Ana Sofia Branco dos Santos

Licenciada em Química Aplicada

Sustainable synthesis of heterocyclic compounds on a soluble polymer support

Dissertação para obtenção do Grau de Mestre em Química Bioorgânica

Orientador: Maria Manuel S. B. Marques, Investigadora com Agregação, FCT-UNL

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Resumo

Os compostos heterocíclicos são uma importante classe de compostos presentes em diversas moléculas com interesse medicinal incluindo fármacos e produtos naturais. Neste projeto exploraram-se duas reações catalisadas por metal de forma a sintetizar duas estruturas privilegiadas, o núcleo de indole e o núcleo de azaindole, usando como suporte um polímero solúvel.

Sendo assim este estudo foi iniciado usando como materiais de partida anilinas de forma a originar o núcleo de indole, uma vez que as anilinas são compostos de mais fácil manuseamento do que as aminopiridinas (que originam azaindoles).

O primeiro desafio envolveu a optimização de reações de PEGilação usando como parceiro de acoplamento diferentes anilinas, o que levou à síntese de diversos substratos PEGilados estando estes ligados à PEG de diversas maneiras: via ligação éster, amida e por fim éter. Assim, com este método foi possível preparar diversos substratos PEGilados com rendimentos bons a excelentes (máximo 94%).

Uma vez sintetizados os substratos, estes foram mais tarde usados numa reação em cascata envolvendo acoplamento cruzado C-N e uma reação de Heck, e diferentes condições foram testadas incluindo sistemas catalíticos, bases, solventes e tempo de reação. Depois de vários ensaios o sistema $Pd_2(dba)_3$/DavePhos/*t*-BuONa foi o que originou a estrutura indólica desejada com 82% de rendimento, usando um substrato com uma ligação éter em posição *meta*- relativamente ao grupo amina.

Foram explorados métodos alternativos tais como reações de N-arilação e Sonogashira para sintetizar derivados de indole. Para isso foram utilizados dois substratos PEGilados, um que possuía um átomo de iodo e outro que possuía um bromo. Utilizando a anilina iodada foi possível executar a reação de Sonogashira à temperatura ambiente, seguida de ciclização usando KH como base numa solução de NMP, dando origem ao indole PEGilado com 62% de rendimento.

Estas condições foram também utilizadas num derivado de aminopiridina de modo a originar o azaindole, mas esta reação necessita de mais estudos de optimização

Por fim um novo método para síntese de azaindoles 1,2-substituidos foi desenvolvido envolvendo N-arilação/Sonogashira/Ciclização dando origem a diversos azaindoles com rendimentos até 68%.

Termos Chave

Polietileno glicol; reações de acoplamento cruzado; heterociclos; reações catalisadas por paládio

Abstract

Heterocyclic compounds are an important class of compounds present in several molecules with medicinal interest. So in this project we explored two main metal-catalyzed reactions for assembling privileged structures like indole and azaindole, using a soluble polymer support. It was decided to initiate the study using anilines to afford the indole nucleus, since anilines are easier to handle then the aminopyridines (that afford azaindoles).

The first challenge involved optimization of PEGylation reaction conditions using as coupling partner different anilines, which led to the assembly of PEGylated substrates with ether, ester and amide linkers to PEG. Thus, with this method several PEGylated substrates were prepared in yields up to 94%.

Once the substrates were synthesized they were later employed in cascade C-N cross-coupling/Heck reactions and after several attempts one indole structure was obtained in 82% yield, using a substrate with an ether linker in *meta*- position relative to the amine group, as starting material and using$Pd_2(dba)_3$/DavePhos/NaO*t*Bu system.

In order to explore alternative methods to afford indole derivatives, N-arylation and Sonogashira reactions were also studied. Thus, two PEGylated substrates were used, one possessing iodine and the other bromine. Using the iodinated compound it was possible to perform the Sonogashira reaction at room temperature, followed by cyclization using KH in NMP, affording the PEGylated indole with 62% yield. These conditions were also employed in aminopyridines to afford the desired azaindole, but more optimization studies are needed.

Thus, it was possible to synthesize the desired indole structure with moderate to good yields, using two different routes: one involving a cascade C-N cross-coupling/Heck reaction and another involving N-arylation and Sonogashira reactions showing that is possible to combine these metal-catalysed reactions with a soluble polymer support.

Lastly, a new method for assembling azaindole structures was also developed involving N-arylation/Sonogashira/cyclization affording several azaindoles with yields up to 68%.

Thus, in this project we explored the use of PEG on several Pd-catalyzed reactions to improve the synthesis and functionalization of heterocyclic compounds, avoiding the side-products, laborious purifications and poor yields associated with traditional reaction conditions.

Keywords

Poly(ethyelene glycol); cross-coupling reactions; heterocycles; Pd-catalysed reactions

Table of contents

List of figures

List of schemes

List of tables

Abbreviations and symbols

Ac	Acetyl
Ar	Aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*Tert*-butyloxycarbonyl
bp	Boiling point
CDK	Cyclin-dependent kinase
COX	Cyclooxygenase
Cy	Cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DCM	Dichloromethane
DIC	*N,N'*-Diisopropylcarbodiimide
DIPEA	*N,N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DMEDA	*N,N'*- Dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EI	Electron impact
equiv.	Equivalents
Et	Ethyl
GC	Gas chromatography
IR	Infrared spectroscopy
L	Ligand
LDA	Lithium diisopropylamide
m/z	Mass-to-charge ratio
Me	Methyl
MS	Mass spectroscopy
MW	Microwaves
*n*Bu	*n*-Butyl
NMP	*N*-methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance spectroscopy
NSAID	Nonsteroidal anti-inflammatory drug
PEG	Polyethylene glycol
Ph	Phenyl

PTLC	Preparative thin-layer chromatography
rt	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetrabutylammonium iodide
*t*Bu	*Tert*-Butyl
*t*BuOH	*Tert*-butanol
TEA	Triethylamine
Tf	Triflate
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilane
TMSA	Trimethylsilylacetylene
Ts	Tosyl

NMR chart

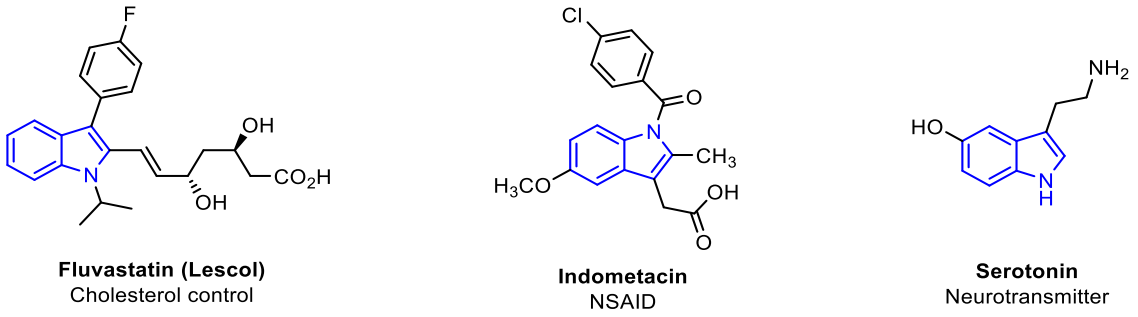
s	Singlet
d	Doublet
t	Triplet
m	Multiplet
δ	Chemical shift

I. Introduction

I.1–Indole and azaindole in medicinal chemistry

Heterocyclic compounds are important scaffolds that are present in bioactive compounds so there is an increasing need of finding new and sustainable methodologies that allow an easy access to these heterocyclic cores as well as its diverse functionalization.

Indole scaffold is a privileged structure with potential applications in the field of medicinal chemistry (**Scheme I.1**). Compounds containing the indole nucleus exist in compounds that are naturally present in our body, and when properly functionalized can exhibit a wide range of pharmacological properties including anticancer, antioxidant and anti-inflamatory activities. For instance, the non-steroidal anti-inflammatory drugs (NSAIDs), like Indometacin, constitute the most important class of therapeutic agents for the treatment of inflammatory diseases.[1]



Fluvastatin (Lescol)
Cholesterol control

Indometacin
NSAID

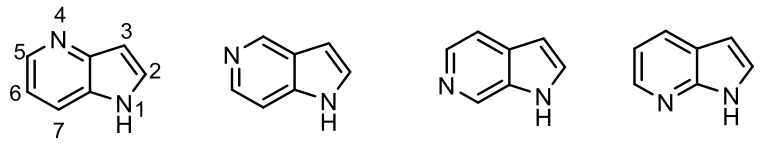
Serotonin
Neurotransmitter

Scheme I.1 - Natural and synthetic compounds containing indole nucleus

NSAIDs were widely accepted for the treatment of rheumatoid osteoarthritis, arthritis and pain since, it was discovered that they inhibit prostaglandin synthesis through COX (cyclooxygenase) inhibition. The inhibition of this enzyme (COX) can provide relief from symptoms of inflammation and pain. However, the side effects of these drugs represent a major drawback of its chronic use, involving gastric and intestinal toxicity.[2]

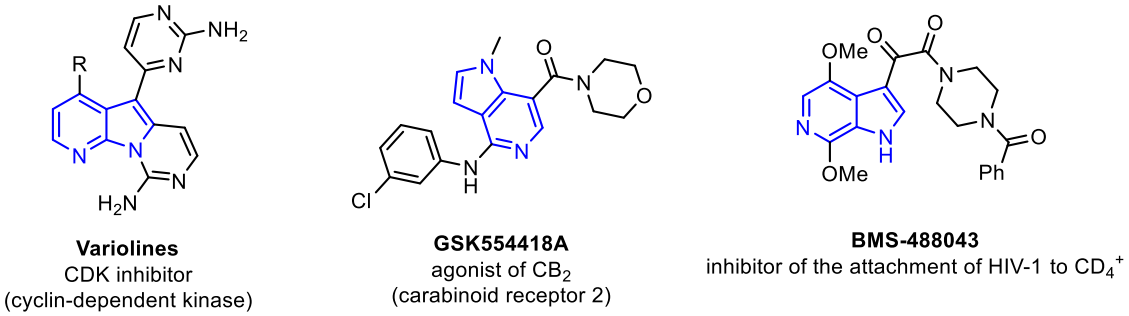
Azaindoles are bioisosteres of the indole nucleus, and are also considered as privileged structures, which have enticed the interest of the scientific community for their pharmacological properties. Substituted azaindoles are interesting scaffolds in drug discovery since, unlike other heterocycles, their properties can be modulated by changing the substitution pattern or the position of the endocyclic nitrogen.[3]

These structures are rare in nature but can be obtained from aminopyridines as starting materials,[4]similarly to indole synthesis from anilines. The existence of different isomers of this structure, allows the access to different substitution patterns depending on the aminopyridine type (**Scheme I.2**).



Scheme I.2 - Structures of 4-, 5-, 6- and 7-azaindole

Recently, several bioactive azaindole have been described, including the synthetic analogues of the natural variolins, possessing CDK (cyclin-depent kinase) inhibitory activity. Variolines, GSK554418A and BMS-488043 are representative examples of azaindole based compounds with relevant biological activity (**Scheme I.3**).[5]

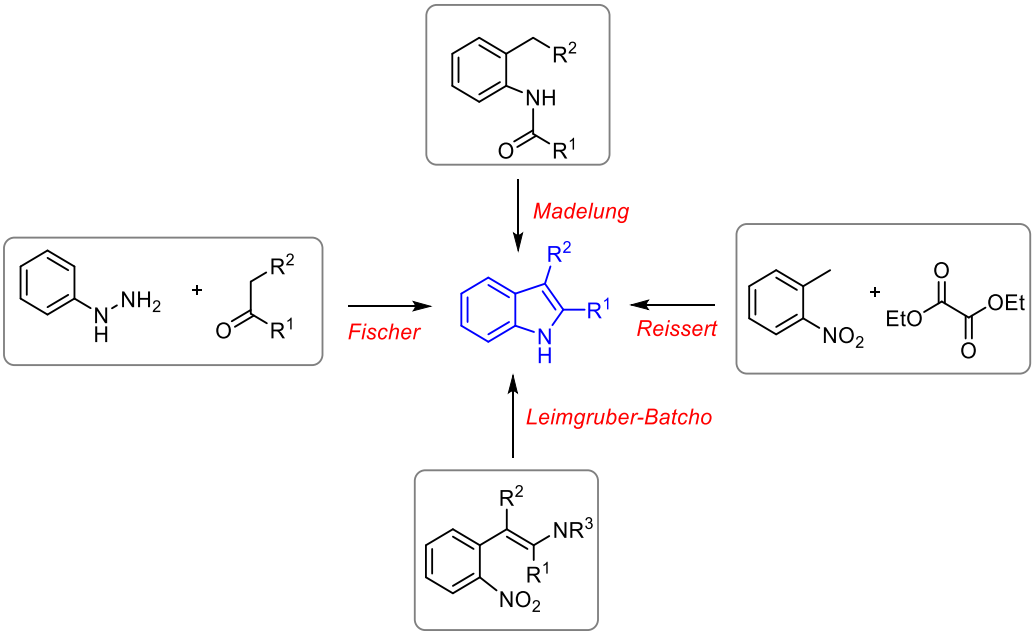


Scheme I.3 - Sctrutures of bioactive compounds containg azaindole nucleus.

I.2– Indole and azaindole synthesis

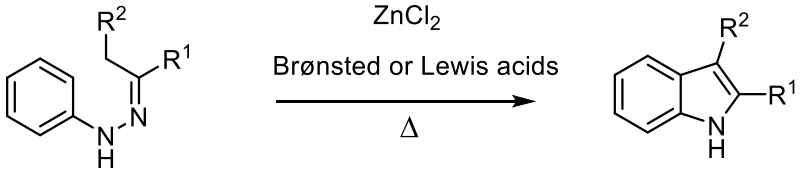
I.2.1 – Classic methods for indole synthesis

The great interest of the scientific community in the indole scaffold, and the continuous search for drugs with fewer side effects has led to an enormous development of synthetic methods. Several methods for indole synthesis using anilines, nitrobezenes or phenylhydrazines have already been reported.[6] These reactions can be further divided into two broad classes: those using transition-metal catalysis like Bartoli indole synthesis and those using classic methods, like Fischer and Mandelung indole synthesis (**Scheme I.4**).[7]



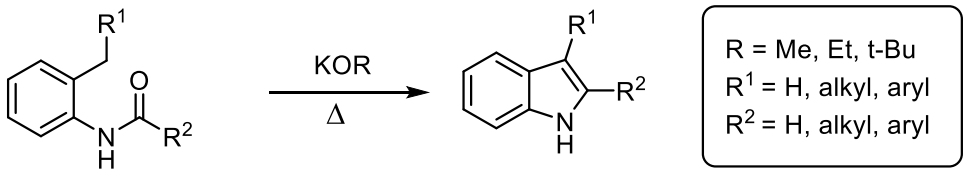
Scheme I.4 - Representation of classic methods for indole synthesis

The Fischer reaction was firstly reported in 1883 and still remains as one of the most important indole synthesis methods.[8,9] The Fischer indole synthesis is a method that relies on the condensation reaction between an arylhydrazine and a ketone or aldehyde under acidic conditions to produce the indole nucleus (**Scheme I.5**). One of the biggest drawbacks of this reaction is the small range of arylhydrazines that are commercially available, and the harsh conditions used.



Scheme I.5 - General scheme for Fisher indole synthesis

In 1912, Mandelung indole synthesis was described as an intramolecular cyclization of N-phenylamides using a strong base at high temperatures (**Scheme I.6**).[10]



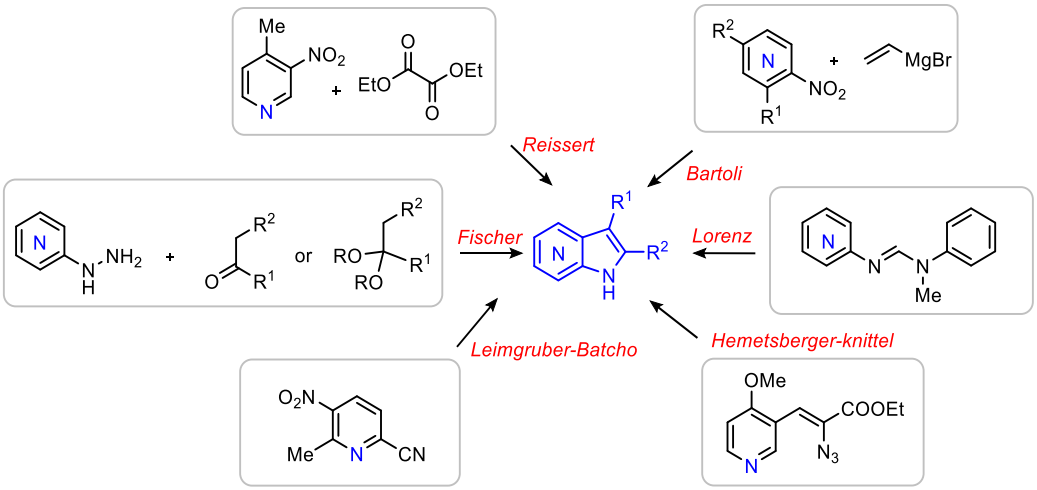
Scheme I.6 - General scheme for Mandelung indole synthesis.[10]

Several efforts have been made to improve reaction conditions by using stronger bases like sodium amide and lithium amide, which made possible for the reaction to occur at a lower temperature.

I.2.2 – Methods for azaindole synthesis

The synthetic strategy to prepare azaindoles is achieved starting from aminopyridines followed by building up the pyrrole ring. This approach parallels the indole synthesis from anilines however, due to the electron-deficient nature of pyridine ring that alters the electronic properties of the conjugate system, many classic indole synthetic methods are not as efficient or just do not work and though constitute a synthetic challenge.[11]

For example, the Fischer indole synthesis is a reliable method that uses arylhydrazones to afford indoles in high yields (**Scheme I.7**), though when applied to hydrazinylpyridines the method was ineffective.[12–14] Nevertheless, the reaction was shown to proceed using 3-hydrazinylpyridines bearing an electron-donor group, resulting in 4- and 6-azaindoles in moderate to good yields and using 2-hydrozinylpyridines to afford 7-azaindole in moderate yields.



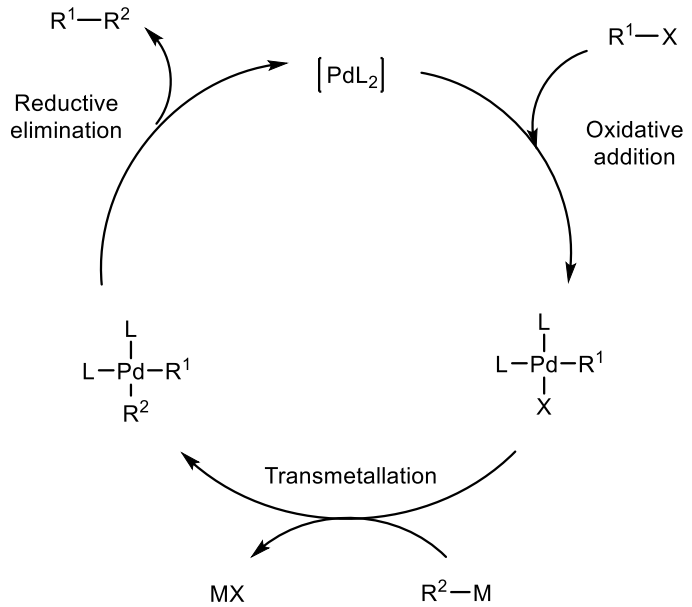
Scheme I.7 - Representation of classic methods adapted for azaindole synthesis.

Another classic method for the preparation of indoles is Bartoli indole synthesis (**Scheme I.7**). This method uses nitrobenzenes and vinyl Grignard reagents and usually works better with ortho substituted nitroarenes, as without them nucleophilic attack occurs at the nitrogen rather than at the oxygen atom of the nitro group.[15]When applied to azaindole synthesis this method requires a large excess of vinyl Grignard and only affords 4- azaindole and 6-azaindole in generally low yields.[16]

To sum up, all these classic methods have proven to have poor versatility, (e.g Reissert and Hemetsberger-knittel synthesis, are limited to few isomers, 6-azaindole and 7-azaindole, respectively) and additionally, can only afford azaindole structures in low to moderate yields.[17,18]

I.2.3 – Metal catalysed cross-coupling reactions in indole and azaindole synthesis

The use of transition metals as catalysts has revolutionized modern organic chemistry and changed the way we look at the construction of C–C, C–N, C–O and C–S bonds. The appearance of new C–C cross-coupling reactions has expanded our ability to construct complex molecules in the laboratory. Based on transition-metal catalysis, this newly acquired ability to forge carbon–carbon bonds between or within functionalized substrates provided new opportunities. Many transition metals are used for coupling reactions, including copper, nickel, iron and ruthenium, but the most explored is palladium (**Scheme I.8**).[19]

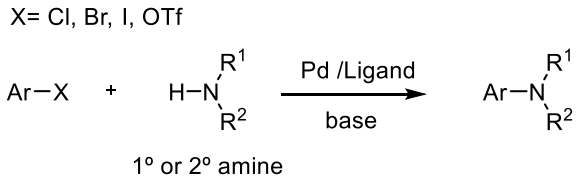


Scheme I.8 - General catalytic cycle for palladium-catalyzed cross-coupling reactions for C-C bond formation.

I.2.3.1 – Buchwald-Hartwig amination

Buchwald and Hartwig developed and studied a palladium catalysed C-N cross coupling reaction that is now known as Buchwald-Hartwig amination. This reaction uses as starting materials aryl halides and amines in the presence of a strong base to afford aryl amines.

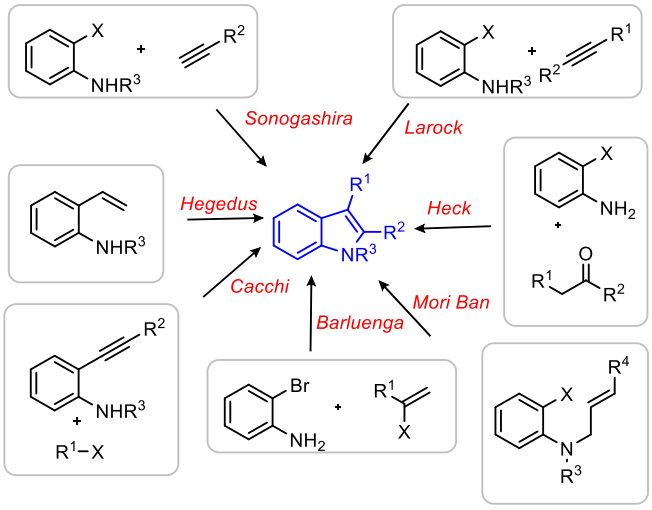
The Buchwald-Hartwig catalytic cycle includes steps similar to those known for palladium catalysed coupling reactions, which include oxidative addition of the aryl halide to the palladium specie to form a complex, addition of the amine to the complex, deprotonation and finally reductive elimination. A general representation of the Buchwald-Hartwig amination reaction is depicted in (**Scheme I.9**).[20]



SchemeI.9 - General representation of Buchwald-Hartwig amination.

I.2.3.2 – Indole synthesis mediated by transition metal catalysis

The growing importance of the indole scaffold in biological chemistry has led to an enormous development of new and improved methodologies for its preparation. Metal catalyzed cross-coupling reactions have proved to be a current alternative for the classical indolization methods, using anilines as starting materials (**Scheme I.10**).

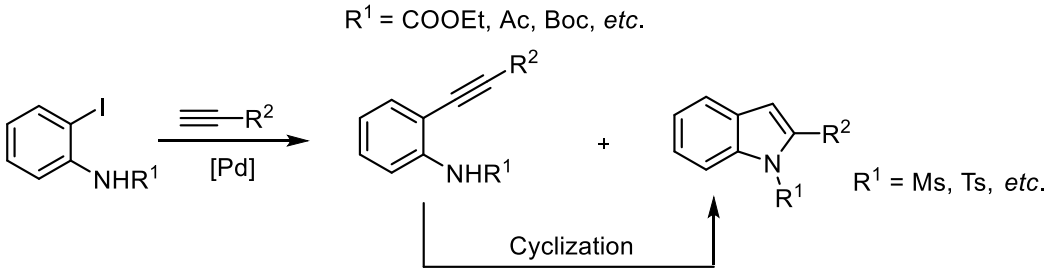


Scheme I.10 -Representation of metal-catalysed reactions for indole synthezises.

I.2.3.2.1 – Sonogashira reaction

The Sonogashira cross-coupling reaction was first reported by K. Sonogashira in 1975 and was established as a method for preparation of aromatic alkynes via palladium-catalysed coupling of terminal alkynes with aryl halides or allyl halides.[21]

In 2003 N. Suzuki and co-workers reported a one-pot indole synthesis from 2-iodoanilines and terminal alkynes using a palladium catalyst in the presence of TBAF (**Scheme I.11**).[22]



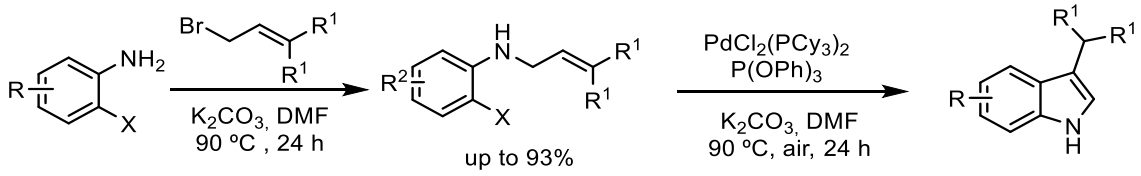
SchemeI.11 - One-pot indole synthesis from 2-iodoanilines and terminal alkynes with subsquent cyclization reaction.[22]

This group proved that TBAF could be used as both a base in the Sonogashira and also a crucial reagent in the cyclization reaction.

I.2.3.2.2 – Heck reaction

The Heck reaction is described as a palladium catalysed coupling between aryl halides and activated alkenes in the presence of a base.

H. Yang *et al*. reported, in 2013, a Pd-catalysed synthesis of indoles from 2-halo-N-allylamine under low temperature in the presence of a commercially available ligand (**Scheme I.12**).[23]



X = I, Br
R^1 = H, Me
R^2 = F, Cl, Me

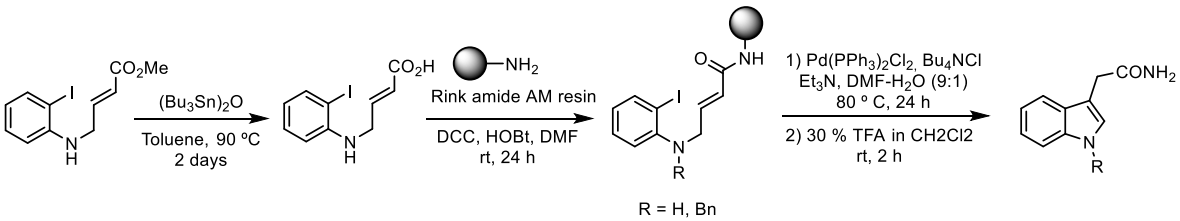
SchemeI.12 – General scheme for indoles synthesis via intramolecular Heck reaction from 2-halo-N-allylanilines.[23]

This work led to the development of a new protocol toward the synthesis of indole derivatives via intramolecular Heck reaction from 2-iodoanilines and allyl bromides, in the presence of $[PdCl_2(PCy_3)_2]$ as the catalyst and $[P(OPh)_3]$ as co-ligand.

I.2.3.2.3 – Mori Ban reaction

First reported in 1976 by Mori and Ban, this reaction consisted on the synthesis of indole derivatives by an intermolecular Heck Reaction of *ortho*-halo-N-allylanilines catalysed by a low-valence metal complex. This reaction can be applied for the synthesis of indole and indoline derivatives.[24,25]

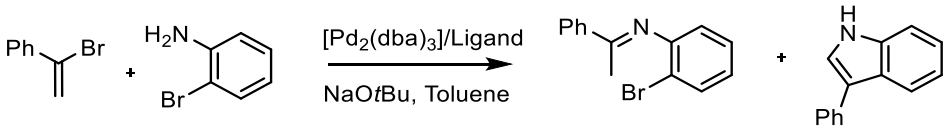
In 1997 H. Zang and co-workers reported a new solid-phase methodology for indole and benzofuran synthesis using a palladium-mediated, intramolecular Heck-type reaction, a mild and versatile method for carbon-carbon bond formation (**Scheme I.13**). Through this method it was possible to synthesize several indole derivatives in high yields.[26]



Scheme I.13–First model for sythesis of the indole derivative using solid-phase method.[26]

I.2.3.2.4 – Buchwald-Hartwig amination/Heck reaction approach

Reported in 2005 by J. Barluenga[27]*et al.* as an extension of the well-developed Buchwald-Hartwig amination, this approach described a Pd-catalysed amination of alkenyl and aryl bromides. This procedure consisted on the use of *ortho*-bromoanilines and akenyl halides in a Pd-catalysed process that involved an alkenyl amination followed by an intramolecular Heck reaction to synthesize indoles (**Scheme I.14**).



Scheme I.14 - Model reaction of ortho-bromoaniline with α-bromostyrene to investigate optimal reaction conditions for the sequential alkenyl amination/Heck cyclization.[27]

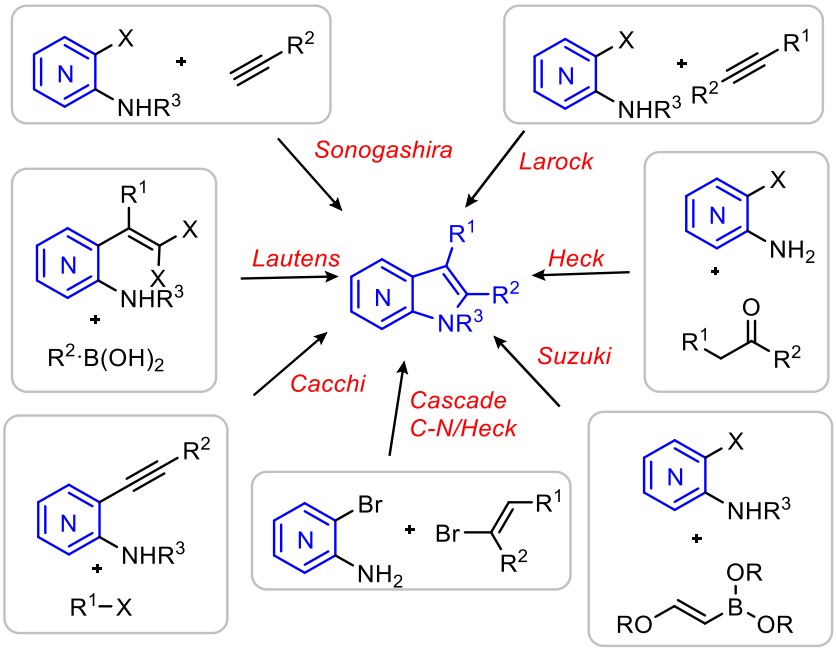
In order to optimize all reaction conditions, the relative reactivity of aryl and alkenyl bromides and chlorides towards Pd-catalysed amination was investigated. An extensive screening of ligands, bases and reaction conditions revealed that the $[Pd_2(dba)_3]$/DavePhos, NaO*t*Bu, toluene combination at 100ºC were the optimal reaction conditions to carry out the cascade process.

I.2.3.3 – Azaindole synthesis mediated by transition metal catalysis

The awarding of the 2010 Nobel prized in chemistry to E.Negishi, R.Heck and A.Suzuki underlines the importance of direct bond formation between carbon atoms in a metal-catalysed approach.[28] These methods have transformed the procedures for the construction and functionalization of a wide range of building blocks.[5]

Aminopyridines are one of the most common starting materials for azaindole synthesis, since different substitution patterns can be attained depending on the aminopyridine used.[5] Thus, functionalization of these structures is highly important; however this has proven to be a challenging task. Metal-catalysed cross-coupling reactions, which constitute a very modern and emergent topic in organic synthesis, can be highly useful for the construction and derivation of these aminopyridine-containing heterocycles.[29]

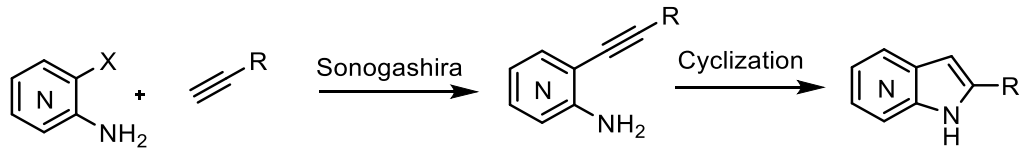
So far, several synthetic routes have been reported for the preparation of azaindoles from aminopyridines, including Sonogashira, Larock-type, Heck and Suzuki couplings; Pd-catalysed reactions, also applied for indole synthesis, such as the Larock indole synthesis and the more recent Cacchi and Lautens protocols (**Scheme I.15**).



Scheme I.15 - Representation of several metal-catalysed reactions for azaindole synthezises.

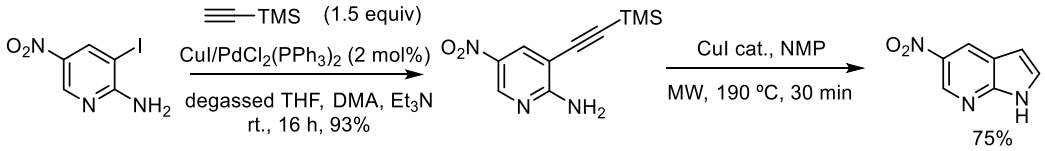
I.2.3.3.1 – Sonogashira reaction

Halo-substituted aminopyridines can be coupled with terminal alkynes by Sonogashira coupling, and this reaction is normally adopted to set up the conditions for a later ring forming step, which involves strong bases, like potassium hydride[30], or copper-mediated cyclization(**Scheme I.16**).[31]



Scheme I.16 - General scheme for azaindole synthesis by Sonogashira coupling followed by ring closing.[5]

In order to explore microwave assisted copper-mediated cyclization S. Person[32] reported the performance of several Sonogashira reactions with nitro-substituted aminopyridines. The first step involved a Sonogashira reaction of 2-amino-3-iodo-5-nitropyridine with TMSA in a THF/dimethylacetamide (DMA) mixture, followed by cyclization to the azaindole structure using catalytic CuI under microwave irradiation (**Scheme I.17**).



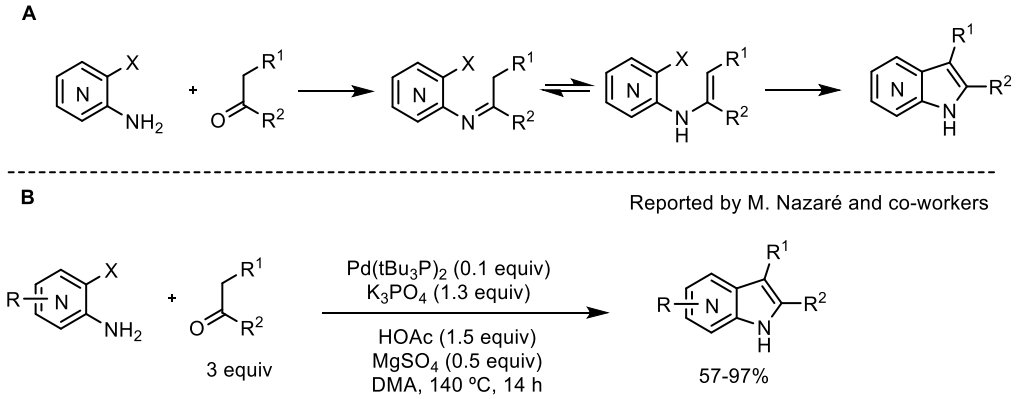
Scheme I.17 - Sonogashira mediated synthesis of 5-nitro-7-azaindole.[32]

I.2.3.3.2 – Heck- type reaction

In the 1990s the first application of the Heck reaction for the coupling of alkenes with multiple halo-substituted aminopyridines was reported. Mori[33] was the first to report the Heck cyclization as the most commonly used Heck-type coupling on aminopyridines to form azaindoles.

Azaindole synthesis by this method involves direct Pd-catalysed annulations of *ortho*-amino-halopyridines with an aldehyde or ketone through in situ enamine formation followed by Heck reaction (**Scheme I.18**; A).

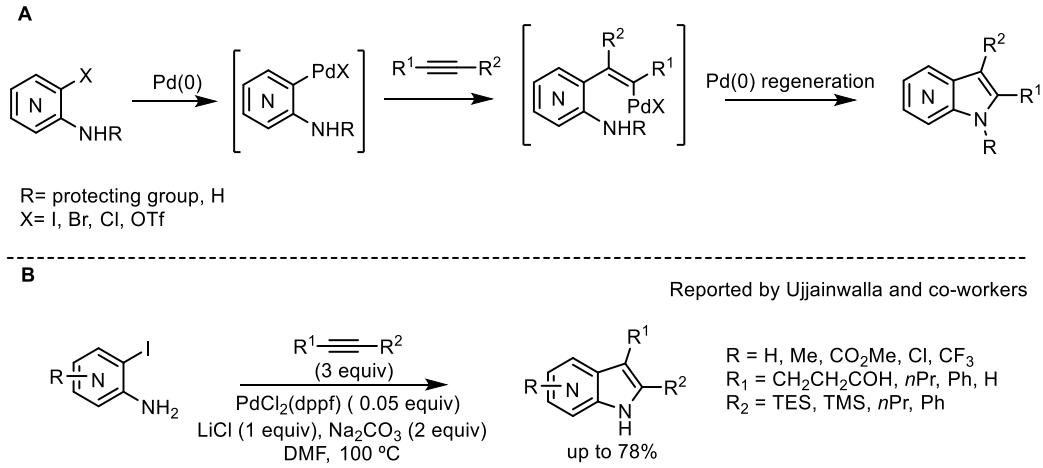
In 2004 M. Nazaré and co-workers reported a Pd-catalysed annulations of *ortho*-amino-chloropyrdines with cyclic or acyclic ketones through in situ enamine formation followed by Heck reaction. After optimization of the described method the best results were obtained with K_3PO_4, HOAc and Pd(tBu$_3$P)$_2$ in DMA at 140 °C, leading to several important azaindole derivatives (**Scheme I.18**; B)**.**[34]



Scheme I.18–General scheme for intramolecular Heck reaction with in situ enamine formation for azaindole synthesis (A) and Palladium-catalysed annulation of *ortho*-amino-chloropyridinesand ketones (B).[34]

I.2.3.3.3 – Larock type-heteroannulation

Pd- catalysed hetereoannulation of internal alkynes was first reported in 1991 by Larock[35]as a method for indole synthesis, and has been widely applied for the preparation of several azaindoles (**Scheme I.19**).



Scheme I.19 – General scheme for Larock type-hetereoannulation for azaindole synthesis (A) and regioselective Larock type-heteroannulation for 5-, 6- and 7- azaindoles synthesis (B).[36]

The mechanism for the Pd-catalysed heteroannulation for azaindole synthesis involves the following steps in the catalytic cycle: (a) reduction of Pd(II) to Pd(0) to initiate the catalytic cycle;(b) coordination of the halogen to palladium; (c) oxidative addition of aryl iodide to Pd(0); (d) coordination of alkyne to palladium and subsequent regioselective *syn*-insertion into the arylpalladium bond; (e) nitrogen displacement of the halide in the resulting vinylic palladium

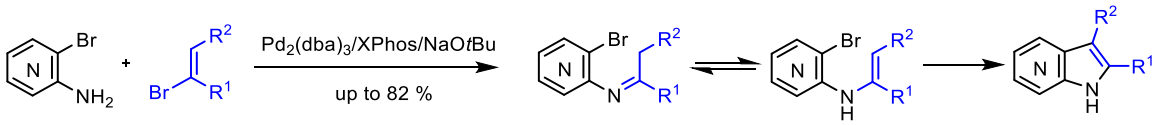
intermediate and (f) reductive elimination to form azaindole and the regenerated Pd(0) reenters the catalytic cycle.[37]The regioselectivity of the reaction depends on the difference between R^1 and R^2, as well as on the amine protecting group R (**Scheme I.19**; A).[5]

In 1998Ujjainwalla and co-workers reported a methodology for regioselective synthesis of 5-, 6- and 7-azaindoles. Using unprotected amino-iodopyridines and alkyl/silyl- and alkyl/alkyl-disubstituted alkynes in the presence of $PdCl_2$(dppf) as catalyst, LiCl and Na_2CO_3 in DMF they were able to obtained the respective 2,3-disubstituted azaindoles in good yields (**Scheme I.19**; B).[36]

All the procedures and approaches described above represent a great advanced in the search for new and better ways to synthesise indole and azaindole scaffolds. However, there are still some drawbacks. Most of these methods still have poor regioselectivity and are limited to few isomers which limit the substrate scope. To afford the product harsh conditions, N-protection of the aminopyridine and electron-withdrawing groupsare sometimes required, so there's a need to continue to study and improve these reactions in order to find better and less harsh synthetic methods.[5]

I.2.3.3.5 – Cascade C−N Cross-Coupling/Heck Reaction

Our research group has recently reported a Pd-catalysed cascade amination/Heck coupling as a practical method to synthesize azaindoles, from amino-*ortho*-bromopyridines and alkenyl bromides (**Scheme I.20**).[4]



Scheme I.20 - General scheme of cascade akenyl amination/Heck reaction with amino-*o*-bromopyridines.[4]

The first synthetic step consisted of a C-N cross coupling of amino-*ortho*-bromopyridines with alkenyl bromides involving in situ imine/enamine formation followed by Heck reaction, affording the azaindole nucleus. The $Pd_2(dba)_3$/XPhos/NaO*t*Bu system has proven to be suitable for a novel straightforward synthesis of substituted 4-, 5-, 6- and 7-azaindoles. Despite of the readiness of the protocol to prepare 2-substituted azaindoles, it did not work when applied to N-aryl amino-*ortho*-bromopyridines, which limits the access to 1,2-diaryl azaindoles. Alternative procedures to attain these substituted azaindoles are being investigated, avoiding the difficult N-arylation of 2-substituted-azaindoles.[38,39]

I.3 – PEG supported cross-coupling reactions

The grown interest in palladium-catalysed and copper-catalysed cross-coupling reactions has led to more sustainable versions of these reactions during recent years. In particular, poly(ethyleneglycol) (PEG) has been largely explored as an alternative solvent and support in several cross-coupling reactions (**Figure I.1**).[40] The use of PEG as an alternative solvent and support has grown since PEG is available in a broad range of average molecular weights (the most used are 200 to 4000), is non-toxic, inexpensive, thermally stable and recoverable. Based on these properties, PEG appears as an environmental friendly alternative to the use of volatile, toxic and hazardous organic solvents.[40]

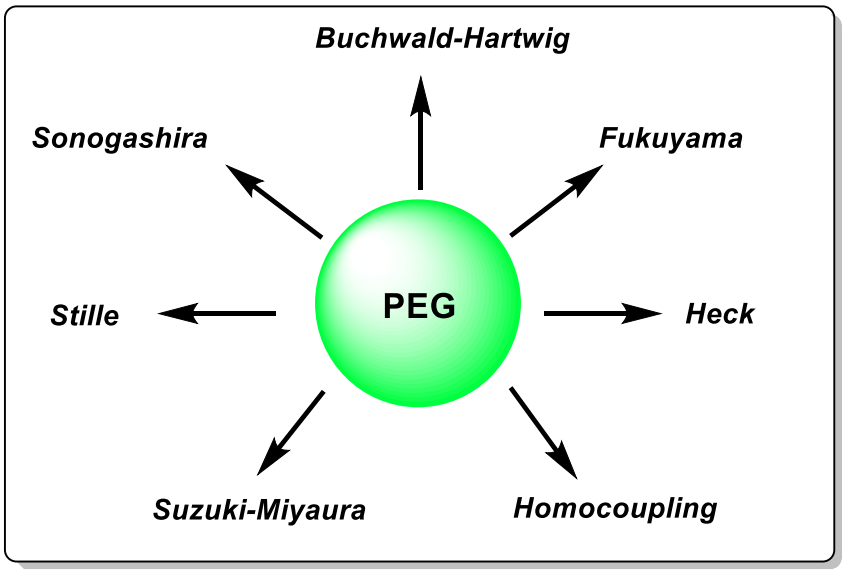


Figure I.1 – Application of PEG to several metal-catalysed reaction as solvent and support.

Metal catalysed cross-coupling reactions are known as essential tools in organic chemistry to synthesize certain nucleus. However, these methods sometimes require harsh conditions, such as high temperature, as well as the use of toxic solvents, so there's a continuous search to find greener alternatives. So far PEG has been used as solvent or support in several metal catalysed reactions, reported as more efficient and cheaper medium, avoiding laborious purifications and improving the reaction yield.

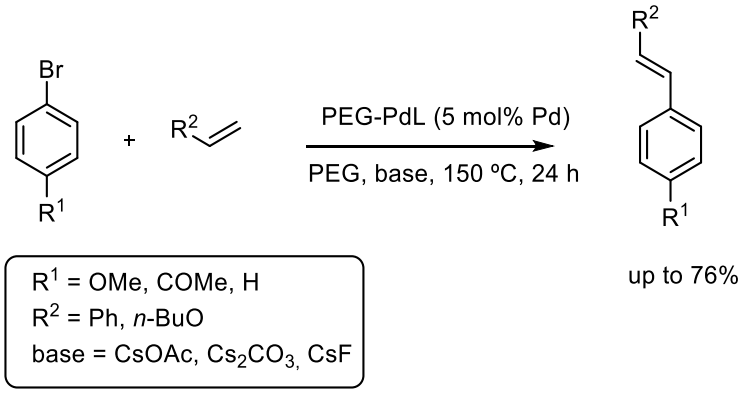
I.3.1–PEG in Heck Reactions

As previously mentioned the Heck reaction is described as an important method for preparation of di-substituted olefins, consisting of the formation of a C-C bond by palladium-catalysed reaction.[40]

The first application of PEG as solvent in the Heck reaction was reported by Chandrasekhar and co-workers.[41] Their work demonstrated that PEG with molecular weight 2000 (or lower) works as an efficient reaction medium for the regioselective Heck reaction of aryl bromides with several olefins, with easy recyclability of solvent and the Pd catalyst.

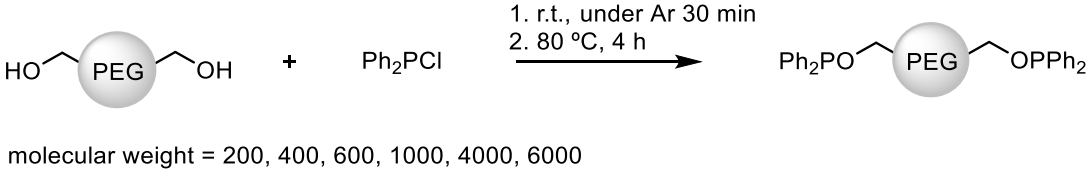
PEG has been investigated as a polymer support for palladium catalysts and as a ligand support in the Heck reaction.

In 2006, Corma, Garcìa and Levya explored PEG as a soluble support for an oxime carbapalladacycle and its application in the Heck, Suzuki and Sonogashira reactions.[42] Indeed PEG has a double role in the Heck reaction, acting both as solvent and catalyst support for an active and reusable posphine-free Pd catalyst (**Scheme I.21**).



Scheme I.21 - PEG as a support and solvent for reusable Heck coupling.

Later, In 2013 Iranpoor and co-workers reported the phosphorylation of PEGs with different molecular weights (M_W =200, 400, 1000) as a simple and practical route for the synthesis of PEG-bases phospinite ligands (**Scheme I.22**).[43]



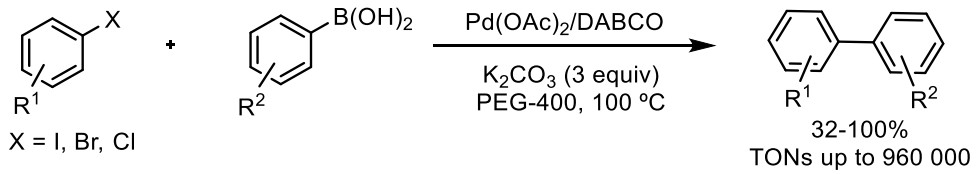
Scheme I.22 - In situ generated nano-Pd(0)/DPPPEG 200 for Heck reaction of aryl halides with olefins.[43]

These ligands were then reduced to generate nano-Pd(0) catalysts that were applied in efficient Heck- Mizoroki reactions of several haloarenes under solvent-free conditions. This system allowed recycling and reusing the catalyst.

I.3.2 – PEG in Suzuki–Miyaura Reactions

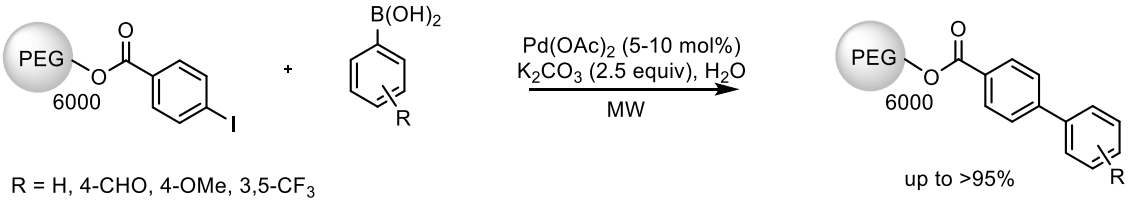
The Suzuki-Miyaura reaction, also known as Suzuki coupling is a palladium catalysed cross-coupling reaction between organic boronic acid and halides. This reaction requires a base, which works as the organic boronic acid activator, and usually phospine ligands.[44]

In 2001, PEG was reported as media for the Suzuki-Miyaura reaction. PEG-400 was used as a substituent for volatile organic solvents and employed in efficient microwave-assisted Suzuki-Miyaura.[45] Thisgroup also studied PEG-400 as solvent, together with $Pd(OAc)_2$, K_2CO_3 and DABCO as a recyclable system for the coupling of aryl iodides and bromides to several boronic acids with high yields and TONs, under heating conditions (**Scheme I.23**).[46,47]



SchemeI.23 - Suzuki-Miyaura cross- coupling of aryl halides with arylboronic acid in PEG 400.[46,47]

In 1999, Schotten and co-workers were the first to report the use of PEG as soluble polymer support.[48,49]The authors used PEG-6000 as a support to immobilize aryl iodides, bromides, triflates and nonflates, on several different scales, and performed a cross-coupling with arylboronic acids using “lingadless” palladium acetate catalysis in water (**Scheme I.24**).[48]



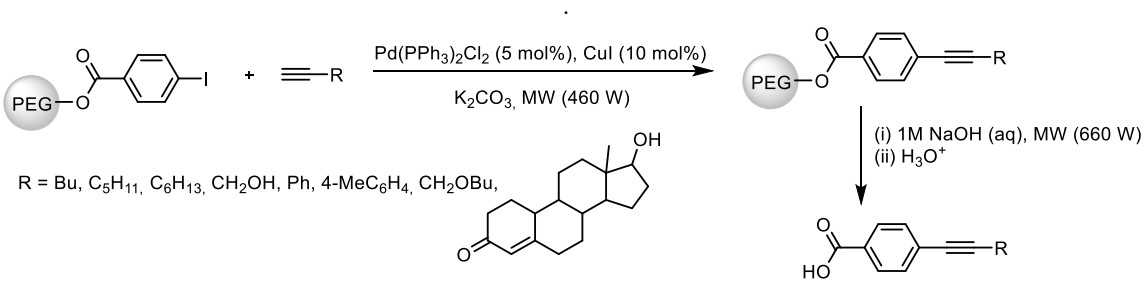
Scheme I.24 - Suzuki reaction of PEG-6000-bound aryl iodides under microwave conditions.[48]

The coupling reaction was explored using conventional heating conditions, which proved to cause cleavage of the ester bond off the polymeric support. Then microwave conditions were tested and polymer support as well as the ester remained stable.

I.3.3– PEG in Sonogashira Reactions

The Sonogashira reaction is a simple method for the preparation of aromatic alkynes via palladium-catalysed coupling of terminal alkynes with aryl halides or allyl halides. This reaction usually requires the use of organic solvents that are toxic, so PEG comes as a viable alternative that can also be used as support.

In 2002, the first example of a microwave activated Sonogashira reaction was described by Wang and Xia.[50] They prepared substituted alkynylbenzoic acids, under phase-transfer catalysis conditions, using PEG-400 both as solvent and polymeric support (**Scheme I.25**).



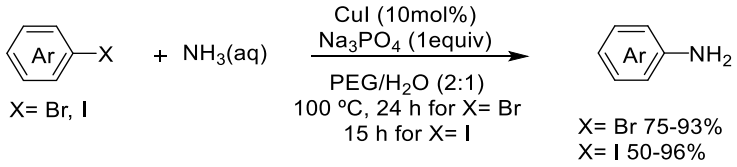
Scheme I.25 - Sonogashira coupling reaction of 4-iodobenzoic acid with terminal alkynes using PEG-400 as polymer support and cleavage of products to other terminal alkynes.[50]

To sum up this two-step microwave activated coupling and cleavage reaction not only diminish the reaction time and improved the yields, but also provided excellent purity, due to the triple roles of PEG-400 as phase-transfer catalyst, solvent and polymer support.

I.3.4 – PEG in Buchwald–Hartwig Reactions

In the Buchwald-Hartwig amination reaction PEG has been reported as an alternative solvent and, though less explored, as a support for substrates. Although the Buchwald-Hartwig reactions are usually performed with a palladium catalyst, copper catalyst have proven to be of great importance, especially when combining PEG as solvent.[40]

Chen and co-workers reported the use of PEG as a solvent in a one-step reaction, to convert aryl iodides and bromides into aniline derivatives using CuI as catalyst and PEG-400 as solvent (**Scheme I.26**).[51]

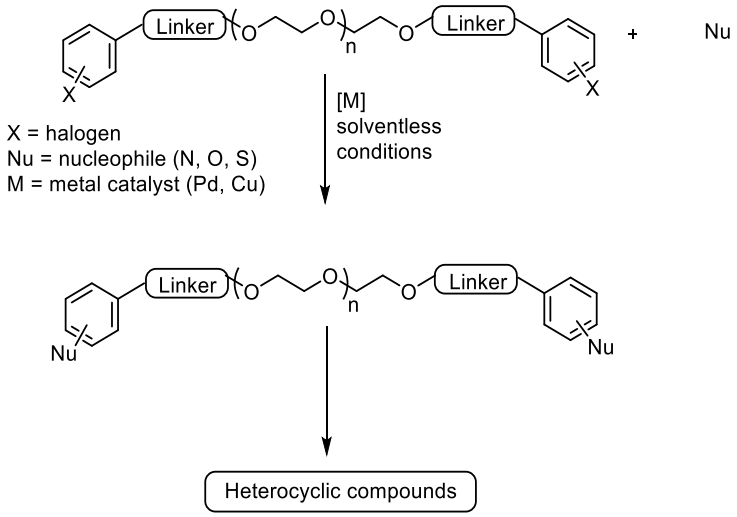


Scheme I.26 – CuI catalysed amination of aryl halides with aqueous ammonia in PEG-400.[51]

This protocol proved to be versatile and afforded primary arylamines with the advantage of not requiring a ligand.

To date, the role of PEG in Buchwald-Hartwig reactions has been mainly described as an alternative solvent, and it has been less explored as a polymer support for substrate, due to the heterogeneous character of this system.

In 2013, our group described an innovative protocol for palladium – catalysed N-arylation, using aryl halides supported on PEG-2000 as a soluble support (**Scheme I.27**).[52]



Scheme I.27 - Pd-catalysed amination on soluble polymer support arylation of anilines (Nu = anilines) witg PEG-supported aryl halides.[52]

This protocol consisted of the first Buchwald-Hartwig amination on a soluble polymeric support, with the advantage of being a solvent-free process, without isolation, avoiding the use of high volumes of organic solvents. The use of a soluble polymer support also allowed an easy monitoring of the reaction by ^{1}H-NMR with no need of cleaving the substrate from the resin.

II. Results and discussion

II.1 – Background

Heterocyclic systems represent an important class of compounds in biologically active pharmaceuticals, natural products, materials and therefore the synthesis and selective functionalization of these molecules is of great interest. Indole and azaindole nucleus are part of an extremely important class of compounds present in heterocyclic systems, for that reason the scientific community is continuously searching for new and better methods that can afford these structures. Metal-catalysed cross-coupling reactions are among the most used methods to achieve these nucleuses and in spite of representing a great advance, there are still some drawbacks. Most of these methods require the use of "non-green" solvents in large amounts, harsh conditions and laborious purifications. Thus, the use of a soluble polymer support, like PEG-2000, in a combinatorial approach would tremendously improve heterocyclic compounds preparation, overcoming the difficulty of solid-phase synthesis, while maintaining its advantages. PEG-2000 is a polymer derived from ethylene glycol and has an average molecular weight of 2000 g/mol. However the appropriate molecular weight is a range between 1900-2200 g/mol, which is equivalent to a ***n*** value range between 43-50 units of $-OCH_2CH_2-$. PEG-2000 is also a solid compound at room temperature, very soluble in a large variety of organic compounds and it easily precipitates by simple addition of diethyl ether.

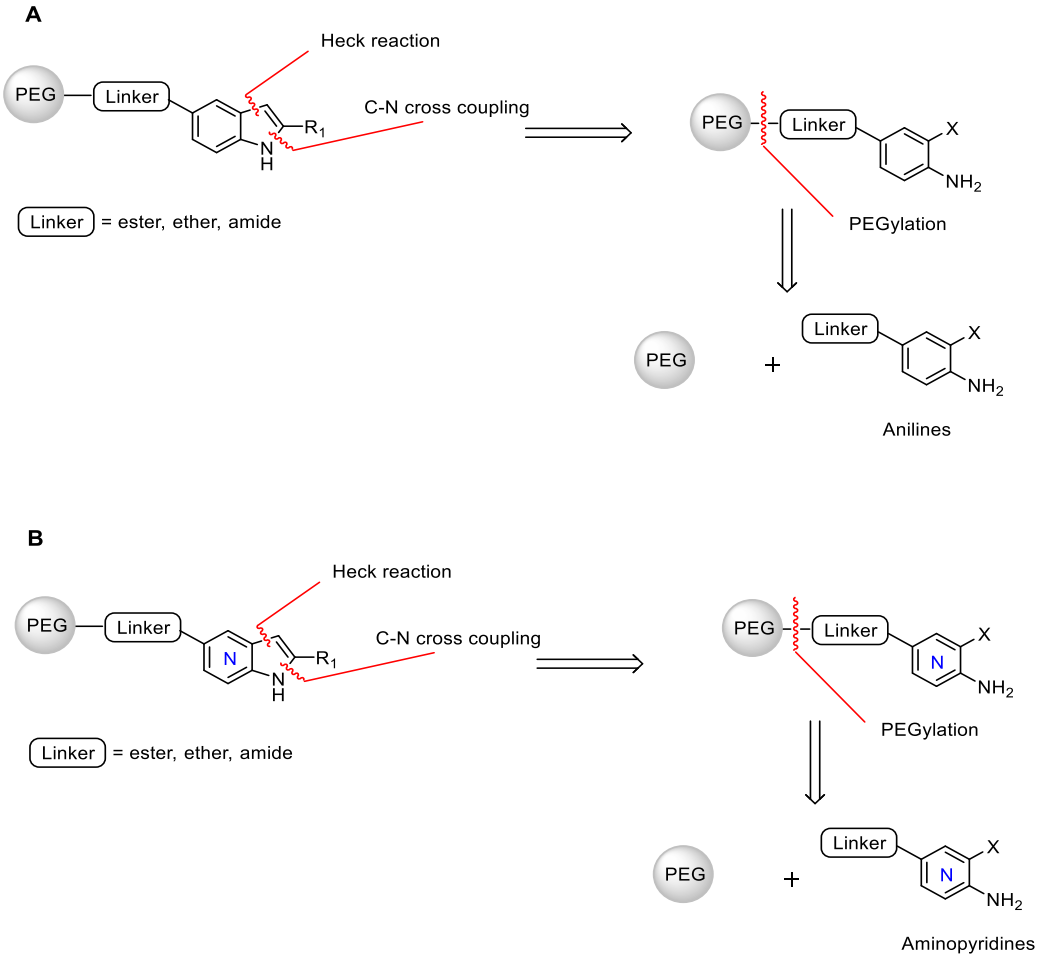
Therefore, this work aimed to study and improve the compatibility between metal-catalysed cross-coupling reactions and the use of soluble polymer support to immobilize the substrate while facilitating its isolation and purification. This way the synthesis of privileged structures like indole and azaindole could be achieved using greener methods that tremendously improve reactions yields and facilitate isolation of products that are usually difficult to purify via conventional methods.

The recent advances on the use of metal-catalysed cross-coupling reactions reported by our group inspired the investigation of PEG-2000 for the preparation of heterocyclic compounds, in particular indole and azaindole based.[4,5,52]

In 2013 our group reported a Pd-catalysed amination on a soluble polymer support, which proved that metal-catalysed cross-coupling reactions are compatible with solid phase synthesis, and that optimization of reaction conditions enabled the preparation of different PEG bound aryl halides derivatives.[52]

In 2016 the group reported a novel and straightforward way of synthesizing different azaindoles using a cascade C-N cross coupling/Heck reaction. This method proved to be suitable to prepare substituted azaindole using as starting materials amino-*ortho*-halopyridines and alkenyl bromides. Given the difficulties associated with azaindole synthesis, the development of a PEG-2000 based protocol combined with metal-catalysed reactions would consist on an improvement on the sustainability and versatility of the synthetic approaches to attain azaindoles and its

isolation. Thus, in this study the previously cascade approach reported by the team was applied to substrates immobilized on PEG-2000, to investigate whether PEG-2000 would allow a fast access to azaindoles while facilitating its isolation.[4] However, due to the challenging nature of aminopyridines,[5] anilines were first explored as model compounds, since they are also cheaper than the corresponding aminopyridines, affording indoles (**Scheme II.1**).[4,27]



Scheme II.1 - Retrosynthetic analysis of the desired PEGylated indoles (A) and azaindoles (B).

This Master thesis aimed to:

- Develop a solid-phase synthesis version of the cascade approach to prepare azaindoles and indoles, combining metal catalysed reactions with the advantages of using a soluble polymer support;
- Prepare PEG-bound functionalysed aminopyridines/anilines;
- Optimize the reaction conditions for resin-bound substrate and vinyl bromides;
- Explore alternative metal-catalysed methods to prepare substituted indoles and

azaindoles with potential application on PEG-2000;

This way we hope to avoid the need for laborious purifications of azaindoles and indoles, improving reaction yields and developing a more sustainable synthesis of these privileged structures.

II.2 – Preliminary studies

II.2.1 – Using non pegylated substrate as model compound

In order to explore the cascade approach towards azaindoles on PEG-bound substrate, the first step consisted on the evaluation of the cascade C-N cross coupling/Heck reaction using as starting materials functionalized anilines. The functional groups at the aromatic ring were chosen to allow coupling of the aniline to the polymer. Thus, substituents such as hydroxyl or carboxylic acid groups were investigated to provide ethers and amide bounds, respectively. Furthermore, the relative position of the substituents was also tested, in particular the *meta*- and *para*- positions to the amine group.[4,27]

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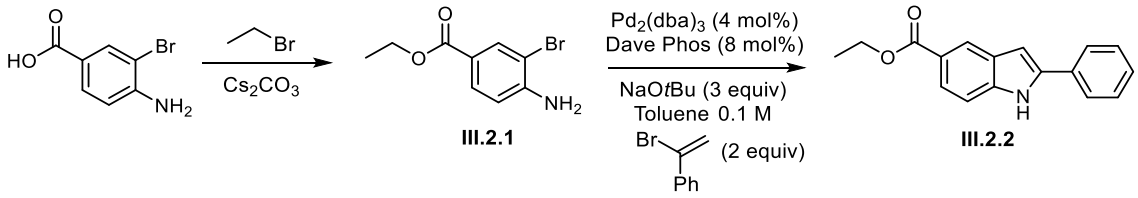
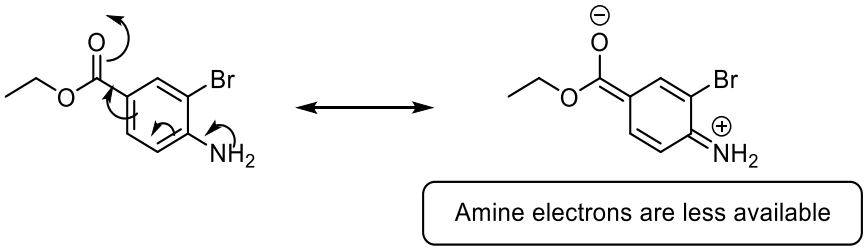
For that purpose, 4-amino-3-bromobenzoic acid (**Scheme II.2**) was used and protected with an ethyl group to mimic the ester linkage to PEG that would be formed once this compound is coupled to PEG (**Scheme II.2**).



Scheme II.2 - General scheme for esterification and subsequent cascade reaction using 4-amino-3-bromobenzoic acid as a model compound.

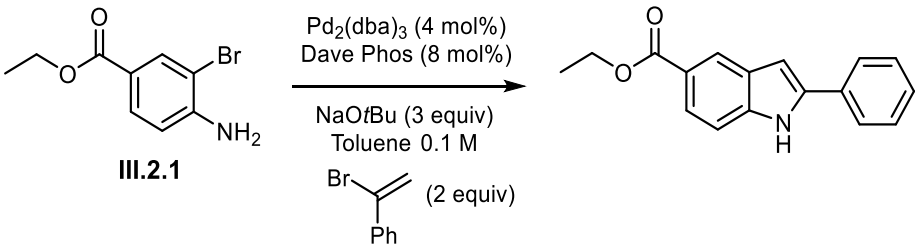
After the esterification reaction, the resulting compound **III.2.1** was used in a cascade reaction in order to form the corresponding indole derivative. In the first trial a $Pd_2(dba)_3$/DavePhos system was used, as well as NaO*t*Bu as a base in toluene as solvent. The mixture was stirred for 24h at 110ºC, and TLC analysis suggested that the reaction was incomplete. When observing the ^{1}H-NMR spectrum of the crude only signals of the starting material were observed, which suggested that the presence of the ester group, an electron withdrawing group in *para*-position to the amine, was deactivating the amine, which would restrain the amine attack to α-bromostyrene (**Scheme II.3**).



Scheme II.3 - Ressonance effect of the electron-withdrawing group (ester) in the para-position.

Next, the mixture was allowed to react for 48 h, in the expectation that product formation could be observed, and indeed significant changes were observed. The TLC analysis revealed that no starting materials were present and only a very fluorescent compound was formed, that could correspond to the indole structure (**Table II.1**).

Table II.1 - Preliminary studieson thereaction ofethyl 4-amino-3-bromobenzoatewith the α-bromostyrene.

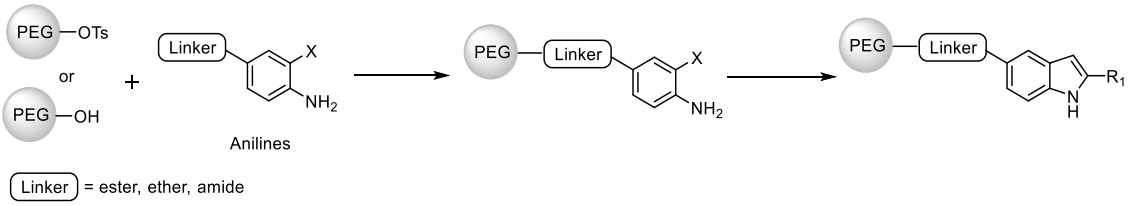


Entry	Ligand	Temperature (ºC)	Time (h)	TLC	^{1}H-NMR
1	DavePhos	110	24	Compounds with fluorescence	Only signals from starting material
2	DavePhos	110	48	New fluorescent compound	No starting material's signals

Even though ^{1}H-NMR examination did not allow a clear observation due to the presence of a mixture of compounds. However, this last experiment was promising, and the investigation proceeded.

II.3–Cascade approach towards indole synthesis on PEG-2000

In this Master thesis one of the main goals was to establish conditions to effectively couple our starting materials to PEG and then to make sure that the metal catalyzed reactions used were compatible with a soluble polymer support. Thus, the indole scaffold was chosen as a model to perform the preliminary studies (**Scheme II.4**), and the investigations on the azaindole core were proposed in a more advanced stage of the study. Indoles can be synthesized from commercially available anilines, thus the indole seemed like a promising starting point.

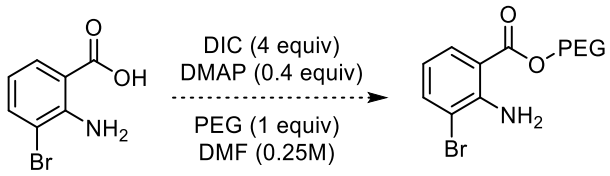


Scheme II.4 – Synhetic path involved in the cascade approach

II.3.1 – Establishing the conditions for coupling anilines with PEG–2000 using 2-amino-3-bromobenzoic acid

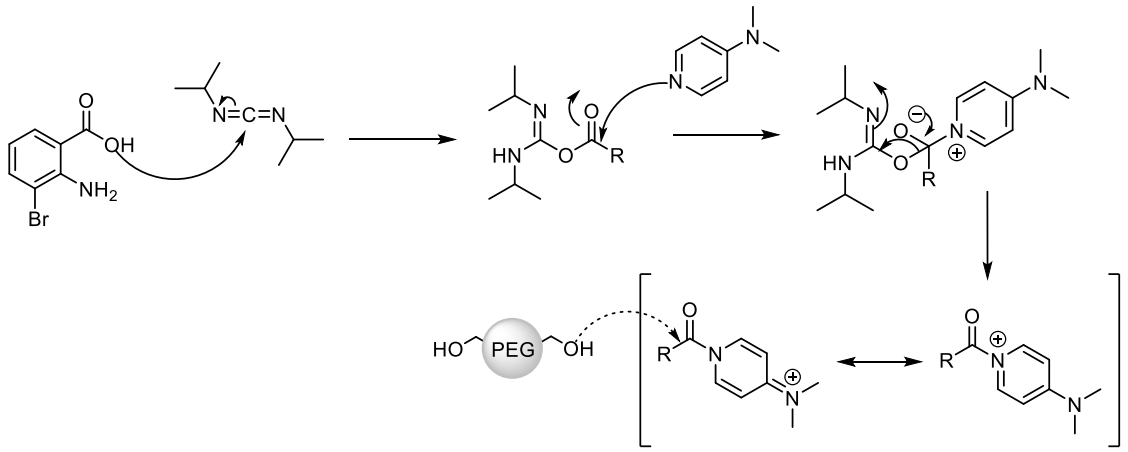
According to the proposed synthetic strategy, the first step consisted on using several aniline derivatives (some commercial others to be prepared) that could be coupled to PEG-2000 through different linkers, for further use in the cascade reaction.

First attempts were carried with **2-amino-3-bromobenzoic acid** as coupling partner, by treatment with DIC and DMAP in DMF.



Scheme II.5 - Conditions for 2-amino-3-bromobenzoic acid coupling with PEG

This way using DIC, a carbodiimide, the acid would be activated and the attack from PEG with be more favorable. However, no reaction was observed, despite of the activation of the starting material that would make it more susceptible of nucleophilic attack, this may not have been sufficient. So, the coupling was unsuccessful and it required strong nucleophilic hydroxyl groups from PEG to attack the activated acid.



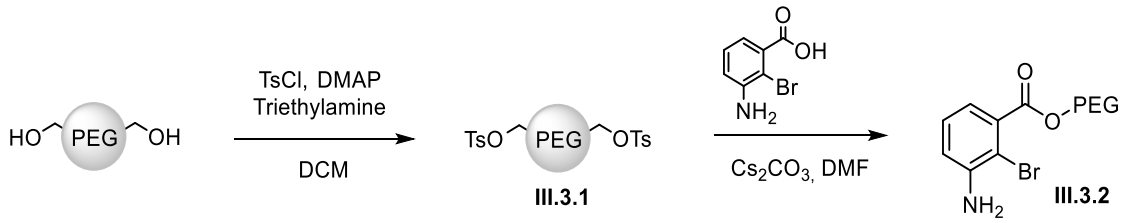
Scheme II.6 - Mechanism of activation of 2-amino-3-bromobenzoic acid using DIC as coupling reagent

Since this method was ineffective there was a need to find a different and more efficient method of coupling PEG with the corresponding carboxylic acid.

An alternative approach consisted on the use of PEG-OTs the electrophile in the reaction with **3-amino-2-bromobenzoic acid**, that in the presence of Cs_2CO_3 (pKa of conjugate acid (H_2O) = 10.33) works as the nucleophile.[53,54] After preparation of PEG-OTs the coupling reaction would be facilitated, since tosyl is a good leaving group.

The tosylation reaction was performed treating PEG-2000 with TsCl in the presence of trimethylamine, and PEG-OTs was obtained in quantitative yield.

After formation of PEG-OTs, the coupling reaction was tested using **3-amino-2-bromobenzoic acid**.



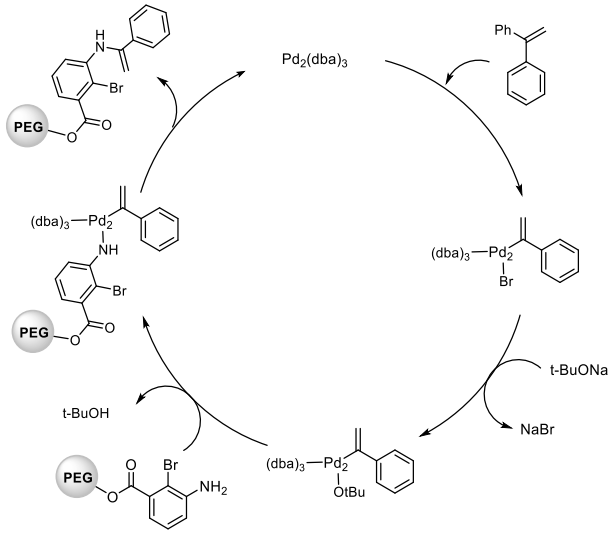
Scheme II.7 – Conditions for PEG tosylation and **3-amino-2-bromobenzoic acid** coupling with PEG.

After 24 h the reaction was complete and compound **III.3.2** was isolated with 93% yield.

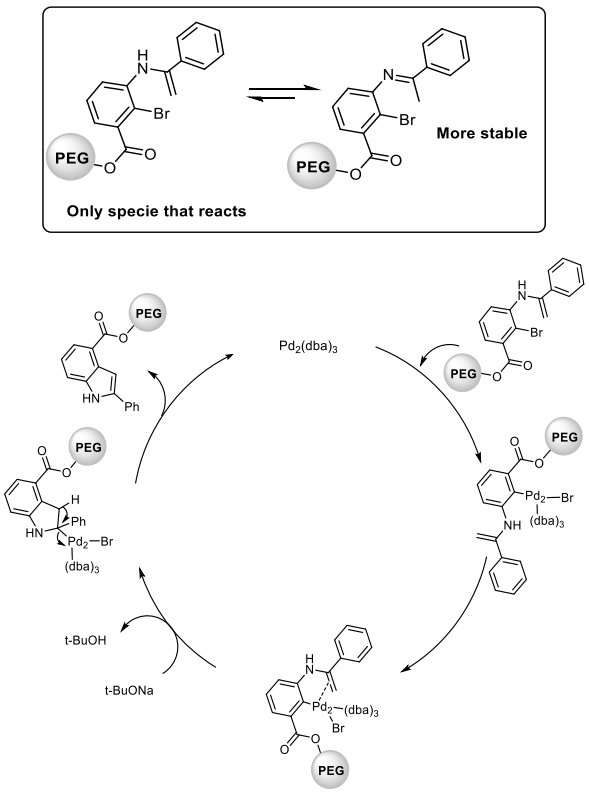
II.3.2 – Testing cascade C – N cross coupling/Heck reaction conditions on a soluble polymer support (PEG-2000)

Since the pegylated product was successfully formed, the next step was to test the cascade reaction conditions. This reaction involves two steps: a Buchwald-Hartwig amination of alkenyl

bromides, which has been reported to involve in situ imine/enamine formation followed by intramolecular Heck reaction that results in the formation of the indole structure.



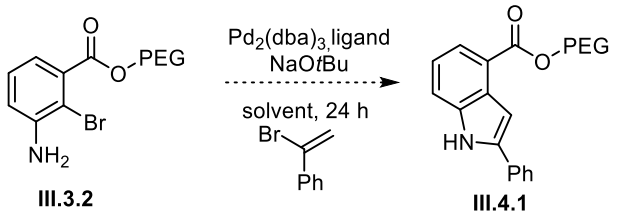
Scheme II.8 - Catalytic cycle for palladium-catalyzed C – N cross coupling reaction using a PEGylated substrate



Scheme II.9 - Catalytic cycle for Heck reaction using PEGylated substrate and imine/enamine equilibrium.

To do that two sets of conditions were employed, one reported by our group using $Pd_2(dba)_3$/XPhos/NaO*t*Bu system in *t*BuOH and the other one reported by J.Barluenga that uses $Pd_2(dba)_3$/DavePhos/NaO*t*Bu system in toluene (Table II.2).[4,27]

TableII.2 - Influence of Pd/ligand and solvent in the cascade C-N cross coupling/Heck reaction with PEG bis (3-amino-2-bromobenzoate).



III.3.2 III.4.1

Entry	α-bromostyrene (equiv./terminal)	Ligand	Base	Time (h)	Solvent	$Pd_2(dba)_3$ (mol%/terminal)
1	1.5	XPhos	NaO*t*Bu	24	*t*BuOH	4
2	1.5	DavePhos	NaO*t*Bu	24	Toluene	4

These conditions were chosen because there were evidences that they were efficient in achieving indole and azaindole nucleus. Both conditions use Buchwald ligands, a group of ligands constituted by bulky electron-rich biphenyl phosphines, (e.g. Dave Phos, SPhos, XPhos, JohnPhos and JackiePhos) and a bidentate ligand (e.g. XantPhos) (Figure II.1).

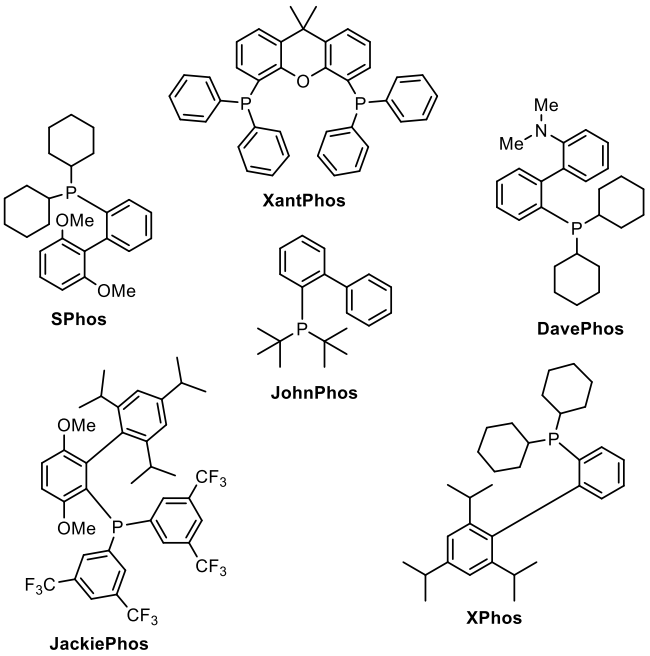


Figure II.1–Buchkwald ligands.

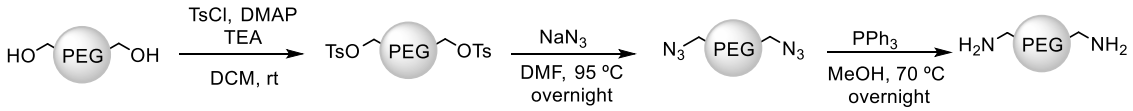
The first tested system was the $Pd_2(dba)_3$/XPhos/NaO*t*Bu (entry 1). The pegylated product was tested in these conditions at 110ºC and after 24h the resulting compound was isolated by precipitation. After analysis of the ^{1}H-NMR spectrum it was concluded that the isolated precipitate was only PEG 2000 in its free form, which means that even if the indole structure was formed, the reaction conditions led to the hydrolysis of the pegylated substrate. In order to find out whether the indole structure was formed and released from PEG, the supernatant was analyzed. Using PTLC (Hexane:AcOEt 2:1) no product was detected, and only starting material (**III.3.4A**) in its free form was isolated, proving that under the tested conditions the indole structure was not formed and that this system was leading to the hydrolysis of the pegylated starting material.

Reported as suited for *ortho*-bromoanilines, the $Pd_2(dba)_3$/DavePhos/t-BuONa system in toluene was applied in the pegylated substrate **III.3.2** (entry 2).

After 24 h the resulting compound was isolated by precipitation and analyzed using ^{1}H-NMR. The results obtained indicated that no reaction occurred under the tested conditions, since the isolated compound proved to be pegylated starting material (**III.3.2**). To draw more conclusions the corresponding supernatant was purified using PTLC (Hexane:AcOEt 2:1) and two compounds were isolated. Due to the low amount of compound isolated the ^{1}H-NMR data was unclear, but it was possible to observe that the isolated compound was not starting material in its free form, which means that even if the indole nucleus was formed it had been hydrolyzed from PEG.

To overcome this problem, another approach was design and instead of using PEGylated aniline via an ester bound, an amide bound was explored starting from PEG-NH_2. Thus, the coupling reaction would form an amide linker which is more stable, and resistant to the conditions used, avoiding hydrolysis of both substrate and product.

The PEG-NH_2 used in this work was synthesized by a co-worker (MSc Marina Pires) according with the following scheme.[55]



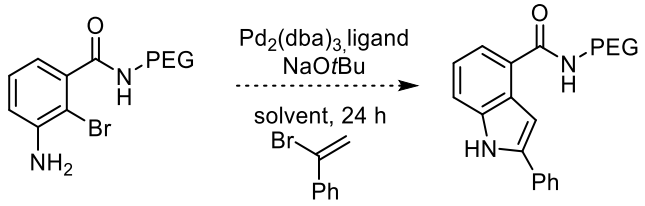
Scheme II.10 - Synthesis of homobifunctionalized polyethylene glycol - PEG diamine (PEG-NH_2).[55]

For this new approach PEG-NH_2 was coupled with **3-amino-2-bromobenzoic acid** using Cs_2CO_3 as base and DMF as solvent. After 24 h compound **III.3.3** was precipitated using cold diethyl ether with 88% yield.

In the following step, the pegylated substrate **III.3.3** was tested using the

$Pd_2(dba)_3$/XPhos/NaO*t*Bu system in *t*BuOH and the $Pd_2(dba)_3$/DavePhos/NaO*t*Bu system in toluene (Table II.3).

Table II.3 - Influence of Pd/ligand and solvent in the cascade C – N cross coupling/Heck reaction using substrate PEG bis (3-amino-2-bromobenzamide).



III.3.3 **III.4.2**

Entry	α-bromostyrene (equiv./terminal)	Ligand	Base	Time (h)	Solvent	$Pd_2(dba)_3$ (mol%/terminal)
1	1.5	XPhos	NaO*t*Bu	24	*t*BuOH	4
2	1.5	DavePhos	NaO*t*Bu	24	Toluene	4

The first catalytic system tested was the one reported by our group (entry 1).[4] After 24 h of reaction, efforts were made for isolation of the compound by precipitation, but that was not possible. Precipitation depends heavily on the components of the reaction mixture and the presence of contaminants can hamper the precipitation process.

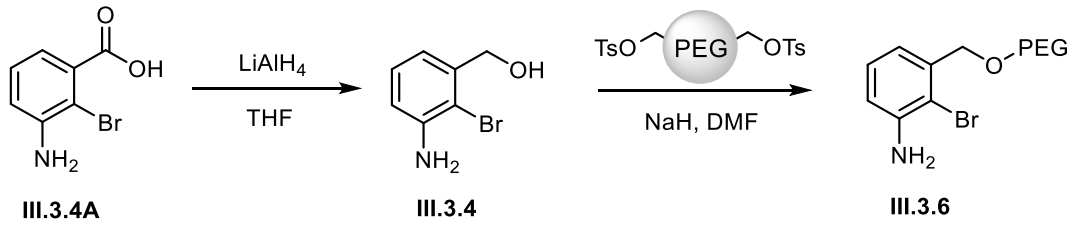
Given that the precipitation did not occur, the compound was isolated as an orange oil and later analysed by NMR. Following analysis of the isolated product by ^{1}H-NMR, led to the conclusion that the pegylated substrate had suffered hydrolysis, given that the only compound that could be identified was PEG-NH_2.

This method proved to be inefficient, so alternative conditions were employed (entry 2).[27]After reaction completion the mixture was extracted and concentrated to originate an oil in trace amounts. Further analysis proved that this was not the expected pegylated product, but a complex mixture probably resulting from the catalytic system. Given that the pegylated substrate was not in the organic layer, we proceeded to the examination of the aqueous layer. Several washes with ethyl acetate were made,in order to extract the pegylated compound from the aqueous layer. After analysis the pegylated compound was identified as the pegylated starting material (**III.3.3**), and not has the expected indole derivative (**III.4.2**).

The results obtained suggested that the tested conditions were not promoting the cascade reaction and that the catalytic system as well as the base needed optimization. Regarding the linker the cascade reaction conditions didn't seem to be compatible with the ester and amide bound, probably because the reaction involves the use of a strong base at high temperatures (110ºC), which if e.g. the solvent used is not well dried, can compromise the stability of the pegylated compound and lead to hydrolysis (in the case of the substrates bound via an ester

bound).

To overcome this difficulty a different substrate was investigated, involving coupling of the substrate to PEG-2000 via an ether bond (**Scheme II.11**).



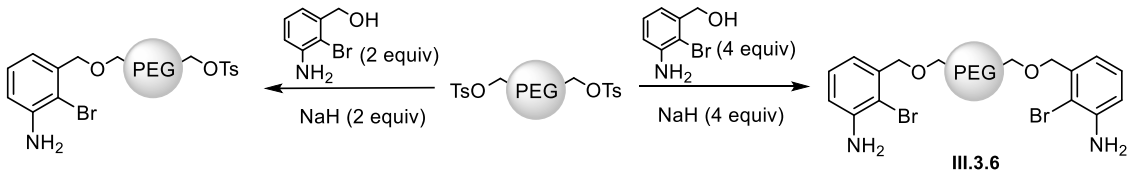
III.3.4A **III.3.4** **III.3.6**

Scheme II.11 - Preparation of PEGylated substrate using (3-amino-2-bromophenyl) methanol

In this approach **3-amino-2-bromobenzoic**was reduced to the alcohol, thus when coupled with PEG-OTs, the resulting compound would have an ether linker that can work as an electron-donating group which can facilitate the cascade reaction, instead of the ester or amide groups previously used that are electron-withdrawing groups and deactivate the amine group. This linker is much more stable, which means that under cascade conditions this bond would not suffer hydrolysis.

The reduction conditions were adapted from a protocol reported by N. Umezawa[56]**.** The reduction of **3-amino-2-bromobenzoic** was first carried out using 1.5 equiv. of $LiAlH_4$, which proved not to be enough, so the quantity was scaled up until 4.5 equiv and after 24h **(3-amino-2-bromophenyl) methanol** (**III.3.4**) was obtained as a light brown solid with 62% yield.

After the alcohol was synthesized, the coupling conditions to PEG-OTs were tested and optimized. In the first essay 2 equiv. (1equiv.per terminal) of NaH and **(3-amino-2-bromophenyl) methanol** (**III.3.4**) were used, which proved to be insufficient, since the isolated pegylated product was only the mono-substituted. So the quantity was increased to 4 equiv and the pegylated product (**III.3.6**) was successfully obtained with 77% yield.



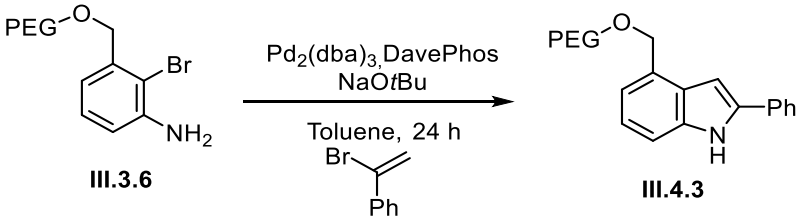
III.3.6

Scheme II.12 - Optimization of conditions for coupling reaction between PEG-OTs and (3-amino-2-bromophenyl) methanol.

Similarly to the previously used pegylated anilines, this pegylated compound **III.3.6** was submitted to the conditions reported by Barluenga, since these were more suitable for anilines.[27] The *ortho*-bromoanilines explored in the literature were limited to few substrates (e.g. methyl group or chloro in *para*-position to the amine group). Thus, the *ortho*-bromoanilines substitution

pattern used in thesis (e.g. ester, amide and ether groups in *ortho*- position) as well as the fact that are polymer-bound substrates have not been explored yet and require a detailed study of the reaction conditions. Thus, several essays were preformed to study the influence of Pd/ligand system and solvent, in order to optimize reaction conditions and afford the indole compounds on PEG-2000 (Table II.4). A $Pd_2(dba)_3$/DavePhos/NaO*t*Bu system was employed using compound **III.3.6** as starting material.

Table II.4 - Influence of Pd/ligand and solvent in the cascade C – N cross coupling/Heck reaction.



III.3.6 **III.4.3**

Entry	**α-bromostyrene** (equiv/terminal)	**Ligand**	**Base**	**Time** (h)	**Solvent**	**$Pd_2(dba)_3$** (mol%/terminal)	**Yield** (%)
1[a]	2	DavePhos	NaO*t*Bu	24	Toluene	4	-
2[a]	4	DavePhos	NaO*t*Bu	24	Toluene	4	-
3	4	DavePhos	NaO*t*Bu	48	Toluene	4	-
4	4	DavePhos	NaO*t*Bu	48	Dioxane	4	-
5	1	DavePhos	NaO*t*Bu	24	Toluene	4	82

Conditions: DavePhos (8 mol%/terminal),NaO*t*Bu (3 equiv/terminal), solvent (0.1 M)

a – this essay was repeated twice

Several conditions were tested, and it was observed that in entry 1 the reaction was not complete, since two signals corresponding to the CH_2 between PEG and the heterocycle, were present at 4.68ppm and 4.58ppm. This indicated that two different pegylated compounds were present at the PEG terminals. Given that the reaction, if successful was incomplete, the complexity of the crude complicated the detection and identification of the desired product in the ^{1}H-NMR (**Figure II.2**).

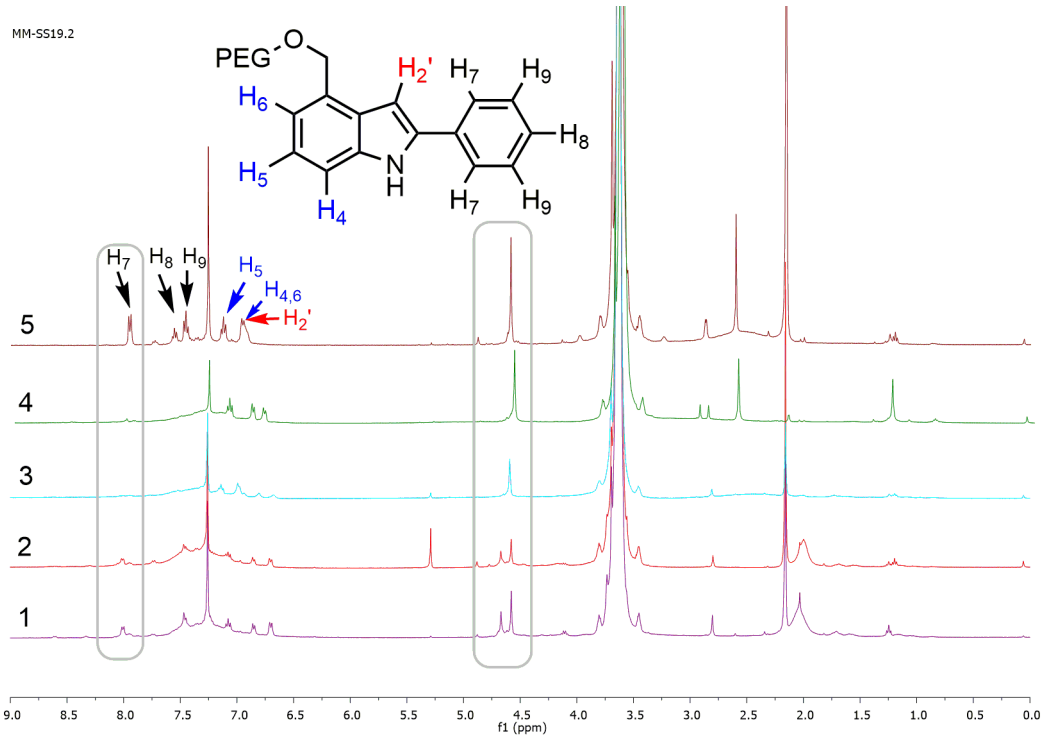


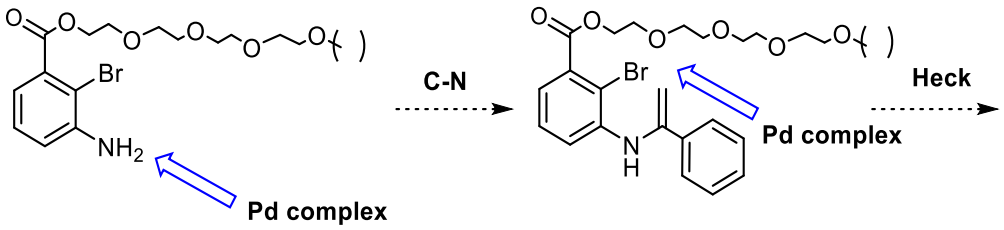
Figure II.2 - ^{1}H-NMR spectrum of essays 1 to 5 (protons form Ph indicated by black arrow; protons form Ar-H indicated by blue arrow; proton from indolic alkene indicated by red arrow)

To overcome this problem the loading of α-bromostyrene was increased (entry 2) and similarly to entry 1, still two signals of the CH_2 group were observed. This result suggested that the incomplete reaction was not caused by lack of one of the reagents, so it was decided to increase the reaction time. In entry 3 and 4 the reaction time was increased to 48 h and when observing the ^{1}H-NMR it was concluded that the reaction was unsuccessful, with PEGylated starting material being the only compound that was possible to isolate (**Figure II.2**).

To conclude the most promising result was obtained when a lower amount of α-bromostyrene was used (entry 5), as the formation of the indole compound **III.4.3** was observed in 82% yield. This indicates that the increase loading of α-bromostyrene can prevent the reaction from occurring, and make the analysis of the crude reaction mixture difficult due to the formation of side-products. Identification of indole compound **III.4.3** by ^{1}H-NMR was complemented by two-dimensional NMR including COSY, HSQC and HMBC experiences that confirmed the shifts corresponding to the phenyl ring. The search for an indolic compound that was similar to this one but with no polymer support showed that the identification of this compound (**III.4.3**) was accurate.[57]

After testing this method and trying to optimize all conditions it was apparent that the cascade

reaction even successful was sometimes incomplete. The lower conversion of the starting material into the indole could have been caused by two factors: steric hindrance caused by the presence of PEG structure; and electronic effects, due to the presence of an ester or amide groups *para* to the amine group, the resonance effect of this electron-withdrawing groups could have made the reaction more difficult.

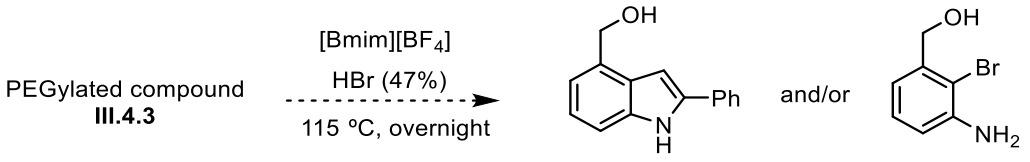


Scheme II.13 - Representation of the influence of the steric hindrance of PEG in the palladium insertion (oxidative addition).

The use of PEG-2000 as soluble polymer support could be interfering with the reaction, since this polymer was coupled to the substrate in an *ortho*-position relative to the bromine and in a *meta*- position relative to the amine group. Thus, a possible steric hindrance effect might be responsible by blocking the C – N cross-coupling reaction or even preventing the Heck coupling from happening.

To draw conclusions regarding the compounds being formed when the cascade reaction seemed incomplete, efforts were made towards cleavage of the compounds with the ether linker from PEG. Using the method reported by S.K. Boovanahalli[58] for the cleavage of ethers efforts were performed to cleave several of PEGylated compounds that resulted from the cascade reactions (Table II.5).

Table II.5 -Cleavage of compounds bound toPEGvia an ether linkage,resultantfrom the cascade C-N cross-coupling/Heck reaction



Entry	Substrate	[Bmim][BF_4] (Equiv)	Temperature (ºC)	Time (h)	Purification PTLC
1	III.4.3[a]	5.4	115	19	($CHCl_3$: MeOH 10:1), (Hexane: AcOEt 2:1)
2	III.4.3[b]	5.4	115	19	(Hexane: AcOEt 2:1)

Observations: a- compound III.4.3 from entry 3 in table II.4; b- compound III.4.3 from entry 4 in table II.4

Thus, the method for cleavage of compounds from PEG relied on a green approach involving the use of an ionic liquid combined with HBr. In this method the halide anion of the ionic liquid [Bmim][BF_4] exhibits a pivotal role as an efficient nucleophile acting in the presence of an effective proton donor to achieve this important and general transformation.
So this methodology was applied to compounds **III.4.3** (obtained from entries 3 and 4; Table II.4) and the reaction ran during 19 h. Then the mixtures were analyzed, and it was possible to observe that both compounds originated the same TLC pattern (entries 1 and 2; Table II.5), so both samples were combined and later purified by PTLC. When ^{1}H-NMR was performed, it was only possible to isolate PEG-2000, which means that the cleavage reaction was successful, but still it was not possible to identify any products, probably because after all operations carried only trace amounts of isolated compounds were obtained (~3mg).

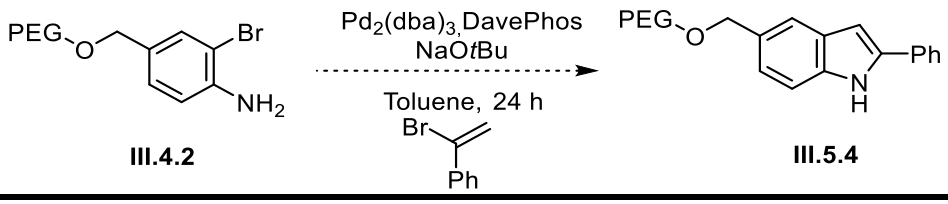
As previously mentioned, the use of the pegylated **3-amino-2-bromobenzoic** (**III.3.2**) and **(3-amino-2-bromophenyl) methanol** (**III.3.6**) as starting material in cascade C – N cross coupling/Heck reaction was not always successful. This fact was attributed to steric hindrance caused by PEG being coupled to this starting material in *ortho*- and *meta*- position but to the electronic effect caused by the ester and amide group. To overcome this issue, another synthetic approach was formulated in order to achieve the desired indole structures.

II.3.3– Testing cascade C – N cross coupling/Heck reaction conditions on a soluble polymer support (PEG-2000): new substrates

Thus, **4-amino-3-bromobenzoic acid** was used as starting material, on the expectation that the presence of PEG would not hinder any reaction, since this polymer would be linked to the carboxylic acid in *para*-position relative to the amine group. Based on the previous results the first explored substrate was the one with the ether linker, since the ester bound substrates were easily hydrolyzed under the tested reaction conditions.
With the synthetic strategy established **4-amino-3-bromobenzoic acid** (**III.3.5B**) was reduced to **(4-amino-3-bromophenyl) methanol** (**III.3.5**) in 30% yield. The low yield obtained was due to the low reactivity of the starting material.

Subsequently the coupling reaction between **(4-amino-3-bromophenyl) methanol** (**III.3.5**) and PEG-OTs was performed to originate the pegylated starting material **III.4.2** in 83% yield.
Since the cascade reaction with the previous starting materials **III.3.2** and **III.3.3** had failed, it was clear that the optimization of reaction conditions might be required for the new substrate (**Table II.6**).

Table II.6 - Influence of Pd/ligand and solvent in the cascade C-N cross coupling/Heck reaction.



III.4.2 **III.5.4**

Entry	**α-bromostyrene** (equiv/terminal)	**DavePhos** (mol%/terminal)	**Base**	**Time** (h)	**Solvent**	**$Pd_2(dba)_3$** (mol%/terminal)
1	2	8	NaO*t*Bu	24	Toluene	4
2	5	8	NaO*t*Bu	24	Toluene	4
3	5	16	NaO*t*Bu	48	Toluene	8

In the first essay the previously tested conditions used were maintained, since in this case the carbonyl group had been replaced by an alkyl group that was present in the *para*-position and could work as an electron-donor group, facilitating the C – N cross-coupling reaction. Still when analyzing the precipitate by ^{1}H-NMR it was hard to distinguish signals from the product. The TLC of the isolated pegylated compound showed that the mixture was complex, so the precipitate was purified by PTLC (CH_3Cl: MeOH 10:1). Although the compound had fewer impurities it was only possible to distinguish one characteristic signal at 7.96ppm that could belong to the desired indolic structure (**Figure II.3**).

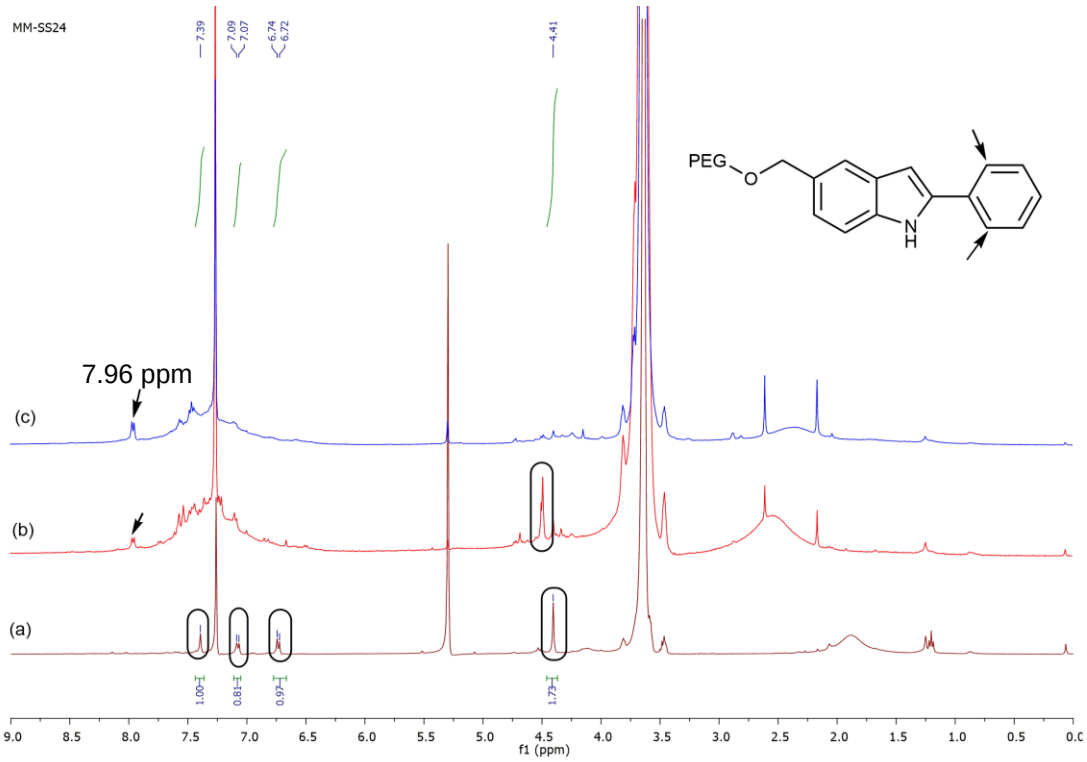


Figure II.3 – ^{1}H-NMR spectrum of (a) starting material **III.4.2**; (b) PEG-bound compound isolated and purified (entry 1); (c) crude.(entry 1)

Additionally, as it is shown in Figure II.3 – (b) spectrum it was possible to distinguish two different signals at 4.41 ppm, corresponding to the CH_2 between the heterocycle and PEG. This suggests that two molecules coupled at the terminal ends of PEG are different. Thus, if the reaction occurred, it might have taken place at only one of the terminals. That could be caused by the low amount of α-bromostyrene used, which was leading to an incomplete reaction.

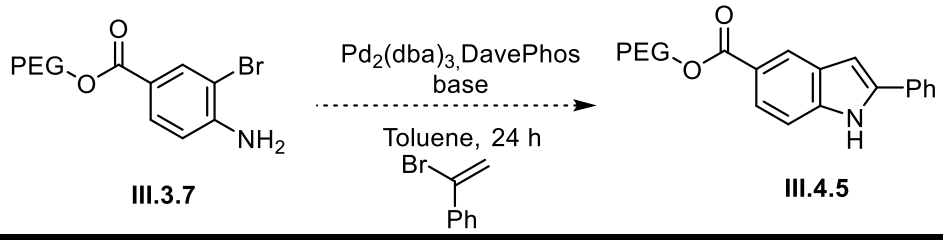
Consequently, 5 equiv per terminal of α-bromostyrene were used (entry 2), the reaction was followed by TLC during24h. By TLC no fluorescent spot was detected, but it was already known that this reaction led to complex mixtures, which complicates the analysis of the crude, being difficult to distinguish the pegylated products in the ^{1}H-NMR. Thus, the crude was purified using PTLC (CH_3Cl: MeOH 10:1) and the major product was isolated. Analysis by ^{1}H-NMR was inconclusive, since the aromatic region of the spectrum showed low resolution and it was difficult to conclude. One plausible explanation for the bad resolution of the NMR spectrum could be due to the swell of the pegylated sample in the deuterated solvent or by the low quantity of compound used. The influence of the resins on the quality of the NMR spectrum is reported, but it has been shown that both resin and solvent can affect the NMR spectrum quality (references cited therein).[59]

Next the loading of the catalytic system$Pd_2(dba)_3$/DavePhos was increased and the reaction mixture was allowed to react for 48 h (entry 3). After the reaction completion a brown solid was isolated, but analysis of the ^{1}H-NMR did not show any signals of the desired product.

The results obtained demonstrated that it is hard to identify the resulting product from the crude and from the precipitated PEG-bound compounds, even when chromatographic purification was carried (maybe due to the low swelling of the PEG-bound compounds). Therefore, to evaluate if the indole was being formed, the next step consisted on performing the reaction followed by cleavage of the products from PEG.

The previous studies indicated that using the ether bound substrates the cleavage would be difficult, since no compounds were isolated other than PEG in its free form. Thus, at this stage it was decided to explore the ester bound substrates, but now using **4-amino-3-bromobenzoic acid** (**III.3.5B**) as starting material. So the PEGylated compound **III.4.1** was successfully synthesized with 92% yield using Cs_2CO_3 as base, and later employed in cascade C-N cross-coupling/Heck reactions (**Table II.7**).

Table II.7 – Reaction of III.4.1 with a-bromostyrene in the presence ofa catalytic system Pd/ligand



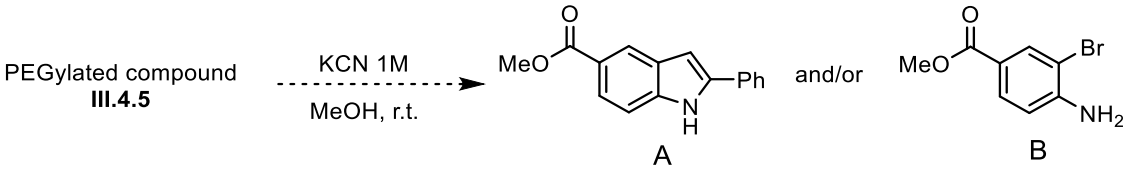
III.3.7 **III.4.5**

Entry	**α-bromostyrene** (equiv/terminal)	**DavePhos** (mol%/terminal)	**Base**	**Time**	**Solvent**	**$Pd_2(dba)_3$** (mol%/terminal)
1	5	8	Cs_2CO_3	24 h	Toluene	4
2	5	8	NaO*t*Bu	24 h	Toluene	4
3	5	8	Cs_2CO_3	3 days	Toluene	4
4	5	8	NaO*t*Bu	3 days	Toluene	4

In order to avoid hydrolysis of the compounds from PEG, it was decided to use a weaker base, Cs_2CO_3 to perceive if under these conditions the indole compound would be formed, or if the reaction only proceeds using a stronger base like NaO*t*Bu (entry 1). In all experiments the resulting compound was precipitated using cold diethyl ether and was later identified as PEGylated starting material, which means that the reaction didn't proceed under the conditions

described above (Table II.7), which can be attributed to the substitution pattern of the starting material **III.3.7** (entries 1 to 4). The *para*-position of the ester group relative to the amine might hinder the reaction, since this electron-withdrawing group has a direct resonance effect that can reduce the availability of the nitrogen electron pair and consequently the amine's attack to the palladium complex with the bromostyrene. In order to conclude if any product was formed, the crude was treated with KCN 1M in MeOH to cleave the resulting compound (entries 1, 3 and 4; Table II.7).

The cleavage of the compound resulting from the reaction carried under the conditions described in entry 1 originated a complex mixture that was purified by PTLC. After purification it was possible to isolate the methylated starting material in its free form (B), which proved that the cascade reaction didn't work when using Cs_2CO_3 as base (**Scheme II.14**). Similarly, the experiments described in entries 3 and 4 did not afford any products.



Scheme II.14 – Cleavage of compounds bounded to PEG via an ester groupresulting from the cascade C-N cross-coupling/Heck reaction

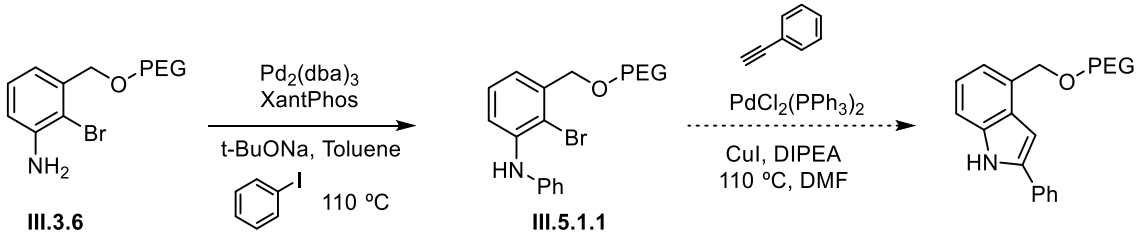
To conclude, even though compound **III.3.7** seemed promising it was not possible under the tested conditions to carry the cascade reaction using this substrate.

II.4 –N-arylation and Sonogashira approach towards indole and azaindole synthesis on PEG-2000

II.4.1–N-arylation and Sonogashira reaction on PEG-2000

Since the application of the cascade C – N cross coupling/Heck reaction to the pegylated substrates tested revealed to be difficult and required further investigation of the reaction conditions, it was decided to explore another approach. Using similar starting materials N-arylation and Sonogashira reaction were tested to achieve the indole derivatives. The first step of the Sonogashira reaction occurs between the aryl halide and the palladium catalyst, with the possibility of affording the Sonogashira product at high temperatures, if the halogen contains bromine, or affording the Sonogashira product at room temperature, if the halogen contains an iodine.[60]

The first attempt to perform N-arylation reaction and subsequent Sonogashira reaction was performed using compound **III.3.6** as starting material (**Scheme II.15**).

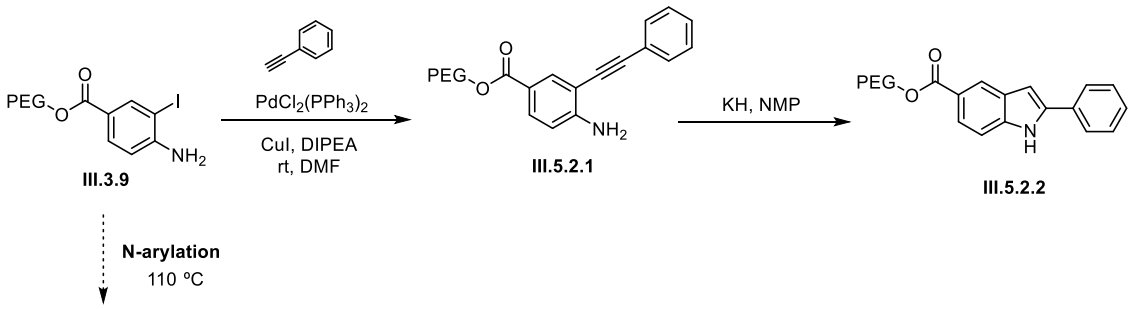


Scheme II.15 - Conditions for N-arylation and Sonogashira reaction using PEG bis (2-bromoaniline)

N-arylation reaction was performed using a $Pd_2(dba)_3$/XantPhos/NaO*t*Bu system that was already reported as being the optimal system for this type of compounds, and the N-arylated product was successfully obtained with 90% yield.[61] In order to achieve the desired PEGylated indole structure, compound **III.5.1.1** was employed in a Sonogashira reaction, so a system of $PdCl_2(PPh_3)_2$/CuI was used at 110 ºC, with the expectation that the Sonogashira product would be formed followed by in situ cyclization. After reaction completion, the PEGylated compound was precipitated and through ^{1}H-NMR analysis it was concluded that the isolated compound was starting material (**III.5.1.1**), which means that the Sonogashira reaction did not occur. This reaction failure may be related to the steric hindrance caused by PEG being linked to the anilines at an *ortho*-position relative to the bromine. The first step of the Sonogashira coupling involves activation of Pd(II) by a reduction to Pd(0), then this activated palladium catalyst reacts with our PEGylated aryl halide to produce a Pd(II) intermediate. This step is crucial in this reaction, and the fact that PEG is bounded to this compound at an *ortho*-position might have highly prevented this step.

At this point, the project was focused on the use of starting materials with an ester group in the *para*- position, since the cleavage reaction is easier, facilitating the product cleavage from PEG and the relative position of the substituents would prevent any steric hindrance issues. So in this new approach it was decided to use a starting material with the same substitution pattern as the one used before, with the acid in *para*-position relative to the amine, but using a iodo-aniline instead of bromo-aniline. The use of the iodo-aniline would allow performing the Sonogashira reaction at room temperature, which diminishes the possibility of products cleavage.

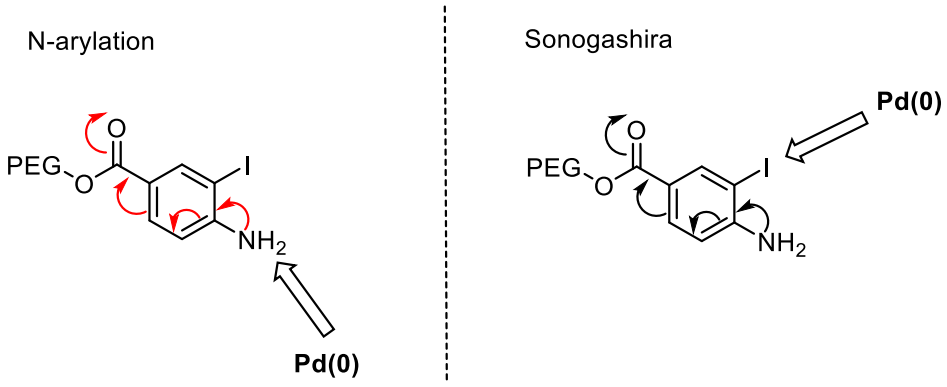
The first step consisted on the coupling of **4-amino-3-iodobenzoic acid** with PEG-OTs and afterwards to employ the Sonogashira coupling conditions, but at room temperature (**Scheme II.16**).



Scheme II.16 - Conditions for N-arylation, Sonogashira reaction and cyclization using PEG bis (4-amino-3-iodobenzoate)

After 48 h the Sonogashira product was successfully isolated with 73% yield, which proved that the conditions applied for the Sonogashira reaction were compatible with the soluble polymer support (PEG-2000) and that it was possible to purify this compound by precipitation. Once this reaction took place at room temperature there was no possibility of in situ cyclization, so it was necessary to find a method for cyclization of the Sonogashira product but still take into account the presence of a labile linker. Inspired by a protocol reported by C. Koradin[30] we used KH as base in a solution of dried NMP to afford the PEGylated indole with 62% yield. The use of a non-nucleophilic base like KH prevents the cleavage of the desired indole from PEG and allowed the isolation of this product by precipitation.

Ultimately it was decided to test the N-arylation reaction conditions into this same substrate but unfortunately the desired arylated product was not observed. N-arylation reaction of aryl iodide compounds have already been reported to give lower yield than the ones performed with aryl bromines, but the use of a substrate with an ester group in the *para*-position may have also contributed to the reaction failure (**Scheme II.17**).

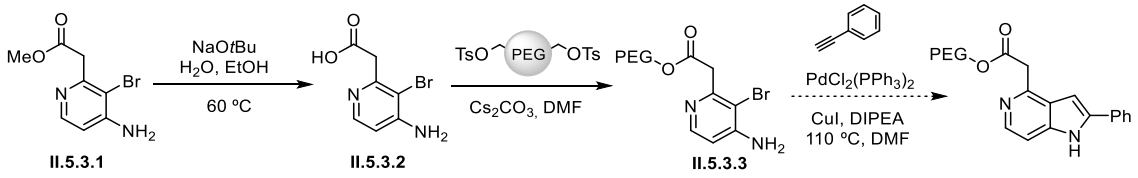


Scheme II.17 - Effect of the electron withdrawing group in para- position relative to the amine in N-arylation and Sonogashira reaction.

Despite that, the results obtained represent a promising advance in purification of indole derivatives. The use of metal-catalysed reactions in the synthesis of these heterocyclic

structures tends to lead to complex mixtures, which makes the product purification hard and expensive, since it requires the use of large amounts of silica and organic solvents. With this reaction it was demonstrated that it is possible to synthesize an indole derivative using PEG-2000 as a soluble polymer support via metal-catalysed cross-coupling reactions. Importantly, it was possible to isolate the product from the crude by precipitation with cold ether, with no need of further purification.

Since this system proved to be successful in affording the desired indole product only by precipitation with 62% yield, it was decided to apply these conditions for more challenging substrates like aminopyridines. Using a functionalized aminopyridine **III.5.3.1** (**Scheme II.18**), synthesized by a co-worker, the coupling reaction with PEG-OTs was attempted, using the same conditions previously described for compounds bound to PEG via a ester group.



Scheme II.18 - Conditions for PEGylation followed by Sonogashira reaction using aminopyridine **III.5.3.1**.

Thus, compound **III.5.3.3** was obtained with 95% yield and then employed in a Sonogashira reaction using a $PdCl_2(PPh_3)_2$/CuI system at 110 ºC. After 40 h the resulting product was isolated, and ^{1}H-NMR showed only signals corresponding to PEG-OH, which could indicate that the compound had been cleaved. Further analysis led to the conclusion the use of PEGylated aminopyridines as Sonogashira substrates requires deeper investigation. Aminopyridines are challenging starting materials for these reactions, due to the electron-withdrawing nature of pyridines, which reduces the nucleophilicity of the amine group however, as demonstrated for indole, metal-catalysed methods allow establishment of reactions once the optimal conditions are found. The literature has demonstrated that metal-catalysed reactions successfully allow synthesis of azaindoles, where the classic indole synthesis fails. Due to time limitation no further experiments were carried.

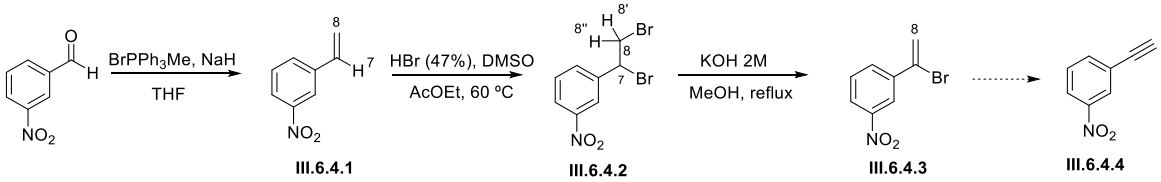
As part of this project involving metal-catalysed reactions using PEG as a soluble polymer support, we published a paper regarding the importance of PEG in several metal-catalysed reactions:

- Pires, M. J.; Purificação, S. I.; Santos, A. S.; Marques; M. M. B. Synthesis **2017**, 49 (11), 2337 – 2350

II.5 – Azaindole synthesis using non pegylated aminopyridine

II.5.1 – Synthesis of alkynes

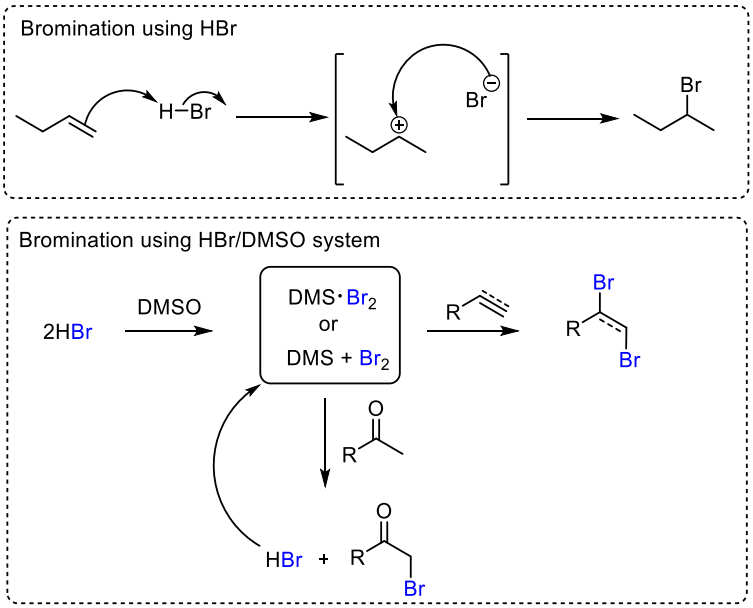
In order to expand the scope of the one-pot reaction several alkynes structures were synthesize. These alkynes were then employed in the Sonogashira reactions. My contribution to this project involved the synthesis of an alkyne using as starting material **3-nitrobenzaldehyde**.



SchemeII.19 – First synthetic strategy to prepare 1-ethynyl-3-nitrobenzene (**III.6.4.4**)

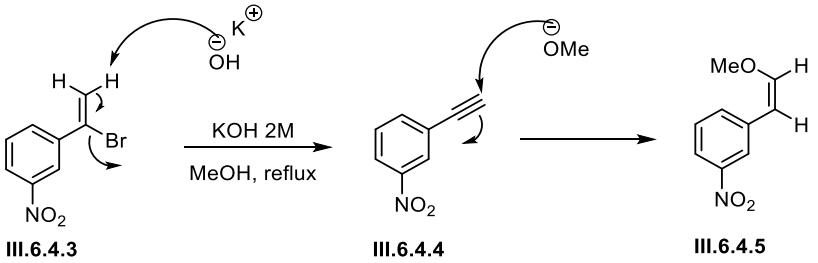
The first reaction consisted on a Wittig reaction between the aldehyde and the phosphonium ylide, which led to the formation of the alkene **III.6.4.1** in a moderate yield (52%), followed by a bromination.

Unlike the typical bromination using Br_2a protocol reported by S.Song[62] was adopted, that uses a combination of HBr and DMSO. Usually when HBr is used as a bromination agent the resulting product is the monobromide however, under the tested conditions monobromination did not occur. Described as an oxidative bromination, this reaction allows the production of Br_2using HBr as the brominating reagent and DMSO as the mild oxidant (**Scheme II.20**).



Scheme II.20 - Mechanism for the bromination reaction using HBr, and proposed mechanism for bromination using HBr/DMSO system.[62]

Using this protocol, the dibromide **III.6.4.2** was obtained in high yields. Next the compound **III.6.4.2** was treated with a solution of KOH 2M in methanol, so that the elimination reaction could take place (**Sheme II.19**). In this reaction two eliminations were expected: one to form the akenyl halide; and the second to form the alkyne. The first step provided the mono-bromide product, that was isolated with high yields (83%), but the second step did not afford the desired alkyne. Compound **III.6.4.3** was treated with 2 equiv of KOH 2M solution and the reaction was followed by TLC. After 17 h the conversion of the starting material was incomplete, thus 2equiv of KOH 2M solution were added, followed by 1 equiv of TBAI.



III.6.4.3 **III.6.4.4** **III.6.4.5**

Scheme II.21 - Proposed mechanism for failed synthesis of 1-ethynyl-3-nitrobenzene.

After 72 h the reaction was complete and the product was isolated using PTLC (Hexane:AcOEt 15:1). The ^{1}H-RMN spectrum revealed that the isolated compound was not the alkyne. Instead the **III.6.4.5** was formed (**Scheme II.21**). This reaction was performed using a strong base, KOH in MeOH. In a strong basic media MeOH can be deprotonated and form methanolate specie that can act as a nucleophile.

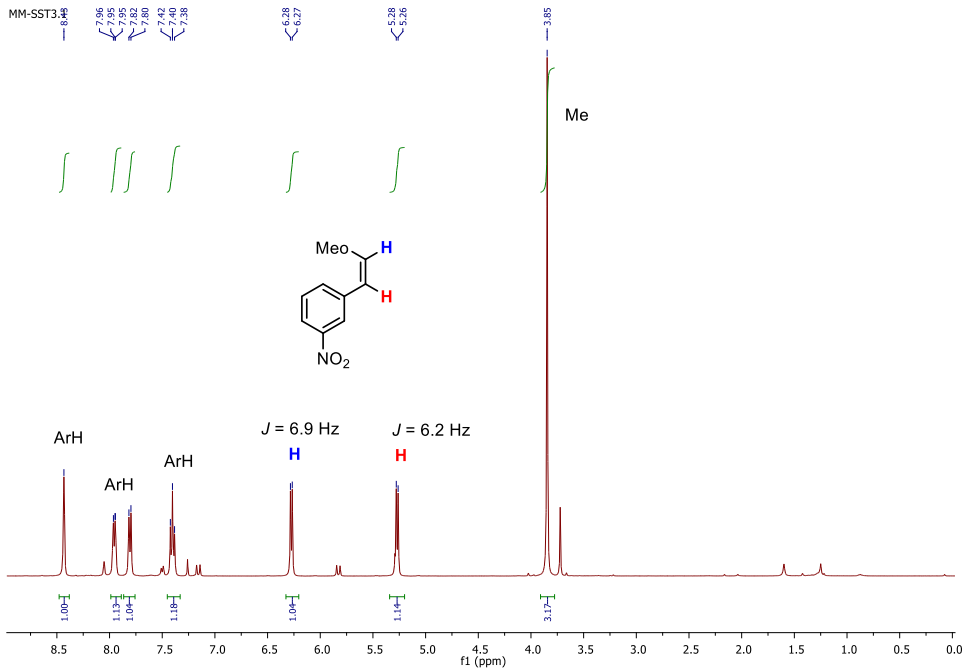


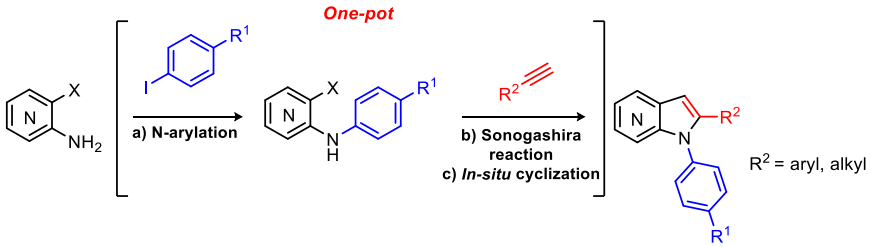
Figure II.4 – ^{1}H-NMR spectrum of resulting product by treatment of **III.6.4.3** with KOH 2M in methanol

After elimination of the second bromine the alkyne was formed but immediately suffered attack from the methanolate specie, which led to the formation of (Z)-1-(2-methoxyvinyl)-3-nitrobenzene (**Figure II.4**). Through the coupling constant values it was possible to conclude which isomer was formed. Typical values for J_{H-H} are 11-18 Hz for (E)-alkenes and 6 -14 Hz for (Z)-alkenes.

In order to obtain the desired alkyne, instead of the (Z)-1-(2-methoxyvinyl)-3-nitrobenzene, the reaction should be carried using a different solvent, like H_2O that in a basic media doesn't form strong nucleophilic species.

II.5.2 – One-pot synthesis of 1,2-disubstituted 4-,5-,6- and 7-azaindoles[60]

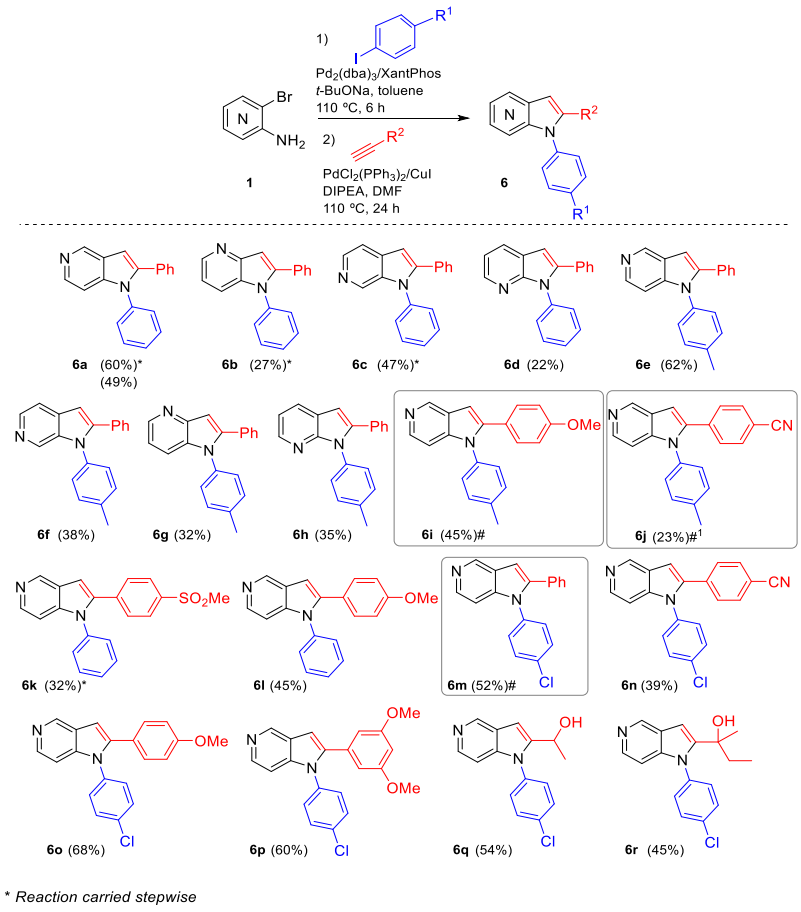
Our group has been focused on the development new and improved routes to achieve important privileged structures such as azaindoles. The previous methodology reported by the team involved a palladium-catalysed cascade C – N cross-coupling/Heck reaction that allowed a straightforward synthesis of substituted 4-, 5-, 6-, and 7-azaindoles, but did not work when applied to N-aryl amino-*ortho*-bromopyridines. Recently, a novel methodology for the one-pot synthesis of azaindoles has been investigated (**Scheme II.22**).



Scheme II.22 - General scheme for the one-pot synthesis of 1,2-disubstituted 4-,5-,6- and 7- azaindoles.

II.5.2.1 – Improving reaction scope

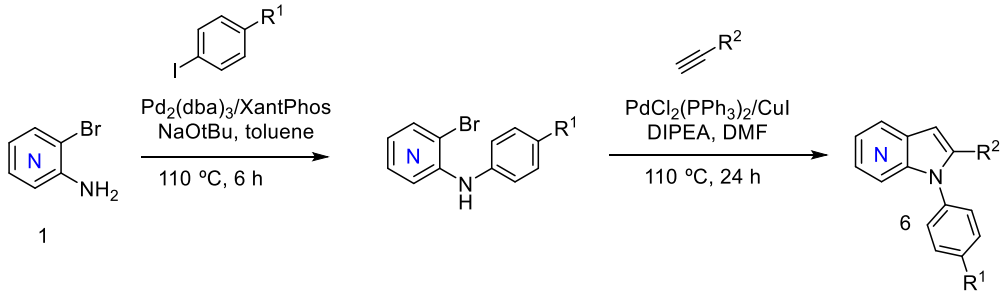
The cascade procedure involves a palladium-catalysed N-arylation followed by Sonogashira reaction and subsequent cyclization in a one-pot approach. In order to study the reaction scope several iodides were employed in the N-arylation reaction, as well as several alkynes were tested in the Sonogashira reactions. The results obtained demonstrate that this methodology exhibits a wide scope and compatibility with electron-withdrawing and electron-donating groups (**Scheme II.23**).



SchemeII.28 - Scope of the one-pot N-arylation/Sonogashira/cyclization reaction from amino-ortho-bromopyridines.

My contribution to this work involved the synthesis of two azaindole structures (#) and purification of (#[1]).

The first step to prepare (#) consisted on the N-arylation reaction using as starting material the commercially available 4-amino-3-bromopyridine (1).



Scheme II.24 - General synthetic scheme for N-arylation and Sonogashira followed by in situ cyclization of several aminopyridines.

This reaction was carried out using $Pd_2(dba)_3$/Xant Phos/NaO*t*Bu in toluene at 110ºC. The products from N-arylation were not isolated, and after solvent removal and resuspension in dry DMF, $PdCl_2(PPh_3)_2$/CuI and the corresponding alkyne were added, and the mixture heated at 110ºC for 24h to afford the azaindole structures (6) (**Scheme II.24**). Although the reaction was successful, the purification was laborious due to the high polarity of the azaindole nucleus making it hard to extract from the aqueous phase and hard to purify using silica gel chromatography, which can explain the moderate yields obtained.

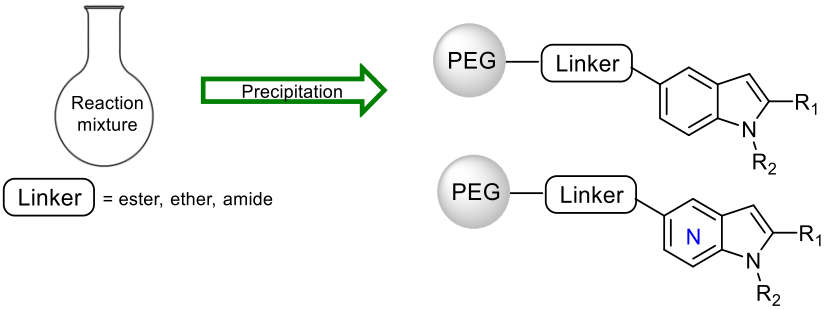
To sum up this strategy represents an advancement in azaindole chemistry with a straightforward approach towards 1,2-substituted azaindoles, while avoiding complex N-arylations of hindered 2-substituted azaindoles and difficult purification steps of intermediates.

The discovery of a new and improved method to afford 1,2-substituted azaindoles using a one-pot N-arylation/Sonogashira/cyclization reaction awarded us with the following publication:

- Purificação, S. I.; Pires, M. J.; Rippel R.; Santos A. S.; Marques, M. M. B. Org. Lett. **2017**, 19(19), 5118–5121

II.5 ─ Final Remarks

The main goal of this master thesis was to develop a sustainable synthesis of heterocyclic compounds using metal-catalysed cross-coupling reactions combined with a soluble polymer support, thus improving yields and avoiding laborious purifications (**Scheme II.25**).



Scheme II.25- General scheme for the strategy investigated

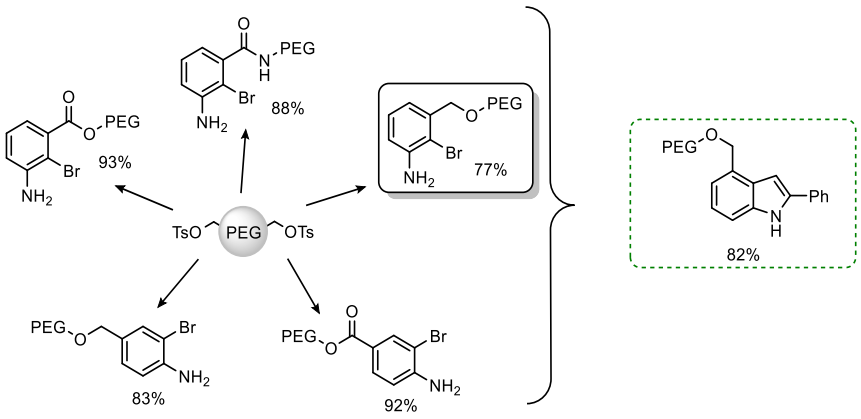
So for that purpose two different approaches were explored involving crucial metal-catalysed reactions that are known to afford indole and azaindole structures. For optimization purposes it was decided to initiate the study using anilines to afford the indole nucleus, since anilines are easier to handle then the aminopyridines (that afford azaindoles) (**Scheme II.25**).

The first experiments envisaged the establishment of the conditions for the synthesis of appropriate PEGylated substrates that could be later applied in a cascade C-N cross-coupling/Heck reaction to achieve the desired indole structures.

For the synthesis of the PEGylated substrates two coupling procedures were explored. The first involved activation of 2-amino-3-bromobenzoic acid followed by coupling reaction with PEG-OH, which proved to be unsuccessful. The second attempt involved the synthesis of PEG-OTs and coupling with 3-amino-2-bromobenzoic. This route proved to be efficient and versatile affording the desired PEGylated substrates in high yield (up to 94% yield), and was later applied to the synthesis of several PEGylated substrates using 4-amino-3-bromobenzoic acid as starting material (**Scheme II.26**).

After the conditions for coupling reactions were established, the different pegylated substrates were submitted to the conditions reported for the cascade C-N cross-coupling/Heck reaction using a $Pd_2(dba)_3$/DavePhos or XPhos/NaO*t*Bu or Cs_2CO_3.

Using PEG - bis (2-bromoaniline) as starting material and employing a $Pd_2(dba)_3$/DavePhos/NaO*t*Bu system, at 110ºC, it was possible to obtain the desired indole product by precipitation with 82% yield.

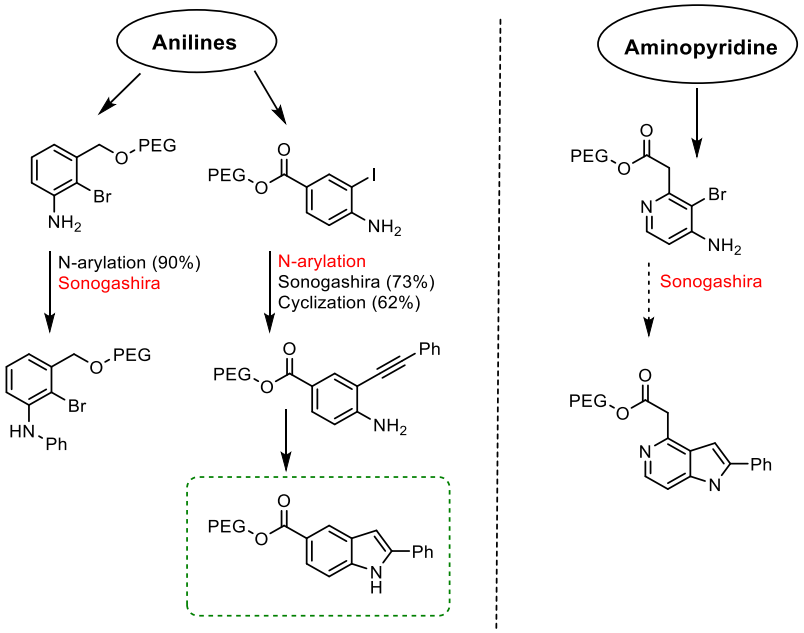


Scheme II.26 - Different pegylated substrates prepared and applied in the cascade approach

The only substrate that afforded the indole product was the one with the ether linker. The results obtained with the ester and amide bounded substrates can be explained due to their electron-withdrawing effect.

Besides this, the fact that the starting material has PEG coupled in an *ortho*- position to the bromine and *meta*- position to the amine might hinder the reaction. PEG-2000 is a large polymer that can cause steric hindrance preventing palladium insertion during the cascade C-N cross-coupling/Heck reaction. Regarding the PEGylated substrates with the ester linker in the *para*- position relative to the amine, the presence of the ester group in this position might have diminished the amine's reactivity.

In the second part of the project, two types of PEGylated substrates were used in N-arylation and Sonogashira reactions (**Scheme II.27**). The Sonogashira reaction is a known reaction that can be applied to prepare the indole nucleus by coupling of halo-anilines with terminal alkynes, which products can be subsequently cyclized. This reaction depends on the halogen at the aromatic ring, occurring at 110ºC when the halogen is bromine and at room temperature when the halogen is iodine.



Scheme II.27 - Synthetic studies performed on the pegylated substrates: N-arylation and Sonogashira reaction.

The first compound, PEG bis (2-bromoaniline), was used for N-arylation reaction and subsequent Sonogashira reaction. The N-arylated product was afforded as a solid with high yields, but the Sonogashira reaction did not seem to occur, which may again be associatedto the steric hindrance caused by PEG being linked to the anilines in an *ortho*-position relative to the bromine. This fact led us to explore another substrate, the PEG bis (4-amino-3-iodobenzoate). This compound allowed to perform the Sonogashira reaction at room temperature using $PdCl_2(PPh_3)_2$ as catalyst, CuI as co-catalyst and the desired Sonogashira product was obtained in good yield, followed by subsequent cyclization using KH in NMP affording the PEGylated indole with 62% yield.

Since this system proved to be successful in affording the desired indole product, it was decided to apply these conditions for more challenging structures like aminopyridines. In order to do that 2-(4-amino-3-bromopyridin-2-yl)acetic acid was coupled with PEG-OTs in high yields and this product was later used in the Sonogashira reaction. After analysis of the results obtained, it was concluded that the desired azaindole was not obtained probably because aminopyridines are challenging starting materials for these reactions, due to the electron-withdrawing nature of pyridines, which reduces the nucleophilicity of the amine group, so this reaction needs further investigation.

Finally, despite all issues a successful methodology was developed, that can be a promising in purification of indole derivatives structures. So with this work we developed two successful

paths to afford indole structures one involving Cascade C-N/Heck reaction and another involving N-arylation and Sonogashira reaction.

The use of metal-catalyzed reactions in the synthesis of these structures tends to lead to complex mixtures, which makes the product purification hard and expensive, since it requires the use of large amounts of silica and organic solvents. With this reaction we have proven to be able to synthesize an indole derivative using PEG-2000 as a soluble polymer support, and more important, it was possible to isolate the product from the crude by precipitation with cold ether, with no need of further purification.

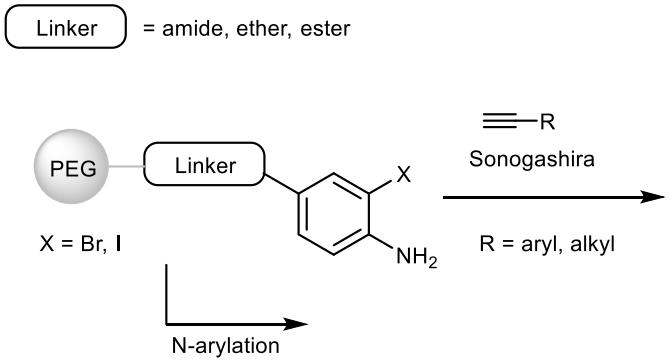
As part of this work we also developed a new route to attain 1,2-disubstituted azaindole derivatives involving N-arylation/Sonogashira/Cyclization. To do that commercially available aminopyridines were coupled with several alkynes (commercially available and prepared) using a $Pd_2(dba)_3$/CuI system to afford several azaindole structures with 22 – 68% yield.

Regarding this work our discoveries awarded us with two publications:

- Pires, M. J.; Purificação, S. I.; Santos, A. S.; Marques; M. M. B. Synthesis **2017**, 49 (11), 2337 – 2350
- Purificação, S. I.; Pires, M. J.; Rippel R.; Santos A. S.; Marques, M. M. B. Org. Lett. **2017**, 19(19), 5118–5121

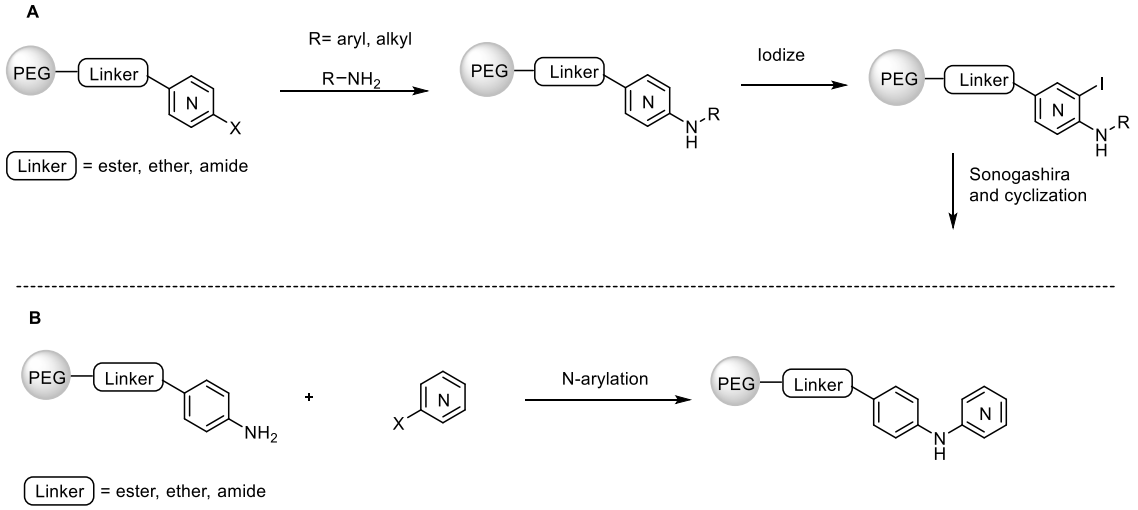
II.6 ─ Future perspectives

For the future work of this project, we intend to continue developing and optimizing all conditions for the synthesis of indole and azaindole structures through metal-catalysed reaction using PEG-2000 as soluble polymer support. This way different linkers can be explored using derivatives of PEGylated substrates with iodine and bromine that can be employed in the Sonogashira reaction, and also optimize the N-arylation reactions of these structures (**Scheme II.28**).



Scheme II.28 - Plan for future work : optimization of sonogashira and N-arylation reaction conditions using different alkynes and N-arylation reagents

On a later stage we also intended to apply this methodology involving PEG-2000 to other synthetic strategies to prepare heterocyclic compounds. Using PEG-2000 not only as a support for aminopyridines that can later be used in Sonogashira and cyclization reactions (**Scheme II.29**; A), but also as support of N-arylation reagents (**Scheme II.29**; B).



Scheme II.29 - Plan for future work: Development of methodology using PEG as a solid support for aminopyridines and optimization of Sonogashira and cyclization conditions (A);Development of methodology using PEG as a solid support for N-arylation reagents and optimization of N-arylation conditions (B) .

Conclusively, following optimization of these reactions, the designed strategies will be applied to prepare the desired azaindole derivatives. The advances made in this work will prove essential for the synthesis and purification of these compounds, leading to a development of a greener and simpler methodology and will hopefully improve purification and isolation of diverse privileged structures.

III. Experimental

III.1 – General information

The experimental part of this work involved the use of general laboratory procedures.

All reagents and solvents were acquired commercially and used without further purification, unless otherwise mentioned. All of the mentioned solvents were, when necessary, dried using typical methods.[63] Molecular sieves were activated by heating at 300 °C in a muffle furnace for 3h.

Analytical TLC was performed on Merck Kieselgel GF 254 0.2 mm plates supported on aluminum. Preparative TLC was performed using Merk Kieselgel 60GS_{254} silica gel for TLC supported on a glass surface with the described eluent for each case. Column chromatography was performed using Merck Kieselgel 60A silica gel (70-200 mesh) and the described eluent for each case.

Melting points were measured using a Reichert Thermovar melting point apparatus, equipped with a Kofler plate. Measured melting points were not corrected.

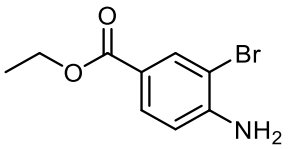
IR spectrum were acquired using a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer. Transmittance of the sample was acquired on between 4000 and 600 $cm^{-1}$and the samples were supported on KBr pellets or NaCl pellets.

NMR spectrum were acquired with Bruker ARX 400 or Bruker Avance III 400 spectrometers. ^{1}H-NMR and ^{13}C-NMRspectrum were measured at 400 and 101 MHz, respectively. The samples were prepared on 5 or 3 mm NMR tubes using $CDCl_3$ or DMSO-d_6 as solvents and the corresponding trace $CHCl_3$ or DMSO as reference signals. The NMR signals are described with chemical shift (δ, in ppm), source of signal (R-H) and relative intensity of signal multiplicity (nH, with n being the number of protons) of NMR signals are described as singlet (s), doublet (d), triplet (t) and multiplet (m) with coupling constant (J) being given in Hz.

Mass spectrum were acquired with GC-MS using a MicroTOF gas chromatographer and ESI-FIA-TOF. Details of mass spectrum are given as mass-to-charge ratio (m/z), attributed molecular formula and relative intensity of the molecular fragment.

III.2 – Preliminary studies:

III.2.1 – Ethyl 4-amino-3-bromobenzoate (SS36)[64]



To a round bottom flask were added 4-amino-3-bromo benzoic acid (**II.2.1**) (100mg, 1equiv, 0.47mmol) and Cs_2CO_3 (151 mg, 1equiv) and then the flask was sealed with a suba-seal, evacuated and backfilled with nitrogen twice. DMF (5mL) was added and the mixture was placed in an ice bath. Then ethyl bromide (35µL, 1equiv) was added and the solution was stirred for 2h at room temperature. The mixture was diluted in AcOEt and washed twice with water, then dried over Na_2SO_4 and evaporated to dryness. The product was obtained as a light brown solid by precipitation. (quant.)

IR (KBr) ν_{max} (cm^{-1}): 3475, 3363, 2984, 2954, 2928, 2859, 1745.

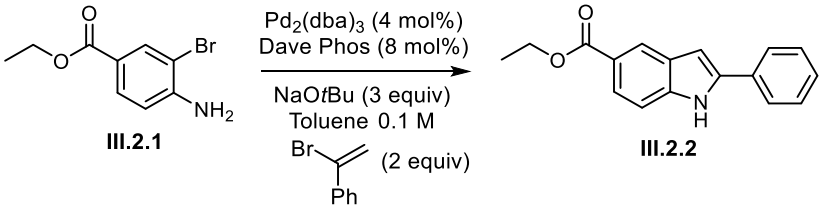
^{1}H-NMR (400MHz; $CDCl_3$) δ (ppm): 8.12 (d, ArH, *J* = 1.3 Hz, 1H), 7.79 (dd, ArH, *J* = 8.4, 1.3 Hz, 1H), 6.73 (d, ArH, *J* = 8.4 Hz, 1H), 4.32 (q, CH_2*J* = 7.1 Hz, 2H), 1.36 (t, CH_3*J* = 7.1 Hz, 3H).

III.2.2 –Cascade C-N Cross coupling/Heck reactions

General procedure for the Cascade C-N cross coupling/Heck reaction

A sealed tube equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (4mol%), ligand (8mol%), base (3equiv), and substrate (1equiv). The tube was sealed with a suba-seal, evacuated and backfilled with nitrogen thrice. Solvent (0.1M) was then added, followed by α-bromo styrene (2equiv) and the reaction was stirred for 24h at 110ºC. The solution was allowed to cool to room temperature and then filtered over a celite pad and concentrated. After that the mixture was diluted in DCM and a saturated solution of NH_4Cl was added. Aqueous layer was extracted several times (at least 3). Combined organic layers were dried with Na_2SO_4, filtered and concentrated. The resulting oil was dissolved in a small amount of DCM and precipitated and washed with cold ether, to obtain the product.

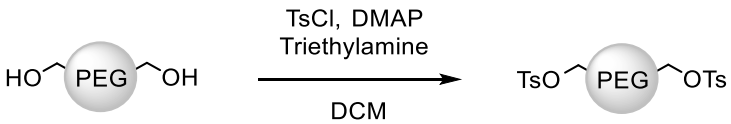
Table III.1 – Preliminary optimization of condition for cascade C-N cross-coupling/Heck reaction with ethyl 4-amino-3-bromobenzoate.



III.2.1 III.2.2

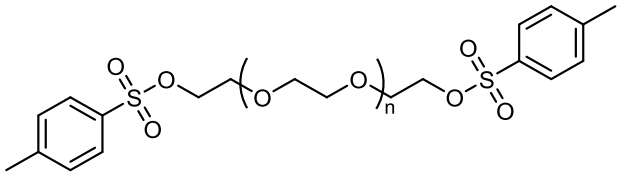
Entry	Substrate	Ligand	Temperature (ºC)	Time (h)	TLC
1	III.2.1	DavePhos	110	24	Compounds with fluorescence
2	III.2.1	DavePhos	110	48	New fluorescent compound

III.3 – Established conditions for synthesis of PEGylated starting materials



III.3.1

III.3.1 – PEG - bis(4-methylbezenesulfonate)



To a PEG 2000 (1g, 1equiv) solution in DCM (10.3mL) was added triethylamine (214µL). The flask was placed in an ice bath and TsCl (293mg, 2equiv) and DMAP (19mg, 0.2equiv) were added. The mixture was allowed to slowly rise to room temperature and stirred at this temperature 24h. The mixture was washed twice with saturated NH_4Cl solution, water and dried over Na_2SO_4 and evaporated to dryness. The resulting oil was dissolved in a small amount of DCM and precipitated and washed with cold ether, to obtain the compound as a white solid. (quant.).

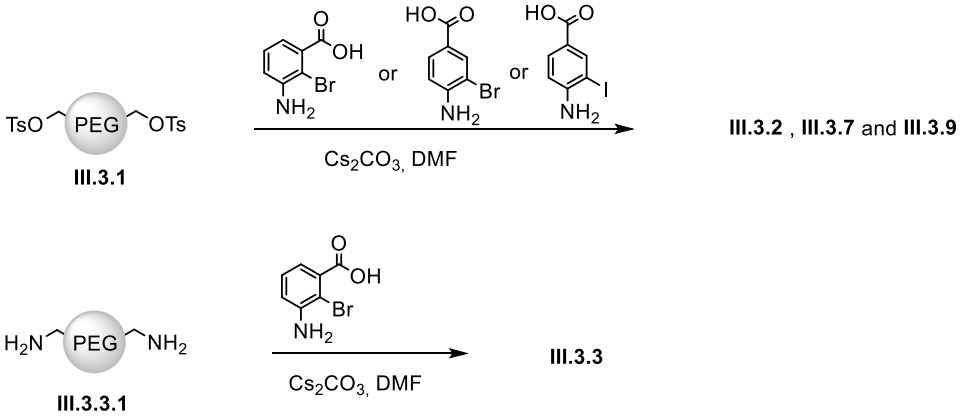
IR (KBr) ν_{max} (cm^{-1}): 3436, 2880, 1645, 1467, 1345 1114.

^{1}H-NMR (400MHz; $CDCl_3$) δ (ppm):7.78 (d, ArH, J= 8.2 Hz, 2H), 7.33 (d, ArH, J=8.Hz, 2H), 4.14

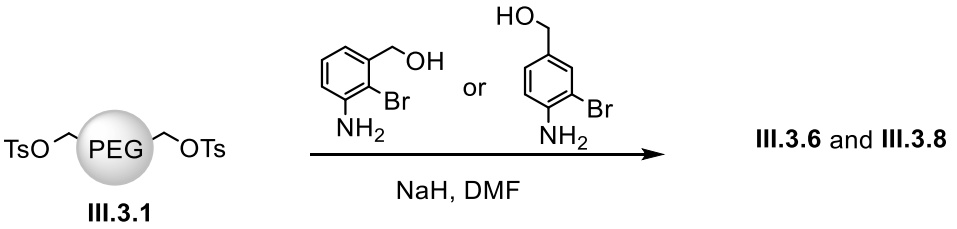
(t, PEG CH_2, J=4.5 Hz, 2H),3.80-3.57 (m, PEG CH_2, 34H), 2.43 (s, CH3, 3H).

^{13}C-NMR (101MHz; $CDCl_3$) δ(ppm):144.8 (CAr), 113.1 (CAr), 129.9 (2xCAr), 128.0 (2xCAr), 70.8 (CH_2 PEG), 70.6 (CH_2 PEG), 69.3 (CH_2 PEG), 68.7 (CH_2 PEG), 21.7 (CH_3).

General procedure for PEGylation reaction

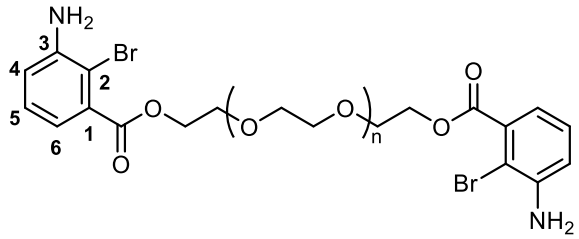


Using ester and amide bound substrates: To a PEG-OTs or PEG-NH_2 (1equiv) solution in DMF (1.1 mL) was added Cs_2CO_3 (3equiv) and **aniline**(3equiv). The mixture was stirred at room temperature for 24 h. The mixture was washed with water, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and evaporated do dryness. The resulting oil was dissolved in a small amount of DCM and precipitated and washed with cold ether, to obtain the compound as a solid.



Using ether bound substrates: To a reduced aniline (4equiv) solution in DMF (100µL) was added NaH (4equiv) at 0ºC under N_2 atmosphere and the mixture was stirred for 40minutes. Then a solution of PEG-OTs (1equiv) in DMF (342µL) was slowly added to the alkoxide and the mixture was stirred at 0ºC for 15minutes. After that the mixture was stirred at room temperature during 24h. The mixture was washed with water, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and evaporated do dryness. The resulting oil was dissolved in a small amount of DCM and precipitated and washed with cold ether, to obtain the compound as a solid.

III.3.2 – PEG - bis (3-amino-2-bromobenzoate)



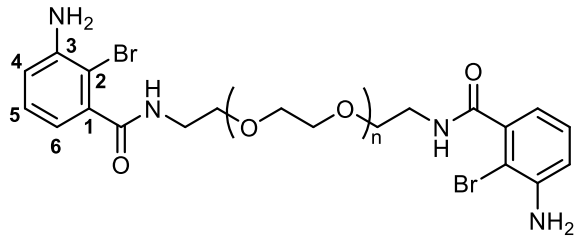
Compound was obtained as a white solid. (484.3mg, 93%).

IR (KBr) ν_{max} (cm^{-1}): 3466, 3352, 2919, 1967, 1731, 1621, 1455, 1349, 1110.

^{1}H-NMR (400MHz; DMSO) δ (ppm): 7.14 (t, ArH, *J* = 8.2 Hz, 1H), 6.93 (m, ArH, 1H), 6.80 (d, *J* = 7.3 Hz, 1H), 4.40 – 4.27 (m, PEG CH_2, 2H), 3.72 – 3.69 (m, PEG CH_2, 2H), 3.63 – 3.41 (m, PEG CH_2, 84H)

^{13}C-NMR (101MHz; DMSO) δ (ppm): 166.7 (C=O), 146.8 (C-3), 133.9 (C-1), 127.8 (C-5), 117.4 (C-4), 117.1 (C-6), 104.6 (C-2), 69.7 (CH_2 PEG), 68.1 (CH_2 PEG), 64.2 (CH_2 PEG).

III.3.3 – PEG - bis (3-amino-2-bromobenzamide)



Compound was obtained as a white solid. (183.4mg, 88%).

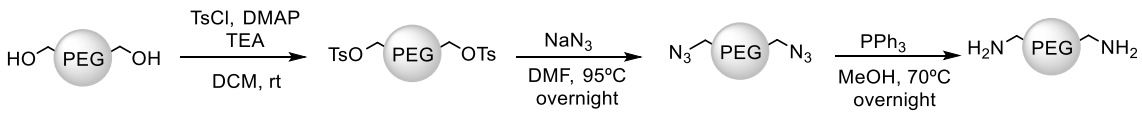
IR (KBr) ν_{max} (cm^{-1}):3466, 3353, 2921, 1957, 1723, 1621, 1455, 1349, 1113.

^{1}H-NMR (400MHz; $CDCl_3$) δ (ppm):7.23 (d, ArH,J = 7.6 Hz, 1H), 7.16 (t, ArH,J = 7.7 Hz, 1H), 6.92 (d, ArH,J = 7.8 Hz, 1H), 3.98 – 3.91 (m, CH_2 PEG, 1H), 3.86 – 3.81 (m, CH_2 PEG, 1H), 3.80 – 3.52 (m, CH_2 PEG,162H), 3.52 – 3.45 (m, CH_2 PEG,2H).

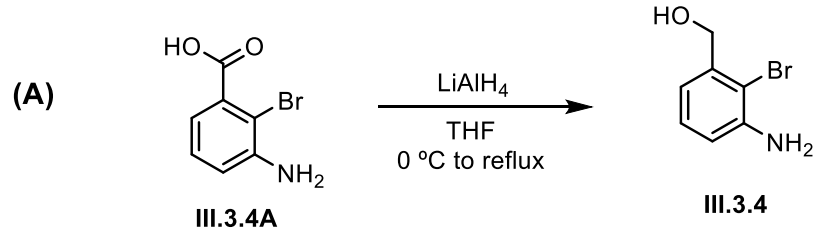
^{13}C-NMR (101MHz; $CDCl_3$) δ(ppm):* 70.70 (CH_2 PEG)

***low concentration of the sample didn't allow observation of all shifts

III.3.3.1 – PEG diamine synthetic path (synthesize by a co-worker)

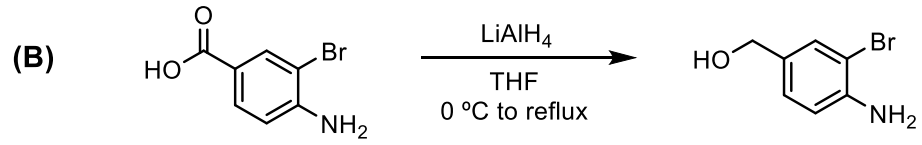


III.3.4 – 3-amino-2-bromobenzoic acid (A) and III.3.5 –4-amino-3-bromobenzoic acid reduction (B)



III.3.4A

III.3.4

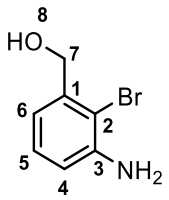


III.3.5B

III.3.5

To a $LiAlH_4$ (4.5equiv) was slowly added THF (2.8M) at 0ºC under an atmosphere of N_2. To the mixture was slowly added **amino-bromobenzoic acid compound** (1equiv) in THF (0.6M). The reaction mixture was stirred at 0ºC under an atmosphere of N_2 for 30 minutes, and then refluxed in an oil bath for 24h. The resulting mixture was cooled to 0ºC. Water, 15% NaOH aq and water were added successively at 0ºC, and the mixture was stirred at room temperature for 48h. Then the mixture was acidified with HCl 1M and extracted several times with AcOEt, dried over Na_2SO_4 and evaporated do dryness to obtain the compound as a solid.

III.3.4 – (3-amino-2-bromophenyl) methanol



III.3.4

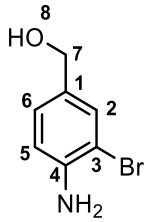
Isolated as a light brown solid (291.4mg, 62%)

IR (KBr) ν_{max} (cm^{-1}):3415, 1563, 1505, 1447, 1399.

^{1}H-NMR (400MHz; $CDCl_3$) δ (ppm):7.12 (t, ArH-5, *J* = 7.7 Hz, 1H), 6.86 (d, ArH-5, *J* = 7.2 Hz, 1H), 6.73 (d, ArH-4, *J* = 7.2 Hz, 1H), 4.72 (s, H-7, 2H).

^{13}C-NMR (101MHz; $CDCl_3$) δ (ppm): 144.89 (C-3), 133.08 (C-1), 129.93 (C-5), 128.09 (C-6), 70.83 (C-4), 69.35 (C-2), 68.77 (C-7).

III.3.5 – (4-amino-3-bromophenyl) methanol



III.3.5

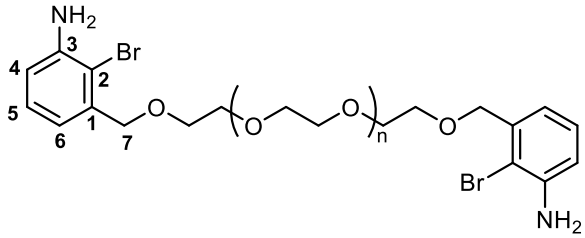
Isolated as a light orange solid (65.8mg,30%)

IR (KBr) ν_{max} (cm^{-1}):3350, 2927, 2874, 1621, 1504, 1415.

^{1}H-NMR (400MHz;$(CD_3)_2CO$) δ (ppm):8.05 (s, ArH-2, *J* = 1.3 Hz, 1H), 7.77 (d, ArH-6, *J* = 1.3 Hz, 1H), 6.91 (d, ArH-5, *J* = 8.5 Hz, 1H), 5.67 (s, H-7, 2H).

^{13}C-NMR (101MHz; $(CD_3)_2CO$) δ (ppm): 143.73 (C-4), 132.30 (C-1), 131.82 (C-2), 127.77 (C-6), 115.84 (C-5), 109.29 (C-3), 64.68 (C-7).

III.3.6 – PEG - bis (2-bromoaniline)



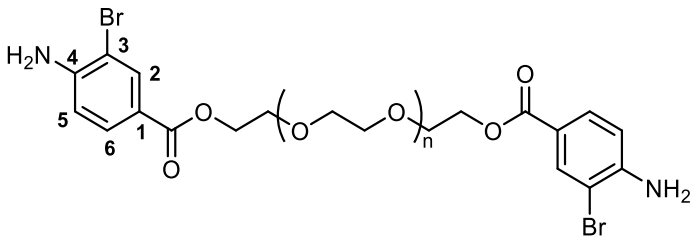
Compound was obtained as a light yellow solid (157.8mg, 77%).

IR (KBr) ν_{max} (cm^{-1}):3584, 3354, 2921, 1985, 1621, 1470, 1379, 1114.

^{1}H-NMR (400MHz; $CDCl_3$) δ (ppm):7.15 – 7.03 (m, ArH, 1H), 6.87 (d, ArH, *J* = 7.2 Hz, 1H), 6.73 (d, ArH, *J* = 7.7 Hz, 1H), 4.58 (s, H-7, 2H), 3.68 (m, PEG CH_2, 162H).

^{13}C-NMR (101MHz; $CDCl_3$) δ (ppm):144.31 (C-3), 138.28 (C-1), 127.74 (C-5), 118.55 (C-6), 114.82 (C-4), 109.61 (C-2), 73.06 (C-7), 70.69 (CH_2 PEG), 70.56 (CH_2 PEG), 70.03 (CH_2 PEG)

III.3.7– PEG - bis(4-amino-3-bromobenzoate)



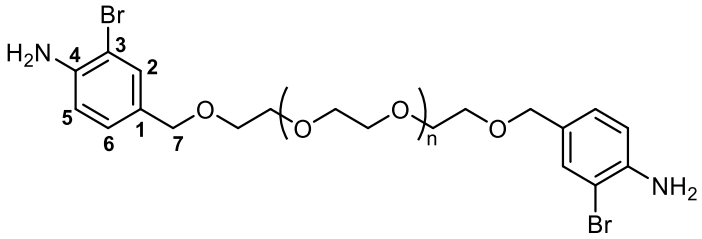
Compound was obtained as a white solid. (240.8mg, 92%).

IR (KBr) ν_{max} (cm^{-1}):3583, 3470, 3347, 2871, 1707, 1626, 1455, 1349, 1108.

^{1}H-NMR (400MHz; $(CD_3)_2CO$) δ (ppm): 8.09 (s, ArH, 1H), 7.76 (d, Ar-H, *J* = 8.0 Hz, 1H), 6.75 (d, Ar-H, *J* = 8.3 Hz, 1H), 4.39 – 4.38 (m, PEG CH_2, 2H), 3.79 – 3.78 (m, PEG CH_2, 2H), 3.61 (m, PEG CH_2,98H).

^{13}C-NMR (101MHz; $(CD_3)_2CO$) δ (ppm): 165.73 (C=O), 150.88 (C-4), 134.98 (C-2), 131.04 (C-6), 120.17 (C-1), 115.11 (C-5), 107.37 (C-3), 71.25 (CH_2 PEG), 69.80 (CH_2 PEG), 64.50 (CH_2 PEG)

III.3.8 – PEG - bis(3-bromoaniline) (SS24)



Compound was obtained asa light yellow solid (109.1mg, 83%).

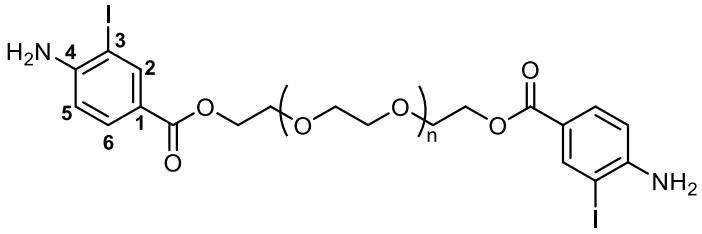
IR (KBr) ν_{max} (cm^{-1}):3582, 3346, 2870, 1624, 1349, 1107.

^{1}H-NMR (400MHz; $CDCl_3$) δ (ppm): 7.42 (s, ArH, 1H), 7.10 (d, ArH, *J* = 7.9 Hz, 1H), 6.76 (d, ArH, *J* = 8.1 Hz, 1H), 4.43 (s, H-7,2H), 3.86 – 3.81 (m, CH_2 PEG, 2H), 3.76 – 3.58 (m, CH_2 PEG, 94H).

^{13}C-NMR (101MHz; $CDCl_3$) δ(ppm):*

***low concentration of the sample didn't allow this spectrum to be obtained

III.3.9 – PEG -bis (4-amino-3-iodobenzoate) (SS31)



Compound was obtained as a light yellow solid. (200mg, 94%).

IR (KBr) ν_{max} (cm^{-1}):3458, 3345, 3210, 2857, 1957, 1705, 1622, 1454, 1349, 1117.

^{1}H-NMR (400MHz; $(CD_3)_2CO$) δ (ppm): 8.27 (s, ArH, 1H), 7.78 (dd, ArH, J = 8.5, 1.5 Hz, 1H), 6.88 (d, ArH, J = 8.5 Hz, 1H), 4.37 (t, CH_2 PEG, J = 6 Hz, 2H), 3.79 (t, CH_2 PEG, J = 6 Hz, 2H),

3.71 – 3.52 (m, CH_2 PEG, 88H).

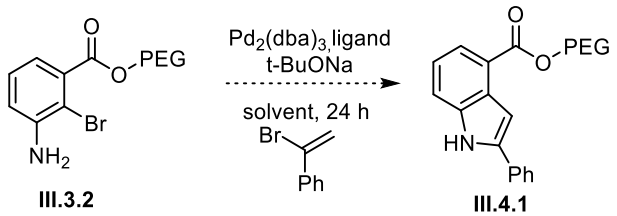
^{13}C-NMR (101MHz; $(CD_3)_2CO$) δ (ppm): 164.61 (C=O), 152.63 (C-4), 140.78 (C-2), 130.96 (C-6), 119.84 (C-5), 113.06 (C-1), 80.62 (C-3), 70.36 (CH_2 PEG), 68.93 (CH_2 PEG), 63.59 (CH_2 PEG).

III.4 – Cascade C-N Cross coupling/Heck reactions using PEG-2000 as solid support

III.4.1 – Cascade C-N Cross coupling/Heck reaction using PEG – bis (3-amino-2-bromobenzoate) as starting material

A sealed tube equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (4mol%), ligand (8mol%), base (3equiv), and PEGylated compound **III.3.2** (1equiv). The tube was sealed with a suba-seal, evacuated and backfilled with nitrogen thrice. Solvent (0.1M) was then added, followed by α-bromostyrene (2equiv) and the reaction was stirred for 24h at 110ºC. After work up (see general procedure) all compounds were isolated by precipitation with cold ether.

Table III.28 - Influence of Pd/ligand and solvent in the cascade C-N cross coupling/Heck reaction with PEG bis (3-amino-2-bromobenzoate).



III.3.2 **III.4.1**

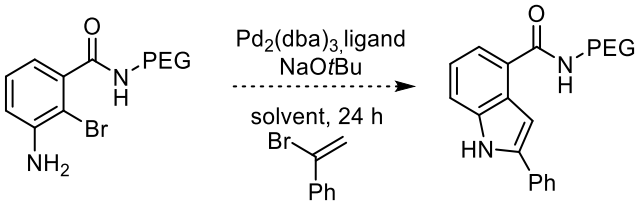
Entry	α-bromostyrene (equiv./terminal)	Ligand	Base	Time (h)	Solvent	$Pd_2(dba)_3$ (mol%/terminal)
1	1.5	XPhos	NaO*t*Bu	24	*t*BuOH	4
2	1.5	DavePhos	NaO*t*Bu	24	Toluene	4

Observations: entry 1 – only possible to isolate PEG-2000; entry 2 – Only PEGylated starting material was isolated

III.4.2 – Cascade C-N Cross coupling/Heck reaction using PEG – bis (3-amino-2-bromobenzamide) as starting material

A sealed tube equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (4mol%), ligand (8mol%), base (3equiv), and PEGylated compound **III.3.3** (1equiv). The tube was sealed with a suba-seal, evacuated and backfilled with nitrogen thrice. Solvent (0.1M) was then added, followed by α-bromo styrene (2equiv) and the reaction was stirred for 24h at 110ºC. After work up (see general procedure) all compounds were isolated by precipitation with cold ether.

TableIII.39 -- Influence of Pd/ligand and solvent in the cascade C-N cross coupling/Heck reaction with PEG bis (3-amino-2-bromobenzamide).



III.3.3 **III.4.2**

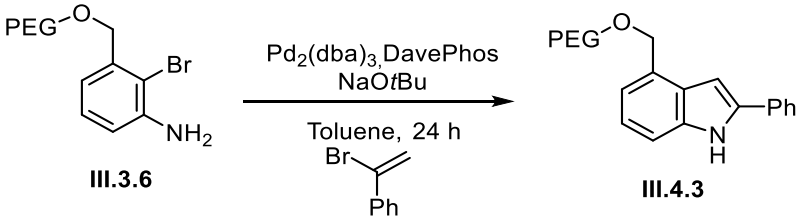
Entry	α-bromostyrene (equiv./terminal)	Ligand	Base	Time (h)	Solvent	$Pd_2(dba)_3$ (mol%/terminal)
1	1.5	XPhos	NaO*t*Bu	24	*t*BuOH	4
2	1.5	DavePhos	NaO*t*Bu	24	Toluene	4

Observations: entry 1 – Only PEG-2000 was isolated; entry 2 – this essay led to a complex mixture

III.4.3 – Cascade C-N Cross coupling/Heck reaction using PEG – bis (2-bromoaniline) as starting material

A sealed tube equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (4mol%), ligand (8mol%), base (3equiv), and PEGylated compound **III.3.6** (1equiv). The tube was sealed with a suba-seal, evacuated and backfilled with nitrogen thrice. Solvent (0.1M) was then added, followed by α-bromo styrene (2equiv) and the reaction was stirred for 24h to 48 h at 110ºC. After work up (see general procedure) all compounds were isolated by precipitation with cold ether.

TableIII.4 - Influence of Pd/ligand and solvent in the cascade C-N cross coupling/Heck reaction with PEG bis (2-bromoaniline).



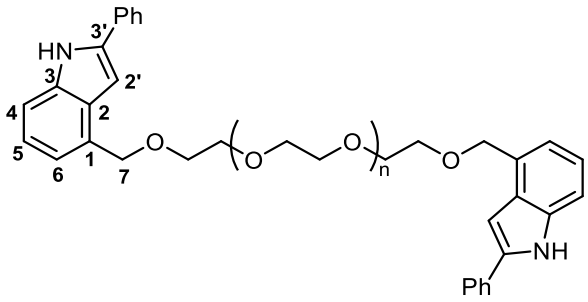
III.3.6 III.4.3

Entry	α-bromostyrene (equiv/terminal)	Ligand	Base	Time (h)	Solvent	$Pd_2(dba)_3$ (mol%/terminal)	Yield (%)
1[a]	2	DavePhos	NaO*t*Bu	24	Toluene	4	-
2[a]	4	DavePhos	NaO*t*Bu	24	Toluene	4	-
3	4	DavePhos	NaO*t*Bu	48	Toluene	4	-
4	4	DavePhos	NaO*t*Bu	48	Dioxane	4	-
5	1	DavePhos	NaO*t*Bu	24	Toluene	4	82

Conditions: DavePhos (8 mol%/terminal),NaO*t*Bu (3 equiv/terminal), solvent (0.1 M)

Observations:a– this essay was repeated twice; entry 1 and 2 – isolated PEG with two different compounds in each terminal; entry 3 and 4 – only PEGylated starting material was isolated.

III.4.3.1–PEG bis (2-phenyl-1H-indol-4-yl)



This compound was obtained as a yellow solid (25.2mg, 82%).

IR (KBr) ν_{max} (cm^{-1}): 2915, 2869, 1457, 1349, 1104.

^{1}H-NMR (400MHz; ($CDCl_3$) δ (ppm): 7.95 (d, ArH, *J* = 7.9 Hz, 2H), 7.56 (t, ArH, *J* = 7.2 Hz, 1H), 7.46 (t, ArH, *J* = 7.6 Hz, 2H), 7.13 (t, H-5, *J* = 7.5 Hz, 1H), 6.96 (d, H-4,6,2'*J* = 7.4 Hz, 3H), 4.59 (s, H-7,*J* = 11.2 Hz, 2H), 3.88 – 3.31 (m, CH_2 PEG,298H).

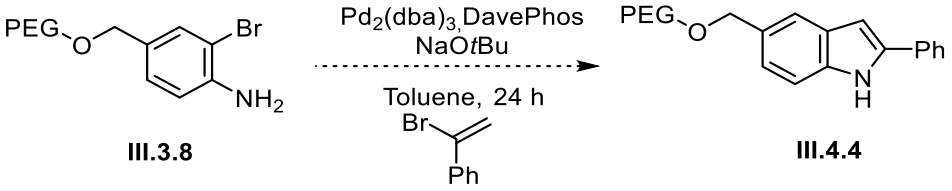
^{13}C-NMR (101MHz; ($CDCl_3$) δ (ppm):128.69 (CAr), 128.42 (CAr), 127.96 (C-5), 120.55 (C-7),

116.85 (C-4 and C-6), 73.06 (C-9), 70.68 (CH_2 PEG).

III.4.4 – Cascade C-N Cross coupling/Heck reaction using PEG – bis (3-bromoaniline) as starting material

A sealed tube equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (4mol%), ligand (8mol%), base (3equiv), and PEGylated compound **III.3.8**(1equiv). The tube was sealed with a suba-seal, evacuated and backfilled with nitrogen thrice. Solvent (0.1M) was then added, followed by α-bromo styrene (2equiv) and the reaction was stirred for 24h at 110ºC. After work up (see general procedure) all compounds were isolated by precipitation with cold ether.

TableIII.5 - Influence of Pd/ligand and solvent in the cascade C-N cross coupling/Heck reaction with PEG bis (3-bromoaniline).



III.3.8 **III.4.4**

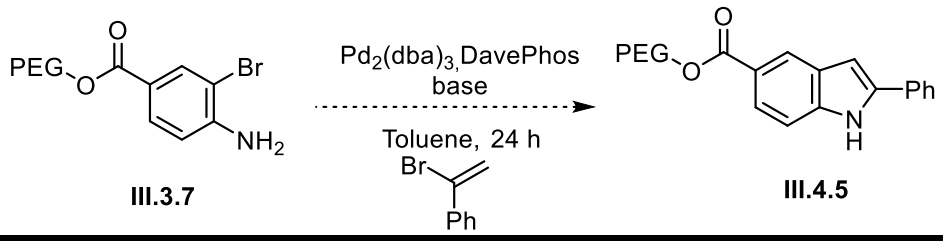
Entry	α-bromostyrene (equiv/terminal)	DavePhos (mol%/terminal)	Base	Time (h)	Solvent	$Pd_2(dba)_3$ (mol%/terminal)
1	2	8	NaO*t*Bu	24	Toluene	4
2	5	8	NaO*t*Bu	24	Toluene	4
3	5	16	NaO*t*Bu	48	Toluene	8

Observations: entry 1 – Identification of a complex mixture, led to purification but no structure was identified in the ^{1}H-NMR; entry 2 – Isolated compound could not be identified,^{1}H-NMR spectrum had low resolution; entry 3 – Isolated compound could not be identified, aromatic area in ^{1}H-NMR had no resolution.

III.4.5 – Cascade C-N Cross coupling/Heck reaction using PEG – bis (4-amino-3-bromobenzoate) as starting material

A sealed tube equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (4mol%), ligand (8mol%), base (3equiv), and PEGylated compound **III.3.7** (1equiv). The tube was sealed with a suba-seal, evacuated and backfilled with nitrogen thrice. Solvent (0.1M) was then added, followed by α-bromo styrene (2equiv) and the reaction was stirred for 24h at 110ºC. After work up (see general procedure) all compounds were isolated by precipitation with cold ether.

TableIII.6 - Influence of Pd/ligand and solvent in the cascade C-N cross coupling/Heck reaction with PEG bis (4-amino-3-bromobenzoate).



III.3.7 **III.4.5**

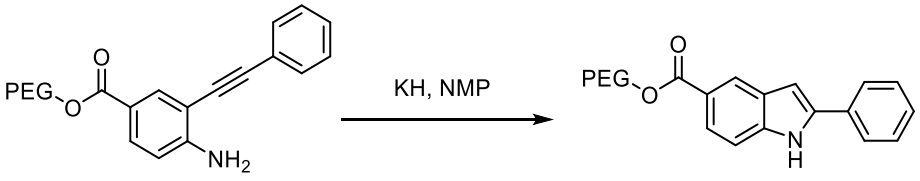
Entry	α-bromostyrene (equiv/terminal)	DavePhos (mol%/terminal)	Base	Time	Solvent	$Pd_2(dba)_3$ (mol%/terminal)
1	5	8	Cs_2CO_3	24 h	Toluene	4
2	5	8	NaO*t*Bu	24 h	Toluene	4
3	5	8	Cs_2CO_3	3 days	Toluene	4
4	5	8	NaO*t*Bu	3 days	Toluene	4

Observations: entry 1 and 2 – Only PEGylated starting material was isolated; entry 3 and 4 – ^{1}H-NMR analysis showed only PEGylated starting material so all isolated precipitates were cleaved.

III.5–PEG supported N- arylation and Sonogashira reactions

The following structures were synthesized according with general procedure for one-pot N-arylation and Sonogashira reactions, but using a multistep approach with twice as much quantity of each reagent (per terminal), and then isolated by precipitation using cold diethyl ether.

Cyclization of pegylated Sonogashira products

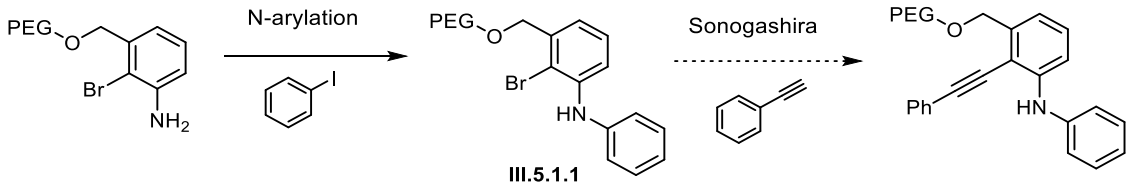


III.5.2.1 **III.5.2.2**

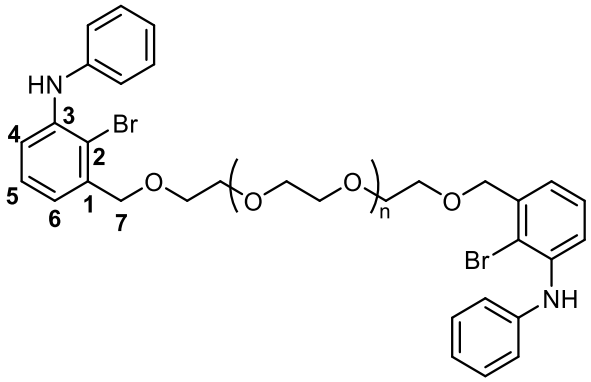
A sealed tube equipped with a magnetic stir bar was charged with pegylated Sonogashira product (1 equiv) and dried NMP was added (0.0185M). A solution of KH (2.1equiv) in dried NMP (0.3885M) was prepared under N_2 atmosphere. This solution was added to the reaction mixture and then stirred for 24h-48h at room temperature. The crude reaction product was diluted in DCM and washed twice with water and twice with brine. Combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated. The resulting oil was dissolved in a small

amount of DCM and precipitated and washed with cold ether, to obtain the product.

III.5.1 – N-arylation and Sonogashira reactions - PEG - bis (2-bromoaniline) as starting material



III.5.1.1 – PEG bis (2-bromo-N-phenylaniline)



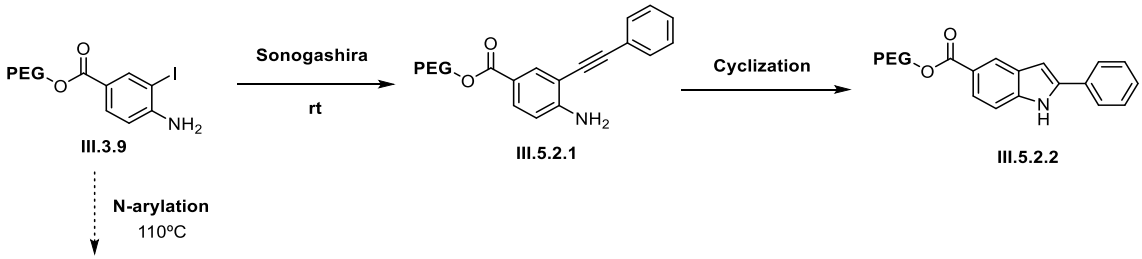
This compound was isolated as a brown solid (90%)

IR (KBr) ν_{max} (cm^{-1}): 3521, 2871, 1961, 1643, 1594, 1468, 1109.

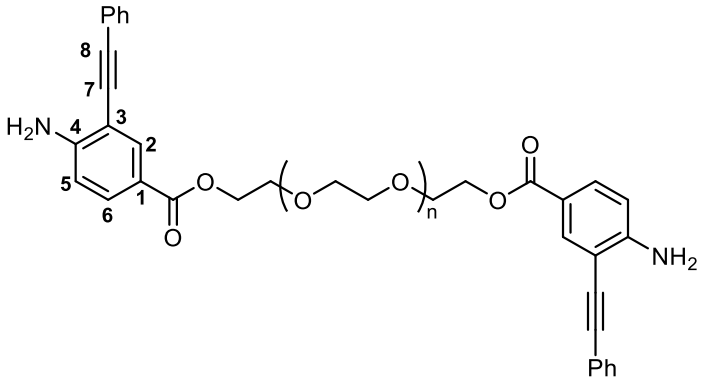
^{1}H-NMR (400MHz; $(CD_3)_2CO$) δ (ppm): 7.36 – 7.29 (m, ArH, 3H), 7.19 – 7.10 (m, ArH, 3H), 7.05 – 7.00 (m, ArH, 2H), 4.64 (s, H-7, 2H), 3.77 – 3.57 (m, CH_2 PEG, 112H).

^{13}C-NMR (101MHz; $(CD_3)_2CO$) δ (ppm): 141.96 (C-3), 141.70 (CAr), 138.90 (C-1), 129.59 (CAr), 127.70 (CAr), 122.80 (C-6), 120.47 (CAr), 115.23 (C-2), 73.37 (C-7), 70.86 (CH_2 PEG), 70.71 (CH_2 PEG), 70.29 (CH_2 PEG).

III.5.2 – N-arylation and Sonogashira reactions - PEG -bis (4-amino-3-iodobenzoate) as starting material



III.5.2.1 – PEG bis (4-amino-3-(phenylethynyl)benzoate)



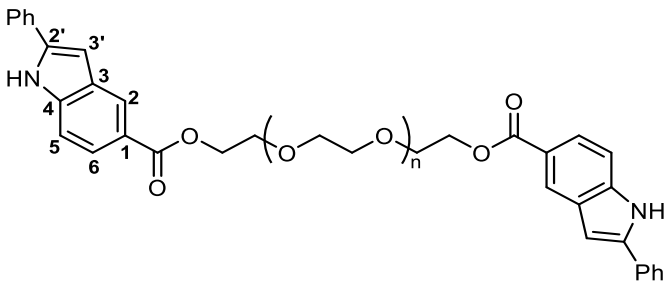
This compound was isolated as a brown solid (73%)

IR (KBr) ν_{max} (cm^{-1}):3466, 3350, 3217, 2916, 1962, 1705, 1622, 1454, 1118.

^{1}H-NMR (400MHz; $(CD_3)_2CO$) δ (ppm):8.01 (s, ArH-2, 1H), 7.79 (dd, ArH-6,*J* = 8.6, 1.7 Hz, 1H), 7.67 – 7.60 (m, ArH, 2H), 7.43 (d, ArH, *J* = 5.9 Hz, 3H), 6.88 (d, ArH-5, *J* = 8.6 Hz, 1H), 4.39 (t, CH_2 PEG *J* = 6 Hz, 2H), 3.81 (t, CH_2 PEG,*J* = 4 Hz, 2H), 3.72 – 3.51 (m, CH_2 PEG, 102H).

^{13}C-NMR (101MHz; $(CD_3)_2CO$) δ (ppm):166.27 (C=O), 154.25 (C-4), 135.00 (C-2), 132.39 (C-6), 132.29 (CAr), 129.44 (CAr), 129.34 (CAr), 124.11 (C-1), 114.18 (C-5), 106.80 (C-3), 95.35 (C-8), 86.08 (C-7), 71.29 (CH_2 PEG), 69.91 (CH_2 PEG), 64.40 (CH_2 PEG),

III.5.2.2 – PEG bis (2-phenyl-1H-indole-5-carboxylate)



This compound was obtained according to the general procedure for cyclization of pegylated sonogashira products and isolated as a light brown solid (62%)

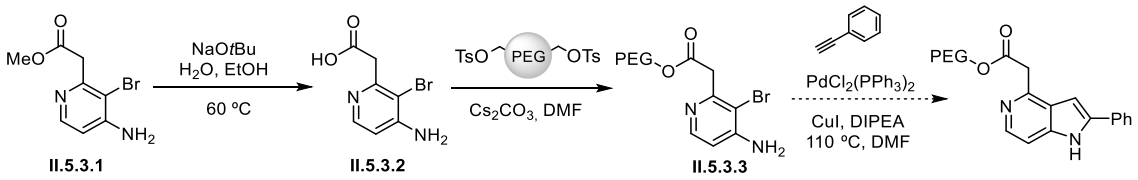
IR (KBr) ν_{max} (cm^{-1}): 3467, 2880, 1706, 1644, 1467, 1113.

^{1}H-NMR (400MHz; $(CD_3)_2CO$) δ (ppm):8.36 (s, H-2, 1H), 7.93 (d, ArH, J = 7.4 Hz, 2H), 7.85 (d, H-6, J = 8.4 Hz, 1H), 7.56 – 7.46 (m, H-5 and ArH, 3H), 7.40 – 7.33 (m, ArH, 1H), 7.07 (s, H-3', 1H), 4.45 (t, CH_2 PEG, J = 4 Hz, 2H), 3.86 (t, CH_2 PEG, J = 4 Hz, 2H), 3.57 (m, CH_2 PEG, 394H).

^{13}C-NMR (100MHz; $(CD_3)_2CO$) δ (ppm):206.26 (CAr), 129.89 (CAr), 126.22 (C-6+C-2), 123.89 (C-5), 111.98 (s), 100.97 (C-3'), 73.58 (CH_2 PEG), 71.26 (CH_2 PEG)*.

*low quantity of sample didn't allow identification of all carbons present in the molecule

III.5.3 – Sonogashira reactions - Aminopyridines as starting material



III.5.3.2 – 2-(4-amino-3-bromopyridin-2-yl)acetic acid

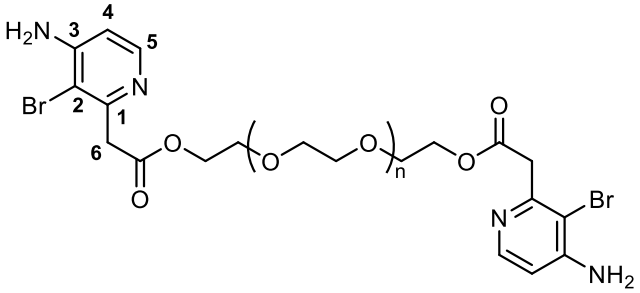
A rond-bottomed flask was charged with the **2-(4-amino-3-bromopyridin-2-yl)acetic acid** (50mg,1.05equiv), water (16µL) and ethanol (1.7mL), the reaction mixture was stirred in 60ºC oil bath. To this, a solution of potassium tert-butoxide (21mg, 1.05equiv) in ethanol (220µL) was added dropwise over 15minutes. After completion of addition, the reaction mixture was stirred at 60ºC until consumption of the starting material. After removing the ethanol solvent by slow evaporation, AcOEt was added. The mixture was extracted with water and then HCl 1M. Combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated. The product was obtained as a yellow solid. (39.2mg, 83%)

IR (KBr) ν_{max} (cm^{-1}):3432, 3369, 2922, 2853, 1715, 1588.

^{1}H-NMR (400MHz; CD_3OD) δ (ppm):7.84 (d, ArH, *J* = 5.7 Hz, 1H), 6.48 (d, ArH, *J* = 5.7 Hz, 1H), 3.72 (s, CH_2, 2H).

^{13}C-NMR (101MHz; CD_3OD) δ (ppm):173.70 (C=O), 152.33 (C-1), 147.19 (C-3), 142.57 (C-5), 108.59 (C-4), 107.46 (C-2), 46.25(C-6).

III.5.3.3 – PEG bis (2-(4-amino-3-bromopyridin-2-yl)acetate)



To a PEG tosyl (85mg, 1equiv) solution in DMF (187 µL) was added Cs_2CO_3 (37 mg, 3equiv) and **sodium 2-(4-amino-3-bromopyridin-2-yl) acetate** (30mg, 3equiv). The mixture was stirred at room temperature for 24h. The mixture was washed with water, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and evaporated do dryness. The resulting oil was dissolved in a small amount of DCM and precipitated and washed with cold ether, to obtain the compound as a light yellow solid. (84mg, 95%)

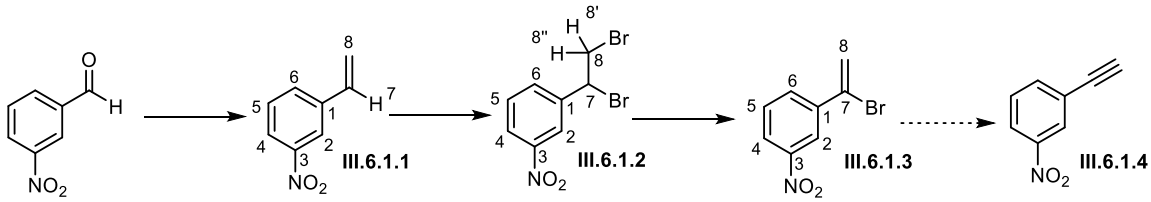
IR (KBr) ν_{max} (cm^{-1}): 3521, 2872, 1966, 1748, 1643, 1583, 1455, 1118.

^{1}H-NMR (400MHz; $(CD_3)_2CO$) δ (ppm): 7.83 (d, ArH, J = 8.2 Hz, 1H), 7.50 (d, ArH, J = 8.0 Hz, 1H), 4.17 (t, CH_2 PEG, J= 4 Hz,1H), 3.68 (t, CH_2 PEG, J=4 Hz,2H), 3.56 (m, CH_2 PEG and H-6, 146H).

^{13}C-NMR (101MHz; $(CD_3)_2CO$) δ (ppm): 153.28 (C=O), 148.90 (C-1), 134.39 (C-3), 130.86 (C-5), 128.76 (C-4), 107.06 (C-2), 73.55 (CH_2 PEG), 71.20 (CH_2 PEG), 62.00 (CH_2 PEG), 45.25 (C-6).

III.6 – Azaindole synthesis using non pegylated aminopyridines

III.6.1– Alkyne synthesis



III.6.1.1 – 1-nitro-3-vinylbenzene[65]

A schlenk equipped with $BrPPh_3Me$ (3.55g, 1.5 equiv) was sealed with a suba-seal, evacuated and backfilled with nitrogen thrice. Then dried THF (20mL) was added and the mixture was placed in a -10ºC bath, NaH (238 mg, 1.5 equiv) wasslowly added. The mixture was stirred

overnight and afterward place in a -78ºC bath.**3-nitrobenzaldehyde** (1g, 1equiv) was added and the reaction was allowed to reach room temperature and stirred for 5 h. After reaction completion, the mixture was extracted twice with water and brine. The combined organic layers were dried over Na_2SO_4, the desiccant filtered and the product concentrated and vacuum dried. The product was isolated after purification by column chromatography (silica gel, hexane: ethyl acetate with gradient) as a brown oil. (515.7mg, 52%)

IR (NaCl) ν_{max} (cm^{-1}): 3091, 2925, 2854, 1736, 1531, 1350.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.24 (s, ArH-2, 1H), 8.09 (d, ArH-4, *J* = 8.1 Hz, 1H), 7.70 (d, ArH-6 *J* = 7.7 Hz, 1H), 7.49 (t, ArH-5 *J* = 7.9 Hz, 1H), 6.76 (dd, H-7, *J* = 17.6, 10.9 Hz, 1H), 5.89 (d, H-8, *J* = 17.6 Hz, 1H), 5.44 (d, H-8, *J* = 10.9 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 148.76 (C-3), 139.40 (C-1), 134.89 (C-7), 132.21 (C-6), 129.59 (C-5), 122.56 (C-4), 121.02 (C-2), 117.22 (C-8).

III.6.1.2 – 1-(1, 2-dibromoethyl)-3-nitrobenzene[62]

An aqueous solution of HBr (47%, 2.4equiv, 1mL) was added to a solution of olefin **III.6.1.1** (515.7mg, 1equiv) and DMSO (320µL, 1.2equiv) in AcOEt (14.8mL) at 60ºC. The solution was stirred at 60ºC for 30min under an air atmosphere. After reaction completion, the mixture was extracted several times with water and sat. $NaHSO_3$.The combined organic layers were dried over Na_2SO_4, the desiccant filtered and the product concentrated and vacuum dried. The product was obtained as a yellow oil (936.2mg, 88%).

IR (NaCl) ν_{max} (cm^{-1}): 3089, 2925, 2854, 1731, 1531, 1353.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.28 (s, ArH-2, 1H), 8.22 (d, ArH-4, *J* = 8.1 Hz, 1H), 7.74 (d, ArH-6, *J* = 7.7 Hz, 1H), 7.59 (t, ArH-5, 2*J* = 8.0 Hz, 1H), 5.19 (dd, H-7, *J* = 11.3, 4.9 Hz, 1H), 4.11 (dd, H-8', *J* = 10.4, 4.9 Hz, 1H), 4.00 (t, H-8'',*J* = 10.9 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ(ppm): 148.59 (C-3), 140.94 (C-1), 133.91 (C-6), 130.09 (C-5), 124.16 (C-2), 123.00 (C-4), 48.12 (C-7), 34.26 (C-8).

III.6.1.3 – 1-(1-bromovinyl)-3-nitrobenzene[66]

To a **1-(1,2-dibromoethyl)-3-nitrobenzene** (936.2mg, 3.03mmol) solution in PA methanol (14mL) was added dropwise a solution of KOH 2M in methanol (1.9mL). The mixture was stirred for 20 min and then refluxed for 1.5 h. After reaction completion, the mixture was diluted in diethyl ether and extracted twice with water and brine. The combined organic layers were dried over Na_2SO_4, the desiccant filtered and the product concentrated and vacuum dried. The product was obtained as brown solid (577mg, 83%).

IR (KBr) ν_{max} (cm^{-1}): 3087, 2943, 2924, 2855, 1704, 1610, 1528, 1351.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.45 (s, ArH-2, 1H), 8.19 (d, ArH-4, *J* = 8.1 Hz, 1H), 7.92 (d,

ArH-6,*J* = 7.8 Hz, 1H), 7.54 (dd, ArH-5,*J* = 18.0, 10.0 Hz, 1H), 6.27 (d, H-8,*J* = 2.1 Hz, 1H), 5.94 (d, H-8,*J* = 2.1 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ(ppm): 134.61 (C-3), 133.18 (C-1), 130.35 (C-6), 129.55 (C-7), 128.29 (C-5), 124.00 (C-4), 122.38 (C-2), 120.44 (C-8).

III.6.2– Azaindole synthesis

General procedure for one-pot N-arylation and Sonogashira reactions

C-N cross-coupling reaction

A sealed tube equipped with a magnetic stirring bar was charged with Pd_2dba_3 (4 mol %), XantPhos (8 mol %), NaO*t*Bu (2 equiv) and amino-*ortho*-bromopyridine (1 equiv) and dry toluene (c = 0.2 M), followed by iodides (1.2 equiv). The reaction was stirred for 6 hours at 110 ºC. The crude reaction product was concentrated and vacuum dried.

Sonogashira reaction and in-situ cyclization

DMF was previously degassed 7 times by applying vacuum when the mixture is completely frozen and then flushed with nitrogen.

Three solutions were prepared with the degassed DMF and the solids were dried under vacuum before DMF addition:

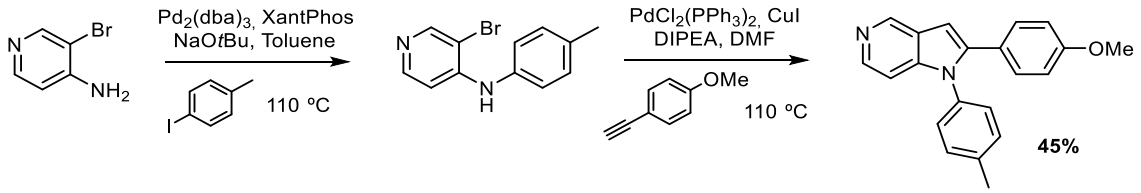
Solution A – A round-bottom flask was charged with product of C-N cross-coupling reaction (1 equiv), DIPEA (3.2 equiv,) and DMF (c = 0.47 M) and the final solution degassed thrice.

Solution B – A round-bottom flask was charged with CuI (5 mol %), $PdCl_2(PPh_3)_2$ (3 mol %) and DMF (c = 0.0137M) and the final solution degassed thrice.

Solution C – A round-bottom flask was charged with ethynylbenzene (2.1 equiv.) and DMF (c = 0.5M) and the final solution degassed thrice.

To solution B, solution A was added via syringe, then degassed twice; and finally, solution C. The mixture was degassed one more time and then allowed to warm up to 110ºC and stirred for 24 h. After reaction completion, DMF was evaporated; DCM was added to the residue and washed with sat. NH_4Cl and water. The combined organic layers were dried over Na_2SO_4, the desiccant filtered and the product concentrated and vacuum dried

III.6.2.1–2-(4-Methoxyphenyl)-1-(*p*-tolyl)-5-azaindole



The product was obtained as yellow oil byPTLC using EtOAc/hexane (1:1) followed by PTLC using EtOAc/hexane/EtOH (5:5:0.5)

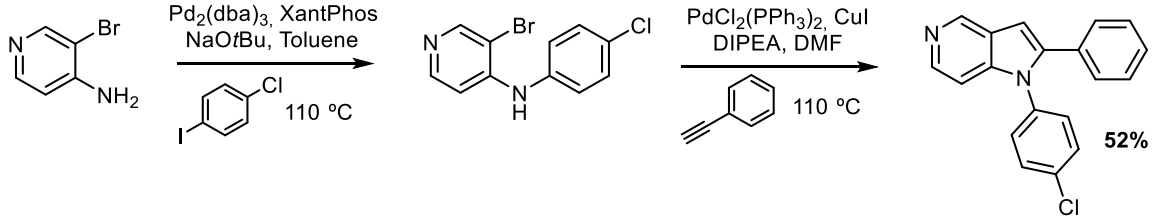
IR (NaCl) ν_{max} (cm^{-1}): 3041, 2926, 2833, 1607, 1500, 1459, 1255

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.89 (s, 1H), 8.19 (d, *J* = 5.84 Hz, 1H), 7.19 – 7.08 (m, 6H), 7.03 (d, *J* = 8.08 Hz, 1H), 6.74 – 6.71 (m, 3H), 3.72 (s, 3H), 2.34 (s, 3H)

^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 159.6, 142.7, 140.8, 140.5, 137.4, 134.7, 130.4, 130.3, 127.8, 127.5, 125.2, 124.0, 113.9, 106.0, 101.5, 55.4, 21.3

HRMS (EI) calcd for $C_{21}H_{18}N_2O$ (M+1):315.1452; **Found:**315.1492

III.6.2.2 –1-(4-Chlorophenyl)-2-phenyl-5-azaindole



The product was obtained as yellow oil by PTLC using EtOAc/hexane (1:1) followed by PTLC using EtOAc/hexane (2:1)

IR (NaCl) ν_{max} (cm^{-1}): 3042, 2923, 2848, 1497, 1462, 744.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.89 (s, 1H), 8.23 (d, *J* = 5.0 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.21 – 7.16 (m, 5H), 7.07 (d, *J* = 8.5 Hz, 3H), 6.76 (s, 1H)

^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 143.8, 142.4, 141.8, 135.9, 133.8, 131.3, 129.8, 129.1, 128.9, 128.6, 128.3, 127.7, 125.2, 105.7, 102.9

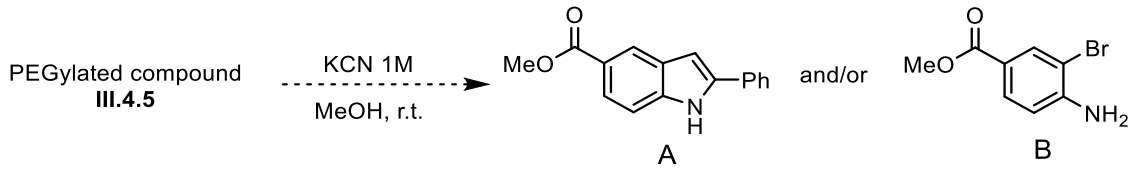
HRMS (EI) calcd for $C_{19}H_{15}ClN_2$ (M+1): 305.0845; **Found:** 305.0840

III.7 – Compounds cleavage from PEG

General procedure for compounds cleavagefrom PEG:

Ester bound substrates: The PEG bound compound (1equiv) was dissolved in methanol and a 1M solution of potassium cyanide (2equiv) in methanol was added. The mixture was stirred at ambient temperature for 24h. After completion of the reaction, the inorganic material was removed by filtration and then precipitated out with excess of cold ether and removed by filtration. The filtrate was evaporated to dryness and the product was obtained as the corresponding methyl ester.

Table III.10 - Cleavage of compounds bounded to PEG via an ester group resulting from the cascade C-N cross-coupling/Heck reaction

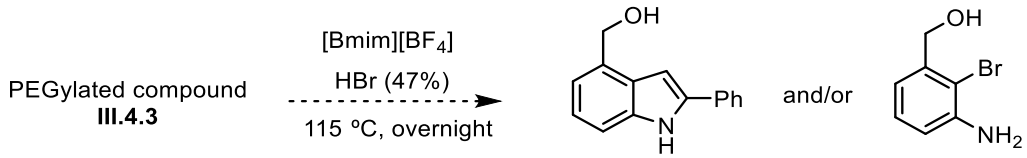


Entry	Substrate	KCN 1M (equiv)	Temperature	Time (h)	Purification	Isolated compound
1	III.4.5[a]	2	rt	24	PTLC (Hexane:AcOEt 8:1)	B
2	III.4.5[b]	2	rt	24	PTLC ($CHCl_3$:MeOH 10:1)	-
3	III.4.5[c]	2	rt	24	PTLC ($CHCl_3$:MeOH 10:1)	-

Observations: a- compound III.4.5 from entry 1 in table II.7; b- compound III.4.5 from entry 3 in table II.7; c- compound III.4.5 from entry 4 in table II.7

Ether bound substrates: The PEG bound compound (1 equiv) and concentrated hydrobromonic acid (48%, 2 equiv) in [Bmim][BF_4] (1.0mL) were stirred at 115 ºC for . The reaction time was determined by TLC analysis. The reaction mixture was extracted with diethyl ether (4x 10mL), then the aqueous phase was neutralized using NaOH 1M and extracted twice with AcOEt. The combined extracts were concentrated under reduced pressure, and the resulting product was diluted in DCM and precipitated in cold diethyl ether.

Table III.11 - Cleavage of compounds bounded to PEG via an ether group resulting from the cascade C-N cross-coupling/Heck reaction



Entry	Substrate	[Bmim][BF_4] (equiv)	Temperature (ºC)	Time (h)	Purification PTLC
1	III.4.3[a]	5.4	115	19	($CHCl_3$: MeOH 10:1), (Hexane: AcOEt 2:1)
2	III.4.3[b]	5.4	115	19	(Hexane: AcOEt 2:1)

Observations: a- compound III.4.3 from entry 3 in table II.4; b- compound III.4.3 from entry 4 in table II.4

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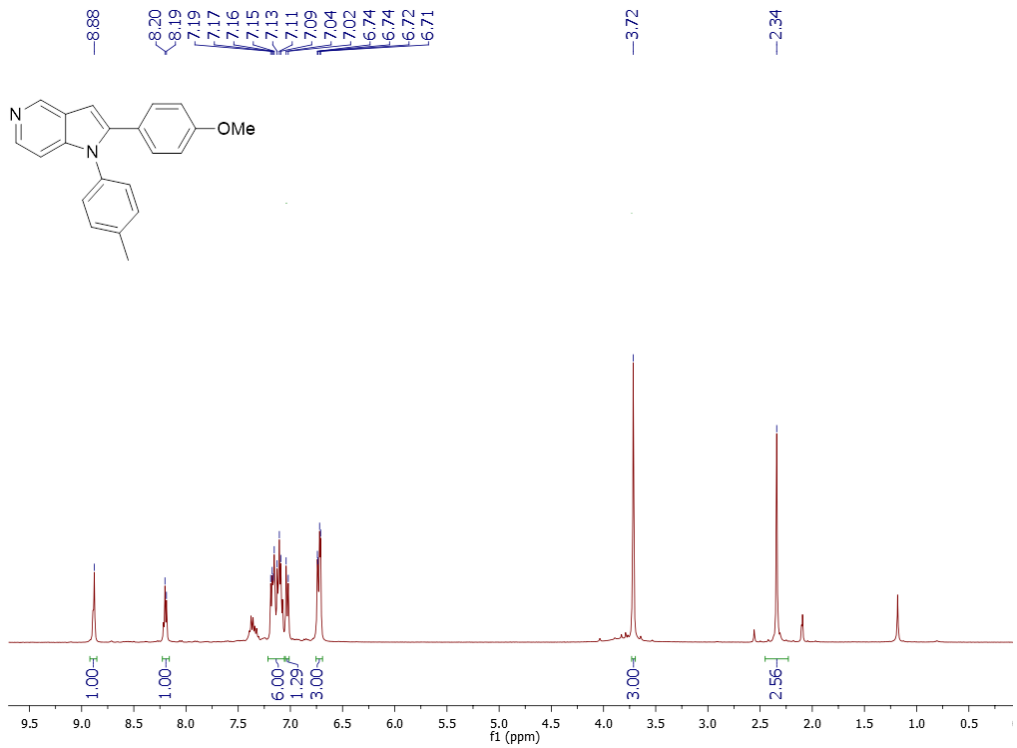
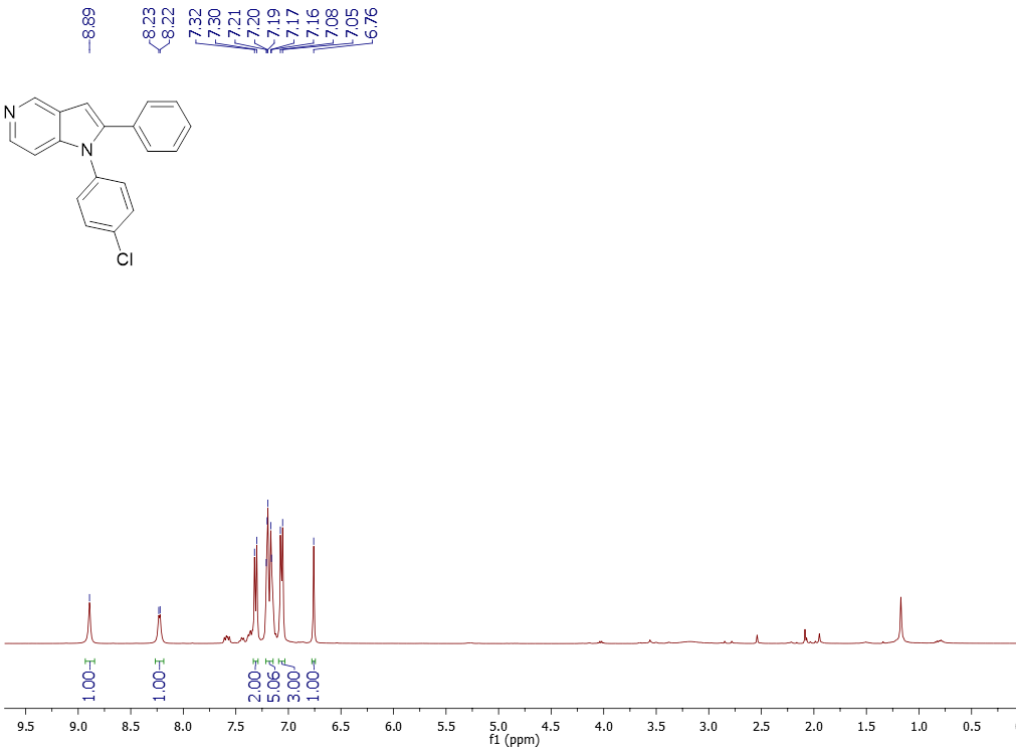
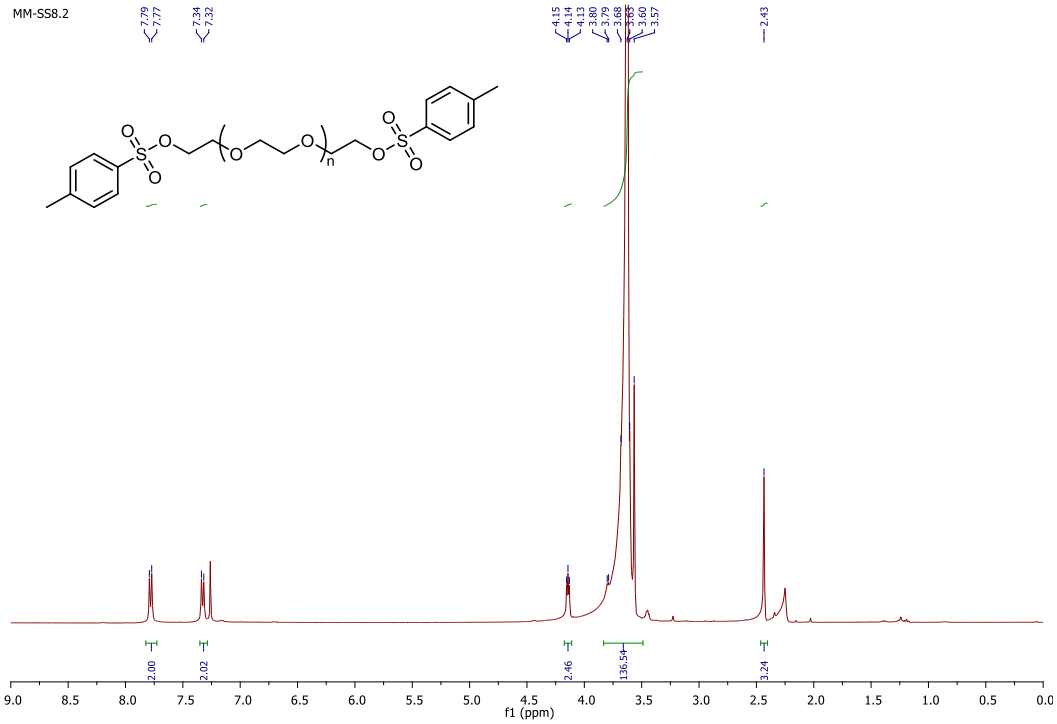
Appendix



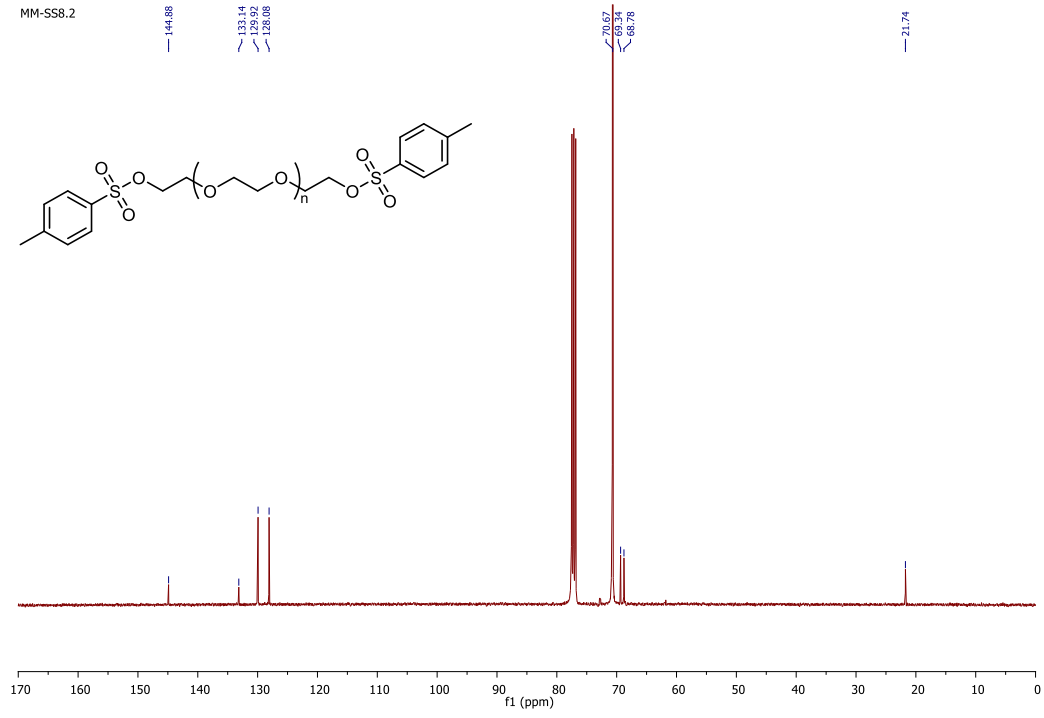
Spectrum 1 – ^{1}H-NMR spectrum of 2-(4-Methoxyphenyl)-1-(*p*-tolyl)-5-azaindole (III.6.1.1)



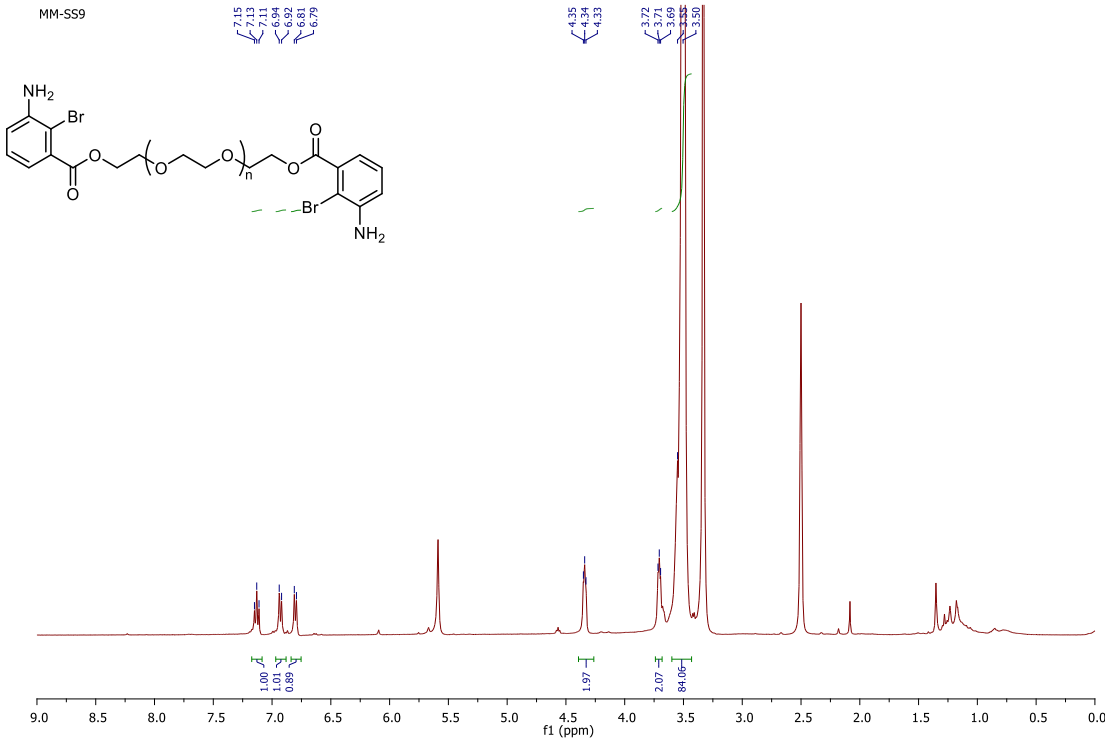
Spectrum 2 – ^{1}H-NMR spectrum of 1-(4-Chlorophenyl)-2-phenyl-5-azaindole (III.6.1.2)



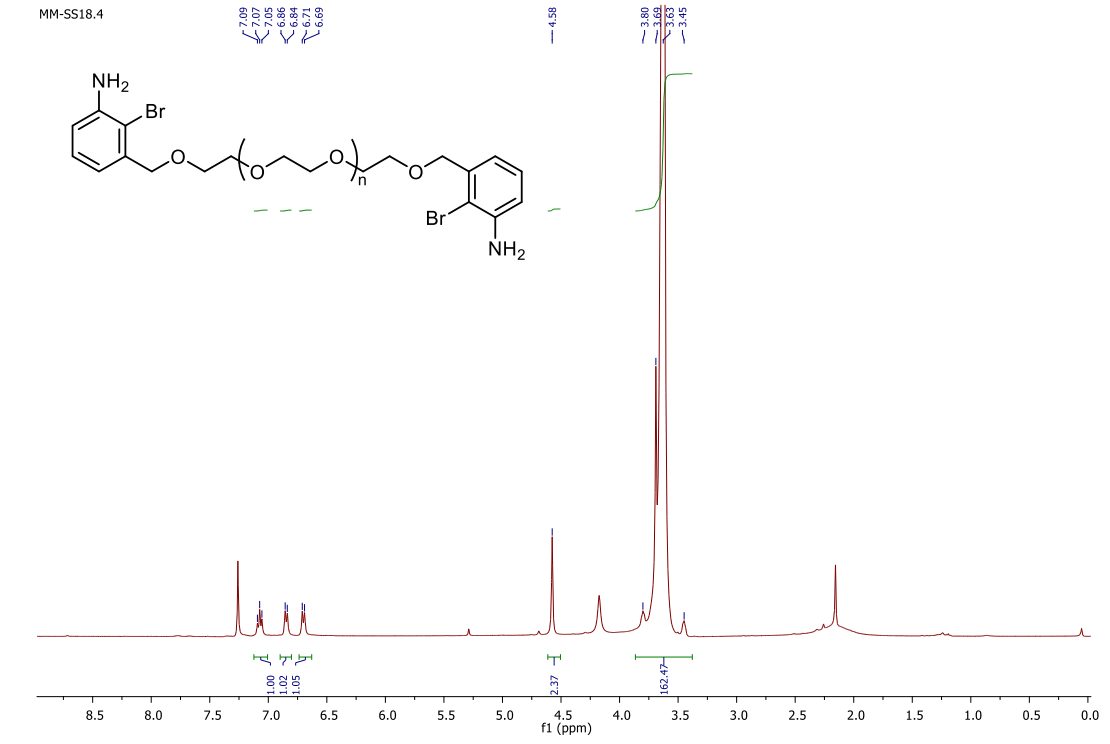
Spectrum 3–^{1}H-NMR spectrum of PEG - bis (4-methylbezenesulfonate) (III.3.1)



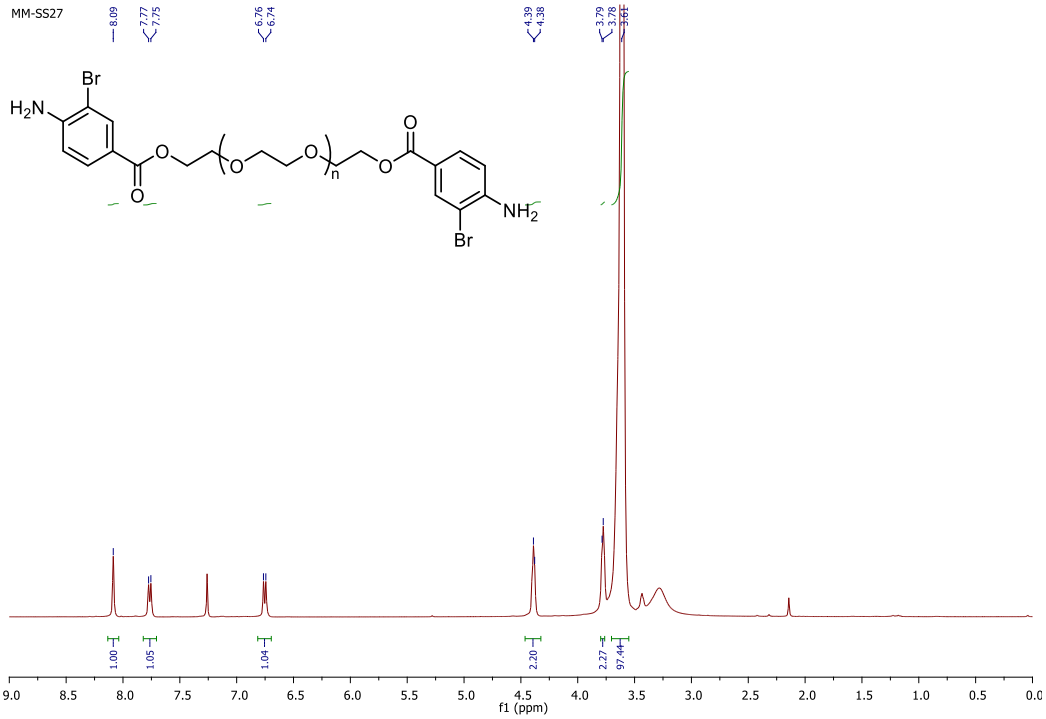
Spectrum 4– ^{13}C-NMR spectrum of PEG - bis (4-methylbezenesulfonate) (III.3.1)



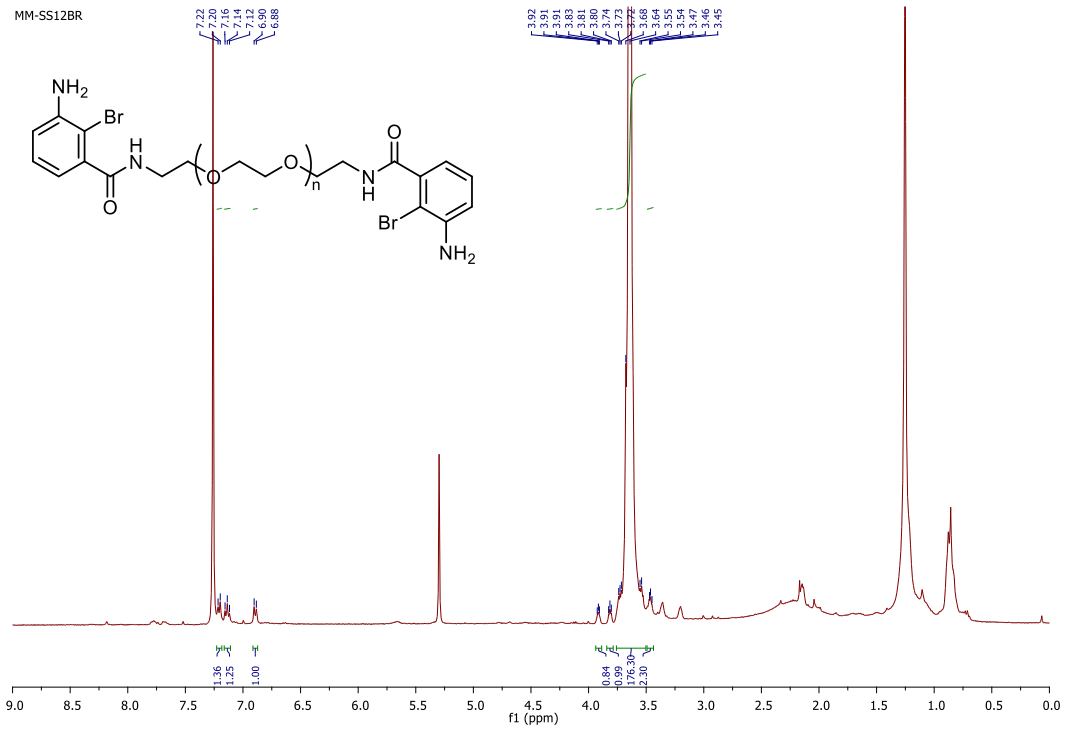
Spectrum 5–^{1}H-NMR spectrum of PEG - bis (3-amino-2-bromobenzoate) (III.3.2)



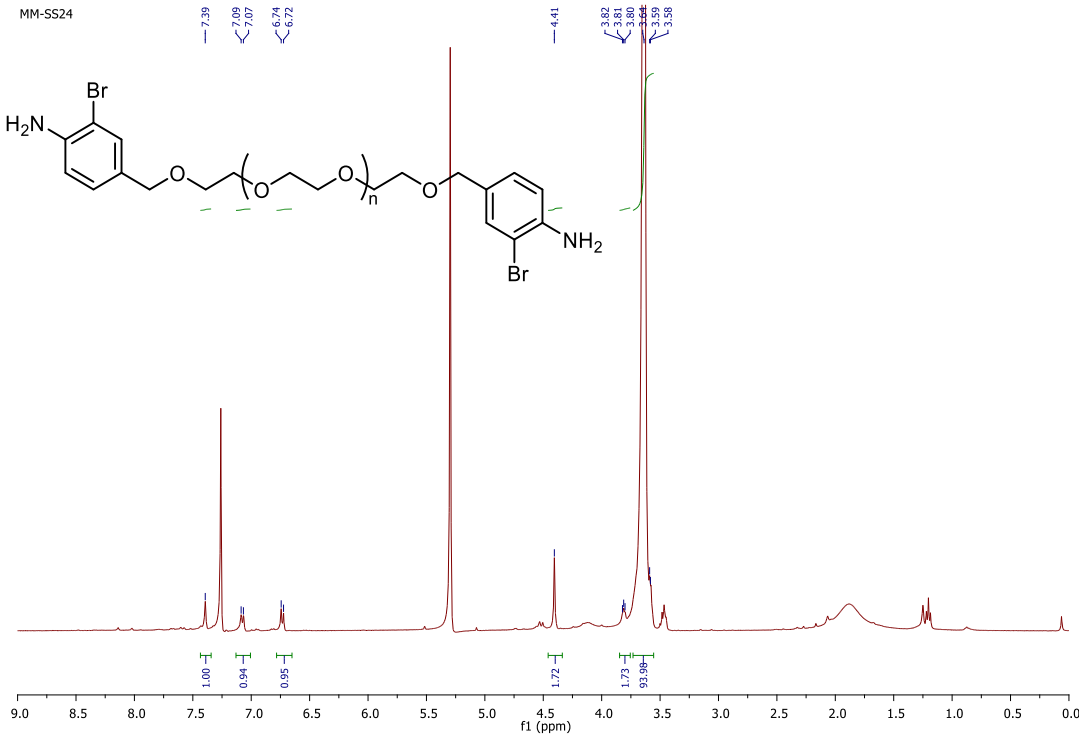
Spectrum 6–^{1}H-NMR spectrum of PEG – bis (2-bromoaniline) (III.3.6)



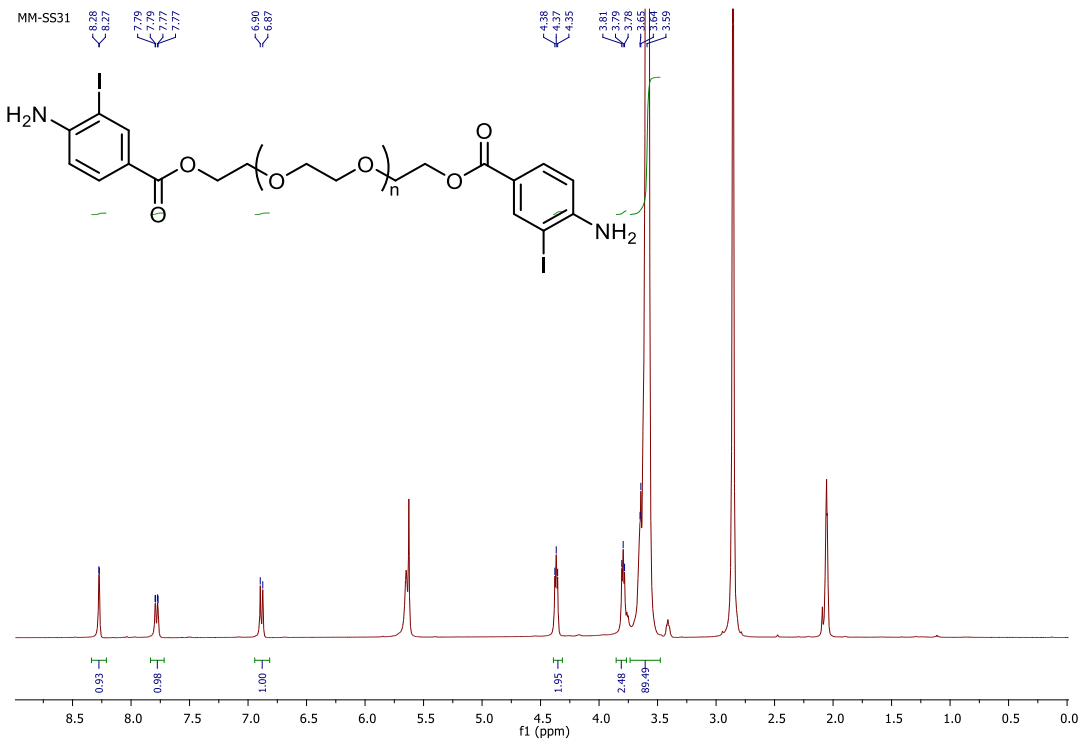
Spectrum 7 – ^{1}H-NMR spectrum of PEG – bis (4-amino-3-bromobenzoate) (III.3.7)



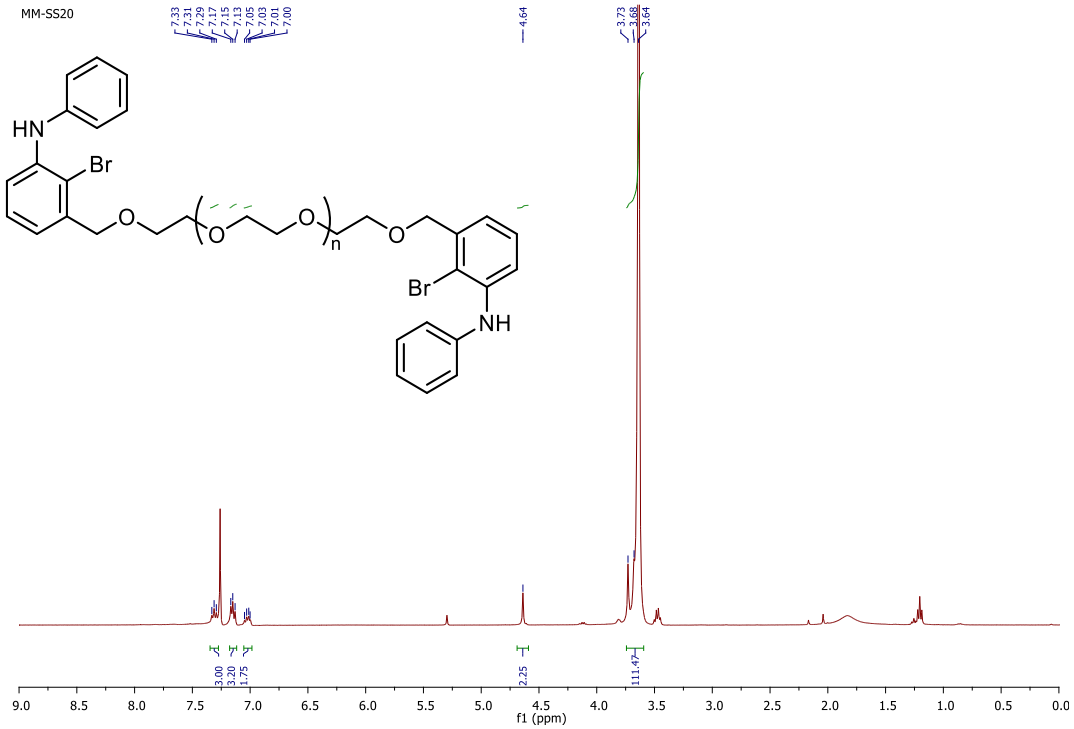
Spectrum 8 –^{1}H-NMR spectrum of PEG – bis (3-amino-2-bromobenzamide) (III.3.3)



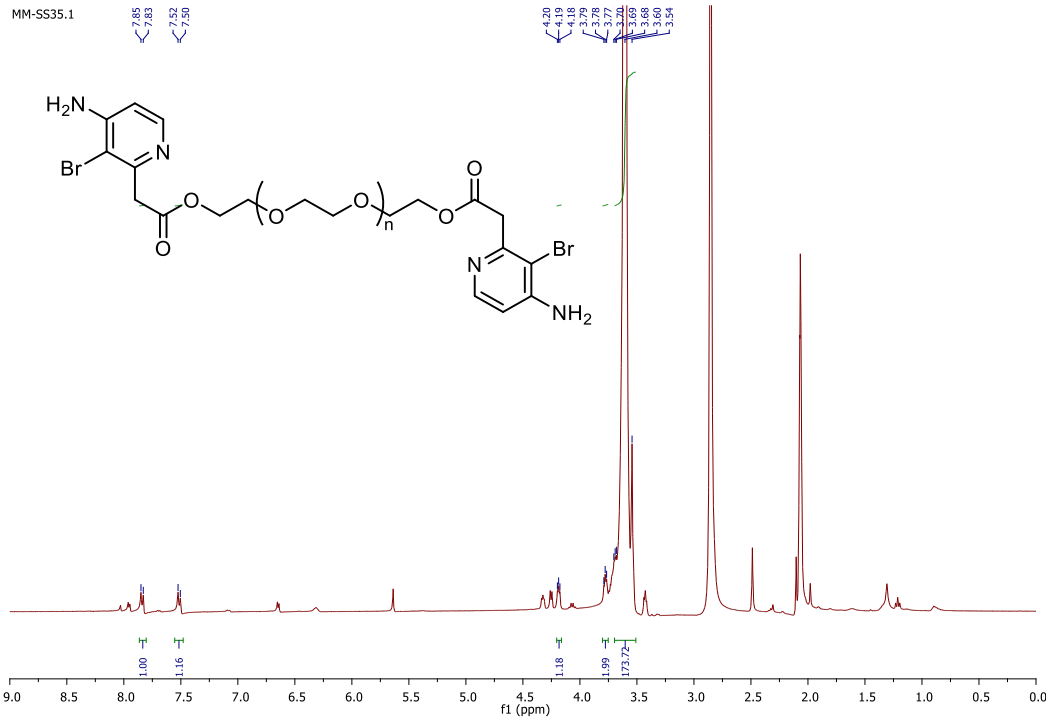
Spectrum 9– ^{1}H-NMR spectrum of PEG – bis (3-bromoaniline) (III.3.8)



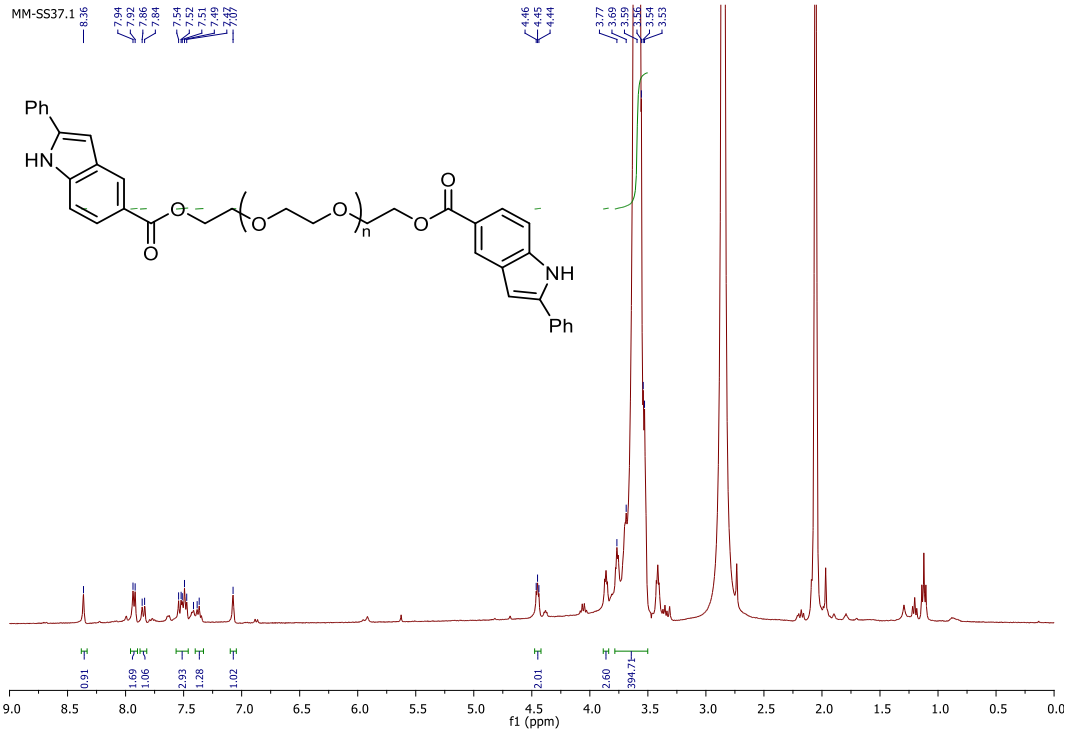
Spectrum 10 –^{1}H-NMR spectrum of PEG – bis (4-amino-3-iodobenzoate) (III.3.9)



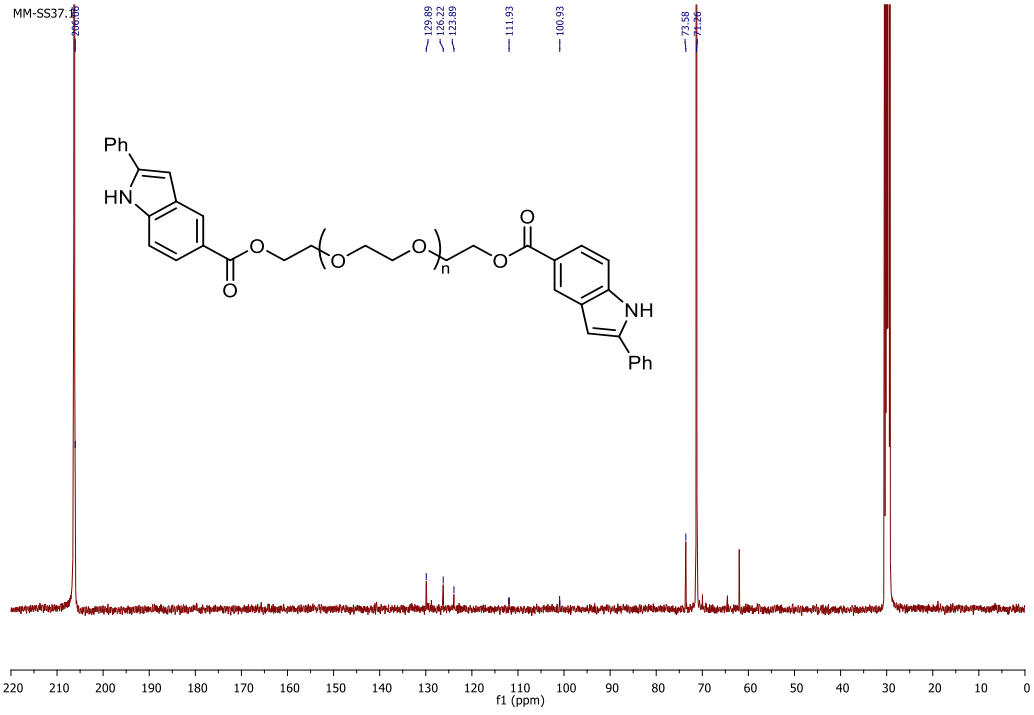
Spectrum 11–^{1}H-NMR spectrum of PEG – bis (2-bromo-N-phenylaniline) (III.5.1.1)



Spectrum 12 –^{1}H-NMR spectrum of PEG – bis (2-(4-amino-3-bromopyridin-2-yl)acetate) (III.5.3.3)



Spectrum 13–^{1}H-NMR spectrum of PEG – bis (2-phenyl-1H-indole-5-carboxylate) (III.5.2.2)



Spectrum 14 – ^{13}C-NMR spectrum of PEG – bis (2-phenyl-1H-indole-5-carboxylate) (III.5.2.2)