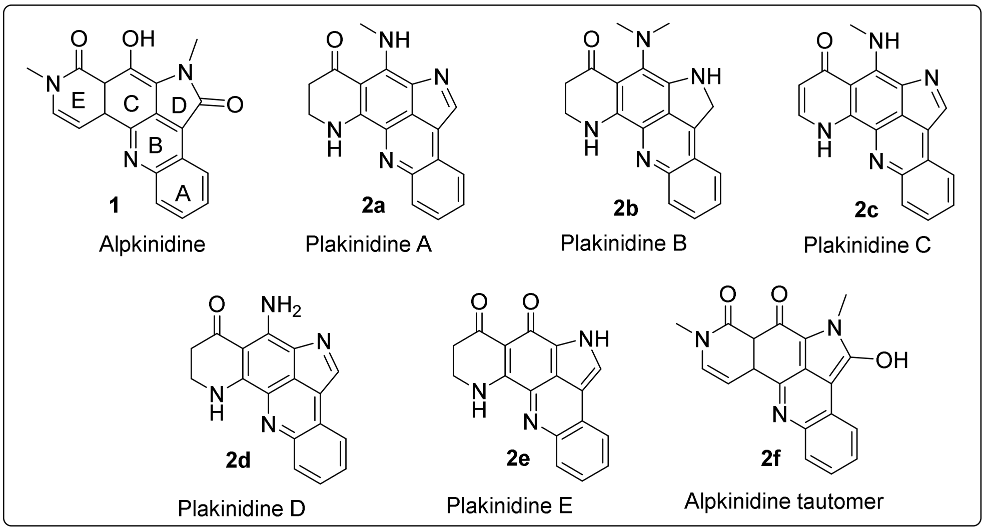


Figure 1: Members of pyrroloacridine family.

The rings of pentacyclic framework of alpkinidine are marked as A, B, C, D& E ring as shown in figure 1. The structure of this alkaloid consists of an acridine ring system fused to a pyridone nucleus (E) which makes it less soluble in most of organic solvents. Alpkinidine is also expected to exist as its tautomer **2f** in solution phase. These reasons *viz.* lack of solubility and existence in the tautomeric form, as well as the lack of availability of this alkaloid have resulted in lack of spectral data of this molecule. Alpkinidine has been assigned structure based on its X-ray crystallographic analysis.[1a]

Members of this family are not well explored, but are closely related to members of another pyridoacridine class of compounds *viz*. Amphimedine **3a**, neoamphimedine **3b** and others (Figure 2).[2a-d] It can be seen that the structural ring arrangement of neoamphimedine (rings A, B & E) is similar and is believed to be a co-metabolite of alpkinidine. Also isolation of these alkaloids was associated along with members of pyridoacridines like **3b**.[1a]

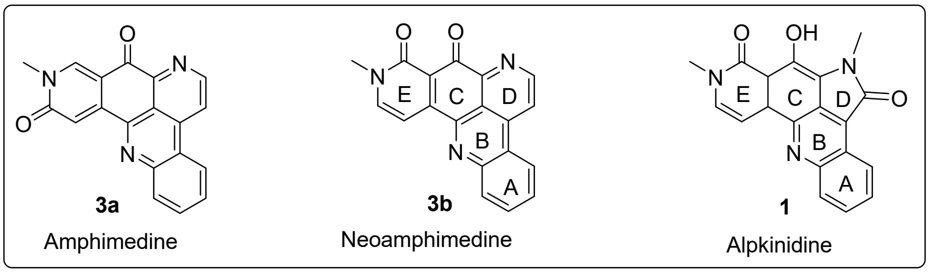


Figure 2: Structural similarities between **1** and pyridoacridine alkaloids

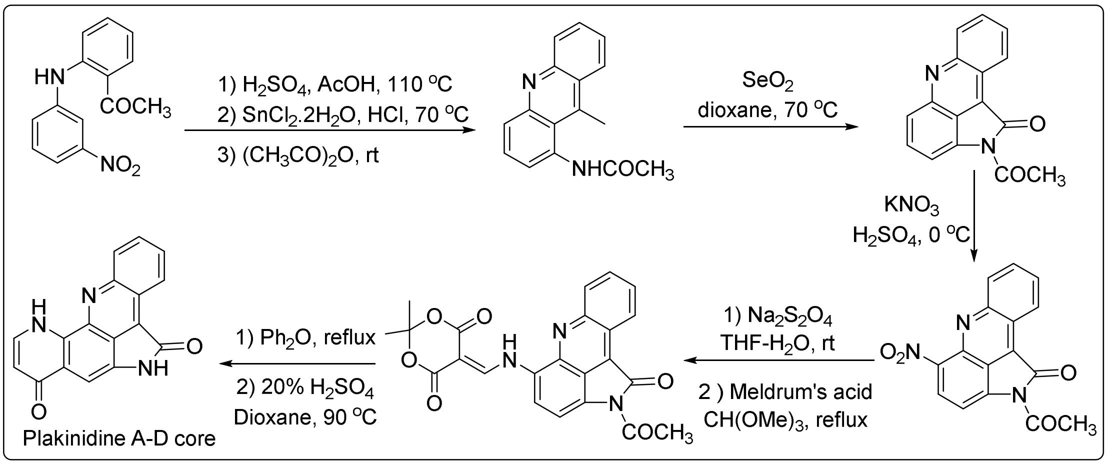
Members of pyridoacridine family isolated from marine source are highly colored alkaloids containing 11*H*-pyrido[4,3,2-*mn*]acridine ring system. Based on biosynthetic pathway it is proposed that this family comprise, of over 100 alkaloids out of which several are yet to be isolated.[3a] Members of this family are targeted for their wide range of biological activities like antiviral, antiparasitic, antifungal, insecticidal, cytotoxic and antibacterial. For the same reason members of this family is also interesting synthetic targets.[3b-c]

Modelling study have indicated that the CE ring system of neoamphimedine **3b** which is also present in alpkindine is a vital functionality for binding interaction with topisomerase IIa, and selective cytotoxicity towards solid tumor cell lines, suggesting that **1** could have similar activities as that of **3b**.[4a] It is also noteworthy that A, B, E ring system shows potent activity towards inhibition of xenograft tumor in mice. [4b]

5. A. 2: Literature Reported Methods

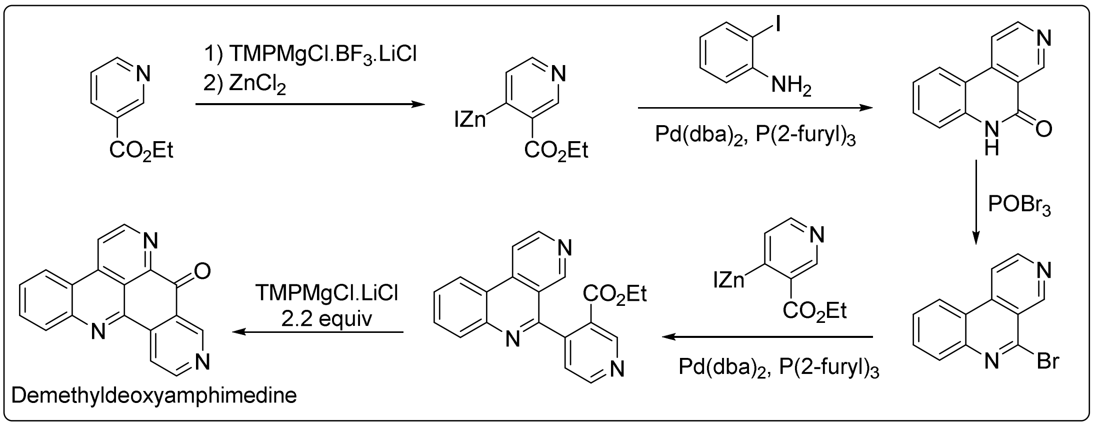
Till date to our knowledge, there is no report on total synthesis of alpkindine in the literature. However, only one report on the synthesis of plakinidine core reported which is presented below.

Kitahara *et al.* [5a] in 2004 reported a route to synthesize the pentacyclic pyrroloacridine framework present in plakinidine A-E alkaloids (Scheme 1). 2-Acetyl-3-nitrodiphenylamine on intramolecular cyclisation followed by reduction and acetylation gave acridine intermediate, which on subsequent cyclisation with SeO_2 furnished the tetracyclic core. Nitration of this intermediate with KNO_3/H_2SO_4 followed by reduction of the nitro group and reacting the resulting amine with Meldrum’s acid, trimethyl orthoformate gave an unsaturated adduct, which on heating and decarboxylation gave plakinidine core.


1) H_2SO_4, AcOH, 110 °C
2) $SnCl_2.2H_2O$, HCl, 70 °C
3) $(CH_3CO)_2O$, rt
SeO$_2$
dioxane, 70 °C
KNO$_3$
H_2SO_4, 0 °C
1) $Na_2S_2O_4$
THF-H_2O, rt
2) Meldrum's acid
$CH(OMe)_3$, reflux
1) Ph_2O, reflux
2) 20% H_2SO_4
Dioxane, 90 °C
Plakinidine A-D core

Scheme 1

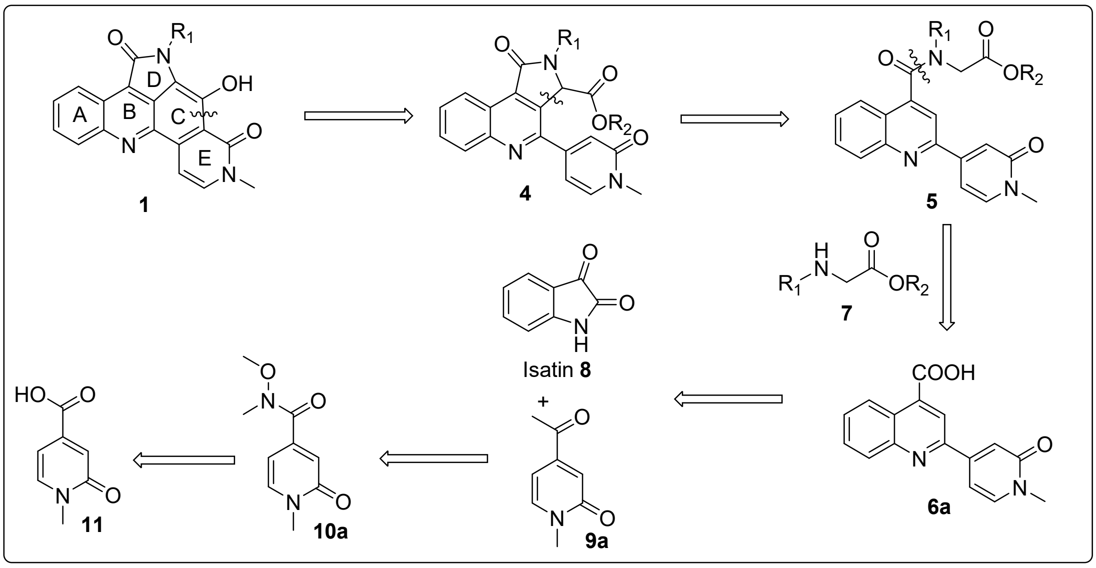
Recently in 2014 Bracher *et al.* [5b] developed an interesting route for the synthesis of pyridoacridine alkaloid demethydeoxyamphimedine (Scheme 2). In this method ethyl nicotinate was metallated and then *trans*-metallated to give a zinc reagent which was subjected to Negishi coupling with 2-iodoanilne in the presence of palladium catalyst followed by lactamisation to obtain benzo[*c*][2,7]naphthyridin-5(6*H*)-one. This intermediate on treatment with phosphorous oxybromide followed by a second Negishi coupling with the same zinc intermediate gave ethyl 2-(benzo[c][2,7]naphthyridin-5-yl)benzoate. Further direct metalation followed by intramolecular acylation gave the desired alkaloid demethyldeoxyamphimedine in 6.4 % overall yield over 4 steps.


1) TMPMgCl.BF$_3$.LiCl
2) ZnCl$_2$
Pd(dba)$_2$, P(2-furyl)$_3$
POBr$_3$
Pd(dba)$_2$, P(2-furyl)$_3$
TMPMgCl.LiCl
2.2 equiv
Demethyldeoxyamphimedine

Scheme 2

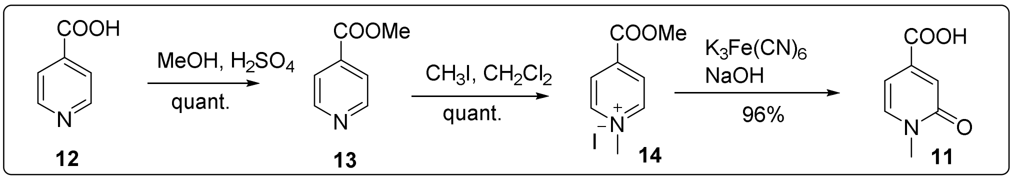
5. A. 3: Results and Discussion

Our strategy towards the synthesis of alpkinidine was based on the retrosynthetic pathway depicted in below scheme 3. We envisaged that the C ring of **1** could be constructed from its corresponding ester derivative **4** *via* a straight forward intramolecular acylation. Construction of D ring could be achieved from its amide derivative **5** by dehydrogenative coupling. Amide **5** could be obtained from its corresponding acid derivative **6a** by coupling reaction. Synthesis of quinoline acid **6** was visualized from isatin **8** and 4-acetyl-1-methylpyridin-2(1*H*)-one **9a** using Pfitzinger reaction. Intermediate **9a** could be achieved from corresponding Weinreb amide **10a** which could be obtained from known acid 1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid **11**. [6a]



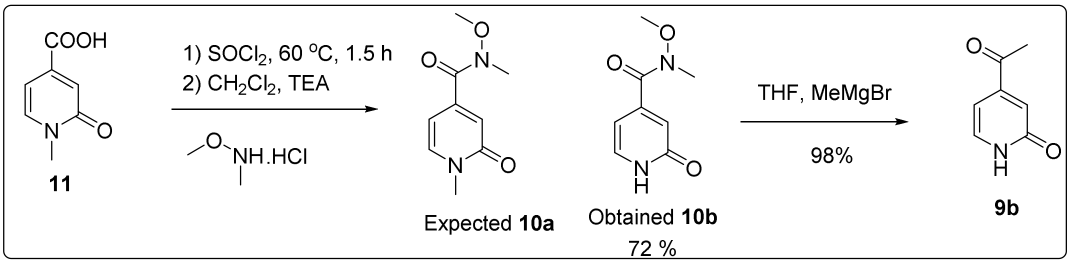
Scheme 3

Synthesis of 1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid **11** was carried out using a reported procedure (Scheme 4). [6a] Esterification of pyridine-4-carboxylic acid **12** to its methyl ester and further treatment with methyl iodide gave the bright red pyridium iodide salt **14** . Oxidative hydrolysis of **14** under basic conditions in the presence of potassium ferricyanide gave intermediate **11** in excellent overall yield.



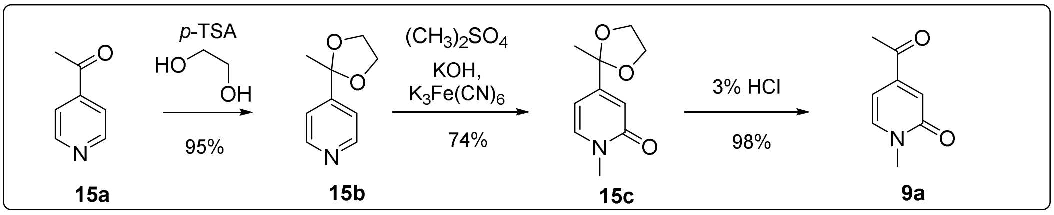
Scheme 4

The acid intermediate **11** was then reacted with thionyl chloride at 60 °C to give the corresponding acid chloride, which on insitu treatment with *N,O*-dimethyl hydroxyl amine hydrochloride gave a yellow viscous liquid, which was expected to give Weinreb amide **10a**. However, its ^{1}H NMR showed only two peaks accounting for the methyl groups at 3.29 and 2.70 ppm instead of three. Further spectral analysis by ^{13}C NMR confirmed the structure of the product to be **10b** and not **10a**. The Weinreb amide **10b** on further reacting with methyl magnesium bromide (2.1 equiv) gave excellent yields of 4-acetylpyridin-2(1*H*)-one **9b**.



Scheme 5

Since the above method provided us with the demethylated derivative **9b** an alternative route [6b] for the synthesis of **9a** was adopted. Thus, 4-acetyl pyridine **15a** was subjected to acetal formation with ethylene glycol in the presence of *p*-TSA. A white solid was obtained which on methylation, followed by a base mediated hydrolysis in the presence of potassium ferricyanide gave the acetal derivative **15c**. Hydrolysis of **15c** with 3 % HCl solution gave the desired compound **9a** as a white solid. Its ^{1}H NMR showed two distinct methyl groups at 3.58 and 2.54 ppm in ^{1}H NMR accounting for N-CH_3 and –CO-CH_3 respectively. The aromatic protons were seen at 7.38 (*o*-coupled) and 6.61 (*o*-coupled) and at 7.07 ppm (*m*-coupled).



Scheme 6

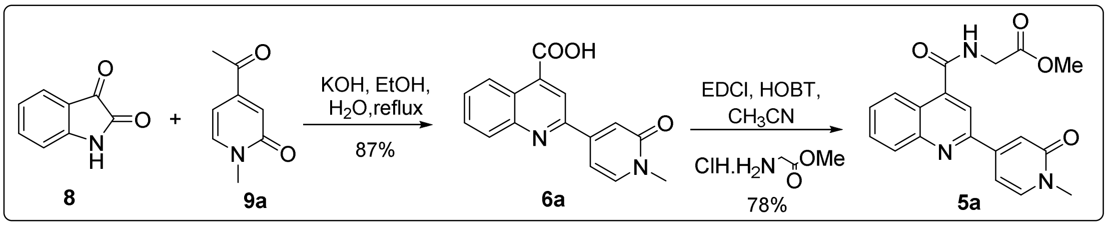
Spectral data of 4-acetyl-1-methylpyridin-2(1*H*)-one (9a):[6b]

IR (KBr): $\tilde{\nu}$ = 3088, 3035, 1928, 1687, 1656, 1589, 1485, 1234, 796 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.61 (dd, *J* = 6.8 Hz, 2.0 Hz, 1H), 3.58 (s, 3H), 2.54 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0 (C), 163.0 (C), 145.9 (C), 138.9 (CH), 121.2 (CH), 102.4 (CH), 37.5 (CH_3), 26.3 (CH_3).

The intermediate **9a** was then condensed with isatin **8** according to Pfitzinger reaction (Pfitzinger-Borsche reaction) [7] conditions to obtain a white solid which in its IR spectrum showed a broad peak in the region 3542 -2457 cm^{-1} accounting for acid functionality and two sharp peaks at 1658 and 1608 cm^{-1} indicating the presence of carbonyl groups of amide and acid respectively. Structure of **6a** was further confirmed using ^{1}H NMR, ^{13}C NMR and HRMS analysis (Scheme 7).



Scheme 7

Spectral data of 2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylic acid (6a):

IR (KBr): $\tilde{\nu}$ = br 3542-2457, 1658, 1608, 1581, 1290, 771 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 8.66 (d, J = 8.4 Hz, 1H), 8.44 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.92-7.88 (m, 2H), 7.78 (t, J = 8.4 Hz, 1H), 7.27 (s, 1H), 7.13 (d, J = 6.4 Hz, 1H), 3.52 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 167.3 (C), 162.0 (C), 152.9 (C), 148.1 (C), 148.0 (C), 140.1 (CH), 137.9 (C), 130.5 (CH), 130.0 (CH), 128.7 (CH), 125.3 (CH), 123.9 (C), 119.0 (CH), 116.7 (CH), 103.0 (CH), 36.5 (CH_3).

HRMS (ESI): calcd for $C_{16}H_{12}N_2O_3Na$ [M + Na]$^+$ 303.0746, found 303.0745.

On trying several amidation conditions between acid **6a** and 2-methoxy-2-oxoethan-1-aminium chloride **7a**, amide **5a** was obtained in 78 % yield using EDCl and HOBT in acetonitrile. Spectral data of the product are shown below.

Spectral data of methyl-(2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carbonyl)glycinate (5a):

IR (KBr): $\tilde{\nu}$ = 3196, 3045, 1751, 1654, 1581, 1367, 1203, 771 cm^{-1}.

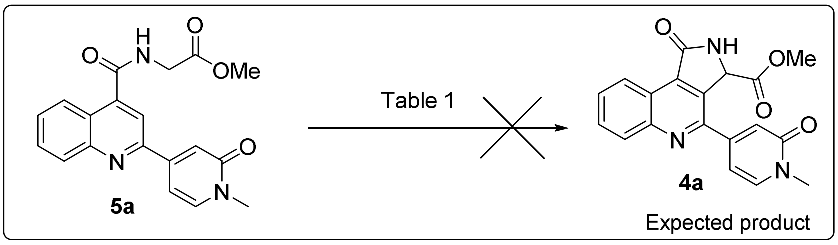
^{1}H NMR (400 MHz, DMSO-d6): δ 9.38 (t, J = 6.0 Hz, 1H), 8.33 (dd, J = 8.4 Hz, 0.8 Hz, 1H), 8.19-8.16 (m, 2H), 7.91-7.86 (m, 2H), 7.74 (dt, J = 7.2 Hz, 1.2 Hz, 1H), 7.29 (d, J = 1.6 Hz, 1H), 7.14 (dd, J = 7.2 Hz, 2.0 Hz, 1H), 4.17 (d, J = 5.6 Hz, 2H), 3.75 (s, 3H), 3.51 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 170.1 (C), 167.0 (C), 162.1 (C), 152.9 (C), 148.4 (C), 147.6 (C), 142.5 (C), 140.1 (CH), 130.6 (CH), 129.8 (CH), 128.1 (CH), 125.4 (CH), 124.0 (C), 116.8 (CH), 116.7 (CH), 103.0 (CH), 51.9 (CH_3), 41.1 (CH_2), 36.6 (CH_3).

HRMS (ESI): calcd for $C_{19}H_{17}N_3O_4H$ [M + H]$^+$ 352.1297, found 352.1296.

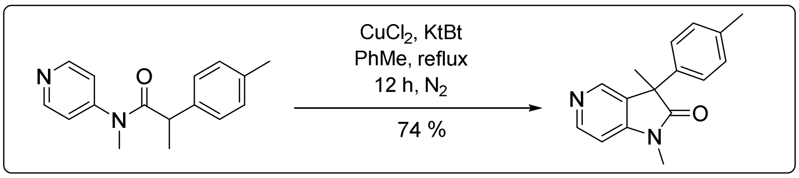
Having obtained **5a** it was further subjected to some dehydrogenative conditions, as listed in table 1. All attempts towards oxidative coupling [8a-e] of **5a** using TBHP in the presence of molecular iodine, NBS, CuBr resulted in mixtures of products (entry 1-3) which were not isolated further.

Table 1: Attempted dehydrogenative conditions.



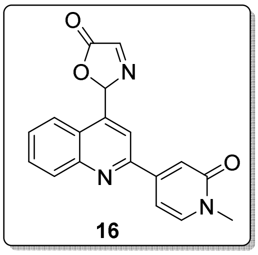
Sr. No	Reaction condition	Observation
1	TBHP, CuBr, 60 °C	Mixtures of compounds
2	I_2, TBHP, rt	Mixtures of compounds
3	NBS, TBHP, rt	Mixtures of compounds
4	$CuCl_2$, K-*t*-butoxide, toluene, reflux, 18 h, N_2	Off white compound obtained

Dey *et al.*[9a] have reported intramolecular nucleophillic substitution reaction of 4-substituted pyridine to synthesize oxyazaindole (Scheme 8). The same reaction conditions were experimented to cyclise **5a** (entry 4).



Scheme 8

During this reaction an off white solid was obtained, however on spectral analysis it was observed that intramolecular lactamisation had taken place instead of a nucleophillic attack on pyridyl ring. The compound showed $[M + H]^+$ peak at 320.1035, on further interpreting ^1H and ^{13}C NMR, a probable structure was assigned as **16**. [9b]



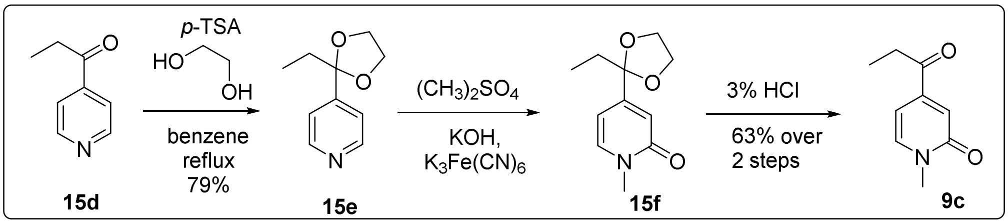
IR (KBr): $\tilde{\nu}$ = 3182, 3055, 1743, 1654, 1572, 1360, 1200, 779 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 8.36-8.30 (m, 3H), 8.19-8.14 (m, 2H), 8.00 (s, 1H), 7.90-7.85 (m, 2H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.34 (s, 1H), 7.15 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 3.51 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 168.2 (C), 162.1 (C), 152.9 (C), 148.4 (C), 147.6 (C), 142.9 (C), 140.0 (CH), 130.3 (CH), 129.7 (CH), 127.9 (CH), 125.4 (CH), 123.9 (C), 116.8 (CH), 116.6 (CH), 103.1 (CH), 36.6 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{13}N_3O_3H$ $[M + H]^+$ 320.1035, found 320.1035.

With the difficulties to obtain **4a**, we next thought it might be advantageous to have a methyl group at the 3-position of the quinoline ring to make the annulation easier (Scheme 9). Hence, 1-(pyridin-4-yl)propan-1-one **15d** was reacted in a similar fashion as in scheme 6 to give 1-methyl-4-propionylpyridin-2(1*H*)-one **9c** in 50 % overall yield over 3 steps.



Scheme 9

Spectral data of 1-methyl-4-propionylpyridin-2(1*H*)-one (9c):

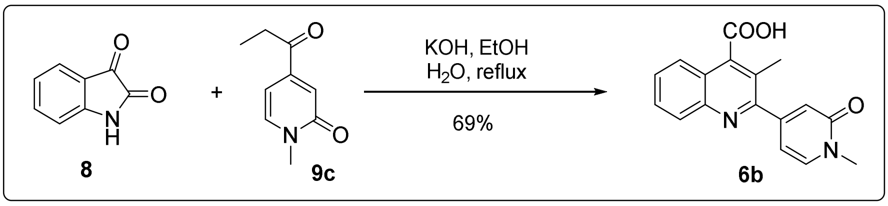
IR (KBr): $\tilde{\nu}$ = 3039, 2978, 1689, 1656, 1589, 1336, 1203, 792 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 6.8 Hz, 1H), 7.10 (s, 1H), 6.63 (td, *J* = 6.8 Hz, 1.2 Hz, 1H), 3.58 (s, 3H), 2.90 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7 (C), 163.1 (C), 145.8 (C), 139.0 (CH), 120.4 (CH), 102.7 (CH), 37.6 (CH_3), 31.8 (CH_2), 7.7 (CH_3).

HRMS (ESI): calcd for $C_9H_{11}NO_2Na$ $[M + Na]^+$ 188.0688, found 188.0687.

Again base mediated ring opening of isatin **8** with **9c** gave expected acid **6b** as a white solid in 69 % yield (Scheme 10). The structure was confirmed by its spectral data.



Scheme 10

Spectral data of 3-methyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylic acid (6b):

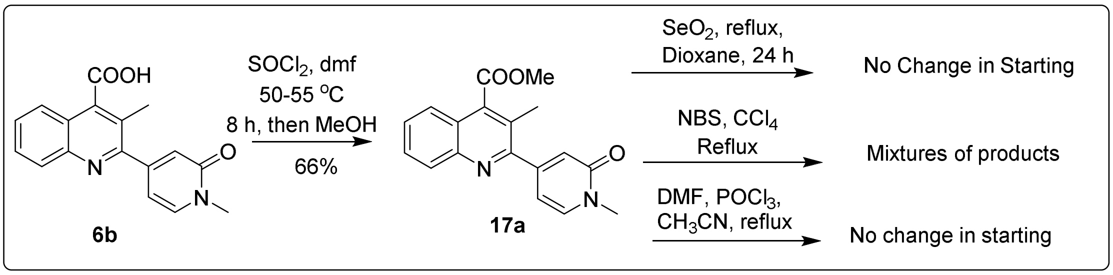
IR (KBr): $\tilde{\nu}$ = br 3562-2461, 1660, 1602, 1236, 1053, 725 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 8.07 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.85-7.79 (m, 3H), 7.72 (dt, J = 6.4 Hz, 1.2 Hz, 1H), 6.56 (d, J = 1.6 Hz, 1H), 6.45 (dd, J = 6.8 Hz, 2.0 Hz, 1H), 3.52 (s, 3H), 2.41 (s, 3H) .

^{13}C NMR (100 MHz, DMSO-d6): δ 168.5 (C), 161.5 (C), 157.4 (C), 150.9 (C), 145.2 (C), 140.9 (C), 139.6 (CH), 129.7 (CH), 129.2 (CH), 128.1 (CH), 124.2 (CH), 123.5 (C), 122.6 (C), 118.5 (CH), 105.9 (CH), 36.6 (CH_3), 16.9 (CH_3).

HRMS (ESI): calcd for $C_{17}H_{14}N_2O_3Na$ $[M + Na]^+$ 317.0902, found 317.0902.

Having obtained acid **6b**, it was converted to the corresponding methyl ester **17a** *via* acid chloride using thionyl chloride. The product was confirmed from peak due to methyl group at 4.04 ppm in the ^{1}H NMR spectrum (Scheme 11). During this reaction temperature was maintained between 50-55 ^{o}C to avoid demethylation of methyl on pyridone moiety.



Scheme 11

Spectral data of methyl 3-methyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylate (17a):

IR (KBr): $\tilde{\nu}$ = 3477, 2954, 1728, 1664, 1602, 1579, 1230, 1055, 765 cm^{-1}.

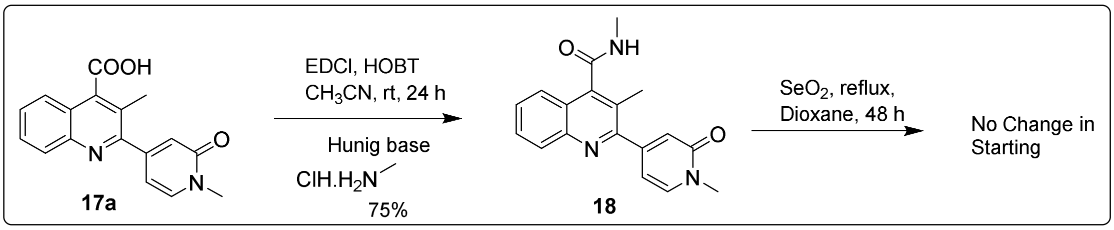
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.4 Hz, 1H), 7.72-7.67 (m, 2H), 7.60-7.55 (m, 1H), 7.39 (d, J = 6.8 Hz, 1H), 6.68 (d, J = 1.6 Hz, 1H), 6.36 (dd, J = 6.8 Hz, 2.0 Hz, 1H), 4.04 (s, 1H), 3.57 (s, 1H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0 (C), 162.6 (C), 157.0 (C), 151.1 (C), 145.7 (C), 140.0 (C), 138.6 (CH), 129.9 (CH), 129.5 (CH), 128.3 (CH), 124.9 (C), 124.2 (CH), 123.7 (C), 120.2 (CH), 107.0 (CH), 52.9 (CH_3), 37.7 (CH_3), 17.4 (CH_3).

HRMS (ESI): calcd for $C_{18}H_{16}N_2O_3Na$ $[M + Na]^+$ 331.1059, found 331.1058.

We then tried to oxidize the methyl group at 3 position of the quinoline using selenium dioxide [5a] to obtain the corresponding aldehyde intermediate. However, even after refluxing **17a** in dioxane for 24 h with SeO_2 starting material was found to remain intact (monitored by TLC). Use of excess selenium dioxide also did not show any change in the starting material. We then treated **17a** with NBS in refluxing CCl_4, to introduce a bromo group at the benzylic methyl, but a complex mixture of compounds was seen on TLC. Attempt to formylate pyridone nucleus using Vilsmeier-Haack condition didn't provide any change in the starting material.

As an alternative we thought an amide linkage in place of ester might help the oxidation of the methyl group. Hence amide **18,** was synthesized from **17a** using EDCl and HOBt. Coupled product was obtained in 75 % yield after column purification. Its structure was confirmed using IR, ^{1}H, ^{13}C NMR and HRMS analysis.



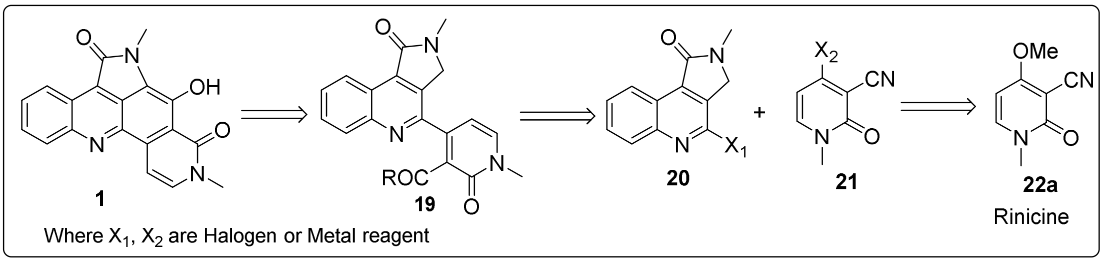
Scheme 12

Spectral data of *N*,3-dimethyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxamide (18):

IR (KBr): $\tilde{\nu}$ = 3261, 3088, 2954, 1668, 1653, 1583, 1298, 763 cm^{-1}.
^{1}H NMR (400 MHz, DMSO-d6): δ 8.70 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 6.8 Hz, 1H), 7.80-7.30 (m, 2H), 7.66 (dt, J = 8.0 Hz, 0.8 Hz, 1H), 6.49 (d, J = 1.2 Hz, 1H), 6.39 (dd, J = 7.2 Hz, 1.6 Hz, 1H), 3.52 (s, 3H), 2.91 (d, J = 4.8 Hz, 3H), 2.33 (s, 3H) .
^{13}C NMR (100 MHz, DMSO-d6): δ 166.8 (C), 161.6 (C), 157.3 (C), 151.2 (C), 145.4 (C), 144.0 (C), 139.7 (CH), 129.5 (CH), 129.0 (CH), 127.7 (CH), 124.8 (CH), 123.9 (C), 123.8 (C), 118.4 (CH), 105.9 (CH), 36.7 (CH$_3$), 25.7 (CH$_3$), 16.7 (CH$_3$).
HRMS (ESI): calcd for $C_{18}H_{17}N_3O_2H$ [M + H]$^+$ 308.1399, found 308.1399.

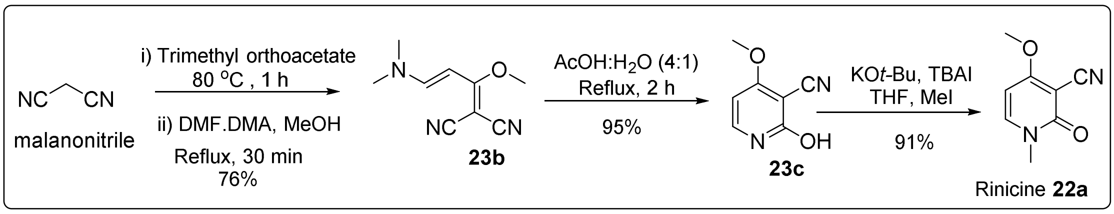
Again oxidation of the methyl group at 3-position of quinoline with SeO$_2$ in refluxing dioxane did not give any product. The starting material remained unchanged (monitored by TLC) even after refluxing mass for 2 days.

Having failed to obtain the desired product, an alternative route was visualized for the construction of ring C as shown in scheme 13. We intended to construct alpkinidine using intramolecular cyclization of intermediate **19** *via* anion formation on isoindolinone. Intermediate **19** could inturn be synthesized from 4-halo-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one [10a] **20** and 4-halo-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **21**. The latter could be obtained from the corresponding 4-methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **22a**. [10b]


1
19
20
21
22a
Rinicine
ROC
X1
X2
Where X1, X2 are Halogen or Metal reagent

Scheme 13

The required intermediate **22a** known as rinicine,[10b] was synthesized using known literature reports as shown in scheme 14. Intermediate **23c** was prepared over 3 steps from malanonitrile and trimethylorthoacetate in 87 % overall yield as reported by Yano *et al*.[10c] Selective *N*-methylation of **23c** to give rinicine **22a** was achieved using potassium *t*-butoxide and TBAI according to the protocol descrided by Conreaux *et al*.[10b]


malanonitrile
i) Trimethyl orthoacetate
80 °C , 1 h
ii) DMF.DMA, MeOH
Reflux, 30 min
76%
23b
AcOH:H2O (4:1)
Reflux, 2 h
95%
23c
KOt-Bu, TBAI
THF, MeI
91%
Rinicine 22a

Scheme 14

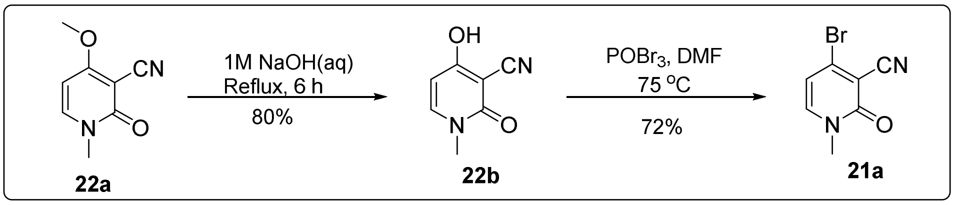
Spectral data of 4-methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (22a):[10b]

IR (KBr): $\tilde{\nu}$ = 2970, 2846, 2229, 1656, 1640, 1537, 1494, 1251, 786 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 8.11 (d, *J* = 7.6 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 3.98 (s, 3H), 3.36 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 172.5 (C), 160.8 (C), 146.0 (CH), 114.6 (C), 93.6 (CH), 85.6 (C), 57.5 (CH_3), 36.7 (CH_3).

Nucleophillic displacement of the methoxy group of rinicine under refluxing conditions using 1M NaOH gave the hydroxyl intermediate **22b** in 80 % yield (Scheme 15).


22a
1M NaOH(aq)
Reflux, 6 h
80%
22b
POBr3, DMF
75 °C
72%
21a

Scheme 15

Further reaction of **22b** with phosphorous oxybromide at 75 °C in anhydrous DMF gave a white solid which in its IR spectrum showed band at 2226 cm^{-1} and 1660 cm^{-1} corresponding to a cyano group and the amidic CO group respectively. Also, no band due to -OH group was observed. The compound was characterized further using ^{1}H, ^{13}C NMR and HRMS and structure **21a** was assigned to it.

Spectral data of 4-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (21a)

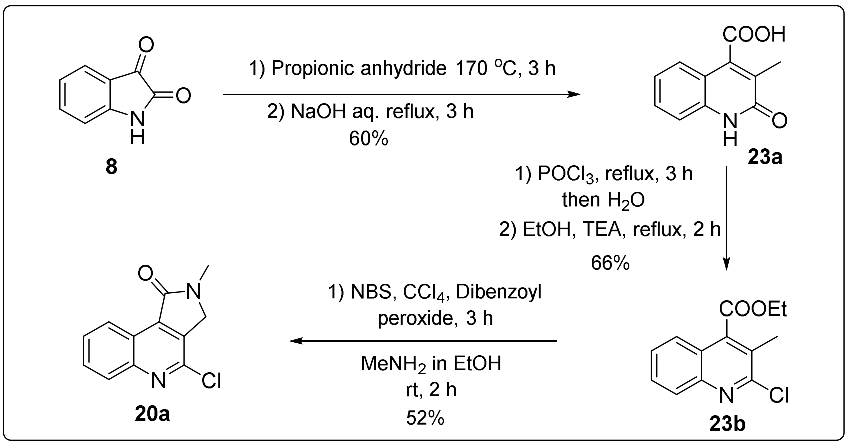
IR (KBr): $\tilde{\nu}$ = 3072, 2983, 2226, 1660, 1593, 1527, 1346, 1209, 765 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 8.08 (d, J = 6.8 Hz, 1H), 6.79 (d, J = 7.2 Hz, 1H), 3.46 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 159.0 (C), 145.1 (CH), 142.6 (C), 115.5 (C), 109.5 (CH), 105.0 (C), 37.4 (CH$_3$).

HRMS (ESI): calcd for $C_7H_5BrN_2ONa$ [M + Na]$^+$ 234.9483, found 234.9483.

The other intermediate 4-chloro-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **20** was synthesized using the protocol described by Cappelli *et al.* [10a] from isatin in 21 % overall yield in 5 steps (Scheme 16).



8
1) Propionic anhydride 170 °C, 3 h
2) NaOH aq. reflux, 3 h
60%
COOH
23a
1) POCl3, reflux, 3 h
then H2O
2) EtOH, TEA, reflux, 2 h
66%
COOEt
23b
1) NBS, CCl4, Dibenzoyl peroxide, 3 h
MeNH2 in EtOH
rt, 2 h
52%
20a

Scheme 16

Spectral data of 4-chloro-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one (20a):[10a]

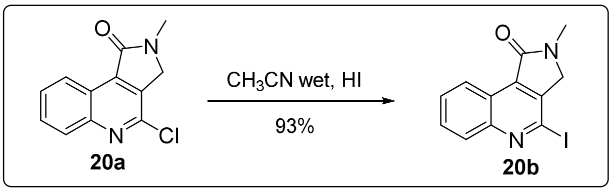
IR (KBr): $\tilde{\nu}$ = 2927, 1691, 1591, 1506, 1460, 1313, 1055, 777 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 9.04 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.82 (dt, J = 8.4 Hz, 1.2 Hz, 1H), 7.72 (dt, J = 8.0 Hz, 0.8 Hz, 1H), 4.52 (s, 2H), 3.32 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 166.9 (C), 148.2 (C), 144.7 (C), 137.9 (C), 134.0 (C), 130.9 (CH), 128.4 (2 X CH), 123.6 (CH), 122.6 (C), 50.5 (CH$_2$), 29.6 (CH$_3$).

HRMS (ESI): calcd for $C_{12}H_9ClN_2ONa$ [M + Na]$^+$ 255.0301, found 255.0301.

Next iodo compound **20b** was synthesized by reacting **20a** with hydroiodic acid [11] in wet acetonitrile (Scheme 17). The product was obtained as a white powder and its IR and ^{1}H NMR spectra were very similar to **20a**. However, in its ^{13}C NMR spectrum peak due to C-2 appeared at 113.9 ppm which was seen at 134.0 ppm in **20a**. Further confirmation of the structure was done from its mass spectrum analysis.



Scheme 17

Spectral data of 4-iodo-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one (20b):

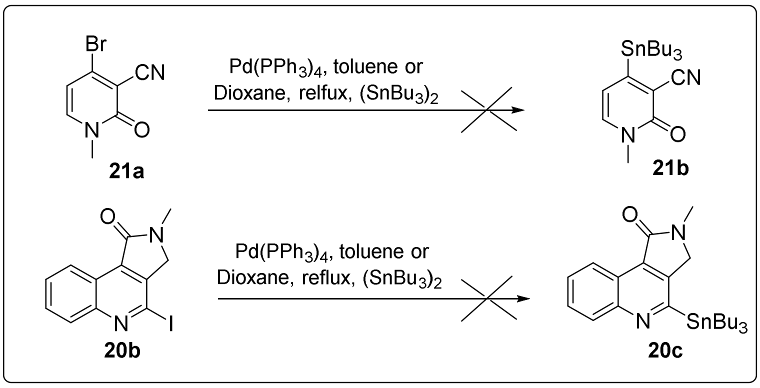
IR (KBr): $\tilde{\nu}$ = 3039, 2927, 1689, 1579, 1502, 1313, 1155, 771 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 8.96 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.74 (dt, J = 8.4 Hz, 1.6 Hz, 1H), 7.65 (dt, J = 8.4 Hz, 1.6 Hz, 1H), 4.28 (s, 2H), 3.24 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 167.4 (C), 149.8 (C), 140.5 (C), 135.7 (C), 130.7 (CH), 128.7 (CH), 128.6 (CH), 123.9 (CH), 122.8 (C), 113.9 (C), 54.2 (CH$_2$), 29.6 (CH$_3$).

HRMS (ESI): calcd for $C_{12}H_9IN_2ONa$ [M + Na]$^+$ 346.9657, found 346.9657.

Attempts to convert intermediate **20b** and **21a** to their corresponding stannyl derivatives with Pd(PPh$_3$)$_4$ and (SnBu$_3$)$_2$ under refluxing condition with toluene or dioxane [12a] failed to induce any change in the starting material (Scheme 18).

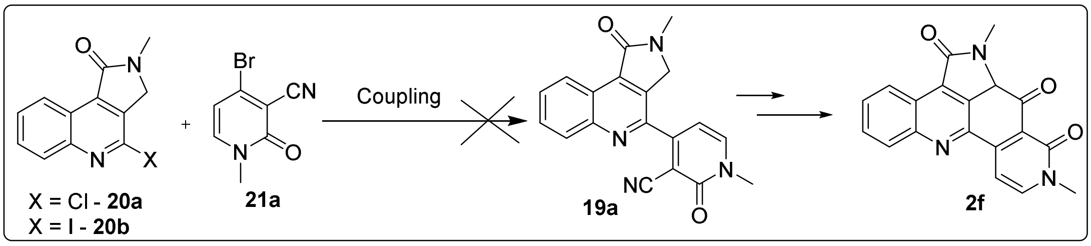


Pd(PPh$_3$)$_4$, toluene or
Dioxane, relfux, (SnBu$_3$)$_2$
21a
21b
Pd(PPh$_3$)$_4$, toluene or
Dioxane, reflux, (SnBu$_3$)$_2$
20b
20c

Scheme 18

Compound **20b** was treated with reaction conditions established by Krasovskiy *et al.* [12b] to form zinc intermediate and on further insitu treatment with **21a** in the presence of Pd(PPh$_3$)$_4$ in refluxing THF, gave a complex mixture of compounds (Table 2, entry 1). Similarly, treating **21a** to form zinc intermediate and insitu reaction with **20b** under similar conditions again failed to give coupled product **19a** (Table 2, entry 2). Compound **20a** was treated with conditions established by Jin *et al.* [12c] to insert zinc in C-Cl bond but again gave a mixture of compounds (Table 2, entry 3). Also treating **21a** with *tert*-butyl lithium and further transmetalation with $ZnCl_2$ and then treating with **20b** in the presence of palladium (0) gave a mixture of compounds (Table 2, entry 4).

Table 2: Attempted coupling conditions to obtain **19a**.



Sr. No	Reaction condition	Observation
1	**20b**, Zn, LiCl, THF, dibromoethane (5 mol%), trimethylsilyl chloride (1 mol%) then **21a**,Pd(PPh_3)$_4$, reflux	Mixtures of compounds
2	**21a**, Zn, LiCl, THF, dibromoethane (5 mol%), trimethylsilyl chloride (1 mol%) then **20b**,Pd(PPh_3)$_4$, reflux	Mixtures of compounds
3	**20a**, Zn, LiCl, THF, dibromoethane (5 mol%), trimethylsilyl chloride (1 mol%), $CoCl_2$, Xanthphos, 50 ^oC then **21a**, Pd(PPh_3)$_4$, reflux	Mixtures of compounds
4	**21a**, THF,t- BuLi, -95 ^oC, $ZnCl_2$ then **20b**,Pd(PPh_3)$_4$, reflux	Mixtures of compounds

5. A. 4: Conclusion

Various attempts towards the synthesis of C & D ring of alpkinidine were attempted. Failure in these attempts could be attributed to the low reactivity of quinoline nucleus.

Coupling strategy for construction of alpikinidines C ring was proposed and both the key intermediates for coupling were synthesized successfully. However, all the attempts to couple the intermediates failed in our hands.

Section B:Synthesis of benzo derivative of Alpkinidine

5. B. 1: Introduction

Alpkinidine, as discussed in the section A of this chapter has an unusual ring E which is believed to be vital for its activity along with the C ring. For synthetic simplicity and to develop a method we thought of replacing the E ring of alpkinidine with a phenyl ring as shown in Figure 3. This structure having a fused pentacyclic ring system would also posses the keto-enol tautamerism as shown by alpkinidine.

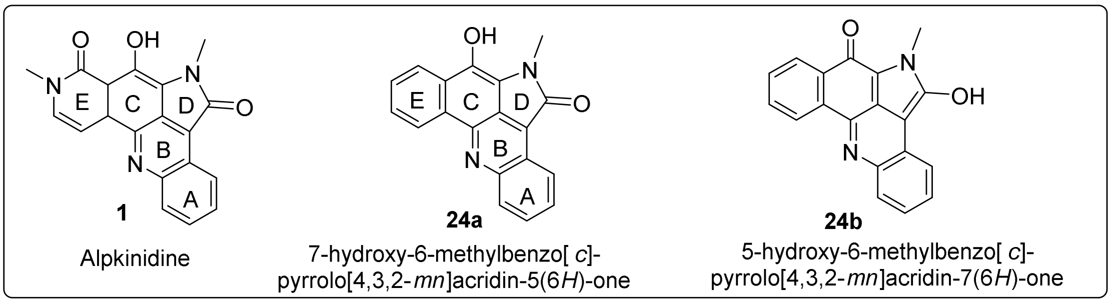
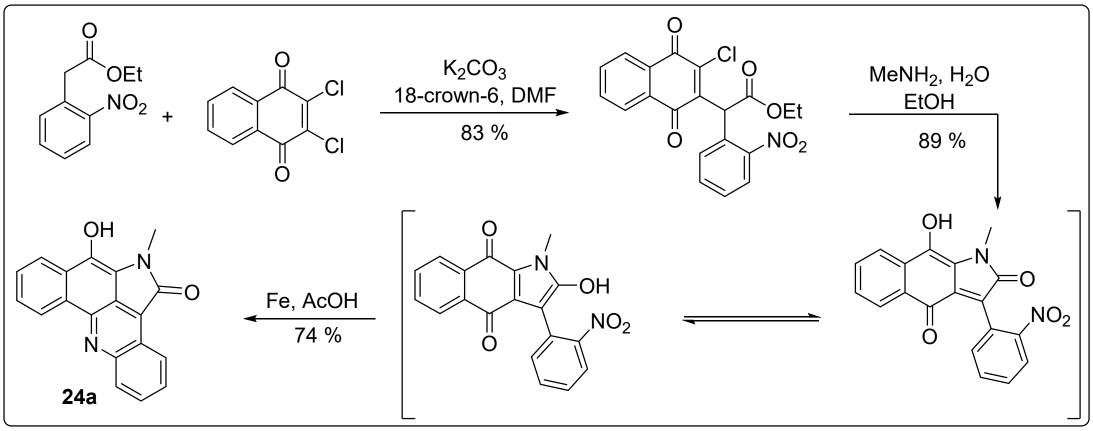

O
OH
N
E
C
D
O
B
N
A
1
Alpkinidine
OH
N
E
C
D
O
B
N
A
24a
7-hydroxy-6-methylbenzo[c]-pyrrolo[4,3,2-mn]acridin-5(6H)-one
O
N
OH
N
24b
5-hydroxy-6-methylbenzo[c]-pyrrolo[4,3,2-mn]acridin-7(6H)-one

Figure 3. Alpkinidine and its structure varying in E ring

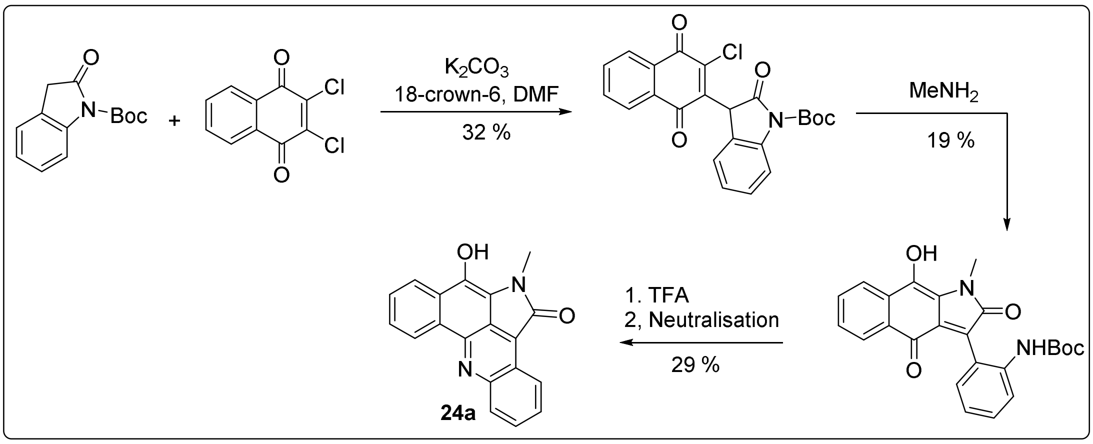
5. B. 2: Literature Reported Methods

In literature there is only one report for the synthesis of **24a**/**24b**, developed by Piggott *et al.*[13] in 2013. Two successful routes for the synthesis of **24a** which contains ABCD ring structure possessed in alpkinidine were developed (Scheme 19). In the first route reaction of ethyl ester derivative of *o*-nitrophenyl acetic acid and 2,3-dichloro-1,4-naphthoquinone in the presence of K_2CO_3 and a crown ether gave an adduct, which on treatment with methyl amine fetched D ring system and subsequent reduction with Fe/AcOH furnished compound **24a** in 3 steps with overall yield of 55%.


O
OEt
NO2
+
O
Cl
Cl
O
K2CO3
18-crown-6, DMF
83 %
O
Cl
O
OEt
O
NO2
MeNH2, H2O
EtOH
89 %
OH
N
O
N
24a
Fe, AcOH
74 %
O
N
OH
O
NO2
OH
N
O
O
NO2

Scheme 19

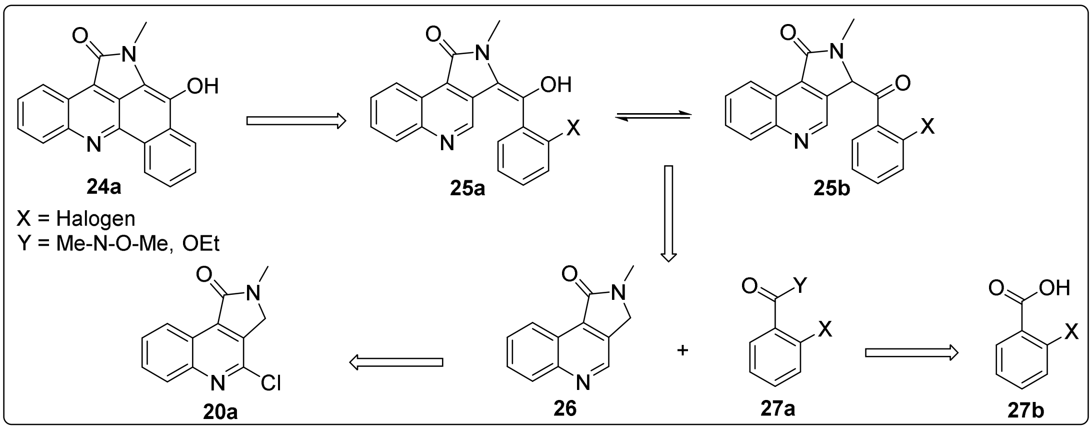
The above strategy was then modified by the authors by replacing *o*-nitrophenyl acetic acid with *N*-boc-oxyindole. However, the yield of this reaction was found to be less. Further construction of the D ring system using methyl amine and deprotection of *N*-boc group gave **24a** with overall yield of 1.76 % over 3 steps (Scheme 20).


N-Boc
+
Cl
Cl
K_2CO_3
18-crown-6, DMF
32 %
MeNH$_2$
19 %
OH
NHBoc
1. TFA
2, Neutralisation
29 %
24a

Scheme 20

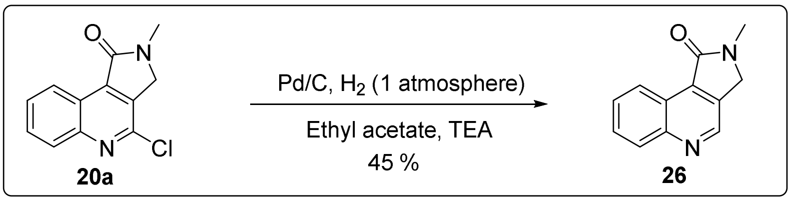
5. B. 3: Results and Discussion

In our very first attempt towards synthesis of **24a** we intended to construct ring B using intramolecular coupling of intermediate **25a** *via* metal mediated or radical cyclization. [14a] The intermediate **25a** can be drawn in its keto form as **25b** synthesis of which could be achieved from 2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **26** by reacting with carbonyl compound **27a**. Compound **26** could be synthesized by dehalogenation of **20a** [14b] and **27a** could be obtained from 2-iodobenzoic acid **27b** (Scheme 21).


24a
25a
25b
X = Halogen
Y = Me-N-O-Me, OEt
20a
26
+
27a
27b

Scheme 21

Compound **20a,** whose synthesis is discussed earlier was subjected to hydrogenation with Pd/C at 1 atmosphere for 1 h in ethyl acetate in the presence of triethyl amine to give dehalogenated derivative 2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **26** in 45 % yield (Scheme 22). However, the by-products formed in the reaction had almost same retention time on TLC as that of the desired compound **26**, thus making its purification difficult. The structure of the product was confirmed using ^{1}H NMR, which showed one extra proton merging at 9.01-8.99 ppm and ^{13}C DEPT NMR show acarbon singlet at 144.7 ppm differing from its starting compound.



Scheme 22

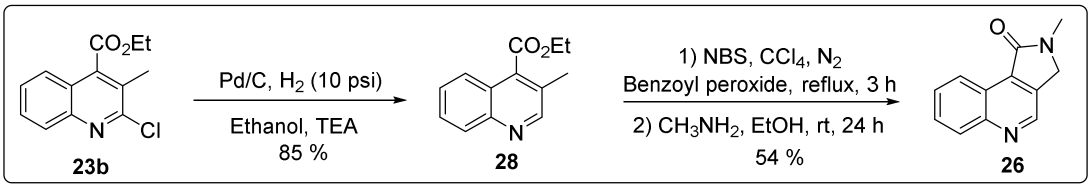
Spectral data of 2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one (26): [14b]

IR (KBr): $\tilde{\nu}$ = 3062, 2922, 1687, 1514, 1433, 1278, 779 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 9.01-8.99 (m, 2H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.75 (dt, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.64 (dt, *J* = 8.0 Hz, 1.2 Hz, 1H), 4.50 (s, 2H), 3.23 (s, 3H).

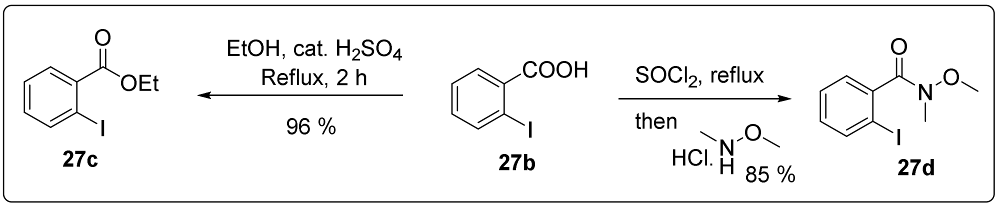
^{13}C NMR (100 MHz, DMSO-d6): δ 167.9 (C), 147.8 (C), 144.7 (CH), 135.2 (C), 134.5 (C), 130.0 (CH), 129.2 (CH), 128.3 (CH), 123.7 (CH), 123.5, 50.4 (CH$_2$), 29.6 (CH$_3$).

Since the yield of **26** was low a slightly different route for its synthesis from **23b**[14b] was adopted (Scheme 23). Thus, hydrogenolysis of **23b** at 10 psi in EtOH/TEA in the presence of Pd/C gave **28** which on treatment with NBS followed by reacting with methyl amine in ethanol gave **26** in 46 % overall yield over 3 steps.



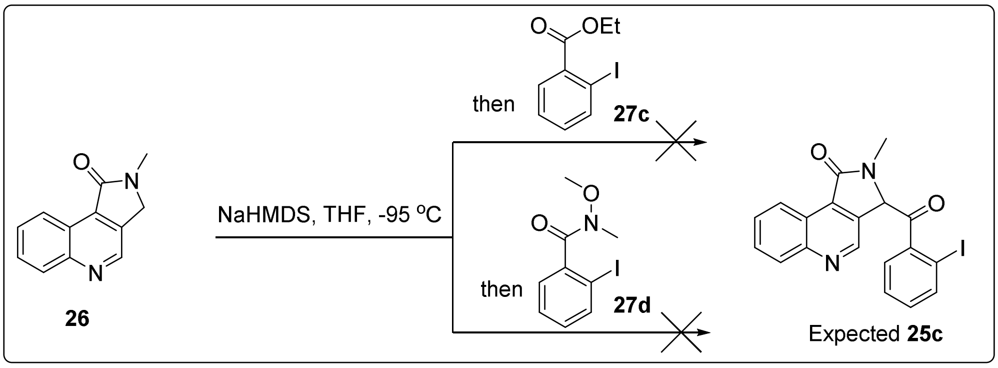
Scheme 23

Ethyl 2-iodobenzoate **27c** was prepared by refluxing 2-iodobenzoic acid with ethanol in the presence of catalytic amount of H_2SO_4. [15a] 2-Iodobenzoic acid was also subjected to amidation by converting it to its acid chloride by treatment with $SOCl_2$ followed by reacting with *N*-*O*-dimethyl hydroxylamine hydrochloride to give 2-iodo-*N*-methoxy-*N*-methylbenzamide[15b] as brown oil in 85 % yield (Scheme 24).


EtOH, cat. H2SO4
Reflux, 2 h
96 %
COOH
OEt
SOCl2, reflux
then
HCl.
85 %
27c
27b
27d

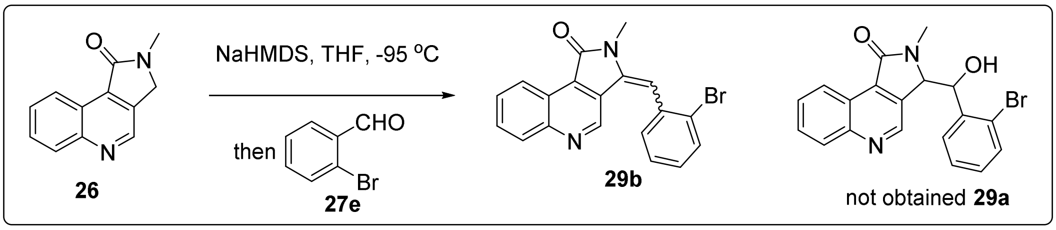
Scheme 24

Metallation of isoindolinone [16a-b] moiety **26** in THF with NaHMDS at -95 °C gave deep green colored anion which on treatment with ethyl 2-iodobenzoate **27c** failed to give any change in the starting material (Scheme 25). Similarly, treating the anion formed with 2-iodo-*N*-methoxy-*N*-methylbenzamide **27d** gave unreacted starting material back.


NaHMDS, THF, -95 °C
then
27c
then
27d
26
Expected 25c

Scheme 25

Having failed to form a C-C bond between the anion of **26** and ester **27c** or Weinreb amide **27d,** the anion was reacted with 2-bromo benzaldehyde during which a dehydrated product **29b** was obtained in 90 % yield (Scheme 26). This clearly indicated that failure of the above reactions were due to less reactivity of **27c** and **27d** and not because of compound **26**. No success in these reactions was achieved even under refluxing conditions at higher temperature.


NaHMDS, THF, -95 °C
then
CHO
Br
26
27e
29b
not obtained 29a

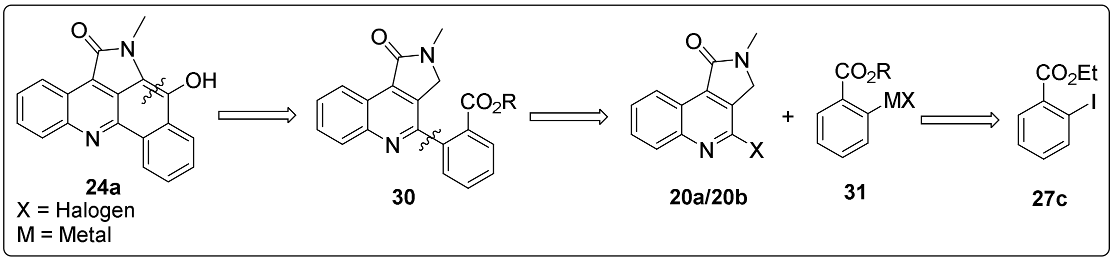
Scheme 26

Spectral data of 3-(2-bromobenzylidene)-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one (29b):

IR (KBr): $\tilde{\nu}$ = 3307, 2866, 1703, 1440, 1367, 1056, 1024, 750 cm^{-1}.

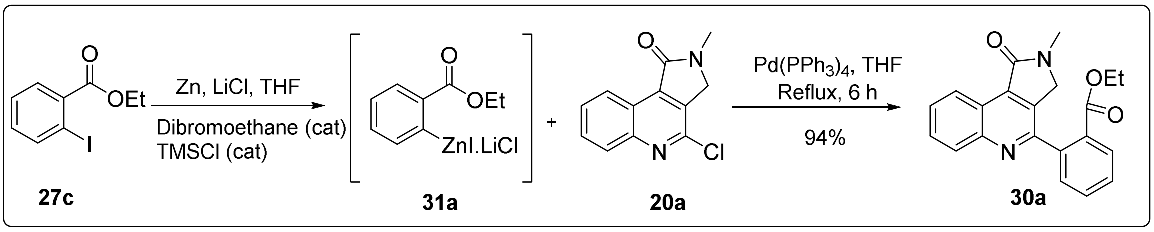
^{1}H NMR (400 MHz, DMSO-d6): δ 9.42 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 8.53 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.67-7.55 (m, 3H), 7.42 (d, J = 7.2 Hz, 1H), 7.27 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 7.18 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 6.53 (s, 1H), 3.38 (s, 3H).
^{13}C NMR (100 MHz, DMSO-d6): δ 165.7 (C), 147.8 (C), 142.2 (CH), 136.4 (C), 135.0 (C), 133.2 (CH), 132.0 (C), 131.7 (CH), 130.6 (CH), 130.3 (CH), 129.0 (CH), 128.8 (CH), 128.0 (C), 127.7 (CH), 124.8 (C), 124.4 (CH), 122.6 (C), 112.5 (CH), 26.3 (CH_3).
HRMS (ESI): calcd for $C_{19}H_{13}BrN_2ONa$ $[M + Na]^+$ 387.0109, found 387.0109.

As above route failed, we chose an alternate method for the synthesis of **24a** using an intramolecular cyclisation of intermediate **30**, which could be obtained by coupling from intermediate **20a**/**20b** and metallated compound **31** (Scheme 27).


O
N
OH
N
24a
X = Halogen
M = Metal
O
N
CO2R
N
30
O
N
N
X
20a/20b
+
CO2R
MX
31
CO2Et
I
27c

Scheme 27

We chose zinc metal for coupling and zinc was inserted in C-I bond of **27c** using procedure described in literature.[12b] (Scheme 28). The aryl zinc compound **31a** thus produced, without further purification, was reacted insitu with chloro intermediate **20a** under Negishi condition using $Pd(PPh_3)_4$ in refluxing THF to obtain coupled product ethyl 2-(2-methyl-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-yl)-benzoate **30a** in excellent yield. It was characterized from its IR spectrum, which showed two distinct carbonyl stretching at 1728 and 1687 cm^{-1} accounting for ester and amide functionality respectively. Further confirmation of the structure was done using NMR and mass spectral techniques.


O
OEt
I
27c
Zn, LiCl, THF
Dibromoethane (cat)
TMSCl (cat)
O
OEt
ZnI.LiCl
31a
+
O
N
N
Cl
20a
Pd(PPh3)4, THF
Reflux, 6 h
94%
O
N
OEt
O
N
30a

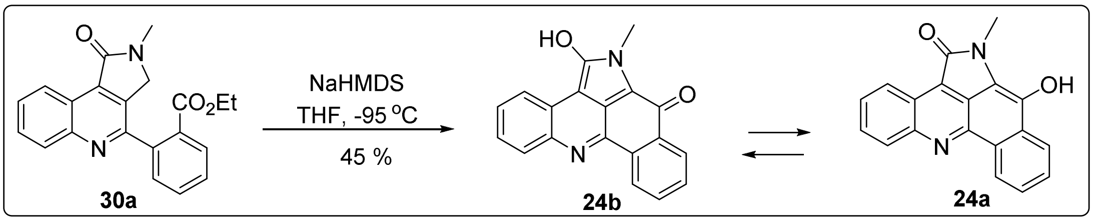
Scheme 28

Spectral data of ethyl 2-(2-methyl-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-yl)benzoate (30a):

IR (KBr): $\tilde{\nu}$ = 2983, 1728, 1687, 1290, 1251, 1128, 786 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.16 (dd, J = 8.4 Hz, 0.8 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.14 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 7.83 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 7.76-7.68 (m, 2H), 7.62 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 7.53 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 4.31 (s, 2H), 4.04 (q, J = 7.6 Hz, 1H), 3.26 (s, 3H), 0.88 (t, J = 7.6 Hz, 1H).
^{13}C NMR (100 MHz, CDCl$_3$): δ 168.1 (C), 166.7 (C), 155.2 (C), 147.6 (C), 139.2 (C), 134.8 (C), 134.6 (C), 132.3 (CH), 130.8 (CH), 130.3 (C), 130.0 (CH), 129.7 (CH), 129.3 (C), 129.2 (CH), 128.0 (CH), 123.6 (CH), 122.8 (C), 61.1 (CH$_2$), 51.0 (CH$_2$), 29.5 (CH$_3$), 13.7 (CH$_3$).
HRMS (ESI): calcd for $C_{21}H_{18}N_2O_3Na$ $[M + Na]^+$ 369.1215, found 369.1215.

Having obtained **30a**, it was then subjected to a base mediated cyclization using NaHMDS at -95 ^{o}C as shown below (Scheme 29).The progress of the reaction was monitored using TLC, which showed completion in 2 h. On acidic treatment and purification on a silica gel column a red colored compound was obtained. Further, the structure of **24a** was confirmed from its ^{1}H NMR spectrum, which matched perfectly with its reported values.



Scheme 29

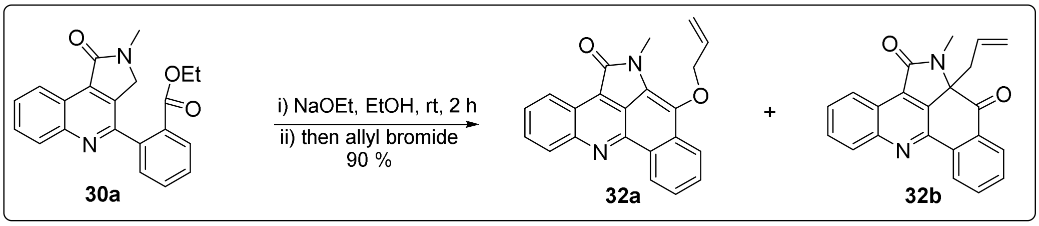
Spectral data of 7-hydroxy-6-methylbenzo[c]pyrrolo[4,3,2-*mn*]acridin-5(6*H*)-one (24a):[13]

^{1}H NMR (400 MHz, DMSO-d6): δ 10.65 (brs, 1H), 9.05 (d, J = 7.6 Hz, 1H), 8.77 (d, J = 8.0 Hz, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.95-7.84 (m, 3H), 7.76 (t, J = 7.6 Hz, 1H), 3.72 (s, 3H).
^{13}C NMR (100 MHz, DMSO-d6): δ 166.1 (C), 147.6 (C), 142.5 (C), 136.0 (C), 132.8 (C), 130.3 (CH), 130.1 (CH), 129.2 (C), 129.1 (CH), 128.7 (CH), 127.1 (CH), 124.2 (C), 123.9 (CH), 123.5 (CH), 122.7 (CH), 122.6 (C), 122.5 (C), 118.0 (C), 28.6 (CH$_3$).

While purification of **24a** by column chromatography a purple colored compound eluted. This purple compound was the tautomeric form **24b** of compound **24a**. This color change could also be observed when **24a** was treated with saturated solution of NaHCO$_3$.[13]

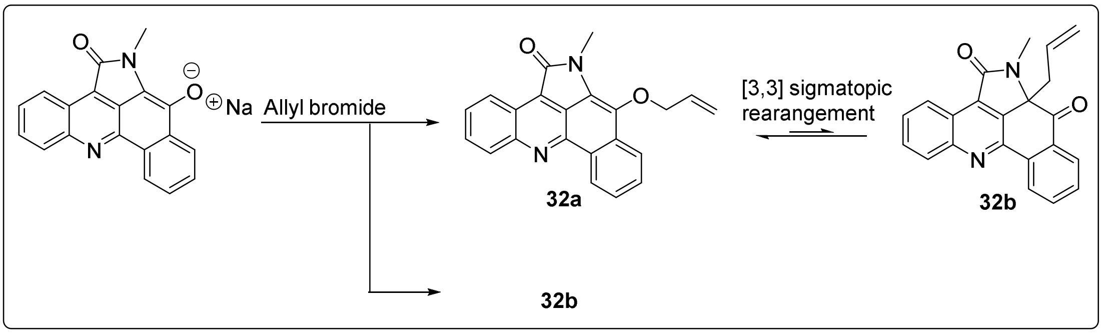
The slightly less yield (45 %) of **24a** was attributed to its lower solubility in most organic solvents. Secondly, to its existence in the as keto-enol tautomeric form resulting in low isolated yield of **24a**.

Hence, to increase the yield of this reaction, we thought to isolate it as its alkyl derivative which would increase the solubility of this compound as well as eliminate the problem of tautomerism (Scheme 30). Thus, on treating **30a** with sodium ethoxide at room temperature and after cyclization the anion was further reacted with allyl bromide in the same pot to provide two distinct compounds **32a** and **32b** after column purification. Both the compounds were characterized based on IR, ^{1}H, and ^{13}C NMR and HRMS data and were found to be *o*-allyl and *c*-allyl isomers.



Scheme 30

The formation of product **32b** could be accounted for either *via* C-allylation of intermediate phenoxide ion or by a 3,3-sigmatopic rearrangement of the product **32a** (Scheme 31). As expected the combined yield of **32a** and **32b** had increased to 84 %.



Scheme 31

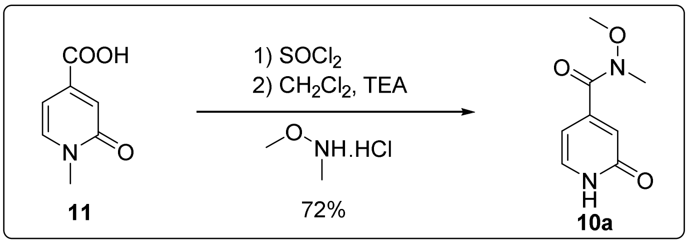
5. B. 4: Conclusion

A benzo analogue of alpkinidine has been successfully synthesized using Negishi coupling followed by a base mediated cyclization *via* metallation on isoindolinone.

Thus, a method for the synthesis of analogue containing the ABCD ring structure of alpkindine and differing in the E ring from the naturally occurring alkaloid is demonstrated in this chapter.

5. 5: Experimental

5.5.1: *N*-Methoxy-*N*-methyl-2-oxo-1,2-dihydropyridine-4-carboxamide (10a):



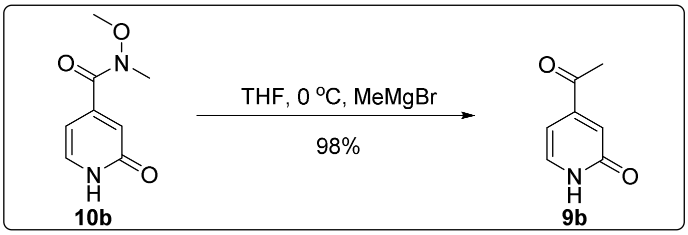
To a magnetically stirred solution of distilled thionyl chloride (10 mL) was added 1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid **11** [6a] (0.42 g, 2.74 mmol) in a 50 mL round bottom flask and heated at 60 °C for 1.5 h. Excess thionyl chloride was then removed under reduced pressure and reaction mass was cooled to room temperature. DCM 10 mL, *N*,*O*-dimethyl hydroxyl amine hydrochloride (0.295 g, 3.01 mmol) added to the above acid chloride and cooled to 0 °C using ice bath. Triethyl amine (2 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature. Water (15 mL) was added to the reaction mass, the organic layer was then separated and washed with sat. $NaHCO_3$ (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product obtained was purified using silica gel column purification employing 40 % ethyl acetate in petroleum ether as an eluent to obtain *N*-methoxy-*N*-methyl-2-oxo-1,2-dihydropyridine-4-carboxamide **10a** in 72 % (0.36 g) yield as a yellow viscous oil.

IR (KBr): $\tilde{\nu}$ = 3098, 3048, 1684, 1666, 1590, 1486, 1221, 790 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 5.2 Hz, 1H), 7.49 (s, 1H), 7.39 (d, *J* = 5.2 Hz, 1H) 3.29 (s, 3H) 2.70 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0 (C), 151.6 (C), 149.8 (CH), 144.6 (C), 122.9 (CH), 120.8 (CH), 61.6 (CH_3), 32.9 (CH_3).

5.5.2: 4-Acetylpyridin-2(1*H*)-one (9b):



To a magnetically stirred solution of *N*-methoxy-*N*-methyl-2-oxo-1,2-dihydropyridine-4-carboxamide **10b** (0.25 g, 1.37 mmol) in dry THF (mL), under N_2 atmosphere at 0 °C was added methyl magnesium bromide (3M in cyclohexane) (0.96 mL, 2.88 mmol) dropwise over a minute. The reaction mixture was then stirred for 3 h at room temperature. The resulting solution was quenched with 5 % NH_4Cl (10 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified over silica column using 10 % ethyl acetate in petroleum ether as an eluent to give 4-acetylpyridin-2(1*H*)-one **9b** in 98 % (0.18 g) yield.

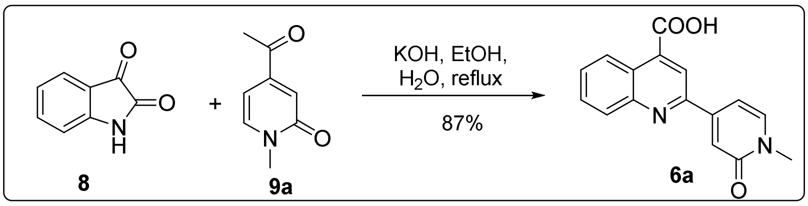
White solid, m.p. 112-114 °C.

IR (KBr): $\tilde{\nu}$ = 3090, 3035, 1922, 1680, 1651, 1592, 1490, 1233, 799 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.84 (s, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.10 (s, 1H), 6.68 (d, *J* = 6.8 Hz, 1H), 2.56 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.1 (C), 162.6 (C), 144.8 (C), 137.2 (CH), 120.9 (CH), 103.0 (CH), 26.2 (CH_3).

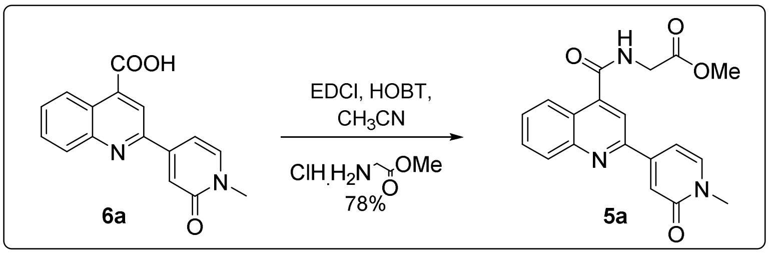
5.5.3: 2-(1-Methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylic acid (6a):



In a 100 mL RBF with magnetic stirring bead, isatin **8** (1.62 g, 11.03 mmol), 4-acetyl-1-methylpyridin-2(1*H*)-one **9a** (2 g, 13.23 mmol), KOH (2.47 g, 44.10 mmol), ethanol (20 mL) and water (6 mL) was taken and the reaction mass was heated to reflux for 18 h. Ethanol was removed under reduced pressure and water (50 mL) was added and washed with diethyl ether (30 mL). The aqueous layer was acidified with acetic acid and then filtered to give a white solid, which was washed with water (30 mL), diethyl ether (15 mL) and finally with acetone (15 mL) to give 2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylic acid **6a** in 87 % (0.270 g) yield.

White solid, m.p. 188-190 °C.

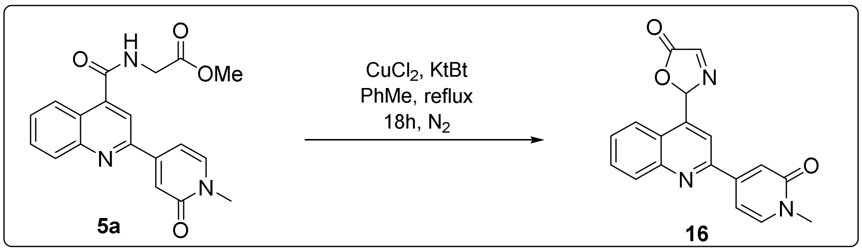
5.5.4: Methyl (2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carbonyl)-glycinate (5a):



To the stirred suspension of 2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylic acid **6a** (1.41 g, 5 mmol) in 60 mL mixture of acetonitrile and DMF (5:1), was added methyl glycinate hydrochloride (0.69 g, 5.5 mmol), EDCl (1.15 g, 6 mmol), HOBT (0.81 g, 6 mmol) and triethyl amine (0.76 g, 5.5 mmol). The reaction mass was then stirred at room temperature for 16 h. To the reaction mixture water (30 mL) was added and extracted with ethyl acetate (3 X 20 mL). The combined organic layer was then washed with sat. $NaHCO_3$ solution (2 X 20 mL) and dried over anhydrous Na_2SO_4. On removal of solvent a white solid of methyl (2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carbonyl)glycinate **5a** was obtained in 78 % (1.37 g) yield.

White solid, m.p. 162-164 ^oC.

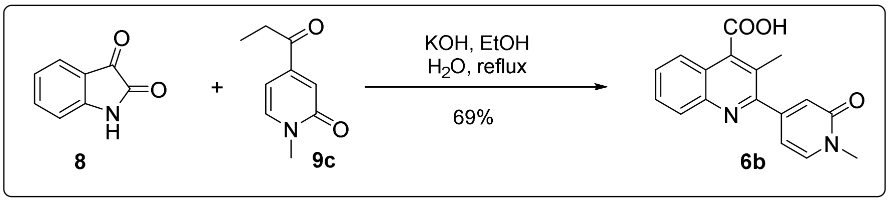
5.5.5: 2-(2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinolin-4-yl)oxazol-5(2*H*)-one (16):



In a sealed tube flushed with Nitrogen, a mixture of methyl (2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carbonyl)glycinate **5a** (0.015 g, 0.043 mmol), anhydrous $CuCl_2$ (0.013 g, 0.093 mmol) and potassium *t*-butoxide (0.029 g, 0.256 mmol) in toluene (4 mL) was refluxed for 22 h. On cooling, water (5 mL) was added and reaction mass extracted with ethyl acetate (10 mL). The organic layer was separated and dried over Na_2SO_4. Removal of the solvent and purification of the crude product using column chromatography with 30 % ethyl acetate in petroleum ether gave **16** in 59 % (0.008 g) yield.

White solid, m.p. 142-144 ^oC.

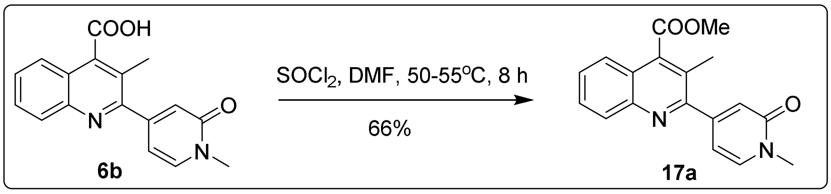
5.5.6: 3-Methyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylic acid (6b):



Following the similar protocol described in section 5.5.3 with isatin **8** (1.32 g, 9 mmol), 1-methyl-4-propionylpyridin-2(1*H*)-one **6b** (1.64 g, 9.9 mmol) KOH (2.01 g, 36 mmol), EtOH (20 mL) and water (6 mL) gave 3-methyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylic acid **6b** in 69 % (1.83 g).

White solid, m.p. 180-182 ^oC.

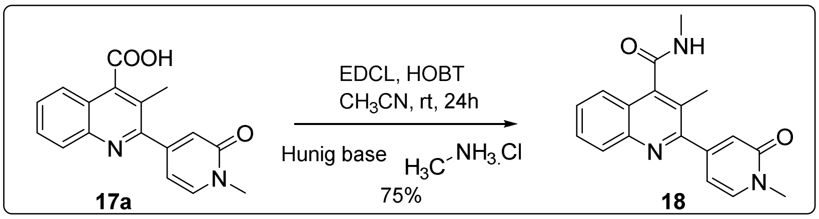
5.5.7: Methyl 3-methyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylate (17a):



Following the similar protocol described in section 5.5.1 with 3-methyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylic acid **6b** (0.52 g, 1.76 mmol), $SOCl_2$ (10 mL), DMF (2 drops) for 8 h then removing excess thionyl chloride and treating with methanol (20 mL) and refluxing for 2 h gave methyl 3-methyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylate **17a** in 66 % (0.36 g).

White solid, m.p. 132-134 °C.

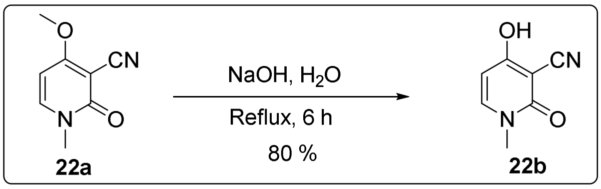
5.5.8: *N*,3-dimethyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxamide (18):



Following the protocol described in section 5.5.4 with3-methyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxylic acid **17a** (0.29 g, 1.0 mmol), EDCl (0.231 g, 1.20 mmol), HOBT (0.152 g, 1.2 mmol), acetonitrile (15 mL), methyl amine hydrochloride (0.076 g, 1.1 mmol) and Hunig's base (0.2 mL) gave *N*,3-dimethyl-2-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)quinoline-4-carboxamide **18** in 75 % (0.232 g) yield.

Pale yellow solid, m.p. 158-160 °C.

5.5.9: 4-Hydroxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (22b):



A stirred suspension of 4-methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **22a** (1.079 g, 6.48 mmol), 1M NaOH solution (5 mL) and 3 mL water was heated to reflux for 6 h. On cooling 2M HCl was added and the solid obtained was filtered and washed with diethyl ether (2 x 10 mL) to give 4-hydroxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **22b** in 80 % (0.783 g) yield.

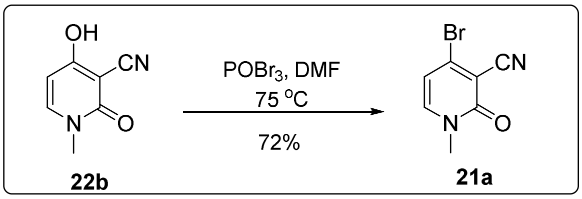
White solid, m.p. 146-148 °C.

IR (KBr): $\tilde{\nu}$ = 3307, 2630, 2222, 1645, 1573, 1487, 1240, 806 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 12.63 (br s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 6.03 (d, J = 7.6 Hz, 1H), 3.36 (s, 3H).

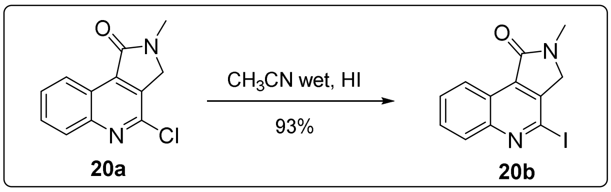
^{13}C NMR (100 MHz, DMSO-d6): δ 171.0 (C), 161.4 (C), 144.5 (C), 115.1 (C), 97.7 (CH), 85.0 (C), 36.4 (CH_3).

5.5.10: 4-Bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (21a):



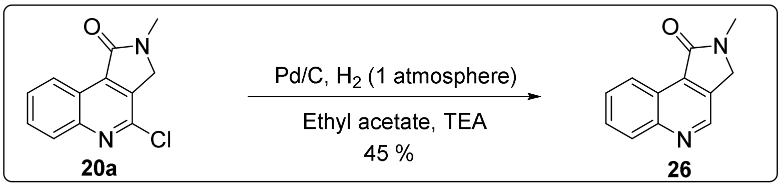
To a stirred solution of 4-hydroxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **22b** (0.78 g, 5.16 mmol) in anhydrous DMF (12 mL) was added $POBr_3$ (2.96 g, 10.33 mmol) in small portions over 15 minutes. The reaction mass was heated at 75 °C for 6 h and then quenched with water (20 mL). The mixture was extracted with ethyl acetate (3 X 15 mL) and the combined organic layers were washed with a sat. $NaHCO_3$ solution (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 4-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **21a** in 72 % (0.80 g) yield.
White solid, m.p. 108-110 °C.

5.5.11: 4-Iodo-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one (20b):



To a stirred solution of 4-chloro-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **20a** in acetonitrile (100 mL) was added 1 mL water and cooled to 0 °C using ice. Hydroiodic acid (10 mL) was added drop wise over a period of 10 minutes, then the reaction mass was stirred at room temperature for 12 h. Acetonitrile was removed under reduced pressure and 20 mL water added and then extracted with ethyl acetate (3 X 15 mL). The organic layer was combined and washed with a sat. $NaHCO_3$ solution (20 mL). The organic layer dried over Na_2SO_4 and concentrated under reduced pressure to give 4-iodo-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **20b** in 93 % (0.302 g) yield.
White solid, m.p. 114-116 °C.

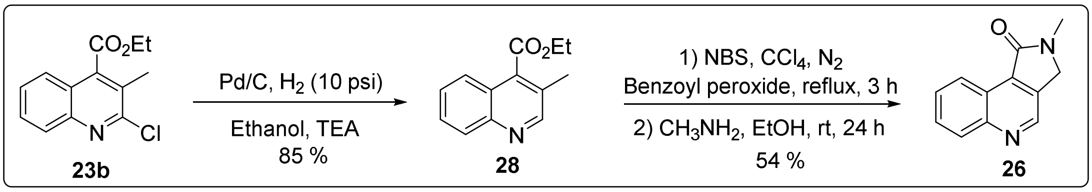
5.5.12: 2-Methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one (26):



In a hydrogenation flask, 4-chloro-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **20a** (0.05 g, 0.21 mmol) was dissolved in dry ethanol (20 mL). To this, triethyl amine (1 mL) was added and the flask degassed with hydrogen. Pd/C (5 %) (0.01 g) was added in the flask and hydrogen pressure of 10 psi was maintained for 1 h under agitation. On completion of the reaction (monitored by TLC) Pd/C was filtered and the volatiles were removed under reduced pressure. To the residue water (10 mL) was added and extracted with $CHCl_3$ (3 X 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to a give a crude product, which was purified using silica gel column purification with 20 % ethyl acetate in petroleum ether to give 2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **26** in 45 % (0.02 g) yield.

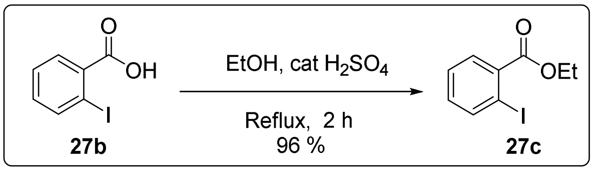
White solid, m.p. 106-108 ^{o}C.

5.5.13: 2-Methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one (26):



In a hydrogenation flask ethyl 2-chloro-3-methylquinoline-4-carboxylate **23b** (0.80 g, 3.45 mmol), triethyl amine (2.5 mL) were mixed with dry ethanol (30 mL)and the flask degassed with hydrogen. Pd/C (5 %) (0.06 g) was added to the flask and hydrogen pressure of 10 psi was maintained for 1 h under agitation. On completion of the reaction (monitored by TLC) Pd/C was filtered and volatiles were removed under reduced pressure. Water (10 mL) was added to the residue and extracted with $CHCl_3$ (3 X 10 mL) to afford ethyl 3-methylquinoline-4-carboxylate **28** on removal of solvent. The crude product was treated with NBS (6.14 g, 3.45 mmol), in 30 mL CCl_4 and refluxed for 3 h under N_2 atmosphere in the presence of benzoyl peroxide (0.07 g, 0.345 mmol) as initiator. Succinamide formed was removed by filtration and the crude mixture was dissolved in 20 mL ethanol. To this methyl amine (2 M in ethanol) (3.45 mL 6.90 mmol) was added and stirred at rt for 12 h. The volatiles were removed under reduced pressure, to this residue 5 % NH_4Cl (10 mL) was added and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The residue was concentrated under reduced pressure and flash chromatographed with 30 % ethyl acetate in hexanes to afford 2-methyl-2,3-dihydro-1H-pyrrolo[3,4-*c*]quinolin-1-one **26** in 46 % (0.286 g) yield over 3 steps.

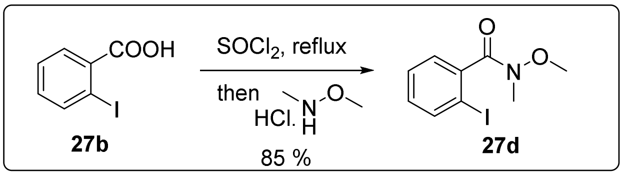
5.5. 14: Ethyl 2-iodobenzoate (27c):[15a]



To a magnetically stirred solution of 2-iodo benzoic acid **27b** (1.24 g, 5 mmol) in 20 mL ethanol was added conc. sulphuric acid (0.12 g) and refluxed for 2 h. The mixture was then cooled and concentrated under reduced pressure. It was then partitioned between 15 mL water and 25 mL ethyl acetate. The organic layer was further washed with sat. $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. Concentration under reduced pressure afforded ethyl 2 benzoate **27c** in 96 % (1.437 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H).

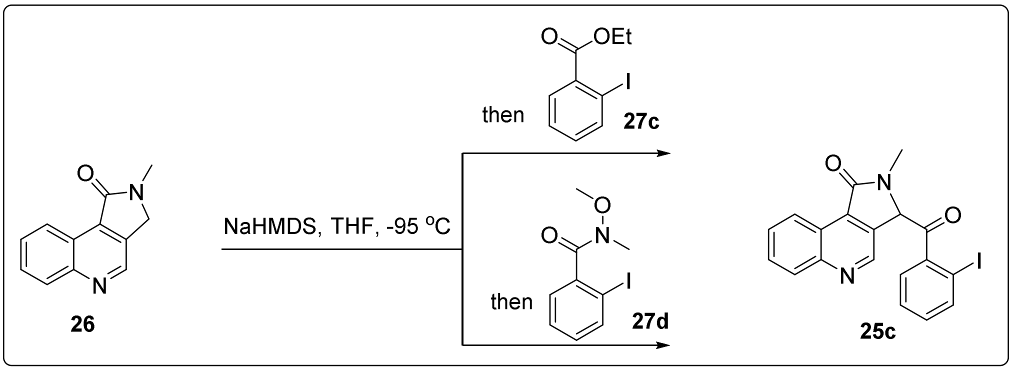
5.5.15: 2-Iodo-*N*-methoxy-*N*-methylbenzamide (27d):[15b]



To a magnetically stirred solution of 2-iodo benzoic acid **27b** (1.24 g, 5 mmol) in a 50 mL round bottem flask was added thionyl chloride (15 mL) and heated at 60 ^oC for 2 h. Excess thionyl chloride was then removed under reduced pressure and reaction mass cooled to room temperature. DCM (20 mL), *N,O*-dimethyl hydroxyl amine hydrochloride (0.536 g, 5.5 mmol) added to the acid chloride and cooled to 0 ^oC using ice bath. Triethyl amine (3 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature. Reaction mass was quenched with 20 mL water and the phases were separated. The organic layer was washed with sat. $NaHCO_3$ and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product obtained was purified by silica gel column using 10 % ethyl acetate in petroleum ether to give 2-iodo-*N*-methoxy-*N*-methylbenzamide **27d** in 85 % (1.23 g) yield as viscous brownish oil.

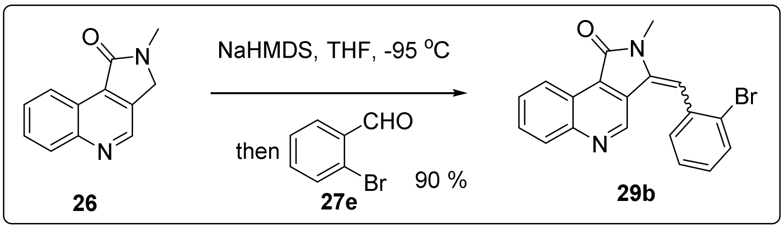
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.82 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 6.5 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 3.67 (br s, 1H), 3.47-3.41 (br d, 4H), 3.08 (br s, 1H).

5.5.16: Attempted synthesis of 3-(2-iodobenzoyl)-2-methyl-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-1-one (25c):



To a magnetically stirred solution of 2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **26** (0.099 g, 0.5 mmol) in dry THF (15 mL) in N_2 atmosphere at -95 °C was added NaHMDS (2M in THF) (0.27 mL, 0.55 mmol) slowly over a minute and stirred at this temperature for an additional 1-1.5 h. To this ethyl 2-iodobenzoate **27c** (0.15 g, 0.55 mmol) or 2-iodo-*N*-methoxy-*N*-methylbenzamide **27d** (0.16 g, 0.55 mmol) was added and stirred at the same temperature for an additional 30 minutes. The mixture was then allowed to attain room temperature overnight. The resulting solution was quenched with 5 % NH_4Cl (10 mL) and extracted with ethyl acetate (20 mL), which showed only unreacted starting on a TLC plate.

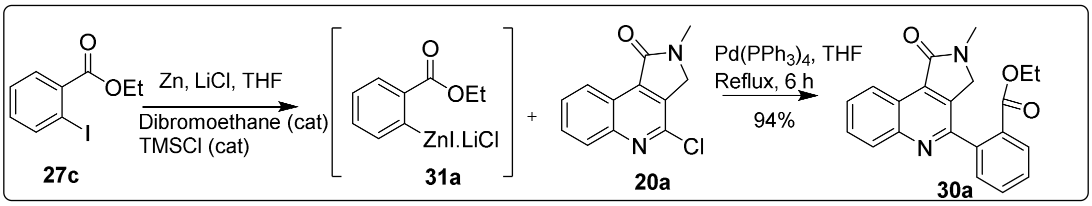
5. 5. 17: 3-(2-Bromobenzylidene)-2-methyl-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-1-one (29b):



To a magnetically stirred solution of 2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **26** (0.099 g, 0.5 mmol) in dry THF (15 mL) in N_2 atmosphere at -95 °C was added NaHMDS (2M in THF) (0.27 mL, 0.55 mmol) slowly over a minute and stirred at this temperature for an additional 1-1.5 h. To this 2-bromo benzaldehydes **27e** (0.127 g, 0.55 mmol) was added and stirred at the same temperature for an additional 30 minutes. The mixture was allowed to attain room temperature overnight. The resulting solution was quenched with 5 % NH_4Cl (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The residue was concentrated under reduced pressure and flash chromatographed with 30 % ethyl acetate in hexanes to afford 3-(2-bromobenzylidene)-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **29b** in 90 % (0.184 g) yield.

Yellow solid, m.p. 128-130 °C.

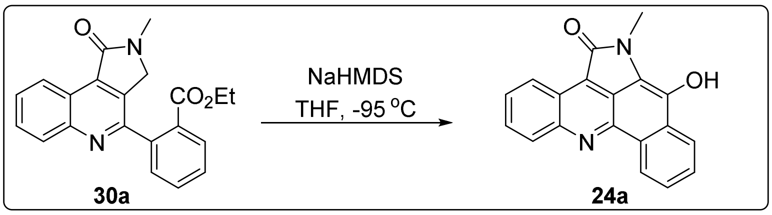
5.5.18: Ethyl 2-(2-methyl-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-yl)benzoate (30a):



In a 25 mL two neck RBF anhydrous LiCl (0.848 g, 2.0 mmol) was placed and flushed with argon. It was heated at 170 °C at 1 mbar vacuum for 10 minutes. Then zinc dust (0.197 g, 3.0 mmol) was introduced and the mixture again heated under vacuum at same parameters for 10 minutes. The flask was cooled to room temperature and anhydrous THF (4 mL) was added and degassed with argon. Dibromoethane(0.018 g, 0.1 mmol), and trimethylsilyl chloride (1 drop) were added to activate the zinc, followed by ethyl-2-iodobenzoate **27c** (0.552 g, 2.0 mmol) and stirred for 1 h. 4-Chloro-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **20a** (0.178 g, 0.77 mmol), $Pd(PPh_3)_4$ (0.09 g, 0.077 mmol) were added and the reaction mixture refluxed for 6 h. The resulting mass was quenched with 5 % NH_4Cl (10 mL), and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was flash chromatographed with 50 % ethyl acetatein hexanesto affordethyl 2-(2-methyl-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-yl)benzoate **30a** 94 % (0.250 g) yield.

Off white solid, m.p. 96-98 °C.

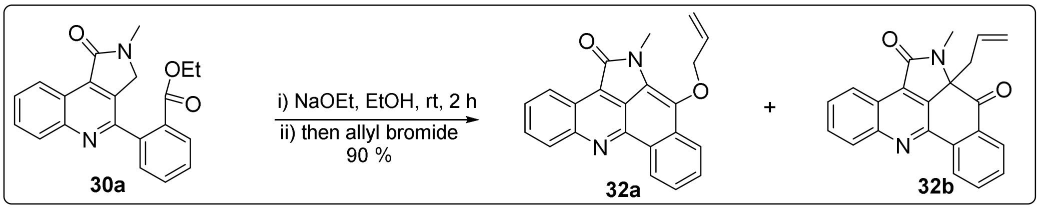
5.5.19: 7-Hydroxy-6-methylbenzo[*c*]pyrrolo[4,3,2-*mn*]acridin-5(6*H*)-one (24a):



To a magnetically stirred solution of ethyl 2-(2-methyl-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-yl)benzoate **30a** (0.072 g, 0.20 mmol) in dry THF (10 mL), under N_2 atmosphere at -95 °C was added NaHMDS (2M in THF) (0.25 mL, 0.50 mmol) slowly over a minute and stirred at this temperature for an additional 10 minutes. The reaction mixture was then allowed to attain room temperature over 4 h. The resulting deep red solution was quenched with 5 % NH_4Cl (10 mL), and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was flash chromatographed withethyl acetateto afford7-hydroxy-6-methylbenzo[*c*]pyrrolo[4,3,2-*mn*]acridin-5(6*H*)-one **24a** in 45 % (0.028 g) yield.

Red solid, m.p. 158-160 °C.

5.5. 20: 7-(Allyloxy)-6-methylbenzo[*c*]pyrrolo[4,3,2-*mn*]acridin-5(6*H*)-one (32a) and 6a-allyl-6-methyl-6,6a-dihydrobenzo[c]pyrrolo[4,3,2-mn]acridine-5,7-dione (32b):



To a magnetically stirred solution of ethyl 2-(2-methyl-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)benzoate **30a** (0.346 g, 1.0 mmol) in dry ethanol (10 mL) under N_2 atmosphere was added freshly prepared sodium ethoxide(0.07 g, 1.5 mmol) at room temperature and stirred for 2 h (monitoring by TLC). Allyl bromide (0.18 g, 1.5 mmol) was added and continued stirring for an additional 6 h. On completion of the reaction (monitored by TLC), the volatiles were removed under reduced pressure and the residue was quenched with 5 % NH_4Cl (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was flash chromatographed with 30 % ethyl acetate in petroleum ether to afford7-(allyloxy)-6-methylbenzo[*c*]pyrrolo[4,3,2-*mn*]acridin-5(6*H*)-one **32a** in 54 % (0.118 g) yieldas a bright yellowish-orange solid and 6a-allyl-6-methyl-6,6a-dihydrobenzo[*c*]pyrrolo[4,3,2-*mn*]acridine-5,7-dione **32b** in 34 % (0.116 g) yield as an off white solid.

7-(Allyloxy)-6-methylbenzo[*c*]pyrrolo[4,3,2-*mn*]acridin-5(6*H*)-one (32a):

Bright yellowish-orange solid, m.p. 162-164 °C.

IR (KBr): $\tilde{\nu}$ = 3068, 2937, 1687, 1483, 1249, 1087, 960, 773 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 9.18 (dd, *J* = 8.8 Hz, 1.2 Hz, 1H), 8.91 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 8.48 (d, *J* = 8.8 Hz, 1H), 8.09 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.89 (dt, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.82–7.69 (m, 3H), 6.26-6.19 (m, 1H), 5.58 (dd, *J* = 17.2 Hz, 1.2 Hz, 1H), 5.42 (dd, *J* = 10.4 Hz, 1.2 Hz, 1H), 4.70 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d6): δ 167.8 (C), 149.7 (C), 143.7 (C), 136.6 (C), 133.1 (C), 132.5 (CH), 130.6 (CH), 130.3 (C), 130.0 (CH), 129.7 (CH), 128.6 (CH), 127.0 (CH), 126.7 (C), 125.3 (C), 124.8 (CH), 123.8 (CH), 123.2 (CH), 123.1 (C), 123.0 (C), 118.7 (CH), 76.3 (CH_2), 28.5 (CH_3).

HRMS (ESI): calcd for $C_{22}H_{16}N_2O_2H$ [M + H]$^+$ 341.1290, found 341.1290.

6a-allyl-6-methyl-6,6a-dihydrobenzo[*c*]pyrrolo[4,3,2-*mn*]acridine-5,7-dione (32b):

Off white solid, m.p. 102-104 ^{o}C.

IR (KBr): $\tilde{\nu}$ = 3072, 2912, 1708, 1698, 1517, 1346, 773 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d6): δ 8.84 (qd, J = 8.4 Hz, 0.8 Hz, 1H), 8.61 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.96 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.87 - 7.79 (m, 2H), 7.69 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 7.63 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 5.13-5.08 (m, 1H), 4.99-4.92 (m, 2H), 3.46 (s, 3H), 3.01 (d, J = 7.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d6): δ 196.5 (C), 167.7 (C), 149.8 (C), 146.9 (C), 136.5 (C), 135.8 (C), 135.1 (CH), 134.3 (C), 133.3 (C), 131.3 (CH), 130.4 (CH), 129.9 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 124.6 (CH), 124.1 (CH), 122.2 (CH), 121.9 (CH_2), 71.4 (C), 38.8 (CH_2), 27.6 (CH_3).

HRMS (ESI): calcd for $C_{22}H_{16}N_2O_2H$ [M + H]$^+$ 341.1290, found 341.1290.

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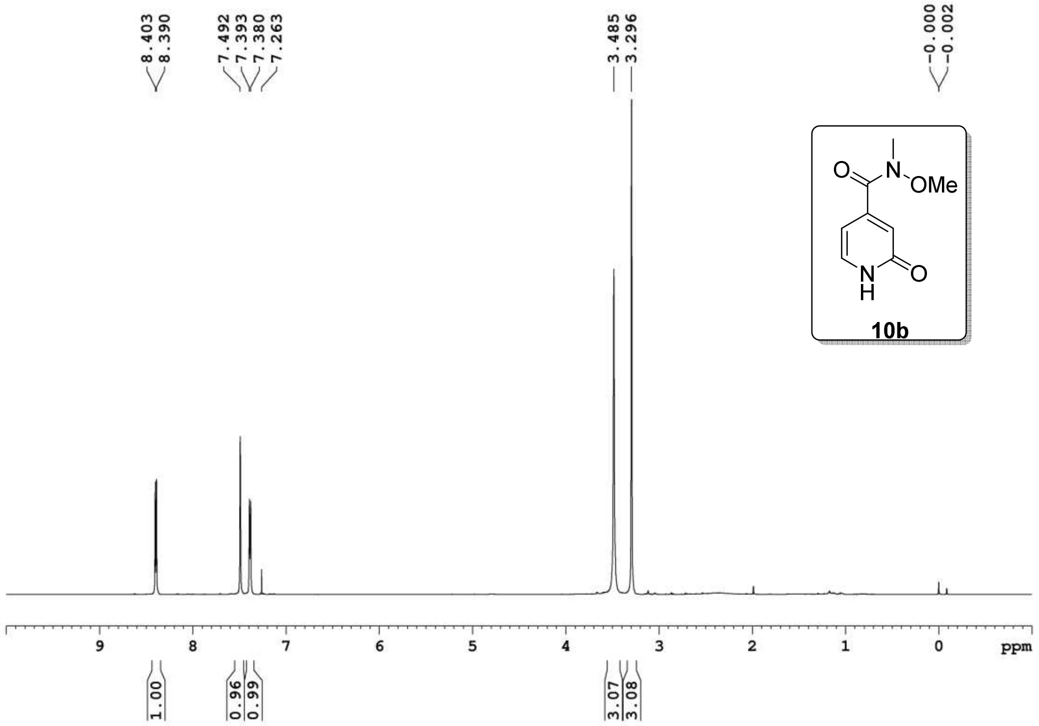
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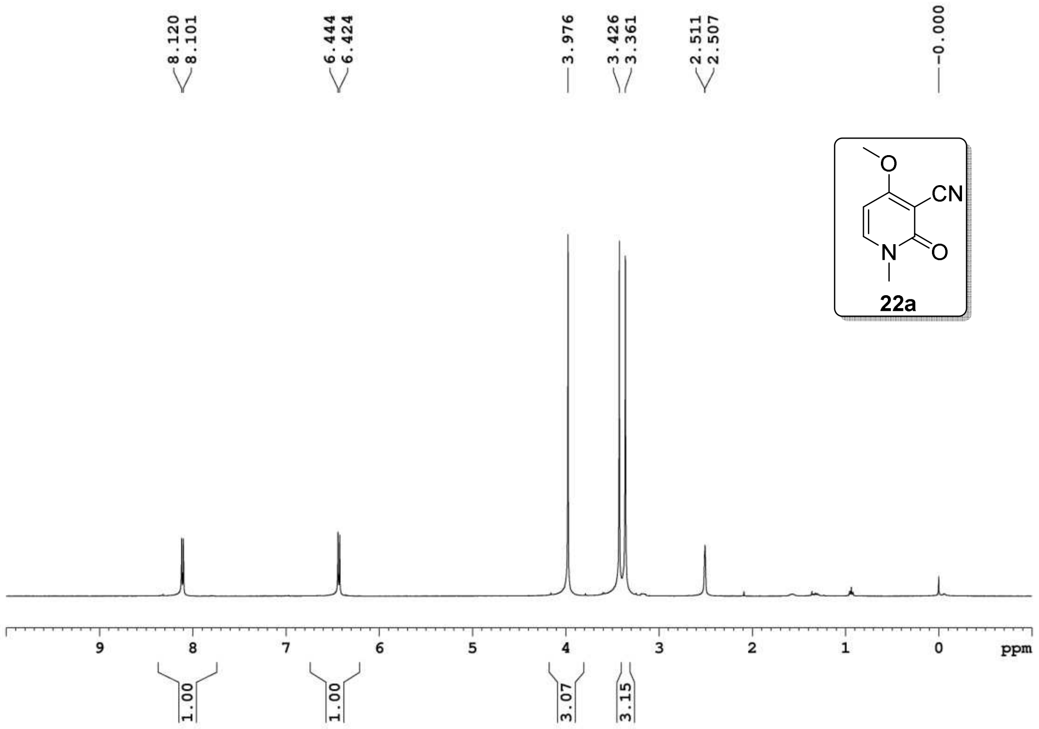
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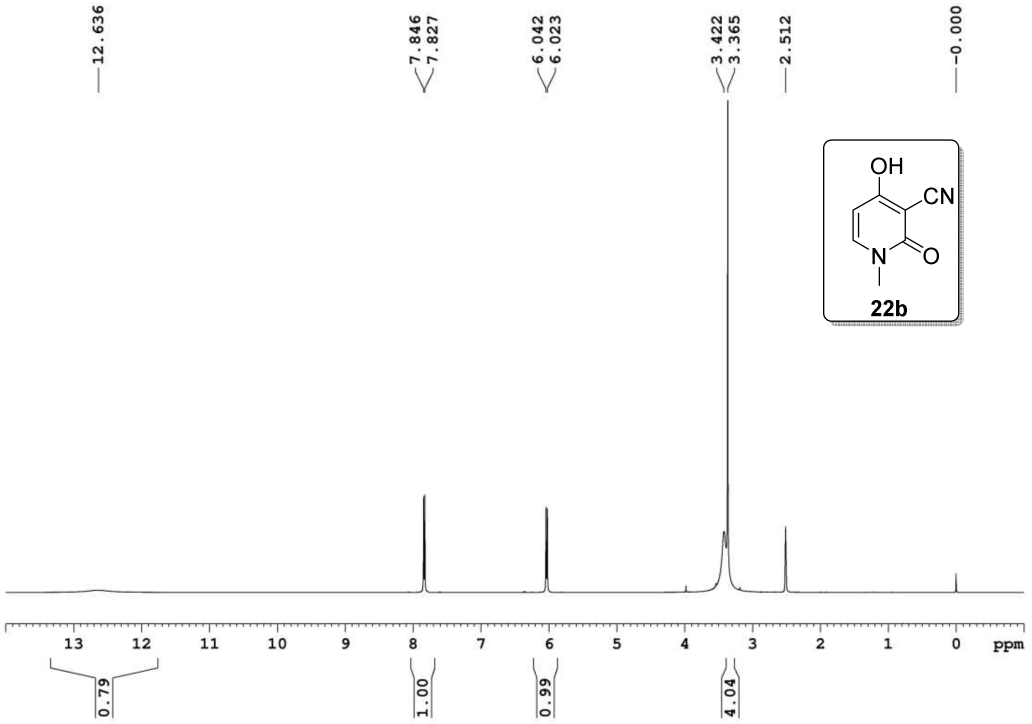
22b

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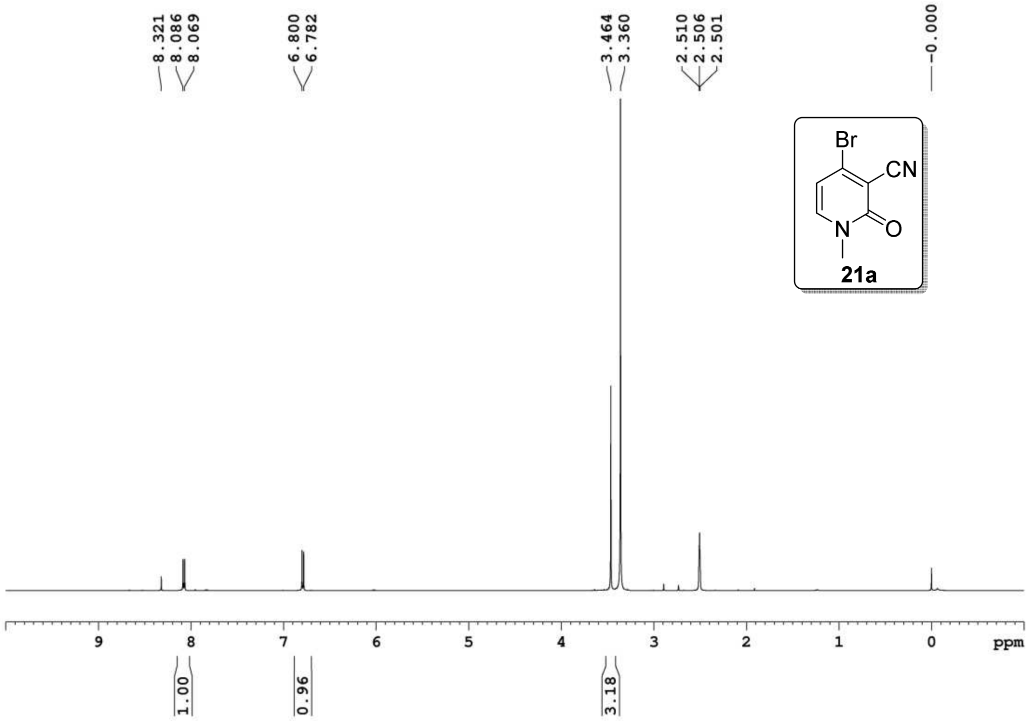
0.99
4.04


21a

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8.086
8.069
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6.782
3.464
3.360
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2.506
2.501
0.000
Br
CN
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9
8
7
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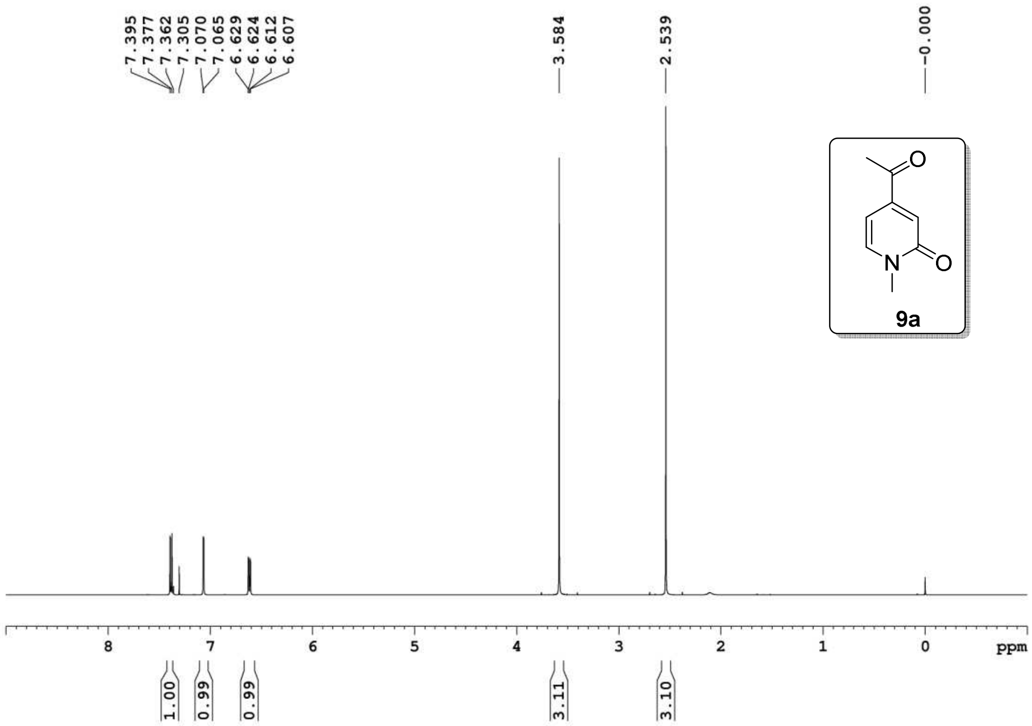
3.18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6.624
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-0.000
O
N
O
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0.99
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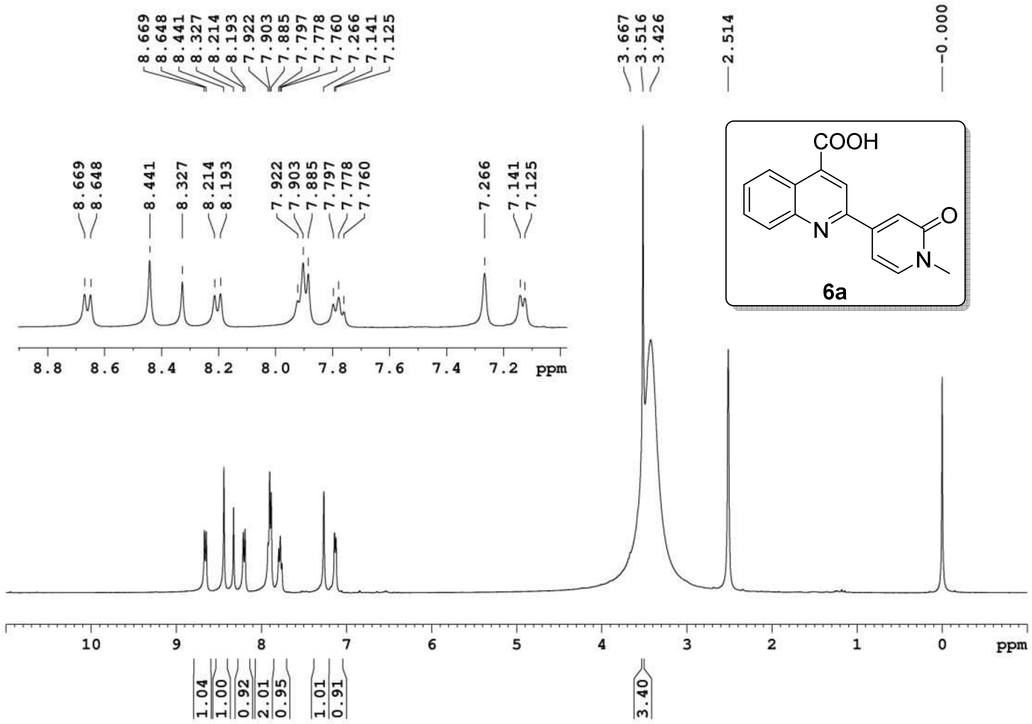
3.10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7.797
7.778
7.760
7.266
7.141
7.125
3.667
3.516
3.426
2.514
-0.000
COOH
N
O
N
6a
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
ppm
10
9
8
7
6
5
4
3
2
1
0
ppm
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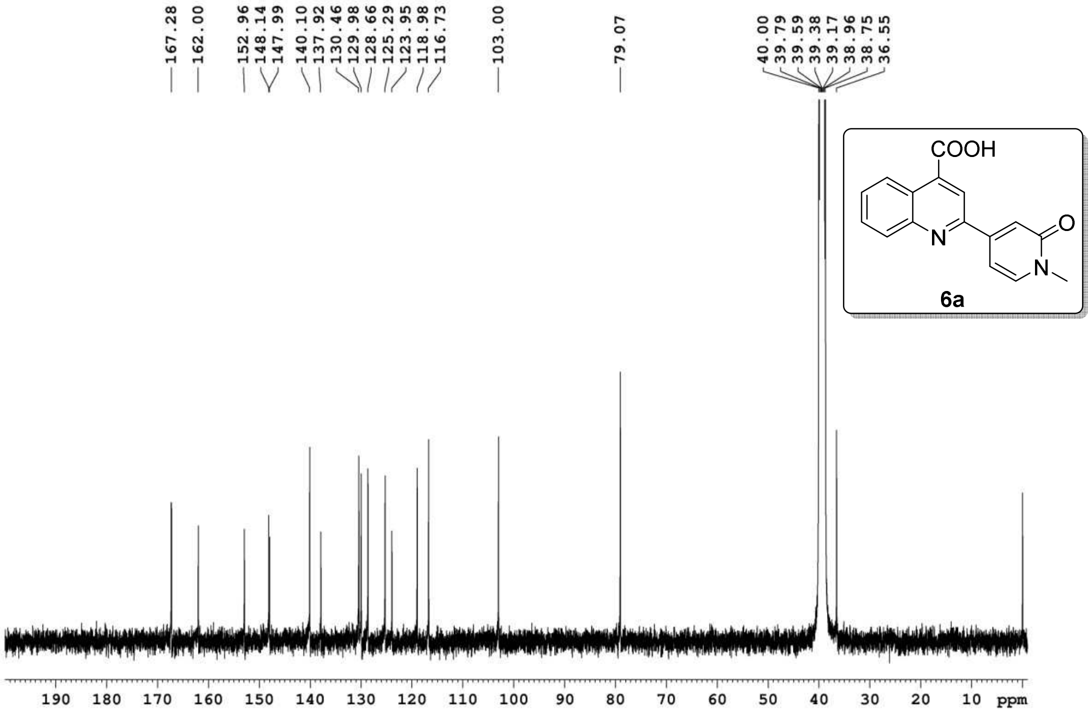
1.00
0.92
2.01
0.95
1.01
0.91
3.40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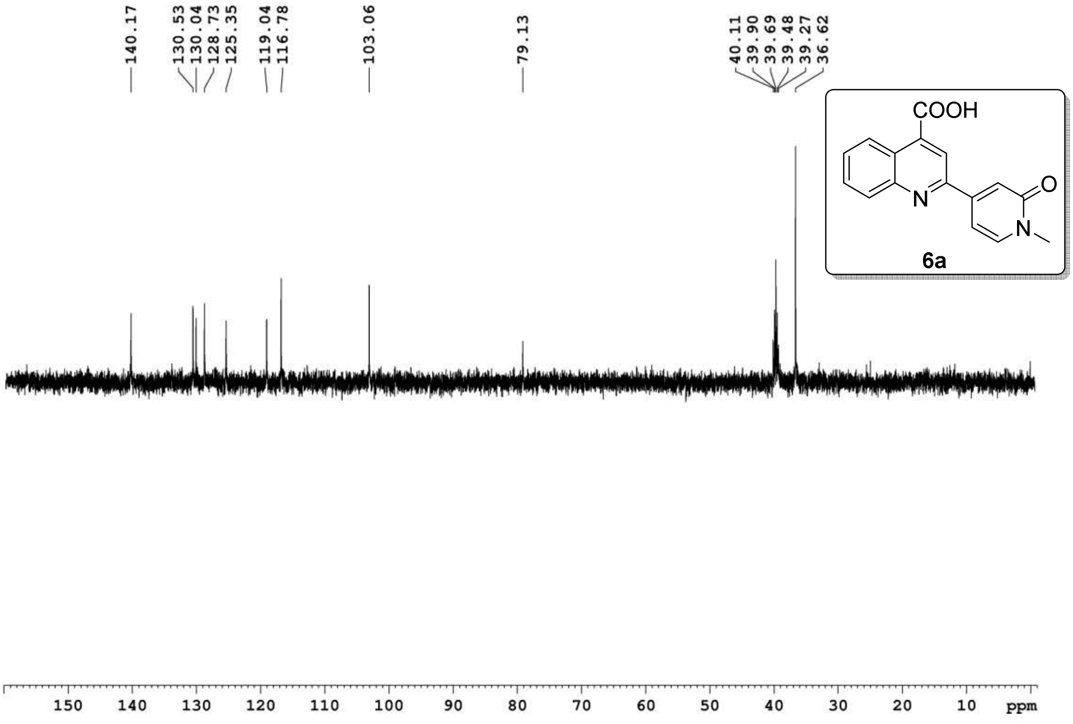
140.10
137.92
130.46
129.98
128.66
125.29
123.95
118.98
116.73
103.00
79.07
40.00
39.79
39.59
39.38
39.17
38.96
38.75
36.55
COOH
N
O
N
6a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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103.06
79.13
40.11
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39.27
36.62
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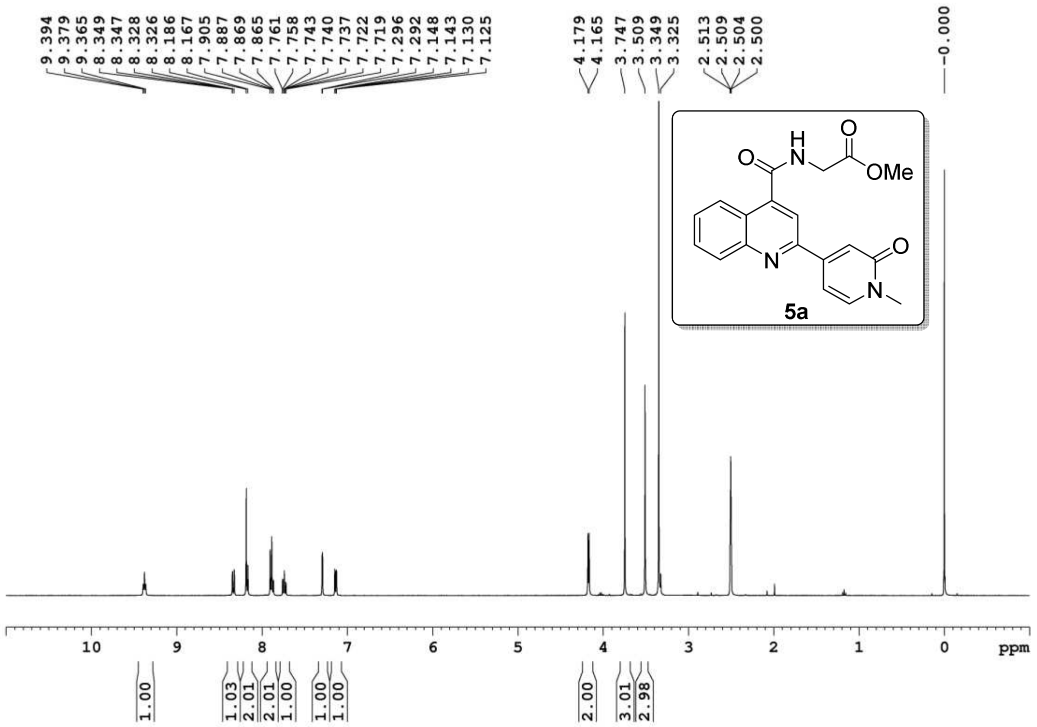
N
6a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.326
8.186
8.167
7.905
7.887
7.869
7.865
7.761
7.758
7.743
7.740
7.737
7.722
7.719
7.296
7.292
7.148
7.143
7.130
7.125
4.179
4.165
3.747
3.509
3.349
3.325
2.513
2.509
2.504
2.500
-0.000
O
H
N
O
OMe
N
O
N
5a
10
9
8
7
6
5
4
3
2
1
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ppm
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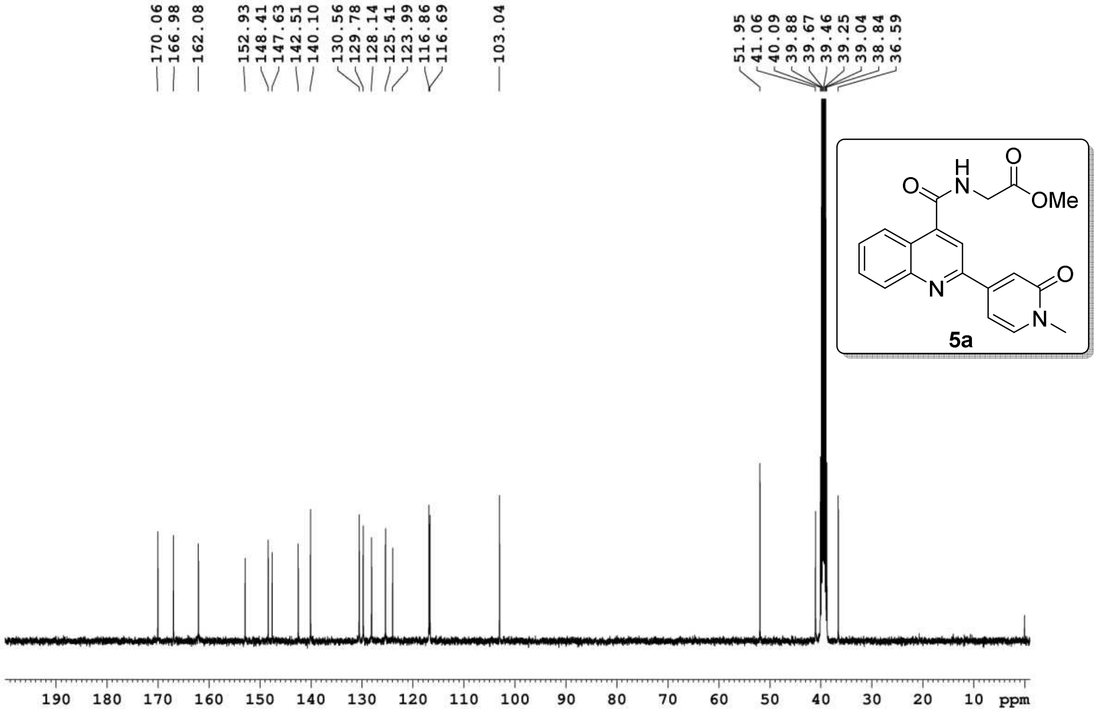
1.03
2.01
2.01
1.00
1.00
1.00
2.00
3.01
2.98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142.51
140.10
130.56
129.78
128.14
125.41
123.99
116.86
116.69
103.04
51.95
41.06
40.09
39.88
39.67
39.46
39.25
39.04
38.84
36.59
O
H
N
O
OMe
N
O
N
5a
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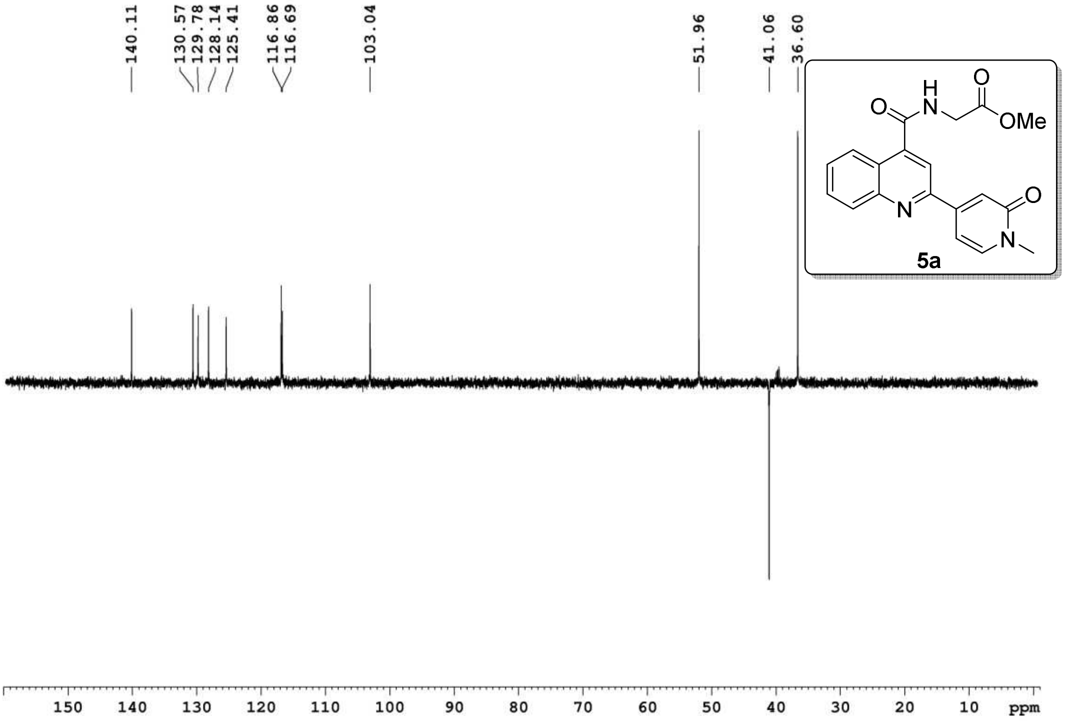
50
40
30
20
10
ppm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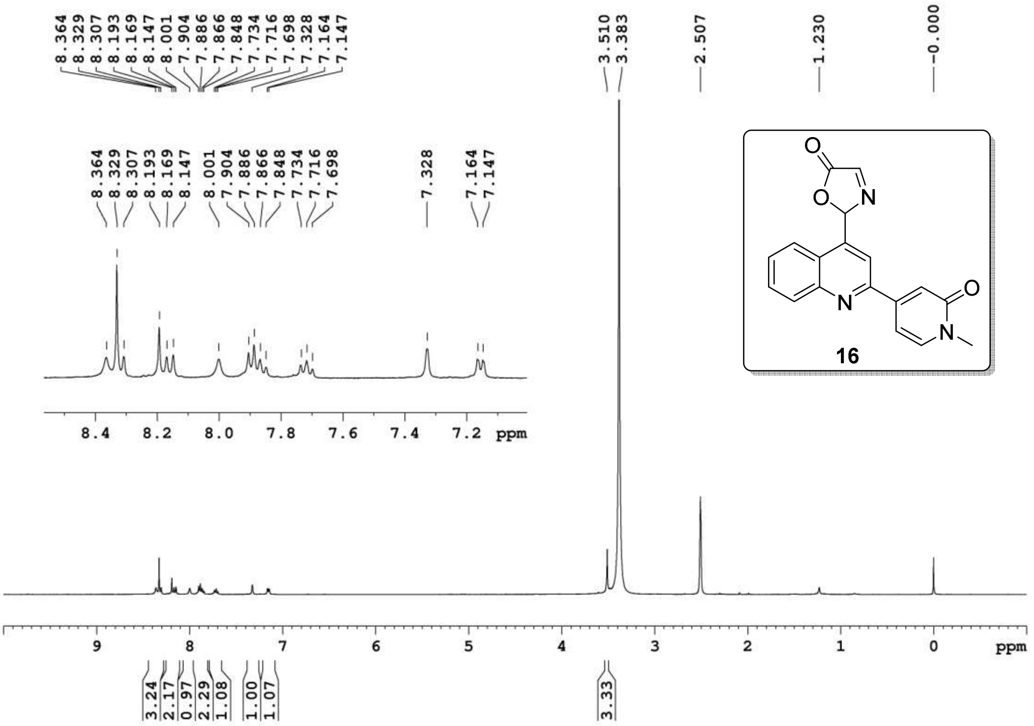
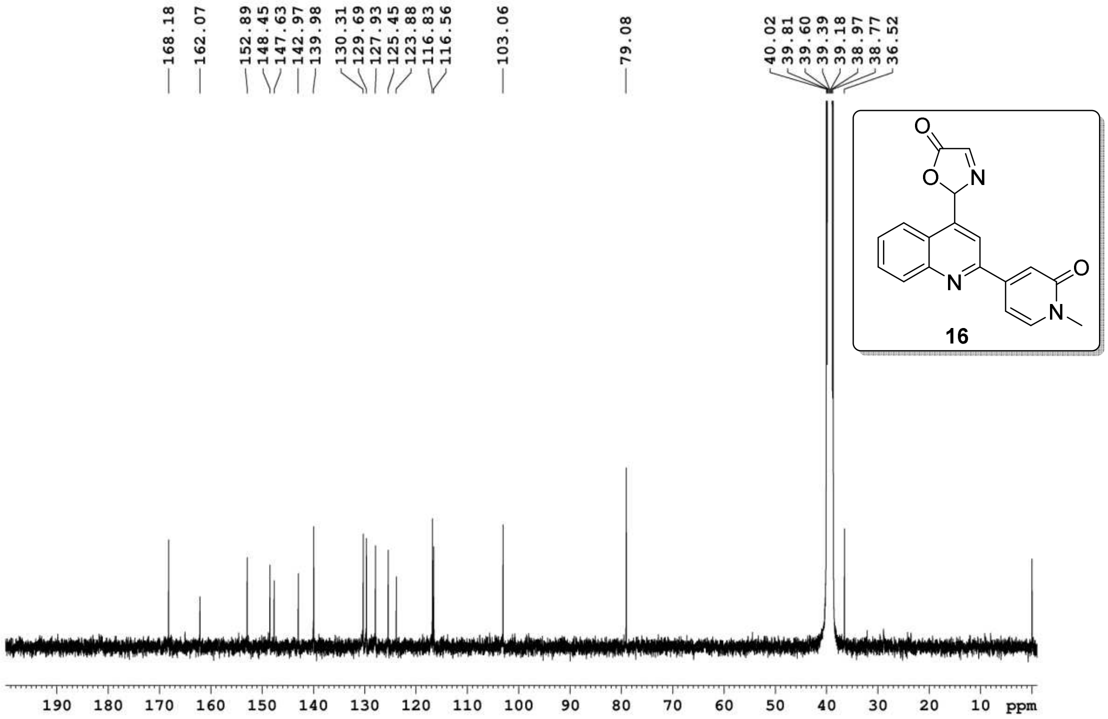
130.57
129.78
128.14
125.41
116.86
116.69
103.04
51.96
41.06
36.60
O
H
N
O
OMe
N
O
N
5a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.364
8.329
8.307
8.193
8.169
8.147
8.001
7.904
7.886
7.866
7.848
7.734
7.716
7.698
7.328
7.164
7.147
3.510
3.383
2.507
1.230
-0.000
8.4 8.2 8.0 7.8 7.6 7.4 7.2 ppm
O
O
N
N
O
N
16
9 8 7 6 5 4 3 2 1 0 ppm
3.24
2.17
0.97
2.29
1.08
1.00
1.07
3.33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162.07
152.89
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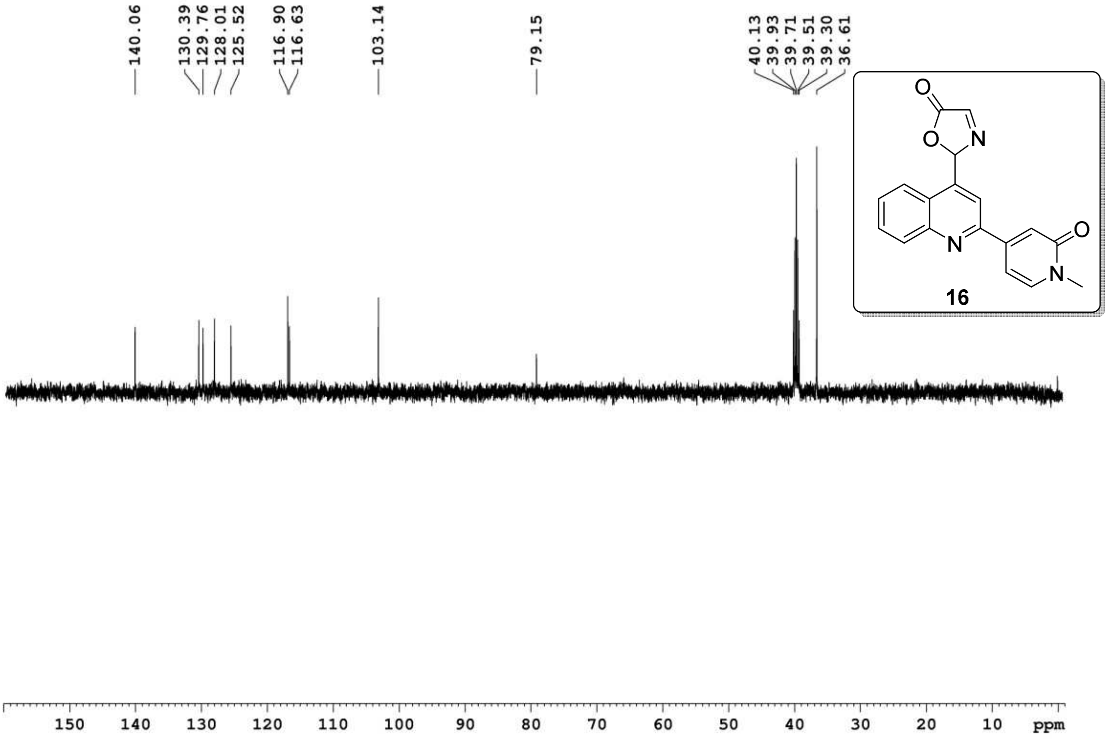
147.63
142.97
139.98
130.31
129.69
127.93
125.45
123.88
116.83
116.56
103.06
79.08
40.02
39.81
39.60
39.39
39.18
38.97
38.77
36.52
O
O
N
N
O
N
16
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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130.39
129.76
128.01
125.52
116.90
116.63
103.14
79.15
40.13
39.93
39.71
39.51
39.30
36.61
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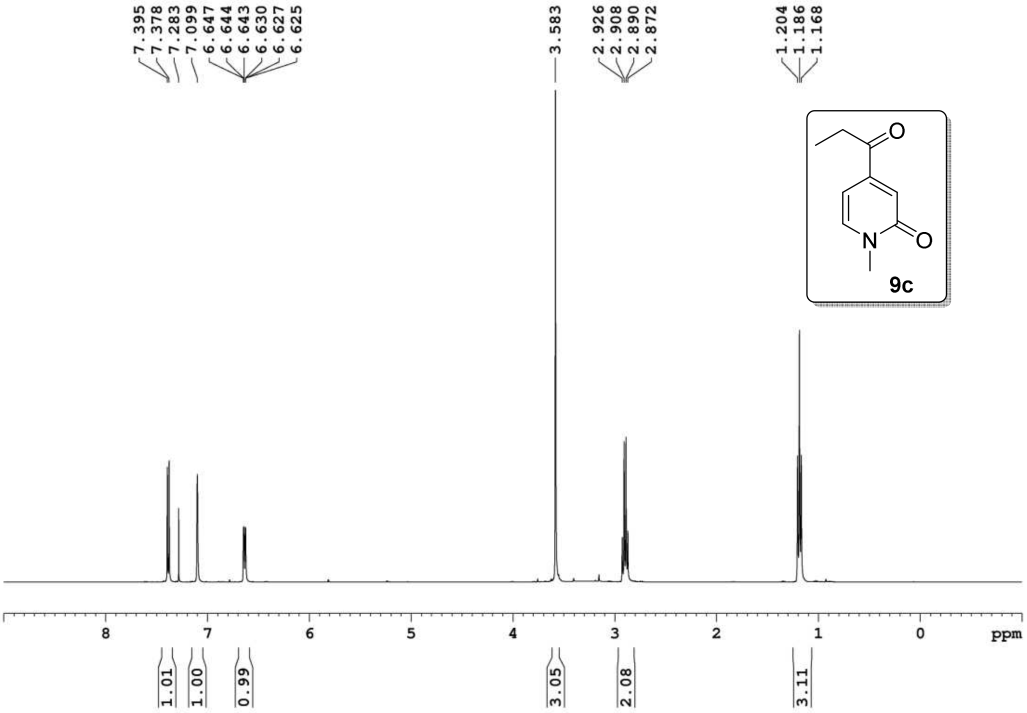
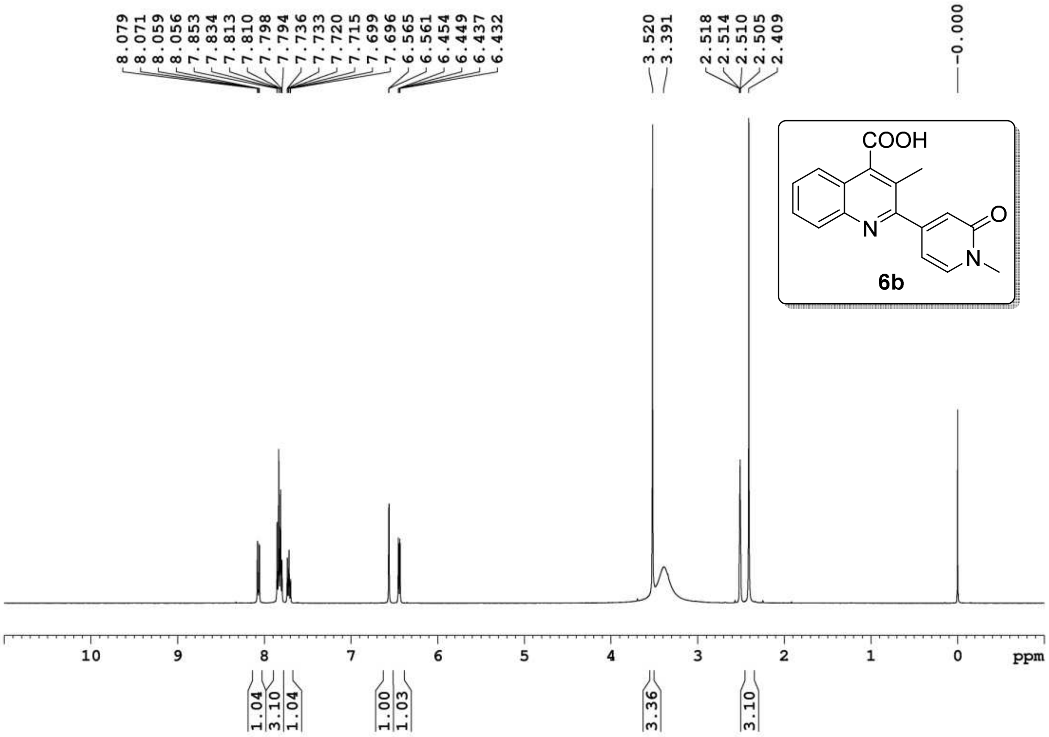
O
N
N
O
N
16
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.395
7.378
7.283
7.099
6.647
6.644
6.643
6.630
6.627
6.625
3.583
2.926
2.908
2.890
2.872
1.204
1.186
1.168
O
N
O
9c
8
7
6
5
4
3
2
1
0
ppm
1.01
1.00
0.99
3.05
2.08
3.11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8.056
7.853
7.834
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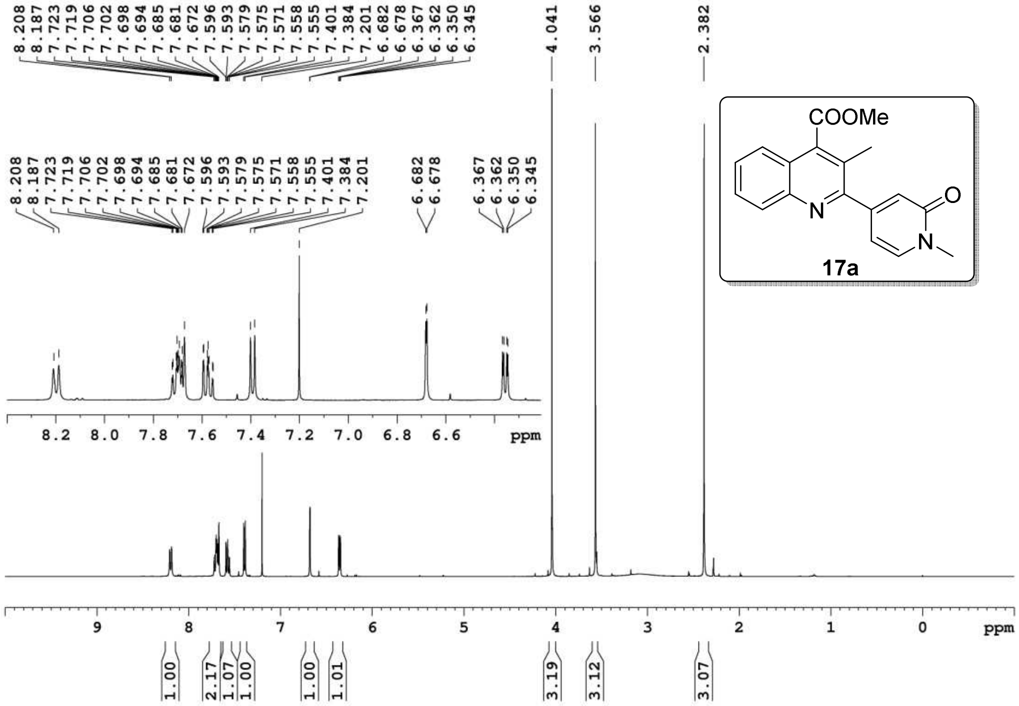
7.810
7.798
7.794
7.736
7.733
7.720
7.715
7.699
7.696
6.565
6.561
6.454
6.449
6.437
6.432
3.520
3.391
2.518
2.514
2.510
2.505
2.409
-0.000
COOH
N
O
N
6b
10
9
8
7
6
5
4
3
2
1
0
ppm
1.04
3.10
1.04
1.00
1.03
3.36
3.10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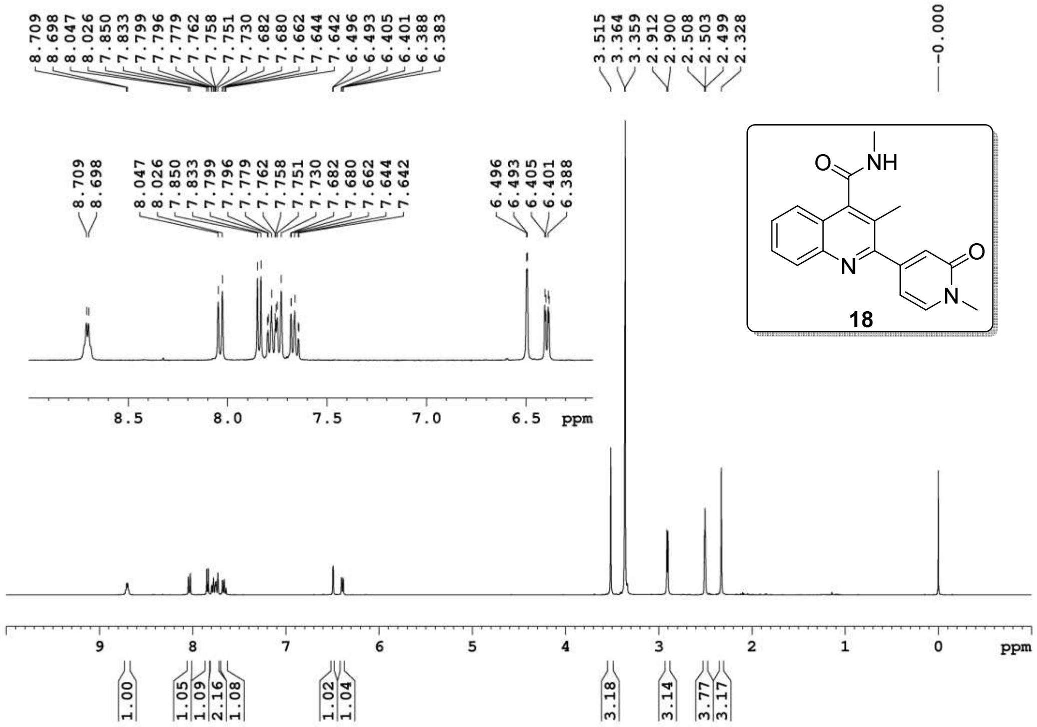
4.041
3.566
2.382
COOMe
N
O
N
17a
8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 ppm
9 8 7 6 5 4 3 2 1 0 ppm
1.00 2.17 1.07 1.00 1.00 1.01 3.19 3.12 3.07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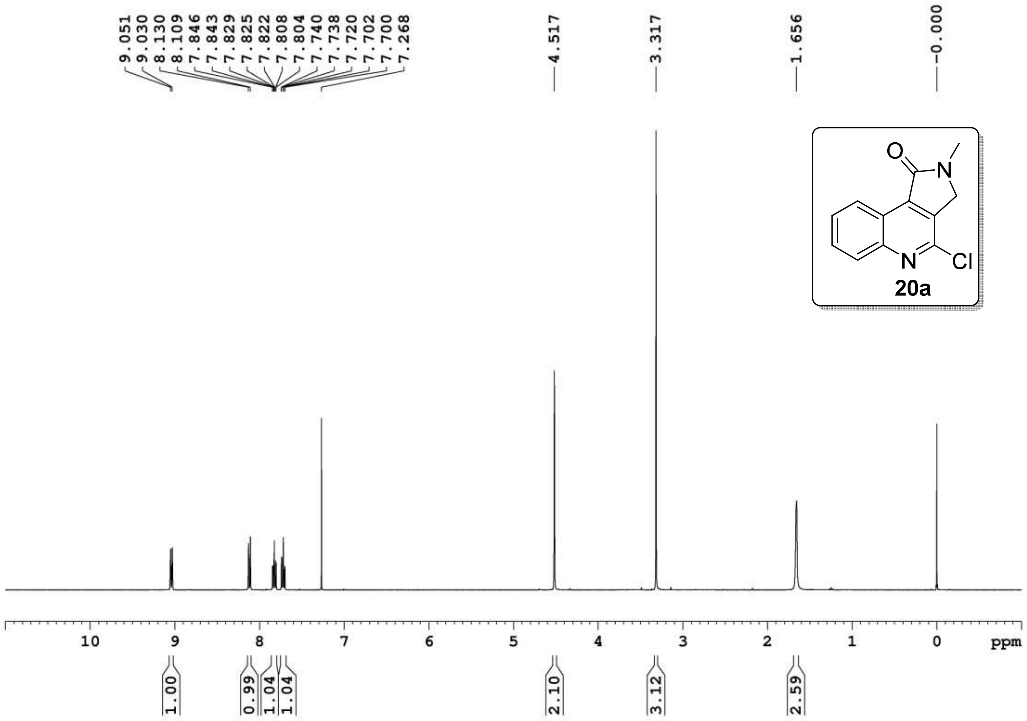
3.515 3.364 3.359 2.912 2.900 2.508 2.503 2.499 2.328
-0.000
O
NH
N
O
N
18
8.5 8.0 7.5 7.0 6.5 ppm
9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.05 1.09 2.16 1.08 1.02 1.04 3.18 3.14 3.77 3.17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9.030
8.130
8.109
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7.843
7.829
7.825
7.822
7.808
7.804
7.740
7.738
7.720
7.702
7.700
7.268
4.517
3.317
1.656
-0.000
O
N
N
Cl
10
9
8
7
6
5
4
3
2
1
0
ppm
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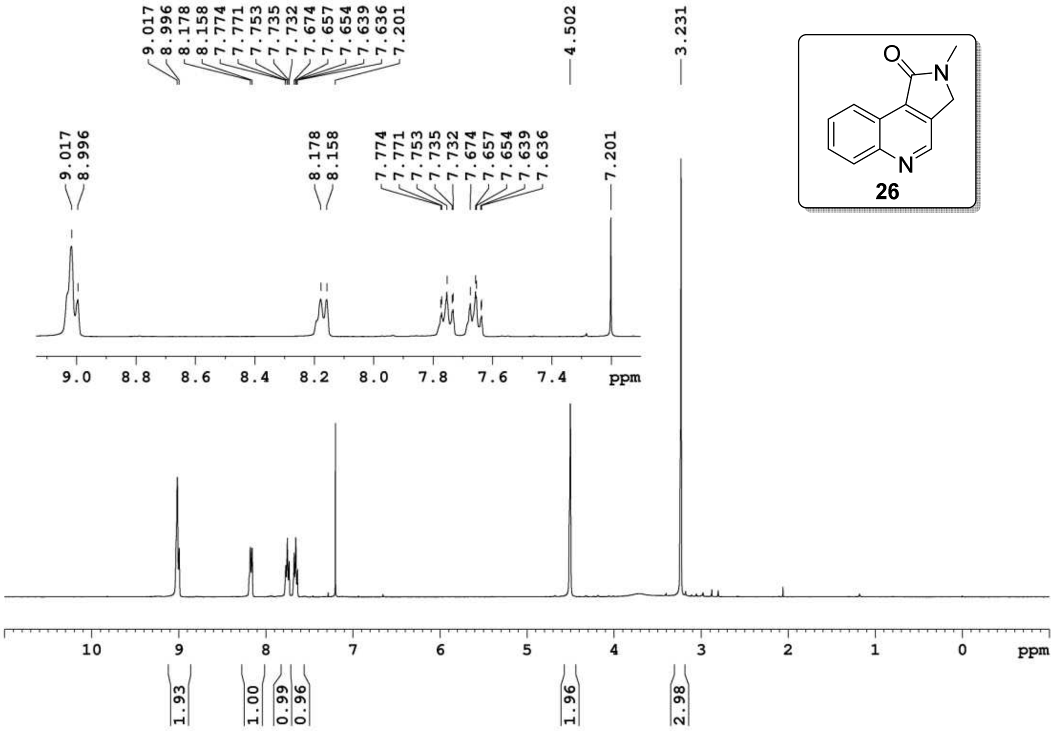
0.99
1.04
1.04
2.10
3.12
2.59

20a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7.771
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7.735
7.732
7.674
7.657
7.654
7.639
7.636
7.201
4.502
3.231
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
ppm
O
N
N
10
9
8
7
6
5
4
3
2
1
0
ppm
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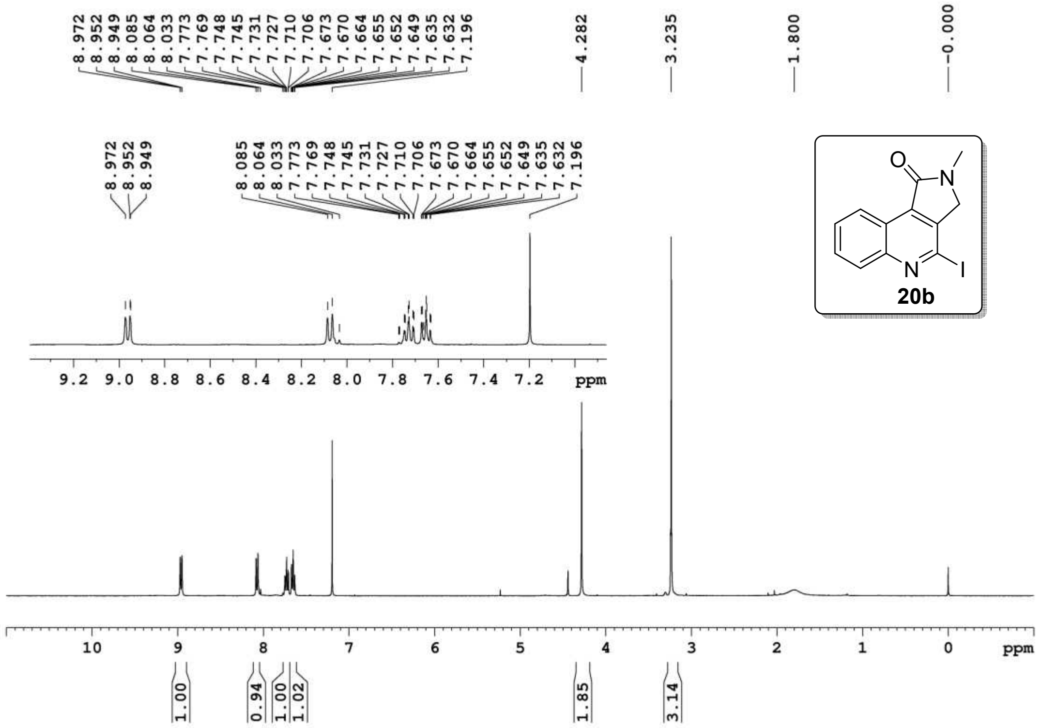
1.00
0.99
0.96
1.96
2.98

26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8.949
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8.033
7.773
7.769
7.748
7.745
7.731
7.727
7.710
7.706
7.673
7.670
7.664
7.655
7.652
7.649
7.635
7.632
7.196
4.282
3.235
1.800
-0.000
O
N
N
I
20b
9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
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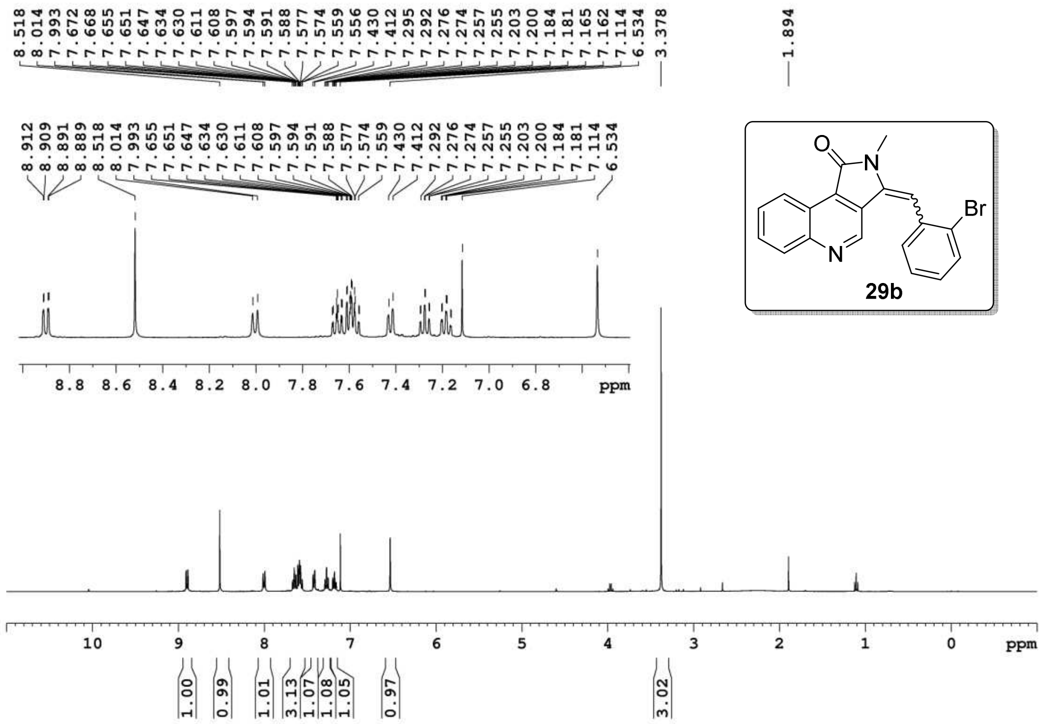
0.94
1.00
1.02
1.85
3.14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7.993
7.672
7.668
7.655
7.651
7.647
7.634
7.630
7.611
7.608
7.597
7.594
7.591
7.588
7.577
7.574
7.559
7.556
7.430
7.412
7.295
7.292
7.276
7.274
7.257
7.255
7.203
7.200
7.184
7.181
7.165
7.162
7.114
6.534
3.378
1.894
8.912
8.909
8.891
8.889
O
N
Br
N
29b
8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 ppm
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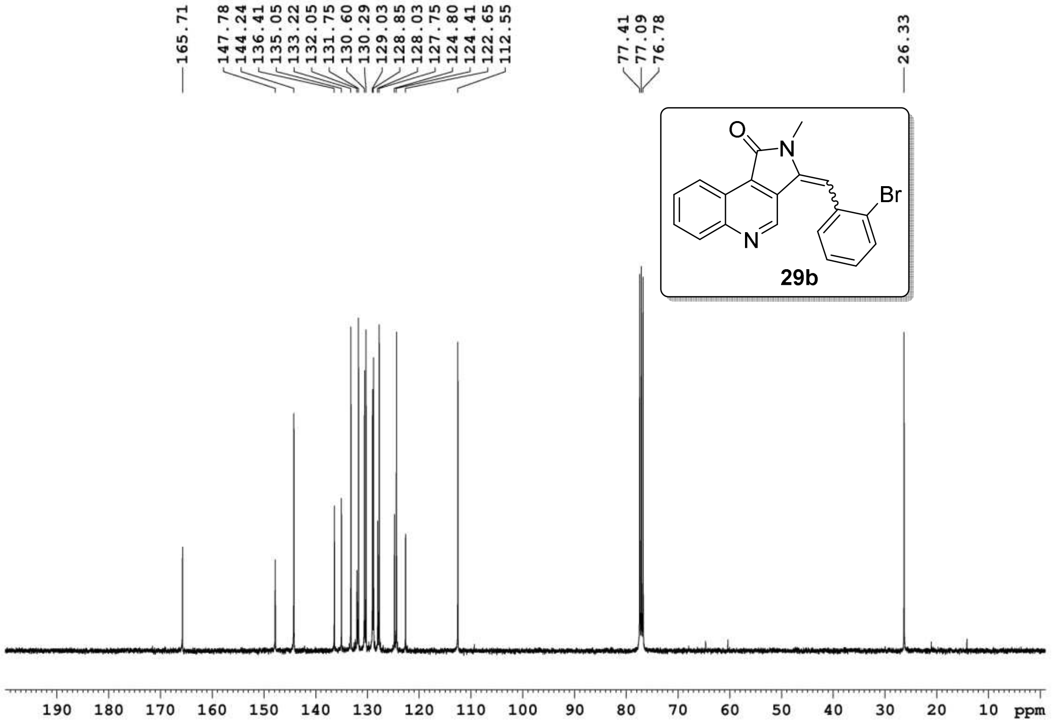
1.01
3.13
1.07
1.08
1.05
0.97
3.02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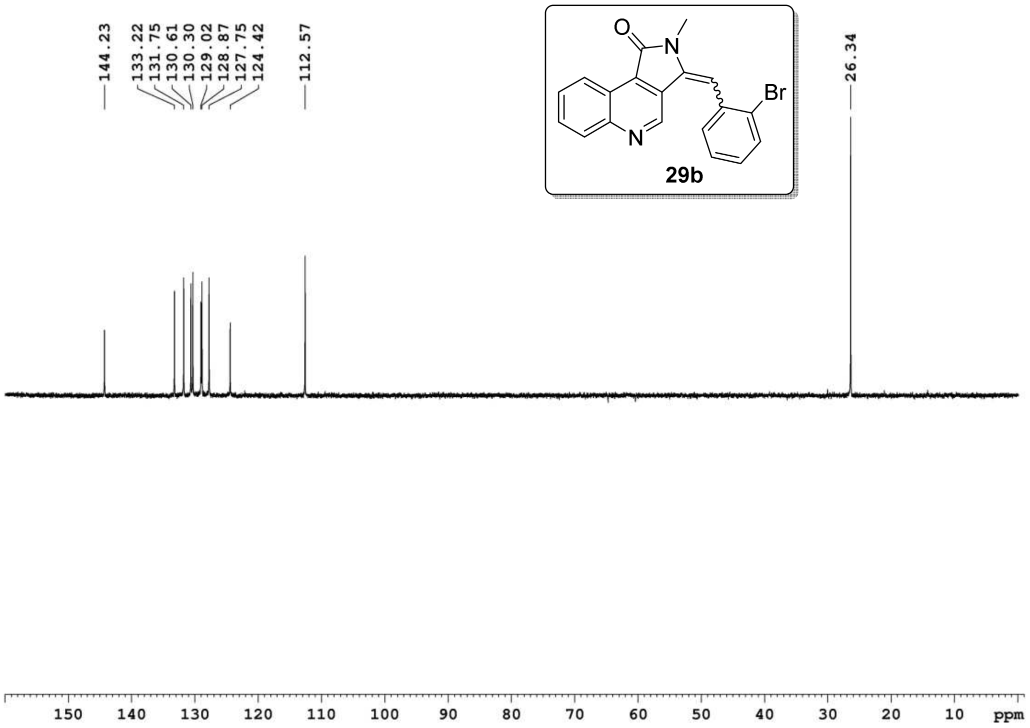
147.78
144.24
136.41
135.05
133.22
132.05
131.75
130.60
130.29
129.03
128.85
128.03
127.75
124.80
124.41
122.65
112.55
77.41
77.09
76.78
26.33
O
N
N
Br
29b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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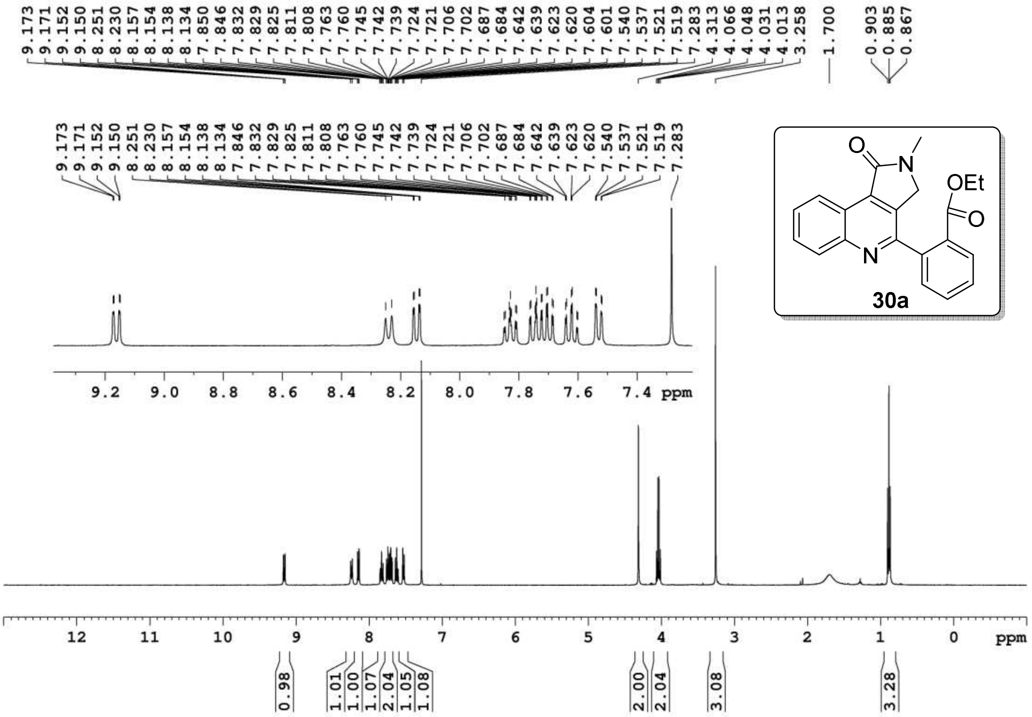
131.75
130.61
130.30
129.02
128.87
127.75
124.42
112.57
26.34
O
N
N
Br
29b
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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8.230
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8.154
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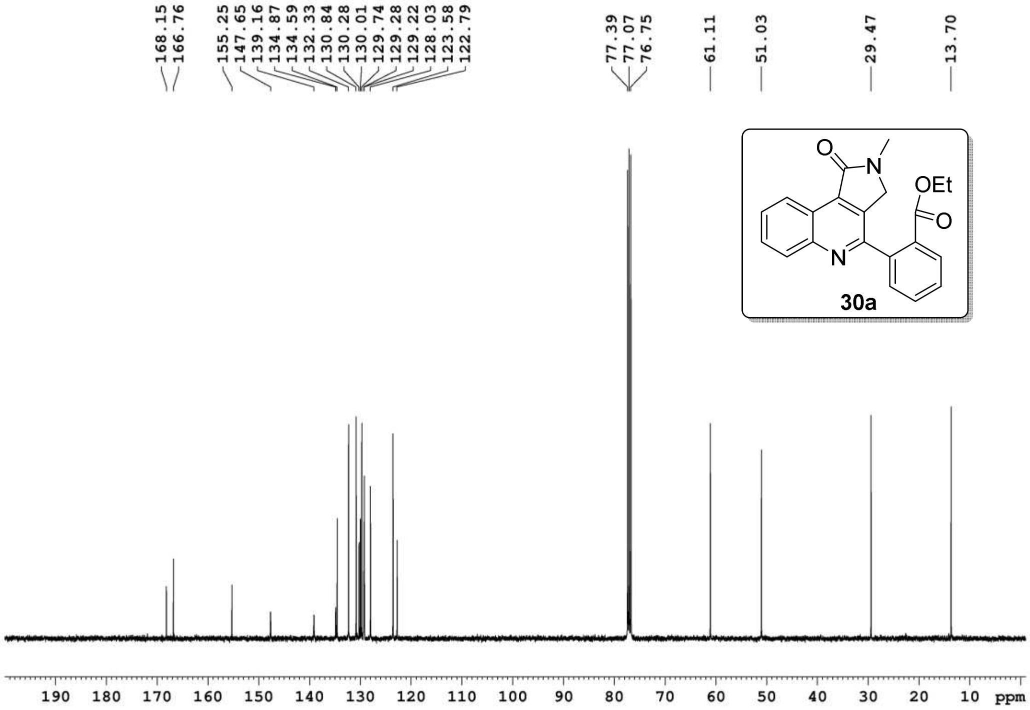
8.134
7.850
7.846
7.832
7.829
7.825
7.811
7.808
7.763
7.760
7.745
7.742
7.739
7.724
7.721
7.706
7.702
7.687
7.684
7.642
7.639
7.623
7.620
7.604
7.601
7.540
7.537
7.521
7.519
7.283
4.313
4.066
4.048
4.031
4.013
3.258
1.700
0.903
0.885
0.867
9.2 9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 ppm
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.98
1.01
1.00
1.07
2.04
1.05
1.08
2.00
2.04
3.08
3.28
O
N
OEt
O
N
30a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147.65
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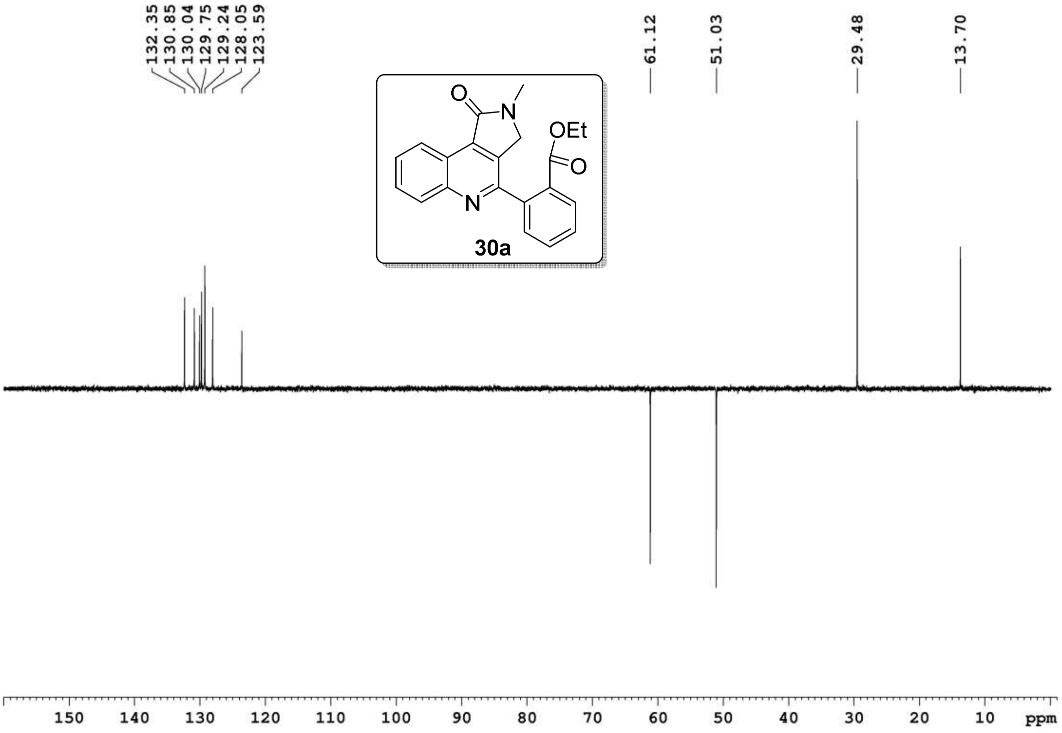
134.87
134.59
132.33
130.84
130.28
130.01
129.74
129.28
129.22
128.03
123.58
122.79
77.39
77.07
76.75
61.11
51.03
29.47
13.70
O
N
OEt
O
N
30a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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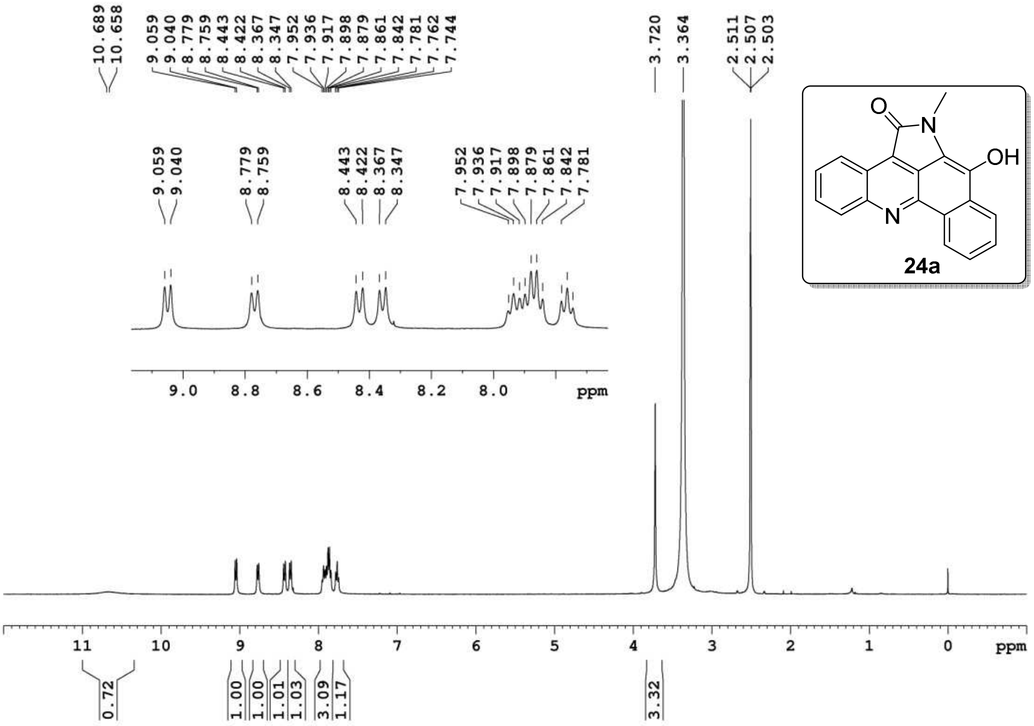
130.85
130.04
129.75
129.24
128.05
123.59
61.12
51.03
29.48
13.70
O
N
OEt
O
N
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

30a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8.759
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8.422
8.367
8.347
7.952
7.936
7.917
7.898
7.879
7.861
7.842
7.781
7.762
7.744
3.720
3.364
2.511
2.507
2.503
9.059
9.040
8.779
8.759
8.443
8.422
8.367
8.347
7.952
7.936
7.917
7.898
7.879
7.861
7.842
7.781
9.0
8.8
8.6
8.4
8.2
8.0
ppm
O
N
OH
N
11
10
9
8
7
6
5
4
3
2
1
0
ppm
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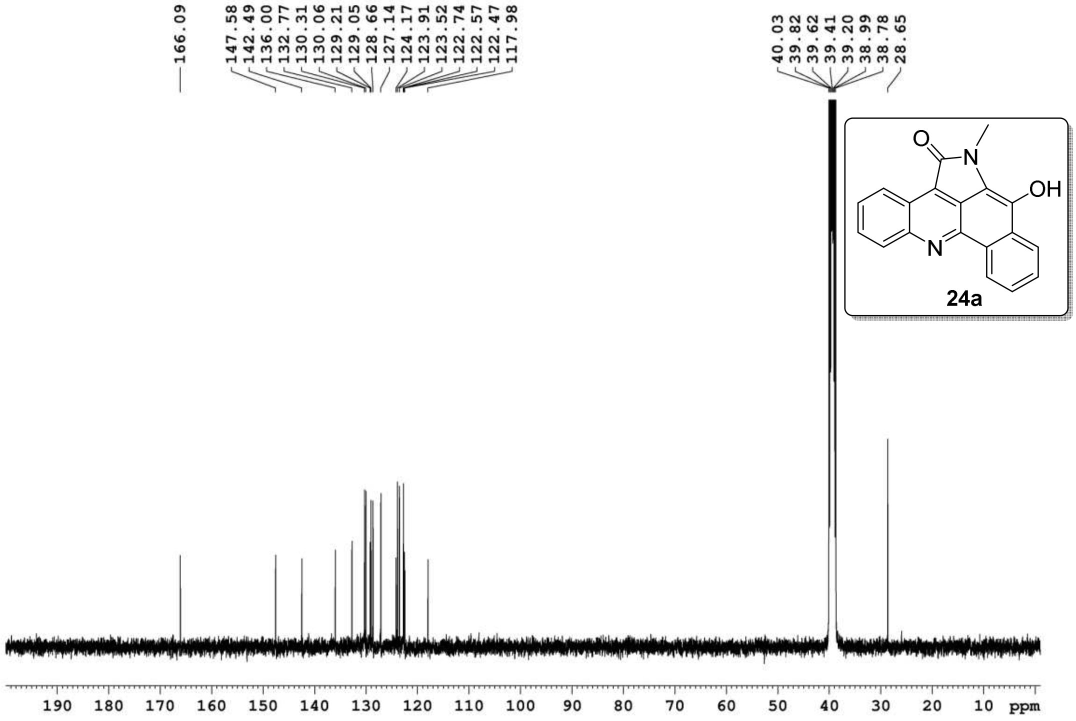
1.01
1.03
3.09
1.17
3.32

24a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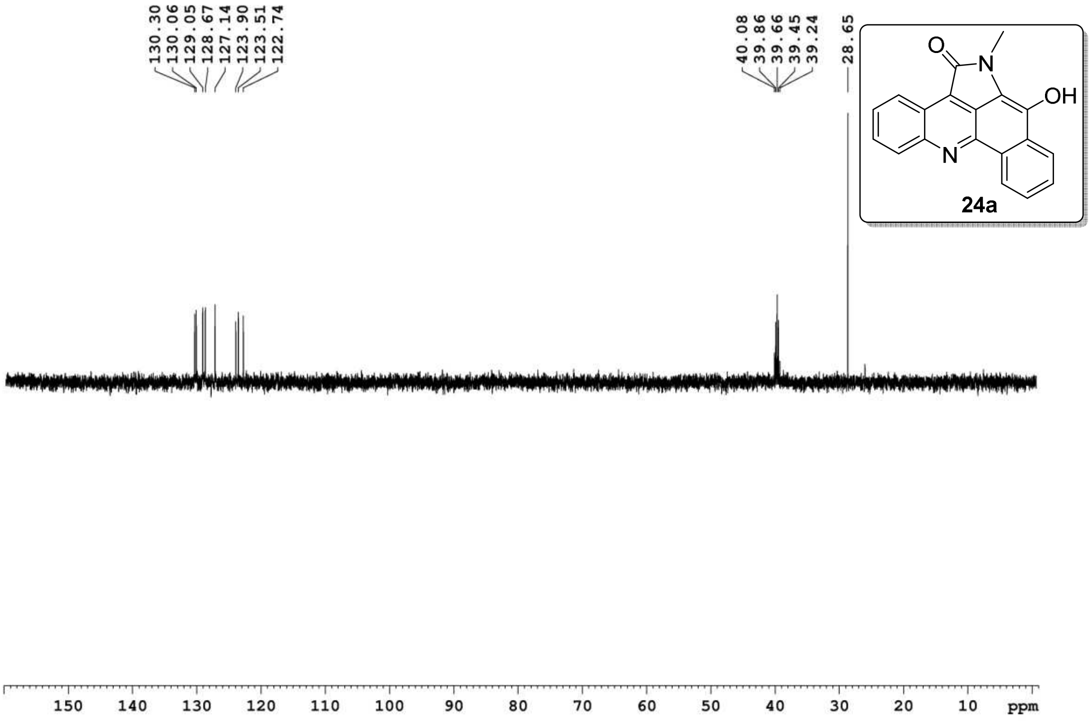
128.66
127.14
124.17
123.91
123.52
122.74
122.57
122.47
117.98
40.03
39.82
39.62
39.41
39.20
38.99
38.78
28.65
O
N
OH
N
24a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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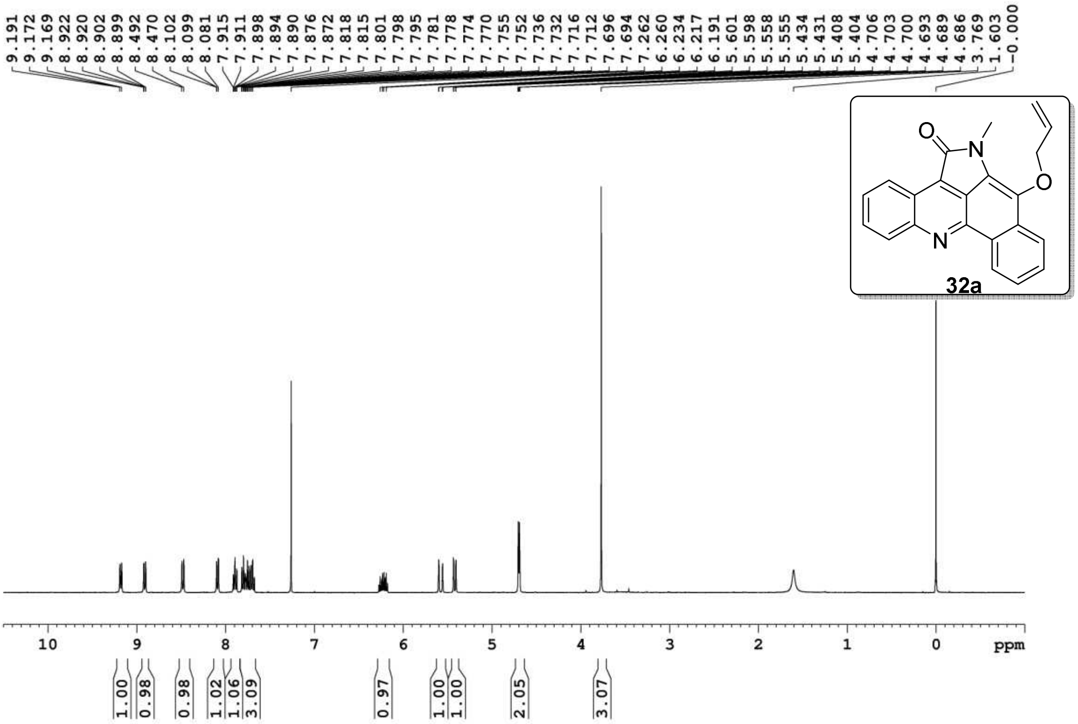
130.06
129.05
128.67
127.14
123.90
123.51
122.74
40.08
39.86
39.66
39.45
39.24
28.65
O
N
OH
N
24a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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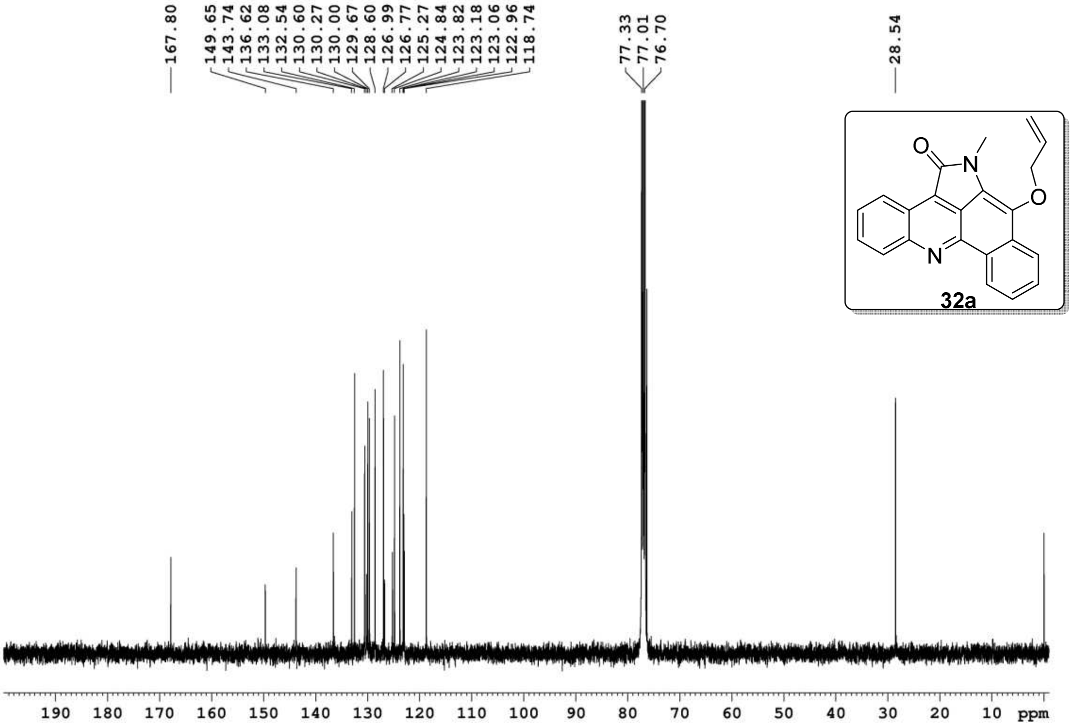
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76.70
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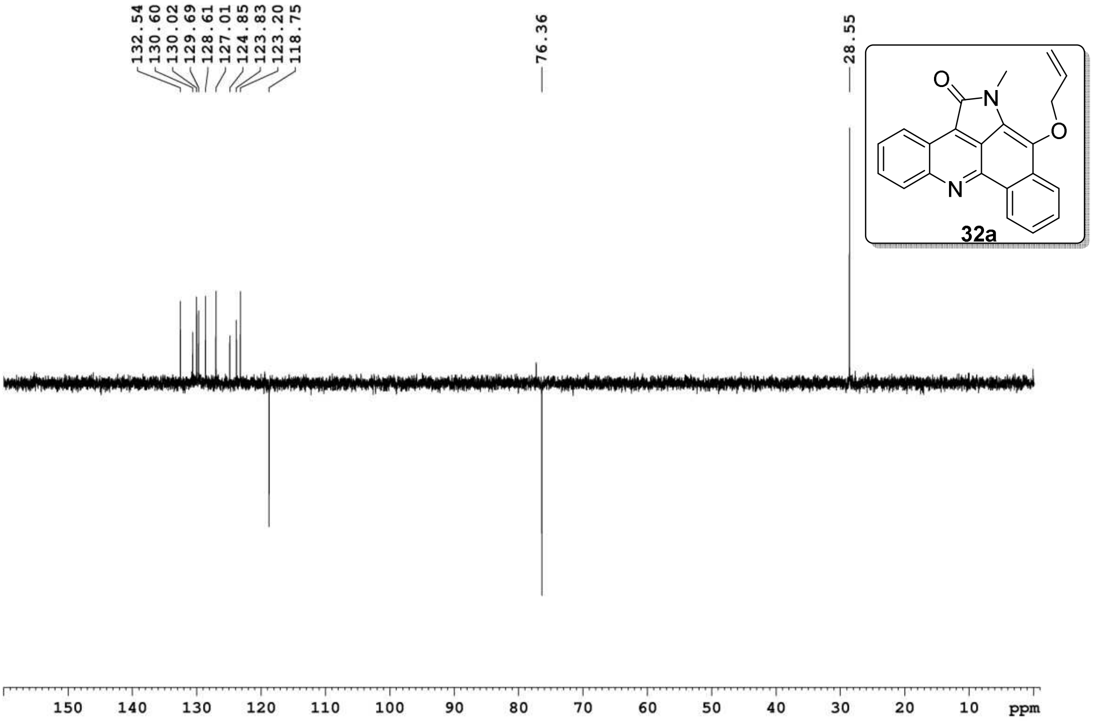
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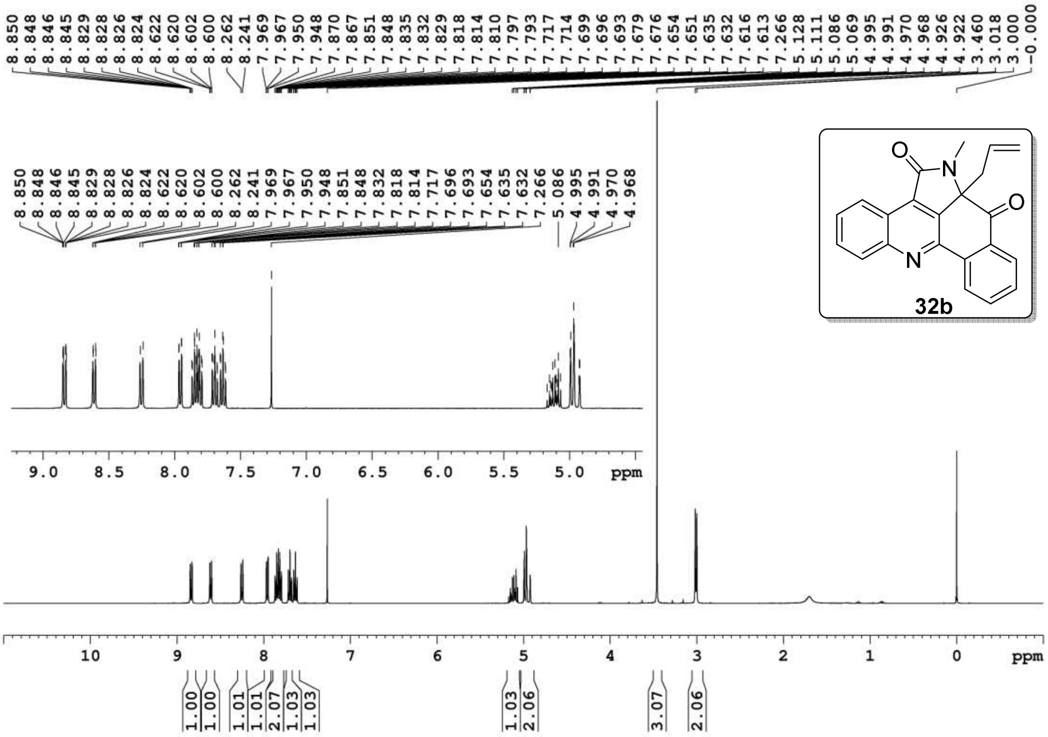
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7.829
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7.797
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7.717
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7.699
7.696
7.693
7.679
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7.654
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7.635
7.632
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7.613
7.266
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5.086
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4.922
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8.0
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6.5
6.0
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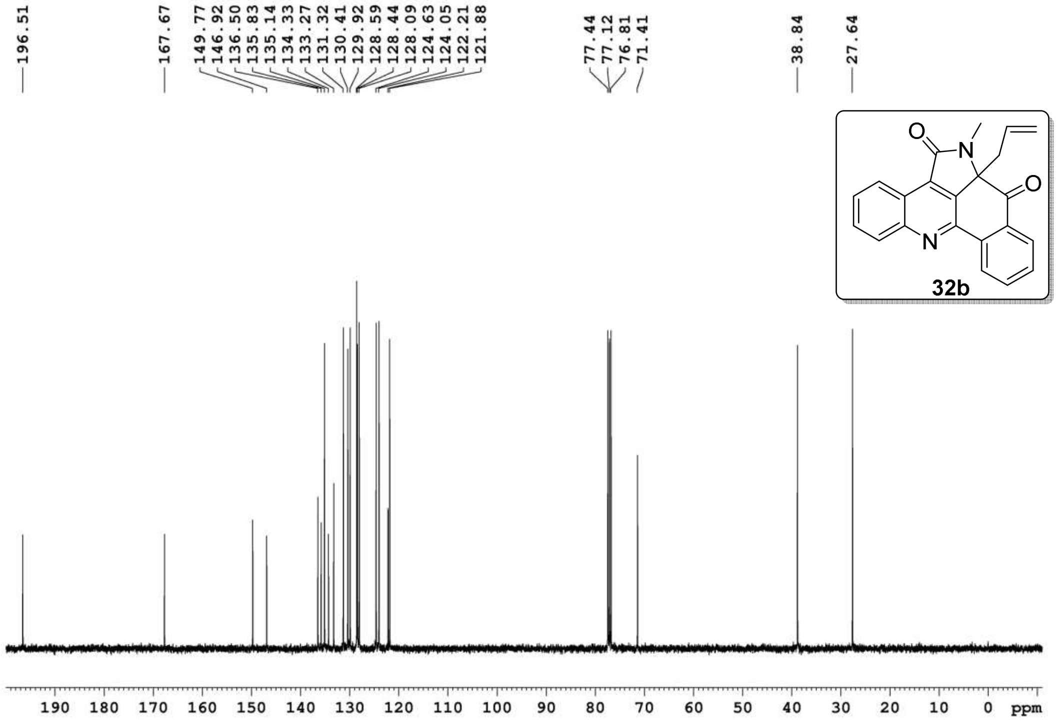
2.06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128.09
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124.05
122.21
121.88
77.44
77.12
76.81
71.41
38.84
27.64
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O
N
32b
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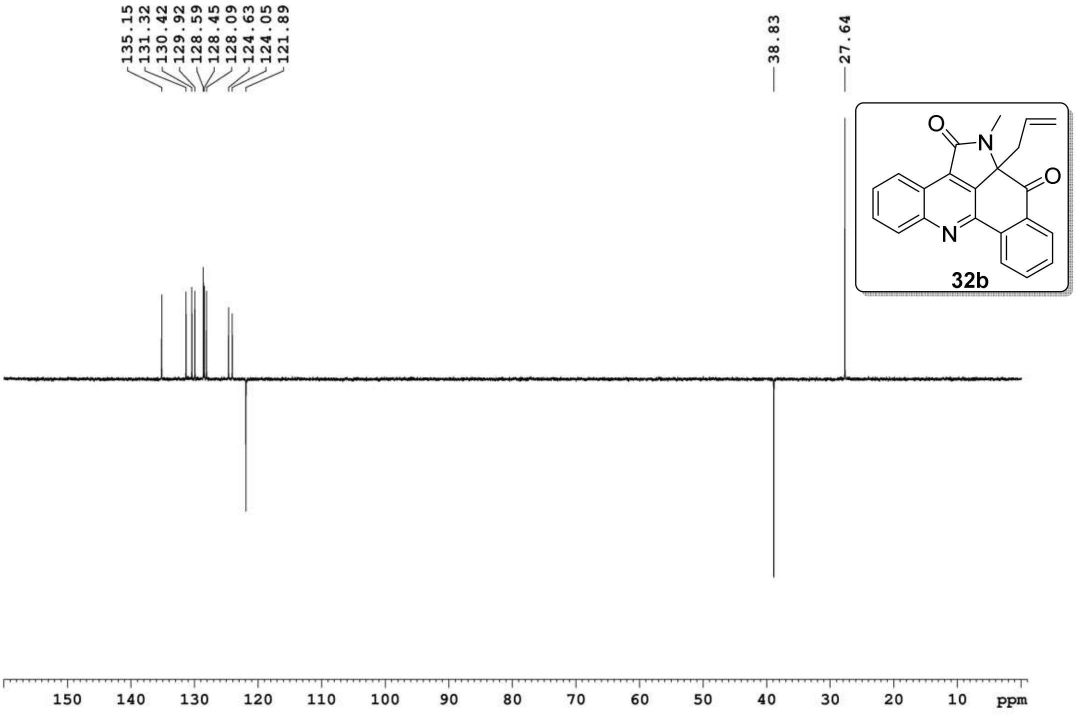
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ppm