Ana Cristina da Costa Mortinho

Licenciada em Química Aplicada

Novel synthetic routes towards azaindoles
Exploring one-pot metal-catalysed reactions

Dissertação para obtenção do Grau de Mestre em
Química Bioorgânica

Orientador: Doutora Maria Manuel S. B. Marques, Professora Auxiliar com Agregação, FCT-UNL

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Presidente: Doutora Ana Maria F. Costa Lourenço

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Outubro, 2018

FACULDADE DE CIÊNCIAS E TECNOLOGIA
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'It´s just a spark
But it´s enough
To keep me going'

Paramore

Acknowledgements

Ana Sofia Santos, Diogo Poeira, João Macara, Fausto Queda, Cátia Santos, Daniela Peixoto, Edgar Teixeira, Mónica, Gabi, Vanessa, Patrícia, Rafael Rippel(obrigado 205!!!) obrigado por me terem acolhido tão bem no laboratório , Ana Teresa (técnica de NMR mais querida de sempre), Professora Maria Manuel por me ter acolhido com tanto carinho no grupo de investigação e por me ajudar sempre a solucionar os problemas que apareciam em todas as etapas da tese e por ter orientado a minha tese de mestrado de uma maneira incansável, um muito obrigado é insuficiente. Professora Paula Branco e Luísa Ferreira e Ana Lourenço por serem incansáveis em todas as questões relacionadas com o curso e tudo o mais. Obrigado à minha família em especial à minha mãe que sempre foi a luz neste caminho do desconhecido. Um especial obrigado aos meus amigos que sabem quem são e à pessoa que me faz crescer a cada dia como química e como pessoa, obrigado meu salvador, meu Rafa.

Resumo

Azaindoles são heterociclos com escassa presença na natureza, mas de elevada relevância em química medicinal, e como tal, é imperativo desenvolver novos métodos para obter estes núcleos. As estratégias estabelecidas para a síntese destes compostos envolvem geralmente a combinação de mais do que um sistema de catálise metálica como é o caso do acoplamento cruzado C-N seguido por reação de Heck ou reação de Sonogashira seguida por ciclização, partindo ambas as aproximações de amino-halopiridinas. Este projecto teve como objetivo ultrapassar a necessidade de funcionalização das aminopiridinas comerciais, como por exemplo as reações de halogenação que são geralmente de baixo rendimento, através do desenvolvimento de uma nova metodologia rápida, escalável e de etapa única para a síntese de azaindoles.

A primeira aproximação baseou-se numa reação já bem conhecida do nosso grupo, o acoplamento cruzado C-N entre uma aminopiridina e um brometo de vinilo, seguida de uma reação de ativação da ligação C-H, catalisada por um metal. Nos estudos preliminares utilizou-se 2,5-dimetilanilina e α-bromo estireno, tendo-se obtido o composto **II.2** com 50% de rendimento. Mais tarde foram testadas diferentes aminopiridinas e diferentes brometos utilizando catálise de paládio e um passo de ativação C-H/ciclização oxidativa nunca antes utilizado para a síntese de azaindoles. Esta estratégia proporcionou apenas um regioisómero, um 4-azaindole (**II.4**) com 70% de rendimento, tendo funcionado apenas com aminopiridinas possuindo substituintes electro-doadores. No entanto, o método demonstrou algumas limitações em termos de versatilidade.

Desenvolveu-se então uma segunda estratégia em que o intermediário imina/enamina foi preparado por reação de condensação entre uma amina e uma cetona, seguido de uma reação de ativação C-H/ciclização oxidativa catalisada por paládio. Os primeiros ensaios foram realizados com anilinas, obtendo-se o indole **II.2** com 51% de rendimento e, uma vez verificadas as condições experimentais, aplicou-se a mesma estratégia usando aminopiridinas e diferentes acetofenonas. Foram preparados vários 4-azaindoles (14 exemplos dos quais 13 descritos nesta dissertação) com rendimentos até 96% possuindo diversos grupos substituintes. Utilizou-se para tal, um protocolo simples, envolvendo uma reação de ativação C-H, raramente explorada nesta classe de compostos.

Palavras-chave: Reações de etapa única; azaindoles; heterociclos; catálise de paládio; acoplamento cruzado C-N; ciclização oxidativa; ativação C-H; aminopiridinas

Abstract

Azaindoles are heterocyclic compounds scarce in nature, although interesting scaffolds in medicinal chemistry so there is a need of developing sustainable synthetic methods to obtain these cores. To date several methods involving more than one metal-catalysed reaction, like C-N cross-coupling,Heck coupling or the Sonogashira have been developed towards azaindoles. However, these methods require the use of amino-halopyridines as starting materials, which are difficult to prepare.

This project aimed to surpass the need of functionalization of aminopyridines conceiving a fast and scalable one-pot methodology towards azaindole synthesis. The first strategy envisaged a well-established reaction in our group, the C-N cross-coupling reaction, to prepare an imine/enamine *in situ*, followed by a C-H activation / oxidative cyclization reaction catalysed by a metal. The preliminary studies were made using 2,5-dimethylaniline and α-bromo styrene and other synthetized bromides. The indole compound **II.2** was isolated in 50% yield, and under the same conditions different aminopyridines and bromides were tested using palladium catalysis in an unprecedented approach for azaindole synthesis. This strategy afforded only one regioisomer, a 4-azaindole (**II.4)** with a 70% yield and worked only with aminopyridines that possess electro-donating groups. However, this method proved to be limited to few substrates. Thus, an alternative approach was attempted in which the imines/enamines were formed *in situ* by condensation of an amine with a ketone, followed by C-H activation/oxidative cyclization catalysed by palladium. Preliminary studies were carried with 2,5-dimethylaniline and acetophenone and afforded the corresponding indole **II.2** in 51% yield. Next, the same strategy was applied to aminopyridines. The reaction demonstrated to be effective when acetophenones were used. Thus, a variety of 4-azaindoles (14 examples, 13 synthesized in this thesis) were synthesized by this methodology with yields ranging from 24 % up to 96%, possessing electron-withdrawing and electron donating groups. The method developed consists on a simple protocol, a one-pot reaction, involving a C-H activation reaction scarcely explored in the synthesis of this class of compounds.

Keywords: One-pot reaction; azaindoles; heterocycles; palladium catalysis; C-N cross-coupling; C-H activation; oxidative cyclization; aminopyridines

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Abbreviations and symbols

Ac Acetyl
ADME absorption, distribution, metabolism and excretion
Aq. aqueous
Ar aryl
BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc *Tert*-butyloxycarbonyl
Bu butyl
CDC cross-dehydrogenative coupling
CDK cyclin-dependent kinase
CHK check-point kinase
c-Met tyrosine kinase receptor
COX cyclooxygenase
Cy cyclohexyl
dba dibenzylideneacetone
DCM dichloromethane
DMF *N,N*-dimethylformamide
DMSO dimethylsulfoxide
EI electron impact
equiv. equivalents
Et ethyl
GC gas chromatography
GSK glycogen synthase kinase
IR infrared spectroscopy
L ligand
LDA lithium diisopropylamide
m *meta*
Me methyl
M.P. melting point
MS mass spectroscopy
m/z mass-to-charge ratio
M.S. molecular sieves
MW microwaves
m multiplet
naph naphthalene
***n*-BuLi** *n*-Butyl lithium
NMR nuclear Magnetic Resonance spectroscopy
NSAID non-steroidal anti-inflammatory drug
o *ortho*
p *para*
quant. quantitative
q quartet
PEG Polyethylene glycol
PGI2 prostacyclin
PGH-2 prostaglandin
Ph phenyl
PLK polo-like kinases
PTLC preparative thin layer chromatography
r.t. room temperature
s singlet
TBAB tetrabutylammonium bromide
t triplet
t *tert*
TXA2 thromboxan
THF tetrahydrofuran
TLC thin layer chromatography

I Introduction

I.1 Inflammation and COX

The human genome of kinases (kinome) possesses more than 500 kinase proteins making them the biggest gene family. Kinases possess a regulatory role like cellular expression and immunoresponse. When there is a misregulation of these proteins it can take to inflammatory diseases [1], diabetes[2], heart related [3], nervous system [4] and oncological[5].

As a response to these conditions, strategies have been explored for the inhibition of this type of enzymes and isoenzymes responsible for metabolism, immune response and cellular growing cycles like the cyclin-dependent kinases (CDK), checkpoint kinases (CHKs), aurora kinases, polo-like kinases (PLKs) and COX (Cyclooxygenase).

Inflammation is generally described as an immune response of the body to stimuli that can be harmful. Some inflammations occur silently and don´t cause any pain because most of the organs don´t have any sensitivity to pain. For the initiation of the inflammatory process 4 steps are required: recognize the inflammatory agent, recruitment of the auxiliary cells of the process (leucocytes, plasma proteins, and others.), and removal of the inflammatory agent and inflammation resolution, **Figure I.1**.

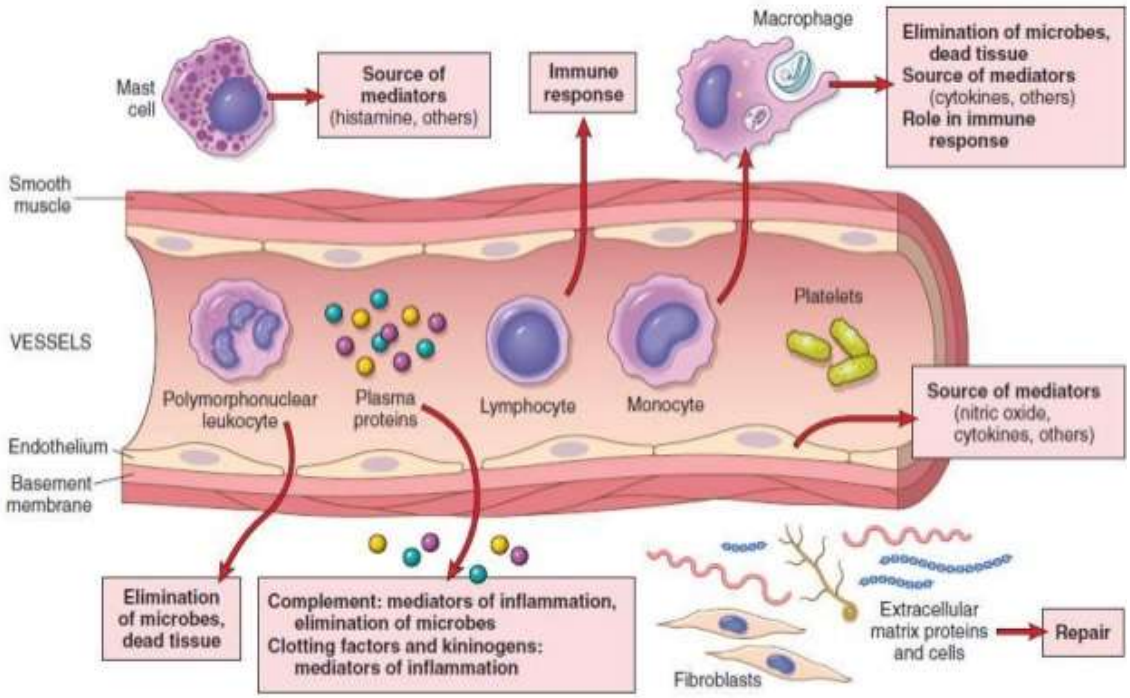


Figure I.1 - Acute and chronical inflammatory response components and their main functions. Adapted from Robbins Basic Approachology, 2013.

Inflammation can either be acute or chronic, having the same origin mechanism. What differentiates them is the exposure time, the responsible agent and the type of immune response. In the case of the acute inflammation, this one is related to a fast response to

an infection or strange body. This type of inflammation can be cured, regenerated or progress to the chronic disease. Chronic inflammation can take years to full recovery and is associated to carcinogenic diseases. [6]

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most used for the treatment of diseases like: arthritis, rheumatism and pain due to their antipyretic and analgesic properties. The first NSAID with therapeutic use was aspirin being used in more than 100 years. [7] In 1971, Vane discovered the mechanism of action of aspirin via inhibition of cyclooxygenase (COX) [8]. COX produces prostaglandin H2 (PGH-2) from arachidonic acid. PGH-2 is then converted to prostanoids (prostaglandins, prostacyclins and thromboxanes) by specific enzymes of the membrane.

There are two known basic isoforms of COX: COX-1 and COX-2. Initially, it was thought that COX-1 would be the constitutive form of the enzyme having a role on the physiologic functions of the human body. On the other hand, COX-2 was considered inductive and responsible for pain and inflammation. Recently it was proved that COX-2 is permanently present in many body membranes and participates in various physiologic processes, **Figure I.2**. [9]

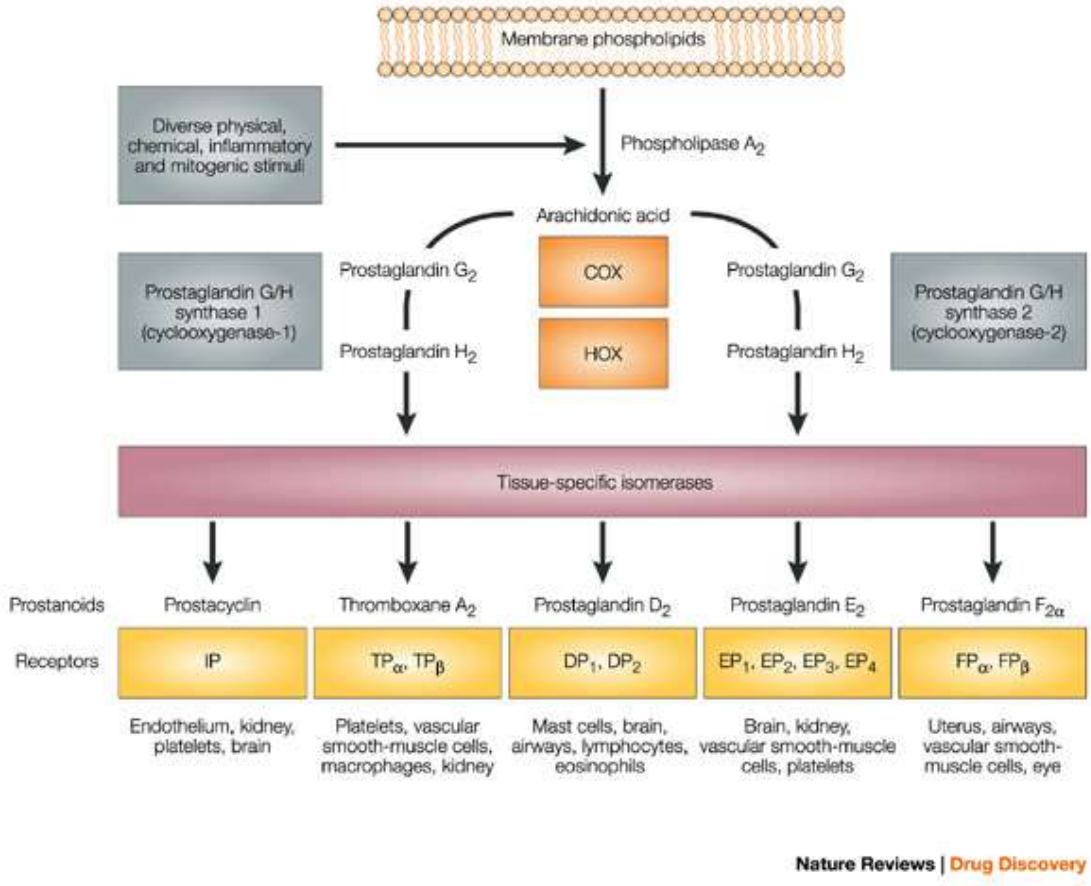


Figure I.2 - COX isoforms, their stimuli of origin and respective target tissues/organs.

Prolonged inhibition of COX-1 would prevent the formation of the prothrombotic TXA2 (thromboxane A2), which might counterbalance the effect of inhibition of COX-2 that is involved in PGI2 (prostacyclin) biosynthesis. Because NSAIDS are not selective to one COX isoform, there are side-effects such as vasoconstriction, platelet aggregation and thrombosis, increasing cardiovascular risk, leading to myocardial infarctions. **Our group have invested the last few years in studying the mechanisms of COX inhibition and regulation.**[10] Recently, it has been proposed that the key to regulate thrombotic events can rely on a balanced inhibition of both COX-1 and COX-2 isoenzymes to ensure a prostacyclin/thromboxane balance in the body.[11]Following our previous studies on COXs inhibition, we aimed to develop a new class of inhibitors that present a balanced COX-1/COX-2 inhibition and also that allow the investigation of new binding modes with COXs. The group has investigated benzimidazole and indole cores towards novel COX's inhibitors. [10] Due to the critical side-effects of the marketed drugs, there is still a need to develop new agents to fight inflammatory related diseases safely. [12] Azaindole, an indole bioisoster, has the particularity of having an extra N atom comparing to indole. This characteristic enables this core to act like a H-bond donor or acceptor in a bidentate H-bonding pattern, enhancing the potency of a drug (**Figure I.3**).

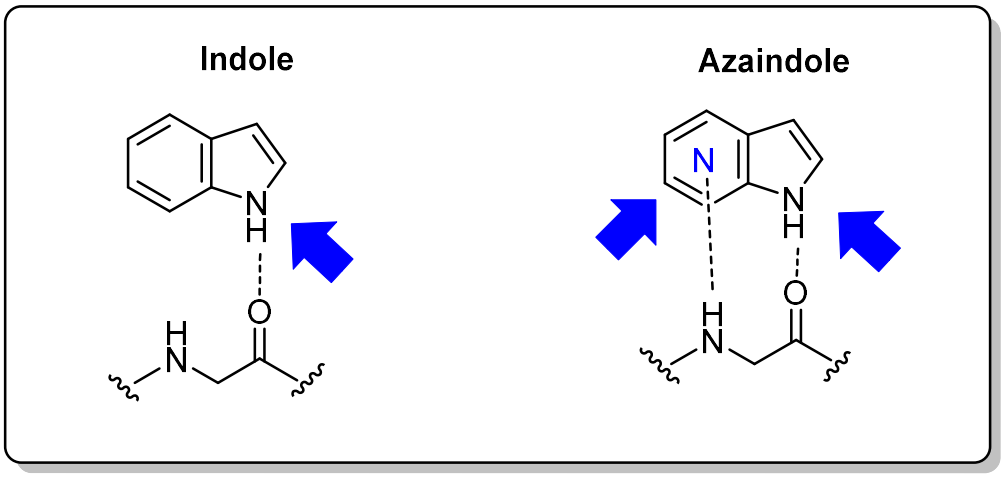


Figure I.3 . Indole and azaindole structures and their main interactions.

I.2 Azaindole origins

The indole core (**Figure I.4**) is a privileged structure present in known bioactive compounds such as indomethacin, bufotenin and tryptophan.

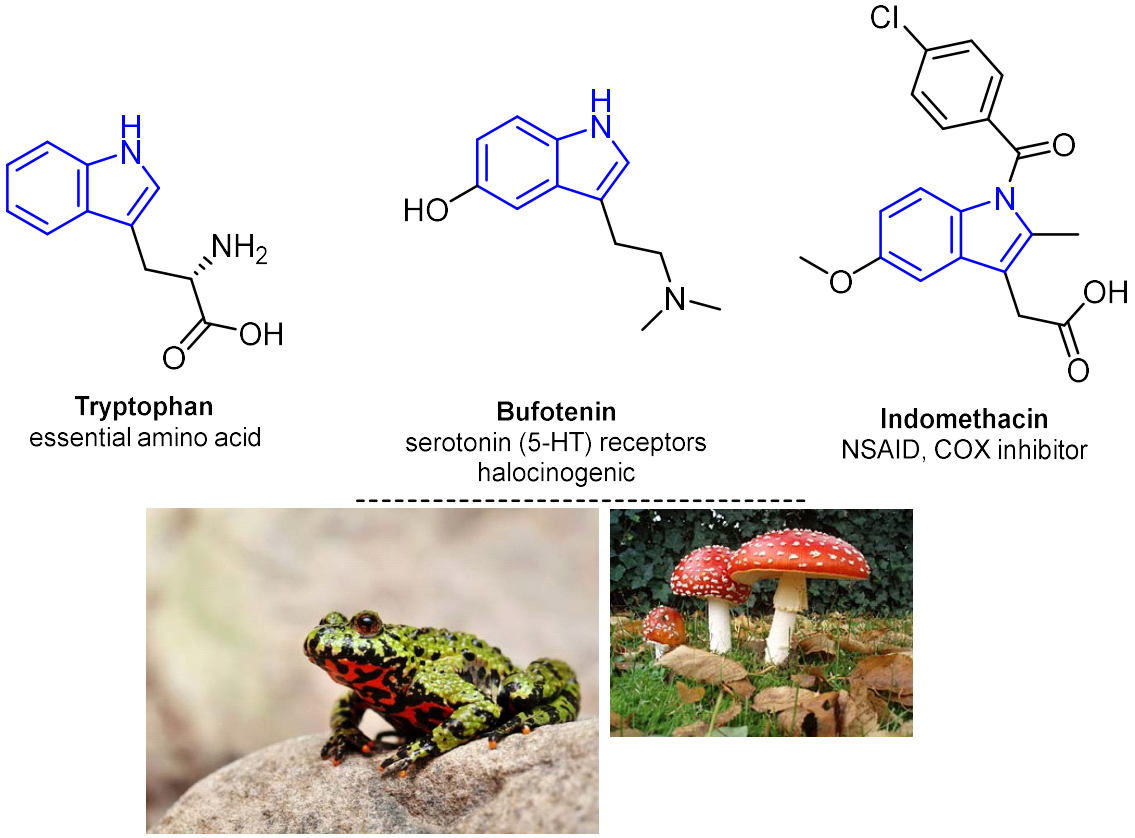


Figure I.4 - Natural and synthetic compounds containing indole nucleus.

This powerful core is interesting from the pharmacological point of view because with it is possible to modify the Lipinski rule of five (it defines if a drug is suitable for oral intake): solubility, pKa, lipophilicity, target bonding and ADME.

For instance, many azaindoles can or have superior bioactivity than the corresponding indoles considering their extra interaction given by the nitrogen atom of the pyridine ring that can make hydrogen bonds [13]
Azaindoles are found in bioactive compounds such as variolins and meriolins extracted from various marine invertebrates, **Figure I.5**. These structures are scarce in nature and there is a need of synthetic methods to achieve the azaindole core. [14]

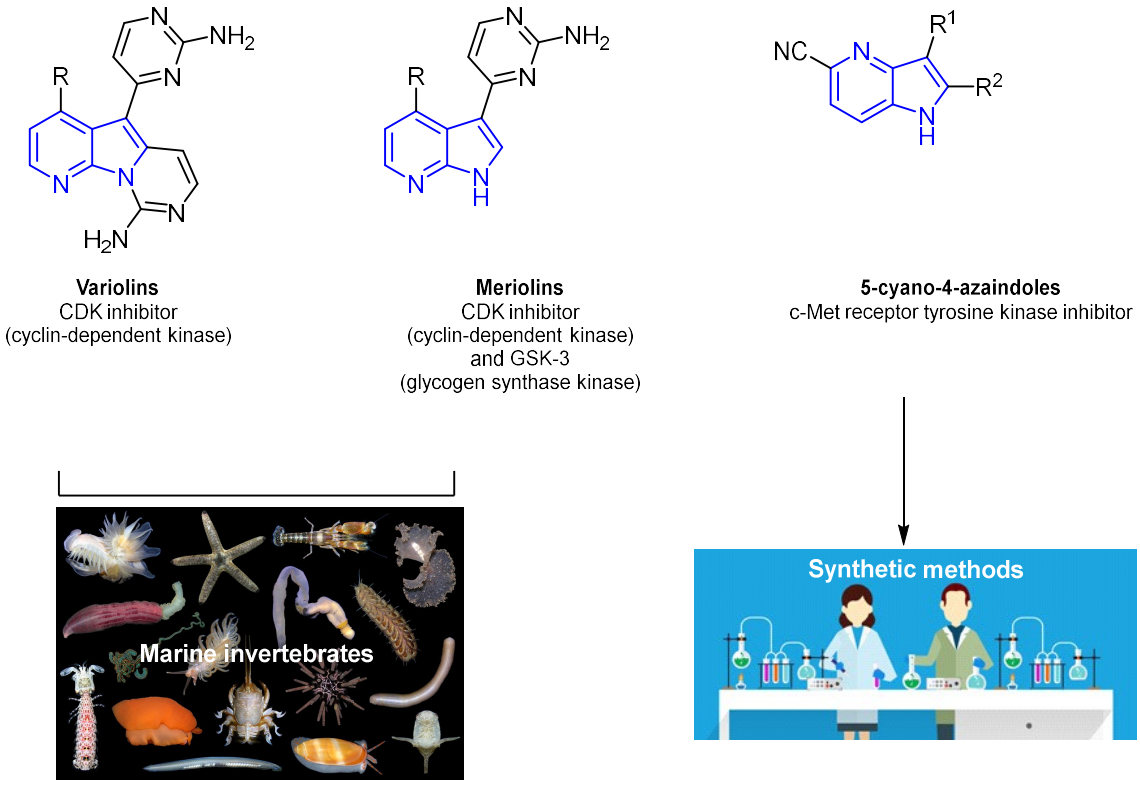
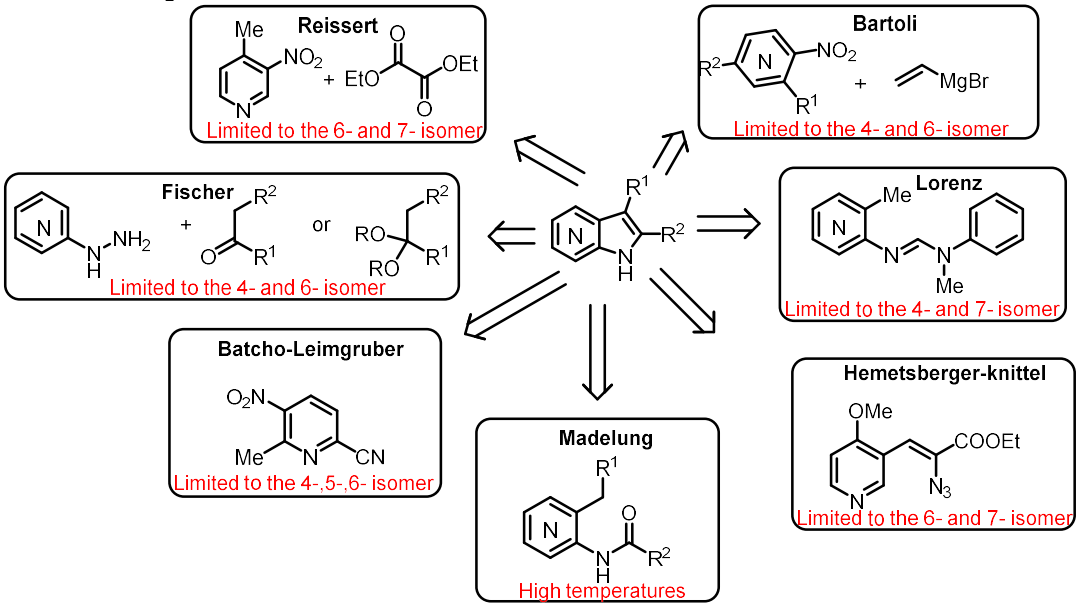


Figure I.5 - Natural and synthetic compounds containing azaindole nucleus.

I.3 Azaindole synthesis – metal-free routes

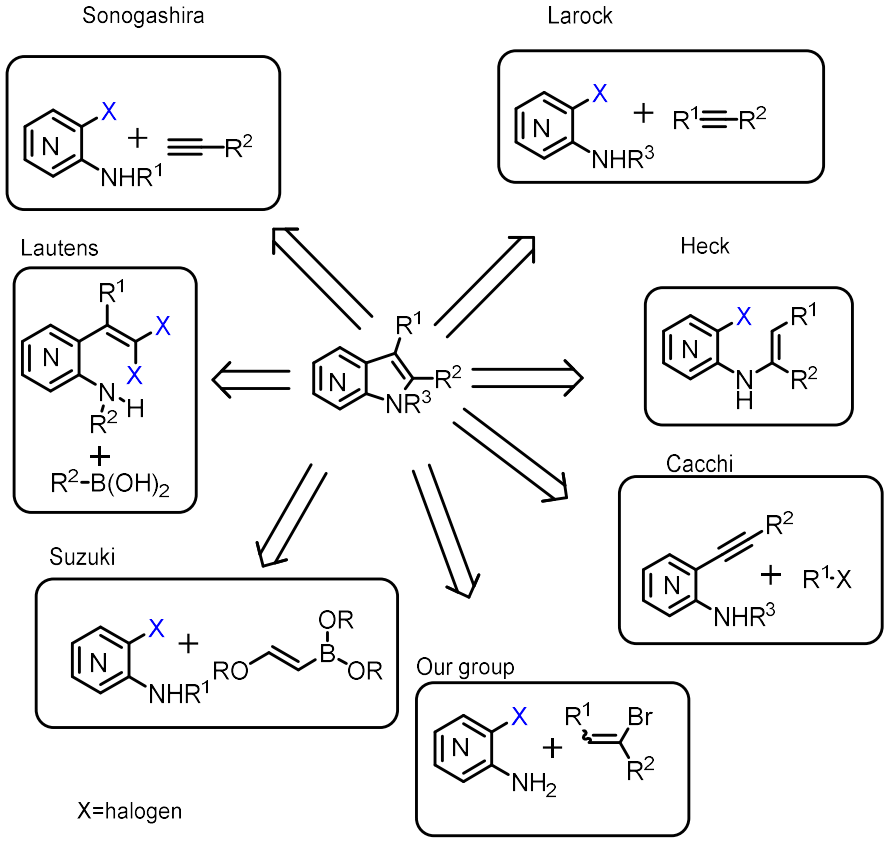
There are many classic methods for azaindole synthesis inspired and traditionally used to access indoles, like Reissert, Bartoli, Leimgruber-Batcho, Lorenz, Hemestsberger-Knittel Fischer [15] and Madelung [16] reactions. However, these approaches present low yields, narrow scope and harsh conditions. [17] (**Scheme I.1**).



Scheme I.1 - Synthetic strategies previously used for indole to access azaindoles.

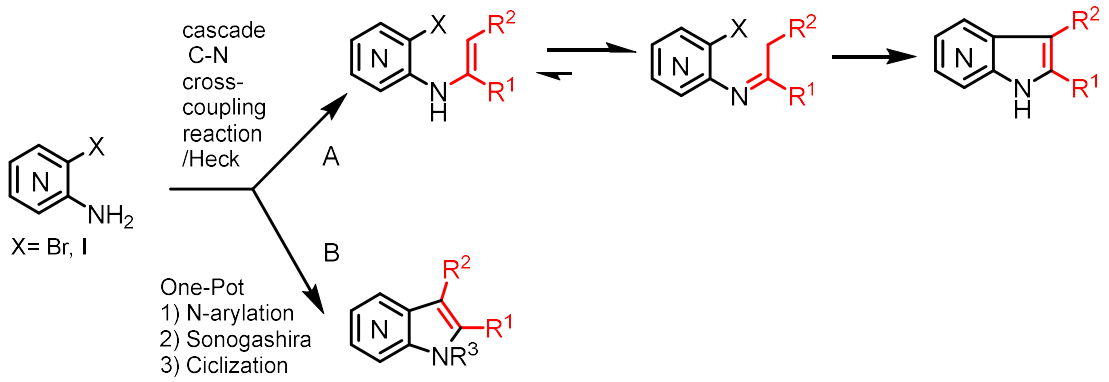
I.4 Azaindole synthesis – metal-catalysed routes

Along with the traditional methods, metal-catalysed methods have been developed, more specifically using palladium catalysts, that will be discussed next. (**Scheme I.2)**.



Scheme I.2 - Synthetic strategies to access azaindole using palladium catalysis.

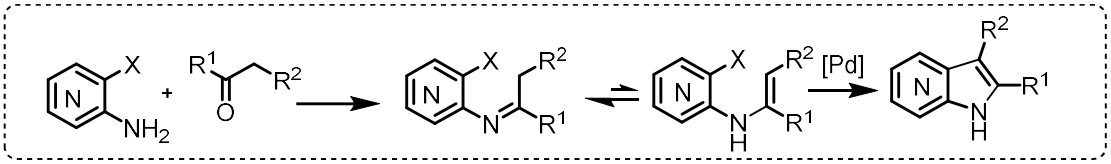
Recently, our research group developed innovative synthetic strategies to achieve azaindoles. The first strategy consisted on cascade reaction involving a C-N cross-coupling reaction followed by a Heck C-C coupling; and a second approach that consisted in an arylation reaction of an amino-halopyridine followed by **Sonogashira** and cyclization reaction. (**Scheme I.3)**[18]



Scheme I.3 - Cascade reaction of C-N cross-coupling followed by Heck reaction and one-pot reaction of arylation followed by Sonogashira/cyclization reaction explored by our group.[18]

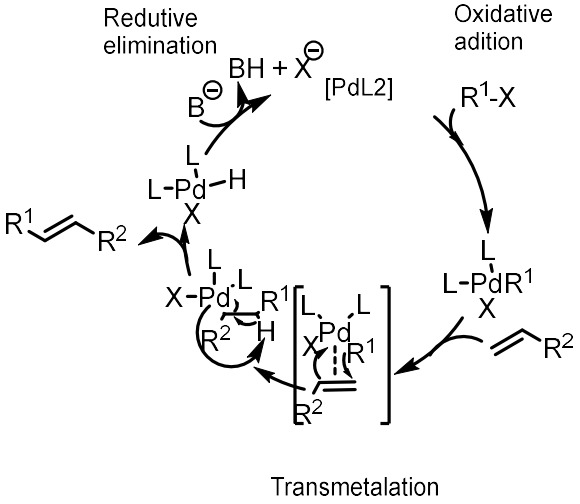
I.4.1 Heck reaction

The Heck reaction was first applied to azaindole synthesis in 1999 (**Scheme I.4**). [19] This reaction starts with a condensation between a halo-aminopyridine with an aldehyde or ketone with imine/enamine formation. Followed by palladium insertion in the C-X bond via oxidative insertion with intramolecular C-C coupling of the enamine.



Scheme I.4 - Heck reaction for azaindole synthesis.

The mechanism of the Heck reaction is depicted in **Scheme I.5**.

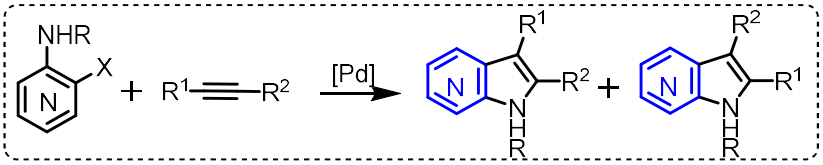


Scheme I.5 - Heck reaction catalytic cycle.

I.4.2 Larock reaction

Larock heteroannulation is one of the most notable methods for azaindole synthesis. This method is based in internal alkyne heteroannulation palladium catalysed. In spite of the great success of this reaction, when asymmetric alkynes are used, the regioselectivity is lower. [20] The regioselectivity of this reaction not only depends on the presence of different alkyne substituents but also on the amine protecting group. (**Scheme I.6**).

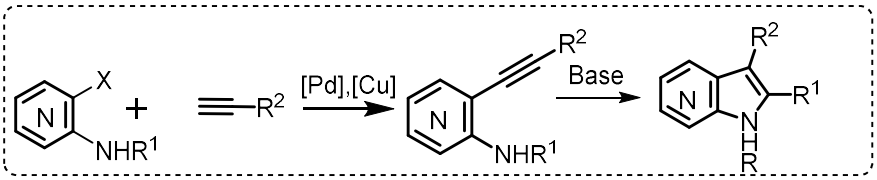
The first methodology employing the Larock procedures for azaindole was reported in 1993 by Gronowitz *et al*. [21], this method was used to reach substituted 5- and 6-azaindole with yields up to 40%.



Scheme I.6 - Larock reaction Pd catalysed.

I.4.3 Sonogashira reaction

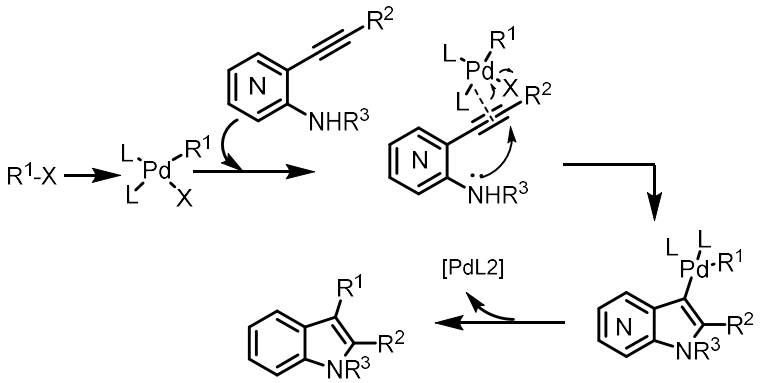
In 1975, Sonogashira *et al*. described for the first time [22] a simple method for the preparation of aromatic alkynes and conjugated alkynes with alkenes, using palladium catalysis coupling of terminal alkynes with aryl halides or allylic halides. This cyclization reaction is possible because after the formation of the alkyne intermediate it can occur a heteroannulation with the use of a strong base like potassium *tert*-butoxide, or by means of a copper mediated cyclization (**Scheme I.7**). This method is wide applicable and extensively used for the azaindole preparation substituted in the C-2 position.



Scheme I.7 - Sonogashira coupling and cyclization for azaindole formation.

I.4.4 Cacchi Reaction

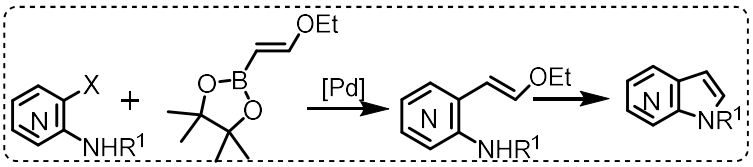
Cacchi approach involves a Sonogashira reaction and conversion of the Sonogashira product into the corresponding azaindole. This method is efficient in the synthesis of the C-3 substituted azaindoles, and relies only in one reaction step for azaindole synthesis, a cascade C-N/C-C coupling that results in an heteroannulation and functionalization of the C-3 position (**Scheme I.8**). This method have proved to be direct and versatile for the 4- and 7–azaindole synthesis dissubstituted at C-2 and C-3 position.[23]



Scheme I.8 - Cacchi reaction for azaindole synthesis.

I.4.5 Suzuki Reaction

Suzuki-Miyaura coupling was first described in 1992 for indole synthesis. [24] This method is used for azaindole synthesis, using halo-aminopyridine coupling with boronic esters that results in a Suzuki product that suffers an intramolecular cyclization. (**Scheme I.9**).

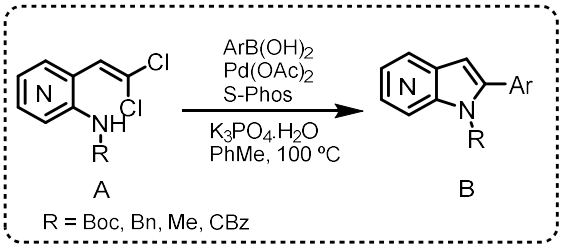


Scheme I.9 - Suzuki coupling for azaindole synthesis.

In addition of the fact that this reaction gives high yields when using the correct catalytic system [25], it is compatible with water giving us the option of using cheaper solvents and do less harm to the environment. [26] Besides of the fact that the Suzuki coupling has become one of the most important reaction for C-C coupling, and for azaindole synthesis, this method was not fully optimized.

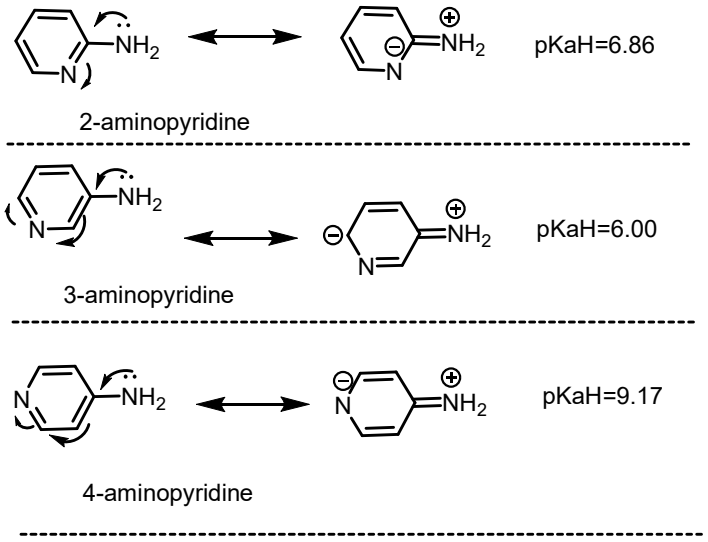
I.4.6 Lautens Reaction

A tandem intramolecular C-N/intermolecular Suzuki coupling towards the synthesis of azaindoles was developed by Mark Lautens group, involving a palladium-catalysed reaction of gem-dichloro olefins **A** and a boronic acid. The method proved to be a very extensible protocol to prepare the four azaindole isomers **B** in good to excellent yields (**Scheme I.10**) [27].



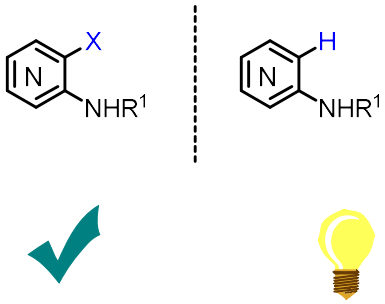
Scheme I.10 - Synthesis of azaindoles via tandem intramolecular C-N/intermolecular Suzuki coupling by Mark Lautens group.

This reaction requires the presence of halogens and protection of the free -NH_2 group otherwise catalyst poisoning would have occurred.
So, it is imperative to find new synthetic approaches. The low reactivity and Lewis basicity of the starting aminopyridines can be defying and must be taken in account, because when there is a change in the nitrogen atom position of the pyridine ring, the reactivity is completely altered **(Scheme I.11**).[28]



Scheme I.11 - Aminopyridine isomers and their corresponding pKa of the conjugated acids. [29]

As can be observed, almost all the metal catalysed strategies require the presence of a halogen group in the aminopyridine. Pre-functionalization of aminopyridines, such as halogenation is time-consuming and suffers from regioselectivity. So, it is urgent to seek for more efficient methodologies. With all these observations regarding metal-catalysed reactions, a question can be raised: *Is it possible to build azaindole heterocycles in the absence of a halogen X group at the aminopyridine (**Scheme I.12**)?*



Scheme I.12 – Amino-halopyridine versus non-amino halopyridines.

Organic Synthesis have changed radically due to the introduction of metal mediated reactions like the previously described **Heck, Suzuki** and other reactions like α-arylation of carbonylic compounds and metathesis reaction of several types of bonds. [30] Furthermore, for these reactions to occur it is necessary the presence of reactive functional groups in both starting materials.

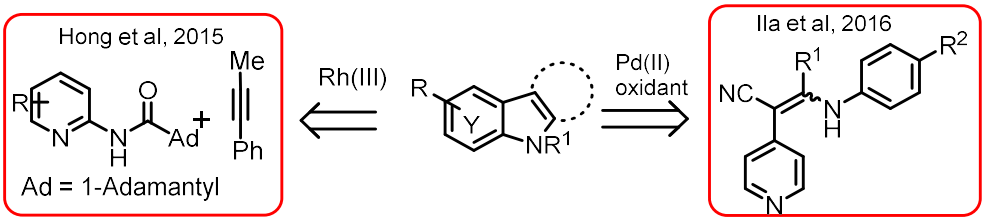
Consequently, there it is emergent to improve this demand and reduce the number of needed functionalities for coupling reactions like in the case of C-C coupling through C-H activation. [31] This method would be in a great advance if only one of the coupling partners needed to have a reactive group. [32]

I.4.7 C-H Activation reaction

C-H bonds are common and can take us to new disconnections. Like all strategies, C-H activation may also have challenges like regioselectivity because sp2 and sp3 C-H bonds are ubiquitous, the low reactivity of starting materials since there is a great energy barrier to break a C-H bond (104 kcal/mol) and the chemoselectivity - functionalized product can be more reactive [33]

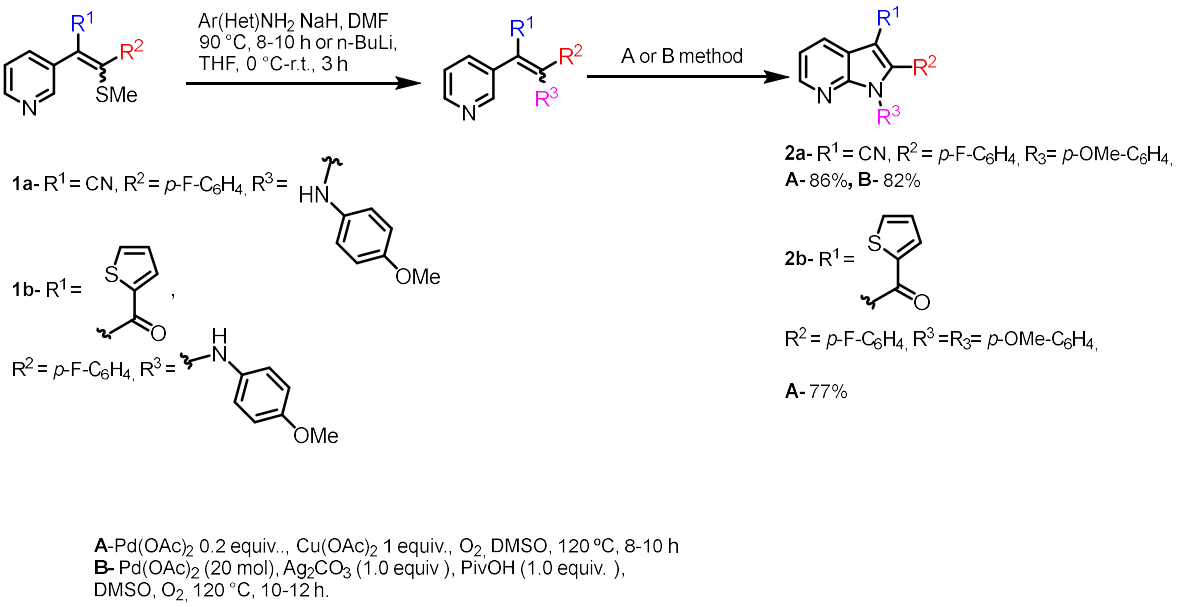
Multiple synthetic approaches have been developed for indole synthesis through C-H activation. Some strategies rely on the extra use of alkynes (Ackerman [34], Larock [35]), protected anilines (Singh [36]) or enamines (Rueping, Åkermark-Knölker [37], Glorius [38]) and imines (Yoshikai). [39]

But the previous strategies although with good to very good yields, have never been employed to azaindole synthesis. So far, only two approaches using C-H activation were used for azaindole synthesis, using rhodium or palladium catalysis and, giving access exclusively to the 7-azaindole isomer (**Scheme I.13**).



Scheme I.13 - Representation of the described approaches for azaindole synthesis through metal-catalysed C-H activation. [40] [43]

In 2016, Ila *et al.* [40] defined an efficient strategy for the access of 1- N-aryl/NH-2-(het)aryl/alkyl-3 cyano/arylindoles and analogues via oxidative funcionalization-amination by a palladium(II) catalyzed intramolecular C-H activation reaction from 2,3-(het)aryl-3-N-aryl/acylenaminonitriles and enaminones (**Scheme I.14**).



A-$Pd(OAc)_2$ 0.2 equiv.., $Cu(OAc)_2$ 1 equiv., O_2, DMSO, 120 °C, 8-10 h
B- $Pd(OAc)_2$ (20 mol), Ag_2CO_3 (1.0 equiv), PivOH (1.0 equiv.),
DMSO, O_2, 120 °C, 10-12 h.

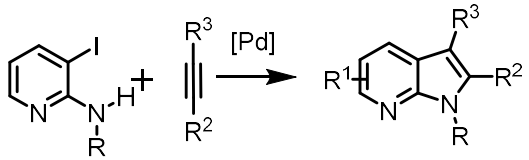
Scheme I.14 - 7-azaindole synthesis from 2,3-(het) aryl-3-N-aryl/acylenaminonitriles and enaminones.

The great particularity of this procedure is the use of aminoaryl group both as directing group and partner of the nucleophilic coupling in the process of C-H heterofunctionalization. This reaction presents high regioselectivity and good functional group tolerance in various positions and high yields in the cyclization process.

Despite it is in analysis a suitable mechanism for this reaction, it is one of few examples that presents an aryl C-H bond that is activated by an aminoaryl directing group and is used for azaindole synthesis.

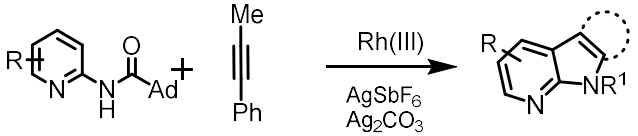
It is well established that aminopyridines present low reactivity as starting materials and that fact is an obstacle for azaindole construction [41]. These difficulties led to the need of pre-functionalization of the substrate thus methods such Larock rely on the use

of amino *ortho*-halogenatedpyridines to access different substitution patterns on 7-azaindole (**Scheme I.15**). [42]



Scheme I.15 - Larock type reaction for azaindole synthesis using *ortho*-halogenated aminopyridines.

With the increasing need of new methodologies for obtaining substituted 7-azaindoles, *Hong´s* group [43] created a strategy in 2015 that involved a C-H activation using rhodium(III) catalysis from aminopyridines and alkynes. For the reduction of the Lewis basic properties of the aminopyridines they opted for the use of a Lewis acid so that, the coordination that occurs (between the nitrogen atom of the N of the pyridine ring and the Lewis acid) would facilitate the process of C-H/annulation (**Scheme I.16**).



Scheme I.16 - Azaindole synthesis from alkynes and N-substituted aminopyridines rhodium(III) catalysed.

On the follow-up of our previous approaches and considering the potential of C-H activation reactions, we envisaged to investigate an unprecedented approach towards azaindoles involving a C-H activation reaction (**CDC**) of imines/enamines generated from aminopyridines. One of the challenges is the presence of the nitrogen atom at the pyridine ring, since it can coordinate with a catalyst. This coordination can lead to catalyst poisoning or functionalization at an undesirable position, a fact that limits the application of the C-H activation reaction for drug synthesis based in heterocycles. [44–47] Despite of all challenges posed, application of this reaction has prompted interest from the industrial and pharmaceutical point of view. [46-48]

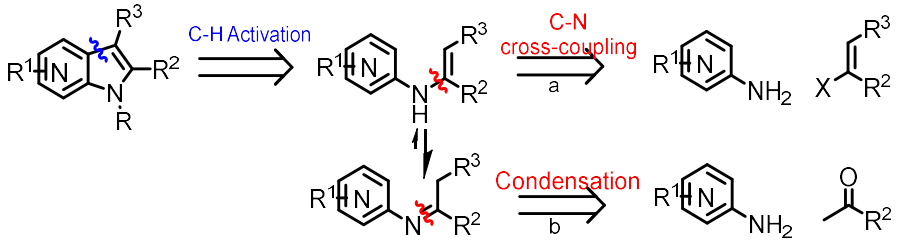
II Results and discussion

II.1 Background

The work advanced here comes in alignment with a project that is being developed in our group that envisions the synthesis of azaindoles with promising biological activity, more specifically the inhibition of enzymes that are responsible for metabolic and inflammatory processes like COX. Taking in account the limitations presented by the methods described before for azaindole synthesis (**chapter I.3 and I.4**), it is imperative the development of new and versatile alternative synthetic routes.

In this project we have chosen to make a retrosynthetic analysis with the objective of rationalize our different synthetic hypothesis. With that in mind and given our previous experience on in situ formation of enamines/imines [18], the chosen strategy was initially based on a C-N cross coupling using palladium catalysis, followed by an C-H activation/oxidative cyclization as we can see on **Scheme II.1**, **approach a**. It was expected the formation of an imine/enamine from aminopyridines and vinyl bromides [18] followed by C-H activation (CDC) that would afford the corresponding azaindoles.

The alternative **approach b** was based in a condensation reaction between ketone and aminopyridine, followed by a C-H activation reaction using a similar strategy developed for indole synthesis [39].



Scheme II.1 - Alternative retrosynthesis for Azaindole.

This first reaction step is very important because it involves the formation of an imine/enamine intermediate which is crucial for the following transformation. In the case of the condensation reaction, (**approach b**, amine and ketone) water production occurs, so it must be removed from the system by using molecular sieves or drying agents. Thus, **approach a,** relying on a C-N cross-coupling reaction (**approach a**, amine and vinyl bromide), would represent an advantage because there is no water production.

The second step relies on a C-H activation by means of a cross-dehydrogenative coupling Pd(II) catalysed and here the stability of the intermediate has to be

balanced because we are dealing with the life-time of the imine form (more stable) in solution and with the necessary time for the cyclization to occur because C-H bonds are extremely unreactive.

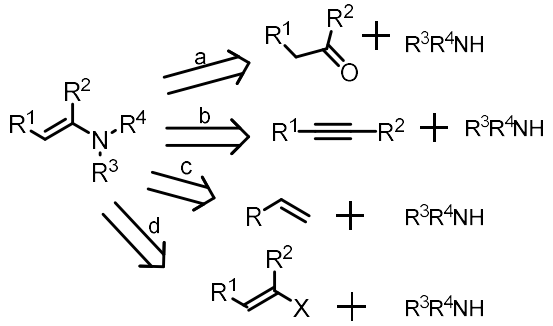
II.2 Azaindole synthesis: approach a via C-N cross-coupling / C-H activation

Regarding all the possible strategies for azaindole synthesis either using metallic catalysis or not, it is useful to know some approaches towards imine/enamine synthesis to apply to our synthetic strategy based in these versatile intermediates.

The main strategy for enamine/imine synthesis is the acid catalysed/or not condensation between an amine and a carbonylic compound (**approach a, Scheme II.2**). Behind the appealing side of this reaction this approach can present limitations such as: harsh conditions, low functional group tolerance and low chemo and stereoselectivity. [50]

In consequence, new strategies have been developed towards enamines and imines. [51] Other used transformations that give origin to these versatile intermediates are alkyne hydroamination(**approach b, Scheme II.2**) [52] and oxidative amination of alkenes. [53] Further approaches to enamine synthesis rely on the use of olefins and amines as substrate in hydroformylation reactions catalysed by ruthenium (**approach c, Scheme II.2**). [54]

Recently, a powerful synthetic approach was reported, inspired by the Buchwald-Hartwig aryl-amination, [55] and it is getting attention since 2002 [56]: a cross-coupling reaction between amines and alkyl halides or pseudo-halides, catalysed by palladium, and copper complexes. (**approach d, Scheme II.2**). [57] The C-N cross-coupling reaction is described in chapter II.2 with more detail.

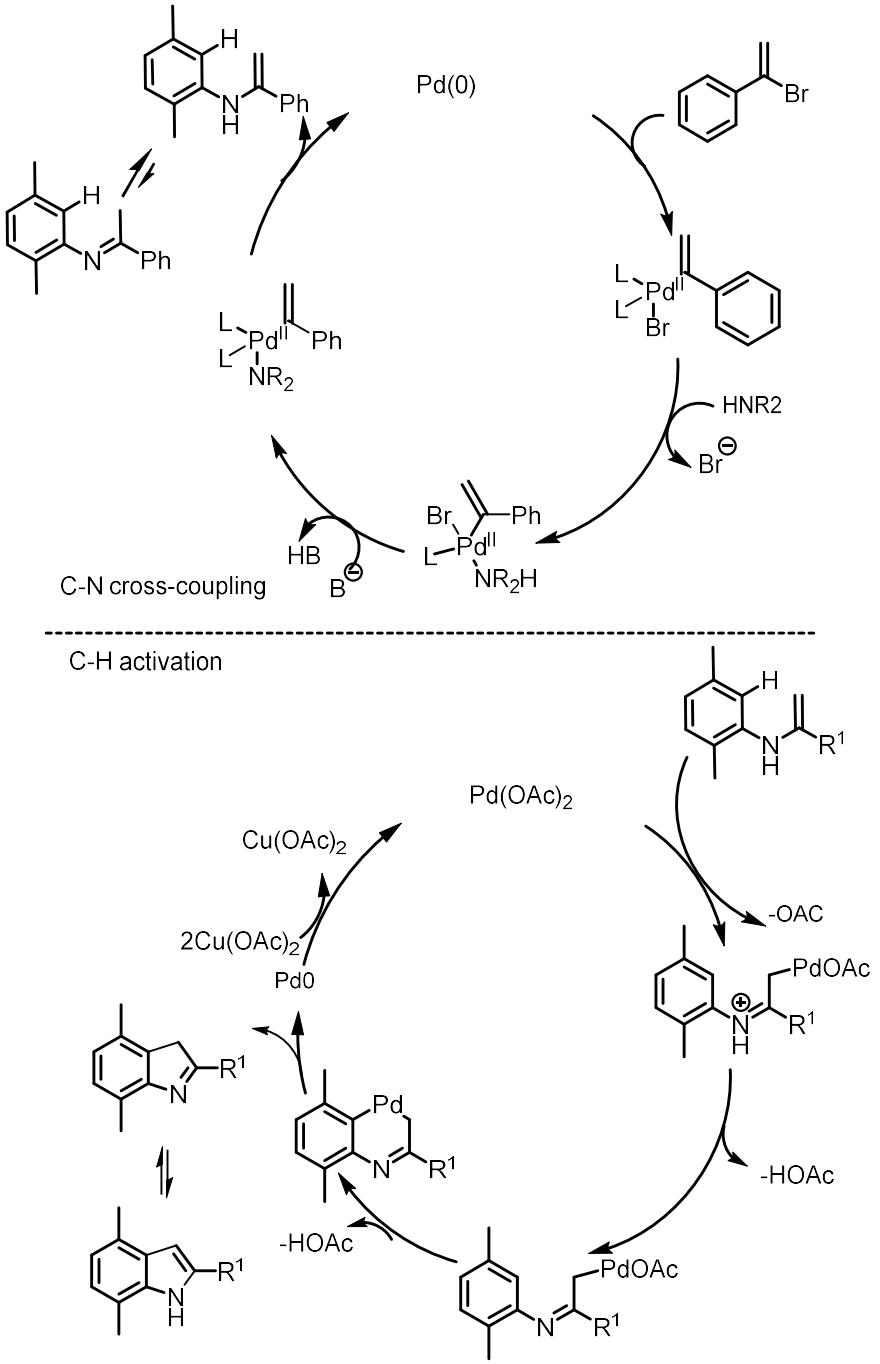


Scheme II.2 - Most used strategies for enamine synthesis from amines.

On the basis of the results obtained by our group concerning the *in situ* formation of imines/enamines via a C-N cross-coupling reaction catalysed by

palladium(II) [18], we have tested a one-pot strategy of C-N cross-coupling/C-H activation.

To evaluate the method´s versatility, the first experiments were carried with anilines. Thus, different commercial vinyl bromides were applied with 2,4-dimethylaniline (**Table II.2**). In this C-N cross-coupling reaction, there is an insertion of palladium in the C-Br bond, via an oxidative addition step, next the aniline enters the cycle establishing a coordination by the N atom of the NH_2 group within the formed complex between the palladium and bromide. The base, in this case *t*-BuONa, eliminates a proton from the aniline. At the end, in the step of reductive elimination, the product is formed, and the palladium catalyst is regenerated (**Scheme II.3**). [49]



Scheme II.3 – Proposed catalytic cycles of the formation of imine/enamine through C-N cross-coupling followed by C-H activation reaction, for azaindole synthesis.

II.2.1 Preliminary studies with aniline

The system used for this C-N cross-coupling reaction was inspired by the previously reported protocol used by our group in 2016. [18] Since anilines are more activated than aminopyridines, these starting materials are a great start for our approach since we have few information on this combination of different catalytic systems using aminopyridines. To know the compatibility of the

catalytic systems for the two reactional steps we decided to make a screening of different ligands and solvents in order to test the stability and formation of the final product, the indole. Thus, the aniline was maintained and two different bromides (**1a - α-bromo styrene** and **1b – α-bromo naphtalene**) were used to test also the stability of the intermediate that is formed (imine formation). The best conditions for the overall reaction were using toluene as solvent and DavePhos as the ligand of palladium, for the second reaction (C-H aactivation reaction) the used conditions are already described in the literature being TBAB a phase-transfer catalyst that to enhance the rate of transition-metal-catalyzed but also a stabilization of nano-sized metal colloids that can be formed by reduction of the added metal source, the surfactant preventing undesired agglomeration to unreactive species such as palladium black by forming a monomolecular layer around the metal core. [58] This one-pot approach, in which the intermediate **3** was not isolated, afforded indoles with yields up to 50% and is already described in the literature (**Table II.1**).

Regarding product **II.1**, the reaction mixture that originated this compound after the C-N cross-coupling/ C-H activation was analysed by TLC and was not observed full conversion of the starting materials (**1** and **2**) into a new compound. By analysing the ^{1}H-NMR spectra of the crude mixture (**Figure II.1**) the compound formed was assigned as imine **3** and with that information the reaction proceeded to the second step, the C-H activation reaction. The indole product derived from this imine was not attained even when the temperature was raised to 80 ºC.

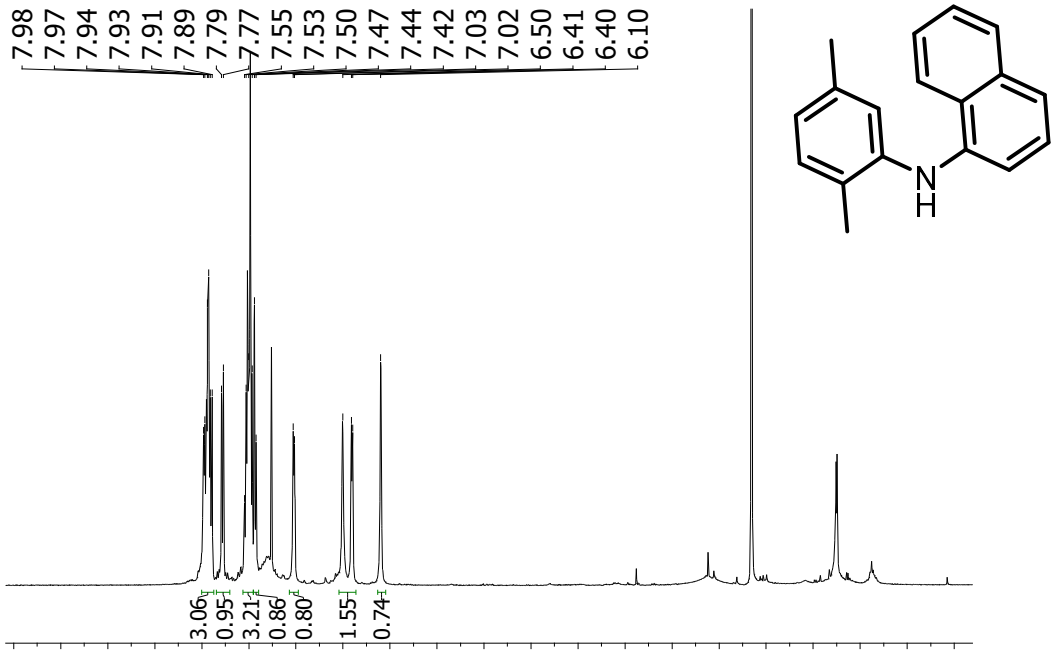
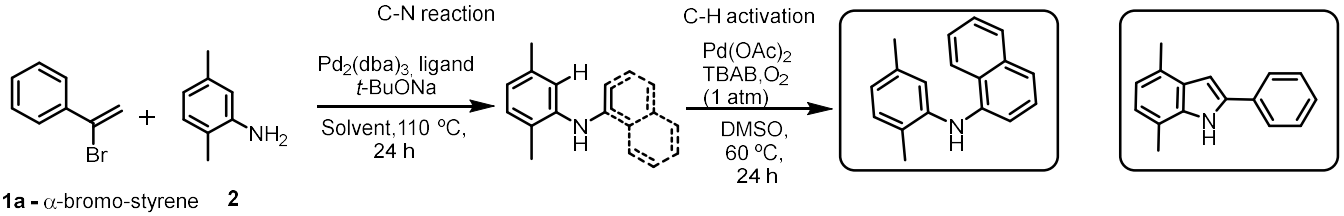


Figure II.1 - ^{1}H-NMR spectra of the crude of the first reaction.

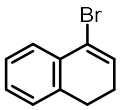
Spectra not attributed due to 2D spectra not being in accordance with the structure, the compound precipitates in solution possibly decomposed after the spectra recordings.

Characterization of the products **II.1** and **II.2** was made by ^{1}H and ^{13}C NMR, melting point and FTIR spectroscopy, which results are presented in chapter III and all were in accordance with the literature having the characteristic ^{1}H-NMR signals for indoles/azaindoles (near 8-8.5 ppm for the NH proton).

Table II.1 - Indole synthesis from vinyl bromides and aniline.



1a - α-bromo-styrene **2** **3** **II.1** **II.2**



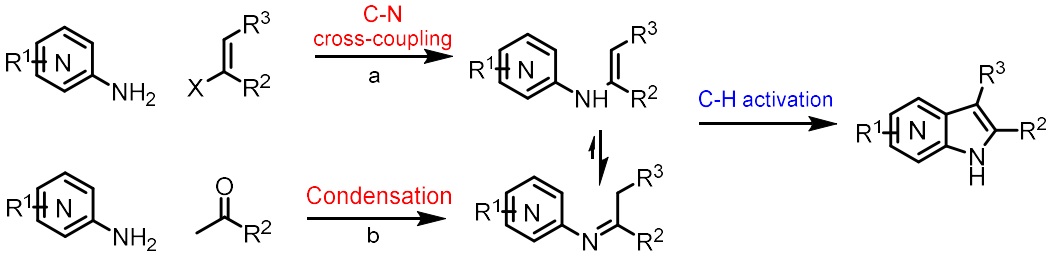
1b - 1-bromo naphtalene

		C-N reaction		
Entry	**Bromide 1.5 equiv.**	**Solvent**	**Ligand**	**Final product yield (%)**
1	**1a**	Toluene	XPhos	-[a]
2	**1a**	Toluene	DavePhos	**II.2** / 50
3	**1b**	Toluene	DavePhos	**II.1**/18[b]
4	**1a**	*t*-BuOH	XPhos	-[a]
5	**1a**	Toluene	XPhos	-[a]
6	**1a**	Toluene	BINAP	-[a]
7	**1a**	*t*-BuOH	BINAP	-[a]

[a] imine formation observed in the TLC plate but decomposed during the workup;
[b] isolated the enamine product

II.2.2 Azaindole synthesis from bromides and aminopyridines

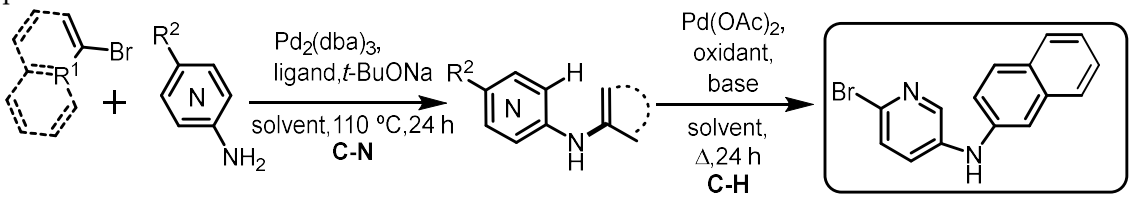
As mentioned before (chapter I.1), for azaindole synthesis, two methods were considered: **a**- C-N cross-coupling followed by C-H activation and **b**-ketone condensation with aminopyridines followed by C-H activation (**Scheme II.4**). Since the results with the **approach a** were so far promising for indoles, we decided to use the same conditions for the azaindole synthesis. Keeping the strategy in mind we started with the optimization studies on the C-N cross-coupling and on the C-H activation reaction (CDC).



Scheme II.4 - Synthetic strategies for azaindole synthesis.

The **approach a** start with the use of different bromides (**1a** and **1b**) and aminopyridines (**2a** and **2b**) as starting materials to screen different conditions for the C-N cross-coupling reaction and for the C-H activation reaction. Since the imines formed from anilines and aminopyridines have different stability the conditions can also be different than the previous established for indole formation.

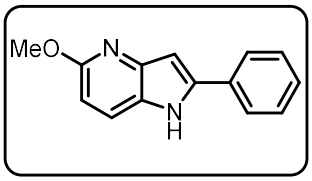
Table II.1 - Azaindole synthesis from aminopyridines and vinyl bromides, C-N step optimization.



II.3

1a - R^1 = Ph
1b - R^1 = naph.

2a - R^2 = Br
2b - R^2 = OMe



II.4

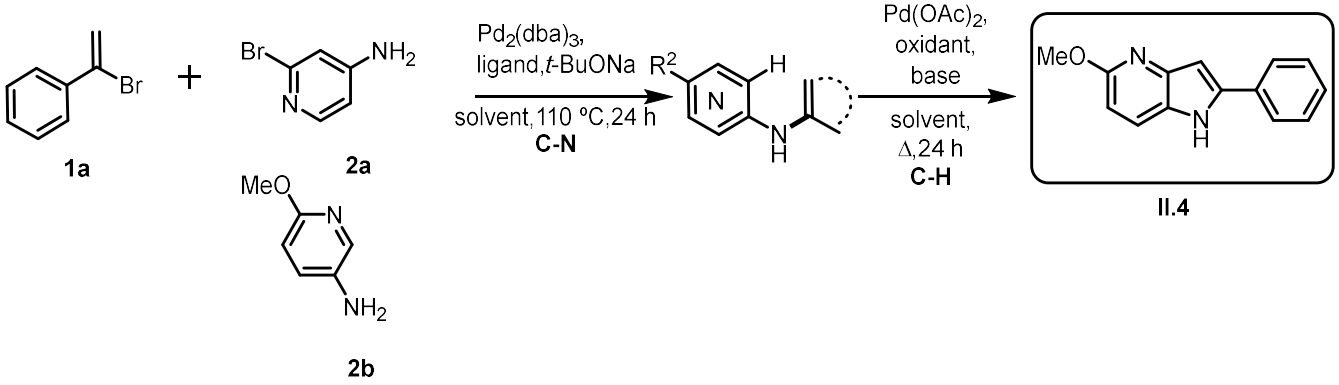
C-N reaction				
Entry	**Bromide 1.5 equiv.**	**Solvent**	**Ligand**	**Imine[c]**
1	**1a**	*t*-BuOH	XPhos	yes
2	**1a**	Toluene	DavePhos	yes
3	**1b**	Toluene	XPhos	yes
4	**1a**	*t*-BuOH	DavePhos	yes

[c]*detected with Ehrlich´s reagent stain in TLC*

Best results were obtained using *t*-BuOH as solvent and XPhos as ligand as expected based on the previous experience of our investigation group on enamine synthesis from amino-halopyridines (results based on TLC observation with higher and faster conversion). The next step after the C-N reaction consisted on the evaporation of the solvent until dryness, so that the formed enamine could be used in the next step without isolation.

It is observed in **Table II.2**, that the best conditions achieved for the C-H activation reaction were those similar to a reported protocol for indole synthesis: [39] DMSO as solvent, Cs_2CO_3 (3 equiv.). as the base and using 20 mol% of $Pd(OAc)_2$ catalyst and 6 equiv. of $Cu(OAc)_2$ as an oxidant. This approach led to a yield of 70% of one single **4-azaindole isomer (II.4)**. The role of oxygen as an oxidant of the palladium catalyst was expected to be more valuable than it showed (even saturating the reaction medium with molecular oxygen by bubbling it into the reaction vessel), instead the copper diacetate oxidized palladium effectively.
The use of other catalysts mentioned in the literature for indole synthesis such as $PdCl_2$ and other polar solvents like DMF (Cacchi *et al*[64] , Glorius *et al* [38]) or THF did not favour the reaction . The role of DMSO is probably to insure a strongly polar media in the reaction.
From this optimization studies two products, **II.3** and **II.4** were obtained, that are already known in the literature. These products were characterized based on ^1H and ^{13}C-NMR spectra, melting point and FTIR spectra and all the results were in accordance with the literature (this information is reported in chapter III).

Table II.2 - Azaindole synthesis from aminopyridines and vinyl bromides, C-H step optimization.



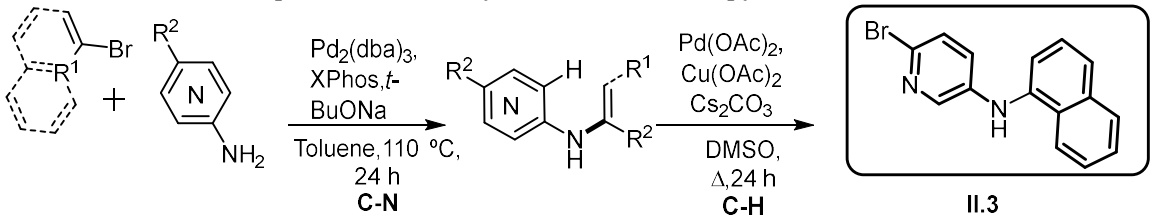
C-H reaction						
Entry	**Starting materials**	**Base (3 equiv.)**	**Solvent**	**Catalyst (mol%)**	**Oxidant**	**Yield of II.4 (%)**
1	**1a + 2a**	-	DMSO	10	$Cu(OAc)_2$ 3 equiv.	-a
2	**1a + 2a**	-	DMSO	20	$Cu(OAc)_2$ 6 equiv.	-a
3	**1a + 2b**	-	DMSO	10	$Cu(OAc)_2$ 3 equiv.	19
4	**1a + 2b**	-	DMSO	20	$Cu(OAc)_2$ 6 equiv.	41
5	**1a + 2b**	K_2CO_3	DMSO	10	$Cu(OAc)_2$ 3 equiv.	45
6	**1a + 2b**	Cs_2CO_3	DMSO	20	$Cu(OAc)_2$ 6 equiv.	70
7	**1a + 2b**	Cs_2CO_3	DMSO	10	$Cu(OAc)_2$ 3 equiv.	64
8	**1a + 2b**	Ag_2CO_3[c]	DMSO	10	$Cu(OAc)_2$ 3 equiv.	49
9	**1a + 2b**	-	THF	[b] 10	$CuCl_2/O_2$ 3equiv.	-
10	**1a + 2b**	-	DMF	[c] 10	$Cu(OAc)_2$ 3 equiv.	-
11	**1a + 2b**	-	DMF	10	$Cu(OAc)_2$	-

					3 equiv.	
12	**1a + 2b**		DMSO	10	O_2	16

In all entries $Pd(OAc)_2$ was used as catalyst and experiments carried at 40 ºC, excluding entries 9 and 10. [a] imine observation; [b] $PdCl_2$, reflux; [c] $PdCl_2$, 100 ºC; [d] using of Ag_2CO_3 as base/Lewis acid [63]

Thus, this protocol presented excellent results for azaindole synthesis, and the extension of the reaction was tested under the optimal conditions. The scope of the reaction was made varying the starting materials such as different aminopyridines(**2a**-**2d**) and bromides(**1a**-**1g**) as seen in **Table II.5**.
Characterization of **II.3** and **II.4** is described in chapter III and were previously mentioned in this chapter.

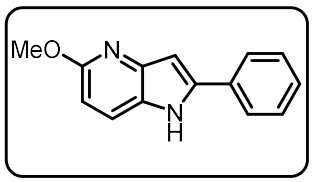
Table II.3 - Reaction scope for azaindole synthesis from aminopyridines and bromides



II.3

1a - α-bromo styrene
1b - 1H-bromo naphtalene
1c - 4-bromo-1,2-dihydronaphthalene
1d - 4-(1-bromovinyl)benzonitrile
1e - (*Z*)-2-bromobut-2-ene
1f - β-bromo styrene
1g - bromoethene

2a - 2-bromo-4-aminopyridine
2b - 6-methoxy 3-aminopiridine
2c - 2-aminopyridine
2d - methyl 2-aminoisonicotinate

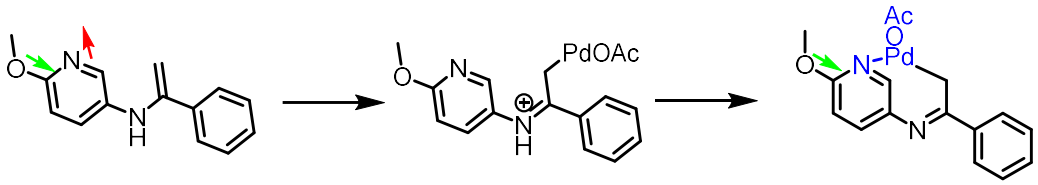


II.4

Entry	Starting materials	Yield (%)
1	**1a + 2a**	-[a]
2	**1b + 2a**	**II.3**/11 [b]
3	**1a + 2b**	**II.4**/64
4	**1d + 2b**	-[a]
5	**1c + 2b**	-[a]
6	**1b + 2b**	-a
7	**1e + 2b**	-a
8	**1a+ 2c**	-a
9	**1a + 2d**	-
10	**1f + 2b**	-c
11	**1g + 2b**	-

[a] imine hydrolysis after workup, [b] recovered imine, [c] C-H reaction in xylene 150 ºC.

The results obtained using vinyl bromides and aminopyridines for azaindole synthesis it suggests that possibly the reactivity of the starting material influences the stability of the imine intermediate.
The best result obtained for this method was using 6-methoxy 3-aminopyridine (**2b**) and α-bromostyrene (**1a**). That demonstrated that for this specific reaction a rich distribution of π-electrons in the imine structure is required for the C-H activation to succeed and without it the reaction is not happening or is too slow. The presence of an electron-donating group (methoxy) in the pyridine moiety and an N atom of the pyridine grants an electron-withdrawing capacity, and we were prompt to study these effects in the cyclization step. In these synthetic approaches only one azaindole isomer was formed, suggesting that that the N atom of the pyridine might act as a directing group of the Pd insertion step as depicted in **Scheme II.5**.



Scheme II.5 - Proposed Pd insertion step in the enamine based on experimental results and Yoshikai *et al* method for indole synthesis.

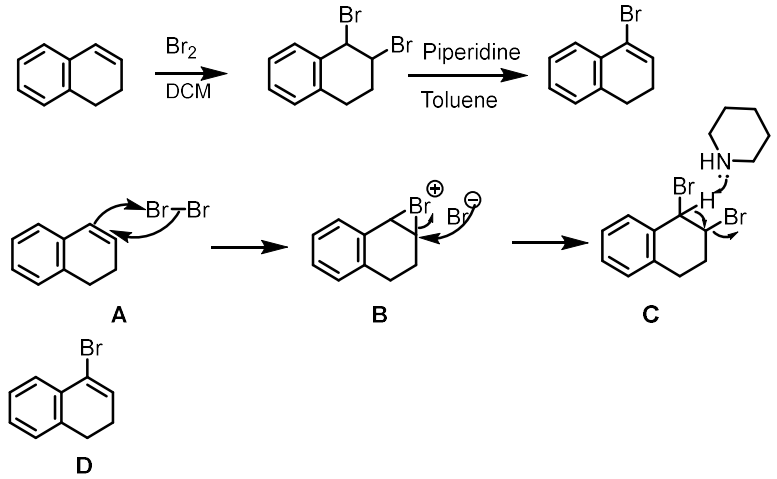
Furthermore, the combination of the two metal-catalysed systems (for the amination and cyclization reaction) might also compromise the success of the reaction. To test this hypothesis, it was proposed to prepare the imine intermediate using an alternative approach that would avoid the use of two different Pd-catalysed reactions.

II.2.3 Synthesis of vinyl bromides

Synthesis of vinyl bromides from alkenes

For the azaindole synthesis through the **approach a** (**Scheme II.4)** vinyl bromides were used, to extend the scope of the reaction. Thus, it was necessary to prepare different vinyl bromides. Several methods for the synthesis of vinyl bromide are described next starting from commercially available compounds.
The first strategy used was adapted from Prabhu *et al*. [59] The mechanism of formation of the bromide from alkene, proposed by the authors, starts with the bromination of the double bond forming the bromonium ion (**A**), followed by the opening of this ion (**B**) by the bromine anion. At last, the base takes the most

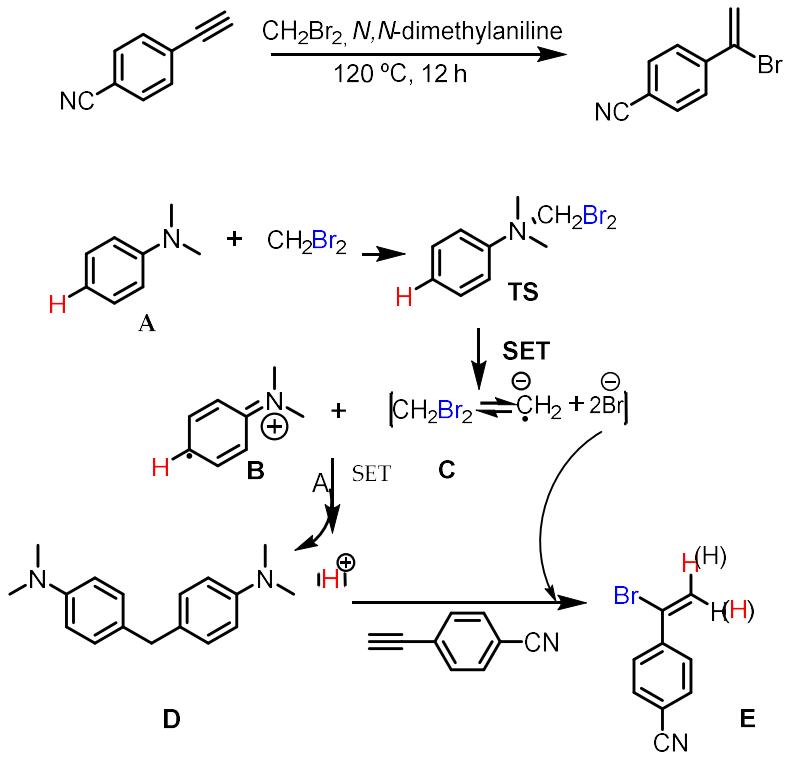
acidic proton followed by an elimination reaction E2 (**C**) **(Scheme II.6).** By applying this protocol compound **D**, was prepared with 83% yield.



Scheme II.6 - Mechanism of bromination of alkenes using bromine.

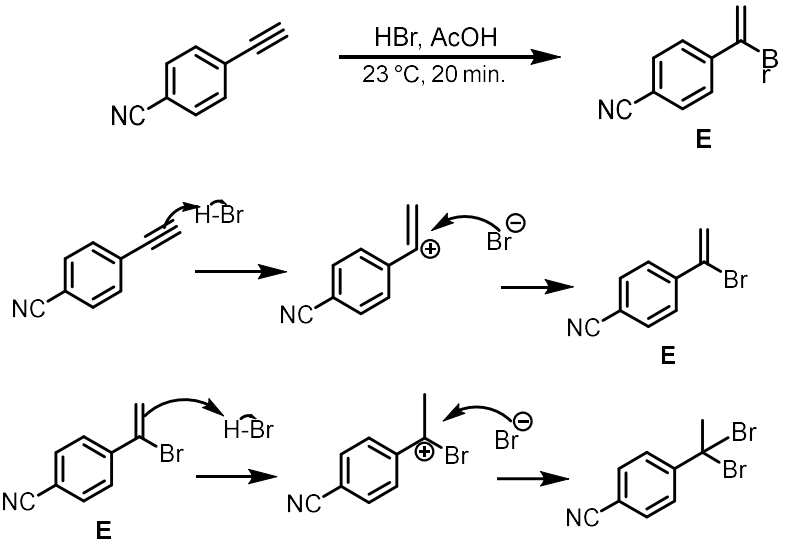
Synthesis of vinyl bromides from aromatic alkynes

Vinyl bromides can also be synthesized from alkynes, and the next strategy was described by Yin *et al*[60]. The mechanism of this reaction, proposed by the authors, starts with the coordination of *N,N*-dimethylaniline with CH_2Br_2 leading to a transition state (TS), where a C-H bond is activated in the sp2 *para* position of the amino group. Subsequently, there is the formation of radicals B and C through a single electron transfer (SET). [60] The bromine anion is generated through the breakage of the C-H bond of the radical **C**. Product **D** is achieved after another SET and deprotonation. The released proton and the bromine anion react with the triple bond taking to the formation of a Markovnikov-type vinyl bromide (**E**) (**Scheme II.6**). This reaction afforded the product **E** with 37% of yield.



Scheme II.5 - Proposed mechanism for hydrobromination of *N,N*-dimethylaniline and CH_2Br_2.[60]

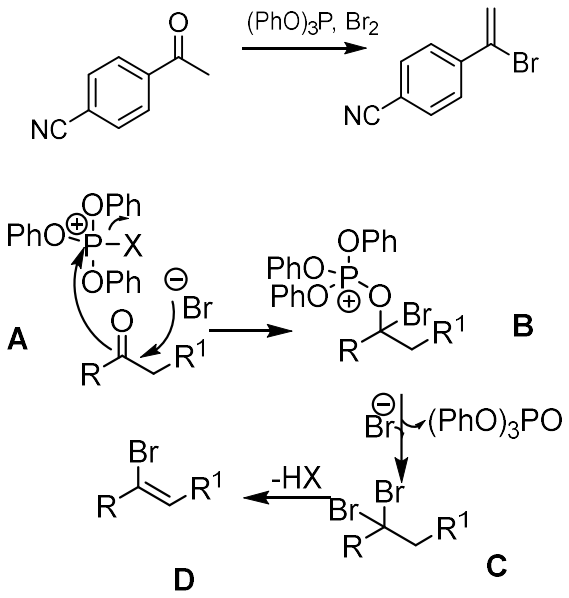
The next strategy also relies on alkynes and was described by Rosiak *et al* [61], **Scheme II.7**. The authors proposed a mechanism for this reaction that starts with an addition of the triple bond to the proton of HBr, next the bromine ion attacks the carbocation previously formed achieving the brominated compound **E** *in situ* when adding 1 equiv. of HBr. If there is addition of 2 equiv. the double bond will protonate, and the bromine attacks the formed carbocation, obtaining the dibrominated product. [61] With this approach it was not possible to attain the product **E.**



Scheme II.6 - Bromination of alkynes using bromidic acid.

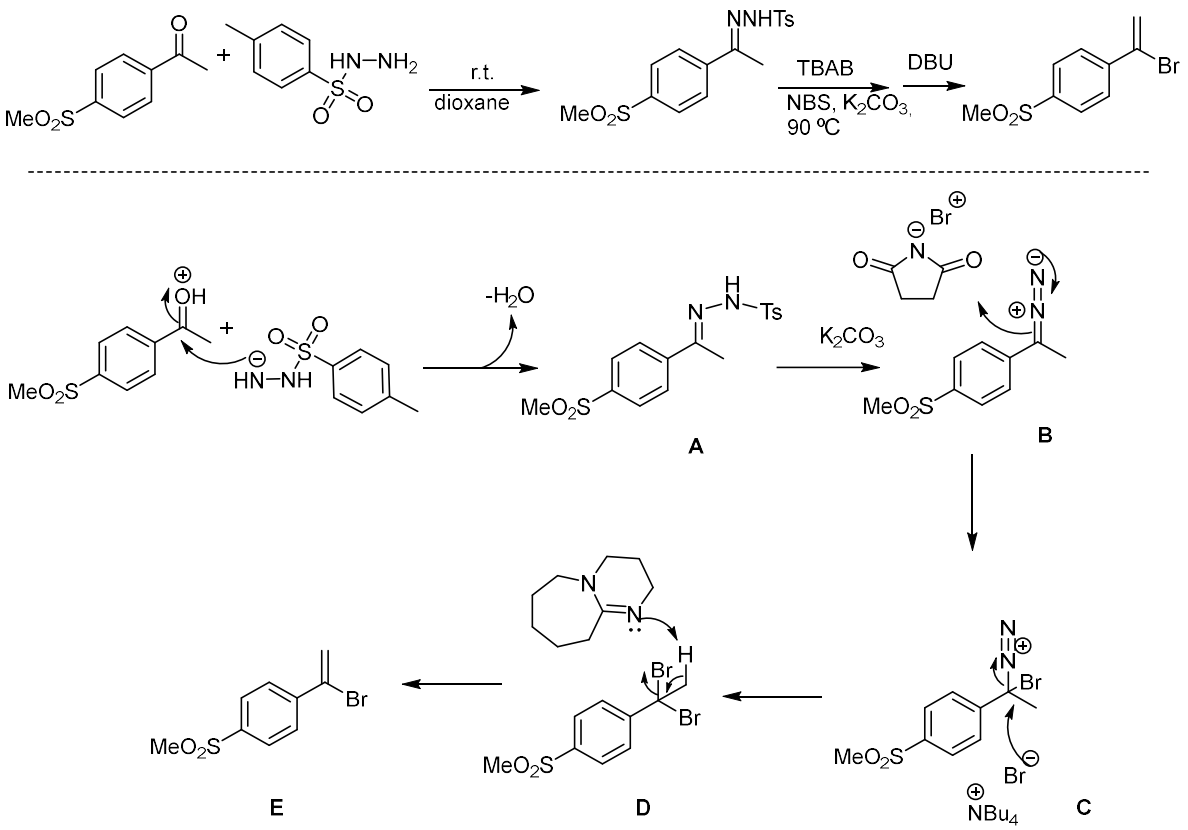
Synthesis of vinyl bromides from acetophenones

Spaggiari *et al* [62]. presented a method for vinyl bromides based in acetophenones and using triphenylphosphine and bromine. In this case the reaction starts with the formation of TPPBr (triphenylphosphite bromide) next there is the attack from the bromine to the carbonyl group (**A**). The intermediate has a good leaving group and the bromine ion attacks, causing the loss of triphenylphosphite (**B**) and, elimination of one bromine (**C e D**, **Scheme II.8**). [62] Product **D** was not obtained using this method.



Scheme II.7 - Bromination of ketones with TPPBr.

Prabhu *et al.* [59] described a protocol to achieve vinyl bromides from acetophenone and tosylhydrazide**.** This mechanism starts with the formation of the hydrazone (**A**) followed by the loss of the tosyl group (**B**) by adding potassium carbonate. Then there is the bromination of the *ipso* position to the diazo group (**C**) using *N*-bromosuccinimide followed by the bromination in the same position (**D**) mentioned before using tetra-butylammonium bromide, followed by an elimination reaction using DBU (**E**) **Scheme II.9**. Product **E** was not attained using this method.



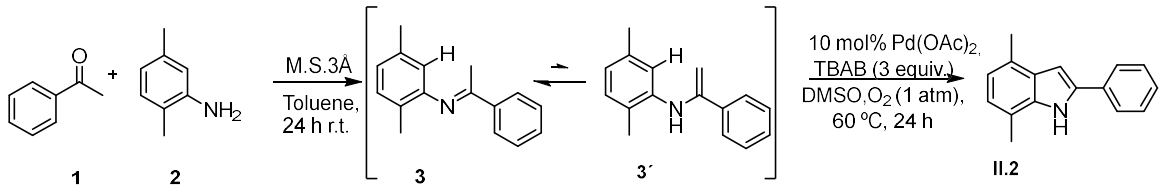
Scheme II.8 - Mechanism of the synthesis of bromo-styrene derivatives from acetophenone and hydrazine.

II.3 Azaindole synthesis: approach b via condensation/C-H activation

The methods reported for the indole synthesis using metal-catalysed C-H activation reactions, rely on the use of anilines as starting materials [39]. These methods involve an oxidative cyclization of imines by palladium(II) catalysis and the use of an oxidant like molecular oxygen or copper diacetate.

II.3.4 Preliminary studies with aniline

Opposing to anilines, aminopyridines have been scarcely investigated on C-H activation reactions (CDC), as previously shown in Chapter I. Thus, our group decided to investigate an alternative route for azaindole synthesis that could offer the advantages of catalytic methods, avoiding the difficulties associated to imine/enamine preparation as intermediates of the reaction.
In a first stage of the project a one-pot reaction for indole synthesis using acetophenone **1** and aniline **2** was tested as a model system to gain an experimental insight into the reaction conditions under a one-pot protocol (**Scheme II.11**).



Scheme II.9 - Indole synthesis condensation approach followed by C-H activation.

After the first step the reaction mixture was analysed by TLC and the full conversion of the starting materials (**1** and **2**) into a new compound was observed. By analysing the ^{1}H-NMR spectra of the crude (**Figure II.2**) the compound formed was assigned as imine **3** and with that information the reaction proceeded to the second step, the C-H activation reaction.

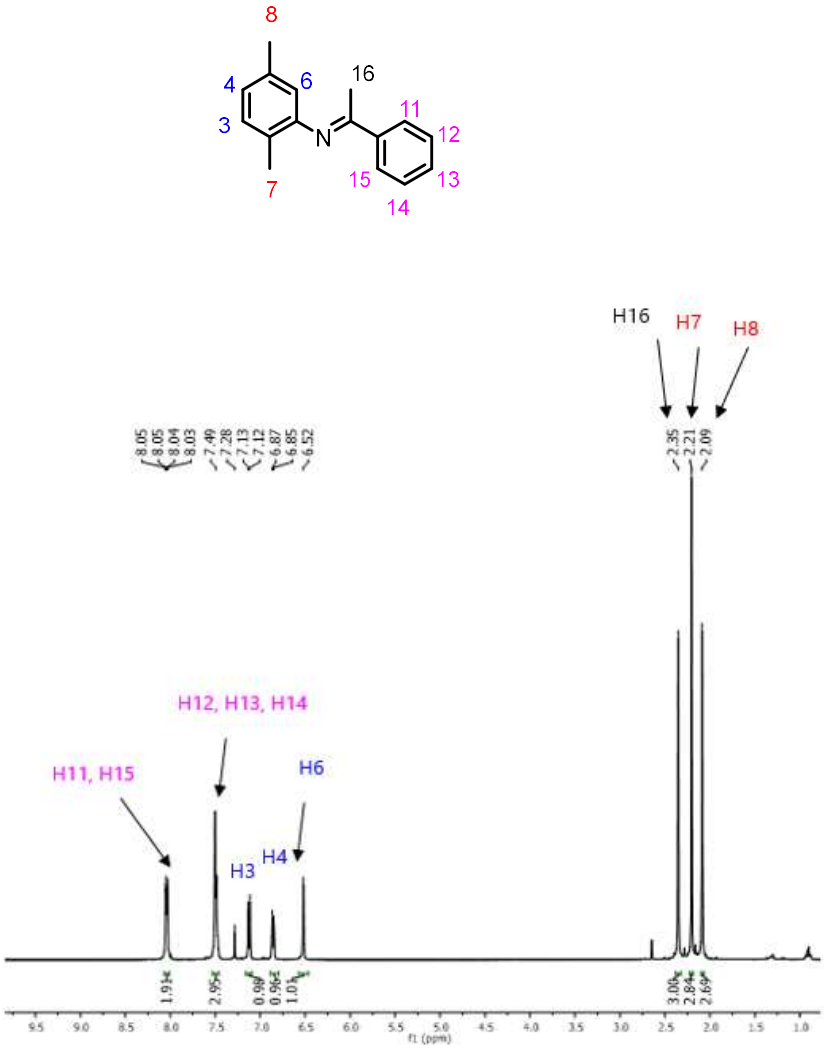


Figure II.2 - ^{1}H-NMR spectra of the crude of the first reaction.

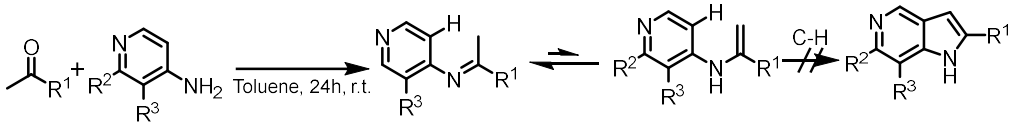
Thus, imine 3 was used without isolation in the next step that consisted on addition of $Pd(OAc)_2$ (10 mol%), O_2 (1 atm) and DMSO at 40 ºC for 24 h.

After the second step, a new fluorescent compound was observed on TLC, however without observation of full conversion of the imine and the product was isolated from the crude mixture by means of PTLC. After the observation of the ^{1}H-NMR and ^{13}C-NMR spectra of the isolated product, the indole product **II.1** was confirmed in 50% yield. The obtained product is already described in the literature and the characteristic signs referring to NH protons in ^{1}H-NMR are near 8.22 ppm.

So, we concluded that Yoshikai´s methodology [39] was applicable for one-pot reactions using acetophenones as starting material. Similar approaches towards indole indoles starting from anilines already exist. In 2009, Glorius *et al*[38]. developed a palladium(II)-catalysed oxidative cyclization of N-aryl enamines. Unfortunately, this method required the use of stabilized enamine substrates and stoichiometric amounts of $Cu(OAc)_2$ as the oxidant. Jiao *et al*. reported a one-pot

indole synthesis from simple anilines and electron-deficient alkynes using O_2 as the oxidant. [65]Cacchi *et al*. [64] described a copper-catalysed approach to the construction of multisubstituted indoles from N-aryl enaminones. Zhao *et al* [66]. disclosed a PIDA-mediated indole synthesis) from N-aryl enamines. Liang *et al*. [67] explored an iron-catalysed system for indole synthesis from N-aryl enaminones. Nevertheless, the use of specific starting materials determines the limitations of the scope of the reaction, and this substrate problem remains.
The applicability of the one-pot method proposed in **approach b** (chapter II) was tested, and next it was investigated whether this is suitable for aminopyridines and ketones. Using for the initial insights, substituted amino-pyridines (**2a** or **2b**) that could easily be functionalized and aromatic or cyclic ketones (**1a,1b** or **1c**) were tested and the results obtained summarized in **Table II.1**.

Table II.4 – Preliminary results on the one-pot method for azaindole synthesis from ketones and amino-halopyridines.



1a R^1 = Ph
1b R^1 = *p*-PhCl
1c R1 = *p*-$PhSO_2$

2a $R^2 = CH_2COOMe$, R^3 = H
2b R^2 = H, R^3=I

3 3´ 4

Entry	Aminopyridine	Ketone	TLC analysis
1	**2b**	**1b**	No reaction
2	**2a**	**1c**	No reaction
3	**2a**	**1a**	Imine was observed

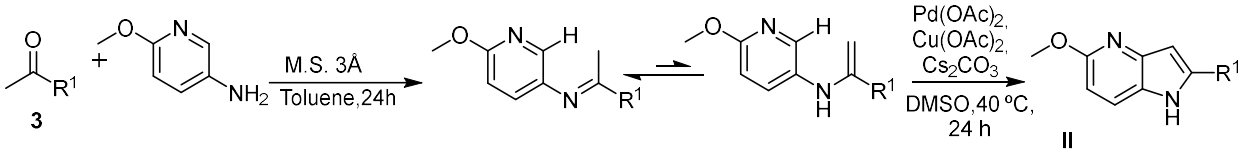
With this approach the formation of imines from aminopyridines is extremely slow due to their electron withdrawing properties. The formation of imine has only been observed in one example of the **Table II.1** were R^1 = Ph and R^2 = CH_2COOMe; and since they are susceptible to hydrolysis, there was no azaindole **4** formation. After the isolation/workup of the supposed imine, it decomposed into the starting materials **1** and **2**.

Although α-bromostyrene (1a) is a commercially available material, the access to a large range of other vinyl bromides would require their preparation via a bromination/dehydrobromination sequence,[59] or according to more recent approaches, a nucleophilic vinylation of tosylhydrazones.[59-61] as discussed previously in chapter II.2.3.

II.3.5 Azaindole synthesis from ketones and aminopyridines

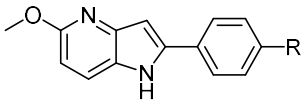
Concerning a more versatile and easier to perform methodology, we consider applying the studied conditions to imines prepared from the corresponding ketones that are commercially available. Thus, acetophenones and other ketones (**1a** - **1o**) with an aminopyridine possessing an electron-donating group were then considered and the results obtained are summarized in Table II.6, the yields where from low to excellent (24-96%).

Table II.5 - Azaindole synthesis from acetophenones and aminopyridines - reaction scope.

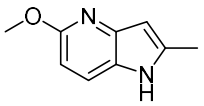


3 II

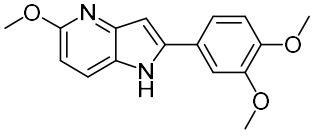
1a, 4-methoxyphenylacetone
1b, 4-bromoacetophenone
1c, 4-chloroacetophenone
1d, 4-nitroacetophenone
1e, 4-methylacetophenone
1f, 4-iodoacetophenone
1g, 4-*tert*-buthylacetophenone
1h, 4-methylsulphonylacetophenone
1i, acetophenone
1j, propanone
1k, 4-imidazolylacetophenone
1l, 4-methoxyacetophenone
1m, 2´-methoxyacetophenone
1n, 3,4-dimethoxyacetophenone
1o, 1-(benzo[*d*][1,3]dioxol-5-yl)etanone
1p, 2-methoxy acetophenone
1q, 3-methoxy acetophenone
1r, 1-(4-butylphenyl)ethan-1-one
1s, 3,4-dihydronaphthalen-1(2H)-one



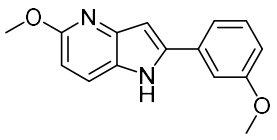
II.4 (R = H)
II.5 (R = OMe)
II.6 (R = Br)
II.7 (R =Cl)
II.8 (R=NO_2)
II.9 (R = Me)
II.10 (R = *t*-Bu)
II.11 (R = Bu)



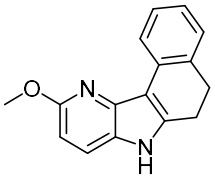
II.12



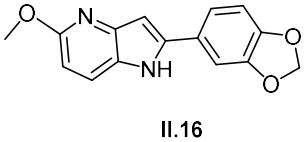
II.13



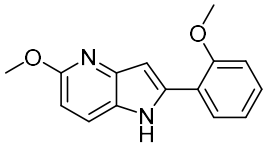
II.14



II.15



II.16



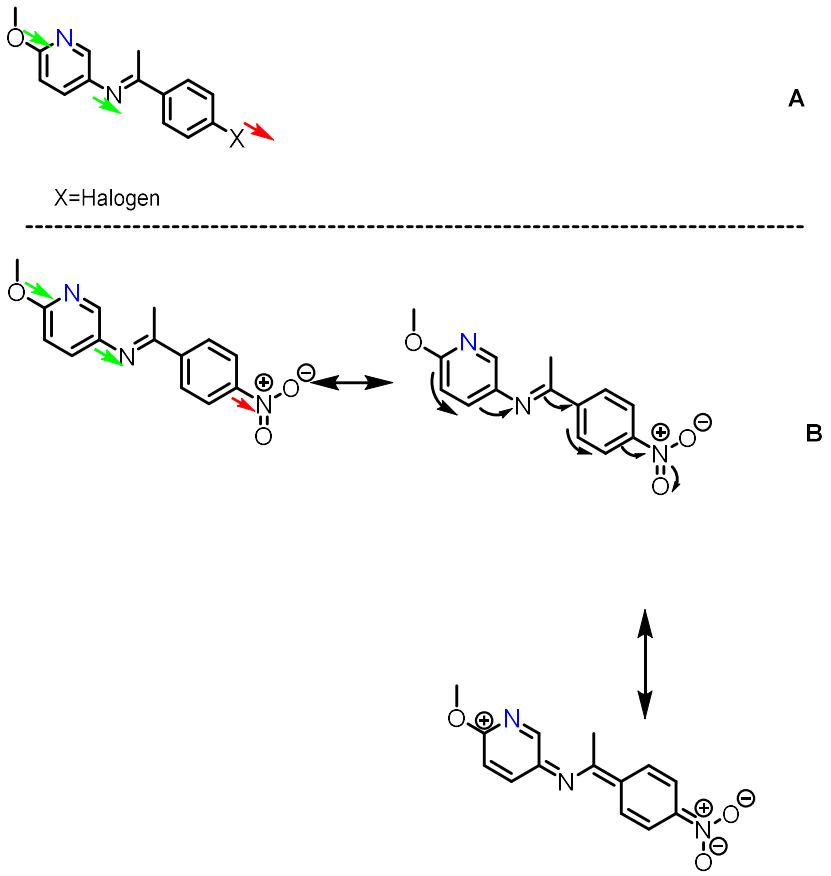
II.17

Entry	Ketone	Yield of II (%)	Entry	K*etone*	Yield of II (%)
1	**3m**	n.r.	**9**	**3i**	96
2	**3b**	27	**10**	**3j**	75
3	**3c**	42	***11***	**3k**	Trace
4	**3d**	Trace	***12***	**3l**	90
5	**3e**	69	**13**	**3p**	87

6	**3f**	n.r.	***14***	**3n**	64
7	**3g**	72	**15**	**3o**	83
8	**3h**	n.r	**16**	**3q**	61
17	**3j**	75			
18	**3s**	73			

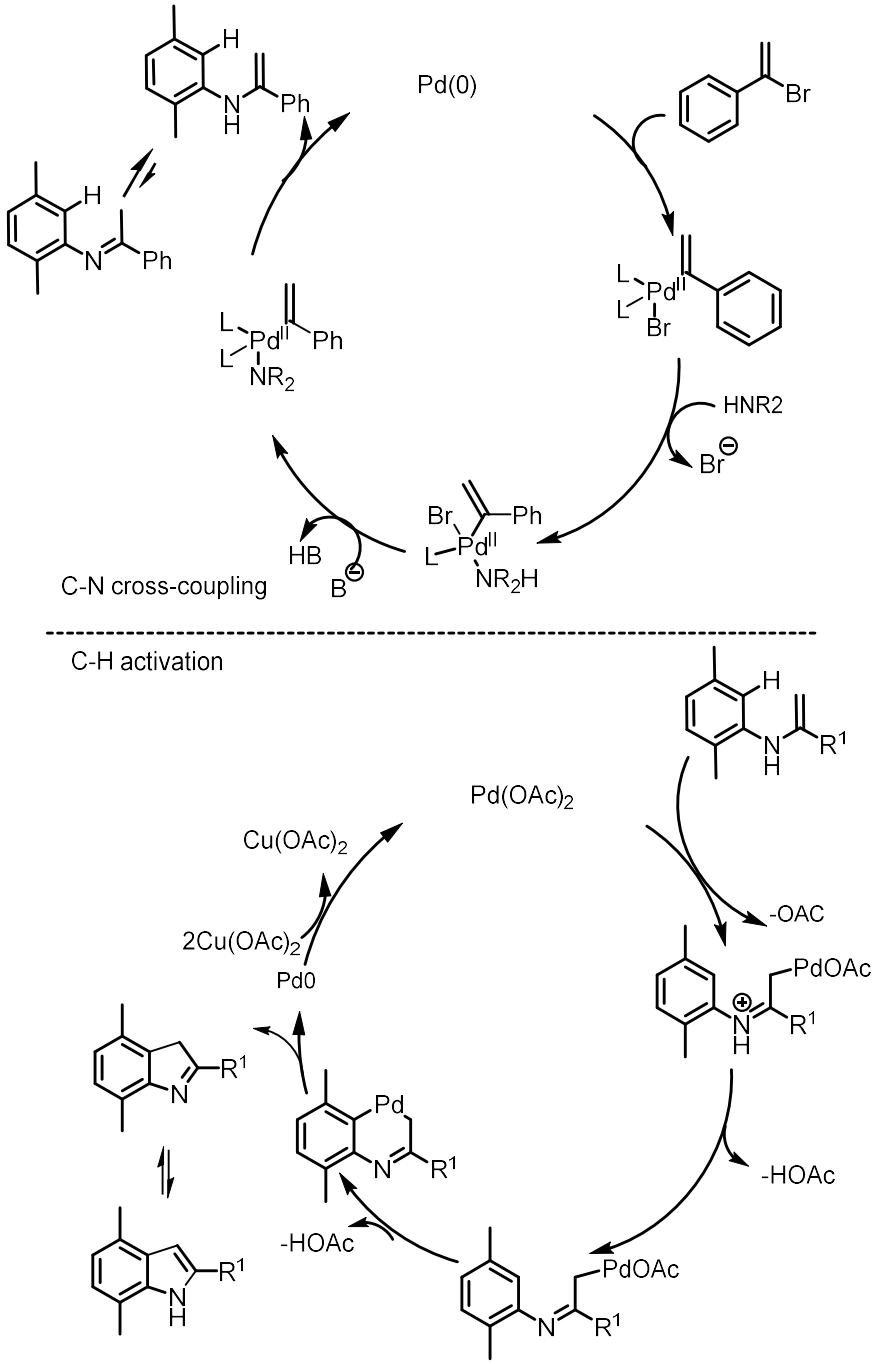
To characterize new products (**II.5, II.7, II.9, II.10, II.11, II.13, II.14, II.15, II.16, II.17**) it was used ^{1}H-NMR, ^{13}-C-NMR spectroscopy, 2D-NMR (HSQC and COSY) to make the correct attribution of the 1D spectra. It was also made FTIR spectra, GC-MS and melting points of the solid compounds. To rapidly characterize these azaindoles we can search for the NMR peaks of the characteristic NH (8 ppm), the ^{13}C-NMR (160 ppm, adjacent carbon of methoxy group derived from the original aminopyridine) the FTIR spectra (approximately 3000 $cm^{-1}$for the NH vibration) With these results we can say that products 3i, 3l,3p and 3o are great examples of excellent yields obtained using this approach when using electron-donating moieties in the ketone substrates. The presence of an electron-withdrawing substituents (Entries 4,6, 8 and 11) in the aromatic ring of the starting ketone, does not favour imine conversion to the azaindole product (as far as we can see, products were not formed or were found in trace amount) A plausible explanation for this fact is the lack of available electrons to proceed to the cyclization step.

In the case the substituent is an halogen atom (**A**), a resonance effect takes place and in the case of groups like NO_2 and SO_2Me (**B**) the effect is inductive and by resonance (only in this case because the substituents are in *para* position) as described in **Scheme II.12**.



Scheme II.10 - Deactivating groups effect in the imine.

With these insights we can propose a mechanism similar to the one proposed by Yoshikai for indole [39] The following **Scheme II.13** describes a mechanism that starts by the enamine **1** generated via tautomerization of imine **1**′ would be electrophilically attacked by $Pd(OAc)_2$ (**A**), followed by elimination of HOAc to give an α-palladated imine **B**. The intermediate **B** would then undergo intramolecular aromatic C–H palladation to give a six-membered palladacycle **C**. Subsequent reductive elimination affords azaindole **2**' and Pd(0). The former tautomerizes quickly to azaindole **2** while the latter is oxidized back to Pd(II) with the aid of copper acetate.



Scheme II.11 - Proposed catalytic cycles of the formation of imine/enamine through C-N cross-coupling followed by C-H activation reaction, for indole synthesis.

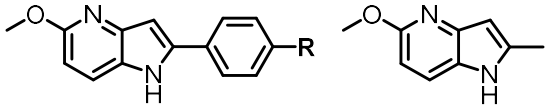
Sometimes it was not easy to distinguish the starting acetophenones from imines in the TLC plates because of the similar retention factors. For that we used Ehrlich´s reagent that showed yellow (imine and amine) to purple staining(enamine). This developing reaction is based on a reaction with *p*-dimethyl benzaldehyde that forms colored compounds with amino groups. [68]

In conclusion, both approaches a and b were sucessful (both led to azaindoles). Only approach b was extendend and had a more variety of scope. This strategy

is completely new, versatile, has a great atom-economy and makes some great advance for azaindole synthesis and can possibly be tuned for other types of isomers.

II.3.6 Biological evaluation of synthesized azaindoles

The compounds represented in **Figure II.3** were sent to biological essays.



II.4 (R = H)
II.5 (R = OMe)
II.6 (R = Br)
II.7 (R =Cl)
II.9 (R = Me)
II.10 (R = t-Bu)

II.12

Figure II.3 - Azaindoles tested in biological essays.

We expected them to have some biological activity since other analogues like the family of compounds represented in **Figure II.4** have showed results towards c-Met, a tyrosine kinase receptor that when overexpressed, can mutate and be present in several cancer types. [20]

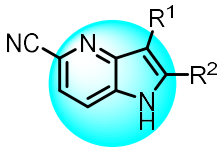


Figure II.4 - 4-azaindole family of compounds that are c-Met inhibitors. [20]

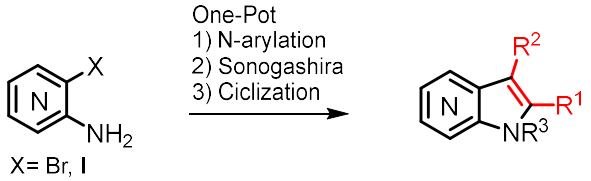
These strategies consist on the first protocol to prepare azaindoles directly from aminopyridines, without the need of protecting groups, under mild conditions and relying on a C-H activation reaction catalysed by palladium. This innovative approach overcomes the need of using amino-halopyridines required for most metal-catalysed cross-coupling reactions.

Furthemore, the compounds were submitted to evaluation regarding its activity as COXs inhibitors.

Cancer stem cells (CSCs) are a subpopulation of cancer cells implied in tumor formation, metastases and recurrence due to their long-lasting properties and chemotherapy resistance [69]. The effectiveness of a set of chemical compounds, was evaluated from several in-house (iMed.ULisboa, Professora Cecília Rodrigues) and external libraries, as potential anti-CSC agents. At Prof Cecília Rodrigues Lab, a high-throughput screening platform was optimized and validated to identify novel molecules from large compound libraries that

specifically impact on colorectal CSC phenotype. HT29 human colorectal adenocarcinoma were plated in 96-well plates (100 cell/well) in undifferentiated medium in ultra-low attachment conditions for sphere formation and treated with a previously reported CSC-targeting agent (salynomicin; 1 μM - positive control), testing compounds (1μM) or vehicle controls. Following 7 days of incubation, cell viability was assessed based on measurement of ATP, using the CellTiter-Glo™ Luminescent Cell Viability Assay (Promega). Until now, ~1420 compounds were screened using this platform. For hit selection, a cut-off threshold < 30% of ATP depletion led to ~150 hits, corresponding to 11% hit rate for the full library, with some compound series particularly rich in active compounds.
None of the mentioned compounds were active towards the tested stem cells.

Besides this project, our group was working in a one-pot Arylation/Sonogashira/cyclization strategy for azaindole synthesis [18] following the steps in **Scheme II.16**.



Scheme II.12 - One-pot Arylation/Sonogashira/cyclization strategy for azaindole synthesis.

Some of the presented compounds were subjected to bioactivity tests (performed by Professor Eduarda Fernandes, University of Porto) concerning COX inhibition (**Figure II.5**), the selected compound was prepared by me using the optimized conditions of our group.[18]

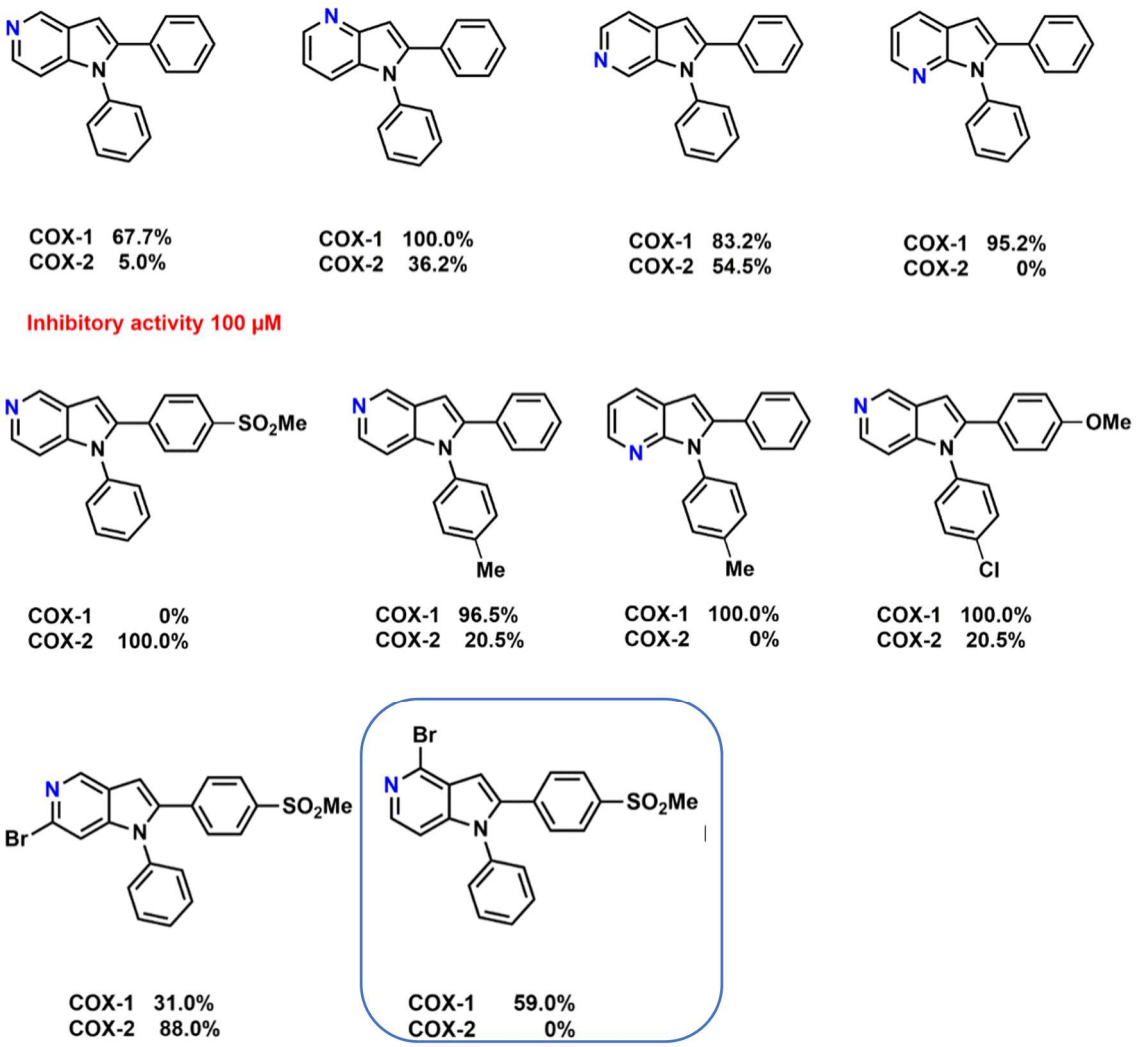
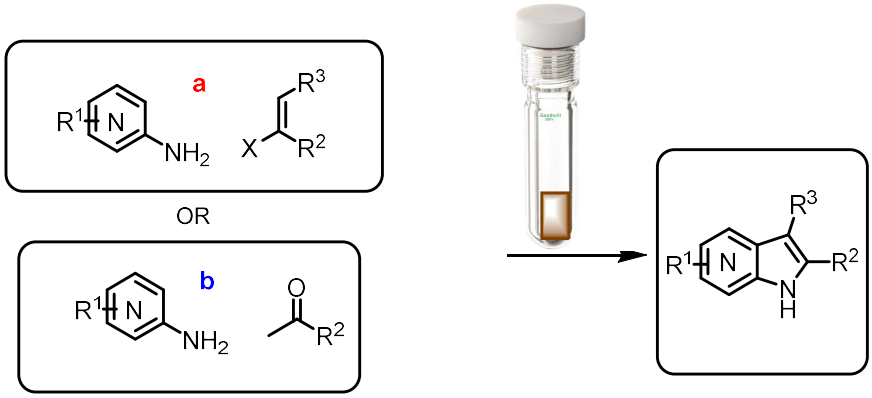


Figure II.5 – COX inhibition by several synthesized azaindoles (% of inhibition for each COX isoform), the compound prepared by me is highlighted in blue.

As it can be observed, the highlighted product has a specific inhibitory activity for COX-1 isoform. One compound showed a strong selective inhibition of COX-2 (the isoform expressed during inflammation). However, more studies are ongoing in order to determine the IC50 of the compounds of interest.

II.4 Final Remarks

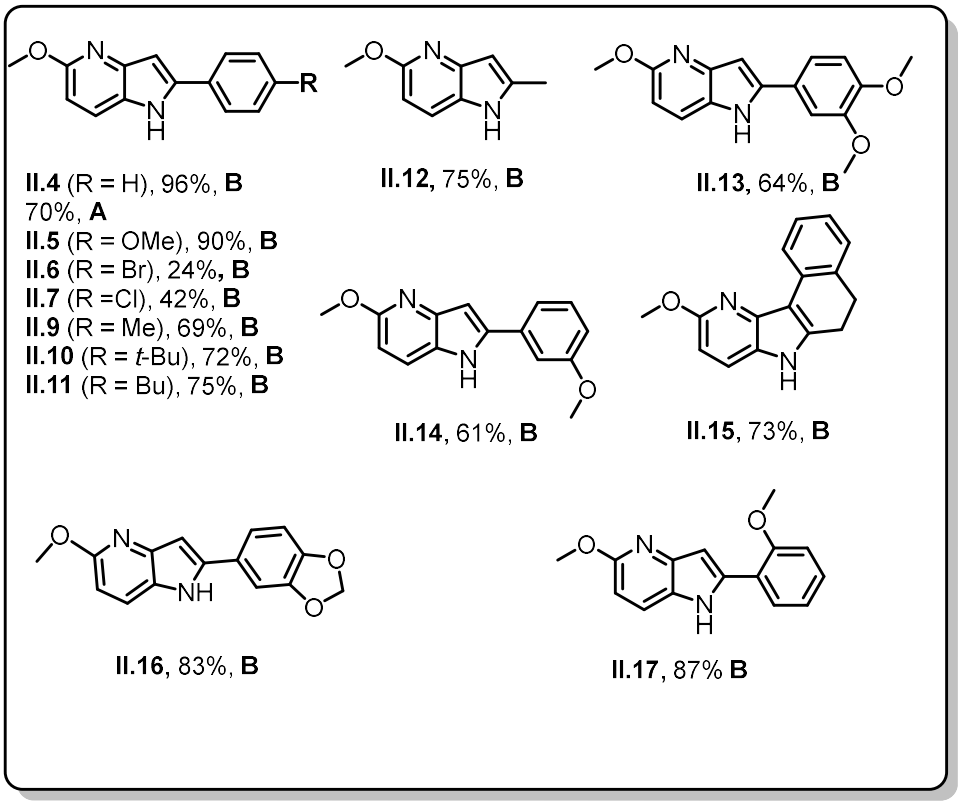
The purpose of this master thesis was to develop new route to access azaindoles using metal-catalysed reactions. The route established consist of a one-pot methodology that affords azaindoles, a challanging synthetic corewithout the need of purification of the intermediates, avoiding time-consuming while being beneficial to the environment because there is no need of harsh conditions or additional protection-deprotection steps.



Scheme II.13 - Generic synthetic methods applied during this thesis.

To achieve this core two approaches were explored (**Scheme II.19**). **Approach a** aimed at forming an enamine intermediate *in-situ* through a C-N cross-coupling (previously studied by our group) followed by a C-H activation to afford the azaindole product without the presence of moisture caused by the condensation that we observe in **approach b**. So, **approach a** was expected to be more efficient than approach **b** but, unfortunately this method showed to be limited to few substrates and there might be compatibility problems with the use of two different catalytic systems, or catalyst poisoning. The only starting materials that proved suitable for this reaction were the activated aminopyridines and α-bromo styrene reaching yields up to 70%. The synthesis of various vinyl bromides was attempted using different methods, however, only two methods were reliable, reducing the possible vinyl bromides to be used in the strategy. This approach was not further investigated and instead an alternative procedure was considered.

In **approach b**, based on a condensation reaction of an aminopyridine and a ketone, followed by a C-H activation there was the need to first test the one-pot reaction of condensation between acetophenone and aniline to gain some insights of the reaction. The best conditions involved activated aminopyridines, 20 mol% $Pd(OAc)_2$, ketones without electron-withdrawing groups, 6 equiv. of $Cu(OAc)_2$ as the oxidant and 3 equiv. of Cs_2CO_3 as the base at 40 ºC. The **approach b** afforded several 4-azaindoles (14 examples, 13 synthesized in this thesis) with yields up to 96%, **Scheme II.16**.

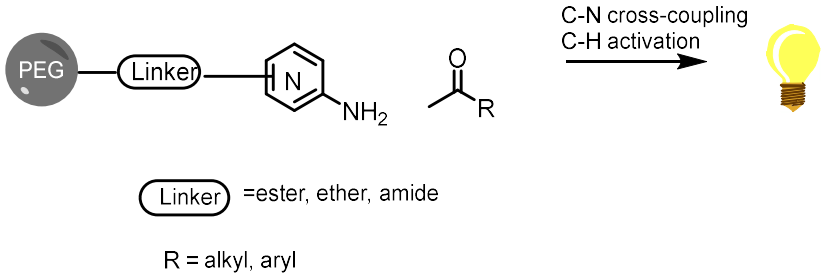


Scheme II.14 - Scope of obtained azaindoles during this master thesis. **A**-approach a, **B**-approach b.

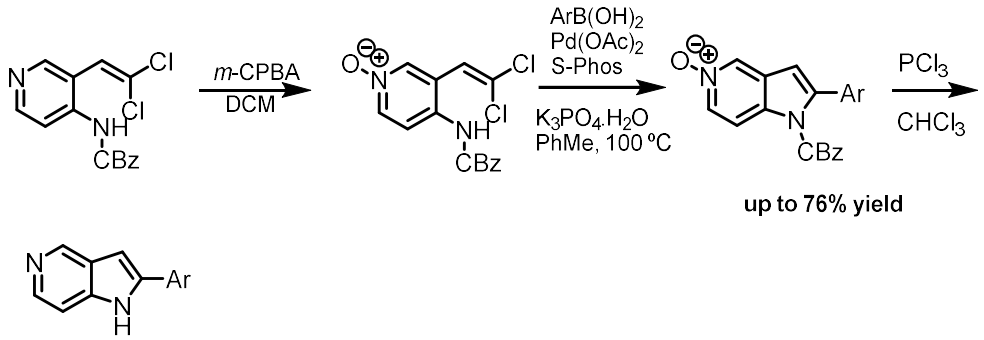
The work made in this master thesis have led to two submitted publications in two different scientific journals (Molecules and Angewandte) and presented at MedChemSicily 2018 as an oral communication (M. M. B. Marques).

II.5 Future Perspectives

The future of this project relies on continuing the **approach b**, using ketones and aminopyridines to obtain different azaindole isomers and implement this methodology in solid support synthesis, using for example PEG-2000 [70].



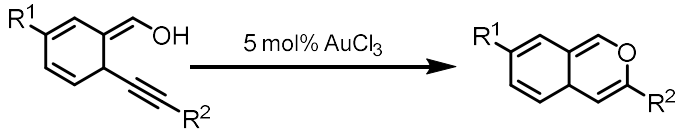
Alternative strategies will be explored in order to e use non-activated aminopyridines. The oxidation of the N atom of the aminopyridine is one hypothesis that can avoid the extreme deactivation of the pyridine ring making the reactivity of the aromatic ring almost similar to an aniline. This proposed idea was used by Lautens *et al*. [27] in 2007 and his co-workers when they attempted to synthesize 4-azaindole from N-protected aminopyridines and these syntheses formed a complex mixture of products. They proposed the formation of vinyl palladium complexes wherein coordination to the pyridyl nitrogen retards the C-N bond formation. Under these circumstances, they protected the pyridyl nitrogen as the N-oxide, and following oxidation with *m*-CPBA, successfully underwent a tandem coupling to afford the desired *N*-oxy-4-azaindole in good to excellent yield. [27]



Scheme II.17 - Synthesis of 4-Azaindoles by Lautens *et al*[27]. using N-oxidation protection of the aminopyridine.

Another possible strategy in advance for azaindole synthesis would be the change of catalyst. Gold catalysis have been recently explored for heterocycle synthesis using C-H benzylic activation for isochromene synthesis. [78] This

strategy relies on a Sonogashira reaction for the insertion of the alkyne into the benzyl moiety and then the C-H activation is facilitated by Au(III).



Scheme II.15- Gold-catalysed conversion to obtain isochromene.

There is the possibility of using amino-halopyridines as substrate to perform this reaction to obtain azaindoles.

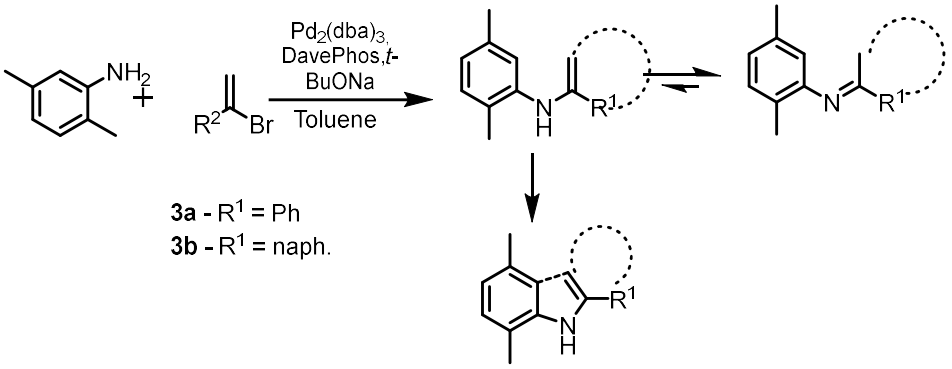
III Experimental

General Information

The experimental part of this work involved the use of general laboratory procedures. All reagents and solvents were acquired commercially and used without further purification, unless otherwise mentioned. All of the mentioned solvents were, when necessary, dried using typical methods. Molecular sieves were activated by heating at 300°C in a muffle furnace for 3h. Analytical TLC was performed on Merck Kieselgel GF 254 0.2 mm plates supported on aluminum. Preparative TLC was performed using Merk Kieselgel 60GS254 silica gel for TLC supported on a glass surface with the described eluent for each case. Column chromatography was performed using Merck Kieselgel 60A silica gel (70-200 mesh) and the described eluent for each case. Melting points were measured using a Reichert Thermovar melting point apparatus, equipped with a Kofler plate. Measured melting points were not corrected. IR spectrum were acquired using a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer. Transmittance of the sample was acquired on between 4000 and 600 $cm^{-1}$and the samples were supported on KBr pellets or NaCl pellets. NMR spectrum were acquired with Bruker ARX 400 or Bruker Avance III 400 spectrometers. ^{1}H-NMR and ^{13}C-NMR spectrum were measured at 400 and 101 MHz, respectively. The samples were prepared on 5 or 3 mm NMR tubes using $CDCl_3$ or DMSO-d_6 as solvents and the corresponding trace $CHCl_3$ or DMSO as reference signals. The NMR signals are described with chemical shift (δ, in ppm), source of signal (R-H) and relative intensity of signal multiplicity (nH, with n being the number of protons) of NMR signals are described as singlet (s), doublet (d), triplet (t) and multiplet (m) with coupling constant (*J*) being given in Hz.
Mass spectrum were acquired with GC-MS using a MicroTOF gas chromatographer and ESI-FIATOF. Details of mass spectrum are given as mass-to-charge ratio (m/z), attributed molecular formula and relative intensity of the molecular fragment.

III.1 Azaindole synthesis: approach a via C-N cross-coupling / C-H activation

III.1.1 Preliminary studies with aniline

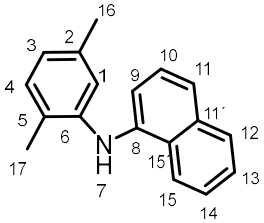


General procedure for azaindole synthesis from bromides and aminopyridines using O_2 as oxidant.

In a previously dried sealed tube, equipped with a magnetic stirrer, it was added $Pd_2(dba)_3$ (0.04 equiv), ligand (0.08 equiv), *t*-BuONa (3 equiv.) and aniline/aminopyridine (30 mg, 0.2 mmol). Next to that, the tube was sealed with a suba-seal stopper and then evacuated with vacuum pump and refilled with gaseous nitrogen using a needle making three cycles of this procedure. Then, it was added dried toluene (c = 1.65 M), followed by the vinyl bromide (1.5 equiv.). The reactional mixture was under stirring at 110 ºC for 24 h. Then the mixture was allowed to cool to room temperature and evaporated until dryness and was added $Pd(OAc)_2$ (0.1 equiv) and TBAB (2 equiv.). After this addition, the tube was evacuated using a vacuum pump and refilled with gaseous O_2 and under an atmosphere of O_2 was added dried DMSO (c = 0.2 M), the tube was left with a O_2 balloon (1 atm). The reaction was under stirring at 60 °C all through 24 h. When the reaction was completed or almost completed (total consumption of starting materials), the mixture was diluted in ethyl acetate, filtrated through a celite pad and evaporated to dryness. The crude products were purified by preparative thin layer chromatography or Flash chromatography.

N-(2,5-dimethylphenyl)naphthalen-1-amine (II.1)

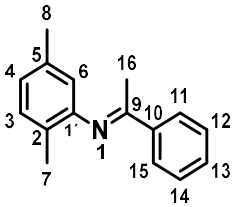
Compound **II.1** was obtained has a red brown solid in 18%(5,36 mg) yield using a PTLC Hexane/EtOAc (12:1)



^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (dd, *J* = 5.9, 3.4 Hz, 1H, H12,H15), 7.71 – 7.64 (m, 1H, H9, H10), 7.11 (d, *J* = 7.7 Hz, 1H, H11, H14), 6.88 (d, *J* = 12.6 Hz, 2H, H3,H4), 6.75 (s, 1H, H1), 6.50 (s, 1H, H5), 2.30 (s, 3H, H16), 2.10 (s, 3H, H17).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.29 (C8), 151.28 (C6), 137.96 (C2), 135.52 (C11´), 132.90 (C5,C12), 132.34 (C4,C10), 127.66 (C14, C15´), 127.55 (C13), 127.21 (C1, C3, C11), 121.82 (C9,C15), 19.81 (C16), 15.91 (C17).
IV(NaCl) $\upsilon_{máx}$: 3371 (N-H), 2918 (C-H), 1600 (C=C), 1250 (C-N).
M.P. = 95-100 ºC[71]

1, N-(2,5-dimetylphenyl) -1-phenyletan-1-imine

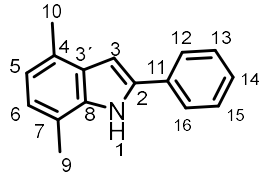
This intermediate was not purified in order to perform this characterization.



^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (dt, *J* = 8.6, 3.8 Hz, 2H, H11, H15), 7.53 – 7.46 (m, 3H, H12, H13, H14), 7.13 (d, *J* = 7.6 Hz, 1H, H3), 6.86 (d, *J* = 7.3 Hz, 1H, H4), 6.52 (s, 1H, H6), 2.35 (s, 3H, H16), 2.21 (s, 3H,H7), 2.09 (s, 3H,H8).
IV(NaCl) $\upsilon_{máx}$: 2918 (C-H), 1637 (C=C), 1245 (C-N).

4,7-dimethyl-2-phenyl-1H-indole (II.2)

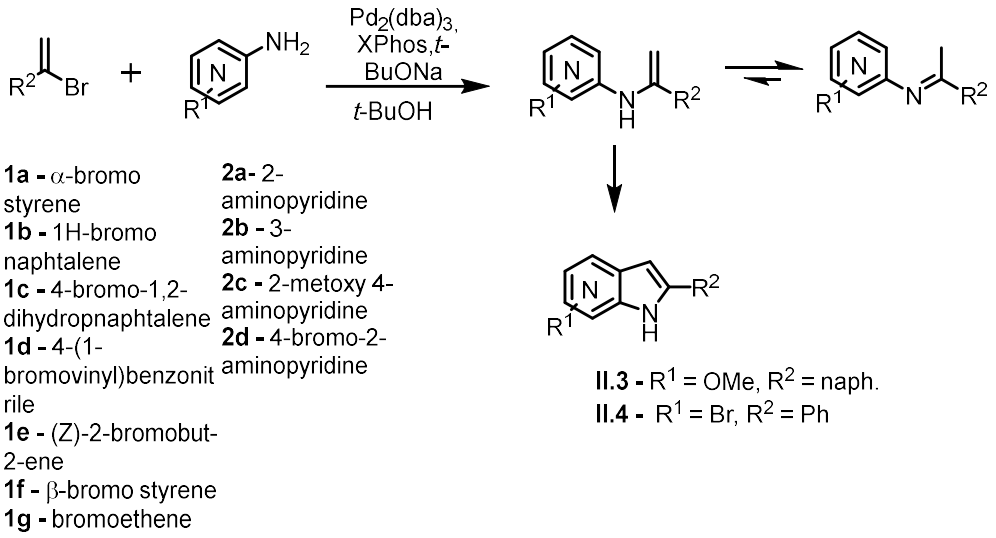
The crude product was purified by preparative thin layer chromatography Hexane /EtOAc (12:1,) achieving the indole **II.2** as a red oil with 51% yield (15.16 mg mg).



^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (s, 1H, H1), 7.72 (d, *J* = 7.7 Hz, 2H, H12, H16), 7.47 (t, *J* = 7.7 Hz, 2H, H13, H15), 7.34 (t, *J* = 7.4 Hz, 1H, H14), 6.93 (d, *J* = 7.2 Hz, 1H, H6), 6.87 (d, *J* = 7.6 Hz, 2H, H3, H5), 2.58 (s, 3H, H10), 2.53 (s, 3H, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 137.11 (C2), 136.08 (C8), 132.71 (C11), 129.01 (C13,C15), 128.72 (C14), 127.81 (C12, C16), 127.54 (C4), 125.17 (C5), 123.01 (C3′), 120.49 (C6), 117.52 (C7), 99.18 (C3), 18.55 (C10), 16.53 (C9). [72]
IV(NaCl) $\upsilon_{máx}$: 3371 (N-H), 2918 (C-H), 1600 (C=C), 1250 (C-N).

III.1.2 Azaindole synthesis: approach a via C-N cross-coupling / C-H activation: from aminopyridines and bromides



A-General procedure for azaindole synthesis from bromides and aminopyridines using O_2 as oxidant.

In a previously dried sealed tube, equipped with a magnetic stirrer, it was added $Pd_2(dba)_3$ (0.04 equiv.), ligand (0.08 equiv.), *t*-BuONa (3 equiv.) and aminopyridine (30 mg, 0.2 mmol). Next to that, the tube was sealed with a suba-seal stopper and then evacuated with vacuum pump and refilled with gaseous nitrogen using a needle making three cycles of this procedure. Then, it was added dried *t*-BuOH (0.1 M), followed by the vinyl bromide (1.5 equiv.). The reactional mixture was under stirring at 110 ºC for 24 h. Then the mixture was allowed to cool to room temperature and evaporated until dryness and was added $Pd(OAc)_2$ (0.1 equiv.) and TBAB (2 equiv.). After this addition, the tube was evacuated using a vacuum pump and refilled with gaseous O_2 and under an atmosphere of O_2 was added dried DMSO (c = 0.2 M), the tube was left with a O_2 balloon (1 atm). The reaction was under stirring at 60 °C all through 24 h. When the reaction was completed or almost completed (total consumption of starting materials), the mixture was diluted in ethyl acetate, filtrated through a celite pad and evaporated to dryness. The crude products were purified by preparative thin layer chromatography or Flash chromatography.

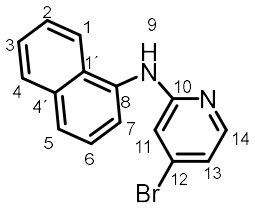
B-General procedure for azaindole synthesis from from bromides and aminopyridines using $Cu(OAc)_2$ as oxidant.

In a previously dried sealed tube, equipped with a magnetic stirrer, it was added $Pd_2(dba)_3$ (0.04 equiv.), ligand (0.08 equiv.), *t*-BuONa (3 equiv.) and aminopyridine (30 mg, 0.2 mmol). Next to that, the tube was sealed with a suba-seal stopper and then evacuated with vacuum pump and refilled with gaseous nitrogen using a needle making three cycles of this procedure. Then, it was added dried *t*-BuOH (0.1 M), followed by the vinyl bromide (1.5 equiv.). The reactional mixture was under stirring at 110 ºC for 24 h. After this time, the solvent was evaporated to dryness and was added $Pd(OAc)_2$ (0.2 equiv.), $Cu(OAc)_2$ (6 equiv.) and Cs_2CO_3 (3 equiv.). After this addition, it was made cycles of purge vacuum /gaseous N_2 and under an atmosphere of N_2 dried DMSO (c = 0,2 M) and put the reactional mixture under stirring at 40 °C all through 24 h. When the reaction was completed or almost completed (total consumption of starting materials), the mixture was diluted in ethyl acetate, filtrated through a celite pad and extracted thrice with water. The aqueous phase was extracted with ethyl acetate until all the reaction products were recovered. The organic phases were dried over anhydrous sodium sulphate, the desiccant filtered and the product concentrated and vacuum dried.

The crude products were purified by preparative thin layer chromatography or Flash chromatography.

4-bromo-N-(naphtalenyl)pyridin-2-amine (II.3)

The compound **II.3** was obtained as brown oil using procedure A in 11% yield (18.89 mg) after a column (100% Hexane to 1%MeOH in EtOAc) followed by a PTLC Hexane/EtOAc (1:1).



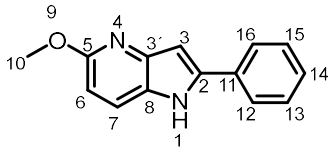
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (ddd, *J* = 14.1, 10.7, 6.6 Hz, 3H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.40 (m, 3H), 7.02 (d, *J* = 5.1 Hz, 1H), 6.50 (d, 1H), 6.40 (d, *J* = 5.5 Hz, 1H), 6.10 (s, 1H, H11).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.97 ,149. 62, 142.72, 134.73, 129.59, 128.70, 127.48, 127.04, 126.71 , 126.64, 125.85, 122.68, 122.49 , 114.73, 111.55.

IV(NaCl) $\upsilon_{máx}$: 3300 (N-H), 1586 (C=C), 1417 (C-N).

methoxy-2-phenyl-1H-pyrrolo[3,2-b] pyridine (II.4)

The compound **II.4** was obtained using procedure A in 19% yield (5.01 mg) and B in 64% (34.99 mg) yield after a PTLC 1%MeOH/$CHCl_3$.

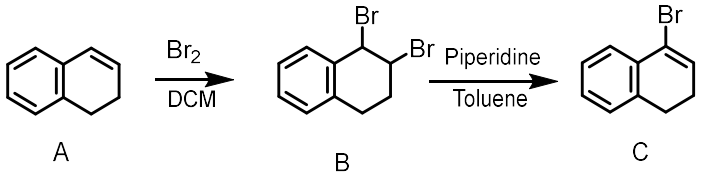


^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (s, 3H, H1), 7.66 (d, *J* = 7.8 Hz, 2H,H12,H16), 7.59 (d, *J* = 8.7 Hz, 1H, H7), 7.44 (t, *J* = 7.6 Hz, 2H, H13, H15), 7.34 (t, *J* = 7.4 Hz, 1H, H14), 6.89 (s, 1H, H3), 6.60 (d, *J* = 8.7 Hz, 1H, H6), 4.01 (s, 3H, H10).[73]
^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.64 (C5), 144.02 (C11), 140.09 (C2), 132.21 (C8), 129.25 (C13, C15), 128.25 (C14), 125.82 (C7), 125.27 (C12, C16), 121.78 (C3´), 106.08 (C3), 100.16 (C6), 53.50 (C10).
IV(NaCl) $\upsilon_{máx}$: 2851 (O-CH_3), 1583 (C=C), 1296 (C-N).
MS (EI) calcd for $C_{14}H_{12}N_2O$ (M+1): 224.09 **Found:** 223.99
M.P. = 160-170 ºC

III.2 Bromination Methods

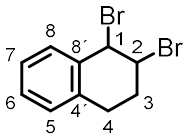
III.2.3 From alkenes

General procedure for bromide synthesis from alkenes-Prabhu method



1,2-Dihydronaphtalene (1 equiv., 400 μL, 3.0 mmol) was dissolved in dry dichloromethane (7 mL), then Br_2 (2 equiv., 308 μL, 6 mmol) was added dropwise at 0 ºC. After 2 h 30 min. the reaction the reaction was quenched with a saturated aq. solution of sodium thiosulfate (14 mL) and stirred for 15 min.. The organic layer was extracted, and the aqueous layer was washed twice with dichloromethane. The combined organic layers were washed twice with a saturated aq. solution of sodium thiosulfate and brine; then dried over anhydrous $MgSO_4$, filtered and dried under vacuum. The product **B** was attained as a yellow solid with quantitative yield and it was used for the next step without further purification.

1,2-dibromo-1,2,3,4- tetrahydronaphthalene(B)

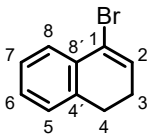


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 – 7.05 (m, 4H, Ar-H), 5.65 (s, 1H, H1), 4.99 – 4.87 (m, 1H, H2), 3.27 (ddd, *J* = 17.7, 11.9, 6.1 Hz, 1H, H4), 2.94 (dd, *J* = 17.4, 6.0 Hz, 1H, H4), 2.87 – 2.76 (m, 1H, H3), 2.24 – 2.15 (m, 1H, H3).[75]

To a round-bottom flask charged with piperidine (3 equiv., 818 μL, 8.28 mmol) at 0 ºC was added a solution of the crude product 1,2-dibromo-1,2,3,4-tetrahydronaphtalene (1 equiv., 800 mg, 2.76 mmol) in dry toluene (1.6 mL) dropwise for 2 h (about 66 μL/5 min.). The reaction was left overnight at room temperature and then heated for 2h 30 min at 90 ºC. The reaction crude was neutralized by slowly adding this mixture to a solution of 1 M HCl (6.90 mL). The organic layer was separated and the aqueous was washed thrice with Et_2O. The combined organic layers were washed with water, then dried over anhydrous $MgSO_4$, filtered and dried under vacuum. The product **C** was isolated

after purification by a large and short column chromatography (silica gel, hexane 100%) and attained with 83% yield as unstable colourless oil.

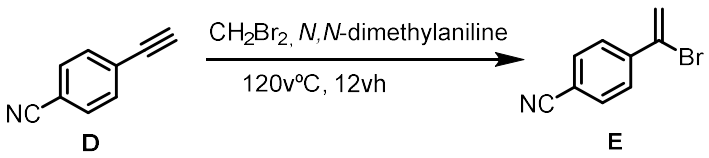
4-bromo-1,2- dihidronaphthalene(C)



^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.25 – 7.13 (m, 2H, Ar-H), 7.10 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.45 (t, *J* = 4.8 Hz, 1H, H2), 2.84 (t, *J* = 8.1 Hz, 2H, H4), 2.37 (td, *J* = 8.1, 4.9 Hz, 2H, H3).[74]
^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.31 (s), 133.05 (s), 131.88 (C5), 130.71 (C8), 128.27 (C9), 127.23 (C6), 126.78 (C7), 126.50 (C3), 121.40 (C4), 27.63 (C1), 25.43 (C2).

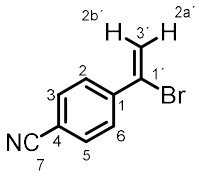
III.2.4 From aromatic alkynes

General procedure for bromide synthesis from alkynes-Yin method

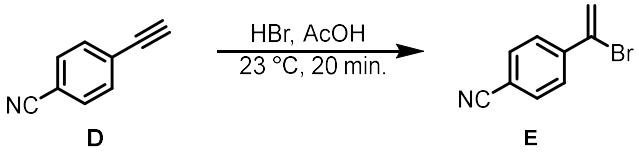


In a dried Schlenk equipped with a magnetic stirrer, was charged with **D** (150 mg, 1.18 mmol, 1 equiv.) and quickly evacuated, closed under vacuum, and then refilled with nitrogen. Then it was added dibromomethane (5 equiv.) and *N,N*-dimethylaniline (3 equiv.) The resulting mixture was stirred at 120 °C for 24 h. Upon cooling to room temperature, the reaction mixture was washed with a saturated solution of Na_2HCO_3., followed by extracting thrice with ethyl acetate. The organic phase was dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using 100% petroleum ether. The product **E** was attained in 37% yield has a unstable colourless oil.

4-(1-bromovinyl) benzonitrile (E)



^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 8.6 Hz, 2H, H3, H5), 7.65 (d, *J* = 8.6 Hz, 2H, H2, H6), 6.24 (d, *J* = 2.4 Hz, 1H, H2b´), 5.94 (d, *J* = 2.3 Hz, 1H, H2a´).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 145.13 (C1), 131.80 (C3, C5), 127.39 (C2, C6), 119.89 (C1´), 118.23 (C7), 117.25 (C3´), 112.32 (C4).
Rf: 0.68, Hexane/EtOAc (3:1)

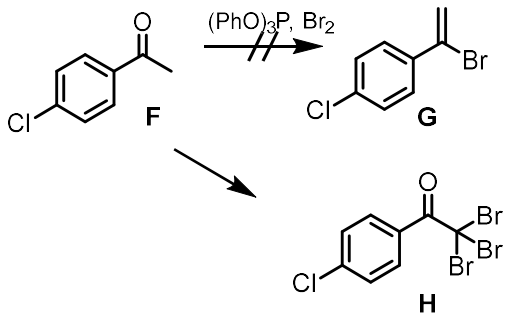


D **E**

A round-bottom flask equipped with a magnetic stirrer was charged with the alkyne **E** (150 mg, 1.18 mmol, 1 equiv.). The flask was quickly evacuated, closed under vacuum, and then refilled with nitrogen then HBr/acetic acid (33%, 1 equiv., 203.70 μL) was added dropwise at 0 ºC. After 25 min. the reaction the reaction was quenched with 1.5 mL of water and 0.94 mL of DCM. The organic layer was extracted and the aqueous layer was washed thrice with 0.7 mL of dichloromethane. The combined organic layers were washed twice 0.9 mL with a saturated solution of $NaHCO_3$, 0.9 mL distilled water then dried over anhydrous Na_2SO_4, filtered and dried under vacuum. Product **E** was not attained.

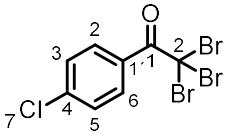
III.2.5 From acetophenones

General procedure for bromide synthesis from acetophenones-Sppagiari method



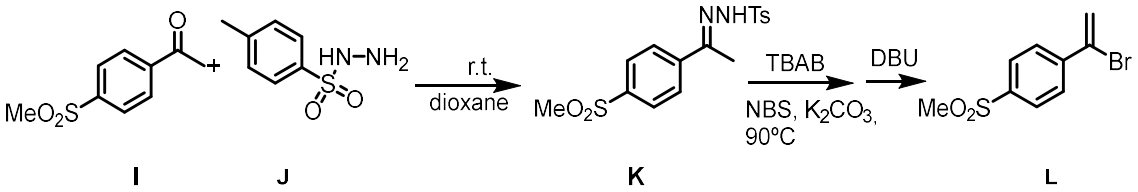
A round-bottom flask equipped with a magnetic stirrer was charged with TPPO (371 μL, 1.41 mmol) and DCM (3 mL). The flask was quickly evacuated, closed under vacuum, and then refilled with nitrogen then added Br_2 (397 μL, 1.55 mmol), TEA (236 μL, 1.69 mmol), and ketone **F** (168 μL, 1.29 mmol) at -60 ºC. The mixture was under stirring for. 18 h and then dried under vacuum and purified by flash chromatography Hexane/EtOAc (12:1). [The product **G** was not attained but probably **H** formed in 50% yield as a colourless oil, and it decomposed rapidly.

2,2,2-tribromo-1-(4-chlorophenyl) ethan-1-one (H)



^{1}H NMR (400 MHz, $CDCl_3$) δ: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H).
Rf: 0.64, (5:1-Hexane/EtOAc)

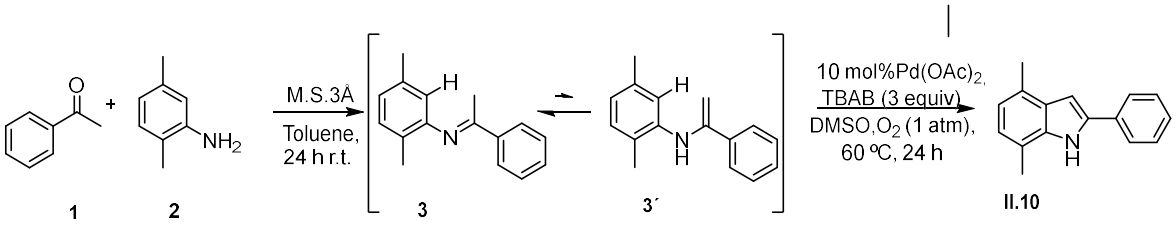
General procedure for bromide synthesis from acetophenones-Prabhu method



A round-bottom flask equipped with a magnetic stirrer was charged with ketone I (200 mg, 1 equiv.),tosylhydrazone **J** (193.7 mg, l equiv.), TBAB (975.7 mg, 2.5 equiv.) and K_2CO_3 (418.3 mg,3 equiv.). The flask was quickly evacuated, closed under vacuum, and then refilled with nitrogen then added dried dioxane (2.5 mL) followed by recrystalized NBS (269.4 mg, 1.5 equiv.). The mixture was under stirring for. 12 h at 90 ºC. After that time was added DBU (1.5 equiv.) and the mixture was stirring at 50 ºC for an 1 h. Upon cooling to room temperature, the reaction mixture was diluted in hexane, followed by filtration through a pad of celite. The filtrate was concentrated under vacuum [The product **L** was not attained.

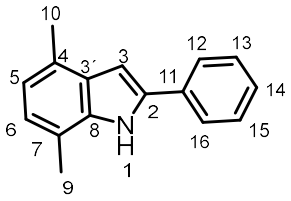
III.3 Azaindole Synthesis approach b via condensation/C-H activation:

III.3.6 General procedure for preliminary studies



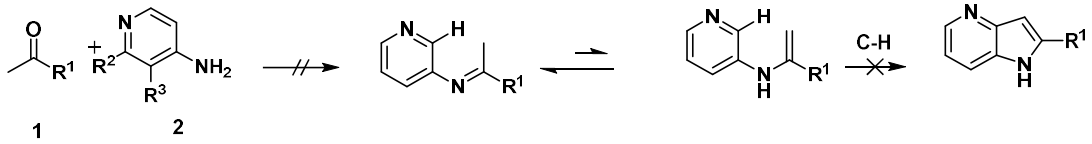
In a previously dried sealed tube, equipped with a magnetic stirrer, it was added aniline (30 mg, 0.2 mmol), ketone (1.3 equiv.) and molecular sieves 3Å. Next to that, the tube was sealed with a suba-seal stopper and then applied cycles of purge with vacuum pump/gaseous nitrogen using a needle. Then, it was added dried toluene (c = 1.65 M) under nitrogen atmosphere. The reactional mixture was under stirring at room temperature for 24 h. Imine **3** was attained as an orange oil with 100% yield.

dimethyl-2-phenyl-1H-indole (II.2)



The product was obtained after a PTLC Hexane /EtOAc (12:1,) achieving the indole **II.2** as a red oil with 50% yield (13,42 mg). [72]

III.3.7 General procedure for azaindole synthesis from ketones and deactivated aminopyridines



1a, 4-methylsulphonylacetophenone
1b, acetophenone
1c, 4-chloroacetophenone

2a, 4-amino-3-iodopyridine
2b, 2-methyl-(4-amino-3-iodopyridin-2-yl)acetate

General procedure for the synthesis of azaindole from halogenated aminopyridines and ketones-O_2 as oxidant in C-H activation reaction

In a previously dried sealed tube, equipped with a magnetic stirrer, it was added aminopyridine (30 mg, 0.2 mmol), ketone (1.3 equiv.) and molecular sieves 3Å. Next to that, the tube was sealed with a suba-seal stopper and then applied cycles of purge with vacuum pump/gaseous nitrogen using a needle. Then, it was added dried toluene (c = 1,65 M) under nitrogen atmosphere. The reactional mixture was under stirring at room temperature for 24 h.
After this time, the solvent was evaporated to dryness and was added $Pd(OAc)_2$ (0.1 equiv.) and TBAB (2 equiv.). After this addition, the tube was evacuated using a vacuum pump and refilled with gaseous O_2 and under an atmosphere of O_2 was added dried DMSO (c = 0.2 M), the tube was left with a O_2 balloon (1 atm). The reaction was under stirring at 60°C all through 24 h. When the reaction was completed or almost completed (total consumption of starting materials), the mixture was diluted in ethyl acetate, filtrated through a celite pad and evaporated to dryness.
The crude products were purified by preparative thin layer chromatography or Flash chromatography.

General procedure for the synthesis of azaindole from halogenated aminopyridines and ketones- $Cu(OAc)_2$ as oxidant

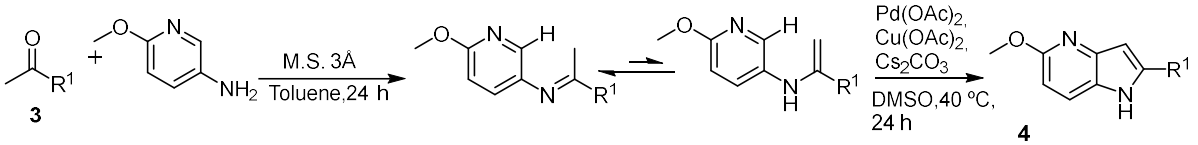
In a previously dried sealed tube, equipped with a magnetic stirrer, it was added aminopyridine (30 mg, 0.2 mmol), ketone (1.3 equiv.) and molecular sieves 3Å. Next to that, the tube was sealed with a suba-seal stopper and then evacuated with vacuum pump and refilled with gaseous nitrogen using a needle making three cycles of this procedure. Then, it was added dried toluene (c = 1.65 M) under nitrogen atmosphere. The reactional mixture was under stirring at room temperature for 24 h.

After this time, the solvent was evaporated to dryness and was added $Pd(OAc)_2$ (0.2 equiv.), $Cu(OAc)_2$ (6 equiv.) and Cs_2CO_3 (3 equiv.). After this addition, it was made cycles of purge vacuum /gaseous N_2 and under an atmosphere of N_2 dried DMSO (c = 0,2 M) and put the reactional mixture under stirring at 40 °C all through 24 h. When the reaction was completed or almost completed (total consumption of starting materials), the mixture was diluted in ethyl acetate, filtrated through a celite pad and extracted thrice with water. The aqueous phase was extracted with ethyl acetate until all the reaction products were recovered. The organic phases were dried over anhydrous sodium sulphate, the desiccant filtered and the product concentrated and vacuum dried.

The crude products were purified by preparative thin layer chromatography or Flash chromatography.

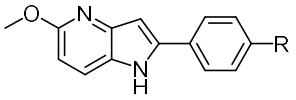
III.4 Azaindole Synthesis from non-halogenated aminopyridines and ketones

III.4.8 General procedure for the one-pot reaction condensation/C-H activation

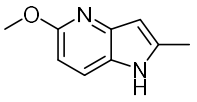


3 4

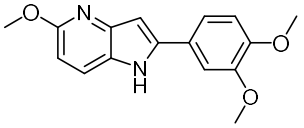
1a, 4-metoxyphenylacetone
1b, 4-bromoacetophenone
1c, 4-chloroacetophenone
1d, 4-nitroacetophenone
1e, 4-methylacetophenone
1f, 4-iodoacetophenone
1g, 4-tert-buthylacetophenone
1h, 4-metilsulphonylacetophenone
1i, acetophenone
1j, propanone
1k, 2-methoxyacetophenone
1l, 4-imidazolylacetophenone
1m, 3,4-dimethoxyacetophenone
1n, 3-methoxyacetophenone
1o, 3,4-dihydronaphthalen-1(2*H*)-one
1p, 1-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-one
1q, 2´-methoxyacetofenone
1r, 1-(4-butylphenyl)ethan-1-one



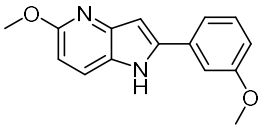
II.4 (R = H)
II.5 (R = OMe)
II.6 (R = Br)
II.7 (R =Cl)
II.8 (R=NO_2)
II.9 (R = Me)
II.10 (R = *t*-Bu)
II.11 (R = Bu)



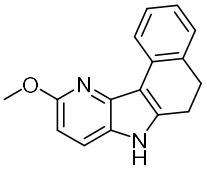
II.12



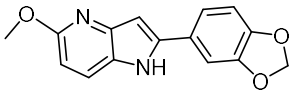
II.13



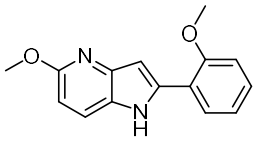
II.14



II.15



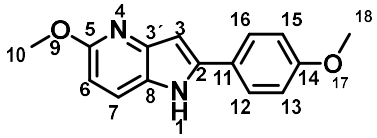
II.16



II.17

A sealed tube equipped with a stirrer bar was charged with a magnetic stirrer, it was added aminopyridine (30 mg, 0.2 mmol), ketone (1.3 equiv.) and molecular sieves 3Å. The sealed tube was evacuated and refilled with N_2 for three times, followed by addition of dried toluene (2 mL) under nitrogen atmosphere. The reactional mixture was under stirring at room temperature for 24 h. The reaction mixture was evaporated to dryness then added $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (6 equiv.) and Cs_2CO_3 (3 equiv.). The tube was evacuated and refilled with N_2 for three times, followed by addition of DMSO (2 mL). The tube was sealed with a Teflon screwcap and then the reaction mixture was stirred at 40 °C for 24 h. Upon cooling to room temperature, the reaction mixture was diluted with 5 mL of ethyl acetate, followed by filtration through a pad of celite. The filtrate was washed with water (10 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel to afford the azaindole product.

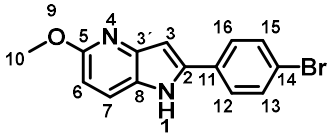
5-methoxy-2-(4-methoxyphenyl) -1H-pyrrolo[3,2-b] pyridine (II.5)



The product **II.5** was attained has a yellow oil with 90% yield (55.03 mg from 30 mg of aminopyridine) after a flash chromatographic column using a gradient of 10:1(Hexane/AcOEt) to 10%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (s, 1H, H1), 7.57 (t, *J* = 8.6 Hz, 1H, H7, H12, H16), 6.98 (d, *J* = 8.7 Hz, 1H, H13, H15), 6.78 (s, 1H, H3), 6.57 (d, *J* = 8.7 Hz, 1H,H6), 4.01 (s, 1H, H10), 3.86 (s, 1H, H18).
^{13}C NMR (151 MHz, $CDCl_3$) δ: 160.87 (C14), 159.88 (C5), 142.24 (C2), 142,40 (C8), 134.67 (C11), 128.40 (C7), 128.08 (C3´), 126.85 (C12), 126.64 (C16), 114.55 (C13,C15), 111.40 (C3), 110.65 (C6), 59.59 (C18), 5500(C10).
IV(NaCl) $\upsilon_{máx}$: 2925 (C-H), 1463 (C=C), 1378 (C-N).
MS (EI) calcd for $C_{15}H_{14}N_2O_2$ (M+1): 254.1 **Found:** 253.99

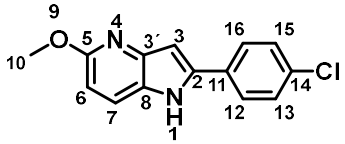
2-(4-bromophenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.6)



The product **II.6** was attained has a yellow solid with 24% yield (14.77 mg from 30 mg of aminopyridine) after flash chromatography column using a gradient of Hexane/ethyl acetate (10:1) to 10%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45 (s, 1H, H1), 7.60 (dd, *J* = 8.5, 4.9 Hz, 3H, H7, H12, H16), 7.53 (d, *J* = 8.5 Hz, 2H, H13, H15), 6.90 (s, 1H, H3), 6.64 (d, *J* = 8.7 Hz, 1H, H6), 4.03 (s, 3H, H10).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.1 (C5), 145.2 (C11), 139.2 (C8), 132.0 (C13,C15), 130.9 (C2), 126.5 (C14), 125.8 (C12, C16), 122.0 (C7), 121.6 (C3´), 106.4 (C3), 100.5 (C6), 53.4 (C10).
IV(NaCl) $\upsilon_{máx}$: 2962 (C-H), 1586 (C=C), 1362 (C-N), 810 (C-Br).
M.P. = 205-207 ºC (**M.P. lit. =** 205 ºC)[76]
MS (EI) calcd for $C_{14}H_{11}BrN_2O$ (M+1): 302.01 **Found:** 301.94

2-(4-chlorophenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.7)

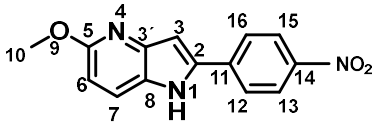


The product **II.7** was attained has a yellow oil with 44% yield (28.28mg from 30 mg of aminopyridine) after a PTLC using Hexane /AcOEt (1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (s, 1H, H1), 7.59 – 7.53 (m, 3H, H7, H12, H16), 7.39 (d, *J* = 8.4 Hz, 2H, H13, H15), 6.84 (s, 1H, H3), 6.60 (d, *J* = 8.7 Hz, 1H, H6), 4.00 (s, 3H, H10).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.56 (C5), 143.68 (C14), 138.80 (C11), 133.87 (C2), 130.56 (C8), 129.28 (C13, C15), 126.31 (C12, C16), 121.65 (C7), 105.96 (C3´), 100.14 (C3), 53.47 (C6), 53.47 (C10).
IV(NaCl) $\upsilon_{máx}$: 2947 (C-H), 1583 (C=C), 1362 (C-N), 756 (C-Cl).
M.P.= 131-135 ºC
MS (EI) calcd for C14H11ClN2O (M+1): 258.06 **Found:** 257.95

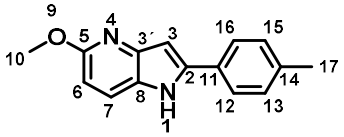
5-methoxy-2-(4-nitrophenyl) -1H-pyrrolo[3,2-b] pyridine (II.8)



The product **II.8** was attained has orange crystals in trace amount (8.04 mg from 30 mg of aminopyridine) after a PTLC using 1%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 3H), 6.59 (d, *J* = 3.8 Hz, 1H), 6.09 (s, 1H), 3.87 (s, 3H).
This product decomposed after NMR experiences.

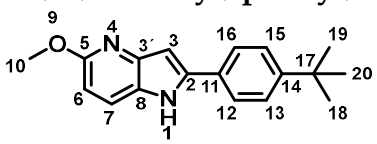
5-methoxy-2-(p-tolyl) -1H-pyrrolo[3,2-b] pyridine (II.9)



The product **II.9** was attained has a yellow solid with 69% yield (39.88 mg from 30 mg of aminopyridine) after a PTLC using 1%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, *J* = 8.0 Hz, 1H, H7), 7.73 (s, 1H, H1), 7.46 (d, *J* = 13.2 Hz, 2H, H12, H16), 7.08 (d, *J* = 7.5 Hz, 2H, H13, H15), 6.73 (s, 1H, H3), 6.40 (d, *J* = 8.0 Hz, 1H, H6), 3.91 (s, 3H, H10), 2.27 (d, *J* = 9.1 Hz, 3H, H17).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.9 (C5), 138.2 (C11), 134.6 (C14), 129.7 (C13, C15), 129.3 (C2), 128.4 (C8), 125.7 (C7), 125.1 (C12, C16), 122.0 (C3´), 104.8 (C3), 99.0 (C6), 53.8 (C10), 20.9 (C17).
IV(NaCl) υ_{max}: 2945 (C-H), 1583 (C=C), 1294 (C-N).
M.P. = 95-100 ºC
MS (EI) calcd for $C_{15}H_{14}N_2O$ (M+1): 240.12 **Found:** 240.90.

2-(4-(tert-butyl) phenyl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine (II.10)

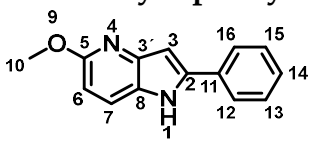


The product **II.10** was attained has a yellow solid with 72% yield (48.92mg from 30 mg of aminopyridine) after a PTLC using 1%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (s, 1H, H1), 7.90 (d, *J* = 8.4 Hz, 1H, H7), 7.61 (d, *J* = 7.8 Hz, 2H, H12, H16), 7.48 (dd, *J* = 17.0, 8.9 Hz, 2H,H13, H15), 6.84 (s, *J* = 12.8 Hz, 1H, H3), 6.55 (m, 1H, H6), 3.99 (s, 3H, H10), 1.35 (s, 9H, H18, H19, H20).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.32 (C5), 156.88 (C14), 151.50 (C11), 140.52 (C2), 129.12 (C8), 128.31 (C7), 126.06 (C13, C15), 125.23, 107.94 (C3´), 105.00 (C6), 53.56 (C10), 34.72 (C17), 31.25 (C18, C19, C20).
IV(NaCl) $\upsilon_{máx}$: 2964 (C-H), 1607 (C=C), 1275 (C-N).

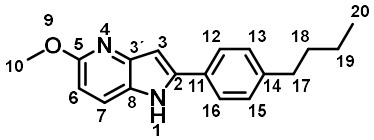
M.P. = 90-95 ºC
MS (EI) calcd for $C_{18}H_{20}N_2O$ (M+1): 280.16 **Found:** 280.07.

5-methoxy-2-phenyl-1H-pyrrolo[3,2-b] pyridine (II.4)



The product II.4 was attained has a yellow solid with 96% yield (52.52 mg from 30 mg of aminopyridine) after flash chromatography column using a gradient of Hexane/ethyl acetate (10:1) to 10%MeOH/$CHCl_3$. The spectroscopic data was described previously in chapter III.1.2.

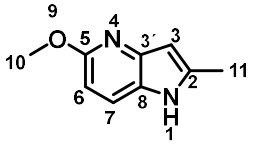
2-(4-butylphenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.11)



The product was attained has a brown oil with 75% yield (50.93 mg from 30 mg of aminopyridine) after flash chromatography column using a gradient of Hexane/ethyl acetate (10:1) to 10%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (s, 1H, H1), 8.03 (s, 1H, H7), 7.58 – 7.55 (m, 2H, H12,H16), 7.27 – 7.24 (m, 2H, H13,H15), 6.84 (s, 1H, H3), 6.58 (d, *J* = 8.7 Hz, 1H, H6), 4.01 (s, 3H,H10), 2.64 (t, *J* = 7.7 Hz, 2H, H17), 1.63 (dt, *J* = 15.3, 7.5 Hz, 2H, H18), 1.40 (d, *J* = 7.4 Hz, 2H, H19), 0.94 (t, *J* = 7.3 Hz, 3H, H20).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.1 (C5), 143.6 (C14), 143.3 (C11), 140.4 (C2), 129.3 (C8), 129.1 (C13, C15), 125.5 (C7), 125.0 (C12, C16), 121.5 (C3´), 105.1 (C3), 99.2 (C6), 53.4 (C10), 35.4 (C17), 33.2 (C18), 21.8 (C19), 13.6 (C20).
IV(NaCl) $\upsilon_{máx}$: 1605 (C=C), 1255 (C-N), 1081 (C-O).
MS (EI) calcd for $C_{18}H_{20}N_2O$ (M+1): 280.16 **Found:** 280.06.

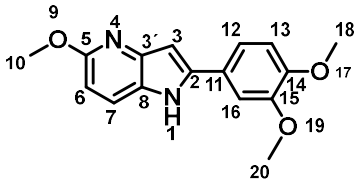
5-methoxy-2-methyl-1H-pyrrolo[3,2-b] pyridine (II.12)



The product **II.12** was attained has a yellow solid with 75% yield (28.28 mg from 30 mg of aminopyridine) after flash chromatography column using a gradient of Hexane/ethyl acetate (10:1) to 10%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (s, 1H, H1), 8.11 (d, *J* = 7.8 Hz, 2H), 6.52 (d, *J* = 9.3 Hz, 1H), 6.33 (s, 1H), 4.01 (s, 3H), 2.48 (s, 3H).
^{3}C NMR (101 MHz, $CDCl_3$) δ: 160.2 (C5), 147.3 (C12), 138.1 (C8), 134.1 (C7), 131.4 (C3´), 111.4 (C6), 95.8 (C3), 52.8 (C10), 23.0 (C11).
IV(NaCl) υ_{max}: 2954 (C-H), 1638 (C=C).,1282 (C-N)
M.P. = 105-110 ºC
MS (EI) calcd for $C_9H_{10}N_2O$ (M+1): 163.05 **Found:** 162.76[77]

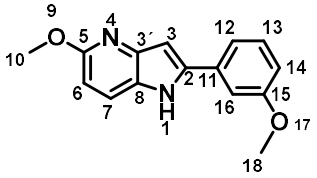
- 2-(3,4-dimethoxyphenyl) -5-methoxy-1H-pyrrolo [3,2-b] pyridine (II.13)



The product **II.13** was attained has a yellow oil with 64% yield (43.98 mg from 30 mg of aminopyridine) after flash chromatography column using a gradient of Hexane/ethyl acetate (8:1) to 10%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, MeOD) δ: 8.23 – 8.18 (m, 1H, H7), 7.81 (d, *J* = 7.1 Hz, 1H), 7.53 – 7.48 (m, 1H, H16), 7.12 (d, *J* = 8.5 Hz, 1H, H12), 6.99 (d, *J* = 6.3 Hz, 1H, H13), 6.87 (s, 1H, H3), 6.81 (d, *J* = 7.8 Hz, 1H, H6), 4.17 (s, 3H, H20), 3.97 (s, 3H,H18), 3.93 (s, 3H, H10).
^{13}C NMR (101 MHz, MeOD) δ: 160.36 (C5), 150.85 (C15), 149.63 (C14), 137.96 (C11), 132.63 (C2), 127.65 (C7), 119.50 (C12), 111.84 (C3´), 109.46 (C3, C16), 99.32 (C6), 56.42 (C20), 55.16 (C18), 52.78 (C10).
IV(NaCl) $\upsilon_{máx}$: 1596 (C=C), 1271 (C-N), 1026 (C-O).
MS (EI) calcd for $C_{16}H_{16}N_2O_3$ (M+1): 284.12 **Found:** 281.99

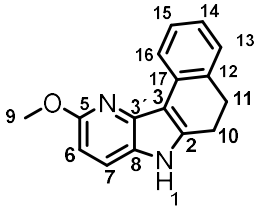
- 5-methoxy-2-(3-methoxyphenyl) -1H-pyrrolo[3,2-b] pyridine (II.14)



The product was attained has yellow needles with 61% yield (37.48 mg from 30 mg of aminopyridine) after flash chromatography column using a gradient of Hexane/ethyl acetate (10:1) to 10%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (s, 1H, H1), 7.59 (d, *J* = 8.7 Hz, 1H, H7), 7.35 (t, *J* = 7.9 Hz, 1H, H13), 7.25 (d, *J* = 8.2Hz, 1H, H12), 7.19 (s, 1H, H16), 6.89 (d, *J* = 8.5 Hz, 2H, H3, H14), 6.60 (d, *J* = 8.7 Hz, 1H, H6), 4.01 (s, 3H, H18), 3.86 (s, 3H, H10).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.00 (C15), 142.88 (C5), 139.80 (C11), 133.25 (C8), 130.15 (C2), 125.83 (C7), 117.69 (C12), 113.68 (C3´), 110.97 (C14), 105.54 (C16), 99.57 (C3), 55.21 (C6), 29.72 (C18), 22.50 (C10).
IV(NaCl) $\upsilon_{máx}$: 1491 (C=C), 1378 (C-N), 1029 (C-O).
M.P. = 140-150 ºC(with decomposition)
MS (EI) calcd for $C_{15}H_{14}N_2O_2$ (M+1): 254.11**Found:** 253.99.

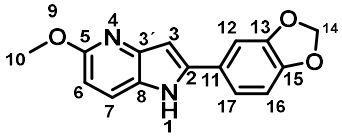
10-methoxy-6,7-dihydro-5H-benzo[e] pyrido [3,2-b] indole (II.15)



The product was attained has a brown oil with 73% yield (44.02 mg from 30 mg of aminopyridine) after flash chromatography column using a gradient of Hexane/ethyl acetate (10:1) to 10%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (s, 1H, H1), 8.01 – 7.84 (m, 1H,H16), 8.02 – 7.97 (m, 1H, H7),7.01 (d, *J* = 7.3 Hz, 1H, H14), 6.66 (dd, , *J* = 8.7 Hz, 1H, H6), 4.02 (m, 3H, H11), 3.94 (s, 3H, H9), 3.06 (s, 2H, H10).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.48 (C10), 140.15 (C11), 138.91 (C9), 134.62 (C6), 133.87 (C3´), 132.75 (C7), 128.69 (C3), 125.60 (C16), 121.42 (C15), 120.88 (C13), 111.48 (C14), 110.96 (C8), 53.16 (C17), 29.40 (C12), 22.55 (C5).
IV(NaCl) $\upsilon_{máx}$: 1492 (C=C), 1277 (C-N), 1000 (C-O).
MS (EI) calcd for $C_{16}H_{14}N_2O$ (M+1): 250.11**Found:** 249.99.

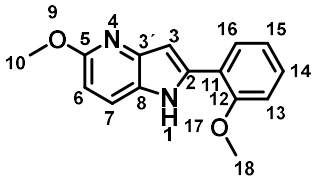
- 2-(benzo[d] [1,3] dioxol-5-yl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.16)



The product was attained has a brown oil with 83% yield (54.42 mg from 30 mg of aminopyridine) after flash chromatography column using a gradient of Hexane/ethyl acetate (10:1) to 10%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, MeOD) δ: 8.21 (d, *J* = 8.6 Hz, 1H, H7), 7.89 (s, 1H, H1), 7.43 (d, *J* = 8.2 Hz, 1H, H6), 7.37 (s, 1H, H12), 6.99 (d, *J* = 8.1 Hz, 2H, H16, H17), 6.82 (s, 1H, H3), 6.06 (s, 2H, H14), 4.16 (s, 3H, H10).
^{13}C NMR (101 MHz, MeOD) δ: 159.20 (C5), 149.71 (C13), 148.66 (C15), 128.10 (C2, C11), 126.93 (C8), 125.69 (C7), 124.05 (C17), 120.53 (C3´), 118.71 (C12, C16), 108.54 (C3), 105.85 (C6), 101.76 (C14), 56.36 (C10).
IV(NaCl) υ_{max} : 1464 (C=C), 1378 (C-N), 1036 (C-O).
MS (EI) calcd for $C_{15}H_{12}N_2O_3$ (M+1): 268.08 **Found:** 266.27.

5-methoxy-2-(2-methoxyphenyl) -1H-pyrrolo[3,2-b]pyridine (II.17)



The product was attained has a brown oil with 87% yield (53.82 mg from 30 mg of aminopyridine) after flash chromatography column using a gradient of Hexane/ethyl acetate (10:1) to 10%MeOH/$CHCl_3$.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.72 (s, 1H,H1), 7.82 (d, *J* = 7.7 Hz, 1H, H16), 7.59 (d, *J* = 8.7 Hz, 1H, H7), 7.29 (t, *J* = 7.8 Hz, 1H, H14), 7.10 – 7.00 (m, 2H, H13, H15), 6.97 (s, 1H, H3), 6.58 (d, *J* = 8.7 Hz, 1H, H6), 4.02 (s, 3H, H10), 4.01 (s, 3H, H18).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.13 (C5), 155.81 (C12), 142.87 (C16), 138.30 (C8), 133.66 (C2), 130.26 (C14), 128.83 (), 128.39 (C7), 124.77 (C15), 121.64 (C3´), 120.09 (C11), 111.79 (C13), 105.37 (C3), 99.66 (C6), 55.93 (C18), 53.39 (C10).
IV(NaCl) $\upsilon_{máx}$: 1580 (C=C), 1283 (C-N), 1026 (C-O).

MS (EI) calcd for $C_{15}H_{14}N_2O_2$ (M+1): 254.11**Found:** 254.00.

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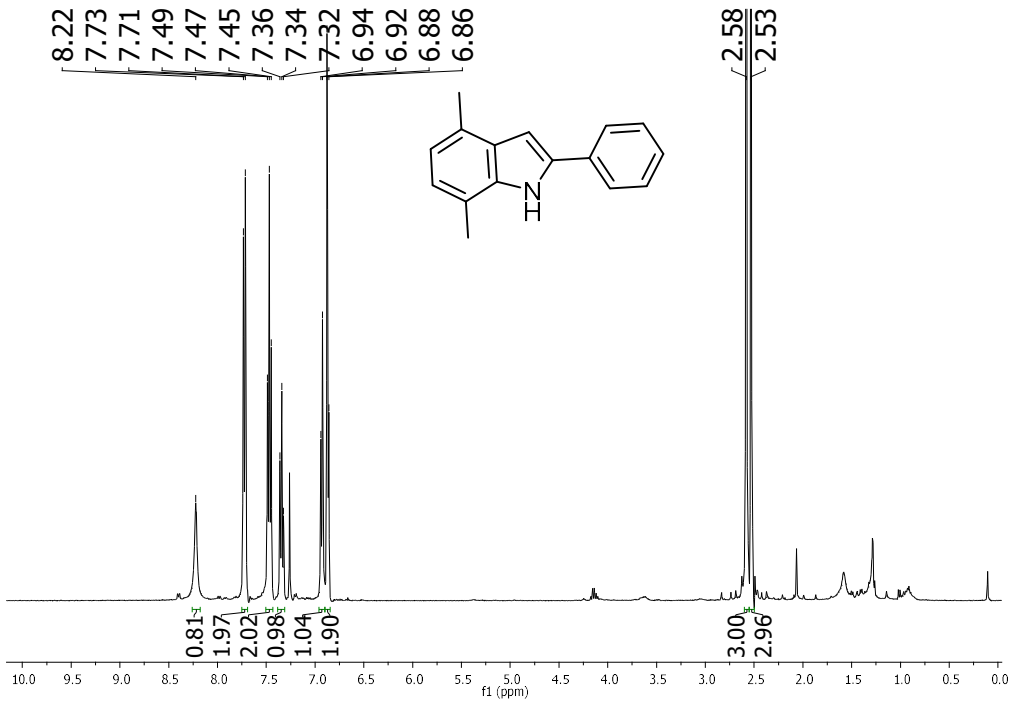
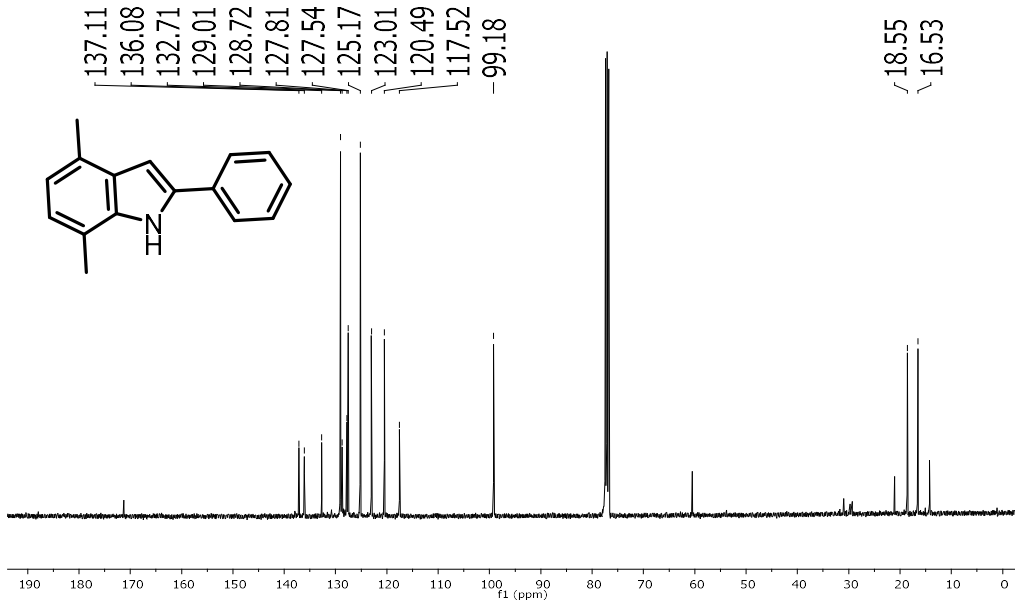
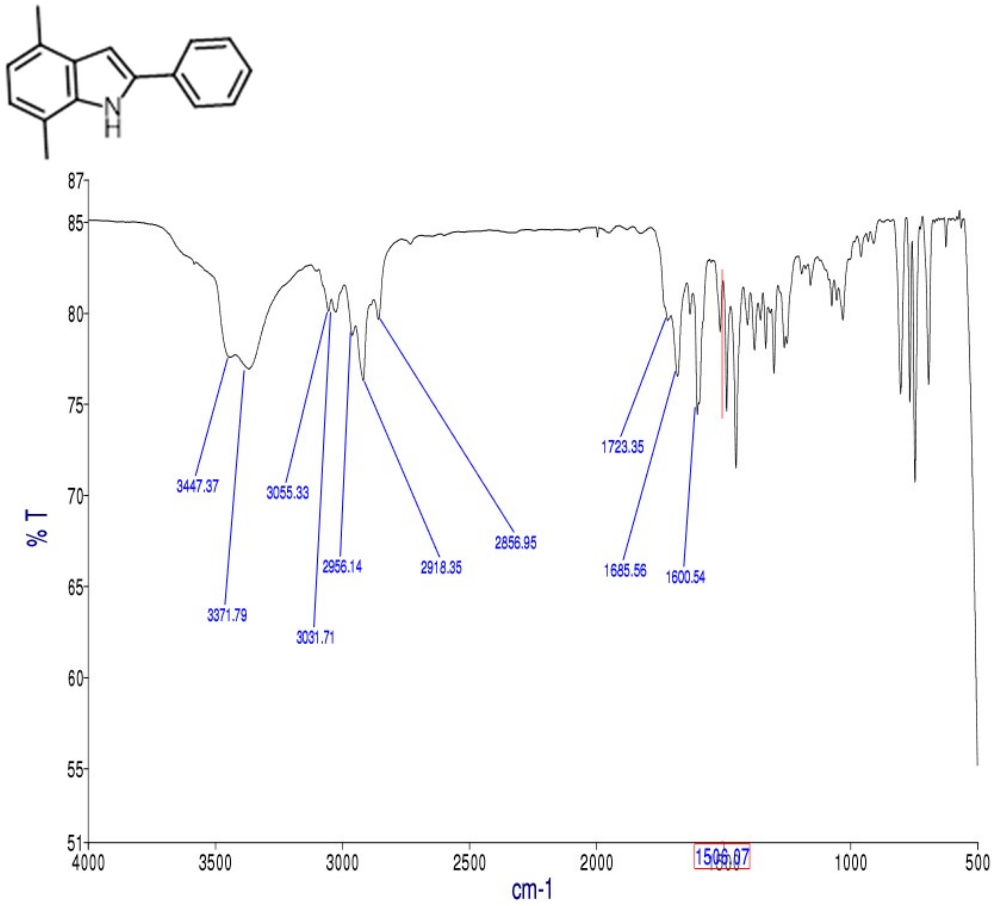


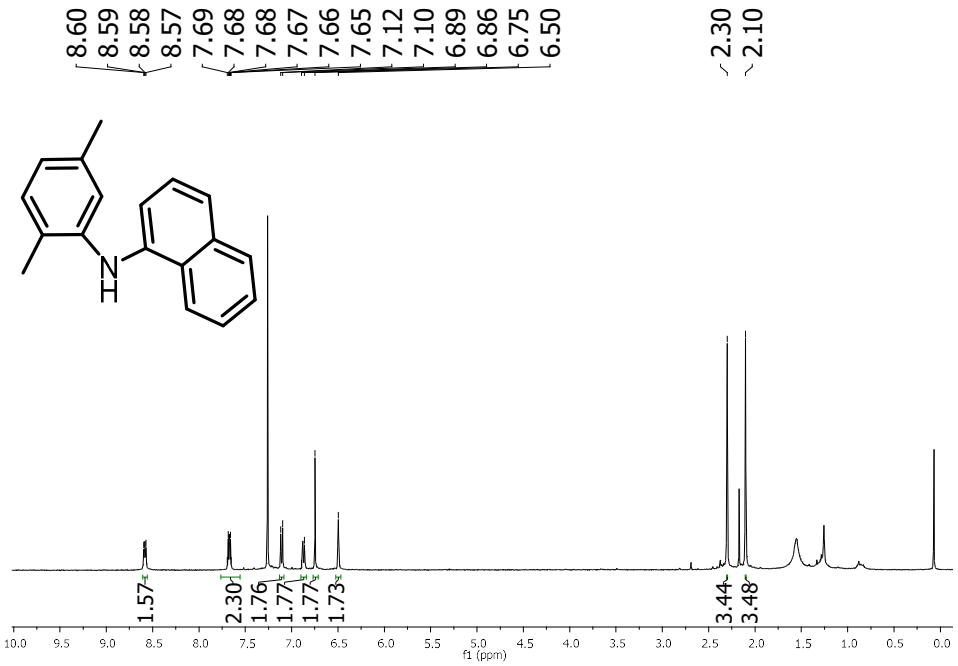
Spectrum 1- ^{1}H-NMR spectrum of 4,7-dimethyl-2-phenyl-1H-indole (II.1)



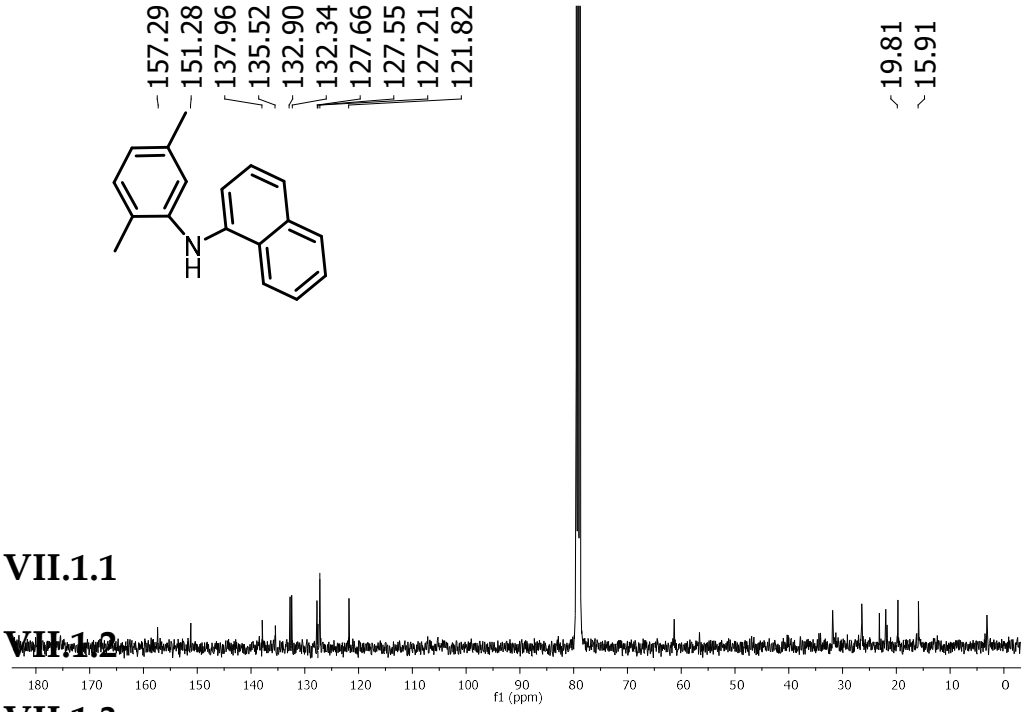
Spectrum 2 – ^{13}C-NMR spectrum of 4,7-dimethyl-2-phenyl-1H-indole (II.1)



Spectrum 3- IR spectrum of 4,7-dimethyl-2-phenyl-1H-indole (II.1).



Spectrum 4- ^{1}H-NMR spectra of N-(2,5-dimethylphenyl)naphthalen-1-amine(II.2)



VII.1.1

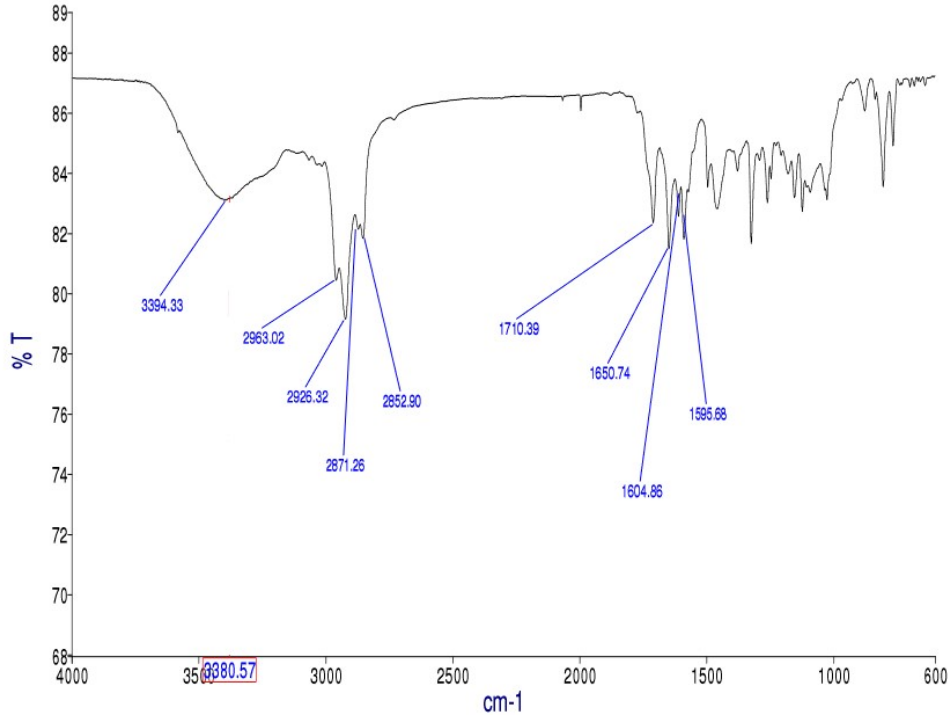
VII.1.2

VII.1.3

VII.1.4

Spectrum 5- ^{13}C-NMR spectrum of N-(2,5-dimethylphenyl)naphthalen-1-amine(II.2)

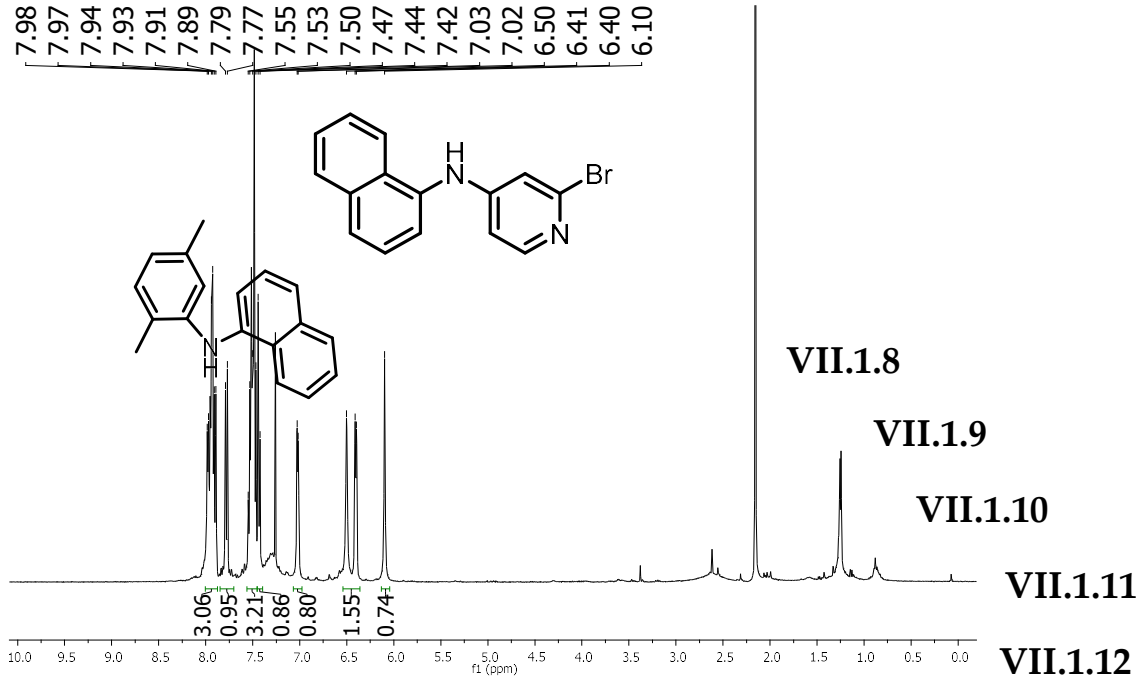
VII.1.5



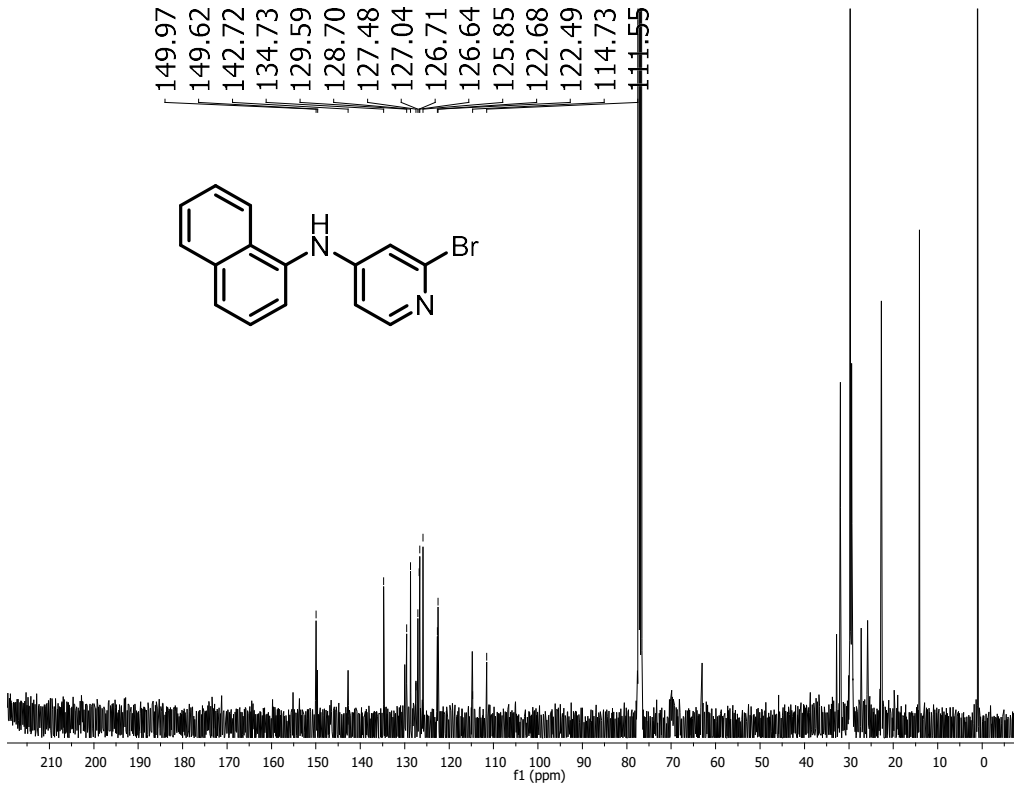
VII.1.6

VII.1.7

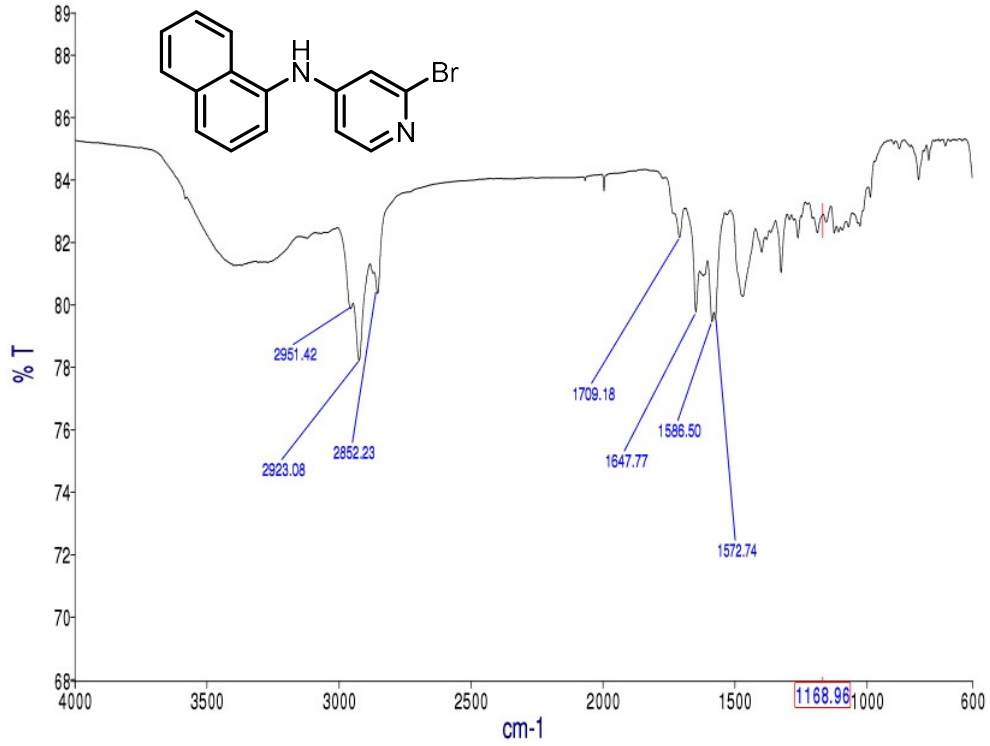
Spectrum 6- IR spectrum of N-(2,5-dimethylphenyl)naphthalen-1-amine(II.2)



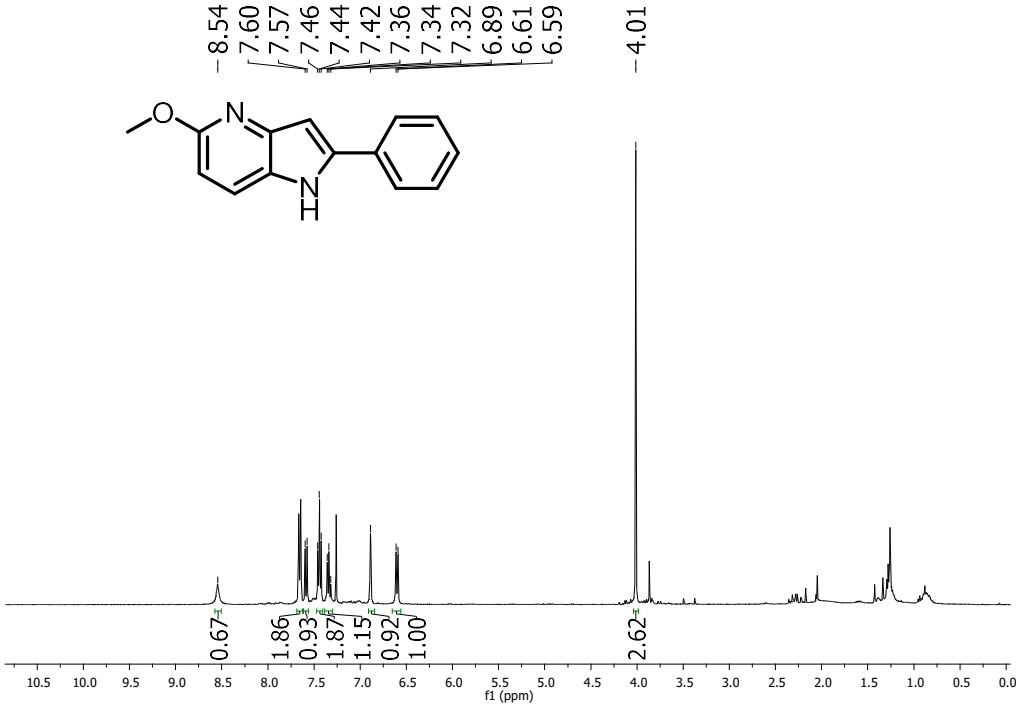
Spectrum 7 – *[1]H-NMR spectrum of 4-bromo-N-(naphtalenyl)pyridin-2-amine (II.3*)



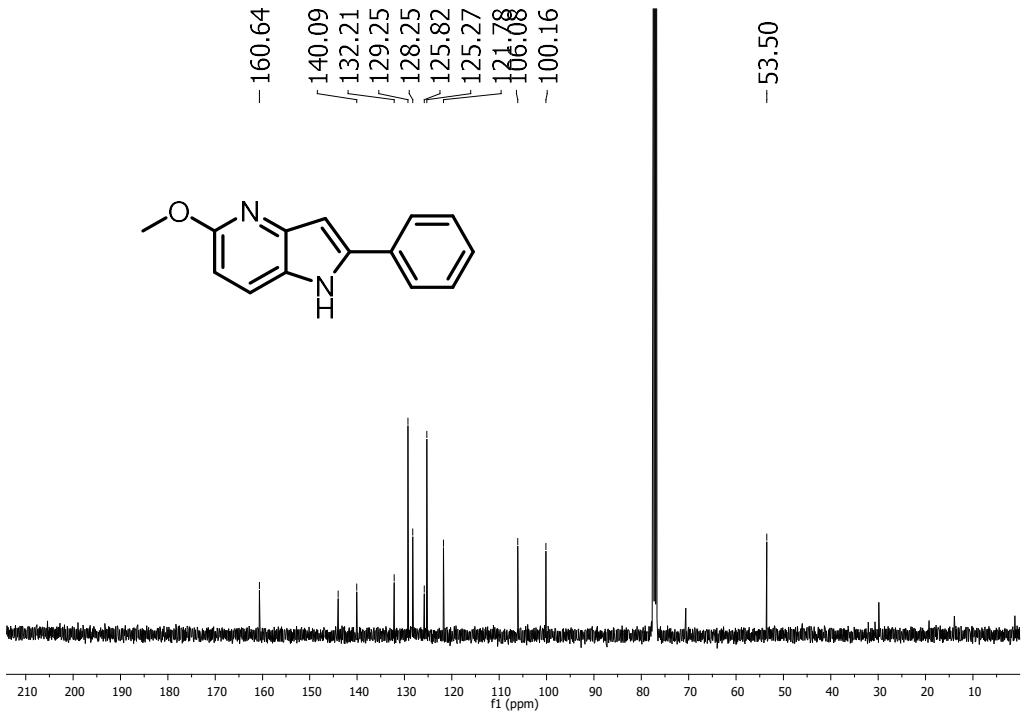
Spectrum 8- [13]C-NMR spectrum of 4-bromo-N-(naphtalenyl)pyridin-2-amine (II.3)



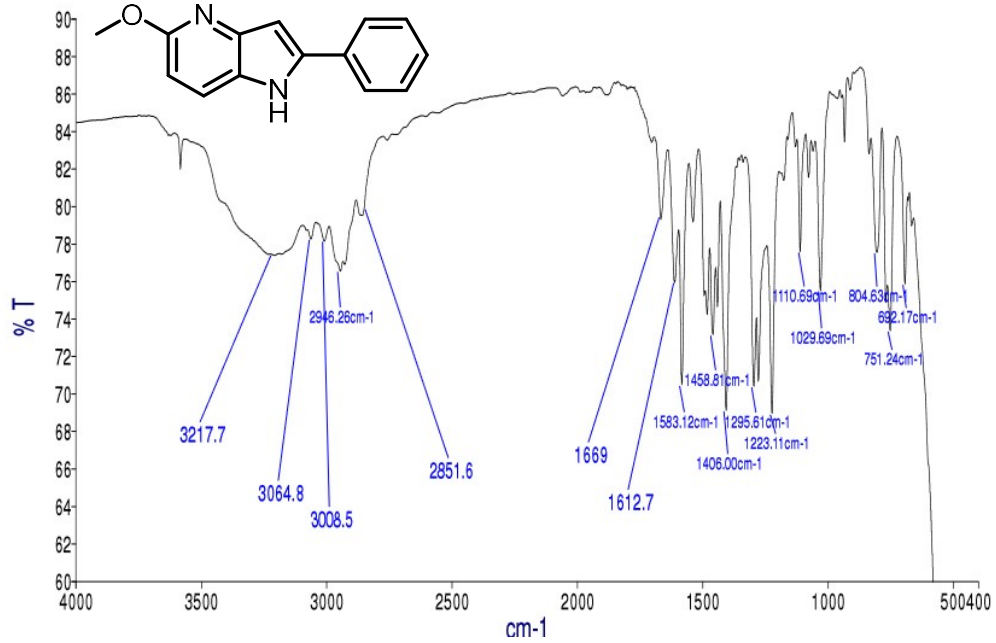
Spectrum 9- IR spectrum of 4-bromo-N-(naphtalenyl)pyridin-2-amine (II.3*)*



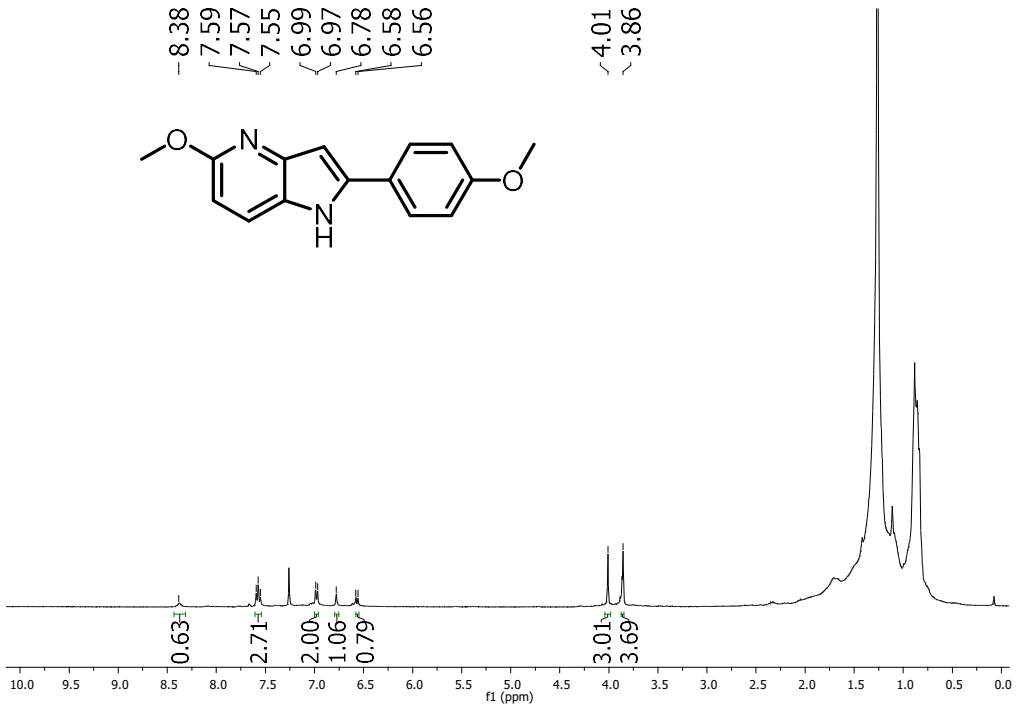
Spectrum 10- ^{1}H-NMR spectrum of 5-methoxy-2-phenyl-1H-pyrrolo[3,2-b] pyridine (II.4*)*



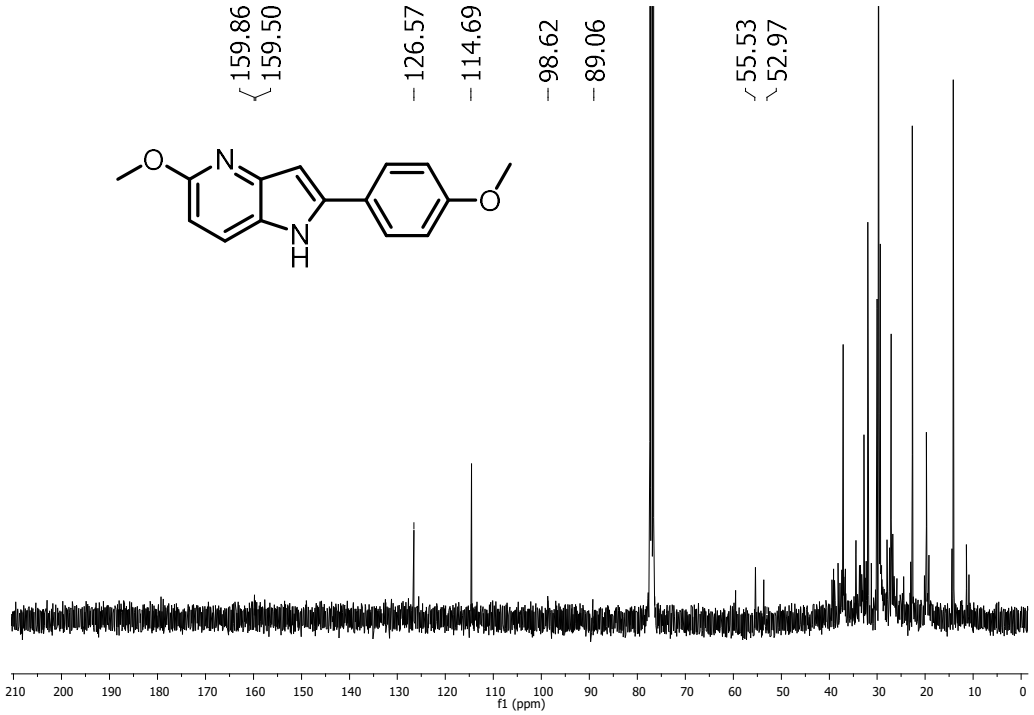
Spectrum 11- ^{13}C-NMR spectrum of 5-methoxy-2-phenyl-1H-pyrrolo[3,2-b] pyridine (II.4)



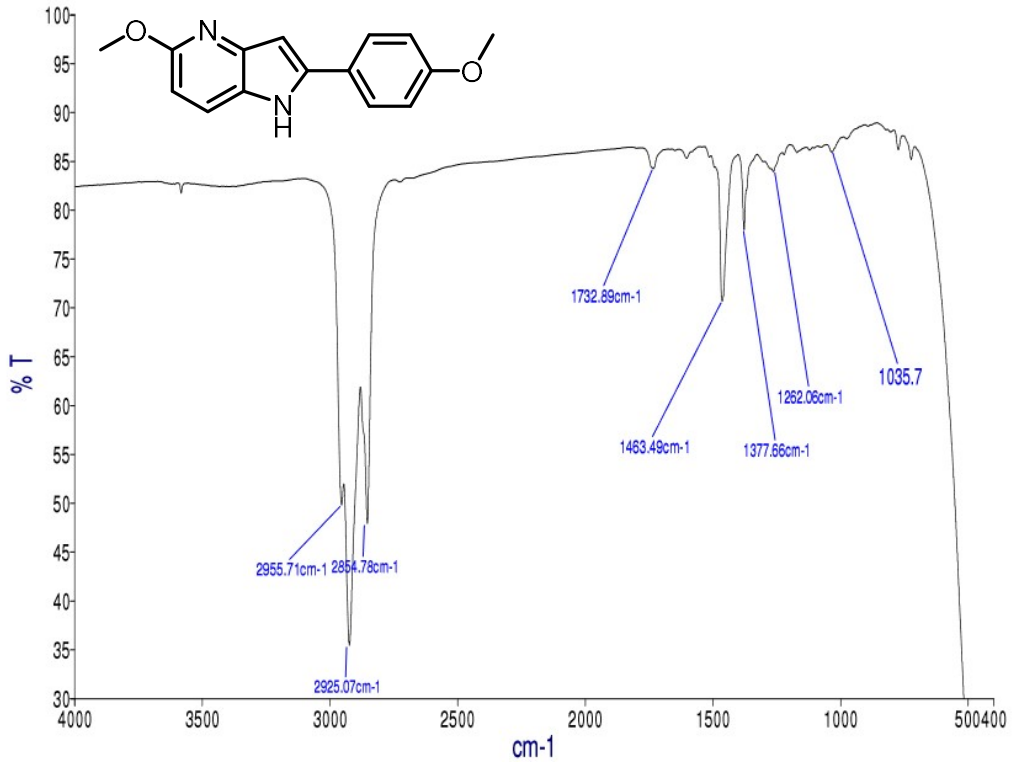
Spectrum 12- IR spectrum of 5-methoxy-2-phenyl-1H-pyrrolo[3,2-b] pyridine (II.4)



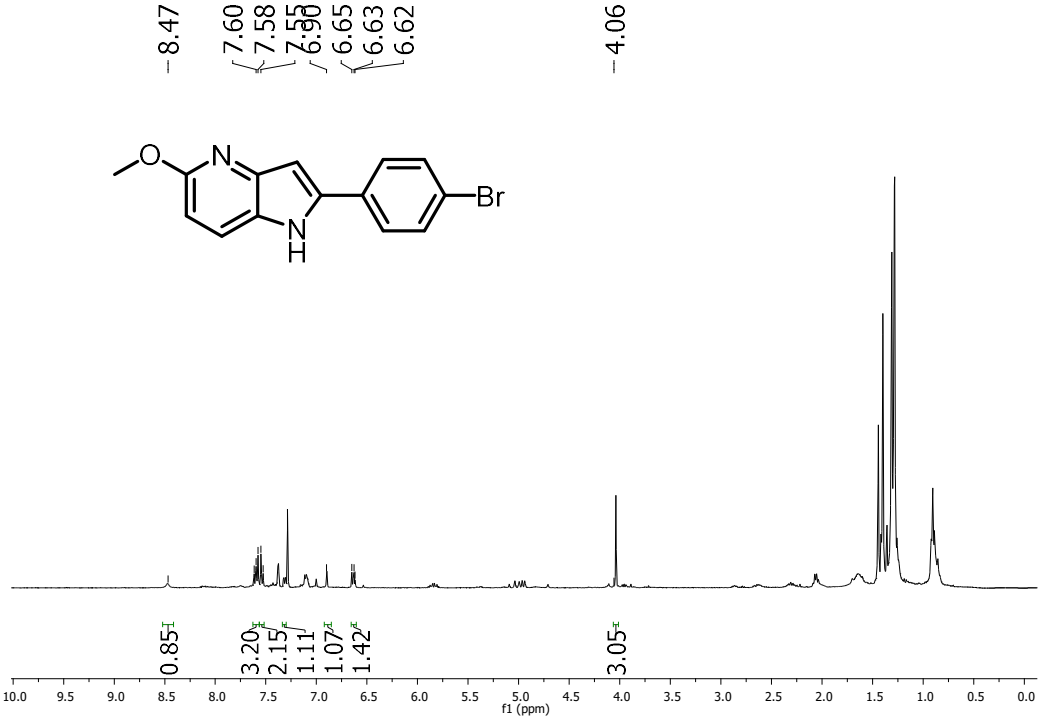
Spectrum 13- ^{1}H-NMR spectrum of 5-methoxy-2-(4-methoxyphenyl) -1H-pyrrolo[3,2-b] pyridine (II.5)



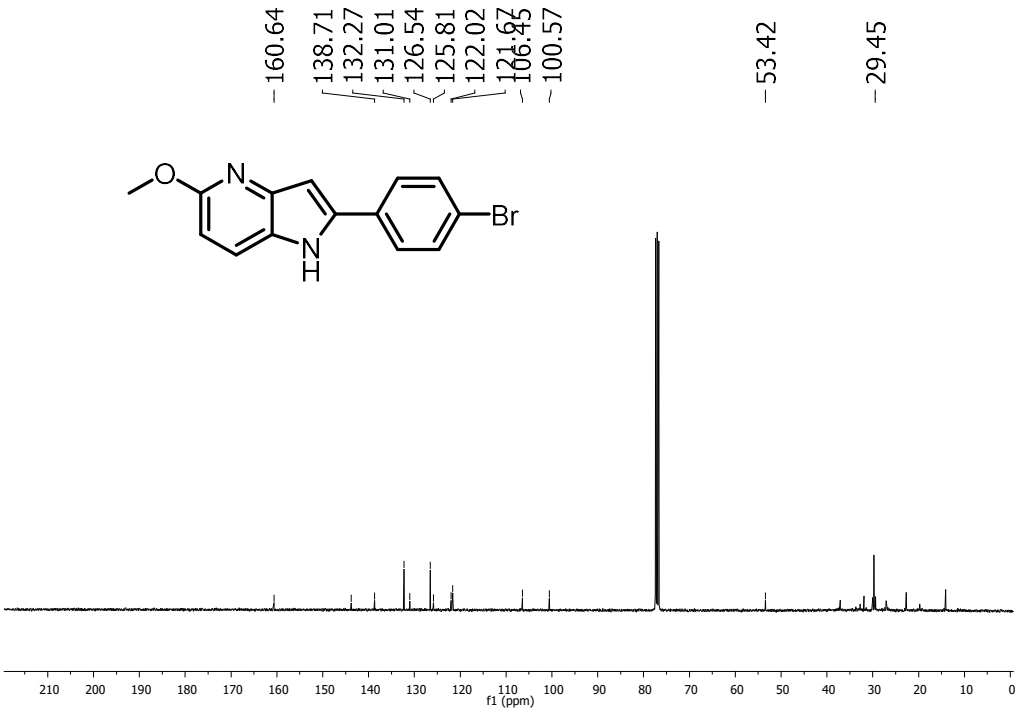
Spectrum 14- ^{13}C-NMR spectrum of 5-methoxy-2-(4-methoxyphenyl) -1H-pyrrolo[3,2-b] pyridine (II.5)



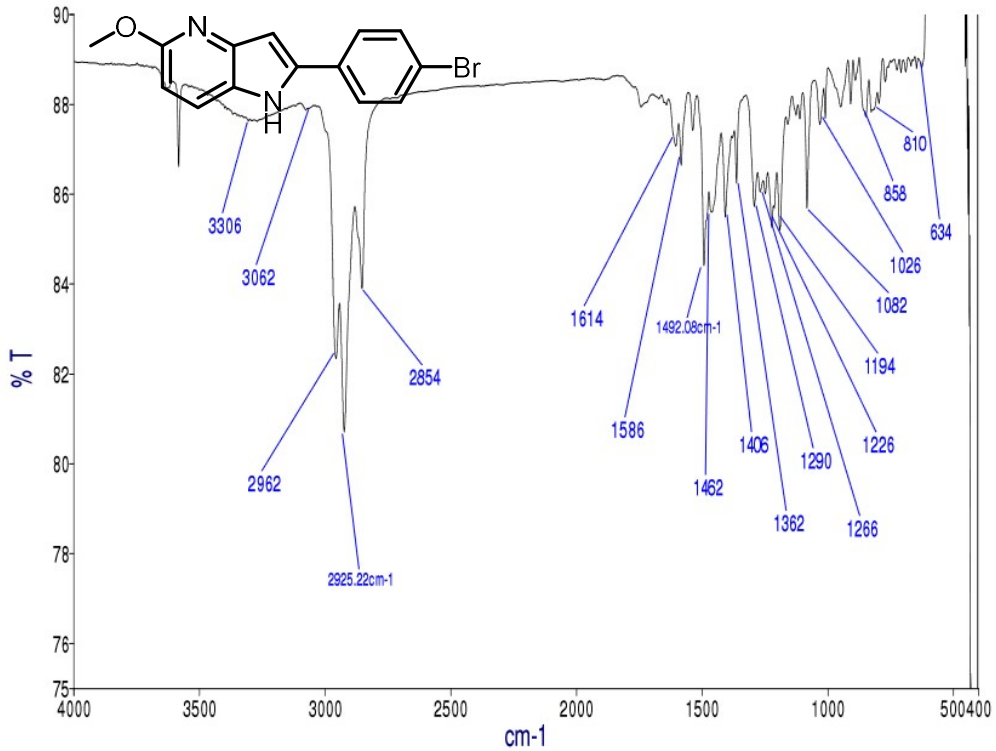
Spectrum 15- IR spectrum of 5-methoxy-2-(4-methoxyphenyl) -1H-pyrrolo[3,2-b] pyridine (II.5)



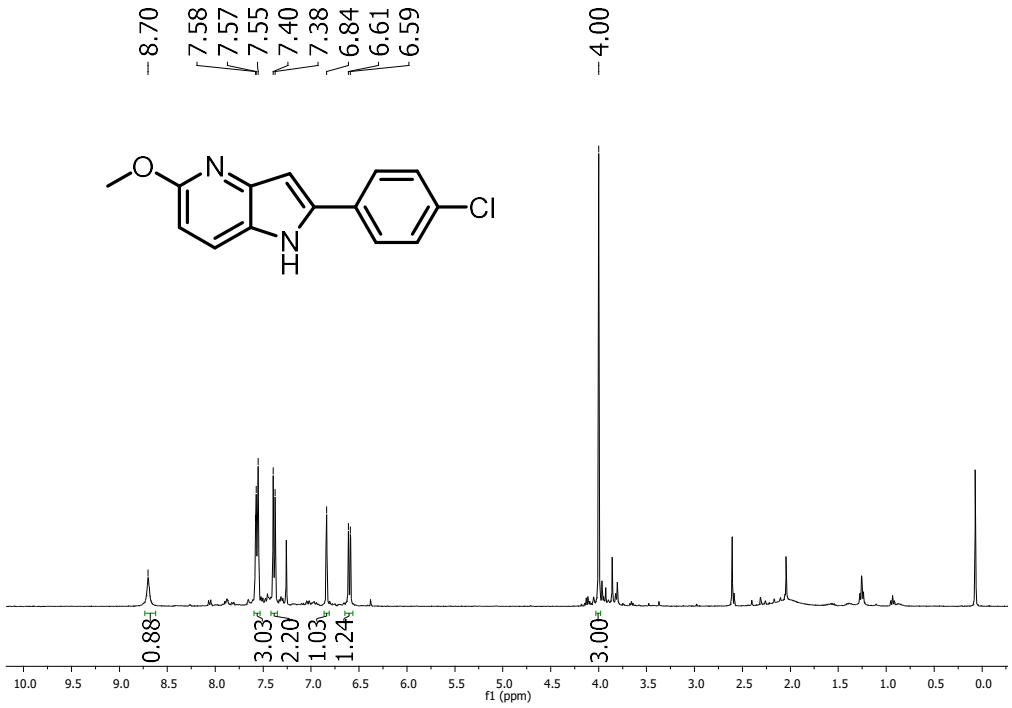
Spectrum 16- -^{1}H-NMR spectrum of 2-(4-bromophenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.6)



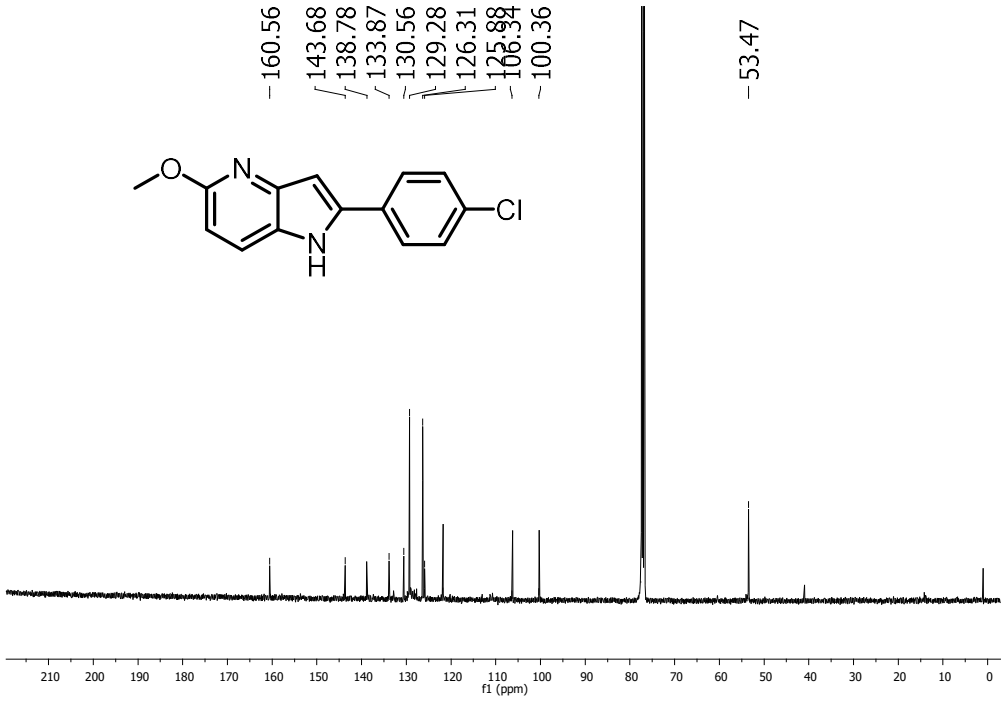
Spectrum 17- ^{13}C-NMR spectrum of 2-(4-bromophenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.6)



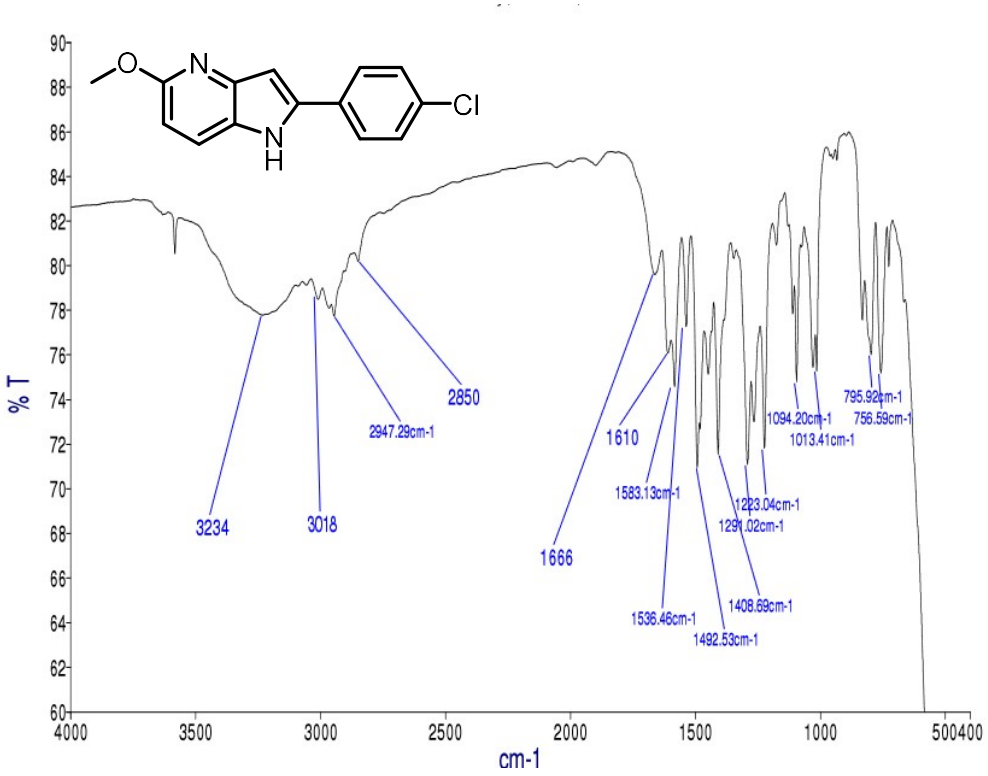
Spectrum 18- IR spectrum of 2-(4-bromophenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.6)



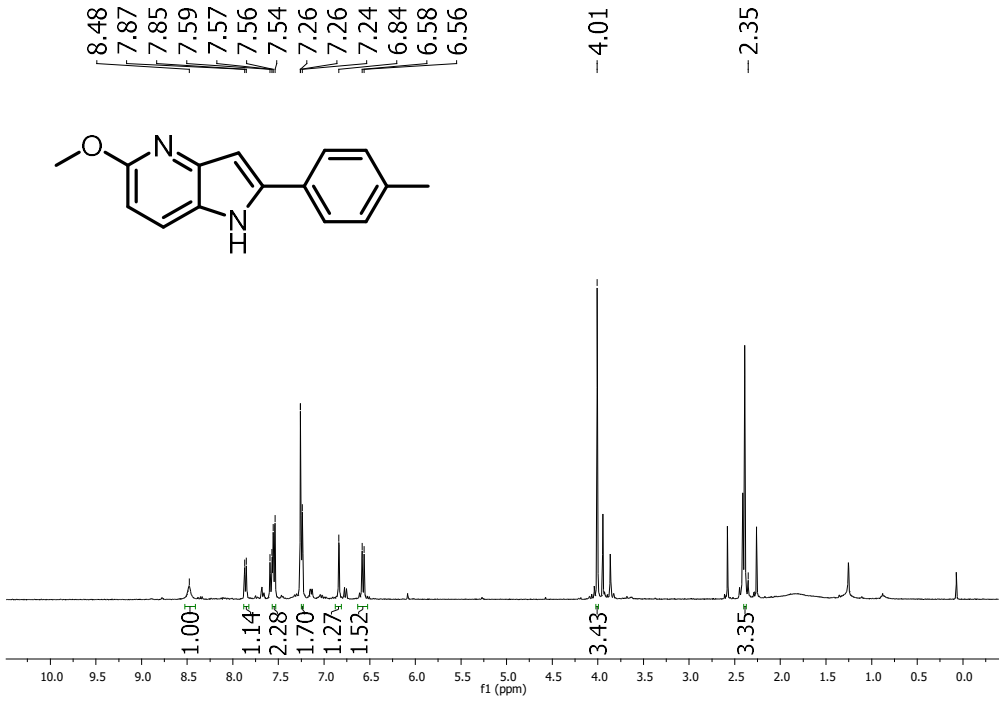
Spectrum 19- ^{1}H-NMR spectrum of 2-(4-chlorophenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.7



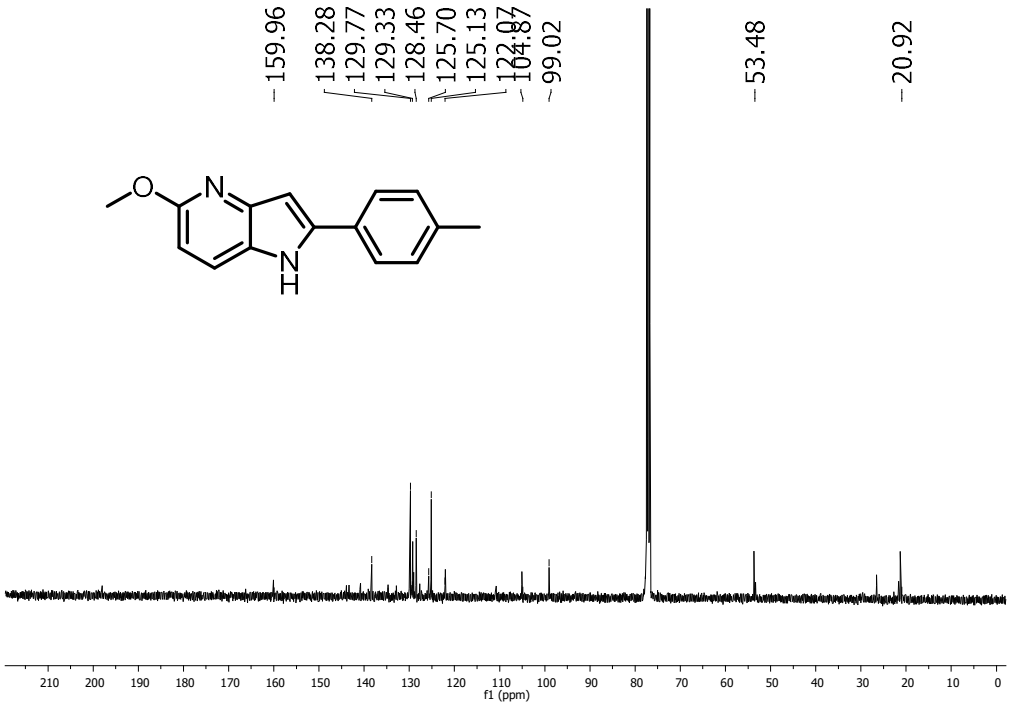
Spectrum 20- ^{13}C-NMR spectrum of 2-(4-chlorophenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.7)



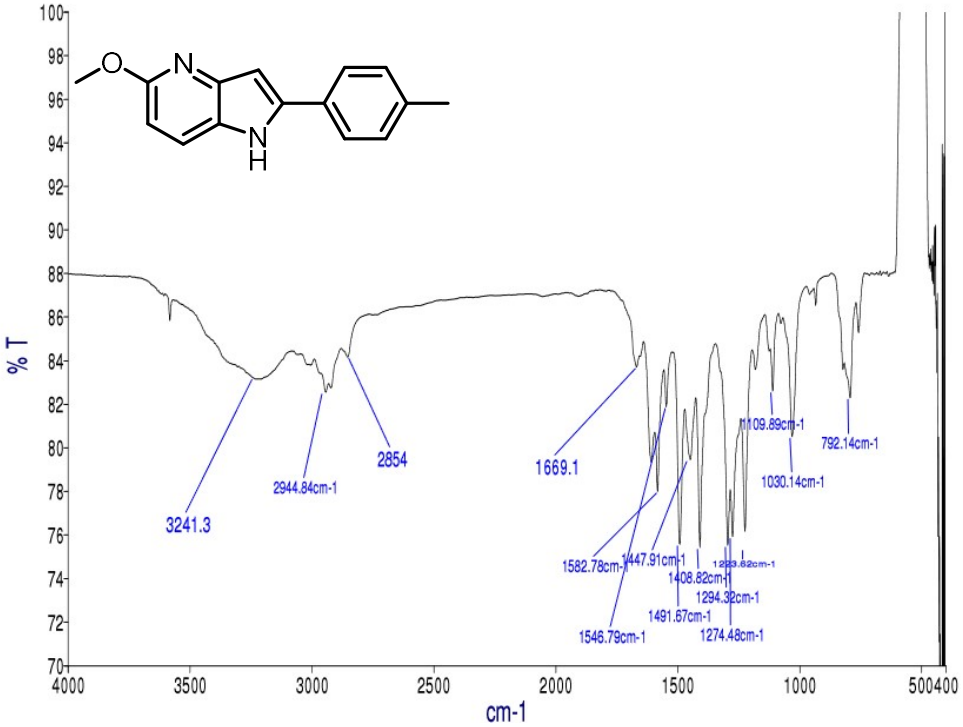
Spectrum 21- IR spectrum of 2-(4-chlorophenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.7)



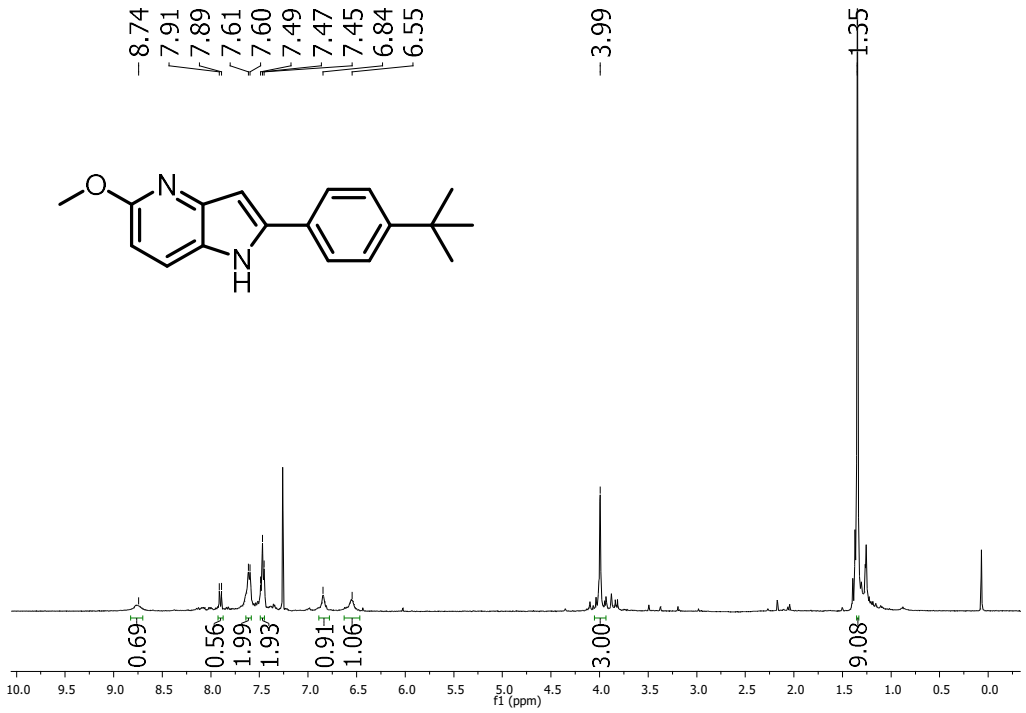
Spectrum 22- ^{1}H-NMR spectrum of 5-methoxy-2-(p-tolyl) -1H-pyrrolo[3,2-b] pyridine (II.9)



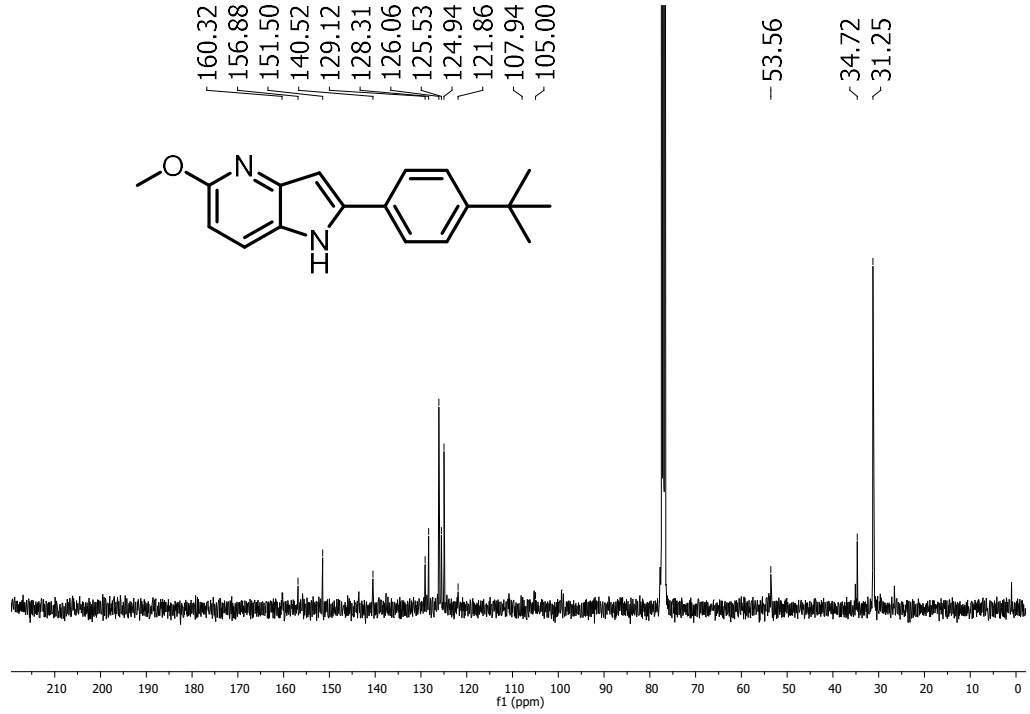
Spectrum 23- ^{13}C-NMR spectrum of 5-methoxy-2-(p-tolyl) -1H-pyrrolo[3,2-b] pyridine (II.9)



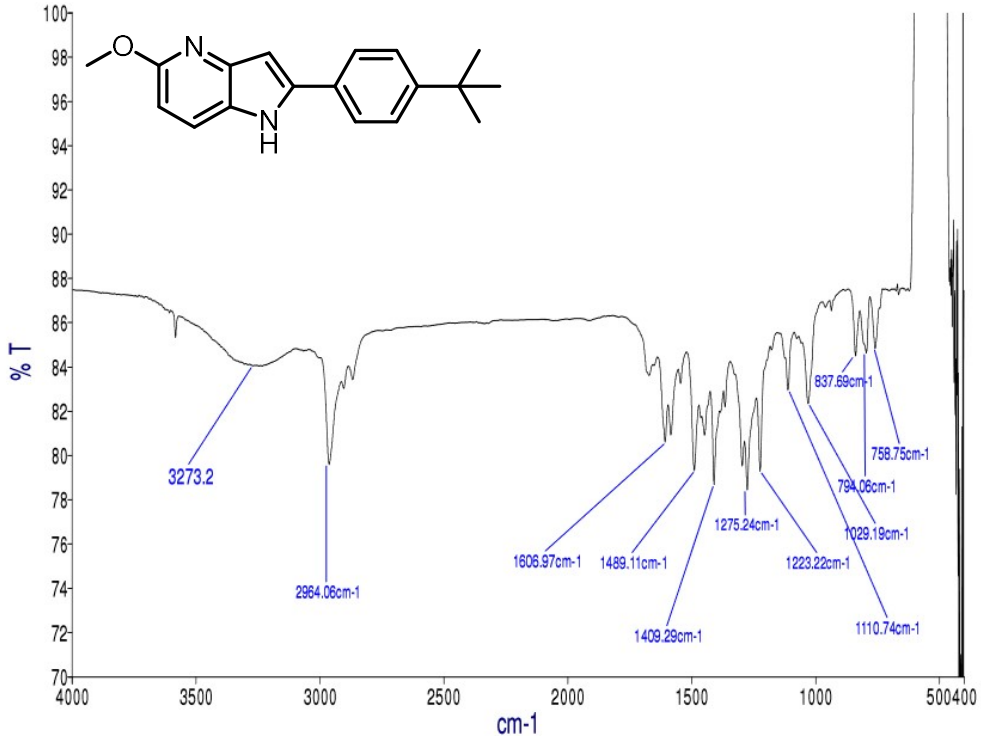
Spectrum 24- IR spectrum of 5-methoxy-2-(p-tolyl) -1H-pyrrolo[3,2-b] pyridine (II.9)



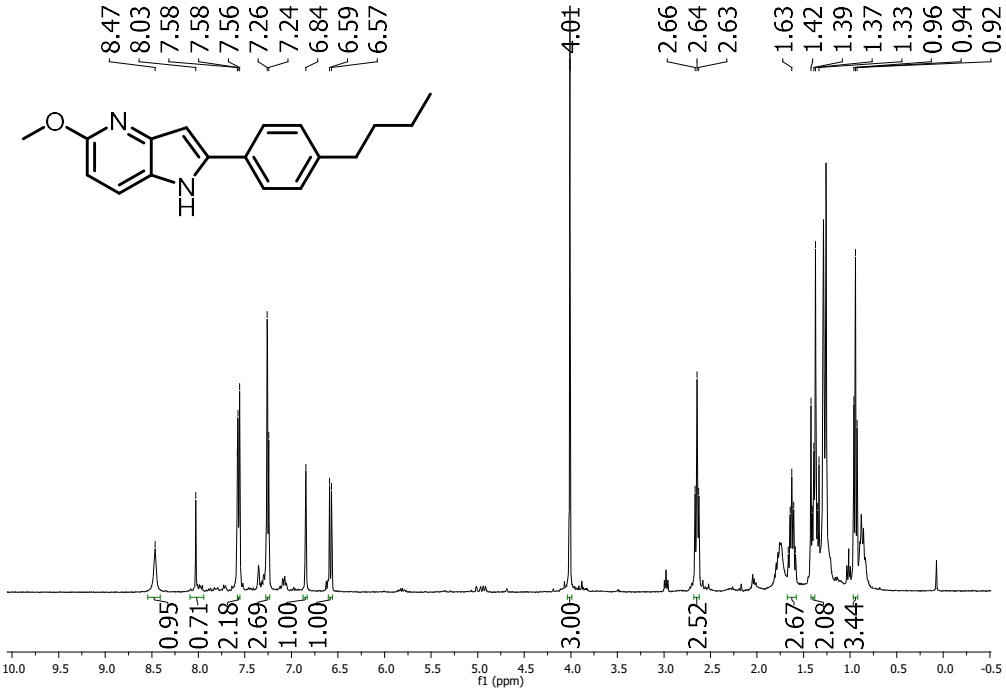
Spectrum 25- ^{1}H-NMR spectrum of 2-(4-(tert-butyl) phenyl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine (II.10)



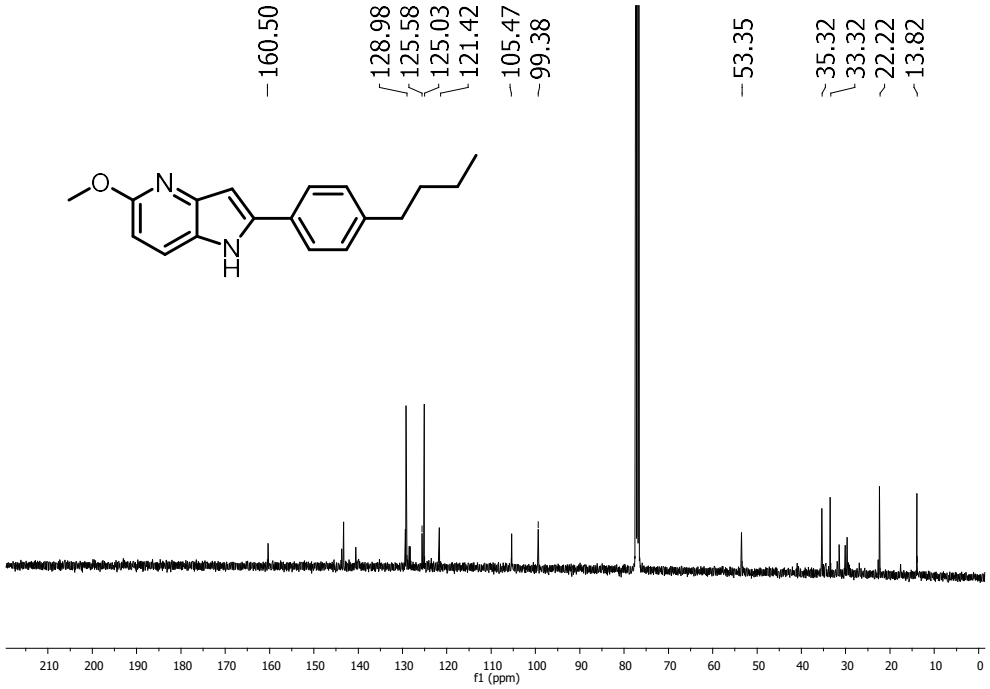
Spectrum 26- ^{13}C-NMR spectrum of 2-(4-(tert-butyl) phenyl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine (II.10)



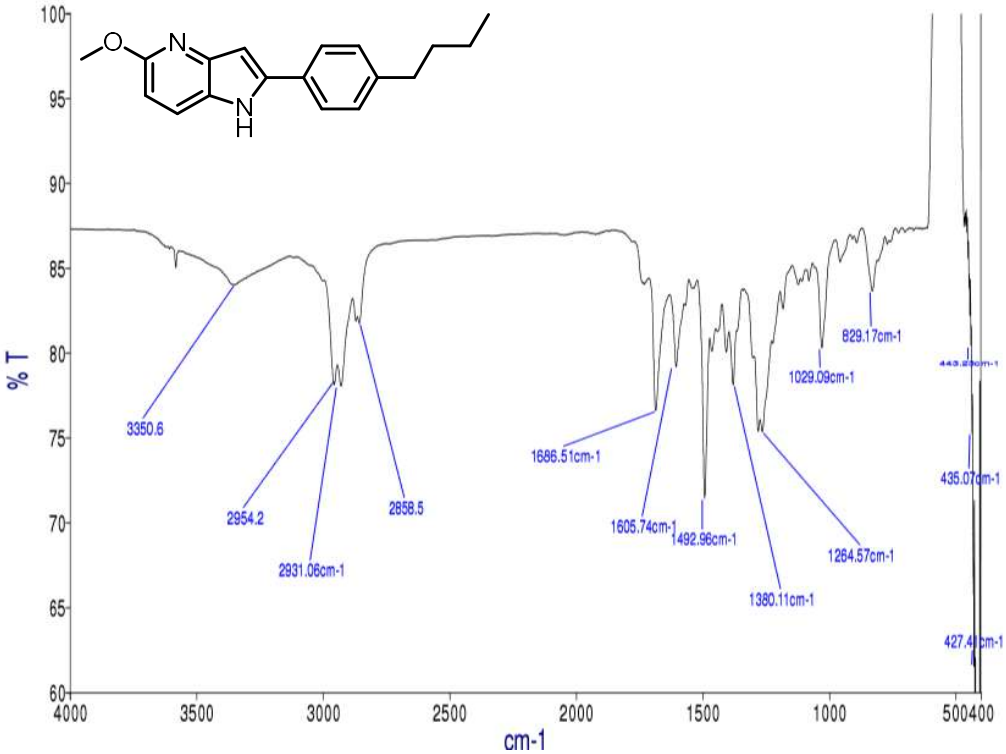
Spectrum 27- IR spectrum of 2-(4-(tert-butyl) phenyl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine (II.10)



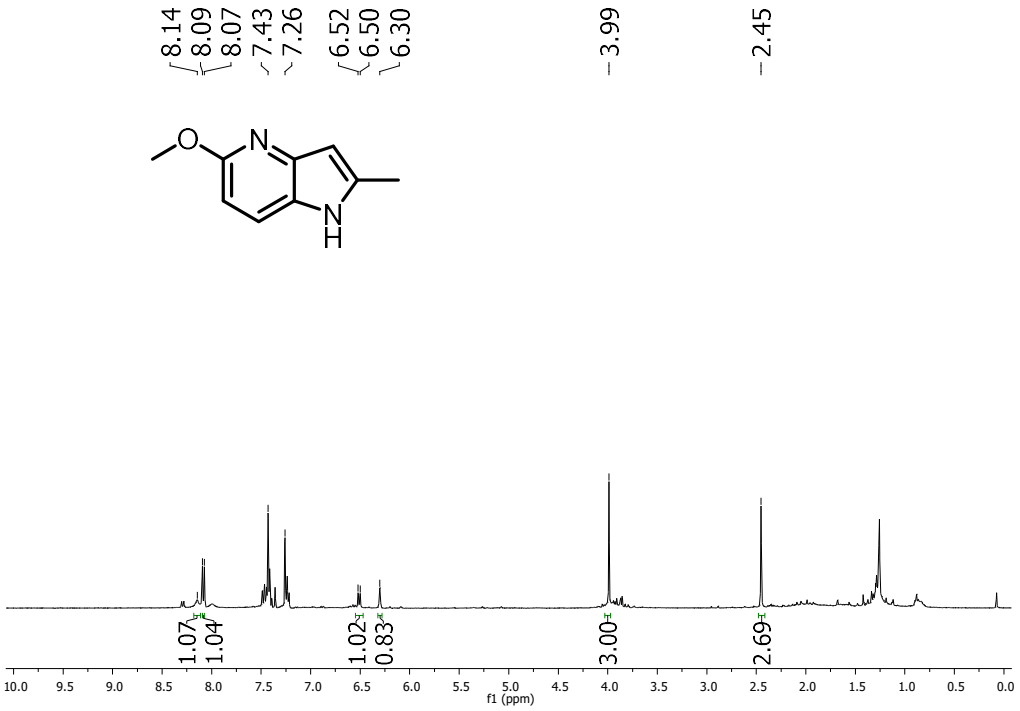
Spectrum 28- ^{1}H-NMR spectra of 2-(4-butylphenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.11)



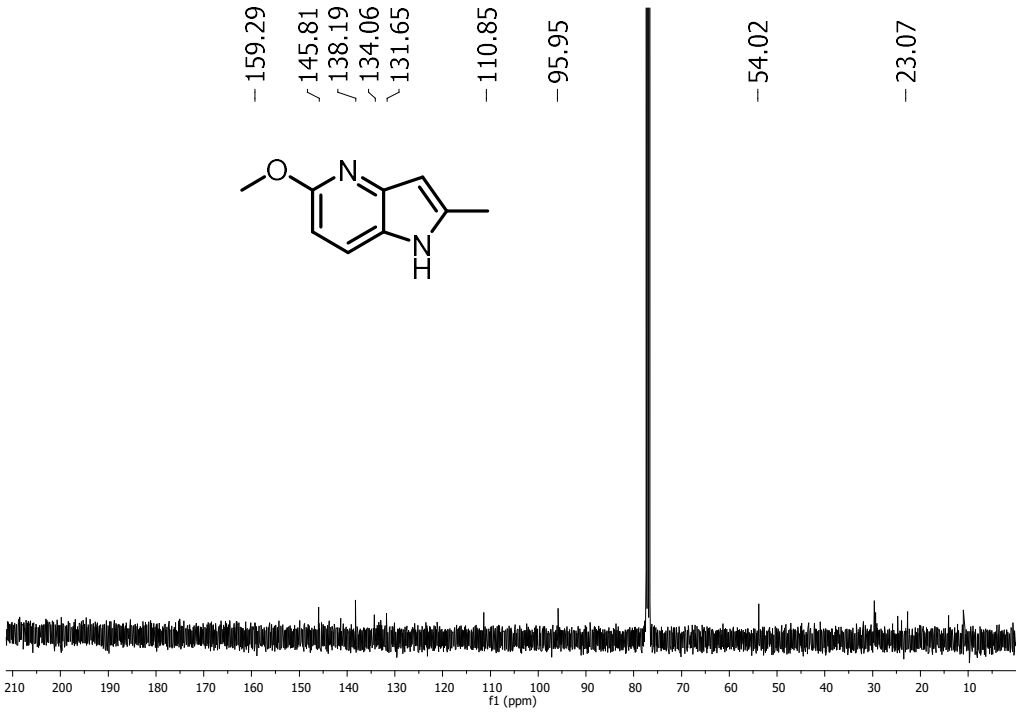
Spectrum 29- ^{13}C-NMR spectra of 2-(4-butylphenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.11)



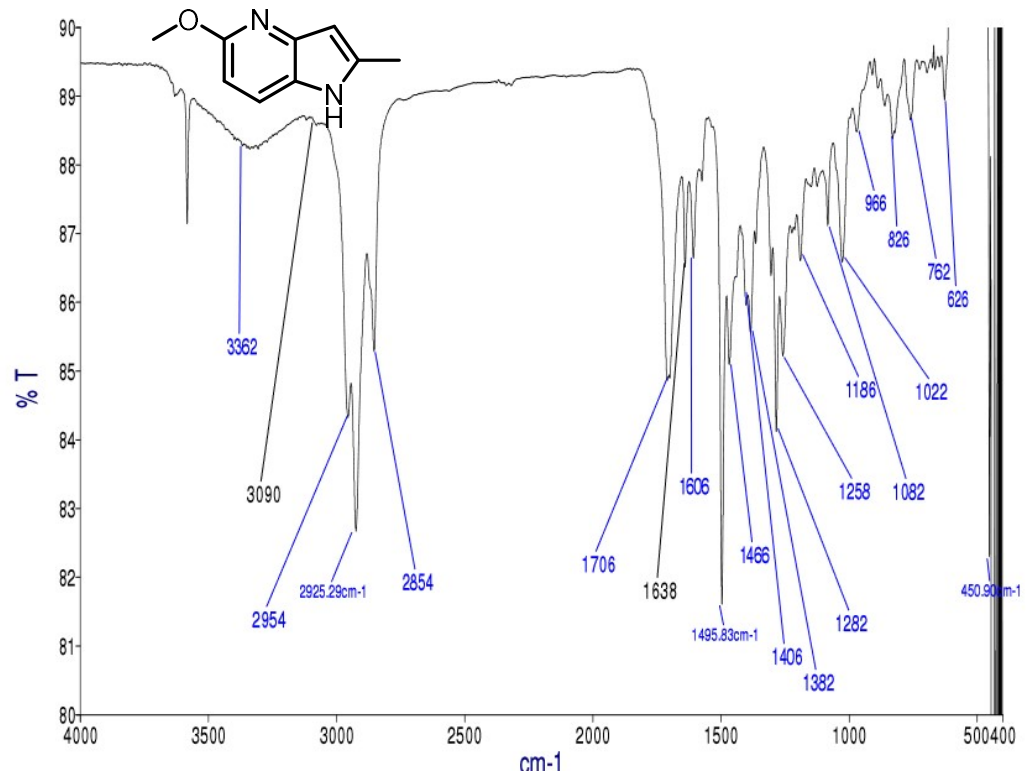
Spectrum 30- IR spectra of 2-(4-butylphenyl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.11)



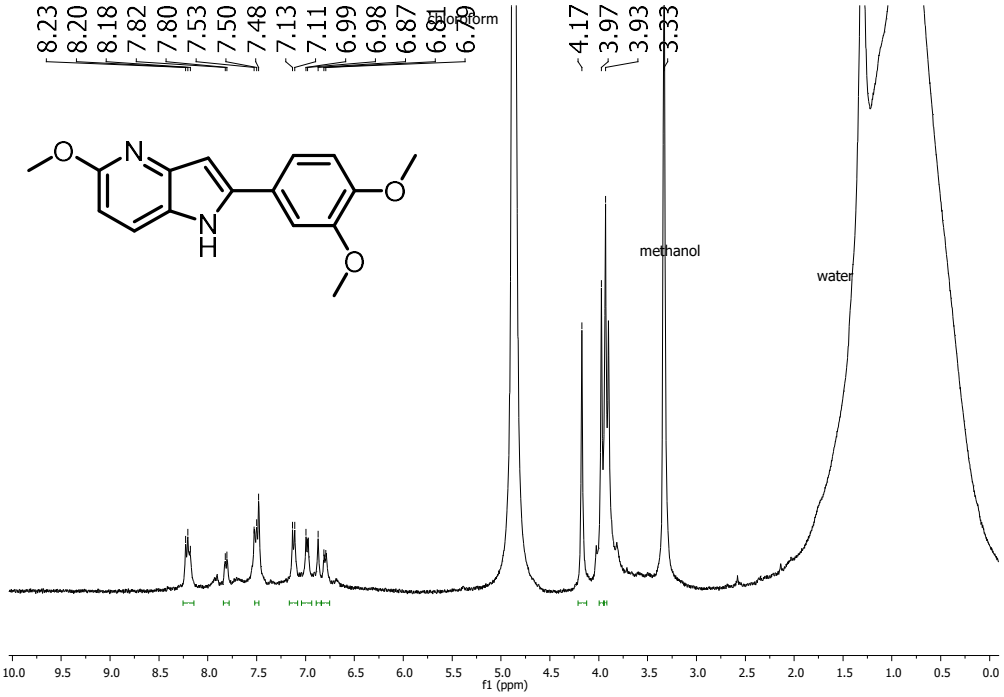
Spectrum 31- ^{1}H-NMR spectra of 5-methoxy-2-methyl-1H-pyrrolo[3,2-b] pyridine (II.12)



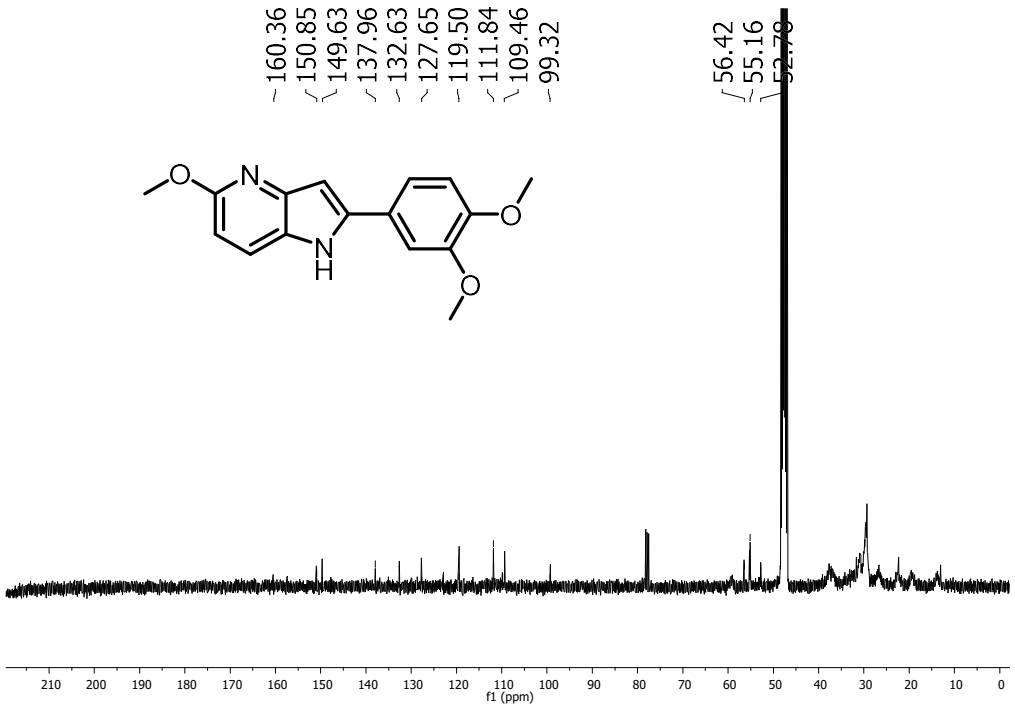
Spectrum 32- ^{13}C-NMR spectra of 5-methoxy-2-methyl-1H-pyrrolo[3,2-b] pyridine (II.12)



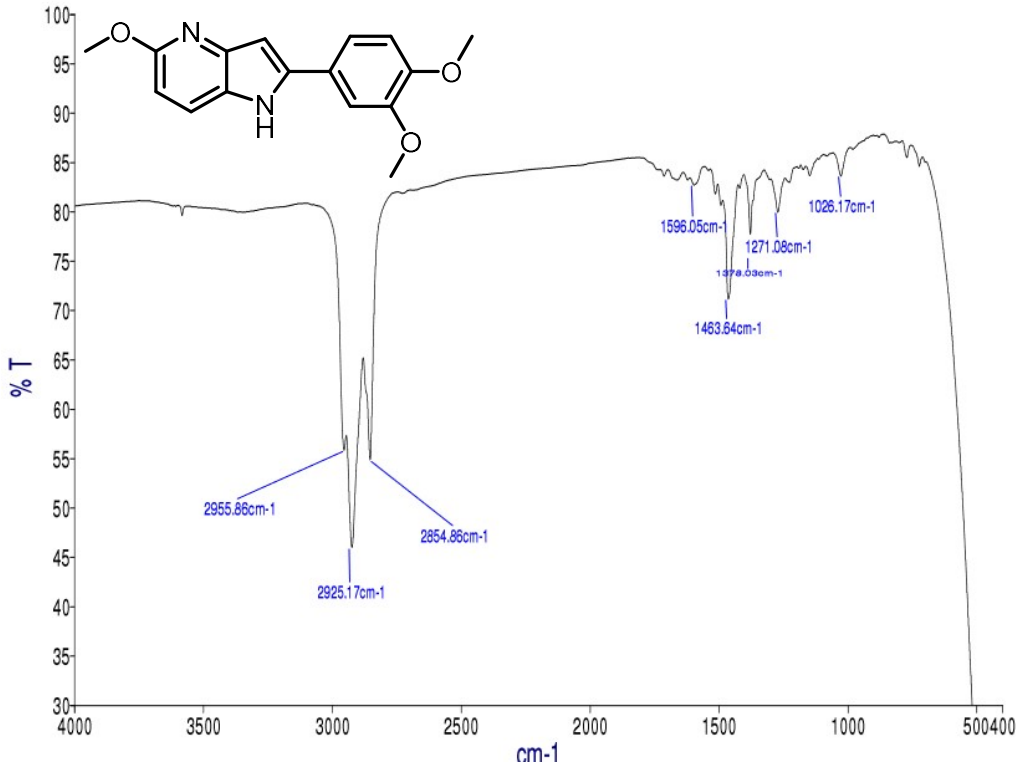
Spectrum 33- IR spectrum of 5-methoxy-2-methyl-1H-pyrrolo[3,2-b] pyridine (II.12)



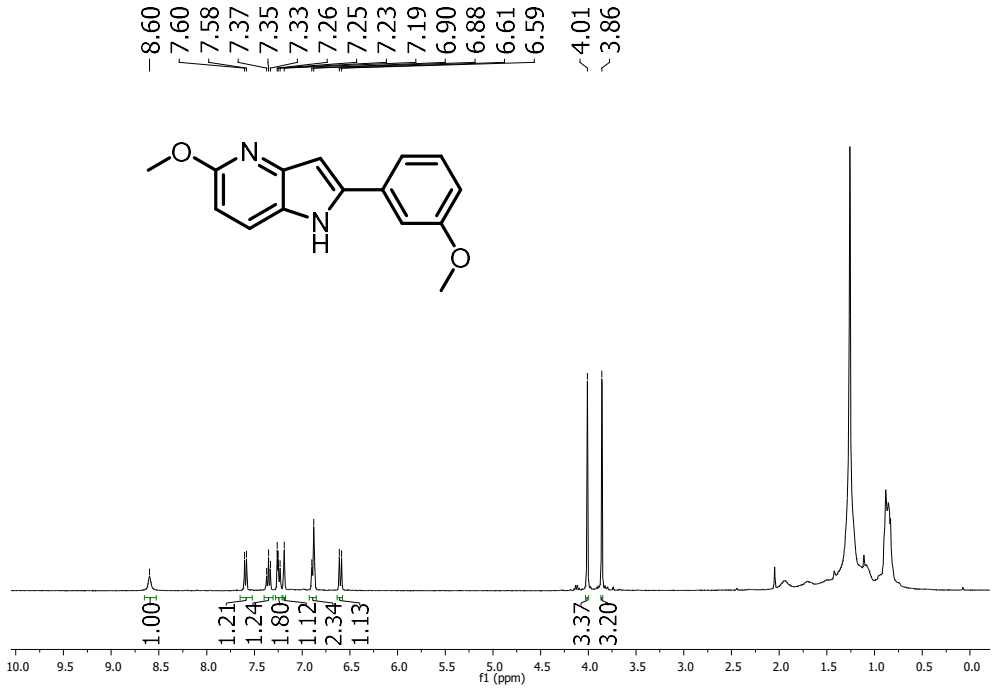
Spectrum 34- ^{1}H-NMR spectrum of 2-(3,4-dimethoxyphenyl) -5-methoxy-1H-pyrrolo [3,2-b] pyridine (II.13)



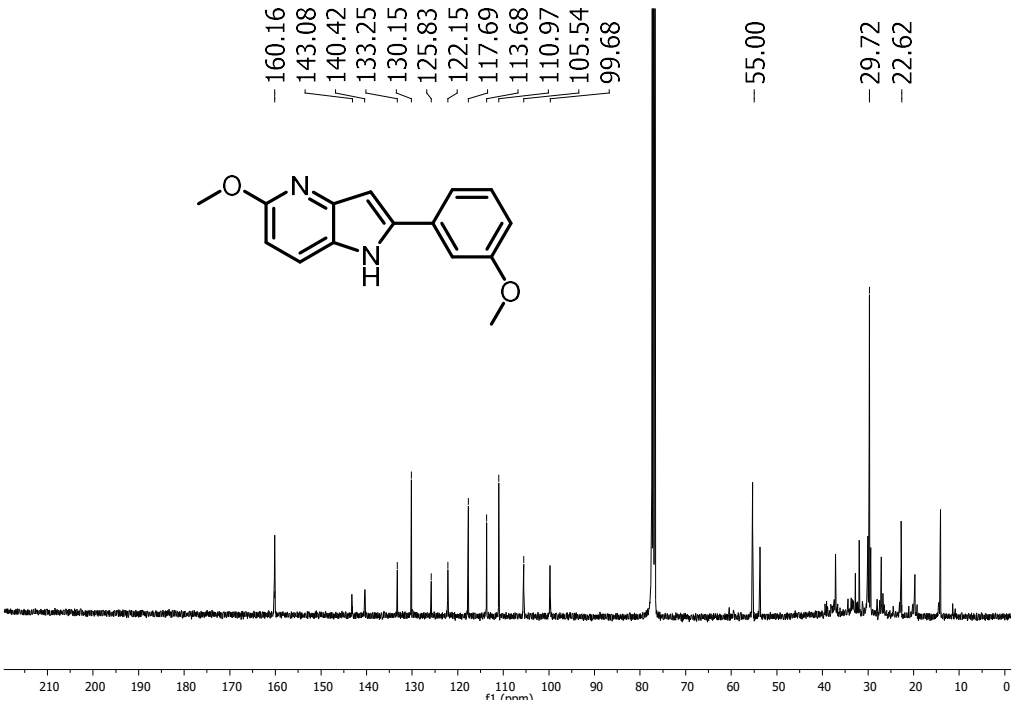
Spectrum 35- ^{13}C-NMR spectrum of 2-(3,4-dimethoxyphenyl) -5-methoxy-1H-pyrrolo [3,2-b] pyridine (II.13)



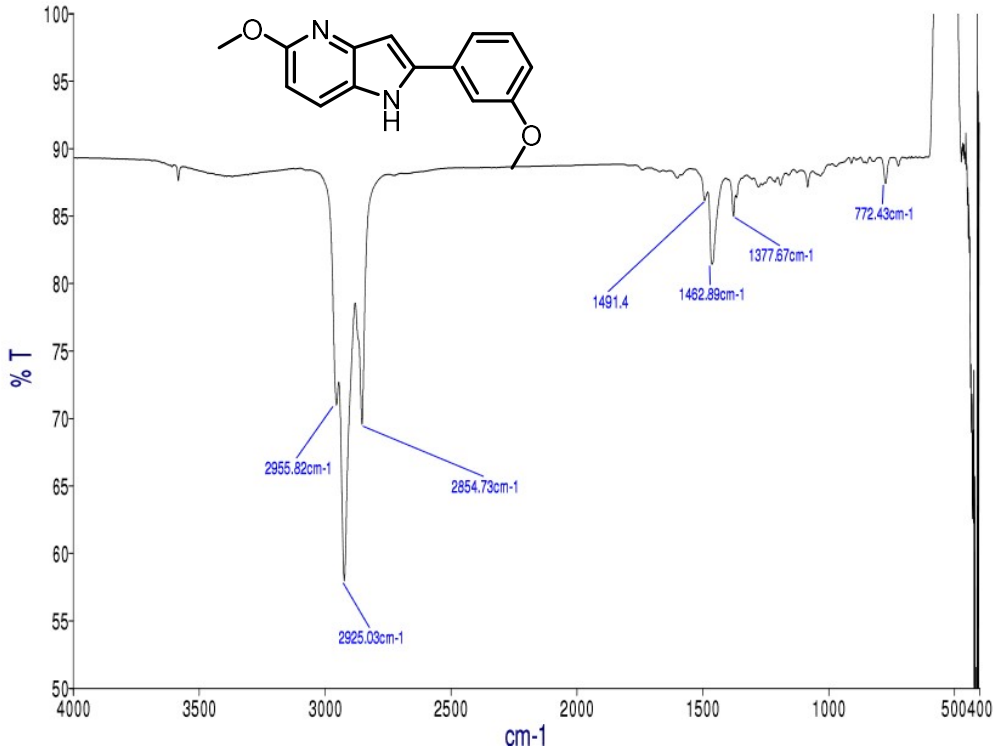
Spectrum 36- IR spectrum of 2-(3,4-dimethoxyphenyl) -5-methoxy-1H-pyrrolo [3,2-b] pyridine (II.13)



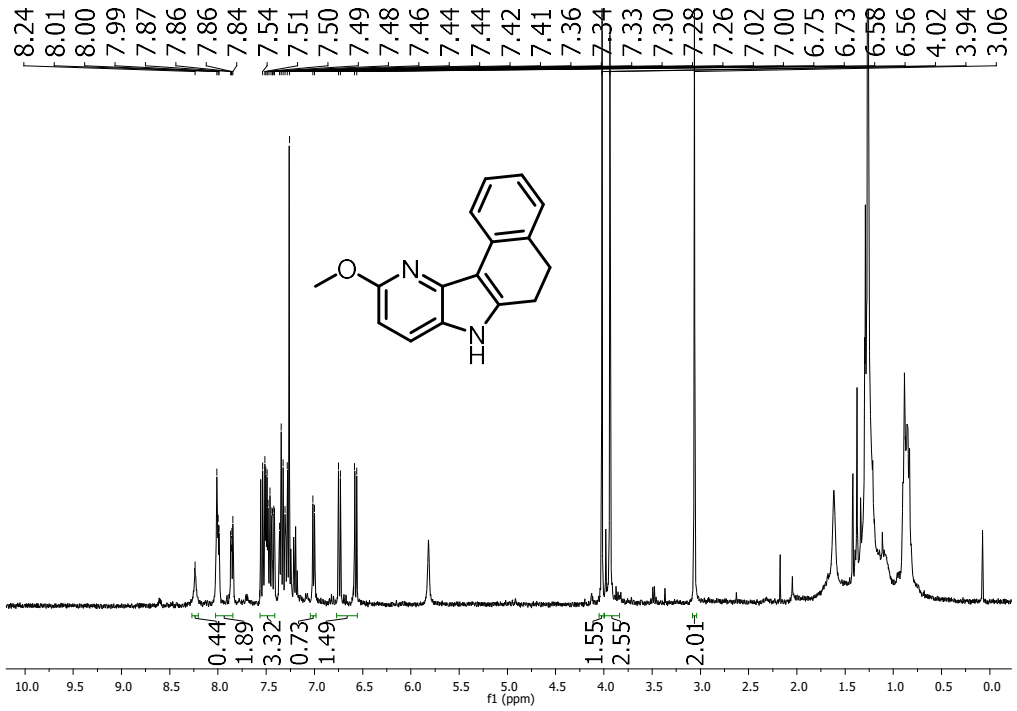
Spectrum 37- ^{1}H-NMR spectrum of 5-methoxy-2-(3-methoxyphenyl) -1H-pyrrolo[3,2-b] pyridine (II.14)



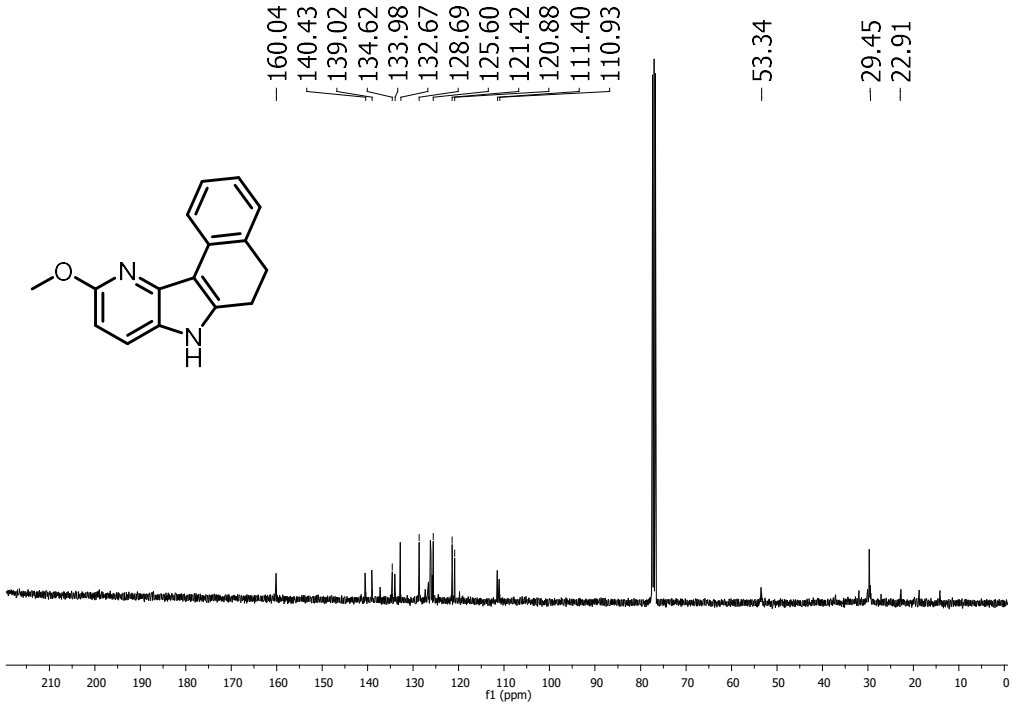
Spectrum 38- ^{13}C-NMR spectrum of 5-methoxy-2-(3-methoxyphenyl) -1H-pyrrolo[3,2-b] pyridine (II.14)



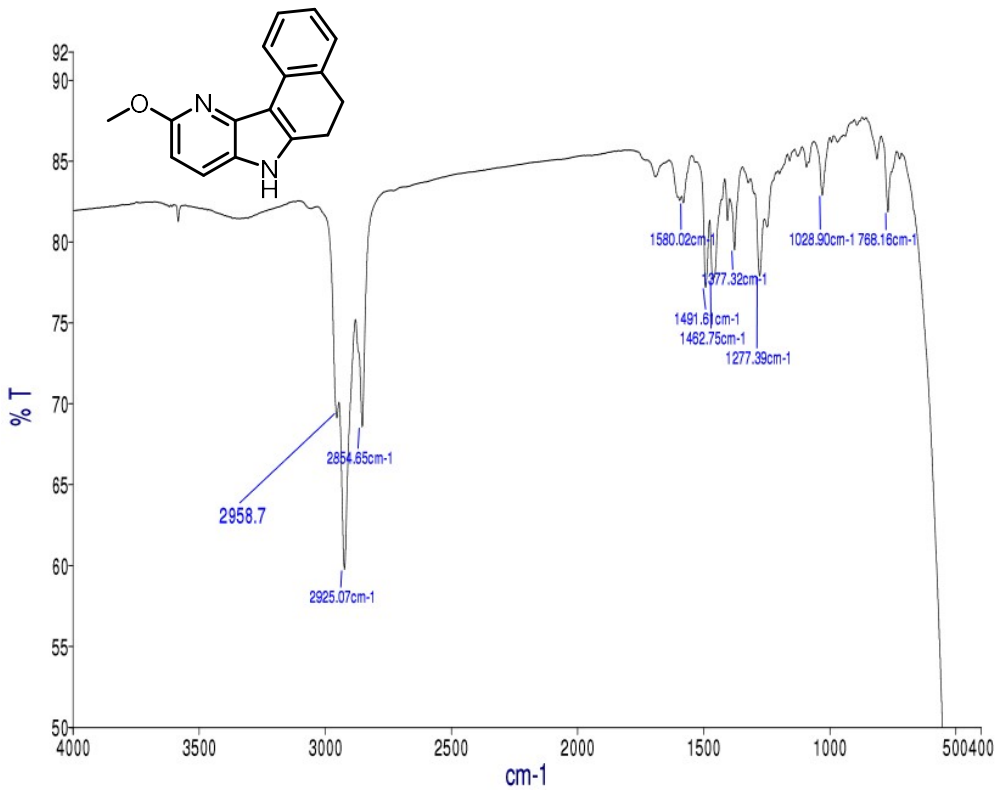
Spectrum 39- IR spectrum of 5-methoxy-2-(3-methoxyphenyl) -1H-pyrrolo[3,2-b] pyridine (II.14)



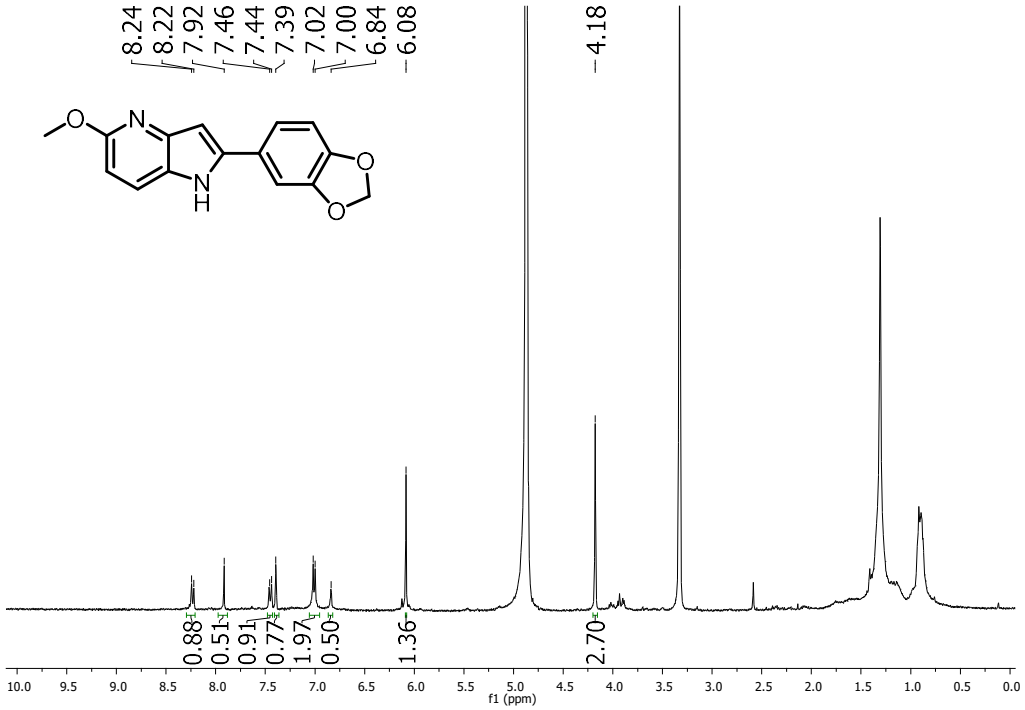
Spectrum 40- ^{1}H-NMR spectrum of 10-methoxy-6,7-dihydro-5H-benzo[e] pyrido [3,2-b] indole (II.15)



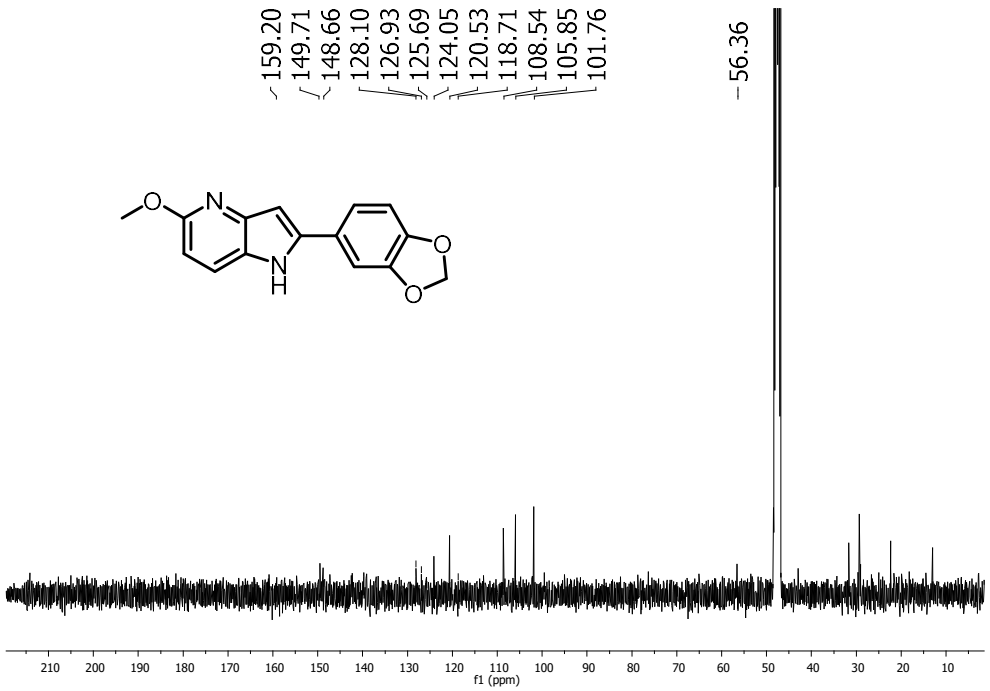
Spectrum 41- ^{13}C-NMR spectrum of 10-methoxy-6,7-dihydro-5H-benzo[e] pyrido [3,2-b] indole (II.15)



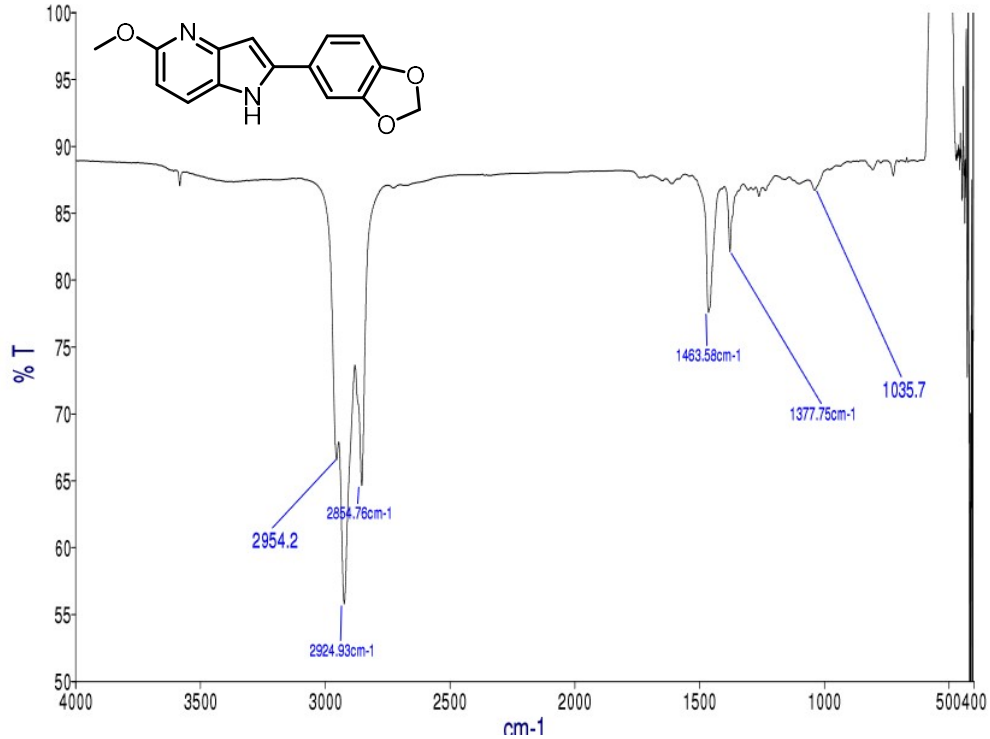
Spectrum 42- IR spectrum of 10-methoxy-6,7-dihydro-5H-benzo[e] pyrido [3,2-b] indole (II.15*)*



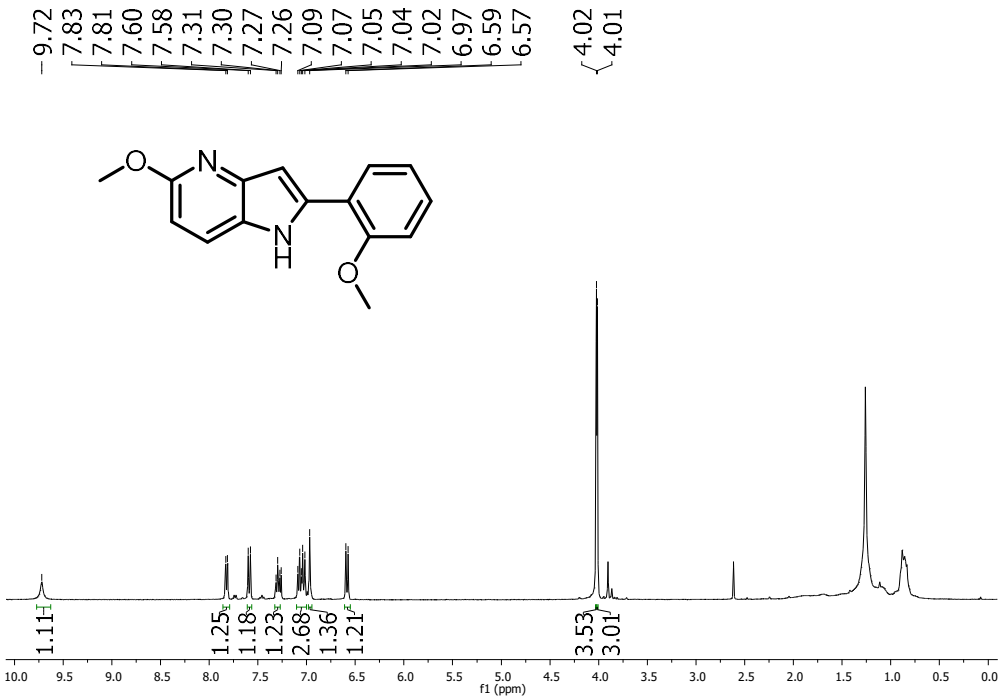
Spectrum 43- ^{1}H-NMR spectrum of 2-(benzo[d] [1,3] dioxol-5-yl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.16)



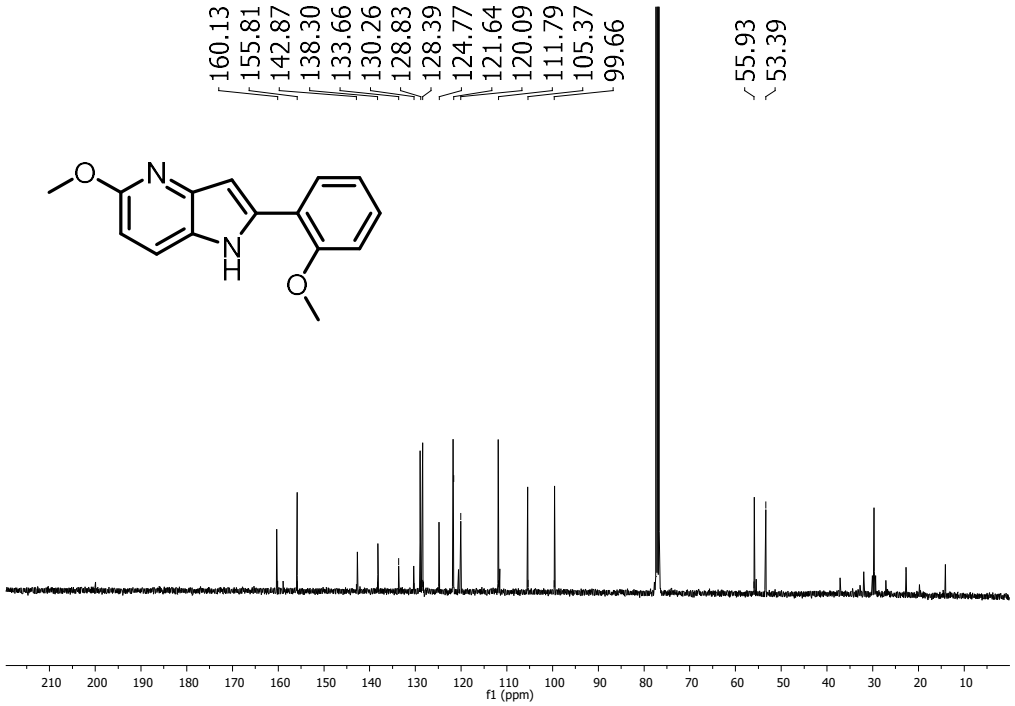
Spectrum 44- ^{13}C-NMR spectrum of 2-(benzo[d] [1,3] dioxol-5-yl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.16)



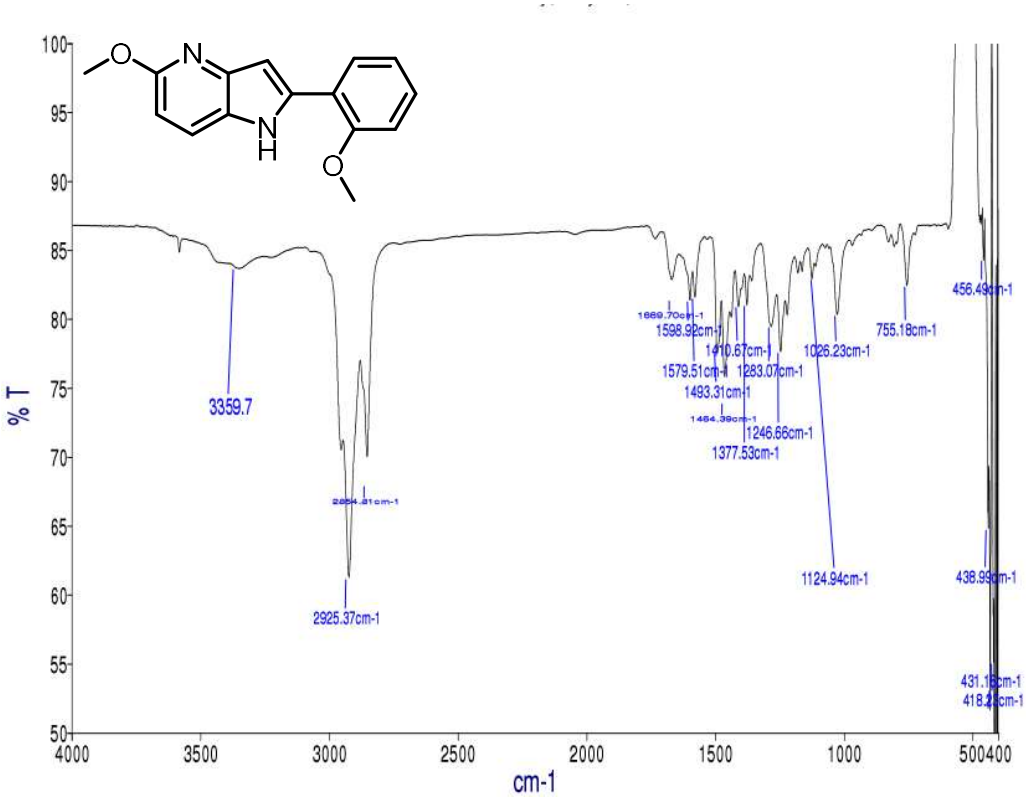
Spectrum 45- IR spectrum of 2-(benzo[d] [1,3] dioxol-5-yl) -5-methoxy-1H-pyrrolo[3,2-b] pyridine (II.16)



Spectrum 46- ^{1}H-NMR spectra of 5-methoxy-2-(2-methoxyphenyl) -1H-pyrrolo[3,2-b]pyridine (II.17)



Spectrum 47- ^{13}C-NMR spectra of 5-methoxy-2-(2-methoxyphenyl) -1H-pyrrolo[3,2-b]pyridine (II.17)



Spectrum 48- IR spectra of 5-methoxy-2-(2-methoxyphenyl) -1H-pyrrolo[3,2-b]pyridine (II.17)