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The Synthesis of Pyrido-fused 8-Methoxy Carbazoles by Using a Light-Assisted, Base-Mediated Cyclization Reaction

Bongi F. Magagula

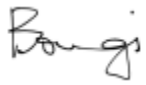
Supervised by Dr S. Ntsimango and Prof C. B. de Koning.

A dissertation submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science.

DECLARATION

I declare that the work presented in this dissertation was carried out by myself under the supervision of Dr S. Ntsimango and Professor C.B. de Koning. It is being submitted for the degree of Master of Science at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Bongi Florence Magagula



16 August 2023

ABSTRACT

Nitrogen-containing compounds such as indoles and carbazoles are significant classes of the *N*-heterocycles that show great promise as anti-cancer compounds. Indoles such as 2,3-diarylindole, 3-pyranyl indole and carbazoles such as 9-methoxyellipticine are compounds which possess anticancer or antitumor properties. Due to the favourable biological activities of *N*-heterocyclic compounds, medicinal and synthetic chemists have developed numerous methodologies for their synthesis. In this research project, the broad aim was to synthesize pyrido-fused carbazoles from 5-methoxyindole using methodologies that have been previously used in our laboratories and by other chemists while changing the position of the nitrogen atom on the pyrido-fused carbazoles.

The first step in the synthesis of these carbazoles was the treatment of 5-methoxyindole with di-*tert*-butyl dicarbonate in the presence of 4-dimethylaminopyridine (DMAP) which gave the desired protected indole, *tert*-butyl 5-methoxy-1*H*-indole-1-carboxylate in excellent yields (90-99%). Exposure of the *tert*-butyl 5-methoxy-1*H*-indole-1-carboxylate to lithium 2,2,6,6-tetramethypiperidide followed by quenching with triisopropyl borate and hydrochloric acid gave (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid. Using this and various halogen substituted pyridines, for example 3-bromo-4-methylpyridine in the Suzuki-Miyaura coupling reaction gave *tert*-butyl 5-methoxy-2-(4methylpyridin-3-yl)-1*H*-indole-1-carboxylate (83% yield). This was further reacted with paraformaldehyde and iron (III) chloride or phosphorus oxychloride and DMF. After the removal of *tert*-butoxycarbonyl protecting group utilizing various methods this produced 5-methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde (48% yield). 5-Methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde possesses all the carbons of the final compounds and is suitably functionalized to partake in the key photo-induced and base-mediated cyclization reaction. Previous studies pointed to the necessity of an alkyl protecting group on the indole-*N* atom. As a result, the indole nitrogen atom was then protected again with a methyl or a benzyl group; where the *N*-benzyl could be removed at a later stage. For example, reaction of 5-methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde dissolved in THF, potassium hexamethyldisilazide and benzyl bromide furnished 1-benzyl-5-methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde (83% yield).

The key step in this synthesis was the light-assisted, base-mediated cyclization reaction which has been reported by de Koning and co-workers, where a solution of 1-benzyl-5-methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde dissolved in dry DMF and potassium *tert*-butoxide was heated and irradiated with medium mercury lamp yielding the desired pyrido fused carbazole, 11-benzyl-8-methoxy-11*H*-pyrido[3,4-*a*]carbazole in a good yield of 70%. Following the outlined synthetic procedure depicted above, we were able to synthesize 5 analogues of 11-benzyl-8-methoxy-1*H*-pyrido[3,4-*a*]carbazole.

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LIST OF ABBREVIATIONS

Bn	Benzyl (Ph-CH_2-)
n-BuLi	*n*-Butyllithium
Boc	*tert*-Butoxycarbonyl
DMAP	4-*N*,*N*-Dimethylamino pyridine
DMA	Dimethyl acetamide
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EtOH	Ethanol
EtOAc	Ethyl acetate
FDA	Food and Drug Administration
H	hour(s)
hv	Photon of light
HRMS	High-resolution mass spectrometry
KHMDS	Potassium bis(trimethylsilyl)amide/ Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
LED	Light-emitting diode
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
MeI	Methyl iodide

Min	minute(s)
NMR	Nuclear magnetic resonance
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
RNA	Ribonucleic acid
r.t	room temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

Chapter 1

1. Introduction

1.1 Cancer and anticancer treatments

Cancer is a dynamic disease in which the genome undergoes rapid changes[1]. The change of normal cells into cancer cells over time is caused by a series of genetic alterations, each offering a different type of growth advantage[2]. There are over 100 different types of cancer, with subtypes of tumors found in specific organs. The enormous number of cancer cell genotypes is thought to be the result of six key physiological changes in cells that collectively determine malignancy in growth signals[3]. Self-sufficiency in growth signals, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis are the six physiological changes or acquired capabilities. Each of these physiological alterations indicates that an anticancer defense mechanism built into cells and tissue have been successfully breached during tumor development[3]. While all cancer cells must develop the same six signature capacities or acquired capabilities, the mechanisms and timelines by which they do so will differ dramatically[3] leading to application of different anticancer treatment strategies.

Cancer is one of the leading causes of deaths throughout the world. In recent years, the number of cancer cases are on a steep rise and anti-cancer drug resistance is becoming more common[4,5]. As a result, it is critical to invest in research and development of new, effective cancer treatments[4]. There are several cancer treatments available which include surgery, radiation, chemotherapy, targeted therapy, immunotherapy, stem cell or bone marrow transplant and hormone therapy. In this review, our focus is on chemotherapy which is the use of chemicals to treat a disease[6,7], cancer in this case. Several chemotherapies are available, some common chemotherapies include treatment with the organic nitrogen containing compounds, temozolomide **1**, procarbazine **2**, carmustine **3**, lomustine **4** (Fig. 1) and vincristine. These compounds act by alkylating or causing cross-links in DNA which leads to inhibition of DNA synthesis, RNA production and protein

synthesis leading to cell death at different stages of the cell cycle. Many cancer tumors acquire chemoresistance, thus treatment with single anticancer drugs alone is insufficient for long term treatment[7]. The most difficult objective for researchers is to develop a new treatment that can treat cancer with minimal side effects[9] or improve the properties of the already existing anticancer drugs. Aside from the four mentioned drugs, several others are utilized in chemotherapy and the majority of these drugs have heterocycles as their core structures[9].

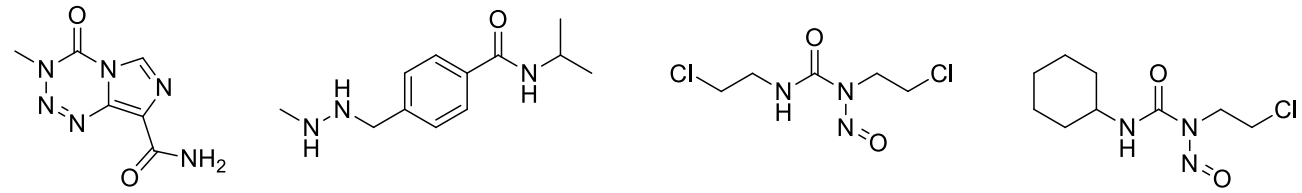


Fig 1. Common drugs used in chemotherapy.

1.2 Heterocyclic compounds

Heterocyclic compounds are cyclic organic compounds which contain at least one hetero atom such as oxygen, sulfur or nitrogen[10,11], to name a few. Unlike most of their carbocyclic counterparts, heterocyclic compounds can act as hydrogen-bond acceptors or donors, which can greatly alter their physical and chemical properties and most importantly their pharmacological properties[11].

These compounds mimic cyclic organic compounds that contain only carbon atoms in the rings, but the addition of heteroatoms gives these heterocyclic compounds physical and chemical properties that differ significantly from their carbon-containing ring analogs[11]. Simple heterocyclic compounds include compounds such as pyridine, pyrrole, furan and thiophene. Because of their biological and pharmacological properties, heterocyclic compounds are regarded as one of the most important classes of organic compounds[10]. There are a great number of pharmacologically active heterocyclic compounds which are used clinically such as vincristine, morphine, chloroquine, sulphadiazine, *etc*[12]. The most common heterocycles are six-membered rings and

five-membered rings[13] which are more stable than three, four, seven or larger rings. These ring systems are found in major biological molecule skeletons such as DNA and RNA.

Due to the favourable biological activities of these *N*-heterocyclic compounds, medicinal and synthetic chemists have developed numerous methodologies to make this family of compounds.

1.3 Indoles and Carbazoles

Indoles and carbazoles represent a significant class of *N*-heterocycles that show great promise in various applications. Indole **5a** is an aromatic heterocyclic organic compound with a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered pyrrole[14] (Fig. 2). The indole scaffold is one of the most common *N*-heterocycles in the naturally occurring and synthetic bioactive compounds[15]. These compounds have numerous biological and pharmaceutical activities[16] such as antimicrobial, antiviral and anti-inflammatory activities[17,18]. For example, indomethacin **6** is a non-steroidal anti-inflammatory drug which consists of the indole moiety. Arbidol **7** is another example of an antiviral drug which is used for the treatment of influenza through preventing viral entry into the target cell and stimulating an immune response. 3-Aryl(heteroaryl)indole **8** has antimicrobial activity and therefore can be used as an antimicrobial agent and indol-3-yl-pyridines **9** which exhibits antimicrobial and antioxidant activities[17].

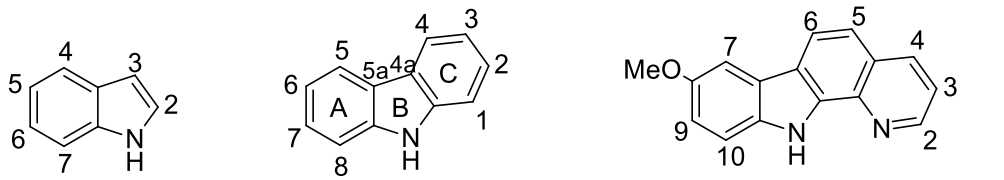


Fig 2. The structure of simple indole, carbazole nucleus and pyrido fused carbazole with popular numbering system.

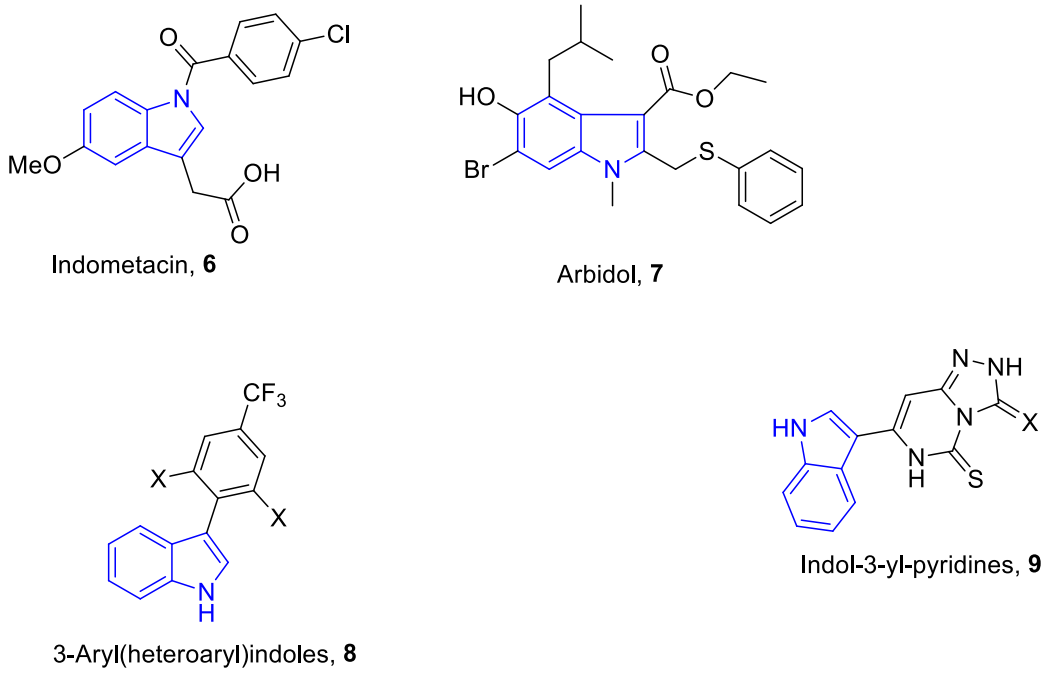


Fig 3. Indole containing compounds with different properties.

The importance of the indole nucleus has resulted in the synthesis of a wide range of bioactive compounds with various substituents at various positions of the indole ring. Because of its biodiversity and versatility, it has been highlighted as a highly favoured motif for target-based design and development of anticancer therapies. Numerous studies have identified various indole-based compounds with various techniques for producing potential anticancer activity, demonstrating the importance of the indole motif in the development of anticancer medications[15].

Indoles such as phenylindole-3-carbaldehyde **10** have been reported as antitumor agents that act by suppressing tubulin polymerization, thus inhibiting breast cancer cell growth[17]. Other indoles that are substituted at position 2 or 3 with various aryl groups have also been shown to inhibit tubulin polymerization[17]. Some examples of indole-containing anti-cancer agents which have been synthesized include 2,3-diaryindole **11**, 3-pyranyl indole **12** and 2-arylamino-5-(indolyl)-1,3,4-thiadiazoles **13** (Fig. 4)[17].

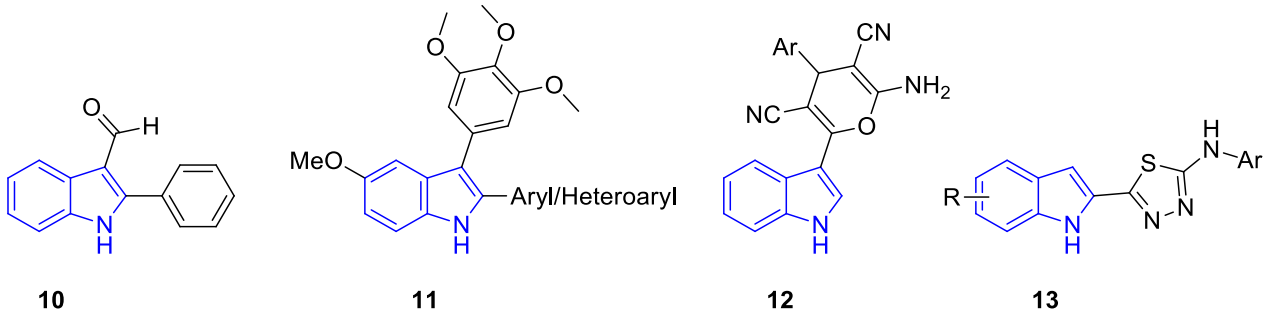


Fig 4. Some examples of anti-cancer compounds containing the indole framework.

Structurally similar to indoles are carbazoles **5b** which bear an extra benzene ring fused to the pyrrole of the indole. These compounds are of great interest due to their tricyclic structure and wide distribution in nature. Like indoles, carbazoles show interesting biological activities and pharmacological properties. Many biologically active compounds, both natural and synthetic, have a carbazole nucleus as a significant structural motif[5]. Synthetic and natural carbazole derivatives have been synthesized and were shown to possess various types of biological and pharmacological properties such as antioxidant, anti-inflammatory, anti-bacterial, antiviral, anti-diabetic and anti-tumor activities[5,19]. More importantly, carbazoles were found to have effective antiproliferative activity on tumor cells[20]. For example, clausine B **14** is a naturally occurring carbazole that was found to be active against four human cancer cell lines including breast, cervical, ovarian and hepatic cancer[20].

Ellipticine **15** is another example of a naturally occurring carbazole-containing compound isolated from *Ochrosia elliptica* (Apocynacae) and has anticancer properties. The ellipticine framework has a carbazole moiety fused with a pyridine ring forming an extended aromatized hydrophobic compound[21]. This compound and its derivatives function through multiple mechanisms leading to cell cycle arrest and initiation of apoptosis. Intercalation into DNA and inhibition of topoisomerase II were the suggested dominant mechanisms[21]. Among these ellipticines, those having free phenol substituent at the position 9 (ellipticine numbering) exhibit both cytotoxic and antitumor activity. A study of DNA interaction parameters in this series of drugs has clearly demonstrated that the presence of phenol does not modify their mode of DNA binding. It was suggested that the presence of the phenol should have properties not directly related to DNA binding. It was then hypothesized

that 9-hydroxy ellipticine and related derivatives are oxidized under physiological conditions to the corresponding electrophilic quinoneimines[21].

The simple structure of ellipticine has prompted chemists to design various structural modifications in order to obtain more active derivatives[21]. Girinimbine **16** is another carbazole alkaloid extracted from stem bark of *Murraya koenigii* and it displayed an anti-tumor promoting activity[5]. The plants of *Clausena* have been widely investigated and many anti-cancer carbazole alkaloids were identified, murrayanine **17** is one of the compounds found in these plants (Fig. 5)[22].

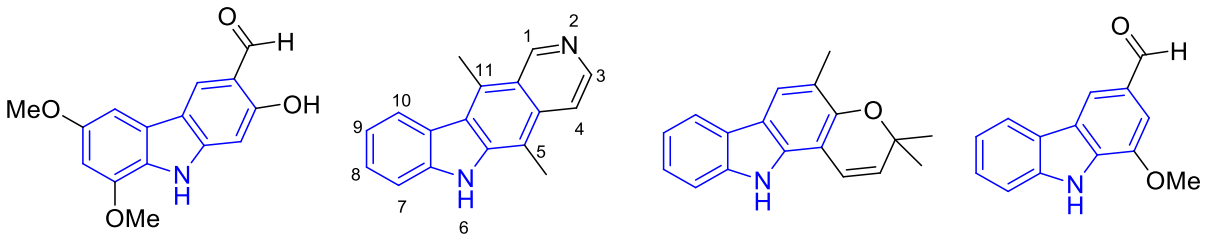
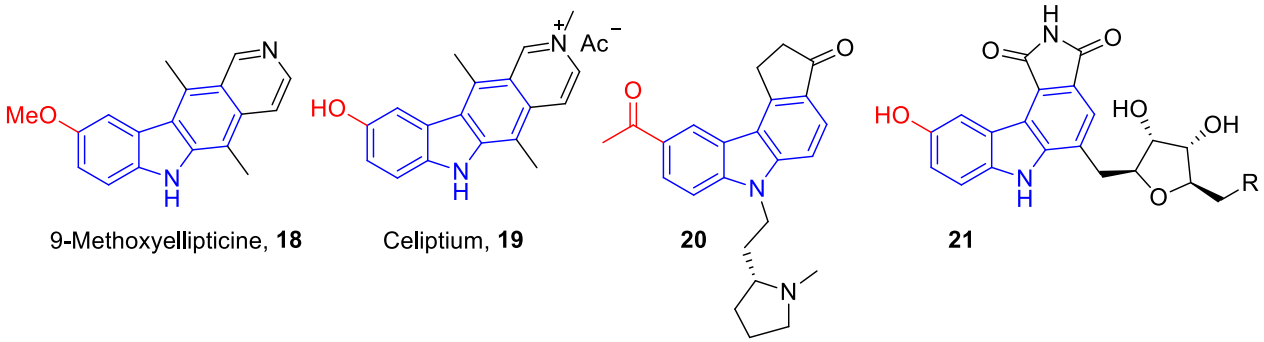


Fig 5. Some naturally occurring carbazoles with anti-cancer activities.

Many synthetic compounds are derivatives of the naturally occurring carbazoles. The natural carbazole extracted from plants led to the development and synthesis of unnatural carbazoles such as celiptium **19**, an ellipticine analogue, which is also known as *N*-methyl-9-hydroxyellipticium acetate. 9-Hydroxy derivatives such as celiptium **19** are active on different experimental tumors such as murine leukemia, sarcoma and colon[5]. The antitumoral properties of ellipticine **15** and some of its derivatives are thought to be related to their DNA binding ability since they bind with high affinity to DNA by intercalation between base pairs[23]. 9-Methoxyellipticine **18**, another ellipticine derivative, was also reported to have antitumor activity. The mechanism of action of this compound was investigated. The DNA intercalating property of **18** led to the synthesis of other ellipticine derivatives such as celiptium **19** which was used in the treatment of metastatic breast cancer and as reported, it acted as a topoisomerase II inhibitor and intercalating agent, stabilizing topoisomerase II and inducing DNA breakage[5, 24].

Other carbazoles such as compound **20** were synthesized and investigated against renal cell carcinoma and were found to possess high activity against these cells when an acetyl group is

present at position C-6 and *N*-9 substituted with (1-methylpyrrolidin-2-yl)ethyl[5] using numbering on carbazole **5b** (Fig. 2) as reference. The acetyl group as a moderate electron-withdrawing group and the bulkiness of the *N*-substituent enhanced the antitumor activity of these compound[5]. For compound **21**, adding a hydroxyl group as an electron donating group at position C-6 also enhanced the antitumor activity of these compounds[24]. The work of Issa and co-workers revealed that adding methoxy, acetyl or substituted carboxyl groups and hydroxy group at position C-6 of these carbazoles enhanced the antitumor activity of these compound[5].



9-Methoxyellipticine, **18** Celiptium, **19** **20** **21**

Fig 6. Carbazole compounds with antitumor properties.

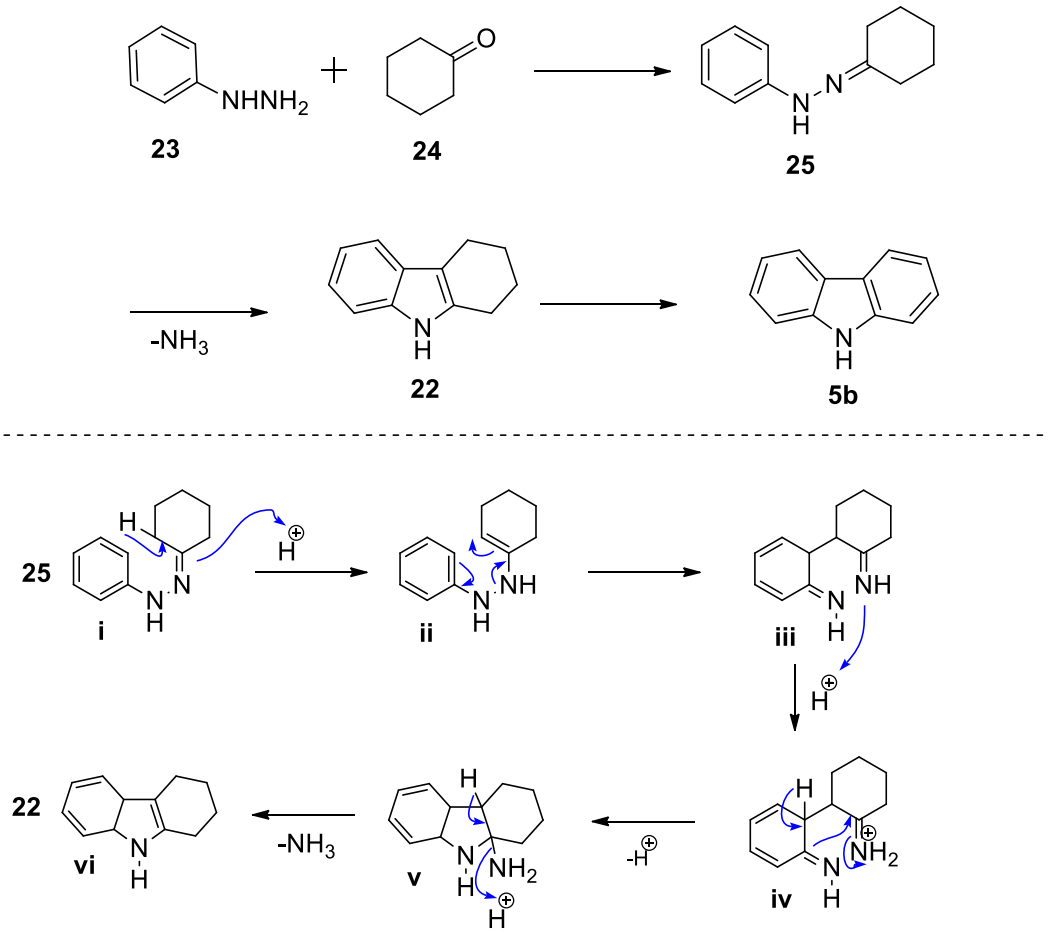
1.4 Synthesis of Carbazoles

Owing to their bioactivities, carbazoles are a class of compounds that has enjoyed sustained attention from synthetic and medicinal chemists. The synthesis of carbazoles has been achieved using multistep synthetic routes that involve acid-, base-, and metal-catalyzed protocols, which were performed under heat or UV-irradiation. The key steps in the synthesis of carbazoles usually include both inter- and intra-molecular $C(sp^2)–C(sp)$, $C(sp^2)–N$, or $C(sp^2)–C(sp^2)$ coupling reactions of suitably substituted building blocks[24].

Some of the classical approaches employed to construct the carbazole framework include oxidative cyclization of diarylamines, various indoles and biphenyls with *o*-nitrogen substituents are some of the widely used precursors during the synthesis of carbazoles. Non-classical procedures such as transition metal-mediated and catalyzed processes are also used for the synthesis of carbazoles[25]. Figure 2 shows a simple structure of carbazole nucleus **5b** and the common numbering system used, substituents can be added to both rings A and C. Some of these strategies will be briefly discussed below.

1.4.1 Synthesis of carbazoles through the formation of ring B

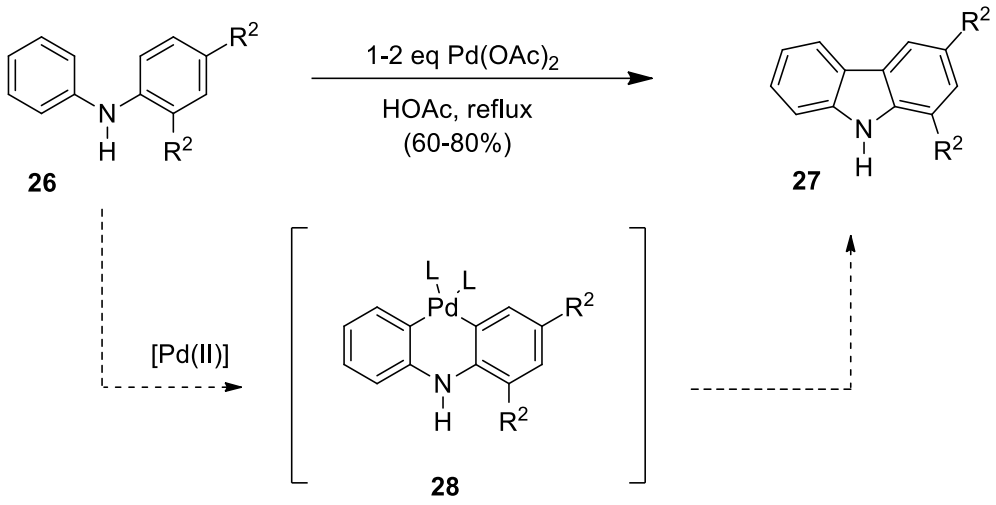
Perhaps one of the commonly used approach to carbazoles involves the construction of ring B. This strategy is reflected on the classical Borsche–Drechsel cyclization (sometimes called Fischer-Borsche reaction), which leads to the synthesis of 1,2,3,4-tetrahydrocarbazoles **22**. The Borsche–Drechsel cyclization involves the condensation reaction of phenyl hydrazine **23** and cyclohexanone **24** to form arylhydrazone **25**, which then cyclizes to 1,2,3,4-tetrahydrocarbazoles **22** as shown in **Scheme 1**. Tetrahydrocarbazole **22** could then be transformed to carbazole **5b** through an oxidation reaction or dehydrogenation.



Scheme 1. Preparation of carbazole through the classical Borsche–Drechsel cyclization.

The construction of ring B is not limited to classical methods. Modern routes heavily involve metal catalyzed transformations such as the palladium catalyzed Heck reaction, which was utilized to forge the C(5a)-C(4a) bond in suitably halogenated diphenylamines[25]. Direct oxidative cyclization

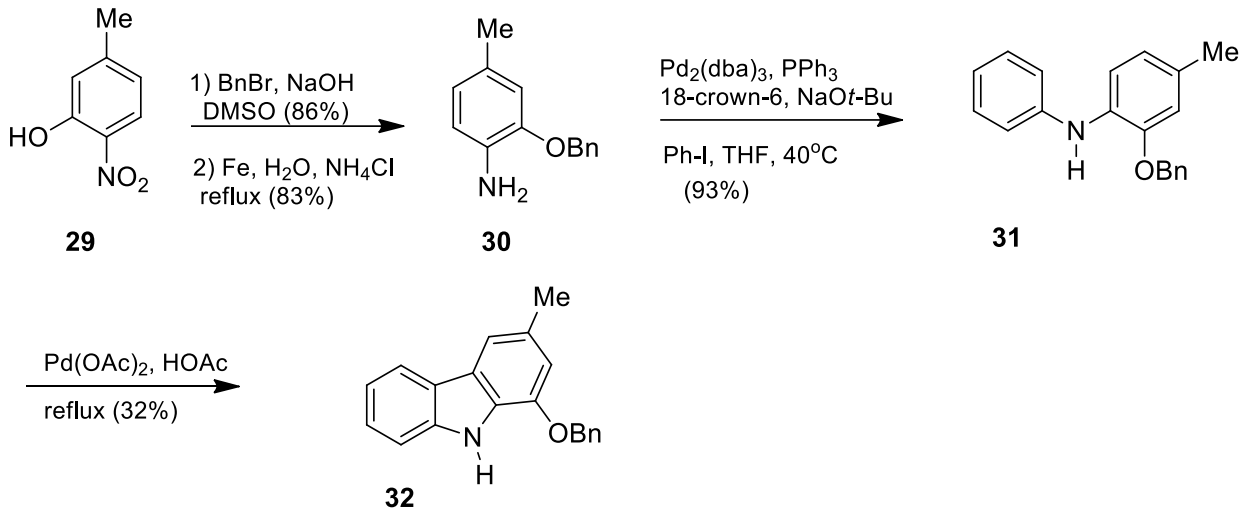
of non-halogenated diphenylamines has been demonstrated using stoichiometric amounts of palladium. For example, Åkermark and co-workers heated diphenylamines **26** with palladium (II) acetate in acetic acid under reflux, the ensuing cyclization led to the formation of carbazole derivatives **27**[25]. The cyclization required acid additives such as trifluoroacetic acid or methanesulfonic acid in catalytic amounts. The key cyclization step is believed to proceed *via* palladacycle **28** that was formed by an electrophilic attack of a palladium(II) species at the aromatic rings (**Scheme 2**)[25]. This oxidative cyclization has a wide substrate scope as it tolerates numerous substituents. However, 1 equivalent of palladium(II) acetate is required for cyclization of diphenylamines which contain electron-donating groups. Longer reaction times and 2 equivalents of palladium acetate are required for strong electron-withdrawing groups such as NO_2 or COOH. In addition, other transition metals such as iron and molybdenum have been used for the synthesis of carbazole nucleus and some of these metals such as palladium are recoverable. The Pd(0) species generated can be reoxidized to Pd(II).



Scheme 2. Synthesis of carbazole by palladium-mediated cyclization of diphenylamine.

Another example for the formation of ring B is the cyclodehydrogenation of diphenylamines, **Scheme 3**. Lin *et al.* reported[26] the synthesis of 1-(benzyloxy)-3-methyl-9*H*-carbazole **32** through cyclodehydrogenation of diarylamine **31**. The starting material used was 2-hydroxy-4-methylnitrobenzene **29**. The hydroxyl group of **29** was protected as a benzyl ether and the nitroarene produced was reduced to the corresponding amine **30**. Using Buchward conditions, the

key intermediate, 2-(benzyloxy)-4-methyl-*N*-phenylaniline **31**, was obtained by amination of 2-(benzyloxy)-4-methylaniline **30**. Oxidative cyclization of diarylamine **31** with palladium (II) acetate in acetic acid gave the carbazole **32** in 32% yield (**Scheme 3).** The low yield of the synthesis of this carbazole was attributed to the electron-donating effects of the methyl and benzyloxy substituents in the benzene ring[26]. Knölker and co-workers also employed a similar strategy in their total synthesis of naturally occurring compounds possessing a cabazole nucleus. Knölker and Reddy summarized some of this work in a recent review (see reference 26).



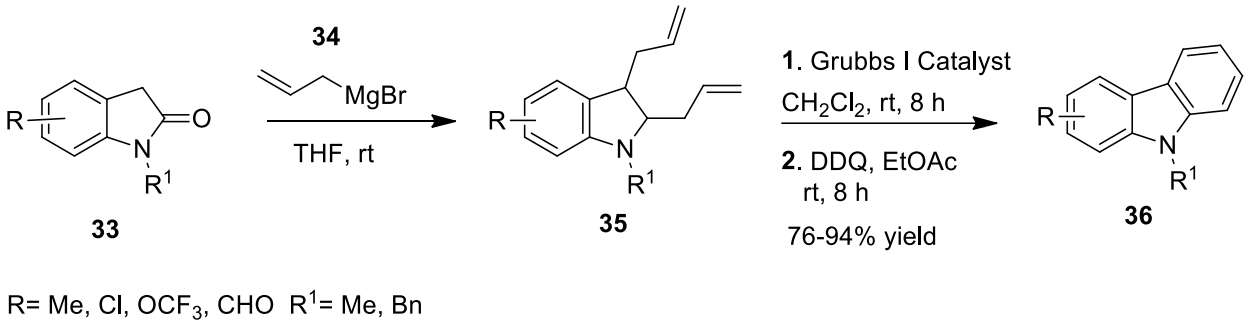
29 **30** **31** **32**

Scheme 3. Palladium-mediated synthesis of a substituted carbazole.

1.4.2 Synthesis of carbazoles through the formation of ring C

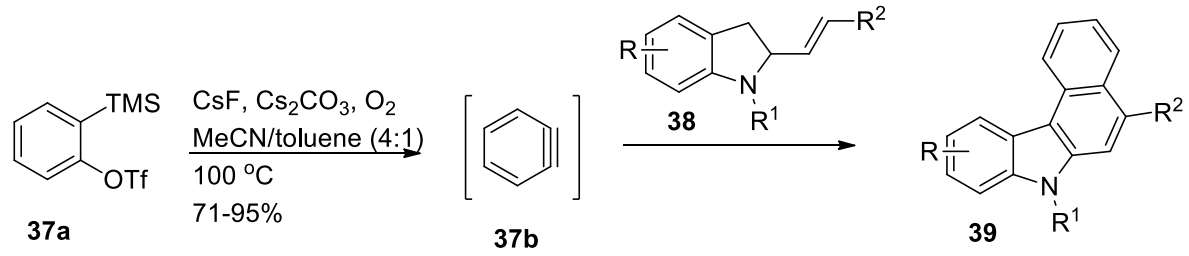
An alternative approach to the synthesis of carbazoles involves the formation of ring C on a preformed indole nucleus. This strategy holds promise owing to the commercial availability of various indoles. Reactions such as metal-catalyzed-, cycloaddition-, electrophilic cyclization and three-component reactions have been used for the formation of ring C of carbazole. Dash and co-workers reported the synthesis of carbazoles *via* a metathesis reaction using Grubbs catalyst[27] (**Scheme 4**). The reaction was initiated with oxoindole **33** and ally magnesium bromide **34** in the presence of Grignard reagents to generate 2-ally and 2,3-disubstituted diallyl indole derivatives **35** which later underwent ring-closing metathesis in the presence of Grubbs I catalyst followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation to give carbazoles **36** (**Scheme 4**). This synthesis highlighted Grignard addition to substituted 2-oxoindoles as a tool for synthesis of

carbazoles[27]. The substrate scope for this reaction is not general. One of the limitations for Grignard reaction is that it cannot take place in presence of water or acidic proton such as alcohols or thiols as this can destroy the alkyl magnesium halide. Oxoindoles which possess acidic protons also cannot be used in this reaction.



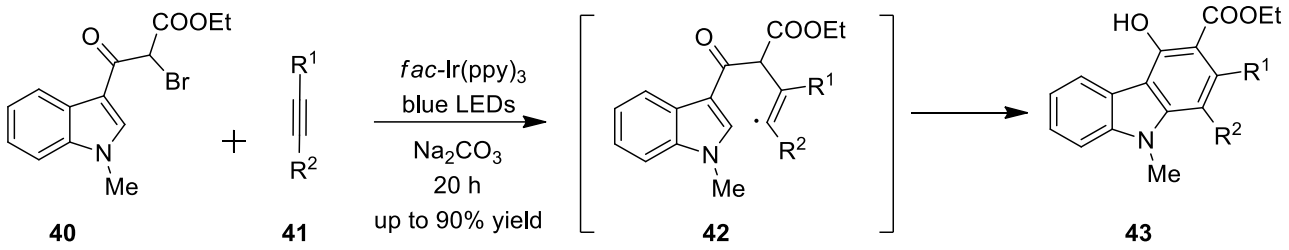
Scheme 4. Ruthenium-catalyzed olefin metathesis on dially indoles.

Another reaction used for formation of ring C in carbazoles is the cycloaddition reaction which employs mild conditions as seen in **Scheme 5**. Wu and co-workers reported the synthesis of benzo[*c*]carbazole **39** *via* the Diels-Alder reaction of arynes **37b** (generated from **37a**) and 2-alkenyindoles **38**. By controlling the conditions of the reaction, carbazole **39** was obtained in good yields[27].



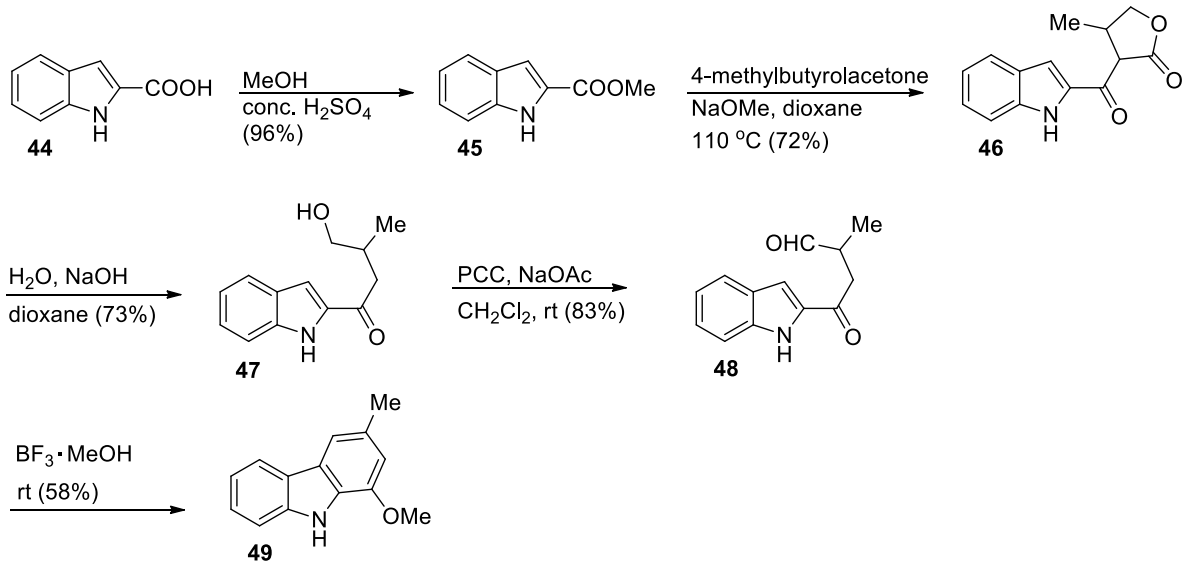
Scheme 5. Synthesis of benzocarbazoles using the Diels-Alder reaction.

Scheme 6 also represents a cycloaddition reaction where visible light-driven photocatalytic reaction was used. Under LED irradiation at room temperature, highly functionalized carbazoles **43** were synthesized from ethyl 2-bromo-3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanoate **40** and alkynes **41** proceeding through intermediate **42**[27]. Despite the reaction time of 20 h, this reaction employs mild reaction conditions as the reaction proceeds at room temperature and uses visible light with fewer substrates.



Scheme 6. Ir-catalyzed [4+2] annulations for carbazole synthesis.

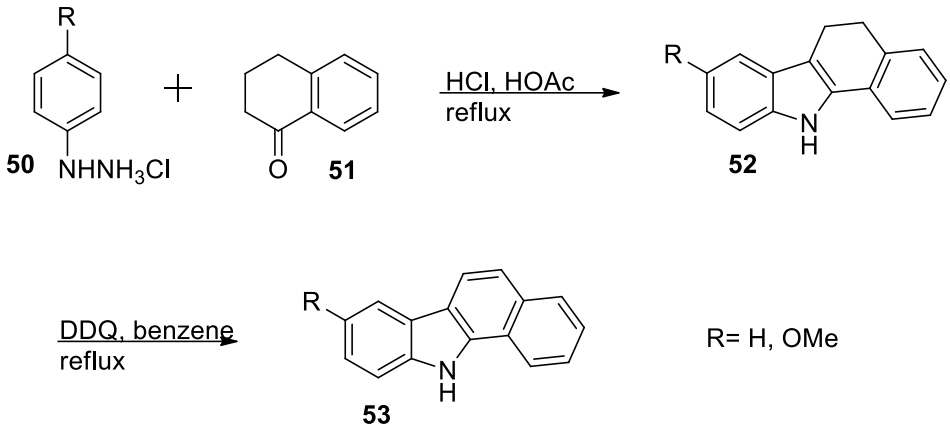
Moody *et al.* developed[28] a general synthetic route for 1-oxygenated carbazoles using indole-2-carboxylic acid **44** as the starting material. The first step involved the conversion of carboxylic acid **44** to methyl ester **45** *via* the action of methanol in the presence of concentrated sulphuric acid. Claisen condensation of the indole ester **45** with 4-methylbutyrolactone to yield lactone **46** is one of the key steps in this synthesis. The lactone underwent alkaline hydrolysis and decarboxylation to afford alcohol **47**, which was then oxidized with pyridinium chlorochromate (PCC) to form aldehyde **48.** Aldehyde **48** was subsequently subjected to a Lewis acid-assisted cyclization furnishing Murrayofoline A **49**, as shown in **Scheme 7**. This compound was synthesized over five steps in 25% overall yield which is low and attempts to extend this methodology to the synthesis of other carbazole alkaloids such as 2-prenyl-substituted carbazoles were unsuccessful due to decomposition of the corresponding aldehydes prior to Lewis acid-assisted cyclization[27].



Scheme 7. Synthesis of Murrayofoline A (carbazole) by intramolecular electrophilic substitution.

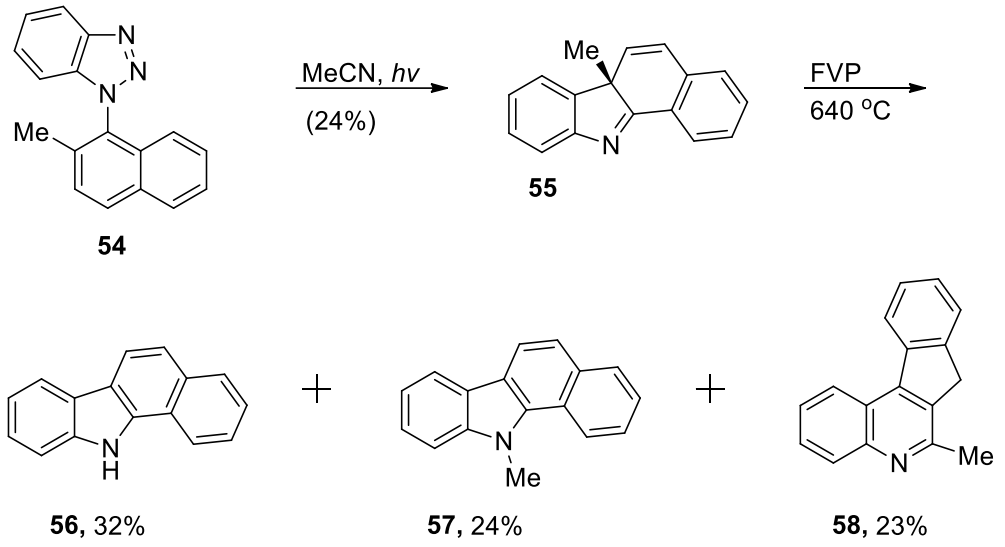
1.4.3 Synthesis of benzo[*a*]carbazoles

Methods that are employed for the synthesis of carbazole compounds vary from polar or ionic to radical to pericyclic type of reactions[25]. One example for the synthesis of benzo[*a*]carbazoles which was reported by Rogers and Corson, involves reacting arylhydrazine hydrochloride **50** with α-tetralone **51** forming intermediate **52**, 5,6-dihydro-11*H*-benzo[*a*]carbazole[26]. Dehydrogenation of this intermediate with DDQ in refluxing benzene provided 11*H*-benzo[*a*]carbazole **53**. This method forms a carbon-carbon bond C4-C5 of carbazole **5b**[29].



Scheme 8. Synthesis of benzo[*a*]carbazole.

Kulagowski *et al.*[30] achieved the synthesis of benzo[*a*]carbazoles *via* photochemical means. This was exemplified by the synthesis of 6a*H*-Benzo[*a*]carbazole **55** from benzotriazole **54**, which can be prepared using Graebe-Ullman synthesis. Subjected to a flash vacuum pyrolysis (FVP) at 640 °C and 3.94×10^{-5} atm, compound **55** yielded the 11*H*-benzo[*a*]carbazoles **56** and **57** in 32 and 24% respectively[30] Indenoquinoline **58** was also produced along with the two carbazoles in 23% yield. This synthesis route requires harsh conditions and leads to the formation of isomeric benzocarbazoles.

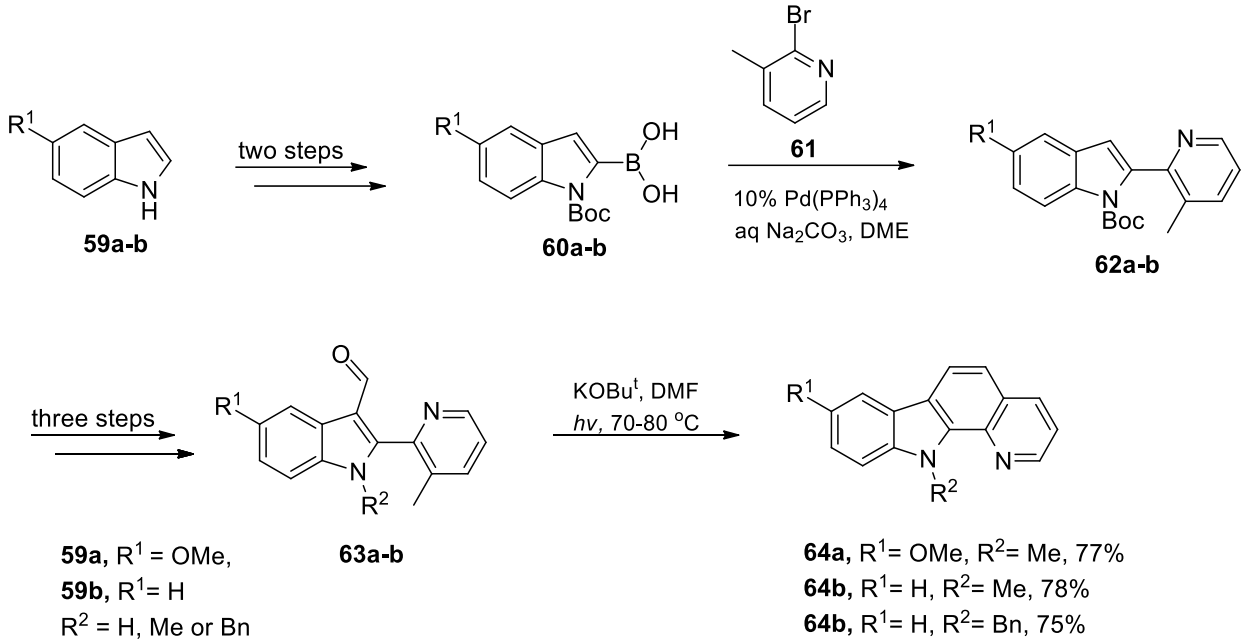


Scheme 9. Synthesis of benzo[*a*]carbazole using FVP.

Here at Wits University, the key step used in our synthesis of carbazoles involved a novel light-assisted base mediated reaction which enabled the formation of carbazole, by forming the carbon-carbon bond between C-3 and C-4 of compound **5b** as the last step. This unique cyclization reaction is thought to take place *via* photo-enol intermediate[18]. There are several methods for the synthesis of benzo[*a*]carbazoles and pyrido[2,3-*a*]carbazoles but none of these methods reported the formation of the carbon-carbon bond (C3-C4 bond) in carbazole **5b** which is the final step.

In the route that was used at Wits, indole-2-boronic acid **60** was synthesized in two steps from indole **59** (**Scheme 10**). The boronic acid underwent Suzuki coupling with the pyridine **61** to yield compound **62**. The Suzuki Coupling reaction, a palladium catalyzed reaction, is one the main reactions used in our laboratories for the synthesis of these carbazole compounds. This reaction is commonly used for the synthesis of biphenyls, poly-olefins and styrenes as it forges a new carbon-carbon bond[31]. Boronic acids are commonly available, less toxic and environmentally friendly. In addition, other requisite reagents for this reaction are easily prepared and relatively cheap and the reaction conditions are relatively mild. Palladium based catalysis is important in the pharmaceutical industry for forming carbon-carbon bonds. Due to these reasons, the Suzuki coupling method is preferred over other similar coupling reactions.

Compound **62** was then transformed to compound **63** in three steps including a formylation reaction. 3-Formylindoles are versatile starting materials for the synthesis of many indole derivatives since their carbonyl group can readily undergo a variety of transformations such as C-C and C-N coupling reactions and reductions[32]. Compound **63** is suitable to undergo *t*-BuOK-mediated photocyclization as developed by de Koning and colleagues where an aldehyde and methyl functional groups are required. Indeed, exposure of **63** to de Koning conditions gave carbazole **64** (**Scheme 10**). The synthesis of carbazoles **64** proceeded a good overall yield in only seven steps from indole **59**[18].



Scheme 10. The reaction scheme that was used to synthesize carbazoles at Wits University

1.5 Aims and Objectives

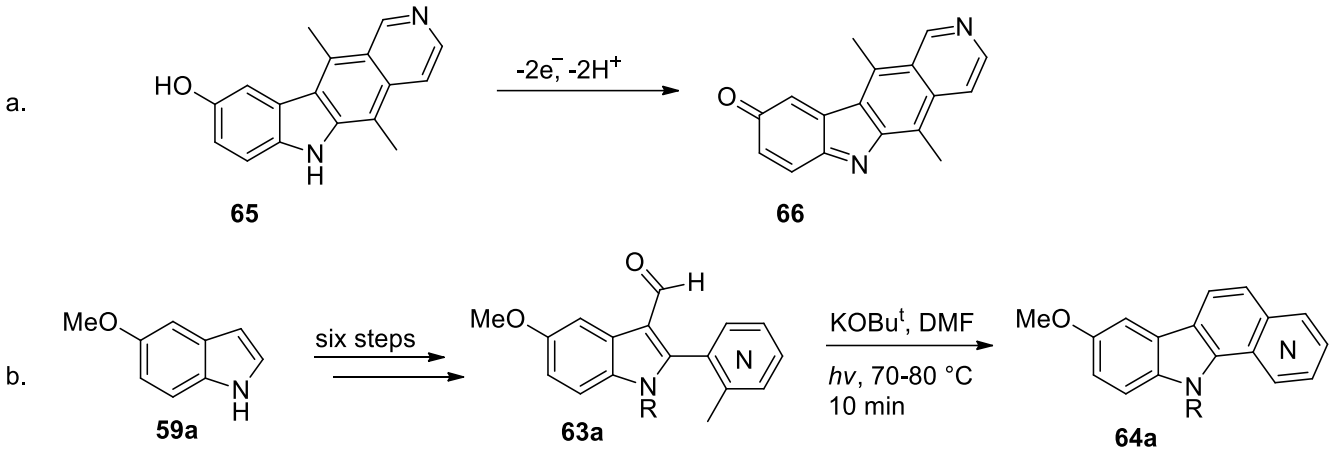
Results obtained in previous work about the cytotoxic activity and antitumor efficiency of various ellipticine analogs indicated that carbazoles with an oxygen containing functional group at position 9 (position 6 of compound 5b) exhibit more cytotoxic activity against certain cancer cells *in vitro* and these compounds can be oxidized into reactive compounds[24].

Inspired by this work and the work of de Koning and co-workers[18], we hypothesized that having a methoxy group at position 8 of pyrido fused carbazoles **5c** will improve the biological activity of carbazoles. This stems from the realization that compounds bearing an oxygen functional group

such as hydroxy or methoxy *para* to the carbazole **65** nitrogen atom under physiological environment suffer *O*-demethylation followed by oxidation furnishing the highly reactive iminocyclohexa-2,5-dienone fragment **66** (**Scheme 11a**) that attacks biomolecules leading to cell death.

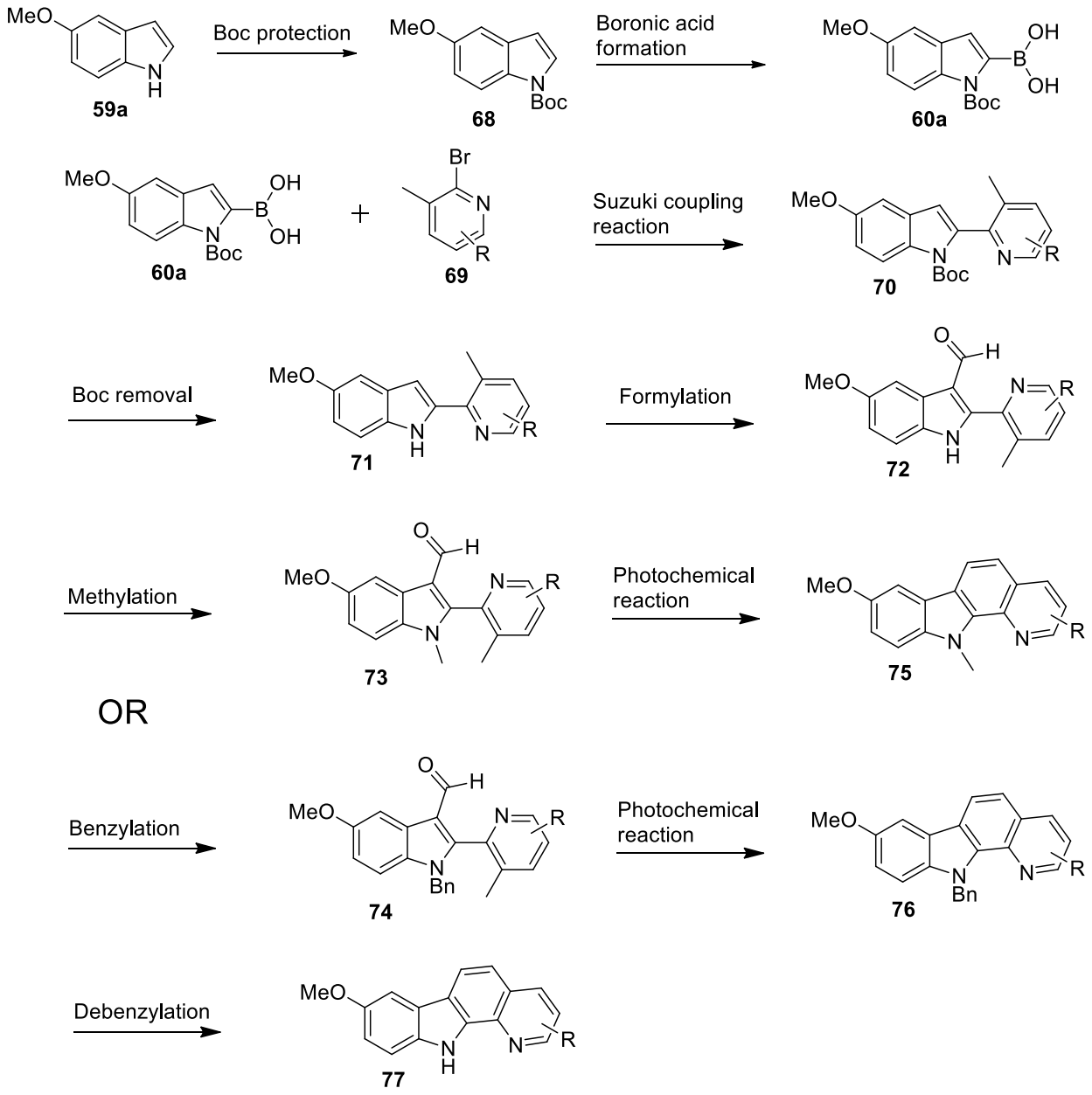
The project was aimed at the synthesis of pyrido fused carbazoles bearing a methoxy group at position 8 starting from 5-methoxyindole **59a** using methodologies that have been previously used in our laboratories and by other chemists. Another objective was to synthesize these compounds while changing the position of the nitrogen atom on the carbazole which is a function of the structure of pyridine used in the Suzuki coupling reaction.

In this work, we planned to synthesize various 8-methoxy pyrido-fused carbazoles **64a** from 5-methoxyindole-3-carbaldehyde substates **63a** using the light-assisted, base-mediated intramolecular cyclization reaction as the key step in forming ring C using the reaction conditions provided in **Scheme 11b**. The 5-methoxyindole-3-carbaldehyde substrates can be synthesized from 5-methoxy indole **59a** in of six steps.



Scheme 11. a) Proposed oxidation of 8-hydroxy ellipticine under physiological conditions; **b)** the key reaction in the planned synthesis of pyrido-fused carbazole derivatives.

The planned synthesis of these compounds began with the synthesis of (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid **60a** which involves protection of indole **59a** into *Boc*-protected indole **68**, followed by the synthesis of the (5-methoxy-1*H*-indol-2-yl)boronic acid **60a** (**Scheme 12**).



Scheme 12. The reactions used in the synthesis of pyrido fused carbazoles, where R represents different substituents on the pyridine ring.

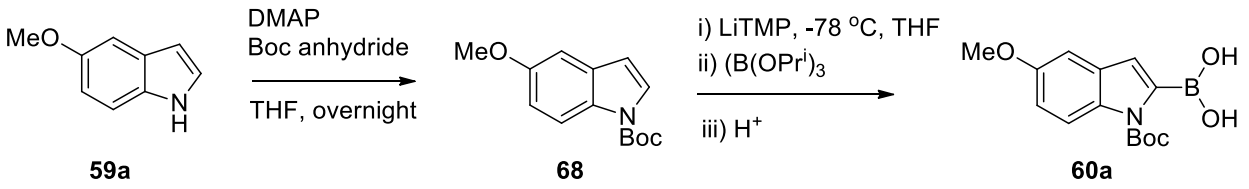
The boronic acid would then be coupled with various 2-bromo-3-methylpyridines **69**, which should lead to biarylindoles **70**. The protecting group would then be removed yielding compound **71** where a formyl group would be installed forming carbaldehyde substrates **72**. Another protecting group would be installed before doing the light-assisted, base-mediated cyclization reaction which we anticipated would yield carbazole **74** or **76** from the protected carbaldehyde compound **73** or **76**. Removing the protecting group from the pyrido fused carbazoles would yield compound **77** as shown in the reaction **Scheme 12** below.

Chapter 2

2. Results and Discussion

2.1 Boronic acid synthesis

The synthesis of pyrido fused 8-methoxy-carbazoles **64** began with the synthesis of the corresponding boronic acids after protecting 5-methoxy-indole **59a** with *tert*-butoxycarbonyl group. Following the procedure reported by de Koning and co-workers (**Scheme 13**)[18], 5-methoxy indole **59a** was reacted with di-*tert*-butyl dicarbonate in the presence of dimethylamino pyridine (DMAP) giving the *boc*-protected 5-methoxy indole **68** as a white solid in quantitative yield. The ^{1}H and ^{13}C NMR spectra obtained confirmed the successful synthesis of this compound. A peak at 1.49 ppm which integrates for 9 protons and the disappearance of the broad NH peak at 8.03 ppm in the ^{1}H NMR spectrum was observed. Three new peaks were also observed in the ^{13}C NMR spectrum, a 3 × CH_3 peak at 28.2 ppm, the carbonyl carbon at 155.4 ppm and quaternary carbon at 83.5 ppm. The *Boc*-protected indole **68** was then transformed to (5-methoxy-1*H*-indol-2-yl)boronic acid **60a** upon treatment with LiTMP and $B(OPr^i)_3$, followed by acid work up to give the desired boronic acid, which was used in the subsequent Suzuki coupling reaction without further purification or characterization. The Boc group is one of the *N*-protecting groups that is used to effect metal stabilization at position 2 of the indole nucleus by lone pair donating properties of the protecting group to allow directed *ortho* metalation (DOM effect). In other words the protecting group assists in C-2 lithiation. When indole **68** is treated with lithium 2,2,6,6-tetramethylpipedide (LiTMP) at low temperatures, it afforded a regioselective 2-lithation product which was then quenched with triisopropyl borate then acid work up to afford boronic acid **60a**, a 2-substituted indole.

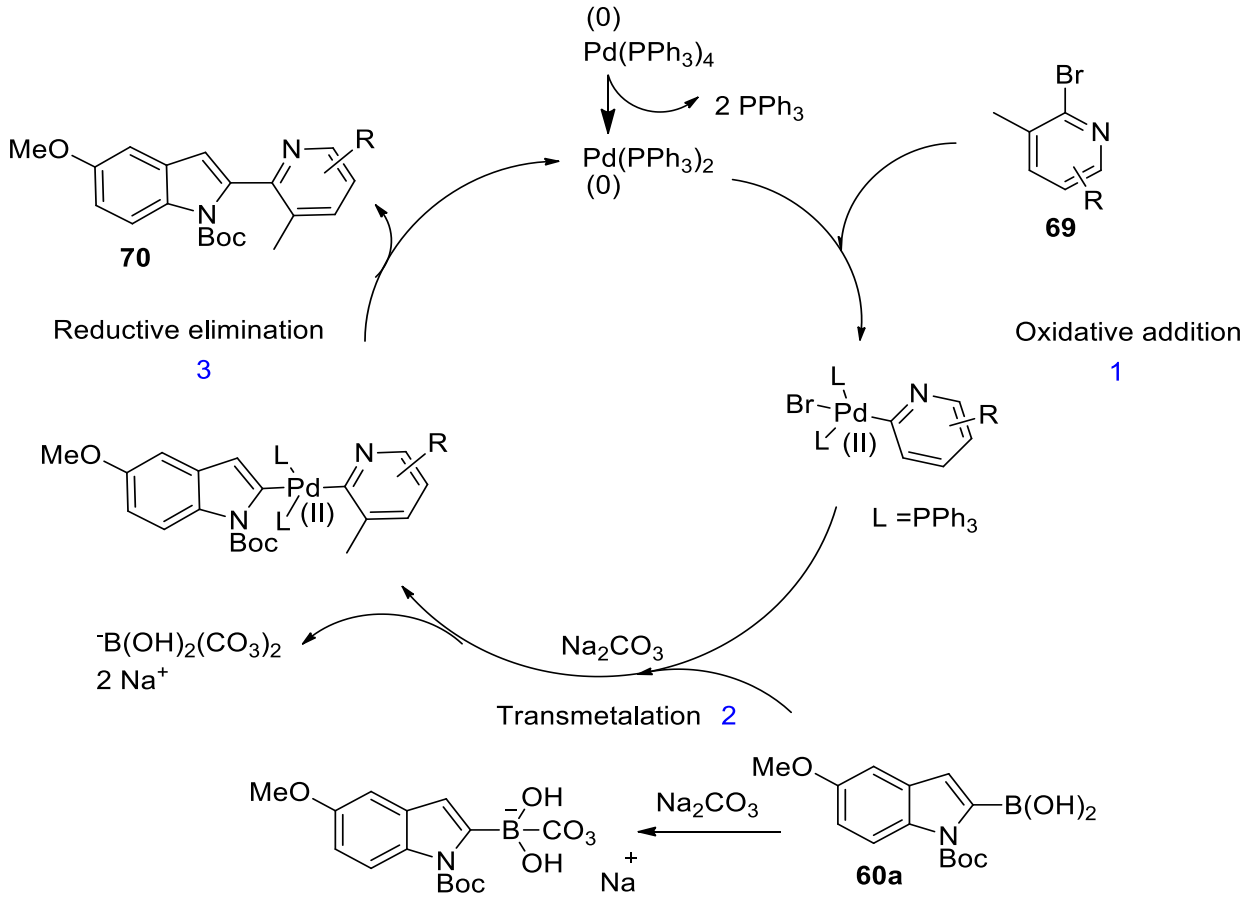


59a **68** **60a**

Scheme 13. Synthesis of *boc*-protected indole and boronic acid.

2.2 Suzuki coupling reactions

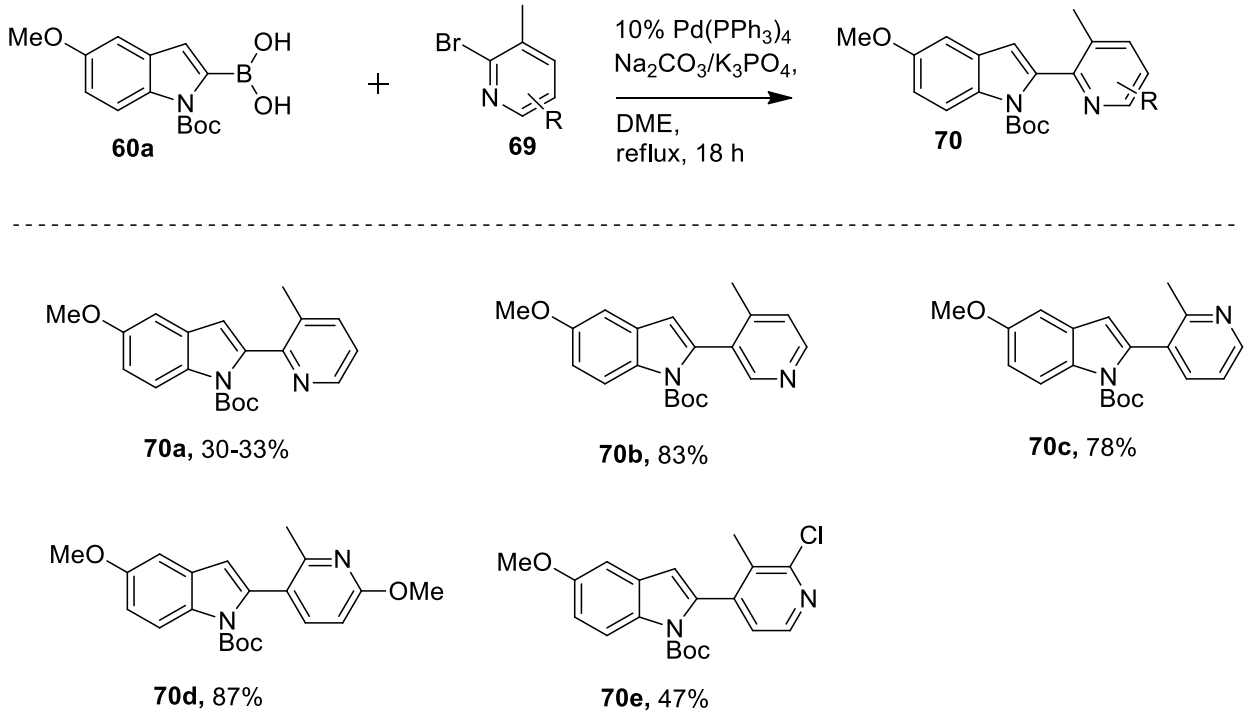
The (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid **60a** was coupled with a variety of substituted aryl halides **69** utilizing the Suzuki coupling reaction. This coupling reaction has been used successfully in our group for the formation of Csp^2-Csp^2 bonds[19]. The reaction is green, easy to perform and gives good yields and selectivities. The first step in the mechanism of the Suzuki coupling reaction involves the oxidative addition of aryl halide to palladium(0) complex, forming a palladium(II) intermediate. Transmetallation of the boronic acid with palladium(II) then occurs in the presence of a base. The last step is the reductive elimination to give the desired product and regenerates the original palladium(0) complex[31] (**Scheme 14a**).



Scheme 14a: The mechanism for Suzuki coupling reaction.

Using the procedure and conditions (**Scheme 14b**) reported,[18] *tert*-butyl 5-methoxy-2-(methylpyridin-2-yl)-1*H*-indole-1-carboxylates **70a-e** were synthesized in low to good yields (30-87%). The low yield for indole **70a** (30-33%) could be attributed to use of previously synthesized $Pd(PPh_3)_4$ catalyst and (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid **60a**. Not using a freshly prepared catalyst and unpurified boronic acid may have led to low yields of **70a**. However, we did have sufficient amounts of this substrate to carry on with our planned synthesis. In fact after several unsuccessful attempts to try and purify the boronic acid we synthesized, we decided to purchase the requisite (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid **60a** as it is commercially available. In addition, we prepared a fresh batch of $Pd(PPh_3)_4$ catalyst. The freshly prepared $Pd(PPh_3)_4$ catalyst and boronic acid **60a** from Sigma-Aldrich were used in our synthesis of substrates **70b-e**, which were obtained in good isolated yields.

For **70e**, the low yield could be due to a competition between the two halides (bromine and chlorine) on the pyridine fragment. ^1H, ^{13}C NMR spectral analysis as well as HRMS analysis was used to confirm the compounds synthesized. The ^1H NMR spectra of the biarylindoles **70a-e** showed the diagnostic methyl chemical shifts (δ 2.17-2.42 ppm) from the pyridine moiety, while the methoxy chemical shifts were observed at δ 3.80-3.88 ppm. The peaks for the *tert*-butoxycarbonyl group appeared between δ 1.22-1.27 ppm. The expected number of aromatic protons in each compound accompanied these chemical shifts. For example, *tert*-butyl-5-methoxy-2-(3-methylpyridin-2-yl)-1*H*-indole-1-carboxylate **70a,** seven aromatic protons were seen in addition to the diagnostic methyl and methoxy groups at 2.24 and 3.86 ppm respectively. In the ^{13}C NMR spectrum, the methyl chemical shift from the pyridine was observed at chemical shifts of 17.2-22.9 ppm, the *tert*-butoxycarbonyl carbon at 27.5-28.2 ppm and methoxy group at 55.7-55.9 ppm. The mass of **70a-c** measured was 339.1708, **70d** 369.1986 and **70e** 373.1341 a.u. and they were all corresponding to the calculated $[M + H]^+$ *m*/*z* values (i.e. **70a-c** at 339.1703, **70d** at 369.1809 and **70e** at 373.1313, respectively). These results proved the success of the Suzuki coupling reactions for these substrates.

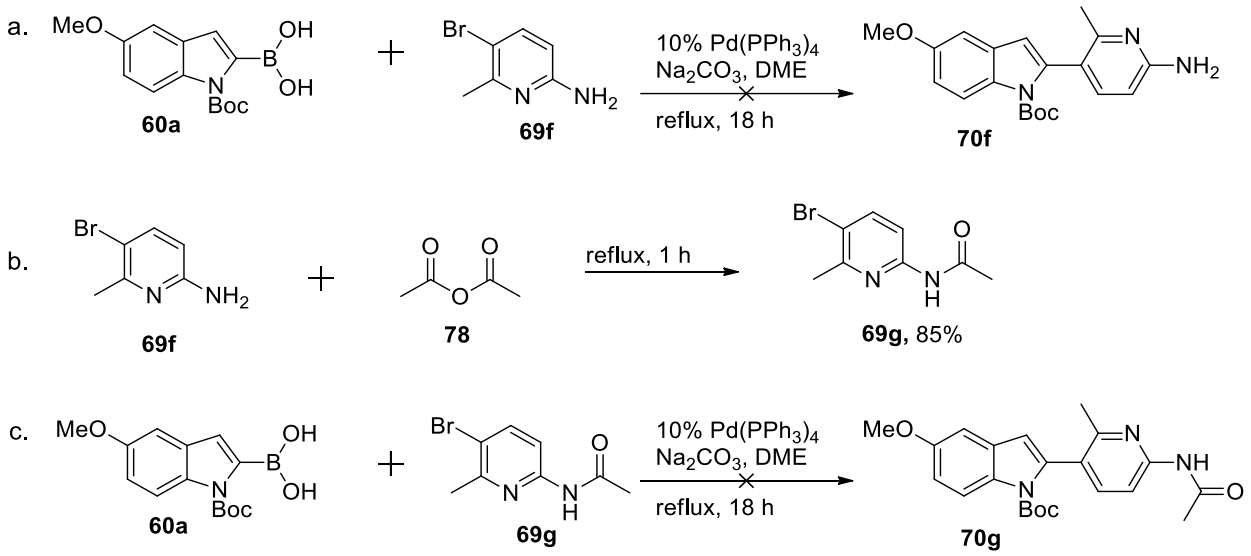


Scheme 14b. The conditions for Suzuki coupling reaction.

When using 6-amino-2-bromo-3-methylpyridine **69f** (**Scheme 15a**) as one of the coupling halide coupling partners, the Suzuki reaction did not work. Three spots were observed on the TLC plate, these were subsequently separated using column chromatography. From ^{1}H NMR spectrum analysis of the spots revealed that they belong to pyridine **69f**, indole **59a** and **68**. Indoles **59a** and **68** are presumably formed from deprotection (in case of **59a**) and the loss of the boronic acid group (in case of **68**). It was thought that the catalyst was rendered inactive through the reaction with amino group, instead of the intended insertion between the carbon-bromide bond. Compounds which have labile protons such as amines might not be suitable coupling partners in the Suzuki coupling reaction.[33]

The amino group of amino pyridine **69f** was then acylated in neat acetic anhydride **78**, forming *N*-(6-bromo-5-methylpyridin-2-yl)acetamide **69g** in a very good yield (**Scheme 15b**). In the ^{1}H NMR spectrum, a NH broad peak at 8.17 ppm and an extra methyl group at 2.46 ppm was observed. In addition, the characteristic carbonyl carbon chemical shift was observed at 168.7 ppm, thus verifying the installation of the acetyl group. The synthesized acetamide **69g** was then used to repeat the reaction using the same Suzuki coupling reaction condition (**Scheme 15c**).

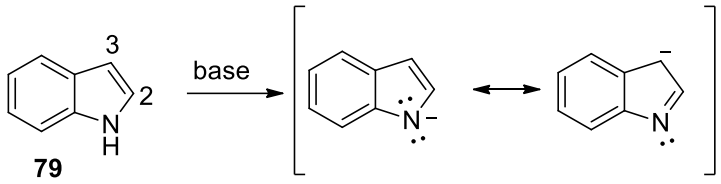
Unfortunately, the reaction still did not work and the starting materials were recovered. At this point, it was decided to move forward with the substrates that worked. Therefore, the biaryl compounds **70a-e** that were obtained from the successful Suzuki coupling reactions were reacted further in the subsequent planned reactions.



Scheme 15. a) Suzuki coupling reaction between indolyl-boronic acid **60a** and 5-amino-2-bromo-2-methylpyridine **69f** b) acetylation of amino pyridine c) Suzuki coupling reaction using indolyl-boronic acid **60a** and *N*-acylated-amino pyridine **69g**.

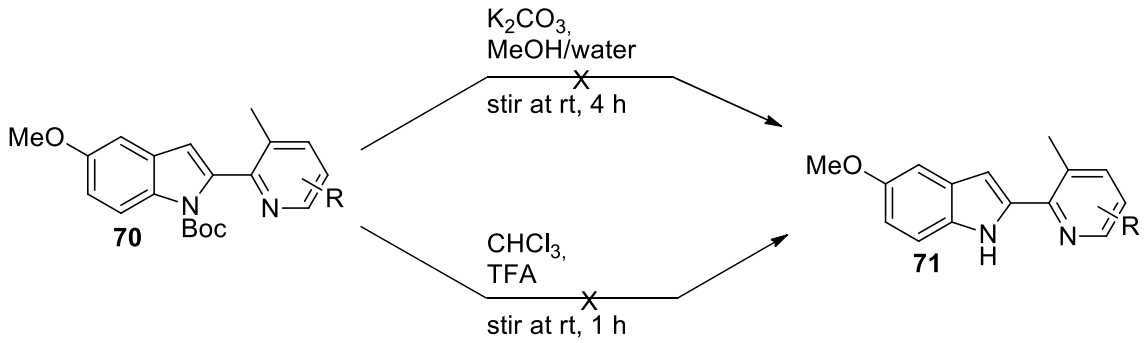
2.3 *Boc*-deprotection

In order to perform the formylation reactions of compounds **70a-e**, it was necessary to remove the *Boc*-protecting group. During the multistep synthesis of many compounds, a formylation reaction is often necessary as the carbonyl can readily undergo a variety of transformations such as C-C and C-N coupling reactions and reductions[34]. The NH group of indoles **79** is relatively acidic and increases the reactivity at C-3 position towards electrophiles. Therefore, the indolyl anion has ambident properties towards alkylation and acylation reactions[32]. During the formylation of indoles, a stable mesomeric cation is formed as seen in the **Scheme 16** below. The proton from the free NH forms part of this mesomeric effect which is one of the reasons for the *Boc*-protecting group to be removed before conducting the formylation reaction.



Scheme 16. The indolyl anion, the mesomeric effect.

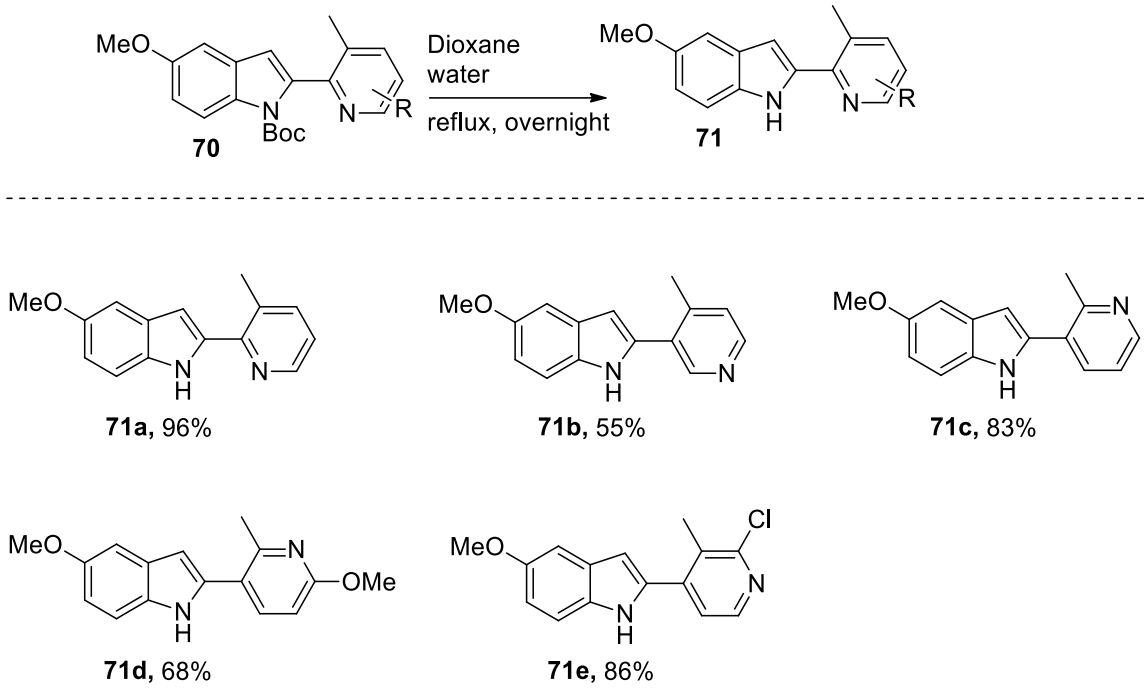
Different reaction conditions from literature[35,36] were used to remove the *Boc*-protecting group but most of these conditions failed to give us the desired compound. For example, the *N-Boc* group was not cleaved in basic conditions such as K_2CO_3 in methanol/water as reported in literature[35] or acidic conditions were trifluoroacetic acid was used[36] (**Scheme 17**).



Scheme 17. Boc deprotection using basic and acidic reaction conditions.

After these failed attempts, thermolysis reaction conditions were used. This procedure used water as solvent which is one of the greenest solvents. As a result, compounds **70a-e** were dissolved in dioxane: water (1:9) mixture and refluxed to give compounds **71a-e**, as shown in **Scheme 18**. Some substrates reacted slower (overnight) than others (3-4 hours). TLC plate was used to follow the reaction progress before quenching with water and work-up. NMR spectroscopy was then used to confirm the identity of the products. For example, the ^{1}H NMR spectrum we obtained for the sample showed a disappearance of the peak at 1.26 ppm on the 5-methoxy-2-(2-methylpyridin-3-yl)-1*H*-indole **71c**. In addition, a new broad peak at 8.61 ppm confirmed the existence of a new NH bond. The disappearance of the peaks at 27.6, 83.4 and 148.7 ppm as seen in the ^{13}C NMR spectrum can be attributed to the absence of the *tert*-butoxycarbonyl residue in the product. The HRMS data of the biarylindole **71c** was measured and found to have a mass of 239.1155 amu.,

which corresponds to 239.1179 amu [M+H$^+$] as calculated. This confirmed that the *Boc* group was no longer appended to this compound. Similar data was obtained for substrates **71a-b**,**d-e**.

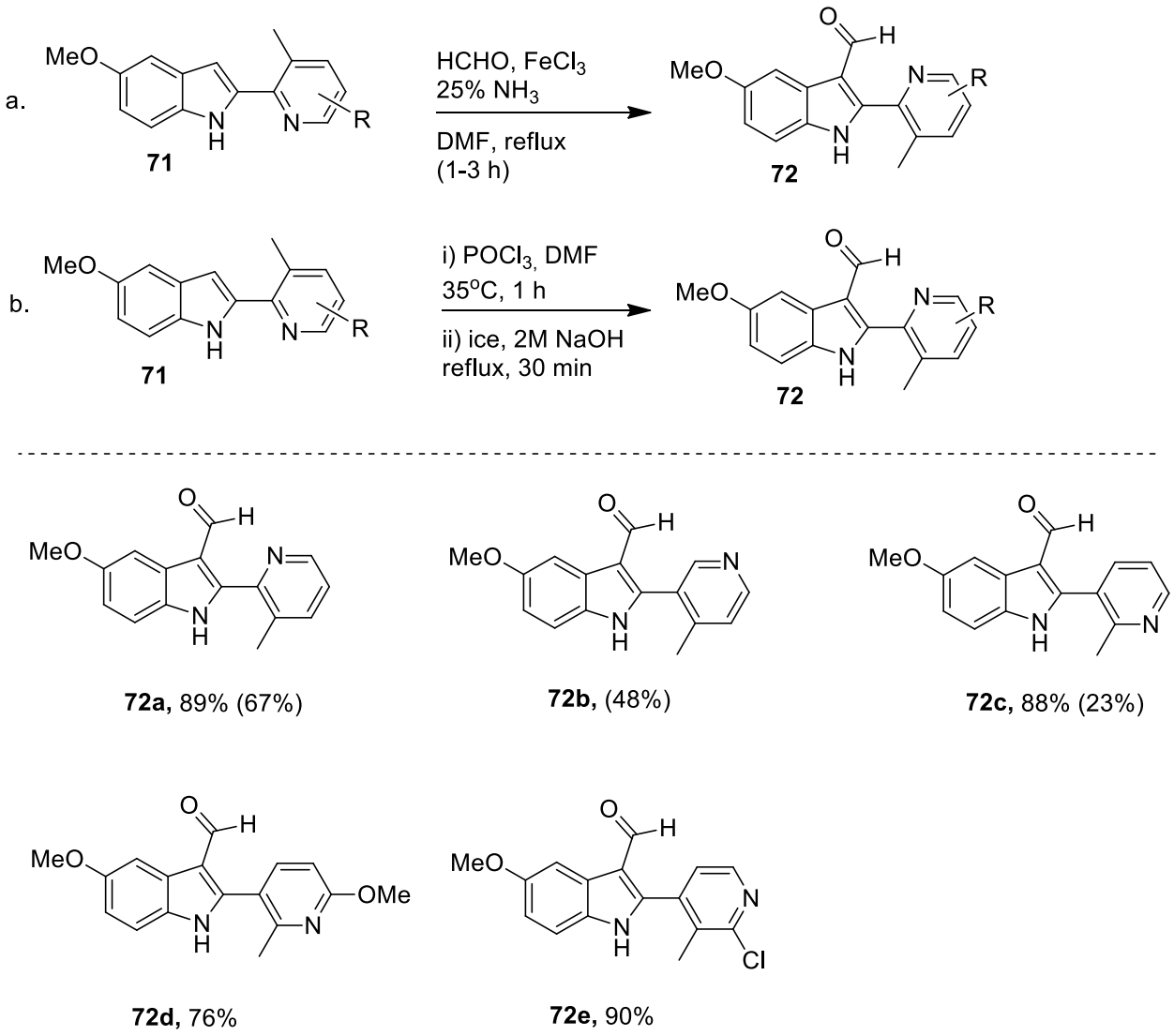


Scheme 18. *Boc* protecting group removal reaction conditions.

2.4 Formylation reactions

With the deprotected biarylindoles in hand, we proceeded to install the formyl group at position 3 of the aryl indoles **71a-e** by reaction with paraformaldehyde and ammonia solution in the presence of iron(III) chloride to give aldehyde **72a-c** as shown in **Scheme 19a**. An aldehyde proton peak usually appears in the 9-10 ppm range in the ^{1}H NMR spectra. For example, using 5-methoxy-2-(4-methylpyridin-2-yl)-1*H*-indole-3-carbaldehyde **72b**, the existence of the peak at 9.67 ppm with the expected number of aromatic protons in the ^{1}H NMR spectrum confirmed that the formyl group was successfully installed. The two doublets with *J* coupling constants of 2.0 and 8.8 Hz and a doublet of doublet with *J* coupling of 8.8 and 2.2 correspond to the anisole ring protons and the disappearance of the aromatic singlet at 6.45 ppm which corresponds to position 3 of the starting biarylindole **71b** ruled out the possibility of the formyl group being installed on the anisole fragment. The ^{13}C NMR spectrum showed a peak at 185.8 ppm, characteristic of a formyl carbonyl

group, in addition to the biarylindole peaks at 157.6-103.2 ppm (aromatic), 55.9 ppm (methoxy) and 23.2 ppm (methyl group). Some of the yields were disappointingly low (ranging from 23-67%). The low yields can possibly be the result of co-ordination between iron metal and the nitrogen atom of the indole fragment. Considering that we still had three or four steps to conduct before reaching our final target compound; we decided to try a different formylation procedure that could give improved yields.



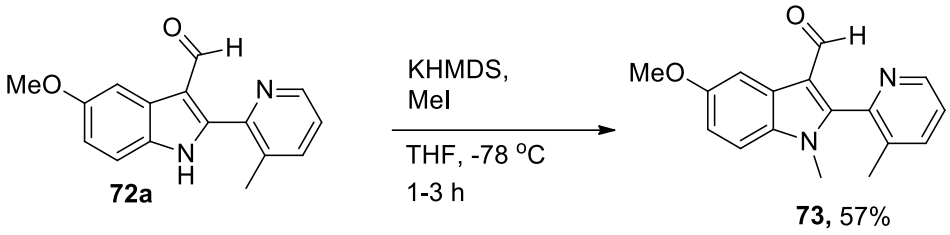
Scheme 19. Formylation of biaryl indoles *via* a) $FeCl_3$-mediated reaction, b) Vilsmeier-Haack reaction. The yields for the $FeCl_3$-mediated formylation reaction are shown in parentheses.

To improve the yields of our aldehydes we applied the Vilsmeier–Haack reaction, which has been used successfully in the Organic Laboratories here at Wits University[18]. Following the procedure reported in our group[19], the biarylindoles were formylated using DMF in the presence of phosphorous oxychloride. The reaction conditions in **Scheme 19b** were used to synthesize compound **72d** and **72e** which were obtained in very good yields of 76 and 90% respectively. Using the same conditions (**Scheme 19b**), yields for compounds **72a** and **72c** were also improved to 89 and 88%, respectively. The conversion of **71b** to **72b** *via* the Vilsmeier-Haack formylation was not successful. We isolated a compound whose identity we could not ascertain (i.e. some of the expected peaks for **72b** are missing). Some of the notable peaks that were missing include the methyl group from the pyridine residue. The CH_3 peak which is expected around 2.5 ppm in ^1H and 57.0 ppm in the ^{13}C NMR was not detected. In summary, we had to settle for the 48% yield we obtained when using the $FeCl_3$ method for this substrate **72b**.

2.5 *N*-Alkylation reactions

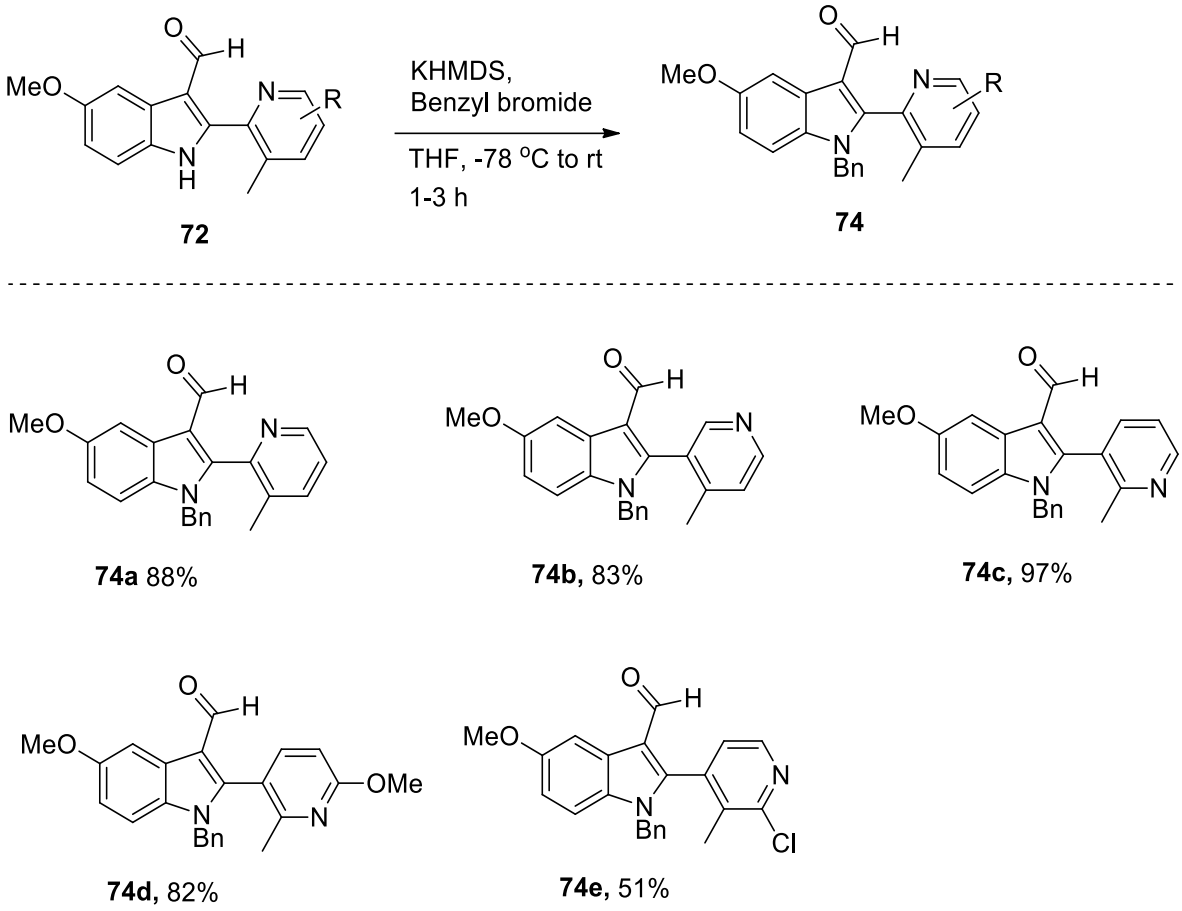
The step before the intramolecular cyclization in the synthesis of pyrido fused carbazoles was the protection once again of the NH of the indole moiety. Abstraction of the hydrogen atom from the N-H bond of indoles can occur in presence of concentrated aqueous alkali or in systems containing stronger bases[37]. Potassium *tert*-butoxide is a strong base which could remove the proton from the NH of the indole nucleus leading to side reactions occurring on the NH position instead of the desired positions. Indole structure has 4 reactive sites or positions namely C3 position, the π C2-C3 bond, the C2-N σ bond and the indole nitrogen atom 1[38]. Three of these sites are already occupied leaving us with the indole nitrogen position. Therefore, as the nitrogen attached to the hydrogen of the indole can undergo reaction protection of the NH is required to prevent a reaction from occurring at that position. This was achieved by reacting compound **72a** with potassium hexamethyldisilazide solution and methyl iodide under the conditions stated in **Scheme 20**. The desired methylated product **73** was obtained in a yield of 57%. The disappearance of the broad peak at 9.50 ppm in the ^1H NMR spectrum and an extra methyl peak at 3.57 ppm along with the expected aromatic protons and aldehyde confirmed that the protecting group was installed. A new peak which appeared at 33.2 ppm was seen in the ^{13}C NMR spectrum. The HRMS measured for

73 was 281.1307 amu which corresponded to $[M + H]^+$ calculated value of 281.1285 a.u. for indole derivative **73**.



Scheme 20. *N*-Methylation of biaryl indole **72a**

As we wished to remove the *N*-protecting group after performing the key photochemical induced ring closure reaction, a *N*-benzyl group was also considered instead of methyl group as the NH protecting group since *N*-methyl group is not easily removed. Compounds **72a-e** were reacted with potassium hexamethyldisilizide solution and benzyl bromide-similar conditions as the example above, with methyl iodide replaced with benzyl bromide (**Scheme 21**) to afford indole **74a-e**. The aromatic peaks appearing between 7.07 - 7.20 ppm and doublets integrating for the CH_2 of the benzyl substituent at 5.10 and 4.96 ppm (J = 16.2 Hz) were seen in the ^{1}H NMR spectrum for compound **74c**. In the ^{13}C NMR spectrum, a peak at 47.8 (CH_2) and the extra aromatic peaks confirmed the successful installation of the *N*-benzyl substituent onto indoles **74a-e**.

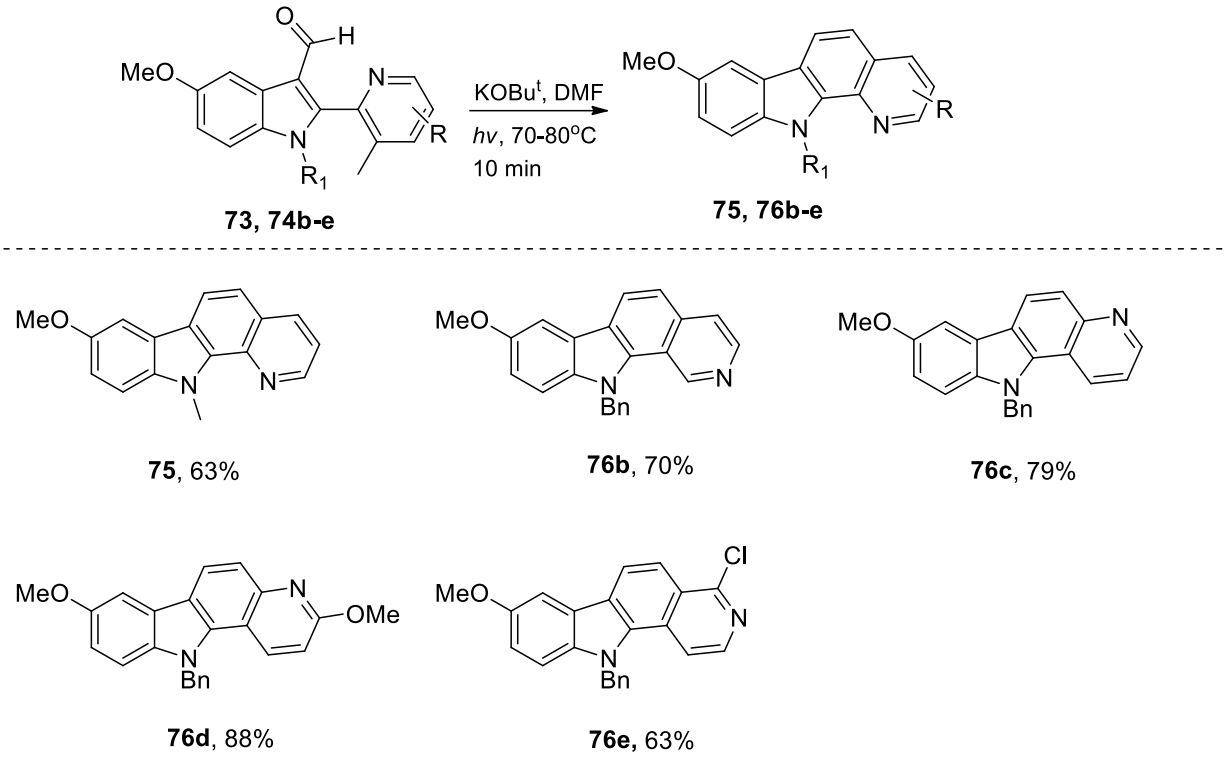


Scheme 21. Benzylation of carbaldehyde compounds.

2.6 Light-mediated intramolecular cyclization

Having obtained compounds **73** and **74a-e**, the stage was set for the light-assisted, base-mediated intramolecular cyclization reaction, to form the desired pyrido fused 8-methoxy-carbazoles. Indeed, treatment of methylated indole **73** or benzylated indoles **74b-e** in DMF with potassium *tert*-butoxide and irradiation from a medium-pressure mercury lamp (450 W) as shown in **Scheme 22** resulted in the formation of carbazoles **75** and **76b-e** in good yields. Evidence for the formation of the desired products was obtained from the NMR spectra. For example, the ^{1}H NMR spectrum for compound **76c** shows that the aldehyde and methyl group from the carbaldehyde have been replaced by two doublets at 8.37 and 7.94 ppm (J = 8.7 Hz) which can be assigned to the 2 new aromatic protons resulting from the cyclization reaction. The HRMS expected for compound **76c**

was 339.1492 and 339.1506 amu was found which corresponds to $[M + H]^+$. Similar changes were also observed for other substrates, thus confirming the successful formation of the pyrido fused 8-methoxy-carbazoles **75** and **76b-e**.

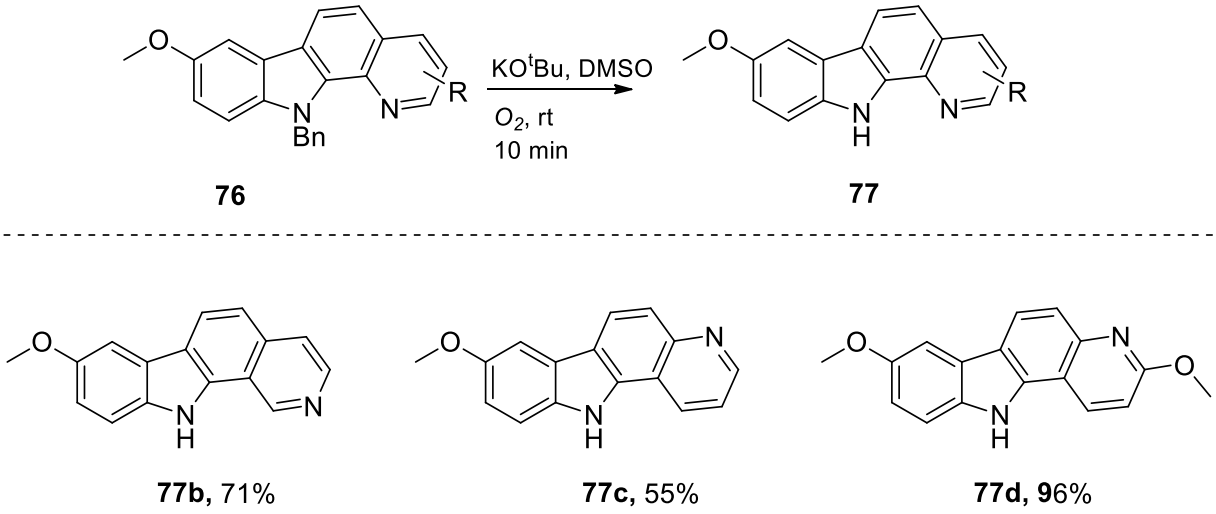


Scheme 22. Reaction conditions for cyclization reaction.

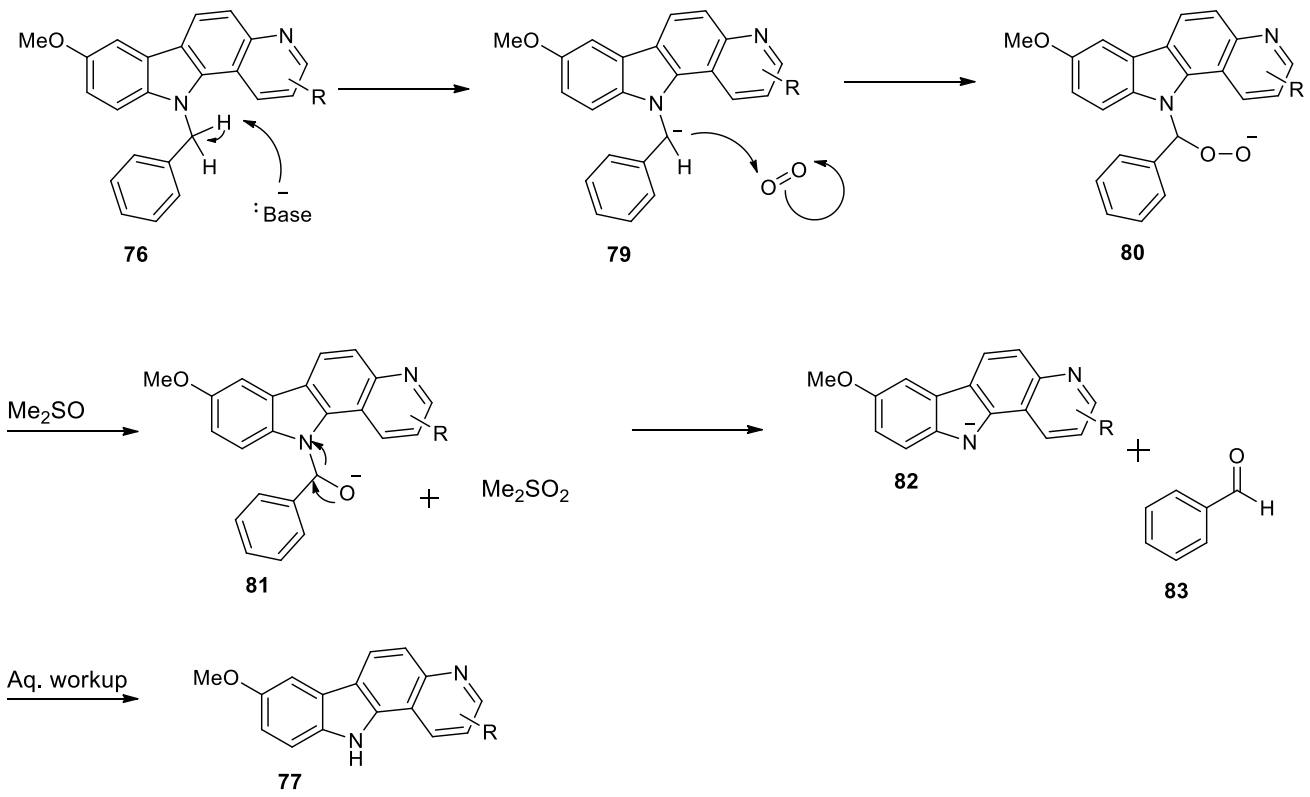
2.7 Debenzylation reaction

After synthesizing our desired pyrido fused 8-methoxy-carbazoles **76b-e**, the benzyl group from some of the carbazoles was removed. The removal of the benzyl protecting group of **76b-e** using the reaction conditions provided in **Scheme 23** below gave debenzylated pyrido fused 8-methoxy-carbazoles **77b-d**. Treatment of **76b-d** in DMSO with potassium *tert*-butoxide and bubbling the solution with oxygen gas led to the desired debenzylated carbazoles. The disappearance of the two protons (CH_2) of the benzyl substituent at 5.1 ppm, the aromatic protons (7.0-7.75 ppm) and the appearance of NH peak at around 9.00 ppm (12.01 ppm for **77d**) in the ^{1}H NMR spectrum confirmed the successful removal of the benzyl group from our pyrido-containing carbazoles.

This conclusion was supported by the disappearance of the peaks at 49.5 ppm (CH_2) and 125.8-132.9 ppm (phenyl carbons) in the ^{13}C NMR spectra. The mechanism for the removal of this protecting group is shown in **Scheme 24**. The first step of the mechanism involves potassium *tert*-butoxide deprotonation of the protecting group forming a benzylic anion **79**. While bubbling oxygen in the reaction mixture, the newly formed benzylic anion will react with the oxygen. The intermediate peroxy anion **80** is then reduced by DMSO to form anion **81** which results in a reaction to afford benzaldehyde **83** and the desired deprotected carbazole **82**. Quenching the reaction with saturated ammonium chloride then gave the pyrido-fused carbazole **77** which was supported by the NMR data as stated above.



Scheme 23. Debenzylation reaction condition of carbazoles.



Scheme 24: Reaction mechanism for debenzylation of carbazoles.

Chapter 3

3. Conclusion and Future Work

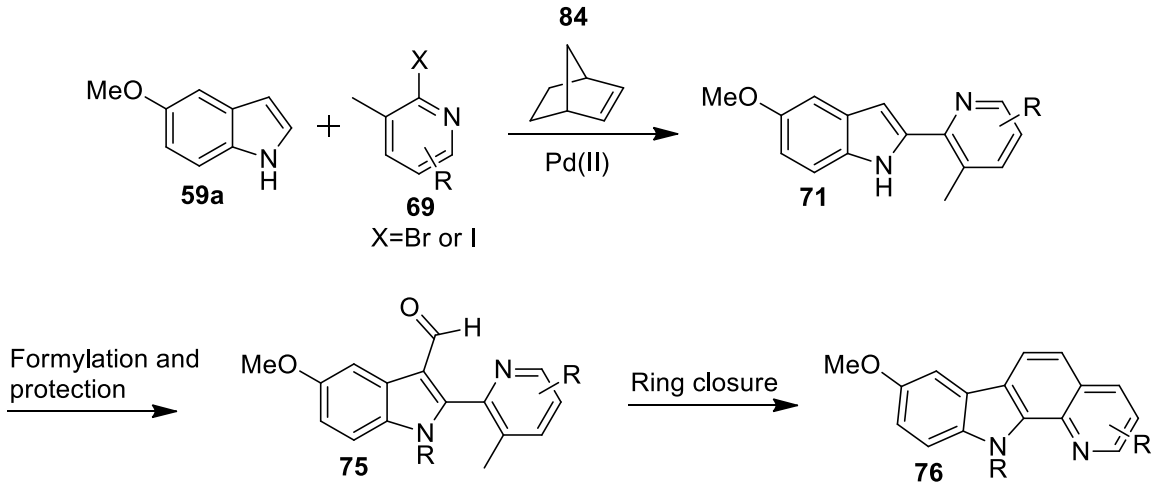
3.1 Synthesis of carbazoles via boronic acid route

In summary, we were able to synthesize the pyrido fused carbazoles **76a-e** while changing the position of the nitrogen atom following the procedure reported by de Koning and co-workers[19]. The synthesis of pyrido fused carbazoles achieved in seven steps (excluding debenzaylation) from the 5-methoxyindole **59a** using the light-assisted, base-mediated reaction as the key step in the synthesis of these compounds. To the best of our knowledge, the synthesis of pyrido-fused carbazoles with the nitrogen atom at different positions of the pyrido moiety *via* the formation of a new bond C3-C4 has not been reported before. Similar compounds have been reported[39,40]; however, the synthesis of these compounds utilized different routes, formation of new C-C bonds. Lescot. *et al*[391] reported the synthesis *via* formation of C1-C1a bond while Pelaprat. *et al.*[40] reported the synthesis with formation of bond C4-C4a. Carbazole with the nitrogen atom at position 1 (figure 2) of the pyrido fused carbazoles is the only carbazole of this nature that is reported in literature by de Koning and co-workers[18]. We have managed to synthesize carbazoles with the nitrogen atom at position 2, 3 and 4 of the pyrido moiety as shown in compound **5c,** figure 2 (**Section 1.3, page 3**).

With different substituents in the pyrido moiety and the oxygen containing functional group at position 8, these compounds might display anti-cancer properties. As it has been reported before that compounds bearing an oxygen functional group or methoxy *para* to the carbazole nitrogen atom under physiological environment suffer *O*-demethylation followed by oxidation furnishing the highly reactive imonocyclohexa-2,5-dienone fragment those attacks biomolecules leading to cell death.[24] For future work, these compounds will be synthesized on a larger scale and will be sent to Wits Medical School for testing against different cancer cell lines.

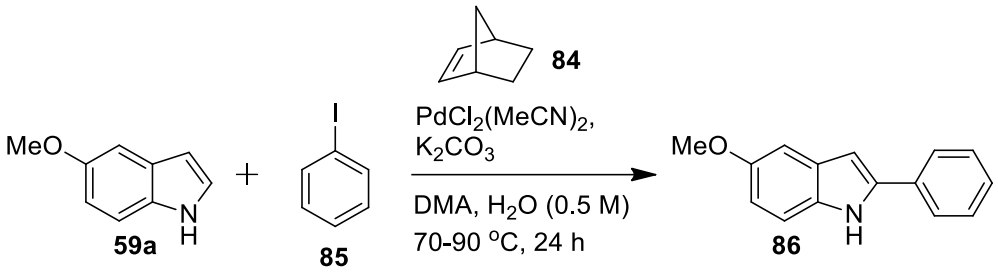
3.2 Future work

The project will benefit immensely from a fewer number of steps required to get to the final product. The current route to the final, debenzylated pyrido carbazoles **77** require eight steps, four of which are protection/deprotection steps. We think this could be achieved if we make use of C-H activation, to install the requisite pyridyl substituent at position 2 of an unsubstituted 5-methoxy-indole **59a**. An obvious choice is the Catellani reaction, which has been shown to couple indoles with iodobenzene, among other substituents[37-38]. Thus 5-methoxy-indole **59a** could be directly coupled with suitably substituted pyridine analogues **69** to generate biaryl indole **71** (**Scheme 25**). Formylation and protection could lead to compound **75**, which could be cyclized to **76** using the de Koning method. Debenzylation will give the unprotected 8-methoxypyrido-carbazoles **77**.



Scheme 25: Proposed scheme using the Catellani reaction route

We have undertaken some preliminary studies to work out the feasibility of the proposed route. Using the reaction conditions that were reported in literature[42] by Bach and co-workers, we set out to test this reaction. Using iodobenzene **85** as the aryl halide, 5-methoxy indole **59a**, DMA/H_2O as the solvent, $PdCl_2(MeCN)_2$ as the catalyst and norbornene **84** as co-catalysts, the reaction gave us a product **86** with a yield of 51%.



Scheme 26. Test reaction conditions.

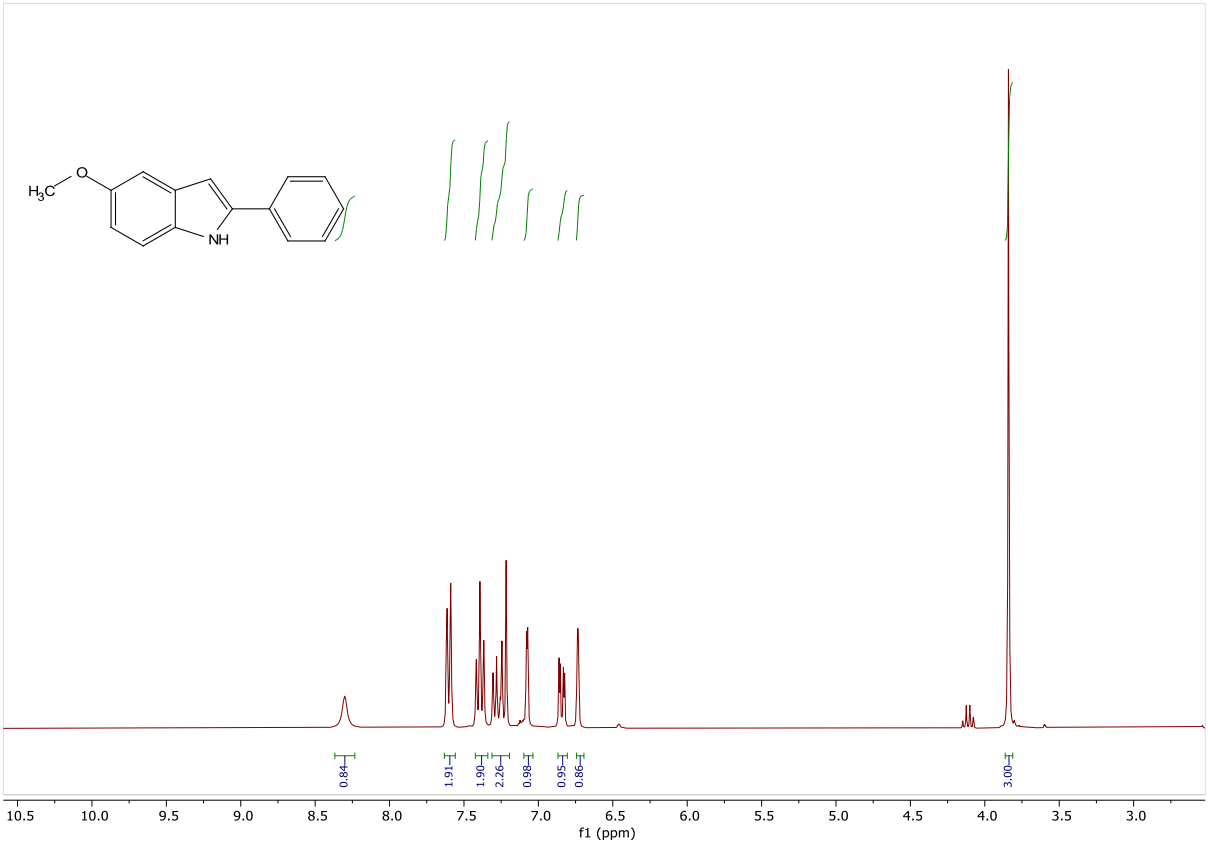
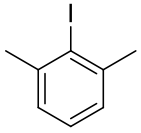
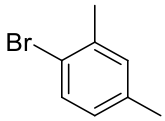
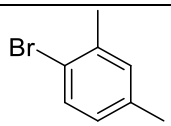
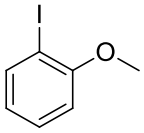
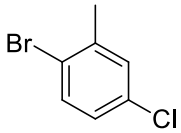
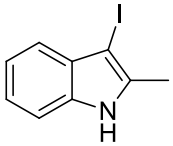
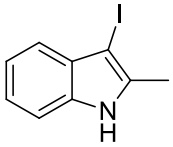
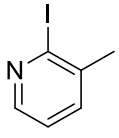
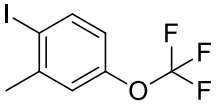


Fig 9. ^{1}H NMR spectrum of 5-methoxy-2-phenyl-1*H*-indole synthesized using Catellani reaction.

Examination of the ^{1}H NMR spectrum indicated that there were ten aromatic protons between 6.75 and 8.50 ppm which corresponds to the number of expected protons in addition to the characteristic methoxy peak at around 3.85 ppm. This meant that the reaction had worked. A methyl group next the newly constructed C-C bond is required for our final step which is the light-assisted, base-mediated cyclization reaction, therefore we could attempt the next reaction with 5-methoxy-2-phenyl-1*H*-indole **87** synthesized as it lacked the methyl group which is a requirement. Using

different substrates which have methyl group *ortho* to the halide, more test reactions were performed. Several substrates were used as shown in table 1.

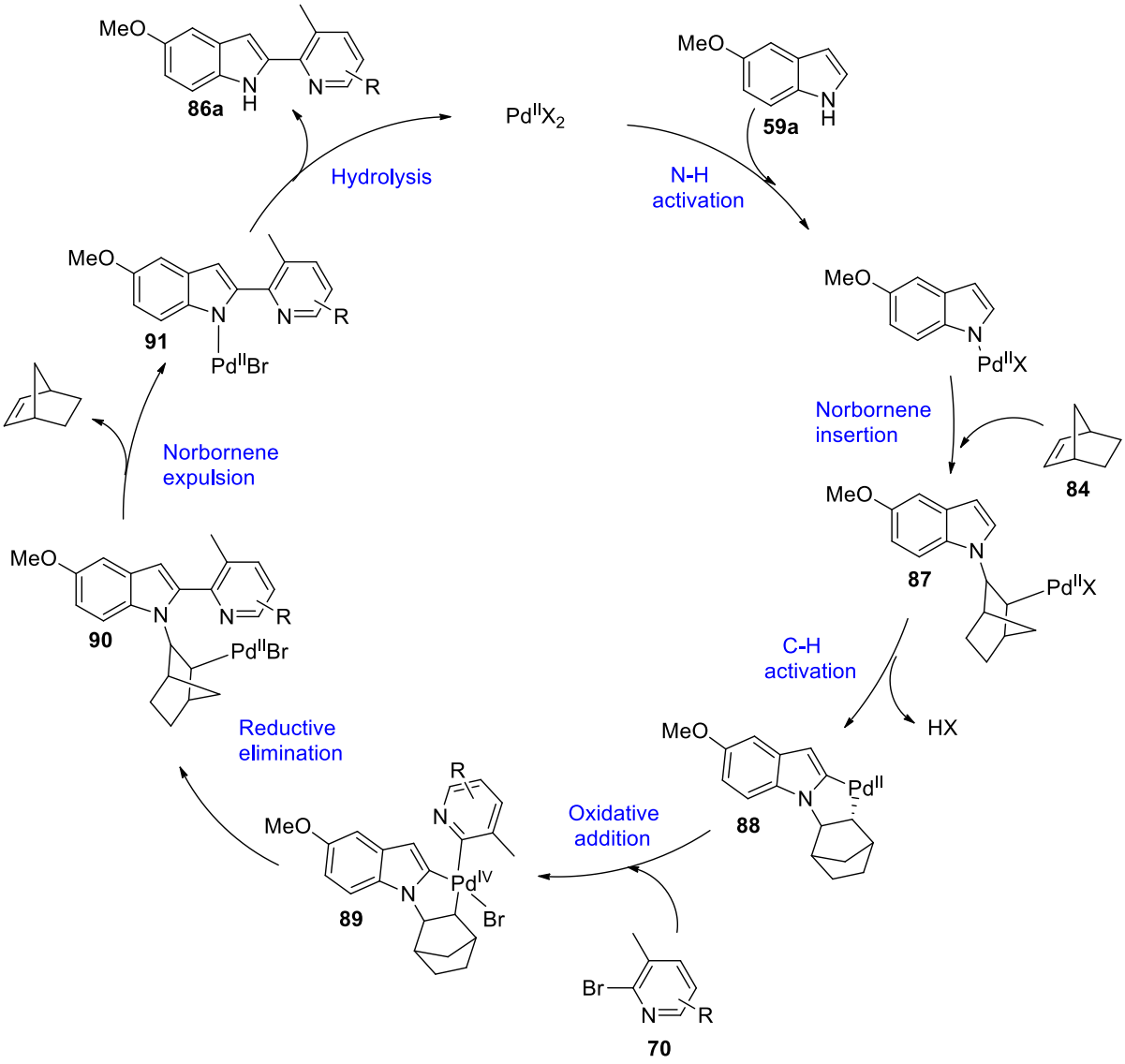
Table 1: Reaction conditions and substrates used in the Catellani reaction.

RUN	X-R (X= Br or I)	CONDITIONS	YIELD
1		24-48 h, 120-130 °C, DMA, H_2O (0.5 M)	-
2		24 h, 90 °C, DMA, H_2O (0.5 M)	-
3		24 h, 120-130 °C, DMA, H_2O (0.5 M)	8%
4		48 h, 120-130 °C, DMA and H_2O	-
5		24 h, 120-130 °C, DMA, H_2O	15%
6		24 h, 90-130 °C, DMA	-
7		24 h, 120-130 °C, DMA, H_2O (0.5 M)	-
8		24 h, 120-130 °C, DMA, H_2O (0.5 M)	-
9		24 h, 120-130 °C, DMA, H_2O (0.5 M)	-

Several reaction conditions (varying time, temperature and solvent mixtures) were tested in order to establish if the reaction works and if it does, to improve the reaction yields. Thus, 2-iodo-1,3-dimethylbenzene was used as the starting material under the same conditions as shown on **Scheme 26.** The reaction did not work. We speculated that steric hindrance could be the reason for the failure of the reaction. A substrate containing one methyl group *ortho* to a chlorine atom was then used. Using 1-bromo-2,4-dimethylbenzene, the reaction still did not work. Increasing the temperature from 90 °C to 120-130 °C while keeping everything else the same led to a low yielding product (8%) which was a great improvement. Encouraged by these results, more substrates were used. Unfortunately, most of the reactions did not work, only starting materials were recovered. For the reactions that worked, the yields were too low for us to move to the next step. From literature, iodobenzene was the only aryl halide reported. Alkyl halides were mostly reported[37] and the reactions were successful.

Bach and co-workers[42] speculated that the reaction starts from *N*-palladation where aminopalladation intermediate **87** is formed from the indole **59a**, norbornene **84** and palladium catalsyt. A subsequent C-H activation step then follows where the palladacycle **88** is delivered. Oxidative addition into the alkyl bromide then occurs and it also the rate determining step which upon reductive elimination and norbornene expulsion leads to *N*-palladaindole **91**. Protonation reaction then furnishes the final product and regenerates the Pd(II) species[42], this is seen in **Scheme 27.**

In summary, we were not able to synthesize the desired carbazole compounds using the Catellani reaction conditions reported. Catellani route is a better choice or route since as it is two steps lesser than the Suzuki coupling route. The first step being the direct C-H activation and C-C bond forming while on the other route, *Boc* protection followed by boronic acid synthesis is required before you can form the new C-C bond using Suzuki coupling reaction conditions. In future, more research or investigation on the Catellani reaction should be performed and different palladium containing catalysts should be investigated.



Scheme 27. Catalytic cycle of the Catellani reaction on indoles.

Chapter 4

4. Experimental

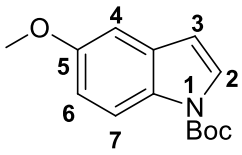
4.1 General experimental procedures

The reagents were purchased from ACE Chemicals or Sigma-Aldrich Merck and were used without further purification. All solvents except 1,2-dimethoxyethane (DME) and *N*,*N*-dimethylformamide (DMF) were distilled under nitrogen atmosphere prior to use. Purification of reaction products was achieved by flash column chromatography on EM Reagent silica gel. Thin layer chromatography was carried out on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was achieved with UV light, dinitrophenylhydrazine (DNP) and Curcumin stains. NMR spectra were recorded on a Bruker Avance-300 and Bruker Avance-400 and were measured at 300 or 400 MHz for ^{1}H NMR and 101 MHz or 75 MHz for ^{13}C NMR. Spectra were recorded using $CDCl_3$ or d_6-DMSO as solvents and reported in ppm using tetramethylsilane (TMS) as an internal standard.

4.2 Synthesis

4.2.1 *Boc* protected of 5-methoxy-indole

tert-Butyl 5-methoxy-1*H*-indole-1-carboxylate 59a

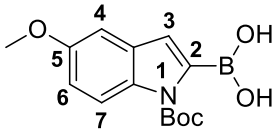


A round bottom flask equipped with a stirrer bar was charged with 5-methoxyindole (2.00 g, 13.6 mmol) dissolved in THF and treated with di-*tert*-butyl dicarbonate (3.26 g, 14.9 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (16.62 mg, 0.07 mmol, 0.01 equiv.). The contents of the flask were stirred at room temperature under an argon atmosphere overnight. Upon completion of the reaction, the solvent was removed under reduced pressure and purification of the crude residue was done using silica column chromatography (5-20% ethyl acetate/hexane mixtures). The desired product was obtained as a clear oil that crystallized on standing to a white solid (1.76-3.03 g, 96-99%), identical to what is reported in the literature.[1]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.0 Hz, 1H, H-7), 7.59 (d, *J* = 3.7 Hz, 1H, H-2), 7.05 (d, *J* = 2.5 Hz, 1H, H-4), 6.95 (dd, *J* = 9.0, 2.6 Hz, 1H, H-6), 6.52 (d, *J* = 3.7 Hz, 1H, H-3), 3.87 (s, 3H, OCH_3), 1.69 (s, 9H, $CO_2C(CH_3)_3$. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 155.8, 149.7, 131.4, 129.9, 126.5, 115.8, 113.0, 107.1, 103.4, 83.5, 55.7, 28.2. **Mp** 77-78 °C. lit.,[8] 76 °C].

4.2.2 Preparation of *N-boc*-indole-2-boronic acid

(1-(*tert*-Butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid 60a



METHOD A

In a 100 ml two-necked round bottomed flask, 2,2,6,6-tetramethylpiperidine (0.87 mL, 5.15 mmol, 1.1 equiv.) in dry THF (10 mL) was cooled to -78 °C under nitrogen atmosphere and treated with *n*-BuLi (5.32 ml, 5.85 mmol, 1.25 equiv.). The mixture was stirred at -78 °C for 10 min, then warmed to 0 °C within 30 min. The mixture was cooled to -78 °C again and the lithium tetramethylpiperidine (LiTMP) generated was treated with *tert*-butylindole-1-carboxylate-5-methoxy (1.16 g, 4.69 mmol, 1.0 equiv.) dissolved in dry THF. The contents of the flask were stirred at -78 °C for 80 min. Freshly distilled triisopropyl borate (1.62 mL, 7.02 mmol, 1.5 equiv.) in dry THF was then added and the reaction mixture was stirred for 30 min before being warmed to room temperature. Upon completion, the reaction was quenched with water and acidified with aqueous 10% hydrochloric acid solution. The product **59a** was extracted with ethyl acetate and dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the title compound.

METHOD B

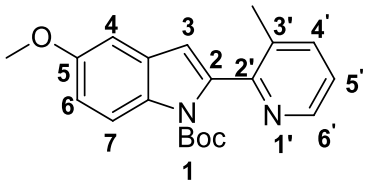
In a round bottomed flask, diisopropymamine (0.22 mL, 1.57 mmol, 1.21 equiv.) was dissolved in THF and the resulting solution was cooled to -78 °C. *n*-BuLi solution (1.4 M in THF) (1.03 mL, 1.44 mmol, 1.1 equiv) was then added, and the mixture was stirred at -78 °C for 15-30 min. To the resulting LDA, *tert*-butyl 5-methoxy-1*H*-indole-1-carboxylate (0.20 g, 0.81 mmol, 1.0 equiv.)

dissolved in dry THF was added using a dropping funnel at -78 °C. Triisopropyl borate (1.21 mmol, 0.35 mL, 1.5 equiv.) dissolved in dry THF was also added and the reaction mixture was left to stir for 60 min before being warmed to room temperature. Upon completion, the reaction was quenched with water, acidified and the product **69** was extracted with ethyl acetate.

4.2.3General procedure for Suzuki coupling reactions

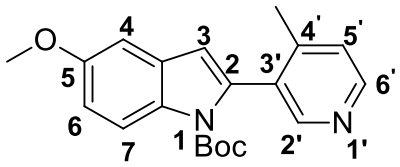
To a deoxygenated solution of (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid (1.0 equiv.) and aryl halide/pyridine (0.7 equiv.) in DME was added [$Pd(PPh_3)_4$[(10 mol%) under a nitrogen atmosphere with stirring. Deoxygenated aqueous sodium carbonate solution (2 M, 2.8 equiv.) or aqueous potassium phosphate (2 M, 2.0 equiv.) was added and a condenser was fitted onto the flask. The mixture was heated under reflux overnight. TLC was used to monitor the progress of the reaction. Upon completion, the mixture was cooled to room temperature and quenched with water. The product was extracted with ethyl acetate (3 × 20 mL) and the organic layers were combined and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was then purified using column chromatography (using 10-50% ethyl acetate/hexane mixtures).

***tert*-Butyl 5-methoxy-2-(3-methylpyridin-2-yl)-1*H*-indole-1-carboxylate 70a**



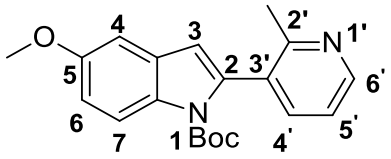
Prepared from (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid (1.5 g, 5.15 mmol), 2-bromo-3-methylpyridine (0.59 g, 3.41 mmol, 0.38 mL), [$Pd(PPh_3)_4$] (0.25 g, 0.32 mmol) and K_3PO_4 (2 M, 6.87 mL), a light yellow oil was obtained as the title compound, yield (1.06 g, 91%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.49 (dd, *J* = 4.8 Hz, 1.6, 1H, H-6'), 8.15 (d, *J* = 9.0 Hz, 1H, H-7), 7.55 (dd, *J* = 7.6 Hz, 0.8, 1H, H-4'), 7.22 (dd, *J* = 7.7 Hz, 4.8, 1H, H-5'), 7.04 (d, *J* = 2.5 Hz, 1H, H-4), 6.97 (dd, *J* = 9.0, 2.6 Hz, 1H, H-6), 6.54 (s, 1H, H-3), 3.86 (s, 3H, OCH_3), 2.24 (s, 3H, $ArCH_3$), 1.25 (s, 9H, $COC(CH_3)_3$). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 156.0, 153.5, 149.7, 146.2, 138.3, 137.3, 132.4, 131.4, 130.0, 122.8, 116.3, 113.4, 109.9, 103.2, 83.0, 55.7, 27.6, 19.0. **HRMS** (ESI+): calcd. for $C_{20}H_{22}N_2O_3$ $[M + H]^+$ 339.1630; found $[M + H]^+$ 339.1624.

***tert*-Butyl 5-methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole-1-carboxylate 70b**



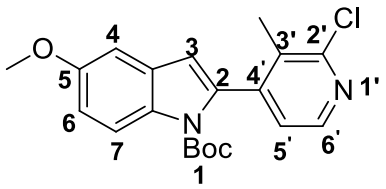
Prepared from (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid (1.00 g, 3.43 mmol), 3-bromo-4-methylpyridine (0.25 mL, 2.29 mmol), [$Pd(PPh_3)_4$] (10% mol) and K_3PO_4 (2 M, 3 mL). The title compound was obtained as a light-yellow oil, yield (1.13 g, 83%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.50 (d, *J* = 4.9 Hz, 1H, H-6'), 8.47 (s, 1H, H-2'), 8.17 (d, *J* = 9.0 Hz, 1H, H-7), 7.19 (d, *J* = 5.0 Hz, 1H, H-5'), 7.05 (d, *J* = 2.5 Hz, 1H, H-4), 6.98 (dd, *J* = 9.1, 2.6 Hz, 1H, H-6), 6.45 (s, 1H, H-3), 3.88 (s, 3H, OCH_3), 2.21 (s, 3H, $ArCH_3$), 1.27 (s, 9H, $COC(CH_3)_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 156.1, 149.7, 149.4, 149.0, 146.6, 135.9, 131.9, 131.7, 129.8, 124.5, 116.6, 113.5, 110.7, 103.0, 83.4, 55.7, 27.6, 19.6. **HRMS** (ESI+): calcd. for $C_{20}H_{22}N_2O_3$ $[M + H]^+$ 339.1630; found $[M + H]^+$ 339.1707.

***tert*-Butyl 5-methoxy-2-(2-methylpyridin-3-yl)-1*H*-indole-1-carboxylate 70c**



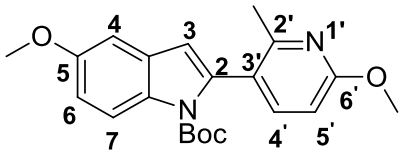
Prepared from (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid (1.00 g, 3.43 mmol), 3-bromo-2-methylpyridine (0.25 mL, 2.29 mmol), [$Pd(PPh_3)_4$] (0.23 mmol, 0.26 mg) and K_3PO_4 (2 M, 3 mL). The expected product was obtained as a yellow oil, yield (1.06 g, 78%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.52 (dd, *J* = 5.0 Hz, 1.8, 1H, H-6'), 8.19 (d, *J* = 9.0 Hz, 1H, H-7), 7.56 (dd, *J* = 7.6 Hz, 1.8, 1H, H-4'), 7.19 (dd, *J* = 7.6 Hz, 4.9, 1H, H-5'), 7.04 (d, *J* = 2.6 Hz, 1H, H-4), 6.98 (dd, *J* = 9.1, 2.6 Hz, 1H, H-6), 6.43 (s, 1H, H-3), 3.87 (s, 3H, OCH_3), 2.42 (s, 3H, $ArCH_3$), 1.26 (s, 9H, $COC(CH_3)_3$)**. ^{13}C NMR (101 MHz, $CDCl_3$)** δ 157.5, 156.1, 149.7, 148.1, 137.5, 137.0, 131.5, 131.0, 129.9, 120.5, 116.5, 113.4, 110.2, 103.0, 83.3, 55.7, 27.6, 22.9. **HRMS (ESI+):** calcd. for $C_{20}H_{22}N_2O_3$ $[M + H]^+$ 339.1630; found $[M + H]^+$ 339.1708.

***tert*-Butyl 2-(2-chloro-3-methylpyridin-4-yl)-5-methoxy-1*H*-indole-1-carboxylate 70e**



Prepared from (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid (0.66 g, 2.25 mmol), 4-bromo-2-chloro-3-methylpyride (0.38 g, 1.50 mmol), [$Pd(PPh_3)_4$] (0.17 g, 0.15 mmol) and Na_2CO_3 (2 M, 3.0 mL), a brown solid (0.28 g, 47%) was obtained. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.20 (d, *J* = 4.8 Hz, 1H, H-6'), 8.10 (d, *J* = 9.0 Hz, 1H, H-7), 7.09 (d, *J* = 4.6 Hz, 1H, H-5'), 6.97 (d, *J* = 2.6 Hz, 1H, H-4), 6.93 (dd, *J* = 9.0, 2.6 Hz, 1H, H-6), 6.38 (s, 1H, H-3), 3.80 (s, 3H, OCH_3), 2.17 (s, 3H, $ArCH_3$), 1.22 (s, 9H, $COC(CH_3)_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 156.3, 151.8, 149.3, 146.2, 136.0, 132.0, 131.5, 129.6, 123.6, 116.6, 114.0, 110.4, 103.1, 84.0, 77.2, 55.7, 27.5, 17.2. **Mp** 130-132 °C. **HRMS** (ESI+): calcd. for $C_{20}H_{21}ClN_2O_3$ $[M + H]^+$ 373.1241; found $[M + H]^+$ 373.1341.

***tert*-Butyl 5-methoxy-2-(6-methoxy-2-methylpyridin-3-yl)-1*H*-indole-1-carboxylate 70d**

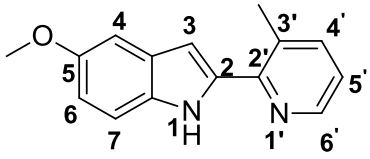


Prepared from (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid (1.00 g, 3.44 mmol), 3-bromo-6-methoxy-3-methylpyridine (0.20 mL, 2.06 mmol), [$Pd(PPh_3)_4$] (0.24 g, 0.21 mmol) and Na_2CO_3 (2M, 6.0 mL). The product was obtained as a yellow oil, yield (0.80 g, 87%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.08 (d, *J* = 9.1 Hz, 1H, H-7), 7.35 (d, *J* = 8.3 Hz, 1H, H-4'), 6.95 (d, *J* = 2.6 Hz, 1H, H-4), 6.88 (dd, *J* = 9.1, 2.6 Hz, 1H, H-6), 6.54 (d, *J* = 8.3 Hz, 1H, H-5'), 6.31 (s, 1H, H-3), 3.88 (s, 3H, NC-OCH_3), 3.80 (s, 3H, OCH_3), 2.24 (s, 3H, $ArCH_3$), 1.23 (s, 9H, $COC(CH_3)_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.1, 156.0, 155.0, 149.9, 140.0, 138.0, 131.5, 129.9, 123.3, 116.5, 113.0, 110.1, 106.5, 102.9, 83.1, 55.7, 53.6, 27.7, 22.7. **HRMS** (ESI+): calcd. for $C_{21}H_{24}N_2O_4$ $[M + H]^+$ 369.1736; found $[M + H]^+$ 369.1986.

4.2.4 Deprotection of biaryl indole derivatives - *Boc* group removal

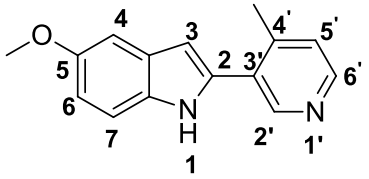
tert-Butyl 5-methoxy-2-(3-methylpyridin-2-yl)-1*H*-indole-1-carboxylate (1.0 equiv.) was dissolved in dioxane (1 ml) and water (19 ml), a condenser was fitted to the flask and the mixture was heated under reflux overnight. Upon completion of the reaction, the product was extracted with ethyl acetate and purified using column chromatography (5%-50% ethyl acetate/hexane mixtures).

5-Methoxy-2-(3-methylpyridin-2-yl)-1*H*-indole 71a



Prepared from *tert*-butyl 5-methoxy-2-(3-methylpyridin-2-yl)-1*H*-indole-1-carboxylate (0.26 g, 0.78 mmol).The title compound was obtained as an off white solid, yield (0.18 g, 96%), **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.11 (br s, 1H, NH), 8.33 (d, *J* = 4.6 Hz, 1H, H-6'), 7.39 (d, *J* = 7.7 Hz, 1H, H-7), 7.12 (d, *J* = 2.4 Hz, 1H, H-4), 7.01 (s, 1H, H-3), 6.94 (dd, *J* = 6.4 Hz, 1H, H-5'), 6.79-6.77 (m, 2H, H-6 and H-4'), 3.73 (s, 3H, OCH_3), 2.50 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.2, 148.7, 146.4, 139.4, 136.7, 130.9, 130.6, 129.7, 121.5, 114.0, 112.0, 103.9, 102.4, 55.8, 21.5. **Mp** 121-122 °C. **HRMS** (ESI+): calcd. for $C_{15}H_{14}N_2O$ $[M + H]^+$ 239.1106; found $[M + H]^+$ 239.1190.

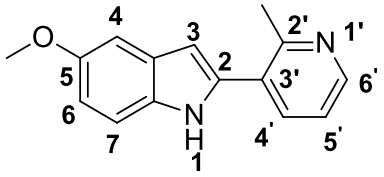
5-Methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole 71b



Prepared from *tert*-butyl 5-methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole-1-carboxylate (1.13 g, 3.34 mmol). The product was obtained as an off white solid, yield (0.44 g, 55%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.63 (s, 1H, NH), 8.54 (s, 1H, H-2'), 8.36 (d, *J* = 5.1 Hz, 1H, H-6'), 7.27 (d, *J* = 8.8 Hz, 1H, H-7), 7.16 (d, *J* = 5.1 Hz, 1H, H-5'), 7.05 (d, *J* = 2.4 Hz, 1H, H-4), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H, H-6), 6.54 (d, *J* = 2.1 Hz, 1H, H-3), 3.80 (s, 3H, OCH_3), 2.45 (s, 3H, $ArCH_3$). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 154.5, 149.0, 148.1, 145.2, 134.3,

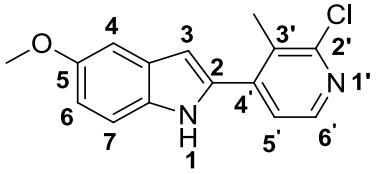
131.8, 129.3, 129.1, 125.9, 113.1, 111.8, 104.0, 102.1, 55.9, 20.6. **HRMS** (ESI+): calcd. for $C_{15}H_{14}N_2O$ $[M + H]^+$ 239.1106; found $[M + H]^+$ 239.1149.

5-Methoxy-2-(2-methylpyridin-3-yl)-1*H*-indole 71c



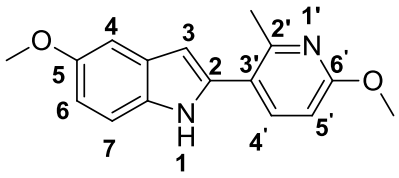
Prepared from *tert*-butyl 5-methoxy-2-(2-methylpyridin-3-yl)-1*H*-indole-1-carboxylate (1.06 g, 3.14 mmol). The title compound was obtained as brown solid, yield (0.62 g, 83%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.61 (br s, 1H, NH), 8.47 (dd, *J* = 5.0, 1.7 Hz, 1H, H-4'), 7.74 (dd, *J* = 7.7, 1.7 Hz, 1H, H-6'), 7.29 (d, *J* = 8.9 Hz, 1H, H-7), 7.19 (dd, *J* = 7.8, 4.9 Hz, 1H, H-5'), 7.12 (d, *J* = 2.4 Hz, 1H, H-4), 6.89 (dd, *J* = 8.8, 2.5 Hz, 1H, H-6), 6.59 (s, 1H, H-3), 3.86 (s, 3H, OCH_3), 2.70 (s, 3H, $ArCH_3$). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 156.1, 154.5, 148.0, 136.6, 136.0, 131.8, 129.1, 128.5, 121.2, 113.0, 111.8, 103.6, 102.2, 55.9, 23.9. **Mp** 160-161 °C. **HRMS** (ESI+): calcd. for $C_{15}H_{14}N_2O$ $[M + H]^+$ 239.1106; found $[M + H]^+$ 239.1155.

2-(2-Chloro-3-methylpyridin-4-yl)-5-methoxy-1*H*-indole 71e



Prepared from *tert*-butyl 2-(2-chloro-3-methylpyridin-4-yl)-5-methoxy-1*H*-indole-1-carboxylate (0.24 g, 0.64 mmol). The title compound was obtained as an off white solid (0.15 g, 86%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.30 (s, 1H, NH), 8.17 (d, *J* = 5.0, 1H, H-6'), 7.26 (d, *J* = 8.8, 1H, H-7), 7.23 (d, *J* = 5.1, 1H, H-5'), 7.05 (d, *J* = 2.4 Hz , 1H, H-4), 6.87 (dd, *J* = 8.8, 2.5, 1H, H-6), 6.61 (s, 1H, H-3), 3.80 (s, 3H, OCH_3), 2.51 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.7, 153.3, 146.4, 143.1, 134.3, 131.9, 129.8, 128.8, 122.2, 114.3, 112.1, 105.6, 102.2, 55.8, 17.8. **Mp** 172-173 °C. **HRMS** (ESI+): calcd. for $C_{15}H_{13}ClN_2O$ $[M + H]^+$ 273.0789; found $[M + H]^+$ 273.0910.

5-Methoxy-2-(6-methoxy-2-methylpyridin-3-yl)-1*H*-indole 71d



Prepared from *tert*-butyl 5-methoxy-2-(6-methoxy-2-methylpyridin-3-yl)-1*H*-indole-1-carboxylate (0.49 g, 1.34 mmol). The desired product was obtained as an off white solid (0.24 g, 68%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.97 (s, 1H, NH), 7.53 (d, *J* = 8.4 Hz, 1H, H-4'), 7.19 (d, *J* = 8.7 Hz, 1H, H-7), 7.02 (d, *J* = 2.4 Hz, 1H, H-4), 6.79 (dd, *J* = 8.8, 2.4 Hz, 1H, H-6), 6.56 (d, *J* = 8.4 Hz, 1H, H-5'), 6.41 (s, 1H, H-3), 3.89 (s, 3H, NC-OCH_3), 3.79 (s, 3H, OCH_3), 2.53 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.8, 154.5, 154.1, 139.5, 136.7, 131.4, 129.3, 121.1, 112.3, 111.5, 107.7, 102.7, 102.2, 55.9, 53.5, 23.6. **Mp** 224-225 °C. **HRMS** (ESI+): calcd. for $C_{16}H_{16}N_2O_2$ $[M + H]^+$ 269.1285; found $[M + H]^+$ 269.1408.

4.2.5 Formylation reaction

METHOD A

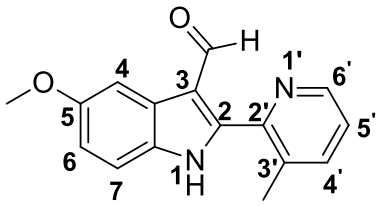
A round bottomed flask equipped with a stirrer bar was charged with substituted indole (1.0 equiv.), paraformaldehyde (1.0 equiv.), 25% aqueous ammonia solution (2.0 equiv.), iron (III) chloride (20 mol%) and DMF (5-10 mL). The contents of the flask were heated under reflux at 130 °C under open air. Upon completion of the reaction, the mixture was cooled to room temperature, diluted with a saturated aqueous sodium chloride solution (10 mL) and 0.5 M aqueous hydrochloric acid solution (2 mL) and then extracted with ethyl acetate (3 × 7 mL). The organic layers were collected and washed with aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over $MgSO_4$ and concentrated under reduced pressure. The crude compounds were purified using column chromatography (5-20% ethyl acetate/hexane mixtures), for small-scale reactions, preparative TLC was used as a purification technique.

METHOD B

Phosphorus oxychloride (1.1 equiv.) was added dropwise to dry DMF (4.4 equiv.) at 0 °C. The resulting mixture was warmed to room temperature and treated with 3-methylpyridin-4-yl-5-methoxy-1*H*-indole (1.0 equiv.) in DMF. The mixture was heated to 35 °C and left stirring under

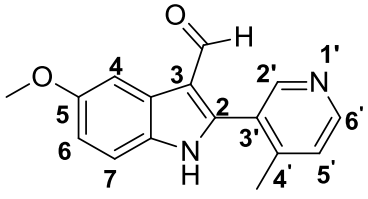
nitrogen atmosphere for 60 min. After this time, ice was added and the mixture was made basic with 2 M aqueous sodium hydroxide. The mixture was then heated under reflux for 30 min. The mixture was cooled and the organic layer was extracted with ethyl acetate (3 × 20 mL), dried over $MgSO_4$ and purified using mixtures of 20-50% ethyl acetate-hexane followed by 10% methanol-ethyl acetate.

5-Methoxy-2-(3-methylpyridin-2-yl)-1*H*-indole-3-carbaldehyde 72a



Prepared from METHOD A, 5-methoxy-2-(3-methylpyridin-2-yl)-1*H*-indole (0.17 g, 0.73 mmol), paraformaldehyde (22 mg, 0.73 mmol), 25% ammonia solution (56 µL, 1.45 mmol), iron (III) chloride (23.6 mg, 0.15 mmol, 20 mol%). Title compound was obtained as light-yellow solid, yield (0.13 g, 67%). Using METHOD B, phosphorus oxychloride (0.20 mL, 2.18 mmol), DMF (0.67 mL, 8.71 mmol) and 5-methoxy-2-(3-methylpyridin-2-yl)-1*H*-indole (0.53 g, 1.98 mmol). The title compound was obtained as a light-yellow solid, yield (0.45 g, 89%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.89 (s, 1H, CHO), 9.53 (br s, 1H, NH), 8.60 – 8.47 (m, 1H, H-4'), 7.85 (d, *J* = 2.5 Hz, 1H, H-4), 7.71 (d, *J* = 7.9 Hz, 1H, H-7), 7.33 (m, 1H, H-5'), 7.27 (d, *J* = 5.5 Hz, 1H, H-6'), 6.94 (dd, *J* = 8.9, 2.4 Hz, 1H, H-6), 3.91 (s, 3H, OCH_3), 2.44 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.1, 156.7, 148.5, 147.3, 145.4, 139.2, 133.7, 130.5, 126.3, 124.2, 115.8, 115.2, 112.3, 103.2, 55.8, 19.6. **Mp** 177-179 °C. **HRMS** (ESI+): calcd. for $C_{16}H_{14}N_2O_2$ $[M + H]^+$ 267.1055; found $[M + H]^+$ 267.1142.

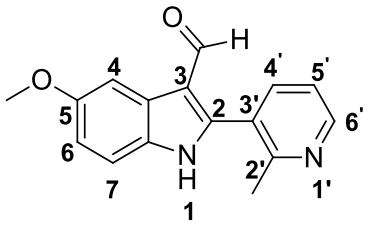
5-Methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde 72b



Prepared using METHOD A, from 5-methoxy-2-(4-methylpyridin-3-yl)-1H-indole (0.42 g, 1.77 mmol), paraformaldehyde (55.0 mg, 1.77 mmol), 25% ammonia solution (0.14 mL, 3.55 mmol), iron (III) chloride (59.0 mg, 20 mol %). The product was obtained as a yellow solid, yield (0.23 g, 48%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.65 (s, 1H, CHO), 9.09 (s,

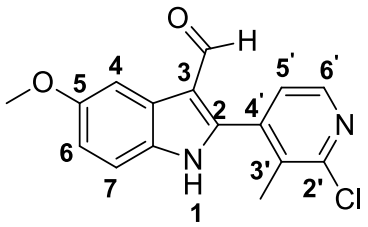
1H, NH), 8.58 (d, *J* = 4.6 Hz, 1H, H-6'), 7.81 (s, 1H, H-2'), 7.68 (d, *J* = 2.0 Hz, 1H, H-4), 7.28 (d, *J* = 8.8 Hz, 1H, H-7), 7.23 (d, *J* = 6.4 Hz, 1H, H-5'), 6.93 (dd, *J* = 8.8, 2.2 Hz, 1H, H-6), 3.85 (s, 3H, OCH_3), 2.45 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 183.6, 158.6, 149.8, 148.2, 136.7, 135.9, 129.4, 129.2, 125.8, 120.1, 114.7, 111.6, 110.5, 102.2, 55.8, 29.6. **HRMS** (ESI+): calcd. for $C_{15}H_{14}N_2O$ $[M + H]^+$ 239.1106; found $[M + H]^+$ 239.1155.

5-Methoxy-2-(2-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde 72c



Prepared using METHOD A, 5-methoxy-2-(2-methylpyridin-3-yl)-1*H*-indole (0.62 g, 2.60 mmol), paraformaldehyde (79.0 mg, 2.60 mmol), 25% ammonia solution (0.20 mL, 5.19 mmol), iron (III) chloride (84.0 mg, 20 mol %). Title product was obtained as a yellow solid, yield (0.16 g, 23%). Using METHOD B, phosphorus oxychloride (0.10 mL, 1.10 mmol), DMF (0.34 mL, 4.41 mmol) and 5-methoxy-2-(2-methylpyridin-3-yl)-1*H*-indole (0.24 g, 1.00 mmol). Title compound was obtained as a yellow solid, yield (0.23 g, 88%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.67 (s, 1H, CHO), 8.74 (br s, 1H, NH), 8.60 (d, *J* = 2.2 Hz, 1H, H-6'), 7.82 (s, 1H, H-4), 7.67 (d, *J* = 7.7 Hz, 1H, H-4'), 7.28 (d, *J* = 8.8 Hz, 1H, H-7), 7.23 (m, 1H, H-5'), 6.93 (d, *J* = 8.8 Hz, 1H, H-6), 3.85 (s, 3H, OCH_3), 2.48 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 185.8, 157.6, 156.9, 150.3, 146.2, 139.0, 130.5, 126.2, 125.4, 120.8, 116.4, 115.2, 112.1, 103.2, 55.9, 23.2. **Mp** 222-224 °C. **HRMS** (ESI+): calcd. for $C_{16}H_{14}N_2O_2$ $[M + H]^+$ 267.1128; found $[M + H]^+$ 267.1089.

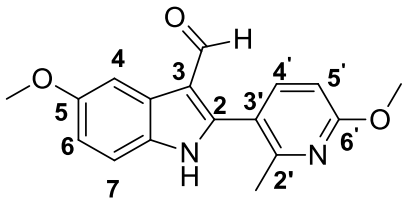
2-(2-Chloro-3-methylpyridin-4-yl)-5-methoxy-1H-indole-3-carbaldehyde 72e



Prepared using METHOD B, from phosphorus oxychloride (0.05 mL, 0.55 mmol), DMF (0.16 mL, 2.00 mmol) and 2-(2-chloro-3-methylpyridin-4-yl)-5-methoxy-1*H*-indole (0.12 g, 0.46 mmol). An off-white solid was obtained as the title compound, yield (0.12 g,

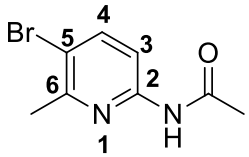
90%). **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 9.62 (s, 1H, CHO), 8.39 (d, *J* = 4.9 Hz, 1H, H-6'), 7.66 (d, *J* = 2.5 Hz, 1H, H-4), 7.54 (d, *J* = 4.9 Hz, 1H, H-5'), 7.44 (d, *J* = 8.8 Hz, 1H, H-7), 6.96 (dd, *J* = 8.9, 2.5 Hz, 1H, H-6), 3.80 (s, 3H, OCH_3), 2.26 (s, 3H, $ArCH_3$). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ 183.8, 154.8, 150.4, 145.4, 143.0, 139.3, 130.3, 129.4, 124.3, 124.2, 113.5, 112.9, 111.9, 101.1, 54.1, 15.9. **Mp** 176-179 °C. **HRMS** (ESI+): calcd. for $C_{16}H_{13}ClN_2O_2$ $[M + H]^+$ 301.0738; found $[M + H]^+$ 301.0733.

5-Methoxy-2-(6-methoxy-2-methylpyridin-3-yl)-1H-indole-3-carbaldehyde 72d



Prepared using METHOD B, phosphorus oxychloride (0.08 mL, 0.86 mmol), DMF (0.27 mL, 3.45 mmol) and 2-(2-chloro-3-methylpyridin-4-yl)-5-methoxy-1*H*-indole (0.21 g, 0.78 mmol). The title compound was obtained as an off-white solid, yield (0.18 g, 76 %). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.64 (s, 1H, CHO), 8.77 (s, 1H, NH), 7.79 (d, *J* = 2.5 Hz, 1H, H-4), 7.51 (d, *J* = 8.4 Hz, 1H, H-4'), 7.26 (d, *J* = 8.8 Hz, 1H, H-7), 6.89 (dd, *J* = 8.8, 2.5 Hz, 1H, H-6), 6.61 (d, *J* = 8.3 Hz, 1H, H-5'), 3.92 (s, 3H, NC-OCH_3), 3.83 (s, 3H, OCH_3), 2.38 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.1, 164.2, 156.8, 155.8, 147.1, 141.4, 130.3, 126.2, 117.5, 116.2, 114.8, 112.0, 107.7, 103.2, 55.9, 53.9, 23.0. **Mp** 182-184 °C. **HRMS** (ESI+): calcd. for $C_{17}H_{16}N_2O_3$ $[M + H]^+$ 297.1234; found $[M + H]^+$ 297.1158.

2-Acetylamino-5-bromo-6-methylpyridine 72g



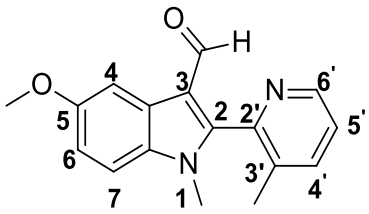
6-Amino-3-bromo-2-methylpyridine (0.72 g, 3.84 mmol, 1 equiv.) was dissolved in acetic anhydride (10.0 mL). The mixture was heated under reflux for 30 – 60 min. Water was added to quench the reaction and product was extracted into ethyl acetate (3 × 10 mL). The title compound was obtained as a white solid, yield (0.75 g, 85%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.17 (s, 1H, NH), 7.86 (d, *J* = 8.7 Hz, 1H, H-4), 7.69 (d, *J* = 8.7 Hz, 1H, H-3), 2.46 (s, 3H, $ArCH_3$), 2.11 (s, 3H, $COCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.7, 155.3, 149.5, 141.9,

115.1, 112.7, 24.7, 24.5. **Mp** 143-145 °C. **HRMS** (ESI+): calcd. for $C_8H_9BrN_2O$ $[M + H]^+$ 228.9971; found $[M + H]^+$ 228.9982.

4.2.6 NH protection

4.2.6.1 *N*-Methylation of biaryl indole derivatives

5-Methoxy-1-methyl-2-(3-methylpyridin-2-yl)-1*H*-indole-3-carbaldehyde 73



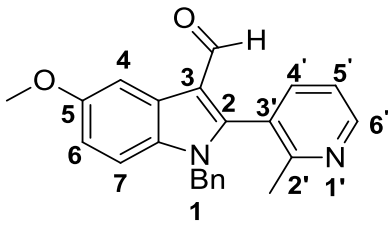
5-Methoxy-2-(3-methylpyridin-2-yl)-1*H*-indole-3-carbaldehyde (0.37 g, 1.38 mmol, 1.0 equiv.) dissolved in THF (20.0 mL) was cooled to -78 °C and treated with potassium hexamethyldisilizide (0.41 g, 2.07 mmol, 1.5 equiv.) added dropwise. The reaction mixture was stirred for 30 min before adding methyl iodide (0.21 mL, 3.45 mmol, 2.5 equiv.) at -78 °C. After stirring for 30 min, the mixture was warmed to room temperature. Upon completion of the reaction, water was added to quench the reaction and the product was extracted with ethyl acetate (3 × 15 mL). Column chromatography was used to purify the product using solvent mixtures of ethyl acetate and hexane. An orange-brown solid was obtained as the title compound, yield (0.22 g, 57%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.59 (s, 1H, CHO), 8.66 (dd, *J* = 4.8 Hz, 1.6, 1H, H-6'), 7.89 (d, *J* = 2.5 Hz, 1H, H-4), 7.73 (dd, *J* = 7.8, 1.7 Hz, 1H, H-4'), 7.40 (dd, *J* = 7.8, 4.8 Hz, 1H, H-5'), 7.31 (d, *J* = 8.9 Hz, 1H, H-7), 7.02 (dd, *J* = 8.9, 2.5 Hz, 1H, H-6), 3.93 (s, 3H, OCH_3), 3.57 (s, 3H, NCH_3), 2.25 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 207.0, 185.4, 157.0, 147.6, 138.4, 134.8, 132.4, 125.8, 124.4, 114.6, 110.7, 103.4, 77.2, 55.9, 30.9, 19.1. **HRMS** (ESI+): calcd. for $C_{17}H_{16}N_2O_2$ $[M + H]^+$ 281.1212; found $[M + H]^+$ 281.1307.

3.2.6.2 *N*-Benzylation of biaryl indole derivatives

5-Methoxy-2-(2-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde (1.0 equiv.) was dissolved in THF and cooled to -78 °C. While stirring, potassium hexamethyldisilizide (KHMDS) (1.5 equiv.) was added dropwise and the contents of the flask were left to stir. After 30 min, benzyl bromide (1.5 equiv.) was added and the reaction was left to stir for 30 min before being warmed to room temperature. Upon completion, the reaction was quenched with water and extracted using ethyl

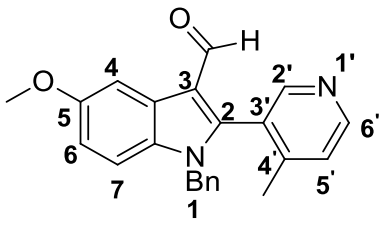
acetate. Column chromatography was used to purify the product using mixtures of ethyl acetate and hexane.

1-Benzyl-5-methoxy-2-(2-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde 74c



Prepared from 5-methoxy-2-(2-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde (0.13 g, 0.47 mmol), KHMDS (0.14 g, 0.70 mmol) and benzyl bromide (0.08 mL, 0.70 mmol). Title compound was obtained as a yellow oil, yield (0.162 g, 96%). **^{1}H NMR (300 MHz, CDCl$_3$)** δ 9.51 (s, 1H, CHO), 8.59 (dd, *J* = 4.8, 1.7 Hz, 1H, H-6'), 7.85 (d, *J* = 2.5 Hz, 1H, H-4), 7.48 (dd, *J* = 7.7, 1.7 Hz, 1H, H-4'), 7.20 – 7.07 (m, 5H, H-7, H-5' and ArH), 6.89 (dd, *J* = 8.9, 2.5 Hz, 1H, H-6), 6.82 – 6.70 (m, 2H, ArH), 5.10 (d, *J* = 16.2 Hz, 1H, NC*H*$_2$Ph), 4.96 (d, *J* = 16.2 Hz, 1H, NC*H*$_2$Ph), 3.85 (s, 3H, OCH$_3$), 2.23 (s, 3H, ArCH$_3$). **^{13}C NMR (75 MHz, CDCl$_3$)** δ 185.5, 158.4, 157.1, 150.8, 148.0, 139.0, 135.7, 131.9, 128.9, 128.0, 126.3, 126.0, 124.2, 120.7, 116.5, 114.9, 111.6, 103.4, 55.9, 47.8, 23.0. **HRMS** (ESI+): calcd. for $C_{23}H_{22}N_2O_2$ $[M + H]^+$ 357.1598; found $[M + H]^+$ 357.1540.

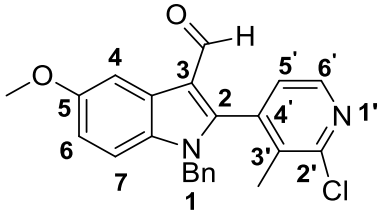
1-Benzyl-5-methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde 74b



Prepared from 5-methoxy-2-(4-methylpyridin-3-yl)-1H-indole-3-carbaldehyde (0.16 g, 0.61 mmol), KHMDS (0.18 g, 0.91 mmol) and benzyl bromide (0.11 mL, 0.91 mmol). The title compound was obtained as yellow oil, yield (0.18 g, 83%). **^{1}H NMR (300 MHz, CDCl$_3$)** δ 9.60 (s, 1H, CHO), 8.64 (d, *J* = 5.0 Hz, 1H, H-6'), 8.43 (s, 1H, H-2'), 7.93 (d, *J* = 2.5 Hz, 1H, H-4), 7.31 (d, *J* = 5.1 Hz, 1H, H-5'), 7.17 – 7.14 (m, 4H, H-7 and 3 × ArH), 6.99 (dd, *J* = 9.0, 2.6 Hz, 1H, H-6), 6.90 – 6.82 (m, 2H, ArH), 5.14 – 4.95 (m, 2H, NC*H*$_2$Ph), 3.86 (s, 3H, OCH$_3$), 1.98 (s, 3H, ArCH$_3$). **^{13}C NMR (75 MHz, CDCl$_3$)** δ 185.4, 157.1, 150.4, 150.3, 148.9,

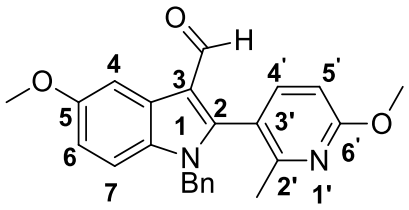
145.9, 135.6, 132.1, 128.9, 128.1, 126.3, 126.0, 117.1, 115.0, 111.6, 103.3, 55.9, 47.9, 19.6. **HRMS** (ESI+): calcd. for $C_{23}H_{22}N_2O_2$ $[M + H]^+$ 357.1598; found $[M + H]^+$ 357.1561.

1-Benzyl-2-(2-chloro-3-methylpyridin-4-yl)-5-methoxy-1H-indole-3-carbaldehyde 74e



Prepared from 5-methoxy-2-(2-chloro-3-methylpyridin-4-yl)-1*H*-indole-3-carbaldehyde (0.13 g, 0.44 mmol), KHMDS (0.13 g, 0.66 mmol) and benzyl bromide (0.078 mL, 0.66 mmol). The title compound was obtained as a clear oil, yield (88.3 mg, 51%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.50 (s, 1H), 8.25 (d, *J* = 4.9 Hz, 1H, H-6'), 7.82 (d, *J* = 2.1 Hz, 1H, H-4), 7.17 (m, 4H, H-7 and 3 × ArH), 7.07 (d, *J* = 4.9 Hz, 1H, H-5'), 6.91 (dd, *J* = 9.0, 2.3 Hz, 1H, H-6), 6.79 – 6.72 (m, 2H, ArH), 5.13 – 4.93 (m, 2H, NC*H*$_2$Ph), 3.85 (s, 3H, OCH_3), 2.00 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 184.9, 157.2, 153.1, 146.6, 145.7, 139.7, 135.3, 133.3, 132.0, 129.0, 128.2, 126.3, 125.9, 124.5, 116.3, 115.4, 111.6, 103.3, 55.9, 48.0, 17.4. **HRMS** (ESI+): calcd. for $C_{23}H_{19}ClN_2O_2$ $[M + H]^+$ 391.1208; found $[M + H]^+$ 391.1194.

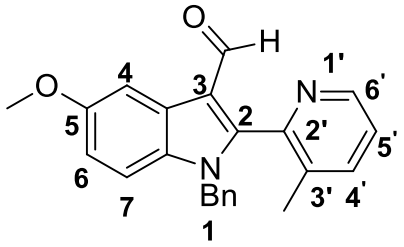
1-Benzyl-5-methoxy-2-(6-methoxy-2-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde 74d



Prepared from 5-methoxy-2-(6-methoxy-2-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde (0.18 g, 0.60 mmol), KHMDS (0.18 g, 0.90 mmol) and benzyl bromide (0.11 mL, 0.90 mmol). A light brown oil was obtained, yield (0.19 g, 82%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.52 (s, 1H, CHO), 7.84 (d, *J* = 3.0 Hz, 1H, H-4), 7.30 (d, *J* = 8.3 Hz, 1H, H-4'), 7.14 (m, 3H, ArH), 7.10 (d, *J* = 8.9 Hz, 1H, H-7), 6.84 (d, *J* = 8.7 Hz, 1H, H-6), 6.81 – 6.75 (m, 2H, ArH), 6.55 (d, *J* = 8.4, 1H, H-5'), 5.23 – 4.91 (m, 2H, NC*H*$_2$Ph), 3.90 (s, 3H, NC-OCH_3), 3.84 (s, 3H, OCH_3), 2.14 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.0, 164.5, 157.0, 156.7, 149.2, 141.1, 135.9, 131.8, 128.9, 127.9, 126.3, 126.1, 116.5, 116.0, 114.6, 111.7, 107.8, 103.3,

55.9, 53.7, 47.7, 22.9. **HRMS** (ESI+): calcd. for $C_{24}H_{22}N_2O_3$ $[M + H]^+$ 387.1703; found $[M + H]^+$ 387.1701.

1-Benzyl-5-methoxy-2-(3-methylpyridin-2-yl)-1*H*-indole-3-carbaldehyde 74a

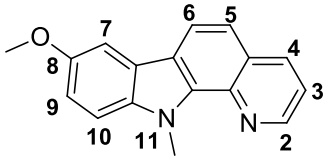


Prepared from 5-methoxy-2-(3-methylpyridin-3-yl)-1H-indole-3-carbaldehyde (0.45 g, 1.69 mmol), KHMDS (0.51 g, 2.54 mmol) and benzyl bromide (0.30 mL, 2.54 mmol). Title compound was obtained as a light-yellow oil, yield (0.53 g, 88%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.65 (s, 1H, CHO), 8.62 (d, *J* = 4.7 Hz, 1H, H-6'), 7.94 (d, *J* = 2.5 Hz, 1H, H-4), 7.56 (dd, *J* = 7.8, 1.6 Hz, 1H, H-5'), 7.34 – 7.30 (m, 1H, H-4'), 7.28 (d, *J* = 9.2 Hz, 1H, H-7), 7.16 (m , 3H, ArH), 6.96-6.91 (m, 3H, H-6 and ArH), 5.21 (s, 2H, NC*H*$_2$Ph), 3.89 (s, 3H, OCH_3), 2.00 (s, 3H, $ArCH_3$). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 185.4, 156.9, 148.1, 148.0, 147.5, 138.4, 136.1, 135.1, 128.7, 127.8, 126.8, 125.9, 124.4, 115.9, 114.6, 111.6, 103.5, 55.8, 47.9, 18.9. **HRMS** (ESI+): calcd. for $C_{23}H_{22}N_2O_2$ $[M + H]^+$ 357.1598; found $[M + H]^+$ 357.1612.

4.2.7 Photochemical cyclization

In a deep well photochemical reactor equipped with a pyrex jacket and stirrer bar, 5-methoxy-1-methyl-2-(3-methylpyridin-2-yl)-1*H*-indole-3-carbaldehyde (1.0 equiv.) dissolved in dry DMF and potassium *tert*-butoxide (4.0 equiv.) was added. The mixture was heated to 80 °C under argon atmosphere and irradiated with a medium pressure mercury lamp (450 W) for 10 min. Upon completion, the reaction was quenched with water and extracted with ethyl acetate (50 mL). Flash column chromatography was used to purify the product.

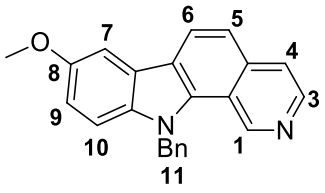
8-Methoxy-11-methyl-11*H*-pyrido[2,3-*a*]carbazole 75



Prepared from 5-methoxy-1-methyl-2-(3-methylpyridin-2-yl)-1*H*-indole-3-carbaldehyde (0.22 g, 0.78 mmol) and potassium *tert*-butoxide (0.85 g, 3.11 mmol). A

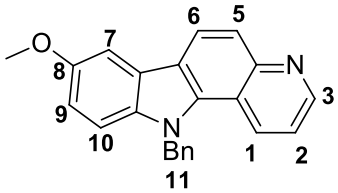
brown-orange solid was obtained as the product in a yield (0.13 g, 63%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.92 (dd, *J* = 4.3, 1.8 Hz, 1H, H-2), 8.27 (dd, *J* = 8.2, 1.8 Hz, 1H, H-4), 8.18 (d, *J* = 8.4 Hz, 1H, H-10), 7.63 (d, *J* = 2.5 Hz, 1H, H-7), 7.51 (dd, *J* = 8.6, 2.3 Hz, 2H, H-4 and H-6), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H, H-3), 7.20 (dd, *J* = 8.9, 2.5 Hz, 1H, H-9), 4.71 (s, 3H, OCH_3), 3.98 (s, 3H, NCH_3). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.1, 147.3, 139.6, 136.23, 136.2, 134.9, 127.8, 122.9, 120.9, 120.0, 119.8, 118.1, 115.2, 110.3, 102.0, 56.1, 33.2. **Mp** 120-121 °C. **HRMS** (ESI+): calcd. for $C_{17}H_{14}N_2O$ $[M + H]^+$ 263.1106; found $[M + H]^+$ 263.1192.

11-Benzyl-8-methoxy-11*H*-pyrido[3,4-a]carbazole 76b



Prepared from 1-benzyl-5-methoxy-2-(4-methylpyridin-3-yl)-1*H*-indole-3-carbaldehyde yield (0.12 g, 0.34 mmol) and potassium *tert*-butoxide (0.15 mg, 1.34 mmol). The title compound was obtained as an off-white solid, yield (0.08 g, 70%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.56 (s, 1H, H-1), 8.41 (d, *J* = 5.7 Hz, 1H, H-3), 8.36 (d, *J* = 8.5 Hz, 1H, H-5), 7.76 (dd, *J* = 5.6, 0.9 Hz, 1H, H-4), 7.61 (d, *J* = 2.5 Hz, 1H, H-7), 7.56 (d, *J* = 8.5 Hz, 1H, H-6), 7.39 (d, *J* = 8.9, 1H, H-10), 7.27 – 7.20 (m, 3H, ArH), 7.11 (m, 3H, H-9 and 2 × ArH), 5.93 (s, 2H, NC*H*$_2$Ph), 3.91 (s, 3H, OCH_3). **HRMS** (ESI+): calcd. for $C_{23}H_{18}N_2O$ $[M + H]^+$ 339.1492; found $[M + H]^+$ 339.1506

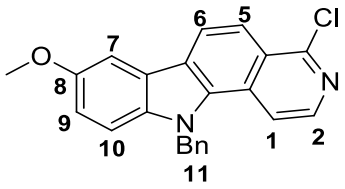
11-Benzyl-8-methoxy-11*H*-pyrido[3,2-a]carbazole 76c



Prepared from 1-benzyl-5-methoxy-2-(2-methylpyridin-3-yl)-1H-indole-3-carbaldehyde (0.16 g, 0.45 mmol) and potassium *tert*-butoxide (0.20 g, 1.81 mmol). The title compound was obtained as a low melting yellow solid, yield (0.12 g, 79%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.78 (d, *J* = 4.3 Hz, 1H, H-3), 8.48 (d, *J* = 8.6 Hz, 1H, H-5), 8.37 (d, *J* = 8.6 Hz, 1H, H-6), 7.94 (d, *J* = 8.7 Hz, 1H, H-1), 7.61 (d, *J* = 2.5 Hz, 1H, H-7), 7.34 (d, *J* = 8.9 Hz, 1H, H-

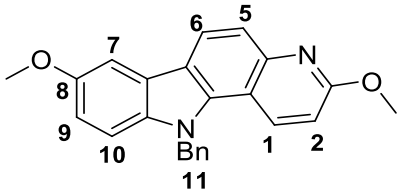
10), 7.29 – 7.21 (m, 4H, H-9, H-2, 2 × ArH), 7.09 (dt, *J* = 8.9, 2.3 Hz, 3H ArH), 5.87 (s, 2H, NC*H*$_2$Ph), 3.91 (s, 3H, OCH$_3$). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 154.9, 136.6, 136.4, 134.4, 129.3, 127.8, 125.7, 123.3, 123.1, 119.8, 119.4, 115.6, 110.1, 56.1, 49.7. **HRMS** (ESI+): calcd. for $C_{23}H_{18}N_2O$ $[M + H]^+$ 339.1492; found $[M + H]^+$ 339.1506

11-Benzyl-8-methoxy-4-methyl-11*H*-pyrido[4,3-a]carbazole 76e



Prepared from 1-benzyl-2-(2-chloro-3-methylpyridin-4-yl)-5-methoxy-1H-indole-3-carbaldehyde (78.0 mg, 0.20 mmol) and potassium *tert*-butoxide (90.0 mg, 0.80 mmol), a low-melting solid product was obtained, yield (30.0 mg, 63%, calculated from recovered starting material (28.0 mg)). **^{1}H NMR (300 MHz, CDCl$_3$)** δ 8.26 (d, *J* = 8.8, 1H, H-2), 8.11-8.09 (m, 2H, H-5 and H-6), 7.82 (d, *J* = 6.1 Hz, 1H, H-1), 7.59 (d, *J* = 2.5 Hz, 1H, H-7), 7.34 (d, *J* = 9.0 Hz, 1H, H-10), 7.28 – 7.19 (m, 3H, ArH), 7.13 (dd, *J* = 9.0, 2.5 Hz, 1H, H-9), 7.06 (d, *J* = 7.5 Hz, 2H, ArH), 5.84 (s, 2H, NC*H*$_2$Ph), 3.91 (s, 3H, OCH$_3$). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 155.0, 152.4, 141.1, 137.0, 136.6, 135.8, 133.7, 129.3, 127.9, 126.6, 125.8, 125.7, 125.6, 122.9, 122.6, 121.6, 117.7, 117.1, 115.0, 110.6, 102.2, 56.0, 49.6. **HRMS** (ESI+): calcd. for $C_{23}H_{17}ClN_2O$ $[M + H]^+$ 373.1102; found $[M + H]^+$ 373.1090.

11-Benzyl-3,8-dimethoxy-11*H*-pyrido[3,2-a]carbazole 76d



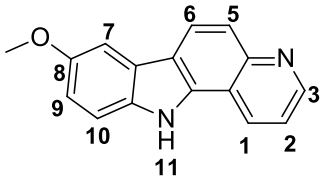
Prepared from 1-benzyl-5-methoxy-2-(6-methoxy-2-methylpyridin-3-yl)-1H-indole-3-carbaldehyde (0.14 g, 0.36 mmol) and potassium *tert*-butoxide (0.16 g, 1.43 mmol). The title compound obtained as a yellow oil, yield (0.12 g, 88%). **^{1}H NMR (300 MHz, CDCl$_3$)** δ 8.26 (d, *J* = 5.1 Hz, 1H, H-5), 8.23 (d, *J* = 4.6 Hz, 1H, H-6), 7.64 (d, *J* = 8.7 Hz, 1H, H-1), 7.56 (d, *J* = 2.5 Hz, 1H, H-7), 7.28 – 7.17 (m, 4H, H-10, 3 × ArH), 7.11 – 7.05 (m, 2H, ArH), 7.00 (dd, *J* = 8.9, 2.5 Hz, 1H, H-9), 6.70 (d, *J* = 9.2 Hz, 1H, H-2), 5.76 (s, 2H, NC*H*$_2$Ph), 4.00 (s, 3H, N-OCH$_3$), 3.89 (s, 3H, OCH$_3$). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 161.1, 154.6, 147.3,

137.0, 136.2, 132.9, 129.2, 127.6, 125.8, 123.5, 122.4, 119.8, 118.0, 114.3, 113.0, 110.9, 109.9, 102.1, 56.1, 53.3, 49.6. **HRMS** (ESI+): calcd. for $C_{24}H_{20}N_2O_2$ $[M + H]^+$ 369.1587; found $[M + H]^+$ 369.1598.

4.2.8 Debenzylation of pyrido fused carbazole derivatives

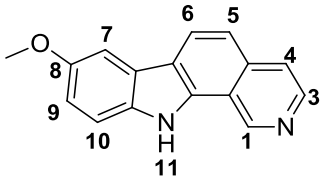
In 50 ml round bottomed flask containing 11-benzyl-8-methoxy-11*H*-pyrido[3,2-*a*]carbazole (1.0 equiv.) dissolved in dry DMSO (10.0 equiv.), potassium *tert*-butoxide (7.0 equiv) dissolved in dry THF was added while stirring the contents of the flask. Oxygen gas was then bubbled into the solution for 10 min via a gas dispersion tube. The reaction was quenched with saturated ammonium chloride and product extracted into ethyl acetate and purified using column chromatography (using 10-50% ethyl acetate/hexane mixtures).

8-Methoxy-11*H*-pyrido[3,2-*a*]carbazole 77c



Prepared from 8-methoxy-11*H*-pyrido[3,2-*a*]carbazole (0.12 g, 0.36 mmol), DMSO (0.25 mL, 3.58 mmol) and potassium *tert*-butoxide (0.28 g, 2.50 mmol). The title compound was obtained as a yellow solid, yield (26.4 mg, 55%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.89 (dd, *J* = 4.3, 1.7 Hz, 1H, H-3), 8.72 (s, 1H, NH), 8.42 (d, *J* = 8.4 Hz, 1H, H-1), 8.27 (d, *J* = 8.8 Hz, 1H, H-6), 7.84 (d, *J* = 8.8 Hz, 1H, H-10), 7.54 (d, *J* = 2.5 Hz, 1H, H-7), 7.44 (dd, *J* = 8.7, 3.6 Hz, 2H, H-5 and H-2), 7.06 (dd, *J* = 8.8, 2.5 Hz, 1H, H-9), 3.91 (s, 3H, OCH_3). **HRMS** (ESI+): calcd. for $C_{16}H_{12}N_2O$ $[M + H]^+$ 249.1022; found $[M + H]^+$ 249.1026.

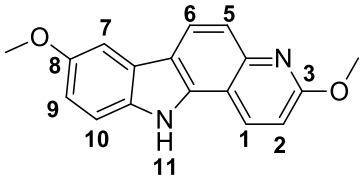
8-Methoxy-11*H*-pyrido[3,4-*a*]carbazole 77b



Prepared from 8-methoxy-11*H*-pyrido[3,4-*a*]carbazole (76.6 mg, 0.23 mmol), DMSO (0.16 mL, 2.26 mmol) and potassium tert-butoxide (0.18 g, 1.58 mmol). A brown solid product was obtained as the title compound, yield (39.7 mg, 71%). **^{1}H NMR (300 MHz,**

DMSO-*d*$_6$) δ 9.83 (s, 1H, H-1), 9.37 (s, 1H, D_2O exchange, H-11), 8.53 (d, *J* = 5.6 Hz, 1H, H-3), 8.47 (d, *J* = 8.6 Hz, 1H, H-6), 7.91 (dd, *J* = 5.7, 1.0 Hz, 1H, H-4), 7.78 (d, *J* = 2.4 Hz, 1H, H-7), 7.60 (dd, *J* = 8.8, 1.3 Hz, 2H, H-5 and H-9), 7.10 (dd, *J* = 8.8, 2.5 Hz, 1H, H-10), 3.87 (s, 3H, OCH_3). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ 153.8, 146.2, 142.4, 134.5, 134.4, 133.5, 124.6, 123.1, 121.2, 118.7, 116.7, 116.6, 114.9, 112.3, 102.1, 55.5. **Mp** 249-251 °C. **HRMS** (ESI+): calcd. for $C_{16}H_{12}N_2O$ $[M + H]^+$ 249.1022; found $[M + H]^+$ 249.1138.

3,8-dimethoxy-11*H*-pyrido[3,2-a]carbazole 77d



Prepared from 11-benzyl-3,8-dimethoxy-11*H*-pyrido[3,2-*a*]carbazole (40.3 mg, 0.11 mmol), DMSO (0.08 mL, 1.09 mmol) and potassium tert-butoxide (86.0 mg, 0.77 mmol). The title compound was obtained as a light orange solid, yield (29.1 mg, 96%). **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 12.01 (s, 1H, NH), 8.76 (d, *J* = 8.9 Hz, 1H, H-5), 8.35 (d, *J* = 8.7 Hz, 1H, H-6), 7.73 (d, *J* = 2.5 Hz, 1H, H-7), 7.51 (dd, *J* = 8.7, 5.9 Hz, 2H, H-1 and H-10), 7.12 (d, *J* = 8.9 Hz, 1H, H-2), 7.04 (dd, *J* = 8.9, 2.5 Hz, 1H, H-9), 4.02 (s, 3H, $NCOCH_3$), 3.87 (s, 3H, OCH_3). **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 161.7, 154.0, 145.9, 136.4, 134.3, 134.0, 123.8, 123.5, 118.3, 117.0, 114.4, 112.7, 112.4, 111.5, 102.8, 56.0, 53.5. **HRMS** (ESI+): calcd. for $C_{17}H_{15}N_2O_2$ $[M + H]^+$ 279.1128; found $[M + H]^+$ 279.1131.

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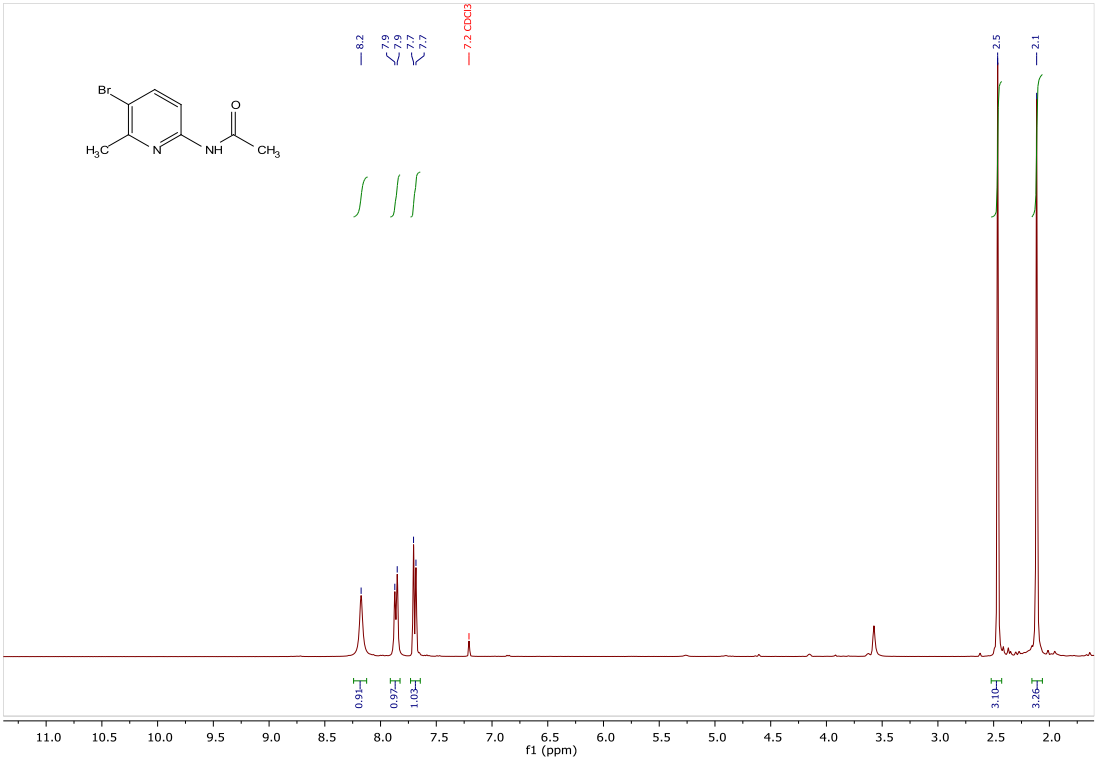
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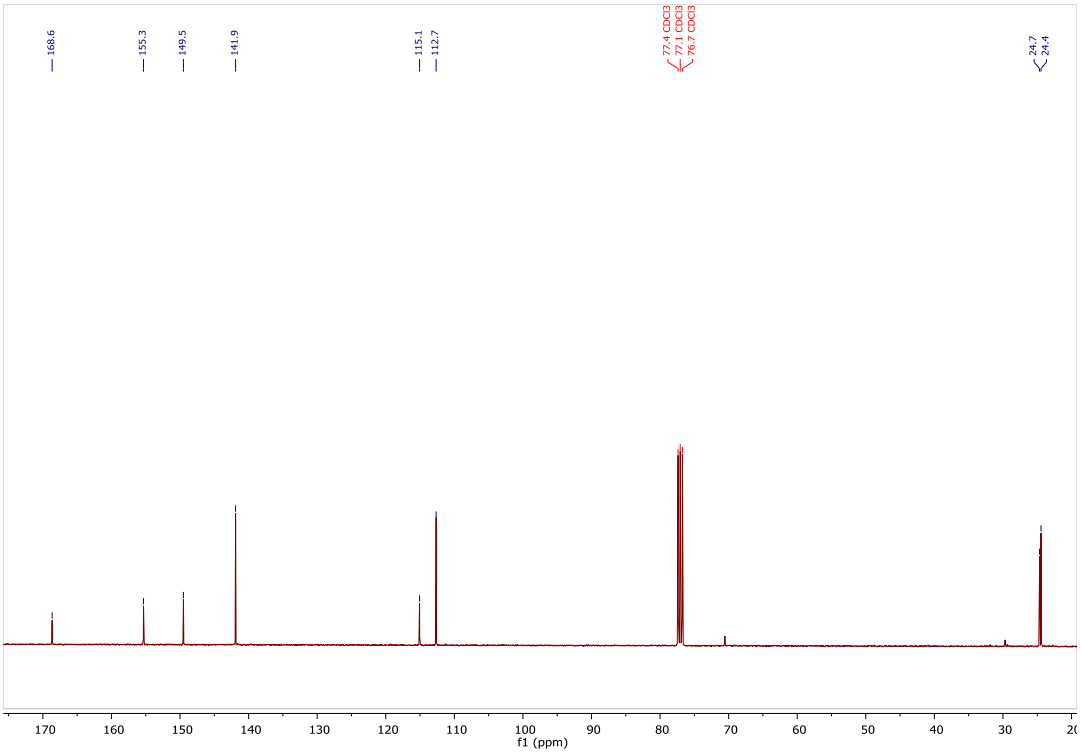
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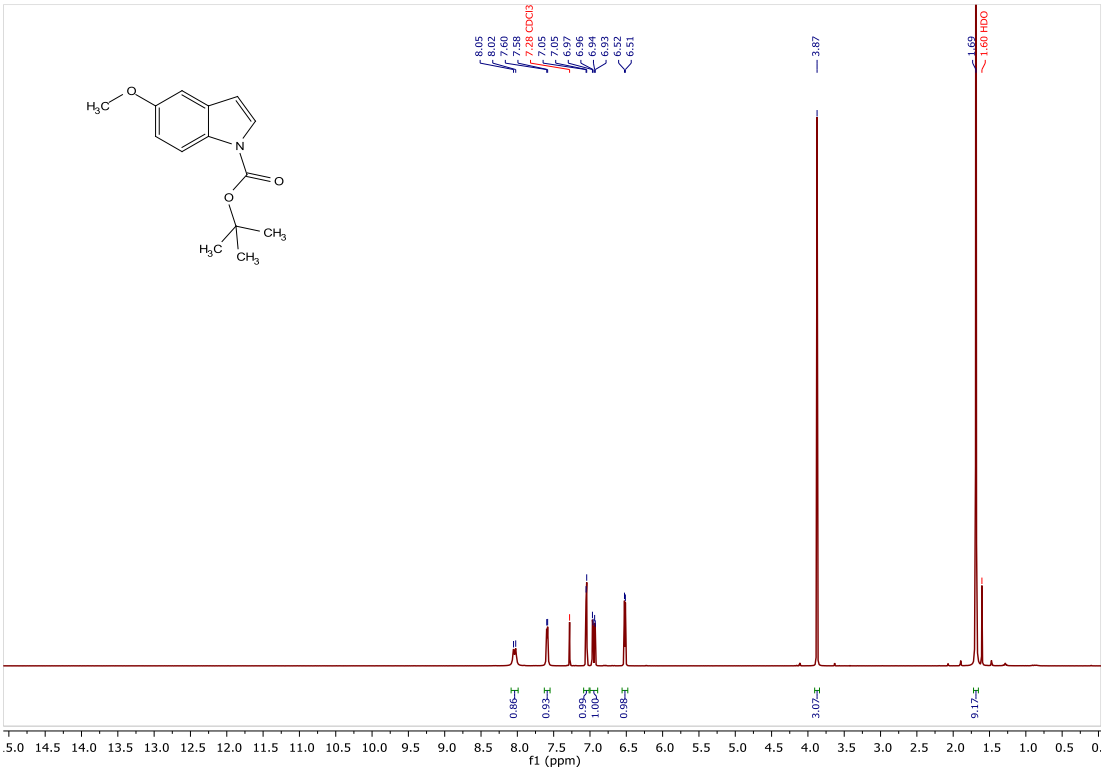
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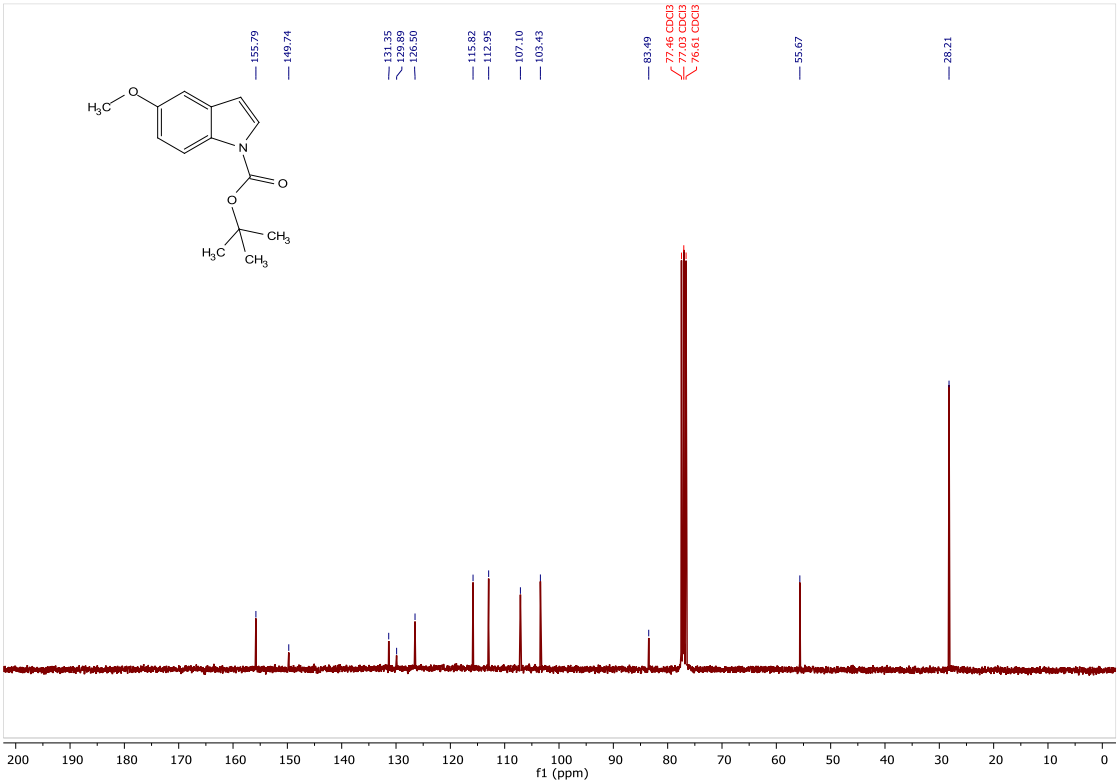
Appendices


Br
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H_3C
N
NH
CH_3
8.2
7.9
7.9
7.7
7.7
7.2 CDCl3
2.5
2.1
0.91
0.97
1.03
3.10
3.26
f1 (ppm)

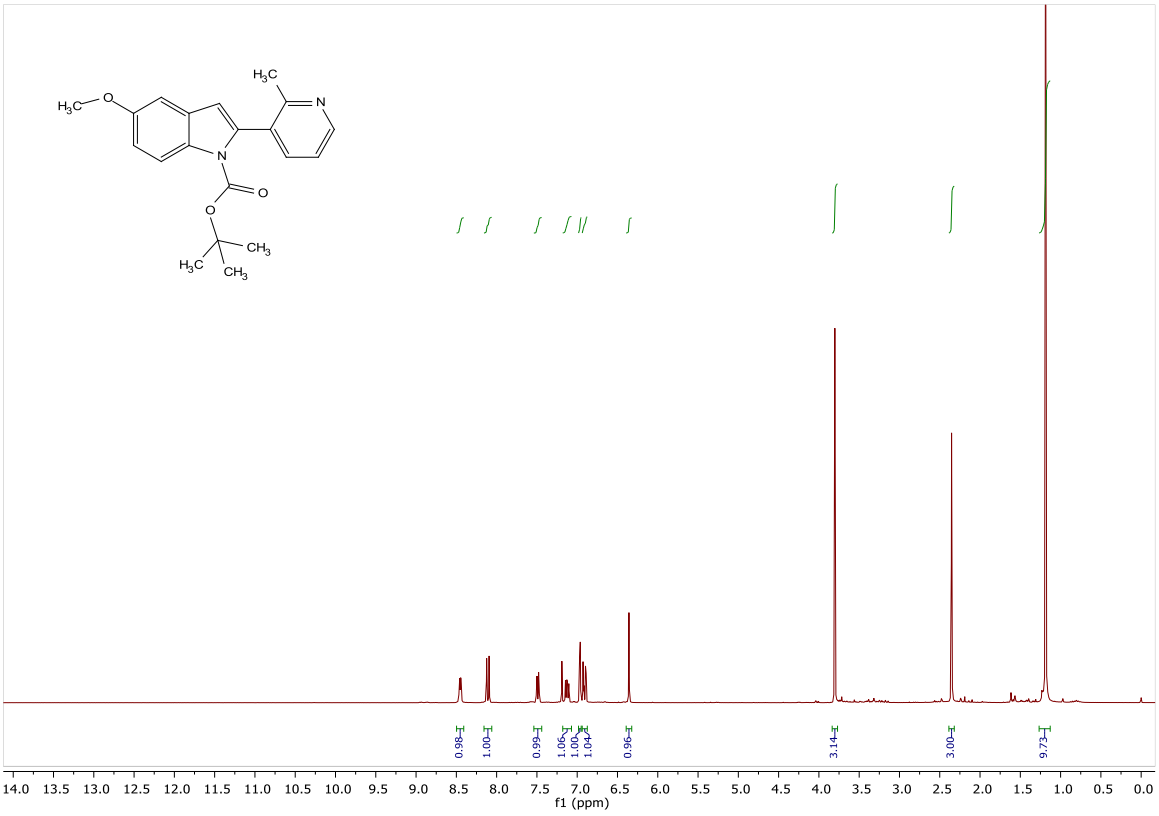

168.6
155.3
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141.9
115.1
112.7
77.4 CDCl3
77.1 CDCl3
76.7 CDCl3
24.7
24.4
f1 (ppm)

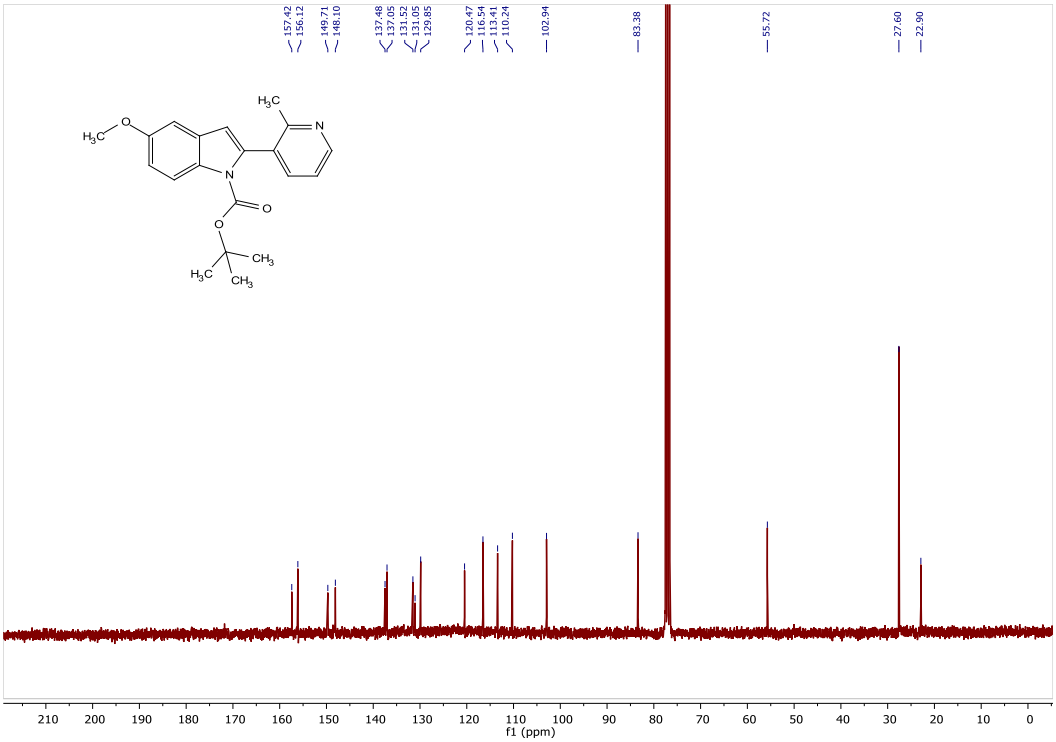
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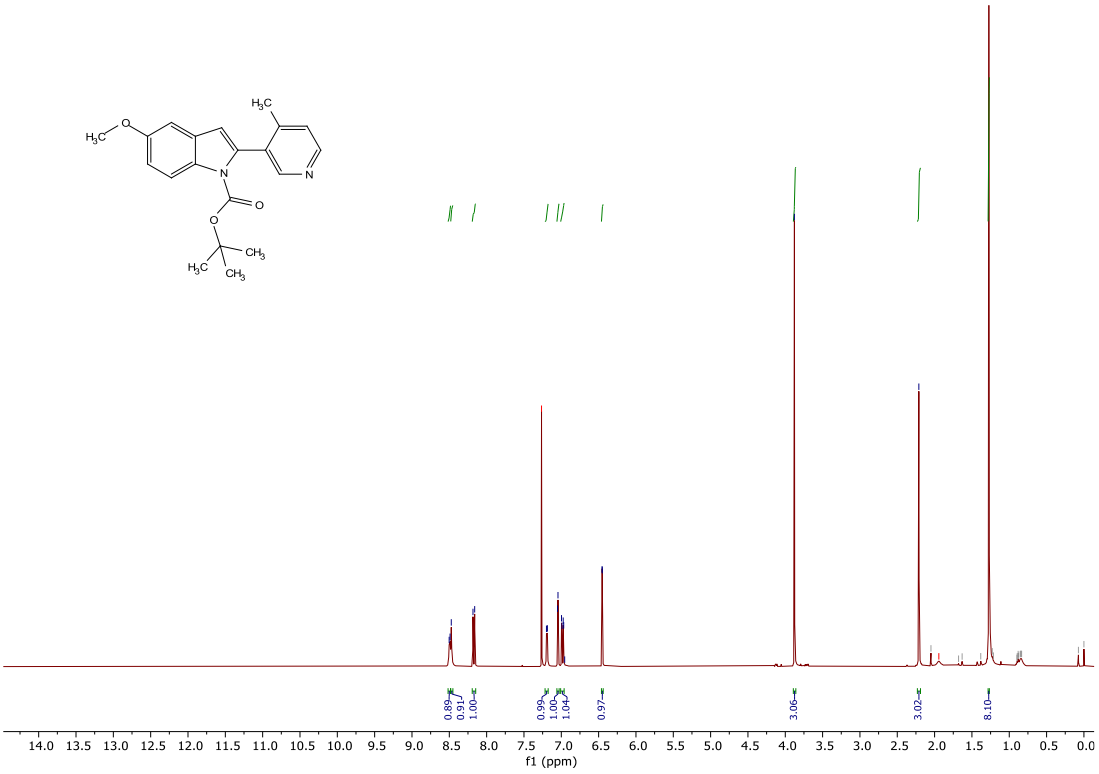


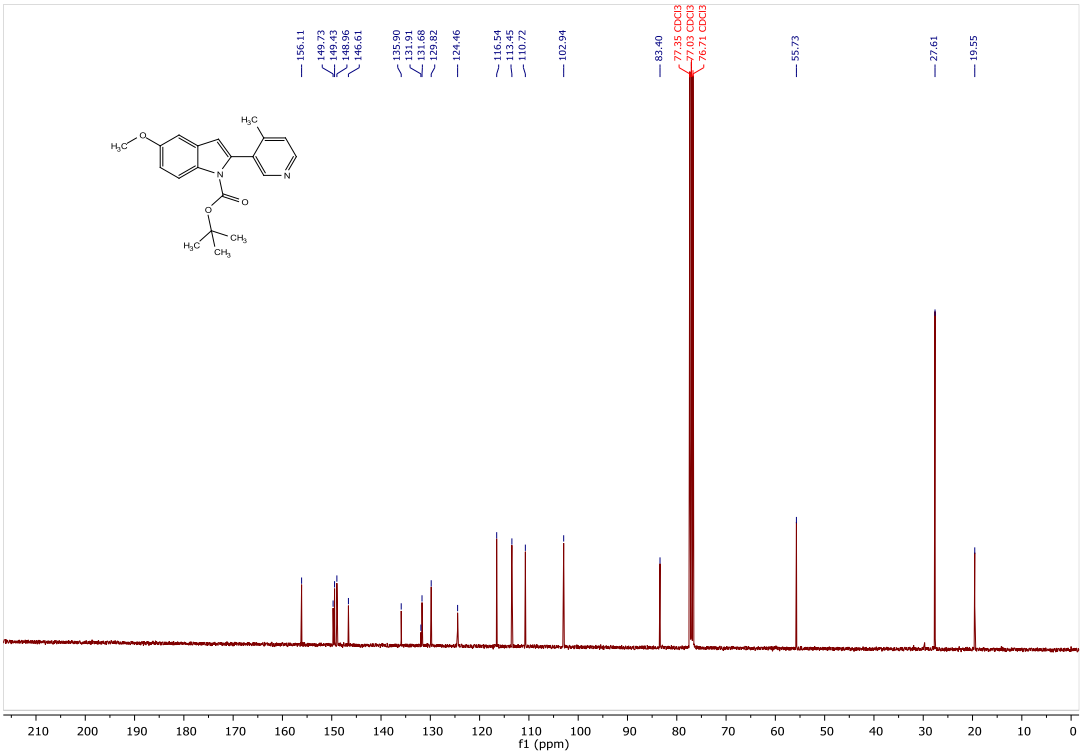


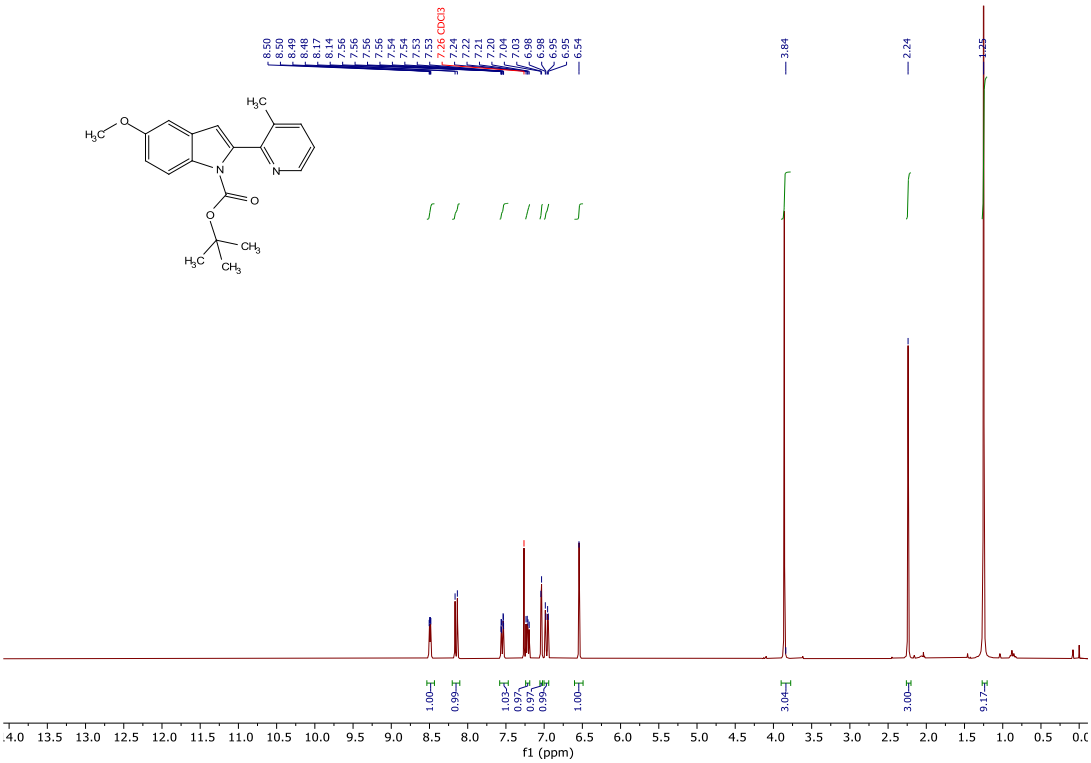
Suzuki coupling reaction

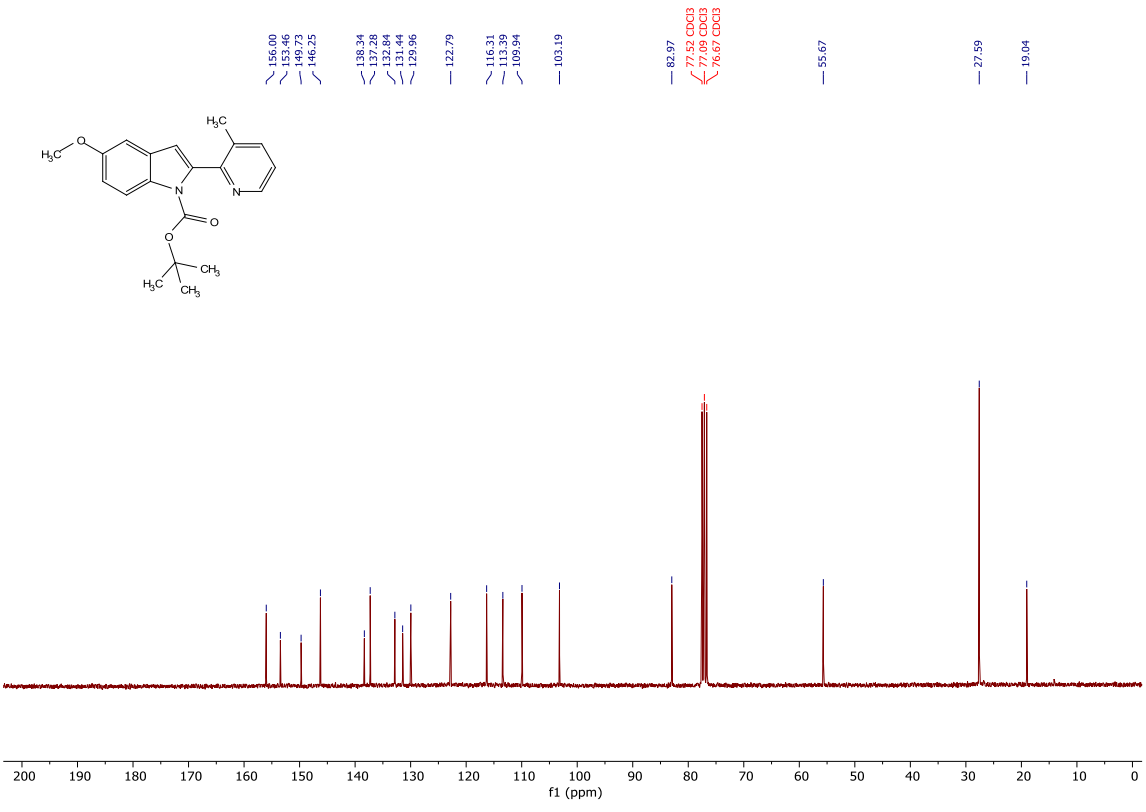


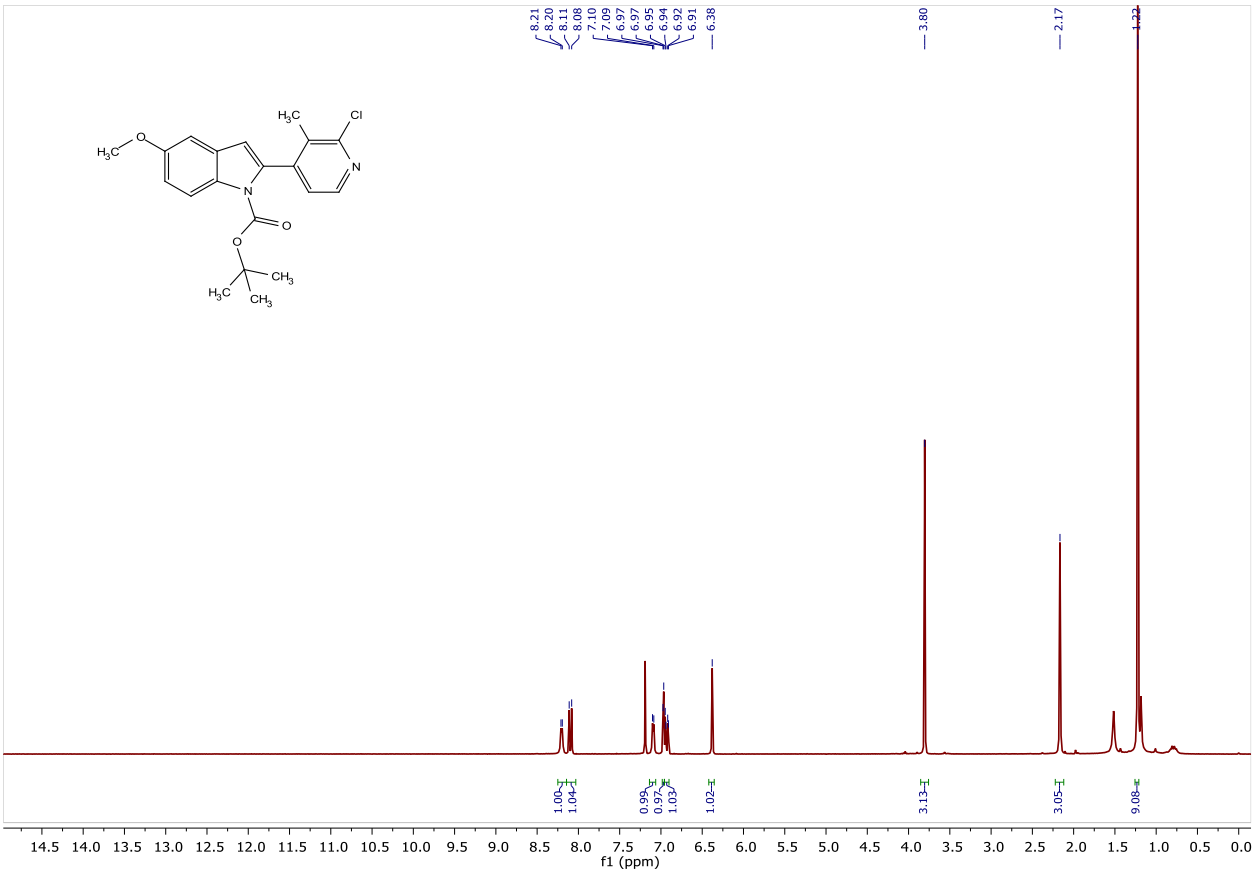


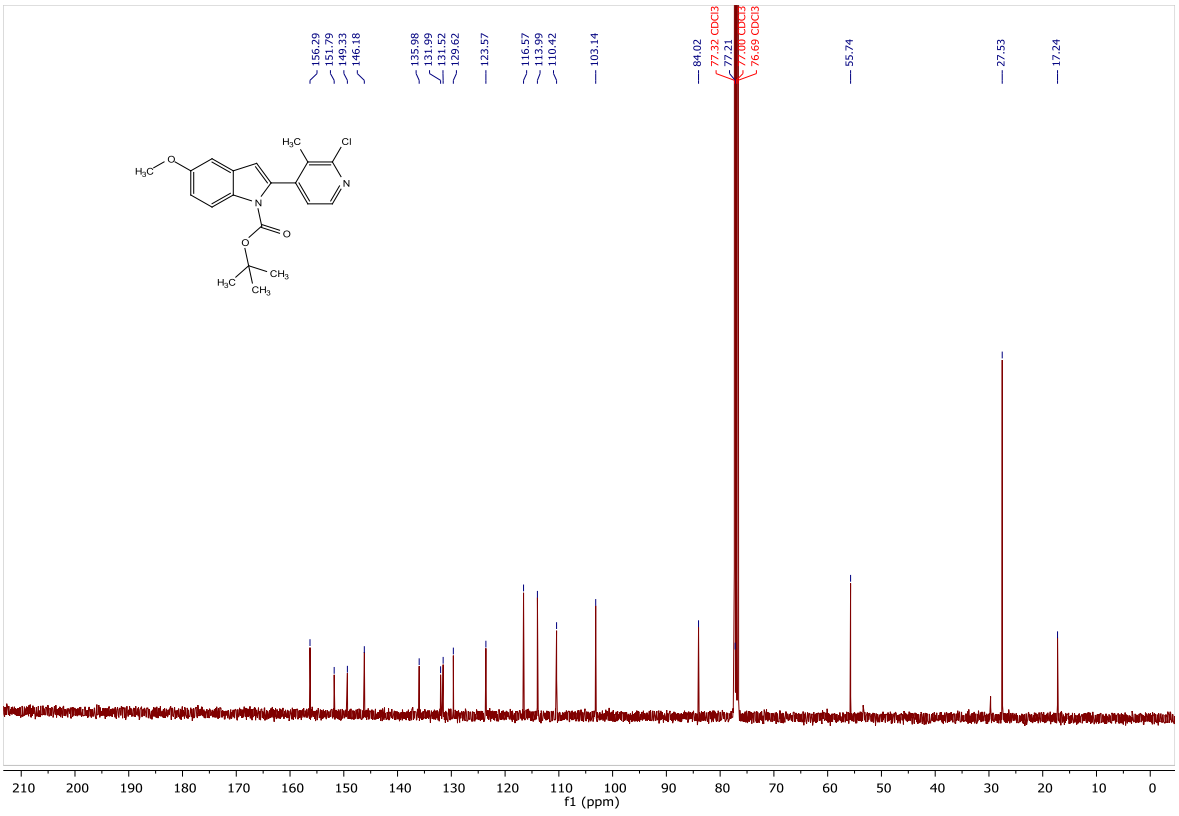

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14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

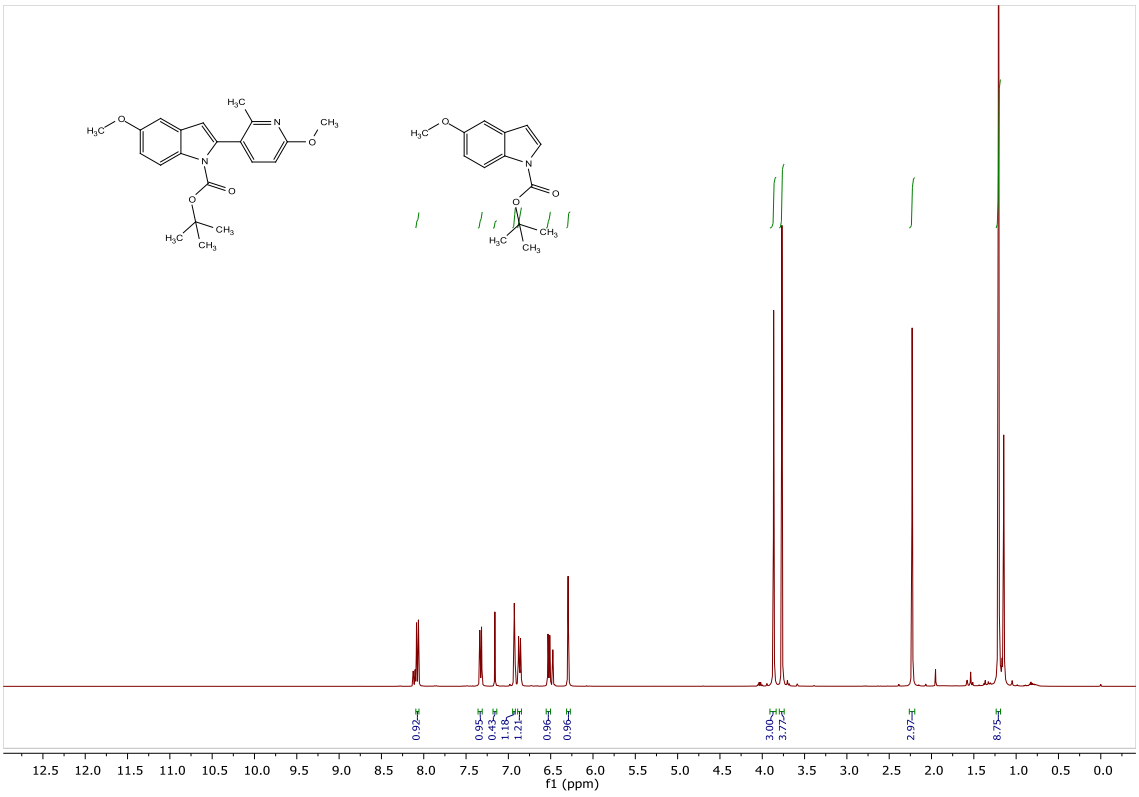

156.11
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210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

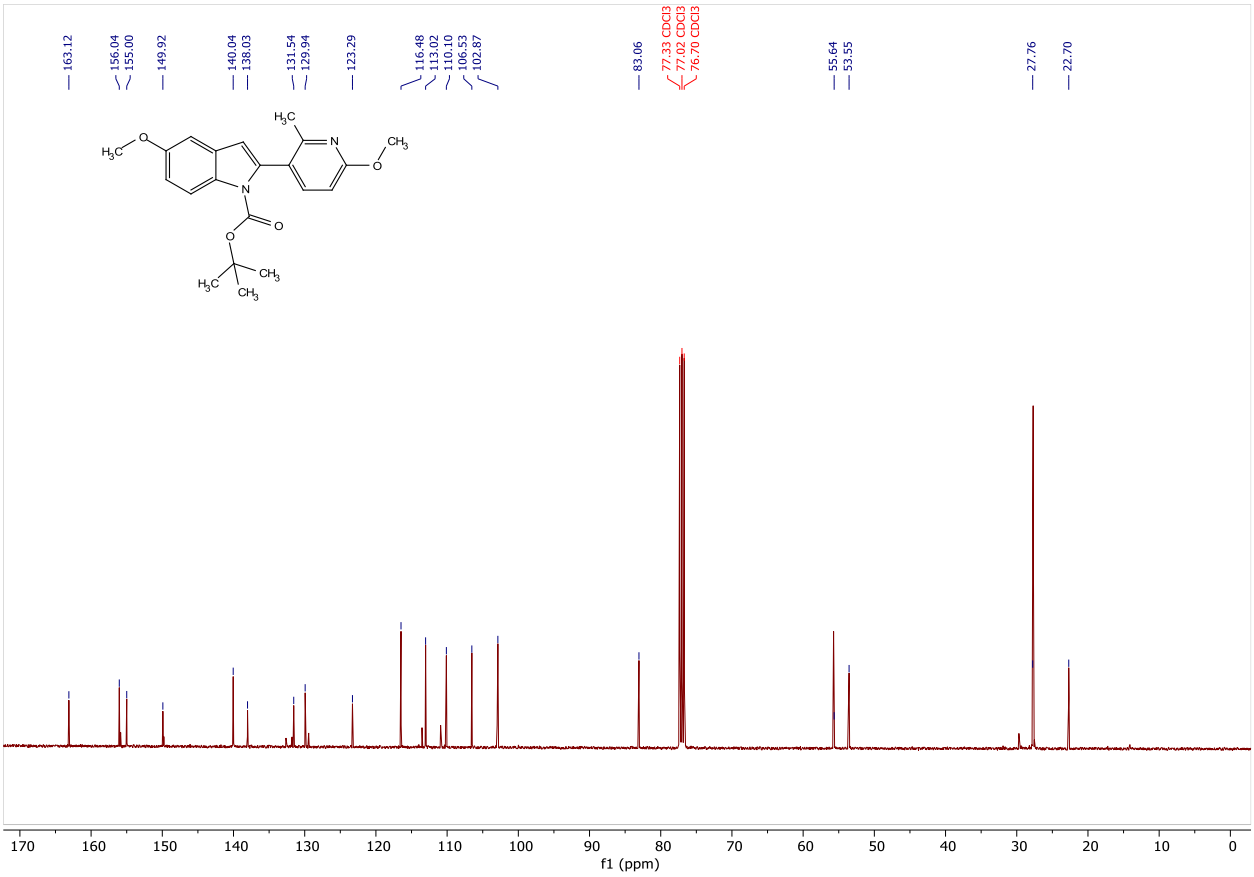

8.50
8.50
8.49
8.48
8.17
8.14
7.56
7.56
7.56
7.56
7.54
7.54
7.53
7.53
7.26 CDCl3
7.24
7.22
7.21
7.20
7.04
7.03
6.98
6.96
6.95
6.54
3.84
2.24
1.25
1.00
0.99
1.03
0.97
0.97
0.99
1.00
3.04
3.00
9.17
f1 (ppm)


156.00
153.46
149.73
146.25
138.34
137.28
132.84
131.44
129.96
122.79
116.31
113.39
109.94
103.19
82.97
77.52 CDCl3
77.09 CDCl3
76.67 CDCl3
55.67
27.59
19.04
f1 (ppm)

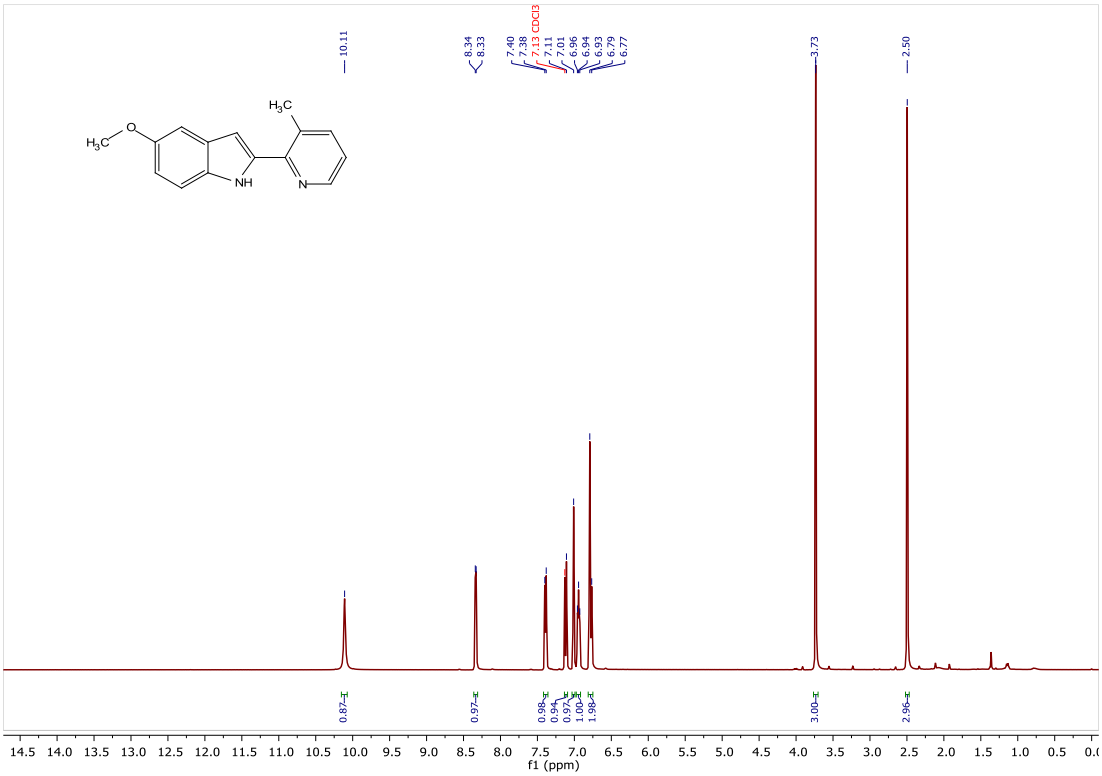

8.21
8.20
8.11
8.08
7.10
7.09
6.97
6.97
6.95
6.94
6.92
6.91
6.38
3.80
2.17
1.22
1.00
1.04
0.99
0.97
1.03
1.02
3.13
3.05
9.08
f1 (ppm)

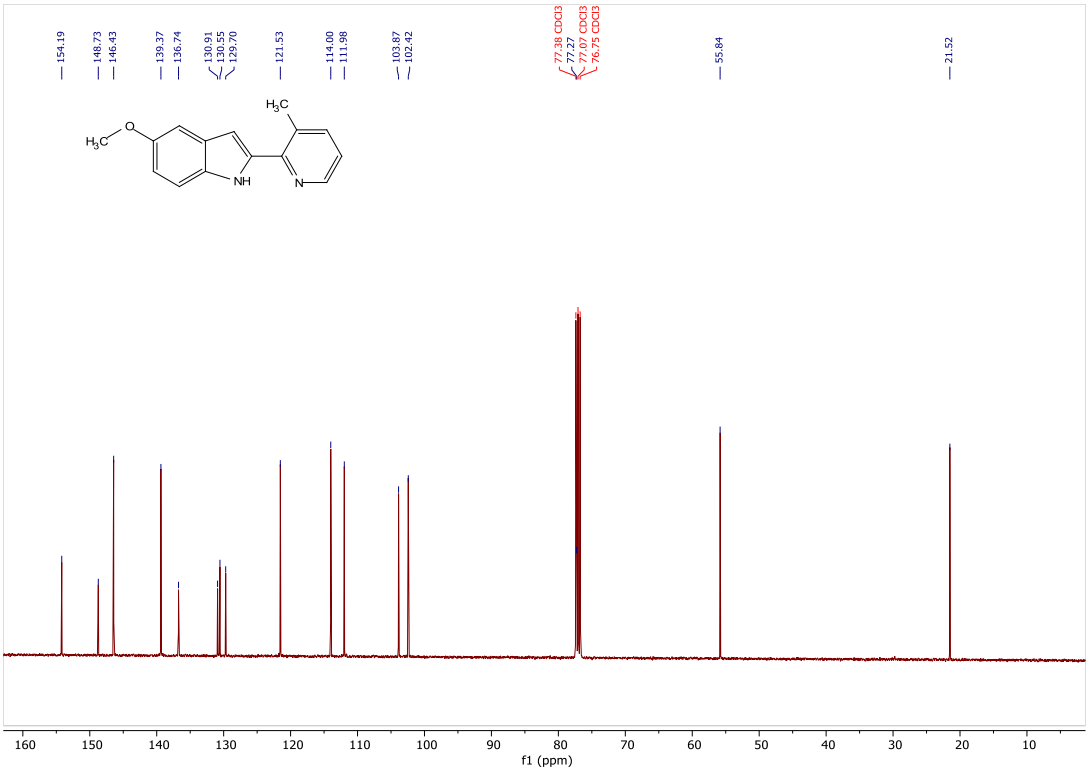

156.29
151.79
149.33
146.18
135.98
131.99
131.52
129.62
123.57
116.57
113.99
110.42
103.14
84.02
77.32 CDCl3
77.21
77.00 CDCl3
76.69 CDCl3
55.74
27.53
17.24
f1 (ppm)

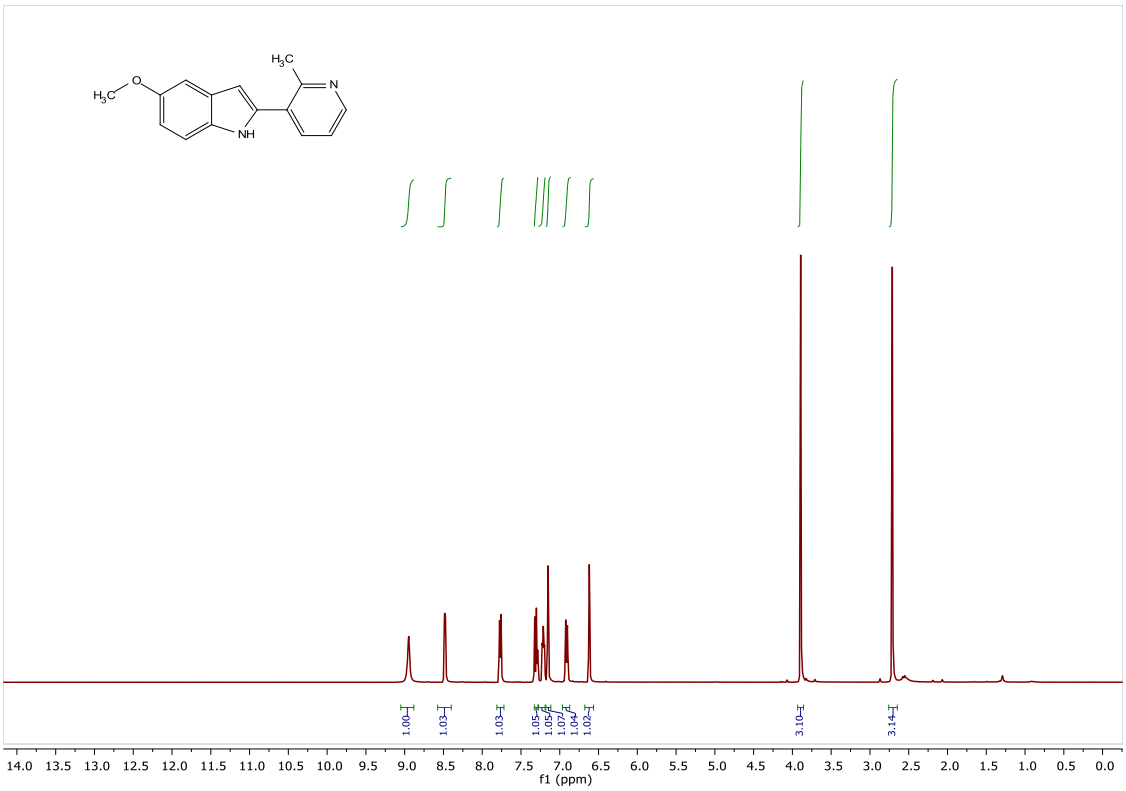

0.92
0.95
0.43
1.18
1.21
0.96
0.96
3.00
3.77
2.97
8.75
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

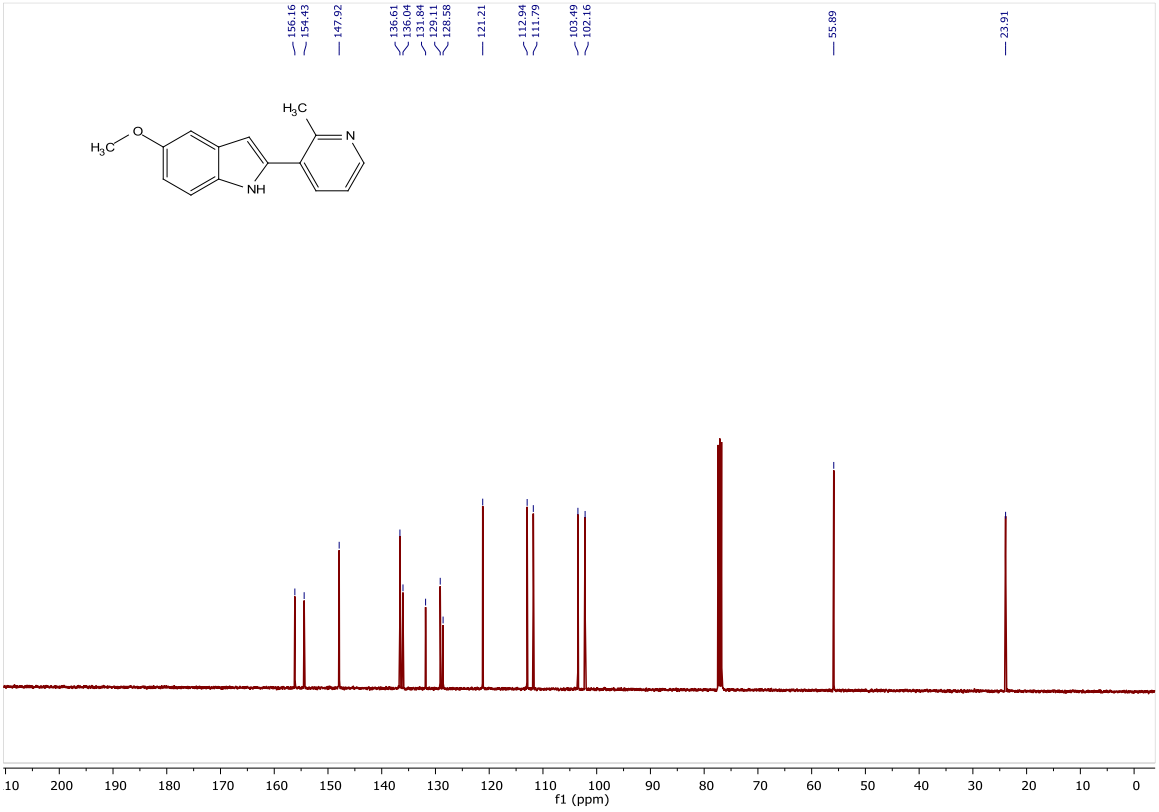

163.12
156.04
155.00
149.92
140.04
138.03
131.54
129.94
123.29
116.48
113.02
110.10
106.53
102.87
83.06
77.33 CDCl3
77.02 CDCl3
76.70 CDCl3
55.64
53.55
27.76
22.70
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

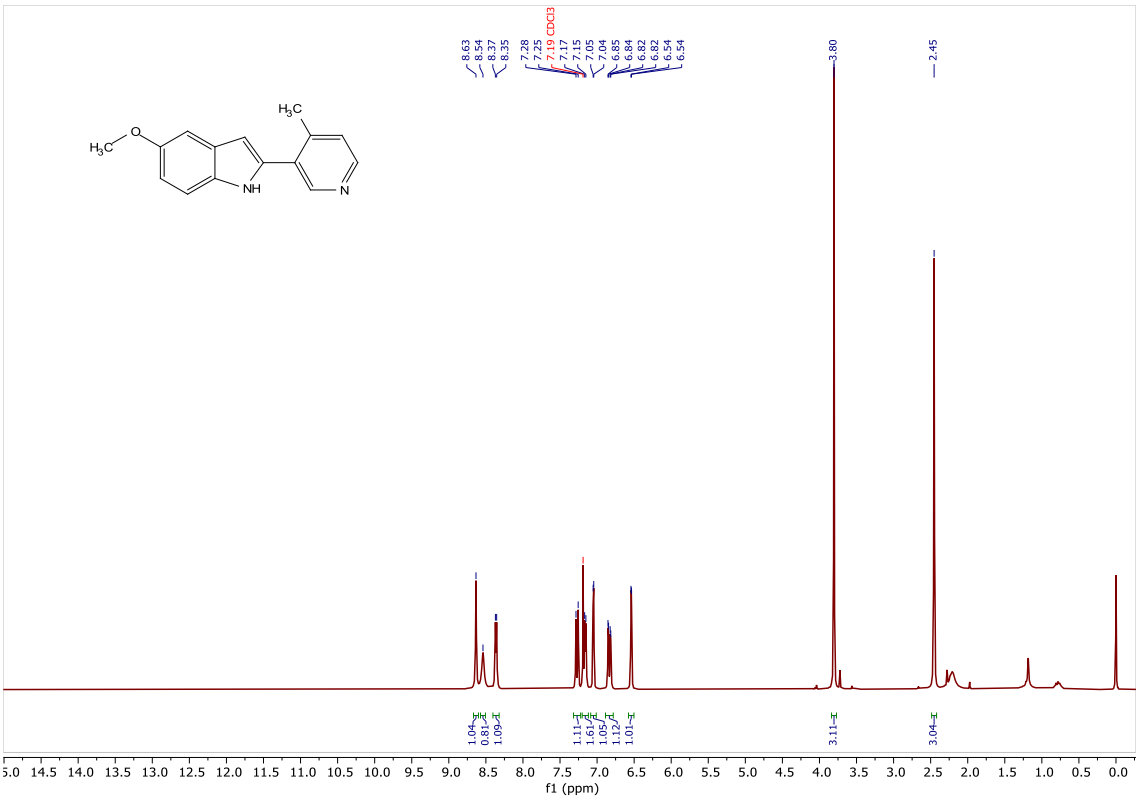
Boc-deprotection

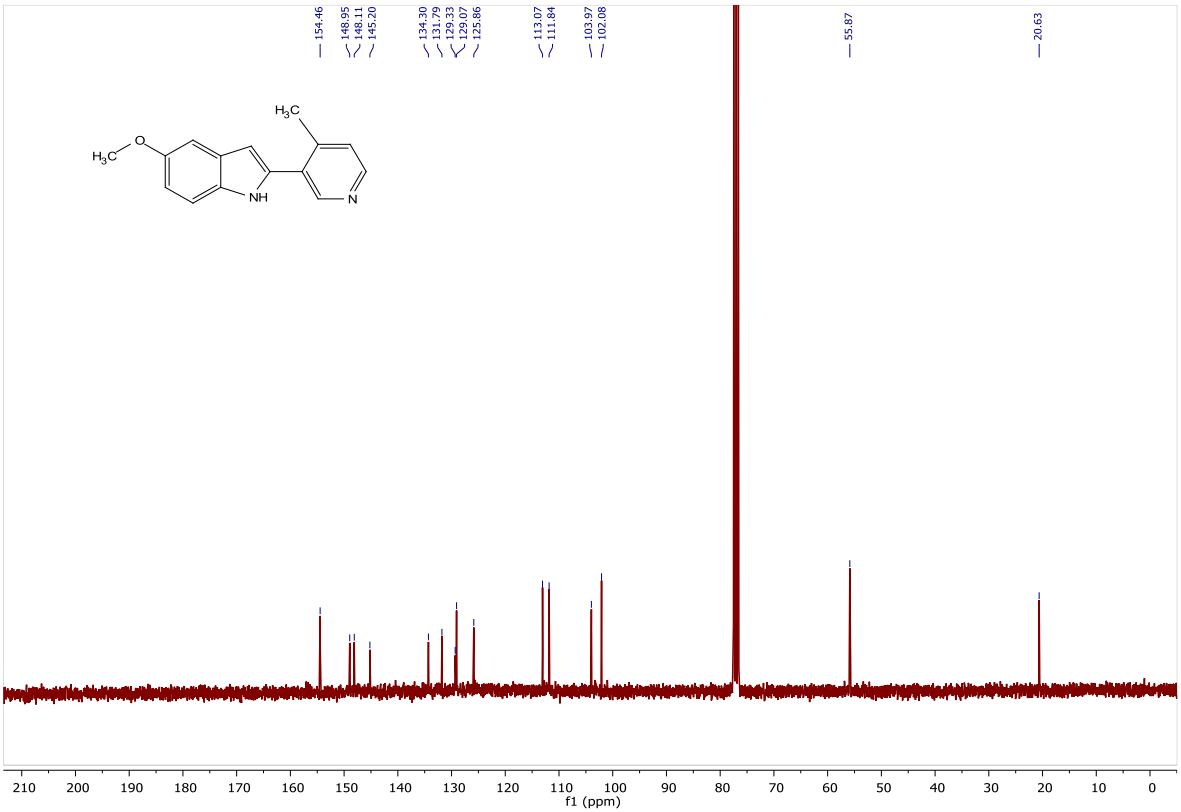


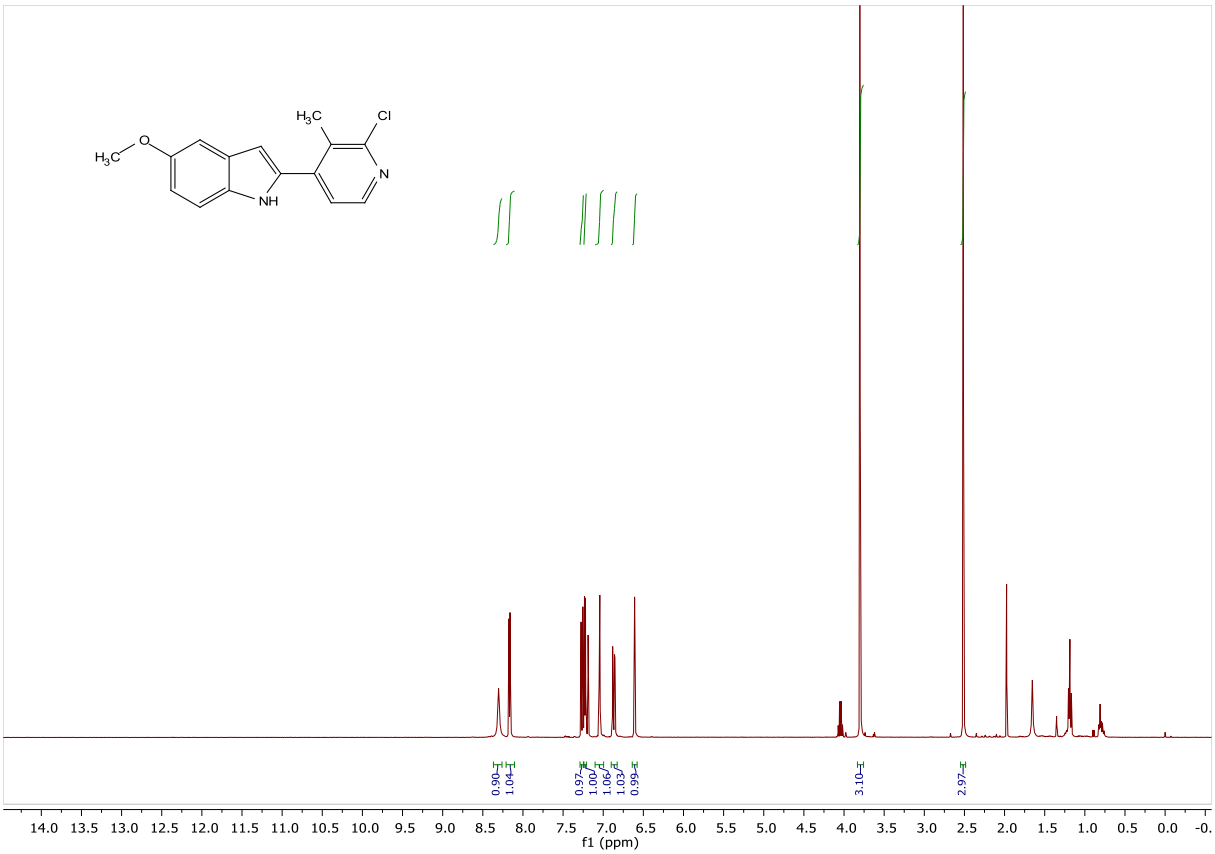


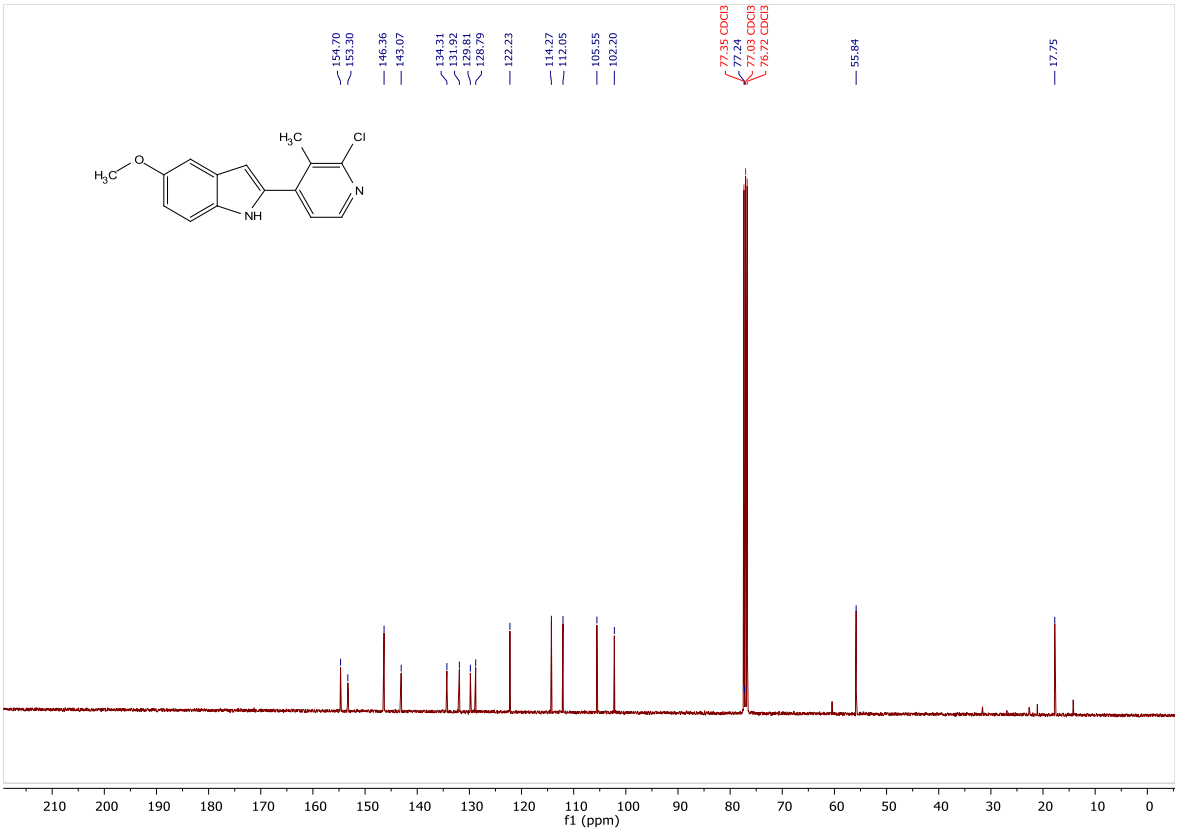

H3C
O
H3C
N
NH
1.00
1.03
1.03
1.05
1.05
1.07
1.04
1.02
3.10
3.14
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

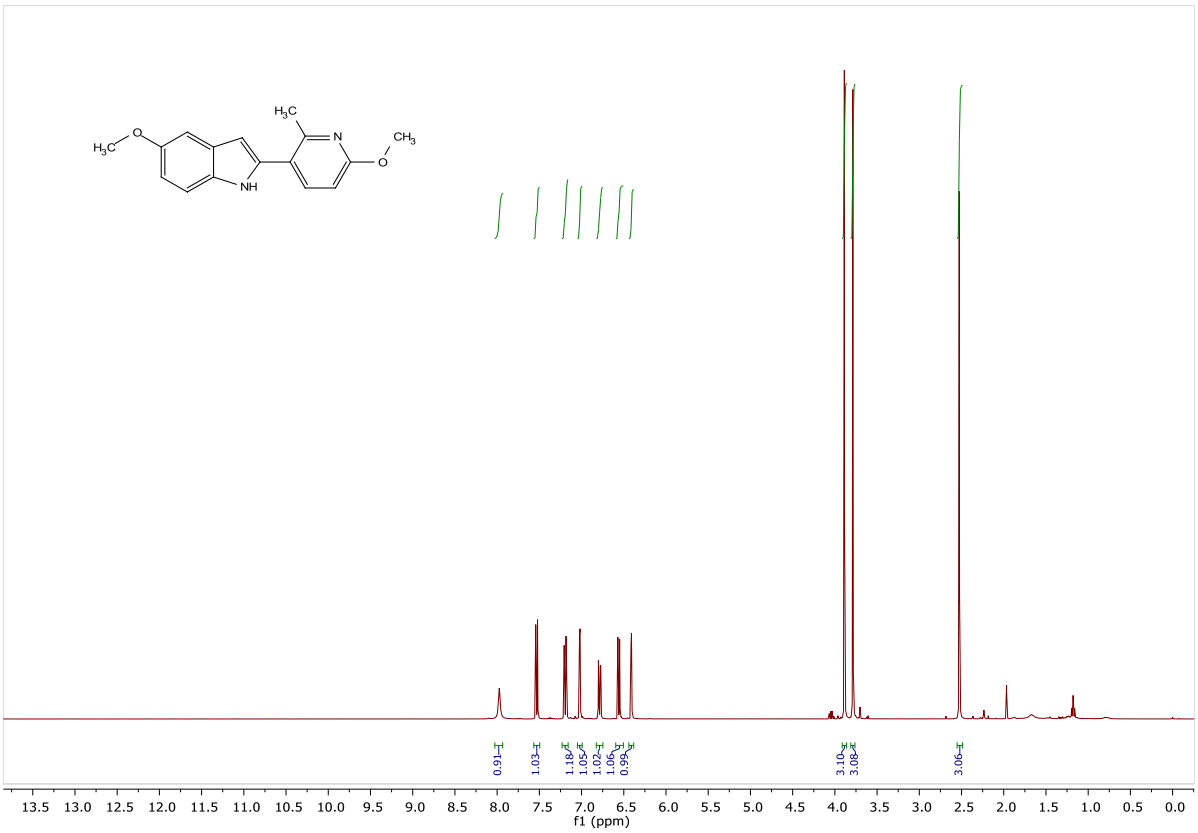

156.16
154.43
147.92
136.61
136.04
131.84
129.11
128.58
121.21
112.94
111.79
103.49
102.16
55.89
23.91
H3C
O
H3C
N
NH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

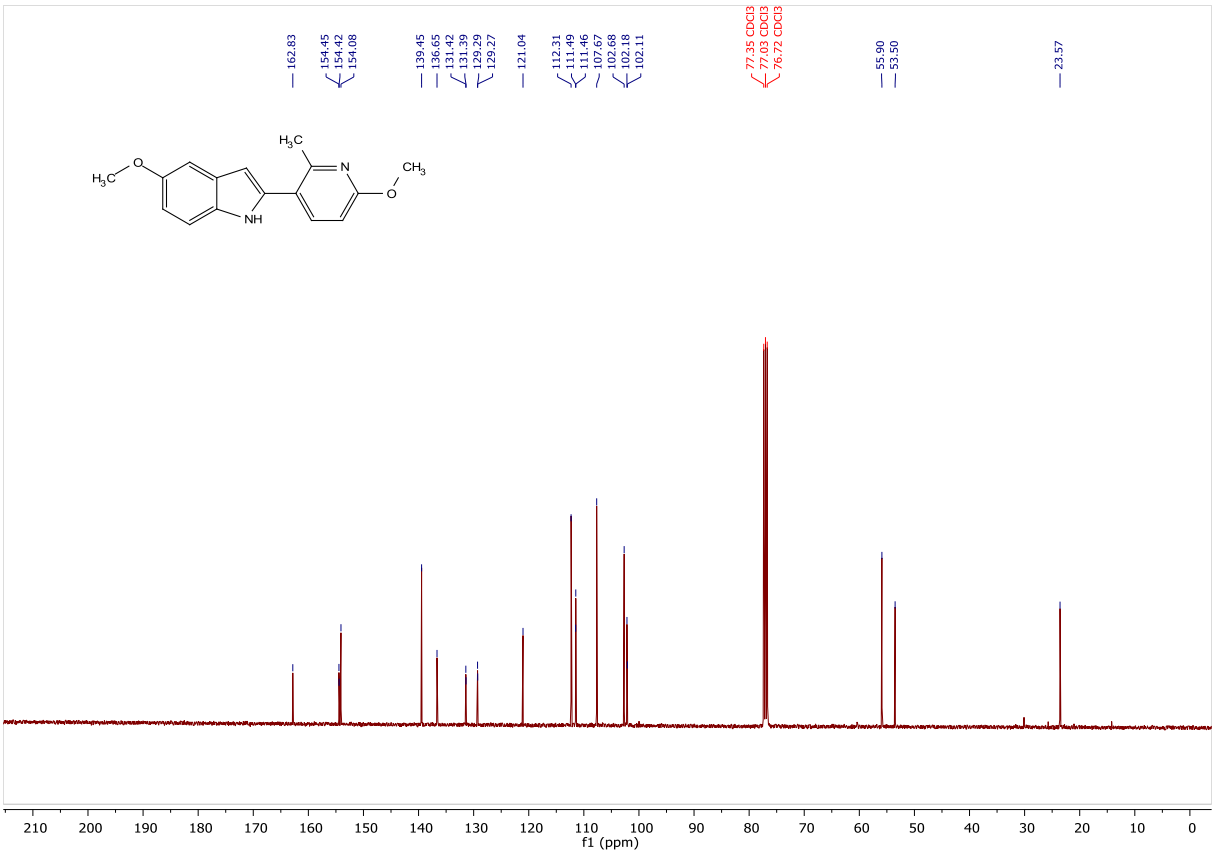

8.63
8.54
8.37
8.35
7.28
7.25
7.19 CDCl3
7.17
7.15
7.05
7.04
6.85
6.84
6.82
6.82
6.54
6.54
3.80
2.45
1.04
0.81
1.09
1.11
1.61
1.05
1.12
1.01
3.11
3.04
f1 (ppm)


154.46
148.95
146.11
145.20
134.30
131.79
129.33
129.07
125.86
113.07
111.84
103.97
102.08
55.87
20.63
f1 (ppm)

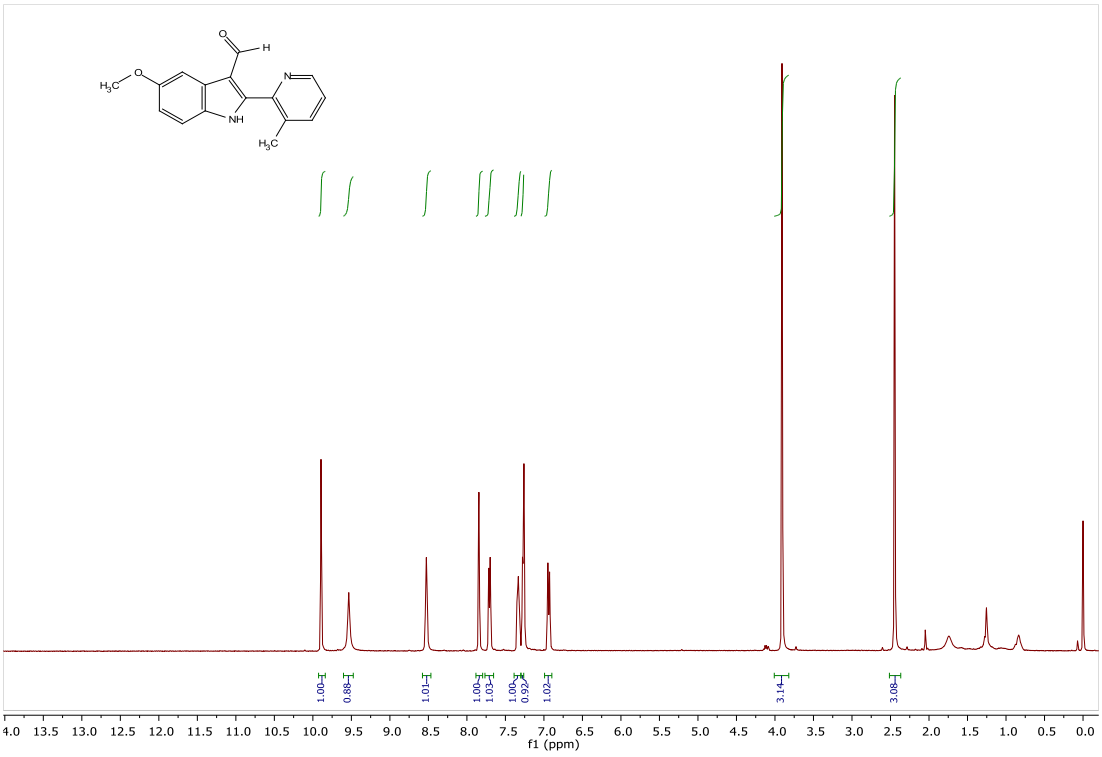

H3C
Cl
O
H3C
N
NH
0.90
1.04
0.97
1.00
1.06
1.03
0.99
3.10
2.97
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

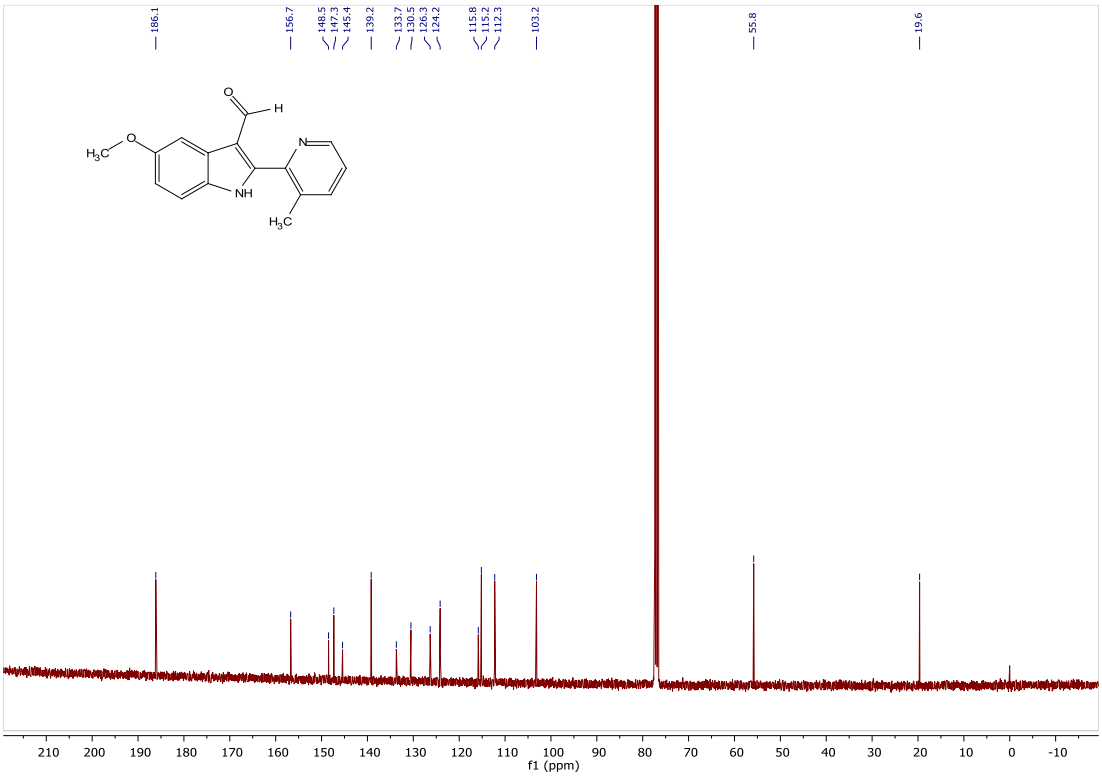

154.70
153.30
146.36
143.07
134.31
131.92
129.81
128.79
122.23
114.27
112.05
105.55
102.20
77.35 CDCl3
77.24
77.03 CDCl3
76.72 CDCl3
55.84
17.75
H3C
Cl
O
H3C
N
NH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

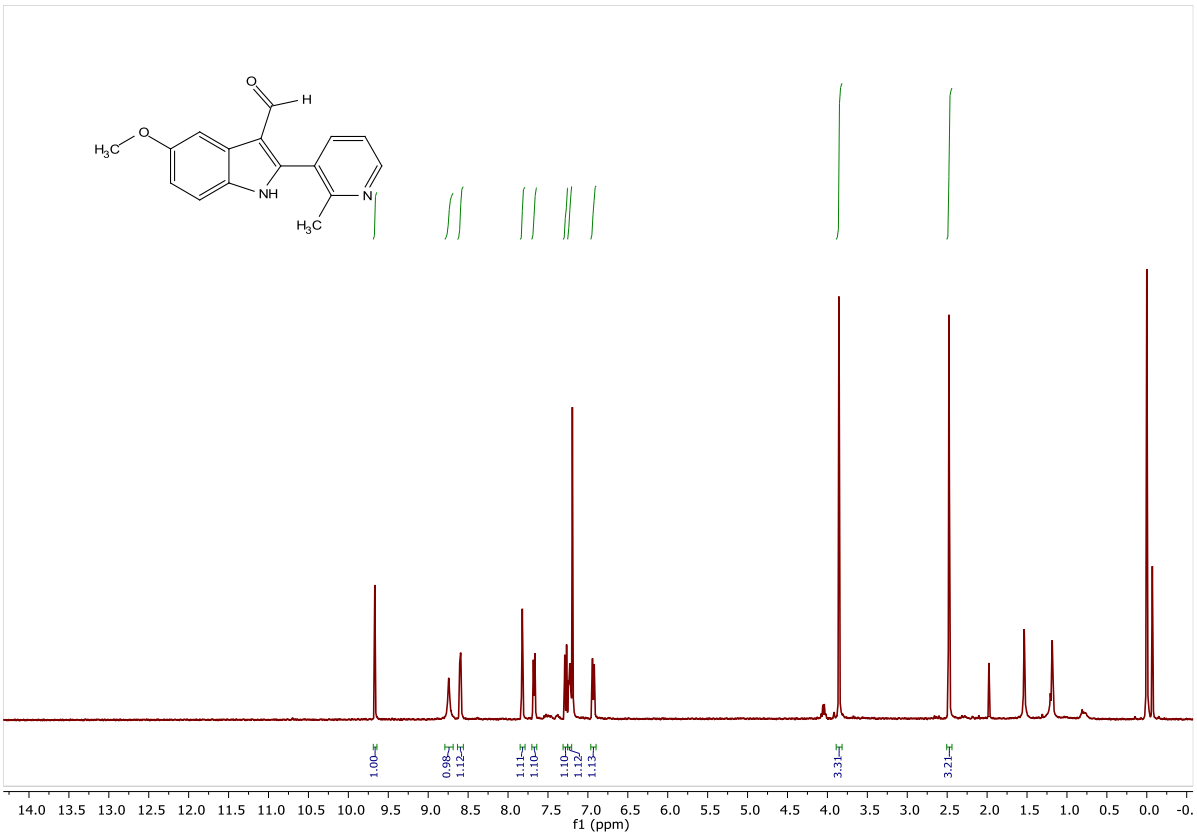

H3C
O
H3C
N
CH3
O
NH
0.91
1.03
1.18
1.05
1.02
1.06
0.99
3.10
3.08
3.06
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

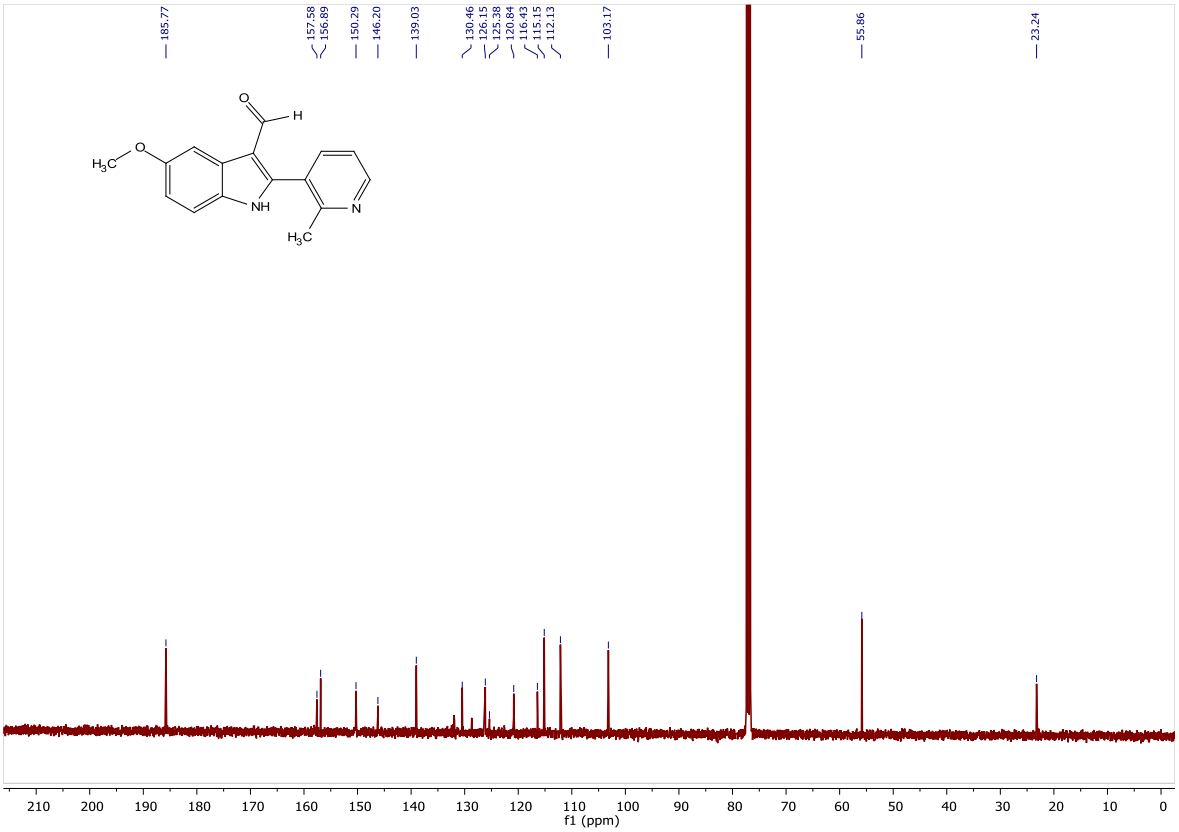

162.83
154.45
154.42
154.08
139.45
136.65
131.42
131.39
129.29
129.27
121.04
112.31
111.49
111.46
107.67
102.68
102.18
102.11
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
55.90
53.50
23.57
H3C
O
H3C
N
CH3
O
NH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

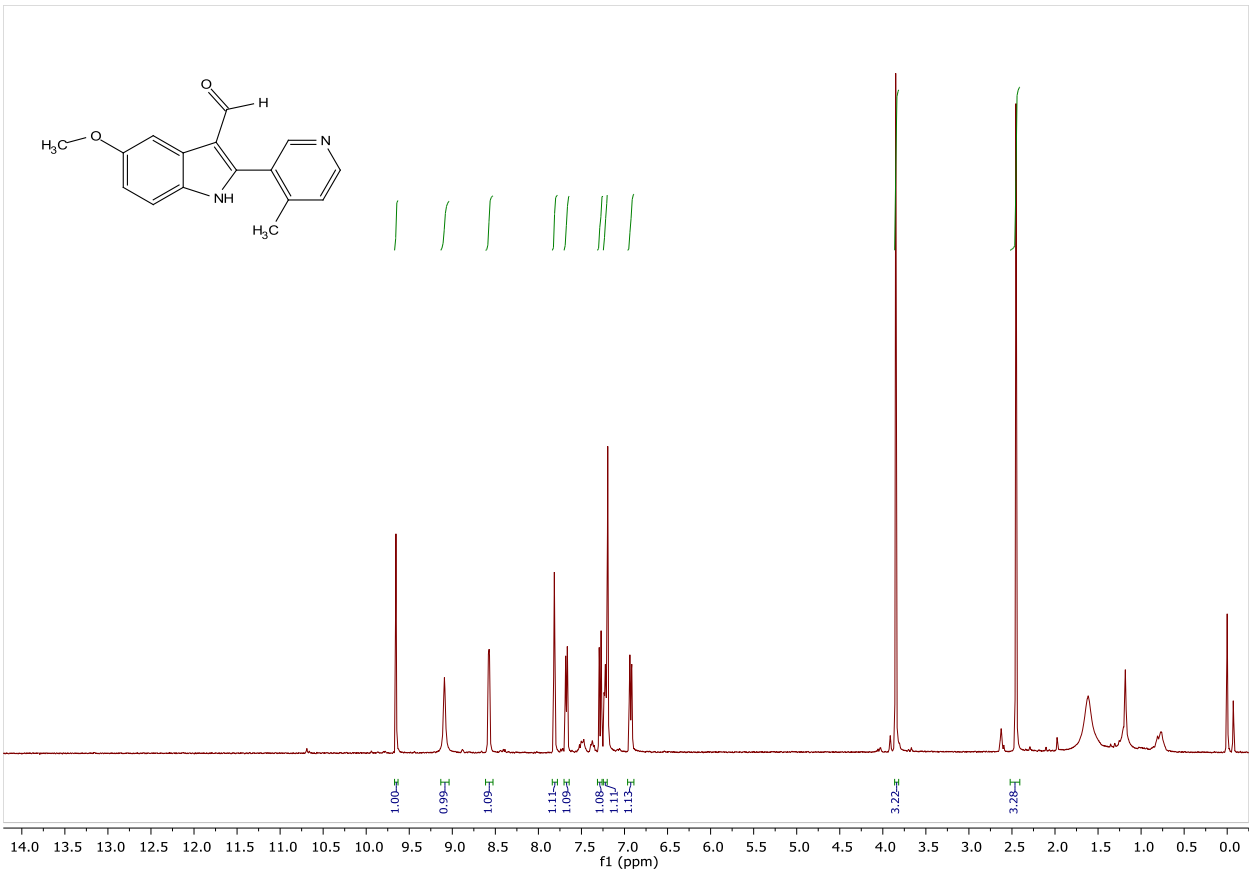
Formylation

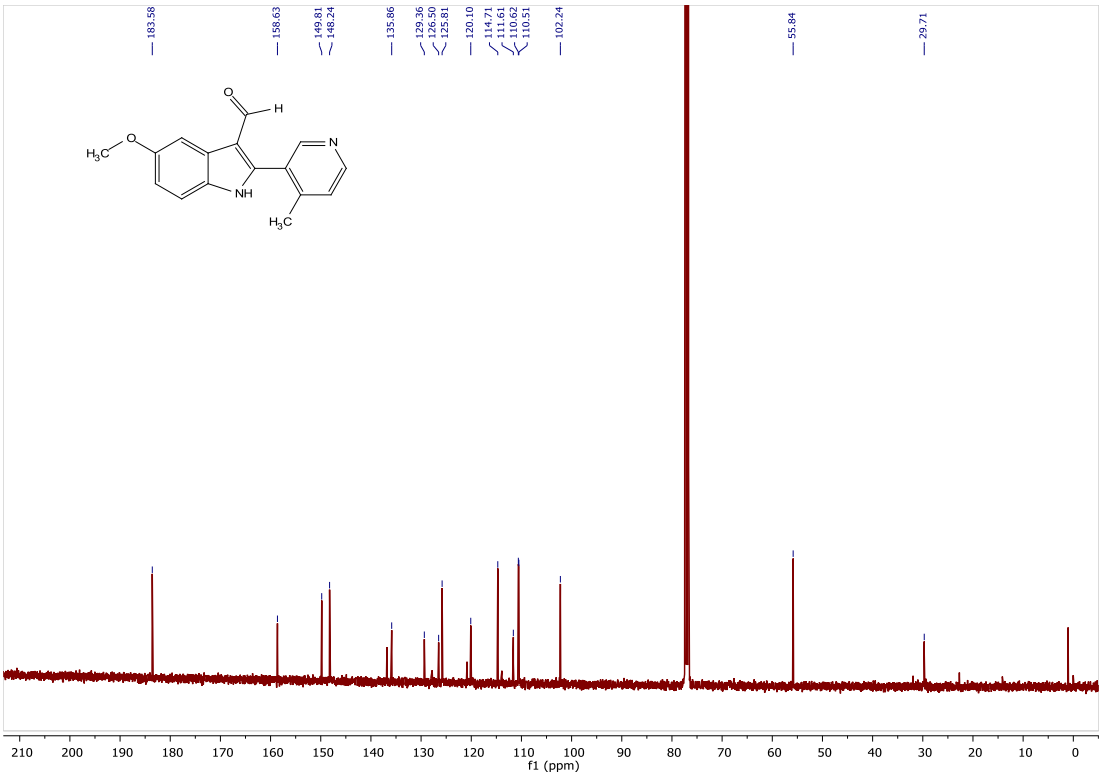


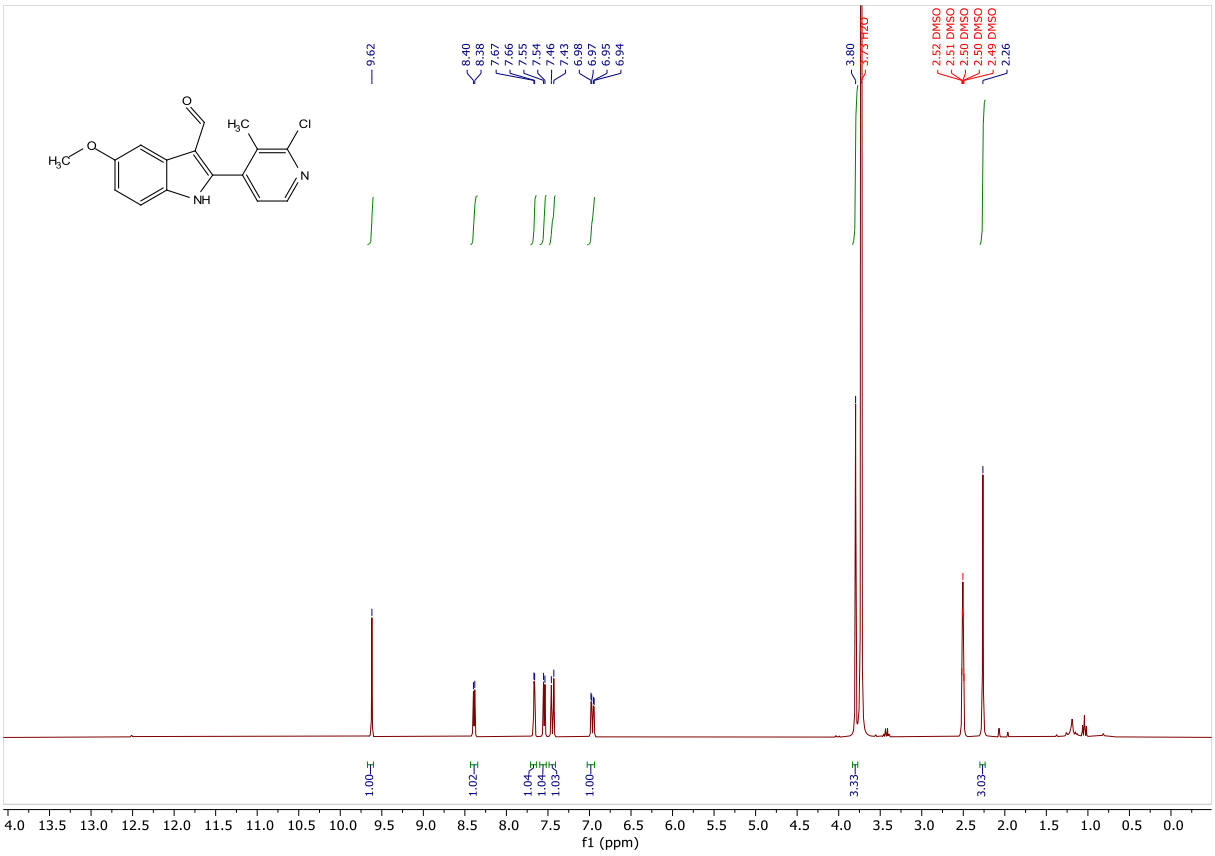


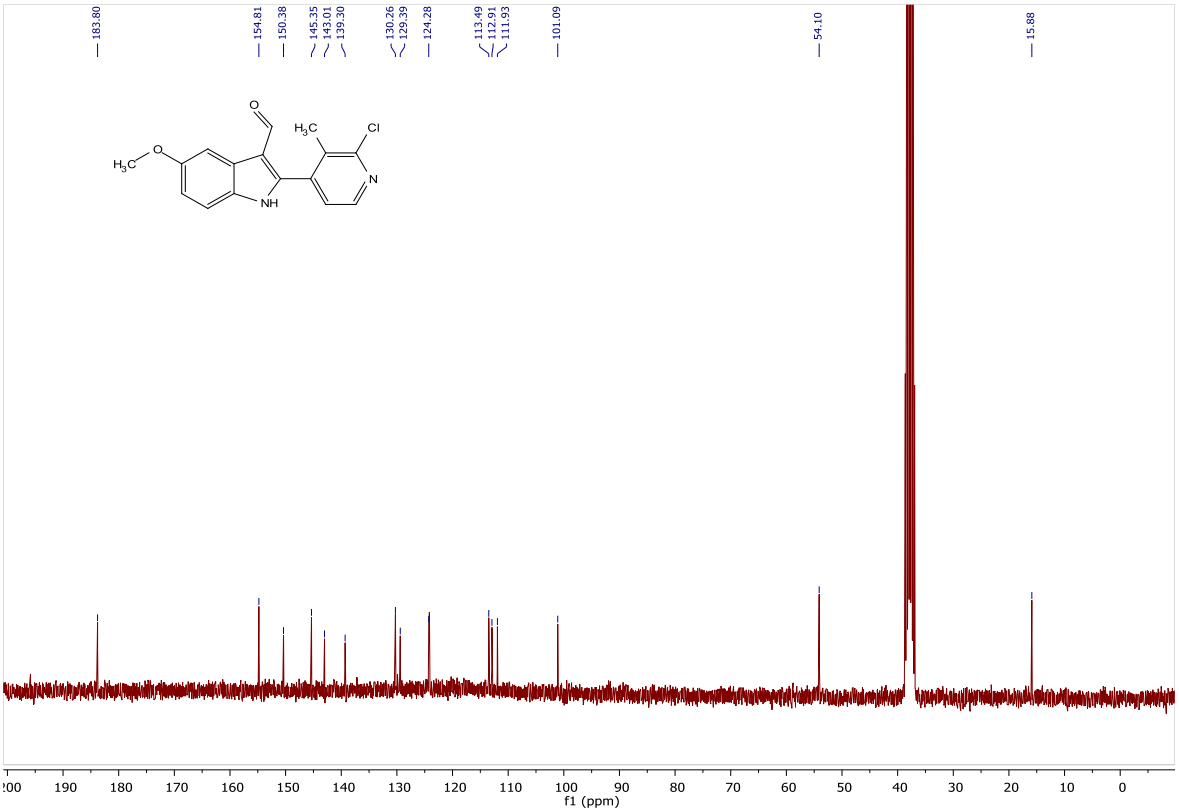

O
H
H3C
O
NH
N
H3C
1.00
0.98
1.12
1.11
1.10
1.10
1.12
1.13
3.31
3.21
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

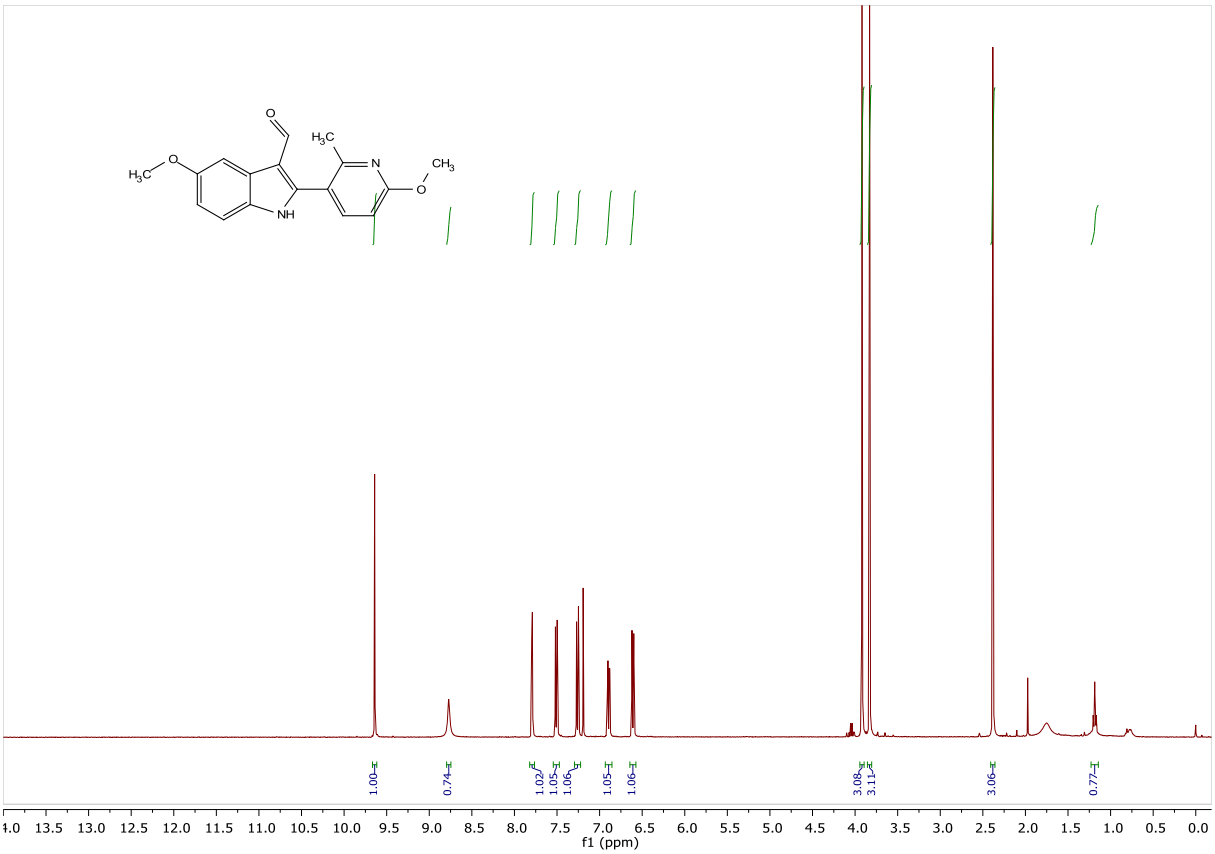

185.77
157.58
156.89
150.29
146.20
139.03
130.46
126.15
125.38
120.84
116.43
115.15
112.13
103.17
55.86
23.24
O
H
H3C
O
NH
N
H3C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

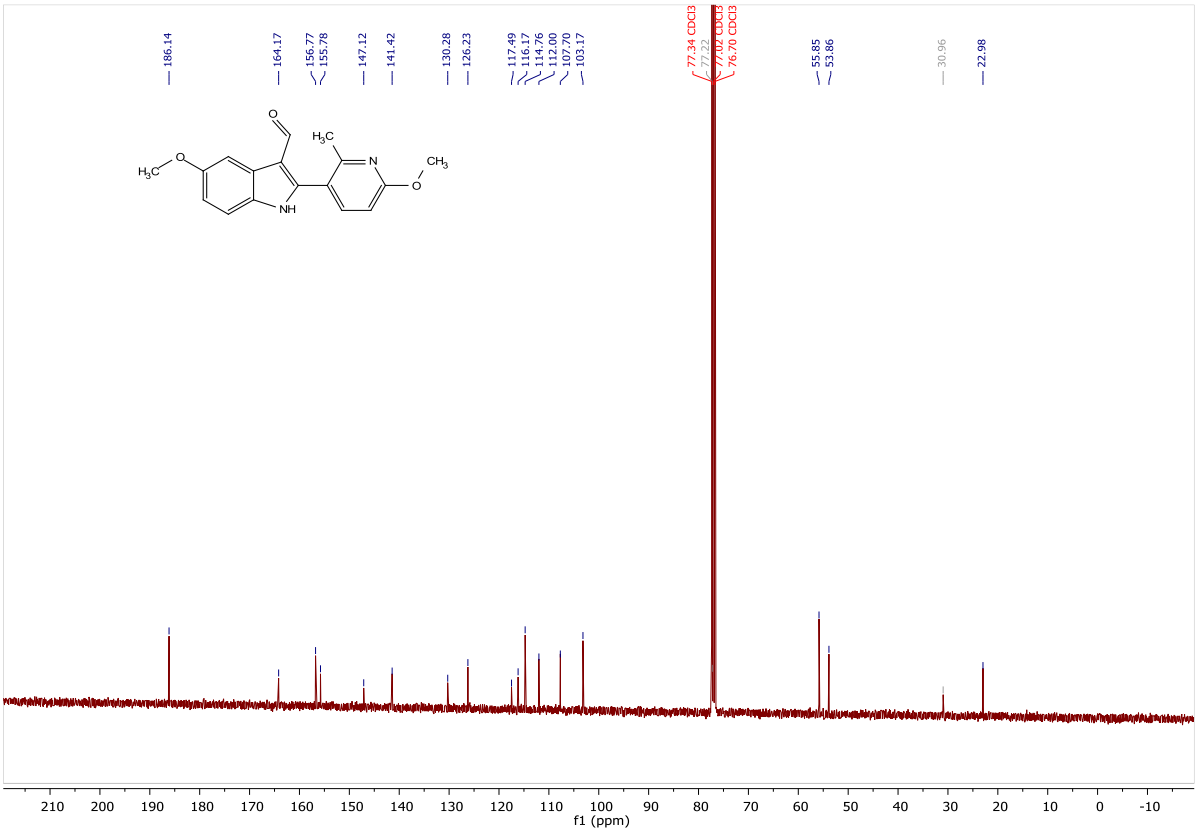

O
H
H3C
O
N
NH
H3C
1.00
0.99
1.09
1.11
1.09
1.08
1.11
1.13
3.22
3.28
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


183.58
158.63
149.81
148.24
135.86
129.36
126.50
125.81
120.10
114.71
111.61
110.62
110.51
102.24
55.84
29.71
O
H
H3C
O
N
NH
H3C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

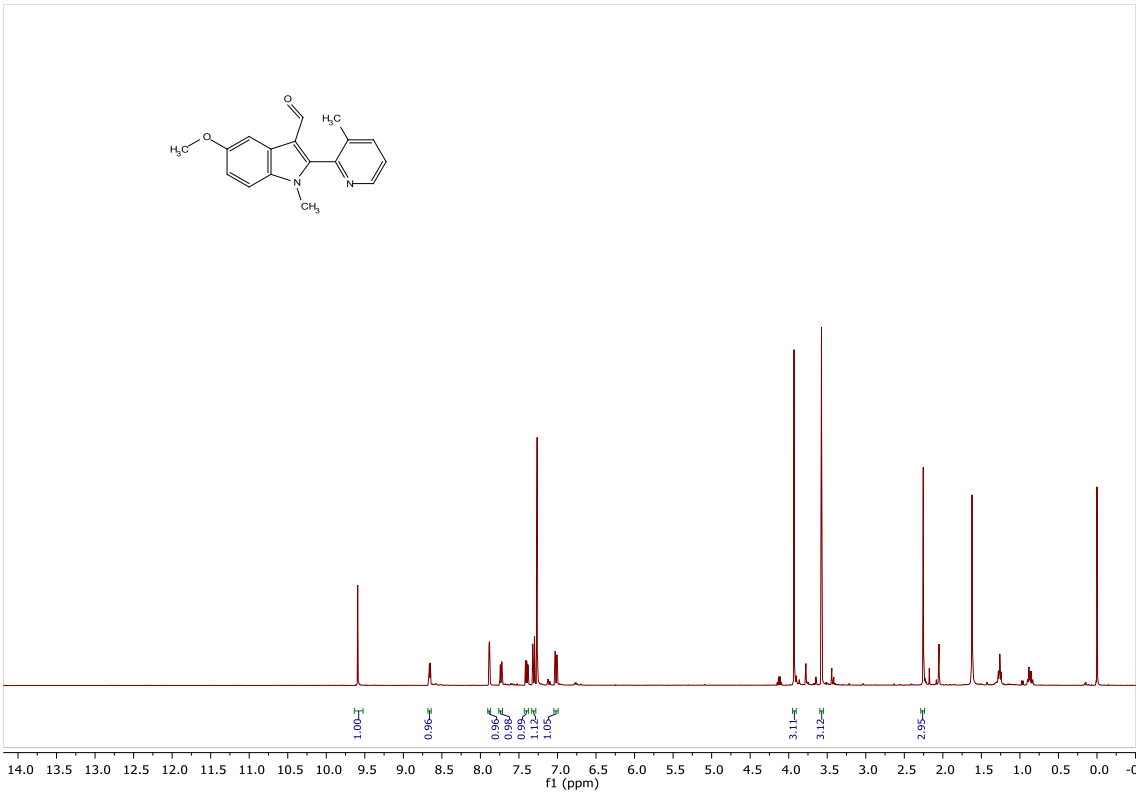

9.62
8.40
8.38
7.67
7.66
7.55
7.54
7.46
7.43
6.98
6.97
6.95
6.94
3.80
2.52 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.49 DMSO
2.26
1.00
1.02
1.04
1.04
1.03
1.00
3.33
3.03
f1 (ppm)

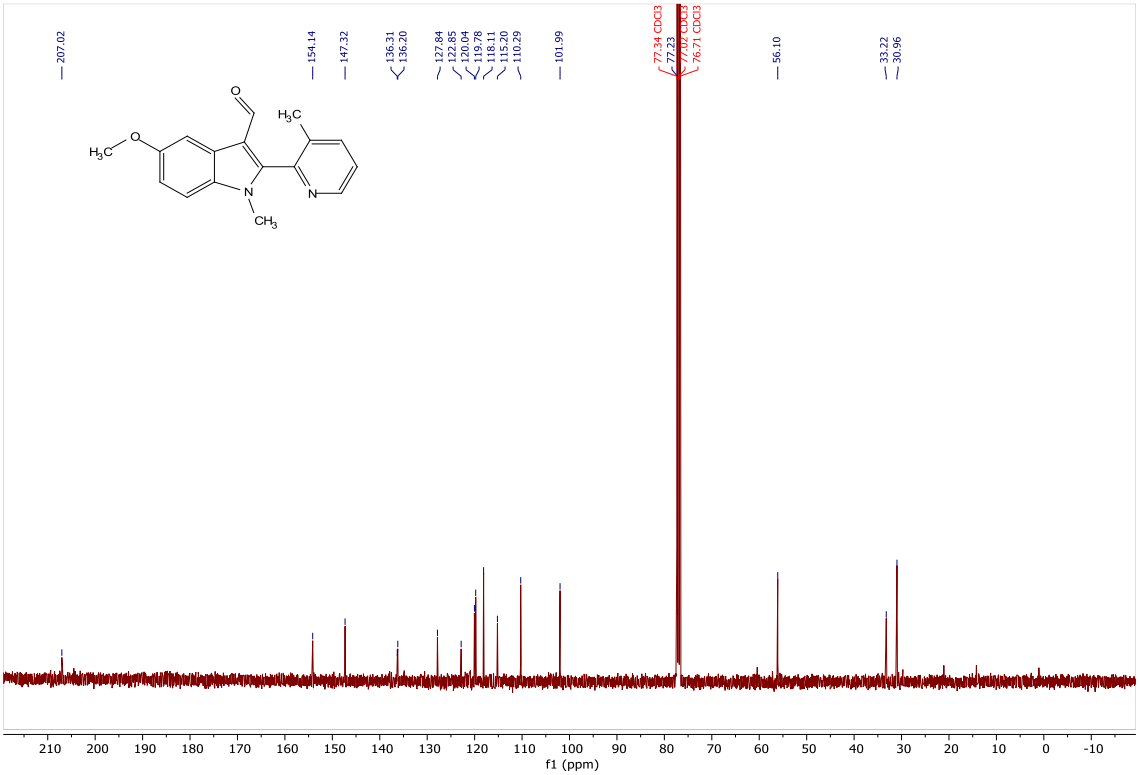

183.80
154.81
150.38
145.35
143.01
139.30
130.26
129.39
124.28
113.49
112.91
111.93
101.09
54.10
15.88
f1 (ppm)

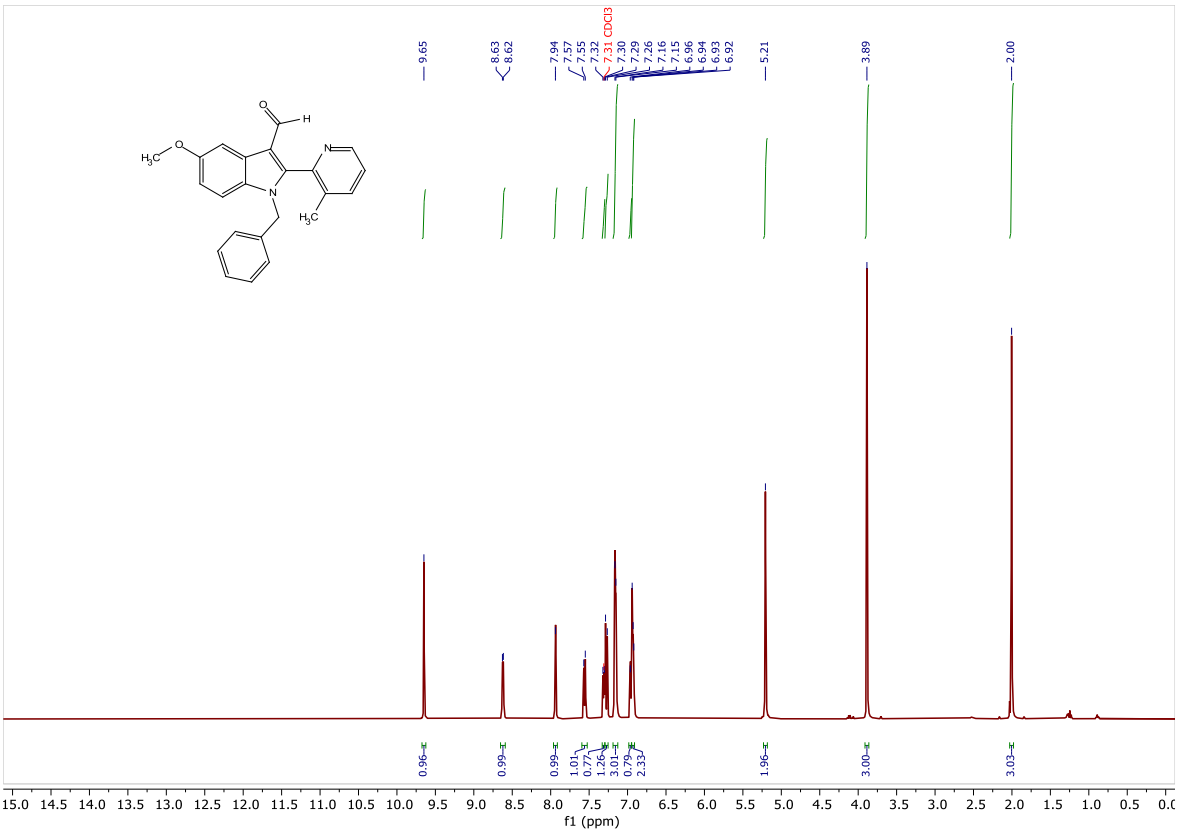

1.00
0.74
1.02
1.05
1.06
1.05
1.06
3.08
3.11
3.06
0.77
f1 (ppm)

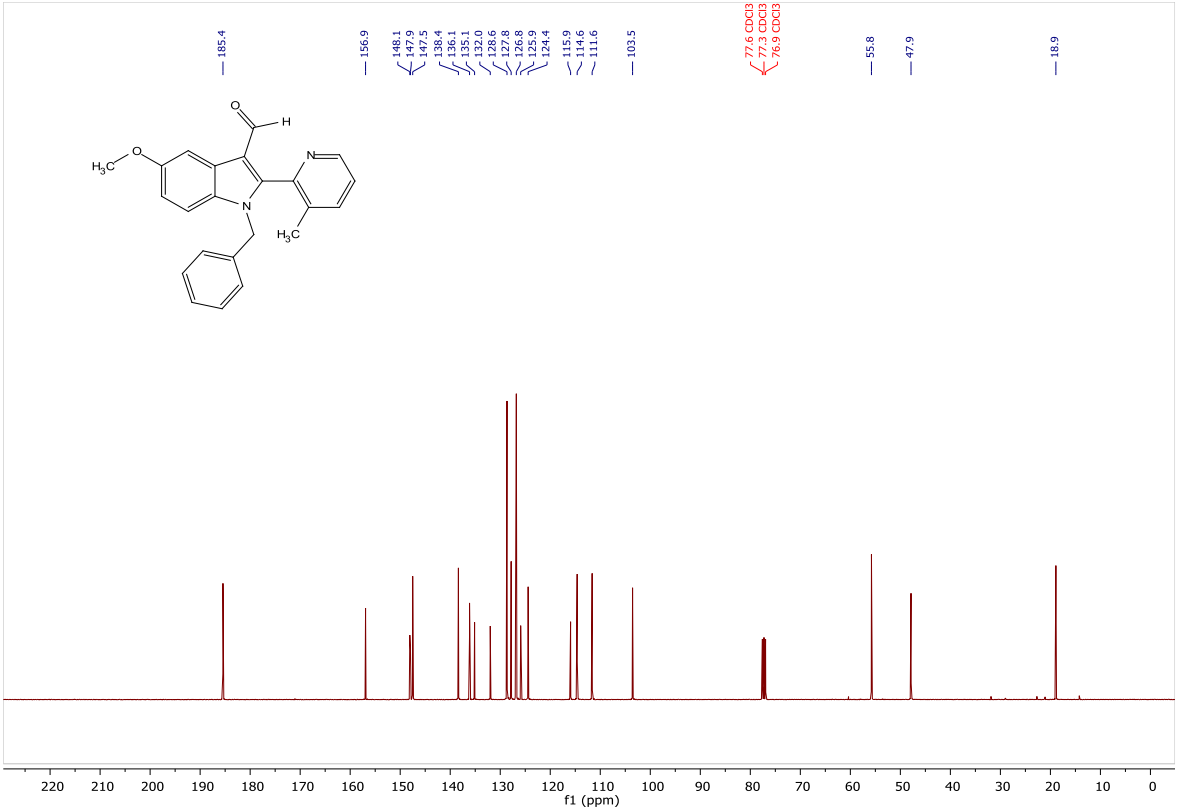

186.14
164.17
156.77
155.78
147.12
141.42
130.28
126.23
117.49
116.17
113.76
112.00
107.70
103.17
77.34 CDCl3
77.22
77.02 CDCl3
76.70 CDCl3
55.85
53.86
30.96
22.98
f1 (ppm)

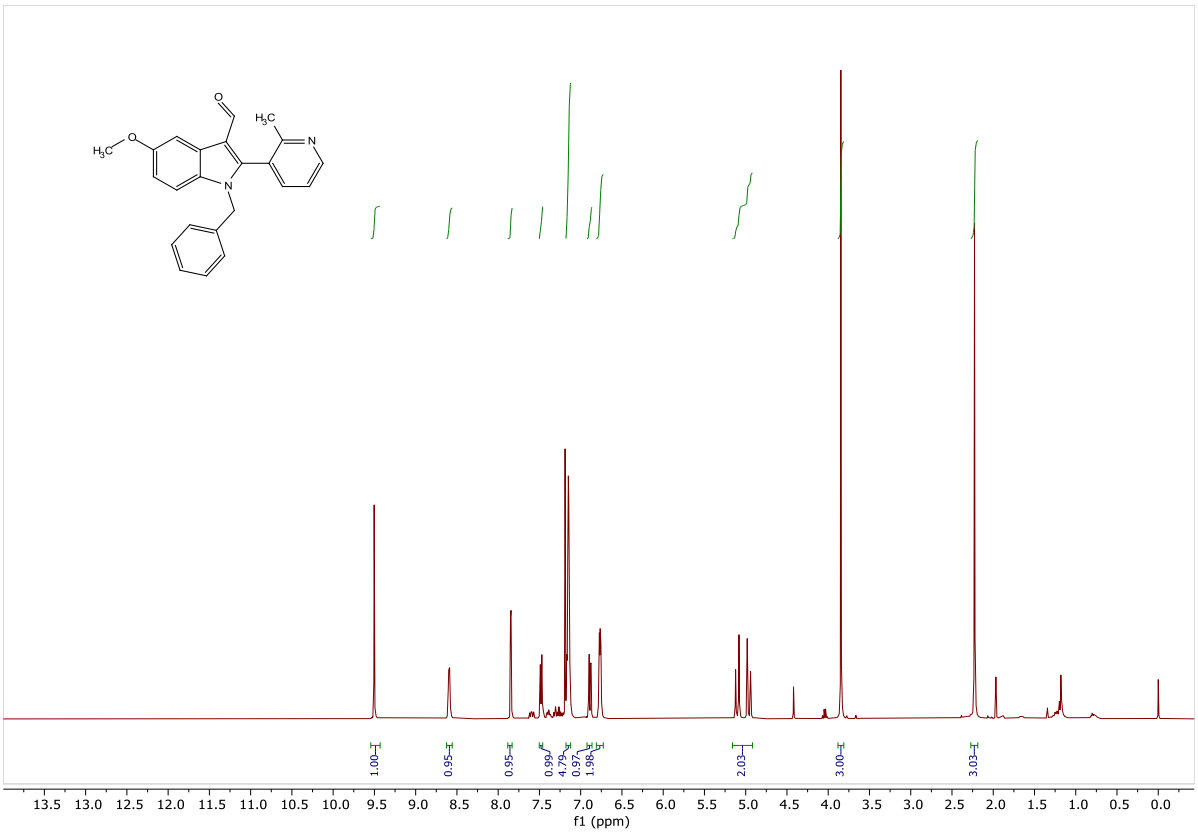
Methylation/Benzylation

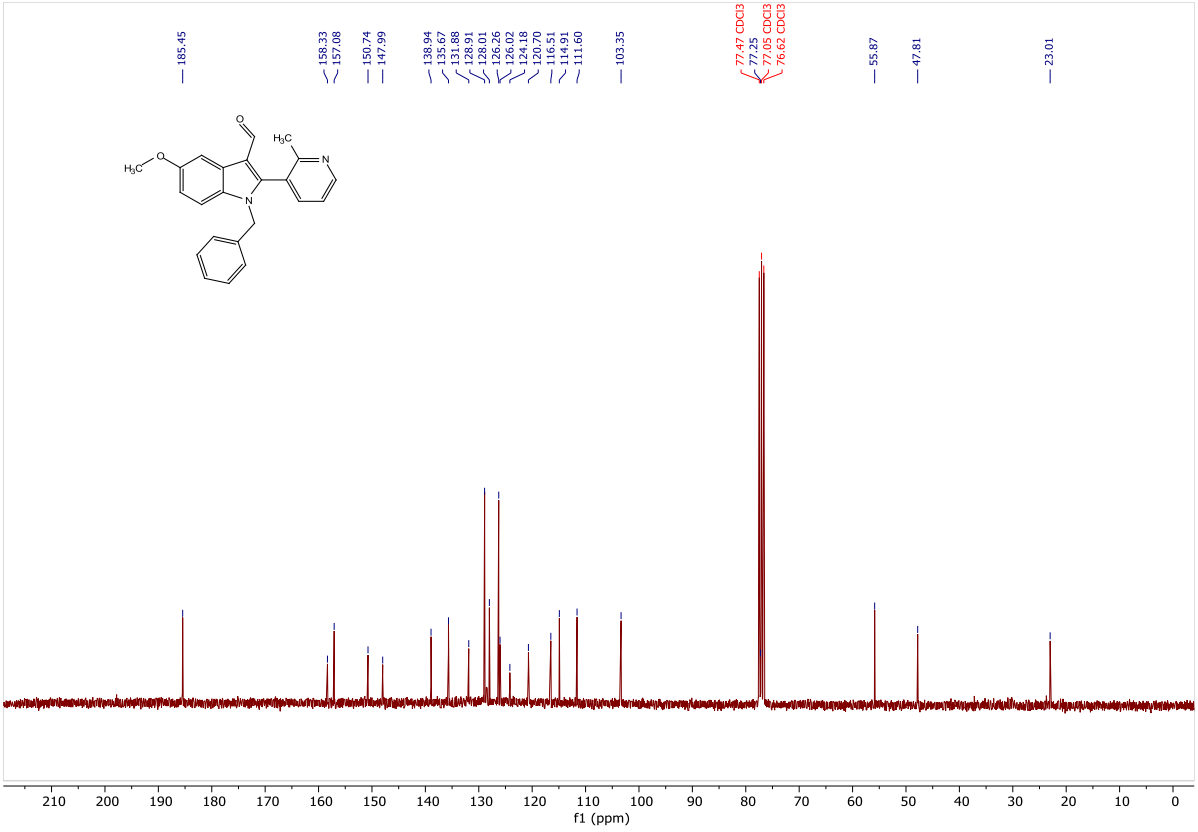


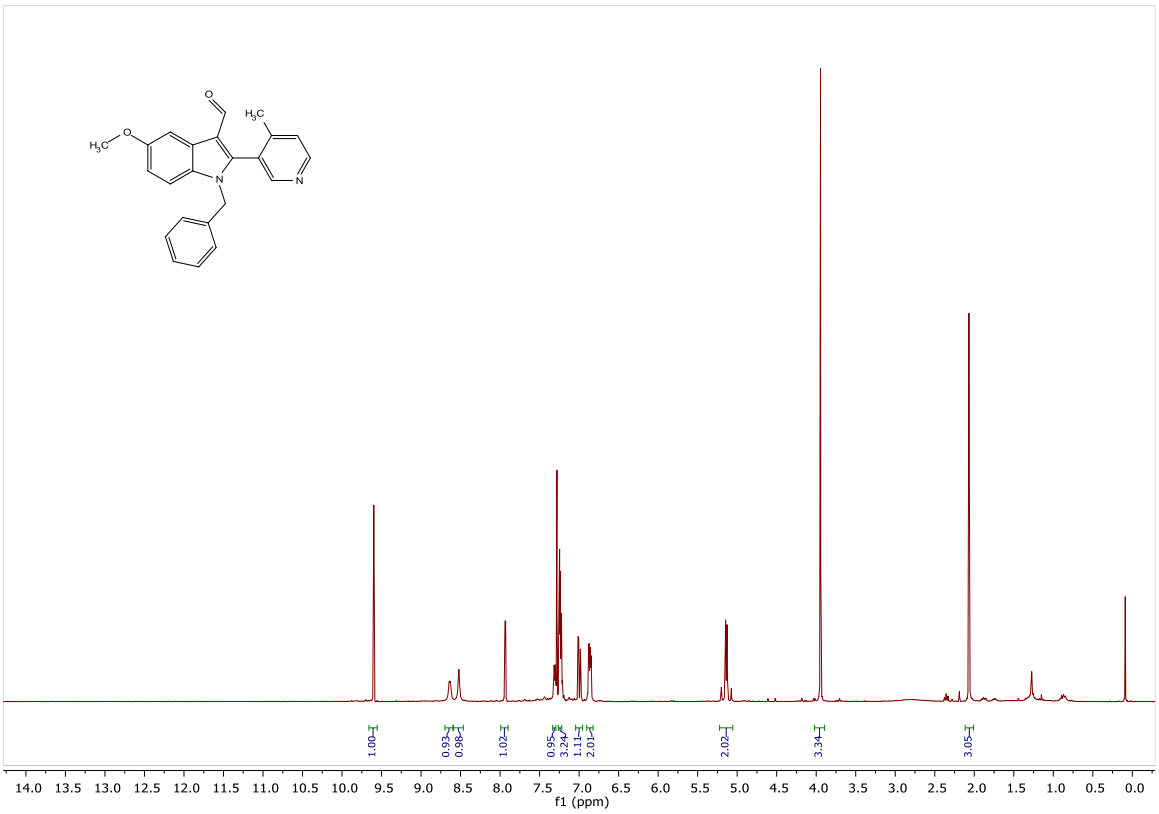


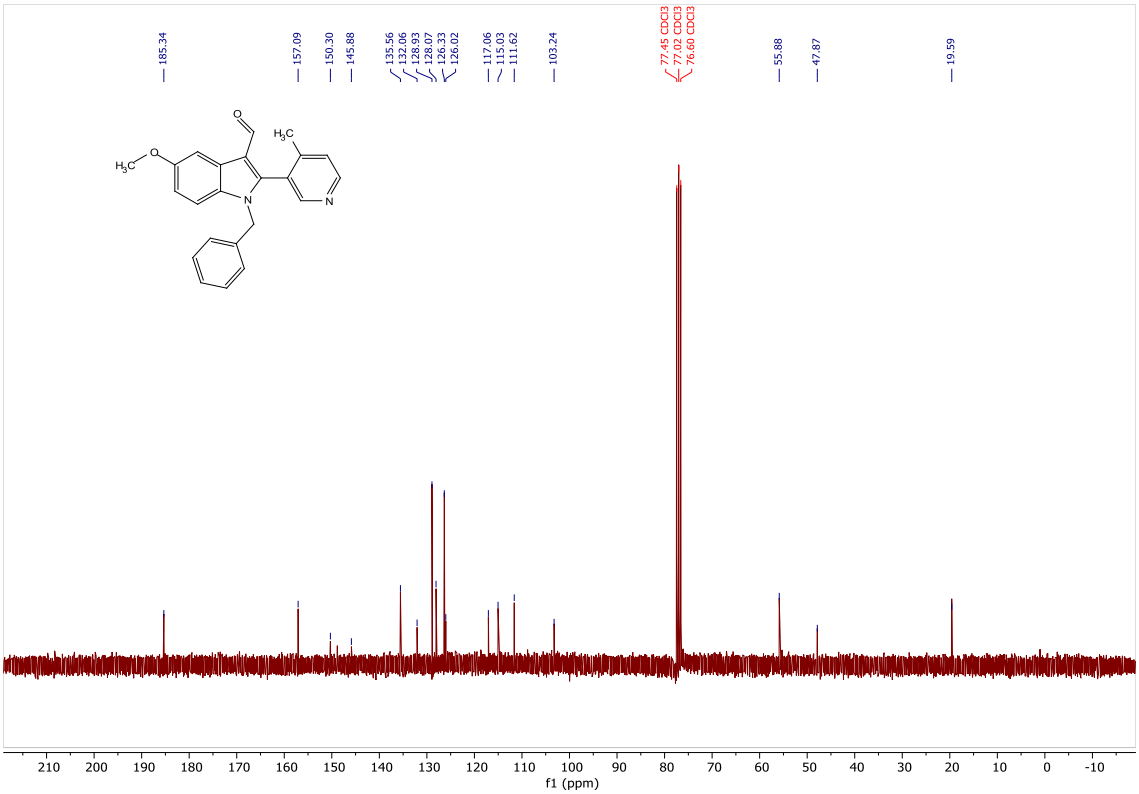

9.65
8.63
8.62
7.94
7.57
7.55
7.33
7.31 CDCl3
7.30
7.29
7.26
7.16
7.15
6.96
6.94
6.93
6.92
5.21
3.89
2.00
0.96
0.99
0.99
1.01
0.77
1.26
3.01
0.79
2.33
1.96
3.00
3.03
f1 (ppm)

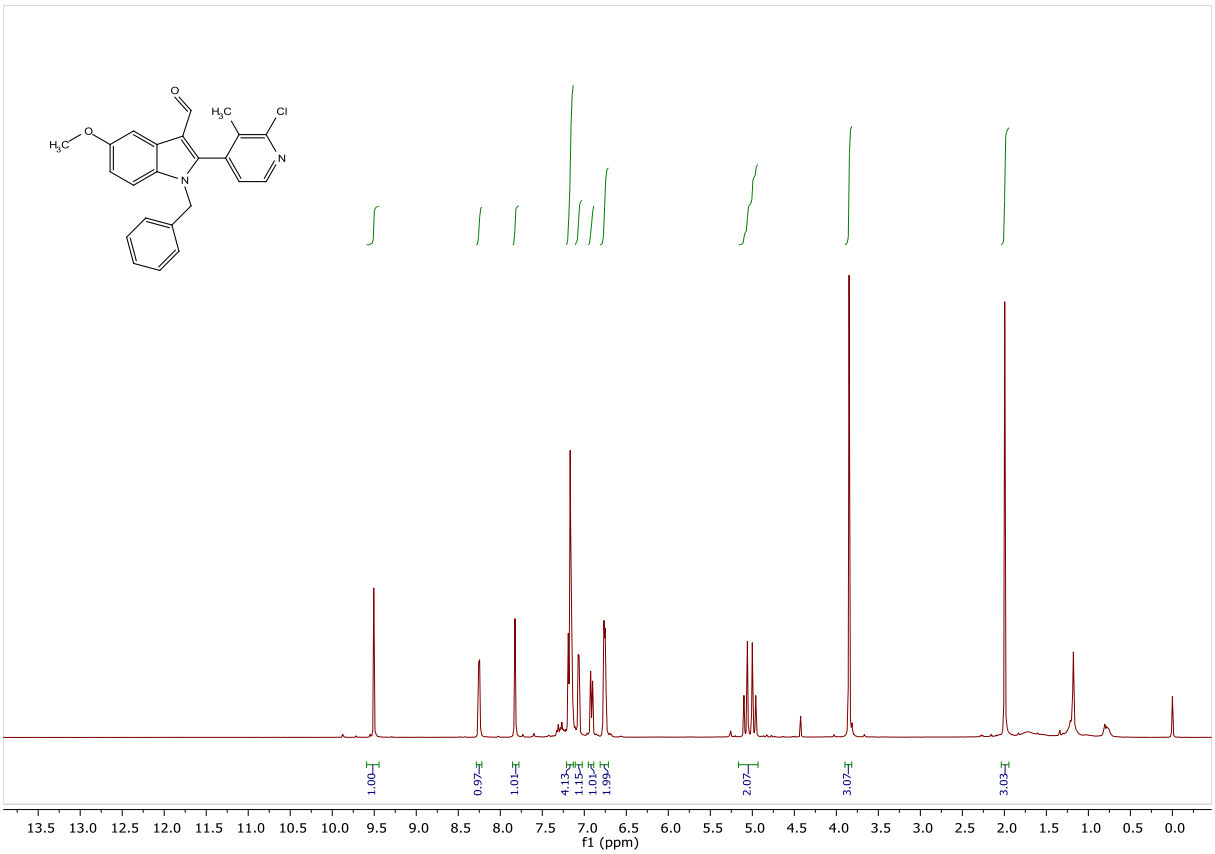

185.4
156.9
148.1
147.9
147.5
138.4
136.1
135.1
132.0
128.6
127.8
126.8
125.9
124.4
115.9
114.6
111.6
103.5
77.6 CDCl3
77.3 CDCl3
76.9 CDCl3
55.8
47.9
18.9
f1 (ppm)

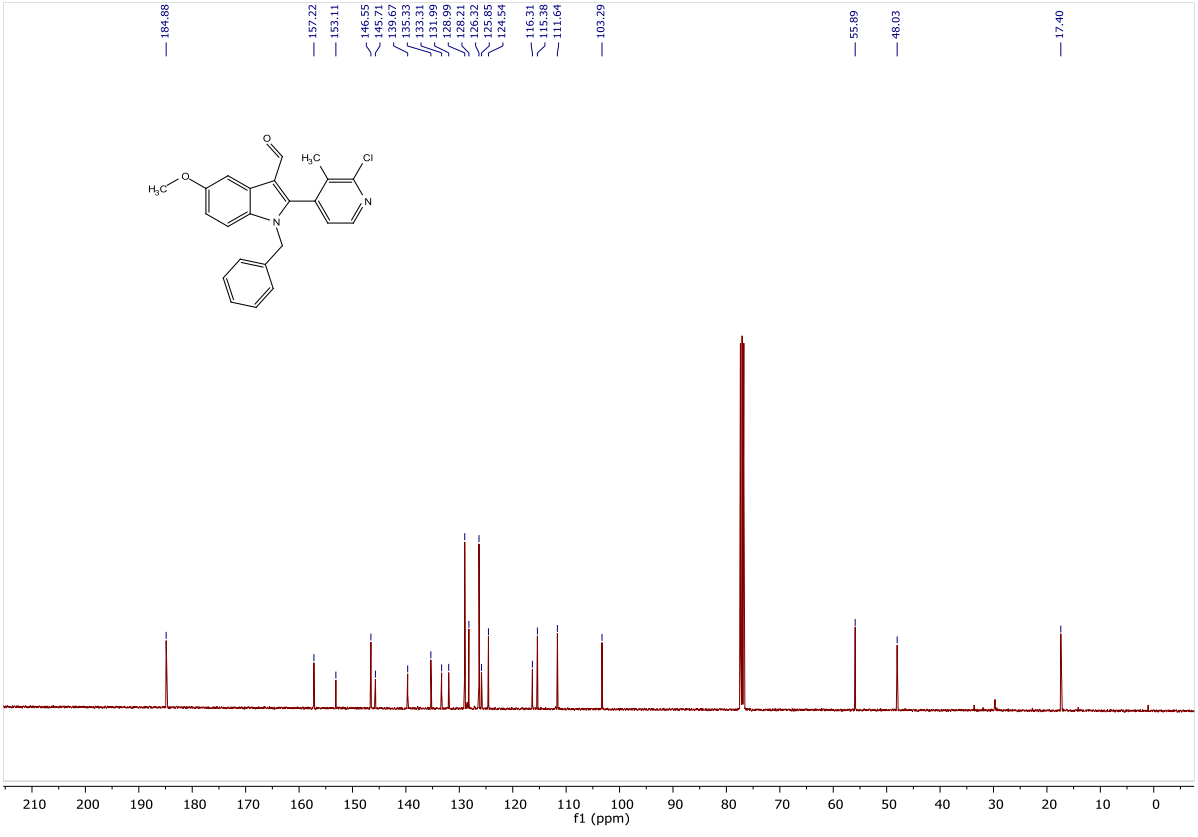

1.00
0.95
0.95
0.99
4.79
0.97
1.98
2.03
3.00
3.03
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

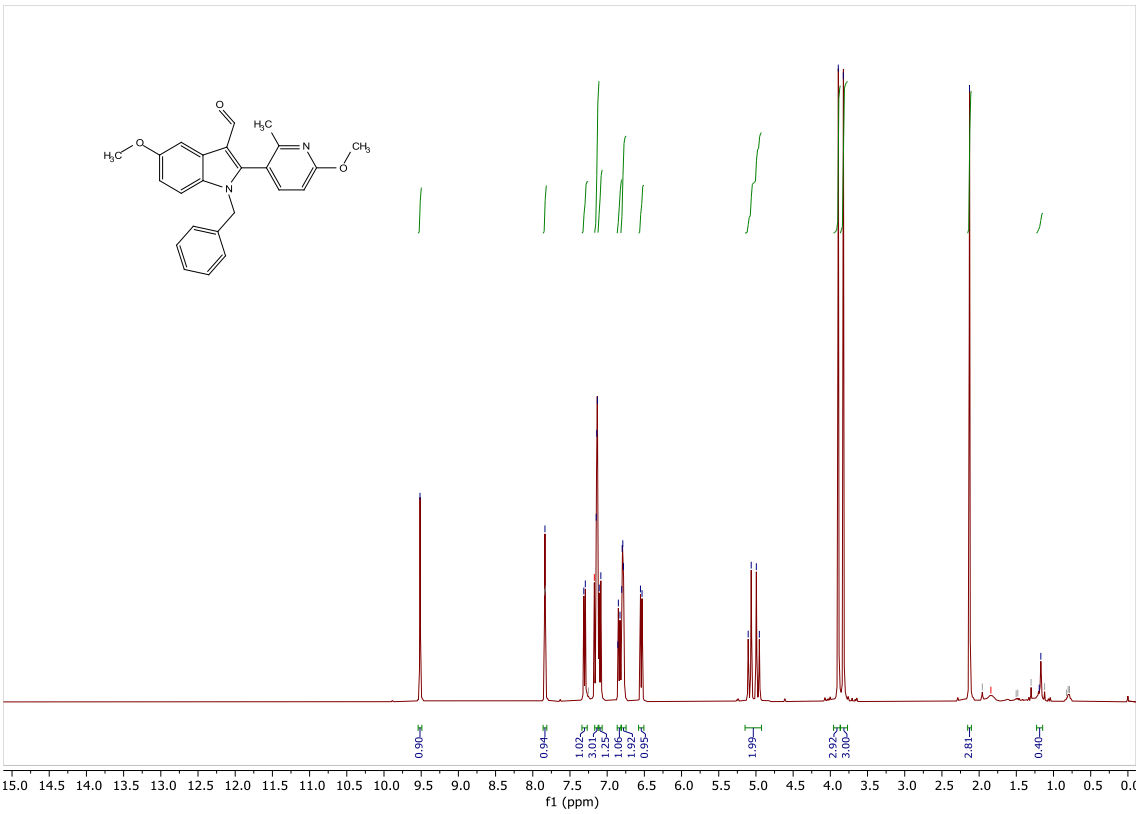

185.45
158.33
157.08
150.74
147.99
138.94
135.67
131.88
129.91
128.01
126.26
126.02
124.18
120.70
116.51
114.91
111.60
103.35
77.47 CDCl3
77.25
77.05 CDCl3
76.62 CDCl3
55.87
47.81
23.01
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

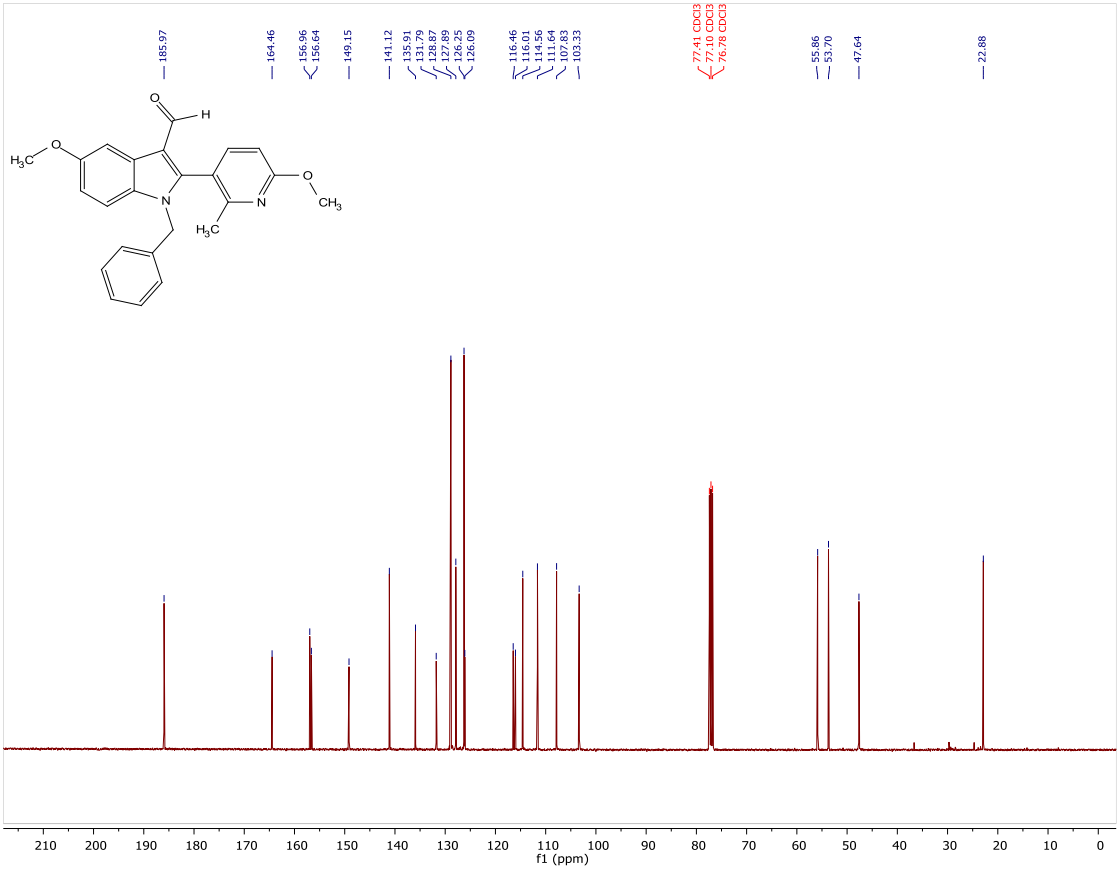

1.00
0.93
0.98
1.02
0.95
3.24
1.11
2.01
2.02
3.34
3.05
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


185.34
157.09
150.30
145.88
135.56
132.06
128.93
128.07
126.33
126.02
117.06
115.03
111.62
103.24
77.45 CDCl3
77.02 CDCl3
76.60 CDCl3
55.88
47.87
19.59
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

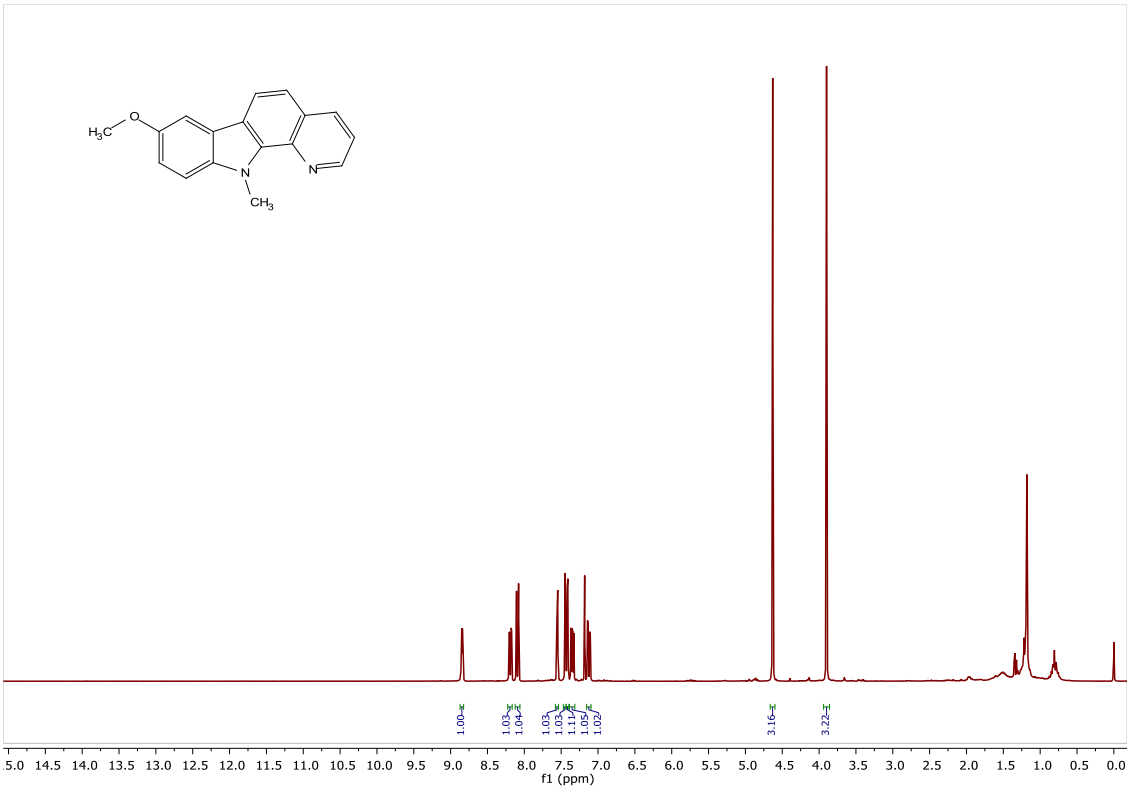

1.00
0.97
1.01
4.13
1.15
1.01
1.99
2.07
3.07
3.03
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

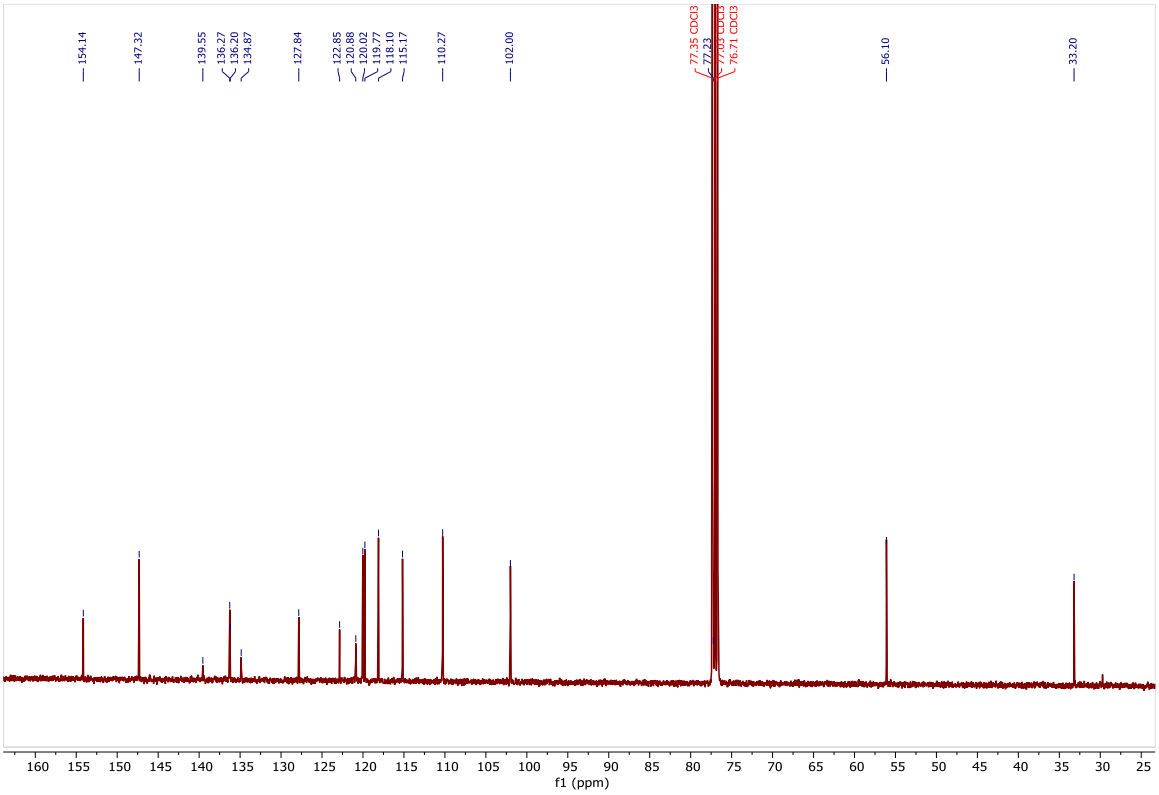

184.88
157.22
153.11
146.55
145.71
139.67
135.33
133.31
131.99
128.99
128.21
126.32
125.85
124.54
116.31
115.38
111.64
103.29
55.89
48.03
17.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

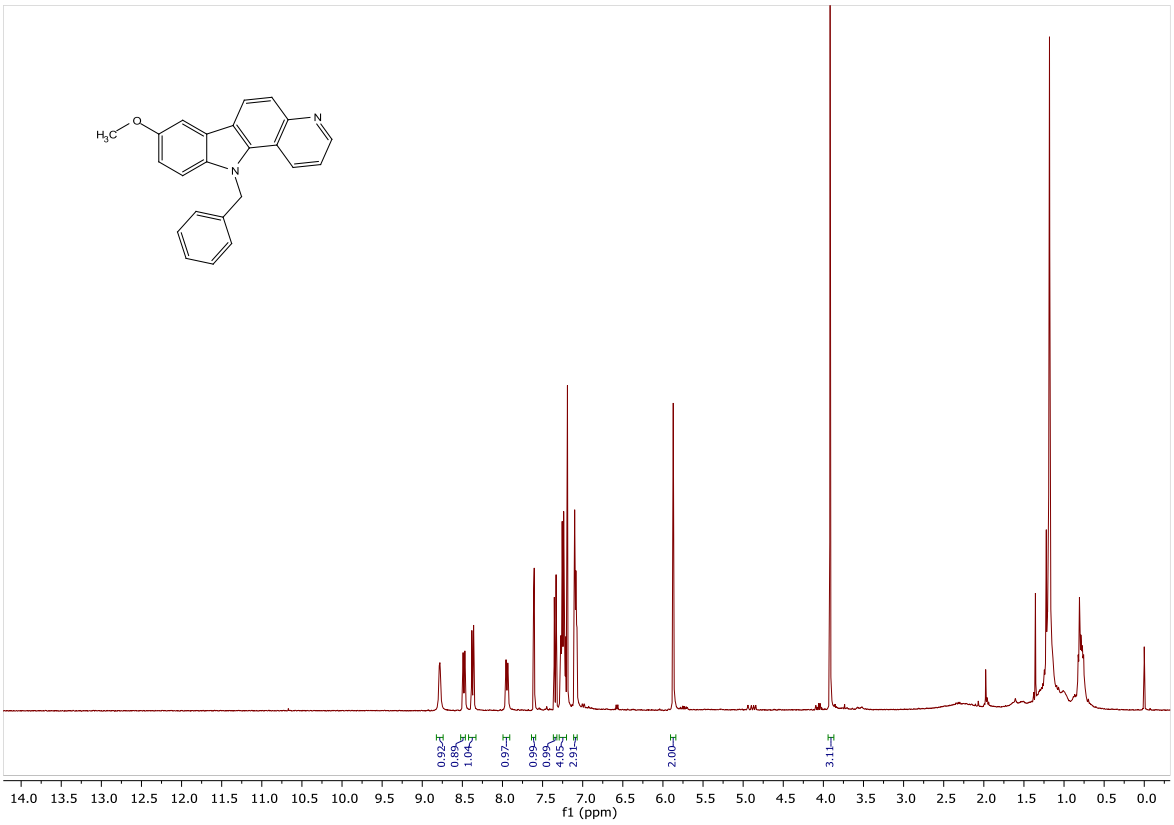

0.90
0.94
1.02
3.01
1.25
1.06
1.92
0.95
1.99
2.92
3.00
2.81
0.40
15.0 14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


185.97
164.46
156.96
156.64
149.15
141.12
135.91
131.79
128.87
127.89
126.25
126.09
116.46
116.01
114.55
111.64
107.83
103.33
77.41 CDCl3
77.10 CDCl3
76.78 CDCl3
55.86
53.70
47.64
22.88
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

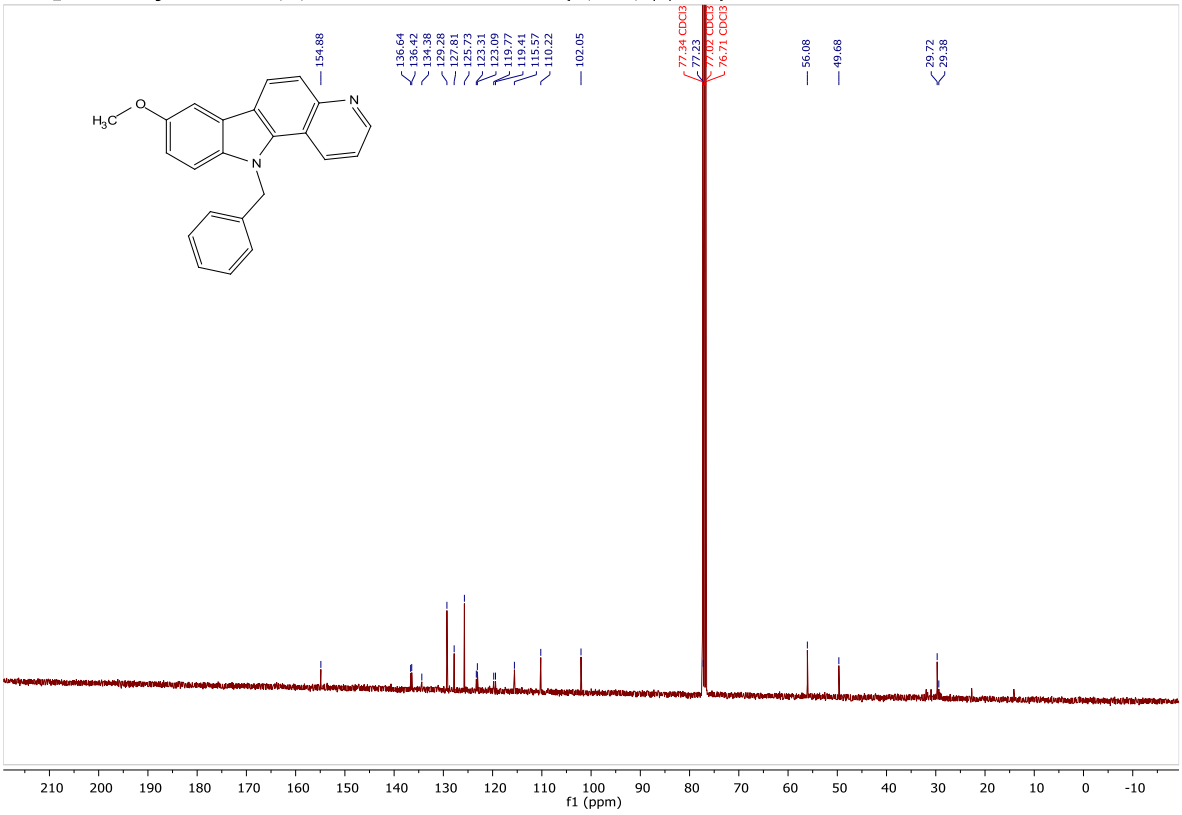
Intramolecular cyclization

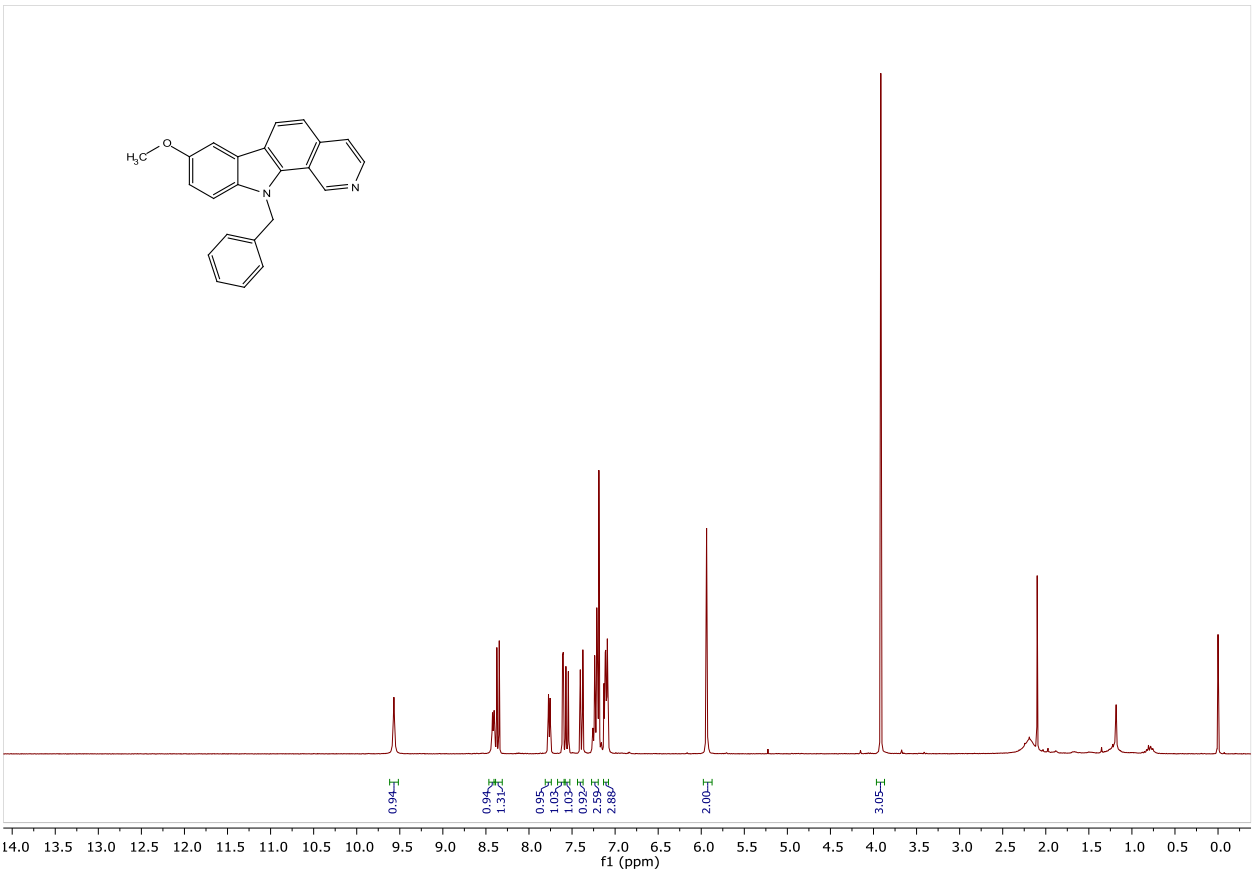




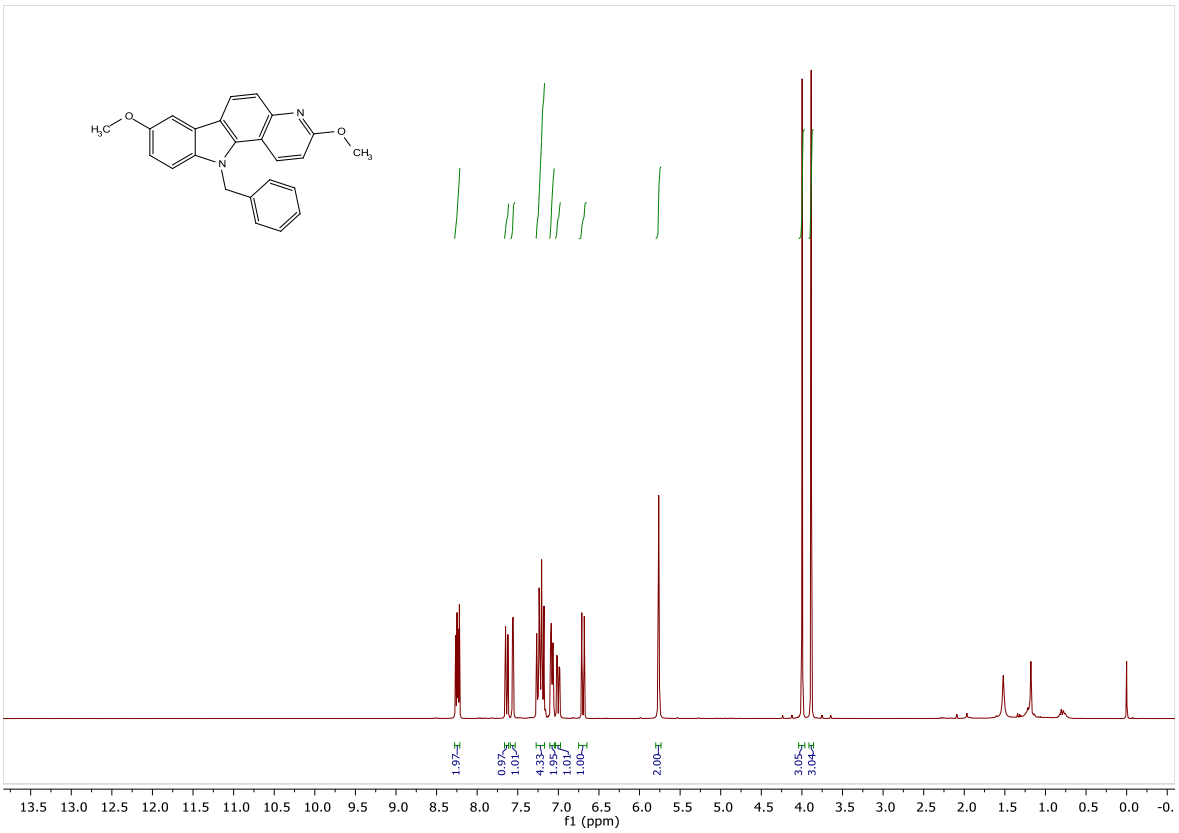


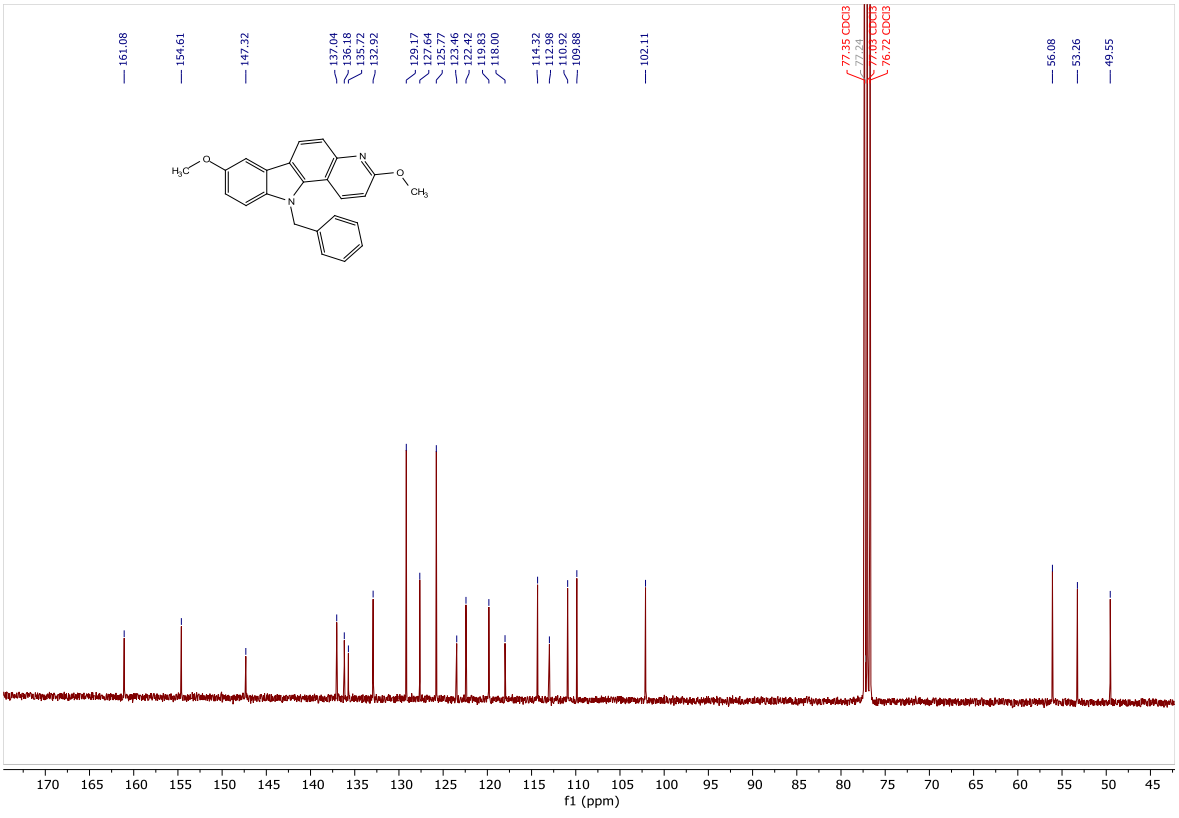
BM-087_1.11.fid — Bongi BM-087 CDCl3 22/04/2022 1H SN 400 MHz — C13CPD CDCl3 {C:\Bruker\TopSpin3.6.2} Users 19

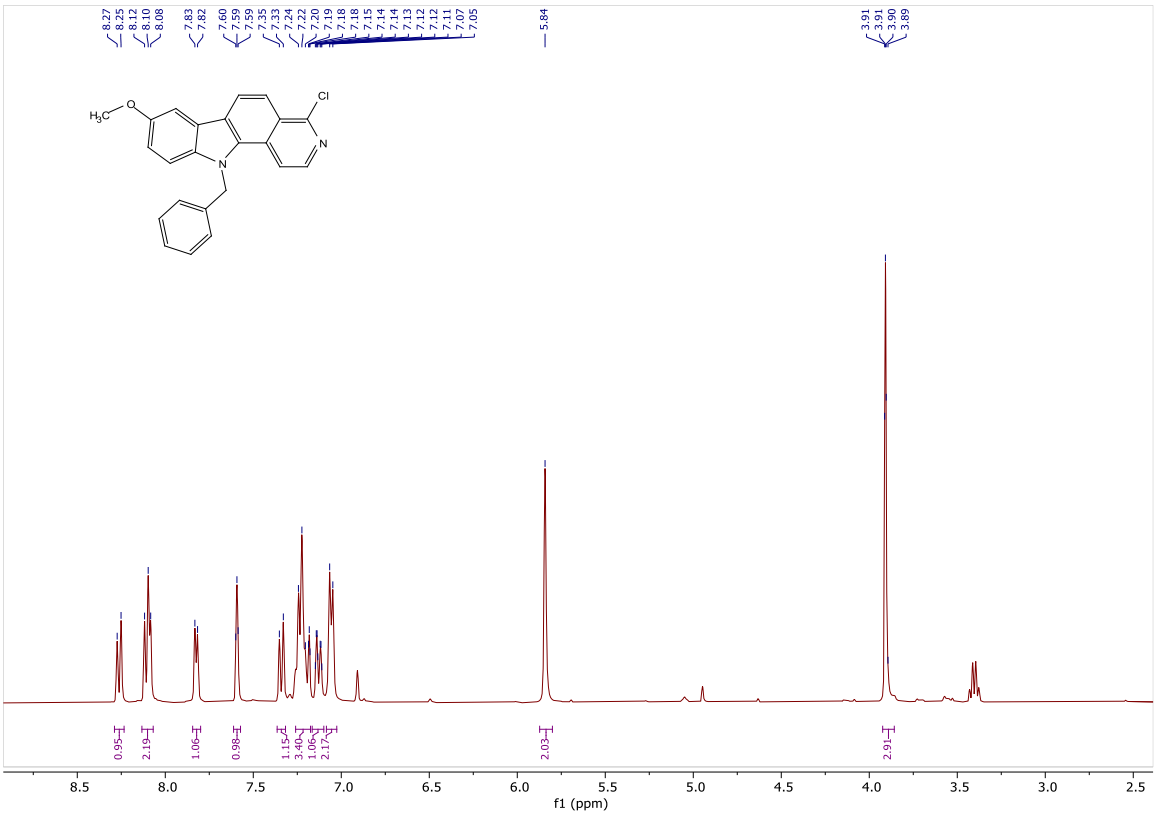


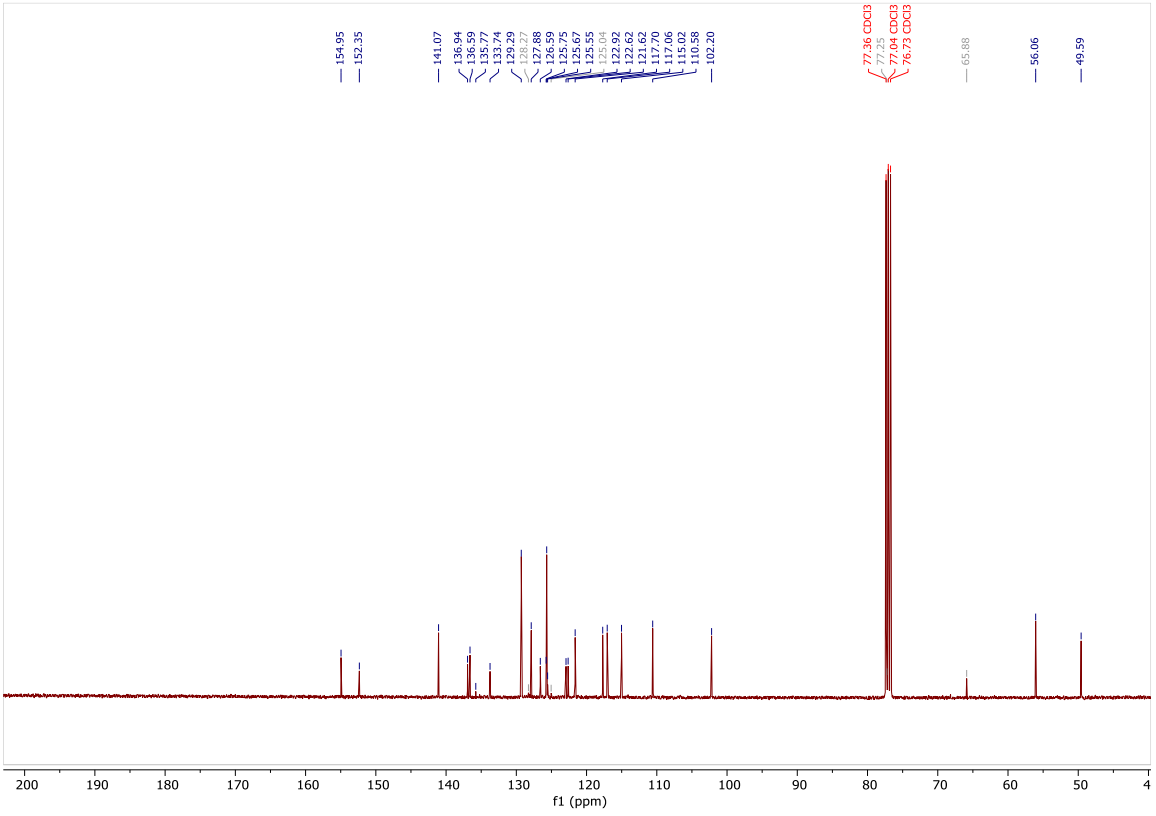


BM-086 CARBON

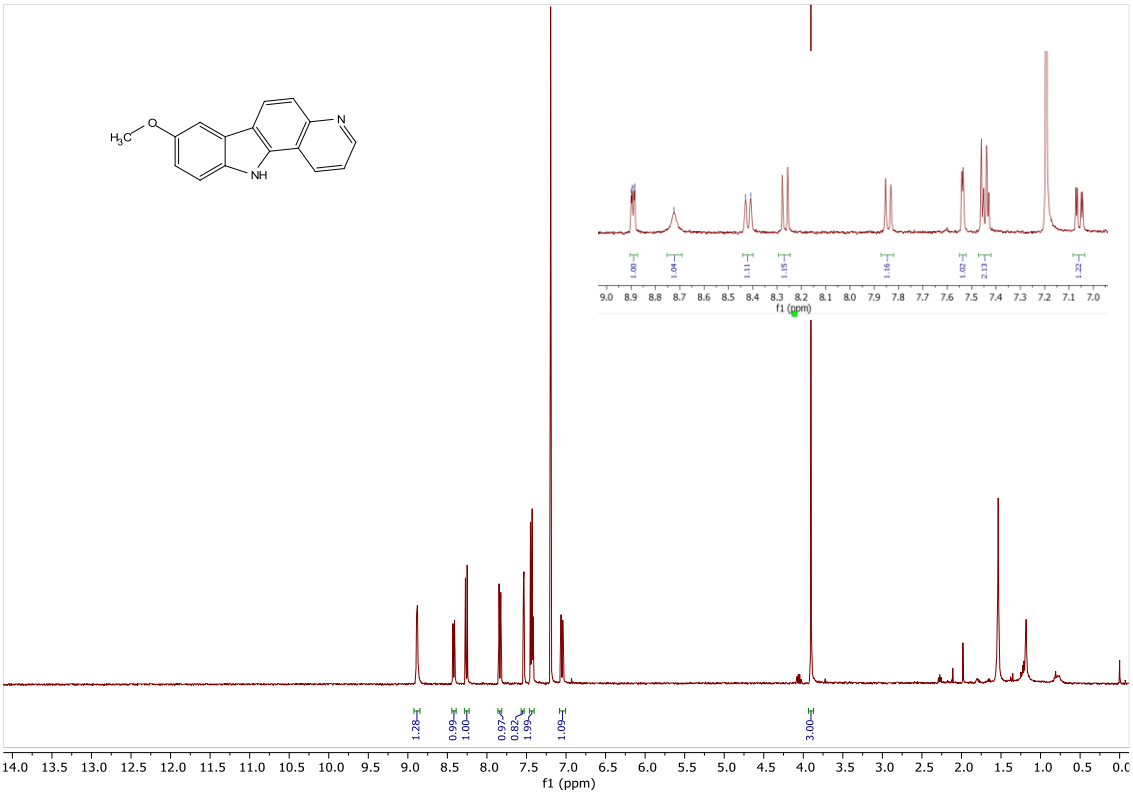

1.97
0.97
1.01
4.33
1.95
1.01
1.00
2.00
3.05
3.04
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)


161.08
154.61
147.32
137.04
136.18
135.72
132.92
129.17
127.64
125.77
123.46
122.42
119.83
118.00
114.32
112.98
110.92
109.88
102.11
77.35 CDCl3
77.24
76.72 CDCl3
56.08
53.26
49.55
170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45
f1 (ppm)

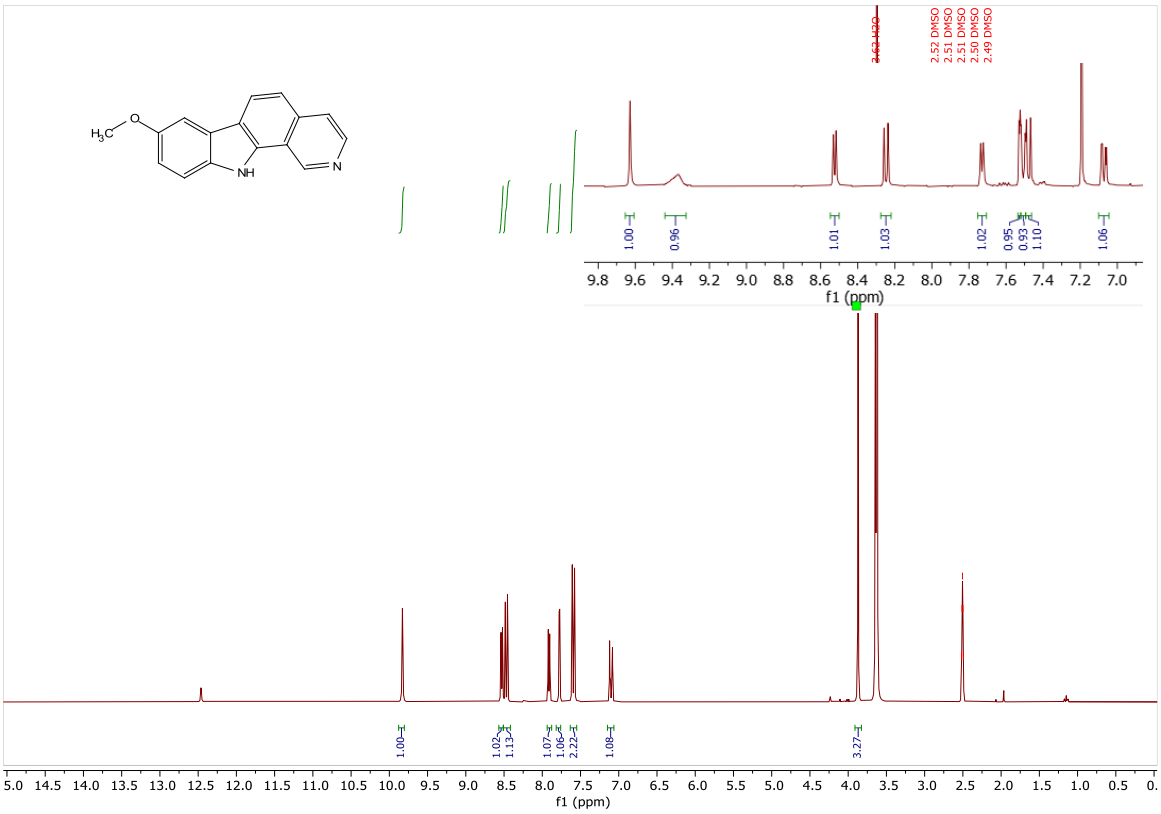

8.27
8.25
8.12
8.10
8.08
7.83
7.82
7.60
7.59
7.59
7.35
7.33
7.24
7.22
7.20
7.19
7.18
7.18
7.15
7.14
7.14
7.13
7.12
7.12
7.11
7.07
7.05
5.84
3.91
3.91
3.90
3.89
O
H3C
Cl
N
N
0.95
2.19
1.06
0.98
1.15
3.40
1.06
2.17
2.03
2.91
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)

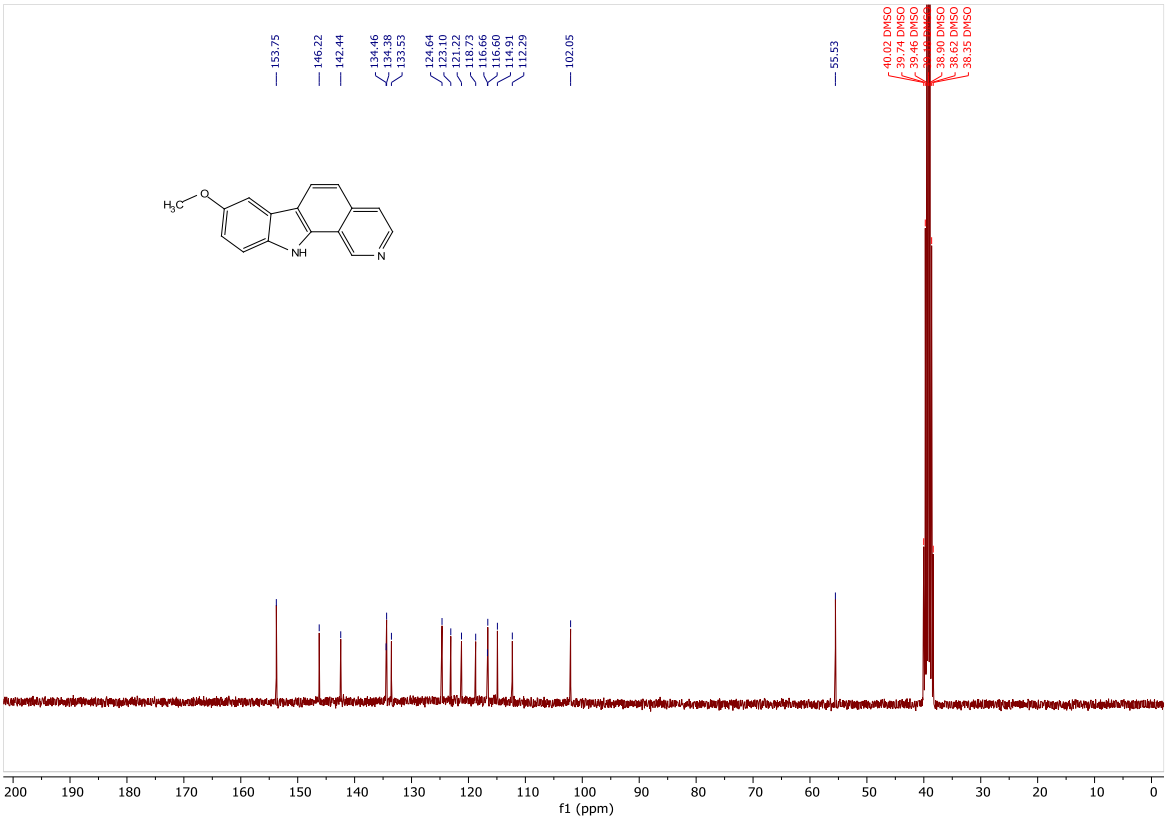

154.95
152.35
141.07
136.94
136.59
135.77
133.24
129.29
128.27
127.88
126.59
125.75
125.67
125.55
125.04
122.92
122.62
121.62
117.70
117.06
115.02
110.58
102.20
77.36 CDCl3
77.25
77.04 CDCl3
76.73 CDCl3
65.88
56.06
49.59
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
4
f1 (ppm)

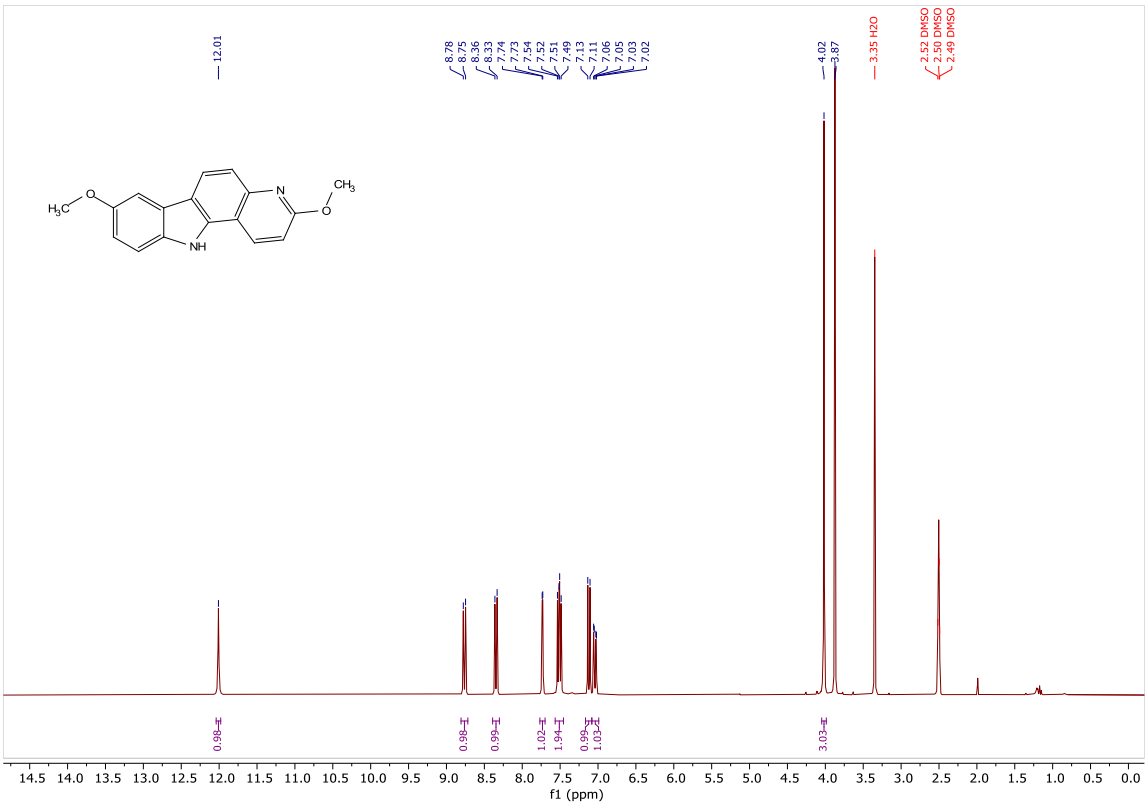
Debenzylation

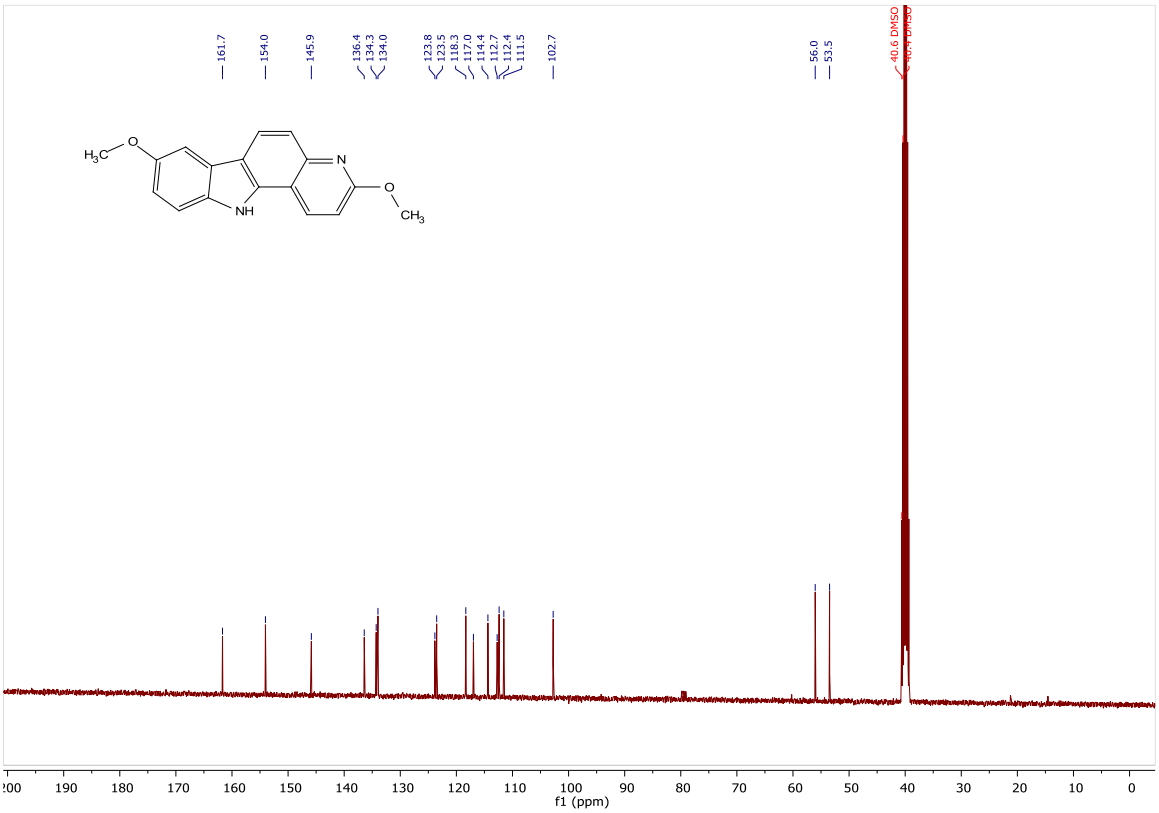


BM-089 CARBON


2.52 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.49 DMSO
1.00
0.96
1.01
1.03
1.02
0.95
0.93
1.10
1.06
f1 (ppm)
1.00
1.02
1.13
1.07
1.06
2.22
1.08
3.27
f1 (ppm)


153.75
146.22
142.44
134.46
134.38
133.53
124.64
123.10
121.22
118.73
116.66
116.60
114.91
112.29
102.05
55.53
40.02 DMSO
39.74 DMSO
39.46 DMSO
38.90 DMSO
38.62 DMSO
38.35 DMSO
f1 (ppm)


12.01
8.78
8.75
8.36
8.33
7.74
7.73
7.54
7.52
7.51
7.49
7.13
7.11
7.06
7.05
7.03
7.02
4.02
3.87
3.35 H2O
2.52 DMSO
2.50 DMSO
2.49 DMSO
0.98
0.98
0.99
1.02
1.94
0.99
1.03
3.03
f1 (ppm)


161.7
154.0
145.9
136.4
134.3
134.0
123.8
121.5
119.3
117.0
114.4
112.7
112.4
111.5
102.7
56.0
53.5
40.6 DMSO
40.4 DMSO
f1 (ppm)