

# **The Suzuki-Miyaura Cross Coupling Reaction as a Key Step for the Synthesis of Oxygen and Nitrogen Containing Hetero-aromatic compounds**

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## **Declaration**

I declare that the work presented in this thesis was carried out exclusively by myself under the supervision of Prof. C.B. de Koning and Dr A.L. Rousseau. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

June 2015

Signed: Priyamvada Pradeep

## Abstract

The first two chapters of this thesis deals with the synthesis of 6*H*-benzo[*d*]-naphtho[1,2-*b*]pyran-6-one motif found in gilvocarcin as well as related aromatic compounds containing the aromatic pyranone moiety. The synthesis was undertaken by employing the Suzuki-Miyaura cross coupling reaction and a novel *N*-bromosuccinimide induced ring cyclization reaction to afford the pyranone. It was established that the treatment of both [2-(1,4-dimethoxynaphthalen-2-yl)phenyl]methanol and (2',5'-dimethoxy-[1,1'-biphenyl]-2-yl)methanol separately with *N*-bromosuccinimide results in the unexpected synthesis of a naphthopyranone ring system in the form of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one and 2-methoxy-6*H*-benzo[*c*]chromen-6-one respectively. Application of the same methodology for the attempted synthesis of related compounds namely, 1-hydroxy-12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one and 8-fluoro-12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one unfortunately did not generate the desired results. Attempts were made to elucidate the mechanism of this reaction. The most apparent mechanism indicates that *N*-bromosuccinimide, in the presence of air, oxidizes the benzylic alcohol to an aldehyde which is then converted to an acid bromide allowing for the ring closure with the adjacent aromatic ether to afford the desired pyranone.

In Chapter 3 and 4 of this thesis we dealt with the synthesis of benzo[*b*]phenanthridine-7,12-dione motif, the backbone of biologically important secondary metabolite jadomycin B. Again, a key step involves employing the Suzuki-Miyaura cross coupling reaction. The synthetic methodology also sheds some light on the dynamics of the ring closure of benzylic amines onto naphthoquinones resulting in the synthesis of benzo[*j*]phenanthridine-11,12-dione, 12-methoxybenzo[*j*]phenanthridine and 1-hydroxybenzo[*j*]phenanthridine-11,12-dione.

The synthesis of benzo fused phenanthridines has been undertaken in Chapter 5 and 6 by employing Suzuki-Miyaura cross coupling reaction and a potassium *t*-butoxide and light mediated cyclization reaction as the key steps. The synthesis of 5-phenylbenzo[*j*]phenanthridine was undertaken successfully but attempts to execute the same methodology to form a compound library of related benzo-fused phenanthridines was unsuccessful.

The same methodology employing a Suzuki-Miyura cross coupling reaction and potassium *t*-butoxide and light mediated cyclization reaction was applied in Chapter 7 and 8 of the thesis directed towards the synthesis of 13*H*-indolo[3,2-*c*]acridine and 3-methoxy-13*H*-indolo[3,2-*c*]acridine. The successful synthesis of the 13*H*-indolo[3,2-*c*]acridine is reported using this methodology.

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*Only mankind is interested in results. Nature only wants to know your intentions. They don't judge you by your performance or your results. They just want to know whether your intentions are proper, your heart is in the right place and that you are giving your best to whatever you are doing. Everything else is just pure statistics.*

**The Fakir - Ruzbeh N. Bharucha**

**Abbreviations:**

|                                      |                                               |
|--------------------------------------|-----------------------------------------------|
| • (2-furyl) <sub>3</sub> P           | Tri(2-furyl)phosphine                         |
| • 1,2-DCE                            | 1,2-Dichloroethane                            |
| • Ac <sub>2</sub> O                  | Acetic anhydride                              |
| • AcOH                               | Acetic Acid                                   |
| • AcONa                              | Sodium acetate                                |
| • Ag <sub>2</sub> O                  | Silver(I) oxide                               |
| • AIBN                               | Azobisisobutyronitrile                        |
| • AlCl <sub>3</sub>                  | Aluminium chloride                            |
| • B(OMe) <sub>3</sub>                | Trimethylborate                               |
| • BBr <sub>3</sub>                   | Boron tribromide                              |
| • BCl <sub>3</sub>                   | Boron trichloride                             |
| • BEt <sub>3</sub>                   | Triethyl borate                               |
| • BF <sub>3</sub>                    | Boron trifluoride                             |
| • BINAP                              | (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) |
| • BnBr                               | Benzyl bromide                                |
| • BOM                                | Benzyloxymethyl acetal                        |
| • BOMCl                              | Benzyl chloromethyl ether                     |
| • Br <sub>2</sub>                    | Bromine                                       |
| • Bu <sub>3</sub> SnCl               | Tributyl tin chloride                         |
| • C <sub>2</sub> H <sub>5</sub> MgBr | Ethylmagnesium bromide                        |
| • CAN                                | Ceric ammonium nitrate                        |
| • CBr <sub>4</sub>                   | Tetrabromomethane                             |
| • CBzCl                              | Benzyl chloroformate                          |
| • CCl <sub>4</sub>                   | Carbontetrachloride                           |
| • CH <sub>3</sub> CN                 | Acetonitrile                                  |
| • CH <sub>3</sub> COOH               | Acetic acid                                   |
| • CH <sub>3</sub> COONa              | Sodium acetate                                |
| • CHCl <sub>3</sub>                  | Chloroform                                    |
| • CO <sub>2</sub>                    | Carbon dioxide                                |
| • COCl <sub>2</sub>                  | Cobalt(II)chloride                            |
| • Cs <sub>2</sub> CO <sub>3</sub>    | Cesium carbonate                              |
| • CuBr                               | Copper(I)bromide                              |
| • CuI                                | Copper(I)iodide                               |
| • DBU                                | 1,8-Diazabicyclo[5.4.0]undec-7-ene            |
| • DCC                                | <i>N,N'</i> -Dicyclohexylcarbodiimide         |
| • DCM                                | Dichloromethane                               |
| • DDQ                                | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone     |
| • DEE                                | Diethylether                                  |
| • DHP                                | Dihydropyran                                  |
| • DIAD                               | Diisopropyl azodicarboxylate                  |
| • DIBAL                              | Diisobutylaluminium hydride                   |
| • DIPEA                              | <i>N,N</i> -Diisopropylethylamine             |
| • DMA                                | Dimethylacetamide                             |
| • DMAD                               | Dimethyl acetylenedicarboxylate               |
| • DMAP                               | 4-Dimethylaminopyridine                       |
| • DMF                                | Dimethylformamide                             |
| • DMSO                               | Dimethyl sulfoxide                            |
| • DNA                                | Deoxyribonucleic acid                         |
| • Et <sub>2</sub> O                  | Diethyl ether                                 |
| • Et <sub>3</sub> N                  | Triethyl amine                                |
| • EtOH                               | Ethanol                                       |
| • H <sub>2</sub>                     | Hydrogen                                      |
| • H <sub>2</sub> O                   | Water                                         |

|                                                 |                                                             |
|-------------------------------------------------|-------------------------------------------------------------|
| • H <sub>2</sub> O <sub>2</sub>                 | Hydrogen peroxide                                           |
| • H <sub>2</sub> SO <sub>4</sub> ..             | Sulphuric acid                                              |
| • HBF <sub>4</sub>                              | Fluoroboric acid                                            |
| • HCl                                           | Hydrochloric acid                                           |
| • HNO <sub>3</sub>                              | Nitric acid                                                 |
| • HOAc                                          | Acetic acid                                                 |
| • Hr                                            | Hour                                                        |
| • I <sub>2</sub>                                | Iodine                                                      |
| • IBX                                           | 2-iodoxybenzoic acid                                        |
| • <i>i</i> Pr <sub>2</sub> Net                  | <i>N,N</i> -Diisopropylethylamine,                          |
| • K <sub>2</sub> CO <sub>3</sub>                | Potassium carbonate                                         |
| • K <sub>3</sub> PO <sub>4</sub>                | Potassium phosphate                                         |
| • KOBut                                         | Potassium <i>tert</i> butoxide                              |
| • KOH                                           | Potassium hydroxide                                         |
| • LDA                                           | Lithium diisopropylamide                                    |
| • LiAlH <sub>4</sub>                            | Lithium aluminium hydride                                   |
| • LiCl                                          | Lithium chloride                                            |
| • LiClO <sub>4</sub>                            | Lithium perchlorate                                         |
| • LiHMDS                                        | Lithium bis(trimethylsilyl)amide                            |
| • LiI                                           | Lithium iodide                                              |
| • LiOH                                          | Lithium hydroxide                                           |
| • mCPBA                                         | meta-Chloroperoxybenzoic acid                               |
| • Me <sub>2</sub> SO <sub>4</sub>               | Dimethyl SulfateMeCN                                        |
| • MeI                                           | Methyl iodide                                               |
| • MeOH                                          | Methanol                                                    |
| • Mg                                            | Magnesium                                                   |
| • MnO <sub>2</sub>                              | Manganese dioxide                                           |
| • MOM                                           | Methoxymethyl ether                                         |
| • MOMCl                                         | Methyl chloromethyl ether                                   |
| • Na <sub>2</sub> CO <sub>3</sub>               | Sodium carbonate                                            |
| • Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub> | Sodium dithionite                                           |
| • NaBH <sub>3</sub> CN                          | Sodium cyanoborohydride                                     |
| • NaBH <sub>4</sub>                             | Sodium borohydride                                          |
| • NaClO <sub>4</sub>                            | Sodium perchlorate                                          |
| • NaCN                                          | Sodium cyanide                                              |
| • NaH <sub>2</sub> PO <sub>4</sub>              | Monosodium phosphate                                        |
| • NaNO <sub>2</sub>                             | Sodium nitrite                                              |
| • NaOAc                                         | Sodium acetate                                              |
| • NaOMe                                         | Sodium methoxide                                            |
| • NBS                                           | <i>N</i> -Bromosuccinimide                                  |
| • <i>n</i> Bu <sub>3</sub> SnCl                 | <i>n</i> butyltin chloride                                  |
| • <i>n</i> BuLi                                 | <i>n</i> Butyllithium                                       |
| • NH <sub>3</sub>                               | Ammonia                                                     |
| • NH <sub>4</sub> Cl                            | Ammonium chloride                                           |
| • NH <sub>4</sub> OAc                           | Ammonium acetate                                            |
| • NiCl <sub>2</sub> dppp                        | 1,3-Bis(diphenylphosphino)propane nickel(II) chloride       |
| • NMO                                           | <i>N</i> -Methylmorpholine- <i>N</i> -Oxide                 |
| • NMP                                           | <i>N</i> -Methyl-2-pyrrolidone                              |
| • NTG                                           | Nitroglycerin                                               |
| • O <sub>2</sub>                                | Oxygen                                                      |
| • OsO <sub>4</sub>                              | Osmium tetroxide                                            |
| • P(OEt) <sub>3</sub>                           | Triethyl phosphite                                          |
| • PCC                                           | Pyridinium chlorochromate                                   |
| • PCl <sub>2</sub> dppf                         | [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) |
| • Pd(0)                                         | Palladium(0)                                                |
| • Pd(OAc) <sub>2</sub>                          | Palladium(II)acetate                                        |
| • Pd(PPh <sub>3</sub> ) <sub>4</sub>            | Tetrakis(triphenylphosphine)palladium(0)                    |

|                                                      |                                                   |
|------------------------------------------------------|---------------------------------------------------|
| • Pd/C                                               | Palladium on carbon                               |
| • Pd <sub>2</sub> (dba) <sub>3</sub>                 | Tris(dibenzylideneacetone)dipalladium(0)          |
| • PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | Bis(triphenylphosphine)palladium(II)dichloride    |
| • PhH                                                | Benzene                                           |
| • PhMe                                               | Toluene                                           |
| • PhNTf <sub>2</sub>                                 | <i>N</i> -Phenyl-bis(trifluoromethanesulfonimide) |
| • PIFA                                               | Phenyliodine bis(trifluoroacetate)                |
| • POCl <sub>3</sub>                                  | phosphorus oxychloride                            |
| • PPH <sub>3</sub>                                   | Triphenylphosphine                                |
| • PPTS                                               | Pyridinium <i>p</i> -toluenesulfonate             |
| • PTSA                                               | <i>p</i> -Toluenesulfonic acid                    |
| • pTSA                                               | <i>p</i> -Toluenesulfonic acid                    |
| • Rt                                                 | retention factor                                  |
| • sBuLi                                              | <i>sec</i> -butyllithium                          |
| • SnCl <sub>4</sub>                                  | Tin(IV)chloride                                   |
| • TBAF                                               | Tetra- <i>n</i> -butylammonium fluoride           |
| • <i>t</i> BuOH                                      | <i>tert</i> -Butyl alcohol                        |
| • <i>t</i> BuOLi                                     | lithium <i>tert</i> -butoxide                     |
| • Tf <sub>2</sub> O                                  | Trifluoromethanesulfonic anhydride                |
| • TFA                                                | Trifluoroacetic acid                              |
| • THF                                                | Tetrahydrofuran                                   |
| • TMEDA                                              | Tetramethylethylenediamine                        |
| • TsOH                                               | <i>p</i> -Toluenesulfonic acid                    |
| • Zn                                                 | Zinc                                              |

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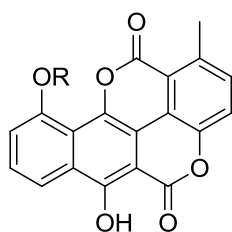
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## Chapter 1: Introduction, Literature Review and Aims: The Gilvocarcins

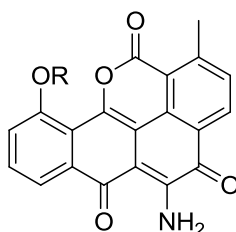
### 1.1 The Naphthopyranone Derivatives

Aromatic polyketides featuring an oxygenated benzo-fused naphthopyranone motif form one of the major families of secondary metabolites found in nature and they are a major source of novel chemotherapeutics. These compounds are particularly known for their anti-bacterial, anti-viral, anti-tumour and enzyme inhibitory activity.<sup>1,2</sup> As a result of their unique structural complexities and profound biological importance this class of compounds is of considerable interest to synthetic organic chemists. A few representatives of the class of oxygenated benzo-fused naphthopyranones are chartreusin **1**, chrymutasin A **2**, arnottin **1** **3**, hayumicinone **4** and gilvocarcins **5** as shown in **Figure 1**.<sup>1,2</sup>

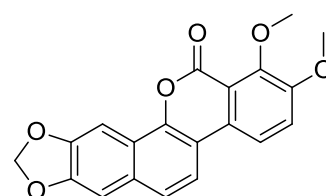


Chartreusin **1**

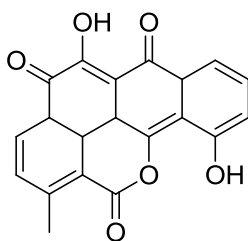
(R = 2-O- $\alpha$ -digitaloxy- $\beta$ -D-fucosyl)



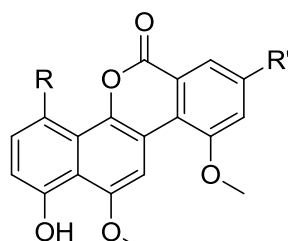
Chrymutasin A **2**



Arnottin **1** **3**



Hayumicinone **4**



R = sugar  
R' = alkyl or alkenyl

Gilvocarcins **5**

Representatives of the class of oxygenated benzo-fused naphthopyranone

**Figure 1**

Chartreusin **1**, a naphthopyranone derivative with an aromatic polyketide glycoside structure, was first isolated in 1959 from the cultures of *Streptomyces chartreusis*.<sup>2</sup> It is known for its potent anti-tumor activity against various cell lines such as murine P388 and L1210 leukemia cell lines, and B16 melanoma cells along with significant antibacterial activity. Unfortunately, there have been some setbacks in the development of chartreusin **1** as a drug due to its unfavorable pharmacokinetics caused by its rapid biliary excretion and slow gastrointestinal absorption.<sup>3</sup>

Chrymutasin A **2**, is a glycosidic antibiotic produced by the fermentation of a mutant strain of *Streptomyces chartreusis* obtained by NTG (*N*-methyl-*N'*-nitro-*N*-nitrosoguanidine) treatment. The mutant strain produces chrymutasin, which differs in the aglycone moiety from chartreusin **1**, and related compounds.<sup>4</sup> The anti-tumor activity of chrymutasin A **2** has been found to be better *in vivo* than that of chartreusin **1**, the cytotoxic activity against cell lines *in vitro* is equivalent, and the antimicrobial spectrum is narrower.<sup>4</sup>

Arnottin I **3** is a dibenzo[*c,h*]chromen-6-one derivative and was isolated from the bark of *Xanthoxylum arnottianum* by Ishikawa and co-workers in 1977 and no biological activity to-date has been reported.<sup>5</sup>

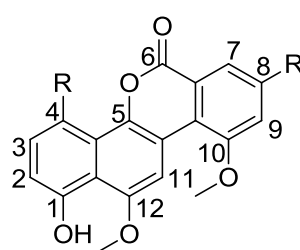
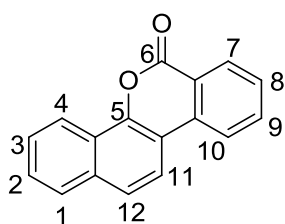
Hayumicinone **4** and related compounds are isolated from the culture of a strain of *Actinomadura sp.*, ATCC 55432. These compounds are known for their anti-tumour as well and antibacterial activity.<sup>6</sup>

Gilvocarcins **5** are a family of polyketide metabolites isolated from *Streptomyces sp.* Members of this family are known to exhibit exceptionally high antimicrobial and anti-tumour activities and very low toxicity.<sup>7</sup> The gilvocarcins **5** are discussed in more detail in the following sections of this **Chapter**.

### 1.1.1 The Gilvocarcin Family

This distinctive class of potent anticancer antibiotics often referred to as gilvocarcin-type aryl-*C*-glycosides exhibit low toxicity and have been shown to be especially resistant to enzymatic and acidic hydrolysis. The gilvocarcins **5** and structurally related compounds are polyketide glycosides which are the metabolites of a variety of *Streptomyces sp.* and constitute a novel class of aryl *C*-glycoside antibiotics or glycosylarenes. These compounds share a common tetracyclic aromatic nucleus, the 6*H*-dibenzo[*c,h*]chromen-6-one **6**, to

which a carbohydrate moiety is attached at C-4, an alkyl group at C-8, two methoxyl groups at C-10 and C-12 and a phenolic group is present at C-1, **7** as shown in **Figure 2**.<sup>7,8,9</sup>



R = carbohydrate

R' = an alkyl or alkenyl group

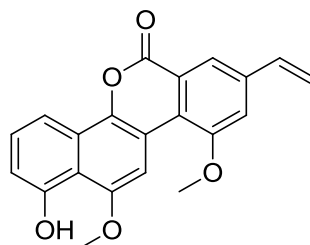
6*H*-Dibenzo[*c,h*]chromen-6-one **6**

Substituted 6*H*-dibenzo[*c,h*]chromen-6-one **7**

**Figure 2**

### 1.1.2 Members of the Gilvocarcin Family

In 1980, Hatano *et al.* published a report describing the isolation of an antibiotic (antibiotic B-21085), which he first presented at the Annual Meeting of the Agricultural Chemical Society of Japan in 1971, as yellow crystals from the mycelium of the culture broth of *Streptomyces* sp. No. B-21085 and named it toromycin.<sup>10</sup> Toromycin was found to be active against gram-positive bacteria, mycobacteria, mycoplasma, DNA viruses (vaccinia virus and Herpes Simplex virus) and some bacteriophages.<sup>10</sup> Later the same year Horii *et al.* elucidated the structure of toromycin aglycone **8**, describing it as 6-oxo-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran skeleton with a C-glycosyl group at C-4, a vinyl group at C-8 and two methoxy groups at C-10 and C-12 (**Figure 3**).<sup>11</sup>



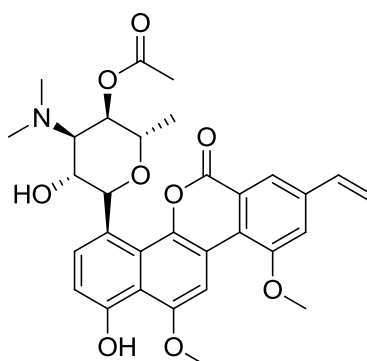
Toromycin aglycone **8**

**Figure 3**



In the same year, Sehgal *et al.* isolated an antibiotic from the fermentation broth of *Streptomyces ravidus* and named it ravidomycin **9**. It was found to exert strong inhibitory effect on gram positive bacteria and displayed potent anti-tumour activity (**Figure 4**).<sup>12</sup>

The following year, in 1981, Findlay *et al.* proposed the structure for ravidomycin **9** based on the results of chemical and spectroscopic studies and found it to be consisting of a 6-oxo-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran skeleton with an amino sugar at C-4, a vinyl group at C-8, two methoxy groups at C-10 and C-12 and a phenolic hydroxyl group at C-1 (**Figure 4**).<sup>13,14</sup>

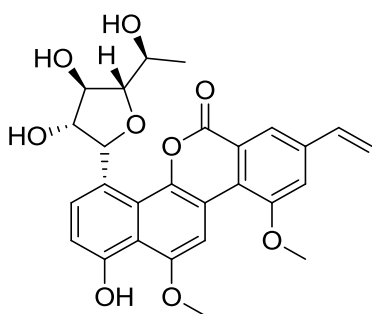
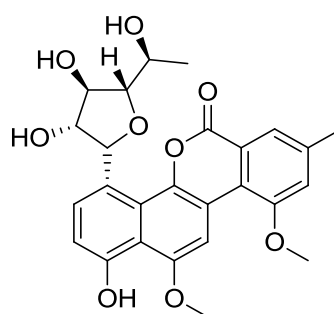


Ravidomycin **9**

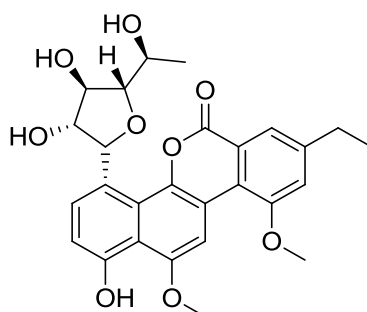
**Figure 4**

Nakano *et al.* reported the isolation of two related compounds in 1981, gilvocarcin V **10** and gilvocarcin M **11** (**Figure 5**). These compounds were discovered in culture broths of *Actinomycete* DO-38, which was subsequently recognized to be a new species and was named *Streptomyces gilvotanareus* (NRRL 11382). Both gilvocarcin V **10** and M **11** were isolated from the ethyl acetate extract and by using silica gel chromatography. These compounds were found to exhibit activity against gram-positive bacteria and experimental tumours such as mouse sarcoma 180 and mouse leukemia P388.<sup>15</sup>

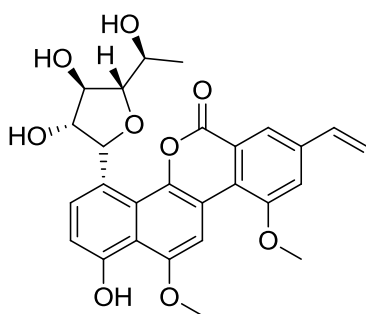
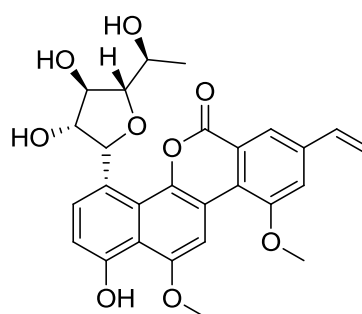
The same year, Takahashi *et al.* also described gilvocarcin V **10** and M **11**, isolated from *Streptomyces gilvotanareus*, and established the structure and stereochemistry by means of X-ray crystallographic analysis. Gilvocarcin M **11** contains a methyl group at C-8 while gilvocarcin V **10** analogue contains a vinyl substituent at the same position. Other features were found to be similar in both the molecules with a fucose (in furanosyl form) present at C-4, two methoxy groups each at C-10 and C-12 and a phenolic hydroxyl group at C-1 was observed (**Figure 5**).<sup>16</sup>

Gilvocarcin V **10**Gilvocarcin M **11**Structures of Gilvocarcin V **10** and M **11****Figure 5**

Later the same year, Balitz and co-workers, isolated and elucidated the structure of another gilvocarcin: gilvocarcin E **12** along with gilvocarcin V **10** and M **11** from a culture of *Streptomyces anandii* subsp. *araffinosus* strain C-22437 (ATCC-31431). Gilvocarcin E **12** was found to have similar structural features to gilvocarcin V **10** and M **11** with the only difference being in the presence of an ethyl group at C-8 (**Figure 6**).<sup>17</sup>

Gilvocarcin E **11****Figure 6**

Two years later, Jain *et al.* isolated toromycin **13** from a strain of *Streptomyces species* (AAC-324) and from chemical and spectroscopic studies inferred its structure and stereochemistry. From these studies, it was realised that toromycin **13** and gilvocarcin V **10** are the same compounds (**Figure 7**), though the name gilvocarcin V **10** is more widely accepted.<sup>18</sup>

Toromycin **13**Gilvocarcin V **10**

Toromycin **13** and gilvocarcin V **10** are structurally identical

**Figure 7**

In 1989, Weiss *et al.* identified the components of the yellow antibiotic chrysomycin, which was first reported in 1955 by Strelitz *et al.*, as chrysomycin A **14** and chrysomycin B **15** as depicted in **Figure 8**.<sup>19, 20</sup> These differed only by the substituent at C-8, which is a vinyl group in chrysomycin A **14** and a methyl group in chrysomycin B **15**. Structural elucidation of chrysomycins A **14** and B **15** revealed a very close similarity with gilvocarcin V **10** and M **11** respectively. The only difference being in the C-glycosidic side-chain, which is a methylpentose in the gilvocarcins **5** and a 3,5-dimethylpentose in the chrysomycins (**14** and **15**).<sup>20</sup> The same year, Matson *et al.* illustrated the effectiveness of chrysomycins A **13** and B **14** in inhibiting three mouse tumours and P388 lymphatic leukemia.<sup>21</sup>

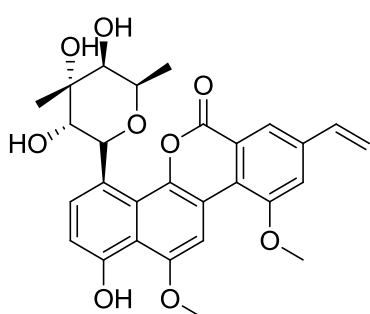
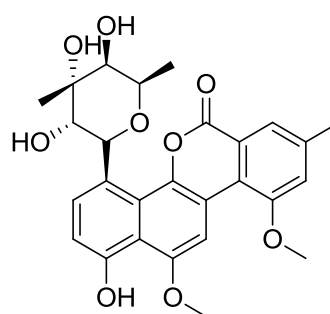
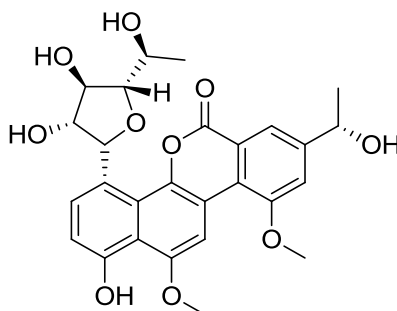
Chrysomycin A **14**Chrysomycin B **15**

**Figure 8**

Recently, a new antimicrobial polyketide glycoside – Gilvocarcin HE **16** (**Figure 9**) has been isolated along with three known compounds, gilvocarcins E **12**, V **10** and M **11** from the ethyl

acetate extract of *Streptomyces* sp., QD01-2. The structure has been established by spectroscopic analysis, X-ray single crystal diffraction and CD spectra. The new compound showed potent antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Candida albicans*, and showed weak cytotoxicity against the MCF-7, K562 and P388 cancer cell lines.<sup>7</sup>



Gilvocarcin HE **16**

**Figure 9**

In this section we have discussed a variety of gilvocarcin-type polyketide glycosides. As observed from their structural features they all contain a 6*H*-dibenzo[*c,h*]chromen-6-one **6** skeleton with two methoxy groups at C-10 and C-12 and a phenolic hydroxyl group at C-1 (Figure 2). They only differ in the presence of different carbohydrate moieties present at C-4 as well as a variety of different substituents at C-8 such as vinyl, methyl or alkyl. Structurally, this group of naturally occurring polyketide antibiotics are known as gilvocarcin-type polyketide glycosides as the gilvocarcins **5** are the prototypes of this class.<sup>7</sup> We will focus further discussion on the aglycones of gilvocarcins, since the intercalation of aglycones is known to be the main source of free energy of binding in any intercalated drug–DNA complex.<sup>22</sup> Furthermore, the focus of this PhD is on the 6*H*-dibenzo[*c,h*]chromen-6-one **6** (Figure 2) skeleton, rather than the carbohydrate moiety.

## 1.2 Biological Importance of Gilvocarcins and Mechanism of Action

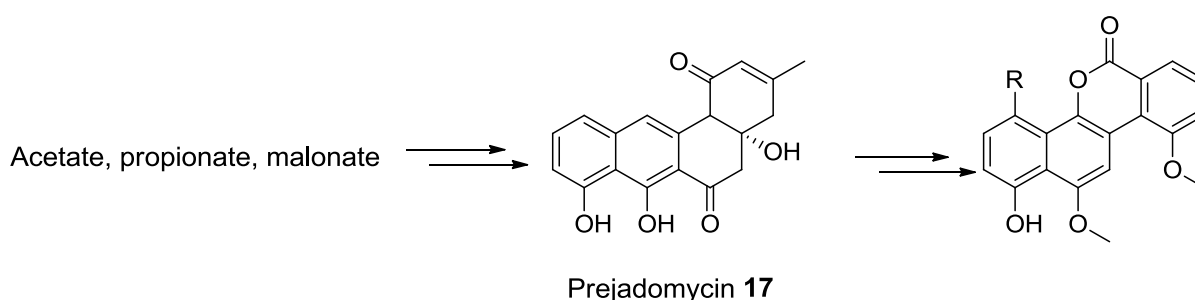
As has already been mentioned, gilvocarcins **5** are known for their remarkable antitumour activity and exceptionally low toxicity. Wei *et al.*, Tomita *et al.* and Shishido *et al.* have in separate studies suggested that Gilvocarcin V **10** interacts with double-stranded DNA by intercalation.<sup>23, 24, 25</sup> They are known to be DNA targeting agents with potent intercalating ability, leading to covalent binding or strand breaking upon photoirradiation. The presence of

the vinyl group as present in Gilvocarcin V **10** is known to enhance anti-tumour activity under irradiation with low-energy UV or visible light. Recent studies have proven that it undergoes photoactivated [2+2]-cycloaddition with thymine residues of DNA under irradiation with low energy UV or visible light.<sup>26, 27</sup> The carbohydrate moiety seems to be essential for the observed gilvocarcin-mediated cross-linking of histone H3 or heat shock protein GRP78 with DNA resulting in the disruption of DNA replication and transcription.<sup>28</sup>

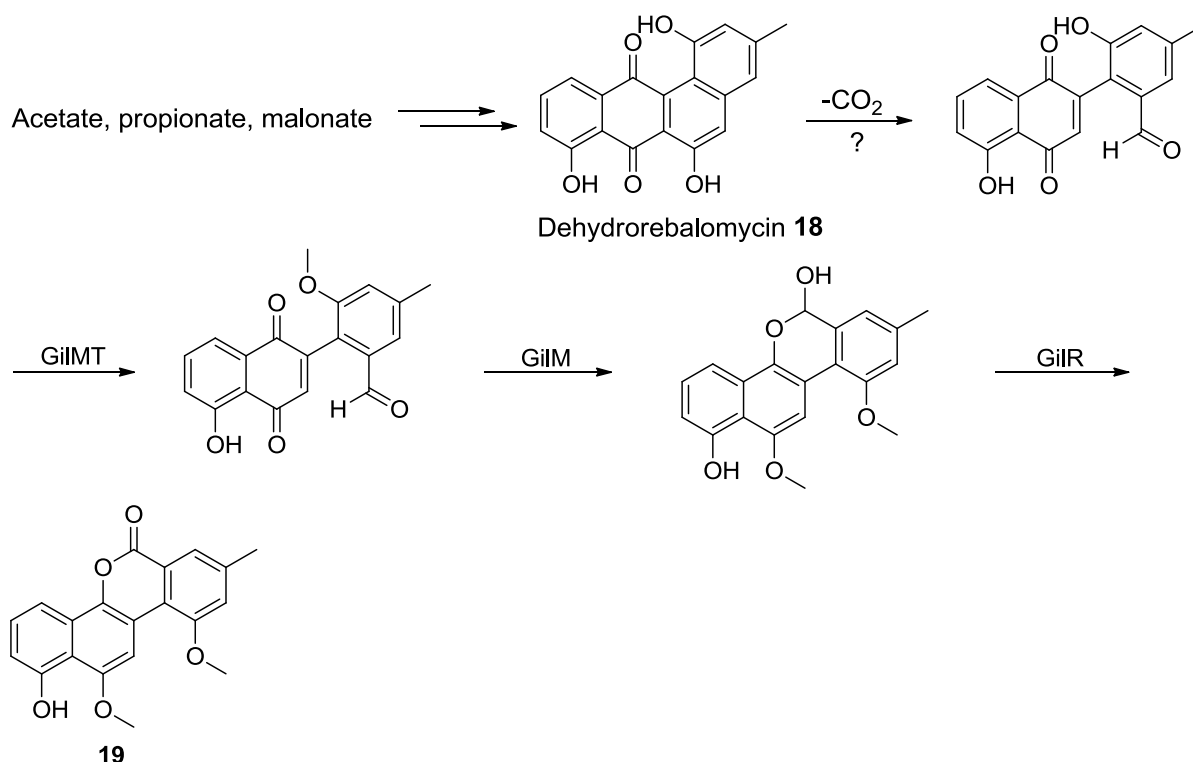
Gilvocarcins **5** are also known to exhibit strong antibacterial and antiviral properties however, the characteristic poor solubility of these molecules seems to be a major obstacle in their development as antibiotics.<sup>27</sup>

### 1.3 Biosynthesis of Gilvocarcins

Initial biosynthetic studies started with the addition of various <sup>13</sup>C labelled acetate and propionate substrates to the fermentation broth of *Streptomyces gilvotanareus* to elucidate the biosynthetic origin of carbon atoms in the unique 6*H*-dibenzo[*c,h*]chromen-6-one **6** skeleton of the gilvocarcins **5** (**Figure 2**).<sup>27</sup> Genetic and biochemical analysis of gilvocarcin V **10** gave way to the biosynthesis which started with the isolation and sequence analysis of its biosynthetic gene cluster from *Streptomyces griseoflavus* Go 3592.99 The gilvocarcin gene (gil) cluster was found to consist of twenty seven open reading frames (ORFs), including genes encoding the polyketide synthase (PKS) as well as several post-PKS tailoring and deoxysugar biosynthetic genes. Biosynthetically, the polyketide-derived backbone of the gilvocarcins **5** is produced from acetate, propionate, and malonate subunits by the action of a type-II polyketide synthase (PKS). It has been proven that the early biosynthetic steps generate an angucyclinone intermediate (e.g., prejadomycin **17** and dehydrorabelomycin **18**) that subsequently undergoes a complex structural rearrangement via an oxidative C5–C6 bond cleavage to form the benzonaphthopyranone skeleton of the gilvocarcins **5** (**Scheme 1** and **2**).<sup>29, 30, 31, 32</sup>



**Scheme 1:** Biosynthesis of gilvocarcins **5**.<sup>29</sup>



**Scheme 2:** Biosynthesis of gilvocarcin M aglycone **19**.<sup>29</sup>

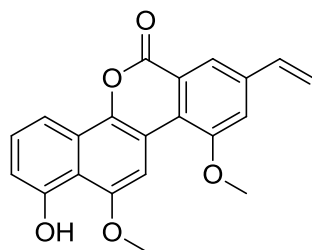
## 1.4 Selected Synthetic Approaches Towards Gilvocarcin Aglycones

As a result of the biological activity of these compounds and their interesting structures, many attempts at the synthesis of these compounds have been made. In this section a few selected syntheses will be highlighted.

### 1.4.1 Jung and Jung Approach Towards the Synthesis of O-Benzyl-Gilvocarcin M Aglycon **20**.<sup>33</sup>

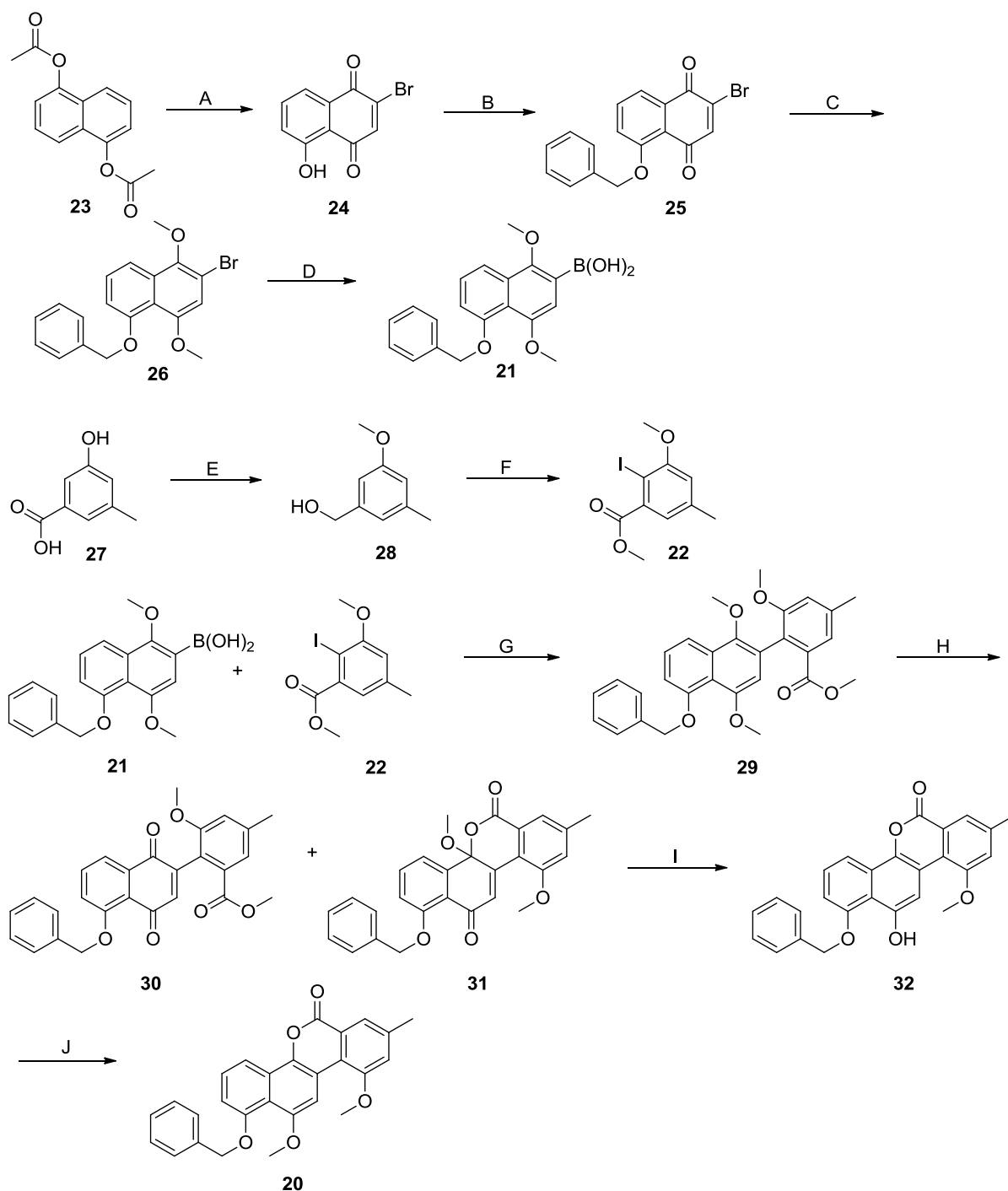
Jung and Jung in 1988, demonstrated a short and efficient synthesis of the 1-benzylated aglycone of gilvocarcin M **20** as presented in **Scheme 3**. The key step of the synthesis is a Suzuki-Miyaura cross coupling reaction between [5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl]boronic acid **22** and **22**. The desired boronic acid **21** was prepared starting from 1,5-diacetoxynaphthalene **23** which was converted into 2-bromo-5-hydroxynaphthoquinone **24** in two steps. Benzylation of the free naphthol group **25** followed and subsequent reduction of the quinone followed by dimethylation gave the boronic acid precursor **26**. The second fragment, a substituted aryl iodide **22** was synthesized from 3-hydroxy-5-methylbenzoic acid

**27.** Methylation followed by reduction of 3-hydroxy-5-methylbenzoic acid **27** afforded the alcohol **28** which on treatment with *n*butyllithium followed by the addition of iodine and oxidation to the ester gave the desired iodide **22**. A Suzuki coupling reaction between these two synthesized fragments gave a biaryl compound **29** which was subjected to ceric ammonium nitrate oxidation to obtain a mixture of two products **30** and **31**. Treatment of the mixture of **30** and **31** to zinc in acetic acid gave the desired hydroxylactone **32**. Methylation of the free phenol yielded the desired benzyl protected aglycone of gilvocarcin M **20**. The synthetic scheme presents an efficient approach towards the generation of the benzyl protected aglycone of gilvocarcin M **20** but if the same approach could be used for the total synthesis of gilvocarcin M **11** is still doubtful. Though, this synthetic methodology could also be applied to the synthesis of aglycone of gilvocarcin V **33** (**Figure 10**).



Aglycone of gilvocarcin V **33**

**Figure 10**

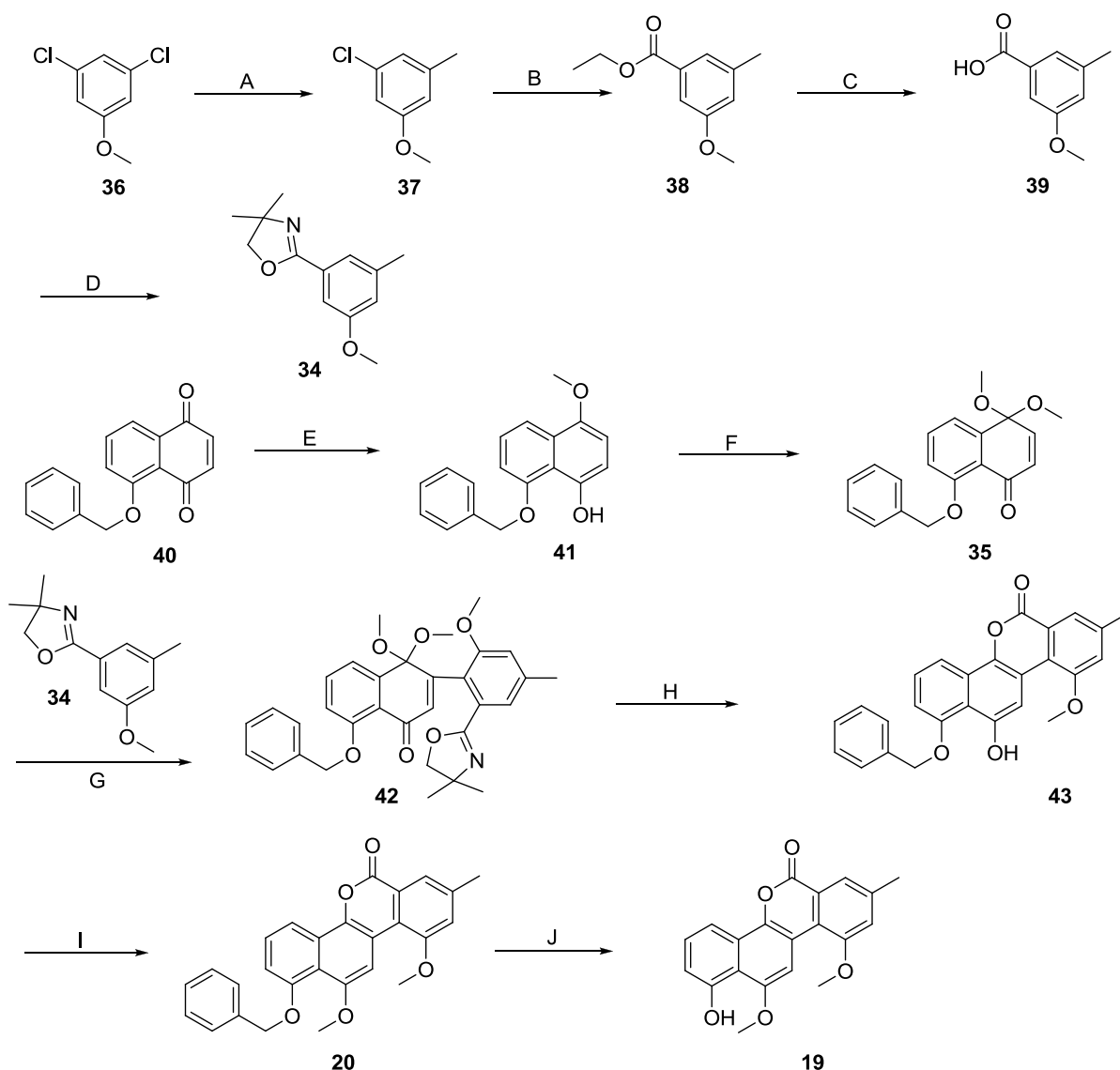


**Scheme 3:** Reagents and conditions: A) 1) NBS, AcOH; 2) H<sub>2</sub>O, H<sub>2</sub>SO<sub>4</sub>, EtOH, 91%; B) Ag<sub>2</sub>O, BnBr, 85%; C) Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, Me<sub>2</sub>SO, 87%; D) *n*BuLi/THF, -100°C, B(OMe)<sub>3</sub>, -78 °C-25 °C, H<sup>+</sup>; E) MeI, K<sub>2</sub>CO<sub>3</sub>, acetone, LiAlH<sub>4</sub>, 89%; F) 1) *n*BuLi, I<sub>2</sub>, hexane, Et<sub>2</sub>O(10:1), -78°C, 59%; 2) PCC, MnO<sub>2</sub>/HOAc, NaCN/MeOH, 91%; G) Na<sub>2</sub>CO<sub>3</sub>/EtOH, Pd(PPh<sub>3</sub>)<sub>4</sub>, 61%; H) CAN, CH<sub>3</sub>CN, H<sub>2</sub>O; I) Zn, HOAc, 52% **29** and 37% **30**; J) 1) Me<sub>2</sub>SO, K<sub>2</sub>CO<sub>3</sub>, acetone, 100%; 2) H<sub>2</sub>, Pd/C Ac<sub>2</sub>O, Pyr/DMAP, 80%.<sup>33</sup>



#### 1.4.2 Hart's Approach Towards the Synthesis of Defucogilvocarcin M **19**.<sup>34</sup>

The key step in the synthesis described by Hart involved the methyl aluminium bis-(2,6-di-*t*-butyl-4-methylphenoxide) (MAD)-mediated conjugate addition of an aryllithium derived from oxazoline **34** to the naphthoquinone monoketal **35** (**Scheme 4**). The oxazoline derivative **34** was prepared in four steps starting from 3,5-dichloroanisole **36**. Treatment of the starting material **36** with Rieke magnesium and dimethyl sulfate gave **37** followed by another reaction with Rieke magnesium which afforded ester **38** on exposure to ethyl chloroformate. Subsequent saponification gave the carboxylic acid **39**. Finally, sequential treatment of **39** with thionyl chloride, 2-amino-2-methylpropanol and thionyl chloride yielded oxazoline **34**. On the other hand, the naphthoquinone ketal **35** was prepared in four steps starting from juglone, which was first converted to benzyl ether **40**, followed by reduction and methylation of the least hindered hydroxyl group to yield **40**. The naphthol obtained was converted to monoketal **35** using an electrochemical procedure. The coupling of naphthoquinone monoketal **35** and oxazoline **34** was performed using methyl aluminium bis-(2,6-di-*t*-butyl-4-methylphenoxide) (MAD) as a key reagent to give **42**. Ketal and oxazoline hydrolysis, aromatization, and intramolecular lactone formation afforded **43**. Subsequent methylation yielded **20** and hydrogenolysis of the resulting benzyl ether afforded defucogilvocarcin M **19**. This synthetic approach employed by Hart towards the synthesis of the aglycone of gilvocarcin M **19** was efficient and high yielding.

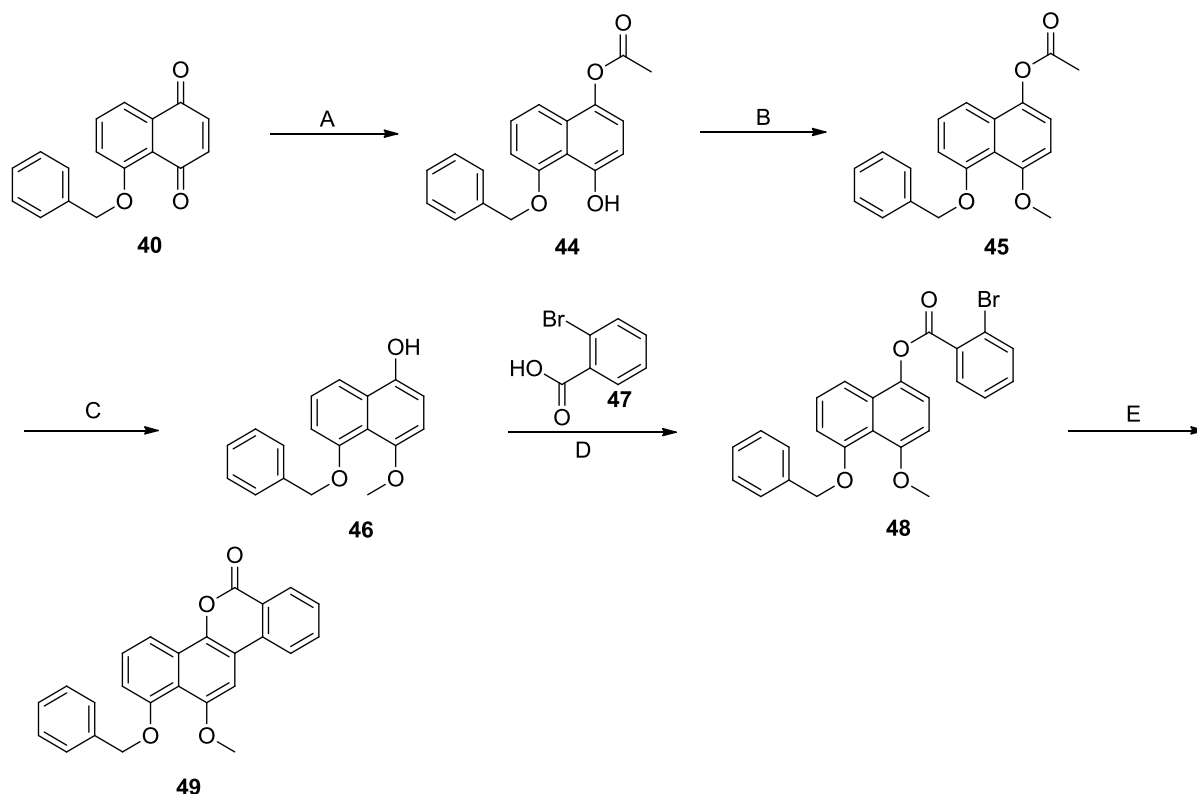


**Scheme 4:** Reagents and conditions: A) 1) Rieke Mg, THF, rt; 2)  $\text{Me}_2\text{SO}_4$ , THF, rt, 53%; B) Rieke Mg,  $\text{ClCO}_2\text{Et}$ ; C) KOH, MeOH- $\text{H}_2\text{O}$  (3:1), heat, 71%; D)  $\text{SOCl}_2$ , PhH, heat;  $\text{HOCH}_2\text{C}(\text{Me})_2\text{NH}_2$ , DCM;  $\text{SOCl}_2$ , 87%; E)  $\text{Na}_2\text{S}_2\text{O}_4$ ,  $\text{H}_2\text{O}$ ,  $\text{Et}_2\text{O}$ ,  $\text{Me}_2\text{SO}_4$ ,  $\text{K}_2\text{CO}_3$ , acetone, heat, 64%; F) anodic oxidation, MeOH, 2%  $\text{LiClO}_4$ , 88%; G)  $n\text{BuLi}$ , THF, MAD, PhMe,  $-78^\circ\text{C}$ , 72%; H) HCl, THF,  $\text{H}_2$ , heat, 95%; I)  $\text{Me}_2\text{SO}_4$ ,  $\text{K}_2\text{CO}_3$ , DCM, heat, 98%; J)  $\text{H}_2$ , Pd/C, THF, 82%.<sup>34</sup>

#### 1.4.3 Deshpande's Approach Towards the Synthesis of Gilvocarcin Aglycones.<sup>35</sup>

As illustrated in **Scheme 5**, Deshpande and co-workers were also able to synthesize gilvocarcin aglycone but the strategy involved the making of the ester that was to become part of the lactone of the final product as the first step. Starting from benzylated juglone **40**, 8-(benzyloxy)-4-acetoxynaphthalen-1-ol **44** was obtained over three steps by utilizing

reduction and selective acetylation. This was followed by methylation **45** and deacetylation which yielded **46**. A DCC-mediated esterification of the resulting product with *O*-bromobenzoic acid **47** afforded benzoate **48** which on treatment with bis(triphenylphosphine)palladium(II)dichloride ( $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ ) promoted the desired cyclization and gave 1-(benzyloxy)-12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **49** skeleton albeit in low yield. The same methodology was then used to synthesize the aglycones of gilvocarcin M **19**, V **33** and E **50**.

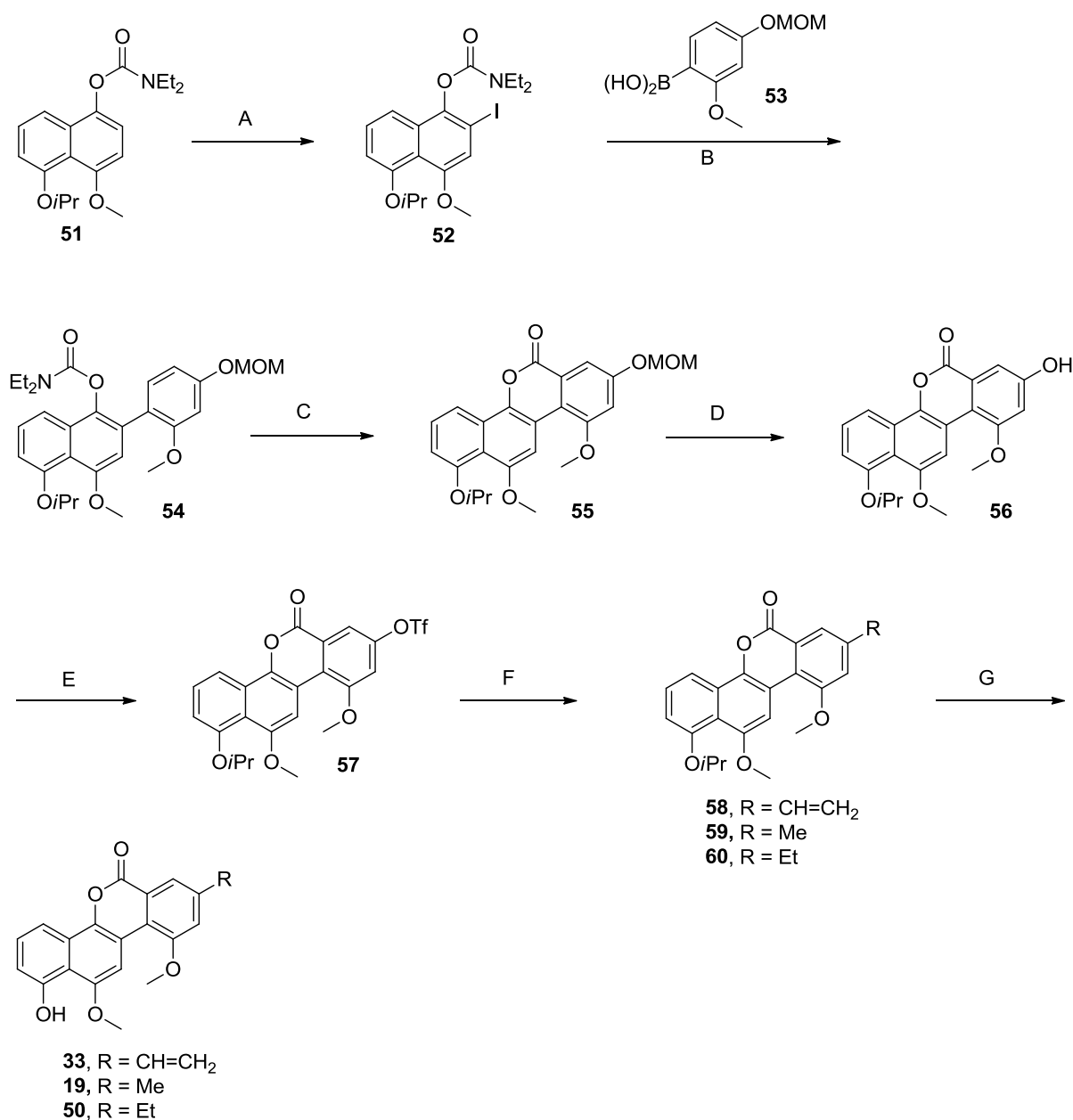


**Scheme 5:** Reagents and conditions: A) Zn,  $\text{Ac}_2\text{O}$ , Py/ $\text{CHCl}_3$ , heat, 80%; B) MeI,  $\text{K}_2\text{CO}_3$ , acetone, heat, 96%; C) KOH, MeOH, 60%; D) DCC, DMAP, DCM, 51%; E)  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ , NaOAc, DMA, 130 °C, 2 hrs, 40%.<sup>35</sup>

#### 1.4.4 Snieckus Approach Towards the Synthesis of Aglycones of Gilvocarcin V **33**, M **19** and E **50**.<sup>36, 37</sup>

James and Snieckus in 1997 and later in 2009 reported the total synthesis of defucogilvocarcin V **32**, M **18** and E **49** as depicted in **Scheme 6**.<sup>36, 37</sup> The key step employed in this case was the remote anionic Fries rearrangement. To carry out the synthesis, a differentially protected trioxxygenated naphthalene species **51** was iodinated and the resulting compound **52** was utilized in a Suzuki-Miyaura cross coupling reaction with a

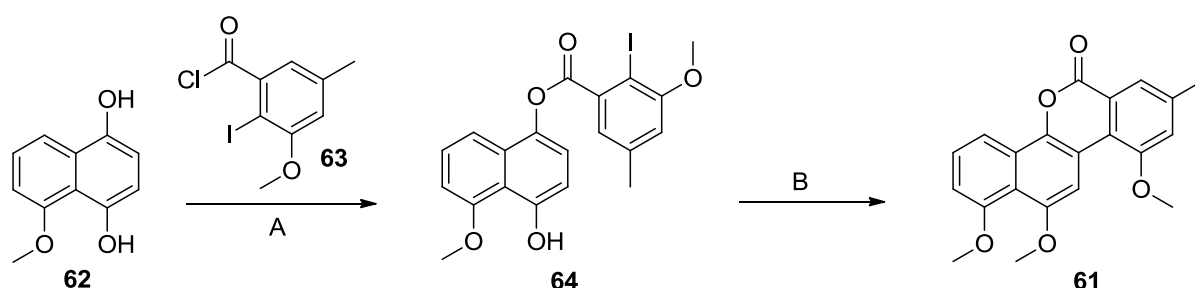
MOM protected arylboronic acid **53** to furnish the biaryl compound **54**. Cyclization to the desired lactone **55** was achieved by using lithium diisopropylamide. Deprotection of the MOM group was carried out under acidic conditions to give **56**, followed by conversion of the free phenolic hydroxyl group into the required triflate **57**. Treatment of **57** with vinyltributyltin under modified Stille conditions (2 mol%  $\text{Pd}_2(\text{dba})_3/\text{LiCl}/(2\text{-furyl})_3\text{P}/\text{NMP}$ ) yielded **58**. Negishi coupling using  $\text{MeZnBr}$  (5 mol%  $\text{NiCl}_2\text{dppp}/\text{THF}$ ) and Suzuki–Miyaura coupling with  $\text{BET}_3$  (5 mol%  $\text{PdCl}_2\text{dppf}/\text{K}_2\text{PO}_4/\text{THF}$ ) yielded the methyl **59** and ethyl **60** analogues respectively. Finally, selective deprotection afforded defucogilvocarcin V **33**, M **19** and E **50** respectively.



**Scheme 6:** Reagents and conditions: A) 1) *s*BuLi/TMEDA/THF/-78°C; 2) I<sub>2</sub>, 94%; B) Pd(0), 95%; C) LDA/THF, reflux, H<sup>+</sup>; D) 1) 50% aq. HOAc, 70%; E) Tf<sub>2</sub>O/Et<sub>3</sub>N/DCM, -78 °C, 81%; F) For R = CH=CH<sub>2</sub> **57**, CH<sub>2</sub>=CHSn[CH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>]<sub>3</sub>, 2 mol% Pd<sub>2</sub>(dba)<sub>3</sub>/LiCl/(2-furyl)<sub>3</sub>P/NMP, rt, 5 hrs, 69%; For R = CH<sub>3</sub> **58**, MeZnBr (5 mol% NiCl<sub>2</sub>dppp, THF, rt, 12 hrs, 75%; For R = C<sub>2</sub>H<sub>5</sub> **59**, BEt<sub>3</sub>(5mol% PdCl<sub>2</sub>dppf, K<sub>3</sub>PO<sub>4</sub>, THF, reflux, 1 hr, 59%; G) BCl<sub>3</sub>, DCM, 0°C, 10 mins, For R = CH=CH<sub>2</sub> **32**, 90%, For, R = CH<sub>3</sub> **18**, 83%, For R = C<sub>2</sub>H<sub>5</sub> **49**, 86%.<sup>36</sup>

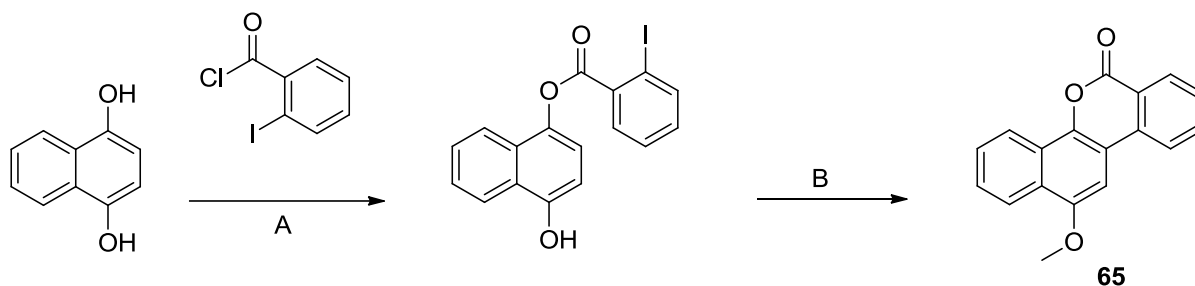
#### 1.4.5 Qabaja and Jones' Approach.<sup>38</sup>

In their synthesis of the benzo[*b*]fluorene skeleton, Qabaja and Jones devised a synthesis of the methoxy derivative of gilvocarcin M aglycone **61**. This product was isolated as an intermediate in their synthesis of benzo[*b*]fluorene. The synthesis of the benzonaphthopyranone was carried out by the reaction of 5-methoxy hydroquinone **62** with 2-iodo-3-methoxybenzoyl chloride **63** which resulted in the generation of an ester **64**. The ester intermediate obtained was first methylated and then subjected to a palladium catalysed intramolecular ring closure reaction to generate *O*-methoxy gilvocarcin M aglycone **61** as shown in **Scheme 7**.



**Scheme 7:** Reagents and conditions: A) DMAP, *i*-Pr<sub>2</sub>NEt, THF, 71%; B) 1) Me<sub>2</sub>SO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, acetone; 2) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, NaOAc, DMA, 75%.<sup>38</sup>

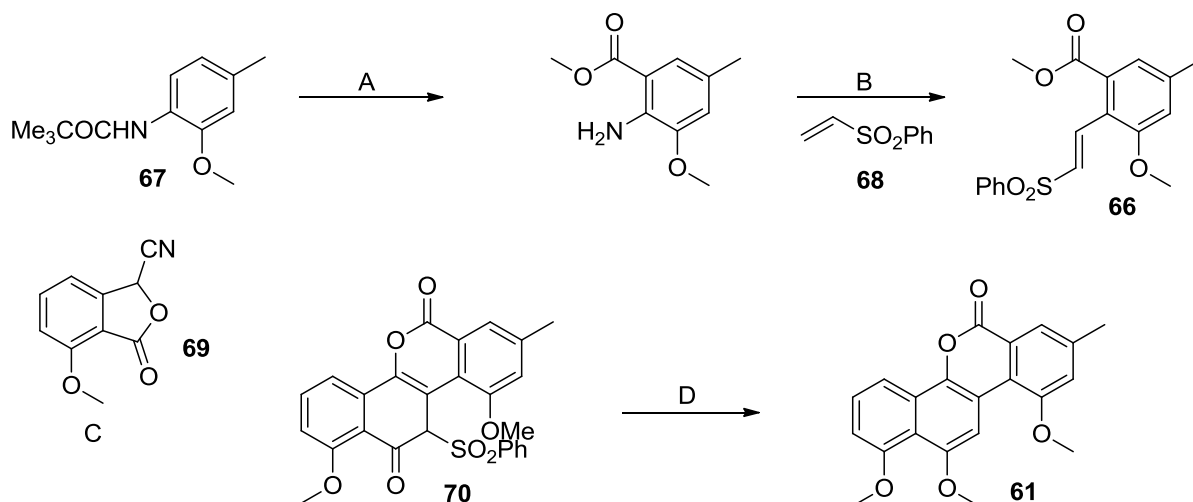
Using the same methodology, the authors also demonstrated the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65**, as depicted in **Scheme 8**, a framework which is native to all the members of the gilvocarcin family.



**Scheme 8:** Reagents and conditions: A) DMAP, *i*-Pr<sub>2</sub>NEt, THF; 88%; B) 1) Me<sub>2</sub>SO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, acetone; 2) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, NaOAc, DMA, 58%.<sup>38</sup>

#### 1.4.6 Patra's Approach Towards the Synthesis of Defucogilvocarcin M.<sup>39</sup>

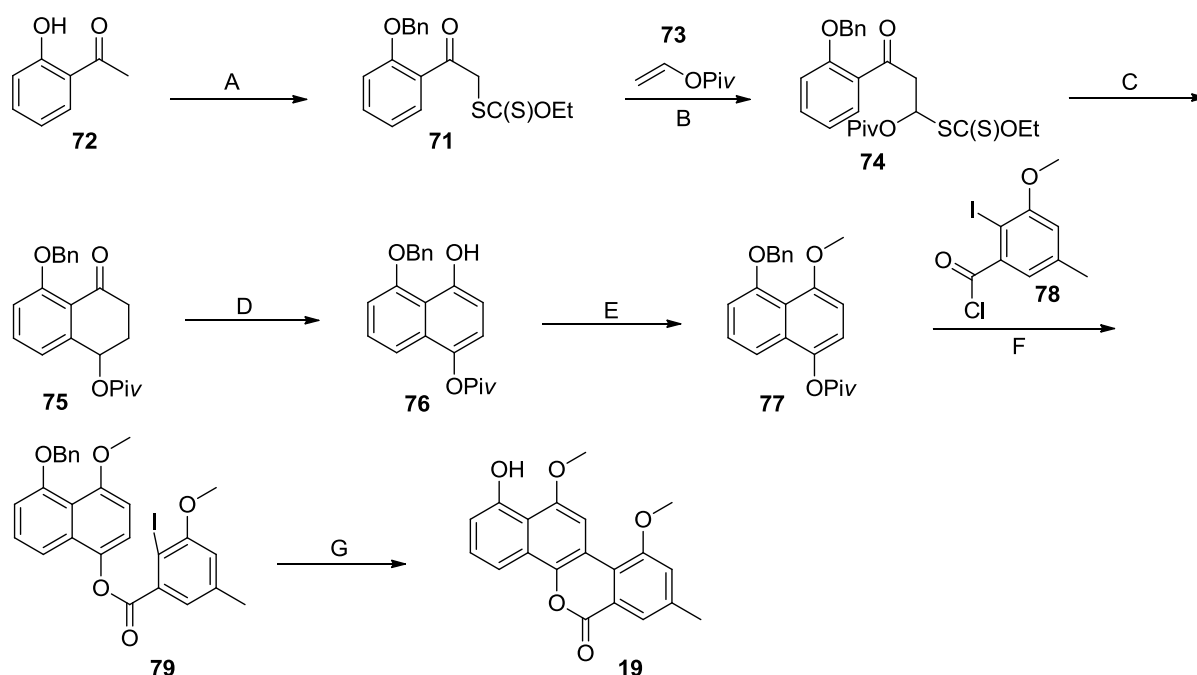
In 2005, Patra *et al.* reported the synthesis of 1-methoxydefucogilvocarcin M **61** employing the Hauser annulation as a key step. A styryl sulfone **66** which was used as an acceptor in the annulation reaction was prepared in four steps from 2-Methoxy-4-methylpivalanilide **67** using a Heck-coupling with vinyl sulfone **68**. Following a reaction with cyanophthalide **69** this afforded the tetracyclic gilvocarcin skeleton **70**. Subsequent radical initiated desulfonation and an aromatization reaction led to the synthesis of 1-methoxy defucogilvocarcin M **61** as illustrated in **Scheme 9**.



**Scheme 9:** Reagents and conditions: A) 1) *n*BuLi, CO<sub>2</sub>, THF, HCl; 2) MeOH, reflux; 3) SOCl<sub>2</sub>, MeOH, reflux, 62%; B) HBF<sub>4</sub>, NaNO<sub>2</sub>, H<sub>2</sub>O, MeOH, Pd(OAc)<sub>2</sub>, reflux, 88%; C) *t*BuOLi, THF, -60 °C, 93-98%; D) 1) Bu<sub>3</sub>SnCl, NaBH<sub>3</sub>CN, AIBN, *t*BuOH, 1 hr, 94%; 2) Me<sub>2</sub>SO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, acetone, 88%.<sup>39</sup>

### 1.4.7 Cortezano-Arellano's Approach Towards Defucogilvocarcin M **19**.<sup>40</sup>

The synthesis described by Cortezano-Arellano started with the generation of the radical precursor **71** from 2-hydroxyacetophenone **72** over three steps. This was followed by the addition of vinyl pivalate **73** along with dilauroyl peroxide (DLP) to afford adduct **74**. Another reaction with DLP facilitated the ring closure to form the desired  $\alpha$ -tetralone **75**. Subsequently, the aromatization of the  $\alpha$ -tetralone **75** was accomplished by performing a bromination followed by the elimination of hydrobromic acid to give **76**. Methylation of the free phenol provided **77**. The reduction of the pivaloyl ester followed by the treatment of the crude naphthol with substituted aromatic acid chloride **78** afforded compound **79**. Finally, a palladium-catalyzed cyclization of **79**, followed by hydrogenolysis of the benzyl ether, gave the aglycone of gilvocarcin M **19**. This generalised synthetic scheme could be used for the synthesis of other aglycones of the gilvocarcin family.

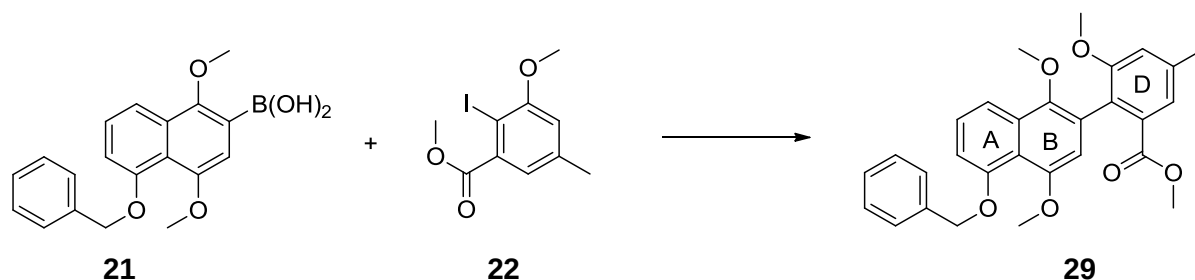


**Scheme 10:** Reagents and conditions: A) 1) BnBr, K<sub>2</sub>CO<sub>3</sub>, DMF, rt; 2) Br<sub>2</sub>, Et<sub>2</sub>O, 0 °C-rt; 3) KSC(S)OEt, acetone, 0 °C-rt, 90%; B) DLP, 1,2-DCE, reflux, 80%; C) DLP, 1,2-DCE, reflux, 42%; D) 1) NBS/Et<sub>2</sub>O, CH<sub>3</sub>CN, 0 °C; 2) DBU, DCM, rt, 87%; E) MeI, K<sub>2</sub>CO<sub>3</sub>, DMF, 80-90 °C, 68%; F) DIBAL, DCM, -78 °C, 81%; G) 1) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, AcONa, DMA, 65%; 2) H<sub>2</sub>, Pd/C, THF, 80%.<sup>40</sup>

## 1.5 Comparative Analysis of the Synthetic Approaches Towards the Gilvocarcin Aglycones

A few selected examples of synthetic approaches towards the synthesis of the aglycones of gilvocarcin antibiotics have been discussed in the previous sections. In this section an analysis of the methodology used will be outlined.

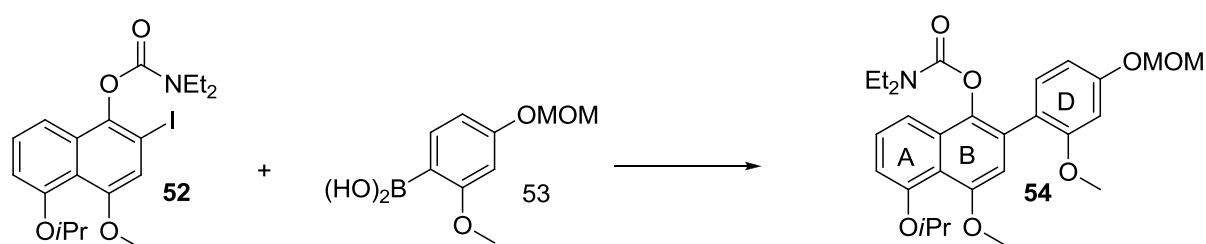
From one of the earliest synthesis described by Jung *et al.* in 1988 it was clear that a key step of the synthetic methodology would be the Suzuki-Miyaura cross coupling reaction to generate biaryl axis between ring B and D as shown in **Scheme 11**.<sup>33</sup>



**Scheme 11:** Reagents and conditions:  $\text{Na}_2\text{CO}_3/\text{EtOH}$ ,  $\text{Pd}(\text{PPh}_3)_4$ , 61%.

The work done by Jung *et al.* laid the foundation for the use of Suzuki-Miyaura cross coupling reaction to generate biaryl axis for the synthesis of gilvocarcin tetracyclic framework.<sup>33</sup> The use of this methodology featured in later syntheses of the same class of compound.

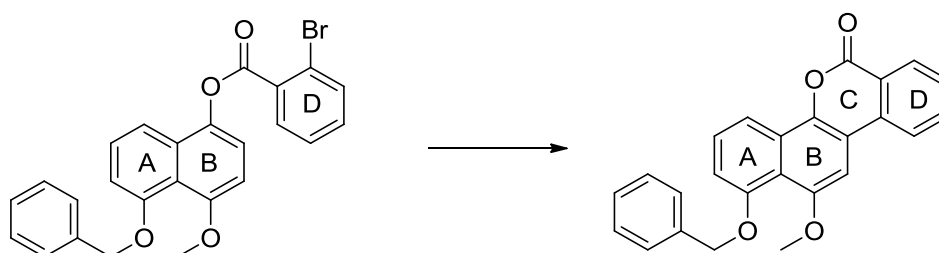
For example, later, in the year 1997 and again in 2009, James and Snieckus also employed palladium catalysed Suzuki-Miyaura cross coupling reaction to form the biaryl axis for the synthesis of aglycones to form linkage between rings B and D of the tetracyclic system as illustrated in **Scheme 12**.<sup>36,37</sup>



**Scheme 12:** Reagents and conditions:  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{DME}/\text{H}_2\text{O}$ , 48 hrs, 95%

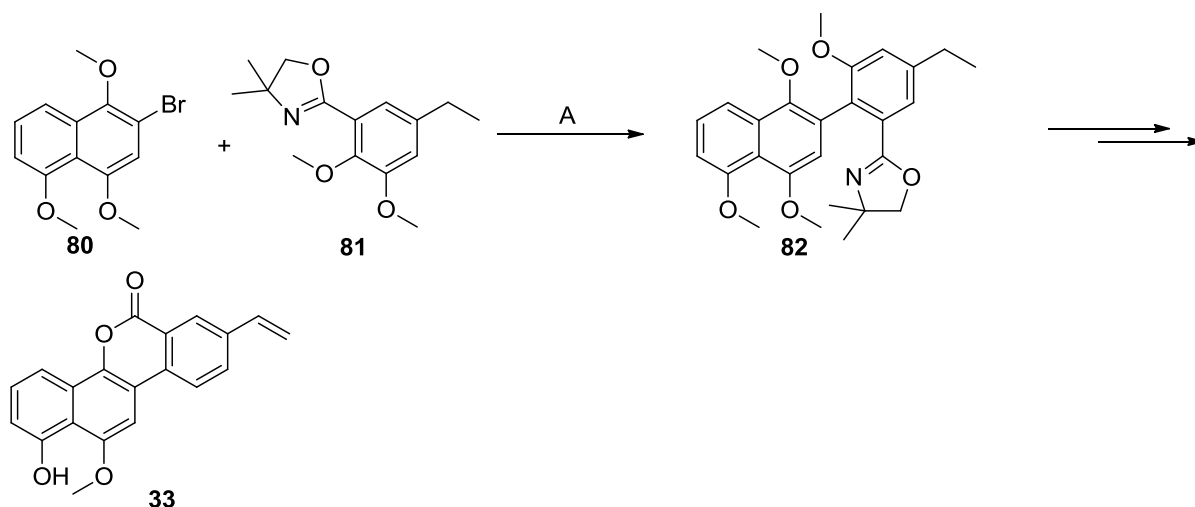


Other related synthetic approaches employed used towards the generation of benzonaphthopyranone skeleton of gilvocarcin family, include the palladium-catalysed intramolecular aryl coupling for ring closure to generate the ring C. This kind of approach was first used by Bringmann *et al.* in 1986 and was used for the synthesis of aglycones of gilvocarcins by Deshpande *et al.*, Qabaja *et al.* and Cortezano *et al.* as discussed in the previous **Sections 1.4.3, 1.4.5 and 1.4.7.**<sup>35,38,40,41</sup> One general example of palladium mediated ring closure to generate ring C of the gilvocarcin framework is depicted in **Scheme 15.**



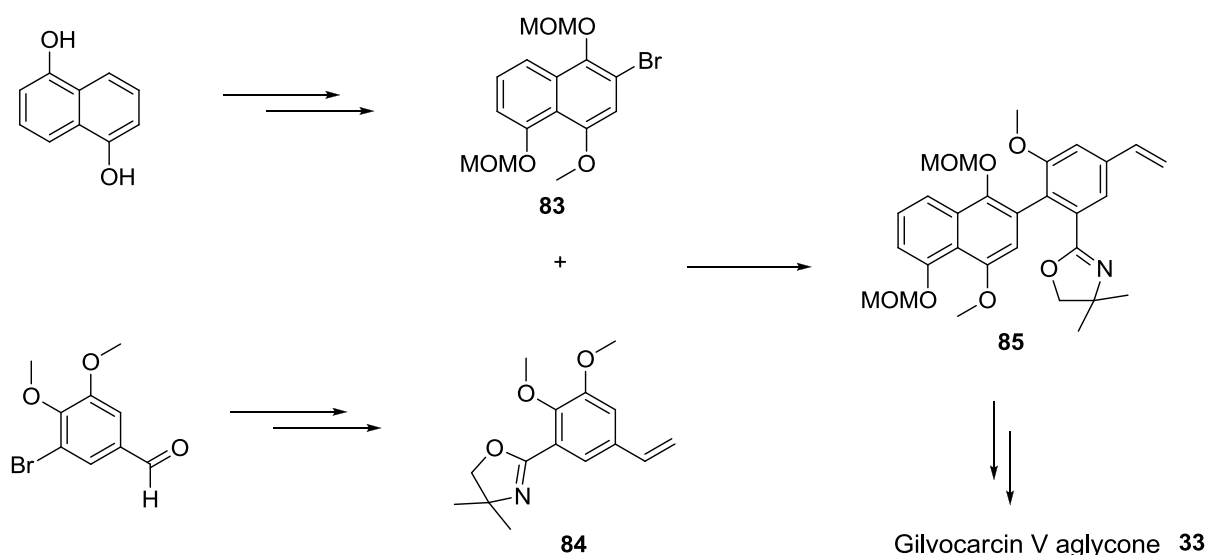
**Scheme 15**

The Meyers coupling reaction also appears to be a common approach for the construction of the desired biaryl axis as shown for example by Hart *et al.* where the authors managed to synthesize aglycone of gilvocarcin V **33** by coupling an appropriately functionalized Grignard precursor of naphthalene **80** with the protected and substituted derivative of benzoic acid **81** via the Meyers nucleophilic aromatic substitution reaction which led to the generation of biaryl coupled product **82** as illustrated in **Scheme 13.**<sup>34</sup>



**Scheme 13:** Reagents and conditions: Reagents and conditions: 1) Mg, I<sub>2</sub>, dry THF, reflux, 0.25 hrs; 2) rt, 15 hrs, 81%

Patten *et al.* have also employed the Meyers coupling reaction between **83** and **84** to generate **85** which could later be converted to aglycone of gilvocarcin V **33** to synthesize the aglycone of gilvocarcin V **33** as shown in **Scheme 14**.<sup>42,43</sup>



**Scheme 14**

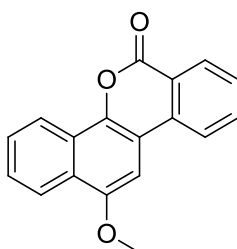
Thus, the use of the Meyers coupling reaction proved to be a versatile and applicable methodology for the synthesis of aglycones of gilvocarcins.

Perhaps not surprisingly the Hauser-Kraus annulation reaction is used extensively for the synthesis of this class of heterocycle. In this thesis only one example is shown but others are evident in the literature. In the example shown Patra *et al.* managed to synthesize aglycone of gilvocarcin M **19** by employing Hauser-Kraus annulation followed by an in-situ lactone generation as illustrated in **Scheme 9**.<sup>39</sup> The authors suggested that the route could be applied towards the synthesis of other polycyclic aromatic natural products like the phenanthrovirdins, and a review published in 2007 outlines the utility of this reaction.<sup>44</sup>

Analyzing the methods that have been used for the synthesis of the benzonaphthopyranone framework, we realized that the Suzuki-Miyaura cross coupling reaction, that has been used extensively in our laboratories could be applied towards the synthesis of 6H-

dibenzo[*c,h*]chromen-6-one **6** frameworks as seen in gilvocarcin as will be described in the following sections.

In order to continue our on-going research in the field of heteropolyaromatics, we wanted to try and develop new methodology for the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65** motif which is a general framework of all the molecules of the gilvocarcin family (**Figure 12**). Later, we hope to extend the methodology to the synthesis of more complex counterparts and finally, various gilvocarcin aglycones.

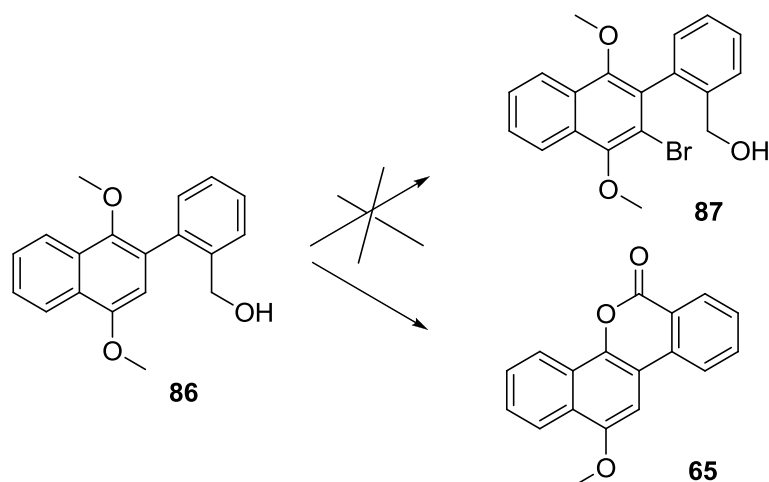


12-Methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65**

**Figure 12**

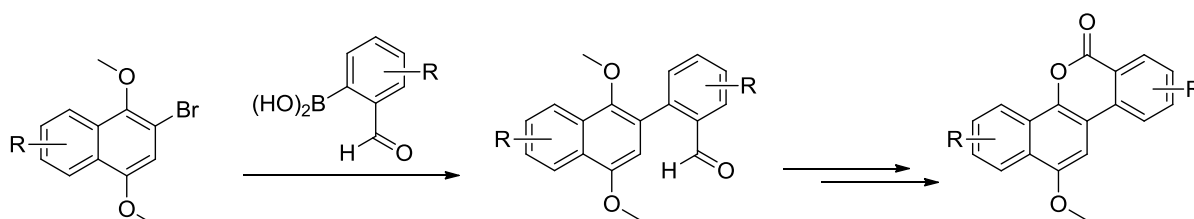
### 1.6 Related Work Done Previously at Wits University on the Synthesis of Chromen-6-ones

During the work carried out by Ms Reynolds for her MSc research project, an unexpected and interesting observation was made. It was noted that the treatment of biaryl alcohol **86** with *N*-bromosuccinimide led to an unexpected ring closure, which resulted in the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65** instead of resulting in bromination of the electron rich naphthalene ring to afford **87** (**Scheme 12**).<sup>45</sup>



### Scheme 16

As a part of this PhD research project, we wanted to investigate this unprecedented reaction resulting in an intramolecular ring closure carried out by *N*-bromosuccinimide and determine the exact mechanism of the reaction as well as subject other substrates to these conditions to ascertain if this was a general reaction. To synthesize the substrates required for the reaction, a key Suzuki-Miyaura cross coupling reaction between a brominated and protected substituted naphthoquinone moiety and a substituted formylphenyl boronic acid would be used. We would then be in a position to test the *N*-bromosuccinimide induced intramolecular ring closure reaction as described in general terms in **Scheme 17**. The next section will introduce the key Suzuki-Miyaura cross-coupling reaction.

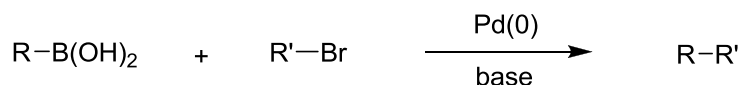


### Scheme 17

### 1.7 Palladium Catalyzed Suzuki-Miyaura Cross-Coupling Reaction

Carbon-carbon (C-C) bond formation is one of the most important aspects of organic chemistry. Suzuki, Miyaura and Yamada laid the foundation for one of the most useful palladium-catalyzed C-C bond formation reactions which is now commonly known as the Suzuki-Miyaura cross coupling reaction. The work was first published in 1979 and reported

coupling reactions of alkenyl boronates with alkenyl bromides in the presence catalytic amount of tetrakis(triphenylphosphine)palladium(0) and a base as shown in **Scheme 18**.<sup>46</sup>



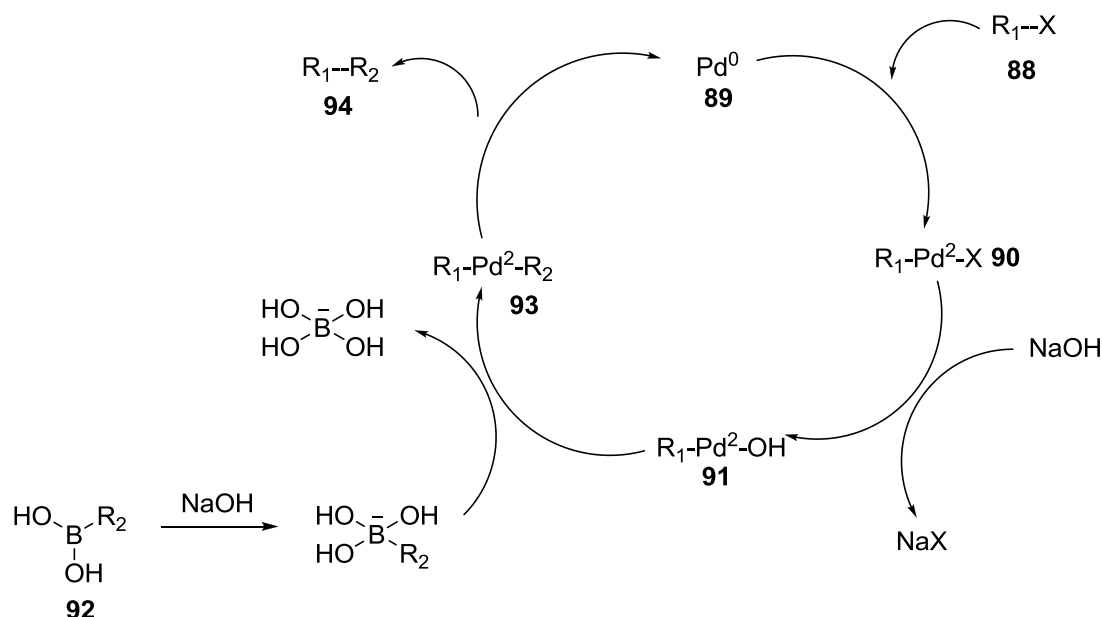
**Scheme 18**

Since then, vast and extensive research has been carried out by Miyaura, Yamada, and Suzuki and a number of other groups which has led to vast improvements in this methodology. Developments have been made in the way of reaction scope, ability to conduct couplings at very low catalyst loadings, using less harsh reaction conditions and also recently with the use of microwave irradiation, which dramatically reduces the time taken for completion of the reaction.<sup>47,48</sup> Furthermore, it is now possible to cross-couple hindered substrates, and even asymmetric molecules could be coupled.<sup>47,49</sup> A large variety of substrates apart from boronic acids, including potassium trifluoroborates, organoborates and boronate esters and triflates could also be used.<sup>47</sup> For this extensive work in palladium-catalyzed cross coupling reactions, Richard F. Heck and Eiichi Negishi along with Akira Suzuki won the Nobel Prize in Chemistry in 2012.

### 1.7.1 Mechanism of Suzuki-Miyaura Cross Coupling Reaction

The major advantage of this reaction is that it can be carried out under relatively mild conditions and with a wide variety of boronic acids, both commercially available and unique substrates could be used. Most boronic acids are less toxic than other organometallic compounds.<sup>50</sup> The reaction uses a palladium(0) complex as catalyst and the most commonly used catalyst is tetrakis(triphenylphosphine)palladium(0) which could be synthesized previously or made *in situ*.<sup>50</sup> One major drawback of this reaction is that all oxygen must be excluded from the reaction system to keep the catalyst active by preventing catalyst oxidation.<sup>50</sup>

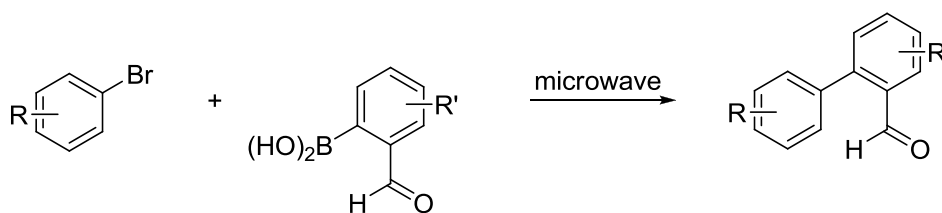
The mechanism of the Suzuki-Miyaura cross coupling reaction could be explained through a general catalytic cycle which involves the oxidative addition-transmetalation-reductive elimination sequences as outlined in **Scheme 14**.<sup>51,52</sup>



Scheme 19

The first step involves the oxidative addition of the carbon electrophile **88** to the palladium(0) species **89** to obtain organo-palladium intermediate **90**. This intermediate reacts with a base (in this case sodium hydroxide) to give rise to the key intermediate R<sub>1</sub>-Pd<sup>2</sup>-OH **91**.<sup>53</sup> Here, the base comes into play by offering the counter-ion to the halide, which forms a salt, and prevents the reverse reaction.<sup>51</sup> The following step is the transmetalation of the nucleophilic carbon from the boron complex **92** to the organo-palladium species to generate intermediate R<sub>1</sub>-Pd<sup>2</sup>-R<sub>2</sub> **93**. Base also plays an important role in this transmetalation step.<sup>53</sup> As organo-boron compounds are weakly electrophilic in nature, the coordination of the negatively charged base to the boron atom helps in improving the nucleophilicity of the organic group to be transferred. The last step in the catalytic cycle is the reductive elimination of the cross-coupling product **94** and regeneration of the palladium(0) species **89**.<sup>53</sup>

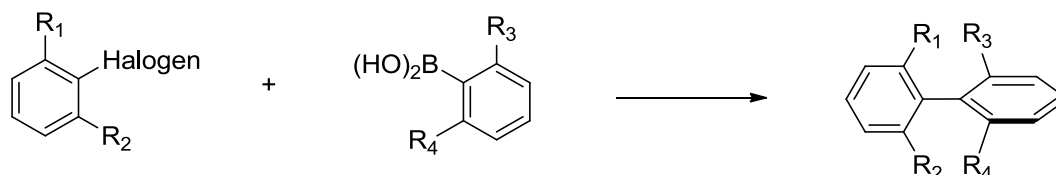
The Suzuki-Miyaura cross coupling reaction has been used extensively in this PhD as it is one of the most versatile synthetic procedures for the generation of biaryl compounds.<sup>48</sup> However, most of the classical procedures are associated with relatively long reaction times.<sup>48</sup> In 2007, Sharma *et al.* reported an efficient method for conducting this coupling reaction under microwave irradiation, with the advantage of improved reaction rates and reduced reaction times (**Scheme 20**).<sup>48</sup> This is the methodology that we often used during the course of this PhD.



Scheme 20

### 1.7.2 Atropisomerism in molecules with biaryl axis

Today, the Suzuki–Miyaura coupling reaction is certainly one of the most widely used method for the construction of the biaryl axis due to its great versatility and relatively environmental friendly nature. One important aspect of this reaction is that if the biaryl axis formed is restricted in rotation axial chirality can result otherwise known as atropisomerism. Atropisomerism or also referred to as helical chirality, is a type of stereoisomerism that arises from the hindered rotation about the  $sp^2$ - $sp^2$  (aryl-aryl) carbon-carbon single bond in axially chiral biaryls.<sup>54</sup> This phenomenon arises due to the presence of at least two bulky substituents in the *ortho* position to the biaryl bond.<sup>56</sup> as shown in **Scheme 21**.<sup>56</sup>



Scheme 21

These axially chiral biaryl compounds have attracted significant attention because of the growing number of known biologically active natural products that contain the biaryl motif for example, vancomycin, steganone, and a class of compounds known as the michellamines.<sup>54</sup> The rigid biaryl unit is also a key feature in the sartan family of drugs for high blood pressure: losartan, valsartan, irbesartan, or candesartan.<sup>54</sup> The stereogenic axis also affords rigid molecular frameworks to design highly efficient tools in asymmetric synthesis, for example chiral ligands like BINAP.<sup>57</sup>

In reference to the examples discussed previously, intermediate **29** depicted in the paper by Jung using Suzuki-Miyaura cross coupling reaction as shown in **Scheme 3**, could offer

hindered rotation across the biaryl axis as all the *ortho* positions across the biaryl axis are occupied this is as an example of atropisomerism (**Figure 13**).<sup>33</sup>

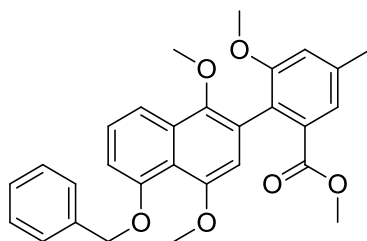


**Figure 13**

Having discussed in detail about the gilvocarcin family of antibiotics and studied the various methodologies undertaken in the past to synthesize their benzonaphthopyranone skeletons, we planned to undertake the synthesis of benzonaphthopyranone motif based on the Suzuki-Miyaura cross coupling reaction and *N*-bromosuccinimide ring closure reaction as undertaken in the past in the organic chemistry laboratories of the University of the Witwatersrand.

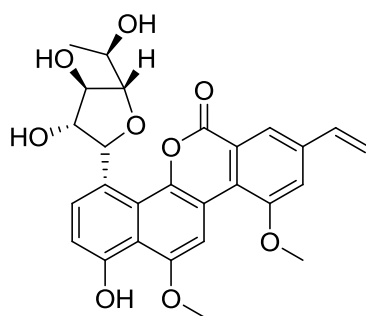
In the following **Chapter**, an approach to the synthesis of the gilvocarcin skeleton using Suzuki-Miyaura cross coupling reaction and the *N*-bromosuccinimide ring closure reaction as key steps will be described.



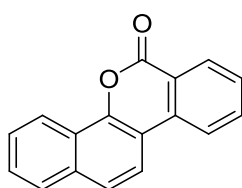
## Chapter 2: Results and Discussion: Synthetic Approaches to the 6*H*-dibenzo[*c,h*]chromen-6-one Analogues as found in Gilvocarcins

### 2.1 Introduction

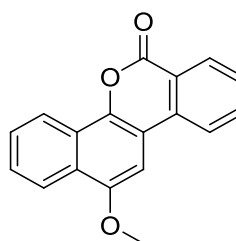
As has been outlined in the previous **Chapter**, gilvocarcins **5** and closely related polyketide metabolites represent a small but major class of novel C-glycoside antibiotics isolated from *Streptomyces sp.* which are known for their high anti-tumour and antibacterial activity and exceptionally low toxicity. All these compounds share a common tetracyclic anti-tumour nucleus, 6*H*-dibenzo[*c,h*]chromen-6-one **6**, with gilvocarcin V **10** being the most prominent member of this class. The importance of these glycoside antibiotics engendered our interest towards the synthesis of the gilvocarcin backbone, namely the 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65** nucleus (**Figure 14**). Only a few syntheses have been reported for the synthesis of gilvocarcin V **10** and its aglycone **33**. Most of these approaches employ harsh conditions, use expensive chemicals or are highly time consuming. In this section, we will discuss the synthesis of the 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65** motif using a novel *N*-bromosuccinimide induced ring closure reaction which was discovered in our laboratories. This unusual reaction in the presence of *N*-bromosuccinimide and air leads to generation of the benzonaphthopyranone skeleton from suitable substituted biaryl precursors. In this PhD we have also attempted to elucidate a possible mechanism of this reaction and additionally address the applicability of this methodology to the synthesis of gilvocarcin V **10** and related molecules in the future.



Gilvocarcin V **10**



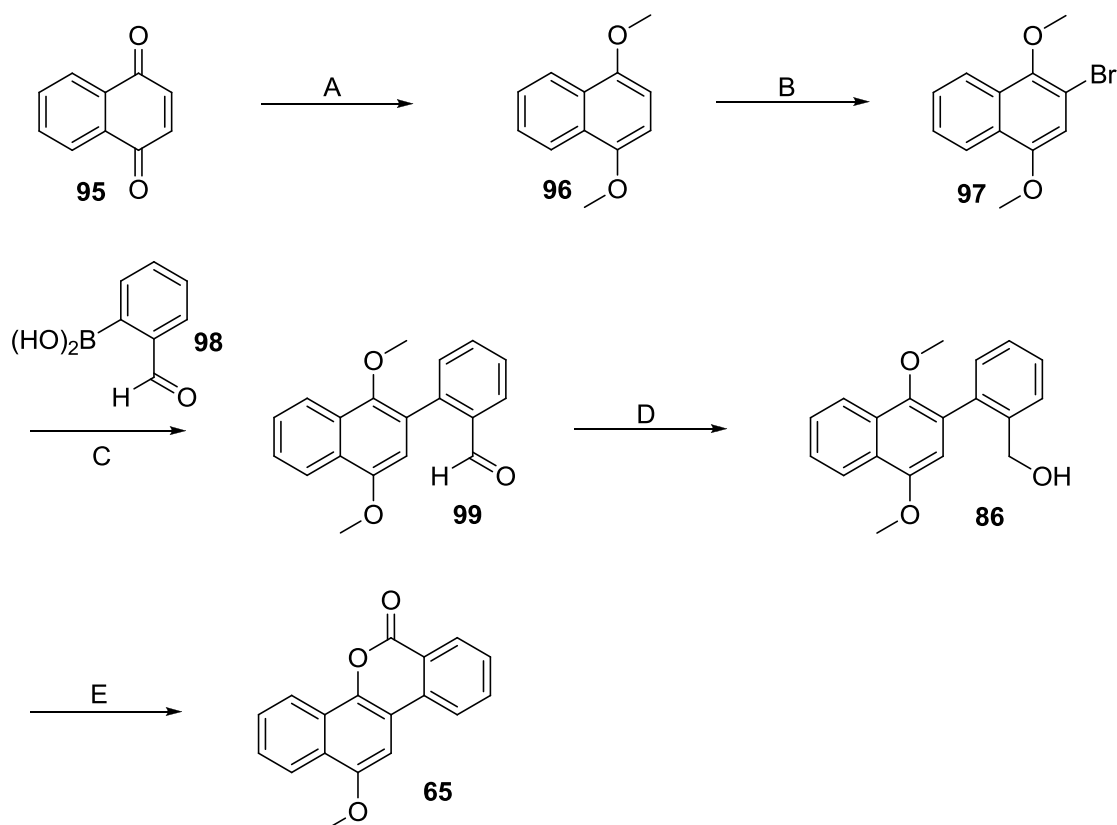
6*H*-dibenzo[*c,h*]chromen-6-one **6**



12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65**

**Figure 14**

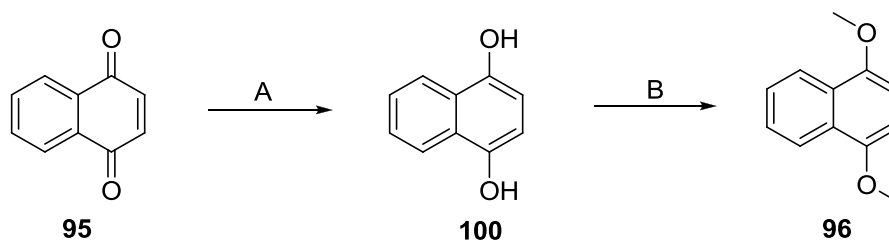
## 2.2 Synthesis of 12-Methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65**



**Scheme 22:** Proposed synthetic strategy for the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65**: Reagents and conditions: A)  $\text{Na}_2\text{S}_2\text{O}_4$ , DEE,  $\text{H}_2\text{O}$ , rt; 2)  $\text{K}_2\text{CO}_3$ ,  $\text{Me}_2\text{SO}_4$ , acetone; B) NBS, DCM, rt; C) 2-formylphenyl boronic acid,  $\text{Pd}(\text{PPh}_3)_4$ , CsF, DMF, microwave irradiation; D)  $\text{LiAlH}_4$ , dry THF; E) NBS, DCM, atmospheric conditions.

The scheme shown above illustrates our initial synthetic plans to achieve the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65**. Starting with the commercially available 1,4-naphthoquinone **95** we planned to reduce the quinone followed by subsequent protection to obtain 1,4-dimethoxynaphthalene **96**, (which is also commercially available). Monobromination at the *ortho* position would lead to the formation of a substrate **97** for Suzuki-Miyaura cross coupling reaction with 2-formylphenyl boronic acid **98** to eventually afford the compound **99** containing a biaryl axis. Reduction of the carbonyl group of **99** would produce the benzylic alcohol **86**, our substrate for the novel *N*-bromosuccinimide-mediated ring closure to afford the desired backbone **65**.

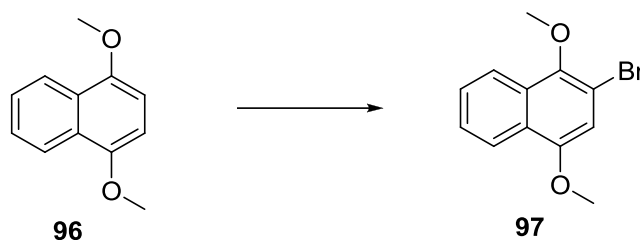
### 2.2.1 Synthesis of 1,4-Dimethoxynaphthalene **96**



**Scheme 23:** Reagents and Conditions: A)  $\text{Na}_2\text{S}_2\text{O}_4$ , DEE,  $\text{H}_2\text{O}$ , rt, 1 hr; B)  $\text{K}_2\text{CO}_3$ ,  $\text{Me}_2\text{SO}_4$ , acetone, reflux, 18 hrs, 85%

The starting point of the synthetic scheme was the reduction and then protection of the commercially available 1,4-naphthoquinone **95** as 1,4-dimethoxynaphthalene **96**, which was achieved using a procedure available in literature.<sup>58</sup> Sodium dithionite, a reducing agent, reduces 1,4-naphthoquinone **95** to naphthalene-1,4-diol **100**. The dark brown colour of 1,4-naphthoquinone **95** disappeared during the course of reaction and the mixture changed in colour to produce a clear solution confirming completion of the reduction. The product so obtained was immediately used in the next step owing to its inherent instability and tendency to oxidize back to naphthoquinone in the presence of air. Subsequent to the work up and the removal of solvent, the intermediate product **100** was immediately dissolved in dry acetone and potassium carbonate was again added to it under inert conditions assisted with vigorous stirring. Potassium carbonate being a base abstracts a proton from the diol **100**, leaving a nucleophile capable of reacting with the electrophilic methyl group from the dimethyl sulfate which was added to the reaction mixture after fifteen minutes. The reaction progress could also be confirmed by a change in colour as the diol, which is being light brown in acetone turned to dark brown after addition of the base, indicating the formation of a resonance stabilized anion. Upon addition of dimethyl sulfate to this anion, the dark colour disappeared after some time which indicated that the anion was being quenched. The reaction was stirred under reflux for a further eighteen hours and was collected as a white crystalline solid after work up and column chromatography in 85% yield. The product **96** so obtained was characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and the spectroscopic data correlated well with the values reported in the literature.<sup>58</sup>

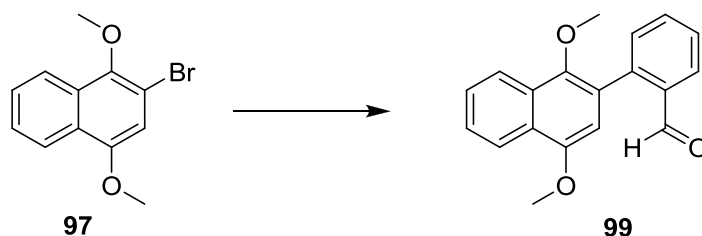
### 2.2.2 Synthesis of 2-Bromo-1,4-dimethoxynaphthalene **97**



**Scheme 24:** Reagents and Conditions: NBS, DCM/acetone, rt, 18 hrs, 84%

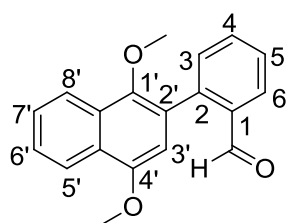
Having successfully synthesized 1,4-dimethoxynaphthalene **96**, we now wished to brominate it at the position *ortho* to the methoxy group to obtain a substrate for the Suzuki-Miyaura cross-coupling reaction. The desired product was obtained by dissolving 1,4-dimethoxynaphthalene **96** in dichloromethane and allowing it to react with *N*-bromosuccinimide at room temperature. The yield of the reaction was not very high as *N*-bromosuccinimide is not readily soluble in dichloromethane. Heating under reflux did not improve the yield, but resulted in decomposition, which was seen through thin layer chromatography. However, the addition of acetone, which acts as co-solvent and aids in dissolution *N*-bromosuccinimide helped improving the yield of reaction. When the reaction was tested in acetone as solvent, the starting material **96** was consumed but with a low yield of product **97**. Thus the best solvent system for the reaction was dichloromethane containing a few milliliters of acetone. Subsequent to work-up and column chromatography, the product **97** was obtained in 84% yield as a light pink oil which solidified on standing. Spectroscopic analysis of the product was in agreement with that in the literature.<sup>59</sup>

### 2.2.3 Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)benzaldehyde **99**



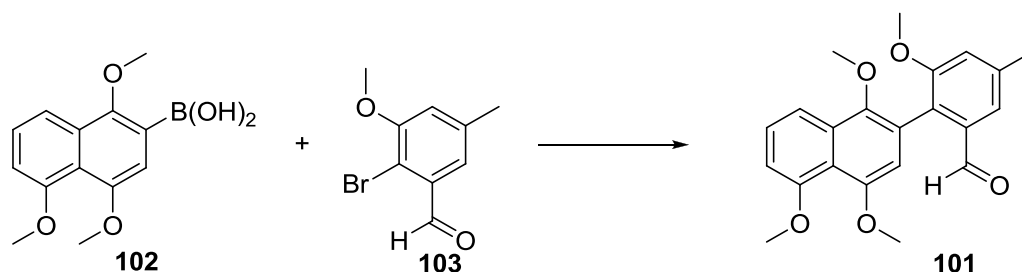
**Scheme 25:** Reagents and Conditions: 2-Formylphenyl boronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub>, CsF, DME, microwave irradiation, 150 °C, 150 W, 30 mins, 76%

We were now in a position to test the key Suzuki-Miyaura cross coupling reaction step to obtain the desired biaryl compound **99** as shown in **Scheme 25**. The reaction was easily carried out in the microwave reactor. All the reagents and starting material were dissolved in previously degassed dimethoxyethane and the resulting solution was subjected to microwave conditions (150 °C and 150 W), for thirty minutes. It was soon realized that a concentrated reaction solution helped in improving the yield of the reaction. The progress of the reaction was followed by thin layer chromatography and subsequent to work-up and column chromatography product **99** was obtained as an off-white solid in 76% yield.



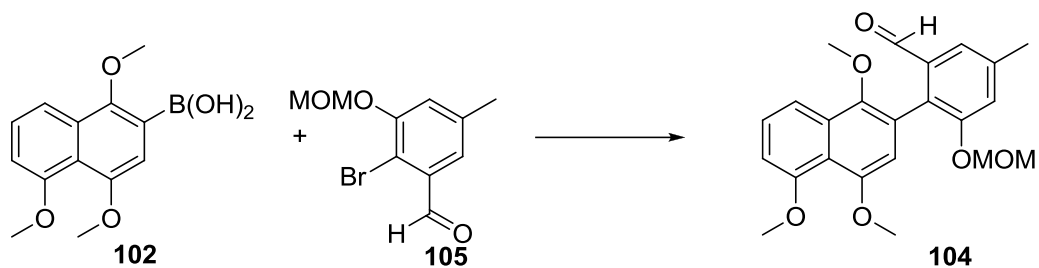
The synthesis of the desired product was confirmed by the presence of the characteristic peak for the carbonyl proton of the aldehyde: a singlet at 9.90 ppm in the  $^1\text{H}$  NMR spectrum and a signal at 192.42 ppm in the  $^{13}\text{C}$  NMR spectrum. Also, two peaks for the two methoxy groups could be seen at 4.01 and 3.40 ppm in the  $^1\text{H}$  NMR spectrum and at 60.94 and 55.80 ppm in the  $^{13}\text{C}$  NMR spectrum. This confirmed that the Suzuki-Miyaura coupling was successful. A singlet upfield at 6.74 ppm in the  $^1\text{H}$  NMR spectrum integrating for one proton denotes a single proton H-3', on the electron rich naphthalene ring. A characteristic signal at  $1726\text{ cm}^{-1}$  in the FTIR spectrum also confirmed the presence of the aldehyde group. Furthermore, the HRMS indicated the correct exact mass of the expected product, which was calculated for  $\text{C}_{19}\text{H}_{17}\text{O}_3$  ( $\text{M}^+ + \text{H}$ ) as 293.1178.

Suzuki-Miyaura cross coupling reaction is being widely used for the synthesis of related compounds having biaryl axis as present in compound **99**. For example, Koyama *et al.* in 1998 managed to synthesize **101** by coupling **102** and **103** employing Suzuki-Miyaura cross coupling reaction as illustrated in **Scheme 26**.<sup>60</sup>



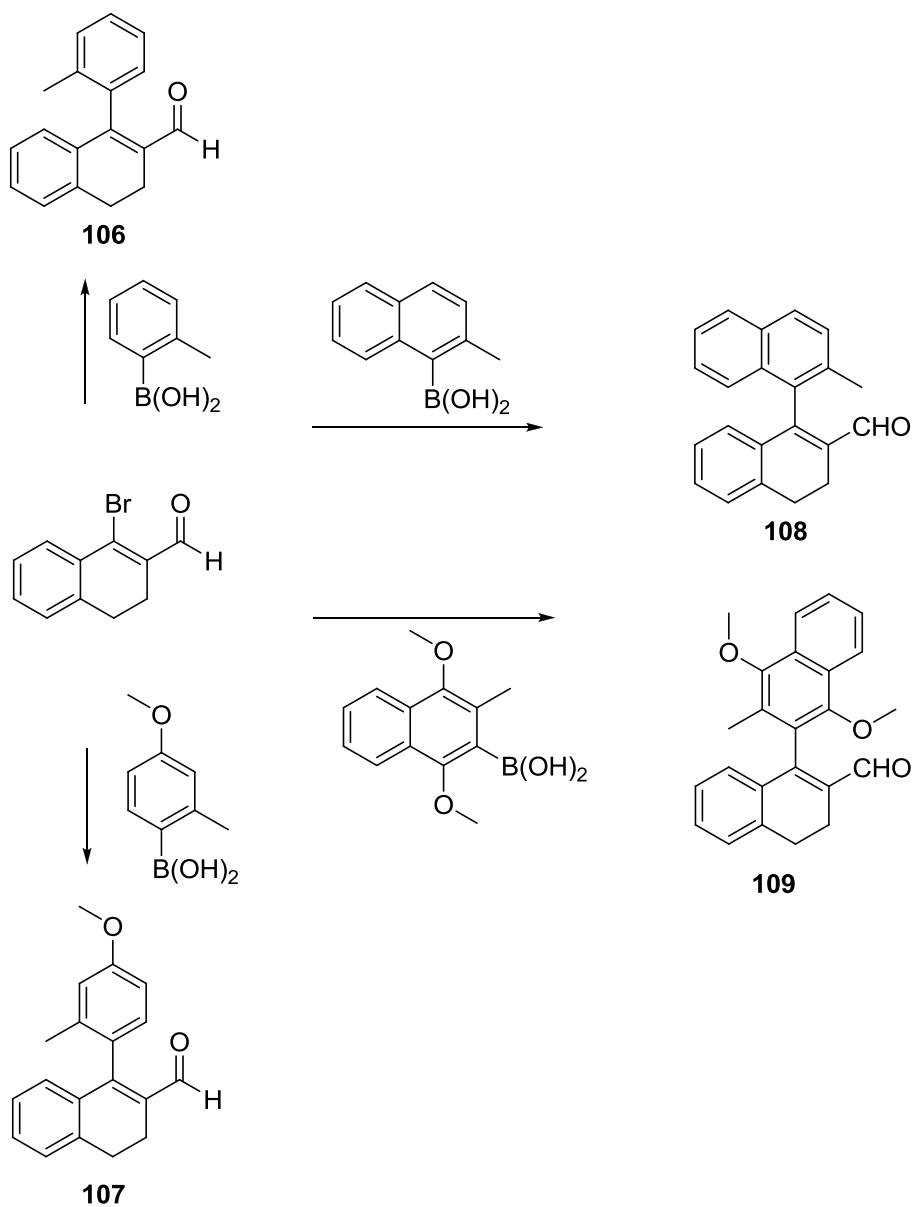
**Scheme 26:** Reagents and Conditions:  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Na}_2\text{CO}_3$ , DME, reflux, 100%.

A very similar compound **104** was synthesized using similar Suzuki-Miyaura cross coupling reaction by Kimura *et al.* in 2011 by coupling **102** and **105** as shown in **Scheme 27**.<sup>61</sup>



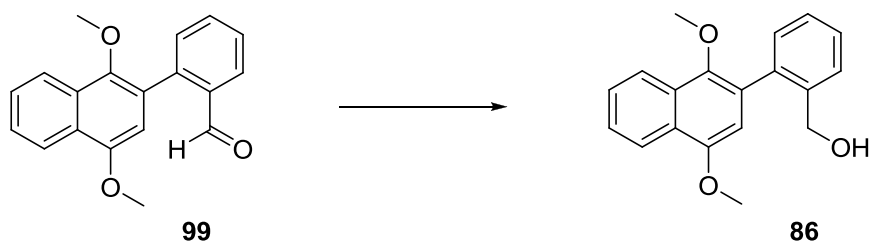
**Scheme 27:** Reagents and Conditions:  $\text{Pd(PPh}_3)_4$ ,  $\text{Na}_2\text{CO}_3$ , DME, 90 °C, 48 hrs, 97%.

de Koning and co-workers have also employed the Suzuki-Miyaura cross coupling strategy to generate a range of compounds having biaryl axis as shown in **Scheme 28**.<sup>62</sup>



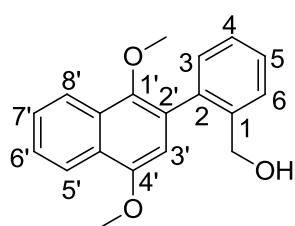
**Scheme 28:** Reagents and Conditions:  $\text{Pd(PPh}_3)_4$ ,  $\text{Na}_2\text{CO}_3$ , DME–EtOH, 46 hrs, 106 = 88%; 107 = 100%; 108 = 58%; 109 = 72%.

#### 2.2.4 Synthesis of (2-(1,4-Dimethoxynaphthalen-2-yl)phenyl)methanol **86**



**Scheme 29:** Reagents and Conditions:  $\text{LiAlH}_4$ , dry THF, 0 °C–rt, 1 hr, 96%.

The next step in our synthesis was the reduction of the aldehyde in 2-(1,4-dimethoxynaphthalen-2-yl)benzaldehyde **99** to the benzylic alcohol **86**. The reaction was carried out by dissolving the starting material **99** in freshly distilled and dry tetrahydrofuran. Lithium aluminium hydride was added in portions to the reaction mixture at 0 °C. The reaction was then allowed to stir at room temperature under inert conditions for an hour and the progress of the reaction was monitored by thin layer chromatography. After conversion of all of the starting material **99**, the excess lithium aluminium hydride was quenched followed by work-up and column chromatography to afford the product **86** as a white solid in 96% yield.



In the  $^1\text{H}$  NMR spectrum, a broad singlet at 3.60 ppm clearly indicated the presence of the hydroxyl group. The two benzylic protons were seen at 4.43 ppm and 4.37 ppm as two doublets ( $J = 11.7$  Hz), with a corresponding peak at 64.0 ppm in the  $^{13}\text{C}$  NMR spectrum for the benzylic carbon. The absence of the aldehydic proton and carbonyl carbon in both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra clearly confirms the reduction of the aldehyde **99** into the alcohol **86**. Both FTIR and HRMS analysis further confirmed this, with the disappearance of the aldehyde peak, which was present at  $1726\text{ cm}^{-1}$  and the appearance of a broad signal at  $3442\text{ cm}^{-1}$  in the FTIR spectrum.

One important point which needs to be mentioned here is that the biaryl axis of compound **86** displays restricted rotation. The two benzylic protons around the biaryl axis, appears as



two doublets because it is an AB system resulting from non-equivalence of the two benzylic hydrogens arising from the restricted rotation (atropisomerism) about the biaryl axis. This could be seen in the **Figure 15** where part of the  $^1\text{H}$  NMR spectrum is displayed.

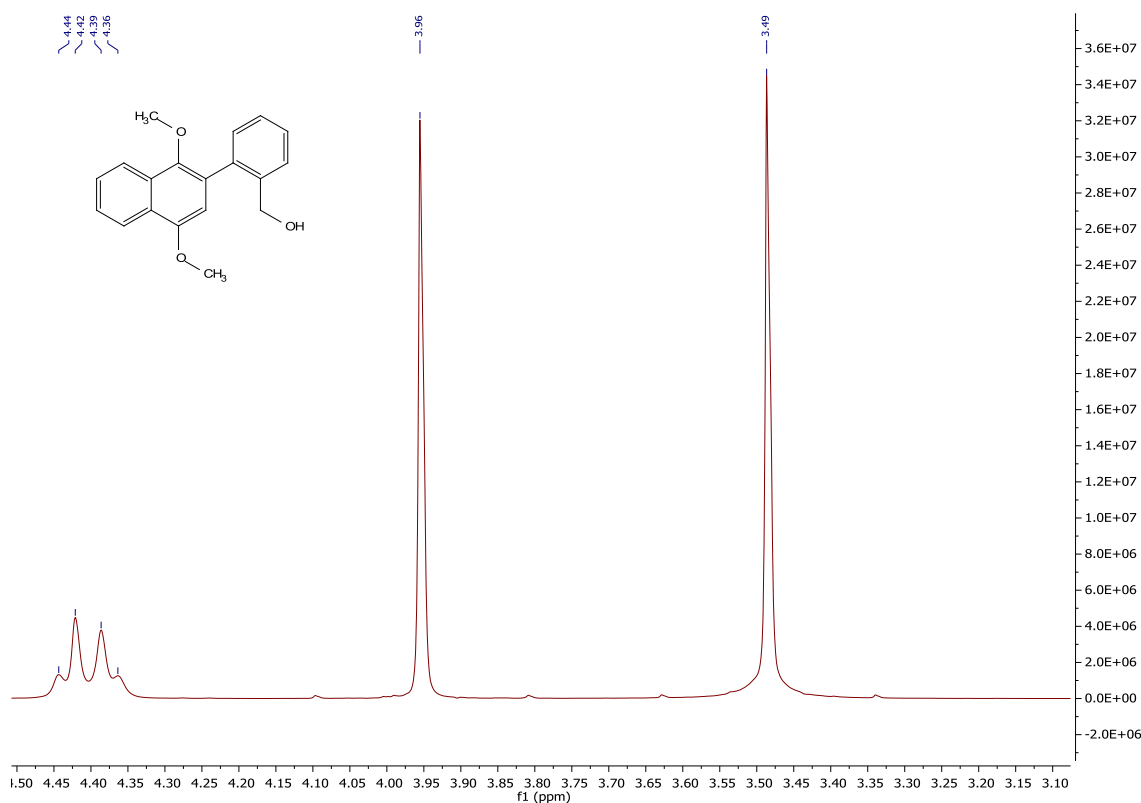


**Figure 15**

In order to examine the phenomenon of atropisomerism in this particular case we decided to conduct further  $^1\text{H}$  NMR spectroscopy experiments. We performed  $^1\text{H}$  NMR spectroscopy on **86** at the elevated temperatures of 40 °C and later at 50 °C and as expected we observed that the two doublets coalesced into two broad signals at 40 °C (**Figure 16**) and then into one singlet (**Figure 17**) at 50 °C. The reason for this observation could be attributed to the fact that as the temperatures increased the rotation around the biaryl axis became unhindered and the two benzylic protons became equivalent.

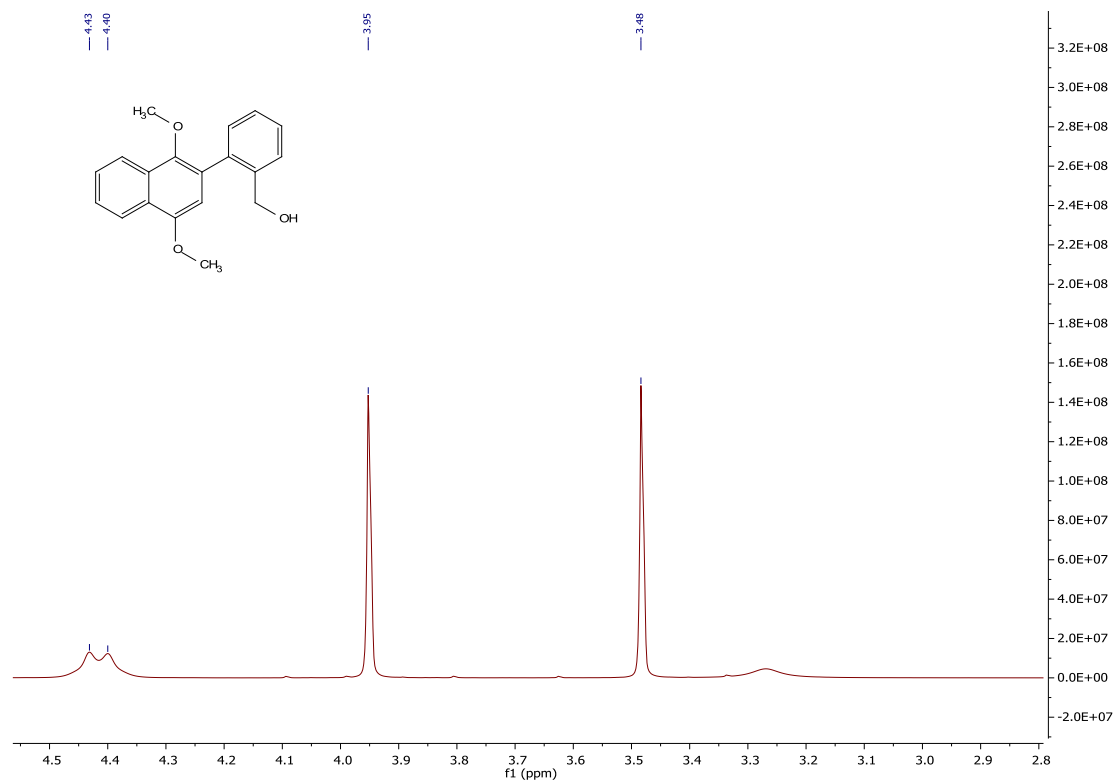


Figure 16

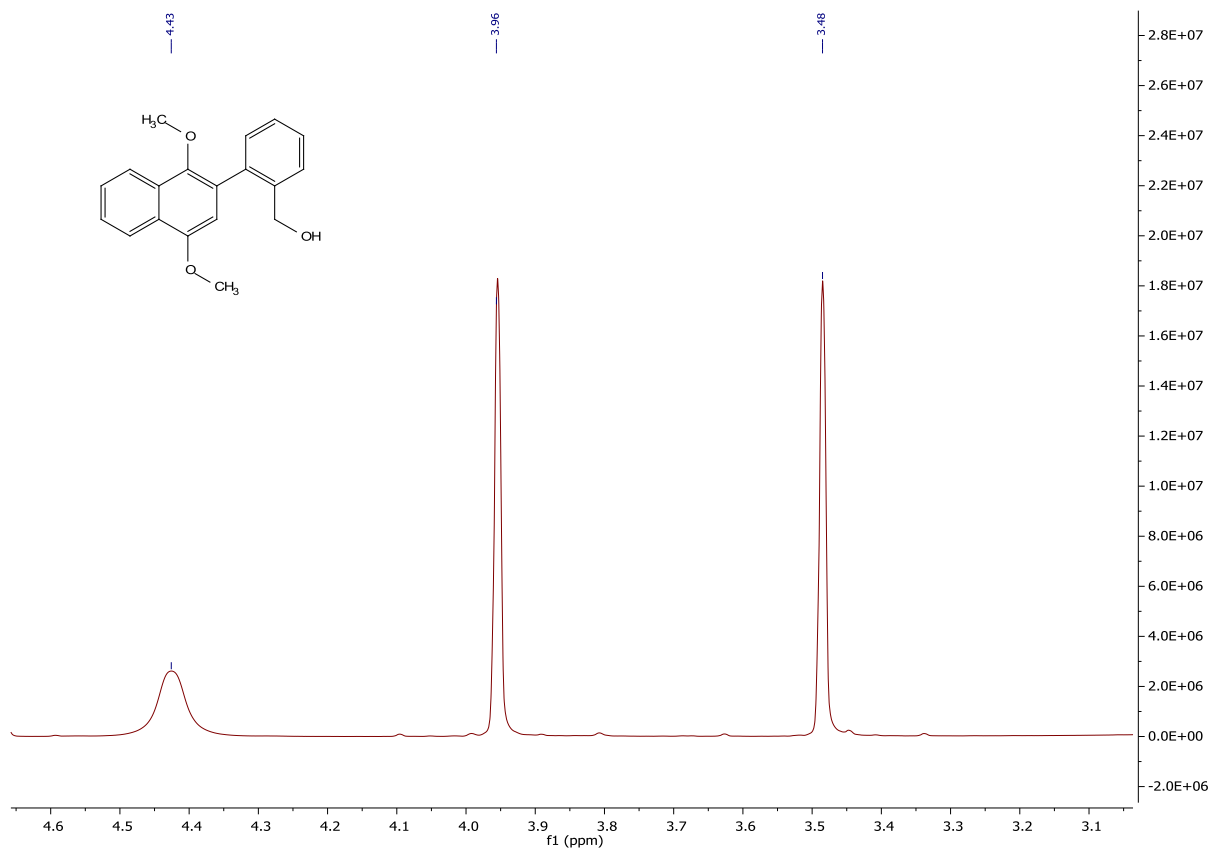
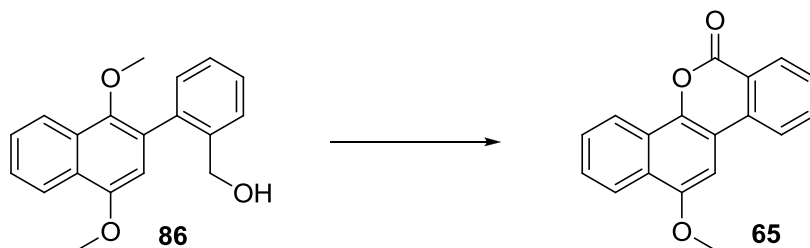


Figure 17

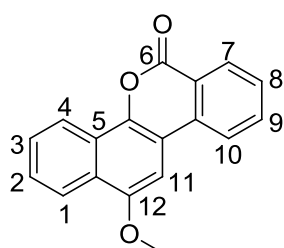
### 2.2.5 Synthesis of 12-Methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65**



**Scheme 30:** Reagents and Conditions: NBS, DCM, rt, atmospheric conditions, 8 hrs, 53%.

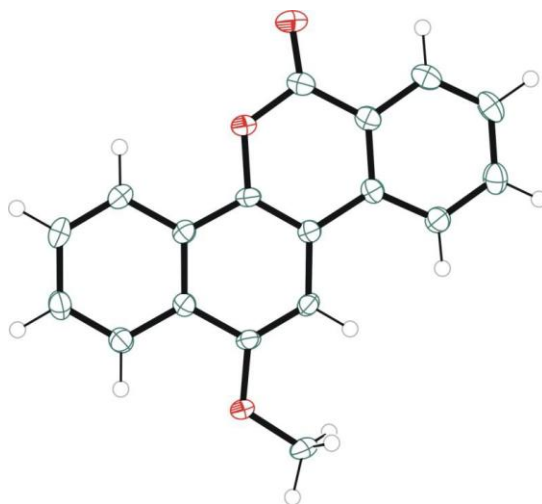
As we had successfully prepared (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **86**, we now wanted to attempt our ring closure reaction induced by *N*-bromosuccinimide to afford the lactone **65**. To carry out the reaction, we dissolved our starting material **86** and *N*-bromosuccinimide in dichloromethane under inert conditions and stirred the reaction for twenty four hours over which time the reaction mixture turned bright red in colour. Unfortunately, analysis by thin layer chromatography showed decomposition of the starting material **86**. NMR spectroscopy did not show any signals for the product expected **65** or the starting material **86**. We then attempted the reaction a number of times varying the temperature and other factors like concentration of the reactants and equivalents of *N*-bromosuccinimide added, but to our frustration none of these modifications afforded the desired product **65**.

Finally when we tested the reaction at room temperature, with one equivalent of *N*-bromosuccinimide in dichloromethane and left the reaction exposed to *air*, and under these conditions we obtained our desired product **65**. The reaction goes from a clear solution to red in colour and at that point thin layer chromatography shows the formation of a major spot of different  $R_f$ . After isolation and purification by column chromatography **65** was obtained as light tan solid in 53% yield. From this observation we deduced that oxygen from air is essential for this reaction. When the reaction is conducted under nitrogen or argon, these inert conditions resulted in eventual decomposition of the starting material **86** without giving the desired product **65**.



Our spectroscopic data agreed with that of Qabaja and Jones which confirmed that we had synthesized 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65**.<sup>38</sup> The  $^1\text{H}$  NMR spectrum showed one peak integrating for three methoxy hydrogens at 4.10 ppm

compared to the two signals for methoxy protons present in the starting material **86**. The peak for the methoxy carbon appeared at 55.79 ppm in the  $^{13}\text{C}$  NMR spectrum. A carbonyl signal in the  $^{13}\text{C}$  NMR spectrum was also seen at 161.37 ppm. The signal for the benzylic protons and carbons and the primary hydroxyl group of the starting material were no longer present. The final confirmation came from the single crystal X-ray structure. As shown in **Figure 18**.



Single crystal X-ray structure: 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65**

**Figure 18**

There have been reports suggesting that *N*-bromosuccinimide could be used as an oxidizing agent where it converts aldehydes into esters.<sup>63</sup> Here in this particular case, *N*-bromosuccinimide could be oxidizing the alcohol functional group into an aldehyde, which could be converted into an acid bromide, which would facilitate ring closure. We carried out further experiments as discussed in the following sections to determine a possible mechanism for this reaction. We also tried to perform this *N*-bromosuccinimide ring closure reaction on a variety of substrates to prove the generality of the reaction and this is also described in the following sections.

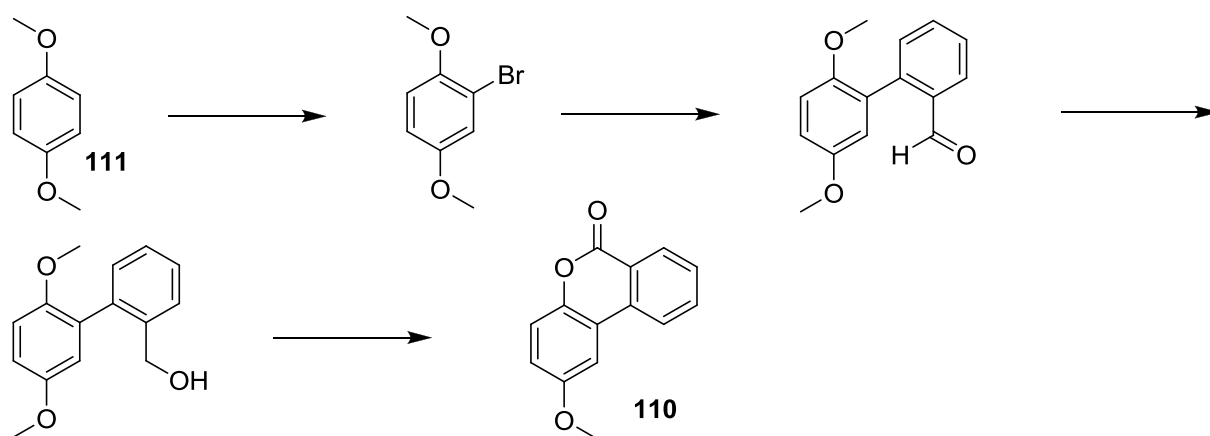
### 2.3 Synthesis of Related Naphthopyranone Scaffolds to Prove Wider Application of the Methodology

Having successfully synthesized 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65** using our novel *N*-bromosuccinimide induced ring closure reaction, we wanted to extend our

methodology to the synthesis of a variety of other naphthopyranone scaffolds to establish the application of the methodology on a range of substrates.

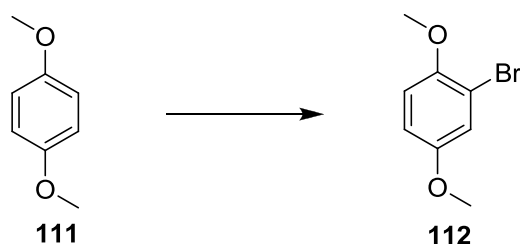
### 2.3.1 Synthesis of 2-Methoxy-6*H*-benzo[*c*]chromen-6-one **110**

We first decided to ascertain if simpler commercially available starting materials like 1,4-dimethoxybenzene **111** could be elaborated to afford possible substrates for our novel *N*-bromosuccinimide-mediated ring closure reaction as shown in **Scheme 30**.



**Scheme 30**

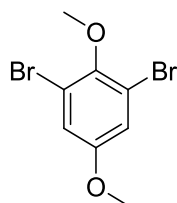
#### 2.3.1.1 Synthesis of 2-Bromo-1,4-dimethoxybenzene **112**



**Scheme 31:** Reagents and conditions: NBS, DCM, reflux, 72 hrs, 90%.

The first step in our synthetic scheme was the bromination of commercially available 1,4-dimethoxybenzene **111**. 1,4-Dimethoxybenzene **111** was dissolved in freshly distilled dry dichloromethane and *N*-bromosuccinimide was added. The brominated product **112** has a slightly higher  $R_f$  when checked by thin layer chromatography than the starting material **111**. On completion of the reaction, a saturated solution of sodium sulfite was added followed by isolation and column chromatography to yield the product **112** as clear oil in 90% yield. Care

was taken to use exactly one equivalent of *N*-bromosuccinimide, as excess *N*-bromosuccinimide results in the formation of the di-brominated product 1,3-dibromo-2,5-dimethoxybenzene **113** as shown in **Figure 19**.

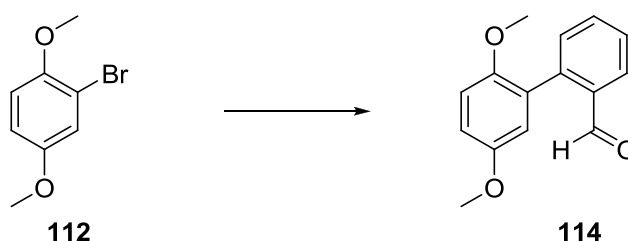


1,3-dibromo-2,5-dimethoxybenzene **113**

**Figure 19**

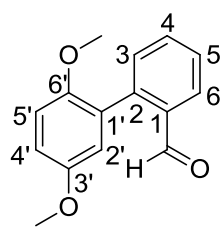
Characterization of the product **112** was achieved by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and was found to be in agreement with the data in the literature.<sup>59</sup>

#### 2.3.1.2 Synthesis of 2',5'-Dimethoxybiphenyl-2-carbaldehyde **114**



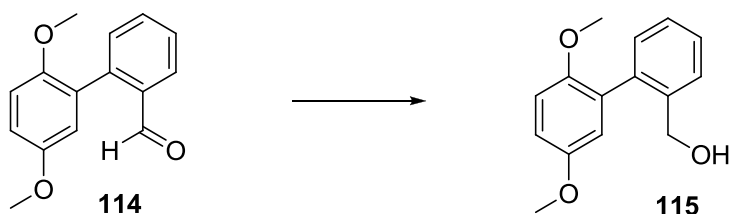
**Scheme 32:** Reagents and conditions: 2-Formylphenyl boronic acid,  $\text{Pd}(\text{PPh}_3)_4$ , CsF, DMF, microwave irradiation, 150 °C, 150 W, 30 mins, 88%

Having successfully synthesized 2-bromo-1,4-dimethoxybenzene **112**, the next step in our synthesis was the generation of a biaryl axis utilizing the Suzuki-Miyaura cross coupling reaction. The reaction was carried out using the same standard microwave procedure as employed previously which involves transfer of all reagents along with the starting material **112** to the microwave vial and addition of the freshly degassed solvent. The reaction mixture was then subjected to microwave irradiations under the above mentioned conditions (**Scheme 32**). Upon completion of the reaction, work up and column chromatography were done to isolate pure product **114** as a white solid in 88% yield which was then characterized by NMR spectroscopy. Spectroscopic results were found in accordance with literature.<sup>64</sup>



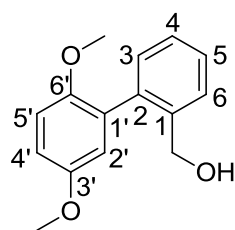
A singlet at 9.79 ppm in the  $^1\text{H}$  NMR spectrum which integrates for one proton indicates the presence of an aldehyde functional group with the corresponding peak in the  $^{13}\text{C}$  NMR spectrum at 192.58 ppm. Two singlets in the  $^1\text{H}$  NMR spectrum at 3.81 and 3.67 ppm are very distinct for six protons each representing two methoxy groups with peaks in the  $^{13}\text{C}$  NMR spectrum visible at 55.92 and 55.81 ppm. Signals in the region 8.01-6.87 ppm in the  $^1\text{H}$  NMR spectrum accounts for the correct number of aromatic protons present in the molecule and also it confirms that we have obtained the product from the Suzuki-Miyaura cross coupling reaction. There are a total of twelve aromatic carbons giving signals in the aromatic region of 153.77 to 111.78 ppm in the  $^{13}\text{C}$  NMR spectrum, which accounts for the number of non-equivalent carbons expected in the molecule.

### 2.3.1.3 Synthesis of (2',5'-Dimethoxybiphenyl-2-yl)methanol **115**



**Scheme 33:** Reagents and conditions:  $\text{LiAlH}_4$ , dry THF, 0  $^\circ\text{C}$ -rt, 1 hr, 100%

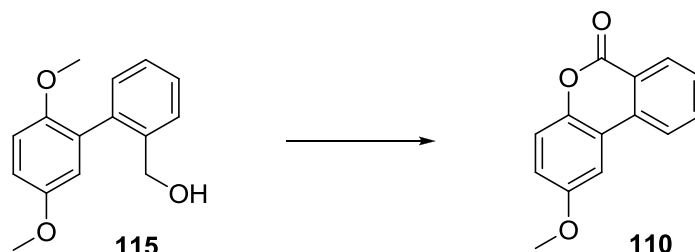
Following the successful synthesis of 2',5'-dimethoxybiphenyl-2-carbaldehyde **114**, the next step was the reduction of the aldehyde group to a benzylic alcohol which was achieved easily using lithium aluminium hydride as the reducing agent in dry tetrahydrofuran. The additions were done at 0  $^\circ\text{C}$ . The product **115** was obtained as white solid in 100% yield after isolation and purification. The identification of the obtained product was done by NMR spectroscopy.



Examination of the NMR spectroscopic data, showed that the peak for the aldehyde proton in the  $^1\text{H}$  NMR spectrum and respective carbon in the  $^{13}\text{C}$  NMR spectrum were no longer present. The peak for the hydroxyl proton could be seen as a broad singlet upfield at 2.41 ppm in the  $^1\text{H}$  NMR spectrum. The two benzylic protons could be seen at 4.44 ppm and 4.40 ppm as doublet of doublet and the corresponding peak in the  $^{13}\text{C}$  NMR spectrum could be seen at 63.81 ppm. Apart from these characteristic signals all other expected peaks could also be seen, including the two methoxy groups at 3.79 and 3.68 ppm;

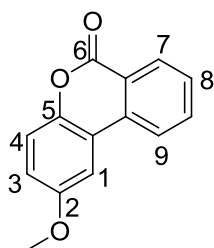
and at 56.70 and 55.73 ppm in the  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra respectively. The FTIR spectrum showed a stretching band at  $3422\text{ cm}^{-1}$  characteristic of the hydroxyl group. HRMS analysis also gave the correct exact mass of the product.

#### 2.3.1.4 Synthesis of 2-Methoxy-6*H*-benzo[*c*]chromen-6-one **110**



**Scheme 34:** Reagents and conditions: NBS, AIBN, carbon tetrachloride, reflux, atmospheric conditions, 18 hrs, 49%.

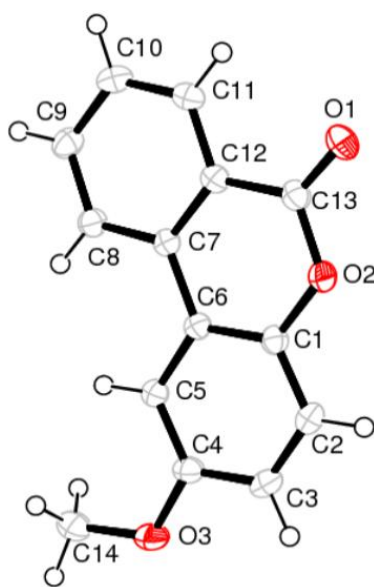
Having successfully synthesized the precursor needed to attempt the *N*-bromosuccinimide mediated reaction, (2',5'-dimethoxybiphenyl-2-yl)methanol **115** was subjected to *N*-bromosuccinimide and air in order to obtain the naphthopyranone 2-methoxy-6*H*-benzo[*c*]chromen-6-one **110**. To begin with, we dissolved the starting material **115** in dichloromethane and added *N*-bromosuccinimide and left the reaction mixture to stir at room temperature under atmospheric conditions. However, no change was seen by thin layer chromatography, we then heated the mixture to reflux for some days but still no change was observed. Addition of the radical initiator azobisisobutyronitrile (AIBN) also had no effect. We then decided to use carbon tetrachloride as this solvent can provide a higher boiling point for the reaction as compared to dichloromethane. Dissolving the starting material **115** in carbon tetrachloride, we added *N*-bromosuccinimide along with AIBN and heated the reaction under reflux for eighteen hours. By thin layer chromatography, we observed that all of the starting material **115** had been consumed and a spot appeared at a higher  $R_f$ , than starting material **115** appeared. After isolation and purification by column chromatography our desired product **110** was obtained in a mediocre yield of 49%.



The disappearance of one methoxy substituent and the benzylic protons in the NMR spectra was an indication that we had converted (2',5'-dimethoxybiphenyl-2-yl)methanol **115** into 2-methoxy-6*H*-benzo[*c*]chromen-6-one **110**. A quaternary peak at 161.27 ppm in the  $^{13}\text{C}$  NMR spectrum is characteristic of the aromatic lactone C-6. In addition,



the number of protons and carbons expected in the product corresponded exactly to that in the  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra. The FTIR spectrum showed a stretching band at  $1722\text{ cm}^{-1}$  characteristic to the carbonyl group and exact mass was confirmed from the HRMS results where there a molecular ion for  $\text{C}_{14}\text{H}_{11}\text{O}_3$  ( $\text{M}^+\text{+H}$ ) was found at 227.0701 for the calculated value of 227.0709. Finally confirmation came from a single crystal X-ray structure of the compound **110** as shown in **Figure 20**.

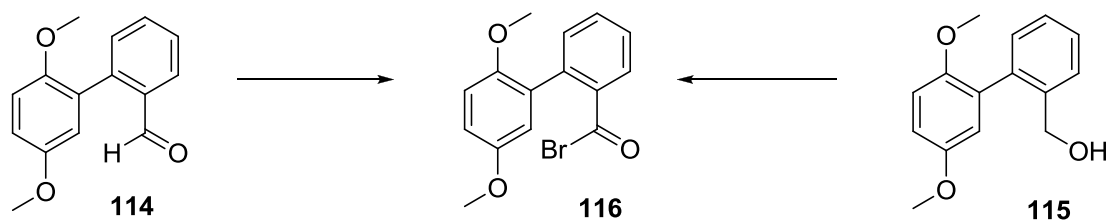


Single crystal X-ray structure: 2-methoxy-6*H*-benzo[*c*]chromen-6-one **110**

**Figure 20**

## 2.4 Mechanistic Studies to Elucidate Lactone Ring Formation Induced by NBS and Air

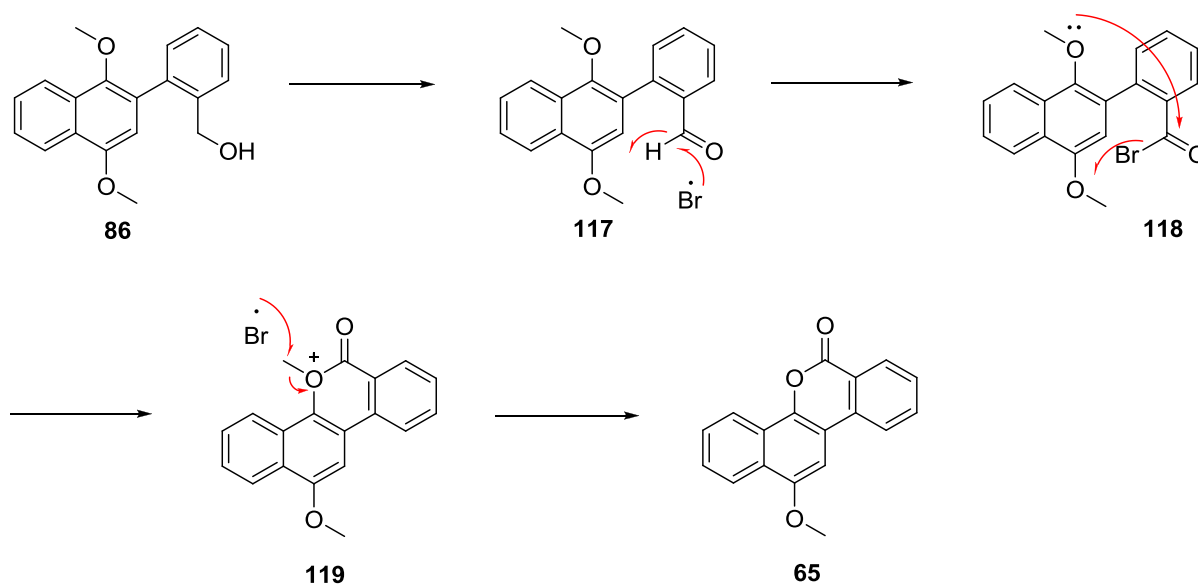
As a result of these findings we were interested in investigating the mechanistic aspects of this unusual ring closure reaction we discovered induced by *N*-bromosuccinimide and air. There is literature precedent to show that *N*-bromosuccinimide can oxidize aldehydes into the corresponding acid bromide and further leading to the generation of esters.<sup>63</sup> We anticipated that a similar process could be occurring in our reaction. Unfortunately as acid bromides are unstable intermediates that could not be isolated. We hoped to assess whether the alcohol **115** or the aldehyde **114** would lead to the synthesis of 2-methoxy-6*H*-benzo[*c*]chromen-6-one **110** via the acid bromide **116**, as shown in **Scheme 35**.



Scheme 35

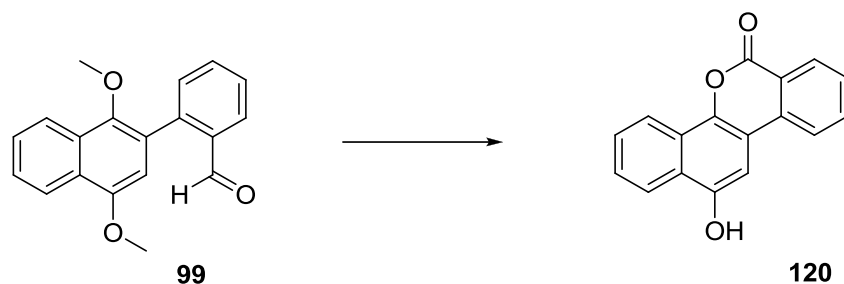
#### 2.4.1 Synthesis of 12-Methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65** Using Aldehyde Intermediate.

One proposed mechanism for the synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65** is, as mentioned previously, that it proceeds via an aldehyde intermediate. As *N*-bromosuccinimide is an oxidizing agent, it oxidizes the benzylic alcohol **86** into an aldehyde intermediate leading to the release of radicals into the solution affording **117**. *N*-Bromosuccinimide could then also oxidize the aldehydes into an acid bromide **118** under these radical conditions, which is a known process. After the generation of the activated and unstable acid bromide **118**, the carbonyl carbon is attacked by the nucleophilic methoxy group and bromine leaves leading to the ring closure to afford the lactone **119** and in the last step methyl group is removed by another bromine radical leading to the generation of lactone **65** (Scheme 36). It is also observed during the course of reaction that in the absence of air, the reaction fails to deliver any product and the reaction mixture decomposes. The importance of air in the reaction could be attributed to the fact that oxygen in the air aids in the oxidation reaction of the alcohol **86** to the aldehyde **99**.



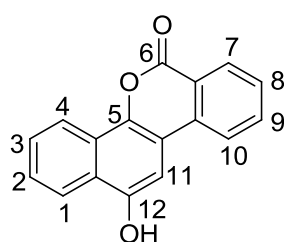
Scheme 36

Hence, we carried out a number of reactions in order to determine whether the proposed mechanism is actually feasible, where the alcohol is initially oxidized into the aldehyde and then converted to the very activated and unstable acid bromide leading to the ring closed product **65**. To test the theory, we took previously synthesized aldehyde, 2-(1,4-dimethoxynaphthalen-2-yl)benzaldehyde **99** and dissolved it in dichloromethane. This solution was then charged with *N*-bromosuccinimide and the reaction was allowed to stir at room temperature and under atmospheric conditions for eighteen hours. The reaction was monitored by thin layer chromatography, where major spot was observed having much lower  $R_f$  than the starting material **120**. On completion of the reaction, unreacted *N*-bromosuccinimide was quenched followed by work-up and column chromatography to isolate the major product of the reaction. On spectroscopic analysis of the product obtained we found that the desired ring closure reaction had taken place to yield **120** in 57% yield as shown in **Scheme 37**.



**Scheme 37:** Reagents and conditions: NBS, DCM, rt, atmospheric conditions, 18 hrs, 57%.

In this case, the product **120** contained a phenolic alcohol rather than a methoxy group as was present in compound **65**. This could be attributed to the presence of hydrogen bromide in the reaction mixture which could have resulted in the cleavage of the methyl group allowing for the generation of the alcohol **120**.

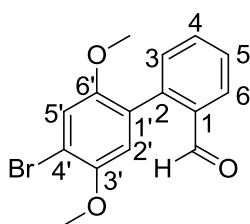


Initially, we were surprised to see no signal for a methoxy group in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. Rather a singlet at 9.95 ppm in the  $^1\text{H}$  NMR spectrum was present as a result of the phenolic proton in the  $^1\text{H}$  NMR spectrum with the corresponding peak at 150.90 ppm in the  $^{13}\text{C}$  NMR spectrum. Unfortunately due to the instability of the product we were unable to obtain HRMS data or single crystal X-ray structure data.

#### 2.4.2 Synthesis of 4'-Bromo-2',5'-dimethoxybiphenyl-2-carbaldehyde **121** from (2',5'-Dimethoxybiphenyl-2-yl)methanol **115**

Further indicators about the mechanism of the *N*-bromosuccinimide ring closure reaction came from the synthesis of 4'-bromo-2',5'-dimethoxybiphenyl-2-carbaldehyde **121**. In our various attempts to obtain the product 2-methoxy-6*H*-benzo[*c*]chromen-6-one **110**, we had to test a number of chlorinated solvents in order to allow for the reaction to succeed. When dichloromethane failed to give us the desired result, we tested the reaction with chloroform and finally carbon tetrachloride. For the reaction in chloroform, the starting material (2',5'-dimethoxybiphenyl-2-yl)methanol **115**, was dissolved in the solvent and *N*-bromosuccinimide and AIBN were added to it. The reaction was heated at reflux for eighteen hours under atmospheric conditions, after which time reaction solution turned orange in colour. Thin layer chromatography showed that all of the starting material **115** had been consumed and a major spot was seen at higher  $R_f$  than starting material **115**. After work up and column

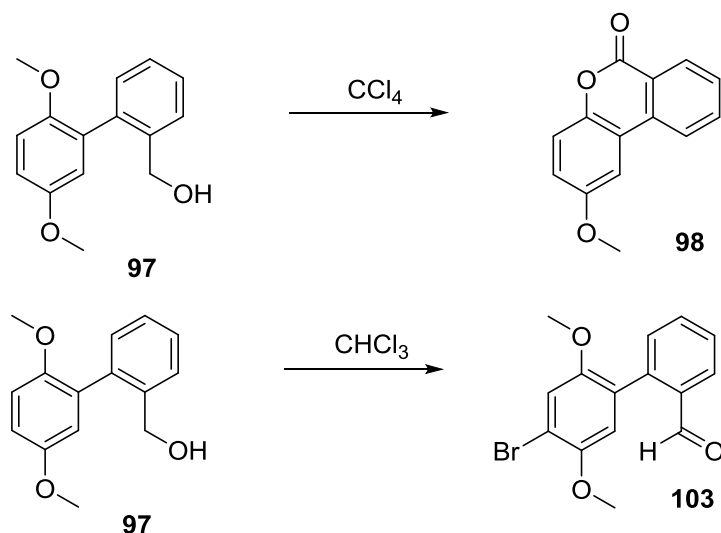
chromatography a white solid was isolated in 63% which, when analyzed by NMR spectroscopy, did not look like the product we were expecting.



In the  $^1\text{H}$  NMR spectrum at 9.78 ppm, observed a singlet integrating for one proton, characteristic of an aldehydic proton, which suggested that we had isolated an aldehyde from the alcohol **115**. Also we were expecting signals integrating for seven aromatic protons and the integration of the aromatic region of the  $^1\text{H}$  NMR spectrum we obtained six aromatic protons, two of them giving rise to singlets. *N*-bromosuccinimide is a known brominating agent, and is also known to oxidize alcohols into aldehydes. In this reaction, when we wanted to convert (2',5'-dimethoxybiphenyl-2-yl)methanol **115** to 2-methoxy-6*H*-benzo[*c*]chromen-6-one **110**, we obtained an intermediate 4'-bromo-2',5'-dimethoxybiphenyl-2-carbaldehyde **121**. All three positions *ortho* to the two methoxy groups could undergo bromination, however, bromination took place at C-4', *ortho* to the methoxy group and *para* to the biaryl axis. This could easily be seen in the  $^1\text{H}$  NMR spectrum by the presence of two singlets at 6.86 and 7.18 ppm in the aromatic region, for the protons at C-2' and C-5' respectively. Two singlets at 3.88 and 3.69 ppm in the  $^1\text{H}$  NMR spectrum each integrating for three protons accounted for the two methoxy groups. In the  $^{13}\text{C}$  NMR spectrum, we could clearly see a peak at 192.09 ppm representing a carbonyl carbon. Two peaks at 150.83 and 150.40 ppm represent the aromatic carbons attached to the two methoxy groups, C-3' and C-6'. There are two peaks at 56.99 and 56.20 ppm for the two methoxy groups. There are a total of six quaternary peaks in the  $^{13}\text{C}$  NMR spectrum as expected from the structure of the molecule.

Hence, we had isolated 4'-bromo-2',5'-dimethoxybiphenyl-2-carbaldehyde **121** when trying to do the *N*-bromosuccinimide mediated ring cyclization reaction of (2',5'-dimethoxybiphenyl-2-yl)methanol **115**.

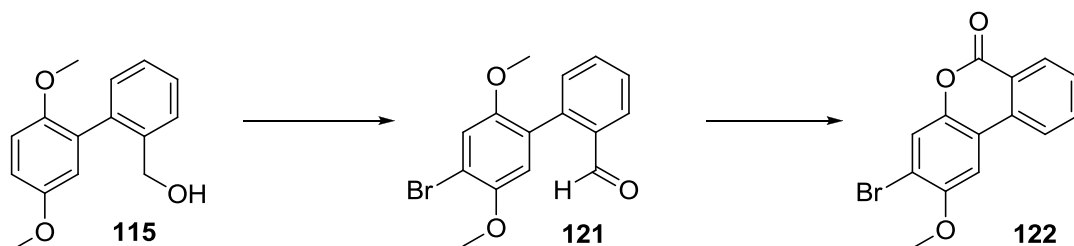
An interesting observation was made here as both the conversions, **115** to **110** and **115** to **121** were carried out the same way, the only difference being in the solvent used, carbon tetrachloride in the previous case and chloroform in the later, which resulted in the generation of the two different products **110** and **121** as illustrated in **Scheme 38**.



Scheme 38

The only tentative explanation for this difference must be related to the different boiling points of the two solvents. Carbon tetrachloride with a boiling point of 76.7 °C provides more energy to the reaction as compared to chloroform, which has a boiling point of 61.2 °C.

We propose that this unusual result could shed some light on the possible mechanism of this novel reaction suggesting that the reaction could proceed via the aldehyde intermediate **121**.

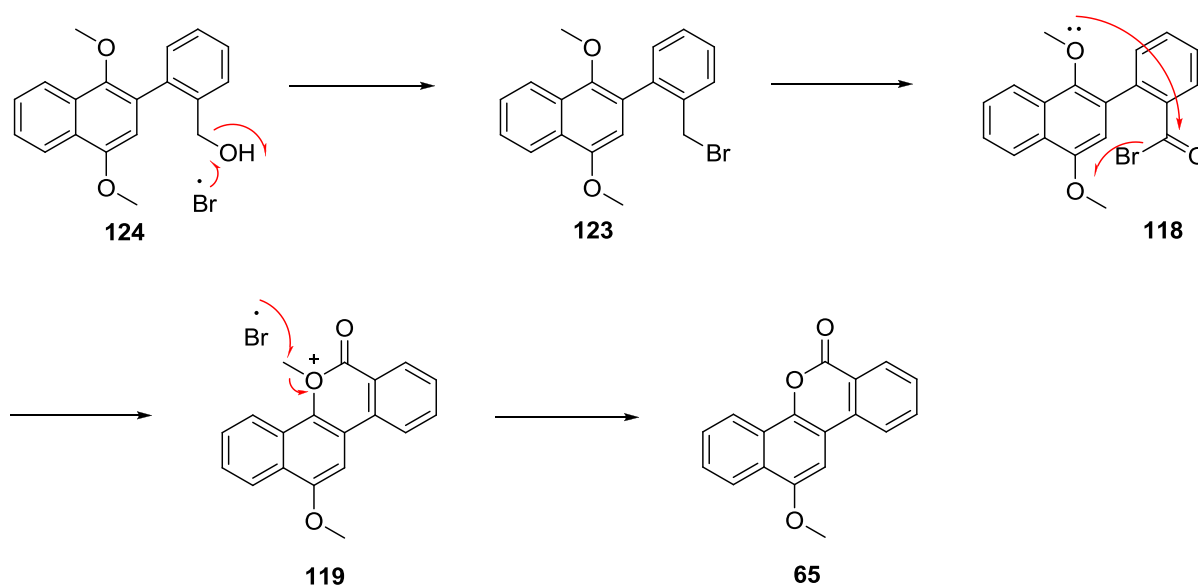


Scheme 39

Ms Reynolds in her MSc research project obtained 3-bromo-2-methoxy-6*H*-benzo[*c*]chromen-6-one **122** from (2',5'-dimethoxybiphenyl-2-yl)methanol **115**, using *N*-bromosuccinimide with chloroform as a solvent however she allowed the reaction to proceed for thirty six hours.<sup>45</sup>

### 2.4.3 Synthesis of 12-Methoxy-6H-dibenzo[c,h]chromen-6-one **65** Using Benzylic Alcohol Intermediate

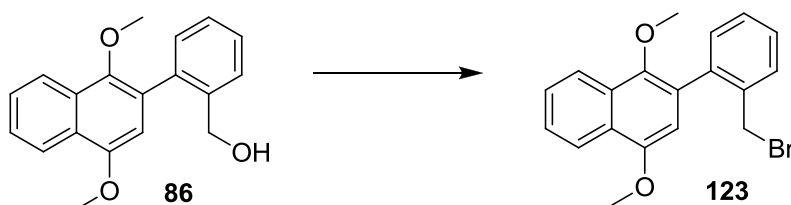
Another proposal for the mechanism of the reaction we wished to explore is the initial formation of the benzylic bromide **123** from benzylic alcohol **124** under the radical conditions of the reaction. This benzylic bromide **123** could in turn be converted to the acid bromide **118** under the influence of *N*-bromosuccinimide and oxygen, thereby leading to the desired ring closed product **65** as shown in **Scheme 40**.



**Scheme 40**

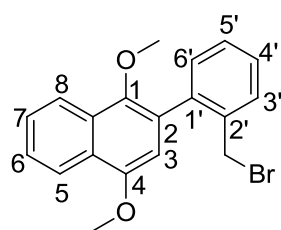
To test this hypothesis we would first have to synthesize the benzyl bromide intermediate **123** from the alcohol **86** and then subject it to *N*-bromosuccinimide in a suitable solvent.

### 2.4.4 Synthesis of 2-(2-(Bromomethyl)phenyl)-1,4-dimethoxynaphthalene **123**



**Scheme 41:** Reagents and conditions:  $\text{PPh}_3$ ,  $\text{CBr}_4$ , DCM, rt, 3 hrs, 67%.

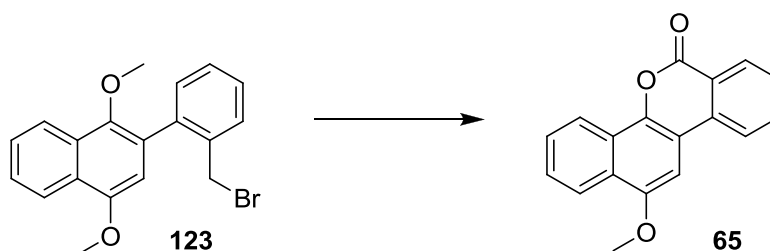
To carry out the reaction, (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **86** was dissolved in freshly distilled dry dichloromethane in a flame dried flask. Triphenylphosphine and carbon tetrabromide were added to the reaction mass and the solution was allowed to stir at room temperature for three hours, over which time the reaction mixture was seen to turn orange in colour. This was followed by work-up and column chromatography and the product **123** was obtained in 67% yield as a pale yellow oil which solidified on standing.



Formation of the product was seen clearly from  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy. The disappearance of the proton of the hydroxyl group in the  $^1\text{H}$  NMR spectrum was observed. An upfield shift of the benzylic carbon to 32.46 ppm in the  $^{13}\text{C}$  NMR spectrum from 64.1 ppm in the starting material in the  $^{13}\text{C}$  NMR spectrum further corroborated our findings.

After the successful synthesis of the benzylic bromide **123**, we continued our efforts to elucidate the reaction mechanism by subjecting this intermediate to the conditions of our *N*-bromosuccinimide ring closure reaction.

#### 2.4.5 Attempted Synthesis of 12-Methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65** from 2-(2-(Bromomethyl)phenyl)-1,4-dimethoxynaphthalene **123**



**Scheme 42:** Reagents and conditions: NBS, AIBN, DCM, rt, atmospheric conditions, 72 hrs.

2-(2-(Bromomethyl)phenyl)-1,4-dimethoxynaphthalene **123** was dissolved in dichloromethane, treated with *N*-bromosuccinimide, and the reaction mixture was allowed to stir for twenty four hours at room temperature and under atmospheric air conditions. Analysis by thin layer chromatography showed no change after this time. AIBN was then added to the reaction, and the mixture was allowed to stir for another forty eight hours under the same conditions, during which time the solution turned yellow in colour. Thin layer chromatography showed that all the starting material **123** had been consumed, and four new spot appeared

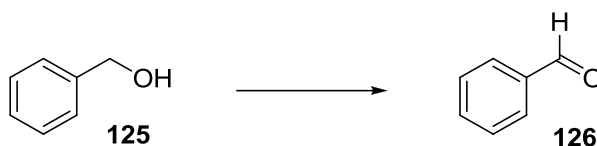


all at a much higher  $R_f$  than the starting material **123**. When each of these spots were isolated and analyzed by NMR spectroscopy it was found that none of them was our desired product **65**. Rather, it looked as though we had isolated mixtures of dibrominated products where bromination had taken place at the aromatic positions of 2-(2-(bromomethyl)phenyl)-1,4-dimethoxynaphthalene **123**. The failure of this reaction led us to the conclusion that the benzylic bromide is not a likely intermediate in our novel *N*-bromosuccinimide mediated ring cyclization reaction.

In conclusion we propose that this novel *N*-bromosuccinimide and air induced ring closure reaction to form fused 3,4-dihydro-2*H*-pyran-2-ones proceeds through the aldehyde intermediate **121** rather than the benzylic bromide intermediate **123**. This hypothesis is also supported by reports of *N*-bromosuccinimide to oxidizing aldehydes to acid bromides under radical conditions.<sup>63</sup> One major and crucial factor controlling this oxidative lactonisation reaction is air or oxygen and the reaction seems to decompose when performed under inert conditions.

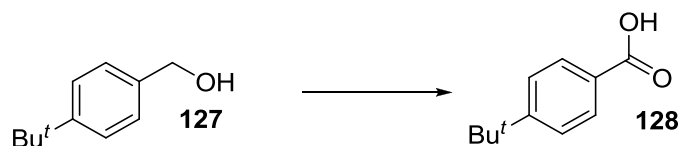
#### 2.4.6 Role of Oxygen in *N*-Bromosuccinimide Mediated Oxidation Reactions

The role of oxygen together with *N*-bromosuccinimide or another bromine source is evident in a few examples in the literature. For example, Minisci *et al.* has shown that the oxidation of primary benzylic **125** alcohols into the corresponding aromatic aldehydes **126** in the presence of nitric acid and oxygen, catalyzed by bromine can take place as illustrated in **Scheme 43**.<sup>65</sup>



**Scheme 43:** Reagents and conditions:  $\text{HNO}_3$ ,  $\text{O}_2$ ,  $\text{Br}_2$

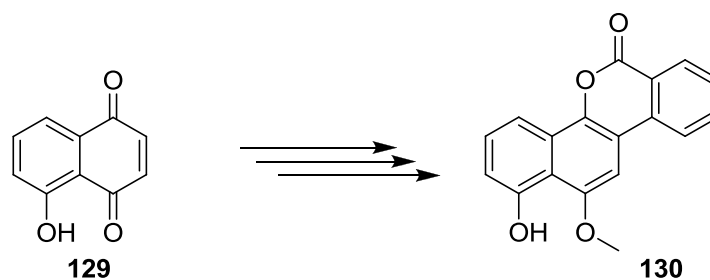
Kuwabra *et al.* has also showed the importance of molecular oxygen directly in the presence of catalytic amount of *N*-bromosuccinimide and irradiation through high pressure mercury lamp leads to the oxidation of benzylic alcohol **127** into carboxylic acid **128** as shown in **Scheme 44**.<sup>66</sup>



**Scheme 44:** Reagents and conditions: O<sub>2</sub>, NBS

The authors demonstrated that when the reaction was performed under argon atmosphere, the yield of the product decreased substantially. The authors also postulated a radical mechanism indicating the role of *N*-bromosuccinimide and oxygen for this kind of oxidation reaction.<sup>66</sup>

So far, happy with these results of *N*-bromosuccinimide and oxygen mediated ring closure reaction, we wanted to probe the generality of this reaction by testing the methodology on structurally similar substrates in order to generate a library of lactone-containing aromatic compounds. The first choice that came to mind was to start our synthesis from commercially available juglone **129** which would, if successful, yield 1-hydroxy-12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **130** as the final product. The reason for using this starting material was that the product formed would contain the core features of the natural product gilvocarcin **5**, and the methodology could be applied to the synthesis of the natural product in the future.

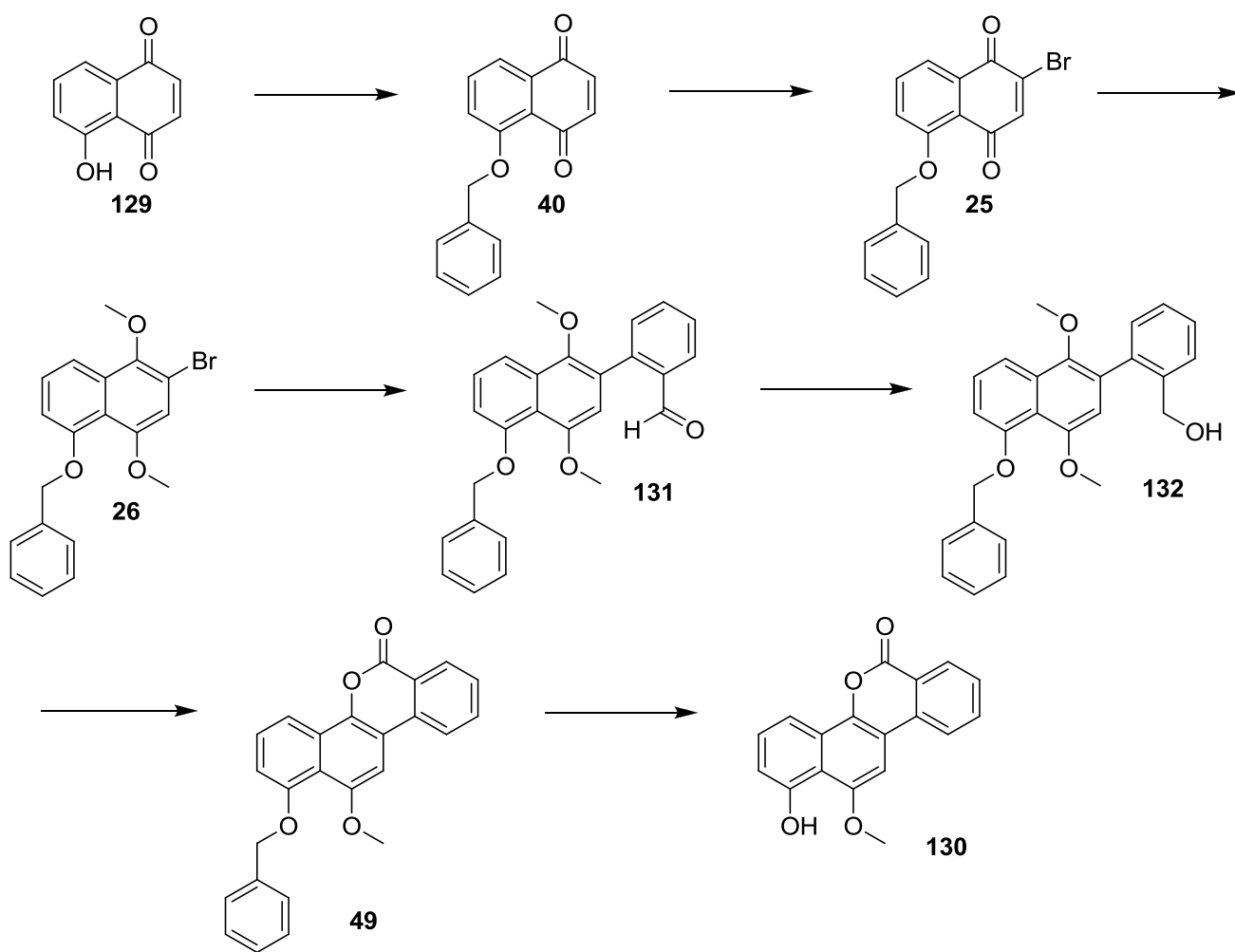


**Scheme 45**

## 2.5 Synthesis of 1-Hydroxy-12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **130**

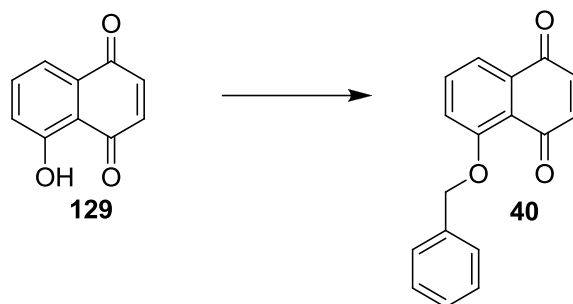
Commencing from commercially available juglone **129**, it was envisioned that the free naphthol of juglone **129** could be protected with a benzyl group to afford **40** and then a bromine could be introduced at the 2-position of the molecule to give **25**, using literature procedures.<sup>67</sup> After that, the quinone could be reduced and then protected to furnish 5-(benzyloxy)-2-bromo-1,4-dimethoxynaphthalene **26**. 5-(Benzyloxy)-2-bromo-1,4-

dimethoxynaphthalene **26** would act as a substrate for our Suzuki–Miyaura cross coupling reaction to synthesize biaryl compound **131** using 2-formylphenyl boronic acid **98** as shown in **Scheme 46**. The aldehyde in the product could then be reduced to a benzylic alcohol **132** and this compound **132** could then be subjected to *N*-bromosuccinimide and air to obtain the desired final ring closed product **49**. A final deprotection step would afford 1-hydroxy-12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **130**.



**Scheme 46**

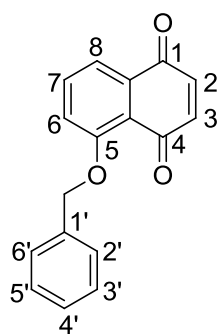
### 2.5.1 Synthesis of 5-(Benzyloxy)naphthalene-1,4-dione **40**



**Scheme 47:** Reagents and conditions: BnBr, Ag<sub>2</sub>O, CCl<sub>4</sub>, reflux, 72 hrs, 88%.

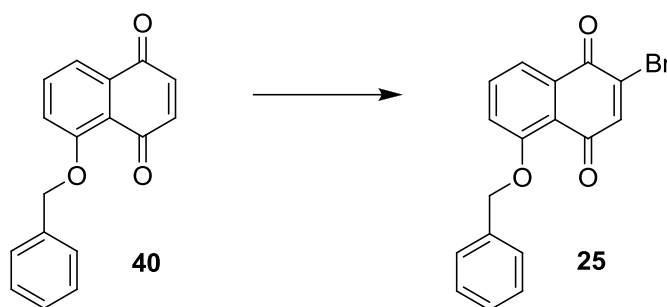
The first step in our synthetic scheme was the protection of the free naphthol of juglone **129**. Our choice of protecting group was a benzyl protecting group as there is literature precedent for accomplishing this reaction, and it can be easily removed at a later stage of the synthesis. The reaction was carried out by dissolving the starting material **129** in carbon tetrachloride and adding silver(I)oxide and benzyl bromide, and heating the reaction mixture under reflux for seventy two hours. On completion of the reaction, the mixture was filtered to remove the solid silver salt. Column chromatography afforded the product **40** as a bright yellow solid in 88% yields.

When we initially attempted this reaction, we struggled with low yields of product and incomplete conversion of the starting material **129**. This was frustrating as this was the first step in our synthetic scheme. Fortunately by changing the solvent from chloroform to carbon tetrachloride, and adding additional equivalents of silver(I)oxide at regular intervals of twelve hours ensured complete conversion of the starting material **129** and resulted in good yields of 5-(benzyloxy)naphthalene-1,4-dione **40**.



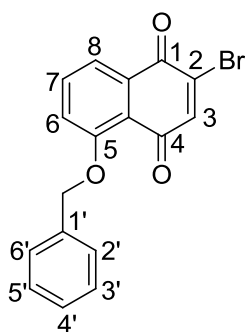
The spectroscopic result was found to be in agreement with that of the literature.<sup>68</sup> The spectroscopic data clearly indicated the formation of 5-benzyl protected juglone **40**. There was no peak visible for the proton of the free hydroxyl group of juglone **129** and there were signals from five extra protons in the aromatic region of the <sup>1</sup>H NMR spectrum due to the protons of the benzyl group. The most prominent indication came from the presence of a signal due to the two benzylic protons in the <sup>1</sup>H NMR spectrum which appeared as a singlet at a chemical shift of 5.30 ppm with the corresponding carbon signal at a chemical shift of 70.9 ppm in the <sup>13</sup>C NMR spectrum.

### 2.5.2 Synthesis of 5-(Benzyloxy)-2-bromonaphthalene-1,4-dione **25**



**Scheme 48:** Reagents and conditions: 1) Bromine, DCM, 0 °C, inert conditions, 15 mins. 2) 10% Acetic acid, ethanol, reflux, 15 mins, 74%.

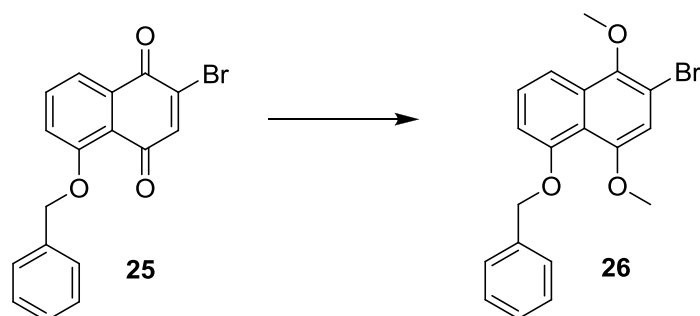
Following the successful protection of the free hydroxyl group of juglone, the following step was the bromination at the 2-position of 5-(benzyloxy)naphthalene-1,4-dione **40**. After trying quite a few literature procedures that met with failure, we tried the procedure for bromination published in 1979 by Hannan *et al.*<sup>67</sup> The procedure worked well and gave the product in good yield when care was taken to use only one equivalent of bromine to prevent the generation of by-products. To carry out the reaction, starting material **40** was dissolved in dichloromethane under inert conditions and the temperature of the solution was maintained at 0 °C. To this stirred solution was added bromine dissolved in dichloromethane and maintained at 0 °C. The reaction mixture was allowed to stir under the same conditions for fifteen minutes. Following this, the solvent was removed under reduced pressure, and the residue was treated with 10% aqueous acetic acid and the thick slurry obtained was again subjected to reduced pressure for five minutes and then the ethanol was added. The solution was then refluxed for fifteen minutes, followed by work-up and column chromatography to yield the product **25** as orange needles in 74% yield. The product was characterized by NMR spectroscopy, and the results were found to be in agreement with the literature.<sup>69</sup>



The <sup>1</sup>H NMR spectrum of 5-(benzyloxy)-2-bromonaphthalene-1,4-dione **25**, showed one less proton than observed in the starting material **40** which indicated that aromatic quinone proton had been substituted with a bromine atom. The benzylic protons were observed as a singlet at 5.31 ppm in the <sup>1</sup>H NMR spectrum with the benzylic carbon giving rise to a signal at 70.99 ppm in the <sup>13</sup>C NMR spectrum. Two carbonyl carbons of the quinone carbons, C-1 and C-4 could be seen at 181.26

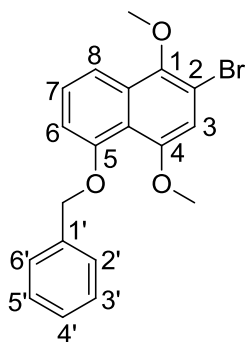
and 178.26 ppm in the  $^{13}\text{C}$  NMR spectrum. At 158.83 ppm in  $^{13}\text{C}$  NMR a signal due to C-5 was observed.

### 2.5.3 Synthesis of 5-(Benzyloxy)-2-bromo-1,4-dimethoxynaphthalene **26**



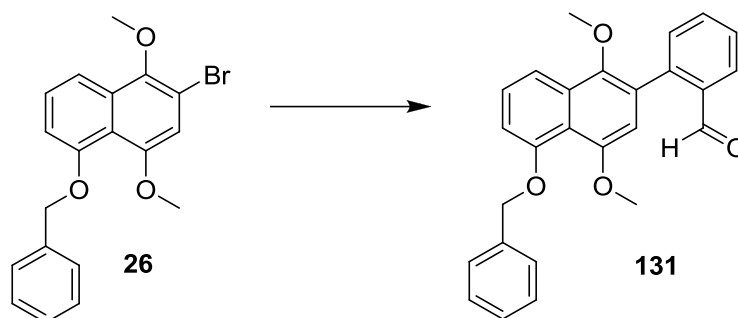
**Scheme 49:** Reagents and conditions: 1)  $\text{Na}_2\text{S}_2\text{O}_4$ , DEE,  $\text{H}_2\text{O}$ , rt, 1 hr. 2)  $\text{K}_2\text{CO}_3$ ,  $\text{Me}_2\text{SO}_4$ , acetone, reflux, 24 hrs, 74%.

Reduction of the quinone and the subsequent protection of the hydroquinone as methyl ether was done the same way as in the synthesis of 1,4-dimethoxy naphthalene **96**. The reaction was accomplished in two steps, with the first step being the reduction of the quinone to obtain a 1,4-diol intermediate. This reduction was achieved by stirring a solution of starting material **25** in diethyl ether with a solution of sodium dithionite in water. After work up, the intermediate hydroquinone was dissolved in acetone and potassium carbonate and dimethyl sulfate were added. Subsequently, work-up and column chromatography facilitated the isolation of the product **26** as a white solid in 74% yield. The product was characterized by NMR spectroscopy and the spectroscopic data was found to be in agreement with that reported in the literature.<sup>70</sup>



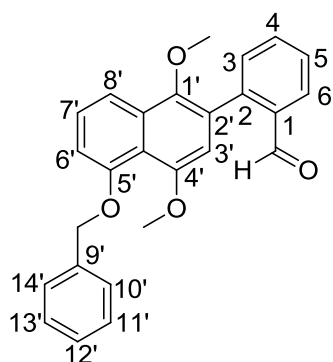
Most notably, the appearance of two singlets at 3.91 and 3.89 ppm in the  $^1\text{H}$  NMR spectrum indicated the presence of the two methoxy groups, with the corresponding carbon peaks visible at 61.24 and 56.60 ppm in the  $^{13}\text{C}$  NMR spectrum. Three peaks at 156.57, 154.04 and 146.64 ppm represent three carbons attached to oxygen C-1, C-4 and C-5 in the  $^{13}\text{C}$  NMR spectrum. Conclusive C-Br peak in the  $^{13}\text{C}$  NMR spectrum could be identified at 137.32 ppm.

### 2.5.4 Synthesis of 2-(5-(Benzyloxy)-1,4-dimethoxynaphthalen-2-yl)benzaldehyde **131**



**Scheme 50:** Reagents and conditions: 2-formylphenyl boronic acid,  $\text{Pd}(\text{PPh}_3)_4$ , CsF, DMF, microwave irradiation, 150 °C, 150 W, 30 mins, 93%.

2-(5-(Benzyloxy)-1,4-dimethoxynaphthalen-2-yl)benzaldehyde **131** was prepared by the standard microwave method for the Suzuki-Miyaura cross coupling reaction we had used previously in the synthesis of 2-(1,4-dimethoxynaphthalen-2-yl)benzaldehyde **99**. 5-(Benzyloxy)-2-bromo-1,4-dimethoxynaphthalene **26** and all the other reagents were added to dry and freshly degassed dimethoxyethane in a microwave reaction vial. This reaction mixture was subjected to microwave irradiation under the above mentioned conditions. This was followed by work-up and column chromatography and the product **131** was obtained as a yellow solid in a 93% yield.



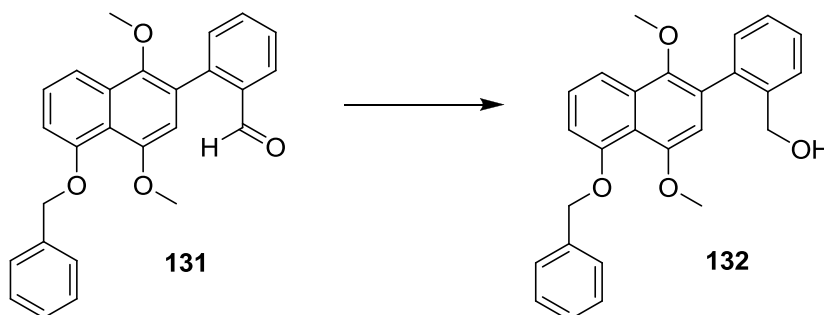
Analysis of the product **131** was done by NMR spectroscopy and the results were found to be as expected. Signals from both the starting materials, 5-(benzyloxy)-2-bromo-1,4-dimethoxynaphthalene **26** and 2-formylphenylboronic acid **98** were evident. At 9.90 ppm in the  $^1\text{H}$  NMR spectrum a singlet could be seen integrating for one proton, which is characteristic of an aldehyde functional group. The corresponding carbonyl carbon could be seen at 192.37 ppm in the  $^{13}\text{C}$  NMR spectrum.

At 5.25 ppm a signal integrating for two protons due to the benzylic protons was visible in the  $^1\text{H}$  NMR spectrum and the corresponding carbon signal was observed at 71.54 ppm in the  $^{13}\text{C}$  NMR spectrum.

Having results from previous reactions that the *N*-bromosuccinimide reaction could proceed through an aldehyde intermediate we planned to subject 2-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)benzaldehyde **108** to *N*-bromosuccinimide in a chlorinated solvent

(both dichloromethane and chloroform were used) in order to obtain 1-(benzyloxy)-12-methoxy-6H-dibenzo[*c,h*]chromen-6-one **48**. When we proceeded with this reaction we were unable to isolate any of the desired product **48**. Within a few seconds, when monitored by thin layer chromatography the reaction gave rise to multiple faint spots on thin layer chromatography plate which were difficult to purify and isolate.. We therefore planned to reduce 2-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)benzaldehyde **108** to (2-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **109** and then attempt the ring cyclization.

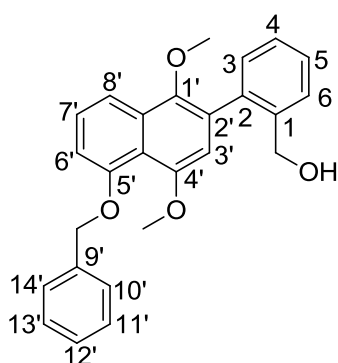
### 2.5.5 Synthesis of (2-(5-(Benzyloxy)-1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **132**



**Scheme 51:** Reagents and conditions: NaBH<sub>4</sub>, Dry THF, rt, 12 hrs, 99%.

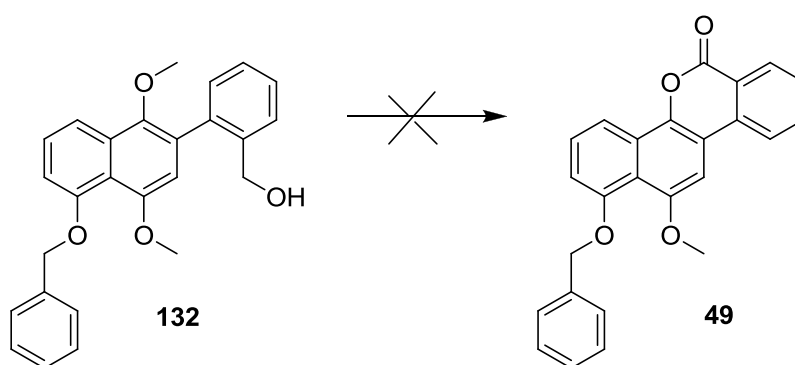
Proceeding further with our synthesis, we were now in a position to reduce the aldehyde functionality of the **131** into the benzylic alcohol **132** to obtain our substrate required for the *N*-bromosuccinimide mediated ring closure reaction. In our initial attempts to obtain the product **132** we used lithium aluminium hydride as the reducing agent in tetrahydrofuran. Thin layer chromatography of the reaction mixture showed that all of the starting material had been consumed and two spots of almost equal intensity appeared at much lower *R<sub>f</sub>* than the starting material **131**. As we were expecting our product to be more polar than the starting material **132** because of the presence of the hydroxyl group, we thought that one of these spots would be our desired product. However, we were unable to separate these products by column chromatography as they always eluted as a mixture. We therefore decided to change our reducing agent to milder conditions and sodium borohydride was our next choice. The starting material **131** was therefore dissolved in dry and freshly distilled tetrahydrofuran, sodium borohydride was added and the mixture was stirred for twelve hours. After work up of the reaction and column chromatography of the mixture our desired product **132** was isolated in 99%.





In both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, peaks for the aldehyde functional group were absent. At 4.41 ppm and 4.39 ppm in the  $^1\text{H}$  NMR spectrum, a doublet of doublet for the two benzylic protons ( $\text{CH}_2\text{OH}$ ) were seen with the corresponding peak in  $^{13}\text{C}$  NMR spectrum observed at 56.55 ppm.

### 2.5.6 Attempted Synthesis of 1-(benzyloxy)-12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one 49

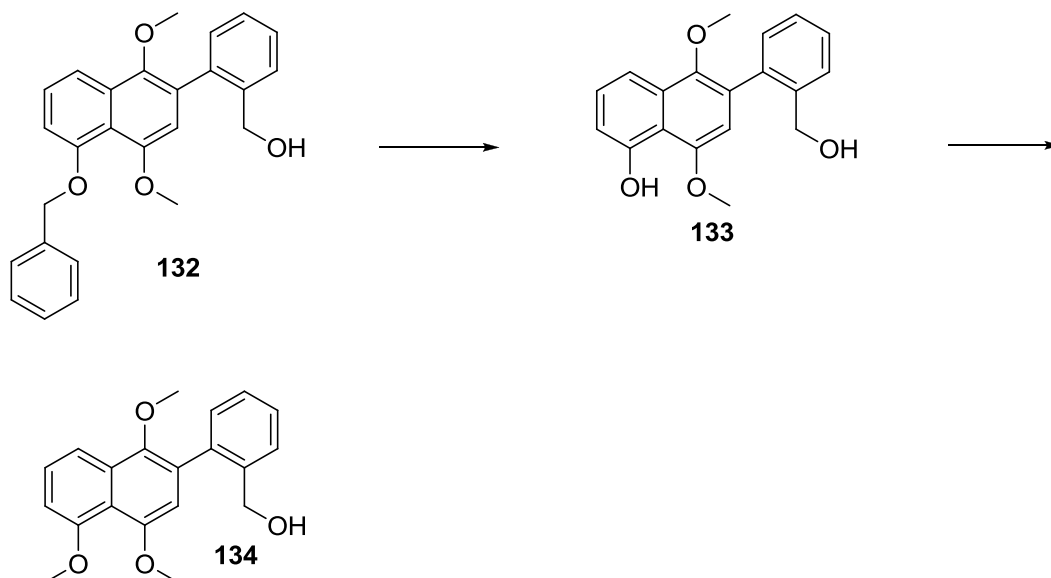


**Scheme 52:** Reagents and conditions: NBS, DCM, rt, atmospheric conditions, 5 mins.

The next step was to try our ring closing reaction using *N*-bromosuccinimide on the substrate (2-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2 yl)phenyl)methanol **132**. To the stirred solution of the starting material **132** dissolved in dichloromethane, *N*-bromosuccinimide was added. It was observed that the reaction mixture turned dark red in colour in a few seconds on addition of *N*-bromosuccinimide, and thin layer chromatography showed that starting material **132** had been consumed and four new faint spots had formed. The products were separated by preparative thin layer chromatography and all the fractions obtained were analyzed by NMR spectroscopy. Unfortunately, none of them were found to be our expected product **49**. It appeared that the reaction was too fast to be controlled at room temperature, and possibly the intermediates and/or product were unstable, so we decided to try this reaction at lower temperatures. A range of temperatures were tested, ranging from 0 °C to -80 °C without success. At this stage we speculated that the presence of a *O*-benzyl protecting substituent might be interfering with the reaction and preventing the desired ring

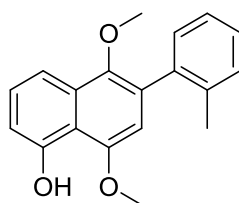
closure from occurring. We therefore decided to test the reaction on a similar system, but using a different protecting group, where a methyl group was used instead.

In order to proceed with a methyl protecting group instead of the benzyl protecting, the first thing we attempted was to perform a debenzylation reaction on **132** and then protect the free naphthol **133** with methyl protecting group to isolate (2-(1,4,5-trimethoxynaphthalen-2-yl)phenyl)methanol **134** as shown in **Scheme 53**.



**Scheme 53**

On attempting the *O*-debenzylation reaction for the conversion of **132** to **133**, by subjecting **132** to hydrogenation in presence of palladium on carbon and dichloromethane as the solvent, we isolated the toluene derivative, 5,8-dimethoxy-6-*o*-tolynaphthalen-1-ol **135** rather than **133**.



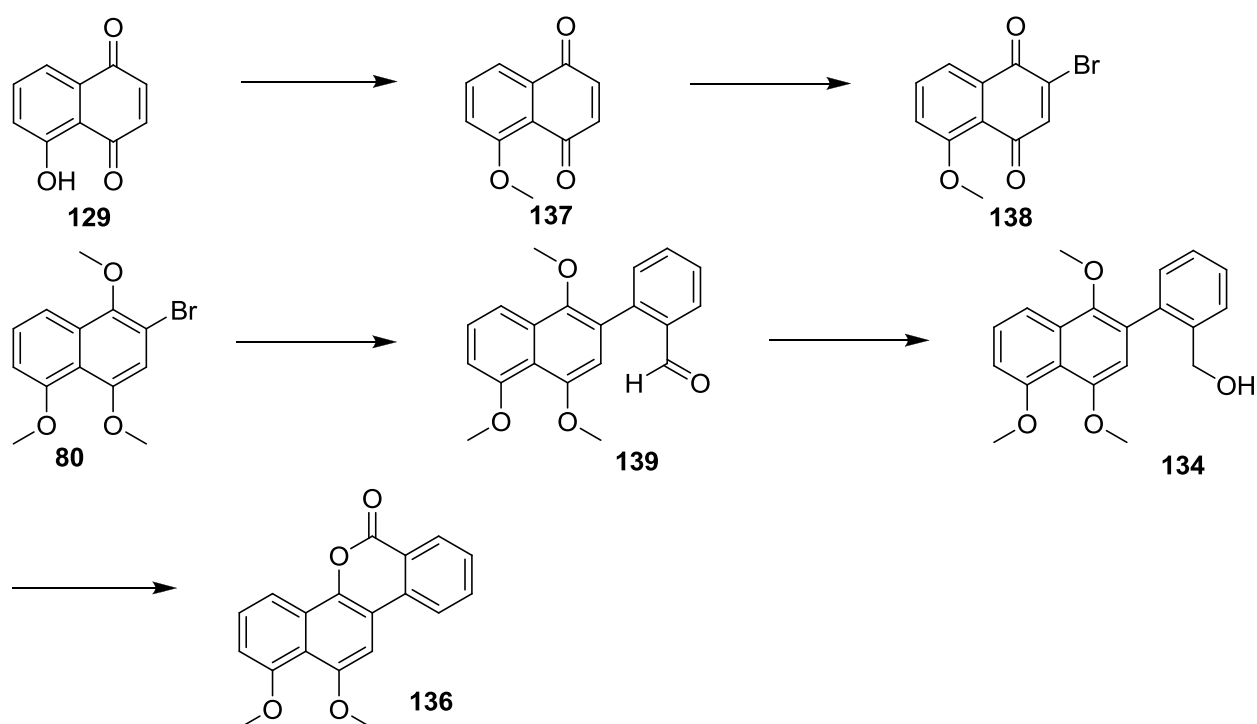
5,8-dimethoxy-6-*o*-tolynaphthalen-1-ol **135**

**Figure 21**

As, a result of this unfavorable product obtained we decided to abandon this approach and synthesize the desired substrate **134** form juglone **129**.

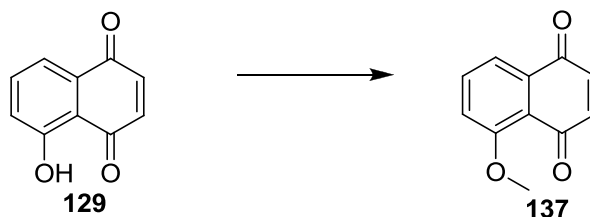
## 2.6 Synthesis of 1,12-Dimethoxy-6*H*-dibenzo[*c,h*]chromen-6-one **136**

As before our prospective plan to synthesize 1,12-dimethoxy-6*H*-dibenzo[*c,h*]chromen-6-one **136** would begin with protecting the free hydroxyl group of juglone **129** with a methyl group to give **137**, followed by bromination at the 2-position of this compound to yield 2-bromo-5-methoxynaphthalene-1,4-dione **138**. The quinone would then be reduced and protected as methyl ether to give **80**, the substrate **80** for our Suzuki Miyaura cross coupling reaction with 2-formyl phenyl boronic acid **98**. The resulting biaryl compound **139** could be reduced to the benzylic alcohol **134**, which we would be able to try our *N*-bromosuccinimide induced ring closure reaction on. Ideally, this should afford the product **136** as shown in **Scheme 54**.



**Scheme 54**

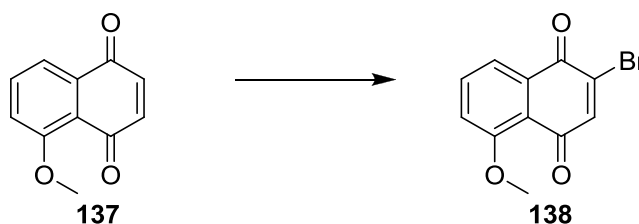
### 2.6.1 Synthesis of 5-Methoxynaphthalene-1,4-dione **137**



**Scheme 55:** Reagents and conditions: MeI, Ag<sub>2</sub>O, DCM, rt, inert conditions, 48 hrs, 73%

To begin our synthesis, commercially available juglone **129** was methylated using methyl iodide as the methyl source. Juglone **129** was dissolved in dichloromethane and silver(I)oxide and methyl iodide were added to it. Progress of the reaction was monitored by thin layer chromatography and to our surprise it was observed that the product formed had lower R<sub>f</sub> compared to the starting material **129**. This could be attributed to the fact that the free naphthol forms a hydrogen bond in juglone **129**. On completion of the reaction the silver salt was filtered off and the residue was purified by column chromatography to afford the product **137** as a bright yellow solid in 73%. The structure of the product **137** obtained was confirmed by NMR spectroscopy and was found to be in agreement with that of the literature.<sup>71</sup>

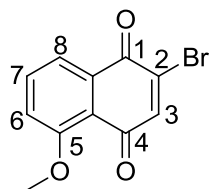
### 2.6.2 Synthesis of 2-Bromo-5-methoxynaphthalene-1,4-dione **138**



**Scheme 56:** Reagents and conditions: 1) Br<sub>2</sub>, DCM, 0 °C, inert conditions, 15 mins; 2) 10% Acetic acid, ethanol, reflux, 15 mins, 73%.

After methyl protection of the phenolic substituent in juglone our next step in the synthesis was bromination at the 2-position of 5-methoxynaphthalene-1,4-dione **137**. This was achieved by dissolving the starting material **137** in dichloromethane and reducing the temperature of the solution to 0 °C. Bromine dissolved in dichloromethane at 0 °C was added drop-wise to the stirred solution of our starting material **137** and the reaction was

allowed to stir for fifteen minutes at the same temperature and under inert conditions. This was followed by work-up and purification by column chromatography, the product **138** was obtained as orange needles in 73% yield.



Identification of the product **138** was done by NMR spectroscopy. Spectral data was in agreement with the data found in the literature.<sup>67</sup> In particular what was notable was that on conversion from 5-methoxynaphthalene-1,4-dione **137** to 2-bromo-5-methoxynaphthalene-1,4-dione **138**, there was one less proton signal observed in the  $^1\text{H}$  NMR spectrum of the product **138**.

Although this bromination reaction worked well in terms of the yields extreme care was taken to prevent large quantities of other by-products forming during the reaction, such as 2-bromo-8-methoxynaphthalene-1,4-dione **140** and 2,3-dibromo-5-methoxynaphthalene-1,4-dione **141** as shown in **Figure 22**.

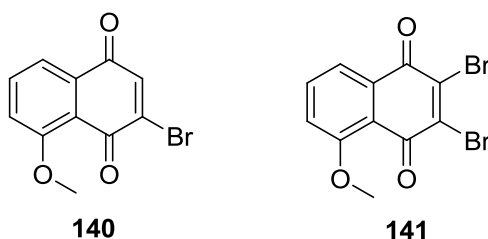
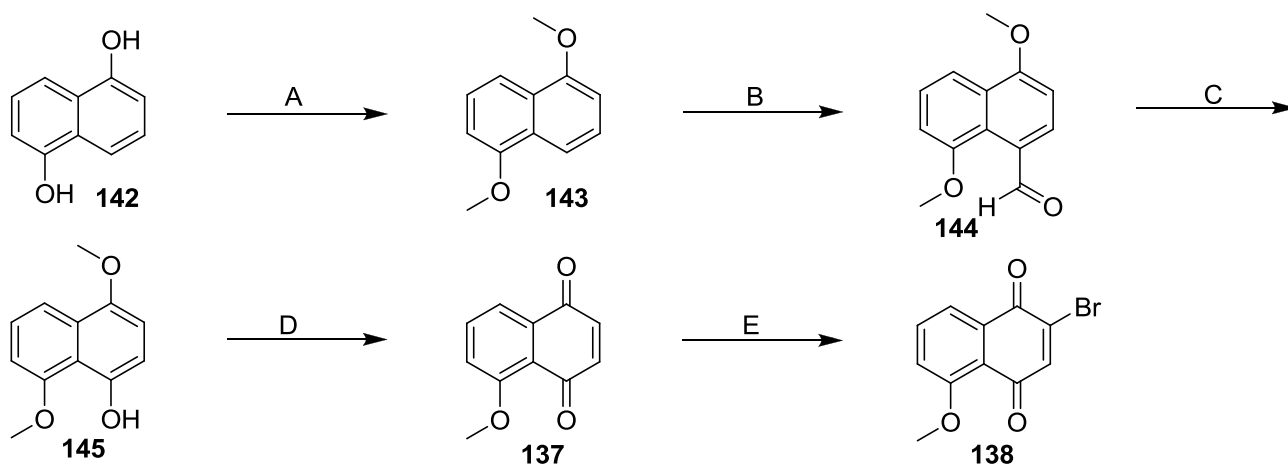


**Figure 22**

Unfortunately even a slight excess of bromine led to the formation of these by-products (**140** and **141**), along with the expected product **138**. In addition, even when strictly one equivalent of bromine was added, the starting material **137** was not consumed during the course of the reaction due to by-product formation. As all of these compounds had very close  $R_f$  values, with almost equal intensity on the thin layer chromatography plate and hence purification of the product was difficult.

Owing to the cost of buying commercially available juglone **129**, we considered synthesizing the required brominated analogue by an alternative route starting from 1,5-dihydroxy naphthalene **118**.

### 2.6.3 Synthesis of 2-Bromo-5-methoxynaphthalene-1,4-dione **138** From 1,5-Dihydroxy naphthalene **142** – Method 1

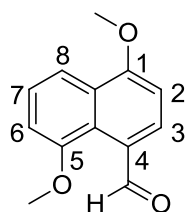


**Scheme 57:** Reagents and conditions: A)  $\text{K}_2\text{CO}_3$ ,  $\text{Me}_2\text{SO}_4$ , acetone, reflux, 12 hrs, 86%; B)  $\text{POCl}_3$ , DMF, toluene, 0 °C-rt- reflux, 3.5 hrs, 79%; C)  $\text{H}_2\text{O}_2$ ,  $\text{H}_2\text{SO}_4$ , methanol, 0 °C-rt, 12 hrs, 80%; D) CAN,  $\text{CH}_3\text{CN}$ :  $\text{H}_2\text{O}$  (1:1), rt, atmospheric conditions, 5 mins, 99%; E) 1) Bromine, DCM, 0 °C, inert conditions, 15 mins; 2) 10% Acetic acid, ethanol, reflux, 15 mins, 73%.

To this end, 1,5-dihydroxynaphthalene **142** was methylated to afford 1,5-dimethoxynaphthalene **143**. The reaction was carried out by dissolving the starting material **142** in acetone and adding potassium carbonate to the solution. On completion of the reaction the desired product **143** precipitated out of the solution by the addition of aqueous ammonia. The product was isolated by filtration and dried. NMR spectroscopic analysis confirmed the formation of the desired product **143** which was also found to be in agreement with literature.<sup>72</sup>

Having protected the hydroxyl groups, the next step was to generate the desired naphthoquinone. This was achieved by initially formylating 1,5-dimethoxynaphthalene **143** using the classical Vilsmeier-Haack formylation reaction with phosphorus oxychloride and dimethylformamide and employing toluene as the solvent. To carry out the reaction, starting material **143** was dissolved in dimethylformamide and toluene to obtain a thick slurry. The temperature was maintained at 0 °C and phosphorus oxychloride was added slowly. The reaction was allowed to stir at the same temperature for thirty minutes before warming it up to room temperature and then was heated under reflux for another two hours. Over this time the reaction mixture changes colour from dark brown to dark red. After work-up with sodium

hydroxide and purification by column chromatography, the product **144** was obtained as a yellow solid in 79% yield.



The product 4,8-dimethoxy-1-naphthaldehyde **144** was characterized by NMR spectroscopy and was found to be in accordance with literature.<sup>73</sup> The characteristic peak for the aldehydic proton was observed at 11.04 ppm in the  $^1\text{H}$  NMR spectrum and the corresponding carbonyl carbon was seen at 194.60 ppm in the  $^{13}\text{C}$  NMR spectrum. Two methoxy peaks were observed at 4.05 and 4.00 ppm in the  $^1\text{H}$  NMR spectrum and at 55.90 and 55.62 in the  $^{13}\text{C}$  NMR spectrum.

After introduction of the formyl group at the 4-position of the naphthalene nucleus, we were now in a position to oxidize this system to produce methoxy protected juglone **137**.

To carry out the reaction, we dissolved the starting material **144** in methanol and both hydrogen peroxide and sulfuric acid were added dropwise at 0 °C. The reaction was then allowed to stir at room temperature for twelve hours, while monitoring the progress of the reaction by thin layer chromatography. On completion, a basic work-up was done and the crude product was purified by column chromatography. Close inspection of the spectroscopic data showed that we had in fact isolated the intermediate 4,8-dimethoxynaphthalen-1-ol **145**. We were not unhappy with this result as we anticipated that it would be easy to oxidize to the desired product **137**. The spectroscopic result was found to be in agreement with the data found in literature.<sup>74</sup>

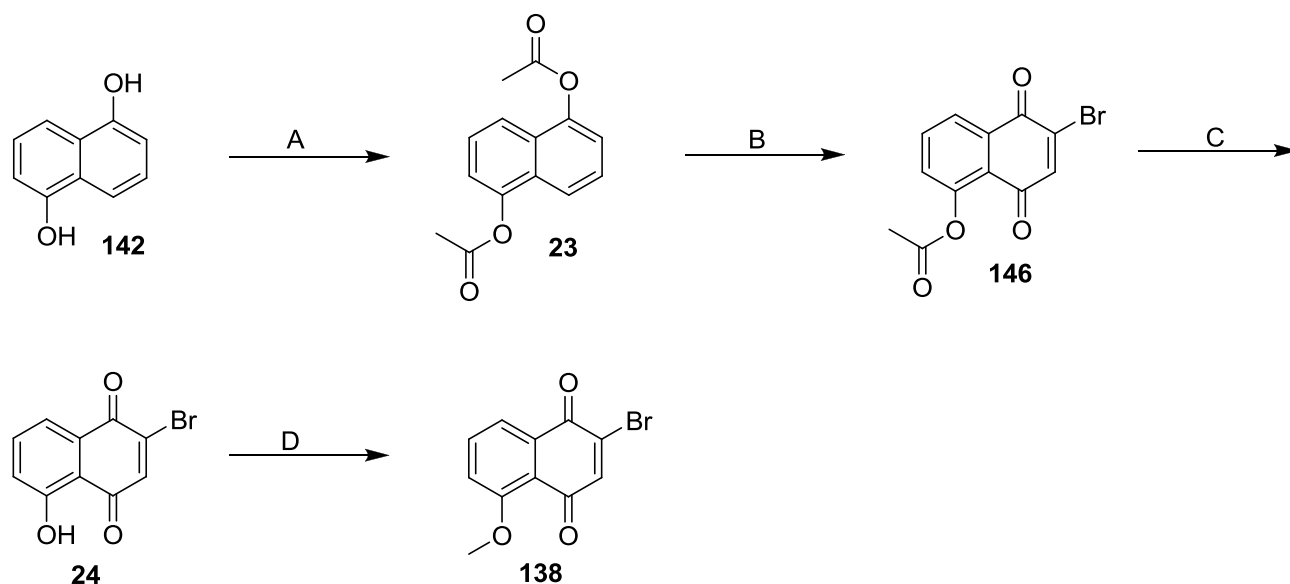
After identification of the intermediate 4,8-dimethoxynaphthalen-1-ol **145**, we next attempted the oxidation of this compound to obtain 5-methoxynaphthalene-1,4-dione **137**. Ceric ammonium nitrate was used as the oxidizing agent for this step. The reaction was carried out by dissolving the starting material **145** in a mixture of acetonitrile and water, and ceric ammonium nitrate was added to the stirred solution. The reaction was allowed to stir at room temperature and exposed to air for twelve hours. After work-up and purification by column chromatography, the desired product **137** was obtained as orange needles in 99% yield. Analysis of the product by NMR spectroscopy was found to be in agreement with that reported in the literature.<sup>67</sup> The methoxy protected juglone **137** that we had synthesized over four steps was further brominated using the same procedure as discussed previously (**Scheme 57**). This gave 2-bromo-5-methoxynaphthalene-1,4-dione **138**, which was characterized by NMR spectroscopy.

Although the product **138** was easily prepared by this route (**Scheme 57**), we were still unhappy with the outcome of the last step, bromination of 5-methoxynaphthalene-1,4-dione **137**. As discussed previously, this reaction was unpredictable and it was difficult to isolate pure product **138** from the complex mixture of by-products (**116** and **117**) and starting material **110**. In addition, the by-products (**140** and **141**) formed in the reaction were reactive in the following steps of the synthesis, making purification at this step crucial.

We therefore sought alternative route for the preparation of 2-bromo-5-methoxynaphthalene-1,4-dione **138**. During our literature search we came across a paper, where the problems arising from the bromination step could be overcome by carrying out the bromination at an earlier stage in the synthesis.<sup>75</sup>

#### 2.6.4 Synthesis of 2-Bromo-5-methoxynaphthalene-1,4-dione **138** from 1,5-Dihydroxy naphthalene **142** – Method – 2

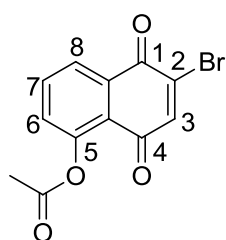
In this method for the synthesis of 2-bromo-5-methoxynaphthalene-1,4-dione **111**, we avoided two major problems that were arising in our previous two synthetic schemes: protection of the juglone **106** and bromination of the resulting product. Also, the synthesis appeared to be both time and cost efficient.



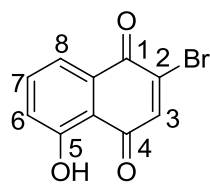
**Scheme 58:** Reagents and conditions: A) Acetic anhydride, pyridine, rt, 12 hrs, 98%; B) NBS, CH<sub>3</sub>COOH, H<sub>2</sub>O, 45 mins, 60 °C, 45 mins, inert conditions, 79%; C) 3 N H<sub>2</sub>SO<sub>4</sub>, ethanol, reflux, 90 mins, 98%; D) MeI, Ag<sub>2</sub>O, CHCl<sub>3</sub>, 48 hrs, rt, inert conditions, 87%.



The reaction was conducted by the dropwise addition of a warm solution of our starting material **23** in acetic acid to a stirred solution of *N*-bromosuccinimide in a mixture of water and acetic acid and allowing this reaction mixture to stir for further forty five minutes at 60 °C under inert conditions. On completion of the reaction, the mixture was quenched with water and the product was extracted in to chloroform and was precipitated from the solution by addition of ethanol. This gave the desired product **146** as orange needles in 79% yield. The product **146** was characterized by NMR spectroscopy and the results were found to be in agreement with the literature.<sup>75</sup>



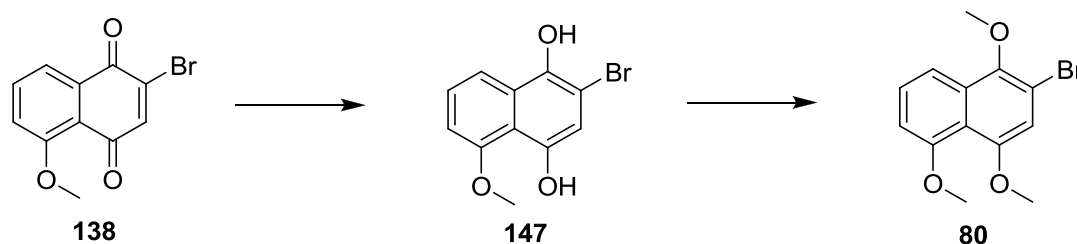
Having synthesized the brominated quinone 6-bromo-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate **146**, the next step in our synthesis was the removal of the acetyl group from **146** to obtain free hydroxyl group which could be re-protected with a more robust protecting group. The deprotection reaction was carried out by refluxing the mixture of starting material **146** in ethanol with a 3 N sulfuric acid solution for ninety minutes. The product was isolated and purified by column chromatography to afford an orange solid in 98% yield and characterized by NMR spectroscopy. The results were found to be in agreement with literature.<sup>70</sup>



In the NMR spectra of the product **24**, there were no signals from the acetyl protecting group as expected. Instead, a singlet was visible at 11.81 ppm in the  $^1\text{H}$  NMR spectrum due to the proton of the hydroxyl group with a signal for the phenolic carbon C-5 at 147.11 ppm in the  $^{13}\text{C}$  NMR spectrum.

The last step in the synthesis of the intermediate 2-bromo-5-methoxynaphthalene-1,4-dione **138** was the protection of the free hydroxyl group of 2-bromo-5-hydroxynaphthalene-1,4-dione **24**. This was achieved by dissolving the starting material **24** in dichloromethane and treating the solution with silver(I)oxide and methyl iodide which acts as a methyl source. Upon completion of the reaction, the product was isolated and purified by column chromatography followed by isolation of the product in 87% yield as a yellow solid. The product **138** obtained was analyzed by NMR spectroscopy and the data was found to correspond to the results obtained previously, (**Section 2.6.2**) and also with the data in the literature.<sup>70</sup>

### 2.6.5 Synthesis of 2-Bromo-1,4,5-Trimethoxynaphthalene 80



**Scheme 59:** Reagents and conditions:  $\text{Na}_2\text{S}_2\text{O}_4$ , AIBN, KOH,  $\text{Me}_2\text{SO}_4$ , THF, rt, 18 hrs, 76%.

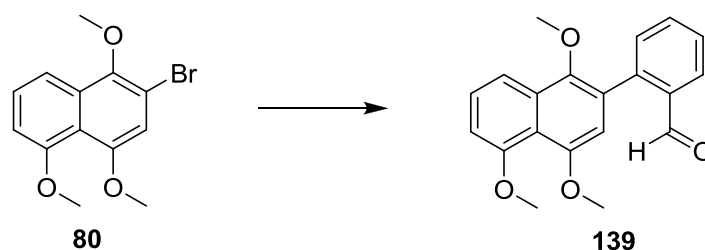
Initially we attempted the reduction of the quinone **138** using the conventional procedure by stirring the starting material **138** in diethyl ether with sodium dithionite in water for thirty minutes. After this time, the solvent was removed and the unstable intermediate **147** obtained was immediately dissolved in dry acetone and treated with potassium bicarbonate and dimethyl sulphate, to afford the product **80**.

We also tested an alternate procedure for the synthesis of **80** from **138**. In this procedure, the starting material **138** was dissolved in dry tetrahydrofuran under inert conditions and treated with aqueous sodium dithionite and AIBN to reduce the quinone. This could be observed as the reaction mixture changes colour from dark brown to almost pale yellow.

After ten minutes, an aqueous solution of potassium hydroxide was added to the reaction mixture, which abstracts protons from the newly formed methoxynaphthalene-1,4-diol **147**, with a colour change from pale yellow to very dark brown. To this solution, dimethyl sulfate was then added, giving rise to our desired product **80**. Progress of the reaction was carried out by thin layer chromatography. After work-up and purification by column chromatography, the pure product **80** was isolated as a white solid in 76% yield.

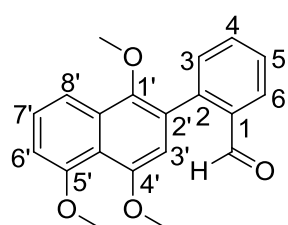
This procedure provided a convenient way to synthesize 2-bromo-1,4,5-trimethoxynaphthalene **80** from 2-bromo-5-methoxynaphthalene-1,4-dione **138**, in one pot, with shorter reaction time and using very mild conditions when compared with our previous procedure.

#### 2.6.6 Synthesis of 2-(1,4,5-Trimethoxynaphthalen-2-yl)benzaldehyde **139**



**Scheme 60:** Reagents and conditions: 2-Formylphenyl boronic acid,  $\text{Pd}(\text{PPh}_3)_4$ , CsF, DMF, microwave irradiation, 150 °C, 150 W, 30 mins, 64%.

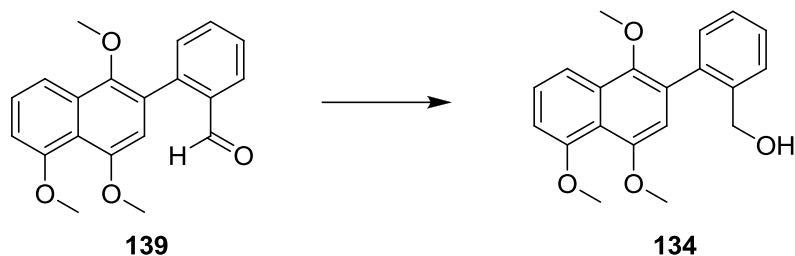
We were finally in a position to test the Suzuki-Miyaura cross coupling reaction on **80** to produce the desired biaryl compound **139**. The reaction was carried out in a microwave reactor using the same standard procedure used previously. The product **139** was isolated as an off-white solid in 64% yield.



Characterization of the product by NMR spectroscopy showed the correct number of protons and carbons in the respective NMR spectra expected for the biaryl compound **139**. A singlet at 9.89 ppm was visible in the  $^1\text{H}$  NMR spectrum characteristic for the aldehyde proton, and the corresponding carbonyl carbon, gave signal at 192.36 ppm in the  $^{13}\text{C}$  NMR spectrum. In addition to this new peak, all other characteristic peaks were visible. There were three peaks due to the methoxy groups in both the  $^1\text{H}$  and

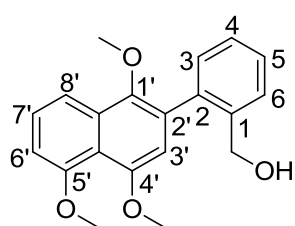
$^{13}\text{C}$  NMR spectra at 4.01, 3.98 and 3.37 ppm in the  $^1\text{H}$  NMR spectrum and at 60.72, 56.93 and 56.57 ppm in the  $^{13}\text{C}$  NMR spectrum.

### 2.6.7 Synthesis of (2-(1,4,5-Trimethoxynaphthalen-2-yl)phenyl)methanol



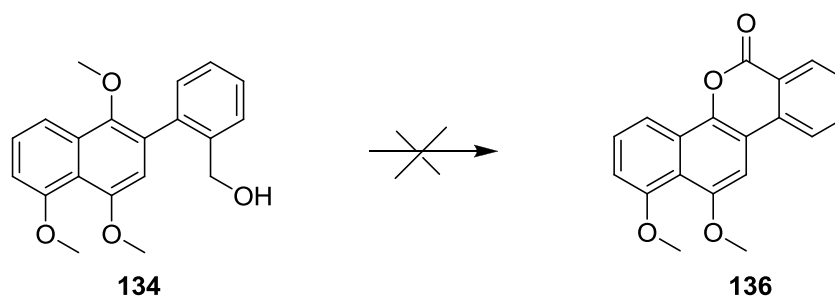
**Scheme 61:** Reagents and conditions:  $\text{NaBH}_4$ , dry THF, rt, 12 hrs, 100%

Reduction of the aldehyde **139** to alcohol **134** to afford the substrate for our novel ring closing reaction was readily carried out. The same procedure was employed as previously done for the reduction of 2-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)benzaldehyde **131** to (2-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **132** as discussed in **Section 2.5.5**. 2-(1,4,5-Trimethoxynaphthalen-2-yl)benzaldehyde **139** was dissolved in dry freshly distilled tetrahydrofuran and sodium borohydride was added to this solution under inert conditions and at room temperature. Isolation of the product **134** and purification gave the product as a white solid in 100% yield.



The  $^1\text{H}$  NMR spectrum confirmed that the reduction of the aldehyde to an alcohol had taken place as the signal for the aldehyde proton at 9.89 ppm in the  $^1\text{H}$  NMR spectrum was missing. A new doublet of doublet appeared in the  $^1\text{H}$  NMR spectrum: due to two benzylic protons at 4.31 ppm and 4.33 ppm, which appeared as a doublet and integrated for two protons and a broad multiplet at 0.85 – 0.71 ppm due to the proton of the hydroxyl group. A peak at  $3384\text{ cm}^{-1}$  in the FTIR spectrum also clearly indicated the presence of an alcohol functional group.

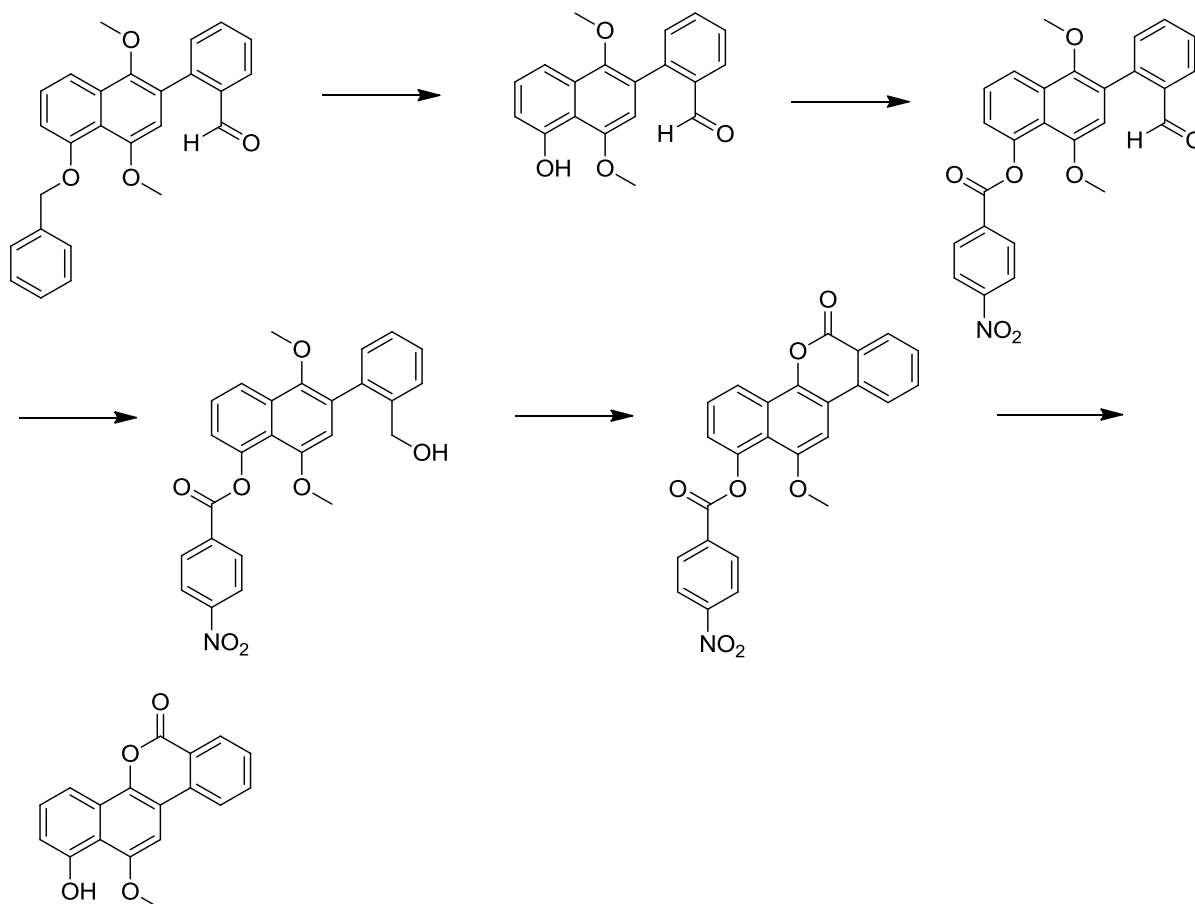
### 2.6.8 Attempted Synthesis of 1,12-Dimethoxy-6*H*-dibenzo[*c,h*]chromen-6-one **136**



**Scheme 62:** Reagents and conditions: NBS, DCM, rt, atmospheric conditions, 5 mins.

The final *N*-bromosuccinimide induced ring closure reaction was carried out the same way as described for the conversion of (2-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **132** to 1-(benzyloxy)-12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **49** (Section 2.5.6), but unfortunately it did not afford the desired product **136** in this case. Immediately upon addition of *N*-bromosuccinimide to the stirred solution of (2-(1,4,5-trimethoxynaphthalen-2-yl)phenyl)methanol **134** in dichloromethane at room temperature and under inert conditions, the reaction mixture turned dark red. Thin layer chromatography of the reaction mixture showed that all the starting material **134** had been consumed and four new spots appeared which were isolated employing column chromatography but none of them showed signals of the desired product **136**, as shown by NMR spectroscopy. Also substrate: 2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **139**, which, is a possible intermediate in the reaction, also failed to produce the desired product.

We were very disappointed with this result, but had to conclude that the reaction was not successful when a slightly more electron rich substrate is used. One possibility that could be tested is the use of an electron withdrawing protecting group such as *p*-nitrobenzoyl chloride, in the last step. This will help in decreasing electron density from the ring system, and may result in the formation of the desired product as shown in **Scheme 63**.

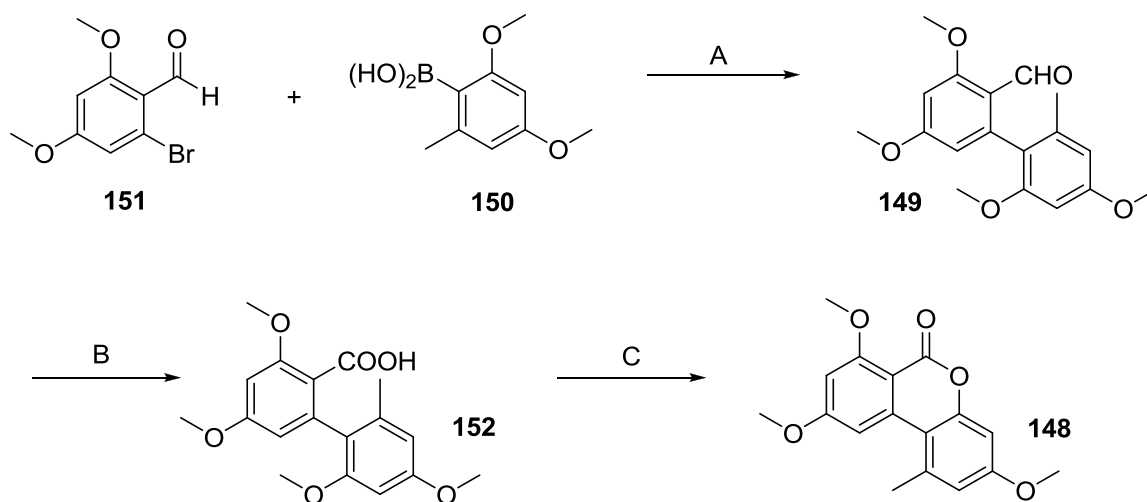


Scheme 63

Unfortunately, due to time constraints this alternative strategy was not tested, however, it will be considered for the future work.

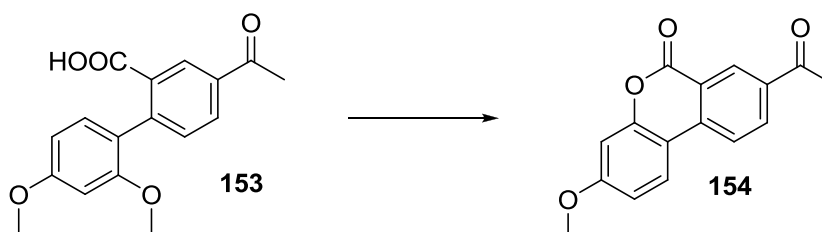
The other possibility to synthesize the desired lactone framework **65** could be by converting aldehyde into a carboxylic acid and then trying the oxidative lactonization reaction. There are several examples in the literature where this kind of approach has been employed to synthesize related lactones, but this would not fall in the ambit of the *N*-bromosuccinimide-mediated reactions that we were studying.

For example, Koch *et al.* in 2005 demonstrated the synthesis of alternariol **148** where Suzuki-Miyaura cross coupling reaction was employed to form a biaryl axis **149** between the substituted boronic acid **150** with a brominated resorcylic aldehyde **151**.<sup>76</sup> Later the aldehyde in **149** was oxidized to the carboxylic acid **152** which was followed by a lactone ring forming reaction in the presence of boron tribromide to afford alternariol **148** as shown in **Scheme 64**.



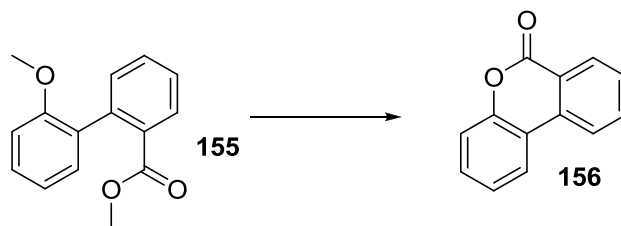
**Scheme 64:** Reagents and conditions: A)  $\text{K}_2\text{CO}_3$ ,  $\text{Pd}(\text{PPh}_3)_4$ , DMF,  $100\text{ }^\circ\text{C}$ , 4 hrs, 78%; B)  $\text{NaH}_2\text{PO}_4$ ,  $\text{NaClO}_4$ , 2-methyl-2-butene,  $t\text{BuOH}/\text{H}_2\text{O}$  (5:1), 2 hrs, 85; C)  $\text{BBr}_3$ , DCM,  $0\text{ }^\circ\text{C}$ , 24 hrs, 73%.

Schmidt *et al.* also synthesized benzo fused pyranone framework by performing lactonization reaction between a carboxylic acid and methoxy group across the biaryl axis of **153** to afford **154** as shown in **Scheme 65**.<sup>77</sup>



**Scheme 65:** Reagents and conditions:  $\text{SOCl}_2$ ,  $\text{AlCl}_3$ , DCM, rt, 90%

Nguyen *et al* also in 2005, demonstrated the synthesis of similar benzo-fused pyranone frameworks by subjecting the substrate having a biaryl axis **155** with methoxy and ester substituents on the ortho position of each ring. Such molecule was subjected to boron tribromide to afford lactonization to generate **156** as shown in **Scheme 66**.<sup>78</sup>



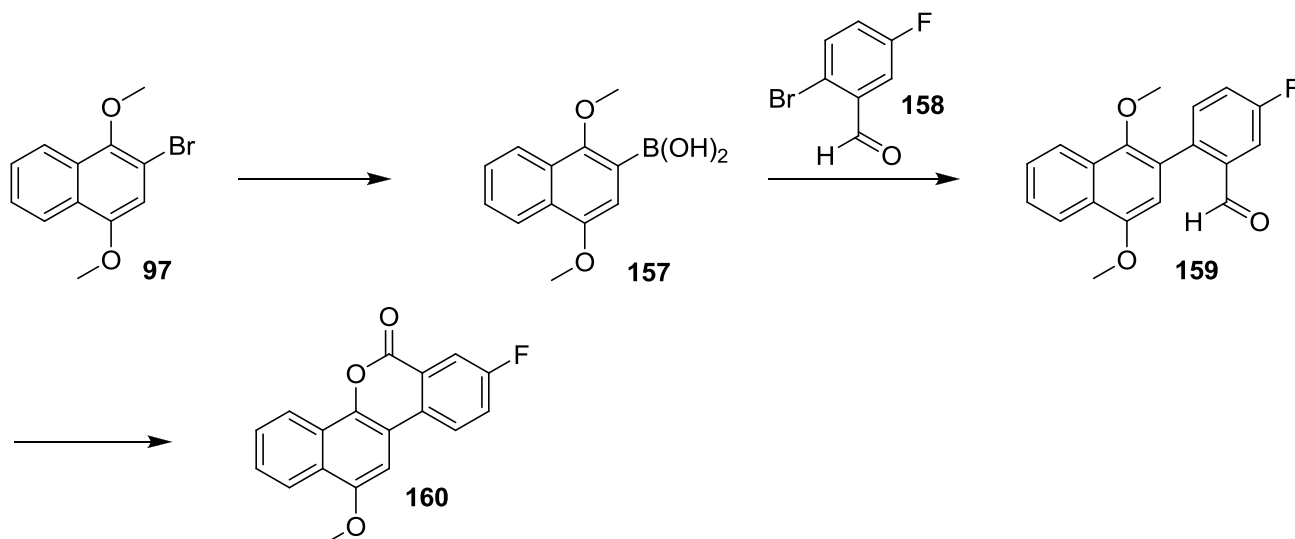
**Scheme 66:** Reagents and conditions:  $\text{BBr}_3$ , DCM, 0-20 °C, 18 hrs; 2) KOBut,  $\text{H}_2\text{O}$ , 15 mins, 20 °C, 71%.

## 2.7 Synthesis of Halogenated Naphthopyranones

Still continuing with our novel *N*-bromosuccinimide and air induced ring closure reaction, we wanted to check its applicability on other similar substrates. This time we wanted to see if we could synthesize some halogenated naphthopyranones, and in particular fluoronaphthopyranones.

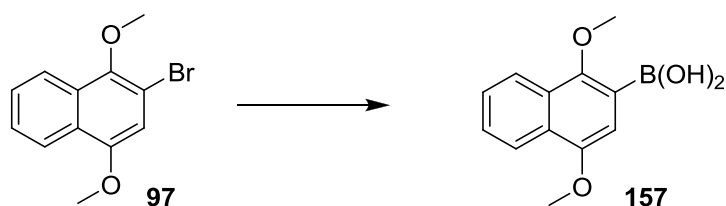
In our quest to synthesize fluorine containing naphthopyranones, we envisioned that if we could synthesize 1,4-dimethoxynaphthalen-2-ylboronic acid **157** from previously synthesized 2-bromo-1,4-dimethoxynaphthalene **97** we could then perform a Suzuki Miyaura reaction with 2-bromo-5-fluorobenzaldehyde **158**. We anticipated that the Suzuki Miyaura coupling would take place between the bromine end of the boronic acid **158** rather than on fluorine substituent of **158** as bromine is a better leaving group.<sup>79</sup> If we were able to prepare the biaryl compound **159** we could then subject this molecule to the conditions of the *N*-bromosuccinimide-mediated reaction to obtain the ring closed product, or we could reduce the aldehyde functional group to an alcohol and then subject the resulting product to these conditions. As we have already seen that the reaction proceeds via an aldehyde intermediate we decided to initially test the *N*-bromosuccinimide ring closure reaction on aldehyde intermediate **159**.





Scheme 67

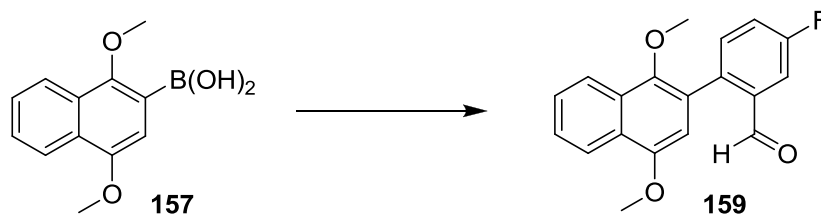
### 2.7.1 Synthesis of 1,4-Dimethoxynaphthalen-2-ylboronic acid **157**



**Scheme 68:** Reagents and conditions: *n*BuLi, triisopropylborate, dry THF, 78 °C-rt.

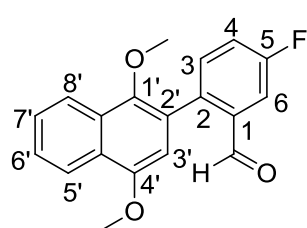
From previously prepared 2-bromo-1,4-dimethoxynaphthalene **97**, we synthesized 1,4-dimethoxynaphthalen-2-ylboronic acid **157**, using a reported procedure for the synthesis of boronic acids.<sup>62 - 80</sup> Before carrying out the reaction, triisopropyl borate and tetrahydrofuran were distilled and the molarity of the *n*butyllithium was calculated by titration. 2-Bromo-1,4-dimethoxynaphthalene **97** then dissolved in tetrahydrofuran under inert conditions, cooled to 78 °C and treated with *n*butyllithium. The reaction mixture was stirred under the same conditions for one hour before the addition of triisopropyl borate, and then allowed to slowly warm to room temperature for two hours. After acidic work up the organic phase was collected and the solvent was removed under reduced pressure. The product **157** was isolated by precipitation from acetone at 0 °C. The product **157** was obtained as a white solid and was used immediately in the next step without further characterization due to possible instability.

### 2.7.2 Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)-5-fluorobenzaldehyde **159**



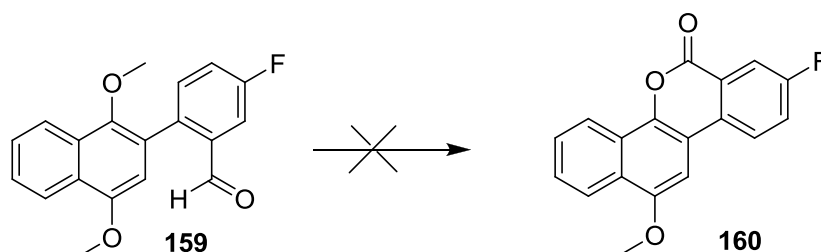
**Scheme 69:** Reagents and conditions: 2-bromo-5-fluorobenzaldehyde,  $\text{Pd(PPh}_3)_4$ ,  $\text{CsF}$ , DMF, microwave irradiation, 150 °C, 150 W, 30 mins, 62%.

Boronic acid intermediate **154** was immediately subjected to a Suzuki-Miyaura cross coupling reaction with 2-bromo-5-fluorobenzaldehyde **159** under microwave conditions. The pure product was obtained after isolation and purification by column chromatography as a yellow solid in 62%.



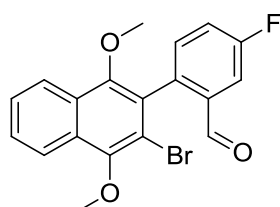
Product formation was confirmed by NMR spectroscopy. There were signals seen from both the fragments used in the reaction in the spectra of the product obtained. There was a characteristic aldehyde peak at 9.83 ppm in the  $^1\text{H}$  NMR spectrum which appeared as a doublet. The corresponding peak for the carbonylic carbon was seen at 191.08 ppm in the  $^{13}\text{C}$  NMR spectrum. Two methoxy peaks were seen as singlets in the  $^1\text{H}$  NMR spectrum at 4.01 and 3.40 ppm. The corresponding methoxy were seen at 60.92 and 55.81 ppm in the  $^{13}\text{C}$  NMR spectrum. One aromatic proton at H-3' gave rise to a singlet upfield at 6.71 ppm in the  $^1\text{H}$  NMR spectrum.

### 2.7.3 Attempted Synthesis of 8-Fluoro-12-methoxy-6H-dibenzo[*c,h*]chromen-6-one **160**



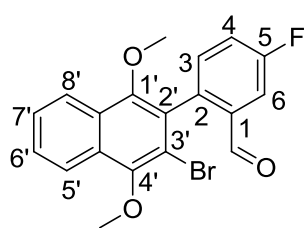
**Scheme 70:** Reagents and conditions: NBS, DCM, rt, 18 hrs, atmospheric conditions.

After having successfully synthesized the biaryl compound **126**, we next wanted to try our *N*-bromosuccinimide induced ring closure reaction on this substrate. The starting material **159** was dissolved in dichloromethane and *N*-bromosuccinimide was added. The reaction was allowed to stir at room temperature and under atmospheric conditions for eighteen hours. During this time the reaction progress was monitored by thin layer chromatography. A new spot of higher  $R_f$  was visible just above the starting material **159** on the thin layer chromatography plate. The product was isolated and characterized by NMR spectroscopy. However, this showed that we had not synthesized the expected product **160**. In this case, *N*-bromosuccinimide acted as a bromine source and brominated position C-3' instead of facilitating the desired cyclization. *N*-bromosuccinimide is known to brominate *ortho* to aromatic methoxy groups, and this system acted as the perfect substrate for *ortho* bromination, affording 2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)-5-fluorobenzaldehyde **161** as shown in **Figure 23**.



2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)-5-fluorobenzaldehyde **161**

**Figure 23**



place.

Confirmation of the identity of the product came from the disappearance of the singlet in the  $^1\text{H}$  NMR spectrum due the proton H-3', which indicated that a substitution reaction has taken place. Also, the existence of peaks for the two methoxy groups and an aldehyde confirmed that the cyclization reaction had not taken

## 2.8 Conclusion

In our quest towards the synthetic approaches to 6*H*-dibenzo[*c,h*]chromen-6-one analogues **65**, as found in gilvocarcins **5**, we successfully managed to synthesize 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **65** and 2-methoxy-6*H*-benzo[*c*]chromen-6-one **110** using our novel *N*-bromosuccinimide induced ring closure reaction. We also managed to elucidate the

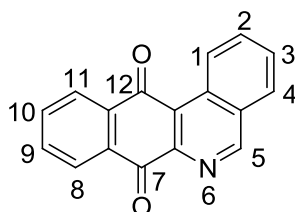
probable mechanism of the reaction, which we believe proceeds via an aldehyde intermediate. Unfortunately, when we tried to extend our methodology towards the synthesis of 1-hydroxy-12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **130** and later halogenated naphthopyranones as 8-fluoro-12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **160**, we failed to execute the methodology to allow for the formation of the desired products. There are literature precedents where lactonization could be achieved by using carboxylic acid intermediate instead of aldehyde intermediate. However, these processes did not demonstrate the use of *N*-bromosuccinimide and oxygen on aldehydes or alcohols for the lactonization process.<sup>77</sup> Factors like, substituents on C-1 of this benzonaphthopyranone system plays an important role here and this aspect could be considered in the future.

## Chapter 3: Introduction, Literature Reviews and Aims: The Jadomycins

### 3.1 Introduction

Nature is an abundant source of medicinally beneficial biologically active molecules. A large amount of research is being carried out to identify such molecules that can either be used in their native forms or derivatized to modify their activities in order to achieve higher specificity and selectivity against a particular target, with lower toxicity. In fact, more than half of the drugs on the market today are derived from natural products.<sup>81, 82</sup> The requirement to identify and develop new and potent therapeutic agents to address a wide array of disease and health-related conditions, has encouraged scientists to discover versatile and efficient routes for the biosynthesis and synthesis of new biologically active natural products.

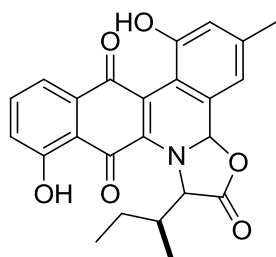
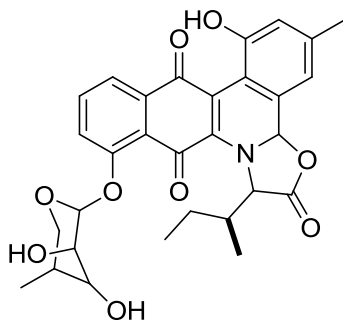
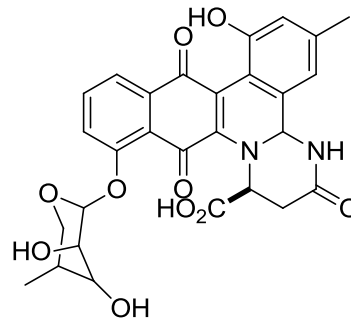
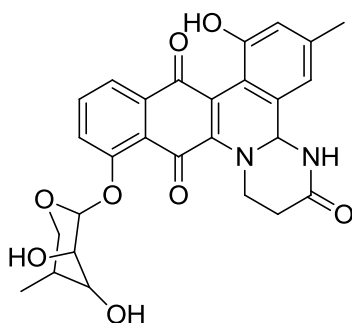
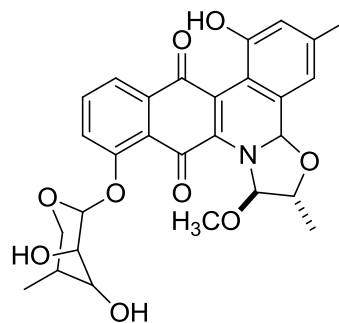
Jadomycins are a unique class of novel angucycline polyketide natural products produced by soil-borne gram positive *Streptomyces venezuelae* ISP5230 (ATCC10712) bacteria under stress and nutrient limitation conditions like heat shock, phase infection, or exposure to toxic concentrations of ethanol.<sup>29</sup> These natural products contain an unusual benzo[*b*]phenanthridine-7,12-dione **162** (**Figure 23**) backbone with variously fused nitrogen and oxygen-containing heterocycles (e.g., oxazolidine, pyrimidine, oxazinone) and carbohydrate attached to the nucleus.



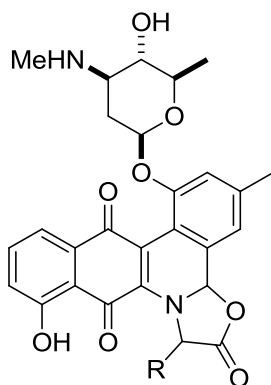
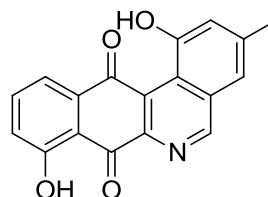
Benzo[*b*]phenanthridine-7,12-dione **162**

**Figure 23**

Some well-known examples of the jadomycins are jadomycin A **163**, B **164**, N **165**, ala **166** and dalomycin **167** (**Figure 24**). With the exception of jadomycin A **163** all the jadomycins are glycosylated with a L-digitoxose carbohydrate unit. Their unique structural complexity and commendable biological activities have stimulated extensive study of their biological activity, biosynthesis and synthesis.<sup>83</sup> The following section covers some reported developments in the study of the jadomycin class of antibiotics.

Jadomycin A **163**Jadomycin B **164**Jadomycin N **165**Jadomycin ala **166**Dalomycin **167****Figure 24**

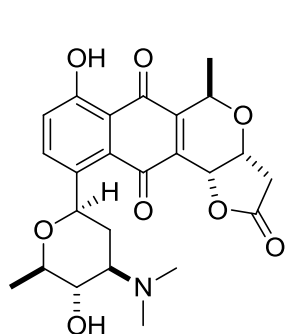
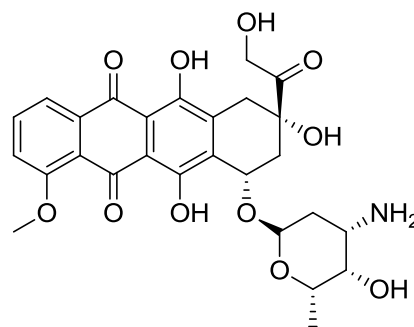
Ayer *et al.* isolated jadomycin A **163** for the first time in 1991 followed by the isolation of jadomycin B **164** in 1993, both from *Streptomyces venezuelae*.<sup>84, 85</sup> This was later followed by isolation and identification of other jadomycins. Interestingly, a year before the isolation of jadomycin A **163**, Fendrich *et al.* reported the isolation of the first naturally occurring benzo[*b*]phenanthridine ring systems, phenanthrovirdin **168** and its aglycone **169** as shown in **Figure 25**, both from *Streptomyces viridochromogenes* (DSM3972) and both these compounds were found to be active against the lung carcinoma MBA9812 in mice.<sup>86</sup>

Phenanthrovirdin **168**Phenanthrovirdin aglycone **169****Figure 25**

It is clearly evident that all these molecules have a characteristic benzo[*b*]phenanthridine-7,12-dione **129** ring system as their skeleton

### 3.2 Biological Importance

Jadomycins are known for their commendable range of biological activities ranging from anti-bacterial properties to activity against both gram positive and gram negative bacterial strains, anti-yeast activity and effectiveness against some drug resistant cancer cell lines.<sup>87, 88</sup> More than 250 structurally defined angucycline compounds have been reported, with a large number of them showing anti-tumour activity although, the mode of action is still not fully understood.<sup>89, 90</sup> It has been suggested that jadomycin B **164** and its related analogues may act as selective protein kinase B (PKB) inhibitors, owing to their structural resemblance to lactoquinomycin A **170**, where the mechanism of action involves the opening of a lactone ring to form the methide that reacts with the thiol functionality in the regulatory region of the PKB.<sup>91</sup> Structural similarities between jadomycin, lactoquinomycin A **170** and doxorubicin **171** (**Figure 26**) further implicate thiol-reactive intermediates that may inhibit DNA-gyrase and topoisomerase, which is another possible possibility for the cytotoxic behavior of jadomycins.<sup>91</sup>

Lactoquinomycin A **170**Doxorubicin **171****Figure 26**

The presence of a quinone system could also be the reason for the potent biological activity of jadomycins. In a system of rapidly dividing cells and/or bacteria, an oxygen deficient area is generated due to constant and rapid consumption of oxygen. Quinones undergo reduction to hydroquinones under this reductive, hypoxic conditions *in-vivo* and consequently act as bisalkylating agents which interact with the DNA of rapidly dividing cells responsible for the reductive system.<sup>92</sup>

Four human tumour cell lines were used to evaluate the cytotoxicity of these jadomycin derivatives including HepG2 (human hepatocellular carcinoma) ATCC HB-8065, IM-9 (human lymphoblast, immunoglobulin-secreting cell line derived from a multiple myeloma) ATCC CCL159, IM-9 subline IM-9/Bcl-2 and H460 (non-small-cell lung cancer). All the jadomycin derivatives tested suppressed the proliferation of tumour cells *in vitro*.<sup>87</sup>

To assess the antimicrobial activity of this class of compounds the jadomycins were evaluated against several microbial strains including *Streptomyces aureus*, *Streptomyces epidermidis*, *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Bacillus subtilis* strains. In general, the jadomycins were observed to be more active against gram-positive microorganisms than gram-negative ones when erythromycin control was used.<sup>93</sup>

### 3.3 Biosynthesis of Jadomycin

The distinctive structure of the jadomycins has inspired extensive study of their biosynthesis with jadomycin B **164** being the prototype. The polyketide synthase (PKS) genes which are accountable for jadomycin B **164** biosynthesis in *Streptomyces venezuelae* ISP5230 (ATCC10712) were first cloned and characterized in 1994.<sup>94</sup> Thereafter, more detailed

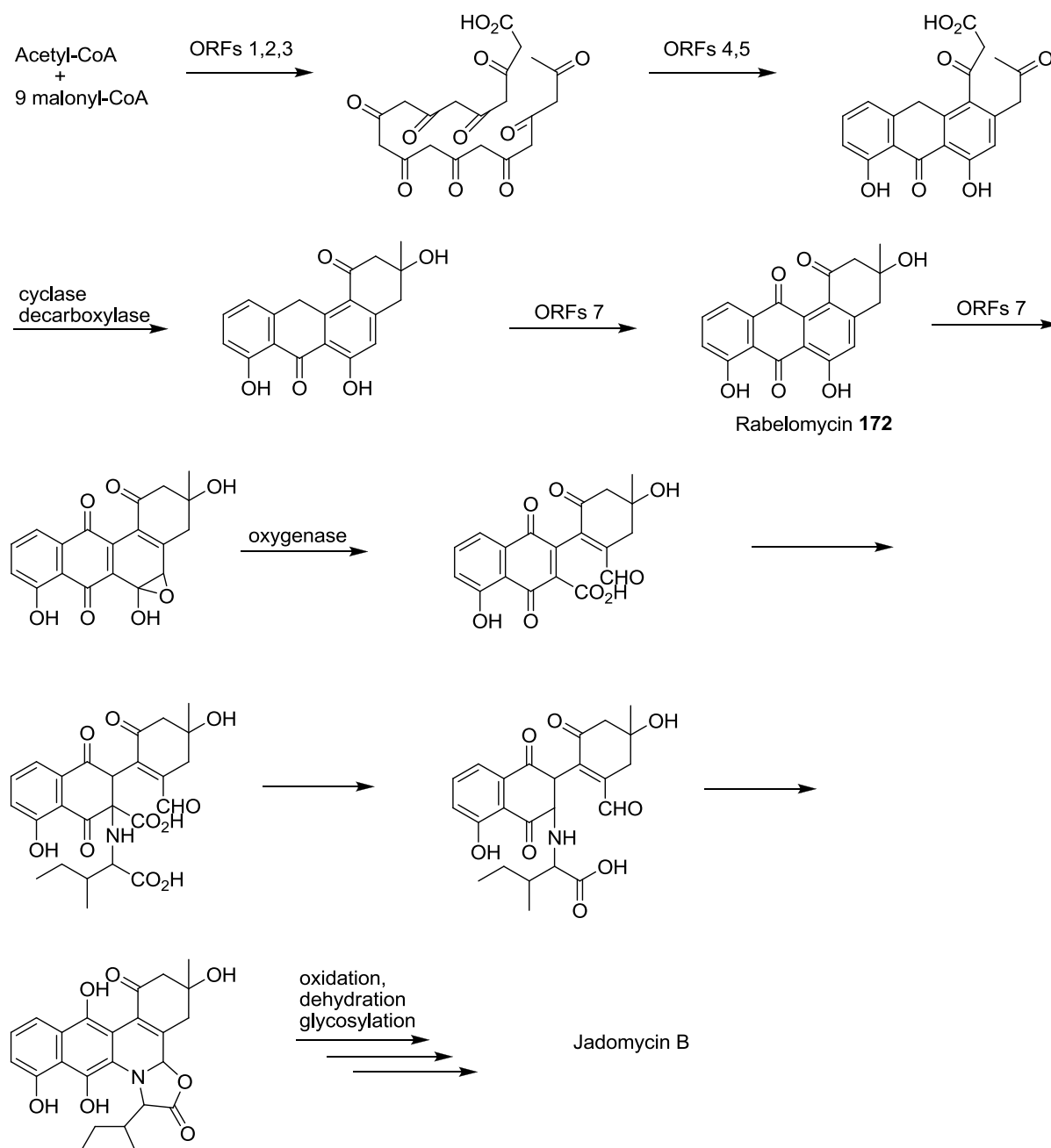


studies of the gene clusters were performed by Yang and co-workers.<sup>95</sup> The genome sequence of *Streptomyces venezuelae* ISP5230 (ATCC10712) has recently been reported which assisted in the better understanding of the biosynthetic pathway of jadomycins.<sup>96</sup>

Stressful conditions on *Streptomyces venezuelae* leading to induction of jadomycin production is quite unique, which suggests the presence of some sort of control mechanism.<sup>97</sup> Evidence for this control mechanism can be found in the genetic code for jadomycin A **163**. 196 Amino acid sequence (jadR2) is known to be encoded by an Open Reading Frame (ORF) upstream of type-II PKS, which resembles identified proteins like MtrR, AcrR, TetC, and TcmR. This jadR2 repressor gene in *Streptomyces venezuelae* regulates the resistance to xenobiotic exposure. When its nucleotide sequence was disrupted, jadomycin B **164** was formed, and overproduction was seen on exposed to ethanol stress.<sup>98</sup> This outcomes leads to the conclusion that jadR2 negatively regulates the expression of biosynthetic genes coding for jadomycin B **164** in *Streptomyces venezuelae*.<sup>97</sup>

Studies conducted by Vining *et al.* in 2001 suggested a second regulatory gene (jadR1) encoding for 234 amino acids and found immediately upstream of the repressor gene (jadR2) may play a role.<sup>99</sup> The mutants produced by disruption or deletion of jadR1 did not lead to the production of jadomycin B **164**, suggesting that the gene acts as a positive regulator in the antibiotic biosynthesis. When a disrupted chromosomal copy of jadR1 was complemented with a cloned gene, recovery of the wildtype phenotype was observed. In addition, a negative effect on the growth of *Streptomyces venezuelae* occurred upon increasing the copy number of jadR1 in the plasmid. This investigation led to the conclusion that both jadR1 and jadR2 form an interacting stress-responsive regulatory system for the biosynthesis of jadomycin B **164**.<sup>99</sup>

Apart from the ORF responsible for encoding jadR1 and jadR2, there is complete ORF6 and two incomplete ORFs (ORF4 and ORF7). The amino acid sequences for ORF6 and ORF7 resemble those of oxygenases. Transformation of *Streptomyces venezuelae* with an ORF6 disruption vector gave a mutant that blocked jadomycin B **164** biosynthesis. Instead, the mutant accumulated a non-nitrogenous secondary metabolite rabelomycin **172**, which is also produced by *Streptomyces olivaceus*.<sup>100</sup> This suggested that rabelomycin **172** is an intermediate in the biosynthesis of jadomycin, where ORF4, ORF6, and ORF7 encode for oxygenases that are involved in the oxidative cleavage of the B ring in the angucycline to afford an aldehyde.<sup>101,102</sup> Other steps in the biosynthesis of jadomycin B **164** are A **163** ring include dehydration/aromatization, isoleucine incorporation, oxazoline ring formation, and glycosylation. However, the specific order of these sequences is still in doubt. (**Scheme 71**).

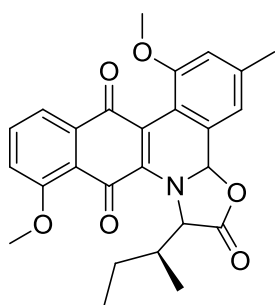


First reported biosynthetic pathway of Jadomycin B **164**

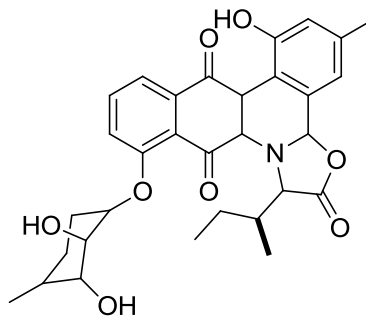
**Scheme 71**

### 3.4 Approaches Towards the Total Synthesis of Jadomycins

So far, there have been only two reported syntheses focused on the total synthesis of jadomycins. The first report came in 2010 by Ishikawa *et al.* where the synthesis of dimethyl protected jadomycin A **173** was accomplished.<sup>98</sup> Later the same year O'Doherty *et al.* reported an efficient synthesis of jadomycin A **163** and the carbasugar analogue of jadomycin B **174**.<sup>69</sup>



Dimethyl jadomycin A **173**

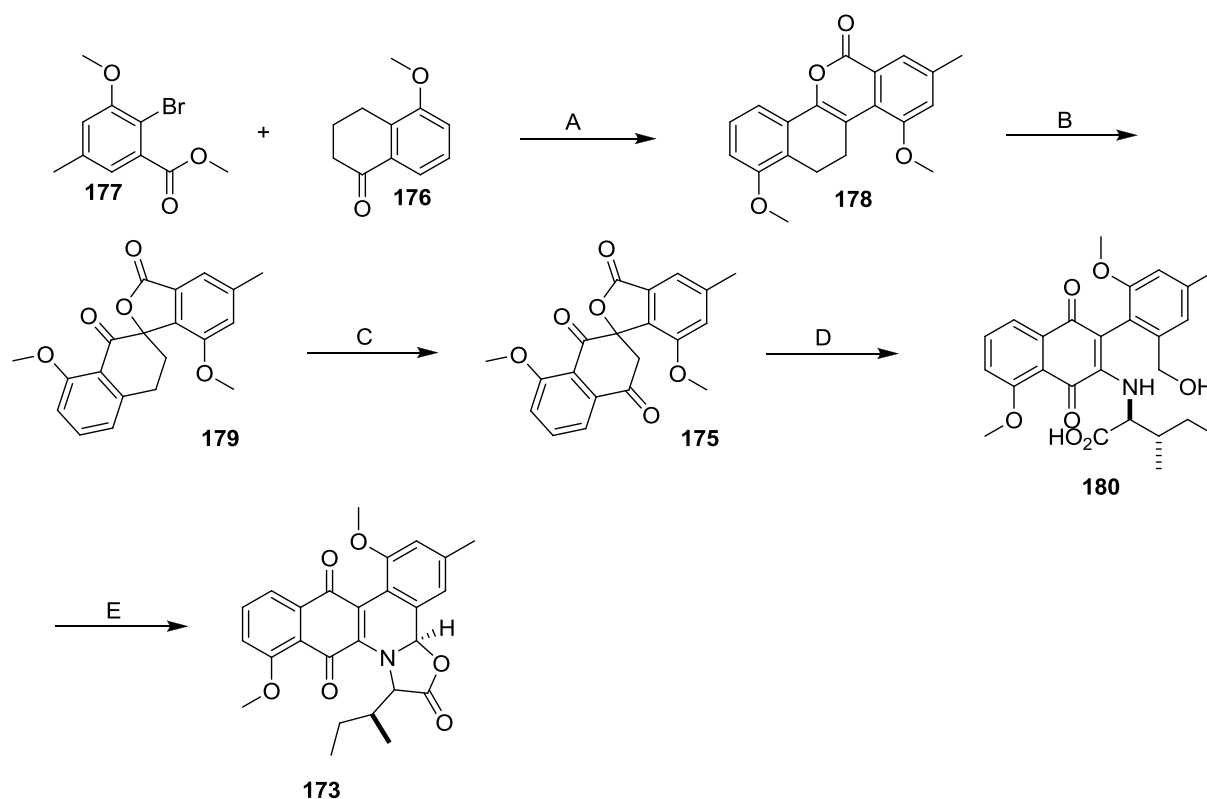


Carbasugar analogue of jadomycin B **174**

Figure 27

#### 3.4.1 Ishikawa's Approach<sup>98</sup>

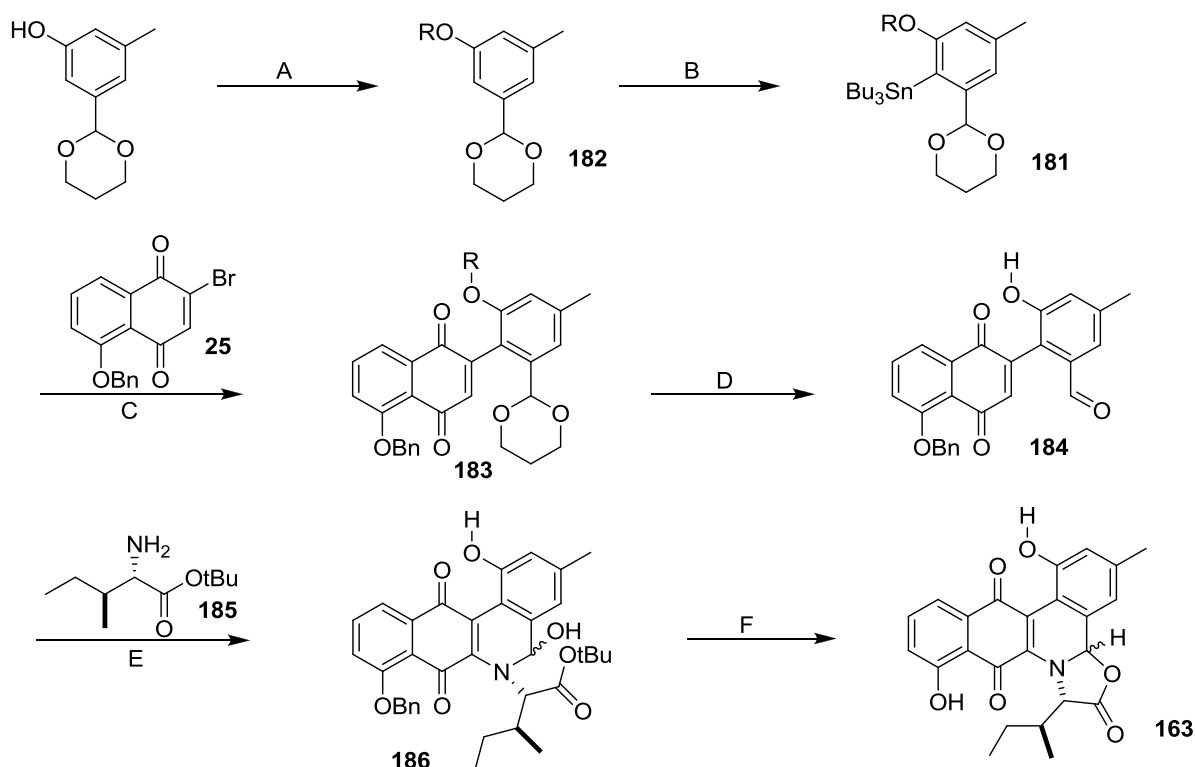
The approach described by Ishikawa utilizes an  $\alpha$ -spirolactonedihydroquinone **175** as the key intermediate for building the jadomycin ring system as shown in **Scheme 72**. The route started with a palladium-catalyzed coupling of 5-methoxytetralone **176** with *O*-bromobenzoate **177** leading to an enol-lactone intermediate **178** which after dihydroxylation and rearrangement led to spiro[lactone-tetralone]-type molecule **179**. This molecule was subjected to bromination at the benzylic position,  $S_N^2$  displacement and later an allylic oxidation led to the generation of the key intermediate  $\alpha$ -spirolactonedihydroquinone **175**. This intermediate **175** was reduced with borane-tetrahydrofuran complex and the isoleucine methyl ester was hydrolyzed with lithium hydroxide to afford naphthoquinone derivative **180**. Oxidation of this molecule to an aldehyde with manganese dioxide facilitated condensation of the aldehyde with the secondary amine to form an iminium system which was immediately trapped by carboxylate to form the dimethylated jadomycin A **173**.<sup>98</sup> Ishikawa described the first synthesis of dimethylated jadomycin A **173** using  $\alpha$ -spirolactonedihydroquinone **175** as the key intermediate. It is not clear if this approach could be used for the synthesis of jadomycin.



**Scheme 72:** Reagents and conditions: A)  $\text{Pd}_2(\text{dba})_3$ , xantphos,  $\text{K}_3\text{PO}_4$ ,  $\text{Na}_2\text{S}_2\text{O}_5$ , *o*-xylene, 130 °C, 5 hrs, 56%; B)  $\text{OsO}_4/\text{NMO}$ , Acetone, rt, 7 d, 95%; C) 1) NBS, AIBN; 2)  $\text{THF}/\text{H}_2$ ; 3) IBX, DMSO, 59% in three steps; D) 1)  $\text{BF}_3\text{-THF}$ , 36%, 0 °C, 15 hrs, 41%; 2) methylisoleucine, LiOH,  $\text{THF}/\text{H}_2\text{O}$ , 0 °C, 1 d, 83%; E)  $\text{MnO}_2$ , DCM, rt, 40 hrs, 61%.<sup>98</sup>

### 3.4.2 O'Doherty Approach<sup>69</sup>

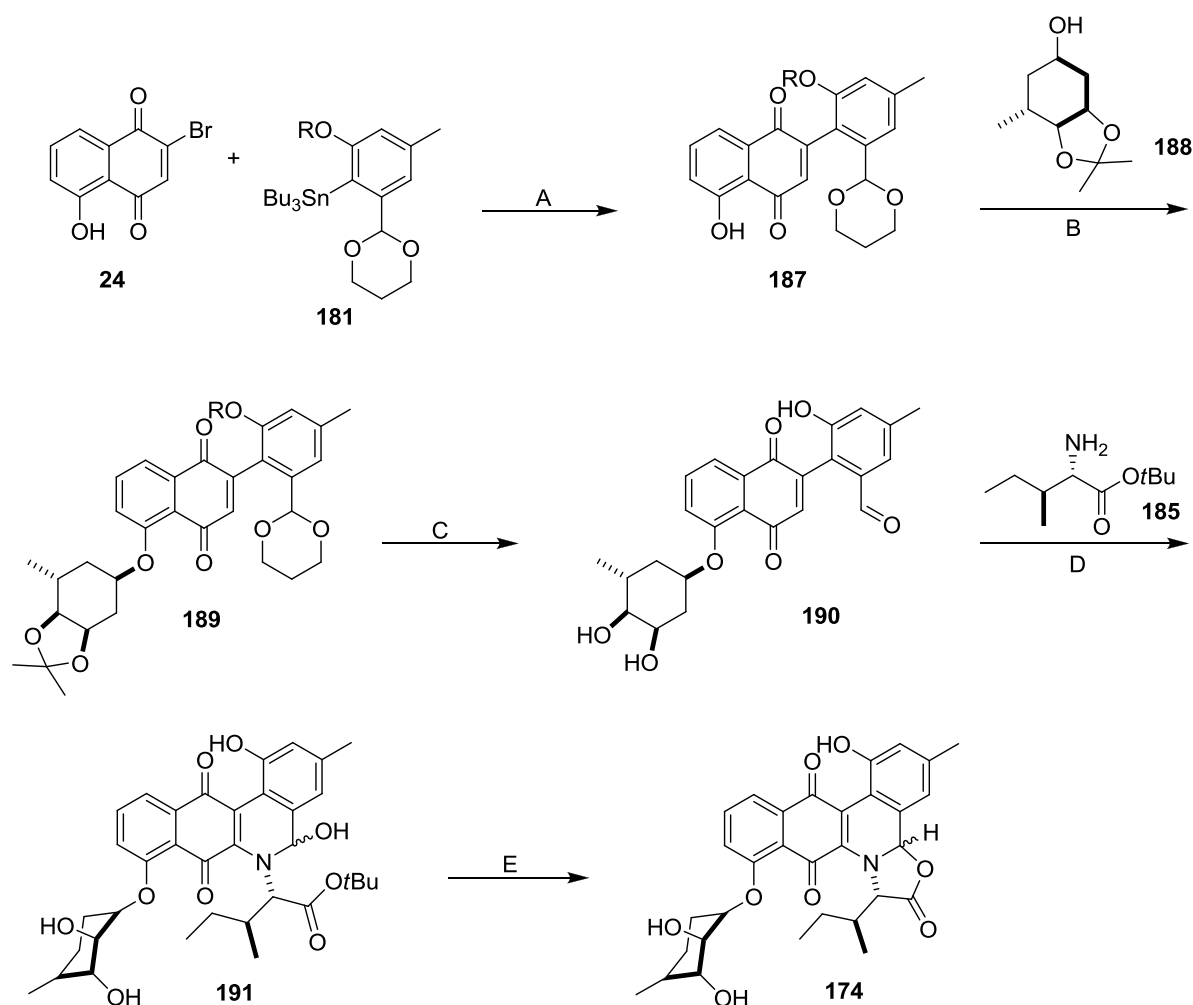
Synthesis of jadomycin A **163** and the jadomycin B carbasugar analogue **174** was carried out by O'Doherty *et al.* in 2010 as depicted in **Scheme 73** and **74** respectively. Here the key reaction was a 6- $\pi$ -electrocyclic ring closure. To commence with the synthesis, Stille coupling was employed between benzylated bromojuglone **25** and a suitably substituted stannane **181** which was made by directed-*ortho* metalation of MOM or BOM protected 3-(1,3-dioxan-2-yl)-5-methylphenol **182**. Acetal protection on the resulting tricyclic adduct **183** was removed to generate an aldehyde **184**, which was then condensed with butyl isoleucine **185** which generated **186** via a 6- $\pi$ -electrocyclic ring closure. The final steps were the acid promoted oxazole ring formation and debenzoylation to obtain jadomycin A **163**.



**Scheme 73:** Reagents and conditions: A) For R = MOMCl, DIPEA, DCM, rt, 12 hrs, 60%; For R = BOMCl, DIPEA, DCM, rt, 12 hrs, 70%; B) *n*BuLi, Bu<sub>3</sub>SnCl<sub>3</sub>, hexane, 0 °C, 2 hrs, For R = MOM, 68%, For R = BOM, 49%; C) Pd<sub>2</sub>(dba)<sub>3</sub>, CHCl<sub>3</sub>, PPh<sub>3</sub>, CuI, THF, 75 °C, 2 hrs, 73%; D) HCl(aq.), CH<sub>3</sub>CN, rt, 4-8 mins, 77%; E) Toluene, rt, 24 hrs, 91%; F) TFA, rt, 74%.<sup>69</sup>

Synthesis of jadomycin B carbasugar analogue **174** was carried out by Stille cross-coupling of 2-bromo-5-hydroxynaphthalene-1,4-dione **24** with a suitably substituted stannane **181**. On the resulting product **187**, Mitsunobu reaction was carried out with previously synthesized cyclitol donor **188** to lead to the generation of stable product **189** which was then globally deprotected to generate **190**. Subsequently the condensation of aldehyde **190** with protected isoleucine **185** and then a 6- $\pi$ -electrocyclic ring closure resulted in the formation of the desired ring system **191**. Finally acid-catalyzed transesterification leads to the formation of carbasugar analogue of jadomycin B **174** as described in **Scheme 74**.

O'Doherty and co-workers successfully demonstrated the synthesis of jadomycin A **130** and the jadomycin B carbasugar analogue **174** employing a 6- $\pi$ -electrocyclic ring closure as the key reaction.



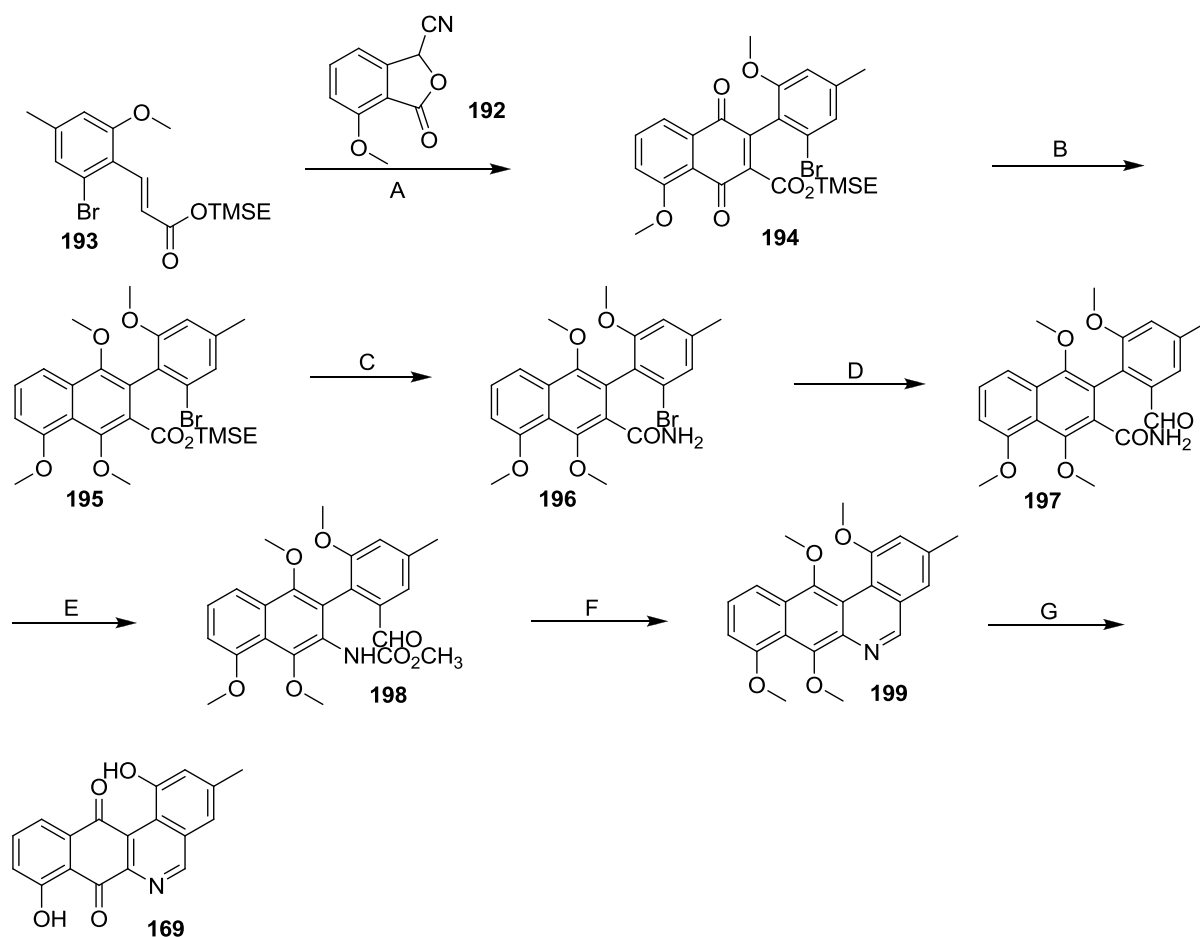
**Scheme 74:** Reagents and conditions: A)  $\text{Pd}_2(\text{dba})_3$ ,  $\text{CHCl}_3$ ,  $\text{PPh}_3$ ,  $\text{CuI}$ , THF, 75 °C, 2 hrs, For R = MOM, 76%, For R = BOM, 54%; B)  $\text{PPh}_3$ , DIAD, THF, rt, 30 mins, For R = MOM, 84%, For R = BOM, 91%; C) 2.4 M  $\text{HCl}/\text{MeCN}$ , 8 mins, For R = MOM, 56%, For R = BOM, 59%; D) Toluene, rt, 4 hrs; E) TFA, rt, 2 hrs, 55%.<sup>69</sup>

### 3.5 Synthesis of Phenanthrovirdin Aglycone 169

As discussed previously, jadomycins, phenanthrovirdin **168** and its aglycone **169** are characterized by a common benzo[*b*]phenanthridine-7,12-dione **162** core. Due to structural intricacy and instability linked with jadomycins, mainly with the glycosidic bond, there have only been two total syntheses reported thus far. On the other hand, there have been a few successful approaches towards the synthesis of the substituted benzo[*b*]phenanthridine-7,12-dione which is the common core in all the jadomycins.

### 3.5.1 Gore's Approach<sup>86</sup>

The first report on the synthesis of the phenanthrovirdin aglycone **169** came in 1991 authored Gore *et al.* The aglycone was constructed by initially coupling cyanophthalide **192** with previously synthesized substituted bromocinnamate **193** which was then followed by air oxidation to yield the quinone **194**. The resulting molecule **194** was then reduced and methylated to generate the aromatic ether **195**. Later, the ester was deprotected followed by functional group conversion into an amide to give **196**. Subsequently, formylation was achieved by substitution of bromine to generate **197**. Later, employing modified Hoffman rearrangement conditions carbamate was obtained **198** which on hydrolysis and cyclization generated ring B to give **199**. Finally, deprotection and oxidation to quinone gave phenanthrovirdin aglycone **169**.

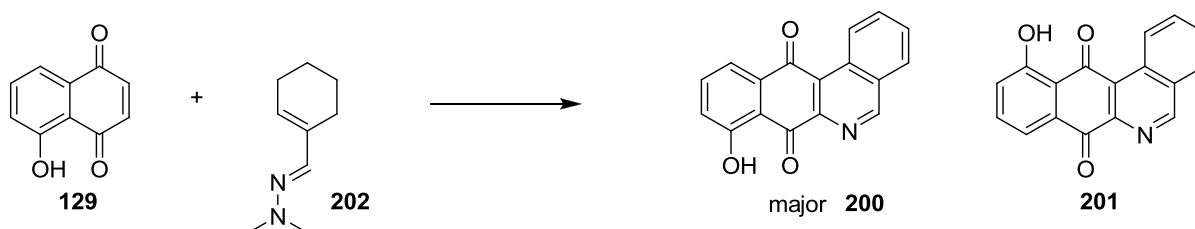


**Scheme 75:** Reagents and conditions: A) 1) LDA, THF, -78 °C, 20 hrs, 68%; B) K<sub>2</sub>CO<sub>3</sub>/Me<sub>2</sub>SO<sub>4</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, acetone, reflux, 24 hrs, 77%; C) 1) TBAF/THF; 2) Tf<sub>2</sub>O/pyridine; 3) NH<sub>3</sub>,

83%; D) 1) *t*BuLi; 2) DMF, 80%; E) NaOMe/Br<sub>2</sub>, MeOH; F) 1) H<sub>2</sub>O, reflux, 30 mins, 82% G) 1) BBr<sub>3</sub>/ DCM, -78 °C; 2) aq. NaOH, O<sub>2</sub>, -78 °C, rt, quantitative yield.<sup>86</sup>

### 3.5.2 Valderrama's Approach<sup>103</sup>

Later in 1997, Valderrama *et al.* reported the synthesis of the 8-hydroxybenzo[*b*]phenanthridine-7,12-dione **200** framework along with minor product **201** by using a hetero Diels–Alder reaction as the key step as depicted in **Scheme 76**. The B ring was built by a regioselective [4+2] cycloaddition of *N,N*-dimethylhydrazone **202** with 5-hydroxy-1,4-naphthoquinone **129** which was followed by air oxidation and aromatization. The remarkable regioselectivity of this cycloaddition reaction was attributed to the polarization of the azadiene and the directing effect of the free hydroxyl group present on juglone **129**.

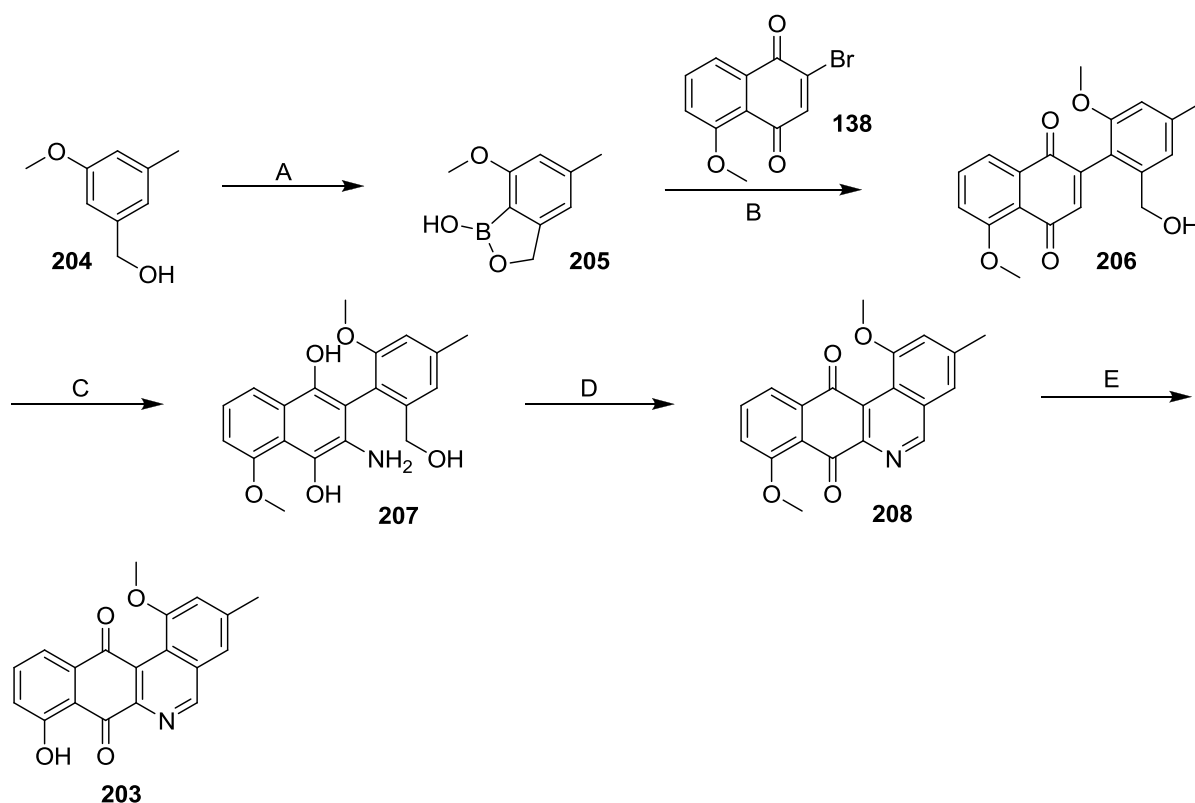


**Scheme 76:** Reagents and conditions: CH<sub>3</sub>CN, air, 5 days.

### 3.5.3 Mohri's Approach<sup>104</sup>

Mohri and co-workers also accomplished the synthesis of 1-methoxy-phenanthrovirdin aglycone **203** as shown in **Scheme 77**. Starting from commercially available substituted benzyl alcohol **204**, oxaborole **205** was synthesized employing a directed *orthometallation*-trimethylborate quench protocol. It was then coupled with 5-methoxybromojuglone **138** by doing a Suzuki-Miyaura cross-coupling reaction to furnish the biaryl axis **206**. The molecule obtained was dissolved in aqueous ammonia leading to the generation of hydroquinone **207** followed by treatment with manganese dioxide facilitated an oxidative cyclization to generate **208**. Later selective cleavage of the methylether was accomplished by using with BBr<sub>3</sub> to generate the final product, 1-methoxy-phenanthrovirdin aglycone **203**.

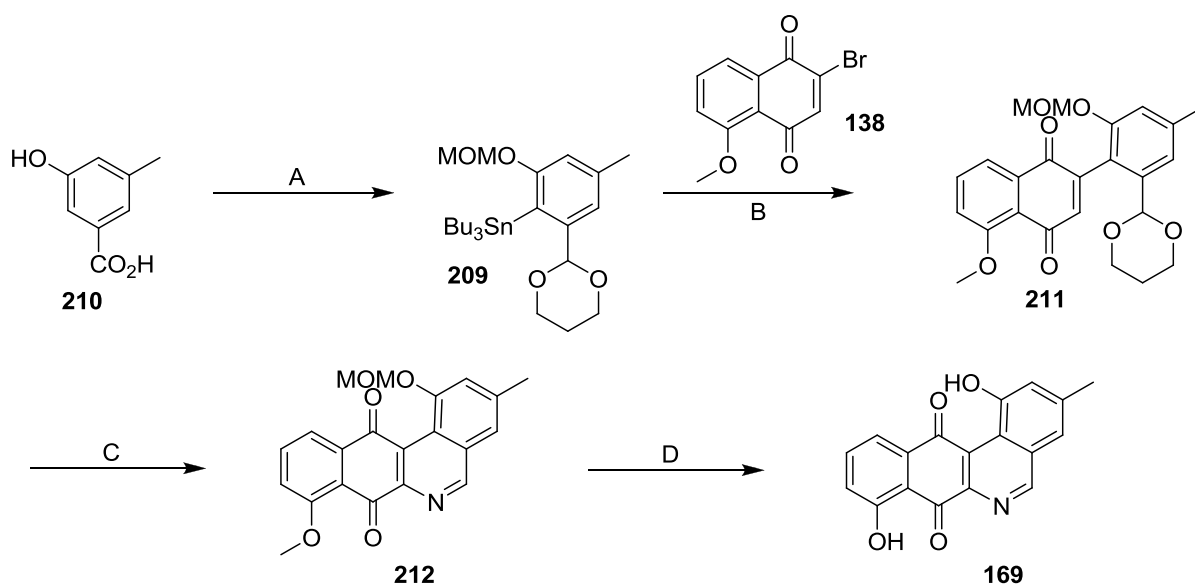




**Scheme 77:** Reagents and conditions: A) 1)  $n\text{BuLi}/\text{Et}_2\text{O}$ , 0-25 °C; 2)  $\text{B}(\text{OMe})_3$ , 42%; B)  $\text{PdCl}_2$ ,  $\text{K}_2\text{PO}_4$ , DMF, rt, 42%; C)  $\text{NH}_3(\text{aq.})$ , MeCN, 50%; D)  $\text{MnO}_2$ , DCM, 78%; E)  $\text{BBr}_3$ , DCM, quantitative yield.

### 3.5.4 de Frutos's Approach<sup>105</sup>

de Frutos *et al.* described the synthesis of phenanthrovirdin aglycone **169** in 2001 as shown in **Scheme 78**. The key step in this synthesis was a palladium-catalysed Stille coupling of 5-methoxybromojuglone **138** with a sterically hindered arylstannane **209** which was synthesized from 3-hydroxy-5-methylbenzoic acid **210** over seven steps. The biaryl compound **211** obtained was treated with aqueous ammonia to afford an intermediate hydroquinone which was treated immediately with aqueous acid to facilitate the ring closure to afford **212**. Lithium iodide in 2,6-lutidine effectively cleaved the MOM protection to yield the desired phenanthrovirdin aglycone **169**.



**Scheme 78:** Reagents and conditions: A) 1) MeOH, H<sub>2</sub>SO<sub>4</sub> (cat.), 23 °C, 14 hrs, 94%; 2) DHP, PPTS (cat.), DCM, 23 °C, 48 hrs, 63%; 3) LiAlH<sub>4</sub>, THF, 23 °C, 13 hrs, 93%; 4) PCC, NaOAc, DCM, 23 °C, 3 hrs, 81%; 5) 1,3-propanediol, TsOH (cat.), toluene, reflux, 3 hrs, 74%; 6) Chloromethyl methyl ether/*i*Pr<sub>2</sub>EtN, DCM, 40 °C, 24 hrs, 80%; 7) *n*BuLi, *n*Bu<sub>3</sub>SnCl, hexane, 0 °C, 97%; B) Pd(PPh<sub>3</sub>)<sub>4</sub>, CuI, THF, 70 °C, 12 hrs, 65%; C) 1) NH<sub>4</sub>Cl, NaOAc, EtOH, 80 °C, 12 hrs; 2) aq HCl, 3 hrs, 21%; D) LiI, 2,6-lutidine, 140 °C, 6 hrs, 63%.<sup>105</sup>

### 3.6 Conclusion

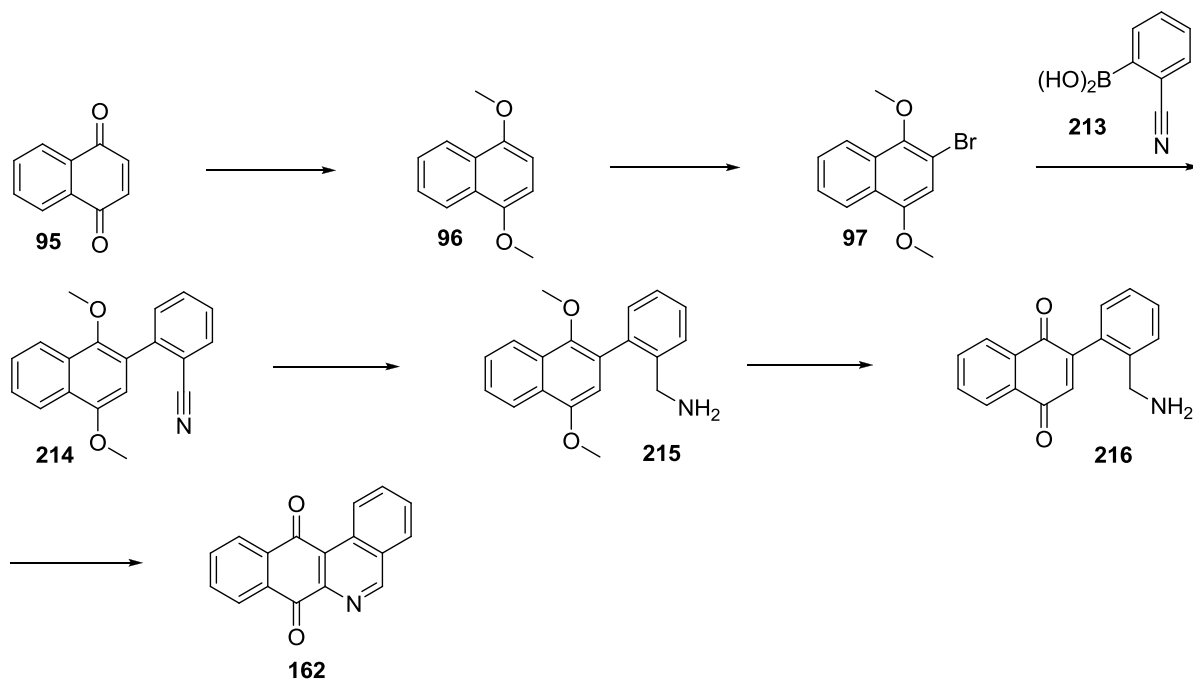
In conclusion, we have discussed the biological importance of jadomycins, their biosynthesis and various synthetic approaches towards the total synthesis of jadomycins or the benzophenanthridine core, the phenanthrovirdin aglycone **169**. These polyketides are known for their extensive therapeutic applications and intrinsic structural features. Most of the synthetic approaches are known to be long with some harsh reaction conditions and often resulting in low yields. This is why developing new synthetic routes has always been a challenge for organic chemists. So, as a part of this PhD research programme we wished to develop a new methodology to synthesize benzo[*b*]phenanthridine **162** as found in jadomycins using the Suzuki-Miyaura cross coupling reaction as the key step as we had this expertise in our laboratories.

### 3.7 Aims

From our previous discussion in this chapter we realized the biological importance and therapeutic application of the naphthoquinone molecule jadomycin. The discussion also outlined the fact that limited synthetic methods exist for the synthesis of benzo[*b*]phenanthridine-7,12-dione **162** motif and therefore we wished to conduct research on this problem. We later plan to extend our methodology to related complex molecules and hopefully towards the synthesis of the natural product itself.

As outlined in **Scheme 79**, we could easily prepare 2-bromo-1,4-dimethoxynaphthalene **97**. This could be utilized as the substrate for a Suzuki-Miyaura cross-coupling reaction with 2-cyanophenylboronic acid **213** to generate the biaryl compound **214**. Reduction of the nitrile **214** to an amine **215**, followed by re-generation of the quinone **216** by oxidation would allow for an intramolecular Michael addition to hopefully afford the desired benzo[*b*]phenanthridine-7,12-dione motif **162**.

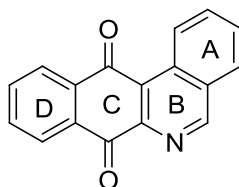
Once the methodology was successfully tested and established by carrying it out on simple aromatic systems, we wish to extend it to more complex starting materials hoping to develop a general procedure for the synthesis of this class of compounds.



**Scheme 79**

## Chapter 4: Results and Discussion: Synthetic Approaches Towards the Benzo[*b*]phenanthridine-7,12-dione Core of Jadomycin

The following **Chapter** will concentrate on the synthesis of the benzo[*b*]phenanthridine-7,12-dione **129** motif which forms the backbone of important class of secondary metabolites the jadomycins known for their potent antibiotic, anti-cancer and enzyme-inhibitory activities.<sup>87,106</sup>

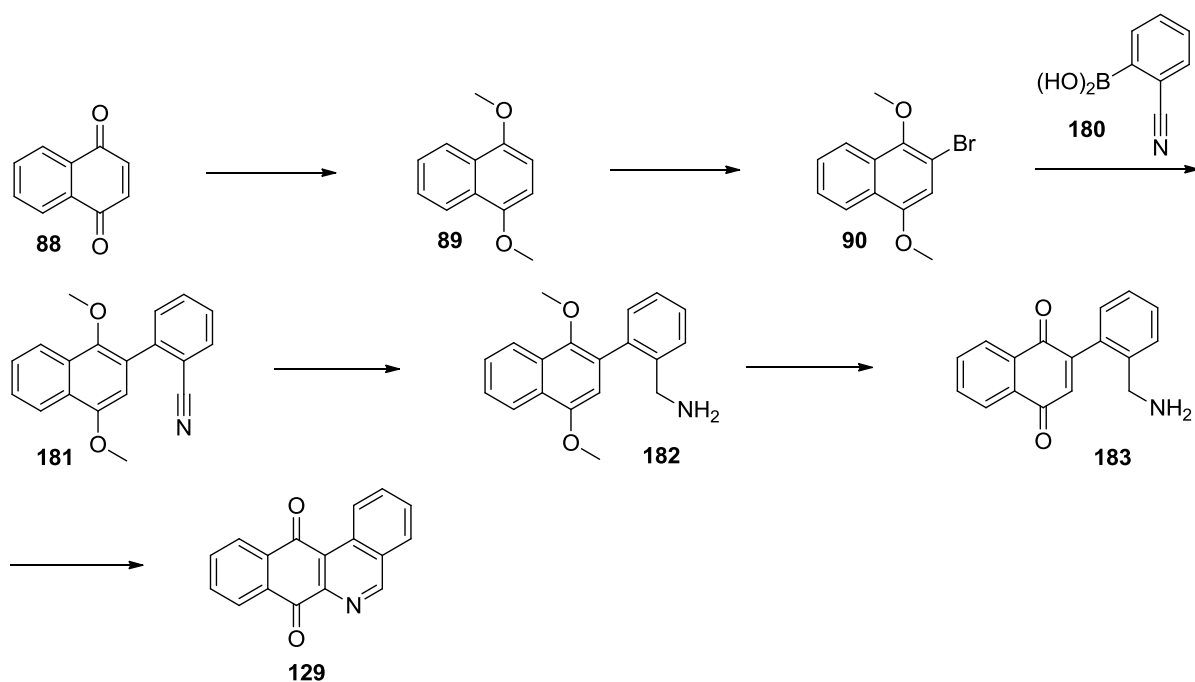


Benzo[*b*]phenanthridine-7,12-dione **162**

**Figure 28**

### 4.1 Attempted Synthesis Towards Benzo[*b*]phenanthridine-7,12-dione **162**

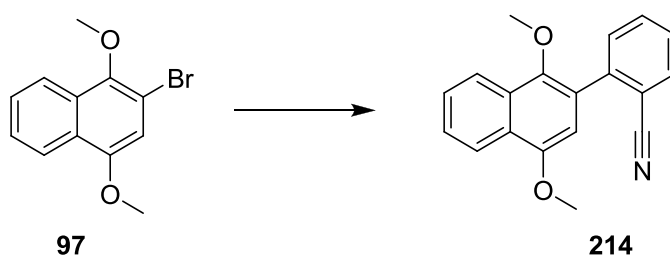
The synthetic scheme depicted below summarizes how we plan to synthesize the target benzo[*b*]phenanthridine-7,12-dione **162**. Starting from the commercially available 1,4-naphthoquinone **95** we planned to protect the starting material as 1,4-dimethoxynaphthalene **96** followed by an *ortho*-bromination to afford **97**. With the brominated compound in hand, we then wished to couple it with a relevant boronic acid, such as 2-cyanophenylboronic acid **213** employing the palladium-catalyzed Suzuki-Miyaura cross coupling reaction to generate the aromatic compound **214** containing a biaryl axis. Reduction of the nitrile to an amine **215** followed by oxidation of the 1,4-dimethoxynaphthalene to a naphthoquinone **216** could then be carried out. This compound would be an ideal substrate for an intramolecular Michael addition reaction leading to the formation of ring B and hence completing the synthesis of the benzo[*b*]phenanthridine-7,12-dione **162** moiety as described in **Scheme 79**.



Scheme 79

The synthesis and characterization of 1,4-dimethoxynaphthalene **96** and 2-bromo-1,4-dimethoxynaphthalene **97** have been described previously in **Chapter 2**. We will therefore focus on the synthesis of the benzo[*b*]phenanthridine-7,12-dione core **162** from the advanced precursor, 2-bromo-1,4-dimethoxynaphthalene **97**, in this section.

#### 4.1.1 Synthesis of 2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **214**.



**Scheme 80:** Reagents and conditions: 2-Cyanophenylboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ , 2 M aq.  $\text{Na}_2\text{CO}_3$ , DME, EtOH, reflux, 24 hrs, 51% or 2-cyanophenylboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ , CsF, DME, microwave irradiations, 150 °C, 150 W, 30 mins, 76%

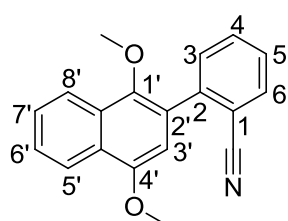
Having 2-bromo-1,4-dimethoxynaphthalene **97** in hand we planned to construct the biaryl axis with commercially available 2-cyanophenylboronic **213** acid to obtain the 2-(1,4-

dimethoxynaphthalen-2-yl)benzonitrile **214** motif. Initially, the reaction was carried out using conventional heating to facilitate the Suzuki-Miyaura cross coupling reaction. In this procedure tetrakis(triphenylphosphine)palladium(0) under inert conditions together with 2-bromo-1,4-dimethoxynaphthalene **97** and 2-cyanophenylboronic acid **213** were dissolved in dry dimethoxyethane and ethanol and the reaction was stirred at room temperature for ten minutes. After this time, a 2 M aqueous sodium carbonate solution was added and the reaction was heated to reflux for twenty four hours. On completion of the reaction, as determined by thin layer chromatography, the mixture was quenched with water and the crude product was purified by column chromatography to afford the desired product **214** in a moderate yield of 51%.

We were not able to improve the yields of this Suzuki-Miyaura cross coupling reaction by performing this reaction in the conventional reflux manner, by changing the reaction time and also by changing the solvent from dimethoxyethane to dimethyl formamide. In an attempt to improve the yield of the reaction, we decided to perform the reaction in a microwave reactor.<sup>48</sup> 2-Bromo-1,4-dimethoxynaphthalene **97**, 2-cyanophenylboronic acid **213**, palladium catalyst and cesium fluoride as the base were suspended in dry dimethoxyethane. The reaction mixture was heated up to 150 °C and irradiated at 150 W for thirty minutes after which time the reaction appeared to be complete as observed by thin layer chromatography. The desired product was isolated as yellow crystalline powder in an improved yield of 76%. Modification of the reaction conditions (temperature, power and time of the reaction) did not further improve the yield of the product.

One disadvantage with the microwave procedure is that it could only be conducted on a small scale, with only 250 mg of starting material used in the reaction owing to the size of the microwave vial. The reaction was therefore repeated several times and the crude product was combined for purification.

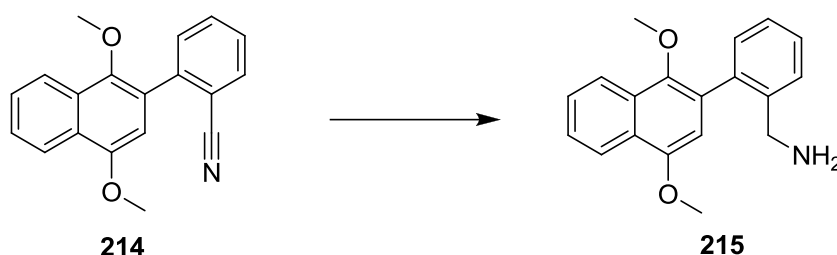
Also it was realized that 2.5 mL solvent was appropriate for the reaction as larger amounts of solvent did not stir well. Also this concentrated reaction mixture gave the maximum yield (76%) of the product **214**.



Characterization by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy confirmed the formation of the biaryl compound **214**. Two peaks arising from the methoxy protons were prominent at 4.01 and 3.53 ppm respectively in the  $^1\text{H}$  NMR spectrum with peaks in the  $^{13}\text{C}$  NMR spectrum at

61.9 and 55.9 ppm. A key identifying feature came from the  $^{13}\text{C}$  NMR spectrum, where a peak was observed at 118.5 ppm which corresponded to the carbon of the nitrile group. Finally the proton on H-3' gave rise to a singlet which appears upfield at 6.73 ppm with the corresponding carbon signal appearing at 105.4 ppm in the  $^{13}\text{C}$  NMR spectrum. On analyzing the FTIR spectrum of the product, a very prominent stretching band at  $2225\text{ cm}^{-1}$  was observed which clearly signifies the presence of a nitrile functionality. HRMS also confirmed the molecular formula of the compound.

#### 4.1.2 Synthesis of (2-(1,4-Dimethoxynaphthalen-2-yl)phenyl)methanamine **215**

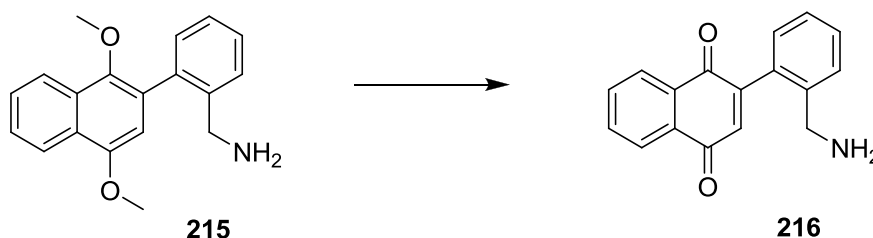


**Scheme 81:** Reagents and conditions:  $\text{LiAlH}_4$ , dry THF, reflux, 6 hrs, 63%.

Having successfully formed the biaryl axis with a nitrile substituent on the aromatic ring, our next step was to reduce the nitrile group of **214** to an amine **215**. This reduction proved to be the most challenging step in our synthesis as the nitrile group was very resistant to reduction due to stabilization by conjugation with the aromatic ring. A variety of reducing agents were employed in attempts to reduce the nitrile functionality including the borane tetrahydrofuran complex, Raney nickel, palladium on carbon, sodium borohydride with nickel chloride and lithium aluminium hydride. Unfortunately none of these methods successfully reduced the cyanide into an amine functional group. We then attempted the use of lithium aluminium hydride in a ten fold excess and performed the reaction by heating under reflux in tetrahydrofuran. For this reaction we dissolved 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **214** in dry tetrahydrofuran and cooled the solution to  $0\text{ }^{\circ}\text{C}$ . Lithium aluminium hydride was then added and the reaction mixture was allowed to warm up to room temperature before being heated at reflux for twelve hours. The progress of the reaction was monitored by thin layer chromatography and a new spot of lower  $R_f$  compared to the starting material was seen to be forming. This was expected as the amine functionality is much more polar than a nitrile functional group.

On completion of the reaction, purification by silica gel column chromatography was attempted. However this was not successful in obtaining the product in pure form. Also because of the sticky resinous nature of the product, attempts to purify the product by recrystallization were also unsuccessful. Owing to these issues we decided to treat the product as an intermediate and conducted the next step of the synthesis without further purification. For characterization we relied on FTIR which showed a very prominent broad peak characteristic of the amine functionality at  $3400\text{--}3300\text{ cm}^{-1}$ . A comparison with the FTIR of the starting material also showed that the reaction had been a success as no stretching band was observed in the region of  $2260\text{ cm}^{-1}$  which is characteristic for the nitrile functionality.

#### 4.1.3 Attempted Synthesis of 2-(2-(Aminomethyl)phenyl)naphthalene-1,4-dione **216**



**Scheme 82:** Reagents and conditions: Ceric Ammonium Nitrate (CAN),  $\text{CH}_3\text{CN}:\text{H}_2\text{O}$  (1:1), 4 hrs, rt, atmospheric conditions.

After having successfully synthesized (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanamine **215** we were now in a position to oxidize the 1,4-dimethoxynaphthalene system to the quinone **216** to obtain the required substrate for our intra-molecular Michael addition reaction. There are reports in the literature for this type of oxidation using ceric ammonium nitrate to produce a naphthoquinone from a protected hydroquinone.<sup>107</sup> We therefore dissolved the starting material **215** in acetonitrile in an open vessel at room temperature and then added an aqueous solution of ceric ammonium nitrate. The reaction mixture immediately changed colour to bright orange, which was an indication that the reaction was proceeding. Analysis by thin layer chromatography showed that the starting material **215** had been consumed and a very bright spot of higher  $R_f$  than the starting material **215** had appeared. Happy with these observations, we isolated the new product after work-up and subjected it to purification by column chromatography.



To our surprise, the spectroscopic data did not show the expected signals in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. All the peaks observed in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were in the aromatic region. There were signals integrating for nine protons in the aromatic region of the  $^1\text{H}$  NMR spectrum and signals arising from sixteen carbons in  $^{13}\text{C}$  NMR spectrum. There were two characteristic signals for carbonyl carbons at 182.8 and 179.8 ppm respectively in the  $^{13}\text{C}$  NMR spectrum, which indicated that oxidation had in fact taken place. Characteristic peaks of the methoxy protons and carbons were also absent.

It appeared that during the course of the oxidation facilitated by ceric ammonium nitrate, that the Michael addition reaction to afford a benzophenanthridine dione system had taken place. Much to our disappointment further characterization confirmed that the formation of benzo[*c*]phenanthridine-11,12-dione **217** and not the desired benzo[*b*]phenanthridine-7,12-dione **162** has taken place.

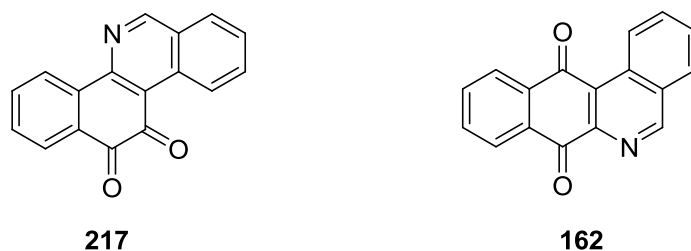
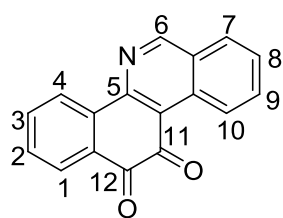


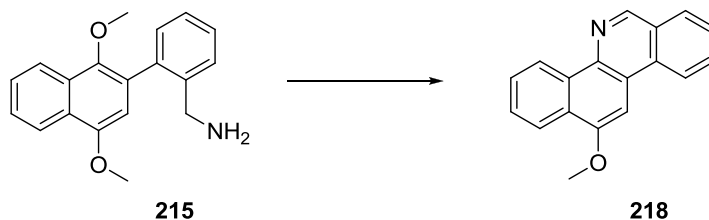
**Figure 29**



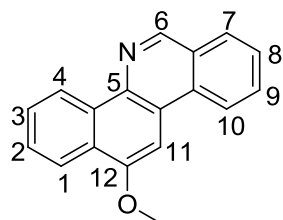
Spectroscopic analysis of **217** showed all peaks in the aromatic regions of both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. Two peaks at 182.8 and 179.8 ppm in the  $^{13}\text{C}$  NMR spectrum suggested two aromatic carbonyl groups were present in the molecule probably as an *ortho* quinone. Confirmation that **217** was an *ortho* quinone came from

HMBC analysis where it was observed that C-12 couples with H-1 as its three bonds away while C-11 does not couple with any proton. In case of **162** both the carbonyl carbons should show similar coupling pattern in the HMBC spectrum. We also tried to obtain the crystal structure of the compound **217** which indicated conclusively the arrangement of the rings as in **217** rather than **162**. Unfortunately we were not able to obtain a final crystal structure of the molecule as the crystals were too thin to reveal the exact structure of the molecule.. Additionally, HRMS analysis of the product corresponded with the molecular formula of the product **217**.

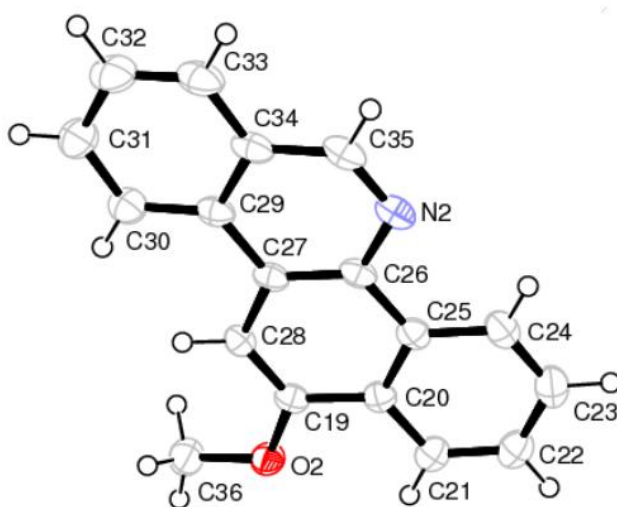
By performing column chromatography a second minor product was isolated from the reaction mixture and was identified to be 12-methoxybenzo[*c*]phenanthridine **218**. The exact mechanism for this process is still not clear but a proposed mechanism for the formation of both **217** and **218** is outlined later.



**Scheme 83**



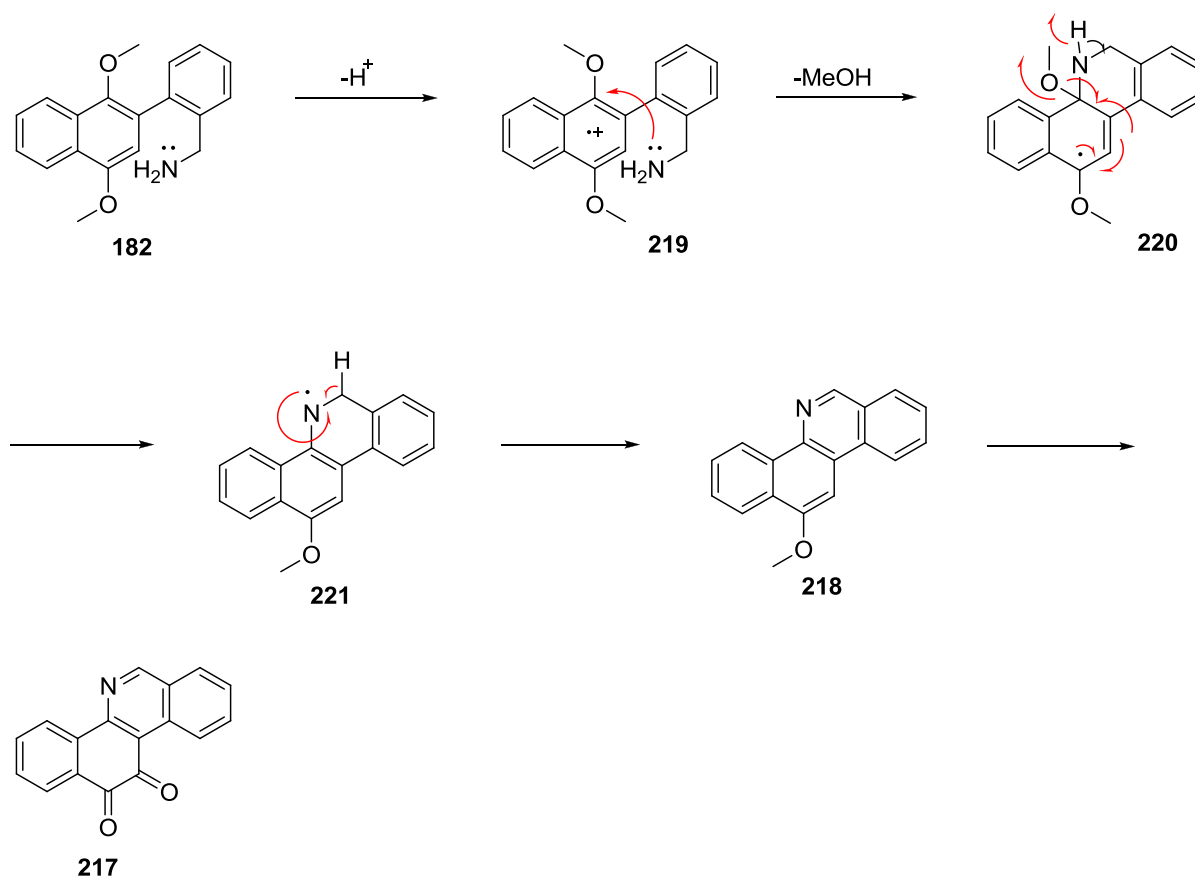
Spectroscopic results were found to be in agreement with literature.<sup>108</sup> The  $^1\text{H}$  NMR spectrum of 12-methoxybenzo[*c*]phenanthridine **218** shows the presence of a methoxy group with a singlet at 4.17 ppm integrating for three protons with the corresponding peak at 55.6 ppm in the  $^{13}\text{C}$  NMR spectrum. A singlet at 7.64 ppm in the  $^1\text{H}$  NMR spectrum was assigned to the proton H-11 and correlated with the peak in the  $^{13}\text{C}$  NMR spectrum at 95.8 ppm. Carbons, C-12, C-6 and C-5 gave rise to the signals 154.7, 149.3 and 137.1 ppm respectively. The FTIR spectrum also clearly showed the ether functionality with a sharp peak at  $1253\text{ cm}^{-1}$ . HRMS analysis confirmed the correct mass for the product. However, structure validation was confirmed by single crystal X-ray crystallography (**Figure 30**).



Single crystal X-ray of 12-methoxybenzo[*c*]phenanthridine **218**

Figure 30

A possible mechanism for the synthesis of benzo[*c*]phenanthridine-11,12-dione **184** and **185** is outlined in **Scheme 69**. A similar mechanism of reaction was proposed by Johnson *et al.*<sup>109</sup> The ceric ammonium nitrate -mediated oxidation of **215** is believed to initially afford the radical cation **219**. Nucleophilic addition of lone pair of electrons of the amine group to the aromatic radical cation of **182** will result in the radical intermediate **220**, which on elimination of methanol provides intermediate **221** which then undergoes aromatization to afford the minor product **218**. Further oxidation will then allow for the formation of benzo[*c*]phenanthridine-11,12-dione **217** in the presence and oxygen (from atmosphere) but the exact mechanism for this step is not very clear (**Scheme 84**).



Scheme 84

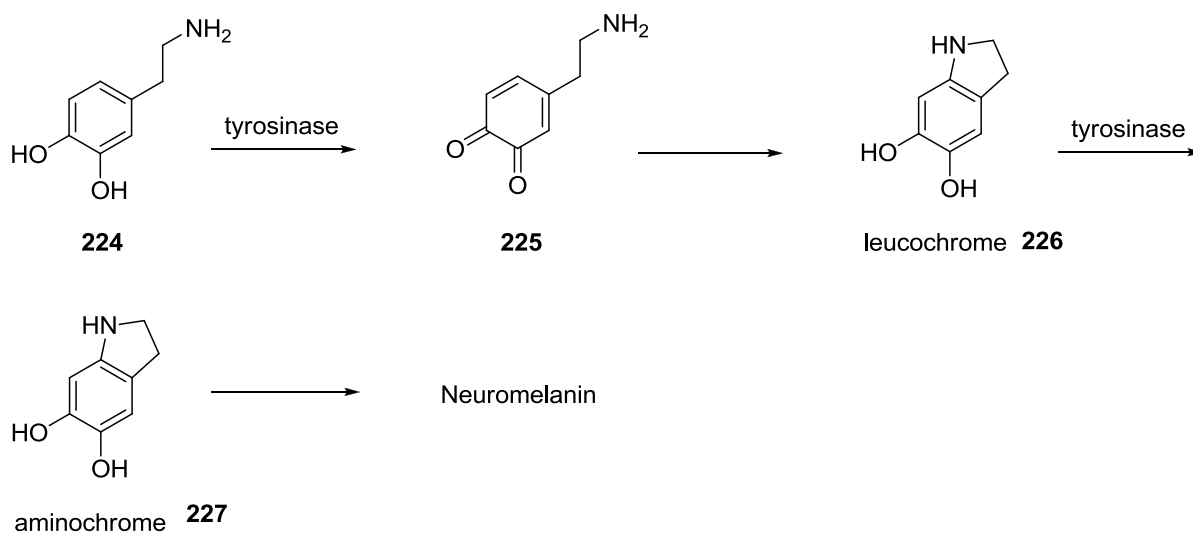
Watanabe *et al.* in 2003 also demonstrated the synthesis of 3,4,13-trimethoxy-5-methyl-5,6-dihydrobenzo[*c*][1,3]dioxolo[4,5-*j*]phenanthridine **222** and 3,4,13-trimethoxybenzo[*c*][1,3]dioxolo[4,5-*j*]phenanthridine **223**, which are similar molecules like **218**.<sup>110</sup>



Figure 31

The successful synthesis of the *ortho* quinone benzo[*c*]phenanthridine-11,12-dione **218**, raises the issue of possible important applications of compounds possessing an *ortho* quinone moiety. In the literature there are examples where compounds containing precursors to the *ortho* quinone fragment have very important biological consequences.

For example, dopamine **224** which is responsible for the synthesis of neuromelanin, takes place by oxidation of dopamine **224** to its *ortho* quinone **225**, as shown in Scheme 85 followed by an intramolecular Michael addition type cyclization to form leucochrome **226**. Leucochrome **226** which gets oxidized into aminochrome **227** and further polymerises into neuromelanin, which is a pigment of substantia nigra (**Scheme 85**). Disregulation of this process leads to the *ortho* quinone **225** binding to DNA and could possibly cause mutations that could initiate neuro degradation disorders such as Parkinson's disease.<sup>111</sup>



Scheme 85

VPQ **229** is another example of an *ortho* quinone, which is a metabolite of known anti-cancer drug etoposide (VP-16) **228**. Etoposide **228** constitutes an important class of anti-cancer agents and acts by trapping topoisomerase II/DNA complex. This process takes place by

conversion of etoposide **228** to metabolite VPQ **229** which is a powerful inhibitor of topoisomerase (**Figure 32**).<sup>112</sup>

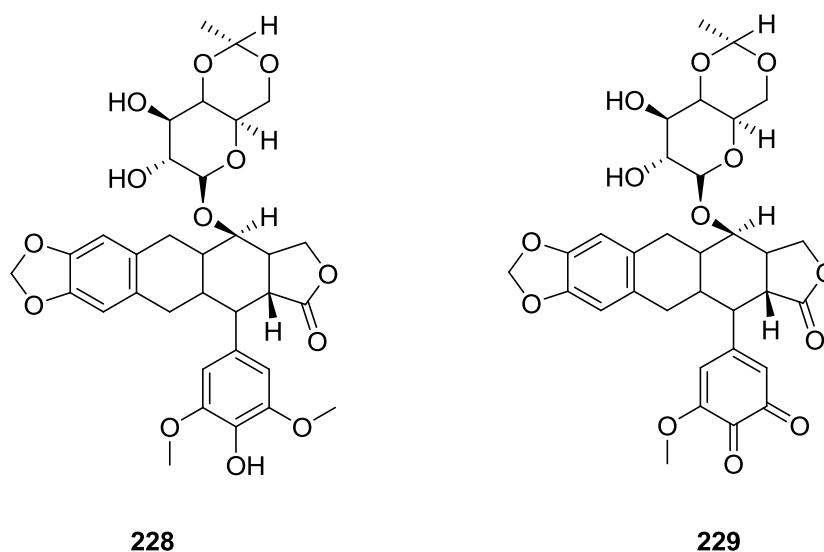
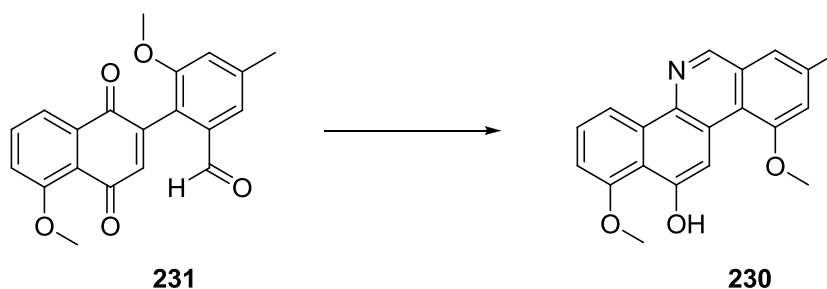


**Figure 32**

Considering the significance as illustrated by these two examples of *ortho* quinones in biology we speculate that the synthesized benzo[*c*]phenanthridine-11,12-dione **217** could have uses in medicinal chemistry and other related fields. The area needs to be explored in the future.

#### 4.2 B Ring Formation In Benzo[*b*]phenanthridine-7,12-dione **162** Skeleton.

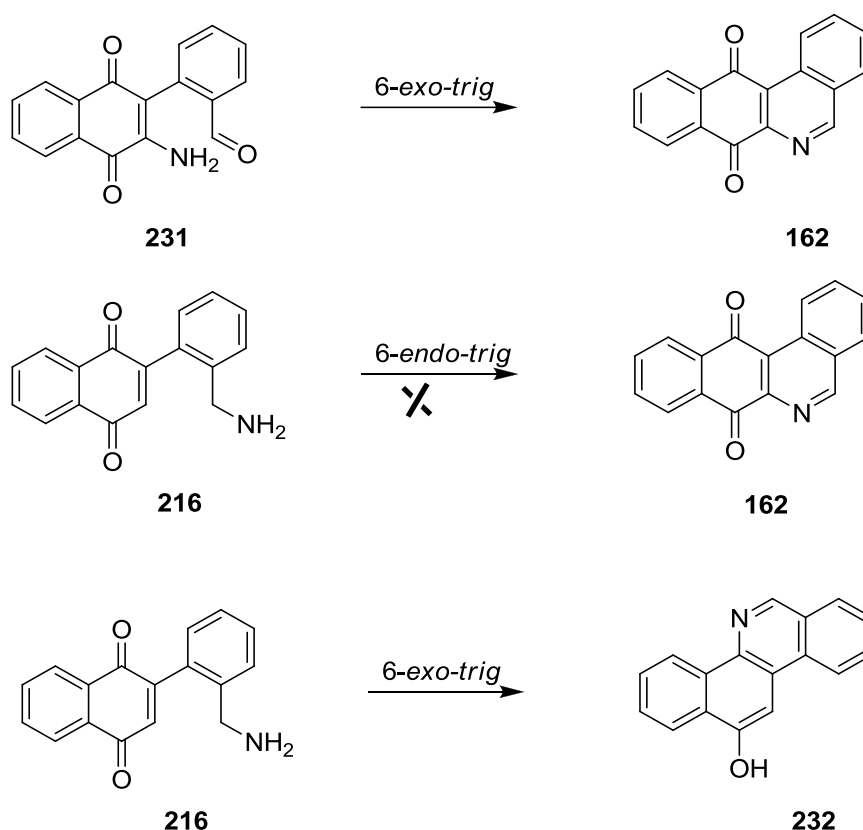
It was reported in 2001 by de Frutos *et al.* that 1,10-dimethoxy-8-methyl-11,12-dihydrobenzo[*c*]phenanthridin-12-ol **230** was isolated, when ammonia was added to 3-methoxy-2-(5-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-5-methylbenzaldehyde **231** (**Scheme 84**) in an attempt to use a Michael-type reaction in order to synthesize the benzo[*b*]phenanthridine-7,12-dione **162** framework.<sup>105</sup>



**Scheme 84:** Reagents and conditions: NH<sub>4</sub>OAc, HOAc, 118 °C, 24 hrs.

In 2010, O'Doherty and co-workers also suggested that the benzo[c]phenanthridine framework would be isolated when trying to synthesize ring B in benzo[b]phenanthridine-7,12-dione **162**. This reaction proceeds via 6-exo-trig cyclization process.<sup>69</sup>

From all the studies directed either towards the total synthesis of jadomycins or the synthesis of the phenanthrovirdin core **168**, it can be concluded that, for reasons pertaining to stereoelectronics, the B ring should be constructed from the cyclization of a 2-amino-3-phenyl-naphthoquinone **231**.<sup>105</sup> rather than onto the 3-position of an anthraquinone **216**, where 6-exo-trig cyclization takes place to give benzo[c]phenanthridine **232** (Scheme 84).<sup>69,105</sup>

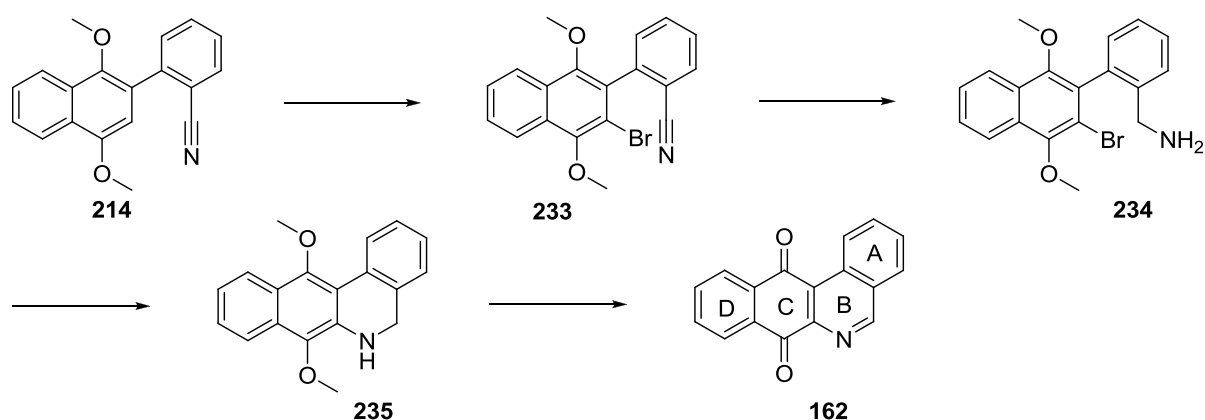


**Scheme 84**

The findings by de Frutos *et al.* and O'Doherty *et al.* thus demonstrated that the result we obtained by having synthesized benzo[c]phenanthridine-11,12-dione **217** and 12-methoxybenzo[c]phenanthridine **218** was not totally unexpected.

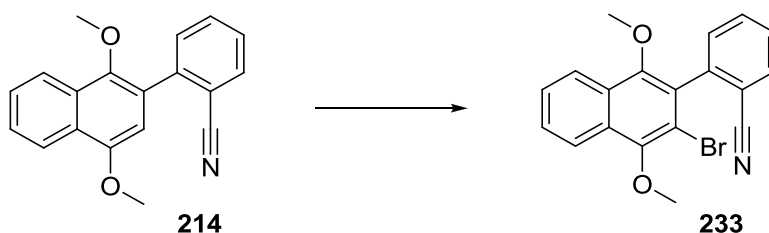
### 4.3 Attempted Synthesis of Benzo[b]phenanthridine-7,12-dione **162** Using the Buchwald-Hartwig Reaction

In our quest to synthesize benzo[*b*]phenanthridine-7,12-dione **162**, we had to go back and look for an alternative route as our proposed route failed to give us the desired product. As a possible option we utilized the previously prepared 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **214** and attempt to brominate the position *ortho* to the methoxy group of the naphthalene as this ring is electron rich. This compound **233** could then be subjected to conditions to reduce nitrile **233** into an amine **234**. This molecule could then be subjected to the conditions of Buchwald-Hartwig amination reaction which would result in cyclization in the presence of the palladium catalyst leading to the generation of ring B of **235**. Then this could then be oxidized to afford the desired benzo[*b*]phenanthridine-7,12-dione **162** (Scheme 85).



Scheme 85

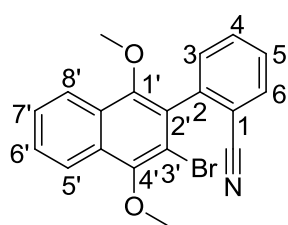
#### 4.3.1 Synthesis of 2-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)benzonitrile **233**



**Scheme 86:** Reagents and conditions: NBS, CH<sub>3</sub>COONa, acetic acid, rt, 4 hrs, 83%.

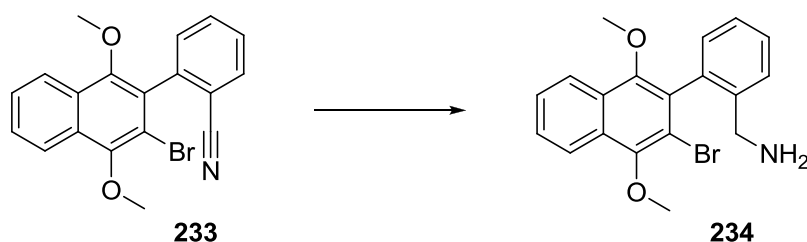
We therefore attempted bromination of the previously prepared 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **214** as it is known that on the electron rich naphthalene ring the methoxy group is *ortho* directing and in this case the C-3' position is the only electron rich site favorable for the desired bromination. The reaction was carried out by dissolving the starting

material in acetic acid. *N*-Bromosuccinimide and sodium acetate were added to this stirred solution at room temperature under inert conditions and left to stir for four hours before being quenched. The desired product **233** was isolated from the reaction mixture by column chromatography purification.



The structure of the product **233** was confirmed by NMR spectroscopy by the disappearance of a singlet at 6.73 ppm in the  $^1\text{H}$  NMR spectrum, characteristic of the proton *ortho* to the methoxy group. This clearly proved that the substitution reaction has taken place. Also, signals occurring for one less proton compared to the starting material 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **214** were visible in the aromatic region of the  $^1\text{H}$  NMR spectrum. Two methoxy gave rise to signals at 3.99 and 3.58 ppm in  $^1\text{H}$  NMR spectrum and at 62.1 and 62.1 ppm in the  $^{13}\text{C}$  NMR spectrum.

#### 4.3.2 Synthesis of (2-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)phenyl)methanamine **234**



**Scheme 87:** Reagents and conditions:  $\text{LiAlH}_4$ , dry THF, 5 hrs, 34%

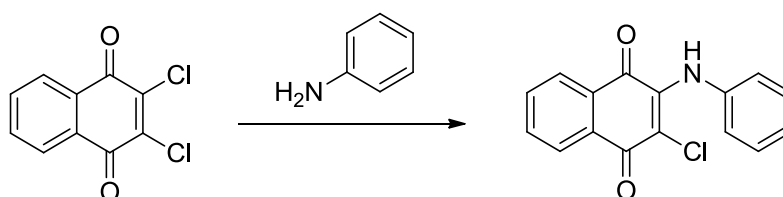
After the successful introduction of the bromine at the position *ortho* to the methoxy group, the following reduction of the nitrile group to an amine was carried out as described previously. Once again, purification of the amine **234** proved difficult and this product **234** was treated as an intermediate. Progress of the reaction was monitored by thin layer chromatography and it was observed that a spot appeared at very low  $R_f$  compared to the starting material. A prominent broad peak at  $3521\text{ cm}^{-1}$  was observed in the FTIR spectrum which indicated the presence of the amine functionality in the molecule. The compound **234** was used without further purification in the subsequent step. Also, the reaction was low yielding (34%) despite several attempts to improve the yield by increasing/decreasing reaction time, increasing equivalents of lithium aluminium hydride, but this did not improve matters.



#### 4.3.3 Attempted Synthesis of 7,12-Dimethoxy-5,6-dihydrobenzo[*b*]phenanthridine 235

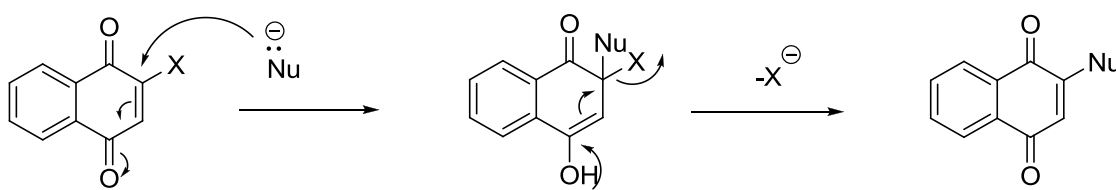
The solution was stirred at room temperature before adding cesium carbonate to the reaction mixture, which was then heated to reflux and left to stir for two days. Unfortunately, starting material **234** was not consumed during the reaction. Variations on the procedure were attempted including the use of tetrakis(triphenylphosphine)palladium(0) and a range of solvents without success. Although disappointed we once again searched the literature for alternative procedures.

Reports have been documented where nucleophilic substitution reactions with halogenated 1,4-quinones have been carried out under aqueous conditions as show in **Scheme 91**.<sup>115,116,117</sup>



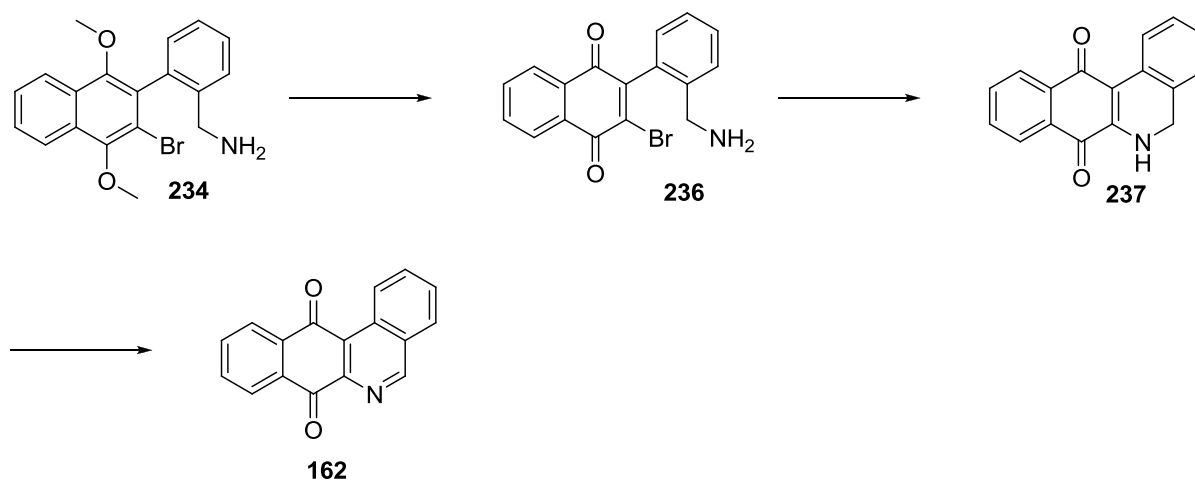
**Scheme 91:** Reagents and conditions: water, rt, 15 mins, 100%

The reaction is known to proceed by nucleophilic displacement of the halogen atom with a nitrogen nucleophile (**Scheme 92**).<sup>114</sup>



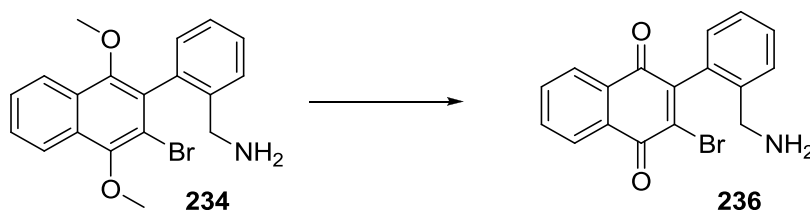
**Scheme 92**

With this information in hand, we decided to see if this approach would be feasible on our precursor for the synthesis of benzo[*b*]phenanthridine-7,12-dione **162**. Oxidation of the 1,4-dimethoxy system of (2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)phenyl)methanamine **234** to the 1,4-quinone system **236** could give us a substrate **236** for this cyclization reaction, which would result in the generation of ring B by nucleophilic substitution in the presence of water generating product **237**. Oxidation of the secondary amine generated could give us our desired product, benzo[*b*]phenanthridine-7,12-dione **162** (**Scheme 78**).



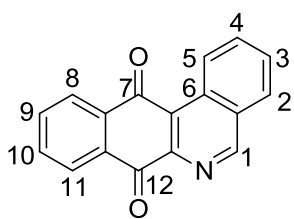
Scheme 93

#### 4.3.4 Attempted Synthesis of 2-(2-(Aminomethyl)phenyl)-3-bromonaphthalene-1,4-dione 236



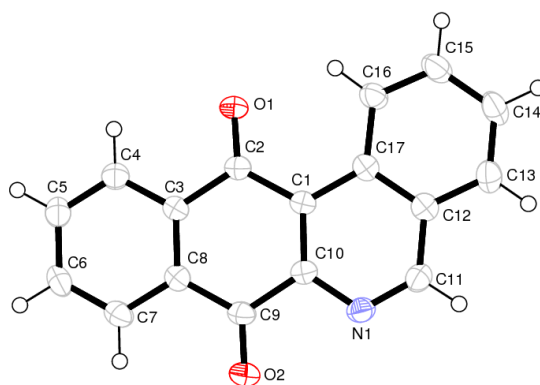
**Scheme 94:** Reagents and conditions: PIFA, CH<sub>3</sub>CN: H<sub>2</sub>O (1:1), rt, 2 hrs, 56%

The first step in the synthesis of our substrate for the intramolecular nucleophilic substitution reaction was the oxidation of (2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)phenyl)methanamine **234** to the 2-(2-(aminomethyl)phenyl)-3-bromonaphthalene-1,4-dione **236**. To achieve this, we used phenyliodine bis(trifluoroacetate) which has been used to oxidize hydroquinones to quinones.<sup>107</sup> Using this reagent and the conditions specified in the experimental a product was isolated which was bright orange in colour which suggested that we may have produced our desired quinone as many quinones are bright orange or yellow in colour. However, when we characterized it by NMR spectroscopy, we were happy to observe that the product obtained in 56% yield was not 2-(2-(aminomethyl)phenyl)-3-bromonaphthalene-1,4-dione **236** rather benzo[*b*]phenanthridine-7,12-dione **162** which was further confirmed by X-ray crystallography.



In both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, there were no signals observed for benzylic protons or carbons. Also the two protons previously observed for the amine group were not present in the  $^1\text{H}$  NMR spectrum. Both  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra indicated the presence of a complete aromatic framework with the two carbonyl carbons giving rise to signals at 186.2 and 182.3 ppm for C-12 and C-7 respectively. A singlet was observed downfield at 9.58 ppm in the  $^1\text{H}$  NMR spectrum which could be due to proton H-1.

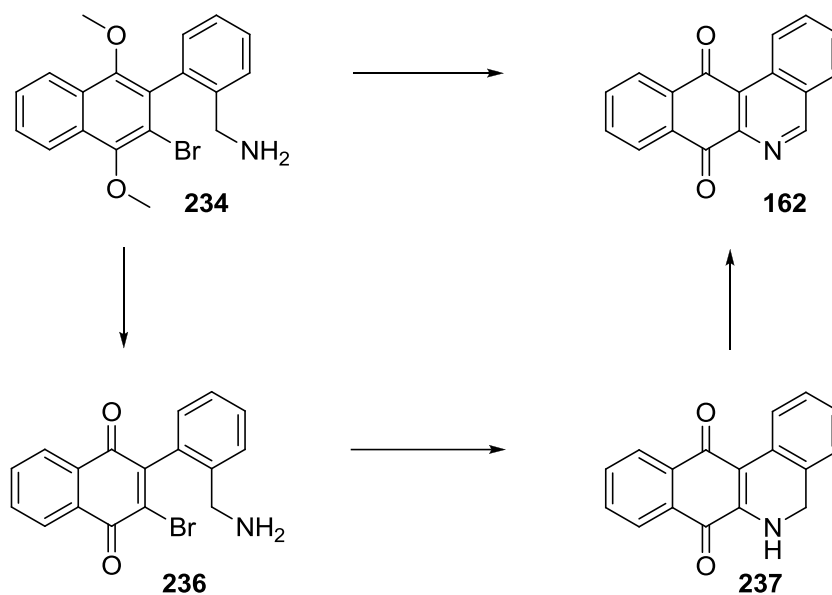
The structure of the product was confirmed by X-ray crystallography (**Figure 31**). The crystal was obtained from slow evaporation in chloroform.



Single crystal X-ray of benzo[*b*]phenanthridine-7,12-dione **162**

**Figure 31**

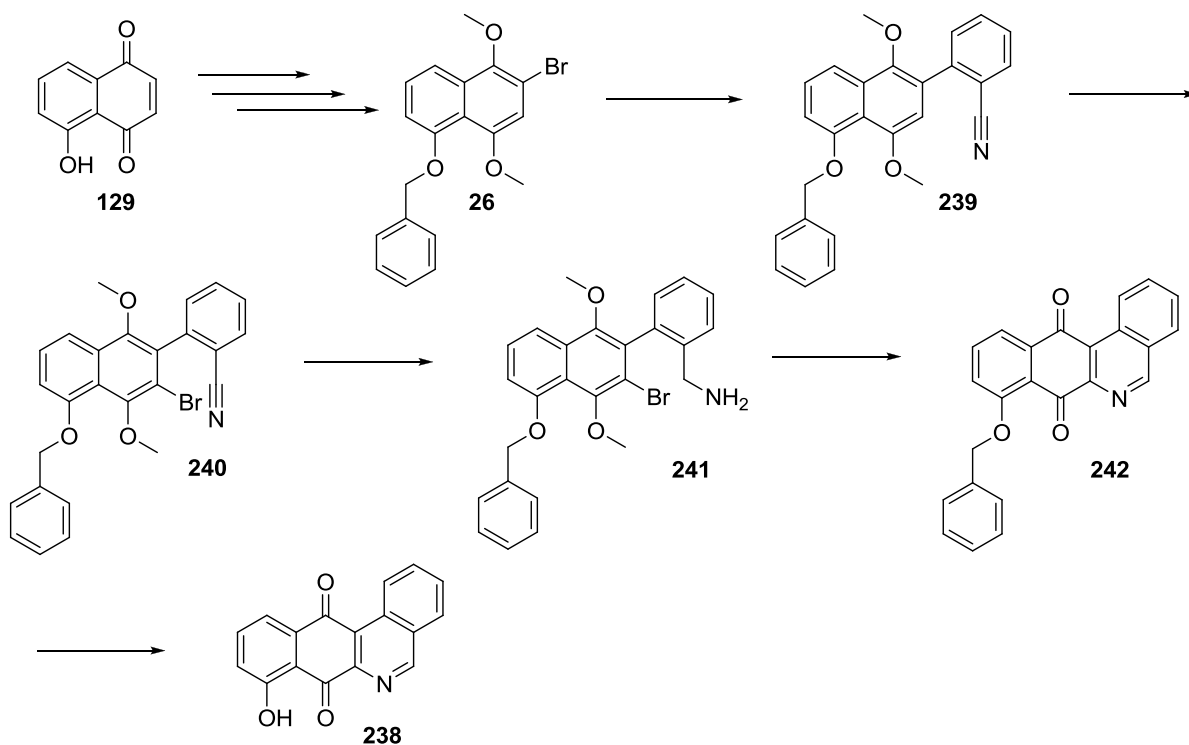
It appeared, not unexpectedly that during the course of the reaction three reactions took place consecutively in one pot. The first reaction was oxidation of the 1,4-dimethoxynaphthalene **234** into a 1,4-naphthoquinone **236** induced by phenyliodine bis(trifluoroacetate). This was followed by an intra-molecular substitution reaction, where the nitrogen nucleophile displaced the bromine atom leading to **237**. Finally, the secondary amine **237** would have been oxidized by phenyliodine bis(trifluoroacetate) to give **162**. So, to summarize, we managed to isolate our desired product **162** in one step from (2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)phenyl)methanamine **234** when we were planning to carry out three individual reactions namely; oxidation, ring cyclization and re-oxidation.



Scheme 95

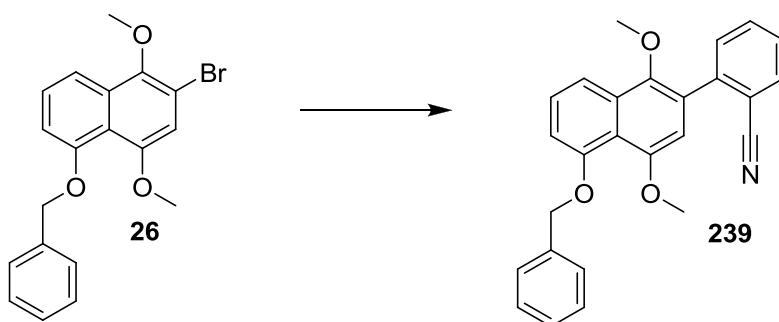
#### 4.4 Synthesis Towards 8-Hydroxybenzo[*b*]phenanthridine-7,12-dione **238**

Having successfully synthesized the desired framework of the jadomycin antibiotics, we wanted to test our methodology on a more complex system. The synthesis of 8-hydroxybenzo[*b*]phenanthridine-7,12-dione **238** could be achieved using this methodology starting from benzyl protected and 2-brominated juglone **26**. Reduction of the quinone and subsequent protection with methyl groups affords 5-(benzyloxy)-2-bromo-1,4-dimethoxynaphthalene **26** as discussed in **Chapter 2**. We envisaged that 5-(benzyloxy)-2-bromo-1,4-dimethoxynaphthalene **26** could be subjected to a Suzuki-Miyaura cross coupling reaction with 2-cyanophenyl boronic acid **213** to afford **239**. This molecule could then be subjected to bromination, which we anticipated would afford a product **240** with the bromine atom *ortho* to the methoxy group. The nitrile functional group could then be reduced to afford an amine **241**. Compound **241** could then be treated with phenyliodine bis(trifluoroacetate) to afford the desired 8-(benzyloxy)benzo[*b*]phenanthridine-7,12-dione **242**. Finally, the benzyl group could be cleaved to afford the free hydroxyl group as shown in **Scheme 96**.



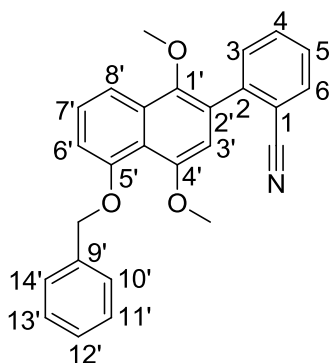
Scheme 96

#### 4.4.1 Synthesis of 2-(5-(Benzyloxy)-1,4-dimethoxynaphthalen-2-yl)benzonitrile **239**



**Scheme 97:** Reagents and conditions: 2-Cyanophenylboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ , CsF, DME, microwave irradiations, 150 °C, 150 W, 30 mins, 95%.

With the advanced substrate for the Suzuki-Miyaura cross coupling reaction in hand, we subjected 5-(benzyloxy)-2-bromo-1,4-dimethoxynaphthalene **26** to 2-cyanophenyl boronic acid **213** in the presence of palladium(0) catalyst and base under microwave irradiation conditions. Under the above mentioned conditions product **239** was furnished as a yellow solid in 95% yield.

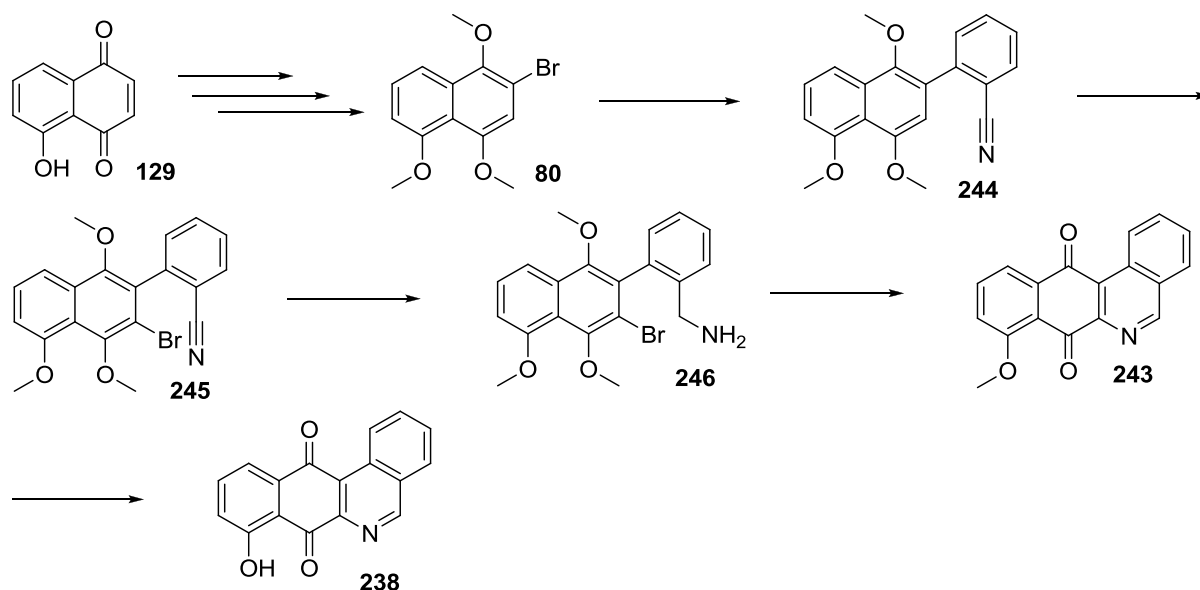


Characterization of the product was easily done using  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy. Notably, four additional protons in the aromatic region of  $^1\text{H}$  NMR spectra were observed, originating from the cyanophenyl moiety. Additionally, there are two singlets at 3.89 and 3.42 ppm integrating for six protons in total accounting for the two methoxy groups and a singlet at 5.16 ppm for the two benzylic protons in the  $^1\text{H}$  NMR spectrum. A singlet at 6.71 ppm which represents the proton H-3' was also observed in the  $^1\text{H}$  NMR spectrum. In the  $^{13}\text{C}$  NMR spectrum, twenty six peaks are visible which accounts for number of carbons expected for the product. Three peaks at 156.3, 153.5 and 147.1 ppm represent the three aromatic carbons attached directly to oxygen: C-4', C-1' and C-5' respectively. Two peaks at 61.7 and 56.7 ppm represent the two methoxy carbons, while the benzylic carbon appears as a signal at 71.6 ppm. The nitrile carbon could be seen as a signal at 119.2 ppm.

After the successful synthesis of 2-(5-(benzyloxy)-1,4-dimethoxynaphthalen-2-yl)benzonitrile **196**, we were now able to attempt brominate at carbon C-3' using the same procedure as we used for 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **233**. Unfortunately, after a number of attempts and variations on the method we never managed to obtain the desired product. It was concluded that the addition of an extra electron donating substituent on the other ring of the naphthalene was leading to multiple bromination products. It was also possible that the benzyl substituent allowed for bromination to take place on this protecting group.

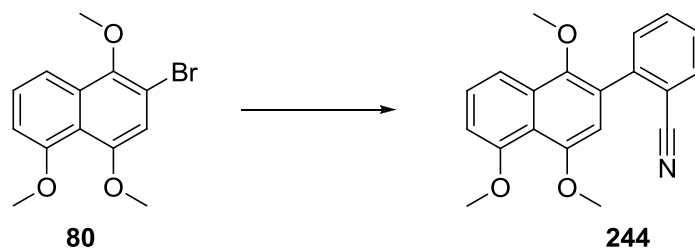
#### 4.5 Synthesis Towards 8-Methoxybenzo[*b*]phenanthridine-7,12-dione **243**

At this point, we decided to abandon the steps described in **Scheme 96** and start the synthesis with a different protecting group such as a simple methyl which is less bulky and would not allow for bromination. The remainder of the synthetic scheme would be carried out as before to afford the desired substrate for the coupling reaction, 2-bromo-1,4,5-trimethoxynaphthalene **80**. The synthesis and characterization of 2-bromo-1,4,5-trimethoxynaphthalene **80** has been previously discussed in **Chapter 2**. Suzuki-Miyaura cross coupling of 2-bromo-1,4,5-trimethoxynaphthalene **80** with 2-cyanophenyl boronic acid **213** would give us the required biaryl compound **244**, which could be subjected to a bromination reaction to introduce bromine *ortho* to the methoxy group to generate **245**. Reduction of the cyano group to an amine **246** followed by oxidation using phenyliodine bis(trifluoroacetate) would afford **243**. The methoxy group could be removed in a final deprotection step to yield the desired product **238** as shown in **Scheme 98**.



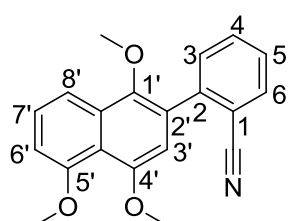
Scheme 98

#### 4.5.1 Synthesis of 2-(1,4,5-Trimethoxynaphthalen-2-yl)benzonitrile 244



**Scheme 99:** Reagents and conditions: 2-Cyanophenylboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ , CsF, DME, microwave irradiations, 150 °C, 150 W, 30 mins, 85%

Having 2-bromo-1,4,5-trimethoxynaphthalene **80** in hand, we subjected this to the conditions of the Suzuki-Miyaura cross coupling reaction with 2-cyanophenylboronic acid **213** to form the biaryl axis found in compound **244**. The product **244** was prepared using the microwave procedure previously used to afford after work up and purification by column chromatography, the product **200** as white solid in 85% yield.

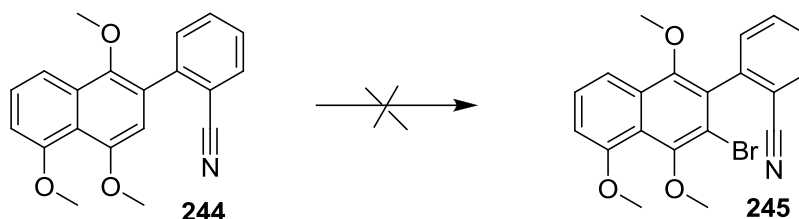


Characterization of the resulting product by NMR spectroscopy confirmed that the coupling reaction had been successful. Characteristic peaks for methoxy protons as singlets could be seen at 4.00, 3.99 and 3.50 ppm in the  $^1\text{H}$  NMR spectrum with peaks in



the  $^{13}\text{C}$  NMR spectrum visible at 61.64, 56.98 and 56.63 ppm respectively. The proton H-3' could be identified as a singlet at 6.79 ppm in the  $^1\text{H}$  NMR spectrum. Carbons C-4', C-1' and C-5' gave rise to signals with characteristic chemical shifts of 157.5, 153.4 and 147.2 ppm in the  $^{13}\text{C}$  NMR spectrum respectively.

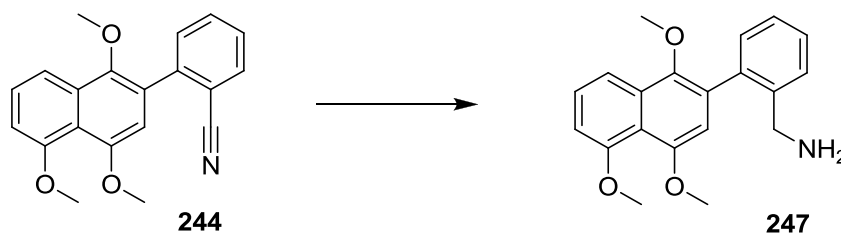
#### 4.5.2 Attempted Synthesis of 2-(3-Bromo-1,4,5-trimethoxynaphthalen-2-yl)benzonitrile **245**



**Scheme 100:** Reagents and conditions: NBS,  $\text{CH}_3\text{COONa}$ , acetic acid, rt, 4 hrs.

After the successful construction of the biaryl axis of **244**, the following step was the bromination at the position *ortho* to the methoxy group to provide us with the substrate **245** for the intramolecular substitution reaction. The reaction was carried out the same way as described previously for the synthesis 2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)benzonitrile **233** by dissolving the starting material in acetic acid followed by the addition of sodium acetate and *N*-bromosuccinimide. The reaction was stirred at room temperature for four hours but unfortunately no change was observed by thin layer chromatography. The reaction mixture was then heated to reflux, however this led to decomposition of the starting material **244**. At this stage we decided to proceed with the reduction of the nitrile **244** to an amine **247** and we would then attempt bromination on the reduced compound **247** as shown in **Scheme 101**.

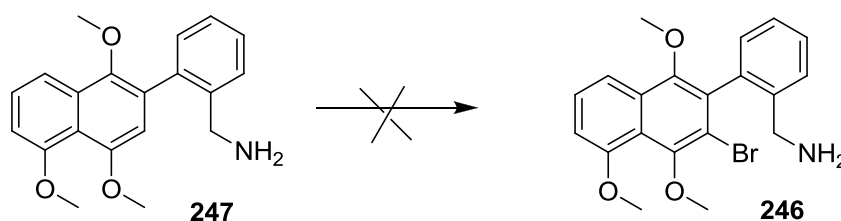
#### 4.5.3 Synthesis of (2-(1,4,5-Trimethoxynaphthalen-2-yl)phenyl)methanamine **247**



**Scheme 101:** Reagents and conditions:  $\text{LiAlH}_4$ , dry THF, reflux, 6 hrs, 58%

Having previously reduced the nitrile functionality for example in 2-(1,4-dimethoxynaphthalen-2-yl)benzonitrile **215** using an excess of lithium aluminium hydride, we knew that the reduction of 2-(1,4,5-trimethoxynaphthalen-2-yl)benzonitrile **244** would require similar conditions. Therefore, the starting material **244** in tetrahydrofuran and a large excess of the lithium aluminium hydride was added and the reaction mixture was heated at reflux for six hours. The crude product was isolated by basic work up, but attempts to purify the product **247** by column chromatography failed. NMR spectroscopic analysis of the crude product **247** confirmed formation of amine by the appearance of signals arising from the benzylic carbon and protons in NMR spectra of the product **247**. As before, therefore we treated the amine as an intermediate and carried the crude product into the next step without further purification as all the attempts failed owing to sticky resinous nature of the product **247**.

#### 4.5.4 Attempted Synthesis of (2-(3-Bromo-1,4,5-trimethoxynaphthalen-2-yl)phenyl)methanamine **246**

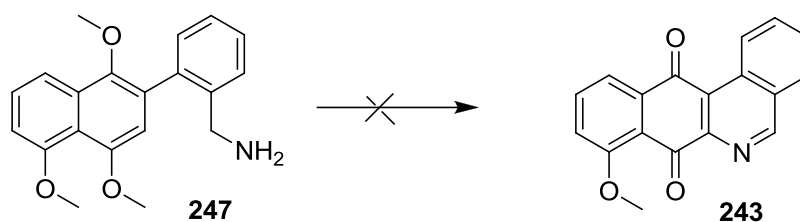


**Scheme 102:** Reagents and conditions: Br<sub>2</sub>, CCl<sub>4</sub>, 0 °C, 15 mins.

As we had been unable to brominate 2-(1,4,5-trimethoxynaphthalen-2-yl)benzonitrile **244**, we now attempted bromination of the reduced compound (2-(1,4,5-trimethoxynaphthalen-2-yl)phenyl)methanamine **247**. The amine **246** obtained was an extremely polar molecule, and was found to be insoluble in most of the organic solvents except for acetic acid. When the reaction was carried out under the above mentioned conditions with *N*-bromosuccinimide and sodium acetate in acetic acid the expected product was not formed. Even variations in the procedure did not help in the reaction.

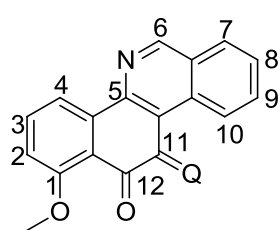
We therefore decided to attempt intramolecular nucleophilic substitution reaction on (2-(1,4,5-trimethoxynaphthalen-2-yl)phenyl)methanamine **247** using phenyliodine bis(trifluoroacetate) rather than ceric ammonium nitrate. As phenyliodine bis(trifluoroacetate) is much milder oxidizing agent compared to ceric ammonium nitrate, and we were curious to know whether this reagent could provide us with the desired product **246**.

#### 4.5.5 Attempted Synthesis of 8-Methoxybenzo[*b*]phenanthridine-7,12-dione **243**



**Scheme 103:** Reagents and conditions: PIFA, CH<sub>3</sub>CN: H<sub>2</sub>O (1:1), rt, 4 hrs, 63%

The final reaction leading to ring closure and re-oxidation was attempted on (2-(1,4,5-trimethoxynaphthalen-2-yl)phenyl)methanamine **247** by dissolving it in acetonitrile and adding phenyliodine bis(trifluoroacetate) dissolved in water. The reaction was stirred for four hours and progress was monitored by thin layer chromatography. The starting material **247** was consumed and a new very bright red spot of higher *R<sub>f</sub>* appeared, which was isolated and purified by column chromatography to afford a very bright red solid, which we anticipated to be a benzophenanthridine, in 63% yield.



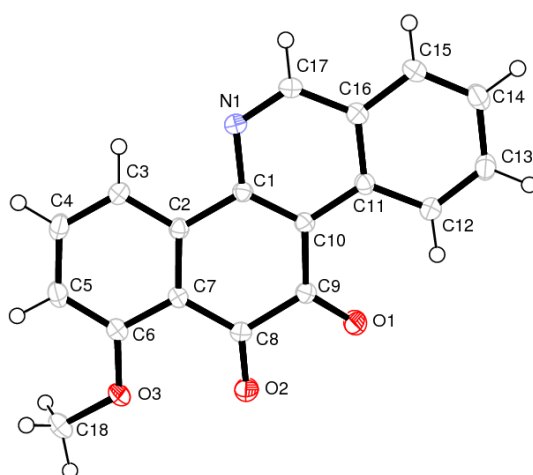
The product obtained was characterized by NMR spectroscopy. It was clearly evident that we had formed a quinone as in both <sup>1</sup>H and <sup>13</sup>C NMR spectra there were peaks for only one methoxy group compared to three in the starting material **247**. Furthermore, in the <sup>13</sup>C NMR spectrum signals at 184.1 and 179.7 ppm characteristic of carbonyl carbons were visible. Eight protons could be seen in the aromatic region of the <sup>1</sup>H NMR spectrum with fifteen carbon peaks observed in the aromatic region of the <sup>13</sup>C NMR spectrum. However, although the NMR spectroscopic evidence indicated that ring cyclization had taken place along with oxidation, we were still not very sure of the arrangement of the rings in the product, as both 8-methoxybenzo[*b*]phenanthridine-7,12-dione **243** and 1-methoxybenzo[*c*]phenanthridine-11,12-dione **248** could have formed as shown in **Figure 32**.



**Figure 32**

A crystal structure was obtained for the product we had isolated and confirmed that the actual product that had formed during the reaction was reaction was not unexpected but disappointingly 1-methoxybenzo[*c*]phenanthridine-11,12-dione **248** (Figure 33).

Isolation of the 1-methoxybenzo[*c*]phenanthridine-11,12-dione **248** and benzo[*c*]phenanthridine-11,12-dione **217** using this method suggested that without the bromine substituent, the 6-endo trig cyclization is favored. In order to isolate the desired benzo[*b*]phenanthridine-7,12-dione **162** the presence of a halogen at the position *ortho* to the methoxy group appears to be essential.



Single crystal X-ray structure of 1-methoxybenzo[*c*]phenanthridine-11,12-dione **248**

**Figure 33**

#### 4.6 Conclusion

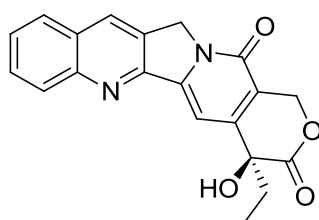
**Chapter 4**, addressed the synthetic approaches taken towards the benzo[*b*]phenanthridine-7,12-dione **162**, which constitutes the core of the jadomycin antibiotics using time and cost efficient methodology. We also tried to extend the methodology towards the synthesis of 8-methoxybenzo[*b*]phenanthridine-7,12-dione **238**, but resulted in the synthesis of the 1-methoxybenzo[*c*]phenanthridine-11,12-dione **248** framework. The complete synthesis of 1-methoxybenzo[*c*]phenanthridine-11,12-dione **248** and benzo[*c*]phenanthridine-11,12-dione **217** also sheds some light on the dynamics of the ring closure in the phenanthrovirdin aglycone **169**.

## Chapter 5: Introduction, Literature Reviews and Aims: Benzo[*a*]phenanthridines

### 5.1 Topoisomerase I-Targeting Activity

The topological state of DNA is regulated by DNA topoisomerases, enzymes that catalyze and regulate the breaking and rejoining of DNA strands.<sup>118</sup> These enzymes are also involved in controlling the template supercoiling during RNA transcription.<sup>119</sup> On the basis of difference in their initial mechanisms where a single or double-stranded DNA break is implicated, there are two major subtypes of this class of nuclear enzymes, topoisomerase I (TOP I) and topoisomerase II (TOP II). Both these enzymes are major targets of many anti-cancer drugs.<sup>120</sup> The anticancer activity of topoisomerase targeting agents is based on their ability to stabilize the enzyme-DNA cleavable complex. This drug induced stabilization of the enzyme-DNA cleavable complex changes these essential components of the replication machinery of the cell into a cellular poison.<sup>121</sup>

Camptothecin **249**, an alkaloid, was first isolated from the stem wood of *Camptotheca acuminata*, by Wall *et al.* in 1966, and was found to exhibit potent antileukemic and antitumour activities in animals.<sup>122</sup> Later, it was found to be strong inhibitor of nucleic acid synthesis in mammalian cells, and a potent inducer of strand breaking in chromosomal DNA. It acts by blocking the rejoining step of the breakage-reunion reaction of mammalian DNA TOP I which ultimately leads to cell death.<sup>123,124</sup>



Camptothecin **207**

**Figure 34**

Camptothecin **249** has been studied extensively and it has resulted in the development of structurally related analogues and in the development of two clinical TOP 1-targeting drugs, topotecan **250** (hycamptin) and irinotecan **251** (CPT-11/camptosar) (**Figure 35**).<sup>124,125</sup>

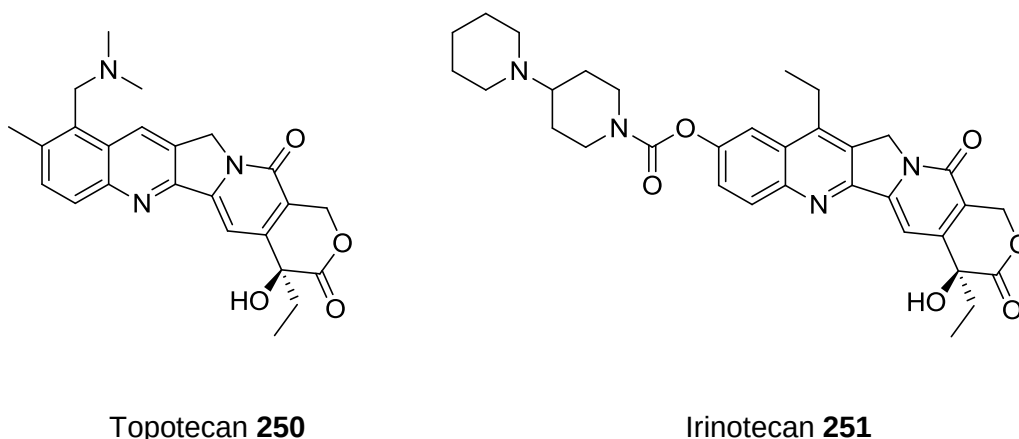


**Figure 35**

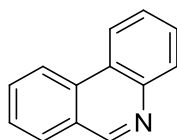
These clinical agents, topotecan **250** and irinotecan **251**, incorporate the camptothecin ring system, which includes the presence of an  $\delta$ -lactone. During drug metabolism, hydrolysis of this lactone takes place which results in an inactive derivative that possesses high affinity for human serum albumin. Both topotecan **250** and irinotecan **251** suffer from metabolic instability and are substrates for efflux transporters associated with multidrug resistance. This disadvantage of these clinical drugs has encouraged further studies on the development of novel TOP I-targeting agents.<sup>126,127</sup>

## 5.2 Non-camptothecin TOP I-Targeting Agents.

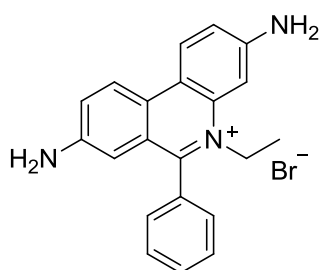
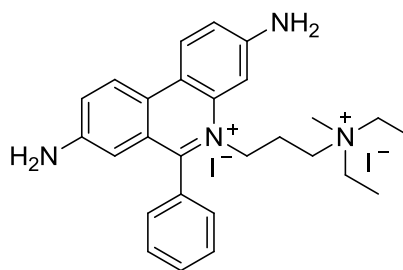
Although camptothecin derivatives are widely used clinically for anti-tumour intervention, their drawbacks: lack of chemical stability, toxicity, severe drug resistance and other undesirable side effects have paved the way for the generation of non-camptothecin based TOP I-targeting agent with better pharmacokinetic and pharmacological profiles.<sup>128</sup>

The most encouraging scaffolds identified as non-camptothecin TOP I-targeting agents are indolocarbazoles, indenoisoquinolines, and phenanthridines **252**.<sup>129</sup>

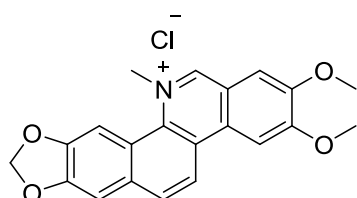
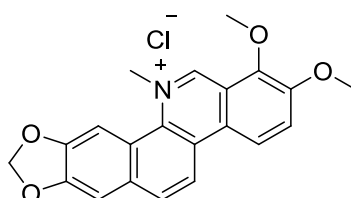
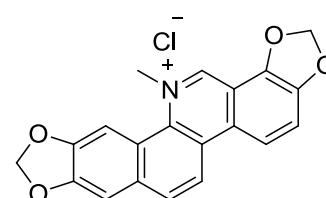
The phenanthridine skeleton **252** forms a small but important class of a heterocycles found in a large number of naturally occurring and bioactive compounds showing widespread pharmacological activities and applications.<sup>130</sup>

Phenanthridine **252****Figure 36**

The phenanthridine ring system forms the basis of ethidium bromide **253** and propidium iodide **254**, both of which are used extensively in molecular biology laboratories as nucleic acid stains and act by binding to double stranded DNA by intercalating between the base pairs.<sup>131</sup>

Ethidium bromide **253**Propidium iodide **254****Figure 37**

Alkaloids such as nitidine chloride **255**, chelerythrine chloride **256** and sanguinarine chloride **257** also have a phenanthridine ring system fused to a benzene ring or other heterocyclic compounds and are known for their high biological importance.<sup>130,131</sup>

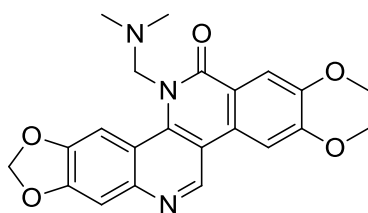
Nitidine chloride **255**....Chelerythrine chloride **256**.....Sanguinarine chloride **257****Figure 38**

Nitidine chloride **255** is a benzophenanthridine alkaloid found in species of the genus *Zanthoxylum*, notably in *Zanthoxylum nitidum*, and is a known TOP I inhibitor as well as a potential anti-malarial agent. Its capacity to complex haem and inhibit  $\beta$ -haematin formation suggests a mechanism of action similar to that of chloroquine.<sup>132,133</sup>

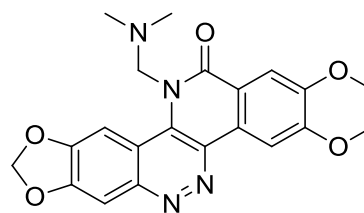
Chelerythrine chloride **256** is a benzophenanthridine alkaloid extracted from greater celandine (*Chelidonium majus*) and is known for its potent, and selective protein kinase C inhibition.<sup>134</sup>

Sanguinarine chloride **257**, an alkaloid isolated from bloodroot plant *Sanguinaria canadensis*, possesses remarkable anticancer effects along with antimicrobial, anti-inflammatory and antioxidant properties.<sup>135</sup>

Numerous 5-(2-aminoethyl)dibenzo[*c,h*][1,6]naphthyridin-6-ones have been recognized as active TOP I-targeting agents having exceptionally good anti-tumour activity, including dibenzo[*c,h*][1,6]naphthyridin-6-one (ARC-111, topovale) **258** and the 11-aza analogue of ARC-111, isoquino[4,3-*c*]cinnolin-12-one **259** and related compounds.<sup>136</sup>



ARC-111, topovale **258**

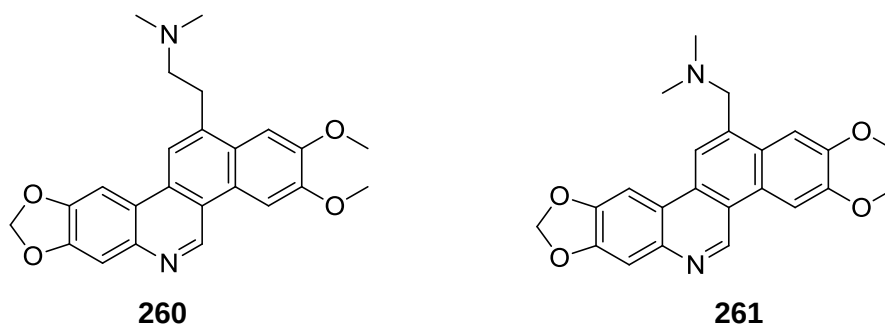


Isoquino[4,3-*c*]cinnolin-12-one **259**

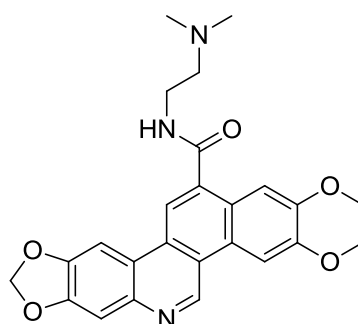
**Figure 39**

Replacing the C-ring of topovale with a phenyl group results in benzo[*l*]phenanthridine containing compounds such as **260** and **261** (Figure 40), which have also shown comparable TOP I-targeting activity to camptothecin **249** or topovale **258**.<sup>128,137</sup>



**Figure 40**

Substituted benzo[7]phenanthridines have been known to possess TOP I-targeting activity and cytotoxicity against a number of human tumour cell lines.<sup>138</sup> AR-VIII-83 **262**, which also has a benzo[7]phenanthridine skeleton has the potential to be further developed as a non-camptothecin TOP I-targeting agent, owing to the promising biological activities associated with it. The occurrence of the aminoalkyl group attached to the 12-carboxamide provides the much needed hydrophilic character to the compound improving the pharmacokinetics of the compound.<sup>136</sup>

**AR-VIII-83 262****Figure 41**

LaVoie and co-workers have explored this fact of, improving pharmacokinetic properties by introducing hydrophilic groups, by making numerous analogues of nitidine **255** in the form of substituted benzo[7]phenanthridines which have also shown potential TOP I inhibition activity.<sup>121,124,138,139,140,137</sup>

A few representatives of the molecules containing a benzo[*l*]phenanthridine framework that were synthesized by LaVoie and co-workers having TOP I inhibitor activity are shown in **Figure 42**.

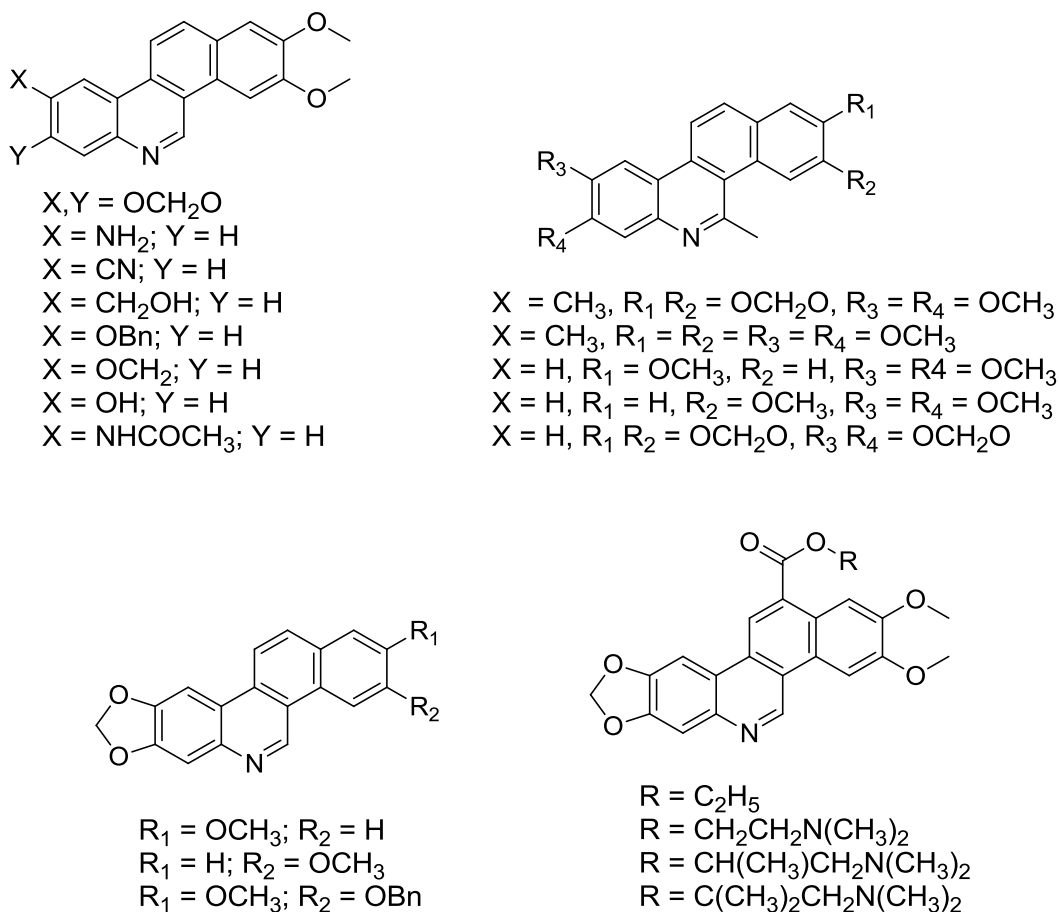
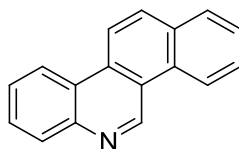


**Figure 42**

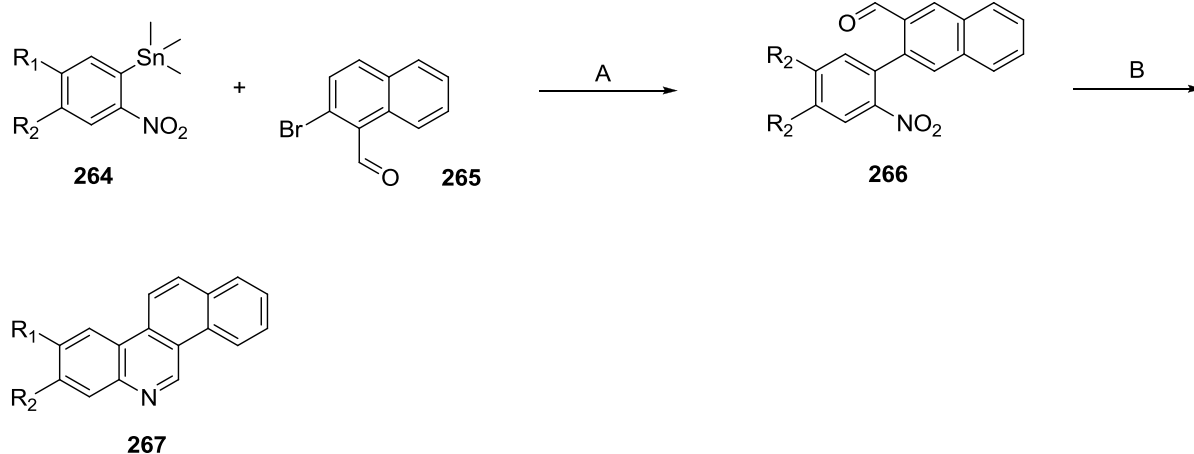
### 5.3 Selected Synthetic Approaches to the Benzo[*l*]phenanthridine Ring System

The importance of benzo[*l*]phenanthridine **263** ring system as a TOP I inhibitor prompted us to consider the use of a novel approach for the synthesis of this class of compounds. In the following section, selected reported synthetic approaches towards the benzo[*l*]phenanthridines **263** will be discussed.

Benzo[7]phenanthridine **263****Figure 43**

### 5.3.1 Li *et al.* Approach Towards the Synthesis of Benzo[7]phenanthridine Derivatives.<sup>141</sup>

Li *et al.* proposed the use of substituted *o*-nitrostannanes **264** for the preparation of a variety of substituted phenanthridine and benzo[7]phenanthridine derivatives. Reaction of **264** with 2-bromo-1-naphthaldehyde **265** generated substituted 2-(2-nitrophenyl)-1-naphthaldehydes **266**. Subsequent treatment of these 2-(2-nitrophenyl)-1-naphthaldehydes **266** with zinc dust in acetic acid at reflux yielded 8,9-benzo[7]phenanthridines **267** in good yields as shown in **Scheme 104**.

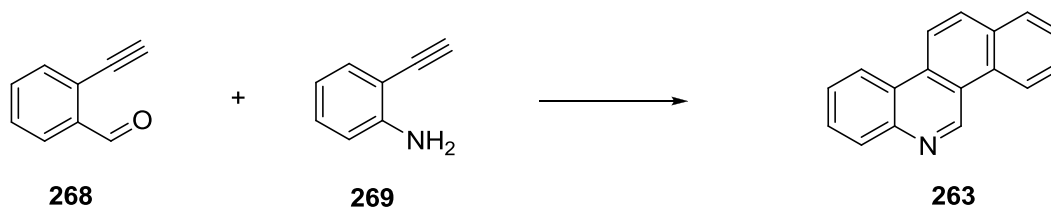


**Scheme 104:** Reagents and conditions: A) cat. Pd(PPh<sub>3</sub>)<sub>4</sub>, CuBr, reflux, THF, 70-90%; B) Zn dust, acetic acid, 60-95%.<sup>141</sup>

### 5.3.2 Yanada *et al.* Approach<sup>142</sup>

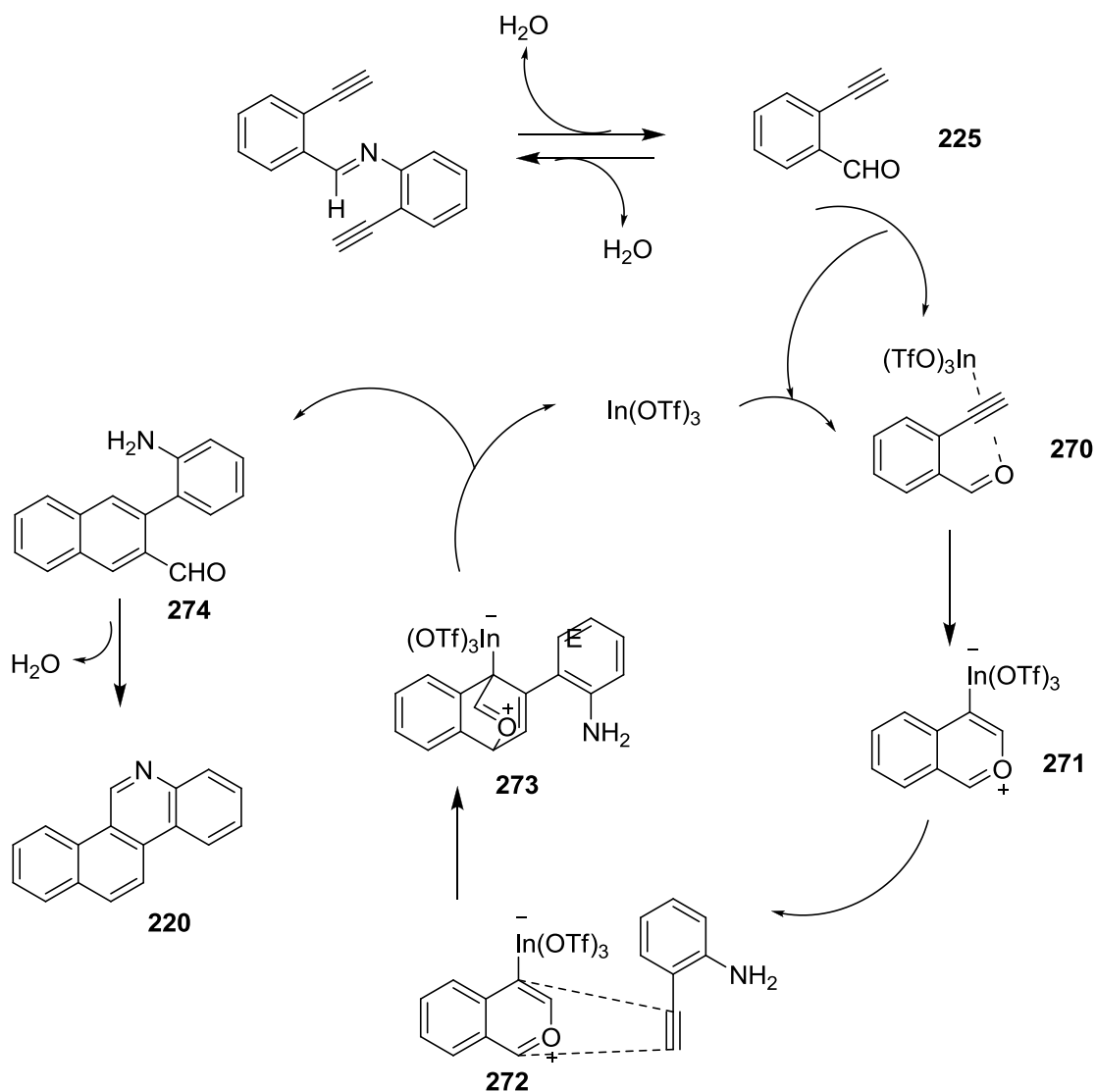
In the synthesis proposed by Yanada *et al.*, an  $\pi$ -acidic metal-catalyzed tandem reaction was employed to synthesize the benzo[7]phenanthridine **263** framework. In the synthesis, a Lewis acid catalyzed annulation of *ortho*-alkynylbenzaldehydes **268** with *ortho*-

alkynylanilines **269** sequentially proceeds to form one carbon-nitrogen and two carbon-carbon bonds of benzophenanthridine **263** in one step.



**Scheme 105:** Reagents and conditions: In(OTf)<sub>3</sub>, DMF, 80 °C, 24 hrs, 93%.<sup>142</sup>

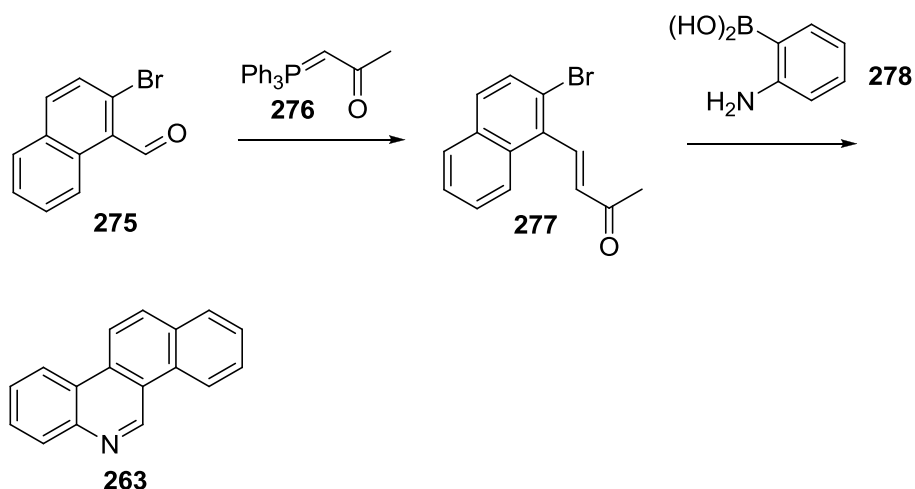
A proposed mechanism for this indium(III)-catalyzed tandem reaction is shown in Scheme **106**, where coordination of In(OTf)<sub>3</sub> with the triple bond of **225** to give **270** enhances the electrophilicity of alkyne and subsequent nucleophilic attack of the carbonyl oxygen to the electron-deficient alkyne results in the formation of the 6-endo-dig-cyclized pyrylium cation intermediate **271**. Followed by Diels-Alder-type cycloaddition of **271** with *ortho*-alkynylaniline **226** would occur as shown in **272** to give the intermediate **273** with the same high regioselectivity. Subsequent bond rearrangement proceeds to afford **274** with regeneration of In(OTf)<sub>3</sub>. Dehydration of **274** produces ring-condensed heteroaromatic compound **220** as illustrated in **Scheme 106**.



Scheme 106

### 5.3.3 Ghosh *et al.* Approach<sup>143</sup>

Ghosh *et al.* have developed an efficient method for the synthesis of benzo[7]phenanthridines analogues employing a ligand-free domino Suzuki coupling–Michael addition reaction catalyzed by *in situ* generated palladium nanoparticles in water. The first step was the Wittig reaction of 2-bromocarboxaldehydes **275** with 1-(triphenylphosphoranylidene)-2-propanone **276** which generated  $\beta$ -(2-bromoaryl)- $\alpha,\beta$ -unsaturated carbonyl intermediate **277**. This intermediate was treated with 2-aminophenylboronic acid **230** to give rise to benzo[7]phenanthridines **263** via a ligand-free domino Suzuki coupling–Michael addition reaction with the elimination of acetone molecule as shown in **Scheme 106**.

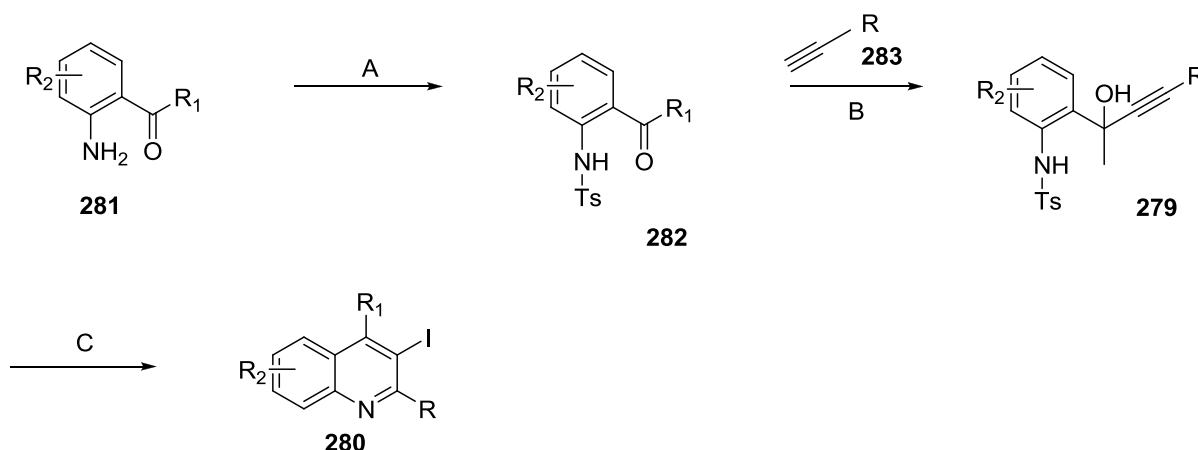


**Scheme 106:** Reagents and conditions: A) DCM, 0 °C, rt, 3 hrs, 90%; B) Pd(OAc)<sub>2</sub>, K<sub>3</sub>PO<sub>4</sub>, TBAB, H<sub>2</sub>O, 90 °C, 70%.<sup>143</sup>

Due to the biological importance of benzo-fused phenanthridines and the fact that only a few synthetic approaches to these compounds have been employed in the past, we planned to undertake the synthesis of substituted benzo[7]phenanthridines using a novel approach.

#### 5.4 Proposed Synthesis of Substituted Benzo[7]phenanthridine

The synthetic approach we envisioned for the synthesis of the benzo[7]phenanthridine **263** skeleton was inspired by a research publication by Ali *et al.* in 2011, where the authors demonstrated the synthesis of functionalized, halogen substituted quinolines using an iodine-mediated ring cyclization as the key step.<sup>144</sup> The approach employed the treatment of suitably substituted aliphatic and aromatic 2-tosylaminophenylprop-1-yn-3-ols **279** with molecular iodine leading to iodocyclization in a 6-endo-dig fashion to generate a library of substituted 3-iodoquinolones **280** as shown in **Scheme 107**. 2-Tosylaminophenylprop-1-yn-3-ols **279** were in turn prepared from suitably substituted 1-(2-aminophenyl)ketones **281**, which were protected with a tosyl group, and the resulting product **282** was treated with a substituted terminal alkyne **283** under basic conditions to yield **279**.



**Scheme 92:** Reagents and conditions: A) PTSA, pyridine, rt, 4 hrs, B)  $\text{C}_2\text{H}_5\text{MgBr}$ , THF, 4 hrs, rt-heating under reflux; C)  $\text{I}_2$ , MeOH, 60 °C, 6 hrs.<sup>144</sup>

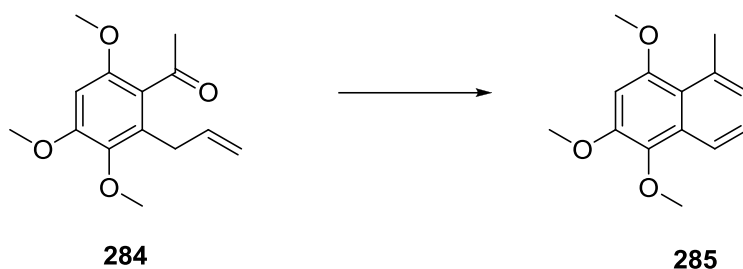
We envisioned utilizing the aromatic iodine present in the substituted quinolones as synthesized by Ali *et al.* as a handle for the further functionalization in order to synthesize substituted benzo[*l*]phenanthridines.<sup>144</sup>

To achieve our target we planned to carry out two key reactions: a Suzuki-Miyaura cross coupling reaction with a suitably substituted 2-carbonylphenylboronic acid to generate a biaryl compound and a potassium *t*-butoxide and light induced ring cyclization to generate the substituted benzo[*l*]phenanthridine structure.

### 5.5 Potassium *t*-butoxide and Light Induced Ring Cyclization

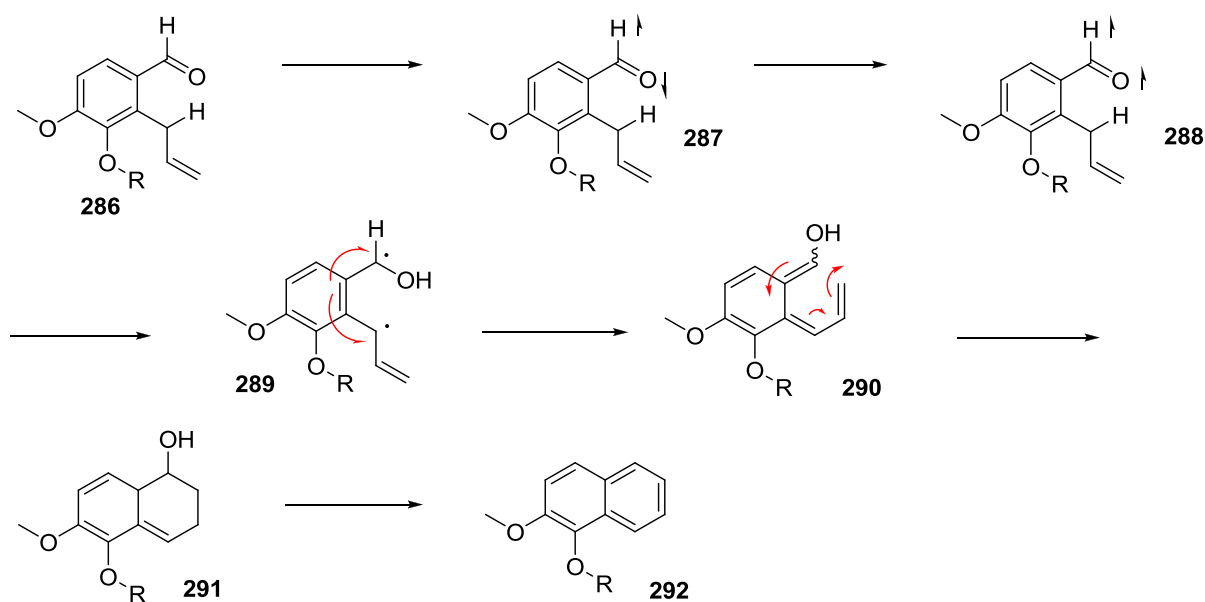
A vast amount of research has been conducted on the synthesis of polyaromatic and polyheteroaromatic compounds in the laboratories of the University of the Witwatersrand employing potassium *t*-butoxide and light to induce ring cyclization to form a new aromatic ring.

While studying the synthesis of substituted naphthalenes, de Koning *et al.* demonstrated that when 1-(2-allyl-3,4,6-trimethoxyphenyl)ethanone **284** was subjected to potassium *t*-butoxide in presence of dimethylformamide and light from a high pressure mercury lamp (400 W), ring cyclization took place to yield 1,2,4-trimethoxy-5-methylnaphthalene **285** as shown in **Scheme 108**.<sup>145</sup>



**Scheme 108:** Reagents and conditions: KOBut, DMF,  $h\nu$ , 80 °C, 10 mins.

The mechanism of this ring closure reaction was proposed to proceed by photoenolization by an initial Norrish type II process. Direct irradiation from a high pressure mercury lamp (400 W) leads to the excitation of the carbonyl group of **286** to an excited singlet state **287**, which, as a result of the inter-system crossing, immediately decays into the triplet state **288**. This triplet state intermediate **288** abstracts hydrogen to afford the diradical **289** which quickly rearranges to photoenol **290**. Further a  $6\pi$  electrocyclic process affords the alcohol **291** which, after dehydration, yields the naphthalene product **292** (**Scheme 109**).<sup>146</sup>

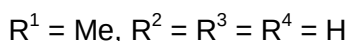
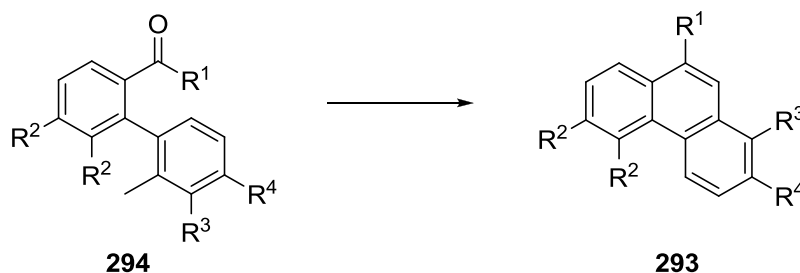


**Scheme 109**

This novel light and base-assisted cyclization reaction to form a centrally-positioned aromatic ring has been employed extensively and successfully to generate a variety of polyaromatic and poly-heteroaromatic molecules.



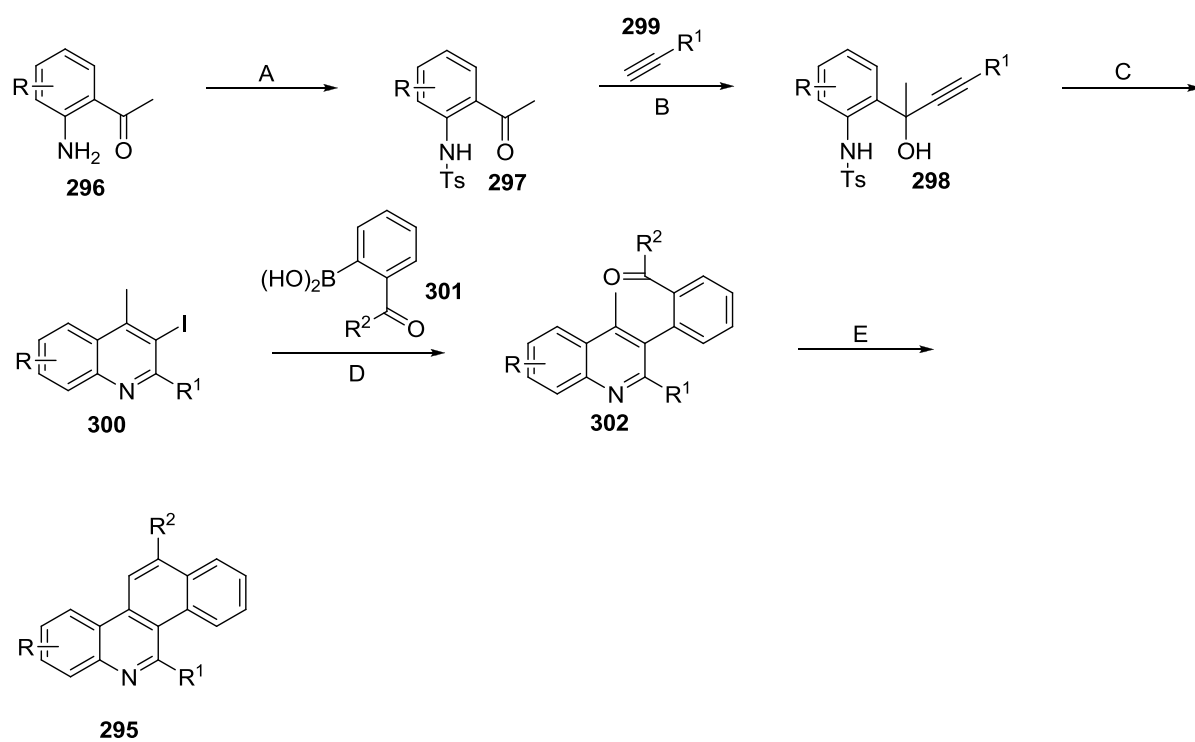
For example, de Koning *et al.* demonstrated the synthesis of substituted phenanthrenes **293** using this ring cyclization method.<sup>147</sup> The procedure involved subjecting a compound possessing a biaryl axis **294** and bearing both a carbonyl group and a methyl group *ortho* to the biaryl axis but on opposite rings, to potassium *t*-butoxide and light. This led to the formation of the phenanthrenes of general structure **293**.



**Scheme 110:** Reagents and conditions: KOBut, DMF, light, 70-80 °C

## 5.6 Aim of the Project

Based on the findings by Ali *et al.* and having knowledge of the potassium *t*-butoxide and light induced ring cyclization and Suzuki-Miyaura cross coupling reactions, we envisioned a synthesis for the generation of substituted benzo[*l*]phenanthridines **295**, using these key reactions.<sup>144</sup> We planned to begin with the tosyl protection of suitably substituted 1-(2-aminophenyl)ethanones **296** to afford tosylated intermediates **297**, which could then be converted into **298** by treatment with a substituted terminal alkyne **299**. The resulting product **298** could then be subjected to the iodine induced cyclization reported by Ali *et al.* to yield **300**.<sup>144</sup> A Suzuki-Miyaura cross coupling reaction could then follow between **300** and a suitably substituted 1-carbonyl boronic acid **301** to generate the biaryl compound **302**. Compound **302** would then be a suitable substrate for potassium *t*-butoxide and light induced ring cyclization as it possesses the required methyl and carbonyl substituents, to finally generate **295** as shown in **Scheme 111**.



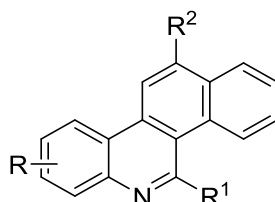
$R^1$  = Aryl, alkyl

$R^2$  = H, Me

**Scheme 111**

## Chapter 6: Results and Discussion: Benzo[*l*]phenanthridines

The importance of benzo[*l*]phenanthridines in therapeutics as TOP I inhibitors prompted us to synthesize substituted benzo[*l*]phenanthridines using our novel potassium *t*-butoxide and light induced cyclization reaction as a key step as discussed in **Chapter 5**.

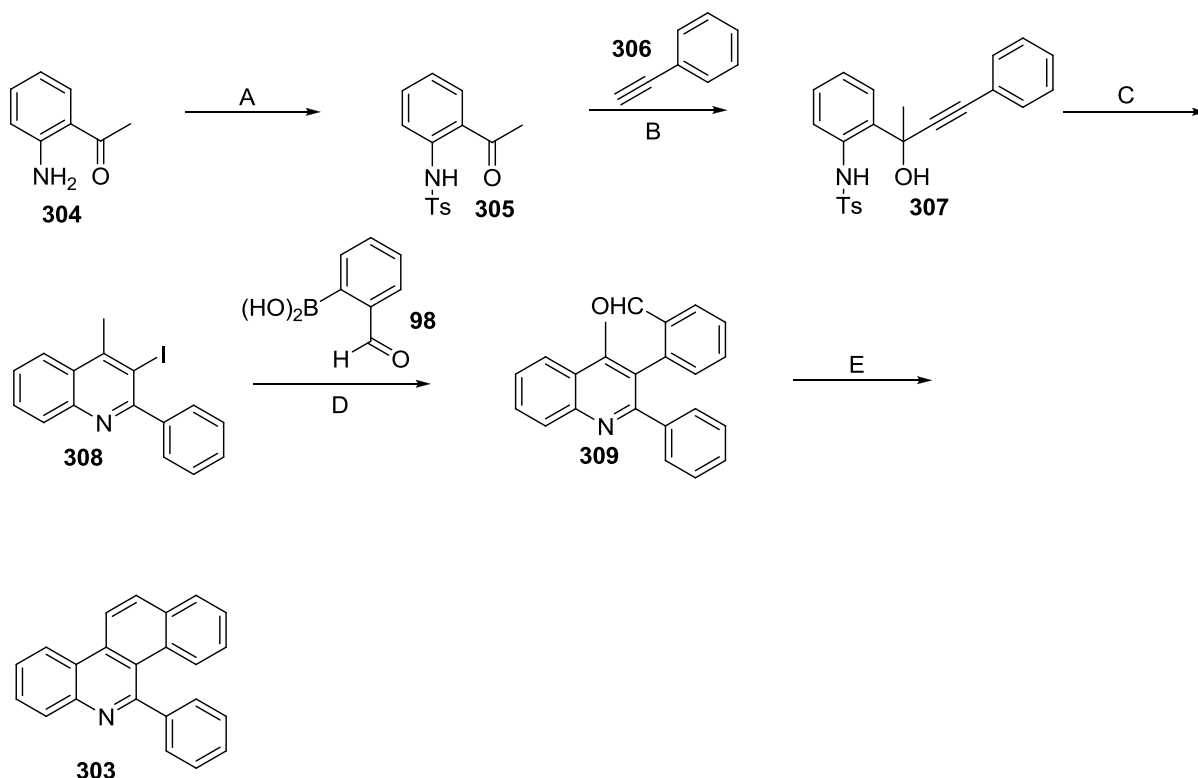


Substituted benzo[*l*]phenanthridines **295**

**Figure 44**

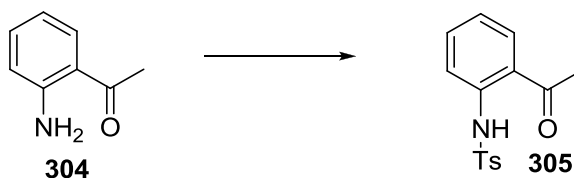
### 6.1 Approaches Towards the Synthesis of 5-Phenylbenzo[*l*]phenanthridine **303**

To proceed with the synthesis, we first planned to synthesize a simple analogue of the benzo[*l*]phenanthridines, namely, 5-phenylbenzo[*l*]phenanthridine **303**. We envisioned the synthesis would commence from 1-(2-aminophenyl)ethanone **304**. The primary amine of **304** would be tosyl protected as the first step to afford **305**. Treatment with phenylacetylene **306** under basic conditions would yield *N*-(2-(2-hydroxy-4-phenylbut-3-yn-2-yl)phenyl)-4-methylbenzenesulfonamide **307**. The molecular iodine-mediated cyclization would follow as the next step to give 3-iodo-4-methyl-2-phenylquinoline **308**. Subsequently, a Suzuki-Miyaura cross coupling reaction with 2-formylphenyl boronic acid **98** would afford 2-(4-methyl-2-phenylquinolin-3-yl)benzaldehyde **309**. Finally, subjecting **309** to the conditions of potassium *t*-butoxide and light would yield 5-phenylbenzo[*l*]phenanthridine **303** as shown in **Scheme 112**.



Scheme 112

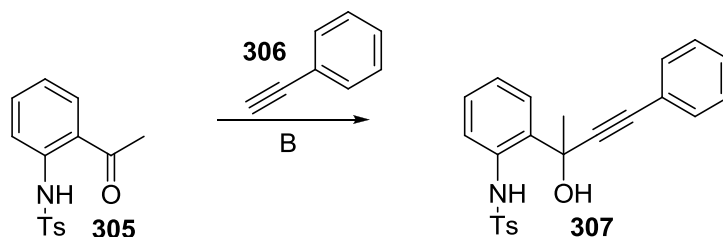
### 6.1.1 Synthesis of *N*-(2-Acetylphenyl)-4-methylbenzenesulfonamide **305**



**Scheme 113:** Reagents and conditions: *p*TsCl, pyridine, rt, 4 hrs, 100%

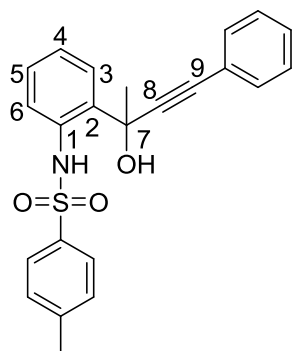
To carry out the synthesis of *N*-(2-acetylphenyl)-4-methylbenzenesulfonamide **305**, commercially available 1-(2-aminophenyl)ethanone **304** was taken up in pyridine and treated with tosyl chloride. The reaction was stirred under inert conditions and at room temperature for four hours over which time the reaction mixture becomes a white slurry. On completion of the reaction, the mixture was quenched with cold water to facilitate the precipitation of the product **305** as a white solid, which was then dried and used directly in the following step without further characterization.

### 6.1.2 Synthesis of *N*-(2-(2-Hydroxy-4-phenylbut-3-yn-2-yl)phenyl)-4-methylbenzenesulfonamide **307**



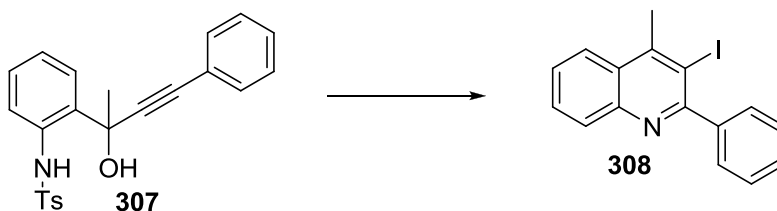
**Scheme 114:** Reagents and conditions: C<sub>2</sub>H<sub>5</sub>MgBr, dry THF, 0 °C-rt- reflux, 4 hrs, 99%

Crude *N*-(2-acetylphenyl)-4-methylbenzenesulfonamide **305**, was then subjected to the next step in our synthesis which was the addition of phenylacetylene **306** under basic conditions. Initially, generation of phenylacetylene anion was achieved using ethylmagnesium bromide as the base. Under inert conditions, phenylacetylene dissolved in dry tetrahydrofuran was added to ethylmagnesium bromide in tetrahydrofuran at 0 °C, with the liberation of ethane gas clearly evident. After fifteen minutes, starting material **305** dissolved in dry tetrahydrofuran was added to the reaction mixture, which was then allowed to warm to room temperature, and subsequently heated to reflux for four hours. The progress of the reaction was monitored by thin layer chromatography and on completion, isolation of the product **307** and purification by column chromatography was performed to obtain the product **307** as a white solid in 99% yield.



The characterization of the product was done by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and the results were found to be in agreement with that of the literature.<sup>144</sup> The <sup>1</sup>H NMR spectrum showed the presence of a hydrogen attached to nitrogen, as a singlet visible at 9.21 ppm. At 3.22 ppm a broad peak for the proton of the hydroxyl group was present, and, two singlets at 2.33 and 1.76 ppm, integrating for three protons each, confirmed that the two methyl groups were present in the molecule. Signals from the <sup>13</sup>C NMR spectrum also correlated with the signals present in the <sup>1</sup>H NMR spectrum. There were two peaks at 31.3 and 21.5 ppm which signified the two carbons of the two methyl groups. At 90.8 and 86.5 ppm were the two peaks for the two carbons of the triple bond C-8 and C-9. Finally, a signal at 72.2 ppm confirmed the presence of the quaternary carbon C-7.

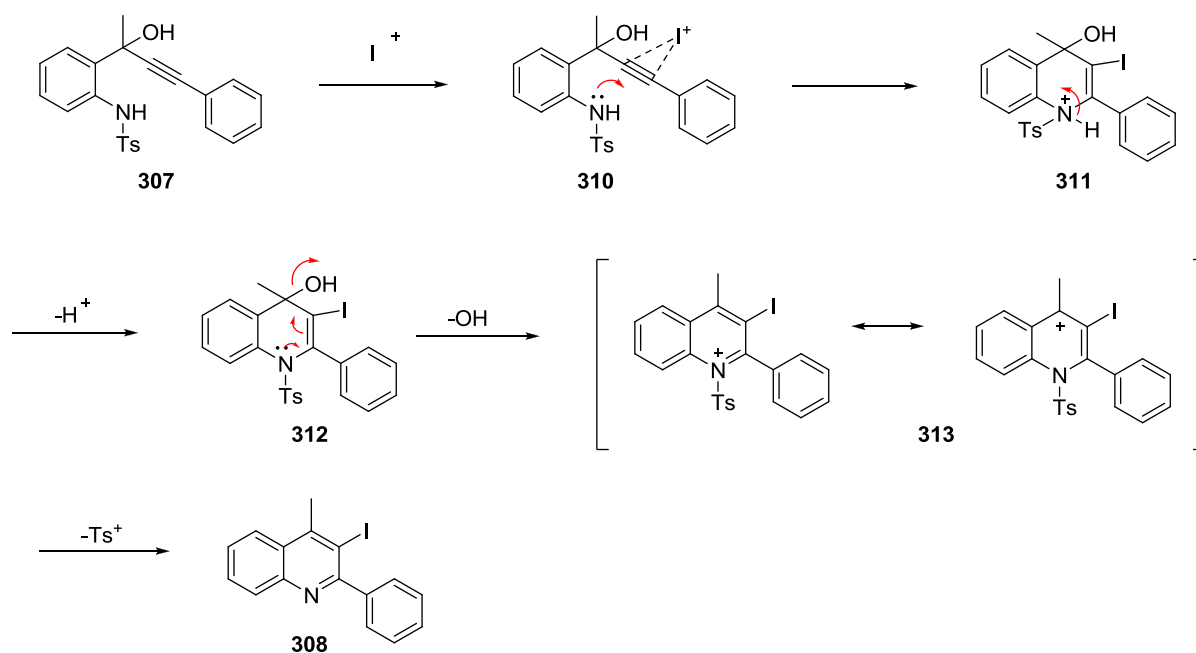
### 6.1.3 Synthesis of 3-Iodo-4-methyl-2-phenylquinoline 308



**Scheme 115:** Reagents and conditions: I<sub>2</sub>, methanol, 60 °C, 6 hrs, 32%.

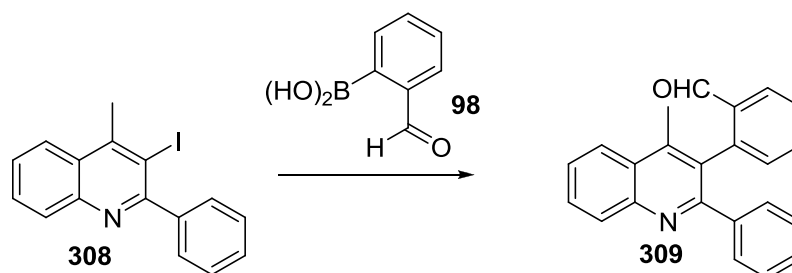
To carry out the synthesis of 3-iodo-4-methyl-2-phenylquinoline **308**, the starting material **307** was dissolved in methanol and iodine was added. The reaction was allowed to stir for six hours at 60 °C, after which time the mixture was quenched. The product was isolated and then purified by column chromatography to afford **308** as a white powder in a disappointing yield of 32%. Despite numerous attempts to improve the yield of the reaction, this was the best yield of the product **308** we obtained. We were never able to get complete conversion of the starting material **307** into the product **308** in this reaction.<sup>144</sup>

The mechanism of this iodocyclization reaction of conversion of **307** to **308** has been explained by Ali *et al.* where the reaction involves anti attack of the electrophile and the nitrogen of the tosylated amino group on the alkyne moiety of **310** to generate an intermediate **311**, which then undergoes a proton removal by the iodide present in the reaction mixture to give compound **312**. In protic solvents **312** loses hydroxyl ion to give cation **313** and finally, **313** gains full aromaticity by eliminating a tosyl group to form quinoline derivative **308** as illustrated in **Scheme 116**.<sup>144</sup>



The spectroscopic results of the product **308** were found to be in agreement with the literature.<sup>144</sup> A clear singlet at 3.03 ppm integrating for three protons in the <sup>1</sup>H NMR spectrum referred to the methyl group at C-3 in the molecule with the corresponding peak at 25.9 ppm in the <sup>13</sup>C NMR spectrum. The remaining signals in the aromatic region of the <sup>1</sup>H NMR spectrum integrated for nine protons as expected.

#### 6.1.4 Synthesis of 2-(4-Methyl-2-phenylquinolin-3-yl)benzaldehyde **309**



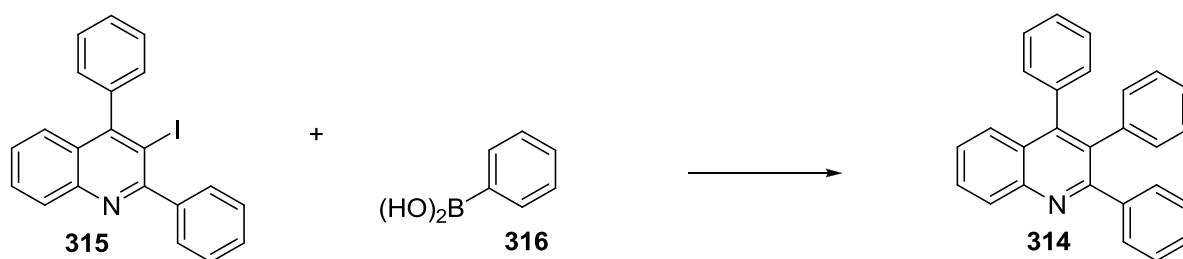
**Scheme 117:** Reagents and conditions: Method 1): 2-Formylphenyl boronic acid, Pd(OAc)<sub>2</sub>, sodium carbonate, DMF:H<sub>2</sub>O (2:1), reflux, 4 hrs, 79%; Method 2) 2-Formylphenyl boronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub>, CsF, DME, 15 mins, 120 W, 120 °C, microwave irradiation, 70%.

After the successful synthesis of 3-iodo-4-methyl-2-phenylquinoline **308**, albeit in low yield, the next step in our synthesis was the generation of the biaryl axis utilizing the aromatic

iodide **308** by employing a Suzuki-Miyaura cross coupling reaction with 2-formylphenyl boronic acid **98** to yield **309**. Two methods were tested for this reaction, a conventional method and the reaction in a microwave reactor.

**Method 1:** In this classical method for the Suzuki-Miyaura cross coupling reaction, starting material **308** was dissolved in dry, degassed dimethylformamide treated with catalytic palladium(II)acetate. The reaction was allowed to stir under inert conditions and at room temperature for ten minutes, before the addition of 2-formylphenyl boronic acid **98** and sodium carbonate. The reaction mixture was then heated to reflux for four hours. The product **309** was isolated after work-up and purification by column chromatography as an off-white solid in 79% yield.

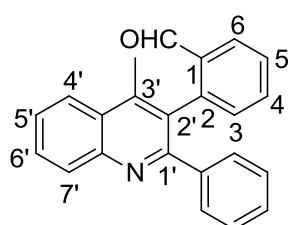
Ali *et al.* carried out a similar Suzuki-Miyaura cross coupling reaction where the authors managed to generate biaryl axis in 2,3,4-triphenylquinoline **314** by coupling 3-iodo-2,4-diphenylquinoline **315** with phenylboronic acid **316** as shown in **Scheme 118**.<sup>148</sup>



**Scheme 118:** Reagents and conditions: Pd(OAc)<sub>2</sub>, Na<sub>2</sub>CO<sub>3</sub>, DMF:H<sub>2</sub>O (2:1), reflux, 4 hrs, 92%.

**Method 2:** In the microwave method for the Suzuki-Miyaura cross coupling reaction, all the reagents along with starting material **308** and solvent were added to a microwave reaction vial and then subjected to microwave irradiation at 120 W, 120 °C for ten minutes. This was followed by work-up and purification by column chromatography to afford the product **309** in 70% yield.

Although both methods worked very well in terms of isolated yield of the product **309**, the microwave method proved to be more convenient in terms of time taken for the reaction.

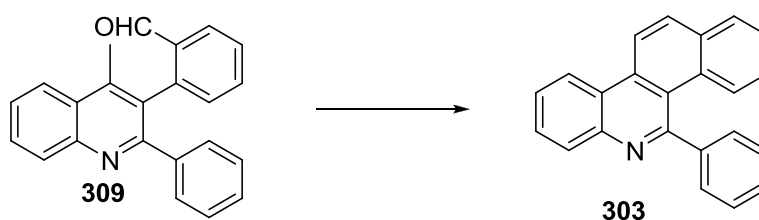


The characterization of the product **309** was done by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. The appearance of a singlet at 9.76 ppm in the



$^1\text{H}$  NMR spectrum, integrating for one proton, indicated the presence of the aldehyde functional group, with the corresponding peak for the carbonyl carbon present in the  $^{13}\text{C}$  NMR spectrum at 191.0 ppm. A singlet at 2.48 ppm integrating for three protons in the  $^1\text{H}$  NMR spectrum represented the protons of the methyl group, with the signal for the methyl carbon visible at 29.7 ppm in the  $^{13}\text{C}$  NMR spectrum. There were thirteen peaks in the aromatic region of the  $^1\text{H}$  NMR spectrum ranging from 8.24-7.17 ppm, along with eighteen signals in the aromatic region of the  $^{13}\text{C}$  NMR spectrum from 158.6 to 124.1 ppm.

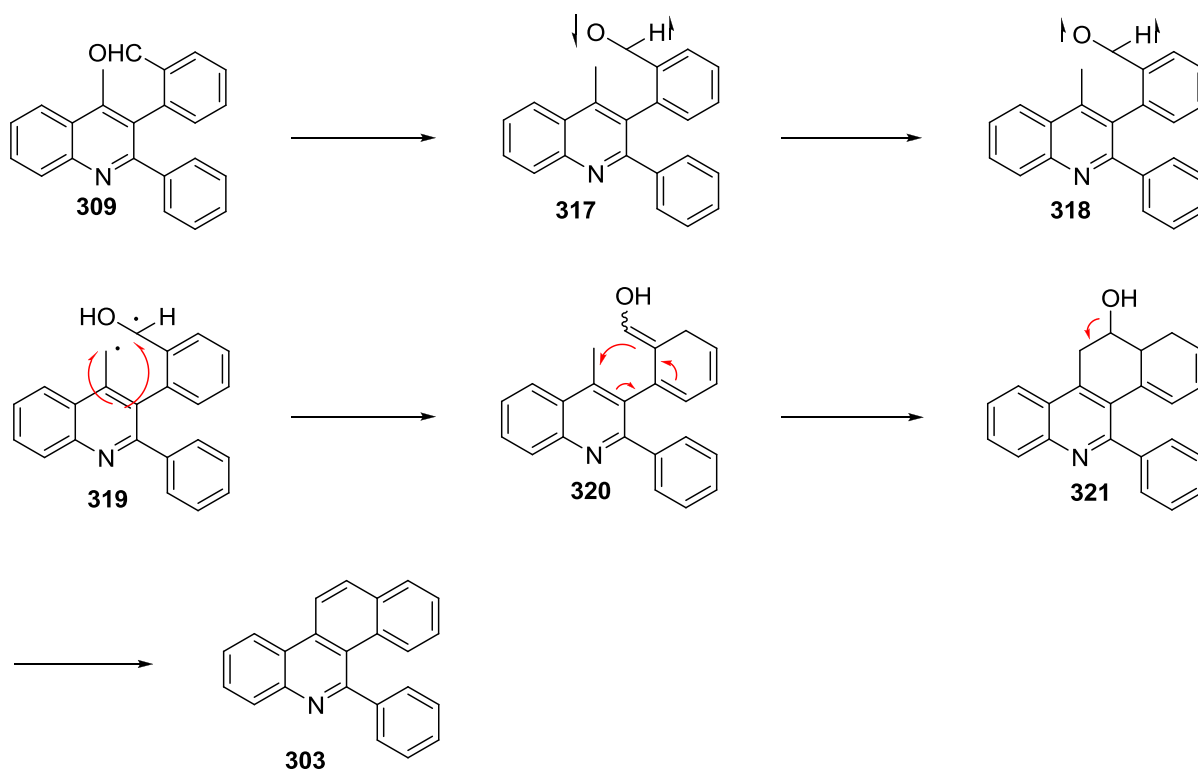
### 6.1.5 Synthesis of 5-Phenylbenzo[*l*]phenanthridine **303**



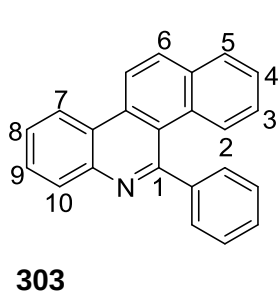
**Scheme 119:** Reagents and conditions: KOBut, dry DMF, 80 °C, Hg-lamp with quartz filter, 10 mins, 84%.

We were now in a position to test the novel ring cyclization on **309** to hopefully afford 5-phenylbenzo[*l*]phenanthridine **303**. To this end, 2-(4-methyl-2-phenylquinolin-3-yl)benzaldehyde **309** was dissolved in dry dimethylformamide and the resulting solution was degassed for ten minutes. Potassium *t*-butoxide was added to the reaction mixture, and the solution immediately turned dark black in colour. Then reaction mixture was allowed to stir for ten minutes at 80 °C and was continuously irradiated with a high pressure Hg-lamp through a quartz filter. On completion of the reaction as monitored by thin layer chromatography, the mixture was quenched, and pure product **303** was isolated after work-up and purification by column chromatography as a yellow solid in 84% yield. The product was re-crystallized from chloroform/hexane by slow evaporation.

The mechanism of this ring closure reaction has already been mentioned in **Chapter 5**, which suggests that the reaction proceeds by photoenolization by an initial Norrish type II process. Direct irradiation from a high pressure mercury lamp (400 W) leads to the excitation of the carbonyl group of **309** to an excited singlet state **317**, which, as a result of the inter-system crossing, immediately decays into the triplet state **318**. This triplet state intermediate **318** abstracts hydrogen to afford the diradical **319** which quickly rearranges to photoenol **320**. Then a  $6\pi$  electrocyclic process affords the alcohol **321** which, after dehydration, yields the desired heterocycle as illustrated in **Scheme 120**.<sup>146</sup>



Scheme 120



The spectroscopic data for both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra was found to be in accordance with literature.<sup>149</sup> There were signals integrating for fifteen protons in the aromatic region of the  $^1\text{H}$  NMR spectrum as expected. Finally, the single crystal X-ray structure confirmed that we had synthesized 5-phenylbenzo[7]phenanthridine

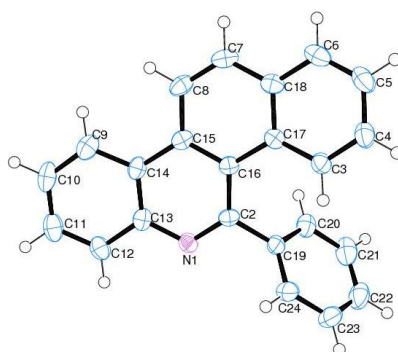
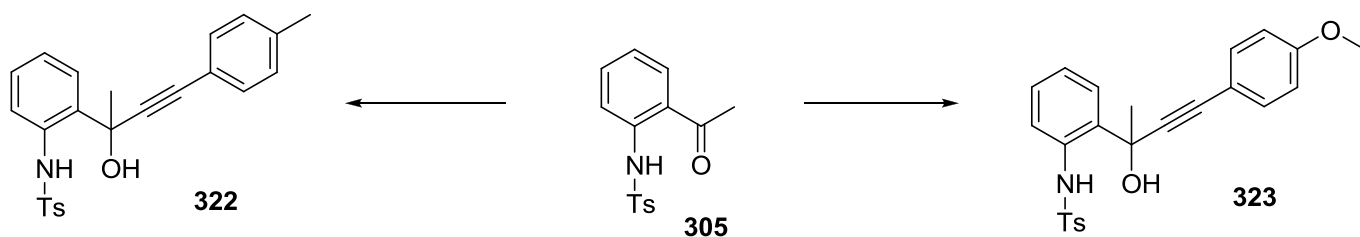
Single crystal X-ray structure of 5-phenylbenzo[7]phenanthridine **303**

Figure 45

## 6.2 Approaches Towards Synthesis of Related Substituted Benzo[*j*]phenanthridines

As a result of the success of this synthetic sequence we now wished to extend the synthesis to the use of other acetylenes. As shown in **Scheme 121**, two other acetylenes were tested.



**Scheme 121:** Reagents and conditions:  $\text{C}_2\text{H}_5\text{MgBr}$ , dry THF, 1-ethynyl-4-methylbenzene and 1-ethynyl-4-methoxybenzene, 0 °C-rt- reflux, 4 hrs.

We anticipated the synthesis of **322** and **323** to be the same as that of *N*-(2-(2-hydroxy-4-phenylbut-3-yn-2-yl)phenyl)-4-methylbenzenesulfonamide **307**, with the only difference being the use of different acetylenes in these cases. Instead of using phenylacetylene, as for the synthesis of **303**, we used 1-ethynyl-4-methylbenzene or 1-ethynyl-4-methoxybenzene. However, both of these reactions were unsuccessful, even after a number of trials using the same procedure as before. The problem appeared to be the generation of the anion at the terminal acetylene.

Therefore we decided to test other bases to abstract the proton from the terminal acetylene. We decided to use lithium diisopropylamide as base for the reaction and managed to obtain the products **322** and **323**, but in very low yields. Unfortunately, due to time constraints we were not able to continue with this work. We are however, confident that the yields for these reactions could be improved, and this will be considered for future work.

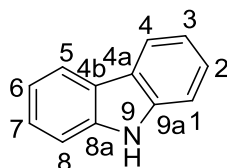
## 6.3 Conclusion

In summary, we were pleased with the results obtained for the synthesis of 5-phenylbenzo[*j*]phenanthridine **303**. Although we were unsuccessful in the synthesis of analogues of **295**, we are hopeful that variations in the procedure could lead to the synthesis of a library of benzo[*j*]phenanthridines **295** in the near future.

## Chapter 7: Introduction, Literature Reviews and Aims: Quinoline[2,3-a]carbazoles

### 7.1 Carbazoles

Carbazole **324** is an aromatic, heterocyclic organic compound with a tricyclic structure containing two six membered benzene rings fused on each side of a five membered nitrogen containing ring (**Figure 46**). Naturally occurring carbazoles form a small part of nitrogen containing compounds called the alkaloids.<sup>150</sup>



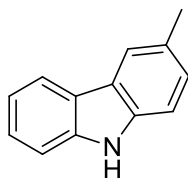
Carbazole **324**

**Figure 46**

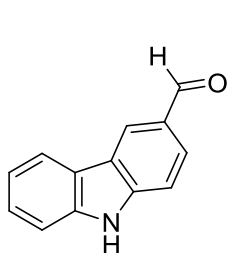
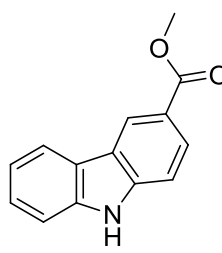
Carbazole **324** was isolated for the first time in 1872 from the anthracene fraction of coal tar by Graebe and Glazer in 1872.<sup>151</sup> A century later, Chowdhury *et al.* reported the isolation of carbazole for the first time from a plant source -*Glycosmis pentaphylla*.<sup>152,153</sup>

#### 7.1.1 Simple Functionalized Carbazoles: Isolation and Biological Importance

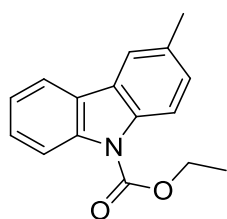
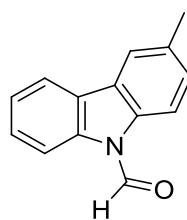
3-Methylcarbazole **325** was isolated independently by Roy *et al.*, Joshi *et al.* and Ngadjui *et al.* from the roots of a variety of *Clausena* species such as *Clausena heptaphylla*, *Arn Clausena indica* Oliv., and *Clausena anisata*.<sup>154,155,156</sup> Later in 1987, Chowdhury *et al.* described the isolation of 3-methylcarbazole **325** from the root bark of *Glycosmis pentaphylla*.<sup>157</sup> Almost a decade later, 3-methylcarbazole **325** was isolated by Chakrabarty *et al.* from the roots of *Murraya koenigii* and the following year Wu *et al.* isolated 3-methylcarbazole **325** from the root bark of *Murraya euchrestifolia*.<sup>158,159</sup>

3-Methylcarbazole **325****Figure 47**

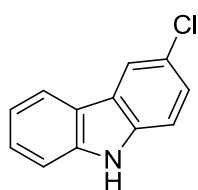
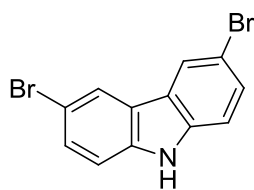
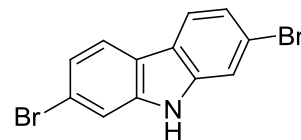
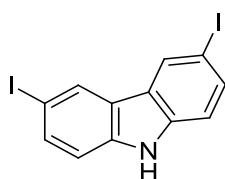
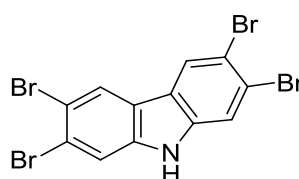
3-Formylcarbazole **326** was isolated for the first time in 1988 by Wu *et al.* from the root bark of *Murraya euchrestifolia* and three years later by Li *et al.*, along with the ester methyl carbazole-3-carboxylate **327**, from the roots of *Clausena lansium*.<sup>160,161</sup> Diverse parts of this plant are used in traditional medicine in China, Taiwan, and the Philippines for the treatment of a number of conditions including, bronchitis, malaria, asthma, gastrointestinal inflammation, ulcers, influenza, colds and colic pains.<sup>162</sup> 3-Formylcarbazole **326** was also isolated from *Glycosmis pentaphylla* in 1992 by Jash *et al.*<sup>163</sup> (**Figure 48**)

3-Formylcarbazole **326**Methyl carbazole-3-carboxylate **327****Figure 48**

9-Carbonyl-substituted carbazoles, 9-carbethoxy-3-methylcarbazole **328** and 9-formyl-3-methylcarbazole **329**, were isolated by Chakrabarty *et al.*, from the roots of *Murraya koenigii*.<sup>158</sup> These compounds show weak cytotoxicity against mouse melanoma B16 and adriamycin-resistant P388 mouse leukemia cell lines (**Figure 49**).<sup>158</sup>

9- Carbethoxy-3-methylcarbazole **328**9-Formyl-3-methylcarbazole **329****Figure 49**

The first time a carbazole alkaloid was isolated from a mammalian source was in 1983 by Luk *et al.*, when they isolated 3-chlorocarbazole **330** from female bovine urine.<sup>164</sup> Lee and co-workers reported the isolation of the dibromocarbazole alkaloids, 3,6-dibromocarbazole **331**, 2,7-dibromocarbazole **332** and 3,6-diiodocarbazole **333** from the cyanobacterium *Kyrtuthrix maculans* in 1999.<sup>165</sup> 2,7-Dibromocarbazole **332** is reported as neuroprotective compound P7C3. In 2005, Zhu *et al.* reported the isolation of 1,3,6,8-tetrabromocarbazole **334** from the sediment cores of lake Michigan (**Figure 50**).<sup>166</sup>

3-Chlorocarbazole **330**3,6-Dibromocarbazole **331**2,7-Dibromocarbazole **332**3,6-Diiodocarbazole **333**1,3,6,8-Tetrabromocarbazole **334****Figure 50**

Extracts of the leaves and bark of shrubs of the genus *Murraya* (family Rutaceae), flourishing in Southern Asia, are used as traditional medicine for the treatment of eczema, rheumatism, and dropsy. This class represents the chief source for 1-oxygenated carbazole alkaloids. The earliest reports of the isolation of oxygenated carbazoles were in 1969 and

1971, when mukoeic acid **335** and the corresponding methyl ester, mukonine **336** were isolated from the stem bark of *Murraya koenigii* (**Figure 51**).<sup>167</sup> In 1983, Wu *et al.* and Furukawa *et al.* reported the isolation of murrayafoline-A **337** from the root bark of *Murraya euchrestifolia* while Cuong *et al.* isolated the same alkaloid **337** from *Glycosmis stenocarpa* *Guillaumin* in 2004.<sup>168,169,170</sup> Koenoline **338**, a carbazole alkaloid known for its cytotoxic properties was isolated from *Murraya koenigii* and *Clausena heptaphylla* both of the Rutaceae family.<sup>171</sup> Cuong *et al.* isolated murrayanine **339**, which is known for its antimicrobial activity against human pathogenic fungi, from another genus of the Rutaceae family, *Glycosmis stenocarpa* *Guillaumin*.<sup>170</sup>

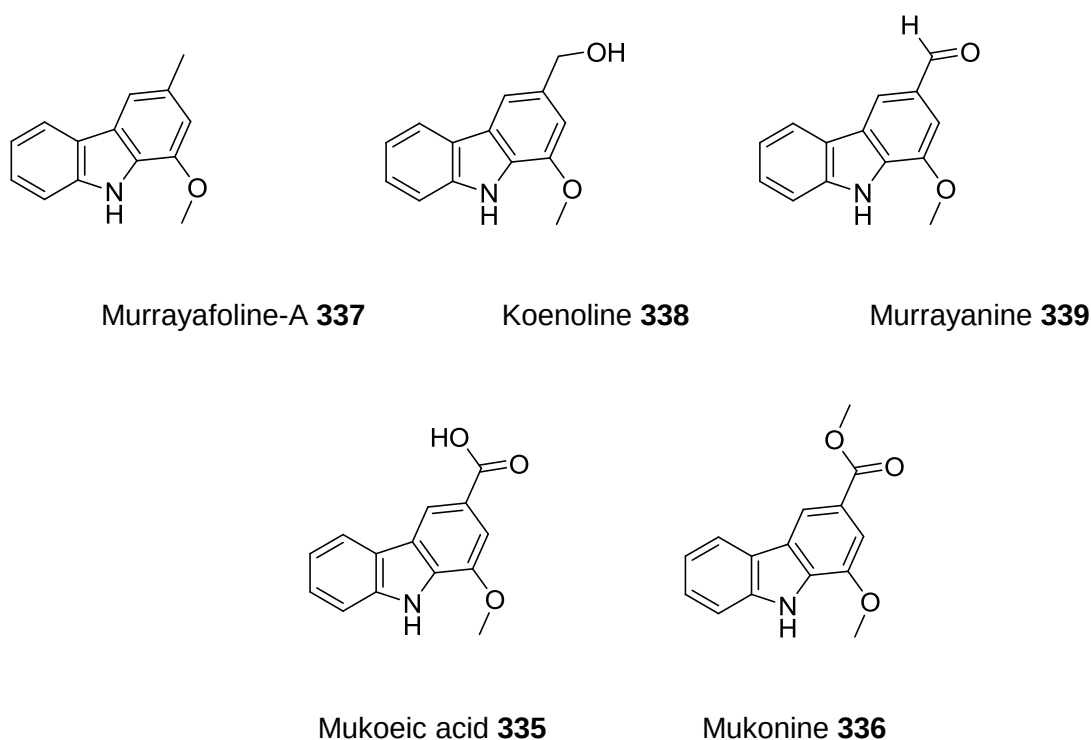
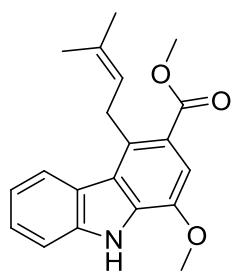
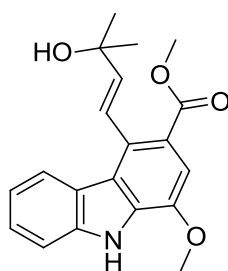
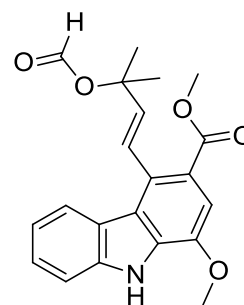
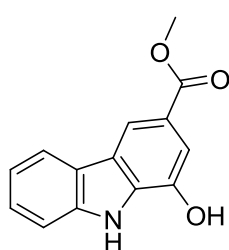
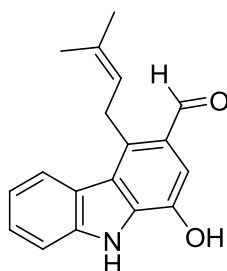
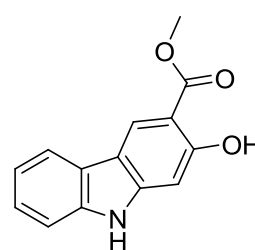


**Figure 51**

Ito *et al.* in 2000, isolated peroxygenated carbazole alkaloids: clausamine D **340**, clausamine E **341** and clausamine G **342** from the branches of *Clausena anisata*. These alkaloids displayed anti-tumour activity (**Figure 52**).<sup>172</sup>

Clausamine D **340**Clausamine E **341**Clausamine G **342****Figure 52**

From the plant *Clausena excavata*, clauzoline-I **343** was isolated by Ito *et al.* and clausine D **344** and mukonidine **345** were isolated by Wu *et al.*<sup>173,174</sup> These alkaloids are known for their platelet aggregation inhibition property (**Figure 53**).

Clauzoline-I **343**Clausine D **344**Mukonidine **345****Figure 53**

The first carbazole-1,4-quinone alkaloid identified, murrayaquinone B **346**, was isolated from the root bark of *Murraya euchrestifolia*.<sup>168,169</sup> This was followed by the reported isolation of murrayaquinone A **347**, which was seen to exhibit significant cytotoxicity against SK-MEL-5 and Colo-205 cells, along with cardiotonic activity. Murrayaquinone B **346** was shown to inhibit the leukemia cell line CCRF-CEM. Clausenaquinone A **348**, isolated from *Clausena excavata* exhibited powerful inhibitory activity towards rabbit platelet aggregation induced by arachidonic acid, along with cytotoxicity toward HCT-8, RPMI-7951, and TE671 tumour cells (**Figure 54**).<sup>175</sup>



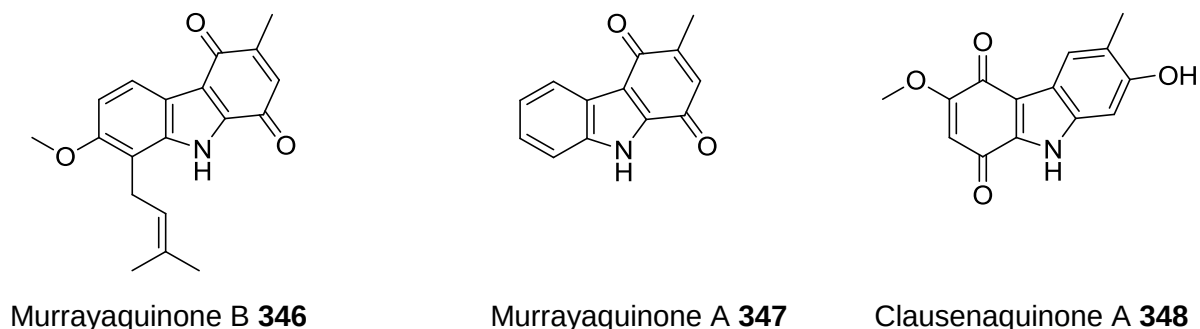


Figure 54

### 7.1.2 Fused Carbazoles: Isolation and Biological Importance

Frequently, naturally occurring alkaloids are observed where the carbazole ring **324** is fused with other aromatic, heteroaromatic or heterocyclic rings, with girinimbine **349** being the first pyranocarbazole alkaloid isolated from *Murraya koenigii* and *Clausena hepataphylla*.<sup>153,176</sup> Murrayanine **350** was isolated in 2003 by Hao *et al.* from *Murraya koenigii* which in addition to a pyran ring fused to the carbazole nucleus, also contains an annulated furan ring.<sup>177</sup> (Figure 55).

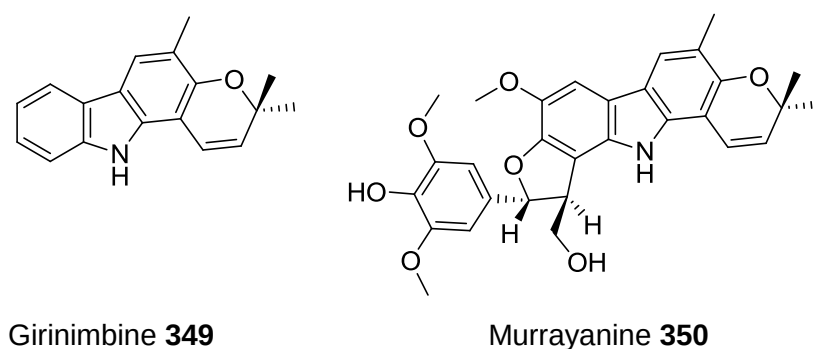
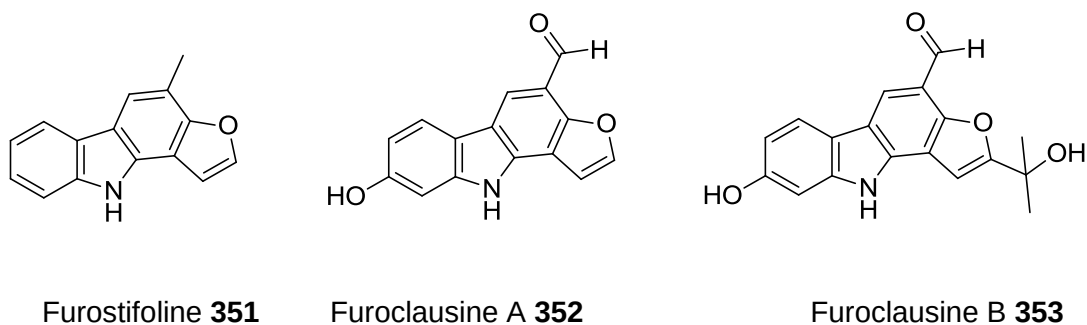
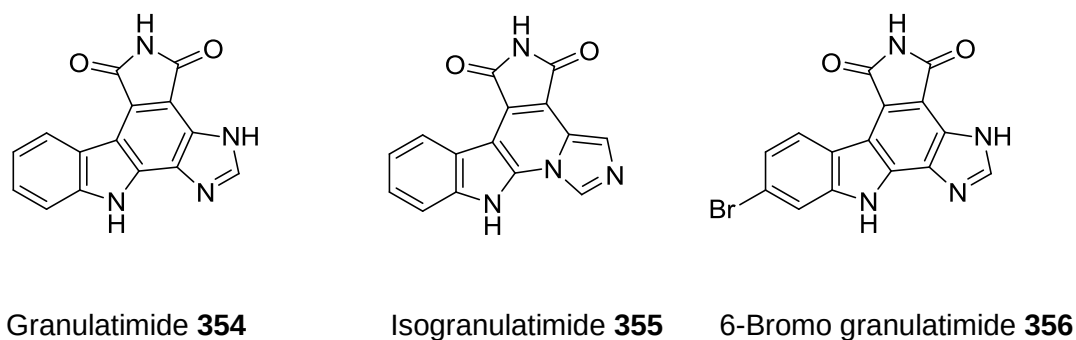


Figure 55

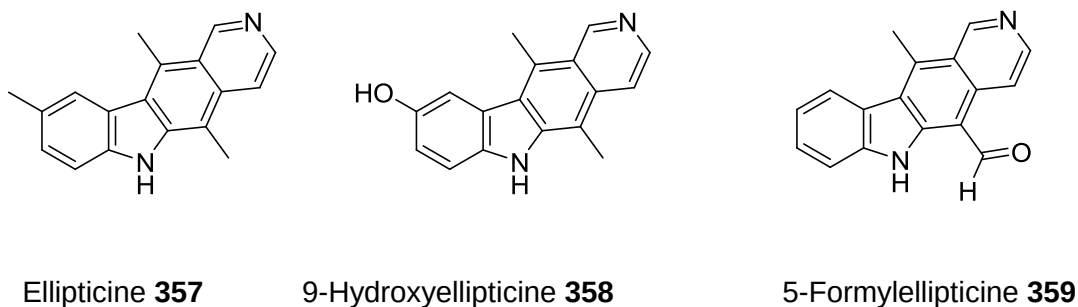
Furostifoline **351** was the first furo[3,2-*a*]carbazole alkaloid collected from the root bark of *Murraya euchrestifolia* Hayata by Ito *et al.* Various parts of this plant are used in Chinese folk medicine.<sup>178</sup> Later, Wu *et al.* described the isolation of two other furocarbazole alkaloids, furoclausine-A **352** and furoclausine-B **353** from *Clausena excavata*.<sup>159</sup>

**Figure 56**

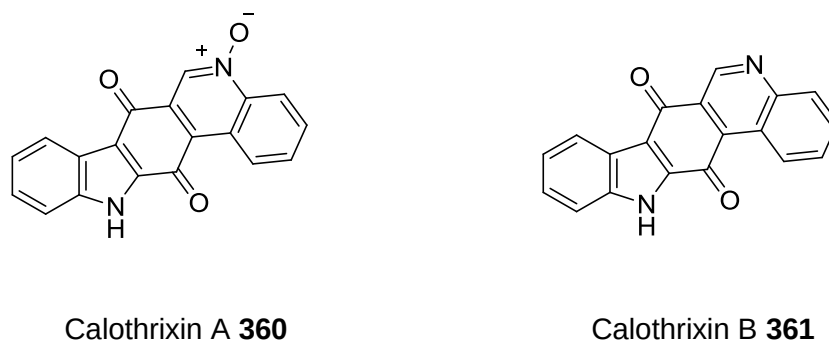
An interesting class of imidazo-pyrrolocarbazoles has been found in extracts isolated from various natural sources and include the compounds granulaticide **354**, isogranulaticide **355** and 6-bromo granulaticide **356** (**Figure 57**). These molecules represent a new class of inhibitors of the cell division cycle.<sup>179,180</sup>

**Figure 57**

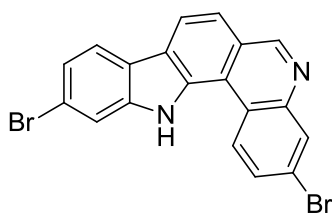
Pyridocarbazole containing alkaloids have attracted widespread interest since the first isolation of ellipticine **357** and its analogues, 10-hydroxyellipticine **358** and 5-formylellipticine **359** from various natural sources (**Figure 58**). These molecules have been shown to exhibit potent antineoplastic activity in a number of human tumour systems, by DNA intercalation and/or inhibition of topoisomerase.<sup>181,182,183</sup>

**Figure 58**

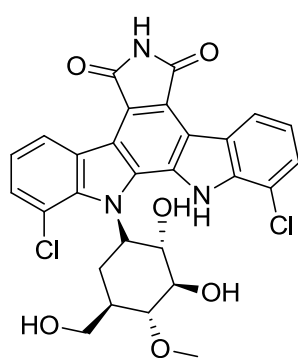
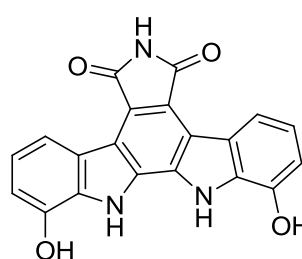
Two quinolino[4,3-*b*]carbazole-1,4-quinones, calothrixin A **360** and B **361** were isolated from the blue green algae *Calothrix* cyanobacteria. These quinoline fused carbazoles have been shown to prevent the growth of a chloroquine resistant strain of the malaria parasite *Plasmodium falciparum* and human HeLa cancer cells.<sup>184</sup> Later it was reported that calothrixin A **360** is redox-active and induces the intracellular formation of reactive oxygen species. Hecht and co-workers reported calothrixin A **360** and B **361** and their *O*- and *N*-methylated derivatives which act as human DNA topoisomerase I poisons, capable of stabilizing the enzyme–DNA covalent binary complex and leading to topoisomerase I-dependent cell death (**Figure 59**).<sup>185,186</sup>

**Figure 59**

In 2012 Lyakhova reported the isolation of a bromoindolophenanthridine **362** from marine sponge *Penaras* sp. in the South China Sea. The biological importance of the molecule is yet to be explored **Figure 60**.<sup>187</sup>

**362****Figure 60**

Indolocarbazoles are another well-studied class of biologically active carbazole alkaloids that contain a fused indole moiety. Representatives from this class of carbazole alkaloids are known to possess a wide range of biological activities such as anti-tumour, antifungal, hypotensive, antimicrobial, protein kinase C (PKC) inhibition and antiplatelet aggregation activity. Presently, several indolo[2,3-*a*]-carbazole alkaloids are in clinical trials for their potential use in cancer therapy.<sup>188</sup> These naturally occurring indolo-pyrrolocarbazole have been isolated from a wide diversity of natural sources. Rebeccamycin **363** and related compounds are known to bind to DNA and exhibit antitumour properties.<sup>177</sup> Kojiri *et al.* reported the isolation of BE-13793C **364**, from the culture broth of *Streptoverticillium mobaraense* strain BA13793. This indolo-pyrrolocarbazole showed significant inhibitory activity against topoisomerases I and II and inhibited the growth of doxorubicin or vincristine-resistant P388 murine leukemia cell lines (**Figure 61**).<sup>177,189</sup>

Rebeccamycin **363**BE-13793C **364****Figure 61**

The first indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloid to be isolated was staurosporine **365**, which was isolated in 1977 from a culture of *Streptomyces* strain by Omura *et al.* Since then, a number of analogues of the same skeleton have been isolated and are known for their

interesting bioactive properties.<sup>177,190</sup> Staurosporine **365** exhibits promising biological activities including antimicrobial, antihypertensive and cytotoxic properties, nanomolar inhibition of protein serine/threonine kinases (such as PKC and protein tyrosine kinase), and inhibition of platelet aggregation.<sup>191</sup> 11-Hydroxystaurosporine **366** and 3,11-dihydroxystaurosporine **367** are active against human nasopharyngeal cancer cells and 11-hydroxystaurosporine **366** is more potent than staurosporine **365** in protein kinase C (PKC) inhibition. Staurosporinone **368** has shown cytotoxicity against HeLa, jurkat, and vincristineresistant KB/VJ300 cells, along with the inhibition of protein tyrosine kinase, whereas 6-hydroxystaurosporinone **369** has demonstrated protein tyrosine kinase inhibition (**Figure 62**).<sup>192</sup>

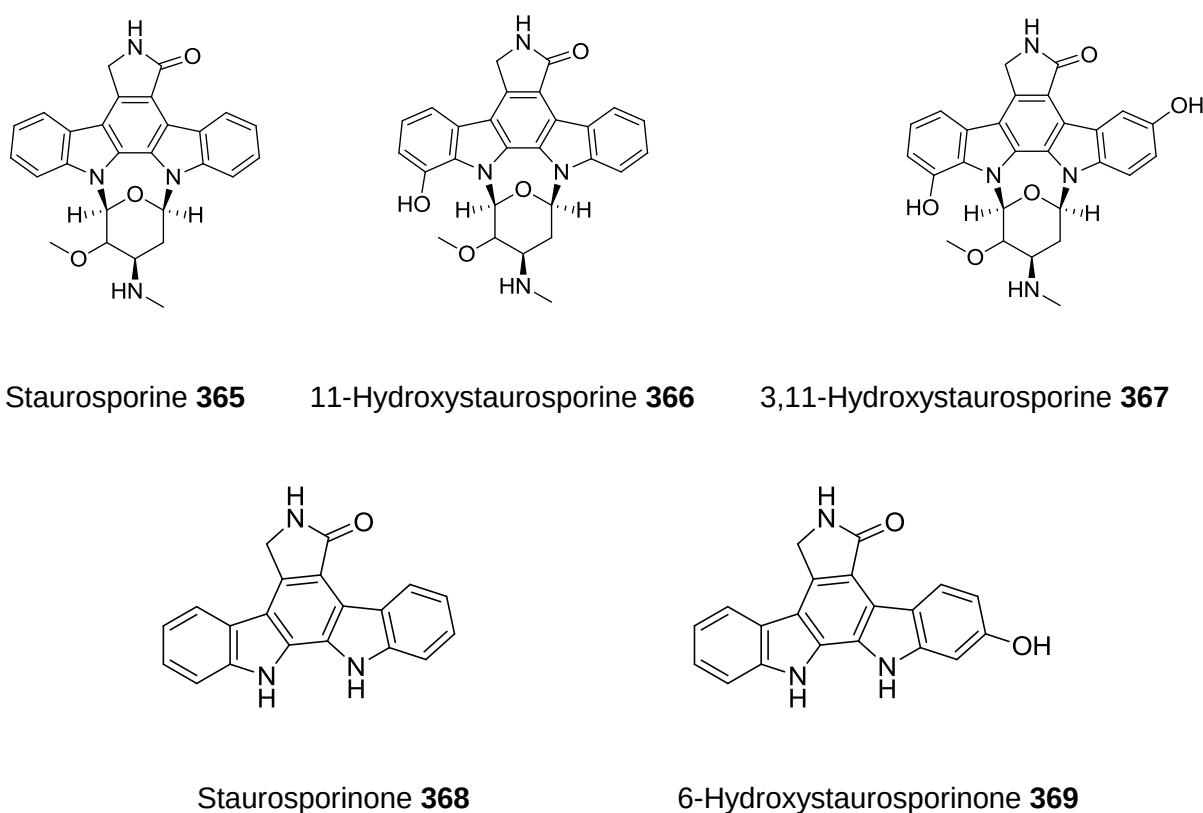


**Figure 62**

## 7.2 Quinoline Fused Carbazoles: Synthetic Approaches

As discussed earlier in this **Chapter**, the carbazole **234** skeleton is widely present in nature either alone or fused with other heterocycles. One such class of fused heterocycles is the carbazole fused quinolones, in which we are specifically interested. To date, only three molecules of this class are known in the nature, calothrixin A **360** and B **361**, quinolino[4,3-

*b*]carbazole-1,4-quinones.<sup>184,185,186</sup> and the non-quinone containing dibromo-quinolino[4,3-*a*]carbazole **362**, isolated recently from a marine sponge source (**Figures 59 and 60**).

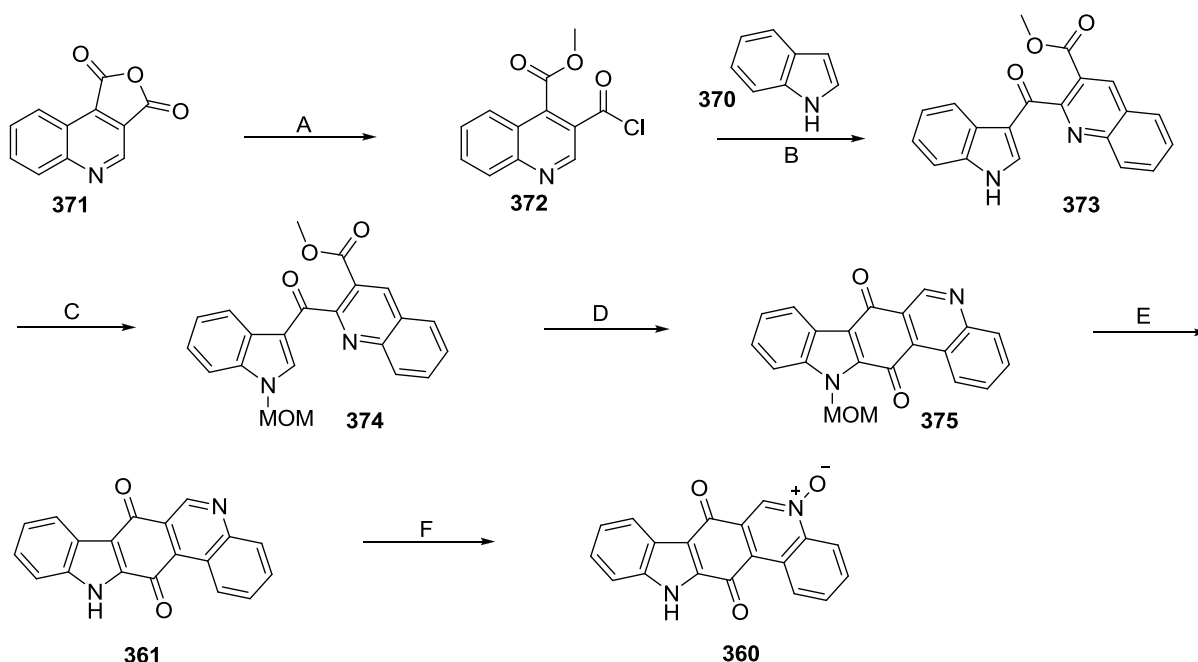
There are a number of reported synthetic approaches directed to calothrixin A **360** and calothrixin B **361**, but no synthesis has been reported for the recently isolated dibromo-quinolino[4,3-*a*]carbazole **362** framework as yet.

## 7.2.1 Approaches Towards the Synthesis of Quinolino[4,3-*b*]carbazole-1,4-quinones

### 7.2.1.1 Bernardo's Approach Towards the Synthesis of Calothrixin A **360** and B

**361**<sup>193,194</sup>

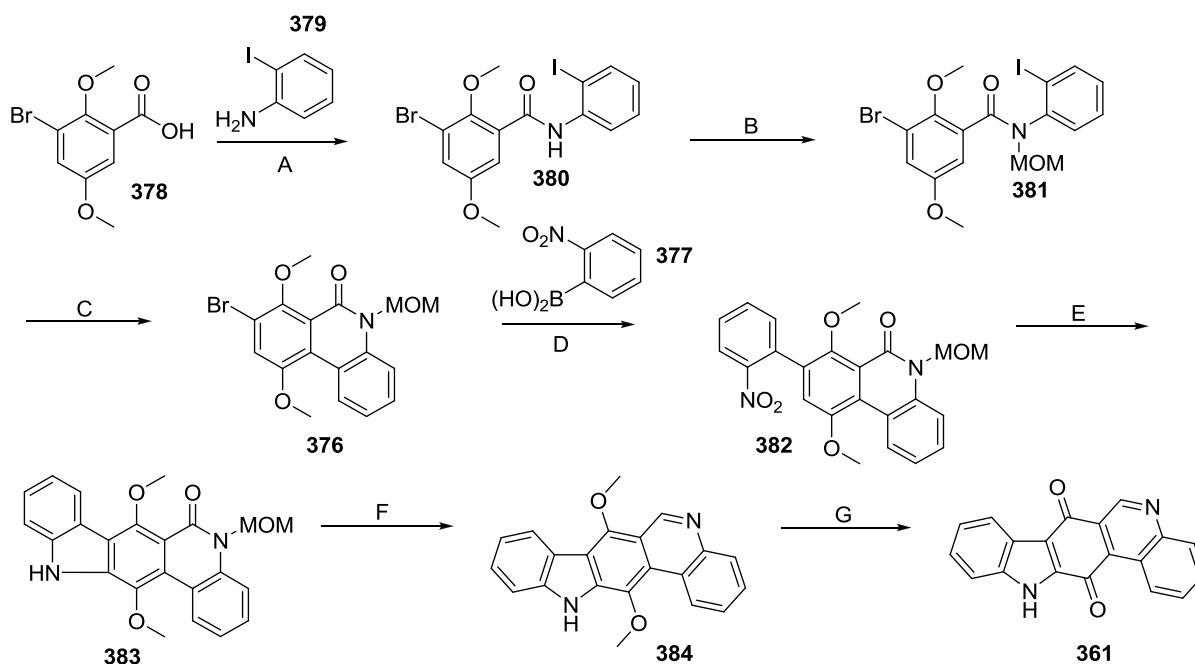
In 2002, Bernardo *et al.* reported a simple and brief synthetic route to calothrixin B **361** starting from readily available indole **370** and quinoline-3,4-dicarboxylic anhydride **371**. The quinoline-3,4-dicarboxylic anhydride **371** was converted into the acid chloride **372** which was then used in the Friedel Crafts acylation reaction with indole **370** to give **373**. The free nitrogen of **373** was protected to yield **374**, followed by lithation and intramolecular nucleophilic substitution of the ester leading to the generation of *N*-MOM-calothrixin B **375**. Cleavage of the protecting group was done finally to afford calothrixin B **361** in five steps starting from **371**. Transformation of calothrixin B **361** to calothrixin A **360** was achieved by using *m*-perchlorobenzoic acid as oxidant and refluxing the reaction in dichloromethane as shown in **Scheme 122**.



**Scheme 122:** Reagents and conditions: A) 1) Methanol, reflux; 2)  $\text{SOCl}_2$  (neat), 70%; B)  $\text{ZnCl}_2$ ,  $\text{CH}_3\text{MgBr}$ , 90%; C)  $\text{NaH}$ ,  $\text{MOMCl}$ , THF,  $0^\circ\text{C}$ , 90%; D)  $\text{LiHMDS}$ ,  $\text{TMEDA}$ , THF,  $-78^\circ\text{C}$ , 92%; E)  $\text{HCl}$ ,  $\text{DMSO}$ ,  $100^\circ\text{C}$ , 83%; F)  $m\text{CPBA}$ ,  $\text{DCM}$ , reflux, 70%.<sup>193,194</sup>

#### 7.2.1.2 Bernardo's Palladium Catalyzed Approach Towards the Synthesis of Calothrixin B **361**<sup>195</sup>

Bernardo *et al.* again in 2007 reported an efficient palladium-catalyzed route for the synthesis of calothrixin B **361**, using the phenanthridinone **376** and 2-nitrophenylboronic acid **377** as the precursors of Suzuki-Miyaura cross coupling reaction (**Scheme 123**). The synthesis was started with the transformation of 3-bromo-2,5-dimethoxybenzoic acid **378** into an acid chloride, which was then coupled with 2-iodoaniline **379** leading to the generation of the amide **380**. The free secondary nitrogen of the amide **380** was then protected to yield **381** and this was followed by a palladium-catalyzed Heck cyclization reaction generating the phenanthridinone **376**. Another palladium catalyzed reaction, a Suzuki-Miyaura coupling of the bromophenanthridinone **376** with 2-nitrophenylboronic acid **377** was carried out to synthesize *o*-nitrophenylphenanthridinone **382**. Cadogan cyclization of *o*-nitrophenylphenanthridinone **382** provided the indolophenanthridinone **383**. Later, the reduction of the amide group followed by an acidic work-up afforded the dimethoxyindolophenanthridine **384**. Finally, oxidative demethylation and quenching of the reaction with anhydrous methanol in the presence of air led to the synthesis of calothrixin B **361**.

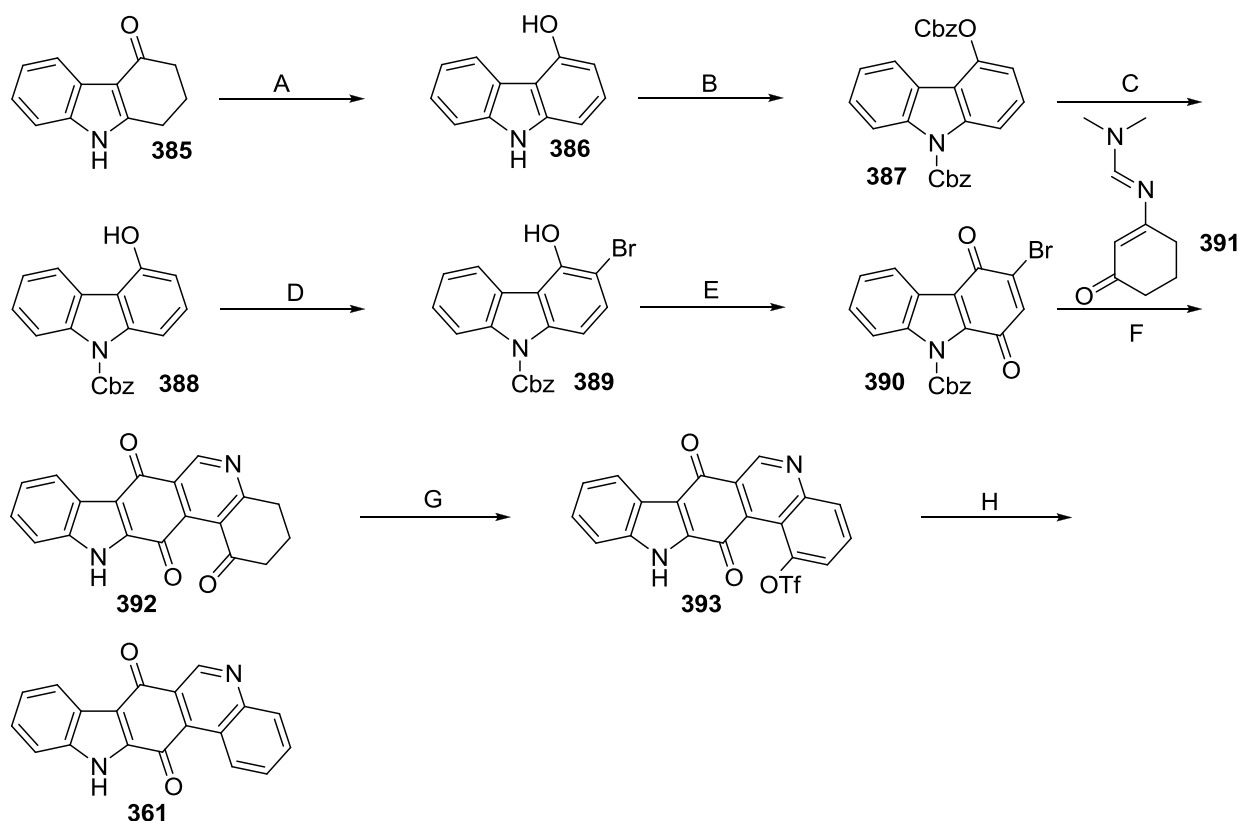


**Scheme 123:** Reagents and conditions: A) 1)  $\text{SOCl}_2$ , reflux; 2) 2-Iodoaniline,  $\text{K}_2\text{CO}_3$ , THF, rt, 91%; B) NaH, MOMCl, THF, 30 °C, 98%; C) Cat.  $\text{Pd}(\text{OAc})_2$ , cat.  $\text{PPh}_3$ ,  $\text{K}_2\text{CO}_3$ , DMF, 100 °C, 92%; D) Cat.  $\text{Pd}(\text{OAc})_2$ , cat.  $\text{PPh}_3$ ,  $\text{K}_2\text{CO}_3$ , DMF, 150 °C; E)  $\text{P}(\text{OEt})_3$ , 174 °C, 89%; F) 1)  $\text{LiAlH}_4$ , THF, rt; 2) 6 N HCl, rt; G) 1)  $\text{BBr}_3$ , DCM, rt; 2) Air, methanol, rt, 97%.<sup>195</sup>

### 7.2.1.3 Sissouma's Approach Towards the Synthesis of Calothrixin B 361.<sup>196,197</sup>

Sissouma *et al.* have also described a new synthetic route for the assembly of calothrixin B **361** as shown in Scheme 124. The dehydrogenation of tetrahydro-4*H*-carbazol-4-one **385** using palladium on activated carbon gave 4-hydroxy-9*H*-carbazole **386**, which, after *bis*-protection with a carboxybenzyl protecting group, led to **387**. Chemoselective monodeprotection of **387** using aqueous sodium hydroxide gave the *N*-Cbz-protected 4-hydroxy-9*H*-carbazole **388**, which was brominated to afford the 3-bromocarbazole derivative **389**. Oxidation of **389** with diacetoxyiodobenzene provided the quinone dienophile **390**, which was used in the Diels Alder cycloaddition with 2-azadiene **391** affording the cycloadduct **391**, along with *in situ* removal of the Cbz group. Deprotonation of cycloadduct **392** followed by treatment with *N*-phenyl-bis-(trifluoromethanesulfonimide) afforded aryl triflate **393**. Finally, a palladium(0)-catalyzed defunctionalization led to the generation of calothrixin B **361**.<sup>196,197</sup>



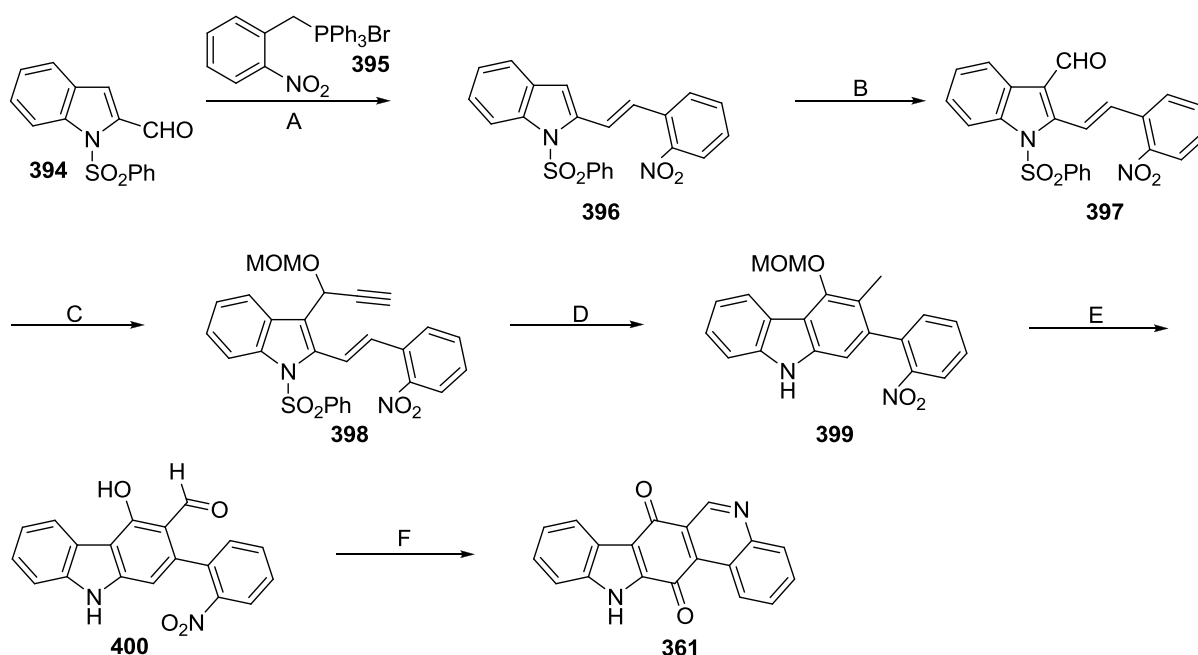


**Scheme 124:** Reagents and conditions: A) 10% Pd/C, Ph<sub>2</sub>O, 1,2,3-trimethylbenzene, 250 °C, 90%; B) NaH, CbzCl, DMF, 0 °C-rt, 91%; C) NaOH, dioxane/H<sub>2</sub>O, 40 °C, 90%; D) NBS, MeCN, rt, 94%; E) PhI(OAc)<sub>2</sub>, methanol, TFA, rt, 83%; F) MeCN, 40 °C, 80%; G) 1) LiHMDS, THF, HMPA, -78 °C; 2) PHNTf<sub>2</sub>, THF, -78 °C; H) Pd(PPh<sub>3</sub>)<sub>4</sub>, Et<sub>3</sub>N, HCOOH/dioxane, reflux, 75%.<sup>196,197</sup>

#### 7.2.1.4 Tohyama's Approach Towards the Synthesis of Calothrixin B 361<sup>198</sup>

In 2005, Tohyama *et al.* reported a new synthesis of calothrixin B **361** with an allene-mediated electrocyclic reaction of a 6 $\pi$ -electron system as shown in **Scheme 125**. Wittig olefination of 2-formyl-*N*-benzenesulfonylindole **394** with (2-nitrobenzyl)triphenylphosphonium bromide **395** gave the trans-styrylindole **395** which on reaction with 1,1-dichloromethyl methyl ether and aluminium chloride afforded **397**. The next step was the Grignard reaction of **397** with ethynylmagnesium bromide leading to the generation of corresponding propargyl alcohol, which was then protected as the methoxymethyl ether **398**. This intermediate was then subjected to an allene-mediated electrocyclic reaction with potassium *t*-butoxide to afford the desired 4-oxygenated carbazole **399**. Oxidation of this product with DDQ followed by the removal of the protecting group generated the 3-formyl-4-hydroxy-carbazole **400**. Finally, reduction of the nitro group of **400**

followed by intramolecular condensation and then oxidation to a quinone provided calothrixin B **361**.<sup>198</sup>

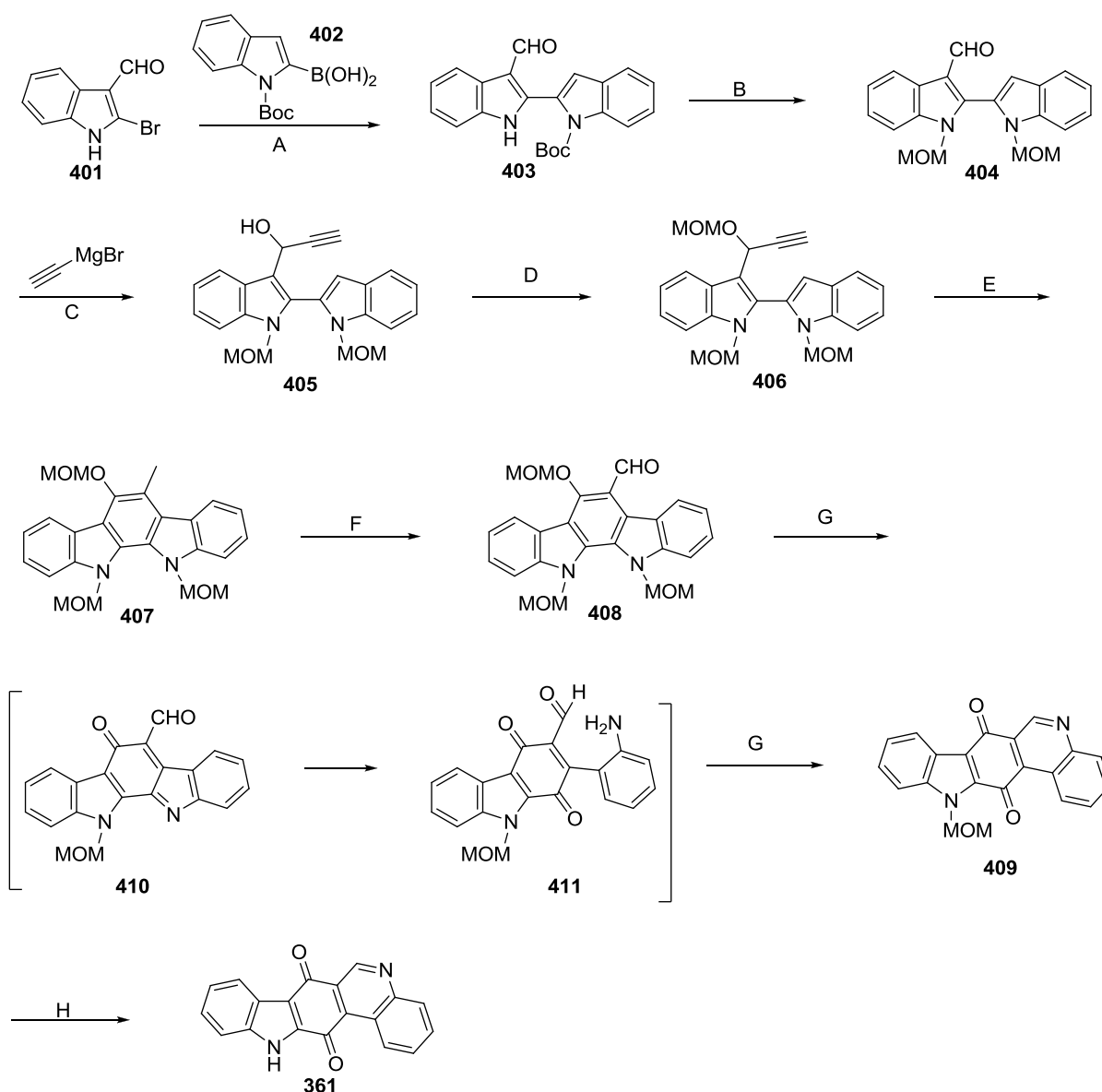


**Scheme 125:** Reagents and conditions: A) *n*BuLi, THF, 0 °C, 96%; B) MeOCHCl<sub>2</sub>, AlCl<sub>3</sub>, DCM, -78 °C, 96%; C) 1) THF, 0 °C; 2) MOMCl, *i*-Pr<sub>2</sub>NEt, DCM, 86%; D) KOBut, HOBut/THF, 90 °C, 29%; E) 1) DDQ, LiClO<sub>4</sub>, DCM/H<sub>2</sub>O, rt; 2) 6 N HCl, ethylene glycol, THF, 60 °C, 70%; F) 1) H<sub>2</sub>, Pd/C, HOEt, rt; 2) CAN, MeCN/H<sub>2</sub>O, 0 °C, 67%.<sup>198</sup>

#### 7.2.1.5 Yamabuki's Approach for Synthesis of Calothrixin B **361**<sup>199</sup>

Later in 2006, Yamabuki *et al.* described a biomimetic approach towards the synthesis of calothrixin B **361** with the key step involving an electrocyclic reaction (**Scheme 126**). The synthesis started with a Suzuki–Miyaura coupling of **401** with indol-2-ylboronic acid **402** generating 2,2-bisindole derivative **403**. Cleavage of the *N*-Boc protecting group followed by the protection of both nitrogen atoms with methoxymethyl chloride led to the di-protected bisindole **404**. This was followed by a Grignard reaction of **404** with ethynylmagnesium bromide, which yielded the corresponding propargyl alcohol **405**, which was then protected as the methoxymethylether **406**. An allene-mediated electrocyclic reaction of **406** provided the desired indolocarbazole **407**. Subsequent oxidation of the 6-methylindolocarbazole **407** afforded 6-formylindolocarbazole **408** which was subjected to another oxidation reaction mediated by DDQ. This resulted in the formation of *N*-protected-calothrixin B **409**, via

quinone imine **410** and quinone **411** as intermediates. Final deprotection of the methoxymethyl protecting group gave calothrixin B **361**.

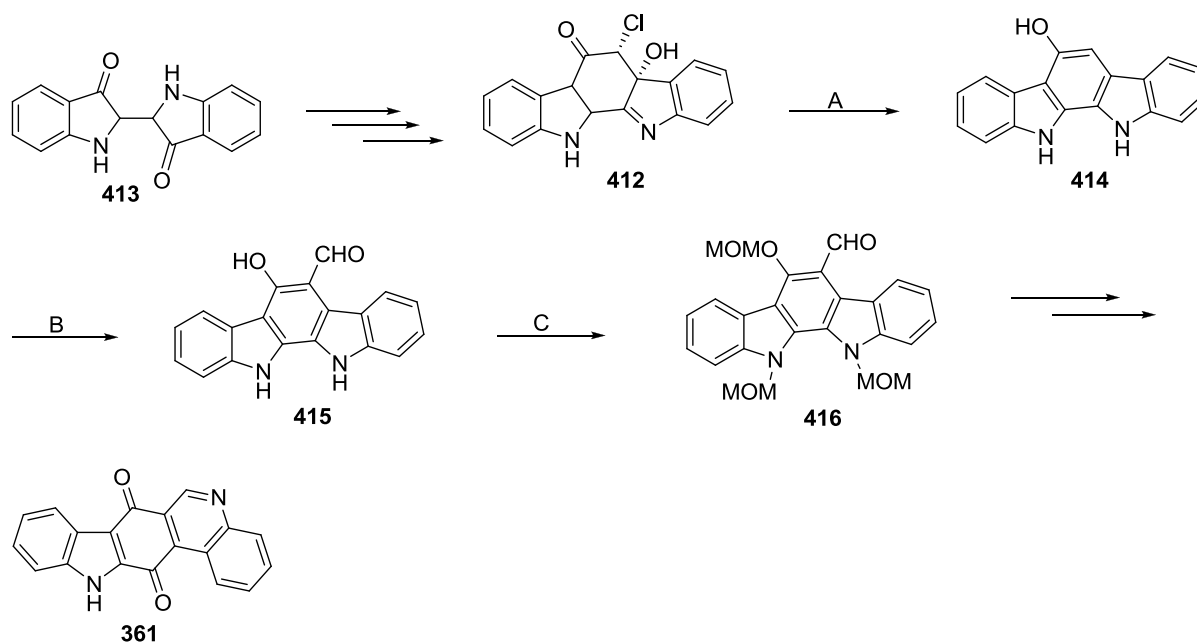


**Scheme 126:** Reagents and conditions: A)  $\text{PdCl}_3$ , 2 M  $\text{Na}_2\text{CO}_3$ , toluene, 80 °C, 99%; B) 1) TFA, 0 °C; 2) NaH, MOMCl, DMF, rt, 83%; C) THF, 0 °C, 93%; D) MOMCl,  $i\text{-Pr}_2\text{NEt}$ , DCM, 50 °C, 93%; E) KOBut, HOBut, THF, 90 °C, 93%; F) DDQ, DMF, rt, 74%; G) CAN, methanol/ $\text{H}_2\text{O}$ , 0 °C, 40%; H) HCl, THF, 50-55 °C, 48 hrs, 65%.<sup>199</sup>

#### 7.2.1.6 Sperry's Approach for the Synthesis of Calothrixin B **361**<sup>200, 201</sup>

Sperry *et al.* reported their synthesis of calothrixin B **361** in 2007. In their synthetic scheme, cis-chlorohydrin **412** was obtained from Indigo **413** using a literature procedure.<sup>202</sup> Reduction

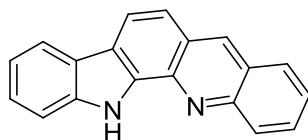
of the cis-chlorohydrin **412** led to the synthesis of 5-hydroxyindolo[2,3-*a*]carbazole **414**, which, on subsequent Vilsmeier formylation provided 5-hydroxyindolo-[2,3-*a*]carbazole-6-carboxaldehyde **415**. Protection of the free NH and OH groups using excess of methoxymethylchloride, gave the highly protected product **416**. This product could be converted over two steps using the method provided by Hibino *et al.* in to calothrixin B **361** (Scheme 127).<sup>200, 201</sup>



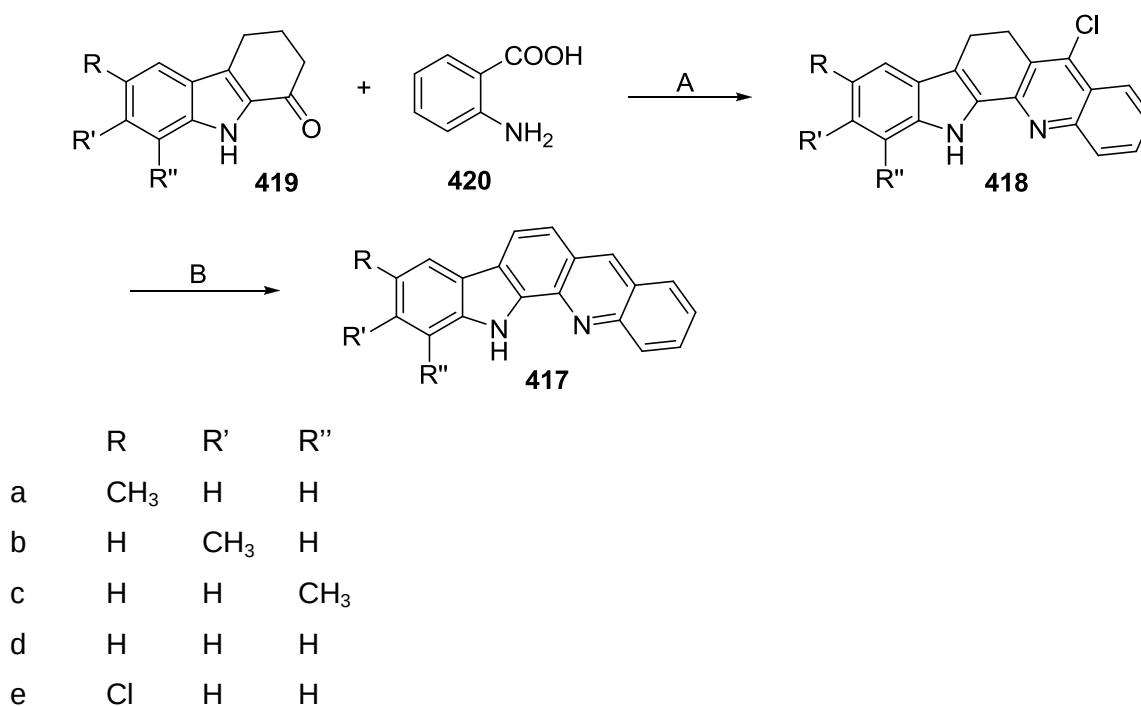
**Scheme 127:** Reagents and conditions: A) Zn, NH<sub>4</sub>Cl, THF/Methanol, rt, 55%; B) POCl<sub>3</sub>, DMF, 0 °C, 82%; C) NaH, MOMCl, DMF, 44%.

### 7.3 Synthesis of Quinolino[2,3-*a*]carbazoles **417**

There are a number of reported approaches to the synthesis of the quinolino[4,3-*b*]carbazole **417** framework which have been directed towards the synthesis of calothrixin A **360** and B **361** as discussed in the preceding section. The quinolino[2,3-*a*]carbazole **417** skeleton or it could also be referred to as indolo[3,2-*c*]acridines **417** is another arrangement of a carbazole fused to a quinoline, and to the best of our knowledge, only a few procedures have been reported for the synthesis of these ring-fused systems.<sup>203</sup>

Quinolino[2,3-a]carbazoles **417****Figure 63**

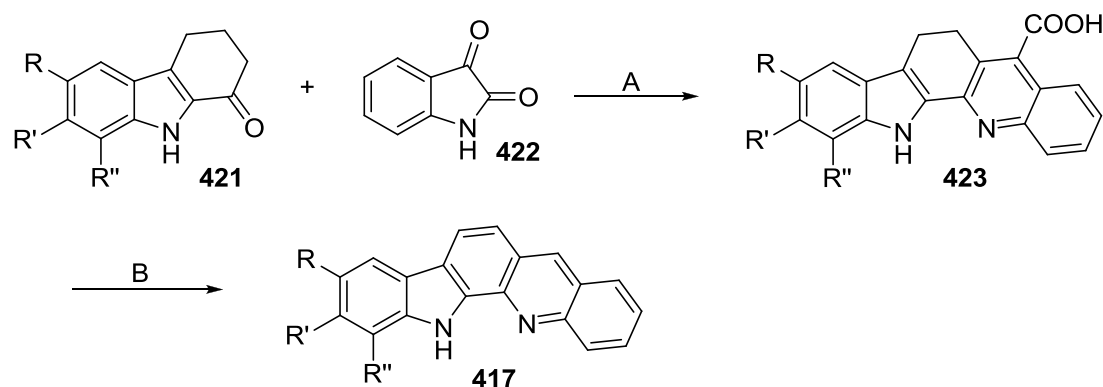
Prabakarana *et al.* reported the synthesis of quinolino[2,3-a]carbazoles (13*H*-indolo[3,2-*c*]acridines) **417** in 2010. The synthesis began with generation of 7-chloro-5,6-dihydro-13*H*-indolo[3,2-*c*]acridine **418**, by reacting 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones **419** with anthranilic acid **420** in the presence of phosphorus oxychloride at 130-140 °C for sixteen hours. This was followed by treatment of **418** with Pd/C in diphenyl ether under reflux to obtain the quinolino[2,3-a]carbazoles (13*H*-indolo[3,2-*c*]acridines) **417** (**Scheme 127**).



**Scheme 127:** Reagents and conditions: A) POCl<sub>3</sub>, 130-140 °C, 16 hrs; B) Pd/C, diphenyl ether.

An alternative method was also outlined in the same report directed towards the synthesis of quinolino[2,3-a]carbazoles **417**, where 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones **421** and isatin **422** were reacted under Pfitzinger conditions to obtain 5,6-dihydro-13*H*-indolo[3,2-*c*]acridine-

7-carboxylic acids **423**.<sup>203</sup> The carboxylic acids **423** were dehydrogenated and decarboxylated to afford the quinolino[2,3-*a*]carbazoles **417** (Scheme 128).

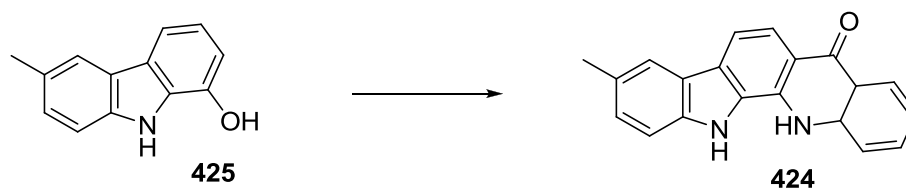


|   | R               | R'              | R''             |
|---|-----------------|-----------------|-----------------|
| a | CH <sub>3</sub> | H               | H               |
| b | H               | CH <sub>3</sub> | H               |
| c | H               | H               | CH <sub>3</sub> |
| d | H               | H               | H               |
| e | Cl              | H               | H               |

**Scheme 128:** Reagents and conditions: A) NaOH/KOH, ethanol-H<sub>2</sub>O; B) Pd/C, diphenyl ether.

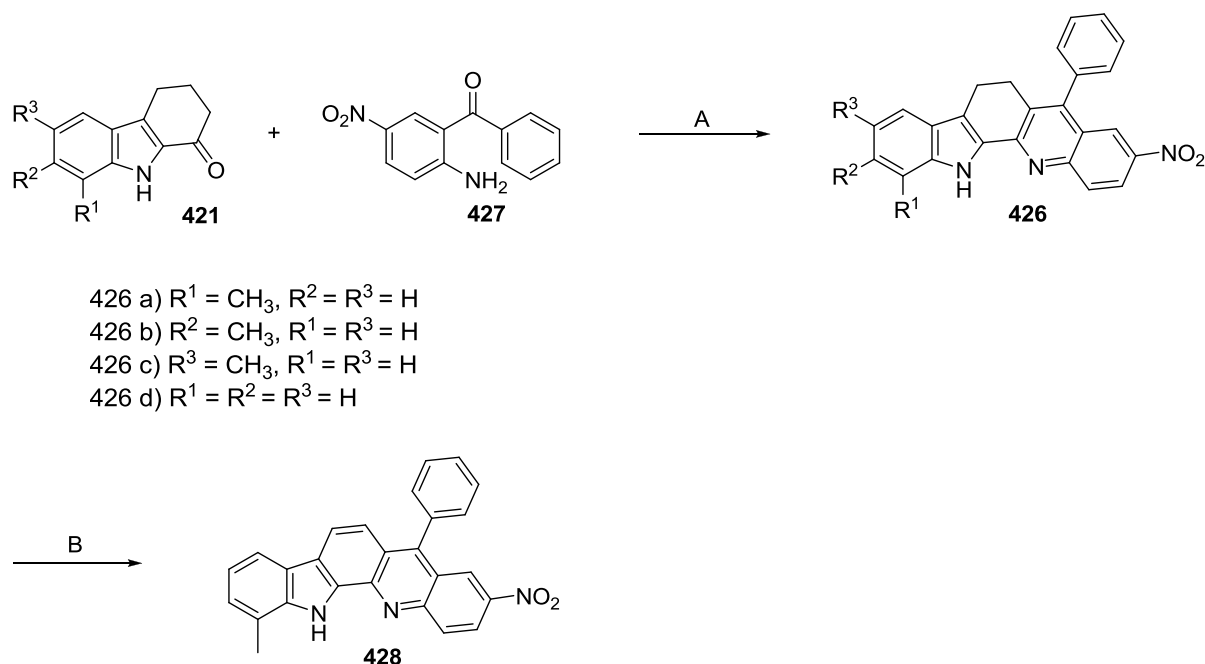
The same research group published numerous reports where they managed to synthesize substituted quinolino[2,3-*a*]carbazoles (13*H*-indolo[3,2-*c*]acridines) **417**.

Prasad and co-workers in 2006, accomplished the synthesis of 12,13-dihydro-5-oxo-9-methylquinolino[2,3-*a*]carbazole **424** by stirring 1-hydroxy-6-methylcarbazole **425** and anthranilic acid **420** in zinc chloride and phosphorous oxychloride at room temperature as shown in Scheme 129.<sup>204</sup>



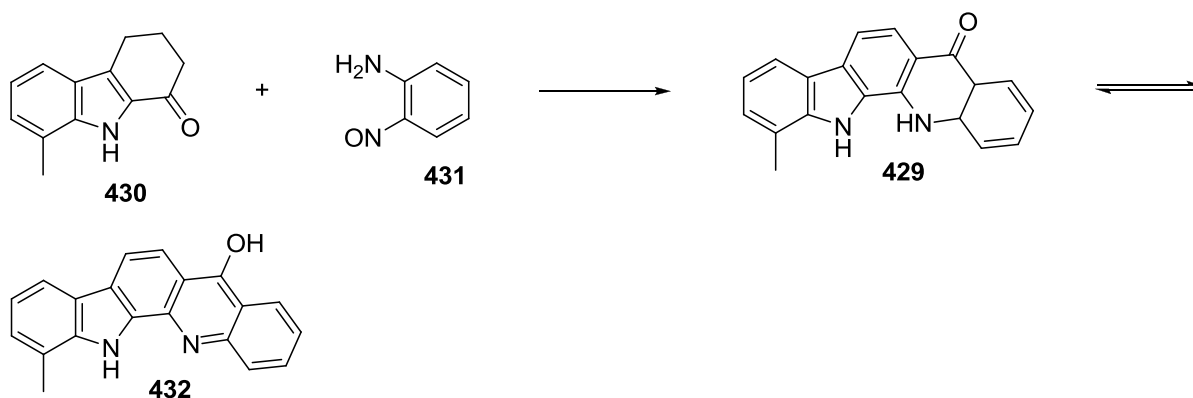
**Scheme 129:** Reagents and conditions: Anthranilic acid, ZnCl<sub>2</sub>, POCl<sub>3</sub>, 30%.

The same authors also carried out synthesis of similar kind of quinolino[2,3-*a*]carbazole (indolo[3,2-*c*]acridines) framework **417**. 9-Nitro-7-phenyl-5,6-dihydro-indolo[3,2-*c*]acridines **426** have been synthesized by refluxing a mixture of 2,3,4,9-tetrahydro-1*H*-carbazole-1-one **421** and 2-amino-5-nitro-benzophenone **427** in acetic acid and a few drops of sulfuric acid. The product obtained was treated with palladium on carbon in diphenyl ether afforded 1-methyl-9-nitro-7-phenyl-indolo[3,2-*c*]acridine **428** as shown in **Scheme 130**.<sup>205</sup>



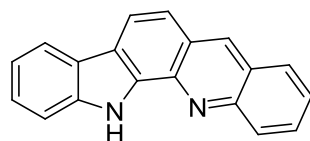
**Scheme 130:** Reagents and conditions: A) AcOH/H<sub>2</sub>SO<sub>4</sub>, reflux, 426 a) = 42%, 426 b) = 38%, 426 c) = 39%, 426 d) = 36%; B) Pd/C, diphenyl ether, 428) = 42%.

Synthesis of quinocarbazoles **429** which are also known as substituted pyridocarbazole derivatives were also synthesized by Prasad and co-workers from condensation of 8-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one **430** with *o*-aminobenzonitrile **431** under acidic condition as illustrated in **Scheme 131**.<sup>206</sup> The product **429** obtained exists in its keto-enol form with **432** in 1:1 ratio.



**Scheme 131:** Reagents and conditions: A) *p*-TsOH, dry toluene, 6 hrs, 75%.

As little research has been done on the synthesis of quinolino[2,3-*a*]carbazoles such as **417**. We were interested in the synthesis of these heteroaromatic compounds as they mimic the framework of the indolocarbazoles and could be seen as an analogue of the aromatic framework of staurosporine **365** or rebeccamycin **363** (**Figure 64**).



Quinoline[2,3-*a*]carbazoles **356**

**Figure 64**

Furthermore, this specific carbazole would provide a rigid framework which could be suitable for metal chelation. Meggers *et al.* have employed this type of approach to synthesize staurosporine **365** and related analogues which resulted in molecules which could bind to the specific active site of the GSK-3 protein.<sup>207,208,209</sup> In this case, ruthenium complexes, compound A **433** and compound B **434** (**Figure 65**) were assembled as the metal chelates and were completely inert biologically, resulting in no toxicity issues.



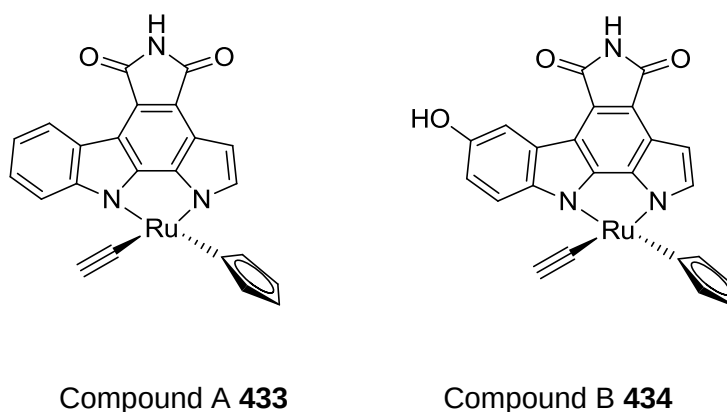
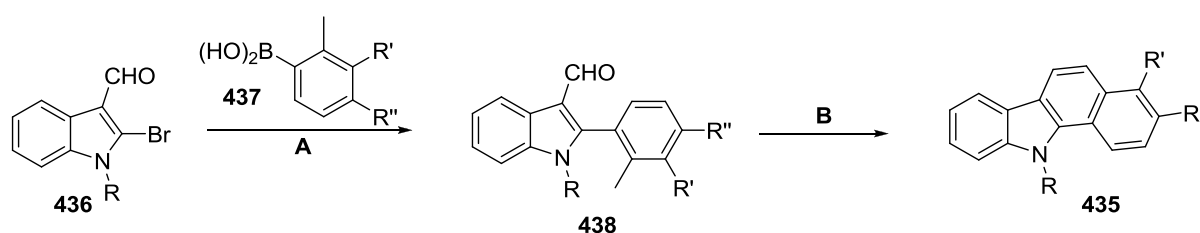


Figure 65

#### 7.4 Synthesis of Carbazole Ring – The Wits Approach

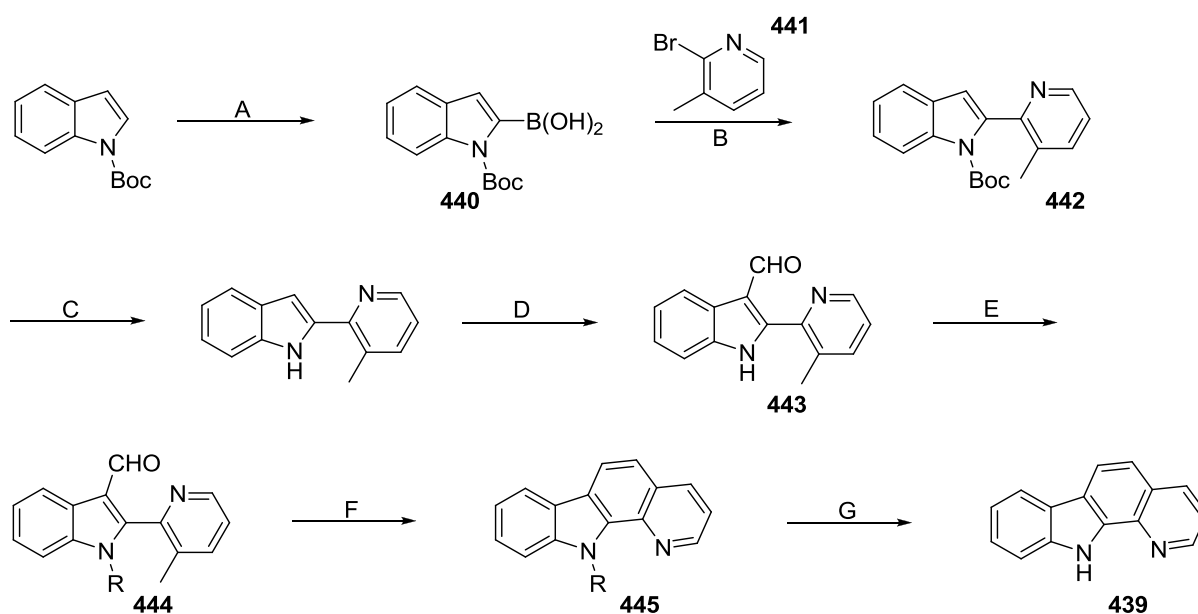
For this PhD a strategy towards the synthesis of quinolino[2,3-*a*]carbazoles **417**, was developed based on the work done previously in the organic chemistry research laboratories of the University of the Witwatersrand. The synthesis of polyaromatic and polyheteroaromatic systems including carbazole and fused carbazole system, has been accomplished in our laboratories using the potassium *t*-butoxide and light mediated ring cyclization. This novel potassium *t*-butoxide and light mediated ring cyclization reaction has been described extensively in **Chapter 5**.

Employing this potassium *t*-butoxide and light mediated ring cyclization approach, the synthesis of benzo[*a*]carbazoles **435** have been demonstrated by de Koning and co-workers.<sup>147</sup> For the synthesis of benzo[*a*]carbazoles **435**, 2-bromoindole-3-carbaldehyde **436** or its *N*-methyl analogue were subjected to Suzuki-Miyaura cross coupling with a variety of boronic acids **437** to afford the biaryl compounds. The free indole nitrogen was protected at this point by treatment of potassium(bis(trimethylsilyl)amide) (KHMDS) and then methyl iodide, to afford the *N*-methyl precursor **438**. Treatment of the 2-arylindoles **438** with potassium *t*-butoxide as described previously afforded the desired benzo[*a*]carbazoles **435** in good yields as shown in **Scheme 132**.



**Scheme 132:** Reagents and conditions: A)  $\text{Pd}(\text{PPh}_3)_4$ , aq.  $\text{Na}_2\text{CO}_3$ , DME; B) 1) For  $\text{R} = \text{H}$ , KHDMS, MeI,  $0^\circ\text{C}$ , DCM; 2) KOBut, DMF,  $h\nu$ ,  $70\text{--}80^\circ\text{C}$ .<sup>147</sup>

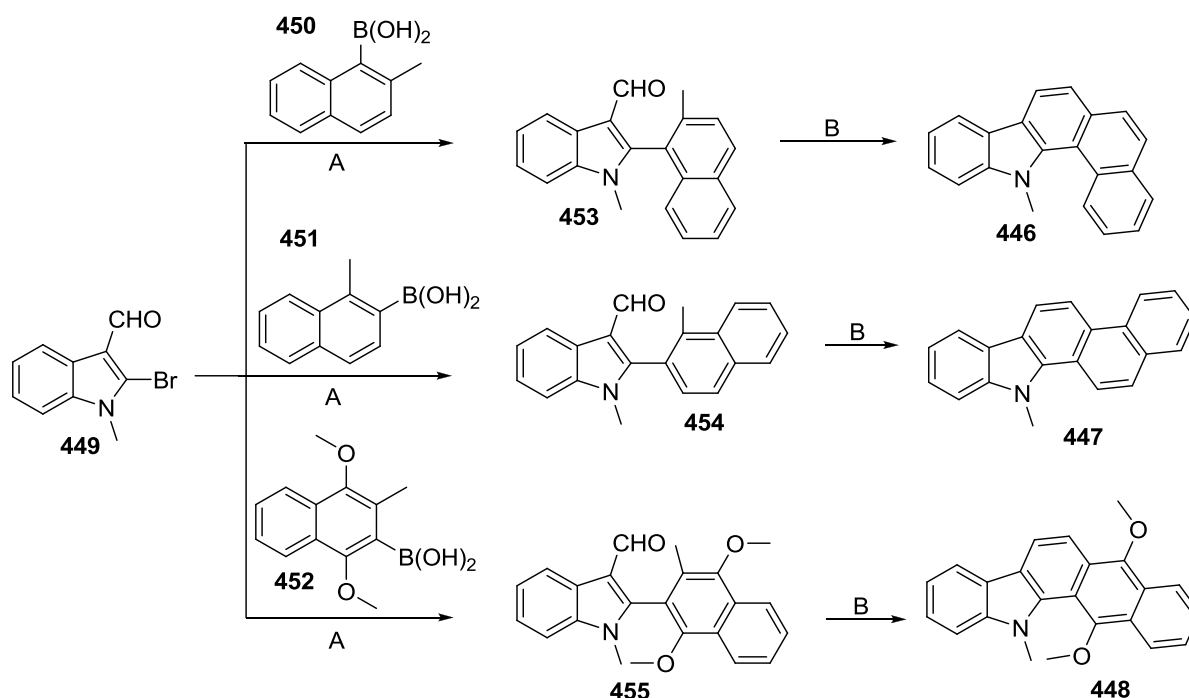
Using the same ring closing methodology, de Koning *et al.* published another report in 2000 demonstrating the synthesis of substituted pyrido[2,3-*a*]carbazoles **439**.<sup>210</sup> The synthetic scheme was initiated by a palladium catalysed Suzuki-Miyaura cross coupling reaction taking place between *N*-Boc protected indole-2-boronic acid **440** and 2-bromo-3-methylpyridine **441**. Carbon-carbon bond formation between C-2 of the indole nucleus and the pyridine subunit to give **442** is often problematic in the synthesis of carbazoles and this method proved to be a very efficient for this purpose.<sup>210,211</sup> Having generated the biaryl compound **442**, the Boc protecting group was removed followed by formylation to yield **443**. Before proceeding to the key potassium *t*-butoxide induced ring closure step, the free indole nitrogen was again protected to afford **444**. The desired ring closed product **445** was then produced using potassium *t*-butoxide in the presence of light. A final deprotection reaction was performed to afford the pyrido[2,3-*a*]carbazoles **439** (Scheme 133).



**Scheme 133:** Reagents and conditions: A) 1) LiTMP,  $-78^\circ\text{C}$ , THF; 2)  $\text{B}(\text{OPr})_3$ ; 3)  $\text{H}^+$ , 100%; B) 10%  $\text{Pd}(\text{PPh}_3)_4$ , aq.  $\text{Na}_2\text{CO}_3$ , DME, 99%; C)  $\text{SiO}_2$ , microwave oven, 3 mins, 96%; D)  $\text{POCl}_3$ , DMF, 91%; E) KHDMS, MeI, THF for  $\text{R} = \text{Me}$ , 99%; BnBr, KHDMS, THF for  $\text{R} = \text{Benzyl}$  84%; F) KOBut, DMF,  $h\nu$ ,  $70\text{--}80^\circ\text{C}$ ; G)  $\text{AlCl}_3$ ,  $0^\circ\text{C}$ , benzene, 80%.<sup>210</sup>

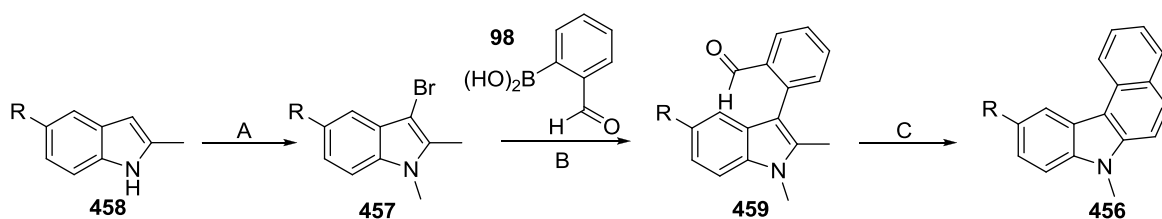
In 2003, de Koning *et al.*, reported the synthesis of naphtho[*a*]carbazoles and benzo[*c*]carbazoles from indole precursors using the standardised key reaction for the ring closure employing the use of potassium *t*-butoxide and light.<sup>212</sup> For the generation of

naphtho[1,2-*a*]carbazole **446**, naphtho[2,1-*a*]carbazole **447** and naphtho[2,3-*a*]carbazole **448** commercially available *N*-methyl-2-bromoindole-3-carbaldehyde **449** was used as a common substrate. **449** was treated with three different boronic acids (**450**, **451** and **452**) under Suzuki coupling reaction conditions to generate the desired biaryl compounds **453**, **454** and **455**. Each of these compounds were subjected to the ring closing reaction conditions using potassium *t*-butoxide and light to afford the desired naphtho-fused carbazoles **446**, **447** and **448** as shown in **Scheme 134**.



**Scheme 134:** Reagents and conditions: A) 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, DME/EtOH, 2 M aq Na<sub>2</sub>CO<sub>3</sub>, reflux 48 hrs; 60-99%; B) KOBut, DMF, *hν*, 10 mins; 56-86%.

Formation of benzo[*c*]carbazole **456** was also achieved by first generating the bromo indole precursor **457** by the reaction of 2-substituted indoles **458** with molecular bromine or *N*-bromosuccinimide, followed by protection of the free nitrogen by *N*-methylation afforded **457**. Subsequent treatment with 2-formylphenyl boronic acid **98** under Suzuki coupling conditions generated the desired biaryl compound **459** which was lastly exposed to potassium *t*-butoxide in the presence of light to result in the desired benzo[*c*]carbazole **456** (**Scheme 135**).<sup>212</sup>

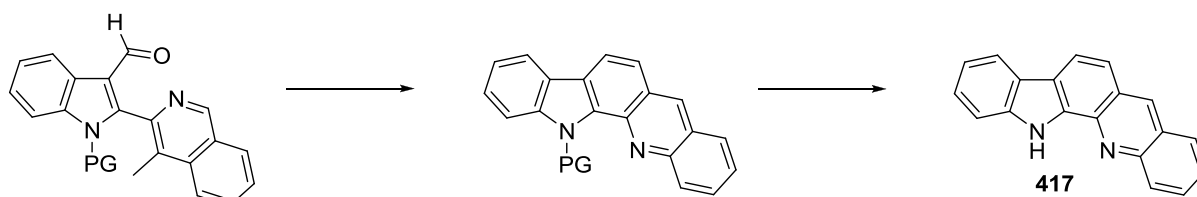


**Scheme 135:** Reagents and conditions: A) 1) For R = H, Br<sub>2</sub>, DMF, rt, 83%; For R = OMe, NBS, DCM, cat. SiO<sub>2</sub>, 30 min, 99%; 2) (MeO)<sub>2</sub>SO<sub>2</sub>, NaH, THF, For R = H, 18 hrs, 99%, For R = OMe, 48 hrs, 94%; B) 20 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, DMF, K<sub>3</sub>PO<sub>4</sub>, 100 °C, 65 hrs, For R = H, 83%; For R = OMe, 80%.; C) KOBut, DMF, *hν*, 10 min, R = H, 80%; For R = OMe, 70%.

## 7.5 Aims of this Section

Having seen the large variety of carbazole nuclei in nature and the importance of these in nature, synthetic organic chemists are inspired to assemble this framework. There are many new methods directed towards the synthesis of functionalized carbazoles or carbazole nuclei embedded in more complex molecules fused with other cyclic, aromatic or heteroaromatic rings.

With the knowledge gained about carbazoles from research previously done in our laboratories previously, we decided to use this same methodology and direct it towards the synthesis of the quinolino[2,3-*a*]carbazole **417** skeleton employing what we hoped would be the potassium *t*-butoxide and light induced ring closure reaction as the key step, as shown in **Scheme 136**.



**Scheme 136**

The aim of this section is therefore to synthesize quinolino[2,3-*a*]carbazole **417** framework employing potassium *t*-butoxide and light induced ring closure reaction as the key step.

## Chapter 8: Results and Discussion: Base and Light Mediated Approach Towards the Synthesis of Quinolino[2,3-*a*]carbazoles

### 8.1 Introduction

We have discussed in the previous **Chapter** the abundance of carbazoles in nature and their wide range of applications as therapeutics.<sup>213</sup> Carbazoles fused with quinolines are rare in nature, but possess a wide range of biological activities. Only three compounds are known in nature being a quinoline fused with the carbazole skeleton, and these are: calothrixins A **360** and B **361** with a quinolino[4,3-*b*]carbazole-1,4-quinone arrangement, and the recently isolated dibromo-quinolino[4,5-*a*]carbazole **362**. There are a number of reports describing the synthesis of calothrixin A **360** and B **361** in literature. But, to the best of our knowledge, to date only a few studies has been reported for the synthesis the of quinolino[2,3-*a*]carbazole **417** framework. For these reasons, we wished to explore new approaches to the synthesis of quinolino[2,3-*a*]carbazoles such as **417** (**Figure 66**).<sup>203</sup>

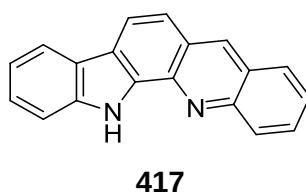
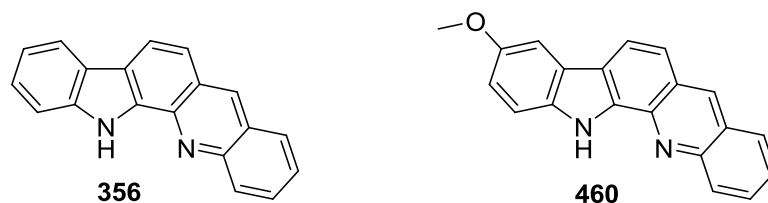


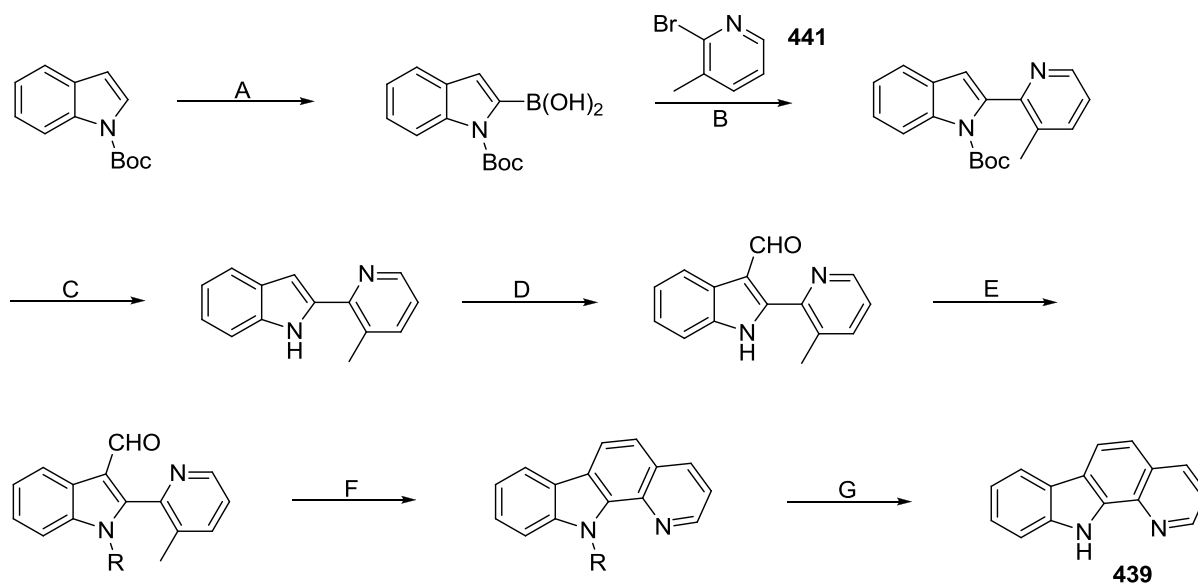
**Figure 66**

The two nitrogens in quinolino[2,3-*a*]carbazole **417**, we believed in theory could bind with metals to form metal complexes, a property of quinolino[2,3-*a*]carbazoles **417** that is not yet explored.

With all the necessary background regarding carbazole fused quinolines, we decided to start with two targets in mind: quinolino[2,3-*a*]carbazole **417** and 7-methoxy-quinolino[2,3-*a*]carbazole **460** (**Figure 59**).

**Figure 67**

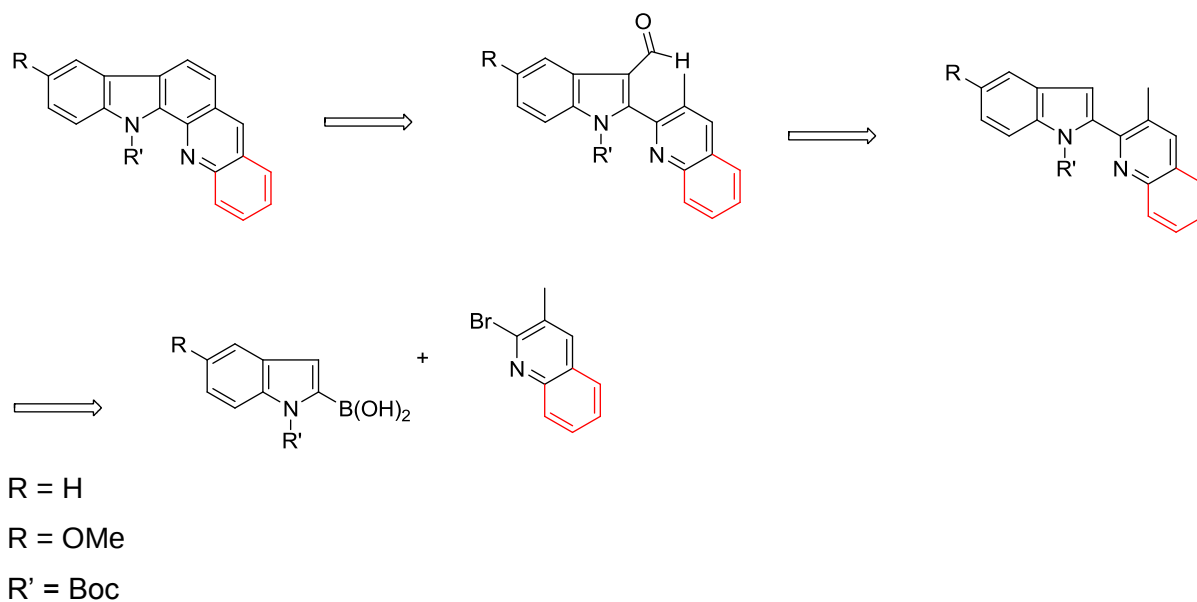
The first step towards our synthetic targets was to do a retrosynthetic analysis. Having our preliminary knowledge of the synthesis of pyrido[2,3-*a*] carbazoles **439** which was published previously by our group (**Scheme 137**), we envisioned that our synthesis could be accomplished in a similar manner, with two fragments coming from indole **370** and 3-methyl quinoline **461** rather than the 2-bromo-3-methylpyridine **441** used as was reported. These two fragments could be coupled using Suzuki-Miyaura cross coupling reaction and later a potassium *t*-butoxide and light induced reaction could be carried out to form the final aromatic ring.<sup>210</sup>



**Scheme 137:** Reagents and conditions: A) 1) LiTMP, -78 °C, THF; 2) B(O<sup>*i*</sup>Pr)<sub>3</sub>; 3) H<sup>+</sup>, 100%; B) 10% Pd(PPh<sub>3</sub>)<sub>4</sub>, aq. Na<sub>2</sub>CO<sub>3</sub>, DME, 87%; C) SiO<sub>2</sub>, microwave oven, 3 mins, 100%; D) POCl<sub>3</sub>, DMF, 91%; E) KHDMS, MeI, THF for R = Me; BnBr, KHDMS, THF for R = Benzyl, 77%; F) KOBut, DMF, *hν*, 70-80 °C, 75%; G) AlCl<sub>3</sub>, 0 °C, benzene, 80%.<sup>210</sup>

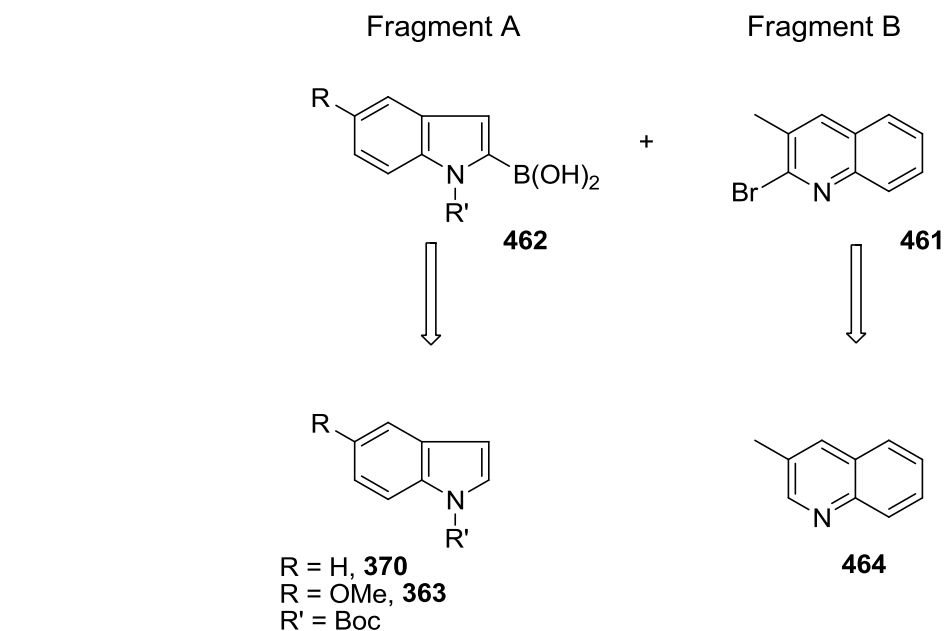
## 8.2 An Envisaged Retro Synthesis of Substituted Quinoline[2,3-a]carbazoles

Based on the results published by de Koning *et al.* for the synthesis of pyrido[2,3-a]carbazoles (**Scheme 137**) we envisioned synthesizing quinoline[2,3-a]carbazole **417** skeleton as shown in **Scheme 138**.<sup>210</sup>



**Scheme 138**

Specifically we wished to couple 1*H*-indol-2-ylboronic acid **462** and 2-bromo-3-methylquinoline **461**. These two fragments could be synthesized from indole **370** (5-methoxyindole **463**) and 3-methyl quinoline **464** respectively, both of which are available commercially.



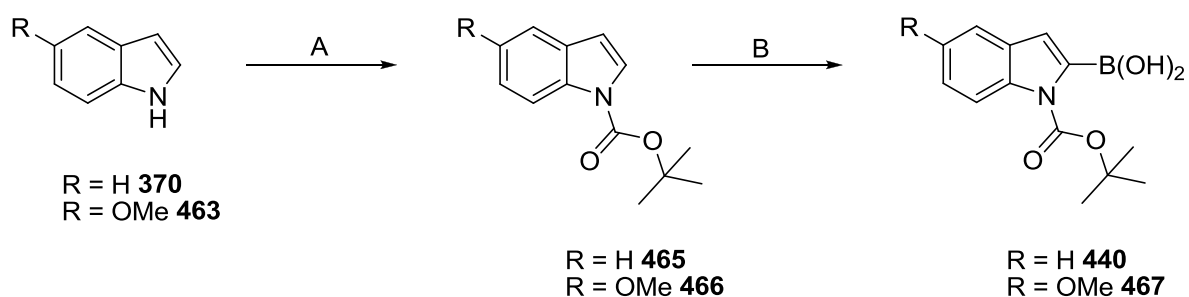
### Scheme 139

Once we have synthesized the fragments **462** and **461** we hoped, they could be coupled employing Suzuki-Miyaura cross coupling reaction methodology.

To commence with our synthetic scheme we wanted to first synthesize both the fragments which could be coupled using the palladium catalyzed Suzuki-Miyaura cross coupling reaction.

### 8.3 Synthetic Approaches towards Quinolino[2,3-a]carbazole 417 and 7-Methoxyquinolino[2,3-a]carbazole 460

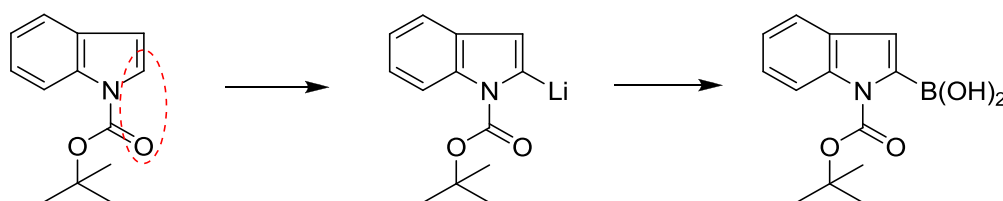
### 8.3.1 Syntheses of Fragment A 462





**Scheme 140:** Reagents and conditions: A) Di-*t*-butyl dicarbonate, DMAP, dry THF, rt, 18 hrs, For R = H, 98%, For R = OMe, 100%; B) DIPA, *n*BuLi, trimethyl borate, dry THF, 5 hrs, -78 °C-0 °C-rt, For R = H, 95%, For R = OMe, 93%.

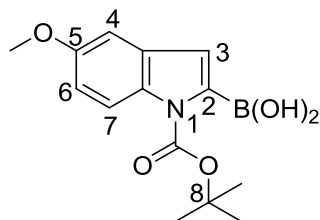
The Boc protection of commercially available indole **370** and 5-methoxy-1*H*-indole **463** was carried out by stirring the two starting materials separately, in freshly distilled and dry tetrahydrofuran. Dimethylaminopyridine and di-*t*-butyl dicarbonate were added to the reaction mixture which, was allowed to stir for eighteen hours under inert conditions and at room temperature before being quenched. Work up and column chromatography followed to afford the product in each case in quantitative yields. Thin layer chromatography showed that the products (**465** and **466**) in both cases had much higher  $R_f$  values as compared to the starting materials (**370** and **463**). Examination of the NMR spectra showed that there was some residue from the di-*t*-butyl dicarbonate present even after purification by the column chromatography in both the products (**465** and **466**). Fortunately, this did not pose any problems for future steps and we were able to purify the products after the next reaction. The spectral data was found to be in agreement with that observed in the literature.<sup>214</sup> One reason for using Boc protection at this point of the synthesis was that the Boc group is that it will allow for directed *ortho* metalation (DOM) which will be useful in the next step of our scheme: synthesis of the required boronic acid as shown in **Scheme 141**.



**Scheme 141**

We were now in a position to introduce a boronic acid substituent in the 2-position of the two Boc protected indoles **465** and **466** in order to couple them with 2-bromo-3-methylquinoline **461** through the Suzuki-Miyaura cross coupling reaction. The first synthesis of these two boronic acids, **440** and **467**, was reported by de Koning *et al.* of the organic chemistry laboratories of University of the Witwatersrand.<sup>210</sup> The Boc group in each compound facilitates directed *ortho* lithation which, when quenched, with trimethyl borate, leads to the formation of the borate ester. The addition of dilute hydrochloric acid during work-up of each reaction leads cleavage of each ester to afford the two boronic acids **440** and **467**.

To carry out the reaction, diisopropylamide was added to dry tetrahydrofuran under inert conditions and the solution was cooled to -78 °C. *n*Butyllithium was added dropwise to the stirred solution and the reaction was allowed to warm up to 0 °C for another thirty minutes.

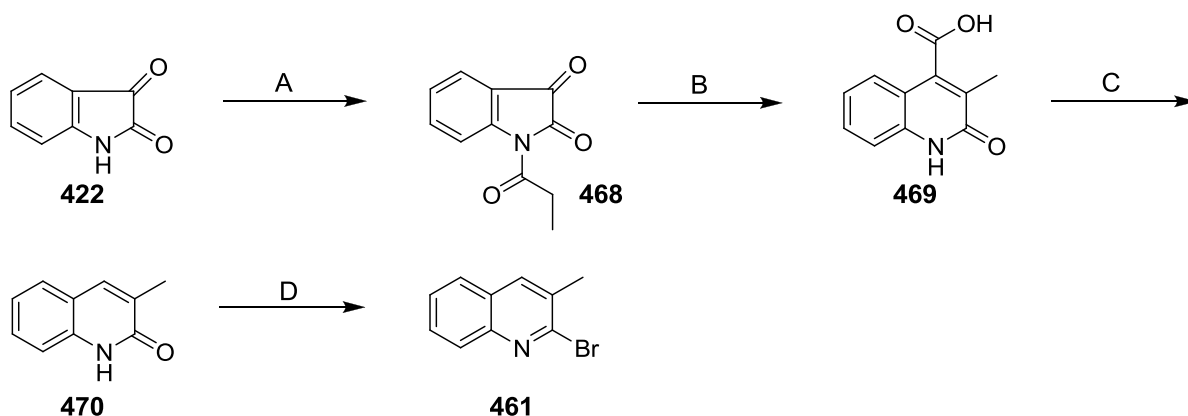


After the *in situ* preparation of lithium *di*-isopropylamine, the reaction mixture was cooled again to -78 °C and *N*-*boc*-indole dissolved in tetrahydrofuran was added dropwise to the reaction mixture. Triisopropyl borate was added and on completion of the reaction, the mixture was quenched by the careful addition of ice

cold water and 2 M hydrochloric acid. Subsequent to work up, solvent was removed under reduced pressure to one fourth of its original volume. At this stage, the thick slurry obtained was stirred vigorously at 0 °C and ice cold hexane was added to facilitate precipitation of the boronic acid, which was filtered, dried and stored in the freezer. These boronic acids are stable if stored at low temperature, and could even be characterized by NMR spectroscopy. The spectroscopic data of 1-(*t*-butoxycarbonyl)-1*H*-indol-2-ylboronic acid **440** was found to be in agreement with that reported in the literature.<sup>215,216</sup> Similarly, the spectroscopic data of *t*-butyl 5-methoxy-1*H*-indole-1-carboxylate **467** was found to be in accordance with that reported in the literature.<sup>210, 217</sup>

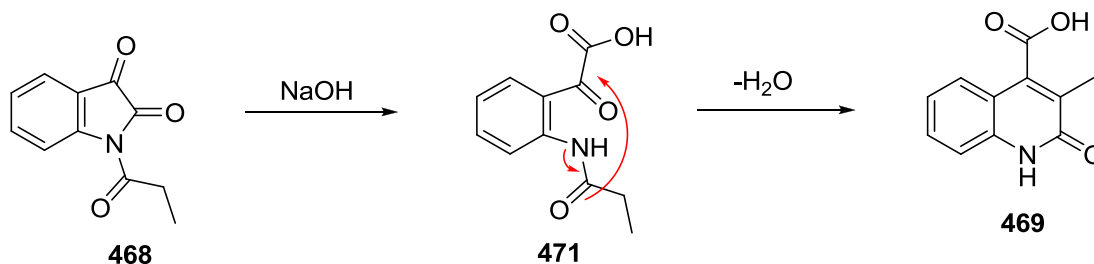
### 8.3.2 Synthesis of Fragment B

We now wished to tackle the synthesis of fragment B: 2-bromo-3-methylquinoline **461**. A literature search unearthed a paper where the synthesis of this quinoline has been demonstrated. The procedure involved a Pfitzinger reaction on isatin **422** with propionic anhydride to yield 1-propionylisatin **468**, which was later heated with sodium hydroxide to obtain 3-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylic acid **469**. Further treatment with copper powder led to decarboxylation to afford **470**. Finally, reaction with phosphoryl bromide gave the heteroaromatic bromide **461** as shown in **Scheme 142**.<sup>218</sup>



**Scheme 142:** Conditions and reagents: A)  $(\text{EtCO})_2\text{O}$ , reflux, 2.5 hrs, 81%; B) NaOH, heat, 1 hr, 81%; C) Cu powder, quinoline, reflux, 5 hrs; D)  $\text{POBr}_3$ , 140 °C.

In our hands, we were able to synthesize 3-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylic acid **469** using the reported literature procedure.<sup>218</sup> Conversion of **468** to **469** proceeds by Halberkann variation of Pfitzinger reaction where **469** is converted into the keto acid **471** in the presence of sodium hydroxide, which then undergoes cyclization through the CO and  $\text{CH}_2$  groups to give quinolone **469** as illustrated in **Scheme 143**.<sup>219</sup>

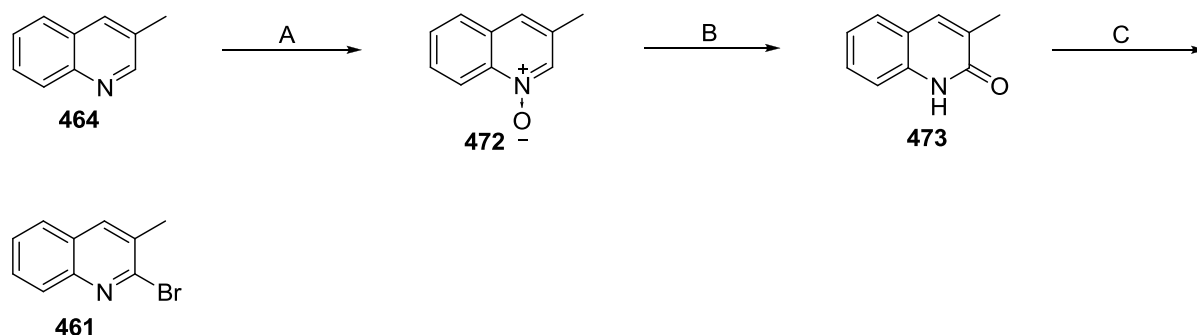


**Scheme 143**

The decarboxylation of **469** using copper powder never yielded the desired product **470**. We recovered starting material **469** from this reaction with no trace of product. Alternative methods for decarboxylation were also tested but these also failed to afford the desired product **470**.

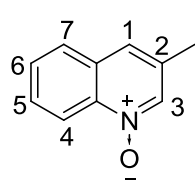
As this synthetic route for the synthesis of fragment B **461** was unsuccessful, we attempted alternative procedures. In the literature search, we found a procedure which involved the rearrangement of 3-methylquinoline-1-oxide **472** as the key step.<sup>220</sup> Here, treatment of commercially available 3-methylquinoline **464** with a peroxide source leads to 3-

methylquinoline-1-oxide **472**. A rearrangement with *p*-tosylchloride in the presence of base generates 3-methylquinolin-2(1*H*)-one **473**, which can be converted to fragment B **461** by reaction with phosphoryl bromide, as described in **Scheme 143**.



**Scheme 143:** Reagents and conditions: A) *m*CPBA, dry DCM, atmospheric conditions, 0 °C-rt, 45 mins, 87%; B) *p*TSA, K<sub>2</sub>CO<sub>3</sub>, CHCl<sub>3</sub>:H<sub>2</sub>O, rt, inert conditions, 5 hrs, 83%; C) POBr<sub>3</sub>, neat reaction, 140 °C, 3 hrs, 83%.

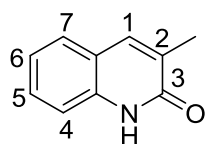
We therefore embarked on this synthesis of fragment B **461** with commercially available 3-methyl quinoline **464** by dissolving it in dry dichloromethane cooled down to 0 °C. *m*-Chloroperbenzoic acid was added in portions, and the reaction started to bubble vigorously. When all of the starting material **464** had been consumed, the reaction was quenched, and the product isolated after work-up and purification by column chromatography. The product **472** was obtained as a light yellow solid and was characterized by NMR spectroscopy. The data obtained was found to be in agreement with that reported in the literature.<sup>220</sup>



<sup>1</sup>H and <sup>13</sup>C NMR spectroscopy showed the correct number of signals as expected in the product **472**. A singlet for the methyl protons was seen at 2.46 ppm in the <sup>1</sup>H NMR spectrum, with the corresponding peak at 13.5 ppm in the <sup>13</sup>C NMR spectrum. There were two singlets observed in the <sup>1</sup>H NMR spectrum at 8.45 ppm and 7.55 ppm which are likely to be due to protons H-1 and H-3 respectively.

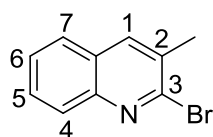
After the successful synthesis of 3-methyl quinoline oxide **472**, the next step in the synthesis of fragment B **461** was the rearrangement of **472** to form 3-methylquinolin-2(1*H*)-one **473**. This was achieved by dissolving the starting material **472** in chloroform and treating it with *p*-toluene sulfonic acid and potassium hydroxide in water. The solution was stirred for five hours at room temperature and under inert conditions. Thin layer chromatography showed the emergence of a new product at higher R<sub>f</sub> than the starting material **472**. On completion

of the reaction, work up and column chromatography were performed to obtain the product as an off-white solid in 83% yield. Analysis by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy confirmed the formation of the desired product, and the spectroscopic data was found to be in agreement with that reported in the literature.<sup>221</sup>



The most characteristic feature came from the  $^{13}\text{C}$  NMR spectrum with a peak at 164.5 ppm indicating the presence of a carbonyl carbon. In the  $^1\text{H}$  NMR spectrum, a singlet integrating for one proton at 11.80 ppm, characteristic of an NH group was observed. The other singlet arising from proton H-1 was seen at 7.65 ppm in the  $^1\text{H}$  NMR spectrum. The three protons of the methyl group gave rise to a signal at 2.31 ppm in the  $^1\text{H}$  NMR spectrum, and the corresponding peak in the  $^{13}\text{C}$  NMR spectrum could be observed at 16.8 ppm.

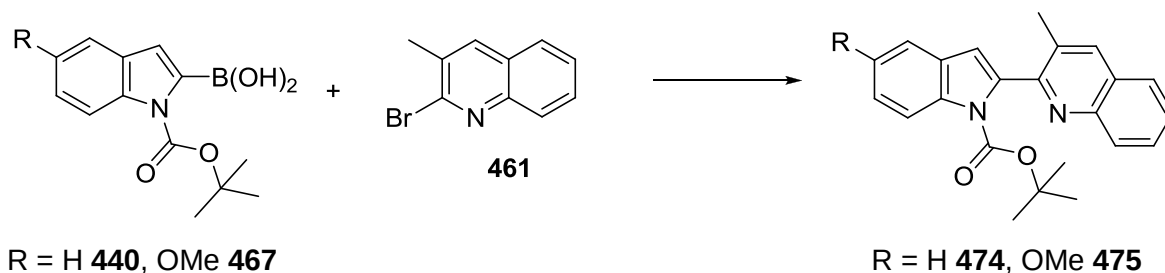
The final step in the synthesis of fragment B **461** was the functional group interconversion to allow for the formation of bromide which could later be utilized in the Suzuki Miyaura cross coupling reaction. The product **461** was obtained by heating 3-methylquinolin-2(1H)-one **473** with phosphoryl bromide at 140 °C for three hours, during which time the formation of the new spot of higher  $R_f$  than the starting material **473** was observed by thin layer chromatography. Work up and purification by column chromatography gave the desired product **461** as a light brown solid in 83% yield. The spectroscopic data was found to be in agreement with that reported in the literature.<sup>222</sup>



Disappearance of the singlet at 11.80 ppm in the  $^1\text{H}$  NMR spectrum due to the secondary amine was major indication of product formation. Furthermore, in the  $^{13}\text{C}$  NMR spectrum the signal for the carbonyl carbon at 164.5 ppm was no longer visible indicating that the carbonyl group was no longer present. A singlet for proton H-1 could be seen at 7.93 ppm in the  $^1\text{H}$  NMR spectrum and the corresponding peak in the  $^{13}\text{C}$  NMR spectrum could be seen at 22.4 ppm.

### 8.3.3 Suzuki Miyaura Cross Coupling Reaction to Couple Fragment A **462** and B **461**

On having successfully synthesized both of the required fragments, we were now able to attempt the formation of a biaryl axis using the Suzuki Miyaura cross coupling reaction (Scheme 123).



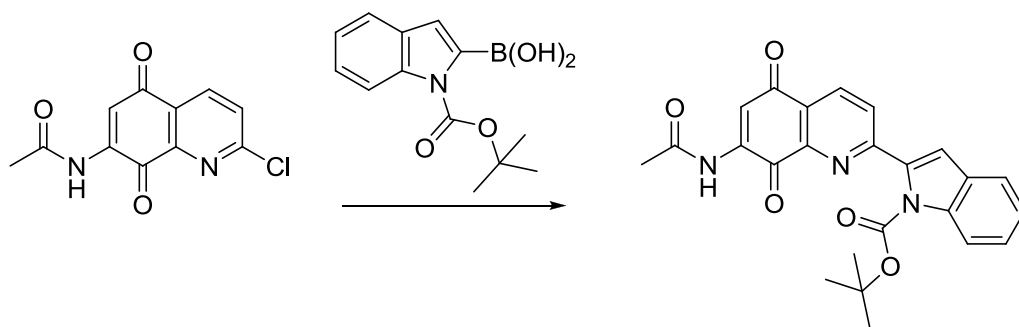
**Scheme 144:** Reagents and condition:  $\text{Pd}(\text{PPh}_3)_4$ , aq. 2 M  $\text{Na}_2\text{CO}_3$ , DME, rt-reflux, inert conditions, 18 hrs, For R = H, 95%, For R = OMe, 80%.

The same synthetic procedure was followed for the preparation of **474** and **475**, gave the desired products in excellent yields in both cases. However, care was taken to degas all solvent and water, used in the reaction and all glassware used were thoroughly dried prior to use. The starting materials, **440** or **467** in dry dimethoxyethane were added to the palladium catalyst and the resulting solution was stirred for ten minutes at room temperature and under inert conditions. An aqueous solution of the base was then added to the resulting mixture and was allowed to stir at reflux for eighteen hours. After work-up and purification by column chromatography, the products **474** and **475** in both cases were obtained as solids in very good yields.

Significantly, if the reaction was carried out too dilute, then reaction took much longer and resulted in lower yields of the product. Also the concentration of the aqueous solution of base had a profound impact on the yield of the product obtained, where concentrations higher than 2 M substantially decreased the yield of product.

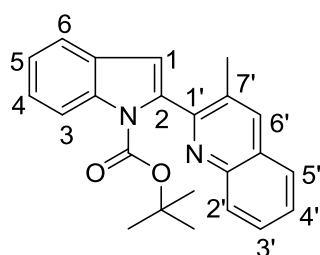
We also tested the reaction in the microwave reactor using tetrakis(triphenylphosphine) palladium(0) as catalyst, cesium fluoride as base and dimethoxyethane as solvent. The reaction mixture was subjected to microwave irradiation at 150 °C and 150 W. On spectroscopic analysis of the product we isolated revealed that the Suzuki-Miyaura cross coupling reaction had taken place along with deprotection of the Boc group. Although deprotection of the Boc group was planned as the following step in our synthesis, we decided not to pursue this approach as the yields obtained were significantly lower than when conventional heating was used in the reaction.

Keyari *et al.* in 2013 reported a similar type of Suzuki-Miyaura cross coupling reaction for the synthesis of biaryl axis in 7-aminoquinoline quinones **476** under microwave irradiation.<sup>223</sup>

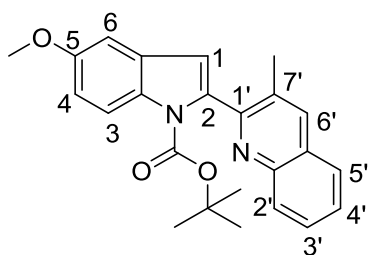


**Scheme 145:** Reagents and conditions: Pd(PPh<sub>3</sub>)<sub>4</sub>, DME/Na<sub>2</sub>CO<sub>3</sub>, 110 °C, 25 mins, 73%.

To our surprise, the Boc group stayed intact during the microwave conditions as reported by Keyari *et al.* contrary to our results of the Suzuki-Miyaura cross coupling reaction under microwave conditions.<sup>223</sup> Using slightly milder conditions might have helped in this case but we decided to stick to the conventional procedure of Suzuki-Miyaura cross coupling reaction as the yields were good.



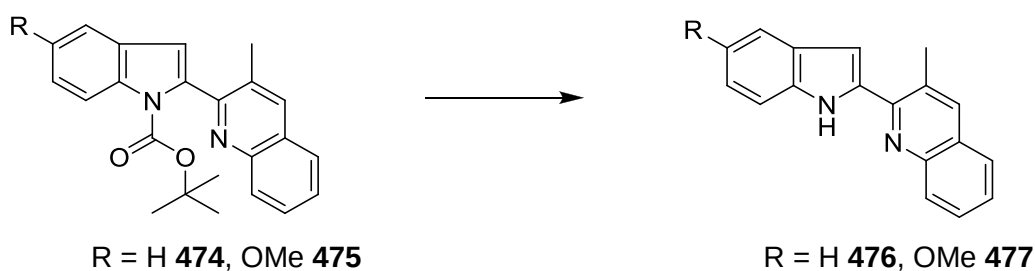
Identification of *t*-butyl 2-(3-methylquinolin-2-yl)-1*H*-indole-1-carboxylate **474** was done by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, where peaks from both fragment A **341** and B **390** were visible in the spectrum. Signals arising from the Boc protecting group *viz.* a singlet at 1.12 ppm integrating for nine protons in the <sup>1</sup>H NMR spectrum and the corresponding peak at 27.4 ppm in the <sup>13</sup>C NMR spectrum were observed. The carbonyl group from the Boc was seen as a signal at 154.9 ppm in the <sup>13</sup>C NMR spectrum. The methyl protons on carbon C-7' were observed at 2.35 ppm as a singlet integrating for three protons in the <sup>1</sup>H NMR spectrum with the corresponding peak in the <sup>13</sup>C NMR spectrum at 19.3 ppm. Two singlets were visible at 7.93 ppm for proton H-6' and at 6.71 ppm for proton H-1 respectively in the <sup>1</sup>H NMR spectrum. FTIR spectral analysis depicted characteristic peaks for the Boc group with a peak at 1721 cm<sup>-1</sup> for the carbonyl group and one at 1328 cm<sup>-1</sup> for a C-O stretch. Additionally, at 1258 cm<sup>-1</sup> a peak was observed which is characteristic of a C=N group. The molecular ion peak for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>+H) was observed at 359.1750 in the HRMS analysis, and correlated with the expected value.



*t*-Butyl 5-methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-1-carboxylate **475** was also easily identified by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. Peaks pertaining to the Boc protecting group could be seen in both <sup>13</sup>C and <sup>1</sup>H NMR spectra. A singlet for

the methyl group was visible in the  $^1\text{H}$  NMR spectrum at 2.37 ppm, with the corresponding peak in the  $^{13}\text{C}$  NMR spectrum at 19.4 ppm. The three methoxy protons were observed at 3.88 ppm in the  $^1\text{H}$  NMR spectrum with the corresponding signal at 55.7 ppm in the  $^{13}\text{C}$  NMR spectrum. Two singlets in the  $^1\text{H}$  NMR spectrum at 7.97 ppm and 6.64 ppm corresponded to the protons H-6' and H-1. Proton H-6 appeared as a doublet at 7.06 ppm in the  $^1\text{H}$  NMR spectrum with a coupling constant of 2.5 Hz due to *meta* coupling with H-4. Apart from NMR spectroscopic analysis, FTIR and HRMS analysis further confirmed the formation of the product. In the FTIR spectrum, a peak at  $1725\text{ cm}^{-1}$  due to the carbonyl group and a C-O stretch at  $1320\text{ cm}^{-1}$  further confirmed the presence of product **475**. Peaks at  $1272\text{--}1259\text{ cm}^{-1}$  due to the C=N bond were also visible in the FTIR spectrum. HRMS analysis of the product gave the molecular ion as 389.1848 for  $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_3$  ( $\text{M}^+\text{H}$ ), which correlated with the calculated value.

#### 8.3.4 Deprotection Reaction of the Boc Group



**Scheme 146:** Reagents and conditions:  $\text{AlCl}_3$ , DCM,  $0\text{ }^\circ\text{C}$ -rt, 1 hr, For R = H, 68%, For R = OMe, 69%

The formylation reaction of indoles usually occurs in the more reactive 3-position of the indole molecules as it is the most nucleophilic site. To ensure that the next step in our synthesis, formylation occurs at the desired position, we decided to deprotect the indole nitrogen to render the 3-position more nucleophilic and most suitable for formylation. Therefore, we carried out deprotection of the Boc groups from our two compounds, *t*-butyl 2-(3-methylquinolin-2-yl)-1H-indole-1-carboxylate **474** and *t*-butyl 5-methoxy-2-(3-methylquinolin-2-yl)-1H-indole-1-carboxylate **475**.

The deprotection reaction was carried out by dissolving the starting materials separately in dichloromethane and cooling down the solution to  $0\text{ }^\circ\text{C}$ . The Lewis acid, aluminium chloride was added carefully in portions, and the reaction mixture was stirred for one hour at room temperature under inert conditions. The progress of the reaction was monitored every fifteen



minutes by thin layer chromatography. If the reaction was left for extended periods of time some decomposition occurred which was seen by the emergence of multiple spots on the thin layer chromatography plate. Surprisingly the  $R_f$  value of the product was higher than that of the starting material in both cases, when we were expecting the opposite. However, intramolecular hydrogen bonding between the hydrogens of the indole moiety with the nitrogen of quinoline moiety could be an explanation for this as shown in **Figure 60**.

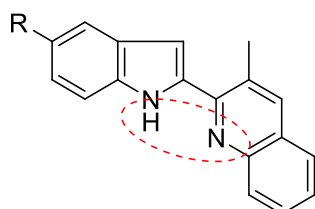
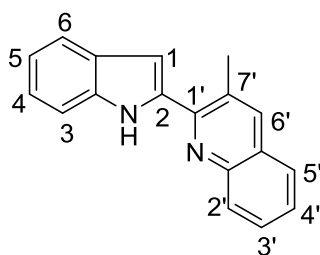
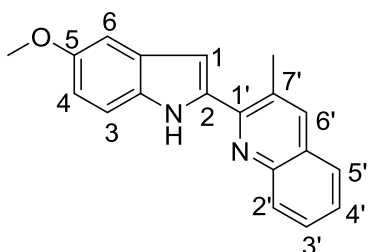


**Figure 68**

After completion of the reaction, the mixture was quenched and the product isolated after work-up and column chromatography. The product in each case was obtained as a bright yellow solid and in moderate yields: 68% for **476** and 69% for **477**.



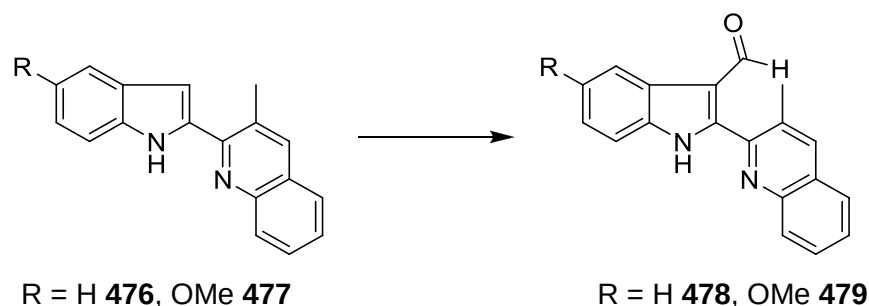
The characteristic signals of the Boc group were absent from the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of 2-(1*H*-indol-2-yl)-3-methylquinoline **476**. Also, a singlet appeared at 10.13 ppm in the  $^1\text{H}$  NMR spectrum integrating for one proton which is characteristic of the free hydrogen of the secondary amine. The signal for the methyl group could be seen at 2.80 ppm in the  $^1\text{H}$  NMR spectrum with the corresponding peak at 21.8 ppm in the  $^{13}\text{C}$  NMR spectrum. Two singlets could be seen at 7.94 ppm and 7.15 ppm for protons H-7' and H-1 respectively in the  $^1\text{H}$  NMR spectrum. A characteristic peak for the amine group was observed at  $3289\text{ cm}^{-1}$  in the FTIR spectrum, which further confirmed the absence of the Boc group. Finally, the molecular ion for  $\text{C}_{18}\text{H}_{14}\text{N}_2$  ( $\text{M}^+ + \text{H}$ ) was observed at  $m/z$  259.1230 in the HRMS.



2-(5-Methoxy-1*H*-indol-2-yl)-3-methylquinoline **477** was also identified easily from the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. At 10.05 ppm in the  $^1\text{H}$  NMR spectrum a singlet due to the free hydrogen of the indole nucleus was visible. A singlet for H-6' was seen at 7.90 ppm, and singlets for the three protons of each of the methoxy group and for the methyl group were observed at 3.86 ppm and 2.76 ppm respectively. In the  $^{13}\text{C}$  NMR spectrum, a signal for C-5

was observed at 154.2 ppm. A broad N-H stretch was observed in the FTIR spectrum at  $3147\text{ cm}^{-1}$ . HRMS gave the expected mass with  $m/z$  289.1331

### 8.3.5 Formylation of 3-Position on Indole Moiety



**Scheme 147:** Conditions and reagents: Dichloromethyl methyl ether,  $\text{SnCl}_4$ , dichloromethane,  $-70\text{ }^{\circ}\text{C}$ - $0\text{ }^{\circ}\text{C}$ , 3 hrs, For  $\text{R} = \text{H}$ , 75%, For  $\text{R} = \text{OMe}$ , 65%.

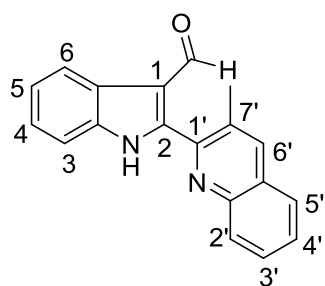
After successfully preparing 2-(1*H*-indol-2-yl)-3-methylquinoline **476** and 2-(5-methoxy-1*H*-indol-2-yl)-3-methylquinoline **477** we wanted to introduce a formyl substituent at the 3-position of the indole moiety of each of these molecules which would be used later for the potassium *t*-butoxide induced ring closure reaction. To proceed with the synthesis, a classical Vilsmeier reaction was employed, which involved the use of phosphoryl chloride, dimethyl formamide and toluene as solvent. Unfortunately, this method was not successful on either substrate **476** or **477**, even after multiple attempts.

While searching for an alternative procedure we came across a reaction which uses dichloromethyl methyl ether as the formylating agent.<sup>224</sup> We decided to test this method on our substrate 2-(1*H*-indol-2-yl)-3-methylquinoline **476**. To proceed with the reaction starting material **476** was added to dry dichloromethane under argon and at room temperature. Dichloromethyl methyl ether was then added to the stirred reaction mixture and reaction mass turned bright yellow. After that, the reaction mixture was cooled to  $-70\text{ }^{\circ}\text{C}$  and treated with tin(IV)chloride. The reaction mixture was then allowed to warm to  $0\text{ }^{\circ}\text{C}$  and was stirred at the same temperature for three hours under inert conditions.

The progress of the reaction was monitored by thin layer chromatography and after three hours all of the starting material **476** had been consumed and a new spot, which had higher  $R_f$  value compared to the starting material, appeared. After work up and column chromatography, the product **478** was obtained as a yellow solid. However the product was

particularly unstable, possibly due to the presence of both the free secondary amine and the formyl group. Similar problems were encountered in the synthesis of 5-methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **479**, with the more electron rich indole ring making this compound even more unstable.

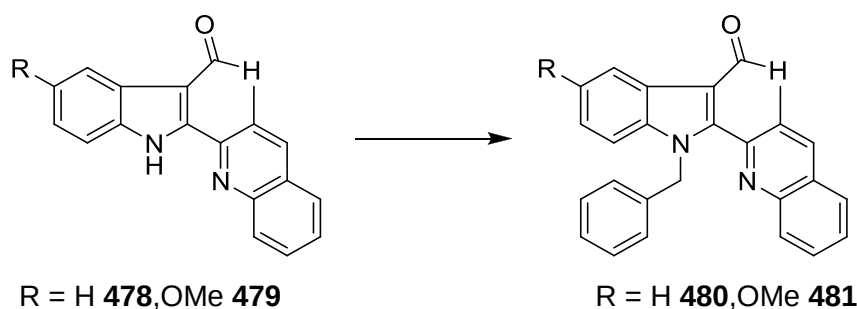
Due to the instability of these products, we were only able to obtain a  $^1\text{H}$  NMR spectrum for 2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **478**. 5-Methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **479** was treated as an intermediate and used in the next step without any further characterization.



The  $^1\text{H}$  NMR spectrum of **478** showed, a clear peak at the chemical shift of 9.80 ppm, integrating for one proton characteristic of an aldehyde group. At 12.50 ppm, a singlet indicating the presence of the free indole amine was visible and another singlet at 8.41 ppm, integrating for one proton was characteristic of the proton at C-6'. A singlet at 3.32 ppm confirmed the presence of three protons of the methyl group. Although we were unable to fully characterize this compound, the presence of a signal in the  $^1\text{H}$  NMR spectrum indicating an aldehyde clearly showed that we had successfully introduced the formyl group to afford the carbaldehyde **478**.

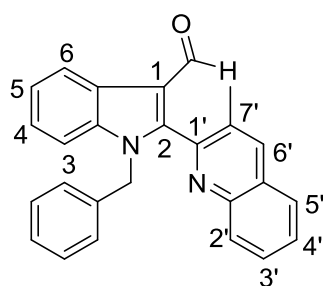
### 8.3.6 Reprotection of the Indole Nitrogen

Following the successful formylation of the indole moiety of the molecule to obtain **478** and **479**, it was necessary to protect the indole nitrogen, before performing the potassium *t*-butoxide mediated ring closure reaction, as the free NH group would hinder the formation of the final aromatic ring. We decided to use a benzyl protecting group as the benzyl group can also be removed at the end of the synthesis if necessary.

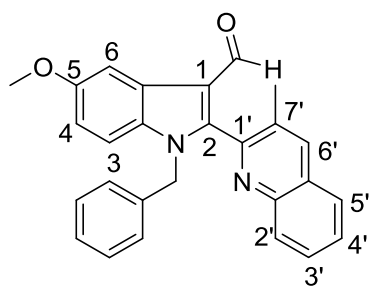


**Scheme 148** Reagents and conditions: NaH, BnBr, DMF, rt, 1 hr, For R = H, 93%, For R = OMe, 97%.

To carry out the reaction on both aldehydes, **478** and **479** were treated separately with sodium hydride in dimethylformamide. Each reaction was allowed to stir at room temperature under inert conditions for one hour, after which benzyl bromide was added. Purification of the products was achieved by column chromatography of the products. **480** and **481** were isolated as off white solids. Analysis of the products was done by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy.



The most diagnostic signal in the  $^1\text{H}$  NMR spectrum was the appearance of a peak representing the two benzylic protons at 5.29 ppm, with the corresponding peak in the  $^{13}\text{C}$  NMR spectrum visible at 47.9 ppm. The total number of aromatic signals in the  $^1\text{H}$ -NMR had increased by five protons which clearly shows that a benzyl substituent was present. The characteristic peak for the carbonyl group was also seen in the FTIR spectrum at  $1708\text{ cm}^{-1}$ . The HRMS gave the expected mass for  $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}$  ( $\text{M}^+ + \text{H}$ ), 377.1646 further corroborating the result obtained.



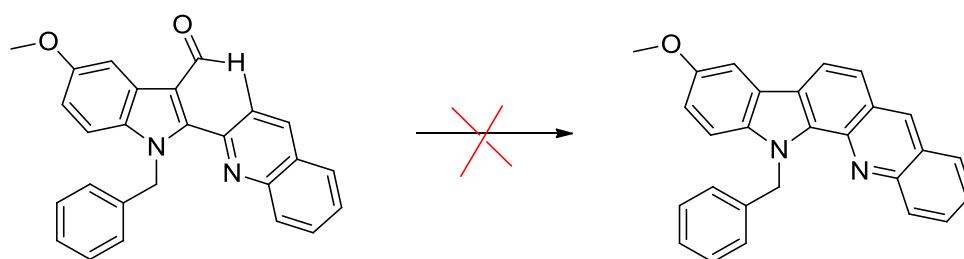
In the NMR spectroscopic analysis of 1-benzyl-5-methoxy-2-(3-methylquinolin-2-yl)-1H-indole-3-carbaldehyde **481** we were also able to identify all of the required signals. A peak at 5.59 ppm in the  $^1\text{H}$  NMR spectrum and at 56.9 ppm in the  $^{13}\text{C}$  NMR spectrum indicated the presence of the benzylic protons and carbon respectively. In both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra there was an increase the integration of the signals in the aromatic region due to the introduction of the benzyl group. The characteristic peak for the aldehyde functional group in the FTIR spectrum was observed at  $1718\text{ cm}^{-1}$ . Also the HRMS gave the molecular ion for  $\text{C}_{27}\text{H}_{22}\text{N}_2\text{O}_2$ , ( $\text{M}^+ + \text{H}$ ) at 407.1752, which corresponded well with the calculated value.

### 8.3.7 Potassium *t*-butoxide and Light Induced Ring Closure Reaction



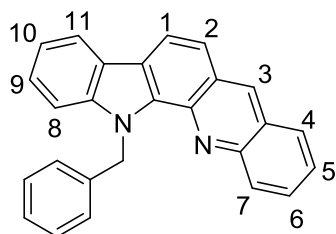
**Scheme 149:** Conditions and reagents: KOBut,  $h\nu$ , DMF, 80 °C, 10 mins, For R = H, 80%; For R = OMe, no reaction.

Having previous knowledge of the ring closing reaction induced by base and a source of light, we tested the reaction on each substrate **480** and **481** in dimethylformamide at 80 °C with potassium *t*-butoxide. Starting with **480**, the reaction mixture was analyzed by thin layer chromatography and a spot with much higher  $R_f$  value compared to the starting material **480** was observed. The product **482** was isolated and purified by column chromatography. Unfortunately, even after numerous attempts we failed to isolate the desired product **483** when we did the same reaction on 1-benzyl-5-methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **481**.



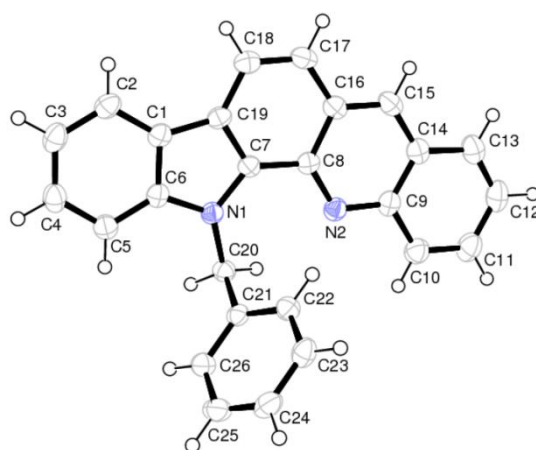
**Scheme 150**

The presence of the methoxy group, which renders the substrate **481** more electron rich, may play a role in this. We were not in a position to optimize this reaction at this stage and it will be considered for the future work.



For the product **482**, there were sixteen protons observed in the aromatic region of the  $^1\text{H}$  NMR spectrum which corresponded

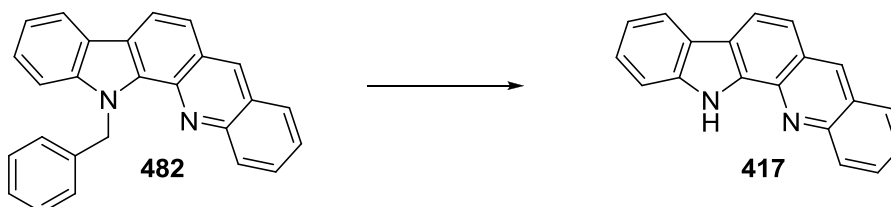
with the structure expected. There was one singlet seen at 8.79 ppm which is most likely due to proton H-3 as it does not couple to any other protons. Interestingly in the  $^1\text{H}$  NMR spectrum, the signal from the two benzylic protons shifted downfield to 6.86 ppm as compared to 5.59 ppm in the starting material. This could be attributed to the fact that due to the ring closure, the compound is fully aromatic and rigid. The  $^{13}\text{C}$  NMR spectrum also depicted the correct number of signals in the aromatic region as we were expecting twenty two peaks in total. In the FTIR spectrum, there was no carbonyl peak to be seen, which indicated conversion of the starting material to the product. Also HRMS gave  $m/z$  of 359.1542 for  $\text{C}_{26}\text{H}_{18}\text{N}_2$  ( $\text{M}^+ + \text{H}$ ), which correlated well with what we were expecting. Final confirmation came from the single crystal X-ray structure obtained for our product corroborated our result as shown in **Figure 69**.



Single X-ray crystal structure of quinolino[2,3-a]carbazole **482**

**Figure 69**

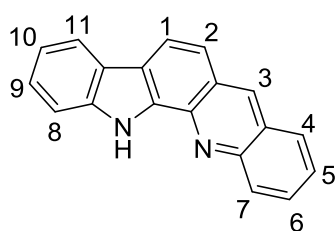
### 8.3.8 Benzylic Deprotection to form Quinolino[2,3-a]carbazole **417**



**Scheme 151:** Conditions and reagents:  $\text{AlCl}_3$ , benzene,  $0\text{ }^\circ\text{C}$ -rt, 2 hrs, 79%.

We were very happy to isolate quinolino[2,3-a]carbazole **482** using the potassium *t*-butoxide and light induced cyclization reaction, which was the key step in our synthetic scheme.

Having synthesized the desired quinoline fused carbazole **482** the final step was the benzyl deprotection from the indole nitrogen. The reaction was carried out using a literature reported procedure in which a strong Lewis acid in a non-polar solvent was used. Starting material **482** was dissolved in benzene and aluminium chloride was added to the reaction mixture at 0 °C.<sup>210</sup> The reaction mass was slowly allowed to warm to room temperature and was stirred at this temperature for two hours. During the course of the reaction a colour change of the solution was observed from yellow to bright red. Progress of the reaction was monitored by thin layer chromatography and a new spot was observed just below the starting material **482**. Subsequent to work-up and column chromatography product **417** was isolated as a yellow solid in 79% yield.



NMR spectroscopic studies were carried out to confirm the structure and were found to be in accordance with the literature.<sup>203</sup> The proton of the free indole nitrogen could be seen as a singlet in the  $^1\text{H}$  NMR spectrum downfield at 10.61 ppm.

Signals from eleven protons could be seen in the aromatic region in the  $^1\text{H}$  NMR spectrum. Nineteen signals could be seen in the  $^{13}\text{C}$  NMR spectrum, all in the aromatic region which complies well with the expected structure. Also, it was clear that we had successfully deprotected the nitrogen as there were no peaks for the benzylic group in either the  $^1\text{H}$  or the  $^{13}\text{C}$  NMR spectrum. In the FTIR spectrum, a broad peak at 3216  $\text{cm}^{-1}$  which is characteristic of the free secondary amine, could be observed. HRMS result was also found to be in agreement with that of the expected product.

## 8.4 Conclusion

In this part of the PhD, we were successful in synthesizing quinolino[2,3-*a*]carbazole **482**, demonstrating a further use of the light and potassium *t*-butoxide mediated ring closure reaction. Unfortunately we were not able to isolate 7-methoxy-quinolino[2,3-*a*]carbazole **460**, by the same process but this would be considered for the future work.

## Chapter 9: Experimental Procedures

### 9.1. General Experimental Procedures

#### 9.1.1. Purification of Solvents and Reagents

Solvents utilized for chromatographic techniques (ethyl acetate and *n*-hexane) were distilled preceding use by means of conventional distillation processes. The solvents employed in reactions were first dried over the suitable drying agent, followed by distillation under an inert atmosphere (argon or nitrogen gas). Acetonitrile and dichloromethane were distilled over calcium hydride, whereas tetrahydrofuran was distilled over sodium with benzophenone as an indicator. All the required chemicals or reagents were obtained from FLUKA, SIGMA ALDRICH or MERCK and were used without further purification.

#### 9.1.2. Chromatography Procedures

Normal chromatography was performed with silica gel 60 (Macherey-Nagel, particle size 0.063-0.200 mm) adsorbent, with both isocratic and gradient eluent systems being employed. Thin layer chromatography (TLC) of the compounds was executed on Macherey-Nagel Alugram Sil G/UV254 plates pre-coated with 0.25 mm silica gel 60. The TLC plates were viewed under UV light (254 nm and 366 nm).

#### 9.1.3. Spectroscopic and Physical Data

Nuclear magnetic resonance (NMR) spectra were recorded on either a Bruker AVANCE 300 MHz or a Bruker AVANCE III 500 MHz spectrometer. All spectra were recorded in chloroform-*d* or dimethylsulfoxide-*d*<sub>6</sub>. All chemical shift values are reported in parts per million referenced against trimethylsilane which is given an assignment of zero parts per million. Coupling constants (*J*-values) are given in Hertz (Hz).

The infra-red spectra were recorded on a Bruker Tensor 27 standard system spectrometer. Measurements were made by loading the sample directly onto a diamond cell. The measurements are reported on the wavenumber scale ( $\text{cm}^{-1}$ ).

Melting points were determined on a Reichert hot-stage microscope, and remain uncorrected. All crystalline compounds were recrystallized in the appropriate solvents prior to melting point determination.



High resolution mass spectra were obtained with a Waters-LCT-Premier mass spectrometer. The sample was dissolved in methanol to a concentration of 2 ng/ $\mu$ l and introduced by direct infusion. The ionization mode was electrospray positive with a capillary voltage of 2500 V and a desolvation temperature of 250 °C using nitrogen gas at 250 L/hr.

The intensity data was recorded on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K $\alpha$  radiation (50 kV, 30 mA) with temperature of measurement at 173(2) K, using the APEX 2 data collection software. The collection method involved 4-scans of width 0.5 and 512 $\times$ 512 bit data frames. The data reduction was achieved by means of the program SAINT+ and face indexed absorption corrections were made using XPRE.

Crystal structures were solved employing direct methods using SHELXTL. Nonhydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F<sup>2</sup> using SHELXTL. The hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective precursor atoms. Diagrams and publication material were generated using SHELXTL, PLATON151 and ORTEP-3.

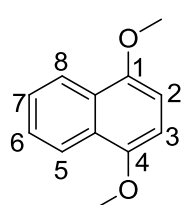
#### 9.1.4. Other General Procedures

All the glass reaction vessels were dried in an oven. The term “in vacuo” refers to the removal of solvent by use of a rotary evaporator. The residual solvent of purified material was removed by utilizing a high vacuum pump (ca.0.1 mm Hg) at ambient temperature until constant mass was achieved.

### 9.2 Preparation of 1,4-Dimethoxynaphthalene<sup>58</sup> **96**

Commercially available 1,4-naphthoquinone **95** (1eq., 4.00g, 25.31mmoles) in diethyl ether (150mL) was added to a vigorously stirring solution of sodium dithionite (10eq., 36.00g, 0.25moles) in water (200mL) for a period of one hour. The colour of the solution changes from dark orange to pale yellow which indicates reduction of quinone. The solution was transferred to a separating funnel and organic layer was collected, washed with brine (200mL $\times$ 2), dried over anhydrous magnesium sulfate, filtered and organic solvent was removed *in vacuo* to obtain crude naphthalene-1,4-diol **93** as a brown solid, which is an unstable intermediate and was used in the next reaction without any characterization. Naphthalene-1,4-diol **93** was dissolve in dry acetone (100mL) and potassium carbonate (4eq., 14.00g, 50.00mmoles) was added to it. The reaction was allowed to stir for thirty

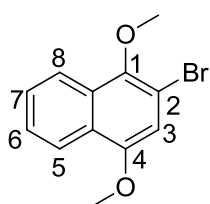
minutes at room temperature under inert conditions. The reaction mixture changes color from light brown to very dark brown which indicates the generation of an anion. Dimethyl sulfate (7eq., 44.00g, 16.6mL, 35.00mmoles) was added to the reaction mixture and the reaction was allowed to stir at reflux for eighteen hours. The reaction was allowed to cool to room temperature and the potassium carbonate was filtered off. The acetone was removed *in vacuo* to obtain a brown oil which was dissolved in diethyl ether (200mL). Aqueous ammonia (100mL) was then added to this solution in portions with stirring till the evolution of bubbles stops. The solution was transferred to a separating funnel and organic layer was collected which was washed with aqueous 10% hydrochloric acid (100mL), water (100×2mL) and brine (100mL). The organic layer was collected, dried over anhydrous magnesium sulfate, filtered and organic solvent removed *in vacuo* to obtain 1,4-dimethoxynaphthalene **89** as a brown solid which was purified by column chromatography (10% EtOAc-Hexane) to obtain product as a white solid (4.10g, 21.60mmoles, 85%).



$R_f$  0.44(20% EtOAc/Hexane);  $^1\text{H NMR}$  (300 MHz, Chloroform-*d*)  $\delta$  8.21 (2H, dd,  $J = 6.4, 3.3$  Hz, ArH), 7.50 (2H, dd,  $J = 6.4, 3.3$  Hz, ArH), 6.68 (2H, s, ArH-2,3), 3.94 (6H, s, OMe×2);  $^{13}\text{C NMR}$  (75 MHz, Chloroform-*d*)  $\delta$  149.5(ArC-1,4), 126.3(ArC), 125.9(ArC), 121.8(ArC), 103.1(ArC), 55.8(OMe×2).<sup>58</sup>

### 9.3 Preparation of 2-Bromo-1,4-dimethoxynaphthalene<sup>59</sup> **97**

1,4-dimethoxynaphthalene **96** (1eq., 1.00g, 5.31mmoles) was dissolved in 25mL dry dichloromethane in a 50mL round bottom flask and *N*-bromosuccinimide (1eq., 1.00g, 5.31mmoles) was added to it. The reaction was stirred under inert conditions at room temperature for eighteen hours. After that time aqueous sodium sulfite (20mL) was added to it to quench the reaction and solution was transferred to a separating funnel. The organic material was extracted into dichloromethane (20mL×3). The combined organic phases were collected and washed subsequently with water (30mL) and brine (30mL), dried over anhydrous magnesium sulfate, filtered and organic solvent was removed *in vacuo* which was purified by column chromatography (10% EtOAc-Hexane) to obtain 2-bromo-1,4-dimethoxynaphthalene **90** as a pale yellow solid (1.20g, 4.47mmoles, 84%).

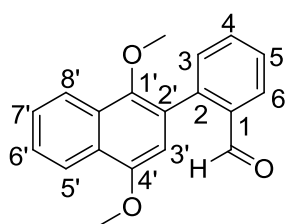


$R_f$  0.28 (20% EtOAc/Hexane);  $^1\text{H NMR}$  (300 MHz, Chloroform-*d*)  $\delta$  8.23 – 8.18 (1H, m, ArH), 8.09 – 8.03 (1H, m, ArH), 7.60 – 7.47 (2H, m, ArH), 6.88 (1H, s, ArH-3), 3.97 (3H, s, OMe), 3.95 (3H, s, OMe);  $^{13}\text{C NMR}$  (75

MHz, Chloroform-*d*)  $\delta$  152.3(ArC-1), 146.9(ArC-4), 129.0(ArC), 127.3(ArC), 125.9(ArC), 125.8(ArC), 122.7(ArC), 121.9(ArC), 112.0(ArC), 108.0(ArC), 61.4(OMe), 55.9(OMe).<sup>59</sup>

#### 9.4 Preparation of 2-(1,4-Dimethoxynaphthalen-2-yl)benzaldehyde **99**

2-Bromo-1,4-dimethoxynaphthalene **97** (1eq., 200mg, 0.751mmoles), 2-formylphenylboronic acid **98** (1.5eq., 169mg, 1.13mmoles), tetrakis(triphenylphosphine)palladium(0) (0.4eq., 47.0mg, 0.302mmoles) and cesium fluoride (2.5eq., 285mg, 1.877mmoles) were added to a microwave vial and freshly degassed dimethoxy ethane (2mL) was added to the mixture. The reaction was set up in a microwave reactor at 150 °C and 150 W power with high stirring for thirty minutes. On completion, the reaction mass was filtered off, adsorbed on silica and subjected to column chromatography (5% EtOAc/Hexane) to obtain the product **99** as an off-white solid (166mg, 0.572mmoles, 76%).

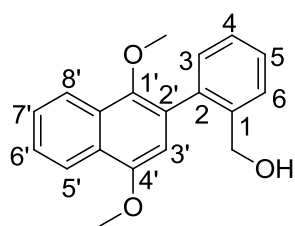


**R<sub>f</sub>** 0.51 (20% EtOAc/Hexane); **mp.** 190-192 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **FTIR**(v/cm<sup>-1</sup>): 2935 (C-H), 1726 (C=O), 1625-1469 (C=C), 1263-1224 (C-O); **<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*)  $\delta$  9.90 (1H, s, CHO), 8.30 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 8.17-8.11 (1H, m, ArH), 8.08 (1H, dd, *J* = 8.1, 1.5 Hz, ArH), 7.71 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 7.64-7.50 (4H, m, ArH), 6.74 (1H, s, ArH-3'), 4.01 (3H, s, OMe), 3.40 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  192.4 (C=O), 152.0 (ArC-4'), 147.0 (ArC-1'), 141.9 (ArC), 133.8(ArC), 133.5 (ArC), 131.0 (ArC), 128.4 (ArC), 127.9 (ArC), 127.2 (ArC), 127.1, 126.64(ArC), 126.2 (ArC), 125.4(ArC), 122.4(ArC), 122.3(ArC), 105.9(ArC-3'), 60.9 (OMe), 55.8 (OMe); **HRMS** (ESI<sup>+</sup>): Found M<sup>+</sup>+ H 293.1169, C<sub>19</sub>H<sub>17</sub>O<sub>3</sub> (M<sup>+</sup>+ H) requires 293.1178, m/z 293.1169(100%), 292.1092(50%).

#### 9.5 Preparation of (2-(1,4-Dimethoxynaphthalen-2-yl)phenyl)methanol **86**

2-(1,4-Dimethoxynaphthalen-2-yl)benzaldehyde **99** (1eq., 657mg, 2.25mmoles) was dissolved in 10mL of freshly distilled dry tetrahydrofuran under inert conditions in a 25mL round bottom flask. Lithium aluminium hydride (3eq., 255mg, 6.75mmoles) was added to the mixture carefully. The reaction was allowed to stir at room temperature under inert conditions for two hours. When completed, the reaction was cooled down to 0 °C and a 2% aqueous sodium hydroxide (10mL) was added dropwise to quench the unreacted lithium aluminium hydride and then diluted with ice-cold water (25mL). The organic material was extracted into ethyl acetate (20mL×3) and combined organic phases were washed with brine (50mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed in vacuum to

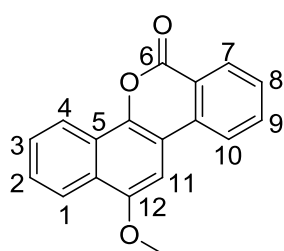
obtain crude product which was then subjected to column chromatography (40% EtOAc/Hexane) to obtain product **79** as a white solid (638mg, 2.17mmoles, 96%).



**R<sub>f</sub>** 0.38 (50% EtOAc/Hexane); **mp.** 114-115 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **FTIR**(v/cm<sup>-1</sup>): 3442 (OH), 2930 (C-H), 1625-1454 (C=C), 1273-1229 (C-O); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 8.34-8.22 (1H, m, ArH), 8.16-8.05 (1H, m, ArH), 7.65-7.32 (6H, m, ArH), 6.62 (1H, s, ArH-3'), 4.44 (1H, d, *J* = 11.1 Hz, one of CH<sub>2</sub>OH), 4.37 (1H, d, *J* = 11.1 Hz, one of CH<sub>2</sub>OH), 3.93 (3H, s, OMe), 3.61 (1H, s, OH), 3.47 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) δ 152.0(ArC-4'), 146.2(ArC-1'), 139.5(ArC), 137.9(ArC), 130.1(ArC), 129.9(ArC), 129.1(ArC), 128.4(ArC), 128.3 (ArC), 127.8(ArC), 127.1(ArC), 126.2(ArC), 125.8(ArC), 122.4(ArC), 122.1(ArC), 106.4(ArC-3'), 64.1(CH<sub>2</sub>OH), 61.6 (OMe), 55.7 (OMe); **HRMS** (ESI-): Found M<sup>+</sup>-OH 277.1240, C<sub>19</sub>H<sub>17</sub>O<sub>2</sub> (M<sup>+</sup>-OH) requires 277.1240, *m/z* 277.124(100%), 294.1244(30%).

## 9.6 Preparation of 12-Methoxy-6H-dibenzo[*c,h*]chromen-6-one<sup>38</sup> **65**

(2-(1,4-Dimethoxynaphthalen-2-yl)phenyl)methanol **86** (1eq., 265mg, 0.903 mmoles) was dissolved in dichloromethane (10mL) and to this stirring solution was added *N*-bromosuccinimide (2eq., 320mg, 1.80mmoles) and the reaction mass was allowed to stir at room temperature and under atmospheric conditions for eight hours. On completion of the reaction aqueous saturated solution of sodium sulfite (10mL) was added to quench the reaction. The organic layer was collected and washed with water (10mL) and brine (10mL), dried over anhydrous magnesium sulfate, filtered and the organic solvent was removed under reduced pressure to obtain the crude product which was purified by column chromatography (10% EtOAc-Hexane) to isolate 12-methoxy-6H-dibenzo[*c,h*]chromen-6-one **65** as light tan solid (129mg, 0.474mmoles, 53%). The spectroscopic data was found to be in agreement with that of Jones and Qabaja.<sup>38</sup>

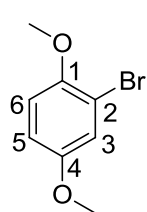


**R<sub>f</sub>** 0.88 (20% EtOAc/Hexane); **mp.** 228-230 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **FTIR**(v/cm<sup>-1</sup>): 2935 (C-H), 1722 (C=O), 1664-1418 (C=C), 1277-1225 (C-O); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 8.58-8.43 (2H, m, ArH), 8.26 (1H, d, *J* = 7.7 Hz, ArH), 8.12 (1H, d, *J* = 8.1 Hz, ArH), 7.95-7.82 (1H, m, ArH), 7.63 (3H, ddd, *J* = 9.9, 7.3, 1.4 Hz, ArH), 7.24 (1H, s, ArH-11), 4.12 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) δ 161.4(ArC-6), 152.4(ArC), 141.8 (ArC), 135.5(ArC), 134.7(ArC), 130.7(ArC), 128.4(ArC), 127.7(ArC), 127.3 (ArC), 126.8(ArC), 124.8(ArC), 122.1(ArC), 122.1(ArC), 121.8(ArC), 121.4(ArC), 112.6

(ArC), 95.8(ArC-11), 55.79(OMe), **HRMS** (ESI<sup>+</sup>): Found  $M^+ + H$  277.0865,  $C_{18}H_{12}O_3$  ( $M^+ + H$ ) requires 277.0865,  $m/z$  277.0865(100%), 278.0694(20%).<sup>38</sup>

### 9.7 Preparation of 2-Bromo-1,4-dimethoxybenzene<sup>59</sup> **112**

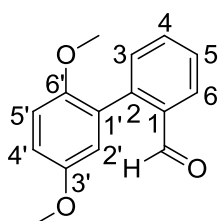
*N*-bromosuccinimide (1eq., 2.57g, 14.40 mmol) was added to a stirring solution of 1,5-dimethoxybenzene **111** (1eq., 2.00g, 14.40mmol) in dichloromethane (20mL) under inert conditions at room temperature. The reaction was allowed to stir under the same conditions for seventy two hours. After this time an aqueous saturated solution of sodium sulfite (20mL) was added and then washed with dichloromethane (20mL×3). The combined organic phases were collected and washed with water (30mL) and then with brine (30mL), dried over anhydrous magnesium sulfate. The resulting solution was filtered and the organic solvent was removed under reduced pressure to isolate the product **112** as a clear oil (2.82g, 12.98 mmol, 90%).



$R_f$  0.66 (20% EtOAc/Hexane) **<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*)  $\delta$  7.11 (1H, d,  $J = 2.6$  Hz, ArH-3), 6.84-6.81 (1H, m, ArH-5), 6.81 (1H, d,  $J = 2.6$  Hz, Ar-6H), 3.82 (3H, s, OMe), 3.74 (3H, s, OMe); **<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*)  $\delta$  154.0(ArC-1), 150.3(ArC-4), 119.0(ArC), 113.6(ArC), 112.9(ArC), 112.0(ArC-2), 56.8(OMe), 55.9(OMe).<sup>59</sup>

### 9.8 Preparation of 2',5'-Dimethoxybiphenyl-2-carbaldehyde<sup>64</sup> **114**

2-Bromo-1,4-dimethoxynaphthalene **112** (1eq., 250mg, 1.15mmol), 2-formylphenylboronic acid **98** (1.5eq., 207mg, 1.38mmol), tetrakis(triphenylphosphine)palladium(0) (0.1eq., 133mg, 0.29mmol) and cesium fluoride (2.5eq., 437mg, 2.88mmol) were added to a microwave vial in dimethoxy ethane (2mL) as solvent and the solution was degassed for two minutes. The reaction mixture was transferred to a microwave reactor at 150 °C and 150 W power with vigorous stirring for thirty minutes. On completion, the reaction mass was filtered off, adsorbed on silica and subjected to column chromatography (5% EtOAc/Hexane) to obtain the product **114** as white low melting solid (246mg, 1.02mmol, 88%).

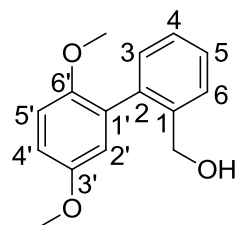


$R_f$  0.40 (20% EtOAc/Hexane); **<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*)  $\delta$  9.79 (1H, s, CHO), 8.01-7.97 (1H, m, ArH), 7.64 (1H, td,  $J = 7.5, 1.2$  Hz, ArH), 7.48 (1H, t,  $J = 7.6$  Hz, ArH), 7.38-7.34 (1H, m, ArH), 6.94 (1H, dd,  $J = 8.9, 3.0$  Hz, ArH), 6.90 (1H, d,  $J = 8.9$  Hz, ArH), 6.87 (1H, d,  $J = 3.0$  Hz,

ArH), 3.81 (3H, s, OMe), 3.67 (3H, s, OMe);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  192.5(C=O), 153.8(ArC), 150.7(ArC), 141.6(ArC), 134.0(ArC), 133.7(ArC), 131.0(ArC), 127.8(ArC), 127.7 (ArC), 126.6(ArC), 117.3(ArC), 114.4(ArC), 111.8(ArC), 55.9(OMe), 55.8(OMe).<sup>64</sup>

### 9.9 Preparation of (2',5'-Dimethoxybiphenyl-2-yl)methanol **115**

2',5'-dimethoxybiphenyl-2-carbaldehyde **114** (1eq., 200mg, 0.826mmoles) was taken up in tetrahydrofuran (20mL) and lithium aluminium hydride (2eq., 63.0mg, 1.65 mmoles) was added to it at 0 °C under inert conditions. The reaction mixture was allowed to warm up to room temperature and reaction was stirred under inert conditions for one hour. On completion the temperature was again reduced to 0 °C and an ice cold aqueous 2 M sodium hydroxide solution (10mL) was added to it dropwise to quench the unreacted lithium aluminium hydride. The mixture was then transferred to a separating funnel and washed repeatedly with diethyl ether (30mL×3). The combined organic phases were washed with water (20mL) and brine (20mL), dried over anhydrous magnesium sulfate, filtered and solvent was removed in vacuum to isolate crude product which was purified using column chromatography (20% EtOAc/Hexane) to isolate the product **97** as a clear oil (244mg, 0.821mmoles, 100%).

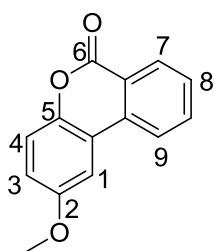


$R_f$  0.30(20% EtOAc/Hexane); FTIR( $\nu/\text{cm}^{-1}$ ): 3422 (O-H), 2999-2835 (C-H), 1600-1439 (C=C), 1274-1210 (C-O);  $^1\text{H}$  NMR (300 MHz, Chloroform-*d*)  $\delta$  7.55 (1H, d,  $J$  = 7.5 Hz, ArH), 7.44-7.34 (2H, m, ArH), 7.25-7.20 (1H, m, ArH), 6.95-6.87 (2H, m, ArH), 6.76 (1H, d,  $J$  = 2.9 Hz, ArH), 4.44 (1H, d,  $J$  = 6.6 Hz, one of  $\text{CH}_2\text{OH}$ ), 4.40 (1H, d,  $J$  = 6.6 Hz, one of  $\text{CH}_2\text{OH}$ ), 3.79 (3H, s, OMe), 3.68 (3H, s, OMe), 2.42 (1H, s, OH);  $^{13}\text{C}$  NMR (75 MHz, Chloroform-*d*)  $\delta$  153.9(ArC-3'), 150.6(ArC-1'), 139.3(ArC), 137.4(ArC), 131.1(ArC), 130.1(ArC), 128.8(ArC), 28.1(ArC), 127.7(ArC), 117.0(ArC), 113.6(ArC), 112.8(ArC), 63.8( $\text{CH}_2\text{OH}$ ), 56.7(OMe), 55.7(OMe); HRMS (ESI-): Found  $\text{M}^+ - \text{OH}$  227.2784,  $\text{C}_{15}\text{H}_{15}\text{O}_2$  ( $\text{M}^+ - \text{OH}$ ) requires 227.2784,  $m/z$  227.1065(100%), 244.1091(15%).

### 9.10 Preparation of 2-Methoxy-6*H*-benzo[*c*]chromen-6-one **110**

(2',5'-Dimethoxybiphenyl-2-yl)methanol **115** (1eq., 50.0mg, 0.204mmoles) was taken up in carbontetrachloride (5mL) and *N*-bromosuccinimide (1.5eq., 54.0mg, 0.307mmoles) was added. AIBN (0.01eq., 0.5mg, 0.002mmoles) was added to this stirring mixture and the reaction was allowed to stir under reflux for eighteen hours. After this time an aqueous

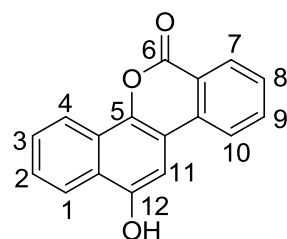
sodium sulfite solution (5mL) was added to the reaction mass to quench unreacted *N*-bromosuccinimide and the solution was transferred to a separating funnel containing water (10mL). The organic phase was separated and the aqueous phase was washed repeatedly with dichloromethane (10mL×3). The combined organic phases were washed with brine (20mL), dried over anhydrous magnesium sulfate, filtered and solvent was reduced under removed pressure to afford the crude product which was purified by column chromatography (10% EtOAc/Hexane) to isolate the product **110** as a white solid (23.0mg, 0.100mmoles, 49%).



**R<sub>f</sub>** 0.45(20% EtOAc/Hexane); **mp.** 117-119 °C CH<sub>2</sub>Cl<sub>2</sub>; **FTIR**(v/cm<sup>-1</sup>): 2938 (C-H), 1722 (C=O), 1664-1420 (C=C), 1277-1225 (C-O); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 8.41 (1H, dd, *J* = 7.9, 1.0 Hz, ArH), 8.07 (1H, d, *J* = 8.1 Hz, ArH), 7.83 (1H, td, *J* = 7.8, 1.4 Hz, ArH), 7.64-7.55 (1H, m, ArH), 7.50 (1H, d, *J* = 2.9 Hz, ArH), 7.31 (1H, d, *J* = 9.0 Hz, ArH), 7.05 (1H, dd, *J* = 9.0, 2.9 Hz, ArH), 3.91 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) δ 161.3(C=O), 156.4(ArC), 145.7(ArC), 134.7(ArC), 134.7(ArC), 130.7(ArC), 129.0(ArC), 121.7(ArC), 121.4(ArC), 118.7(ArC), 118.6(ArC), 117.1(ArC), 106.4(ArC), 55.9(OMe); **HRMS** (ESI<sup>+</sup>): Found *M*<sup>+</sup> + H 227.0701, C<sub>14</sub>H<sub>11</sub>O<sub>3</sub> (*M*<sup>+</sup> + H) requires 227.0709, *m/z* 227.0701(100%), 226.0625(30%).

### 9.11 Preparation of 12-hydroxy-6*H*-dibenzo[*c,h*]chromen-6-one **120**

2-(1,4-Dimethoxynaphthalen-2-yl)benzaldehyde **99** (1eq., 50.0mg, 0.171mmoles), *N*-bromosuccinimide (2eq., 61.0mg, 0.342mmoles) and 5mL of dichloromethane were added to a round bottom flask. The reaction was allowed to stir at room temperature under atmospheric conditions for eighteen hours over which time the colour changed from yellow to bright red. On completion, an aqueous saturated solution of sodium sulfite (10mL) was added to quench unreacted *N*-bromosuccinimide and then the organic material was extracted into dichloromethane (5mL×3). The organic phases were collected and washed with brine (20mL), dried on anhydrous magnesium sulfate, filtered and solvent was removed under reduced pressure to obtain a residue which was subjected to column chromatography (20% EtOAc/ Hexane) to obtain the product **120** as yellow solid (26.2mg, 0.099mmoles, 57%).

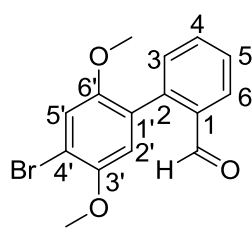


**R<sub>f</sub>** 0.80 (20% EtOAc/Hexane); **mp.** 99-101 °C CH<sub>2</sub>Cl<sub>2</sub>; **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 9.95 (1H, s, OH), 8.26 (1H, dd, *J* = 5.5, 3.4

Hz, ArH), 8.12 (1H, dd,  $J = 5.5, 3.5$  Hz, ArH), 8.02 – 7.94 (1H, m, ArH), 7.85-7.67 (5H, m, ArH), 7.38 (1H, d,  $J = 7.2$  Hz, ArH);  $^{13}\text{C}$  NMR (75 MHz, Chloroform- $d$ )  $\delta$  191.3(ArC), 181.0(ArC), 177.8(ArC), 150.9(ArC), 136.8(ArC), 135.1(ArC), 134.3(ArC), 134.1(ArC), 134.0(ArC), 133.9(ArC), 133.6(ArC), 131.9(ArC), 131.3(ArC), 130.2(ArC), 129.8(ArC), 127.7(ArC), 127.4(ArC); HRMS (ESI-): Found  $M^+ - H$  261.0545,  $\text{C}_{17}\text{H}_{10}\text{O}_3$  ( $M^+ - H$ ) requires 261.06,  $m/z$  261.0545(100%), 262.0620(55%).

### 9.12 Preparation of 4'-Bromo-2',5'-dimethoxybiphenyl-2-carbaldehyde **121**

*N*-bromosuccinimide (1.5eq., 54.0mg, 0.307mmoles) was added to a stirring solution of (2',5'-dimethoxybiphenyl-2-yl)methanol **115** (1eq., 50.0mg, 0.204mmoles) in chloroform (5mL) and then AIBN (0.01eq., 0.5mg, 0.002mmoles) was added to this stirring mixture. The reaction was allowed to stir under reflux for eighteen hours. On completion an aqueous sodium sulfite solution (5mL) was added to the reaction mass to quench the unreacted *N*-bromosuccinimide and the solution was transferred to a separating funnel containing water (10mL). The organic phase was separated and aqueous phase was washed repeatedly with dichloromethane (10mL $\times$ 3). The combined organic phases were washed with brine (20mL), dried over anhydrous magnesium sulfate, filtered and then the solvent was removed under reduced pressure to isolate the crude product which was purified by column chromatography (10% EtOAc/Hexane) to furnish the product **121** as a low melting white solid (41.2mg, 0.127mmoles, 63%).



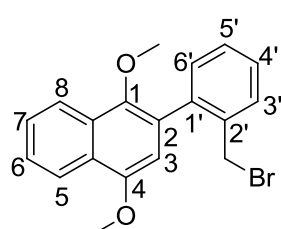
$R_f$  0.61(20% EtOAc/Hexane); FTIR( $\nu/\text{cm}^{-1}$ ): 2934-2748(C-H), 1691(CHO), 1596(C=C), 1208(C-O), 656(C-Br);  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  9.78 (1H, s, CHO), 8.02-7.97 (1H, m, ArH), 7.65 (1H, d,  $J = 1.2$  Hz, ArH), 7.51 (1H, s, ArH), 7.34 (1H, d,  $J = 7.6$  Hz, ArH-3), 7.18 (1H, s, ArH-5'), 6.86 (1H, s, ArH-2'), 3.88 (3H, s, OMe), 3.69 (3H, s, OMe);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  192.1 (C=O), 150.8 (ArC-3'), 150.4(ArC-6'), 140.7(ArC), 134.0(ArC), 133.7(ArC), 130.9(ArC), 128.2(ArC), 126.9(ArC), 126.7(ArC-4'), 116.3(ArC), 115.2(ArC), 112.1(ArC), 57.0(OMe), 56.2(OMe); HRMS (ESI+): Found  $M^+ + H$  321.0120,  $\text{C}_{15}\text{H}_{14}\text{BrO}_3$  ( $M^+ + H$ ) requires 321.0127,  $m/z$  320.0043(100%), 322.0043(97%).

### 9.13 Preparation of 2-(2-(Bromomethyl)phenyl)-1,4-dimethoxynaphthalene **123**

(2-(1,4-Dimethoxynaphthalen-2-yl)phenyl)methanol **86** (1eq., 100mg, 0.340mmoles) was dissolved in dry dichloromethane (10mL). Triphenyl phosphine (5eq., 446mg, 1.70mmoles) and carbontetrabromide (5eq., 563mg, 1.70mmoles) were added to it and the reaction was



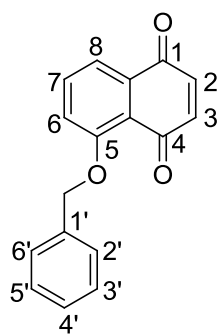
allowed to stir at room temperature and under an argon atmosphere for three hours after which time the reaction mixture goes from clear to bright orange in color. On completion of the reaction the dichloromethane was removed under vacuum and the resulting orange residue was subjected to column chromatography (10% EtOAc/Hexane) to obtain product **105** as a yellow oil (85.0mg, 0.237mmoles, 67%).



**R<sub>f</sub>** 0.35 (20% EtOAc/Hexane); **FTIR**( $\nu/\text{cm}^{-1}$ ): 3056(C-H), 1591(C=C), 1365(C-O), 690(C-Br); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  8.29 (1H, d,  $J$  = 7.7 Hz, ArH), 8.13 (1H, d,  $J$  = 8.3 Hz, ArH), 7.56 (3H, ddd,  $J$  = 15.1, 11.3, 5.8 Hz, ArH), 7.39 (3H, s, ArH), 6.76 (1H, s, ArH-3), 4.55 (1H, d,  $J$  = 10.2 Hz, one of  $\text{CH}_2\text{Br}$ ), 4.47 (1H, d,  $J$  = 10.2 Hz, one of  $\text{CH}_2\text{Br}$ ), 3.99 (3H, s, OMe), 3.49 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  151.5(ArC-4), 146.5(ArC-1), 138.6(ArC), 136.2(ArC), 130.9(ArC), 130.7(ArC), 128.7(ArC), 128.3(ArC), 128.2(ArC), 127.9(ArC), 126.9(ArC), 126.3(ArC), 125.8(ArC), 122.3(ArC), 122.2(ArC), 106.3(ArC), 61.5(OMe), 55.8(OMe), 32.5( $\text{CH}_2\text{Br}$ ).

#### 9.14 Preparation of 5-(Benzyloxy)naphthalene-1,4-dione<sup>68</sup> **40**

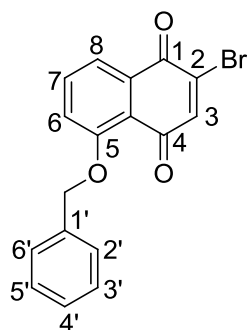
Commercially available juglone **129** (1eq., 2.50g, 14.30mmoles) was dissolved in carbontetrachloride (50mL) in a 100mL round bottom flask. To this solution benzyl bromide (2q, 4.91g, 3.4mL, 28.00mmoles) and silver oxide (2eq., 6.65g, 28.00mmoles) were added. The reaction mixture was then heated under reflux and inert conditions for seventy two hours. The reaction was allowed cooled to room temperature and was filtered through celite to get rid of the solid silver oxide. Water was then added to the crude mixture and the mixture was transferred to a separating funnel. The crude mixture obtained was washed with chloroform (50mL $\times$ 3). The combined organic phases were washed with brine (100mL), dried over anhydrous magnesium sulfate, filtered and then the solvent was removed in *vacuo* to obtain 5-(benzyloxy)naphthalene-1,4-dione **40** as yellow solid (3.10g, 12.40mmoles, 88%).



**R<sub>f</sub>** 0.68 (20% EtOAc/Hexane); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) 7.74 (1H, dd,  $J$ =7.6, 0.9 Hz, ArH), 7.65 (1H, dd,  $J$ =8.0, 7.5 Hz, ArH), 7.58 (2H, d,  $J$ =7.3 Hz, ArH), 7.42 (2H, t,  $J$ = 7.3 Hz, ArH), 7.33–7.37 (2H, m, ArH), 6.89 (2H, s, ArH-2,3), 5.30 (2H, s,  $\text{CH}_2$ ); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) 185.2(ArC-1), 184.1(ArC-4), 158.5(ArC-5), 136.0(ArC), 140.9 (ArC), 136.2(ArC), 134.8(ArC), 134.1 (ArC), 130.2(ArC), 128.7 (ArC), 128.0 (ArC), 126.6 (ArC), 119.6 (ArC), 119.5(ArC), 70.9( $\text{CH}_2$ ).<sup>68</sup>

### 9.15 Preparation of 5-(Benzyloxy)-2-bromonaphthalene-1,4-dione<sup>69</sup> **25**

Bromine (1.09eq., 35.0mg, 0.01mL, 0.436mmoles) in dichloromethane (5mL) maintained at 0 °C was added dropwise to a stirring solution of 5-(benzyloxy)naphthalene-1,4-dione **40** (1eq., 100mg, 0.400mmoles) in dichloromethane (5mL) also at 0 °C and reaction was allowed to stir for fifteen minutes at 0 °C under inert conditions. After that the reaction was allowed to warm up and solvent and unreacted bromine was removed *in vacuo* until most of dichloromethane evaporated. To this residue 10% aqueous acetic acid (1mL) was added and the mixture was again subjected to vacuum to leave behind an oily residue. Ethanol (10mL) was added to the thick mixture and the reaction was stirred under reflux for fifteen minutes after which it was allowed to cool down to room temperature. Water (10mL) was added and the mixture transferred to a separating funnel and solution was then extracted with dichloromethane (10mL×3). The organic phase was combined and washed with aqueous saturated solution of sodium bicarbonate (10mL) and brine (10mL) respectively, dried over anhydrous magnesium sulfate, filtered and solvent was removed in *vacuo* to obtain 5-(benzyloxy)-2-bromonaphthalene-1,4-dione **25** as a crude product which was further purified by column chromatography (20% EtOAc/hexane) to obtain the product **25** as a bright yellow solid (97.0mg, 0.282mmoles, 74%).

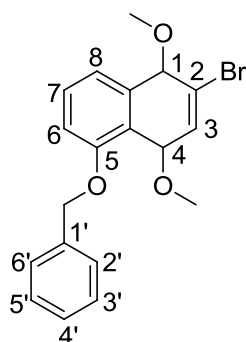


**R<sub>f</sub>** 0.75 (15% EtOAc/Hexane); <sup>1</sup>H NMR (300 MHz, Chloroform-*d*) δ 7.87-7.80 (1H, m, ArH), 7.64 (1H, t, *J* = 8.1 Hz, ArH), 7.56 (2H, d, *J* = 7.2 Hz, ArH), 7.38 (5H, dt, *J* = 17.9, 7.1 Hz, ArH), 5.31 (2H, s, CH<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, Chloroform-*d*) δ 181.3(ArC-4), 178.3(ArC-1), 158.8(ArC-5), 142.3(ArC), 136.9(ArC), 135.8(ArC), 134.9(ArC), 133.1(ArC), 128.7(ArC), 128.1(ArC), 126.7(ArC), 120.9(ArC), 120.1(ArC), 119.8(ArC), 72.0(CH<sub>2</sub>).<sup>69</sup>

### 9.16 Preparation of 5-(Benzyloxy)-2-bromo-1,4-dimethoxynaphthalene<sup>70</sup> **26**

5-(Benzyloxy)-2-bromonaphthalene-1,4-dione **25** (1eq., 1.24g, 3.79mmoles) was dissolved in diethyl ether (100mL) and the solution was vigorously stirred. To this, sodium dithionite (10eq., 5.39g, 37.90mmoles) dissolved in water (100mL) was added slowly. The mixture was allowed to stir for thirty minutes over which time the solution changed colour from dark brown to almost clear pale yellow solution. The reaction mixture was transferred to a separating funnel and organic phase was collected and washed with brine (100mL), dried over anhydrous magnesium sulfate, filtered and solvent was removed in *vacuo* to obtain 5-(benzyloxy)-2-bromonaphthalene-1,4-diol as dark brown oil which was an unstable

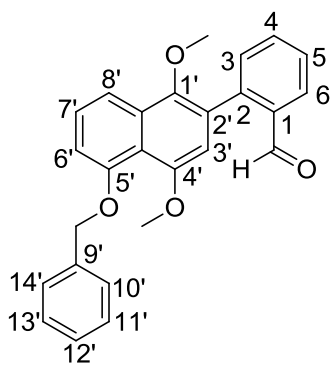
intermediate. Immediately 50mL of dry acetone was added to the flask containing 5-(benzyloxy)-2-bromonaphthalene-1,4-diol under inert conditions and the solution was stirred vigorously. To this solution, potassium carbonate (12eq., 6.24g, 45.28moles) was added followed by dimethyl sulfate (7eq., 3.33g, 2.5mL, 26.40moles) and the reaction was allowed to stir under inert conditions at reflux for eighteen hours. After this time the reaction was allowed to cool down to room temperature, was filtered through celite to remove potassium carbonate and the solvent was removed in *vacuo* to obtain a dark brown oil which was dissolved in stirring diethyl ether (100mL). Aqueous ammonia was slowly added to this stirring solution in portions (5mL) until bubbling stopped. The solution was transferred to a separating funnel and organic layer was collected which was washed with 15% hydrochloric acid (50mL), water (50mL) and brine (50mL) respectively. The organic layer was collected, dried over anhydrous magnesium sulfate, filtered and solvent was removed in *vacuo* to obtain a as light brown solid which was further purified by column chromatography (5% EtOAc/Hexane) to yield the product **26** as a white solid (960mg, 2.5moles, 74%).



**R<sub>f</sub>** 0.65 (20% EtOAc/Hexane); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  7.70 (1H, d, *J* = 8.4 Hz, ArH), 7.56 (2H, d, *J* = 7.5 Hz, ArH), 7.47-7.27 (4H, m, ArH), 6.95 (1H, d, *J* = 7.8 Hz, ArH), 6.90 (1H, s, ArH-3), 5.17 (2H, s, CH<sub>2</sub>), 3.91 (3H, s, OMe), 3.89 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  156.6(ArC-1), 154.0(ArC-4), 146.6(ArC-5), 137.3(ArC), 131.8(ArC), 128.4(ArC), 127.6(ArC), 127.6(ArC), 126.9(ArC), 118.1(ArC), 115.1(ArC), 112.7(ArC), 109.7(ArC), 109.2(ArC-3), 71.4(CH<sub>2</sub>), 61.2(OMe), 56.6(OMe).<sup>70</sup>

### 9.17 Preparation of 2-(5-(Benzyloxy)-1,4-dimethoxynaphthalen-2-yl)benzaldehyde **131**

5-(Benzyloxy)-2-bromo-1,4-dimethoxynaphthalene **26** (1eq., 250mg, 0.669mmoles), 2-formylphenylboronic acid **98** (1.5eq., 151mg, 1.004moles), tetrakis(triphenylphosphine)palladium(0) (0.1eq., 77mg, 0.067mmoles) and cesium fluoride (2.5eq., 253mg, 1.67mmoles) were transferred to a microwave vial using dimethoxy ethane (2mL) as the solvent. The resulting solution was degassed for two minutes and then subjected to a microwave reactor at 150 °C and 150 W with vigorous stirring for thirty minutes. On completion, the reaction mass was filtered, adsorbed on silica and then subjected to column chromatography (5% EtOAc/Hexane) to obtain the product **131** as a yellow solid (249mg, 0.625mmoles, 93%)

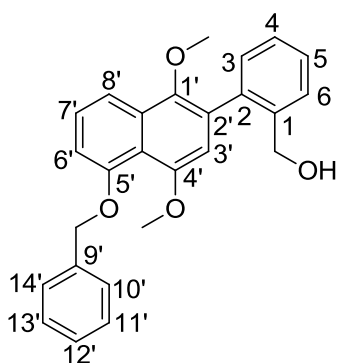


**R<sub>f</sub>** 0.35 (30% EtOAc/Hexane); **mp.** 117-118 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **FTIR**(ν/cm<sup>-1</sup>): 2925(C-H), 1700(CHO), 1596(C=C), 1127(C-O); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 9.90 (1H, s, CHO), 8.09 (1H, d, *J* = 7.7 Hz, ArH), 7.80 (1H, d, *J* = 8.3 Hz, ArH), 7.71 (1H, t, *J* = 7.3 Hz, ArH), 7.62 (2H, d, *J* = 7.3 Hz, ArH), 7.59-7.52 (2H, m, ArH), 7.45 (3H, dt, *J* = 13.5, 7.7 Hz, ArH), 7.35 (1H, d, *J* = 7.1 Hz, ArH), 7.03 (1H, d, *J* = 7.6 Hz, ArH), 6.79 (1H, s, ArH-3'), 5.25 (2H, s, CH<sub>2</sub>), 3.96 (3H, s, OMe), 3.38 (3H, s, OMe); **<sup>13</sup>C**

**NMR** (75 MHz, Chloroform-*d*) δ 192.4 (C=O), 156.4(ArC), 153.8(ArC), 146.9(ArC), 141.6(ArC), 137.4(ArC), 133.7(ArC), 133.5(ArC), 131.3(ArC), 130.9(ArC), 128.4(ArC), 128.0(ArC), 127.6(ArC), 127.4(ArC), 127.1(ArC), 127.0(ArC), 126.1(ArC), 119.0(ArC), 115.6(ArC), 109.6(ArC), 108.1(ArC-3'), 71.5(CH<sub>2</sub>), 60.7(OMe), 56.7(OMe).

### 9.18 Preparation of (2-(5-(Benzyloxy)-1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **132**

2-(5-(Benzyloxy)-1,4-dimethoxynaphthalen-2-yl)benzaldehyde **131** (1eq., 260mg, 0.634mmoles) was dissolved in freshly distilled dry tetrahydrofuran (20mL) in a 50mL round bottom flask under inert conditions. To this stirring solution was added sodium borohydride (3eq., 72.0mg, 1.90mmoles) and the reaction mass was allowed to stir at room temperature for twelve hours over which time the reaction changes its color from a yellow to a clear solution. On completion of the reaction, ice cold water (10mL) was added drop wise to the reaction mass to quench the unreacted sodium borohydride. The solution was transferred to a separating funnel and organic material was extracted into diethyl ether (20mL×3). The combined organic phases were washed with brine (30mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo* to afford a residue which was purified by means of column chromatography (30% EtOAc/Hexane) to furnish pure product **109** as a white solid (260mg, 0.631mmoles, 99%,).



**R<sub>f</sub>** 0.44 (50% EtOAc/Hexane); **mp.** 115-117 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **FTIR**(ν/cm<sup>-1</sup>): 3489(OH), 2934(C-H), 1573(C=C), 1257(C-O); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 7.82-7.72 (1H, m, ArH), 7.67-7.57 (3H, m, ArH), 7.51-7.28 (7H, m, ArH), 6.99 (1H, d, *J* = 7.4 Hz, ArH), 6.66 (1H, s, ArH-3'), 5.23 (2H, s, CH<sub>2</sub>), 4.43 (1H, d, *J* = 10.5 Hz, one of CH<sub>2</sub>OH), 4.37 (1H, d, *J* = 10.5 Hz, one of CH<sub>2</sub>OH), 3.90 (3H, s, OMe), 3.46 (3H, s, OMe); **<sup>13</sup>C NMR** (300

MHz, CDCl<sub>3</sub>)  $\delta$  156.5(ArC-4'), 153.7(ArC-1), 146.1(ArC), 139.4(ArC), 137.7(ArC), 137.5(ArC), 131.3(ArC), 130.0(ArC), 129.9(ArC), 129.8(ArC), 128.4(ArC), 128.3(ArC), 127.9(ArC), 127.6(ArC), 127.2(ArC), 127.0(ArC), 118.5(ArC), 115.4(ArC), 109.2(ArC), 108.4(ArC-3'), 71.5(CH<sub>2</sub>), 64.1(OMe), 61.5(OMe), 56.6(CH<sub>2</sub>OH); **HRMS** (ESI<sup>+</sup>): Found M<sup>+</sup>+H 401.1732, C<sub>26</sub>H<sub>23</sub>O<sub>3</sub> (M<sup>+</sup>+H) requires 401.2469, m/z 383.1635(100%), 401.1732(20%).

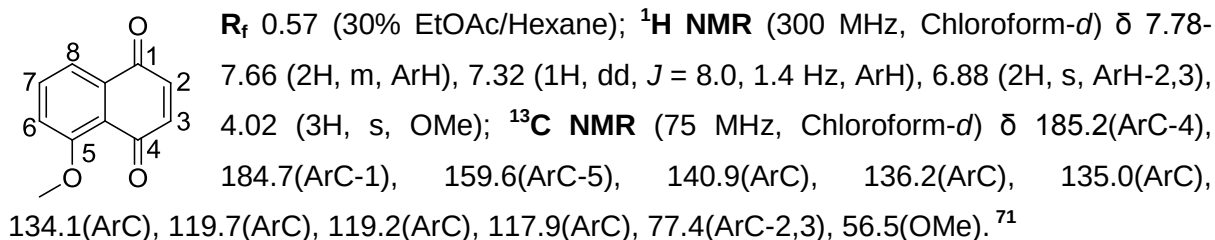
## 9.19 Preparation of 5-Methoxynaphthalene-1,4-dione<sup>71</sup> **137**

### 9.19.1 Method 1

4,8-Dimethoxynaphthalen-1-ol **145** (1eq., 1.40g, 6.82mmoles) was transferred in to a 100mL round bottom flask containing 20mL acetonitrile at room temperature under atmospheric conditions. When this stirring solution became clear, ceric ammonium nitrate (2.5eq., 9.34g, 17.05mmoles) dissolved in 20mL of water was added dropwise. The color of reaction changes immediately from brown to very bright yellow and was allowed to stir at the same conditions for another five minutes after which time the reaction mixture was filtered through a pad of celite, and then transferred to a beaker carrying a 100mL aqueous saturated solution of sodium bicarbonate stirring at room temperature. The solution bubbled vigorously and once the bubbling ceased the solution was transferred to a separating funnel and was extracted with dichloromethane (50mL×3). The organic phases were combined and washed with brine (100mL), dried over anhydrous magnesium sulfate, filtered and then the solvent was removed in *vacuo* to obtain a residue which was subjected to column chromatography (15% EtOAc/Hexane) to obtain pure 5-methoxynaphthalene-1,4-dione **137** (1.27g, 6.75mmoles, 98%).<sup>71</sup>

### 9.19.2 Method 2

Commercially available juglone **129** (1eq., 2.50g, 14.36mmoles) was dissolved in 50mL of dichloromethane in a 100mL round bottom flask. To this mixture, methyl iodide (2eq., 4.08g, 1.78mL, 28.73mmoles) and silver oxide (2eq, 6.65g, 28.73mmoles) were added and the reaction was allowed to stir at room temperature and under inert conditions for forty eight hours. On completion the reaction mixture was filtered through a pad of celite and after evaporation of the solvent it was purified by means of column chromatography to obtain 5-methoxynaphthalene-1,4-dione **137** as off-white powder (1.98g, 10.52mmoles, 73%).



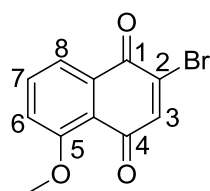
## 9.20 Preparation of 2-Bromo-5-methoxynaphthalene-1,4-dione<sup>67</sup> **138**

### 9.20.1 Method 1

Bromine (1.09eq., 230mg, 0.074mL, 1.44.mmoles) dissolved in chloroform (10mL) was added dropwise to 5-methoxynaphthalene-1,4-dione **137** (1eq., 250mg, 1.32mmoles) in chloroform (25mL) while stirring at 0 °C under argon. The reaction mixture was allowed to stir at the same temperature for fifteen minutes. After this time, chloroform and unreacted bromine were removed in vacuum, until a few mLs of solvent were left. Aqueous 10% acetic acid (2mL) was added and the thick residue was again subjected to vacuum until it became a thick moist mass. Ethanol (25mL) was added to it and the reaction mass was allowed to stir under reflux for fifteen minutes. The reaction was allowed to cool down to room temperature and 50mL of aq. saturated solution of sodium bicarbonate was added. The solution was transferred to a separating funnel and extracted with dichloromethane (25mL×3). The combined organic phases were washed with brine (100mL) and dried over anhydrous magnesium sulfate, then filtered through a pad of celite and solvent was removed in vacuum to afford the crude product as dark brown oil which was purified through column chromatography (20% EtOAc/Hexane) to procure 2-bromo-5-methoxynaphthalene-1,4-dione **138** as bright orange solid in 73% yield (259mg, 0.969mmoles).

### 9.20.2 Method 2

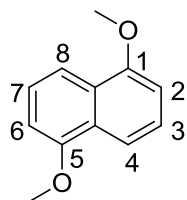
2-Bromo-5-hydroxynaphthalene-1,4-dione **23** (1eq., 758mg, 3.01mmoles) was taken up in a 100mL round bottom flask with 50mL of dichloromethane under inert conditions and at room temperature. To this solution, methyl iodide (2eq., 858mg, 0.38mL, 6.03mmoles) and silver oxide (2eq., 1.37g, 6.03mmoles) were added and the reaction was allowed to stir at the above mentioned reaction conditions for seventy two hours. On completion, the reaction mass was filtered through a pad of celite and then immediately subjected to column chromatography (20% EtOAc/Hexane) to obtain 2-bromo-5-methoxynaphthalene-1,4-dione **138** as a bright orange solid (698mg, 2.61mmoles, 87%).



$R_f$  0.52(30% EtOAc/Hexa)  $^1\text{H NMR}$  (300 MHz, Chloroform-*d*)  $\delta$  7.83 (1H, d,  $J$  = 7.6 Hz, ArH), 7.70 (1H, t,  $J$  = 8.1 Hz, ArH), 7.40 (1H, d,  $J$  = 1.3 Hz, ArH-3), 7.35 (1H, d,  $J$  = 8.5 Hz, ArH), 4.02 (3H, s, OMe);  $^{13}\text{C NMR}$  (75 MHz, Chloroform-*d*)  $\delta$  181.4(ArC-1), 178.2(ArC-4), 160.0(ArC-5), 142.3(ArC), 136.8(ArC), 135.1(ArC), 133.1(ArC), 120.6(ArC), 119.3(ArC), 118.5(ArC), 56.6(OMe).<sup>67</sup>

### 9.21 Preparation of 1,5-Dimethoxynaphthalene<sup>72</sup> **143**

Naphthalene-1,5-diol **142** (1eq., 10.00g, 62.50mmoles) was dissolved in dry acetone (400mL) in a 1L round bottom and the solution was stirred until all of the naphthalene-1,5-diol **142** dissolved. Potassium carbonate (3eq., 25.80g, 18.72mmoles) and dimethyl sulfate (3eq., 23.60g, 17.7mL, 18.72mmoles) were added to the stirring solution before the reaction was allowed to stir under reflux for twelve hours. The progress of reaction was monitored by thin layer chromatography over which time it changes color from black to reddish brown. On completion, the reaction was allowed to cool down to room temperature and filtered through a pad of celite to remove potassium carbonate. The solution was cooled down to 0 °C and aqueous ammonia was added slowly in portions (5mL) to obtain a brown precipitate which were washed with acetone (50mL×3), filtered off and dried in *vacuo* to obtain 1,5-dimethoxynaphthalene **143** as a light brown solid (10.05g, 53.40mmoles, 86%).

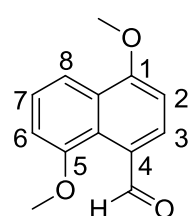


$R_f$  0.35 (20% EtOAc/Hexane);  $^1\text{H NMR}$  (300 MHz, Chloroform-*d*)  $\delta$  7.83 (2H, d,  $J$  = 8.5 Hz, ArH), 7.37 (2H, t,  $J$  = 8.0 Hz, ArH), 6.83 (2H, d,  $J$  = 7.7 Hz, ArH), 3.98 (6H, s, OMe×2);  $^{13}\text{C NMR}$  (75 MHz, Chloroform-*d*)  $\delta$  155.2(ArC-1,5), 126.6(ArC), 125.2(ArC), 114.2(ArC), 104.5(ArC), 55.5(OMe×2).<sup>72</sup>

### 9.22 Preparation of 4,8-Dimethoxy-1-naphthaldehyde<sup>73</sup> **144**

Toluene (18mL) and dimethylformamide (2.4eq., 6.70g, 7.10mL, 91.80mmoles) were added to a 100mL round bottom flask containing 1,5-dimethoxynaphthalene **143** (1eq., 7.20g, 38.25mmoles) under argon while the temperature was maintained at 0 °C. At the same temperature phosphoryl chloride (1.6eq., 9.38g, 5.60mL, 61.20mmoles) was added dropwise. The reaction mixture was allowed to stir for thirty minutes at 0 °C after which it was allowed to reach room temperature and then was refluxed for three hours over which time the reaction changes its colour from dark brown to dark red. On completion, the reaction was allowed to cool down to room temperature and ethyl acetate (100mL) was added. Then this solution was poured over stirring aqueous 10% sodium hydroxide (100mL)

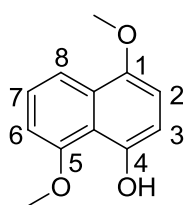
in a 250mL beaker and stirred for five minutes. Later the solution was transferred to a separating funnel and the organic layer was collected. The aqueous phase was washed with ethyl acetate (25mL×3) and the combined organic phases were washed with brine (100mL), dried on anhydrous magnesium sulfate, filtered through a pad of celite and solvent removed in *vacuo* to obtain product **120** as a brown powder (6.57g, 30.25mmoles, 79%).



**R<sub>f</sub>** 0.73 (15% EtOAc/Hexane); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  11.04 (1H, s, CHO), 8.07 (1H, d, *J* = 8.3 Hz, ArH), 7.95 (1H, dd, *J* = 8.5, 0.8 Hz, ArH), 7.44 (1H, t, *J* = 8.1 Hz, ArH), 7.03 (1H, d, *J* = 7.7 Hz, ArH), 6.89 (1H, d, *J* = 8.3 Hz, ArH), 4.05 (3H, s, OMe), 4.00 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  194.6(C=O), 159.5(ArC-4), 156.4(ArC-1), 129.4(ArC), 127.7(ArC), 127.1(ArC), 125.8(ArC), 124.7(ArC), 115.3(ArC), 107.8(ArC), 103.9(ArC), 55.9(OMe), 55.6(OMe).<sup>73</sup>

### 9.23 Preparation of 4,8-Dimethoxynaphthalen-1-ol<sup>74</sup> **145**

At 0 °C, 4,8-dimethoxy-1-naphthaldehyde **144** (1eq., 1.00g, 4.60mmoles) was dissolved in methanol (10mL) in a 100mL round bottom flask and stirred vigorously. To this hydrogen peroxide (1.3eq., 203mg, 0.18mL, 5.90mmoles) was added followed by addition of sulfuric acid (0.1mL). The resulting thick mass was stirred vigorously and eventually everything dissolves. The reaction was allowed to stir for another twelve hours at room temperature under atmospheric conditions. On completion, the reaction mixture was poured onto a stirring solution of aqueous saturated solution of sodium bicarbonate (50mL) maintained at a temperature of 0 °C and was then immediately extracted in ethyl acetate. (50mL×3). The combined organic phases were collected and washed with brine (100mL), dried over anhydrous magnesium sulfate, filtered and then solvent was removed in *vacuo* to obtain the crude product which was then purified through column chromatography (10% EtOAc/Hexane) to yield the product **121** as light brown solid (769mg, 3.76mmoles, 80%).

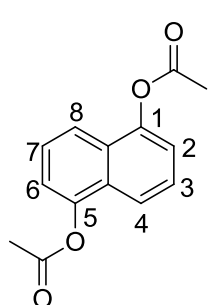


**R<sub>f</sub>** 0.29 (30% EtOAc/Hexane); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  8.94 (1H, s, OH), 7.85 (1H, dd, *J* = 0.8, 8.5 Hz, ArH), 7.33 (1H, dd, *J* = 8.0, 8.1 Hz, ArH), 6.84 (1H, d, *J* = 7.7 Hz, ArH), 6.77 (1H, d, *J* = 8.4 Hz, ArH-2) 6.75 (2H, *J* = 8.4 Hz ArH-3), 4.05 (3H, s, OMe), 3.93 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  155.9(ArC-4), 148.1(ArC-5), 147.9(ArC-1), 127.9(ArC), 125.1(ArC), 115.9(ArC), 115.6(ArC), 109.0(ArC), 106.28(ArC), 104.9(ArC), 56.1(OMe), 56.0(OMe).<sup>74</sup>



## 9.24 Preparation of Naphthalene-1,5-diyl diacetate<sup>75</sup> **22**

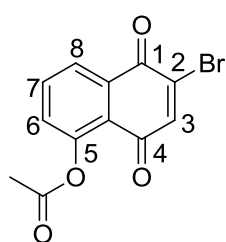
Commercially available naphthalene-1,5-diol **142** (1eq., 10.00g, 62.40mmol), acetic anhydride (5eq., 57.36g, 53mL, 56.19mmol) and pyridine (10eq., 49.35g, 50.4mL, 62.40mmol) were added to a 250mL round bottom flask and stirred at room temperature under argon for twelve hours. On completion, water (1000mL) was added to the reaction to quench unreacted acetic anhydride and reaction was cooled down to 0 °C, by doing so the product precipitated out of solution which was then filtered and dried to obtain naphthalene-1,5-diyl diacetate **22** as a light brown powder (14.98g, 61.33mmoles, 98%).



<sup>1</sup>H NMR (300 MHz, Chloroform-*d*) δ 7.77 (2H, d, *J* = 8.5 Hz, ArH), 7.49 (2H, t, *J* = 8.0 Hz, ArH), 7.28 (2H, d, *J* = 7.5 Hz, ArH), 2.44 (6H, s, CH<sub>3</sub>×2); <sup>13</sup>C NMR (75 MHz, Chloroform-*d*) δ 169.3(C=O×2), 146.7(ArC-1,5), 128.1(ArC), 126.0(ArC), 119.3(ArC), 118.8(ArC), 21.0(CH<sub>3</sub>×2).<sup>75</sup>

## 9.25 Preparation of 6-Bromo-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate<sup>75</sup> **146**

Naphthalene-1,5-diyl diacetate **22** (1eq., 2.40g, 10.00mmol) was dissolved in 100mL of warm acetic acid in a 500mL round bottom flask and to the stirring solution was added dropwise a solution of *N*-bromosuccinimide (4eq., 7.20g, 40.00mmol) in 200mL acetic acid and 100mL water maintained at a temperature of 65 °C. This reaction was then stirred under inert conditions and a temperature of 65 °C for forty five minutes. After which time, the reaction was allowed to warm up to room temperature and then 200mL of water was added and transferred to a separating funnel where it was extracted with chloroform (250mL×3). The organic phases were combined and washed with brine (500mL), dried over anhydrous magnesium sulfate, filtered through a pad of celite and then the chloroform was removed in *vacuo* to provide the crude product which was further recrystallized from ethanol to obtain pure 6-bromo-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate as a bright orange powder (2.30g, 77.70mmoles, 79%).

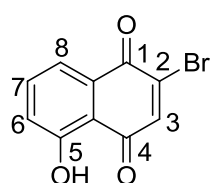


*R*<sub>f</sub> 0.71 (30% EtOAc/Hexane); <sup>1</sup>H NMR (300 MHz, Chloroform-*d*) δ 8.09 (1H, dd, *J* = 7.6, 1.6 Hz, ArH), 7.96 (1H, s, ArH-3), 7.62 (1H, d, *J* = 7.6 Hz, ArH), 7.57 (1H, dd, *J* = 8.1, 1.6 Hz, ArH), 2.52 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR

(75 MHz, Chloroform-*d*)  $\delta$  174.9(ArC-1), 167.9(C=O), 148.8(ArC-4), 148.7(ArC-5), 134.1(ArC), 131.0(ArC), 130.0(ArC), 126.8(ArC), 124.9(ArC), 120.0(ArC), 41.8(ArC-3), 21.6(CH<sub>3</sub>).<sup>75</sup>

## 9.26 Preparation of 2-Bromo-5-hydroxynaphthalene-1,4-dione<sup>70</sup> **23**

6-Bromo-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate **146** (1eq., 2.00g, 6.70mmoles) was stirred in a 200mL round bottom flask with 75mL ethanol. To this stirring solution, 22.5mL of 3 N sulfuric acid was added dropwise and the reaction mixture was stirred under reflux for two hours. After which, the reaction was allowed to cool down to room temperature and solvent was removed in *vacuo*. The residue left was dissolved in water (50mL) and extracted with chloroform (25mL×3). The combined organic phases were washed with brine (100mL), dried over anhydrous magnesium sulfate, filtered and then concentrated in *vacuo* to obtain crude product which was later purified by column chromatography to furnish pure product **23** as a bright orange solid (1.66g, 6.53mmoles, 98%).



**R<sub>f</sub>** 0.28 (30% EtOAc/Hexane); <sup>1</sup>H NMR (300 MHz, Chloroform-*d*)  $\delta$  11.81 (1H, s, OH), 7.73 (1H, d, *J* = 7.4 Hz, ArH), 7.67 (1H, d, *J* = 8.2 Hz, ArH), 7.32 (1H, d, *J* = 8.3 Hz, ArH), 7.20 (1H, s, ArH-3); <sup>13</sup>C NMR (75 MHz, Chloroform-*d*)  $\delta$  187.9(ArC-1), 161.7(ArC-5), 147.1(ArC-4), 136.5(ArC), 135.8(ArC), 131.1(ArC), 125.3(ArC), 120.7(ArC), 114.6(ArC).<sup>70</sup>

## 9.27 Preparation of 2-Bromo-1,4,5-trimethoxynaphthalene<sup>75</sup> **80**

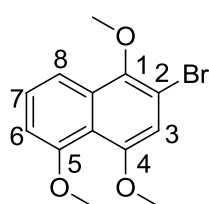
### 9.27.1 Method 1

2-Bromo-5-methoxynaphthalene-1,4-dione **138** (1eq., 2.00g, 7.46mmoles) was dissolved in diethyl ether (200mL) and then transferred to a 1L round bottom flask carrying a solution of water (200mL) and sodium dithionite (10eq., 10.05g, 74.69mmoles). The solution was allowed to stir at room temperature and under atmospheric conditions for thirty minutes over which time it changed colour from bright orange to pale yellow. The organic layer was collected and washed with brine (250mL), dried over anhydrous magnesium sulfate, filtered and concentrated in *vacuo* to get 2-bromo-5-methoxynaphthalene-1,4-diol as light brown solid which being unstable was immediately dissolved in dry acetone (100mL) in a 200mL round bottom flask stirring under argon. Potassium carbonate (7eq., 7.21g, 52.28mmoles) and dimethyl sulfate (7eq., 6.58g, 4.90mL, 52.28mmoles) were then added. The reaction was allowed to stir under reflux for eighteen hours. On completion, the reaction mass was

allowed to cool down to room temperature and was filtered through a pad of celite. The solvent was removed in *vacuo* and diethyl ether (100mL) was added. Aqueous ammonia was slowly added in portions (5mL) with stirring until the bubbling stopped. The solution was then transferred to a separating funnel and the organic layer was collected. The aqueous layer was washed with diethyl ether (50mL×3). The combined organic layers were washed with aqueous 10% hydrochloric acid (150mL), water (150mL) and brine (150mL) respectively. The organic layer was collected, dried on anhydrous magnesium sulfate, filtered and concentrated in *vacuo* to obtain crude product as a brown solid which was subjected to column chromatography (10% EtOAc/Hexane) to obtain 2-bromo-1,4,5-trimethoxynaphthalene **80** (1.65g, 5.60mmoles, 75%).

### 9.27.2 Method 2

2-Bromo-5-methoxynaphthalene-1,4-dione **138** (1eq., 504mg, 1.88mmoles) was dissolved in tetrahydrofuran (25mL) in a 100mL round bottom flask at room temperature under an argon atmosphere. To this stirring solution was added sodium dithionite (6eq., 1.97g, 1.13mmoles) dissolved in water (10mL) and tetrabutyl ammonium iodide (0.09eq., 62.0mg, 0.169mmoles). Fifteen minutes later potassium hydroxide (23eq., 2.43g, 43.42mmoles) dissolved in water (10mL) was added which immediately changes the colour of reaction from light orange to dark brown. The reaction was allowed to stir at the above mentioned conditions for one hour after which time dimethyl sulfate (21eq., 5.00g, 3.75mL, 39.64mmoles) was added and it was allowed to stir for six hours under the same conditions. The reaction mixture slowly changes its colour from dark brown to pale yellow. On completion, the reaction mass was transferred to a 250mL round bottom flask carrying ethyl acetate (50mL) stirring at room temperature and under atmospheric conditions. Aqueous ammonia was added in portions (5mL) until effervescence ceased. The solution was then transferred to a separating funnel and extracted with diethyl ether (50mL×3). The organic phases were combined and washed with aqueous 10% hydrochloric acid (50mL), water (50mL) and brine (50mL), dried over anhydrous magnesium sulfate, filtered and then the solvent removed in *vacuo* to obtain crude product as a brown solid which was purified by column chromatography (10% EtOAc/Hexane) to obtain 2-bromo-1,4,5-trimethoxynaphthalene **80** as a white solid (496g, 1.67mmoles, 89%).

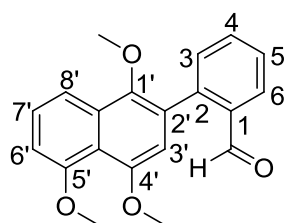


$R_f$  0.53 (20% EtOAc/Hexane);  $^1H$  NMR (300 MHz, Chloroform-*d*)  $\delta$  7.68 (1H, dd,  $J$  = 8.4, 0.8 Hz, ArH), 7.44 (1H, t,  $J$  = 8.1 Hz, ArH), 6.89 (2H, d,  $J$  = 8.0 Hz, ArH), 3.96 (3H, s, OMe), 3.94 (3H, s, OMe), 3.92 (3H, s, OMe);

**$^{13}\text{C}$  NMR** (75 MHz, Chloroform-*d*)  $\delta$  157.5(ArC-1), 153.9(ArC-4), 146.7(ArC-5), 131.7(ArC), 127.5(ArC), 117.6(ArC), 114.6(ArC), 112.6(ArC), 109.8(ArC), 106.9(ArC), 61.2(OMe), 56.8(OMe), 56.4(OMe).<sup>75</sup>

## 9.28 Preparation of 2-(1,4,5-Trimethoxynaphthalen-2-yl)benzaldehyde **139**

2-Bromo-1,4,5-trimethoxynaphthalene **80** (1eq., 50.0mg, 0.185mmoles), 2-formylphenylboronic acid **98** (1.5eq., 42.0mg, 0.277mmoles), tetrakis(triphenylphosphine)palladium(0) (0.5eq., 107mg, 0.092mmoles) and cesium fluoride (2.5eq., 70.0mg, 0.462mmoles) were added to a microwave vial together with dimethoxy ethane (2mL) and then the solution was degassed for nearly two minutes. The reaction was transferred to a microwave reactor and heated at 150 °C and 150 W with vigorous stirring for thirty minutes. On completion, the reaction mass was filtered, adsorbed on silica and subjected to column chromatography (10% EtOAc/Hexane) to obtain the product **139** as an off-white solid (35.2mg, 0.118mmoles, 64%).

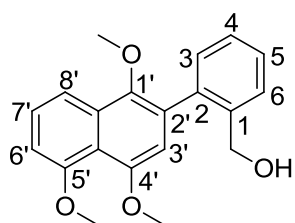


**R<sub>f</sub>** 0.77 (20% EtOAc/Hexane); **mp.** 98-100 °C CH<sub>2</sub>Cl<sub>2</sub>; **FTIR** (v/cm<sup>-1</sup>): 2837(C-H), 1687(CHO), 1583(C=C), 1263(C-O);  **$^1\text{H}$  NMR** (300 MHz, Chloroform-*d*)  $\delta$  9.89 (1H, s, CHO), 8.08 (1H, dd, *J* = 8.1, 1.5 Hz, ArH), 7.78 (1H, dd, *J* = 8.5, 1.0 Hz, ArH), 7.71 (1H, d, *J* = 1.5 Hz, ArH), 7.55 (2H, dd, *J* = 5.5, 2.2 Hz, ArH), 7.49 (1H, t, *J* = 8.1 Hz, ArH), 6.96 (1H, dd, *J* = 7.8, 1.0 Hz, ArH), 6.78 (1H, s, ArH-3'), 4.01 (3H, s, OMe), 3.98 (3H, s, OMe), 3.37 (3H, s, OMe);  **$^{13}\text{C}$  NMR** (75 MHz, Chloroform-*d*)  $\delta$  192.4(C=O), 157.4(ArC-4'), 153.7(ArC-1'), 147.0(ArC-5'), 141.6(ArC), 133.7(ArC), 133.5(ArC), 131.3(ArC), 130.9(ArC), 128.0(ArC), 127.4(ArC), 127.1(ArC), 126.1(ArC), 115.2(ArC), 108.2(ArC), 107.4(ArC-3'), 60.7(OMe), 56.9(OMe), 56.6(OMe); **HRMS** (ESI<sup>+</sup>): Found  $\text{M}^+ + \text{H}$  323.1268, C<sub>20</sub>H<sub>19</sub>O<sub>4</sub> ( $\text{M}^+ + \text{H}$ ) requires 323.1284, *m/z* 323.1268(100%), 322.1193(40%).

## 9.29 Preparation of (2-(1,4,5-Trimethoxynaphthalen-2-yl)phenyl)methanol **134**

2-(1,4,5-Trimethoxynaphthalen-2-yl)benzaldehyde **139** (1eq., 34.2mg, 0.117mmoles) was dissolved in freshly distilled, dry tetrahydrofuran (10mL) under argon in a 25mL round bottom flask and sodium borohydride (3eq., 13.4mg, 0.350) was added carefully. The reaction was allowed to stir at room temperature for twelve hours over which time it changes its colour from bright yellow to hazy white solution. On completion, the reaction was cooled down to 0 °C and ice cold water (10mL) was added carefully to quench any unreacted sodium borohydride. The solution was then transferred to a separating funnel and the organic

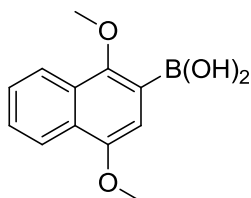
material was extracted in diethyl ether (10mL×3). The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, filtered and solvent was removed under reduced pressure to obtain the crude product which was then subjected to column chromatography (30% EtOAc/ Hexane) to obtain the product as a white solid **134** (34.7mg, 0.107mmoles, 100%).



**R<sub>f</sub>** 0.47 (50% EtOAc/Hexane); mp 118-120 °C CH<sub>2</sub>Cl<sub>2</sub>; **FTIR** (v/cm<sup>-1</sup>) 3384(OH), 2930(C-H), 1584(C=C), 1237(C-O); **<sup>1</sup>H NMR** (300 MHz, Chloroform-d) δ 7.66 (1H, d, *J* = 8.4 Hz, ArH), 7.52 (1H, dd, *J* = 6.7, 2.1 Hz, ArH), 7.43-7.24 (4H, m, ArH), 6.85 (1H, d, *J* = 7.7 Hz, ArH), 6.58 (1H, s, ArH-3'), 4.34 (1H, d, *J* = 11.1 Hz, one of CH<sub>2</sub>OH), 4.29 (1H, d, *J* = 11.1 Hz, one of CH<sub>2</sub>OH), 3.92 (3H, s, OMe), 3.85 (3H, s, OMe), 3.38 (3H, s, OMe), 0.85 – 0.71 (1H, m, OH).

### 9.30 Preparation of 1,4-Dimethoxynaphthalen-2-ylboronic acid **157**

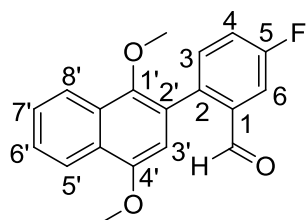
2-Bromo-1,4-dimethoxynaphthalene **97** (1eq., 500mg, 1.88mmoles) together with freshly distilled, dry tetrahydrofuran (30mL) in a two neck round bottom flask was degassed for nearly ten minutes. The reaction mixture was then cooled down to -78 °C and *n*butyllithium (1.1eq., 1.89mL, 1.1 M/THF, 132mg) was added slowly via a syringe and the resulting solution was stirred at -78 °C and under inert conditions for one hour. Triisopropyl borate (1.2eq., 424mg, 0.518mL) was then added slowly. The reaction was stirred at -78 °C for another one hour and then was slowly allowed to warm up to room temperature and then stirred for another two hours before being quenched with 10% aqueous hydrochloric acid (50mL). The organic material was extracted with diethyl ether (30mL×3). The organic phases were combined and washed with brine (50mL), dried over anhydrous magnesium sulfate, filtered and solvent was then removed under reduced pressure till only a few mLs were left. This thick residue was cooled down to 0 °C and cold acetone (20mL) was added to it with



vigorous stirring. While doing so, the product precipitates as a white solid which was immediately filtered off and was washed with cold acetone to isolate crude product **157** (94%, 408mg, 1.76mmoles). The product **157** was not characterized due to solubility and stability problems and was used as such in the next step.

### 9.31 Preparation of 2-(1,4-Dimethoxynaphthalen-2-yl)-5-fluorobenzaldehyde **159**

1,4-Dimethoxynaphthalen-2-ylboronic acid **157** (1eq., 200mg, 0.866mmoles), 2-bromo-5-fluorobenzaldehyde **158** (1.5eq., 264mg, 1.30mmoles), tetrakis(triphenylphosphine) palladium (0.08eq., 80.0mg, 0.069mmoles) and cesium fluoride (2.5eq., 329mg, 2.17mmoles) were transferred to a microwave vial in dimethoxyethane (2mL). The resulting solution was degassed for two minutes before being subjected to reaction in a microwave reactor at 150 °C, 150 W and vigorous stirring for thirty minutes. On completion, the reaction mass was filtered, adsorbed onto silica and subjected to column chromatography (5% EtOAc/Hexane) to obtain 2-(1,4-dimethoxynaphthalen-2-yl)-5-fluorobenzaldehyde as a yellow solid **159** (165mg, 0.530mmoles, 62%).

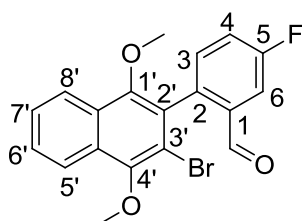


**R<sub>f</sub>** 0.51 (20% EtOAc/Hexane); **mp.** 132-134 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **FTIR** (v/cm<sup>-1</sup>): 2938(C-H), 1687(CHO), 1589(C=C), 1213(C-O), 1102(C-F); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 9.83 (1H, d, *J* = 3.3 Hz, CHO), 8.30 (1H, dd, *J* = 7.7, 2.0 Hz, ArH), 8.18-8.07 (1H, m, ArH), 7.75 (1H, dd, *J* = 8.9, 2.8 Hz, ArH), 7.65-7.50 (3H, m, ArH), 7.40 (1H, td, *J* = 8.2, 2.8 Hz, ArH), 6.71 (1H, s, ArH-3'), 4.01 (3H, s, OMe), 3.40 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) δ 191.1(C=O), 162.3(d, *J*<sub>CF</sub> = 249 Hz, ArC), 155.2(ArC), 147.0(ArC), 137.8(ArC), 135.6(ArC), 135.5(ArC), 132.9(d, *J*<sub>CF</sub> = 7.3 Hz, ArC), 128.4(ArC), 126.8(ArC), 126.7(ArC), 124.5(ArC), 122.4(ArC), 122.3(ArC), 120.7(d, *J*<sub>CF</sub> = 22.1 Hz, ArC), 114.0(d, *J*<sub>CF</sub> = 22.3 Hz, ArC), 105.7(ArC-3'), 60.9(OMe), 55.8(OMe); **HRMS** (ESI<sup>+</sup>): Found *M*<sup>+</sup>+ H 311.1083, C<sub>19</sub>H<sub>16</sub>FO<sub>3</sub> (*M*<sup>+</sup>+ H) requires 311.1084, *m/z* 311.0995(100%), 311.1062(60%), 279.0622(20%).

### 9.32 Preparation of 2-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)-5-fluorobenzaldehyde **161**

2-(1,4-Dimethoxynaphthalen-2-yl)-5-fluorobenzaldehyde **159** (1eq., 50.0mg, 0.161mmoles) and *N*-bromosuccinimide (1eq., 57.0mg, 0.322mmoles) were transferred to a 10mL round bottom flask and 5mL dichloromethane was added. The reaction was allowed to stir for eighteen hours under atmospheric conditions and room temperature. On completion, the reaction was quenched with aqueous saturated solution of sodium sulfite (10mL) and the mixture was transferred to a separating funnel where it was extracted into dichloromethane (10mL×3). The organic phases were combined, washed with brine (20mL), dried over anhydrous magnesium sulfate, filtered and solvent was removed under reduced pressure to

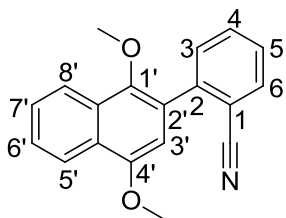
obtain 2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)-5-fluorobenzaldehyde **161** as a yellow solid (28.0mg, 0.073mmoles, 45%).



**R<sub>f</sub>** 0.62(20% EtOAc/Hexane); **mp** 118-120 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **FTIR** (v/cm<sup>-1</sup>): 2929(C-H), 1690(CHO), 1585(C=C), 1239(C-O), 1143(CHO); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 9.74 (1H, d, *J* = 3.1 Hz, CHO), 8.23-8.15 (1H, m, ArH), 8.15-8.08 (1H, m, ArH), 7.78 (1H, d, *J* = 8.7 Hz, ArH), 7.63 (2H, dd, *J* = 6.5, 2.7 Hz, ArH), 7.47-7.38 (2H, m, ArH), 4.03 (3H, s, OMe), 3.48 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) δ 190.3(C=O), 162.6 (d, *J*<sub>CF</sub> = 250.1 Hz, ArC), 151.1(ArC-4'), 150.6(ArC-1'), 136.3(ArC), 136.2(ArC) 136.0(ArC), 135.9(ArC), 134.1(d, *J*<sub>CF</sub> = 7.3 Hz, ArC), 129.1(ArC), 127.9(ArC), 127.3(ArC), 127.0(ArC), 123.1(ArC), 122.7(ArC), 120.7 (d, *J*<sub>CF</sub> = 22.1 Hz, ArC), 113.7(d, *J*<sub>CF</sub> = 22.5 Hz, ArC), 61.6(OMe), 61.5(OMe); **HRMS** (ESI<sup>+</sup>): Found M<sup>+</sup>+H 388.0095, C<sub>19</sub>H<sub>15</sub>BrFO<sub>3</sub> (M<sup>+</sup>+ H) requires 389.0184, *m/z* 388.0095(100%), 390.0072(95%), 391.0128(30%).

### 9.33 Preparation of 2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **214**

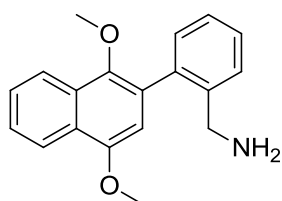
2-Bromo-1,4-dimethoxynaphthalene **97** (1eq., 250mg, 0.939mmoles), 2-cyanophenylboronic acid **213** (1.5eq., 207mg, 1.41mmoles), tetrakis(triphenylphosphine)palladium(0) (0.2eq., 217mg, 0.188mmoles) and cesium fluoride (2.5eq., 356mg, 2.35mmoles) were transferred to a microwave reactor vial. Dimethoxyethane (2mL) which was previously degassed for ten minutes was added to the reaction. The reaction mixture was placed in a microwave reactor at 150 °C and 150 W for thirty minutes. After that time reaction mixture was filtered to get rid of the solid palladium and then purified by column chromatography (5% EtOAc/Hexane) to obtain product **181** as a yellow solid (207mg, 0.716mmoles, 76%).



**R<sub>f</sub>** = 0.44(20% EtOAc/Hexane); **mp.** 166-168 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **FTIR** (v/cm<sup>-1</sup>) 2966-2842(C-H), 2225(CN), 1624-1591(C=C), 1266-1227(C-O); **<sup>1</sup>H NMR** (300 MHz,) δ 8.33-8.26 (1H, m, ArH), 8.21-8.14 (1H, m, ArH), 7.82 (1H, d, *J* = 7.7 Hz, ArH), 7.68 (2H, d, *J* = 3.9 Hz, ArH), 7.63-7.45 (5H, m, ArH), 6.73 (1H, s, ArH-3'), 4.01 (s, OMe), 3.53 (s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) δ 151.8(ArC-1'), 147.3(ArC-4'), 142.9(ArC), 133.2(ArC), 132.4(ArC), 131.4(ArC), 128.8(ArC), 127.7(ArC), 127.0(ArC), 126.9(ArC), 126.3(ArC), 126.2(ArC), 122.5(ArC), 122.4(ArC), 118.5(ArCN), 113.0(ArC), 105.4(ArC-3'), 61.9(OMe), 55.8(OMe); **HRMS** (ESI<sup>+</sup>): Found M<sup>+</sup>+H 290.1068, C<sub>19</sub>H<sub>16</sub>NO<sub>2</sub> (M<sup>+</sup>+H) requires 290.1182, *m/z* 290.1068 (M<sup>+</sup>+H, 100%), 289.1086(50%)

### 9.34 Preparation of (2-(1,4-Dimethoxynaphthalen-2-yl)phenyl)methanamine **215**

2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **214** (1eq., 276mg, 0.957mmoles,) was dissolved in freshly distilled tetrahydrofuran (25mL) in a 50 mL round bottom flask and the temperature of the solution was maintained at 0 °C. Lithium aluminium hydride (10eq., 361mg, 9.57mmoles) was added in portions under inert conditions at 0 °C. Slowly the temperature of the reaction was allowed to rise to room temperature and followed by heating the reaction under reflux and inert conditions for twelve hours after which the reaction was allowed to cool down to room temperature. The temperature of the reaction mass was reduced to 0 °C and a 4% aqueous sodium hydroxide was added drop wise to quench the unreacted lithium aluminium hydride. After the bubbling stopped, ice cold water was added and the crude mixture was transferred to a separating funnel where organic material was extracted into diethyl ether (20mL×3). The organic phases were then combined and washed with brine (30mL), dried over anhydrous magnesium sulfate, filtered and then the solvent was removed under *vacuo*. The crude product was purified by column chromatography (EtOAc and 2% of triethylamine) after which to afford the product **215** was obtained as a brown sticky resin (177mg, 0.606mmoles, 63%).

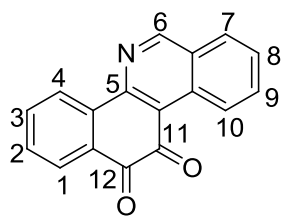


$R_f$  = 0.80(10% MeOH/DCM); **mp.** 73-75 °C ( $C_2H_5)_2O$ ; **FTIR** ( $\nu/cm^{-1}$ ): 3400-3330(N-H<sub>2</sub>), 2928-2848(C-H), 1625-1592(C=C), 1268-1225(C-O); **HRMS** (ESI<sup>+</sup>): Found  $M^+ + H$  294.1480,  $C_{19}H_{20}NO_2$  ( $M^+ + H$ ) requires 294.1495,  $m/z$  294.1480 ( $M^+ + H$ , 40%), 295.1517 (10%)

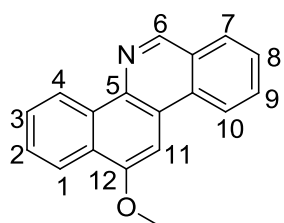
### 9.35 Preparation of Benzo[c]phenanthridine-11,12-dione **217** and 6-Methoxybenzo[c]phenanthridin-12(11H)-one<sup>108</sup> **218**

(2-(1,4-Dimethoxynaphthalen-2-yl)phenyl)methanamine **215** (1eq., 164mg, 0.559mmoles) was added to acetonitrile (2mL) in a 10mL round bottom flask at room temperature and was allowed to dissolve completely under atmospheric conditions. Ceric ammonium nitrate (3eq., 920mg, 1.68mmoles) was dissolved in water (2mL) and added drop wise to the stirring mixture. The reaction immediately turned orange in colour. The reaction was allowed to stir under the same conditions further for four hours. Water (5mL) was added and the mixture was transferred to a separating funnel, washed with dichloromethane (10mL×3). The combined organic phases were washed with brine (20mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under *vacuo* to obtain crude product which was purified by column chromatography (20% EtOAc/Hexane) to obtain **217** and **218**.





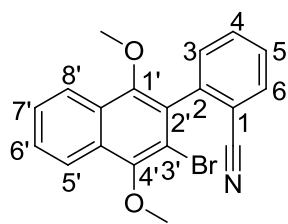
Bright orange solid of **217**. (59.5mg, 0.227mmoles, 41%);  $R_f$  = 0.48(30% EtOAc/Hexane); **mp.** 101-103 °C  $\text{CHCl}_3$ ; **FTIR** ( $\nu/\text{cm}^{-1}$ ): 2922(C-H); 1662(C=O), 1637(C=C), 1333(ArC-N); **UV absorption**  $\lambda_{\text{max}}^{\text{DCM}}$  nm( $\epsilon$ ): 205.0(3.550), 215.1(4.206), 290.0(0.686), 440.0(0.275);  **$^1\text{H}$  NMR** (300 MHz, Chloroform- $d$ )  $\delta$  9.35 (2H, d,  $J$  = 7.0 Hz, ArH), 8.75 (1H, d,  $J$  = 7.9 Hz, ArH), 8.12(1H, d,  $J$  = 7.5 Hz, ArH), 7.98 (1H, d,  $J$  = 8.1 Hz, ArH), 7.88 (1H, t,  $J$  = 7.8 Hz, ArH), 7.75 (1H, t,  $J$  = 7.6 Hz, ArH), 7.66 (1H, t,  $J$  = 7.5 Hz, ArH), 7.52 (1H, t,  $J$  = 7.5 Hz, ArH);  **$^{13}\text{C}$  NMR** (75 MHz, Chloroform- $d$ )  $\delta$  182.8(ArC-11), 179.8(ArC-12), 158.9(ArC), 151.3(ArC), 137.4(ArC), 136.2(ArC), 134.7(ArC), 134.0(ArC), 130.8(ArC), 130.5(ArC), 129.5(ArC), 128.8(ArC), 128.6(ArC), 127.6(ArC), 126.3(ArC), 119.4(ArC); **HRMS** (ESI+): Found  $M^+ + H$  260.0699,  $\text{C}_{17}\text{H}_{10}\text{NO}_2$  ( $M^+ + H$ ) requires 260.0721,  $m/z$  260.0699 ( $M^+ + H$ , 100%), 262.0875 (30%)



Pale yellow solid of **218** (17.4mg, 0.066mmoles, 39%);  $R_f$  = 0.71(30% EtOAc/Hexane); **mp.** 132-134 °C  $\text{CHCl}_3$ ; **FTIR** ( $\nu/\text{cm}^{-1}$ ): 2850(C-H), 1707(C=N), 1253(C-O);  **$^1\text{H}$  NMR** (300 MHz, Chloroform- $d$ )  $\delta$  9.39 – 9.25 (2H, m, ArH), 8.52 (1H, d,  $J$  = 8.3 Hz, ArH), 8.37 (1H, d,  $J$  = 8.0 Hz, ArH), 8.07 (1H, d,  $J$  = 7.8 Hz, ArH), 7.80 (2H, dt,  $J$  = 13.4, 7.6 Hz, ArH), 7.74 – 7.67 (1H, m, ArH), 7.64 (1H, s, ArH), 4.17 (3H, s, OMe);  **$^{13}\text{C}$  NMR** (75 MHz, Chloroform- $d$ )  $\delta$  154.71(ArC-12), 149.28(ArC), 137.09(ArC), 132.769(ArC), 132.29(ArC), 130.25(ArC), 128.67(ArC), 127.58(ArC), 127.09(ArC), 127.03(ArC), 126.98(ArC), 126.82(ArC), 124.57(ArC), 122.09(ArC), 121.94(ArC), 121.87(ArC), 95.79(ArC), 55.61(OMe); **HRMS** (ESI+): Found  $M^+ + H$  260.1071,  $\text{C}_{18}\text{H}_{14}\text{NO}$  ( $M^+ + H$ ) requires 260.1076,  $m/z$  260.1071 ( $M^+ + H$ , 100%), 261.1104 (20%).

### 9.36 Preparation of 2-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)benzonitrile **233**

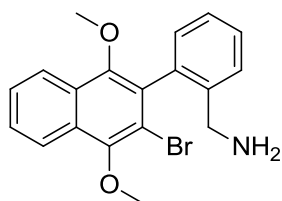
2-(1,4-Dimethoxynaphthalen-2-yl)benzonitrile **214** (1eq., 195mg, 0.675mmoles) was dissolved in acetic acid (20mL) in a 50mL round bottom flask. Sodium acetate (1.2eq., 67.2mg, 0.896mmoles) was added followed by *N*-bromosuccinimide (1.2eq., 144mg, 0.896mmoles). The reaction was allowed to stir at room temperature under inert conditions for four hours. On completion, an aqueous saturated solution of sodium sulfite (20mL) was added and the solution was transferred to a separating funnel and then washed with dichloromethane (20mL $\times$ 3). The organic phases were collected, washed with brine (50mL), dried over anhydrous magnesium sulfate, and then the solvent was removed *in vacuo*. The crude product obtained was purified by column chromatography (10% EtOAc/Hexane) to yield the product **233** as an off-white solid (206mg, 0.568mmoles, 83%).



**R<sub>f</sub>** 0.76(20% EtOAc/Hexane); **mp.** 184-186 °C CH<sub>2</sub>Cl<sub>2</sub>; **FTIR** ( $\nu/cm^{-1}$ ) 2967-2841(C-H), 2228(CN), 1625-1570(C=C), 1285-1251(C-O), 690-655 (C-Br); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  8.21-8.14 (2H, m, ArH), 7.81 (1H, dd, *J* = 7.9, 1.4 Hz, ArH), 7.70 – 7.64 (1H, m, ArH), 7.63 – 7.48 (4H, m, ArH), 3.99 (3H, s, OMe), 3.58 (3H, s, OMe); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  150.6(ArC-4'), 143.9(ArC-1'), 137.6(ArC), 137.4(ArC), 132.6(ArC), 132.3(ArC), 131.8(ArC), 129.4(ArC), 128.3(ArC), 127.4(ArC), 127.2(ArC), 126.5(ArC), 123.3(ArC), 123.0(ArC), 122.4(ArC), 117.9(ArC), 114.3(ArC), 62.1(OMe), 62.1(OMe); **HRMS**(ESI-): Found  $M^+ - H$  365.1497, C<sub>19</sub>H<sub>15</sub>NO<sub>2</sub>Br( $M - H$ ) requires 366.0128,  $m/z$  365.1497 ( $M^+ + H$ , 100%), 371.1081 (10%).

### 9.37 Preparation of (2-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)phenyl)methanamine **234**

2-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)benzonitrile **233** (1eq, 172mg, 0.466mmoles) was dissolved in 10mL dry tetrahydrofuran in a 25mL round bottom flask and lithium aluminium hydride (10eq., 176mg, 4.66mmoles) was added. The reaction was refluxed for five hours. On completion, the reaction was cooled down to 0 °C and 2% sodium hydroxide (10mL) was added drop wise to quench the reaction. The solution was transferred to a separating funnel and washed with dichloromethane (20mL×3). The combined organic phases were washed with brine (20mL), dried over anhydrous magnesium sulfate and then the solvent was removed under reduced pressure and then purified by flash chromatography (20% MeOH/DCM) to obtain the intermediate **234** as a brown resinous solid (59.1mg, 0.159mmoles, 34%).

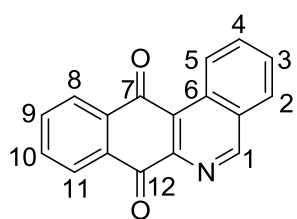


**R<sub>f</sub>**: 0.52 (20% MeOH/DCM); **mp.** 102-104 °C CH<sub>2</sub>Cl<sub>2</sub>; **FTIR** ( $\nu/cm^{-1}$ ) 3521(N-H), 2934-2840(C-H), 1608-1541(C=C), 1270-1256(C-O), 681-657 (C-Br).

### 9.38 Preparation of Benzo[*b*]phenanthridine-7,12-dione **162**

(2-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)phenyl)methanamine **234** (1eq., 59.4mg, 0.158mmoles) was dissolved in acetonitrile (2mL) in a 10mL round bottom flask and phenyliodine bis(trifluoroacetate) (2eq., 137mg, 0.318mmoles) already dissolved in water (2mL) was added. The solution changed its color from light yellow to red immediately. The reaction was stirred at room temperature, under atmospheric conditions for two hours before

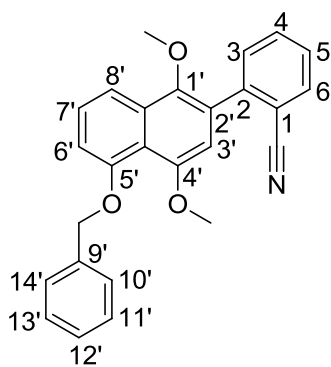
it was quenched by adding an aqueous saturated solution of sodium bicarbonate (10mL) and then the organic material was extracted into ethyl acetate (15mL×3). The organic phases were combined and washed with brine (20mL), dried over anhydrous magnesium sulfate, filtered and organic solvent was removed *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc/Hexane) to afford benzo[*b*]phenanthridine-7,12-dione **162** as a bright yellow solid (23.0mg, 0.089mmoles, 56%).



**R<sub>f</sub>** 0.77(50% EtOAc/Hexane); **mp.** 167-170 °C CHCl<sub>3</sub>; **FTIR** ( $\nu/cm^{-1}$ ) 2923(C-H), 1667(C=N), 1660(C=O), 1587-1588(C=C); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  9.67 (1H, d, *J* = 8.7 Hz, ArH), 9.58 (1H, s, ArH-1), 8.36 (1H, d, *J* = 9.0 Hz, ArH), 8.29 (1H, d, *J* = 9.0 Hz, ArH), 8.11 (1H, d, *J* = 8.1 Hz, ArH), 7.98 (1H, ddd, *J* = 8.6, 7.0, 1.4 Hz, ArH), 7.87 – 7.79 (3H, m, ArH); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  186.2(ArC-12), 182.3(ArC-7), 158.4(ArC), 145.5(ArC), 134.4(ArC), 134.1(ArC), 134.1(ArC), 134.0(ArC), 132.8(ArC), 132.2(ArC), 130.6(ArC), 130.2(ArC), 128.7(ArC), 127.9(ArC), 127.2(ArC), 127.1(ArC), 124.5(ArC); **HRMS** (ESI<sup>+</sup>): Found *M*<sup>+</sup>+H 260.0713, C<sub>17</sub>H<sub>10</sub>NO<sub>2</sub> (*M*<sup>+</sup>+H) requires 260.0712, *m/z* 260.0703 (*M*<sup>+</sup>+H, 100%), 261.0744 (20%).

### 9.39 Preparation of 2-(5-(Benzyloxy)-1,4-dimethoxynaphthalen-2-yl)benzonitrile **239**

5-(Benzyloxy)-2-bromo-1,4-dimethoxynaphthalene **26** (1eq., 388mg, 0.981mmoles), (2-cyanophenyl)boronic acid **213** (1.5eq., 216mg, 1.47mmoles), cesium fluoride (2.5eq., 370mg, 2.45mmoles) and tetrakis(triphenylphosphine)palladium(0) (0.08eq., 86.2mg, 0.078mmoles) were transferred to a microwave vial, dimethoxy ethane (2mL) was added and the reaction was allowed to run in a microwave reactor at 150 °C and 150 W with high stirring for thirty minutes. After completion solution was filtered and purified by column chromatography to obtain the product **239** as a yellow solid (390mg, 0.986mmoles, 95%).

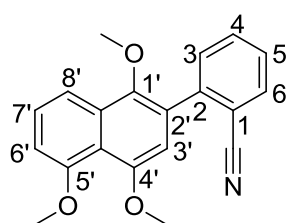


**R<sub>f</sub>** 0.32 (20% EtOAc/Hexane); **mp.** 135-137 °C CH<sub>2</sub>Cl<sub>2</sub>; **FTIR** ( $\nu/cm^{-1}$ ) 2951-2843(C-H), 2225(CN), 1595-1578 (C=C), 1258-1241( C=O); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  7.75 (2H, t, *J* = 6.5 Hz, ArH), 7.65 – 7.50 (4H, m, ArH), 7.37 (5H, dd, *J* = 19.4, 7.6 Hz, ArH), 6.95 (1H, d, *J* = 7.4 Hz, ArCH), 6.71 (1H, s, ArH-3'), 5.16 (2H, s, OCH<sub>2</sub>), 3.89 (3H, s, OMe), 3.42 (3H, s, OMe); **<sup>13</sup>C NMR** (75MHz, Chloroform-*d*)  $\delta$  156.4(ArC-4'), 153.5(ArC-1'), 147.1(ArC-5') 142.5(ArC), 137.5(ArC), 133.2(ArC), 132.4(ArC), 131.7(ArC), 131.3(ArC), 128.4(ArC), 127.8(ArC), 127.6(ArC), 127.2(ArC), 127.0(ArC),

126.9(ArC), 119.3(ArC), 118.5(CN), 115.8(ArC), 112.9(ArC), 109.9(ArC), 107.7(ArC), 71.6(OCH<sub>2</sub>), 61.7(OMe), 56.7(OMe); **HRMS** (ESI<sup>+</sup>): Found  $M^+ + H$  396.1585, C<sub>26</sub>H<sub>22</sub>NO<sub>3</sub> ( $M^+ + H$ ) requires 396.1600,  $m/z$  396.1585 ( $M^+ + H$ , 100%), 397.1612 (25%).

#### 9.40 Preparation of 2-(1,4,5-Trimethoxynaphthalen-2-yl)benzonitrile **244**

2-Bromo-1,4,5-trimethoxynaphthalene **80** (1eq., 200mg, 0.673mmoles), (2-cyanophenyl)boronic acid **213** (1.5eq., 148mg, 1.00mmoles), tetrakis(triphenylphosphine)palladium(0) (0.2eq., 155mg, 0.135mmoles) and cesium fluoride (2.5eq., 255mg, 1.68mmoles) were added to a microwave vial together with dimethoxy ethane (2mL). The reaction was set in the microwave reactor under conditions of vigorous stirring, 150 °C and 150 W. On completion the reaction mixture was filtered, washed with ethyl acetate and the residue obtained after evaporation of the organic solvent was adsorbed onto silica and subjected to column chromatography (15% EtOAc/Hexane) to procure the pure product **244** as a yellow solid (182mg, 0.570mmoles, 85%).

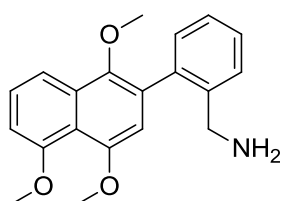


**R<sub>f</sub>** 0.30 (20% EtOAc/Hexane); **mp.** 95-97 °C CH<sub>2</sub>Cl<sub>2</sub>; **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 7.81 (2H, dd, *J* = 8.5, 1.0 Hz, ArH), 7.72 – 7.64 (2H, m, ArH), 7.48 (2H, t, *J* = 8.1 Hz, ArH), 6.95 (1H, d, *J* = 7.7 Hz, ArH), 6.79 (1H, s, ArH-3'), 4.00 (3H, s, OMe), 3.99 (3H, s, OMe), 3.50 (3H, s, OMe). **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) δ 157.5(ArC-4'), 153.4(ArC-1'), 147.2(ArC-5'), 142.5(ArC), 133.2(ArC), 132.4(ArC), 131.6(ArC), 131.3(ArC), 127.7(ArC), 127.2(ArC), 126.8(ArC), 118.8(ArC), 118.4(ArC), 115.3(ArC), 112.9(ArC), 107.9(ArC), 107.6(ArC), 61.6(OMe), 57.0(OMe), 56.6(OMe); **HRMS** (ESI<sup>+</sup>): Found  $M^+ + H$  320.1281, C<sub>20</sub>H<sub>18</sub>NO<sub>3</sub> ( $M^+ + H$ ) requires 320.1287,  $m/z$  320.1281 ( $M^+ + H$ , 100%), 321.1312 (20%).

#### 9.41 Preparation of (2-(1,4,5-Trimethoxynaphthalen-2-yl)phenyl)methanamine **247**

2-(1,4,5-Trimethoxynaphthalen-2-yl)benzonitrile **244** (1eq., 100mg, 0.313mmoles) was transferred to a 25mL round bottom flask in freshly distilled dry tetrahydrofuran (10mL) and the temperature of the solution was maintained at 0 °C. Lithium aluminium hydride (10eq., 119mg, 3.15mmoles) was added carefully and in portions at the same temperature. The temperature of the reaction mixture was allowed to rise up to room temperature slowly and then stirred under reflux for six hours. On completion the reaction mixture was allowed to cool down to room temperature and the temperature was further maintained at 0 °C. An aqueous 2% sodium hydroxide was added drop wise until all of unreacted lithium aluminium

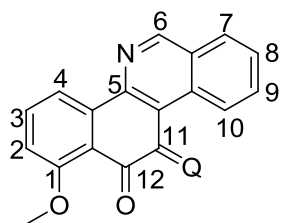
hydride was quenched. Ice cold water (20mL) was added and the solution was extracted in diethyl ether (25mL×3). The organic phases were collected and washed with brine (30mL) and then dried over anhydrous magnesium sulfate, filtered and concentrated in *vacuo* to obtain a residue which was subjected to column chromatography (10% MeOH/DCM) to afford (2-(1,4,5-trimethoxynaphthalen-2-yl)phenyl)methanamine **247** (59.0mg, 0.182mmoles, 58%) as a brown resinous solid. Due to solubility and polarities issues the product was considered as an intermediate as was used as such in the next step without further characterization.



**R<sub>f</sub>**: 0.44 (20% MeOH/DCM).

#### 9.42 Preparation of 1-Methoxybenzo[c]phenanthridine-11,12-dione **248**

(2-(1,4,5-Trimethoxynaphthalen-2-yl)phenyl)methanamine **247** (1eq., 50.0mg, 0.154mmoles) was transferred to a 10mL round bottom flask containing acetonitrile (2mL) which was stirred at room temperature and under atmospheric conditions. Phenyliodine bis(trifluoroacetate) (3.5eq., 232mg, 0.539mmoles) dissolved in water (2mL) was added drop wise to the stirring mixture. The reaction was allowed to stir under the same conditions for four hours. Water (5mL) was added and the mixture was transferred to a separating funnel where the organic material was extracted into dichloromethane (10mL×3). The combined organic phases were washed with brine (20mL), dried over anhydrous magnesium sulfate, filtered and then the solvent was removed under *vacuo* to obtain the crude product which was purified using column chromatography (15% EtOAc/Hexane) to obtain product **248** as a bright red solid (28.2mg, 0.096mmoles, 63%).

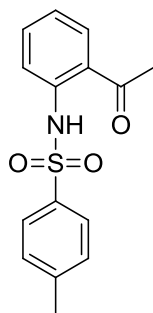


**R<sub>f</sub>**: 0.50(30% EtOAc/Hexane); **mp.** 114-116 °C CHCl<sub>3</sub>; **<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 9.44 (1H, s, ArH-6), 9.34 (1H, d, *J* = 8.5 Hz, ArH), 8.52 (1H, d, *J* = 7.6 Hz, ArH), 8.05 (1H, d, *J* = 7.9 Hz, ArH), 7.91 (1H, t, *J* = 7.4 Hz, ArH), 7.73 (2H, dt, *J* = 19.6, 7.6 Hz, ArH), 7.15 (1H, d, *J* = 8.3 Hz, ArH), 4.04 (3H, s, OMe); **<sup>13</sup>C NMR** (126 MHz,

Chloroform-*d*) δ 184.1(ArC-12), 179.7(ArC-11), 162.3(ArC-1), 158.5(ArC), 151.2(ArC), 139.2(ArC), 137.2(ArC), 134.4(ArC), 133.6(ArC), 128.7(ArC), 128.6(ArC), 128.5(ArC), 126.1(ArC), 120.4(ArC), 119.2(ArC), 118.9(ArC), 114.6(ArC), 56.4(OMe); **HRMS** (ESI<sup>+</sup>):

Found  $M^+ + H$  290.0807,  $C_{18}H_{12}NO_3$  ( $M^+ + H$ ) requires 290.0818,  $m/z$  290.0807 ( $M^+ + H$ , 100%), 290.2681 (30%).

#### 9.43 Preparation of *N*-(2-Acetylphenyl)-4-methylbenzenesulfonamide<sup>144</sup> **305**

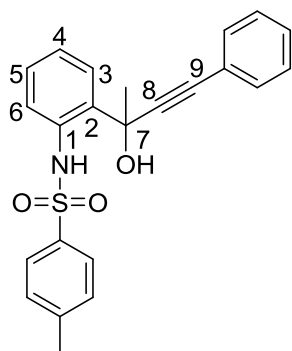


Commercially available 1-(2-aminophenyl)ethanone **255** (1eq., 250mg, 1.85mmoles) was added to pyridine (1mL) and *p*-toluenesulfonyl chloride (5eq., 529mg, 2.77mmoles) under an argon atmosphere. The thick solution obtained was stirred at room temperature for four hours. When completed, the reaction mixture was quenched with the addition of water (20mL). The precipitate was filtered off and dried in vacuum to afford *N*-(2-acetylphenyl)-4-methylbenzenesulfonamide as a white powder in 100% yield (289mg, 1.83mmoles). The known product was not characterized and immediately used

in the next step.

#### 9.44 Preparation of *N*-(2-(2-Hydroxy-4-phenylbut-3-yn-2-yl)phenyl)-4-methylbenzenesulfonamide<sup>144</sup> **307**

Ethyl magnesium bromide (3eq., 691mg, 1.73mL (3M in THF), 5.18mmol) was added to dry distilled tetrahydrofuran (10mL) at room temperature under an argon atmosphere. To this stirring solution was added phenyl acetylene **306** (3eq., 529mg, 5.60mL, 5.18mmol) drop wise and the resulting solution was stirred at the same conditions for fifteen hours. To this solution, *N*-(2-acetylphenyl)-4-methylbenzenesulfonamide (1eq., 500mg, 1.73mmoles) dissolved in dry tetrahydrofuran (10mL) was added drop wise using a syringe. The reaction was then refluxed for four hours. On completion, reaction was allowed to cool down to room temperature and was quenched by addition of an aqueous saturated solution of ammonium chloride (25mL). The resultant mixture was then was extracted with diethyl ether (25mL×3). The combined organic phases were washed with brine (100mL), dried over anhydrous magnesium sulfate, filtered and concentrated to obtain the crude product which was purified by column chromatography (15% EtOAc/Hexane) to furnish the product **307** as an off-white solid in 99% yield (672mg, 1.71mmoles).

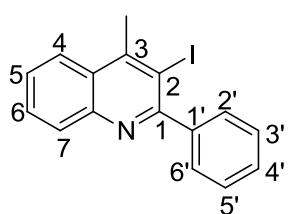


$R_f$ : 0.41(30% EtOAc/Hexane);  $^1H$  NMR (300 MHz, Chloroform- $d$ )  $\delta$  9.21 (1H, s, NH), 7.77 (2H, d,  $J$  = 8.3 Hz, ArH), 7.66-7.53 (2H, m, ArH), 7.50-7.42 (2H, m, ArH), 7.37-7.30 (3H, m, ArH), 7.26-7.14 (3H, m, ArH), 7.06-6.98 (1H, m, ArH), 3.22 (1H, s, OH), 2.33 (3H, s,

CH<sub>3</sub>), 1.76 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, Chloroform-*d*) δ 143.7(ArC), 137.1(ArC), 135.7(ArC), 131.8(ArC), 131.3(ArC), 129.6(ArC), 129.0(ArC), 128.9(ArC), 128.4(ArC), 127.3(ArC), 123.4(ArC), 121.9(ArC), 119.8(ArC), 90.8(C-8), 86.5(C-9), 72.2(C-7), 31.3(CH<sub>3</sub>), 21.5(CH<sub>3</sub>).<sup>144</sup>

#### 9.45 Preparation of 3-Iodo-4-methyl-2-phenylquinoline<sup>144</sup> **308**

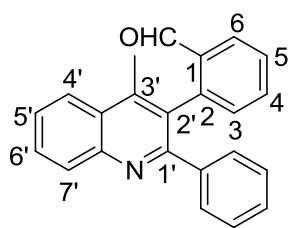
*N*-(2-(2-Hydroxy-4-phenylbut-3-yn-2-yl)phenyl)-4-methylbenzenesulfonamide **307** (1eq., 114mg, 0.198mmoles) was added to dry methanol (5mL) in a 25mL round bottom flask and iodine (1.5eq., 76.0mg, 0.289mmoles) was added to it under inert conditions. The reaction mixture was stirred at 60 °C for six hours. On completion, the reaction was quenched by addition of an aqueous saturated solution of sodium dithionite (20mL) and was extracted with diethyl ether (20mL×3). The combined organic phases were transferred to a separating funnel and washed with aqueous sodium bicarbonate (50mL) and brine (50mL) respectively, dried over anhydrous magnesium sulfate, filtered off and evaporation of the solvent afforded the crude product which was then purified by column chromatography (4% EtOAc/Hexane) to obtain the pure product **308** as a light yellow solid (35.0mg, 0.101mmoles, 32%).



**R<sub>f</sub>** 0.62 (30% EtOAc/Hexane); <sup>1</sup>H NMR (300 MHz, Chloroform-*d*) δ 8.15 (2H, t, *J* = 7.1 Hz, ArH), 7.78 (1H, t, *J* = 7.4 Hz, ArH), 7.61 (3H, d, *J* = 19.3 Hz, ArH), 7.51 (3H, d, *J* = 6.8 Hz, ArH), 3.03 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, Chloroform-*d*) δ 162.0(ArC), 149.1(ArC), 146.5 (ArC), 144.2(ArC), 130.1(ArC), 129.8(ArC), 129.1(ArC), 128.4 (ArC), 127.2(ArC), 127.1(ArC), 124.2(ArC), 100.4(ArC), 25.9(CH<sub>3</sub>).<sup>144</sup>

#### 9.46 Preparation of 2-(4-Methyl-2-phenylquinolin-3-yl)benzaldehyde **260**

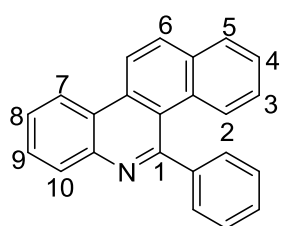
3-Iodo-4-methyl-2-phenylquinoline **259** (1eq., 23.0mg, 0.070mmoles), (2-formylphenyl)boronic acid **98** (2eq., 21.0mg, 0.141mmoles), cesium fluoride (2.5eq., 25.0mg, 0.175mmoles) and tetrakis(triphenylphosphine)palladium(0) (0.1eq., 80.0mg, 0.070mmoles) were transferred to a microwave vial and 2mL of freshly degassed dimethoxy ethane was added to it. The mixture was then set up in a microwave reactor for reaction with vigorous stirring and temperature and power of 150 °C and 150 W respectively. On completion the reaction was filtered off then subjected to column chromatography (10% EtOAc/Hexane) to obtain pure 2-(4-methyl-2-phenylquinolin-3-yl)benzaldehyde **260** (15.1mg, 0.046mmoles, 70%) as a yellow powder.



**R<sub>f</sub>** 0.48 (30% EtOAc/Hexane); **mp.** 94 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O melting point? **<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*)  $\delta$  9.76 (1H, s, CHO), 8.24 (1H, d, *J* = 8.4 Hz, ArH), 8.10 (1H, d, *J* = 8.4 Hz, ArH), 7.87 (1H, d, *J* = 7.8 Hz, ArH), 7.81-7.76 (1H, m, ArH), 7.65 (1H, t, *J* = 7.6 Hz, ArH), 7.58-7.54 (1H, m, ArH), 7.45 (1H, t, *J* = 7.6 Hz, ArH), 7.26-7.21 (3H, m, ArH), 7.17 (3H, dd, *J* = 5.2, 1.6 Hz, ArH), 2.48 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*)  $\delta$  191.0(C=O), 158.6(ArC), 147.2(ArC), 143.1(ArC), 142.3(ArC), 140.7(ArC), 134.4(ArC), 133.5(ArC), 132.4(ArC), 130.4(ArC), 130.0(ArC), 129.7(ArC), 129.4(ArC), 128.4(ArC), 128.2(ArC), 127.9(ArC), 127.8(ArC), 127.0(ArC), 124.1(ArC), 29.7(CH<sub>3</sub>).

#### 9.47 Preparation of 5-Phenylbenzo[7]phenanthridine<sup>149</sup> **303**

2-(4-Methyl-2-phenylquinolin-3-yl)benzaldehyde **309** (1eq., 13.0mg, 0.039mmoles) was added to dry dimethylformamide (2mL) in a 10mL round bottom flask and the solution was degassed for two minutes. To this was added potassium *t*-butoxide and the reaction was stirred at 80 °C under argon and the flask was irradiated with a high pressure mercury lamp through a quartz filter in a dark room. On completion, the reaction was allowed to cool down to room temperature and diluted with water (10mL) and then extracted in diethyl ether (15mL×3) before being dried over anhydrous magnesium sulfate. The reaction mixture was filtered and then the solvent removed in *vacuo* to yield the crude product which was then purified by column chromatography (10% EtOAc/Hexane) to obtain the product as a yellow solid (12.0mg, 0.039mmoles, 84%).



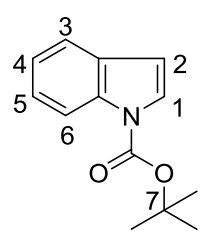
**R<sub>f</sub>** 0.40 (30% EtOAc/Hexane); **<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*)  $\delta$  8.68 (2H, dd, *J* = 8.5, 4.6 Hz, ArH), 8.31 (1H, d, *J* = 7.9 Hz, ArH), 8.20 (1H, d, *J* = 9.0 Hz, ArH), 7.95 (1H, d, *J* = 7.9 Hz, ArH), 7.80 (2H, dd, *J* = 7.6, 6.1 Hz, ArH), 7.75-7.69 (1H, m, ArH), 7.66-7.62 (2H, m, ArH), 7.54-7.48 (4H, m, ArH), 7.21 (1H, ddd, *J* = 8.5, 6.9, 1.4 Hz, ArH).<sup>149</sup>

#### 9.48 Preparation of *t*-Butyl 1*H*-indole-1-carboxylate<sup>210</sup> **465**

Indole **370** (1eq., 2.00g, 17.07mmoles) was dissolved in dry tetrahydrofuran (45mL) in a 100mL round bottom flask under inert conditions. To this stirring solution, 4-dimethylaminopyridine (0.015eq, 31.0mg, 0.256mmol) and di-*t*-butyl dicarbonate (1.5eq., 5.58g, 25.60mmoles) were added at room temperature. The reaction was stirred under the same conditions for eighteen hours. On completion, the reaction mixture was quenched using water (50mL) and neutralized by



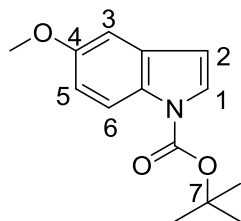
adding an aqueous sodium bicarbonate solution (50mL). The organic material was extracted into ethyl acetate (100mL×3), separated and organic layer was washed with water (100mL×2). The organic phases were combined and washed with brine (100mL), dried over anhydrous magnesium sulfate and the solvent was removed under vacuum to obtain the residue which was purified by column chromatography (20% EtOAc/Hexane) to obtain *t*-butyl 1*H*-indole-1-carboxylate **465** as a pale yellow oil (3.62g, 16.66mmoles, 98%).



$R_f$  0.19 (30% EtOAc/Hexane);  $^1\text{H NMR}$  (300 MHz, Chloroform-*d*)  $\delta$  8.17 (1H, d,  $J$  = 8.2 Hz, H-1), 7.54 (1H, d,  $J$  = 3.7 Hz, ArH), 7.49 (1H, d,  $J$  = 7.7 Hz, ArH), 7.35-7.21 (1H, m, ArH), 7.22-7.10 (1H, m, ArH), 6.49 (1H, d,  $J$  = 3.7 Hz, H-2), 1.60 (9H, s,  $\text{CH}_3 \times 3$ );  $^{13}\text{C NMR}$  (75 MHz, Chloroform-*d*)  $\delta$  149.6(C=O), 146.8(ArC), 130.6(ArC), 125.8(ArC), 124.1(ArC), 122.6(ArC), 120.9(ArC), 115.2(ArC), 107.2(ArC), 83.4(C-7), 28.0( $\text{CH}_3 \times 3$ ).<sup>210</sup>

#### 9.49 Preparation of *t*-Butyl 5-methoxy-1*H*-indole-1-carboxylate<sup>210</sup> **466**

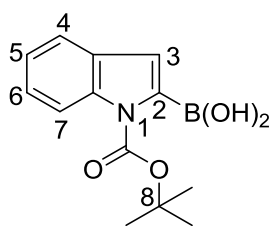
5-Methoxy-1*H*-indole **463** (1eq., 2.00g, 13.59mmoles) was dissolved in dry tetrahydrofuran (45mL) in a 100mL round bottom flask under inert conditions. To this solution, 4-dimethylaminopyridine (0.015eq., 25.0mg, 0.203mmoles) and di-*t*-butyl dicarbonate (1.5eq., 4.40g, 20.25mmoles) was added. The resulting solution was stirred at room temperature and under argon for eighteen hours. On completion, the reaction was quenched by the addition of water (50L) and then the mixture was neutralized by addition of an aqueous saturated solution of sodium bicarbonate (50mL). The solution was transferred to a separating funnel and the organic material was extracted into ethyl acetate (100mL×3). The combined organic phases were then washed with brine (100mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to furnish crude product which was purified by column chromatography to obtain the pure product **466** as a light pink solid in 100% yield (3.30g, 13.55mmoles).



$R_f$  0.21 (30% EtOAc/Hexane);  $^1\text{H NMR}$  (300 MHz, Chloroform-*d*)  $\delta$  8.02 (1H, d,  $J$  = 8.8 Hz, ArH), 7.56 (1H, d,  $J$  = 3.6 Hz, ArH), 7.02 (1H, d,  $J$  = 2.5 Hz, ArH), 6.92 (1H, d,  $J$  = 9.0 Hz, ArH), 6.66-6.37 (1H, m, ArH), 3.84 (3H, s, OMe), 1.52 (9H, s,  $\text{CH}_3 \times 3$ );  $^{13}\text{C NMR}$  (75 MHz, Chloroform-*d*)  $\delta$  155.9(ArC-4), 149.7(C=O), 146.8(ArC), 131.4(ArC), 126.5(ArC), 115.8(ArC), 113.0(ArC), 107.1(ArC), 103.5(ArC), 85.1(C-7), 55.7(OMe), 28.2( $\text{CH}_3 \times 3$ ).<sup>210</sup>

### 9.50 Preparation of (1-(*t*-Butoxycarbonyl)-1*H*-indol-2-yl)boronic acid<sup>210, 215, 216</sup> **440**

In a 50mL flame dried two neck round bottom flask, 30mL of tetrahydrofuran was added under inert conditions. Diisopropyl amine (2.5eq., 3.14g, 4.30mL, 28.76mmoles) was added to it and the solution was cooled down to -78 °C. *n*Butyllithium (2.4eq., 1.15 M in THF, 27.60mmoles, 1.70g, 23.89mL) was added drop wise to the stirring solution at the same temperature. The reaction was warmed up to 0 °C and stirred for thirty minutes. The solution turned slightly yellowish which indicated the generation of lithium diisopropylamide. The reaction was again cooled down to -78 °C and 2.80g of *t*-butyl 1*H*-indole-1-carboxylate **465** (11.50mmoles) dissolved in tetrahydrofuran (10mL) was added drop wise to the reaction and was allowed to stir at same temperature for two hours. Reaction changes colour from pale yellow to bright orange. Triisopropyl borate (2.5eq., 5.40g, 13.25mL, 28.76mmoles) was added drop wise to the reaction and the reaction was slowly warmed up to room temperature over two hours. By this time the reaction becomes cloudy light orange in color. The reaction mixture was quenched by adding ice cold water drop wise and 2 M hydrochloric acid carefully to hydrolyze borate ester. The organic material was extracted using diethyl ether (50mL×3). The organic phases were then combined and washed with brine (50mL), dried over anhydrous magnesium sulfate and solvent was removed under *vacuum*, till a few mLs of solvent was left. Cold hexane (25mLs) was added to it and stirred vigorously at 0 °C which resulted in precipitation of the expected boronic acid. The solid was filtered and dried under reduced pressure to obtain (1-(*t*-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid **440** as a white solid (2.84g, 10.87mmoles, 95%)

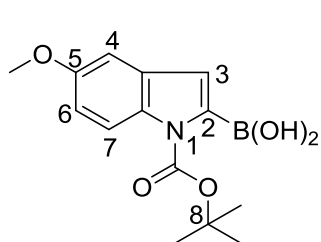


<sup>1</sup>H NMR (300 MHz, Dimethylsulphoxide-*d*<sub>6</sub>) δ 8.19 (2H, s, B(OH)<sub>2</sub>), 8.10 (1H, d, *J* = 8.2 Hz, ArH), 7.57 (1H, d, *J* = 7.7 Hz, ArH), 7.29 (1H, t, *J* = 7.6 Hz, ArH), 7.21 (1H, t, *J* = 7.4 Hz, ArH), 6.64 (1H, s, ArH-3), 1.62 (9H, s, CH<sub>3</sub>×3); <sup>13</sup>C NMR (75 MHz, Dimethylsulphoxide-*d*<sub>6</sub>) δ 150.3(C=O), 136.6(ArC), 131.1(ArC), 124.3(ArC), 122.9(ArC), 121.0(ArC), 114.9(ArC), 112.5(ArC), 84.4(C-8), 28.0(CH<sub>3</sub>×3).<sup>210</sup>

### 9.51 Preparation of 1-(*t*-Butoxycarbonyl)-5-methoxy-1*H*-indol-2-ylboronic acid<sup>210, 217</sup> **467**

Diisopropyl amine (2.5eq., 2.20g, 3mL, 20.30mmoles) was added in a 50mL flame dried two neck round bottom flask and 30mL of freshly distilled, dry tetrahydrofuran was added and the solution was cooled to -78 °C. *n*Butyllithium. (2.4eq., 1.5 M in THF, 1.24g, 12.90mL, 19.40mmoles) was added drop wise to the stirring solution at the same temperature under inert conditions. The reaction was warmed up to 0 °C and stirred for thirty minutes. The solution turned slight yellowish which indicated generation of lithium diisopropylamide. The reaction was again cooled down to -78

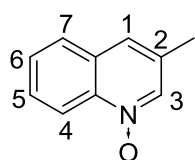
°C and *t*-butyl 5-methoxy-1*H*-indole-1-carboxylate **466** (1eq., 2.00g, 8.12mmoles) dissolved in tetrahydrofuran (10mL) was added drop wise to the reaction and allowed to stir at same temperature for two hours. The reaction changes colour from pale yellow to bright orange which indicated the generation of anion. Trimethyl borate (2.5eq., 2.10g, 2.20mL, 20.30mmoles) was added drop wise to the stirring solution and the reaction was slowly warmed up to room temperature over two hours. By this time the reaction becomes cloudy light orange in color. The reaction mixture was quenched by adding ice cold water drop wise and 2 M hydrochloric acid carefully to hydrolyse borate ester. The organic material was extracted using diethyl ether (50mL×3). The organic phases were combined and washed with brine, dried over anhydrous magnesium sulfate and solvent was removed under vacuum, till a few mL of solvent was left. Cold hexane (25mLs) was added to it and stirred vigorously at 0 °C which resulted in precipitation of the expected boronic acid. The solid was filtered and dried under reduced pressure to obtain (1-(*t*-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid **467** as a white solid (2.15g, 7.38mmoles, 93%).



<sup>1</sup>H NMR (300 MHz, Dimethylsulphoxide-*d*<sub>6</sub>) δ 8.18 (2H, s, B(OH)<sub>2</sub>), 7.96 (1H, d, *J* = 9.0 Hz, ArH), 7.09 (1H, d, *J* = 2.1 Hz, ArH), 6.89 (1H, dd, *J* = 8.9, 2.2 Hz, ArH), 6.56 (1H, s, ArH-3), 3.78 (3H, s, OMe), 1.60 (9H, s, CH<sub>3</sub>×3); <sup>13</sup>C NMR (75 MHz, Dimethylsulphoxide-*d*<sub>6</sub>) δ 155.8(ArC-5), 150.3(C=O), 132.0(ArC), 131.2(ArC), 115.6(ArC), 113.0(ArC), 112.5(ArC), 103.5(ArC-3), 84.2(C-8), 55.7(OMe), 28.1(CH<sub>3</sub>×3).<sup>210</sup>

### 9.52 Preparation of 3-Methylquinoline 1-oxide<sup>220</sup> **472**

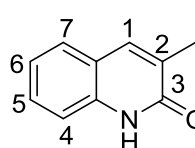
3-Methylquinoline **464** (1eq., 2.50g, 17.45mmoles) was dissolved in freshly distilled dichloromethane (20mL) and *m*-chloroperbenzoic acid (2eq., 6.02g, 34.91mmoles) was added to the stirring reaction solution in portions. The reaction mixture bubbled and changed color from very light yellow to dark yellow. The reaction was then allowed to stir at room temperature under air for forty five minutes after which time reaction goes very hazy dark yellow. An aqueous saturated solution of sodium bicarbonate (20mL) was added to quench the excess *m*-chloroperbenzoic at 0 °C and then the solution was transferred to separating funnel and washed with dichloromethane (50mL×3). The organic phase were combined and washed with brine (100mL), dried over magnesium sulfate and purified using column chromatography (5% MeOH/DCM) to afford the product **472** as light a yellow solid (2.40g, 15mmoles, 87% yield)



**R<sub>f</sub>** 0.86 (EtOAc); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  8.69 (1H, d, *J* = 8.6 Hz, ArH), 8.45 (1H, s, ArH-3), 7.79 (1H, d, *J* = 8.1 Hz, ArH), 7.70 (1H, t, *J* = 7.2 Hz, ArH), 7.66-7.57 (1H, m, ArH), 7.55 (1H, s, ArH-1), 2.46 (3H, s, CH<sub>3</sub>).; **<sup>13</sup>C NMR** (75 MHz, Dimethylsulphoxide-*d*<sub>6</sub>)  $\delta$  134.5(ArC), 131.8(ArC), 126.0(ArC), 125.0(ArC), 124.1(ArC), 123.5(ArC), 122.2(ArC), 120.3(ArC), 114.3(ArC), 13.5(CH<sub>3</sub>).<sup>220</sup>

### 9.53 Preparation of 3-Methylquinolin-2(1H)-one<sup>221</sup> **473**

3-Methylquinoline 1-oxide **472** (1eq., 2.40g, 15.00mmoles) was dissolved in chloroform (50mL) in a 100mL round bottom flask and *p*-toluene sulfonic acid (1.2eq., 3.45g, 18.11mmoles) was added. Potassium carbonate (3.5eq., 7.29g, 52.81mmoles) was dissolved in water (25mL) and added to the reaction mixture. The reaction was allowed to stir for five hours at room temperature under inert conditions. On completion the reaction mixture was cooled to 0 °C, and an aqueous saturated solution of sodium bicarbonate (100mL) was added to it slowly and carefully to quench unreacted *p*-toluene sulfonic acid. While doing so, reaction mixture bubbled vigorously. When bubbling ceased the solution was transferred to a separating funnel and extracted with chloroform (50mL×3). The organic layers were collected together, dried over anhydrous magnesium sulfate, filtered off and solvent was then removed in *vacuo* to obtain the crude product which was then purified by column chromatography (30% EtOAc/Hexane) to furnish pure 3-methylquinolin-2(1H)-one **473** as an off-white solid (2.00g, 12.00mmoles, 83%).

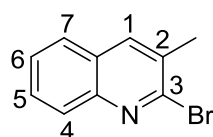


**R<sub>f</sub>** 0.48 (EtOAc); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  11.80 (1H, s, NH), 7.65 (1H, s, ArH), 7.44 (3H, dt, *J* = 22.8, 7.9 Hz, ArH), 7.19 (1H, t, *J* = 7.3 Hz, ArH), 2.31 (3H, s, CH<sub>3</sub>).; **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  164.5(C=O), 137.5(ArC), 130.1(ArC), 129.3(ArC), 126.8(ArC), 122.4(ArC), 120.32(ArC), 115.6(ArC), 16.8(CH<sub>3</sub>).<sup>221</sup>

### 9.54 Preparation of 2-Bromo-3-methylquinoline<sup>222</sup> **461**

3-Methylquinolin-2(1H)-one **473** (1eq., 93.0mg, 0.657mmoles) and phosphorus oxybromide (1.5eq., 274mg, 0.954mmoles) were transferred to a 10mL round bottom flask and stirred at 140 °C for three hours. On completion, the reaction mixture was immediately poured in a beaker carrying ice cold water (20mL) and was transferred to a separating funnel and was then extracted in dichloromethane (20mL×3). The combined organic phases were washed with brine (50mL) and dried over anhydrous magnesium sulfate, filtered and the solvent was

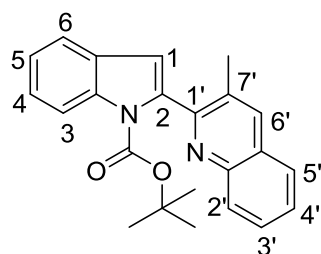
removed in *vacuo* to obtain crude product. Column chromatography (20% EtOAc/Hexane) was performed to obtain product **461** in pure form as a light brown powder (101mg, 0.454mmoles, 83%).



**R<sub>f</sub>** 0.31 (EtOAc); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  8.01 (1H, d, *J* = 8.4 Hz, ArH), 7.93 (1H, s, ArH-1), 7.73 (1H, d, *J* = 8.1 Hz, ArH), 7.70-7.62 (1H, m, ArH), 7.58-7.49 (1H, m, ArH), 2.58-2.50 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  147.0(ArC), 145.5(ArC), 137.0(ArC), 132.3(ArC), 129.5(ArC), 128.3(ArC), 127.7(ArC), 127.0(ArC), 126.9(ArC), 22.4(CH<sub>3</sub>).<sup>222</sup>

### 9.55 Preparation of *t*-Butyl 2-(3-methylquinolin-2-yl)-1*H*-indole-1-carboxylate **474**

A flame dried 2-neck 50mL round bottom flask was charged with tetrakis(triphenylphosphine) palladium(0) (0.1eq., 442mg, 0.38mmoles) under inert conditions and at room temperature. 1.00g (3.88mmoles) of (1-(*t*butoxycarbonyl)-1*H*-indol-2-yl)boronic acid **440** and 2-bromo-3-methylquinoline **473** (1eq., 850mg, 3.83mmoles) were added to 20mL of dimethoxyethane. The solution was degassed for ten minutes and transferred to the flask from a dropping funnel. Mixture was allowed to stir for ten minutes at room temperature. An 2 M aqueous sodium carbonate (4mL) was degassed for ten minutes and transferred to the reaction flask via a dropping funnel. The reaction was allowed to stir at reflux for eighteen hours under inert conditions, over which time reaction turns from milky yellow to clear brown solution. The reaction was cooled and quenched using water (20mL) and the solution was transferred to a separating funnel and organic material was extracted using ethyl acetate (50mL×3). The organic phases were combined, washed with brine (50mL), dried over anhydrous magnesium sulfate and the solvent was removed under vacuum to obtain the crude product, which was then purified by column chromatography (10% EtOAc/Hexane) to obtain *t*-butyl 2-(3-methylquinolin-2-yl)-1*H*-indole-1-carboxylate **474** as a pale yellow solid (1.30g, 36.26 mmoles, 95%).

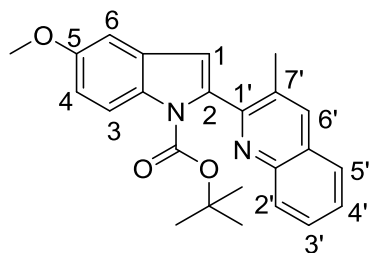


**Mp.** 45 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **R<sub>f</sub>** 0.50 (30% EtOAc/Hexane); **FTIR** (v/cm<sup>-1</sup>): 2978-2930(C-H), 1721(CO<sub>2</sub>O), 1601-1560(ArC=C), 1328(C-O), 1258(C=N), 1226(C-N); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  8.31 (1H, d, *J* = 8.0 Hz, ArH), 8.11 (1H, d, *J* = 8.3 Hz, ArH), 7.93 (1H, s, ArH-6'), 7.75 (1H, d, *J* = 8.0 Hz, ArH), 7.61 (2H, dd, *J* = 13.2, 7.8 Hz, ArH), 7.51 (1H, d, *J* = 7.4 Hz, ArH), 7.35 (1H, d, *J* = 7.7 Hz, ArH), 7.27 (1H, d, *J* = 7.4 Hz, ArH), 6.71 (1H, s, ArH-1), 2.35 (3H, s, CH<sub>3</sub>), 1.12 (9H, s, CH<sub>3</sub>×3); **<sup>13</sup>C NMR** (75MHz, Chloroform-*d*)  $\delta$  154.9(C=O), 149.7(ArC), 146.0(ArC), 137.8(ArC), 136.7(ArC), 135.3(ArC), 130.8(ArC), 129.3(ArC), 129.2(ArC), 128.8(ArC), 127.8(ArC), 126.7(ArC), 124.7(ArC), 123.0(ArC), 120.9(ArC), 115.5(ArC),

110.4(ArC), 83.3(O-C(CH<sub>3</sub>)<sub>3</sub>), 27.4(CH<sub>3</sub>×3), 19.4(CH<sub>3</sub>); **HRMS** (ESI<sup>+</sup>): Found M<sup>+</sup>+H 359.1750, C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>+H) requires 359.1750, m/z 359.1750 (M<sup>+</sup>+H, 100%), 360.1778 (25%).

### 9.56 Preparation of *t*-Butyl 5-methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-1-carboxylate **475**

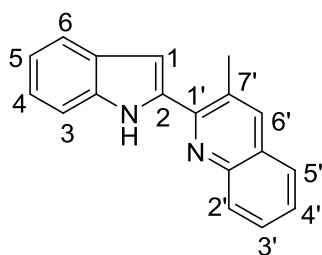
In a flame dried 2-neck 50mL round bottom flask tetrakis(triphenylphosphine) palladium(0) (0.1eq., 198mg, 0.172mmoles) was added under inert conditions and at room temperature. 1-(*t*-Butoxycarbonyl)-5-methoxy-1*H*-indol-2-ylboronic acid **467** (1eq., 500mg, 1.72mmoles) and 2-bromo-3-methylquinoline **473** (1eq., 381mg, 1.72mmoles) were added to 10mL of dimethoxy ethane and the solution was degassed for ten minutes and then transferred to the flask from a dropping funnel. The resulting mixture was allowed to stir for ten minutes at room temperature and an aqueous 2 M sodium carbonate (3mL) was degassed for ten minutes and transferred to the reaction flask via a dropping funnel. The reaction was allowed to stir at reflux for eighteen hours under inert conditions, over which time reaction turns from milky yellow to clear brown solution. The reaction was cooled and quenched using water (10mL). The mixture was then transferred to a separating funnel and organic material was extracted using ethyl acetate (15mL×3). The organic phases were combined, washed with brine (50mL), dried over anhydrous magnesium sulfate and the solvent was removed in vacuum to obtain the crude product, which was purified by column chromatography (10% EtOAc/Hexane) to obtain *t*-butyl 2-(3-methylquinolin-2-yl)-1*H*-indole-1-carboxylate as yellow solid **475** (536mg, 1.37 mmoles, 80%).



**Mp.** 49 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **R<sub>f</sub>** 0.43 (30% EtOAc/Hexane); **FTIR** (v/cm<sup>-1</sup>): 2920-2850(C-H), 1725(CO<sub>2</sub>R), 1602-1560(ArC=C), 1320(C-O), 1272-1259(C=N), 1219(C-N); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 8.14 (2H, dd, *J* = 17.7, 8.7 Hz, ArH), 7.97 (1H, s, ArH), 7.79 (1H, d, *J* = 8.0 Hz, ArH), 7.66 (1H, dd, *J* = 8.4, 1.3 Hz, ArH), 7.60-7.49 (1H, m, ArH), 7.06 (1H, d, *J* = 2.5 Hz, ArH), 6.99 (1H, dd, *J* = 9.0, 2.5 Hz, ArH), 6.64 (1H, s, ArH), 3.88 (3H, s, OMe), 2.37 (3H, s, CH<sub>3</sub>), 1.14 (9H, s, CH<sub>3</sub>×3); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) δ 156.1(ArC-5), 155.0(C=O), 149.7(ArC), 146.1(ArC), 138.4(ArC), 135.3(ArC), 131.45(ArC), 130.9(ArC), 130.1(ArC), 129.3(ArC), 128.8(ArC), 127.9(ArC), 126.8(ArC), 126.7(ArC), 116.4(ArC), 113.6(ArC), 110.2(ArC), 103.3(ArC), 83.3(O-C(CH<sub>3</sub>)<sub>3</sub>), 55.7(OMe), 27.5(CH<sub>3</sub>×3), 19.4(CH<sub>3</sub>); **HRMS** (ESI<sup>+</sup>): Found M<sup>+</sup>+H 389.1848, C<sub>24</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>+H) requires 389.1866, m/z 389.1848 (M<sup>+</sup>+H, 100%), 390.1896 (25%).

### 9.57 Preparation of 2-(1*H*-Indol-2-yl)-3-methylquinoline 476

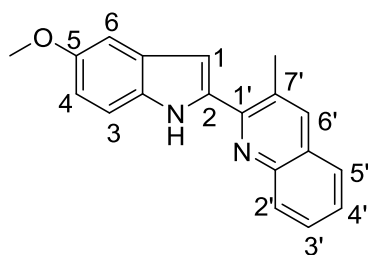
*t*-Butyl 2-(3-methylquinolin-2-yl)-1*H*-indole-1-carboxylate **474** (1eq., 1.00g, 2.79mmoles) was dissolved in dry dichloromethane (20mL) in a 50mL round bottom flask under inert conditions and the temperature was cooled down to 0 °C. Aluminium chloride (1.3eq., 484mg, 3.63mmoles) was added to the reaction in one portion. The reaction immediately changed color from light yellow to bright red. The reaction was allowed to stir for one hour under the same conditions. The reaction was quenched using ice cold water and red colour disappears immediately and changed to yellow. The organic material was extracted in to dichloromethane (20mL×3). The organic phases were combined, washed with brine (50mL), dried over anhydrous sodium sulfate and the solvent was removed in vacuum to obtain the crude product, which was purified by flash column chromatography (5% EtOAc/Hexane) to obtain 2-(1*H*-indol-2-yl)-3-methylquinoline **476** as a yellow solid (480mg, 36.26 mmoles, 68%).



**Mp.** 155-157 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O; **R<sub>f</sub>** 0.35 (30% EtOAc/Hexane); **FTIR** (v/cm<sup>-1</sup>): 3289(N-H), 3046-2972(C-H), 1616-1559(ArC=C), 1240(C=N); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 10.13 (1H, s, NH), 8.06 (1H, d, *J* = 8.4 Hz, ArH), 7.94 (1H, s, ArH), 7.71 (2H, t, *J* = 7.5 Hz, ArH), 7.64 (1H, t, *J* = 7.6 Hz, ArH), 7.48-7.43 (2H, m, ArH), 7.26 (1H, t, *J* = 7.5 Hz, ArH), 7.15 (1H, s, ArH), 7.12 (1H, t, *J* = 7.5 Hz, ArH), 2.80 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) δ 149.5(ArC), 146.2(ArC), 137.6(ArC), 136.2(ArC), 135.8(ArC), 129.4(ArC), 129.0(ArC), 129.0(ArC), 128.6(ArC), 127.2(ArC), 126.7(ArC), 126.2(ArC), 123.7(ArC), 121.54(ArC), 119.9(ArC), 111.2(ArC), 105.3(ArC), 21.8(CH<sub>3</sub>); **HRMS** (ESI<sup>+</sup>): Found M<sup>+</sup>+H 259.1230, C<sub>18</sub>H<sub>14</sub>N<sub>2</sub> (M<sup>+</sup>+H) requires 259.1236, m/z 259.1230 (M<sup>+</sup>+H, 100%), 260.1259 (20%).

### 9.58 Preparation of 2-(5-Methoxy-1*H*-indol-2-yl)-3-methylquinoline 477

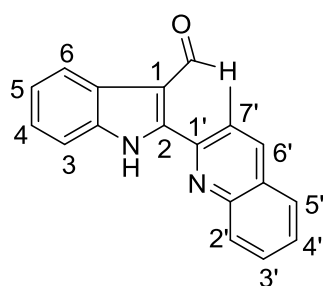
*t*-Butyl 5-methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-1-carboxylate **475** (1eq., 1.08g, 2.79mmoles) was dissolved in dry dichloromethane (20mL) under an argon atmosphere and temperature was cooled down to 0 °C. Aluminium chloride (1.3eq., 0.481mg, 3.61mmoles) was added to the reaction in one portion. The reaction immediately changed color from light yellow to bright red and was allowed to stir for one hour under the same conditions. On completion, reaction was quenched using ice cold water (30mL), the red colour disappeared immediately turning to yellow. The organic material was extracted in dichloromethane (30mL×3). Organic phases were combined, washed with brine (50mL), dried over anhydrous sodium sulfate and solvent was removed in vacuum to obtain the crude product, which was purified using flash column (5% EtOAc/Hexane) to obtain 2-(1*H*-indol-2-yl)-3-methylquinoline **405** as a yellow solid (553mg, 1.91 mmoles, 69%).



**Mp.** 175-177 °C ( $\text{C}_2\text{H}_5\text{O}$ ); **R<sub>f</sub>** 0.64 (30% EtOAc/Hexane); **FTIR** ( $\text{v}/\text{cm}^{-1}$ ): 3147(N-H), 3069-2934(C-H), 1622-1594(ArC=C), 1322(C-O), 1292(C+n); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  10.05 (1H, s, NH), 8.04 (1H, d,  $J$  = 8.4 Hz, ArH), 7.90 (1H, s, ArH), 7.74-7.58 (2H, m, ArH), 7.49-7.39 (1H, m, ArH), 7.30 (1H, d,  $J$  = 8.8 Hz, ArH), 7.12 (1H, d,  $J$  = 2.3 Hz, ArH), 7.05 (1H, d,  $J$  = 1.4 Hz, ArH), 6.93 (1H, dd,  $J$  = 8.8, 2.4 Hz, ArH), 3.86 (3H, s, OMe), 2.76 (3H, s,  $\text{CH}_3$ ); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  154.2(ArC-5), 149.5(ArC), 146.2(ArC), 137.6(ArC), 136.7(ArC), 131.2(ArC), 129.7(ArC), 129.0(ArC), 128.9(ArC), 128.6(ArC), 127.2(ArC), 126.7(ArC), 126.1(ArC), 114.5(ArC), 112.0(ArC), 105.0(ArC), 102.6(ArC), 55.8(OMe), 21.8( $\text{CH}_3$ ); **HRMS** (ESI<sup>+</sup>): Found  $\text{M}^+\text{+H}$  289.1331,  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$  ( $\text{M}^+\text{+H}$ ) requires 289.1342,  $m/z$  289.1331 ( $\text{M}^+\text{+H}$ , 100%), 290.1364 (20%).

### 9.59 Preparation of 2-(3-Methylquinolin-2-yl)-1H-indole-3-carbaldehyde 478

2-(1H-Indol-2-yl)-3-methylquinoline **476** (1eq., 430mg, 1.66mmoles) was transferred to a 50mL round bottom flask carrying 20mL dichloromethane and to this stirring solution was added dichloromethyl methyl ether (2eq., 383mg, 0.30mL, 3.33mmol) at room temperature and under argon. The solution was then cooled down to -70 °C and tin(IV)chloride (1.5eq., 650mg, 0.29mL, 2.49mmoles) was added carefully to the reaction mixture. The reaction mass was allowed to warm up to 0 °C and then was stirred for three hours at 0 °C under argon. On completion, the reaction was quenched using water (50mL) and then an aqueous saturated solution of sodium bicarbonate (20mL) was added. The solution was then transferred to a separating funnel and was washed with dichloromethane (25mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered off and the solvent was removed under reduced pressure to obtain crude product which was subjected to column chromatography (25% EtOAc/Hexane) to yield 2-(3-methylquinolin-2-yl)-1H-indole-3-carbaldehyde **478** as a yellow solid (358mg, 1.25mmoles, 75%).

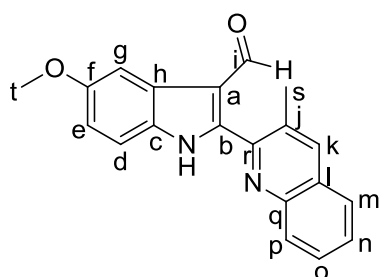


**R<sub>f</sub>** 0.53 (50% EtOAc/Hexane); **<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  12.55 (1H, s, NH), 9.81 (1H, s, C=O), 8.41 (1H, s, ArH), 8.23 (1H, d,  $J$  = 7.7 Hz, ArH), 8.08 (1H, d,  $J$  = 8.4 Hz, ArH), 8.02 (1H, d,  $J$  = 8.1 Hz, ArH), 7.79 (1H, t,  $J$  = 7.6 Hz, ArH), 7.68 (1H, t,  $J$  = 7.5 Hz, ArH), 7.57 (1H, d,  $J$  = 7.9 Hz, ArH), 7.32 (2H, dt,  $J$  = 21.9, 7.2 Hz, ArH), 3.32 (3H, s,  $\text{CH}_3$ ).



### 9.60 Preparation of 5-Methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **479**

2-(5-Methoxy-1*H*-indol-2-yl)-3-methylquinoline **477** (1eq., 123mg, 0.429mmoles) was added to a 20mL round bottom flask and dichloromethane (5mL) was added. To this solution dichloromethyl methyl ether (2eq., 98.0mg, 0.08mL, 0.858mmol) was added at room temperature under inert conditions. The reaction mixture was then cooled down to -70 °C and tin(IV)chloride (1.5eq., 176mg, 0.07mL, 0.643mmoles) was added carefully. The reaction mixture was allowed to warm up to 0 °C and under these conditions stirred for another three hours. On completion, the reaction was quenched using water (10mL) and an aqueous saturated solution of sodium bicarbonate (10mL) was added. The solution was then transferred to a separating funnel and the organic material was extracted with dichloromethane (10mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered off and solvent was removed under reduced pressure to procure crude product which was subjected to column chromatography (25% EtOAc/Hexane) to obtain 5-methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **479** as a dark yellow solid (88.0mg, 0.279mmoles, 65%-crude yield).

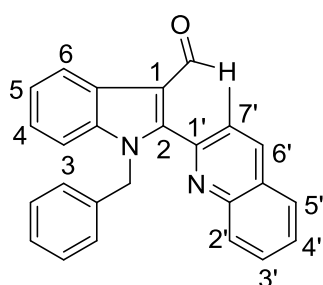


**R<sub>f</sub>** 0.39 (30% EtOAc/Hexane). Due to stability and solubility problems this product was considered as an intermediate and was used in the following step without any characterization.

### 9.61 Preparation of 1-Benzyl-2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **480**

2-(3-Methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **478** (1eq., 188mg, 0.657mmoles) together with dimethylformamide (2mL) under argon was added to a 10mL round bottom flask. Sodium hydride (2eq., 53.0mg of 60%, 1.31mmoles) was added and the reaction mixture was allowed to stir for ten minutes. Benzyl bromide (2eq., 225mg, 0.156mL, 1.31mmoles) was added and the reaction mixture was allowed to stir under argon and at room temperature for one hour. On completion, the reaction was cooled down to 0 °C and was quenched by adding ice cold water (10mL) carefully and then was transferred to a separating funnel where it was washed with dichloromethane (10mL×3). The combined organic phases were washed with brine (25mL), dried over anhydrous magnesium sulfate, filtered off through a pad of celite and then solvent was removed in *vacuo* to obtain the crude product which was purified by column chromatography (20% EtOAc/ Hexane) to obtain pure

1-benzyl-2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **480** as an off-white solid (230mg, 0.610mmoles, 93%).

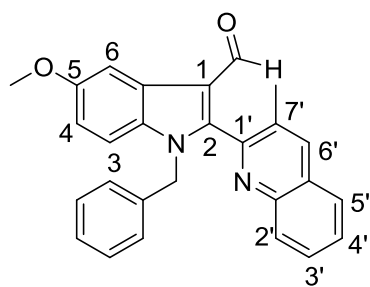


**Mp.** 67-70 °C ( $C_2H_5$ )<sub>2</sub>O; **R<sub>f</sub>** 0.39 (50% EtOAc/Hexane); **FTIR** ( $\nu/cm^{-1}$ ): 3030-2922(C-H), 1708(CHO), -1661-1598(ArC-C), 1237(C=N), 1202(C-N); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*)  $\delta$  9.73 (1H, s, CHO), 8.43 (1H, dd,  $J$  = 5.6, 3.0 Hz, ArH), 8.12 (1H, d,  $J$  = 8.4 Hz, ArH), 8.03 (1H, s, ArH-6'), 7.84 (1H, d,  $J$  = 8.1 Hz, ArH), 7.74 (1H, t,  $J$  = 7.2 Hz, ArH), 7.62 (1H, t,  $J$  = 7.5 Hz, ArH), 7.44 (1H, dd,  $J$  = 5.9, 3.0 Hz, ArH), 7.41-7.33 (2H, m, ArH), 7.14 (3H, q,  $J$  = 5.9 Hz, ArH), 6.91 (2H, d,  $J$  = 6.4 Hz, ArH), 5.30 (2H, s, CH<sub>2</sub>), 2.14 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*)  $\delta$  185.3(C=O), 150.1(ArC-1), 147.5(ArC), 146.5(ArC), 137.3(ArC), 136.8(ArC), 136.0(ArC), 131.6(ArC), 129.6(ArC), 129.5(ArC), 128.6(ArC), 128.2(ArC), 127.9(ArC), 127.8(ArC), 127.0(ArC), 127.0(ArC), 125.3(ArC), 124.3(ArC), 123.4(ArC), 122.3(ArC), 116.5(ArC), 110.6(ArC), 47.9(CH<sub>2</sub>), 19.3(CH<sub>3</sub>); **HRMS** (ESI<sup>+</sup>): Found  $M^+ + H$  377.1646,  $C_{26}H_{21}N_2O$  ( $M^+ + H$ ) requires 377.1655,  $m/z$  377.1646 ( $M^+ + H$ , 100%), 378.1678 (30%);

## 9.62 Preparation of 1-Benzyl-5-methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **481**

5-Methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **479** (1eq., 38.0mg, 0.122mmoles) was dissolved in dry dimethylformamide (2mL) under inert conditions and the temperature of the solution was reduced to 0 °C. To this solution was added sodium hydride (2eq., 6.0mg, 0.244mmoles) and the reaction mixture was allowed to stir for ten minutes and slowly the temperature was allowed to rise to room temperature when benzyl bromide (2eq., 0.02mL, 42.0mg, 0.244mmoles) was added. The reaction was allowed to stir for another one hour at this temperature. On completion, the reaction was again cooled down to 0 °C and ice-cold water (10mL) was added carefully to quench the reaction. The solution was transferred to a separating funnel and extracted with dichloromethane (10mL×3). The organic phases were combined and washed with brine (25mL), dried over anhydrous magnesium sulfate, filtered off through a pad of celite and then the solvent was removed in *vacuo* to obtain the crude product which was purified by column chromatography (20% EtOAc/ Hexane) to obtain pure 1-benzyl-5-methoxy-2-(3-methylquinolin-2-yl)-1*H*-indole-3-carbaldehyde **481** as a white solid (48.0mg, 0.118mmol, 97%).

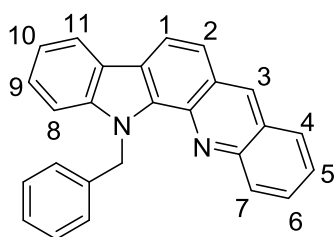
**Mp** 79-81 °C ( $C_2H_5$ )<sub>2</sub>O; **R<sub>f</sub>** 0.50 (30% EtOAc/Hexane); **FTIR** ( $\nu/cm^{-1}$ ): 2920-2850(C-H), 1718(CHO), 1660(ArC-C), 1230(C=N), 1175(C-N), 1341(C-O); **<sup>1</sup>H NMR** (300 MHz,



Chloroform-*d*)  $\delta$  10.75 (1H, s, CHO), 8.04-7.98 (2H, m, ArH), 7.76 (1H, d,  $J$  = 8.1 Hz, ArH), 7.68 (1H, s, ArH-5), 7.65 (1H, s, ArH-6'), 7.58-7.50 (2H, m, ArH), 7.13-7.09 (3H, m, ArH), 6.91 (1H, d,  $J$  = 9.0 Hz, ArH), 6.84 (2H, dd,  $J$  = 6.5, 2.7 Hz, ArH), 5.59 (2H, s, CH<sub>2</sub>), 3.96 (3H, s, OMe), 2.48 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, Chloroform-*d*)  $\delta$  190.7(C=O), 159.5(ArC-5), 152.1(ArC-1), 146.3(ArC), 141.6(ArC), 138.1(ArC), 137.0(ArC), 133.4(ArC), 131.0(ArC), 129.2(ArC), 128.9(ArC), 128.4(ArC), 127.5(ArC), 127.2(ArC), 127.0(ArC), 126.8(ArC), 126.4(ArC), 126.2(ArC), 118.0(ArC), 115.8(ArC), 107.6(ArC), 106.2(ArC), 56.9(CH<sub>2</sub>), 47.7(OMe), 20.5(CH<sub>3</sub>); **HRMS** (ESI<sup>+</sup>): Found  $M^+$ +H 407.1752, C<sub>27</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>, ( $M^+$ +H) requires 407.1760,  $m/z$  407.1752 ( $M^+$ +H, 100%), 406.1787(30%).

### 9.63 Preparation of 13-Benzyl-13H-indolo[3,2-c]acridine 482

1-Benzyl-2-(3-methylquinolin-2-yl)-1H-indole-3-carbaldehyde **480** (1eq., 148mg, 0.394mmoles) was dissolved in dimethylformamide (2mL) and the solution was degassed for two minutes. To this solution, potassium *t*-butoxide (4eq., 176mg, 1.57mmoles) was added and the reaction mixture was allowed stirred at 80 °C under argon while the flask was irradiated with a high pressure mercury lamp through a quartz filter under dark for ten minutes. When completed, the reaction was allowed to cool down to room temperature and then diluted with water (10mL) and the organic material was extracted in diethyl ether (10mL×3). The combined organic phases were washed with brine (25mL), dried over anhydrous magnesium sulfate, filtered and solvent was removed in vacuum to obtain the crude product which was purified by column chromatography (5% EtOAc/Hexane) to obtain 13-benzyl-13H-indolo[3,2-c]acridine **482** as a bright yellow solid (113mg, 0.316mmoles, 80%).

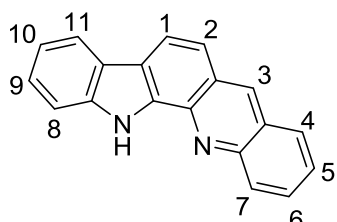


**Mp.** 183-185 °C CHCl<sub>3</sub>; **R<sub>f</sub>** 0.21 (30% EtOAc/Hexane); **FTIR** ( $\nu$ /cm<sup>-1</sup>): 3055-2919(C-H), 1604(ArC-C), 1256(C=N), 1197(C-N); <sup>1</sup>H NMR (300 MHz, Chloroform-*d*)  $\delta$  8.79 (1H, s, ArH-3), 8.19 (3H, t,  $J$  = 7.3 Hz, ArH), 7.99 (1H, d,  $J$  = 8.3 Hz, ArH), 7.70 (2H, d,  $J$  = 8.5 Hz, ArH), 7.61 (1H, d,  $J$  = 8.2 Hz, ArH), 7.55-7.44 (2H, m, ArH), 7.33 (3H, d,  $J$  = 7.6 Hz, ArH), 7.23-7.12 (3H, m, ArH), 6.86 (2H, s, CH<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, Chloroform-*d*)  $\delta$  147.1(ArC), 141.4(ArC), 140.4(ArC), 139.4(ArC), 135.5(ArC), 133.1(ArC), 129.5(ArC), 129.3(ArC), 128.4(ArC), 127.9(ArC), 127.0(ArC), 126.8(ArC), 126.8(ArC), 125.7(ArC), 125.3(ArC), 123.4(ArC), 120.6(ArC), 120.1(ArC), 120.1(ArC),

119.9(ArC), 119.7(ArC), 110.5(ArC), 49.3(CH<sub>2</sub>); **HRMS** (ESI<sup>+</sup>): Found M<sup>+</sup>+H 359.1542, C<sub>26</sub>H<sub>19</sub>N<sub>2</sub> (M<sup>+</sup>+H) requires 359.1549, m/z 359.1542 (M<sup>+</sup>+H, 100%), 360.1569 (25%)

#### 9.64 Preparation of 13H-indolo[3,2-c]acridine<sup>203</sup> **417**

13-Benzyl-13H-indolo[3,2-c]acridine **482** (1eq., 50.0mg, 0.139mmoles) was dissolved in 3mL of benzene under inert conditions and to the resulting solution was added aluminium chloride (4eq., 37.0mg, 0.558mmoles) at 0 °C. The resulting reaction mixture was allowed to warm up to room temperature and was stirred at this temperature under inert conditions for two hours. After this time, the reaction was quenched using water (10mL) and then the organic material was extracted into ethyl acetate (10mL×3). The combined organic phases were washed with an aqueous saturated solution of sodium bicarbonate (20mL), followed by brine (20mL). The organic phases were collected, dried over anhydrous magnesium sulfate, filtered and solvent was removed under reduced pressure to obtain the crude product. Later column chromatography (10% EtOAc/Hexane) was carried out to isolate pure product **417** as a yellow solid (29.0mg, 0.110mmoles, 79%).



**Mp.** 107-109 °C (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O (*lit.* 110 °C); **R<sub>f</sub>** 0.39 (30% EtOAc/Hexane); **FTIR** (ν/cm<sup>-1</sup>): 3216(N-H), 3046-2921(ArC-C), 1242(C=N); **<sup>1</sup>H NMR** (300 MHz, Chloroform-*d*) δ 10.61 (1H, s, NH), 8.85 (1H, d, *J* = 10.0 Hz, ArH), 8.28 (1H, t, *J* = 7.8 Hz, ArH), 8.20-8.10 (1H, m, ArH), 8.08-8.00 (1H, m, ArH), 7.80-7.67 (2H, m, ArH), 7.58-7.51 (1H, m, ArH), 7.49-7.38 (1H, m, ArH), 7.33-7.26 (2H, m, ArH), 7.24-7.18 (1H, m, ArH); **<sup>13</sup>C NMR** (75 MHz, Chloroform-*d*) δ 147.5(ArC), 138.5(ArC), 136.3(ArC), 130.0(ArC), 128.9(ArC), 128.5(ArC), 128.4(ArC), 128.4(ArC), 126.4(ArC), 126.0(ArC), 126.0(ArC), 125.4(ArC), 125.3(ArC), 124.0(ArC), 120.5(ArC), 120.1(ArC), 120.1(ArC), 119.3(ArC), 111.8(ArC); **HRMS** (ESI<sup>+</sup>): Found M<sup>+</sup>+H 269.1073, C<sub>19</sub>H<sub>13</sub>N<sub>2</sub> (M<sup>+</sup>+H) requires 269.1079, m/z 269.1073 (M<sup>+</sup>+H, 100%), 270.1104 (20%).

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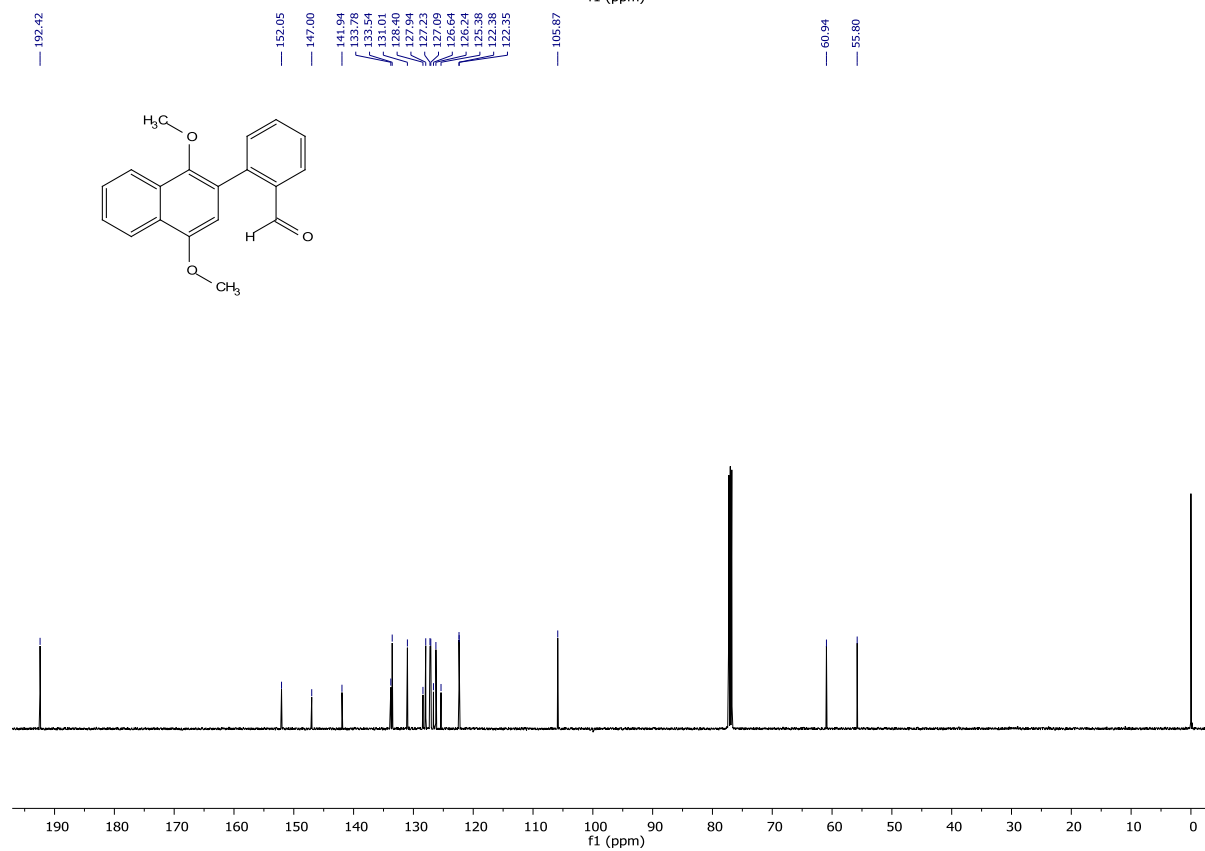
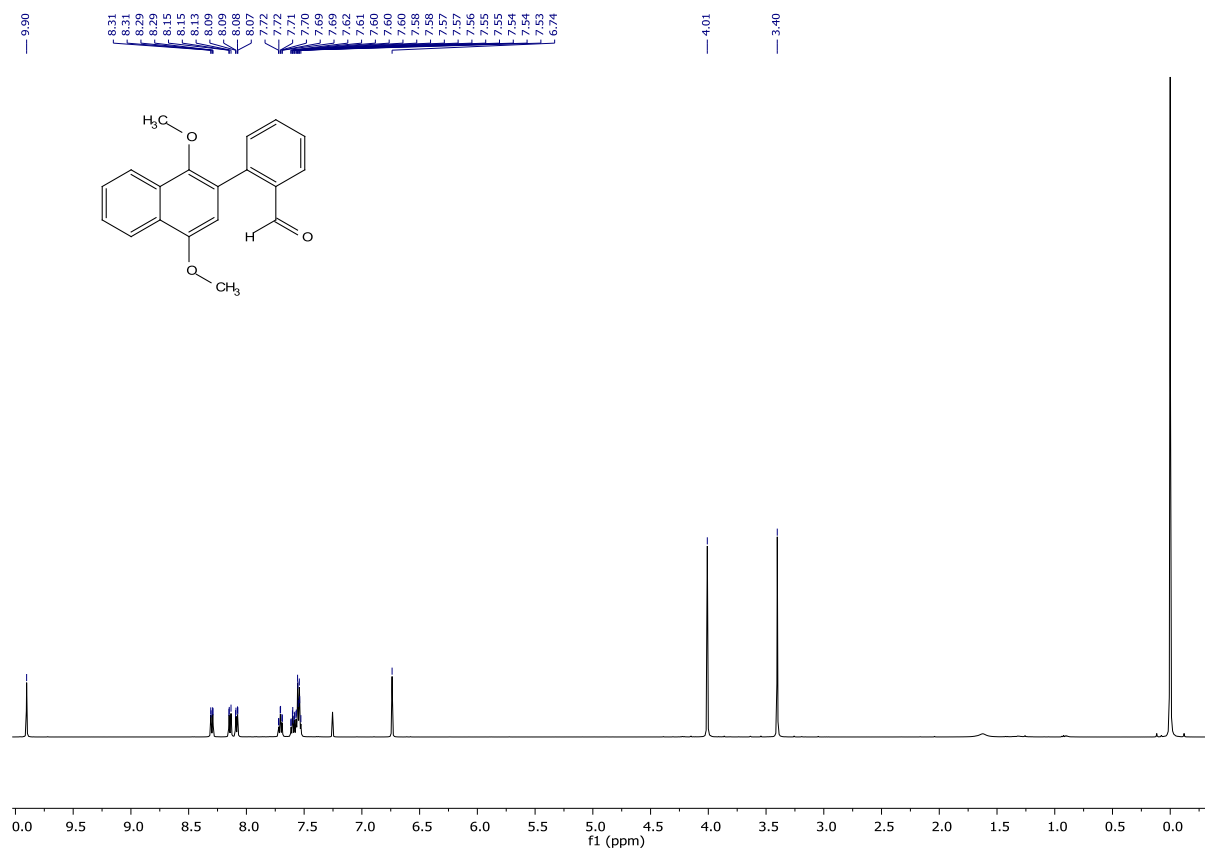
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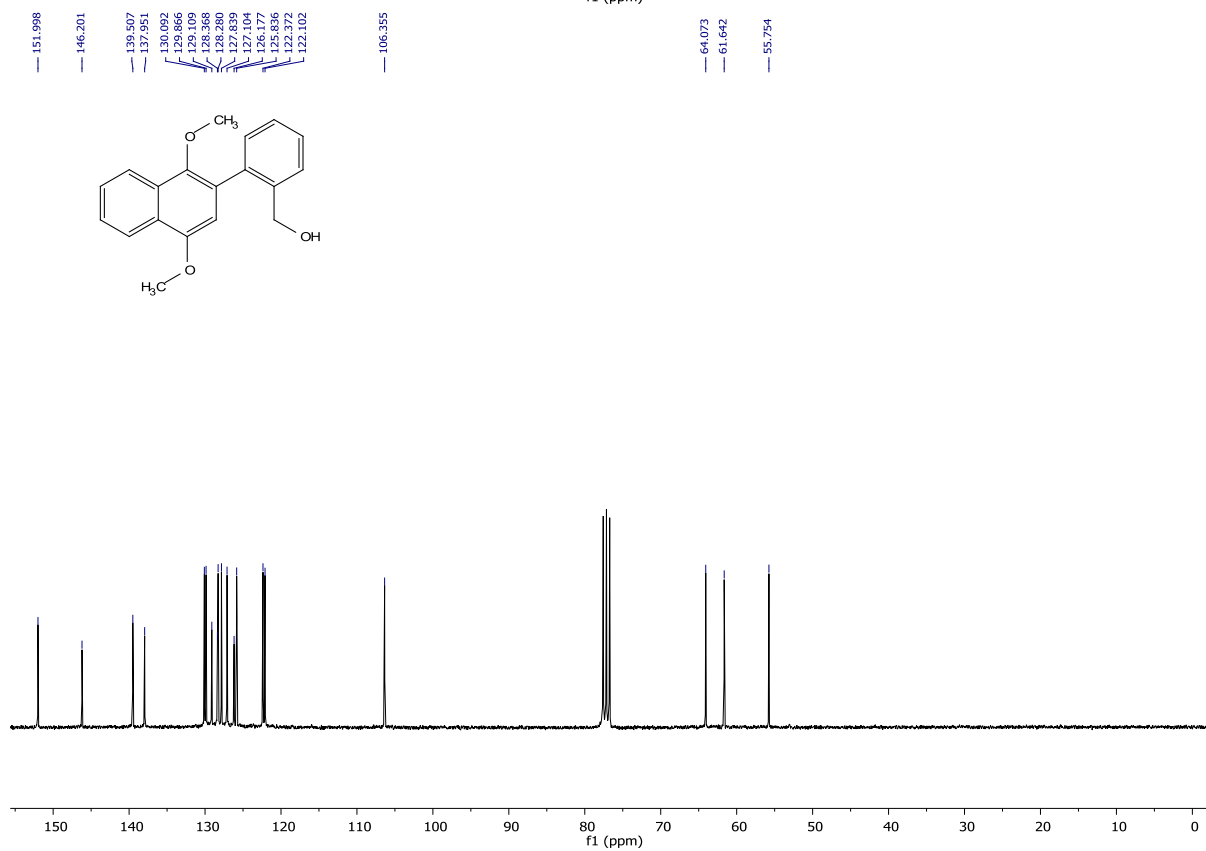
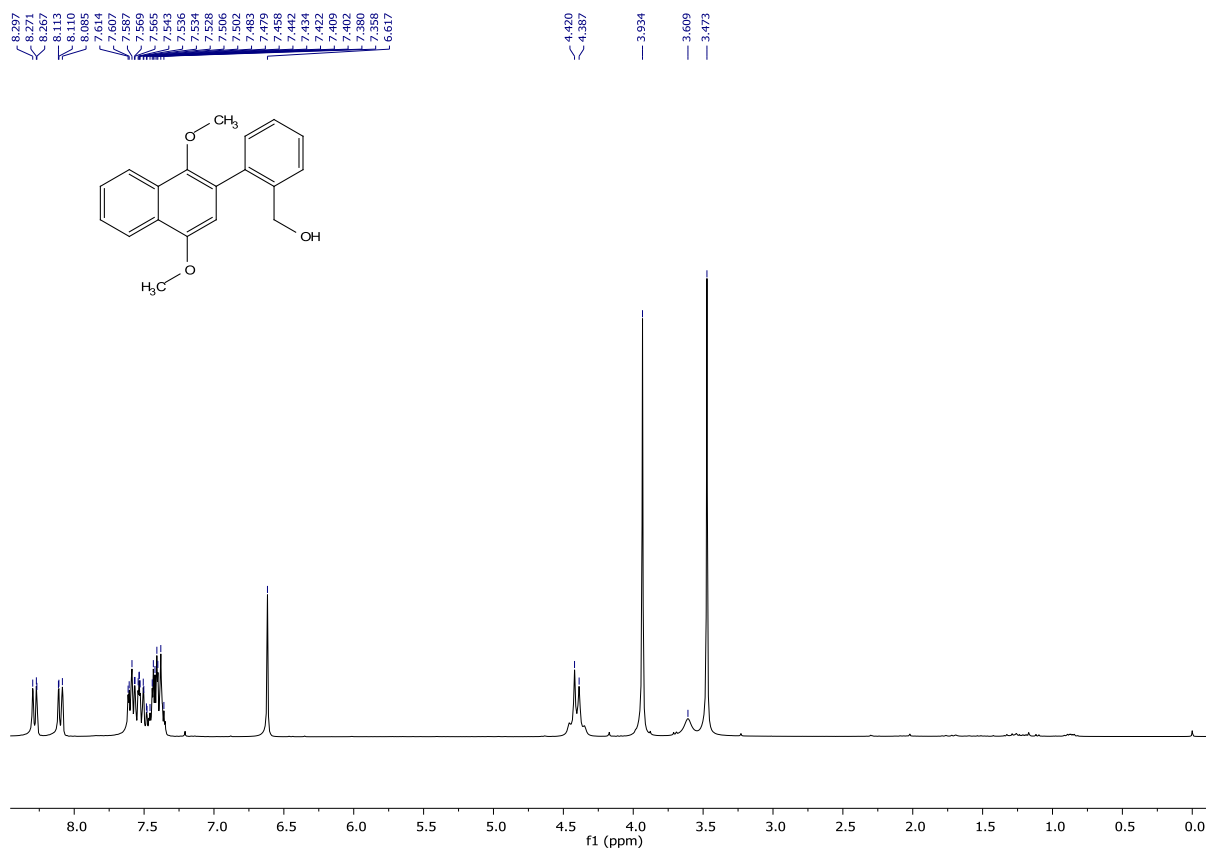
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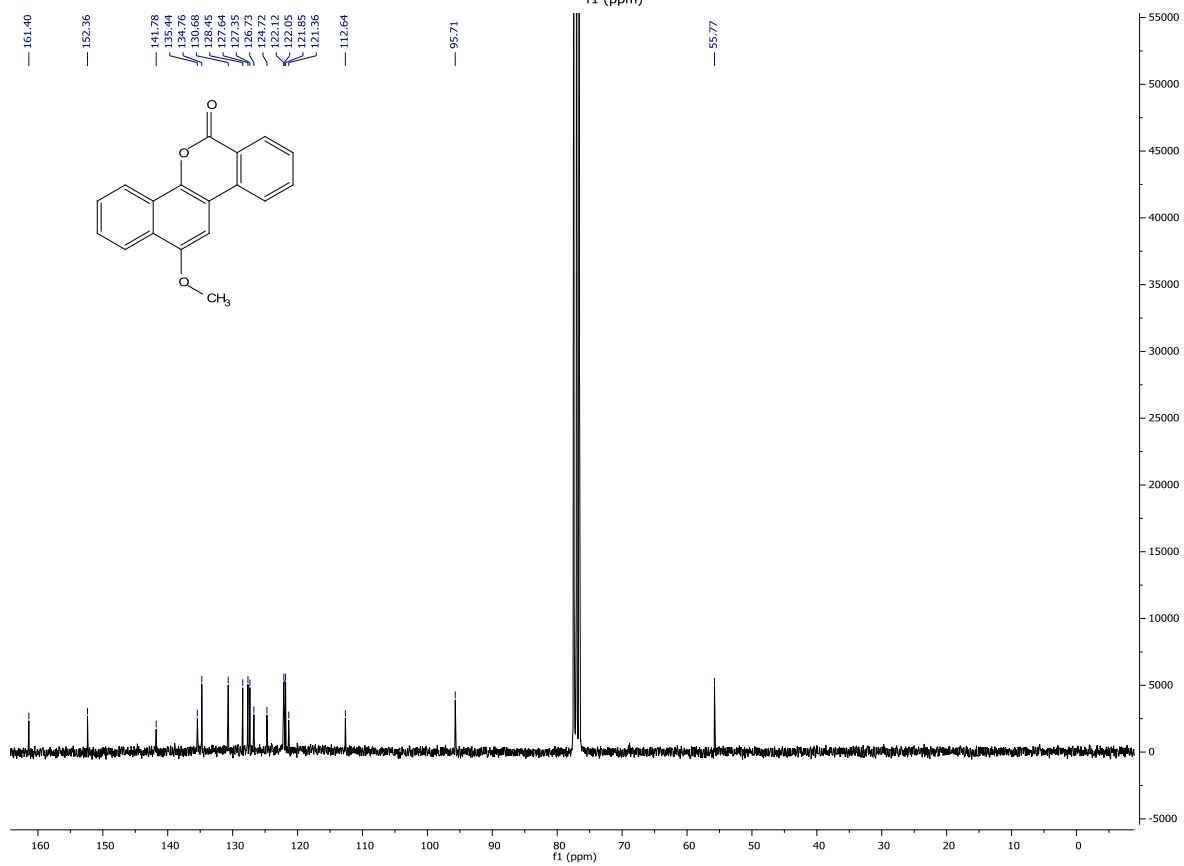
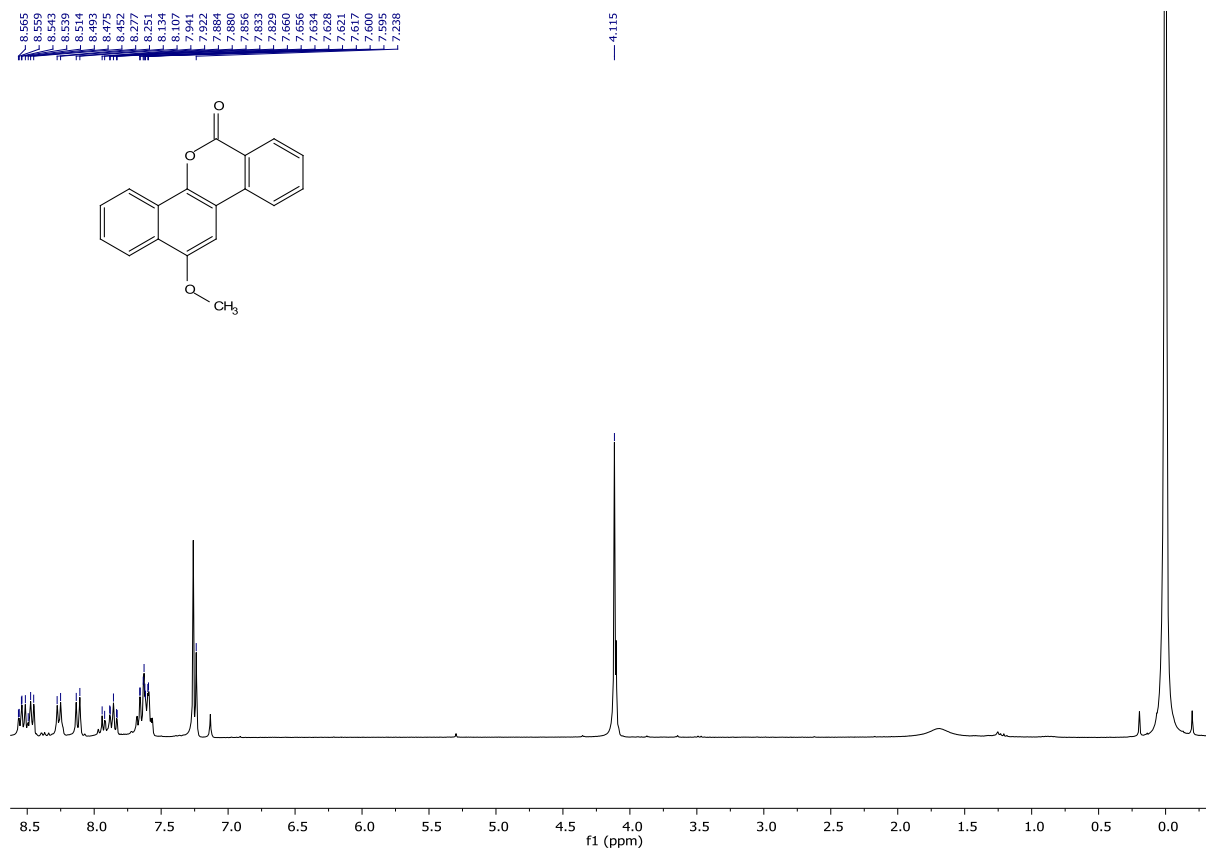
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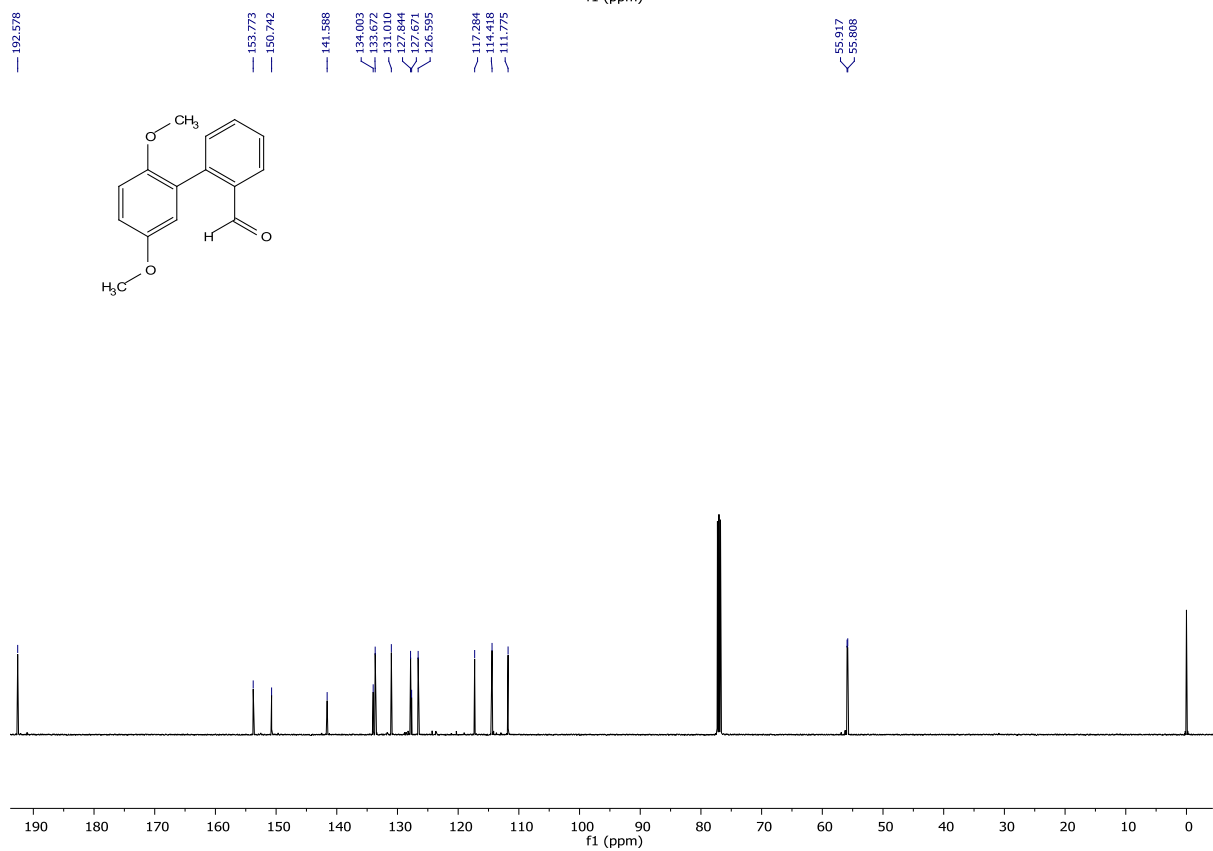
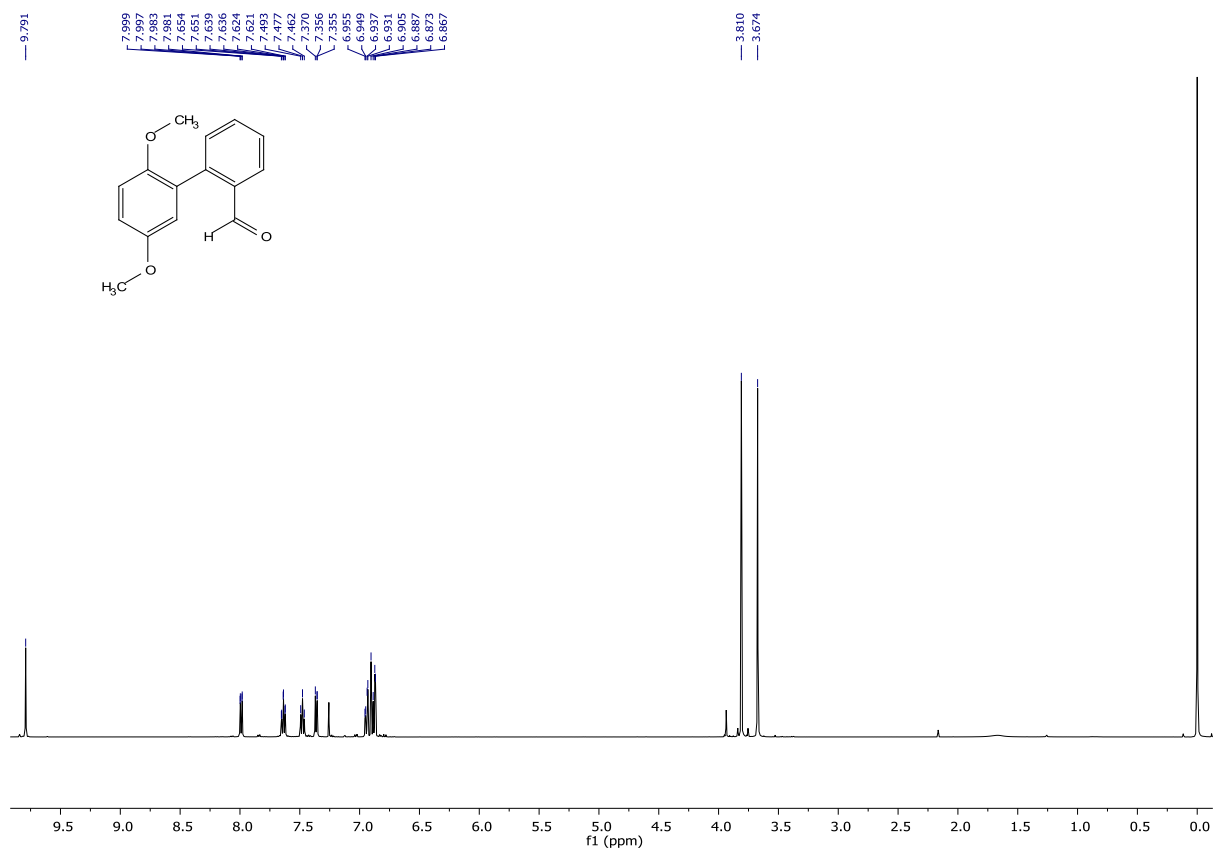


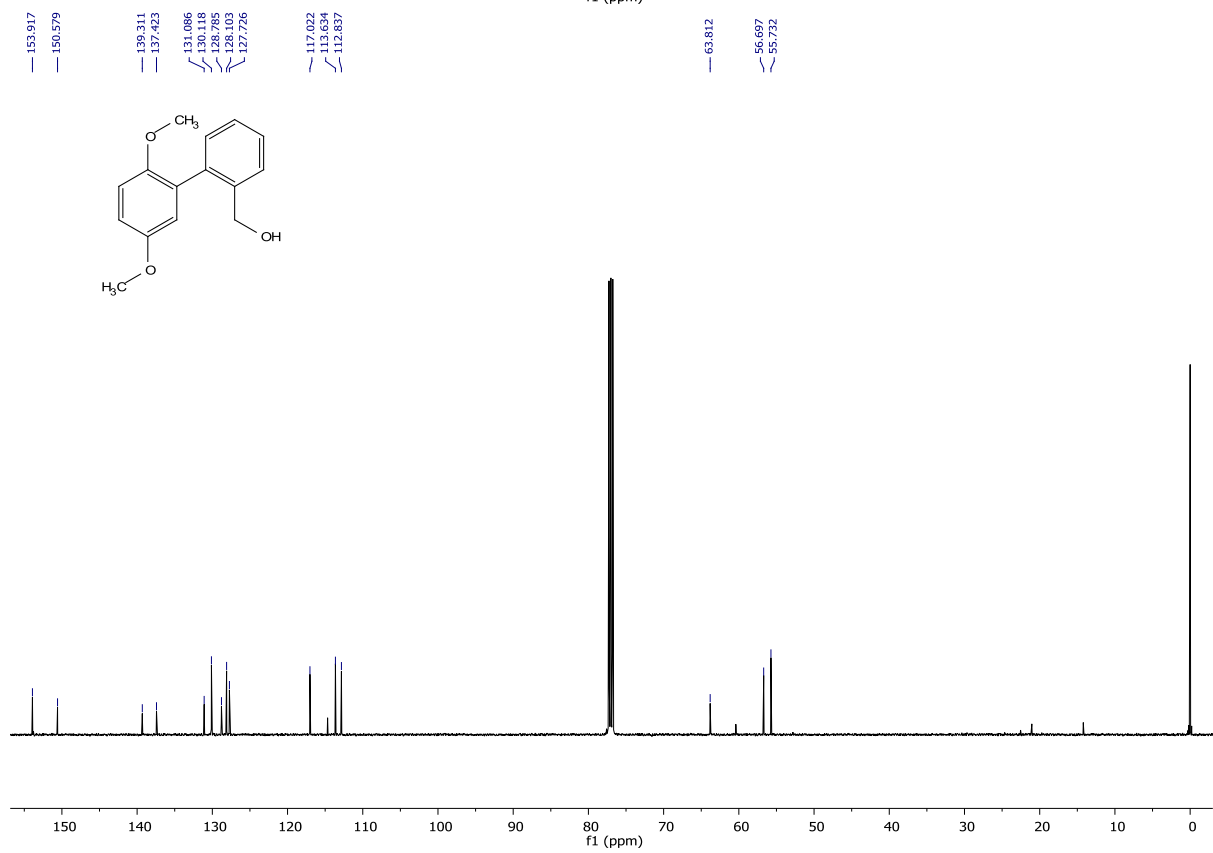
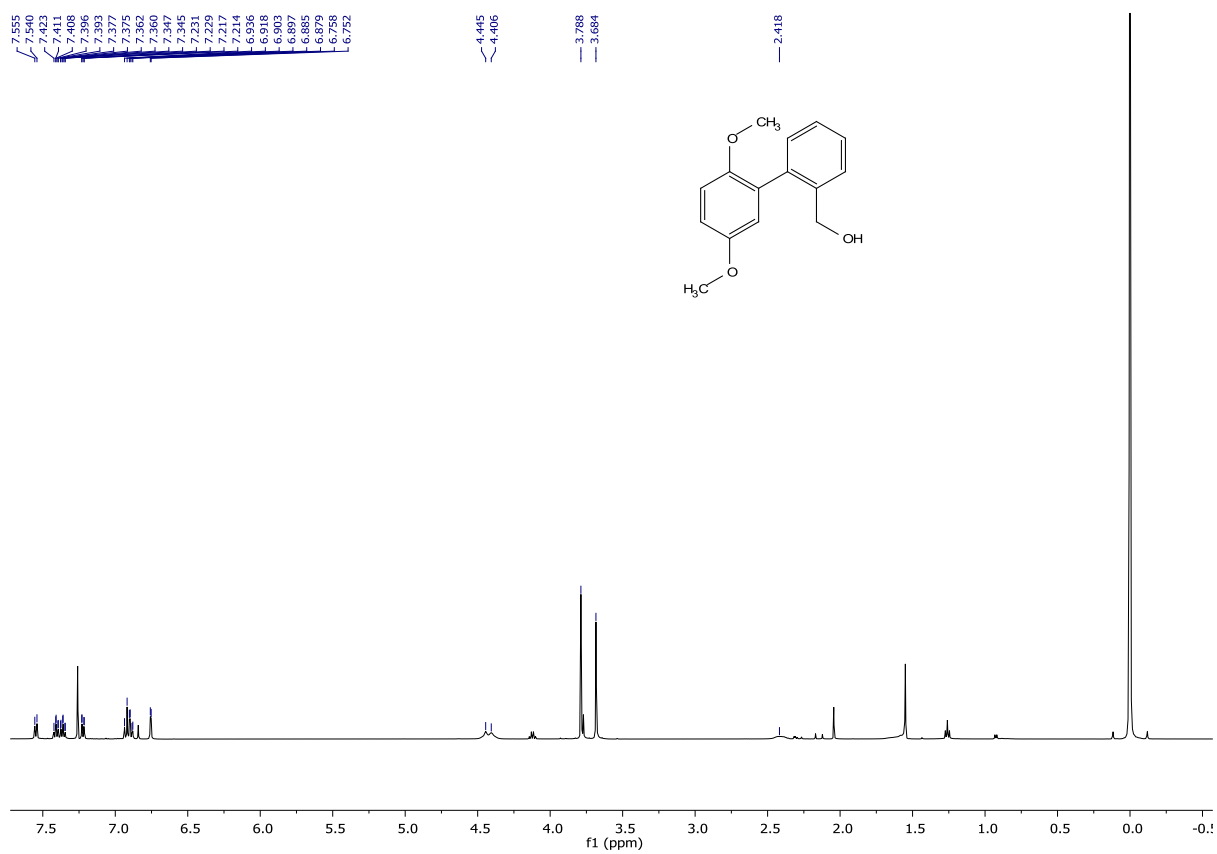
**Appendix A: Selected NMR spectra**

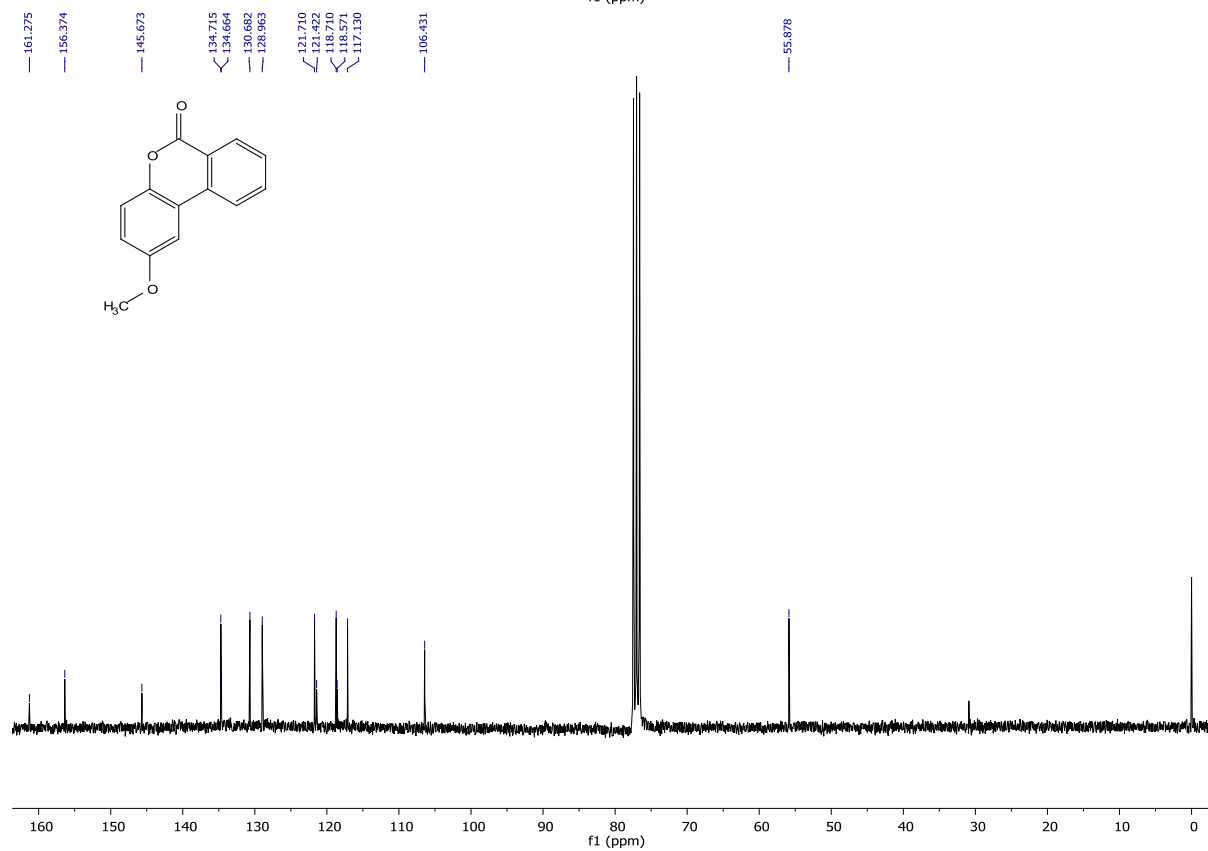
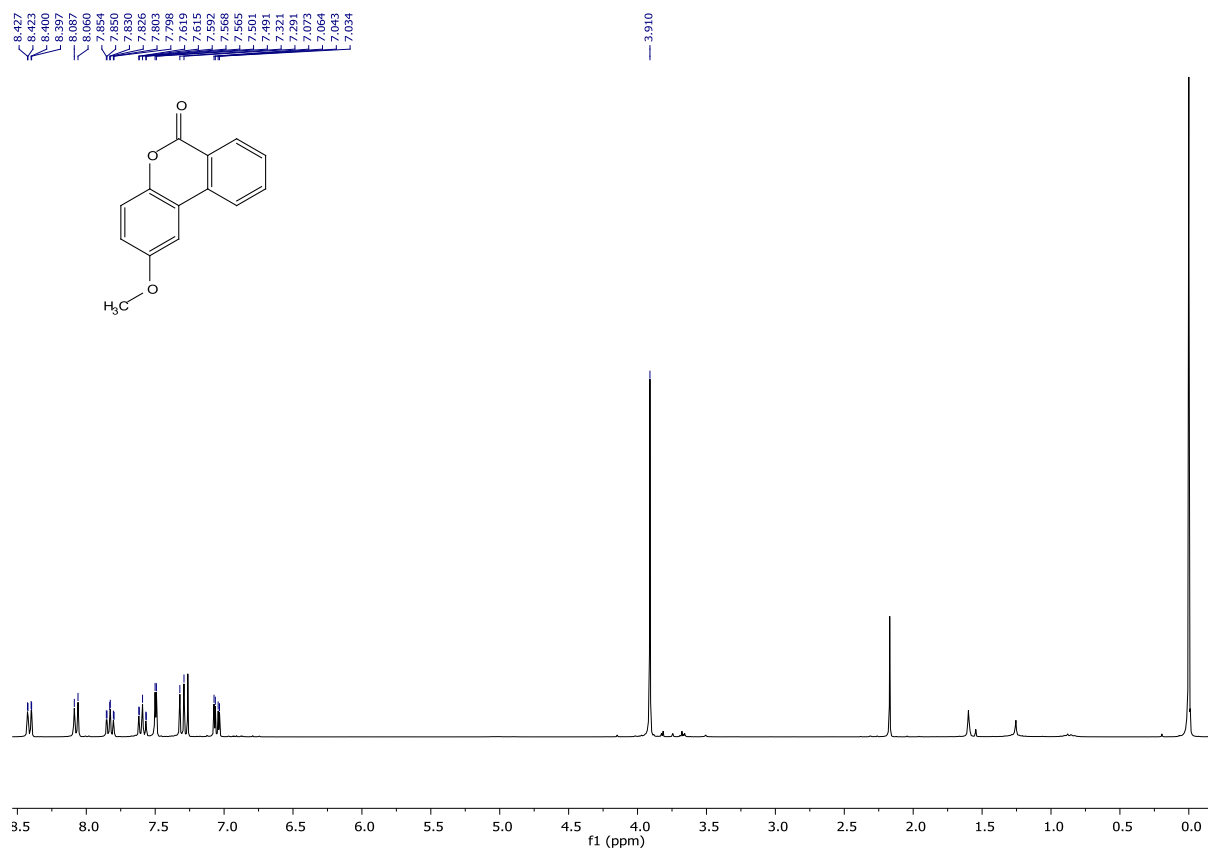


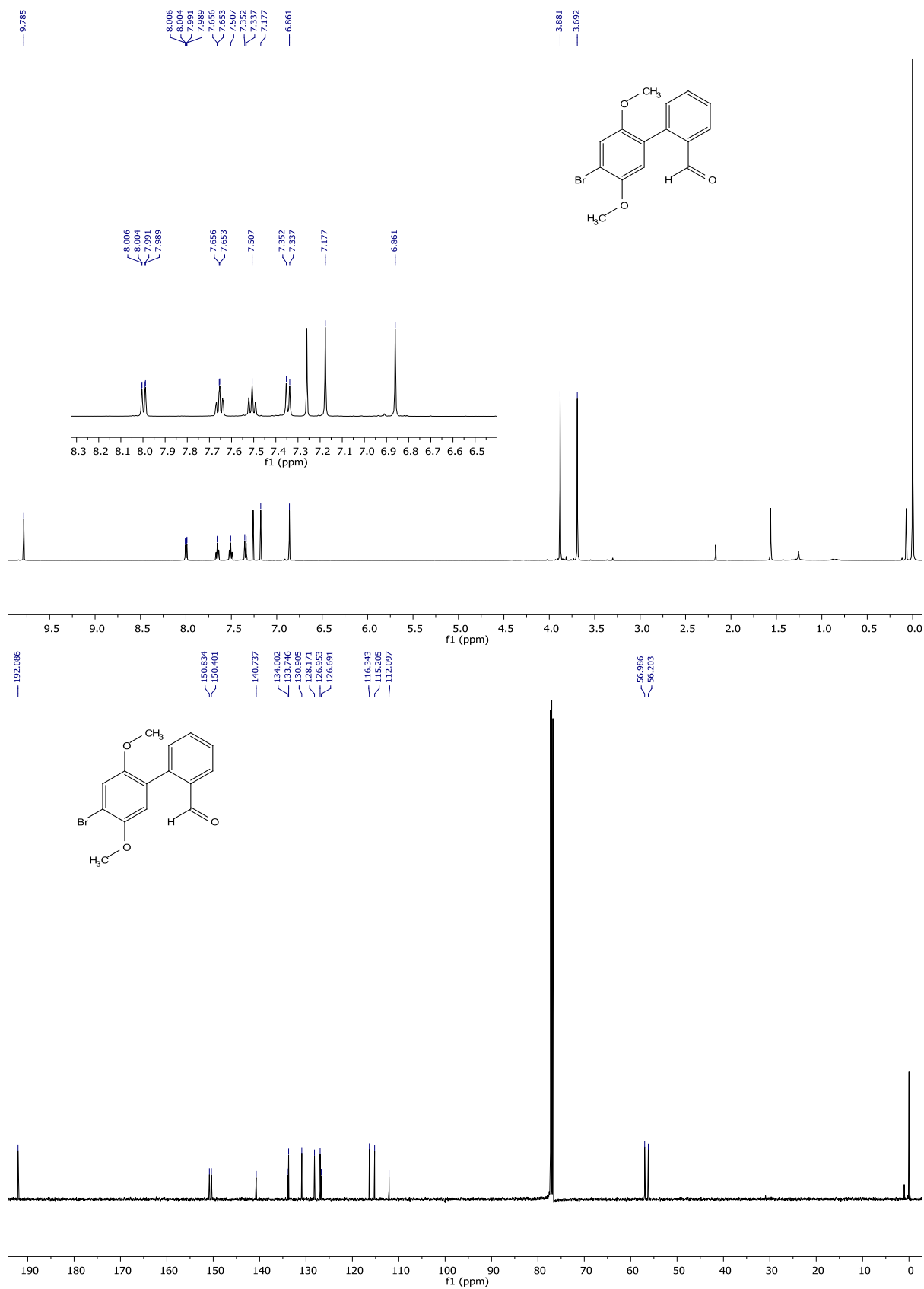




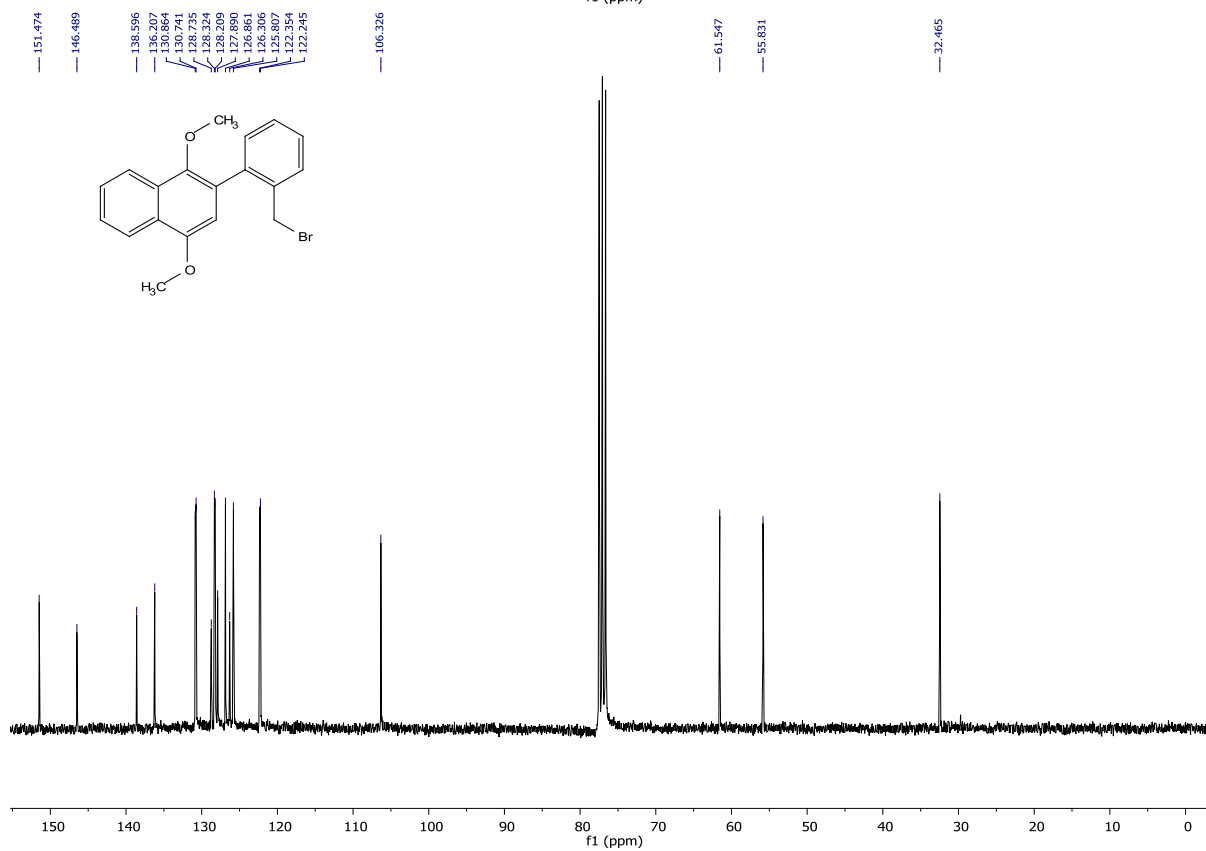
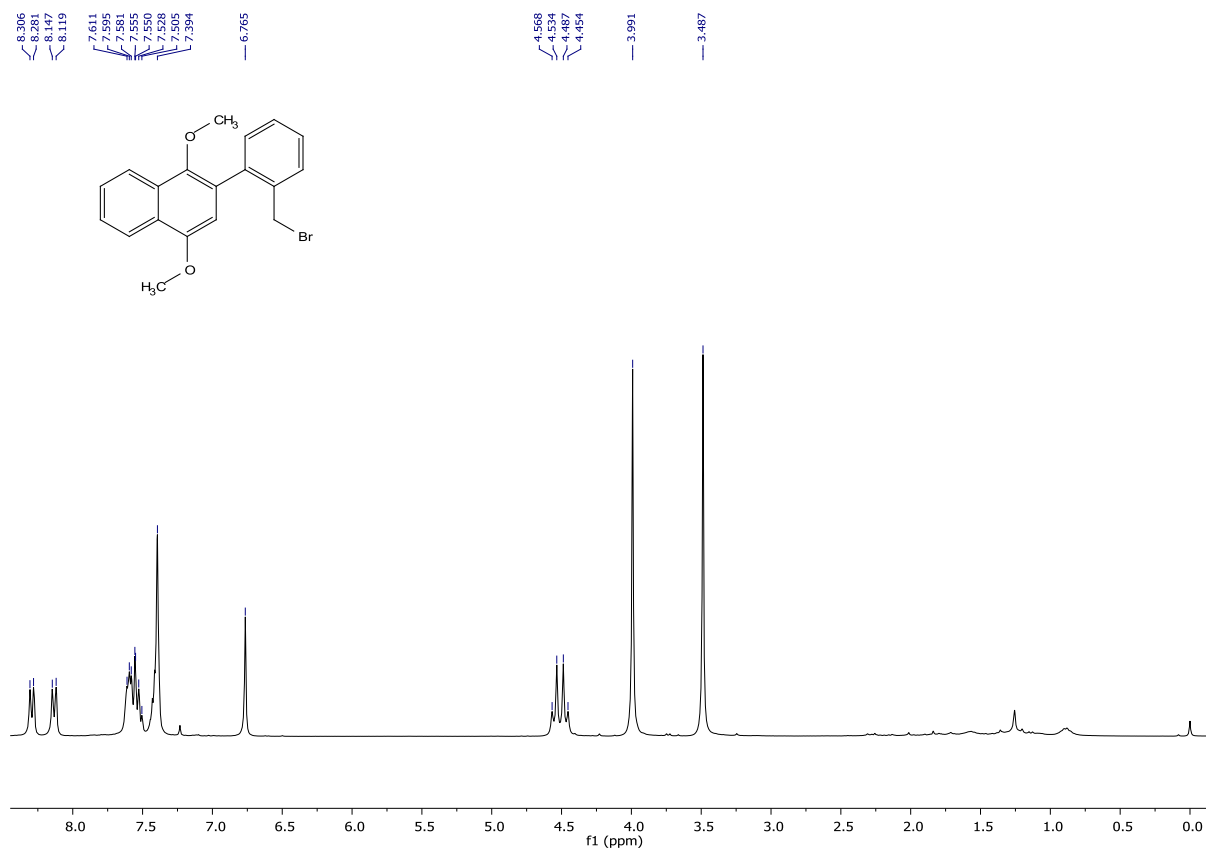


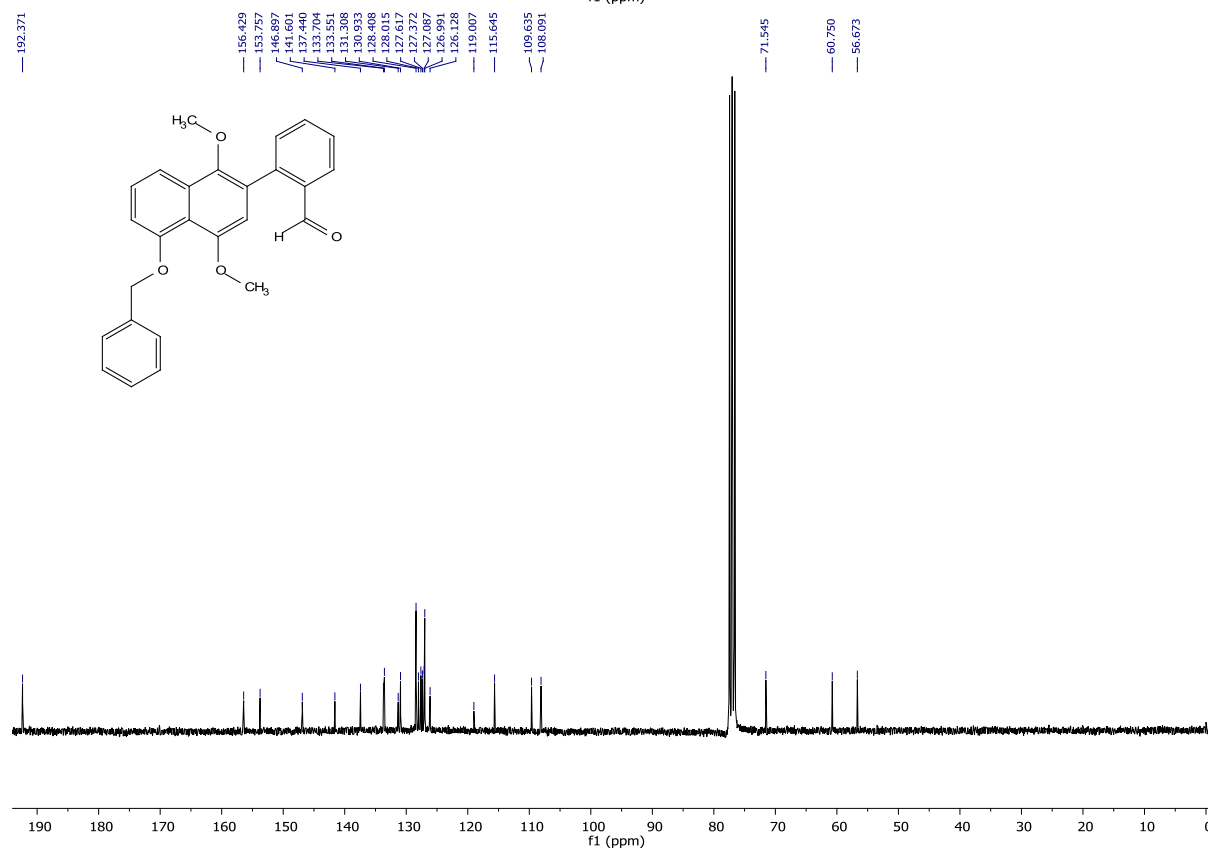
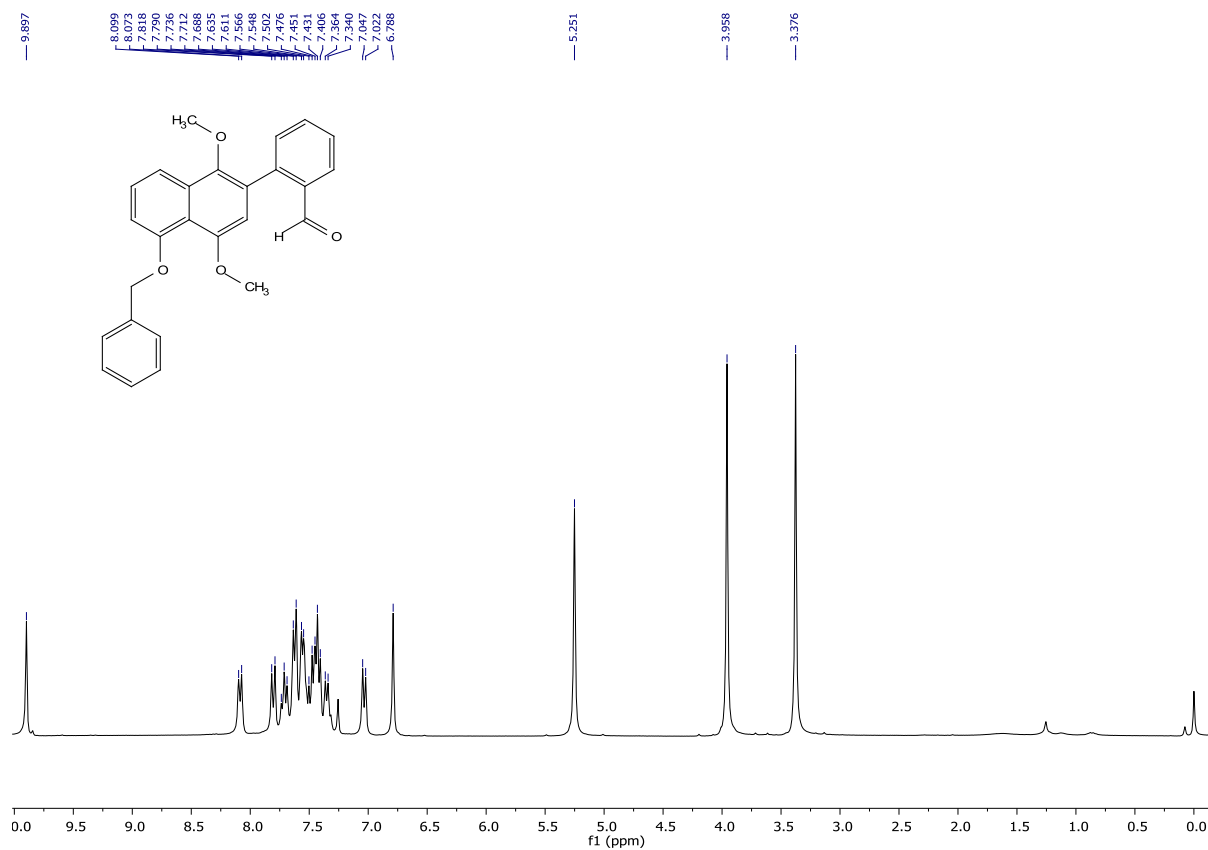


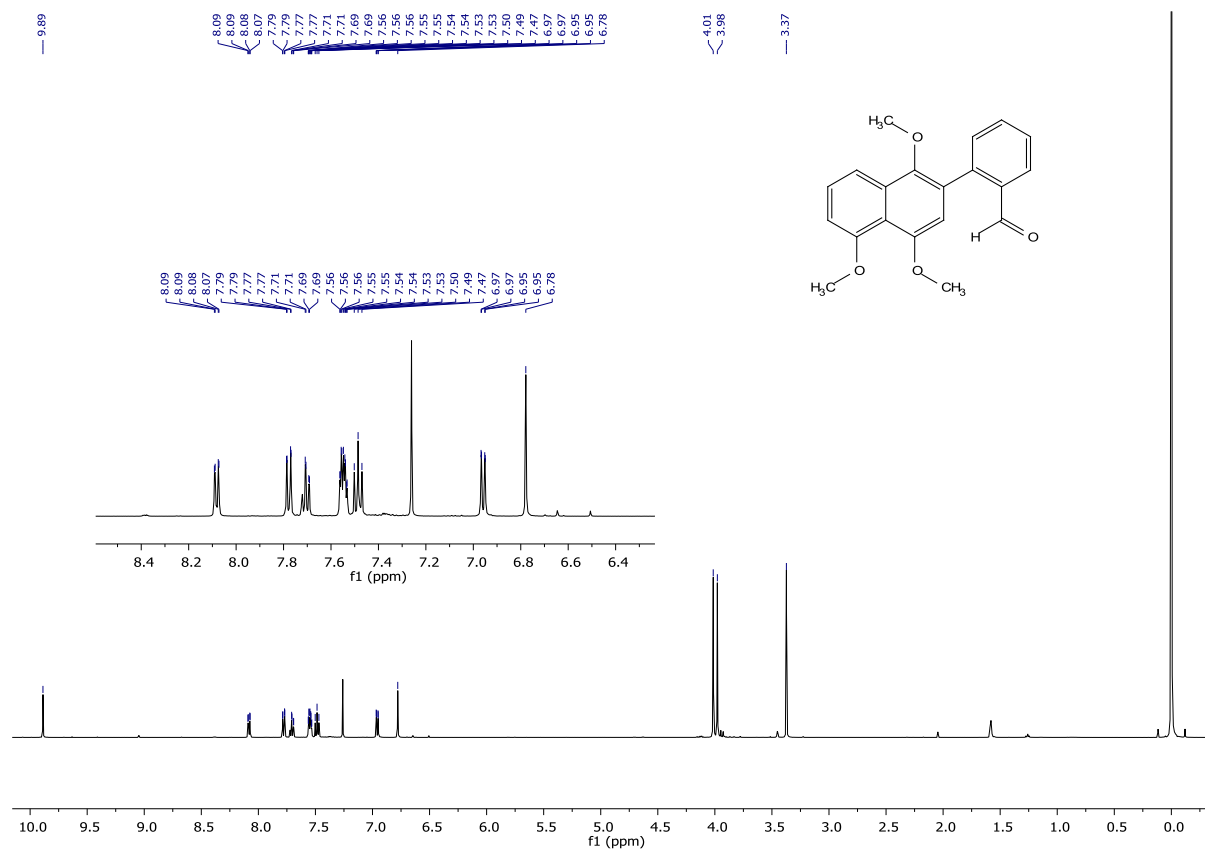
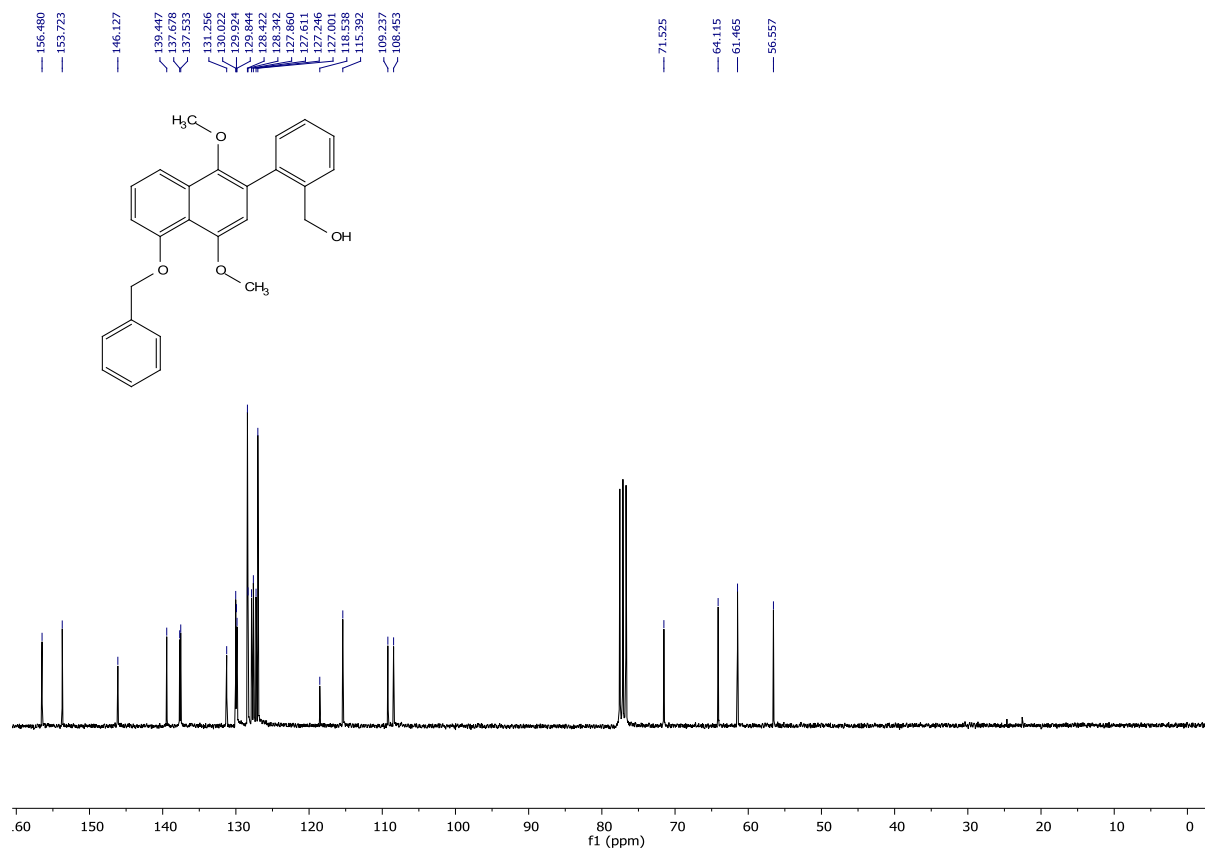


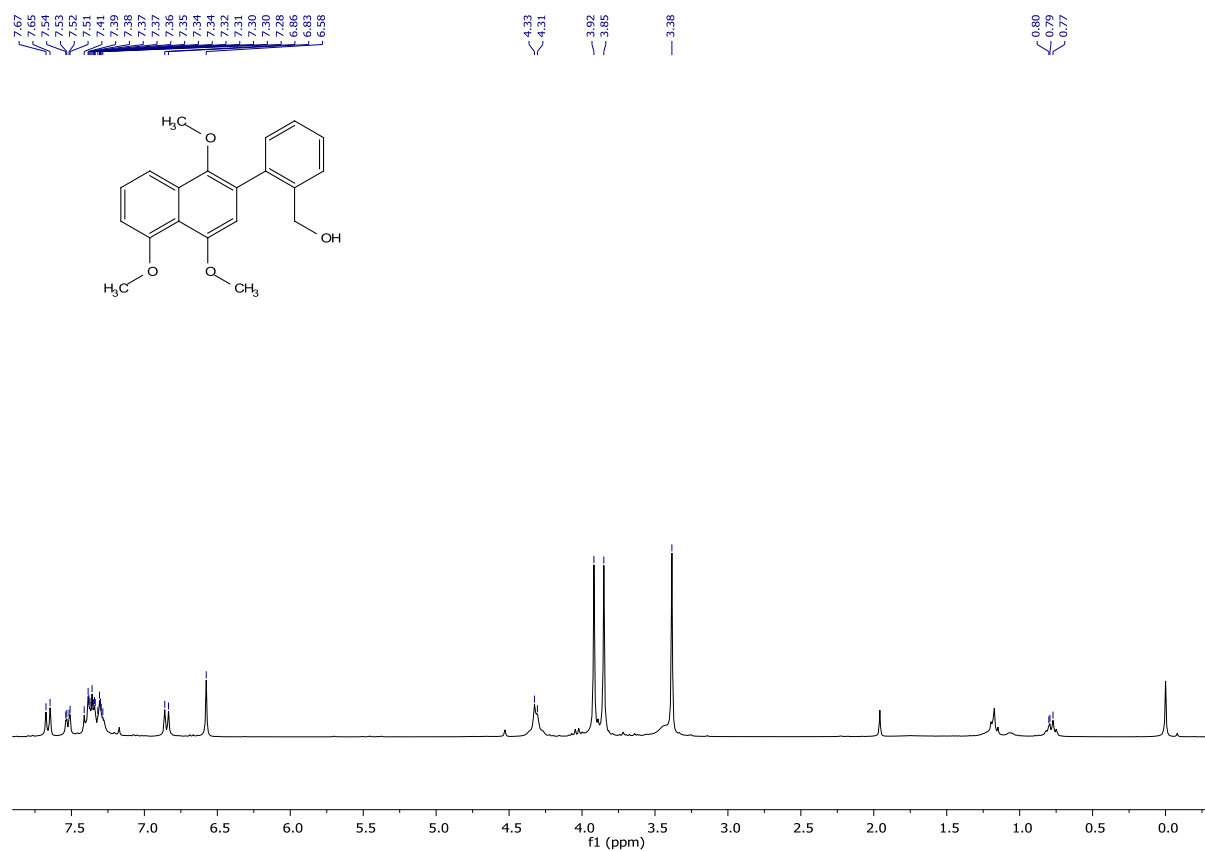
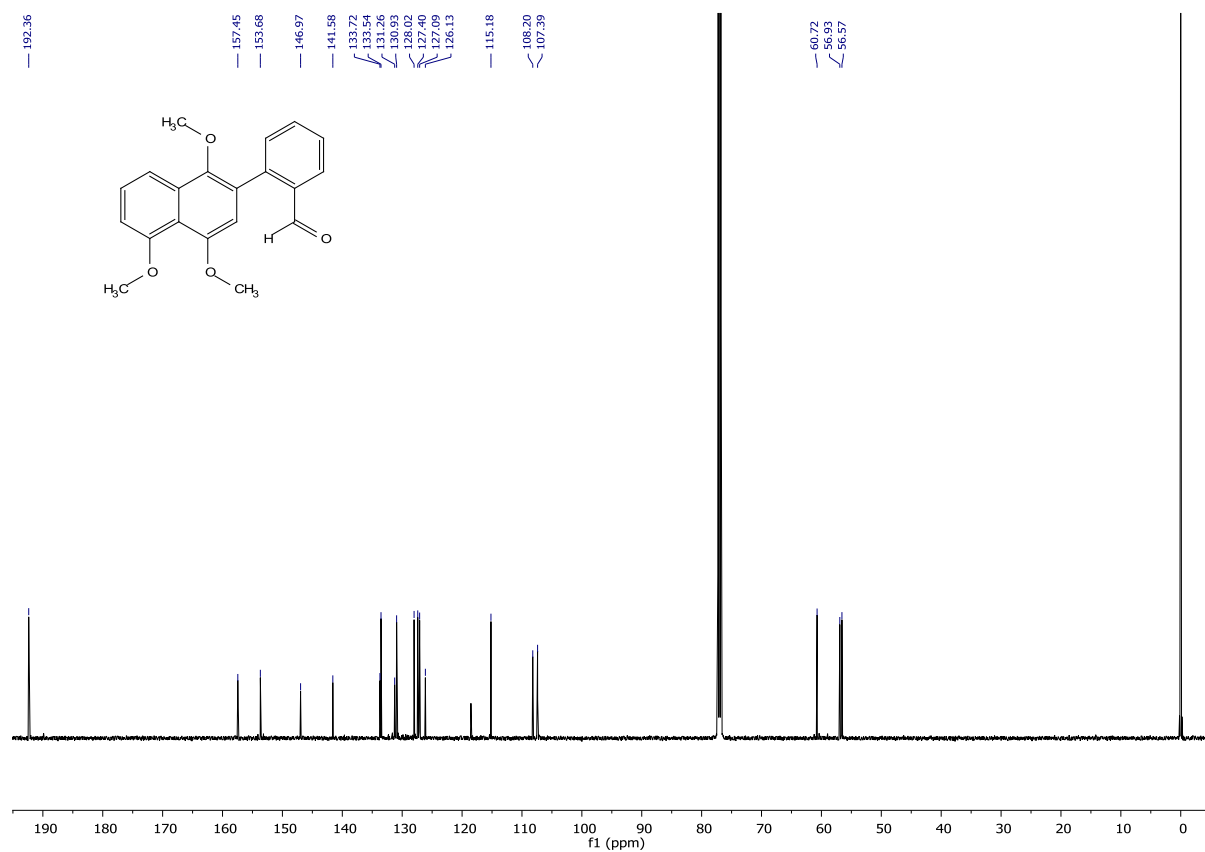


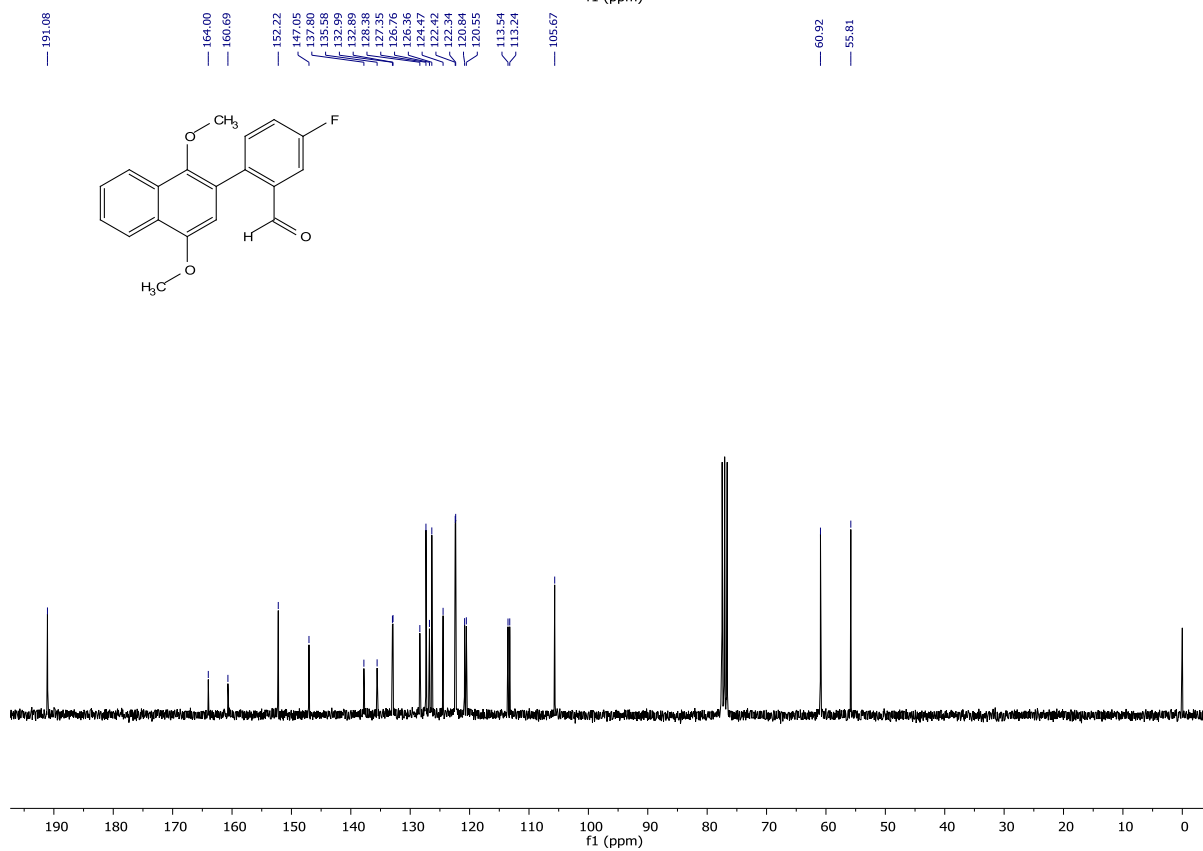
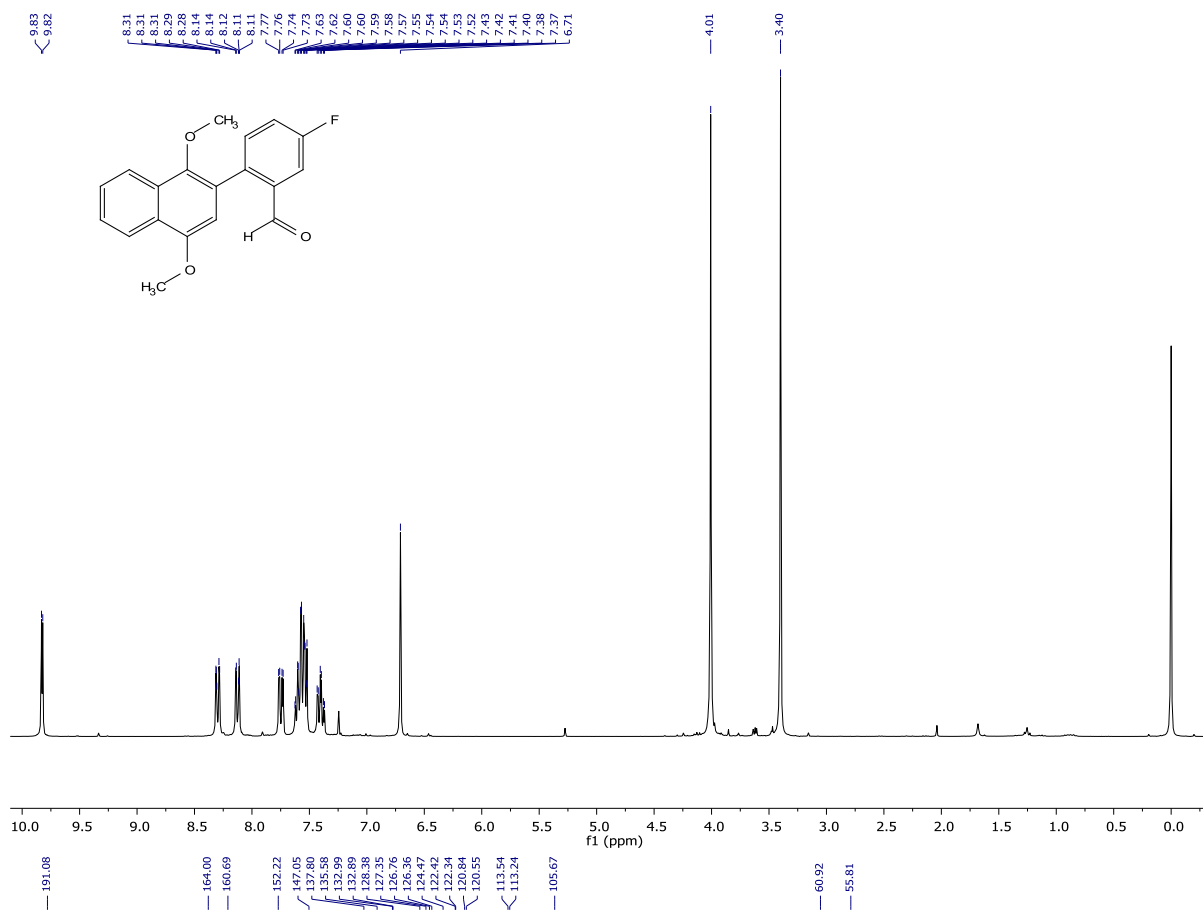


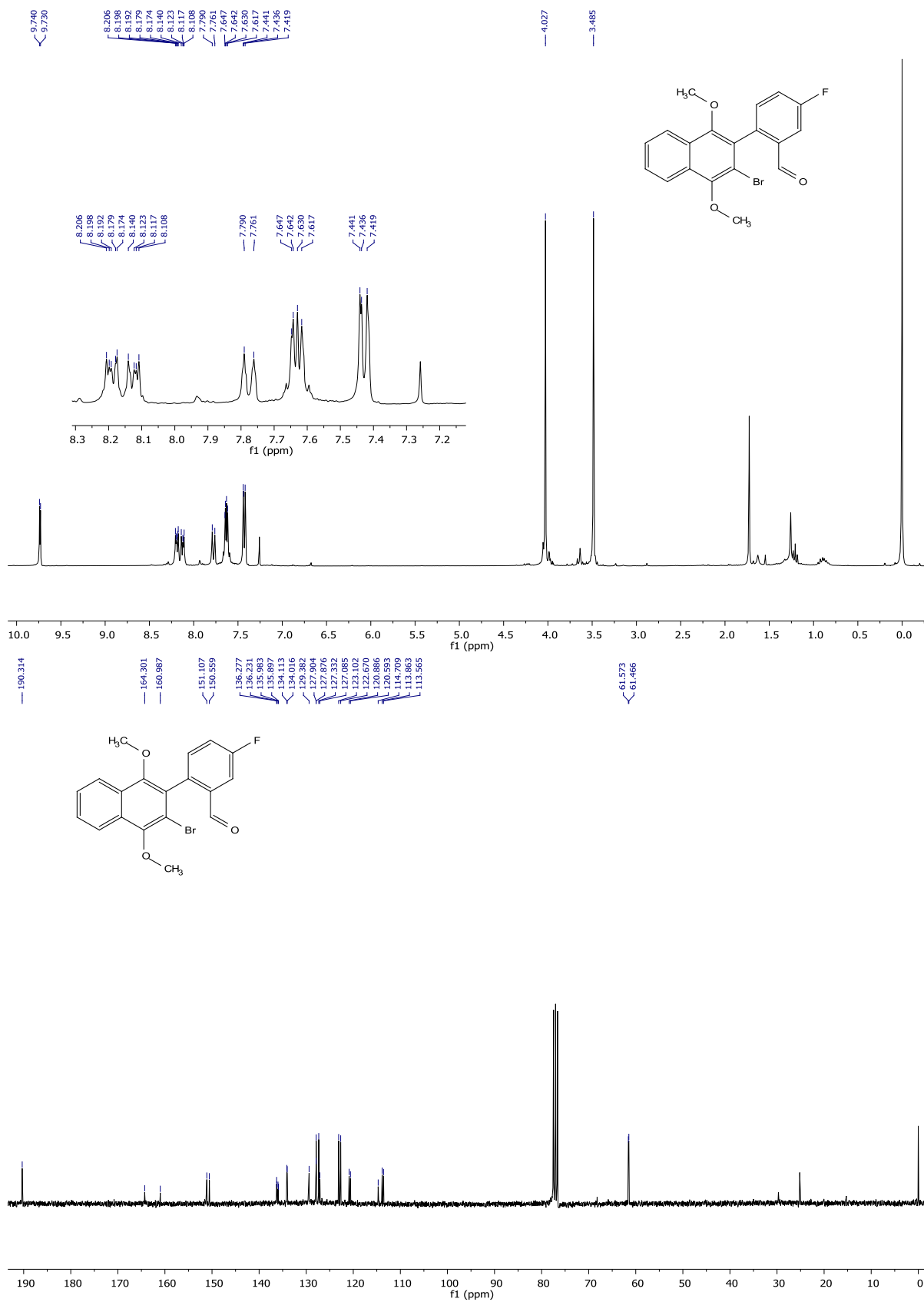


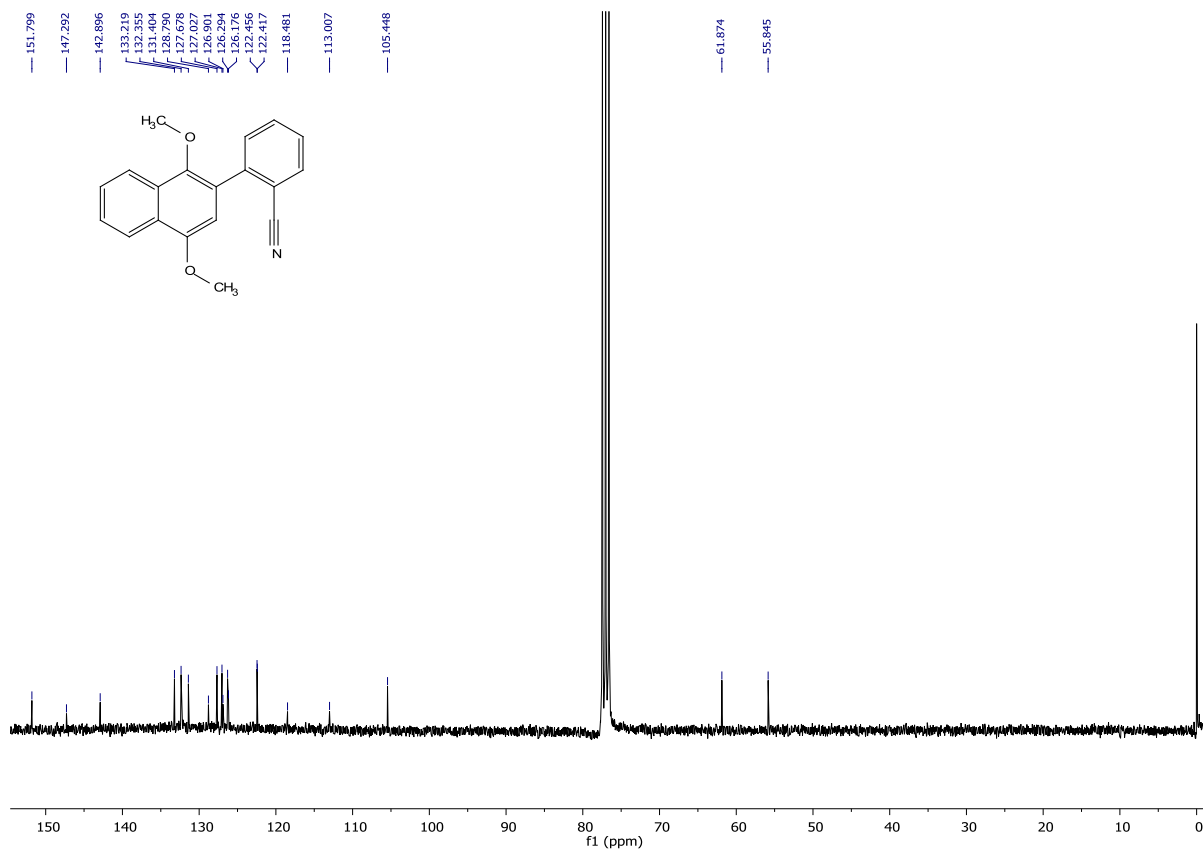
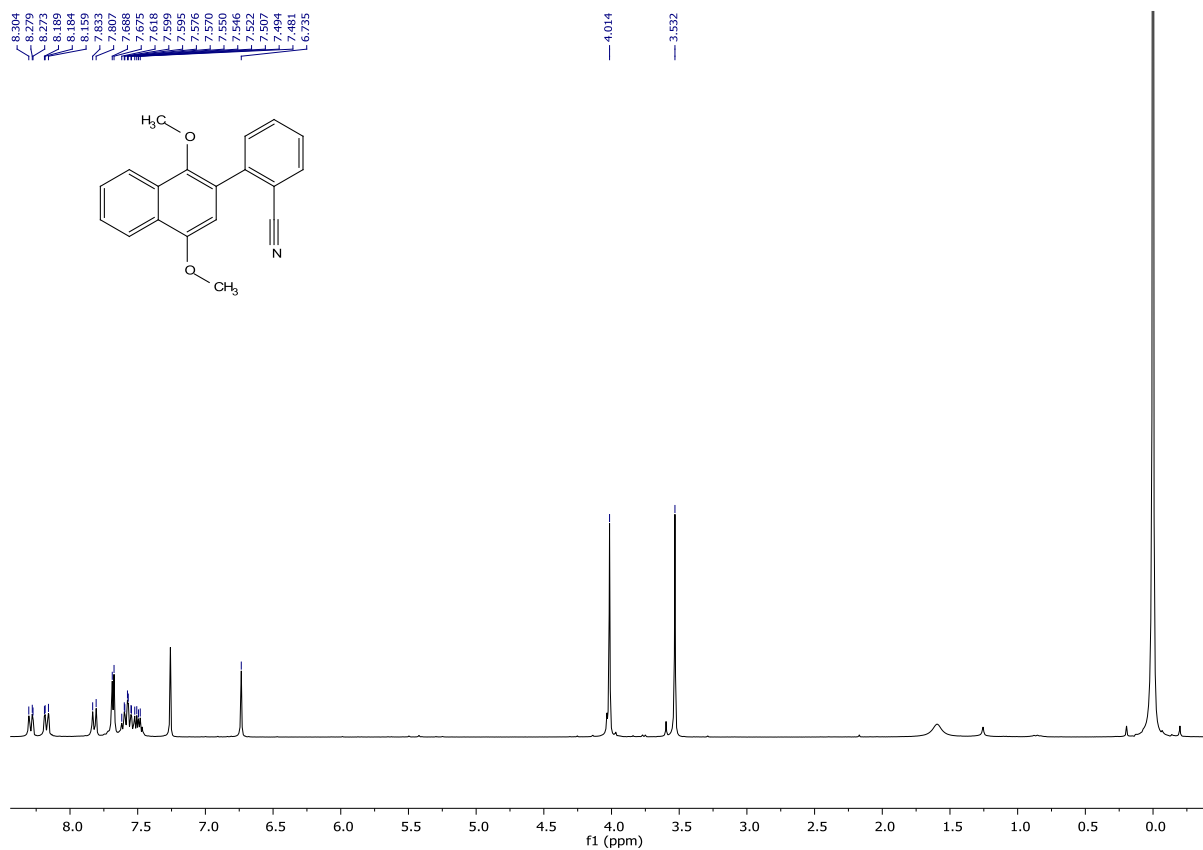


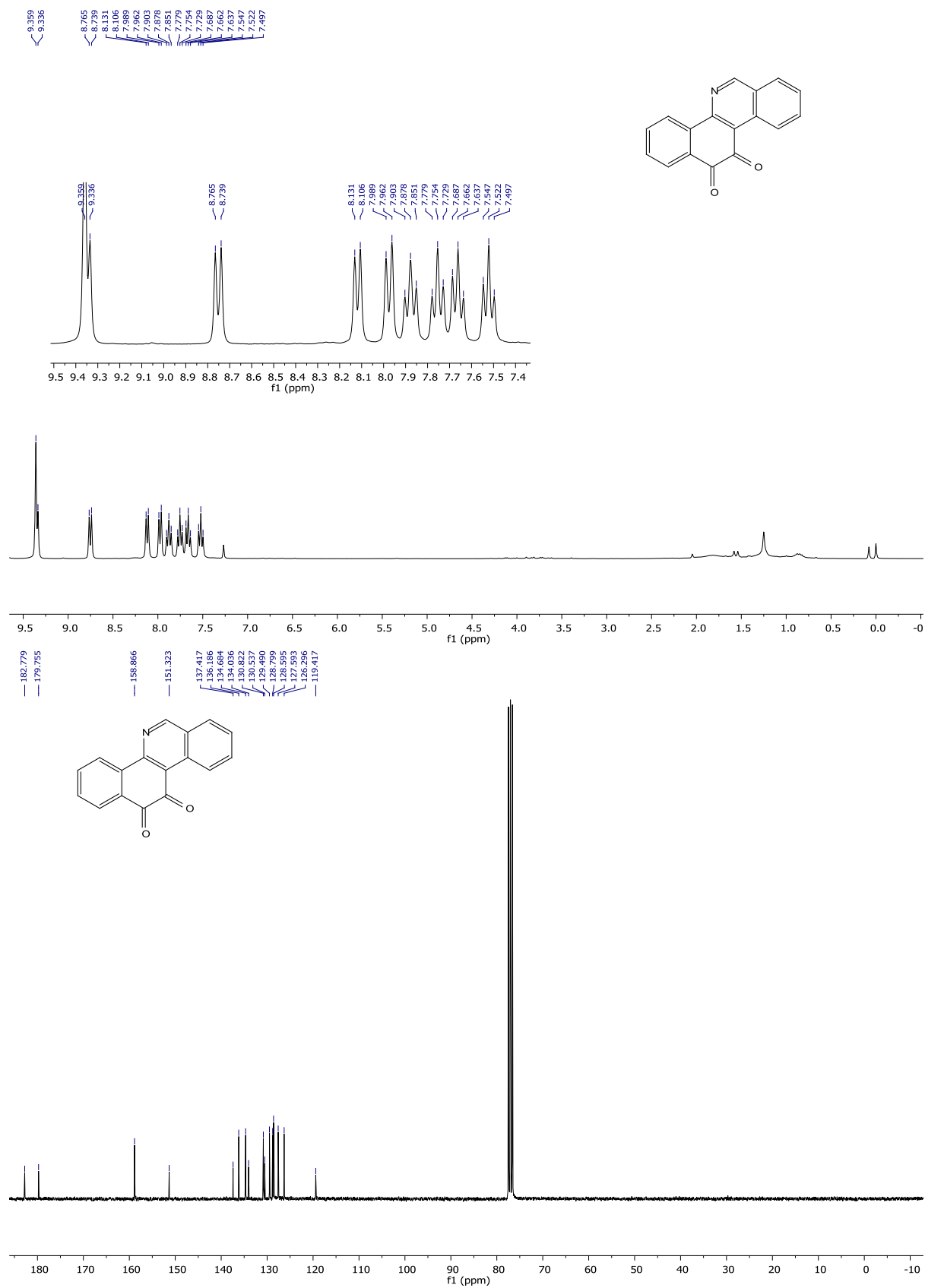




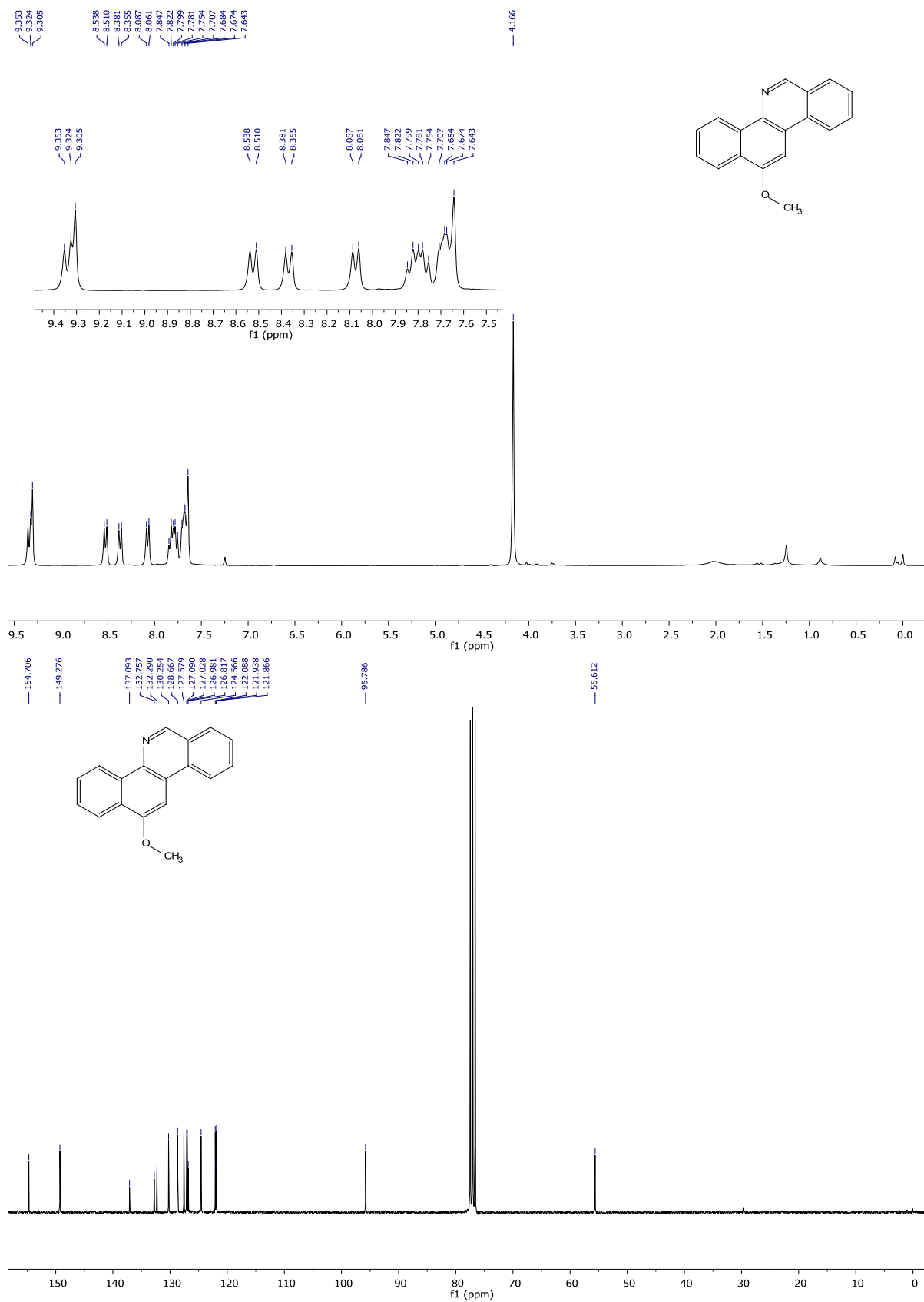




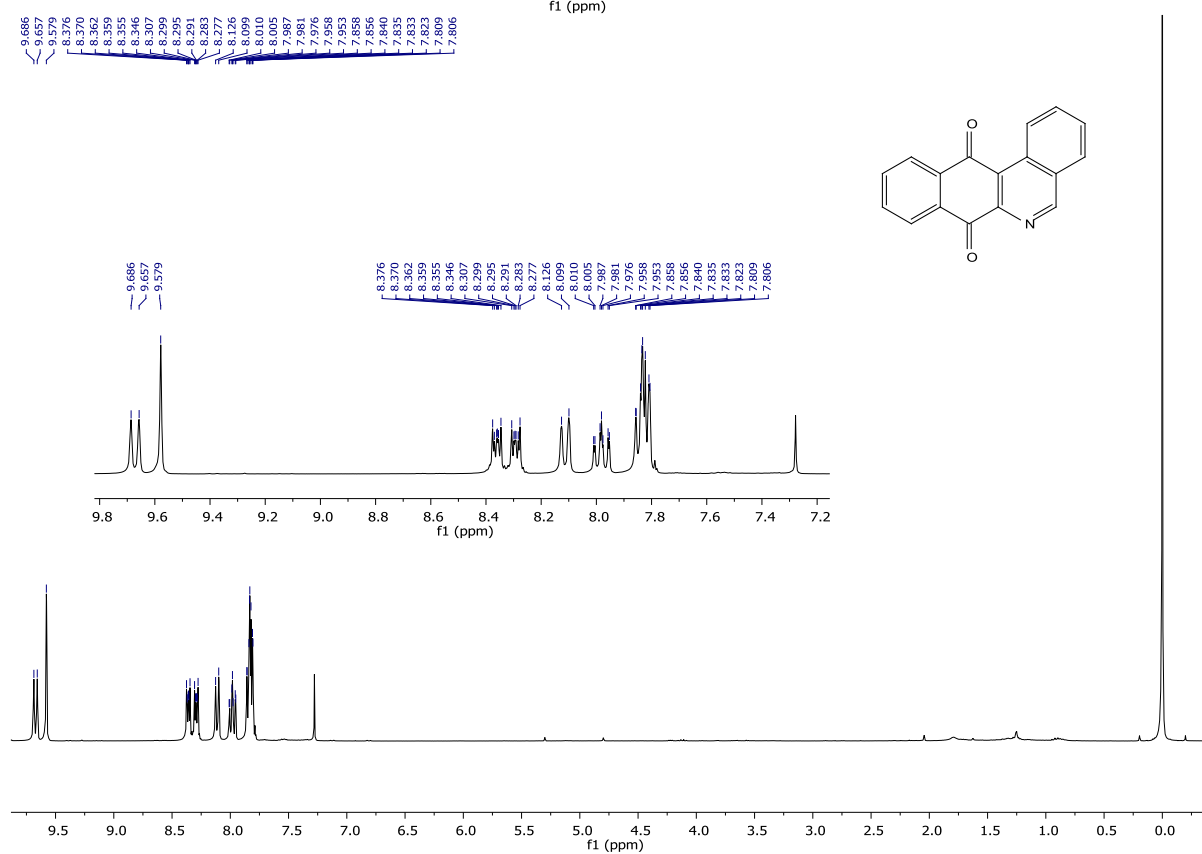
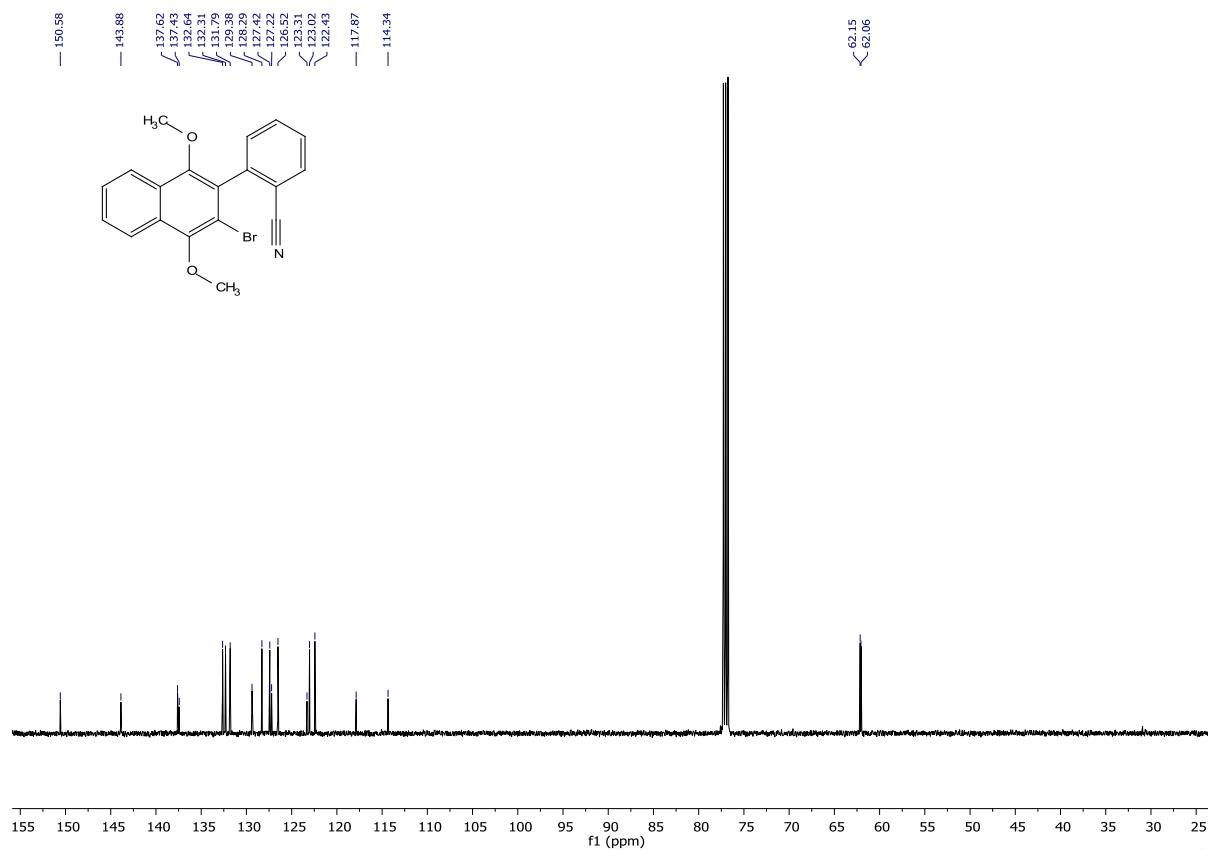


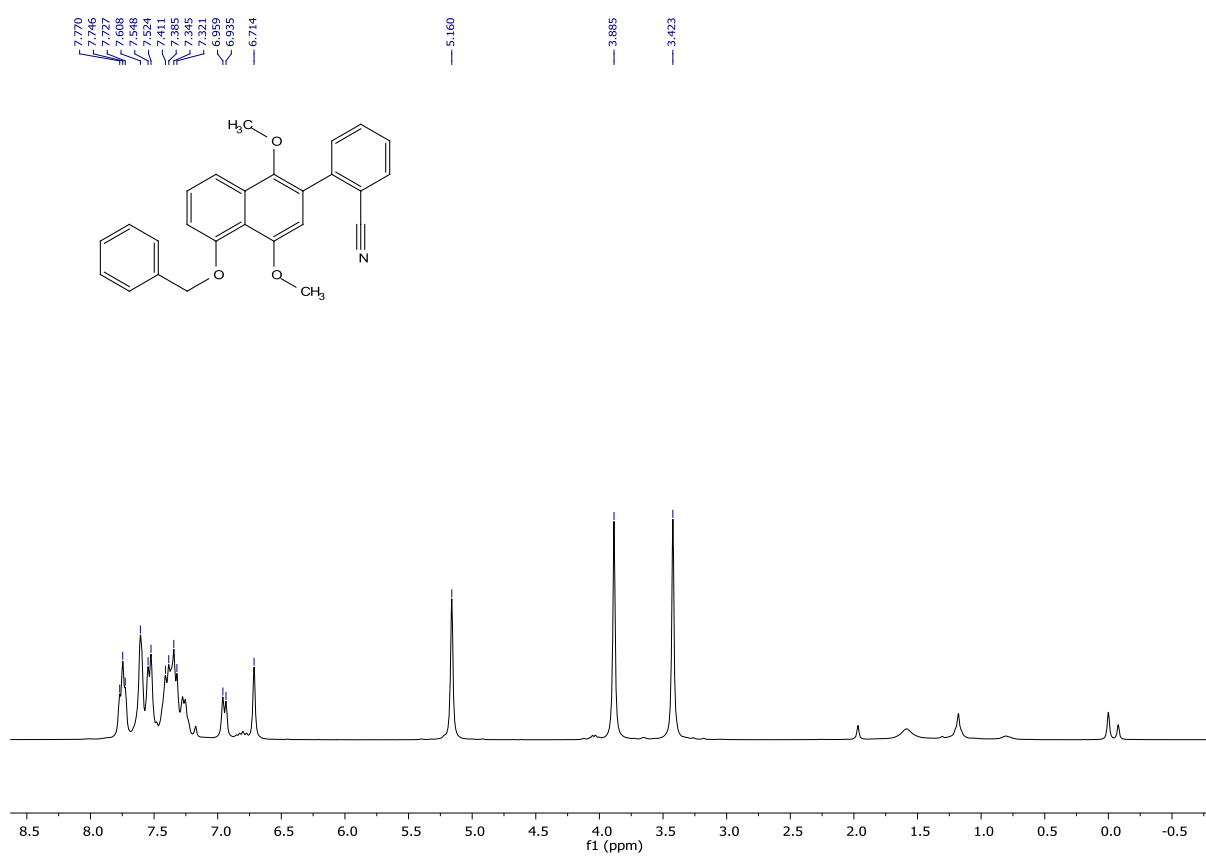
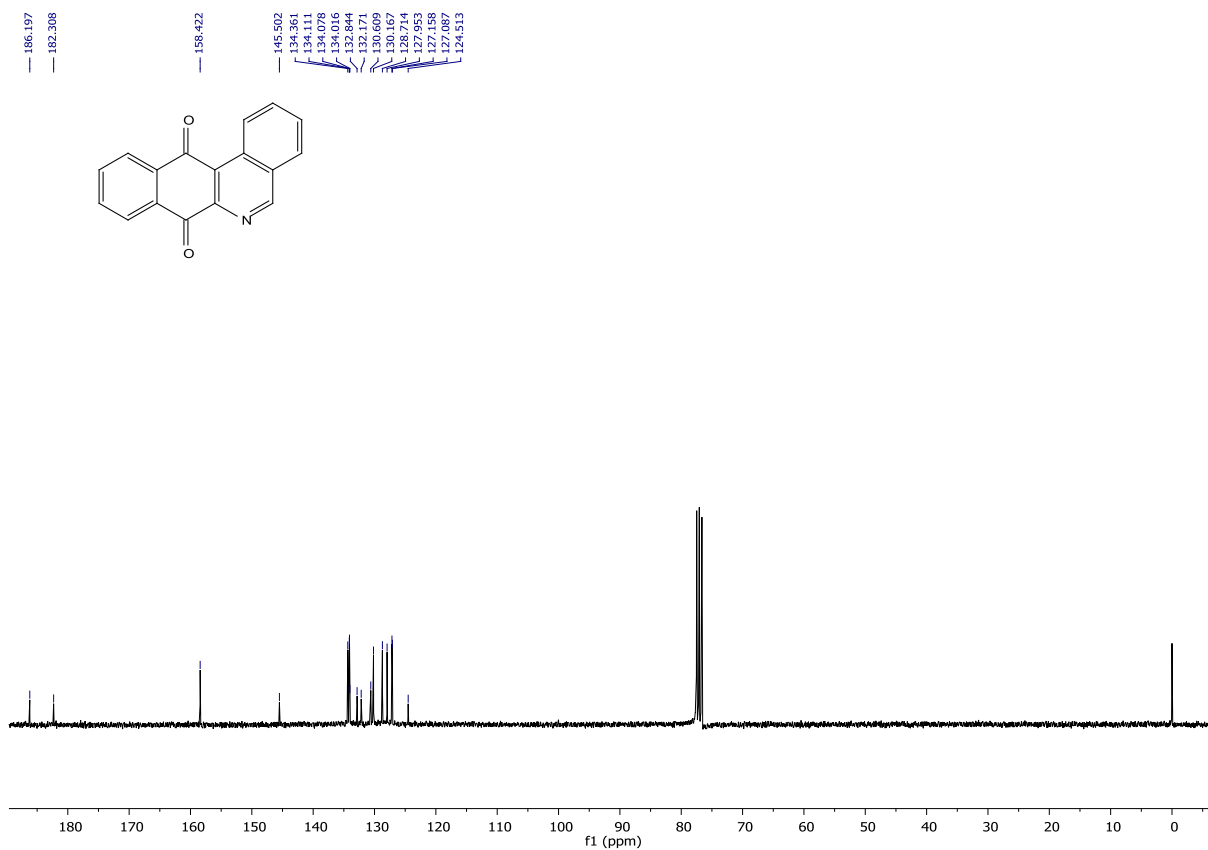


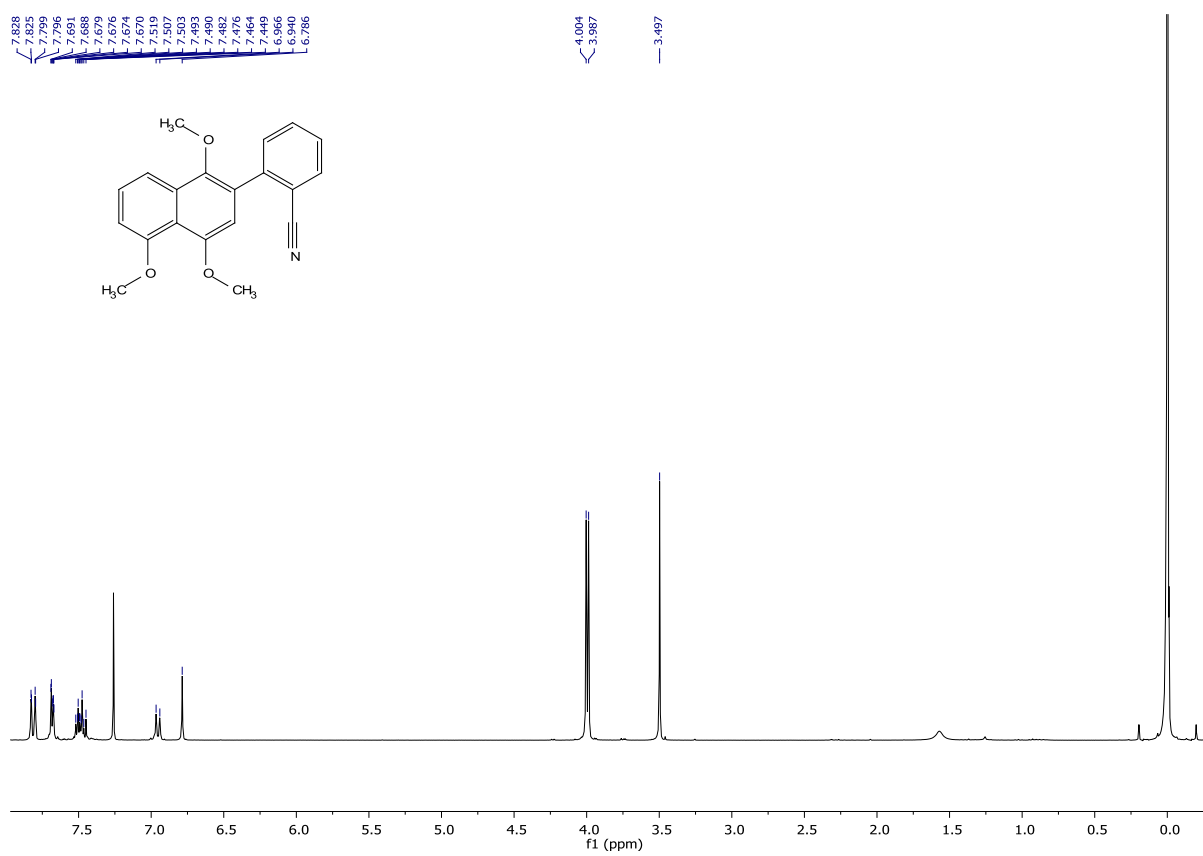
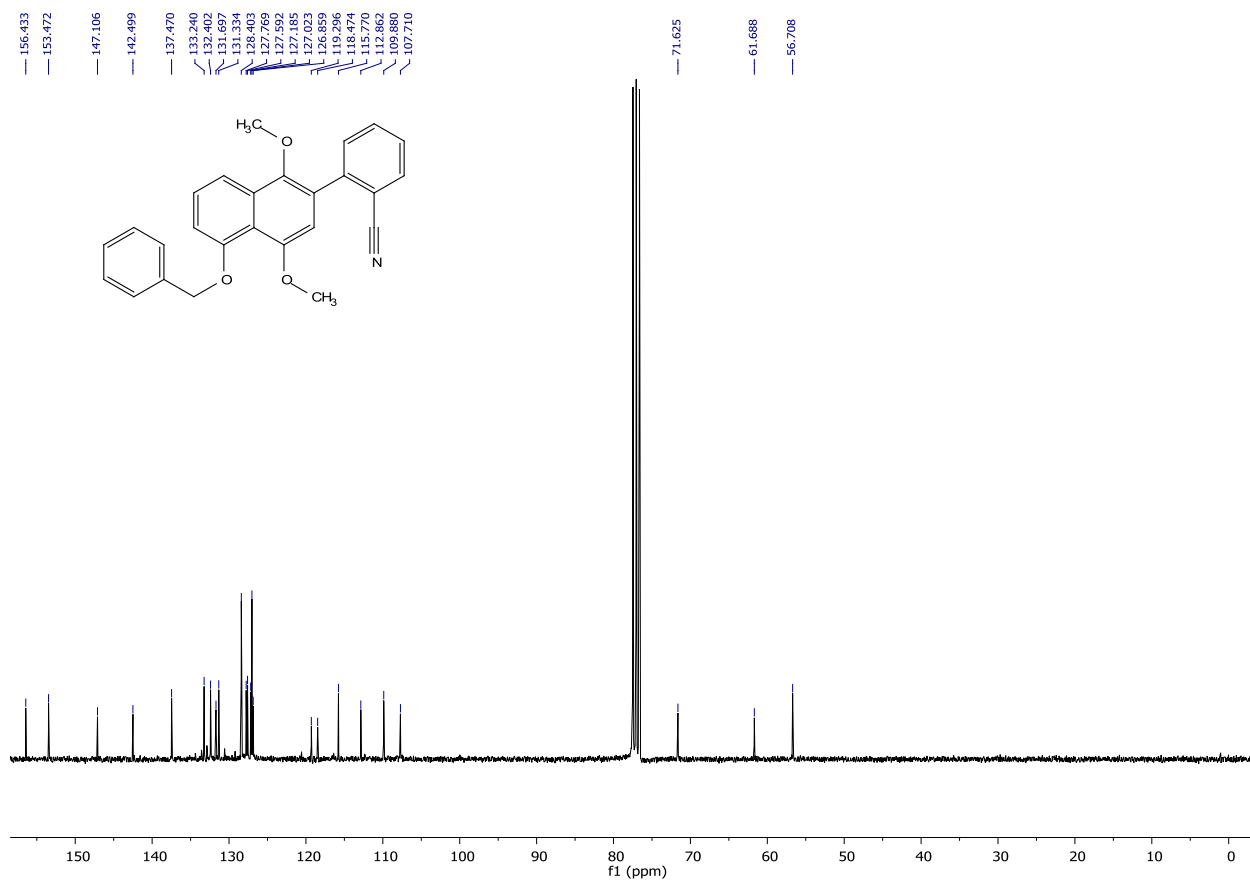


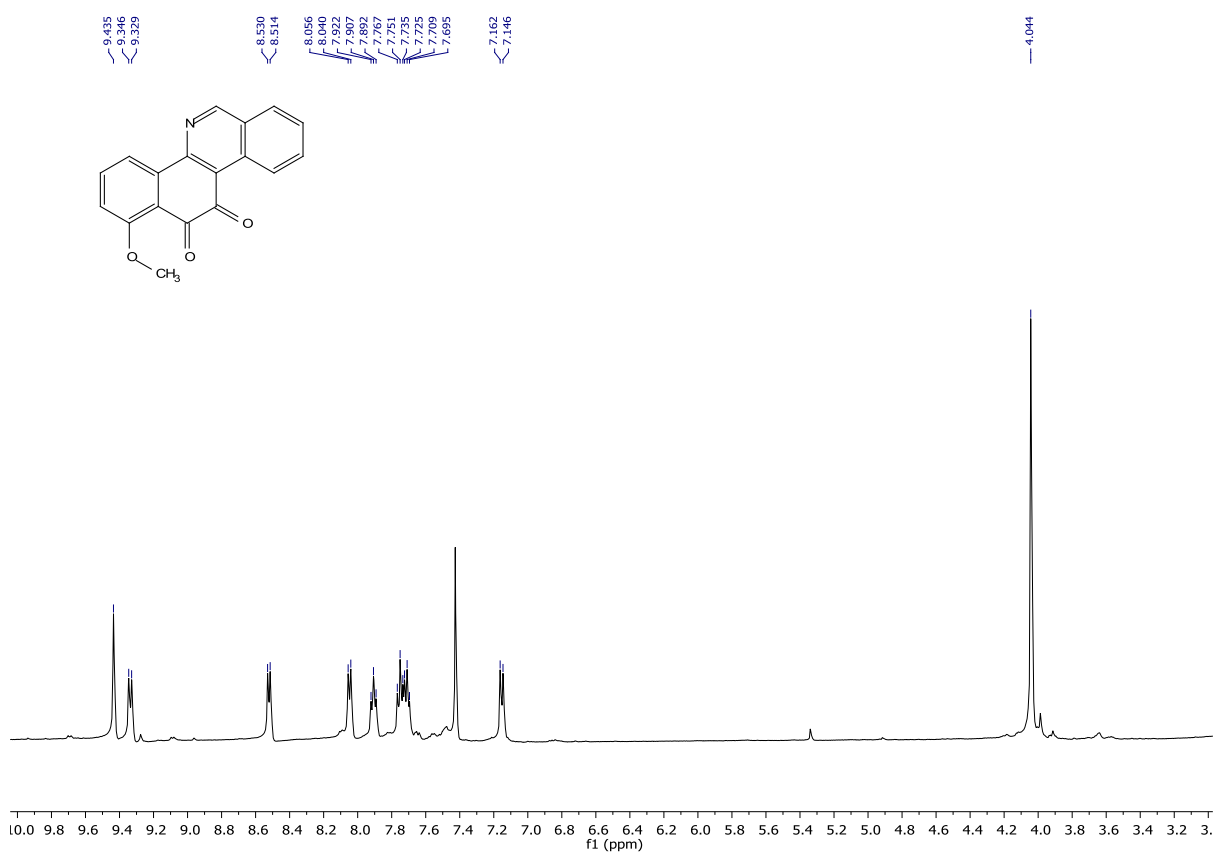
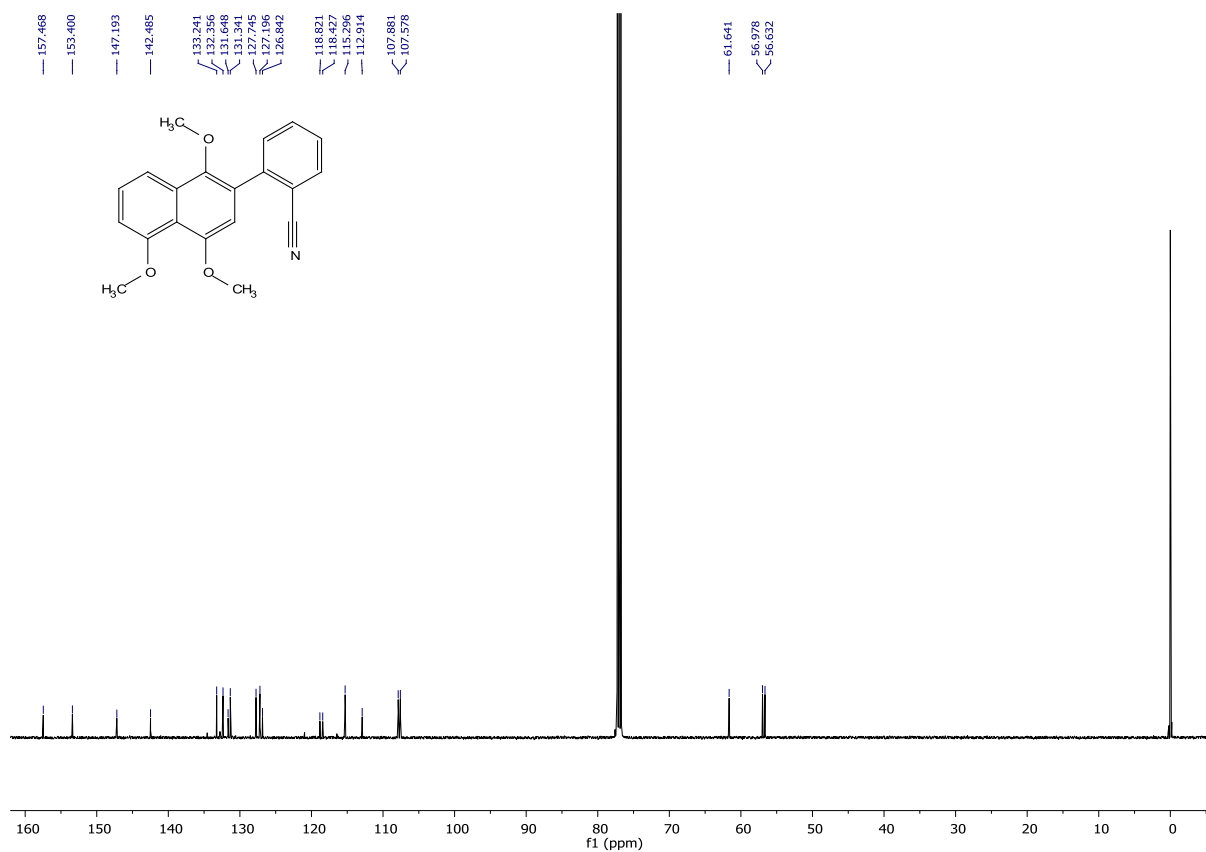


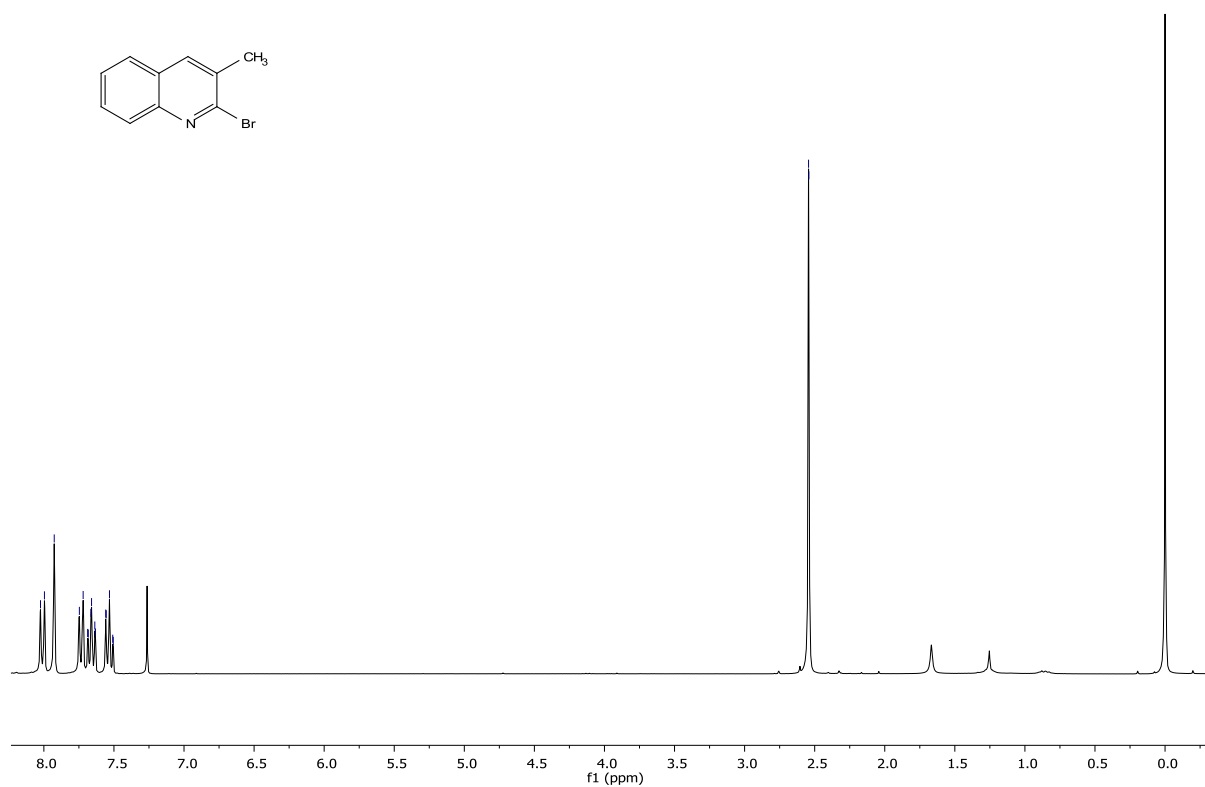
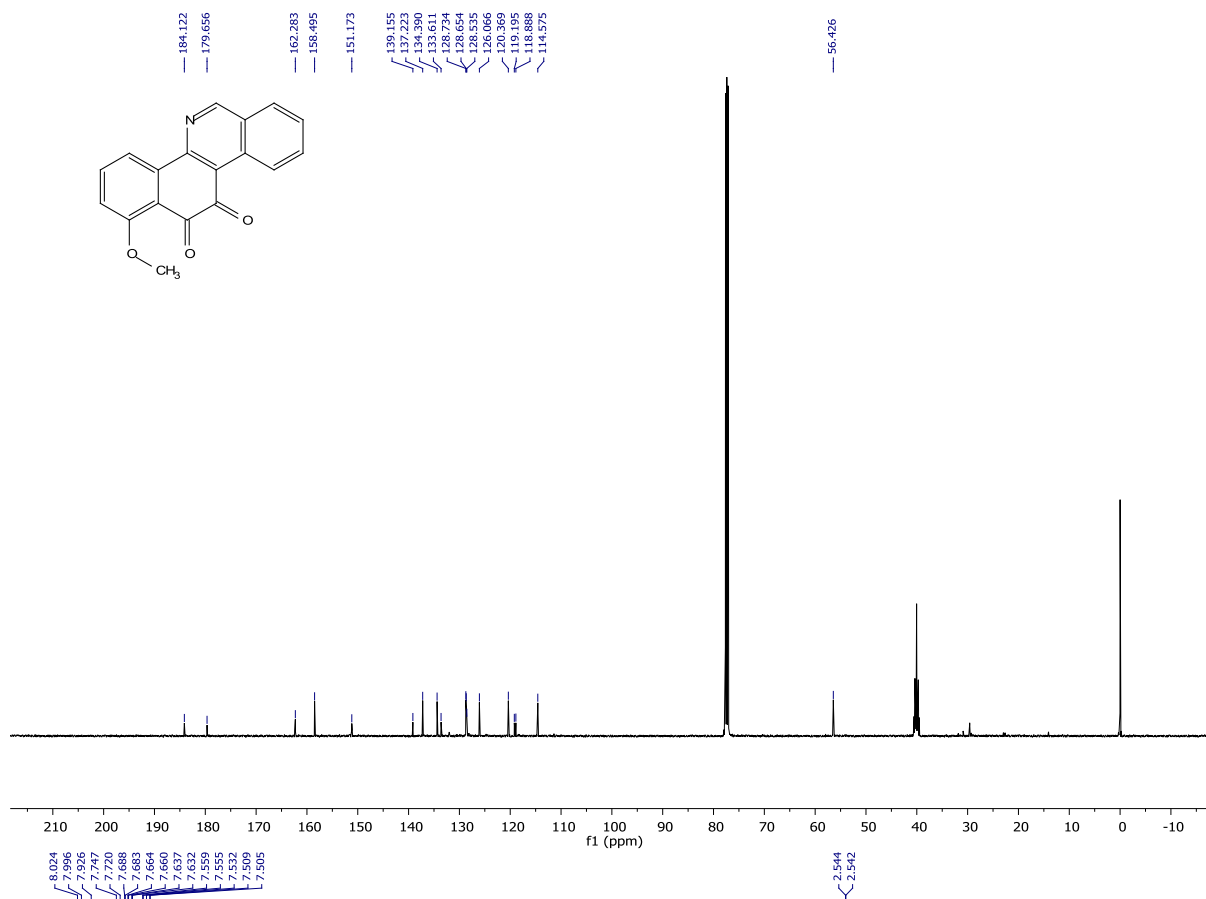


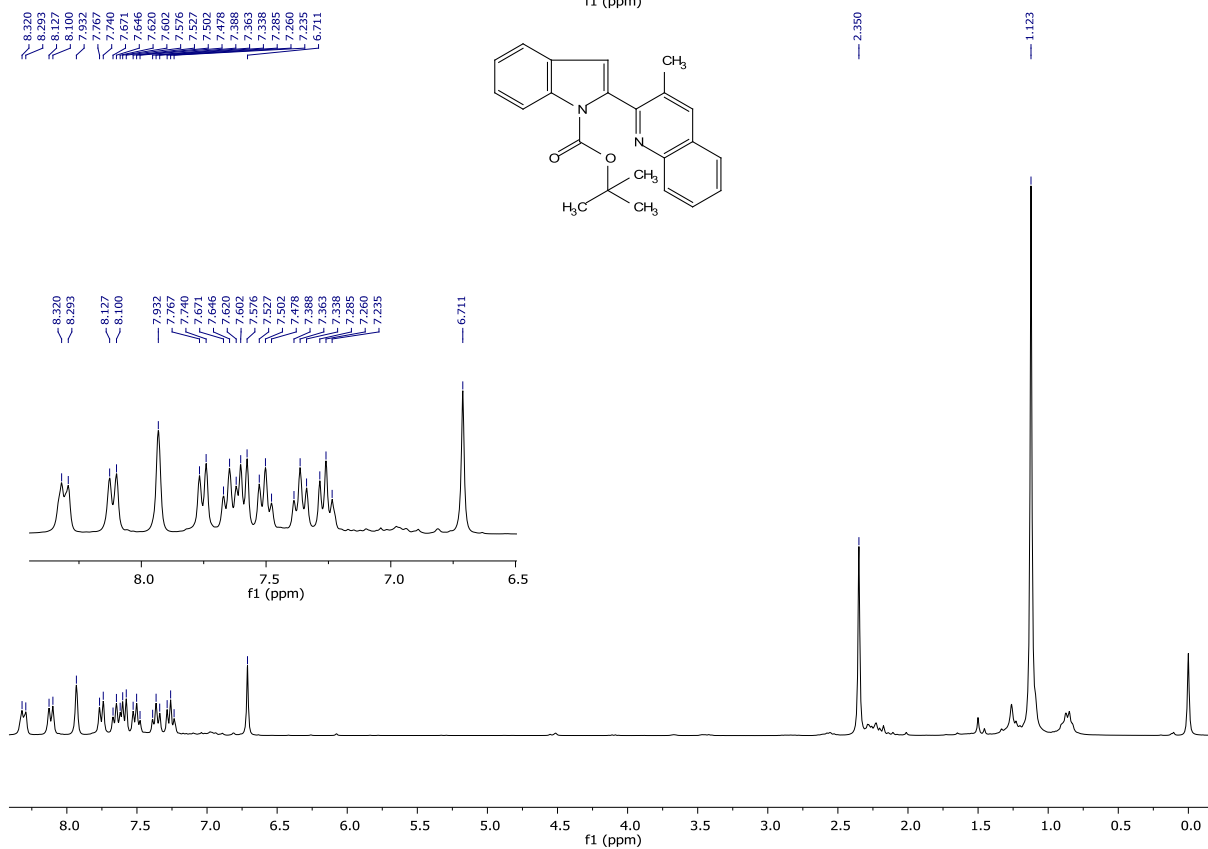
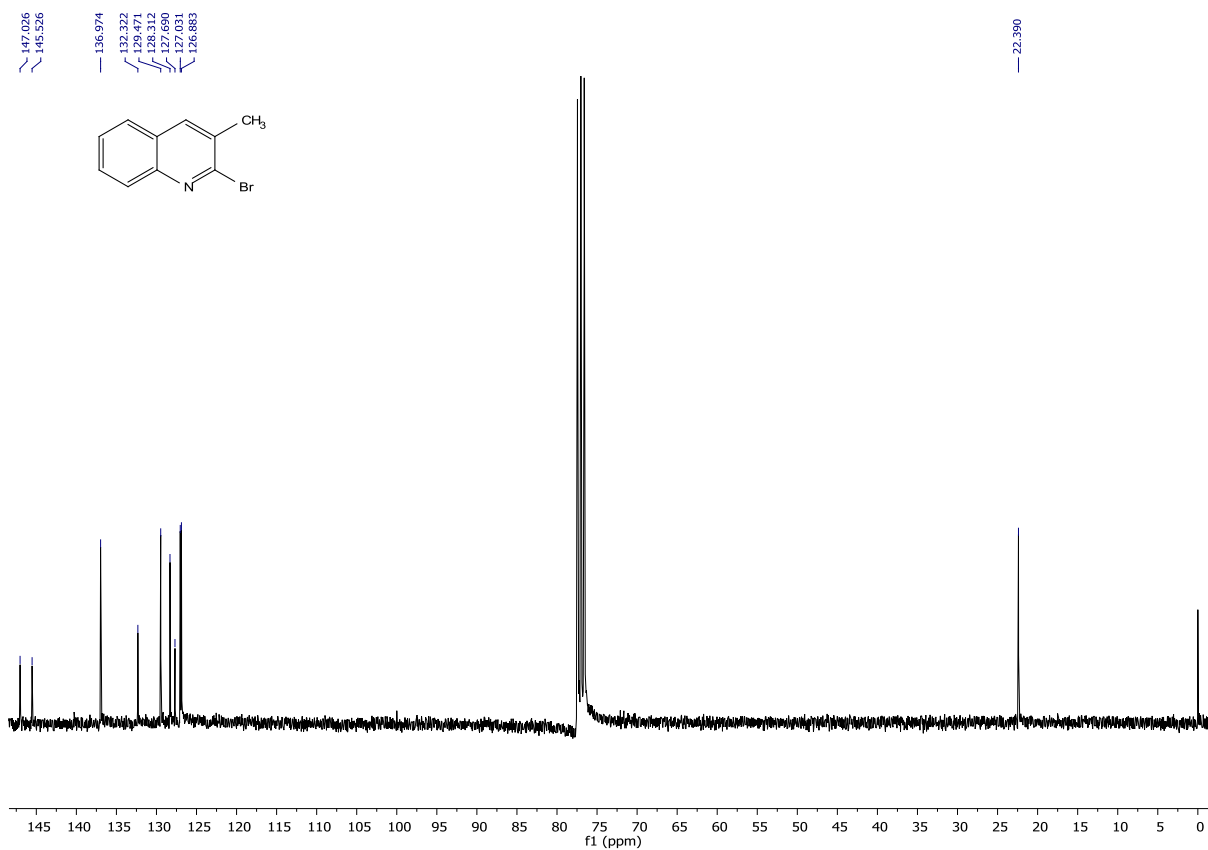




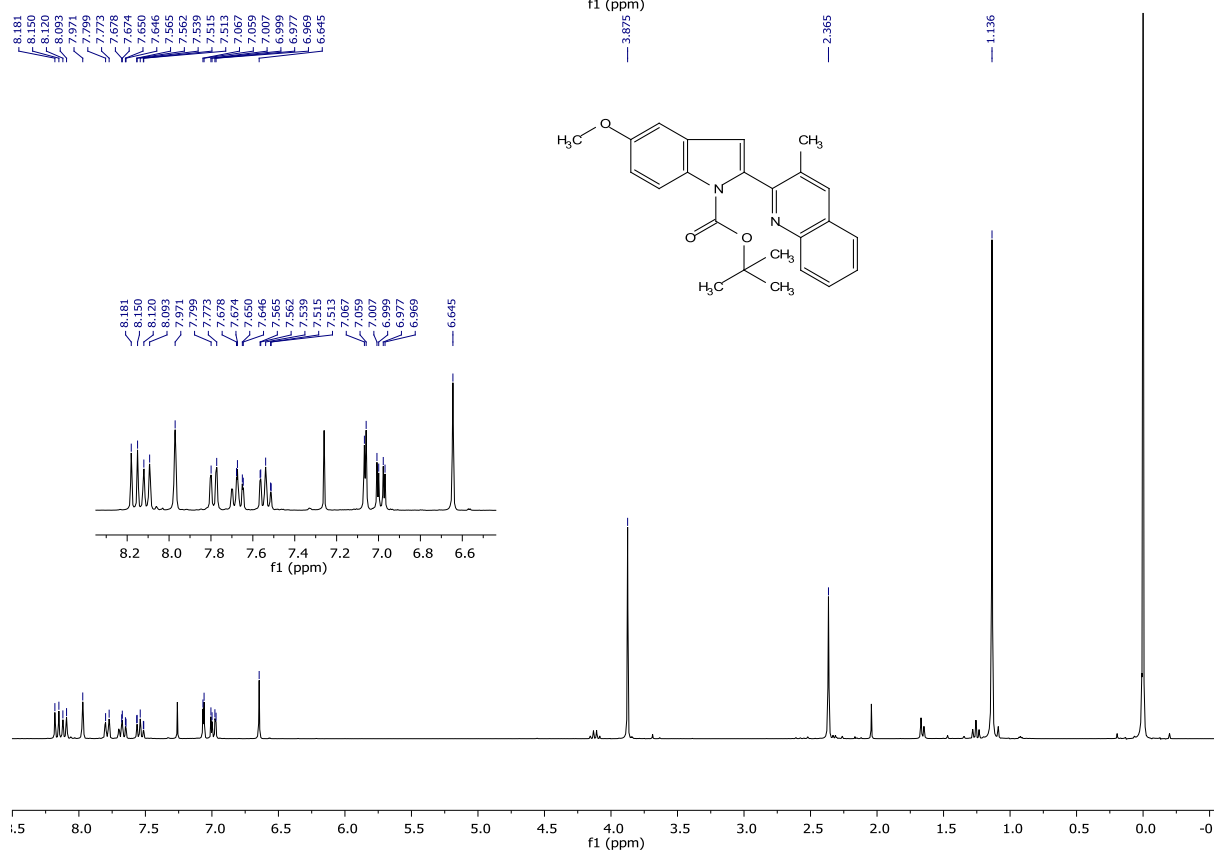
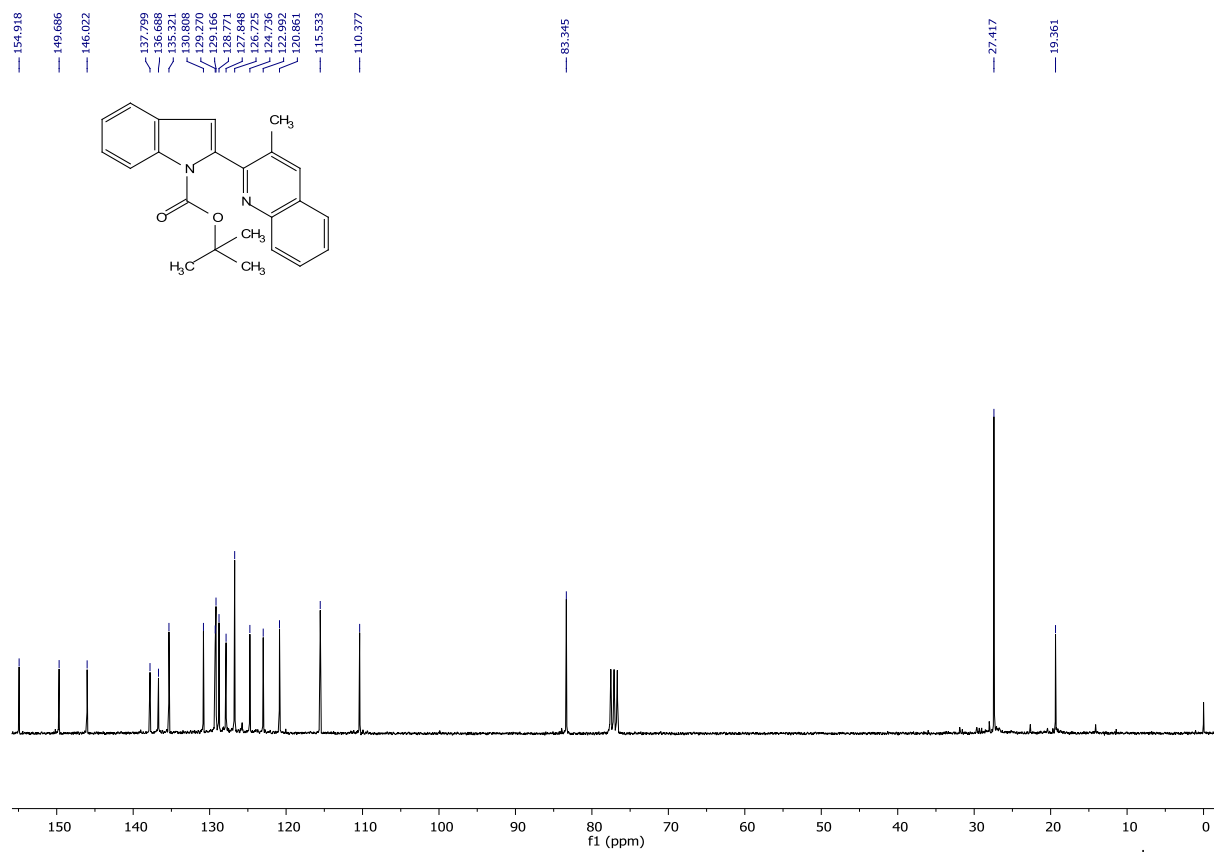


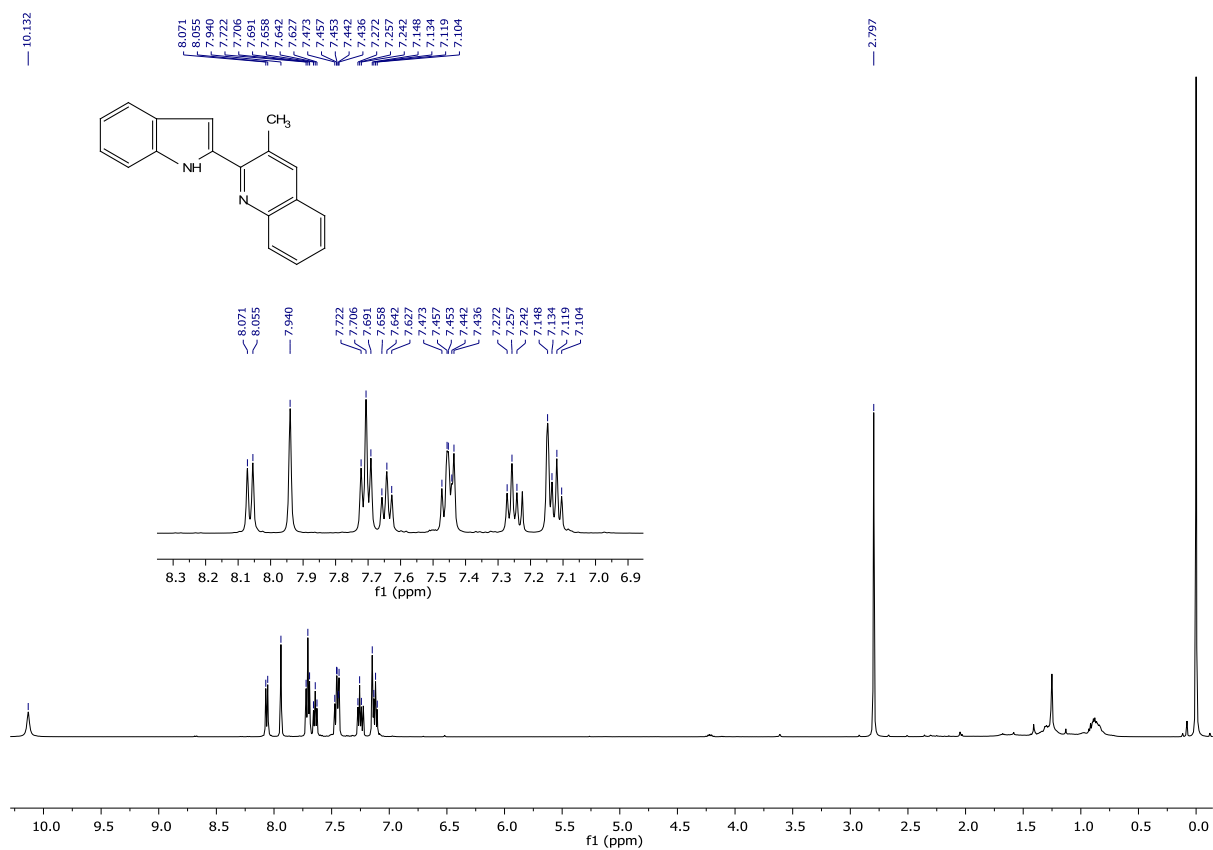
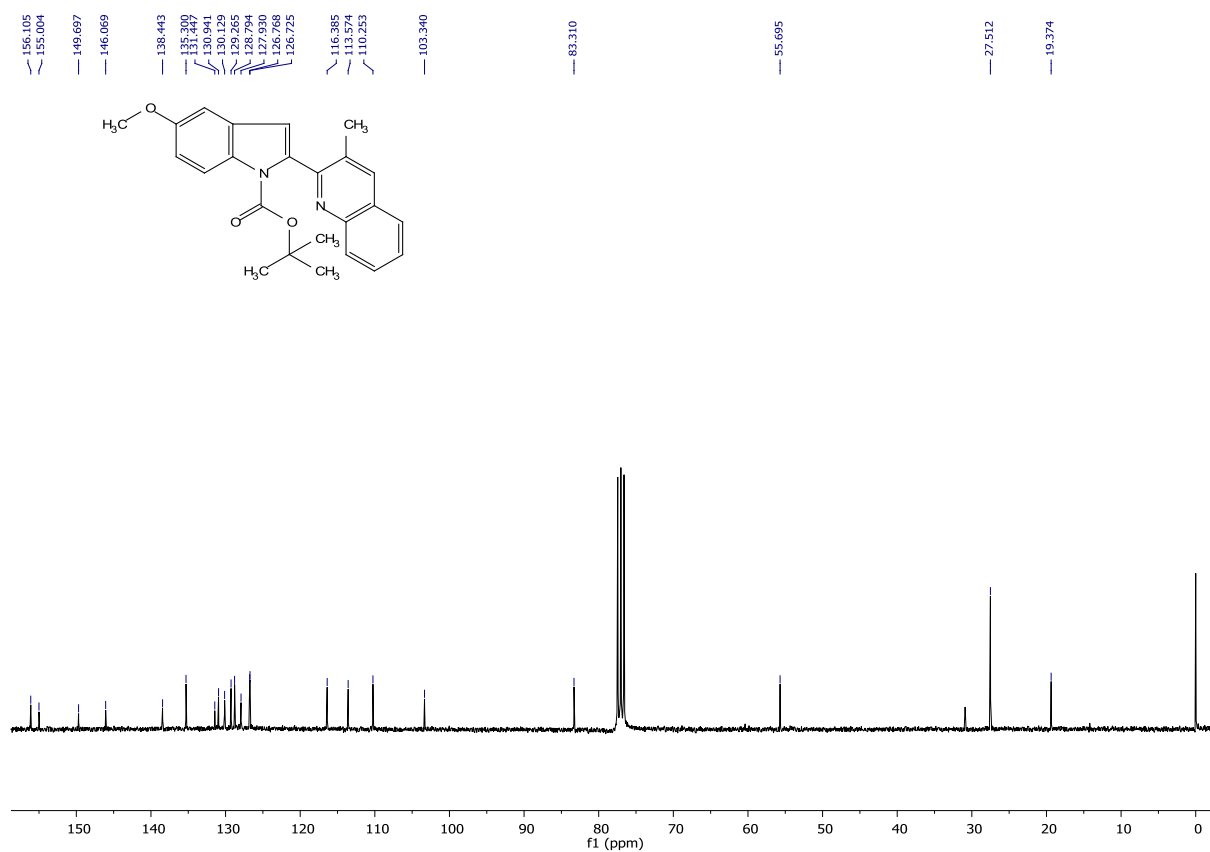


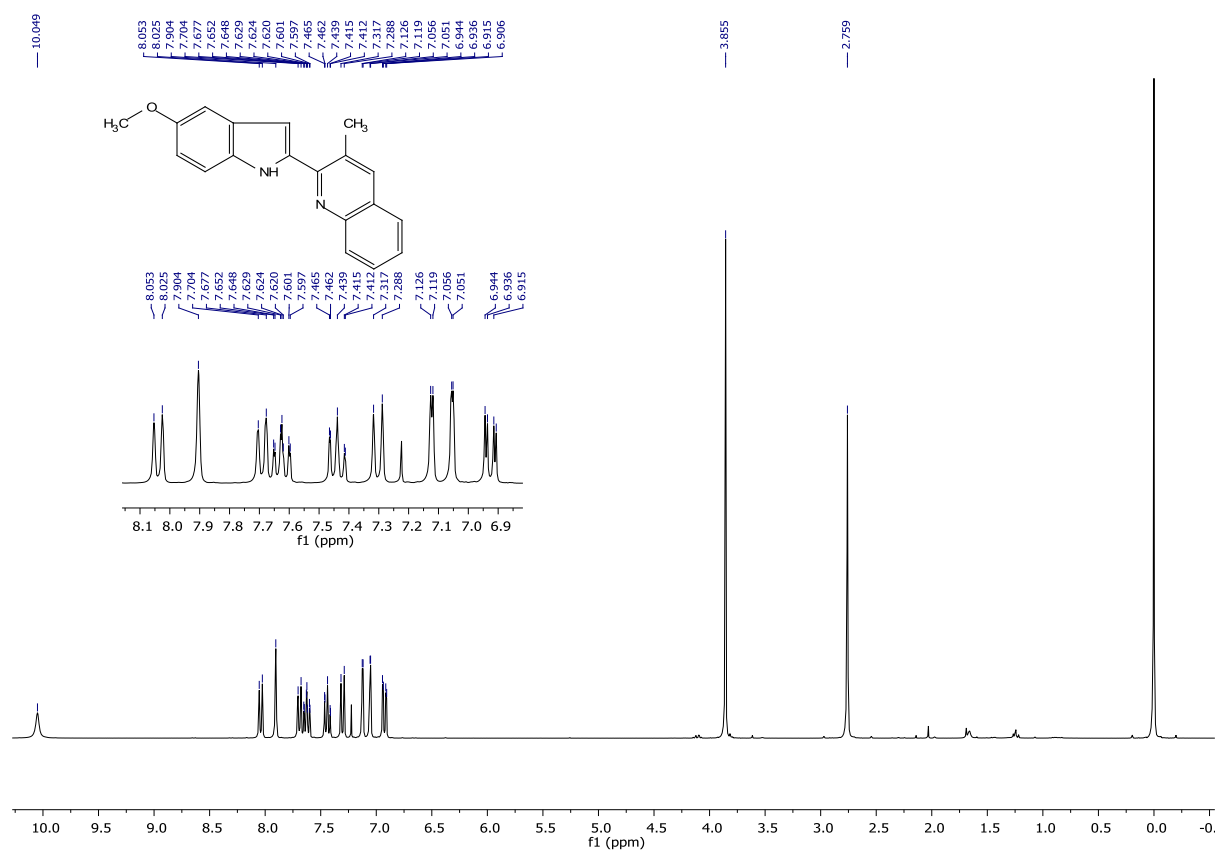
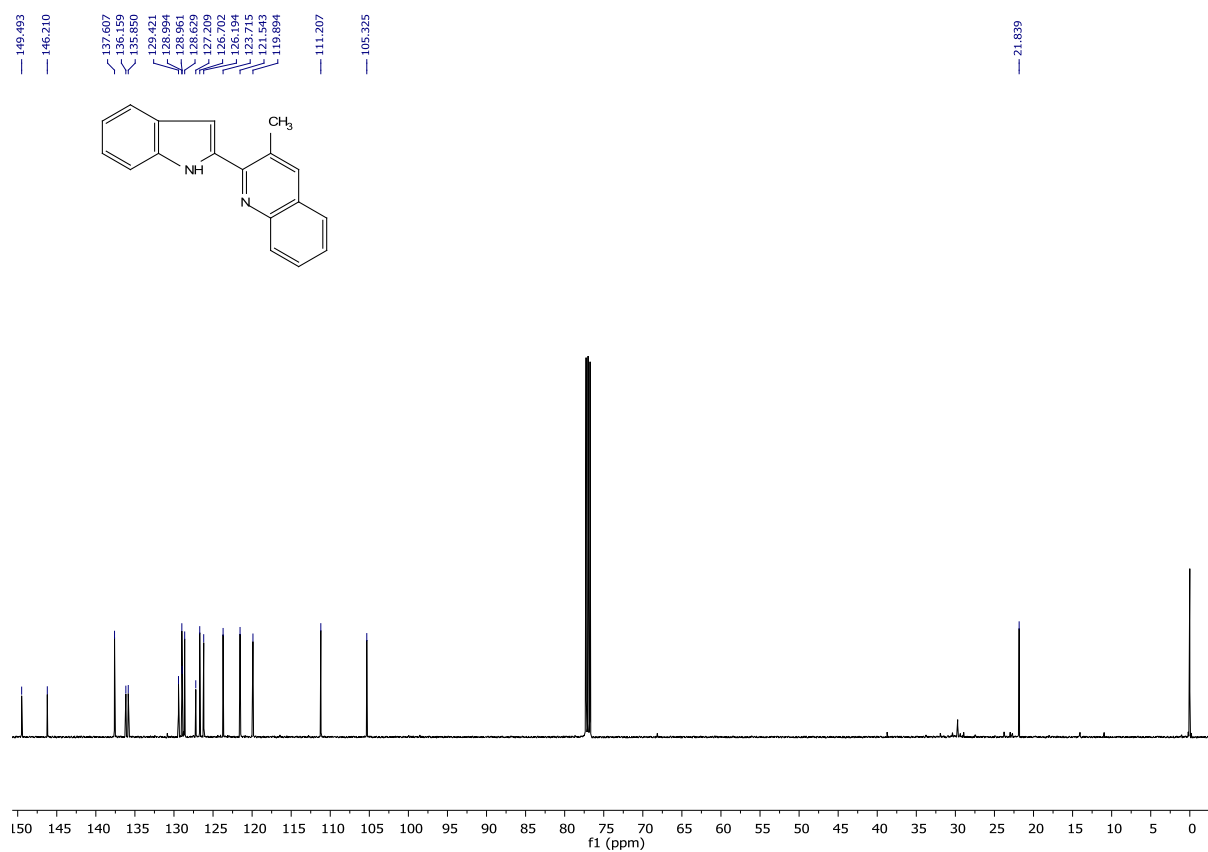


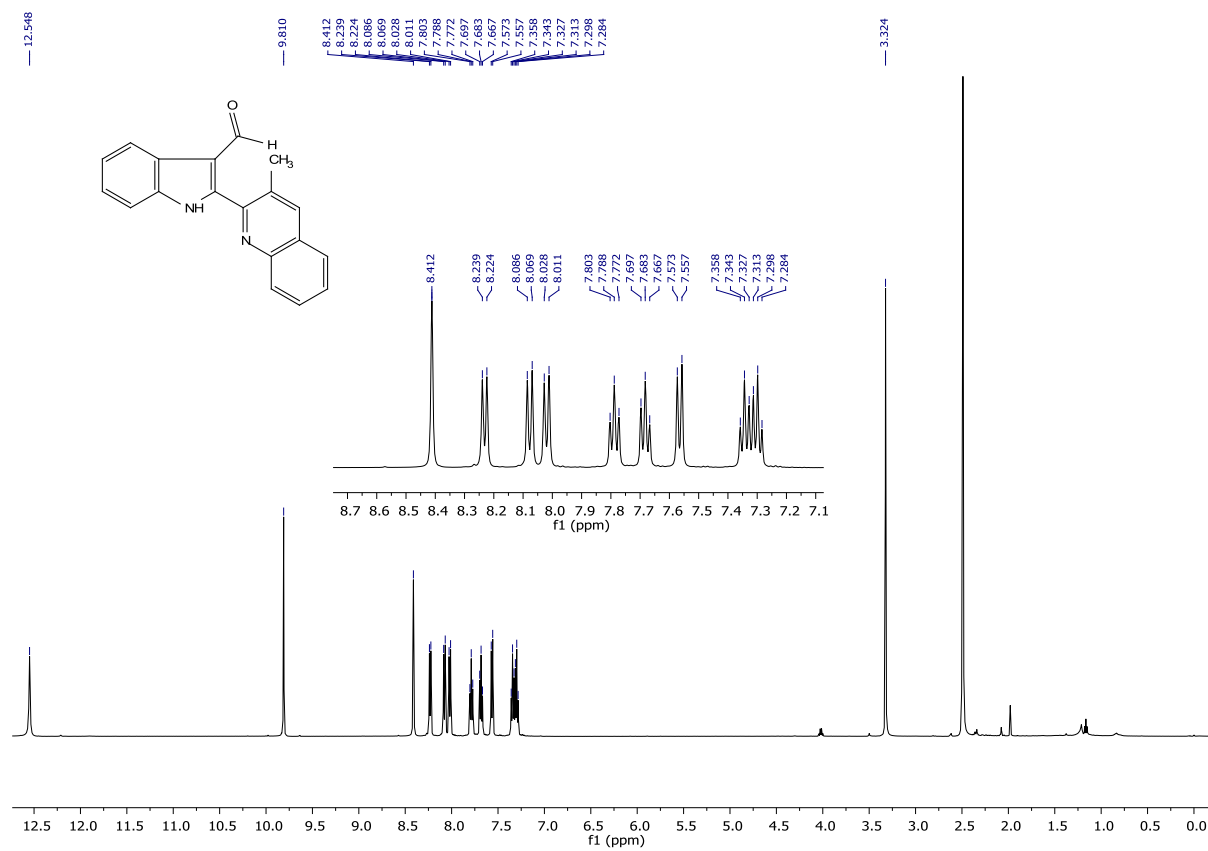
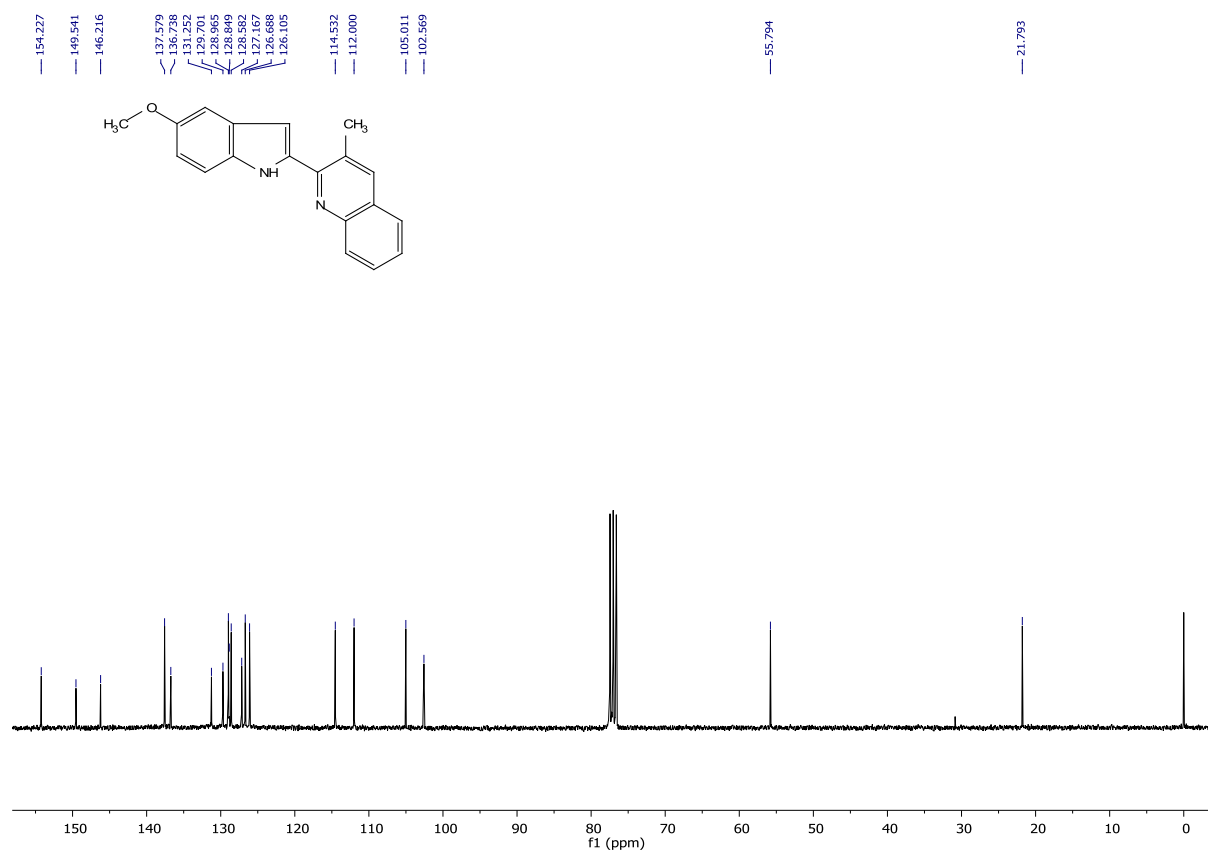


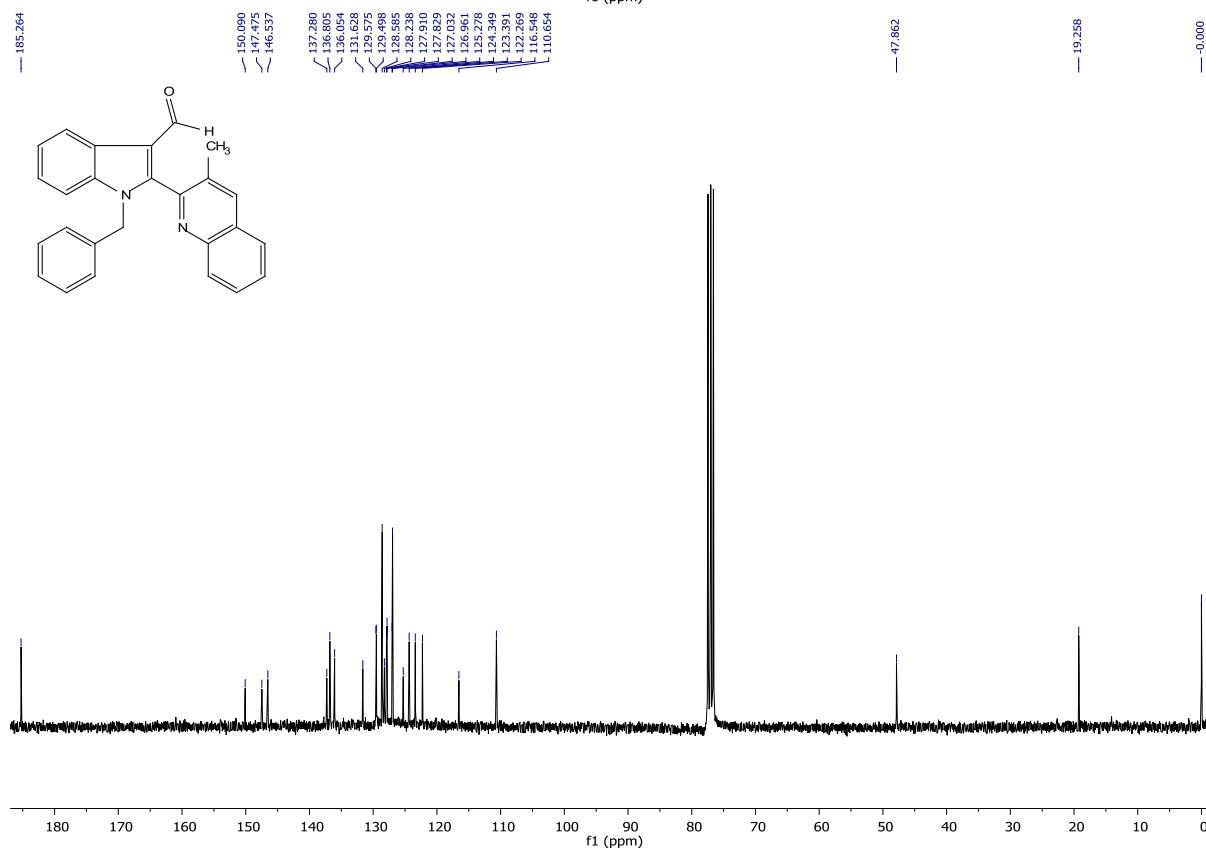
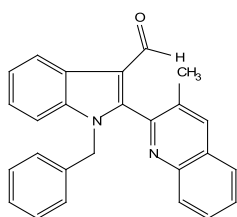
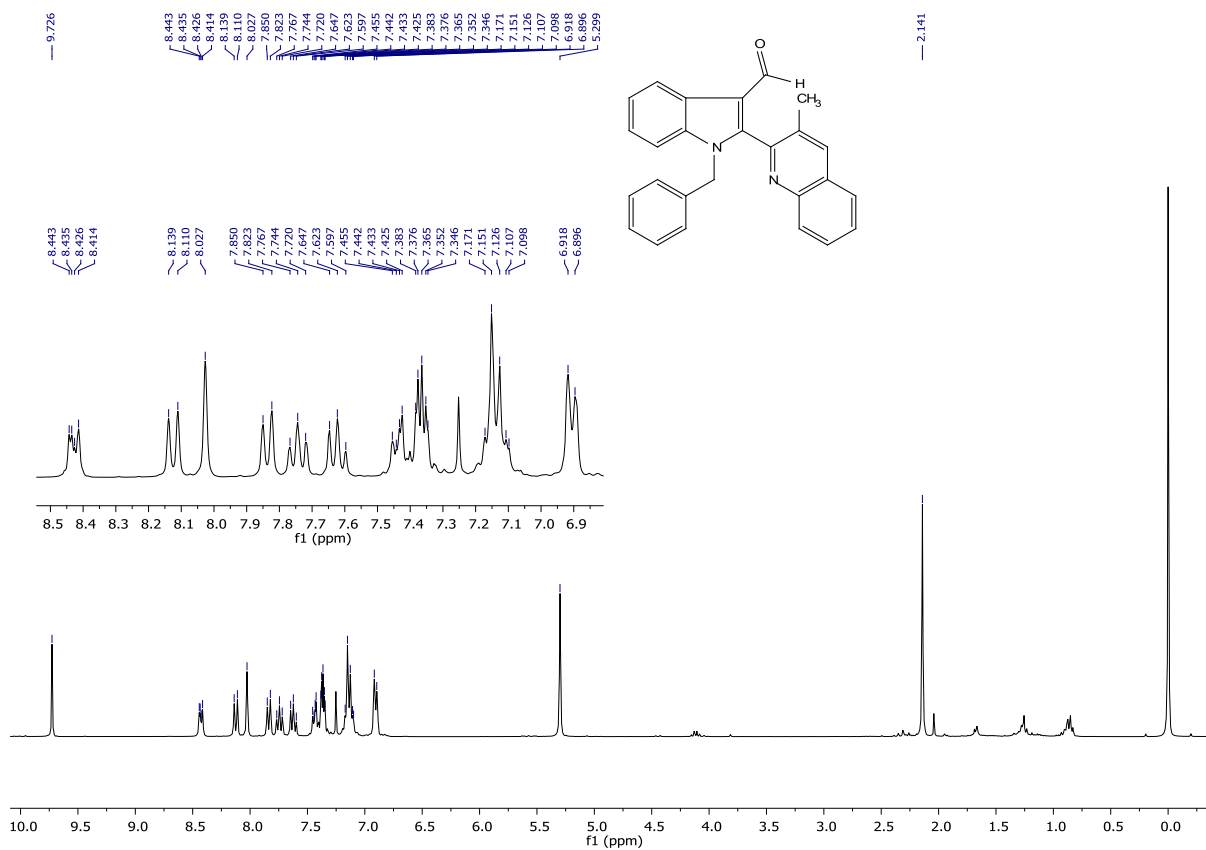


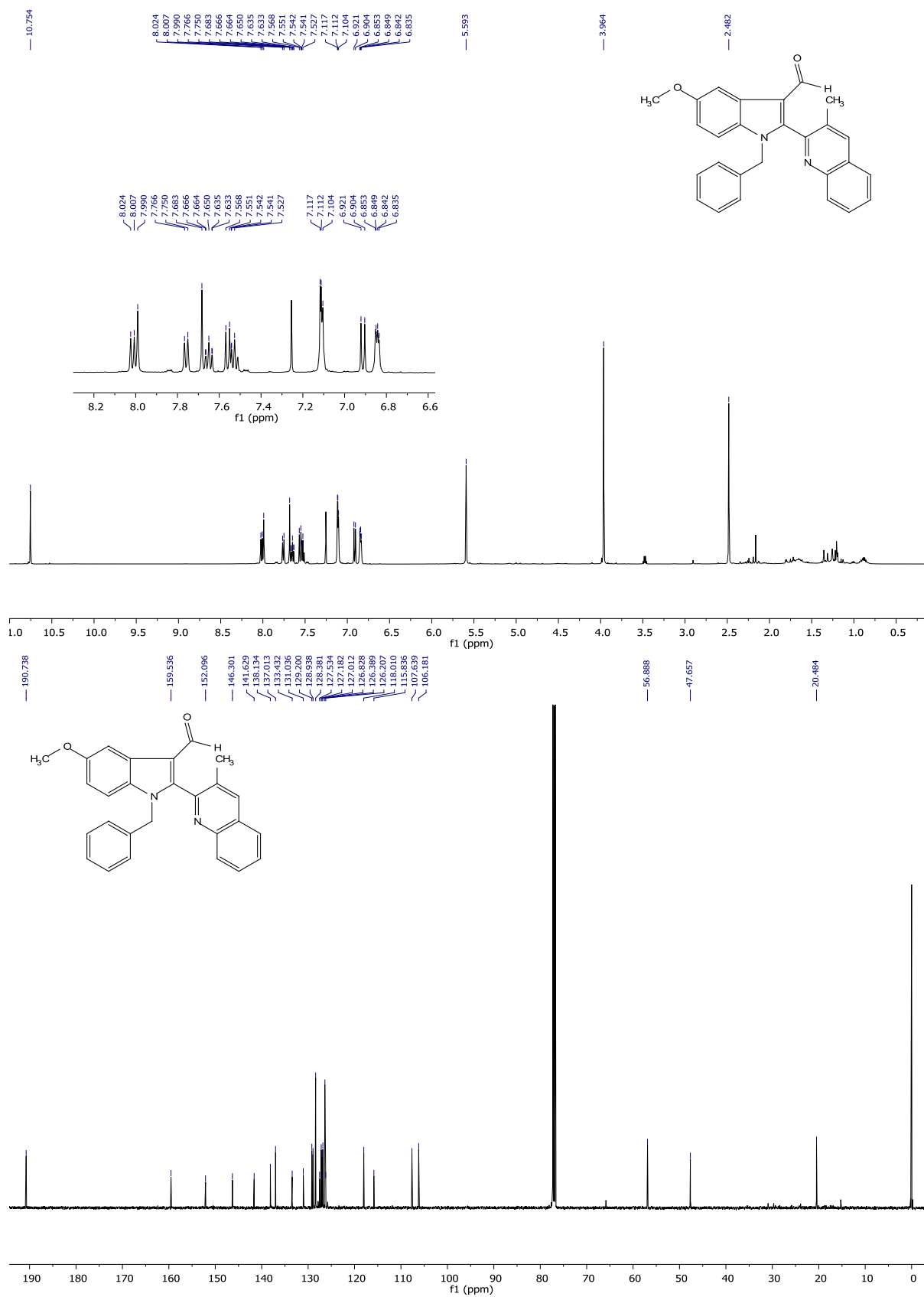


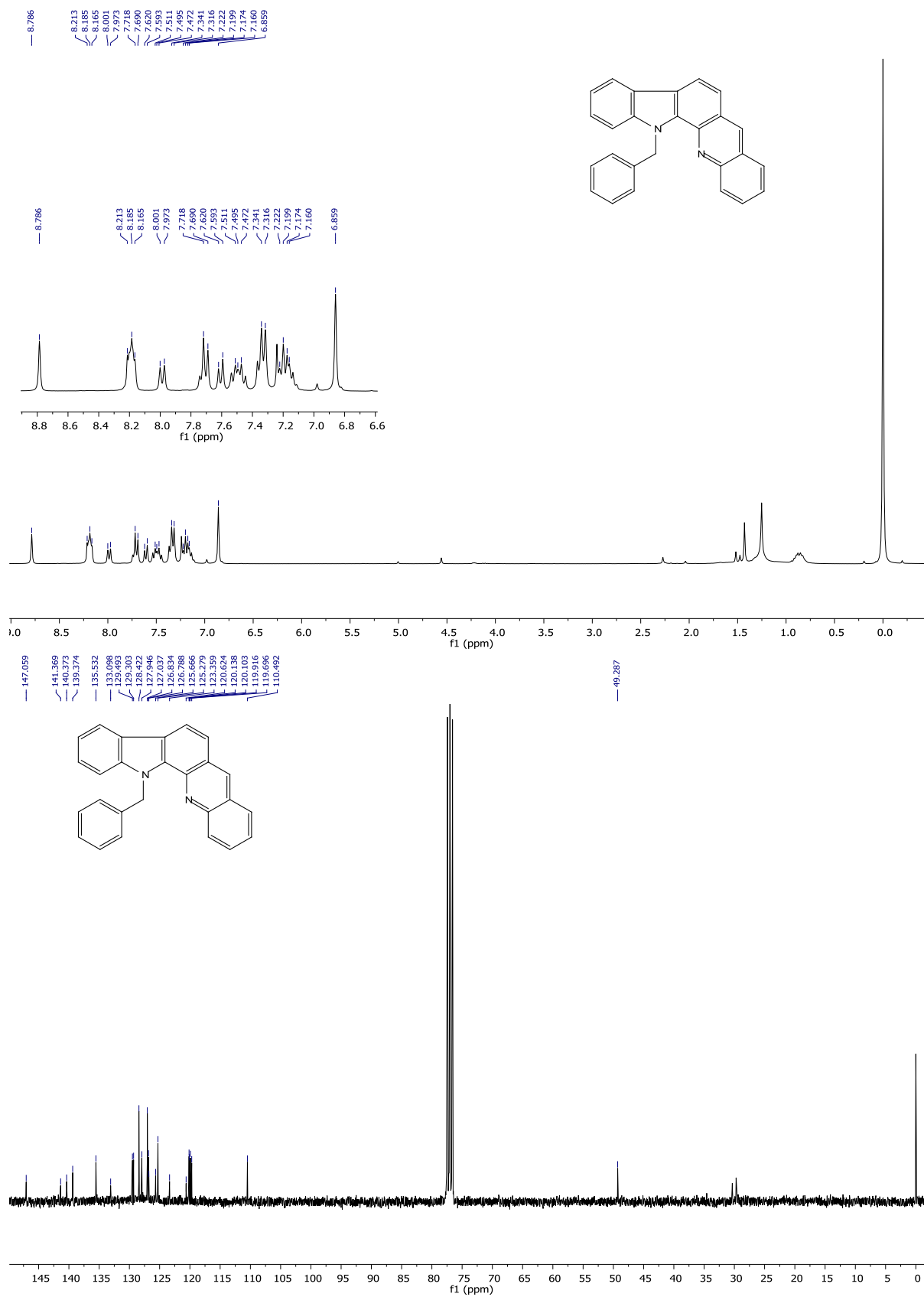


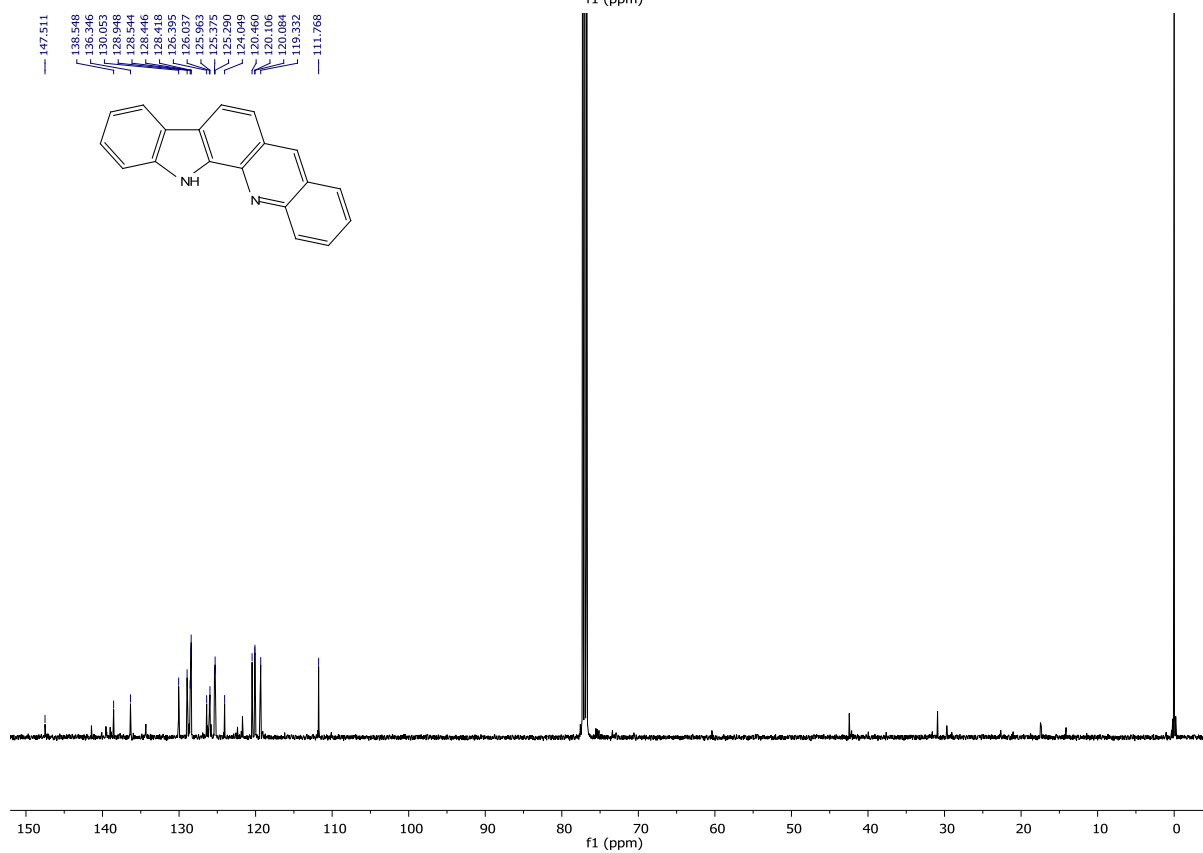
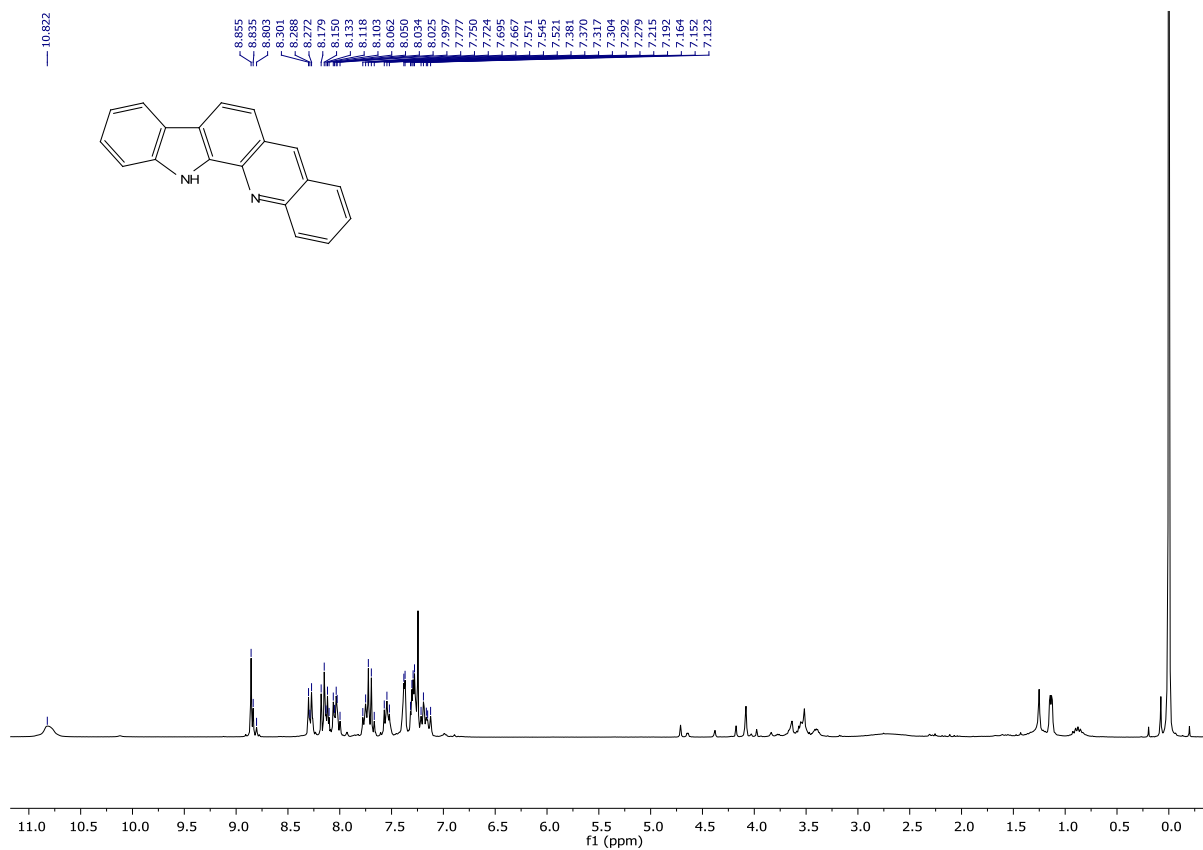






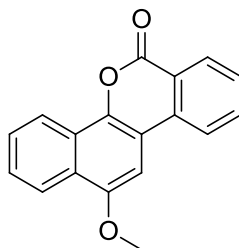




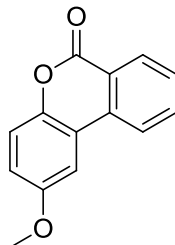




**Appendix B: Single Crystal X-ray Differection Data**

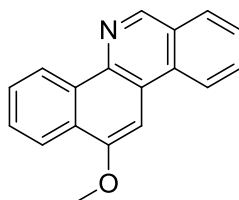
Crystal Structure Data for 12-methoxy-6H-dibenzo[*c,h*]chromen-6-one **64****Table 1:** Crystal data and structure refinement for compound **64**

|                                   |                                                                                                                                                                                |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Empirical formula                 | C <sub>18</sub> H <sub>12</sub> O <sub>3</sub>                                                                                                                                 |
| Formula weight                    | 276.28                                                                                                                                                                         |
| Temperature                       | 173(2) K                                                                                                                                                                       |
| Wavelength                        | 0.71069 Å                                                                                                                                                                      |
| Crystal system                    | Triclinic                                                                                                                                                                      |
| Space group                       | P-1                                                                                                                                                                            |
| Unit cell dimensions              | $a = 7.1970(7) \text{ Å}$ $\alpha = 103.237(3)^\circ$ .<br>$b = 9.0700(9) \text{ Å}$ $\beta = 105.722(3)^\circ$ .<br>$c = 10.8400(11) \text{ Å}$ $\gamma = 104.026(3)^\circ$ . |
| Volume                            | 627.07(11) Å <sup>3</sup>                                                                                                                                                      |
| Z                                 | 2                                                                                                                                                                              |
| Density (calculated)              | 1.463 Mg/m <sup>3</sup>                                                                                                                                                        |
| Absorption coefficient            | 0.100 mm <sup>-1</sup>                                                                                                                                                         |
| F(000)                            | 288                                                                                                                                                                            |
| Crystal size                      | 0.62 x 0.14 x 0.04 mm <sup>3</sup>                                                                                                                                             |
| Theta range for data collection   | 2.06 to 27.00°.                                                                                                                                                                |
| Index ranges                      | -9 ≤ h ≤ 9, -11 ≤ k ≤ 10, -13 ≤ l ≤ 13                                                                                                                                         |
| Reflections collected             | 6387                                                                                                                                                                           |
| Independent reflections           | 2743 [R(int) = 0.0758]                                                                                                                                                         |
| Completeness to theta = 27.00°    | 100.0 %                                                                                                                                                                        |
| Absorption correction             | None                                                                                                                                                                           |
| Max. and min. transmission        | 0.9960 and 0.9409                                                                                                                                                              |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                                                                                                                    |
| Data / restraints / parameters    | 2743 / 0 / 191                                                                                                                                                                 |
| Goodness-of-fit on F <sup>2</sup> | 0.874                                                                                                                                                                          |
| Final R indices [I > 2σ(I)]       | R1 = 0.0479, wR2 = 0.1016                                                                                                                                                      |
| R indices (all data)              | R1 = 0.0902, wR2 = 0.1190                                                                                                                                                      |
| Largest diff. peak and hole       | 0.229 and -0.271 e.Å <sup>-3</sup>                                                                                                                                             |

Crystal Structure Data for 2-methoxy-6*H*-benzo[*c*]chromen-6-one **98****Table 2:** Crystal data and structure refinement for compound **98**

|                                 |                                                                                                                                                 |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Empirical formula               | C <sub>14</sub> H <sub>10</sub> O <sub>3</sub>                                                                                                  |
| Formula weight                  | 226.22                                                                                                                                          |
| Temperature                     | 173(2) K                                                                                                                                        |
| Wavelength                      | 0.71073 Å                                                                                                                                       |
| Crystal system                  | Triclinic                                                                                                                                       |
| Space group                     | P-1                                                                                                                                             |
| Unit cell dimensions            | $a = 7.4581(8)$ Å $\alpha = 83.115(4)^\circ$<br>$b = 10.7427(12)$ Å $\beta = 83.963(4)^\circ$<br>$c = 13.7087(15)$ Å $\gamma = 73.844(4)^\circ$ |
| Volume                          | $1044.4(2)$ Å <sup>3</sup>                                                                                                                      |
| Z                               | 4                                                                                                                                               |
| Density (calculated)            | 1.439 Mg/m <sup>3</sup>                                                                                                                         |
| Absorption coefficient          | 0.101 mm <sup>-1</sup>                                                                                                                          |
| F(000)                          | 472                                                                                                                                             |
| Crystal size                    | 0.50 x 0.16 x 0.06 mm <sup>3</sup>                                                                                                              |
| Theta range for data collection | 2.85 to 28.00°                                                                                                                                  |
| Index ranges                    | -9 ≤ h ≤ 9, -14 ≤ k ≤ 14, -18 ≤ l ≤ 18                                                                                                          |
| Reflections collected           | 44613                                                                                                                                           |
| Independent reflections         | 5037 [R(int) = 0.0294]                                                                                                                          |
| Completeness to theta = 28.00   | 99.8%                                                                                                                                           |
| Absorption correction           | Semi-empirical from equivalents                                                                                                                 |
| Max. and min. transmission      | 0.9937 and 0.9506                                                                                                                               |
| Refinement method               | Full-matrix least-squares on F <sup>2</sup>                                                                                                     |

|                                      |                                    |
|--------------------------------------|------------------------------------|
| Data/restraints/parameters           | 5037/0/309                         |
| Goodness-of-fit on $F^2$             | 1.017                              |
| Final R indices [ $I > 2\sigma(I)$ ] | $R1 = 0.0381$ , $wR2 = 0.1033$     |
| R indices (all data)                 | $R1 = 0.0481$ , $wR2 = 0.1115$     |
| Largest diff. peak and hole          | 0.328 and -0.227 e.Å <sup>-3</sup> |

Crystal Structure Data for 12-methoxybenzo[c]phenanthridine **185****Table 3:** Crystal data and structure refinement for **185**

|                                   |                                                                                    |
|-----------------------------------|------------------------------------------------------------------------------------|
| Empirical formula                 | C <sub>18</sub> H <sub>13</sub> NO                                                 |
| Formula weight                    | 259.29                                                                             |
| Temperature                       | 173(2) K                                                                           |
| Wavelength                        | 0.71073 Å                                                                          |
| Crystal system                    | Orthorhombic                                                                       |
| Space group                       | P2(1)                                                                              |
| Unit cell dimensions              | a = 18.0958(19) Å α = 90°<br>b = 8.9270(11) Å β = 90°<br>c = 15.7941(19) Å γ = 90° |
| Volume                            | 2551.4(5) Å <sup>3</sup>                                                           |
| Z                                 | 8                                                                                  |
| Density (calculated)              | 1.350 Mg/m <sup>3</sup>                                                            |
| Absorption coefficient            | 0.084 mm <sup>-1</sup>                                                             |
| F(000)                            | 1088                                                                               |
| Crystal size                      | 0.22 x 0.17 x 0.16 mm <sup>3</sup>                                                 |
| Theta range for data collection   | 3.46 to 27.99°                                                                     |
| Index ranges                      | -22 ≤ h ≤ 23, -11 ≤ k ≤ 11, -20 ≤ l ≤ 20                                           |
| Reflections collected             | 18478                                                                              |
| Independent reflections           | 3176 [R(int) = 0.0333]                                                             |
| Completeness to theta = 27.99     | 99.6%                                                                              |
| Absorption correction             | Semi-empirical from equivalents                                                    |
| Max. and min. transmission        | 0.9866 and 0.9818                                                                  |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                        |
| Data/restraints/parameters        | 3176/1/363                                                                         |
| Goodness-of-fit on F <sup>2</sup> | 1.031                                                                              |
| Final R indices [I > 2σ(I)]       | R1 = 0.0389, wR2 = 0.0967                                                          |

R indices (all data)

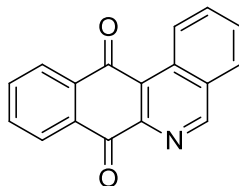
$R_1 = 0.0503$ ,  $wR_2 = 0.1040$

Absolute structure parameter

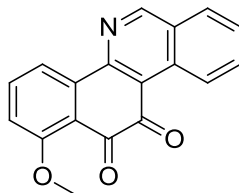
10(10)

Largest diff. peak and hole

0.247 and -0.142 e.Å<sup>-3</sup>

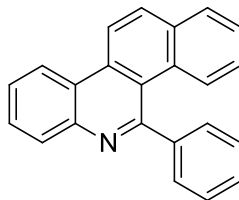
Crystal Structure Data for benzo[b]phenanthridine-7,12-dione **129****Table 4:** Crystal data and structure refinement for compound **129**

|                                   |                                                                                             |
|-----------------------------------|---------------------------------------------------------------------------------------------|
| Empirical formula                 | C <sub>17</sub> H <sub>9</sub> N O <sub>2</sub>                                             |
| Formula weight                    | 259.25                                                                                      |
| Temperature                       | 173(2) K                                                                                    |
| Wavelength                        | 0.71073 Å                                                                                   |
| Crystal system                    | Monoclinic                                                                                  |
| Space group                       | C2/c                                                                                        |
| Unit cell dimensions              | a = 10.5737(6) Å α = 90°.<br>b = 11.0912(6) Å β = 98.998(2)°.<br>c = 20.0250(11) Å γ = 90°. |
| Volume                            | 2319.5(2) Å <sup>3</sup>                                                                    |
| Z                                 | 8                                                                                           |
| Density (calculated)              | 1.485 Mg/m <sup>3</sup>                                                                     |
| Absorption coefficient            | 0.099 mm <sup>-1</sup>                                                                      |
| F(000)                            | 1072                                                                                        |
| Crystal size                      | 0.40 x 0.38 x 0.31 mm <sup>3</sup>                                                          |
| Theta range for data collection   | 3.56 to 25.50°.                                                                             |
| Index ranges                      | -12 ≤ h ≤ 12, -13 ≤ k ≤ 13, -19 ≤ l ≤ 24                                                    |
| Reflections collected             | 8630                                                                                        |
| Independent reflections           | 2020 [R(int) = 0.0264]                                                                      |
| Completeness to theta = 25.50°    | 93.6 %                                                                                      |
| Absorption correction             | Semi-empirical from equivalents                                                             |
| Max. and min. transmission        | 0.9699 and 0.9620                                                                           |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                                 |
| Data / restraints / parameters    | 2020 / 0 / 181                                                                              |
| Goodness-of-fit on F <sup>2</sup> | 1.072                                                                                       |
| Final R indices [I > 2σ(I)]       | R <sub>1</sub> = 0.0485, wR <sub>2</sub> = 0.1212                                           |
| R indices (all data)              | R <sub>1</sub> = 0.0620, wR <sub>2</sub> = 0.1312                                           |
| Largest diff. peak and hole       | 0.286 and -0.152 e.Å <sup>-3</sup>                                                          |

Crystal Structure Data for 1-methoxybenzo[c]phenanthridine-11,12-dione **205****Table 5:** Crystal data and structure refinement for compound **205**

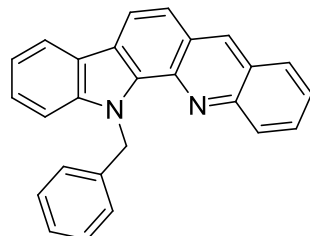
|                                   |                                                                                           |
|-----------------------------------|-------------------------------------------------------------------------------------------|
| Empirical formula                 | C <sub>18</sub> H <sub>11</sub> NO <sub>3</sub>                                           |
| Formula weight                    | 289.28                                                                                    |
| Temperature                       | 173(2) K                                                                                  |
| Wavelength                        | 0.71073 Å                                                                                 |
| Crystal system                    | Monoclinic                                                                                |
| Space group                       | C2/c                                                                                      |
| Unit cell dimensions              | a = 17.5504(8) Å α = 90°.<br>b = 7.1638(3) Å β = 96.459(2)°.<br>c = 20.5142(9) Å γ = 90°. |
| Volume                            | 2562.83(19) Å <sup>3</sup>                                                                |
| Z                                 | 8                                                                                         |
| Density (calculated)              | 1.499 Mg/m <sup>3</sup>                                                                   |
| Absorption coefficient            | 0.103 mm <sup>-1</sup>                                                                    |
| F(000)                            | 1200                                                                                      |
| Crystal size                      | 0.36 x 0.26 x 0.16 mm <sup>3</sup>                                                        |
| Theta range for data collection   | 3.60 to 28.00°.                                                                           |
| Index ranges                      | -20 ≤ h ≤ 23, -9 ≤ k ≤ 9, -27 ≤ l ≤ 27                                                    |
| Reflections collected             | 17130                                                                                     |
| Independent reflections           | 3089 [R(int) = 0.0296]                                                                    |
| Completeness to theta = 28.00°    | 99.7%                                                                                     |
| Absorption correction             | Semi-empirical from equivalents                                                           |
| Max. and min. transmission        | 0.9837 and 0.9638                                                                         |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                               |
| Data / restraints / parameters    | 3089 / 0 / 200                                                                            |
| Goodness-of-fit on F <sup>2</sup> | 1.040                                                                                     |
| Final R indices [I > 2σ(I)]       | R1 = 0.0487, wR2 = 0.1356                                                                 |
| R indices (all data)              | R1 = 0.0546, wR2 = 0.1417                                                                 |
| Largest diff. peak and hole       | 0.568 and -0.523 e.Å <sup>-3</sup>                                                        |



Crystal Structure Data for 5-phenylbenzo[*j*]phenanthridine **254****Table 6:** Crystal data and structure refinement for **254**

|                                   |                                                                                                        |
|-----------------------------------|--------------------------------------------------------------------------------------------------------|
| Empirical formula                 | C <sub>23</sub> H <sub>15</sub> N                                                                      |
| Formula weight                    | 305.36                                                                                                 |
| Temperature                       | 173(2) K                                                                                               |
| Wavelength                        | 0.71073 Å                                                                                              |
| Crystal system                    | Orthorhombic                                                                                           |
| Space group                       | P2(1)2(1)2(1)                                                                                          |
| Unit cell dimensions              | a = 5.7490(5) Å $\alpha$ = 90°.<br>b = 11.6180(11) Å $\beta$ = 90°.<br>c = 22.756(2) Å $\gamma$ = 90°. |
| Volume                            | 1519.9(2) Å <sup>3</sup>                                                                               |
| Z                                 | 4                                                                                                      |
| Density (calculated)              | 1.334 Mg/m <sup>3</sup>                                                                                |
| Absorption coefficient            | 0.077 mm <sup>-1</sup>                                                                                 |
| F(000)                            | 640                                                                                                    |
| Crystal size                      | 0.268 x 0.068 x 0.052 mm <sup>3</sup>                                                                  |
| Theta range for data collection   | 3.62 to 25.50°.                                                                                        |
| Index ranges                      | -6 ≤ h ≤ 6, -14 ≤ k ≤ 14, -26 ≤ l ≤ 27                                                                 |
| Reflections collected             | 19610                                                                                                  |
| Independent reflections           | 1605 [R(int) = 0.0581]                                                                                 |
| Completeness to theta = 25.50°    | 96.8%                                                                                                  |
| Absorption correction             | Semi-empirical from equivalents                                                                        |
| Max. and min. transmission        | 0.99 and 0.98                                                                                          |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                                            |
| Data / restraints / parameters    | 1605 / 0 / 217                                                                                         |
| Goodness-of-fit on F <sup>2</sup> | 1.050                                                                                                  |
| Final R indices [I > 2sigma(I)]   | R1 = 0.0404, wR2 = 0.0823                                                                              |
| R indices (all data)              | R1 = 0.0562, wR2 = 0.0879                                                                              |

|                              |                                    |
|------------------------------|------------------------------------|
| Absolute structure parameter | 10(10)                             |
| Largest diff. peak and hole  | 0.154 and -0.154 e.Å <sup>-3</sup> |

Crystal Structure Data for 13-benzyl-13*H*-indolo[3,2-*c*]acridine **410****Table 7:** Crystal data and structure refinement for **410**

|                                   |                                                                                                                                    |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Empirical formula                 | C <sub>26</sub> H <sub>18</sub> N <sub>2</sub>                                                                                     |
| Formula weight                    | 358.42                                                                                                                             |
| Temperature                       | 173(2) K                                                                                                                           |
| Wavelength                        | 0.71073 Å                                                                                                                          |
| Crystal system                    | Monoclinic                                                                                                                         |
| Space group                       | P2(1)                                                                                                                              |
| Unit cell dimensions              | $a = 18.7377(12)$ Å $\alpha = 90^\circ$<br>$b = 4.3336(3)$ Å $\beta = 105.903(2)^\circ$<br>$c = 22.6892(15)$ Å $\gamma = 90^\circ$ |
| Volume                            | $1771.9(2)$ Å <sup>3</sup>                                                                                                         |
| Z                                 | 4                                                                                                                                  |
| Density (calculated)              | 1.344 Mg/m <sup>3</sup>                                                                                                            |
| Absorption coefficient            | 0.079 mm <sup>-1</sup>                                                                                                             |
| F(000)                            | 752                                                                                                                                |
| Crystal size                      | 0.64 x 0.06 x 0.04 mm <sup>3</sup>                                                                                                 |
| Theta range for data collection   | 3.30 to 25.50°                                                                                                                     |
| Index ranges                      | -22 ≤ h ≤ 22, -5 ≤ k ≤ 4, -27 ≤ l ≤ 27                                                                                             |
| Reflections collected             | 24135                                                                                                                              |
| Independent reflections           | 3289 [R(int) = 0.0600]                                                                                                             |
| Completeness to theta = 25.50°    | 99.8%                                                                                                                              |
| Absorption correction             | Semi-empirical from equivalents                                                                                                    |
| Max. and min. transmission        | 0.9969 and 0.9512                                                                                                                  |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                                                                        |
| Data/restraints/parameters        | 3289/0/253                                                                                                                         |
| Goodness-of-fit on F <sup>2</sup> | 01.030                                                                                                                             |
| Final R indices [I > 2σ(I)]       | R1 = 0.0455, wR2 = 0.0932                                                                                                          |
| R indices (all data)              | R1 = 0.0789, wR2 = 0.1076                                                                                                          |

Largest diff. peak and hole

0.182 and -0.210 e Å<sup>-3</sup>