Design and Synthesis of Carbazole Derivatives as Novel Therapeutic Candidates Against Acute Myeloid Leukaemia

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Thank you,
Kjetil Eraker Storli

Abstract

Acute myeloid leukaemia (AML) is a diverse group of blood cancers characterised by the uncontrolled growth of cells in the myeloid cell line. This disease group is associated with poor survival rates, especially amongst elderly patient, for whom AML is more common than in any other age group. Todays mainline treatment against AML is the “7+3” regime, consisting of administration of the drug cytarabine followed by the administration of an anthracycline. This treatment has been in use since the 1960’s and is associated with severe side effects. In recent years, one of the research activities in the Bjørsvik group has been to develop new potential drug candidates against AML. One such candidate has been a modification of an intermediate in the total synthesis of carbazomycin G, which has shown significant cytotoxic effect against AML cell lines. In this thesis attempts have been made at further modification of this potential drug candidate, with the addition of two vicinal hydroxy group upon one of the rings of the carbazole structure. This has led to the synthesis of three protected carbazole structures, of which none were made in adequate amount to attempt deprotection.

Abstrakt

Akutt myelogen leukemi (AML) er ein heterogen gruppe blodkreft, karakterisert ved ukontrollert vekst av celler i den myelogene celle linja. Denne sjukdomsgruppa er assosiert med låg overlevingsrate, særleg hos eldre pasientar kor AML er vanlegare enn hos nokon anna aldersgruppe. Dagens viktigaste behandling for AML er «7+3» regimet, som er samansett av administrasjon av lækjemiddelet cytarabine, etterfølgt av administrasjon av ein antrasyklin. Denne behandlingsforma har vore i bruk sidan 1960-talet, og er assosiert med kraftige biverknader. Forskningsgruppa Bjørsvik har difor arbeidd med å utvikla nye lækjemiddel kandidatar mot AML. Ein slik kandidat har vore ein modifisert versjon av eit intermediat funne i totalsyntesen av carbazomycin G. Kandidaten har vist tydeleg cytotoksisk effekt mot AML celle linjer. I denne oppgåva har det vorte gjort vidare forsøk på å modifisera denne potensielle lækjemiddelkandidaten. Ein modifikasjon var å leggje til to vicinale hydroksyl grupper på den eine ringen i carbazol strukturen. Arbeidet har ført til syntesen av tre beskytta carbazol strukturar, der ingen har vorte syntetisert i nok mengde til at avbeskyttelse kunne vorte prøvd.

Abbreviations

AcCl	Acetyl chloride
ArCHO	Benzaldehyde
BBr_3	Boron tribromide
Bn	Benzyl
Br_2	Bromine
$Bu_4N{\cdot}Br$	Tetrabutylammonium bromide
$CHCl_3$	Chloroform
$CoSO_4{\cdot}7H_2O$	Cobaltous (II) sulphate heptahydrate
$Cu(OAc)_2$	Copper (II) acetate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMA	Dimethylacetamide
Et_3N	Triethylamine
H_2O_2	Hydrogen peroxide
H_2SO_4	Sulphuric acid
ICH	Iodo-cyclohexane
Imes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
In	Indium
K_2CO_3	Potassium carbonate
Na_2CO_3	Sodium carbonate
$NaBH_4$	Sodium borohydride
NBS	*N*-bromosuccinimide
NH_4Cl	Ammonium chloride
$Ni(bpu)_3Br_2$	Trisbipyridylnickel dibromide
$Pd(OAc)_2$	Palladium acetate
$Pd(PPh_3)_4$	Palladium-tetrakis(triphenylphosphine)
PhMe	Toulene
PIDA	(Diacetoxyiodo)benzene
TBAB	Tetrabutylammonium bromide
TFA	Trifluoroacetic acid

Content

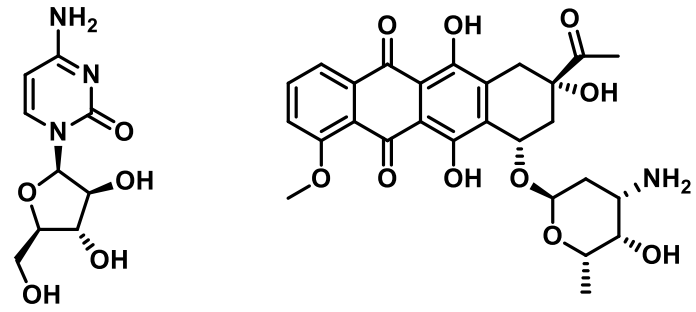
1. Introduction

1.1 Acute Myeloid Leukaemia

Acute myeloid leukaemia (AML) is a diverse group of blood cancers characterised by the uncontrolled growth of cells in the myeloid cell line. Through the acquisition of mutations and chromosomal rearrangements myeloid hematopoietic precursors become cancerous, leading to proliferation and subsequent accumulation in the bone marrow, inhibiting the normal process of hematopoiesis.[1] This disease group is in general associated with poor survival rates, especially amongst elderly patients, for whom AML is more common than in any other age group. Survival rates are today only between 5% and 10% for such patients. AML is also the second most common form of cancer in children, although survival rates in this age group has improved significantly in the last few decades.[2,3] At an average, 5-year survival rate for adult AML patients in Norway is about 30%.[4] It is therefore obvious that while improvements in the treatment of AML have been made there is still a dire need for novel therapeutic agents against this disease.

It is invaluable in the design and development of therapeutic agents against any disease to also understand some of biological background for the disease. The World Health Organisation (WHO) classifies AML into six distinct groups based primarily upon genetic sequencing. These different groups are directly correlated with the disease prognosis, highlighting the heterogeneity of AML.[5] Of special significance are the NMP1 and FLT3 mutations. Patients who have AML with a mutation in the *FLT3* gene have a significant decrease in survival rate compared to the average, while patients with a mutation in the *NPM1* gene have an increased survival rate.[6] Thus the genetic profile of AML in each patient is important for the treatment of the disease, and should be considered as relevant in the development of novel therapeutic agents.

Today's mainline treatment for AML patients is the "7+3" regime, consisting of administration of cytarabine for 7 days, followed by administration of an anthracycline for 3 days (**Figure 1.1**).[7] Together these drugs present the best chance of survival for most patients diagnosed with AML, though this treatment has now been in use since the 1960's and is associated with severe side-effects such as bone marrow suppression.[7,8] As is clear by the mortality rate associated with AML described earlier, alternatives to the 7+3 regime should be sought whether it be because of ineffectual treatment or side effects.

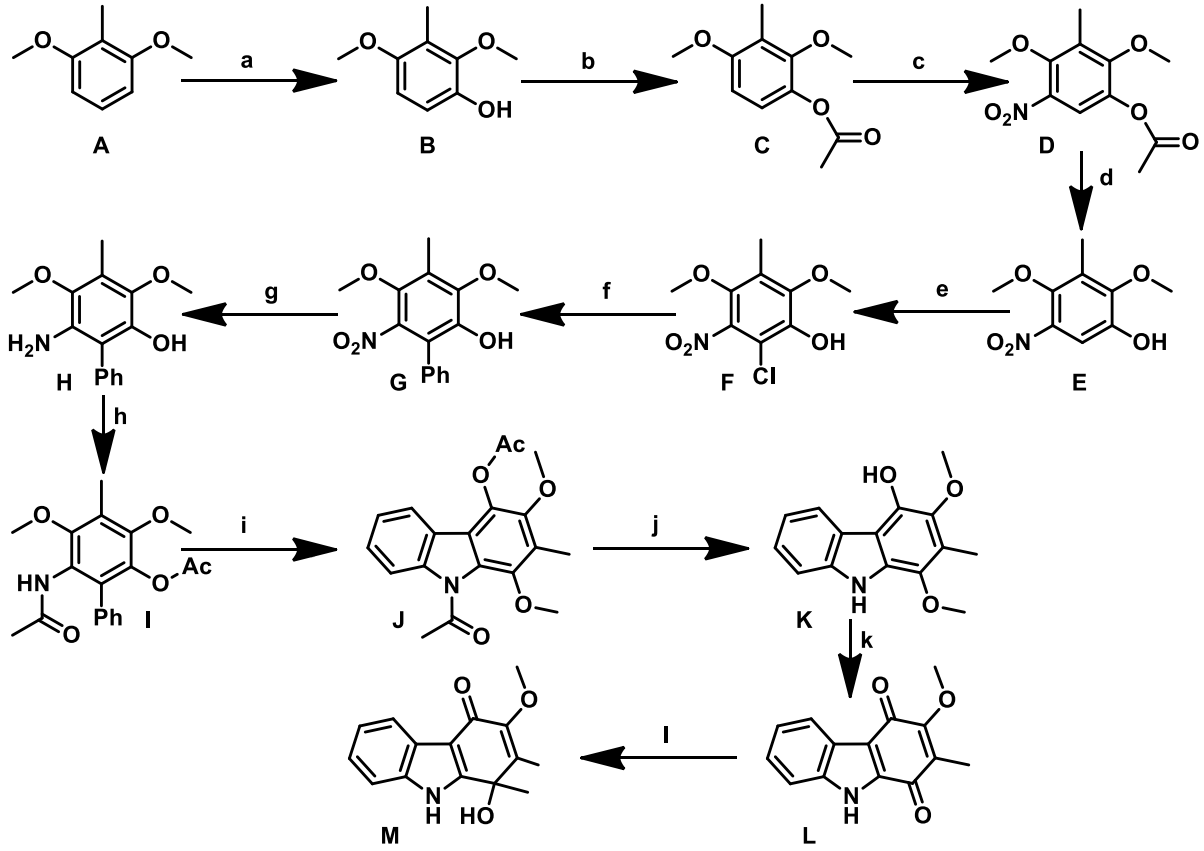


Cytarabine **Daunorubicin**

Figure 1.1: The drugs that comprise the 7+3 regimen, with cytarabine shown on the left, and the most common anthracycline daunorubicin shown on the right.

1.2 Carbazole Derivatives and the Carbazomycin G Project

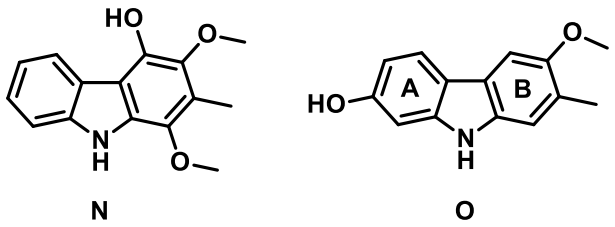
The 9*H*-carbazole is a natural product and alkaloid isolated from coal tar in 1872.[9] Since its isolation a vast array of other natural carbazole alkaloids have been isolated and identified as active anticancer, antibacterial and antifungal compounds.[10] This has led to a significant effort to synthesise both novel carbazole derivatives and natural carbazole alkaloids, from which new pharmaceutical agents may be found. Amongst these are the carbazomycin A-H compounds, a series of closely related natural products that have both been successfully synthesised, and have shown anticancer activity.[11] The Bjørsvik research group found particular interest in the carbazomycin G structure, which presented unique synthetic challenges such as Suzuki-coupling of a very crowded substrate. A novel total synthesis of carbazomycin G was thus developed by the research group in 2018 (**Scheme 1.1**).[12]



Scheme 1.1: The total synthesis of carbazomycin G (**M**) as made by the Bjørsvik research group. (a) H_2O_2 (35%), TFA, 75°C, 2 h., (85%), (b) AcCl, $CHCl_3$ (dry), reflux, 2h., (94%), (c) HNO_3 (65%), AcOH/Ac_2O, 0-5°C, (77%), (d) MeOH, conc. HCl, reflux, 1 h., (>99%), (e) DCH, H_2SO_4, EtOH, r.t., (>99%), (f) $PhB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, TBAB, MeOH/H_2O, 120°C, 30 min., µW, (50%), (g) In, NH_4Cl, EtOH, H_2O, 120°C, 3 h., (96%), (h) Ac_2O, Et_3N, DCM, r.t., 1 h., (94%), (i) $Pd(OAc)_2$, Imes, H_2O_2 (35%), AcOH, µW, 120°C, 5 h., (94%), (j) MeOH, conc. HCl, reflux, 1 h., (94%) (k) HNO_3 (90%), AcOH, 0-20°C, 30 min., (83%), (l) CH_3Li, THF, -78°C, 30 min., (51%).[12]

Throughout this work significant method development was made with regards to the synthesis of carbazole structures. Most interesting was the development of a versatile Suzuki cross-coupling method for congested arenes, as well as a method for intramolecular C-H activation followed by C-N coupling with congested biphenyl.[13,14] Carbazomycin G and all intermediates from the total synthesis were sent for cytotoxicity testing against the AML cell lines MOLM-13 and HL-60.[15] This revealed several intermediates with notable cytotoxic effect, especially against cell line HL-60. By structure-activity relationship analysis (SAR) of these results some carbazole derivatives were seen as likely candidates for the development of novel therapeutic against AML. Foremost among these were compound **N** (**Figure 1.2**).

Attempts were made to synthesise analogues of compound **N**, in which the least substituted ring would be modified (**Figure 1.2**).[16] This developed into a new set of compounds from which further SAR-analysis could be made, and of which all were sent for cytotoxic testing against a variety of AML cell lines. It was discovered that a free hydroxy substituent upon the A ring of the carbazole derivative as in compound **O** gave a significant increase in cytotoxic property, as compared to corresponding methoxy substituents. The most active compound **O** had a cytotoxic effect comparable to that of the standard mainline drug cytarabine (**Figure 1.2**).[16]

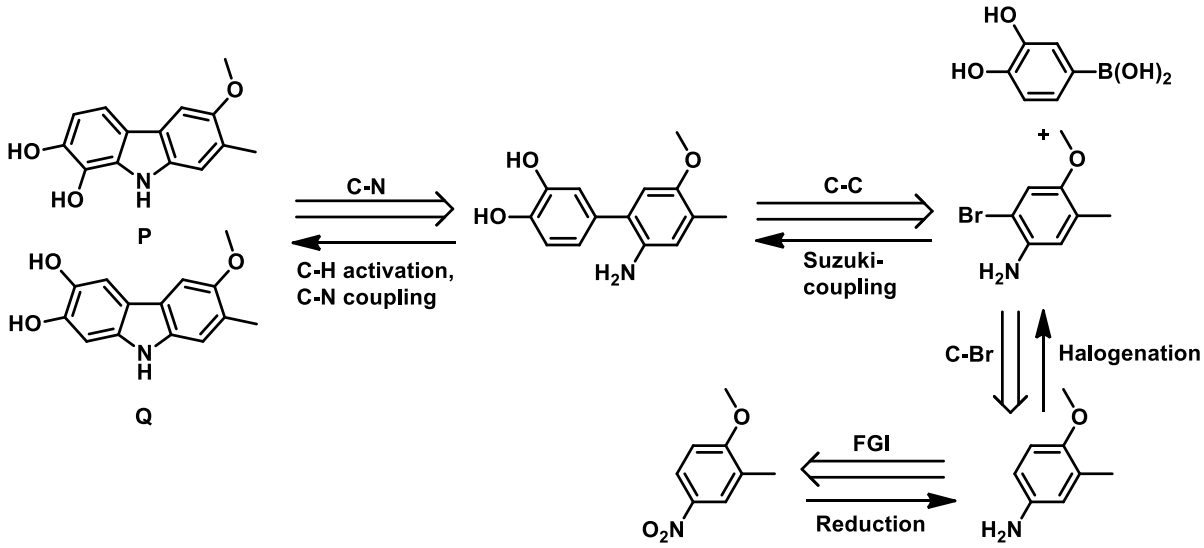


N **O**

Figure 1.2: The most active cytotoxic intermediate **N** from the total synthesis of carbazomycin shown on the left,[16] and the most active cytotoxic analogue developed, **O**, with a free hydroxy substituent on the A ring shown on the right.[15]

1.3 The Catechol Carbazole Derivatives

After the promising cytotoxic effect compound **O** had had against AML cell lines, an interest in whether the structure could be further modified to increase its cytotoxic ability against AML arose. Ideally, should a drug candidate contend with the current mainline drug Cytarabine, it would have to have a stronger cytotoxic effect upon AML cell lines than Cytarabine itself. Due to the significant increase in cytotoxic effect that the carbazole derivatives had shown when a hydroxy group had been added to ring A, exemplified by compound **O**, it was decided that further modification should then be done by adding two hydroxy groups unto ring A. Thus, a more complete SAR-analysis of the structure could be made, and another set of promising carbazole structures could be tested against AML cell lines. While there would be several possible dihydroxylated carbazole structures of interest, the structure with a catechol moiety, two vicinal hydroxy groups upon the A ring, was to be the primary focus of the project. A retrosynthetic analysis was performed upon compound **P**, to give an indication of how the synthesis should proceed (**Scheme 1.2**).



Scheme 1.2: Retrosynthetic analysis of target molecules **P** and **Q**.

By **Scheme 1.2**, the synthesis of the catechol carbazole would lead to two structural isomers **P** and **Q**. Due to rotation around the central biphenyl bond, selective C-H activation by tandem C-N coupling can likely not be made. Furthermore, the necessary boronic acid for the Suzuki-coupling as presented in **Scheme 1.2** was not available commercially. A similar boronic acid with the vicinal hydroxy groups protected by a methylene bridge would be used in its stead.

1.4 Aim of Study

Through cytotoxic testing a series of monohydroxylated carbazole derivatives had shown potent effect against acute myeloid leukaemia (AML) cell lines. This then led to an interest in corresponding dihydroxylated carbazole derivatives, and whether they would have an even stronger cytotoxic effect upon AML cell lines. If not, the results would still strengthen the SAR model that had been developed for the carbazole scaffold, as seen by **Figure 1.3**. The primary aim of the study would be the synthesis of target molecule **P.** Throughout the project structures with different protective groups were also synthesised, both with two methoxy groups on the A ring, and with both acetyl protection and benzyl protection on the amine.

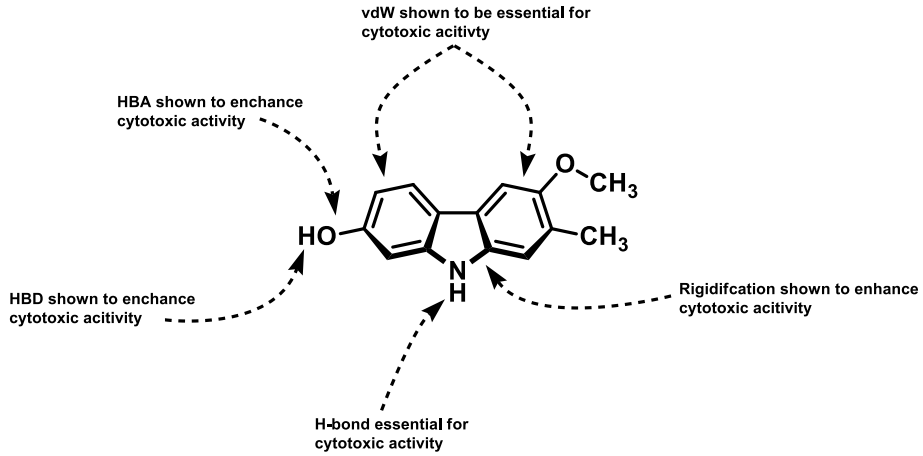
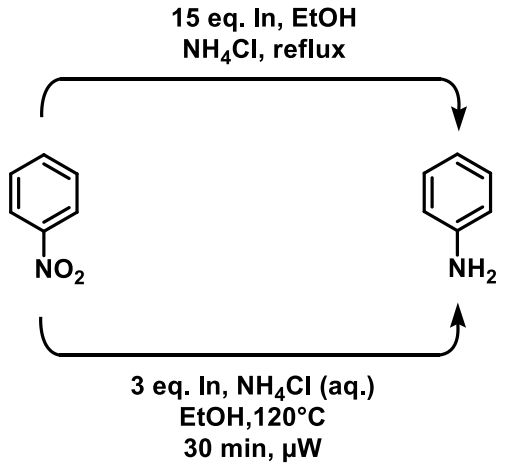


Figure 1.3: SAR analysis of compound **O.**[16]

2. Theory and Methods

2.1 Reduction of Aromatic Nitro Compounds

The reduction of aromatic nitro compounds is an important transformation in organic chemistry, and is used for the production of pharmaceuticals, pigments and a wide variety of other chemicals.[17] It has traditionally been performed by reduction in acid with the presence of iron, known as the Béchamp process.[18] In more modern methods it has been performed by catalytic hydrogenation.[19] In this work, two different methods for the reduction of aromatic nitro compounds were utilised; microwave assisted reduction utilising indium powder (**Scheme 2.1)**, as well as reduction using sodium borohydride and Co(II) salts (**Scheme 2.3)**.

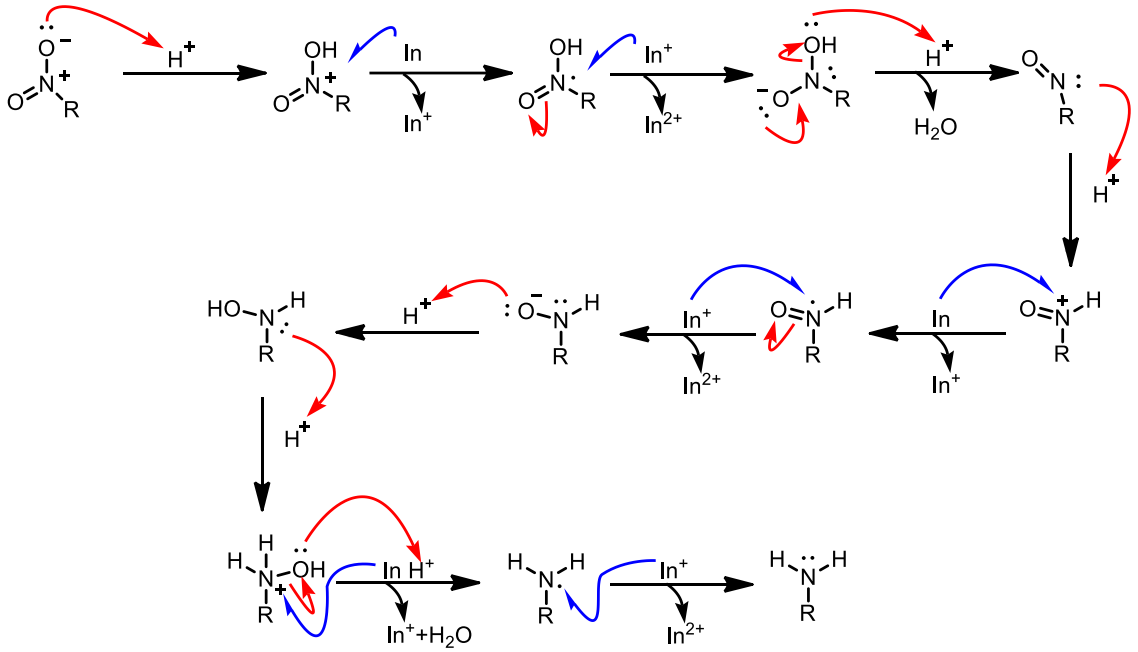


Scheme 2.1: Reduction of an aromatic nitro compound by use of the indium reduction method to give aniline. The topmost method is that developed by Moody and colleagues,[20] while the lower indium reduction method is that developed by Elumalai *et al.*[21]

The method for reduction of nitro compounds utilising indium was originally developed by Moody and colleagues.[20] Due to the first ionisation potential of indium (5.8 eV), which is comparable to that of the alkali metals, indium was considered as likely to participate in single electron transfer processes. Their work established this property, as well as indiums ability to readily reduce a variety of functional groups, such as imines, oximes, nitro compounds, and alkenes. This reduction is more tolerant with regard to other functional groups than that of the more common catalytic hydrogenation process. Nitro groups may be reduced even in the presence of carbonyl groups, nitriles, halides and alkenes.[20]

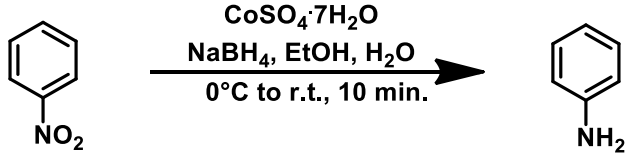
Further work was made to improve this method of reduction by Elumalai *et al*.[21] They compared the Moody method to reduction by zinc, which is raised from an oxidation state of 0 to +2 during the reaction. Base on this assumption, they developed an improved method

requiring only three equivalents of indium with a simplified workup compared to that of the Moody method, which they argue is indicative of the mechanism of indium reduction indeed being similar to that of zinc reduction. The proposed mechanism of indium reduction is given in **Scheme 2.2**.



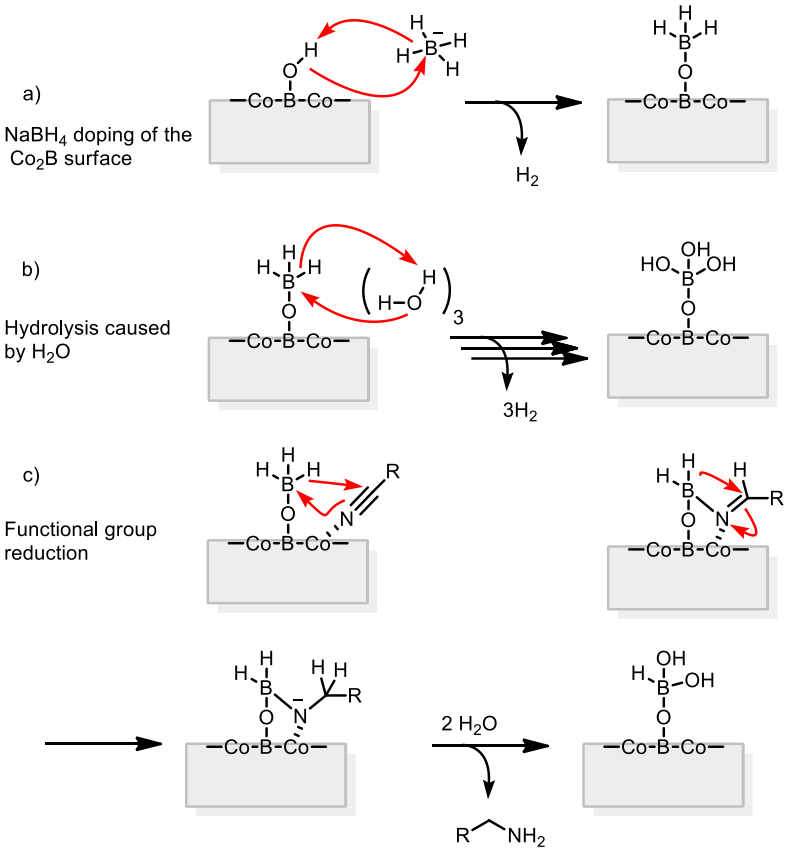
Scheme 2.2: The proposed mechanism of indium reduction is as given in Scheme 2.2.[21] Note that three equivalents of indium are necessary to achieve complete reduction.

In **Scheme 2.2** a nitro group is reduced by three equivalents of indium. The nitro group is first protonated, before indium donates an electron to the positively charged nitrogen. Further donation by indium causes a shift in electron density placing a negative charge upon the oxygen atom. This allows for further protonation, and the subsequent loss of a molecule of water. This donation of electrons from indium and protonation repeats leaving no oxygen left, and the nitro group completely reduced to an amine with the total loss of two molecules of water per nitro group. An alternative method for the reduction of nitro compounds, as well as alkenes, alkynes, azides, and nitriles was later developed in the Bjørsvik research group by Lundevall *et al.* (**Scheme 2.3**).[22]



Scheme 2.3: Reduction of an aromatic nitro compound by use of the Co(II) salt and sodium borohydride, to give aniline.

The reduction protocol was based upon an earlier reported redox system of sodium borohydride with cobalt(II)chloride.[23] However, optimisation of this redox system lead to the use of cobalt(II)sulphate heptahydrate as an alternative salt, with a protic solvent system consisting of water and ethanol. Fast reaction times as well as mild conditions provide a practical method for reduction of a variety of functional groups. The mechanism of action is suggested to proceed through sodium borohydride doping of an *in situ* generated Co_2B surface, by which functional groups may readily be reduced (**Scheme 2.4**).[22]



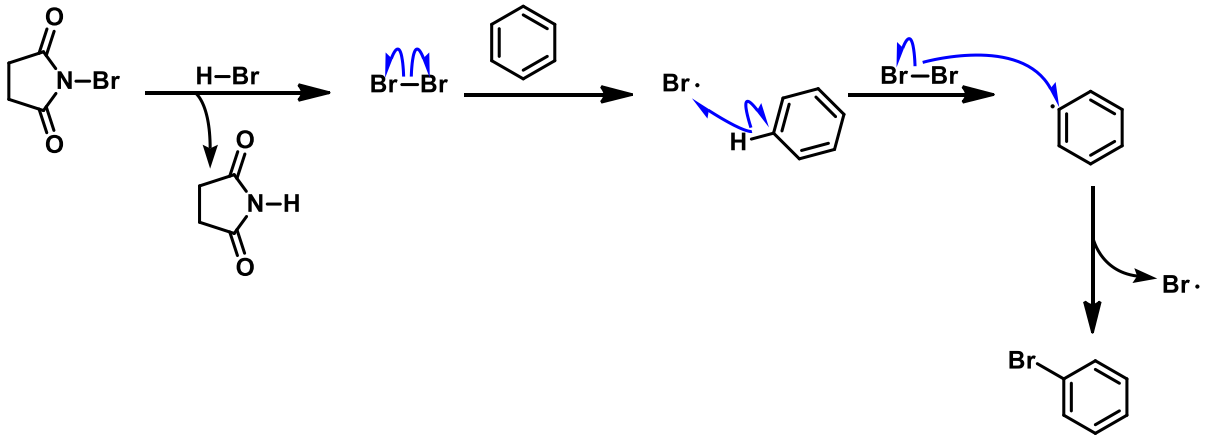
Scheme 2.4: Proposed mechanism of reduction by Cobolt (II) salt and sodium borohydride: (a) Co_2B surface is doped by borohydride. (b) Hydrolysis of sodium borohydride in water. (c) Functional group (nitrile) is reduced by Co_2B doped with borohydride.[22]

In **Scheme 2.4** a Co_2B structure is doped by borohydride, whereupon a functional group like nitrile can be reduced by hydride reduction after the nitrile has coordinated and been activated by the cobalt. As reduction occurs water reacts with the borohydride, saturating the boron with -OH groups and deactivating the catalyst.

2.2 Aromatic Bromination

Bromination of arenes gives useful intermediates to be utilised in a variety of cross coupling reactions.[23] One of the most common methods for aromatic bromination is by use of the hazardous reagents bromine or hydrogen bromide, both of which react according to a common electrophilic aromatic substitution mechanism.[24,25]

More modern attempts at bromination are often made by safer and milder reagents, such as *N*-bromosuccinimide (NBS).[26] This brominating reagent is safer to handle than bromine, releases only harmless succinimide, and gives alongside an appropriate catalyst good selectivity and high yields.[27] While bromination by bromine proceeds in a familiar electrophilic aromatic mechanism, NBS will often react by a radical mechanism.[26,28] NBS steadily releases small amounts of bromine *in situ*, catalysed by trace amounts of hydrogen bromide present in the reagent. This newly formed bromine is homolytically cleaved producing radicals. These radicals may then abstract hydrogens from the substrate, whereby bromine can react giving the desired brominated compound and regenerating the bromine radical (**Scheme 2.5**).[29, 30]

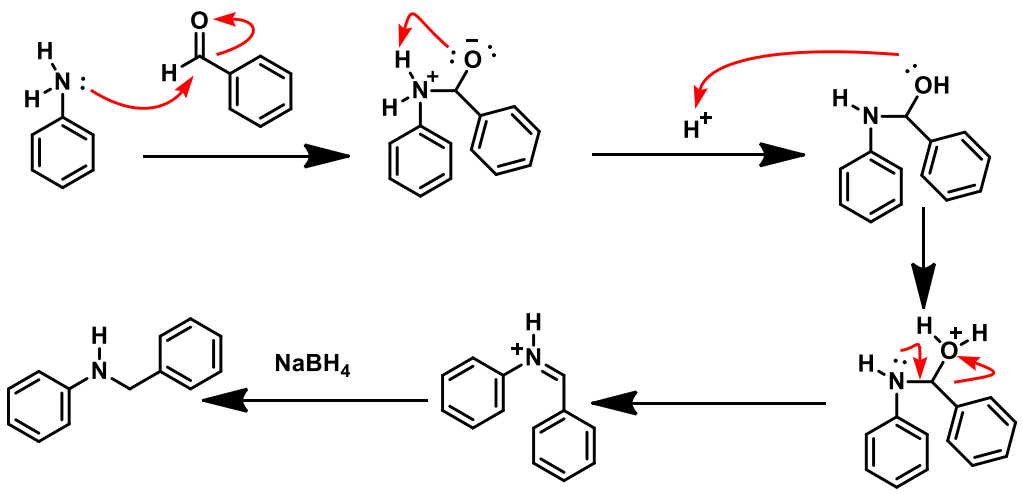


Scheme 2.5: Proposed mechanism for radical NBS bromination.[29, 30]

2.3 Protective Group Chemistry

The chemistry of protective groups is varied, interesting and essential for any attempts at complex organic synthesis, and even more so when reactive amines or alcohols are a part of the compound of interest. Therefore, a selection of protective groups were utilised in this work. The benzyl protective group attached by reductive amination, and the acetyl group attached by a common acetylation reaction were investigated in this project.

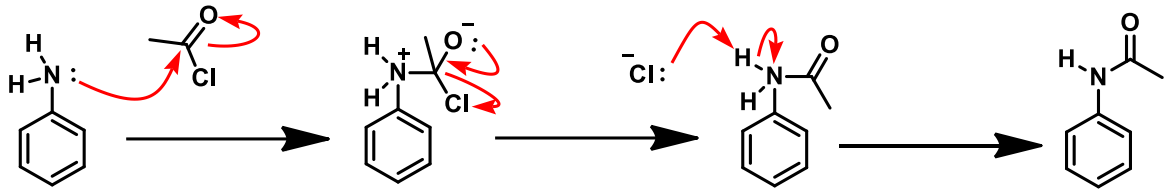
The benzyl moiety as a protective group is effective both for the protection of amines and alcohols.[31] For alcohols benzyl protection remove an acidic proton, lessening the chance for unintended side reactions. The benzyl moiety is also of meaningful size, thereby introducing an element of steric hindrance. In the case of amines, a single benzyl protective group may not substitute all the reactive hydrogens, depending on whether the amines is primary or secondary. In the case of primary amines, a single benzyl protective group will consequently only lessen reactivity, not remove it. Similar to the benzyl protected alcohols, there will also be an element of steric hindrance introduced. Note that the benzyl group does not have a very significant electronic deactivation of amines nor alcohols, in contrast to other notable protective groups, such as the aforementioned acetyl group. The benzyl moiety is attached to alcohols by common chemistry such as the Williamson Ether synthesis.[32] For primary amines a single benzyl group must be attached by reductive amination to avoid repeated benzylation (**Scheme 2.6**).[33, 34]



Scheme 2.6: Proposed mechanism for benzylation of aniline by reductive amination.

The acetyl protective group differs from that of the benzyl group, in that it also introduces an important electronic effect. For the acetylation of amines, an amide functional group will be created. This functional groups has a very deactivated nitrogen, hindering unwanted reactions with the amine under most conditions. The necessity of protecting amines during organic

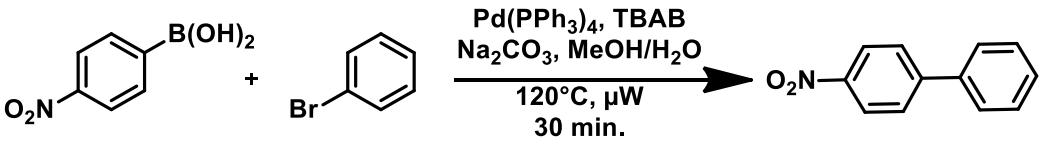
synthesis, coupled with the inherent functionality of amide functional groups make *N*-acetylation an important process in synthesis.[35] It is traditionally performed by reacting the amine with reagents such as acetic anhydride or acetyl chloride (**Scheme 2.7**).



Scheme 2.7: Proposed mechanism for acetylation of aniline by use of acetyl chloride.

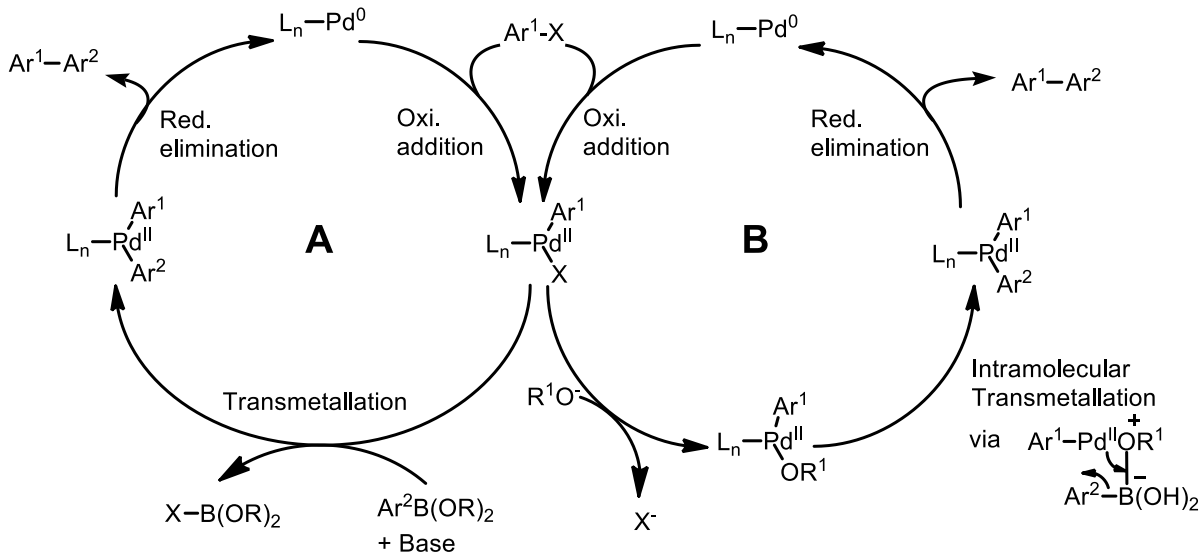
2.4 Suzuki-Miyaura Coupling

To synthesise C-C connections is an essential task for the organic chemist. One of the most common ways of making such connections is the Suzuki cross-coupling reactions. Originally disclosed by Suzuki and colleagues in 1979, this method of cross-coupling could by Pd-catalysation connect an alkenyl borane with an alkenyl halide, forming a $C(sp^2)$-$C(sp^2)$ connection.[36] Further improvements revealed the general method as robust and versatile, capable of creating most $C(sp^2)$-$C(sp^2)$ connections.[37] In the Bjørsvik research group work was made to improve a variation of the Suzuki method provided by Freeman and colleagues in 2005.[38] This Freeman method afforded challenging nitrobiphenyls in good yields, albeit with long reactions times. A highly efficient microwave-assisted Suzuki coupling method giving nitrobiphenyls in good yield with short reaction times was achieved by the Bjørsvik group.[13] Additionally, the method was usable with the generally difficult chloroarenes as substrates (**Scheme 2.8**).



Scheme 2.8: General method for biaryl Suzuki coupling by the Bjørsvik method.[13]

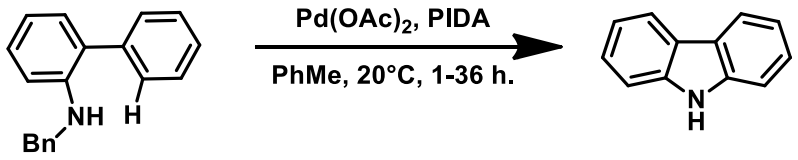
In **Scheme 2.9** the general mechanism of Suzuki-coupling with ligands may be seen. Path A illustrates the most common representation of Suzuki-coupling, with oxidative addition of an arylhalide to Pd^0 to form a coordination complex. By transmetallation a boronic acid replaces the halide, with subsequent reductive elimination to give the biphenyl and regenerate Pd^0. Path B illustrates another possible but similar pathway, in which the base replaces the halide and coordinates to Pd^{II}. The boronic acid then replaces the base, with subsequent reductive elimination to give the biaryl and regenerate Pd^0.[39]



Scheme 2.9: Proposed mechanism for Suzuki-coupling.[39]

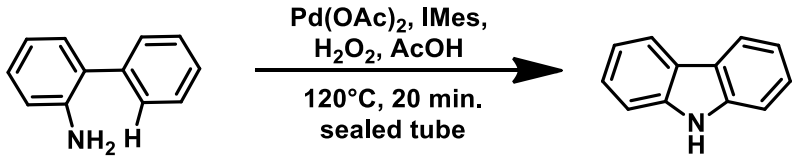
2.5 C-H Activation with C-N Coupling

Another important class of cross-coupling reactions are the C-H activation followed by subsequent C-N coupling reactions. These may be divided into two sub-classes, the cross-dehydrogenative C-N couplings (CDC) and the electrophilic amination reactions (EAR). Cross-dehydrogenative C-N couplings rely on an external oxidant and a metal catalyst, preferably palladium, in order to couple unfunctionalised arenes with amines.[40] This method of forming C-N connections removes the need for complex pre-functionalisation, and is by its nature a greener, more atom-efficient method of synthesis. However, it does often require rare earth metals as catalysts, and sometimes complex ligands. Most reactions also require protection of the amine to be coupled in the C—N formation. Several reactions of this type have been reported, such as those by Gaunt and Buchwald (**Scheme 2.10**).[41,42]



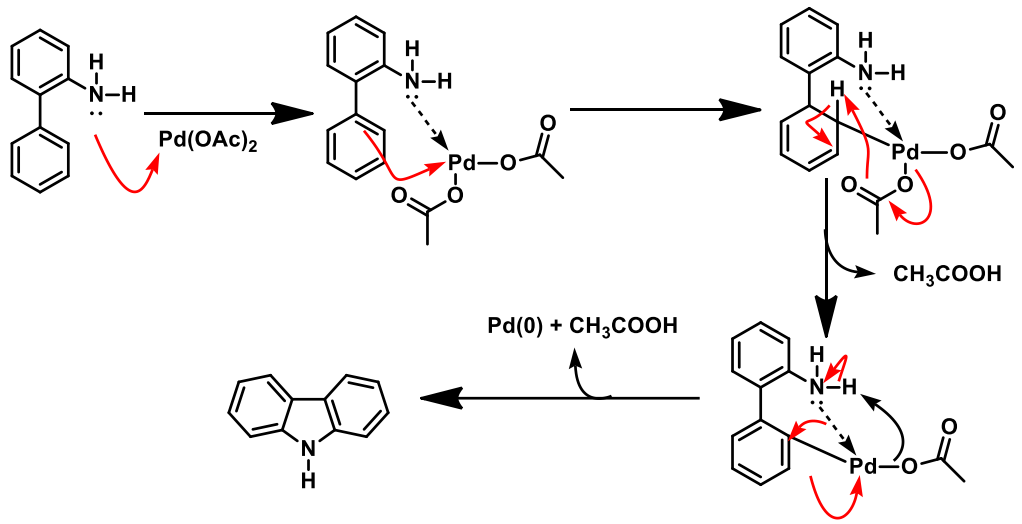
Scheme 2.10: Cross-dehydrogenative coupling by the Gaunt method.[41]

The main drawback of these methods have been the necessity of protecting the amine, adding two additional synthetic steps to most synthesis's. Furthermore, the Gaunt method though being a considerable improvement upon earlier methods, still produces large quantities of reduced oxidant throughout the reaction. Therefore, a significant effort was made by the Bjørsvik research group to develop a new method of CDC that could improve upon some of these weaknesses. In this new method a direct coupling between unfunctionalised arenes and bare amines was developed using $Pd(OAc)_2$ and the complex ligand IMes (**Scheme 2.11**).[14]



Scheme 2.11: Cross-dehydrogenative coupling by the Bjørsvik CDC method.[14]

In **Scheme 2.12** the proposed mechanism for CDC by the Bjørsvik method may be seen. The lone electron pair of the nitrogen coordinates to the Pd centre, before the aromatic ring donates electrons to it. Bond formation occurs, and acetic acid acts as a leaving group. This occurs once more, with acetic acid acting as a leaving group and with the lone pair of the amine attacking the aromatic ring. This displaces palladium and generates the carbazole structure.[14]



Scheme 2.12: Proposed mechanism for coupling by the Bjørsvik CDC method.[14]

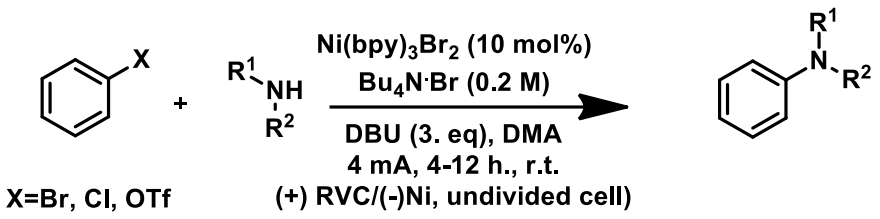
2.6 Electrochemical Synthesis

Electrochemical synthesis is an exciting and active area of research in organic synthesis. Traditional methods for large-scale electrochemical synthesis have been around for many years, but it has lately found new life as a green, efficient and chemoselective method for synthesising all manner of molecules.[43] By utilising electric current hazardous, toxic and expensive reagents can be avoided, as reagents necessary to make a reaction thermodynamically favourable are not as needed in electrochemical synthesis.[44, 45]

Simply put, electrochemical synthesis utilises an electrochemical cell to aid or force a reaction. This cell largely consists of an anode, a cathode, a power supply and an appropriate reaction medium. The power supply pulls electrons from the anode, and forces them to the cathode. This creates an oxidative, electron poor milieu by the anode, and a corresponding reductive, electron-rich milieu by the cathode. The solvent, and often an appropriate electrolyte facilities movement of the substrate and any necessary additives. If reduction of the substrate is desired, it will occur by the cathode and often sacrifice the anode in the process. If oxidation is desired, it will occur by the anode, with proton reduction occurring at the cathode. Naturally, oxidation and reduction will always happen simultaneously in the electrochemical cell, and one of the reaction types cannot happen in isolation.[46]

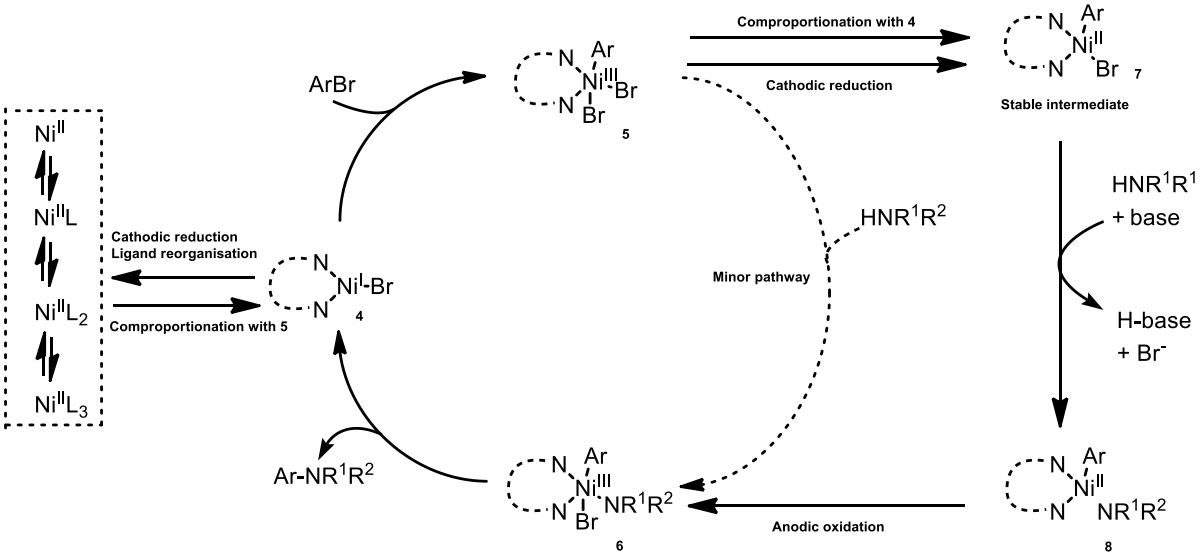
One of the significant challenges with electrochemical synthesis is the fact that a much larger potential than what the reaction theoretically requires is often needed. This permits for unwanted side reactions, eliminating the chemoselectivity that is so desirable in electrochemical synthesis.[44] This can be solved by using a mediator, an additive which itself reacts with the anode or cathode, with the substrate instead reacting with the mediator. This can significantly lower the overpotential necessary, and may further increase the selectivity of the synthesis.[45]

One of these modern electrochemical synthetic methods is that developed by Kawamata *et al*.[47] This method utilises an inexpensive nickel catalyst with a simple ligand to perform e-amination, a form of C-N cross coupling. It has been successful even in synthesising complex molecules such as sugars, oligopeptide and other natural products (**Scheme 2.13**).



Scheme 2.13: Synthesis of amine by Kawamata *et al* protocol.[47]

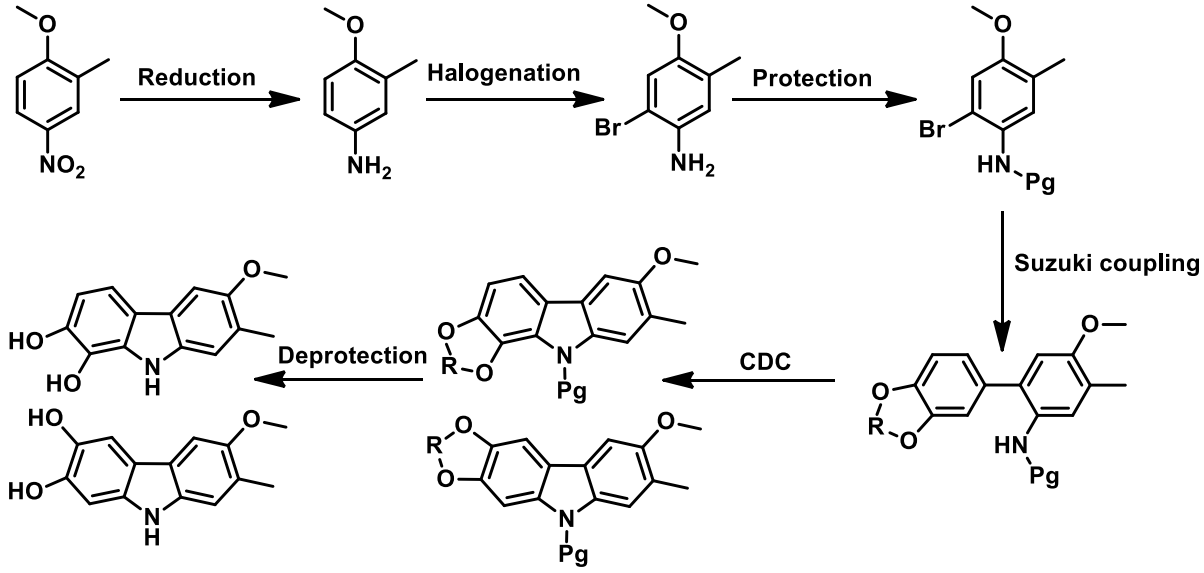
In **Scheme 2.14** a proposed mechanism for the Kawamata method of e-amination is illustrated. The nickelbromo-complex reacts with ArBr by oxidative addition to a Ni^{III} complex, before cathodic reduction and comproportionation with the Ni^{I} species generates a new Ni^{II} complex. The amine then substitutes the bromide by nucleophilic attack, before the nickel complex is oxidised by the anode to a Ni^{III} complex. This then undergoes reductive elimination to regenerate the catalyst, and create the arylated amine of interest.[47]



Scheme 2.14 : Proposed mechanism for e-amination by Kawamata *et al.*[47]

3. Results and Discussion

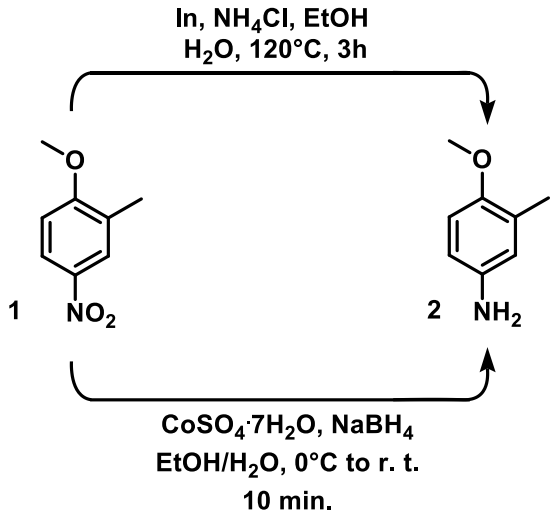
Through consideration of the retrosynthetic analysis outlined for the synthesis of the catechol carbazole derivatives as given earlier, some important aspects become evident (**Scheme 1.2**). First, protection of both the amine and the hydroxy groups on the A ring will be important. If it can be avoided it will shorten the synthesis, but this may not be possible. Secondly, the last ring closure step will in theory produce two structural isomers which will have to be separated if any biological testing is to be done upon the final structures. In **Scheme 3.0**, the total synthesis of target molecules **P** and **Q** is outlined.



Scheme 3.0: Total synthesis of target molecule **P** and **Q**. Pg denotes a classical protective group to protect the amine. R denotes the aliphatic protective group used to protect the hydroxy groups in this project.

3.1 Reduction - Synthesis of 4-methoxy-3-methylaniline (2)

The first step towards synthesising the desired carbazole derivatives was to reduce 1-methoxy-2-methyl-4-nitrobenzene (**1**) to 4-methoxy-3-methylaniline (**2**). 4-Methoxy-3-methylaniline (**2**) has been synthesised previously in the research group, using an indium reduction which afforded a modest yield of 40%.[16] For the reaction, fresh indium, ammonium chloride and **1** were mixed in ethanol and water before heating to give a red solid (**Scheme 3.1**).[21]



Scheme 3.1: Synthesis of 4-methoxy-3-methylaniline (**2**) by reduction from 1-methoxy-2-methyl-4-nitrobenzene (**1**).

The significant drawback with this procedure has been difficulties with scale-up of the reaction. An increase of 1.5 mmol to 3 mmol starting material led to a significant fall in yield (**Table 3.1, Entry 1-2**). The up-scaled reaction was attempted by microwave irradiation as mode of heating, without any improvement in yield (**Table 3.1, Entry 3**). Improvements in work-up technique, as well as a more appropriate solvent system for column-chromatography may have led to the increase in yield by **Entry 4** (**Table 3.1**). Any further attempt at variation of reaction conditions were postponed indefinitely by the success of the reduction using Co(II) salt and sodium borohydride (**Table 3.2**).

Table 3.1: Overview of reagents and relevant reaction conditions for the synthesis of 4-methoxy-3-methylaniline (**2**) from 1-methoxy-2-methyl-4-nitrobenzene (**1**) by indium reduction.[21]

Entry	Comp. 1 [mmol.]	Indium [Equiv.]	NH_4Cl [Equiv.]	Yield (%)
1	1.5	2.8	2.3	36
2	3.0	3.0	2.0	11
3*	3.0	3.0	2.0	8
4	3.2	2.9	1.9	22

*µW heating

To explore a more robust synthesis of 4-methoxy-3-methylaniline (**2**), a reduction using cobalt sulphate and sodium borohydride was attempted (**Scheme 3.1**).[22] 1-Methoxy-2-methyl-4-nitrobenzene (**1**) was dissolved in ethanol, before cobalt(II) sulphate heptahydrate dissolved in water was added to the mixture. Sodium borohydride was slowly added while the mixture was cooled in an ice bath, then the reaction was stirred for ten minutes at room temperature. Product is seen as a red solid when appropriately purified, contrary to earlier reports of a red oil.[16] Variation in the amount of sodium borohydride proved to be the deciding factor for increasing the yield of the reaction, with nearly quantitative yields seen when 6 equivalents of sodium borohydride were added. (**Table 3.2, Entry 5**). Notably, no issues were encountered by up-scaling of the reaction.

Table 3.2: Overview of reagents for the synthesis of 4-methoxy-3-methylaniline (**2**) from 1-methoxy-2-methyl-4-nitrobenzene (**1**) by cobalt sulphate reduction.[22]

Entry	Comp. 1 [mmol]	$CoSO_4 \cdot 7H_2O$ [Equiv.]	$NaBH_4$ [Equiv.]	Yield (%)
1	0.5	1.0	4.5	11
2	0.5	1.0	3.9	3
3	0.5	2.0	4.0	19
4	0.5	1.0	5.0	60
5	5.0	1.0	6.0	90

The ^{1}H-NMR spectrum reveals three aromatic protons as well as the expected proton signals from the methoxy and methyl group in 4-methoxy-3-methylaniline (**Figure 3.1**). Most useful for characterisation however is the appearance of 2H proton signals from the amine moiety at 4.49 ppm, confirming that the desired product has indeed been formed. The use of d-DMSO as solvent is likely necessary to allow for the exchangeable hydrogens of the amine to appear.

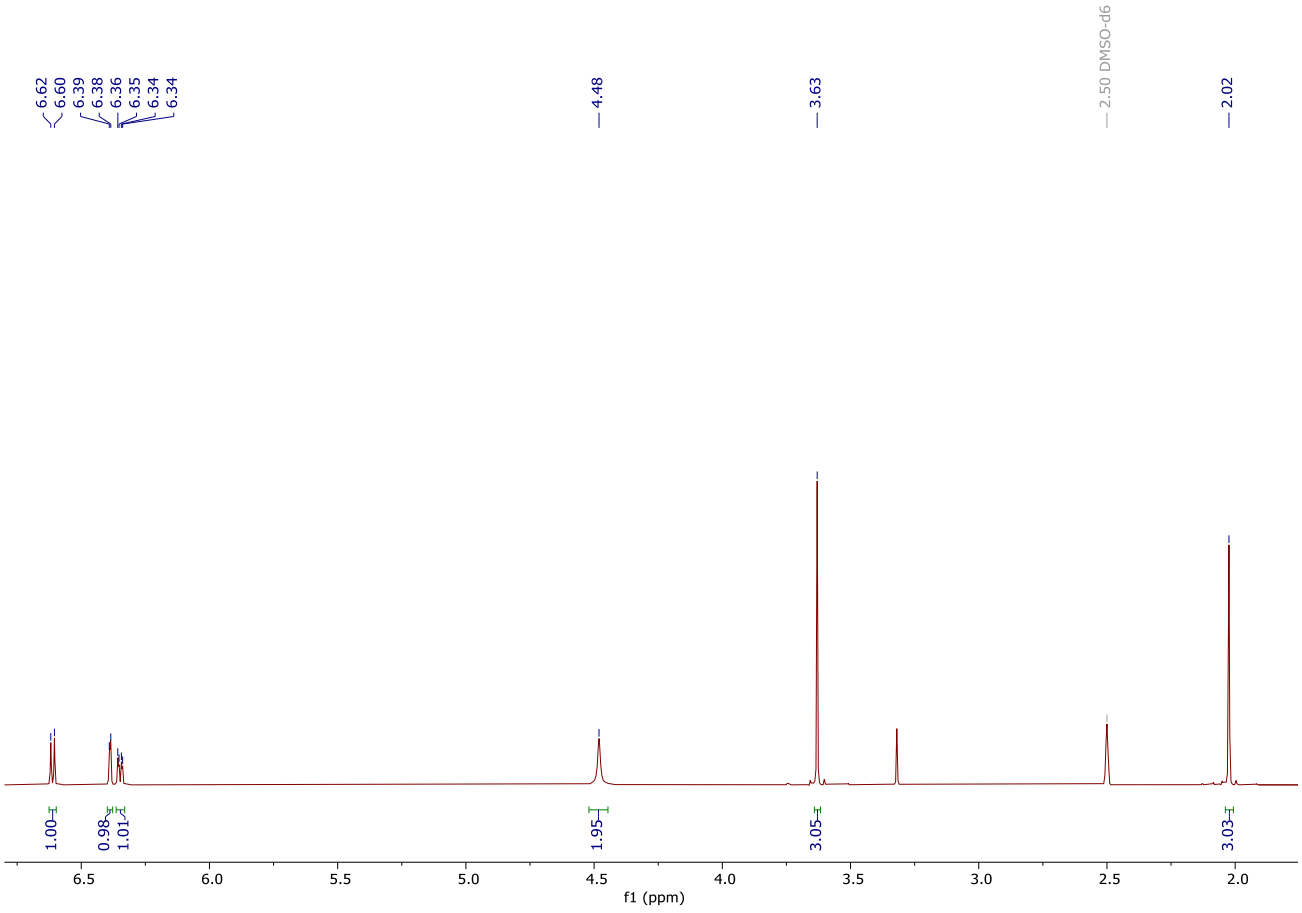
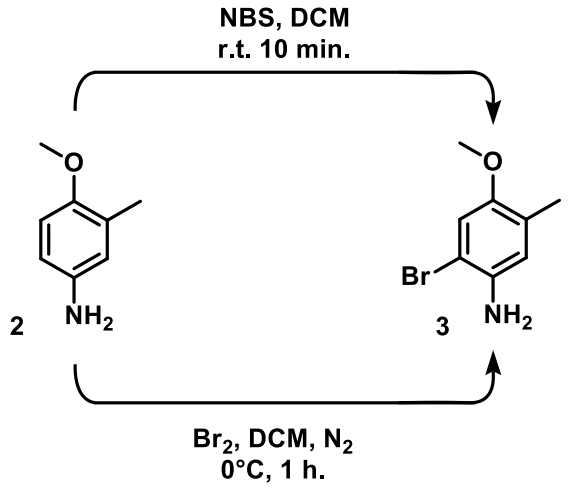


Figure 3.1: ^{1}H-NMR spectrum of compound 2, with d-DMSO as solvent.

3.2 Bromination - Synthesis of 2-bromo-4-methoxy-5-methylaniline (3)

The synthesis of 2-bromo-4-methoxy-5-methylaniline (**3**) had also been performed earlier in the research group. In this synthesis the hazardous reagent bromine was used, and it gave a yield of about 40%.[16] Attempts were made to improve upon this yield, and to eliminate bromine as a reagent. For this purpose the brominating reagent NBS was used. 4-Methoxy-3-methylaniline (**2**) was mixed with NBS in DCM, and stirred at room temperature for ten minutes, before purification to give a dark red solid (**Scheme 3.2**).[26]



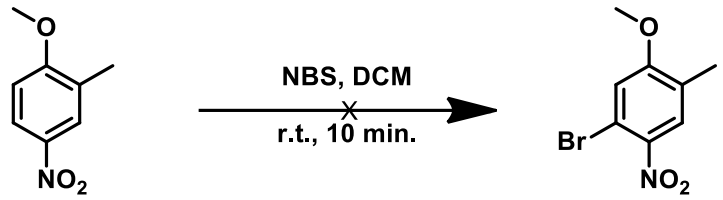
Scheme 3.2: Synthesis of 2-bromo-4-methoxy-5-methylaniline (**3**) from 4-methoxy-3-methylaniline (**2**) by bromination.

Unfortunately, yields were in all attempts with NBS disappointing with comparably low yields for all experiments (**Table 3.3, Entry 1-3**). One further attempt was made with catalytic amounts of ammonium chloride, which did not succeed in increasing the yield (**Table 3.3, Entry 4**).[27] If further attempts at NBS bromination are to be made it might be interesting to try higher temperature microwave reactions.[48]

Table 3.3: Overview of reagents, solvents and relevant reaction conditions for the synthesis of 2-bromo-4-methoxy-5-methylaniline (**3**) from 4-methoxy-3-methylaniline (**2**) by use of NBS.[26, 27]

Entry	Comp. 2 [mmol]	NBS [Equiv.]	Solvent	Reaction time	Reaction temperature°C	Additive [Equiv.]	Yield [%]
1	1.0	1.0	DCM	10 min.	20	-	17
2	0.8	1.0	DCM	10 min.	40	-	12
3	1.0	1.0	DCM	18 h.	20	-	13
4	1.0	1.0	ACN	10 min.	20	0.1 NH_4Cl	4

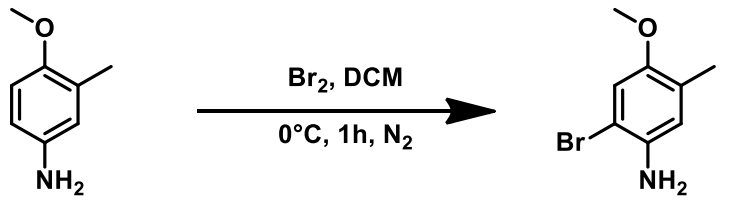
To investigate whether the electron-donating amine was interfering with the NBS-bromination of **2**, an attempt was made to synthesise 1-bromo-5-methoxy-4-methyl-2-nitrobenzene (**4**) (**Scheme 3.3**). This did not give the desired product, though perhaps not unexpectedly as literature suggests that electron-poor molecules rarely react in normal NBS-bromination.[49] A more specialised protocol for electron poor aryls, such as with sulphuric acid as a solvent might have seen more success.[50]



1 4

Scheme 3.3: Synthesis of 1-bromo-5-methoxy-4-methyl-2-nitrobenzene (**4**) from 1-methoxy-2-methyl-4-nitrobenzene (**1**) by use of NBS.

As initial results from bromination by NBS had not been promising, further attempts at bromination were made with bromine.[24] Bromine was slowly added to a solution of 4-methoxy-3-methylaniline (**2**) in DCM under an atmosphere of nitrogen, while the mixture was cooled in an ice bath. The reaction was allowed to run for an hour, affording a dark red solid after subsequent purification (**Scheme 3.4**). The experiments were all successful, and the desired product was made in greatest yield when the reaction was done at large-scale.



2 3 (54%)

Scheme 3.4 Overview of reagents, solvents and reaction conditions for the synthesis of 2-bromo-4-methoxy-5-methylaniline (**3**) from 4-methoxy-3-methylaniline (**2**) by use of bromine.

The ^{1}H-NMR spectrum of **3** shows 2 aromatic protons, the expected methoxy and methyl groups as well as the characteristic 2 protons from the amine (**Figure 3.2**). No splitting is observed of the peaks in the aromatic region, suggesting that these protons are in a para orientation to each other. However, it can not from a ^{1}H-NMR spectrum be ruled out that they are meta orientated to each other either.

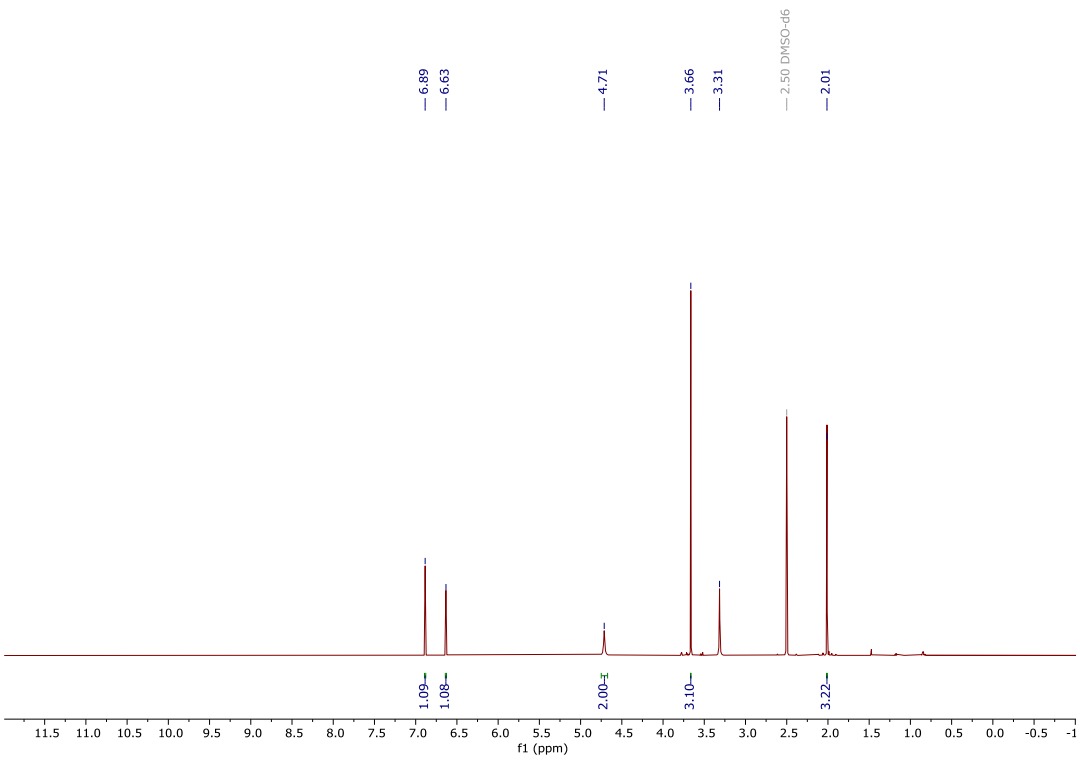


Figure 3.2: ^{1}H-NMR spectrum of compound **3**.

To determine whether the desired isomer had been formed during bromination, a series of 2D-NMR experiments were run. The 1,1-ADEQUATE experiment, which shows J_1 and J_2 coupling between hydrogens and carbon indicates that there is no carbon to which both aromatic hydrogens couple in the isolated product, suggesting that 2-bromo-4-methoxy-5-methylaniline (**3**) and not 3-bromo-4-methoxy-5-methylaniline had been synthesised, see **Figure 3.3**.

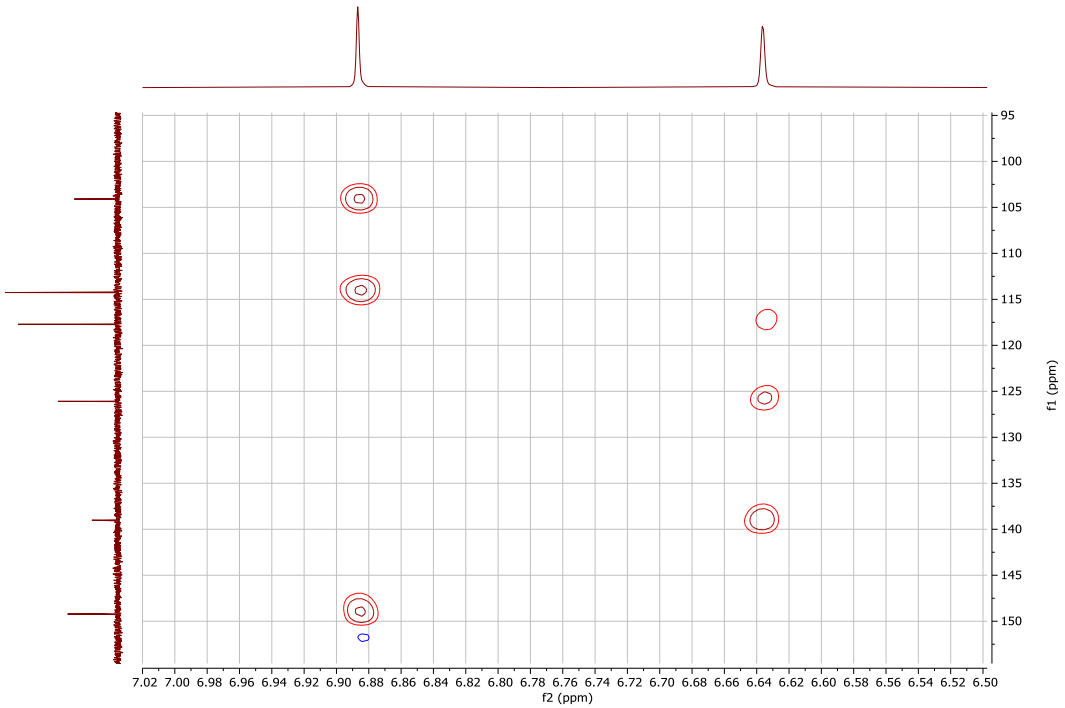
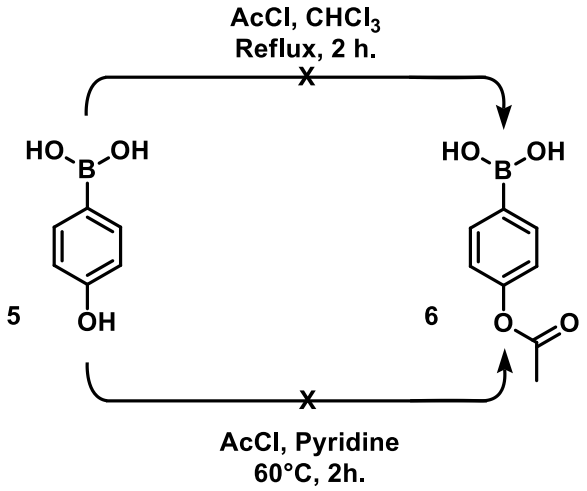


Figure 3.3: 1,1-ADEQUATE 2D-NMR experiment upon 2-bromo-4-methoxy-5-methylaniline (**3**)

3.3 Suzuki-Miyaura Cross-Coupling

3.3.1 Synthesis of (4-acetoxyphenyl)boronic acid (6)

To synthesise the desired biphenyl compounds, adequately protected boronic acids were necessary. These boronic acids were to be coupled by Suzuki-coupling with 2-bromo-4-methoxy-5-methylaniline (**3**). A variety of methoxylated boronic acids were readily available, but there was an appeal in using boronic acids in which the hydroxylated moiety was protected by an easily removable protective group. Therefore, initial attempts were made at protecting the available 4-hydroxyphenylboronic acid (**5**) as proof of concept. Compound **5** was dissolved in DCM before acetyl chloride was added. The reaction mixture was stirred at room temperature for two hours (**Scheme 3.5**).[12] This did not yield the desired product **6**. Another attempt at acetylation was made using pyridine as catalyst, which also did not give product **6**.[51]

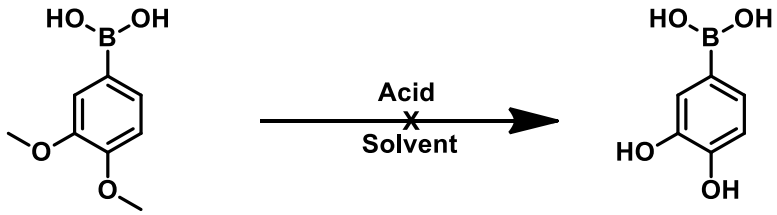


Scheme 3.5: Synthesis of (4-acetoxyphenyl)boronic acid (**5**) from 4-hydroxyphenylboronic acid (**5**) by use of acetyl chloride.

Unfortunately, none of the performed experiments gave the desired product **6.** It is possible that the unprotected boronic acid is sensitive to the conditions used for this protection, and that it should itself be protected before any attempt at protecting the free hydroxy group. However, as attention in the projected turned towards the synthesis of carbazole derivatives with a catechol moiety, this route was not pursued further.

3.3.2 Synthesis of (3,4-dihydroxyphenyl)boronic acid (8)

Biological testing of carbazole derivatives with one hydroxy group had as discussed previously been promising, but there was also a great interest for testing similar carbazole derivatives with two adjacent hydroxy groups, which is frequently called a catechol moiety. To proceed with the synthesis of biphenyls with a catechol moiety, an appropriately protected dihydroxylated boronic acid was necessary. This type of compound was not commercially available, so it was decided that 3,4-dimethylphenylboronic acid (**7**) would be demethylated, and subsequently protected with a more suitable protective group. As earlier experiences revealed high sensitivity of the boronic acids, different acidic demethylation protocols were screened to discover if any were mild enough to spare the boronic acid moiety (**Scheme 3.6**).[52, 53, 54, 55]



7 **8**

Scheme 3.6: Acidic demethylation of 3,4-dimethylphenylboronic acid (**7**) to (3,4-dihydroxyphenyl)boronic acid (**8**).

In all experiments the boronic acid moiety was seemingly removed by the added acid (**Table 3.4, Entry 1-5**). It thus became explicitly clear that the boronic acid would have to be protected if any modification is to be done upon this structure. Alternatively, non-acidic demethylation by nucleophilic agents might be successful.[56]

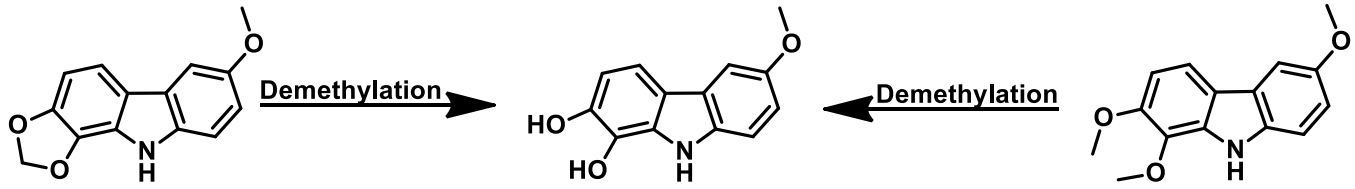
Table 3.4: Overview of the relevant reagents and reaction conditions for the attempted deprotection of 3,4-dimethylphenylboronic acid.

Entry	Comp. 7 [mmol]	Acid [Equiv.]	Acid	Reaction time	Reaction temperature [°C]	Yield [%]
1	1.0	2.0	BBr_3	18 h.	20	0
2	1.3	74.6	H_2SO_4	18 h.	70	0
3*	1.0	25.4	TFA	1 min.	120	0
4	1.0	9.3	ICH	2.5 h.	155	0
5	1.0	2.1	BBr_3	5 h.	-78 to 20	0

*µW heating

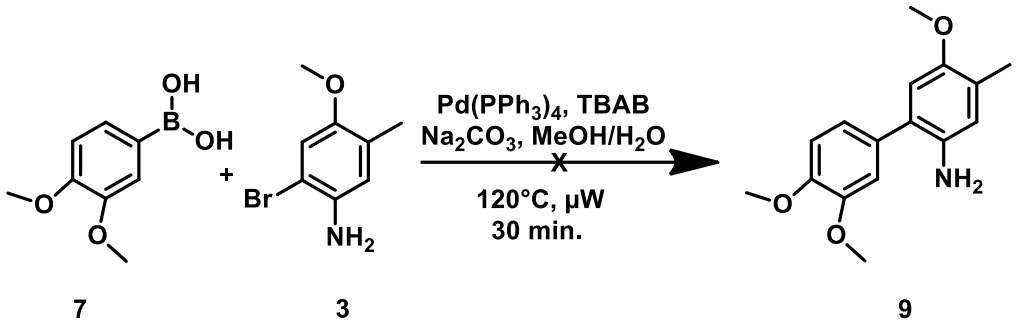
3.3.3 Synthesis of 3',4',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-amine (9) and synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylaniline (11)

As attempts for the exchange of the methoxylated substituents on the (3,4-dimethoxyphenyl)boronic acid (**7)** with more appropriately protected hydroxy groups had failed, further experiments were instead made to Suzuki-couple the methoxylated boronic acid **7** with 2-bromo-4-methoxy-5-methylaniline (**3**) (**Scheme 3.8**). The two adjacent methoxy groups could then be demethylated as a final synthetic step, after the carbazole structure had been made. This would introduce some selectivity issues, as there would be a similar methoxy substituent on the B ring of the of the structure. Benzo[d][1,3]dioxol-5-ylboronic acid (**10**), thus became the primary boronic acid of interest as the project developed, due to its methylene bridge differing enough from the methoxy substituent of **3** to afford some selectivity when the time would come to demethylate the carbazole structure. (**Scheme 3.7)**



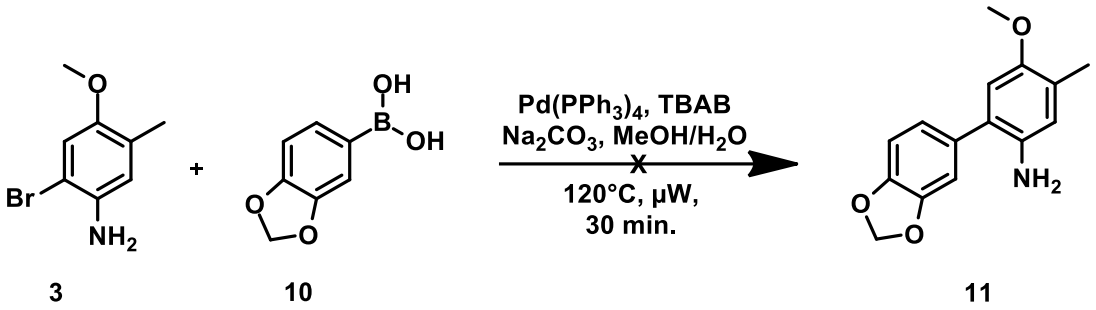
Scheme 3.7: Overview of the final demethylation reaction to produce the desired carbazole derivative from the protected carbazole structures. Note the difficulty in selective demethylation of the right-side structure, due to three similar methoxy groups.

Substrate **7** and substrate **3** were attempted coupled through Suzuki conditions. Both were added to a microwave tube with $Pd(PPh_3)_4$, TBAB, and sodium carbonate. Methanol and water was added, before the reaction mixture was heated.[13] Analysis by GC-MS and NMR showed that none of the desired product **9** was formed.



Scheme 3.8: Synthesis of 3',4',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-amine (**9**) from (3,4-dimethoxyphenyl)boronic aid (**7**) and 2-bromo-4-methoxy-5-methylaniline (**3**) by the Bjørsvik method of Suzuki-coupling.

The synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylaniline (**11**) was attempted by the same Bjørsvik method of Suzuki-coupling, as described earlier. (**Scheme 3.9**)



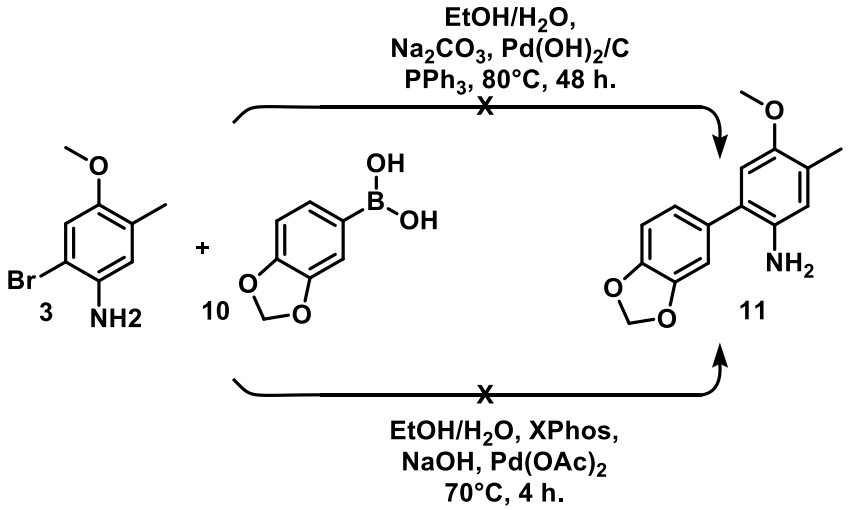
Scheme 3.9: Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylaniline (**11**) from benzo[d][1,3]dioxol-5-ylboronic acid (**10**) and 2-bromo-4-methoxy-5-methylaniline (**3**) by the Bjørsvik method of Suzuki-coupling.

Unfortunately the various attempts at the direct synthesis of **11** failed and none of the desired product was observed (**Table 3.5**). The starting material was consumed in the reaction, but no easily identifiable products were made. Explanation to this could be polymerisation, or degradation of the starting material, but is difficult to establish without further analysis. The Bjørsvik method had previously been successful with free amines, though most other methods of Suzuki coupling do require some protection. It may then be that the substrates used here were too reactive to achieve coupling without protection.

Table 3.5: Overview of reagents and relevant reaction conditions for the attempted synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylaniline (**11**) from benzo[d][1,3]dioxol-5-ylboronic acid (**10**) and 2-bromo-4-methoxy-5-methylaniline (**3**).

Entry	Comp. 3 [mmol]	Comp. 10 [Equiv.]	$Pd(PPh_3)_4$ [mol%]	TBAB [mol%]	Na_2CO_3 [Equiv.]	Reaction time	Yield [%]
1	1.0	1.5	2.8	9	1.1	30 min.	0
2	1.0	2.0	2.5	8	1.1	4 h.	0
3	1.0	1.5	2.6	8	2.7	30 min.	0

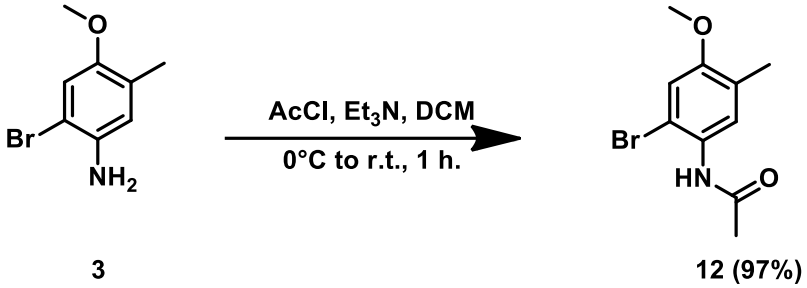
As the Bjørsvik method for Suzuki-cross coupling is somewhat uncommon in that no ligands are necessary, the failure of this method led to two further attempts with older procedures that do use ligands. The first was with the Pearlman catalyst and triphenylphosphine as ligand,[57] while the second method was with palladium on carbon, and Xphos as ligand.[58] The experiments gave none of the desired product (**Scheme 3.10**). Therefore, a protection of the amine was considered necessary due the challenges met with this Suzuki coupling with free amines.



Scheme 3.10: Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylaniline (**11**) from benzo[d][1,3]dioxol-5-ylboronic acid (**10**) and 2-bromo-4-methoxy-5-methylaniline (**3**). The topmost protocol is that of Felpin, F.X *et al.*,[57] while the bottommost protocol is that of Yang, J. *et al*.[58]

3.3.4 Synthesis of *N*-(2-bromo-4-methoxy-5-methylphenyl)acetamide (12)

To be able to continue with the Suzuki coupling, the amine of 2-bromo-4-methoxy-5-methylaniline (**3**) would have to be protected. Earlier attempts of Suzuki coupling with protective groups had in the research group been achieved with acetylated amines, which was therefore chosen as the most practical protective group. *N*-acetylation of compound **3** was performed by adding Et_3N to a solution of **3** in DCM in an icebath, followed by a slow addition of AcCl. The reaction was stirred at room temperature to afford a red solid (**Scheme 3.11**).[21]



3 **12 (97%)**

Scheme 3.11: Synthesis of *N*-(2-bromo-4-methoxy-5-methylphenyl)acetamide (**12**) from 2-bromo-4-methoxy-5-methylaniline (**3**) by N-acetylation.

The acetylation reaction performed well and the protected compound **12** was afforded in great yield, especially so at large scale.

In the EI-MS spectrum of **12**, the molecular ion of may be seen at an m/z of 257 (**Figure 3.4**). As expected for a brominated compound, it has a M+2 peak. The most interesting fragment is that of the peak at m/z 215, corresponding to the loss of a acetyl fragment, confirming that the substrate **3** has been acetylated as desired. The peak at 200 m/z corresponds to a further loss of a methyl group, while the peak at 178 m/z is from the loss of bromine. Note the expected loss of the characteristic isotopic +2 peak for the 178 m/z peak.

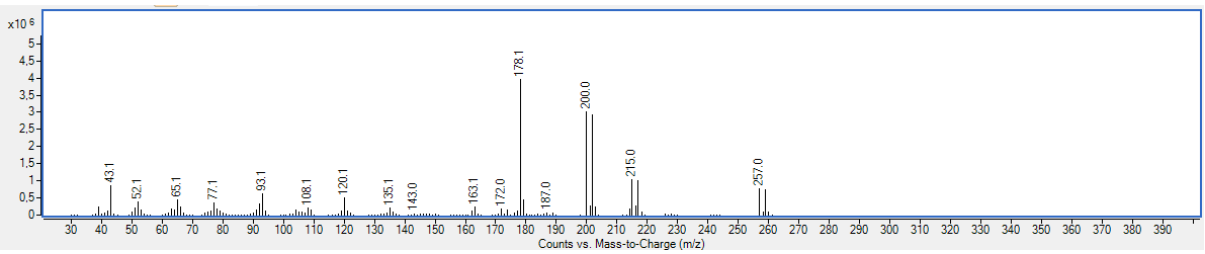
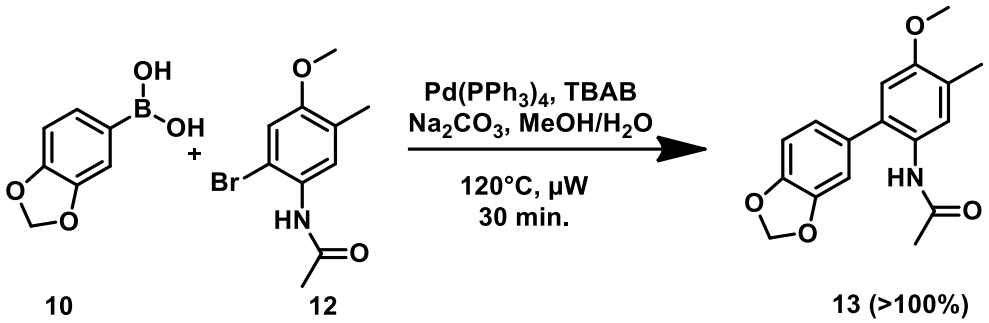


Figure 3.4: EI-MS spectrum of N-(2-bromo-4-methoxy-5-methylphenyl)acetamide (**12**)

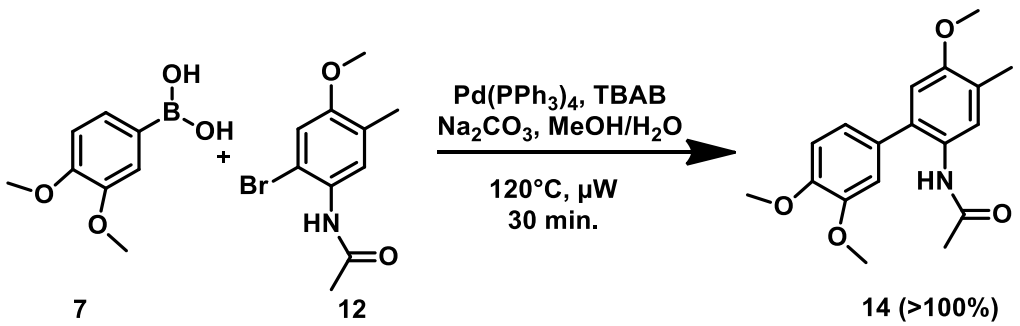
3.3.5 Synthesis of *N*-(2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylphenyl)acetamide (13) and *N*-(3',4',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl)acetamide (14)

With the acetylated amine **12** in hand, new attempts were made at the Suzuki-couplings using the Bjørsvik method which previously had failed. Compound **10** and compound **12** were added to a microwave tube with $Pd(PPh_3)_4$, TBAB, and sodium carbonate. Methanol and water was added, before the reaction mixture was heated. The synthesis of *N*-(2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylphenyl)acetamide (**13**) was successful, in quantitative yields (**Scheme 3.12**).



Scheme 3.12: Synthesis of *N*-(2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylphenyl)acetamide (**13**) from *N*-(2-bromo-4-methoxy-5-methylphenyl)acetamide (**12**) and benzo[d][1,3]dioxol-5-ylboronic acid (**10**)

Attempts were also made at synthesising *N*-(3',4',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl)acetamide (**14**). Following the Bjørsvik method, all attempts at synthesising **14** were successful, also in quantitative yields (**Scheme 3.13**).



Scheme 3.13: Synthesis of *N*-(3',4',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl)acetamide (**14**) from (3,4-dimethoxyphenyl)boronic acid (**7**) and *N*-(2-bromo-4-methoxy-5-methylphenyl)acetamide (**12**).

Some product will usually be lost through extraction and column chromatography. Therefore, it is unlikely that all the experiments gave 100% yield. Analysis of the purified product by GC-MS did reveal some stubborn traces of triphenylphosphine, and analysis by NMR revealed

some contamination of one or more organic compounds (**Appendix).** There is also the possibility of palladium remains in the product, which is known to be difficult to entirely remove from product.[59] Nonetheless, the purified yields were positive.

In the EI-MS spectrum of **13** the molecular ion may be observed at an m/z of 299 (**Figure 3.5**). The primary fragments are that of the loss of an acetyl fragment, giving a peak at an m/z of 257, and the subsequent loss of a methyl fragment, giving a peak at an m/z of 242. From **Figure 3.6**, the molecular ion of **14** may be observed at an m/z of 315. The primary fragments are similar to that of **13**, the loss of an acetyl fragment giving a peak at m/z 273, with the subsequent loss of a methyl fragment giving a peak at an m/z of 258.

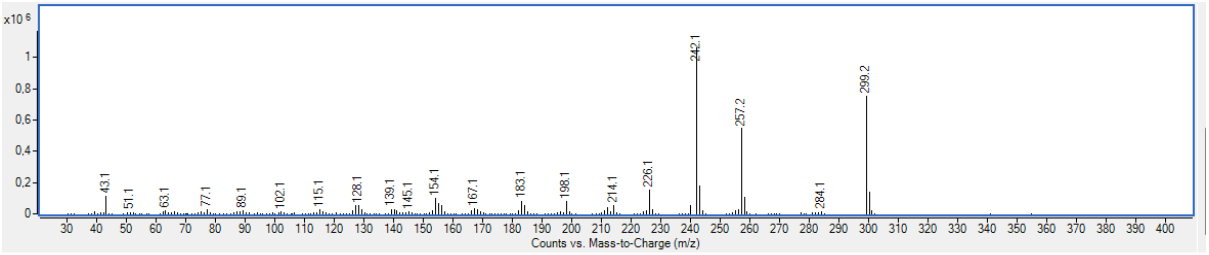


Figure 3.5: EI-MS spectrum of N-(2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylphenyl)acetamide (**13**)

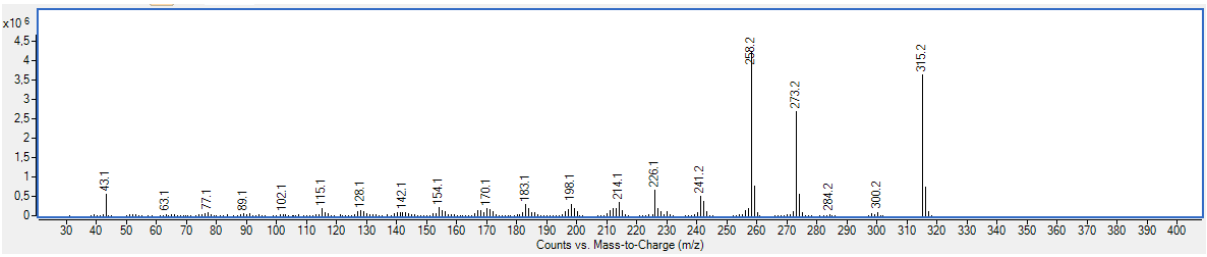
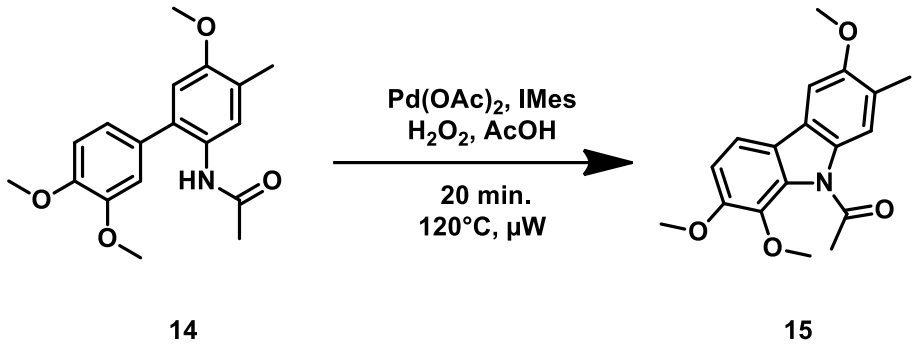


Figure 3.6: EI-MS spectrum of N-(3',4',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl)acetamide (**14)**

3.4 Cross-Dehydrogenative Coupling

3.4.1 Synthesis of 1-(1,2,6-trimethoxy-7-methyl-9H-carbazol-9-yl)ethenone (15)

The ring closure of the biphenyl **14** could be made by cross-dehydrogenative coupling. This was done by the Bjørsvik method of tandem C-H activation and C-N bond formation.[21] Compound **14** was with $Pd(OAc)_2$ and IMes added to a reactor tube, and dissolved in glacial acetic acid. Hydrogen peroxide was added, and the reaction mixture was irradiated in a microwave reactor at 120°C to give a dark red oil (**Scheme 3.14**).



Scheme 3.14: Synthesis of 1-(1,2,6-trimethoxy-7-methyl-9H-carbazol-9-yl)ethenone (**15**) by cross-dehydrogenative cross coupling from *N*-(3',4',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl)acetamide (**14**).

Several different reaction conditions were attempted in order to increase the yield of the reaction. However, at best a yield of 4% was achieved (**Table 3.6, Entry 3**). Analysis by GC-MS reveals that the starting material seems unreactive, and is mostly not consumed. It may be that harsher conditions, or a change of oxidant is necessary to force the reaction.

Table 3.6: Overview of reagents and relevant reaction conditions for the synthesis of 1-(1,2,6-trimethoxy-7-methyl-9H-carbazol-9-yl)ethenone (**15**).

Entry	Comp. 14 [mmol]	$Pd(OAc)_2$ [mol%]	IMes [mol%]	H_2O_2 [Equiv.]	Reaction time	Yield [%]
1	0.4	5	5	3	20 min.	Traces
2	0.5	25	6	3	3.5 h.	Traces
3	0.5	20	22	3	20 min	4

The EI-MS spectrum of compound **15** shows the molecular ion at m/z 313. Its primary fragments are that of the deacetylated moiety at m/z 271, and of the deacetylated and demethylated moiety at m/z 256. This corresponds well with the fragmentation pattern one would expect from compound **15**.

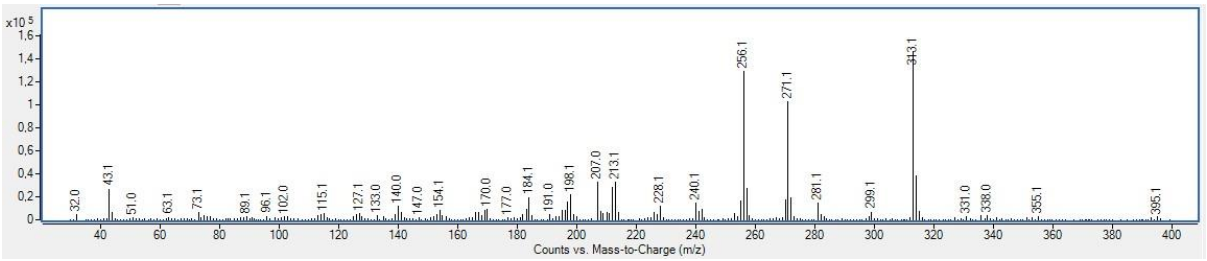
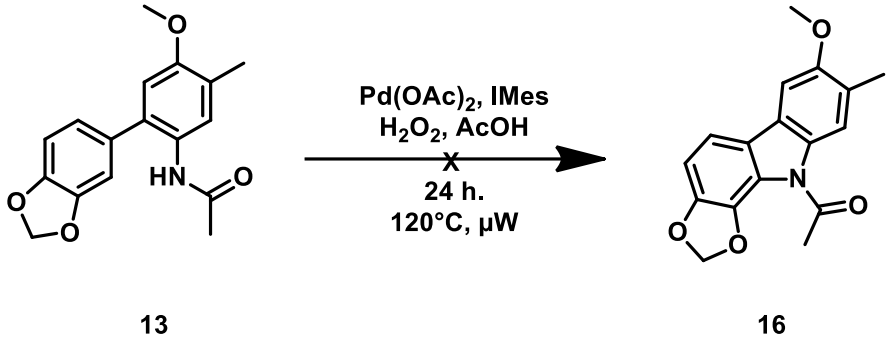


Figure 3.7: EI-MS spectrum of 1-(1,2,6-trimethoxy-7-methyl-9H-carbazol-9-yl)ethenone (**15**)

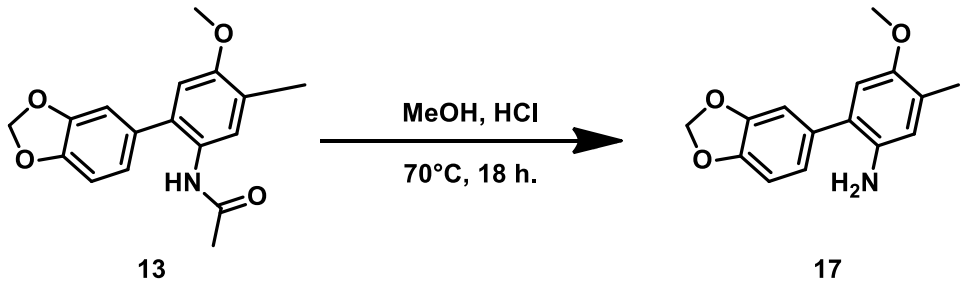
3.4.2 Synthesis of 8-methoxy-7-methyl-5H-[1,3]dioxolo[4,5-b]carbazole (18)

As discussed earlier, there were obvious selectivity issues in the deprotection of 1-(1,2,6-trimethoxy-7-methyl-9H-carbazol-9-yl)ethenone (**15**), in addition to that the yield should be improved. Therefore, further experiments were made to synthesise 8-methoxy-7-methyl-5H-[1,3]dioxolo[4,5-b]carbazole (**18**). A final attempt was made at ring closure with the acetylamine **13**, even though it was expected to fail due to the similarities between substrates **13** and **14** (**Scheme 3.15**).



Scheme 3.15: Synthesis of 1-(7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazol-10-yl)ethenone (**16**) from *N*-(2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylphenyl)acetamide (**13**).

The starting material **13** was not consumed in the attempted synthesis of **16**, similar to what observed for the attempted synthesis of **15**. The acetylated amines are known for low reactivity, so a free amine was considered the appropriate substrate to achieve the desired cross-dehydrogenative coupling. Deacetylation was performed under acidic conditions by refluxing substrate **13** with HCl in methanol. (**Scheme 3.16**).



Scheme 3.16: Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylaniline (**17**) from *N*-(2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylphenyl)acetamide (**13**).

The initial attempt at deprotection of **13** failed, but an increase in reaction time was enough to give a reasonable yield of 74% (**Table 3.7**). It may be that 18 hours is in excess of the necessary reaction time to deprotect compound **17**.

Table 3.7: Overview of reagents and relevant reaction conditions for the synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylaniline (**17**) from *N*-(2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylphenyl)-acetamide (**13**).

Entry	Comp. 13 [mmol.]	HCl [mL]	Reaction time	Yield [%]
1	0.5	2	1 h.	0
2	0.3	2	18 h.	74

From the EI-MS spectrum in **Figure 3.8**, a peak corresponding to the molecular ion of **17** is present at m/z of 257. The most dominant fragment is that of the loss of a methyl group, giving a peak at an m/z of 242. Notably, no major fragment corresponding to the loss of an acetyl group can be observed, confirming that the substrate **13** had been successfully deacetylated.

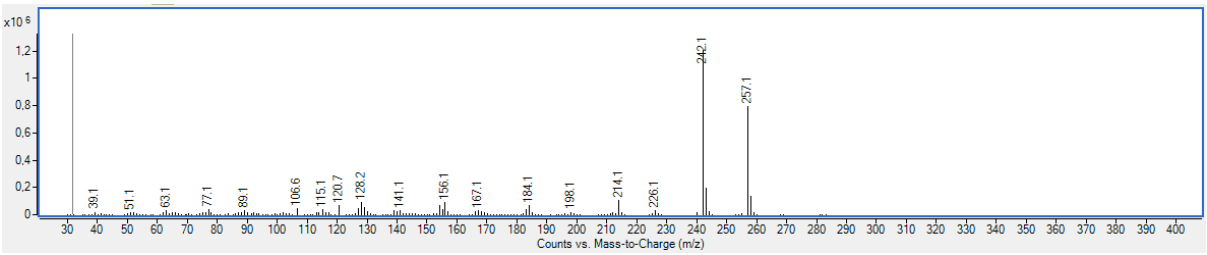
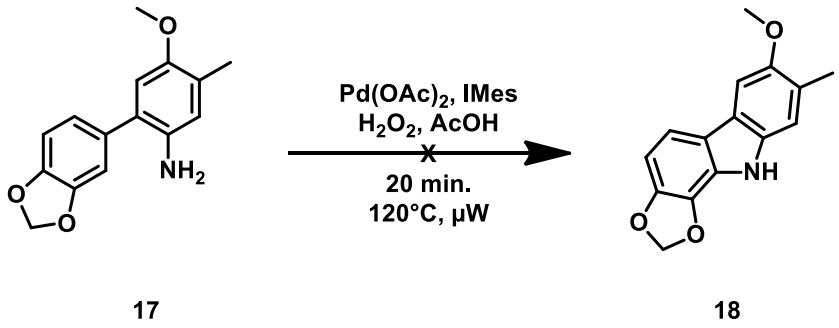


Figure 3.8: EI-MS spectrum of 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylaniline (**17**)

With the successful deacetylation of **13** to give **17**, further attempts could be made at synthesising the carbazole 8-methoxy-7-methyl-5H-[1,3]dioxolo[4,5-b]carbazole (**18**). Similar to earlier attempts of cross-dehydrogenative coupling, the substrate **17** was with catalyst and ligand added to a microwave tube, before glacial acetic acid and hydrogen peroxide was added. The mixture was subjected to microwave radiation at 120°C for 20 minutes (**Scheme 3.17**).



17 **18**

Scheme 3.17: Synthesis of 8-methoxy-7-methyl-5H-[1,3]dioxolo[4,5-b]carbazole (**18**) from 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylaniline (**17**).

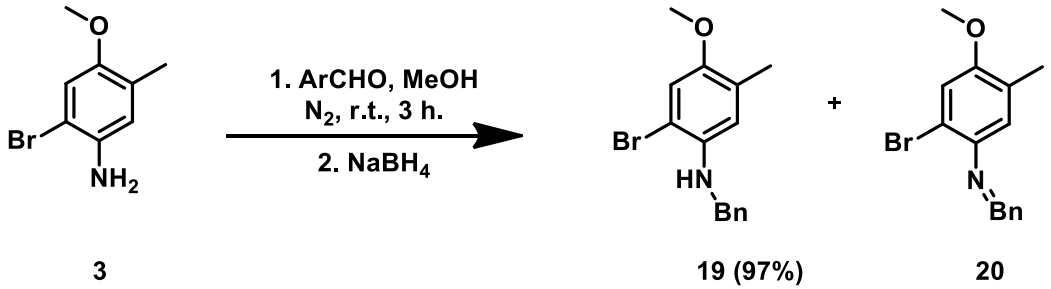
When the oxidant H_2O_2 was added to the reaction mixture, the mixture turned dark red. GC-MS analysis of crude after reaction showed no starting material, nor any other major

compound. LC-MS analysis combined with IR did not suggest that there was any significant demethylated derivative of **17** or **18** present either. It may be that the substrate **17** has by addition of hydrogen peroxide polymerised, however a more extensive analysis would be necessary to confirm this.

3.5 Synthesis of Carbazole Derivative with Benzyl Protective Group

3.5.1 Protection - Synthesis of *N*-benzyl-2-bromo-4-methoxy-5-methylaniline (19)

Synthesis of a carbazole derivative from the free amine of **17** had thus failed, due to the apparent over-reactivity of the substrate. It had likewise failed with the acetylated substrate **13** and **14**, due to lack of reactivity of substrate, leaving unreacted starting material after the reaction. In light of these findings, a different protective group was chosen so as to reduce the reactivity of the free amine, but without the complete deactivation of the acetyl protective group. A benzyl group was chosen as it does not have a significant electronic effect upon the amine, but does introduce steric hindrance to the compound, and removes one of the reactive amine hydrogens. This protection was achieved by reductive amination. Compound **3** was stirred with benzaldehyde in methanol under an inert atmosphere at room temperature for 3 hours, before sodium borohydride was mixed in to give a red solid (**Scheme 3.18**).[33]



Scheme 3.18: Synthesis of *N*-benzyl-2-bromo-4-methoxy-5-methylaniline (**19**) from 2-bromo-4-methoxy-5-methylaniline (**3**).

The best yields of the protection was achieved when upscaled. This may be due to the greater scale of the reaction limiting the percentage of product lost in work-up. A slight increase in sodium borohydride was also used in the up-scaled experiment, which could also have led to the increase in product.

From the EI-MS spectrum in **Figure 3.9**, the molecular ion of **19** may be seen at m/z 305, with the expected M+2 peak of a brominated compound. Primary fragments are that of the loss of a methyl group at m/z 290, and the further loss of a phenyl group with a peak at m/z 214. The peak at 91 m/z is likely from the tropylium ion. After purification by flash chromatography the product still contained small amounts of the imine intermediate **20** from the attachment of the benzyl protective group. The EI-MS spectrum of this compound may be seen from **Figure 3.10**, in which the molecular ion is observed at m/z 303. The lack of a tropylium ion in the mass

spectrum supports the presence of an imine double bond, which would not allow for the loss of the tropylium ion as readily as for compound **19**.

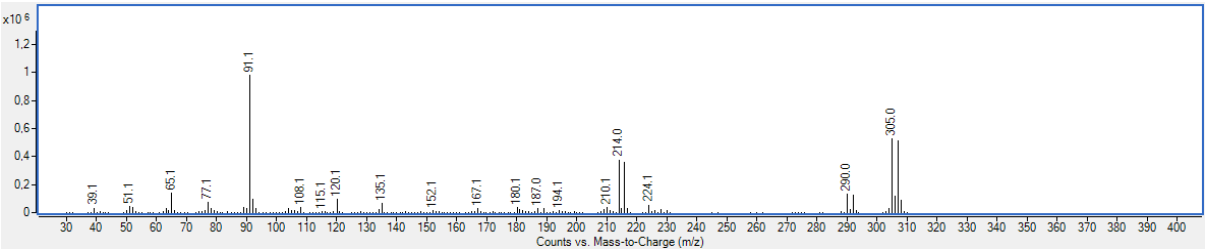


Figure 3.9: EI-MS spectrum of N-benzyl-2-bromo-4-methoxy-5-methylaniline (**19)**

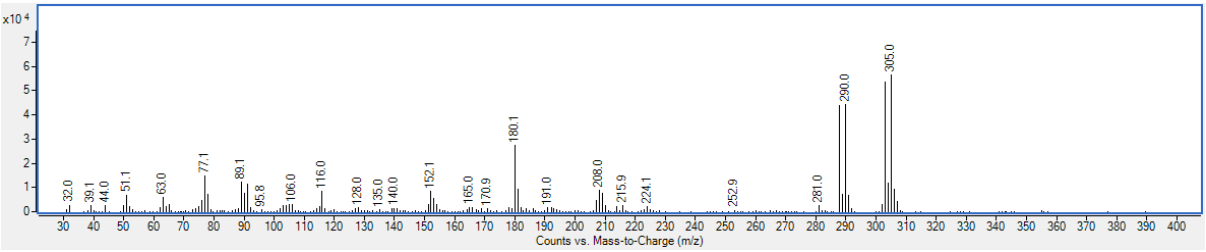
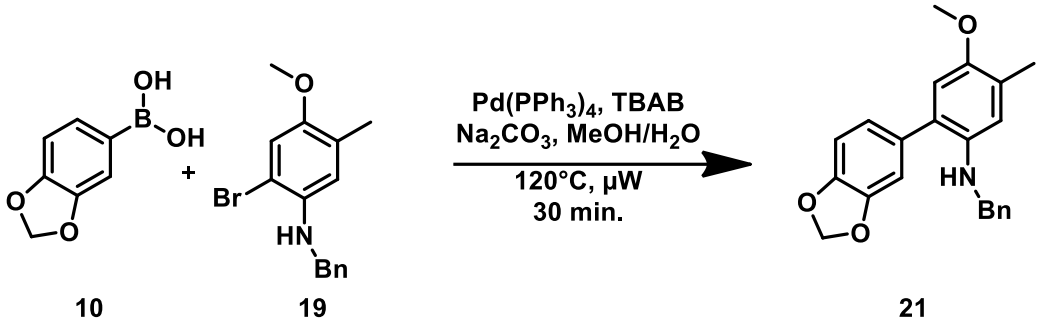


Figure 3.10: EI-MS spectrum of 2-(benzo[d][1,3]dioxol-5-yl)-N-benzylidene-4-methoxy-5-methylaniline (**20**)

3.5.2 Suzuki-Coupling - Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-*N*-benzyl-4-methoxy-5-methylaniline (21)

With the successful synthesis of **19**, the next synthetic step towards the desired carbazole derivative was the Suzuki-coupling of **19** with the boronic acid **10**. Substrate **19**, boronic acid **10**, and catalyst $Pd(PPh_3)_4$ was added to a microwave tube. Sodium carbonate and TBAB were then added, before a mixture of water and methanol. The mixture was subjected to microwave radiation at 120°C to give the biaryl **21** (**Scheme 3.19**).



Scheme 3.19: Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-*N*-benzyl-4-methoxy-5-methylaniline (**21**) from benzo[d][1,3]dioxol-5-ylboronic acid (**10)**, and *N*-benzyl-2-bromo-4-methoxy-5-methylaniline (**19**).

For the synthesis of **21**, the greatest yields were achieved for the up-scaled reaction as seen by **Entry 3** in **Table 3.8**. Lower catalyst loading did not seem to have any significant impact upon the yield of the reaction, though it can from literature minimise byproducts.[13]

Table 3.8. Overview of reagents for the synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-*N*-benzyl-4-methoxy-5-methylaniline (**21**).

Entry	Comp. 19 [mmol]	Comp. 10 [Equiv.]	Na_2CO_3 [Equiv.]	$Pd(PPh_3)_4$ [mol%]	TBAB [mol%]	Yield [%]
1	0.4	2.0	1.2	17	21	59
2	1.0	3.1	1.5	20	5	70
3	6.7	3.5	1.1	5	5	79

As may be seen from the EI-MS spectrum in **Figure 3.11** the molecular ion of compound **21** is present at an m/z of 347. The fragment at m/z 332 is from the loss of a methyl group, while the fragment at m/z 226 is likely from the loss of the A ring, that which originates from the boronic acid. The large peak at 91 m/z is again from a tropylium ion, likely from the loss of the benzyl protective group.

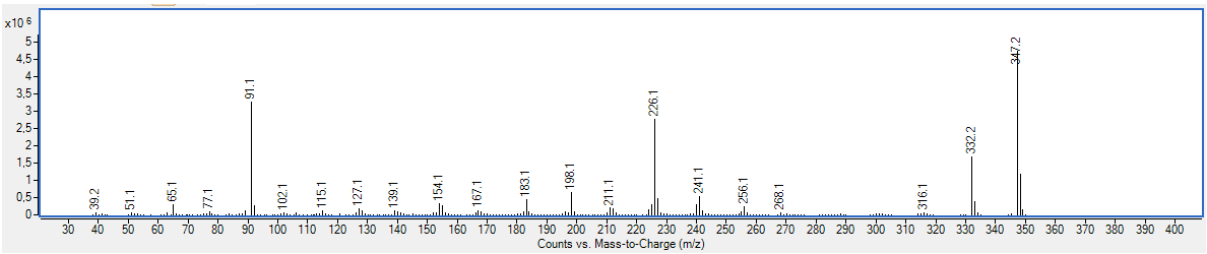
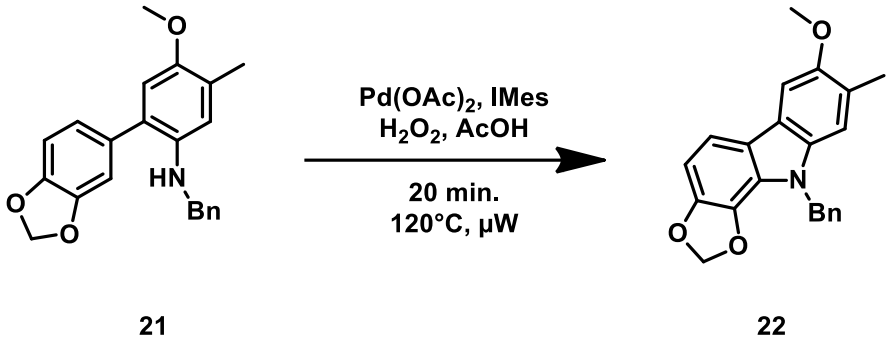


Figure 3.11: EI-MS spectrum of 2-(benzo[d][1,3]dioxol-5-yl)-N-benzyl-4-methoxy-5-methylaniline (**21**).

3.5.3 Cross-Dehydrogenative Coupling – Synthesis of 10-benzyl-7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazole (22)

The next step towards the desired carbazole derivative was a intramolecular cross-dehydrogenative coupling of compound **21** using the Bjørsvik method. A microwave tube was charged with substrate **21**, $Pd(OAc)_2$, and Imes, before glacial acetic acid and hydrogen peroxide was added. The mixture was heated to give the product **22** (**Scheme 3.20**).



Scheme 3.20: Synthesis of 10-benzyl-7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazole (**22**) from 2-(benzo[d][1,3]dioxol-5-yl)-*N*-benzyl-4-methoxy-5-methylaniline (**21**).

The yields were unfortunately in all cases low (**Table 3.9**). The greatest yield was achieved with short reaction times, and low substrate loading (**Table 3.9, Entry 1**). As the ring closure reaction had given low yields with both acetylated and benzylated amines, as well as with a free amine, it was decided that further attempts would be made with alternative methods of CDC.

Table 3.9: Overview of reagents and relevant reaction conditions for the synthesis of 10-benzyl-7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazole (**22**) from 2-(benzo[d][1,3]dioxol-5-yl)-*N*-benzyl-4-methoxy-5-methylaniline (**21**).

Entry	Comp. 21 [mmol]	H_2O_2 [Equiv.]	$Pd(OAc_2)$ [mol%]	Imes [mol%]	Reaction time	Yield [%]
1	0.2	3.0	19	9	20 min.	17
2	0.3	2.8	23	8	5 h.	4
3	1.0	3.0	20	5	20 min.	4

The molecular ion of compound **22** can be observed from the MS-EI spectrum in **Figure 3.12**, at m/z 345. The loss of a methyl fragment can be seen by the peak at 330 m/z, and the loss of a benzyl group can be seen by the peak at 254 m/z. The peak at 239 m/z is likely from the loss of both a benzyl group and a methyl group, while the peak at 91 m/z is from the tropylium ion.

The cross-dehydrogenative couplings may yield two structural isomers. The ^{1}H-NMR spectrum as seen in **Figure 3.13** shows only one of these isomers, **22b**. The corresponding structural isomer **22a** would have two vicinal hydrogens on the A ring, which would form two clear doublets. This is not seen in the ^{1}H-NMR spectrum. However, there is some contamination of an unknown compound, though it is unlikely to be **22a** as no complete set of peaks can be assigned to this structure. Analysis of the ^{13}C-spectrum shows that there are not enough carbon peaks for there to be both **22a** and **22b** present in the sample (**Appendix**). It may be that the steric hindrance introduced by the benzyl group is enough to shift the reaction towards only one of these structural isomers, **22b**.

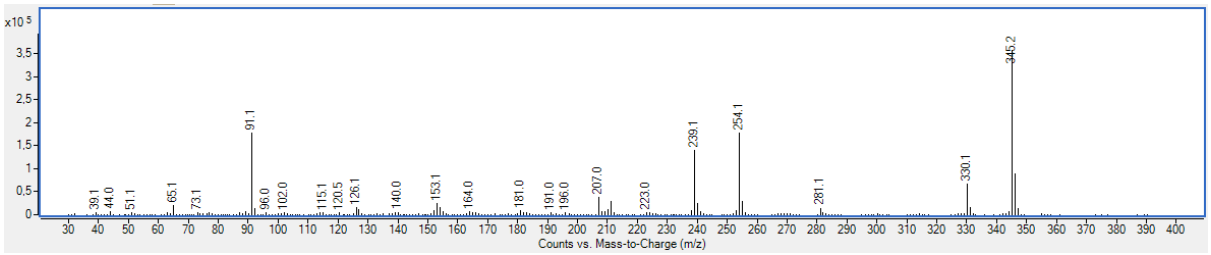


Figure 3.12: MS-EI spectrum of 10-benzyl-7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazole (**22**).

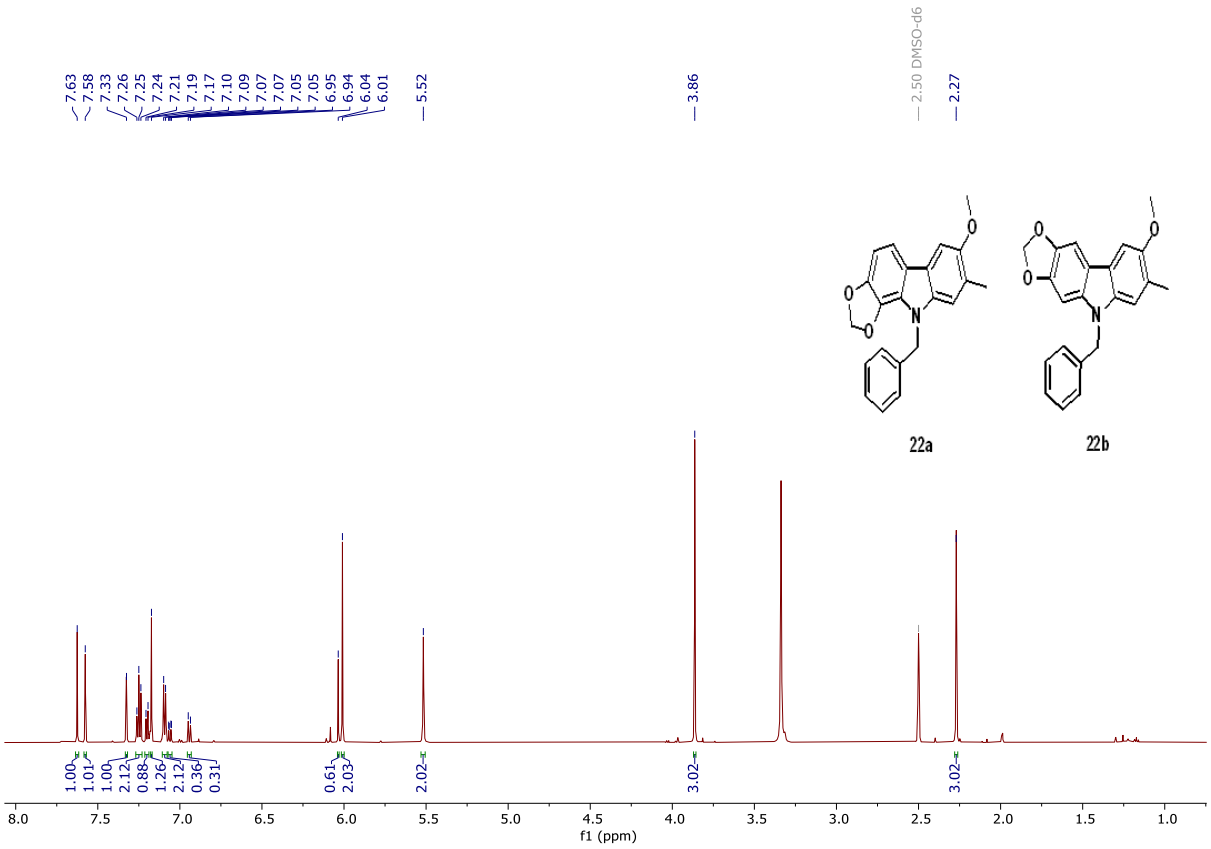
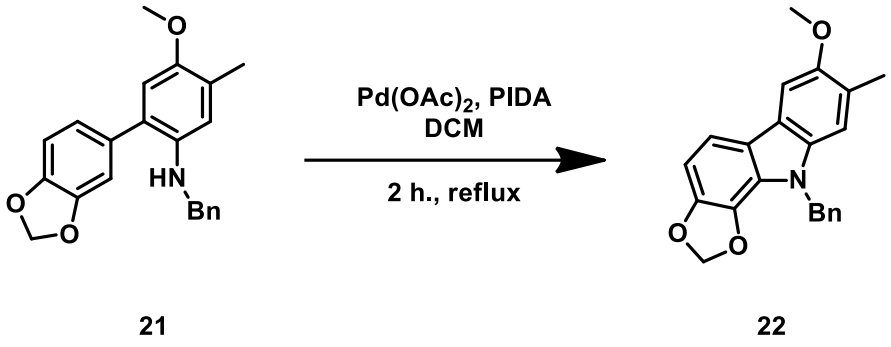


Figure 3.13: ^{1}H-NMR spectrum of 10-benzyl-7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazole (**22**).

To investigate whether other methods of cross-dehydrogenative coupling could be viable, the Gaunt method, which utilises the oxidant PIDA instead of hydrogen peroxide was attempted.[42] The method had also previously been tried with the benzyl protective group, which was considered favourable. Substrate **21** was dissolved in DCM, before $Pd(OAc)_2$ was added along with PIDA. The reaction mixture was stirred for 2 hours under reflux (**Scheme 3.21**).



21 **22**

Scheme 3.21: Synthesis of 10-benzyl-7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazole (**22**) from 2-(benzo[d][1,3]dioxol-5-yl)-*N*-benzyl-4-methoxy-5-methylaniline (**21**).

Unfortunately low to no yields were observed in all experiments (**Table 3.10**). It is difficult to identify which conditions achieved the best conversion to compound **22** from **Table 10**. Traces of compound **22** were in three experiments detected by GC-MS. The colour of the reaction mixture turns from pale yellow to dark red as the oxidant is added, as in earlier experiments with oxidative conditions. It may be that the starting material is consumed and polymerised by the oxidant, since analysis by GC-MS and LC-MS could not detect any major compound in the small-molecule range in the crude mixture.

Table 3.10: Overview of reagents and relevant reaction conditions for the synthesis of 10-benzyl-7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazole (**22**) from 2-(benzo[d][1,3]dioxol-5-yl)-*N*-benzyl-4-methoxy-5-methylaniline (**21**).

Entry	Comp. 21 [mmol]	$Pd(OAc)_2$ [mol%]	PIDA [Equiv]	Solvent	Temp. [°C]	Time	Yield [%]
1	0.3	26	1.3	DCM	40	2 h.	Traces
2*	0.3	23	1.3	DCM	60	2 h.	0
3	0.4	20	1.2	DCM	40	18 h.	0
4	0.3	7	1.1	Toluene	20	18 h.	Traces
5**	0.4	5	1.8	Toluene	20	18 h.	Traces
6	0.3	7	1.2	Toluene+ AcOH	20	18 h.	0

* μW heating.

** 0.6 equiv. of PIDA were added 1 hour before reaction was quenched.

During analysis of the experiments from Table 3.15, a curious challenge was met upon. By GC-MS monitoring of the reactions, starting material was seemingly consumed and reacted into product **22** as the reaction was progressing. This was due to the starting material reacting, and disappearing from the MS-EI spectrum. The only remaining compound of significance in the MS-EI spectrum was then the imine intermediate **20** mentioned earlier, which became more and more prominent in the spectrum as the starting material **21** was consumed. This imine intermediate is of the same molecular mass as the desired product **22**, giving the impression that desired product was actually being created in large amounts in the reaction. Analysis by NMR dispelled this false impression, as there were obvious discrepancies in the ^{1}H-NMR spectra of the imine compound (**Figure 3.15**). Note the lack of protons from the methylene bridge in the benzyl protective group, which should be about 4-5 ppm. The hydrogen from the imine bond is instead found at 8.6 ppm. Additionally, there is one more aromatic proton in the aromatic region than one would expect from compound **22** in the ^{1}H-NMR spectrum.

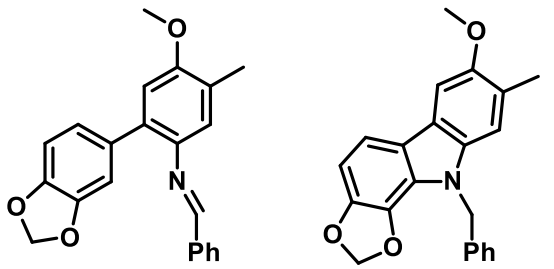


Figure 3.14: Overview of the imine intermediate **20**, and the carbazole **22** with exact masses as given.

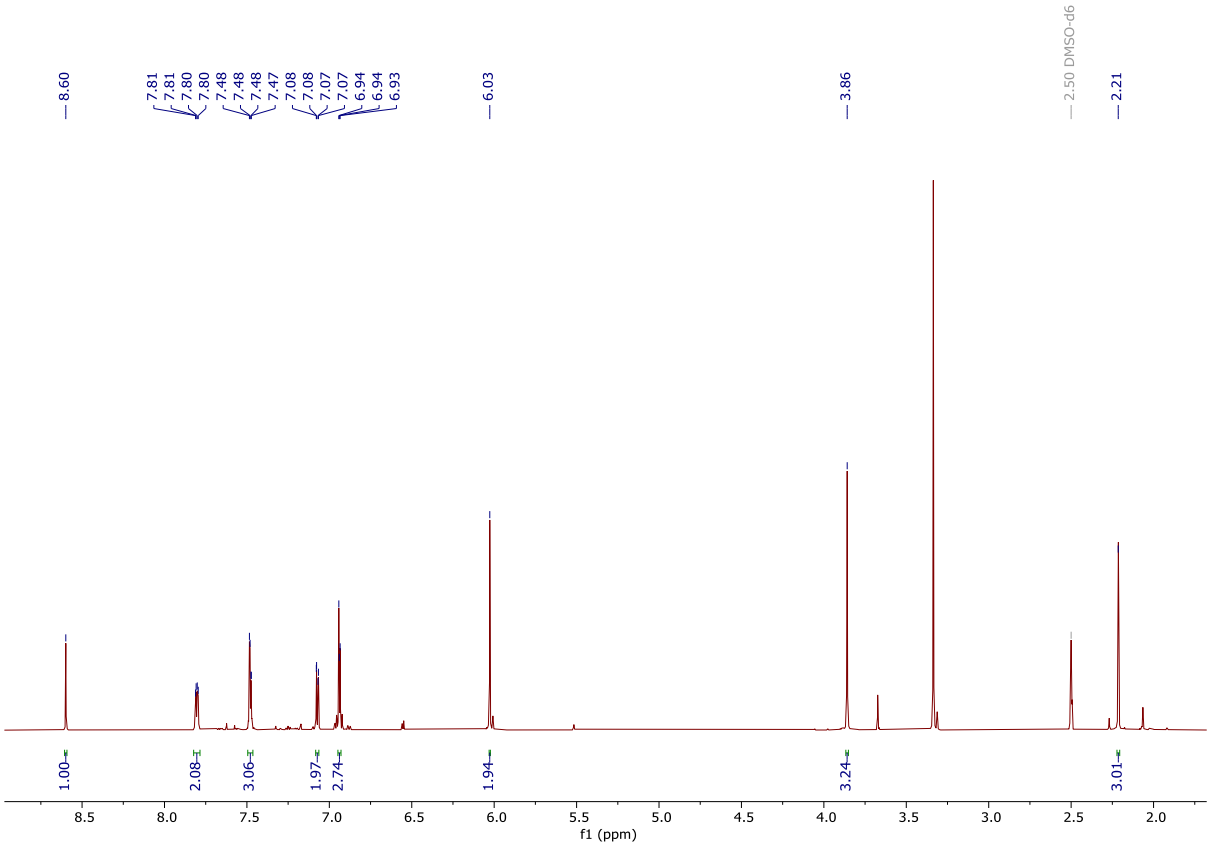
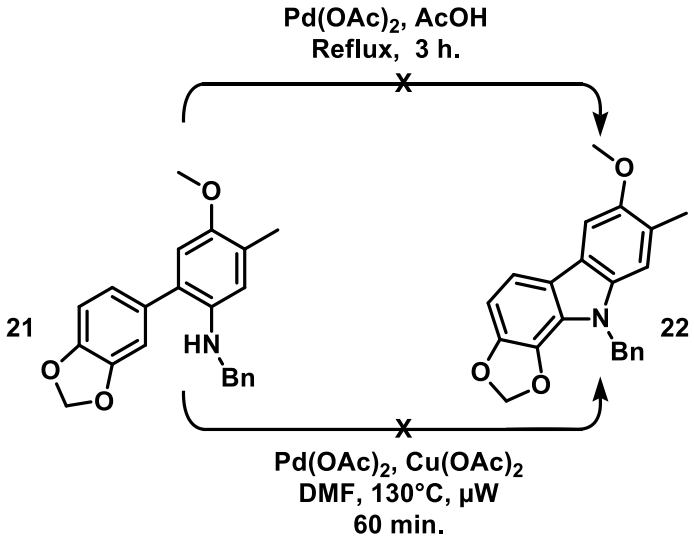


Figure 3.15: ^{1}H-NMR spectrum of the imine intermediate **20.**

As it was theorised that the substrates used so far in the synthesis of carbazoles were sensitive to oxidative conditions, two further experiments without as harsh oxidants were attempted. The first by the Sridharan method[60] utilises the mild oxidant $Cu(OAc)_2$, while the second more traditional experiment is by the Akermark method[61] and does not utilise any external oxidant, but instead stoichiometric amounts of palladium catalyst (**Scheme 3.22**).



Scheme 3.22: Synthesis of 10-benzyl-7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazole (**22**) from 2-(benzo[d][1,3]dioxol-5-yl)-*N*-benzyl-4-methoxy-5-methylaniline (**21**).

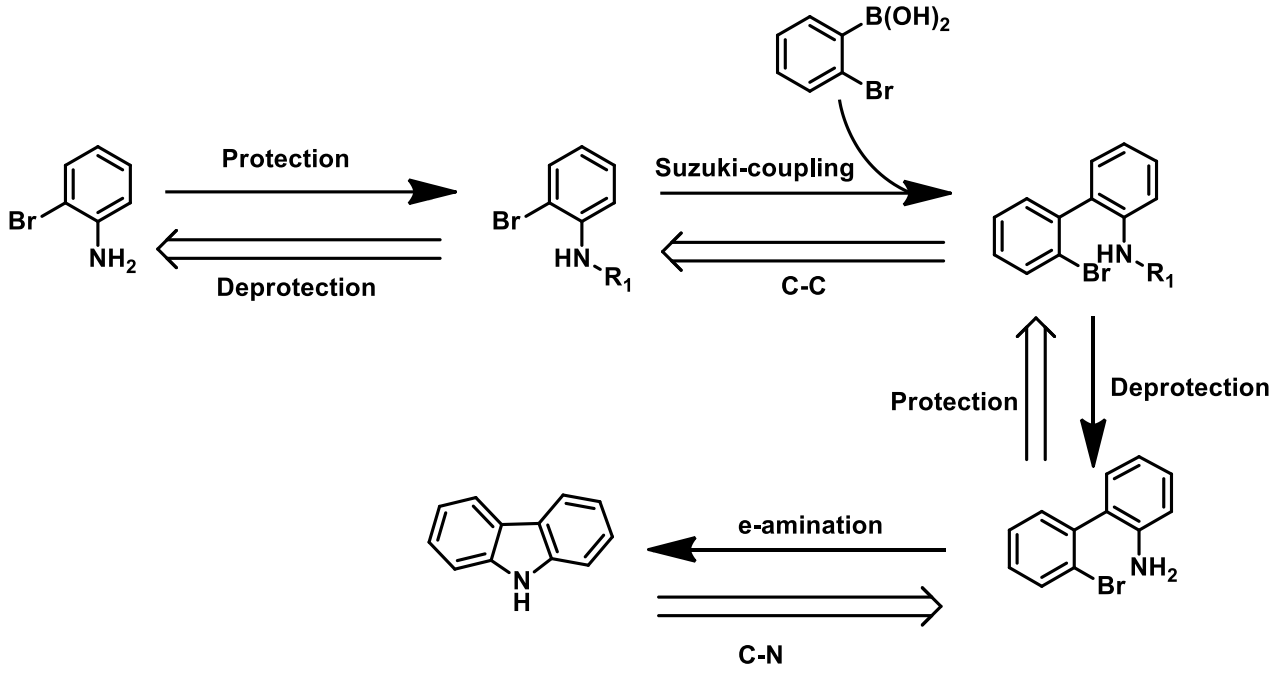
The reaction by the Sridharan method, utilizing $Cu(OAc)_2$ as oxidant did not consume any starting material. A longer reaction time may be necessary to force the reaction to proceed. The Akermark method in which **21** was refluxed in acetic acid was monitored by GC-MS as it progressed. There was some of the desired product made after 1 hour, however after 2 hours none of the desired product nor starting material could be observed. The product likely degraded due to the harsh, acidic conditions or by oxidation from air.

Several methods of ring closure had been attempted, and different protective groups for the amine had been tested as substrates for the ring closure. This had not given any robust method to ring close the substrates in adequate yield. In several of the reactions results were indicative of polymerisation through oxidation of the substrates. This led to the conclusion that to make the ring-closure reaction in good yield, a different synthetic approach would have to be taken.

3.6 Electrochemical Synthesis of 9*H*-Carbazole

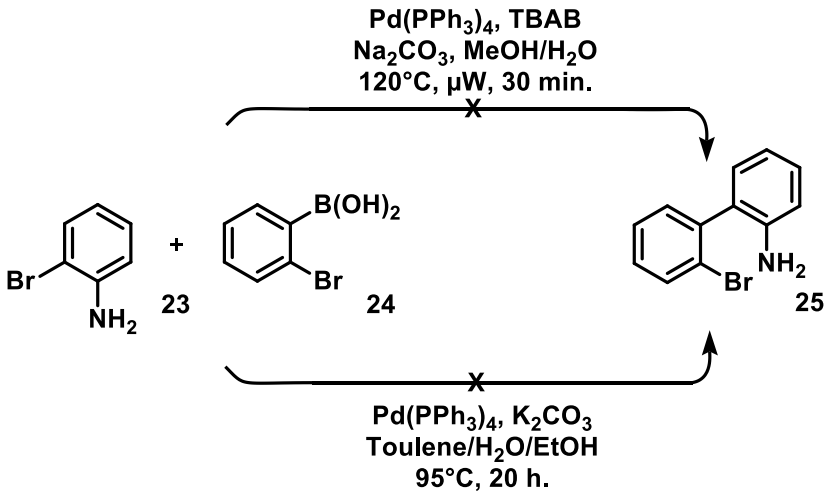
3.6.1 Direct Synthesis of 2'-bromo-[1,1'-biphenyl]-2-amine (25)

Several different approaches to cross-dehydrogenative coupling had been attempted to synthesise the catechol carbazoles in acceptable yield. Unfortunately, no attempt was to that end successful. Electrochemical synthesis was explored as an alternative to make this difficult C-N coupling. As a proof of concept the unsubstituted carbazole structure 9*H*-Carbazole (**28**) was first to be synthesised (**Scheme 3.23**).



Scheme 3.23: Retrosynthetic analysis of 9*H*-Carbazole (**29**).

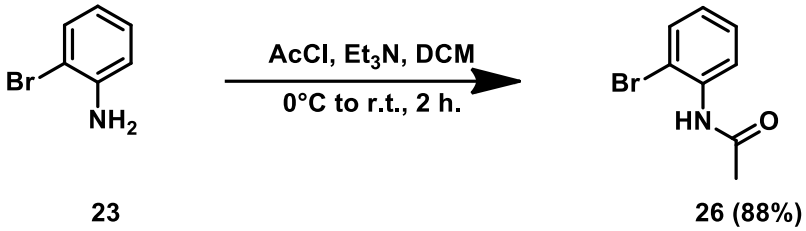
Initial attempts were made at direct a Suzuki-coupling between the unprotected 2-bromoaniline (**23**) and (2-bromophenyl)boronic acid (**24**). This reaction was attempted by two different methods, the first being the Bjørsvik method of Suzuki coupling,[13] and the second a method by Plietker[62] which had been successful with these exact substrates (**Scheme 3.24**). For both methods the crude mixture was analysed by GC-MS after heating. Several unidentified byproducts were observed, but crucially none of the desired product 2'-bromo-[1,1'-biphenyl]-2-amine (**25**). Therefore it was decided that the free amine of **23** would have to be protected before further attempts at Suzuki-coupling.



Scheme 3.24: Attempted synthesis of 2'-bromo-[1,1'-biphenyl]-2-amine (**25**) from 2-bromoaniline (**23**) and (2-bromophenyl)boronic acid (**24**). Bjørsvik method[13] of Suzuki-Coupling shown at the top, Plietker method[62] shown at the bottom.

3.6.2 Synthesis of *N*-(2-bromophenyl)acetamide (26)

To proceed with the Suzuki-coupling of 2-bromoaniline (**23**) with (2-bromophenyl)boronic acid (**24**), a protection of **23** seemed to be necessary. This was to be done by acetylation, as this had been successful in the main carbazole synthesis of the project. Compound **23** was dissolved in DCM with Et_3N, with acetyl chloride slowly added to give a white powder (**Scheme 3.25**).



Scheme 3.25: Synthesis of *N*-(2-bromophenyl)acetamide (**26**) from 2-bromoaniline (**23**)

The protected amine **26** was synthesised in good yield (88%). From the ^{1}H-NMR spectrum in **Figure 3.16**, the amine proton can be seen at 9.45 ppm, significantly deshielded due to the acetylation. Additionally, 4 aromatic protons can be seen in the aromatic region, corresponding to the 4 aromatic protons of **26**. At 2.07 ppm the methyl substituent from the acetyl-moiety can be observed.

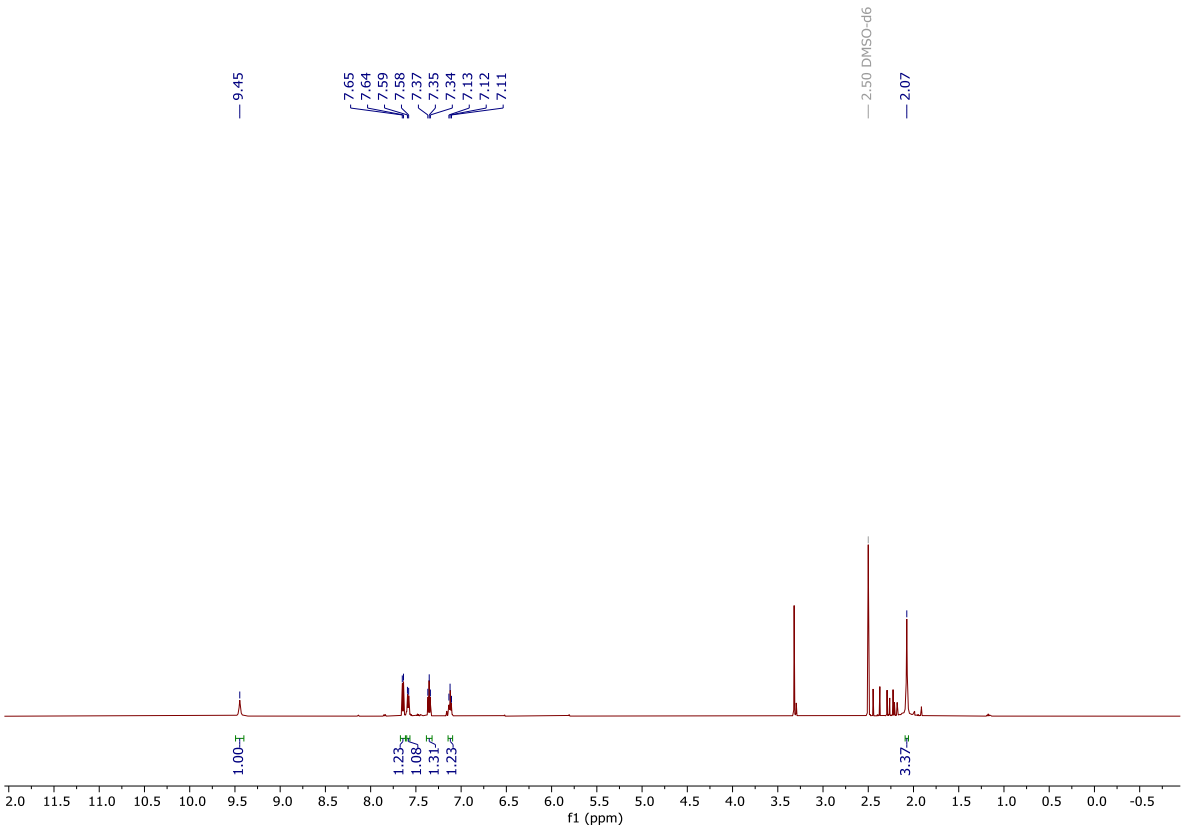
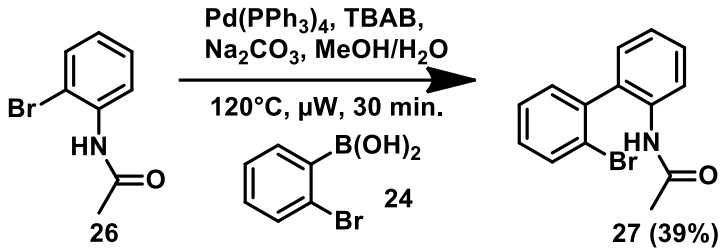


Figure 3.16: ^{1}H-NMR spectrum of compound **26**.

3.6.3 Synthesis of *N*-(2'-bromo-[1,1'-biphenyl]-2-yl)acetamide (27)

With the successful synthesis of the acetylated *N*-(2-bromophenyl)acetamide (**26**), attempts of Suzuki-coupling with the boronic acid **24** could be conducted. The Bjørsvik method of Suzuki-coupling was first attempted.[13] Compound **26** was added to a microwave tube, together with compound **24**, $Pd(PPh_3)_4$, and Na_2CO_3. Methanol and water were added, before the mixture was heated by microwave irradiation at 120°C to give a pale thick oil (**Scheme 3.26**)



Scheme 3.26: Synthesis of *N*-(2'-bromo-[1,1'-biphenyl]-2-yl)acetamide (**27**) from *N*-(2-bromophenyl)acetamide (**26**) and (2-bromophenyl)boronic acid (**24**).

Suzuki-coupling of the boronic acid **24** with the acetylated amine **26** was performed in decent yield (39%). As the boronic acid **24** is functionalised with a halogen, it may be possible for it to undergo homocoupling under Suzuki-conditions. This could lead to byproduct, and lower the purified yield of the reaction.

From the EI-MS spectrum in **Figure 3.17**, the weak molecular ion of compound **27** can be seen at an m/z of 289. This molecular ion also has a characteristic M+2 peak from the bromine isotope. The weak peak at 247 may be from loss of the acetyl moiety by a rearrangement, whereby a mass of 42 is lost from the molecular ion. The peak at 210 is from the loss of bromine from the molecular ion, while the peak at 168 is from the subsequent loss of bromine after the loss of the acetyl fragment by rearrangement.

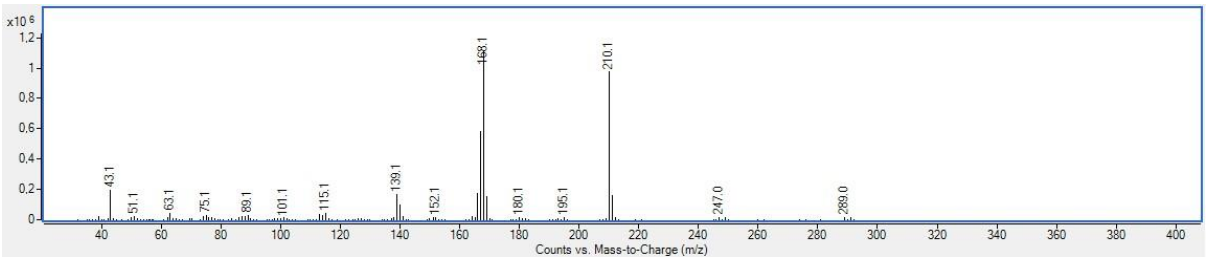
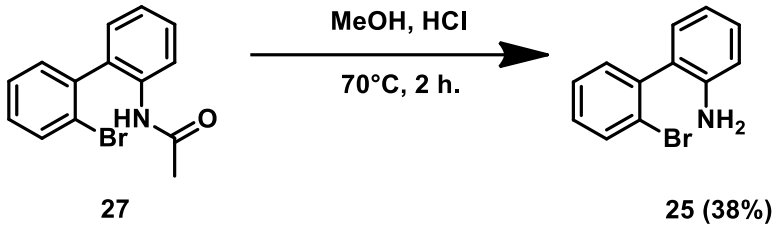


Figure 3.17: EI-MS spectrum of *N*-(2'-bromo-[1,1'-biphenyl]-2-yl)acetamide (**27**).

3.6.4 Synthesis of 2'-bromo-[1,1'-biphenyl]-2-amine (25) by Deprotection

The main challenge to be overcome in the electrochemical synthesis of 9*H*-Carbazole (**28**), is the weak nucleophilic ability of aniline relative to aliphatic amines.[47] Because of this, the acetylated amine was considered a disadvantage, due to its electronic properties. It was concluded that the acetyl protective group should be removed before the electrochemical C-N coupling could take place. Compound **27** was dissolved in methanol and HCl, before being refluxed for two hours. The final product was a pale thick oil (**Scheme 3.27**)



27 **25 (38%)**

Scheme 3.27: Synthesis of 2'-bromo-[1,1'-biphenyl]-2-amine (**25**) from *N*-(2'-bromo-[1,1'-biphenyl]-2-yl)acetamide (**27**).

The deprotection of **27** was made in decent yield (38%). The molecular ion of compound **25** can be seen from the EI-MS spectrum at an m/z of 247 (**Figure 3.18**). The characteristic isotopic M+2 peak can also be observed from the spectrum. The dominant fragment can be seen at 168 m/z from the loss of bromine.

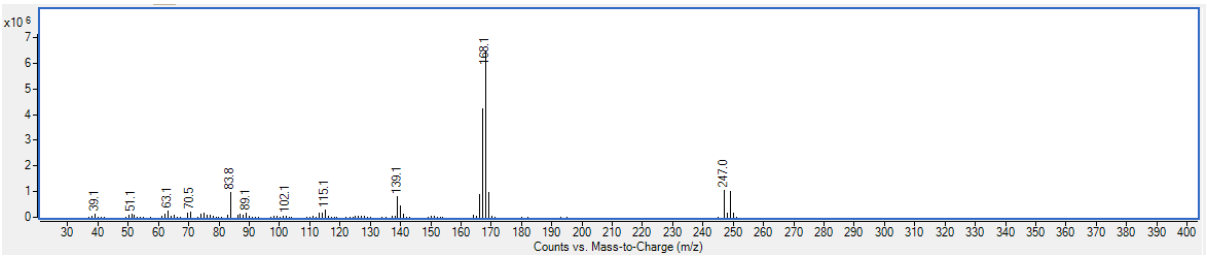
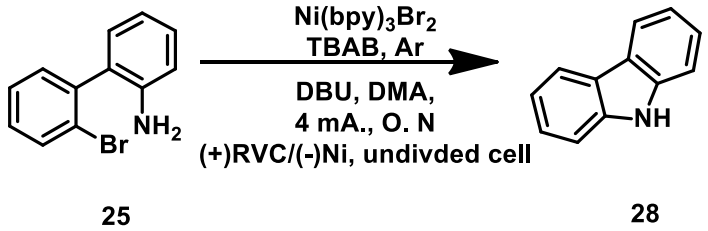


Figure 3.18: EI-MS spectrum of 2'-bromo-[1,1'-biphenyl]-2-amine (**25**)

3.6.5 Synthesis of 9*H*-Carbazole (28)

Attention could now be turned towards the electrochemical synthesis of 9H-Carbazole (**28**) as the necessary substrate 2'-bromo-[1,1'-biphenyl]-2-amine (**25**) was successfully synthesised. This reaction was as previously mentioned not considered possible by literature, as the aromatic amine is too deactivated to function as an effective nucleophile in the reaction.[47] However, the reaction had not been attempted intramolecularly, only in intermolecular reactions. Thus, there was a possibility that the reaction would be thermodynamically favoured, even though an intramolecular reaction would also introduce a steric effect that could be detrimental. The reaction was performed by mixing **25** in a vessel, with TBAB, DBU, DMA and the nickel catalyst $Ni(bpy)_3Br_2$. The vessel was evacuated and flushed with argon. The mixture was then subjected to a current of 4 mA to give a dark thick oil (**Scheme 3.28**).[63] Note that the synthetic procedure used a nickel foam electrode and a standard RVC electrode, while we used a RVC foam electrode and a standard nickel electrode.



Scheme 3.28: Electrochemical synthesis of 9*H*-Carbazole (**29**) from 2'-bromo-[1,1'-biphenyl]-2-amine (**28**).

The synthesis was first attempted with a reaction time of 4 hours, but did not yield any of the desired compound **28** (**Table 3.11, Entry 1**). GC-MS analysis indicated that the products formed were a combination of debrominated structures, as well as some undesired homocoupled structures. Another attempt was done with the reaction allowed to run over night, as well as with an increase in DBU. This was done as it was suggested in literature to increase the nucleophilicity of the amine in the reaction.[47] This provided compound **28** in 4% yield.

Table 3.11: Overview of reagents and relevant reaction conditions for the synthesis of 9*H*-Carbazole (**28**) from 2'-bromo-[1,1'-biphenyl]-2-amine (**25**).

Entry	Comp. 25 [mmol]	$Ni(bpy)_3Br_2$ [mol%]	TBAB [M]	DBU [Equiv.]	Reaction time	Yield [%]
1	0.2	10	0.2	3	4 h.	0
2	0.2	10	0.2	5	18 h.	4

From the ^{1}H-NMR spectrum of **28**, 8 aromatic protons from 4 distinct peaks can be observed (**Figure 3.19**). These likely correspond to the aromatic protons of the carbazole structure, which due to an axis of symmetry will appear as only 4 peaks. Furthermore, a significantly deshielded proton may be observed at a ppm of 11.23, likely originating from the amine. Some small impurities can be seen at and around 1 ppm.

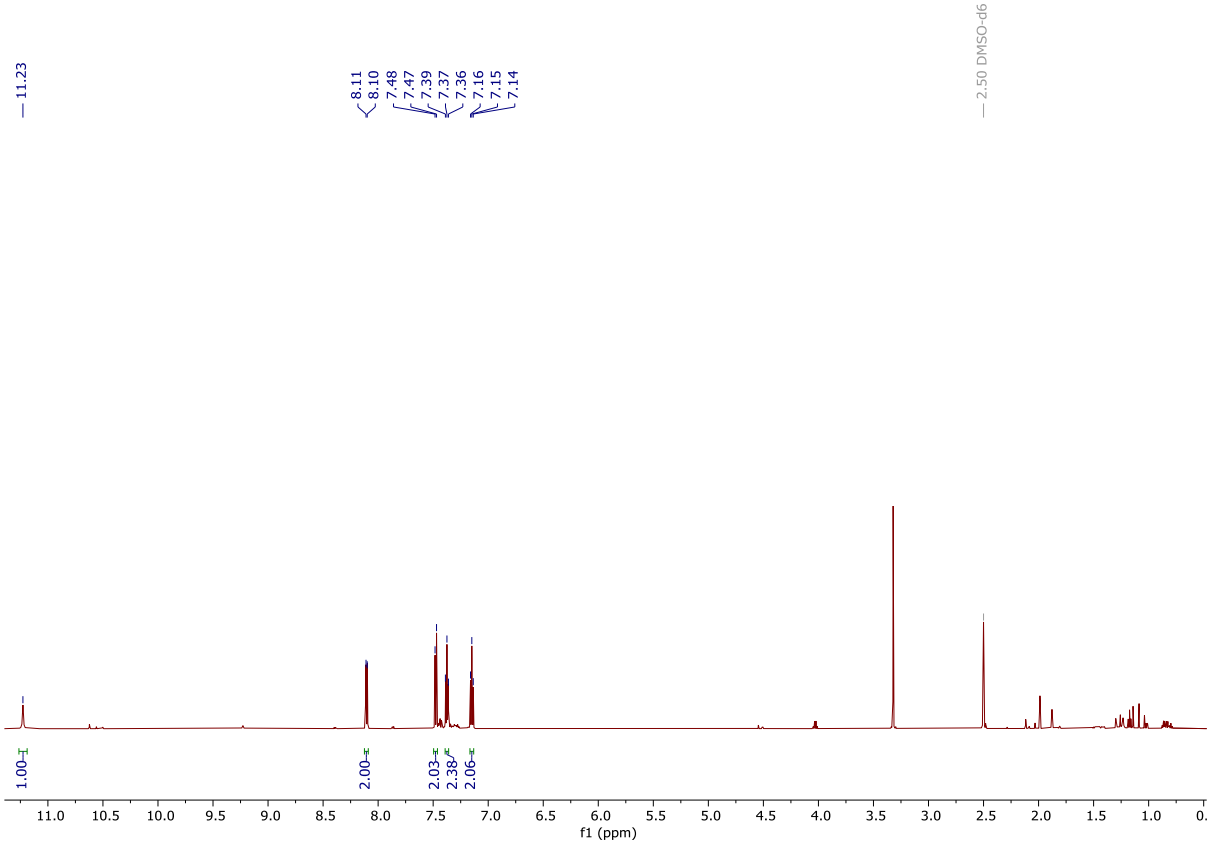


Figure 3.19: ^{1}H-NMR spectrum of 9*H*-Carbazole (**28)**

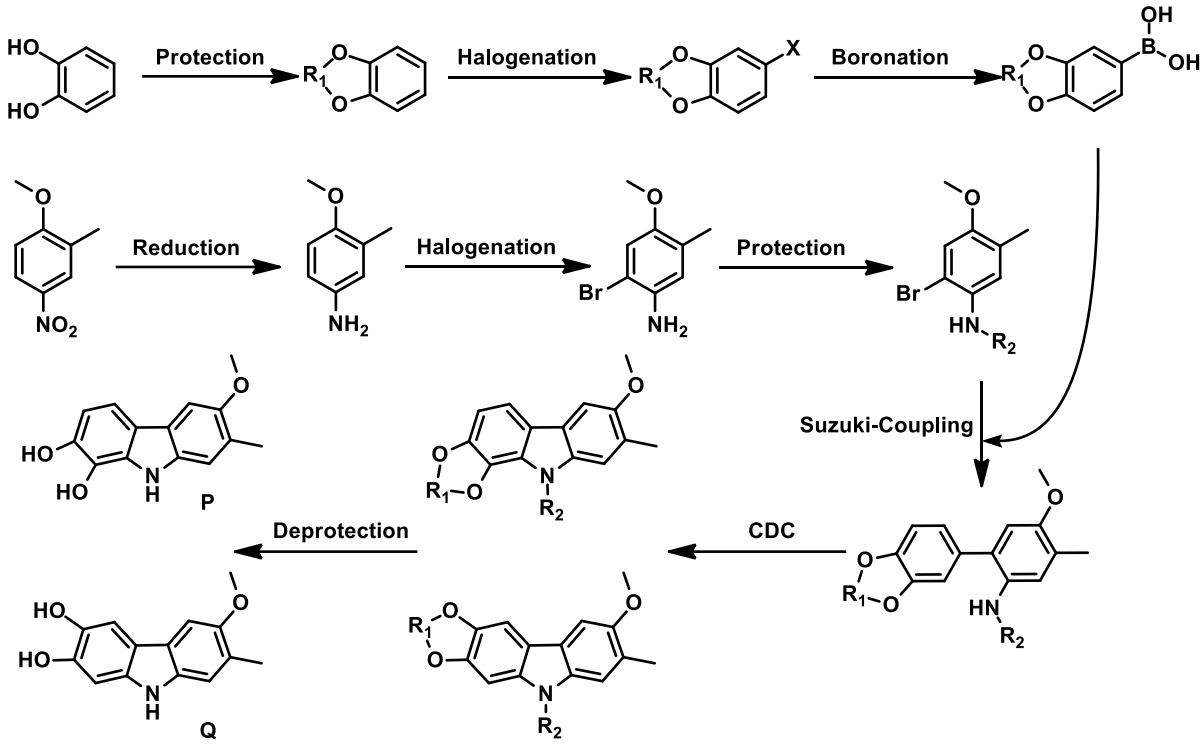
There was unfortunately no time to explore the electrochemical synthesis further in this project. Optimalisation of reaction conditions and applied currency could maybe improve the yield of **28**. To aid in this endeavour cyclic voltammetry (CV) should be attempted so as to determine the standard potential of the ring-closure reaction.[46] This would help in fine-tuning the applied currency so as to limit overpotential and production of byproducts. It would also be interesting to attempt the electrochemical ring closure with the substrates used for making the catechol carbazole derivatives. These substrates are in general more electron-rich due to several methoxy substituents, which could hopefully help in making the ring closure more favourable.

4 Summary and Further Work

Throughout this project the primary task had been to synthesise a carbazole derivative with a free catechol moiety. This has succeeded only in part, with the protected carbazoles **15, 16** and **22** synthesised, albeit in low yield. The issue with low yield was prevalent across all methods of cross-dehydrogenative coupling (CDC), and comparably low with different amine protective groups. This suggests that it may be the oxygenated A ring, that which should undergo C-H activation that is interfering with the CDC reaction. Somewhat low yield (30%) was also obtained for a similar substrate in an earlier work in the Bjørsvik group, in which the A ring was functionalised with one methoxy group.[12] To avoid this issue one should consider prefunctionalisation of the A ring with a halogen, which would allow for several other more traditional methods of C-N coupling to be performed, some of which may be more tolerant of the methoxylation of the A ring. Other possible strategies would involve using an auxiliary group for the oxygens on the A ring, in order to reduce their electron-donation to the aromatic ring.

Halogenation of the A ring would also allow for attempts at cross-coupling with electrochemistry. Proof of concept was established in this project that intramolecular cross-coupling with formation of a C-N bond is possible even with an aniline as nucleophile, which was not thought possible using this method since aniline is a relatively weak nucleophile.[47] However, we theorised that as our reaction would be intramolecular in nature, it would be possible nonetheless. Low yields were achieved (4%) for this synthesis, and optimisation would likely be necessary if this method is to be of further use. One strategy would be to employ cyclic voltammetry (CV) to analyse the reaction, so as to establish the standard potential of the redox reaction. This would allow for fine tuning of applied currency which can reduce overpotential and limit production of byproducts.[46]

Besides this some preliminary work has been done to see if the necessary boronic acids for this project could be directly modified without protecting the boronic acid. This work clearly showed that protection of the boronic acids used here was necessary for any further modification. The most robust synthetic pathway to such protected boronic acids would be to simply produce the boronic acids from catechol itself. Thus, the vicinal hydroxy groups could be protected by a more appropriate protective- or auxiliary group. The catechol moiety could be protected by cyclic ester formation, which would also help in deactivating their electron-donation to the aromatic ring. A suggested total synthesis is given by **Scheme 4.1.**



Scheme 4.1: Suggested total synthesis for catechol carbazole derivatives **P and Q** with complete synthesis of the necessary boronic acids, with appropriate protection for vicinal diols. R_1 and R_2 indicate protective/auxiliary groups.

The SAR-analysis has not been updated as the free catechol carbazoles could not be synthesised in time. Therefore, no toxicological testing has been performed upon the structures synthesised in this project.

5 Experimental

Chemicals

All reagents and solvents were obtained commercially and used as they were, except for acetyl chloride which was distilled before use due to age.

General methods

TLC analysis was performed with silica gel on TLC al foil, and observed by UV light under wavelengths 254 nm and 366 nm.

Purification by manual flash chromatography was done with a column packed with silica gel (Pore size 60 Å. Mesh particle size 230-400. Particle size 40-63 μm), with solvent systems as indicated in procedures.

NMR analysis was performed with a Bruker BioSpin AVANCE NEO 600 MHz instrument, and a Bruker BioSpin AVANCE III HD 850 MHz. Chemical shift is reported as parts per million (ppm) relative to residual protons in deuterated solvent for DMSO-d6 (δ_H 2.50 ppm and δ_C 39.52) and $CDCl_3$ (δ_H 7.26 ppm and δ_C 77.16). All coupling constants are given in Hz.

GC-MS analysis was performed with the MS module Agilent 5977A MSD using EI with a single quadrupole mass analyser. The MS module was connected to the GC module Agilent 7890A GC system, with a fused silica column and helium as carrier gas.

LC-MS analysis was performed with an Agilent 6420A triple quadrupole mass analyser, using ESI as ionisation mode. The MS module was connected to the Agilent 1200 series LC module, with the column Agilent ZORBAX SB-C18 (RRHT; 2.1 x, 50 mm, 1.8 μm).

Procedures

4-Methoxy-3-methylaniline (2).

1-Methoxy-2-methyl-4-nitrobenzene (**1**) (0.836g, 5.0 mmol) was dissolved in ethanol (50 mL), and added to a round bottom flask. $CoSO_4 \cdot 7H_2O$ (1.406g, 5.0 mmol) was dissolved in water (7mL), and added to the round bottom flask. The vessel was cooled in an ice bath, and $NaBH_4$ (1.135g, 30 mmol) was slowly added. The reaction was stirred for 10 minutes, before being carefully quenched with water. The mixture was washed with DCM (100 mL), before the organic solvent layer was washed with sat. solution of EDTA (100 mL), and brine (100 mL). The organic phase was dried with $MgSO_4$, filtrated and concentrated to afford **2** as a red solid. (0.617g, 4.5 mmol, 90%). ^{1}H-NMR (600 MHz, DMSO): δ 6.61 (d, J=8.58 Hz, 1H), 6.39 (d, J=3.54 Hz, 1H), 6.35 (dd, J=2.88 Hz, 8.46 Hz, 1H), 4.48 (s, 2H), 3.63 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (600 MHz, DMSO): δ 148.8, 141.9, 125.8, 116.9, 111.7, 111.6, 55.6, 16.0. MS (EI) m/z [M^+] calcd. for $C_8H_{11}NO$ 137.08; Found 137.1

2-Bromo-4-methoxy-5-methylaniline (3).

4-Methoxy-3-methylaniline (**2**) (2.771g, 20.2 mmol) was added to a round bottom flask, and subsequently dissolved in DCM (80 mL). The flask was capped with a septum, and placed under a N_2 atmosphere and in an ice bath. Bromine (1.2 mL, 23.4 mmol) was added slowly by syringe through the septum. The reaction was stirred in the ice bath for 1 hour. The crude mixture was diluted with ethyl acetate (100 mL), and washed with sat. $Na_2S_2O_3$ (100 mL), sat. $NaHCO_3$ (100 mL) and sat. brine (100 mL). The organic phase was dried with $MgSO_4$, filtrated and concentrated. The isolated product was dry loaded onto a column, and by flash chromatography (EtOAc/Hexane 10:90) purified to afford **3** as a dark red solid (2.370g, 11.0 mmol, 54%). R_f=0.30 (EtOAc/Hexane 10:90). ^{1}H-NMR (600 MHz, DMSO): δ 6.89 (s, 1H), 6.63 (s, 1H), 4.71 (s, 2H), 3.66 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (600 MHz, DMSO): δ 149.2, 139.1, 126.1, 117.7, 114.2, 104.0, 55.8, 15.7 MS (EI) m/z [M^+] calcd. for $C_8H_{11}BrNO$ 214.99; Found 215.0

***N*-(2-bromo-4-methoxy-5-methylphenyl)acetamide (12).**

2-Bromo-4-methoxy-5-methylaniline (**3**) (1.070g, 4.95 mmol) was added to a round bottom flask, and dissolved in DCM (20 mL). Et_3N (0.83 mL, 6.0 mmol) was added, and the round bottom flask was submerged in an ice bath. AcCl (0.41 mL, 6.01 mmol) was slowly added to the reaction mixture, and the mixture was raised from the ice bath, and stirred at room temperature for 1 hour. The reaction mixed was diluted with DCM (100 mL), and washed with water (100 mL), sat. $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried with $MgSO_4$, filtrated and concentrated to afford **12** as a dark red solid (1.236g, 4.79 mmol, 97%). MS (EI) m/z [M^+] calcd. for $C_8H_{11}BrNO$ 257.01; Found 257.0

***N*-(2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylphenyl)acetamide (13).**

A microwave reaction vessel was charged with benzo[d][1,3]dioxol-5-ylboronic acid (**10**) (0.762g, 4.6 mmol), *N*-(2-bromo-4-methoxy-5-methylphenyl)acetamide (**12**) (1.0 g, 3.8 mmol), $Pd(PPh_3)_4$ (0.022g, 0.019 mmol), TBAB (0.015g, 0.047 mmol) and Na_2CO_3 (0.510g, 4.8 mmol). EtOH (8 mL) and water (2 mL) were added to the vessel, before it was capped and flushed with nitrogen. The reaction was submerged in a microwave reactor for 30 minutes at 120°C. The crude mixture was diluted with water (100 mL) and washed with ethyl acetate (3x 100 mL). The organic phases were combined, dried with $MgSO_4$, filtrated and concentrated. Crude product was dry loaded onto a silica gel column, and by flash chromatography (EtOAc/Hexane 10:90) purified, to afford **13** as a dark red oil (1.263g, 4.2 mmol, >100%). R_f=0,10 (EtOAc/Hexane 10:90). MS (EI) m/z [M^+] calcd. for $C_{17}H_{17}NO_4$ 299.1; Found 299.2

***N*-(3',4',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl)acetamide (14).**

A microwave reaction vessel was charged with (3,4-dimethoxyphenyl)boronic acid (**7**) (0.365g, 2.0 mmol), N-(2-bromo-4-methoxy-5-methylphenyl)acetamide (**12**) (0.342g, 1.3 mmol), $Pd(PPh_3)_4$ (0.046g, 0.04 mmol), TBAB (0.047g, 0.15 mmol) and Na_2CO_3 (0.301g, 2.84 mmol). EtOH (8 mL) and water (2 mL) were added to the vessel, before it was capped and flushed with nitrogen. The reaction was submerged in a microwave reactor for 30 minutes at 120°C. The crude mixture was diluted with water (100 mL) and washed with ethyl acetate (3x 100 mL). The organic phases were combined, dried with $MgSO_4$, filtrated and concentrated. The crude was dry loaded onto a silica gel column, and by flash chromatography (MeOH/DCM 5:95) purified, to afford **14** as a dark red oil (0.485g, 1.54 mmol, >100%). R_f=0,30 (MeOH/DCM 5:95). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.78 (s, 1H), 6.99 (d, J=8.1 Hz, 1H), 6.94 (d, J=8.2 Hz, 1H), 6.69 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 2.24 (s, 3H), 1.99 (s, 3H). ^{13}C-NMR (600 MHz, $CDCl_3$): δ 168.5, 154.8, 149.1, 148.6, 148.5, 132.1, 131.2, 127.1, 126.5, 125.8, 121.3, 112.4, 111.5, 111.4, 110.7, 56.0, 55.8, 55.6, 24.2, 16.1. MS (EI) m/z [M^+] calcd. for $C_{18}H_{21}NO_4$ 315.2; Found 315.2

1-(1,2,6-Trimethoxy-7-methyl-9H-carbazol-9-yl)ethenone (15).

A microwave reaction vessel was charged with *N*-(3',4',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl)acetamide (**14**) (0.167g, 0.53 mmol). Imes (0.036g, 0.12 mmol), $Pd(OAc)_2$ (0.025g, 0.11 mmol) and AcOH (2 mL) were also added to the reaction mixture, before the vessel was sealed. The vessel was flushed with N_2, before H_2O_2 (35%) (0.2 mL, 2.3 mmol) was added by syringe. The reaction vessel was submerged in a microwave reactor for 20 minutes at 120°C. The crude mixture was diluted with EtOAc (100 mL), and washed with water (100 mL), sat. $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated. The crude product was dry loaded onto a silica gel column, and by flash chromatography (MeOH/DCM 3:97) purified, to afford **15** as a dark red oil (0.007g, 0.022 mmol, 4%). R_f=0,72 (MeOH/DCM) 3:97). MS (EI) m/z [M^+] calcd. for $C_{18}H_{19}NO_4$ 313.1; Found 313.2.

2-(Benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylaniline (17).

N-(2-(benzo[d][1,3]dioxol-5-yl)-4-methoxy-5-methylphenyl)acetamide (**13**) (0.082g, 0.27 mmol) was added to a round bottom flask. Methanol (15 mL) was added to the flask, before it was submerged in an ice bath. HCl (2 mL) was slowly added to the reaction mixture, before the flask was raised from the ice bath, and heated to 70°C overnight. The crude mixture was washed with water (100 mL), sat. $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried with $MgSO_4$, filtrated and concentrated to afford **17** as a dark red oil (0.052g, 0.20 mmol, 74%). MS (EI) m/z [M^+] calcd. for $C_{15}H_{15}NO_3$ 257.1; Found 257.1

***N*-benzyl-2-bromo-4-methoxy-5-methylaniline (19)**

A round bottom flask was charged with 2-bromo-4-methoxy-5-methylaniline (**3**) (0.320g, 1.48 mmol), ArCHO (0.15 mL, 1.5 mmol) and MeOH (15 mL). The reaction vessel was capped with a septum, flushed with nitrogen, and subsequently stirred for 3 hours at room temperature. Then the septum was removed and $NaBH_4$ (0.093g, 2.5 mmol) was carefully added. The crude mixture was diluted with ethyl acetate (100 mL) and washed with water (100 mL), sat. $NaHCO_3$ (100 mL) and brine (100 mL), before being dried with $MgSO_4$, filtrated and concentrated to afford **19** as a red solid (0.442g, 1.44 mmol, 97%). ^{1}H-NMR (600 MHz, DMSO): δ 7.32 (m, 4H), 7.21 (t, J=8.64 Hz, 1H), 7.00 (s, 1H), 6.46 (s, 1H), 5.26 (t, J=6.24 Hz, 1H), 4.34 (d, J=6.24 Hz, 2H), 3.66 (s, 3H), 1.97 (s, 3H). ^{13}C-NMR (600 MHz, DMSO): δ 149.0, 140.1, 138.9, 128.3, 126.9, 126.6, 115.1, 114.3, 105.2, 55.9, 46.9, 16.1. MS (EI) m/z [M^+] calcd. for $C_{15}H_{16}BrNO$ 305.0; Found 305.1

2-(Benzo[d][1,3]dioxol-5-yl)-*N*-benzyl-4-methoxy-5-methylaniline (21)

A microwave reaction vessel was charged with benzo[d][1,3]dioxol-5-ylboronic acid (**10**) (3.92g, 23.6 mmol), *N*-benzyl-2-bromo-4-methoxy-5-methylaniline (**19**) (2.05 g, 6.7 mmol), $Pd(PPh_3)_4$ (0.397g, 0.343 mmol), TBAB (0.114g, 0.353 mmol) and Na_2CO_3 (0.783g, 7.4 mmol). EtOH (16 mL) and water (4 mL) were added to the vessel, before it was capped and flushed with nitrogen. The reaction was submerged in a microwave reactor for 30 minutes at 120°C. The crude mixture was diluted with ethyl acetate (100 mL), and washed with water (100 mL), sat. $NaHCO_3$ (100 mL), and brine (100 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated. The crude product was dry load onto a silica column, and by flash chromatography (EtOAc/Hexane 10:90) purified to afford **21** as a yellow oil (1.847g, 5.32 mmol, 79%). R_f=0.4 (EtOAc/Hexane 10:90). MS (EI) m/z [M^+] calcd. for $C_{22}H_{21}NO_3$ 347.2; Found 347.2

10-Benzyl-7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazole (22b)

A microwave reaction vessel was charged with 10-benzyl-7-methoxy-8-methyl-10H-[1,3]dioxolo[4,5-a]carbazole (**21**) (0.079g, 0.23 mmol). Imes (0.006g, 0.02 mmol), $Pd(OAc)_2$ (0.010g, 0.04 mmol) and AcOH (2 mL) were also added to the reaction mixture, before the vessel was sealed. The vessel was flushed with N_2, before H_2O_2 (35%) (0.06 mL, 0.69 mmol) was added by syringe. The reaction vessel was submerged in a microwave reactor for 20 minutes at 120°C. The crude mixture was diluted with EtOAc (100 mL), and washed with water (100 mL), sat. $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated. The isolated product was dry loaded onto a silica gel column, and by flash chromatography (EtOAc/Hexane 10:90) purified, to afford structural isomer **22b** as pale yellow oil (0.013g, 0.04 mmol, 17%). R_f=0.31 (EtOAc/Hexane 10:90). ^{1}H-NMR (600 MHz, DMSO): δ 7.63 (s, 1H), 7.58 (s, 1H), 7.33 (s, 1H), 7.25 (t, J=7.08, 2H), 7.20 (d, J=7.44, 1H), 7.17 (s, 1H), 7.10 (d, J=6.9, 2H), 6.01 (s, 2H), 5.52 (s, 2H), 3.86 (s, 3H), 2.27 (s, 3H). ^{13}C-NMR (600 MHz, DMSO): δ 151.7, 147.8, 141.4, 138.1, 135.8, 134.6, 128.5, 127.1, 126.6, 123.4, 120.8, 115.5, 110.9, 100.7, 100.6, 99.3, 91.2, 55.6, 45.6, 17.2 MS (EI) m/z [M^+] calcd. for $C_{22}H_{19}NO_3$ 345.1; Found 345.1

***N*-(2-bromophenyl)acetamide (26)**

2-Bromoaniline (**23**) (2.534g, 14.73 mmol) was added to a round bottom flask, and subsequently dissolved in DCM (50 mL). Et_3N (2.46 mL, 17.6 mmol) was added to the round bottom flask, before AcCl (1.26 mL, 17.6 mmol) was slowly added by syringe while the reaction mixture was cooled in an ice bath. The reaction mixture was raised from the ice bath, and stirred for 2 hours at room temperature. The crude was diluted with EtOAc (100 mL), and washed with water (100 mL), sat. $NaHCO_3$ (100 mL), and brine (100 mL). The organic phase was dried with $MgSO_4$, filtrated and concentrated. The crude product was dry loaded onto a silica column and by flash chromatography (EtOAc/Hexane 30/70 + 1%TEA) purified to afford **26** as a white powder (2.774g, 12.96 mmol, 88%). R_f=0.25 (EtOAc/Hexane 30/70 + 1%TEA). ^{1}H-NMR (600 MHz, DMSO): δ 9.45 (s, 1H), 7.65 (d, J=7.98, 1H), 7.59 (d, J=7.92, 1H), 7.35 (t, J=9.18, 1H), 7.12 (t, J=7.62, 1H), 2.07 (s, 3H). MS (EI) m/z [M^+] calcd. for C_8H_8BrNO 213.0; Found 213.0

***N*-(2'-bromo-[1,1'-biphenyl]-2-yl)acetamide (27)**

A microwave reaction vessel was charged with (2-bromophenyl)boronic acid (**24**) (3.906g, 19.4 mmol), *N*-(2-bromophenyl)acetamide (**26**) (2.773 g, 12.96 mmol), $Pd(PPh_3)_4$ (0.368g, 0.32 mmol), TBAB (0.314g, 0.97 mmol) and Na_2CO_3 (1.669g, 15.8 mmol). EtOH (16 mL) and water (4 mL) were added to the vessel, before it was capped and flushed with nitrogen. The reaction was submerged in a microwave reactor for 30 minutes at 120°C. The crude mixture was diluted with ethyl acetate (100 mL), and washed with water (100 mL), sat. $NaHCO_3$ (100 mL), and brine (100 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated. The isolated product was dry load onto a silica column, and by flash chromatography (EtOAc/Hexane 30:70 + 1% TEA) purified to afford **27** as a thick white oil (1.448g, 4.99 mmol, 39%). R_f=0.38 (EtOAc/Hexane 30:70 + 1% TEA). ^{1}H-NMR (600 MHz, DMSO): δ 8.94 (s, 1H), 7.71 (d, J=8.8 Hz, 1H), 7.60 (d, J=8.8 Hz, 1H), 7.44 (t, J=8.1 Hz, 2H), 7.31 (t, J=8.8 Hz, 2H), 7.27 (d, J=8.2, 1H), 7.23 (t, J=8.1 Hz, 1H), 1.99 (s, 3H). ^{13}C-NMR (600 MHz, DMSO): δ 170.3, 168.3, 139.3, 132.5, 131.8, 130.4, 129.3, 128.3 128.1, 127.5, 125.5, 124.6, 123.0, 20.7. MS (EI) m/z [M^+] calcd. for $C_{14}H_{12}BrNO$ 289.0; Found 289.0

2'-bromo-[1,1'-biphenyl]-2-amine (25)

A round bottom flask was charged with *N*-(2'-bromo-[1,1'-biphenyl]-2-yl)acetamide (**27**) (0.268g, 0.92 mmol), and subsequently dissolved in MeOH (15 mL). HCl (2 mL) was added while the reaction mixture was cooled in an ice bath. The reaction mixture was then heated to 70°C, and stirred for 2 hours. The crude mixture was diluted in ethyl acetate (100 mL), and washed with water (100 mL), sat. $NaHCO_3$ (100 mL), and brine (100 mL). The organic phase was dried with $MgSO_4$, filtrated and concentrated before being dry loaded onto a silica column and by flash chromatography (EtOAc/Hexane 30/70 +1% TEA) purified to afford **25** as a pale-yellow oil (0.086g, 0.35 mmol, 38%). R_f=0.50 (EtOAc/Hexane 30/70 +1% TEA). ^{1}H-NMR (600 MHz, DMSO): δ 7.68 (d, J=8.04, 1H), 7.48 (d, J=7.92, 1H), 7.41 (m, 2H), 7.36 (t, J=7.62, 1H), 7.21 (m, 2H), 7.15 (t, J=7.8, 1H). ^{13}C-NMR (600 MHz, DMSO): δ 136.8, 133.5, 132.1, 131.5, 130.4, 129.3, 127.8, 124.3. MS (EI) m/z [M^+] calcd. for $C_{12}H_{10}BrNO$ 247.0; Found 247.0

9*H*-Carbazole (28)

A vial for electrochemical synthesis was charged with 2'-bromo-[1,1'-biphenyl]-2-amine (**25**)(0.054g, 0.22 mmol), TBAB (0.126g, 0.39 mmol) and $Ni(bpy)_3Br_2$ (0.014g, 0.02 mmol). DBU (0.164 mL, 1.1 mmol) and DMA (2 mL) were then added, before the vessel was sealed. The flask was evacuated and flushed with argon five times. The reaction mixture was subjected to a current of 4 mA overnight and at room temperature. The crude mixture was diluted with ethyl acetate (100 mL), and washed with water (100 mL), sat. $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried with $MgSO_4$, filtrated and concentrated. The isolated product was dry loaded onto a silica column and purified by flash chromatography (EtOAc/Hexane 30/70 +1% TEA) to afford **28** as a pale yellow oil. R_f=0.4 (EtOAc/Hexane 30/70 +1% TEA). ^{1}H-NMR (600 MHz, DMSO): δ 11.23 (s, 1H), 8.11 (d, J=6.54, 2H), 7.48 (d, J=8.1, 2H), 7.37 (t, J=8.28, 2H), 7.15 (t, J=6.96, 2H). ^{13}C-NMR (600 MHz, DMSO): δ 139.6, 125.4, 122.3, 120.1, 118.4, 110.8. MS (EI) m/z [M^+] calcd. for $C_{12}H_{10}BrNO$ 167.1; Found 167.0

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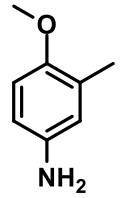
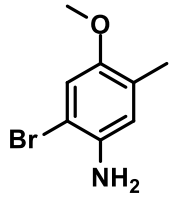
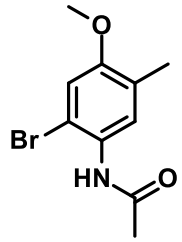
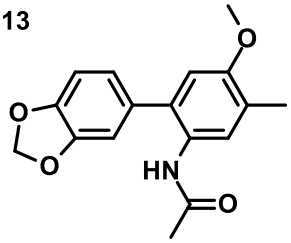
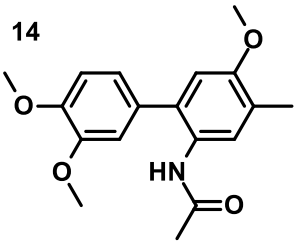
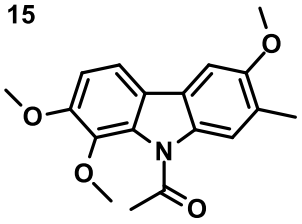
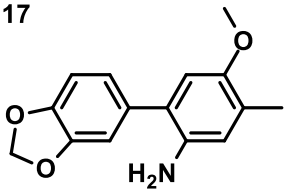
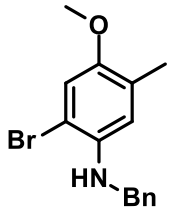
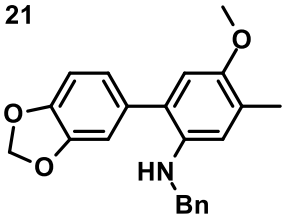
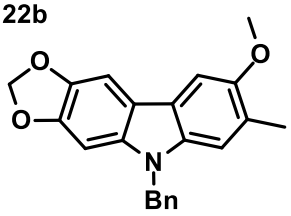
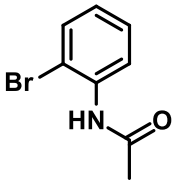
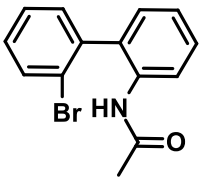
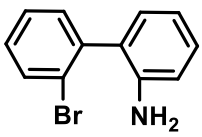
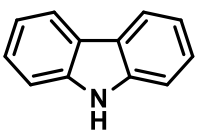
7. Appendix

Overview of synthesised compounds

2 	3 
12 	13 
14 	15 
17 	19 
21 	22b 
26 	27 
25 	28 

7.1 Analysis of compound 2

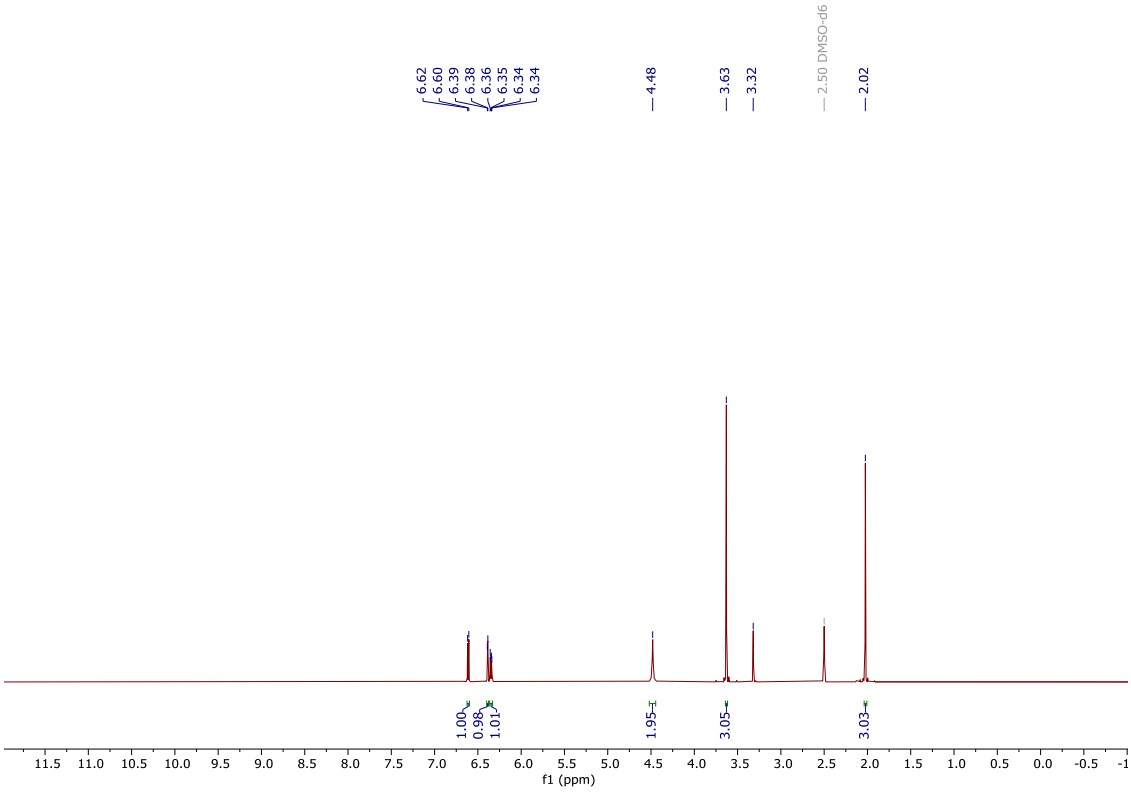


Figure 7.1: ^{1}H-NMR (600 MHz) spectrum of compound **2.**

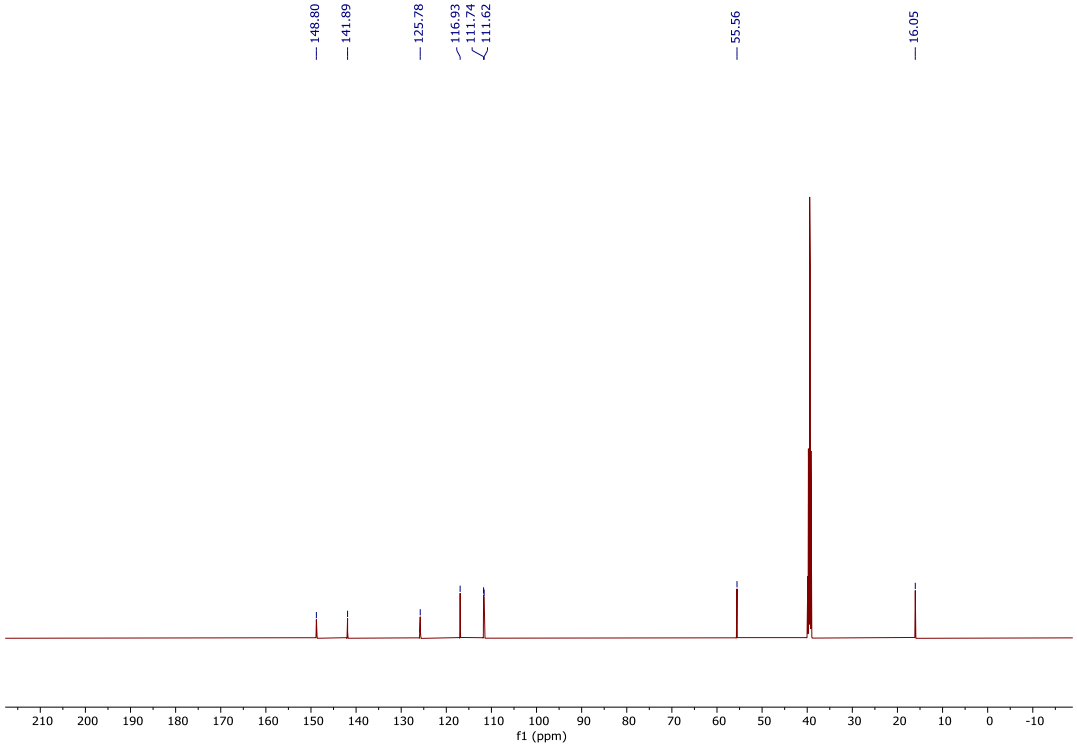


Figure 7.2: ^{13}C-NMR (600 MHz) spectrum of compound **2**.

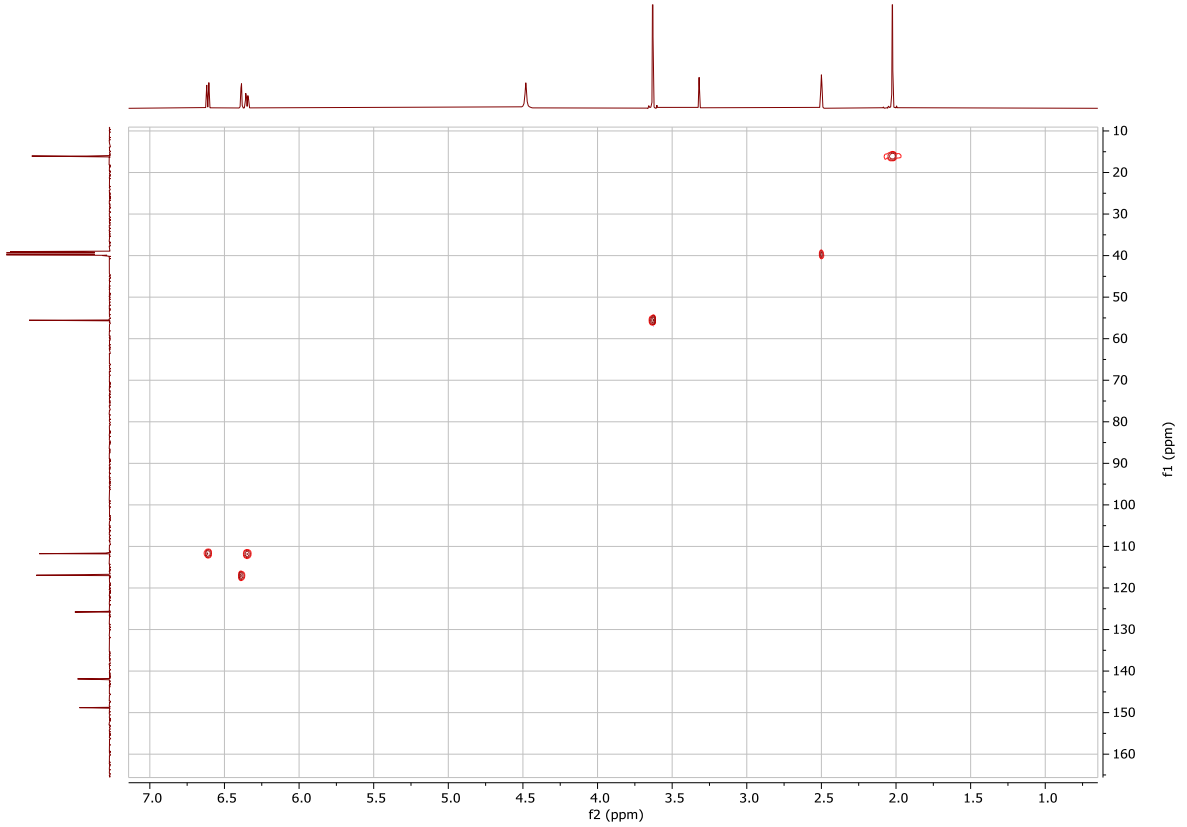


Figure 7.3: HSQC (MHz) spectrum of compound **2**.

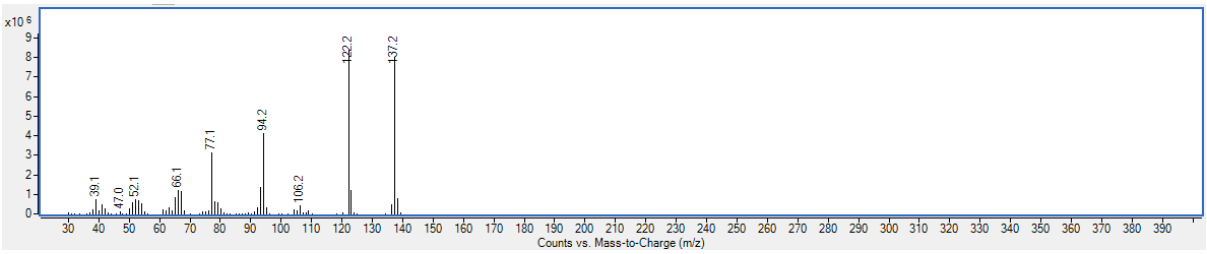


Figure 7.4: EI-MS spectrum of compound **2**.

7.2 Analysis of compound 3

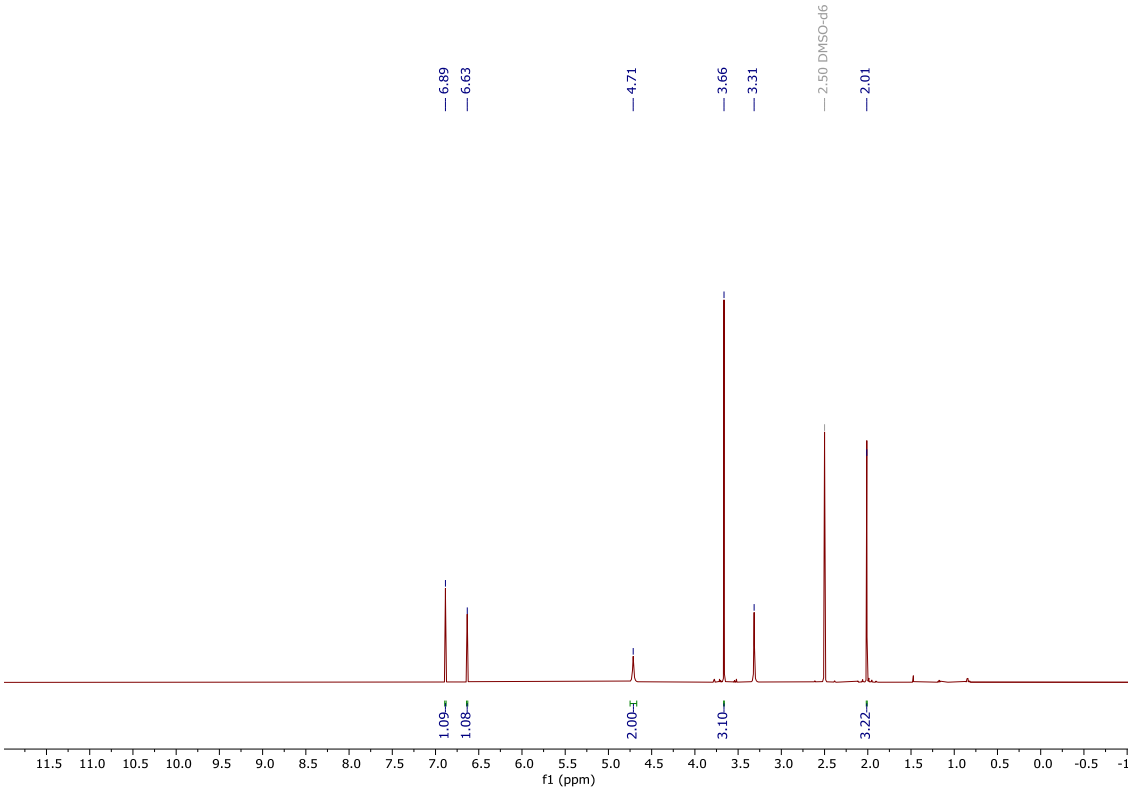


Figure 7.5: ^{1}H-NMR (600 MHz) spectrum of compound **3**.

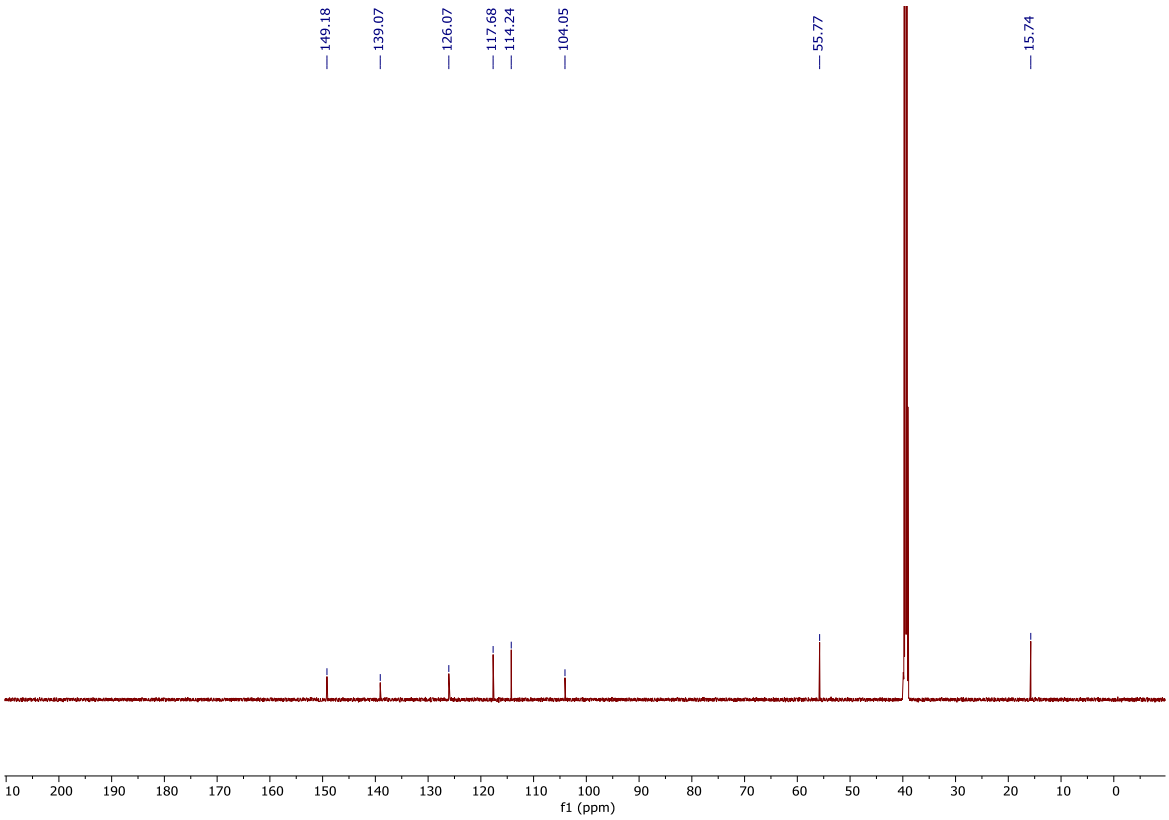


Figure 7.6: ^{13}C-NMR (600 MHz) spectrum of compound **3**

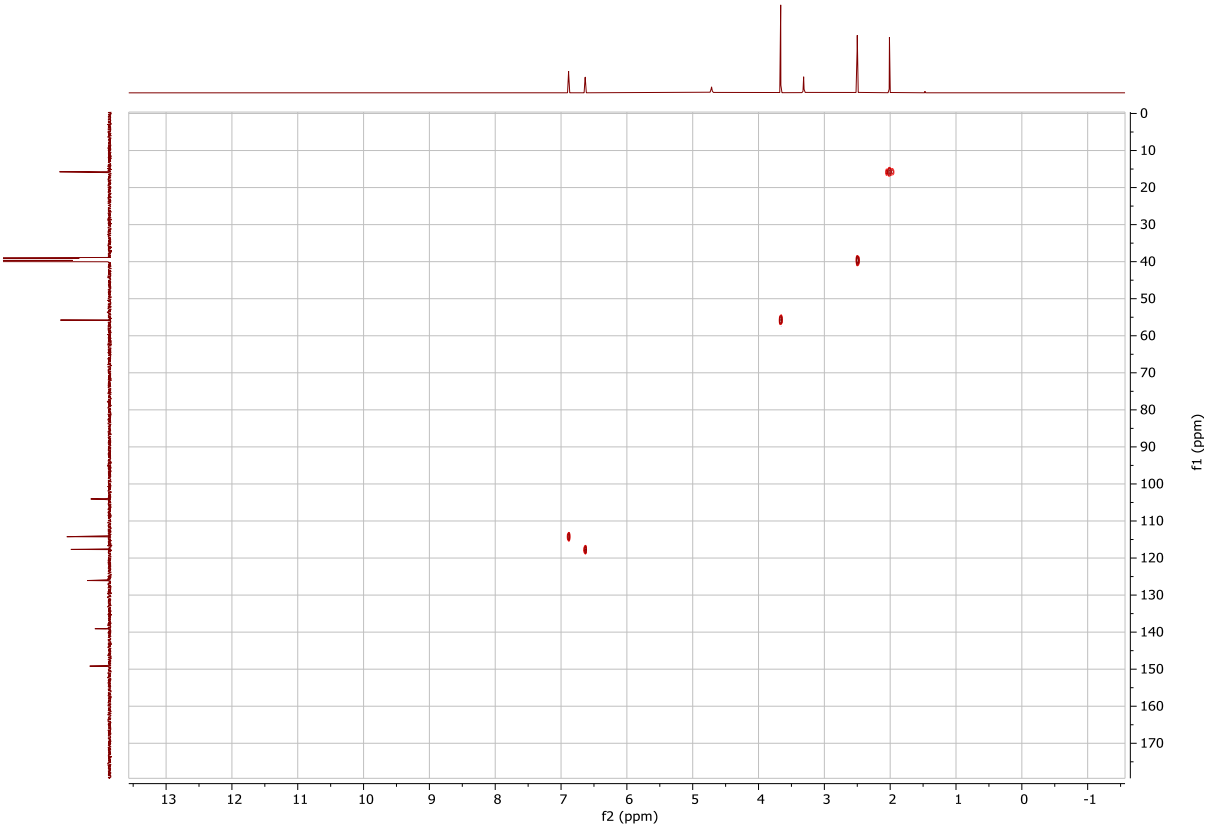


Figure 7.7: HSQC (600 MHz) spectrum of compound **3**.

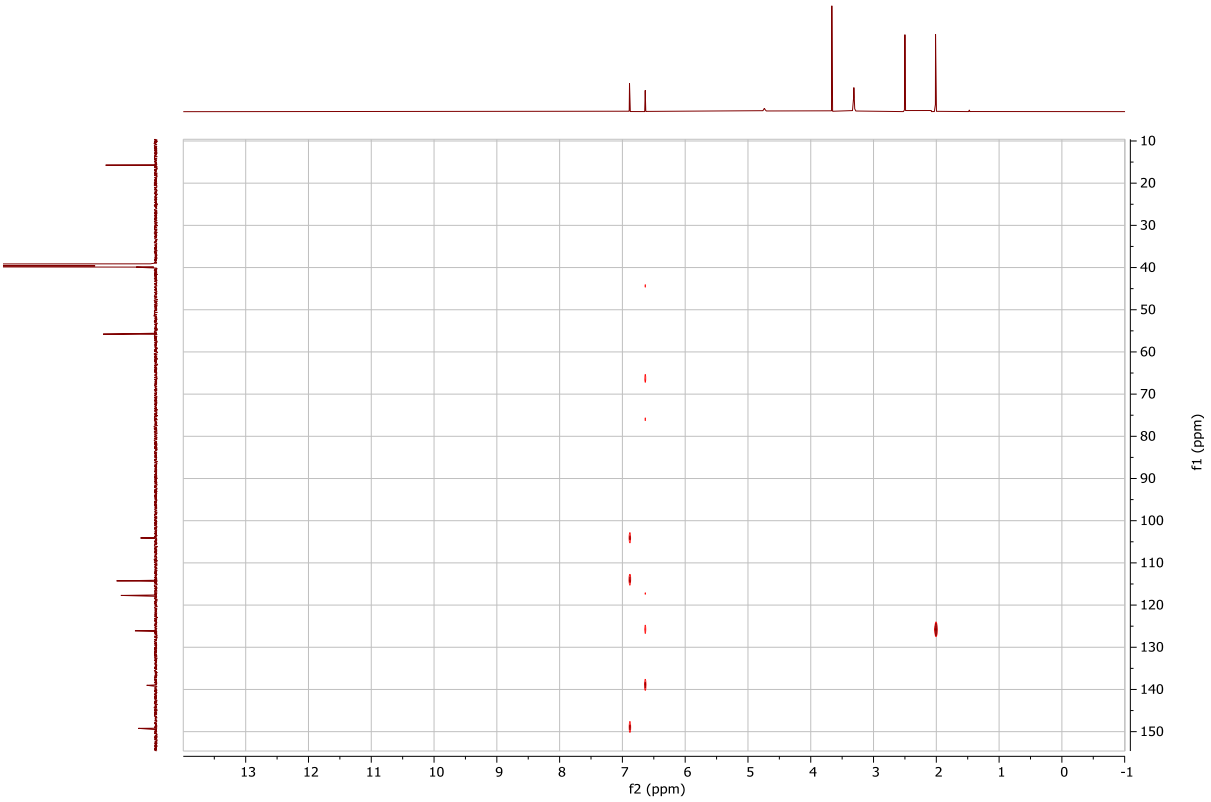


Figure 7.8: 1,1-Adequate (850 MHz) spectrum of compound **3**.

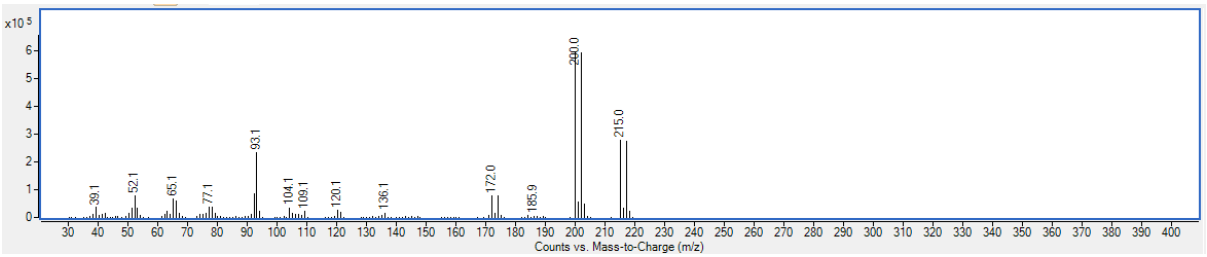


Figure 7.9: EI-MS spectrum of compound **3**.

7.3 Analysis of compound 12

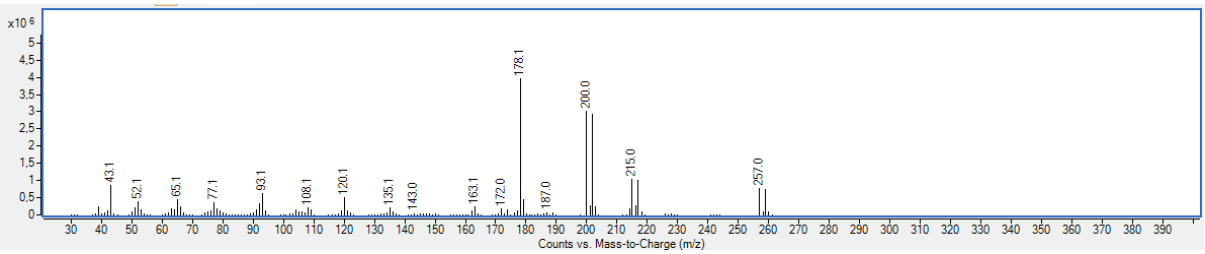


Figure 7.9: EI-MS spectrum of compound **12**.

7.4 Analysis of compound 13

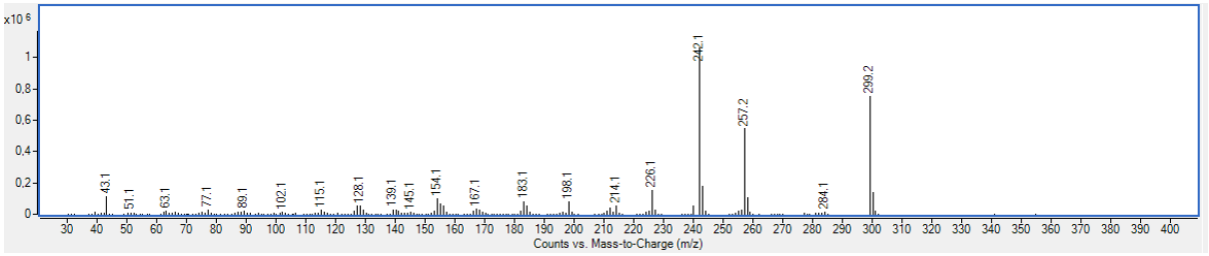


Figure 7.10: EI-MS spectrum of compound **13.**

7.5 Analysis of compound 14

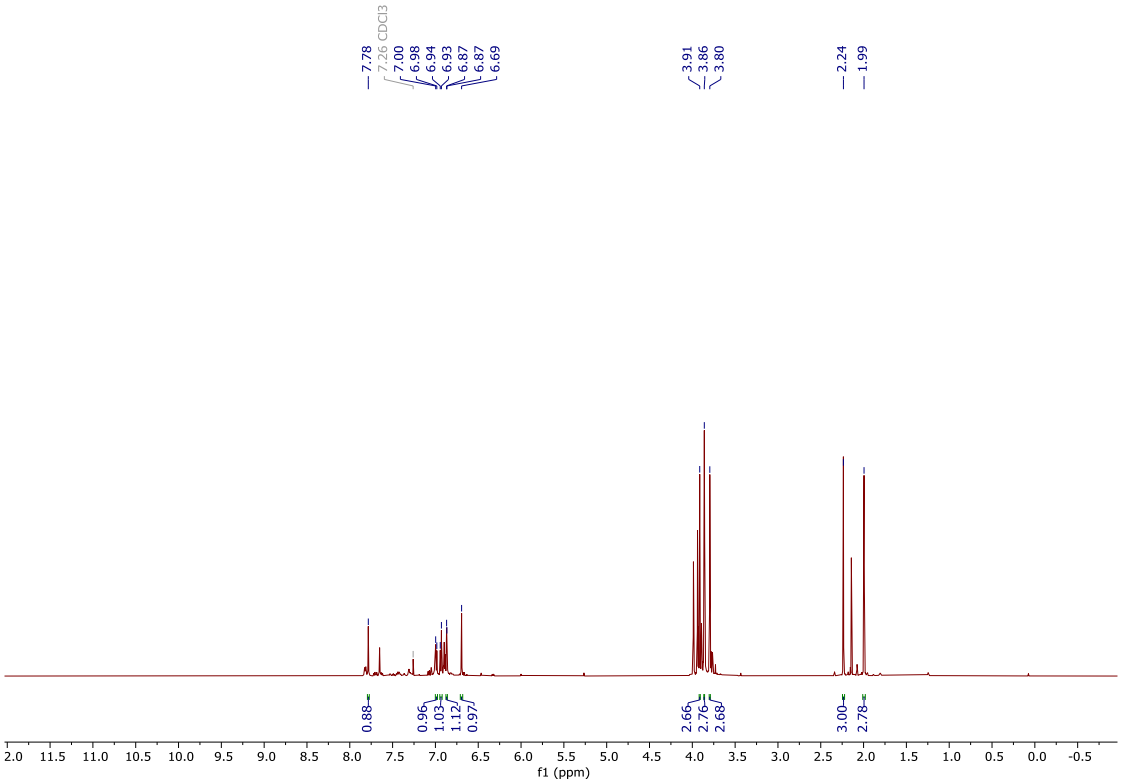


Figure 7.11: ^{1}H-NMR (600 MHz) spectrum of compound **14.**

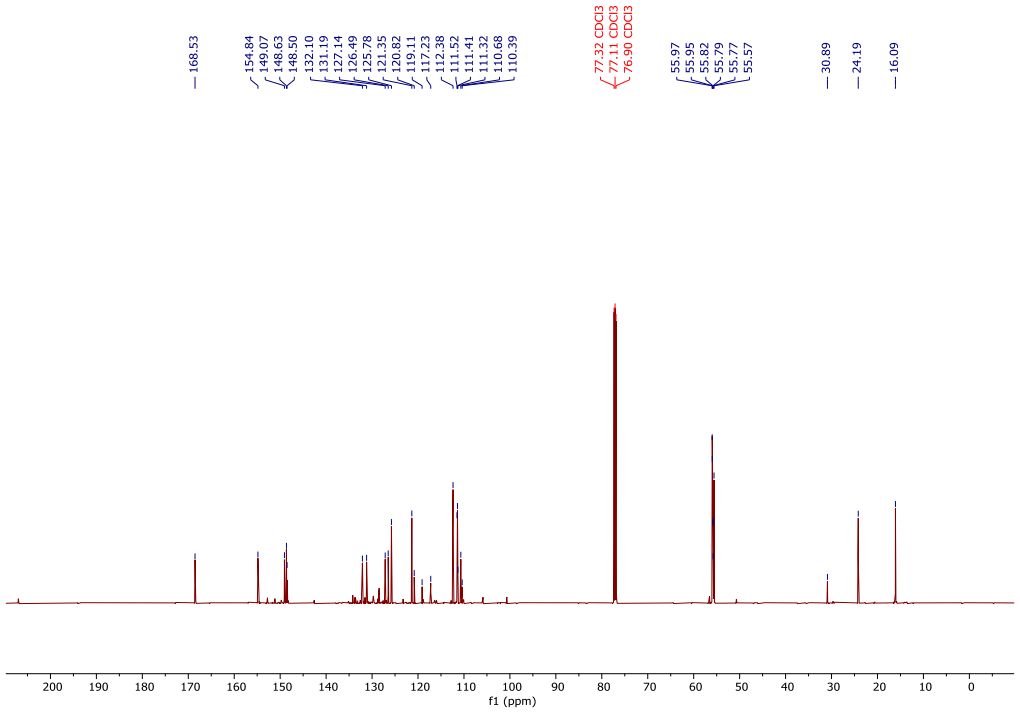


Figure 7.12: ^{13}C-NMR (600 MHz) spectrum of compound **14**.

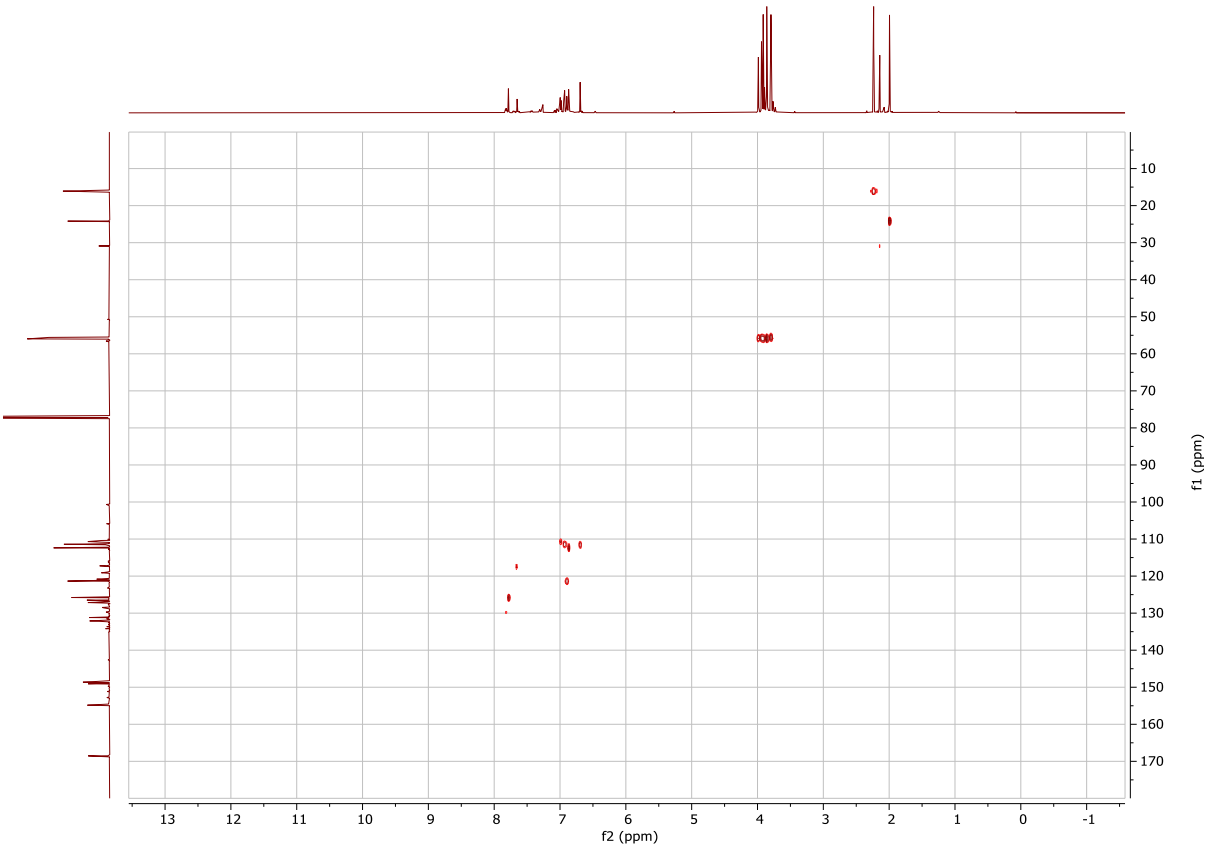


Figure 7.13: HSQC (600 MHz) spectrum of compound **14.**

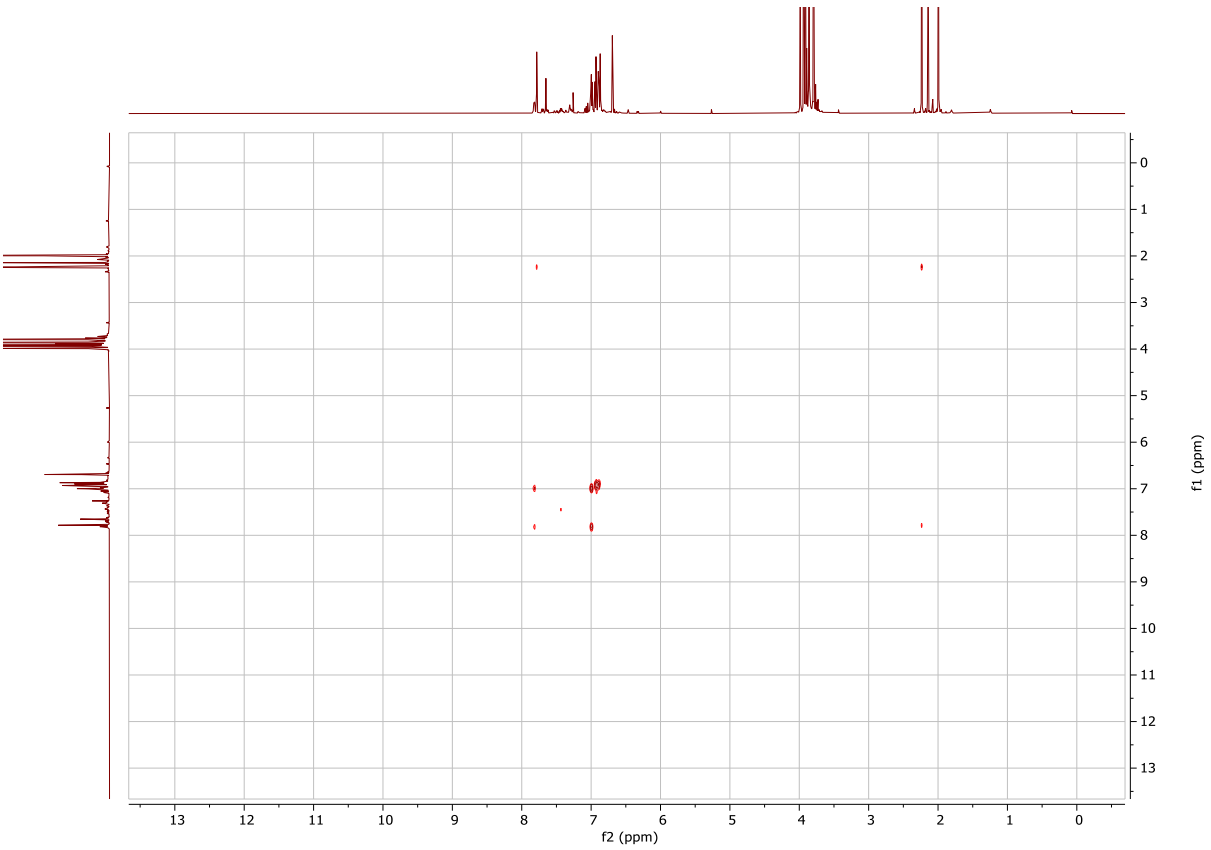


Figure 7.14: COSY (600 MHz) spectrum of compound **14**.

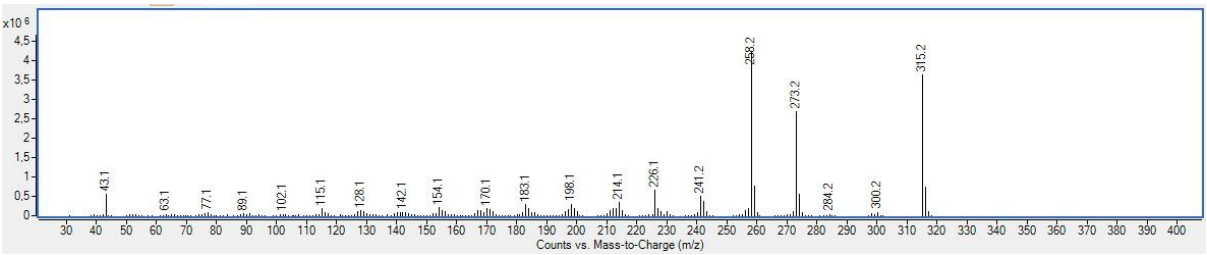


Figure 7.15: EI-MS spectrum of compound **14.**

7.6 Analysis of compound 15

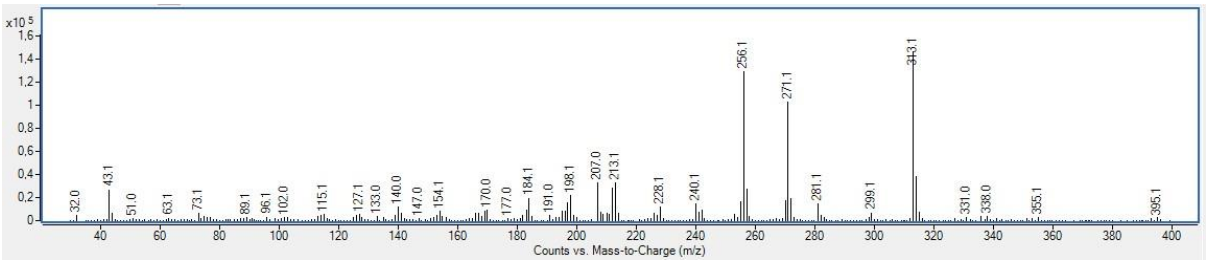


Figure 7.16: EI-MS spectrum of compound **15.**

7.7 Analysis of compound 17

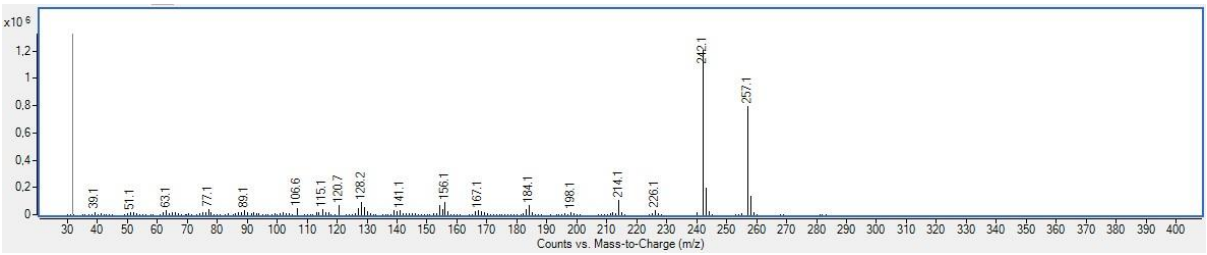


Figure 7.17: EI-MS spectrum of compound **17.**

7.8 Analysis of compound 19

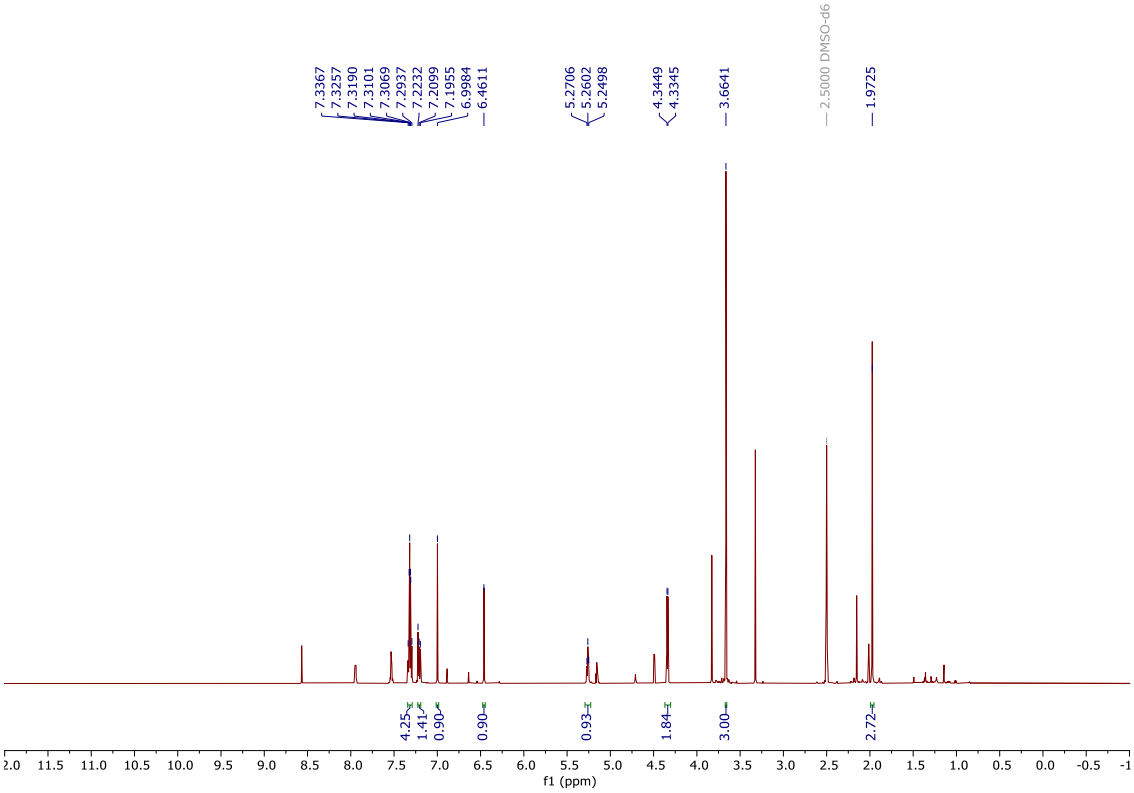


Figure 7.18: [1]H-NMR (600 MHz) spectrum of compound **19.**

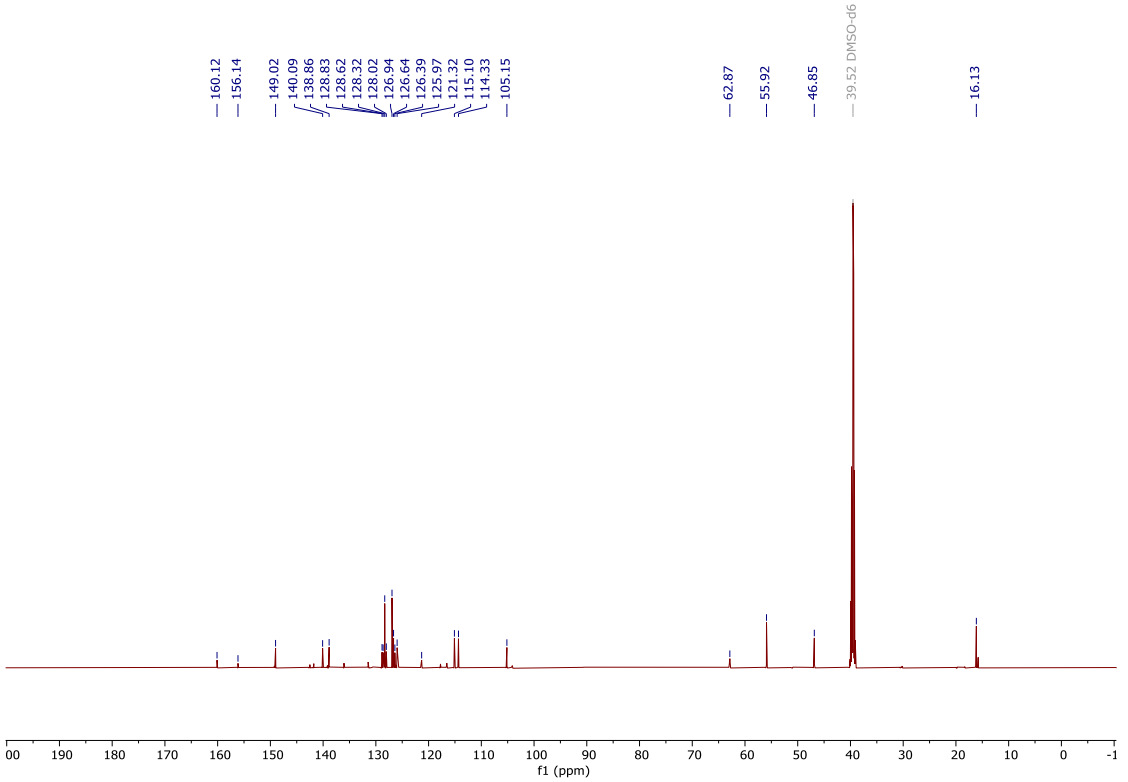


Figure 7.19: [13]C-NMR (600 MHz) spectrum of compound **19**.

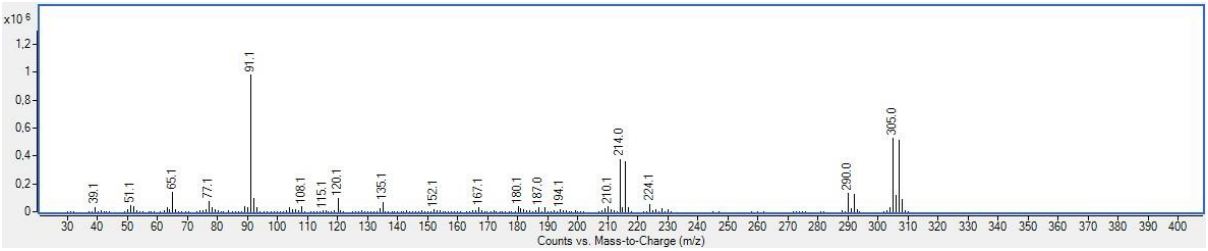


Figure 7.20: EI-MS spectrum of compound **19.**

7.9 Analysis of compound 21

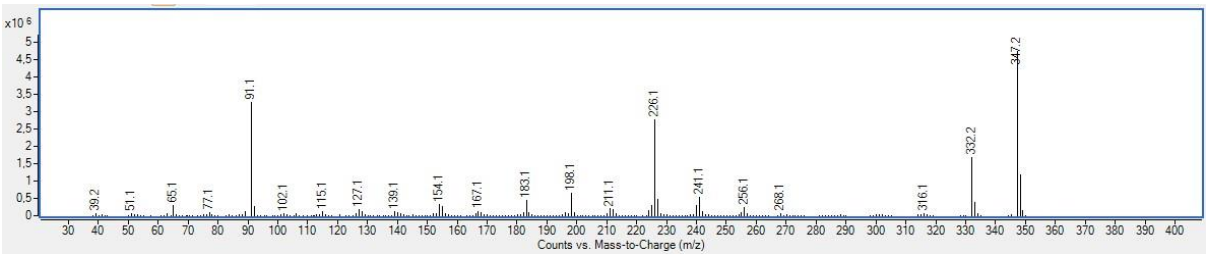


Figure 7.21: EI-MS spectrum of compound **21.**

7.10 Analysis of compound 22b

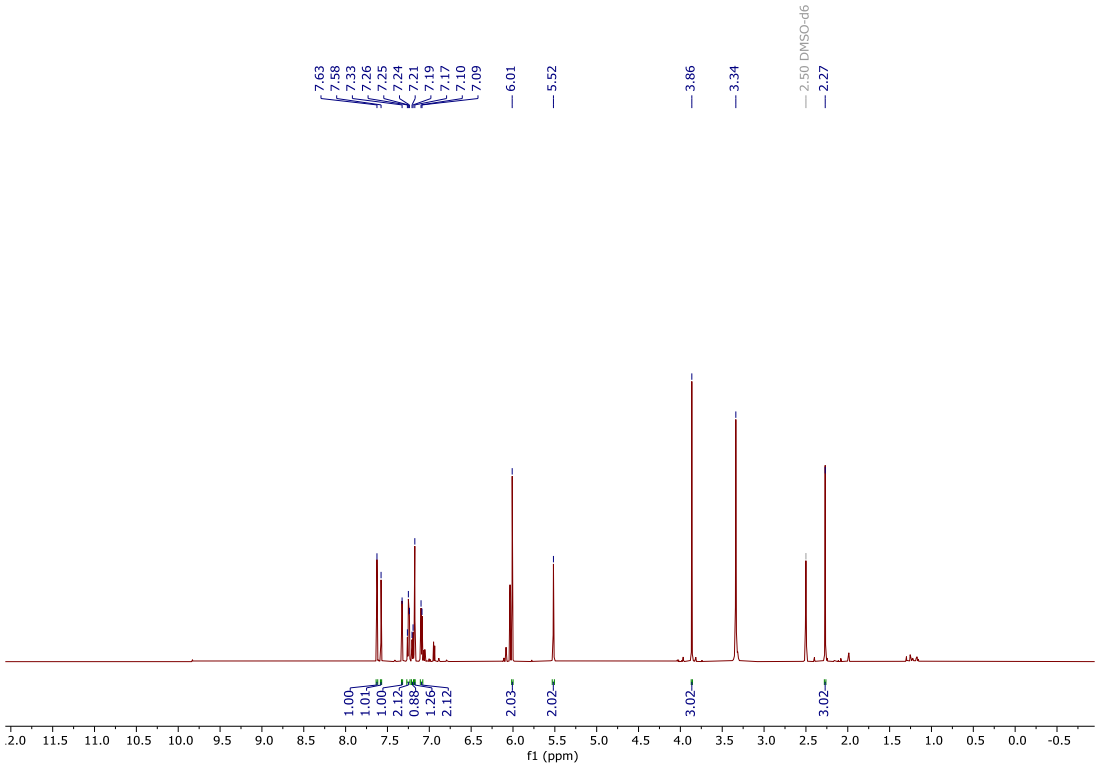


Figure 7.22: [1]H-NMR (600 MHz) spectrum of compound **22b**.

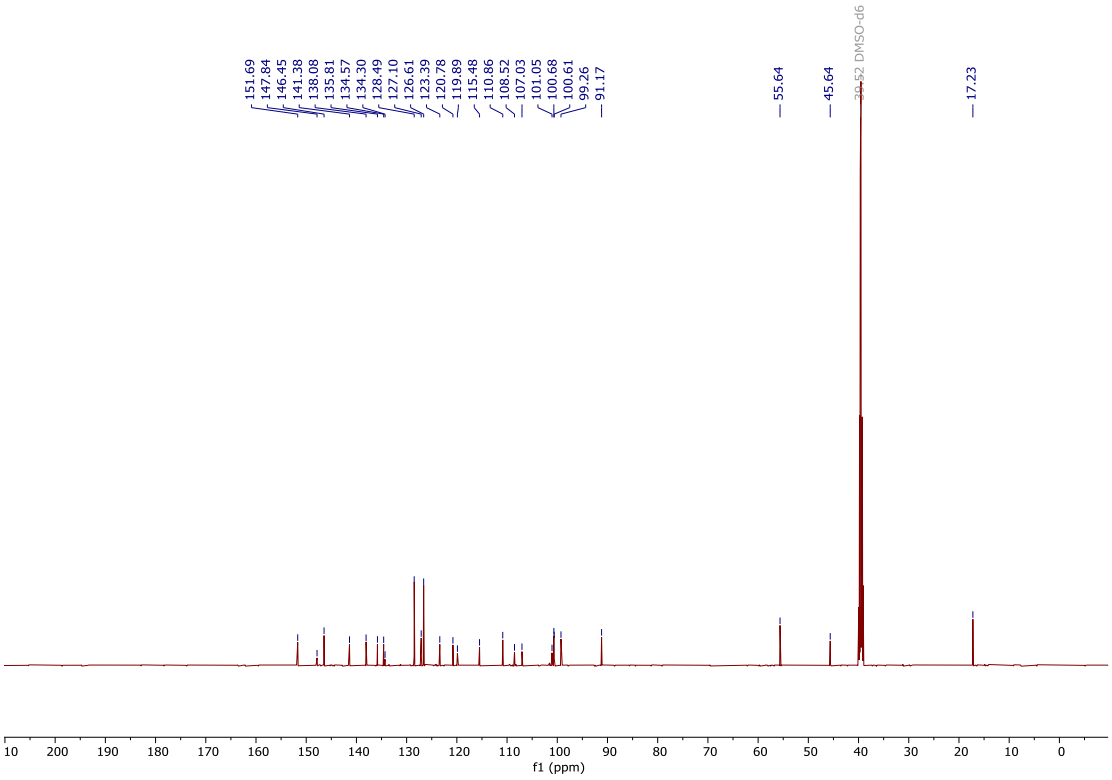


Figure 7.23: [13]C-NMR (600 MHz) spectrum of compound **22b**.

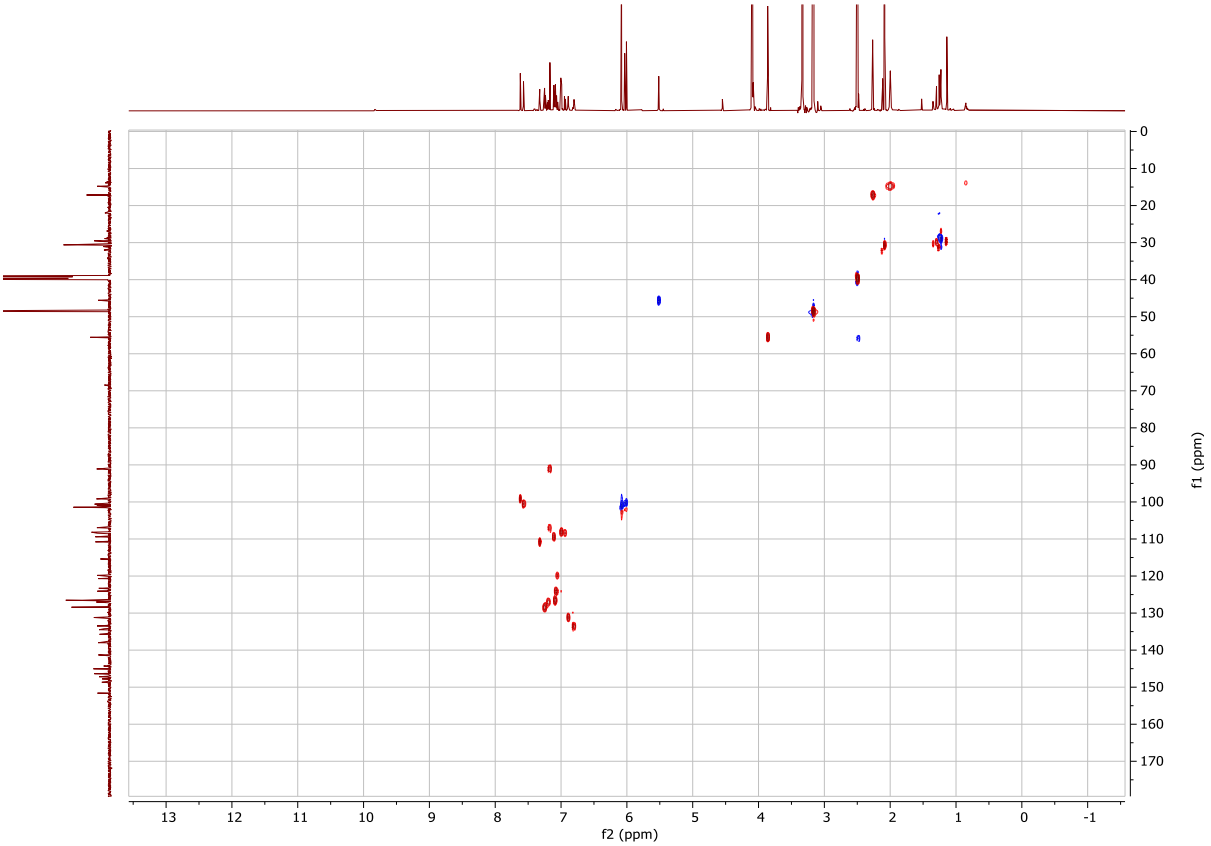


Figure 7.24: HSQC (600 MHz) spectrum of compound **22b**.

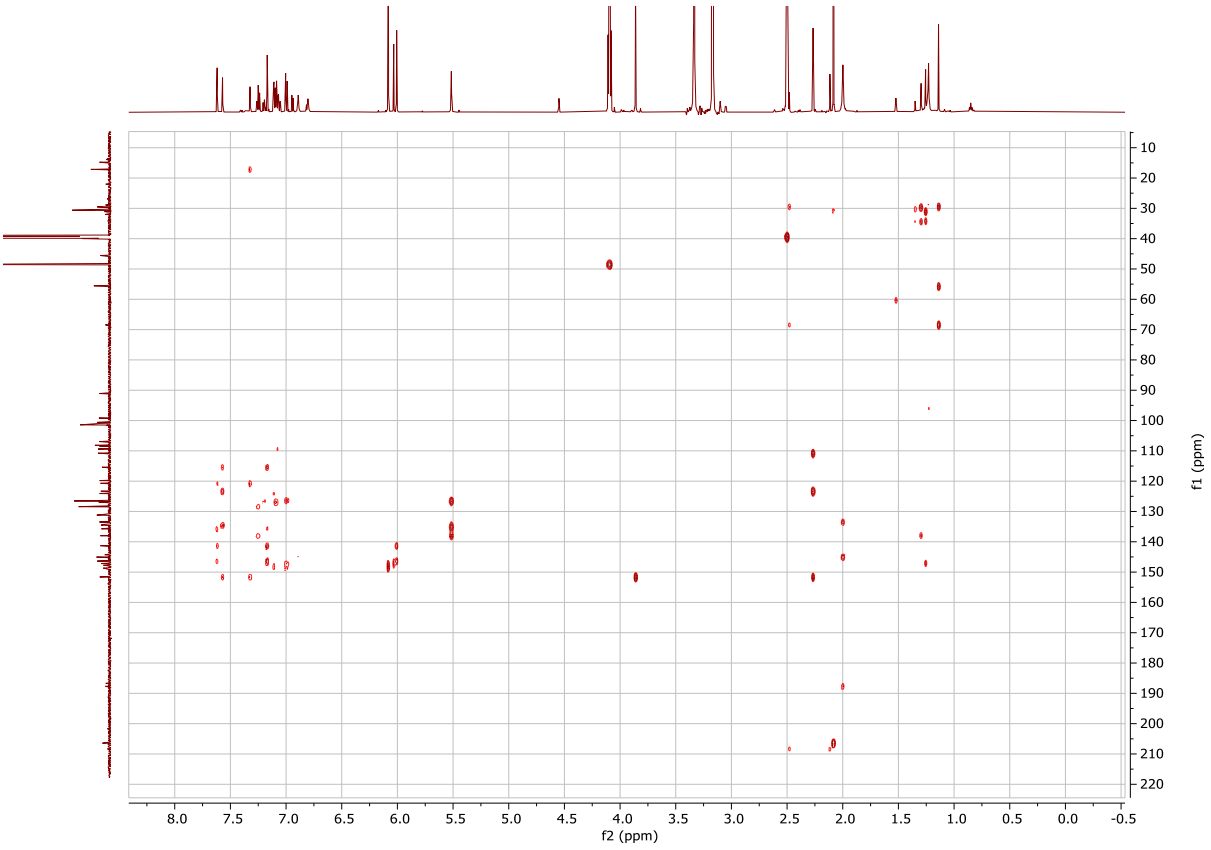


Figure 7.25: HMBC (600 MHz) spectrum of compound **22b**.

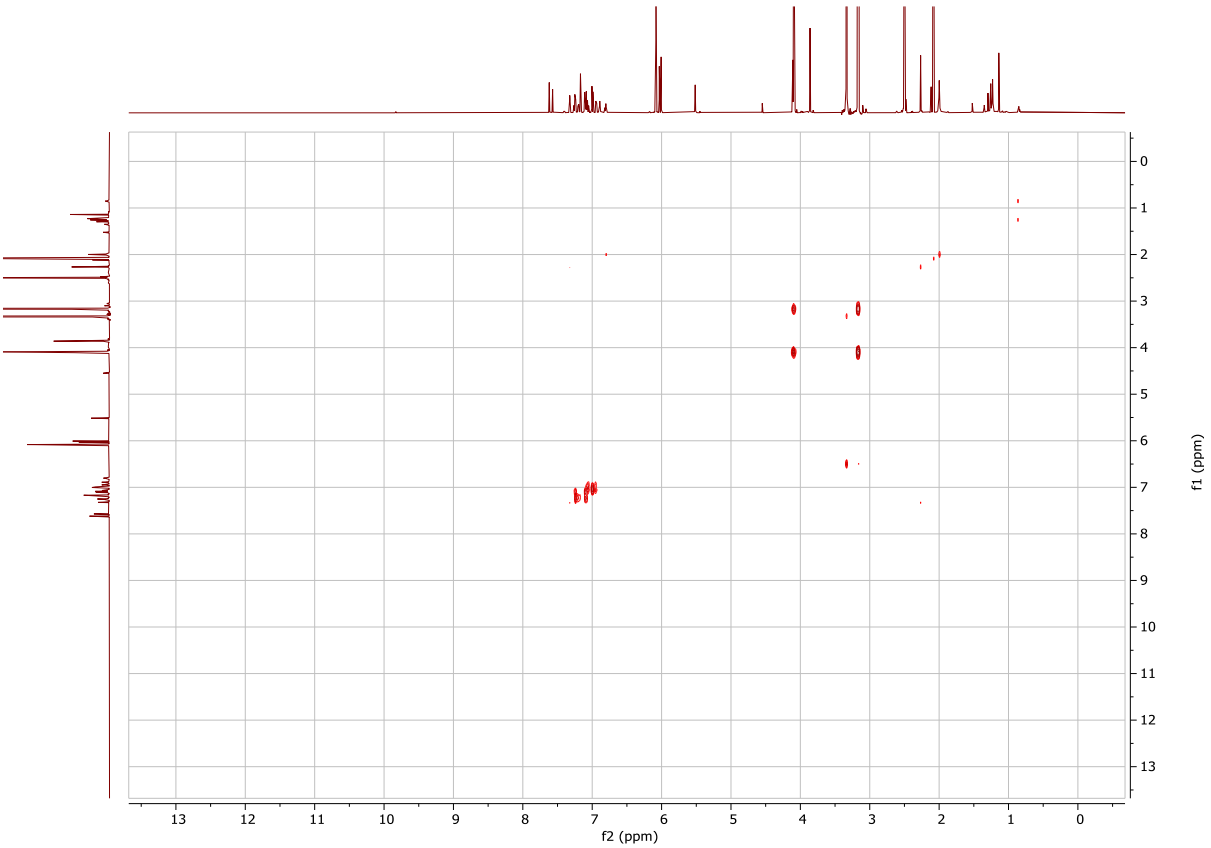


Figure 7.26: COSY (600 MHz) spectrum of compound **22b**.

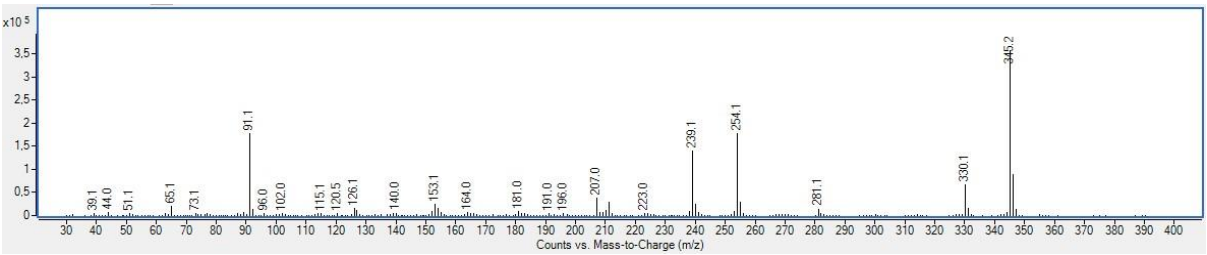


Figure 7.27: EI-MS spectrum of compound **22b**.

7.11 Analysis of compound 26

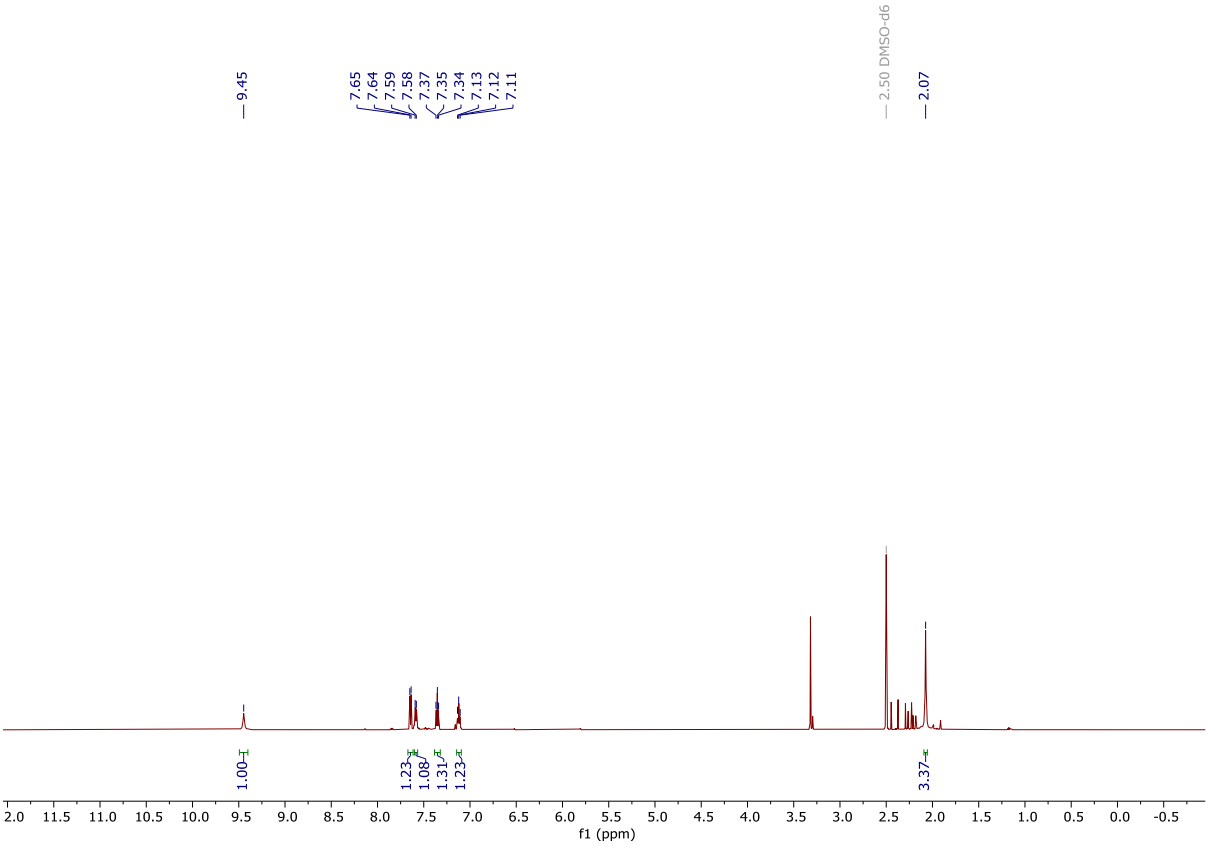


Figure 7.28: ^{1}H-NMR (600 MHz) spectrum of compound **26**.

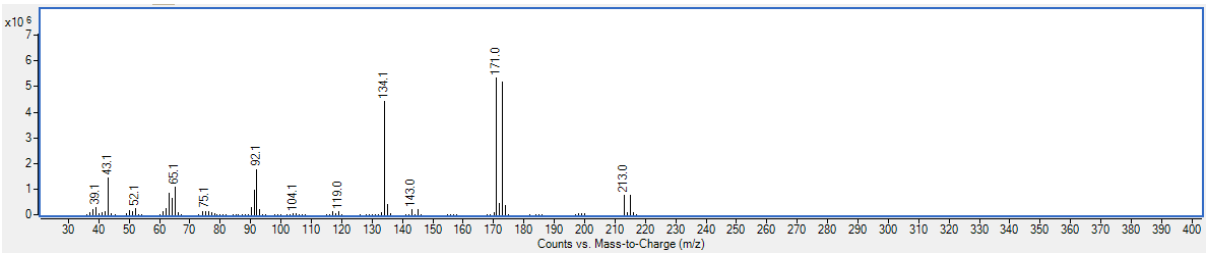


Figure 7.29: EI-MS spectrum of compound **26**.

7.12 Analysis of compound 27

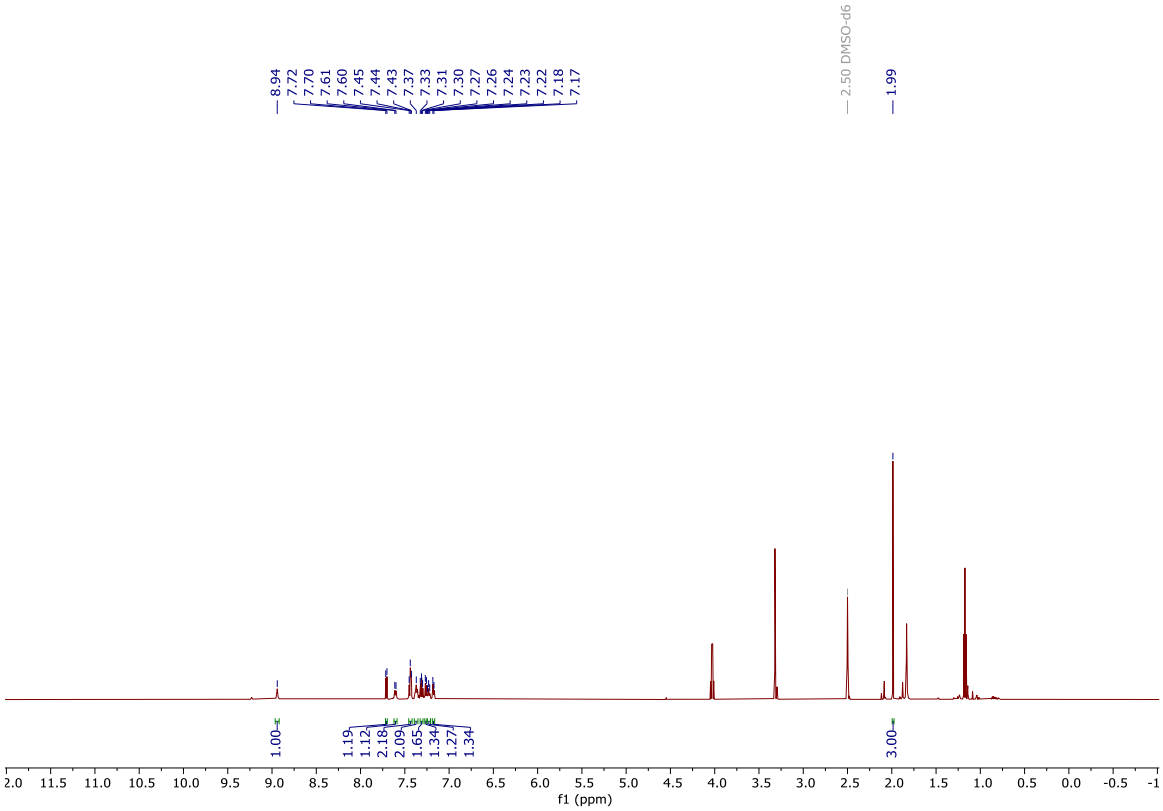


Figure 7.30: ^{1}H-NMR (600 MHz) spectrum of compound **27**.

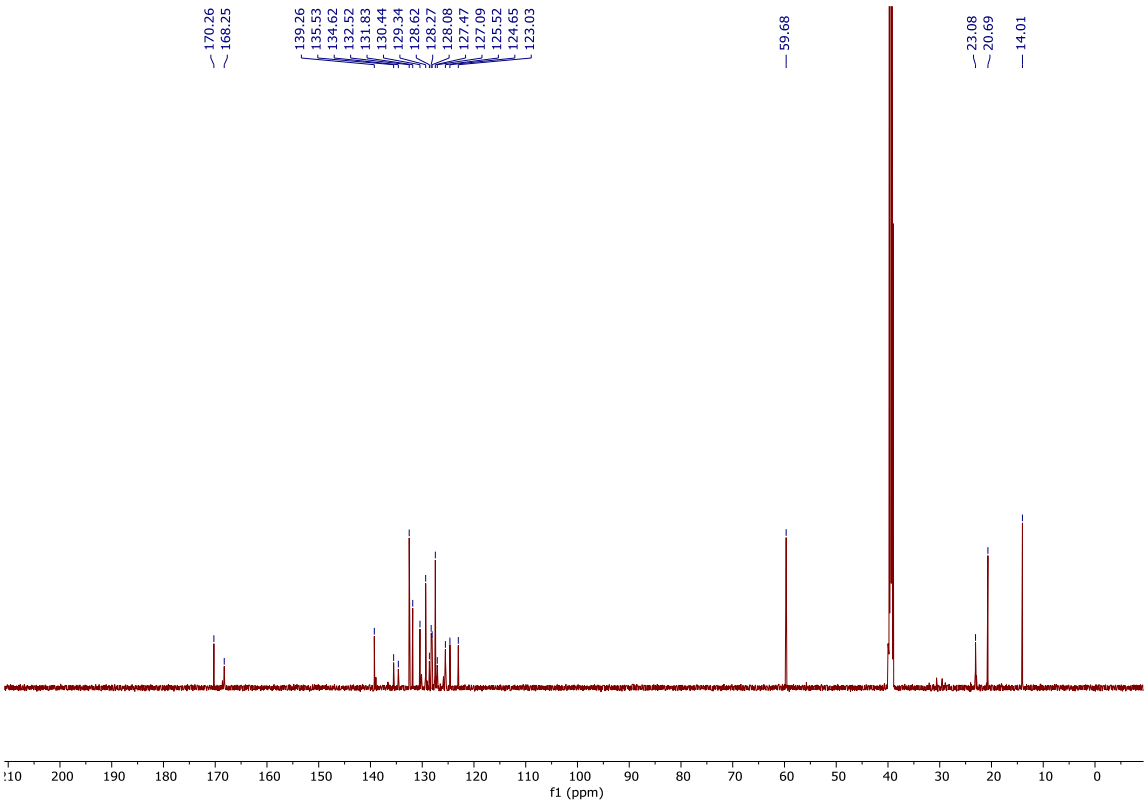


Figure 7.31: ^{13}C-NMR (600 MHz) spectrum of compound **27**.

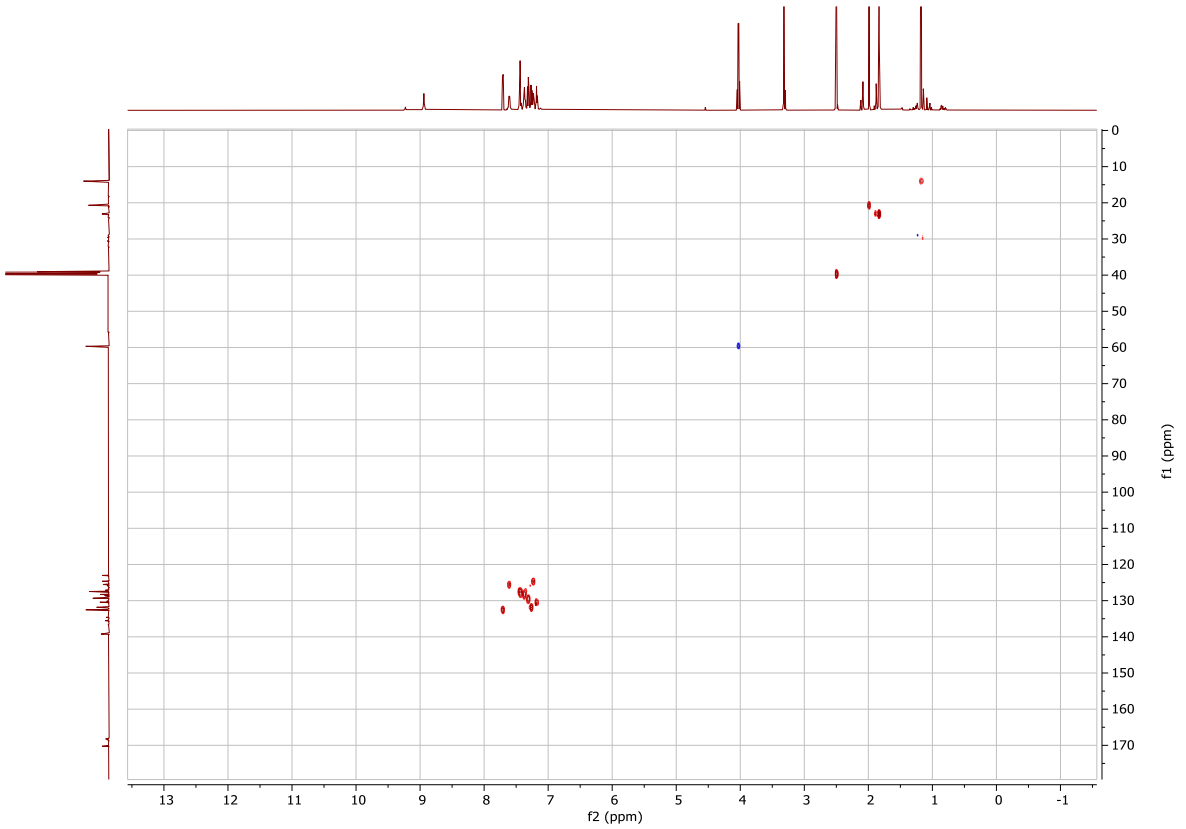


Figure 7.32: HSQC (600 MHz) spectrum of compound **27**.

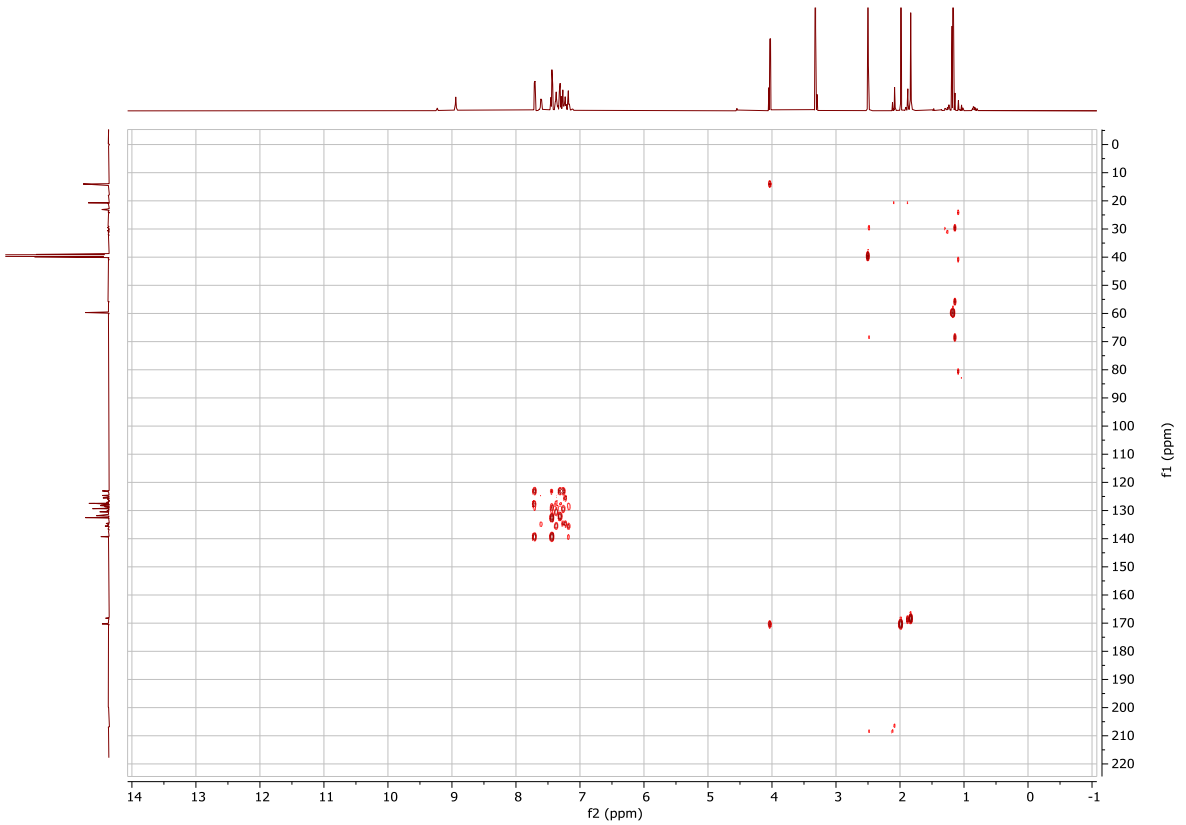


Figure 7.33: HMBC (600 MHz) spectrum of compound **27**.

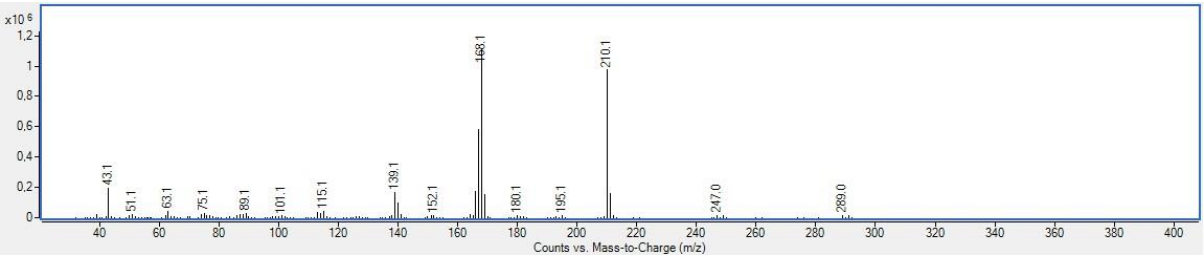


Figure 7.34: EI-MS spectrum of compound **27**.

7.13 Analysis of compound 25

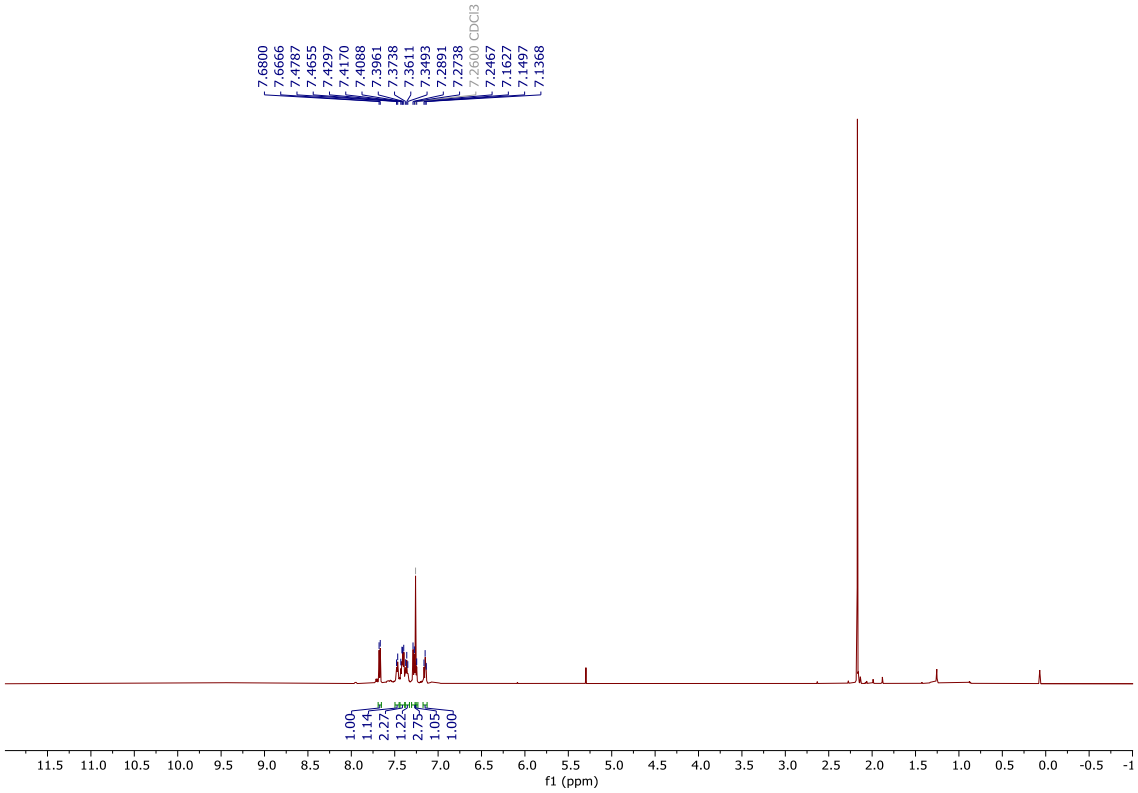


Figure 7.35: ^{1}H-NMR (600 MHz) spectrum of compound **25**.

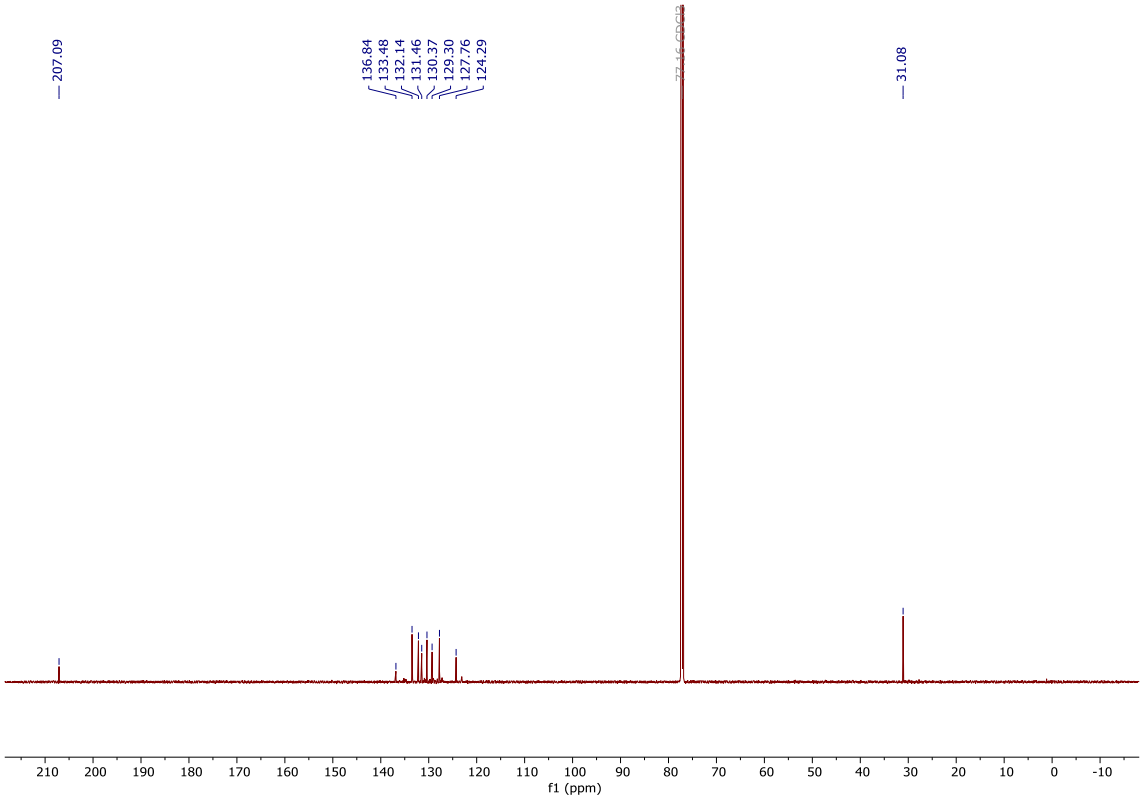


Figure 7.36: ^{13}C-NMR (600 MHz) spectrum of compound **25.**

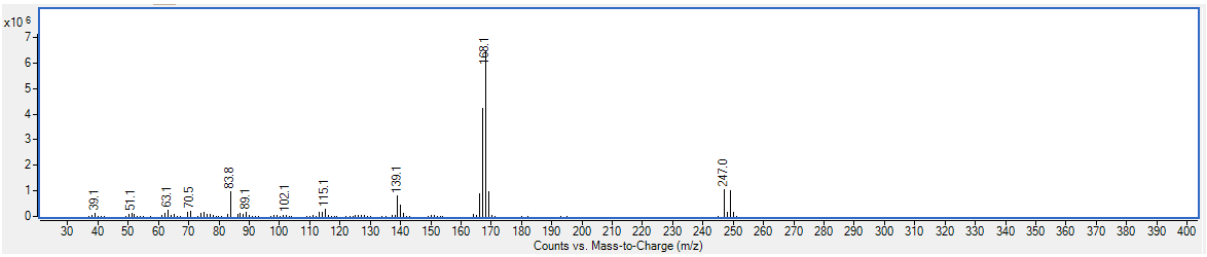


Figure 7.37: EI-MS spectrum of compound **25.**

7.14 Analysis of compound 28

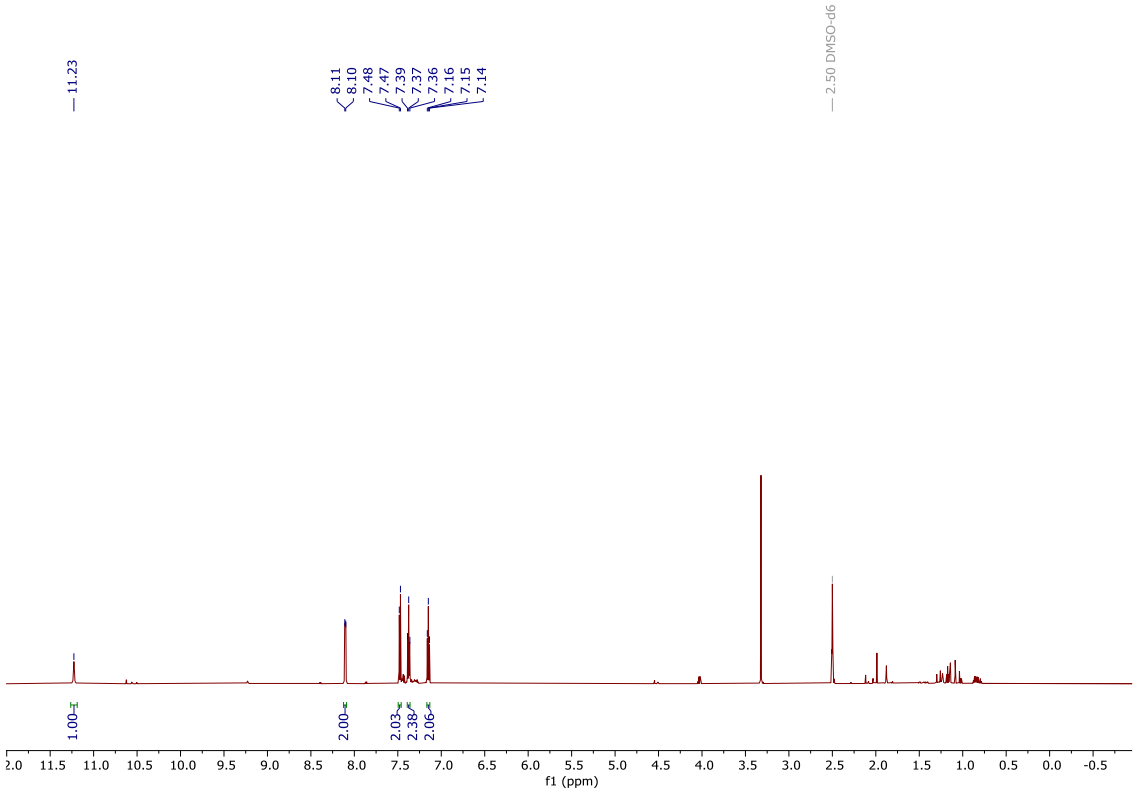


Figure 7.38: ^{1}H-NMR (600 MHz) spectrum of compound **28.**

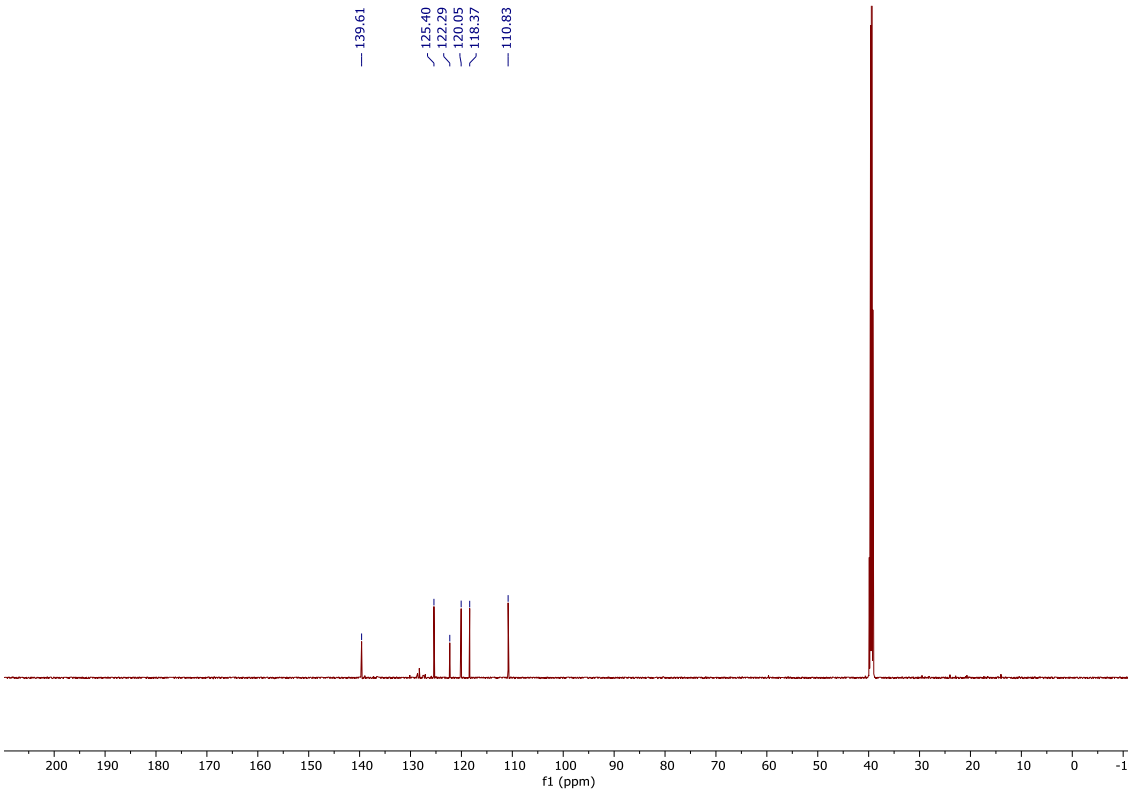


Figure 7.39: ^{13}C-NMR (600 MHz) spectrum of compound **28**.

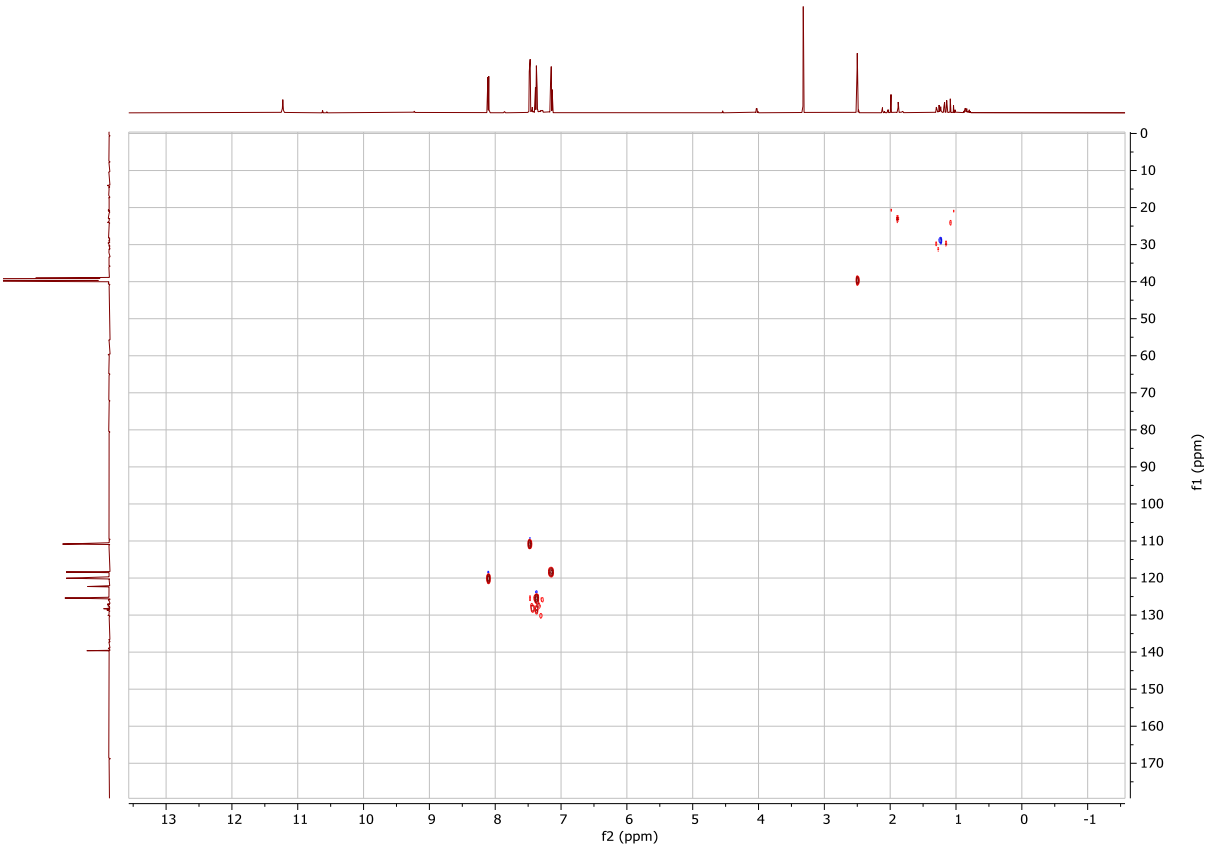


Figure 7.40: HSQC (600 MHz) spectrum of compound **28**.

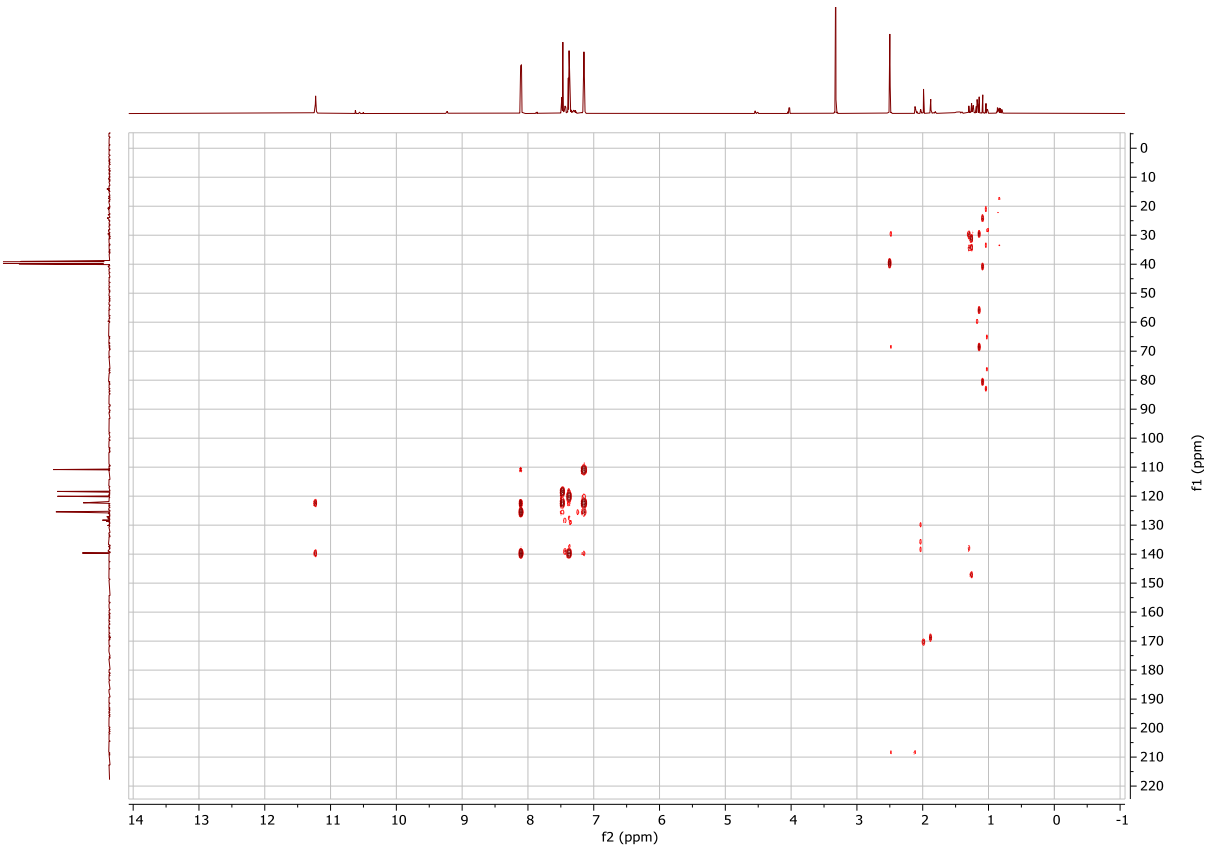


Figure 7.41: HMBC (600 MHz) spectrum of compound **28.**

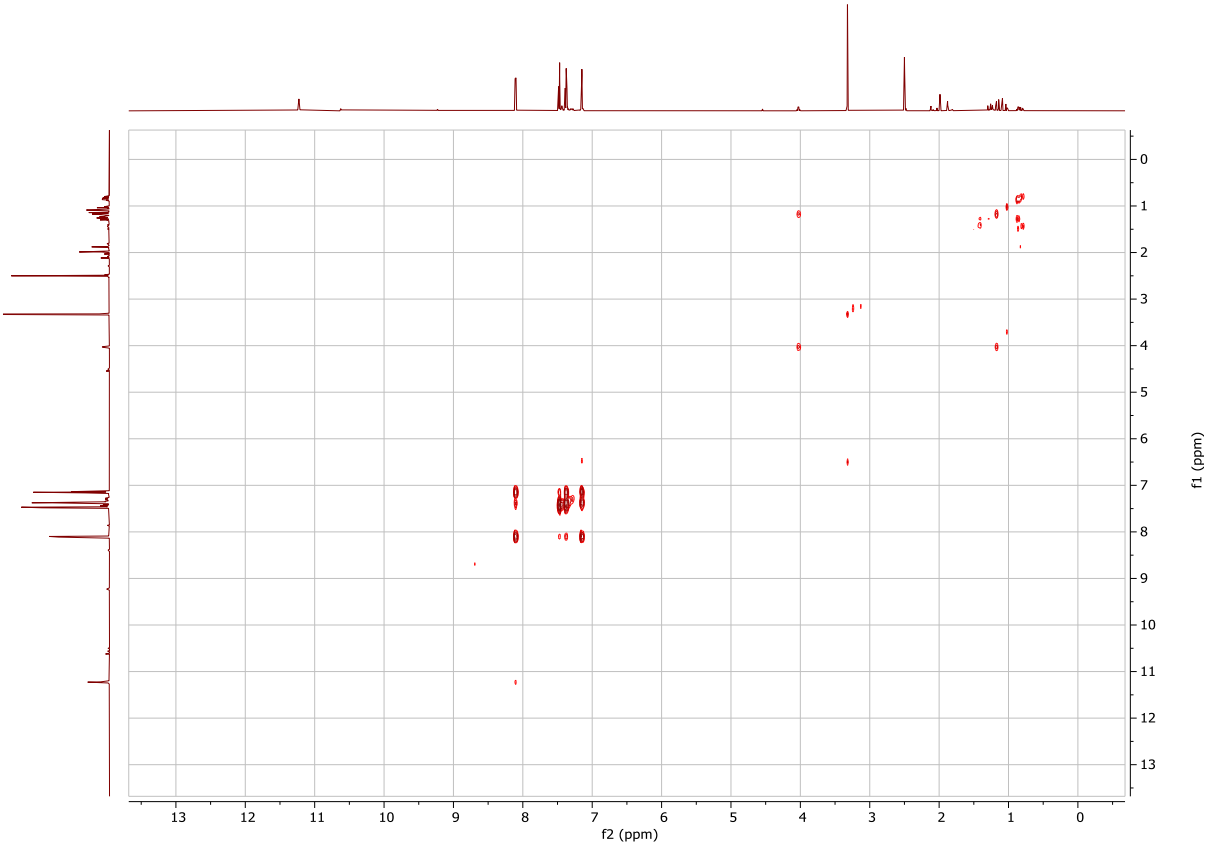


Figure 7.42: COSY (600 MHz) spectrum of compound **28**.

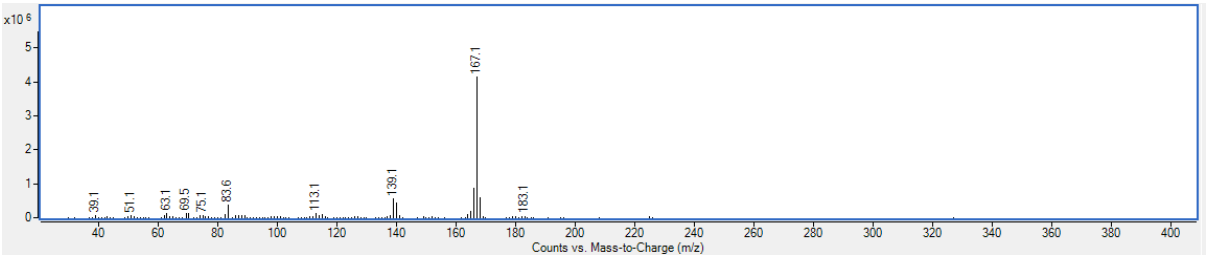


Figure 7.43: EI-MS spectrum of compound **28**.