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Novel Syntheses of 5- and 7-Azaindole Derivatives

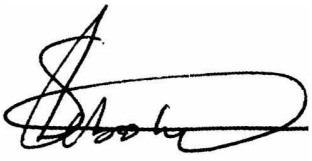
Tlabo Caiphus Leboho

A Thesis submitted to the Faculty of Science,
University of the Witwatersrand,
Johannesburg,
in fulfillment of the requirement for the
degree of Doctor of Philosophy.

09 September 2013

Declaration

I declare that the work presented in this thesis was carried out exclusively by me under the supervision of Professors C. B. de Koning and J. P. Michael. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.



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on the 9th day of September 2013

Abstract

This thesis describes the application of the Sonogashira coupling reaction to access a variety of 5-and 7-azaindoles derivatives. The background chapter paints a picture about the importance of indole-containing compounds and azaindole-containing compounds. In this first chapter, discovery, synthesis, properties and reactivity of indole and azaindoles were explained.

In Chapter 2 of this thesis, the Sonogashira coupling reaction was applied in combination with base mediated ring closure and ring closing metathesis afforded pyrrolo-7-azaindoles (**1-63**) and the third chapter of this thesis covered the work relating to the synthesis of 2,5-disubstituted-7-azaindoles. In this third chapter, our focus was to combine the triazole functionality with the 7-azaindole nucleus with the hope of producing molecules with improved biological properties (**1-64**).

As we continued to enjoy the wide applications of the Sonogashira coupling reaction, it was also used in Chapter 4 for the synthesis of 2,3,5-trisubstituted-7-azaindoles. In this chapter, the application of the Cacchi reaction in combination with quinoxaline synthesis using palladium chloride, DMSO and microwave irradiation gave the much anticipated 2,3,5-trisubstituted-7-azaindole derivatives (**1-66**). We also hope that the combination of quinoxaline functionality and 7-azaindole nucleus would create molecules with superior biological properties.

The application of the Sonogashira coupling in combination with the trifluoroacetic acid/acetic anhydride mixture in acetonitrile at 100 °C, yielded substituted-7-azaindole derivatives (**1-67**) in good yields for Chapter 5 of this thesis. The synthesis of 5-azaindole derivatives (**1-65**) was also conducted and this is discussed in Chapter 6 of this thesis.

Acknowledgements

I would like to sincerely thank my supervisor and mentor Professor Charles de Koning. This project would have not been a success without his support, guidance, inputs, and most of all, for giving me the opportunity to work with him. Thank you Charles for the wonderful work you have done.

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A big thank you to the reliable men in the store of the School of Chemistry, Elias Valoyi and David Moloto, Amanda Morgan thank you for ordering the chemicals required for my research, and the entire Administration of the School of Chemistry, thank you.

Special thanks you to NRF and CSIR for their financial support. A warm thank you goes to Fulbright South Africa for giving me the chance to visit and learn few tricks from the USA counterparts.

Dedications

This thesis is especially dedicated my Family,
My late father Ngoako Lebogo,
My mother Mosibudi Lebogo,
And all my brothers and sisters

Your support throughout the years cannot be measured.

Montshepetša bošego, ke mo leboga bosele!
Moya mahlong a tau, o ya a swere serumula!
Kudumela moepa thutse, gao lehumo le tšwang kgauswi!

List of Abbreviations

AcOH	acetic acid
Ar	aromatic
Boc_2O	di-*tert*-butyl-dicarbonate
BuLi	*n*-butyllithium
CuI	copper(I) iodide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
h	hour
HIV	human immunodeficiency virus
HCl	hydrochloric acid
HNO_3	nitric acid
H_2SO_4	sulfuric acid
h*v*	light
KO^tBu	potassium *tert*-butoxide
LDA	lithium diisopropylamide
M	molar
Me	methyl
MeOH	methanol
min	minutes
NaOMe	sodium methoxide
NMR	nuclear magnetic resonance
OMe	methoxy
Ph	phenyl
rt	room temperature
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran

List of Abbreviations

TsCl	*p*-toluenesulfonyl chloride (tosyl chloride)
TMS	trimethylsilyl
W	Watts

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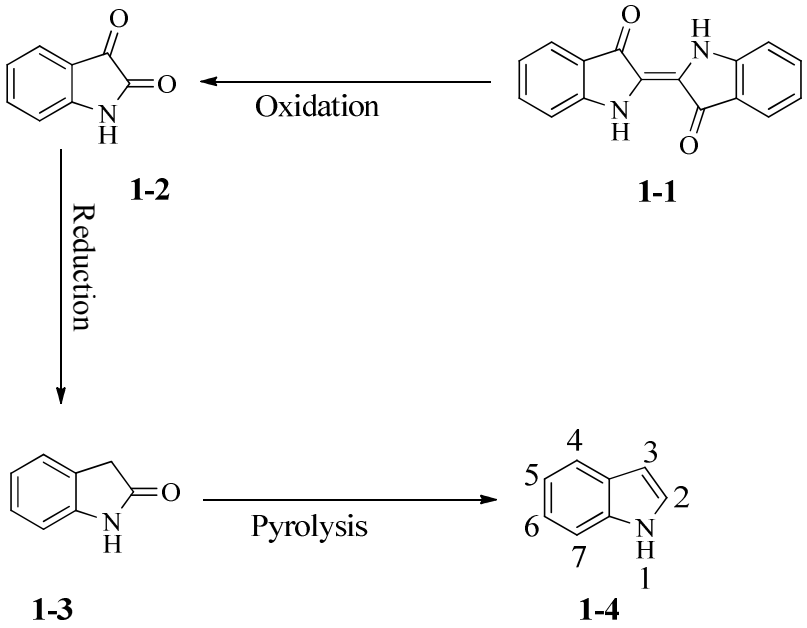
Chapter 1: Background

1.1 Indole

The indole ring is present in an array of natural products such as the alkaloids, fungal metabolites and marine natural products.[1] The main source of indole itself is extraction from coal tar, although industrial preparation from reagents such as aniline, ethylene glycol and others has also been demonstrated.[1] It was first prepared by Adolf Baeyer in 1886 by pyrolysis of oxindole (**1-3**) using zinc dust to give indole (**1-4**). Oxindole (**1-3**) was obtained by reducing isatin (**1-2)** which in turn was synthesized by oxidation of the natural insoluble dark blue dye called indigo (**1-1**) (**Scheme 1**).[2]

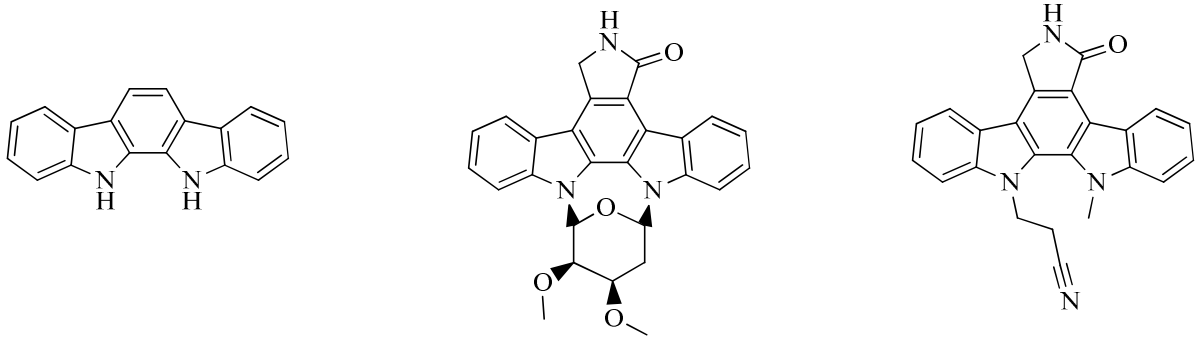


Scheme 1

Indole reacts with electrophiles mainly through position 3 when the hydrogen on the nitrogen atom at position 1 is substituted. Position 1 is the most reactive towards electrophiles followed

by position 3. When both positions 1 and 3 are taken by substituents other than hydrogen, position 2 becomes the most reactive followed by other positions on the benzene ring.[3]

In addition to the hundreds of well-known indole plant alkaloids, the indole ring is also present in an array of other organisms.[4] Thus, the indole nucleus forms an integral component of many biologically active natural products and many more medicinally useful synthetic products.[5] As such, indole and its derivatives are some of the most important heteroaromatic compounds and could be found for example embedded in the carbazoles. For example, the indolo[2,3-*a*]carbazole **1-5** framework is found in many natural products which have a broad range of potent biological activities, such as antifungal, antimicrobial, antitumor, and antihypertensive activity.[6] Staurosporine **1-6** and Gö 6976 **1-7** both contain the indolo[2,3-*a*]carbazole nucleus. Staurosporine **1-6** (**Figure 1**) has interesting biological activity including cytotoxicity, antimicrobial activity, inhibition of protein kinase C, and platelet aggregation inhibition.[6] Staurosporine **1-6** was also found to be one of the best ATP competitive kinase inhibitors with IC_{50} values in the nanomolar range for the serine kinases, protein kinase C, CDK2, CDK4, and CDK6.[6] On the other hand, Gö 6976 **1-7** (**Figure 1**) a non-glycosidic indolo[2,3-*a*]carbazole, exhibits a selective inhibition of protein kinase C and also acts as an antagonist of the Human Immunodeficiency Virus 1 (HIV-1).[7]

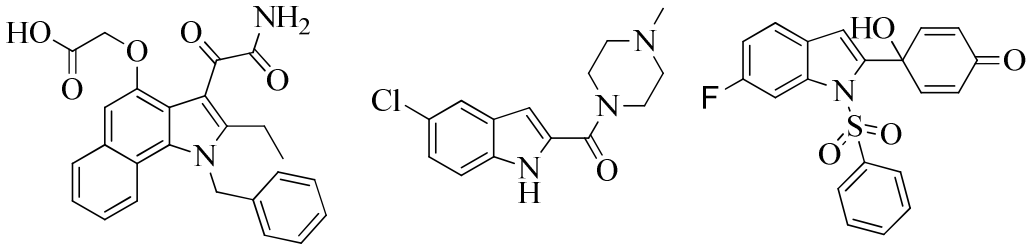


indolo[2,3-*a*]carbazole **1-5** staurosporine **1-6** Gö 6976 (**1-7**)

Figure 1

Apart from the biological relevance shown by fused indoles (carbazoles), substituted indoles are also of similar importance. Various substituted indoles were screened as potential phospholipase

A_2 (PLA_2s) inhibitors (PLA_2s are water-soluble enzymes that catalyze the hydrolysis of phospholipids at the water-lipid interface) and was also found to possess both antibacterial and antiviral activity. Thus, the use of substituted indole **1-8** as a possible PLA_2s inhibitor yielded positive results as **1-8** was found to inhibit nearly all human and mouse PLA_2s in the low nanomolar range.[8] On the other hand, the substituted indole **1-9** was found to be an antagonist for the H_4 histamine receptor with high affinity and selectivity.[9] Furthermore, evaluation of the growth-inhibitory properties of the novel quinol **1-10** was undertaken in two human colon cancer cell lines (HCT 116 and HT 29). The evaluation results showed that 4-(1-phenylsulfonyl-1*H*-6-fluoroindol-2-yl)-4-hydroxycyclohexa-2,5-dienone (**1-10**) was potent against the cell lines with a mean GI_{50} value of 16 nM and mean LC_{50} value of 2.2 μM[10] (**Figure 2**).



1-8 **1-9** **1-10**

Figure 2

Indigo **1-1** has found application as one of the most used dyes mainly in the textile industry. It should also be noted that indole-containing dyes have also found application as fluorescent probes in nucleic acid imaging, used in medical diagnostics and are also applied in food and cosmetics.[11] Other examples include amisulbrom **1-11** which is used as a fungicide while etoladac **1-12**, which has found application as a veterinary drug, is administered as a nonsteroidal anti-inflammatory drug for treating dogs with osteoarthritis, hip dysplasia and other joint diseases.[11] Furthermore, melatonin **1-13** is one of the few drugs that found application in both animal health and human medicine. In animals **1-13** is used to treat dogs that are sensitive to loud noises and is used to treat sleep disorders and the reduction of jet lag in humans.[11] Tryptophan **1-14** is known as one of the essential amino acids and also acts as a precursor to the synthesis of serotonin, melatonin and niacin which play a very important role in animals. Indole-3-carbinol **1-15** found mainly in cruciferous vegetables, is sold over-the-counter as a supplement and is

believed to modulate cancer-causing estrogen metabolites[36] (**Figure 3**). These are some of the few indole-containing compounds explored and more indole-containing compounds continue to find application in medicinal chemistry.[12]

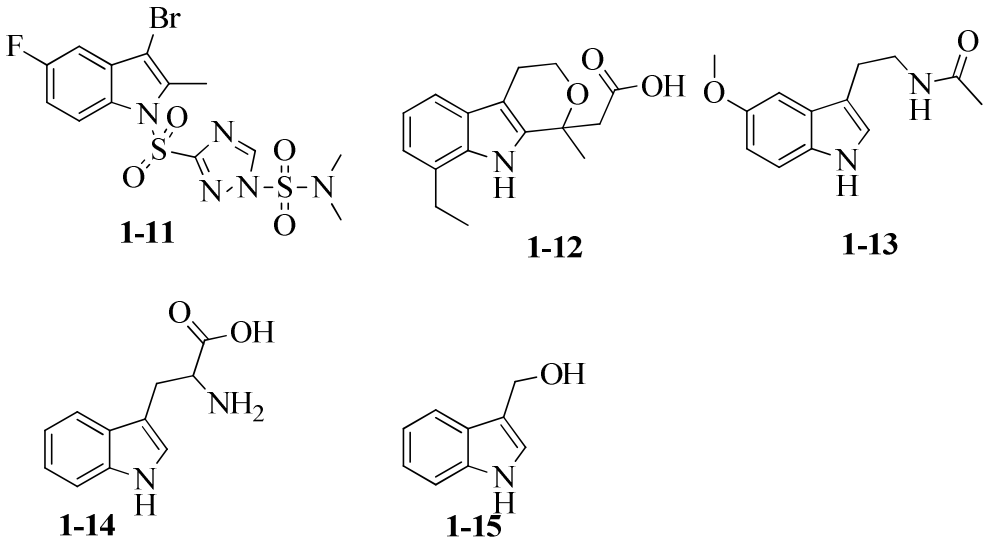


Figure 3

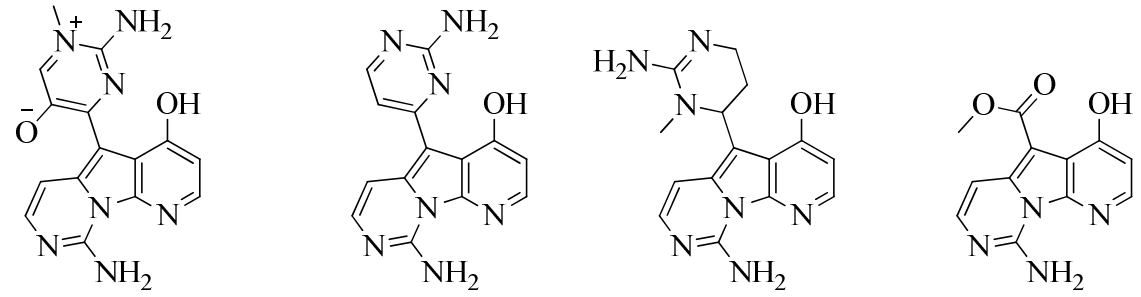
As a result of the wide applications and importance of indole-containing compounds, for the purpose of this PhD we turned our attention to the azaindoles, also known as indole isosteres for compounds with potentially improved medicinal and other properties. The adoption of an extra nitrogen atom on the benzene ring of the indole replaces the carbon atom to form the azaindoles and results in the formation of compounds with different physical and chemical properties compared to indoles. In the paragraphs to follow, azaindoles, their properties and their preparations will be explored in greater detail.

1.2 Azaindoles

Although the natural occurrences of azaindoles are scarce compared to indoles, a few naturally occurring azaindole-containing compounds have been isolated. A good example is the variolins. The variolins are a group of alkaloids that were isolated from the Antarctic sponge *Kirkpatrickia*

varialosa.[13] These variolins (A – D) possess a fused tricyclic heteroaromatic core, also known as a pyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine and possesses different of substituents at the C-5 position. The type of substituent at this position represents a different variolin. For example, variolin A (**1-16**) consists of 2-amino-1-methylpyrimidin-1-ium-5-olate functionality at the C-5 position while variolin B (**1-17**) contains a pyrimidin-2-amine group at the C-5 position (**Figure 4**). Variolins C (**1-18**) and D (**1-19**) (**Figure 4**) were also isolated together with variolins A and B and as outlined above, they posses different substituents at C-5.

The variolins were also found to possess antiviral, antibacterial and antifungal activity. Of the discussed variolins, variolin B (**1-17**) was the most studied due to its biological activity. In adition to the antiviral activity shown by variolin B, it also had an IC_{50} value of 210 ng/ml against the P388 murine leukemia cell line.[13, 14] As a result; synthetic methods have been devised for the synthesis of variolin B and its derivatives including other variolin analogues such as the meridianins and meriolins.[14]



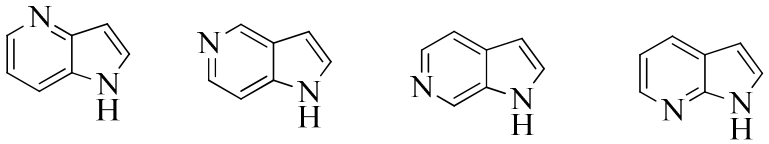
Variolin A (**1-16**) | Variolin B (**1-17**) | Variolin C (**1-18**) | Variolin D (**1-19**)

Figure 4

Even though the azaindoles lacked natural abundance, they have fueled considerable synthetic interest as indole bioisosteres[15] in which the adoption of an additional nitrogen atom in the aromatic ring confers unique properties to the azaindoles.[16] Owing to the natural unavailability of azaindoles, most azaindoles have been prepared traditionally by classical methods such as Fischer, Madelung and Reissert procedures.[16] The interesting properties displayed by azaindoles make them attractive compounds to the research chemists. For example, the combination of

azaindoles with oligothiophenes display unique electronic and optical properties and could find application in several fields such as field-effect transistors, organic light-emitting diodes (OLEDs) or photocopiers.[17] Azaindoles also form luminescent[18] organometallic compounds when complexed with metals such as zinc, boron and beryllium. These types of complexes are particularly useful in electroluminescent displays due to their high stability.[19] They have also showed an increased fluorescence intensity as compared to indoles.[7]

Figure 5 below shows the different structural types of azaindoles, 4-azaindole (**1-20**), 5-azaindole (**1-21**), 6-azaindole (**1-22**) and 7-azaindole (**1-23**) where often the difference in properties is influenced by the position of nitrogen atom in the pyridine ring of the azaindoles. In the following section the properties and synthesis of two of these azaindoles will be discussed.



1-20 **1-21** **1-22** **1-23**

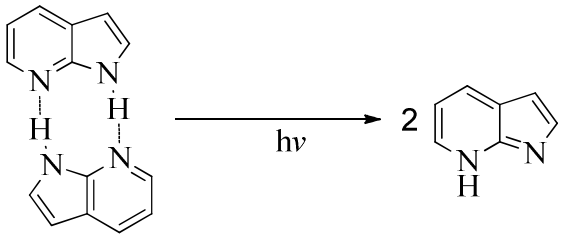
Figure 5

1.2.1 Properties and Synthesis of 7-Azaindoles

1.2.1.1 Properties of 7-azaindoles

One of the more common azaindoles, 7-azaindole (also known as pyrrolo[1,2-*b*]pyridine) was first reported by Perkin.[20] Later 7-azaindole was obtained from coal tar by Kruber, who also managed to prepare derivatives and obtained evidence for the constitution of the compound by oxidation of its benzenesulfonamide to 2-benzenesulfonamido-nicotinic acid and conversion of the latter into the known 2-aminonicotinic acid.[21] The 7-azaindole (**1-23**) contains one nitrogen atom in the five-membered pyrrole ring and one nitrogen atom in the six-membered pyridine ring where the two rings are fused to afford the title compound. Some theoretical studies have been performed on 7-azaindoles and it was found that the pyridine ring acted as a π and σ-acceptor while the pyrrole ring acted as a π donor and σ-acceptor. Fluorescence spectroscopic studies

found that the proton transfer reactions took place at room temperature, leading to tautomers of 7-azaindole (**1-23**) (**Scheme 2**) that were very rapidly formed and no dimeric emissions could be observed. However, when the temperature was lowered, the emissions from the dimer were observed when the 7-azaindole dimer **1-24** gave the 7-azaindole isomer **1-25**.[15]

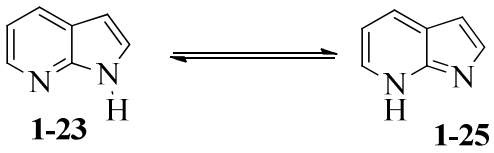


1-24 **1-25**

Scheme 2

7-Azaindoles are usually compared to indoles but there are some differences in their physical and chemical properties. For example, 7-azindoles are stronger bases than indoles with *p*Ka of 4.59 for azaindole **1-23** and this is influenced by the involvement in the condensed bicyclic system of two nitrogen heteroaromatic rings with opposite electron properties.[15] It was found that the excited state double proton transfer of 7-azaindole (**1-23**) occurs well in hydrocarbons and alcohol solvents through the formation of hydrogen-bonded dimers and solute/solvent interactions respectively. This resulted in the observation of two fluorescence bands in alcohols and concentrated hydrocarbon solutions at room temperature. On the other hand, the spectroscopic behavior of azaindole **1-23** in water was different to the one in alcohols and hydrocarbons, showing only one fluorescence band and this could be attributed to the unique properties of 7-azaindoles in water, their acidity which leads to one water molecule accommodating as many as four hydrogen bonds and hence water behaves distinctly different from alcohols and hydrocarbons.[22] It was also found that the fluorescence of 7-azaindole was relatively weak due to dimer formation which in turn caused double proton transfer in the excited state. Methylation of *N*-1 nitrogen prevented the dimer formation, and increased the fluorescence significantly.[23]

The study of hydrogen bonding is of great importance due to the importance of hydrogen bonding in chemistry and biology. The dimer **1-24** of 7-azaindole shown in **Scheme 2** is recognized as a simple model for the hydrogen-bonded base pair of DNA and could provide information on the possible role of tautomerism in mutations.[24] Because 7-azaindole contains two nitrogens on two different rings, the reactivity of either nitrogen would depend on site selectivity which in turn would depend on the reaction conditions. Studies showed that 7-azaindole exists as a tautomer as shown in **Scheme 3**, but the most dominant form is 7-azaindole (**1-23**).[25] For example, under vigorous conditions, one gets proton exchange which results in dialkylation on both nitrogens. Subsequent dealkylation leads to equilibrium with the consequent preferential formation of the pyrrole *N*-alkylated product. In contrast, the alkylation of the corresponding anionic systems under mild alkaline conditions occurs smoothly at room temperature, mostly favouring the pyrrole *N*-alkylation.[25]



1-23 **1-25**

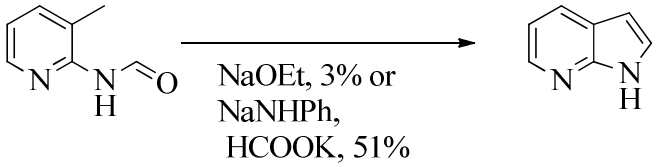
Scheme 3

1.2.1.2 Synthesis of 7-azaindoles

7-Azaindoles have been the target of extensive synthetic efforts as a result of their potent biological activities[15] and are usually exploited as bioisosteres of indoles in the design of biologically interesting molecules. They have also found application in material synthesis and coordination chemistry. The synthesis of azaindoles presents a unique challenge. For example, a frequently employed strategy for the synthesis of azaindoles is to start with substituted pyridines and build up a pyrrole ring, but the electron-deficient nature of the pyridine ring makes it difficult for the most classical methods for the preparation of indole to be used.[26]

The classical indole synthetic methods such as the Madelung or the Fischer synthesis are often limited due to their narrow scope[15]. For example, the use of harsh conditions in the Madelung synthesis precludes the survival of most of the functional groups and resulted in poor yields;

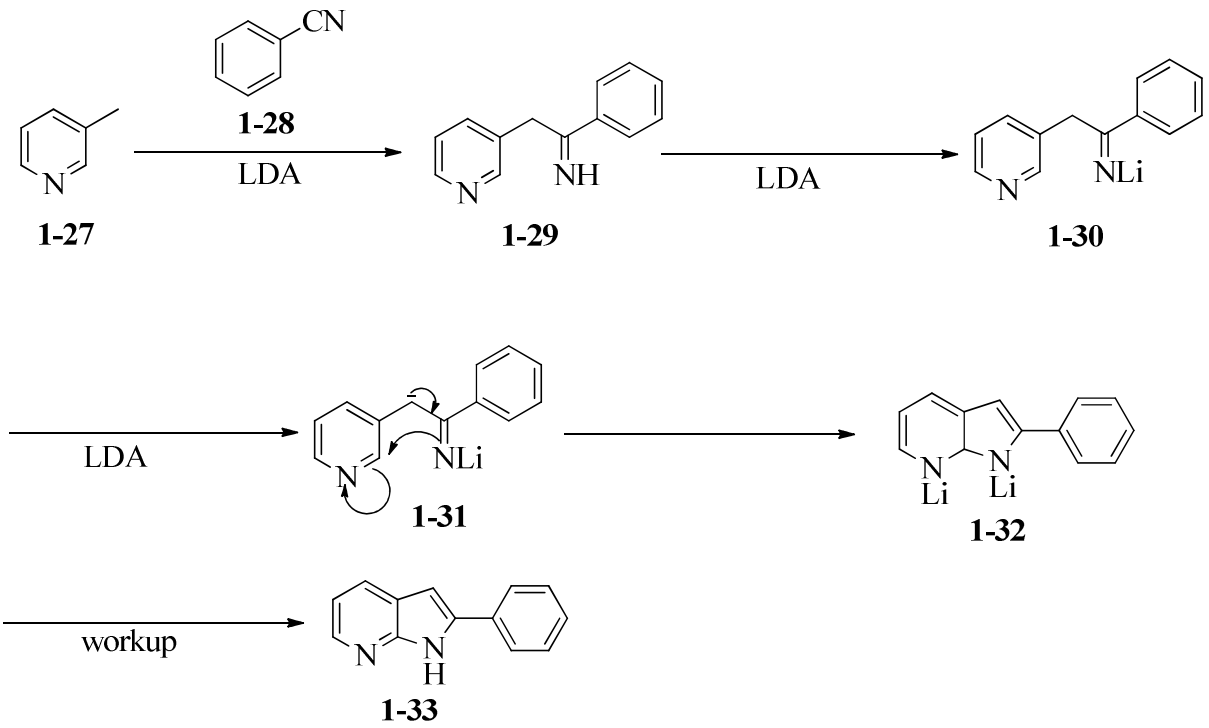
while the cyclization reaction of pyridylhydrazones corresponding to the Fischer type reaction usually affords products in low yields.[27] Early methods used to synthesize 7-azaindoles include the use of the Madelung synthesis whereby 2-formamido-3-picoline (**1-26**) was treated with sodium ethoxide and afforded 7-azaindole (**1-23**) but in very poor yield of 3% (**Scheme 4**). It was found that by changing sodium ethoxide to sodium anilide in the presence of potassium formate, azaindole **1-23** was isolated in moderate yields of up to 51%.[21]



1-26 **1-23**

Scheme 4

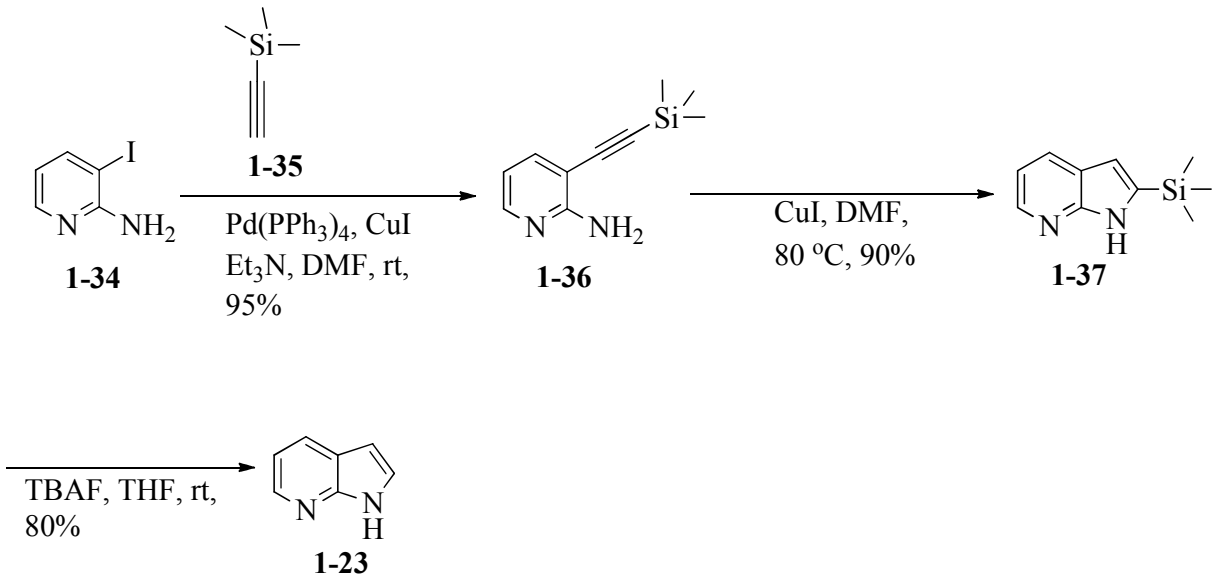
Another method for the synthesis of 7-azaindoles includes starting from β-picoline (**1-27**). The methyl group is weakly acidic and can be deprotonated by lithium diispropylamide (LDA) and subsequently treated with electrophiles[28]. For example, treatment of β-picoline (**1-27**) with benzonitrile (**1-28**) in the presence of LDA results in the formation of 1-phenyl-2-(pyridin-3-yl)ethanimine (**1-29**). Further treatment of **1-29** with LDA gave an intermediate **1-30** which was treated with an excess LDA to yield an intermediate **1-31** which was cyclized to dilithio-7-azaindole **1-32**, which upon workup gave 2-phenyl-7-azaindole (**1-33**) in good yields of about 90% (**Scheme 5**). The higher yields of up to 90% were achieved by using an excess of LDA. The workup involved the elimination of lithium hydride.[28]



Scheme 5

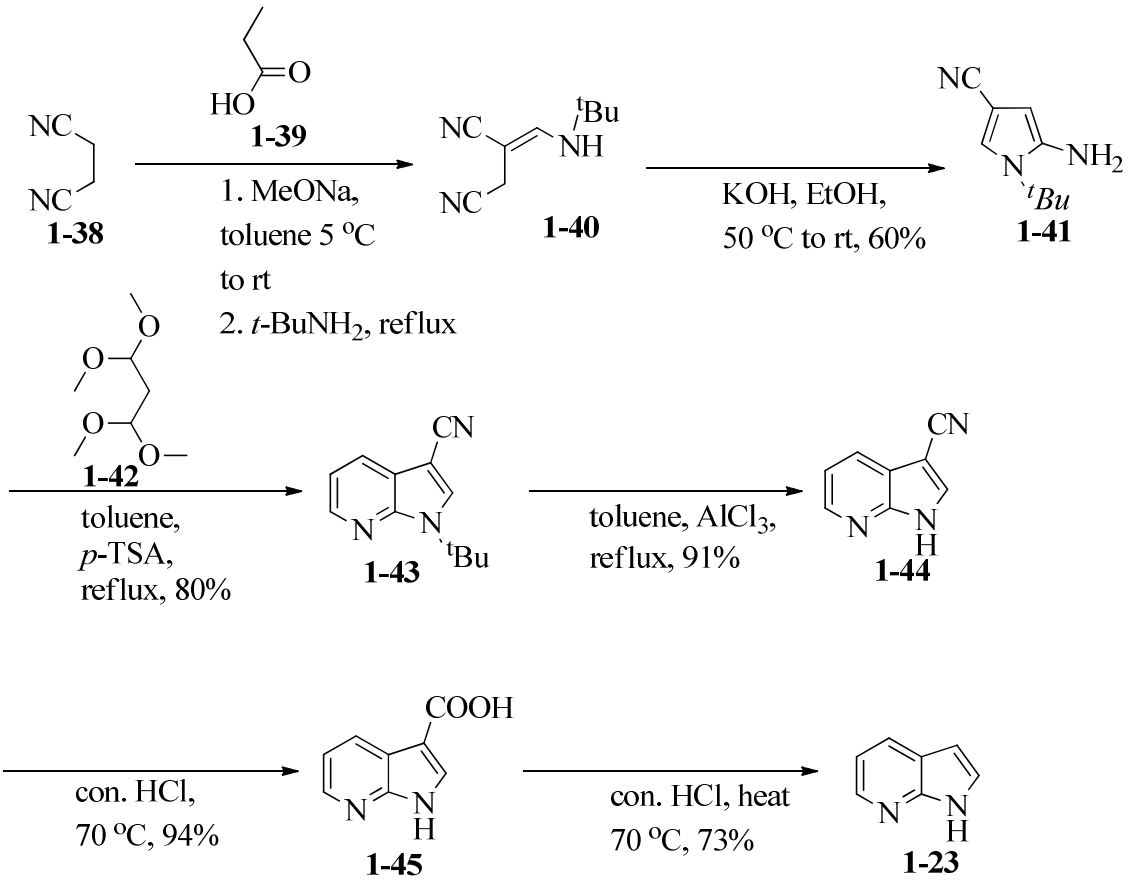
The recent advances in organometallic chemistry directed towards synthetic organic chemistry have paved the way for the assembly and functionalization of 7-azindoles, particularly with regard to the use of transition metals and directed *ortho* lithiation chemistry. This is because these methods have a broader substrate scope and offer better synthetic efficiencies. One of the most used transition metals in synthesis is palladium in the form of a catalyst, and it has been employed extensively in the synthesis of indoles. There are a variety of methods using palladium for the synthesis of 7-azaindoles. One such method uses Sonogashira reaction conditions starting from aminohalopyridines and terminal alkynes followed intramolecular cyclization, whereas other reactions with internal alkynes and aminohalopyridines proceed through the annulation pathway. When compared to the traditional Madelung synthesis, this type of reaction produces 7-azaindoles in fair to high yields. For example, starting from 2-amino-3-iodopyridine (**1-34**) in the presence of the palladium catalyst and copper(I) iodide and triethylamine as a base, and with trimethylsilylacetylene (**1-35**) as a source for the alkyne, 2-amino-3-(2-trimethylsilylethynyl)pyridine (**1-36**) was obtained in 95% yield (**Scheme 6**). The subsequent copper(I) iodide catalyzed cyclization in dimethylformamide at about 80 °C afforded 2-

substituted 7-azaindole **1-37** in good yield of 90% and the trimethylsilyl group could easily be removed to give 7-azaindole (**1-23**) (**Scheme 6**).[26]



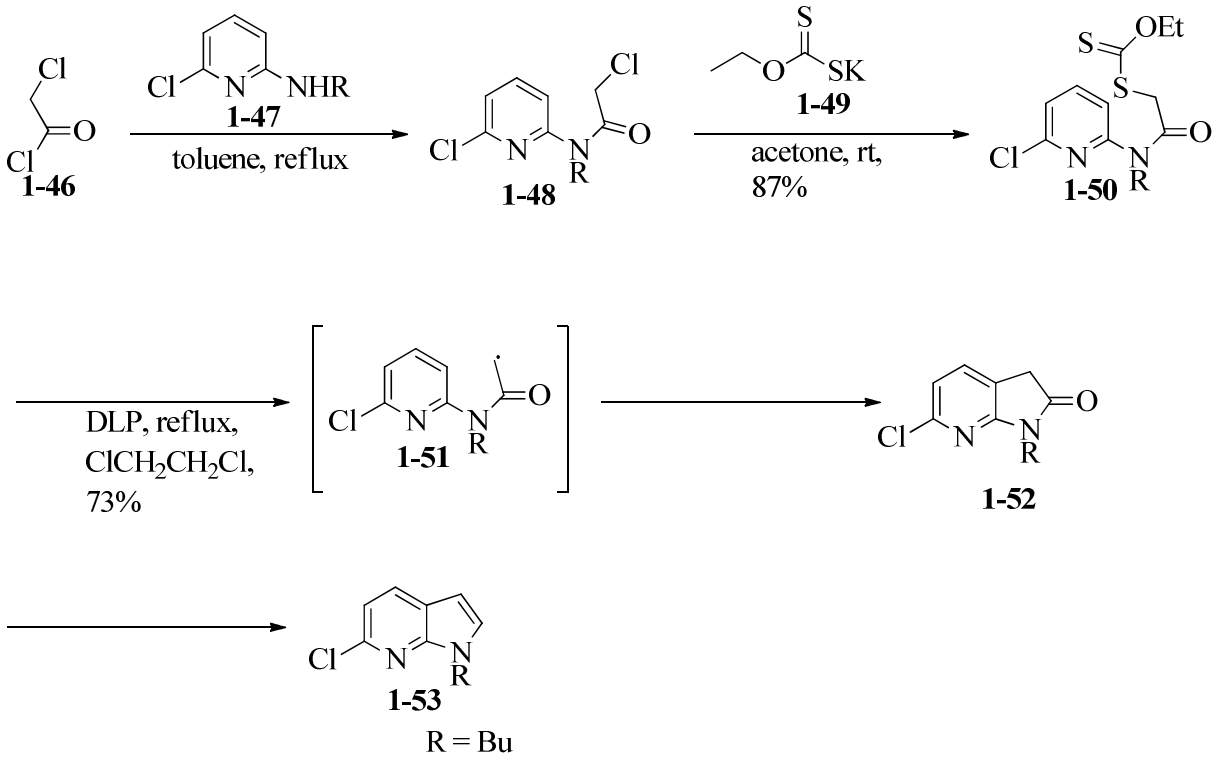
Scheme 6

While many methods for the synthesis of 7-azaindoles usually start with substituted pyridines, only few methods are available which start with the construction of the pyrrole ring first followed by the formation of the pyridine ring. Recently an optimized cost-effective method for the synthesis of 7-azaindoles was discovered as a convenient route to 7-azaindoles. For example, inexpensive propionic acid (**1-38**) and succinonitrile (**1-39**) were condensed in the presence of sodium methoxide and *tert*-butylamine to give the corresponding (*E*)-2-[(*tert*-butylamino)methylene]succinonitrile (**1-40**) (**Scheme 7**). Treatment of nitrile **1-40** with a base led to the formation of 2-amino-1-*tert*-butyl-1*H*-pyrrole-4-carbonitrile (**1-41**) which was further reacted with 1,1,3,3-tetramethoxypropane (**1-42**) in the presence of a catalytic amount of *p*-toluenesulfonic acid to give cyclized substituted 7-azaindole **1-43** in good yield. The *ter*t-butyl group was removed using aluminum(III) chloride to afford 3-cyano-7-azaindole (**1-44**) and acidic hydrolysis of 7-azaindole **1-44** led to 7-azaindole-3-carboxylic acid (**1-45**), which was easily converted into 7-azaindole (**1-23**) by heating under reflux with concentrated hydrochloric acid[29] (**Scheme 7**).



Scheme 7

While the synthesis of 7-azaindoles has enjoyed a relatively broad scope of methodologies, radical cyclization reactions have been rarely applied. However, a radical cyclization reaction on the pyridine has appeared to be a possible method towards 7-azaindoles and their derivatives.[30] Reaction of 2-chloroacetyl chloride (**1-46**) with 2-alkylamino-6-chloropyridine (**1-47**) gave the amide **1-48** which was further reacted with potassium-*O*-ethyldithiocarbonate (**1-49**) to give the xanthate derivative **1-50** (**Scheme 8**). The xanthate-mediated radical cyclization was chosen due to its numerous advantages including experimental simplicity, the absence of heavy or toxic metals as well as functional group compatibility. The xanthate derivative **1-50** was then refluxed in dichloromethane and in the presence of lauroyl peroxide (DLP) and this resulted in the formation of radical intermediate **1-51** which cyclized to form azaindole **1-52** in 73% yield[29] which could then be converted into substituted 7-azaindole **1-53** (**Scheme 8**).[31]

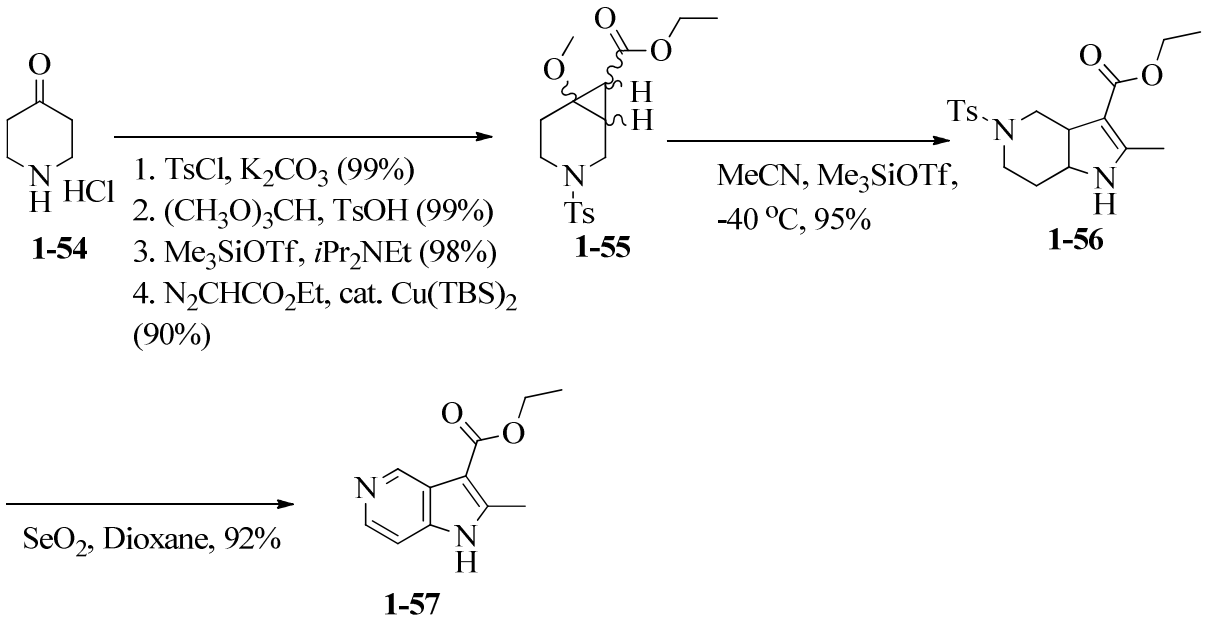


Scheme 8

1.2.2 Synthesis of 5-Azaindoles

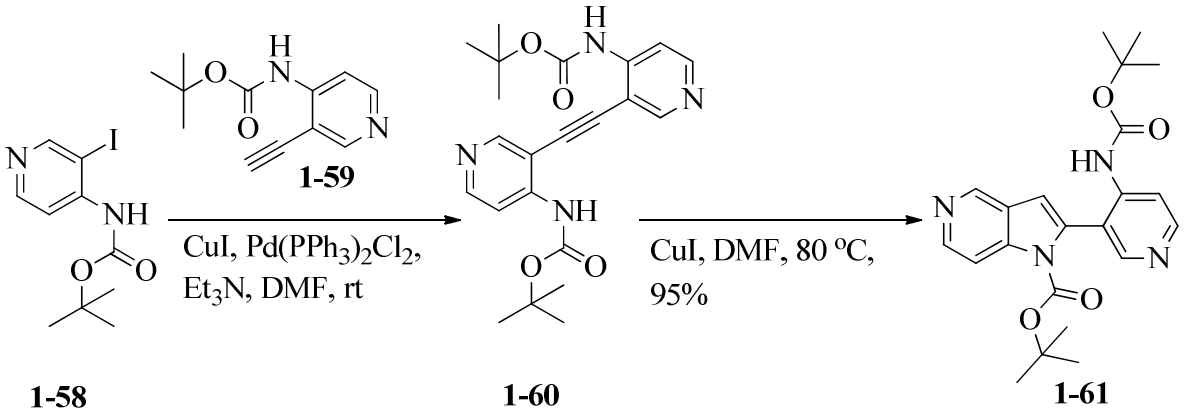
Although there are many synthetic methods to access indoles, only a few methods are available for the preparation of the 5-azaindoles. To address this shortage, Moustafa *et al*. devised the synthesis of 5-azaindole derivatives from cyclopropanes and nitriles (**Scheme 9**).[32] At the heart of this synthetic methodology is the ability of cyclopropanes to act as both electron donors and acceptors. Thus, 5-azaindole derivatives were prepared from cyclopropanes that were accessed from piperidin-4-ones. Hence, the hydrochloride salt of piperidin-4-one **1-54** was treated with tosyl chloride in the presence of potassium carbonate followed by treatment with acidic methanol to form an acetal. The resulting acetal was treated with trimethylsilyl triflate in the presence of di*iso*propylethylamine followed by treatment with ethyl diazoacetate in the presence of a copper catalyst to give the desired cyclopropane **1-55** as a mixture of diastereomers. Treatment of cyclopropane **1-55** with acetonitrile in the presence of trimethylsilyl triflate at -40 °C resulted in the formation of the tetrahydropyrrolopyridine **1-56** in 95% yield, which was easily oxidized

using selenium oxide and the 5-azaindole derivative **1-57** was isolated in 92% yield (**Scheme 9**).[32]



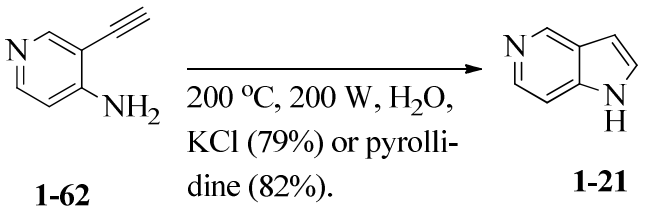
Scheme 9

The Sonogashira coupling reaction has also enjoyed a wide application in the preparation of 5-azaindole derivatives and azaindoles in general.[33] Taking advantage of the wide applications and functional group tolerance[34] of this methodology, Xu and co-workers reported the use of this methodology using transition metals to access 5-azaindole derivatives. This was achieved by treating Boc-protected-3-iodo-4-aminopyridine **1-58** with a terminal alkyne **1-59** in the presence of copper(I) iodide, triethylamine as a base and a palladium catalyst to give an internal alkyne **1-60** in quantitative yield (**Scheme 10**). Further treatment of internal alkyne **1-60** with mercury(II) salts failed to produce the desired 5-azaindole derivative **1-61** instead returning the starting material. However, replacing mercury(II) salts with copper(I) iodide in DMF at 80 °C saw 5-azaindole **1-61** isolated in 95% yield (**Scheme 10**).[35]



Scheme 10

Carpita and co-workers[36] recently reported the use of microwave reaction conditions in conjunction with a Sonogashira coupling reaction to access a variety of indole and azaindole derivatives in moderate to high yields. Remarkably, the reactions in this case were performed in water as a solvent and neutral simple salts such as potassium chloride were used to facilitate the ring closing reactions. In addition to using simple neutral salts, readily available nitrogen-containing neutral bases such as triethylamine, pyridine and others were also examined for their ability to produce indoles and azaindoles from the corresponding Sonogashira products. Indeed, when internal alkyne **1-62** was irradiated with microwaves (200 W, 200 °C) in the presence of potassium chloride, 5-azaindole (**1-21**) was isolated in good yield of 79%. When potassium chloride was replaced with pyrrolidine as a base, 5-azaindole (**1-21**) was isolated in a slightly increased yield of 82% (**Scheme 11**).[36] For a comprehensive review of the synthesis and funtionalization of azaindoles using organometallic reagents, see Song *et al*.[26]



Scheme 11

1.3 Aims of this PhD project

In this PhD project we wished to develop new methodology to gain access to various functionalized 5-azaindoles and 7-azaindoles. At the centre of this PhD project is the application of the Sonogashira coupling reaction on aminopyridines on which all parts of this project are based. The project is divided into five parts with each part dealing with the synthesis and characterization of a range of azaindole derivatives.

The first part of this project dealt with the synthesis of pyridopyrrolizine derivatives **1-63** (**Figure 6**) and our attempts at the synthesis of 7-azaindolo-fused pyrans. The application of the Sonogashira coupling in combination with ring closing metathesis led to the successful synthesis of pyridopyrrolizines **1-63**.

The second part of the project dealt with the synthesis of 2,5-disubstituted-7-azaindole derivatives **1-64** (**Figure 6**) with special interest in adding a triazole functionality at the 5-position of the 7-azaindole nucleus. This part of the project saw the application of the Sonogashira coupling reaction followed by ring closing reaction to form 7-azaindole derivatives which were further functionalized under the azide Click reaction conditions to furnish the desired triazole derivatives **1-64**.

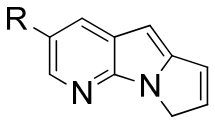
The third part of this project involved the synthesis of 5-azaindole-phosphonic acid derivatives **1-65** (**Figure 6**). The use of the Sonogashira coupling reaction followed by a base mediated ring closure gave 5-azaindoles. These azaindoles were functionalized to yield the desired phosphonic acid derivatives.

In part four of the project we used the Sonogashira coupling in conjunction with the Cacchi reaction followed by the oxidation of the internal alkyne to gain access to 2,3,5-trisubstituted-7-azaindoles **1-66** (**Figure 6**) for this PhD project.

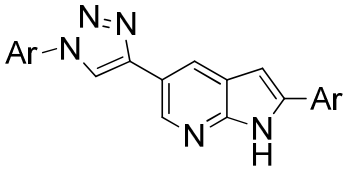
Finally, the use of the Sonogashira coupling reaction on halogenated aminopyridines followed by treatment of the resulting products with trifluoroacetic acid and trifluoroacetic anhydride at high

temperatures resulted in the formation of 2-substituted-7-azaindole derivatives **1-67** (**Figure 6**) which formed part five of this PhD project.

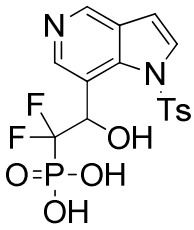
All the resulting 5-azaindole and 7-azaindole derivatives will or have been screened for biological activity against various pathogens, HIV and cancer cell lines but did not form a major thrust of this PhD thesis. The last chapter of the PhD outlines some of the antibacterial and antifungal activity of selected azaindoles.



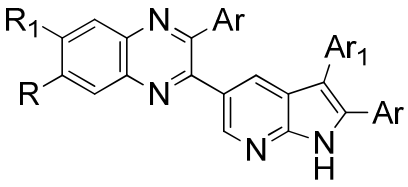
Pyridopyrrolizines **1-63**



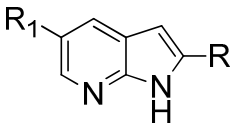
2,5-Disubstituted-7-azaindoles **1-64**



5-Azaindole-phosphonic acid **1-65**



2,3,5-Trisubstituted-7-azaindoles **1-66**



2-Substituted-7-azaindoles **1-67**

Figure 6

1.4 References

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Chapter 2: Synthesis of 6*H*-pyrido[3,2-*b*]pyrrolizines

2.1 Synthesis and properties of pyrroloindoles

2.1.1 Introduction

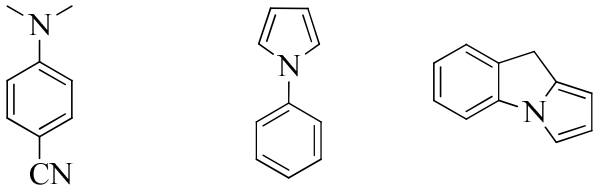
One of our interests lies in the condensed pyrroloindole framework which shares similar chemical properties to 6*H*-pyrido[3,2-*b*]pyrrolizines or simply pyrrolo-7-azaindoles which are the subject of investigation in this chapter. In the first part of this chapter we will be exploring the reported methods for the synthesis of pyrroloindoles in the coming paragraphs as well as highlighting some of the biological properties of these compounds. This will then be followed by our research towards the synthesis of this molecular framework.

2.1.2 Properties of pyrroloindoles

2.1.2.1 Electroluminescent properties

Molecules such as *N*,*N*-dimethyl-4-aminobenzonitrile (**2-1**) and *N*-phenylpyrrole (**2-2**) (Figure 1), which have the ability to act as both electron donors and electron acceptors, are also able to emit fluorescence from two relaxed singlet excited states. Photoexcitation leads to the formation of a locally excited state from which an intramolecular charge transfer state with larger dipole moment is formed.[1,2] For example, with *N*,*N*-dimethyl-4-aminobenzonitrile (**2-1**), the dipole moment increased from 6.6 D in the electronic ground state through 10 D in the low excited state to 17 D in the intramolecular charge transfer state[3] and *N*-phenypyrrole follows the same pattern.[4] Following the successful study of electronic properties of *N*-phenylpyrroles, Yoshihara and co-workers turned their attention to pyrroloindoles, in particular pyrroloindole **2-3** (Figure 1). The fluorescence spectrum of pyrroloindole **2-3** in acetonitrile at -45 °C consisted of two well-separated bands consistent with the low excited state and intramolecular charge transfer

state previously measured for *N*-phenylpyrrole. It was also found that the band intensity was solvent dependent, with polar solvents showing increased intensity and non-polar solvents showing decreased intensity. However, it should be noted that non-polar solvents decreased the intensity of the intramolecular charge transfer state while the low excited state remained unaffected. The dipole moment observed for pyrroloindole **2-3** was 1 D for the low excited state and 13 D for the intramolecular charge transfer state.[5] Apart from showing electroluminescent properties, pyrroloindoles and related compounds also exhibit a wide range of biological properties as will be explained in the next section.

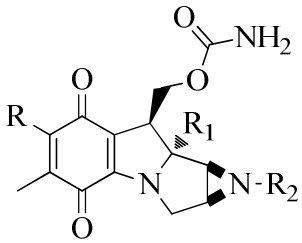


2-1 **2-2** **2-3**

Figure 1

2.1.2.2 Biological importance of pyrroloindoles

The mitomycins are a group of potent antibiotics that belong to the family of antitumour quinones isolated from *Streptomyces caespitosus*, *Streptomyces ardus* and *Streptomyces verticillatus*. These metabolites have attracted much attention due to their biological properties. This group of compounds contains a dense set of functional groups such as a quinone, an aziridine and a carbamate which are arranged in a compact structure on a pyrroloindole nucleus. Of particular interest here are mitomycins A (**2-4**), B (**2-5**) and C (**2-6**) (**Figure 2**). Among these compounds, mitomycin A (**2-4**) was found to posses good activity towards solid tumours and was also less toxic than mitomycins B (**2-5**) and C (**2-6**). Although all three compounds were active against solid tumours, mitomycin A's effectiveness and lower toxicity was linked to its ability to cross-link the DNA with higher efficiency and specificity than B and C.[6]



Mitomycins A (**2-4**) R = NH_2, R_1 = OMe, R_2 = H

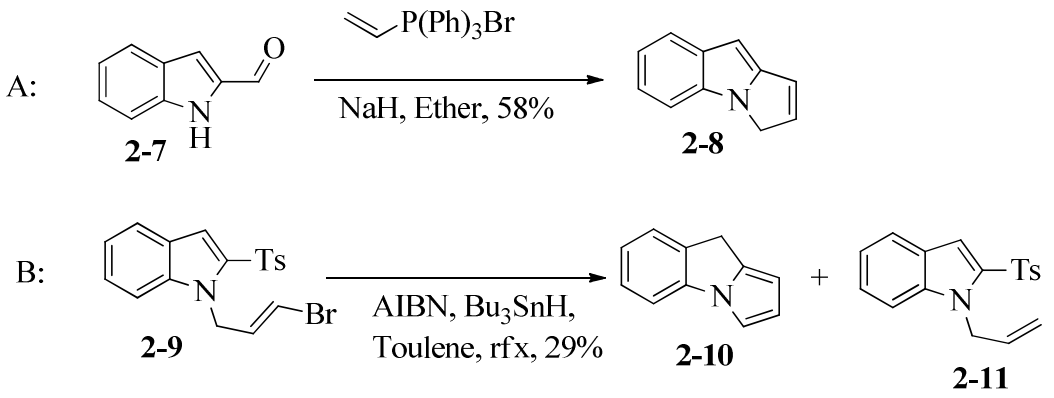
B (**2-5**) R = OMe, R_1 = OMe, R_2 = H

C (**2-6**) R = OMe, R_1 = OH, R_2 = Me

Figure 2

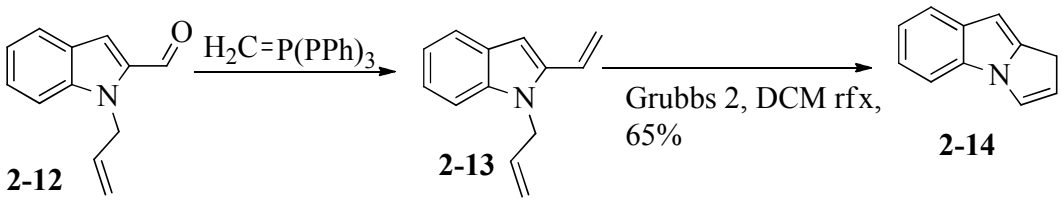
2.1.3 Reported synthesis of pyrroloindoles

The synthesis of simple pyrroloindole-related compounds, not including the mitomycins, can be traced back to the 1960s. In 1966, Schweizer and Light demonstrated the use of vinyltriphenylphosphonium bromide in the synthesis of this class of compounds. Thus, when 2-formylindole (**2-7**) was treated with vinyltriphenylphosphonium bromide salt in the presence of sodium hydride in diethyl ether, pyrroloindole **2-8** was isolated in 58% yield after heating the reaction mixture at reflux for 24 hours (**Scheme 1**).[7] Some 30 years later, the team of Caddick, Aboutayab, Jenkins and West reported the synthesis of pyrroloindoles from 2-tosylindoles using radical chemistry. The treatment of *N*-alkylated 2-tosylindole **2-9** with tributyltin hydride in the presence of AIBN in refluxing toluene afforded pyrroloindole **2-10** in 29% yield, unfortunately as a 1:1 inseparable mixture with **2-11** also being produced (**Scheme 1**). As observed, product **2-10** was not the expected product and it was suggested that it may have been formed *via* 1,5-sigmatropic rearrangement of the initially expected product. Unfortunately, further efforts to improve the yield of the desired product did not materialize.[8]



Scheme 1

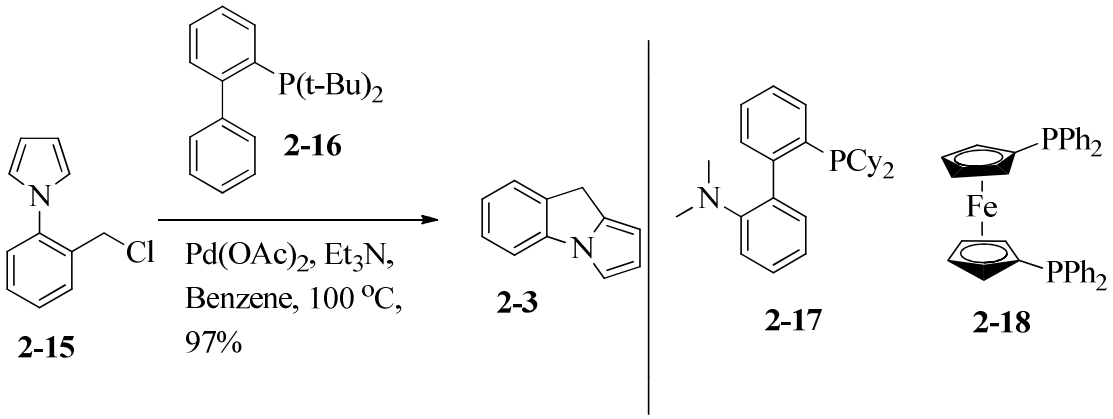
With the yields of the two reactions in **Schemes 1** above disappointing, there was a need for new approaches to these compounds. The use of transition metals in organic chemistry has proved to be beneficial, especially in terms of improved yields.[9] One of the most important recently developed synthetic methods is ring closing metathesis (RCM).[10,11] González-Pérez *et al*. took advantage of the mild reaction conditions of ring closing metathesis to access pyrroloindoles. Thus, 1-allyl-2-vinyindole (**2-13**), which was prepared by treating 1-allyl-2-formylindole (**2-12**) with methylenetriphenylphosphorane under Wittig reaction conditions and used in *situ* due to its instability, was treated with Grubbs 2nd generation catalyst in refluxing dichloromethane to give pyrroloindole **2-14** in a slightly improved yield of 65% due to 1,3-sigmatropic H shift of the allyl group(**Scheme 2**).[12]



Scheme 2

One of the topical important reactions using transition metals is C-H activation reactions. Knochel and Ren demonstrated the use of a palladium catalyzed intramolecular C-H activation reaction in the synthesis of pyrroloindole from 1-(2-bromophenyl)-2,5-dimethyl-1*H*-pyrrole in relatively good yield.[13] Encouraged by results obtained by Knochel, Hwang and co-workers took

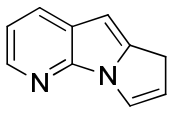
advantage of this methodology in the synthesis of pyrroloindoles. Hence, when 1-[(2-(chloromethyl)phenyl)]-1*H*-pyrrole (**2-15**) was treated with catalytic palladium diacetate in the presence of triethylamine and phosphine ligand **2-16**, pyrroloindole **2-3** was obtained in 97% yield (**Scheme 3**). Furthermore, they have demonstrated that other ligands such **2-17** and **2-18** could achieve the desired pyrroloindole in moderate yields.[14]



Scheme 3

2.2 Chemistry

As the pyrroloindole skeleton occupies an important place in chemistry, we wondered if the synthesis of related pyrroloazaindole **2-50** (**Fugure 3**) could be assembled. In this PhD as will be detailed in the following paragraphs, we have successfully managed to synthesize the desired precursors towards the synthesis of pyrroloazaindoles.

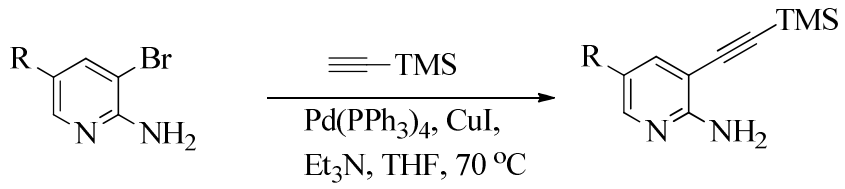


2-50

Figure 3

2.2.1 Synthesis of *bis*-*tert*-butyl-3-ethynylpyridin-2-yldicarbamates

The first step in our synthesis of pyrroloazaindoles was to perform a Sonogashira coupling reaction on aminopyridines **2-19** and **2-20** as this seemed the most logical way to assemble our target compounds.[15,16] This reaction involved the coupling between a terminal alkyne and an aromatic halide in the presence of copper(I) iodide, base and either palladium(0) or palladium(II) catalyst in a solvent such as THF, DMF or DMSO.[17] In our case, both **2-19** and **2-20** were treated with trimethylsilylacetylene in THF at reflux in the presence of $Pd(PPh_3)_4$, copper(I) iodide and triethylamine or any alkylamine as a base. It should also be noted that other bases like potassium carbonate, cesium carbonate and other metal-containing bases could also be used.[16] After 8 hours under a nitrogen atmosphere, the reaction mixture was worked up and purified using flash silica gel column chromatography to afford compounds **2-21** and **2-22** as cream white solids in 95% and 93% yield respectively (**Scheme 4**). Although these are known compounds,[18] ^{1}H NMR and ^{13}C NMR spectra were ran to verify the success of the reaction. When the ^{1}H NMR spectrum was examined, a distinctive signal at 0.032 ppm was found corresponding to the trimethylsilyl group due to **2-21** and **2-22**. Furthermore, examination of the ^{13}C NMR spectrum revealed the presence of a C-C triple bond with signals at around 98 and 83 ppm, in addition to the presence of a signal at around 0.060 ppm due to the trimethylsilyl group. Encouraged by these results, we proceeded to the next step, which involved protecting the amino substituent of the pyridine.



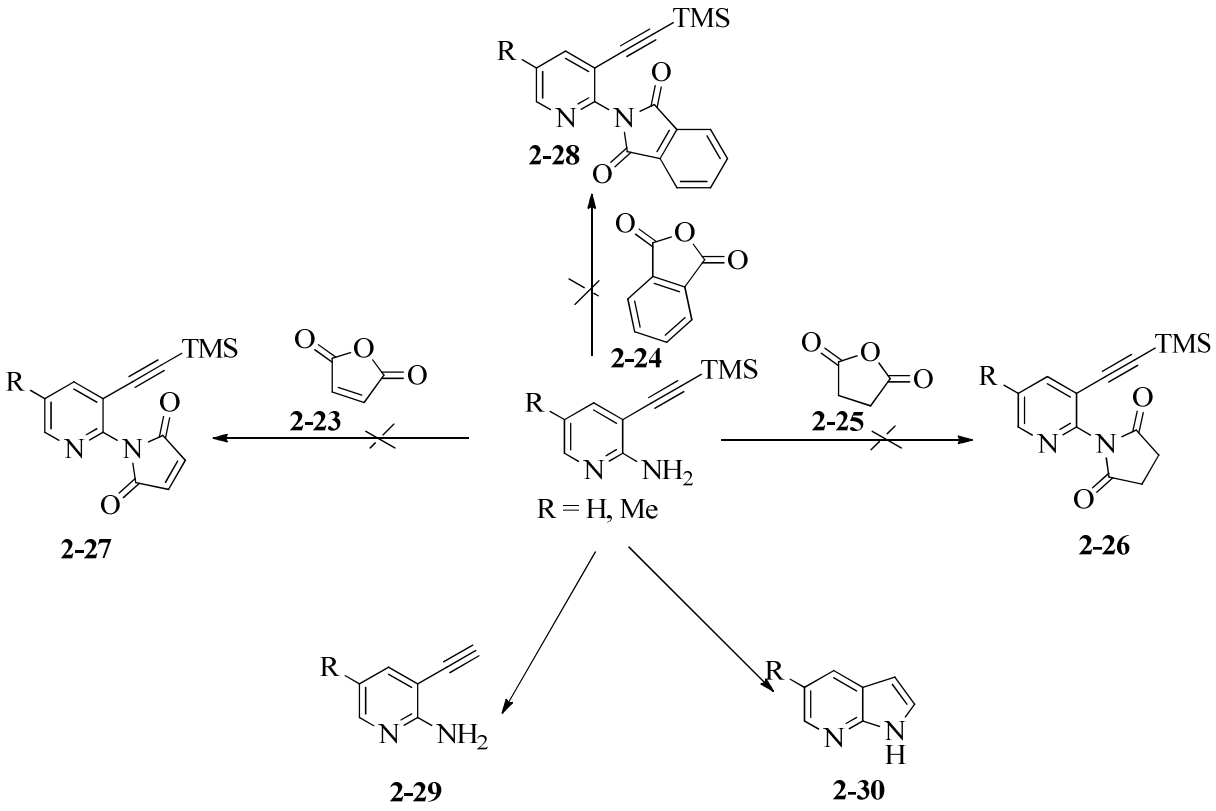
(**2-19**) R = H
(**2-20**) R = Me

(**2-21**) R = H (95%)
(**2-22**) R = Me (91%)

Scheme 4

The protection of aminopyridine substituent could be achieved using quite a variety of protecting groups but we also had to keep in mind the ease with which the group could be removed. Since we were looking to protect the primary amine group, the first protecting groups assessed were

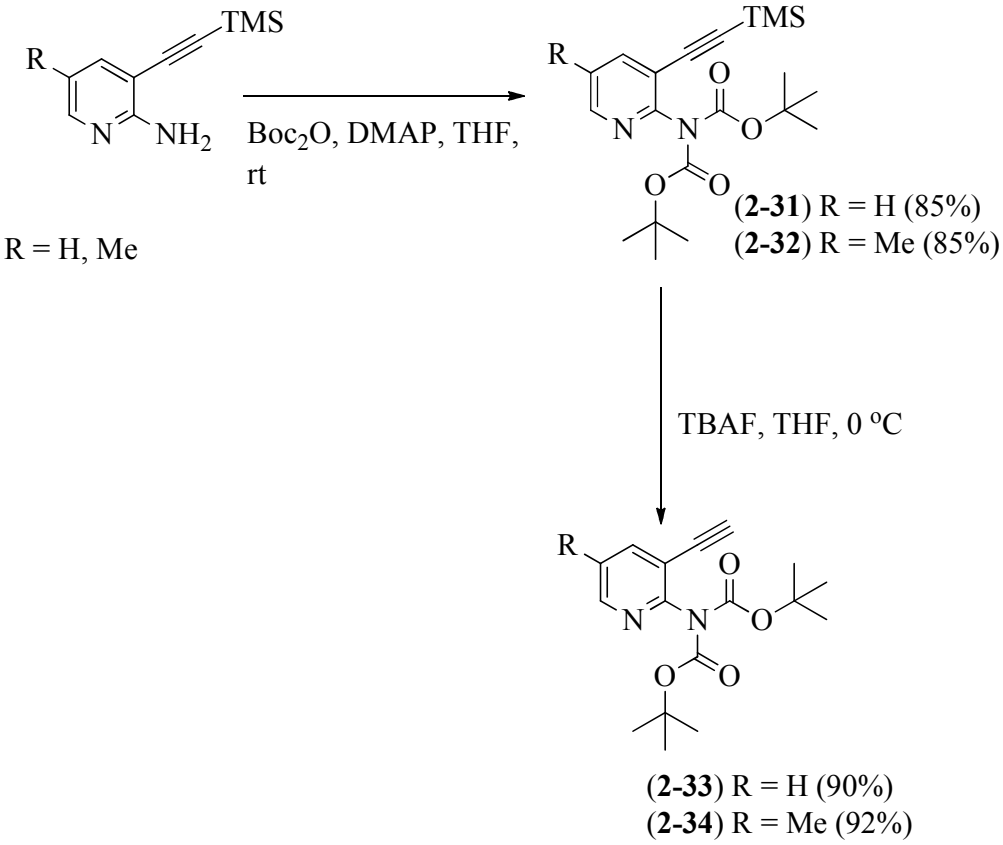
amine diprotecting groups. The diprotecting groups examined were succinic anhydride, maleic anhydride and phthalic anhydride. Thus, **2-21** and **2-22** were each treated with maleic anhydride (**2-23**) in the presence of sodium acetate in toluene,[19] phthalic anhydride (**2-24**) in refluxing acetic acid[20] and even succinic anhydride (**2-25**) in refluxing acetic acid[20] but the expected products **2-26**, **2-27** and **2-28** were not obtained (**Scheme 5**). Instead side products such as silyl deprotected alkyne **2-29** and 7-azaindole **2-30** were obtained in undetermined yields (**Scheme 5**). We then turned our attention to monoprotecting groups for amine groups with our focus again on a protecting group that could be easily removed as well as easily attached. Tosyl chloride and boc anhydride came to mind as versatile protecting groups that could be used. Although they are both easy to attach, it appeared that the boc protecting group was the easier of the two protecting groups to remove.[21]



Scheme 5

Thus, **2-21** and **2-22** were treated with Boc anhydride in the presence of a catalytic amount of 4-(dimethylamino)pyridine in THF for 16 hours.[22] To our surprise, we could not isolate mono-

protected products under these conditions as suggested[22] but only the diprotected products **2-31** and **2-32** (**Scheme 6**). We changed the solvent to dichloromethane with no change in the results. However, it was later discovered that if **2-21** and **2-22** were treated with boc anhydride in tertiary butyl alcohol at about 60 °C, the mono-protected product could be obtained in relatively good yield, although 7-azaindole **2-30** was also isolated under these conditions.[23] Since we originally wanted to protect the amino group, the protected compounds **2-31** and **2-32** could be utilized in our next synthetic step. The formation of the desired products was confirmed through NMR spectroscopic analysis that showed the disappearance of the NH_2 signal at about 5 ppm (2H) and the appearance of a new signal at about 1.4 ppm integrating for 18 protons due to the tertiary butyl groups. Furthermore, we analyzed the ^{13}C NMR spectrum which also showed new signals in addition to those of the starting materials. We observed signals at about 18 ppm and 81 ppm due to the tertiary butyl group and at 153 ppm due to a C=O group of the carbamate. The presence of a C=O group was also confirmed by infrared (IR) spectroscopy as a stretching band appearing around 1780 cm^{-1} as was the absence of a strong NH stretch which usually is evident above 3300 cm^{-1} was also noted. With these encouraging results, we sought to attempt the removal of the silyl protecting group to obtain expected terminal alkynes **2-33** and **2-34**. This was easily achieved by treating **2-31** and **2-32** with TBAF at 0 °C in dry THF under a nitrogen atmosphere for one hour.[24] The reaction mixture was quenched with water and extracted with ethyl acetate, dried over magnesium sulfate and excess solvent removed and the resulting mixture purified by flash chromatography to give **2-33** and **2-34** as cream white solids (**Scheme 6**). The most distinguishing feature in the ^1H NMR spectra of these compounds was the disappearance of the signal at 0.06 ppm due to the trimethylsilyl group and appearance of a new signal at about 3.5 ppm due to the proton on the the terminal alkyne. These results set the stage for the next reaction where the terminal alkyne would be coupled with allyl bromide in order to provide substrates that could be utilized to obtain the title compounds.



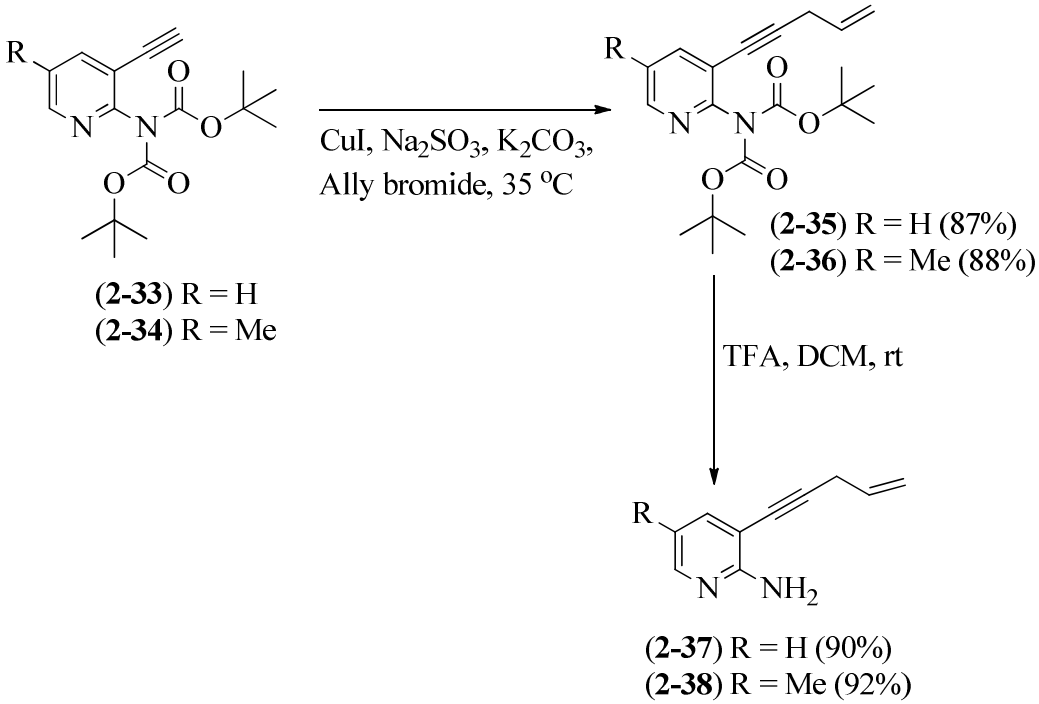
Scheme 6

2.2.2 Synthesis of 1,2-diallyl-1*H*-pyrrolo[2,3-*b*]pyridines

The coupling of a terminal alkyne with allyl bromide could be achieved in a number of ways which include the use of a Grignard reagent in conjunction with copper(I) iodide[25] and the use of *n*-butyllithium in conjunction with copper(I) bromide.[26] Other methods include using *n*-butyllithium in combination with zinc bromide and palladium catalyst[27] and using copper(I) iodide in combination with inorganic salts such as sodium carbonate and sodium sulfite with DBU as an additive,[28] amongst many other methods available. Of the four methods mentioned above, the Grignard reagent and *n*-butyllithium mediated methods have the ability to add to the Boc protecting group of compounds **2-33** and **2-34** and thus we decided to try the method using inorganic salts and DBU. Thus, **2-33** and **2-34** were dissolved separately in dry DMSO and treated with sodium sulfite, sodium carbonate, DBU and finally allyl bromide. The reaction mixture in each case was then heated to 35 °C for 24 hours. After quenching the reaction with

water, it was extracted with ethyl acetate, dried over magnesium sulfate, solvent was removed and purification by flash silica gel column chromatography for each of the reactions gave both **2-35** and **2-36** as brown oils (**Scheme 7**). This was confirmed primarily using ^{1}H NMR spectroscopy, where the terminal alkyne signal at about 3.5 ppm was no longer present. Also observed in the ^{1}H NMR spectra were the allyl group signals with the CH_2 signal found at around 3.2 ppm, an alkene CH found at around 5.8 ppm and finally the alkene CH_2 signals ranging from 5.16 to 5.37 ppm due to the nonequivalence of the two hydrogen atoms. With the coupling reaction successfully completed, the Boc protecting groups have served their purpose, which was to prevent the allyl group from reacting with the aminopyridine, and could now be removed.

The Boc protecting group could be easily cleaved by treatment with acid.[29] Hence, **2-35** and **2-36** were each dissolved in dichloromethane and the solutions were cooled in an ice/water mixture, followed by addition of trifluoroacetic acid. In each case, the reaction mixture was allowed to stir at room temperature for two hours. The dichloromethane and trifluoroacetic acid were removed and the resulting oil was re-dissolved in dichloromethane and was washed with an aqueous sodium carbonate solution. Purification by flash column chromatography of the two reaction mixtures led to products **2-37** and **2-38** in their respective yields of 90% and 92% (**Scheme 7**). The reappearance of the NH_2 signal around 5 ppm and the disappearance of the *tert*-butyl group around 1.4 ppm in the ^{1}H NMR spectra of **2-37** and **2-38** was evidence enough that we had successfully synthesized products **2-37** and **2-38**. With the Boc groups successfully removed, the stage was now set for ring closing of the respective compounds **2-37** and **2-38** to give the 2-allyl-7-azaindole derivatives **2-39** and **2-40** respectively as shown in **Scheme 8**.

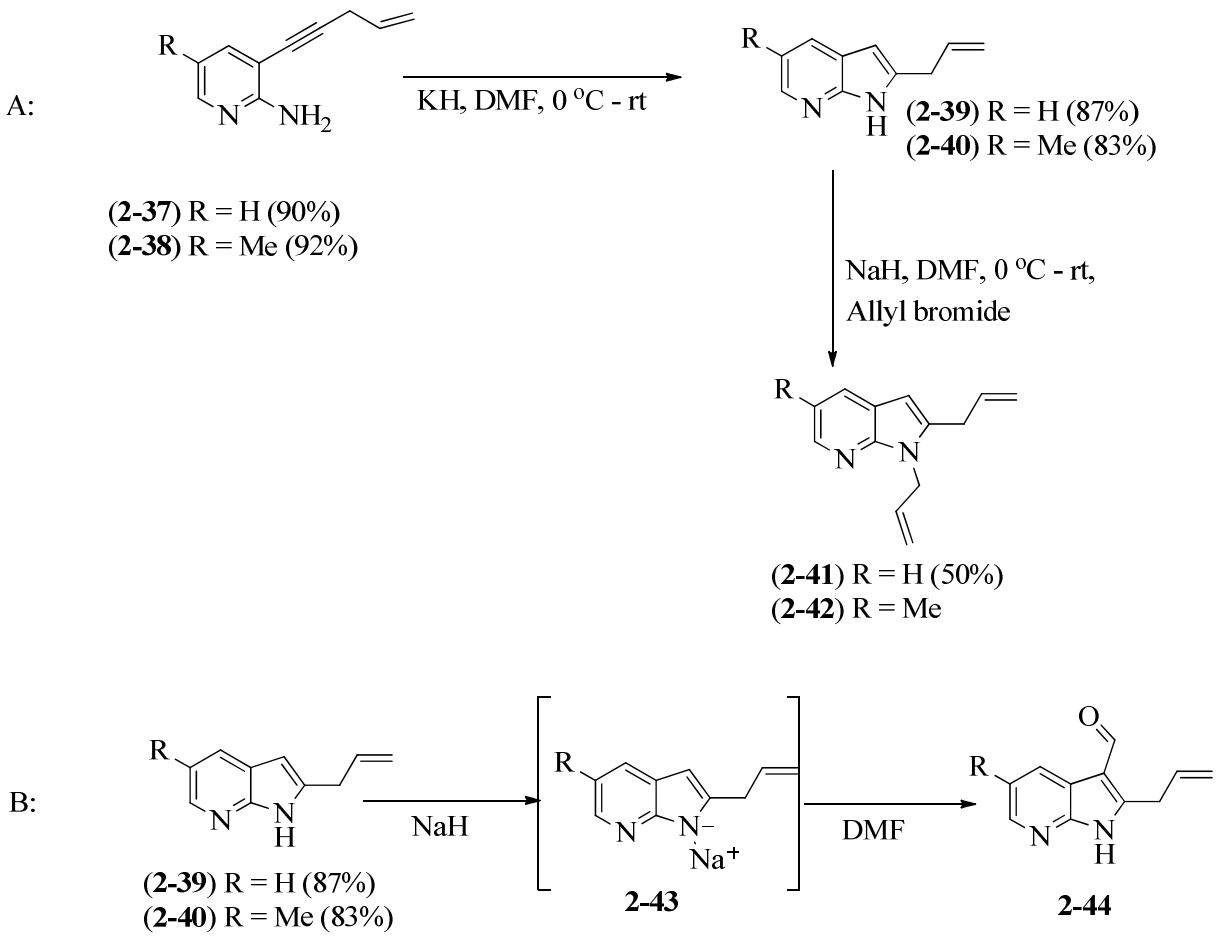


Scheme 7

The ring closing of **2-37** and **2-38** to give the desired azaindoles could be achieved in a number of ways. Some of the most recently used methods include the use of base such as potassium *tert*-butoxide at room temperature or at elevated temperatures,[29] potassium hydride at low temperatures,[30] microwave heating in the presence of inorganic salts in water[31] and several metal catalysts usually at elevated temperatures.[32] With so many choices on the table, one has to consider the efficiency of the reaction as a whole and the time required to complete it. This led us to believe that either potassium hydride or potassium *tert*-butoxide would be suitable for our reactions as they could take place at room temperature or even lower. The lower temperatures usually help with slowing the reaction that may possibly be fast and exothermic, resulting in the formation of undesired byproducts. We tried the reaction in either DMF or 1-methyl-2-pyrrolidinone at 0 °C with warming to room temperature thereafter. Although the reactions were successful yielding azaindoles **2-39** and **2-40** with both bases, potassium hydride was found to be superior to potassium *tert*-butoxide as it led to cleaner reactions, shorter reaction times and the reactions were easy to work up compared to the potassium *tert*-butoxide reaction work up. Therefore, **2-37** and **2-38** were each added dropwise to an ice-cooled suspension of potassium hydride in DMF and the reaction were allowed to warm to room temperature. Purification using

flash silica gel column chromatography gave the desired products **2-39** and **2-40** (**Scheme 8**). Examination of the ^{1}H NMR spectra of **2-39** and **2-40**, showed a singlet signal at 6.33 ppm, indicative of a proton at the 3-position of the 7-azaindole, the disappearance of the broad signal at 5 ppm due to NH_2 group and appearance of another broad signal at 12.39 due to an aromatic ring NH. The ^{13}C NMR spectra of **2-39** and **2-40** were not expected to be significantly different from that of the starting materials however, the two signals previously found at about 90 and 70 ppm due to a C-C triple bond were no longer present as expected. The latter were replaced by a C-H signal at 116 ppm and a quaternary carbon signal at 126 ppm. With the structure of products **2-39** and **2-40** confirmed, we proceeded with *N*-allylation of **2-39** and **2-40** using allyl bromide.

N-Alkylation of **2-39** and **2-40** could be achieved using various bases and solvents. The use of potassium *tert*-butoxide in diethyl ether, sodium hydride in DMF and potassium hydroxide in DMSO have been documented.[33-35] We decided to use sodium hydride in DMF as our preferred conditions to effect *N*-alkylation. Thus, **2-39** and **2-40** were dissolved separately in DMF, cooled in an ice-water bath, treated with sodium hydride and stirred for at least 30 minutes before being treated with allyl bromide at the same temperature. The reaction mixtures were allowed to warm to room temperature and stirred for a further 4 hours. Flash silica gel column chromatography after reaction work-up using ethyl acetate/hexane mixture gave **2-41** as a cream white solid (**Scheme 8**). Unfortunately, **2-42** could not be isolated as a pure compound even after using flash column chromatography. Although **2-41** was isolated, it was observed by ^{1}H NMR spectroscopy that it was also not 100% pure due to the presence of what appeared to be an aldehyde signal in the spectrum and this was also observed in the mixture of **2-42**. The aldehyde signal could be due to a product that was possibly formed when the 7-azaindole intermediate **2-43** reacted with DMF as depicted below (**Scheme 8**) to form aldehyde **2-44**. This is because lithium and magnesium derivatives of **2-43** have been shown to react in this manner, thereby functionalizing the 3-position of the indole.[36] Compound **2-41** was identified by ^{1}H NMR spectroscopy where the signal at 12.39 ppm due to the pyrrole NH was no longer present and the new *N*-allyl signals appeared at 4.84 ppm and between 6 ppm and 5 ppm due to the CH_2 bonded to the nitrogen and the alkene region respectively. With these results in hand, we wanted to try ring closing metathesis using Grubbs 2nd generation catalyst to afford the desired target, pyrroloindoles **2-45** and **2-50**.

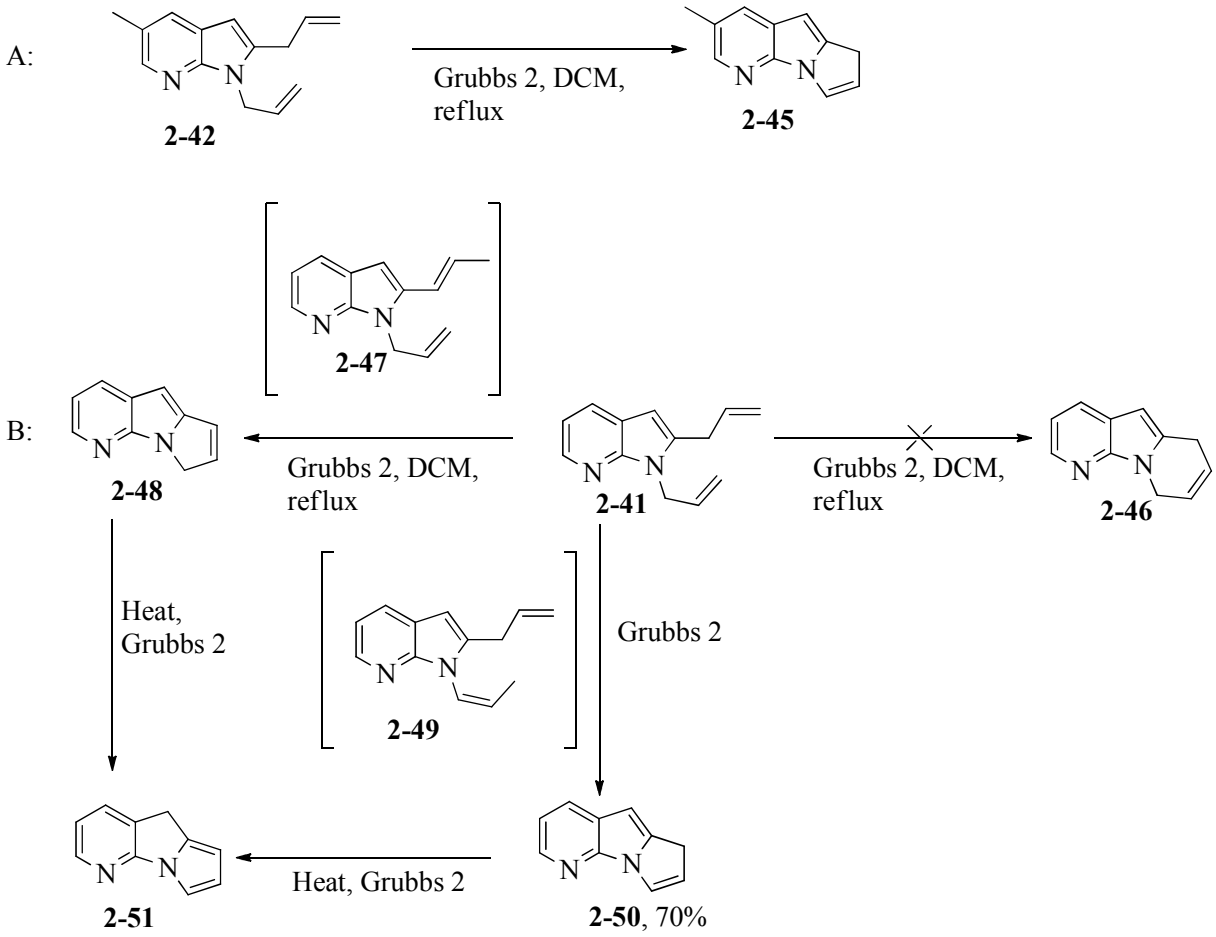


Scheme 8

2.2.3 Synthesis of pyrrolo-7-azaindoles

Despite problems with isolating pure material, we decided to try ring closing metathesis on both the relatively pure compound **2-41** and an impure mixture of **2-42** contaminated with unknown compounds. Our first attempt at this type of reaction was on **2-41** in dichloromethane with 5% Grubbs 2 catalyst at room temperature.[37] The reaction was monitored using thin layer chromatography where it was found that after 24 hours, the starting material was untouched even after increasing the amount of the catalyst. It was reported that this type of reaction could also be done at reflux in dichloromethane[38] and we decided to raise the temperature to 50 °C and monitor the reaction. To our surprise, we isolated something that did not look anything like our

expected product **2-46** (**Scheme 9**) but appeared to be the desired pyrroloazaindole. The isolated product retained the features of the 7-azaindole ring although the two allyl groups were no longer observed in the ^{1}H NMR spectrum. The expected features for **2-46** were two CH_2 signals from the newly formed ring, however, the isolated compound showed only one CH_2, probably bonded to an aromatic ring due to its chemical shift of 3.84 ppm. A closer examination of the ^{1}H NMR spectrum led us to believe the reaction could be proceeding through either intermediates **2-47** or **2-49** before consequently leading to either **2-48** or **2-50** (**Scheme 9**) in 70% yield. Indeed, it has been shown that Grubbs catalyst could isomerize terminal alkenes into internal alkenes although in these cases additives were used to achieve the isomerization.[39] Even though this provided some explanation as to how the reaction may be proceeding, we thought perhaps the solvent used may be affecting the reaction pathway favouring isomerization. We changed solvent to THF[40] and toluene[38] at reflux achieving the same results. After analyzing the ^{1}H NMR spectrum, the following information was revealed: a CH_2 at 3.84 ppm as a singlet, a CH at 6.15 ppm as a doublet, a signal at 6.43 ppm as a triplet, a signal at 7.00 ppm as a doublet of doublets, a signal at 7.36 ppm as a doublet, a signal at 7.65 ppm as a doublet and finally a signal appearing at 8.23 ppm as a doublet. This led us to believe that something else was happening possibly after the formation of either **2-48** or **2-50**. Indeed, it has been shown that compounds of the form of either **2-48** or **2-50** could lead to **2-51** in the presence of silica gel in dichloromethane at room temperature.[41] In our case, we believe the catalyst may be responsible for this type of transformation. Therefore, we came to the conclusion that we had synthesized the desired pyrroloazaindole **2-51** (**Scheme 9**).[27] However, another compound was isolated in 55% yield for which analysis of the ^{1}H NMR spectrum revealed the presence of a singlet CH_2 at 4.73 ppm, characteristic of compound **2-48** although according to the structure, the CH_2 should be at least a doublet. Schweizer *et al*. have synthesized the indole analogue of **2-48** and it was also found to display a singlet CH_2 group suggesting that the isolated compounds could be **2-48** or **2-50**.[7] Using the same ring closing metathesis conditions, we also managed to transform the aromatic methyl analogue **2-42** to **2-45** (**Scheme 9**) with ease from the previously discussed crude mixture, even though we could not calculate the percentage yield.



Scheme 9

With the ring closing metathesis completed, our attention shifted to the attempted synthesis of 2,5-disubstituted 7-azaindole derivatives as we believed that these compounds might display interesting biological properties. In addition, these results could pave the way for the synthesis of more complex substituted pyrrolo-7azaindoles.

2.4 Conclusion and future work

Starting from commercially available 3-bromopyridines, we had successfully managed to synthesize pyrrolo-7-azaindoles using the ring closing metathesis. Our attempts to synthesize the expected 6,9-dihydropyrido[3,2-b]indolizine (**2-46**) failed due to the isomerization of the allyl group before ring closing. Future work in in this chapter could include screening other catalysts

for the synthesis of **2-46** and a thorough study of the mechanism of the isomerization. More importantly, biological screening of final products obtained and in some cases, the intermediates could also be carried out.

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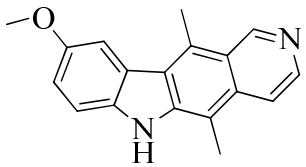
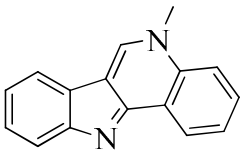
Chapter 3: Novel Triazole Derivatives of 7-Azaindoles

3.1 Introduction

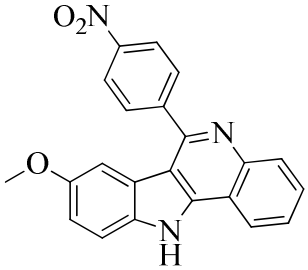
2,5-Disubstituted indoles have also received a great deal of interest due to their biological activities.[1] For example, 2,5-disubstituted indoles have found their way into the preparation of well-known alkaloids with varying biological activities such as ellipticine analogue (**3-1**)[2] and isocryptolepine (**3-2**) derivative 5-methoxyindole **3-2a** (**Figure 1**).[3] Furthermore, the use of 2,5-disubstituted indoles as therapeutic agents has been explored. This includes their use as inhibitors of proteases involved in coagulation,[4] as nociceptin/orphanin FQ receptor antagonists.[5] as inhibitors of endothelin-converting enzyme,[6] as well as antiangiogenic tyrosine kinase inhibitors.[7] Therefore, methods of preparation of these biologically important heterocyclic compounds have been the subject of considerable scrutiny. Various methods have been applied to gain access to these important compounds including, but not limited to, the Fischer indole synthesis, the use of Sonogashira coupling reaction as a key step and the Madelung indole synthesis. In the following paragraphs, we will be discussing various methods to access 2,5-disubstituted indoles, the 7-azaindole analogs and their biological importance.



5-Methoxyellipticine (**3-1**)



Isocryptolepine **3-2**

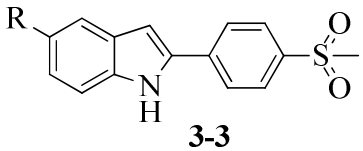


3-2a

Figure 1

3.1.2 Biological importance of 2,5-disubstituted indoles and 7-azaindoles

Cyclooxygenase (COX) is an enzyme that is responsible for the synthesis of prostanoids. Prostanoids, which are known to be involved in inflammatory responses, are further divided into three main groups, namely prostaglandins, prostacyclins and thromboxanes. Cyclooxygenase is also found to exist in two isoforms known as COX-1 and COX-2. These two isoforms are known to perform different functions. COX-1 is responsible for physiological phenomena while COX-2 is responsible for pathological phenomena. Therefore, selective inhibition of one over the other is very important. Of more interest is COX-2 and a series of nonsteroidal ant-inflammatory drugs have been synthesized to specifically target COX-2, although some drugs could not differentiate between COX- 1 and COX-2.[8] With COX-2 in mind, Zarghi *et al*. designed and synthesized some 2,5-disubstituted indoles as COX-2 inhibitors.[9] For example, 2,5-disubstituted indoles of general formula **3-3** (**Figure 2**) were found be inhibitors of COX-2 with minimum inhibitory concentrations (IC_{50}) ranging from 0.028 to 0.26 μM with selectivity indices of between 30 and 291 towards COX-2. Furthermore, a structure-activity relationship study revealed that **3-3d** was the most selective while **3-3a** was the least selective towards COX-2[9] (**Figure 2**).



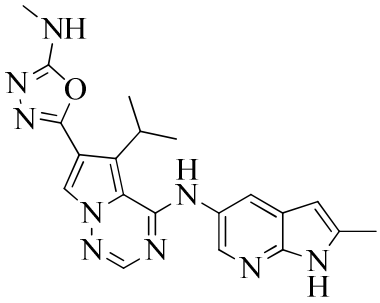
3-3

R = Cl (**3-3a**)
R = F (**3-3b**)
R= Me (**3-3c**)
R = OMe (**3-3d**)

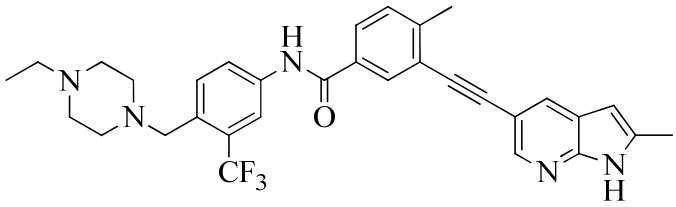
Figure 2

The related 7-azaindoles are no exception to the rich biological properties experienced by 2,5-disubstituted indoles. Various 2,5-disubstituted azaindoles have recently been synthesized and evaluated for their biological activities. For example 2,5-disubstituted 7-azaindole **3-4** was found to inhibit vascular endothelial growth factor 2 (VEGF-2), which is considered to be the principal kinase as compared to VEGF-1 and VEGF-3, with an IC_{50} value of 0.025 μM[10] while **3-5** was

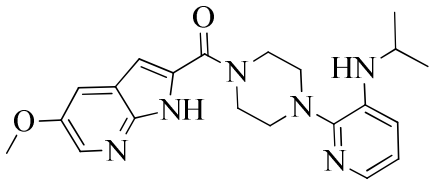
found to inhibit T315I Bcr-Abl tyrosine kinase.[11] On the other hand, 2,5-disubstituted indole **3-6** was found to be active against the reverse transcriptase which is encoded by human immunodeficiency virus 1 (HIV-1), and is used to convert the viral geonomic ribonucleic acid into proviral deoxyribonucleic acid[12] (**Figure 3**).



3-4



3-5



3-6

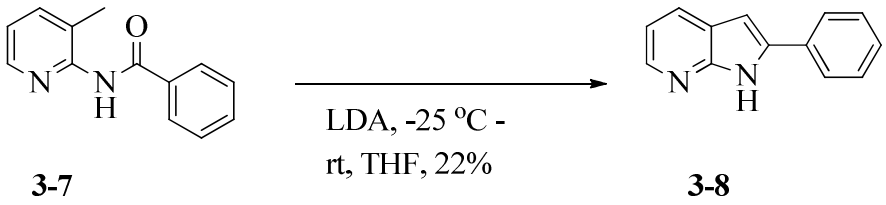
Figure 3

3.1.3 Synthesis of 2,5-disubstituted indoles and the related 7-azaindoles

3.1.3.1 Access to 2,5-disubstituted indoles using Madelung indole synthesis

First reported in 1912, the Madelung indole synthesis is a reaction in which *N*-acylated-*O*-alkylanilines are reacted with strong bases at high temperatures, typically above 200 °C, to produce indoles.[13] However, due to the high temperatures needed to accomplish the reaction, various reports have been published on a modified Madelung indole synthesis that requires lower temperatures. For example, Schulenberg introduced electron-withdrawing groups on *O*-alkylanilines[14], Orlemans *et al*. reported the use of trimethylsilyl chloride with potassium *tert*-

butoxide at room temperature[15] and Le Corre *et al*. reported the Wittig-type modified Madelung indole synthesis to access indoles.[16] As a result, Houlihan and co-workers reported the synthesis of substituted indoles using *n*-butyllithium to treat *N*-acylated-*O*-alkylanilines at lower temperatures of about -25 °C to room temperature although excess *n*-butyllithium was required to complete the reaction. When the same reaction conditions were used to synthesize 7-azindole derivatives, nothing could be isolated, but replacing *n*-butyllithium with less nucleophilic base lithium diisopropylamide yielded 7-azaindole derivative **3-8** from amide **3-7** in rather poor yield of 22% (**Scheme 1**).[17] Apart from Madelung indole synthesis used to acess azaindoles, 2,5-disustituted 7-azaindoles could also be obtained through the Sonogashira coupling reaction, as will be outlined in the next section.



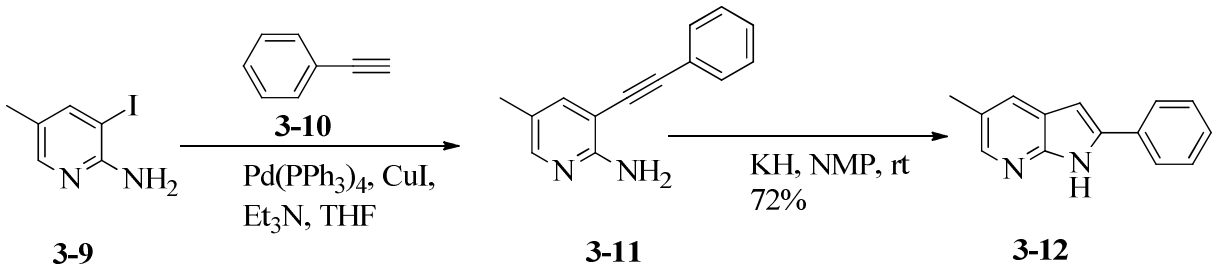
3-7 **3-8**

Scheme 1

3.1.3.2 Access to 2,5-disubstituted 7-azaindoles using the Sonogashira coupling reaction.

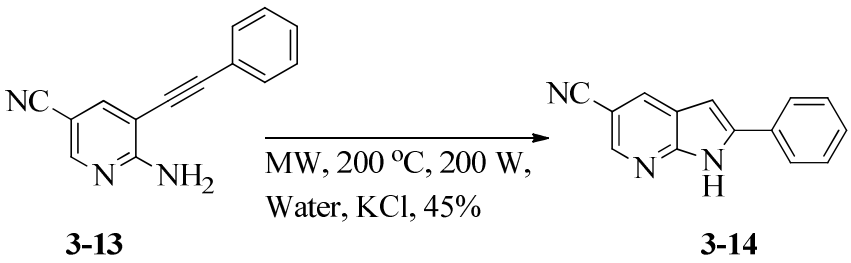
Most notably, for this PhD the Sonogashira coupling reaction[18-24] has been used to prepare 2-substituted indoles[25] and 2-substitiuted azaindoles,[26] 2,5-disubstituted indoles,[27] as well as 2,5-disubstituted 7-azaindoles by replacing the aniline moiety with an amino pyridine moiety. Typically, 2,5-disubstituted 7-azaindoles are obtained from 2-amino-3-alkyne-5-substituted pyridines by treating them with various reagent such as bases, metal salts, acids, catalysts and other reagents in the process called heteroannulation. Recently, Koradin *et al*. reported the synthesis of 2,5-disubstituted 7-azaindoles using mild potassium and cesium bases for the pyrrole ring-forming step.[28] The bases used in this research were cesium hydroxide, potassium hydride and potassium tertiary butoxide in *N*-methylpyrrolidinone (NMP) as a solvent. Thus, when 2-amino-5-methyl-3-phenylethynylpyridine (**3-11**), obtained from the Sonogashira coupling reaction of 2-amino-3-iodo-5-methylpyridine (**3-9**) with phenylacetylene (**3-10**), was

treated with potassium hydride in NMP at room temperature, 5-methyl-2-phenyl-7-azaindole (**3-12**) was obtained in a satisfying yield of 72%[28] (**Scheme 2**).



Scheme 2

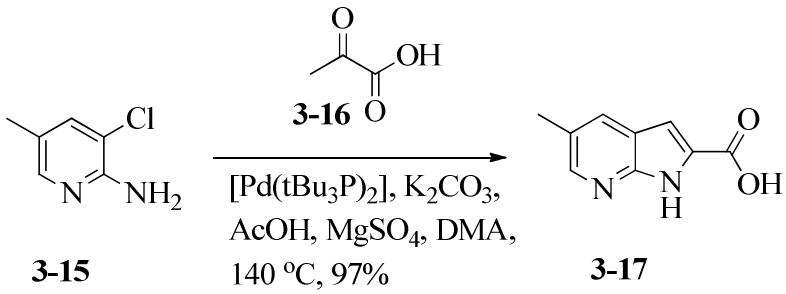
The use of water as a solvent has attracted a lot of attention due to the fact that water is regarded as the cheapest, safest and most non-toxic solvent of all time. In addition, reactions that are carried out in water as a solvent are known as "green" reactions or green chemistry. Quite recently, various reports have been published where water was used as a solvent to perform organic reactions including Mannich-type reactions[29], Heck reactions[30], Wittig reactions[31], acyl coupling reactions[32], allylation reactions[33] and oxidation reactions.[34] Taking advantage of these early reports, Carpita *et al*. reported the use of microwave irradiation and water as a solvent for the synthesis of azaindole derivatives from aminopyridines containing an alkyne *ortho* to the amine. As such, substrate **3-13** was irradiated at 200 W and 200 °C in water in the presence of potassium chloride salt to give 2,5-disubstituted 7-azaindole **3-14** in an acceptable yield of 45% (**Scheme 3**). In addition, a range of indole derivatives and azaindole derivatives were prepared using this methodology.[35]



Scheme 3

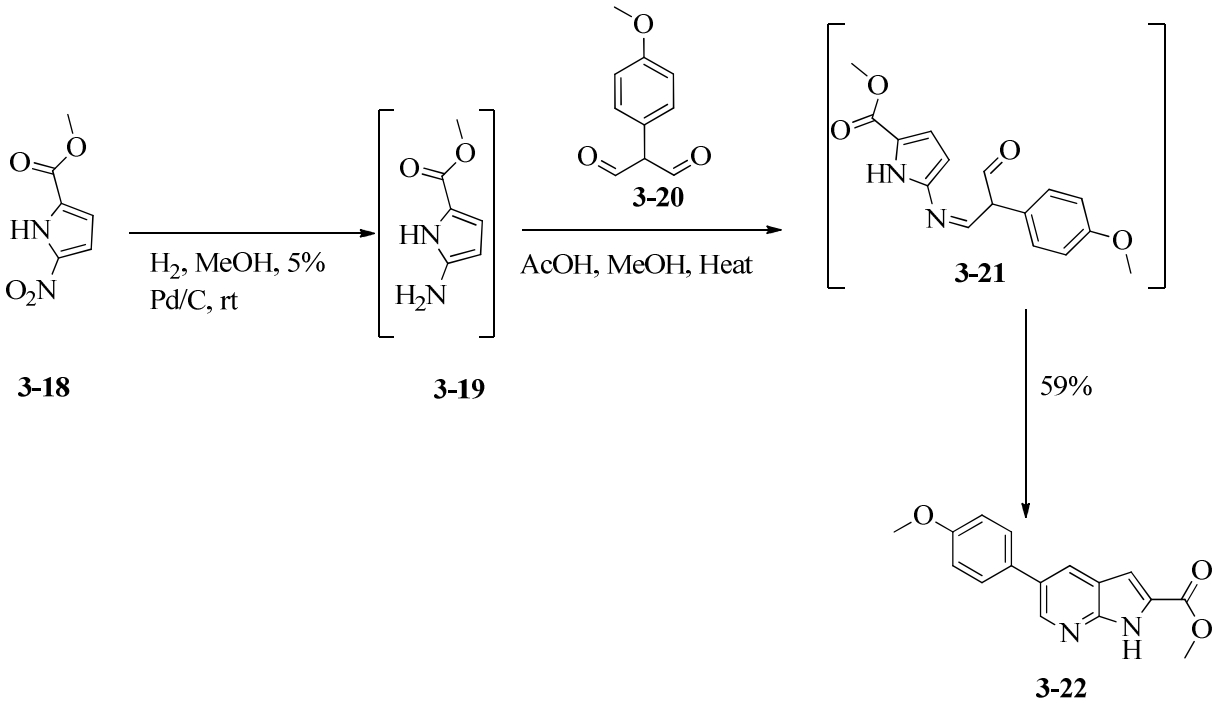
3.1.3.3 Access to 2,5-disubstituted 7-azaindoles using non-classical methods

A variety of non-classical methods have been reported for the preparation of 2,5-disubstituted 7-azaindoles. One such method was introduced by Nazaré and co-workers using chloroaminopyridines and ketones in the presence of a base, an acid and a palladium catalyst at relatively high temperatures to produce azaindoles. Thus, 2-amino-3-chloro-5-methylpyridine (**3-15**) was treated with pyruvic acid (**3-16**) in the presence of catalytic amounts of $Pd(tBu_3P)_2$, potassium carbonate and acetic acid in dimethylacetamide at 140 °C while magnesium sulfate was used as a water binder. The result was the formation of 2,5-disubstituted 7-azaindole **3-17** in an excellent yield of 97% (**Scheme 4**).[36]



Scheme 4

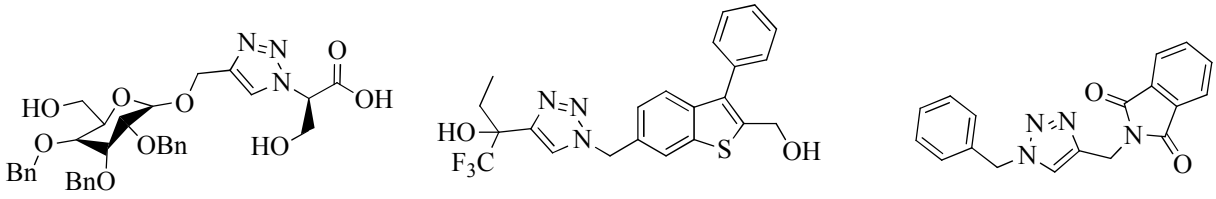
Since acid-catalyzed syntheses of indoles have been widely used, Wu *et al*. took advantage of these reaction conditions to prepare 2,5-disubstituted 7-azaindoles.[37] They first started by treating substituted pyrrole **3-18** with hydrogen in the presence of Pd/C in methanol to obtain an intermediate amine **3-19**. Without isolation, amine **3-19** was further treated with aldehyde **3-20** in the presence of acetic acid to yield the mono-imine intermediate **3-21** which upon exposure to heat and acid resulted in the formation of the 2,5-disustituted 7-azaindole **3-22** in a moderate yield of 59% (**Scheme 5**).[37]



Scheme 5

3.1.4 Linking the triazole with the 7-azaindole functionality

Other nitrogen-containing scaffold such as the triazole functionality has been shown to be very useful especially with regard to their biological activity. For example, triazole **3-23** (**Figure 4**) was found to inhibit protein tyrosine phosphatase[38a] which is suspected to play a role in the development of Alzheimer's disease while triazole **3-24** (**Figure 4**) which is based on benzothiophene moiety was found to possess good inhibitory activity against 5-lipoxygenase enzyme which is responsible for the synthesis of leukotrienes.[38b] Additionally, triazole **3-25** (**Figure 4**) was found to be active against resistant strains of *Staphylococcus aureus*.[38c]



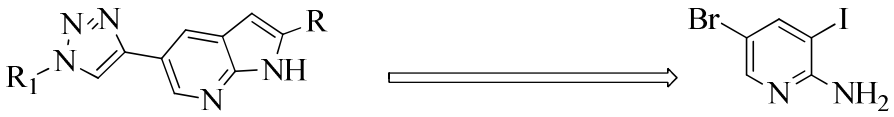
3-23 **3-24** **3-25**

Figure 4

Due to the biological activities shown by triazole functionality, we thought that a covalent linkage between a triazole functionality and 7-azaindole derivatives which has proved to be a biologically active scaffold would result in the formation of compounds with superior biological activity.

3.2 Chemistry: Preparation of 2,5-disubstituted 7-azaindoles

For this PhD project, the preparation of the desired triazole 2,5-disubstituted 7-azaindoles could be achieved by using the dihalogenated 2-aminopyridine **3-26** as the starting material, provided this could be easily prepared. We hoped to take advantage of the Sonogashira coupling reaction to allow for the preparation of **3-27** (**Scheme 6**) where we would take advantage of the different reactivity of the aromatic iodide as compared to the bromide.

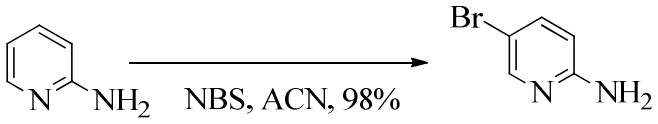


3-27 **3-26**

Scheme 6

3.2.1 Synthesis of 3,5-dihalogenated-2-aminopyridines

Our route to access the desired 2,5-disubstituted 7-azaindoles started with halogenation of a commercially available cheap 2-aminopyridine (**3-28**). Our first attempt was made using molecular bromine followed by treatment with sodium hydrogen carbonate in carbon tetrachloride, to no avail as starting material was recovered unchanged.[39] Changing our solvent to either chloroform[40] or acetic acid[41] but still using molecular bromine did not improve the reaction as we were unable to isolate any brominated product **3-29**. This changed when molecular bromine was replaced by *N*-bromosuccinimide (NBS) in various solvents.[42] After experimenting with various solvents, we finally settled on acetonitrile as it resulted in clean reactions. Thus, 2-aminopyridine (**3-28**) was dissolved in acetonitrile and treated with NBS at room temperature for 24 hours. After this time, the solvent was removed on a rotary evaporator and the resulting white solid was purified by flash chromatography to give 5-bromo-2-aminopyridine (**3-29**)[42] in an excellent yield of 98% (**Scheme 7**). The formation of **3-29** was confirmed by ^{1}H NMR spectroscopy. Analysis of the ^{1}H NMR spectrum revealed the following information: δ 8.08 (s, 1H), δ 7.48 (dd, *J* = 8.7, 2.4, 1H), δ 6.41 (d, *J* = 8.7, 1H), δ 4.44 (s, 2H) which was consistent with the structure of **3-29**. Since our goal was to synthesize 3-iodo-5-bromo-2-aminopyridine, our next step was iodination of **3-29** specifically in the 3-position of the pyridine nucleus.

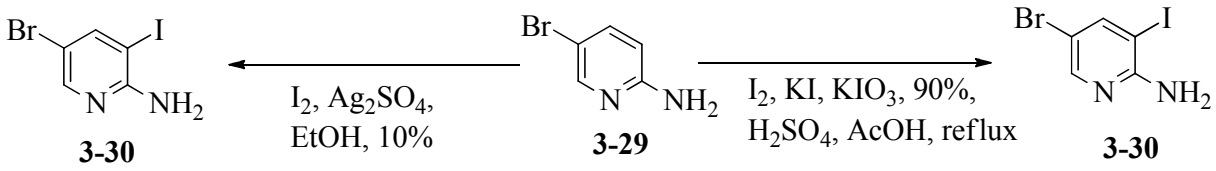


3-28 **3-29**

Scheme 7

Our route to iodination of **3-29** started with the treatment of **3-29** with molecular iodine in the presence of silver sulfate in ethanol as a solvent.[28] Unfortunately, the reaction could never reach completion no matter how long it was allowed to proceed. Hence, the desired product 3-iodopyridine **3-30** was isolated in only 10% yield with mostly starting material being recovered (**Scheme 8**). With these unsatisfying results, we continued to search for a better method for

iodination of substrate **3-29**. A method by Ujjainwalla and Walsh in which silver sulfate was replaced by silver tetrafluoroborate in ethanol[43], the use of iodine chloride in methanol[44] and the use of slightly harsher conditions in which sulfuric acid, potassium iodide and potassium iodate are employed at high temperatures[45] were found in the literature. We decided to try the slightly harsher conditions for iodination of **3-29**, employing iodine, potassium iodate, sulfuric acid and potassium iodide in acetic acid as a solvent to effect the iodination of **3-29**. Our only worry was whether the iodine could possibly replace bromine under these conditions. However, research showed that reagents such as copper(I) iodide are mostly required for iodine to replace bromine, especially on aromatic systems.[46] When **3-29** was treated with iodine in the presence of potassium iodide and potassium iodate, 3-iodo-5-bromo-2-aminopyridine (**3-30**) was isolated in an excellent yield of 90%[45] (**Scheme 8**). A close examination of the ^{1}H NMR spectrum of **3-30** revealed the presence of three singlet signals at δ 8.05 and δ 7.95 ppm, characteristic of pyridine protons and at 5.03 ppm, integrating for 2 protons characteristic of the NH_2 functionality of the pyridine. The formation of **3-30** was further confirmed by the ^{13}C NMR spectrum which indicated the presence of two CH signals in the aromatic region. Now that we had dihalogenated product **3-30** in hand, our next step was to perform a Sonogashira coupling reaction on this substrate.



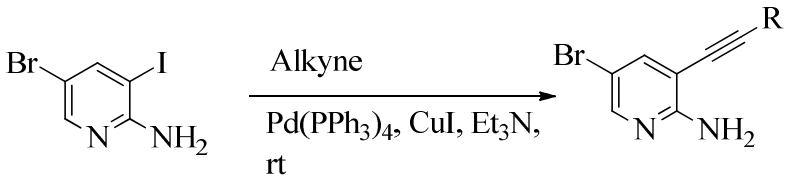
Scheme 8

3.2.2 The Sonogashira coupling reaction of 2-amino-5-bromo-3-iodopyridine (3-30)

As discussed earlier, the Sonogashira coupling reactions allow for C-C bond formation by reacting terminal alkynes with aromatic halides. However, aromatic halides have varying degrees of of reactivity and thus some reactions are able to be carried out at room temperature while other reactions require elevated temperatures. For example, it has been found that most if not all

reactions involving aromatic iodides will take place at room temperature[47] while reactions involving aromatic bromides almost exclusively take place at elevated temperatures.[48] As observed, our substrate **3-30** was able to undergo Sonogashira coupling reaction at room temperature with the iodine substituent and at elevated temperature with the bromine substituent, however performing the reaction on the dihalogenated substrate at elevated temperatures would result in both the iodo and the bromo groups participating in the coupling reaction. As a result, we believed that our substrate would allow us to perform the Sonogashira coupling reaction selectively at the iodo functionality at room temperature.

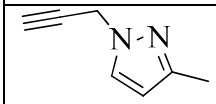
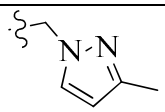
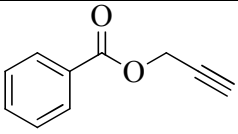
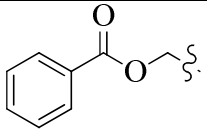
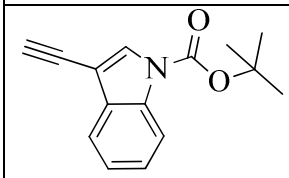
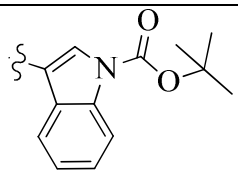
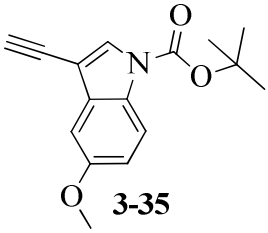
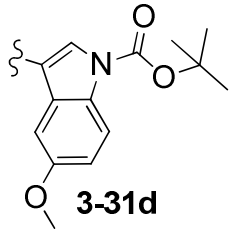
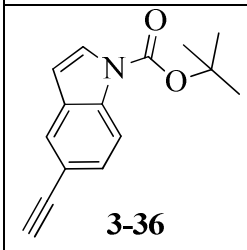
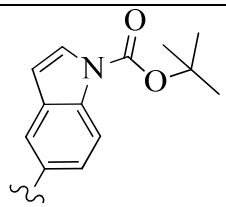
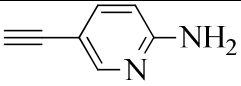
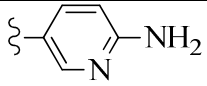
Therefore, we decided to perform the Sonogashira coupling reaction on substrate **3-30** at room temperature. 2-Amino-5-bromo-3-iodopyridine (**3-30**) was treated with various terminal alkynes in the presence of a palladium catalyst ($Pd(PPh_3)_4$) and copper(I) iodide as a co-catalyst. Triethylamine was used as a base while tetrahydrofuran (THF) was used as a solvent. The reaction was allowed to stir at room temperature under an argon atmosphere for 8 hours before being quenched, worked up and purified by flash chromatography using 30% EtOAc/hexane mixture to give products of general structure **3-31**. The reaction shown in **Scheme 9** was conducted with a variety of alkynes (some commercial and others prepared in our laboratories) shown in Table 1, together with the isolated yields.

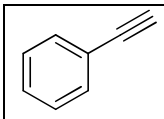
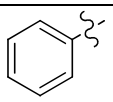
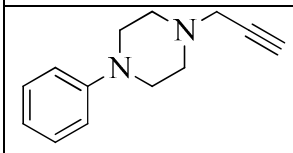
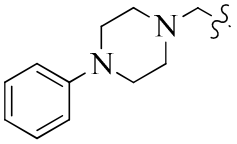
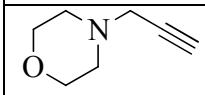
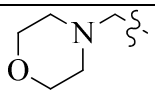
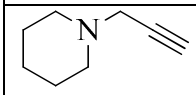
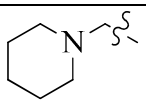
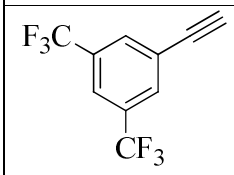
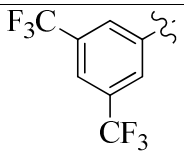
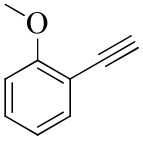
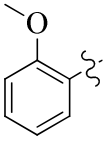


3-30 **3-31**

Scheme 9

Table 1: Sonogashira coupling reactions of various alkynes with **3-30**

Alkyne	R/ Product ID	% Yield	Distinct NMR information (^{1}H NMR & ^{13}C NMR) /ppm
 **3-32**	 **3-31a**	89	^{1}H: 7.47 (d, *J* = 5.7, 1H), 6.06 – 6.03 (m, 1H), 5.14 (s, 2H), 4.86 (s, 2H), 2.31 (d, *J* = 4.7, 3H). ^{13}C: 90.34, 80.53 (triple bond), 42.25 (N-CH_2), 13.86 (CH_3).
 **3-33**	 **3-31b**	91	^{1}H: 7.63 – 7.53 (m, 3H), 7.45 (t, *J* = 7.6, 2H), 5.14 (s, 2H). ^{13}C: 166.30 (C=O), 130.12(2 x ArCH), 128.80 (ArCH), 90.95, 81.23 (triple bond), 53.41 (O-CH_2-).
 **3-34**	 **3-31c**	95	^{1}H: 7.86 (s, 1H), 7.70 – 7.63 (m, 1H), 7.36 (m, 2H), 1.69 (s, 9H). ^{13}C: 157.63 (C=O), 89.11, 86.85 (triple bond), 85.00, 28.47 (*tert*-butyl)
 **3-35**	 **3-31d**	80	^{1}H: 7.82 (s, 1H), 7.09 (d, *J* = 2.5, 1H), 6.99 (dd, *J* = 9.0, 2.5, 1H), 3.88 (s, 3H), 1.67 (s, 9H). ^{13}C: 157.68 (C=O), 89.13, 86.84 (triple bond), 84.84, 28.46 (*tert*-butyl), 56.09 (OMe).
 **3-36**	 **3-31e**	88	^{1}H: 7.62 (d, *J* = 3.7, 1H), 7.44 (dd, *J* = 8.6, 1.6, 1H), 6.54 (d, *J* = 3.7, 1H), 1.67 (s, 9H). ^{13}C: 157.76 (C=O), 97.73, 84.45 (triple bond), 82.19, 28.42 (*tert*-butyl).
 **3-37**	 **3-31f**	96	^{1}H: 7.58 (dd, *J* = 8.6, 2.3, 1H), 6.46 – 6.41 (m, 5H). ^{13}C: 94.60, 83.47 (triple bond).

 **3-38**	 **3-31g**	95	^{1}H: 7.57 – 7.45 (m, 2H), 7.42 – 7.31 (m, 3H). ^{13}C: 131.86, 128.82 (ArCH), 96.85, 83.47 (triple bond).
 **3-39**	 **3-31h**	91	^{1}H: 7.32 – 7.21 (m, 2H), 6.87 (t, *J* = 7.3, 1H), 3.31 – 3.19 (m, 4H), 2.84 – 2.72 (m, 4H). ^{13}C: 129.42, 116.46 (ArCH), 92.11, 80.04 (triple bond), 52.37, 49.37, 48.10 (N-CH_2-).
 **3-40**	 **3-31i**	86	^{1}H: 3.80 – 3.66 (m, 4H), 3.53 (s, 2H), 2.66 – 2.50 (m, 4H). ^{13}C: 91.93, 80.05 (triple bond), 67.05 (OCH_2-), 52.68, 48.38 (N-CH_2-).
 **3-41**	 **3-31j**	83	^{1}H: 3.50 (s, 2H), 2.52 (m, 4H), 1.61 (dt, *J* = 11.0, 5.6, 4H), 1.42 (d, *J* = 5.1, 2H). ^{13}C: 92.92, 79.53 (triple bond), 53.75, 48.81, 26.16, 24.09 (-CH_2-).
 **3-42**	 **3-31k**	70	^{1}H: 7.94 (s, 2H), 7.86 (s, 1H). ^{13}C: 133.03 – 132.22 (CF_3), 93.49, 86.93 (triple bond).
 **3-43**	 **3-31l**	73	^{1}H: (dd, *J* = 7.5, 1.5, 1H), 7.40 – 7.29 (m, 1H), 7.00 – 6.91 (m, 2H), 3.92 (s, 3H). ^{13}C: 93.51, 88.04 (triple bond), 55.81 (OMe).

Deductions from Table 1:

The formation of all products in Table 1 was confirmed using NMR spectroscopy as our main tool. In analyzing the ^{1}H NMR spectrum of each compound, the following data helped us to

confirm that we had indeed formed the desired products. For example, the ^{1}H NMR spectrum for product **3-31a** showed the presence of two extra protons in the aromatic region, one being a doublet at δ 7.47 ppm and the other a multiplet between 6.06 and 6.03 ppm, in addition to the presence of N-CH_2 signal observed at 5.14 ppm as singlet and a methyl group at 2.13 ppm as a doublet. This was further confirmed by the ^{13}C NMR spectrum which showed the presence of a C-C triple bond with signals at 90.34 and 80.53 ppm while the presence of methylene adjacent to nitrogen signal at 42.25 ppm and a methyl group at 13.86 ppm further consolidated our belief that we have made the desired product **3-31a**. Using NMR spectroscopy, we also managed to confirm the formation of **3-31b** through the ^{1}H NMR spectrum revealing the presence of a phenyl group (7.63 – 7.53 (m, 3H), 7.45 (t, *J* = 7.6, 2H)) and the presence of methylene adjacent to oxygen signal at 5.14 ppm, while the ^{13}C NMR spectrum revealed the presence of a C=O at 166.30 due to the ester functionality, the presence of a C-C triple bond with signals at 90.95 and 81.23 ppm and the presence of methylene adjacent to oxygen signal at 53.41 ppm. These were some of the key features used to confirm the formation of product **3-31b**.

Furthermore, the formation of products **3-31c**, **3-31d** and **3-31e** was confirmed using ^{1}H NMR spectroscopy where each of the products revealed the presence of a *tert*-butyl group at around 1.60 ppm. In addition to the presence of a *tert*-butyl group, the presence of indole protons in the aromatic region was also used to prove the formation of these products and the methoxy group was also used to further confirm the formation of **3-31d**. When the ^{13}C NMR spectra were analyzed, the presence of a C=O was observed around δ 157 ppm, the presence of a C-C triple bond was observed with signals at between 80 and 90 ppm, while the presence of a *tert*-butyl group was confirmed by the presence of a signal around 82 ppm for the quaternary carbon and a signal around 28 ppm for the methyl functionality. Additionally, signals corresponding to indole carbons were also observed in the aromatic region. The increased number of carbons in the aromatic region further confirmed that products **3-31c**, **3-31d** and **3-31e** were successfully synthesized.

Continuing with Sonogashira coupling reaction products, formation of compound **3-31g** was comfirmed with data from the ^{1}H NMR spectrum showing the presence of a phenyl group (7.57 – 7.45 (m, 2H), 7.42 – 7.31 (m, 3H)) while the data from the ^{13}C NMR spectrum showed the

presence of a C-C triple bond with signals at 96.85 and 83.47 ppm. Additionally, the presence of a mono-substituted benzene group was observed in the ^{13}C NMR spectrum as indicated by two signals at 131.86 and 128.82 ppm, each representing two equal CH's in the aromatic region. With the formation of **3-31g** confirmed, our attention was shifted to the formation of products **3-31h**, **3-31i** and **3-31j**. As can be seen in Table 1, **3-31h**, **3-31i** and **3-31j** all contain similar aliphatic functionality while **3-31h** has a phenyl group in addition to the aliphatic functionality. Starting with the ^{1}H NMR spectra of these products, methylenes adjacent to the nitrogen were observed for all these products in the region of 2.50 – 3.55 ppm. In addition, **3-31h** showed the presence of a mono-substituted benzene functionality due to the presence of five extra protons in the aromatic region. Product **3-31i** showed the presence of methylene adjacent to oxygen in the region of 3.66 – 3.88 ppm and **3-31j** showed the presence of more aliphatic signals in the region between 1.42 and 1.61 ppm. Apart from the presence of a C-C triple bond with signals observed in the region between 79 and 92 ppm for each product **3-31h**, **3-31i** and **3-31j** in the ^{13}C NMR spectra, the presence of a phenyl group was further observed for **3-31h** due to an increased number of aromatic carbon signals. The presence of methane adjacent to nitrogen carbon signals was observed for all products in the region of 48 and 53 ppm. Additionally, **3-31h** showed an increase in the number of carbon signals in the aromatic region due to the presence of a phenyl ring while **3-31i** showed the presence of methane adjacent to oxygen signals at 67.07 ppm and for **3-31j**, more aliphatic carbon signals were observed in the region of 24 and 26 ppm in the ^{13}C NMR spectrum due to the presence of the piperidine ring. Lastly, we used both ^{1}H and ^{13}C NMR spectroscopy to confirm the formation of both **3-31k** and **3-31l**.

Thus, analysis of the ^{1}H NMR spectra of both **3-31k** and **3-31l** revealed some important information. Firstly, the ^{1}H NMR spectrum of **3-31k** revealed the presence of two signals at δ 7.94 ppm (2H) and 7.86 ppm (1H) which is a characteristic of a trisubstituted benzene ring. Secondly, the ^{1}H NMR spectrum of **3-31l** showed an increase in the number of protons in the aromatic region due to the presence of disubstituted benzene ring and in addition, the presence of a methoxy group was also observed for **3-31l**. An increase in the number of carbon signals in the aromatic region was observed for both **3-31k** and **3-31l** in the ^{13}C NMR spectra, but of more value was the observation of a CF_3 group in the ^{13}C NMR spectrum of **3-31k** present as a quartet at 133.03 – 132.22 ppm. The presence of a carbon signal in the ^{13}C NMR spectrum of **3-31l** at

55.81 ppm due to the methoxy functionality further confirmed the formation of product **3-31l**. Additionally, the presence of a C-C triple bond was observed for both **3-31k** and **3-31l** with signals in the region between 86 and 94 ppm. Having the Sonogashira coupled products in hand, our next mission was to treat these products with either metal catalysts or bases to gain access to the desired substituted 7-azaindoles.

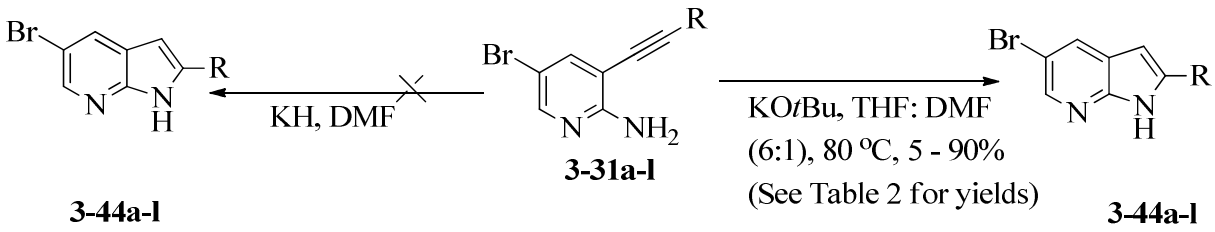
3.2.3 Synthesis of 5-bromo-2-substituted-7-azaindoles

As discussed in previous sections, it was demonstrated that substrates generated by means of Sonogashira coupling reactions could be further converted to either indoles or 7-azaindoles depending on whether aminopyridine or aniline was used. As such, potassium bases, particularly potassium *tert*-butoxide and potassium hydride at ambient temperature have been used to gain access to indoles and 7-azaindoles from the Sonogashira products.[28,48-52] Taking advantage of these available methodologies, our route to the synthesis of 7-azaindoles from **3-31** started when **3-31** was treated with potassium hydride in dry *N*,*N*-dimethylformamide (DMF) at room temperature. Unfortunately, we could not isolate any of the desired 7-azaindole derivatives **3-44** (**Scheme 10**). Changing solvent to *N*-methylpyrrolidin-2-one (NMP) did not improve matters as the starting material was recovered unused. With potassium hydride giving no promising results, we turned our attention to metal catalysts for better results.

At our disposal, we had two metal catalysts namely copper(I) iodide and palladium chloride. Although the use of these two catalysts has been reported to afford 7-azaindole or indole derivatives[53], we faced the possibility of the bromine in our substrate **3-31** undergoing reaction with these metal catalysts. Copper(I) iodide is known to facilitate nucleophilic attack on halogenated aromatic systems[46] although copper(I) iodide has been shown to work very well in the presence of halogenated aromatics[54] while palladium chloride is mostly used in cross-coupling reactions involving halogenated aromatic systems.[55] With uncertainty surrounding metal catalysts, our first attempt was made using metal base potassium *tert*-butoxide instead. Thus, we treated **3-31** with potassium butoxide in dry THF as a solvent of choice at room temperature although the use of DMF was mostly encouraged due to the insolubility of potassium *tert*-butoxide in other solvents such as THF. To our surprise, analysis of the ^{1}H NMR

spectrum of the crude material revealed the presence of **3-44** even though it was estimated to be lower than 5% conversion level. When the temperature was increased to 80 °C, 7-azaindole **3-44** was isolated in a low 25% yield (**Scheme 10**). Indeed, the solubility of the base played a very important role and as expected, solubility in most cases will increase with increasing temperature. Determined to use THF as our solvent of choice, we decided to add a small amount of dry DMF to THF.

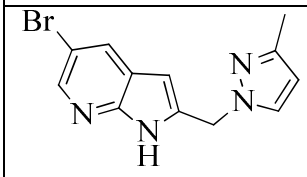
After testing several combinations, we settled on a 6:1 THF:DMF ratio. Thus, substrates **3-31a-l** were dissolved in a 6:1 THF/DMF mixture and treated with potassium *tert*-butoxide under argon or a nitrogen atmosphere and the resulting heterogeneous mixtures were heated at 80 °C for 8 hours. After this time, each reaction mixture was allowed to cool to room temperature, water was added and the precipitate was collected through a filter paper, were washed with hexane and dried in the presence of potassium hydroxide. As such, several 7-azaindole derivatives **3-44a-l** (**Scheme 10**) were obtained from this methodology in the yields ranging from a disappointing 5% to a very good 90%. **Scheme 10** is representative of the overall reaction and the full results are included in Table 2.

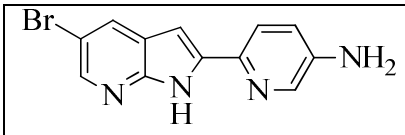
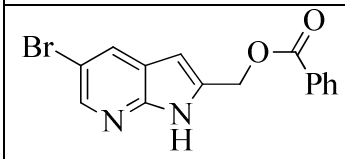
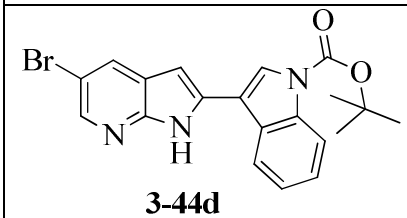
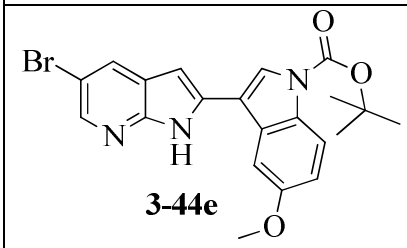
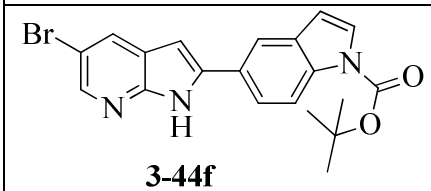
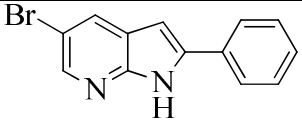
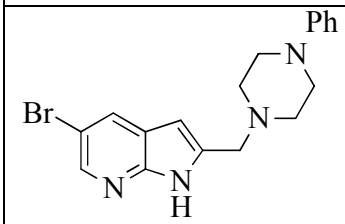


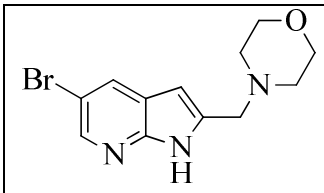
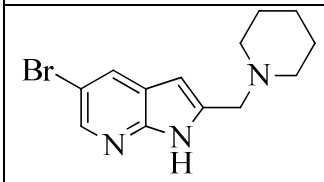
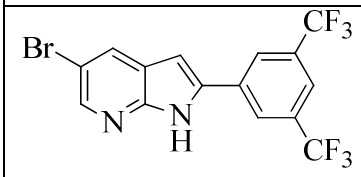
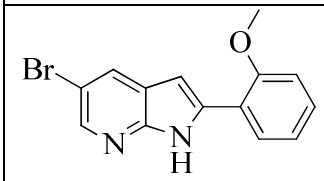
3-44a-l **3-44a-l**

Scheme 10

Table 2: Treatment of **3-31a-l** with KO^{t}Bu in THF:DMF mixture at 80 °C

Product	% Yield	Distinct NMR information (^{1}H & ^{13}C) ppm
 **3-44a**	90	^{1}H: 10.97 (s, 1H), 6.37 (s, 1H).

 **3-44b**	93	^{1}H: 12.43 (s, 1H), 6.67 (s, 1H).
 **3-44c**	0	No reaction.
 **3-44d**	35	^{1}H: 11.34 (s, 1H), 6.79 (s, 1H).
 **3-44e**	25	^{1}H: 12.17 (s, 1H), 6.76 (s, 1H).
 **3-44f**	5	^{1}H: 11.30 (s, 1H), 6.73 (s, 1H).
 **3-44g**	75	^{1}H: 12.38 (s, 1H), 6.91 (s, 1H).
 **3-44h**	72	^{1}H: 9.70 (s, 1H), 6.29 (d, *J* = 1.6, 1H).

 **3-44i**	52	^{1}H: 11.21 (s, 1H), 6.28 (s, 1H).
 **3-44j**	55	^{1}H: 10.55 (s, 1H), 6.23 (s, 1H).
 **3-44k**	70	^{1}H: 11.69 (s, 1H), 6.43 (s, 1H)
 **3-44l**	75	^{1}H: 10.38 (s, 1H), 6.78 (d, *J* = 2.1, 1H).

Deductions from Table 2:

The formation of products **3-44a-l** was confirmed using both ^{1}H and ^{13}C NMR spectroscopy. In analyzing the ^{1}H NMR data from the respective spectra of products **3-44a-l**, one could deduce that the signal previously found between 5 and 6 ppm due to the presence of the pyridine amino functionality had disappeared. However, two new signals were seen in the ^{1}H NMR spectrum of each product. One signal was observed at 6.23 ppm in the case of **3-44j** and at 6.91 ppm in the case of **3-44g** while signals for other products were observed between these two signals. These signals are consistent with the proton at position 3 of 7-azaindoles, present in all the products. Indeed, it has been shown that depending on the substituents on the 7-azaindole ring, the position of this proton was mostly observed below 7.00 ppm as a singlet (when position 2 is occupied) although sometimes it exhibits long range coupling with other protons on the azaindole.[28] The

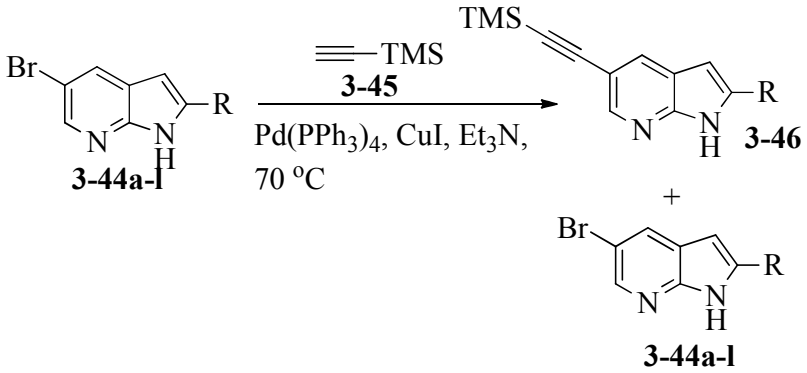
second signal which appeared broad in nature was observed at 9.70 ppm for **3-44h** and at 12.38 ppm in the case of **3-44g**. This signal is a characteristic of the NH of the azaindole. This was further confirmed by comparison with other available 2,5-disubstituted 7-azaindoles which showed the NH functionality could be in the same region but will heavily depend on the substituents on the azaindole[26,28]. Although we celebrated the successful synthesis of a number of 7-azaindole derivatives, we could not isolate any of the desired product **3-44c** or even recover the starting material. Initially, we thought perhaps transesterification was to blame for this unsuccessful reaction, however, we soon realized that even with the use of excess potassium *tert*-butoxide we could not form the *tert*-butyl ester derivative of the 7-azaindole **3-44c**.

Although most of the yields in Table 2 are moderate, three of them were indeed disappointing with **3-44f** at 5%, **3-44e** at 25% and **3-44d** at 35%. These rather disappointing results were not expected as we thought that potassium *tert*-butoxide would not affect the carbamate functionality in the substrates. However, it has been reported that long exposure of carbamates to potassium *tert*-butoxide at high temperatures led to complex mixtures with reduced yields.[56] Therefore, we suspected this problem was the same in our case, which led to these disappointing results. Even though some results were not as impressive as we hoped, we decided to continue with our aim to gain access to triazole derivatives of 7-azaindoles using Click reaction conditions.

3.2.4 Synthesis of 7-azaindole derivatives of triazoles using the Click reaction conditions

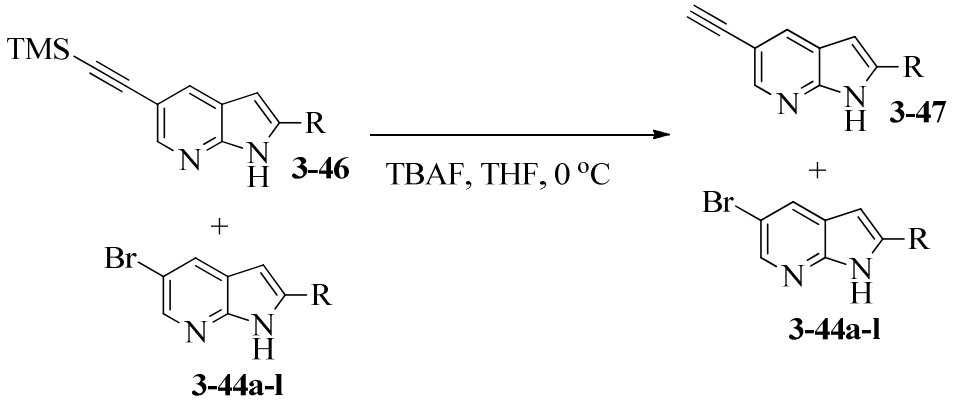
The next step in the synthesis of triazole derivatives started with the preparation of terminal alkynes using Sonogashira coupling reaction using the available bromine substituent of azaindoles we had prepared. Initially, we decided to couple trimethylsilylacetylene (**3-45**) with our substrates **3-44a-l** under Sonogashira coupling reaction conditions in order to obtain product **3-46**. Unfortunately, the reactions resulted in the formation of our desired azaindole **3-46** plus unreacted **3-44a-l** (**Scheme 11**). Disappointingly, our efforts to separate our desired products **3-46** from the starting materials were unsuccessful. With this reaction not going to completion, we decided to repeat the reaction under the same reaction conditions only increasing the time from 8 hours to 24 hours, but without success. Furthermore, the addition of sodium iodide to the reaction did not have any effect whatsoever, no matter how long the reaction was carried out.

Although the reaction failed to go to completion and we could not separate the desired product from starting material, we decided to continue with the mixture to the next step without separation.



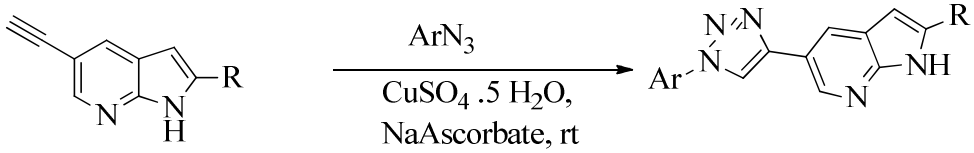
Scheme 11

Since we had decided to carry on with the mixture, our next step was to remove the protecting trimethylsilyl group to obtain terminal alkynes for performing the Click chemistry reaction. There are various reaction conditions that could be employed to remove the trimethylsilyl group including the use of potassium fluoride in methanol[57], the use of sodium hydroxide in methanol[26] and the use of tetrabutylammonium fluoride (TBAF) in THF.[58] We decided to use TBAF in our case and thus, the mixture of **3-44a-l** and **3-46** was dissolved in THF and the resulting solution cooled in ice-water mixture followed by treatment with TBAF. After 1 hour, a saturated aqueous ammonium chloride solution was added and the mixtures were extracted with ethyl acetate, the solvent was removed on a rotary evaporator and the resulting crude materials were passed through silica gel in a column to remove TBAF and its byproducts to give a mixture of **3-44** and **3-47** (**Scheme 12**). It should be noted that no further attempts were made to try and separate terminal alkynes **3-47** from starting materials **3-44a-l**. The mixtures were again taken without further purification to synthesize 1,2,3-triazole derivatives using the Click reaction.



Scheme 12

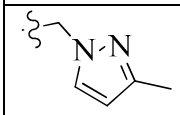
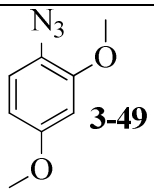
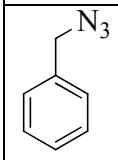
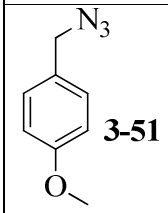
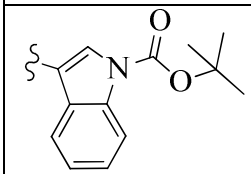
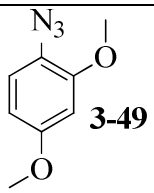
The Click reaction was fully explained in 2001 and since its discovery, it has been widely used.[59] Since its introduction, various reaction conditions have been reported to accomplish the formation of triazoles including neat reactions at elevated temperatures[60], the use of sodium ascorbate and copper sulfate[61], the use of ruthenium catalysts[62] and microwave assisted reactions.[63] We decided to adopt the use of copper sulfate in the presence of sodium ascorbate for the preparation of triazole derivatives of our alkyne substituted 7-azaindoles. Thus, the mixtures of **3-47** and various aromatic azides were dissolved in THF and were treated with copper sulphate, followed by the addition of sodium ascorbate and each reaction mixture was allowed to stir for 24 hours at room temperature. After workup with dichloromethane, the resulting crude mixture was purified by flash column chromatography to give the corresponding triazoles represented by the general structure **3-48a-u**. **Scheme 13** is representative of the overall reaction and the full results are included in Table 3. It should be noted that the yields of triazole derivatives were calculated based on the initial amount of 7-azaindole derivatives **3-44a-l** (that is over three steps since we failed to isolate terminal alkyne **3-47**). The azides **3-49**, **3-50**, and **3-51** (**Figure 5**) were prepared in our laboratory according to known procedures[64] and were used without further purification or isolation of pure material.

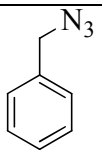
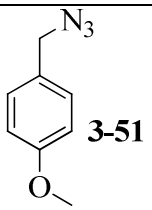
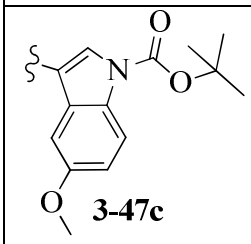
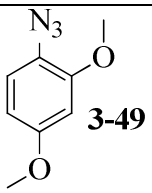
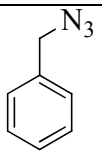
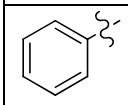
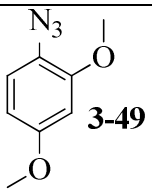
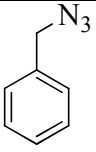
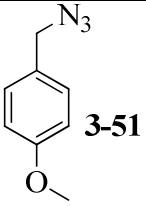


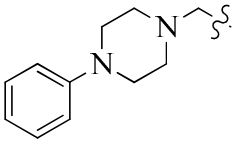
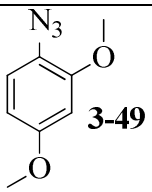
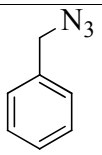
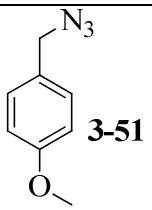
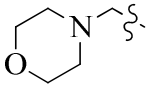
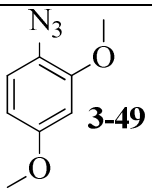
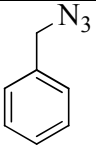
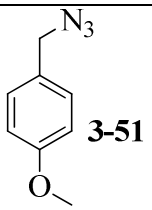
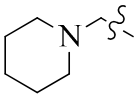
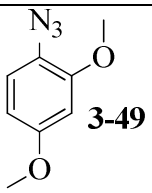
3-47 **3-48a-u**

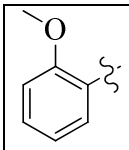
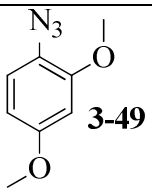
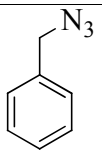
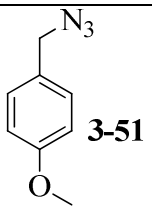
Scheme 13

Table 3: Synthesis of triazole derivatives of 7-azaindoles

R	ArN_3	Product ID (%Yield)	Distinct NMR data information (^1H & ^{13}C) ppm
 **3-47a**	 **3-49**	**3-48a** (80)	^1H: 8.48 (s, 1H), 3.89 (s, 6H). ^{13}C: 161.28, 56.04, 55.73.
	 **3-50**	**3-48b** (75)	^1H: 8.66 (s, 1H), 5.62 (s, 2H). ^{13}C: 153.04, 54.31.
	 **3-51**	**3-48c** (78)	^1H: 8.35 (s, 1H), 7.30 (d, *J* = 8.6, 2H), 6.92 (d, *J* = 8.6, 2H), 5.52 (s, 2H). ^{13}C: 55.36, 53.88.
 **3-47b**	 **3-49**	**3-48d** (65)	^1H: 8.64 (s, 1H), 3.90 (2 x s, 6H). ^{13}C: 161.33, 56.05, 55.75.

	 **3-50**	**3-48e** (60)	^{1}H: 8.72 (s, 1H), 5.68 (s, 2H). ^{13}C: 148.44, 53.04.
	 **3-51**	**3-48f** (67)	^{1}H: 8.51 (s, 1H), 7.31 (d, *J* = 8.5, 2H), 6.95 (d, *J* = 8.5, 2H), 5.54 (s, 2H). ^{13}C: 160.00, 55.37, 53.83.
 **3-47c**	 **3-49**	**3-48g** (61)	^{1}H: 8.65 (s, 1H), 3.87 (3 x s, 9H). ^{13}C: 161.37, 56.05, 55.80, 55.76.
	 **3-50**	**3-48h** (63)	^{1}H: 8.55 (s, 1H), 5.61 (s, 2H). ^{13}C: 156.35, 54.24.
 **3-47d**	 **3-49**	**3-48i** (76)	^{1}H: 8.81 (s, 1H), 3.88 (2 x s, 6H). ^{13}C: 161.24, 56.19, 55.73.
	 **3-50**	**3-48j** (81)	^{1}H: 8.69 (s, 1H), 5.68 (s, 2H). ^{13}C: 149.40, 53.04.
	 **3-51**	**3-48k** (73)	^{1}H: 8.63 (s, 1H), 5.58 (s, 2H), 3.75 (s, 3H). ^{13}C: 159.15, 66.99, 55.13.

 **3-47e**	 **3-49**	**3-48l** (85)	^{1}H: 8.82 (s, H), 3.89 (2 x s, 6H). ^{13}C: 161.23, 67.96, 56.01, 55.71.
	 **3-50**	**3-48m** (88)	^{1}H: 8.71 (s, 1H), 5.56 (s, 2H). ^{13}C: 151.19, 55.91, 54.26, 53.27.
	 **3-51**	**3-48n** (88)	^{1}H: 8.72 (s, 1H), 5.49 (s, 2H), 3.81 (s, 3H). ^{13}C: 159.97, 55.90, 55.36, 53.83, 53.27.
 **3-47f**	 **3-49**	**3-48o** (74)	^{1}H: 8.77 (s, 1H), 3.89 (2 x s, 6H). ^{13}C: 161.29, 66.77, 56.06, 55.73, 53.55.
	 **3-50**	**3-48p** (79)	^{1}H: 8.73 (s, 1H), 5.60 (s, 2H). ^{13}C: 148.76, 66.95, 56.35, 54.30, 53.70.
	 **3-51**	**3-48q** (78)	^{1}H: 8.70 (s, 1H), 7.30 (d, J = 8.6, 2H), 6.93 (d, J = 8.7, 2H), ^{13}C: 160.00, 66.97, 56.32, 55.36, 53.86, 53.70.
 **3-47g**	 **3-49**	**3-48r** (80)	^{1}H: 8.68 (s, 1H), 3.82 (s, 6H). ^{13}C: 161.26, 56.03, 55.71.

 **3-47h**	 **3-49**	**3-48s** (80)	^{1}H: 8.79 (s, 1H), 3.90 (2 x s, 6H). ^{13}C: 161.28, 56.06, 55.85, 55.73.
	 **3-50**	**3-48t** (79)	^{1}H: 8.46 (s, 1H), 5.60 (s, 2H). ^{13}C: 156.02, 55.80, 54.29.
	 **3-51**	**3-48u** (77)	^{1}H: 8.68 (s, 1H), 5.50 (s, 2H), 3.81 (s, 3H). ^{13}C: 159.98, 55.79, 55.35, 53.84.

Deductions from Table 3:

The formation of products **3-48a-u** was confirmed using both ^{1}H and ^{13}C NMR spectroscopy. In analyzing ^{1}H NMR spectral data from the respective spectra of products **3-48a-u**, one could observe an increase in the number of protons in the aromatic and aliphatic regions, accompanied by an increased number of carbons in the aromatic and aliphatic regions. One of the most notable feature in the ^{1}H NMR spectra of products **3-48a-u** was the presence of a broad singlet signal appearing at 8.35 ppm in the case of product **3-48c** and at 8.82 ppm in the case of product **3-48l** due to the triazole ring. As far as this range was concerned, one could deduce that the position of the signal was mainly influenced by two things namely, the type of an azide used and the substituents at two positions of 7-azindoles. For example, signals in which 1-(azidomethyl)-4-methoxybenzene **3-51** was used appear mostly upfield as compared to the signals in which 1-azido-2,4-dimethoxybenzene **3-49** and (azidomethyl)benzene **3-50** were used, in which signals appeared more downfield. Of the three azides used, (azidomethyl)benzene **3-50** without the methoxy groups had signals appearing more downfield than the other two azides. Thus, one could say the presence of the methoxy groups which are electron donating clearly affects the position of the triazole ring proton.

Apart from using this single signal due to the triazole ring as a way of confirming the formation of our desired products, the ^{1}H NMR spectrum of each product was further analyzed. For example, in analyzing the ^{1}H NMR spectra for products **3-48a**, **3-48d**, **3-48g**, **3-48i**, **3-48l**, **3-48o**, **3-48r** and **3-48s** in which 1-azido-2,4-dimethoxybenzene (**3-49**) was used, the two methoxy groups present in **3-49** could also be observed in the region between 3.87 ppm and 3.90 ppm integrating for 6 protons for each of the products. Furthermore, the ^{1}H NMR spectra of products **3-48b**, **3-48e**, **3-48h**, **3-48j**, **3-48m**, **3-48p** and **3-48t** in which (azidomethyl)benzene (**3-50**) was used displayed a unique signal in the regions between 5.60 ppm and 5.68 ppm due to methylene next to nitrogen to the triazole ring as a singlet for two protons. The formation of products **3-48b**, **3-48e**, **3-48h**, **3-48j**, **3-48m**, **3-48p** and **3-48t** was further confirmed by the presence of a phenyl ring which increased the number of protons in the aromatic region. Additionally, the presence of N-CH_2 in the region between 5.48 ppm and 5.58 ppm to the triazole ring integrating for two protons and the presence of a *para*-methoxy group on the azide also observed in the region between 3.75 ppm and 3.81 ppm was good enough to help us confirm the formation of products **3-48c**, **3-48f**, **3-48k**, **3-48n**, **3-48q** and **3-48u**. In addition to ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy was also used to confirm the formation of products **3-48a-u**.

Thus, analysis of the ^{13}C NMR spectra of products **3-48a**, **3-48d**, **3-48g**, **3-48i**, **3-48l**, **3-48o**, **3-48r** and **3-48s** in which 1-azido-2,4-dimethoxybenzene (**3-50**) was used revealed the presence of a methoxy functionality in the region between 55 and 57 ppm in addition to an increased number of carbon signals in the aromatic region. Additionally, analysis of the ^{13}C NMR spectra of products **3-48b**, **3-48e**, **3-48h**, **3-48j**, **3-48m**, **3-48p** and **3-48t** showed the presence of *N*-CH_2 in the region between 54 and 55 ppm accompanied by an increased number of carbon signals in the aromatic region due to the presence of a phenyl ring. Furthermore, the ^{13}C NMR spectra of products **3-48c**, **3-48f**, **3-48k**, **3-48n**, **3-48q** and **3-48u** were also analyzed and the presence of *N*-CH_2 in the region between 54 and 55 ppm was noted. The presence of methoxy functionality in the region between 55 and 57 ppm was also observed. With this information in hand, we concluded that we had successfully managed to synthesize our desired products in fair to good yields. It should also be noted that although our chosen methodology for the synthesis of triazoles is known to produce 1,4-disubstited-1,2,3-triazoles (**Figure 5**) exclusively[59], during the analysis of our spectra, especially the ^{1}H NMR spectra for some products, the other isomer

believed to be 1,5-disubtituted-1,2,3-triazoles (**Figure 5**) was also evident as a very minor product. As a result, we used other NMR spectroscopy experiments to prove that the 1,4-regioisomer was a major product as will be discussed in the following paragraphs.

3.2.5 1,2,3-Triazole regioisomer elucidation using NOESY and HMBC

The reaction between terminal alkynes and azides could result in the formation of two regioisomers namely 1,4- and 1,5-triazoles (**3-52** and **3-53**) (**Figure 5**) depending on the reaction conditions employed. The mechanism for this reaction has been extensively studied.[65] Different reaction conditions are documented to favor one isomer over the other. For example, the use of copper catalysts was reported to produce 1,4-triazole regioisomer over the 1,5-regioisomer while thermal reaction conditions often produced the mixture of the two isomers.[66] In this PhD project, a copper catalyst was used for the synthesis of the 1,2,3-triazole derivatives, thus we expect the product to be almost exclusively 1,4-regioisomer. Our area of study in the structure of the triazole derivatives was mainly the triazole ring, protons and carbons found in the proximity of this ring. Prior to using ^{1}H-^{1}H (spatial interactions) NOESY and ^{1}H-^{13}C (C-H interaction over 3 bonds) HMBC NMR spectroscopy experiments as the cornerstone for determining the isomer, other experiments such as ^{1}H-^{1}H (3 bonds) COSY and ^{1}H-^{13}C (1 bond) HSQC were considered. However, we concluded that both COSY and HSQC experiments would not be that useful in this matter especially in determining the isomer, but were useful only in assigning the protons on the triazole ring and 7-azaindole moiety.



1,4-triazole (**3-52**) 1,5-triazole (**3-53**)

Figure 5

To ascertain the formation of 1,4-regioisomer with special focus around the triazole ring, ^{1}H-^{1}H NOESY NMR experiment was performed on triazole **3-48u**. In this experiment, we wished to

establish spatial H-H interactions on this triazole. It should also be noted that interactions in this experiment will depend heavily on the orientation of the molecule and this will influence the interaction of protons in space. With the help of COSY and HSQC, we managed to distinguish between H1, H2 and H3 as labeled in **Figure 6**. From the H-H NOESY spectrum, we were able to establish the interaction between H-1 and H-3 while we could not establish any interaction for H-2. However, the interaction between H-1 and H-3 does not really establish which regioisomer had been assembled. The important interaction however was observed between H3 and H4. This interaction between H3 and H4 was the determining factor to establish the type of regioisomer. For example, if we had 1,5-regioisomer, we would have seen the strong interaction between H-2 and H-4 and probably a weak interaction between H-2 and H-5 and this interaction was not observed. Furthermore, we observed a weak interaction between H-3 and H-5 (**Figure 6**) further confirming the presence of 1,4-regiosomer of triazole **3-48u**.

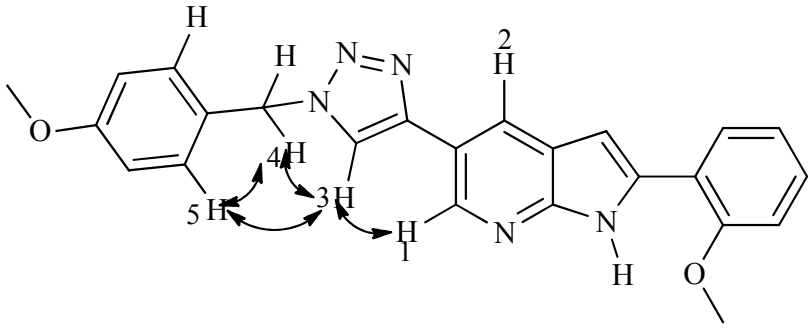


Figure 6 ^{1}H-^{1}H NOESY spectroscopy correlation

To further confirm the formation of 1,4-regioisomer, an additional NMR spectroscopy experiment was performed, in this case ^{1}H-^{13}C correlation over multiple bonds (3 bonds). HMBC seemed like the perfect experiment. Various C-H HMBC correlations are shown in **Figure 7**. Although we have shown several correlations, only few will be able to help us further consolidate the formation of 1,4-regioisomer. For example, for 1,5-regioisomer, we would have expected H-1, H-2 and H-4 to correlate to the same carbon, C-5' and this was not observed in the HMBC NMR spectrum of **3-48u**. On the contrary, the C-H correlation was observed between H-3 and C-7' and the reverse correlation between H-4 and C-6' (**Figure 7**) was also observed. To further consolidate this, we established the correlation between H-5 and C-7' as also observed for H-3. Notably, the correlation between H-4 and C-6' would not be observed if 1,5-regioisomer

was present. With this information, we concluded that we had synthesized the 1,4-regioisomer as the major product and this correlates with the literature view that copper-catalyzed Click reactions yield 1,4-regioisomer triazoles almost exclusively.[65]

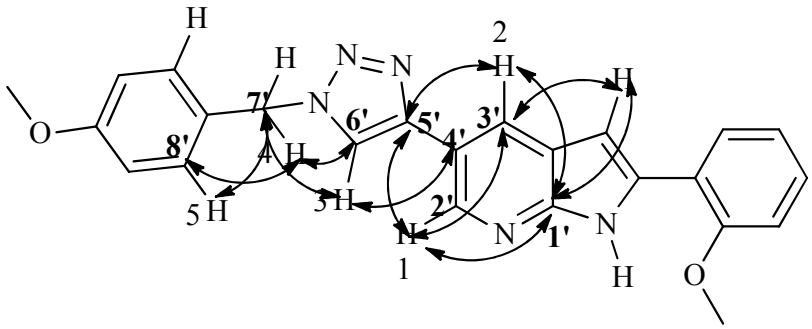


Figure 7 Various C-H correlations in HMBC NMR spectroscopy

3.3 Conclusion and future work

Starting from commercially available 2-aminopyridine, we synthesized triazole derivatives of 7-azaindoles. The synthesis of these triazole derivatives was achieved by using Sonogashira coupling reaction as a key step followed by ring closing of the Sonogashira products under thermal basic conditions to form 7-azaindole derivatives. Unfortunately, our thermal basic conditions using potassium *tert*-butoxide were not suitable for all the substrates leading to some products forming in as little as 5% yield. Eventhough we managed to synthesize triazole derivatives, it has come to our attention that in fact we have synthesized the mixture of the two possible regioisomers in some cases with the 1,4-regioisomer favored over the 1,5-regioisomer triazole. In future, the following may be done:

- Use a different base or alternative methods for the synthesis of products **3-44d**, **3-44e** and **3-44f** in order to obtain these products in better yields.
- Create a bigger library of compounds by using a variety of azide substrates.
- Find better Sonogashira coupling reaction conditions especially suited to synthesizing compounds of general structure **3-46** from the bromide of general structure **3-44**.
- Conduct biological screening of the triazole derivatives against cancer cell lines, bacteria, fungi, HIV, malaria etc.

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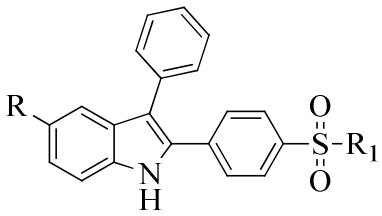
Chapter 4: Novel Synthesis of 2,3,5-Trisubstituted 7-Azaindoles

4.1 Biological importance of 2,3,5-trisubstituted indoles and the related 7-azaindoles

Cyclooxygenase (COX) has been the subject of various investigations due to its association with inflammatory process.[1] As such, COX has been the target for the discovery of the nonsteroidal inflammatory drugs.[2] With this in mind, Hu and co-workers designed, synthesized and evaluated 2,3,5-trisubstituted indoles for the inhibition of COX-2 selectively. Indeed, the compounds of general formula **4-1** were found to be active and selective towards COX-2. Furthermore, the following IC_{50} (nM) values for each compound were determined: 0.14 for **4-1a**, 0.36 for **4-1b** and 0.02 for **4-1c** (**Figure 1**) indicating their activity against COX-2. They also were shown to have IC_{50} (nM) greater than 10 for COX-1.[3] Apart from being COX-2 inhibitors, 2,3,5-trisubstituted indoles also found applications as apoptosis inducers as will be discussed in the next paragraph.



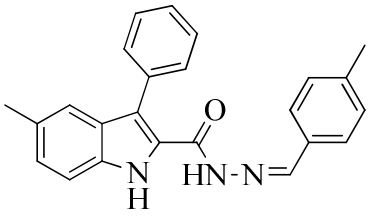
4-1

$R = Cl, R_1 = NH_2$ (**4-1a**)
$R = Cl, R_1 = CH_3$ (**4-1b**)
$R = CH_3, R_1 = NH_2$ (**4-1c**)

Figure 1

Apoptosis, also known as programmed cell death, is the process that occurs in multicellular organisms in which the cells shrink, show blebs followed by marked nuclear chromatin condensation and finally fragmentation. This process plays a very important role in embryonic

development and normal adult life.[4] Recently, Zhang and co-workers embarked on a mission to develop and evaluate 2,3,5-trisubstituted indoles for inducing apoptosis. Therefore, compound **4-2** was developed and tested against T47D breast cancer cell lines. This 2,3,5-trisubstituted indole **4-2** (**Figure 2**) was found to be very potent against T47D cancer cell lines giving an EC_{50} (μM) value of 0.1.[5] Indeed, compounds containing the indole nucleus proved to be rich in biological activity.



4-2

Figure 2

In addition to the biological activities shown by 2,3,5-trisubstituted-indoles, 2,3,5-trisubstituted-7-azaindoles proved to be of similar importance. For example, 2,3,5-trisubstituted-7-azaindole **4-3** and was found to be an excellent v-raf murine sarcoma viral oncogen homolog B1 (b-RAF) inhibitor with an IC_{50} value of 0.165 μM.[6] Additionally, Gelbard and co-workers designed, synthesized and evaluated various substituted-7-azaindoles against mammalian protein kinases and it was found that 7-azaindole derivatives **4-4**, **4-5** and **4-6** (**Figure 3**) were able to inhibit mixed lineage kinase 3 (MLK3) which is one of the most expressed of the mixed lineage kinases (MLKs) with IC_{50} values ranging from 0.1 – 1μM.[7]

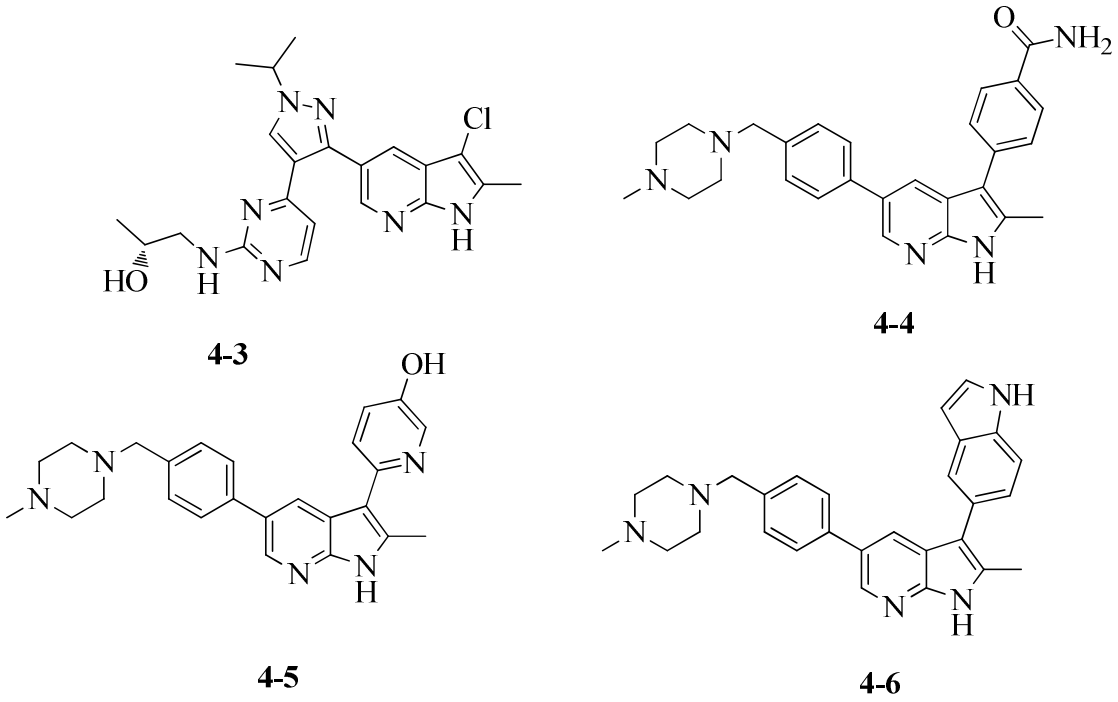


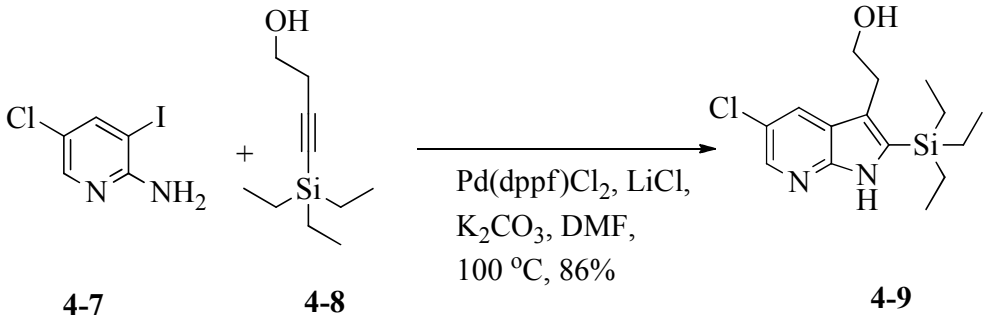
Figure 3

4.2 Methods for the synthesis of 2,3,5-trisubstituted indoles and the related 7-azaindoles

4.2.1 Access to 2,3,5-trisubstituted 7-azaindoles *via* the Larock indole synthesis

The Larock indole synthesis is a chemical reaction in which 2-iodoanilines are reacted with excess internal alkynes and bases such as potassium carbonate or sodium acetate with palladium used as a catalyst. Ligands are usually used to increase the reactivity of the palladium species. Salts such as lithium chloride or ammonium chloride are used to increase the yields of the reaction while also affecting the selectivity.[8] Since its inception, the Larock indole synthesis has been used to prepare 2,3-disubstituted indoles[9] and 2,3-disubstituted azaindoles. It has also been used for the synthesis of trisubstituted 7-azaindoles. For example, Ujjainwalla and co-workers have applied the Larock indole synthesis for the synthesis of trisubstituted 7-azaindole. Thus, treatment of 3-iodo-2-aminopyridine **4-7** with an internal alkyne **4-8** in the presence of palladium

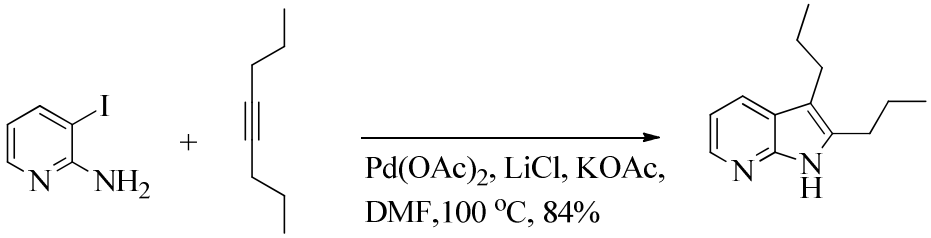
catalyst ($Pd(dppf)Cl_2$) as a catalyst with lithium chloride as a salt of choice resulted in the formation of 2,3,5-trisubstituted 7-azaindole **4-9** in a good yield of 86% yield[10] (**Scheme 1**).



4-7 **4-8** **4-9**

Scheme 1

Park *et al*. later employed the Larock indole synthesis to synthesize 2,3-disubstituted 7-azaindoles. In their publication, various quartenary ammonium chlorides were screened for their ability to effect the synthesis of azaindoles. However, in comparison, lithium chloride showed superior results in terms of selectivity and yields. Hence, a mixture of 3-iodopyridine **4-10**, palladium acetate, potassium acetate and alkyne **4-11** was heated to 100 °C in DMF to afford 2,3-disubstituted 7-azaindole **4-12** in 84% yield[11] (**Scheme 2**).

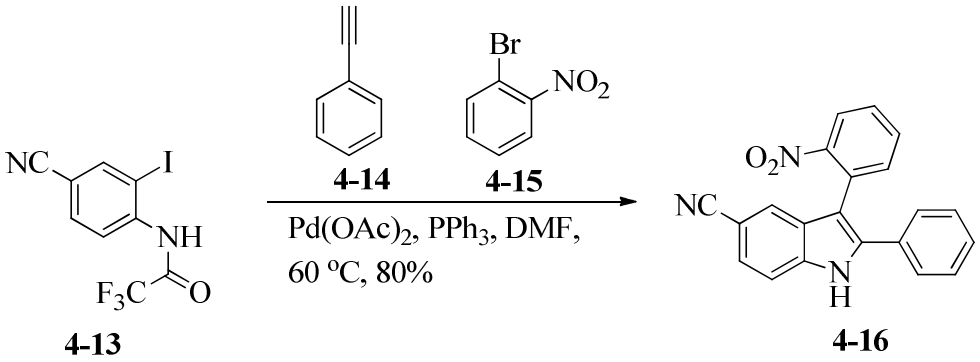


4-10 **4-11** **4-12**

Scheme 2

4.2.3 Access to 2,3,5-trisubstituted indoles and the related azaindoles *via* the Sonogashira coupling reaction

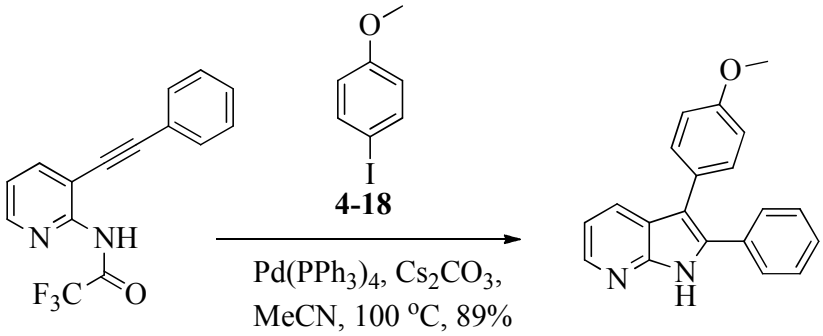
One of the methods that could be used to access the desired indoles is Sonogashira coupling reaction. The preparation of indoles from the Sonogashira coupling reaction[12-21] was usually achieved by performing ring closure of the Sonogashira adducts using bases, metal salts, metal catalysts, acids and other reagents. An extension to this known as the Cacchi reaction has recently been reported. Cacchi *et al*. reported the synthesis of 2,3-disubstituted indoles from 2-alkynylanilines using palladium as a catalyst and potassium carbonate as a base in the presence of vinyl triflates or aryl halides.[22] Recently, Lu *et al*. took advantage of this methodology to prepare trisubstituted indoles. Unlike the original method, Lu *et al*. prepared the Sonogashira adduct *in situ* and subjected it to the conditions used by Cacchi *et al*. to prepare trisubstituted indoles. Thus, 2-iodoaniline **4-13** was treated with a terminal alkyne **4-14** in the presence of potassium carbonate, palladium catalyst and aryl bromide **4-15**. Heating this mixture in DMF at 60 °C gave 2,3,5-trisubstituted indole **4-16** in a good yield of 80% (**Scheme 3**). This type of reaction is considered to be a one-pot synthesis and it eliminates the need for the isolation of the Sonogashira adducts.[23]



Scheme 3

Since its introduction in 1992, the so-called Cacchi reaction has been the subject of many investigations. For example, Cacchi *et al*. investigated the use of arenediazonium tetrafluoroborates in the presence of tetrabutylammonium iodide using palladium as a catalyst[24] while Chen *et al*. investigated the use of a microwave irradiation for one-pot application of the

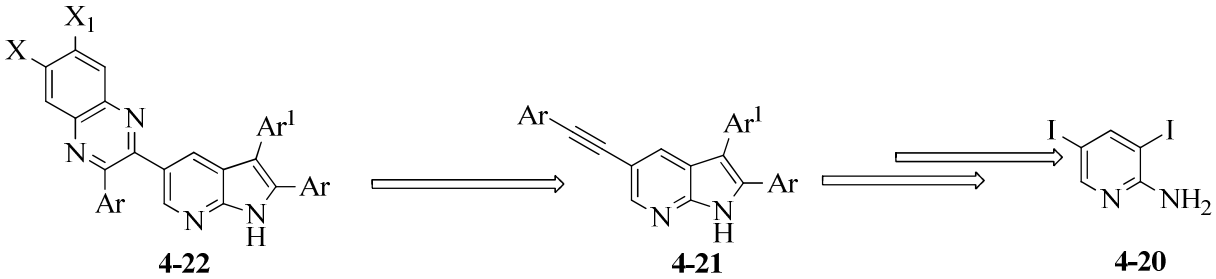
Cacchi reaction.[25] Recently, Cacchi and co-workers investigated the synthesis of azaindoles using cesium carbonate as a substitute for potassium carbonate in the Cacchi reaction. When alkyne **4-17** was treated with an aryl iodide **4-18** in the presence of cesium carbonate and palladium catalyst in acetonitrile at 100 °C, the 2,3-disubstituted 7-azaindole **4-19** was obtained in 89% yield[26] (**Scheme 4**) where the trifuoroacetate group is believed to assist in the activation of the amino group. The wide applications and mild conditions used in the Cacchi reaction made it very suitable for the preparation of various trisubstituted indoles. Apart from their interesting structures, 2,3,5-trisubstituted indoles are also of biological importance.



Scheme 4

4.3 Chemistry

For the purpose of this PhD, we hoped to synthesize 7-azaindoles containing a quinoxaline functionality which would be covalently linked at the 5-position of the 7-azaindole. For this PhD project, 2,3,5-trisubstituted-7-azaindole derivatives of general structure **4-22** could be obtained from the possible oxidation of a C-C triple bond on azaindole **4-21** under microwave conditions with reagents such as palladium chloride in the presence of aryl-1,2-diamines. On the other hand, 7-azaindole **4-21** could be synthesized from the possible combination of the Sonogashira coupling reaction and the Cacchi reaction with **4-20** as the starting material (**Scheme 5**).



Scheme 5

Quinoxaline and its derivatives are important nitrogen-containing compounds with various biological activities.[27] For example, quinoxaline **4-23** was found to be a 5-HT_3 antagonist inhibitor[28] while quinoxaline **4-24** was found to a potent inhibitor of Jnk Stimulatory Phosphatase-1 (JSP-1), an important member of dual-specificity proteins (**Figure 4**).[29] Additionally, quinoxaline derivative **4-25**, which was designed and synthesized by Chen and co-workers was found to be active against various cancer cell lines.[30] Moreover, the quinoxaline functionality was also found embedded in drugs such as varenicline[31] (**4-26**), a drug used to treat smoking addiction, and in bromodine (**4-27**), a drug used for the treatment of open-angle glaucoma (**Figure 4**).[32]

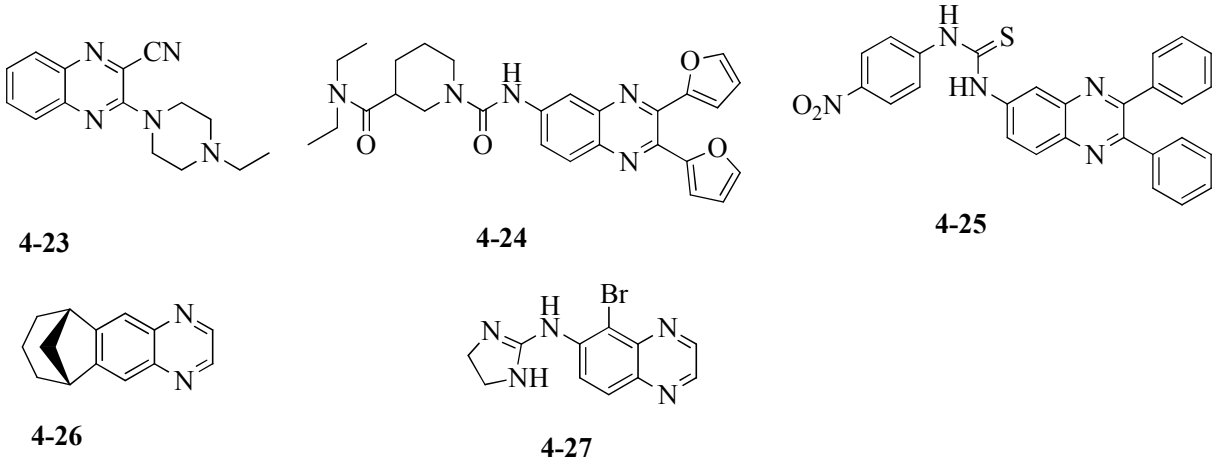
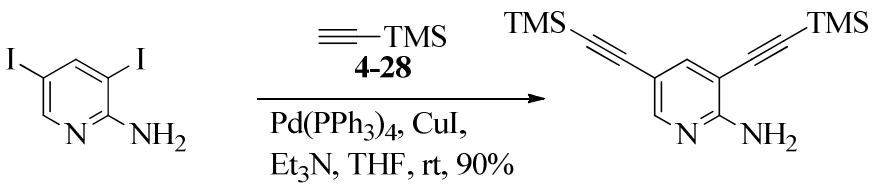


Figure 4

Thus, with these interesting biological activities shown by the quinoxaline functionality, our plan was to synthesize 7-azaindoles containing a quinoxaline functionality for compounds with potentially interesting biological activities.

4.3.1 Synthesis of 3,5-*bis*[(4-methoxyphenyl)ethynyl]pyridin-2-amine (4-32)

Our route to the synthesis of 2,3,5-trisubstituted 7-azaindoles started with commercially available 2-amino-3,5-diiodopyridine (**4-20**). Our first step was to perform a Sonogashira coupling reaction on **4-20** using a palladium catalyst and copper(I) iodide as a co-catalyst. A degassed solution of **4-20** in THF was treated with a palladium catalyst, copper(I) iodide, degassed triethylamine and finally a degassed solution of excess trimethylsilylacetylene (**4-28**) (**Scheme 6**).[33] The resulting mixture was stirred at room temperature for 18 hours under an argon atmosphere. After normal workup and purification by flash silica gel column chromatography, 3,5-*bis*[(trimethylsilyl)ethynyl]pyridin-2-amine (**4-29**) was obtained in a good yield of 90%. The formation of **4-29** was confirmed by both ^{1}H NMR and ^{13}C NMR spectroscopy. A close examination of the ^{1}H NMR spectrum of **4-29** showed a signal at 0.03 ppm, indicating the presence of a trimethysilyl group on the newly formed molecule, in addition to the presence of the aminopyridine signals found at 7.90, 7.41 and 5.02 ppm. The analysis of the ^{13}C NMR spectrum indicated the presence of a C-C triple bond with signals at 94.99 and 99.25 ppm due to the presence of the alkyne functionality plus trimethylsilyl group signal appearing at 0.06 ppm. Furthermore, the formation of the product **4-29** was confirmed by the infrared spectrum which showed the presence of a C-C triple bond at 2250 cm^{-1}. Due to the success of this first step, we were set for the next step of our synthesis towards 2,3,5-trisubstituted azaindoles.

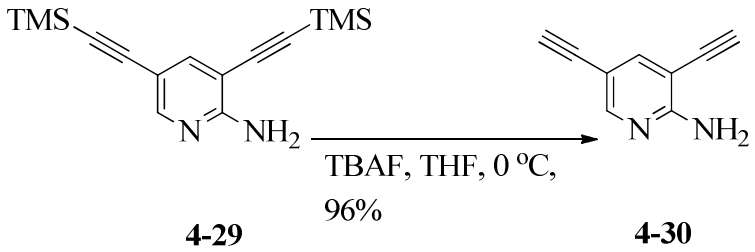


4-20 **4-29**

Scheme 6

Next, we decided to remove the trimethylsilyl protecting group in order to gain access to terminal alkynes which can be further functionalized. The silyl protecting group could be removed by using potassium fluoride in methanol[34] or tetrabutylammonium fluoride (TBAF) in THF[43] usually at lower temperatures. The use of both these reagents proved successful but we

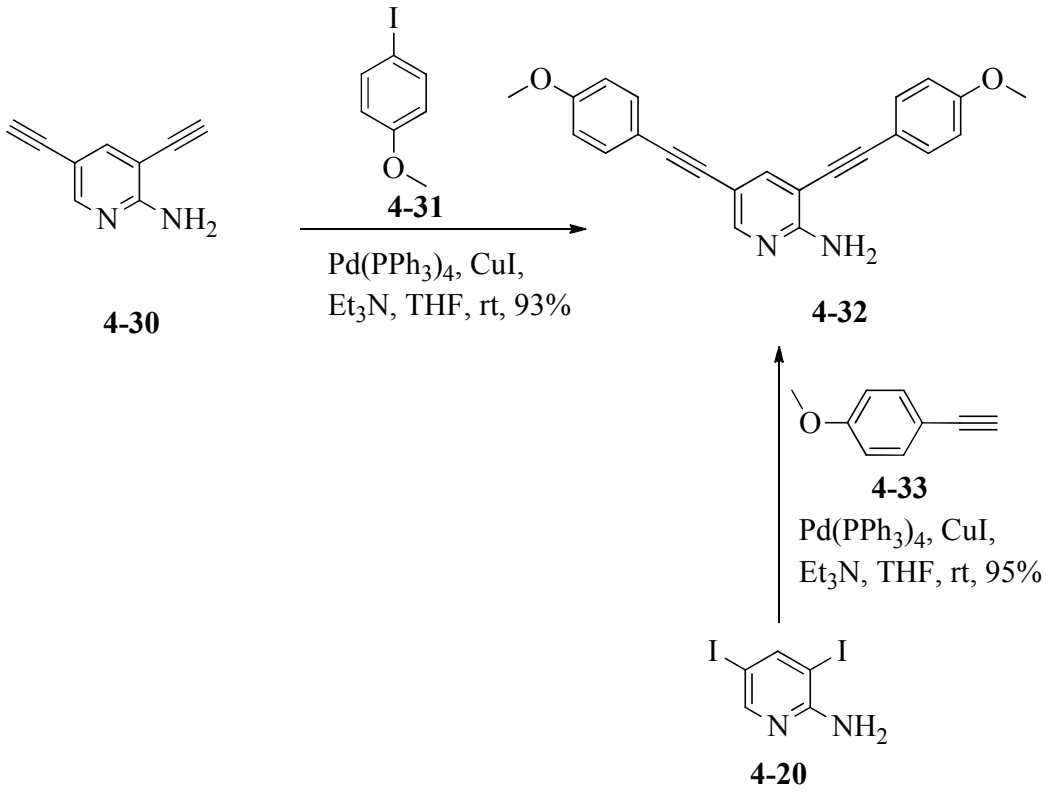
later settled on TBAF due to shorter reaction times. Thus, **4-29** was dissolved in THF and the solution was cooled in an ice-water mixture before being treated slowly with TBAF. The resulting crude product was purified by flash column chromatography to yield the desired product **4-30** (**Scheme 7**). The absence of a signal previously found at 0.03 ppm due to the trimethylsilyl group and the appearance of new signals at 3.42 and 3.06 ppm due to the presence of the two terminal alkyne hydrogen atoms in the ^{1}H NMR spectrum and the disappearance of a signal previously found at 0.06 ppm due to the trimethylsilyl group in the ^{13}C NMR spectrum were evidence that we had formed the desired product **4-30**. Our next step was to functionalize the newly formed terminal alkyne.



Scheme 7

Although there are a handful of reactions available for the functionalization of terminal alkynes, our reaction of choice was the Sonogashira reaction as we were interested in synthesizing trisubstituted 7-azaindoles. We treated terminal alkyne **4-30** under Sonogashira coupling reaction conditions previously described[33] in the presence of *p*-iodoanisole (**4-31**) and this resulted in the formation of an internal alkyne **4-32** in an excellent yield of 93% (**Scheme 8**). It should also be noted that **4-32** could also be accessed directly by treating diiodopyridine **4-20** with *p*-ethynylanisole (**4-33**) under the Sonogashira coupling reaction conditions (**Scheme 8**). In this case, **4-32** was isolated in slightly improved yield of 95%. Even though the direct route has slightly improved yield of **4-32** in one step, the downside is the cost of reagent **4-33** which is about R500 per gram. Besides, the overall yield of preparing **4-32** over two steps was over 90%, which was acceptable and also cost effective. In addition, it allowed for the formation of acetylenes that are not commercially available. The formation of **4-32** was confirmed by analyzing the ^{1}H NMR spectrum which indicated the disappearance of two signals previously found at 3.41 and 3.06 ppm due to the presence of the terminal alkyne hydrogen atomo. Further

examination of the ^{1}H NMR spectrum showed the presence of a new signal at 3.85 ppm integrating for six hydrogen atoms, consistent with the presence of two aromatic methoxy groups. Furthermore, the appearance of two new signals at 55.37 and 55.32 was ppm also consistent with the presence of two methoxy groups, as observed upon analyzing the ^{13}C NMR spectrum. With this NMR spectral data in hand, we were satisfied that we had managed to synthesize our desired product **4-32**. With alkyne **4-32** successfully synthesized, we now planned to attempt the Cacchi reaction with various aryl iodides.

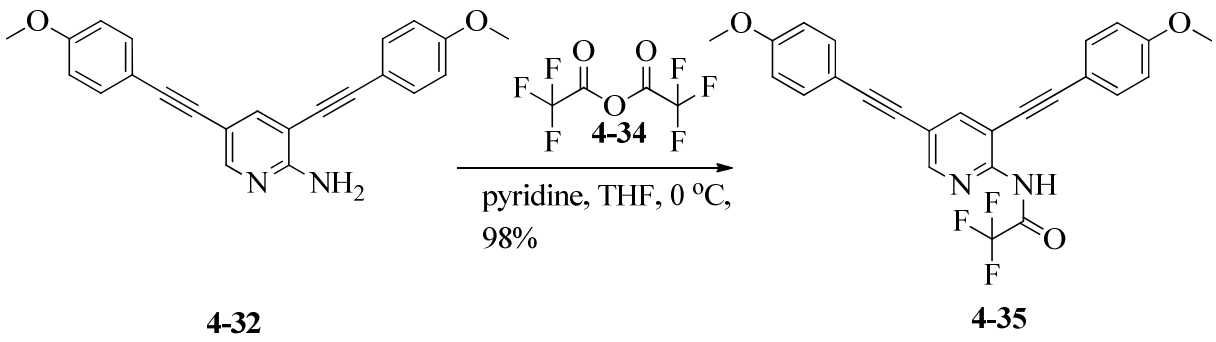


Scheme 8

4.3.2 Synthesis of 7-azaindole derivatives by the Cacchi reaction

Before we could begin with the Cacchi type reactions, we had to acylate the primary amine on **4-32** with a strong electron-withdrawing group such as a Trifluoroacetic acid moiety to form the required amide. The presence of electron-withdrawing groups was thought to increase the

reactivity of the NH group, thereby facilitating a smooth ring closing reaction under the Cacchi conditions to afford azaindoles.[22] There were various conditions available for protection of the amino group of pyridine using trifluoroacetic anhydride. The use of ultrasound[35], potassium carbonate in 1,4-dioxane[36], triethylamine in THF[37] and pyridine in THF at 0 °C have been documented. Initially, we tried the use of potassium carbonate in dioxane but only isolated the mixture of mono-protected plus *bis*-protected products. Secondly, we tried the use of pyridine in THF at low temperature and only isolated the desired mono-protected product **4-35**. Therefore, a mixture of **4-32** and pyridine was cooled in an ice-water mixture before being treated dropwise with anhydride **4-34**. The desired product **4-35** was produced in 98% yield (**Scheme 9**). The absence of the NH_2 signal formerly appearing at 5.02 ppm and the appearance of a broad distinct signal at 8.91 ppm due to the amide in the ^{1}H NMR spectrum was used to confirm the formation of the product. This was further supported by the ^{13}C NMR spectrum which showed the presence of an amide signal at 160.85 ppm and the infrared spectrum showed a broad NH absorption signal at 3343 cm^{-1} and a C=O absorption signal at 1721 cm^{-1}. With this data, we were convinced we had the right product and we sought to test our substrate in the Cacchi reaction.

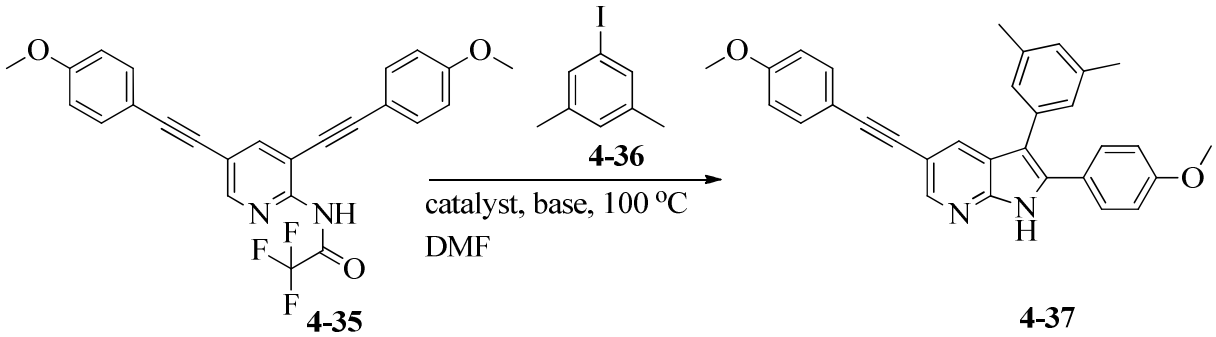


4-32 **4-35**

Scheme 9

Under the original Cacchi reaction conditions, $Pd(PPh_3)_4$ was used as a catalyst in the presence of potassium carbonate as a base.[22] This methodology was later extended by Arcadi *et al*. for the synthesis of 2-sustituted-3-acylindoles, again in the presence of $Pd(PPh_3)_4$ as a catalyst and potassium carbonate as a base. Other catalysts such as $Pd(OAc)_2(PPh_3)_2$ and $Pd(dba)_2P(o\text{-tolyl})_3$ were investigated but were found to yield only moderate results.[38] In 1997, Cacchi *et al*. demonstrated the use of $Pd(dba)_3$ in the presence of ligands such as triphenylphosphine with

potassium carbonate as a base for the preparation of 3-substituted indoles.[39] Recently, Cacchi *et al*. prepared 2,3-disubstituted azaindoles using the same methodology but using cesium carbonate as a base instead of potassium carbonate.[26] In reviewing this methodology, the two most used catalysts were $Pd(PPh_3)_4$ and $Pd(dba)_3$ in the presence of various bases and solvents. However, depending on the substrates to be used, some reactions performed well in the presence of $Pd(PPh_3)_4$[40] while others did well in the presence of $Pd(dba)_3$.[41] In order for us to utilize the Cacchi reaction, we had to determine optimum reaction conditions. Thus, we treated **4-35** with iodoaryl **4-36** under different conditions to afford the trisubstituted 7-azaindole **4-37** (**Scheme 10**).



Scheme 10

Table 1 below shows the different conditions employed to determine optimal conditions for the Cacchi reaction.

Table 1: Reaction of alkyne **4-35** with iodo **4-36** to form azaindole **4-37** under different conditions.

Entry	Catalyst	Base	Solvent	Time (h)	Temp. (°C)	Conversion %[a]
1	$Pd(PPh_3)_4$	–	DMF	18	100	0
2	$Pd(dba)_3$	–	DMF	18	100	0
3	$Pd(dba)_3$	Na_2CO_3	DMF	16	100	0
4	$Pd(PPh_3)_4$	Na_2CO_3	DMF	16	100	10
5	$Pd(dba)_3$	K_2CO_3	DMF	14	100	25
6	$Pd(PPh_3)_4$	K_2CO_3	DMF	14	100	50

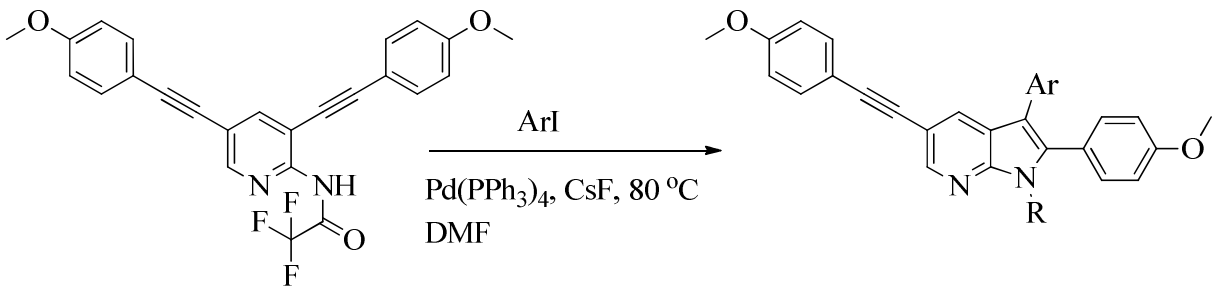
7	$Pd(dba)_3$	KH_2PO_4	DMF	20	100	0
8	$Pd(PPh_3)_4$	KH_2PO_4	DMF	20	100	0
9	$Pd(dba)_3$	Cs_2CO_3	DMF	10	100	60
10	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	10	100	100
11	$Pd(dba)_3$	CsF	DMF	12	100	70
12	$Pd(PPh_3)_4$	CsF	DMF	12	100	100
13	$Pd(PPh_3)_4$	CsF	DMF	8	80	100

[a]All conversions are ^{1}H NMR spectra estimates relative to the starting material present.

Deductions from Table 1:

We first tried the Cacchi reaction with both $Pd(PPh_3)_4$ and $Pd(dba)_3$ in the absence of a base in DMF due to the solubility of the starting material in DMF (entry 1 and 2) but we could not isolate anything including any recovered starting material. This indeed proved that the base was essential in the reactions involving palladium catalysts. However, when sodium carbonate was introduced, 10% conversion was observed with $Pd(PPh_3)_4$ while $Pd(dba)_3$ showed no improvement. The change of base from sodium carbonate to potassium carbonate saw conversions improve to 25% with $Pd(dba)_3$ and 50% with $Pd(PPh_3)_4$, although the use of potassium dihydrogen phosphate gave no results. The best results were obtained when cesium carbonate and cesium fluoride were used as bases (entries 9-13). Even though both $Pd(dba)_3$ and $Pd(PPh_3)_4$ showed remarkably improved conversions, $Pd(PPh_3)_4$ showed the most improved conversions and the reactions were also cleaner. Cesium fluoride produced cleaner reactions compared to cesium carbonate with overall improved yields and 100% conversion was obtained even at the lower temperature of 80 °C. In conclusion, we managed to determine our optimum conditions for the Cacchi reaction to be $Pd(PPh_3)_4$ as a catalyst and cesium fluoride (CsF) as a base at 80 °C for 8 hours. In general, short or longer reaction times did not affect either the reaction yields or conversions. With these optimum conditions, we attempted the Cacchi reaction with various aryl iodides.

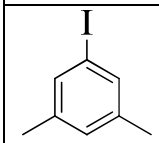
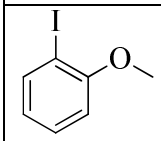
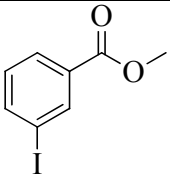
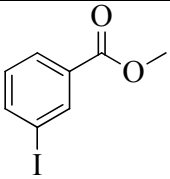
Scheme 11 is shown below for the Cacchi reaction under the optimum conditions and the results are displayed in Table 2.

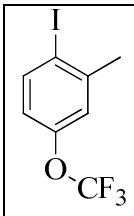
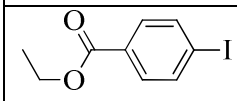


4-35 **4-38**

Scheme 11

Table 2: Treatment of **4-35** with various aryliodides in the presence of CsF and $Pd(PPh_3)_4$.

ArI	R =	Yield %[b]	Cpd ID	Distinct NMR spectarinformation (^1H and ^{13}C) ppm
 **4-36**	H	83	**4-37**	^1H : 7.09 (s, 2H), 2.36 (s, 6H). ^{13}C: 21.42 (CH_3),
 **4-39**	H	89	**4-38a**	^1H: 7.28 (t, *J* = 7.8, 1H), 3.56 (s, 3H). ^{13}C: 55.32 (OCH_3),
 **4-40**	H	15	**4-38b**	^1H: 8.07 (d, *J* = 1.5, 1H), 8.00 (d, *J* = 7.8, 1H), 7.56 (d, *J* = 7.7, 1H), 3.93 (s, 3H). ^{13}C: 167.11 (C=O), 52.20 (OCH_3).
 **4-40**	Me	80	**4-38c**	^1H: 8.05 (s, 1H), 7.88 (dd, *J* = 7.4, 1.5, 1H), 3.90 (s, 3H), 3.84 (s, 3H). ^{13}C: 167.12 (C=O), 52.11 (OMe), 29.72 (NMe).

 **4-41**	H	80	**4-38d**	^{1}H: 7.17 (s, 1H), 7.13 (d, *J* = 8.2, 1H), 2.06 (s, 3H). ^{13}C: 20.31 (Me).
 **4-42**	H	90	**4-38e**	^{1}H: 4.41 (q, *J* = 7.1, 2H), 3.82 (s, 6H), 1.42 (t, *J* = 7.1, 3H). ^{13}C: 166.63 (C=O), 60.93 (OCH_2), 14.40 (Me).

[b]Isolated yields.

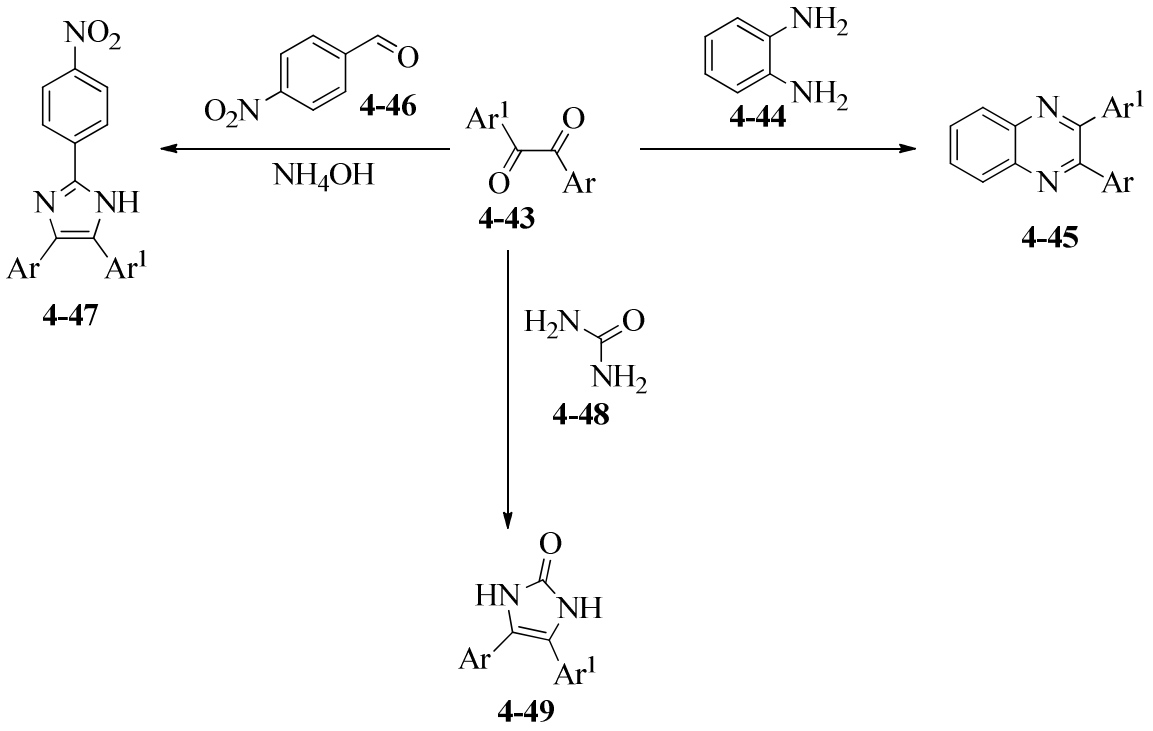
Deductions from Table 2:

The formation of compounds **4-37**, **4-38a-e** was confirmed by examining the ^{1}H and ^{13}C NMR spectra of each compound and the results are shown in Table 2 above. Included in Table 2 are distinct or additional signals from both ^{1}H and ^{13}C spectra as compared with the starting material **4-35**. The ^{13}C NMR spectra of all the compounds indicated the absence of one C-C triple bond as it was involved in the formation of the 7-azaindole ring and the infrared spectra of all the compounds indicated that the absorption signal previously found around 1700 cm^{-1} due to C=O was also absent. Compounds **4-38b**, **4-38c** and **4-38e** however retained a signal in the same region due to the presence of an ester group in each molecule. In general, due to the NMR spectral data presented in Table 2, we were convinced that we had successfully synthesized the desired Cacchi products and we decided to move to the next step, functionalizing the remaining C-C triple bond.

4.3.3 Microwave assisted synthesis of diketone 4-50

In our continued search for the functionalization of a C-C triple bond, we are interested in synthesizing 1,2-diketones which are of interest due to their potential biological activities and as precursors to biologically important compounds. If accessed, 1,2-diketones could be functionalized further to form quinoxaline derivatives **4-45**, imidazole derivatives **4-47** and 1*H*-

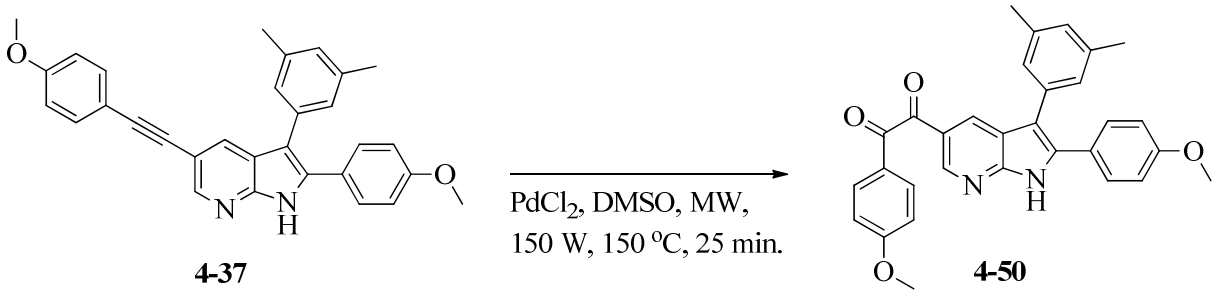
imidazole-2(3*H*)-one derivatives **4-49** which are also of biological importance as outlined in **Scheme 12**.[42] The preparation of 1,2-diketones from acetylenes has been extensively studied. Various methods for the preparation of 1,2-diketones from internal alkynes have been reported including the use of DMSO-PdI_2[42], DMSO-$PdCl_2$[43], Wacker-type oxidation using oxygen[44], $KMnO_4$[45] and palladium on carbon.[46] We adopted the use of DMSO-$PdCl_2$[43] due to the availability of palladium chloride ($PdCl_2$) in our laboratories.



Scheme 12

Thus, when 7-azaindole **4-37** was subjected to microwave irradiation at 150 W and 150 °C in the presence of catalytic amounts of palladium chloride in dimethyl sulfoxide (DMSO) as a solvent, 1,2-diketone **4-50** was obtained in 70% yield (**Scheme 13**). The identity of the product was confirmed using ^{13}C NMR and infrared spectroscopy. The infrared spectrum showed a strong absorption signal at 1730 cm^{-1} due to C=O and the absence of a C-C triple bond absorption signal previously found at 2240 cm^{-1}. The ^{13}C NMR spectrum indicated the absence of a C-C triple bond with signals previously found at 89.57 and 86.74 ppm and the presence of two new

signals at 193.85 and 192.90 ppm an indication of a ketone functionalities. The purpose of synthesizing 1,2-diketones was to functionalize them further to assemble quinoxaline derivatives.



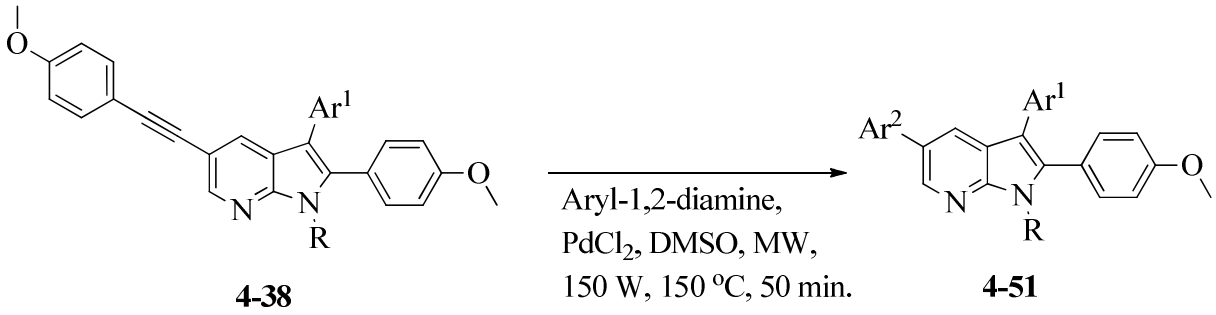
4-37 **4-50**

Scheme 13

4.3.4 Microwave assisted synthesis of quinoxaline derivatives

Bhosale and co-workers reported the use of molecular iodine for the synthesis of quinoxaline derivatives from 1,2-diketones and aryl-1,2-diamines at room temperature.[47] However, the use of a one-pot synthesis of quinoxaline derivatives has also been reported and Chandrasekhar *et al*. reported the one-pot synthesis of quinoxalines using aryl-1,2-diamines, a mixture palladium chloride and copper(II) chloride in poly(ethylene glycol).[48] With evidence of the formation of a 1,2-diketone in hand, we were poised to follow a one-pot synthetic strategy without isolating the 1,2-diketone intermediates.

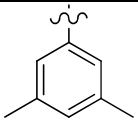
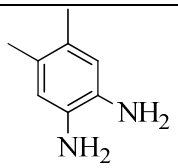
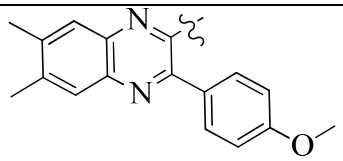
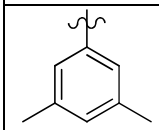
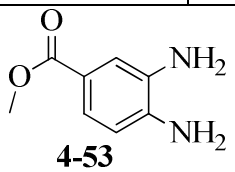
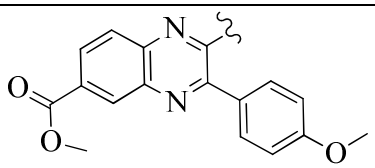
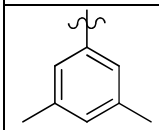
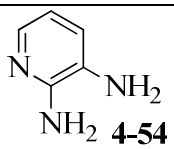
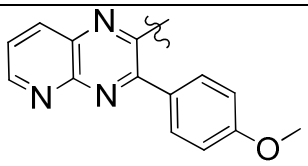
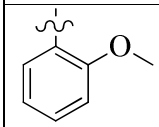
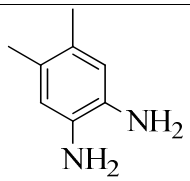
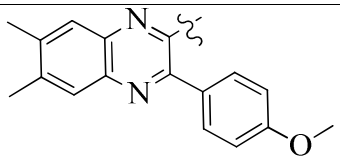
Hence, substrates of general formula **4-38** were irradiated in a microwave reactor in the presence of palladium chloride in DMSO as a solvent. The temperature and power were set at 150 °C and 150 W respectively for 25 minutes. After allowing the reaction to cool to room temperature, the mixture was then treated with aryl-1,2-diamines and irradiated further at the same temperature and power for a further 25 minutes. It was also established that at temperatures and power settings lower than 150 °C and 150 W, the reaction required longer times while temperatures and power settings higher than 150 °C and 150 W led to decomposition of starting material. The reaction mixture was then allowed to cool to room temperature. Purification by flash silica gel column chromatography led to the isolation of products of general formula **4-51** (**Scheme 14**). Different substrates were utilized which led to the products as shown in Table 3.

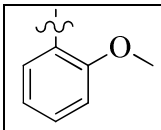
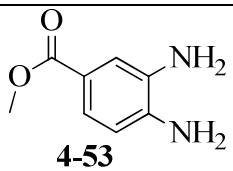
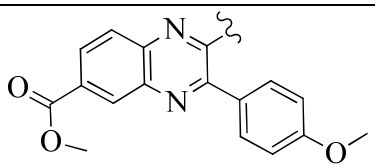
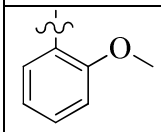
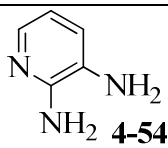
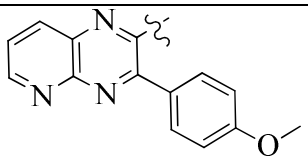
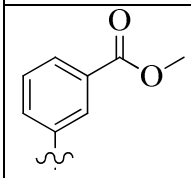
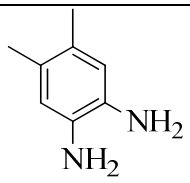
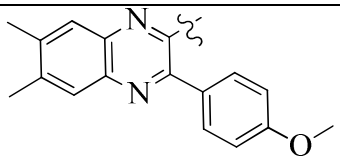
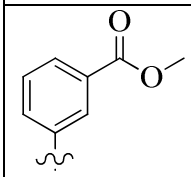
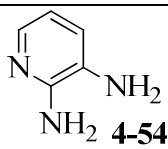
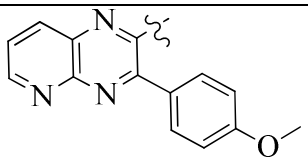
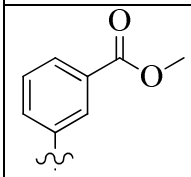
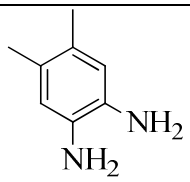
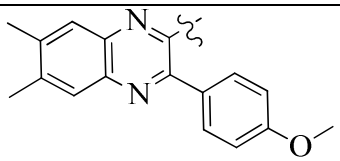
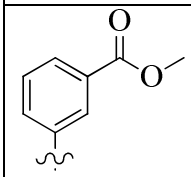
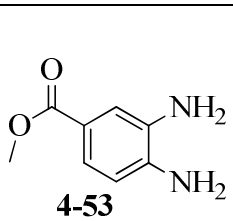
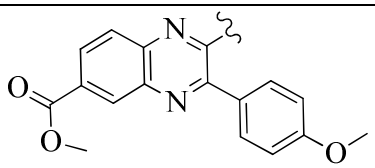
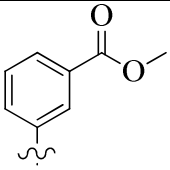
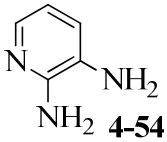
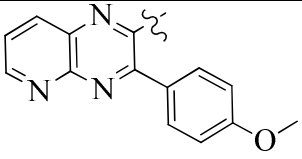


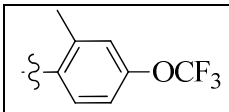
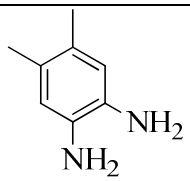
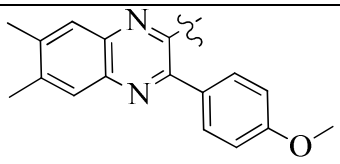
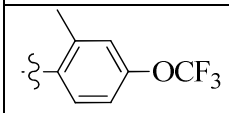
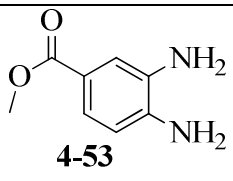
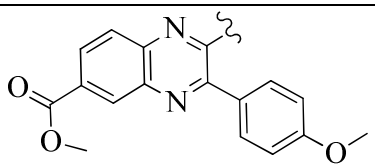
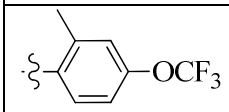
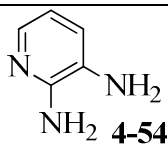
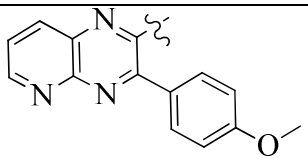
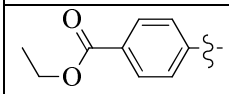
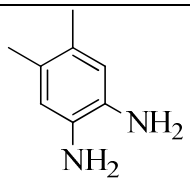
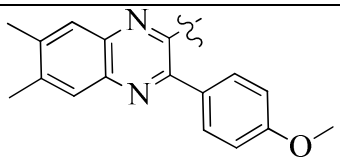
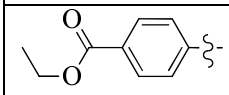
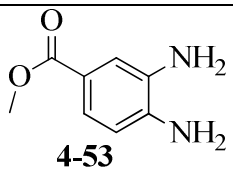
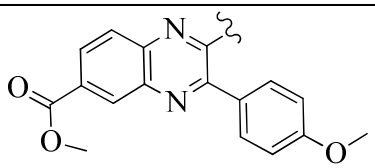
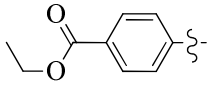
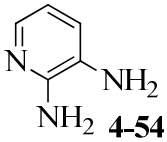
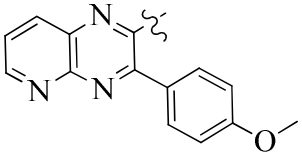
4-38 **4-51**

Scheme 14

Table 3: Treatment of substrate **4-38** with various aryl-1,2-diamines under microwave conditions.

Ar^1	Aryldiamine	Ar^2	R =	Yield %[b]	Product ID
	 **4-52**		H	73	**4-51a**
	 **4-53**		H	69	**4-51b**
	 **4-54**		H	67	**4-51c**
	 **4-52**		H	66	**4-51d**

	 **4-53**		H	69	**4-51e**
	 **4-54**		H	72	**4-51f**
	 **4-52**		H	61	**4-51g**
	 **4-54**		H	64	**4-51h**
	 **4-52**		Me	68	**4-51i**
	 **4-53**		Me	67	**4-51j**
	 **4-54**		Me	66	**4-51k**

	 **4-52**		H	70	**4-51l**
	 **4-53**		H	60	**4-51m**
	 **4-54**		H	72	**4-51n**
	 **4-52**		H	65	**4-51o**
	 **4-53**		H	59	**4-51p**
	 **4-54**		H	75	**4-51q**

[b]Isolated yields.

All products as shown in Table 3 were obtained in moderate yields. The formation of these products was confirmed using both NMR and IR spectroscopy. In this case, infrared spectroscopy played a very important role especially in determining the absence of a C-C triple bond in the newly formed products. Furthermore, infrared spectroscopy was used to monitor the completion of the reaction, especially in determining the presence of diketones. Therefore, using infrared spectroscopy, we managed to confirm the absence of a C-C triple bond absorption signal

previously found at around 2250 cm^{-1} in all alkynes **4-37**, **4-38a-e**. The absence of a C-C triple bond was further confirmed by ^{13}C NMR spectroscopy where the analysis of the ^{13}C NMR spectra of products **4-51a-q** showed that the C-C triple bond signals previously found between 89.57 and 86.74 ppm were no longer present. Since only three aryl-1,2-diamines **4-52**, **4-53** and **4-54** were used, their structure was then confirmed using ^{1}H NMR spectroscopy. Although it was a little easier to identify the structure of the products using diamine **4-52**, both diamines **4-53** and **4-54** gave rise to a mixture of products due to lack of regioselectivity of the reactions. This made it more difficult to identify the newly formed products. Nonetheless, the presence of a signal at around 2.50 ppm (for 6 protons) due to two methyl groups on **4-52** was present in the ^{1}H NMR spectra of all products where **4-52** was employed as an aryldiamine. This was evidence enough that the reactions involving **4-52** were successful. As mentioned before, products involving diamines **4-53** and **4-54** were not easy to deal with due to the presence of inseparable regioisomers in the products formed. However, the presence of regioisomers in the newly formed products could also indicate the success of the reactions involving these two aryldiamines. Thus, we had successfully managed to synthesize 2,3,5-trisubstituted 7-azaindole derivatives (substituted quinoxaline derivatives) and confirmed their formation using NMR and infrared spectroscopy. It should be noted that attempts to separate the regioisomers formed when diamine **4-53** and **4-54** were used by flash silica gel column chromatography were repeatedly met with failure. As a result, for the purpose of this PhD project one regioisomer was randomly chosen as the product without further confirming the formation of the isomer.

4.4 Closing remarks

In short, starting from diiodopyridine, we had successfully managed to synthesize a range of 2,3,5-trisubstituted 7-azaindole derivatives which under further reactions formed quinoxaline derivatives (**Figure 5**). We also had managed to investigate the effect of different bases on the Cacchi reaction conditions and this revealed that the choice of base was very important in such reactions, and that the reactions will not proceed without a base. The yields of quinoxaline derivatives obtained were moderate and possibly there is still room for improvement of these yields. Although the reactions involving diamines **4-53** and **4-54** were successful, the products were obtained as a mixture of regioisomers and perhaps the reaction conditions could be further

investigated in order to obtain a single isomer from the reactions. In general, quinoxaline derivatives (2,3,5-trisubstituted 7-azaindole derivatives) **4-55**, **4-56** and **4-57** were successfully synthesized from the combination of the Sonogashira coupling reaction and the Cacchi reaction where the products of the Cacchi reaction were subjected to the oxidation of a C-C triple bond followed by reaction with aryl-1,2-diamines. Biological screening of the resulting quinoxaline derivatives against cancer cell lines, malaria and other pathologies will be carried out in the future.

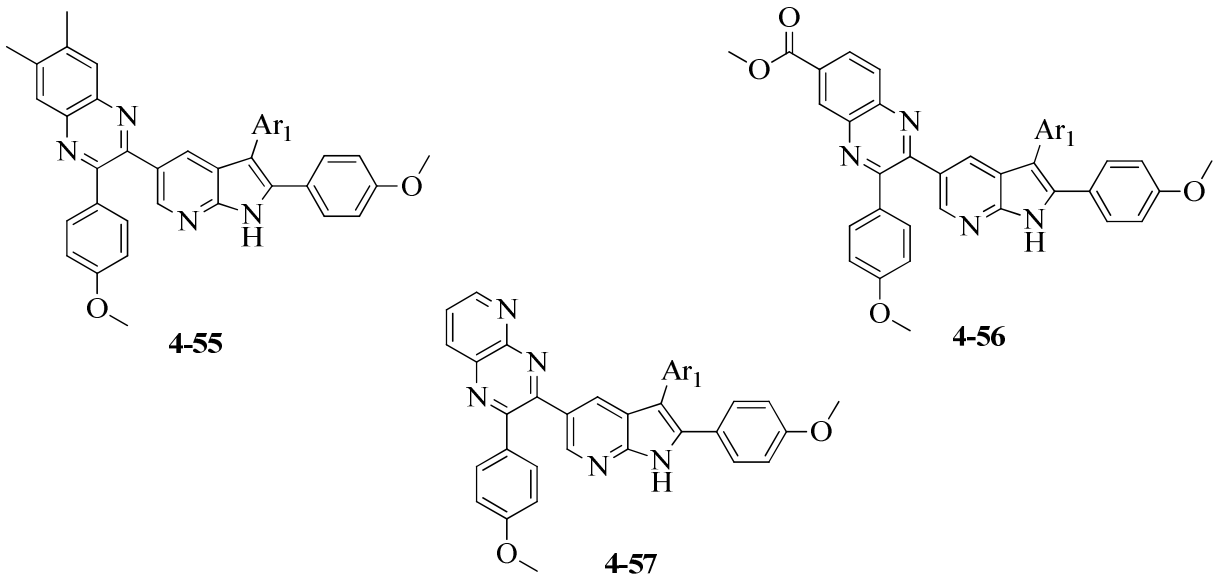


Figure 5

4.5 References

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2) Zhang Y., Mills G. L., Nair M. G., *J. Agric. Food Chem*., **2002**, *50*, 7581.
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4) Trump B. E., Berezesky I.K., Chang S. H., Phelps P. C., *Toxicol. Pathol*., **1997**, *25*, 82.
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Chapter 5: TFAA/TFA Mixture, a Novel Methodology for the Synthesis of 7-Azaindole Derivatives

5.1 Introduction

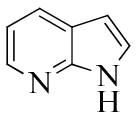
The Sonogashira coupling reaction[1-7] has seen wide application in the preparation of substituted alkynes. This methodology has also been used as a key step towards the synthesis of indoles and azaindoles.[8,9] In the previous chapters, the Sonogashira coupling reaction was used to preparesubstrates as precursors for 7-azaindoles. In those chapters, we described several reaction conditions that were employed to convert the precursors into 7-azaindoles including the use of potassium bases. Taking advantage of this mild and widely applied methodology, we wanted to investigate the development of new and cheap reagents and reaction conditions to convert 2-amino-3-alkynyl pyridines into 7-azaindoles.

For the purpose of this PhD, we were interested in employing acid catalysts in the conversion of 2-amino-3-alkynyl pyridines into 7-azaindoles, where these precursors were obtained using the Sonogashira coupling reaction. Various acids would be screened for their ability to convert 2-amino-3-alkynyl pyridines into 7-azaindoles, including the use of various solvents as we continued the search for the best reaction conditions.

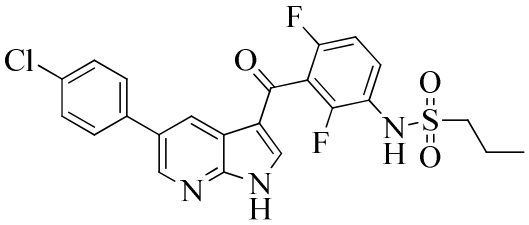
5.2 Biological relevance of 7-azaindole derivatives

The biological importance of 7-azaindoles derivatives has been well investigated. As a result, they were found to be active over a wide range of pathogens. For example, a study by Stoit *et al*. investigated various 2-substituted-7-azaindoles for their ability to be partial nicotinic agonists.[10] On the other hand, Hong *et al*. investigated various 3-substitued-7-azaindoles for their role as phosphoinositide 3-kinase inhibitors,[11] while the ability of 7-azaindole derivatives to inhibit cell division cycle 7 kinases was explored by Ermoli and co-workers.[12] Additionally, 7-azaindole derivatives were found to be useful as selective inhibitors of glycogen synthase kinase-3[13] while

the antiproliferative activities of rebeccamycin analogues with two 7-azaindole moieties have been explored.[14] Furthermore, the application of 3-substituted-7-azaindoles as monocarboxylate transporter 1 blockers was investigated by Guile and co-workers[15] while some 3,5-disubstituted-7-azaindoles where investigated as Trk inhibitors and were further found to possess anticancer and antiangiogenic activities.[16] Moreover, the 7-azaindole **5-1** was investigated as a potential antibacterial agent. Indeed, the basic skeleton **5-1** was interestingly active against a range of fungi and bacteria including but not limited to *Staphylococcus aureus* AB188, *Micrococcus luteus*, *Micrococcus luteus* ATCC 9341, *Bacillus subtilis* ATCC, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Proteus micrabilis*.[17] Furthermore, the 7-azaindole derivative **5-2** is currently in clinical trials as a potential anticancer drug[18] (**Figure 1**).



5-1



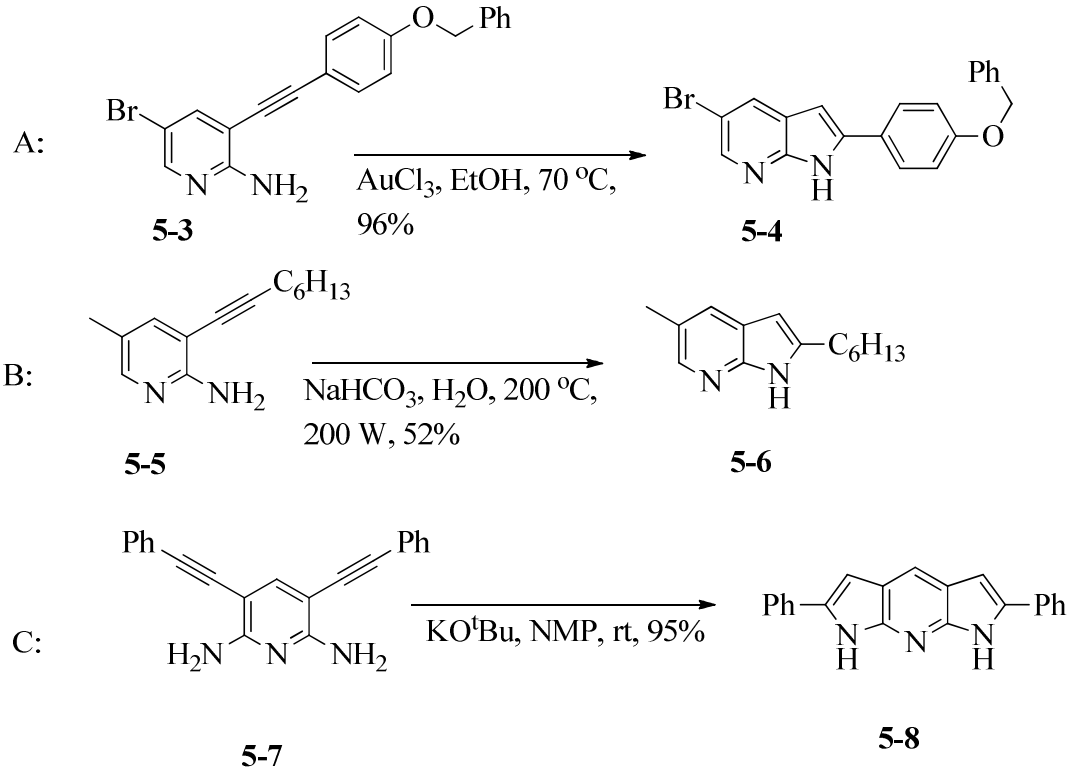
5-2

Figure 1

5.3 Literature methods used to convert Sonogashira substrates into 7-azaindoles

Various methods have been employed with the aim of converting the Sonogashira coupling substrates into indoles and azaindoles. Functional group tolerance, high yields, shorter reaction times, easy workup procedures and other factors are the area of focus as researchers explore ways to convert the Sonogashira coupling products into indoles and azaindoles. This led to reagents ranging from bases to metal salts being employed in order to achieve these conversions. For example, Majumdar and co-workers investigated the use of gold(III) chloride as a catalyst in refluxing ethanol to convert *o*-alkynylaminopyridine **5-3** and *o*-alkynylanilines to the corresponding indoles and azaindole **5-4** respectively in good yields (**Scheme 1**).[19] Additionally, the use of ruthenium catalysts to convert aminopyridines into azaindoles has been at the attention

of organic researchers due to the reactivities associated with ruthenium-based catalysts.[20] The use of microwave irradiation assisted synthesis for the preparation of azaindole **5-6** from internal alkyne **5-5** using bases (**Scheme 1**)[21] and the use of rhodium and iridium metal complexes as catalysts for the synthesis of indoles[22] have been reported. Moreover, in 2003, Koradin and co-workers reported the synthesis of indoles and azaindoles mediated by cesium and potassium bases. In their publication, they described the use of potassium hydride, potassium *tert*-butoxide and cesium *tert*-butoxide to gain access to these biologically important heterocycles. Additionally, the yields were excellent with the exception of aniline and aminopyridine derivatives bearing the electron-withdrawing nitro group. Thus, when the 2-aminopyridine derivative **5-7** was treated with potassium *tert*-butoxide in *N*-methylpyrolidinone (NMP) at room temperature, the *bis*-7-azaindole derivative **5-8** was obtained in an excellent yield of 95% (**Scheme 1**).[23]



Scheme 1

However, as some of the reaction conditions described above are low yielding, require expensive reagents or intolerant of a range of functional groups, there is always a need to continue searching for superior reaction conditions that will deliver high yields and tolerate a variety of functional groups. The use of microwave irradiation to gain access to heterocycles is such superior methodology. The application of microwave reactions has been on the rise because microwave reactions are often considered to be "green" because water could be used as a solvent, the reaction times are short and small amounts of solvent are required.[24,9c] Unfortunately, the inability of microwave to tolerate certain acids and bases makes it unsuitable to use under all reaction conditions. In the sections that follow, our results on the application of the Sonogashira coupling reactions followed by novel ring closing reaction conditions to gain access to 7-azaindole derivatives will be discussed.

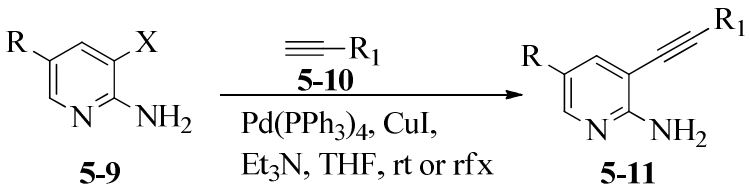
5.4 Results and Discussion

For the purpose of this PhD project, we wished to develop novel methodology for the synthesis of 7-azaindoles from the respective Sonogashira products. Various acids and solvents will be screened for this purpose. For us to successfully develop new methodology for the ring closure of Sonogashira products, first the Sonogashira coupling reaction conditions would be used to synthesize 2-amino-3-alkyne-containing pyridines. Following this step, our novel TFA/TFAA mediated methodology would be employed to convert 2-amino-3-alkyne-containing pyridines into 7-azaindole derivatives. The following section will cover in greater detail the synthesis and characterization of 2-amino-3-alkyne-containing pyridines using the Sonogashira coupling reaction conditions.

5.4.1 Sonogashira coupling reactions

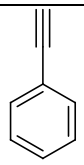
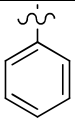
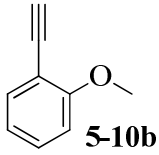
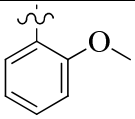
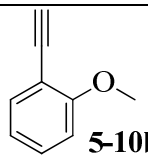
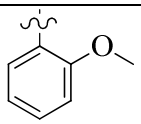
The required Sonogashira coupling reaction, as discussed earlier in this chapter, usually employs 2-amino-3-halogen-containing pyridines with halogen being either bromine or iodine in most cases. Thus, our access to 7-azaindole derivatives started with Sonogashira coupling of 2-amino-3-halogen-containing pyridines of general formula **5-9** where the R group was varied. Hence, **5-9**

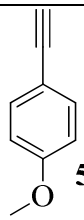
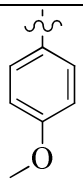
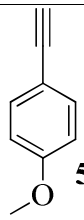
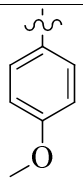
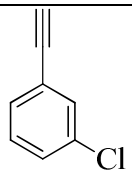
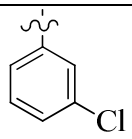
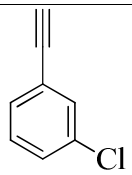
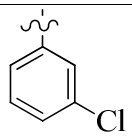
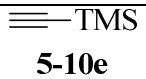
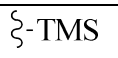
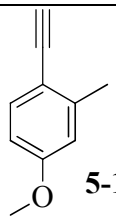
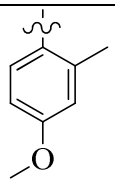
was treated with a terminal alkyne of general formula **5-10**. A palladium catalyst and copper(I) iodide as a co-catalyst were used with tetrahydrofuran as a solvent. Triethylamine was used as a base for this reaction. As discussed in a previous chapters, the Sonogashira coupling reaction of bromopyridines[25] and bromoanilines[26] usually takes place at elevated temperatures while those of iodopyridines[9] takes place at room temperature. Hence, for our substrates the mixture was heated to reflux for 8 hours under an argon atmosphere for the 3-bromopyridine derivatives and was stirred at room temperature for the 3-iodopyridine derivatives. After the reaction was deemed to be complete, a saturated aqueous ammonium chloride solution was added. The resulting crude product was purified by flash chromatography to give product of general formula **5-11** (**Scheme 2**). Table 1 below shows the results obtained for the different R and R_1 groups.

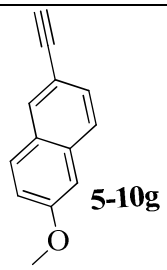
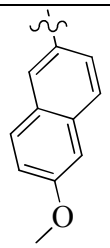
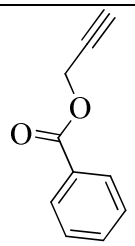
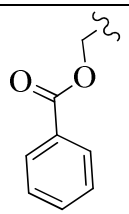
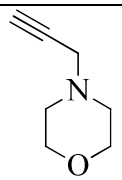
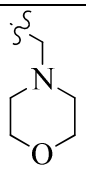
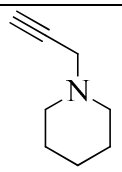
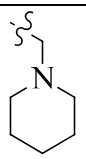
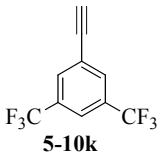
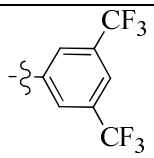


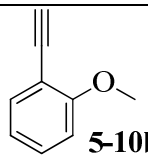
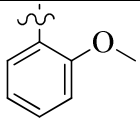
Scheme 2

Table 1: The Sonogashira coupling reaction results with varying R and R_1 groups

Entry	X/R	Alkyne	R^1	Product (% yield)	Temp./ °C	NMR Information/ppm (^{1}H and ^{13}C)
1	Br/Me **5-9a**	 **5-10a**		**5-11a** (90)	70	^{1}H: 7.57 – 7.49 (m, 2H), 7.38 – 7.29 (m, 3H) ^{13}C: 95.30, 84.58 (C-C triple bond)
2	Br/H **5-9b**	 **5-10b**		**5-11b** (75)	70	^{1}H: 6.98 – 6.89 (m, 2H), 6.62 (d, *J* = 7.5, 1H), 3.92 (s, 3H). ^{13}C: 92.26, 89.30 (C-C triple bond), 55.82 (OMe).
3	Br/Me **5-9a**	 **5-10b**		**5-11c** (70)	70	^{1}H: 7.49 – 7.39 (m, 2H), 6.94 (dd, *J* = 11.0, 4.6, 2H), 3.92 (s, 3H).

						^{13}C: 92.05, 89.43 (C-C triple bond), 55.80 (OMe).
4	Br/H **5-9b**	 **5-10c**		**5-11d** (80)	70	^{1}H: 7.50 – 7.41 (m, 2H), 6.93 – 6.83 (m, 2H), 3.83 (s, 3H). ^{13}C: 95.49, 83.14 (C-C triple bond), 55.34 (OMe).
5	Br/Me **5-9a**	 **5-10c**		**5-11e** (82)	70	^{1}H: 7.46 – 7.43 (m, 2H), 6.91 – 6.85 (m, 2H), 3.82 (s, 3H). ^{13}C: 95.30, 83.30 (C-C triple bond, 55.33 (OMe).
6	Br/H **5-9b**	 **5-10d**		**5-11f** (86)	70	^{1}H: 7.40 (d, *J* = 7.2, 1H), 7.37 – 7.27 (m, 2H), 6.67 (s, 1H). ^{13}C: 94.04, 85.60 (C-C triple bond).
7	Br/Me **5-9a**	 **5-10d**		**5-11g** (83)	70	^{1}H: 7.45 (s, 1H), 7.39 (d, *J* = 7.3, 1H), 7.31 (dt, *J* = 10.3, 6.8, 2H). ^{13}C: 93.87, 85.78 (C-C triple bond).
8	I/Cl **5-9c**	 **5-10e**		**5-11h** (92)	23	^{1}H: 0.27 (s, 9H).
9	I/Cl **5-9c**	 **5-10f**		**5-11i** (87)	23	^{1}H: 7.41 (d, *J* = 8.4, 1H), 6.79 (s, 1H), 6.74 (d, *J* = 8.4, 1H), 3.83 (s, 3H), 2.48 (s, 3H). ^{13}C: 95.67, 85.77 (C-C triple bond), 55.31 (OMe), 21.18 (ArMe).

10	I/Cl **5-9c**	 **5-10g**		**5-11j** (83)	23	^{1}H: 7.72 (d, *J* = 8.6, 2H), 7.60 (s, 1H), 7.18 (d, *J* = 8.8, 1H), 7.13 (s, 1H), 3.94 (s, 3H). ^{13}C: 97.19, 82.86 (C-C triple bond), 55.39 (OMe).
11	I/Br **5-9d**	 **5-10h**		**5-11k** (88)	23	^{1}H: 7.63 – 7.53 (m, 3H), 7.45 (t, *J* = 7.6, 2H), 5.14 (s, 2H). ^{13}C: 166.30 (C=O), 130.12(2 x ArCH), 128.80 (2 x ArCH), 90.95, 81.23 (triple bond), 53.41 (O-CH_2-).
12	I/Br **5-9d**	 **5-10i**		**5-11l** (86)	23	^{1}H: 3.80 – 3.66 (m, 4H), 3.53 (s, 2H), 2.66 – 2.50 (m, 4H). ^{13}C: 91.93, 80.05 (triple bond), 67.05 (2 x OCH_2-), 52.68, 48.38 (3 x N-CH_2-).
13	I/Br **5-9d**	 **5-10j**		**5-11m** (83)	23	^{1}H: 3.50 (s, 2H), 2.52 (m, 4H), 1.61 (dt, *J* = 11.0, 5.6, 4H), 1.42 (d, *J* = 5.1, 2H). ^{13}C: 92.92, 79.53 (triple bond), 53.75, 48.81, 26.16, 24.09 (5 x –CH_2-).
14	I/Br **5-9d**	 **5-10k**		**5-11n** (70)	23	^{1}H: 7.94 (s, 2H), 7.86 (s, 1H). ^{13}C: 133.03 – 132.22 (CF_3), 93.49, 86.93 (triple bond).

15	I/Br **5-9d**	 **5-10b**		**5-11o** (73)	23	^{1}H: (dd, *J* = 7.5, 1.5, 1H), 7.40 – 7.29 (m, 1H), 7.00 – 6.91 (m, 2H), 3.92 (s, 3H). ^{13}C: 93.51, 88.04 (triple bond), 55.81 (OMe).

Represented in Table 1 is also the NMR spectroscopy information of the individual products **5-11a-o**. The formation of products **5-11a-o** was confirmed using both ^{1}H and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectrum of **5-11a** showed the presence of a phenyl ring while the ^{13}C NMR spectrum of **5-11a** confirmed the presence of a C-C triple bond (Entry 1) which allowed for the assignment of **5-11a**. On the other hand, the formation of **5-11b** and **5-11c** which were synthesized using the same terminal alkyne **5-10b** were also subjected to NMR spectroscopic analysis. Thus, the ^{1}H NMR spectra of **5-11b** and **5-11c** showed the presence of *ortho*-substituted benzene ring in addition to the presence of a methoxy group at 3.92 ppm. The ^{13}C NMR spectra of **5-11b** and **5-11c** further confirmed their assignment with the presence of a C-C triple bond between 89 and 93 ppm and a methoxy group at 55.80 ppm (Entries 2 and 3). Similarly, **5-11d** and **5-11e** were synthesized from the same alkyne **5-10c** and hence have similar NMR spectra. Analysis of the ^{1}H NMR spectra of **5-11d** and **5-11e** revealed the presence of the *para*-disubstituted benzene ring with the presence of a methoxy group at *para* position observed at 3.80 ppm. Analysis of the ^{13}C NMR spectra of **5-11d** and **5-11e** further revealed the presence of a C-C triple bond as well as the presence of a methoxy group on both **5-11d** and **5-11e** (Entries 4 and 5).

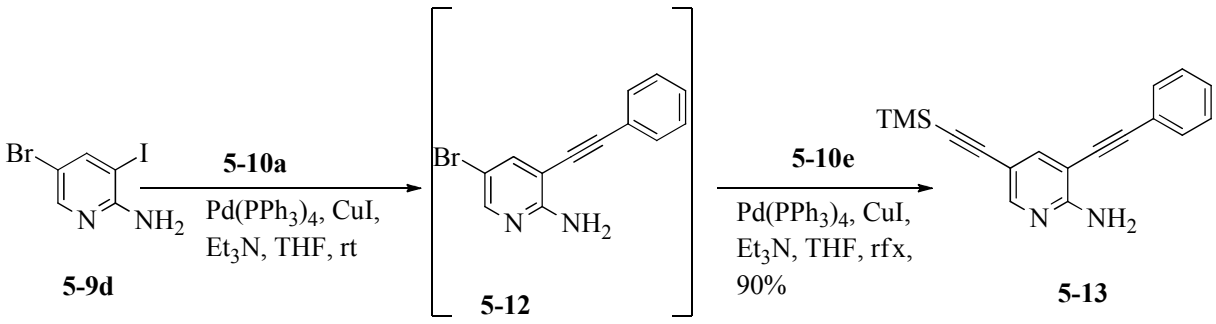
The synthesis of **5-11f** and **5-11g** was achieved by employing the same terminal alkyne **5-11d**. Their formation was confirmed with the aid of NMR spectroscopy. Thus, the presence of a *meta*-substituted benzene ring was observed in the ^{1}H NMR spectra of both **5-11f** and **5-11g** while ^{13}C NMR spectra of **5-11f** and **5-11g** showed the presence of a C-C triple bond, further confirming their successful synthesis (Entries 6 and 7). In Entry 8 of Table 1, the presence of a signal due to the trimethylsilyl group found at 0.27 ppm on the ^{1}H NMR spectrum of **5-11h** which was synthesized using a terminal alkyne **5-10e** was significant and it was also consistent with the

chemical shift of the same group on **5-11h** in the literature.[27] Continuing with Sonogashira coupling reaction products **5-11a-o**, ^{1}H and ^{13}C NMR spectroscopy remained central in confirming the formation of these products. Thus, analysis of the ^{1}H NMR spectrum of **5-11i**, synthesized from terminal alkyne **5-10f** showed the presence of a trisubstituted benzene ring with the methoxy and methyl groups observed at 3.83 and 2.48 ppm respectively. Additionally, the ^{13}C NMR spectrum of **5-11i** further confirmed the presence of the methoxy and methyl groups at 55.31 and 21.18 ppm respectively (Entry 9) and thus confirming the formation of **5-11i**. On the other hand, the use of a terminal alkyne **5-10g** resulted in the formation of **5-11j** in a good yield. Analysis of the ^{1}H NMR spectrum of **5-11j** confirmed the presence of a disubstituted naphthalene group and the presence of a methoxy group was also observed at 3.94 ppm. The presence of a C-C triple bond and additional aromatic carbon signals were observed on the ^{13}C NMR spectrum of **5-11j** further confirming its formation (Entry 10).

The ^{1}H NMR spectrum of **5-11k** showed the presence of a phenyl ring as well as the presence of a methylene group directly bonded to oxygen substituent at 5.14 ppm while the presence of the morpholine group and the methylene substituent on nitrogen functionality was observed on the ^{1}H NMR spectrum of **5-11l** (Entries 11 and 12). The ^{1}H NMR spectrum of **5-11m** showed the presence of the piperidinyl group in addition to the presence of the *N*-CH_2 functional group at 3.50 ppm while the ^{1}H NMR spectrum of **5-11n** showed the presence of a trisubstituted benzene ring with two singlet signals observed at 7.94 and 7.86 ppm respectively (Entries 13 and 14). Finally, the synthesis of **5-11o** from a terminal alkyne **5-10b** was confirmed by ^{1}H NMR spectroscopy where the ^{1}H NMR spectrum of **5-11o** showed the presence of an *ortho*-disubstituted benzene ring with a methoxy signal observed at 3.92 ppm (Entry 15). Additionally, the ^{13}C NMR spectra of products **5-11a-o** confirmed the presence of C-C triple bonds for each product with chemical shifts ranging from 79.53 to 93.51 ppm (Entries 11 and 12). This further confirmed the successful synthesis of products **5-11a-o**.

The employment of 2-amino-5-bromo-3-iodopyridine (**5-9d**) in Sonogashira coupling reactions has advantages due to its ability to undergo the coupling reaction twice with two different alkynes. First, the coupling could be achieved at room temperature where the iodo functionality will take part in the reaction. Second, after the iodo functionality has undergone the reaction, the

bromo functionality could also undergo the Sonogashira coupling reaction at elevated temperatures. We took advantage of this reactivity of pyridine **5-9d** to synthesize the dialkyne **5-13** using terminal internal alkynes **5-10a** and **5-10e** respectively. Thus, we initially treated pyridine **5-9d** with **5-10a** under the Sonogashira coupling reaction conditions at room temperature. After workup, the solvent was removed under reduced pressure and the crude material was assumed to be **5-12**. This was subjected to another Sonogashira coupling reaction, this time at elevated temperatures in the presence of a terminal alkyne **5-10e**. After workup and chromatographic separations, **5-13** was obtained in an overall yield of 90% based on **5-9d** (**Scheme 3**). The synthesis of **5-13** was confirmed using NMR spectroscopy. Thus, analysis of the ^{1}H NMR spectrum of **5-13** revealed the presence of a phenyl ring (7.57 – 7.46 (m, 2H), 7.37 (dd, J = 9.6, 6.1, 3H)). In addition to the trimethylsilyl group observed at 0.26 ppm, further confirmation came from the analysis of the ^{13}C NMR spectrum of **5-13** which revealed the presence of two different C-C triple bonds signals at 101.84, 95.90, 94.99, and 83.38 ppm with the presence of trimethylsilyl group at 0.01 ppm. With this information in hand, we concluded that we have successfully synthesized **5-13**. Since we successfully synthesized products **5-11a-o** in addition to **5-13**, our next goal was to obtain 7-azaindole derivatives from these aminopyridines.

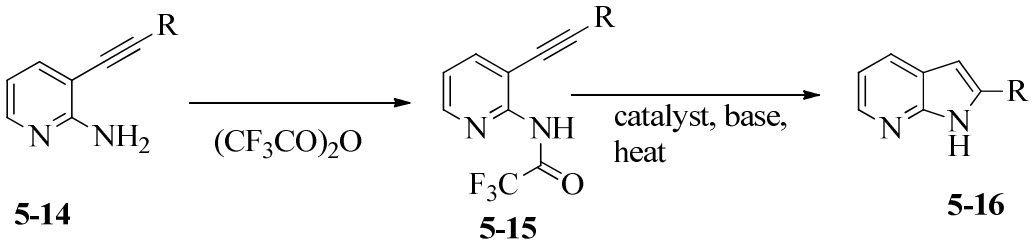


Scheme 3

5.4.2 Ring closing reactions with a TFAA/TFA mixture

Trifluoroacetic anhydride (TFAA) has been used mostly in combination with metal catalysts such as palladium and copper to assemble azaindoles. A good example is the Cacchi reaction. In

the original Cacchi reaction conditions, $Pd(PPh_3)_4$ was used as a catalyst in the presence of potassium carbonate as a base.[28] This methodology was later extended by Arcadi *et al*. for the synthesis of 2-substituted-3-acylindoles again in the presence of $Pd(PPh_3)_4$ as a catalyst and potassium carbonate as base although other catalysts such as $Pd(OAc)_2(PPh_3)_2$ and $Pd(dba)_2P(o\text{-tolyl})_3$ were investigated but found to yield moderate results.[29] In 1997, Cacchi *et al*. demonstrated the use $Pd(dba)_3$ in the presence of other ligands such as triphenylphosphine in the presence of potassium carbonate as a base for the preparation of 3-substituted indoles.[30] Recently, Cacchi *et al*. prepared 2,3-disubstituted azaindoles using the same methodology but using cesium carbonate as a base instead of potassium carbonate.[31] In general, the reaction proceeds a depicted in **Scheme 4**.



5-14 **5-15** **5-16**

Scheme 4

As demonstrated in reaction **Scheme 4**, **5-16** was obtained over two steps where the first step involved the synthesis of amide **5-15** from aminopyridine **5-14**. This was then followed by the use of a catalyst and base to afford azaindole **5-16**.

In this section, we will discuss the results of our investigation into the synthesis of **5-16** *via* **5-15** strating from **5-14** in one step. It should also be noted that there are other reaction conditions that could afford **5-16** from **5-14** without going through **5-15** as an intermediate.[32-38] However, low yields, expensive reagents, simplicity of the reaction conditions and incomplete reactions have inspired researchers to develop reaction conditions such as those in **Scheme 4** to synthesize 7-azaindole derivatives. Our investigation was essentially based on attempting the use of acids (TFA, AcOH, HCl, H_2SO_4, HNO_3) to gain access to 7-azaindole derivatives from 2-amino-3-alkyne-containing pyridines. Thus, our investigations were based on the conversion of **5-11a** to **5-17** (**Scheme 5**) in various acids and solvents. Hence, **5-11a** was dissolved in a variety of

solvents or acids as shown in Table 2 and heated to between 80 and 100 °C. TFAA was added in some instances before heating. After 5 hours, the reaction mixture was allowed to cool to room temperature, then made basic with sodium hydroxide solution and the crude mixture was extracted with dichloromethane. The solvent was removed under reduced pressure and resulting crude material was purified by flash chromatography where suitable.

The data shown in Table 2 below represents the conversion of **5-11a** to **5-17** using different acidic conditions at elevated temperatures.

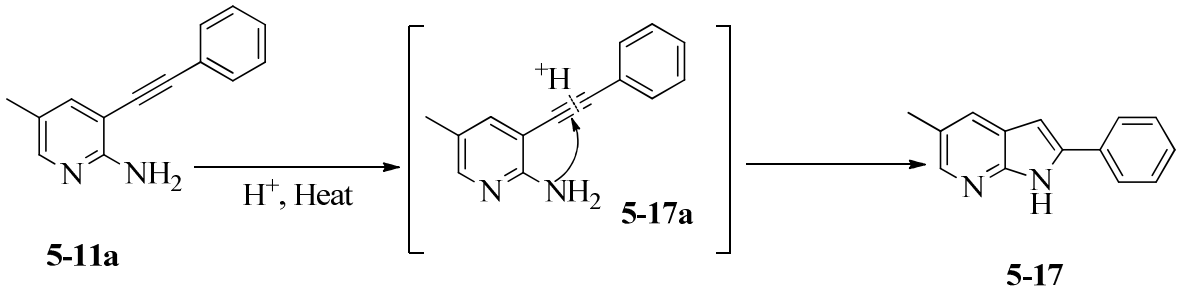
Table 2: Conversion of **5-11a** to azaindole **5-17** under different acidic conditions

Entry	Solvent	Acid (eq)	TFAA (eq)	Temp./°C	% Conversion[a]
1	HCl	HCl	0	80	<5
2	H_2SO_4	H_2SO_4	0	80	<5
3	TFA	TFA	0	80	>10
4	Acetonitrile	TFA (0.2)	1.3	100	40 (100)[b]
5	Acetonitrile	TFA (0.4)	1.3	100	60 (100)[b]
6	Acetonitrile	TFA (0.6)	1.3	100	70 (100)[c]
7	Acetonitrile	TFA (0.8)	1.3	100	80 (100)[c]
8	Acetonitrile	TFA (1)	1.3	100	100
9	Acetonitrile	TFA (1.5)	1.3	100	95
10	Acetonitrile	TFA (2)	1.3	100	75
12	Acetonitrile	TFA (3)	1.3	100	70
13	Acetonitrile	TFA (4)	1.3	100	62
14	Acetonitrile	HCl (1)	1.3	100	50
15	Acetonitrile	H_2SO_4 (1)	1.3	100	30
16	Acetonitrile	AcOH (1)	1.3	100	80
17	Acetonitrile	HNO_3 (1)	1.3	100	60
18	Acetonitrile	0	1.3	100	45

[a]All conversion are estimates from ^{1}H NMR spectroscopy after 5 hours. [b]After 12 hours. [c]After 8 hours.

Table 2 analysis:

We started by heating **5-11a** in concentrated hydrochloric acid (Entry 1) and sulfuric acid (Entry 2) at 80 °C for 5 hours to determine whether acid alone could effect ring closing to form azaindole **5-17**. Unfortunately, the conversion of aminopyridine **5-11a** into azaindole **5-17** from these two reaction conditions was very low (<5%). However, trifluoroacetic acid (TFA) showed significant improvement where the conversion of internal alkyne **5-11a** to azaindole **5-17** was estimated at 10% (Entry 3). The conversion of **5-11a** into azaindole **5-17** was thought to take place through intermediate **5-17a** before yielding azaindole **5-17** (**Scheme 5**).

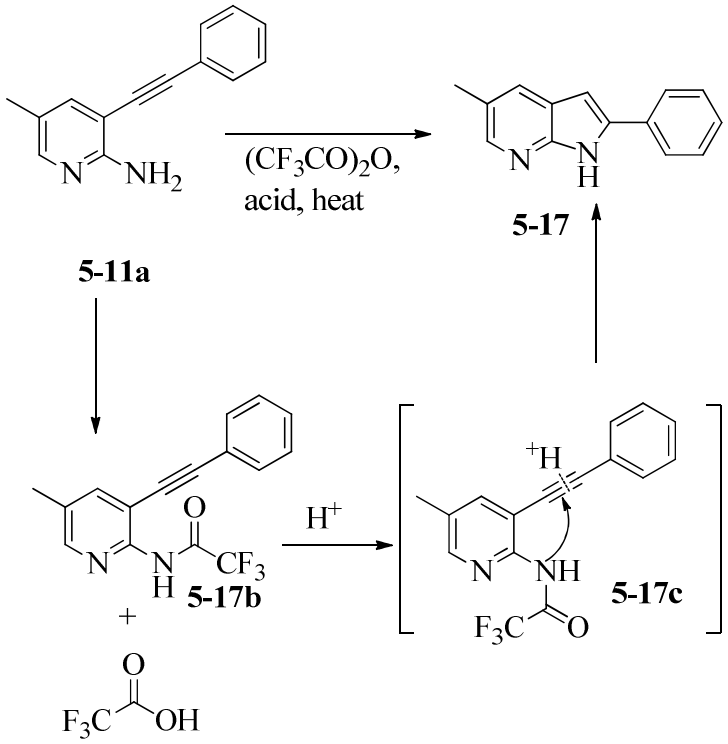


Scheme 5

The low conversion rates obtained (Entries 1 – 3) was thought to be influenced by the nucleophilicity of the amino group. The presence of electron-withdrawing groups was thought to increase the reactivity of the NH_2 group, thereby facilitating a smooth ring closing reaction under the Cacchi conditions to afford azaindoles as was discussed in the previous chapter.[31] This prompted us to investigate the use of acids in acetonitrile, in the presence of TFAA. Acetonitrile was our solvent of choice because of its polarity, ability to perform reactions at high temperatures (>100 °C) and could easily be removed on a rotary evaporator. Since TFA was the most promising of the three acids, we first treated **5-11a** with TFA (1eq) followed by the addition TFAA (1.3eq) in acetonitrile followed by heating at 100 °C for 5 hours. To our surprise, the reaction was complete in just 5 hours (Entry 8). Encouraged by this excellent result, we decided to investigate the role the number of equivalents of TFA played in the reaction. Reducing the quantity of TFA to 0.2 equivalents also resulted in less conversion of **5-11a** in 5 hours. However, longer reaction times gave rise to higher conversion rates even at low

equivalents of TFA (Entry 4). In general, we observed an increase in conversion of **5-11a** to azaindole **5-17** with increasing equivalents of TFA (Entries 5 – 8) which also followed the same pattern of achieving higher conversion with longer reaction times.

The sudden increase in the rate observed in the conversion of pyridine **5-11a** into 7-azaindole **5-17** (Entry 4) was believed to be facilitated by the introduction of TFAA. TFAA was believed to react with aminopyridine **5-11a** to form amide **5-17b** in which the presence of the CF_3CO electron-withdrawing group was known to increase the reactivity of the NH group thereby facilitating a smooth ring closure (**Scheme 6**). Finally, the effect of acid forms the intermediate **5-17c** in which the acid activates the C-C triple bond, thereby increasing its electrophilicity. This in turn allowed for the smooth formation of **5-17** (**Scheme 6**).



Scheme 6

More than 1 equivalent of TFA did not have a positive effect on the conversion of **5-11a** to azaindole **5-17**. For example, 1.5 equivalents of TFA reduced the conversion rate of an internal alkyne **5-11a** to 95% in 5 hours (Entry 9). This trend continued (Entries 10 – 13) where the

conversion rate of **5-11a** dropped to as much as 60% within the same time of 5 hours. Although TFA showed outstanding results, we decided to screen other acids to assess their performance in converting **5-11a**. Thus, when TFA was replaced by hydrochloric acid (1 equivalent), only 50% of **5-11a** was converted (Entry 14) while sulfuric acid gave the worst conversion rate (30%) and the reaction was not as clean as for when it was conducted with TFA and hydrochloric acid (Entry 15). Additionally, nitric acid gave moderate conversion rate (60%, Entry 17) while acetic acid was very comparable with TFA, with the conversion rate of 80% in 5 hours (Entry 16). However, when no acid was used (Entry 18), the conversion rate of **5-11a** was estimated to be 45%. This was a huge surprise to us considering our notion that acid played a very important role in converting **5-11a** to azaindole **5-17**. We attributed this conversion rate to TFA formed when **5-11a** reacted with TFAA to form **5-17b** (**Scheme 6**) which in the presence of acid would proceed through intermediate **5-17c** to finally form **5-17**. Thus, from Table 2 above, the optimum conditions required to convert **5-11a** to **5-17** was in Entry 8. With these interesting results in hand, we briefly sought to see what effects other solvents would have on the conversion of **5-11a** to azaindole **5-17**. Table 3 shows the effect other solvents of than acetonitrile.

Table 3: Treatment of **5-11a** with TFA/TFAA in different solvents

Entry	Solvent	Acid (eq)	TFAA eq	Temp/°C	Time/h	%Conversion[a]
1	Methanol	TFA (1)	1.3	60	12	15
2	Ethanol	TFA (1)	1.3	80	12	30
3	THF	TFA (1)	1.3	70	5	8
4	1,4-Dioxane	TFA (1)	1.3	100	5	15
5	Toluene	TFA (1)	1.3	100	5	75

[a]All conversion are estimates from ^{1}H NMR spectroscopy.

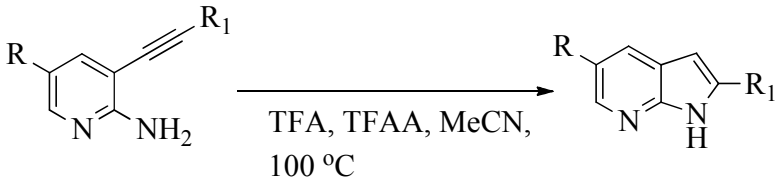
Table 3 analysis:

Although acetonitrile gave us the best conversion rate in 5 hours, we were looking to reduce the reaction time even further. So far the temperature required for achieving a 100% conversion rate was 100 °C and below this temperature, the reaction rate slowed down considerably. We started our screening by using lower boiling methanol to see if we could achieve the conversion of **5-**

11a to azaindole **5-17** at low temperatures. Unfortunately, approximately 15% of **5-11a** was converted to **5-17** after 5 hours (Entry 1). After changing the solvent to ethanol, the rate of conversion increased to 30% at 80 °C (Entry 2). However, the use of ethers (THF and 1,4-dioxane) did not have any positive effect on the conversion rate of **5-11a** to **5-17** with both resulting in a conversion rate below 20% (Entries 3 and 4). On the other hand, the use of toluene as a solvent was promising with the conversion rate of 75% in 5 hours (Entry 5).

In conclusion, acetonitrile gave us the best conversion rate with toluene being the second best solvent. The temperature played a very important role, with high temperatures (100 °C) required to achieve conversions in shorter times. At temperatures below 100 °C, the conversion rate was slow requiring longer reaction times. Solvent was also found to play a crucial role, with the high boiling solvent providing the best results. For example, both toluene and acetonitrile can be heated to 100 °C or above while solvents such as methanol, ethanol and THF have lower boiling points. The role of the solvent was also observed when 1,4-dioxane was used. Even though 1,4-dioxane could be heated to 100 °C, the conversion rate was also very poor (15%) indicating that the choice of solvent was very important. With our optimum reaction conditions in hand, our next mandate was to convert the remaining precursors **5-11b-o** into 7-azaindole derivatives.

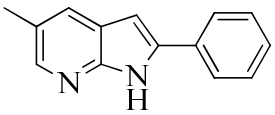
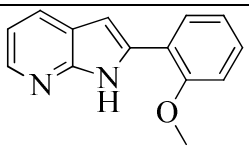
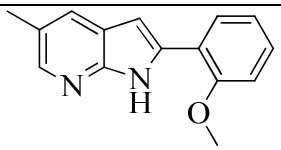
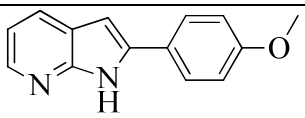
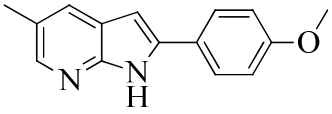
Thus, 2-amino-3ethynyl-containing pyridine derivatives of general formula **5-11** were dissolved in acetonitrile. To the resulting solution was added trifluoroacetic acid (1 eq) in one portion followed by the addition of trifluoroacetic anhydride (1.3 eq) dropwise. The resulting mixture was then heated to 100 °C for 5 hours and allowed to cool to room temperature. The solvent was removed on a rotary evaporator and the resulting crude material was re-dissolved in dichloromethane and was washed with 10% aqueous sodium carbonate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to give the respective 7-azaindole derivatives of general formula **5-18** (**5-18a-o**) in generally excellent yields (**Scheme 7**). Table 4 below shows the conversion of **5-11b-o** to azaindoles **5-18a-o** under acidic conditions.

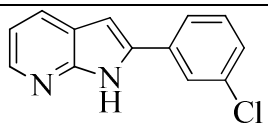
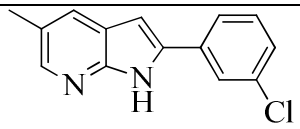
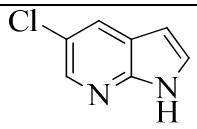
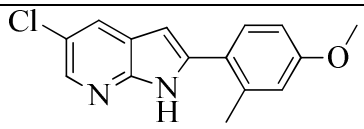
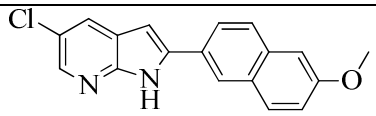
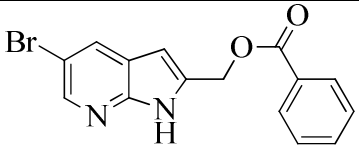
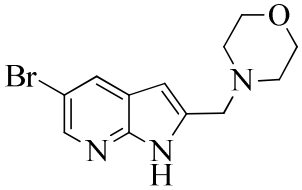


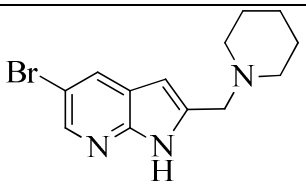
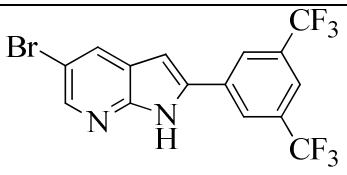
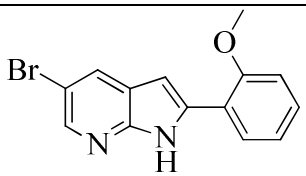
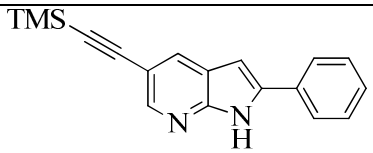
5-11 **5-18**

Scheme 7

Table 4: Conversion of internal alkynes **5-11a-o** and **5-13** using TFA/TFAA to 7-azaindole derivatives **5-18a-o**

Entry	Product	Yield (%)[a]	Temp./°C	NMR Information/ppm (^{1}H and ^{13}C)
1	 **5-17**	86	100	^{1}H: 11.98 (s, 1H), 6.84 (s, 1H).
2	 **5-18a**	92	100	^{1}H: 10.47 (s, 1H), 6.84 (s, 1H).
3	 **5-18b**	94	100	^{1}H: 10.21 (s, 1H), 6.75 (s, 1H).
4	 **5-18c**	88	100	^{1}H: 12.35 (s, 1H), 6.67 (s, 1H).
5	 **5-18d**	85	100	^{1}H: 6.64 (s, 1H).

6	 **5-18e**	81	100	^{1}H: 11.82 (s, 1H), 6.82 (s, 1H).
7	 **5-18f**	82	100	^{1}H: 12.07 (s, 1H), 6.97 (s, 1H).
8	 **5-18g**	84	100	^{1}H: 10.89 (s, 1H), 7.46 – 7.35 (m, 1H), 6.62 – 6.24 (m, 1H)
9	 **5-18h**	80	100	^{1}H: 10.13 (s, 1H), 6.44 (s, 1H).
10	 **5-18i**	82	100	^{1}H: 13.71 (s, 1H).
11	 **5-18j**	83	100	^{1}H: 6.60 (s, 1H).
12	 **5-18k**	79	100	^{1}H: 11.21 (s, 1H), 6.28 (s, 1H).

13	 **5-18l**	83	100	^{1}H: 10.55 (s, 1H), 6.23 (s, 1H).
14	 **5-18m**	78	100	^{1}H: 11.69 (s, 1H), 6.43 (s, 1H).
15	 **5-18n**	80	100	^{1}H: 10.38 (s, 1H), 6.78 (s, 1H).
16	 **5-18o**	91	100	^{1}H: 11.56 (s, 1H), 6.75 (s, 1H).

[a] Isolated yields

Comments from Table 4:

In order for us to determine the successful synthesis of 7-azaindole derivatives **5-18a-o**, ^{1}H and ^{13}C NMR spectroscopy was used. Thus, analysis of the ^{1}H NMR spectra of **5-18a-o** revealed the absence of a broad signal previously appearing between 5 and 6 ppm due to the presence of the $ArNH_2$ functional group. In addition to the absence of the NH_2 functionality, the presence of another broad signal was observed in the ^{1}H NMR spectra of the products **5-18a-o** in the region between 10 and 13 ppm due to the presence of the 7-azaindole NH functional group. Furthermore, the ^{1}H NMR spectra of **5-18a-o** showed the presence of a singlet in the region between 6 and 7 ppm due to the proton on the 3-position of the 7-azaindole derivatives **5-18a-o**

with the exception of **5-18g**. Although the ^{1}H NMR spectrum of **5-18g** showed the presence of a broad NH signal above 10 ppm, it also showed the presence of two additional signals as doublets at 6.46 and 7.37 ppm due to the loss of the trimethylsilyl group. It should be noted that the loss of the trimethylsilyl group was common depending on the reaction conditions being used.[24,39] Furthermore, the ^{13}C NMR spectra of **5-18a-o** showed the absence of a C-C triple bond where the two carbons of the acetylene were part of the pyrrole ring in azaindoles **5-18a-o**. The C-C triple bond previously appeared in the region between 80 and 95 ppm in the ^{13}C NMR spectra of **5-11a-o** including that of **5-13**. With this NMR spectroscopy information in hand, we were convinced that we had successfully synthesized 7-azaindole derivatives **5-18a-o**.

5.5 Closing remarks

We successfully developed new methodology based on the use of TFA and TFAA for the synthesis of 7-azaindole derivatives **5-18a-o** in good yields of between 70 and 90%. Thus, we had managed to synthesize 7-azaindole derivatives **5-18a-o** in two steps from aminopyridines. The first step involved the application of the Sonogashira coupling reaction to access 2-amino-alkyne-containing pyridines **5-11a-o**. The second step involved the application of the newly developed acid-catalyzed methodology to convert these intermediates **5-11a-o** into the corresponding 7-azaindole derivatives **5-18a-o**. The formation of these products was confirmed using ^{1}H and ^{13}C NMR spectroscopy. Yields of some products, especially those below 80% could still be improved. The synthesis of **5-18a-o** was carried out in 5 hours in acetonitrile and we believe there is still room for improvement especially with reducing reaction times as well as the reaction temperature. More research will be required to determine if other functional groups such carboxylic acids, amides and others could be employed to ascertain if these functional groups are tolerant of the conditions employed. Of significance will be the biological screening of 7-azaindole derivatives **5-18a-o** against bacteria and fungi.

5.6 References

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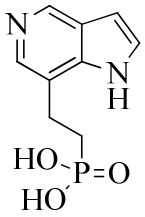
Chapter 6: Synthesis of 5-Azaindole Phosphonic Acids

6.1 Introduction

Azaindoles[1-3] have been screened against low molecular weight protein tyrosine phosphatases. Low molecular weight protein tyrosine phosphatases (PTPs) are a group of enzymes whose function is to regulate dephosphorylation of tyrosine residues on all proteins, while protein kinases are responsible for their phosphorylation. Additionally, it has been suggested that almost 30% of cellular proteins make use of protein kinases for phosphorylation. It is believed that protein phosphorylation and dephosphorylation play a very important role in phenomena such as cell signalling, cell metabolism, cell growth and cell differentiation.[4] Zhang and co-workers at Purdue University isolated the crystal structure of human low molecular weight phosphatase with two major isoenzymes known as slow and fast isoforms. These isoforms were known as HCPTPA (A form) (fast) and HCPTPB (B form) (slow).[5] Furthermore, it was suggested that the two isoforms may be performing different functions and this was confirmed when it was established that adenine was able to activate HCPTPB isoform while inhibiting HCPTPA isoform. On the other hand, hypoxanthine was found to be inactive towards HCPTPA and active towards the HCPTPB isoform.[6] In 2004, Zabell *et al*. performed inhibition studies of PTPs with identification of the small molecules as suitable candidates, including 5-azaindole.[7] Thus, 5-azaindole phosphonate **6-1** synthesized by Weitgenant and co-workers in 2006[8] (**Figure 1**) was tested against both A and B isoforms. The inhibition constant (K_i) for **6-1** was found to be 1.79 mM for the A isoform and 2.76 mM for the B isoform[24]. Even though K_i values appear high, it should be noted that the values for **6-1** for the inhibition of both isoforms were found to be better than previously synthesized and tested molecules indicating that 5-azaindole derivatives have the ability to inhibit PTPs.[7]



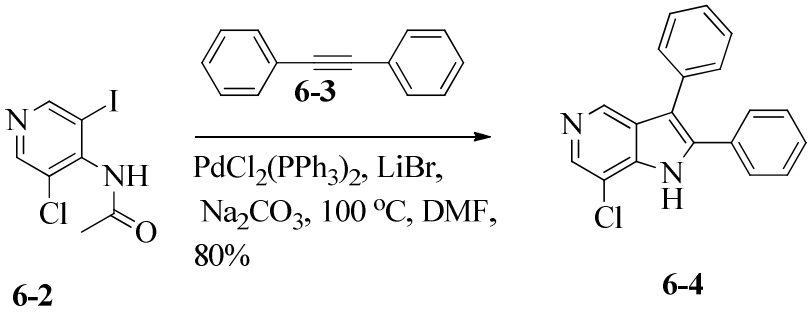
6-1

Figure 1

In the following paragraphs, various methods used to prepare 5-azaindoles will be explored. This will be followed by the preparation of 5-azaindole derivatives in our laboratories. Although 5-azaindoles are known as indole bioisosteres, their methods of preparation are quite limited as compared to indoles.

6.1.2 Synthesis of 5-azaindole derivatives using the Larock indole synthesis reaction

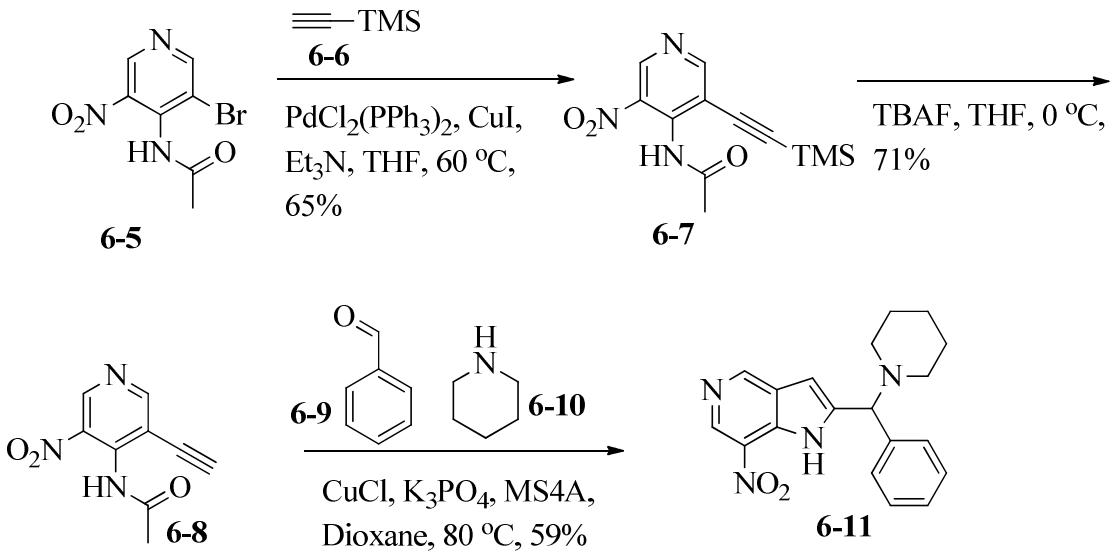
Due to mild conditions of the Larock indole synthesis,[9-11] it has also found application in the preparation of 5-azaindole derivatives. For example, the use of palladium-catalyzed heteroannulation reaction for the preparation of substituted 5-azaindoles has been recently reported. Calvet and co-workers found that the treatment of *N*-acetylated iodopyridines with internal alkynes in the presence of a palladium catalyst at elevated temperatures resulted in the formation of substituted 5-azaindoles (**Scheme 1**). Thus, when *N*-(3-chloro-5-iodopyridin-4-yl)acetamide (**6-2**) was treated with internal alkyne **6-3** in the presence of a palladium catalyst, sodium carbonate as a base and lithium bromide in DMF, the trisubstituted 5-azaindole **6-4** was obtained in 80% yield (**Scheme 1**). However, it was found that substituting chlorine with bromine in **6-2** led to diminished reactivity, leading to incomplete reactions[12] (**Scheme 1**).



Scheme 1

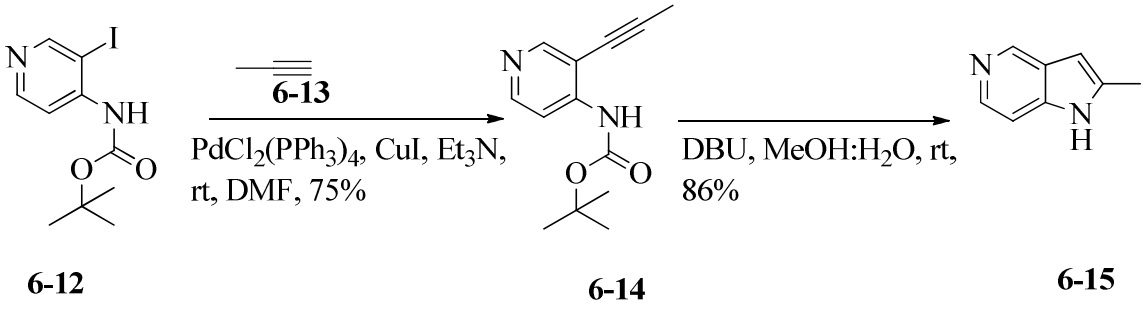
6.1.3 Preparation of 5-azaindole derivatives through a Sonogashira coupling reaction

Apart from using the Larock indole synthesis to access 5-azaindoles, their preparation could also be achieved through the Sonogashira coupling reactions.[13-21] Hou *et al*. recently reported the use of the Mannich-type three component coupling reaction to make the title compounds. In this case, copper(I) iodide proved to be a very useful reagent as it was used as a co-catalyst in the application of Sonogashira coupling reaction and later could be used to cyclize the resulting Sonogashira products although it gave lower yields of the expected products. *N*-(3-Bromo-5-nitropyridin-4-yl)acetamide (**6-5**) was treated with trimethylsilyacetylene (**6-6**) in the presence of triethylamine as base and copper(I) iodide as a co-catalyst resulting in the formation of alkyne **6-7** in a moderate yield of 65% (**Scheme 2**). Subsequent treatment of **6-7** with the tetrabutylammonium fluoride (TBAF) in THF at 0 °C gave the terminal alkyne **6-8** in 71% yield. The use of copper(I) chloride in combination with molecular sieves 4A (MS4A) and potassium phosphate as a base gave rise to the desired products through a Mannich-type reaction without forming unnecessary side products. As such, treatment of **6-8** with benzaldehyde (**6-9**) and piperidine (**6-10**) in the presence of copper (I) chloride and molecular sieves 4A using potassium phosphate as a base resulted in the formation of 5-azaindole derivative **6-11** in moderate yield of 59% (**Scheme 2**).[22]



Scheme 2

In other examples, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is used in a key step for forming the pyrrole ring of 5-azaindoles. The reaction conditions are mild enough to be suitable for most functional groups although this will mostly depend on the solvent used. For example, Choi-Sledeski and co-workers reported the synthesis of the biologically active 5-azaindole derivatives from the Boc protected aminopyridines in the presence of DBU in dimethylformamide (DMF) with the retention of the Boc protecting group.[23] Some few years later, Harcken *et al*. took advantage of this mild methodology to prepare a range of azaindoles using the mixture of water and methanol. Interestingly, under these conditions, the azaindoles were isolated in good yields although the Boc protecting group was not retained. Surprisingly, when the same reaction was performed on free amines, no products could be isolated indicating that the Boc protecting group played a very important role in the cyclization step.[24] A specific example of this was the treatment of the Boc protected iodopyridine **6-12** under Sonogashira coupling reaction conditions with a terminal alkyne **6-13** to give an internal alkyne **6-14** which upon exposure to aqueous DBU resulted in the formation of 2-methyl-5-azaindole (**6-15**) in 86% yield (**Scheme 3**) where the Boc protecting group was lost.[24]



Scheme 3

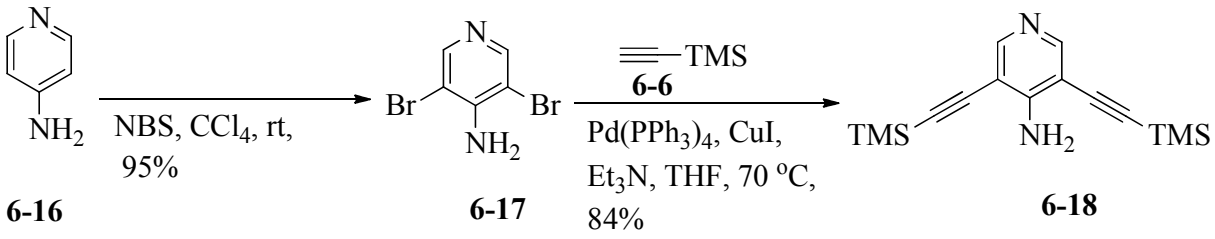
6.2 Results and discussions

For the purpose of this PhD, we wished to develop novel methodology for the synthesis of 5-azaindole phosphonic acid derivatives. The synthesis of 5-azaindole phosphonic acid derivatives would utilize the Sonogashira reaction as our starting point. Thereafter pyrrole ring forming reaction to possibly construct the 5-azaindoles, as well as hydrogenation and oxidation reactions would form the basis of this chapter of the PhD.

6.2.1 Synthesis of 3,5-*bis*[(trimethylsilyl)ethynyl]pyridin-4-amine (6-18)

Our journey towards the synthesis of the 5-azaindole phosphonic acid derivatives started with the bromination of 4-aminopyridine (**6-16**).This was done by dissolving **6-16** in carbon tetrachloride and treating the resulting solution with *N*-bromosuccinimide. This was followed by covering the reaction flask with aluminium foil as the reaction needed to be conducted in the dark. The reaction mixture was allowed to stir at room temperature for 24 hours, the solvent was removed on a rotary evaporator, the resulting crude product was purified by flash chromatography and it gave 4-amino-3,5-dibromopyridine (**6-17**) in an excellent yield of 95% (**Scheme 4**). The formation of **6-17** was confirmed by comparing the ^{1}H NMR spectrum of **6-17** with that of the previously synthesized **6-17** by Cañibano and co-workers and was found to be identical.[25] With the formation of product **6-17** completed (**Scheme 4**), our next step was to perform a Sonogashira coupling reaction with compound **6-17**.

Therefore, **6-17** was treated with a terminal alkyne **6-6** in the presence of a palladium catalyst and copper (I) iodide as a co-catalyst in tetrahydrofuran as a solvent. Triethylamine was used as a base for this reaction. The resulting reaction mixture was heated to reflux for 8 hours under an argon atmosphere. The resulting crude material was purified by flash chromatography to give 3,5-*bis*[(trimethylsilyl)ethynyl]pyridin-4-amine (**6-18**) as a cream white solid in good yield of 84% (**Scheme 4**). The formation of **6-18** was confirmed using both ^{1}H and ^{13}C NMR spectroscopy. Thus, analysis of the ^{1}H NMR spectrum of **6-18** revealed the presence of a signal found at 0.34 ppm accounting for 18 protons. The position of the signal and the number of protons is consistent with the presence of the two trimethylsilyl groups on **6-18**. Additionally, two more signals were observed in the ^{1}H NMR spectrum, a singlet in the aromatic region appearing at 8.27 ppm and a broad singlet consistent with the presence of the amino substituent of the pyridine at 5.24 ppm. A close inspection of the ^{13}C NMR spectrum of **6-18** revealed the presence of extra signals in addition to the signals observed in the ^{13}C NMR spectrum of **6-17**. Of importance were the three signals appearing at 103.62 and 97.97 ppm, which were consistent with the presence of a C-C triple bond, and at 0.19 ppm, which was consistent with the presence of the trimethylsilyl group. With the synthesis of **6-18** successfully completed and confirmed, our next step was to functionalize **6-18** to obtain 7-ethynyl-1*H*-pyrrolo[3,2-*c*]pyridine, more commonly known as the 5-azaindole nucleus.



Scheme 4

6.2.2 Synthesis of 7-ethynyl-1*H*-pyrrolo[3,2-*c*]pyridine (6-20)

In our attempts to synthesize 7-ethynyl-1*H*-pyrrolo[3,2-*c*]pyridine (**6-20**) (**Scheme 6**) from **6-18**, we have noted in the literature that attempting ring closing of substrates such as **6-18** usually led

to low yields and the loss of trimethylsilyl (TMS) group.[26] In order for us to obtain **6-20** in good yields, we had to first remove the TMS protecting groups on **6-18** as both are not needed in the future reactions. The removal of silyl protecting groups is one of the most explored methods in organic chemistry.[27-30] For our purposes **6-18** was dissolved in methanol and treated with potassium fluoride and reaction mixture stirred at room temperature for 12 hours.

After the reaction was complete, the resulting crude material obtained after workup was purified by flash chromatography to give 3,5-diethynylpyridin-4-amine (**6-19**) as a cream white solid in 90% yield (**Scheme 5**). The success of this synthesis was confirmed using ^{1}H and ^{13}C NMR spectroscopy. As expected in the ^{1}H NMR spectrum of **6-19**, the trimethylsilyl signal previously found at 0.34 ppm was absent and a new signal was observed at 3.88 ppm for two protons, which was consistent with the presence of the two terminal alkynes. Additionally, analysis of the ^{13}C NMR spectrum of **6-19** showed the absence of the trimethylsilyl groups that were previously observed at 0.19 ppm. This was further complemented by a shift in the position of C-C triple bonds from 103.62 and 97.97 ppm for **6-18** to 86.07 and 75.75 ppm for **6-19**. With terminal alkyne **6-19** in hand, we then attempted the ring closing reactions to gain access to **6-20**.



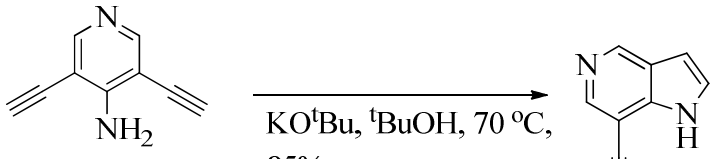
6-18 **6-19**

Scheme 5

There is literature precedent for the conversion of terminal alkyne **6-19** to azaindole **6-20**. Of importance to us is the cleanness, functional group tolerance, reproducibility and the ability of the reaction conditions to yield our desired products in high yields. As such, the use of potassium bases, particularly potassium *tert*-butoxide and potassium hydride at lower temperatures for the preparation of indoles and azaindoles has been reported.[31] The use of potassium *tert*-butoxide in *tert*-butyl alcohol at elevated temperatures was reported to give good yields and complete reactions.[32] Indeed, our first attempt of this method on small scale provided complete conversion of compound **6-19** to product **6-20** in 8 hours. Thus, **6-19** was dissolved in *tert*-butanol and

potassium *tert*-butoxide was added in portions. The resulting reaction mixture was heated at 70 °C for 8 hours under an argon atmosphere. The product was purified by flash chromatography to give the desired 5-azaindole **6-20** in 85% yield (**Scheme 6**).

In order for us to confirm the formation of **6-20**, the ^{1}H and ^{13}C NMR spectra of **6-20** were recorded and analyzed. Upon analyzing the ^{1}H NMR spectrum of **6-20** in comparison to that of **6-20**, we observed the absence of the broad signal previously found at 5.24 ppm due to the presence of the amino group of the pyridine. It has been demonstrated that upon ring closing of the Sonogashira substrates such as **6-19**, the ^{1}H NMR spectrum of the resulting 5-azaindole derivative would reveal the presence of a broad NH signal downfield at 10 ppm in addition to the two signals appearing downfield at about 6 ppm and 7 ppm respectively.[17] Taking this as our point of reference, the ^{1}H NMR spectrum of **6-20** showed the presence of two doublet signals, one found at 6.55 ppm while the other signal was observed at 7.24 ppm. Additionally, the ^{13}C NMR spectrum of **6-20** showed the presence of new two signals in the aromatic region (126.99 and 105.52 ppm), most notably as a result of the formation of the pyrrole ring of the 5-azaindole derivative **6-20**. It should also be noted that only one C-C triple bond was involved in ring closing to form **6-20** with no significant shift in the position of the remaining C-C triple bond in the spectrum. This information was enough for us to conclude that we had successfully managed to synthesize the 5-azaindole (**6-20**). Now that we have **6-20** in our possession, our next step was to functionalize the C-C triple bond of **6-20** to hopefully yield the desired 5-azaindole phosphonates which we believed could be accessed *via* the corresponding alkene which could further be converted to the desired aldehyde.



6-19 **6-20**

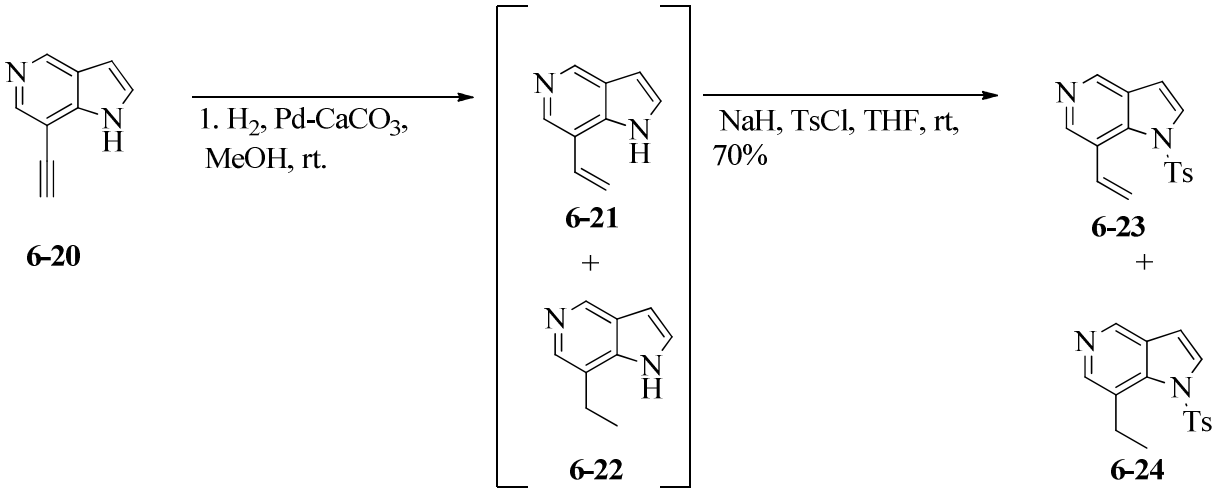
Scheme 6

6.2.3 Synthesis of 1-tosyl-1*H*-pyrrolo[3,2-*c*]pyridine-7-carbaldehyde (6-25)

Unfortunately the direct conversion of C-C triple bonds directly to aldehydes is an underdeveloped methodology. However, conversion of C-C triple bonds to alkenes is a well developed methodology. The use of hydrogen in the presence of palladium on carbon[33], the use of hydrogen in the presence of palladium on barium sulfate[34], the use of hydrogen in the presence of Lindlar's catalyst[35] and the use of hydrogen in the presence of palladium-copper catalyst facilitated by quinoline[36] have been reported. Although these methods are of equal importance, the use palladium on carbon has been widely used to convert C-C triple and double bonds to C-C single bonds[37] while Lindlar's catalyst is well known to convert C-C triple bonds to alkenes.[38] Hence, we decided to use Lindlar's catalyst to convert azaindole **6-20** to alkene **6-21**. Thus, **6-20** was dissolved in methanol and Lindlar's catalyst was added in one portion and the resulting heterogeneous mixture was stirred at room temperature for 2 days. After this time, reaction mixture was filtered through celite, methanol was removed and resulting crude material was purified by flash chromatography to give a mixture of alkene **6-21** and saturated azaindole **6-22** (**Scheme 7**). Unfortunately, we could not isolate **6-21** as a pure material due to the presence of **6-22**. Our repeated attempts to separate **6-21** and **6-22** were met with failure, thus prompting us to protect the NH functionality of the azaindoles **6-21** and **6-22** and attempt to separate the two resulting related azaindoles.

The mixture of **6-21** and **6-22** was dissolved in tetrahydrofuran and sodium hydride was added to the solution in portions and was stirred at room temperature for 30 minutes before tosyl chloride (TsCl) was introduced in portions.[39] The reaction mixture was monitored by thin layer chromatography (TLC) until it was complete. The crude mixture was purified by flash chromatography. To our surprise, **6-23** was easily separated from **6-24**, and **6-23** was obtained in a good 75% yield based on **6-20** as the starting material (**Scheme 7**). The ^{1}H NMR spectrum of **6-23** revealed the presence of the tosyl protecting group (7.71 (d, J = 8.0, 2H), 7.55 (d, J = 8.0, 2H) and 2.32 (s, 3H)). Of great significance to us was the conversion of the C-C triple bond to a C-C double bond. Comparing the ^{1}H NMR spectrum of **6-23** to that of **6-20**, showed the absence of a signal previously found at 3.81 due to the presence of a terminal alkyne. Next, in the analysis of the ^{1}H NMR spectrum of **6-23**, we had to determine the presence of terminal alkene

on **6-23**. Indeed, the following data: 7.46 ppm (dd, *J* = 17.2, 11.0, 1H) and 5.49 ppm (dd, *J* = 21.5, 14.1, 2H) was used to quantify the presence of the terminal alkene functional group. Additionally, ^{13}C NMR spectroscopy was employed to further confirm the successful synthesis of **6-23**. Thus, analysis of the ^{13}C NMR spectrum of **6-23** showed the presence of two signals at 138.98 and 136.50 ppm due to the terminal alkene and additional signals found at 130.72, 127.73 and 21.98 ppm due to the presence of a tosyl protecting group. The next step in the synthesis was the conversion of the terminal alkene of **6-23** into an aldehyde.

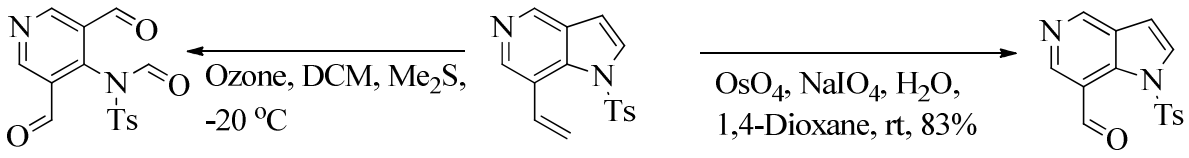


Scheme 7

The conversion of alkenes to aldehydes is a well developed methodology. As a result, various methods have been reported for this conversion including the use of iron oxide nanocatalyst,[40] the use of molecular oxygen catalyzed by palladium,[41] the use of ruthenium on carbon,[42] ozonolysis,[43] and the use of hydrogen peroxide.[44] Of the above mentioned methods, ozonolysis is one of the most used methods due to the short times required to complete the reaction and high yields of the products isolated. Encouraged by short time required and high yielding reactions of ozonolysis, we attempted this method in an effort to convert **6-23** to aldehyde **6-25** (**Scheme 8**). Thus, **6-23** was dissolved in dichloromethane (DCM) and ozone bubbled through the solution at -20 °C for 5 minutes after which the reaction mixture was quenched with dimethyl sulfide. As usual, we decided to run a ^{1}H NMR spectrum of the crude mixture. To our surprise, the two protons of the pyrrole ring of **6-23** could not be observed in the ^{1}H NMR spectrum. Furthermore, the desired terminal alkene of **6-23** was cleaved to form an aldehyde, our desired functional

group. On close inspection of the ^{1}H NMR spectrum of the crude material, it appeared that the pyrrole ring of **6-23** was also cleaved by ozonolysis to form **6-26** (**Scheme 8**) even though we could not fully conclude that **6-26** was formed as we did not have sufficient spectroscopic data. Based on this theory, we concluded that the pyrrole ring of azaindole **6-23** was not stable enough to withstand the reaction conditions of ozonolysis. Thus we decided not to use ozonolysis for this transformation and we continued to search for milder reaction conditions for the conversion of **6-23** into aldehyde **6-25**.

One of the methods used to convert alkenes to aldehydes involved the use of osmium tetraoxide in combination with sodium periodate.[45] However, the toxicity associated with osmium tetraoxide makes this methodology less attractive although these are milder reaction conditions than ozonolysis. With osmium tetraoxide available in our laboratories, we decided to attempt the conversion of **6-23** to **6-25** using this reagent. Hence, **6-23** was dissolved in 1,4-dioxane and water was added to the solution followed by the addition of osmium tetraoxide solution (in water) to the reaction mixture. The reaction mixture was stirred at room temperature for 30 minutes followed by the addition of sodium periodate and the reaction mixture was allowed to stir for a further 10 hours. The crude product was purified by flash chromatography. Gratifyingly, aldehyde **6-25** was isolated in 83% yield (**Scheme 8**). Using ^{1}H NMR spectroscopy, we managed to confirm the absence of the terminal alkene signals previously found at 7.46 and 5.49 ppm and the presence of a new singlet found at 10.81 ppm in the ^{1}H NMR spectrum of **6-25**, a characteristic of the aldehyde functional group. This was further confirmed where the ^{13}C NMR spectrum of **6-25** revealed the presence of a new signal at 190.58 ppm, characteristic of C=O functionality in addition to the absence of the terminal alkene signals previously found at 138.98 and 136.50 ppm. With the aldehyde **6-25** in hand, its functionalization to form the desired azaindole phosphonates was on the cards.



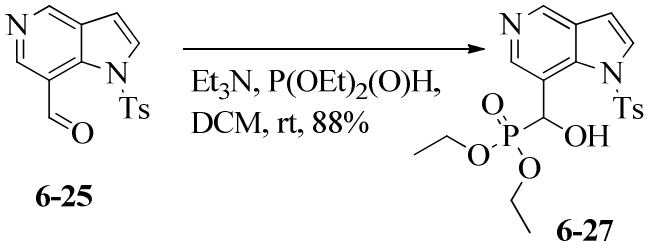
6-26 **6-23** **6-25**

Scheme 8

6.2.4 Synthesis of 5-azaindole phosphonic acid derivatives

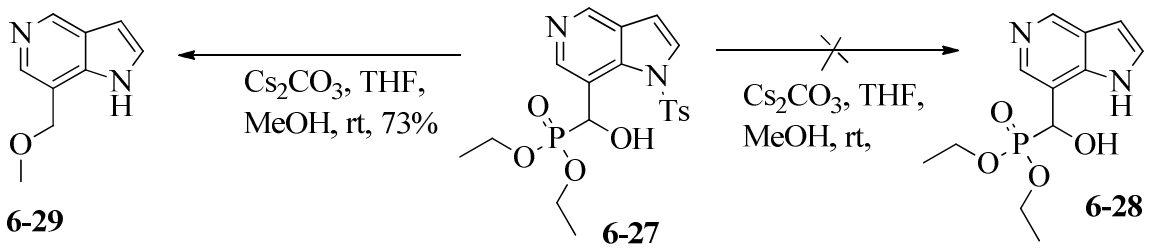
6.2.4.1 1H-pyrrolo[3,2-c]pyridin-7-yl)methyl)phosphonic acid (6-30)

Phosphonates and phosphonic acid derivatives have in recent years attracted the attention of organic chemists due to their biological activities.[46] For this reason, their method of preparation from aldehydes and phosphites has been well explored. For example, the use of methodology involving the use of magnesium oxide,[47] ultrasound irradiation,[48] iodine,[49] lithium perchlorate[50] and triethylamine[51] have been reported to convert aldehydes to phosphonates. Hence, aldehyde **6-26** was dissolved in dichloromethane and diethyl hydrogen phosphate was added followed by the slow addition of triethylamine.[51] The reaction mixture was stirred at room temperature for 24 hours. After this time, the solvent was removed and the resulting oil was purified by flash chromatography to give phosphonate **6-27** in 88% yield (**Scheme 9**). We again employed spectroscopic techniques to ascertain that indeed phosphonate **6-27** had been successfully synthesized. When analyzing the ^{1}H NMR spectrum of **6-27**, firstly we looked for the presence of the aldehyde signal that was previously found at 10.81 ppm. Fortunately, we could not observe this signal. Further analysis of the ^{1}H NMR spectrum of **6-27** revealed the presence of the phosphonate group, where signals for the ethyl group were observed at 4.18 ppm for the methylene group directly bonded to oxygen substituent and 1.20 ppm for the methyl functionality. Furthermore, the ^{13}C NMR spectrum of **6-27** revealed the absence of C=O signal previously found at 190.58 ppm and the new signal was observed at 66.24 ppm (C-OH) in addition to the signals for the ethyl functionality of the phosphonate group appearing at 63.59 and 16.38 ppm. Additionally, the ^{31}P NMR spectrum of **6-27** showed the presence of the phosphorus signal at 28.42 ppm, further confirming the successful synthesis of the phosphonate **6-27**.



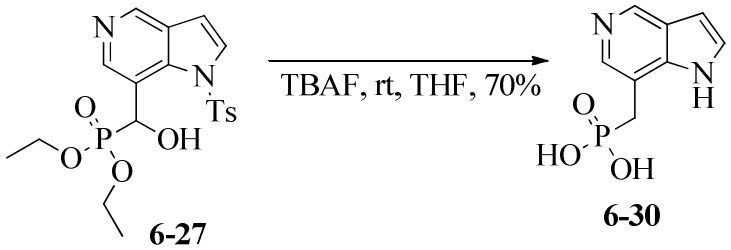
Scheme 9

Deprotection of phosphonates under acidic conditions should give rise to the corresponding phosphonic acid although in our case, to obtain the desired product we attempted to remove the tosyl protecting group of the azaindole first. Deprotection of the tosyl protecting group is a well documented reaction. Various reaction conditions have been designed for this purpose including the use of cesium carbonate,[52] magnesium,[53] phenyldimethylsilyllithium,[54] and potassium hydroxide.[55] For our purposes, **6-27** was dissolved in a mixture of THF:MeOH (2:1) and treated with cesium carbonate (**Scheme 10**). The reaction mixture was purified with flash silica gel column chromatography. Interestingly, the phosphonate and the hydroxyl functionalities of **6-27** could not be observed in the ^{1}H NMR spectrum of our newly formed product. A close inspection of the ^{1}H NMR spectrum of this product suggested that the hydroxyl group was no longer present and that a methanol substitution reaction of the phosphonate functional group on the azaindole **6-27** had taken place to give **6-29** (**Scheme 10**). Even though the results did not yield our desired target, it proved that indeed cesium carbonate could be used to remove the tosyl protecting group. It was also evident that the phosphonate group was not stable enough under these reaction conditions and the unwanted methanol substitution reaction had taken place. Disappointed by these results, we continued to search for even milder reaction conditions under which the phosphonate group would be stable.



Scheme 10

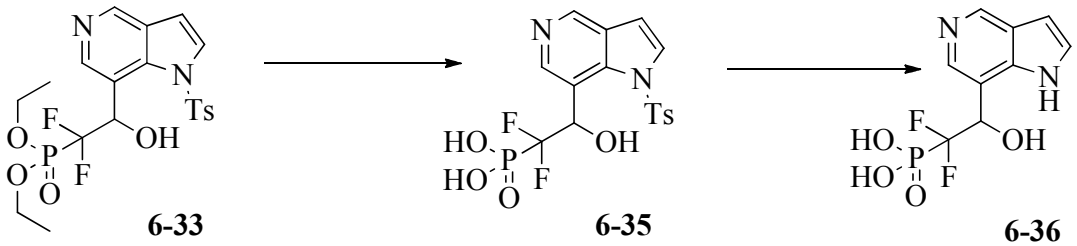
The use of tetrabutylammonium fluoride (TBAF) for the detosylation of indoles was reported to take place at temperatures between 50 and 60 °C although no reaction mechanism has been proposed.[56] We thought that maybe these reaction conditions could be mild enough that they would not cause problems with the phosphonate functional group. Thus, **6-27** was dissolved in THF and treated with TBAF under an argon atmosphere at room temperature. The reaction mixture was then heated to 60 °C for 3 hours (**Scheme 11**). To our surprise, not only the *N*-detosylation took place but the benzylic secondary alcohol functional group was also no longer present. Furthermore, the ethyl protecting groups on the phosphonate functionality could not be observed in the ^{1}H NMR spectrum of the newly formed product **6-30**. We thought the high temperatures could be responsible for this type of reaction and the reaction was repeated at room temperature and 0 °C in order to assess this. We established through the use of ^{1}H NMR spectroscopy that the secondary alcohol functionality and the tosyl protecting group were the first to be cleaved at room temperature followed by the cleavage of the *O*-ethyl substituents while no reaction took place at 0 °C. From these results, we concluded that the hydroxyl functional group was the least stable. Hence, we concluded that we have synthesized the azaindole phosphonic acid **6-30**. The absence of the tosyl protecting group (7.46 ppm (dd, J = 17.2, 11.0, 1H) and 5.49 ppm (dd, J = 21.5, 14.1, 2H)) was confirmed using ^{1}H and ^{13}C NMR spectroscopy. Further analysis of the ^{1}H NMR spectrum of **6-30** revealed the absence of the ethyl substituents (4.18 and 1.20 ppm). The presence of phosphorus in azaindole **6-30** was confirmed by the presence of a signal with the following data: 5.74 (d, J = 48.1, 2H) for the methylene group bonded directly to a phosphorus substituent. The size of the coupling constant was evident to the presence of the phosphorus atom. Furthermore, the ^{13}C Dept135 NMR performed on azaindole **6-30** where it confirmed the presence of a CH_2 group as a doublet with a coupling constant value of 162.9 Hz, clearly indicating the presence of the phosphorus atom. Unfortunately, our attempts to obtain the ^{31}P NMR spectrum of the azaindole **6-30** repeatedly failed.



Scheme 11

6.2.4.2 Synthesis of [1,1-difluoro-2-hydroxy-2-(1-tosyl-1H-pyrrolo[3,2-c]pyridin-7-yl)ethyl]phosphonic acid (6-35)

Now that we had successfully managed to synthesize 5-azaindole phosphonic acid derivative **6-30** albeit lacking the benzylic hydroxyl substituent, our next mission was to synthesize the fluorinated 5-azaindole phosphonic acid derivative **6-36** (**Scheme 12**). Thus, the route to the synthesis of azaindole **6-36** could be achieved through the synthesis of the azaindole **6-33** where further functionalization would result in the formation of the azaindole **6-35**. The synthesis of the azaindole **6-33** would therefore be based on starting from aldehyde **6-25**.

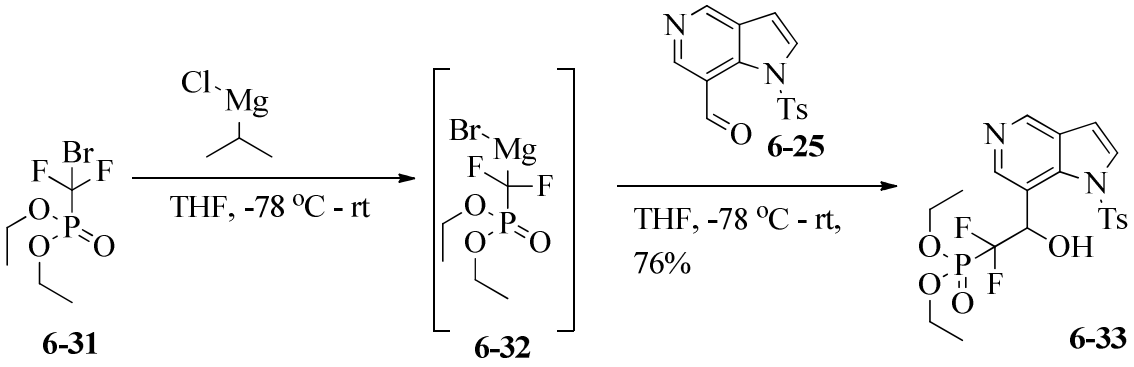


Scheme 12

Therefore, starting from aldehyde **6-25**, we attempted to synthesize [1,1-difluoro-2-hydroxy-2-(1-tosyl-1*H*-pyrrolo[3,2-*c*]pyridin-7-yl)ethyl]phosphonic acid (**6-35**). Aldehydes such as **6-25** have the ability to undergo addition reactions. For example, aldehydes react with alkylzinc reagents in what is known as the Barbier reaction to form alcohols.[57] Additionally, aldehydes also react with alkyl or arylmagnesium halide reagents known as Grignard reagents to generate alcohols.[58] Taking advantage of the reactivity of the aldehydes, we sought to add an appropriate nucleophilic version of a diethyl (difluoro)methylphosphonate group **6-31** to aldehyde **6-25** to

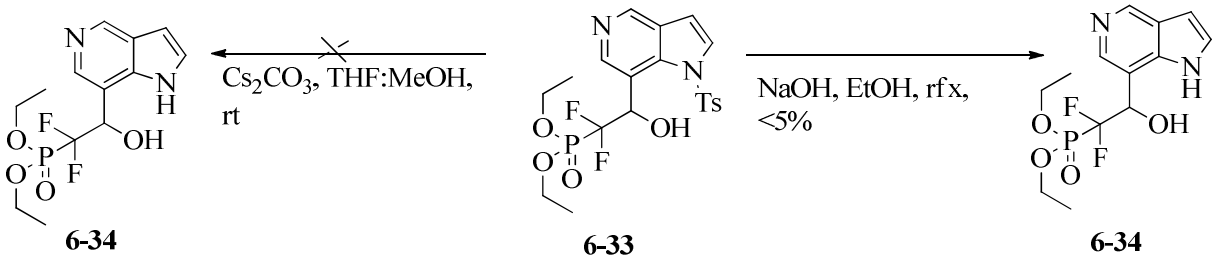
gain access to alcohol **6-33**. We first had to convert diethyl bromo(difluoro)methylphosphonate (**6-31**) into a nucleophile before it could be added to aldehyde **6-25** to form the azaindole **6-33**.

Hence, we turned our attention to using lithium or magnesium metal to convert **6-31** to a nucleophile. In 1997, Waschbüsch *et al*. reported the use of a Grignard reagent to convert **6-31** to a nucleophile using *iso*propylmagnesium chloride.[59] Taking advantage of this methodology, **6-31** was dissolved in THF and the solution cooled to -78 °C. The solution of *iso*propylmagnesium chloride was then added slowly at the same temperature and stirred for a further 10 minutes before the aldehyde **6-25** in THF was introduced into the reaction dropwise. After flash chromatography the desired alcohol **6-33** was furnished in 76% yield as a brown oil (**Scheme 13**). The reaction is understood to go through the formation of nucleophile **6-33** which then reacted with aldehyde **6-25** to form alcohol **6-33** (**Scheme 13**). To confirm the formation of alcohol **6-33**, ^{1}H, ^{13}C, ^{31}P and ^{19}F spectroscopy were used. In analyzing the ^{1}H NMR spectrum of **6-33**, we managed to confirm the absence of the aldehyde signal (10.81 ppm) and the presence of new signals due to the phosphonate group. First was the doublet at 6.72 ppm with coupling constant of 23.9 Hz due to proton coupling to fluorine. Second were the multiplet signals at 4.41 and 1.43 ppm due to the ethyl groups on the phosphonate functional group. Additionally, the ^{13}C NMR spectrum of **6-33** further confirmed the absence of aldehyde C=O signal at 190.58 ppm and the presence of new signals due to the phosphonate functional group at 67.15, 65.28 and 16.34 ppm. Furthermore, the ^{31}P NMR spectrum of **6-33** showed the presence of a multiplet signal at 15.07 ppm due to phosphorus coupling with fluorine, carbon and possibly proton while the ^{19}F NMR spectrum of **6-33** showed two signals at -111.79 and -125.83 ppm each as a doublet of doublets (dd). With the formation of **6-33** confirmed, the next step would involve the removal of the tosyl and the ethyl substituents of alcohol **6-33**.



Scheme 13

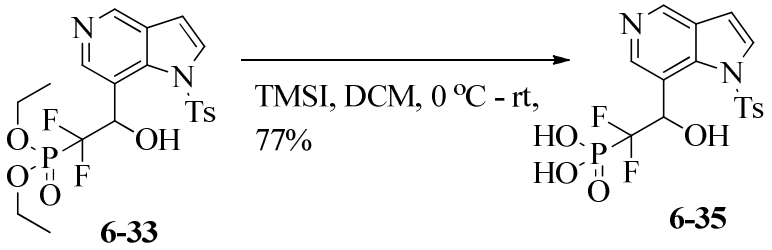
Our initial plan was to first remove the tosyl protecting group followed by the ethyl phosphonate protecting groups. Earlier in this chapter, we discussed different conditions that could be used to remove tosyl protecting groups including the use of cesium carbonate,[52] magnesium,[53] phenyldimethylsilyllithium,[54] and potassium hydroxide.[55] However, our attempts to use cesium carbonate to remove tosyl protecting group on **6-33** to form **6-34** were met with failure as we obtained a complex mixture that we were unable to analyze (**Scheme 14**). With these unsatisfying results, we then tried using sodium hydroxide in refluxing ethanol (**Scheme 14**). Although these reaction conditions were promising, **6-34** could only be isolated in very small quantities (<5% yield). Due to time constraints, we decided to try to see if it will be possible for us to rather produce the phosphonic acid before the removal of the *N*-tosyl substituent.



Scheme 14

We decided to use trimethylsilyl iodide (TMSI) to cleave the ethyl protecting groups in this case although the literature contains an example of trimethylsilyl bromide.[61,62] Hence, phosphonate **6-33** in dichloromethane at 0 °C was slowly treated with TMSI and the reaction mixture allowed to warm to room temperature and stirred for a further 12 hours (**Scheme 15**). Workup of the

reaction allowed for the formation of phosphonic acid **6-35** which precipitated out of solution and was collected as a cream white solid. When the ^{19}F NMR spectrum of **6-35** was analyzed, it revealed the presence of two signals: a doublet of doublets at -115.15 ppm while the signal at -124.07 ppm was revealed as a multiplet. It should also be noted that there was a significant shift in the position of the two signals in the spectrum. Further confirmation of the successful formation of **6-35** was provided by ^{31}P NMR spectroscopy where the ^{31}P NMR spectrum of **6-35** showed the presence of a triplet signal at 2.81 ppm due to the phosphorus atom. Again, we have witnessed a significant shift in the position of the phosphorus signal from 15.07 ppm in **6-33** to 2.81 ppm in **6-35**. Furthermore, the ^{1}H NMR spectrum of **6-35** showed the absence of the signals due to the ethyl substituents previously found at 4.41 and 1.43 ppm. Although we managed to synthesize **6-35**, efforts need to be dedicated to completing the synthesis, especially in removing the tosyl protecting group. For the purpose of this PhD, time constraints did not allow us to experiment further.



6-33 **6-35**

Scheme 15

6.3 Comments and future work

Even though we were unable to successfully synthesize our target molecule **6-36** (without tosyl protecting group), we have successfully managed to synthesis azaindole **6-35** in appreciable yields. Furthermore, we have successfully managed to synthesize azaindole **6-30**. In the future work to be done on this project may include the following:

- Protect the secondary alcohol on both azaindoles **6-27** and **6-33** and try the reactions that failed to determine whether the alcohol substituent had an influence on those reactions.

- Try different method for activating zinc metal to be used in the formation of **6-32** and try forming **6-32**, as zinc reagents of type **6-32** (**Figure 2**) are known to be more stable even at room temperature.
- Find alternative reaction conditions that are mild enough not to affect phosphonate functionality while removing the tosyl protecting group of azaindole **6-35**.
- Use a different protecting group other than tosyl to protect 5-azaindole derivative **6-25**.
- Remove the secondary alcohol on **6-33**, thereby gaining access to another phosphonate **6-37** that could also be converted to another phosphonic acid derivative **6-38** (**Figure 2**).
- Improve yields of reaction steps that provided the desired products with yields less than 70%.
- Devise alternative ways if any of accessing these phosphonic acids.
- Perform biological screening against cancer cell line, bacteria and fungi of our final products (phosphonic acids **6-30**, and **6-35**) (**Figure 2**).

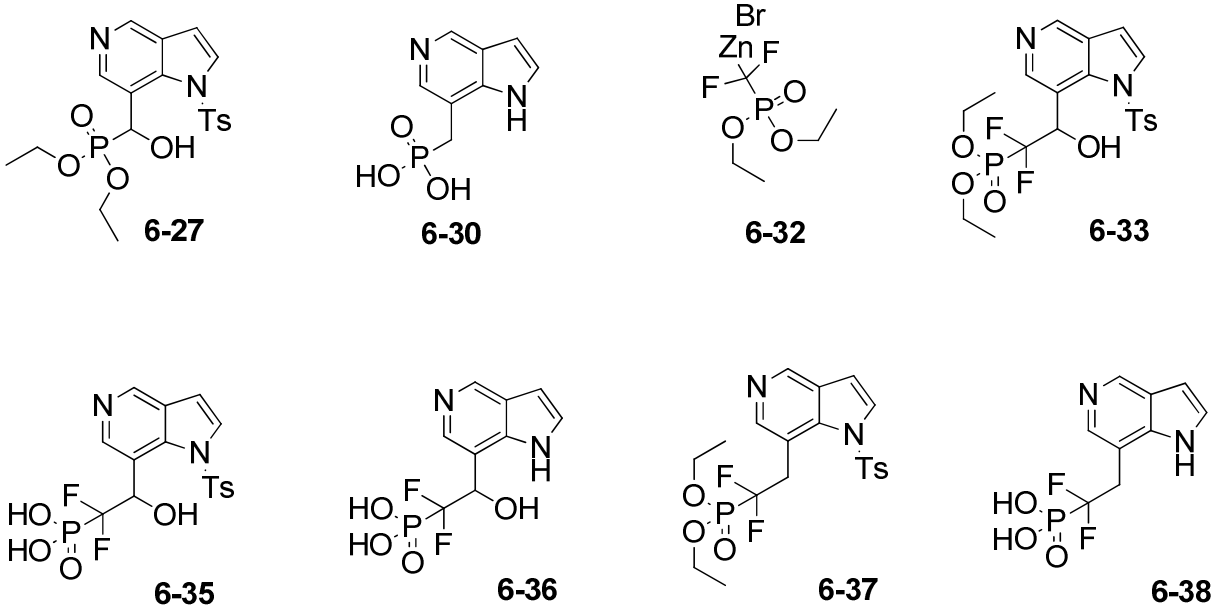


Figure 2

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Chapter 7: Biological Screening of Selected 7-Azaindole Derivatives

One of the aims of this PhD project was to subject the synthesized 7-azaindole derivatives to a variety of biological screens including against various cancer cell lines, HIV, fungi and bacteria. However, it should be noted that biological testing was not a major part of this PhD project and is currently an ongoing exercise even though the thesis has been submitted for examination.
In this section of the PhD project, we will be dealing with the biological screening of selected 7-azaindole derivatives against a panel of bacteria and fungi. In the paragraphs to follow, bacteria and fungi used in this chapter for biological screening will be explained in more detail.

7.1 The bacteria used for screening

The bacteria are made up of a large number of prokaryotic microorganisms and are found almost everywhere on earth including soil, water, nuclear waste, live bodies of animals, plants and other places on the planet.[1] The majority of the bacteria in the body are considered harmless by the protective effects of the immune system while some are beneficial to the body. However, some species of bacteria are pathogenic and cause infectious diseases such as cholera[2], syphilis[3], anthrax[4]and leprosy.[5] Other uses of bacteria include for example, lactic acid bacteria which is used in the preparation of fermented foods[6] while other bacteria find application in oil spill cleanups[7] and in chemistry (biocatalysis) for the production of enantiomerically pure chemicals.[8] Thus, bacteria could either be useful or harmful to human beings, plants, animals. Selected 7-azaindole derivatives were screened against the following bacteria:

- *Pseudomonas aeruginosa* which is an opportunistic bacterium found in soil, skin flora and water and usually affects people with compromised immune systems. It is responsible for infections resulting from burns and wounds, in lungs and urinary tracts as well as most cross-infection in hospitals and clinics.[16]
- *Escherichia coli* is a Gram-negative bacterium normally found in the lower intestines of warm-blooded animals and could cause food poisoning. It is responsible for most product recalls because of food contaminations.[17]

- *Staphylococcus aureus* is a bacterium that is mainly present in the human skin and the respiratory tract. It could cause a range of diseases such as skin infections, pneumonia, meningitis and other diseases.[18]
- *Enterococcus faecalis* is a Gram-positive bacterium found mainly in the gastrointestinal tracts of human beings and other mammalian animals. It is usually responsible for the infections of urinary tracts, but could cause meningitis including bacteremia among other infections.[19]
- *Klebsiella pnuemoniae* is a Gram-positive bacterium with habitats including mouth, skin and the intestines. It could cause various infections in the urinary tract, respiratory tract and is responsible for diseases like pneumonia, diarrhea, meningitis and other diseases.[20]

7.2 The fungi used for screening

The fungi are made up of large number eukaryotic microorganisms such as yeast, molds and mushrooms.[9] Like bacteria, fungi could be useful or harmful to humans, plants and animals. For example, fungi are serious pathogens to cultivated plants and could cause extensive damage to agriculture and forestry with examples including rice blast, chestnut blight and as pathogens to other plants.[10] On the bright side, the fungi are applied in everyday life for various functions and are also a source of biologically active compounds used in drug discovery. For example, penicillin which is produced by *penicillium chrysogenum*[11] and griseofulvin isolated from *penicillium griseofulvum*[12] are some of the useful drugs obtained from fungi. Other uses of fungi include their use in fermentation processes for the preparation of wheat-based products,[13] their use in pest control[14] and their use in bioremediation.[15] Selected 7-azaindole derivatives were screened against the following fungi:

- *Candida albicans* is an opportunistic fungus that infects oral and genital organs in human beings and infects people with compromised immune system.[21]
- *Cryptococcus neoformans* is a fungus that lives in both animals and human beings. It mainly causes lung infections but fungal meningitis in people with compromised immune system is also commom.[22]

- *Candida tropicalis* is an opportunistic fungus affecting mostly people with compromised immune system.[23]

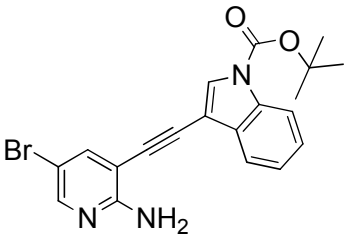
As discussed above, bacteria and fungi are responsible for many infectious diseases affecting human beings, animals and plants. As a result, investigations into how these infections could be prevented or cured once they have occurred is an ongoing research area. However, it should also be noted that as discussed above some bacteria and fungi are useful to humans by providing them with drugs for medicinal use and are also applied in everyday life in various roles.

For the purpose of this PhD, 26 7-azaindole derivatives **7-4** – **7-26** and their precursors aminopyridines **7-1** – **7-3** (**Figure 1**) that had been successfully synthesized were screened against the panel of bacteria and fungi. The results of the biological screening including the method of preparation for the solution of these compounds will be discussed in the following paragraphs.

7.3 Results and Discussion

7.3.1 Antibacterial and antifungal testing

Stock solutions of the 26 pure synthetic compounds **Figure 1** were prepared in acetone at the same concentration of 1000 µg/ml. The antibacterial and antifungal activity of these compounds was assessed against five bacteria, *Pseudomonas aeruginosa* NTC 9027, *Escherichia coli* ATCC 8739, *Staphylococcus aureus* ATCC 25873, *Enterococcus faecalis* ATCC 29212, and *Klebsiella pnuemoniae* ATCC 13883; and three fungi, *Cryptococcus neoformans* ATCC 90112, *Candida tropicalis* ATCC 201380 and *Candida albicans* ATCC 10231. The bioassay was done by myself at the Department of Pharmacy and Pharmacology, University of Witwatersrand, Medical School, Johannesburg, South Africa.



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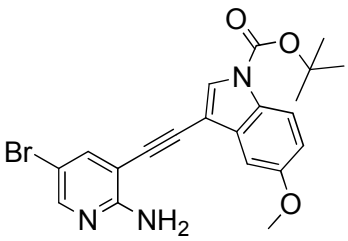

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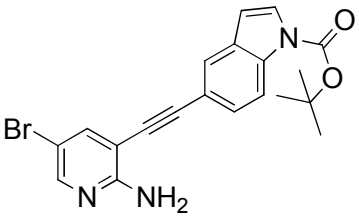

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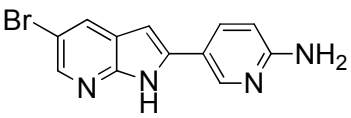

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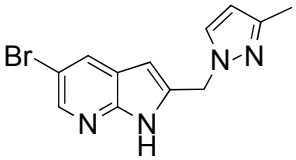

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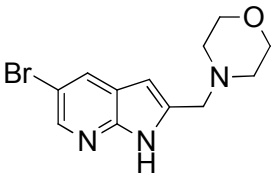

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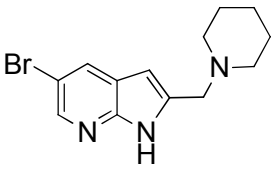

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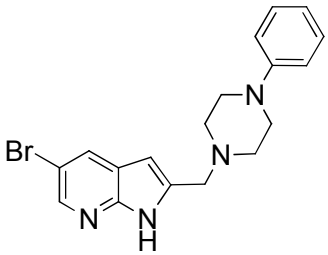

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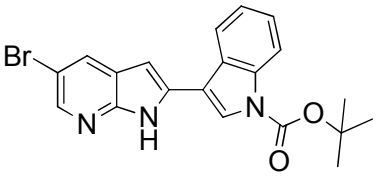

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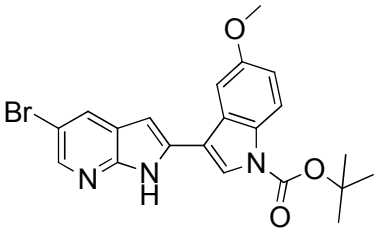

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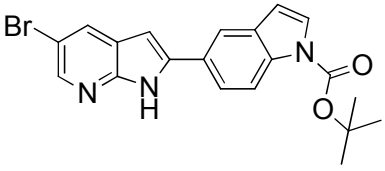

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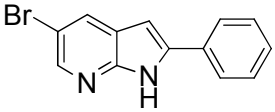

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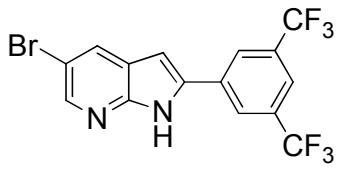

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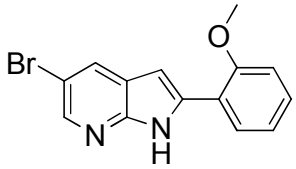

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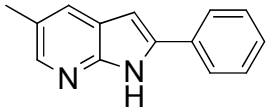

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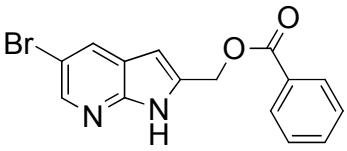

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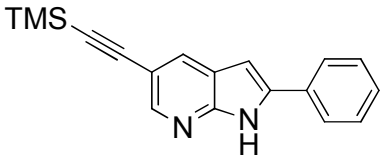

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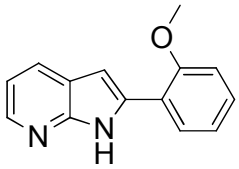

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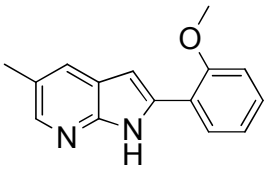

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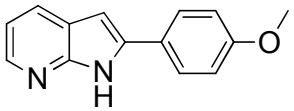

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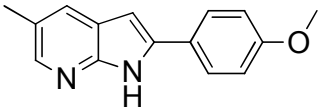
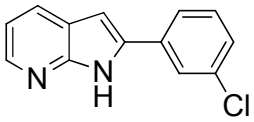
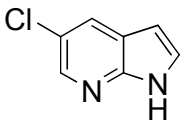


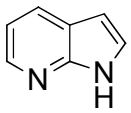
7-21



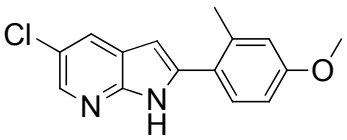
7-22



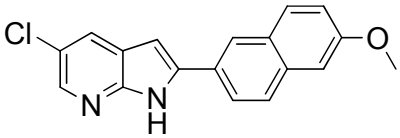
7-23



7-24



7-25



7-26

Figure 1

7.3.2 Method of preparation

- Twenty six samples (**7-1** – **7-26**) and the negative control (water) were dissolved in acetone making a concentration of 1000 µg/ml each.
- 100 µl of sterilized water was added in 96 well plates. 100 µl of each sample, negative control, positive control and broth (culture) control were put in 96 well plates in duplicate for each bacterial and fungal species used for screening.
- Ciprofloxacin was used as a positive control for antibacterial assay, whilst, amphotericin B was used for the fungal assay.
- Serial dilution was done for each duplicate making different concentrations (µg/ml); 250, 125, 62.5, 31.3, 15.6, 7.8, 3.6 and 2.0.
- 500 µl of each bacterium was mixed with 50 ml of broth separately and shaken well before putting 100 µl to all samples at different concentrations in the 96 well plates.
- 500 µl of each fungus was mixed with 50 ml of broth separately and shaken well before putting 100 µl to all samples at different concentration in the 96 well plates.
- Well plates were incubated in an oven at 37 °C for 24 hrs for the bacteria and 48 hrs for the fungi.
- 0.08 g of Iodonitrotetrazolium chloride (INT) was dissolved in 200 ml of water making 80,000 µl (0.0004 g/ml) and shaken for 30 min and kept in the fridge.
- After incubation, 40 µl of INT was drawn and put in each well plate and left at room temperature for 3.5 hrs for bacterial assay and for 24 hrs for fungal assay before reading results.
- Purple colour solution in well plates indicated the growth of bacteria and fungi; whilst clear solution indicated the inhibition of growth for both bacteria and fungi.
- The results were tabulated as shown on pages 148 and 149.

Table 1: The average MIC values for the growth inhibition of selected pathogens

Sample no:	MIC (μg/ml)							
	P. aeruginosa NCTC 9027	*E. coli* ATCC 8739	*S. aureus* ATCC 25923	*E. faecalis* ATCC 29212	*K. pnuemoniae* ATCC 13883	*C. neoformans* ATCC 90112	*C. tropicalis* ATCC 201380	*C. albicans* ATCC 10231
7-1	31.3	31.3	125	250	62.5	31.3	125	250
7-2	31.3	31.3	125	250	31.3	**15.6**	62.5	250
7-3	31.3	31.3	31.3	250	46.9	**15.6**	31.3	250
7-4	31.3	93.8	31.3	250	**15.6**	**10**	31.3	250
7-5	**7.8**	250	62.5	62.5	46.9	**3.9**	31.3	31.3
7-6	31.3	31.3	62.5	62.5	31.3	**8.0**	31.3	31.3
7-7	31.3	31.3	62.5	62.5	31.3	**15.6**	31.3	31.3
7-8	31.3	31.3	62.5	62.5	31.3	**15.6**	31.3	31.3
7-9	31.3	31.3	62.5	62.5	31.3	**15.6**	31.3	31.3
7-10	31.3	31.3	250	62.5	31.3	**7.8**	**15.6**	31.3
7-11	46.9	31.3	62.5	250	125	**3.9**	31.3	31.3
7-12	62.5	31.3	62.5	250	62.5	**3.9**	31.3	31.3
7-13	62.5	31.3	31.3	250	62.5	**15.6**	31.3	**15.6**
7-14	62.5	31.3	62.5	250	31.3	**15.6**	31.3	**15.6**
7-15	31.3	31.3	62.5	250	31.3	**7.8**	31.3	**15.6**
7-16	31.3	31.3	31.3	250	46.9	**7.8**	**15.6**	**23.5**
7-17	46.9	250	250	125	31.3	**3.9**	31.3	31.3
7-18	31.3	62.5	31.3	93.8	31.3	**4.0**	**3.9**	**7.8**

7-19	**7.8**	62.5	31.3	125	31.3	**3.9**	31.3	31.3
7-20	31.3	62.5	31.3	125	31.3	**7.8**	31.3	**15.6**
7-21	31.3	46.9	31.3	62.5	31.3	**7.8**	**15.6**	31.3
7-22	31.3	31.3	31.3	62.5	**23.5**	**15.6**	31.3	31.3
7-23	31.3	62.5	62.5	125	31.3	**15.6**	**15.6**	31.3
7-24	46.9	46.9	62.5	125	31.3	**17.0**	**15.6**	31.3
7-25	31.3	31.3	250	125	31.3	**15.6**	**15.6**	250
7-26	31.3	31.3	62.5	125	**46.9**	**15.6**	**15.6**	46.9
Ciproflaxacin	1.0	2.5	0.6	2.5	0.6			
Amphotericin B						0.6	1.3	1.3
Water	>250	125	>250	>250	>250	>250	125	125
Culture control	>250	>250	>250	>250	>250	>250	>250	>250

Amino pyridines **7-1** – **7-3** performed poorly against all pathogens with the exception of *C. neoformans*. This poor activity may be attributed to the lack of 7-azaindole nucleus. Indeed, the presence of the 7-azaindole nucleus in compounds **7-9** – **7-11** resulted in increased activity of these compounds with the greatest activity observed for azaindole **7-11** against *C. neoformans* with the MIC value of 3.9 μg/ml followed by azaindole **7-10** with the MIC value of 7.8 μg/ml while MIC value of 15.6 μg/ml was observed for azaindole **7-9**. In comparing the activity of compounds **7-4** – **7-8** and **7-12** – **7-14** with 5-bromo-7-azaindole nuclei, 7-azaindole **7-5** was the most active with the MIC value of 3.9 μg/ml against fungus *C. neoformans*. This remarkable activity could be attributed to the pyrazole substituent on the 2-position possibly due to its hydrogen bonding ability. Additionally, other compounds gave impressive activity against fungus *C. neoformans* with the MIC values ranging from 3.9 μg/ml to 15.6 μg/ml. The 7-azaindole **7-5** also gave good activity against other pathogens with the exception of bacteria *E. faecalis*, *S. aureus* and *E. coli* indicating the important role played by the pyrazole substituent. However, depending on the substituent on the 2-position, other compounds showed better activity against certain pathogens compared to azaindole **7-5**. For example, all compounds gave better activity than **7-5** against *E. coli*. Compound **7-10** gave even better activity (15.6 μg/ml) against *C. tropicalis* while compounds **7-13** and **7-14** gave better activity (15.6 μg/ml) against *C. albicans* as compared to the 7-azaindole **7-5**. 7-Azaindole **7-5** also showed good activity against bacterium P. aeruginosa (7.8 μg/ml) while **7-4** showed good activity against fungus *C. neoformans* (10.0 μg/ml).

The 7-azaindole derivative **7-18** showed remarkable activity against all pathogens with the best activity obtained against fungi *C. neoformans* and *C. tropicalis* giving the MIC value of 3.9 μg/ml. However, the activity of **7-19**, the analogue of **7-18** with methyl group at the 5-position decreased considerably as compared to the activity of 7-azaindole **7-18** against all the fungi with the activity against *C. neoformans* staying the same at 4.0 μg/ml. There was no doubt that the methyl group influenced the activity of these compounds. Surprisingly, the effect of the methyl group on the activity of 7-azaindole **7-21** versus that of 7-azaindole **7-20** did not follow the pattern shown by 7-azaindoles **7-18** and **7-19**. While the methyl group reduced the activity of 7-azaindole **7-19** compared to **7-18**, it increased the activity of azaindole **7-21** compared to azaindole **7-20** thus indicating that the position of the methoxy group (*ortho* versus *para*) in

these compounds played an important role in their activity. Additionally, the role of substituents around the 7-azaindole nucleus was noticeable when the activity of unsubstituted 7-azaindole **7-24** was compared to that of substituted 7-azaindole compounds. As observed in Table 1, most substituted 7-azaindoles showed excellent activity compared to 7-azaindole **7-24**, indicative of the important role played by the substituents around the 7-azaindole nucleus. Finally, compounds **7-23**, **7-25** and **7-26** with the 5-chloro-7-azaindole nucleus were also screened for possible activity against pathogens. Indeed, these compounds were active against most pathogens tested in this assay with the best MIC value of 15.6 μg/ml obtained against fungi *C. neoformans* and *C. tropicalis*. Otherwise, the effect of the substituents on the 2-position was not immediately observable because these compounds had similar activity against both bacteria and fungi.

The results obtained in this study were very interesting. All compounds showed excellent activity against most of the pathogens although some pathogens were very resistant. Secondly, we also noticed that the presence of different functional groups on these compounds played a very important role in their activity. These functional groups resulted in some of the compounds being selective inhibitors of certain pathogens. For example, indoles **7-2** and **7-3** favoring the inhibition of *C. neoformans* as compared to other pathogens with the MIC value of 15.6 μg/ml. However, the best selectivity towards *C. neoformans* was shown by azaindoles **7-11**, **7-12** and **7-17** with the MIC value of 3.9 μg/ml. Although other azaindoles were not as selective, they have shown excellent activity against several pathogens. For example, azaindoles **7-16**, **7-18** and **7-26** showed excellent activity against more than two pathogens while most of the azaindoles showing excellent activity against at least one pathogen.

In short, most of the compounds screened were active against both bacterial and fungal pathogens used in this assay. Moreover, this also revealed that substituents on the 7-azaindole nucleus often resulted in the increased activity of the related substituted compounds. Structure-activity relationship revealed that the position of the substituents played an important role in the activity of these compounds. In comparing the pathogens used in this study, most bacteria were found to be more resistant compared to fungi. Of the above screened pathogens, the bacterium *E. faecalis* was the most resistant with the lowest MIC value of 62.5 μg/ml followed by the bacteria *S. aureus* and *E. coli* with the lowest MIC value of 31.3 μg/ml obtained for both. On the other

hand, the fungus *C. neoformans* was the least resistant with the lowest MIC value of 3.9 μg/ml obtained followed by the fungi *C. tropicalis*, *C. albicans* and bacterium *P. aeruginosa* with the lowest MIC value of 7.8 μg/ml obtained. Bacterium *K. pnuemoniae* was found to have MIC value of 15.6 μg/ml.

7.4 References

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Chapter 8: Experimental Section

8.0 General Experimental Procedures

8.0.1 Purification of Solvents and Reagents

All solvents used for reactions and preparative chromatography were distilled prior to use unless otherwise stated. Where necessary, they were also purified by standard methods as recommended by Perrin *et al*. (*Purification of Laboratory Chemicals*, Pergamon Press, Oxford, **1998**). Solvents were distilled as follows: Tetrahydrofuran from the sodium benzophenone ketyl radical, dichloromethane, triethylamine from calcium hydride and toluene from sodium. Where required, solvents were stored over activated molecular sieves (4 Å) under nitrogen or argon atmosphere. Unless otherwise stated, other reagents were obtained from commercial sources and employed without further purification.

8.0.2 Chromatographic Separations

Thin layer chromatography (TLC) was carried out on aluminum-backed Macherey-Nagel Alugram Sil G/UV_{254} plates pre-coated with 0.25 mm silica gel 60. Detection was done by using ultraviolet light at 254 nm. Preparative column chromatography was carried out on dry-packed columns using Macherey-Nagel Kieselgel 60 silica gel 60 (particle size 0.063-0.200 mm) as the adsorbent. Mixtures of EtOAc and hexane, dichloromethane and methanol or EtOAc and methanol were used as the mobile phase.

8.0.3 Spectroscopic and Physical Data

All melting points were obtained on a Stuart melting point apparatus and are uncorrected.
The ^{1}H NMR (nuclear magnetic resonance) spectra were recorded on a Bruker AVANCE 300 (300.13 MHz), a Bruker AVANCE III 400 (400.13 MHz) or a Brucker Avance 500 III (500.13 Mhz) spectrophotometer. Spectra were recorded in deuterated chloroform ($CDCl_3$), deuterated acetone (acetone-d_6), deuterated DMSO (DMSO-d_6) or deuterated methanol (MeOD) and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. Coupling constants are given in Hertz (Hz). Splitting patterns are designated as “s”, “d”, “t”, “q”, and “m”; and these symbols indicate “singlet”, “doublet”, “triplet”, “quartet” and “multiplet” respectively. The ^{13}C NMR (^{1}H decoupled) spectra were recorded on a Bruker AVANCE 300 (75.47 MHz), a Bruker DRX 400 (100.63 MHz) or a Bruker Avance 500 (125.77 MHz) spectrometer. Spectra were recorded in deuterated chloroform ($CDCl_3$), deuterated acetone (acetone-d_6), deuterated DMSO (DMSO-d_6) or deuterated methanol

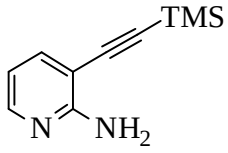
(MeOD) and chemical shifts are reported in parts per million (ppm) relative to the central signal of deuterated solvent, taken as applicable as per solvent.

IR (infrared) spectra were recorded on a Bruker Tensor 27 spectrometer. Samples were placed on a diamond thin film and the signals were reported on the wavenumber scale (ν/cm^{-1}) ranging from 400 – 4000 cm^{-1}. Signals were designated as "s", "m", "w" and "b"; these symbols indicate "strong", "medium", "weak" and "broad" respectively.

Mass spectra were recorded on a Thermo Electron Corporation DFS High Resolution Magnetic Sector mass spectrometer. The polarity was positive, ionization employed was EI and a mass range of 1000 amu (5 kV) was used. Scan rates of 6 secs/decade for magnetic fragmentation data and 30 sec/decade for a high resolution electric scans, were used respectively. Data are quoted in relative abundance (*m/z*).

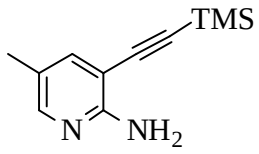
8.1 Experimental to Chapter 2

3-((Trimethylsilyl)ethynyl)pyridin-2-amine (2-21)



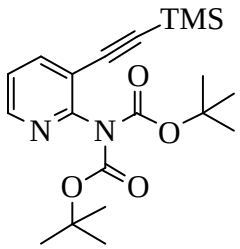
To a mixture of 2-amino-3-bromopyridine (0.4110 g, 2.38 mmol), copper (I) iodide (0.02714 g, 0.143 mmol), trimethylsilylacetylene (1.169 g, 1.67 ml, 0.0119 mol) and triethylamine (1.130 g, 1.56 ml, 0.0110 mol) in tetrahydrofuran (20 ml) was added in one portion $Pd(PPh_3)_4$ (0.1650 g, 0.143 mmol). The resulting yellowish reaction mixture was heated at 65 °C for 8 hours after which it was allowed to cool to room temperature, was quenched with a saturated aqueous ammonium chloride and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered, excess solvent removed under reduced pressure and the product purified by column chromatography using ethyl acetate/hexane (30%) to give 3-((trimethylsilyl)ethynyl)pyridin-2-amine[4] (**2-21**) as a cream white solid (0.3900 g, 86%).^{1}H NMR (300 MHz, CDCl3) δ: 8.07 (d, 1H), 7.62 (m, 1H), 6.57 (m, 1H), 5.07 (s, 2H), 0.13 (s, 9H).

5-Methyl-3-((trimethylsilyl)ethynyl)pyridin-2-amine (2-22)



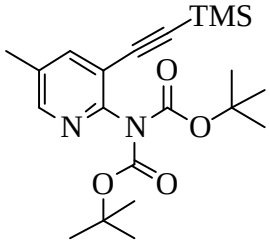
To a mixture of 2-amino-3-bromo-5-methylpyridine (0.4110 g, 2.38 mmol), copper (I) iodide (0.02712 g, 0.132 mmol), trimethylsilylacetylene (1.080 g, 1.54 ml, 0.0119 mol) and triethylamine (1.130 g, 1.56 ml, 0.0110 mol) in tetrahydrofuran (20 ml) was added in one portion $Pd(PPh_3)_4$ (0.1526 g, 0.132 mmol). The resulting reaction mixture was heated at 65 °C for 8 hours after which it was allowed to cool to room temperature, was quenched with a saturated aqueous ammonium chloride and was extracted with dichloromethane. The organic layer was dried over magnesium sulfate, was filtered and excess solvent was removed under reduced pressure. The product was purified by column chromatography using ethyl acetate/hexane (30%) to give 5-methyl-3-((trimethylsilyl)ethynyl)pyridin-2-amine[4] (**2-22**) as a cream white solid (0.4752 g, 98%). ^{1}H NMR (300 MHz, CDCl3) δ: 7.84 (s, 1H), 7.39 (d, 1H), 4.92 (s, 2H), 2.12 (s, 3H), 0.13 (s, 9H).

Di-*tert*-butyl(3-((trimethylsilyl)ethynyl)pyridine-2yl)dicarbamate (2-31)



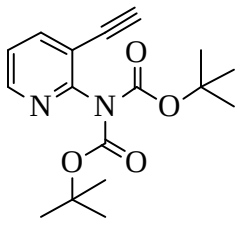
A mixture of 3-((trimethylsilyl)ethynyl)pyridin-2-amine (0.3881 g, 2.04 mmol), DMAP (0.02492 g, 0.204 mmol) and Boc anhydride (1.112 g, 5.10 mmol) in tetrahydrofuran (20 ml) was stirred at room temperature for 24 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate, was extracted with dichloromethane and the combined organic fractions were dried over magnesium sulfate. Excess solvent was removed under reduced pressure followed by purification with column chromatography using ethyl acetate/hexane (30%) to give di-*tert*-butyl(3-((trimethylsilyl)ethynyl)pyridine-2yl)dicarbamate (**2-31**) as cream white solid (0.7113 g, 89%). Melting point: 102 – 105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 4.9, 1.9, 1H), 7.80 (dd, *J* = 7.7, 1.8, 1H), 7.21 (dd, *J* = 7.7, 4.9, 1H), 1.39 (s, 18H), 0.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.01, 150.39, 148.17, 140.96, 122.74, 119.31, 102.19, 98.97, 83.50, 82.90, 28.09. IR (cm^{-1}) 2983 (CH str.), 2160 (alkyne), 1793 (C=O), 1609 (C=N), 1561 (C=C), 1151 (C-O). HRMS (ES^+) Calculated for $C_{20}H_{31}N_2O_4Si$ $[M + H]^+$: 391.2053, found 391.2042.

Di-*tert*-butyl(5-methyl-3-((trimethylsilyl)ethynyl)pyridine-2yl)dicarbamate (2-32)



A mixture of 5-methyl-3-((trimethylsilyl)ethynyl)pyridin-2-amine (0.4433 g, 2.17 mmol), DMAP (0.02651 g, 0.217 mmol) and Boc anhydride (1.184 g, 5.43 mmol) in tetrahydrofuran (20 ml) was stirred at room temperature for 24 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate, was extracted with dichloromethane and the combined organic fractions dried over magnesium sulfate. Excess solvent was removed under reduced pressure followed by purification with column chromatography using ethyl acetate/hexane (30%) to give di-*tert*-butyl(5-methyl-3-((trimethylsilyl)ethynyl)pyridine-2yl)dicarbamate (**2-32**) as a cream white solid (0.8201 g, 94%). Melting point: 100 – 103 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 2.2, 1H), 7.61 (d, *J* = 2.2, 1H), 2.32 (s, 3H), 1.39 (s, 18H), 0.23 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.70, 150.66, 148.61, 141.46, 132.63, 118.62, 101.67, 99.22, 82.84, 28.17, 18.13, 18.11, 0.06. IR (cm^{-1}) 2978 (CH str.), 2130 (alkyne), 1795 (C=O), 1601 (C=N), 1561 (C=C), 1150 (C-O). HRMS (ES^+) Calculated for $C_{17}H_{23}N_2O_4$ $[M + H]^+$ 405.2210: , found 405.2210.

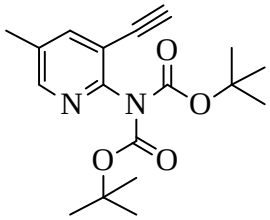
Di-*tert*-butyl(3-ethynyl)pyridine-2yl)dicarbamate (2-33)



Di-*tert*-butyl(3-((trimethylsilyl)ethynyl)pyridine-2yl)dicarbamate (0.1994 g, 0.511 mmol) was dissolved in dry tetrahydrofuran (20 ml) and cooled to 0 °C. TBAF (0.61 ml, 0.613 mmol) was added slowly and the reaction mixture turned brown immediately the TBAF was added. The resulting brown reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. Quenching with water was followed by extraction with dichloromethane. The combined organic fractions were dried over magnesium sulfate, solvent was removed under reduced pressure and the product

purified by column chromatography using ethyl acetate/hexane (30%) to give di-*tert*-butyl(3-ethynyl)pyridine-2yl)dicarbamate (**2-33**) (0.1456 g, 90%) as a cream white solid. Melting point: 109 – 111 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 4.9, 1.8, 1H), 7.89 (dd, *J* = 7.7, 1.8, 1H), 7.29 (dd, *J* = 5.3, 2.3, 1H), 3.36 (s, 1H), 1.42 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.82, 150.19, 148.33, 141.25, 122.47, 117.98, 83.98, 83.95, 82.97, 77.84, 27.77. IR (cm^{-1}) 2986 (CH str.), 2133 (alkyne), 1783 (C=O), 1608 (C=N), 1543 (C=C), 1149 (C-O). HRMS (ES^+) Calculated for $C_{17}H_{23}N_2O_4$ $[M + H]^+$: 347.1813, found 347.1815.

Di-*tert*-butyl(5-methyl-3-(ethynyl)pyridine-2yl)dicarbamate (2-34)

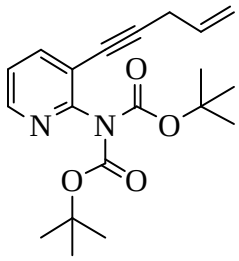


Di-*tert*-butyl(5-methyl-3-((trimethylsilyl)ethynyl)pyridine-2yl)dicarbamate (0.2751 g, 0.0680 mmol) was dissolved in dry tetrahydrofuran (20 ml) and cooled to 0 °C. TBAF (0.82 ml, 0.816 mmol) was then added slowly and the reaction mixture turned brown immediately the TBAF was added. The resulting brown reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. Quenching with water was followed by extraction with dichloromethane. The combined organic fractions were dried over magnesium sulfate and the product was purified with column chromatography using ethyl acetate/hexane (30%) to give di-*tert*-butyl(5-methyl-3-(ethynyl)pyridine-2yl)dicarbamate (**2-34**) as a cream white solid (0.2101 g, 93%). Melting point: 129 – 132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 1.9, 1H), 7.67 (d, *J* = 1.9, 1H), 3.29 (s, 1H), 2.36 (s, 3H), 1.40 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.48, 150.41, 148.73, 141.61, 132.37, 117.25, 83.50, 82.84, 77.99, 27.80, 17.79. IR (cm^{-1}) 2987 (CH str.), 2130 (alkyne), 1782 (C=O), 1607 (C=N), 1568 (C=C), 1148 (C-O). HRMS (ES^+) Calculated for $C_{18}H_{25}N_2O_4$ $[M + H]^+$: 333.1814, found 333.1816.

General procedures for allyl bromide coupling:

A mixture of 3-ethynylpyridine derivative, copper iodide, allyl bromide, potassium carbonate and sodium sulfite in DMF (2 ml) was heated to 35 - 40 °C for 24 hours. After this time, the reaction mixture was put under reduced pressure to collect excess allyl bromide into the trap that was placed in liquid nitrogen. The remaining mixture was taken into water and extracted with ether, washed with water and dried over magnesium sulfate. Excess solvent was removed under reduced pressure and the product purified by column chromatography using ethyl acetate/hexane (30%) to give the desired product.

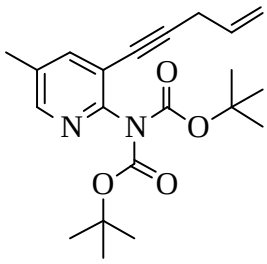
Di-*tert*-butyl (3-(pent-4-en-1-yn-1-yl)pyridin-2-yl)dicarbamate (2-35)



Di-*tert*-butyl(3-ethynyl)pyridine-2yl)dicarbamate (0.1390 g, 0.437 mmol), Copper iodide (1.663 mg, 8.73 μmol), potassium carbonate (6.040 mg, 0.0.437 mmol), sodium sulfite (2.754 mg, 0.219 mmol) and allyl bromide (7.930 mg, 0.656 mmol). Purification by column chromatography gave di-*tert*-butyl (3-(pent-4-en-1-yn-1-yl)pyridin-2-yl)dicarbamate (**2-35**) (0.1351 g, 86%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, *J* = 4.0, 1H), 7.79 (d, *J* = 7.4, 1H), 7.22 (dd, *J* = 7.5, 5.0, 1H), 5.85 (m, 1H), 5.37 (d, *J* = 17.0, 1H), 5.17 (d, *J* = 10.0, 1H), 3.20 (d, *J* = 4.9, 2H), 1.39 (s, 18H). ^{13}C

NMR (75 MHz, $CDCl_3$) δ 153.28, 150.40, 147.34, 140.66, 131.42, 122.48, 119.39, 116.78, 93.69, 82.72, 77.24, 27.79, 23.79. IR (cm^{-1}) 2984 (CH str.), 2159 (alkyne), 1790 (C=O), 1612 (C=N), 1561 (C=C), 1146 (C-O). HRMS (ES^+) Calculated for $C_{20}H_{27}N_2O_4$ $[M + H]^+$: 359.1974, found 359.1963.

Di-*tert*-butyl (5-methyl-3-(pent-4-en-1-yn-1-yl)pyridin-2-yl)dicarbamate (2-36)

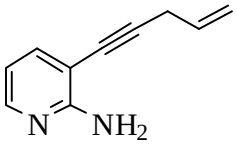


Di-*tert*-butyl(5-methyl-3-(ethynyl)pyridine-2yl)dicarbamate (0.01510 g, 0.0451 mmol), Copper iodide (0.1719 mg, 0.903 μmol), potassium carbonate (6.233 mg, 0.0451 mmol), sodium sulfite (2.842 mg, 0.0226 mmol) and allyl bromide (8.184 mg, 0.0677 mmol). Purification by column chromatography gave di-*tert*-butyl (5-methyl-3-(pent-4-en-1-yn-1-yl)pyridin-2-yl)dicarbamate (**2-36**) (0.01501 g, 90%) as a brown oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.60 (s, 1H), 5.83 (m, 1H), 5.37 (d, *J* = 16.8, 1H), 5.16 (d, *J* = 10.0, 1H), 3.18 (d, *J* = 5.0, 2H), 2.34 (s, 3H), 1.40 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.63, 147.77, 141.09, 132.27, 131.53, 118.65, 116.72, 100.00, 93.14, 82.62, 77.21, 27.84, 23.78, 17.81, 17.78. IR (cm^{-1}) 2965 (CH str.), 2165 (alkyne), 1737 (C=O), 1603 (C=N), 1581 (C=C), 1147 (C-O). HRMS (ES^+) Calculated for $C_{21}H_{29}N_2O_4$ $[M + H]^+$: 373.2127, found 373.2115.

General procedure for removal of the Boc protecting group

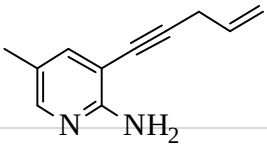
The Di-*tert*-butyl 3-(pent-4-en-1-yn-1-yl)pyridin-2-yl)dicarbamate derivatives **2-35** and **2-36** were dissolved separately in dichloromethane (15 ml) and the resulting mixture cooled to 0 °C before trifluoroacetic acid was added. After the addition, the reaction mixture was allowed to warm to room temperature and stirred at this temperature for 4 hours. After this time, trifluoroacetic acid and dichloromethane were removed under reduced pressure to give a brown oil. The oil was redissolved in dichloromethane (20 ml) and washed with sodium carbonate solution. After drying over magnesium sulfate, solvent was removed on a rotary evaporator and the product purified by column chromatography using ethyl acetate/hexane (30%).

3-(Pent-4-en-1-yn-1-yl)pyridin-2-amine (2-37)



Di-*tert*-butyl (3-(pent-4-en-1-yn-1-yl)pyridin-2-yl)dicarbamate (3.000 mg, 8.37 μmol) and triflouroacetic acid (0.013 ml, 0.167 mmol). Purification by column chromatography gave 3-(pent-4-en-1-yn-1-yl)pyridin-2-amine (**2-37**) (1.250 mg, 95%) as a brown oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 3.9, 1H), 7.55 (dd, *J* = 7.5, 1.7, 1H), 6.63 (dd, *J* = 7.5, 5.3, 1H), 5.90 (m, 1H), 5.38 (dd, *J* = 17.0, 1.5, 3H), 5.19 (dd, *J* = 10.0, 1.5, 1H), 3.26 (d, *J* = 5.3, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.31, 145.21, 140.67, 131.85, 116.69, 113.32, 104.60, 94.01, 77.21, 29.69. IR (cm^{-1}) 3466 (NH str.), 3163 (CH str.), 2119 (alkyne), 1602 (C=N), 1567 (C=C). HRMS (ES^+) Calculated for $C_{10}H_{11}N_2$ $[M + H]^+$: 159.0922, found 159.0932.

5-Methyl-3-(pent-4-en-1-yn-1-yl)pyridin-2-amine (2-38)



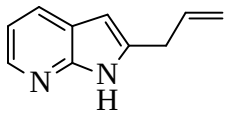
Di-*tert*-butyl(5-methyl-3-(pent-4-en-1-yn-1-yl)pyridin-2-yl)dicarbamate (9.110 mg, 0.00244 mmol) and trifluoroacetic acid (0.038 ml, 0.489

mmol). Purification by column chromatography gave 5-methyl-3-(pent-4-en-1-yn-1-yl)pyridin-2-amine (**2-38**) (0.3901 mg, 93%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.41 (d, *J* = 2.0, 1H), 5.91 (m, 1H), 5.40 (dd, *J* = 17.0, 1.5, 1H), 5.20 (dd, *J* = 10.0, 1.5, 1H), 5.09 (s, 2H), 3.27 (dt, *J* = 5.3, 1.7, 2H), 2.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.59, 145.36, 141.35, 131.96, 122.42, 116.59, 104.07, 93.48, 77.67, 29.69, 23.89. IR (cm^{-1}) 3287 (NH str.), 3006 (CH str.), 2132 (alkyne), 1612 (C=N), 1565 (C=C). HRMS (ES^+) Calculated for $C_{11}H_{13}N_2$ $[M + H]^+$: 173.1079, found 173.1096.

General procedure for ring closing using potassium hydride

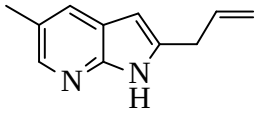
To a solution of potassium hydride in NMP (5 ml) at 0 °C was added slowly a solution of the 3-(pent-4-en-1-yn-1-yl)pyridin-2-amine derivatives **2-37** and **2-38** in NMP separately. After the addition was complete, the temperature was allowed to warm to room temperature and the reaction was stirred at this temperature for 5 hours. The reaction mixture was quenched with water and extracted with ether. The ether extracts were washed with water, dried over magnesium sulfate, were filtered and ether removed on a rotary evaporator. The resulting brown crude was purified by column chromatography using ethyl acetate/hexane (30%).

2-Allyl-1*H*-pyrrolo[2,3-*b*]pyridine (2-39)



3-(Pent-4-en-1-yn-1-yl)pyridin-2-amine (0.01930 g, 0.122 mmol) and KH (0.02928 g, 0.244 mmol). Purification by column chromatography gave 2-ally-7azaindole (**2-39**) (0.01701 g, 87%) as a cream white solid. Melting point: 104 – 107 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.39 (s, 1H), 8.25 (dd, *J* = 4.9, 1.4, 1H), 7.86 (dd, *J* = 7.8, 1.4, 1H), 7.06 (dd, *J* = 7.8, 4.9, 1H), 6.59 – 6.41 (m, 2H), 6.33 (s, 1H), 6.00 (m, 1H), 2.01 (d, *J* = 4.8, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.06, 141.71, 138.61, 136.90, 128.53, 127.48, 122.67, 116.06, 99.01, 18.97. IR (cm^{-1}) 3292 (NH str.), 2988 (CH str.), 1660 (C=N), 1586 (C=C). HRMS (ES^+) Calculated for $C_{10}H_{11}N_2$ $[M + H]^+$: 159.0922, found 159.0929.

2-Allyl-5-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2-40)



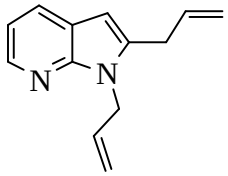
5-Methyl-3-(pent-4-en-1-yn-1-yl)pyridin-2-amine (0.0194 g, 0.113 mmol) and KH (0.02703 g, 0.226 mmol). The crude material was subjected to column chromatography to give 2-ally-5-methyl-7-azaindole (**2-40**) (0.01712 g, 88%) as a cream white solid. Melting point: 158 – 161 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.39 (s, 1H), 8.25 (dd, *J* = 4.9, 1.4, 1H), 7.86 (dd, *J* = 7.8, 1.4, 1H), 7.06 (dd, *J* = 7.8, 4.9, 1H), 6.59 – 6.41 (m, 2H), 6.33 (s, 1H), 6.00 (m, 1H), 2.01 (d, *J* = 4.8, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.06, 141.71, 138.61, 136.90, 128.53, 127.48, 122.67, 116.06, 99.01, 18.99, 18.97. IR (cm^{-1}) 3242 (NH str.), 3006 (CH str.), 1660 (C=N), 1586 (C=C). HRMS (ES^+) Calculated for $C_{11}H_{13}N_2$ $[M + H]^+$: 173.1079, found 173.1082.

Genereal procedure for *N*-allylation of azaindoles 2-39 and 2-40

To an ice-cooled suspension of NaH was added a solution of azaindoles in DMF (5 ml). The reaction mixture was stirred at the same temperature for 30 minutes before allyl bromide (2.53

mmol, 0.3056 g) was introduced dropwise and the reaction mixture was further stirred at the same temperature before being allowed to warm to room temperature. The reaction was left stirring at room temperature for 6 hours after which it was quenched with water and was extracted with ethyl acetate. Excess solvent was removed on a rotary evaporator and the resulting oil was subjected to flash chromatography using 10-30% ethyl acetate/hexane to give the title compounds.

1,2-Diallyl-1*H*-pyrrolo[2,3-*b*]pyridine (2-41)

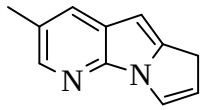


NaH (2.53 mmol, 0.06068 g), **2-39** (1.23 mmol, 0.200 g), allyl bromide (2.53 mmol, 0.3056 g) and gave **2-41** (0.1592 g, 65%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (m, 1H), 7.83 (m, 1H), 7.02 (m, 1H), 6.51 (s, 1H), 6.47 – 6.37 (m, 1H), 6.13 – 5.91 (m, 2H), 5.17 – 5.06 (m, 1H), 5.00 – 4.90 (m, 2H), 4.84 (m, 2H), 1.95 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.14, 142.72, 138.98, 136.49, 133.88, 130.83, 127.88, 127.52, 120.67, 119.97, 118.67, 100.30, 43.56, 18.95. IR (cm^{-1}) 2984 (CH str.), 1674 (C=N), 1594 (C=C). HRMS (ES^+) Calculated for $C_{13}H_{15}N_2$ $[M + H]^+$: 199.1235, found 199.1251.

1,2-Diallyl-5-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2-42)

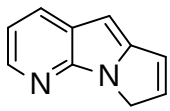
NaH (1.98 mmol, 0.04744 g), **2-40** (0.988 mmol, 0.1700 g), allyl bromide (1.98 mmol, 0.2392 g). No NMR information. Pure **2-42** could not be isolated.

3-Methyl-6*H*-pyrido[3,2-*b*]pyrrolizine (2-45)



A mixture of starting material **2-42** of unknown mass and Grubbs 2 catalyst (0.0532 mmol, 0.04515 g) in dry dichloromethane (15 ml) was heated to reflux for 24 hours under a nitrogen atmosphere. After this time, solvent was removed on a rotary evaporator and the resulting black oil was subjected to flash chromatography using 10-20% ethyl acetate/hexane to give title compound **2-45** in unknown percentage as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.47 (s, 1H), 7.32 (d, *J* = 1.8, 1H), 6.41 (t, *J* = 3.0, 1H), 3.79 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.48, 145.97, 134.68, 134.46, 128.26, 127.80, 113.96, 110.10, 102.64, 27.27, 18.20. IR (cm^{-1}) 2921 (CH str.), 2232 1694 (C=N), 1597 (C=C). HRMS (ES^+) Calculated for $C_{11}H_{11}N_2$ $[M + H]^+$: 171.0922, found 171.0939.

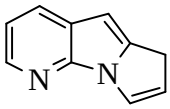
8*H*-Pyrido[3,2-*b*]pyrrolizine (2-48)



The mixture of starting material **2-41** (0.532 mmol, 0.1053 g) and Grubbs 2 catalyst (0.0532 mmol, 0.04515 g) in dry dichloromethane (15 ml) was heated to reflux for 24 hours under a nitrogen atmosphere. After this time, solvent was removed on a rotary evaporator and the resulting black oil was subjected to flash chromatography using 10-70% ethyl acetate/hexane to give **2-48** (0.4521 g, 55%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 4.6, 1H), 7.87 (d, *J* = 7.8, 1H), 7.01 (dd, *J* = 7.8, 4.8,

1H), 6.75 (d, *J* = 6.0, 1H), 6.63 (d, *J* = 5.9, 1H), 6.24 (s, 1H), 4.73 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.23, 141.59, 134.29, 132.53, 129.27, 125.59, 123.34, 115.45, 89.62, 49.56.

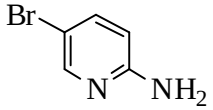
6*H*-Pyrido[3,2-*b*]pyrrolizine (2-50)



A mixture of starting material **2-41** (0.532 mmol, 0.1053 g) and Grubbs 2 catalyst (0.0532 mmol, 0.04515 g) in dry dichloromethane (15 ml) was heated to reflux for 24 hours under a nitrogen atmosphere. After this time, solvent was removed on a rotary evaporator and the resulting black oil was subjected to flash chromatography using 10-70% ethyl acetate/hexane to give **2-50** (0.3551 g, 43%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 4.9, 1H), 7.65 (d, *J* = 7.0, 1H), 7.36 (d, *J* = 1.8, 1H), 7.00 (dd, *J* = 7.2, 5.3, 1H), 6.43 (t, *J* = 2.9, 1H), 6.15 (d, *J* = 1.4, 1H), 3.84 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.31, 146.50, 134.43, 133.52, 128.53, 118.41, 114.39, 110.25, 102.88, 27.39.

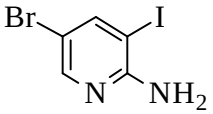
8.2 Experimental to Chapter 3

5-Bromopyridin-2-amine (3-29)



2-Aminopyridine (2.600 g, 0.0276 mol) was dissolved in dry acetonitrile (100 ml), treated with *N*-bromosuccinimide (5.219 g, 0.0293 mol) and stirred for 2 h at room temperature. The solvent was removed and the resulting cream white solid purified by flash chromatography to give 2-amino-5-bromopyridine (**3-29**)[49] as a white solid (4.692 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.48 (dd, *J* = 8.7, 2.4, 1H), 6.41 (d, *J* = 8.7, 1H), 4.44 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.36, 148.88, 140.49, 110.42, 108.56.

5-Bromo-3-iodopyridin-2-amine (3-30)



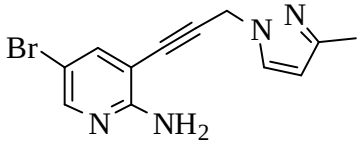
A mixture of 2-amino-5-bromopyridine (**3-29**) (45.00 g, 0.260 mol), iodic acid (11.86 g, 0.0676 mol), iodine (26.40 g, 0.104 mol), sulfuric acid (4.50 ml), acetic acid (150 ml) and water (30 ml) was heated to 80 °C for 8 h. After this time, the reaction mixture was concentrated under vacuum and basified with 12 M sodium hydroxide solution. The basic solution was extracted with dichloromethane, washed with a saturated solution of sodium thiosulfate and then brine, dried over magnesium sulphate and the excess solvent was removed. The resulting cream white solid was purified by flash chromatography to give 2-amino-5-bromo-3-iodopyridine (**3-30**)[52] as a white solid (70.106 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.95 (s, 1H), 5.03 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.75, 148.72, 148.57, 107.58, 77.93.

General Procedure for Sonogashira coupling reactions:

To a flame-dried round-bottom flask under nitrogen or argon atmosphere containing 2-amino-5-bromo-3-iodopyridine (**3-30**) was added CuI (2 mole%) and $Pd(PPh_3)_4$ (2 mole%) in one portion followed by the addition of the degassed alkyne solution in either THF or DMF. Triethylamine

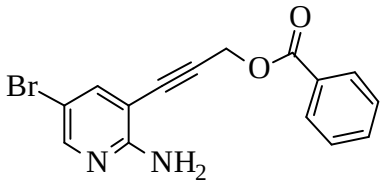
was then added and the reaction mixture was stirred at room temperature, until no starting material was present as monitored by thin layer chromatography (TLC). After this time, the reaction was quenched with a saturated aqueous ammonium chloride solution and was extracted with either dichloromethane or ethyl acetate. The combined organic extracts were dried over magnesium sulphate, was filtered through either silica or celite and the excess solvent was removed on a rotarty evaporator, followed by purification using flash chromatography (30% EthOAc/hexane).

5-Bromo-3-(3-(3-methyl-1*H*-pyrazol-1-yl)prop-1-yn-1-yl)pyridin-2-amine (3-31a)



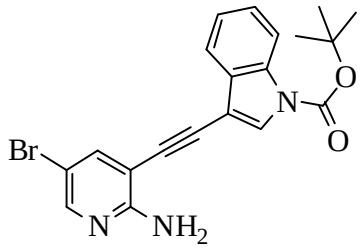
A cream white solid (2.132 g, 89%). Melting point: 113 – 116 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.4, 2H), 8.01 (d, *J* = 2.4, 1H), 7.57 (d, *J* = 2.4, 2H), 7.54 (d, *J* = 2.4, 1H), 7.44 (d, *J* = 2.2, 2H), 7.41 (d, *J* = 1.5, 1H), 6.07 (d, *J* = 2.2, 2H), 6.05 (s, 1H), 5.24 (s, 4H), 5.09 (s, 4H), 5.08 (s, 2H), 2.36 (s, 4H), 2.27 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.28, 149.79, 149.37, 149.27, 142.09, 141.95, 139.42, 138.44, 132.44, 129.91, 106.88, 106.81, 106.49, 106.32, 103.89, 103.84, 90.34, 90.26, 80.53, 79.98, 42.25, 39.98, 13.86, 11.39. IR (cm^{-1}) 3303 (NH str.), 2991 (CH str.), 2319 (alkyne), 1640 (C=N), 1572 (C=C). HRMS (ES^+) Calculated for $C_{12}H_{12}N_4Br$ $[M + H]^+$: 291.0245, found 291.0261.

3-(2-Amino-5-bromopyridin-3-yl)prop-2-yn-1-yl benzoate (3-31b)



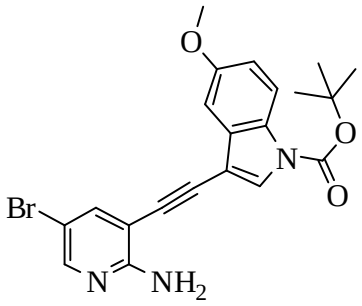
A cream white solid (2.169 g, 91%). Melting point: 126 – 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 – 8.02 (m, 3H), 7.63 – 7.53 (m, 3H), 7.45 (t, *J* = 7.6, 2H), 5.23 (s, 2H), 5.14 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.30, 158.39, 149.54, 142.34, 133.77, 130.12, 129.63, 128.80, 106.91, 103.77, 90.95, 81.23, 53.41. IR (cm^{-1}) 3249 (NH str.), 2989 (CH str.), 2312 (alkyne), 1629 (C=N), 1548 (C=C), 1173 (C-O). HRMS (ES^+) Calculated for $C_{15}H_{12}N_2O_2Br$ $[M + H]^+$: 331.0082, found 331.0080.

***tert*-Butyl 3-((2-amino-5-bromopyridin-3-yl)ethynyl)-1*H*-indole-1-carboxylate (3-31c)**



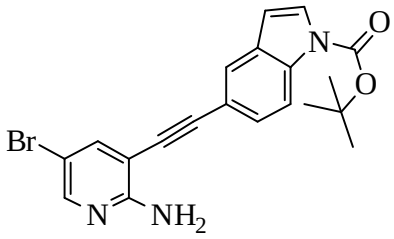
A cream white solid (2.541 g, 95%). Melting point: 169 – 172 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0, 1H), 8.08 (d, *J* = 2.3, 1H), 7.86 (s, 1H), 7.73 (d, *J* = 2.3, 1H), 7.70 – 7.63 (m, 1H), 7.36 (m, 2H), 5.20 (s, 2H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.63, 149.24, 148.62, 141.85, 135.01, 130.38, 129.65, 125.80, 123.80, 120.13, 115.78, 107.42, 105.53, 102.71, 89.11, 86.85, 85.00, 28.47. IR (cm^{-1}) 3290 (NH str.), 2984 (CH str.), 2359 (alkyne), 1630 (C=N), 1554 (C=C), 1148 (C-O). HRMS (ES^+) Calculated for $C_{20}H_{19}N_3O_2Br$ $[M + H]^+$: 412.0661, found 412.0643.

tert-Butyl 3-((2-amino-5-bromopyridin-3-yl)ethynyl)-5-methoxy-1*H*-indole-1-carboxylate (3-31d)



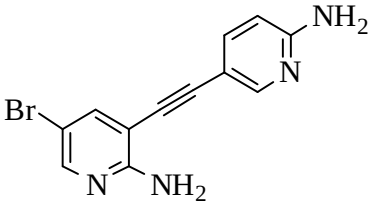
A cream white solid (1.469 g, 80%). Melting point: Melting point: 170 – 173 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 2.3, 1H), 8.03 (d, *J* = 9.0, 1H), 7.82 (s, 1H), 7.72 (d, *J* = 2.4, 1H), 7.09 (d, *J* = 2.5, 1H), 6.99 (dd, *J* = 9.0, 2.5, 1H), 5.21 (s, 2H), 3.88 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.68, 156.90, 149.18, 148.62, 141.85, 131.29, 130.16, 129.63, 116.56, 114.70, 107.39, 105.53, 102.51, 102.41, 89.13, 86.84, 84.84, 56.09, 28.46. IR (cm^{-1}) 3288 (NH str.), 2976 (CH str.), 2101 (alkyne), 1626 (C=N), 1582 (C=C), 1147 (C-O). HRMS (ES^{+}) Calculated for $C_{21}H_{21}N_3O_3Br$ $[M + H]^+$: 442.0766, found 442.0781.

tert-Butyl 5-((2-amino-5-bromopyridin-3-yl)ethynyl)-1*H*-indole-1-carboxylate (3-31e)



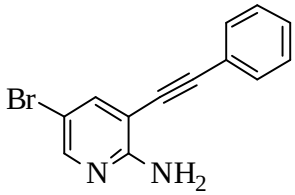
A cream white solid (2.098 g, 88%). Melting point: 162 – 165 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.6, 1H), 8.04 (d, *J* = 2.4, 1H), 7.71 (d, *J* = 1.0, 1H), 7.67 (d, *J* = 2.4, 1H), 7.62 (d, *J* = 3.7, 1H), 7.44 (dd, *J* = 8.6, 1.6, 1H), 6.54 (d, *J* = 3.7, 1H), 5.25 (s, 2H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.76, 149.62, 148.35, 141.65, 135.41, 130.81, 127.83, 127.34, 124.75, 116.49, 115.62, 107.28, 107.19, 105.61, 97.73, 84.45, 82.19, 28.42. IR (cm^{-1}) 3279 (NH str.), 2980 (CH str.), 2210 (alkyne), 1624 (C=N), 1555 (C=C), 1155 (C-O). HRMS (ES^{+}) Calculated for $C_{20}H_{19}N_3O_2Br$ $[M + H]^+$: 412.0661, found 412.0657.

3-((6-Aminopyridin-3-yl)ethynyl)-5-bromopyridin-2-amine (3-31f)



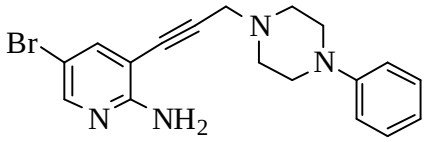
A yellow solid (2.206 g, 96%). Melting point: 209 – 211 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.21 (d, *J* = 2.1, 1H), 7.97 (t, *J* = 4.2, 1H), 7.68 (d, *J* = 2.4, 1H), 7.58 (dd, *J* = 8.6, 2.3, 1H), 6.46 – 6.41 (m, 5H). ^{13}C NMR (126 MHz, DMSO) δ 159.13, 157.80, 151.44, 147.44, 140.13, 139.38, 107.28, 105.78, 104.22, 104.00, 94.60, 83.47. IR (cm^{-1}) 3282 (NH str.), 3001 (CH str.), 2195 (alkyne), 1621 (C=N), 1598 (C=C). HRMS (ES^{+}) Calculated for $C_{12}H_{10}N_4Br$ $[M + H]^+$: 289.0089, found 289.0110.

5-Bromo-3-(phenylethynyl)pyridin-2-amine (3-31g)



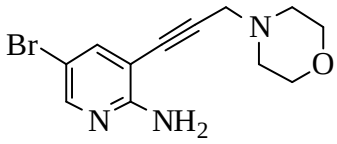
A cream white solid[75] (2.126 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.4, 1H), 7.68 (d, *J* = 2.4, 1H), 7.57 – 7.45 (m, 2H), 7.42 – 7.31 (m, 3H), 5.22 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.76, 148.75, 141.89, 131.86, 129.29, 128.82, 122.46, 107.26, 105.22, 96.85, 83.47. IR (cm^{-1}) 3298 (NH str.), 3001 (CH str.), 2169 (alkyne), 1631 (C=N), 1581 (C=C).

5-Bromo-3-(3-(4-phenylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-2-amine (3-31h)



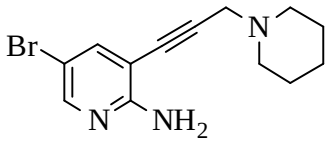
A brown Solid (2.155 g, 91%). Melting point: 94 -95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 2.4, 1H), 7.61 (d, *J* = 2.4, 1H), 7.32 – 7.21 (m, 2H), 6.94 (dd, *J* = 8.7, 0.9, 2H), 6.87 (t, *J* = 7.3, 1H), 5.14 (s, 2H), 3.63 (s, 2H), 3.31 – 3.19 (m, 4H), 2.84 – 2.72 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.94, 151.36, 148.72, 142.22, 129.42, 120.21, 116.46, 107.09, 104.85, 92.11, 80.04, 52.37, 49.37, 48.10. IR (cm^{-1}) 3298 (NH str.), 2931 (CH str.), 2298 (alkyne), 1629 (C=N), 1553 (C=C). HRMS (ES^+) Calculated for $C_{18}H_{20}N_4Br$ $[M + H]^+$: 371.0871, found 371.0873.

5-Bromo-3-(3-morpholinoprop-1-yn-1-yl)pyridin-2-amine (3-31i)



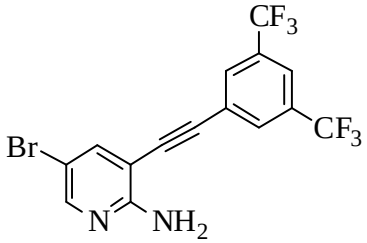
A brown solid (2.119 g, 86%). Melting point: 115 – 118 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.4, 1H), 7.57 (d, *J* = 2.4, 1H), 5.14 (s, 2H), 3.80 – 3.66 (m, 4H), 3.53 (s, 2H), 2.66 – 2.50 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.94, 148.74, 142.22, 107.06, 104.78, 91.93, 80.05, 67.05, 52.68, 48.38. IR (cm^{-1}) 3310 (NH str.), 2959 (CH str.), 2291 (alkyne), 1630 (C=N), 1572 (C=C), 1132 (C-O). HRMS (ES^+) Calculated for $C_{12}H_{15}N_3BrO$ $[M + H]^+$: 296.0398, found 296.0420.

5-Bromo-3-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridin-2-amine (3-31j)



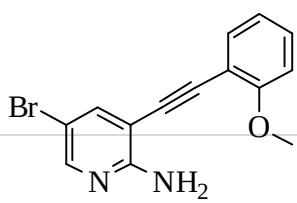
A brown solid (2.110 g, 83%). Melting point: 79 – 81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 2.4, 1H), 7.57 (d, *J* = 2.4, 1H), 5.15 (s, 2H), 3.50 (s, 2H), 2.52 (m, 4H), 1.61 (dt, *J* = 11.0, 5.6, 4H), 1.42 (d, *J* = 5.1, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.99, 148.50, 142.11, 107.04, 105.15, 92.92, 79.53, 53.75, 48.81, 26.16, 24.09. IR (cm^{-1}) 3262 (NH str.), 2988 (CH str.), 2259 (alkyne), 1639 (C=N), 1558 (C=C). HRMS (ES^+) Calculated for $C_{13}H_{17}N_3Br$ $[M + H]^+$: 294.0606, found 294.0613.

3-((3,5-*bis*(Trifluoromethyl)phenyl)ethynyl)-5-bromopyridin-2-amine (3-31k)



A white solid (1.436 g, 70%). Melting point: 194 – 196 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2.4, 1H), 7.94 (s, 2H), 7.86 (s, 1H), 7.74 (d, *J* = 2.4, 1H), 5.10 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.71, 150.16, 142.56, 132.76, 132.49, 131.74, 131.72, 124.92, 124.25, 122.64, 122.08, 107.59, 103.59, 93.49, 86.93. IR (cm^{-1}) 3309 (NH str.), 2995 (CH str.), 2319 (alkyne), 1629 (C=N), 1571 (C=C). HRMS (ES^+) Calculated for $C_{15}H_8N_2BrF_6$ $[M + H]^+$: 408.9775, found 408.9778.

5-Bromo-3-((2-methoxyphenyl)ethynyl)pyridin-2-amine (3-31l)



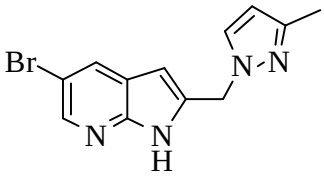
A cream white solid (2.013 g, 73%). Melting point: 126 – 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.3, 1H), 7.67 (d, *J* = 2.3, 1H),

7.46 (dd, *J* = 7.5, 1.5, 1H), 7.40 – 7.29 (m, 1H), 7.00 – 6.91 (m, 2H), 5.51 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.00, 157.82, 148.21, 140.39, 132.47, 130.34, 120.70, 111.56, 110.55, 106.69, 105.26, 93.51, 88.04, 55.81. IR (cm^{-1}) 3310 (NH str.), 3002 (CH str.), 2358 (alkyne), 1627 (C=N), 1571 (C=C), 1181 (C-O). HRMS (ES^+) Calculated for $C_{14}H_{12}N_2BrO$ $[M + H]^+$: 303.0133, found 303.0147.

General method for the formation of 7-azaindoles:

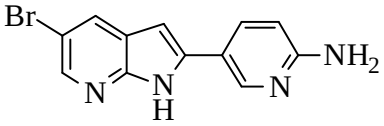
To a solution of starting material **3-31** in a mixture of DMF and THF (1:6) was added potassium *tert*-butoxide portion-wise. The resulting mixture was heated at 80 °C for 8 h under nitrogen or argon gas atmosphere. After this time, THF was removed and water was added. The precipitate was then collected, washed with water and dried over potassium hydroxide. After drying, the solid was washed with hexane to give the resulting products as cream white to white solids which were dried in the presence of potassium hydroxide.

5-Bromo-2-((3-methyl-1*H*-pyrazol-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-44a)



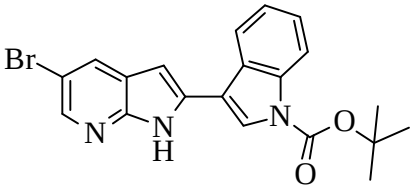
A white solid (2.013 g, 90%). Melting point: 200 – 2003 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.97 (s, 1H), 10.58 (s, 1H), 8.35 (d, *J* = 13.1, 2H), 7.97 (dd, *J* = 12.3, 1.7, 2H), 7.46 (s, 1H), 7.31 (d, *J* = 1.9, 1H), 6.37 (s, 1H), 6.30 (s, 1H), 6.05 (s, 2H), 5.41 (s, 2H), 5.40 (s, 2H), 2.31 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.97, 147.74, 147.68, 144.09, 144.07, 139.67, 138.90, 136.25, 136.09, 131.17, 131.00, 130.46, 122.50, 122.42, 112.20, 112.14, 106.57, 106.45, 99.49, 99.03, 49.39, 46.88, 13.93, 11.40. IR (cm^{-1}) 3214 (NH str.), 2989 (CH str.), 1645 (C=N), 1576 (C=C). HRMS (ES^+) Calculated for $C_{12}H_{12}N_4Br$ $[M + H]^+$: 291.0245, found 291.0265.

5-(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)pyridin-2-amine (3-44b)



A yellow solid (2.511 g, 93%). Melting point: 275 – 278 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 8.91 (d, *J* = 2.1, 1H), 8.61 – 8.43 (m, 1H), 8.05 (d, *J* = 1.8, 1H), 7.90 (dd, *J* = 8.7, 2.3, 1H), 6.95 (d, *J* = 8.7, 1H), 6.67 (s, 1H), 6.31 (s, 2H). IR (cm^{-1}) 3451 (NH str.), 2979 (CH str.), 1650 (C=N), 1574 (C=C). HRMS (ES^+) Calculated for $C_{12}H_{10}N_4Br$ $[M + H]^+$: 289.0089, found 289.0103.

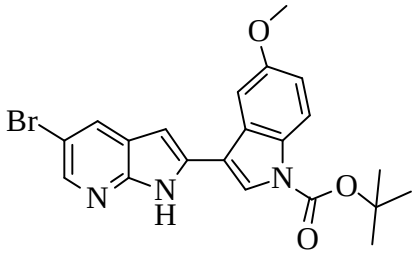
***tert*-Butyl 3-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-indole-1-carboxylate (3-44d)**



A cream white solid (1.0132 g, 35%). Melting point: 336 -338 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.34 (s, 1H), 8.29 (s, 1H), 8.25 (s, 1H), 8.05 (s, 2H), 7.97 (d, *J* = 7.8, 1H), 7.45 (t, *J* = 7.7, 1H), 7.38 (t, *J* = 7.5, 1H), 6.79 (s, 1H), 1.73 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.72, 147.84, 142.97, 136.32, 134.56, 130.72, 128.10, 125.73, 124.15, 123.90, 123.82, 120.40, 116.05, 113.68, 112.18, 98.61, 85.04, 28.54. IR (cm^{-1}) 3211 (NH str.), 2979 (CH str.),

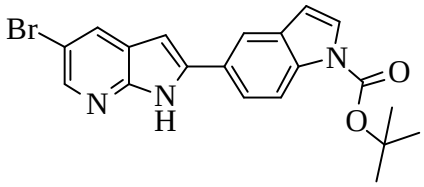
1641 (C=N), 1569 (C=C), 1169 (C-O). HRMS (ES^+) Calculated for $C_{20}H_{19}N_3BrO_2$ $[M + H]^+$: 412.0661, found 412.0643.

tert-Butyl 3-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-5-methoxy-1*H*-indole-1-carboxylate (3-44e)



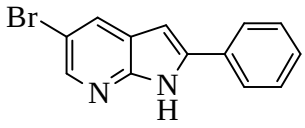
A cream white solid (0.7119 g, 25%). Melting point: 200 – 203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.17 (s, 1H), 8.26 (s, 1H), 8.21 (d, *J* = 8.7, 1H), 8.07 (s, 2H), 7.43 (d, *J* = 2.4, 1H), 7.09 (dd, *J* = 9.1, 2.4, 1H), 6.76 (s, 1H), 3.91 (s, 3H), 1.72 (d, *J* = 8.9, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.53, 149.31, 147.64, 142.39, 134.51, 130.69, 130.36, 128.60, 124.16, 123.95, 116.42, 113.89, 113.20, 111.72, 102.95, 97.90, 84.50, 55.83, 28.18. IR (cm^{-1}) 3299 (NH str.), 2977 (CH str.), 1624 (C=N), 1580 (C=C), 1153 (C-O). HRMS (ES^+) Calculated for $C_{21}H_{21}N_3BrO_3$ $[M + H]^+$: 442.0766, found 442.0757.

tert-Butyl 5-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-indole-1-carboxylate (3-44f)



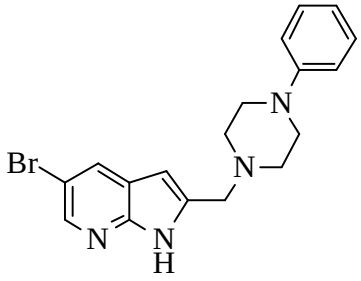
A cream white solid (0.5132 g, 5%). Melting point: 294 – 296 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.30 (s, 1H), 8.32 (s, 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.98 (s, 1H), 7.74 (d, *J* = 7.6, 1H), 7.69 (s, 1H), 6.73 (s, 1H), 6.69 (s, 1H), 1.72 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.89, 148.31, 142.80, 141.81, 131.58, 130.71, 127.59, 126.51, 124.44, 122.60, 118.52, 116.26, 112.27, 107.64, 96.88, 96.85, 84.55, 28.57. IR (cm^{-1}) 3239 (NH str.), 2961 (CH str.), 1629 (C=N), 1570 (C=C), 1179 (C-O). HRMS (ES^+) Calculated for $C_{20}H_{19}N_3BrO_2$ $[M + H]^+$: 412.0661, found 412.0652.

5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (3-44g)



A cream white solid[75] (2.315 g, 75%). ^{1}H NMR (500 MHz, DMSO) δ 12.38 (s, 1H), 8.26 (d, *J* = 1.6, 1H), 8.16 (s, 1H), 7.94 (d, *J* = 7.7, 2H), 7.48 (t, *J* = 7.6, 2H), 7.38 (t, *J* = 7.3, 1H), 6.91 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 148.00, 142.65, 140.06, 131.01, 129.64, 128.97, 128.47, 125.52, 122.78, 111.15, 96.72. IR (cm^{-1}) 3236 (NH str.), 3006 (CH str.), 2259 (alkyne), 1642 (C=N), 1573 (C=C).

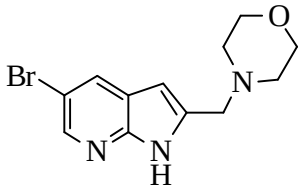
5-Bromo-2-((4-phenylpiperazin-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-44h)



A cream white solid (1.812g, 72%). Melting point: 239 – 241 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.32 (d, *J* = 2.1, 1H), 7.96 (d, *J* = 2.0, 1H), 7.37 – 7.11 (m, 3H), 7.02 – 6.71 (m, 3H), 6.29 (d, *J* = 1.6, 1H), 3.75 (s, 2H), 3.30 – 3.09 (m, 4H), 2.74 – 2.57 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.51, 147.42, 143.38, 130.47, 129.50, 122.94, 120.26, 116.53, 112.08, 99.52, 56.17, 53.67, 49.56. IR (cm^{-1}) 3201 (NH str.), 2975 (CH str.),

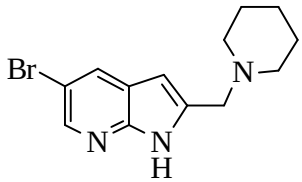
1635 (C=N), 1575 (C=C). HRMS (ES^+) Calculated for $C_{18}H_{20}N_4Br$ $[M + H]^+$: 371.0871, found 371.0885.

4-((5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methyl)morpholine (3-44i)



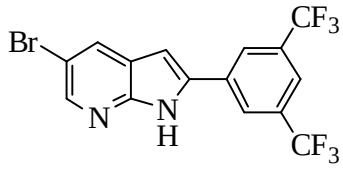
A cream white solid (2.125 g, 52%). Melting point: 189 – 192 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 11.21 (s, 1H), 8.37 (d, *J* = 2.1, 1H), 7.97 (d, *J* = 2.0, 1H), 6.28 (s, 1H), 3.78 – 3.70 (m, 6H), 2.59 – 2.44 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.70, 142.96, 138.67, 130.56, 123.04, 111.75, 99.65, 67.19, 56.72, 54.07. IR (cm^{-1}) 3223 (NH str.), 2969 (CH str.), 1640 (C=N), 1573 (C=C), 1140 (C-O). HRMS (ES^+) Calculated for $C_{12}H_{15}N_3BrO$ $[M + H]^+$: 296.0398, found 296.0401.

5-Bromo-2-(piperidin-1-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-44j)



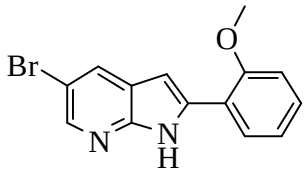
A cream white solid (0.8132g, 55%). Melting point: 194 – 195 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.35 (d, *J* = 2.1, 1H), 7.94 (d, *J* = 2.0, 1H), 6.23 (s, 1H), 3.65 (s, 2H), 2.43 – 2.38 (m, 4H), 1.66 – 1.53 (m, 4H), 1.46 (d, *J* = 4.9, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.50, 142.89, 139.93, 130.25, 123.12, 111.74, 98.93, 57.02, 55.11, 26.28, 24.55. IR (cm^{-1}) 3217 (NH str.), 2989 (CH str.), 1631 (C=N), 1572 (C=C). HRMS (ES^+) Calculated for $C_{13}H_{13}N_3Br$ $[M + H]^+$: 294.0606, found 294.0621.

2-(3,5-*bis*(Trifluoromethyl)phenyl)-5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (3-44k)



A white solid (1.359 g, 70%). Melting point: 251 – 253 °C. ^1H NMR (500 MHz, Acetone) δ 11.69 (s, 1H), 8.60 (s, 2H), 8.33 (d, *J* = 2.2, 1H), 8.21 (d, *J* = 2.2, 1H), 8.03 (s, 1H), 7.30 (s, 1H), 6.43 (s, 1H). ^{13}C NMR (126 MHz, Acetone) δ 149.39, 145.63, 137.75, 134.97, 132.78, 131.55, 126.75, 126.72, 125.47, 123.56, 123.30, 122.19, 112.87, 100.82. IR (cm^{-1}) 3293 (NH str.), 2952 (CH str.), 1641 (C=N), 1576 (C=C). HRMS (ES^+) Calculated for $C_{15}H_8N_2BrF_6$ $[M + H]^+$: 408.9775, found 408.9764.

5-Bromo-2-(2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-44l)

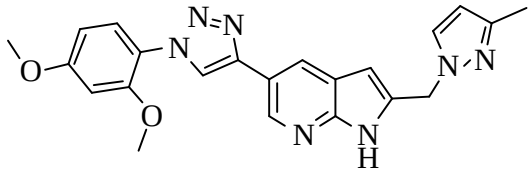


A cream white solid (1.012 g, 75%). Melting point: 196 – 197 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.30 (d, *J* = 1.7, 1H), 8.02 (d, *J* = 1.6, 1H), 7.84 (dd, *J* = 7.8, 1.6, 1H), 7.43 – 7.32 (m, 1H), 7.17 – 7.02 (m, 2H), 6.78 (d, *J* = 2.1, 1H), 4.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.08, 146.82, 143.27, 137.88, 129.87, 129.80, 128.24, 122.21, 121.55, 119.34, 111.96, 97.29, 55.81. IR (cm^{-1}) 3229 (NH str.), 2955 (CH str.), 1624 (C=N), 1576 (C=C), 1160 (C-O). HRMS (ES^+) Calculated for $C_{14}H_{12}N_2BrO$ $[M + H]^+$: 303.0133, found 303.0146.

General Procedure for the synthesis of 1,2,3-triazoles *via* the Click reaction.

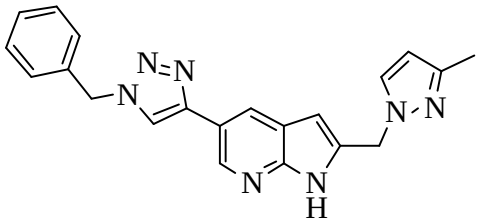
To a flame-dried round-bottom flask under nitrogen or argon containing 5-bromo-2-substituted 7-azaindole **3-44** was added CuI (2 mole%) and $Pd(PPh_3)_4$ (2 mole%) in one portion followed by the addition of the degassed trimethlysilylacetylene solution in THF. Triethylamine was then added and the reaction mixture stirred at reflux for 24 hours. After this time, the reaction was quenched with saturated aqueous ammonium chloride and was extracted with either dichloromethane or ethyl acetate. The combined organic extracts were dried over magnesium sulphate, were filtered using either silica or celite and the excess solvent was removed on a rotary evaporator. The crude material was taken up in THF and was treated with TBAF to remove the silyl protecting group. This was followed by the usual workup, filtration through a pad of silica and the solvent removal on a rotary evaporator gave crude terminal alkyne **3-47** which was employed in the next reaction without further purification. The alkyne was treated with the appropriate azide in THF at room temperature for 48 hours in the presence of copper sulphate (30%), sodium ascorbate (80%) and water (5 ml). Following the usual work up with dichloromethane, the solvent was removed on a rotary evaporator and the resulting crude material was purified by flash chromatography using 5% MeOH/DCM as an eluting solvent to give the corresponding triazole derivative **3-48**.

5-(1-(2,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-methyl-1*H*-pyrazol-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-48a)



Starting material (0.1153 g, 0.493 mmol), Azide (2eq, 0.986 mmol, 0.1765 g), $CuSO_4.2H_2O$ (0.3eq, 0.148 mmol, 0.03696 g), Naascorbate (0.8eq, 0.394 mmol, 0.07805 g). A cream white solid (**3-48a**) was obtained (0.1640 g, 80%). Melting point: 253 – 256 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.48 (s, 1H), 8.25 (s, 1H), 7.70 (d, *J* = 9.2, 1H), 7.38 (s, 1H), 6.64 (s, 2H), 6.56 – 6.45 (m, 1H), 6.07 (s, 1H), 5.41 (s, 2H), 3.89 (2 x s, 6H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.28, 152.66, 149.88, 143.22, 135.09, 130.35, 129.26, 126.56, 121.37, 120.03, 110.73, 105.97, 104.80, 99.65, 67.99, 56.04, 55.73, 49.13, 25.62. IR (cm^{-1}) 3297 (NH str.), 3006 (CH str.), 1615 (C=N), 1511 (C=C), 1161 (C-O). HRMS (ES^+) Calculated for $C_{22}H_{22}N_7O_2$ $[M + H]^+$: 416.1851, found 416.1832.

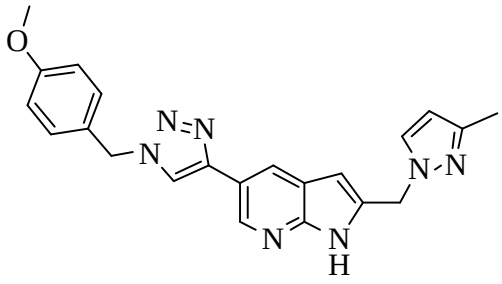
5-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-2-((3-methyl-1*H*-pyrazol-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-48b)



Starting material (0.1175 g, 0.502 mmol), Azide (2eq, 1.00 mmol, 0.1336 g), $CuSO_4.2H_2O$ (0.3eq, 0.151 mmol, 0.03766 g), NaAscorbate (0.8eq, 0.402 mmol, 0.07954 g). A white solid (**3-48b**) was obtained (0.1396 g, 75%). Melting point: 245 – 246 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.66 (s, 1H), 8.38 (s, 1H), 7.72 (d, *J* = 2.7, 1H), 7.48 – 7.33 (m, 6H), 6.44 – 6.20 (m, 1H), 6.05 (d, *J* = 4.9, 1H), 5.62 (s, 2H), 5.42 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ

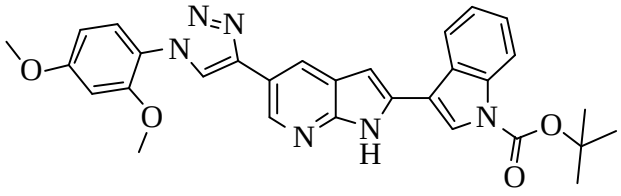
153.04, 149.73, 148.76, 146.80, 141.46, 139.38, 135.14, 134.62, 130.23, 129.19, 128.84, 128.13, 125.93, 118.90, 105.93, 99.75, 54.31, 49.04, 13.60. IR (cm^{-1}) 3348 (NH str.), 2961 (CH str.), 1633 (C=N), 1577 (C=C). HRMS (ES^+) Calculated for $C_{21}H_{20}N_7$ $[M + H]^+$: 370.2008, found 370.1777.

5-(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)-2-((3-methyl-1*H*-pyrazol-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-48c)



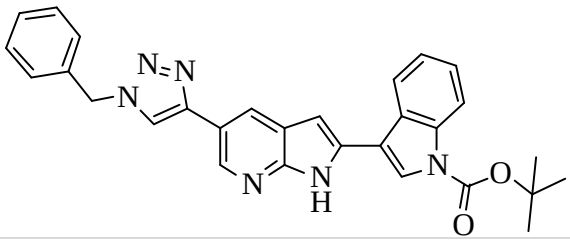
Starting material (0.1302 g, 0.556 mmol), Azide (2eq, 1.11 mmol, 0.1814 g), $CuSO_4.2H_2O$ (0.3eq, 0.167 mmol, 0.04173 g), Naascorbate (0.8eq, 0.445 mmol, 0.08814 g). White solid (**3-48c**) was obtained (0.1740 g, 78%). Melting point: 225 – 227 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.35 (s, 1H), 7.66 (d, *J* = 3.8, 1H), 7.34 (d, *J* = 1.9, 1H), 7.30 (d, *J* = 8.6, 2H), 6.92 (d, *J* = 8.7, 2H), 6.44 (s, 1H), 6.04 (d, *J* = 1.7, 1H), 5.52 (s, 2H), 5.39 (s, 2H), 3.81 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.03, 149.76, 146.76, 141.37, 135.15, 130.26, 129.74, 129.68, 128.74, 126.60, 125.89, 118.72, 114.58, 114.54, 105.95, 99.79, 55.36, 53.88, 49.06, 13.61. IR (cm^{-1}) 3329 (NH str.), 2922 (CH str.), 1621 (C=N), 1567 (C=C), 1182 (C-O). HRMS (ES^+) Calculated for $C_{22}H_{22}N_7O$ $[M + H]^+$: 400.1974, found 400.1870.

***tert*-Butyl 3-(5-(1-(2,4-dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-indole-1-carboxylate (3-48d)**



Starting material (0.1011 g, 0.284 mmol), Azide (2eq, 0.568 mmol, 0.1015 g), $CuSO_4.2H_2O$ (0.3eq, 0.0852 mmol, 0.02130 g), Naascorbate (0.8eq, 0.227 mmol, 0.04499 g). White solid (**3-48d**) was obtained (0.1001 g, 65%). Melting point: 192 – 195 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.12 (s, 1H), 8.64 (s, 1H), 8.30 (s, 3H), 7.68 (d, *J* = 8.2, 1H), 7.45 – 7.35 (m, 1H), 7.00 (s, 1H), 6.65 (d, *J* = 8.2, 2H), 3.90 (2 x s, 6H), 1.61 (d, *J* = 7.0, 10H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.33, 152.93, 135.86, 133.41, 128.04, 126.79, 125.16, 123.48, 123.33, 121.70, 121.68, 120.45, 120.13, 115.56, 113.88, 104.73, 99.62, 99.20, 99.18, 84.49, 56.05, 55.75, 28.05. IR (cm^{-1}) 3385 (NH str.), 2973 (CH str.), 1619 (C=N), 1571 (C=C), 1163 (C-O). HRMS (ES^+) Calculated for $C_{30}H_{29}N_6O_4$ $[M + H]^+$: 537.2250, found 537.2252.

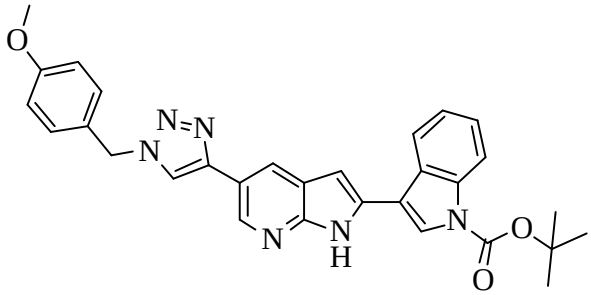
***tert*-Butyl 3-(5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-indole-1-carboxylate (3-48e)**



Starting material (0.1094 g, 0.307 mmol), Azide (2eq, 0.614 mmol, 0.08161 g), $CuSO_4.2H_2O$ (0.3eq, 0.0921 mmol, 0.02303 g), Naascorbate (0.8eq, 0.246 mmol, 0.04863 g). A cream white solid (**3-48e**) was obtained (0.09012 g, 60%).

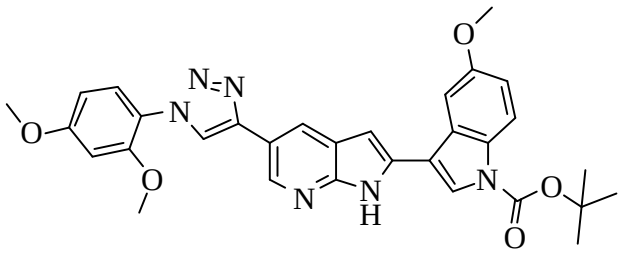
Melting point: 194 – 196 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.25 (s, 1H), 8.72 (s, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 8.38 (d, *J* = 1.5, 1H), 8.19 (dd, *J* = 17.0, 8.0, 2H), 7.48 – 7.31 (m, 7H), 7.12 (d, *J* = 1.6, 1H), 5.68 (s, 2H), 1.69 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 148.84, 148.79, 145.65, 140.63, 136.03, 135.27, 132.81, 128.81, 128.17, 127.93, 127.18, 125.06, 123.99, 123.87, 123.55, 120.91, 120.83, 120.57, 119.24, 115.06, 112.60, 98.39, 84.30, 53.04, 27.69. IR (cm^{-1}) 3226 (NH str.), 2961 (CH str.), 1611 (C=N), 1566 (C=C), 1150 (C-O). HRMS (ES^{+}) Calculated for $C_{29}H_{27}N_6O_2$ [M + H]$^{+}$: 491.2195, found 491.2174.

tert-Butyl 3-(5-(1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-indole-1-carboxylate (3-48f)



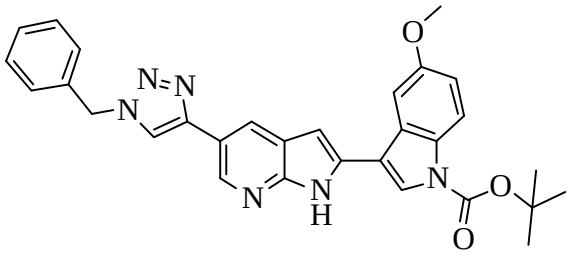
Starting material (0.1049 g, 0.294 mmol), Azide (2eq, 0.588 mmol, 0.09590 g), $CuSO_4.2H_2O$ (0.3eq, 0.0882 mmol, 0.02205 g), Naascorbate (0.8eq, 0.235 mmol, 0.04657 g). A cream white solid (**3-48f**) was obtained (0.1022 g, 67%). Melting point: 200 – 203 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.72 (s, 1H), 8.51 (s, 1H), 8.23 (s, 1H), 8.04 (d, *J* = 8.10, 2H), 7.69 (s, 1H), 7.40 – 7.33 (m, 2H), 7.31 (d, *J* = 8.5, 2H), 6.95 (d, *J* = 8.5, 2H), 5.54 (s, 2H), 3.83 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.00, 149.52, 133.35, 129.64, 127.95, 126.71, 125.15, 124.89, 123.45, 123.31, 122.50, 120.38, 120.12, 119.93, 118.93, 118.91, 118.70, 115.57, 114.58, 114.55, 84.41, 55.37, 53.83, 28.16. IR (cm^{-1}) 3298 (NH str.), 2989 (CH str.), 1618 (C=N), 1551 (C=C), 1152 (C-O). HRMS (ES^{+}) Calculated for $C_{30}H_{29}N_6O_3$ [M + H]$^{+}$: 521.2301, found 521.2295.

tert-Butyl 3-(5-(1-(2,4-dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-5-methoxy-1*H*-indole-1-carboxylate (3-48g)



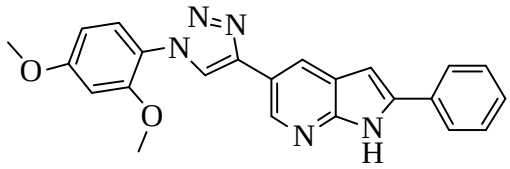
Starting material (0.07480 g, 0.193 mmol), Azide (1.5eq, 0.290 mmol, 0.0.05191 g), $CuSO_4.2H_2O$ (0.3eq, 0.0.0579 mmol, 0.01448 g), Naascorbate (0.8eq, 0.154 mmol, 0.03057 g). White solid (**3-48g**) was obtained (0.06622 g, 61%). Melting point: 183 – 184 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.54 (s, 1H), 8.65 – 8.50 (m, 2H), 8.19 – 7.90 (m, 3H), 7.78 – 7.44 (m, 3H), 6.95 – 6.80 (m, 2H), 6.65 (s, 1H), 3.87 (3 x s, 9H), 1.59 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.37, 160.00, 156.43, 153.06, 149.26, 149.24, 145.69, 140.51, 135.34, 135.31, 133.64, 132.15, 132.07, 130.52, 129.59, 128.55, 126.90, 126.81, 125.68, 124.06, 122.35, 122.32, 121.80, 120.20, 116.27, 114.55, 113.87, 104.73, 103.19, 99.62, 98.87, 84.23, 56.05, 55.80, 55.76, 28.07. IR (cm^{-1}) 3237 (NH str.), 2956 (CH str.), 1645 (C=N), 1516 (C=C), 1152 (C-O). HRMS (ES^{+}) Calculated for $C_{31}H_{31}N_6O_5$ [M + H]$^{+}$: 567.2356, found 567.2350.

tert-Butyl 3-(5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-5-methoxy-1*H*-indole-1-carboxylate (3-48h)



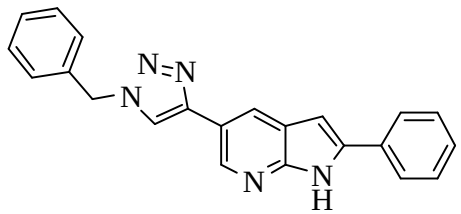
Starting material (0.05430 g, 0.140 mmol), Azide (1.5eq, 0.210 mmol, 0.02793 g), $CuSO_4.2H_2O$ (0.3eq, 0.0420 mmol, 0.01050 g), Naascorbate (0.8eq, 0.112 mmol, 0.02218 g). A cream white solid (**3-48h**) was obtained (0.04601 g, 63%). Melting point: 196 – 197 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.21 (s, 1H), 8.55 (s, 2H), 8.06 (s, 2H), 7.78 (s, 1H), 7.49 – 7.38 (m, 4H), 7.35 (d, *J* = 6.9, 2H), 6.93 (d, *J* = 8.4, 1H), 6.84 (s, 1H), 5.61 (s, 2H), 3.79 (s, 3H), 1.65 (s, 10H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.35, 149.56, 134.80, 133.63, 130.53, 130.50, 129.19, 128.79, 128.00, 125.54, 125.46, 124.10, 119.26, 116.30, 113.82, 113.69, 107.81, 103.10, 98.89, 84.22, 55.73, 54.24, 28.16. IR (cm^{-1}) 3210 (NH str.), 3005 (CH str.), 1613 (C=N), 1549 (C=C), 1151 (C-O). HRMS (ES^+) Calculated for $C_{30}H_{29}N_6O_3$ $[M + H]^+$: 521.2301, found 521.2297.

5-(1-(2,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (3-48i)



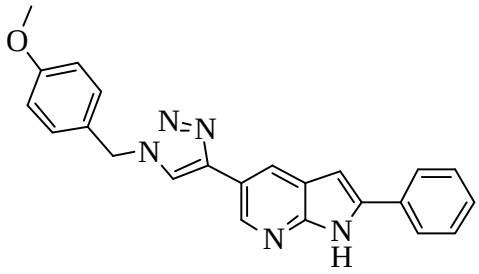
Starting material (0.1016 g, 0.465 mmol), Azide (1.5eq, 0.698 mmol, 0.1138 g), $CuSO_4.2H_2O$ (0.3eq, 0.140 mmol, 0.03488 g), Naascorbate (0.8eq, 0.373 mmol, 0.07381 g). A yellow solid (**3-48i**) was obtained (0.1401 g, 76%). Melting point: 279 – 281 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.30 (s, 1H), 8.81 (s, 1H), 8.46 (s, 1H), 7.98 (d, *J* = 7.7, 2H), 7.58 (d, *J* = 8.7, 1H), 7.50 (t, *J* = 7.7, 2H), 7.39 (d, *J* = 7.4, 1H), 7.03 (s, 1H), 6.88 (d, *J* = 2.5, 1H), 6.74 (d, *J* = 8.7, 1H), 3.88 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 161.24, 153.25, 150.43, 149.46, 145.00, 140.80, 139.19, 134.56, 131.39, 129.47, 129.39, 128.94, 128.18, 126.99, 125.37, 124.25, 122.81, 120.84, 119.21, 108.62, 105.32, 99.55, 97.40, 56.19, 55.73. IR (cm^{-1}) 3219 (NH str.), 2968 (CH str.), 1636 (C=N), 1555 (C=C), 1173 (C-O). HRMS (ES^+) Calculated for $C_{23}H_{20}N_5O_2$ $[M + H]^+$: 398.1611, found 398.1617.

5-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (3-48j)



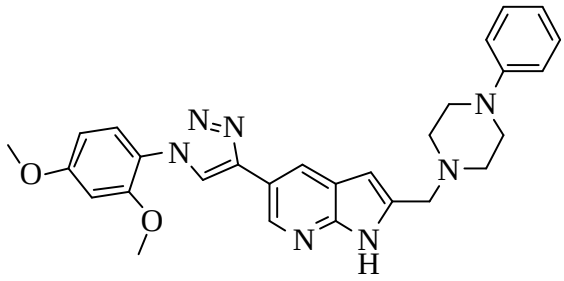
Starting material (0.1016 g, 0.465 mmol), Azide (1.5eq, 0.698 mmol, 0.09283 g), $CuSO_4.2H_2O$ (0.3eq, 0.140 mmol, 0.03488 g), Naascorbate (0.8eq, 0.373 mmol, 0.07381 g). A yellow solid (**3-48j**) was obtained (0.1329 g, 81%). Melting point: 302 – 304 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.26 (s, 1H), 8.72 (d, *J* = 1.9, 1H), 8.69 (s, 1H), 8.37 (s, 1H), 7.97 (d, *J* = 7.7, 2H), 7.49 (t, *J* = 7.7, 3H), 7.39 (m, 6H), 7.00 (d, *J* = 1.9, 1H), 5.68 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 149.40, 145.63, 140.67, 139.15, 136.01, 131.38, 128.93, 128.81, 128.17, 127.94, 125.36, 124.73, 124.17, 120.87, 120.79, 119.41, 97.38, 53.04. IR (cm^{-1}) 3225 (NH str.), 2958 (CH str.), 1645 (C=N), 1581 (C=C). HRMS (ES^+) Calculated for $C_{22}H_{18}N_5$ $[M + H]^+$: 352.1538, found 352.1566.

5-(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (3-48k)



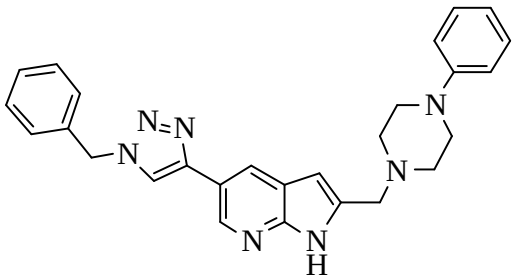
Starting material (0.1016 g, 0.465 mmol), Azide (1.5eq, 0.698 mmol, 0.1138 g), $CuSO_4.2H_2O$ (0.3eq, 0.140 mmol, 0.03488 g), Naascorbate (0.8eq, 0.373 mmol, 0.07381 g). A yellow solid (**3-48k**) obtained (0.1301 g, 73%). Melting point: 286 – 288 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.25 (s, 1H), 8.71 (d, *J* = 1.8, 1H), 8.63 (s, 1H), 8.36 (d, *J* = 1.7, 1H), 7.96 (d, *J* = 7.7, 2H), 7.49 (t, *J* = 7.7, 2H), 7.40 – 7.33 (m, 3H), 6.99 (d, *J* = 1.9, 1H), 6.97 (d, *J* = 8.7, 2H), 5.58 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 159.15, 149.39, 145.57, 140.65, 139.13, 131.38, 129.61, 128.93, 128.15, 127.90, 125.35, 124.14, 120.79, 120.54, 119.45, 114.15, 97.37, 66.99, 55.13. IR (cm^{-1}) 3214 (NH str.), 2959 (CH str.), 1610 (C=N), 1586 (C=C), 1179 (C-O). HRMS (ES^+) Calculated for $C_{23}H_{20}N_5O$ $[M + H]^+$: 382.1644, found 382.1665.

5-(1-(2,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-2-((4-phenylpiperazin-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-48l)



Starting material (0.1736 g, 0.549 mmol), Azide (2eq, 1.10 mmol, 0.2001 g), $CuSO_4.2H_2O$ (0.3eq, 0.165 mmol, 0.04120 g), Naascorbate (0.8eq, 0.439 mmol, 0.08696 g). A cream white solid (**3-48l**) was obtained (0.2298 g, 85%). Melting point: 209 – 212 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.82 (s, 1H), 8.41 (s, 1H), 8.23 (s, 1H), 7.73 – 7.64 (m, 1H), 7.26 – 7.22 (m, 2H), 6.92 (d, *J* = 8.1, 2H), 6.85 (t, *J* = 7.3, 1H), 6.63 (dd, *J* = 6.9, 2.5, 2H), 6.41 (s, 1H), 3.89 (2 x s, 6H), 3.80 (s, 2H), 3.26 – 3.20 (m, 4H), 2.74 – 2.66 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.23, 152.63, 151.20, 148.56, 145.86, 140.79, 137.59, 129.10, 126.53, 125.51, 125.44, 121.26, 120.04, 119.77, 116.11, 104.78, 100.00, 99.96, 99.63, 67.96, 56.01, 55.71, 53.28, 49.20. IR (cm^{-1}) 3311 (NH str.), 2960 (CH str.), 1636 (C=N), 1599 (C=C), 1187 (C-O). HRMS (ES^+) Calculated for $C_{28}H_{30}N_7O_2$ $[M + H]^+$: 496.2488, found 496.2466.

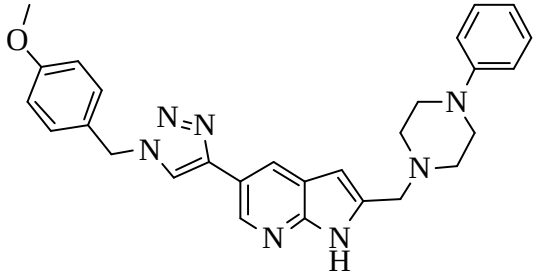
5-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-2-((4-phenylpiperazin-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-48m)



Starting material (0.1543 g, 0.488 mmol), Azide (2eq, 0.977 mmol, 0.1299 g), $CuSO_4.2H_2O$ (0.3eq, 0.146 mmol, 0.03662 g), Naascorbate (0.8eq, 0.391 mmol, 0.07735 g). A cream white solid (**3-48m**) was obtained (0.1902 g, 87%). Melting point: 228 – 230 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.71 (s, 1H), 8.30 (s, 1H), 7.67 (s, 1H), 7.43 – 7.36 (m, 3H), 7.35 – 7.31 (m, 2H), 7.25 (d, *J* = 1.3, 1H), 7.24

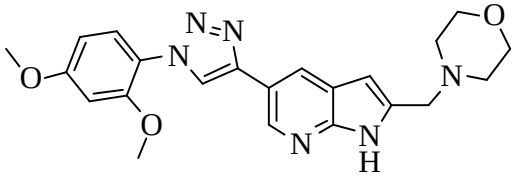
(s, 1H), 6.91 (d, *J* = 7.9, 2H), 6.85 (t, *J* = 7.3, 1H), 6.37 (s, 1H), 5.56 (s, 2H), 3.77 (s, 2H), 3.27 – 3.07 (m, 4H), 2.76 – 2.59 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.19, 148.62, 147.00, 140.64, 137.71, 134.67, 129.17, 129.11, 128.80, 128.11, 125.36, 119.77, 118.88, 116.10, 99.92, 55.91, 54.26, 53.27, 49.16. IR (cm^{-1}) 3321 (NH str.), 2913 (CH str.), 1613 (C=N), 1568 (C=C). HRMS (ES^+) Calculated for $C_{27}H_{28}N_7$ $[M + H]^+$: 450.2634, found 450.2403.

5-(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)-2-((4-phenylpiperazin-1-yl)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-48n)



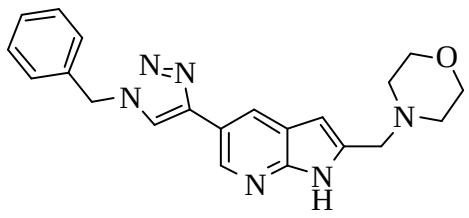
Starting material (0.1560 g, 0.494 mmol), Azide (2eq, 0.987 mmol, 0.1767 g), $CuSO_4.2H_2O$ (0.3eq, 0.146 mmol, 0.03662 g), Naascorbate (0.8eq, 0.391 mmol, 0.07735 g). A cream white solid (**3-48n**) was obtained (0.2090 g, 88%). Melting point: 197 – 200 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.72 (s, 1H), 8.31 (s, 1H), 7.65 (s, 1H), 7.32 – 7.23 (m, 4H), 6.92 (d, *J* = 8.2, 4H), 6.85 (t, *J* = 7.3, 1H), 6.38 (s, 1H), 5.49 (s, 2H), 3.81 (s, 3H), 3.21 (s, 4H), 2.67 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.97, 151.20, 148.52, 146.93, 140.59, 137.71, 129.73, 129.12, 126.63, 125.32, 125.29, 119.78, 118.73, 116.11, 114.53, 99.97, 55.90, 55.36, 53.83, 53.27, 49.17. IR (cm^{-1}) 3402 (NH str.), 3005 (CH str.), 1612 (C=N), 1598 (C=C), 1176 (C-O). HRMS (ES^+) Calculated for $C_{14}H_{12}N_2BrO$ $[M + H]^+$: 303.0133, found 303.0146.

4-((5-(1-(2,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methyl)morpholine (3-48o)



Starting material (0.08700 g, 0.363 mmol), Azide (2eq, 0.725 mmol, 0.1298 g), $CuSO_4.2H_2O$ (0.3eq, 0.109 mmol, 0.03084 g), Naascorbate (0.8eq, 0.329 mmol, 0.05742 g). A cream white solid (**3-48o**) was obtained (0.1135 g, 74%). Melting point: 218 – 220 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.77 (s, 1H), 8.41 (s, 1H), 8.24 (s, 1H), 7.70 (d, *J* = 9.2, 1H), 6.64 (d, *J* = 7.5, 2H), 6.40 (s, 1H), 3.89 (2 x s, 6H), 3.77 (s, 4H), 2.58 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.29, 152.66, 145.81, 126.56, 125.56, 121.27, 120.80, 120.09, 104.86, 99.69, 66.77, 56.06, 55.73, 53.55. IR (cm^{-1}) 3291 (NH str.), 2956 (CH str.), 1639 (C=N), 1573 (C=C), 1160 (C-O). HRMS (ES^+) Calculated for $C_{22}H_{25}N_6O_3$ $[M + H]^+$: 421.1988, found 421.1971.

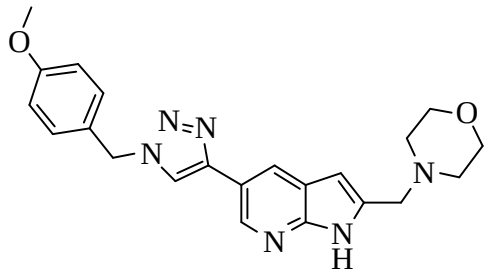
4-((5-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methyl)morpholine (3-48p)



Starting material (0.09910 g, 0.411 mmol), Azide (2eq, 0.822 mmol, 0.1094 g), $CuSO_4.2H_2O$ (0.3eq, 0.123 mmol, 0.02719 g), NaAscorbate (0.8eq, 0.290 mmol, 0.06514 g). A cream white solid (**3-48p**) was obtained (0.1213 g, 79%). Melting point: 227 – 229 °C. ^{1}H NMR

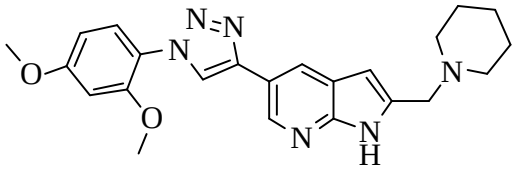
(500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.73 (s, 1H), 8.28 (s, 1H), 7.69 (s, 1H), 7.43 – 7.38 (m, 3H), 7.37 – 7.32 (m, 2H), 6.35 (s, 1H), 5.60 (s, 2H), 3.72 (d, *J* = 5.8, 4H), 2.52 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.76, 147.05, 140.58, 137.48, 134.65, 129.20, 128.84, 128.16, 125.40, 120.93, 119.40, 118.84, 100.03, 66.95, 56.35, 54.30, 53.70. IR (cm^{-1}) 3273 (NH str.), 2969 (CH str.), 1632 (C=N), 1573 (C=C), 1158 (C-O). HRMS (ES^+) Calculated for $C_{21}H_{23}N_6O$ $[M + H]^+$: 375.1933, found 375.1919.

4-((5-(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methyl)morpholine (3-48q)



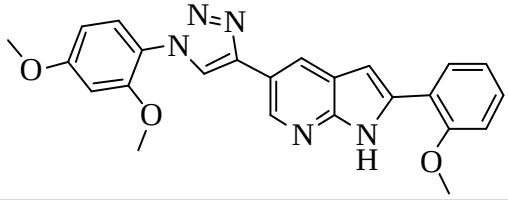
Starting material (0.09170 g, 0.381 mmol), Azide (2eq, 0.761 mmol, 0.1240 g), $CuSO_4.2H_2O$ (0.3eq, 0.114 mmol, 0.02854 g), Naascorbate (0.8eq, 0.304 mmol, 0.06027 g). A cream white solid (**3-48q**) was obtained (0.1201 g, 78%). Melting point: 221 – 223 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.70 (s, 1H), 7.65 (s, 1H), 7.30 (d, *J* = 8.6, 2H), 6.93 (d, *J* = 8.7, 2H), 6.35 (s, 1H), 3.82 (s, 3H), 3.71 (d, *J* = 6.1, 4H), 2.52 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.00, 148.68, 146.92, 140.64, 137.40, 129.76, 126.60, 125.36, 120.89, 119.50, 118.63, 114.55, 100.04, 66.97, 56.32, 55.36, 53.86, 53.70. IR (cm^{-1}) 3229 (NH str.), 2959 (CH str.), 1623 (C=N), 1573 (C=C), 1141 (C-O). HRMS (ES^+) Calculated for $C_{22}H_{25}N_6O_2$ $[M + H]^+$: 405.2039, found 405.2038.

5-(1-(2,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-2-(piperidin-1-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-48r)



Starting material (0.07870 g, 0.240 mmol), Azide (1.5eq, 0.360 mmol, 0.06442 g), $CuSO_4.2H_2O$ (0.3eq, 0.0720 mmol, 0.01800 g), Naascorbate (0.8eq, 0.192 mmol, 0.03802 g). A brown solid (**3-48r**) was obtained (0.08011 g, 80%). Melting point: 86 – 89 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.68 (s, 1H), 8.34 (s, 1H), 8.17 (s, 1H), 7.63 (d, *J* = 9.3, 1H), 6.91 (s, 1H), 6.63 – 6.46 (m, 3H), 6.31 (s, 1H), 3.82 (s, 6H), 3.71 (s, 2H), 2.43 – 2.68 (m, 4H), 2.24 – 2.17 (m, 4H), 1.64 – 1.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.26, 152.65, 151.52, 148.66, 143.40, 141.08, 135.79, 128.25, 126.53, 125.51, 125.41, 121.24, 104.84, 56.03, 55.71, 54.34, 34.22, 29.41, 27.78. IR (cm^{-1}) 3221 (NH str.), 2925 (CH str.), 1613 (C=N), 1518 (C=C), 1160 (C-O). HRMS (ES^+) Calculated for $C_{23}H_{27}N_6O_2$ $[M + H]^+$: 419.2244, found 419.2191.

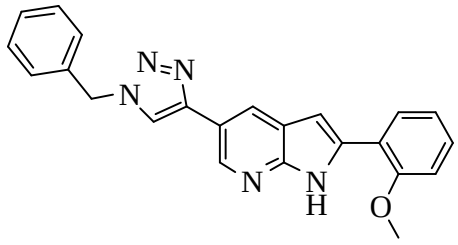
5-(1-(2,4-Dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-2-(2-methoxyphenyl)-1H-pyrrolo[2,3-*b*]pyridine (3-48s)



Starting material (0.1200 g, 0.486 mmol), Azide (2eq, 0.972 mmol, 0.1740 g), $CuSO_4.2H_2O$ (0.3eq, 0.146 mmol, 0.03644 g), Naascorbate (0.8eq, 0.389 mmol, 0.07698 g). A cream white solid (**3-48s**) was obtained

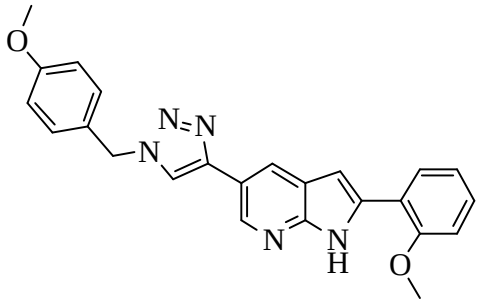
(0.1651 g, 80%). Melting point: 243 – 246 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.79 (s, 1H), 8.47 (s, 1H), 8.26 (s, 1H), 7.88 (d, *J* = 6.6, 1H), 7.71 (d, *J* = 9.2, 1H), 7.34 (t, *J* = 7.2, 1H), 7.08 (dd, *J* = 18.6, 7.9, 2H), 6.90 (s, 1H), 6.67 – 6.59 (m, 2H), 4.03 (s, 3H), 3.90 (2 x s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.28, 156.02, 152.70, 148.39, 145.98, 141.43, 129.50, 128.21, 126.59, 125.23, 121.59, 121.30, 120.15, 119.71, 111.99, 104.85, 101.60, 99.69, 98.11, 56.06, 55.85, 55.73. IR (cm^{-1}) 3421 (NH str.), 2989 (CH str.), 1603 (C=N), 1515 (C=C), 1163 (C-O). HRMS (ES^+) Calculated for $C_{24}H_{22}N_5O_3$ $[M + H]^+$: 428.1723, found 428.1719.

5-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-2-(2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-48t)



Starting material (0.1412 g, 0.572 mmol), Azide (2eq, 1.14 mmol, 0.1521 g), $CuSO_4.2H_2O$ (0.3eq, 0.172 mmol, 0.04278 g), Naascorbate (0.8eq, 0.457 mmol, 0.09055 g). A cream white solid (**3-48t**) was obtained (0.1442 g, 79%). Melting point: 223 – 226 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.46 (s, 1H), 7.86 (d, *J* = 7.2, 1H), 7.72 (s, 1H), 7.44 – 7.28 (m, 7H), 7.12 – 7.00 (m, 3H), 5.60 (s, 2H), 4.00 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.02, 137.28, 134.70, 132.14, 129.54, 129.19, 128.81, 128.23, 128.13, 124.55, 121.50, 119.56, 119.03, 111.91, 98.50, 98.47, 55.80, 54.29. IR (cm^{-1}) 3433 (NH str.), 2919 (CH str.), 1605 (C=N), 1569 (C=C), 1184 (C-O). HRMS (ES^+) Calculated for $C_{23}H_{20}N_5O$ $[M + H]^+$: 382.1668, found 382.1665.

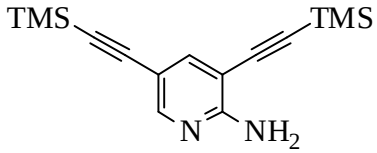
5-(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)-2-(2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3-48u)



Starting material (0.1360 g, 0.551 mmol), Azide (2eq, 1.10 mmol, 0.1795 g), $CuSO_4.2H_2O$ (0.3eq, 0.165 mmol, 0.04130 g), Naascorbate (0.8eq, 0.441 mmol, 0.08722 g). A cream white solid (**3-48u**) was obtained (0.1761 g, 77%). Melting point: 183 – 185 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.68 (s, 1H), 8.37 (s, 1H), 7.85 (d, *J* = 6.8, 1H), 7.67 (s, 1H), 7.36 – 7.32 (m, 1H), 7.30 (d, *J* = 8.6, 2H), 7.10 – 7.02 (m, 2H), 6.95 – 6.91 (m, 2H), 6.88 (s, 1H), 5.50 (s, 2H), 4.00 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.98, 155.99, 148.33, 148.32, 147.02, 137.20, 129.74, 129.51, 128.20, 126.63, 125.02, 121.52, 119.62, 118.71, 114.54, 111.92, 98.17, 55.79, 55.35, 53.84. IR (cm^{-1}) 3449 (NH str.), 2986 (CH str.), 1620 (C=N), 1576 (C=C), 1179 (C-O). HRMS (ES^+) Calculated for $C_{24}H_{22}N_5O_2$ $[M + H]^+$: 412.1774, found 412.1769.

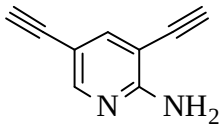
8.3 Experimental to Chapter 4

3,5-*bis*((Trimethylsilyl)ethynyl)pyridin-2-amine (4-29)



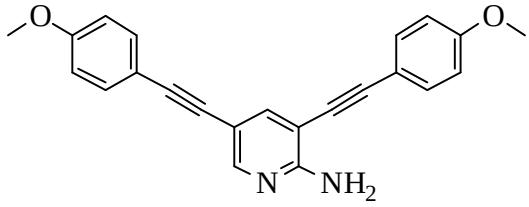
To a mixture of 2-amino-3,5-diiodopyridine (**4-20**) (3.903 g, 11.3 mmol), copper (I) iodide (0.08596 g, 0.451 mmol), trimethylsilylacetylene (2.774 g, 3.96 ml, 0.0283 mol) and triethylamine (5.706 g, 7.86 ml, 0.0565 mol) in tetrahydrofuran was added in one portion $Pd(PPh_3)_4$ (0.5216 g, 0.451 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours after which it was quenched with a saturated aqueous ammonium chloride and was extracted with dichloromethane. The organic layer was dried over magnesium sulphate, was filtered, the excess solvent was removed under reduced pressure and the product was purified by column chromatography (30% EtOAc/hexane) to give 3,5-*bis*((trimethylsilyl)ethynyl)pyridin-2-amine (**4-29**) as a cream white solid (2.901 g, 90%). Melting point: 141 – 143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.8, 1H), 7.41 (d, *J* = 1.9, 1H), 5.02 (s, 2H), 0.03 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.17, 151.46, 143.10, 109.66, 102.75, 101.90, 101.88, 99.25, 94.99, 0.06. HRMS (ES^+) Calculated for $C_{15}H_{23}N_2Si_2$ $[M + H]^+$: 287.1400, found 287.1398.

3,5-Diethynylpyridin-2-amine (4-30)



To a solution of 3,5-*bis*((trimethylsilyl)ethynyl)pyridin-4-amine (**4-29**) (0.7856 g, 2.74 mmol) in THF (20 ml) was added TBAF (3.56 ml, 3.56 mmol) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour. After this time, the reaction mixture was quenched with a saturated aqueous ammonium chloride and was extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulphate and were concentrated under reduced pressure to give a brownish solid which was purified by column chromatography (30% EtOAc/hexane) to give 3,5-diethynylpyridin-4-amine (**4-30**) (0.3741 g, 96%) as a cream white solid. Melting point: 134 – 137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 1.8, 1H), 7.66 (d, *J* = 1.9, 1H), 5.37 (s, 2H), 3.42 (s, 1H), 3.06 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.68, 152.02, 143.46, 108.34, 101.45, 83.98, 80.39, 78.23, 77.95. HRMS (ES^+) Calculated for $C_9H_7N_2$ $[M + H]^+$: 143.0609, found 143.0618.

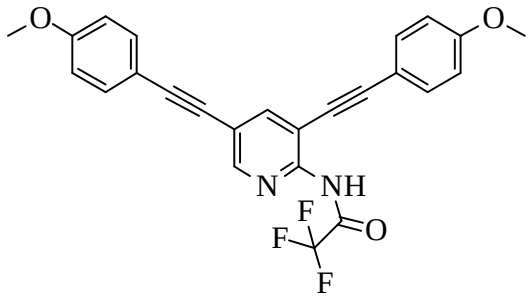
3,5-*bis*((4-Methoxyphenyl)ethynyl)pyridin-2-amine (4-32)



To a mixture of 2-amino-3,5-*bis*ethynylpyridine (**4-30**) (0.5000 g, 3.52 mmol), copper (I) iodide (0.01341 g, 0.0704 mmol), 4-methoxyiodobenzene (2.059 g, 8.80 mol) and triethylamine (1.778 g, 2.45 ml, 0.0176 mol) in THF was added in one portion $Pd(PPh_3)_4$ (0.08139 g, 0.0704 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours after which it was quenched with saturated aqueous solution of ammonium chloride and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, was filtered, the excess solvent was removed under reduced pressure and the product was purified by column chromatography (30%

EtOAc/hexane) to give 3,5-*bis*(4-methoxybenzene)pyridin-2-amine (**4-32**) as a cream white solid (1.161 g, 93%). Melting point: 152 – 155 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 2.1, 1H), 7.73 (d, *J* = 2.2, 1H), 7.50 – 7.44 (m, 4H), 6.94 – 6.87 (m, 4H), 5.26 (s, 2H), 3.85 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.09, 159.58, 157.53, 150.50, 141.80, 133.09, 132.89, 115.37, 114.52, 114.19, 114.05, 110.18, 103.31, 95.91, 89.88, 84.92, 82.35, 55.37, 55.32. IR (cm^{-1}) 3387 (NH str.), 3100 (CH str.), 2250 (alkyne), 1601 (C=N), 1461 (C=C), 1108 (C-O). HRMS (ES^+) Calculated for $C_{23}H_{19}N_2O_2$ $[M + H]^+$: 355.1447, found 355.1439.

***N*-(3,5-*bis*((4-methoxyphenyl)ethynyl)pyridin-2-yl)-2,2,2-trifluoroacetamide (4-35)**

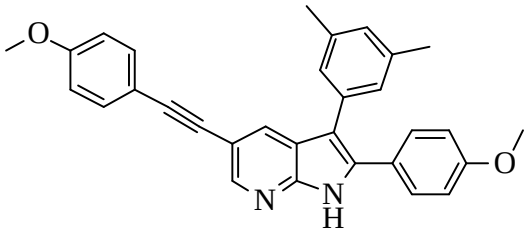


To a solution of 3,5-*bis*(4-methoxybenzene)pyridin-2-amine (**4-32**) (0.4200 g, 1.19 mmol) in THF was added pyridine (0.2848 g, 0.20 ml, 3.56 mmol) and the reaction mixture was cooled to 0 ^{o}C before trifluoroacetic anhydride (0.3249 g, 0.22 ml, 1.55 mmol) was added dropwise. After the addition, the reaction mixture was stirred for a further 2 hours at the same temperature and was determined to be complete by thin layer chromatography. A saturated aqueous ammonium chloride was added and the reaction mixture was extracted with ethyl acetate. The combined organic fractions were dried over magnesium sulphate, the excess solvent was removed on a rotary evaporator and the product was purified by flash chromatography (10% EtOAc/hexane) to give *N*-(3,5-*bis*((4-methoxyphenyl)ethynyl)pyridin-2-yl)-2,2,2-trifluoroacetamide (**4-35**) (0.5223 g, 98%). Melting point: 229 – 231 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.56 (s, 1H), 7.95 (s, 1H), 7.48 (d, *J* = 8.8, 4H), 6.92 (d, *J* = 8.2, 4H), 3.85 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.85, 160.27, 149.78, 147.30, 141.88, 133.31, 133.29, 118.52, 116.73, 114.47, 114.43, 114.20, 113.08, 111.26, 100.10, 93.70, 83.44, 80.17, 55.42, 55.37. IR (cm^{-1}) 3343 (NH str.), 3006 (CH str.), 2214 (alkyne), 1721 (C=O), 1606 (C=N), 1444 (C=C), 1188 (C-O). HRMS (ES^+) Calculated for $C_{25}H_{18}N_2O_3F_3$ $[M + H]^+$: 451.1270, found 451.1253.

General procedure for ring closing using $Pd(PPh)_4$

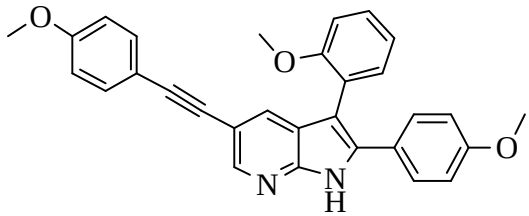
To a mixture of *N*-(3,5-*bis*((4-methoxyphenyl)ethynyl)pyridin-2-yl)-2,2,2-trifluoroacetamide (**4-35**), cesium carbonate or cesium fluoride, and aryl iodide in DMF under nitrogen atmosphere was added $Pd(PPh_3)_4$ in one portion. Afterwards, the reaction mixture was heated at 80 °C for 8 hours followed by cooling to room temperature. Water was added and at some stage, the product precipitated from the solution or was extracted with ethyl acetate. It was either filtered or the combined organic extracts were dried over magnesium sulphate, were filtered and the excess solvent was removed on a rotary evaporator. The resulting residue was purified by flash chromatography (10 – 50% EtOAc/hexane).

3-(3,5-Dimethylphenyl)-2-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-1*H*-pyrrolo[2,3-*b*]pyridine (4-37)



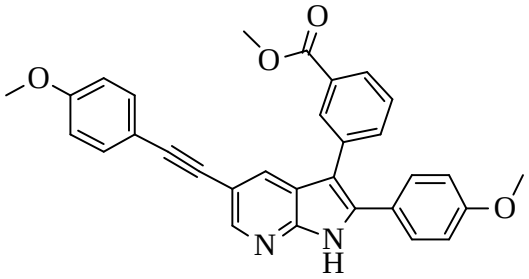
A cream white solid (1.018 g, 83%). Melting point: 249 – 252 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.02 (s, 1H), 8.40 (s, 1H), 8.12 (s, 1H), 7.58 (d, *J* = 8.1, 2H), 7.51 (d, *J* = 8.0, 2H), 7.09 (s, 2H), 6.99 (d, *J* = 7.5, 3H), 6.92 (d, *J* = 8.1, 2H), 3.89 (t, *J* = 13.7, 6H), 2.36 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.71, 159.57, 147.69, 145.27, 138.18, 135.84, 134.07, 132.95, 130.48, 129.78, 128.36, 127.71, 124.61, 121.76, 115.55, 114.23, 114.06, 112.56, 112.16, 89.57, 86.74, 55.34, 55.33, 21.42. IR (cm^{-1}) 3250 (NH str.), 3000 (CH str.), 2240 (alkyne), 1603 (C=N), 1509 (C=C), 1169 (C-O). HRMS (ES^+) Calculated for $C_{31}H_{26}N_2O_2$ $[M + H]^+$: 591.2756 , found 591.2755.

3-(2-Methoxyphenyl)-2-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-1*H*-pyrrolo[2,3-*b*]pyridine (4-38a)



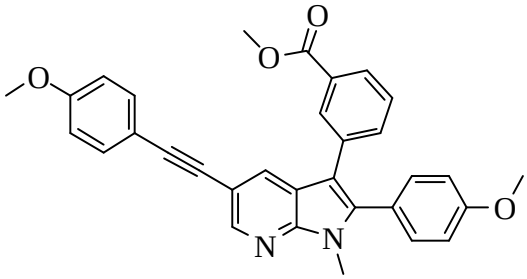
A cream white solid (1.021 g, 89%). Melting point: 247 – 250 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.88 (s, 1H), 8.30 (s, 1H), 7.83 (s, 1H), 7.41 (d, *J* = 7.9, 4H), 7.28 (d, *J* = 7.8, 1H), 7.24 (d, *J* = 7.5, 1H), 6.96 – 6.91 (m, 2H), 6.85 (d, *J* = 8.0, 2H), 6.80 (d, *J* = 7.9, 2H), 3.76 (s, 6H), 3.56 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.55, 159.50, 157.55, 147.78, 145.11, 136.77, 132.92, 132.52, 130.91, 129.06, 128.56, 125.32, 123.15, 122.11, 120.90, 115.64, 114.12, 114.03, 112.41, 111.50, 108.18, 89.34, 86.89, 55.32. IR (cm^{-1}) 3300 (NH str.), 3001 (CH str.), 2230 (alkyne), 1605 (C=N), 1509 (C=C), 1177 (C-O). HRMS (ES^+) Calculated for $C_{30}H_{25}N_2O_3$ $[M + H]^+$: 461.1865, found 461.1864.

Methyl 3-(2-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoate (4-38b)



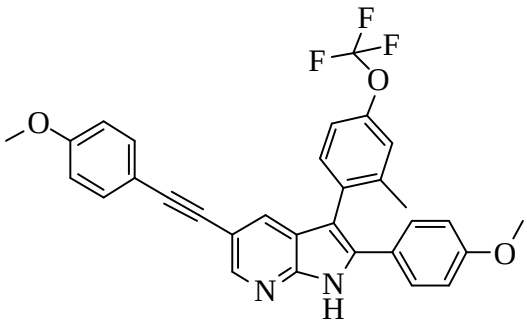
A cream white solid (0.2887 g, 15%). Melting point: 187 – 189 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.46 (s, 1H), 8.39 (d, *J* = 1.6, 1H), 8.18 (s, 1H), 8.07 (d, *J* = 1.5, 1H), 8.00 (d, *J* = 7.8, 1H), 7.56 (d, *J* = 7.7, 1H), 7.50 –7.47 (m, 5H), 6.95 (d, *J* = 8.7, 2H), 6.89 (d, *J* = 8.8, 2H), 3.93 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.11, 159.96, 159.62, 147.48, 145.73, 136.39, 134.75, 134.67, 132.97, 130.85, 130.04, 129.81, 128.86, 127.84, 123.95, 121.29, 115.40, 114.48, 114.05, 113.09, 111.01, 89.90, 86.44, 55.36, 55.32, 52.20. IR (cm^{-1}) 3384 (NH str.), 2900 (CH str.), 2242 (alkyne), 1721 (C=O), 1603 (C=N), 1504 (C=C), 1174 (C-O). HRMS (ES^+) Calculated for $C_{31}H_{25}N_2O_4$ $[M + H]^+$: 489.1814, found 489.1813.

Methyl 3-(2-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoate (4-38c)



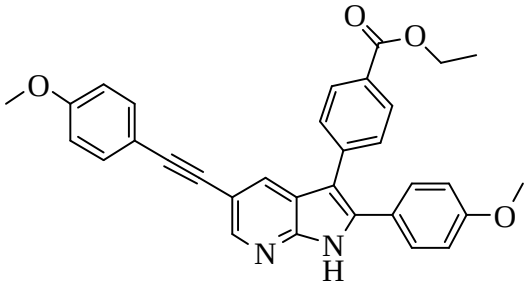
A cream white solid (0.7113 g, 85%). Melting point: 245 – 248 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 1.8, 1H), 8.14 (d, *J* = 1.9, 1H), 8.05 (s, 1H), 7.88 (dt, *J* = 7.4, 1.5, 1H), 7.54 – 7.46 (m, 2H), 7.38 – 7.31 (m, 2H), 7.29 – 7.24 (m, 2H), 6.96 – 6.91 (m, 2H), 6.90 – 6.86 (m, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.12, 159.96, 159.57, 147.19, 146.12, 139.10, 134.65, 134.14, 132.98, 132.08, 130.50, 130.47, 129.79, 128.51, 127.17, 122.67, 119.10, 115.48, 114.23, 114.03, 112.97, 112.04, 89.81, 86.71, 55.31, 52.11, 29.72. IR (cm^{-1}) 3000 (CH str.), 2200 (alkyne), 1722 (C=O), 1603 (C=N), 1508 (C=C), 1172 (C-O). HRMS (ES^+) Calculated for $C_{32}H_{26}N_2O_4$ $[M + H]^+$: 503.1892, found 503.1881.

2-(4-Methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-3-(2-methyl-4-(trifluoromethoxy)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (4-38d)



A cream white solid (1.213 g, 80%). Melting point: 244 – 247 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.71 (s, 1H), 8.43 (d, *J* = 1.8, 1H), 7.78 (d, *J* = 1.8, 1H), 7.48 – 7.43 (m, 2H), 7.41 (d, *J* = 8.8, 2H), 7.35 (d, *J* = 8.3, 1H), 7.17 (s, 1H), 7.13 (d, *J* = 8.2, 1H), 6.94 (d, *J* = 8.8, 2H), 6.88 (d, *J* = 8.8, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.82, 159.62, 148.61, 148.59, 147.55, 145.51, 140.00, 136.36, 132.95, 132.79, 132.35, 130.10, 128.66, 124.45, 122.66, 122.06, 118.41, 115.36, 114.53, 114.05, 112.91, 110.04, 89.85, 86.35, 55.34, 55.32, 20.31. IR (cm^{-1}) 3225 (NH str.), 2980 (CH str.), 2232 (alkyne), 1605 (C=N), 1511 (C=C), 1182 (C-O). HRMS (ES^+) Calculated for $C_{31}H_{23}N_2O_2F_3$ $[M + H]^+$: 529.1661, found 529.1659.

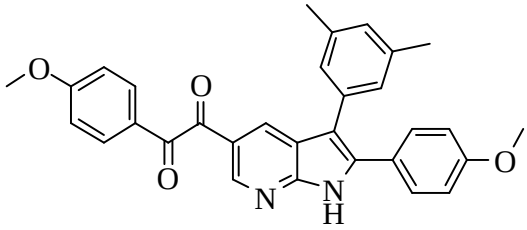
Ethyl 4-(2-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoate (4-38e)



A cream white solid (1.184 g, 90%). Melting point: 182 – 185 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.25 (s, 1H), 8.32 (s, 1H), 8.12 (s, 1H), 8.07 (d, *J* = 8.2, 2H), 7.49 (m, 6H), 6.90 (d, *J* = 8.5, 4H), 4.41 (q, *J* = 7.1, 2H), 3.82 (s, 6H), 1.42 (t, *J* = 7.1, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.63, 160.06, 159.64, 147.63, 145.37, 139.36, 137.10, 132.96, 130.21, 130.04, 130.01, 129.60, 128.33, 123.93, 121.11,

115.36, 114.45, 114.07, 113.09, 110.86, 89.99, 86.37, 60.93, 55.33, 14.40. IR (cm^{-1}) 3385 (NH str.), 2900 (CH str.), 2230 (alkyne), 1709 (C=O), 1604 (C=N), 1509 (C=C), 1172 (C-O). HRMS (ES^+) Calculated for $C_{32}H_{26}N_2O_4$ $[M + H]^+$: 503.1893, found 503.1891.

1-(3-(3,5-Dimethylphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(4-methoxyphenyl)ethane-1,2-dione (4-50)

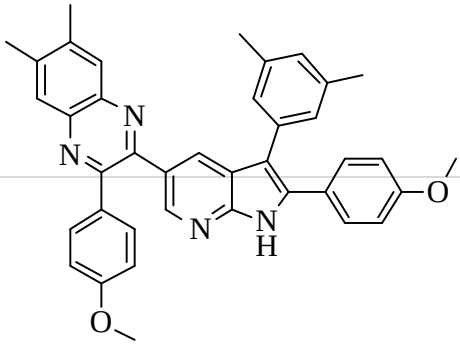


A mixture of 2,3,5-trisubstituted 7-azaindole (**4-37**), palladium chloride and DMSO (2.50 ml) in a 10.00 ml microwave tube was irradiated at 150 W and 150 °C for 25 minutes. After this time, the reaction mixture was allowed to cool to room temperature and water was added. The resulting mixture was extracted with ethyl acetate and was washed with a saturated aqueous ammonium chloride. The combined organic fractions were dried over magnesium sulphate, were filtered through celite and the excess solvent was removed on a rotary evaporator. The resulting crude material was purified by flash chromatography (10 – 50% EtOAc/hexane) to give diketone **4-50** as a yellow solid (0.05342 g, 70%). Melting point: 245 – 247 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.34 (s, 1H), 8.77 (d, *J* = 1.9, 1H), 8.66 (d, *J* = 1.8, 1H), 8.02 – 7.95 (m, 2H), 7.58 – 7.52 (m, 2H), 7.05 (s, 2H), 7.02 – 6.89 (m, 5H), 3.92 (s, 3H), 3.88 (s, 3H), 2.32 (d, *J* = 7.9, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.77, 192.86, 164.98, 160.12, 151.15, 145.72, 138.40, 137.50, 133.26, 132.47, 129.76, 129.35, 128.83, 127.67, 126.25, 123.86, 122.82, 122.73, 114.41, 114.37, 113.59, 55.64, 55.41, 21.40. IR (cm^{-1}) 3325 (NH str.), 3000 (CH str.), 1730 (C=O), 1609 (C=N), 1508 (C=C), 1187 (C-O). HRMS (ES^+) Calculated for $C_{31}H_{27}N_2O_4$ $[M + H]^+$: 491.1971, found 491.1982.

General procedure for microwave assisted synthesis of quinoxaline deravatives

A mixture of 2,3,5-trisubstituted 7-azaindole **4-38**, palladium chloride and DMSO (2.50 ml) in a 10 ml microwave tube was irradiated at 150 W and 150 °C for 25 minutes. After this time, the reaction mixture was allowed to cool to room temperature, was treated with aryldiamine and stirred at room temperature for about 5 minutes before being irradiated under the same conditions (150 W, 150 °C) for 25 minutes. The reaction mixture was cooled to room temperature and water was added. The resulting mixture was extracted with ethyl acetate and washed with a saturated aqueous ammonium chloride. The combined organic fractions were dried over magnesium sulfate, were filtered through celite and the excess solvent was removed on a rotary evaporator. The resulting crude material was purified by flash chromatography (20 – 50% EtOAc/hexane) to give the title compound **4-51**.

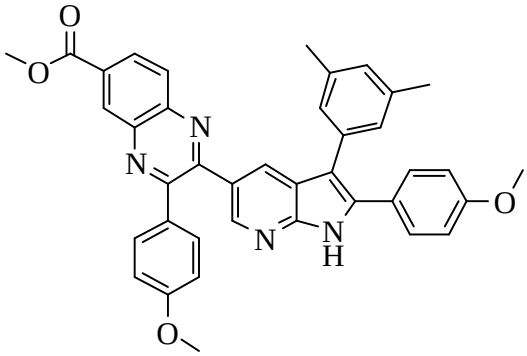
2-(3-(3,5-Dimethylphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-3-(4-methoxyphenyl)-6,7-dimethylquinoxaline (4-51a)



A yellow Solid (0.05512 g, 73%). Melting point: 195 – 198 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.15 (s, 1H), 8.45 (d, *J* = 2.1, 1H), 7.92 (s, 1H), 7.88 (s, 1H), 7.79 (d, *J*

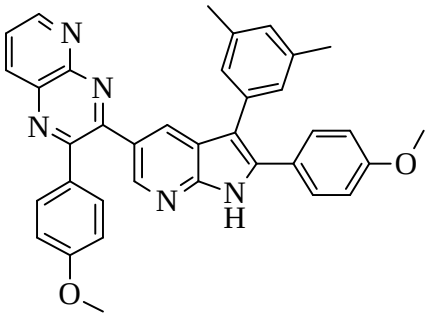
= 2.0, 1H), 7.49 (d, *J* = 8.8, 2H), 7.43 (d, *J* = 8.8, 2H), 6.98 (d, *J* = 8.8, 2H), 6.94 (d, *J* = 8.9, 2H), 6.90 (s, 1H), 6.72 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 2.49 (s, 3H), 2.48 (s, 3H), 2.20 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 159.59, 159.11, 151.81, 150.66, 148.09, 144.31, 140.30, 140.27, 139.41, 139.33, 137.58, 135.17, 133.97, 131.41, 131.26, 129.63, 127.98, 127.81, 127.60, 127.55, 127.34, 127.09, 123.72, 119.55, 113.95, 113.68, 111.38, 55.17, 20.86, 19.86, 19.84. IR (cm^{-1}) 3225 (NH str.), 2900 (CH str.), 1605 (C=N), 1510 (C=C), 1174 (C-O). HRMS (ES^+) Calculated for $C_{39}H_{34}N_4O_2$ $[M + H]^+$: 591.2682, found 591.2678.

Methyl 2-(3-(3,5-dimethylphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-3-(4-methoxyphenyl)quinoxaline-6-carboxylate (4-51b)



A brownish Solid (0.1018 g, 69%) as a mixture of regioisomers. Melting point: 181 – 184 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.53 (d, 1H), 8.91 – 8.85 (m, 1H), 8.63 (dd, *J* = 8.6, 1.8, 1H), 8.38 – 8.31 (m, 1H), 8.19 (d, *J* = 8.7, 1H), 8.10 – 8.03 (m, 1H), 7.60 – 7.56 (m, 3H), 6.96 – 6.91 (m, 4H), 6.83 (d, *J* = 3.9, 2H), 4.02 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 2.26 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.47, 166.42, 160.65, 160.52, 159.65, 154.85, 154.13, 153.77, 153.05, 148.88, 148.85, 143.89, 143.80, 143.17, 143.15, 140.35, 140.34, 138.09, 136.10, 133.94, 133.92, 131.85, 131.67, 131.58, 131.47, 131.00, 130.99, 130.93, 130.88, 129.79, 129.69, 129.62, 129.33, 129.27, 129.21, 129.17, 128.23, 128.22, 127.46, 127.24, 127.23, 124.57, 124.54, 121.30, 121.27, 114.22, 114.13, 112.54, 112.50, 55.35, 55.32, 52.60, 52.58, 21.28. IR (cm^{-1}) 3380 (NH str.), 3000 (CH str.), 1690 (C=O), 1606 (C=N), 1511 (C=C), 1154 (C-O). HRMS (ES^+) Calculated for $C_{39}H_{33}N_4O_4$ $[M + H]^+$: 621.2502, found 621.2495.

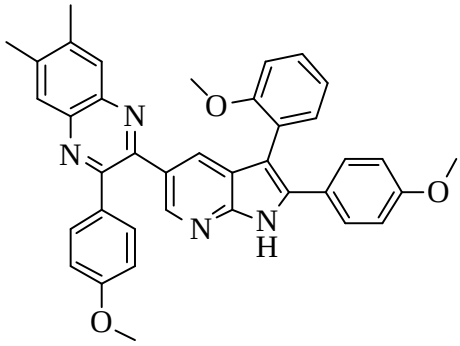
3-(3-(3,5-Dimethylphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-(4-methoxyphenyl)pyrido[2,3-*b*]pyrazine (4-51c)



A yellow solid (0.1031 g, 67%) as a mixture of regioisomers. Melting point: 231 – 233 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.93 (d, 1H), 9.13 (ddd, *J* = 6.0, 4.2, 1.8, 1H), 8.62 (dd, *J* = 38.4, 1.9, 1H), 8.50 (dd, *J* = 8.3, 1.8, 1H), 8.17 (dd, *J* = 17.8, 1.8, 1H), 7.74 – 7.65 (m, 2H), 7.63 – 7.51 (m, 3H), 6.91 (dt, *J* = 8.9, 4.6, 5H), 6.87 (s, 1H), 6.84 (s, 1H), 3.83 (dd, *J* = 18.9, 1.7, 6H), 2.26 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.94, 160.81, 160.61, 159.66, 159.60, 155.91, 155.14, 154.39, 153.76, 153.61, 153.27, 149.89, 149.87, 148.93, 144.18, 143.54, 138.37, 138.11, 138.06, 137.93, 137.81, 137.62, 136.35, 136.15, 136.12, 136.06, 133.97, 133.93, 133.34, 132.47, 131.99, 131.48, 130.80, 130.49, 129.90, 129.81, 129.77, 129.60, 129.24, 128.77, 128.25, 128.22, 127.68, 127.52, 127.50, 127.13, 126.90, 126.24, 124.99, 124.90, 124.57, 124.52, 123.94, 122.74, 122.63, 121.50, 121.42, 114.36, 114.32, 114.22, 114.22, 114.15, 113.91, 113.56, 112.61, 112.44, 55.36, 55.35, 55.31, 55.28, 21.29, 21.28.

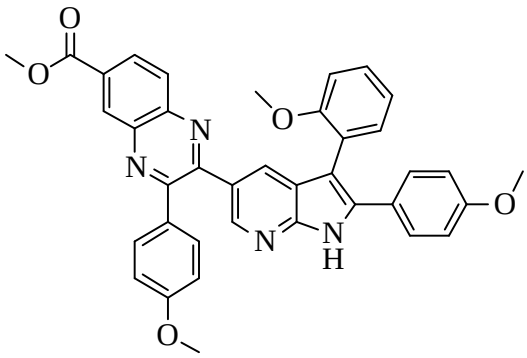
IR (cm^{-1}) 3300 (NH str.), 2900 (CH str.), 1605 (C=N), 1509 (C=C), 1177 (C-O). HRMS (ES^+) Calculated for $C_{36}H_{30}N_5O_2$ $[M + H]^+$: 564.2400, found 564.2385.

2-(4-Methoxyphenyl)-3-(3-(2-methoxyphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-6,7-dimethylquinoxaline (4-51d)



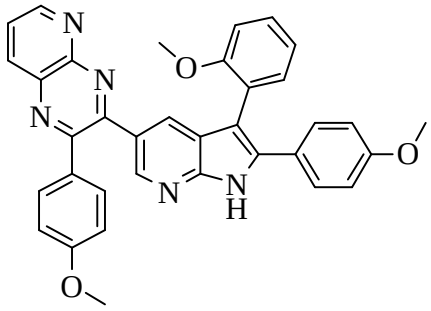
A brownish solid (0.1203 g, 66%). Melting point: 285 – 287 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.76 (s, 1H), 8.50 (d, *J* = 1.8, 1H), 7.95 (d, *J* = 1.6, 1H), 7.90 (d, *J* = 10.5, 2H), 7.49 (d, *J* = 7.5, 4H), 7.33 – 7.27 (m, 1H), 7.15 – 7.11 (m, 1H), 6.98 – 6.90 (m, 2H), 6.87 (t, *J* = 8.1, 4H), 3.83 (s, 3H), 3.79 (s, 3H), 3.50 (s, 3H), 2.51 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.04, 159.35, 157.29, 152.37, 151.21, 148.72, 143.69, 140.29, 140.13, 140.09, 140.07, 136.88, 132.40, 131.99, 131.24, 129.79, 128.88, 128.23, 128.15, 128.12, 127.75, 125.79, 123.35, 121.98, 120.74, 114.02, 113.95, 111.42, 108.27, 55.31, 55.27, 55.25, 20.40, 20.34. IR (cm^{-1}) 3301 (NH str.), 3005 (CH str.), 1606 (C=N), 1509 (C=C), 1173 (C-O). HRMS (ES^+) Calculated for $C_{38}H_{33}N_4O_3$ $[M + H]^+$: 593.2553, found 593.2560.

Methyl 3-(4-methoxyphenyl)-2-(3-(2-methoxyphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)quinoxaline-6-carboxylate (4-51e)



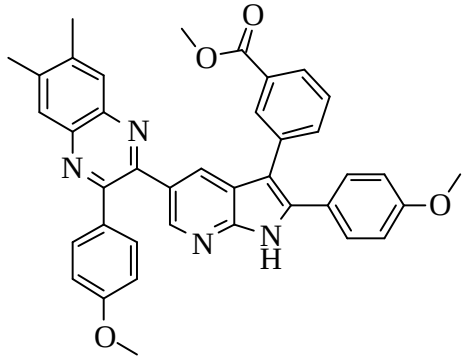
A brownish solid (0.1067 g, 69%) as a mixture of regioisomers. Melting point: 277 – 279 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.78 (d, 1H), 8.89 – 8.84 (m, 1H), 8.54 (t, *J* = 2.3, 1H), 8.32 (dt, *J* = 8.7, 2.2, 1H), 8.21 – 8.13 (m, 1H), 7.99 (dd, *J* = 7.0, 2.0, 1H), 7.58 – 7.51 (m, 2H), 7.49 (dd, *J* = 8.9, 2.6, 2H), 7.45 (d, *J* = 1.9, 1H), 7.43 (d, *J* = 1.9, 1H), 7.38 (d, *J* = 1.9, 2H), 7.32 (td, *J* = 8.0, 1.7, 1H), 7.13 (dd, *J* = 7.7, 1.5, 1H), 6.95 (t, *J* = 7.5, 2H), 6.90 – 6.86 (m, 4H), 6.64 (s, 1H), 6.62 (s, 1H), 4.01 (d, *J* = 1.1, 3H), 3.83 (s, 9H), 3.80 (s, 3H), 3.51 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.37, 166.48, 166.44, 160.65, 160.52, 159.48, 159.47, 157.26, 154.94, 154.22, 153.90, 153.19, 148.97, 148.93, 143.62, 143.52, 143.24, 143.08, 140.44, 140.25, 137.18, 137.18, 133.10, 132.32, 131.80, 131.69, 131.42, 131.32, 131.18, 131.16, 130.87, 130.85, 129.94, 129.88, 129.28, 129.19, 129.15, 128.88, 128.41, 127.04, 125.57, 125.53, 123.23, 123.08, 123.06, 122.04, 120.99, 120.79, 118.31, 114.88, 114.06, 114.05, 111.47, 108.42, 108.38, 55.35, 55.34, 55.31, 55.25, 52.56, 52.55, 51.64. IR (cm^{-1}) 3380 (NH str.), 3000 (CH str.), 1690 (C=O), 1606 (C=N), 1511 (C=C), 1154 (C-O). HRMS (ES^+) Calculated for $C_{38}H_{31}N_4O_5$ $[M + H]^+$: 623.2294, found 623.2280.

2-(4-Methoxyphenyl)-3-(3-(2-methoxyphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyrido[2,3-*b*]pyrazine (4-51f)



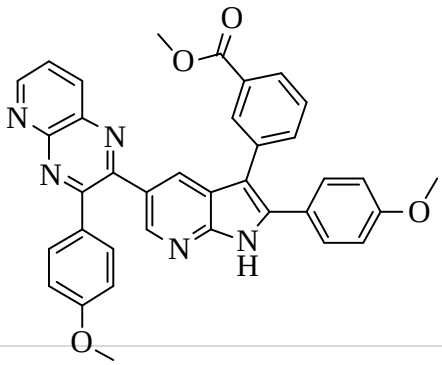
A brownish solid (0.1209 g, 72%) as a mixture of regioisomers. Melting point: Melting point: 256 – 258 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.68 (s, 1H), 9.25 – 8.95 (m, 1H), 8.53 (d, *J* = 1.9, 1H), 8.48 (dd, *J* = 8.3, 1.8, 1H), 8.18 (d, *J* = 1.8, 1H), 7.67 (dd, *J* = 8.3, 4.1, 1H), 7.54 (t, *J* = 12.0, 2H), 7.47 (t, *J* = 6.7, 2H), 7.37 – 7.28 (m, 1H), 7.17 (dd, *J* = 7.4, 1.4, 1H), 7.01 – 6.90 (m, 3H), 6.90 – 6.82 (m, 4H), 3.84 (d, *J* = 2.6, 3H), 3.80 (s, 3H), 3.51 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.64, 159.46, 157.26, 155.28, 154.50, 153.60, 149.98, 148.99, 143.99, 143.41, 137.91, 137.08, 136.03, 132.35, 131.85, 131.30, 131.00, 130.23, 128.92, 128.79, 128.42, 126.77, 125.55, 124.90, 123.02, 122.19, 120.84, 114.13, 114.07, 113.88, 111.42, 108.55, 55.35, 55.27. IR (cm^{-1}) 3329 (NH str.), 2925 (CH str.), 1606 (C=N), 1511 (C=C), 1173 (C-O). HRMS (ES^+) Calculated for $C_{35}H_{28}N_5O_3$ $[M + H]^+$: 566.2192, found 566.2216.

Methyl 3-(2-(4-methoxyphenyl)-5-(3-(4-methoxyphenyl)-6,7-dimethylquinoxalin-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoate (4-51g)



A brownish solid (0.1026 g, 61%). Melting point: 220 – 223 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.73 (s, 1H), 8.48 (d, *J* = 2.0, 1H), 8.10 – 8.05 (m, 2H), 7.99 – 7.94 (m, 1H), 7.91 (d, *J* = 9.7, 2H), 7.51 – 7.45 (m, 4H), 7.39 (dt, *J* = 5.6, 3.3, 2H), 6.95 – 6.84 (m, 4H), 3.89 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 2.52 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.11, 160.10, 159.78, 152.31, 150.80, 148.45, 144.11, 140.38, 140.28, 140.27, 140.17, 136.58, 134.95, 134.58, 131.87, 131.24, 130.87, 130.70, 129.80, 129.14, 128.68, 128.18, 128.09, 127.59, 124.21, 121.29, 114.44, 113.97, 111.20, 55.35, 55.33, 52.10, 20.43, 20.37. IR (cm^{-1}) 3326 (NH str.), 3000 (CH str.), 1721 (C=O), 1606 (C=N), 1507 (C=C), 1173 (C-O). HRMS (ES^+) Calculated for $C_{39}H_{33}N_4O_4$ $[M + H]^+$: 621.2502, found 621.2498.

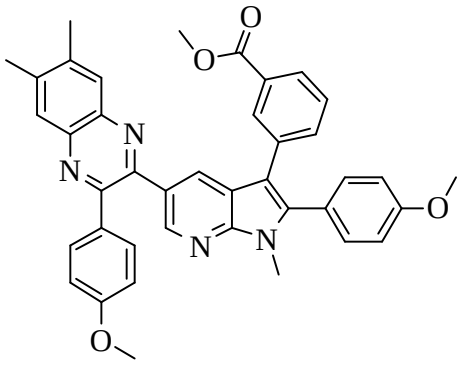
Methyl 3-(2-(4-methoxyphenyl)-5-(3-(4-methoxyphenyl)pyrido[2,3-*b*]pyrazin-2-yl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl)benzoate (4-51h)



A brownish solid (0.1002 g, 64%) as a mixture of regioisomers. Melting point: 213 – 215 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.64 (m, 1H), 9.13 (m , 1H), 8.55 – 8.44 (m, 2H), 8.31 – 8.18 (m, 1H), 8.07 (m, 1H), 7.97 (d, *J* = 6.9, 1H), 7.73 – 7.63 (m, 2H), 7.55 (d, *J* = 8.7, 2H), 7.43 (m, 4H), 6.92 – 6.82 (m, 5H), 3.91 – 3.79 (m, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.05, 160.88, 160.69, 159.90, 159.85, 155.98, 154.91, 154.46, 153.89, 153.71, 153.08,

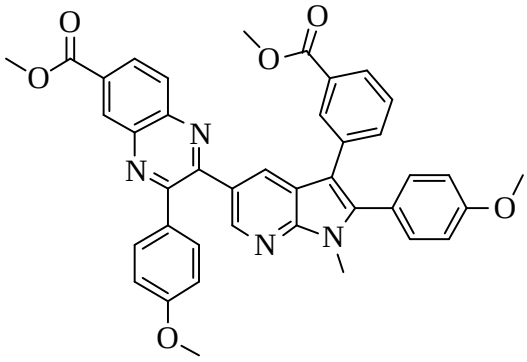
149.92, 149.88, 148.70, 148.68, 144.33, 143.84, 137.96, 137.85, 136.99, 136.74, 136.13, 134.75, 134.69, 134.59, 131.83, 131.31, 130.91, 130.86, 130.79, 130.75, 130.52, 129.78, 129.73, 129.68, 129.12, 128.79, 128.76, 127.75, 127.54, 127.23, 125.06, 124.96, 123.95, 123.92, 121.53, 121.50, 114.65, 114.48, 114.46, 114.16, 113.92, 111.51, 111.34, 55.38, 55.36, 52.14, 52.11. IR (cm^{-1}) 3336 (NH str.), 3001 (CH str.), 1723 (C=O), 1609 (C=N), 1506 (C=C), 1171 (C-O). HRMS (ES^+) Calculated for $C_{36}H_{28}N_5O_4$ $[M + H]^+$: 594.2141, found 594.2114.

Methyl 3-(2-(4-methoxyphenyl)-5-(3-(4-methoxyphenyl)-6,7-dimethylquinoxalin-2-yl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoate (4-51i)



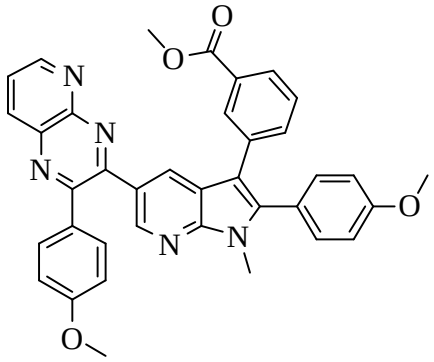
A brownish solid (0.1069 g, 68%). Melting point: 206 – 208 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 1.9, 1H), 8.22 (d, *J* = 2.0, 1H), 7.91 (d, *J* = 8.1, 3H), 7.84 (d, *J* = 7.6, 1H), 7.49 (d, *J* = 8.7, 2H), 7.34 – 7.21 (m, 5H), 6.94 (d, *J* = 8.7, 2H), 6.89 (d, *J* = 8.7, 2H), 3.85 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 2.51 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.09, 160.07, 159.91, 152.44, 150.99, 147.99, 144.91, 140.31, 140.27, 140.19, 140.13, 138.90, 134.76, 134.06, 132.11, 132.09, 131.27, 130.53, 130.36, 128.81, 128.46, 128.37, 128.15, 127.01, 122.82, 119.06, 114.19, 114.02, 112.56, 55.32, 55.32, 52.01, 29.75, 20.41, 20.37. IR (cm^{-1}) 3000 (CH str.), 1721 (C=O), 1606 (C=N), 1507 (C=C), 1173 (C-O). HRMS (ES^+) Calculated for $C_{40}H_{34}N_4O_4$ $[M + H]^+$: 635.2608, found 635.2391.

Methyl 2-(3-(3-(methoxycarbonyl)phenyl)-2-(4-methoxyphenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-3-(4-methoxyphenyl)quinoxaline-6-carboxylate (4-51j)



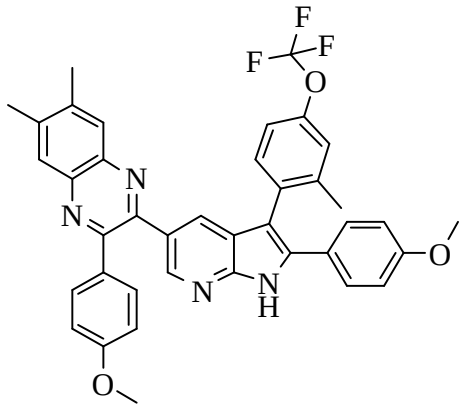
A brownish solid (0.1103 g, 67%) as a mixture of regioisomers. Melting point: 206 – 207 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (d, *J* = 1.8, 1H), 8.57 (dd, *J* = 8.9, 2.0, 1H), 8.34 – 8.30 (m, 1H), 8.28 (t, *J* = 2.2, 1H), 8.17 (dd, *J* = 8.7, 5.1, 1H), 7.95 – 7.91 (m, 1H), 7.88 – 7.83 (m, 1H), 7.58 – 7.51 (m, 2H), 7.35 – 7.20 (m, 5H), 6.94 (t, *J* = 6.9, 2H), 6.91 (dd, *J* = 8.7, 1.5, 2H), 4.01 (d, *J* = 2.5, 3H), 3.86 (d, *J* = 3.0, 3H), 3.85 (s, 3H), 3.83 (t, *J* = 2.1, 3H), 3.79 (d, *J* = 1.1, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.03, 167.02, 166.43, 160.68, 160.55, 159.99, 154.99, 154.29, 153.73, 153.00, 148.25, 148.20, 144.86, 144.77, 143.25, 143.11, 140.47, 140.29, 139.22, 139.19, 134.58, 134.56, 133.98, 132.08, 131.80, 131.42, 131.33, 131.29, 131.26, 130.94, 130.87, 130.49, 130.41, 129.29, 129.26, 129.17, 129.00, 128.92, 128.42, 128.41, 127.74, 127.70, 127.10, 122.65, 122.62, 119.11, 119.08, 114.24, 114.15, 114.14, 112.69, 112.67, 55.34, 55.31, 52.54, 52.53, 52.03, 29.78. IR (cm^{-1}) 3005 (CH str.), 1717 (C=O), 1605 (C=N), 1509 (C=C), 1174 (C-O). HRMS (ES^+) Calculated for $C_{40}H_{32}N_4O_6$ $[M + H]^+$: 665.2350, found 665.2347.

Methyl 3-(2-(4-methoxyphenyl)-5-(2-(4-methoxyphenyl)pyrido[2,3-*b*]pyrazin-3-yl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoate (4-51k)



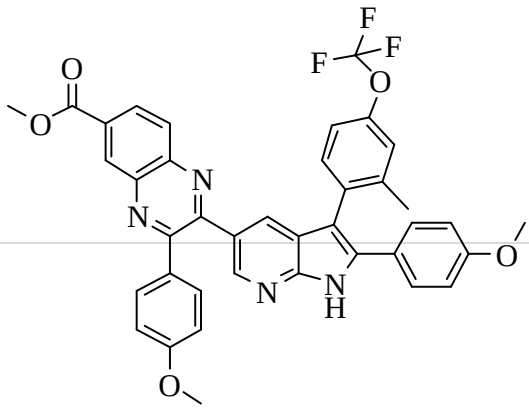
A brownish solid (0.1152 g, 66%) as a mixture of regioisomers. Melting point: 213 – 216 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (td, *J* = 4.0, 1.9, 2H), 8.59 (dd, *J* = 12.6, 2.0, 2H), 8.48 (dt, *J* = 8.3, 2.2, 2H), 8.44 (d, *J* = 2.0, 1H), 8.30 (d, *J* = 2.0, 1H), 8.00 – 7.80 (m, 4H), 7.70 – 7.63 (m, 4H), 7.57 (d, *J* = 8.7, 2H), 7.34 – 7.22 (m, 9H), 6.98 – 6.87 (m, 9H), 3.87 – 3.81 (m, 18H), 3.80 (d, *J* = 3.6, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.09, 167.00, 166.99, 160.80, 160.67, 159.99, 159.95, 156.12, 155.06, 154.57, 153.75, 153.67, 153.22, 149.93, 149.84, 148.30, 148.25, 145.11, 144.73, 139.28, 139.14, 137.94, 137.89, 136.14, 136.02, 134.56, 134.50, 134.06, 133.99, 132.06, 131.84, 131.33, 131.13, 130.78, 130.59, 130.47, 130.41, 130.38, 129.47, 128.82, 128.45, 128.42, 127.66, 127.29, 127.14, 127.10, 124.96, 124.86, 122.62, 122.58, 119.20, 119.10, 114.23, 114.21, 113.94, 112.87, 112.66, 60.36, 55.35, 55.30, 55.29, 52.03, 52.00, 29.80, 29.78, 21.03, 14.19. IR (cm^{-1}) 3000 (CH str.), 1713 (C=O), 1608 (C=N), 1509 (C=C), 1173 (C-O). HRMS (ES^+) Calculated for $C_{37}H_{30}N_5O_4$ $[M + H]^+$: 608.2880, found 608.2250.

2-(4-Methoxyphenyl)-3-(2-(4-methoxyphenyl)-3-(2-methyl-4-(trifluoromethoxy)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-6,7-dimethylquinoxaline (4-51l)



A brownish solid (0.1011 g, 70%). Melting point: 301 – 303 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.83 (s, 1H), 8.66 (d, *J* = 1.6, 1H), 7.91 (d, *J* = 13.2, 2H), 7.66 (s, 1H), 7.44 (d, *J* = 8.3, 4H), 7.13 (d, *J* = 8.3, 1H), 7.09 (s, 1H), 7.04 (d, *J* = 8.0, 1H), 6.92 (d, *J* = 8.6, 2H), 6.85 (d, *J* = 8.6, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 2.52 (s, 6H), 1.91 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.07, 159.67, 152.42, 150.82, 148.60, 148.38, 148.37, 143.99, 140.38, 140.29, 140.27, 140.15, 139.75, 136.60, 132.74, 132.44, 131.90, 131.25, 129.33, 128.68, 128.20, 128.08, 127.97, 127.19, 124.85, 122.49, 121.86, 121.62, 119.57, 118.13, 114.66, 114.51, 113.94, 110.21, 55.30, 20.42, 20.37, 20.17. IR (cm^{-1}) 3200 (NH), 2922 (CH), 1607 (C=N), 1513 (C=C), 1171 (C-O). HRMS (ES^+) Calculated for $C_{39}H_{31}N_4O_3F_3$ $[M + H]^+$: 661.2348, found 661.2340.

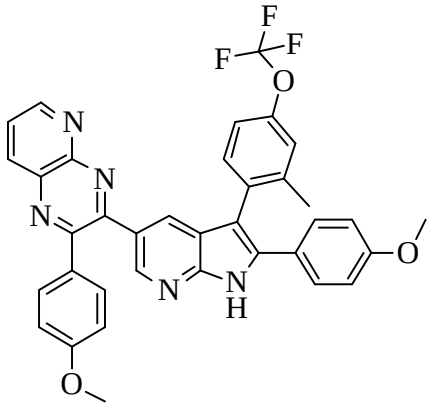
Methyl 3-(4-methoxyphenyl)-2-(2-(4-methoxyphenyl)-3-(2-methyl-4-(trifluoromethoxy)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)quinoxaline-6-carboxylate (4-51m)



A brownish solid (0.1171 g, 60%) as a mixture of regioisomers. Melting point: 270 – 273 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.03 (d, *J* = 22.7, 1H), 8.87

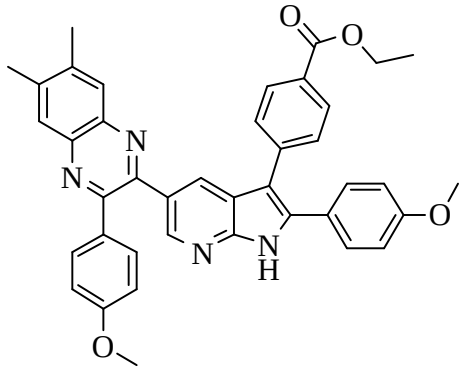
(d, *J* = 7.7, 1H), 8.73 (s, 1H), 8.34 (s, 1H), 8.19 (dd, *J* = 14.5, 8.7, 1H), 7.69 (d, *J* = 2.9, 1H), 7.54 – 7.41 (m, 4H), 7.16 – 7.08 (m, 2H), 7.04 (d, *J* = 8.2, 1H), 6.92 (t, *J* = 11.1, 2H), 6.90 (s, 2H), 4.02 (d, *J* = 3.5, 3H), 3.85 (d, *J* = 5.7, 3H), 3.84 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.41, 166.36, 160.68, 160.56, 159.83, 155.02, 154.29, 153.55, 152.85, 148.92, 148.89, 148.46, 143.91, 143.82, 143.21, 143.14, 140.43, 140.34, 139.73, 136.98, 132.69, 132.22, 132.19, 131.87, 131.67, 131.42, 131.33, 131.11, 131.08, 131.04, 129.48, 129.43, 129.37, 129.32, 129.19, 128.71, 127.24, 124.69, 124.66, 122.55, 121.93, 121.61, 119.57, 118.17, 114.56, 114.08, 114.07, 110.32, 110.29, 55.37, 55.36, 52.59, 52.58, 20.17. IR (cm^{-1}) 3300 (NH), 2900 (CH), 1720 (C=O), 1606 (C=N), 1513 (C=C), 1171 (C-O). HRMS (ES^+) Calculated for $C_{39}H_{30}N_4O_5F_3$ $[M + H]^+$: 691.2168, found 691.2139.

2-(4-Methoxyphenyl)-3-(2-(4-methoxyphenyl)-3-(2-methyl-4-(trifluoromethoxy)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)pyrido[2,3-b]pyrazine (4-51n)



A brownish solid (0.1124 g, 72%) as a mixture of regioisomers. Melting point: 180 – 183 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.07 (d, *J* = 42.8, 1H), 9.24 – 9.01 (m, 1H), 8.66 (dd, *J* = 13.9, 1.4, 1H), 8.49 (t, *J* = 8.4, 1H), 7.92 (s, 0H), 7.79 (s, 1H), 7.73 – 7.66 (m, 1H), 7.62 (d, *J* = 8.7, 1H), 7.52 (d, *J* = 8.6, 1H), 7.43 (d, *J* = 8.4, 2H), 7.18 (dd, *J* = 8.3, 4.3, 1H), 7.11 (s, 1H), 7.03 (d, *J* = 19.7, 1H), 6.93 – 6.82 (m, 4H), 3.84 (s, 3H), 3.82 (d, *J* = 1.4, 3H), 1.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.83, 160.67, 159.81, 159.76, 156.09, 154.89, 154.48, 153.90, 153.77, 153.08, 149.93, 149.89, 148.92, 148.90, 148.47, 144.20, 143.65, 139.79, 139.76, 137.97, 137.82, 137.15, 136.91, 136.13, 132.73, 132.26, 132.22, 131.85, 131.32, 130.92, 130.59, 129.82, 129.35, 128.73, 128.67, 127.23, 127.00, 125.08, 125.00, 124.65, 124.60, 122.61, 122.56, 122.14, 122.09, 121.60, 119.56, 118.26, 118.19, 114.55, 114.14, 113.89, 110.45, 110.31, 55.37, 55.37, 55.35, 55.32, 20.22, 20.20. IR (cm^{-1}) 3290 (NH), 2925 (CH), 1607 (C=N), 1513 (C=C), 1172 (C-O). HRMS (ES^+) Calculated for $C_{36}H_{27}N_5O_3F_3$ $[M + H]^+$: 634.1570, found 634.1415.

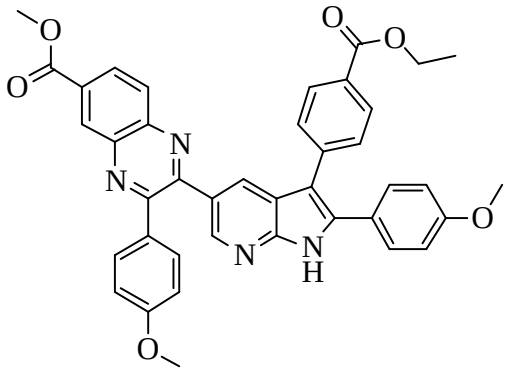
Ethyl 4-(2-(4-methoxyphenyl)-5-(3-(4-methoxyphenyl)-6,7-dimethylquinoxalin-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoate (4-51o)



A brownish solid (0.1203 g, 65%). Melting point: 288 – 291 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.07 (s, 1H), 8.62 (d, *J* = 2.0, 1H), 8.02 (d, *J* = 1.9, 1H), 7.97 (d, *J* = 8.4, 2H), 7.90 (t, *J* = 4.0, 2H), 7.55 – 7.48 (m, 2H), 7.47 (t, *J* = 6.2, 2H), 7.27 (d, *J* = 8.5, 2H), 6.95 (d, *J* = 8.2, 4H), 4.41 (q, *J* = 7.1, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.53 (d, *J* = 1.1, 3H), 2.52 (s, 3H), 1.43 (t, *J* = 7.1, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.16, 159.94, 152.34, 150.48, 148.70, 144.22, 140.36, 140.30, 140.28, 140.08, 139.45, 137.09, 132.08, 131.28, 130.06, 129.85, 129.65, 129.47, 128.20, 128.10, 128.07, 127.87, 124.23, 120.54, 118.59,

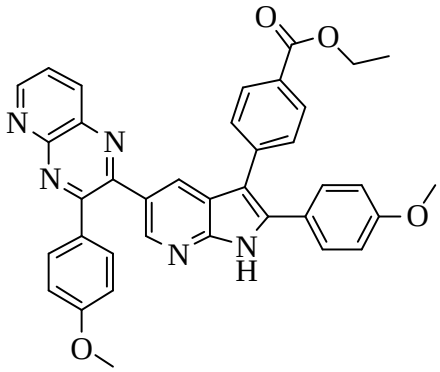
114.49, 114.07, 111.16, 60.88, 55.40, 55.31, 20.44, 20.37, 14.42. IR (cm^{-1}) 3320 (NH str.), 2933 (CH str.), 1711 (C=O), 1606 (C=N), 1512 (C=C), 1175 (C-O). HRMS (ES^+) Calculated for $C_{40}H_{34}N_4O_4$ $[M + H]^+$: 635.2650, found 635.2647.

Methyl 2-(3-(4-(ethoxycarbonyl)phenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-3-(4-methoxyphenyl)quinoxaline-6-carboxylate (4-51p)



A brownish solid (0.1039 g, 59%) as a mixture of regioisomers. Melting point: 257 – 260 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.59 (d, *J* = 24.6, 1H), 8.90 (d, *J* = 1.8, 1H), 8.68 (d, *J* = 2.0, 1H), 8.40 – 8.32 (m, 1H), 8.20 (dd, *J* = 18.3, 8.7, 1H), 8.10 – 8.05 (m, 1H), 7.98 (d, *J* = 8.3, 2H), 7.58 – 7.48 (m, 4H), 7.27 (t, *J* = 4.1, 3H), 7.02 – 6.92 (m, 4H), 4.41 (q, *J* = 7.1, 2H), 4.03 (d, *J* = 4.0, 3H), 3.88 (s, 6H), 1.43 (t, *J* = 7.1, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.62, 166.61, 166.42, 166.37, 160.77, 160.65, 160.11, 154.99, 154.27, 153.29, 152.60, 148.89, 148.85, 144.33, 144.21, 143.25, 143.11, 140.46, 140.32, 139.15, 139.12, 137.21, 131.87, 131.70, 131.45, 131.37, 131.26, 131.08, 131.07, 130.01, 129.90, 129.72, 129.66, 129.43, 129.40, 129.37, 129.21, 128.27, 127.37, 123.95, 123.92, 120.65, 114.68, 114.53, 114.23, 111.43, 111.40, 60.94, 55.46, 55.41, 52.60, 52.59, 14.41. IR (cm^{-1}) 3350 (NH str.), 3000 (CH str.), 1709 (C=O), 1605 (C=N), 1512 (C=C), 1174 (C-O). HRMS (ES^+) Calculated for $C_{40}H_{33}N_4O_6$ $[M + H]^+$: 665.2400, found 665.2402.

Ethyl 4-(2-(4-methoxyphenyl)-5-(3-(4-methoxyphenyl)pyrido[2,3-*b*]pyrazin-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoate (4-51q)



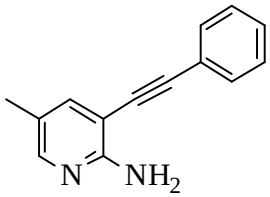
A brownish solid (0.1398 g, 75%) as a mixture of regioisomers. Melting point: 291 – 294 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.02 (d, *J* = 43.2, 1H), 9.15 (td, *J* = 4.2, 1.9, 1H), 8.64 (dd, *J* = 58.1, 1.9, 1H), 8.50 (ddd, *J* = 19.9, 8.3, 1.8, 1H), 8.18 (dd, *J* = 7.4, 1.9, 1H), 7.98 (t, *J* = 8.1, 2H), 7.75 – 7.62 (m, 2H), 7.54 (t, *J* = 10.7, 1H), 7.52 (s, 2H), 7.29 (dd, *J* = 19.0, 8.5, 3H), 6.99 – 6.89 (m, 4H), 4.46 – 4.35 (m, 2H), 3.90 – 3.81 (m, 6H), 1.46 – 1.37 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.63, 166.60, 160.89, 160.73, 160.09, 160.05, 156.06, 154.71, 154.56, 153.89, 153.77, 152.85, 149.93, 149.84, 148.97, 148.92, 144.54, 143.94, 139.20, 139.15, 137.98, 137.83, 137.49, 137.30, 136.18, 136.13, 131.87, 131.38, 131.03, 130.71, 130.03, 130.01, 129.94, 129.90, 129.58, 129.47, 128.27, 128.22, 127.30, 127.02, 125.08, 125.02, 123.94, 123.90, 120.91, 120.70, 114.53, 114.25, 113.99, 111.41, 111.33, 60.94, 60.90, 55.45, 55.41, 14.40. IR (cm^{-1}) 3301 (NH str.), 2923 (CH str.), 1708 (C=O), 1605 (C=N), 1513 (C=C), 1173 (C-O). HRMS (ES^+) Calculated for $C_{37}H_{30}N_5O_4$ $[M + H]^+$: 608.2298, found 608.2275.

8.4 Experimental to Chapter 5

General Procedures for the Sonogashira coupling reactions:[1-3]

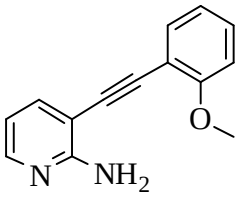
To a flame-dried round-bottom flask under a nitrogen or an argon containing 2-amino-3-bromopyridine or 2-amino-5-chloro-3-iodopyridine was added CuI (2 mole%) and $Pd(PPh_3)_4$ (2 mole%) in one portion followed by the addition of the degassed alkyne solution in either THF or DMF. Triethylamine was then added and the reaction mixture stirred at room temperature in the case of iodopyridines and heated at reflux (70 °C) in case of bromopyridines, monitored by TLC until no starting material was present. After this time, the reaction was quenched with saturated aqueous ammonium chloride and was extracted with either dichloromethane or ethyl acetate. The combined organic extracts were dried over magnesium sulfate, were filtered through either silica or celite and excess solvent was removed on a rotary evaporator followed by purification by flash chromatography using 30% EthOAc/Hexane.

5-Methyl-3-(phenylethynyl)pyridin-2-amine (5-11a)



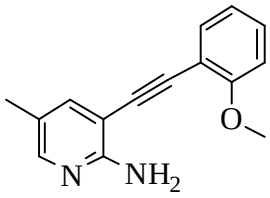
A cream white solid[23] (90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.6, 1H), 7.57 – 7.49 (m, 2H), 7.47 (d, *J* = 1.9, 1H), 7.38 – 7.29 (m, 3H), 4.97 (s, 2H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.86, 147.82, 140.62, 131.47, 128.57, 128.45, 122.77, 122.55, 102.87, 95.30, 84.58, 17.27.

3-((2-Methoxyphenyl)ethynyl)pyridin-2-amine (5-11b)



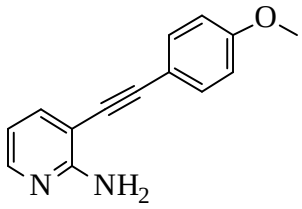
A cream white solid (0.3514 g, 75%). Melting point: 118 – 120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 5.0, 1.6, 1H), 7.57 (dt, *J* = 13.5, 6.7, 1H), 7.46 (dd, *J* = 7.6, 1.6, 1H), 7.32 (td, *J* = 8.4, 1.7, 1H), 6.98 – 6.89 (m, 2H), 6.62 (d, *J* = 7.5, 1H), 5.34 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.92, 159.17, 147.83, 138.83, 132.44, 129.95, 120.65, 113.27, 112.09, 110.53, 103.46, 92.26, 89.30, 55.82. IR (cm^{-1}) 3298 (NH str.), 2997 (CH str.), 2312 (alkyne), 1619 (C=N), 1580 (C=C), 1181 (C-O). HRMS (ES^+) Calculated for $C_{14}H_{13}N_2O$ $[M + H]^+$: 225.1028, found 225.1032.

3-((2-Methoxyphenyl)ethynyl)-5-methylpyridin-2-amine (5-11c)



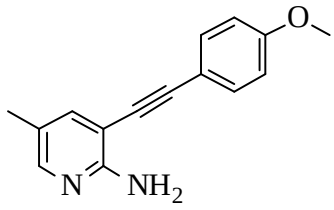
A cream white solid (0.3689 g, 70%). Melting point: 120 – 123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.49 – 7.39 (m, 2H), 7.31 (d, *J* = 1.7, 1H), 6.94 (dd, *J* = 11.0, 4.6, 2H), 5.16 (s, 2H), 3.92 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.90, 157.30, 147.73, 139.55, 132.45, 129.87, 122.17, 120.62, 112.19, 110.53, 103.13, 92.05, 89.43, 55.80, 17.29. IR (cm^{-1}) 3301 (NH str.), 3001 (CH str.), 2212 (alkyne), 1639 (C=N), 1594 (C=C), 1179 (C-O). HRMS (ES^+) Calculated for $C_{15}H_{15}N_2O$ $[M + H]^+$: 239.1184, found 239.1198.

3-((4-Methoxyphenyl)ethynyl)pyridin-2-amine (5-11d)



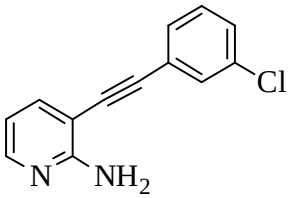
A cream white solid (0.3895 g, 80%). Melting point: 159 – 161 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 4.9, 1.5, 1H), 7.57 (dd, *J* = 7.5, 1.7, 1H), 7.50 – 7.41 (m, 2H), 6.93 – 6.83 (m, 2H), 6.63 (dd, *J* = 7.5, 5.0, 1H), 5.05 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.93, 158.75, 147.69, 139.71, 133.01, 114.79, 114.13, 113.57, 103.54, 95.49, 83.14, 55.34. IR (cm^{-1}) 3245 (NH str.), 2986 (CH str.), 2359 (alkyne), 1619 (C=N), 1558 (C=C), 1144 (C-O). HRMS (ES^+) Calculated for $C_{14}H_{13}N_2O$ $[M + H]^+$: 225.1028, found 225.1039.

3-((4-Methoxyphenyl)ethynyl)-5-methylpyridin-2-amine (5-11e)



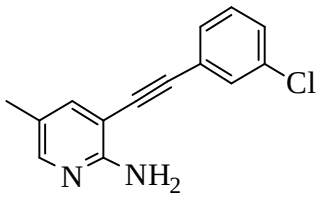
A cream white solid (0.3769 g, 82%). Melting point: 94 – 96 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.6, 1H), 7.46 – 7.43 (m, 2H), 7.42 (d, *J* = 1.9, 1H), 6.91 – 6.85 (m, 2H), 4.92 (s, 2H), 3.82 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.87, 156.86, 147.56, 140.38, 132.97, 122.51, 114.90, 114.12, 103.24, 95.30, 83.30, 55.33, 17.26. IR (cm^{-1}) 3276 (NH str.), 2987 (CH str.), 2238 (alkyne), 1618 (C=N), 1564 (C=C), 1170 (C-O). HRMS (ES^+) Calculated for $C_{15}H_{15}N_2O$ $[M + H]^+$: 239.1184, found 239.1185.

3-((3-Chlorophenyl)ethynyl)pyridin-2-amine (5-11f)



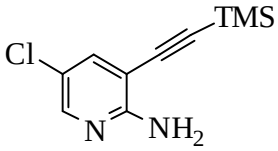
A cream white solid (0.3729 g, 86%). Melting point: 117 – 120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.60 (d, *J* = 7.3, 1H), 7.51 (s, 1H), 7.40 (d, *J* = 7.2, 1H), 7.37 – 7.27 (m, 2H), 6.67 (s, 1H), 5.10 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.72, 148.28, 140.23, 134.37, 131.34, 129.72, 129.61, 128.91, 124.40, 113.66, 102.65, 94.04, 85.60. IR (cm^{-1}) 3326 (NH str.), 3003 (CH str.), 2219 (alkyne), 1627 (C=N), 1565 (C=C), 1198 (C-O). HRMS (ES^+) Calculated for $C_{13}H_{10}N_2Cl$ $[M + H]^+$: 229.0533, found 229.0542.

3-((3-Chlorophenyl)ethynyl)-5-methylpyridin-2-amine (5-11g)



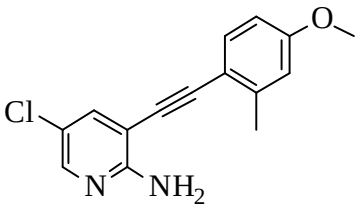
A cream white solid (0.3650 g, 83%). Melting point: 104 – 106 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.50 (s, 1H), 7.45 (s, 1H), 7.39 (d, *J* = 7.3, 1H), 7.31 (dt, *J* = 10.3, 6.8, 2H), 4.93 (s, 2H), 2.20 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.02, 156.84, 148.16, 140.86, 134.35, 131.31, 129.70, 129.58, 128.84, 124.49, 122.68, 102.36, 93.87, 85.78, 17.25. IR (cm^{-1}) 3347 (NH str.), 3005 (CH str.), 2259 (alkyne), 1624 (C=N), 1590 (C=C), 1176 (C-O). HRMS (ES^+) Calculated for $C_{14}H_{12}N_2Cl$ $[M + H]^+$: 243.0689, found 243.0705.

5-Chloro-3-((trimethylsilyl)ethynyl)pyridin-2-amine (5-11h)



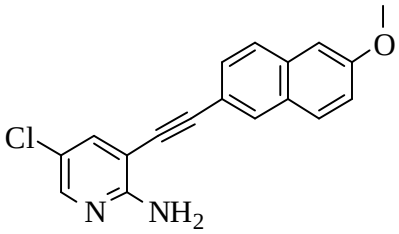
A cream white solid[39] (0.2153 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 2.4, 1H), 7.51 (d, *J* = 2.5, 1H), 5.06 (s, 2H), 0.27 (s, 9H).

5-Chloro-3-((4-methoxy-2-methylphenyl)ethynyl)pyridin-2-amine (5-11i)



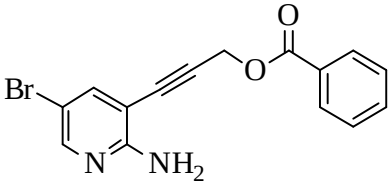
A cream white solid (0.2834 g, 87%). Melting point: 127 – 130 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.55 (s, 1H), 7.41 (d, *J* = 8.4, 1H), 6.79 (s, 1H), 6.74 (d, *J* = 8.4, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.17, 156.92, 145.88, 141.88, 138.66, 133.38, 120.18, 115.32, 114.26, 111.56, 105.04, 95.67, 85.77, 55.31, 21.18. IR (cm^{-1}) 3368 (NH str.), 2989 (CH str.), 2287 (alkyne), 1605 (C=N), 1558 (C=C), 1164 (C-O). HRMS (ES^+) Calculated for $C_{15}H_{14}N_2ClO$ $[M + H]^+$: 273.0795, found 273.0801.

5-Chloro-3-((6-methoxynaphthalen-2-yl)ethynyl)pyridin-2-amine (5-11j)



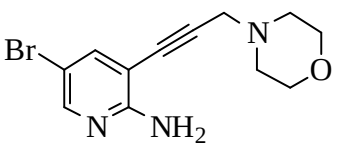
A cream white solid (0.2769 g, 83%). Melting point: 190 – 192 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.96 (s, 1H), 7.72 (d, *J* = 8.6, 2H), 7.60 (s, 1H), 7.18 (d, *J* = 8.8, 1H), 7.13 (s, 1H), 5.12 (s, 2H), 3.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.70, 157.12, 146.18, 138.96, 134.51, 131.54, 129.43, 128.62, 128.40, 127.08, 120.18, 119.75, 116.97, 105.89, 104.59, 97.19, 82.86, 55.39. IR (cm^{-1}) 3366 (NH str.), 3004 (CH str.), 2236 (alkyne), 1628 (C=N), 1552 (C=C), 1160 (C-O). HRMS (ES^+) Calculated for $C_{18}H_{14}N_2ClO$ $[M + H]^+$: 309.0795, found 309.0800.

3-(2-Amino-5-bromopyridin-3-yl)prop-2-yn-1-yl benzoate (5-11k)



A brownish solid (2.169 g, 88%). Melting point: 126 – 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 – 8.02 (m, 3H), 7.63 – 7.53 (m, 3H), 7.45 (t, *J* = 7.6, 2H), 5.23 (s, 2H), 5.14 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.30, 158.39, 149.54, 142.34, 133.77, 130.12, 129.63, 128.80, 106.91, 103.77, 90.95, 81.23, 53.41. IR (cm^{-1}) 3249 (NH str.), 2989 (CH str.), 2312 (alkyne), 1629 (C=N), 1548 (C=C), 1173 (C-O). HRMS (ES^+) Calculated for $C_{15}H_{12}N_2O_2Br$ $[M + H]^+$: 331.0082, found 331.0080.

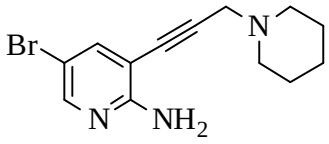
5-Bromo-3-(3-morpholinoprop-1-yn-1-yl)pyridin-2-amine (5-11l)



A brown solid (2.119 g, 86%). Melting point: 115 – 118 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.4, 1H), 7.57 (d, *J* = 2.4, 1H), 5.14 (s, 2H), 3.80 – 3.66 (m, 4H), 3.53 (s, 2H), 2.66 – 2.50 (m,

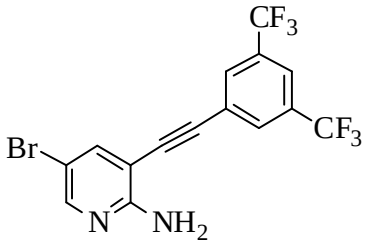
4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.94, 148.74, 142.22, 107.06, 104.78, 91.93, 80.05, 67.05, 52.68, 48.38. IR (cm^{-1}) 3310 (NH str.), 2959 (CH str.), 2291 (alkyne), 1630 (C=N), 1572 (C=C), 1132 (C-O). HRMS (ES^+) Calculated for $C_{12}H_{15}N_3BrO$ $[M + H]^+$: 296.0398, found 296.0420.

5-Bromo-3-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridin-2-amine (5-11m)



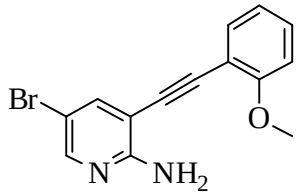
A brown solid (2.110 g, 83%). Melting point: 79 – 81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 2.4, 1H), 7.57 (d, *J* = 2.4, 1H), 5.15 (s, 2H), 3.50 (s, 2H), 2.52 (m, 4H), 1.61 (dt, *J* = 11.0, 5.6, 4H), 1.42 (d, *J* = 5.1, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.99, 148.50, 142.11, 107.04, 105.15, 92.92, 79.53, 53.75, 48.81, 26.16, 24.09. IR (cm^{-1}) 3262 (NH str.), 2988 (CH str.), 2259 (alkyne), 1639 (C=N), 1558 (C=C). HRMS (ES^+) Calculated for $C_{13}H_{17}N_3Br$ $[M + H]^+$: 294.0606, found 294.0613.

3-((3,5-*bis*(Trifluoromethyl)phenyl)ethynyl)-5-bromopyridin-2-amine (5-11n)



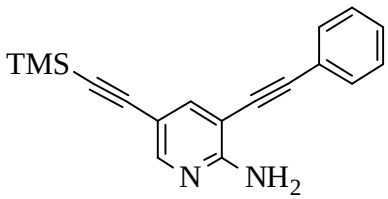
A white solid (1.436 g, 70%). Melting point: 194 – 196 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2.4, 1H), 7.94 (s, 2H), 7.86 (s, 1H), 7.74 (d, *J* = 2.4, 1H), 5.10 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.71, 150.16, 142.56, 132.76, 132.49, 131.74, 131.72, 124.92, 124.25, 122.64, 122.08, 107.59, 103.59, 93.49, 86.93. IR (cm^{-1}) 3309 (NH str.), 2995 (CH str.), 2319 (alkyne), 1629 (C=N), 1571 (C=C). HRMS (ES^+) Calculated for $C_{15}H_8N_2BrF_6$ $[M + H]^+$: 408.9775, found 408.9778.

5-Bromo-3-((2-methoxyphenyl)ethynyl)pyridin-2-amine (5-11o)



A cream white solid (2.013 g, 73%). Melting point: 126 – 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.3, 1H), 7.67 (d, *J* = 2.3, 1H), 7.46 (dd, *J* = 7.5, 1.5, 1H), 7.40 – 7.29 (m, 1H), 7.00 – 6.91 (m, 2H), 5.51 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.00, 157.82, 148.21, 140.39, 132.47, 130.34, 120.70, 111.56, 110.55, 106.69, 105.26, 93.51, 88.04, 55.81. IR (cm^{-1}) 3310 (NH str.), 3002 (CH str.), 2358 (alkyne), 1627 (C=N), 1571 (C=C), 1181 (C-O). HRMS (ES^+) Calculated for $C_{14}H_{12}N_2BrO$ $[M + H]^+$: 303.0133, found 303.0147.

3-(Phenylethynyl)-5-((trimethylsilyl)ethynyl)pyridin-2-amine (5-13)

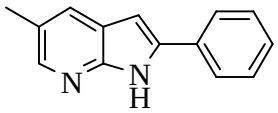


A yellowish solid (1.326 g, 85%). Melting point: 155 – 158 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 1.9, 1H), 7.71 (d, *J* = 2.1, 1H), 7.57 – 7.46 (m, 2H), 7.37 (dd, *J* = 9.6, 6.1, 3H), 5.34 (d, *J* = 23.2, 2H), 0.26 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.79, 151.11, 142.72, 131.56, 128.89, 128.53, 122.35, 109.63, 102.85, 101.84, 95.90, 94.99, 83.38, 0.01. IR (cm^{-1}) 3283 (NH str.), 2956 (CH str.), 2144 (alkyne), 1625 (C=N), 1583 (C=C). HRMS (ES^+) Calculated for $C_{14}H_{12}N_2BrO$ $[M + H]^+$: 291.2238 , found 291.2237.

General methodology for ring closing with TFAA/TFA mixture

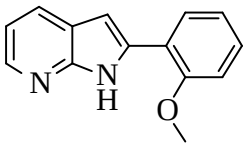
The corresponding 2-amino-3ethynylpyridine derivatives **5-11a-o** were dissolved in acetonitrile. To the resulting solution was added trifluroacetic acid (1 eq) in one portion followed by the addition of trifluoroacetic anhydride (1.3 eq) dropwise. The resulting mixture was then heated to 100 °C for 8 hours and was allowed to cool to room temperature. The solvent was then removed on a rotary evaporator and the resulting crude material was re-dissolved in dichloromethane and washed with aqueous sodium carbonate (10%). Purification by flash silica using ethyl acetate/hexane mixture (10 – 50%) gave title compounds **5-18a-o** in good yields.

5-Methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (5-17)



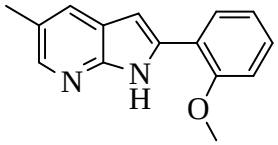
A cream white solid[23] (86%). ^{1}H NMR (500 MHz, DMSO) δ 11.98 (s, 1H), 8.07 (d, *J* = 1.3, 1H), 7.93 (d, *J* = 7.5, 2H), 7.72 (s, 1H), 7.46 (t, *J* = 7.7, 2H), 7.34 (t, *J* = 7.4, 1H), 6.84 (d, *J* = 1.8, 1H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 148.33, 143.62, 138.25, 131.71, 128.84, 127.83, 127.56, 125.19, 124.37, 120.73, 96.49, 18.09.

2-(2-Methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5-18a)



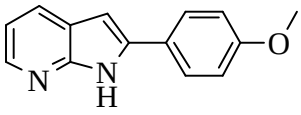
A cream white solid (0.1236 g, 92%). Melting point: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.30 – 8.20 (m, 1H), 7.93 – 7.87 (m, 1H), 7.84 (dd, *J* = 7.7, 1.5, 1H), 7.36 – 7.27 (m, 1H), 7.12 – 6.98 (m, 3H), 6.84 (d, *J* = 1.6, 1H), 3.98 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.08, 148.60, 142.91, 136.27, 129.31, 128.23, 128.04, 121.46, 120.66, 120.05, 116.14, 111.91, 98.09, 55.76. IR (cm^{-1}) 3234 (NH str.), 2933 (CH str.), 1626 (C=N), 1578 (C=C), 1179 (C-O). HRMS (ES^+) Calculated for $C_{14}H_{13}N_2O$ $[M + H]^+$: 225.1028, found 225.1042.

2-(2-Methoxyphenyl)-5-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (5-18b)



A cream white solid (0.1001 g, 94%). Melting point: 169 – 171 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.10 (s, 1H), 7.83 (dd, *J* = 7.8, 1.6, 1H), 7.69 (s, 1H), 7.33 – 7.26 (m, 1H), 7.05 (ddd, *J* = 13.7, 10.3, 4.6, 2H), 6.75 (d, *J* = 2.0, 1H), 3.98 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.99, 147.26, 143.95, 136.31, 129.14, 128.10, 127.97, 125.04, 121.45, 120.41, 120.14, 111.91, 97.37, 55.75, 18.60. IR (cm^{-1}) 3240 (NH str.), 2981 (CH str.), 1624 (C=N), 1579 (C=C), 1178 (C-O). HRMS (ES^+) Calculated for $C_{15}H_{15}N_2O$ $[M + H]^+$: 239.1184, found 269.1190.

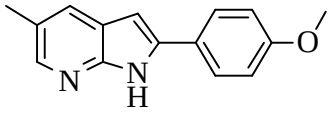
2-(4-Methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5-18c)



A cream white solid (0.1542 g, 88%). Melting point: 182 – 184 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.35 (s, 1H), 8.25 (d, *J* = 3.3, 1H), 7.92 (d, *J* = 7.7, 1H), 7.82 (d, *J* = 8.8, 2H), 7.15 – 6.97 (m, 3H), 6.67 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.83, 149.92,

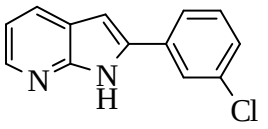
141.64, 139.57, 128.25, 127.21, 125.15, 122.56, 116.06, 114.52, 96.24, 55.44. IR (cm^{-1}) 3281 (NH str.), 2986 (CH str.), 1671 (C=N), 1594 (C=C), 1176 (C-O). HRMS (ES^+) Calculated for $C_{14}H_{13}N_2O$ $[M + H]^+$: 225.1028, found 225.1035.

2-(4-Methoxyphenyl)-5-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (5-18d)



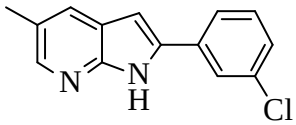
A cream white solid (0.1011 g, 85%). Melting point: 245 – 247 °C. ^1H NMR (500 MHz, MeOD) δ 7.99 (s, 1H), 7.78 (d, *J* = 8.8, 2H), 7.75 (s, 1H), 7.04 (d, *J* = 8.8, 2H), 6.64 (s, 1H), 3.87 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 161.32, 149.06, 143.26, 140.97, 129.54, 129.51, 127.96, 126.28, 126.05, 115.41, 96.61, 55.83, 18.50. IR (cm^{-1}) 3298 (NH str.), 2972 (CH str.), 1635 (C=N), 1575 (C=C), 1168 (C-O). HRMS (ES^+) Calculated for $C_{15}H_{15}N_2O$ $[M + H]^+$: 239.1184, found 239.1190.

2-(3-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5-18e)



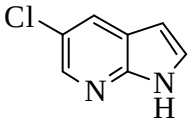
A cream white solid (0.08213 g, 81%). Melting point: 205 – 207 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 11.82 (s, 1H), 8.37 (s, 1H), 7.98 (d, *J* = 7.9, 1H), 7.86 (s, 1H), 7.72 (d, *J* = 7.5, 1H), 7.44 (t, *J* = 7.9, 1H), 7.37 (d, *J* = 7.8, 1H), 7.14 (s, 1H), 6.82 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.76, 143.05, 137.60, 135.14, 134.05, 130.36, 129.12, 128.18, 125.73, 123.79, 122.03, 116.56, 98.53. IR (cm^{-1}) 3255 (NH str.), 2987 (CH str.), 1631 (C=N), 1588 (C=C). HRMS (ES^+) Calculated for $C_{13}H_{10}N_2Cl$ $[M + H]^+$: 229.0533, found 229.0536.

2-(3-Chlorophenyl)-5-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (5-18f)



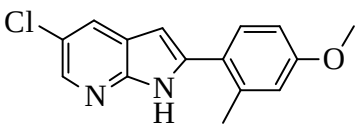
A cream white solid (0.1012 g, 82%). Melting point: 239 – 242 °C. ^1H NMR (500 MHz, DMSO) δ 12.07 (s, 1H), 8.10 (s, 1H), 8.03 (s, 1H), 7.90 (d, *J* = 7.7, 1H), 7.75 (s, 1H), 7.48 (t, *J* = 7.6, 1H), 7.39 (d, *J* = 7.8, 1H), 6.97 (s, 1H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 148.34, 144.28, 136.55, 133.85, 133.80, 130.69, 127.90, 127.46, 124.75, 124.63, 123.76, 120.52, 97.78, 18.07. IR (cm^{-1}) 3347 (NH str.), 2947 (CH str.), 1630 (C=N), 1587 (C=C). HRMS (ES^+) Calculated for $C_{14}H_{12}N_2Cl$ $[M + H]^+$: 243.0689, found 243.0697.

5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine (5-18g)



A cream white solid[39] (0.1032 g, 84%). ^1H NMR (300 MHz, $CDCl_3$) δ 10.89 (s, 1H), 8.29 (d, *J* = 2.0, 1H), 7.94 (d, *J* = 2.0, 1H), 7.46 – 7.35 (m, 1H), 6.62 – 6.24 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.94, 141.20, 128.27, 126.86, 123.80, 121.28, 100.59. IR (cm^{-1}) 3288 (NH str.), 2969 (CH str.), 1629 (C=N), 1553 (C=C).

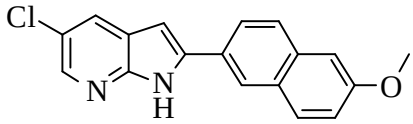
5-Chloro-2-(4-methoxy-2-methylphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5-18h)



A yellow solid (0.08109 g, 80%). Melting point: 209 – 211 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.10 (s, 1H), 7.88 (s, 1H), 7.47 (d, *J* = 8.2, 1H), 6.89 (s, 2H), 6.44 (s, 1H), 3.88 (s, 3H),

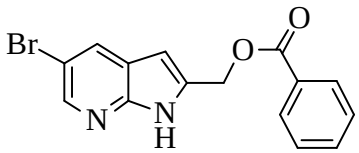
2.50 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.87, 147.00, 140.74, 140.15, 137.90, 130.45, 127.34, 124.29, 123.95, 122.37, 116.68, 111.72, 99.84, 55.36, 21.28. IR (cm^{-1}) 3210 (NH str.), 2989 (CH str.), 1637 (C=N), 1571 (C=C), 1182 (C-O). HRMS (ES^+) Calculated for $C_{15}H_{14}N_2ClO$ $[M + H]^+$: 273.0795, found 273.0803.

5-Chloro-2-(6-methoxynaphthalen-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (5-18i)



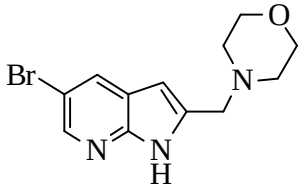
A yellow solid (0.1125 g, 82%). Melting point: 302 – 305 °C. ^{1}H NMR (500 MHz, DMSO) δ 13.71 (s, 1H), 12.44 (s, 1H), 8.45 (s, 1H), 8.20 (s, 1H), 8.09 – 8.01 (m, 2H), 7.97 (d, *J* = 8.6, 1H), 7.92 (d, *J* = 8.5, 1H), 7.86 (d, *J* = 8.8, 1H), 7.38 (s, 1H), 7.23 (d, *J* = 8.9, 1H), 3.94 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 157.82, 148.07, 143.37, 140.62, 140.56, 134.14, 129.68, 128.40, 127.38, 126.61, 126.45, 126.24, 124.15, 124.12, 122.76, 122.09, 119.32, 106.10, 96.79, 55.28. IR (cm^{-1}) 3298 (NH str.), 3006 (CH str.), 1638 (C=N), 1573 (C=C), 1179 (C-O). HRMS (ES^+) Calculated for $C_{18}H_{14}N_2ClO$ $[M + H]^+$: 309.0795, found 309.0805.

(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methyl benzoate (5-18j)



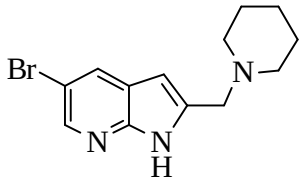
A cream white solid (0.4211 g, 83%). Melting point: 181 – 184 °C. ^{1}H NMR (500 MHz, MeOD) δ 8.33 (s, 1H), 8.27 (d, *J* = 2.2, 1H), 8.15 (d, *J* = 2.2, 1H), 8.10 – 8.07 (m, 2H), 7.64 (t, *J* = 7.5, 1H), 7.50 (t, *J* = 7.8, 2H), 6.60 (s, 1H), 5.52 (s, 2H). ^{13}C NMR (126 MHz, MeOD) δ 167.67, 148.54, 144.41, 137.76, 134.49, 132.25, 131.11, 130.77, 130.71, 129.68, 123.83, 112.41, 101.66, 60.78. IR (cm^{-1}) 3368 (NH str.), 3000 (CH str.), 1605 (C=N), 1559 (C=C), 1164 (C-O). HRMS (ES^+) Calculated for $C_{15}H_{12}N_2BrO_2$ $[M + H]^+$: 331.0082, found 331.0100.

4-((5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methyl)morpholine (5-18k)



A cream white solid (0.159 g, 79%). Melting point: 189 – 192 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.21 (s, 1H), 8.37 (d, *J* = 2.1, 1H), 7.97 (d, *J* = 2.0, 1H), 6.28 (s, 1H), 3.78 – 3.70 (m, 6H), 2.59 – 2.44 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.70, 142.96, 138.67, 130.56, 123.04, 111.75, 99.65, 67.19, 56.72, 54.07. IR (cm^{-1}) 3223 (NH str.), 2969 (CH str.), 1640 (C=N), 1573 (C=C), 1140 (C-O). HRMS (ES^+) Calculated for $C_{12}H_{15}N_3BrO$ $[M + H]^+$: 296.0398, found 296.0401.

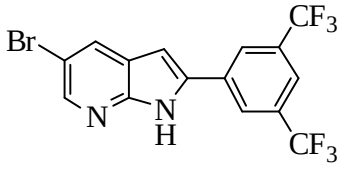
5-Bromo-2-(piperidin-1-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5-18l)



A cream white solid (0.1131 g, 83%). Melting point: 194 – 195 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.35 (d, *J* = 2.1, 1H), 7.94 (d, *J* = 2.0, 1H), 6.23 (s, 1H), 3.65 (s, 2H), 2.43 – 2.38 (m, 4H), 1.66 – 1.53 (m, 4H), 1.46 (d, *J* = 4.9, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.50, 142.89, 139.93, 130.25, 123.12, 111.74, 98.93, 57.02, 55.11, 26.28, 24.55. IR (cm^{-1}) 3217 (NH str.), 2989 (CH str.), 1631 (C=N),

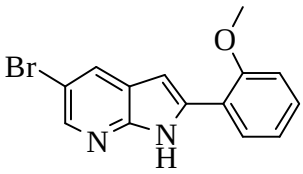
1572 (C=C). HRMS (ES^+) Calculated for $C_{13}H_{13}N_3Br$ $[M + H]^+$: 294.0606, found 294.0621.

2-(3,5-bis(Trifluoromethyl)phenyl)-5-bromo-1H-pyrrolo[2,3-b]pyridine (5-18m)



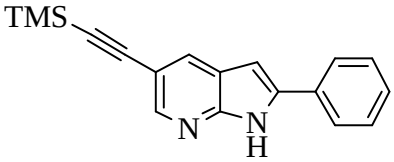
A white solid (0.1009 g, 78%). Melting point: 251 – 253 °C. ^1H NMR (500 MHz, Acetone) δ 11.69 (s, 1H), 8.60 (s, 2H), 8.33 (d, *J* = 2.2, 1H), 8.21 (d, *J* = 2.2, 1H), 8.03 (s, 1H), 7.30 (s, 1H), 6.43 (s, 1H). ^{13}C NMR (126 MHz, Acetone) δ 149.39, 145.63, 137.75, 134.97, 132.78, 131.55, 126.75, 126.72, 125.47, 123.56, 123.30, 122.19, 112.87, 100.82. IR (cm^{-1}) 3293 (NH str.), 2952 (CH str.), 1641 (C=N), 1576 (C=C). HRMS (ES^+) Calculated for $C_{15}H_8N_2BrF_6$ $[M + H]^+$: 408.9775, found 408.9764.

5-Bromo-2-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine (5-18n)



A cream white solid (0.1069, 80%). Melting point: 196 – 197 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.30 (d, *J* = 1.7, 1H), 8.02 (d, *J* = 1.6, 1H), 7.84 (dd, *J* = 7.8, 1.6, 1H), 7.43 – 7.32 (m, 1H), 7.17 – 7.02 (m, 2H), 6.78 (d, *J* = 2.1, 1H), 4.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.08, 146.82, 143.27, 137.88, 129.87, 129.80, 128.24, 122.21, 121.55, 119.34, 111.96, 97.29, 55.81. IR (cm^{-1}) 3229 (NH str.), 2955 (CH str.), 1624 (C=N), 1576 (C=C), 1160 (C-O). HRMS (ES^+) Calculated for $C_{14}H_{12}N_2BrO$ $[M + H]^+$: 303.0133, found 303.0146.

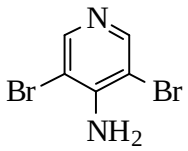
2-Phenyl-5-((trimethylsilyl)ethynyl)-1*H*-pyrrolo[2,3-*b*]pyridine (5-18o)



A cream white solid (0.4236 g, 91%).Melting point: 255 – 258 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 11.56 (s, 1H), 8.40 (d, *J* = 1.7, 1H), 8.05 (d, *J* = 1.6, 1H), 7.85 – 7.76 (m, 2H), 7.53 (t, *J* = 7.7, 2H), 7.47 – 7.38 (m, 1H), 6.75 (d, *J* = 2.0, 1H), 0.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.74, 146.08, 140.24, 131.93, 131.78, 129.19, 128.64, 125.75, 121.46, 112.42, 103.65, 97.73, 94.57, 0.06. IR (cm^{-1}) 3249 (NH str.), 2957 (CH str.), 1609 (C=N), 1586 (C=C). HRMS (ES^+) Calculated for $C_{18}H_{19}N_2Si$ $[M + H]^+$: 291.1318, found 291.1327.

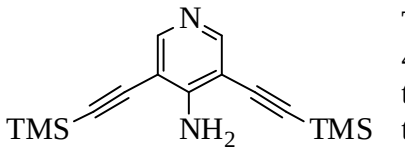
8.5 Experimental to Chapter 6

3,5-Dibromopyridin-4-amine (6-17)



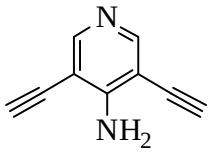
A mixture of 4-aminopyridine (5.001 g, 0.0532 mol) and *N*-bromosuccinimide (NBS) (23.668 g, 0.0133 mol) in carbon tetrachloride (40 ml) was covered with aluminium foil and stirred under a nitrogen atmosphere for 24 hours. After this time, the solvent was removed under reduced pressuere and the resulting cream white solid was purified by column chromatography using 50% EtOAc/Hexane. This gave **6-17** as a cream white solid[25] (12.00 g, 95%) with recovery of starting material and mono brominated product. ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 2H), 5.08 (s, 2H).

3,5-*bis*((Trimethylsilyl)ethynyl)pyridin-4-amine (6-19)



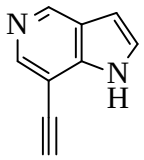
To a mixture of 4-amino-2,6-dibromopyridine (**6-17**) (1.061 g, 4.21 mmol), copper (I) iodide (0.03208 g, 0.168 mmol), trimethylsilylacetylene (2.068 g, 2.95 ml, 0.0119 mol) and triethylamine (5.650 g, 7.80 ml, 0.0550 mol) in tetrahydrofuran was added in one portion $Pd(PPh_3)_4$ (0.1947 g, 0.168 mmol). The resulting reaction mixture was heated at 65 °C for 8 hours after which, it was allowed to cool to room temperature, was quenched with saturated aqueous ammonium chloride and was extracted with dichloromethane. The combined rganic layers were dried over magnesium sulfate, was filtered through celite and the excess solvent was removed under reduced pressure. Purification by column chromatography of the product gave 3,5-bis((trimethylsilyl)ethynyl)pyridin-4-amine (**6-19**) as a cream white solid (1.050 g, 84%). Melting point: 123 – 125 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 2H), 5.24 (s, 2H), 0.34 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.38, 151.82, 104.02, 103.62, 97.97, 0.19. IR (cm^{-1}) 3429 (NH str.), 2959 (CH str.), 2144 (alkyne), 1618 (C=N), 1570 (C=C). HRMS (ES^+) Calculated for $C_{15}H_{23}N_2Si_2$ $[M + H]^+$: 287.1400, found 278.1408.

3,5-Diethynylpyridin-4-amine (6-20)



To a solution of 2,6-bis((trimethylsilyl)ethynyl)pyridin-4-amine (**6-19**) (0.2310 g, 0.806 mmol) in methanol (10 ml) was added potassium fluoride (0.14505 g, 2.42 mmol) in one portion. The resulting mixture was stirred at room temperature for 14 hours. Methanol was then removed under reduced pressure and the resulting brown solid was taken into water, was basified with saturated aqueous sodium carbonate and was extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate and concentrated under a reduced pressure to give a brownish solid. The solid was purified by column chromatography to give 3,5-diethynylpyridin-4-amine (**6-20**) (0.1036 g, 90%) as a white solid. Melting point: 99 – 102 °C. ^{1}H NMR (300 MHz, MeOD) δ 8.01 (s, 2H), 3.88 (s, 2H). ^{13}C NMR (75 MHz, MeOD) δ 155.76, 150.88, 102.96, 86.07, 75.75. IR (cm^{-1}) 3311 (NH str.), 2986 (CH str.), 2169 (alkyne), 1605 (C=N), 1568 (C=C). HRMS (ES^+) Calculated for $C_9H_7N_2$ $[M + H]^+$: 143.0609, found 143.0618.

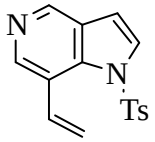
7-Ethynyl-1*H*-pyrrolo[3,2-*c*]pyridine (6-21)



To a solution of potassium hydride (0.1853 g, 4.52 mmol) in NMP (5 ml) at 0 °C was added slowly the solution of 3,5-diethynylpyridin-4-amine (**6-20**) (0.2141 g, 1.51 mmol) in NMP. After the addition was complete, the temperature was allowed to warm to room temperature and stirred at this temperature for 5 hours. The reaction mixture was quenched with water and was extracted with ether. The combined ether extracts were washed with water, were dried over magnesium sulfate and were filtered through celite. The ether was removed on a rotary evaporator to give a brown solid. The resulting brown solid was purified by column chromatography to give 7-ethynyl-5-azaindole (**6-21**) (0.18201 g, 85%) as white solid. Melting point: 202 – 204 °C. ^{1}H NMR (300 MHz, MeOD) δ 8.59 (s, 1H), 8.07 (s, 1H), 7.24 (d, *J* = 3.3, 1H), 6.51 (d, *J* = 3.3, 1H), 3.81 (s, 1H). ^{13}C NMR (75

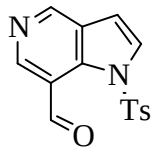
MHz, MeOD) δ 144.56, 144.49, 142.66, 129.48, 126.99, 105.52, 103.86, 86.37, 78.85. IR (cm^{-1}) 3268 (NH str.), 2963 (CH str.), 2359 (alkyne), 1611 (C=N), 1581 (C=C). HRMS (ES^+) Calculated for $C_9H_7N_2$ $[M + H]^+$: 143.0613, found 143.0613.

1-Tosyl-7-vinyl-1*H*-pyrrolo[3,2-*c*]pyridine (6-24)



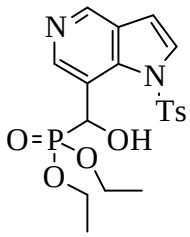
Sodium hydride (23.1 mmol, 0.5539 g) was added to a solution of 7-vinyl-5-azaindole (**6-23**) (7.69 mmol, 1.108 g) in THF (70 ml) followed by the addition of tosyl chloride (11.5 mmol, 2.192 g). The reaction mixture was then stirred at room temperature for 24 hours, was quenched with saturated aqueous ammonium chloride and was extracted with dichloromethane. The combined organic fractions were dried over magnesium sulfate, were filtered through a pad of celite and the excess solvent was removed on a rotary evaporator. The resulting solid was purified by flash chromatography using 30% (EtOAc/Hexane) to yield 5-azaindole derivative **6-24** in 70% yield (1.569 g) as a cream white solid. Melting point: 135 – 137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.42 (s, 1H), 8.04 (d, *J* = 3.6, 1H), 7.71 (d, *J* = 8.0, 2H), 7.46 (dd, *J* = 17.2, 11.0, 1H), 7.21 (d, *J* = 8.1, 2H), 7.14 (d, *J* = 3.6, 1H), 5.49 (dd, *J* = 21.5, 14.1, 2H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.34, 142.41, 140.33, 138.98, 136.50, 134.63, 134.45, 133.97, 130.72, 129.37, 127.73, 126.24, 125.10, 123.08, 108.07, 21.98. IR (cm^{-1}) 2966 (CH str.), 1626 (C=N), 1541 (C=C). HRMS (ES^+) Calculated for $C_{16}H_{15}N_2O_2S$ $[M + H]^+$: 299.0854, found 299.0872.

1-Tosyl-1*H*-pyrrolo[3,2-*c*]pyridine-7-carbaldehyde (6-26)



To a solution of the protected 5-azaindole **6-24** (4.95 mmol, 1.477 g) in a mixture of 1,4-dioxane (26 ml) and water (18 ml) was added dropwise osmium oxide solution in water (0.0990 mmol, 2.25 ml) followed by the addition of sodium periodate (14.9 mmol, 3.178 g) in one portion. The resulting reaction mixture was then stirred at room temperature for 10 h. After this time, the solvent was removed under reduced pressure, the resulting solid was redissolved in water and extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered through silica and excess solvent was removed on a rotary evaporator to give a cream white solid. The solid was purified by flash chromatography using 10% MeOH/EtOAc to give 1-tosyl-1*H*-pyrrolo[3,2-c]pyridine-7-carbaldehyde (**6-26**) as a white solid (1.231 g, 83%). Melting point: 161 – 164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.81 (s, 1H), 9.02 (s, 1H), 8.78 (d, *J* = 22.3, 1H), 7.80 (d, *J* = 3.8, 1H), 7.57 (d, *J* = 8.4, 2H), 7.25 (d, *J* = 8.2, 2H), 6.91 (d, *J* = 3.8, 1H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.58, 148.44, 146.65, 145.18, 137.33, 134.23, 130.67, 128.86, 127.20, 120.38, 108.41, 21.96. IR (cm^{-1}) 2969 (CH str.), 1682 (C=O), 1618 (C=N), 1569 (C=C). HRMS (ES^+) Calculated for $C_{15}H_{13}N_2O_3S$ $[M + H]^+$: 301.0647, found 301.0654.

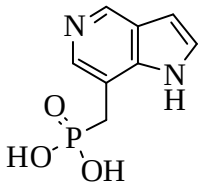
Diethyl (hydroxy(1-tosyl-1*H*-pyrrolo[3,2-*c*]pyridin-7-yl)methyl)phosphonate (6-28)



To a solution of 1-tosyl-1*H*-5-azaindole-7-carbaldehyde (**6-26**) (20.09 mg, 0.0697 mmol) in dichloromethane (5 ml) was added diethyl phosphonate (0.01923 g, 0.139 mmol) in one portion followed by the addition of triethylamine (7.0536 mg, 0.0697 mmol) dropwise. The reaction mixture was stirred at room temperature for 24 hours. After this time, the solvent was

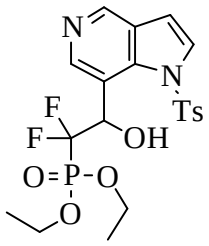
removed and the resulting oil was purified with 10% MeOH/EtOAc to give diethyl (hydroxy(1-tosyl-1*H*-pyrrolo[3,2-c]pyridin-7-yl)methyl)phosphonate (**6-28**) as a white solid (0.02703 g, 88%). Melting point: 162 – 165 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (d, *J* = 1.7, 1H), 8.80 (s, 1H), 7.75 (d, *J* = 3.8, 1H), 7.69 (d, *J* = 8.4, 2H), 7.23 (d, *J* = 8.2, 2H), 6.78 (d, *J* = 3.8, 1H), 6.56 (d, *J* = 14.7, 1H), 4.18 – 3.95 (m, 4H), 2.33 (s, 3H), 1.20 (m, 6H). ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.42. ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.58, 143.76, 137.87, 137.76, 134.86, 130.87, 130.21, 128.52, 126.91, 120.30, 107.77, 66.24, 64.08, 63.68, 63.59, 63.15, 63.05, 21.59, 16.38, 16.31. IR (cm^{-1}) 3401 (OH str.), 2989 (CH str.), 1603 (C=N), 1541 (C=C, 1175 (C-O). HRMS (ES^+) Calculated for $C_{19}H_{24}N_2O_6SP$ $[M + H]^+$: 439.1093, found 439.1087.

((1*H*-Pyrrolo[3,2-*c*]pyridin-7-yl)methyl)phosphonic acid (6-31)



To a solution of diethyl (hydroxy(1-tosyl-1*H*-pyrrolo[3,2-c]pyridin-7-yl)methyl)phosphonate (**6-28**)(0.1437 g, 0.328 mmol) in THF under an argon atmosphere was added tetrabutylammonium fluoride (0.43 ml, 0.426 mmol) dropwise. After the addition was complete, the resulting reaction mixture was heated to 60 °C for 3 hours. After this time, the solvent was removed under reduced pressure and the resulting oil was purified by flash chromatography to give ((1*H*-pyrrolo[3,2-c]pyridin-7-yl)methyl)phosphonic acid (**6-31**) as a white solid (0.04901 g, 70%). Melting point: 161 – 163 °C. ^{1}H NMR (500 MHz, MeOD) δ 8.82 (d, *J* = 1.7, 1H), 8.16 (d, *J* = 1.9, 1H), 7.45 (d, *J* = 3.6, 1H), 6.73 (d, *J* = 3.6, 1H), 5.74 (d, *J* = 48.1, 2H). ^{13}C NMR (126 MHz, MeOD) δ 144.64, 144.62, 139.97, 139.92, 128.38, 126.95, 126.94, 117.32, 117.18, 102.65, 81.81, 80.52. IR (cm^{-1}) 3329 (NH str.), 3005 (CH str.), 1601 (C=N), 1592 (C=C). HRMS (ES^+) Calculated for $C_8H_9N_2O_3P$ $[M + H]^+$: 213.0379, found 213.0317.

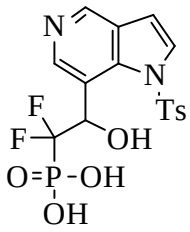
Diethyl (1,1-difluoro-2-hydroxy-2-(1-tosyl-1*H*-pyrrolo[3,2-*c*]pyridin-7-yl)ethyl)phosphonate (6-34)



The solution of diethyl bromo(difluoro)methylphosphonate (**6-32**) (0.2000 g, 0.746 mmol) in THF was cooled to -78 °C under an argon atmosphere. To this was added a solution of *iso*propylmagnesium chloride (0.43 ml, 0.746 mmol) prepared by reacting magnesium with *iso*propyl chloride in THF. The reaction mixture was stirred for a further 5 minutes before being allowed to warm to -25°C over an hour. After this time, the reaction mixture was cooled to -78 °C and allowed to stay at this temperature for 10 minutes before the solution of 1-tosyl-1*H*-pyrrolo[3,2-c]pyridine-7-carbaldehyde (**6-26**) (0.1790 g, 0.597 mmol) in THF was added dropwise at the same temperature. The reaction mixture was allowed to warm to room temperature over 3 hours and was quenched with saturated aqueous ammonium chloride. The resulting mixture was extracted with ethyl acetate. The combined organic fractions were dried over magnesium sulfate, were filtered over celite and the solvent was removed on a rotary evaporator. The resulting oil was subjected to flash chromatography using 30% EtOAc/hexane to 100% ethyl acetate to give diethyl (1,1-difluoro-2-hydroxy-2-(1-tosyl-1*H*-pyrrolo[3,2-c]pyridin-7-yl)ethyl)phosphonate (**6-34**) (0.2213 g, 76%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (d, *J* = 1.9, 1H), 8.79 (s, 1H), 7.75 (d, *J* = 3.8, 1H), 7.61 (d, *J* = 8.4, 2H), 7.18 (d, *J* = 8.3, 2H), 6.77 (d, *J* = 3.8, 1H), 6.72 (d, *J* = 23.9, 1H), 4.41 – 4.26 (m, 4H), 2.28 (s, 3H), 1.43 – 1.33 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.38, 146.34, 145.57, 144.32, 138.59, 134.74, 131.06,

130.18, 128.57, 126.82, 117.88, 117.81, 107.56, 67.15, 65.28, 65.23, 21.54, 16.34. ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.79 (dd, *J* = 304.5, 97.0, 1F), -125.83 (dd, *J* = 304.3, 107.2, 1F). ^{31}P NMR (202 MHz, $CDCl_3$) δ 15.07 – 13.70 (m, 1P). IR (cm^{-1}) 2998 (CH str.), 1606 (C=N), 1569 (C=C), 1173 (C-O). HRMS (ES^+) Calculated for $C_{20}H_{24}N_2O_6F_2P$ $[M + H]^+$: 489.1038, found 489.1062.

(1,1-Difluoro-2-hydroxy-2-(1-tosyl-1*H*-pyrrolo[3,2-*c*]pyridin-7-yl)ethyl)phosphonic acid (6-36)



To a solution of (1,1-difluoro-2-hydroxy-2-(1-tosyl-1*H*-pyrrolo[3,2-c]pyridin-7-yl)ethyl)phosphonate (**6-34**) (0.4361 g, 0.894 mmol) in dichloromethane at 0 °C was added trimethysilyl iodide (0.30 ml, 1.97 mmol)dropwise under argon atmosphere. The reaction was allowed to warm to room temperature and stirred for a further 12 hours. After this time, solvent and the volatiles were removed on a rotary evaporator. Toluene was then added and was removed on a rotary evaporator to remove more volatiles. The resulting oil was dissolved in acetonitrile, water was added and the mixture was stirred for 3 hours where (1,1-difluoro-2-hydroxy-2-(1-tosyl-1*H*-pyrrolo[3,2-c]pyridin-7-yl)ethyl)phosphonic acid (**6-36**) precipitated and was collected through filter paper in 56% (0.2181 g) as a cream white solid. Melting point: 243 – 243 °C. ^{1}H NMR (500 MHz, MeOD) δ 9.16 (s, 1H), 8.97 (s, 1H), 8.35 (d, *J* = 3.8, 1H), 7.93 (d, *J* = 8.3, 2H), 7.42 (d, *J* = 8.2, 2H), 7.27 (d, *J* = 3.6, 1H), 6.82 (d, *J* = 18.0, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 147.70, 143.97, 138.26, 137.33, 137.11, 134.87, 131.76, 130.95, 128.90, 126.86, 109.19, 70.30, 21.63. ^{19}F NMR (471 MHz, MeOD) δ -115.15 (dd, *J* = 299.1, 86.2, 1F), -124.07 – 125.05 (m, 1F). ^{31}P NMR (202 MHz, MeOD) δ 2.81 (t, *J* = 89.3, 1P). IR (cm^{-1}) 3429 (NH str.), 2983 (CH str.), 1615 (C=N), 1593 (C=C), 1175 (C-O). HRMS (ES^+) Calculated for $C_{16}H_{16}N_2O_6SPF_2$ $[M + H]^+$: 433.0435, found 433.0450.